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10th Edition

ROSEN'S Emergency Medicine

Concepts and Clinical Practice

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ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1600
Philadelphia, PA 19103-2899

ROSEN'S EMERGENCY MEDICINE: CONCEPTS AND CLINICAL PRACTICE, TENTH EDITION
ISBN: 978-0-323-75789-8
VOLUME 1
ISBN: 978-0-323-75847-5
VOLUME 2
ISBN: 978-0-323-75848-2

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Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

ACKNOWLEDGMENTS

Never has family meant so much. To my wife, Barb; my children, Andrew, Blake, and Alexa; and their spouses and children, thank you for reminding me why this work is so important. I was inspired and profoundly moved by the response of our specialty, and our colleagues across the healthcare spectrum, to this pandemic scourge. We embrace a brighter future, with a deep and unwavering look to the past, and with enormous gratitude. To Peter and John, thanks again, for all of it.

RMW

It has been both an honor and a pleasure to serve as an editor of this book for 10 editions, and I would like to express my appreciation to those who made this career-spanning journey for me both professionally fulfilling and personally rewarding. To Peter, John, and Ron for their vision and leadership as editors-in-chief, and for their friendship over the years, in good times and bad; to the 28 other leaders in our discipline who gave generously of their time and talent to serve as editors on different editions of the book; to the Elsevier staff (particularly Laura, Kathy, Stephanie, Kate, and Dee) for the support and encouragement they provided over the years; and to my wife Patty for bringing color, perspective, and broader meaning to my life.

RSH

I would like to thank my family for their continued understanding of my work to improve emergency care. My husband, David, and our three children, Katie, Jeremiah, and Sarah, provide the love, joy, and encouragement that makes participation on endeavors as important as this text worthwhile. Finally, I would like to thank my editor colleagues for their leadership and willingness to work through the pandemic to create a truly state-of-the-art textbook.

MGH

I would like to thank my incredible husband, Peter—I love you more each day—and our three amazing daughters, Sam, Jessie, and Avery—being your mom has been the joy of my life. I would also like to thank Denver Health's humanistic, incredibly talented, and brave Emergency Medicine residents—you are the hope for the future of medicine. And finally, I am deeply indebted to our patients, who allow us to witness their most vulnerable moments, and in doing so, offer us a chance to connect through our shared humanity.

KB

Thanks to my family for their understanding and support of all that pulls me away from time to time. Many thanks to Ron, Bob, Marianne, Tim, and Susan for the opportunity to work on this critical resource for our specialty. It has been an honor and a wonderful learning experience.

CAB

Forged during the scourge of the COVID-19 pandemic, this edition was for me a personal tribute to Peter Rosen, whose voice I can still hear and whose wisdom I still need. Looking forward to a brighter, kinder, safer, and more just future for all we serve, including those most dear to me: Deborah, Jacob, Sally, and Jaylin.

DFMB

With sincerest gratitude to Ron for the opportunity to contribute to this humbling body of work, to Bob, Marianne, Tim, and Susan for their sage wisdom and guidance throughout the process, and to Christine, Marisa, and Matthew—you are a source of perpetual strength, grounding, and encouragement that forever reminds me of the really important things in life.

JED

I extend my heartfelt thanks to Valerie, Camille, Isabelle, Celeste, Julian, and my parents, Robert and Gladys. I also give full credit to my mentors and colleagues in Emergency Medicine, Toxicology, Wilderness Medicine, and Global Humanitarian Health. Special thanks (with deep reverence) to the scientists who helped lay the foundation for us all: Paracelsus, Alice Hamilton, Rosalind Franklin, and Percy Lavon Julian.

TBE

To all the faculty, residents, and staff at the Mount Sinai Department of Emergency Medicine—their commitment to excellence in clinical care, teaching, and research inspires me every day. To Silvana, my wife and closest colleague, for her support and for keeping me focused on the important things in life. To Ron for being a mentor throughout my career; and to John and Peter, who live forever in our hearts and in the soul of our specialty.

ASJ

I am grateful to Ron, Bob, Marianne, Tim, and Susan for their incredible mentorship and patience with me, and to our Elsevier team for their editorial guidance. I also want to thank all the faculty, fellows, and residents at Harbor-UCLA Medical Center for inspiring me to always be the better teacher, learner, faculty member, and physician. Thank you!

AHK

To my wife Ami, thank you for your boundless patience. To all the residents I have played a role in training, I hope you have learned from me as much as I have from you.

LDS

I am grateful to my family who put up with late nights, early mornings and weekends, understanding this labor of love. To the authors for incredible work, and to my senior editors, Bob, Marianne, Tim, and Susan for their tremendous guidance. To Ron, for his incredible leadership and artful mentorship and for bringing me on. To the Elsevier team for first class support. To my late mother, Belle Patricia Tyndall, a teacher of English, who made this all possible for me.

JAT

With love and thanks to my wife, Julie, and my three wonderful kids, Izzy, Jack, and Alex, to my family, ever patient and ever supportive, and to my friends and mentors who continue to advance this critical field. This book is more important than ever as our specialty forms the front line of medicine and faces the most challenging clinical and social issues of our time. I remain inspired by all of the emergency providers everywhere who strive to provide expert care to every patient, every day; thank you. And especially to my daughter, Isabella VanRooyen, who is striving toward a career in medicine. May she be as fortunate as I was to find wonderful colleagues, inspiring mentors, and generous patients to lead her into a fulfilling career in a field that she loves.

MVR

I would like to thank Ron for the opportunity to work with this incomparable team of authors and coeditors. I have learned from each of you. I also want to thank my residents. Over the years, I have been fortunate to work with gifted EM residents who push me each day to be a better physician. Their asking the "why" behind the medicine, wanting to know the evidence, and insisting upon excellence from themselves have elevated my knowledge and practice. I am deeply indebted to you all.

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PREFACE TO THE TENTH EDITION

We introduce this tenth edition of the most important textbook in our field with a deep humility, born of the uncertainty that has shaken our beliefs and our world community. Through the extraordinary challenges of 2020 through 2022 we learned anew the precious and inestimable joy of companionship—of family, friends, loved ones, and colleagues. We learned to rely on one another as never before, and we learned the strength of numbers, of teams, of collective effort to face down a daunting and unfamiliar foe. We learned about the indominable spirit that drives our specialty, and the unquestioning trust our patients place in us. And we affirmed, as never before, the power of science to lift us all up, to transform and respond, to solve and to cure, and to relentlessly breach the faulty logic of the deniers.

This edition of *Rosen's* was born in three labors. In the first, we set about to build a creative new editorial team, one that would make this current edition undeniably better, but also position us to expand the influential leadership position of this book as a source of truth for the next generation of learners and practitioners. We celebrated the contributions of editors departing and welcomed a new and diverse team to lead us into the future. Ron reprised his role as Editor-in-Chief. Tim and Susan joined Bob and Marianne as Senior Editors, Tim moving from his role of Associate Editor for the ninth edition, Susan stepping into the role directly from the solid foundation of her body of work in emergency medicine and critical care. We welcomed our outstanding returning Associate Editors, Katie Bakes, Andy Jagoda, Amy Kaji, and Mike VanRooyen, who generously agreed to again shoulder the enormous load as primary editors. We bolstered our team with new Associate Editors from leading academic centers: Calvin Brown III, David Brown, and Leòn Sanchez, from the Harvard Medical School affiliates Brigham and Women's Hospital and Massachusetts General Hospital; Adrian Tyndall, from the University of Florida; and Jonathan Davis, from Georgetown University. With our outstanding editorial team from Elsevier, we held detailed discussions about how to make the book better, more succinct, easier to access, and with more clear guidance for our readers. We brainstormed new topics and chapters, identified promising new authors, debated whether some existing topics should be consolidated or retired, and what content should be in the book versus available online only. Little did we know, when we held our planning meetings in Cambridge, MA, in June, 2019, that we would never again be together in one room until after the book was in print.

The second labor was, in reality, a pause. When the pandemic hit in full force in spring of 2020, we recognized that neither authors nor editors should be distracted from their complete commitment to caring for their teams, patients, and communities. From month to month, we gathered editors in virtual meetings to discuss the evolving situation, so we could collectively decide when it would be appropriate to turn our attention back to the important work of editing. These meetings kept us together as a team, reminded us of the long future ahead in a post-pandemic world, and also informed us about new information that was sorely needed, such as how to safely intubate patients with high infectivity, high morbidity respiratory disease, and the need to shift coronaviruses from a brief topic in a general chapter on viruses to a chapter all of its own. Through it all, we supported one another and a found common purpose.

The third labor was in bringing the book over the finish line when we resumed our task, reconnected with authors, and attacked the work with renewed energy. Fortunately, at the time of our pause, the book was well ahead of schedule, a tribute to the diligence of our authors and editors, which made the final steps less daunting than otherwise would have been the case. Our editorial team from Elsevier never missed a beat, always ready to help, support, cajole, remind, problem-solve, bolster, and cheer; often with a moment or two of humor, encouragement, and respite.

And we got there. Not just there, not just to a good place, not simply to the relief of finishing, but to the profound satisfaction of producing what we know, without the slightest doubt, represents yet another significant advance in the evolution of Peter Rosen's vision from almost 40 years ago. So, to you, the reader, we submit this, our finest work, born of one of our finest hours, and perhaps the finest hour of our specialty.

Ron M. Walls
Robert S. Hockberger
Marianne Gausche-Hill
Tim Erickson
Susan Wilcox

PREFACE TO THE NINTH EDITION

When we began planning for this ninth edition, we challenged ourselves to make substantial and meaningful improvements to a book that has become the trusted standard in our field. With broad and rapid changes occurring in health care and information sciences, we recognized that relevance is not an accidental or passive concept. To advance in relevance and consolidate the book's position as the defining reference in our specialty, we carefully and deliberately undertook bold changes that we know make the book at once fresh, directive, and current in a way we have never before dared.

First, we created a substantially enhanced role for our editors, one that would demand a great deal more of their time, creativity, and energy. This helped us build a substantially different team of editors, a perfectly balanced blend of those with great experience with prior editions and those who would bring new ideas and challenge our assumptions. Ron Walls was asked to serve as Editor-in-Chief, with Bob Hockberger in his long-standing role as senior editor. Marianne Gausche-Hill, a highly respected academic emergency physician with service as editor on four previous editions, stepped up to complete our senior editorial ranks. At the editor level, Dr. Andy Jagoda returns and is joined by six brilliant new editors drawn from academic programs from coast to coast—Drs. Katherine Bakes, Jill Baren, Timothy Erickson, Amy Kaji, Michael VanRooyen, and Richard Zane. This dynamic and innovative editorial team has dramatically redrawn our text's blueprint by preserving what has served our readers the best, such as well-written discussions of the pathophysiologic basis of illness and injury, while moving in entirely new directions in providing pithy, clear, and succinct recommendations for diagnosis and treatment.

We collectively determined that all references prior to 2010 have been sufficiently long in the public domain that they no longer warrant citation. The infrequent exception to this is for guidelines that were issued in 2007 or later and have not been reissued or supplanted since. Strict adherence to our referencing policy required authors to diligently provide well-researched and detailed updates to their chapter content, based on only the most recent and relevant medical literature. In cases in which the literature is controversial or unclear, we have used the combined experience and expertise of our authors and editors to present cogent analyses of diagnostic and treatment options, make specific recommendations, and give the reader clear indications of the preferred actions. This makes the book much more immediately relevant for emergency clinicians. We recognize that emergency medicine is practiced by specialist emergency physicians, other physicians, residents and other trainees, and a variety of nonphysician practitioners, so were careful to ensure that we are addressing all these groups with the same concise, highest quality information and recommendations.

We revisited page counts for every chapter, adjusting allocations where indicated, and added new chapters on several important topics. We focused anew on consistency and redundancy, enhancing the former and minimizing the latter. We moved some chapters to online access only, allowing us to add new topics of interest, such as drug therapy for older patients, and have provided a rich array of dynamic videos and images, especially in emergency ultrasound. We substantially expanded and reorganized the pediatric emergency medicine section, introducing dedicated pediatric chapters on airway management, procedural sedation, and drug therapy. We introduced significant new material on emergencies in the pregnant woman, the patient with cancer, and a variety of other highly important clinical conditions. And, in every possible case, we insisted on adherence to referencing and writing requirements, a focus on relevant directive information, and appropriate use of prose and illustrations to provide the perfect balance of depth, breadth, and ready accessibility.

We are enormously proud of the result, a different, more readable "Rosen," preserving the gravitas earned over 30 years as the most important book in our specialty while embracing the modern era of emergency medicine practice and research and an entirely new generation of learners and practitioners. For those who have owned prior editions, we appreciate your loyalty over so many years and hope to reward it with a significantly improved and useful companion for your continuing learning and practice of this great specialty. For our newer readers, welcome, and thank you for inspiring us to make significant changes to an iconic and timeless part of our academic heritage.

Ron M. Walls
Robert S. Hockberger
Marianne Gausche-Hill

HOW THIS MEDICAL TEXTBOOK SHOULD BE VIEWED BY THE PRACTICING CLINICIAN AND JUDICIAL SYSTEM

The editors and authors of this text strongly believe that because of the variations of human diseases, the unpredictability of pathologic conditions, and the functions, dysfunctions, and responses of the human body, the complex practice of medicine cannot be definitively explained or comprehensively dictated by any written document. Therefore, it is neither the purpose nor intent of our textbook to serve as the definitive source of truth regarding any medical condition, treatment plan, or clinical intervention. Specifically, our textbook is intended to educate and inform learners and practitioners, and is not to be used to rigorously define a standard of care that should be followed by all clinicians in all settings.

Our written word represents our best efforts to present the clinician with scientifically based and clinically sound information to provide reasonable and reliable clinical guidance. This science is interpreted by our authors and editors through the lenses of their own knowledge, years of clinical experience, teaching of others, and the study of adverse outcomes and human and system error. No textbook can fully account for the range of limited information, varying clinical clues, instincts, judgments, and responses that occur during the care of emergency and critical care patients. In fact, other experts might interpret the same evidence differently, based on their own experience and analysis of available information. No human being can possibly assimilate the entire depth and breadth of the treatments, procedures, and medical conditions described in this textbook—in fact, that is why this book and others exist. Finally, many of the described complications and adverse outcomes associated with implementing or withholding complex medical and surgical interventions may occur, even when the clinicians have used sound clinical judgment and made decisions and performed interventions according to the tenets of this and other standard medical references.

The editors and authors of *Rosen's Emergency Medicine: Concepts and Clinical Practice,* Tenth Edition

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Airway

Calvin A. Brown III and Ron M. Walls

KEY CONCEPTS

- Anticipating the clinical course of the patient's condition and assessing the likelihood of deterioration are crucial to the decision to intubate, especially if the patient is to leave the emergency department (ED) for a period of time (e.g., interfacility transfer, diagnostic testing).
- Although videolaryngoscopy (VL) has reduced the chance of a failed intubation attempt caused by difficult anatomic features that often thwart direct laryngoscopy (DL), an assessment of the patient for potential difficult intubation, bag-mask ventilation (BMV), ventilation using an extraglottic device (EGD), and cricothyrotomy is an essential step before a neuromuscular blocking agent (NMBA) is administered. The mnemonics *LEMON, ROMAN, RODS,* and *SMART* can serve as useful aids.
- Physiologic derangement can contribute to morbidity and mortality during emergency airway management. Cardiovascular optimization with fluids, blood, and pressor agents should be undertaken, when time allows, to reduce the risk of circulatory collapse and cardiac arrest.
- In the absence of a crash patient (agonal, unresponsive to laryngoscopy) or difficult airway, rapid sequence intubation (RSI) is the airway management method of choice for ED patients.
- Tube placement confirmation using end-tidal carbon dioxide ($ETco_2$) is essential after intubation; failure to detect adequate quantities of exhaled CO_2 is evidence of esophageal intubation until proven otherwise.
- VL increases first-attempt intubation success, even when compared with DL combined with various optimization techniques. First-attempt success (FAS) is associated with fewer adverse events and better outcomes. Emergency airway managers should learn, and adopt, VL as the method of choice for emergency intubation.
- Cricothyrotomy is indicated in the "can't intubate, can't oxygenate" failed airway situation and should be performed once this has been identified. Delays may increase the likelihood or severity of hypoxic injury to the patient.
- Etomidate is used in more than 90% of all RSIs. Either rocuronium or succinylcholine is a reasonable NMBA for use during RSI. Rocuronium has less potential for adverse effects but a longer duration of action.
- EGDs are rarely used in ED airway management but offer additional options for rescue oxygenation of the failed airway and are used in many prehospital systems.

PRINCIPLES

Background

Airway management is the cornerstone of resuscitation and is a defining skill for the specialty of emergency medicine. The emergency clinician has primary airway management responsibility, and all emergency airway techniques lie within the domain of emergency medicine. Although rapid sequence intubation (RSI) is the most commonly used method for emergent tracheal intubation, emergency airway management includes various intubation techniques and devices, approaches to the difficult airway, and rescue techniques when intubation fails.

Anatomy, Physiology, and Pathophysiology

The decision to intubate should be based on careful patient assessment and appraisal of the clinical presentation with respect to three essential criteria: (1) failure to maintain or protect the airway; (2) failure of ventilation or oxygenation; and (3) the patient's anticipated clinical course and likelihood of deterioration.

Failure to Maintain or Protect the Airway

A patent airway is essential for adequate ventilation and oxygenation. If a patient is unable to maintain a patent airway, patency should be established by using airway maneuvers such as repositioning, chin lift, jaw thrust, or insertion of an oral or nasal airway. Likewise, the patient must be able to protect against the aspiration of gastric contents, which carries significant risks for morbidity and mortality. Historically, the presence of a gag reflex has been advocated as a reliable indicator of the patient's ability to protect the airway, but this has been definitively proven to be unreliable because the gag reflex is absent in 12% to 25% of normal adults, and there is no evidence that its presence or absence corresponds to airway protective reflexes or predicts the need for intubation. The patient's ability to swallow or handle secretions is a more reliable indicator of airway protection. The recommended approach is to evaluate the patient's level of consciousness; ability to phonate in response to voice command or query, which provides information about the integrity of the upper airway and level of consciousness; and ability to manage his or her own secretions (e.g., pooling of secretions in the oropharynx, absence of swallowing spontaneously or on command). In general, a patient who requires a maneuver to establish a patent airway or who easily tolerates an oral airway requires intubation for airway protection, unless there is a temporary or readily reversible condition, such as an opioid overdose.

Failure of Ventilation or Oxygenation

Gas exchange, both oxygenation and removal of carbon dioxide, is required for vital organ function. Ventilatory failure that is not easily reversible or persistent hypoxemia despite maximal oxygen supplementation is a primary indication for intubation. This assessment is clinical and includes an evaluation of the patient's general status, oxygen saturation by pulse oximetry, and ventilatory pattern. Continuous capnography also can be helpful, but is not essential if oximetry readings are reliable. Arterial blood gases (ABGs) are neither required

to determine the patient's need for intubation, nor practical to obtain before an emergency intubation. In addition, ABGs may be misleading, causing a false sense of security and delay in intubating a deteriorating patient. If obtained, they should be interpreted in the context of the patient's clinical status. Patients who are clinically improving despite severe or apparently worsening ABG alterations may not require intubation, whereas a rapidly tiring asthmatic, for example, may require intubation, even though ABG values are only modestly disturbed. In most cases, clinical assessment, including pulse oximetry with or without capnography, consideration of the timeline of the patient's respiratory emergency, and observation of improvement or deterioration in the patient's clinical condition will lead to a correct decision.

The need for prolonged mechanical ventilation generally mandates intubation. An external mask device, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP) have all been used successfully to manage patients with exacerbations of chronic obstructive pulmonary disease (COPD) and congestive heart failure, obviating the need for intubation (see Chapter 2), but, despite these advances, many patients who need assisted ventilation or positive pressure to improve oxygenation require intubation.

Anticipated Clinical Course

Certain conditions indicate the need for intubation, even without an immediate threat to airway patency or adequacy of ventilation and oxygenation. These conditions are characterized by a moderate to high likelihood of predictable airway deterioration, worsening physiologic derangement, or the need for intubation to facilitate a patient's evaluation and treatment. Intubation may be indicated relatively early in the course of certain overdoses. Although the patient initially may be protecting the airway and exchanging gas adequately, intubation is advisable to guard against the strong likelihood of clinical deterioration, which can occur after the initial phase of care when the patient is no longer closely observed. Patients with septic shock have high metabolic demand, myocardial depression, increased peripheral oxygen extraction, and vascular permeability. The combination of ventilatory fatigue, depressed pump function, and the need for directed fluid resuscitation predictably results in the need for intubation as pulmonary vascular congestion, hypoxia, and the work of breathing worsen. A patient who has sustained significant multiple traumatic injuries may require intubation, even if the patient is ventilating normally through a patent airway and has adequate oxygen levels. For example, a multiple trauma patient with hypotension, an open femur fracture, and diffuse abdominal tenderness warrants early intubation, even if the patient is initially awake and alert, without airway injury or hypoxemia. Active resuscitation, pain control, need for invasive procedures and imaging outside of the emergency department (ED), and inevitable operative management dictate the need for early airway control. In addition, a patient with penetrating neck trauma may have a patent airway and adequate gas exchange. Nevertheless, early intubation is advisable when there is evidence of vascular or direct airway injury, because these patients tend to deteriorate and increasing hemorrhage or swelling in the neck will compromise the airway and confound later attempts at intubation.

The common thread among these indications for intubation is the anticipated clinical course. In each case, it can be anticipated that future events may compromise the patient's ability to maintain and protect the airway or ability to oxygenate and ventilate. Waiting until these occur may result in a difficult airway.

Identification of the Difficult Airway

In most patients, intubation is technically straightforward. Although early ED-based observational registries reported cricothyrotomy rates of approximately 1% for all intubations, more recent studies have shown a lower rate, less than 0.5%.[1] As would be expected with an unselected, unscheduled patient population, the ED cricothyrotomy rate is greater than in the operating room, which occurs in approximately 1 in 200 to 2000 elective general anesthesia cases.[2] Bag-mask ventilation (BMV) is difficult in approximately 1 in 50 general anesthesia patients and impossible in approximately 1 in 600. However, BMV is difficult in up to one-third of patients in whom intubation failure occurs, and difficult BMV makes the likelihood of difficult intubation 4 times higher and the likelihood of impossible intubation 12 times higher. The combined failure of intubation, BMV, and oxygenation in elective anesthesia practice is estimated to be exceedingly rare, approximately 1 in 30,000 patients.[3] These numbers cannot be extrapolated to populations of ED patients who are acutely ill or injured and for whom intubation is urgent and unavoidable. Although patient selection cannot occur, as with a preanesthetic visit, a preintubation analysis of factors predicting difficult intubation gives the provider the information necessary to formulate a safe and effective plan for intubation.

Preintubation assessment should evaluate the patient for anatomic features that would herald a difficult airway. This includes an assessment for potential difficulty with laryngoscopy and intubation, BMV, placement of and ventilation with an extraglottic device (EGD; see later discussion), and cricothyrotomy. Knowledge of all four domains is crucial to successful planning. A patient who exhibits difficult airway characteristics is highly predictive of a challenging intubation, although the emergency clinician should always be ready for a difficult to manage airway because some difficult airways may not be identified by a bedside assessment.[4]

Airway difficulty exists on a spectrum. Some patients may have a single minor anatomic or pathophysiologic reason for airway difficulty, whereas others may have numerous difficult airway characteristics, complicating laryngoscopy, bag ventilation, use of an EGD, and cricothyrotomy. Although both sets of patients represent potential intubation challenges, the latter group, especially if obstructing upper airway pathology is part of the problem, more often has crossed a threshold of difficulty beyond which neuromuscular blockade would be avoided because a "can't intubate, can't oxygenate" (CI:CO) failed airway may ensue. In these cases, the preferred approach is to use topical anesthesia methods, with titrated parenteral sedation, to achieve intubation without the use of a neuromuscular blocking agent (NBMA). This is particularly true when intubation is undertaken with conventional laryngoscopy (versus use of a video laryngoscope or flexible endoscope) or when use of NBMAs would result in immediate physiologic deterioration and instability. Patients with refractory hypoxemia or severe metabolic acidosis may be intolerant to even brief periods of apnea. In such patients, an awake approach is preferred, particularly if anatomic difficulty coexists.[4] Airways predicted to be anatomically difficult when using a traditional laryngoscope may not prove difficult when a videolaryngoscope is used (see later discussion). Occasionally, RSI remains the preferred method, despite assessment that the patient has a difficult airway, as part of a planned approach to airway management. This may include physiologic optimization, use of videolaryngoscopy (VL), and a double setup, in which a rescue approach, such as cricothyrotomy, is fully prepared for immediate use in the event of intubation failure. Regardless of the results of a reassuring bedside assessment for airway difficulty, significant challenges may be encountered with intubation and BMV, and the clinician must be prepared for unanticipated difficulty with every intubation.

Difficult Direct Laryngoscopy: LEMON

Glottic visualization is paramount in emergency airway management. With direct laryngoscopy (DL), if the vocal cords can be seen (Cormack and Lehane [CL] grade I or II view; Fig. 1.1), the chance of

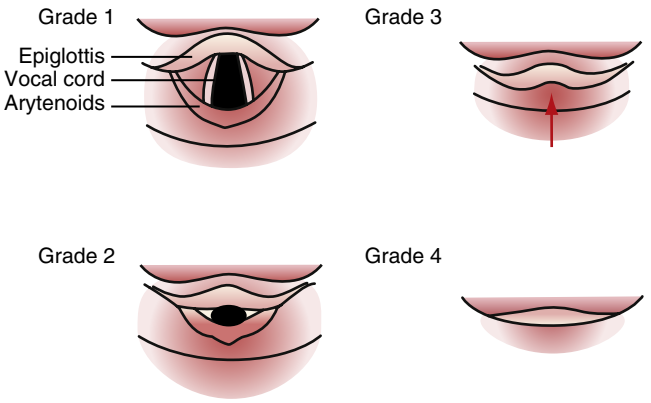

Fig. 1.1 Cormack and Lehane Grading System for Glottic View. (patency.)

BOX 1.1 *LEMON* Mnemonic for Evaluation of Difficult Direct Laryngoscopy.

Look externally for signs of difficult intubation (by gestalt)
Evaluate 3-3-2 rule
Mallampati scale
Obstruction or obesity
Neck mobility

Adapted with permission from The Difficult Airway Course: Emergency and Brown III CA, Mick NM, Sakles JC, editors. *The Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.

intubation success is high. However, when the glottic aperture cannot be visualized (CL grade III or IV), intubation success is less likely. Very few of the difficult airway markers thought to limit DL access have been scientifically validated, yet applying them in combination can provide a reasonable assessment of anticipated airway difficulty. On the other hand, VL rarely fails to provide adequate laryngeal visualization but may introduce difficulty with indirect tube placement. Characterization of difficult VL predictors is not well studied, and although mnemonics exist that attempt to cover predictors of both difficult direct and VL, the components are too broad to be clinically useful (see discussion later).[5] Like DL, adequate video views are highly correlated with intubation success, although the strength of this association can depend on the device used and operator experience. Whether DL or VL is planned, a standard screening process for difficulty should be undertaken with every patient. Our recommended approach uses the mnemonic *LEMON* (Box 1.1), which has been shown to have reasonable sensitivity and high negative predictive value.[6]

L—look externally. The patient first should be examined for external markers of difficult intubation, which are determined based simply on the intubator's clinical impression or initial gestalt. For example, the severely bruised and bloodied face of a combative trauma patient, immobilized in a cervical collar on a spine board, should (correctly) invoke an immediate appreciation of anticipated difficulty. Subjective clinical judgment can be highly specific but insensitive and so should be augmented by other evaluations whether or not the airway appears to be challenging.

E—evaluate 3-3-2. The second step in the evaluation of the difficult airway is to assess the patient's airway geometry to determine suitability for DL. Glottic visualization with a direct laryngoscope necessitates that the mouth opens adequately, the submandibular space is adequate to accommodate the tongue, and the larynx be positioned low enough in the neck to be accessible. These relationships have been explored in various studies by external measurements of mouth opening, oropharyngeal size, neck movement, and thyromental distance. The 3-3-2 rule is an effective summary of these assessments. The 3-3-2 rule requires that the patient be able to place three of his or her own fingers between the open incisors, three of his or her own fingers along the floor of the mandible beginning at the mentum, and two fingers from the laryngeal prominence to the underside of the chin (Fig. 1.2). A patient with a receding mandible and high-riding larynx is exceptionally difficult to intubate using DL because the operator cannot adequately displace the tongue and overcome the acute angle for a direct view of the glottic aperture. In practice, the operator compares the size of his or her fingers with the size of the patient's fingers and then performs the three tests.

M—Mallampati scale. Oral access is assessed with the Mallampati scale (Fig. 1.3). Visibility of the oral pharynx ranges from complete visualization, including the tonsillar pillars (class I), to no visualization at all, with the tongue pressed against the hard palate (class IV). Classes I and II predict adequate oral access, class III predicts moderate difficulty, and class IV predicts a high degree of difficulty. A meta-analysis has confirmed that the four-class Mallampati score performs well as a predictor of difficult laryngoscopy (and, less so, of difficult intubation), but the Mallampati score alone is not a sufficient assessment tool. A Mallampati score necessitates an awake compliant patient to perform the assessment in the way in which it was originally described. Nearly 50% of ED patients requiring intubation cannot cooperate with this assessment, but it can be improvised by using a direct laryngoscope blade as a tongue depressor in obtunded or uncooperative patients.

O—obstruction or obesity. Upper airway (supraglottic) obstruction may make visualization of the glottis, or intubation itself, mechanically impossible. Conditions such as epiglottitis, head and neck cancer, Ludwig angina, neck hematoma, glottic swelling, or glottic polyps can compromise laryngoscopy, passage of the endotracheal tube (ETT), BMV, or all three. Examine the patient for airway obstruction and assess the patient's voice to satisfy this evaluation step. Although obesity alone may not be an independent marker of difficult DL, it likely contributes to challenges in other areas of airway management. Nevertheless, obese patients generally are more difficult to intubate than their nonobese counterparts, and preparations should account for this and for the more rapid oxyhemoglobin desaturation and increased difficulty with ventilation using BMV or an EGD (see later).

N—neck mobility. Neck mobility is desirable for any intubation technique and is essential for positioning the patient for optimal DL. Neck mobility is assessed by flexion and extension of the patient's head and neck through a full range of motion. Neck extension is the most crucial motion but placing the patient in the full sniffing position provides the optimal laryngeal view by DL.[7] Modest limitations of motion do not seriously impair DL, but severe loss of motion, as can occur in ankylosing spondylitis or rheumatoid arthritis, may make DL impossible. Cervical spine immobilization in trauma patients artificially reduces cervical spine mobility, but DL is still highly successful in this group of patients.

A modified mnemonic, *LEMONS*, has been described, with the "S" referring to the patient's oxygen saturation. Although not a direct contributor to difficulty with DL, a low starting oxygen saturation will result in a shorter period of safe apnea and a reduced time to perform laryngoscopy and achieve ETT placement. Some providers may prefer "LEMONS" over "LEMON," but we consider oxygen status (and overall clinical status) a part of preintubation assessment that is distinct from difficult airway assessment. An alternative mnemonic, "HEAVEN" (***H***ypoxemia, ***E***xtremes of size, ***A***natomic challenges, ***V***omit/blood/

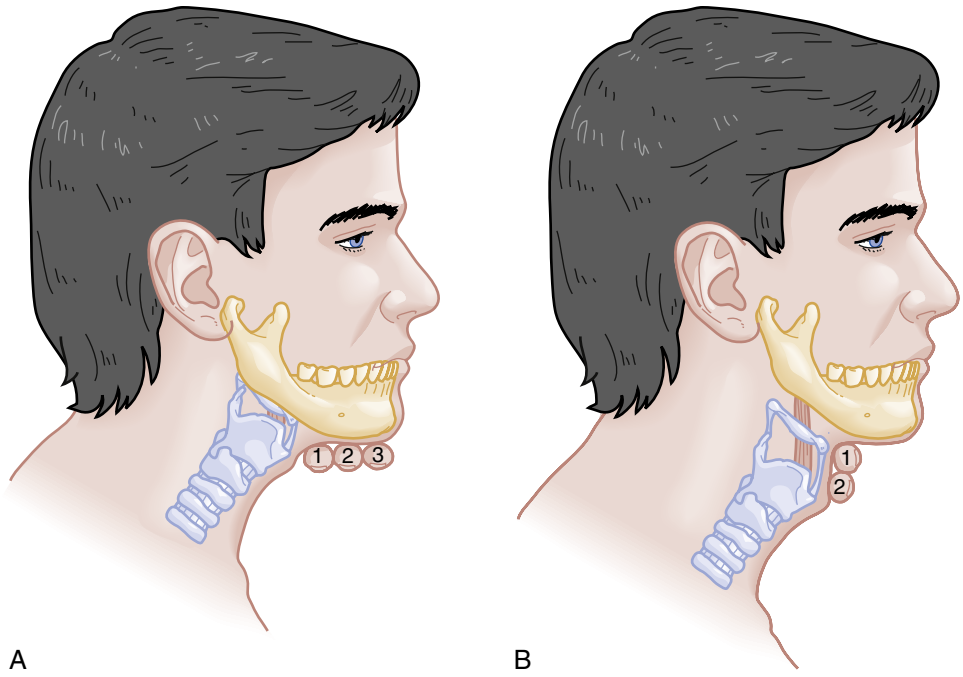

Fig. 1.2 **Final Two Steps of the 3-3-2 Rule.** (A) Three fingers are placed along the floor of the mouth, beginning at the mentum. (B) Two fingers are placed in the laryngeal prominence (Adams apple). (Modified from Brown III CA, Mick NM, Sakles JC, editors. Identification of the difficult and failed airways. In: *The Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.)

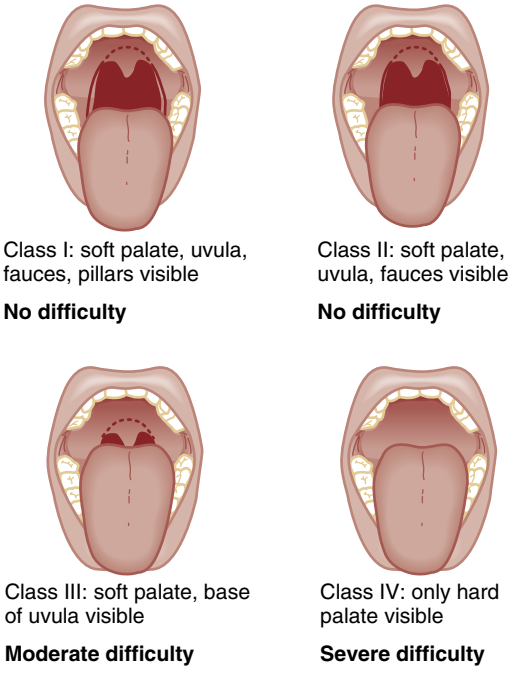

Fig. 1.3 The Mallampati Scale, Classes I to IV, Assesses Oral Access for Intubation. (From Whitten CE. *Anyone Can Intubate*. 4th ed. San Diego, CA; 2004; with permission.)

BOX 1.2 *ROMAN* Mnemonic for Evaluation of Difficult Bag-Mask Ventilation.

Radiation or resistance to ventilation
Obstruction, obesity and obstructive sleep apnea
Mallampati, male, mask seal
A*ged*
No teeth

Adapted with permission from The Difficult Airway Course: Emergency and Brown III CA, Mick NM, Sakles JC, editors. *The Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.

BOX 1.3 *RODS* Mnemonic for Evaluation of Difficult Extraglottic Device Placement.

Restricted mouth opening or ***R***esistance to ventilation
Obstruction, obesity, or obstructive sleep apnea
Distorted anatomy
Short thyromental distance

Adapted with permission from The Difficult Airway Course: Emergency and Brown III CA, Mick NM, Sakles JC, editors. *The Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.

fluid in the airway, ***E***xsanguination, and ***N***eck mobility) has been shown, in a retrospective review of aeromedical RSIs, to predict difficulty with both video and DL.[5] However, the components of HEAVEN are a broad mixture of physiologic and anatomic attributes, some of which are either vague (anatomic challenges) or self-evident (blood/vomit in the airway). The "HEAVEN" mnemonic lacks sufficient detail and specificity required to apply it at the bedside reliably, and we recommend use of the LEMON mnemonic. As noted, identification of a difficult intubation does not preclude use of an RSI technique. The crucial determination is whether the emergency clinician judges that the patient has a reasonable likelihood of intubation success, despite the difficulties identified, and that ventilation with BMV or an EGD will be successful in case intubation fails (hence the value of the BMV and EGD assessments; see Boxes 1.2 and 1.3).

Difficult Bag-Mask Ventilation: ROMAN

Attributes of difficult BMV have largely been validated and can be summarized with the mnemonic *ROMAN* (see Box 1.2).

- ***R***esistance/***R***adiation—Resistance to ventilation (requiring high ventilation pressures) caused by intrinsic pulmonary disease such as asthma, COPD, adult respiratory distress syndrome [ARDS]), or a history of directed head and neck radiation are strong predictors of difficult BMV.
- ***O***bstruction/***O***besity/***O***bstructive sleep apnea—Obstruction of the airway, particularly supraglottic obstruction, or presence of obesity, which results in redundant upper airway tissues, increased chest wall weight, and resistance of abdominal mass, similarly are predictors of difficult BMV.
- ***M***allampati/***M***ask seal/***M***ale—High Mallampati classification, inability to achieve a good mask seal (e.g., because of facial trauma or presence of a beard), and male gender all have associations with challenging rescue mask ventilation.
- ***A***ge—This refers to advanced age and is best judged by the physiologic appearance of the patient, but age older than 55 years increases risk.
- ***N***o *teeth*—Identifies the edentulous patient. Lack of teeth, which form a strut to support the mask for ventilation and also support the upper and lower lips, independently interferes with mask seal and hence successful BMV. The difficulty with BMV of the edentulous patient is the basis of the advice often cited for patients with dentures: "teeth out to intubate, teeth in to ventilate." Another approach involves placing the mask inside the patient's lower lip. This may limit air leaks in patients without teeth and eliminates the risk of aspiration associated with dental prosthetics or rolled gauze (Fig. 1.4).

Difficult BMV is common in the ED and out-of-hospital patients, but, with proper technique, BMV is usually successful. In patients undergoing elective anesthesia, impossible B MV is exceptionally rare (<0.5%) and is associated with the ROMAN mnemonic factors. The likelihood of difficult or impossible BMV increases proportionately to the number of these factors present.

Difficult Extraglottic Device Placement: RODS

Placement of an EGD, such as a laryngeal mask airway (LMA), Combitube, or similar upper airway device, often can convert a CI:CO situation to a "can't intubate, can oxygenate" situation, which allows time for rescue of a failed airway (see following section). Difficulty achieving placement or ventilation with an EGD can be predicted by the mnemonic *RODS* (see Box 1.3).

Fortunately, if the emergency clinician has already performed the LEMON and ROMAN assessments, only the *"D"* for distorted anatomy remains to be evaluated (see Box 1.3). EGDs are placed blindly and have a mask or balloon structure that, when inflated, obstructs the oropharynx proximally and esophageal inlet distally, permitting indirect ventilation. Distorted upper airway anatomy can result in a poor seal and ineffective ventilation. Short thyromental distance, the "S" in RODS, is identified as part of the 3-3-2 measurement during the LEMON assessment. Patients with receded mandibles have tongues that sit more posteriorly in the oral cavity creating an anatomic hurdle that the EGD must traverse to get to its final resting position relative to the glottis.[8]

Difficult Cricothyrotomy: SMART

Difficult cricothyrotomy can be anticipated whenever there is limited access to the anterior neck or the laryngeal landmarks are obscured. This can be assessed using the mnemonic *SMART* (Box 1.4). Prior surgery, hematoma, tumor, abscess, scarring (as from radiation therapy or prior injury), local trauma, obesity, edema, or subcutaneous air each has the potential to make cricothyrotomy more difficult. Perform an examination for the landmarks needed to perform cricothyrotomy as part of the preintubation difficult airway assessment of the patient. Point-of-care ultrasound can be used at the bedside to locate the cricothyroid membrane, thereby allowing the emergency clinician to mark the location on the surface of the neck in high-risk cases.[9] The emergency clinician should not avoid performing a rescue cricothyrotomy when necessary, even in the presence of predicted difficulty. Prediction of the difficulty and identification of the factors causing the difficulty help the clinician to work through the problem to achieve success.

Measurement and Incidence of Intubation Difficulty

The actual degree to which an intubation is difficult is highly subjective, and quantification is challenging. The CL system is the most widely used system for grading a laryngoscopic view of the glottis, which grades laryngoscopy according to the extent to which laryngeal and glottic structures can be seen (see Fig. 1.1). In grade 1 laryngoscopy, all or nearly all of the glottic aperture is seen; in grade 2, the laryngoscopist visualizes only a portion of the glottis (arytenoid cartilages alone or arytenoid cartilages plus part of the vocal cords), in grade 3 only the epiglottis is visualized, and, in grade 4, not even the epiglottis is visible.

Fewer than 1% of stable patients undergoing DL during elective anesthesia yield a grade 4 laryngoscopy, a finding associated with an extremely difficult intubation. Grade 3 laryngoscopy, which represents highly difficult intubation, is found in less than 5% of patients. Grade 2 laryngoscopy, which occurs in 10% to 30% of patients, can be subdivided further into grade 2a, in which the arytenoids and a portion of the vocal cords are seen, and grade 2b, in which only the arytenoids are

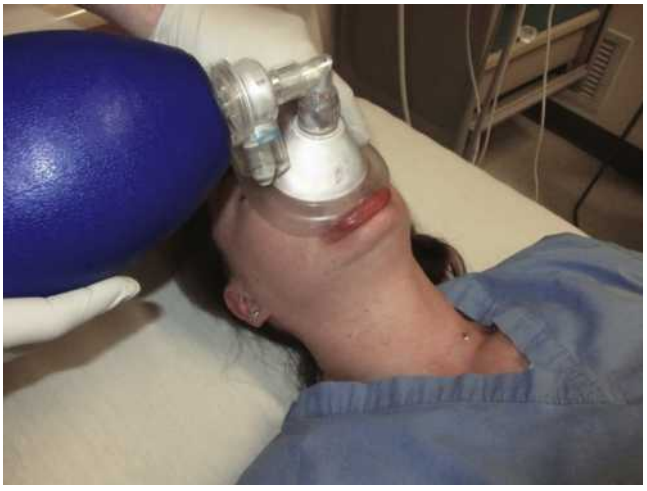

Fig. 1.4 Mask ventilation in edentulous patients can be performed by placing the lower rim of the mask on the inside of the patient's lower lip to improve mask seal. (Courtesy Dr. Tobias Barker.)

BOX 1.4 *SMART* Mnemonic for Evaluation of Difficult Cricothyrotomy.

Surgery
Mass (abscess, hematoma)
Access/anatomy problems (obesity, edema)
Radiation
Tumor

Adapted with permission from The Difficult Airway Course: Emergency and Brown III CA, Mick NM, Sakles JC, editors. *The Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.

seen. Intubation failure occurs in up to two-thirds of grade 2b cases but in less than 1 in 20 grade 2a cases. Approximately 80% of all grade 2 laryngoscopies are grade 2a; the rest are grade 2b. First-attempt intubation success drops off significantly as the glottic view transitions from a grade 2a to 2b; however, a grade 1 view is associated with virtually 100% intubation success. Outside of the operating room, the rate of difficulty may be higher. In one review of emergency adult inpatient intubations, as many as 10% were considered difficult (grade 3 or 4 CL direct view or more than three attempts required).[1] The incidence of difficult ED intubations is unknown but is likely much higher. An alternative system of grading laryngeal view, percentage of glottic opening (POGO), also has been proposed and validated but has not been widely used or studied. The incidence of difficult intubation and the predictors thereof are primarily based on the use of conventional DL and do not apply to VL. In a single-center assessment of ED intubations at an academic ED using VL exclusively, 80% of intubations predicted to be difficult were managed with NBMAs, with a 90% first-attempt success (FAS) rate.[10] Thus predictors of difficult DL do not impact VL to the same degree. Nonetheless, a bedside assessment should still be performed in all patients so potential pitfalls can be identified and avoided.

Confirmation of Endotracheal Tube Placement

Immediately after intubation, the operator should apply an end-tidal carbon dioxide ($ETco_2$) detection device to the ETT and assess it through six manual ventilations. Disposable colorimetric $ETco_2$ detectors are highly reliable, convenient, and easy to interpret, indicating adequate CO_2 detection by color change (Figs. 1.5 and 1.6) and determining tracheal and esophageal intubation in patients with spontaneous circulation. The persistence of detected CO_2 after six manual breaths indicates that the tube is within the airway, although not necessarily within the trachea. CO_2 is detected with the tube in the mainstem bronchus, trachea, or supraglottic space. Correlation of $ETco_2$ detection with the depth markings on the ETT, particularly important in pediatric patients, confirms tracheal placement. Rarely, BMV before intubation or ingestion of carbonated beverages may lead to the release of CO_2 from the stomach after esophageal intubation, causing a transient false indication of tracheal intubation. Washout of this phenomenon universally occurs within six breaths.

Although colorimetric $ETco_2$ measurement is highly sensitive and specific for detecting esophageal intubation, caution is required for patients in cardiopulmonary arrest. In general, patients in early cardiopulmonary arrest (as long as cardiopulmonary resuscitation [CPR] is being performed) still produce sufficient CO_2 (2%) to cause a positive color change. Persistent color change is definitive evidence of correct ETT placement, and lack of color change is indicative of a misplaced (likely esophageal) tracheal tube. Although unlikely, insufficient gas exchange during prolonged cardiac arrest, or with inadequate CPR, might prevent CO_2 detection in the exhaled air, even when the tube is correctly placed within the trachea. However, the absence of color change (i.e., the absence of CO_2 in expired air), even if the patient is in complete or prolonged cardiac arrest, should prompt a careful evaluation to ensure that an esophageal intubation has not occurred. Newer resuscitation guidelines have suggested continuous quantitative measurement of $ETco_2$ during cardiac arrest to gauge the efficacy of CPR. This circumstance arises in approximately 25% to 40% of intubated cardiac arrest patients.

When $ETco_2$ detection is not possible, tracheal tube position can be confirmed using other techniques. One approach involves point-of-care ultrasound. In live patient and cadaver studies, ultrasonography performed over the cricothyroid membrane or upper trachea has accurately confirmed ETT position in the trachea, especially during intubation.[11]

Another method of tube placement confirmation is the aspiration technique, based on the anatomic differences between the trachea and esophagus. The esophagus is a muscular structure with no support within its walls and is therefore collapsible when negative pressure is applied. The trachea is held patent by cartilaginous rings and thus is less likely to collapse when negative pressure is applied. Vigorous aspiration of air through the ETT with the ETT cuff deflated results in occlusion of the ETT orifices by the soft walls of the esophagus, whereas aspiration after tracheal placement of the tube is easy and rapid. Although once quite common, these devices are now rarely used and generally only in austere environments.

A gum elastic bougie can be placed through the center of an ETT to further corroborate tube location. Passing the bougie deeply through the tube, with little or no resistance, suggests an esophageal intubation because the bougie has likely passed beyond the tube and into the esophagus and stomach. If the ETT is in the trachea, the tip of the bougie will encounter resistance after emerging only a couple of inches from the tracheal tube, as it abuts the wall of the right mainstem bronchus. Another technique involves sliding the bougie in an upward and downward motion over a few inches distal to the tracheal tube. A vibration from contact of the deflected tip of the bougie with the anterior tracheal rings may be transmitted to the operator's fingertips.

Quantitative or qualitative $ETco_2$ detection, with ultrasound or the bougie technique as backup, is the primary means of ETT placement

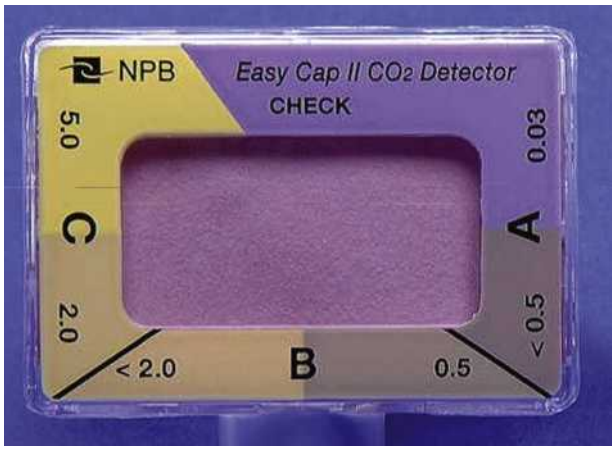

Fig. 1.5 End-Tidal CO_2 Detector Before Application. The indicator is *purple*, which indicates failure to detect CO_2. This also is the appearance when the esophagus is intubated.

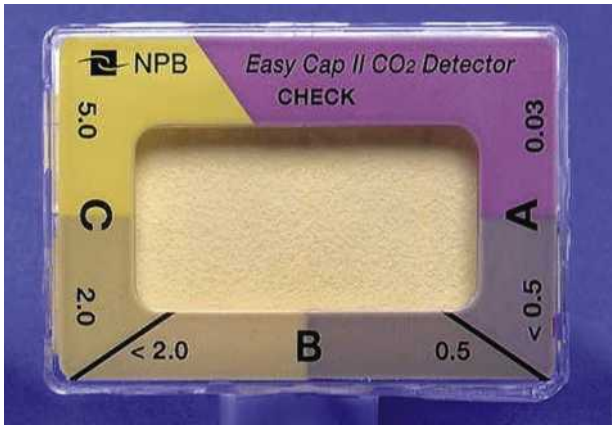

Fig. 1.6 Positive detection of CO_2 turns the indicator *yellow*, indicating tracheal placement of the endotracheal tube.

confirmation. Secondary means include physical examination findings, oximetry, and radiography. The examiner should auscultate both lung fields and the epigastric area but should not rely on these findings alone. Pulse oximetry is indicated as a monitoring technique in all critically ill patients, not just those who require intubation. Oximetry is useful in detecting esophageal intubation but may not show a decreasing oxygen saturation for several minutes after a failed intubation because of the oxygen reservoir (preoxygenation) created in the patient before intubation. Although chest radiography is universally recommended after ETT placement, its primary purpose is to ensure that the tube is well positioned below the cords and above the carina. Because the esophagus lies directly behind the trachea, a single anteroposterior chest radiograph is not sufficient to confirm tracheal intubation, although esophageal intubation may be detected if the ETT is clearly outside the air shadow of the trachea. In cases in which doubt persists, a fiberoptic scope can be passed through the ETT to identify tracheal rings, another "gold standard" for confirmation of tracheal placement.

MANAGEMENT

Decision Making

Algorithms for emergency airway management have been developed and provide a useful guide for planning intubation and rescue in case of intubation failure. The algorithms are applied after the decision to intubate, and the approach is predicated on two key determinations that are to be made before active airway management is initiated (Fig. 1.7).

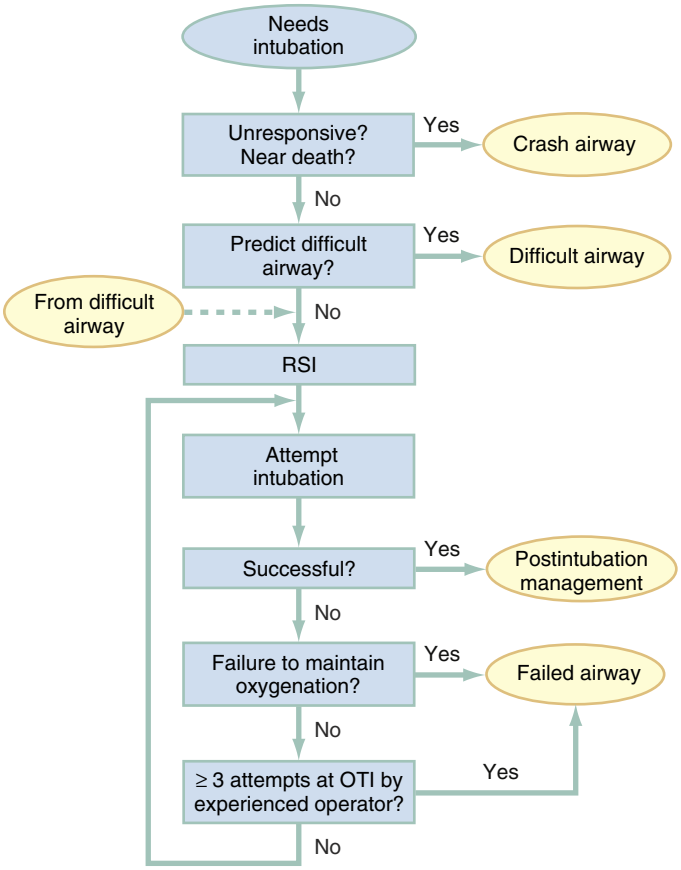

Fig. 1.7 Main Emergency Airway Management Algorithm. *OTI,* Orotracheal intubation; *RSI,* rapid sequence intubation. (Modified from Brown III CA, Mick NM, Sakles JC, editors. *The Emergency Airway Algorithms in the Walls Manual of Emergency Airway Management.* 5th ed. Philadelphia: Wolters Kluwer; 2018.)

The first determination is whether the patient is in cardiopulmonary arrest or a state of near arrest and is likely not to resist attempts at laryngoscopy. Such a patient—agonal, near death, in circulatory collapse—is deemed a "crash" airway patient for the purposes of emergency airway management and is treated using the crash airway algorithm by an immediate intubation attempt without use of drugs; this can be supplemented by a single large dose (2.0 mg/kg intravenous [IV]) of succinylcholine if the attempt to intubate fails and the patient is thought not to be sufficiently relaxed (Fig. 1.8). In a crash scenario, larger doses of succinylcholine are recommended because poor circulation impairs drug delivery, resulting in paralysis that may be slower in onset and incomplete. A higher dosing can help to compensate for this impaired distribution. If a crash airway is not present, the LEMON, ROMAN, RODS, and SMART evaluations are made to determine if a difficult airway is present, and, if so, the difficult airway algorithm is used (Fig. 1.9).

For patients who require emergency intubation but who have neither a crash airway nor a difficult airway, RSI is indicated. RSI provides the safest and quickest method of achieving intubation in such patients.[1] After administration of RSI drugs, intubation attempts are repeated until the patient is intubated or a failed intubation is identified. If more than one intubation attempt is required, oxygen saturation is monitored continuously and, if saturations decrease to 92% or

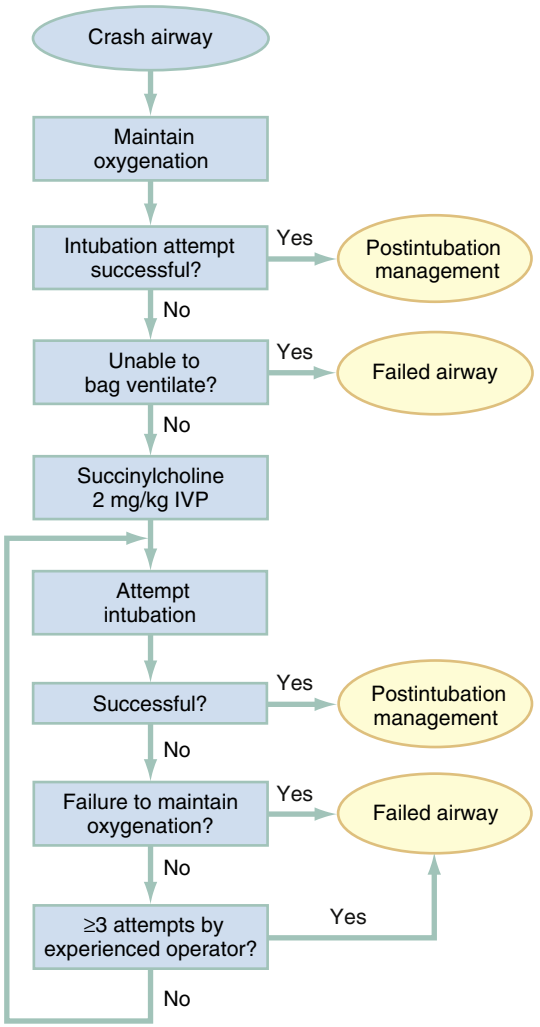

Fig. 1.8 Crash Airway Algorithm. *IVP,* Intravenous push. (Modified from Brown III CA, Mick NM, Sakles JC, editors. *The Emergency Airway Algorithms in the Walls Manual of Emergency Airway Management.* 5th ed. Philadelphia: Wolters Kluwer; 2018.)

less, the laryngoscopic attempt is aborted (unless the operator feels he or she is on the cusp of successful tube placement) and BMV is performed until saturation is sufficiently recovered for another attempt. If the oxygen saturation continues to fall, despite optimal use of BMV or EGD, a failed airway exists. This is referred to as a CI:CO type of failed airway. A second form of failed airway is present when there have been three unsuccessful "best attempts" at laryngoscopy, because subsequent attempts by the same clinician are unlikely to succeed. The three failed laryngoscopy attempts are defined as attempts by an experienced clinician using the best possible patient positioning, device, and technique. Three attempts by a trainee using a direct laryngoscope may not count as best attempts if an experienced emergency clinician is available or VL has not yet been attempted. In addition, the emergency clinician can identify a failed airway after even a single laryngoscopic attempt if it is judged that intubation likely will be impossible (e.g., grade 4 laryngoscopic view with DL, despite optimal patient positioning and use of external laryngeal manipulation) and no alternative device (e.g., videolaryngoscope, intubating LMA) is available. The failed airway is managed according to the failed airway algorithm (Fig. 1.10).

Difficult Airway

The perception of a difficult airway is relative, and many emergency intubations rightly are considered "difficult." Deciding whether to treat the airway as a typical emergency airway or whether to use the difficult airway algorithm is based on the degree of perceived difficulty, operator experience, armamentarium of airway devices, and individual circumstances of the case. The LEMON, ROMAN, RODS, and SMART assessments provide a systematic framework to assist in identifying the potentially difficult airway but are not meant to firmly determine whether any individual patient should, or should not, receive an NMBA.

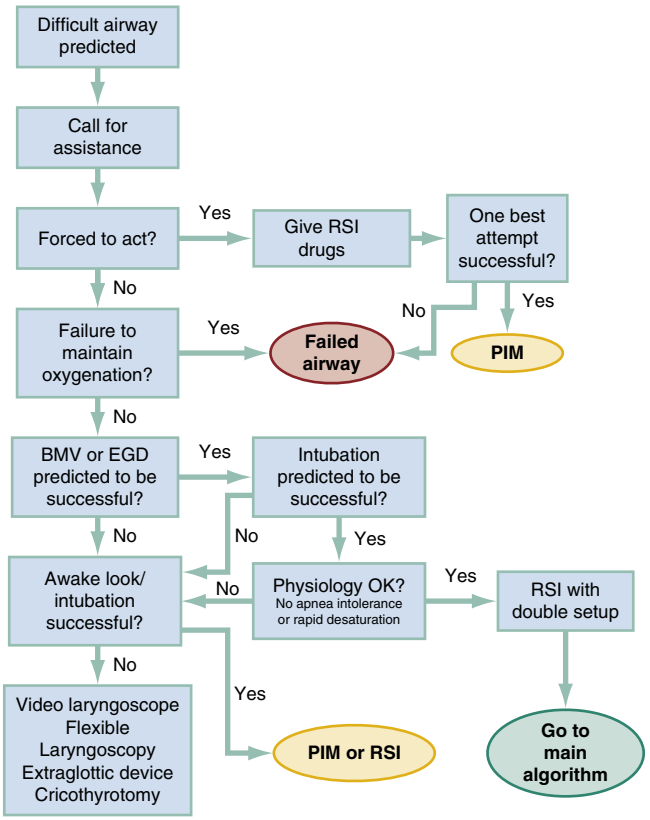

Fig. 1.9 Difficult Airway Algorithm. *BMV,* Bag-mask ventilation; *EGD,* extraglottic device; *PIM,* postintubation management; *RSI,* rapid sequence intubation. (Modified from Brown III CA, Mick NM, Sakles JC, editors. *The Emergency Airway Algorithms in the Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.)

When preintubation evaluation identifies a potentially difficult airway (see Fig. 1.9), the approach is based on the premise that NMBAs generally should not be used unless the emergency clinician believes that (1) intubation is likely to be successful, (2) oxygenation can be maintained via BMV or EGD should the patient desaturate during an intubation attempt, and (3) the patient will not experience cardiovascular catastrophe or arrest from precipitous desaturation or hemodynamic collapse following administration of RSI medications. This is particularly true when intubation is undertaken with a conventional laryngoscope which may result in prolonged laryngoscopy and a lower FAS, even if that attempt is augmented by laryngeal manipulation and use of a bougie.[12,13] In addition, anatomic features of a difficult airway should be considered in the context of deranged physiology, provider experience, and availability of VL. Patients with refractory hypoxemia, right heart failure, or severe metabolic acidosis may be best managed with an awake intubation, especially if anatomic challenges exist, because the possibility of prolonged or repeated laryngoscopy combined with rapid physiologic decline with the onset of hypopnea can result in rapid arrest and anoxic injury. In these cases, if RSI is still deemed the best approach, then all other elements should be optimized to increase FAS. This includes (ideally) use of VL, robust preoxygenation and cardiovascular optimization with fluids, blood, and pressor agents, as necessary. The one exception to this recommendation occurs in the "forced to act" scenario.

A forced to act imperative permits RSI, even in a highly difficult airway situation in which the operator is not confident of the success of laryngoscopy or of sustaining oxygenation. This usually occurs in the setting of a rapidly deteriorating patient with an obviously difficult airway and a presumed clinical trajectory of imminent arrest or airway obstruction. Although this is not yet a crash airway situation, the operator is forced to act—that is, there is a need to act immediately to intubate before orotracheal intubation quickly becomes impossible or the patient arrests. The patient retains sufficient muscle tone and voluntary effort (including combative behavior induced by hypoxia) to require administration of drugs before intubation can be attempted. Consider an agitated patient with rapidly advancing anaphylaxis or angioedema, a morbidly obese patient in severe, end-stage status asthmaticus, or an intensive care unit (ICU) patient with inadvertent or premature extubation, respiratory failure, and difficult airway. Within seconds to minutes, perhaps before a full difficult airway assessment can be done or preparations can be completed for an alternative airway approach (e.g., flexible endoscopy), the patient's rapid deterioration signals impending respiratory arrest. This is a unique situation in which the operator may be compelled to take the one best chance to secure the airway by rapidly administering RSI drugs, despite obvious airway difficulty, and attempting intubation before the airway crisis has advanced to the point that intubation is impossible or delay has caused hypoxic arrest. If laryngoscopy fails, the RSI drugs have optimized patient conditions for cricothyrotomy or insertion of an alternative airway device, depending on the operator's judgment.

Therefore, in the difficult airway algorithm, the first determination is whether the operator is *forced to act*. If so, RSI drugs are given, a best attempt at laryngoscopy is undertaken, and, if intubation is not successful, the airway is considered failed, and the operator moves immediately to the failed airway algorithm. However, in the vast majority of difficult airway situations, the operator is not forced to act, and the first step is to ensure that oxygenation is sufficient to permit a planned orderly approach to airway management. If oxygenation is inadequate,

oxygenation cannot be made adequate by supplementation with BMV, and anatomic challenges are significant, then the airway should be considered a failed airway. Although inadequate oxygenation should be defined on a case-by-case basis, oxygenation saturation decreasing to less than 93% is the accepted threshold, because this represents the point at which hemoglobin undergoes a conformational change, more readily releases oxygen, and increases the pace of further desaturation. Oxyhemoglobin saturations in the mid-80s, if holding steady, might be considered adequate in some circumstances, particularly if the patient is chronically hypoxemic. When oxygenation is inadequate or dropping, the failed airway algorithm should be used because the predicted high degree of intubation difficulty, combined with failure to maintain oxygen saturation, is analogous to the CI:CO scenario.

However, when oxygenation is deemed adequate, the next consideration is whether RSI is appropriate, on the basis of the operator's assessment of the likelihood of (1) successful ventilation with BMV or EGD in case intubation is unsuccessful, (2) the likelihood of successful intubation by laryngoscopy, and (3) the severity of physiologic derangement. If the operator is not confident of successful intubation or rescue oxygenation and time allows, an awake technique can be used. In this context, awake means that the patient continues to breathe and, although IV sedation and analgesia may be administered, can cooperate with caregivers. If the operator judges that anatomic challenges are minimal and would not significantly adversely affect laryngoscopy or rescue oxygenation, then the patient's physiologic vulnerability is considered. If the patient is deemed both hemodynamically stable and not at risk for immediate desaturation, then RSI is performed. However, if the patient is thought to be intolerant of apnea because of severe metabolic acidosis or anticipated precipitous desaturation or exhibits profound, refractory shock such that the vasoplegic effects of sedative/induction agents might precipitate circulatory collapse, then an awake technique is preferred. If RSI is performed on a patient with significant difficult airway attributes identified, then we recommend a double setup, with preparations simultaneously undertaken for rescue cricothyrotomy or another immediate rescue technique.

During an awake intubation, the patient is prepared by applying topical anesthesia with atomized or nebulized lidocaine, ideally preceded by a drying agent such as glycopyrrolate. Titrated doses of sedative and analgesic agents (or ketamine, which provides both actions) may be required for the patient to tolerate the procedure. Once this is accomplished, any of a number of different devices can then be used to attempt glottic visualization, with device selection most often dictated by patient anatomy and pathology. Regardless of the route taken to the airway (nasal or oral), VL, whether flexible or rigid, is preferable to DL. If the glottis is adequately visualized, the patient can be intubated at that time or, in a stable difficult airway situation, the emergency clinician may proceed with planned RSI, now assured of intubation success. If the awake laryngoscopy is unsuccessful, the patient can be intubated with any of numerous techniques shown in the last box in Fig. 1.9. For each of these methods, the patient is kept breathing but is variably sedated and anesthetized. The choice among these methods depends on clinician experience and preference, device availability, and patient attributes.

Failed Airway

Management of the failed airway is dictated by whether the patient can be oxygenated. If adequate oxygenation cannot be maintained with rescue BMV, the rescue technique of first resort is cricothyrotomy (see Fig. 1.10). Multiple attempts at other methods in the context of failed oxygenation only delay cricothyrotomy and place the patient at increased risk for hypoxic brain injury. However, if an alternative device (i.e., an EGD such as an LMA or King LT airway) is readily available and the operator judges it to be an appropriate device for the patient's anatomy, a single attempt can be made to use it simultaneously with preparations for immediate cricothyrotomy as long as initiation of cricothyrotomy is not delayed. If early indications are that the EGD is effective and oxygenation improves, cricothyrotomy can wait; however, the operator must continuously reassess EGD function and oxygenation status. If the EGD subsequently fails, cricothyrotomy must begin without delay.

If adequate oxygenation is possible, several options are available for the failed airway. In almost all cases, cricothyrotomy is the definitive rescue technique for the failed airway if time does not allow for other approaches (i.e., oxygenation cannot be maintained) or if they fail. We distinguish the difficult and failed airway as follows: the difficult airway is something one anticipates; the failed airway is something one experiences. The fundamental difference in philosophy between the difficult and failed airway is that the difficult airway is planned for, and the standard is to place a definitive airway (cuffed ETT) in the trachea. The failed airway is not planned for, and the standard is to achieve any airway that provides adequate oxygenation to avert hypoxic brain injury. Some devices used in the failed airway (e.g., EGDs) are temporary and do not provide definitive airway protection, so are not generally used in the planned management of the difficult airway.

Methods of Intubation

Although many techniques are available for intubation of the emergency patient, four methods are the most common, with RSI being the most frequent approach.[1,14]

Rapid Sequence Intubation

RSI is the cornerstone of emergency airway management and is defined as the nearly simultaneous administration of a potent sedative (induction) agent and NMBA, after a period of preoxygenation and cardiopulmonary optimization, for tracheal intubation. This approach

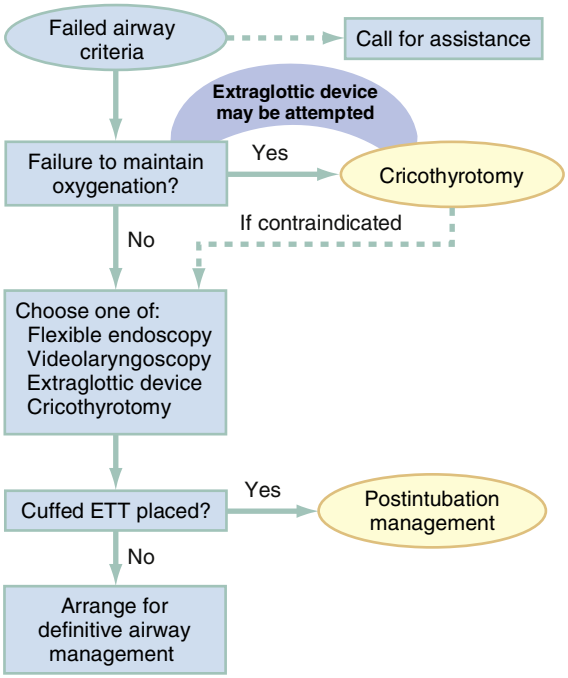

Fig. 1.10 Failed Airway Algorithm. *ETT,* Endotracheal tube. (Modified from Brown III CA, Mick NM, Sakles JC, editors. *The Emergency Airway Algorithms in the Walls Manual of Emergency Airway Management.* 5th ed. Philadelphia: Wolters Kluwer; 2018.)

provides optimal intubating conditions and was initially developed to safely and effectively intubate patients while minimizing the risk of aspiration of gastric contents. There is not compelling evidence that RSI mitigates aspiration risk, although its designed avoidance of BMV during intubation would seem to reduce the likelihood of gastric insufflation and resultant regurgitation of gastric contents. RSI is the most widely used technique for emergency intubation of patients without identifiable difficult airway attributes, with recent large registry data showing that it is used in 85% of all ED intubations.[1,13,14]

The central concept of RSI is to take the patient from the starting point (e.g., conscious, breathing spontaneously) to a state of unconsciousness with complete neuromuscular paralysis and then to achieve intubation without interposed assisted ventilation. The risk of aspiration of gastric contents is thought to be significantly higher for patients who have not fasted before induction and, if adequately preoxygenated, would have a sufficient period of safe apnea such that bagging would not be required. Application of positive pressure ventilation can cause air to pass into the stomach, resulting in gastric distention and increasing the risk of regurgitation and aspiration. For patients considered at high risk for desaturation during RSI, use of careful, controlled mask ventilation between induction and intubation is a reasonable approach as long as the patient is not believed to be at high risk for aspiration (i.e., active upper gastrointestinal bleeding, emesis prior to intubation). A multicenter trial of ICU patients intubated for hypoxic respiratory failure randomized patients to bagging versus no bagging during RSI.[15] The bagging cohort had significantly fewer episodes of desaturation and higher oxygen nadirs when desaturation occurred, compared with the no bagging group. Similar rates of either witnessed aspiration or infiltrate on follow-up chest x-rays were observed between the two groups. Patients who were excluded were more likely to have been fasted, high-risk aspirators, and there was no standardized preoxygenation strategy; therefore these results cannot be broadly extrapolated to emergency airway management. However, balancing risk and consequence of desaturation against risk and consequence of aspiration may appropriately lead to a decision to perform gentle, measured manual ventilation during RSI. As a general rule, RSI is performed without positive pressure ventilation until the ETT is placed correctly in the trachea, with the cuff inflated. This requires a preoxygenation phase, during which mixed alveolar gases (mostly nitrogen) within the lungs' functional residual capacity (FRC) are replaced with oxygen, permitting at least several minutes of apnea (see later discussion) in a healthy normal body habitus adult before oxygen desaturation to less than 90% ensues (Fig. 1.11).

Use of RSI ensures the patient is unaware of the procedure and facilitates successful endotracheal intubation by causing complete relaxation of the patient's musculature, allowing better access to the airway. In patients suffering from a hypertensive emergency such as intracranial hemorrhage, RSI permits administration of sympatholytic agents used to mitigate further spikes in blood pressure and heart rate that might worsen the patient's disease process. RSI is a series of discrete steps, and every step should be planned (Box 1.5).

Preparation. In the initial phase, the patient is assessed for intubation difficulty and abnormal physiology unless this has already been done, and the intubation is planned, including determining dosages and sequence of drugs, tube size, and laryngoscope type, blade, and size. Drugs are drawn up and labeled. All necessary equipment is assembled. All patients require continuous cardiac and pulse oximetry monitoring. At least one and preferably two good-quality IV lines should be established. Redundancy is always desirable in case of equipment or IV access failure. Most importantly, a rescue plan for intubation failure should be developed at this time and made known to the appropriate members of the resuscitation team.

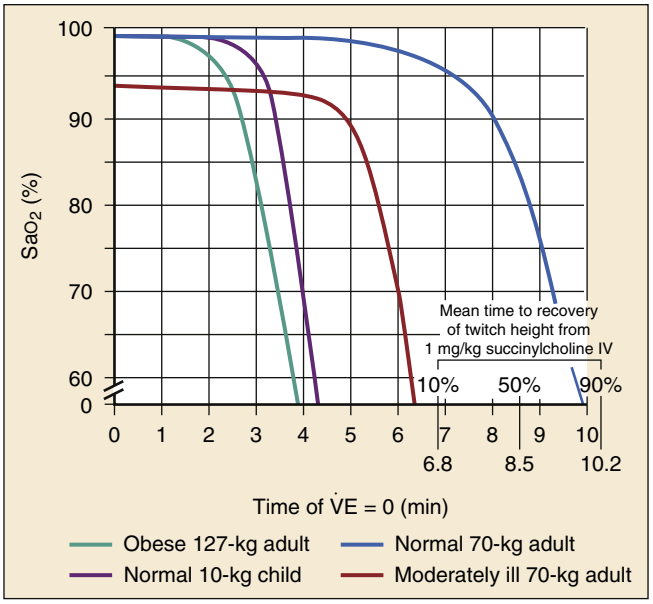

Fig. 1.11 Extrapolated Desaturation Time for Apneic, Fully Preoxygenated Patients. Children, patients with comorbidity, and obese patients desaturate much more rapidly than healthy normal adults. The box on the lower right side of the graph depicts time to recovery from succinylcholine, which in almost all cases exceeds safe apnea time. Note also the precipitous decline of oxygen saturation from 90% to 0% for all groups. *VE,* Expired volume. (Modified from Benumof JL, Dagg R, Benumof R. Critical hemoglobin desaturation will occur before return to unparalyzed state following 1 mg/kg intravenous succinylcholine. *Anesthesiology.* 1997;87:979–982.)

BOX 1.5 The Seven Ps of Rapid Sequence Intubation.

1. ***P***reparation
2. ***P***reoxygenation
3. ***P***reintubation optimization
4. ***P***aralysis with induction
5. ***P***ositioning
6. ***P***lacement of tube
7. ***P***ostintubation management

Preoxygenation. The goal of preoxygenation is denitrogenation of the alveoli and formation of an oxygen-rich reservoir within the lung's FRC. The FRC is an untapped potential space, approximately 30 mL/kg in the average adult, that can be used to create an oxygen reserve from which the pulmonary circulation can continue to use even after the patient is rendered apneic. The traditional method for preoxygenation involved having the patient breathe, for 3 minutes at normal tidal volumes, 100% oxygen at 15 L/min flow through a nonrebreather mask. Inevitable room air entrainment resulted in a fraction of inspired oxygen (Fio_2) of only 65% and an end-tidal oxygen level (ETo_2) of only 50% to 60% with this approach. Administration of flush-rate oxygen (40 to 70 L/min) has been shown to significantly increase both the Fio_2 and ETo_2 by outcompeting room air entrainment around the margin of the mask and should be used as the default preoxygenation flow rate whenever possible.[16,17] Flush rate oxygen flow is accomplished by fully opening the oxygen valve at the base of the wall oxygen regulator. The maximum flow rate will vary depending on the size and manufacturer of each unit but is approximately 50 L/min on average. When preoxygenation is performed effectively, the patient may have as much as 6 to 8 minutes

of safe apnea before oxygen desaturation to less than 90% occurs (see Fig. 1.11). Real-time measurement of ETo_2 using a simple bedside gas analyzer can quantify denitrogenation and better ensure that maximal preoxygenation has been accomplished.[18] The time to desaturation to less than 90% in children, obese adults, late-term pregnant women, and patients who are acutely ill or injured is considerably shorter. Desaturation time also is reduced if the patient does not inspire 100% oxygen or has significant intrapulmonary shunting or dead space. Patients with infiltrative lung disease, pulmonary edema, or ARDS may never achieve adequate preoxygenation despite maximal ambient pressure supplemental oxygen. If saturations remain at 93% or less despite these efforts, then the patient should be transitioned to BiPAP to increase alveolar recruitment, reduce shunting, and increase ETo_2. With this approach, adequate preoxygenation usually can be obtained to permit minutes of safe apnea. If time is insufficient for a full 3-minute preoxygenation phase, eight vital capacity breaths (the largest breaths the patient can take with greatest effort) with high-flow oxygen can achieve oxygen saturations and apnea times that match or exceed those obtained with traditional preoxygenation. Apneic oxygenation (ApOx) takes advantage of a physiologic principle termed *aventilatory mass flow,* by applying continuous oxygen flow during the apneic phase of RSI. Even though there is no ventilatory activity by the patient, circulation is unaltered. The constant diffusion of alveolar oxygen into the pulmonary circulation creates a natural downward gradient promoting passive oxygen movement from the patient's upper airway into the gas-exchanging portions of the lungs. Desaturation time in obese patients can be prolonged by preoxygenating with the patient in a head-up position and by continuing supplemental oxygen (via nasal cannula at a flow rate of 5 to 15 L/min) after motor paralysis and during laryngoscopy until the ETT is successfully placed. In obese patients without preexisting lung disease, ApOx extends the time to desaturation to 95% from 3 to 5 minutes. A randomized trial of ED patients undergoing RSI challenged the use of ApOx when it reported no observable reduction in desaturation events or nadir oxygen levels with apneic nasal oxygen. However, in the study, the vast majority of patients were intubated in less than 2 minutes, thereby removing the possibility of an observable benefit from ApOx.[19] Subsequent meta-analyses, including one focused on pediatric patients, revealed that ApOx significantly reduces the risk of hypoxia.[20–22] A meta-analysis of randomized controlled trials including both ICU and preoperative patients found no reduction in severe desaturation (<80%) or peri-intubation adverse events from the use of high-flow nasal cannula (HFNC) applied during intubation; however, only one of the included trials reported the number of intubation attempts, the type of device used, total intubation time, or glottic view.[23] Patients with prolonged laryngoscopic attempts may be the group most at risk for peri-intubation hypoxia and garner the most benefit from ApOx. On balance, ApOx is noninvasive, cheap, and likely beneficial during emergency airway management. We recommend that oxygen by nasal cannula, be continued at a minimum of 5 L/min, up to 15 L/min, throughout emergency RSI attempts until tracheal intubation is achieved.

Preintubation optimization. Airway management can be made more complex by unstable hemodynamics and impaired patient physiology. Although shock states, severe myocardial depression, or an inability to preoxygenate do not necessarily make the act of laryngoscopy and tracheal tube placement more difficult, they can increase patient morbidity by drastically shortening the time available to safely intubate or by placing the patient at risk for hypoxic injury or peri-intubation circulatory collapse. Preintubation optimization is designed to identify and address areas of physiologic concern that may complicate resuscitative efforts, even if tracheal intubation goes quickly and smoothly. When time permits, abnormal hemodynamic parameters should be improved to the extent possible prior to intubation. Patient outcomes can be compromised in those with hypotension or shock caused by bleeding, dehydration, sepsis, and primary cardiac pathology, even if tube placement is smooth, fast, and successful. Vasoplegia from induction agents can potentiate peripheral vascular dilation and exacerbate hypotension. Patients who present with low intravascular volume, right heart disease, or poor vascular tone can suffer circulatory collapse after RSI drugs are administered, particularly after positive pressure ventilation is initiated. Isotonic fluids, blood products, and pressor agents (typically norepinephrine) may be used, time permitting, to support blood pressure and increase pharmacologic options for RSI. We recommend a balance of fluid or blood product replacement, as indicated, complemented by pressors, optimal oxygenation, and control of any exacerbating factors, such as external hemorrhage.

Paralysis with induction. In this phase, a potent sedative agent is administered by rapid IV push in a dose capable of producing unconsciousness rapidly. This is immediately followed by rapid administration of an intubating dose of an NMBA, either succinylcholine at a dose of 1.5 mg/kg IV or rocuronium at a dose of 1.2 mg/kg IV. An analysis of more than 5000 patients from the National Emergency Airway Registry (NEAR) database revealed that the glottic view obtained, rates of FAS, and adverse events were equivalent between the two drugs when these, or higher doses, were used.[14]

Positioning. The patient should be positioned for intubation as consciousness is lost. Usually, positioning involves head extension, often with flexion of the neck on the body. Although simple extension may be adequate, a full sniffing position with cervical spine extension and head elevation is optimal if DL is used.[7] There is no difference in FAS rates between supine and nonsupine patient positioning regardless of airway difficulty.[24] The Sellick maneuver—application of firm, backward pressure over the cricoid cartilage with the goal of obstructing the cervical esophagus and reducing the risk of aspiration—had long been recommended to minimize the risk of passive regurgitation and hence aspiration but is no longer recommended. The Sellick maneuver is incorrectly applied by a variety of operators, making laryngoscopy or intubation more difficult in some patients, and aspiration often occurs despite use of the Sellick maneuver. In many patients, the cervical esophagus is positioned lateral to the cricoid ring in a relationship that is exaggerated by posterior pressure, rarely resulting in esophageal obstruction. Accordingly, we do not recommend use of the Sellick maneuver. After administration of an induction agent and NMBA, although the patient becomes unconscious and apneic, BMV should not be initiated unless the oxygen saturation falls to 92%.

Placement of tube. Approximately 45 to 60 seconds after administration of the NMBA, the patient is relaxed sufficiently to permit laryngoscopy. This is assessed most easily by moving the mandible to test for mobility and absence of muscle tone. Place the ETT during glottic visualization with the laryngoscope. Confirm placement, as described earlier. If the first attempt is unsuccessful but oxygen saturation remains high, it is not necessary to ventilate the patient with a bag and mask between intubation attempts. If the oxygen saturation is approaching 92%, the patient may be ventilated briefly with a bag and mask between attempts to reestablish the oxygen reservoir.

Postintubation management. After confirmation of tube placement by $ETco_2$, obtain a chest radiograph to confirm that mainstem intubation has not occurred and to assess the lungs. If available, place the patient on continuous capnography. In general, long-acting NMBAs (e.g., pancuronium, vecuronium) are avoided; the focus is on optimal management using opioid analgesics and sedative agents to facilitate mechanical ventilation. An adequate dose of a benzodiazepine (e.g., midazolam, 0.1 to 0.2 mg/kg IV) and opioid

TABLE 1.1 Sample Rapid Sequence Intubation Using Etomidate and Succinylcholine.

Time	Step
Zero minus 10 min	Preparation
Zero minus 5 min	Preoxygenation—100% oxygen for 3 min or 8 vital capacity breaths
Zero minus 3 min	Preintubation optimization—as indicated
Zero	Paralysis with induction • Etomidate, 0.3 mg/kg • Succinylcholine, 1.5 mg/kg
Zero plus 30 s	Positioning—Sellick maneuver optional
Zero plus 45 s	Placement • Laryngoscopy and intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management • Sedation and analgesia as indicated • Initiate mechanical ventilation • NMBA only if needed after adequate sedation, analgesia

NMBA, Neuromuscular blocking agent.

analgesic (e.g., fentanyl, 0.5 to 1 μg/kg IV, or morphine, 0.2 to 0.3 mg/kg IV) is given to improve patient comfort and decrease sympathetic response to the ETT.

Propofol infusion (0.05 to 0.1 mg/kg/min IV) with supplemental analgesia is an effective method for managing intubated patients who do not have hypotension or ongoing bleeding. It is especially helpful for the management of neurologic emergencies because its clinical duration of action is very short (<5 minutes), allowing frequent neurologic examinations. An NMBA is added only if appropriate use of sedation and analgesia fail to control the patient adequately or when ventilation is challenging because of muscular activity. Table 1.1 presents a sample RSI protocol using etomidate and succinylcholine. Zero refers to the time at which the induction agent and succinylcholine are pushed.

Delayed Sequence Intubation

Delayed sequence intubation (DSI) is a technique proposed to maximize preoxygenation in preparation for intubation. Agitation, delirium, and confusion can confound attempts at preoxygenation when a patient is unable to comply with conventional modes of supplemental oxygenation, such as a face mask or BiPAP. DSI considers preoxygenation a procedure and uses dissociative doses of ketamine (1 to 2 mg/kg IV bolus) as procedural sedation to accomplish this. A small, ED- and ICU-based multicenter observational study showed post-DSI oxygen saturations significantly higher than pre-DSI levels. There were no noted adverse outcomes or desaturations when intubation eventually took place in this limited case series.[25] A prehospital investigation that studied the routine use of DSI as part of a multi-interventional bundle (which also included preoxygenation targets and upright patient positioning) to prevent desaturation during airway management showed a 10-fold reduction in rates of peri-intubation desaturation without increased adverse events.[26] However, this approach is not without some risk, as there have been reports of ketamine-induced apnea during DSI.[27] On balance, more investigation is required to determine the possible indications for and safety of DSI when performed in various emergency settings.

Awake Oral Intubation

Awake oral intubation is a technique in which sedative and topical anesthetic agents are administered to permit management of a difficult airway without neuromuscular blockade. Sedation and analgesia are achieved in a manner analogous to that for painful procedures in the ED. Topical anesthesia may be achieved by topically applied anesthetic paste, spray, nebulization, or local anesthetic nerve block. Various sedative agents can be used, but ketamine, which provides dissociative anesthesia, analgesia, maintenance of protective airway reflexes, and minimal respiratory depression, is often the best choice (see later, "Pharmacologic Agents"). Ketamine-induced apnea has been reported, so close observation is required, especially in patients with partial airway obstruction.[28] Starting with small aliquots at doses of 0.25 to 0.5 mg/kg IV every 10 minutes, titrated to the desired level of sedation and procedural tolerance, ketamine anesthesia is an effective method for awake intubation. Dexmedetomidine (Precedex), a centrally acting alpha receptor blocker, has been used successfully, alone or in combination with benzodiazepines, for awake airway evaluations. A typical dose is 1.0 mg/kg IV infused over 5 to 10 minutes. After the patient is sedated, and topical anesthesia has been achieved, gentle flexible or rigid VL is performed to determine whether the glottis is visible and intubation possible. If the glottis is visible, the patient may be intubated during initial laryngoscopy, or the operator, confident that the glottis can be visualized, may opt to perform RSI to benefit from pretreatment, induction, and paralysis, as might be the case in a patient with a head injury.

Awake oral intubation is distinct from the practice of oral intubation with a sedative or opioid agent to obtund the patient for intubation without neuromuscular blockade. This latter technique can be referred to as intubation with sedation alone or, paradoxically, nonparalytic RSI. Intubating conditions and FAS achieved even with deep anesthesia are significantly inferior to what is achieved when neuromuscular blockade is used.[1] In general, the technique of administering a potent sedative agent to obtund the patient's responses and permit intubation in the absence of neuromuscular blockade is ill advised and inappropriate for endotracheal intubation in the ED, unless performed as part of an awake intubation (see earlier), during which different agents and lower amounts are typically used.

Oral Intubation Without Pharmacologic Agents

The arrested or near-death patient may not require pharmacologic agents for intubation, but even an arrested patient may retain sufficient muscle tone to render intubation difficult. If the glottis is not adequately visualized, administration of a single dose of succinylcholine alone may facilitate laryngoscopy (see earlier, "Decision Making"). Success rates for intubating unconscious, unresponsive patients are variable but approach those achieved with RSI, presumably because the patient is in a similar physiologic state (i.e., muscle relaxation, no ability to react to laryngoscopy or tube insertion).[1] This does not apply to patients who are unconscious from neurologic catastrophe or trauma and those who have overdosed or have other medical causes of coma who warrant an induction agent and are intubated with standard RSI procedures (see earlier).

Pharmacologic Agents

Neuromuscular Blocking Agents

NMBAs are highly water-soluble, quaternary ammonium compounds that mimic the quaternary ammonium group on the acetylcholine (ACh) molecule. Their water solubility explains why they do not readily cross the blood-brain barrier or placenta. NMBAs are divided into two main classes, depolarizing and nondepolarizing agents. The depolarizing agent succinylcholine exerts its effects by binding noncompetitively with ACh receptors on the motor end plate, causing sustained

depolarization of the myocyte while preventing transmembrane potentials from reforming and resisting further stimulation from ACh. The other major class of NMBA comprises the competitive, or nondepolarizing, agents, which bind competitively to ACh receptors, preventing access by ACh and preventing muscular activity. The competitive agents are of two pharmacologically distinct types, steroid-based agents (aminosteroid compounds) and benzylisoquinolines. Each of these basic chemical types has distinct properties, but only aminosteroid compounds are used in the ED.

Succinylcholine. Succinylcholine is a combination of two molecules of ACh. Succinylcholine is rapidly hydrolyzed by plasma pseudocholinesterase to succinylmonocholine, which is a weak NMBA, and then to succinic acid and choline, which have no NMBA activity. Pseudocholinesterase is not present at the motor end plate and exerts its effects systemically before the succinylcholine reaches the ACh receptor. Only a small amount of the succinylcholine administered survives to reach the motor end plate. Succinylcholine is active at the motor end plate until it diffuses away. Decreased plasma pseudocholinesterase activity can increase the amount of succinylcholine reaching the motor end plate, prolonging succinylcholine block, but this is of little significance in the emergency setting because the prolongation of action rarely is significant, reaching only 23 minutes at the extreme.

Uses and dosing. Succinylcholine is rapidly active, typically producing intubating conditions within 45 seconds of administration by rapid IV bolus injection. The clinical duration of action before spontaneous respiration is 6 to 10 minutes (see Fig. 1.11). Full recovery of normal neuromuscular function occurs within 15 minutes. The combination of rapid onset, complete reliability, short duration of action, and absence of common serious side effects has kept succinylcholine as the drug of choice for most ED intubations. Time-trended surveillance of ED intubation practices has suggested that succinylcholine is slowly being replaced by rocuronium, with use of the agents approximately equal in a large multicenter assessment of NMBA use during adult ED intubations.[14] There is high, site-specific variation, suggesting that local culture is the primary driver for drug selection. The appropriate dose of succinylcholine for emergency airway management is 1.5 mg/kg IV. Although the effective dose at which paralysis is achieved in 95% of patients (ED_{95}) for succinylcholine paralysis is much lower (0.3 mg/kg), the onset of muscle paralysis is excessively long at these lower doses and is not compatible with emergency intubation. Excellent intubating conditions are best achieved when succinylcholine is dosed at 1.5 mg/kg. Although hydrophilic, multiple studies have confirmed that the dose of succinylcholine is based on the patient's total body weight (TBW) and is not adjusted (downward), regardless of the degree of obesity because pseudocholinesterase activity increases with body habitus.

Cardiovascular effects. As an ACh analogue, succinylcholine binds to ACh receptors throughout the body, not just at the motor end plate. It is difficult to separate the effects of succinylcholine on the heart caused by direct cardiac muscarinic stimulation from those caused by stimulation of autonomic ganglia by succinylcholine and from the effects induced by autonomic responses to laryngoscopy and intubation. Succinylcholine can be a negative chronotrope, especially in children, and sinus bradycardia may ensue after succinylcholine administration. Sinus bradycardia is treated with atropine, if necessary, but is usually self-limiting. Some pediatric practitioners recommend pretreatment with atropine for children younger than 1 year, but there is no evidence for benefit, and we do not agree with this recommendation. Uncommonly, adults may develop bradycardia if succinylcholine is readministered, but bradycardia in the context of intubation should be considered to be caused by hypoxemia until that cause is excluded. Other cardiac dysrhythmias, including ventricular fibrillation and asystole, have been reported with succinylcholine, but it is impossible to distinguish the effects of the drug itself from those caused by the intense vagal stimulation and catecholamine release that accompany laryngoscopy and intubation. In addition, many of these catastrophic complications occur in critically ill patients, further confounding attempts to identify whether the illness or any particular drug or procedure is the cause.

Fasciculations. The depolarizing action of succinylcholine results in fine chaotic contractions of the muscles throughout the body for several seconds during the onset of paralysis in more than 90% of patients. Muscle pain occurs in approximately 50% of patients who receive succinylcholine. Although it has been thought that muscle pains are reduced or abolished by prior administration of a defasciculating dose of a competitive NMBA, the evidence is not conclusive. Use of 1.5 mg/kg of succinylcholine results in less fasciculation and less myalgia than occur with 1 mg/kg.

Hyperkalemia. Succinylcholine has been associated with severe fatal hyperkalemia when administered to patients with specific predisposing clinical conditions (Table 1.2). The mechanism of severe hyperkalemia is related to receptor upregulation on the postsynaptic muscle membrane. When a muscle is deprived of ACh stimulation for as little as 3 days, receptor upregulation begins, causing an increase in receptor density and a change of receptor subtypes on the muscle surface. ACh receptors are primarily K^+ ion channels, and at-risk patients can have an immediate massive efflux of potassium as these newly recruited receptors are depolarized by succinylcholine. This occurs predominantly at the site of injury but may also occur in tissue remote from the original insult. Although the hyperkalemia occurs within minutes after administration of succinylcholine and may be severe or fatal, the patient's vulnerability to succinylcholine-induced hyperkalemia starts as early as 3 days but does not become significant until more than 5 days after the inciting injury or burn, because receptor upregulation and production of protein subunits takes time to develop.

Succinylcholine remains the agent of choice for RSI in acute burn, trauma, stroke, and spinal cord injury if intubation occurs earlier than 5 days after onset of the condition. If doubt exists regarding the onset time, succinylcholine should be replaced with rocuronium. Degenerative neuromuscular disorders, denervation syndromes, or primary myopathies (e.g., multiple sclerosis, amyotrophic lateral sclerosis, Duchenne muscular dystrophy) can be particularly troubling because the risk begins with the onset of the disease and continues indefinitely, regardless of the apparent stability of the symptoms. In patients with denervation caused by a sudden discreet injury or ischemic insult (e.g., stroke, spinal cord injury), the upregulated receptors eventually regress, and the patient can safely receive succinylcholine beginning 6 months after the original insult.

TABLE 1.2 Conditions Associated With Hyperkalemia After Succinylcholine Administration.

Condition	Period of Concern
Burns >10% BSA	>5 days after injury until wounds are healed
Crush injury	>5 days after injury until wounds are healed
Denervation (stroke, spinal cord injury)	>5 days until 6 months postinjury
Neuromuscular disease (ALS, MS, MD)	Indefinitely
Intraabdominal sepsis	>5 days until infection resolves

ALS, Amyotrophic lateral sclerosis; *BSA,* body surface area; *MD,* muscular dystrophy; *MS,* multiple sclerosis.

Potassium release does not occur to any significant extent in the general population. Succinylcholine is not contraindicated in renal failure but should be avoided in patients with known or presumed hyperkalemia (often in the setting of missed dialysis) sufficient to be manifest on the electrocardiogram (ECG). Treatment for succinylcholine-induced hyperkalemia is the same as for any other hyperkalemic emergency.

Masseter spasm. Succinylcholine has rarely been reported to cause masseter spasm, primarily in children and young adults. The clinical significance of this phenomenon is unclear, but administration of a competitive NMBA terminates the spasm. Severe persistent spasm should raise suspicion of malignant hyperthermia.

Malignant hyperthermia. Succinylcholine has been associated with malignant hyperthermia, a perplexing and exceptionally rare syndrome of rapid temperature rise and rhabdomyolysis. Malignant hyperthermia occurs in genetically predisposed individuals who receive certain volatile anesthetic agents or succinylcholine. The condition is extremely rare and has not been reported in the context of ED intubation. Treatment consists of cessation of any potential offending agents, administration of dantrolene (1 to 2.5 mg/kg IV every 5 minutes, to a maximum dose of 10 mg/kg IV), and attempts to reduce body temperature by external means. A national malignant hyperthermia hotline is available for emergency consultation at 1-800-644-9737 (then dial 0).

Competitive agents. Competitive NMBAs are classified according to their chemical structure. The aminosteroid agents include pancuronium, vecuronium, and rocuronium. Vecuronium neither releases histamine nor exhibits cardiac muscarinic blockade and is an excellent agent for the maintenance of neuromuscular blockade when this is desirable. Rocuronium is the best agent for use in RSI as an alternative to succinylcholine or when succinylcholine is contraindicated. When dosed appropriately, rocuronium and succinylcholine are clinically equivalent.[14]

Rocuronium. When a patient has a contraindication to succinylcholine, rocuronium is the paralytic agent of choice. At a dose of 1.2 mg/kg IV, rocuronium achieves intubating conditions similar to those of succinylcholine in approximately 60 seconds and lasts approximately 45 minutes. Onset of paralysis is dose dependent and can be as fast as 30 seconds at doses of 1.5 mg/kg IV. For emergency airway management, there is little additional risk in administering more, rather than less, rocuronium. There are no adverse effects to a larger dose of rocuronium other than prolongation of clinical action. A longer clinical duration of action would not unnecessarily place a patient in jeopardy when, even at lower doses, one can expect at least 45 minutes of neuromuscular blockade, and, in any case, rocuronium is fully reversible by sugammadex. The specter of a partially paralyzed difficult airway makes erring on a lower-dose regimen unwise. There are no absolute contraindications to rocuronium. In the ED, dosing in morbidly obese patients should be based on actual TBW. Although adequate intubating conditions can be obtained when ideal body weight (IBW) is used, this concept is pertinent only to the anesthesiologist who may be titrating neuromuscular blockade to a short anesthetic time. Regardless of which weight-based dosing regimen is used, paralysis is of sufficient duration that the emergency clinician needs to manage the airway successfully before spontaneous respirations return. The potential for inferior intubating conditions using IBW dosing makes this approach undesirable. In the subset of critically ill patients who require frequent, serial, neurologic examinations, a longer duration of paralysis with rocuronium may make it less desirable than succinylcholine; however, in patients who must be reversed, sugammadex can be administered and results in faster muscle twitch recovery than neostigmine.[28] However, sugammadex should not be considered a rescue option for a CI:CO failed airway when rocuronium is used. It is not readily available outside of the operating room, and even if it is immediately ready to administer, the speed and completeness of recovery of spontaneous ventilation is variable and does not address the effects of the induction dose of the sedative agent that may contribute to ongoing hypopnea and hypoxia. The approach to the CI:CO failed airway is in the failed airway algorithm—a rescue EGD can be attempted followed quickly by surgical rescue if efforts to oxygenate fail.

Paralysis after intubation. After intubation, prolonged paralysis may be desired to optimize mechanical ventilation; however, current management is based on use of deep sedation and analgesia, with neuromuscular paralysis used only when necessary to maintain ventilatory control. If neuromuscular blockade is required, vecuronium (0.1 mg/kg IV) can be given. However, longer-term neuromuscular blockade is not to be undertaken without ensuring appropriate sedation and analgesia of the patient and a means to ensure that ongoing sedation and analgesia are adequate. Prolonged paralysis without adequate sedation occurs in up to 20% of patients following RSI in the ED. Risk factors for not receiving sedation after intubation include head injury and use of rocuronium.[29] A sedating dose of a benzodiazepine, such as midazolam (0.1 mg/kg IV), combined with an opioid analgesic, such as fentanyl (0.5 to 1 μg/kg IV) or morphine (0.1 to 0.2 mg/kg IV bolus), is required to improve patient comfort and decrease sympathetic response to the ETT. A sedative strategy using propofol (0.1 mg/kg/min IV) is common, especially in head-injured patients, because of its beneficial cerebroprotective profile and rapid resolution of anesthesia that allows frequent neurologic reassessments. With appropriate attention to achieving optimal sedation and analgesia, ongoing use of an NMBA usually is not necessary. We recommend the use of a standardized sedation scale to ensure that adequate sedation is achieved, both for patient comfort and to optimize physiology.

Induction Agents

A patient with any degree of clinical responsiveness, including reactivity to noxious stimuli, should receive a sedative or induction agent at the time of administration of any NMBA. Patients who are deeply unconscious and unresponsive may require only a reduced dose of an induction agent if the unconscious state is caused by drugs or alcohol, which are themselves general anesthetic agents. Patients who are unconscious because of a central nervous system insult should receive a full induction dose of an appropriate agent to attenuate adverse responses to airway manipulation. Induction agents also potentiate the effect of the NMBA and improve intubation conditions because the intubation is often initiated on the leading edge of paralysis, and the relaxation effects of the induction agent are additive to those of the NMBA.

Etomidate. Etomidate is an imidazole derivative that has been in use since 1972. Its activity profile is similar to that of thiopental, with rapid onset, rapid peak activity, and brief duration, but it is remarkable in its lack of adverse hemodynamic effects. Emergency clinicians have high confidence in etomidate, which is used in up to 90% of all ED intubations.[1] The induction dose is 0.3 mg/kg IV. Because etomidate is able to decrease intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolic rate without adversely affecting systemic mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP), it is an excellent induction agent for patients with elevated ICP, even in cases of hemodynamic instability. Etomidate may cause brief myoclonus, but this is of no clinical significance when administered for RSI. A single dose of etomidate has been shown to reduce serum cortisol levels transiently and blunt the adrenal response to adrenocorticotropic hormone (ACTH) by reversibly inhibiting 11β-hydroxylase, a key

synthetic enzyme in the glucocorticoid pathway. Since discovering this mechanism, much debate has emerged regarding etomidate's impact on survival in sepsis patients. Data from retrospective studies are conflicting, but a large meta-analysis of 18 prospective observational and controlled trials has shown no mortality effect from a single dose of etomidate in septic patients.[30] Ironically, much of the original criticism of etomidate arose from the hypothesis that the adrenocortical response to exogenous corticotropin predicts outcome in patients with septic shock, a theory that has since been discredited. Pending a properly constructed, prospective, randomized clinical trial, there is not sufficient evidence to support the recommendation that etomidate be avoided in patients with septic shock. In fact, etomidate's superior hemodynamic profile makes it an excellent choice in these and other unstable patients, and in a recent large observational cohort of ED patients intubated for sepsis, etomidate was less likely to precipitate peri-intubation hypotension than ketamine.[31]

Ketamine. Ketamine, a phencyclidine derivative, has been widely used as a general anesthetic agent since 1970. After an IV dose of 1.5 mg/kg ketamine produces loss of awareness within 30 seconds, peaks in approximately 1 minute, and has a clinical duration of 10 to 15 minutes. As a dissociative anesthetic agent, ketamine induces a cataleptic state rather than a true unconscious state. The patient has profound anesthesia but may have her or his eyes open. Protective airway reflexes and ventilatory drive usually are preserved.

The principal uses of ketamine in emergency airway management are as a sedative agent for awake intubation (e.g., flexible bronchoscope) and as the induction agent during RSI for patients with acute severe asthma or hemodynamic instability. Because of its hemodynamic profile, ketamine can be considered as a second line agent to etomidate for a hemodynamically unstable patient, such as a patient with sepsis or multiple traumas. Although ketamine generally supports blood pressure, the rate of peri-intubation hypotension may be higher than etomidate.[31,32] However, all sedative induction agents, including ketamine, can provoke further hypotension or cardiovascular collapse in patients with profound refractory shock or those with depressed myocardial contractility and catecholamine depletion. In these settings, dosages are reduced to 50% of the usual dose. Close monitoring for respiratory compromise is necessary when using ketamine as a procedural sedative to facilitate oxygenation (see DSI earlier) as reports of unanticipated apnea have emerged.[27] In patients with status asthmaticus, ketamine may be preferred as an induction agent given its bronchodilatory effects, although no outcome studies have clearly demonstrated its superiority.

Ketamine can also be useful for intermittent administration as part of sedation for mechanical ventilation in patients with severe asthma.

Controversy exists regarding the use of ketamine in patients with elevated ICP because it may increase the cerebral metabolic rate, ICP, and CBF. The evidence that ketamine can produce harm in this way is conflicting and may be outweighed in trauma patients because of its overall favorable hemodynamic profile. Ketamine does not appear to increase the likelihood of an adverse outcome compared with other induction agents in patients with elevated ICP.[33] Ketamine also does not appear to be harmful in children when given in procedural doses to patients with known elevated ICP and may actually lower ICP.

Because it may cause release of catecholamines and increase blood pressure, ketamine should be avoided in traumatic brain injury (TBI) patients with elevated blood pressure. However, we recommend the use of ketamine or etomidate during RSI for induction of patients with TBI and hypotension or risk factors for hypotension. Ketamine may produce unpleasant emergence phenomena, especially disturbing or frightening dreams in the first 3 hours after awakening. These reactions, which are more prominent in adults than in children, in women than in men, in patients receiving larger doses, and in certain personality types, may be mitigated by benzodiazepine administration. Patients who undergo RSI with ketamine should receive a benzodiazepine (e.g., lorazepam, 0.05 mg/kg, or midazolam, 0.1 mg/kg) as part of postintubation management.

Propofol. Propofol is a highly lipophilic alkylphenol with γ-aminobutyric acid (GABA) receptor stimulation activity. Its primary use in the emergency setting has been for postintubation sedation in head-injured patients; however, it increasingly has been used as an induction agent during RSI.[1] It reduces ICP and cerebral oxygen use and is indicated for patients with elevated ICP caused by a medical or traumatic emergency. Because of the propensity of propofol to cause hypotension through vasodilation and direct myocardial depression, the dosage is reduced, or the drug is avoided altogether, in hemodynamically compromised patients. The usual induction dose of propofol is 1.5 mg/kg IV, but reduced dosages should be used in older patients or those with hemodynamic compromise or poor cardiovascular reserve. Propofol is delivered in a soybean oil and lecithin vehicle and should not be used for patients with allergies to these substances. Although propofol has traditionally been avoided in patients with egg allergy, it is likely safe unless a history of anaphylaxis to egg protein exists. Propofol causes pain at the site of administration in as many as 60% of patients. Using a proximal (antecubital) vein in lieu of a distal venous injection site is the most important preventive measure. Pretreatment with IV lidocaine, coadministration of lidocaine mixed with propofol, and pretreatment with opioids or ketamine can limit this common adverse reaction.

Other induction agents. Given the widespread acceptance and familiarity with etomidate, propofol, and ketamine, other drug classes such as barbiturates and benzodiazepines are infrequently used as induction agents for RSI. In North America, nearly all emergency intubations are performed with one of those three agents.[1] Of the benzodiazepines, only midazolam is used as an induction agent. Notably, it is inferior to other, more commonly used agents, such as etomidate and propofol. The usual induction dose for midazolam is 0.2 to 0.3 mg/kg IV. At a dose of 0.3 mg/kg IV, midazolam produces loss of consciousness in approximately 30 seconds (but may take up to 120 seconds) and has a clinical duration of 15 to 20 minutes. Midazolam is a negative inotrope and should be used with caution in hemodynamically compromised and older patients, for whom the dose can be reduced to 0.1 or 0.05 mg/kg. Onset is slower at these reduced doses.

Dexmedetomidine (Precedex) has gained popularity as a solo agent, or in combination with benzodiazepines, for procedural sedation and awake intubation but is not used for induction during RSI given its slow loading rate. The typical loading dose is 1 mg/kg IV over 5 to 10 minutes. At therapeutic levels, it has a minimal effect on the respiratory drive or protective airway reflexes, but its use is limited by bradycardia and hypotension.

Special Clinical Circumstances

This section will discuss several specific clinical scenarios that often warrant modification of the airway management plan. Pediatric airway management is discussed in Chapter 156.

Status Asthmaticus

RSI is the recommended technique for intubation of a patient in status asthmaticus. Difficult airway considerations are complex in an asthmatic patient because of impending respiratory arrest and the patient's inability to tolerate attempts at awake intubation. When a difficult airway is identified, intubation preparation should begin early, so that awake methods, such as flexible endoscopic intubation, may be retained as options. We recommend, when possible, to preoxygenate with BiPAP because the reductions in work of breathing may improve

respiratory dynamics and oxygenation and stave off, temporarily, a precipitous respiratory arrest. Anxiety and air hunger in asthmatic patients may make them resistant to having any mask placed—continuous reassurance, encouragement, and coaching may help. However, even when a difficult airway is identified in an asthmatic patient, RSI usually is the intubation method of choice. Ventilation with a BMV or EGD may be difficult because of high airway resistance, and the technique should be optimized with the use of a low tidal volume and respiratory rate, with a high inspiratory flow rate. Appropriate use of IV epinephrine, often a continuous epinephrine drip, and long-term neuromuscular blockade, may be required to permit adequate ventilation. Reducing the respiratory rate to allow for adequate exhalation, even at the expense of retaining CO_2, is recommended to prevent the development of auto-PEEP (positive end-expiratory pressure), known as breath stacking, which can compromise ventilation and cause barotrauma.

The asthmatic patient has highly reactive airways, and steps should be taken to minimize any additional bronchospasm that may occur during intubation. The bronchoconstriction that occurs with ETT placement is thought to be neurally mediated, and local anesthetics, particularly lidocaine, have been studied as a way to blunt this airway reflex. There have been no high-level human studies supporting its use during RSI, and we do not recommend use of lidocaine for this purpose. High-dose, inhaled β-agonists, such as albuterol, provide maximal protection against reactive bronchospasm during intubation and are indicated for asthmatics with or without active bronchospasm. Ketamine has bronchodilatory properties and may mitigate bronchospasm in patients who are not intubated and in patients who are already intubated and are not improving with mechanical ventilation. Although studies to date have been limited, ketamine is also a reasonable induction agent for the emergency intubation of patients with status asthmaticus (Table 1.3).

TABLE 1.3 Rapid Sequence Intubation for Status Asthmaticus.

Time	Step
Zero minus 10 min	Preparation
Zero minus 5 min	Preoxygenation (as possible) • Continuous albuterol nebulizer • 100% oxygen at flush rate by NRB mask or BiPAP for 3 min.
Zero minus 3 min	Preintubation optimization—albuterol, 2.5 mg nebulized, IV epinephrine or subcutaneous terbutaline
Zero	Paralysis with induction • Ketamine, 1.5 mg/kg • Succinylcholine, 1.5 mg/kg
Zero plus 30 s	Positioning
Zero plus 45 s	Placement • Laryngoscopy with intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management • Sedation and analgesia • NMBA only if required after adequate sedation, analgesia • In-line albuterol nebulization, terbutaline, epinephrine, magnesium • Additional ketamine as indicated

BiPAP, Bilevel positive airway pressure; *IV,* intravenous; *NMBA,* neuromuscular blocking agent; *NRB,* non-rebreather.

Hemodynamic Consequences of Intubation

Laryngoscopy and intubation are potent stimuli for the reflex release of catecholamines. This reflex sympathetic response to laryngoscopy (RSRL) produces a modest increase in blood pressure and heart rate and is of little or no consequence in otherwise healthy patients. The RSRL is of potential clinical significance in two settings, acute elevation of ICP and certain hypertensive cardiovascular emergencies (e.g., intracerebral hemorrhage, subarachnoid hemorrhage, aortic dissection or aneurysm, ischemic heart disease). In these settings, the reflexive release of catecholamines, increased myocardial oxygen demand, and attendant rise in MAP and heart rate may produce deleterious effects. The synthetic opioids (e.g., fentanyl) and β-adrenergic blocking agents (e.g., esmolol) are capable of blunting the RSRL and stabilizing heart rate and blood pressure during intubation. In patients at-risk from acute blood pressure elevation, administration of fentanyl (3 μg/kg) during the preintubation optimization phase of RSI attenuates the heart rate and blood pressure increase. The full sympatholytic dose of fentanyl is much higher, but limiting the dose minimizes the likelihood of precipitating or worsening hypoventilation. Because fentanyl reduces sympathetic tone, it should not be given to patients with hemodynamic compromise (e.g., bleeding, volume depletion, sepsis). The administration of 3 μg/kg is safer than larger doses and can be supplemented with an additional 3 μg/kg immediately after intubation if greater sympathetic blockade is desired or hypertension and tachycardia persist. Fentanyl should be given over 60 seconds and the patient observed for hypoventilation or apnea.

Elevated Intracranial Pressure

When the ICP is elevated as a result of head injury or acute intracranial catastrophe, there are two considerations—maintaining CPP (by avoiding excessive hypotension) and minimizing supranormal surges in the MAP, which can increase ICP. Normally, cerebrovascular autoregulation maintains a constant CBF over a wide range of systemic blood pressures, but this action may be lost in conditions that elevate ICP. Maintenance of the systemic MAP at 100 mm Hg or higher supports CPP and reduces the likelihood of secondary injury. Therefore the RSI induction agent for a patient with suspected elevated ICP should be selected and dosed to minimize the likelihood of exacerbation of hypotension. In patients with suspected or documented elevation of ICP, control of RSRL is desirable to avoid further elevation of ICP. Fentanyl (3 μg/kg) given as a pretreatment drug is the best choice for this purpose in the emergency setting.

In emergency patients who may have elevated ICP, the emergency clinician should choose an induction agent that balances a favorable effect on cerebral dynamics and ICP with a stable systemic hemodynamic profile. We recommend etomidate, although propofol is also a good option when there is no hemodynamic compromise (Table 1.4).

Hypotension and Shock

In critically ill and injured patients, induction agents have the potential to exaggerate preexisting hypotension and, in some cases, precipitate circulatory collapse. Peri-intubation cardiac arrest, typically pulseless electrical activity (PEA), complicates up to 4% of emergency RSIs and is more likely in elderly patients with preexisting cardiac disease and those who present with an elevated shock index (>0.8). In patients with profound shock, all induction agents have the potential to exacerbate hypotension. Shock-sensitive RSI hinges on three primary optimization principles—volume resuscitation with isotonic fluid or blood prior to induction (if time permits), reduced dose of a hemodynamically stable induction agent, and titration of peri-intubation pressor agents (Table 1.5).

TABLE 1.4 Rapid Sequence Intubation for Elevated Intracranial Pressure.

Time	Step
Zero minus 10 min	Preparation
Zero minus 5 min	Preoxygenation (as possible)—100% oxygen for 3 min or eight vital capacity breaths
Zero minus 3 min	Preintubation optimization—fentanyl, 3 mcg/kg (slowly)
Zero	Paralysis with induction • Etomidate, 0.3 mg/kg or Propofol 1.5 mg/kg • Succinylcholine, 1.5 mg/kg[a]
Zero plus 30 s	Positioning
Zero plus 45 s	Placement • Laryngoscopy with intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management—sedation and analgesia; consider propofol to permit frequent reexamination NMBA only if required after adequate sedation, analgesia

NMBA, Neuromuscular blocking agent.
[a]May substitute rocuronium, 1 mg/kg, for succinylcholine.

TABLE 1.5 Rapid Sequence Intubation for Hypotension and Shock.

Time	Step
Zero minus 10 min	Preparation—adequate IV access, possibly central venous access with a volume cordis
Zero minus 5 min	Preoxygenation—100% oxygen at flush rate (40–70 L/min) for 3 min by NRB mask
Zero minus 3 min	Preintubation optimization—Blood and isotonic fluid Norepinephrine infusion at 5–10 mcg/min IV (if still hypotensive after IVFs or blood)
Zero	Paralysis with induction • Ketamine, 0.5–0.75 mg/kg OR Etomidate, 0.1–0.15 mg/kg • Succinylcholine, 1.5 mg/kg IV
Zero plus 30 s	Positioning
Zero plus 45 s	Placement • Laryngoscopy with intubation • End-tidal carbon dioxide confirmation
Zero plus 2 min	Postintubation management—continued volume resuscitation, pressor agents as needed

IV, Intravenous; *IVF,* intravenous fluids; *NRB,* non-rebreather.

When time allows, patients with hypotension should receive isotonic fluid boluses or packed red blood cells (PRBCs) to maximize preload, increase blood pressure, and allow more pharmacologic options during RSI. Norepinephrine should be initiated early (5 to 10 mcg/min IV) and titrated quickly upward by reassessing the patient's blood pressure every 3 to 5 minutes and escalating the norepinephrine by 5 mcg/min if the MAP remains at or less than 60 mm Hg. In addition, induction agent selection should be limited to etomidate or ketamine and the dose should be reduced by 50% for patients who do not respond appropriately to volume and pressor agents. Attention to these details can reduce the incidence of cardiovascular peri-intubation adverse events.

Potential Cervical Spine Injury

Historically, most patients with suspected blunt cervical spine injury were intubated orally by DL with in-line cervical spine immobilization, whether done as an awake procedure or with neuromuscular blockade. However, with this approach, glottic views can be inadequate, and excessive lifting force often is required. Patients with known cervical spine fractures are optimally managed with a flexible bronchoscope to minimize cervical spine motion; however, in the emergency setting, a videolaryngoscope should be used and, if not available, a direct laryngoscope also can be used. A videolaryngoscope, especially one with a hyperangulated blade shape (GlideScope or C-MAC d-blade), provides superior laryngeal views without excessive lifting force or cervical spine movement and has higher intubation success rates when compared with conventional DL.

The intubating laryngeal mask airway (I-LMA) also may result in less cervical spine movement during intubation than DL, although the need for blind intubation devices has greatly diminished with the advent of VL.[1] The Airtraq, King Vision, and Pentax Airway Scope are curved intubation devices that integrate an ETT channel and either a viewing lens or a video screen to facilitate intubation. All three devices have shown high levels of intubation success and minimal cervical spine motion compared with DL. A trial of 135 patients with cervical spine immobilization randomized in the operating room to either a standard geometry C-MAC, a C-MAC d-blade, or King Vision revealed that the three devices exhibited clinical equipoise with glottic view. In addition, all had FAS rates greater than 93%, with the traditionally shaped C-MAC having a 100% FAS.[34] In the absence of a coexistent blunt traumatic mechanism or a neurologic examination indicating spinal cord injury, cervical spine immobilization for intubation of patients with penetrating head and neck trauma rarely is indicated. It is not proven whether patients with gunshot or shotgun injuries to the head or neck are at risk of exacerbation of cervical cord injury during intubation, and there is no report of such a patient, with or without clinical evidence of spinal cord injury, who was injured by intubation. In addition, cervical spine immobilization in patients with penetrating neck injuries may be harmful resulting in delayed transport and patient assessment, added difficulty for airway procedure and an increase likelihood of death.

Airway Devices and Techniques

Direct Laryngoscopy Versus Videolaryngoscopy

The inherent limitations of DL make adequate glottic visualization less likely when compared with video instruments. VL offers the ability to visualize the glottis without creating a direct line of sight, thus making irrelevant many of the issues that complicate DL. Although DL remains a valid technique for tracheal intubation, there is mounting evidence of the clear superiority of modern video devices while DL is increasingly relegated to use as a back-up device or when VL is unavailable. The most recent data from the national emergency airway registry, encompassing 2016 to 2018, show that two-thirds of all first attempts in adult patients in participating centers are now performed with a videolaryngoscope.[14,24] This number has nearly doubled since the last multicenter NEAR report.[1]

Videolaryngoscopes

Modern laryngoscopes incorporate video imaging into specially designed laryngoscope blades to provide glottic visualization superior to that of a direct laryngoscope, without the need to create a straight-line visual axis through the mouth. Videolaryngoscopes can be separated into two large groups based on shape—those that use traditional laryngoscope geometry complemented by a video viewing device (which also can be used as direct laryngoscopes), and those with specially curved or angulated blades, designed specifically for use in a video system and not suitable for DL. In ED intubations, regardless of blade shape, VL has been shown to provide superior glottic views, reduce the rate of esophageal intubations, and facilitate greater

first-pass success when compared with direct laryngoscopes.[13,35–37] If a direct laryngoscope is used and glottic visualization is poor, it can be augmented in real time through external laryngeal manipulation, use of a bougie, and changes to patient positioning (ramping). Criticism of the various ED-based VL studies focused on the fact that VL had not been compared with "optimized" DL. However, a subsequent NEAR analysis of more than 11,000 adult ED intubations showed that first attempt intubation success was more likely with VL compared with DL with any combination of optimization maneuvers. The superiority was greatest for VL with hyperangulated blade designs.[13]

In contrast, recent ICU-based studies have not shown as clear a benefit. In one multicenter randomized trial of ICU intubations, there was no difference in FAS comparing DL with a McGrath Mac VL despite significantly better glottic visualization with VL. However, the majority of patients were intubated by rotating internal medicine interns or junior trainees with poorly defined oversight.[38] A meta-analysis of 12 RCTs including both ED and ICU patients also found no difference in FAS between VL and DL.[39] Three studies were prehospital investigations with one assessing a nonvideo device (Airtraq) to DL, and, most importantly, three-quarters of the studies excluded patients with predicted difficult airways, the exact patient population whom VL is most likely to benefit. Therefore design, sampling, and analytic flaws make these findings hard to extrapolate to ED populations. Since ED intubations are by definition emergent and cannot be rescheduled, operator experience varies, and airways are often difficult, VL is currently the predominant device for emergency intubations. We recommend use of a video laryngoscope for all emergency intubations, unless the operator identifies a specific reason not to do so.

The GlideScope videolaryngoscope system (GVL; Verathon, Seattle) uses a modified Macintosh blade with a straightened, angulated, and elongated tip enclosing a proximally placed camera to provide a wide-angle view of the glottis and surrounding anatomy, even in patients with difficult airways. Video images are transmitted to a high-resolution display that can record still pictures and video clips. Handle and blade sizes range from neonate to obese adult. A variety of GVLs have been developed over the years, including the GVL Ranger, an ultraportable version of the device, and the Cobalt, a version with sleeves designed for a single use, without the need for cleaning. The Cobalt consists of a flexible video wand insert that fits inside a disposable, single-piece transparent blade called a stat and comes in sizes and shapes comparable to those for the standard GVL. The newest generation GVL handles are made of lightweight titanium, with a narrower side profile and come in reusable and single-use varieties (Fig. 1.12). The placement of the camera distally along the blade to create a viewing field essentially negates the obstructive potential of the tongue, so GlideScope laryngoscopy and most other hyperangulated VL is performed with the blade introduced in the midline of the mouth and advanced around the tongue, with minimal lifting. A stylet must be used when intubating using a video laryngoscope. A proprietary rigid, preformed stylet is available for use with GVL systems, or a standard, malleable stylet can be shaped to match the exaggerated curve of the GVL blade. The rigid stylet is less likely to deform during intubation attempts and allows the operator better ETT control on the video screen. Either stylet may be used, although the rigid stylet helps to facilitate tube passage by maintaining its shape despite operator manipulation. The Walls method is to use a four-step technique to use the video laryngoscope and the viewing screen in combination to achieve intubation. The four steps are: (1) look in the mouth directly to insert the scope; (2) look at the screen to position the videolaryngoscope to obtain the best glottic view; (3) look in the mouth directly to insert the (stylet loaded) tracheal tube and align it with the blade of the laryngoscope; and (4) look at the screen to maneuver the tube tip through the vocal cords. Retaining "tip control" of the ETT on the video screen improves FAS and should be used whenever a hyperangulated VL is chosen and the tube needs to be manually passed into the trachea. Hyperangulated VL universally improves glottic visualization compared with DL and, consequently, enhances FAS and reduce peri-intubation adverse events. Given the low clearance profile and acute deflection offered by the blade shape, they can be particularly helpful in patients with reduced mouth opening and cervical spine immobilization.

The C-MAC videolaryngoscope (Fig. 1.13; Karl Storz Endoscopy, Tuttlingen, Germany) incorporates a complementary metal oxide semiconductor (CMOS) video chip into a range of laryngoscope blades to enhance glottic views. Images are displayed on a high-resolution monitor, with image- and video-saving capabilities. The traditionally

Fig. 1.12 GlideScope titanium handles incorporate similar video elements in a lightweight titanium blade with a narrower side profile. Connection to the video display is made by a USB-style cord. (Courtesy Verathon, Seattle, WA.)

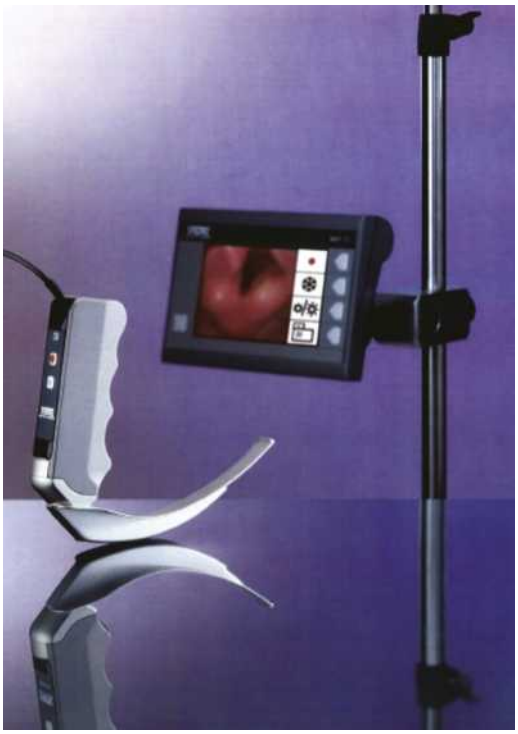

Fig. 1.13 The C-MAC videolaryngoscope (Karl Storz Endoscopy, Tuttlingen, Germany) uses an integrated complementary metal oxide semiconductor (CMOS) video chip to capture a video image from near the distal tip of an otherwise conventional laryngoscope blade. The image is conveyed to a video screen, where it is viewed by the intubator. (Modified from Brown III CA, Mick NM, Sakles JC, editors. *The Walls Manual of Emergency Airway Management*. 5th ed. Philadelphia: Wolters Kluwer; 2018.)

shaped C-MAC blade can be used as a direct laryngoscope by a trainee while a supervisor observes the video output, providing an excellent tool for teaching DL. A hyperangulated version, the d-blade, is available and both single use and reusable versions are manufactured. The C-MAC has been extensively studied and, like other VLs, improves glottic exposure and FAS. It has also been shown to outperform DL when rescuing a failed first attempt using DL.[1,36] In a single-center analysis of patients with anticipated difficult airways, C-MAC use was associated with a 90% FAS rate with RSI.[10] The C-MAC can also be augmented by use of a bougie. A randomized trial of bougie versus stylet-in-tube during C-MAC intubations of patients with at least one difficult airway characteristic showed that use of a bougie resulted in a FAS of 96% compared with 82% when a stylet-in-tube was used.[40] The results of this single-site study may not be generalizable as the study site operators were highly skilled with bougie-assisted intubations. Nevertheless, the study showed promise for the routine use of a bougie with standard geometry VL for ED intubations. The King Vision videolaryngoscope (King Systems, Noblesville, IN) is a single-use, lightweight device with a detachable (and reusable) screen that sits on top of a disposable video blade (Fig. 1.14). There are two blade types, one with an integrated tube channel and one without; the latter requires the operator to place the ETT manually. A newer version that consists of a flexible video wand covered by a single-use plastic blade is now in use. The McGrath Mac is a cordless videolaryngoscope with an integrated screen and handle configuration. It has a hybrid blade that is more akin to a standard geometry laryngoscope blade.

There are several other models of videolaryngoscopes with various sizes and features, such as disposable sheaths or blades, at various price points. Individual evaluation of these devices is important in selecting the best videolaryngoscope for an individual practitioner or practice group. Overall, VL has transformed laryngoscopy and has the potential to render DL obsolete.

Flexible Intubating Scopes

Intubation using a flexible endoscope is an important option for certain difficult airways, particularly in those with distorted upper airway anatomy, such as angioedema or blunt anterior neck trauma. These scopes long relied on fiberoptic technology, but this has largely been supplanted by miniaturized, high-quality video systems in both reusable and single-use versions (Fig. 1.15). After appropriate patient preparation, the endoscope is passed through the vocal cords under continuous visualization, serving as an introducer for an ETT, which is then placed through the glottis. Flexible endoscopic examination also is used for airway assessment to determine whether intubation is needed, such as for patients with smoke inhalation or supraglottitis. Intubation of morbidly obese patients, those with distorted airway anatomy (e.g., penetrating or blunt anterior neck injury), or those with a fixed cervical spine deformity can be achieved with the flexible endoscope with topical anesthesia and judicious sedation, thus preserving the patient's ability to breathe until intubation has been achieved. Flexible scopes also have been used successfully to intubate through a wide array of LMA-type supraglottic airways.

There is a significant learning curve for flexible endoscopic intubation, and proficiency with this device requires training and practice. Fortunately, endoscopic examination of the upper airway to the level of the vocal cords is a similar skill set as that needed to maneuver the scope through the cords to intubate. This is an important alternative method to obtain real-life experience with insertion and manipulation of the scope. Approximately 1% of ED patients are managed with a flexible bronchoscope, possibly reflecting reluctance to select this instrument if the operator does not feel sufficiently trained or competent. The most common indications for flexible bronchoscopic intubation are airway obstruction and angioedema. In the hands of emergency physicians, first-attempt and ultimate intubation success are approximately 50% and 75%, respectively.[1,41] The role of flexible endoscopic intubation in the ED will likely expand as obesity increases in the population and, increasingly, difficult airways are handled in the ED without backup. The transition from

Fig. 1.14 King Vision videolaryngoscope integrates a single-use, curved video blade attached to a top-mounted display. The blades come in two versions, those with endotracheal tube channels, for advancing the endotracheal tube, and those without. (Courtesy Calvin A. Brown III, MD.)

Fig. 1.15 New video flexible bronchoscopes are now available and integrate fully with the C-MAC high-resolution display. (Courtesy Karl Storz Endoscopy, Tuttlingen, Germany.)

fiberoptic to video technology will make these flexible scopes more durable and less prone to fogging, both desirable attributes for emergency intubation. Although the cost required to purchase and maintain a flexible endoscope can make it challenging for some EDs, single-use flexible videoscopes, such as the Ambu aScope (Ambu, Columbia, MD) and the Karl Storz (Tuttlingen, Germany) FIVE-S (Flexible Intubation Video Endoscope), provide less costly options (Figs. 1.16 and 1.17). Emergency clinicians should have immediate access to flexible endoscopes and should acquire training and regular practice in their use.

Extraglottic Devices

Laryngeal mask airways. LMAs collectively include a number of commercially available ovoid, silicone mask devices designed to seal above the glottis and permit ventilation through a central channel with a standard bag. They are used as a primary airway device in elective surgery cases and rarely during difficult airway management in the operating room.[42] There are several models available, and attributes differ among the models, but use and success rates are very similar. The historical standard is the original LMA. Although it is not often used in the ED, all modern LMA-type devices derive from this common ancestor. Reusable and single-use configurations, conventional and intubating formats, are offered by several manufacturers. Most modern LMA-type devices are "second generation" that offer more robust leak pressures through use of thicker plastic material. In addition, they integrate an orogastric tube channel for stomach decompression after being placed. The mask is inserted blindly into the pharynx and then inflated, providing a seal that permits ventilation of the trachea with minimal gastric insufflation. In elective anesthesia, the LMA has an extremely high insertion success rate and low complication rate, including a low incidence of tracheal aspiration. Evaluations of LMA insertion by experienced and inexperienced personnel consistently have shown ease of insertion, high insertion success rates, and successful ventilation. The LMA may be a viable alternative to endotracheal intubation for in-hospital or out-of-hospital treatment of cardiac arrest, particularly when responders are inexperienced airway managers. At a minimum, the device can serve a temporizing role when BMV is difficult or prolonged ventilation is anticipated. In general, all LMAs are safe to be left in place for up to 4 hours without the risk of mucosal injury. They also serve a prominent role as conduits to facilitate either blind or flexible bronchoscopic intubations. The LMA Supreme (Teleflex Inc., Morrisville, NC) is a more robust LMA with a rigid angled tube, similar to an I-LMA; as a second generation LMA, it offers an orogastric tube channel and higher seal pressures than the standard LMA. This is likely the best version for general ED use.

A noninflatable LMA, the i-Gel (Intersurgical, Berkshire, England), has a viscous gel cuff and does not require inflation (Fig. 1.18). Once in place, the warmth and humidity of the hypopharynx allows the gelatinous material to become more fluid and conform to the recesses over the glottis, creating a trapped gas space for oxygenation and ventilation. It is available in a variety of sizes for adult, pediatric, and neonatal patients. The device is placed blindly, and insertion depths are marked

Fig. 1.16 The Ambu aScope is a new, fully disposable video flexible bronchoscope with an integrated suction port and working channel for suctioning and instillation of local anesthetic. Airway images are viewed via a reusable digital display. (Courtesy Calvin A. Brown III, MD.)

Fig. 1.17 The i-gel mask airway (Intersurgical, Berkshire, England) does not have an inflatable cuff and is available in sizes from infant to adult. (Courtesy Dr. Calvin A. Brown, III, MD.)

Fig. 1.18 The intubating laryngeal mask airway is modified to facilitate insertion of an endotracheal tube after placement and ventilation have been achieved. The epiglottic elevator *(arrowhead)* lifts the epiglottis to allow passage of the special endotracheal tube *(arrow)*.

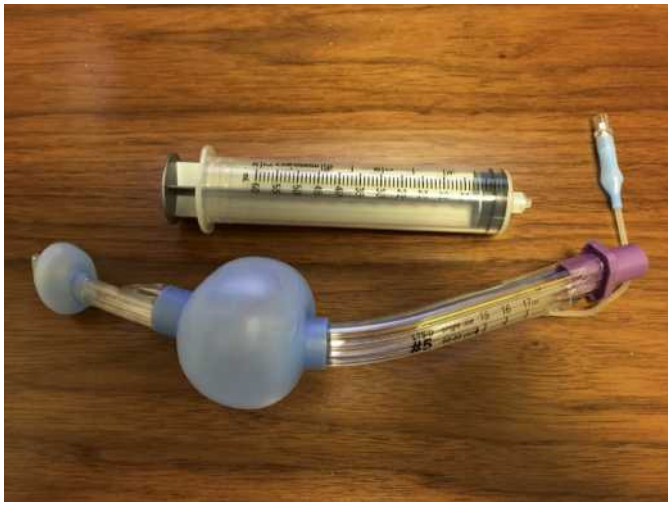

Fig. 1.19 King laryngeal tube incorporates two cuffs but inflates with a single bolus of air. There is a channel in the back for passage of an orogastric tube. It is available in a variety of adult and pediatric sizes.

on the side of the device. It has an integrated bite block and channel for passage of an orogastric tube. Initial experience with the device, even with minimally trained novice users, has been promising, with high insertion success rates and shorter insertion times when compared with the LMA or laryngeal tube airway. They also serve as functional conduits for flexible endoscopic intubation.[43]

The Fastrach LMA or I-LMA is designed to facilitate blind intubation through the mask after correct placement (Fig. 1.19). It differs from the LMA in two main ways. First, the mask is attached to a rigid, stainless steel ventilation tube curved almost to a right angle, and the mask incorporates an epiglottic elevator at its distal end. Placement of the I-LMA results in successful ventilation in almost 100% of cases and successful subsequent blind intubation in approximately 75% to 80% of cases. The I-LMA can also be used for ventilation and intubation in obese patients, with similarly high success rates. The I-LMA has a special ETT and stabilizer rod to remove the mask over the ETT after intubation has been accomplished.

The I-LMA is a better device than the standard LMA for use in the ED because it facilitates rescue ventilation and intubation. When the I-LMA is placed, intubation can be performed blindly or guided by a flexible bronchoscope. The I-LMA comes only in sizes 3, 4, and 5 and so is not suitable for use in patients weighing less than approximately 30 kg (66 lb). For smaller patients, the standard LMA, which has sizes down to size 1 (infant), should be used. Intubation can be achieved through the standard LMA, but the success rate is significantly less than with the I-LMA. Newer LMA-style devices, the Ambu air-Q and Aura-I, can act as standard LMAs for ventilation and oxygenation but can facilitate blind intubation with standard adult ETTs. Both work well intubating a difficult airway, especially when augmented by flexible endoscopy.[44]

In the ED, the primary use of the LMA or I-LMA is as a rescue technique to provide a temporary airway when intubation has failed, BVM ventilation is satisfactory, and the patient has been paralyzed and may require prolonged ventilation. In the "can't intubate, can't ventilate" situation, cricothyrotomy is indicated, but an ILMA may be placed rapidly in an attempt to achieve ventilation (converting the situation to "can't intubate, can ventilate"), as long as this is done in parallel with preparations for cricothyrotomy and does not delay initiation of a surgical airway. Patients may arrive from the field with an EGD in place. The primary technique for managing a prehospital EGD is to first decompress the stomach, deflate the device, remove the EGD, and reintubate using VL.[45]

Other extraglottic devices. In addition to LMAs, which sit above the glottis, there are other types of EGDs that travel behind the laryngeal inlet with the distal tip of the device sitting in the cervical esophagus. These are inserted blindly to provide oxygenation and ventilation through side ports while inflatable balloons occlude the pharynx above and the esophageal inlet below. Because of their positioning behind the larynx, these often are called retroglottic devices. The prototype for these devices was the esophagotracheal Combitube. These are rarely, if ever, used and will not be discussed further.

The King laryngeal tube airway (King LT; King Systems) has a single port through which distal and proximal low-pressure balloons are inflated as a single step (see Fig. 1.19). The distal balloon, when seated correctly, obstructs the cervical esophagus, and the larger proximal balloon obstructs the hypopharynx, preventing regurgitation of air. A newer version of the King LT has a posterior channel that accepts a nasogastric tube, which can be passed through the device into the stomach for aspiration of gastric contents. The King LT is disposable, rapidly placed, easy to use by operators of various skill levels and has seal pressures similar to those of standard LMAs. As mentioned, all EGDs can be safely left in place for 4 hours without mucosal pressure damage. All retroglottic devices are primarily a substitute for endotracheal intubation for non–ETT-trained personnel but are also used by advanced airway managers as a way to oxygenate and ventilate patients during crash and failed airway scenarios. These devices should be considered temporary measures, do not protect against aspiration, and should be exchanged for a definitive airway as soon as possible.

Surgical Airway Management

Needle Cricothyrotomy with Transtracheal Jet Ventilation

With the advent of newer airway devices, especially videolaryngoscopes, surgical airway management, which always has been distinctly uncommon, is required even less frequently.[1] Needle cricothyrotomy, which involves the insertion of a large needle (ideally, a large catheter designed for this purpose) through the cricothyroid membrane into the airway for transtracheal ventilation, may have a limited role in pediatric airway management (see Chapter 156). It is rarely, if ever, the right choice for an adult airway emergency and will not be discussed further here.

Cricothyrotomy

Cricothyrotomy is the creation of an opening in the cricothyroid membrane through which a 6-mm internal diameter ETT, is inserted to permit ventilation. The techniques and variations thereof have been well described elsewhere.[46] When surgical airway management is required, cricothyrotomy is the procedure of choice in the emergency setting, where it is faster, more straightforward, and more likely to be successful than tracheotomy.

Cricothyrotomy is indicated when oral or nasal intubation is impossible or fails and when BMV or EGD cannot maintain adequate oxygen saturation (the can't intubate, can't ventilate situation). ED-based intubation surveillance has suggested that the rate of salvage cricothyrotomy—a surgical airway performed after another technique was attempted first—has dropped and is now approximately 0.3%.[1] Cricothyrotomy is relatively contraindicated by distorted neck anatomy, preexisting infection in the neck, and coagulopathy; however, these contraindications are relative, and establishment of the airway takes precedence over all other considerations. The procedure should be avoided in infants and young children, in whom anatomic limitations make it exceedingly difficult. Studies have suggested that approximately five practice cricothyrotomies on a simulator or animal model are sufficient to achieve at least baseline capability with the procedure, although training intervals for skill maintenance have not been well defined.

The recommended technique for emergency cricothyrotomy is the knife-bougie-scalpel technique. It is simple to perform, requires only a few pieces of readily available equipment, and has been shown to be faster and more successful than other techniques. This approach is

supported by the latest recommendations from the Difficult Airway Society's guidelines on management of the failed airway.[47] After landmark identification, a vertical skin incision is followed by a horizontal incision into the cricothyroid membrane. A bougie is then placed through the opening followed immediately by a 6-0 ETT over the bougie. Percutaneous, needle-guided, or Seldinger technique cricothyrotomies are more likely to result in paratracheal tube placement, especially in patients with indistinct landmarks, and are no longer recommended.

OUTCOMES

The NEAR classification system characterizes potentially adverse occurrences during intubation as adverse events. In the NEAR study, the overall rate of adverse events was 12%, with recognized esophageal or mainstem intubation and hypotension being the most common.[1] Phase III of the NEAR project has reported on more than 17,500 adult ED intubations over an 11-year period (2002 to 2012).[1] The latest data from this multicenter registry have revealed the majority of intubations are now performed with VL with an overall FAS of 91%.[13] Emergency clinicians continue to manage 95% of all patients, and more than 99% were successfully intubated within three attempts. Peri-intubation adverse event rates are between 11% and 12% and are similar regardless of laryngoscope type; however, esophageal intubation is significantly less likely when VL is used. Hypoxia, recognized esophageal intubation, and hypotension are most common. The incidence of cricothyrotomy continues to drop with the rate of rescue cricothyrotomy currently at 0.3%.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 1: QUESTIONS AND ANSWERS

1. Which of the following is considered unreliable for assessing the need to establish an artificial airway?
- **a.** Absence of a gag reflex
- **b.** Absence of swallowing on command
- **c.** Level of consciousness
- **d.** Patient's ability to phonate
- **e.** Pooling of secretions in the oropharynx

Answer: a. The gag reflex can be absent in up to 25% of normal adults. Moreover, there is no evidence that the presence or absence of a gag reflex corresponds to a patient's ability to protect his or her airway. Therefore it should not be used as an indicator of the need for intubation.

2. Which of the following is the most reliable overall method for confirmation of correct tube placement after endotracheal intubation?
- **a.** Chest and gastric auscultation
- **b.** Chest radiography
- **c.** Detection of colorimetric or quantitative end-tidal carbon dioxide ($ETCO_2$)
- **d.** Measurement of exhaled volume

Answer: c. Detection of $ETCO_2$ after endotracheal intubation is the most reliable of the options listed for the confirmation of tube placement. (A fiberoptic scope passed through the endotracheal tube, with visualization of the tracheal rings, is the gold standard but is not generally required.) Limitations of colorimetric CO_2 detection should be appreciated in cardiac arrest patients. In these situations, a bulb aspiration device may provide helpful information, even though this technique is generally not as reliable as $ETCO_2$ detectors. The other listed options, traditional as they may be, are prone to failure and should not be relied on for confirmation of tube placement.

3. During rapid sequence intubation (RSI) of a hypotensive blunt abdominal trauma patient, which of the following will mitigate the risk of circulatory collapse during emergency airway management if performed before medications are administered?
- **a.** Central venous access
- **b.** Choosing propofol instead of ketamine for induction
- **c.** Resuscitating with packed red cells
- **d.** Obtaining an abdominal computed tomography (CT) scan to better characterize the degree of bleeding

Answer: c. Before induction and paralysis, the preintubation optimization step of RSI suggests that volume resuscitation with either isotonic fluids or blood in a hemodynamically unstable patient should be performed, if time allows, to reduce the chance of cardiac arrest during or immediately after intubation.

4. In which of the following conditions is succinylcholine contraindicated?
- **a.** Acute burn <5 days
- **b.** Acute head injury secondary to motor vehicle accident
- **c.** Acute spinal cord injury <5 days
- **d.** Renal failure with a serum potassium level of 4.7 mEq/L
- **e.** Multiple sclerosis

Answer: e. Succinylcholine has been associated with severe fatal hyperkalemia when administered in specific clinical circumstances. The risk of succinylcholine-induced hyperkalemia in patients with denervation syndromes begins with the onset of disease and continues indefinitely. With respect to acute burns, trauma, stroke, spinal cord injury, and intra-abdominal sepsis, the risk of hyperkalemia with succinylcholine use becomes evident 5 days after the onset of injury or disease process. Succinylcholine is not contraindicated in renal failure; however, known elevations in the potassium level may warrant use of another neuromuscular blocking agent.

5. Which of the following provides the highest ETO_2 after 3 minutes of ambient pressure tidal volume breathing?
- **a.** Nonrebreather mask with oxygen flow at 15 L/min
- **b** High-flow nasal cannula
- **c.** Nonrebreather facemask at flush rate oxygen (40 to 90 L/min)
- **d.** Venturi mask

Answer: c. Flush flow rate oxygen using a nonrebreather mask provides an ETO_2 of 85%. This is in comparison with an ETO_2 level in the mid-50s with a nonrebreather mask at 15 L/min flow. The increased inflow rate outcompetes room air entrainment around the margin of the mask and increases the fraction of inspired oxygen (FiO_2) resulting in better nitrogen washout.

6. Until how long after an acute burn is succinylcholine considered safe to use for RSI?
- **a.** 30 minutes
- **b.** 12 hours
- **c.** 24 hours
- **d.** 48 hours
- **e.** 5 days

Answer: e. Succinylcholine can produce severe (and fatal) elevations in serum potassium levels after administration in patients with burns. However, this vulnerability to succinylcholine-induced hyperkalemia is not clinically significant until at least 5 days after the acute burn. As a result, succinylcholine remains the paralytic of choice if rapid sequence intubation occurs less than 5 days after the burn.

2

Mechanical Ventilation and Noninvasive Ventilatory Support

Todd A. Seigel and Nicholas J. Johnson

KEY CONCEPTS

- Noninvasive positive-pressure ventilation (NPPV) is often adequate for reversal of impending respiratory failure due to a rapidly reversible cause, and should be considered as the first-line therapy for patients with exacerbations of chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema (ACPE) in whom immediate intubation is not required.
- NPPV should generally be avoided for definitive management of patients with pneumonia or acute respiratory distress syndrome (ARDS) unless the patient is clearly improving or has a do-not-intubate status. Otherwise, endotracheal intubation and mechanical ventilation are preferred.
- For patients in need of ventilatory support, bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) have clinical equipoise. BiPAP should begin with an inspiratory pressure setting of 10 cm of H_2O and expiratory pressure of 5 cm of H_2O and be evaluated frequently for tolerance and need to titrate up or down.
- Pressure-controlled ventilation (PC) delivers breaths at a predetermined pressure but with variable volume, while volume-controlled ventilation (VC) delivers a predetermined inspiratory volume but variable pressures.
- Assist-control ventilation (A/C) delivers a required number and volume of breaths per minute while synchronized intermittent-mandatory ventilation (SIMV) synchronizes mandatory breaths with spontaneous breaths. Either mode can be PC or VC.
- Invasive mechanical ventilation requires dynamic, ongoing monitoring. After intubation, blood gas analysis should be performed to confirm appropriate ventilation and provide correlation with noninvasive monitoring of oxyhemoglobin saturation and end-tidal CO_2.
- Positive pressure can have adverse hemodynamic consequences.
- Plateau pressure should be maintained below 30 cm H_2O.
- Elevation in ventilation pressures suggests ventilator circuit obstruction, bronchospasm, mainstem intubation, tension pneumothorax or hemothorax, decreased chest wall compliance or increased chest wall rigidity.
- Inappropriately low ventilation pressures, particularly in conjunction with hypoxia, indicates ventilator circuit leak or a faulty connection, endotracheal tube cuff leak, accidental extubation, or esophageal intubation.
- The Richmond Agitation Sedation Score (RASS) or a similar scoring system should be used to manage sedation and analgesia of the mechanically ventilated patient. Avoid unnecessary use of prolonged neuromuscular blockade. When RASS is used, a target score of –2 to 0 avoids both over and under sedation.

FOUNDATIONS

Invasive and noninvasive ventilation are often essential components of a successful resuscitation in critically ill patients. Some patients require support for respiratory failure or as part of comprehensive management of critical illness, whereas other patients require assistance primarily for airway protection. The reasons for initiating ventilatory support are varied and will influence ventilation strategy, hemodynamics, sedation strategy, and subsequent clinical course.

The decision to intubate is discussed in Chapter 1 and in other chapters throughout this text in the context of individual conditions. This chapter describes the modalities and techniques of noninvasive and invasive mechanical ventilation.

Physiology of Positive-Pressure Breathing

A typical respiratory cycle in spontaneously breathing patients begins with negative intrathoracic pressure created by contraction and relaxation of the diaphragm in concert with the intercostal muscles. This elevates the lateral ribs in a bucket-handle fashion, increasing the intrathoracic volume and resulting in a pressure gradient between intra- and extra-thoracic airspaces and net airflow into the lungs. Relaxation of the diaphragm and recoil of the chest wall decreases intrathoracic volume, increases pressure in the chest cavity, and results in passive exhalation. The amount of force required to generate adequate inspiration is influenced by the work of breathing. When the work of breathing increases, patients may be unable to generate enough negative force to sustain successful respiration and require ventilatory support.

Unlike spontaneous breathing, invasive and noninvasive mechanical ventilation are based on the delivery of humidified air with positive pressure. The amount of positive pressure required for adequate ventilation is dependent on the patient's respiratory effort, ranging from mild assistance to full support. Inhalation occurs by driving air into the lungs under positive pressure; air is passively exhaled when the chest wall recoils.

Transition from negative-pressure breathing to positive-pressure breathing affects cardiovascular and pulmonary physiology and can have significant clinical consequences. Pressure changes in the thoracic cavity directly affect pressures in the chambers of the heart. During spontaneous inspiration, decreased intrathoracic pressure augments venous return and preload. Cardiac output is increased, and there is an increased pressure gradient between the left ventricle and aorta. With the initiation of positive-pressure ventilation (PPV), the opposite occurs: venous return is diminished, cardiac output falls, and there is a decreased pressure gradient between the left ventricle and aorta. Hypotension can occur after ventilatory support has been initiated and may be exaggerated in patients with clinical hypovolemia or vasodilatory states.

Invasive Mechanical Ventilation: Control Variable and Ventilator Mode

The primary considerations when initiating mechanical ventilation relate to how gas is delivered to the lungs. This includes the volume,

duration, and frequency of each breath, and the degree of interaction the patient has with the ventilator.

How the ventilator delivers gas to the lungs is referred to as the *control variable*. The amount of air delivered in each breath is either set directly as a specific volume or indirectly as a specific amount of pressure. These are referred to as volume-controlled ventilation (VC) and pressure-controlled ventilation (PC), respectively. The amount of time over which the breath is delivered is defined as the inspiratory time, and the speed at which air travels through the circuit is defined as inspiratory flow rate. The term "cycle" refers to how the ventilator terminates delivery of a breath.

With VC, a breath is defined by delivery of a set tidal volume to the lungs. Inspiratory volume and flow rate are set by the clinician, and the ventilator cycles once a preset tidal volume has been delivered. The inspiratory time is a function of the set flow rate. Lung pressures—peak inspiratory pressures (PIPs) and end-inspiratory alveolar pressures—vary based on respiratory system resistance and compliance, as well as set tidal volume. The main benefit to the use of VC is the ability to control tidal volume and minute ventilation, but in scenarios of impaired respiratory system compliance, delivery of desired tidal volume may result in dangerously high airway pressures and barotrauma.

In PC, a set amount of pressure is applied to the airway to expand the lungs for a specified amount of time. During PC, the inspiratory pressure is set by the clinician, whereas the delivered tidal volume and inspiratory flow rate vary as functions of dynamic lung compliance and airway resistance. An inspiratory time is also set, after which the ventilator cycles by terminating delivery of the set inspiratory pressure. Ability to control the pressure delivered to the lungs is particularly useful to prevent barotrauma, which is described in more detail below. In addition, because inspiratory flow is not fixed, PC may improve ventilator synchrony in intubated patients with a high respiratory drive. A significant disadvantage of PC is that tidal volume can neither be guaranteed nor limited as it changes with acute changes in lung compliance.

The choice between volume-controlled ventilation and pressure-controlled ventilation is driven by the underlying physiology of the condition for which mechanical ventilation is needed, and for patients who do not require strict control of pressure or volume, safe and effective ventilation can be achieved with either strategy (Table 2.1). Volume-controlled ventilation should be used when strict control of tidal volume is mandated. Specifically, this includes patients with known acute respiratory distress syndrome (ARDS), in whom low tidal volume strategies have been proven to reduce mortality. In addition, patients with markedly decreased chest wall compliance should be placed on VC to ensure that adequate tidal volume is delivered. This includes patients with morbid obesity or severe chest wall burns. Conversely, PC offers advantages over VC in clinical conditions in which control of airway pressure is strictly mandated. This includes patients with the potential to develop dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP) such as those with severe asthma or chronic obstructive pulmonary disease (COPD).

Notably, while both VC and PC can have specific advantages, patients with acute derangements in pulmonary mechanics may be difficult to optimize regardless of the ventilator control variable used. Newer ventilators have attempted to address this dynamic interdependence by delivering breaths that combine volume and pressure strategies, referred to as dual-control ventilation. A common dual-control method of ventilation is pressure-regulated volume control (PRVC). A variation of volume control, PRVC is set to deliver a specific tidal volume while simultaneously minimizing airway pressure. In contrast to strict volume control, pressure is measured and modulated by the ventilator with each breath to ensure the delivery of the preset tidal volume. In addition, a pressure limit is set, and the ventilator sounds an alarm when that pressure has been exceeded. Theoretically, this combines the advantages of pressure and volume control to ensure the delivery of a specific tidal volume while the airway pressure is monitored. That said, because the ventilator is set to deliver a specific tidal volume, the disadvantages of volume-controlled ventilation persist. In addition, elevations in airway pressure are still possible and must be addressed if changes in respiratory system compliance occur. The efficacy of PRVC has not been compared to traditional PC or VC but likely does not offer significant advantage over traditional volume- or pressure-controlled ventilation, particularly if strict parameters for airway pressure are desired.

The term *ventilator mode* refers specifically to the amount of respiratory support provided by the ventilator and how often the ventilator initiates a breath for the patient. These can be divided broadly into assist-control mechanical ventilation (A/C), intermittent mechanical ventilation (IMV), and continuous spontaneous ventilation (CSV). The key difference is that A/C and IMV are intended to provide patients with a specific minimum number of preset breaths as defined by the ventilator and can be delivered via pressure or volume control methods. Conversely, in CSV, no mandatory breaths are delivered to a patient; the size and rate of the breaths are determined by the effort of the patient and are augmented with applied pressure or volume to the airway. These methods are compared in Table 2.2. Other, more complex modes of ventilation include proportional assist ventilation (PAV) and airway pressure release ventilation (APRV), although these are rarely used in the emergency department (ED).

A/C is intended to provide full ventilatory support for patients with little or no spontaneous respiratory activity by continuous delivery of breaths at a preset rate. However, if a patient generates respiratory effort while on A/C, that breath will also be assisted by the ventilator. Patients

TABLE 2.1 Features of Pressure Control Versus Volume Control

	Set Parameters	Variable Parameters	Clinical Implications	Clinical Conditions
Pressure-controlled ventilation (PC)	Pressure target, inspiratory time, RR, PEEP	Tidal volume, inspiratory flow rate	Controls airway pressure, but tidal volume becomes a function of lung compliance (no guaranteed tidal volume or minute ventilation). Allows estimation of end-inspiratory alveolar pressure based on ventilator settings. Variable inspiratory flow helpful for patients with high respiratory drive	Severe asthma, COPD, salicylate toxicity
Volume-controlled ventilation (VC)	Tidal volume, RR, inspiratory flow pattern, inspiratory time	PIP, end-inspiratory alveolar pressure	Guaranteed delivery of tidal volume, but may result in high or injurious lung pressures. End-inspiratory alveolar pressure cannot be reliably estimated and must be measured (plateau pressure)	ARDS, obesity, severe burns

ARDS, Acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease; *PIP,* peak inspiratory pressure; *PEEP,* positive end-expiratory pressure; *RR,* respiratory rate.

can trigger a breath at any rate but will always receive at least the preset number of breaths, hence the nomenclature of "assist-control." This is the most useful initial mode of mechanical ventilation in ED patients, because most patients are initially paralyzed and sedated and do not interact with the ventilator.

In A/C mode, breaths can be volume-controlled (AC/VC) or pressure-controlled (AC/PC) as detailed previously. For the promotion of ventilator synchrony, a spontaneous patient-initiated breath will take priority over a preset breath, meaning that if the ventilator is set to deliver 12 breaths/min, a breath is provided every 5 seconds in the absence of spontaneous inspiratory effort. When the patient makes a spontaneous effort, the ventilator provides an additional breath and the timer resets for another 5 seconds. One of the biggest challenges with A/C ventilation, however, is that patient-initiated breaths are not proportional to patient effort; when inspiratory effort is detected, a full-sized breath is delivered. Clinically, this requires adequate sedation of patients when ventilated in the A/C mode to prevent spontaneous respiratory efforts that will result in hyperventilation, air trapping, hypotension, and poor ventilator synchrony.

Intermittent mandatory ventilation provides intermittent ventilatory support to patients by delivering both mandatory and spontaneous breaths. In this mode, mandatory breaths are given at a preset rate, but the breath is synchronized as much as possible with spontaneous patient effort. For this reason, it is most commonly known as synchronized IMV or SIMV. Similar to A/C, the patient will receive at least the minimum number of preset mandatory breaths; if the patient provides no effort, the preset number of breaths will be given. If a patient has a rate of spontaneous respirations lower than the set rate, the ventilator will provide the preset number of full breaths but will deliver as many as possible in synchrony with patient effort. In these scenarios, there is little difference between A/C and SIMV. If a patient has a higher spontaneous respiratory rate than the preset rate, the patient receives all preset full breaths at the set rate. In contrast to A/C, additional breaths generated by the patient will be volume or pressure-supported breaths commensurate with the patient's respiratory effort. This attenuates the effects of air trapping and hyperventilation potentially seen with A/C and is one advantage of SIMV in less sedated patients.

CSV, in contrast to A/C or SIMV, provides no mandatory breaths and only augments a patient's spontaneous respiratory effort. On a ventilator, the most common way to eliminate mandatory delivery of preset breaths is via pressure-supported ventilation (PSV) and is designed to support patients' spontaneous respiratory effort by delivering an applied pressure to the airway on the trigger of a breath. The amount of pressure required to support a full breath is variable and depends on the patient's ability to overcome the work of breathing. When inspiratory flow slows to a prespecified fraction of maximal inspiratory flow (often 25%), this signals the end of inhalation. At this point, pressure support ceases and exhalation is allowed to proceed spontaneously. The level of pressure support is the only set parameter in PSV; inspiratory flow, inspiratory time, and tidal volume are determined by patient effort. This mode of ventilation most closely resembles normal spontaneous breathing and, for this reason, promotes patient control and comfort. In the ED, PSV is rarely used for intubated patients because most patients who require intubation are unable to breathe spontaneously and effectively and may have failed noninvasive support before intubation. PSV may prove to be most useful in awake and interactive patients who have been intubated for temporary airway protection rather than for respiratory failure. If PSV is used, careful monitoring and ventilatory alarms are needed to ensure against undetected hypoventilation or apnea.

TABLE 2.2 Selecting Ventilator Strategy: Features of Potential Options

Mode	Parameters Set by Clinician	Clinical Scenario
Assist-Control Ventilation		
Assist-control volume control (AC-VC)	Tidal volume, inspiratory flow, PEEP, RR	Paralyzed or deeply sedated patient, sedated patients with intermittent spontaneous respiratory effort. Can lead to hyperventilation
Assist-control pressure control (AC-PC)	Target pressure, inspiratory time, PEEP, RR	
Intermittent Mandatory Ventilation (IMV)		
Synchronized intermittent mandatory ventilation (SIMV)	Pressure or volume control, PEEP, RR (backup rate)	Patients with regular but poor spontaneous respiratory effort; if used in deeply sedated patients, set RR will need to be higher
Continuous Spontaneous Ventilation (CSV)		
Pressure-support ventilation (PSV)	Level of pressure support, PEEP	Spontaneously breathing patients with good respiratory effort requiring minimal ventilatory support
Continuous positive airway pressure (CPAP)	Level of CPAP	Alert, spontaneously breathing patients with immediately reversible causes of respiratory distress; COPD and ACPE are classic indications for noninvasive ventilation
Bi-level positive airway pressure (BL-PAP)	IPAP and EPAP	Similar to CPAP

ACPE, acute cardiogenic pulmonary edema; *COPD,* chronic obstructive pulmonary disease; *EPAP,* expiratory positive airway pressure; *IPAP,* inspiratory positive airway pressure; *PEEP,* positive end-expiratory pressure; *RR,* respiratory rate.

Positive End-Expiratory Pressure

Regardless of the ventilatory mode chosen, PEEP is often used during invasive mechanical ventilation. PEEP refers to the maintenance of positive airway pressure after the completion of passive exhalation. During acute respiratory failure, the application of PEEP increases functional residual capacity (FRC), improves oxygenation, and decreases intrapulmonary shunting by preventing alveolar collapse. The use of PEEP also reduces portions of nonaerated lung that may contribute to the development of ventilator-induced lung injury (VILI). PEEP is most effective in diffuse parenchymal lung disease, such as the ARDS. In focal processes, such as lobar pneumonia, it may simply over-distend well-aerated lung units, resulting in worse ventilation-perfusion matching. Notably, by increasing intrapulmonary and intrathoracic pressures, PEEP can also deleteriously affect pulmonary and cardiovascular physiology by reducing venous return, decreasing cardiac output, and creating lung overdistention or pneumothorax.

Applied PEEP must be specifically differentiated from intrinsic PEEP (iPEEP, or auto-PEEP), which may result from improper assisted ventilation when adequate time is not allowed between breaths for complete exhalation (see below).

Noninvasive Techniques

Noninvasive positive-pressure ventilation (NPPV) is the delivery of CSV via sealed mask rather than endotracheal tube. As with PSV, the ventilator is set to provide a defined level of pressure when a patient

takes a breath; inspiratory flow and inspiratory time are completely patient-mediated. The most common types of noninvasive ventilation in the ED are continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BL-PAP). BiPAP, a term commonly used for BL-PAP, is the proprietary name of a portable device that uses this method of noninvasive ventilation rather than a term for the ventilation itself (Philips Respironics, Murrysville, PA). CPAP provides constant positive pressure throughout the respiratory cycle, whereas BL-PAP alternates between higher pressure during inspiration (IPAP) and lower pressure during expiration (EPAP). Although, strictly speaking, CPAP applies positive pressure to the airway during inspiration, the amount of inspiratory assistance is minimal. Conversely, just as with invasive mechanical ventilation, IPAP augments patient respiratory effort by decreasing the work of breathing during inspiration, whereas EPAP acts as PEEP to maintain FRC and alveolar recruitment. Notably, although PEEP, CPAP, and EPAP all represent positive airway pressure at the end of expiration, PEEP, by convention, refers to pressure applied during invasive mechanical ventilation, whereas CPAP is the application of positive pressure (invasively or noninvasively) during spontaneous breathing. The terms are occasionally used interchangeably.

In addition to NPPV, noninvasive oxygen supplementation can also by achieved with high-flow nasal cannula (HFNC). HFNC and other high-flow oxygen delivery devices are specially designed to use high-pressure oxygen and air, a gas blender, humidifier, and large-diameter tubing to deliver oxygen at flow rates often exceeding 60 L/min. The theoretical benefits are as follows: (1) high flow rates more closely match patients' inspiratory flow and volume demands, so more inspired gas comes from the device than ambient air increasing the fraction of inspired oxygen (Fio_2); (2) the high flow washes out anatomic dead space and replaces it with oxygen; (3) Fio_2 and flow rate can be titrated independently (classically, Fio_2 is titrated for hypoxemia and flow rate for dyspnea); (4) many devices deliver a small amount of PEEP (1 to 3 cm H_2O); (5) gas is humidified and heated, which makes the high flow rate more tolerable; and (6) the large nasal prongs on the cannula devices often occlude the entire nares, reducing entrainment of ambient air during closed-mouth breathing. HFNC supplementation is indicated for acute hypoxemic respiratory failure without significant hypercarbia, and in patients for whom supplementary intrathoracic pressure would not be necessary. HFNC cannot be used in patients without a patent upper airway. Other relative contraindications include depressed mental status, facial injury, inability to manage secretions, or respiratory arrest.

MANAGEMENT

Decision Making: Noninvasive Versus Invasive Ventilation

The decision to intubate carries significant implications for patients, including complications related to invasive airway management, the use of neuromuscular blocking agents (NMBAs), and the risk of prolonged mechanical ventilation in the intensive care unit (ICU). NPPV is an appealing option for patients requiring ventilatory assistance with rapidly reversible conditions or for those with "do-not-intubate" directives. Relative contraindications include decreased level of consciousness, lack of respiratory drive, increased secretions, hemodynamic instability, and conditions such as facial trauma that would prevent an adequate mask seal. Although the need for emergent intubation is generally a contraindication to treatment with noninvasive ventilation, noninvasive ventilation may improve preoxygenation prior to intubation when compared to standard methods of oxygen delivery. If NPPV is initiated, patients should be reassessed frequently for progress of therapy, tolerance of the mode of support, and any signs of clinical deterioration that would indicate a need for intubation.

Patients most likely to respond to NPPV in the ED are those with more readily reversible causes of respiratory distress such as COPD exacerbation or cardiogenic pulmonary edema in which fatigue is a significant factor. Robust evidence has supported the use of NPPV for both conditions. In patients with acute COPD exacerbations, NPPV decreases the need for intubation by 65%, decreases hospital length of stay, and improves mortality with NNT of 12 when compared with standard therapy.[1] Treatment failure, defined as a subsequent need for intubation, is predicted by a Glasgow Coma Scale score of less than 11, sustained arterial pH less than 7.25, and tachypnea greater than 35 breaths/min. Several studies highlighted the need for appropriate patient selection in that a failed trial of NPPV was associated with higher mortality when compared to those who received immediate intubation.

In patients with acute cardiogenic pulmonary edema (ACPE), NPPV reduces the work of breathing while simultaneously improving cardiac output. The application of NPPV causes elevations in intrathoracic pressure that decrease left ventricular (LV) ejection pressure and LV transmural pressure, which results in afterload reduction. In addition, decreases in right ventricle (RV) preload may improve LV compliance via ventricular interdependence. Compared with standard therapy, NPPV has been shown to reduce mortality with number needed to treat (NNT) 17 and reduce rates of endotracheal intubation by 50% for patients with ACPE.[2] Benefits were found to be independent of whether patients received CPAP or BL-PAP and, despite suggestions from early clinical data, no increased rate of acute myocardial infarction occurred in patients receiving any form of NPPV. Specific predictors of failure of NPPV in those with congestive heart failure (CHF) have not been systematically examined.

Evidence regarding the use of NPPV in other patients with respiratory compromise, including asthma and pneumonia, is limited. Several small studies have suggested that NPPV may be beneficial for patients with acute asthma exacerbations by improving lung function, decreasing bronchodilator requirements, and shortening overall hospital length of stay, suggesting a potential role for NPPV in these patients (see Chapter 59). Studies have failed to establish a definitive role for NPPV in pneumonia, and the presence of pneumonia has been shown to be an independent risk factor for failure of noninvasive ventilation. In addition, the duration of NPPV prior to intubation has been associated with in-hospital mortality, suggesting that early intubation is preferable for patients who do not rapidly improve on noninvasive therapy.

A recent randomized, controlled trial compared HFNC, standard oxygen therapy, and NPPV in patients with acute hypoxemic respiratory failure.[3] While the trial found no difference in the proportion of patients intubated at day 28 (the primary outcome), there was a mortality benefit favoring HFNC. HFNC has also been trialed post-extubation and after cardiothoracic surgery with favorable results.[4–6] Another trial in immunocompromised patients showed no difference compared with standard oxygen delivery devices.[7] In light of potential mortality benefit, HFNC should be considered early in the treatment of hypoxemic respiratory failure.

Approach to Initial Ventilator Settings

Noninvasive Ventilation

Initial settings for noninvasive ventilation should be determined by the amount of ventilatory assistance required by the patient, as well as patient comfort and cooperation with therapy. The first consideration in the use of NPPV is whether to provide support in the form of CPAP or BL-PAP. As described earlier, there is no clear benefit of one over the other. Support may be provided by a full-face (oronasal) mask or nasal mask; this choice is determined by patient comfort,

ability of the patient to cooperate, and the need for the patient to cough effectively or speak. Notably, nasal masks have been associated with higher leak rate and decreased patient comfort; therefore, a full-face mask as the first method of NPPV is recommended. In the case of BL-PAP, inspiratory support (IPAP) is initiated at 10 cm H_2O and expiratory support (EPAP) at 5 cm H_2O. Subsequent titration of these parameters is based on the patient's clinical response, particularly pressure tolerance, respiratory rate, and oxygen saturation. Although blood gas analysis is confirmatory, improvements in the patient's clinical condition can be observed by decrease in work of breathing, good patient-ventilator synchrony, increased oxygen saturation, and a positive subjective patient report. If required, IPAP and EPAP can be adjusted by 1 to 2 cm H_2O at a time based on the clinical response. Changes in IPAP will predominantly impact ventilation and work of breathing by modulating tidal volume and minute ventilation, whereas EPAP (acting as PEEP) will impact oxygenation by combating atelectasis and promoting alveolar recruitment. IPAP greater than 20 cm H_2O should be avoided, because it can be uncomfortable and cause gastric insufflation.

High-Flow Nasal Cannula

For patients with acute hypoxemic respiratory failure without significant hypercarbia, HFNC or other high-flow oxygen devices may be applied. After positioning the cannula or face mask, a blend of oxygen and air is delivered at flow rates of up to 80 L/min. These devices typically use high-pressure oxygen and air, which is routed to the gas blender, a humidifier, then to the patient interface via large-bore tubing. The nasal prongs are large diameter, which reduces the amount of ambient air entrained around them. Face mask and tracheostomy tube interfaces also exist. Typical initial settings are Fio_2 of 50% and flow rate of 40 L/min, with maximum values of Fio_2 of 100% and 60 liters per minute. Fio_2 should be titrated to achieve the goal Spo_2, and flow can be titrated both for hypoxemia and relief of dyspnea. Recent data suggest that risk of dispersion of potentially infectious respiratory droplets and aerosols is low with these devices.[8,9] Close monitoring is required. An index (termed ROX, and defined as the ratio of (Spo_2 / Fio_2) to respiratory rate) has been derived and validated to predict risk of HFNC failure (defined as need for endotracheal intubation) and success, and may be used as an adjunct to clinical evaluation.[10] A value less than 3.85 indicates a high risk of HFNC failure, and values ≥ 4.88 measured at 2, 6, or 12 hours after HFNC initiation are associated with lower risk of intubation.

Mechanical Ventilation of the Intubated Patient

For the intubated patient, initial ventilator settings should facilitate ventilation that improves gas exchange, promotes ventilator synchrony, and minimizes the potential for complications. For an apneic or paralyzed patient, full ventilatory support is required; therefore, A/C is the recommended mode of initial ventilation for emergent patients. Specific required settings depend on whether the patient is receiving PC or VC, but the principles underlying the selection of settings are similar. Typical initial ventilator settings include a tidal volume of 6 to 8 mL/kg of estimated ideal body weight (IBW) with a rate of 12 to 14 breaths/min or one that matches the patient's pre-intubation respiratory rate. If VC is used, tidal volume can be set directly and, if PC is used, tidal volume is determined by adjusting the targeted pressure to be delivered. Regardless of VC or PC, initial pressure targets should ideally not exceed 30 cm H_2O. The initial Fio_2 should be set at 1.0 and titrated down to maintain an oxygen saturation of 88% to 94%. PEEP is routinely set initially at 5 cm H_2O. Settings for specific clinical conditions such as status asthmaticus are discussed later.

Ongoing Management

Mechanical ventilation requires monitoring and regular adjustment to ensure appropriate gas exchange, safe delivery of desired tidal volume, and prevention of acid-base derangement. Changes to ventilator settings are guided dynamically by multiple factors, including pulse oximetry, end-tidal carbon dioxide ($ETco_2$) measurement, ventilation pressures, and blood gas levels. Blood gases should be measured 15 to 20 minutes after the initiation of ventilatory support to determine pH and adequacy of gas exchange.

Overall, while venous blood gases (VBGs) can be used to titrate ventilator settings, venous blood samples should be interpreted with several caveats. First, while the pH of venous blood samples generally correlates well with the pH of arterial samples, the correlation of Pco_2 between venous and arterial samples is less reliable. In addition, although there is variation in agreement between capnography and blood gas values, capnography generally correlates better with the Pco_2 of arterial samples. Lastly, an arterial sample is required to assess the relationship between the Fio_2 and Pao_2, a key indicator of the severity of hypoxemia in ARDS. For these reasons, arterial blood gases are more useful when adjusting initial ventilator settings.

Once an initial correlation has been established, noninvasive modalities can be used for further adjustment. Data have confirmed the importance of continuous capnography, demonstrating a decrease in the use of blood gases and resultant, significant cost savings.[11] If capnography is difficult to perform or otherwise noncorrelative, arterial blood gas determination remains the definitive test for evaluating Pao_2 and Pco_2.

Pco_2 should be adjusted by changing the minute ventilation, or the volume of air cycled in one minute. Minute ventilation is determined by the tidal volume and respiratory rate. As such, adjustment of these, as indicated by the scenario, can be used to affect the Pco_2.

To avoid oxygen toxicity, Fio_2 should be reduced at the earliest opportunity to the lowest level that provides acceptable oxygen saturation (>90%) as hyperoxemia has been associated with worse outcomes. In a recent cohort study of ED patients, hyperoxemia (defined as Pao_2 >120 mm Hg) was an independent predictor for hospital mortality.[12] In many cases, increases in PEEP will allow better oxygenation for a given Fio_2 but may worsen hypotension or increase intrathoracic pressure.

In addition to maintaining adequate gas exchange, care should be taken to ensure that pressure in the ventilator circuit (including the lungs) is appropriate. The two main measurements are the peak inspiratory (PIP) and plateau (Pplat) pressures. The PIP measures the maximum amount of pressure in the ventilator circuit during a breath cycle. It reflects both respiratory system compliance (including the lungs, pleural spaces, chest wall, and abdomen) and respiratory system resistance (including resistance in the ventilator circuit itself). In PC ventilation, because pressure limits are preset, the PIP is the sum of the set pressure target and PEEP. In this case, PIP also reflects the maximum amount of pressure in the alveoli, an important determinant in the development of VILI. In VC ventilation, PIP can be influenced greatly by airway resistance and therefore is not reflective of the maximal alveolar pressure. Rather, maximal alveolar pressure is determined on the ventilator at the end of inspiration by means of an inspiratory hold, referred to as plateau pressure (Pplat). At the end of inspiration, flow in the circuit stops; therefore, there is no pressure from resistance in the circuit.

Increases in measured pressure indicate increased airway resistance or changes in compliance of the respiratory system and can indicate potentially dangerous clinical deterioration. Sudden increased airway resistance or decreased lung compliance would result in increased airway pressure during VC and reduced tidal volume during PC

ventilation. Decreases in lung pressure, conversely, indicate decreased resistance or decreased airflow in the ventilatory circuit and should prompt investigation of the ventilator circuit for leaks. Large or sudden decreases in pressure suggest disconnection of the ventilator circuit or unintended extubation. For patients with underlying respiratory failure secondary to increased airway resistance such as in asthma or COPD, gradual decreases in PIP indicate clinical improvement.

Pharmacology: Analgesia and Sedation of the Ventilated Patient

Analgesia and sedation are critical in the care and comfort of mechanically ventilated patients. Intubation, mechanical ventilation, and paralysis are a significant cause of pain and anxiety for patients, and analgesia and sedation are required to promote patient comfort and ventilator synchrony.

Analgesia and sedation should be titrated to comfort and therapeutic goals, treating pain and anxiety while avoiding over or under sedation. A large body of ICU literature has documented an association between deep sedation, delirium, prolonged mechanical ventilation, and mortality. Recent data suggest that early deep sedation is common in the ED, carries on to the ICU, and may be associated with worse outcomes.[13,14] The desired level of sedation will differ based on patient tolerance and the clinical scenario; assuming that comfort is maintained, lighter sedation is reasonable for most patients. Deep sedation is required for any patient who has recently received neuromuscular blockade or is undergoing procedures or diagnostic studies.

Multiple validated tools are used to guide appropriate levels of sedation for mechanically ventilated patients. These include the Critical Care Pain Observation Tool (CPOT) and Richmond Agitation-Sedation Scale (RASS). Both allow nurses and clinicians to target analgesia and sedation to specific goals. CPOT uses variables such as facial expression, body movement, muscle tension, and ventilator compliance to allow for titration of analgesia to achieve preselected goals. The RASS is a commonly used scale of +4 to −5. A +4 patient is combative with staff, a 0 is alert and calm, and −5 is unarousable to physical stimulation (Table 2.3). Sedation should be maintained at the highest RASS score at which the patient is comfortable (between 0 and −5) and frequently reassessed. Any patient who has recently received neuromuscular blockade should remain deeply sedated as RASS cannot be obtained in a paralyzed patient. ED-based data have demonstrated that the use of rocuronium during rapid sequence intubation (RSI) is associated with increased time to adequate sedation, as well as decreased overall dose of sedation, when compared to patients intubated with succinylcholine.[15] This is likely because emergency clinicians wrongly ascribe the patient's inability to move or respond to adequate sedation, rather than to the paralysis. When rocuronium is used for RSI, additional sedation should be immediately administered after intubation confirmation.

TABLE 2.3 Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, but movements not aggressive or vigorous
0	Calm	Alert and calm
−1	Drowsy	Not fully alert, but has sustained awakening (>10 s)
−2	Light sedation	Briefly awakens with eye contact to voice (<10 s)
−3	Moderate sedation	Movement or eye opening to voice but no eye contact
−4	Deep sedation	No response to voice but movement or eye opening with physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Adapted from Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289:2983–2991.

After RSI, additional NBMAs should generally not be used unless ventilator dyssynchrony interferes with adequate oxygenation or ventilation despite adequate sedation and analgesia. While NMBAs were previously recommended for patients with moderate-to-severe ARDS, a recent trial demonstrated no benefit when they were given universally to this population.[16] NMBAs still may be used as a rescue strategy for refractory hypoxemia or ventilator dyssynchrony in ARDS. With proper sedation and analgesia, however, NMBAs are usually not required. If needed, single doses of longer-acting agents such as rocuronium and vecuronium may be used; note that impaired hepatic or renal function may increase duration of paralysis. An infusion of cisatracurium may also be used for patients requiring prolonged NMBA and is generally preferred over other agents as its metabolism is independent of organ function.

Analgesia is achieved with opioids; fentanyl and morphine remain the most commonly used agents for analgesia in critically ill patients. Opioids are associated with dose-dependent respiratory depression, a side effect that may be particularly beneficial for patients experiencing ventilator dyssynchrony. Morphine (0.5 to 1 mg/kg IV push) and fentanyl (weight-based, 0.5 to 1 mcg/kg IV push) can be used for analgesia, although dosage requirements will vary based on tolerance and drug metabolism. Sedation and analgesia should therefore be titrated with a standard sedation scale, as discussed earlier. Notably, the active metabolite of morphine (morphine-6-glucuronide) is cleared renally and has potent sedative effects. For this reason, fentanyl may be preferred in patients with renal insufficiency. Fentanyl has a context-sensitive half-life; its duration of action is short when administered as a bolus or low-dose infusion. Because it is lipophilic, large or prolonged doses may dissolve in adipose tissue, leading to drug accumulation and prolonged effect. Remifentanil is an ultra–short-acting opiate that is metabolized by nonspecific plasma esterases. Adjunct non-opioid analgesic agents, such as acetaminophen, gabapentin, ketamine, tricyclic antidepressants, and regional anesthesia may also be useful in patients with coexisting painful conditions or opioid tolerance.

Sedation after intubation can be accomplished via multiple pharmacologic modalities. In the ICU, benzodiazepines had been a common choice for sedation, but data suggest they are associated with increased delirium and prolonged ventilation, so they are falling out of favor. Other agents, such as propofol and dexmedetomidine, are commonly used. A recent, multicenter study of ED sedation practices revealed that propofol was the most commonly used sedative, followed by midazolam and lorazepam.[13] Notably dexmedetomidine does not provide deep sedation and should not be used as a single agent in patients who received long-acting NMBAs.

Propofol is highly lipophilic, rapidly penetrates the blood-brain barrier, and distributes into peripheral resulting in a short duration of its clinical effect. Propofol exerts dose-dependent clinical effects by binding γ-aminobutyric acid (GABA) receptors, first producing anxiolysis and then sedation and hypnosis. Propofol clearance is only minimally impacted by organ dysfunction in critically ill patients. Propofol can precipitate hypotension by increasing venous capacitance and suppressing myocardial contractility, a side effect that is exaggerated in hypovolemic patients. Thus, propofol should be given as an

infusion rather than as a bolus, initiated at low doses (0.1 mg/kg/min) and titrated to the desired level of sedation. In comparison to benzodiazepines, continuous infusions of propofol have been demonstrated to decrease the duration of mechanical ventilation. A rare but potentially deadly propofol infusion syndrome can occur in patients receiving prolonged or high-dose infusion and is characterized by metabolic acidosis, rhabdomyolysis, renal and liver injury, and cardiovascular collapse.

Like propofol, benzodiazepines also bind GABA receptors. Benzodiazepines also cause respiratory depression, which is potentiated by concomitant opioid administration. Therefore, a sedation regimen of opioids and benzodiazepines may improve ventilator dyssynchrony while providing anxiolytic and amnestic effects. Benzodiazepines can be administered as repeated boluses or by continuous infusion although, in critically ill patients, benzodiazepines have altered pharmacokinetics that result in tissue accumulation and prolonged sedation. This is particularly true in obese patients and patients with renal or hepatic insufficiency. For this reason, sedation with benzodiazepines should be first attempted with intermittent bolus administration before a continuous infusion is used. The most commonly used benzodiazepines are midazolam (0.01 to 0.05 mg/kg IV push) and lorazepam (0.02 to 0.04 mg/kg IV push).

Other medications for the sedation of ventilated patients in the ED include dexmedetomidine, ketamine, and haloperidol. Dexmedetomidine is a centrally acting α_2-agonist with sedative and analgesic properties, largely distinguished from other sedative agents by a negligible impact on respiratory drive, even with simultaneous opioid administration. It is administered as a continuous infusion (0.2 to 1.5 mcg/kg/min), and can precipitate bradycardia, transient hypertension, and hypotension in an idiosyncratic fashion. Several multicenter trials demonstrated that dexmedetomidine was associated with a shorter duration of mechanical ventilation as well as decreased sedation-associated delirium compared with continuous infusions of benzodiazepines.[17] A large, multinational trial compared dexmedetomidine with usual care, which consisted mainly of continuous infusions or propofol and occasionally benzodiazepines, and demonstrated no difference in mortality, but more adverse hemodynamic events in the dexmedetomidine arm.[18] Although not systematically studied in ventilated ED patients, dexmedetomidine has emerged as an alternative sedation strategy for critically ill patients and may be considered as an alternative to traditional modalities in clinical settings in which agitation or anxiety limit therapeutic goals.

Ketamine has emerged as a popular agent for sedation and analgesia in the ED for a variety of indications and may have a role for ongoing sedation and analgesia in mechanically ventilated patients. In addition to its main property as a dissociative anesthetic, binding the N-methyl-D-aspartate (NMDA) receptors, it also acts on opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage sensitive calcium ion channels. It has a moderate analgesic effect and may be effective in patients with opioid tolerance. Although data in critically ill patients are limited, it is used widely as an opioid-sparing analgesic agent for postoperative pain, in combat settings, and in the developing world as an anesthetic agent. It has a beneficial side effect profile and is generally safe, but may cause tachycardia, hypertension, and emergence reactions. Ketamine may be administered as IV boluses of 1 to 2 mg/kg or as a continuous infusion (0.5 to 1 mg/kg/h).

Haloperidol and other antipsychotics may be used as an adjunct to traditional sedation regimens in mechanically ventilated patients. Haloperidol may be particularly useful for patients who remain acutely agitated after receiving large doses of other sedative medications, especially because it does not affect hemodynamics. However, haloperidol does not have analgesic or amnestic properties and cannot be used as a single agent for sedation in critically ill patients. Notably, antipsychotics have not been shown to prevent or reduce the duration or severity of delirium in critically ill patients.[19]

Ventilator-Associated Pneumonia Prevention

Ventilator-associated pneumonia (VAP) is a common complication of mechanical ventilation and is associated with poor outcome. Approximately 50% of all cases of VAP occur within the first 4 days of mechanical ventilation. A number of strategies can be initiated in the ED to help prevent VAP later on in the patient's clinical course.

Management of secretions, which is necessary not only for VAP prevention but also patient comfort, is achieved via regular endotracheal suctioning, recognizing a balance between secretion clearance and the disruption of ventilation. Ideally, suctioning occurs using a sterile, enclosed, in-line endotracheal catheter. In addition, a nasogastric or orogastric tube should be placed for gastrointestinal decompression. Finally, evidence has demonstrated that placing the patient in the semi-recumbent position by elevating the head of the bed to at least 30 degrees can also reduce rates of VAP. This can be accomplished in patients undergoing spinal immobilization by placing them in the reverse Trendelenburg position.

The use of VAP care bundles, including elevation of the head of the bed, daily sedation vacations and assessment of extubation readiness, peptic ulcer disease prophylaxis, oral decontamination, gastrointestinal decompression, and other interventions, have decreased the incidence of VAP in the ICU. One study of patients with ARDS demonstrated that an ED ventilator protocol, which included head elevation, was feasible and associated with improved mortality and ventilator-free days.[20]

Endotracheal tube design and management may also affect VAP incidence. A meta-analysis has also demonstrated a decrease in the incidence of VAP with continuous aspiration of subglottic secretions.[21] Several studies also demonstrated reduced incidence of VAP in patients treated with silver-coated endotracheal tubes. Maintenance of endotracheal tube cuff pressure at 20 to 30 cm H_2O may prevent leakage of secretions around the cuff into the lower respiratory tract, though this approach has not been consistently demonstrated to prevent VAP.

Troubleshooting the Ventilator

When a patient's condition suddenly deteriorates during mechanical ventilation, a systematic approach should be applied to assess for life-threatening conditions (Fig. 2.1). The first step in evaluating the ventilated patient who has a change in clinical status is to assess vital signs. Patients with acute, severe hemodynamic compromise, such as profound hypotension or cardiac arrest, should be removed from the ventilator and bagged manually on 100% oxygen. Tension pneumothorax, increased iPEEP, and accidental extubation are the most life-threatening concerns in this situation and must be expeditiously addressed. While the patient is bagged, the chest should be examined to ensure bilateral breath sounds. Changes in breath sounds may indicate a pneumothorax or migration of the endotracheal tube. Clinical examination, oxygen saturation, correlation between set and exhaled tidal volumes, and $ETCO_2$ monitoring can be used to assess tube placement, but suspicion of inadvertent extubation should prompt immediate laryngoscopy or endoscopic evaluation of the location of the endotracheal tube. Acute hypotension can be precipitated by extreme elevations in intrathoracic pressure; compromise from iPEEP will improve once the patient has been disconnected from the ventilator, whereas hypotension from a tension pneumothorax will not be relieved. If the patient's condition remains unstable after she or he has been disconnected from the ventilator circuit, a tension pneumothorax should be treated presumptively with needle decompression or finger thoracostomy and eventual chest tube placement. If the patient remains

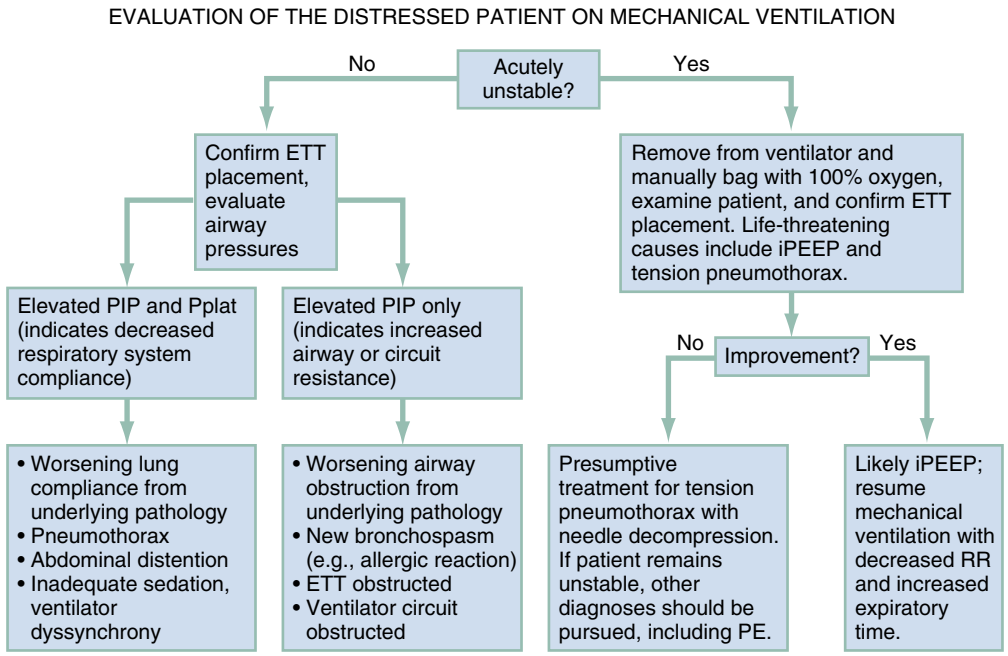

Fig. 2.1 Algorithm for Evaluation of the Distressed Patient on Mechanical Ventilation. *ETT*, Endotracheal tube; *PE*, pulmonary embolism; *PIP*, peak inspiratory pressure; *RR*, respiratory rate.

TABLE 2.4 Troubleshooting the Ventilator: Potential Causes of Acute Respiratory Distress

With Hemodynamic Compromise: Immediately Discontinue Mechanical Ventilation and Manually Bag with 100% Oxygen	
Increased intrinsic positive end-expiratory pressure (iPEEP)	
Tension pneumothorax	
Massive pulmonary embolus	
Without Hemodynamic Compromise: Search for Underlying Cause	
Mechanical	Physiologic
Endotracheal tube migration into bronchus	Worsening lung compliance
Endotracheal tube obstruction	Worsening airway obstruction
Endotracheal tube cuff leak	Abdominal distention
Inadvertent extubation	Pulmonary embolus
Discontinuity in ventilator circuit	Pain or inadequate sedation

unstable after chest decompression, other causes should be pursued. However, decompensation on the ventilator can often be averted by close attention to pressure alarms and waveforms and monitoring for the development of iPEEP in at-risk patients.

Acute distress without hemodynamic changes can be precipitated by multiple factors, mechanical and physiologic (Table 2.4). The initial evaluation should begin by confirming the position and patency of the endotracheal tube before other diagnoses are investigated, including evaluation of the tracheal balloon. Once tube placement has been confirmed, the next step in the evaluation of ventilator-related causes of distress should focus on airway pressures. Acute decreases in PIP indicate discontinuity in the ventilator circuit, which could include inadvertent extubation or disconnection from the circuit. Patients with increased PIP can be considered in two categories—those with concomitant increases in Pplat and those with unchanged Pplat. If both PIP and Pplat acutely increase, this suggests decreased compliance of the respiratory system. Elevated PIP with unchanged Pplat indicates problems with increased airway resistance in the lungs or ventilator circuit. Specific conditions that cause decreased respiratory system compliance or increased airway resistance are detailed in Fig. 2.1.

Special Clinical Circumstances

Although generalizations can be made regarding ventilator management in the ED, certain clinical circumstances merit specific discussion.

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Strategies for managing intubated patients with COPD focus on improving gas exchange while minimizing iPEEP. Reduction of iPEEP is achieved by decreasing airway resistance with bronchodilators and corticosteroids, as well as ensuring adequate expiratory time during mechanical ventilation. Adequate expiratory time is achieved by decreasing respiratory rate, tidal volume, and inspiratory time. Adequate oxygenation (saturation of 88%) is achieved while minimizing barotrauma by deliberately reducing minute ventilation, so-called permissive hypercapnia. While many clinicians select PC in COPD, no data have suggested the advantage of PC over VC, and either method can be used. The ideal ratio of inspiratory-to-expiratory time (I/E ratio) is variable, but should initially be set at 1:4. Studies in asthmatics have suggested that expiratory times longer than 4 seconds have minimal impact on airflow. iPEEP can also result in poor patient-ventilator synchrony, causing ineffective breath triggering. Unlike in patients with acute asthma (see following section), applied PEEP should be used in patients with COPD; it can be set initially at 5 cm H_2O, and may be increased to match iPEEP in the case of ineffective triggering. Initially, deep sedation and analgesia (and sometimes neuromuscular blockade) are required to prevent ventilator asynchrony and permit effective ventilation.

Status Asthmaticus

Management principles for ventilating the acute asthmatic generally parallel those for patients with COPD, with some notable differences.

In acute asthma, respiratory failure is a result of airway obstruction and airway inflammation. Furthermore, unlike COPD, airway obstruction is much less dynamic and occurs predominantly in the large airways. In addition, acute inflammatory changes throughout the lung contribute to decreased lung compliance, which has a direct impact on lung pressures during ventilation. Strategies should focus on low respiratory rates, with emphasis on maximizing expiratory time. The use of PEEP has been debated and is largely thought to contribute to increased lung pressure. Although no studies have definitively supported VC over PC, decreased lung compliance and potential iPEEP may make the delivery of adequate tidal volumes with PC difficult. This is especially problematic for patients with severe, acute respiratory acidosis, for whom adequate ventilation is essential. Recommendations for ventilator settings include VC with tidal volumes of 6 to 8 mL/kg IBW, respiratory rate of 8 to 12 breaths/min, and low PEEP of 3 to 5 cm H_2O in most circumstances. The PEEP should then be further titrated to match approximately 80% of the iPEEP. Decreased inspiratory time allows greater expiratory time and, in VC, is achieved by increasing the inspiratory flow rate. Increases in inspiratory flow rate, however, will increase airway pressures, emphasizing the interplay of inspiratory time, tidal volume, and airway pressure. Like in COPD, a low set respiratory rate matters little if the patient is tachypneic and triggering the ventilator frequently, so analgesia, deep sedation, and occasionally neuromuscular blockade may be necessary.

Acute Respiratory Distress Syndrome

ARDS represents a spectrum of inflammatory lung disease characterized by heterogeneous noncardiogenic pulmonary edema, hypoxemia, reduced lung compliance, and diffuse alveolar injury. The severity of ARDS is classified as mild, moderate, or severe and is defined by the ratio of arterial oxygen concentration to the fraction of inspired oxygen (Pao_2/Fio_2). ARDS can be caused by pulmonary or extrapulmonary insult, including VILI.

Data from cohorts of ventilated ED patients with sepsis suggest that ARDS may be present in 7% to 25% of cases and development of ARDS after ED admission is common.[22] The development of VILI has been associated with lung overdistention and alveolar injury, and attention to ventilation strategy in the ED is warranted. Studies have confirmed that decreased tidal volumes are of clear benefit in the management of patients with ARDS. Most studies examining low tidal volume ventilation strategies, including the landmark ARMA trial conducted by the ARDSnet in 2000, used 4 to 6 mL/kg tidal volumes based on IBW. A meta-analysis of these data has concluded that tidal volumes below 7 mL/kg and Pplat less than 31 cm H_2O confer mortality benefit in patients with ARDS, although more recent work has suggested that low tidal volume ventilation may improve outcome for patients without lung injury as well, including halting progression to ARDS.[22,23] The level of PEEP in patients with ARDS continues to be actively researched and, although higher levels of PEEP have been demonstrated to improve oxygenation, they have not reduced mortality. Therefore, in patients with ARDS ($Pao_2/Fio_2 < 300$), a low tidal volume (≤6 mL/kg of IBW) and low plateau pressure (≤ 30 cm H_2O) ventilation strategy should be used.

Although observational data across multiple settings, including the ED, suggest that ventilation with tidal volumes greater than 8 mL/kg IBW before onset of ARDS is associated with development of ARDS, a randomized trial showed no benefit of lower tidal volume ventilation among patients without ARDS.[23] However, given low risk of harm with protective strategies and potential benefit, we recommend ventilation with tidal volumes of 6 mL/kg IBW in patients with ARDS and 6 to 8 mL/kg IBW in patients at risk for ARDS. Observational data have suggested that adherence to lung-protective ventilation strategies in the ED is just over 50%.[22] Several studies have demonstrated that ED mechanical ventilation protocols that include low-tidal volume ventilation are associated with improved outcomes.[20,22,24]

OUTCOMES

Because of the heterogeneity of ventilation strategies and clinical reasons for respiratory failure, no studies have clearly shown the superiority of one ventilation method over another; considerations in initiating mechanical ventilation are individualized and serially reevaluated. Nonetheless, certain conclusions regarding outcomes can be made. Data have clearly indicated the effectiveness of NPPV in preventing intubation for patients with COPD and ACPE, and these benefits have resulted in decreased admission to the ICU and decreased mortality. In addition, increased alveolar volumes and pressures have been shown to contribute to VILI and increase mortality in patients with ARDS. Although the benefit of low tidal volume ventilation on the prevention of lung injury in patients with normal lungs has not been definitively proven, data suggest that strategies of mechanical ventilation in the ED can improve the subsequent clinical course of critically ill patients.

Finally, although the treatment of mechanically ventilated patients usually extends beyond the ED, delays in ICU admission can have significant implications on ED management of the critically ill ventilated patient because the role of emergency clinicians extends beyond acute stabilization and can include ongoing clinical management. In addition, because of "therapeutic momentum" clinical interventions implemented in the ED are likely to be continued through hospitalization. Finally, when boarding times are long, patients intubated solely for airway protection may be candidates for extubation in the ED if the initial insult has been reversed.

Complications

Although initiated as a lifesaving intervention, mechanical ventilation carries the risk of significant complications. As highlighted earlier, the initiation of mechanical ventilation leads to elevated intrathoracic pressure, which can reduce preload, raise pulmonary vascular resistance, and reduce cardiac output.

Mechanical ventilation can also injure the lungs; this is termed VILI. VILI may be caused by alveolar overdistention and volutrauma due to high tidal volumes. Trauma related to elevated lung inflation pressures can manifest overtly as barotrauma leading to alveolar rupture, pneumothorax, or pneumomediastinum. Biotrauma, characterized by ventilator-induced inflammatory mediator release, and atelectrauma, caused by shearing of alveoli during opening and closing, may also contribute to VILI. VILI is mitigated by limiting pathologic stretch on the alveoli; studies have supported that maximum safe end-inspiratory alveolar pressures are 30 to 32 cm H_2O. Recent studies have demonstrated that minimizing driving pressure, the difference between the end-inspiratory pressure during a pause (or plateau pressure) and PEEP, may be a better target to reduce VILI.[25]

Another potential complication of PPV is the development of intrinsic PEEP (iPEEP or auto-PEEP). Particularly problematic in patients with obstructive lung disease, iPEEP is the accumulation of end-expiratory volume and end-expiratory pressure that occurs when exhalation cannot be fully completed. In patients with obstructive lung disease, expiratory flow is limited by small airway obstruction, dynamic airway collapse, and diminished elastic recoil. The time required for full exhalation may be significantly longer than normal, and, in patients receiving mechanical ventilation, exhalation may not

be complete before the next delivered breath. This phenomenon, often termed *breath stacking*, results in dynamic hyperinflation. iPEEP leads to high PIPs, difficulty triggering breaths, hypotension, and potential circulatory collapse. Ventilation difficulty caused by iPEEP can be improved by decreasing the respiratory rate or inspiratory time, or increasing the inspiratory flow rate, all of which facilitate increased time for exhalation. Increasing set PEEP to match the level of iPEEP may also improve a patient's ability to trigger breaths.

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CHAPTER 2: QUESTIONS AND ANSWERS

1. Which of the following is the most important consideration in the decision to initiate noninvasive positive-pressure ventilation (NPPV)?

a. Degree of acidosis
b. Degree of respiratory distress
c. Hemodynamic profile
d. Level of consciousness

Answer: b. Although NPPV will be helpful for many patients in distress, the need for emergent intubation is an absolute contraindication to NPPV. Both hemodynamic profile and level of consciousness are important determinants in the decision to implement NPPV, but both are relative (rather than absolute) contraindications to its use. Patients with chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema (ACPE), and asthma are more likely to show benefit with NPPV than patients with pneumonia, but NPPV can be initiated for any patient with respiratory distress. Patients with hypoxia or hypercarbia may be acidemic, but the decision to initiate NPPV will be predicated on mental status and work of breathing rather than on degree of acidosis alone.

2. Which of the following is a potential adverse effect of intubation and positive-pressure ventilation?

a. Decreased mean intrathoracic pressure
b. Decreased ventilation/perfusion ratio
c. Increased cardiac output
d. Increased work of breathing

Answer: d. Positive-pressure ventilation (PPV) is associated with several complications. Some of these can quickly become life-threatening. This reality underscores the importance of familiarization with the common problems that arise as a result of PPV. Most complications result from changes in thoracic physiology when positive pressure is present for part or all of the respiratory cycle. Potential adverse effects of PPV include an increased work of breathing because of asynchrony or improperly set triggers, an increase in intrathoracic pressure,

decreased venous return to the heart and decreased cardiac output, an increased ventilation/perfusion ratio, air trapping and intrinsic positive end-expiratory pressure, barotrauma, decreased renal blood flow and glomerular filtration rate with fluid retention, nosocomial infections of the lungs and sinuses, respiratory alkalosis, and agitation and increased respiratory distress.

3. What is the primary physiologic effect of applying positive end-expiratory pressure (PEEP) during mechanical ventilation?
   - **a.** Decrease cardiac output
   - **b.** Decrease intrapulmonary shunting
   - **c.** Decrease ventilation/perfusion mismatch
   - **d.** Increase functional residual capacity (FRC)

Answer: d. Although all of these effects can be attributed to the application of PEEP, its primary physiologic effect is to increase FRC by maintaining patency of injured or flooded alveoli that would otherwise collapse at the end of exhalation. Increasing the FRC may improve both oxygenation and lung compliance. PEEP increases Pao_2 at a constant fraction of inspired oxygen (Fio_2) by decreasing intrapulmonary shunting and ventilation/perfusion mismatch. One of the potential adverse effects to PEEP is decreased cardiac output.

4. Regarding a patient who develops acute distress on mechanical ventilation, which of the following is the most accurate?
   - **a.** Accidental extubation is a common cause of increased airway pressure.
   - **b.** Anaphylaxis would cause immediate increases in both peak inspiratory pressure (PIP) and plateau pressure (Pplat).
   - **c.** All patients in distress should be immediately removed from the ventilator and bagged.
   - **d.** Compared to patients with restrictive lung disease, patients with obstructive lung disease and asthma are more likely to decompensate without an appropriate expiratory time.

Answer: d. One of the most life-threatening complications of mechanical ventilation is loss of adequate cardiac output because of elevated intrathoracic pressure from intrinsic PEEP (iPEEP). Intrinsic PEEP can be precipitated by a respiratory rate that is too high, which does not allow patients to fully exhale before the delivery of another breath. Patients with obstructive lung disease such as COPD or acute asthma are particularly sensitive to this phenomenon, also known as "breath stacking." Although patients with restrictive lung disease may develop iPEEP with an inappropriate respiratory rate, this is much more likely to occur in patients with obstructive conditions. If patients are not hemodynamically unstable, they do not need to be removed from the ventilator, and in hemodynamically unstable patients, pneumothorax should only be presumptively treated if removing the patient from the ventilator does not improve the situation. Accidental extubation is a common cause of decreased airway pressures, and although anaphylaxis would cause increases in PIP, it would not typically cause increases in Pplat.

3

Shock

Michael A. Puskarich and Alan E. Jones

KEY CONCEPTS

- Shock can occur with normal arterial blood pressure and not all patients with arterial hypotension have shock.
- A base deficit more negative than –4 mEq/L or a serum lactate level greater than 4.0 mmol/L warrants a presumptive diagnosis of shock.
- Urine output is a reliable index of vital organ perfusion in patients with suspected shock. Normal urine output is 1.0 mL/kg/h. Output less than 0.5 mL/kg/h indicates severe renal hypoperfusion in patients without preexisting disease.
- A combination of a worsening base deficit, increasing lactate level, and low urine output represents persistent or worsening shock.
- Hemorrhagic shock is preferentially treated with blood products, using a balanced transfusion approach of packed red blood cells, fresh frozen plasma, and platelets.
- Early initiation of balanced fluid resuscitation, vasopressor support, and prompt antimicrobial therapy improve outcomes in patients with septic shock.

FOUNDATIONS

Background and Importance

In philosophic terms, shock can be viewed as a transition between life and death. Whether shock results from hemorrhage, sepsis, or cardiac failure, mortality rates exceed 20%. Shock results from the widespread failure of the circulatory system to oxygenate and nourish the body adequately. At the cellular level, shock alters mitochondrial energy transfer and evokes the production and accumulation of toxic chemicals. The emergency clinician identifies shock by linking the qualitative clinical impression, synthesized from the patient's history of present illness, age, health status, and general appearance, to quantitative data, including vital signs, laboratory tests, urine output, and measurements of systemic oxygenation. When the clinical impression and quantitative data suggest widespread organ hypoperfusion, emergent resuscitation is used to restore tissue oxygenation and substrate delivery to prevent deterioration into a vicious cycle of systemic inflammation, organ dysfunction, and death. Anaphylaxis and its treatment are discussed in Chapter 106.

For years, shock has been classified into four broad categories—distributive, hypovolemic, cardiogenic, and obstructive. This basic organization scheme is useful for discussions of pathophysiology and formation of a differential diagnosis. However, for discussions of management, a system based on the requisite treatment response is more clinically useful. Box 3.1 outlines five categories of shock that generally have specific mechanisms and treatments. The epidemiology of shock in the emergency department (ED) is diverse and evolving. Traumatic, cardiogenic, or septic shock are diagnosed in fewer than 3% of ED patients. Our understanding of the metabolic, systemic, and inflammatory responses that occur in all types of shock and the specific pathophysiology of the major causes of shock has led to dramatic increases in the early identification and treatment of these states, with resultant improvement in outcomes.

Anatomy, Physiology, and Pathophysiology

At the subcellular level, shock first affects the mitochondria. Mitochondria function at the lowest oxygen tension in the body, but they consume almost all the oxygen used by the body. More than 95% of aerobic chemical energy comes from mitochondrial combustion of fuel substrates (fats, carbohydrates, ketones). These substrates combine with oxygen and are converted into carbon dioxide and water. Mitochondria have therefore been referred to as the canaries in the coal mine because they are affected first in conditions of inadequate tissue perfusion. When mitochondria have inadequate oxygen, the cell catabolizes fuels to lactate, which accumulates and diffuses into the blood. In the setting of hypoxia, mitochondria are unable to provide sufficient energy to maintain cellular processes and, at a certain point, an irreversible series of intracellular cascades leads to cellular dysfunction, organ failure, and ultimately death.

Specific Causes

Hemorrhagic Shock

Hemorrhagic shock results from a rapid reduction in intravascular blood volume from any cause. Rapid hemorrhage generally causes an increase in the strength of cardiac contraction and heart rate (HR), followed by baroreceptor activation and peripheral vasoconstriction. Typically, an initial slight increase in the diastolic blood pressure (BP) with a narrowing of the pulse pressure progresses to a decrease in ventricular filling and cardiac output, causing a reduction in systolic BP. This response varies considerably with cardiopulmonary status, age, and presence of vasoactive medications. The responses of HR and BP are therefore notoriously variable in hemorrhage, so no firm conclusion can be made at the bedside about the presence, absence, or degree of hemorrhagic shock by simple evaluation of the HR and BP.

Even before the cardiac output begins to decline, blood flow is directed away from noncritical organs and tissues, and their cells produce and release lactic acid. Consequently, acidemia often precedes any significant decrease in cardiac output. However, the blood contains bicarbonate ions that buffer the blood pH, keeping it near neutral, even as lactic acid accumulates. The base deficit—amount of strong base that would have to be added to 1 L of blood to normalize the pH—represents an index of how far the bloodstream has dipped into this reserve. A normal base deficit is more positive than –2 mEq/L. The arterial and venous blood base deficit can become more negative early in hemorrhage, even while blood pH and BP remain normal. The base deficit, therefore, crudely represents the physiologic endpoint that distinguishes trivial blood loss from clinically significant hemorrhage. In

BOX 3.1 Five Categories of Shock According to Primary Treatment of Causes and Problems

Primarily Infusion of Volume

Hemorrhagic shock
- Traumatic
- Gastrointestinal
- Body cavity

Hypovolemia
- Gastrointestinal losses
- Dehydration from insensible losses
- Third-space sequestration from inflammation

Volume Infusion and Vasopressor Support

Septic shock
Anaphylactic shock
Central neurogenic shock
Drug overdose

Improvement in Pump Function by Infusion of Inotropic Support or Reversal of the Cause of Pump Dysfunction

Myocardial ischemia
- Coronary artery thrombosis
- Arterial hypotension with hypoxemia

Cardiomyopathy
- Acute myocarditis
- Chronic diseases of heart muscle (ischemic, diabetic, infiltrative, endocrinologic, congenital)

Cardiac rhythm disturbances
- Atrial fibrillation with rapid ventricular response
- Ventricular tachycardia
- Supraventricular tachycardia

Septic shock with myocardial failure (hypodynamic shock)
Overdose of negative inotropic drug
- Beta blocker
- Calcium channel antagonist

Structural cardiac damage
- Traumatic (e.g., flail mitral valve)
- Ventriculoseptal rupture
- Papillary muscle rupture

Immediate Relief from Obstruction to Cardiac Output

Pulmonary embolism
Cardiac tamponade
Tension pneumothorax
Valvular dysfunction
- Acute thrombosis of prosthetic valve
- Critical aortic stenosis

Congenital heart defects in newborn (e.g., closure of patent ductus arteriosus, with critical aortic coarctation)
Critical idiopathic subaortic stenosis (hypertrophic obstructive cardiomyopathy)

Specific Antidotes Due to Cellular or Mitochondrial Poisons

Carbon monoxide
Methemoglobinemia
Hydrogen sulfide
Cyanide

addition to chemical buffering, the body responds to small reductions in arterial pH by activating brainstem chemoreceptors, which increase minute ventilation, leading to reduced partial pressure of carbon dioxide in the arterial blood ($Paco_2$), providing an additional means of compensating for evolving acidosis.

With progressive blood loss, cardiovascular reflexes can no longer sustain adequate filling of the vasculature, and frank hypotension supervenes. Arterial hypotension is generally and arbitrarily defined as an arterial BP less than 90 mm Hg. Usually coincident with the development of hypotension, the compensatory chemical and respiratory buffering mechanisms become overwhelmed, resulting in acidosis. The hypothalamic-pituitary-adrenomedullary axis is activated, releasing stress hormones and inducing glycogenolysis, lipolysis, and mild hypokalemia. Significant traumatic hemorrhage in otherwise normal ED patients, therefore, will generally cause an arterial lactate concentration greater than 4.0 mmol/L, $Paco_2$ less than 35 mm Hg, mild hyperglycemia (150 to 170 mg/dL), and mild hypokalemia (3.5 to 3.7 mEq/L). Although hemorrhagic hypotension reduces lung perfusion, arterial hypoxemia should not be attributed simply to blood loss, but instead should prompt investigation for aspiration, airway obstruction, alveolar consolidation, or lung injury.

The second phase of organ injury from hemorrhagic shock occurs during resuscitation. The acute phase of hemorrhage initiates the inflammatory cascade, and resuscitation unleashes these volatile inflammatory mediators on the body, inducing organ injury. During resuscitation, neutrophils become more aggressive, binding to the lung endothelium and causing capillary leakage that characterizes acute respiratory distress syndrome (ARDS). Inflammatory cytokines are liberated, causing additional cellular damage and compounded by persistent microischemia in numerous organs due to an imbalance between vasodilation by nitric oxide (NO) and vasoconstriction by endothelins. The liver demonstrates centrilobular injury, demonstrated clinically by elevated transaminase levels, whereas the kidney may manifest acute spasm of the preglomerular arterioles, with resultant acute tubular necrosis. Although necessary with significant hemorrhage, resuscitation may exert greater injury on end-organs than the actual hypotensive insult.

Septic Shock

Septic shock can result from infection with any microbe, although no specific organism is identified in at least half of cases. Lipopolysaccharide (LPS), a component of the outer cell membrane of gram-negative bacteria, contributes to sepsis pathophysiology and is often used to approximate the disease in animal models. However, gram-positive organisms represent the leading cause of sepsis in hospitalized patients, indicating that the pathophysiology of sepsis cannot be explained by the response to LPS alone.

Although historically presented as the archetype of distributive or vasogenic shock, the clinical progression of septic shock is complex and varies over the course of the disease (see Chapter 127). Septic shock causes three primary effects in variable degrees that must be addressed during resuscitation: hypovolemia, cardiovascular depression, and induction of systemic inflammation. First, septic shock produces both relative and absolute hypovolemia, reducing right ventricular filling. Absolute hypovolemia results from gastrointestinal volume loss, tachypnea, sweating, and decreased fluid intake during development of the illness. Further relative hypovolemia results from increasing venous capacitance in conjunction with increased capillary leak, with the resultant loss of intravascular volume into third spaces.

Second, septic shock causes direct myocardial depression. Measurements of cardiac contractility have shown that mechanical function becomes impaired early in the course of septic shock, even in the

hyperdynamic stages prior to the development of decreased ejection fraction, which can be detected using advanced echocardiographic markers such as global longitudinal strain. The cause of this myocardial dysfunction is complex and incompletely understood but is likely caused by a combination of circulating inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β), overproduction of NO by inducible nitric oxide synthase (iNOS), as well as impairment in mitochondrial oxidative phosphorylation.

Finally, widespread systemic inflammation plays a role in the development and persistence of multisystem organ failure in sepsis through microvascular and mitochondrial dysfunction. Similar to hemorrhagic shock, systemic inflammation causes capillary leak in the lung, resulting in ARDS. Similar processes induce kidney and liver dysfunction as well. Despite the importance of inflammation in the pathophysiology of sepsis, clinical trials to date have yet to consistently demonstrate the effectiveness of specific or general anti-inflammatory therapies in mitigating this response. Although steroids continue to suggest potential benefit, clinical trial results are mixed.[1] Rather, the treatment of septic shock relies primarily on the reversal of shock, source control, and supportive care of evolving organ failure.

Cardiogenic Shock

Cardiogenic shock results when more than 40% of the myocardium becomes dysfunctional from ischemia, inflammation, toxins, or immune injury. Otherwise, cardiogenic shock essentially produces the same circulatory and metabolic alterations as those observed with hemorrhagic shock. Undoubtedly, impaired baseline cardiac function can contribute to the development of shock secondary to infection, hemorrhage, or vasodilatory drug overdose. However, when shock results from a pure cardiac cause, severe left or right ventricular dysfunction will be evident on echocardiography early in the course. Patients with shortness of breath, abnormal cardiac enzymes, ischemia on the EKG, or lacking fever are more likely to have a cardiac etiology of their shock.[2]

Neurogenic Shock

Neurogenic shock results from interrupted sympathetic and parasympathetic input from the spinal cord to the heart and peripheral vasculature, typically resulting from acute traumatic injury. Traditionally, it has been described as peripheral vasodilation in conjunction with bradycardia. However, ED patients with shock from acute spinal injury actually manifest a range of HRs and peripheral vascular resistance, most likely due to variable location of injury and the balance between disrupted efferent sympathetic and parasympathetic tone. As a result, no single presentation adequately summarizes patients with neurogenic shock. It is likely that the downstream pathophysiologic consequences of persistently impaired perfusion mimic those of cardiogenic and hemorrhagic shock.

MANAGEMENT

Decision Making

Patients presenting to the ED in shock frequently have no obvious cause on initial presentation, requiring timely assessment and treatment, sometimes before identifying the etiology. Rapid recognition of shock requires the integration of information from the immediate history and physical examination and is strongly supported by the presence of a worsening base deficit or lactic acidosis. In general, patients with shock exhibit a stress response; they are ill-appearing, asthenic, pale, often sweating, usually tachypneic, and often have a weak and rapid pulse (Box 3.2).

In all patients with shock, HR, BP, and oxyhemoglobin saturation should be continuously monitored. HR can be normal or low in shock and BP initially can be normal because of compensatory adrenergic reflexes. Noninvasive measurement of BP may be inaccurate in severe hypotensive states. Insertion of an arterial pressure monitoring line improves the ability to monitor the dynamic response to therapy, which is particularly important if vasoactive medications are administered, and should be placed if noninvasive measurements are unreliable or inconsistent. BP and HR correlate poorly with the cardiac index (CI) in shock and often underestimate the severity of systemic hypoperfusion. Moreover, children with hypovolemic shock frequently demonstrate a normal BP until they rapidly deteriorate.

BOX 3.2 Empirical Criteria for Diagnosis of Shock

- Ill appearance or altered mental status
- Heart rate >100 beats/min
- Respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg
- Arterial base deficit <–4 mEq/L or lactate level >4 mM/L
- Urine output <0.5 mL/kg/h
- Arterial hypotension >30 min duration, continuous

Regardless of cause, majority should be met in patients with shock.

Beyond vital signs, an assessment of end-organ perfusion can provide additional evidence of shock and a gauge of response to treatment. Urine output provides an excellent indicator of vital organ perfusion and is available with insertion of a Foley catheter. Measurement of urine output, however, requires 30 to 60 minutes for accurate determination of whether output is normal (>1.0 mL/kg/h), reduced (0.5 to 1.0 mL/kg/h), or severely reduced (<0.5 mL/kg/h), and is of limited use in patients with preexisting renal disease. Confusion or altered mental status can be an indicator of decreased cerebral perfusion, but its usefulness is limited in the setting of preexisting dementia or the setting of prescription or recreational drug use. Impaired liver or coagulation system responses are often not clinically evident but can be identified via blood tests. Generally, these organs are slow to respond to treatment, limiting the usefulness of their evaluation in the ED, except for providing ancillary evidence of end-organ injury.

More useful is real-time, arterial or venous lactate concentration and the base deficit. Both provide an accurate assessment of global perfusion and are strongly predictive of patient outcomes. A lactate concentration greater than 4.0 mM or base deficit more negative than −4 mEq/L are associated with circulatory insufficiency severe enough to cause subsequent multiple organ failure. A downward trend of the serum lactate concentration or upward trend of the base deficit, with correspondingly improving vital signs and urine output, reliably gauge the adequacy of resuscitation and prognosis in shock from any cause. A rising lactate concentration, refractory hypotension, or worsening base deficit despite ongoing resuscitation suggests the need for more intensive measures.

Once the diagnosis of shock has been made, the next step is to consider the cause of the shock. Fig. 3.1 shows a potential sequence of decisions to help arrive at a diagnosis in a patient with undifferentiated shock.

The history, vital signs, and physical examination documented by prehospital providers can be useful in ED evaluation and management. Patients with prehospital hypotension, whether of medical or traumatic origin, have up to a fourfold higher in-hospital mortality rate than patients without hypotension, so these values should not be discounted. On physical examination, dry mucous membranes suggest dehydration, whereas jugular venous distention suggests congestive cardiac failure, severe valvular abnormality, or right ventricular strain from pulmonary embolism (PE). Muffled heart sounds with

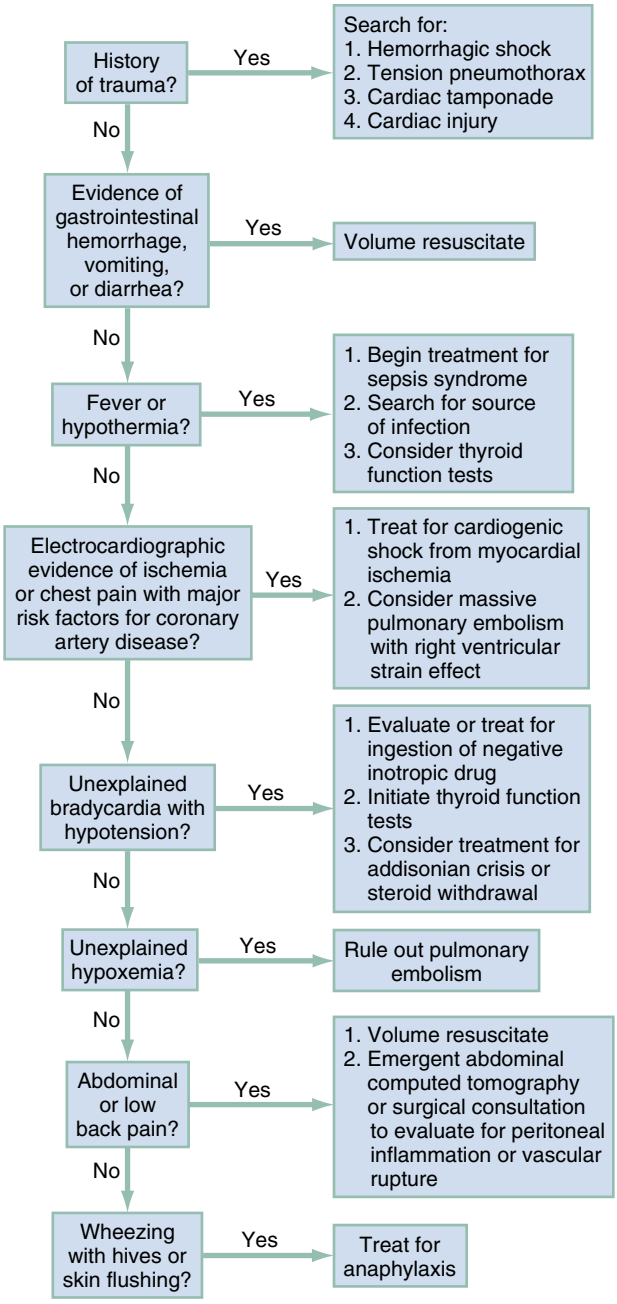

Fig. 3.1 Flow Diagram to Classify Undifferentiated Shock.

jugular venous distention suggest cardiac tamponade, whereas a loud, machine-like, systolic murmur indicates acute rupture of a papillary muscle or interventricular septum. Diffuse rhonchi suggest bronchospasm, cardiac failure, or pneumonia. Abdominal tenderness may indicate peritonitis, intestinal perforation, or occult trauma. The presence of melanic stool on rectal examination indicates gastrointestinal hemorrhage. The neurologic examination documents responsiveness, cognition, and the presence of any focal deficits and can be a means of clinically assessing end-organ perfusion. In children, documentation should include response to parents, appropriateness of crying, symmetry of grimace, symmetry of extremity movements, and motor tone.

Laboratory, radiographic, and other ancillary data can be useful to assess tissue and vital organ perfusion, injury from trauma, the source of infection with sepsis, or the cause of cardiac failure. Chest radiography, electrocardiography, finger stick glucose measurement, complete blood count (CBC), urinalysis, serum electrolyte levels, and kidney and liver function tests should be obtained for most patients with suspected shock. Arterial blood gas determination provides the base deficit and allows correlation of arterial gas tensions (Pao_2 and $Paco_2$) with those measured by pulse oximetry and capnography. Venous or arterial lactate level measurement is performed as early as possible in patients with suspected shock. If the peripheral venous lactate level is used, the effect of time, storage temperature, and tourniquet use have no significant effect if the measurement is done within 15 minutes after the sample was obtained.

Cardiac and abdominal bedside ultrasound scanning can screen for inadequate central venous volume, occult hemoperitoneum, abdominal aortic aneurysm, left ventricular failure, right ventricular dilation or septal bowing, cardiac tamponade, or the presence of a pneumothorax or hemothorax (see Chapter e3). A systematic ultrasound protocol can significantly improve the emergency clinician's ability to accurately diagnose the cause of undifferentiated shock in ED patients, while the finding of hyperdynamic left ventricular function in patients with undifferentiated shock strongly suggests sepsis.[3]

Consensus definitions of shock show the spectrum of hypoperfusion for the following three common causes of shock (Box 3.3):

1. *Hemorrhagic shock.* The American College of Surgeons has divided hemorrhagic shock into four stages, depending on the severity of blood loss and physiologic response to this loss. However, such arbitrary divisions are of little value and are not accurate reflections of degree of hemorrhage in clinical practice. A more useful approach defines hemorrhagic shock as being present when systemic hypoperfusion manifests as lactic acidosis or increasing base deficit with concomitant organ dysfunction.
2. *Septic shock.* International consensus definitions no longer incorporate the systemic inflammatory response syndrome (SIRS), but

BOX 3.3 Definitions and Criteria for Septic, Hemorrhagic, and Cardiogenic Shock

Septic Shock

Sepsis—Suspected or confirmed infection with a new or increased Sequential Organ Failure Assessment (SOFA) score of 2 from baseline (see Table 3.1)

Septic shock—Sepsis plus hypotension requiring vasopressors after fluid loading plus lactate >2 mmol/L (Patients requiring vasopressors with a normal lactate should still be treated as having shock)

Hemorrhagic Shock

Simple Hemorrhage

Suspected bleeding with pulse rate <100 beats/min, normal respiratory rate, normal blood pressure, and normal base deficit

Hemorrhage with Hypoperfusion

Suspected bleeding with base deficit <–4 mEq/L *or* persistent pulse rate >100 beats/min

Hemorrhagic Shock

Suspected bleeding, with at least four criteria listed in Box 3.2

Cardiogenic Shock

Cardiac Failure

Clinical evidence of impaired forward flow of the heart, including presence of dyspnea, tachycardia, pulmonary edema, peripheral edema, and/or cyanosis

Cardiogenic Shock

Cardiac failure plus four criteria listed in Box 3.2

TABLE 3.1 Calculation of Sequential Organ Failure Assessment Score

	0	1	2	3	4
Respiratory (PaO_2/FiO_2 ratio)	>400	301–400	201–300	101–200	≤100
Cardiovascular	Mean arterial pressure >70 mm Hg	Mean arterial pressure <70 mm Hg without vasopressor	Dopamine ≤5 mcg/kg/min or any dose of dobutamine	Dopamine >5 mcg/kg/min or norepinephrine ≤0.1 mcg/kg/min or epinephrine ≤0.1 mcg/kg/min	Norepinephrine >0.1 mcg/kg/min or epinephrine >0.1 mcg/kg/min or Any dose of vasopressin
Coagulation (platelet count; 10^9/L)	>150	100–149	50–99	20–49	<20
Renal (Creatinine; mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5
Liver (Total Bilirubin; mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Neurologic (Glasgow Coma Scale)	15	13–14	10–12	6–9	<6

dL, Deciliter; *FiO_2*, fraction of inspired oxygen; *kg*, kilograms; *mcg*, micrograms; *mg*, milligrams; *min*, minute; *mm Hg*, millimeters of mercury; *PaO_2*, Arterial partial pressure of oxygen.

BOX 3.4 Variables Indicating Tissue Hypoperfusion

Hypotension
Tachycardia
Low cardiac output
Dusky or mottled skin
Delayed capillary refill
Altered mental state
Low urine output
Low central venous oxygen saturation
Elevated lactate level

rather have refocused the condition on the dysfunctional host response to an infection. As such, the most recent Sepsis-3 definitions identify sepsis as the suspicion of infection and a new or increase in the fairly complex Sequential Organ Failure Assessment (SOFA) score (Table 3.1) of 2 or more.[4]

Septic shock, meanwhile, has be redefined as sepsis plus shock requiring vasopressors and a lactate level greater than 2 mmol/L. Patients not meeting Sepsis-3 definitions still exhibit a nontrivial mortality rate, and should still undergo careful evaluation and prompt treatment.[5] Despite this new definition, in the United States the Centers for Medicare and Medicaid Services (CMS) still uses the 2001 definitions of severe sepsis, defined as 2 or more SIRS criteria plus evidence of end-organ dysfunction.[6] While SIRS often precedes shock, the nonspecific criteria for SIRS are found in a large variety of conditions, many of which are benign, so the clinical context is vital to understanding the significance of these physiologic variations. Regardless of the definition, initiation of treatment for empirically diagnosed sepsis should not await the onset of hypotension where possible. Incorporating an indicator of tissue hypoperfusion (Box 3.4) into the clinical assessment may improve identification of hypoperfusion, particularly in subtle cases.

3. *Cardiogenic shock.* Cardiogenic shock should be thought to be present whenever cardiac failure (ischemic, toxic, or obstructive) causes systemic hypoperfusion that manifests as lactic acidosis with organ dysfunction.

Box 3.5 presents the general treatment approach for these three common causes of shock.

BOX 3.5 Clinical Management Guidelines for Three Common Causes of Shock

Hemorrhagic Shock
- Ensure adequate ventilation and oxygenation.
- Provide immediate control of hemorrhage, when possible (e.g., traction for long bone fractures, direct pressure, REBOA), and obtain urgent consultation as indicated for uncontrollable hemorrhage.
- Initiate judicious infusion of isotonic crystalloid solution (10–20 mL/kg).
- With evidence of poor organ perfusion and 30-min anticipated delay to hemorrhage control, begin packed red blood cell (PRBC) infusion (5–10 mL/kg).
- With suspected massive hemorrhage, immediate PRBC transfusion may be preferable as the initial resuscitation fluid, with balanced transfusions of PRBCs, fresh frozen plasma, and platelets.
- Treat coincident dysrhythmias.

Cardiogenic Shock
- Ameliorate increased work of breathing; provide oxygen and positive end-expiratory pressure (PEEP) for pulmonary edema.
- Begin vasopressor or inotropic support; norepinephrine (0.5 mcg/min) and dobutamine (5 mcg/kg/min) are common empirical agents.
- Seek to reverse the insult (e.g., thrombolysis, percutaneous transluminal angioplasty).
- Consider intraaortic balloon pump counterpulsation for refractory shock.

Septic Shock
- Ensure adequate oxygenation; remove work of breathing.
- Administer 30 mL of crystalloid/kg and titrate infusion based on dynamic indices, volume responsiveness, and/or urine output.
- Begin antimicrobial therapy; attempt surgical drainage or debridement.
- Begin PRBC infusion for hemoglobin level <7 g/dL.
- If volume restoration fails to improve organ perfusion, begin vasopressor support with norepinephrine, infused at 0.5 mcg/min.

PRBCs, Packed red blood cells; *REBOA*, resuscitative endovascular balloon occlusion of the aorta.

Monitoring Perfusion Status and Obtaining Intravenous Access

Patients with cardiac failure or renal failure may benefit from closer measurement of dynamic variables of fluid responsiveness that can be measured from an arterial line (e.g., stroke volume variation or

stroke volume index) or a central venous line (central venous pressure [CVP]). A triple-lumen catheter allows for accurate measurement of the CVP, although the clinical utility of these measurements has been debated. However, a triple-lumen catheter can be useful in patients with poor peripheral access as it allows for safe infusion of vasopressors in hypotensive patients unresponsive to an initial fluid bolus, as well as simultaneous infusion of intravenous (IV) fluids and antibiotics when IV access is limited. In children, a 3- or 5-Fr bilumen catheter can be placed in the femoral vein with few complications.

If unable to attain adequate peripheral or central venous access rapidly in patients with shock, intraosseous (IO) access should be established, because it is easy and can provide a temporary method of administering fluid resuscitation and medications to adults and children. In situations where both central venous access and IO access are unavailable, but the patient remains in shock, vasoactive medications should be given through a large-gauge (18g or larger) peripheral catheter at the level of the antecubital fossa or more proximally.

If vasoactive medications are administered, additional peripheral IV catheters are required for infusion of crystalloid and other treatments. Many patients with renal disease or cancer often have indwelling catheters in place. In patients with empirical criteria for shock, this catheter should be used for IV access, unless satisfactory access has already been established at other anatomic sites. In EDs where the standard practice is not to use these ports at the request of other clinicians, a specific hospital policy and training session should be developed to make an exception in the case of shock. In general, the risk of the failure to administer fluids and vasoactive agents rapidly outweighs considerations about preservation of the line for future therapy.

Quantitative Resuscitation

Quantitative resuscitation, also called goal-directed therapy, goal-oriented resuscitation, or hemodynamic optimization, was first described in 1988 and refers to the practice of resuscitating patients to predefined physiologic endpoints (i.e., CVP, central venous oxygen saturations) indicating that systemic perfusion and vital organ function have been restored. In the ED, routine use of central venous monitoring for patients with septic shock does not improve outcomes compared to usual care. Therefore, a central line is typically placed when there is lack of adequate peripheral access or anticipated use of high-dose vasopressor agents.

Over the last 3 decades, many studies have evaluated the efficacy of a quantitative approach to shock. In such an approach, patients are resuscitated early, within the first 6 hours, to achieve normalization of markers of volume status, perfusion, and adequate oxygen delivery. The first description of an ED-based quantitative resuscitation strategy targeted specific volume, perfusion, and oxygen delivery endpoints and was termed *early goal-directed therapy* (EGDT). As mentioned previously, external validation in three large multicenter trials did not demonstrate a mortality advantage for patients receiving EGDT compared to modern usual care of shock. Patients in these studies received 2 to 4 L early volume resuscitation and relatively prompt antibiotic administration, suggesting that early recognition and initiation of fluid and antibiotic therapy, in conjunction with close monitoring and thoughtful care, may be more important than the use of invasive measurements to attain the specific resuscitation goals suggested by earlier studies.

Given these findings, the importance of specific quantitative targets for the resuscitation of ED septic shock is unproven. For complex patients for whom the physician is unclear as to the adequacy of oxygen delivery, it is recommended to use one of two readily available clinical methods, central venous oxygen saturation or lactate clearance. Central venous oxygen saturation drawn from the central circulation (via a triple lumen catheter) was a key component of EGDT and has been used as an indicator of the ratio of oxygen delivery to oxygen consumption. Central access is time-consuming and invasive, therefore, this approach is rarely taken in the ED anymore.

Alternatively, lactate clearance refers to serial measurements of the venous or arterial lactate level. Lactate clearance has been shown to be equivalent to central venous oxygen saturation as an endpoint of early septic shock resuscitation, though it has not been systematically studied in other forms of shock. Lactate clearance measurements are easily obtained from peripheral venous blood and therefore represent a simpler and preferred endpoint of resuscitation. If the lactate concentration has not decreased by 10% to 20% 2 hours after resuscitation has begun, additional steps are undertaken to improve systemic perfusion.

Pharmacology

Volume Replacement

Most patients with shock can be fully resuscitated with peripheral venous access established with at least two 18-gauge catheters. The goal in volume replacement is slightly elevated left ventricular end-diastolic volume, which is difficult to measure in the ED. Historically, CVP has been used to estimate right ventricular filling pressure and has been used in some quantitative resuscitation algorithms. CVP does not accurately reflect left ventricular end-diastolic volume, and poorly predicts the hemodynamic response to a fluid bolus. Thus, fluid resuscitation should not be based solely on CVP. A better approach involves the use of clinical response to fluid resuscitation, such as increases in urine output, BP, and decreasing lactate concentrations, either alone or in combination with CVP measurements. In patients for whom fluid resuscitation may be associated with higher risk of harm (e.g., severe systolic heart failure, dialysis-dependent renal failure), the use of dynamic variables of fluid responsiveness that can be measured from an arterial line (e.g., stroke volume variation, stroke volume index, passive straight leg raise) may be beneficial over empirical fluid boluses, but their use in the ED to guide therapy has not been sufficiently studied to recommend routinely.

Crystalloids. Standard treatment for hemorrhagic shock historically consisted of rapidly infusing several liters of isotonic crystalloid in adults or three successive 20-mL/kg boluses in children. Some studies have endorsed the concept of delayed resuscitation or hypotensive resuscitation for hemorrhagic shock (see Chapter 32), although recent consensus statements have come out against this practice and favor early transfusion and minimization of hypotension.[7]

Recent data suggest balanced isotonic crystalloids (predominantly lactated Ringers) decrease the risk of acute kidney injury in admitted ED patients, while treatment of patients in shock with balanced fluids in the intensive care unit decreases the combination of renal failure and death.[8] Therefore, balanced crystalloids are recommended once a patient is identified as having shock, if available, and in the absence of competing priorities (e.g., medication incompatibility with limited intravenous access). Initial volume replacement consists of the rapid infusion of 20 to 25 mL of isotonic crystalloid per kilogram, though these numbers represent conventional volumes utilized and clear evidence for the superiority of a specific volume of crystalloid bolus is lacking. More rapid initiation of fluid resuscitation may be associated with improved patient outcomes, reiterating the importance of early identification and treatment of shock.[9]

Colloids and hypertonic saline. Colloids offer the theoretical advantage of a high osmotic pressure, which should help maintain normal intravascular volume. Colloids, including albumin, have been used in patients with hemorrhage, but at a considerable increase in cost and without effect on morbidity or mortality. Initial resuscitation fluid treatment with hypertonic saline or hypertonic saline and dextran, compared with normal saline, does not decrease mortality in studies to date.[10]

In the setting of septic shock, initial fluid resuscitation should consist of serial boluses of IV isotonic crystalloid as long as the patient continues to demonstrate a positive hemodynamic response to fluid loading, and the majority of ED patients are initially volume responsive.[11] Persistent hypotension, despite 30 mL/kg of IV fluid, indicates the need to add vasopressors to the resuscitation (see below). If patients require large volumes of crystalloid (>4 L), we recommend adding 5- to 10-mL/kg boluses of a natural colloid (e.g., albumin), rather than additional isotonic crystalloid alone, until further volume fails to improve hemodynamics. We do not recommend the use of synthetic colloids, such as hydroxyethyl hetastarch, which are associated with a higher risk of renal failure. The infusion of hemoglobin-based blood substitutes as alternatives to packed red blood cells (PRBCs) for the resuscitation of hemorrhagic shock has been extensively studied and is associated with significant increased risk of death and myocardial infarction; we recommend against their use.

Blood products. In the setting of hemorrhage *or* a critically low hemoglobin level (<7 g/dL), we recommend transfusion of PRBCs (1 to 2 units in adults or 5 to 10 mL/kg in children) if criteria for shock persist despite crystalloid infusion. Fully crossmatched blood is safest and is always preferable unless the patient's need is considered sufficiently urgent to justify the use of type-specific or even uncrossmatched blood. Use of the latter is generally confined to patients with hemorrhagic shock with persistent, severe, arterial hypotension and massive or uncontrolled hemorrhage. O-negative blood is used in women of childbearing age, and O-positive blood is used in all others (see Chapter 108).

If patients require more than 2 units of PRBCs for hemorrhage, we recommend a balanced resuscitation using PRBCs, fresh-frozen plasma, and platelets in a 1:1:1 ratio, which is associated with better hemostasis and lower death due to exsanguination by 24 hours. We recommend transfusion of PRBCs when hemoglobin levels are less than 7 g/dL in patients with other forms of shock unless specific contraindications exist or patients refuse transfusion.

Vasopressors

The primary goal of vasopressor support is to increase cardiac output and oxygen delivery to vital organs when crystalloid resuscitation alone is inadequate. To reduce the potential for limb damage from extravasation from a peripheral IV injection, vasoactive medications are optimally administered through a central venous catheter, although this is not always feasible in the acute setting. In the setting of hemorrhage, vasopressors represent a purely ancillary means of supporting BP and their use is associated with an increased risk of death, so focus should remain on administration of blood products and control of ongoing bleeding as the primary means of reversing shock.[12]

Patients with septic shock who remain hypotensive after a 30-mL/kg fluid bolus generally require vasopressor support. Norepinephrine is the vasopressor of choice for correction of hypotension in septic shock. In patients who remain in shock after initial crystalloid boluses, norepinephrine should be initiated at a rate of 0.05 mcg/kg/min, or 3 to 5 mcg/min for most adult patients, and titrated at 3- to 5-minute intervals until the mean arterial pressure is greater than 65 mm Hg. There is no clear data to suggest higher BP goals improve outcomes, even in patients with preexisting hypertension,[13] and there are no data regarding an absolute maximum dose. Vasopressin may be added as a second vasopressor agent, be initiated at 0.03 to 0.04 units/min, but there are no data that vasopressin alters outcomes. Vasopressin or phenylephrine can be a useful adjunct or alternative agent if the patient develops a tachydysrhythmia (e.g., atrial fibrillation with rapid ventricular response), to improve both HR and cardiac output. Angiotensin II represents a newly FDA approved vasopressor, but there is insufficient evidence to recommend its routine use at this time.[14]

Following vasopressor initiation, particularly in patients who require high or rapid upward titration of the vasopressor dose, patients should be reassessed for their responsiveness to additional fluid boluses through the use of dynamic variables or empirical 500-mL boluses, with careful attention to the clinical response. Vasopressor support, along with crystalloid therapy, is continued until the patient can maintain the goal mean arterial pressure without vasopressor support, which can be tested at the bedside by weaning the vasopressor agent, such as decreasing norepinephrine at a rate of 2 to 3 mcg/min every 5 to 10 minutes.

Patients with neurogenic shock may need some combination of increased HR, increased contractility, and vasoconstriction. As such, norepinephrine represents a reasonable first choice, although unlike in sepsis, studies have not demonstrated superiority of one vasopressor over another. Phenylephrine may be used if the hypotension appears to be purely a result of peripheral vasodilation or the patient develops a tachydysrhythmia from norepinephrine.

Recent data suggest epinephrine, alone or with other agents, is associated with an increased risk of death in cardiogenic shock.[15] As such, norepinephrine or inotropes are preferred first-line pharmacologic agents for cardiogenic shock.[16]

Inotropes

Dobutamine may be used with norepinephrine to increase cardiac output and maintain adequate oxygen delivery in both cardiogenic and septic shock. In the setting of cardiogenic shock, indications for dobutamine may include some combination of hypotension, cool extremities, poor urine output, and elevated lactate level. In the setting of septic shock, if the lactate level does not decrease at least 10% despite fluid resuscitation and vasopressor administration (see earlier), particularly in the setting of echocardiographic evidence of decreased left ventricular function, dobutamine can be added at a dose of 2 mcg/kg/min and titrated every 5 to 10 minutes, to a maximum of 20 mcg/kg/min. Due to stimulation of vasodilating peripheral beta receptors, dobutamine has the potential to decrease the BP, so careful attention to a patient's individual response is necessary. If simultaneous BP and inotropic support is necessary for septic shock, epinephrine alone, 0.2 mcg/kg/min starting dose, provides similar outcomes and adverse event rates as a combination of norepinephrine plus dobutamine. When norepinephrine is the first pressor initiated and an inotrope is indicated, we recommend the addition of dobutamine, with the ability to titrate each agent individually. However, it is acceptable as an alternative to discontinue the norepinephrine and initiate epinephrine infusion to provide vasopressor and inotropic support via a single agent.

Antimicrobial Therapy

Treatment of the infection with antimicrobial therapy and, where necessary, surgical drainage (see later, "Source Control"), should be instituted as soon as practical in cases of septic shock. Current evidence does not support an absolute time requirement for administration but, when septic shock is the working diagnosis in the ED, we recommend initiation of appropriate antibiotics as soon as practical after the diagnosis is made (see Chapter 127). When there is no focus of infection identified in a patient with presumed septic shock, a semisynthetic penicillin with a β-lactamase inhibitor or fourth generation cephalosporin, in combination with vancomycin, is a rational empirical choice. One such regimen would include piperacillin-tazobactam, 4.5 g IV every 6 hours or cefepime 2 g IV every 8 hours, and vancomycin, 30 mg/kg (maximum dose, 2 g) given every 12 hours, adjusted as appropriate for trough levels and renal failure. Addition of another agent (such as levofloxacin, 750 mg IV every 12 hours) is recommended to provide double

coverage in patients with risk factors for or in areas of high prevalence of multi-drug resistant bacteria, particularly *Enterococcus* and *Pseudomonas* spp. (see Chapter 62). Use of another agent with an alternative mechanism with the intention of increasing bactericidal kill rates and clearances in patients without suspected multi-drug resistant bacteria remains controversial and is not universally recommended.

Patients with neutropenia and sepsis syndrome are at particular risk for progressive sepsis, organ failure, and death. Neutropenia can be suspected in patients who have recently undergone chemotherapy, and these patients often know that they are neutropenic. Antimicrobial administration is particularly urgent for these patients and should occur rapidly after blood cultures are obtained, optimally within the first hour, in parallel with crystalloid administration. Antibiotic considerations for the neutropenic patient are discussed in Chapter 112. Chemotherapy patients with sepsis represent a special challenge because the pathophysiology may be complicated by anemia, thrombocytopenia, dehydration from vomiting, and the effects of adjunctive steroid therapy. Chemotherapy patients often have indwelling catheters, which predispose them to more unusual causes of sepsis, including gram-positive bacteria and fungi.

Corticosteroids

High-dose, short-course corticosteroid therapy in unselected patients with septic shock likely decreases the duration of shock with potential risks of secondary infection and gastrointestinal bleeding. There is no evidence of reduced ICU or in-hospital mortality, but a possible small reduction in mortality at 28 days.[17] Due to the nondefinitive results of steroids trials to date, empiric corticosteroids are not routinely recommended in all ED patients with sepsis. Most current guidelines recommend that low-dose hydrocortisone be administered only to patients receiving chronic steroid replacement and in patients with refractory shock despite adequate fluid and vasopressor support. Corticotropin stimulation testing is no longer considered of value.

Special Cases

Systemic thrombolytic therapy is indicated in patients with shock from PE (see Chapter 74) without contraindications. Specific treatments for shock due to poisoning with vasoactive medications and other toxins are discussed in the relevant chapters in this text.

Devices and Procedures

Ventilation

Rapid sequence intubation is the preferred method of airway control in most patients with refractory shock (see Chapter 1). Tissue hypoperfusion leads to increasing fatigue of the muscles of respiration, and respiratory failure commonly supervenes in patients with persistent shock. Intubation prevents aspiration, increases oxygenation, treats acute respiratory failure, provides initial treatment for metabolic or hypercarbic acidemia, and protects the patient who will be sent to an uncontrolled environment for testing. Intubation reduces the work of breathing, which, in the patient with hypoperfusion, further exacerbates lactic acidemia. Strenuous use of accessory respiratory muscles can increase oxygen consumption by 50% to 100% and decrease cerebral blood flow by 50%. More importantly, if the patient has increased airway resistance (e.g., bronchospasm with anaphylaxis) or a decrease in lung compliance (e.g., pulmonary edema, ARDS), a more negative intrathoracic pressure must be generated to fill the lungs with each inspiration. The greater suction effect is also exerted on the left ventricle, impeding its ability to eject and increasing functional afterload. Positive-pressure ventilation removes this impedance and can improve ventricular function and cardiac output up to 30%. The use of etomidate for airway management in patients with septic shock is discussed in Chapter 1.

Source Control

Controlling hemorrhage remains the cornerstone of treating hemorrhagic shock, and evidence continues to support immediate surgery when direct vascular control cannot otherwise be obtained (see Chapters 32 and 38). In the setting of traumatic shock from an injury distal to the renal arteries without evidence of aortic injury, Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a more recent technology that can maintain cardiac and cerebral perfusion while definitive source control is obtained through the insertion of an intra-aortic balloon via an arterial puncture. However, additional training is required, and it is not universally available.[18] Gastrointestinal bleeding may require urgent endoscopy, often in the ED or ICU, and aortic rupture requires emergency consultation by a vascular surgeon. In septic shock related to an abscess, aggressive infection (e.g., necrotizing fasciitis or perinephric abscess; see Chapter 126), or wound (e.g., toxic shock syndrome; see Chapter 126), removal of the infectious stimulus through surgical intervention should proceed as soon as practical.

Mechanical Circulatory Support and Percutaneous Coronary Intervention

The use of mechanical circulatory support and percutaneous coronary intervention in selected patients with cardiogenic shock or acute cardiovascular emergencies is discussed in Chapters 64 and 67.

Pericardiocentesis and Thrombectomy

Shock caused by mechanical obstruction can be managed by direct intervention. Large, acute pericardial effusions should be managed with pericardiocentesis. Tension pneumothorax or hemothorax should be treated with tube thoracostomy. Surgical thrombectomy for massive PE is performed rarely. Direct thrombolysis via interventional radiology is gaining acceptance as a therapeutic option in patients with shock, particularly if systemic thrombolytics are contraindicated.

OUTCOMES

Outcomes for patients with shock vary with the underlying cause of the shock state and the premorbid or comorbid status of the patient. Outcomes have progressively improved, with emphasis on early diagnosis and treatment. In general, persistent hypotension (refractory shock) is associated with worse outcomes. Patients meeting consensus definitions for hemorrhagic shock have a mortality rate of about 20%, whereas this exceeds 40% in septic and cardiogenic shock.

The references for this chapter are available online at ExpertConsult.com.

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CHAPTER 3: QUESTIONS AND ANSWERS

1. A 72-year-old male presents with crushing substernal chest pain with associated diaphoresis starting 2 hours prior to arrival. Blood pressure is 72/50. ECG shows anterior ST elevation myocardial infarction. Lungs demonstrate diffuse rales, and chest XR demonstrates bilateral infiltrates consistent with pulmonary edema. Bedside ultrasound demonstrates severely impaired left ventricular function. In addition to arranging for rapid reperfusion with either cardiac catheterization or intravenous thrombolytics, which is the most appropriate initial treatment for his cardiogenic shock?

a. Bolus of 30 mL/kg crystalloid fluid.
b. Initiate epinephrine at 0.1 mcg/kg/min.
c. Initiate norepinephrine at 0.1 mcg/kg/min.
d. Transfer patient for placement of an intraaortic balloon catheter.

Answer: c. Norepinephrine (or inotropes such as dobutamine) are first-line agents for cardiogenic shock. Crystalloid fluids should not be administrated to patients with cardiogenic shock and pulmonary edema. Epinephrine carries an increased risk of tachydysrhythmias and no better outcomes than norepinephrine or inotropes in cardiogenic shock. While this patient might benefit from an intraaortic balloon pump, treatment of his shock should not be delayed through transfer.

2. A 56-year-old female presents with fever, dyspnea, and productive cough. Heart rate is 122, respiratory rate is 24, and blood pressure is 82/46. Which of the following is the most appropriate choice for initial fluid resuscitation?

a. Lactated Ringers.
b. Blood products.
c. Hydroxyethyl starch (HES).
d. Normal Saline.

Answer: a. Balanced crystalloids are the preferred choice of fluid for patients with septic shock. Blood products may be indicated for patients with a hemoglobin greater than 7 mg/dL. Synthetic colloids such as HES cause renal failure and should be avoided. Hypertonic saline has not been proven to improve outcomes in sepsis. Normal saline can cause a hyperchloremic metabolic acidosis and acute kidney injury, particularly using large volumes.

3. An 18-year-old unrestrained driver is transported to the emergency department (ED) after being thrown from his vehicle during a motor vehicle collision. He was intubated in the field and received an intravascular bolus of 3 L of normal saline before arrival to the ED. His initial Glasgow Coma Score (GCS) is 7, and his blood pressure on arrival is 80/50 mm Hg. Which of the following would be the most appropriate to initiate immediately on arrival to the ED?

a. Dobutamine.
b. Dopamine.
c. Norepinephrine.
d. Packed red blood cell (PRBC) transfusion.

Answer: d. In patients with signs of hemorrhagic shock, immediate PRBC transfusion should be initiated. This assists with volume expansion and oxygen delivery to the brain. Vasopressors and positive inotropes will be of little benefit before volume replacement, and hetastarch has no proven benefit for initial resuscitation in head injury patients.

4

Brain Resuscitation

Craig A. Williamson and William J. Meurer

KEY CONCEPTS

- Neuronal injury is a dynamic process that continues for hours or days after an ischemic insult to the brain.
- Avoid hypotension and hypoperfusion by maintaining a mean arterial pressure greater than 65 mm Hg and a cerebral perfusion pressure of 60 mm Hg.
- Maintain normal oxygen levels or mild hyperoxemia, with a PaO_2 of 80 to 120 mm Hg and oxyhemoglobin saturations in the high 90s. Avoid hypoxemia and significant hyperoxemia.
- Intracranial pressure (ICP) elevation can further exacerbate ischemic brain injury. Initial management should include optimizing patient positioning while providing adequate analgesia and sedation. Management should then be escalated in a stepwise fashion to include hypertonic therapy, deeper sedation and ultimately barbiturates, hypothermia, and surgery as needed.
- Avoid hyperventilation (target $PaCO_2$ of 35 to 40 mm Hg) as it reduces cerebral blood flow. In the event of life-threatening cerebral herniation or significant ICP elevation, therapeutic hyperventilation is appropriate only as a short-term intervention bridging to more definitive therapy (i.e., craniotomy).
- Promptly treat seizures with intravenous (IV) lorazepam. Prophylactic administration of antiepileptic drugs is not recommended. Initiate continuous electroencephalogram (EEG) monitoring if ongoing seizures are a concern.
- Fever is an important mediator of secondary brain injury. Treat temperatures greater than 38°C with acetaminophen.
- Unresponsive survivors of out-of-hospital cardiac arrest should have rapid initiation of targeted temperature management (TTM) in the emergency department and be maintained at a constant target of 33°C–36°C in an ICU setting for 24 h after resuscitation.
- Because withdrawal of life-sustaining treatment due to perceived poor neurological prognosis is the most common cause of death in cardiac arrest survivors, it is important to provide accurate and evidence-based prognostic information to families. The neurological examination is generally an unreliable predictor of outcome until at least 72 h from normothermia.

FOUNDATIONS

Background and Importance

Despite our recognition of the brain's dominant role in determining quality of life, the ability to intervene and reverse neuronal injury remains limited. Consequently, modern brain resuscitation techniques are focused on restoring cerebral homeostasis and mitigating the effects of secondary brain injuries. Hypoxic-ischemic injury following cardiac arrest can be seen as a model of global ischemic disease, and recent advances in understanding its pathophysiologic mechanisms have led to improvements in neurologic outcomes. Although hypoxic-ischemic injury represents a so-called pure form of brain ischemia, its underlying pathology has significant overlap with other cerebral injuries, such as stroke and traumatic brain injury (TBI). Thus, many of the physiologic principles of brain resuscitation following cardiac arrest apply to these conditions. Therefore, this chapter reviews the pathophysiology of ischemic brain injury and discusses therapies for improving neurologic recovery following cardiac arrest and other critical neurologic illnesses in which cerebral ischemia may occur.

Anatomy, Physiology, and Pathophysiology

The human brain consists of 10 billion neurons, each with multiple connections to other cells, totaling an estimated 500 trillion synapses. Although the brain constitutes only 2% of body weight, it receives 15% of the body's cardiac output and accounts for 20% of its overall oxygen use. When the brain is deprived of adequate blood flow, the resulting ischemia is characterized by a bewildering array of interrelated physiologic and cellular responses that ultimately result in neuronal cell death (Fig. 4.1). Although this complex cascade of events can be triggered by periods of ischemia lasting only a few minutes, the resulting neuronal death is usually delayed by hours or days. Furthermore, the biology of cerebral cell death after global cerebral ischemia follows the pattern of delayed cerebral cell death after stroke, TBI, and other forms of hypoxic or toxic brain injury, with slight variations. Increased understanding of the brain's response to injury during the period between insult and neuronal cell death will eventually allow more specific brain resuscitation therapies.

Elevated Intracranial Pressure

Intracranial pressure (ICP) is an essential consideration in ischemic brain injury because cerebral ischemia can directly result in ICP elevation. Failure of oxidative phosphorylation depletes adenosine triphosphate (ATP) stores, resulting in an inability to actively maintain osmotic gradients. Increased intracellular osmolarity leads to water influx and the development of cytotoxic edema, which usually peaks 48 to 72 hours after injury. By decreasing cerebral perfusion pressure (CPP), elevated ICP is also an important contributor to secondary brain injury. This relationship is discussed in further detail as follows; additional information on ICP management is contained in subsequent sections.

To understand the pathophysiology of elevated ICP, note that the skull is a rigid container whose relatively non-compressible contents include the brain (~80%), blood (~10%), and cerebrospinal fluid (CSF; ~10%). According to the Monro-Kellie doctrine, any addition to the volume of one of these components—for example, increased brain volume due to cerebral edema—must be offset by reducing the volume of the other contents or the ICP will rise.

Typically, adaptation to increased intracranial volume is initially accomplished by shifting CSF from the intracranial to spinal subarachnoid compartment. Approximately two-thirds of cerebral blood volume is contained in the cerebral veins and dural sinuses, and this venous capacitance can be reduced to accommodate increased intracranial volume further. Unfortunately, these mechanisms can become quickly exhausted, resulting in decreased compliance and a rapid increase in ICP (Fig. 4.2). This may occur rapidly with acute cerebral injury or slowly with mass lesions such as tumors.

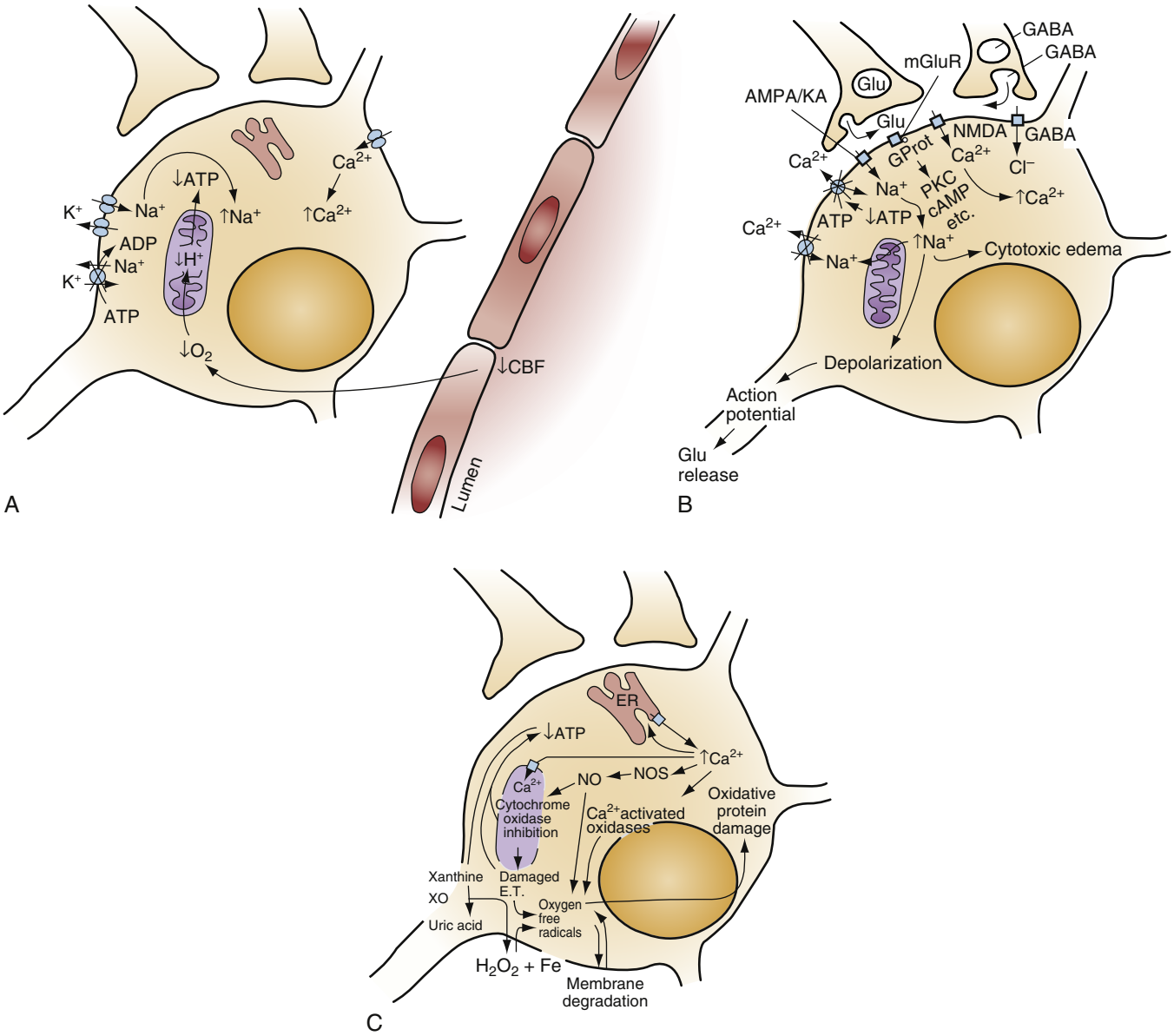

Fig. 4.1 **Synopsis of Events Contributing to Neuron Cell Death Cascade After Ischemia.** (A) Decreased cerebral flow *(CBF)* and arterial oxygen content during ischemia cause decreased adenosine triphosphate *(ATP)* production, failure of ATP-driven ion pump efflux of potassium ions (K^+), and influx of sodium ions (Na^+) and calcium ions (Ca^{2+}) through voltage-gated channels. *ADP,* Adenosine diphosphate. (B) Na^+ influx causes depolarization and glutamate *(Glu)* release, opening Glu receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate *(AMPA)* and kainate *(KA)* channels and exacerbating intracellular Na^+ overload. Increased Na^+ concentration ($[Na^+]i$) leads to cytotoxic edema. Glu-mediated *N*-methyl-D-aspartate *(NMDA)* channels allow intracellular Ca^{2+} overload. Insufficient ATP causes failure of energy-dependent Ca^{2+} pumps, and high $[Na^+]i$ prevents removal of Ca^{2+} by Na^+/Ca^{2+} exchange pumps. γ-Aminobutyric acid *(GABA)* release can attenuate excitatory changes by opening a receptor-gated Cl^-. (C) Increased $[Ca^{2+}]i$ is amplified by calcium-induced release of Ca^{2+} from the endoplasmic reticulum *(ER)*. Mitochondria may be injured attempting to buffer increasing $[Ca^{2+}]i$, resulting in further metabolic failure and diminished ATP. Ca^{2+} activates nitric oxide synthase *(NOS)*, transforming it to nitric oxide *(NO)*, which is amplified by NO activation of NOS. NO contributes to the formation of damaging oxygen free radicals and inhibits mitochondrial cytochrome oxidase function. ATP degradation to xanthine and then uric acid by xanthine oxidase *(XO)* yields hydrogen peroxide (H_2O_2), which reacts with iron to form dangerous oxygen radicals. Oxygen free radicals react with lipids in the cell membrane, which leads to membrane degradation and more free radicals. Oxygen free radicals also can damage proteins.

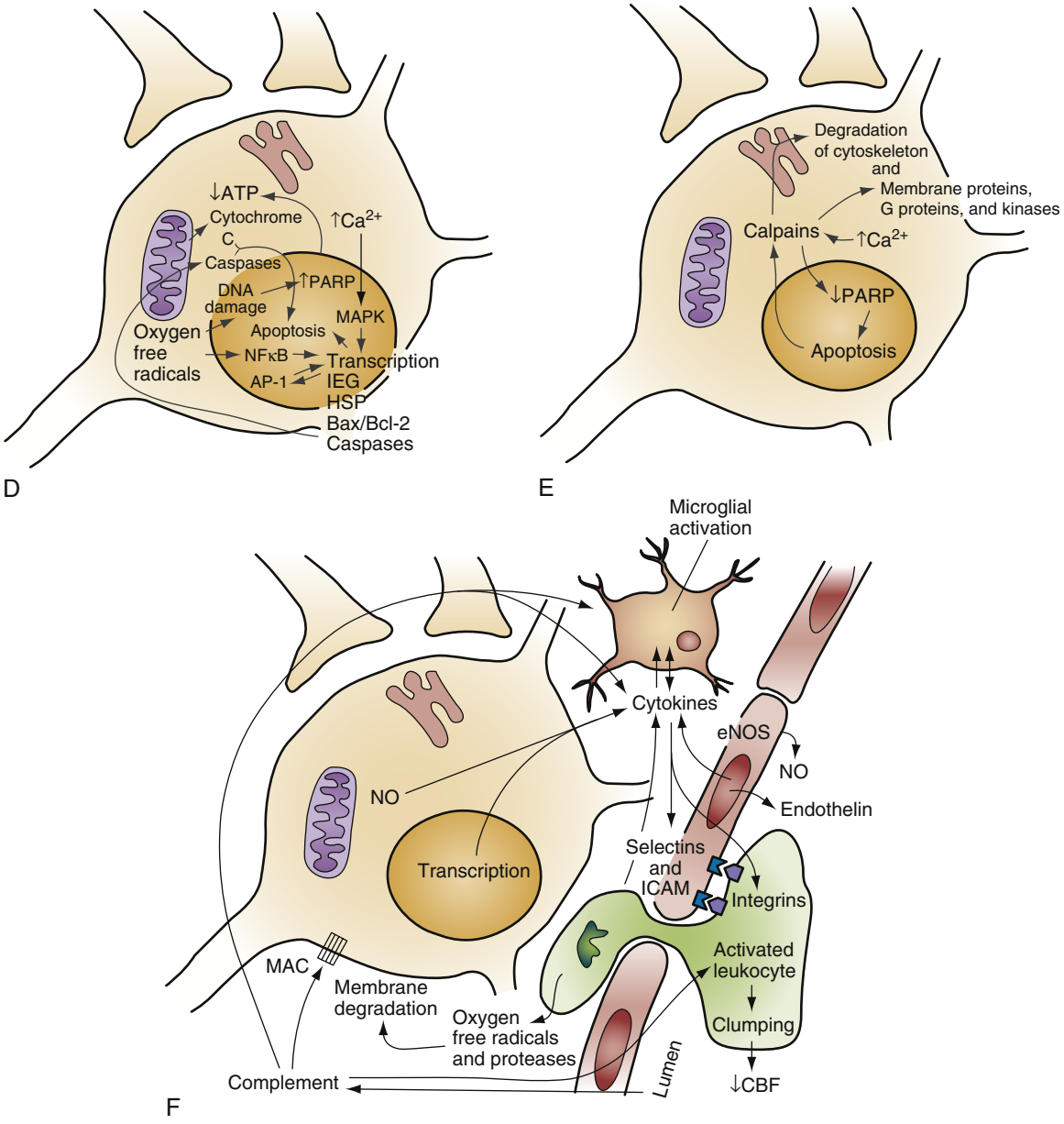

Fig. 4.1 cont'd (D) Ca^{2+} also activates kinase transcription factors, such as mitogen-activated protein kinase *(MAPK)*. Oxygen radicals trigger nuclear factor κB *(NFκB)*, another transcription factor. Many genes, including immediate early genes *(IEGs)*, heat shock protein *(HSP)* genes, genes for caspases, and the *Bax/Bcl-2* systems, are activated. IEG products include AP-1, another transcription factor. Mitochondrial release of cytochrome c, existing and newly formed caspases, and other factors trigger apoptosis. DNA is damaged by oxygen free radicals and by endonucleases formed in apoptosis. DNA damage activates poly(ADP-ribose) polymerase *(PARP)*, which further depletes ATP stores. (E) Ca^{2+} and apoptosis activate calpains, proteases that degrade a variety of structural elements (e.g., cytoskeletal and membrane proteins), signaling elements (e.g., G proteins, kinases), and PARP. (F) Transcription and NO contribute to the neuronal expression of cytokines, chemokines, and growth factors. These intercellular signals activate complement, epithelial cells, leukocytes, and microglia. Complement can amplify chemotactic signals, activate microglia directly, or cause cellular damage by creation of the membrane attack complex *(MAC)*. Leukocyte integrins, epithelial cell selectins, and intercellular adhesion molecules *(ICAMs)* allow demargination. Activated leukocytes cause neuronal injury by releasing potent oxidants and protease. Cerebrovascular resistance may be affected by the epithelial release of NO and endothelin and by leukocyte clumping. *ADP,* Adenosine diphosphate; *$[Ca^{2+}]i$,* Ca^{2+} concentration; *cAMP,* cyclic adenosine monophosphate; *eNOS,* endothelial nitric oxide synthase; *E.T.,* enzyme trafficking; *mGluR,* metabotropic glutamate receptor; *PKC,* protein kinase C.

In its final stages, uncontrolled intracranial hypertension results in downward herniation of the cerebellar tonsils through the foramen magnum, thereby compressing critical cardiorespiratory centers in the medulla. Prior to or concurrently with this, elevated ICP can exacerbate ischemic injury by reducing cerebral blood flow (CBF). CPP is equal to the mean arterial pressure (MAP) minus ICP. As ICP increases, CPP decreases, which is compensated for by cerebral arteriolar vasodilation. Unfortunately, this vasodilation may increase cerebral blood volume, which can additionally increase ICP and further reduce CPP. This vicious cycle is one of the primary inciting

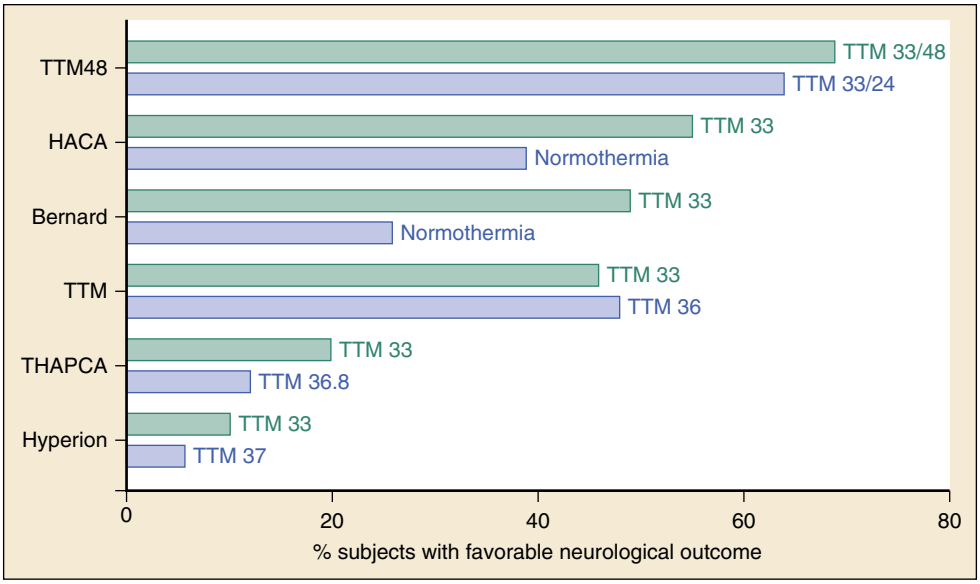

Fig. 4.2 Favorable Neurological Outcomes Across Cardiac Arrest Randomized Trials. Studies of neurologic outcome after out-of-hospital cardiac arrest (OHCA) generally demonstrate better outcomes with 33°C and longer duration of targeted temperature management (TTM). TTM48 demonstrated numerically better outcomes with 48 hours versus 24 hours of cooling but was not powered to detect the difference observed.[7] The 2002 Hypothermia After Cardiac Arrest (HACA) and Bernard trials compared cooling to no temperature management with large treatment effects. The 2013 TTM trial did not demonstrate the superiority of a target of 33°C versus 36°C, although with a median time to bystander CPR of 0 minutes likely enrolled a relatively mildly affected population. The Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial in children with OHCA also demonstrated numerically better outcomes with 33°C. The 2019 HYPERION trial included only non-shockable rhythm patients (and some patients in HYPERION were inpatient arrests), but demonstrated significantly better outcomes with TTM to 33°C.[26]

factors for the prolonged periods of refractory ICP elevation that can occur after global ischemic injury.

MANAGEMENT

Decision Making

Standard medical management of ischemic brain damage involves restoring CBF and preventing secondary insult. Many standard treatments have not been studied in prospective, randomized, controlled trials, but have been supported by clinical experience and limited experimental data. Although proposed and experimental neuroprotectant therapies are generally aimed at specific molecular interventions in the pathophysiology of ischemic brain injuries, as yet none of these have proven effective in clinical trials. In the case of ischemic and other secondary brain injuries following cardiac arrest, the American Heart Association (AHA), the European Resuscitation Council (ERC), and European Society of Intensive Care Medicine (ESICM) published guidelines for post-cardiac arrest care based on the International Consensus on CPR and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR) from the International Liaison Committee on Resuscitation (ILCOR).[1–3] Improvements in post–cardiac arrest care, through an inclusive multisystem approach, can increase the likelihood of meaningful recovery in these patients. However, tremendous disparities in outcomes following cardiac arrest exist, which appear to be driven by substantial variation in processes of care.[4]

In the United States, overall survival to hospital discharge following out-of-hospital cardiac arrest is 12% with three-fourth of those survivors having a favorable neurological outcome, while for in-hospital cardiac arrest, 25% survive to discharge.[5] However, some single-center registries suggest that nearly 50% of patients who are successfully resuscitated from cardiac arrest and receive TTM may achieve a favorable neurological outcome. The majority of patients with primary cardiac arrest enrolled in a recent TTM trial achieved a favorable neurological outcome.[6,7] Implementation of standardized protocols for post-resuscitation care including many or all of the following components have demonstrated increases in survival in patients following cardiac arrest, as well as other conditions where early resuscitation may avoid additional secondary ischemic brain injury.

While families will be most focused on whether their loved one will awaken intact, emergency clinicians must be firm that no historical, exam, imaging, or lab tests available in the emergency department can exclude the possibility of a full recovery. In fact, guidelines recommend waiting at least 72 hours to perform neurological prognostication. Despite this, many cardiac arrest patients have withdrawal of life-sustaining treatment before 72 hours. While families may not want to engage in prolonged intensive care if it is not within the patient's goals of care, the emergency department represents an opportunity to educate families. While there may be appropriate reasons to limit care, such as pre-existing terminal illness or the development of refractory multiple organ failure, families should not immediately limit care due to an assumption that a patient will not wake up. It is important for emergency physicians to temper expectations. Given the inability to predict neurologic prognosis in the first hours to days, it is important that families understand that it takes some time to determine if the brain will recover. Apart from restoring circulation, setting expectations for allowing adequate time and the uncertainty regarding prognosis is where emergency physicians can have the largest impact on increasing survival in this disease.

PHARMACOLOGY

Intracranial Pressure Management

As with other topics discussed in this chapter, successful management of elevated ICP requires a combination of pharmacological

and non-pharmacological interventions deployed in an organized, stepwise fashion. Initial management for all patients with brain injuries at risk of developing elevated ICP should focus on avoiding pain, agitation, and fever. We recommend titrated doses of a hemodynamically stable opioid medication, such as fentanyl 25 to 50 mcg every 5 minutes, as needed. Avoid coughing or ventilator dyssynchrony. This is best accomplished by achieving adequate sedation and analgesia to permit mechanical ventilation, as described in Chapters 2, 151, and 154. Propofol is our sedative agent of choice for this purpose because it decreases cerebral metabolic activity, oxygen demand, and blood flow, and rapidly clears for neurologic assessment. Propofol can cause or contribute to hypotension, which may be avoided by dosage adjustment, but can necessitate starting vasopressors.

Alternatively, dexmedetomidine can also control agitation and promote endotracheal tube tolerance while facilitating frequent neurological examinations. However, dexmedetomidine does not suppress respiratory drive, and therefore, patients may have ventilator dyssynchrony in controlled ventilation. Some patients will not tolerate this agent due to hypotension and bradycardia, and tolerance does develop with long-term use.[8] In refractory cases of intracranial hypertension, induced coma with a barbiturate will further decrease CBF and lower ICP. Pentobarbital is started with a 10 mg/kg loading dose over 30 minutes, followed by a continuous infusion of 1 to 4 mg/kg/h, titrated to achieve electroencephalographic burst suppression. Barbiturate administration is frequently accompanied by hypotension, which often requires vasopressors to maintain adequate CPP, and causes a variety of systemic side effects that should be carefully weighed when initiating treatment. Consideration of barbiturate infusion for severe TBI should simultaneously trigger consideration of a decompressive hemicraniectomy.

Acute spikes in ICP or cerebral herniation syndromes can sometimes be rapidly reversed via osmolar therapy with mannitol or hypertonic saline. Both work by drawing water across an intact blood-brain barrier, thereby lowering ICP. However, the extremely rapid onset of both agents is facilitated by changes in blood viscosity and reductions in cerebral blood volume. Mannitol, 0.25 to 1 g/kg is given every 6 hours, up to a serum osmolality of 320 mOsm/kg. Treating with 30 mL of 23.4% sodium chloride appears to be at least as effective as mannitol at rapidly lowering ICP and reversing herniation, and 30 to 60 mL can be given every 6 hours, up to a maximum serum sodium level of 160 mEq/L. A central line is preferred for safe administration. Hypertonic saline at 3% concentration can also be administered at an initial rate of 30 to 50 mL/hr as a continuous infusion. At present, there are insufficient data to recommend one agent over another, or to determine if continuous infusion or bolus dosing of hypertonic saline is preferred. Because it is a potent diuretic, mannitol is preferred in cases of fluid overload, whereas hypertonic saline can be used as a resuscitative fluid.[9]

Seizure Management

Although the prevention of seizures has not been demonstrated to improve neurologic recovery, seizures can result from global cerebral ischemia and may exacerbate underlying brain injury. Seizure activity can increase brain metabolism by 300% to 400%, worsening the mismatch between oxygen delivery and demand, with greater metabolic failure, neuronal loss and worsened neurologic outcome. When present, prolonged seizures or status epilepticus following cardiac arrest are strongly, although not invariably, associated with a poor neurologic outcome. Non-convulsive status epilepticus has been reported in 12% to 24% of survivors after cardiac arrest; consequently, continuous electroencephalographic monitoring is frequently used in comatose survivors, and we recommend its use for patients who are treated with neuromuscular blockade while receiving therapeutic hypothermia.[10] Electroencephalographic findings have been shown to predict neurologic outcome after cardiac arrest reliably and, in the future, electroencephalographic monitoring may be a core component in prognostication algorithms.[11]

We do not recommend the prophylactic use of anticonvulsant drugs in patients resuscitated from cardiac arrest, but seizures should be quickly and effectively treated. Lorazepam, up to 0.1 mg/kg, with a maximum dose of 4 mg, is the preferred first-line agent to abort seizures and should be followed by continued treatment with an antiepileptic drug. A recent randomized controlled trial suggested that IV loads of fosphenytoin at 20 mg phenytoin equivalents (PE)/kg (max 1500 mg PE), levetiracetam at 60 mg/kg (max 4500 mg), or valproic acid at 40 mg/kg (max 3000 mg) are equally efficacious second-line options.[12] In intracerebral hemorrhage (ICH), the prophylactic use of anticonvulsants has been associated with worse neurologic outcomes, and we concur with current guidelines that do not recommend their routine use.[13] In TBI, prophylaxis with phenytoin reduces early seizures during the first 7 days, but not beyond, and reduction of early seizures has not been shown to improve outcome.[9] Limited data suggest prophylaxis with phenytoin can worsen neurocognitive outcomes, so if prophylaxis is to be used, 7 days of levetiracetam 500 mg bid, adjusted for renal function, is our preferred regimen.[14]

Devices and Techniques

Cardiopulmonary Resuscitation

In the event of cardiac arrest, return of spontaneous circulation is the first priority in cerebral resuscitation. The degree of brain injury after cardiac arrest depends on the duration of complete cerebral ischemia (the downtime, or time before the initiation of cardiopulmonary resuscitation [CPR]) and duration of relative ischemia that occurs during CPR and that may occur from cardiogenic shock preceding or after the period of cardiac arrest. Events occurring after the restoration of flow (e.g., transient hypoxia, hypotension) can exacerbate brain injury in this dynamic and vital early resuscitation period. Extensive evidence on hospital discharge rates and neurologic recovery rates demonstrates that resuscitation success is inversely proportional to cardiac arrest duration. Although duration of arrest generally predicts outcome in the population of patients with sudden cardiac death, it cannot be reliably used to predict the outcome of individual patients. Modern brain resuscitation techniques focus on avoiding further secondary cerebral injury, which also affects outcome. Neurologic outcome of survivors is influenced by patient age, comorbidities, and other individual characteristics.

The efficacy of closed chest CPR in generating adequate cerebral perfusion is somewhat controversial. Cardiac output during optimal standard closed-chest CPR was previously estimated to be only 20% to 30% of normal. However, more recent studies have suggested that higher cardiac outputs are possible and, unquestionably, effective CPR is essential to neurologic recovery after cardiac arrest.

Reperfusion

With cerebrovascular insults due to embolic or thrombotic mechanisms, randomized clinical trials have shown a benefit of revascularization in ischemic stroke. This is discussed in detail in Chapter 87.

Optimizing perfusion and oxygenation. Maintaining cerebral oxygen delivery is a mainstay of therapy after ischemic brain injury. Oxygen delivery requires a sufficiently high CPP, sufficiently low cerebrovascular resistance (CVR), and adequate blood oxygen saturation.

Hypotension can dangerously lower CBF and is associated with worse outcome following cardiac arrest and TBI. Normally, a change in systemic blood pressure triggers corresponding changes in CVR, mediated by cerebral arterial vasodilation or vasoconstriction. This capacity, termed *cerebral autoregulation*, functions to maintain a constant CBF over a wide range of arterial blood pressures. Autoregulation is often lost in the injured brain and, as a result, perfusion of ischemic tissue

becomes passively dependent on CPP. Consequently, hypotension can compromise CBF and result in significant additional brain damage. Therefore, low arterial pressures should be rapidly normalized, with intravascular volume administration and vasopressors used as needed. In the absence of prospective clinical trial data, current recommendations are to maintain a MAP greater than 65 mm Hg and SBP greater than 90 mm Hg[1] for cardiac arrest patients. Although some studies suggest an association between higher blood pressures and improved outcomes, concerns related to disruption of the blood-brain barrier and worsening of vasogenic edema remain, and there is insufficient evidence to recommend inducing hypertension.[3,15]

Blood pressure goals fundamentally differ in ICH, in which elevated blood pressure at presentation is common due to a physiologic pressor response. Hypertension is a known risk factor for hematoma expansion, yet the targeted blood pressure goal in these patients remains controversial due to uncertainty regarding perfusion to the brain tissue surrounding the hematoma (ischemic penumbra). A large, multicenter, randomized controlled trial has demonstrated that rapid lowering of the systolic blood pressure (SBP) to less than 140 mm Hg is safe and may have a small but meaningful benefit on neurologic outcome. This result was not replicated in a subsequent multicenter trial, which also suggested a slightly higher rate of acute kidney injury (AKI) in patients who are rapidly lowered to less than 140 mm Hg.[16] We endorse immediate management with IV antihypertensives. Targeting an SBP less than 140 mm is a reasonable choice, though less than 160 may be preferred in patients with a history of chronic poorly controlled hypertension who are severely hypertensive on presentation. As in other conditions where there is a risk of secondary ischemic injury, hypotension should be diligently avoided by not allowing the MAP to drop below 65 mm Hg.

CVR is a critical determinant of CBF and may be affected by hyperventilation and microvascular patency. Although the cerebral circulation may lose its ability to adjust to blood pressure changes after ischemia, attenuated responsiveness to carbon dioxide and oxygen levels in arterial blood is generally present. Carbon dioxide is a potent vasoactive agent, and lowering the arterial carbon dioxide partial pressure ($Paco_2$) by hyperventilation results in a rapid reduction of CBF of 2% for every 1 mm Hg decrease in the $Paco_2$. Because reductions in CBF reduce total cerebral blood volume, hyperventilation quickly lowers ICP. Induced hyperventilation can transiently abort brainstem herniation in the presence of critically elevated ICP until an alternative therapy can be initiated. However, the vasoconstriction and increased CVR caused by hyperventilation can lead to dangerous reductions in CBF, with resulting cerebral ischemia. We recommend restricting the use of induced hyperventilation to the short-term treatment of immediately life-threatening cerebral herniation and severe intracranial hypertension that is not responsive to other measures, such as osmotic therapy. Chronic or prophylactic hyperventilation should not be used. Specific treatment for elevated ICP is described in the next section. In general, ventilation to maintain a $Paco_2$ of 35 to 40 mm Hg is safe and appropriate, and inadvertent hyperventilation should be avoided.

Normal arterial oxygen saturation following resuscitation from ischemic brain injury is a primary goal. The injured brain may not be able to compensate for hypoxemia by augmenting CBF, and cerebral oxygen delivery may diminish rapidly as the oxygen content of blood decreases. Hyperoxemia secondary to the use of high concentrations of oxygen, however, has also been shown to increase oxidative brain injury in animal models of cardiac arrest and is associated with increased mortality in stroke patients and in post–cardiac arrest patients. Normal oxygen or mild hyperoxemia (arterial partial pressure of oxygen, Pao_2, of 80 to 120 mm Hg with oxyhemoglobin saturation percentage maintained in the high 90s) should be maintained through use of the lowest fraction of inspired oxygen (Fio_2) possible.[10] Because hypoxemia, hypocapnia, and hypercapnia all must be avoided, controlled ventilation is appropriate in the period after resuscitation, with sedation and neuromuscular blockade if needed. Continuous oximetry and capnography, correlated with arterial blood gas determinations, provide the information necessary to optimize ventilation parameters.

Elevated Intracranial Pressure

The presence of intracranial hypertension is suggested by imaging and clinical features. Relevant computed tomography (CT) findings include compressed basal cisterns, diffuse sulcal effacement, and diffuse loss of differentiation between the gray and white matter, although ICP can be elevated without any of these findings. Suggestive clinical features include papilledema, bilateral sixth nerve palsies, and a new third nerve palsy in a comatose patient. Definitive diagnosis requires invasive ICP monitoring placement. The decision to place an ICP monitor should be guided by neurosurgery whenever consultation is available. Most data on the management of elevated ICP is derived from literature on TBI, a condition in which ICP elevation commonly occurs. Although support from randomized controlled trials is lacking, the Brain Trauma Foundation has published guidelines for ICP monitor placement, which we recommend in TBI patients whenever possible. The most recent guidelines reaffirm earlier recommendations that ICP monitors be placed in all TBI patients with an abnormal head CT scan and severe brain injury, defined as a Glasgow Coma Score of 3 to 8.[9]

Guidelines are not available for ICP monitoring in other conditions involving ischemic brain injury, such as stroke, which is generally not indicated. In particular, the clinical impact of intracranial hypertension due to anoxic brain injury following cardiac arrest is unclear and has not been studied in prospective trials. When cytotoxic edema severe enough to cause ICP elevation develops, it portends a very poor prognosis and is generally refractory to medical treatments.[17] Consequently, we do not recommend invasive ICP monitoring to manage global ischemic injury following cardiac arrest.

Medical treatment. Medical treatment for elevated ICP has similarly not been proven effective in randomized controlled trials, and treatment protocols are primarily based on clinical experience and expert opinion. To ensure adequate cerebral perfusion, the MAP should be maintained above 65 mm Hg in all patients at risk for ICP elevation, and a CPP of 60 mm Hg should be targeted when ICP monitoring is available. Although the exact threshold for ICP treatment is unclear and may vary between individual patients, an ICP over 22 mm Hg has been associated with worse neurologic outcomes and should trigger treatment.[9,18]

Management of elevated ICP should proceed in a stepwise fashion, starting with routine interventions that should be employed in all patients at risk of intracranial hypertension, proceeding to more aggressive interventions that also carry a greater risk of side effects. Based on published guidelines[18] and expert opinion, we recommend the following interventions:

1. Position the patient with the head up by elevating the upper half of the bed or gurney to 30 degrees.
2. Maintain a neutral head and neck position to avoid jugular venous compression.
3. Treat fever. Administer antipyretic agents and use mist and surface cooling as necessary, targeting a temperature at or below 37°C.
4. Minimize triggers of ICP increases. This is accomplished by monitoring and, if necessary, minimizing interventions that trigger spikes of ICP, such as frequent turning and suctioning. Laying the patient flat should be avoided if at all possible, and the risk and benefits of imaging studies and other interventions that require transporting the patient should be carefully weighed.[19] Medications to control analgesia and promote sedation can be useful, as described in the pharmacology section.
5. Initiate osmolar therapy, as described in the pharmacology section.

6. CSF drainage via ventriculostomy (if ventriculostomy present)—If possible, a ventriculostomy should be clamped to provide continuous ICP measurement. However, when ICP becomes elevated, opening a ventriculostomy to drain CSF is a safe and frequently effective way to decrease ICP.
7. Treat cases of refractory ICP elevation not amenable to the previous therapies through more aggressive interventions.
   a. A continuous pentobarbital infusion, titrated to achieve deep levels of encephalographic burst suppression, can dramatically decrease cerebral metabolic rate and further reduce elevated ICP.
   b. Mild induced hypothermia is an additional option in highly refractory cases. Endovascular or surface cooling devices should be used to target a temperature of 32°C to 36°C, titrated to achieve ICP control. Once cooled, rapid rewarming should be avoided because this may precipitate a significant ICP elevation. A randomized controlled trial of early induced hypothermia for patients with ICP greater than 20 did not show a significant improvement in neurological outcome, but induced hypothermia remains a consideration for severe cases that are refractory to other medical interventions.[20,21] (Note: targeted temperature management should be initiated on all appropriate cardiac arrest patients as below; these recommendations are for increased ICP from other etiologies.)

Surgical treatment. Surgical options for the management of refractory ICP include decompressive craniectomy and evacuation of intracranial hematoma, when present, and should be guided by neurosurgical consultation. In the event of severe cytotoxic edema following middle cerebral artery stroke, there is a benefit of early (<48 hours) decompressive hemicraniectomy in patients younger than 60 years. A bifrontal craniectomy is typically used to treat refractory ICP in TBI. Since early decompressive craniectomy in patients with ICPs above 20 has been shown to result in worse neurological outcomes, this intervention should be reserved for cases in which most medical interventions have failed. The RescueICP trial randomized severe TBI patients with refractory intracranial hypertension, defined as ICP greater than 25 mm Hg for at least 1 hour, to decompressive craniectomy or medical management, which typically involved initiation of barbiturate infusions. Because there was such a significant mortality reduction in the decompressive craniectomy arm relative to other changes in the extended Glasgow Outcome Scale (GOS-E), the primary hypothesis of an ordinal shift in outcome using the GOS-E could not be statistically tested. Six-month mortality was significantly decreased by 22% in the decompressive craniectomy group, but rates of moderate disability and good recovery were similar in the two groups.[22] Based on these results, decompressive craniectomy remains a consideration for refractory cases prior to initiation of barbiturates, particularly when there is a strong desire to increase survival odds. However, decision making should be individualized, and families should be aware that the procedure is unlikely to increase the likelihood of disability-free survival.

Maintenance of Body Temperature

Hyperthermia exacerbates brain injury and is associated with worse outcome in multiple neurological conditions.[23,24] Elevated body temperature increases cerebral metabolic demand by 8% to 13% per °C, escalates glutamate release, increases oxygen free radical production, and increases cytoskeletal and blood-brain barrier breakdown, with increased vasogenic edema. The core body temperature should be monitored in patients resuscitated from cerebral ischemia, and measures should be initiated to prevent temperature increases in the post-ischemic period. In general, all temperatures higher than 38°C should be treated aggressively with acetaminophen and surface cooling. Targeted temperature management has emerged as a therapy for comatose survivors of hypoxic-ischemic injury following cardiac arrest.

Targeted Temperature Management

Hypothermia was first noted to have a protective effect in global and focal brain ischemia more than 50 years ago. The neuroprotective mechanism is linked to a reduction of glutamate release, metabolic demand, free radical formation, and production of inflammatory cytokines. Cell signaling and genetic responses to cellular injury are also affected, and hypothermia may protect the brain from programmed neuronal cell death.

Mild hypothermia (32°C to 34°C) is easier to achieve and has fewer adverse effects than lower temperatures, and has consistently been found to be neuroprotective in experimental models of cerebral ischemia. In 2002, two prospective, randomized controlled trials of mild hypothermia showed marked improvements in neurologic outcome in comatose survivors of out-of-hospital cardiac arrest (see Fig. 4.2). In these trials, the number needed to treat to have one additional patient with a good neurologic outcome was only about 7. Evidence-based guidelines subsequently recommend cooling unconscious adult patients after cardiac arrest to 33°C for 12 to 24 hours, but widespread adoption of this practice has been slow and incomplete.[25]

More recent investigations in adults and children have compared mild therapeutic hypothermia of 33°C to targeted temperature management of 36°C in patients with out-of-hospital cardiac arrest with an initial shockable rhythm of suspected cardiac etiology. The safety and efficacy outcomes at 33°C versus 36°C were no different. Strong biologic evidence from earlier clinical trials and animal models shows that 33°C provides better neuroprotection. The TTM trial did not provide evidence that one target was easier or safer than the other. Most patients included in these trials had immediate bystander CPR and, by extension, were likely to have less severe neurologic insults than cardiac arrest patients resuscitated in routine practice outside Europe. More recently, a randomized controlled trial compared normothermia to mild hypothermia to 33°C for patients with out-of-hospital cardiac arrest and an initial non-shockable rhythm. Consistent with earlier studies, this demonstrated significantly better neurological outcomes in the hypothermia group.[26] While we anticipate that knowledge in this area will continue to evolve, we recommend rapid initiation of TTM targeting 33°C upon hospital arrival for all unresponsive patients following cardiac arrest.

The optimal method of cooling patients resuscitated from cardiac arrest has not been established, but to accelerate the time to achieving target temperature, guidelines recommend the use of intranasal, intravascular, or surface temperature-modulating devices or cold saline infusions as opposed to older devices like ice packs, cooling fans, and air cooling blankets.[27] Animal experimentation and consensus recommendations have suggested that cooling should be initiated as early and rapidly as possible, but studies of initiation of cooling in the prehospital setting have not demonstrated benefit, and this practice is not recommended.[1] In the early clinical trials, hypothermia at 33°C ± 1°C was achieved by 2 or 8 hours after the return of spontaneous circulation and was maintained for 12 or 24 hours. A recent study did not show the benefit of a longer, 48-hour duration of 33°C TTM compared to 24 hours.[7] An ongoing clinical trial funded by the U.S. National Institutes of Health is addressing the optimal duration of cooling with a target of 33°C (ClinicalTrials.gov Identifier: NCT04217551).

Patients are allowed to rewarm passively or with a combination of passive and slow, active rewarming. Rebound hyperthermia is common with passive rewarming and should be avoided.

Therapeutic hypothermia is the established standard of care for infants with moderate to severe hypoxic-ischemic injury.[28]

The use of surface cooling devices to achieve normothermia may be beneficial to reduce ICP spikes in individuals with brain injury and

BOX 4.1 Abbreviated Protocol for Induced Hypothermia After Cardiac Arrest

- For access to a wide variety of detailed post–cardiac arrest care and hypothermia protocols collected by the University of Pennsylvania, see https://www.med.upenn.edu/resuscitation/hypothermia/.
- Hypothermia is most effective as part of an institutional comprehensive post–cardiac arrest critical care program that begins in the emergency department (ED) and continues into the intensive care unit (ICU) and into recovery and rehabilitation.
- Early resuscitation, excellent cardiopulmonary resuscitation (CPR), rapid return of spontaneous circulation (ROSC), and quick transport to definitive care are fundamental. The value of prehospital cooling is unproven, but if cooling is initiated by emergency medical services (EMS), transport should be to an institution capable of maintaining hypothermia on arrival and avoiding any early (even transient) rewarming.

Skeleton[a]

- Evaluate adult survivors of cardiac arrest by following institutional criteria for appropriateness of induced hypothermia.
- Begin cooling by rapidly infusing 2 L of cold (4°C) intravenous saline immediately after arrival or ROSC.
- Expose patient; avoid external warming—no blankets and no heated ventilator circuit.
- Place temperature-sensing urinary catheter and esophageal temperature probe. (Redundant monitoring allows esophageal temperature probe connection to cooling device and bladder temperature probe to patient monitoring system.)
- Initiate definitive cooling by endovascular or surface-cooling temperature control device at maximal rate to target temperature of 33°C.
- Prevent shivering with sedation and nondepolarizing paralytic—bolus in the ED, bolus or drip in the ICU.
- Avoid hypotension and hypoxia.
- Most ED diagnostic evaluation, if needed, should follow initiation of cooling. (In patients with acute myocardial infarction [MI] who are going to primary coronary intervention, cooling should not delay door to balloon time. Cooling is initiated in the ED if there is time before the catheterization laboratory is ready; otherwise, cooling is initiated in the laboratory.)
- Admit to ICU.
- Continuous electroencephalographic monitoring for occult status epilepticus recommended. Treat seizures if present.
- Manage arterial blood gases in a consistent manner (may choose pH stat or alpha stat).
- At 24 h after initiation of cooling, initiate rewarming to a target temperature of 36.5°C at a rate of 0.15°/h.
- Discontinue paralytics at the onset of warming. Control shivering with sedation, narcotics, and surface counterwarming.
- Lighten sedation as tolerated as rewarming progresses.
- Discontinue endovascular temperature control device after 48 h (may use the device to maintain normothermia after rewarming is complete until it is removed).
- Remove or minimize sedation to allow neurologic evaluation before 72 h to allow the best possible clinical prognostication at that time point; neurology consultation recommended.

[a] Modified from University of Michigan protocol (available at http://dx.doi.org/10.7302/818).

central fever and, as mentioned above, therapeutic hypothermia can be considered in patients with severe intracranial hypertension that is refractory to most other medical interventions. Therapeutic hypothermia following ischemic stroke is not of proven benefit, and we do not recommend its use (Box 4.1).

OUTCOMES

Cerebral ischemia is a frequently fatal and highly morbid condition, but the prognosis for its victims is not universally poor. An increasing body of data provides more precise estimates of survivors' functional outcomes and quality of life, and the results are better than many emergency clinicians assume.

However, identifying reliable prognostic indicators of severe brain injury is hampered by the self-fulfilling prophecy. Counseling provided to families of patients with a presumed poor prognosis leads to withdrawal of life-sustaining treatments, thereby confirming the poor prognosis. There is significant individual and institutional variation in the aggressiveness of care provided to patients with brain injuries. A higher rate of implementation of DNR orders within 24 hours, which is thought to reflect less aggressive early management, has been shown to be strongly associated with mortality, independent of other known risk factors. Consequently, ICH guidelines have emphasized the importance of avoiding assigning new DNR status within the first day of hospital presentation.[13] Prognostication in TBI, which disproportionately affects young adults, can be particularly difficult, and there are many examples of good outcomes despite a prolonged hospital course and severe intracranial hypertension requiring aggressive management.[29]

On the other hand, prolonged survival with significant disability also may be a tragic outcome, and consideration of this may lead emergency clinicians and families to consider changing the goals of care to comfort. Most survivors of cardiac arrest are comatose at the time of admission and without early prognostic findings suggesting which patients will have a favorable outcome. This may account, in part, for the nihilism common among emergency clinicians treating patients with cardiac arrest. Unfortunately, studies suggest that annually thousands of patients who would have a good neurological outcome have care withdrawn early in their hospitalization.[30] Because withdrawal of life-sustaining treatment due to perceived poor neurological prognosis is the most common cause of death in cardiac arrest survivors, it is critically important to provide accurate and evidence-based prognostic information to families. Early examination findings, including an absence of pupillary and corneal reflexes, are poorly predictive of eventual neurological outcome. Consequently, it is well accepted that prognostication cannot accurately be performed until at least 72 hours after cardiac arrest. In practice, because patients receiving TTM typically receive high doses of analgesia and sedation for 24 to 48 hours, accurate examination and prognostication will typically require additional time for these medications to fully clear.[1–3,10]

Older studies and guidelines using data prior to the adoption of therapeutic mild hypothermia identified a number of clinical and laboratory features that were thought to be invariably associated with a poor neurological outcome. However, more recent data suggests that almost all of these individual features are associated with an unacceptably high rate of false positives. We agree with current guidelines from the AHA and ERC which emphasize the importance of taking a stepwise, multimodal approach to neuroprognostication, and allowing greater time for monitoring in uncertain cases (Fig. 4.3).[1,2]

Based on currently available data, a bilaterally absent pupillary light reflex at 72 hours remains highly predictive of a poor outcome with a low false positive rate and narrow confidence interval. Additionally, bilateral absence of a cortical response to somatosensory evoked potentials (SSEPs) after rewarming or 24 to 72 hours from cardiac arrest appears similarly predictive. In conjunction with other findings, additional features suggestive of poor prognosis include absent corneal reflexes, absent reactivity or burst-suppression pattern on EEG, myoclonic status epilepticus, and diffuse anoxic injury on CT or MRI. Higher levels of neuron specific enolase (NSE) are correlated with a worse outcome, but laboratory testing is not standardized, and we do not recommend

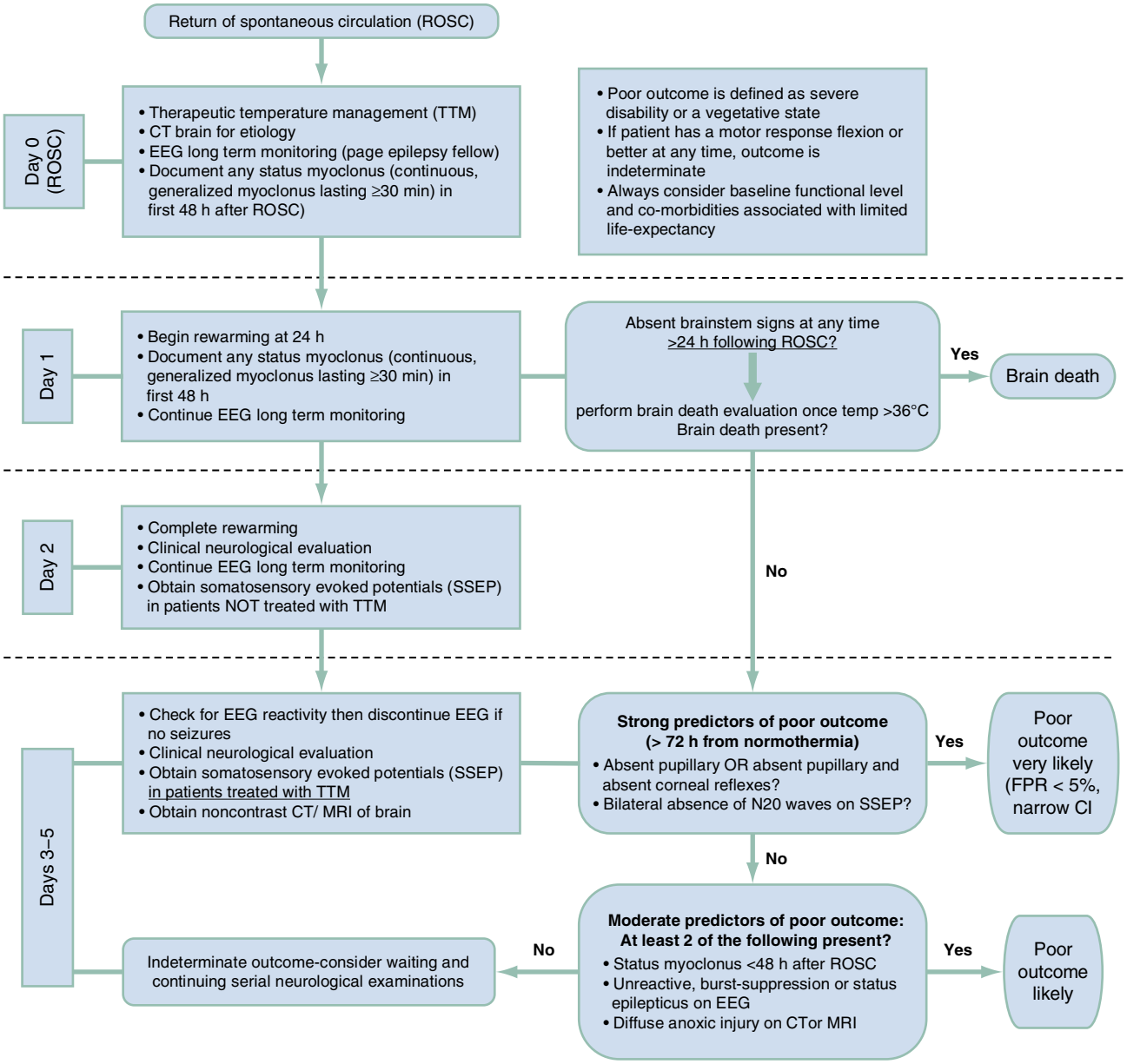

Fig. 4.3 Multi-Modality Neuroprognostication Pathway. (Adapted from Michigan Medicine neuroprognostication protocol and Nolan J, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med.* 2015;41:2039-2056.)

adopting any single threshold to predict poor outcome. It should be noted that the accuracy of any of these findings must be tempered by the potential for confounding due to self-fulfilling prophecies.

Rapidly expanding knowledge of the pathophysiology of post-ischemic brain injury has stimulated the search for effective cerebral resuscitation therapies. Newly proven therapies such as resuscitative hypothermia will continue to be studied and will improve the outcomes of patients with ischemic brain injury in future years. Although experimental work has suggested many potentially promising brain resuscitation therapies, attention should also be paid to determining the benefits of existing standard therapies. Because of the complexity and interconnectedness of the pathophysiologic cascades that occur after cerebral ischemia, it is likely that a multifaceted therapeutic approach targeting mediators of secondary brain injury, rather than a single pharmacologic agent, is needed to reduce neurologic damage after cardiac arrest.

It is crucial that the emergency clinician recognize that the patient resuscitated from ischemic injury is, contrary to his or her outward appearance, in a dynamic stage of brain injury. At present, patients should be protected from further brain injury caused by hypotension, hypoperfusion, ICP elevation, hypoxia, hyperthermia, and seizures. Because early examination and clinical characteristics are unreliable in predicting ultimate neurological outcome and most patients with brain injury die due to withdrawal of life-sustaining treatment, emergency clinicians should avoid therapeutic nihilism and providing an early prognosis to families, instead emphasizing the need to wait several days to obtain reliable information. Unresponsive survivors of out-of-hospital cardiac arrest should undergo targeted temperature management. In the future, cerebral resuscitation may also involve other specific pharmacologic interventions to derail the process whereby brain cells slowly die after ischemic brain injury.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 4: QUESTIONS AND ANSWERS

1. To maximize cerebral blood flow, a patient with a normal intracranial pressure who is undergoing resuscitation should be ventilated to maintain a partial pressure of carbon dioxide ($Paco_2$) within what range?

a. 20 to 25 mm Hg.
b. 25 to 30 mm Hg.
c. 30 to 35 mm Hg.
d. 35 to 40 mm Hg.
e. 40 to 45 mm Hg.

Answer: d. Carbon dioxide is a potent vasoactive agent, and lowering of the $Paco_2$ by hyperventilation results in rapid reduction of cerebral blood flow (CBF). Since reductions in CBF reduce total cerebral blood volume, hyperventilation may transiently abort brainstem herniation in the presence of critically elevated intracranial pressure (ICP) until osmotherapy or ventriculostomy can be initiated. When ICP is not elevated, however, the vasoconstriction and increased cerebrovascular resistance (CVR) caused by hyperventilation can cause potentially dangerous reductions in CBF. In general, ventilation to maintain a $Paco_2$ between 35 and 40 mm Hg is safe and appropriate.

2. Which of the following is a class 1 recommendation from the 2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care?

a. Forty-eight hours from arrest is the earliest time the clinical examination may be used for neuroprognostication.
b. All comatose patients with return of spontaneous circulation (ROSC) after in- and out-of-hospital cardiac arrest, including both shockable and non-shockable rhythms, should receive targeted temperature management.
c. EEG monitoring is not necessary or indicated for comatose patients following cardiac arrest.
d. Infusion of cold saline should be used to induce cooling in the pre-hospital setting following cardiac arrest.

CHAPTER 4: QUESTIONS AND ANSWERS—CONT'D.

Answer: b. The 2015 guidelines update confirms that all comatose (lack of meaningful response to verbal commands) patients with ROSC following cardiac arrest should receive targeted temperature management (TTM), regardless of location of arrest or rhythm type. Because the neurological examination is unreliable in the first few days following arrest, 72 hours is the **earliest** possible time that one may consider using it to provide prognostic information to surrogate decision makers. Non-convulsive seizures are common following cardiac arrest therefore EEG monitoring, if available, should be performed frequently or continuously in comatose survivors of cardiac arrest. Finally, multiple randomized controlled trials showed that cold intravenous fluids in the pre-hospital setting increased the rate of pulmonary edema and rearrest. We do not recommend this practice.

3. Select the best answer. Which of the following statements is false?
   - **a.** Early magnetic resonance imaging (MRI) and serum biomarkers have a clearly established role in determining the prognosis of patients within 48 hours after cardiac arrest.
   - **b.** Recent data suggest that rate of survival to hospital discharge following cardiac arrest is 12%, with 75% of survivors achieving a favorable neurological outcome.
   - **c.** In cardiac arrest survivors presenting to the emergency department , the initial neurological examination is not a reliable predictor of long-term neurological prognosis.
   - **d.** The vast majority of 1-year survivors of cardiac arrest are able to live independently without disability.

Answer: Statement a is false. The role of early imaging, neurophysiologic testing, and serum biomarkers in predicting outcome has not yet been clearly established at any time point, especially not within 48 hours.

4. Which of the following statements about neuronal damage following ischemic injury is correct?
   - **a.** A patient with return of spontaneous circulation after 15 minutes of cardiac arrest has likely already suffered substantial neuronal cell death.
   - **b.** There is a single biological pathway by which ischemia triggers neuronal injury and eventually results in cell death.
   - **c.** Cell death is delayed following cardiac arrest, suggesting that therapeutic interventions may mitigate long-term neuronal injury.
   - **d.** It is not important to avoid secondary neuronal injury following cardiac arrest.

Answer: c. Although a cascade of cellular pathways will have been triggered, the resulting neuronal cell death is usually delayed by hours or days. This suggests that therapeutic interventions, such as targeted temperature management, can reduce cell death and improve outcomes. Careful avoidance of additional secondary insults is also important to maximize the potential for favorable neurological recovery.

5. Select the best answer. Which of the following is associated with worse neurologic outcomes in comatose survivors of cardiac arrest?
   - **a.** All of these.
   - **b.** Hyperthermia.
   - **c.** Hypotension.
   - **d.** Hypoxia.
   - **e.** Only hypotension and hyperthermia.

Answer: Statement a is the best answer. Hypotension, hypoxia, and hyperthermia (as well as hyperglycemia and seizures) are all associated with worse neurologic outcomes in comatose survivors of cardiac arrest.

5

Adult Resuscitation

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KEY CONCEPTS

- Cardiopulmonary resuscitation (CPR) quality is critical to successful resuscitation from cardiac arrest. Important benchmarks of quality CPR include compression rate 100–120 compressions/min, compression depth 5–6 cm, compression fraction at least 80%, full chest recoil between compressions, and a ventilation rate of 10 breaths/min.
- Restoration of adequate cardiac function is the defining factor of return of spontaneous circulation (ROSC). Restoration of good neurologic function is the defining factor of a successful resuscitation.
- Resuscitation of a cardiac arrest victim does not end with ROSC. Rapid diagnosis and proper management of the pathologic condition(s) that precipitated and resulted from the arrest, as well as goal-directed post–cardiac arrest care, can improve outcomes.
- Immediate percutaneous coronary intervention is indicated in patients with ST segment elevation myocardial infarction following ROSC, independent of neurological status.
- Hypothermic targeted temperature management (32°C–36°C [89.6°F–96.8°F] for 24 h) has been shown to improve survival and functional outcome of comatose cardiac arrest survivors.

FOUNDATIONS

Background and Importance

Cardiopulmonary arrest is defined by the triad of unconsciousness, apnea, and pulselessness. It is estimated that more than 340,000 out-of-hospital cardiac arrests (OHCAs) occur annually in the United States, an estimated annual incidence of 140/100,000.[1] Of these, approximately 180,000 are treated by emergency medical services (EMS).[1] Most EMS-treated, OHCAs occur at home (70%) and are unwitnessed (50%).[2] The proportion of EMS-treated cardiac arrest patients with an initial shockable rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) has declined over time to approximately 18%.[2] Furthermore, the number of patients receiving bystander cardiopulmonary resuscitation (CPR) remains low, averaging 40%.[2] Automated external defibrillators (AEDs) are applied prior to EMS arrival in a minority of cases.[2]

Recent epidemiologic data from cardiac arrest registries indicate the survival rate to hospital discharge for EMS-treated, OHCA is about 10%.[2] Comparatively, survival to hospital discharge following in-hospital cardiac arrest (IHCA) is about 26%.[1] Of patients surviving to hospital discharge, independent of neurologic status on presentation, 79% have good neurologic function (cerebral performance category of 1 or 2).[2] For comatose post-cardiac arrest patients who underwent hypothermic targeted temperature management (HTTM), the reported survival rate with good neurologic function has ranged from 20% to 50%.[3] Regional and inter-institutional variability in survival exists after EMS-treated cardiac arrest. The entire system of care affects patient outcomes, and differences in outcomes across the country may reflect local practice variability and differences in delivery of the chain of survival.

Anatomy, Physiology, and Pathophysiology

Awareness of underlying causes of cardiac arrest helps direct therapy and diagnostic testing both during resuscitation and in the immediate post-cardiac arrest period (Table 5.1).

Cardiac arrest with presenting rhythm of VF or pVT often has a primary cardiac origin. Coronary artery disease is a common pathologic condition found in patients who experience OHCA, and multiple observational studies have demonstrated disease rates comparable to those of patients undergoing clinically indicated coronary angiography.[4,5] Other primary cardiac etiologies of cardiac arrest include syndromes associated with sudden cardiac death due to ventricular dysrhythmias, including hypertrophic cardiomyopathy, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and arrhythmogenic right ventricular cardiomyopathy.[1]

Cardiac arrest can result from non-cardiac origins, and common etiologies include circulatory causes, metabolic disturbances, and drug toxicities. Circulatory etiologies of cardiac arrest include tension pneumothorax, pericardial tamponade, pulmonary embolus, and hypovolemia/hemorrhage. These conditions must be recognized early to manage the underlying problem and maximize the chance of a successful resuscitation. The most common electrolyte disturbance leading to cardiac arrest is hyperkalemia, which results in progressive widening of the QRS complex that can deteriorate to pVT, VF, asystole, or pulseless electrical activity (PEA). Cardiac arrest from drug toxicity has specific characteristics, depending on the offending agent and presenting toxidrome. Specific therapy directed at drug toxicity (e.g., naloxone for opiate overdose) is essential, but may not be immediately effective depending on the agent involved. Prolonged resuscitation efforts that provide adequate perfusion may be needed (e.g., veno-arterial extracorporeal membrane oxygenation [VA-ECMO] for refractory cardiac arrest due to local anesthetic systemic toxicity).

Environmental etiologies including electrocution, hypothermia, and drowning can also result in cardiac arrest. Electrocution causes cardiac arrest through primary dysrhythmias or apnea. Alternating current in the range of 100 mA to 1 A (household and light industry) generally causes VF, whereas currents greater than 10 A (heavy industry or electrical transmission infrastructure) can cause ventricular asystole. Lightning produces a massive direct current electrocution that can result in asystole and prolonged apnea (see Chapter 130). Hypothermia-induced cardiac arrest can manifest with any electrocardiographic rhythm, and successful resuscitation

TABLE 5.1 Common Causes of Non-traumatic Cardiac Arrest

General	Specific	Disease or Agent
Cardiac		Coronary artery disease
		Cardiomyopathies
		Structural abnormalities
		Valve dysfunction
Respiratory	Hypoventilation	CNS dysfunction
		Neuromuscular disease
		Toxic and metabolic encephalopathies
	Upper airway obstruction	CNS dysfunction
		Foreign body
		Infection
		Trauma
		Neoplasm
	Pulmonary dysfunction	Asthma, COPD
		Pulmonary edema
		Pulmonary embolus
		Pneumonia
Circulatory	Mechanical obstruction	Tension pneumothorax
		Pericardial tamponade
		Pulmonary embolus
	Hypovolemia	Hemorrhage
	Vascular tone	Sepsis
		Neurogenic
Metabolic	Electrolyte abnormalities	Hypokalemia or hyperkalemia
		Hypermagnesemia
		Hypomagnesemia
		Hypocalcemia
Toxic	Prescription medications	Anti-dysrhythmics
		Digoxin, beta blockers
		Calcium channel blockers
		Tricyclic antidepressants
	Drugs of abuse	Cocaine
		Heroin
	Toxins	Carbon monoxide
		Cyanide
Environmental		Lightning
		Electrocution
		Hypothermia or hyperthermia
		Drowning or near-drowning

CNS, Central nervous system; *COPD,* chronic obstructive pulmonary disease.

depends on rapid rewarming, which often requires invasive measures (e.g., intravascular rewarming, peritoneal or thoracic lavage, or VA-ECMO; see Chapter 128). Once circulation is restored, patients should be warmed to a target of 32°C to 36°C (89.6° to 96.8°F) for 24 hours.[6] Drowning is a form of asphyxia usually resulting in bradyasystolic arrest. Patients experiencing cardiac arrest secondary to hypothermia or drowning may benefit from prolonged resuscitation efforts.

MANAGEMENT

Decision Making

Prehospital

Most cardiac arrest cases managed in the emergency department (ED) initially occur outside the hospital. An increasing number of first responders, nontraditional providers (e.g., teachers, flight attendants), and public venues (e.g., airports, casinos, sports arenas, schools) are being equipped with AEDs. When coupled with regional and statewide campaigns to improve bystander CPR rates, including hands-only and dispatcher-assisted CPR, dramatic resuscitation rates have been achieved in communities where lay public providers feel empowered to respond within the first few minutes of arrest.[7] Programs that fail to improve rates of bystander CPR or AED use within this critical time window are less likely to achieve increased survival rates.

Advanced life support units staffed by paramedics often have standing orders to follow advanced cardiac resuscitation protocols. In cases of cardiac arrest refractory to properly performed advanced prehospital measures, the patient may be pronounced dead at the scene per protocols. However, if advanced hospital-based resuscitation strategies such as extracorporeal cardiopulmonary resuscitation (ECPR) or percutaneous coronary intervention (PCI) are available, then transport to a comprehensive resuscitation center may still be warranted.[8] In systems where patients are transported in cardiac arrest, mechanical CPR results in better quality chest compressions during transport and is likely to be safer for EMS providers. Mechanical CPR can minimize interruptions in chest compressions, eliminate the need to switch rescuers due to provider fatigue, and can deliver consistent depth and rate of compressions.[9]

History and Physical Examination

It is often difficult to determine the cause of cardiac arrest at presentation. Although a differential diagnosis can be formulated based on history, physical examination, and electrocardiographic rhythm on arrival, key information is often unreliable or not available. The differential diagnosis can potentially be narrowed by the patient's age, underlying diseases, and medications, when known.

Historical information from family, bystanders, and EMS personnel provides key information regarding cause and prognosis. Information surrounding the event includes whether the arrest was witnessed, time of arrest, what the patient was doing (e.g., eating, exercising, trauma), possibility of drug ingestion, whether bystander CPR was performed, time of initial CPR, initial electrocardiographic rhythm, and interventions by EMS providers. Important past medical history includes baseline health, previous heart, lung, or renal disease, malignancy, hemorrhage, infection, and risk factors for coronary artery disease and pulmonary embolism. The patient's current medications and allergies should be obtained if possible.

Physical examination of a cardiac arrest patient is necessarily focused on a few key goals: (1) ensuring the adequacy of airway patency and ventilation; (2) confirming the diagnosis of cardiac arrest; (3) finding evidence of the cause; and (4) monitoring for complications of therapeutic interventions. This examination occurs in descending order of importance, simultaneously with therapeutic interventions, and is repeated frequently to assess for response to therapy and occurrence of complications (Table 5.2). After the initial minutes of cardiac arrest, the physical examination may provide little evidence of the duration of arrest. Pupils dilate within 1 minute but may constrict if CPR is initiated immediately and performed effectively. Dependent lividity and rigor mortis develop after hours of cardiac arrest. Temperature is an unreliable predictor of duration of cardiac arrest because it does not

TABLE 5.2 Physical Examination Findings Indicating Potential Cause of Cardiac Arrest and Complications of Therapy

Physical Examination	Abnormalities	Potential Causes
General	Pallor	Hemorrhage
	Cold	Hypothermia
Airway	Secretions, vomitus, or blood	Aspiration
		Airway obstruction
	Resistance to positive-pressure ventilation	Tension pneumothorax
		Airway obstruction
		Bronchospasm
Neck	Jugular venous distention	Tension pneumothorax
		Cardiac tamponade
		Pulmonary embolus
	Tracheal deviation	Tension pneumothorax
Chest	Median sternotomy scar	Underlying cardiac disease
Lungs	Unilateral breath sounds	Tension pneumothorax
		Right mainstem intubation
		Aspiration
	Distant or no breath sounds or no chest expansion	Esophageal intubation
		Airway obstruction
		Severe bronchospasm
	Wheezing	Aspiration
		Bronchospasm
		Pulmonary edema
	Rales	Aspiration
		Pulmonary edema
		Pneumonia
Heart	Diminished heart tones	Hypovolemia
		Cardiac tamponade
		Tension pneumothorax
		Pulmonary embolus
Abdomen	Distended and dull	Ruptured abdominal aortic aneurysm or ruptured ectopic pregnancy
	Distended, tympanitic	Esophageal intubation
	Gastric insufflation	
Rectal	Blood, melena	Gastrointestinal hemorrhage
Extremities	Asymmetrical pulses	Aortic dissection
	Arteriovenous shunt or fistula	Hyperkalemia
Skin	Needle tracks or abscesses	Intravenous drug abuse
	Burns	Smoke inhalation
		Electrocution

decrease significantly during the first hours of arrest, and hypothermia may cause cardiac arrest or be caused by prolonged arrest.

Resuscitation

Management of cardiac arrest occurs in an orchestrated effort by a health care team led by a clinician who can monitor the efficacy and response to therapeutic interventions. Interventions should be performed rapidly and efficiently to maximize the chances of a good neurologic outcome. Restoration of adequate cardiac function is the defining factor of return of spontaneous circulation (ROSC), but restoration of good neurologic function is the defining metric of a successful resuscitation. The likelihood of achieving both of these goals decreases with every minute that the patient remains in cardiac arrest. Fig. 5.1 depicts an algorithm for the management of cardiac arrest.

The goal of CPR is to maintain vital organ perfusion until ROSC is achieved. The quality of CPR is perhaps the most underappreciated component of the resuscitation effort. Important quality performance measures include compression rate (100 to 120 compressions/min), compression depth (5 to 6 cm), chest compression fraction at least 80% (i.e., CPR performed 80 out of every 100 seconds of the pulseless interval), full chest recoil between compressions (no residual leaning between compressions), and ventilation rate (10 ventilations/min).[10]

While chest compression–only CPR (hands-only-CPR) is recommended for lay-providers in the out-of-hospital setting, trained providers who are willing and able to provide ventilations should do so.[10] A 30:2 compression-to-ventilation ratio is currently recommended for health care professionals in all adult resuscitation scenarios until an advanced airway has been established.[11] While either bag-mask ventilation or an advanced airway strategy may be considered in any setting for adult cardiac arrest, the strategy employed should minimize CPR interruptions. If an advanced airway strategy is pursued, a supraglottic airway may be used and can be placed without interruptions to CPR. Endotracheal intubation may also be pursued in settings with high intubation success rates.[12] Once an advanced airway is secured, CPR should be performed continuously, without pausing for ventilation, while providing one ventilation every 6 seconds (10 ventilations/min). Hyperventilation during CPR should be avoided, as it is associated with reduced cardiac output during CPR.[10]

Ventricular Fibrillation and Pulseless Ventricular Tachycardia

Cardiac arrest with presenting rhythm of VF or pVT often has a primary cardiac origin. VF and pVT are treated identically as they are generally caused by the same mechanisms and respond to the same interventions. Therapy for VF and pVT includes defibrillation, high-quality CPR, and administration of vasopressors and anti-dysrhythmic agents.

For a pulseless unresponsive patient in VF or pVT, chest compressions should be initiated immediately and continued until a defibrillator is available. Current consensus favors delivering a single countershock with minimal pause in chest compressions.[13] Defibrillation is followed immediately by the resumption of chest compressions for 2 minutes before a rhythm check and additional defibrillation, as appropriate.[10] If a patient is defibrillated into a different pulseless rhythm (PEA or asystole), subsequent treatment should be modified to address those specific rhythms.

Traditional monophasic defibrillators have almost completely been replaced by defibrillators using biphasic waveforms. With biphasic defibrillation, the energy required for successful defibrillation (the defibrillation threshold) is lower than with monophasic defibrillation. The biphasic waveform increases the likelihood of initial defibrillation success and decreases the likelihood of post–countershock myocardial dysfunction. However, data are currently inadequate to conclude that a biphasic or monophasic waveform is superior in achieving ROSC or survival to hospital discharge. Health professionals should use device-specific manufacturer-recommended countershock energies for biphasic defibrillators,[13] while the recommended energy for a single monophasic defibrillation is 360 J. Assurance of maximal compression fraction can be accomplished by

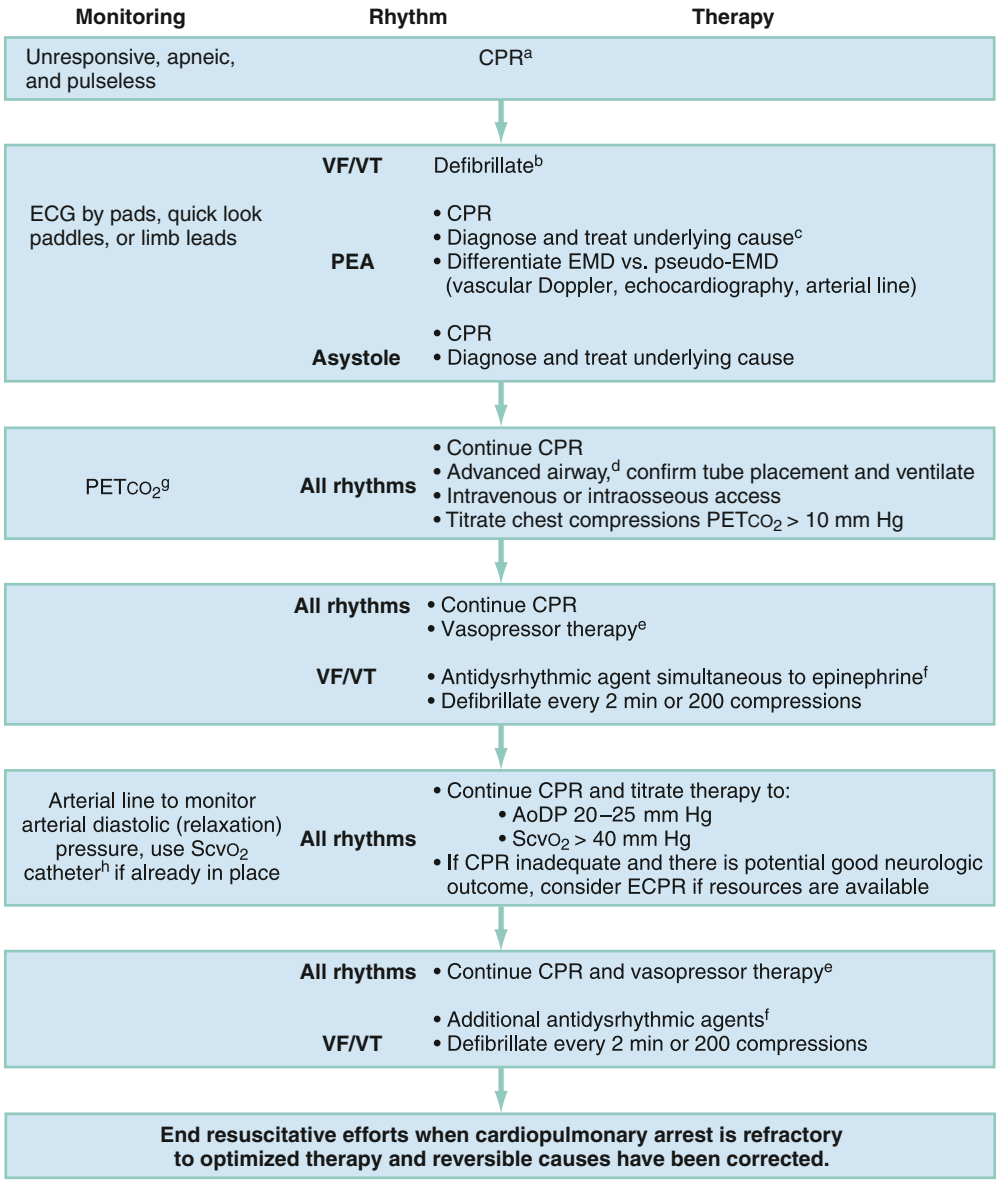

Fig. 5.1 Emergency Treatment Algorithm for Treatment of Cardiac Arrest. [a]If arrest is witnessed and known to be of short duration, immediate rhythm assessment and defibrillation of ventricular fibrillation/ventricular tachycardia *(VF/VT)* precede cardiopulmonary resuscitation *(CPR).* [b]Biphasic defibrillation should use manufacturer-recommended energy versus monophasic defibrillation (360 J). [c]See Table 5.3. [d]Endotracheal intubation or supraglottic airway, when feasible, with minimal interruption in chest compressions. [e]Epinephrine, initial dose of 1 mg IV or IO. Repeat every 3 to 5 minutes. [f]Amiodarone, 300 mg via IV push, followed by 150 mg. Lidocaine is an alternative antidysrhythmic if amiodarone is not available. Magnesium sulfate may be given in torsades de pointes or hypomagnesemia. [g]Changes in the partial pressure of end-tidal carbon dioxide ($PETco_2$) may not be predictive of myocardial blood flow in the setting of high-dose vasopressor therapy. [h]Invasive monitoring should be performed only if adequate personnel are available and if it would not delay therapeutic interventions. *AoDP,* Aortic diastolic pressure; *ECG,* electrocardiogram; *EMD,* electromechanical dissociation; *PEA,* pulseless electrical activity; *$Scvo_2$,* central venous oxygen saturation.

placing defibrillation pads early in the resuscitation sequence, thus not requiring a pause while defibrillation paddles and conducting gel are placed for each shock, and continuing chest compressions while the defibrillator charges.

Pulseless Electrical Activity

PEA is defined as coordinated electrical activity of the heart (other than VF or pVT) without a palpable pulse. PEA can further be characterized as electromechanical dissociation (EMD), in which no myocardial contractions occur, and pseudo-EMD, in which myocardial contractions occur but are inadequate and no pulse can be palpated. Distinguishing EMD from pseudo-EMD may be useful in determining cause and guiding treatment,[14] though in most cases of primary PEA arrest there is a natural progression from hypotension to pseudo-EMD to EMD. Initial assessment of PEA may include echocardiography to distinguish EMD from pseudo-EMD, as volume loading or continuous

TABLE 5.3 Diagnosis and Treatment of Common Causes of Pulseless Electrical Activity

Cause	Diagnosis	Palliative Therapy	Definitive Therapy
Hypovolemia	Response to volume infusion	Volume infusion	Hemostasis if hemorrhage
Hypoxia	Response to oxygenation	Oxygenation, assisted ventilation	Treat underlying cause
Cardiac tamponade	Echocardiogram; jugular venous distention	Pericardiocentesis	Thoracotomy or pericardiotomy
Tension pneumothorax	Asymmetric breath sounds, tracheal deviation	Needle thoracostomy	Tube thoracostomy
Hypothermia	Rectal temperature		Warm peritoneal or thoracic lavage, veno-arterial ECMO
Pulmonary embolus	Risk factors or evidence of deep venous thrombosis	Veno-arterial ECMO	Lytic therapy, pulmonary embolectomy
Drug overdose	History of drug ingestion	Drug-specific	Drug-specific
Hyperkalemia	History of renal failure or elevated serum potassium level	Calcium chloride, insulin and glucose, sodium bicarbonate	Hemodialysis
Acidosis	Arterial blood gas	Hyperventilation, sodium bicarbonate	Treat underlying cause

ECMO, Extracorporeal membrane oxygenation.

vasopressor infusions, which are not used in many cardiac arrest resuscitations, may be helpful in select cases of pseudo-EMD.

True EMD is the result of a primary disorder of electromechanical coupling in myocardial cells. It often is associated with abnormal automaticity and conduction, resulting in bradycardia and a wide QRS complex. Although the mechanism of uncoupling is unclear, it usually is associated with global myocardial energy depletion and acidosis resulting from ischemia or hypoxia. True EMD often occurs after defibrillation following prolonged VF and is associated with hyperkalemia, hypothermia, and drug overdose.

Pseudo-EMD is typically a transient state in the progression to EMD. Cardiac causes of pseudo-EMD include papillary muscle and myocardial wall rupture, in which the ventricle continues to contract but forward flow is greatly diminished, or primary supraventricular tachycardia. Additional extra-cardiac causes of pseudo-EMD include hypovolemia, tension pneumothorax, pericardial tamponade, and massive pulmonary embolism. Pseudo-EMD of extra-cardiac origin most often has narrow complex tachycardia initially, which can progress to bradycardia, with conduction abnormalities and QRS widening.

Treatment of patients with PEA, including both EMD and pseudo-EMD, requires general resuscitation measures, including CPR, assisted ventilation, IV access, administration of vasopressors, and rapid diagnosis and treatment of the underlying cause. A mnemonic "4 H's and 4 T's" is often referenced to aid in rapidly identifying reversible etiologies of PEA arrest: hypoxia, hypovolemia, hypo/hyperkalemia, hypothermia, thrombosis (pulmonary embolism), tamponade (cardiac), toxins, and tension pneumothorax. History and physical examination may provide valuable clues to the underlying cause (Table 5.3). In hypoxia and hypovolemia, the diagnosis is based on response to empiric therapy, whereas other causes such as pericardial tamponade, tension pneumothorax, and hypothermia can be definitively diagnosed during resuscitation.

Asystole

Asystole represents complete cessation of myocardial electrical activity. Although asystole may occur early in cardiac arrest as a consequence of progressive bradycardia, asystole generally represents the end-stage rhythm after prolonged cardiac arrest caused by VF, pVT, or PEA. The potential exists for an organized rhythm or VF to appear as asystole in a single lead if the rhythm vector is completely perpendicular to the lead vector, and thus asystole should be confirmed in at least two limb leads. Although asystole may be difficult to distinguish from extremely fine VF, routine countershock of asystole has not been shown to improve survival.

Treatment of asystole requires general resuscitation measures, including CPR, assisted ventilation, IV access, and repeated administration of vasopressors. Administration of atropine is not beneficial, and asystole in the out-of-hospital setting seldom responds to pacing. To be effective, pacing must be initiated within several minutes of arrest before progression to asystole.

PHARMACOLOGY

Obtain intravenous (IV) or intraosseous (IO) access for an ongoing resuscitation that fails to abort following CPR and defibrillation. Epinephrine 1 mg every 3 to 5 minutes is currently recommended, based on improved survival and ROSC demonstrated in randomized clinical trials.[12,15] Vasopressin offers no advantage as a substitute for epinephrine in cardiac arrest, but use may be considered, typically at a dose of 40 IV push. High-dose epinephrine is not recommended for routine use. Epinephrine should be administered as soon as feasible for patients with non-shockable rhythms, and after initial defibrillation attempts have failed in those with shockable rhythms.

Hemodynamic directed resuscitation involves titrating chest compressions and vasopressor therapy to hemodynamic variables rather than a one-size-fits-all approach. Titration of chest compressions and vasopressor therapy to maintain systolic blood pressure of 90 mm Hg and a coronary perfusion pressure (CPP) of 20 mm Hg during CPR demonstrated improved outcomes in animal models.[16] CPP during CPR is defined as the difference between aortic and right atrial pressures during relaxation (CPR diastole). Although measuring CPP is not practical in most ED resuscitations, these data support the recommendation of titrating vasopressors to an arterial relaxation pressure of at least 20 to 25 mm Hg.

For VF or pVT refractory to defibrillation, anti-dysrhythmics can be administered, and amiodarone (first dose: 300 mg IV/IO; second dose: 150 mg IV/IO) or lidocaine (first dose: 1 to 1.5 mg/kg IV/IO; second dose: 0.5 to 0.75 mg/kg IV/IO) are recommended as first-line agents.[17] In a recent prospective randomized clinical trial, only lidocaine resulted in an increased rate of ROSC, although neither therapy

resulted in statistically significant improvements in survival.[18] Other medications that may be of value in special cases include magnesium sulfate in torsades de pointes (2 to 4g IV), calcium in hyperkalemia (1 g calcium chloride IV or 3 g calcium gluconate IV), sodium bicarbonate in tricyclic antidepressant overdose (1 to 2 mEq/kg), and dextrose in hypoglycemia (25 to 50g IV). Routine administration of atropine outside the setting of bradycardia is not beneficial.

DEVICES AND TECHNIQUES

Monitoring

In addition to monitoring specific CPR performance parameters, physiologic monitoring, if available, can help optimize CPR quality for the individual patient (Table 5.4). If the inadequacy of CPR is recognized early in the resuscitation despite optimized therapy, the clinician may consider more invasive measures such as ECPR or coronary angiography and PCI with ongoing chest compressions if these modalities are readily available and there is significant potential for survival with good neurologic function. After prolonged arrest, however, clear indications that CPR is inadequate (based on appropriate monitoring techniques) can be a contributing factor in the decision to cease resuscitation efforts.

Traditional monitoring during CPR has relied on evaluation of the electrocardiogram (ECG) in one or more leads and palpation of carotid or femoral artery pulses. Electrocardiographic monitoring during cardiac arrest indicates the presence or absence of electrical but not mechanical activity. Myocardial blood flow does not depend on the palpated arterial pressure during chest compression (CPR systole), but rather on CPP. Although these two monitoring modalities may be the best attainable in certain circumstances, they do not provide reliable information regarding the effectiveness of CPR and interventions or prognosis.

No single monitoring technique provides all desired information during a resuscitation, and the modalities discussed below can be challenging to initiate during CPR. A brief overview is provided of CPP, end-tidal carbon dioxide ($ETco_2$), and central venous oxygen saturation ($Scvo_2$) monitoring, which, if available, can be used to detect inadequate CPR with high specificity (see Table 5.4). In addition, several of these techniques are useful in the immediate post–cardiac arrest period.

End-Tidal Carbon Dioxide

The partial pressure of CO_2 in exhaled air at the end of expiration ($PETco_2$) can be a reliable indicator of cardiac output during CPR. This is most reliably measured through waveform capnography after endotracheal intubation, though can also be used with a supraglottic airway device or bag mask.[19] $PETco_2$ depends on CO_2 production, alveolar ventilation, and pulmonary blood flow (i.e., cardiac output) and correlates well with CPP and cerebral perfusion pressure during CPR. Therefore, when minute ventilation is held constant and no exogenous CO_2 is introduced (e.g., with sodium bicarbonate [$NaHCO_3$] administration), only increased cardiac output during CPR will significantly increase $PETco_2$. ROSC causes immediate and significant increases in $PETco_2$.[13] Therefore, $PETco_2$ monitoring can detect ROSC at any time during the chest compression cycle, providing valuable guidance for pharmacologic therapies and minimizing the need for a pulse check when organized rhythms are detected (Fig. 5.2).

Resuscitation after cardiac arrest is likely to fail if $PETco_2$ values of 10 mm Hg or more are not achieved. Therefore, values less than 10 mm Hg should prompt the clinician to enhance the quality of CPR by improving compression rate, depth, or recoil.[13] $PETco_2$ monitoring also can aid in the diagnosis and treatment of PEA. Patients in a state of PEA with mechanical heart activity may have pulsatile flow that simply cannot be detected by palpation of a pulse. In such cases, $PETco_2$ levels may be elevated, even without compressions. Use of ultrasound in such cases can identify corresponding cardiac activity. In these cases, volume expansion or the use of vasopressors and inotropes is indicated. $PETco_2$ monitoring is also useful in rapidly detecting the success of tension pneumothorax decompression, pericardiocentesis for pericardial tamponade, and fluid resuscitation for hypovolemia. Finally, $PETco_2$ monitoring is valuable in patients after ROSC to monitor endotracheal tube placement (waveform capnography recommended), titrate minute ventilation to avoid hyperventilation, and detect sudden hemodynamic deterioration.

Central Venous Oxygen Saturation

Central venous oxygen saturation, $Scvo_2$, when available, provides an additional method to monitor the adequacy of resuscitative measures. The mixed venous blood oxygen saturation in the pulmonary artery (SvO_2) represents the oxygen remaining in the blood after systemic extraction. Studies have shown a close correlation between $Scvo_2$ and SvO_2 during CPR. Because oxygen consumption remains relatively constant during CPR, as does arterial oxygen saturation (Sao_2) and hemoglobin, changes in $Scvo_2$ reflect changes in oxygen delivery by means of changes in cardiac output.

Although continuous $Scvo_2$ monitors have largely fallen out of favor with the diminution of early goal directed therapy for sepsis (see Chapter 127), if available, multi-lumen oximetric $Scvo_2$ catheters can be placed in the same manner as regular central venous catheters and used to monitor $Scvo_2$ in real time. $Scvo_2$ values normally range from 60% to 80%. During cardiac arrest and CPR, these values range from 25% to 35%, indicating greatly enhanced oxygen extraction of tissues owing to the inadequacy of oxygen delivery during CPR. Failure to achieve an $Scvo_2$ of 40% or greater during CPR has had a negative predictive value for ROSC of almost 100%. $Scvo_2$ also helps to detect ROSC rapidly without interruption of chest compressions, because ROSC results in a rapid increase in $Scvo_2$ as oxygen delivery to tissues dramatically increases. $Scvo_2$ monitoring is also useful in the post–cardiac arrest period for hemodynamic optimization and for recognition of any sudden deterioration in the patient's clinical condition as discussed later in this chapter.

Echocardiography

The main use of echocardiography is diagnostic, especially in patients with PEA by distinguishing EMD from pseudo-EMD. It may also help diagnose mechanical causes of PEA such as pericardial tamponade and pulmonary embolism, and in guiding pericardiocentesis. Transesophageal echocardiography (TEE) during CPR is an area of active research and has been associated with shorter chest compression pauses than

TABLE 5.4 Indicators of Inadequate Blood Flow During Cardiopulmonary Resuscitation

Monitoring Technique	Indicator
Carotid or femoral pulse	Not palpable
Coronary perfusion pressure	<15 mm Hg
Arterial relaxation (diastolic) pressure	<20–25 mm Hg
$PETco_2$	<10 mm Hg
$Scvo_2$	<40%

$PETco_2$, Partial pressure of CO_2 in exhaled air at the end of expiration; *$Scvo_2$*, central venous oxygen saturation.

transthoracic echocardiography.[20] TEE may provide an additional visual method to monitor effectiveness of chest compressions in real time by directly visualizing changes in the left ventricle with changes in chest compression technique. In the post-arrest period, echocardiography can prove valuable in evaluating myocardial dysfunction and determining the need for mechanical assistance of the failing heart.

Extracorporeal Cardiopulmonary Resuscitation

Despite lack of supporting evidence from randomized trials, use of VA-ECMO as rescue therapy for refractory adult and pediatric IHCA, deemed ECPR, is a well-established practice in many specialized centers.[21] Observational and case-control studies have suggested benefit in highly selected patients with refractory OHCA, reporting rates of survival with good neurologic function ranging from 11% to 33%.[8,22] Timely arterial and venous access, placement of cannulas, and initiation of ECPR support is critical to success. When used, ECPR is most successful when flow is initiated within 60 minutes of cardiac arrest onset. Survivors typically require 2 to 5 days before they can be successfully weaned from ECMO support. Common complications include coagulopathy, hemorrhage, limb ischemia, vascular injury, renal replacement therapy, and stroke.[22] The implementation of an ECPR program for refractory OHCA is resource-intensive and requires training and coordination among the entire resuscitation system of care—including EMS providers, receiving EDs, designated specialties, and participating intensive care units (ICUs)—to be successful. More research is needed to determine the feasibility and value proposition of implementation outside of high-volume, specialized centers.

Laboratory Testing

Intermittent arterial and venous blood sampling for gas or chemistry analysis is of limited use during CPR. Typical blood gas findings during CPR demonstrate venous respiratory acidosis and arterial respiratory

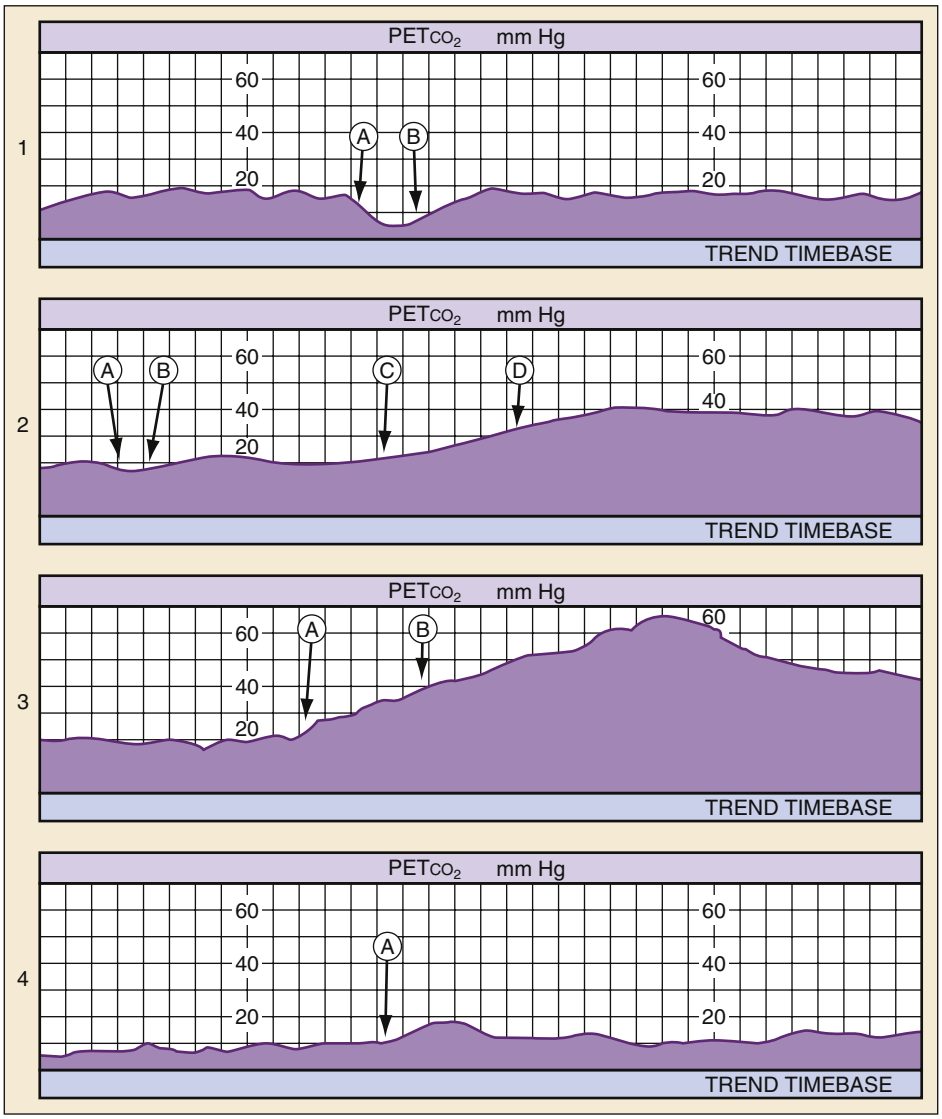

Fig. 5.2 Capnogram tracings of end-tidal carbon dioxide partial pressure *($PETco_2$)* during human cardiopulmonary resuscitation *(CPR)*. **1,** Effect of rescuer fatigue is shown at point A. Point B shows the effect of changing to a fresh rescuer. **2,** Patient with pseudoelectromechanical dissociation. At point A, the patient is pulseless but has a persistent $PETco_2$ value of 20 mm Hg without CPR; at point B, CPR is restarted; at point C, dopamine infusion is started; and at point D, CPR is stopped and a pulse is palpated. **3,** Sudden increase in $PETco_2$ (point A) heralds the return of spontaneous circulation; pulses are palpated at point B. **4,** Point A shows a transient increase in $PETco_2$, such as occurs during bolus administration of sodium bicarbonate.

alkalosis. Sao_2 is usually greater than 94% during CPR and is of little value in titrating resuscitation therapy, except in the case of massive pulmonary embolism or unrecognized esophageal intubation. Although $Scvo_2$ indicates adequacy of CPR, a single measurement may not be as useful as continuous, oximetric $Scvo_2$ monitoring.

Other laboratory studies during CPR are typically not available in time to guide therapy but may serve to confirm a diagnosis following successful resuscitation. Serum electrolyte levels may be ordered to rule out hyperkalemia, hypokalemia, hypomagnesemia, hypercalcemia, and hypocalcemia; however, empirical therapy should be initiated immediately if clinical suspicion exists. Low hemoglobin levels may indicate bleeding, but the initial hemoglobin value may be normal in acute exsanguinating hemorrhage, owing to a lack of rapid vascular and interstitial compartment equilibration.

Arterial Blood Pressure and Coronary Perfusion Pressure

Successful resuscitation of the arrested heart depends on generating adequate CPP during CPR. CPP during CPR is calculated by subtracting right atrial diastolic pressure from aortic diastolic pressure. Animal and human studies have indicated that a minimum CPP of 15 mm Hg is necessary to achieve ROSC if initial defibrillation attempts have failed.

However, CPP monitoring is rarely feasible in ED resuscitations of cardiac arrest patients, as it requires an indwelling arterial pressure catheter and central venous catheter, both transduced properly to provide simultaneous readings. Invasive arterial blood pressure monitoring alone can be helpful in guiding resuscitation and should be used when an indwelling arterial pressure catheter is already in place. When adequate personnel are available, it is often feasible to cannulate the femoral artery during CPR, especially with ultrasound guidance. Human studies have shown that radial or femoral arterial relaxation pressures reliably reflect aortic relaxation pressures during CPR. Monitoring arterial diastolic blood pressure as a surrogate for CPP has been proposed.[13] Titrating resuscitation efforts to arterial relaxation (diastolic) pressure is less reliable than CPP since improper CPR (e.g., leaning on chest during CPR diastole and hyperventilation) can cause undetected elevations in the right atrial pressure, reducing coronary perfusion.

Despite these limitations, it is reasonable to titrate resuscitation efforts to achieve an arterial relaxation (diastolic) pressure of 20 to 25 mm Hg or more when invasive arterial pressure monitoring is available.[10,13] Invasive arterial pressure monitoring during CPR may also help detect ROSC and assist in serial arterial blood gas monitoring. Although arterial and central venous catheters are usually placed in the post–cardiac arrest phase of care, 10% to 20% of patients initially achieving ROSC will re-arrest, making these modalities helpful during the patient's subsequent resuscitation.

OUTCOMES

Post–Cardiac Arrest Care

Resuscitation of a cardiac arrest victim does not end with ROSC. Management includes rapid diagnosis and treatment of the disorders that caused the arrest and complications of prolonged global ischemia. Simultaneous management of these two entities makes caring for a post–cardiac arrest patient particularly challenging. A comprehensive, goal-directed program of post–cardiac arrest care is necessary to optimize survival and neurologic recovery.[23]

Hypothermic Targeted Temperature Management

HTTM in comatose survivors of cardiac arrest has been shown to improve survival and functional outcome in two modestly sized, prospective randomized clinical trials. These studies enrolled only comatose survivors of OHCA that were witnessed arrests and had an initial rhythm of VF. The time to achieve target temperature (<34°C [93.2°F]) ranged from less than 2 hours to a median of 8 hours (interquartile range, 4 to 16 hours), suggesting a broad therapeutic window. HTTM was maintained for 12 to 24 hours, followed by gradual rewarming over 12 to 24 hours. A subsequent large, multicenter international randomized clinical trial of post–cardiac arrest HTTM which enrolled only patients with non-shockable rhythms found no improvement in survival with HTTM at 33°C (91.4°F) for 24 hours, but a near doubling of favorable neurologic function at 90 days (10.2% vs. 5.7%).[3] The largest multicenter international randomized clinical trial of post–cardiac arrest HTTM included all presenting rhythms except unwitnessed asystole and found that outcomes with a target temperature of 33°C (91.4°F) were not superior to those with a target temperature of 36°C (96.8°F). In this study, target temperature was maintained for 28 hours, followed by gradual rewarming at 0.5°C (32.9°F)/h and then maintenance of temperature below 37.5°C (99.5°F) for 72 hours post-ROSC.

Although these studies indicate that post–cardiac arrest HTTM is effective, additional preclinical and clinical data are needed to determine the optimal method of temperature control, time to achieve target temperature, target temperature, duration of therapy, and rate of rewarming. We recommend that emergency clinicians provide HTTM to comatose adult patients who achieve ROSC following cardiac arrest, independent of presenting cardiac rhythm (shockable vs. non-shockable) and location (OHCA vs. IHCA). Furthermore, clinicians should select and maintain HTTM at a constant temperature between 32° and 36°C (89.6° and 96.8°F) for 24 hours after achieving that target temperature.[23]

Although there are no absolute contraindications, relative contraindications may include another obvious reason for coma (e.g., drug overdose, status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. In each of the four randomized HTTM trials, the rates of complications, including bleeding, were not statistically different between groups. Specifically, thrombolytic therapy does not preclude the use of hypothermia.

When the decision is made to treat the comatose post–cardiac arrest patient with HTTM, efforts to achieve and maintain target temperature should begin in the ED, when feasible. However, prehospital cooling after ROSC using cold IV saline has not been shown to improve outcomes in three prospective randomized clinical trials.[24] In the ED, practical methods of rapidly inducing hypothermia include ice packs (applied to the neck, inguinal areas, and axilla), fan cooling of dampened exposed skin, cooling blankets, and disabling of ventilator warming circuits. Rapid IV infusion of limited volumes (1 to 2 L) of 4°C (39.2°F) saline facilitates induction of hypothermia, but additional measures are needed to maintain hypothermia.

No one cooling strategy or device has been demonstrated to result in superior clinical outcomes. A number of automated surface cooling devices are now available that use chest and thigh pads and continuous temperature feedback from bladder or esophageal temperature probes. Although more invasive, automated esophageal and endovascular cooling systems are also available that require placement of an orogastric silicone tube or central venous catheter respectively and offer tighter control of temperature at target (standard deviation usually <0.3°C [32.5°F]).

Shivering, which inhibits cooling, can be prevented with sedation and neuromuscular blockade. Continuous electroencephalographic monitoring during HTTM is strongly encouraged to detect seizures, a common occurrence in post–cardiac arrest patients (5% to 20%).[23] Seizures lasting more than 5 minutes should be treated in a manner similar to other emergency settings, initially with IV lorazepam (0.1 mg/kg/

dose to maximum of 4 mg) or diazepam (0.15 to 0.2 mg/kg/dose to a maximum of 10 mg) or intramuscular midazolam (0.2 mg/kg/dose to maximum of 10 mg), and repeated within 5 minutes.[25] Patients meeting the definition of status epilepticus should be treated with antiepileptics as described in Chapter 88. Target core body temperature is best monitored by an indwelling, temperature-sensitive bladder catheter or esophageal temperature probe. Although the optimal duration of post–cardiac arrest hypothermia is unknown and may be related to the total ischemic time,[26] target temperatures are typically actively maintained for at least 24 hours and routine use of longer intervals is associated with more frequent adverse events and not with improved neurological outcome at 6 months.[27] Following 24 hours at target temperature, patients are gradually rewarmed over 12 to 16 hours and provided active fever suppression at normothermia (37.0°C [98.6°F]) for 72 additional hours.[23]

Coronary Angiography and Primary Percutaneous Coronary Intervention

An immediate concern in a comatose cardiac arrest survivor is whether the patient has an acute coronary syndrome (ACS). Diagnosing ACS in an unconscious patient after cardiac arrest presents a unique challenge. A standard 12-lead ECG should be obtained as soon as feasible after ROSC, with additional right-sided and/or posterior leads as indicated. In one study, 50% of patients achieving ROSC after OHCA were found to have acute coronary occlusion on cardiac catheterization; more than 10% of them did not have ST segment elevation. Subsequent studies have reported that successful, immediate PCI is associated with improved hospital survival in post–cardiac arrest patients, with or without ST segment elevation.

Immediate PCI is indicated for post-ROSC patients with demonstrated ST segment elevation myocardial infarction (STEMI) and should progress via established systems of care.[7,23] Though OHCA patients are often initially comatose, their neurologic status should not be considered a contraindication to immediate angiography and PCI. Initiation of HTTM should not delay PCI; it can be accomplished simultaneously and in concert with interventional cardiology.[23] In the absence of signs of STEMI, a routine immediate angiography and PCI for OHCA was not found to improve survival at 90 days when compared to delayed angiography in one randomized clinical trial.[28] However, when clinical suspicion of ACS is high, rapid post-ROSC angiography and PCI, when indicated, have been associated with improved survival to hospital discharge when a competing non-cardiac cause for OHCA is not immediately evident.

When PCI is indicated but not available, transfer of post–cardiac arrest patients to a center capable of PCI or fibrinolytic therapy should be considered via usual ACS systems of care. Relative exclusion criteria for fibrinolytic therapy unique to the post–cardiac arrest patient include evidence of significant CPR trauma such as pneumothorax, flail chest, or pulmonary contusion with hemorrhage. The effects of HTTM on the efficacy and complications of fibrinolytic therapy in post-arrest patients have not been formally studied. However, an initial randomized TTM trial where fibrinolytics were given to approximately 50% of enrolled subjects demonstrated no increase in complications compared to controls.

Although the immediate post–cardiac arrest period is characterized by a hypocoagulable state, it is rapidly replaced by a hypercoagulable state for up to 72 hours as the post-ROSC surge of activated protein C abates. Dual anticoagulant and antiplatelet therapy (aspirin and a P2Y12 inhibitor) should be strongly considered for post-cardiac arrest patients with diagnosed or suspected ACS in the absence of contraindications. Recent clinical evidence has suggested that ticagrelor results in more effective platelet inhibition than clopidogrel in post–cardiac arrest patients treated with HTTM.

Antidysrhythmic Therapy

There is no proven benefit of prophylactic antiarrhythmic therapy or continuous infusion of an antiarrhythmic drug that has been associated with restoration of a stable rhythm during CPR. Concomitant therapies (e.g., nitrates, beta blockers) are best performed in conjunction with careful hemodynamic monitoring. If indicated, IV preparations of nitrates and short-acting beta blockers (e.g., esmolol) are preferred because of their brief duration of action and ease of titration. In patients with new left bundle branch block, right bundle branch block with left anterior or posterior hemiblock, second-degree type II block, or third-degree block, transthoracic pacing pads should be applied in case they are needed to treat bradycardic rhythms. Placement of a transvenous pacing catheter may be considered, but is less commonly done with the demonstrated efficacy of transthoracic cardiac pacing.

Oxygen Debt and Hemodynamic Management

Inadequate oxygen delivery (Do_2) causes cells to convert to anaerobic metabolism, resulting in increased lactate production (dysoxia). Continued resuscitation efforts are aimed at optimizing Do_2 to prevent subsequent multi-organ dysfunction and recurrent arrest. However, exposure to supranormal arterial oxygen partial pressure (>300 mm Hg) over the first six hours following cardiac arrest can exacerbate oxidative brain injury and cumulative exposure is associated with neurologic outcome in a dose-dependent manner.[29] Therefore, the fraction of inspired oxygen (FIO_2) should be titrated to the minimum concentration required to maintain an arterial oxyhemoglobin saturation of 94% as rapidly as clinically appropriate following cardiac arrest. This level of oxygenation avoids detrimental hyperoxia while ensuring appropriate oxygen delivery.

Serum lactate levels provide an indirect measure of whether Do_2 is adequate to prevent anaerobic metabolism. A single lactate level is almost universally elevated following resuscitation from cardiac arrest. Detection of ongoing lactate production requires monitoring of serial lactate levels. Insufficient Do_2 also causes increased oxygen extraction, resulting in decreased mixed venous oxygen saturation (S_{VO2}). Low S_{VO2} coupled with persistently elevated lactate levels indicates inadequate Do_2. Patients with prolonged duration of CPR and those who have received high-dose vasopressor therapy during CPR may develop impaired tissue oxygen extraction. In such patients, S_{VO2} is abnormally high (venous hyperoxia) in the presence of inadequate Do_2 and likely represents a state of severe systemic shunting resulting in an increase in nonnutritive blood flow. Lactate levels in these cases are persistently elevated. Treatment includes carefully reducing any continuous infusion of vasopressors and providing more aggressive volume loading.[30] The use of guided vasodilator therapy to recruit under perfused tissue beds, as well as consideration of mechanical adjuncts such as an intra-aortic balloon pump or VA-ECMO, may also be necessary in this situation.

The use of combined hemodynamic and metabolic endpoints to guide resuscitation in the ED has been shown to improve the outcome of patients with septic shock. Because the post–cardiac arrest condition represents a complex state of cardiovascular shock, the use of such goal-directed therapy is inherently valuable to reduce mismatches of oxygen delivery and consumption that cannot be determined by a simple physical examination and vital signs.

The use of goal-directed hemodynamic therapy is relatively straightforward and can be frequently accomplished via noninvasive means. Bedside ultrasound can be used to visualize the left ventricle in real time, allowing for direct assessment of cardiac contractility and myocardial wall function. Furthermore, in mechanically ventilated patients, volume responsiveness can also be reliably evaluated by

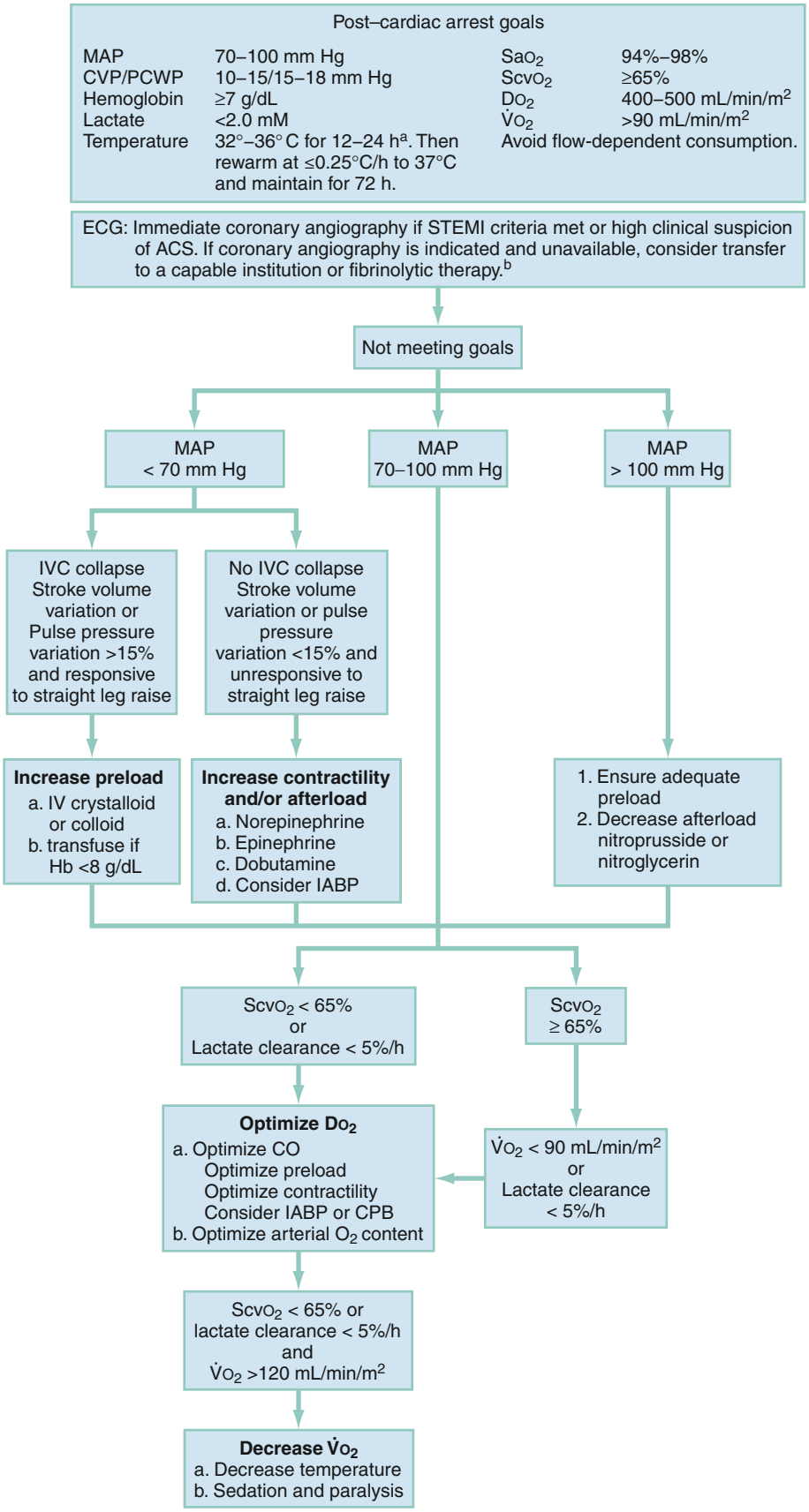

Fig. 5.3 Goal-Directed Post-Arrest Treatment Algorithm. [a]Hypothermic targeted temperature management (HTTM) is indicated in comatose survivors of cardiac arrest. Relative contraindications include uncontrolled bleeding, preexisting coagulopathy, another obvious reason for coma (e.g., drug overdose, status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. [b]Initiation of HTTM is not a contraindication to thrombolytic therapy. *CPB,* cardiopulmonary bypass; *CVP,* central venous pressure; *Do_2,* oxygen delivery; *ECG,* electrocardiogram; *Hb,* hemoglobin; *IABP,* intra-aortic balloon pump; *MAP,* mean arterial pressure; *MI,* myocardial infarction; *NTG,* nitroglycerin; *PCWP,* pulmonary capillary wedge pressure; *Sao_2,* arterial oxygen saturation; *$Scvo_2$,* central venous oxygen saturation; VO_2, oxygen consumption.

measuring the inferior vena cava collapse or passive leg raise. These dynamic noninvasive measures can guide volume expansion to maximize preload without inducing pulmonary edema.

When sonographic measures are unavailable, the placement of a supradiaphragmatic central venous catheter may be used to give further clinical context for intractable shock. If $Scvo_2$, a reliable surrogate for SvO_2, is abnormally low (<65%), but hemoglobin and Sao_2 values are normal, cardiac output is insufficient. Although central venous pressure (CVP) has limitations in certain disease states (e.g., pulmonary hypertension), a CVP can be followed in patients with cardiogenic shock. Although absolute values do not correlate well with volume responsiveness, a patient with a CVP less than 8 mm Hg is unlikely to have volume overload. If intravascular volume is adequate and the patient has a mean arterial pressure of at least 65 mm Hg, unmet resuscitation goals should prompt therapy with an inotropic agent such as dobutamine while reperfusion strategies or mechanical adjuncts are considered.[31]

The response to Do_2-optimizing interventions can be monitored by continuous or serial $Scvo_2$ measurements and serial lactate levels. An increase in $Scvo_2$, coupled with a decrease in lactate levels, indicates improved Do_2. An unchanging $Scvo_2$ level indicates the need to continue to increase delivery. Persistently elevated lactate levels and a low $Scvo_2$, despite maximum pharmacologic support and volume management, signal the need for additional interventions to optimize Do_2. Similarly, in patients with venous hyperoxia and elevated levels of lactate, the combination of these findings indicates severe microvascular dysfunction, which also leads to the accumulation of oxygen debt incompatible with survival. If oxygen debt continues to accumulate, the patient will be at increased risk of developing multisystem organ failure or death. Fig. 5.3 provides a goal-directed guide to care of the post-arrest patient.

Hospital protocols and resuscitation systems of care can be designed to ensure prompt transfer of post–cardiac arrest patients from the ED to the cardiac catheterization laboratory or an ICU, where intensive monitoring can guide subsequent therapy to achieve optimal patient outcomes. Unless prompt transfer to the ICU is anticipated and routinely achieved, comprehensive post–cardiac arrest care should be initiated in the ED.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 5: QUESTIONS AND ANSWERS

1. Which of the following statements regarding the epidemiology of out-of-hospital cardiac arrest is true?
   - **a.** Most patients have an automated external defibrillator applied prior to emergency medical services (EMS) arrival.
   - **b.** Most patients receive bystander CPR.
   - **c.** Most surviving to hospital discharge will not have major persistent neurologic deficits.
   - **d.** Only 2% of EMS-treated out-of-hospital cardiac arrests survive to hospital discharge.

Answer: c. It is estimated that 180,000 patients are treated for out-of-hospital cardiac arrest each year in the United States. The number of patients receiving bystander cardiopulmonary resuscitation (CPR) remains low, averaging 40%. The proportion of emergency medical services (EMS)–treated cardiac arrest patients with an initial shockable rhythm has declined over time to 18% in recent US studies. Automated external defibrillators are applied in a minority of cases prior to EMS arrival. Recent epidemiologic data from cardiac arrest registries indicate the survival rate to hospital discharge for EMS-treated, out-of-hospital cardiac arrest is about 10%. Of patients surviving to hospital discharge, independent of neurologic status on presentation, 79% have good neurologic function.

2. A 75-year-old man presents with return of spontaneous circulation (ROSC) after 2 minutes of ventricular fibrillation and successful defibrillation by EMS. The patient is unresponsive to verbal and painful stimuli. Vital signs on arrival are pulse, 120 beats/min; blood pressure, 130/70 mm Hg; respiratory rate, 10 breaths/min; temperature, 36°C (96.8°F); and oxygen saturation, 94%. The patient has intravenous access. The next most appropriate examination or procedure is:
   - **a.** Anteroposterior (AP) chest radiograph
   - **b.** Arterial blood gas (ABG)
   - **c.** Comprehensive neurologic examination
   - **d.** Electrocardiography

Answer: d. Acute coronary syndrome is a common cause of out-of-hospital cardiac arrest. Electrocardiography should be performed as soon as possible after ROSC to evaluate for ST segment elevation. Because it is impossible to determine survival or neurologic status in the immediate post-arrest period, ST segment elevation myocardial infarction (STEMI) should be treated aggressively with percutaneous coronary intervention (PCI) independently of coma or other laboratory values such as those provided on ABG analysis. Oxygen saturations above 94% are adequate for tissue perfusion, and hyperoxia may be harmful. AP chest radiographs may be important to evaluate ventilatory status if the patient is unstable.

3. Which chest compression/ventilation ratio is recommended during adult resuscitation efforts performed by health care professionals before placement of an advanced airway?
   - **a.** 10:1
   - **b.** 20:1
   - **c.** 20:2
   - **d.** 30:2

Answer: d. A 30:2 compression/ventilation ratio is currently recommended for health care professionals in all adult resuscitation scenarios. Although recent evidence has suggested that chest compression-only CPR is effective when performed by bystanders in the out-of-hospital setting, there is inadequate evidence to recommend this as an alternative strategy for health care professionals, except when inadequate personnel are present to provide compressions, ventilation, and other resuscitative activities.

4. Which of the following statements regarding hypothermic targeted temperature management (HTTM) in comatose survivors of cardiac arrest is true?
   - **a.** Gradual rewarming should occur over 4 hours.
   - **b.** Pregnancy is an absolute contraindication.
   - **c.** Prolonged pharmacologically induced paralysis without sedation is often required to control shivering.
   - **d.** Target core body temperature should be 32° to 36°C.

Answer: d. Induction of prolonged HTTM in comatose survivors of cardiac arrest has been shown to improve survival and functional outcome. A target temperature in the range of 32°C to 36°C (89.6°F to 96.8°F) should be selected and maintained. The time to achieve this temperature has not been clearly defined, and it has been suggested there is a broad therapeutic window. In the studies showing a benefit, maintenance of hypothermia occurred for 12 to 24 hours, followed by gradual rewarming over 12 to 24 hours. There are no absolute contraindications to induced hypothermia after arrest. Shivering, which inhibits cooling, can be prevented with sedation and pharmacologic paralysis. However, prolonged paralysis should be avoided because of the risk of unrecognized seizure activity in post–cardiac arrest patients.

5. For end-tidal pressure of carbon dioxide ($PETCO_2$) to be a reliable indicator of cardiac output during cardiac arrest, which of the following must be present?
   - **a.** Mechanical chest compressions must be performed.
   - **b.** The patient must be in asystole.
   - **c.** The patient must be normothermic
   - **d.** The patient must have relatively constant minute ventilation.

Answer: d. Although $PETCO_2$ will change in direct relationship to cardiac output, alterations in minute ventilation will concentrate or dilute the fixed amount of expired CO_2, influencing the $PETCO_2$ measured independently of cardiac output. Therefore, for $PETCO_2$ to be a reliable indicator of cardiac output, minute ventilation must be held relatively constant. The relationship of $PETCO_2$ and cardiac output during CPR is not dependent on rhythm, mechanisms of chest compressions, or temperature. High-dose vasopressor therapy can cause a decrease in cardiac output during CPR, despite increased myocardial blood flow, which results in a decreased $PETCO_2$.

6

Pain Management

James R. Miner and John H. Burton

KEY CONCEPTS

- Acute pain is an urgent condition for the patient. Pain should be rapidly assessed, treated, and frequently reassessed in tandem with diagnostic evaluations.
- Therapy for acute pain is different than for chronic pain. Chronic pain treatment should be undertaken in consultation with the clinician(s) responsible for the patient's long-term management. In general, opioid analgesic agents should not be administered in the ED or prescribed for outpatient therapy for chronic pain patients unless the plan is agreed to by the responsible outpatient clinician.
- Titrated IV opioid analgesics are the primary therapeutic approach for the treatment of moderate and severe acute pain. When intravenous access is not indicated or attainable, SC administration is preferable to the IM route.
- Opioid therapy should be reserved for pain that has not been or cannot adequately be treated with nonopioid therapies.
- Oral oxycodone, with an onset of action similar to that of IM or SC opioids, can be used for moderate pain when the IV route is not otherwise needed. Oxycodone and other oral opioids should be administered and prescribed as a single-drug preparation, not as part of a combination with acetaminophen.
- Ambulatory treatment with opioids should be confined to the period of acute pain. Most opioid prescriptions from the ED for acute injury should be for 3 to 5 days, after which the patient is transitioned to nonopioid analgesia or reevaluated by an outpatient clinician.
- Acetaminophen and NSAIDs should be added to pain therapy when not contraindicated. Their analgesic effects are additive to those of opioids and each other.
- There is no evidence to support the concept that diagnosis based on physical examination findings will be impaired by administering opioid pain medications to achieve reasonable patient comfort.
- There is no evidence that morphine causes more smooth muscle spasm than other opioids. Morphine is safe and appropriate for patients with acute biliary or renal colic.
- Patients who are known to be diverting or abusing opioids should not be prescribed opioids for use as outpatients. Patients with chronic pain syndromes, or those with chronic conditions that may cause acute pain (e.g., dental caries), should be offered alternative pain management options, and opioids should generally be avoided.
- Topical and local anesthetics can treat pain associated with most ED procedures and should be considered for use in isolated painful conditions.
- Low tissue pH (5 or 6) in infected tissue impairs the effectiveness of local anesthesia.

FOUNDATIONS

Background and Importance

Pain-related complaints represent the primary concern in up to 70% of patients presenting to the emergency department (ED).[1,2] Uncontrolled pain should be considered a medical emergency, and the estimated degree of pain experienced by a patient should play a role in determining a patient's overall acuity and urgency for therapy. Pain estimations, using both clinician- and patient-derived scales, should be obtained and recorded to determine the presence of pain and the response to pain therapy.

Although pain can be present in a wide variety of physical and psychosocial situations, it is typically present in the context of tissue injury. Pain can therefore be assumed to be present in patients with physically apparent disease or injury, even in those who cannot effectively communicate their condition. Important terms relating to analgesic practices are listed in Box 6.1.

A wide variety of treatments are available for both acute and chronic pain. The treatment of pain can be difficult and is often one of the most challenging and frustrating aspects of the practice of emergency medicine.[3]

Patients' perceptions of their ED care are highly influenced by pain treatment.[4-7] Satisfaction with emergency care often depends on the techniques and timeliness of analgesia, as well as the discharge plans for pain relief. In every interaction with a patient in pain, a balance must be achieved between relief of patient suffering and the diagnosis and treatment of the underlying medical condition.

A growing body of evidence has supported the importance of pain management as a central aspect of disease treatment. Unrelieved pain is associated with various potentially negative physiologic outcomes, including increases in sympathetic outflow, peripheral vascular resistance, myocardial oxygen consumption, and the production of carbon dioxide. Other adverse effects of unrelieved pain include hypercoagulability, decreases in gastric motility, and immune function impairment. Poorly treated acute pain can promote the development of chronic pain syndromes and vegetative symptoms, as well as increase the need for pain management during any recovery period. Similarly, pain during serial medical procedures may increase if successful analgesia was not provided during initial procedures. It is also likely that a patient's experience of pain increases his or her ability to perceive pain from similar stimuli in the future.

As an affirmation of the recognized importance of pain management in health care, the Center for Medicare and Medicaid Services and The Joint Commission for accreditation of health care organizations require hospitals to develop quality improvement efforts related to acute pain management, in addition to comprehensive programs for the measurement, documentation, and treatment of pain.[8]

Comprehensive approaches to pain management have become complicated by the widespread abuse of opioids.[9] In the latter part of

BOX 6.1 Definitions of Terms Related to Analgesia

Allodynia—pain from a stimulus that does not normally provoke pain
Amnestic—an agent that suppresses the formation of memories
Local anesthesia—creates an area of insensibility to pain by injection of a local anesthetic agent
Analgesia—relief from pain
Hypnotic—agent that promotes the onset of sleep
Narcotic—term with legal implications describing opioid agents together with various central nervous system depressant drugs of abuse
Nociceptor—receptor that is sensitive and responsible for transmitting pain stimuli
Noxious stimulus—stimulus that is damaging or potentially damaging and results in sensation of pain
Opiate—naturally occurring derivative of opium alkaloid that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Opioid—naturally occurring or semisynthetic derivative of opium alkaloid (includes all opiates) that binds opiate receptors and produces effects similar to those of endogenous endorphins
Pain—unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage
Procedural sedation—pharmacologic induction of a state of sedation or dissociation with amnesia for pain control during a painful procedure
Sedative—agent that decreases a patient's level of awareness

the twentieth century, American clinicians and institutions emphasized using opioid therapy as a cornerstone of acute and chronic pain management. This emphasis rested on the widely held belief that opioid therapy prescribed to patients in pain posed a relatively small risk for chronic addiction, abuse, or harm. A dramatic rise in addiction rates, diversion, and death directly attributed to this practice has been documented in the early part of the twenty-first century.[10-12] This "opioid crisis" has largely been a phenomenon unique to the American health care system and culture. Additionally, chronic opioid therapy has not been demonstrated to confer patient-centric gains in life function, productivity or longevity.

As a result, pain management strategies have quickly shifted to support selective brief periods of opioid therapy in acute pain along with a concurrent reduction, or altogether removal, of opioids as a mainstay in patients with extended, chronic periods of pain.

Emergency medicine as a specialty accounts for 4% of opioid prescriptions in the US,[13] with 17% of patients receiving a median of 15 pills per prescription,[14] so while emergency departments represent a small part of this opioid crisis, there are significant opportunities for improvements in practice.[15]

Anatomy, Physiology, and Pathophysiology

Pain can be generally described by the terms *nociceptive* and *neuropathic*. Nociceptive pain results from the activation of sensory neurons that signal pain (nociceptors) in response to noxious stimuli. Neuropathic pain results from signal-processing changes in the central nervous system (CNS). Neuropathic pain is usually described as burning, tingling, or shooting sensations and includes neuropathies and deafferentiation. Both nociceptive and neuropathic pains involve peripheral and central sensitization with a complex array of mediators to sensitize peripheral nociceptors and perpetuate thalamic signals (Fig. 6.1). At each level in the physiologic process of pain production or transmission, there are interventions and therapeutic opportunities to consider to alter the process and improve the patient's pain experience.

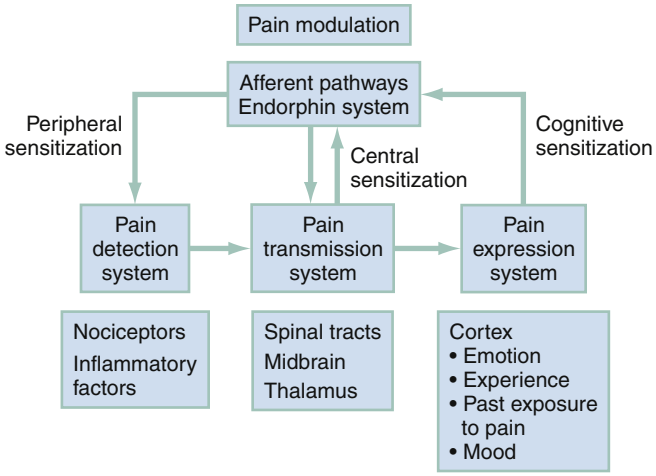

Fig. 6.1 The pain system algorithm.

Pain Conduction Pathways

Pain can be divided into four separate processes (see Fig. 6.1): pain detection, pain transmission, pain modulation, and pain expression (perception).

Pain Detection

The somatosensory system is responsible for detecting pain as well as tactile, proprioceptive, and thermal sensations. Receptors responsible for the detection of pain are termed *nociceptors*. Nociceptors include sensory nerves that are capable of detecting mechanical, thermal, or chemical stimulation. Several different subtypes of nociceptors are present in cutaneous tissues, including mechanoreceptors, polymodal nociceptors (PMNs), and a variety of thermoreceptors.

The threshold of activation of a nociceptor can be modulated—increased or decreased—by various chemical mediators, including prostaglandin, cyclic adenosine monophosphate, leukotrienes, bradykinins, serotonin, substance P, thromboxanes, platelet-activating factor, and endorphins. This change in nociceptor activation thresholds is termed *peripheral sensitization*. Trigger points, for example, are areas of frequent or constant low-level sensory stimulation (e.g., scar tissue or a degenerative joint) that have developed peripheral sensitized nociceptors that perceive pain from otherwise innocuous stimuli (allodynia).

Information Transmission

Peripheral nerve fibers. All sensory neurons are composed of a cell body located in the dorsal root ganglia. The dorsal root ganglia are connected by nerve axon fibers with sensory receptors located in a number of body sites, including dermatomes (cutaneous input), sclerotomes (input from bones), and myotomes (input from muscle). The discrete areas covered by each nerve provide a sensory map of the body surface.

Peripheral nerve fibers can be classified by the roles of each fiber group (Table 6.1). A-δ and C fibers are responsible for the transmission of pain. A-δ fibers transmit sharp, initial pain; C fibers, in contrast, transmit dull, aching, or burning pain. The pain transmitted by A-δ fibers persists only as long as the initial stimulus is in effect, whereas C fiber pain persists longer than the initial stimuli, rendering a prolonged pain sensory experience. The relative concentration of nerve fiber types, both C and A-δ, varies by body tissue.

TABLE 6.1 Peripheral Nerve Fibers

Fiber	Function	Myelin	Mean Diameter (mm)	Ascending Tract	Conduction Velocity (m/s)
A-α	Skeletal muscle motor	Deep	12–20	Ipsilateral dorsal column	70–120
A-β	Light touch and pressure	Superficial	5–15	Contralateral spinothalamic tract	30–70
A-γ	Motor	Superficial	6–8	Ipsilateral dorsal column	15–30
A-δ	Sharp pain (mechanoreceptors, thermoreceptors, PMNs)	Superficial	1–4	Contralateral spinothalamic tract	12–30
B	Sympathetic		1–3	Preganglionic	3–15
C	Long-lasting burning pain	Superficial	0.5–1.5	Contralateral spinothalamic tract	0.5–2

Adapted from Paris PM, Uram M, Ginsburg MJ: Physiological mechanisms of pain. In Paris PM, Stewart RD, editors: Pain management in emergency medicine, Norwalk, CT, 1988, Appleton & Lange.

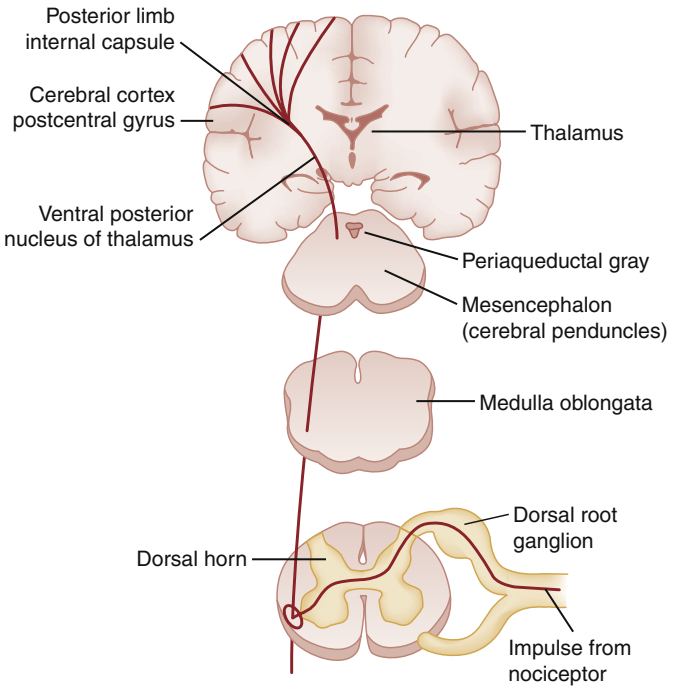

Fig. 6.2 Spinal tracts.

Pain Transmission

Dorsal horn. The dorsal horn is the gray matter of the posterior aspect of the spinal cord (Fig. 6.2). The dorsal horn acts as an integration system in which sensory input is filtered, attenuated, or amplified before being relayed to other spinal segments or the cortex.

The dorsal horn is a processing center for incoming information and is extensively involved in modulating nociceptive input. Afferents from visceral, muscle, bone, and cutaneous areas converge in the dorsal horn and likely account for the cutaneous referred pain associated with noxious visceral, muscular, or bony stimuli from the same spinal level.

Differentiation between innocuous stimuli and nociceptor input occurs in the dorsal horn by stimuli received in cells referred to as wide dynamic range neurons (WDRNs). WDRNs receive modulating input from a variety of chemical pathways, such as opioids, substance P, or inflammatory factors. These cells also receive modulating input from efferent and afferent neuronal pathways.

Visceral pain. The quantity and type of stimuli that produce pain vary among visceral structures. The myocardium, for example, is sensitive to ischemia but not mechanical stimulation. Tissues in the intestine may be severed, crushed, or burned without pain; however, traction or distention produces pain.

The quality of visceral pain is unique from somatic pain. Somatic pain is initially sharp, later becoming burning or throbbing in nature as the response is modulated. In contrast, visceral pain tends to start as poorly localized, burning or throbbing pain, with pronounced autonomic activation. These sensations may then develop into sharp, localized, referred pain as modulation progresses and the associated dermatome is activated. Visceral pain often produces referred pain. For example, periumbilical pain is often associated with appendicitis. This referred pain sensation occurs due to visceral afferents supplying the small bowel and traveling through the celiac ganglia and splanchnic nerves to enter the spinal cord at T10. This input sensitizes the dorsal horn at T10, leading to sensitization of all the dorsal horn nociceptive neurons and ultimately leading to the perception of pain in the T10 dermatome. As appendicitis progresses, the pain localizes to the right lower quadrant as inflammation extends to the parietal peritoneum with the same nerve supply as the overlying dermatome.

Ascending tracts associated with pain. Fibers carrying pain impulses exit the dorsal horn and ascend the spinal cord to the brain. The predominant pathways for pain conduction through the spinal cord are the spinothalamic, spinomesencephalic, and spinoreticular tracts, located in the anterolateral aspect of the spinal cord (Fig. 6.3; see Fig. 6.2).

Pain Modulation

Impulses from nociceptors are modulated by descending tracts in the spinal cord. The two primary descending pathways appear to be serotonergic and noradrenergic. These pathways originate in the midbrain (periaqueductal gray matter and locus ceruleus), and medulla (nucleus raphe magnus and nucleus reticularis gigantocellularis) and are transmitted to the spinal cord via the dorsolateral funiculus.

Electrical stimulation of descending pathways produces analgesia comparable to that produced with opioids. Stimulation of the thalamus can also produce analgesia. Inputs to this system come from the frontal cortex, limbic system, hypothalamus, reticular system, locus ceruleus, and spinal cord. Multiple neurotransmitters are involved in these pathways, including serotonin, norepinephrine, and substance P. It is believed that the activation of this system is responsible for effects such as placebo, acupuncture, and transcutaneous electrical nerve stimulation (TENS) units, as well as stress-associated pain tolerance.

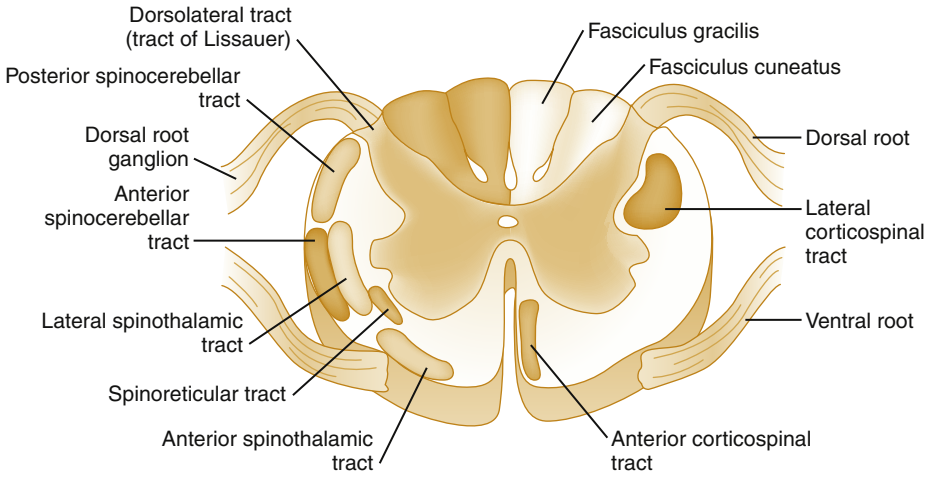

Fig. 6.3 Spinal cord.

Central Sensitization

Central sensitization involves the amplification of nociceptive signals. Central sensitization is mediated by several substances, including nitric oxide, glutamate, substance P, aspartate, prostaglandins, leukotrienes, norepinephrine, and serotonin. It plays a major role in the development of chronic pain and can be the result of damage at any point along the pain transmission system, or more commonly a feedback loop of propagation and sensitization. Central sensitization has been best described in the setting of traumatic and degenerative conditions of the spinal cord and brainstem and can be associated with thalamic strokes, multiple sclerosis, Parkinson's disease, Arnold-Chiari formation, and cervical stenosis.

Pain Expression

The transduction, transmission, and modulation of pain stimuli develop the perception of the subjective emotional experience of pain. Many factors other than the simple stimulation of nociceptors influence the final perception of pain. The discrete cognitive processes and pathways involved in the interpretation and experience of painful stimuli remain a mystery and are affected by cultural expectations, personality, experiences, and the underlying emotional state. Many of these factors, and therefore the subsequent perception of pain, can be greatly influenced by both pharmacologic and nonpharmacologic interventions.

Much of the analgesic effect for drugs such as nitrous oxide and low-dose opioids is due to the cognitive interpretation and emotional reaction to pain rather than an effect on transmission of the pain stimulus. Similarly, noninvasive techniques such as distraction and hypnosis can limit pain perceptions and increase pain tolerance. Changes in how a person experiences pain, based on previous experiences and learned behaviors, are referred to as cognitive (de)sensitization.

Reflex Responses to Pain

There are two types of reflex responses to nociceptor input, spinal segmental (or suprasegmental) and cortical. Spinal reflexes are generated by the transmission of nociceptive impulses from the dorsal horn to motor and autonomic neurons in the spinal cord, provoking a range of responses, including tachycardia, vasoconstriction, paralytic ileus, and muscle spasm (Box 6.2). Suprasegmental reflexes are transmitted through ascending tracts to the brainstem, hypothalamus, and cortex, where withdrawal reflexes and autonomic responses occur in connection with conscious responses. The autonomic reflex responses to pain are variable and cannot be used to quantify pain in an individual.

BOX 6.2 Reflex Responses to Pain

Increased Sympathetic Tone
Vasoconstriction producing increased peripheral resistance
Increased cardiac output from increased stroke volume and heart rate
Increased blood pressure
Increased metabolic rate and oxygen consumption
Decreased gastric tone and gastric emptying (may progress to ileus)
Decreased urinary tract tone (may lead to urinary retention)

Endocrine Responses
Decreased insulin production
Increased cortisol levels
Increased antidiuretic hormone levels
Increased growth hormone levels
Increased renin, angiotensin II, aldosterone levels
Increased glucagon levels
Increased catecholamine levels

Respiratory Responses
Hyperventilation

Cortical Responses
Anxiety and fear

Endorphin System

The endorphin system is a neuroendocrine system that serves to modulate responses to pain and stress. The endorphin system consists of widely scattered neurons that produce three types of opioids—beta-endorphin, met- and leu-enkephalins, and dynorphins. These opioids act as neurotransmitters and neuromodulators at three major classes of receptors—mu, delta, and kappa—and produce analgesia as well as counter the stress response (Table 6.2).

Under normal circumstances, the endorphin system decreases pain and stress after a person has adequately dealt with the inciting noxious stimuli. The endorphin system is typically a responsive system that can increase or decrease effect to produce the appropriate response to a painful event. Like other neuroendocrine systems, increasing stimulation of the endorphin system produces feedback inhibition of endorphin production. During prolonged periods of pain with high stimulation levels, the system can become less responsive and less effective at modulating the pain response.

TABLE 6.2 Opioid Receptors

Opioid Receptor Class	Effects	Associated Endogenous Endorphin
Mu 1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea	Beta-endorphin
Mu 2	Respiratory depression, CV and GI effects, miosis, urinary retention	Beta-endorphin
Delta	Spinal analgesia, CV depression, decreased brain and myocardial oxygen demand	Enkephalin
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system	Dynorphin, beta-endorphin
Epsilon	Hormone	Beta-endorphin
Gamma	Dysphoria, psychomimetic effects	Beta-endorphin

CV, Cardiovascular; *GI*, gastrointestinal.

TABLE 6.3 Acute versus Chronic Pain

Parameter	Acute Pain	Chronic Pain
Inciting factor	Associated pathology present and recovery is expected	Associated pathology not identifiable or not expected to improve; recovery unpredictable or not expected
Relation to healing	Pain improves as the injury heals; limitation of activity due to pain assists healing	Neither pain nor injury expected to improve; pain may limit activities that could improve condition
Psychosocial effects	Limited to acute stress reaction	Negative effects a prominent feature of disease
Treatment	Analgesics, immobilization	Psychosocial aspects must be addressed; analgesics play a smaller role

Like their endogenous counterparts, opiates act at chemical receptors to produce analgesia and undesirable side effects. As opioid drugs are given over prolonged periods, they inhibit a person's endogenous endorphin system, blunting its ability to modulate pain and stress, and decreasing the endorphin system's adaptive effects. As these drugs are withdrawn, the normal effects of the endorphin system can resume over time.

Acute Versus Chronic Pain

Acute pain is usually associated with an identifiable pathologic condition and serves an adaptive function by warning the individual that an illness or injury exists. This sequence will motivate the person to cease activity that is causing the pain, look for a cause, seek help, and avoid the future stimulus.

Acute pain becomes chronic pain when the pain pattern persists, in changed or unchanged form, after the original physiologic insult has resolved. All chronic pain starts as acute pain, but only small subsets of patients with acute pain develop chronic pain (Table 6.3). The physiologic transition from acute to chronic pain is a complex process, with physiologic and psychosocial components. In many cases, the development of chronic pain is likely related to the treatment of acute pain.

Acute pain serves an important purpose in that it stimulates a person to protect the injured area and seek help. Also, the neurochemical factors that contribute to acute pain acknowledgment generally initiate and support recruitment of tissue repair mechanisms. As an injury heals, these adaptive responses may become maladaptive if the pain persists, with the pain leading to a decreased range of motion, decreased function of the area and, ultimately, increased susceptibility to injury and pain. Pain also causes a stress response that is initially adaptive in the face of injury. A prolonged stress response, however, causes an impaired immune system, hypercoagulabilty, sleep disturbances, anxiety, and depression.

MANAGEMENT

Decision Making

Pain Assessment

The early accurate recognition and assessment of a patent's pain are the most important aspects of effective acute pain management. When pain is inadequately treated, inaccurate assessment is often the root cause of the problem.

The degree to which a person experiences pain is a complex and subjective interaction between the physical stimulus and patient's cognitive and emotional state. However, it is clear that the degree of pain a patient perceives is not directly determined by the degree of physiologic injury. Patients in the ED with relatively identical injuries may experience and display completely different amounts of pain. Therefore, pain treatments, analgesic requirements, and how a patient describes pain cannot be uniformly described based on the nature of a patient's injury.

The assessment of pain depends on both the patient's ability to communicate the nature of the painful experience and the clinician's ability to accurately obtain this information. Unfortunately, there is no objective test or physiologic index to measure pain reliably. Objective observations, such as hypertension, diaphoresis, or tachycardia, do not correlate well with the degree of pain. Because pain cannot be objectively measured, a clinician's assessment depends on communication with the patient—verbal and nonverbal. Barriers to communication between patients and clinicians, including linguistic, socioeconomic, and cultural differences, limit the ability to assess pain effectively.

Oligoanalgesia

Because effective treatment is based on the assessment of pain, patients who have difficulty communicating are at risk of undertreatment of their pain (oligoanalgesia). These groups include infants and children, patients whose cultural and linguistic background differs significantly from the treating clinician, or are developmentally delayed, cognitively impaired, under severe emotional stress, or mentally ill. Racial and ethnic disparities have been identified in the treatment of acute pain in the ED.[16,17]

There are a variety of reasons why some patients receive inadequate analgesia. These include ineffective pain assessment, misconceptions about the safety and efficacy of various treatments, and concerns about the effect of analgesic interventions on a patient's evaluation. There may be a significant delay to providing adequate pain control, especially during high-volume periods.[18] Additionally, when opioids are used, they are often given in subtherapeutic doses.

Pain Measurement

The use of numeric rating scales, such as a verbal 0 to 10 score (none to worst imaginable), are ubiquitous (Fig. 6.4). Visual analogue scales, usually consisting of a 10-cm straight line with anchors at either extreme, are frequently used in research to provide continuous data for analysis. These scales offer little practical advantage over verbal reports

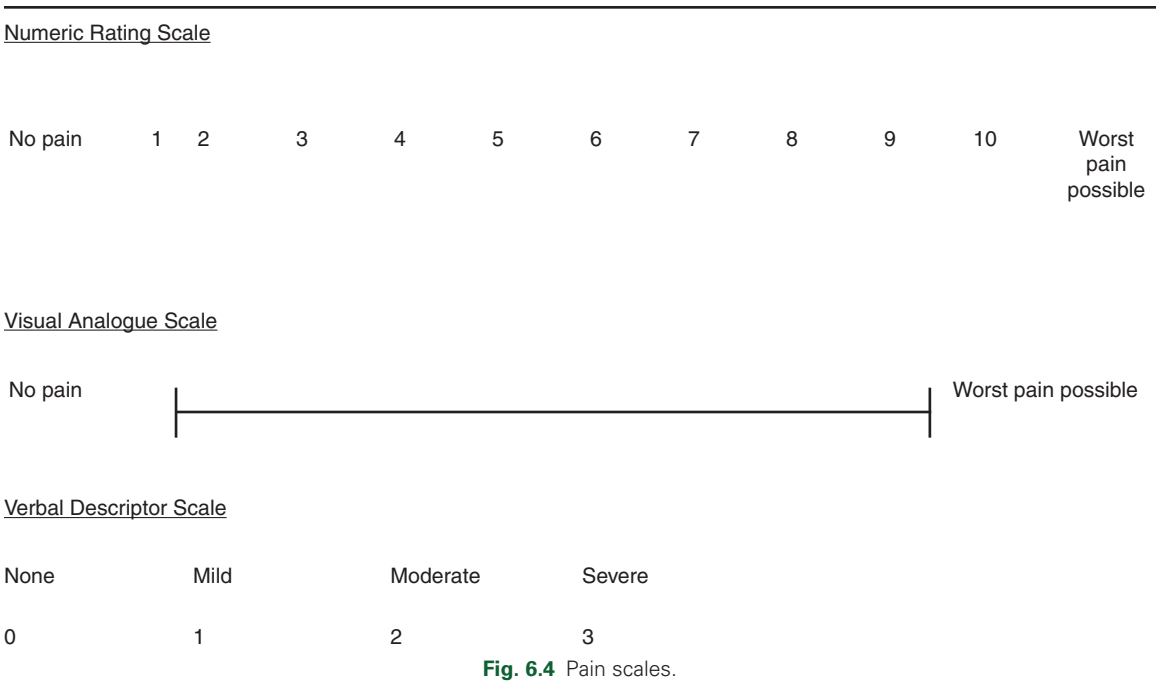

Fig. 6.4 Pain scales.

in the clinical setting. Routine verbal or visual pain scale assessment encourages emergency clinicians to communicate with patients to assess their pain and to evaluate responses to analgesic intervention attempts.

Children require alternative communication techniques to acknowledge and relate pain. The FACES pain scales are designed for children younger than 7 years. This scale has a series of cartoon faces expressing a range of emotions, from happiness to severe distress. The child is asked to point to the face that corresponds to how he or she feels. The FACES pain scale, and others like them, require less of an abstract reference than numeric and verbal scales and are useful in pain assessment for toddlers and cognitively impaired adults.

In preverbal children, observer-derived scales need to be used. These include the Modified Pre-Verbal, Early Verbal Pediatric Pain Scale (M-PEPPS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), and CRIES scale for neonates. These scales use a scoring system for observed criteria that is reproducible among trained observers, making them useful for research, but they have little clinical utility compared to the emergency clinician's or parents' overall impression of a child's pain.

Pain scores are accepted as the most accurate and reliable measure of assessing a patient's pain and response to pain treatment. Pain treatment should be targeted to a goal of reducing the pain score (e.g., by 50%, below 4/10, or referred to as mild/moderate or severe) rather than a specific (maximum) analgesic dose.

BOX 6.3 Common Outpatient Analgesic Agents by Pain Type

Acute Pain
1. Acetaminophen
2. Nonsteroidal antiinflammatory drugs (NSAIDs)
3. Opioids used in combination with NSAIDs and acetaminophen
4. Oxycodone
5. Hydrocodone

Chronic Pain
1. NSAIDs
2. Tramadol
3. Opioids used in combination with NSAIDs and acetaminophen[a,b]
4. Oxycodone, long-acting preparation, or for breakthrough pain
5. Tricyclic antidepressants

Neuropathic Pain
1. Gabapentin
2. Tricyclic antidepressants
3. Carbamazepine

[a] A variety of opioid and acetaminophen combination agents are available.
[b] Chronic opioid management should be managed by the primary outpatient physician.

Treatment Groups

The approach to patients in pain begins with a characterization of pain into four unique treatment groups: (1) acute pain; (2) recurrent pain; (3) chronic pain of malignancy and neuropathic pain; and (4) chronic pain. Other than acute pain, therapy should focus on a long-term, multidisciplinary approach (Box 6.3). Acute and chronic pain patients have different physiologic causes and thus require different treatment approaches based on their specific site and mechanism of affect (Fig. 6.5).

Acute pain. Symptomatic treatment of pain should be initiated promptly, titrated to an acceptable level of relief, and continued while the investigation for a cause is proceeding. Fig. 6.6 presents a common approach to acute pain in the ED setting, beginning at triage to assess pain type and severity and then progressing to clinical assessment, with therapeutic suggestions.

When the cause of acute pain is uncertain, immediate relief of pain occurs in parallel with initial efforts to establish the diagnosis. It is inappropriate to delay analgesic use until a diagnosis has been made. There is no evidence that the administration of adequate doses of opioid analgesia to establish patient comfort impairs the emergency clinician's ability to diagnose the cause of an acutely painful condition. On

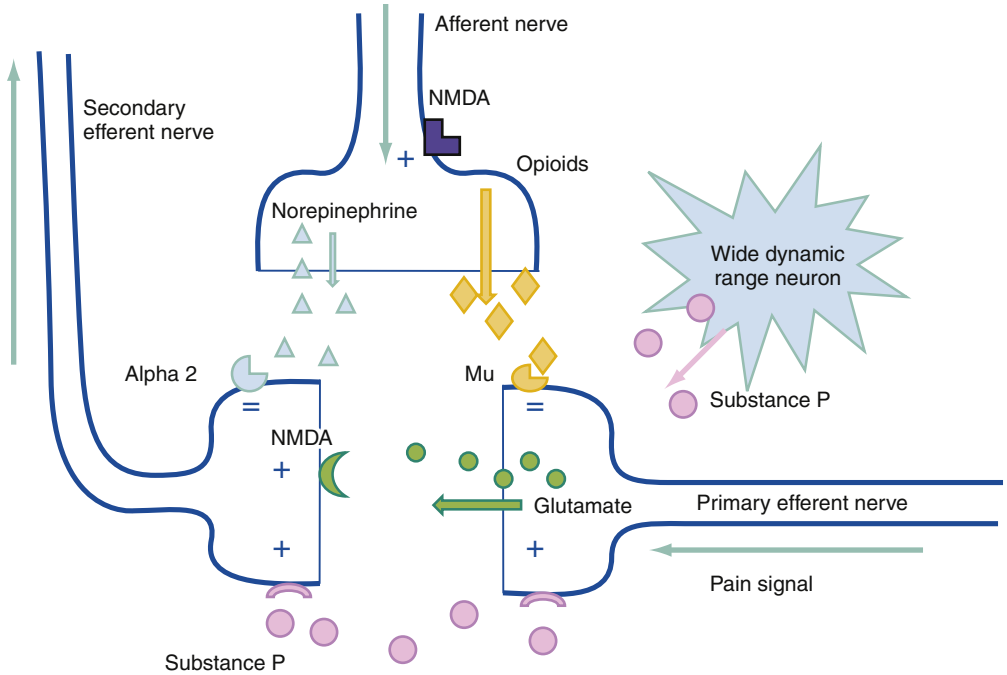

Fig. 6.5 Neurotransmitters and receptors at the dorsal root ganglion. *Mu,* Opioid receptor; *NMDA, N*-methyl-D-aspartate.

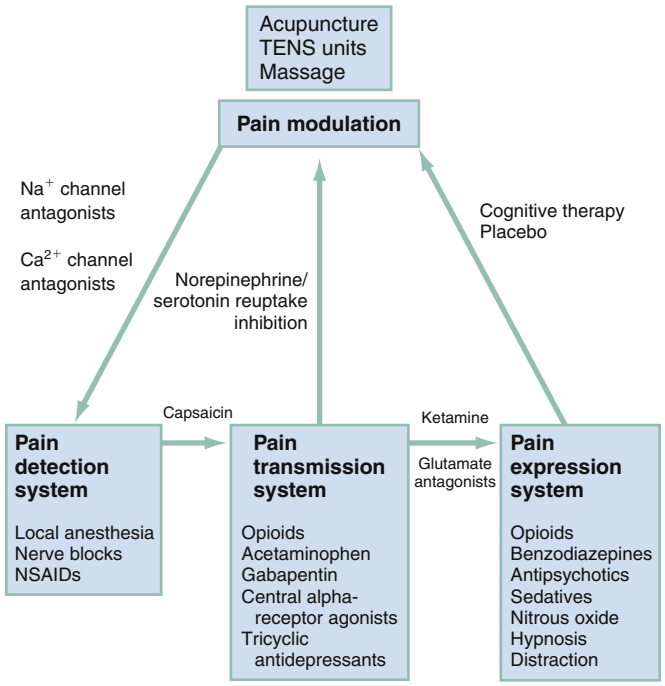

Fig. 6.6 Sites for pain treatment algorithm. *NSAID,* Nonsteroidal anti-inflammatory drug; *TENS,* transcutaneous electrical nerve stimulation.

the contrary, analgesia administration may enhance the accuracy of the physical examination and patient assessment.

Chronic pain. The assessment of pain in the absence of acute or obvious physical injury requires a great deal of communication skill on the part of the clinician and patient. Many patients with chronic pain develop experiences, some adaptive and others maladaptive, in describing their pain and interacting with clinicians to receive pain treatment. Many behaviors such as exaggerating symptoms or attempting to manipulate clinicians are developed around the patient's expectations for obtaining pain therapy or pain relief. These behaviors, combined with the negative psychosocial effects and sense of futility associated with chronic pain, can complicate the evaluation process and care of chronic pain patients.

The assessment of chronic pain represents some of the most challenging situations to obtain an accurate clinical history. Patients who are having difficulty describing their pain should be encouraged with detailed questions about the pain, combined with multiple examples, comparisons, and summarizing statements, to facilitate accurate communication. Assuring the patient that the questions are intended to aid understanding and enable the effective treatment of symptoms can facilitate developing a common goal and help establish the trust necessary to develop an effective treatment strategy.

Patients with chronic pain can exacerbate their chronic pain in the setting of ongoing therapy or with untreated chronic pain due to a gap or lack of ongoing care. These scenarios require different treatment approaches. For chronic pain patients with an exacerbation in their pain exceeding the pain control of their usual treatment strategy, treatment can be approached in a fashion similar to that for acute pain. The goal for these patients should be to control the exacerbation and return the patient to their baseline function and treatment strategy.

Many patients with chronic pain are in comprehensive treatment programs, most of which involve a so-called contract concerning the provision of their pain management. For such patients, a review of the pain management plan in the medical records, or contact with the health care clinician who manages the patient's treatment plan, is a critical element in determining the best short-term strategy in the ED.

Patients with chronic pain who have a gap in their baseline treatment or who have never established appropriate treatment for chronic pain require an approach that addresses the need to establish a consistent treatment plan. Patients with no ongoing treatment plan should have a basic chronic pain treatment plan implemented during their ED visit. This should consist of acetaminophen, if not contraindicated, and a nonsteroidal antiinflammatory drug (NSAID), if tolerated.

Adjuvants appropriate for neuropathic or central pain may be added, if appropriate.

Opioids for chronic pain, whether for a patient already on a treatment plan or without a treatment plan, are rarely indicated in the ED, with the exception of patients who experience pain related to advanced malignancy (see below.) Opioids should neither be administered nor prescribed unless their need is verified with the clinician responsible for the patient's chronic pain management plan. In general, opioids for chronic pain management are the domain of clinicians in ambulatory pain centers or primary care physicians who will follow the patient's therapy, response, and compliance. There is often difficulty communicating this with patients who may have received opioids at many EDs, including the one currently being visited. The establishment of a departmental policy empowers emergency clinicians to administer or prescribe opioids for chronic pain syndromes without judging the patient.

Chronic pain care in the ED should emphasize the use of multimodal treatments and reduce the use of opioid medications.[19] Nonpharmacologic treatments in multimodal chronic pain care include physical rehabilitative therapies, interventional pain procedures, psychological therapy, and integrative approaches. An important aspect of caring for chronic pain is recommending a nonpharmacological treatment, or at least determining if a patient is willing to consider such therapies. The factors associated with a patient's willingness to accept such therapies have not been well defined, and therefore nonpharmacological approaches should be discussed with chronic pain patients presenting to the ED.[20]

Recurrent pain. Recurrent pain is a subset of chronic pain; the term describes patients who have symptoms with repeated episodes of similar pain. Recurrent pain can include back pain, myofascial pain syndrome, migraine syndrome, sickle cell disease, and inflammatory bowel disease. The treatment of recurrent pain in the ED incorporates elements of the treatment of acute pain and chronic pain, and prevention of recurrent pain events must be considered part of the treatment strategy. These therapies may integrate nonpharmacologic approaches, such as physical therapy for back pain, in addition to the use of preventive medications.

Chronic pain of malignancy. Chronic malignant pain is similar to acute pain related to ongoing nociceptive stimulation and similar to chronic pain in its duration and psychobehavioral effects. The medications used, however, are similar to those used for acute pain. The psychosocial effects of the pain of malignancy must be addressed as part of an effective treatment strategy.

Patients with a significant change in the pattern of their chronic pain caused by cancer or a terminal illness, as with other chronic pain patients, should be evaluated for a new process to account for the pain. Opioids, especially in long-acting or transdermal preparations, should be used liberally to bring pain relief for patients with terminal illnesses.

Neuropathic pain. *Complex regional pain syndrome* (CRPS) is a term that includes most sympathetically maintained neuropathic pain. CRPS type 1 (often referred to as reflex sympathetic dystrophy) develops after a painful injury and typically follows the distribution of a peripheral nerve. It is associated with hyperalgesia, allodynia, changes in skin blood flow, and sympathetic dysfunction. This syndrome develops during the healing and recovery phases of acute painful injuries and is generally described as a burning, tingling sensation in the area of the previous injury. This pain is likely related to ongoing stimulation leading to the development of self-sustaining modulation of the pain transmission system.

CRPS type 2, commonly referred to as causalgia, is associated with burning pain and allodynia in the distribution of an injured nerve, with no association with sympathetic symptoms. Opioids are ineffective in preventing CRPS after an injury has occurred. Clonidine, N-methyl-d-aspartate receptor antagonists, and γ-aminobutyric acid receptor agonists are more effective in treating CRPS than opioids. Gabapentin is generally considered a first-line agent, with pregabalin used for patients who cannot tolerate its sedating effects.

Antidepressants have effects on neuropathic pain that appear to be distinct from mood effects. Other antidepressants, such as selective serotonin reuptake inhibitors, may be safer and more effective for patients with chronic pain thought to be unrelated to central or neuropathic origins.

Several anticonvulsants, including gabapentin, phenytoin, carbamazepine, and valproic acid, are described for neuropathic pain with lancinating or burning properties. Carbamazepine is used most frequently for trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Gabapentin is described for both types of CRPS, postherpetic neuralgia, and diabetic neuropathy.

Pharmacologic Therapy

Opioids

In 1680, Sydenham wrote that "Among the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." Centuries later, this statement is still accurate, and titrated opioids remain the therapeutic foundation for severe acute pain.

The beneficial effects of opioids have been well documented for centuries, as have their toxicity and potential for abuse. Unfortunately, opioids are often poorly used in clinical practice. Concerns regarding opioid toxicity or dependence and a poor understanding of the pharmacokinetics of the drugs have led to inadequate dosing and excessively infrequent dosing intervals. In terms of toxicity and the likelihood of causing future dependence, the safety of short-term opioids for acute pain is established. Opioids are the first-line agents in the management of acute severe pain (Table 6.4). This safety is not well established in relation to the treatment of mild or moderate pain, however. The effectiveness of opioids relative to nonopioid analgesics, and a similar comparison of potential adverse effects, including the potential for abuse, argues against their use in mild pain and for sharp limits on their use for moderate pain. To prevent the overuse and misuse of opioids, the quantity and strength of the opioids prescribed should closely match the anticipated duration of the severe pain, and the patient should be transitioned off the opioid analgesia at the earliest appropriate opportunity. For most short-term acute pain episodes, such as a fracture, 3 to 5 days of opioid analgesia is sufficient, pending outpatient follow-up evaluation.

Mechanism of action and toxic effects. Opioids bind to specific endorphin system receptors located throughout the nervous system. These receptors suppress pain detection peripherally, modify pain transmission in the spinal cord and thalamus, and alter pain perception at the level of the cortex. A variety of endorphin receptors are defined (see Table 6.2). The unique actions of opioids are determined by the specific binding properties of the agent to the various receptors.

Both the short- and long-term side effects of opioids can limit the success of therapy. The occurrence of side effects varies among individual patients and opioid agents. Tolerance of many acute side effects develops shortly after the initiation of therapy.

The most common side effect of opioids is constipation. Constipation is attributed to opiate receptors located in the antrum of the stomach and proximal small bowel. Constipation can be anticipated with long-term opioid use (more than a few days). An active laxative, such as senna, lactulose, or bisacodyl, should be prescribed, as needed.

Nausea and vomiting also frequently occur with the administration of opioids, especially in opioid-naïve patients. Both opioids and acute

TABLE 6.4 Opioid Analgesics

Analgesic Agent	INITIAL DOSE		Duration of Action	EQUIPOTENT DOSE		Comments
	Parenteral	Oral		IV	PO	
Morphine	0.1 mg/kg	0.5 mg/kg	3–4 h	10 mg	50 mg	Standard opioid for comparison
Hydromorphone	0.015 mg/kg	0.075 mg/kg	2–4 h	1.5 mg	7.5 mg	Inactive metabolites advantageous to patients with renal or hepatic disease
Methadone	0.1 mg/kg	0.2 mg/kg	4–8 h	10 mg	20 mg	Used for opioid addiction therapy and chronic pain; half-life longer than duration of action
Fentanyl	1.5 μg/kg	3 μg/kg	0.5–1.5 h	100 μg	NA	Oral dose actually transmucosal absorption rather than ingestion; metabolites inactive; transcutaneous patches used for chronic pain
Oxycodone	0.1 mg/kg	0.15 mg/kg	3–4 h	10 mg	15 mg	Excellent bioavailability, so it is an effective oral agent for acute pain
Codeine	1.3 mg/kg	2.5 mg/kg	2–4 h	130 mg	200 mg	Side effect to analgesia ratio is undesirable; pronounced peripheral effects—constipation, nausea and vomiting, cough suppression
Hydrocodone	NA	5–15 mg	3–4 h	NA	30 mg	Commonly used in preparations with acetaminophen; more potent than codeine
Meperidine	0.75 mg/kg	3 mg/kg	2–3 h	75 mg	300 mg	Toxic metabolite normeperidine accumulates at normal doses; generally should not be used for acute analgesia
Oxymorphone	0.01 mg/kg	0.1 mg/kg (PR)	3–4 h	1 mg	10 mg	Rectal dosing more predictable than other agents
Alfentanil	10–20 μg/kg	NA	8–12 min	1 mg	NA	Short duration due to redistribution; duration of action increases with size of dose
Sufentanil	0.1 μg/kg	30 μg (sublingual)	1–1.5 h	10 μg	NA	Minimal cardiovascular side effects
Remifentanil	0.5–1 μg/kg	NA	4–6 min	50 μg	NA	Used as a continuous infusion
Nalbuphine	0.4 mg/kg	0.1 mg/kg	3–4 h	40 mg	NA	Mixed agonist-antagonist; decreased respiratory depression relative to other opioids; limited analgesic effect; used during perinatal period

IV, Intravenous; *NA*, not applicable; *PO*, by mouth; *PR*, per rectum.

pain can cause nausea and vomiting, and it is often difficult to distinguish the two. Routine coadministration of an antiemetic, once an almost universal practice, is not necessary. However, nausea and vomiting in the context of persistent acute pain after opioid administration may require antiemetics and additional opioids. Typical antiemetics include promethazine, prochlorperazine, and odensatron.

Immunoglobulin-mediated allergies are rare for morphine and other opioids. Many patients experience mild pruritus of the trunk and face after parenteral administration. This common side effect is related to histamine release from opioid receptors on mast cells and does not constitute an allergy. To a varying degree, opioids destabilize mast cells in a dose-dependent fashion, causing histamine release and resultant urticaria, pruritus, and orthostatic hypotension. This reaction may appear as localized urticaria tracking up a vein after intravenous (IV) administration of an opioid, especially morphine. Rarely, bronchospasm may be seen in patients with reactive airway disease or atopy. This effect usually subsides rapidly, with no treatment required, although the symptoms can be controlled with the administration of an antihistamine.

Sedation and respiratory depression can occur with opioid administration for acute pain. Opioids decrease medullary sensitivity to carbon dioxide, resulting in respiratory depression. Combining opioids with other sedating agents, such as benzodiazepines, increases the likelihood of respiratory depression. Patients with underlying hepatic or renal dysfunction are also at increased risk because of their inability to clear opiates normally, resulting in the accumulation of active metabolites and a higher risk for sedation or respiratory depression. Patients with decreased cerebral perfusion are also at high risk of developing respiratory depression when treated with opioids, and care should be taken when treating patients in shock or with unstable illnesses.

Pain is a very effective stimulant of respiratory drive, rendering respiratory depression rare in the context of acute severe pain. Fear of respiratory depression should not deter the emergency clinician from treating pain adequately, although monitoring patients receiving significant doses of opioids is advised. It should be noted that patients who had previously tolerated a dose of an opioid may develop respiratory depression if the source of acute pain is removed, such as by local anesthesia or the reduction and stabilization of a fracture. Transient respiratory depression from opioids usually responds to simple verbal or tactile stimulation and, uncommonly, requires more aggressive interventions such as airway repositioning, stimulation, or opioid reversal.

Tolerance, physical dependence, and addiction are common effects of the prolonged use of opioids. Physical dependence is defined as the occurrence of an opioid withdrawal syndrome following abrupt cessation, rapid dose reduction, or administration of an antagonist. Tolerance is an expected phenomenon that occurs after prolonged exposure to opioids and is characterized by the diminution of an opioid's effect over time. The development of tolerance is a normal expected result of the prolonged use of opioids and does not represent addiction.

Addiction is a potential risk associated with prolonged opioid use and often limits use. The term *addiction* refers to a neurobiologic

BOX 6.4 Addiction Behaviors

Behaviors Typically Specific to Addiction

- Injecting oral formulations
- Concurrent abuse of alcohol or illicit drugs
- Selling or diversion of prescription drugs
- Prescription forgery
- Obtaining drugs from nonmedicinal sources
- Repeated dose escalation
- Repeated visits to other EDs without informing prescriber
- Drug-related deterioration in function at work or socially
- Repeated resistance to changes in therapy, despite evidence of adverse drug effects

Behaviors Less Specific to Addiction

- Aggressive complaining about the need for more drug
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Openly acquiring drugs from other medicinal sources
- Occasional dose escalation or noncompliance
- Unapproved use of a drug to treat another symptom
- Resistance to change in therapy associated with tolerable side effects, with expression of anxiety related to the return of severe symptoms

ED, Emergency department.

disease, with many factors influencing its development and manifestations (Box 6.4). Addiction, including opiate use disorder, is characterized by compulsive drug use, continued use despite harm, and drug craving. While the risk of addiction from short-term opioid administration in the ED is small, ED opioid prescriptions may contribute to the development of addiction in some patients, and a patient's long-term risk should be considered in their treatment decisions.[21]

Drug-seeking behavior. Some patients feign or exaggerate pain to receive opioids to abuse medications or sell them to others, an occurrence defined as diversion. Opioid abuse and diversion is recognized as a growing problem, and the rapid growth in the number of opioid prescriptions has played a large role in rising rates of abuse and diversion.[14,15] In recognition of diversion and abuse, many states have developed prescription monitoring programs that allow for information exchange among clinicians to detect frequent opioid prescriptions. Prescription-monitoring programs effectively reduce the number of opioid prescriptions given to patients at risk for abuse or diversion as long as clinicians consider these data as a routine and integrated practice for patient care.[22-25] Some states require consultation with the registry before prescribing opioids.

A physician's impression of behaviors believed to be associated with patient drug-seeking is associated with reducing the treatment of the patient's pain. Unfortunately, prescriber perceptions are often complicated by differences between the health care clinician and the patient in socioeconomic class, ethnic and racial background, and age, making them frequent sources of bias in the treatment of pain.[16,17] Care must be taken to recognize these factors and consider their impact on treatment decisions. A thorough evaluation of drug-seeking behavior for a patient includes a review of medical records, prescription registries, and contact with other clinicians (e.g., hospitals, primary care physicians), as available and appropriate. Patients with chronic conditions that can cause acute pain, such as dental caries, some gastrointestinal (GI) syndromes, or long-standing back pain, should be offered alternative pain management approaches such as nerve block, nonopioid analgesia, or symptomatic treatment with antispasmodic agents until they can resume care with their usual health care clinicians.

Administration of pain control. The goal of opioid administration is to attain effective analgesia with minimal adverse effects. The effects of opioids vary widely among individuals. There is no ceiling effect to their potency. There is no standard, fixed, or weight-related dose that will consistently produce a given clinical effect. The correct dose that a patient requires at a particular time can only be determined by repeated assessment of the degree of pain relief and adverse effects. Therefore, the use of opioids requires titration based on frequent and accurate assessments (Fig. 6.7).

The most effective and safe way to achieve pain relief is to use a deliberate IV titration. The intramuscular (IM) route of administration of opioids has several disadvantages and is not advised to treat acute pain (Box 6.5). The principal limitation of the IM route is its inability to titrate specific doses to desired treatment effects. The time to achieve significant pain relief from an IM injection varies substantially for each patient and offers no therapeutic advantage over an oral medication dosing strategy.

Most patients with mild to moderate pain requiring opioid therapy are best treated with an oral (PO) opioid. If pain is severe or the patient is expected to require multiple doses for management, an IV route is desirable. If an IV line cannot be established, and the patient cannot tolerate PO medications, the subcutaneous (SC) route is preferable to the IM route. SC injection is less painful than IM injection, with a similar onset of pain relief.

Opioids can be delivered through an oral transmucosal or intranasal mucosal route.[26-28] Buprenorphine can be given via a sublingual route; whereas fentanyl is available in an impregnated sweetened matrix called Fentanyl Oralet (PO transmucosal fentanyl citrate). Transmucosal fentanyl, butorphanol, and sufentanil also produce rapid clinical effects via nasal mucosal absorption.[26]

The optimal use of IV opioids requires administering an initial loading dose followed by an assessment of the analgesic effect. Frequent (every 5–15 minutes) repeated doses should be administered until analgesia is achieved, followed by doses at regular intervals to prevent the return of significant discomfort (see Fig. 6.7).

Specific agents

Morphine. IV morphine is frequently used for the treatment of acute severe pain in ED patients. Morphine is the opioid analgesic agent with which all other opioids are compared. When administered IV, morphine reaches a peak of action in 15 to 20 minutes, with a half-life of 1.5 to 2 hours in healthy young adults and slightly longer in older adults. Its duration of action is 3 to 4 hours. An appropriate loading dose of morphine for acute severe pain is 0.1 to 0.15 mg/kg IV of ideal body weight, augmented by repeated doses of approximately half the initial dose every 5 to 15 minutes, depending on the severity of the pain and patient response.

Morphine is effective by oral administration; however, only 20% of the ingested morphine dose will reach tissues after first-pass metabolism, requiring a dose adjustment approximately five times that of an equipotent IV dose. The formerly held belief that morphine causes more smooth muscle spasm than other opioids, rendering it inappropriate for the treatment of patients with biliary or renal colic, has been thoroughly discredited.

Morphine is primarily metabolized by conjugation into three- and six-conjugate forms in the liver. The six-conjugate form morphine metabolite is a strong mu and delta receptor agonist. This form plays an important role in the efficacy and duration of clinical effects. The three-conjugate form (normorphine) has no opioid analgesic activity but has been associated with CNS side effects (e.g., tremors, myoclonus, delirium, seizures) when it accumulates. This risk is greatest in older patients and those with renal insufficiency.

Meperidine. Meperidine (Demerol), although once widely used, has several disadvantages compared with morphine and

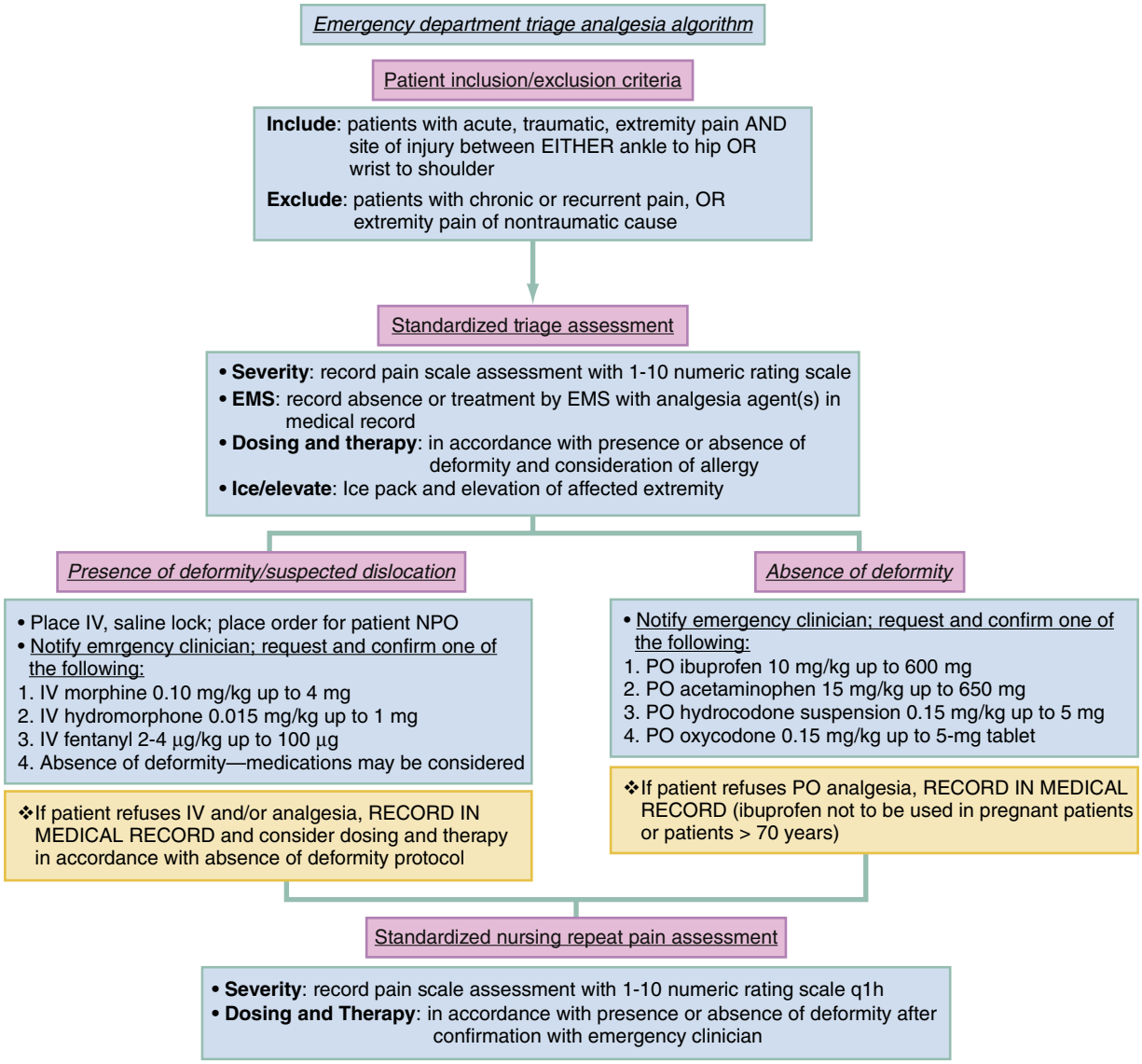

Fig. 6.7 Emergency department triage analgesia algorithm. *EMS,* Emergency medical services.

BOX 6.5 Disadvantages of Intramuscular Opioid Administration

Pain on injection
Delayed onset of action
Inability to predict therapeutic effect
Inability to titrate dosage
Diurnal variation in level achieved
Disease state may affect level achieved
Level dependent on intramuscular injection site

other parenteral opioids. The greatest disadvantage is that it is metabolized by the cytochrome P450 system to the active metabolite, normeperidine. Normeperidine can cause CNS toxicity at therapeutic meperidine doses. Normeperidine has a half-life of 12 to 16 hours and blocks muscarinic receptors, resulting in significant anticholinergic effects, including agitation and delirium. These effects may lead to seizures, hallucinations, and psychosis as the metabolite accumulates. Meperidine is not indicated for use in the ED.

Hydromorphone. Hydromorphone is a semisynthetic derivative of morphine that is a potent analgesic agent, frequently used to manage acute pain in the ED. Hydromorphone is the P450 metabolite of hydrocodone and is approximately seven times more potent than morphine, with a similar duration of action (7 mg of morphine is roughly equivalent to 1 mg of hydromorphone.)

Pruritus, nausea, and vomiting may occur less frequently with hydromorphone administration than with morphine at equianalgesic doses. Hydromorphone is primarily conjugated in the liver to hydromorphone-3-glucuronide (H3G), an inactive metabolite, and is excreted through the renal system. Thus, hydromorphone is better tolerated than morphine, particularly in older patients and those with hepatic impairment. Patients with renal insufficiency may be at some risk of neurotoxicity after prolonged exposure due to H3G accumulation. Patients allergic to morphine do not consistently have cross-reactivity with hydromorphone. Hydromorphone can be given via the IV, SC, PR (per rectum), or PO route.

Fentanyl. Fentanyl is a synthetic opioid that is highly lipophilic; it produces analgesia within 1 to 2 minutes following IV infusion. Fentanyl redistributes rapidly, and its duration of therapeutic action is approximately 30 to 60 minutes.

The P450 system metabolizes fentanyl into inactive metabolites. Drug accumulation and toxicity may occur after tissue saturation following a prolonged infusion, but this is unlikely to occur during acute therapy. The short duration of action for fentanyl makes it highly titratable and useful in patients who require serial examinations, such as trauma patients with possible occult head injury.

Fentanyl causes less histamine release than morphine at equianalgesic doses and is associated with fewer peripheral effects. Fentanyl is an excellent choice for treating pain in patients with bronchospastic lung disease or a history of opioid-associated pruritus. Fentanyl is more frequently associated with respiratory depression than morphine. Patients receiving repeated doses of fentanyl should be monitored with direct observation supplemented by pulse oximetry.

The ED use of fentanyl is associated with a very low incidence (1.1%) of serious complications. High or repeated fentanyl doses may produce muscle rigidity. This side effect, so-called rigid chest syndrome, usually occurs with anesthetic doses greater than 7–15 μg/kg, but also has been reported during use for procedural sedation; it may be so severe that it interferes with respiration. Rigid chest attributed to fentanyl is exceedingly rare at doses typically used for acute analgesia. Chest rigidity may respond to naloxone, but neuromuscular blockade may be necessary if naloxone reversal is not successful.

Fentanyl can be administered IV, transmucosally, or transdermally. Nebulized or intranasal fentanyl has been described to treat acute pain in patients without IV access at doses of 1–3 mcg/kg.[26]

Sufentanil. Sufentanil is a highly lipophilic synthetic opioid. It has been noted to have fewer cardiac effects than other opioids, and no breakdown products, making it an ideal medication for patients undergoing cardiac surgery or with renal or hepatic disease. Due to its high Cmax and initial dosing IV, it is associated with apnea after IV administration and is usually used in intubated patients in the operating room. Recently, its use sublingually has been described for postoperative pain and the treatment of moderate and acute pain in the ED.[26,27,29]

Buprenorphine. Buprenorphine is a synthetic opioid with a high affinity for the opiate receptor. Buprenorphine has no current indication for the treatment of pain. Rather, buprenorphine, either as a sole agent (Subutex) or when combined with naloxone (Suboxone), is used to reduce opioid drug cravings in patients with opiate use disorder. It has been described for the initiation of treatment for opioid use disorder in the ED.[30]

Buprenorphine is highly effective at reducing opioid cravings and therefore has become a mainstay of medication-assisted drug therapy recovery and rehabilitation programs. The combination of buprenorphine and naloxone is the most commonly used agent with the addition of naloxone acting as an intravenous or inhalation abuse deterrent. Naloxone absorbed in the gastrointestinal tract, by sublingual or oral forms, is largely inert; whereas, absorption via inhalation or intravenous routes results in significant uptake to the opiate receptors with resultant blockade of these receptors and the precipitation of acute withdrawal symptoms.

Oxycodone. Oxycodone is a strong opioid agonist that is highly bioavailable in an oral form. Oxycodone is widely sold in combination with acetaminophen as well as by itself and is also available in long-acting PO formulations. Oxycodone for acute pain should be prescribed in the noncombination form to allow a balance between oxycodone and a nonopioid medication to be individualized for the patient needs. Baseline administration of a nonopioid medication, supplemented by titrated doses of oxycodone, will achieve the optimal effect, with the fewest side effects. Oxycodone bioavailability is much higher than other oral opioids. It is quickly and efficiently absorbed, which may be a causative factor in its high abuse potential.

Oxycodone is not available in a parenteral form in the United States, although studies have demonstrated its IV form to be equianalgesic to morphine. Similar to other opioids, the analgesic effects of oxycodone are dose-dependent. A 15-mg oxycodone dose has similar efficacy to 10 mg of IV morphine. The onset of action of PO oxycodone is approximately 20 to 30 minutes.

Oxycodone undergoes hepatic metabolism into oxymorphone, a strong opioid agonist that principally accounts for its analgesic effects. Approximately 10% of patients do not metabolize oxycodone well and cannot generate the functional metabolite, oxymorphone. This defect in metabolism renders these patients unable to achieve clinically meaningful pain relief with typical dosing strategies and may require very large doses to achieve analgesia. This effect can also be caused by agents that compete with oxycodone for CYP2D6 metabolism, such as neuroleptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Cases of serotonin syndrome have been reported when serotonin reuptake inhibitors and oxycodone are given together, likely due to this metabolic interaction.

Hydrocodone. Hydrocodone is metabolized in the liver to hydromorphone and is typically given orally. Hydrocodone provides greater pain relief when combined with acetaminophen or NSAIDs than either component alone. Hydrocodone combinations are less effective than oxycodone-acetaminophen combinations. Hydrocodone clinical analgesia effects typically last 4 hours, with typical dosing of 5 to 20 mg. As with oxycodone, hydrocodone should be prescribed in pure form, not in a combination agent, to allow individual titration of opioid and nonopioid analgesics.

Codeine. Codeine is a weak opioid receptor agonist, usually prescribed in combination with acetaminophen, but has little, if any, role in the modern ambulatory treatment of pain. Codeine is thought to exert its effects through metabolism into morphine and other active hepatic metabolites. Although, like oxycodone, approximately 10% of the population metabolizes it poorly. Although historically prescribed for mild to moderate pain, codeine is a poor choice for analgesia due to its tendency to cause side effects, particularly nausea, cramping, and constipation, at doses that provide minimal analgesia.

Methadone. Methadone has several unique features that distinguish it from other opioids. It has no known neurotoxic or active metabolites and has high bioavailability. In addition to being a strong opioid agonist, methadone also has N-methyl-d-aspartate antagonist and serotonin reuptake inhibitor qualities. Methadone has a slow elimination half-life of 27 hours due to its lipophilicity and tissue distribution. This slow clearance of methadone is the basis for its use in maintenance therapy, given that it can delay the onset of opioid withdrawal symptoms for up to 24 hours. The duration of its analgesic effects is closer to 6 to 8 hours. The discrepancy between the duration of analgesia and the duration of prevention of withdrawal symptoms is due to the biphasic elimination of the drug and its redistribution.

Naloxone. Naloxone is an opioid antagonist that reverses the effects of opioids and is used in the setting of adverse, opioid-induced events, such as opioid overdose. It can precipitate physiologic withdrawal in opioid-dependent patients. The duration of action of naloxone is approximately 45 minutes, which is shorter than that of most opioids, and care must be taken to monitor for the recurrence of opioid adverse events following this period. Naloxone can be given IV, IM, SC, or via an endotracheal tube, but is typically given in titrated doses of 0.2 mg IV until reversal of any adverse opioid effect is observed. In the setting of adverse events from opioid treatment, usually respiratory depression, careful titration allows for the smallest dose possible to be administered to not reverse the analgesic effect of the opioid completely. Naloxone, 0.4-mg autoinjectors, are available for outpatient use to prevent overdose complications. Patients seen in the ED for opioid overdose

are at high risk for subsequent death from overdose.[31] Distributing naloxone autoinjectors to opioid-dependent patients represents an opportunity to intervene and prevent future overdose complications.

Tramadol. Tramadol is a synthetic oral analgesic that is a weak mu agonist, with some serotonin and norepinephrine reuptake qualities. Its analgesic properties are thought to be primarily due to mu receptor agonist activity. Tramadol-induced analgesia is partially reversed by naloxone, suggesting that other properties play a role in its therapeutic effects. As a selective mu agonist without kappa agonist effects, tramadol should not cause physiologic dependence, although tramadol use is associated with abuse. Tramadol should not be considered a nonaddictive alternative to opioids.

Tramadol is metabolized in the liver by the cytochrome P450 system. One of its metabolites, M1, has a greater mu receptor affinity than tramadol and has an elimination half-life of 9 hours. Tramadol appears to affect GABA, norepinephrine, and serotonin receptors and the reuptake of the neurotransmitters. These properties may serve to activate descending pain modulation pathways.

Tramadol may be effective at low doses. At increasing doses, it is associated with nausea and vomiting, limiting its use to low doses and effectively creating a therapeutic ceiling to its clinical use. Tramadol, 37.5 mg, combined with acetaminophen, 325 mg, appears to have similar efficacy to hydrocodone, 5 mg, combined with acetaminophen, 325 mg. As with hydrocodone and oxycodone, tramadol should be prescribed in pure form, allowing accurate dosage adjustment from other agents.

The most common tramadol side effects are nausea, vomiting, dizziness, orthostatic hypotension, and sedation. These side effects are seen in as many as 17% of patients using the drug for chronic pain, with slightly lower rates in patients receiving controlled-release versions. Tramadol lowers the seizure threshold and therefore provokes isolated seizures in selected patients. Tramadol use along with other serotonergic medications (e.g., selective serotonin receptor inhibitors, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors) is associated with serotonin syndrome.

Tapentadol. Tapentadol is a mu opioid agonist and norepinephrine reuptake inhibitor. It is thought to control acute pain via both these pathways. Tapentadol has similar efficacy to oxycodone to treat acute pain, with less frequent nausea and vomiting. Its dual mechanism of action makes it a potentially effective drug for use in chronic pain.[32]

Opioid use for acute abdominal pain. Historically, pain treatment was withheld from patients with abdominal pain to avoid confounding a diagnosis. These recommendations date from the turn of the 20th century, predating modern diagnostic techniques, and have no place in modern emergency care. Multiple studies have confirmed the safety of providing effective opioid analgesia to patients with undiagnosed abdominal pain.

Nonopioid Analgesic Agents

Acetaminophen. Acetaminophen is the first-line agent for treating acute and chronic pain and is the safest pharmacologic option for pain in children and adults. It has a high toxic-to-therapeutic ratio and lacks significant drug interactions compared with other pain medications.

Although acetaminophen has been in use since the 1880s, its pharmacologic mechanism of action is unknown. Acetaminophen has known analgesic and antipyretic activity, with no known peripheral antiinflammatory effects. Its activity may be due to the inhibition of prostaglandin endoperoxide H_2 synthase and a cyclooxygenase isoenzyme centrally. It may also affect the activation of beta-endorphin centrally. The analgesic actions of acetaminophen are comparable in magnitude to those of NSAIDs. The analgesic effects of the combination of acetaminophen with an NSAID are additive.

Acetaminophen is metabolized in the liver primarily through conjugation to a sulfate or glucuronide. A minor pathway for the oxidative metabolism of acetaminophen produces the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification and elimination. Hepatic toxicity can occur when glutathione pathways are overwhelmed by an increase in NAPQI or a decrease in glutathione levels. Hepatic toxicity is rare with ingestions less than 10 g in a 24-hour period, unless underlying liver disease exists or there is concomitant ethanol abuse. In the latter cases, therapeutic doses can cause clinical hepatotoxicity.

Acetaminophen is generally well tolerated when used at therapeutic doses. Mild rashes are rarely reported, as is bone marrow suppression, manifested by neutropenia, thrombocytopenia, and agranulocytosis. Its use is associated with several important drug interactions. Many anticonvulsants, including phenytoin, barbiturates, and carbamazepine, induce hepatic microsomal enzymes. Increased conversion of acetaminophen to its toxic metabolite may occur in patients who are taking anticonvulsants, but this is rarely of clinical significance in the context of the usual doses for pain management.

Although uncommon, drug interactions resulting in an increased international normalized ratio (INR) have been reported for patients taking acetaminophen and warfarin, particularly among patients taking high doses of acetaminophen (>9100 mg/week). Chronic use of acetaminophen should be avoided in patients with hepatic or renal disease. Renal failure can worsen with acetaminophen use, but the mechanism is unknown. Patients with a history of salicylate hypersensitivity characterized by urticaria have an 11% cross-reactivity to acetaminophen, and the agent should be used with caution in this group.

For mild analgesia and fever reduction, acetaminophen is the first-line agent and is the first choice for use in combination with other agents, usually opioids, to treat patients with more severe pain. The recommended dose of acetaminophen for an adult is 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg/day. No increase in analgesic effect has been reported for doses greater than 650 mg (Fig. 6.8).

Nonsteroidal Antiinflammatory Drugs

NSAIDs inhibit cyclooxygenase (COX) and, as a result, the synthesis of prostaglandin, a key mediator of inflammation. The analgesic effect of NSAIDs is peripherally mediated by decreasing prostaglandin levels and effectively raising the threshold of activation of nociceptors. NSAIDs have synergistic effects with opioids and can reduce the amount of opioids needed to achieve pain relief.

Two COX isoenzymes mediate prostaglandin synthesis. COX-1 is present in all cells and plays an important role in homeostatic functions. COX-2 is induced by injury or inflammation and generates prostaglandins as part of the inflammatory process. Nonselective NSAIDs inhibit both COX-1 and COX-2, resulting in multiple beneficial effects (e.g., reduction of inflammation, pain, fever) and some important undesirable effects.

As a group, and because of their common use, NSAIDs are responsible for more serious drug-related side effects than any other analgesic drug class. The major side effects of NSAID analgesic agents are GI bleeding, renal failure, anaphylaxis, and platelet dysfunction. Most of these side effects occur in patients who are taking NSAIDs for chronic conditions. More than 100,000 hospital admissions and approximately 16,500 deaths occur each year from GI bleeding related to NSAID use for osteoarthritis and rheumatoid arthritis. One survey has estimated that for every 100,000 people taking NSAIDs, there are 300 GI-related deaths, 5 hepatic-related deaths, 4 renal-related deaths, and some congestive heart failure–related deaths.

Bone and cartilage healing and repair during NSAID use is a concern in patients with acute fractures. There is limited evidence to

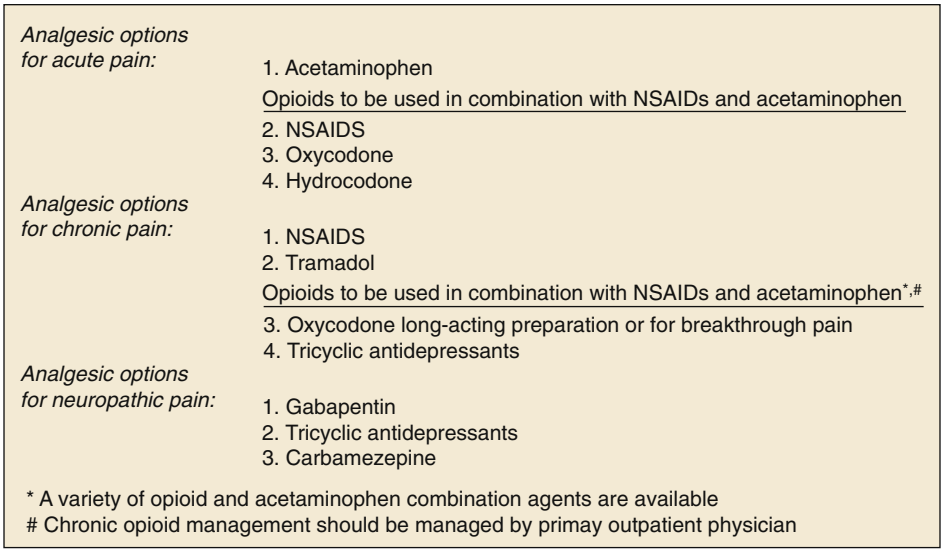

Fig. 6.8 Common outpatient pain treatments by pain type.

suggest that prostaglandins promote bone formation and that NSAIDs might inhibit the process. This issue has not been thoroughly pursued or established through properly conducted studies. There is no human subject evidence that short-term use of NSAIDs for analgesia after fracture is deleterious to healing.

COX also promotes the production of prostacyclin, a vasodilator that increases GI mucosal perfusion. In the stomach, COX-1 increases bicarbonate and mucus production, important for protecting the mucosal lining. Inhibition of COX-1 compromises these protective functions, predisposing patients to ulcerations and bleeding, exacerbated by concomitant NSAID-induced platelet dysfunction.

COX-1 and COX-2 affect the cardiovascular system by producing endothelial prostacyclin (vasodilatory) and thromboxane (platelet aggregation). Inhibition of COX-1 causes antiplatelet activity that may be cardioprotective by inhibiting thromboxane production more than prostacyclin. Inhibition of COX-2 inhibits prostacyclin production more than thromboxane and may produce prothrombotic effects, increasing the risk of cardiovascular events. In the case of nonselective COX inhibitors, these two effects appear to balance each other out, resulting in few changes in cardiovascular risk in studies of these drugs. In the case of selective COX-2 inhibitors, this may increase cardiovascular risk and has limited the use of these agents.

Prostaglandin produced by COX-1 causes renal vasodilation that maintains renal blood flow and the glomerular filtration rate (GFR). Inhibition of COX-1, especially in volume-depleted patients, can result in a decreased GFR and acute kidney injury. Sodium and water retention, hypertension, hyperkalemia, and acute renal failure may also ensue, particularly in patients with congestive heart failure.

The most common adverse effect of NSAIDs is GI mucosal injury. In patients taking NSAIDs continuously for 1 year, it has been found that 10% to 60% will develop abdominal pain, dyspepsia, or nausea and 2% to 4% will develop symptomatic ulcers. Risk factors include age, concomitant use of warfarin or corticosteroids, congestive heart failure, diabetes, and coronary artery disease. Cytoprotective agents such as misoprostol and proton pump inhibitors reduce this risk. The relative risk for GI side effects varies with various NSAIDs and treatment strategies (Table 6.5).

Drug interactions with nonsteroidal antiinflammatory drugs

Aspirin. NSAIDs may impair the cardioprotective effect of aspirin, although the available evidence is unclear, and the use of daily aspirin for cardiac prophylaxis should not deter the prescribing of an NSAID for acute pain or inflammation.

Oral anticoagulants. The antiplatelet effects of NSAIDs add to the anticoagulant properties of warfarin, compounding the risk of significant bleeding complications, especially from GI ulcers. Furthermore, NSAIDs displace protein-bound warfarin and cause subsequent increases in prothrombin times at a constant warfarin dose. NSAID use is generally avoided in patients who are taking warfarin.

Angiotensin-converting enzyme inhibitors. Concurrent use of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors may impair renal function and impair the antihypertensive effects of ACE inhibitors.

Diuretics. Patients taking diuretics have a greater risk of developing renal failure due to NSAID-mediated decreased renal blood flow. Also, the natriuretic response to diuretics depends in part on prostaglandin-mediated vasodilation.

TABLE 6.5 Risk of Serious Gastrointestinal Effects of Nonselective Nonsteroidal Antiinflammatory Drugs (NSAIDs)

NSAID	Relative Risk of Serious GI Toxicity
COX-2 inhibitor	0.6
Ibuprofen	1.0
Diclofenac	1.8
Sulindac	2.1
Naproxen	2.2
Indomethacin	2.4
Tolmetin	3.0
Piroxicam	3.8
Ketoprofen	4.2
Ketorolac	24.7
Risk Reduction When Added to Ibuprofen	
Proton pump inhibitor	0.09
Misoprostol	0.57

GI, Gastrointestinal.

BOX 6.6 Patients at Risk for Adverse Events during Nonsteroidal Antiinflammatory Drug (NSAID) Therapy

1. Patients with dehydration, hypovolemia or who have impaired renal function are at increased risk for decreasing renal function or renal failure.
2. Patients with liver disease or congestive heart failure—in particular, those already taking ACE inhibitors, ARBs, or diuretics—in whom liver or heart conditions may worsen.
3. Older patients are at enhanced risk for GI and renal events.
4. Patients with asthma and known aspirin hypersensitivity are at increased risk of bronchospasm.
5. Women in the third trimester of pregnancy—NSAIDs may prolong gestation or prematurely close the ductus arteriosus.
6. Patients who use tobacco or ethanol with a history of gastritis or peptic ulcer disease are at increased risk for peptic ulcer or GI bleed.

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin II receptor blocker; *GI,* gastrointestinal.

Glucocorticoids. Patients on corticosteroids have an increased risk of peptic ulcer disease. NSAIDs should generally be avoided in patients concurrently taking glucocorticoids unless closely supervised by a physician.

Lithium. NSAIDs enhance lithium reabsorption and may directly reduce lithium excretion, leading to increased lithium levels. CNS symptoms (e.g., drowsiness, confusion, vertigo, convulsions, tremors), cardiac dysrhythmias, and QRS widening are warnings of lithium toxicity. The lithium dosage should be reduced when an NSAID is prescribed

Nonselective cyclooxygenase inhibitor selection. NSAIDs combine analgesia and antiinflammatory effects with low abuse potential and many different side effects compared to opioid agents. Oral NSAIDs can be as effective as oral opioids for mild to moderate pain. Parenteral NSAIDs offer little advantage over their PO forms. Different patients respond differently to the beneficial effects and side effects of different NSAIDs. Therefore, some individual experimentation may be necessary to determine the best NSAID choice for a particular patient. No particular NSAID has been proven to be superior for any indication. Drug selection should depend on availability, side effect profile, convenience, and cost. Patients at risk for adverse events using NSAIDs are listed in Box 6.6.

Ketorolac tromethamine. Ketorolac was the first nonopioid analgesic agent available for parenteral use in the United States. For acute pain management, ketorolac is rarely indicated in the patient able to receive oral medications, given that 60 mg of ketorolac administered IM is not clinically superior to 800 mg of oral ibuprofen. Additionally, NSAID agents can be administered at a fraction of the cost of parenteral routes. A primary indication for ketorolac use is in the early treatment of renal colic because of the difficulty in renal colic patients tolerating oral medications.

Ibuprofen. Ibuprofen is the most widely used agent in the NSAID class. It is available over the counter in various preparations, including tablet, liquid suspension, and suppository forms. Ibuprofen is rapidly absorbed from the upper GI tract and has minimal interaction with other medications. The adult analgesic dose is 400 mg. No NSAID is more effective as an analgesic than ibuprofen, 400 mg, including ibuprofen doses of 600 and 800 mg.

Skeletal muscle relaxants. Skeletal muscle relaxants have been advocated as an adjunct to analgesics in managing musculoskeletal pain with a spasm component, principally back pain. Despite the common use of skeletal muscle relaxants, little data exist supporting their role in the treatment of pain. Studies have demonstrated that muscle relaxants, such as cyclobenzaprine, are indistinguishable from ibuprofen in analgesic effect but have an increased side effect profile.

Skeletal muscle relaxants should not be used to treat acute musculoskeletal pain as a substitute for proper doses of effective analgesics unless there is a high degree of anxiety accompanying the pain. Benzodiazepines are not recommended for the routine treatment of musculoskeletal pain.

Nitrous oxide–oxygen mixtures. The analgesic and anesthetic properties of nitrous oxide were discovered more than 200 years ago, and it is one of the original forms of patient-controlled analgesia. Nitrous oxide–oxygen mixtures can be used in the ED or the out-of-hospital care setting to reduce anxiety in patients and manage mild to moderate pain states. Combined with oxygen, a mixture of nitrous oxide and oxygen in a 50:50 ratio is safe when self-administered by the patient.[33,34]

Dentists have long used nitrous oxide and oxygen administered by nasal mask to treat pain and anxiety. Experience in emergency medicine with nitrous oxide–oxygen mixtures is greatest in the ratio of a 50:50 mixture with a self-administered, hand-held mask.

The mechanism of analgesia and anxiolysis with nitrous oxide have not been fully delineated. The nature of its analgesic effect appears to be similar to that of low-dose opioids, although some of the anxiolytic effects of nitrous oxide appear to have more in common with benzodiazepines than opioids. It has been postulated that nitrous exerts an effect on GABA receptors.

Nitrous preparations are often administered in a two-tank system, with a fixed-ratio nitrous oxide–oxygen mixture delivered to the patient through a demand valve activated with inhalation through a facemask or mouthpiece. A negative pressure of 3 to 5 cm H_2O must be produced within the mask or mouthpiece to activate the gas flow, limiting the use of these devices in very small children. Having the patient hold the mask to the face allows him or her to titrate the dose to an effective level. In 10% to 15% of patients, nitrous oxide is ineffective. It is much more potent as an anxiolytic than as an analgesic agent and can be supplemented with other analgesics.

Nitrous oxide is a folate antagonist and is strictly contraindicated in pregnant patients. Advanced scavenger systems are necessary to allow the safe use of nitrous oxide in the ED to avoid accumulation and toxicity in health care workers, especially if pregnant. Nitrous oxide–oxygen mixtures are contraindicated in patients with a decreased level of consciousness who cannot follow instructions. Patients with severe chronic obstructive pulmonary disease who retain CO_2 should be given nitrous oxide–oxygen mixtures carefully, given that the mixture contains 50% oxygen, which may predispose to hypercapnia. Because nitrous oxide diffuses into body cavities, it can worsen a pneumothorax or bowel obstruction.

Minor side effects of nitrous analgesic gas mixtures have been reported in 5% to 50% of patients. The most common adverse effect is lightheadedness, with paresthesias and nausea reported less frequently. No documented adverse hemodynamic effects have occurred with the self-administered forms of this agent. Side effects attributed to nitrous oxide usually resolve within minutes of discontinuation.

Ketamine. Ketamine is a drug that has typically been used primarily as a dissociative anesthetic for procedural sedation; it is one of the most effective and widely used drugs for procedural anesthesia worldwide. Ketamine has also been evaluated for low-dose use as an analgesic. Low-dose ketamine is similar to morphine in its analgesic effect when used alone and as an additive to opioids when used in conjunction with them at doses of 0.1 to 0.3 mg/kg IV (one-tenth to one-third of a typical dose used for dissociative sedation).

TABLE 6.6 Characteristics of Common Local Anesthetic Agents

Agent	Potency (Lipid Solubility)	Duration of Action (min)	Onset	Comments
Procaine	1	60–90	Slow	Solutions of 0.5%–2% used in infiltration and blocks
Tetracaine	8	180–600	Slow	Topical for ophthalmic use
Lidocaine	3	90–200	Rapid	Most commonly used agent; 1.5 times as toxic as procaine
Mepivacaine	2.4	120–240	Very rapid	Less potent and less toxic than lidocaine
Bupivacaine	8	180–600	Intermediate	Long-acting agent used in infiltration and blocks
Etidocaine	6	180–600	Rapid	Twice as toxic as lidocaine; used mostly in epidurals

Adapted from Paris PM, Weiss LD: Narcotic analgesics: the pure agonists. In Paris PM, Stewart RD, editors: Pain management in emergency medicine, Norwalk, CT, 1988, Appleton & Lange.

The principal side effects of ketamine are dysphoria, vomiting, and hypersalivation. Ketamine appears to be effective via the *N*-methyl-D-aspartate receptor, a different pathway from opioids, acetaminophen, or NSAIDS, giving it potential to affect analgesia when adverse effects limit other agents. The use of low-dose ketamine as an analgesic in the ED setting has increased and represents a consideration for patients with acute pain in whom traditional opioids or NSAIDS are deemed inappropriate or ineffective.[35-41]

Local/Regional Anesthesia

Mechanism of action. Peripheral nerves are responsible for transmitting pain information from pain receptors to the spinal cord. Each fiber consists of an axon surrounded by a covering called the Schwann cell. A myelinated axon is one covered by the projection of a Schwann cell that wraps itself many times around the axon; hence, the term myelin sheath.

Local anesthetics are much more effective at penetrating unmyelinated or lightly myelinated fibers than heavily myelinated ones. This difference explains the finding that local anesthetic agents provide sensory block without motor neuron effects (see Table 6.1).

Local anesthetic agents reversibly block lipid membrane sodium channels and prevent the influx of sodium ions into the axon, blocking depolarization and the nerve action potential. After injection of a local anesthetic, tissue buffers increase the pH of the solution surrounding the agent, driving much of the water-soluble acidic form to its lipid-soluble nonionic form. The lipid-soluble phase of the drug is able to penetrate the axon lipid membrane, where it then ionizes and enters the sodium channel, blocking the ability of sodium to enter the cell.

The use of emergency physician-administered regional anesthesia has increased in recent years and has been described for a wide variety of painful injuries, including rib fractures, hip fractures,[42,43] and dislocations[44,45] in adults and children.[46]

Intravenous lidocaine has also been described for the treatment of central pain syndromes and neuropathic pain, and has been noted to have opioid-sparing effects in the operating room. It has been best described in the ED to treat pain from renal colic[47] and radicular back pain.[48]

Classes of local anesthetic agents. Local anesthetic agents are chemical compounds that consist of an aromatic and amine group separated by an ester (e.g., procaine, chloroprocaine, tetracaine) or an amide (e.g., lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine) intermediate chain. Esters are unstable in solution and are metabolized in the body by the plasma enzyme cholinesterase. The amides, after absorption into the body, are destroyed by enzymes in the liver. The main considerations in the clinical use of these agents are potency, duration of anesthesia, and speed of onset (Table 6.6). The lipid solubility of an agent determines its potency. Less potent local anesthetics must be given in more concentrated forms and larger doses to achieve an equivalent effect.

The duration of anesthetic agent action is determined by its protein-binding affinity to sodium channel proteins. The speed of onset of any local anesthetic agent is directly related to its diffusion through tissues to the nerve, as determined by its pKa (dissociation constant)—the pH at which 50% is ionized. After injection, the anesthetic agent is in two forms, ionized and nonionized. Only the nonionized form of the drug diffuses into nerves. Therefore, solutions with a low pK_a have a more rapid onset of anesthesia.

Low tissue pH (5 or 6) in surrounding infected tissue delays the onset of local anesthesia in cases such as abscess incision and drainage by keeping more of the agent in an ionized state. The onset of action can be hastened by the alkalinization of the solution carrying the drug, decreasing its irritant effect (pain) on injection. This can be done clinically by adding sodium bicarbonate solution to the anesthetic at a ratio determined by the pK_a of the agent. Anesthetic agents, except cocaine, are vasodilators, which tend to shorten the duration of anesthesia. Injection of the solutions into vascular tissues shortens the duration of anesthesia and increases systemic absorption and the chance of systemic toxicity when larger doses are used. Therefore, epinephrine is often added to local anesthetic solutions.

Allergic reactions. True allergies to local anesthetics are rare. When an allergy to local anesthetics is reported, the offending substance is often one of the preservatives used. Because the amide agents and amino ester agents do not cross-react and use different preservatives, a patient may be given medication from another class if the allergy history is consistent with a specific anesthetic group. In those patients who report they are allergic to all "-caine" anesthetic agents, and the allergy is believed to be legitimate, diphenhydramine can be used as an alternative agent. Diphenhydramine may be used with 1 mL of a 50-mg/mL ampule diluted with saline to 5 or 10 mL (1%–0.5% solution) for local infiltration or nerve block. Diphenhydramine may cause direct tissue toxicity and should be avoided in areas with poor collateral circulation.

Local and systemic toxicity

Local toxicity. Local anesthetic agents, depending on the concentration, can be directly toxic to tissue. Also, there are theoretical concerns that the use of a vasoconstrictor in an anesthetic solution may reduce blood flow that could increase wound healing time and vulnerability of the wound to infection. However, this concept has never been formally demonstrated.

Systemic toxicity. Systemic toxicity of local anesthetics occurs when a sufficient quantity of the drug accumulates in the body so that sodium channel blockade occurs in the heart or brain. There is a dose-related clinical progression of local anesthetic toxicity, from subtle neurologic symptoms to seizures to cardiovascular collapse.

TABLE 6.7 Guidelines for Maximum Doses of Commonly Used Local Anesthesia Agents[a]

Agent	Without Epinephrine (mg/kg)	With Epinephrine (mg/kg)
Lidocaine HCl[b]	3–5	7
Mepivacaine HCl	8	7[c]
Bupivacaine HCl[d]	1.5	3

[a]All maximum doses should be reduced 20% to 25% in very young, old, and very sick patients.
[b]A lidocaine level of 0.5 to 2.0 g/mL may be reached for every 100 mg of lidocaine infiltrated for blocks.
[c]Epinephrine adds to the potential cardiac toxicity of this drug.
[d]Not to be used for pudendal blocks or IV regional anesthesia; not recommended for children younger than 12 years.
Adapted from Stewart RD: Local anesthesia. In Paris PM, Stewart RD, editors: Pain management in emergency medicine, Norwalk, CT, 1988, Appleton & Lange.

All local anesthetics produce systemic toxicity at sufficiently high blood or CNS concentration. Each local anesthetic has a range of therapeutic safety beyond which systemic toxicity is more likely to occur (Table 6.7). Overdosage of local anesthetics may occur more commonly in patients with large wounds and patients with a low body mass index.

The more lipophilic anesthetic agents (e.g., etidocaine, bupivacaine) are more cardiotoxic. Cardiac toxicity may also occur if epinephrine-containing anesthetics are inadvertently injected intravenously. Special care should be exercised in children and when performing blocks known to produce high blood levels of the anesthetic agent (e.g., intercostal). In pediatric patients, the maximum agent dose should be calculated before administration.

A wide variety of symptoms may be experienced from local anesthetic toxicity. These include lightheadedness, headache, tinnitus, paresthesias, muscle spasm, and confusion. In addition, benzocaine has been associated with methemoglobinemia. The degree to which CNS symptoms are experienced is directly related to the blood level of the local anesthetic.

CNS toxicity from anesthetic agents may result in seizures. A typical clinical progression usually begins with circumoral paresthesias, dysarthria, and tinnitus or similar auditory phenomenon. These events may be followed by a decreased level of consciousness progressing to confusion, seizures, and coma. Longer-acting, more potent agents (e.g., bupivacaine, etidocaine) are more likely than lidocaine to cause CNS symptoms at lower blood levels. Local anesthetic-induced seizures should be treated with IV benzodiazepines and may be refractory to normal dosing of neuroleptic medications.

Local anesthetic agents also have direct effects on cardiac automaticity, conductivity, contractility, and vascular tone. Management of cardiovascular collapse caused by toxic levels of local anesthetic agents should follow standard advanced cardiac life support guidelines. Unless the overdose is massive, the toxicity should be relatively short-lived, given the redistribution of the lipophilic agents.

Reducing the pain of local anesthetic injection. Many techniques can be used to reduce the pain of anesthetic injection (Box 6.7). Distraction by manual methods such as scratching, jiggling, or repetitively pinching the skin during needle puncture or injection reduces the discomfort experienced during local anesthetic injection. Injecting the agent slowly is the principal method to reduce injection pain. Injection into the edges of a wound is less painful than injection through intact skin. Warming the anesthetic and applying a topical anesthetic agent can also decrease the initial sensation associated with needle injection.

BOX 6.7 Techniques to Reduce the Pain of Injection

- Buffering of local anesthetic agents
- Counterirritation
- Slower rate of injection
- Use of topical anesthetics
- Warming of solution
- Distraction techniques

The addition of sodium bicarbonate to lidocaine before injection reduces anesthetic injection pain. A standard solution of sodium bicarbonate (8.4% in 50 mL) can be added to a syringe containing lidocaine in a ratio of 1 : 10 (e.g., 1 mL bicarbonate to 10 mL lidocaine, or 0.5 mL to 5 mL). Buffered lidocaine can be stocked in the ED and is effective for up to 1 week.

Topical Anesthesia

Topical anesthetics are generally of two types, those that can be applied to intact skin and those used on open skin. Topical agents are particularly useful in pediatric patients intimidated by needles. These agents may help decrease the intensity of superficial stimuli. The long application time and limited analgesia are the principal drawbacks of these strategies. In some patients, however, the strategy of applying the topical anesthetic and delaying the procedure until there will be less pain can be a useful tool in controlling pain and the response to subsequent interventions.

Topical anesthetics applied to intact skin

Eutectic mixture of local anesthetics. A eutectic mixture of local anesthetics (EMLA) is a mixture of lidocaine and prilocaine in an alkaline oil mixture in which the anesthetics are primarily in their nonionized form. This format allows diffusion through intact skin. The term *eutectic* refers to mixtures that result in a melting point higher than that of either agent alone.

For clinical use, an EMLA mixture should be applied to the desired area with an occlusive dressing 30 to 60 minutes before the procedure is performed. Heating EMLA for 20 minutes improves analgesia but is less effective than a routine 60-minute application, with or without heat. The duration of action after a 60-minute application is 1 to 5 hours.

Indications for the use of EMLA include venipuncture, arterial puncture, lumbar puncture, or arthrocentesis when a 30- to 60-minute delay in performing the procedure is not an impediment. EMLA can be applied in triage, particularly for pediatric patients, with an IV started later in the ED with little or no pain.

Ethyl chloride and fluoromethane sprays. Ethyl chloride and fluoromethane sprays are occasionally used for superficial analgesia. The agents evaporate quickly and cool the skin, providing brief (<1-minute) local anesthesia due to the sensation. The induced analgesia is brief. Any injection or incision should be made immediately after the application of the agent.

Agents applied to mucosal surfaces

Cocaine. Cocaine is unique among local anesthetic agents, given that it is a potent vasoconstrictor in addition to being an anesthetic that can be applied to mucosal surfaces. Cocaine is frequently used in the nose, for which a 4% (40 mg/mL) solution provides rapid anesthesia for the treatment of epistaxis and other nasal procedures. Although the maximum safe dose is unknown, no more than 200 mg is typically applied in adults. Cocaine should not be used in patients with known coronary artery disease due to the potential for coronary artery vasoconstriction.

Lidocaine. Both 2% and 4% lidocaine solutions are available in a viscous matrix for mucosal surfaces. Gel lidocaine can be used in nasal procedures, including the passing of nasogastric tubes and gastric lavage tubes. It can also be used for urethral anesthesia during Foley catheter placement. To be effective, lidocaine gel preparations must be injected into the urethra with a catheter tip syringe and be in contact with the area for 5 to 20 minutes. Lidocaine spray (2–10%) is useful for upper airway anesthesia, including intranasal use for nasogastric tube insertion.

Tetracaine. Tetracaine is a potent ester used for surface anesthesia of the cornea. Tetracaine stings when placed in the eye, but only for 10 to 15 seconds, after which there is excellent corneal anesthesia.

Benzocaine. Almost insoluble in water, benzocaine remains on mucous membranes in the mouth and is commonly used to provide superficial analgesia for oral procedures and pain.

Agents applied to open skin: lidocaine, epinephrine, and tetracaine. The combination of lidocaine, epinephrine, and tetracaine, 5 to 10 mL, may be applied to an open wound using sterile cotton, which is then covered and held in place for 10 to 20 minutes. Anesthesia has been described in approximately 85% of cases of wounds of the scalp and face and a lower percentage of extremity wounds. Application of the solution to mucous membranes (eye, intranasal) can result in toxic blood levels of tetracaine and should be avoided.

Nonpharmacologic Interventions

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) systems use electrical stimulation to induce analgesia, likely through the activation of descending sensory pathways and modulation of nociceptive signals at the level of the spinal cord (see Figs. 6.5 and 6.6). TENS units include a pulse generator, amplifier, and electrodes. Studies have demonstrated varying degrees of effectiveness. These devices are rarely indicated for use in the ED.

Out-of-Hospital Analgesia

Out-of-hospital clinicians frequently encounter patients with painful conditions. Patients obtain pain relief more quickly when pain medications are initiated by out-of-hospital personnel, although pain control in this setting is challenging to perform adequately.

The out-of-hospital environment is less controlled than the ED, and information regarding a patient's underlying condition is more limited, making the safe administration of pain medications more difficult. As in the ED, establishing rapport with the patient, providing calm reassurance, and using careful movement and handling, including proper splinting, are the first steps to which pharmacologic support can be added. Pain can be assessed in the out-of-hospital setting using numeric and verbal rating scales, the same as would occur in the ED.

Protocols for the administration of fentanyl and morphine are available in most emergency medical services systems and are usually limited to single-dose therapy prior to obtaining orders from the medical control physician. Morphine, 0.1 mg/kg, is safe for out-of-hospital use and should be considered the first-line agent for severe pain, as it is in the ED.

OUTCOMES: TREATMENT ENDPOINTS

Pain is a subjective experience. In the ED, management of acute pain should specify an initial dose, with a repeat dose and interval determined through a specific desired endpoint, such as pain reduction measured by a standardized assessment tool (see Fig. 6.7). A reasonable endpoint is to achieve sufficient pain relief for the patient to be able to doze or carry on a normal conversation with clinicians or family members.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 6: QUESTIONS AND ANSWERS

1. Which of the following statements is true regarding pain transmission?

a. Cardiac pain is transmitted via the sympathetic system.
b. Central post-stroke neuropathic pain is associated with parietal infarcts.
c. Descending modulation of pain is mediated primarily through γ-aminobutyric acid (GABA).
d. Peripheral neurotransmitters include prostaglandins, histamines, and substance P.

Answer: A. As a general rule, all visceral pain is carried via sympathetic afferents to ganglia and then to the spinal cord. Prostaglandins, substance P, and histamine sensitize peripheral afferents but are not neurotransmitters. The dorsal column tracts can down-modulate ascending pain signals. Central post-stroke pain is clinically seen most often after thalamic strokes. Descending tracts that modulate pain processing at the dorsal horn use norepinephrine and serotonin, with the effect of the former being most important regarding analgesia.

2. Which of the following analgesics is matched with the correct feature?

a. Fentanyl—prolonged QT interval on electrocardiography
b. Hydromorphone—active metabolites
c. Meperidine—muscle rigidity
d. Oxycodone—serotonin syndrome

Answer: D. Oxycodone has been associated with serotonin syndrome when coadministered with selective serotonin reuptake inhibitor (SSRI) medications. This is due to an active metabolite it shares with morphine, hydromorphone, hydrocodone, and codeine. The following are the other correct associations:

Meperidine—anticholinergic toxicity, active metabolites
Fentanyl—muscle rigidity (chest wall)
Hydromorphone—inactive metabolite

3. A 32-year-old male patient undergoing treatment for an ankle sprain returns to the emergency department (ED) because of inadequate pain relief from the medicines he was prescribed. He is currently taking oxycodone, 10 mg PO every 4 hours, and ibuprofen, 400 mg every 4 hours. What is the next most appropriate medicine to add to his pain treatment regimen?

a. Add acetaminophen, 650 mg q4h.
b. Add tramadol, 50 mg PO q4h.
c. Increase ibuprofen to 800 mg.
d. Increase oxycodone to 15 mg.

Answer: A. Acetaminophen provides additive analgesia to nonsteroidal antiinflammatory drugs (NSAIDs) and opioids, with few adverse effects at low doses, and it should be incorporated in acute pain treatment when not contraindicated. The pain-relieving effects of ibuprofen have not been shown to be greater when 800 mg is used versus 400 mg, so increasing the dose of ibuprofen is unlikely to improve pain relief and will increase the risk of adverse effects of the NSAIDs. An increased dose of oxycodone would result in improved pain relief but increases the risk of adverse effects; it should be tried after other nonopioid treatments have failed. In this case, acetaminophen should be attempted first before increasing the oxycodone dose. Tramadol would not be indicated before acetaminophen because of its high rate of dizziness and nausea.

7

Procedural Sedation and Analgesia

Steven A. Godwin and Andrew Schmidt

KEY CONCEPTS

- Safe, effective procedural sedation and analgesia requires high-level experience and sound protocols for patient selection and patient monitoring.
- After procedural sedation, patients should be discharged with and remain in the company of a responsible adult for 4 to 8 h after recovery.
- Propofol is the agent of choice for deep sedation in the emergency department but requires supplementation with an opioid analgesic when a painful procedure is planned.
- The absence of a preprocedure fasting period is not a contraindication to procedural sedation for an emergent or time-sensitive condition.
- Pulse oximetry is mandatory during sedation, and end-tidal CO_2 should be monitored if moderate or deep sedation is planned. Oxygen should be administered to patients undergoing procedural sedation.

FOUNDATIONS

Background and Importance

The performance of diagnostic and therapeutic procedures is common in emergency care. Many of these interventions are often associated with significant pain and anxiety. Procedural sedation and analgesia (PSA) is a fundamental and required skill for emergency clinicians and an integral part of the core training of emergency medicine residents. This chapter will focus primarily on PSA in the adult population; Chapter 157 provides specific guidance for PSA for children.

PSA improves patient care and satisfaction by relieving pain and anxiety and facilitating successful therapeutic or diagnostic procedures.[1,2] These include fracture or joint reduction, incision and drainage of abscesses, cardioversion, tube thoracostomy, lumbar puncture, complex wound repair, and imaging studies in uncooperative patients.

Many of the agents used for PSA have the potential to cause significant respiratory, cardiovascular, or central nervous system (CNS) depression. The Joint Commission (TJC), Centers for Medicare and Medicaid Services (CMS), American College of Emergency Physicians (ACEP), and American Society of Anesthesiologists (ASA) have produced expert consensus and evidence-based guidelines concerning the use of PSA (Box 7.1).[1–3] Although controversy continues about credentialing and oversight of PSA outside the operating room at some institutions, the advent of these guidelines has led to PSA becoming a common emergency department (ED) procedure. The adoption of PSA as a standard procedure in the ED has been further enhanced by the availability of shorter-acting more effective drugs, and noninvasive monitoring devices.

With the wide variety of patient populations and procedural needs, the ability to individualize PSA for each situation is a necessary skill. Knowledge of the characteristics of each sedative is essential but identifying patient characteristics that may increase the risk of adverse events during sedation is more critical in ensuring a safe and patient-centered sedation. This can be best achieved through detailed preprocedural patient assessment, protocols delineating the required personnel and equipment, specific drugs used (including their routes of administration, dosages, effects, interactions, and complications), considerations for special at-risk populations, and patient monitoring, recovery, and discharge criteria.

The following terms are important for understanding the concepts presented in this chapter:

Anxiolysis is a state of decreased apprehension concerning a particular situation in which the patient's level of awareness does not change.

Analgesia refers to the relief of pain without the intentional alteration of mental status, such as occurs in sedation. An altered mental state may be a secondary effect of the medications administered for this purpose.

Dissociation is a trancelike cataleptic state induced by an agent such as ketamine and characterized by analgesia and amnesia. Protective reflexes, spontaneous respirations, and cardiopulmonary stability are retained. Sedation is a controlled reduction of environmental awareness.

Procedural sedation and analgesia is a technique of administering a sedative or dissociative agent, along with an analgesic, to induce a state that allows the patient to tolerate painful procedures while maintaining adequate spontaneous cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously. The drugs, doses, and techniques used are not likely to produce a loss of the protective airway reflexes.

ASA currently recognizes a continuum of depth of sedation, consisting of four subgroups (Fig. 7.1)—minimal sedation, moderate sedation, deep sedation, and general anesthesia.[3] A fifth category, dissociative sedation, has been adopted by ACEP (Table 7.1).[1]

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive functions and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation and analgesia (formerly called *conscious sedation*) refers to a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, auditory only or accompanied by light tactile stimulation. Reflex withdrawal from the painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is always maintained.

Dissociative sedation is a trancelike cataleptic state induced by the dissociative agent ketamine; it is characterized by analgesia and amnesia while protective airway reflexes, spontaneous respirations, and cardiopulmonary stability are maintained.

Deep sedation and analgesia describes a drug-induced depression of consciousness during which patients cannot be easily aroused but

respond purposefully after repeated or painful stimulation. The ability to maintain ventilatory function independently may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even with painful stimulation. The ability to maintain ventilatory function independently is impaired. Patients typically require assistance in maintaining a patent airway, and positive-pressure ventilation is required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

The progression from minimal sedation to general anesthesia is a dynamic continuum that lacks distinct separation between stages. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient. The sedation continuum is not drug-specific, and levels from mild sedation to general anesthesia can be achieved with virtually all the PSA agents. Because of this, emergency clinicians administering PSA should be able to treat patients who are in at least one level greater than the intended level of sedation.

Anatomy, Physiology, and Pathophysiology

Pain experienced by sick and injured patients is the result of multiple pathways in the body. In general, a painful stimulus activates bodily receptors, which then initiates biochemical signals through peripheral and central neural pathways, ultimately ending in the interpretation and perception of pain in the brain. The pharmacologic treatment of this pain comes in many different forms, ranging from local or regional anesthetics directly injected into the affected area, to more systemic-acting analgesics, and finally to sedating or dissociating medications aimed at suppressing the overall central awareness of pain.

Each class of medication utilized in PSA has its own mechanisms of action to treat the perception of pain. The most well-known class of analgesics covered in this chapter is opioids. These medications act on systemic opioid receptors, inhibiting the central pain pathway, while also providing some level of sedation. More pure sedatives, like benzodiazepines, etomidate, and propofol, primarily act on central γ-aminobutyric acid (GABA) receptors, resulting in a decreased level of consciousness and a loss of awareness and of a sense of pain, instead of suppression of pain reception. Dexmedetomidine, another sedative, works on a different class of receptors known as alpha2-adrenoceptors, providing sedation and mild analgesia. Finally, ketamine, a potent analgesic and dissociative agent, produces its actions through antagonism of N-methyl-D-aspartate (NMDA) receptors. By understanding the mechanism of each medication, clinicians can develop a multimodal approach to PSA to ensure comfort and safety.

MANAGEMENT

Decision Making

The approach to procedural sedation requires evaluating conditions that may enhance or impede the effectiveness of procedural sedation. These factors include patient assessment, including the consideration of preprocedural fasting, appropriate personnel, supplies, and equipment, patient monitoring, and postprocedural recovery.

Patient Assessment

Although no outcome-based studies have demonstrated a clear benefit from presedation evaluation beyond vital signs, mental status, and

BOX 7.1 American College of Emergency Policy Statement on Procedural Sedation in the Emergency Department[a]

The American College of Emergency Physicians recommends the following:

- Emergency physicians who have received the appropriate training and skills necessary to safely provide procedural sedation, such as board certification (ABEM/ABOEM) in emergency medicine or graduates of an ACGME accredited emergency medicine program, should be credentialed without additional requirements for procedural sedation.
- The decision to provide sedation and selection of the specific pharmacologic agents should be individualized for each patient by the emergency clinician and should not be otherwise restricted.
- Emergency physicians and staff are expected to be familiar with the pharmaceutical agents they use and be prepared to manage their potential complications.
- To minimize complications, the appropriate drugs and dosages must be chosen and administered in an appropriately monitored setting. Patient evaluation should be performed before, during, and after their use.
- Institutional and departmental guidelines related to the sedation of patients should include the selection and preparation of patients, informed consent, equipment and monitoring requirements, hospital staff training and competency verification, criteria for discharge, and continuous quality improvement.

[a] June 2017.

Adapted from American College of Emergency Physicians Policy Statement: Procedural sedation in the emergency department. June 2017.

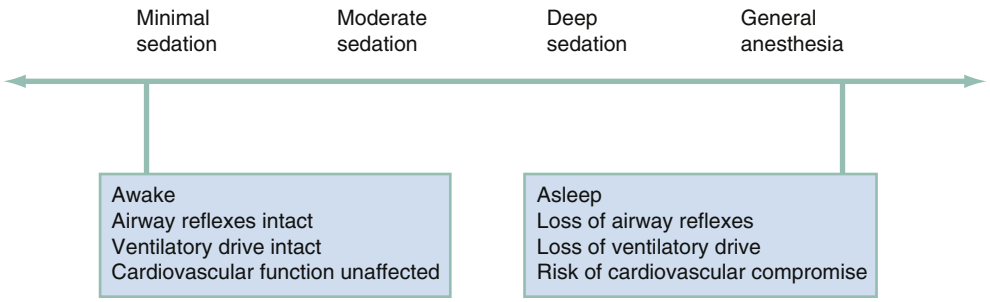

Fig. 7.1 Schematic Representation of the Sedation Continuum. As increasing doses of nondissociative agents are given, patients move along the sedation continuum, experiencing a progressive decline in their level of consciousness and an increased risk of adverse respiratory and cardiovascular events. If medication administration continues, the patient will ultimately reach a state of general anesthesia, with loss of protective airway reflexes and ventilatory drive. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient.

TABLE 7.1 Definition of Levels of Sedation and Analgesia

Parameter	Minimal Sedation (Anxiolysis)	Moderate Sedation and Analgesia (Conscious Sedation)	Deep Sedation and Analgesia	Dissociative Sedation	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response to repeated or painful stimulation	Unarousable, even with painful stimulus	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Adequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	Elevated	May be impaired

TABLE 7.2 American Society of Anesthesiologists Physical Status Classification

Class	Description	Examples	Sedation Risk
I	Normal, healthy patient	No past medical history	Minimal
II	Mild systemic disease without functional limitations	Mild asthma, controlled diabetes	Low
III	Severe systemic disease with functional limitations	Pneumonia, poorly controlled seizure disorder	Intermediate
IV	Severe systemic disease that is a constant threat to life	Advanced cardiac disease, renal failure, sepsis	High
V	Moribund patient who may not survive without procedure	Septic shock, severe trauma	Extremely high

airway and cardiopulmonary assessment, consensus guidelines have suggested that there may be an increased risk of adverse events in subsets of patients. These include patients at the extremes of age, patients with anatomic features predictive of challenging intubation or rescue bag-mask ventilation, and those with underlying significant disease states or impaired cardiopulmonary physiology. A patient's general physical status is conventionally categorized according to the ASA's classification system (Table 7.2).[4] Most practice guidelines require a history and focused physical examination be performed and documented before PSA. No routine diagnostic testing is needed before PSA, other than diagnostic testing driven by the patient's current status, including comorbidities.

The patient's age, current illness or injury for which PSA is intended, comorbidities, previous experiences or problems with PSA or general anesthesia, drug allergies and current medications, and tobacco, drug, and alcohol use are reviewed and recorded. A directed physical examination focuses on the vital signs, heart and lungs, and evaluation of the airway to identify anatomic features of a potentially difficult airway (see Chapter 1).

A discussion including the risks, benefits, and potential side effects of PSA should be held with patients or their families before the procedure. Written consent is preferred unless this is not possible due to the patient's clinical condition or access to the patient's medical surrogate.

Not every patient is an appropriate candidate for PSA in the ED. Therefore, patient selection is essential for the safety of the sedation. Depending on the clinical circumstances, a patient with an anticipated difficult airway or ASA classification of III or IV may require additional clinical resources. These can include additional nursing support or additional providers with expertise in procedural sedation, including emergency clinicians or an anesthesiologist. At times, it may even be advisable to undertake the procedure in the operating room with anesthesia.

Preprocedural Fasting

Evidence supporting preprocedural fasting in PSA has been extrapolated from the literature on general anesthesia. To date, there have been no published outcome-based studies demonstrating an increased risk of aspiration after a liquid or solid meal and no studies showing a benefit of fasting before PSA. Additionally, while anesthesia guidelines provide more conservative fasting recommendations, procedures deemed to be urgent or emergent should not be delayed based on fasting time.[5]

In 2014, ACEP endorsed a level B recommendation regarding preprocedural fasting. It stated that clinicians should not delay procedural sedation in adult or pediatric patients in the ED based on fasting time. The recommendation further noted that preprocedural fasting for any duration has not demonstrated a reduction in the risk of emesis or aspiration during procedural sedation and analgesia. A large 2018 pediatric study found no association between fasting time and serious adverse events, including clinically apparent aspiration.[6]

Subsequent expert consensus statements emphasize considering the patient's risk factors for aspiration, including severe underlying illness, obstructive sleep apnea, obesity, age less than 12 months, upper endoscopy as the procedure requiring sedation, or bowel obstruction, and incorporating this information into the choice of sedative agents and depth of sedation.[1,2]

Personnel

TJC and most institutional policies have suggested that PSA providers should have adequate training to administer the agents effectively and safely. This includes the skill to assess risk, dose, and administer medications appropriately, monitor the patient's response to the medications, and manage all potential complications, in particular airway complications.[2] This generally implies that PSA in the ED should be supervised by an emergency clinician or other appropriately trained and credentialed physician. It is also recommended that a qualified support person (e.g., nurse, respiratory therapist) able to recognize and respond to the complications of PSA be present for continuous monitoring of the patient. Although they may assist with minor interruptible tasks, they should focus on the patient's status and not have any other responsibilities that would interfere with monitoring and documentation from the start of the procedure to completion of the recovery phase.

BOX 7.2 Equipment for Procedural Sedation and Analgesia

High-flow oxygen source
Suction
Airway management equipment
Monitoring equipment
Pulse oximeter
ECG monitor, defibrillator, transcutaneous pacemaker
Blood pressure monitor
Capnography[a]
Vascular access equipment
Reversal agents
Resuscitation drugs
Adequate staff

[a] Capnography carries a level B recommendation by the American College of Emergency Physicians for use as an adjunct to pulse oximetry and clinical assessment to detect early hypoventilation. It is also recommended by the American Society of Anesthesiologists for monitoring the presence of exhaled carbon dioxide during moderate or deep sedation, in addition to the continual observation of qualitative clinical signs of adequate ventilation.
ECG, Electrocardiogram.

Devices and Techniques

Supplies and Equipment

PSA may result in an allergic reaction, oversedation, respiratory depression or, rarely, cardiopulmonary arrest. The incidence of these complications depends on patient selection, drugs used, rate and dosage of administration, and specific patient sensitivities. Consequently, appropriate equipment to monitor the patient's condition continually, manage airway complications, allergic reactions, and drug overdoses, and treat respiratory or cardiopulmonary arrest should be readily available. Supportive equipment includes oxygen, suction, patient-monitoring devices, basic and advanced airway management equipment, a defibrillator, advanced life support medications, reversal or rescue agents, and vascular access equipment (Box 7.2).

With rare exceptions, PSA medications in adult patients should be administered via the intravenous (IV) route. Adults undergoing PSA in the ED should therefore have an IV line placed before the procedure. This need in children is less clear and depends on the presence of comorbid conditions and choice and route of drug to be administered. In children, if the procedure is likely to be lengthy or if multiple doses of drugs will be needed, a peripheral IV line is recommended.

While the requirement for supplemental oxygen, and its benefits during PSA, have not been well studied, emergency department data does suggest its use decreases the incidence of hypoxemic episodes during procedural sedation.[2,7] However, significant respiratory depression in these patients may not be detected because of their normal oxygen saturation. The routine use of capnography eliminates this issue, since ventilatory status is displayed continuously, and is recommended for any planned procedure using more than light levels of sedation or anxiolysis.

The most crucial aspect of monitoring during PSA is the visual observation and assessment of the patient, especially the response to medications and procedures. The patient's ability to follow commands in response to varied levels of stimulation is useful in quantifying the level of consciousness. Furthermore, the patient's ventilatory rate may be readily assessed by direct observation, although depth of respiration or tidal volume is harder to estimate clinically. Pulse oximetry is a reliable and essential monitoring modality. Other components of monitoring, which should be documented, include determination of respiratory rate, heart rate, blood pressure, oxygen saturation, cardiac rhythm, and capnography.

ASA and Joint Commission standards have historically required responsive-based assessments for documenting depth of sedation and a measure for assessing patient comfort. A 2019 ACEP practice guideline on unscheduled procedural sedation challenges this concept as an adequate metric and encourages strong consideration for the incorporation of ventilation-focused assessments as a measure of sedation adequacy. The consensus guideline recommends focusing on respiratory capacity instead of responsiveness alone as a means to enhance patient safety across sedative agents.[2]

Although there is no outcome-based evidence that cardiac monitoring during PSA is of any benefit, it is certainly not harmful, is routinely available, and may be beneficial in some instances. It should be used routinely in older patients and patients with a history of cardiovascular disease, hypertension, or dysrhythmia. Although in young, healthy patients, continuous pulse oximetry alone may be safe (as this will also display the heart rate), we recommend that cardiac rhythm monitoring, if available, should be used in all adult cases.

Capnography (or capnometry) measures end-tidal carbon dioxide (CO_2) partial pressure and has been shown to detect cases of inadequate ventilation earlier than clinical assessment or detection of hypoxemia by oximetry. While the pooled evidence for capnography has not shown a benefit in patient outcomes, studies have demonstrated that its use can significantly reduce hypoxemic events during procedures.[8,9] This, in addition to its lack of harm, ease of use, and increasingly low cost have resulted in most sedation oversight organizations recommending its use. In its 2018 guidelines, the ASA recommended continually monitoring ventilatory function with capnography unless precluded or invalidated by the nature of the patient, procedure, or equipment.[3] The 2014 ACEP guidelines, further supported by more recent organizational statements, endorsed a level B recommendation that capnography may be used as an adjunct to pulse oximetry and clinical assessment to detect hypoventilation and apnea earlier than pulse oximetry or clinical assessment alone in patients undergoing procedural sedation and analgesia in the ED.[1,2]

We recommend that continuous capnography be used when deep sedation is planned due to the inherent risk of respiratory depression. Although optional when only light sedation or anxiolysis is planned, capnography may enhance patient safety by allowing the observer to recognize unintended oversedation and depression of respiratory rate or volume more rapidly.

The bispectral index (BIS) is monitored via a noninvasive device attached to the patient's forehead and determines the depth of sedation level via frontal lobe electroencephalographic measurements. It has been used in the operating room as an objective measure of sedation depth. Though ED studies have revealed a correlation between BIS readings and objective patient sedation levels, no reliable advantage or beneficial role has been demonstrated to support its routine use in PSA monitoring.[10]

When transporting patients outside the ED for diagnostic procedures requiring PSA, every attempt should be made to provide the same level of monitoring during the transport and procedure as would be used within the department.

The highest risk of serious adverse events generally occurs within 5 to 20 minutes of receiving the last dose of IV medication and at the completion of procedures, when the patient remains sedated but is no longer receiving the painful stimulus. Similarly, patients undergoing lengthy procedures in which deeper sedation is desired to reduce

motion (e.g., magnetic resonance imaging [MRI]) are also at an increased risk. Patients should be monitored closely at these times, and this should continue until clinical recovery has occurred.

Recovery

Monitoring should continue until patients are spontaneously awake and able to function independently. The duration of recovery is variable and depends on both the agents used and the depth of sedation. Drowsy patients should not be left unattended, and appropriate measures to prevent falls should be taken.

Post-procedure Recovery and Discharge

Before discharge, baseline cognitive and motor functions such as the ability to follow commands, speech, ambulation, and sitting should be verified. Vital signs and respiratory status should be back to baseline and within normal limits. Residual pain should be addressed. Nausea should be minimal, and vomiting should be resolved. It is preferable that all patients, including adults, be sent home with a responsible adult but, if this is not possible, the patient should remain in the ED until a normal baseline has been achieved.

Patients should be advised not to drive or participate in other dangerous activities for 12 to 24 hours. Despite the short clinical duration of most of the agents used, some patients may exhibit subtle signs of cognitive deficits and mild drowsiness. Therefore, we recommended that they remain in the company of a responsible adult at home for 4 to 8 hours. For children, light play at home should be the extent of activities, with no bicycle riding, swimming, or other complex motor activity until the next day. An antiemetic and progressive diet is helpful if nausea or vomiting is experienced. Standard discharge instructions should also be provided for the presenting complaint as well as for the sedation performed, and all patients should be instructed to immediately return if any confusion or respiratory symptoms arise.

Pharmacology

In selecting agents, clinicians must balance the desired effects, risks and benefits, and logistics of administration for each situation. The 2019 ACEP practice guideline on unscheduled procedural sedation calls for focusing on the sedation depth and ventilatory status of each individual patient as opposed to a specific agent.[2] The clinician should have a clear understanding of the purpose of PSA so he or she can relate it to the procedure being performed. When the procedure is unpleasant but not painful (e.g., endoscopy), pure sedation may be the desired endpoint, and agents such as benzodiazepines, etomidate, or propofol are sometimes used alone. These agents do not provide pain relief and should not be used as the sole agent when pain management is also desired. Analgesic agents such as opioids or nitrous oxide are often added to a sedative agent to provide analgesia for painful procedures. In contrast, ketamine, as a dissociative agent, may be an excellent single drug choice for painful or stimulating procedures. Usually, a combination of analgesic and sedative agents is required. Caution is indicated, however, because their side effects are frequently potentiated when given in combination.

The specific agents for PSA and dosage recommendations for adult patients are provided in Table 7.3. Their benefits and adverse effects are provided in Table 7.4. Individual agents are discussed in greater detail in the following sections.

Routes of Administration

The decision regarding the optimal route of administration should be determined by the procedure and requirements of the specific patient. In general, IV titration to the desired level of sedation and analgesia produces the most rapid, safest, and most predictable results. Drugs given by the intramuscular (IM), oral, transmucosal, intranasal (IN), or rectal routes generally have a slower onset of action, are difficult to titrate, have unpredictable results, and may lead to prolonged sedation. These routes are rarely used for PSA in adults.

In pediatric patients, however, the benefits of IV drug administration may be outweighed by the difficulty and distress to the patient in obtaining IV access. In this situation, drugs given by the alternative routes may be preferred (see Chapter 157). For example, ketamine and midazolam have been shown to provide consistent and predictable results in children through IM or IN routes.[11] Evidence describing the use of inhaled nitrous oxide for PSA in the emergency department primarily involves pediatric patients. It has a predictable behavior when

TABLE 7.3 Procedural Sedation and Analgesia Agents—Recommended Adult Starting Doses

Agent	Class	Main Effect	Route of Administration	Usual Starting Dose
Fentanyl	Opioid	Analgesia	Intravenous	1 mcg/kg
Morphine	Opioid	Analgesia	Intravenous	0.1 mg/kg
Midazolam	Benzodiazepine	Sedation, amnesia	Intravenous	0.05 mg/kg
		Amnesia	Intramuscular	
Ketamine	Phencyclidine derivative	Dissociation, analgesia, sedation, amnesia	Intravenous Intramuscular	1–2 mg/kg 2–5 mg/kg
Etomidate	Imidazole derivative	Sedation, amnesia	Intravenous	0.1 mg/kg
Propofol	Alkylphenol derivative	Sedation, amnesia, antiemetic	Intravenous	1–2 mg/kg
Alfentanil	Opioid analogue	Analgesia	Intravenous	3–8 mcg/kg over 3 min, then 3 mcg/kg q5–20 min
Remifentanil	Semisynthetic mu opioid receptor	Analgesia	Intravenous	0.1–0.15 mcg/kg/min infusion Supplemental boluses: 1- to 2-mcg/kg increments
Dexmedetomidine	α_2-Adrenergic agonist	Analgesia, sedation	Intravenous	0.5–1 mcg/kg over 10 min, then 0.2–1 mcg/kg/h. Titration should be slow, about every 30 min.

TABLE 7.4 Procedural Sedation and Analgesia Agents—Benefits and Adverse Effects

Agent	Route(s) of Administration	Onset (min)	Duration (min)	Advantages	Adverse Effects
Fentanyl	Intravenous, transmucosal	1–2	30–40	Rapid onset	Respiratory depression
		10–30	60–120	Short duration ↓Histamine release Minimal CV effects	Rigid chest syndrome
Morphine	Intravenous	5–10	240–360	Longer lasting	Hypotension Respiratory depression
Midazolam	Intravenous, intramuscular, oral, rectal, intranasal	1–2	30–60	Rapid onset	Respiratory depression
		15–30	60–90	Easy to titrate	
		10–30	60–90	Multiple routes	
		10–15	45–60		
Ketamine	Intravenous, intramuscular, oral, rectal, intranasal	1	15–45	Airway reflexes maintained	Emergence phenomena
		5	15–30	No respiratory depression	Emesis
		30–45	120–240	Predictable	Laryngospasm
		5–10	15–30		↑ICP and ↑IOP
		5–10	30–120		Hypertension Tachycardia
Etomidate	Intravenous	<1	5–10	Rapid onset Short duration Minimal CV effects Cerebroprotective	Respiratory depression Myoclonus Adrenal suppression
Propofol	Intravenous	<1	10–20	Rapid onset Short duration Antiemetic Cerebroprotective	Respiratory depression Hypotension Injection pain
Ketofol	Intravenous	1–3	10–15	Rapid onset Reduction in repeat dosing Reduction in emesis	Recovery agitation Respiratory depression Increased HR
Alfentanil	Intravenous	Immediate	10–30	Rapid onset Short duration Minimal CV effects	Respiratory depression and which can be increased with used as supplement to propofol
Remifentanil	Intravenous	3–6	5–10	Rapid onset Short duration Minimal CV effects	Respiratory depression
Dexmedetomidine	Intravenous	10–15 after initial loading infusion	5–8 half-life; 2-h terminal elimination	Short duration Minimal ventilatory effects	Bradycardia Hypotension

CV, Cardiovascular; *HR,* heart rate; *ICP,* intracranial pressure; *IOP,* intraocular pressure.

used as a sole inhalational PSA agent in children but is also frequently used as an analgesic adjunct to a sedating agent. Within this population, it has been found to be a safe and effective adjunct, especially in minor procedures utilizing local anesthesia.[12,13] However, it does require the appropriate scavenging equipment and safety protocols for providers utilizing these systems.

IV medications should be administered slowly to minimize hypotension or respiratory depression. It is important to allow adequate time between doses to achieve and assess peak effect before an additional dose is given. Lower initial doses should be chosen in sensitive patients or when drugs from multiple classes are being administered. Ketamine is considered the exception because, unlike the other agents described, it possesses a threshold response rather than an additive dose-response continuum. Smaller doses of ketamine cause analgesia and disorientation. Dissociation occurs when a dosage threshold of 1 to 1.5 mg/kg IV in adult patients or 1.5 to 2.0 mg/kg in younger pediatric patients is reached. Higher doses have not been shown to enhance or deepen its dissociative effects.

Opioids

Parenteral opioids are commonly used as analgesics before painful procedures are performed. For PSA, an opioid is rarely optimal as a single agent, and most emergency clinicians combine an opioid with a sedative-amnestic agent to balance sedation-amnesia and analgesia with the least likelihood of respiratory depression. One preferred method of establishing adequate analgesia for a painful procedure when using combined agents is addressing the pain requirements initially in the medication sequencing and then adding the anxiolytic for sedation.

The most commonly used opioids in the ED for PSA are fentanyl and morphine. These are often combined with benzodiazepines such as midazolam for moderate sedation and are used in smaller doses to provide analgesia during deep sedation with etomidate or propofol. An important consideration when co-administering opioids with other sedating medications is the combined effects on respiration and blood pressure. The pharmacokinetics of the opioid, specifically onset of action and maximal effect, should be considered during PSA. The respiratory depression created by any one agent is exaggerated when multiple agents are administered closely together. Patients who receive opioids less than 30 minutes before the start of a sedation have a small increased risk of adverse events, including hypoxemia.[14]

Fentanyl

Fentanyl has many advantages as an analgesic agent for PSA, given its rapid onset of action, short duration of activity, lack of histamine release, and favorable cardiovascular profile. Fentanyl rapidly crosses the blood-brain barrier and produces analgesia in as little as 90 seconds. Serum levels rapidly decline from peak concentrations because of extensive tissue uptake followed by hepatic metabolism. It has a duration of action of 30 to 40 minutes; the peak respiratory depressant effect of a single IV dose of fentanyl is 5 to 15 minutes following injection. These properties permit the titration of multiple small doses to the desired clinical effect. Because fentanyl readily creates a reservoir in adipose tissue, accumulated large doses may result in a progressively increased duration of effect, although this does not generally occur in doses less than 10 mcg/kg.

For deep sedation, a single dose of 0.5 to 2 mcg/kg of fentanyl is often given before the sedating agent. After adequate pain relief has been achieved, a smaller dose of a sedative agent may then be added and titrated to effect to minimize respiratory depression.

For moderate sedation, fentanyl can be titrated, along with a sedative agent such as midazolam, depending on whether the emergency clinician assesses that more sedation (midazolam) or analgesia (fentanyl) is required. Dosage should begin at 1 mcg/kg and be slowly titrated upward every 2 to 4 minutes, until the desired level of analgesia has been achieved. Sufficient analgesia for painful procedures under moderate sedation usually is accomplished with doses of 2 to 3 mcg/kg and under deep sedation with 1 to 2 mcg/kg. Lower doses should be used in older patients or when other CNS depressants have been previously administered (e.g., ethanol).

Respiratory depression is more likely at higher doses, when the drug is given rapidly, or when combined with other CNS depressants, such as benzodiazepines or alcohol. Other side effects may include vomiting and pruritus, although these are less common than with other opioids. Hypotension and bradycardia are rare but may occur with high doses. These adverse effects may be readily reversed by naloxone. Chest wall rigidity and glottic spasm, which may make ventilation difficult, are unique complications seen when high doses (anesthetic) of fentanyl (generally >7 mcg/kg) are given rapidly. These doses are not used for PSA. In the rare event of chest wall rigidity, symptoms may not reliably be antagonized by naloxone and may necessitate neuromuscular blockade and intubation to enable adequate ventilation.

Morphine

Morphine is poorly lipid-soluble and penetrates the blood-brain barrier more slowly after small bolus injections. Onset of action is 5 to 10 minutes, and a period of 10 to 30 minutes is required before its peak effects are seen, although, when used for PSA, morphine performs similarly to fentanyl, with comparable recovery times. A general starting dosage of 0.1 mg/kg is commonly used and then titrated to the desired effect, as with fentanyl. Morphine has much more histamine release and is more likely to produce hypotension, especially in preload-dependent patients. This fact, combined with its slow peak onset time, makes it a less ideal opioid for PSA use. It has potential similar to other opioids for producing respiratory depression, especially when used with other CNS depressants, such as benzodiazepines. Morphine undergoes hepatic metabolism to an active metabolite, followed by renal excretion. Insufficiency of either organ system may lead to increased serum half-life.

Benzodiazepines

Benzodiazepines are potent amnestic, hypnotic, and anxiolytic medications. They also have anticonvulsant and muscle relaxant properties but do not have analgesic effects. Because of this, they are commonly co-administered with an analgesic agent, such as fentanyl or morphine. They may be given IV, IM, via the oral (PO) or IN route or per rectum (PR) but are virtually always used via the IV route for PSA in adults. Midazolam is the most commonly used agent because of its favorable pharmacokinetics.

Midazolam

Midazolam has many benefits for PSA, given its rapid onset of action and short duration of action, compared with other benzodiazepines. Its stronger amnestic properties are an advantage over other benzodiazepines. The starting IV dose is 0.05 mg/kg. Children may need slightly higher doses. The onset of sedation is generally within 1 to 2 minutes, and the duration of action is 30 to 60 minutes. Alternatives to an IV route are often used in children, including IM, PR, IN, and PO routes. Midazolam has been shown to be an extremely safe and effective agent for PSA, both alone and when used in combination with fentanyl.

Side effects include dose-dependent hypoventilation and hypoxemia. Apnea and hypotension are uncommon but occur more often at high doses or when other CNS depressants, such as opioids, are used. Headache, nausea, emesis, coughing, and hiccups have been shown to occur, although rarely. Lower doses should be used for older adults or when other analgesics are given concomitantly. Prolonged effects may be seen in older adults or those with liver dysfunction owing to decreased hepatic or first-pass metabolism. Midazolam is highly lipophilic, and its effects may be significantly amplified in obese patients, resulting in an increased plasma half-life of up to 8 hours with high or repetitive doses. Chronic alcohol users who do not have liver dysfunction may require relatively high doses of midazolam to achieve the same clinical effects due to cross-tolerance.

Ketamine

Ketamine is a well-studied, safe, and predictable agent for use in PSA. It is a derivative of the street drug phencyclidine and is classified as a dissociative agent. It causes disruption between the thalamoneocortical and limbic systems, preventing the higher centers from perceiving visual, auditory, or painful stimuli. Because of this, ketamine leads to profound analgesia, amnesia, and catalepsis. It does not produce unconsciousness, but rather a trancelike state. Patients often experience nystagmus, roving eye movements, and random movements of the extremities, unrelated to painful stimuli. Parents who observe a procedure in which ketamine is used may be disturbed and should be forewarned.

Ketamine has several advantages over other PSA agents. The most notable are its profound analgesic effect and lack of significant respiratory depression. The protective airway reflexes, such as coughing, swallowing, and muscular tone of the tongue and pharynx, are preserved or slightly enhanced. Its use further leads to a blockade of catecholamine reuptake, and blood pressure is generally well supported. It also induces bronchial smooth muscle relaxation and is well tolerated in patients with reactive airway disease. It has a fast onset and offset and

is predictable when given by the IV or IM route. After administration, it is rapidly distributed and taken up by the cerebral tissues. The effects are maintained until the drug redistributes into the peripheral tissues and is metabolized by the liver. As a result, repeat doses are well tolerated in more prolonged procedures. However, emergency clinicians should be aware that repeat doses might lead to longer recovery times and an increased incidence of emesis.

Ketamine may be given by multiple routes but is administered almost exclusively by the IV route in adults. After an IV dose of 1 to 2 mg/kg, a dissociative state results in approximately 1 minute, with duration of action of approximately 15 to 30 minutes. Complete recovery generally requires 1 to 2 hours. Similar cataleptic results may be seen with IM administration of 4 to 5 mg/kg in approximately 5 minutes, with effects lasting 15 to 30 minutes. For pediatric sedation, ketamine is generally administered by the IV or IM route but may also be given via the PO, PR, or IN route. These other routes are infrequently used because of variable onset of action, slow offset, and less predictable results.

The most common side effect seen with ketamine is the emergence phenomenon seen in approximately 15% of patients. The symptoms are often mild and may include unpleasant vivid dreams with nighttime awakenings or hallucinations. Less than 1% to 2% of patients have significant emergence agitation. This is more commonly seen in female patients, adolescents or adults, and in those with underlying psychiatric disorders. There is minimal evidence to support concomitant use of midazolam or haloperidol to reduce the emergence phenomenon.[15] Given the short-term and relatively benign effects of emergence, coupled with the desire to minimize unnecessary polypharmacy during sedation, this practice is not recommended unless it is for the specific treatment of preprocedural anxiety.

Benzodiazepines are useful for treating an emergence phenomenon if it occurs during the recovery phase. Emesis is a common side effect, and concomitant dosing with an antiemetic has been shown to reduce its incidence. Other side effects seen with ketamine use during sedation include transient apnea and laryngospasm; these are rare but have been suggested to be more common with rapid IV administration or larger doses. Doses given slowly, at a rate of 0.5 mg/kg/min, may further limit these events.

Ketamine also stimulates tracheobronchial and salivary secretions. In any patient undergoing airway examination (e.g., flexible video laryngoscopy), pretreatment with glycopyrrolate, 0.01 mg/kg given 10 minutes before the ketamine, may be beneficial. Because airway reflexes are maintained, airway compromise generally is not a concern in other patients. Prophylactic pretreatment with anticholinergics is unnecessary, and this practice is no longer recommended. Post-recovery nausea and vomiting are also frequently seen but are generally short-lived and respond well to typical antiemetics, such as ondansetron.

In patients with known or suspected significant cardiovascular or coronary artery disease, the potential for ketamine to induce catecholamine-mediated hypertension and tachycardia should be considered when weighing the risks and benefits of its use. Finally, given its potential for increasing intraocular pressure as well as inducing nausea and vomiting, alternative agents should be considered when planning for sedation in patients with known or suspected ocular globe ruptures.

Sedative-Hypnotics

Etomidate. Etomidate is a short-acting, sedative-hypnotic agent structurally unrelated to the other PSA agents, with no analgesic properties. It exhibits a very rapid onset of sedation and hypnosis by enhancing neurotransmission at GABA receptors. Etomidate has been used for deep sedation because of its rapid onset, short duration of action and, most importantly, minimal effects on cardiovascular function.

After IV administration, sedation occurs in approximately 1 minute, and patients recover in 5 to 10 minutes. Etomidate induces deep sedation that borders on general anesthesia with higher doses and may be more challenging to titrate than the other sedative-hypnotics. It is generally administered IV, with an initial dose of 0.1 mg/kg given slowly over 1 to 2 minutes. Additional doses of 0.05 to 0.1 mg/kg may be administered every 2 to 3 minutes until the desired level of sedation has been achieved. Smaller initial doses should be considered when etomidate is combined with analgesic agents or given to older adults. Because it has little effect on the cardiovascular system and is cerebroprotective, it is an excellent choice for patients at risk for hemodynamic instability or increased intracranial pressure.

Adverse effects that may limit its usefulness include apnea, respiratory depression, myoclonus, nausea, and vomiting. These side effects are more common with rapid IV administration, when higher doses are used, and in older patients. Myoclonus is the most common side effect and is typically described as mild and brief but, at times, may be severe enough to interfere with the procedure. Although respiratory depression is rare and generally transient, few patients may require brief periods of assisted ventilation. Vomiting is unlikely with doses administered in the ED. Etomidate transiently suppresses endogenous glucocorticoid production by inhibiting 11-β-hydroxylase activity, but this is clinically irrelevant with a single sedating dose.

Propofol. Propofol is another short-acting sedative-hypnotic that is structurally unrelated to the other PSA drugs, with no analgesic properties. It has an extremely rapid onset, short duration of action, and predictable efficacy for inducing deep sedation.

Sedation clears quickly and completely after only a few minutes, permitting superior titration and earlier recovery and discharge. Propofol also possesses potent antiemetic properties and decreases intracranial pressure. Because of this, propofol is a highly desirable and widely used agent for deep sedation in the ED. It does not provide analgesia, however, and should be preceded by an opioid or regional nerve block for painful procedures. As with all sedative agents, the addition of an opioid may increase the risk of deeper than anticipated sedation, respiratory depression, apnea, and hypotension, and smaller starting doses are recommended.

Propofol is administered with an initial IV bolus dose of 1 mg/kg, although a lower starting dose of 0.5 mg/kg can be used for patients with poor cardiovascular reserve or those who received significant presedation opioid analgesia. Propofol is then titrated every 1 to 3 minutes by 0.25- to 0.5-mg/kg aliquots to the desired sedation level. Children may require slightly higher weight-adjusted doses than adults. The onset of sedation occurs in less than 1 minute, and patient recovery occurs in 10 to 20 minutes. For procedures lasting longer than this, additional boluses of 0.5 mg/kg may be administered, or a continuous infusion of 6 to 9 mg/kg/h may be titrated to the desired level of sedation.[16]

Adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Other agents, such as opioids, may intensify these effects. In most cases, apnea is transient, and patients do not experience a significant decrease in their oxyhemoglobin level before recovering their respiratory function. This underscores the value of supplemental oxygen administration during sedation. If the oxygen saturation decreases to the low 90s, the patient may require a brief period of assisted ventilation. Often, a simple jaw thrust can improve oxygenation and ventilation if there is evidence of acute airway obstruction due to relaxed glossal or hypopharyngeal musculature.

Propofol commonly results in a transient decrease in systolic and diastolic blood pressures, which rarely necessitates fluid administration and is well tolerated by healthy patients. The hypotensive effect is exaggerated in older adults and in patients with hypovolemia, and the initial dose of propofol should be reduced to 0.25 to 0.5 mg/kg in

such patients. Pain associated with propofol injection occurs in most patients and can be reduced with small infusions of IV lidocaine before its administration. Despite these concerns, propofol has been shown to be reliable and safe when used with proper monitoring in the ED setting.[16]

Ketamine plus propofol. Ketamine is commonly combined with propofol (known as "ketofol") for PSA. The two are thought to have synergistic effects that balance each other's deficits while decreasing the overall dose of propofol. Ketamine provides the analgesic effects that propofol lacks, while ketamine's cardiorespiratory stimulating effects provide a balance to the respiratory depression and hypotension caused by propofol. Also, vomiting and recovery hallucinations from ketamine are potentially mitigated by the antiemetic and hypnotic effects of propofol.

Though no study to date has shown definitive evidence to help providers choose between ketofol or propofol alone, a trend toward improved provider and patient satisfaction as well as decreased adverse respiratory events has been reported when using ketofol.[17–19] Patients receiving ketofol frequently require less redosing due to the extended effects of the ketamine to maintain a similar depth of sedation. Clinicians should consider this strategy in cases where propofol is desired as a sedative agent, but the patient may be at a higher risk of respiratory depression or hemodynamic instability.

Ultra–fast-acting agents. Emergency department experience with agents such as alfentanil and remifentanil for PSA is limited. Alfentanil is an ultra–short-acting analogue of fentanyl that has been described for PSA in the ED. This agent has been used in anesthesia and is safe and effective when added to propofol for PSA in the ED; the combination has not been shown to provide any additional benefit over more standard agents. Emergency clinicians should be aware that patients who receive supplemental alfentanil may require additional stimulation to induce ventilation during ED PSA and may have extended recovery periods. Although alfentanil is safe when added to propofol, the combination has not been shown to provide any additional benefit.

Remifentanil is an ester derivative of fentanyl and also has ultra–short-acting sedative and analgesic properties. Traditionally used in general anesthesia for sedation and analgesia, it has been described in brief reports for ED PSA. It has the advantage of being metabolized by esterases present in interstitial tissues and red blood cells, and therefore its metabolism is independent of hepatic or renal dysfunction. It can cause significant respiratory depression, but the patient is still often responsive to verbal commands.

Dexmedetomidine is a newer sedative agent for use in the ED. It acts as a highly selective α_2-adrenergic agonist with sedative, anxiolytic, and analgesic properties. Dexmedetomidine induces natural sleep to create its sedative effects. It has been mainly administered via infusion and has been used safely and successfully to facilitate flexible fiberoptic and video intubation, gastrointestinal (GI) procedures, and cardioversions. More intensive care unit (ICU) reports have demonstrated its use as a preferred sedative agent for mechanically ventilated patients. While high-quality ED data are lacking, a 2019 randomized control trial found that it outperformed a combination of midazolam and fentanyl in terms of the level of analgesia and onset of sedation, without increased adverse events, during procedural sedation for shoulder reduction.[20] Given its α_2-adrenergic effects, the primary side effects are bradycardia and hypotension.

Reversal and Rescue Agents. Careful titration of medications to the desired level of sedation is generally the goal in PSA. At times, however, unanticipated deeper levels of sedation may be reached, and respiratory depression or apnea may occur. Airway repositioning, supplemental oxygen, and bag-valve-mask ventilation may be required. If these periods are prolonged, partial or complete reversal of agents such as opioids or benzodiazepines may be necessary. Elective reversal of PSA after completion of the procedure is not recommended. When reversal agents exist, it is advised that they be immediately available for use during PSA if required.

Naloxone. Naloxone is a competitive antagonist of opioids and has been effectively used for the reversal of opioid-induced respiratory depression during PSA. It has a rapid onset of action and a mean plasma half-life of approximately 45 minutes, although its clinical effects last only 15 to 30 minutes. Resedation is generally not a problem for patients who have been given short-acting opioids such as fentanyl or morphine in doses recommended for PSA. Nevertheless, these patients should be observed for a minimum of 1 hour after the administration of naloxone. It is vital for patients who have received large doses of fentanyl to ensure that redistribution of fentanyl within the body does not result in a sedation relapse.

Naloxone may be administered via the IV, IM, subcutaneous, intranasal, or endotracheal route, but it is commonly given by IV. The smallest dose necessary to restore respiratory effort should be used because the reversal of the opioid's respiratory depressant effect is matched by reversal of the analgesia. The initial dosage depends on the patient and the specific goals desired. For partial reversal, titrated doses of 0.1 to 0.2 mg may be used every 1 to 2 minutes to desired effect. Complete reversal is rarely desirable and requires doses of 1 to 2 mg. Similar doses may be used for children. In opioid-dependent patients, these doses may precipitate an acute withdrawal state, and smaller initial doses should be considered. Large doses of naloxone may also make postprocedural pain challenging to control. Naloxone use has little risk, but pulmonary edema, seizure, and dysrhythmia rarely have been reported.

Flumazenil. Flumazenil is a competitive antagonist of benzodiazepines. Although it reverses the sedation effect of benzodiazepines, it is not as effective for reversing respiratory depression. In general, when oversedation occurs, brief support of ventilation permits the patient to recover sufficient spontaneous respiration without the need for reversal. Flumazenil has a rapid onset of action in 1 to 2 minutes, peak effect in 5 to 10 minutes, and individually variable clinical duration of 30 to 90 minutes. Continuous patient monitoring must be ensured when flumazenil is used to reverse respiratory depression associated with longer-lasting benzodiazepines because resedation is likely. Flumazenil has also been shown to be effective in reversing paradoxical excitement in children.

It is generally titrated in doses of 0.1 to 0.2 mg IV every 1 to 2 minutes to the desired effect. A maximum dose of 1 mg is generally sufficient. Common pediatric doses of 0.02 mg/kg are generally used, with a maximum of 0.2 mg. It should be used with extreme caution in patients with benzodiazepine dependence or a history of seizures because it may precipitate life-threatening status epilepticus refractory to standard treatments. Routine reversal of benzodiazepines is not recommended.

Drug Selection and Administration

When choosing a strategy for PSA, it is important to consider the type of procedure being performed (painful or not), length of the procedure, specific procedural requirements (anxiolysis vs. immobility), and whether sedation may need to be prolonged (Table 7.5). The need for IV access generally is an issue only in small children. Planned adjuncts, such as topical, local, or regional anesthesia, are also considered. Patient factors, including age, medications, alcohol and drug use, and comorbid conditions, are considered when selecting the agent and initial dose. Procedures necessitating sedation may be broadly divided into three categories—nonpainful procedures requiring immobilization (e.g., CT, MRI); low-pain, high-anxiety procedures (e.g., laceration repair, lumbar puncture); and highly painful, high-anxiety procedures (e.g., fracture or joint reduction, tube thoracostomy, abscess drainage, cardioversion).

TABLE 7.5 Adult Drug Selection Strategies

Procedure Type	Examples	Recommendation	Alternatives	Comments
Nonpainful	Radiologic imaging	Midazolam (intravenous)	Propofol (intravenous)	Midazolam has considerable support and safety.
Low pain, high anxiety	Central line placement Lumbar puncture	Midazolam (intravenous)	Propofol (intravenous) Ketamine (intravenous)	Analgesia may be accomplished frequently with local or topical agents.
High pain, high anxiety	Fracture or joint reduction Abscess drainage Burn debridement Cardioversion Chest tube placement	Midazolam + fentanyl (intravenous) Propofol + fentanyl (intravenous) Ketamine (intravenous, intramuscular)	Etomidate + fentanyl (intravenous) Propofol + ketamine (intravenous)	There are far more data supporting the safety of fentanyl and midazolam, although the other choices have significant support.

For brief nonpainful procedures requiring complete immobilization, IV midazolam and propofol are excellent choices, and etomidate is a reasonable alternative. For longer procedures, oral or rectal midazolam is reasonable.

For briefly painful procedures requiring minimal to moderate sedation, and when topical or local anesthetics may be used (e.g., to reduce a glenohumeral dislocation for which intraarticular lidocaine will be used), midazolam is a reliable and safe choice. IV propofol, preceded by a modest dose of fentanyl, is an excellent choice for brief painful procedures requiring deep sedation (e.g., cardioversion, joint reduction, other highly painful procedures). Ketamine by the IV and IM routes has been extensively studied in children and is highly effective, with a large margin of safety for children and adults. The same may be said for IV midazolam plus fentanyl in the adult and pediatric populations.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 7: QUESTIONS AND ANSWERS

1. When do most adverse events associated with emergency department procedural sedation occur?

- **a.** During the manipulation or intervention
- **b.** 5 to 20 minutes after the last sedative dose
- **c.** 20 to 30 minutes after the last sedative dose
- **d.** 30 to 60 minutes after the last sedative dose

Answer: b. High-risk times are 5 to 20 minutes after the last medication administration and at the completion of the procedure, when there is no longer a painful stimulus but the patient remains sedated.

2. Which of the following statements is most accurate regarding the use of fentanyl for procedural sedation?

- **a.** Chest wall rigidity is a common occurrence but may be reversed with naloxone.
- **b.** For deep sedation, a single dose of 1 to 2 mcg/kg IV is often given before sedation to achieve good pain control. A smaller dose of sedative agent may then be added and titrated to effect.
- **c.** Rapid IV administration is generally safe.
- **d.** Respiratory depression is less likely with fentanyl than with an equipotent dose of morphine.

Answer: b. For deep sedation, less respiratory depression is generally observed if a single pain-relieving dose of fentanyl is used before sedation, followed by small titrated doses of a sedative agent. Sufficient analgesia is generally attained with fentanyl dosages of 1 to 2 µg/kg IV. Rapid IV administration of large doses is more likely to precipitate respiratory depression or arrest. Chest wall rigidity is very rarely seen and generally only with large, rapid, IV boluses of more than 7 µg/kg IV. If severe chest wall rigidity syndrome is precipitated, it often requires paralysis to ventilate the patient adequately. It is not reversed with naloxone. Equivalent dosages of morphine show more histamine release and hypotension than fentanyl but have similar respiratory depression potential.

3. Which of the following statements regarding the use of ketamine is false?

- **a.** Benzodiazepine coadministration has not been shown to reduce the incidence of emergence phenomenon in children.
- **b.** Despite increased secretions, airway reflexes are generally well maintained.
- **c.** Hypotension is common.
- **d.** Profound analgesic and sedative effects occur with minimal respiratory depression.

Answer: c. Ketamine increases the release of catecholamines on administration and supports blood pressure well. It also decreases smooth muscle tone in the bronchial tree and may have a benefit in patients with reactive airways disease. Several studies have failed to show benefit with the concurrent administration of low to moderate dosages of benzodiazepines in preventing emergence phenomenon in children. These studies have shown a slightly increased risk of side effects. Their routine use is discouraged and should be reserved for the actual treatment of severe emergency phenomena.

4. Which of the following statements regarding the use of propofol is true?
   - **a.** Propofol has a long duration of action and provides significant analgesia.
   - **b.** Propofol has significant antiemetic properties.
   - **c.** Propofol increases intracranial pressure.
   - **d.** Propofol is well tolerated in volume-depleted patients.

Answer: b. Propofol is a short-acting, sedative-hypnotic, cerebroprotective agent with no analgesic but profound antiemetic properties. Its adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Preload-dependent patients are particularly susceptible to hypotension. Its combined use with ketamine is common. The two agents are thought to have synergistic effects that balance each other's deficits. Their combined use has been shown to improve provider satisfaction, sedation quality, and decrease emesis but has not been shown to be clinically superior to either agent used alone in regard to respiratory depression, airway complications, or improved recovery times.

5. Which of the following statements is true regarding the need for fasting before procedural sedation?
   - **a.** A 6-hour period of fasting is required after the ingestion of liquids or solids before procedural sedation.
   - **b.** Preprocedural fasting is required in all cases.
   - **c.** The recommendation for preprocedural fasting is based on controlled trials involving patients undergoing procedural sedation.
   - **d.** The risk of vomiting and loss of the airway protective reflexes is low during procedural sedation.

Answer: d. The American Society of Anesthesiologists (ASA) currently recommends a period of 2 hours after ingestion of clear liquids, 4 hours after ingestion of breast milk, and 6 hours after the ingestion of other liquids or solids before the performance of procedural sedation. This recommendation is based on expert consensus and has been extrapolated from data on patients receiving general anesthesia and manipulation of the airway during intubation and extubation. There are no published studies showing an increased risk of aspiration after a liquid or solid meal nor benefits of fasting before procedural sedation. Large studies have shown no clinically significant differences with airway complications, emesis, or other adverse effects among groups of patients stratified by their preprocedural fasting status. The risks of procedural sedation should be balanced against the risks of delaying a time-sensitive procedure.

8

Fever in the Adult Patient

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KEY CONCEPTS

- Younger adults with fever usually have benign self-limited disease with low mortality. The challenge in this group is to identify rare causes of fever such as meningitis or septic condition when confronted with a predominance of self-limited viral and focal bacterial illness.
- For older patients (greater than 65 years), immune-compromised patients, or those with chronic disease, fever indicates a high risk for serious disease. Temperature elevation may be minimal in these patients, who often are unable to mount a significant febrile response to serious infection. Bacterial infection is the most common cause of fever in these patients. Three body systems—the respiratory tract, urinary tract, and skin and soft tissue—are the target for more than 80% of these infections.
- Atypical symptoms of illness are common in older febrile patients. Altered mental status, difficulty with ambulation, frequent falls, and general functional decline may be the only signs of serious infection in older patients.
- The white blood cell count is not a discriminatory test for patients with fever, may incorrectly indicate serious infection when none is present, or may be normal in the presence of life-threatening infection.
- In febrile patients with serious signs and symptoms, early empirical antibiotic therapy is often indicated as is treatment for severe acute respiratory syndrome (SARS)-2 coronavirus (COVID-19) and as appropriate influenza. The choice of antivirals, antibiotics, and other therapies are based on the likely cause of the fever as well as concomitant conditions, such as absolute neutropenia and end-stage renal disease.

FOUNDATIONS

Epidemiology

Morbidity and mortality rates from febrile illnesses vary dramatically with age. Younger adults with fever usually have benign self-limited disease with low mortality. The challenge in this group is to identify rare causes of fever such as meningitis or sepsis when confronted with a predominance of self-limited viral and focal bacterial diseases. Patients older than 65 years, or those with chronic disease who have fever, represent a group at higher risk for serious disease with higher rates of morbidity and mortality. For example, the incidence of community-acquired pneumonia is 2.6 times greater in adults 65 to 79 compared with younger adults, and in those over 79 years, it is seven times greater.[1] The relative mortality and morbidity rates for any given infection are much higher in the geriatric population; more than 50% of sepsis cases occur in patients older than 65 years, with a resultant mortality up to 26%.[2] Even viral illnesses that are generally not fatal, such as influenza or COVID-19, can be lethal in older adults.[3] Three body systems—the respiratory tract, urinary tract, and skin and soft tissue—are the target for more than 80% of these infections.[2]

Pathophysiology

Body temperature is normally controlled within a narrow range by the preoptic area of the hypothalamus. In the anterior hypothalamus, neurons directly sense the blood temperature. Temperature is subsequently controlled by a combination of vasomotor changes, shivering, changes in metabolic heat production, and behavioral changes. Normal temperature range is usually 36.0°C to 37.8°C (96.8°F to 100.0°F). There is a circadian rhythm within this range, with lower temperatures in the morning and higher temperatures in the late afternoon. Fever occurs when this normal range is reset to a higher value.

There is no consensus on the threshold core temperature that defines fever. The Centers for Disease Control and Prevention define fever as a core temperature greater than 38.0°C (100.4°F) in the absence of fever-reducing medication. However, most authorities agree that a core body temperature of 38.3°C (100.9°F) represents a significant fever. Fever is distinct from hyperthermia. Hyperthermia is an elevation of the temperature related to the inability of the body to dissipate heat; fever is the elevation of body temperature caused by thermoregulatory pathways in response to infections and certain other medical circumstances (Box 8.1). Most cases of temperatures higher than 41.0°C (105.8°F) are a result of hyperthermia, but febrile illness may also be considered.

Fever may be produced by a number of endogenous and exogenous substances termed *pyrogens*. Endogenous pyrogens include a variety of cytokines released by leukocytes in response to infectious, inflammatory, and neoplastic processes. Exogenous pyrogens include a large number of bacterial and viral products and toxins. Toxins induce fever by stimulating cells of the immune system to release endogenous pyrogens. These cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and interferon, travel to the hypothalamus and induce the production of prostaglandin E_2 (PGE_2).

PGE_2 raises the set point of the temperature range by a combination of effects, including peripheral vasoconstriction, increased metabolic heat production, shivering, and behavioral changes that conserve heat. Fever is maintained as long as the levels of endogenous pyrogens and PGE_2 are high. There is also a variety of other humoral and neural pathways that modulate this basic response. Cyclooxygenase

BOX 8.1 Differential Diagnosis—Noninfectious Causes of Fever

Critical Diagnoses
Acute myocardial infarction
Pulmonary embolism or infarction
Intracranial hemorrhage
Cerebrovascular accident
Neuroleptic malignant syndrome
Thyroid storm
Acute adrenal insufficiency
Transfusion reaction
Pulmonary edema

Emergent Diagnoses
Congestive heart failure
Dehydration
Recent seizure
Sickle cell disease
Transplant rejection
Pancreatitis
Deep vein thrombosis

Nonemergent Diagnoses
Drug fever
Malignancy
Gout
Sarcoidosis
Crohn disease
Postmyocardiotomy syndrome

inhibitors, such as aspirin, decrease fever by blocking the production of PGE_2. Age, malnutrition, immunosuppression, and chronic disease may also blunt the febrile response.

Moderate elevations of the body temperature may serve to aid host defenses by increasing chemotaxis, decreasing microbial replication, and improving lymphocyte function. Elevated temperatures may directly inhibit the growth of certain bacteria and viruses.[4] Fever also results in certain increased physiologic effects to the host, including increased oxygen consumption, metabolic demands, protein breakdown, and gluconeogenesis. These effects are particularly problematic in older adults who typically have a smaller margin of reserve for any given body system. Older adults have a blunted febrile response and a lower baseline temperature than younger adults. Some authorities therefore suggest that the threshold for the definition of fever should be considered lower (i.e., 100.4°F) in frail older adults than in younger persons.[5]

The therapeutic benefit of treating febrile patients with antipyretics is controversial and may depend on individual patient factors. For example, some studies indicate that febrile intensive care unit (ICU) patients with sepsis have reduced mortality if allowed to maintain an elevated temperature but that this may not be the case for febrile ICU patients without sepsis.[6] A recent meta-analysis of antipyretic treatment of septic patients showed no mortality benefit at 28 days, but early mortality (14 days) was significantly lower in febrile patients treated with antipyretic therapies.[3] Treatment of fevers makes patients feel more comfortable, however, and because of the detrimental effects of the increased metabolic demands caused by high fevers, it is recommended that patients with temperatures greater than 41°C be treated with antipyretics.

The initial step in the process of fever is resetting the thermostatic set point in the hypothalamus to a higher temperature while the actual body temperature remains normal. This mismatch of the thermostat with the "sensed" body temperature causes the patient to feel chilled (chills). The patient remains chilled until the body temperature rises to near the (elevated) hypothalamic set point. At this point, the patient no longer experiences chills and feels euthermic—but may feel fatigued or ill—but, to the caregiver, the skin temperature or thermometer reading is now elevated. The sequence of chills followed by febrile illness is the basis of the (incorrect) popular belief that getting chilled leads to infection, such as pneumonia. When the thermostatic set point is reduced to normal, the patient suddenly feels hot and sweats until the body temperature falls to match the set point, now normal.

Diagnostic Approach

Differential Considerations

The complete differential diagnosis for the patient in the emergency department (ED) with fever is extensive. The major infectious and noninfectious causes are summarized in Table 8.1 and Box 8.1, respectively. The vast majority of serious causes are infectious in origin. Immediate threats to life are from decompensated shock (usually septic), respiratory failure (related to shock or pneumonia), or central nervous system infection (meningitis). Some critical noninfectious causes of fever also exist (see Box 8.1), but these are relatively rare and frequently do not occur with fever as the primary symptom.

A primary medical decision in acute febrile illness is based on assessment of the patient's stability (Fig. 8.1). Patients with life-threatening signs and symptoms, including significant alterations in mental status, respiratory distress, and cardiovascular instability require rapid resuscitation. Prompt airway management and initiation of monitoring, intravenous access, fluid resuscitation, supplemental oxygen, and respiratory support are often necessary, despite incomplete information concerning the cause of the fever. Sustained temperatures above 41.0°C are rare but can be damaging to neural tissue and require rapid cooling (e.g., misting, fans, cooling blankets).

In the younger, otherwise healthy patient with fever, immediate threats to life such as toxic or septic shock, meningitis, meningococcemia, and peritonitis should be considered and treated empirically. In older, chronically ill patients with fever, most of the serious illnesses originate from infections in the respiratory tract, genitourinary tract, and skin and soft tissues. Meningitis, although less common, can also be a significant cause of morbidity and mortality in this group.

Pivotal Findings

Although the differential diagnosis of fever is broad, most of the treatable causes are of infectious origin. Most of these causes of fever may be diagnosed by careful history and physical examination. Age and the presence of underlying medical conditions can substantially influence the evaluation and subsequent decision making regarding management.

An approach to the diagnosis and management of the healthy, otherwise stable adult patient with acute febrile illness is shown in Fig. 8.2. In younger and otherwise healthy adults, self-limited, localized bacterial infections or benign systemic viral infections are usually the cause of fever. Assessment of risk for acute viral illness, such as influenza and COVID-19, should be made based on comorbid conditions and diagnostic testing and subsequent treatment based on overall risk for complications. The challenge with this group is to identify the rare life-threatening illness, such as meningococcemia, meningitis, or systemic methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

In the older or chronically ill population, fever is frequently a sign of severe illness. Usually, the cause is infectious. In addition to the most common infectious causes of illness (e.g., respiratory, urinary, or skin sources), infections such as meningitis, cholecystitis, appendicitis, and

TABLE 8.1 Differential Diagnoses—Infectious Causes

Organ System	Critical Diagnoses	Emergent Diagnoses	Nonemergent Diagnoses
Respiratory	Bacterial pneumonia with respiratory failure	Bacterial pneumonia, peritonsillar abscess, retropharyngeal abscess, epiglottitis	Otitis media, sinusitis, pharyngitis, bronchitis, influenza, tuberculosis, COVID-19
Cardiovascular		Endocarditis, pericarditis	
Gastrointestinal	Peritonitis	Appendicitis, cholecystitis, diverticulitis, intraabdominal abscess	Colitis or enteritis
Genitourinary		Pyelonephritis, tubo-ovarian abscess, pelvic inflammatory disease	Cystitis, epididymitis, prostatitis
Neurologic	Meningitis, cavernous sinus, thrombosis	Encephalitis, brain abscess	
Skin and soft tissue		Cellulitis, infected decubitus ulcer, soft tissue abscess	
Systemic	Sepsis or septic shock, meningococcemia	Influenza, COVID-19	

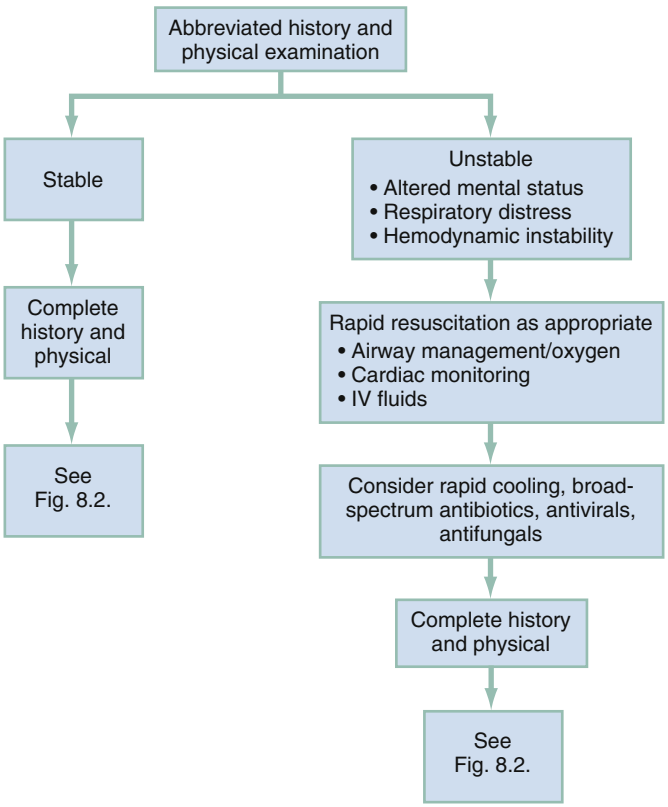

Fig. 8.1 Approach to the Critically Ill Febrile Adult Patient. *IV,* Intravenous.

diverticulitis are considered and may cause atypical signs and symptoms in older adults or immunosuppressed patients. In these populations, subtle changes in behavior may be the only sign of severe infection. Abnormal vital signs, especially significant tachypnea and hypotension, may portend a complicated and severe course.

Symptoms

The onset of the fever, its duration and magnitude, and any associated symptoms help identify possible causes and severity of illness. Localizing symptoms such as dysuria or productive cough are especially helpful. The timing of the fever and its patterns may implicate certain diseases (e.g., malaria). Recent or remote travel, chronic illnesses, past surgeries, hospitalizations, and treatment modalities may raise the suspicion of exotic or nosocomial infections. The presence of prosthetic heart valves or any indwelling device may be critical to the diagnosis. Exposure to other ill persons may impact differential considerations and management.

Community-acquired MRSA is a common cause of skin infections, as recognized in the last decade. Recently, gram-negative and mixed pathogen (gram negative and gram-positive) infections have increased; consideration of this may alter management when antibiotics are being considered for skin and soft tissue infections (SSTIs).[7] For all skin infections, it is important to seek a history of skin infections in close family members or other close contacts, as exposure to a colonized patient is a risk factor for development of SSTIs.

Also important in the medical history is a list of all the patient's medications, including any antipyretic medications, as recent use of antipyretic medications can mask a fever in a patient presenting to the ED. Family members are frequently an important source of information for older and very young patients.

Atypical symptoms of illness are common in older patients. Pneumonia or urinary tract infection in the older patient may be heralded only by a change in mental status, difficulty ambulating, or some other functional decline. Dysuria, frequency, and flank pain often are absent entirely in older adults with a urinary tract infection. Patients with pneumonia may inconsistently demonstrate productive cough or shortness of breath. Other frequent but nonspecific symptoms include anorexia, weight loss, weakness, lethargy, nausea, and recurrent falls. A history of cancer with recent chemotherapy or radiation therapy may be a clue to leukopenia or another immunosuppressed state. In older patients or those who have cognitive impairment, assessment of the patient's baseline mental and physical function often relies on the reports of others who know the patient well.

Signs

The presence and magnitude of fever are important elements of the examination, but the older, very young, or chronically ill patient may not mount a febrile response to significant infection. Temperatures may fluctuate and rechecks may be necessary. Although the most accurate measure of core body temperature is thought to be via the thermistor of a pulmonary artery catheter, central measurements of temperature are usually impractical in the ED; rectal temperature measurements or, when a Foley catheter is indicated, bladder thermistors are the most practical and accurate.[8] Axillary and tympanic temperatures may be unreliable compared to rectal temperature measurements, and may be altered by external conditions.

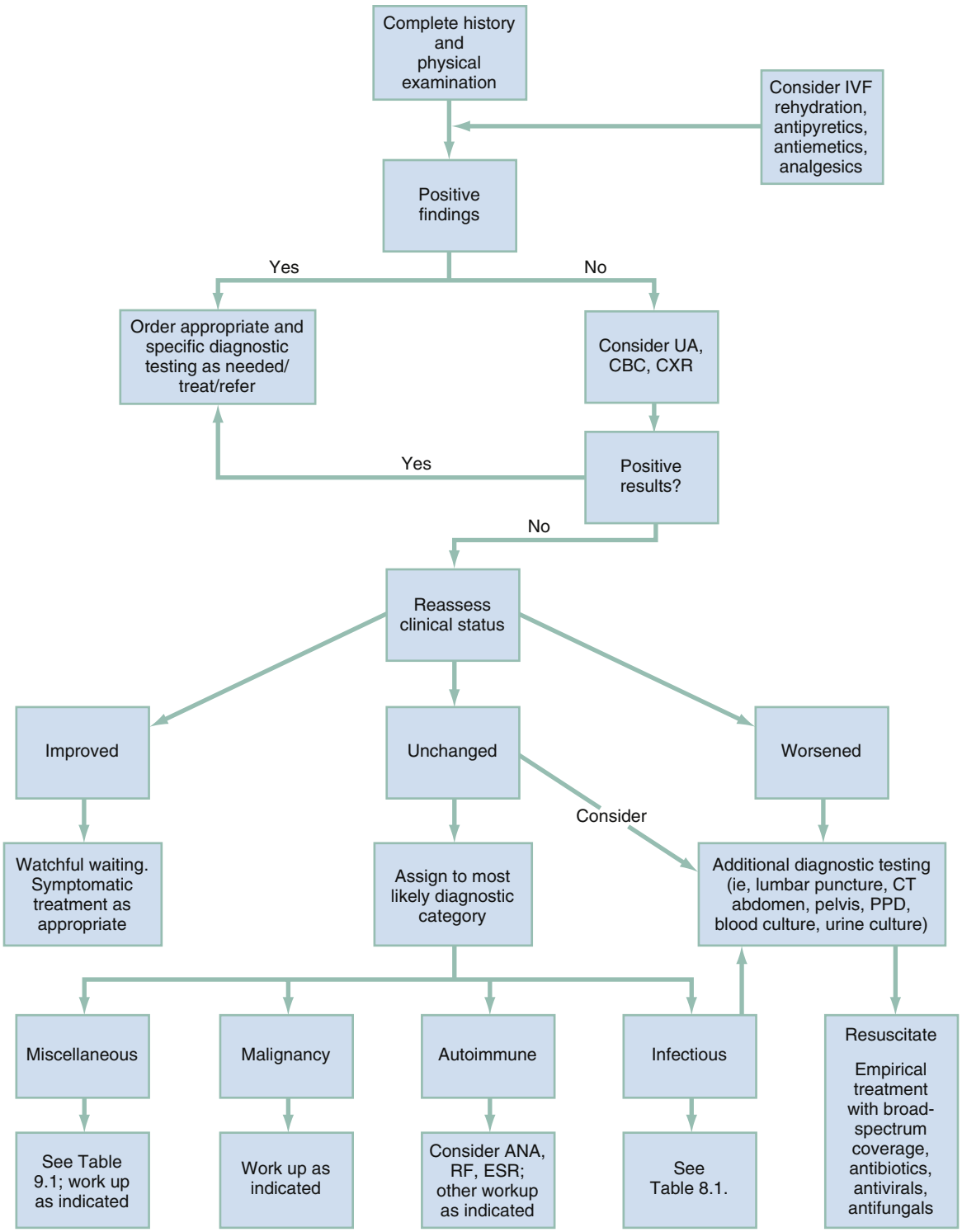

Fig. 8.2 Approach to the Stable Adult With an Acute Febrile Illness. *ANA,* Antinuclear antibody; *CBC,* complete blood count; *CT,* computed tomography; *CXR,* chest x-ray; *ESR,* erythrocyte sedimentation rate; *IVF,* intravenous fluids; *PPD,* purified protein derivative; *RF,* rheumatoid factor; *UA,* urinalysis. (Modified from Holder BM, Ledbetter C. Fever of unknown origin: an evidence-based approach. *Nurse Pract.* 2011;36:46–52.)

Oral temperatures may be transiently distorted by recent ingestion of hot or cold liquids, smoking, or hyperventilation. Rectal temperatures are typically 0.7°C to 1.0°C higher than oral temperatures.[8]

Fever is inconsistently associated with tachycardia and tachypnea. As a rough estimate, the heart rate may increase by 10 beats/min for each 0.55°C- (1°F-) rise in temperature. Relative bradycardia may be caused by medications such as beta blockers, but also can suggest factitious or drug-related fevers, typhoid fever, brucellosis, or leptospirosis. Frank bradycardia may occur with rheumatic fever, Lyme disease, viral myocarditis, and endocarditis. The respiratory rate may increase 2 to 4 breaths/min/°C in febrile illness. More significant tachypnea may be caused by respiratory infection or the acidosis related to shock.

In many patients, the examination is directed by the patient's localization of symptoms. The head and neck examination may identify treatable foci of infection, such as otitis media, sinusitis, pharyngitis, peritonsillar abscess, retropharyngeal abscess, and dental infections. A muffled, so-called hot potato voice with severe sore throat may be a clue to adult epiglottitis or upper airway abscess. Fundoscopy rarely may reveal evidence of disseminated candidiasis, miliary tuberculosis, endocarditis, toxoplasmosis, or leukemia.

The neck is examined for lymphadenopathy, masses, or thyroid pathology (thyromegaly or mass). Nuchal rigidity or pain on flexion of the neck is a useful sign for meningismus if present, but this may not be a prominent finding in many patients, particularly the very young or debilitated patient, even if meningitis is present.

The lungs are examined for rales, pleural rubs, or dullness to percussion. Localized rales or rhonchi may be subtle clues to the presence of pneumonia. The presence of concomitant chronic obstructive pulmonary disease or congestive heart failure, as well as poor respiratory effort, may hamper the diagnosis of pneumonia in older adults. The heart is examined for pericardial rubs or new murmurs.

The abdominal examination may be deceptively benign in older patients, patients with diabetes, or patients taking immunosuppressive drugs or steroids. When indicated by history or other findings, a rectal examination should be performed to check for evidence of enteritis, perirectal abscess, or prostatitis. The external genitalia examination may reveal evidence of a Bartholin abscess, urethral or vaginal discharge, or evidence of epididymitis or orchitis. In women, symptoms of lower abdominal pain, vaginal discharge, and dyspareunia suggest the need for a pelvic examination to evaluate for pelvic inflammatory disease or tubo-ovarian abscess.

The skin and extremities should be evaluated for rash, petechiae, joint inflammation, or evidence of soft tissue infection. In the absence of trauma, tenderness over the long bones or the spine may be evidence of osteomyelitis or neoplastic processes. Older adults and bedridden patients should be checked for the presence of pressure sores or decubitus ulcers.

Ancillary Testing

Ancillary testing is directed by the history and physical examination. The two most useful ancillary tests, especially in older patients, are urinalysis and chest radiography. Chest radiographs are often helpful in the diagnosis of pulmonary infection but may be difficult to interpret in the patient with concurrent chronic obstructive pulmonary disease, congestive heart failure, dehydration, or other chronic lung disease. Urinalysis, although not foolproof, is highly accurate for detecting urinary tract infection, especially in men. Although the white blood cell count has often been used in the evaluation of febrile patients, it lacks the degree of sensitivity and specificity to be of discriminatory value. The white blood cell count may incorrectly indicate serious infection when none is present or may be normal in the presence of life-threatening infection.[5] Other indirect tests of infection and inflammation, such as the erythrocyte sedimentation rate, C reactive protein, and procalcitonin can provide useful information but are plagued with irregular sensitivity and poor specificity. Gram staining of appropriate specimens may be helpful, and cultures may be ordered, although the results do not often influence emergency evaluation and treatment. With the broad scope of causes of SSTI (MRSA, gram negative, and mixed organism infections), it has become increasingly important to obtain cultures from soft tissue skin abscesses in patients considered at risk for significant SSTI.[8] In older or chronically ill patients with acute fever of unclear origin, blood and urine cultures are frequently appropriate. Outpatient blood cultures should rarely be done. Polymerase chain reaction (PCR) testing for respiratory illness including COVID-19 may be done based on the clinical presentation. A patient ill enough to require blood cultures from the ED generally requires hospitalization and empirical antibiotic coverage. Cerebrospinal fluid evaluation should be considered when mental status changes are evident, or if headache, meningismus, or other unexplained neurologic symptoms are present and cannot be clearly accounted for by infection outside the central nervous system. Thyroid function studies may be helpful when thyroid storm is suspected. Arterial or venous blood gas studies may help identify patients with critical disease who require prompt treatment.

Plain films of the abdomen are rarely indicated. Abdominal computed tomography (CT) is helpful if appendicitis, diverticulitis, cholecystitis, intestinal obstruction, perforated hollow viscus, or intraabdominal abscess is suspected. Ultrasonography may be helpful in the patient with potential cholecystitis.

Cranial CT scanning may be indicated before lumbar puncture in febrile patients with focal neurologic findings or a suspected embolic source, such as endocarditis, to exclude mass lesions such as a tumor or brain abscess. Neither CT scanning nor lumbar puncture should delay administration of antibiotics in patients with suspected meningitis.

Diagnostic Algorithm

The differential diagnoses of infectious causes of fever are summarized in Table 8.1. The differential diagnoses of noninfectious causes of fever are listed in Box 8.1. However, differences in patient characteristics can cause different manifestations of the same illness. For example, pneumonia or a urinary tract infection manifests in and is tolerated by an 80-year-old very differently from that of a young adult. A careful history and physical examination, along with strategic ancillary testing, will allow the emergency clinician to determine when a critical condition is present and will determine the operational tempo of subsequent evaluation and treatment.

EMPIRICAL MANAGEMENT

Temperatures higher than 41.0°C can result in damage to neuronal tissue and require prompt and vigorous treatment with antipyretics and external cooling measures. Heat illness, a spectrum of disorders due to environmental heat exposure, can result in extreme hyperpyrexia and lead to heat stroke. Urgent external cooling with fans, mist, and other modalities are required and are discussed in Chapter 129. Although the therapeutic benefit of lowering fever is controversial, it does not appear harmful and patients often feel better when their temperature is lowered.[4,6-9] Rectal and intravenous acetaminophen is as effective as oral acetaminophen and may be used in patients who are unable to take oral medication.

Patients with signs and symptoms of sepsis require prompt evaluation and treatment. Sepsis is characterized by the systemic inflammatory response syndrome (SIRS) to an infectious threat. SIRS is defined by the presence of two or more of these criteria: temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats/min; respiratory rate greater than 20 breaths/min or $Paco_2$ less than 32 mm Hg; and leukocyte count greater than 12,000/μL, less than 4000/μL, or more than 10% immature (band) forms. The reliability of SIRS has increasingly been questioned and low specificity of SIRS has limited its utility as a screening tool for sepsis. Patients with sepsis or septic shock require vigorous management, including intravenous fluid administration and prompt antibiotic therapy. The current guidelines utilize the quick Sequential Organ Failure Assessment (qSOFA) (respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less) as a rapid ED bedside assessment to identify patients with two or more of these features as more likely to have poor outcomes (see Chapter 127).[10]

Patients with evidence of respiratory failure from shock or pneumonia often need ventilator support. Soft tissue infections of the head and neck may compromise the airway because of mechanical obstruction. These may require acute intervention to provide a secure airway.

In many cases, early empirical antibiotic therapy is appropriate. The choice of antibiotics is based on the likely cause of the fever, as well as concomitant conditions, such as absolute neutropenia and end-stage renal disease. If a specific infection is subsequently identified, antibiotic therapy should be specific to that infection. With clinically severe illness in the absence of a clear source of infection, broad-spectrum coverage of gram-positive and gram-negative aerobic and anaerobic bacteria is indicated. In acutely ill febrile patients, especially those who are immunocompromised, antiviral and antifungal treatment are also frequently indicated.

DISPOSITION

Localized bacterial infections can often be treated with outpatient oral antibiotics. Relatively young, healthy patients with systemic viral illness can also be treated on an outpatient basis. These illnesses are often accompanied by vomiting and poor oral intake, and treatment in the ED with antipyretics, anti-nausea medications, and intravenous hydration may help prepare the patient for a successful outpatient course.

When no clear infection is identified in febrile older patients or those with chronic illness, such as diabetes or chronic renal failure, admission to the hospital may be necessary to elucidate the possible causes and clinical course. In this subset of patients, a diligent search for evidence of bacterial infection is required. Also, admission to an inpatient unit or ED observation unit may be advisable when fever or other systemic symptoms accompany an SSTI infection. In patients with unexplained severe febrile illness, blood and urine cultures and broad-spectrum antibiotics are indicated to treat possible life-threatening infection until a specific disease process or pathogen is identified. Indwelling devices, such as percutaneous intravenous access ports, frequently require culture and may need to be removed. Neutropenic patients with fever require prompt treatment with broad-spectrum parenteral antibiotics, pending results of cultures. Patients with unstable vital signs or life-threatening infections may require admission to a special care unit if they cannot be adequately stabilized in the ED before admission.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 8: QUESTIONS AND ANSWERS

1. Which three body systems are the target of more than 80% of bacterial infections in patients older than 65 years?
   - **a.** Central nervous system, respiratory system, genitourinary system
   - **b.** Central nervous system, respiratory system, skin and soft tissue
   - **c.** Central nervous system, urinary system, skin and soft tissue
   - **d.** Respiratory system, genitourinary system, skin and soft tissue

Answer: d. Patients older than 65 years who present with fever represent a group at high risk for serious disease. Morbidity and mortality in this group are significant. Between 70% and 90% are hospitalized, and 7% to 9% die within 1 month of admission. Infection is the most common cause of fever in these patients, and most of these infections are bacterial in nature. More than 80% of these infections originate from the respiratory system, genitourinary system, and skin and soft tissue.

2. A 65-year-old man presents after "briefly collapsing" at a nearby bus stop. On arrival, he is confused, opens his eyes spontaneously, and follows simple commands. A medical information card found in his wallet reveals a history of hypertension and gout. Vital signs reveal a blood pressure of 95/50 mm Hg, heart rate of 95 beats/min, respiratory rate of 24 breaths/min, temperature of 41.5°C, and arterial oxygen saturation (Sao_2) of 95%. His finger-stick glucose level is normal. Pertinent physical examination findings include pallor, dry mucous membranes, Glasgow Coma Score (GCS) of 14, and ataxia. An intravenous bolus of normal saline is started. Which of the following is the most appropriate next step in the management of this patient?
   - **a.** Administer broad-spectrum antibiotics.
   - **b.** Mist the patient with water and place him in front of a fan.
   - **c.** Obtain a head CT scan.
   - **d.** Perform a lumbar puncture.

Answer: b. In terms of initial resuscitative efforts, the most significant finding in this patient is a temperature of 41.5°C. Almost all cases of temperatures higher than 41.0°C (107°F) are due to hyperthermia rather than to fever. Sustained temperatures higher than 41.0°C (106°F) are rare but can be damaging to neural tissue and require rapid, aggressive, cooling measures, such as misting the patient with tepid water and placing him or her in front of a fan, immersion in cool water, or application of cooling blankets. Each of the other four options could potentially be performed during this patient's stay in the emergency department; however, the immediate focus is on temperature reduction.

3. Of the cases of functional decline in nursing home patients, 75% are due to which of the following?
   - **a.** Congestive heart failure
   - **b.** Coronary artery disease
   - **c.** Dementia
   - **d.** Infection

Answer: d. Of the cases of functional decline (e.g., difficulty ambulating, anorexia, decreased activity, new urinary incontinence) in nursing home patients, 75% are due to infection.

4. An 85-year-old man is brought to the emergency department (ED) by his daughter, who says that he has had a fever and has been eating less than normal for 2 days. The patient has a history of hypertension and severe dementia. He can provide no useful information. His present temperature was recorded by the triage nurse to be 38.5°C (101°F). The remainder of his vital signs are within normal limits. The only abnormal findings on physical examination are slightly dry mucous membranes, confusion, and poor social interaction. The daughter confirms his mental status to be at baseline. Which of the following are the two most important ancillary tests to perform in this patient?
   - **a.** Blood culture and urine culture
   - **b.** Urinalysis and chest radiography
   - **c.** Urinalysis and white blood cell count
   - **d.** White blood cell count and chest radiography

Answer: b. The two most important ancillary tests in the evaluation of fever in the adult patient, and especially in older patients, who frequently have atypical presentations, are urinalysis and chest radiography. Chest radiographs are often helpful in the diagnosis of pulmonary infection but may be difficult to interpret in the patient with chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), or other chronic lung disease. Urinalysis, although not foolproof, is highly accurate for urinary tract infection, especially in men. Although the white blood cell count is almost universally used in the evaluation of febrile patients, it lacks sufficient sensitivity and specificity to be of discriminatory value. Cultures are ordered in selected patients; however, the delay in obtaining results precludes any influence in emergency evaluation and treatment. Other tests that have relevance in select patients with fever include Gram staining, cerebrospinal fluid (CSF) analysis, thyroid function studies, ultrasonography, and computed tomography (CT) of the abdomen or head.

9

Weakness

Andrew J. Eyre

KEY CONCEPTS

- Weakness is a common complaint among emergency department (ED) patients, with a preponderance in elders and those with chronic disease, and therefore may require a broad approach to investigating underlying causes.
- Patients may use the term weakness to reflect a variety of vague symptoms including decreased motor strength, fatigue, poor energy, dyspnea, or even depression.
- Global weakness is typically caused by a systemic condition while a focal neurologic deficit or pattern can often be traced to a specific lesion within the central or peripheral nervous systems.
- Although not always detectable in the acute period, lesions to the upper motor neurons (UMNs) tend to produce signs that include spasticity to extension in the upper extremities, spasticity to flexion in the lower extremities, hyperreflexia, pronator drift, and Hoffmann and Babinski signs.
- Lesions to lower motor neurons (LMNs) typically result in flaccidity, decreased reflexes, fasciculations, or muscle cramps.

FOUNDATIONS

Epidemiology

Weakness, a common ED complaint, can reflect a vast array of pathology with varying degrees of severity. Patients may use to the term *weakness* to describe either focal or systemic complaints and often use the broader description of weakness to convey otherwise vague or subjective symptoms, such as fatigue, lethargy, or general malaise. As a result, weakness as chief or associated complaint can be quite challenging, both from a diagnostic and therapeutic perspective.

Up to 10% of ED visits are for generalized weakness, with a preponderance of the complaint among elders. Over half of these patients are identified as having a serious condition, and the diagnoses span cardiovascular, hematologic, neurologic, toxicologic, psychiatric, endocrine, pulmonary, metabolic, and infectious causes.[1]

This chapter focuses on the initial evaluation of the generalized complaint of weakness and the specific evaluation of acute neuromuscular weakness. The latter may be focal or generalized and may originate in central or peripheral nerves, the neuromuscular junction (NMJ), or myofibers themselves. Other chapters in this text provide additional information regarding the diagnosis and management of specific neurologic causes of weakness including the brain and cranial nerves (CNs; see Chapter 91), spinal cord (see Chapter 92), and peripheral nerves (see Chapter 93), as well as neuromuscular disorders (see Chapter 94).

Pathophysiology

There are many diagnostic considerations for the patient presenting with diffuse weakness (Box 9.1). While a singular cause of weakness may be identified, elders and patients with multiple medical problems may have numerous factors contributing to weakness. Alterations in plasma volume, electrolyte imbalance, anemia, decreased cardiac function, drop in systemic vascular resistance, increased metabolic demand (infection, toxin, endocrinopathy), and mitochondrial dysfunction (severe sepsis) can all produce non-localized weakness. A global depression in central nervous system (CNS) activity from sedative effects or stimulant withdrawal can also present as generalized weakness. Focal weakness confined to one area in the face or body (left, right, distal, or proximal) typically indicates a localized neurological issue corresponding to a specific area of the central or peripheral nervous systems (PNSs).

Lesions involving the motor areas of the cerebral hemispheres may cause unilateral weakness, and lesions in the cerebral cortex outside the motor area may cause receptive or expressive aphasias and complex cerebral motor deficits such as apraxia. Peripherally, the spinal nerves extend from the anterior horn of the spinal cord and represent the anatomic origins of the lower motor neuron (LMN). The neuroanatomic distinction between LMNs and upper motor neurons (UMNs) is essential in localizing lesions.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis for generalized weakness is broad. Consideration of systemic causes such as infectious, neurological, toxicologic, metabolic, and physiological causes is important (see Box 9.1). The first step is to address potential life threats, major systemic conditions, and disorders requiring emergent intervention. A detailed history should elucidate the nature, onset, and progression of symptoms, exacerbating or alleviating factors, and fluctuations in severity that may help discern if weakness is a result of cardiovascular disease, pulmonary insufficiency, metabolic disturbance, concurrent infection, toxic ingestion, medication imbalance, or malignancy. Medication reactions or interactions are an important consideration in patients taking multiple medications. A thorough review of systems should also be performed to identify associated signs or symptoms that may help to form a unifying diagnosis. For example, a review of systems might reveal orthopnea and symptoms of congestive heart failure in the fatigued patient with significant cardiac disease, chronic blood loss in the anemic patient, or incontinence in an older adult with a urinary tract infection. Elders often present with less localizing symptoms of infection, such as dysuria or frequency in the case of a possible urinary tract infection, and require a broad diagnostic approach, including laboratory and radiological studies.

Vital sign abnormalities, including bradycardia, tachycardia, tachypnea, fever, hypothermia, or hypotension should prompt immediate intervention and a search for a systemic cause of the weakness. A

BOX 9.1 Nonneurologic Weakness

- Alterations in plasma volume (dehydration)
- Alterations in plasma composition (glucose, electrolytes)
- Derangement in circulating red blood cells (anemia or polycythemia)
- Decrease in cardiac pump function (myocardial ischemia)
- Decrease in systemic vascular resistance (vasodilatory shock from any cause)
- Increased metabolic demand (local or systemic infection, endocrinopathy, toxin)
- Mitochondrial dysfunction (severe sepsis or toxin-mediated)
- Global depression of the central nervous system (sedatives, stimulant withdrawal)

general detailed physical examination, including evaluation of the skin and mucous membranes, may provide evidence of systemic disease. A cardiovascular examination can give the clinician a sense of the adequacy of circulation. A carefully performed neurologic examination is important to determine the occasionally subtle presentations of focal central or PNS lesions.

If history, physical examination, and ancillary testing do not identify a systemic cause of weakness, the investigation should broaden to include consideration of neural or primary muscular causes for weakness. Focal causes of weakness include central and peripheral neurological disease. Conditions involving UMNs tend to produce signs that include spasticity to extension in the upper extremities, spasticity to flexion in the lower extremities, hyperreflexia, pronator drift, and Hoffmann and Babinski signs. UMN signs signify a lesion within the cerebral cortex or corticospinal tract (CST) of the brainstem or spinal cord. Although these findings are not always detectable in the acute period, the presence of even one of them suggests pathology within the CNS. Weakness caused by LMN dysfunction is often accompanied by flaccidity, decreased reflexes, fasciculations, or muscle cramps. Lesions in the anterior horn of the spinal cord and its axonal extensions at the nerve root and peripheral nerve produce these findings.

Diagnostic Algorithm

Critical and Emergent Diagnoses

Fig. 9.1 describes the approach to evaluating acute weakness. Generalized weakness can be explored by systematic consideration of the cardiac, neurological, metabolic, and infectious etiologies that can manifest as generalized weakness. This includes an evaluation of cardiac function, including consideration of acute reduction in cardiac output or worsening contractility leading to congestive heart failure.[1,2] Further evaluation of circulation should include assessment of hemoglobin, oxygen saturation, and systemic vascular tone. Next, assess plasma volume and its composition to evaluate dehydration and altered nutrient (glucose), electrolyte (Na, K, Ca), or waste product (CO_2, urea, bilirubin, ketoacid, ammonia, etc.) levels which can produce diffuse weakness. If substrate delivery and plasma composition appear sufficient, consider disturbances of cellular metabolic machinery secondary to an endocrinopathy, toxin, or mitochondrial dysfunction in the setting of infection. In particular, consideration of infectious causes of generalized weakness should include bacterial, viral, and rickettsial infections that may not be evident from initial laboratory results.

Neurologic examination focuses on identifying acute findings that could support CNS impairment, including acute cerebrovascular events. Although generalized weakness can present deceptively as a focal deficit, particularly in areas already weakened by prior neurologic insult, focal findings, such as lateralizing weakness, numbness, gait instability, or CN defects, should prompt a more detailed exploration of a potential neurologic cause.

After evaluating the potential systemic causes of weakness, the practitioner should then address the specific causes of the focal loss of muscle power. This requires elucidating the pattern of a patient's weakness from the cortical neuron down through the CNS, PNS, NMJ, and myofibers. Table 9.1 lists the most important critical and emergent causes of acute neuromuscular weakness. Common clinical patterns of weakness can be classified and assessed as discussed in the following sections.

Specific Presentations of Neuromuscular Disorders

Unilateral Weakness

Combination of arm, hand, or leg with ipsilateral facial involvement. Weakness involving the combination of arm, hand, or leg with ipsilateral facial involvement is generally caused by a lesion in the contralateral cerebral cortex or the CSTs coursing down the corona radiata and forming the internal capsule. Mild forms can be limited to a loss of dexterity and coordination with hand movements. Moderate loss of power is termed *paresis,* while complete loss of motion is termed *plegia*. UMN signs are useful corroborative findings but may not always be present, especially in the acute phase. Sensory disturbances commonly occur over the areas of weakness. Evaluate for associated neglect, visual field loss, or expressive or receptive aphasia to localize the problem to the cortex.

Patients with equal loss of strength to the face, hand, and leg are more likely to have a subcortical lesion disrupting all these fibers as they funnel close together in the internal capsule. Concomitant headache is concerning for brain hemorrhage or mass lesion, although complex migraines can produce focal neurologic deficits.[1] Sudden onset of this weakness pattern often suggests hemorrhage or acute ischemia, whereas a gradual onset may be seen in demyelination (e.g., multiple sclerosis, acute demyelinating encephalomyelitis) or neoplasm.[1]

Combination of arm, hand, or leg with contralateral facial involvement. Weakness involving the combination of arm, hand, or leg with contralateral facial involvement indicates a brainstem lesion. A careful CN examination can provide more clues. If the patient has contralateral facial findings, there will likely be ptosis (CN III or sympathetic fibers) or a facial droop with forehead involvement (CN VII nucleus). Signs of CN V, VI, VIII, IX, or XII dysfunction will help localize to a particular level within the brainstem. Cerebellar findings or nystagmus may also be present on examination. Sensory disturbances can parallel the weakness, and some patients will report double vision, trouble swallowing, slurred speech, vertigo, or nausea and vomiting. The CST courses ventrally through the brainstem, and extremity weakness with UMN signs in the involved limbs may accompany brainstem lesions. Depressed consciousness can also occur if the brainstem reticular activating system is involved. The two main underlying processes that cause unilateral extremity weakness with contralateral facial involvement are vertebrobasilar insufficiency and demyelinating diseases.

Combination of arm, hand, or leg without facial involvement. Weakness involving the combination of arm, hand, or leg without facial involvement is most likely to be a result of one of the following three processes:

- A lesion in the medial, contralateral, cerebral homunculus (over the area where the lower extremity is represented)
- A discrete internal capsule or brainstem lesion involving only the corticospinal rather than the corticobulbar tracts
- Brown-Séquard internal capsule or brainstem lesion if the patient also has contralateral hemibody pain and temperature sensory disturbances below the level of motor weakness.

Importantly, however, before a patient is placed in this category, a careful examination of facial symmetry is required to determine that subtle facial droop or effacement of the nasolabial fold is not present.

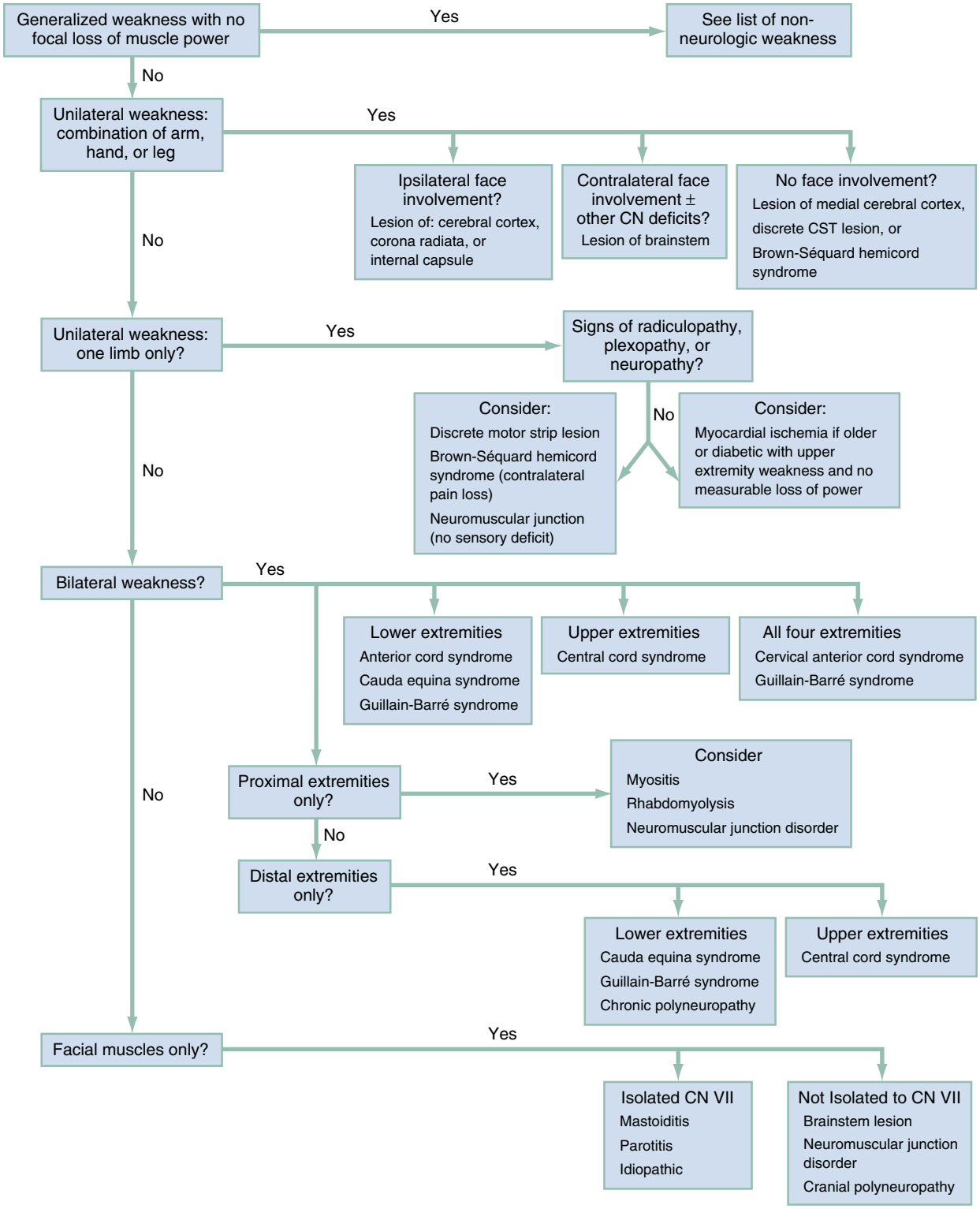

Fig. 9.1 Common Clinical Patterns of Weakness, Classified and Assessed. *CN*, Cranial nerve.

Isolated extremity weakness (monoparesis or monoplegia). Isolated weakness of one extremity is usually caused by a spinal cord or peripheral nerve lesion. Examination for UMN signs in the affected limb will help uncover rare monomelic presentations of CNS lesions. If UMN signs such as hyperreflexia or spasticity are present, a careful evaluation is performed for facial weakness or involvement of the contralateral or other ipsilateral limb as indicative of a central process. If weakness is in the entirety of one lower limb, one should ensure that the patient does not have a contralateral pinprick level indicative of Brown-Séquard hemicord syndrome. Monomelic weakness is often the result of a radiculopathy, plexopathy, peripheral neuropathy, or NMJ disorder. See Table 9.1 for emergent and critical PNS diagnoses.

TABLE 9.1 Critical and Emergent Causes of Neuromuscular Weakness

Diagnosis	Features
Critical Diagnoses	
Cerebral cortex or subcortical	Ischemic or hemorrhagic cerebrovascular accident (CVA)
Brainstem	Ischemic or hemorrhagic CVA
Spinal cord	Ischemia, compression (disk, abscess, or hematoma)
Peripheral nerve	Acute demyelination (Guillain-Barré syndrome)
Neuromuscular junction	Myasthenic or cholinergic crisis Botulism Tick paralysis Organophosphate poisoning
Muscle	Rhabdomyolysis
Emergent Diagnoses	
Cerebral cortex or subcortical	Tumor, abscess, demyelination
Brainstem	Demyelination
Spinal cord	Demyelination (transverse myelitis) Compression (disk, spondylosis)
Peripheral nerve	Compressive plexopathy (hematoma, aneurysm) Paraneoplastic vasculitis uremia
Muscle	Inflammatory myositis

The examination for monomelic weakness presentations includes detailed strength testing and determination of whether weakness localizes to one ventral nerve root myotome or one particular peripheral nerve within the limb. Reflexes with a peripheral nerve disorder will be diminished, not hyperactive. Although radiculopathies can occasionally be purely motor, most peripheral lesions have some sensory component to their presentation; therefore, a careful sensory examination in the distribution of dorsal nerve root dermatomes and peripheral nerves is essential. See Box 9.2 for a list of nonemergent causes of peripheral neuropathy.

NMJ disorders are considered when suspicion is low for a UMN source of isolated extremity weakness, reflexes are intact, and there are no sensory deficits to suggest a nerve or root problem. In such cases, the weakness is often mild, fluctuating, and worse later in the day. It usually involves the proximal arm or leg muscles, wrist extensors, finger extensors, or ankle dorsiflexors. NMJ disorder–induced weakness with only monomelic symptoms will be an uncommon diagnosis in the ED.

Bilateral Weakness

Lower extremities only (paraparesis or paraplegia). When weakness involves the lower extremities only, the first consideration is a spinal cord lesion. If this is the case, UMN signs may be absent in the acute period. Because the lateral spinothalamic tracts (LSTs) run in proximity to the CST, patients with bilateral lower extremity weakness frequently have alterations to their perception of pain or temperature. Examination may reveal a loss of pinprick sensation to a particular spinal level within the thoracic cord or terminal first lumbar segment. The lesion may be as high as T2 without producing upper extremity findings.

The main causes of anterior cord syndrome are external compression, ischemia, or demyelination. In the absence of UMN signs or a clear thoracic pinprick level, evaluation of perianal sensation, rectal tone, and urinary retention can identify deficits that point to cauda equina syndrome, compression of peripheral nerve roots running below the termination of the spinal cord. If the physical examination does not support a cord syndrome or cauda equina compression, the patient may have a peripheral neuropathy affecting the longest nerve tracts first. The acute presentation that is most concerning is Guillain-Barré syndrome (GBS). Rapid demyelination of peripheral nerves can result in symmetric weakness ascending from the feet. Sensory findings parallel the weakness, and reflexes should be decreased at some point in the patient's clinical course. (1)

BOX 9.2 Nonemergent Causes of Peripheral Neuropathy

Connective tissue disorder
External compression (entrapment syndrome, compressive plexopathy)
Endocrinopathy (diabetes)
Paraneoplastic syndromes
Toxins (alcohol)
Trauma
Vitamin deficiency

Upper extremities only. When weakness involves the upper extremities only, the lesion is localized within the central portion of the cervical spinal cord where corticospinal fibers designated for hand and arm strength are located. The patient may have pinprick sensory loss over the upper extremities from the involvement of crossing sensory axons destined for the contralateral LST. However, light touch sensation, mediated by the posterior columns, should remain intact. Common causes of central cord syndrome include cervical spine hyperextension injuries and syringomyelia.

All four extremities without facial involvement (quadriparesis or quadriplegia). When weakness involves all four extremities without facial involvement, the primary concern is a cervical spinal cord injury or process, but the patient is first assessed for medical conditions that produce global weakness. The more dense the extremity weakness, the more likely it is that the patient has a cervical spinal cord problem. Although all four extremities will test poorly for muscle strength, there is frequently some discrepancy between the lower and upper limbs in quadriparesis.

Determination of sensory dermatomes by pinprick testing in the arms and hands, along with strength testing of specific myotomes, will allow localization of the level within the cervical spinal cord. One physical examination confounder in disorders that cause cord compression or ischemia is that upper extremity myotomes corresponding to the site of spine involvement will actually have LMN signs of flaccid weakness and decreased reflexes because anterior cells are involved at this particular level. However, UMN signs may be elicited below that level. A C5 lesion, for example, can cause diminished biceps reflexes but exaggerated triceps and patellar reflexes. Bilateral extremity weakness may occur in patients with GBS that has ascended from the lower extremity peripheral nerve myelin sheaths to the upper extremities. In this case, the lower limbs are usually weaker than the upper limbs.

Proximal portions of extremities only. Weakness confined to the proximal portions of the upper extremities only points to a myofiber disorder, provided that there are no UMN signs or sensory deficits. Patients may report general fatigue or trouble raising the arms above the head, climbing stairs, or rising from a chair. The common acute and progressive causes of proximal muscular weakness are inflammatory diseases such as polymyositis or dermatomyositis, or necrosis, as in rhabdomyolysis from 3-hydroxy-3-methylglutaryl-coenzyme A

(HMG-CoA) reductase inhibitors. Muscles are commonly but not always tender to palpation. Myositis patients can also have dysarthria and dysphagia from weakness of the pharyngeal muscles. Airway protective mechanisms may eventually be compromised.

Chronic or recurrent myofiber pathology includes abnormalities to anchoring proteins supporting fibrils to the cytoskeleton and cell membrane (e.g., muscular dystrophies), dysfunctional ion channels responsible for depolarization of the muscle fiber cell (channelopathies such as hyperkalemic and hypokalemic periodic paralysis), or impaired ability to use carbohydrate and lipid energy sources (e.g., metabolic myopathies, mitochondrial myopathies). The presentation of these varied conditions ranges from insidious and progressive to sudden onset and episodic. Occasionally, a patient with an NMJ disorder will demonstrate proximal extremity or neck muscle weakness mimicking myofiber disease.

Distal portions of extremities only. Weakness involving the distal portions of the extremities only is almost always caused by a peripheral neuropathy (see Box 9.2). Patients will have weakness and poor coordination with fine movements of their feet or hands. If this type of distal weakness is present in both lower extremities only, the patient will most likely have a chronic peripheral neuropathy or an acute demyelinating neuropathy (GBS). The patient will also have some sensory disturbance over the feet. Examination for perianal sensory deficits or issues with fecal or urine continence will help exclude the compressive polyradiculopathy of cauda equina syndrome as a cause of bilateral distal lower extremity weakness. If only the fingers and hands are involved, evaluation for central cord syndrome is performed. Bilateral lower cervical radiculopathies or symmetrical polyneuropathies are possible but much less likely.

Facial Weakness Without Extremity Involvement

Isolated facial weakness will appear in one of two forms.

Unilateral facial droop. Isolated, unilateral weakness of the upper and lower halves of the face is caused by a CN VII problem. Causes for an isolated CN VII neuropathy are Bell palsy, mastoiditis, and parotitis. The examination must confirm that there is no extremity involvement and that other CNs, cerebellar testing results, and visual fields are normal. This will ensure that a brainstem lesion is not causing the weakness.

Facial weakness not limited to cranial nerve VII. Facial weakness not limited to CN VII will be associated with some combination of ptosis, binocular diplopia, dysarthria, or dysphagia. It can be caused by a brainstem lesion, multiple cranial neuropathies, or NMJ problem. If there are no cerebellar findings, visual field deficits, sensory disturbances, or extremity UMN signs, posterior cerebral circulation and brainstem disorders are less likely, and an NMJ disorder is more likely. Dysfunction of one or more ocular, facial, or pharyngeal muscles will be the most common presentation for NMJ pathology. The history may indicate that the facial weakness is acute and progressive (botulism) or chronic and fluctuating (myasthenia gravis). Signs of these diseases can be determined by examining extraocular motion, facial expression, and soft palate rise. Generalized fatigue is often reported, and neck, extremity, and respiratory muscle weakness caused by involvement of these neuromuscular units may be present on examination.

Patients with an abnormality of the presynaptic release of acetylcholine (e.g., botulism, Eaton-Lambert syndrome, organophosphate poisoning) can have autonomic ganglia involvement and hence abnormal pupillary response to light, dry mouth, fluctuations in heart rate and blood pressure, anhidrosis, or gastrointestinal and bladder dysmotility.

Facial weakness from cranial polyneuropathy manifests with more than one CN deficit not localizing to a brainstem level and without any other long tract signs. These patients may have a variant of GBS or irritation of multiple CNs after they have exited the brainstem and pierced through inflamed meninges or malignant skull base metastases.

EMPIRIC MANAGEMENT

The management of neuromuscular weakness is based on evaluating the underlying cause and managing the acute complications of weakness. Airway protection in obtunded patients or those with upper airway compromise is paramount. Neck and pharyngeal muscle weakness, for example, may herald a risk for aspiration or airway obstruction. Diaphragmatic weakness and inadequate hypopharyngeal muscle control or respiratory muscle fatigue should prompt definitive airway protection by endotracheal intubation. During rapid sequence intubation (RSI), succinylcholine should be avoided in suspected cases of progressive denervation of muscle of more than a 3-day duration due to receptor upregulation and the risk for severe hyperkalemia. In this situation, we recommend rocuronium, a nondepolarizing neuromuscular blocking agent.

New quadriparesis or quadriplegia and hypotension without another cause is assumed to be caused by failure of autonomic sympathetic fibers in the cervical spinal cord. Consider a volume load and pressor support in addition to emergent imaging of this area. Although new weakness localizing to the spinal cord calls for immediate imaging, weakness from the spinal roots down does not always necessitate imaging in the ED unless cauda equina syndrome or other acute, emergent pathology is suspected.

Patients with suspected GBS need pulmonary function testing in addition to admission to a critical care setting for further management. An infectious or metabolic trigger is sought in patients with myasthenic crisis. If the patient is currently on acetylcholinesterase inhibitors, consideration should be given to a cholinergic crisis. Be aware of medications that may worsen weakness in patients with NMJ disease (e.g., aminoglycosides, quinolones, beta blockers). Rhabdomyolysis is treated with aggressive fluid resuscitation and intervention directed at the primary cause, if known.

In any patient with a sudden onset of focal weakness, a vascular cause (occlusion or hemorrhage) should be strongly considered until excluded by an adequate imaging study. The presence of a severe headache with unilateral weakness, or midline back pain with lower extremity weakness, alerts the clinician to a compressive space-occupying lesion of the CNS or spinal cord, respectively.

Patients with UMN signs have weakness that localizes to the spinal cord CST or above and are considered to have an emergent problem. They may be at risk for progression to sympathetic autonomic failure or obtundation from enlarging space-occupying spinal or cerebral lesions, respectively. The presence of anorectal or bladder insufficiency without another explanation suggests a UMN or cauda equina lesion. Laboratory tests are most useful for excluding non-neuromuscular causes of weakness (electrocardiography, measurement of hemoglobin, glucose, electrolytes, troponin, and lactate levels, urinalysis). Two exceptions are the creatinine kinase level in inflammatory myositis and potassium level in channelopathies.

DISPOSITION

Patients with generalized weakness should receive treatment and disposition based on the underlying diagnosis and anticipated clinical course, and the range of dispositions will vary based on etiology. Patients with identified central vascular lesions, thrombotic or hemorrhagic, should be aggressively managed in the inpatient setting. Patients with mild LMN or myofiber weakness of benign origin may

be discharged with close follow-up, provided that the condition is not thought to be progressing rapidly. Those with more severe or progressive LMN or myofiber weakness and any patient with new UMN weakness should be admitted for further testing. Patients with suspicion for ascending paralysis should be admitted to an ICU setting for close respiratory observation.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 9: QUESTIONS AND ANSWERS

1. A 65-year-old man with a history of atrial fibrillation, on warfarin, with a supratherapeutic international normalized ratio (INR) of 4, presents with sudden onset right leg weakness and back pain. On examination, he is tachycardic to 108 beats/min and has 3/5 weakness to the right hip flexors and extensors, knee flexors and extensors, as well as ankle dorsiflexion and great toe extension. However, ankle plantar flexion is preserved. His knee reflexes are absent, but Achilles reflexes are normal. He has a normal Babinski reflex and no spasticity. He has sensory deficits throughout the anterior and posterior parts of his proximal leg as well as the anterior lower leg and dorsum of the foot. His posterior lower leg and plantar surface, however, have normal sensation. Rectal tone is normal, and there is no urinary retention. What is the most likely diagnosis?

a. Anterior cord syndrome from epidural hematoma
b. Cauda equina syndrome
c. Guillain-Barré syndrome
d. Hemorrhagic anterior cerebral artery (ACA) distribution stroke
e. Retroperitoneal hematoma with lumbar plexopathy

Answer: e. This patient has a spontaneous retroperitoneal hematoma compressing the lumbar nerve plexus.

2. A 45-year-old man has had gradual onset of progressive weakness to his face and trouble swallowing for 2 days. On examination, he has bilateral ptosis with dilated, poorly reactive pupils, bilateral upper and lower facial muscle weakness, poor soft palate rise, and slurred speech. His oral mucosa is dry. Arms and legs have 5/5 strength. He has no sensory deficits. He has a palpable distended bladder. His symptoms have not abated since onset, and they are getting worse. What is the most likely diagnosis?

a. Brainstem stroke
b. Botulism
c. Muscular dystrophy
d. Myasthenia gravis
e. Organophosphate poisoning

Answer: b. This patient has acute onset of progressive neuromuscular junction weakness. He has autonomic findings of abnormal pupil response to light, dry oral mucosa from decreased salivary production, and a distended bladder. These imply that his problem is with the release of acetylcholine (ACh) rather than the nicotinic receptor. The latter would not have autonomic findings. The most appropriate cause of acute onset, progressive impairment in the release of ACh, as listed in the choices, is botulism.

3. A 23-year-old woman presents with the sudden onset of weakness of her face, arm, and leg 2 hours ago. On examination, she has weakness to her upper and lower face on the left. She cannot abduct her left eye. She has 3/5 strength to her upper and lower extremities on her right side. She has a right pronator drift and an upgoing toe on the right. Sensation is decreased in her right upper and lower extremities as well. There is no aphasia, neglect, or visual field deficit. What is the most likely diagnosis?

a. Midbrain stroke because of cardioembolic stroke
b. Middle cerebral artery (MCA) distribution stroke
c. Multiple sclerosis
d. Myasthenia gravis
e. Pons stroke because of vertebral dissection

Answer: e. This patient has acute onset of crossed face and extremity weakness, with upper motor neuron (UMN) signs in the extremities. Both upper and lower extremities are affected, which makes a corticospinal tract (CST) lesion more likely than a cerebral cortex lesion. Her left-sided facial weakness is representative of a peripheral cranial nerve (CN) VII that is actually due to infarction of the CN VII nucleus in the brainstem. The CN VI deficit on that side is due to proximity of this nucleus as well. The CST runs just anterior to these nuclei within the brainstem. These CN nuclei lie in the pons.

4. A 21-year-old man awoke this morning with weakness to his right hand and right foot. He admits to drinking heavily the night before and falling asleep on the floor. On examination, he appears well, with weakness to right wrist extension and thumb extension, as well as sensory deficits over the dorsal surface of his hand and first and third digits. He also has weakness to ankle dorsiflexion and great toe extension on the right. He has sensory deficits over the anterior lower leg and the dorsum of his foot. Biceps and ankle reflexes are intact, he has no pronator drift, and his toes are downgoing. What is the most likely diagnosis?

a. Brainstem stroke
b. Brown-Séquard syndrome
c. Compressive neuropathy
d. MCA distribution stroke
e. Polyradiculopathy secondary to disk disease

Answer: c. He has radial nerve and peroneal nerve palsies because of compression while lying passed out on the floor for an unspecified time.

5. A 70-year-old man has had trouble swallowing and progressive weakness of his hands over the past 2 months. On examination, his speech is slurred, his voice is nasal, and he has fasciculations to his face, tongue, and over his pectoralis muscles and deltoids bilaterally. He has 4/5 strength to shoulders, biceps, triceps, and hand grip bilaterally. Stiffness to extension is present at both elbows. He has bilateral pronator drift and 3+ biceps reflexes. He tends to smile inappropriately. He has no sensory symptoms. What is the most likely diagnosis?

a. Amyotrophic lateral sclerosis (ALS)
b. Brainstem stroke
c. Chronic demyelinating polyneuropathy
d. Parkinsonism
e. Polymyositis

Answer: a. This patient has lower motor neuron (LMN) signs (fasciculations) and UMN signs (pronator drift and increased reflexes) in similar distribution. The combination of upper and lower motor neuron involvement makes ALS the leading diagnosis among those listed. His dysphagia and inappropriate smiling are due to a release of the medulla from upper motor neuron regulation.

10

Cyanosis

Pranav Shetty and Madonna Fernández-Frackelton

KEY CONCEPTS

- Cyanosis occurs due to an absolute amount of desaturated hemoglobin (~5 g/dL) rather than a percentage; anemic patients exhibit cyanosis at a lower Pa_{O_2} than those with normal hemoglobin levels.
- Cyanosis is an insensitive indicator of tissue oxygenation; its presence suggests hypoxemia, but its absence does not exclude it.
- Central cyanosis is most commonly due to global arterial hypoxemia or abnormal hemoglobin forms; peripheral cyanosis is due to vasoconstriction or reduced flow of normally oxygenated hemoglobin to the peripheral tissues.
- Methemoglobin has a chocolate brown color, even when the blood is exposed to room air; pulse oximetry for patients with methemoglobinemia typically reads 85%, regardless of the Pa_{O_2} or Sa_{O_2}.
- Methemoglobinemia may be due to inherited congenital errors in enzyme function or acquired secondary to exposure to oxidizing agents such as certain drugs and toxins.
- Congenital heart disease is a diagnostic consideration in all infants presenting with cyanosis.
- Sulfhemoglobin is often reported as methemoglobin on CO-oximetry; patients with methemoglobinemia on CO-oximetry who do not respond to methylene blue treatment likely have sulfhemoglobinemia.
- Methylene blue is the treatment of choice for symptomatic methemoglobinemia or at levels of methemoglobin greater than 20%.
- All patients with a first episode of cyanosis or cyanosis of uncertain cause require hospitalization.

FOUNDATIONS

Cyanosis is a blue or purple appearance of the skin or mucous membranes. This clinical finding is most commonly caused by one of two pathologic processes: inadequately oxygenated blood containing deoxygenated hemoglobin or the presence of abnormal hemoglobin forms which are unable to bind oxygen or supply adequate oxygen to end organs and tissues.

Epidemiology

Cyanosis is a relatively rare presenting chief complaint in the emergency department (ED) and is usually noted in patients with a hypo-perfused state or known cardiopulmonary disease, including congenital heart disease. Although carbon monoxide poisoning and cyanide toxicity result in inadequate hemoglobin oxygenation and/or tissue hypoxia, these entities typically do not present with the clinical finding of cyanosis and are discussed in other chapters (see Chapter 148).

Pathophysiology

Cyanosis is evident on physical examination when the absolute amount of desaturated (unoxygenated) hemoglobin in the circulating capillary blood is elevated to ~5 g/dL. It is not caused solely by a percentage of desaturated total hemoglobin mass or decreased amount of oxyhemoglobin. For this reason, patients with anemia exhibit cyanosis at lower arterial partial pressure of oxygen (Pa_{O_2}) and oxygen saturation (Sa_{O_2}) levels than those with normal hemoglobin, while patients with polycythemia may exhibit cyanosis at higher Pa_{O_2} and Sa_{O_2} levels. As such, cyanosis is an insensitive indicator of tissue oxygenation; its presence suggests hypoxemia, but its absence does not exclude it.

Primary causes of hypoxemia include ventilation-perfusion (V/Q) mismatch, hypoventilation, diffusion limitation, and low levels of inspired oxygen. V/Q mismatch is an imbalance between the ventilation and perfusion of alveolar-capillary units and is the most common cause of hypoxemia. High V/Q ratios (increased dead space) can be seen in diseases such as pulmonary emboli, emphysema, and pulmonary hypertension. Low V/Q ratios, with the most extreme example being a right-to-left shunt, occur in pneumonia, asthma, ARDS, and pulmonary edema. Anatomic right-to-left shunts are seen in developmental anomalies, such as congenital heart disease and patent ductus arteriosus. Hypoventilation lowers alveolar P_{O_2} and is most commonly caused by depressed central respiratory drive, respiratory muscle weakness, or morbid obesity. Diffusion limitation refers to the impaired diffusion of oxygen across the alveolar-capillary interface and is seen in diseases such as interstitial pulmonary fibrosis and chronic obstructive pulmonary disease (COPD). This may not cause hypoxemia at rest but may during exercise when the transit time for red blood cells (RBCs) in the pulmonary capillary bed is reduced. Lastly, low levels of inspired oxygen result in reduced alveolar P_{O_2} levels and are seen primarily at high altitude.[1]

Abnormal hemoglobin forms, most commonly methemoglobin, also contribute to cyanotic disease. Under normal conditions, RBCs contain hemoglobin with iron in the reduced ferrous state (Fe^{2+}). Ferrous iron binds oxygen readily to create oxyhemoglobin, and it reverts to the ferrous state when oxygen is released. The iron molecule may be oxidized to the ferric state (Fe^{3+}) spontaneously or by oxidative stress, producing methemoglobin. The ferric iron cannot bind oxygen, impairing the ability of hemoglobin to transport oxygen to the tissues. Any remaining ferrous (Fe^{2+}) binding sites on the hemoglobin molecule have a higher affinity for oxygen, shifting the oxygen-hemoglobin dissociation curve (Fig. 10.1) to the left, further resulting in tissue hypoxia and subsequent lactic acid production.[2]

Methemoglobin normally accounts for less than 1% of total hemoglobin. Cyanosis results when more than 1.5 g/dL of methemoglobin is present (~10% to 25% of the total hemoglobin). Methemoglobin has a dark purple or chocolate-brown color, even when exposed to room air. It is primarily reduced to ferrous (Fe^{2+}) hemoglobin by nicotinamide adenine dinucleotide + hydrogen (NADH)–cytochrome b5 reductase, an enzyme system present in RBCs. A secondary system dependent

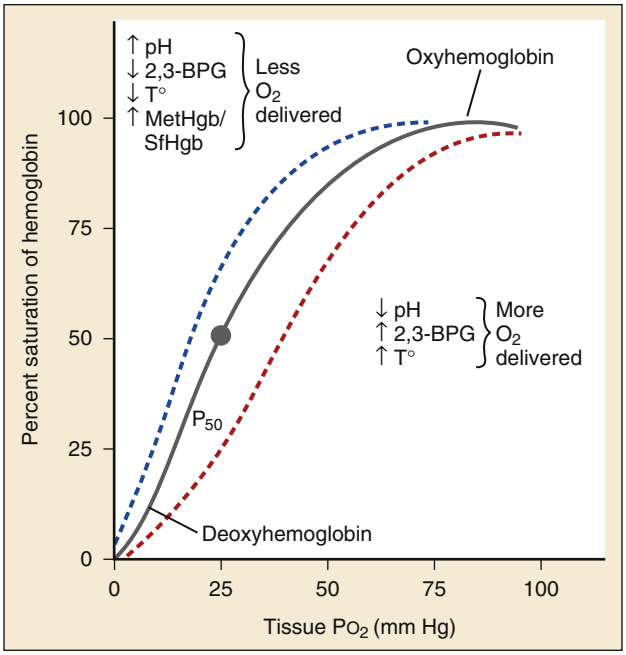

Fig. 10.1 Hemoglobin-Oxygen Dissociation Curve. The solid line represents percent of hemoglobin *(Hgb)* saturation at a given Pa_{O_2}. The *red dotted line* represents factors that favor O_2 delivery to the tissues, so that at a given Pa_{O_2}, the Hgb saturation drops and O_2 is released. Exercising muscle tissue creates an environment with lactic acid production and elevated temperature shifting the curve to the right, which favors the release of O_2. The *blue dotted line* represents a shift to the left with higher O_2 binding at any given Pa_{O_2}. Higher pH and lower temperatures, as in pulmonary capillary beds, favor more O_2 binding. Methemoglobin has a high affinity for oxygen molecules and does not readily release O_2 to the peripheral tissues. This shifts the normal oxygen dissociation curve to the left, resulting in hypoxia and lactic acid production. Lactic acid being produced in the tissues should facilitate O_2 release; however, the high affinity of methemoglobin for O_2 prevents this normal process. *2,3-BPG,* 2,3-Bisphosphoglycerate; *P_{50},* oxygen half- saturation pressure of hemoglobin; *P_{O_2},* partial pressure of oxygen; *T,* temperature. (Redrawn from Koeppen BM, Stanton BA. *Berne & Levy Physiology*. 6th ed., St. Louis: Mosby; 2008.)

on nicotinamide adenine dinucleotide phosphate (NADPH) reductase uses glutathione and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to ferrous hemoglobin. This secondary pathway plays a minor physiologic role but is accelerated significantly by methylene blue.

Primary methemoglobinemia is the result of congenital errors in metabolism caused by diminished levels of NADH reductase or an abnormally functioning enzyme. Patients may have stable compensated cyanosis. Acquired methemoglobinemia occurs when methemoglobin production exceeds the capacity of NADH reductase activity; this is usually a result of a drug reaction.[3] The most common medications that cause methemoglobinemia are local anesthetics, both injected and topical, phenazopyridine, nitroglycerin, and metoclopramide. See Box 10.1 for additional causes. Newborns are at increased risk for methemoglobinemia due to relatively low NADH reductase activity compared with that of adults.

DIAGNOSTIC APPROACH

Differential considerations for patients with cyanosis are listed in Box 10.2.

BOX 10.1 Common Causes of Methemoglobinemia

Hereditary

Hemoglobin M
NADH methemoglobin reductase deficiency (homozygote and heterozygote)

Acquired

Medications

Amyl nitrite
Antineoplastics (e.g., cyclophosphamide, ifosfamide, flutamide)
Dapsone
Local anesthetics (e.g., benzocaine, lidocaine, prilocaine)
Metoclopramide
Nitroglycerin
Nitroprusside
Phenacetin
Phenazopyridine (Pyridium)
Quinones (e.g., chloroquine, primaquine)
Rasburicase
Sulfonamides (e.g., sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

Chemical Agents

Aniline dye derivatives (e.g., shoe dyes, marking inks)
Butyl nitrite
Chlorobenzene
Fire (heat-induced denaturation)
Food high in nitrates
Isobutyl nitrite
Naphthalene (mothballs)
Nitrophenol
Nitrous gases (seen in arc welders)
Paraquat
Silver nitrate
Trinitrotoluene
Well water (nitrates)

Pediatric Cases

Reduced NADH methemoglobin reductase activity in infants (<4 months)
Seen in association with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia

Modified from Goldfrank LR. *Toxicologic Emergencies*. 9th ed. New York: McGraw-Hill; 2010.
NADH, nicotinamide adenine dinucleotide + hydrogen.

Pivotal Findings

Presentation and Symptoms

Common symptoms associated with cyanosis include dyspnea, fatigue, chest discomfort, and decreased exercise tolerance. The onset, duration, time of day of symptoms, and any previous episodes should be noted. Patients with methemoglobin levels less than 20% are often asymptomatic, although cyanosis may be noted. With levels of 20% to 50%, patients may exhibit headaches, fatigue, weakness, dizziness, and dyspnea. Levels greater than 50% result in altered mental status, lethargy, and seizures, and levels greater than 70% are associated with death.[4]

Precipitating factors may include exposure to cold air or water, high altitude, or exercise in patients with a history of cardiopulmonary disease. Additional history should include known congenital heart disease or cardiopulmonary disease, hypercoagulable states, and family history of cyanotic or hematologic disease. A history of exposure to fumes or chemicals should be obtained, including aniline or azo dyes,

BOX 10.2 Differential Diagnosis of Cyanosis

I. Peripheral cyanosis
  A. Low cardiac output states
    1. Shock
    2. Left ventricular failure
    3. Hypovolemia
  B. Environmental exposure (cold)
  C. Arterial occlusion
    1. Thrombosis
    2. Embolism
    3. Vasospasm (Raynaud phenomenon)
    4. Peripheral vascular disease
  D. Venous obstruction
  E. Redistribution of blood flow from extremities
    1. Peripheral arteriovenous fistulae
II. Central cyanosis
  A. Decreased arterial oxygen saturation
    1. High altitude (>8000 ft)
    2. Impaired pulmonary function
      a. Hypoventilation
        1. Drug toxicity
        2. Respiratory muscle weakness
        3. Upper airway compromise
      b. Impaired oxygen diffusion
        1. Interstitial pulmonary fibrosis
        2. Emphysema
      c. Ventilation-perfusion mismatch
        1. Pulmonary embolism
        2. Pulmonary hypertension
      d. Right-to-left shunt
        1. Pneumonia
        2. Large pneumothorax
        3. Acute respiratory distress syndrome (ARDS)
  B. Anatomic shunts
    1. Pulmonary arteriovenous fistulae and intrapulmonary shunts
    2. Cyanotic congenital heart disease
      a. Endocardial cushion defects
      b. Ventricular septal defects
      c. Coarctation of aorta
      d. Tetralogy of Fallot
      e. Total anomalous pulmonary venous return, low pulse oximetry readings
      f. Hypoplastic left ventricle
      g. Pulmonary vein stenosis
      h. Tricuspid atresia and anomalies
      i. Premature closure of foramen ovale
      j. Dextrocardia
  C. Disorders of hemoglobin
    1. Methemoglobinemia
    2. Sulfhemoglobinemia
    3. Polycythemia

shoe polish, and nitrates. A drug history should be reviewed, including use of prescription and over-the-counter medications, supplements, and herbal or alternative preparations. The potential of pseudocyanosis resulting from exposure to dyeing agents, heavy metals, or topically absorbed pigments should be explored.

In infants, congenital heart disease is suggested by difficulty feeding, sweating, lethargy, poor weight gain, or respiratory distress. Episodic cyanotic events, or "tet spells," may be seen in children with tetralogy of Fallot: ventricular septal defect, overriding aorta, pulmonic stenosis or atresia, and right ventricular hypertrophy with outlet obstruction. These patients have cyanosis, tachypnea, and anxiety due to decreased pulmonary blood flow, with shunting of unoxygenated blood into the systemic circulation (see Chapter 165).

Signs

There is significant interobserver variability in detecting cyanosis on physical examination. Room lighting and temperature may affect examination of the skin and mucous membranes. A patient's natural skin tone, thickness, and pigmentation also may alter findings.

The physical manifestation of cyanosis can be divided into two broad categories: central cyanosis and peripheral cyanosis. Central cyanosis is best seen on perioral skin, oral mucosa, or conjunctivae, but may be seen over the entire body surface. Central cyanosis is often secondary to profound arterial hypoxemia or the presence of abnormal hemoglobin. Peripheral cyanosis affects distal capillary circulation and is typically seen in the extremities and nail beds. Peripheral cyanosis is often secondary to low cardiac output, vasoconstriction, or venous stasis which results in reduced forward blood flow, allowing for greater oxygen extraction by the tissues. Differential cyanosis may occur in the upper or lower (or the right or left) half of the body, with the remainder of the body appearing well oxygenated. This form of cyanosis is usually seen in patients with cyanotic heart disease with multiple anomalies.

Vital signs should be obtained from all patients. Temperature is typically normal while blood pressure and heart rate vary, depending on the cause and acuity of cyanosis. Interpretation of pulse oximetry is challenging in the setting of cyanosis. Assessment of peripheral pulses, capillary refill time, and nail bed color may help determine if poor circulation is the cause of low pulse oximetry. Pulse oximetry measures light absorption of oxyhemoglobin and deoxygenated (reduced) hemoglobin using two light wavelengths, 660 nm (red) and 940 nm (infrared). The ratio of these two readings is the basis of the pulse oximetry calculation. By default, standard pulse oximeters assume the absence of abnormal hemoglobin such as carboxyhemoglobin or methemoglobin. Methemoglobin absorbs well at both wavelengths, resulting in a saturation reading of approximately 85%, regardless of actual Pao_2 and Sao_2 values.[5]

Upper airway obstruction and other signs of respiratory insufficiency or compromise should be sought. Infants with cyanosis, increased respiratory depth, periodic apnea episodes, or diaphoresis with feeding may have congenital heart disease. Tachypnea (>60 breaths/min) in a newborn is nonspecific but may indicate a pulmonary disorder, congenital heart disease, infection, metabolic disorder, or gastrointestinal or central nervous system (CNS) pathology.

The general appearance and mental status should be noted. The head, eyes, ears, nose, and throat examination may reveal central cyanosis. Jugular venous distention may be seen on the neck examination in patients with pulmonary edema or pulmonary hypertension. A neurologic examination should focus on mental status, symmetry of motor and sensory function, and any gross deficit. The chest examination may reveal crackles, wheezing, or inadequate chest wall movement with respiration. Heart sounds should be assessed for tachycardia, abnormal rhythm, or gallops and the presence and quality of murmurs, especially in the newborn. Central pulse strength should be noted. The abdomen should be examined for the presence of hepatosplenomegaly, pulsatile mass, or abdominal bruit.

Extremity examination should evaluate for evidence of chronic vascular disease, such as hair loss and temperature difference. Clubbing of the nails may occur due to increased soft tissue and expansion of the capillary beds (Fig. 10.2). Clubbing may be idiopathic or hereditary,

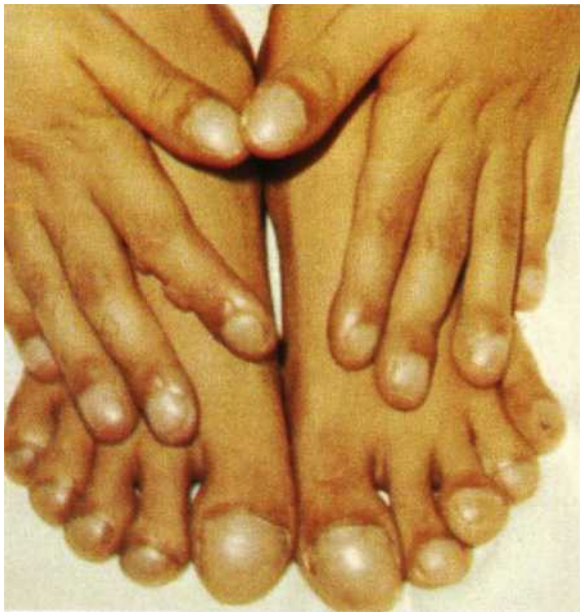

Fig. 10.2 Symmetric Clubbing. Shown here are equal cyanosis and clubbing of the hands and feet resulting from transposition of the great vessels and a ventricular septal defect without patent ductus arteriosus.

but is usually the result of chronic hypoxemic states, such as cyanotic heart disease, infective endocarditis, pulmonary disease, and some gastrointestinal disorders (e.g., cirrhosis, Crohn disease, regional enteritis). Thrombotic events should also be considered in patients with skin and nail bed hemorrhages or end-organ damage (e.g., eye, kidney). Splinter hemorrhages are often associated with infective endocarditis but can be caused by a variety of conditions (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis).

Ancillary Testing

A complete blood count will assess for erythrocytosis, polycythemia, or anemia.[6] A peripheral smear assesses RBC morphology and fragments, as well as the white blood cell differential count. A D-dimer level may be indicated if pulmonary embolism (PE) is suspected.

In the case of methemoglobinemia the peripheral blood typically appears chocolate brown in color. Normally, a small drop of blood placed on a white sheet or filter paper will turn bright red when exposed to 100% oxygen. No change in color is highly suggestive of methemoglobinemia.[7]

Arterial blood gas testing assesses Pao_2 and Sao_2 levels (see Fig. 10.1). In methemoglobinemia, the Pao_2 and Sao_2 may be normal as the partial pressure of oxygen dissolved in the blood should not be affected in the absence of concomitant cardiopulmonary disease and the Sao_2 value is often calculated based on the measured Pao_2.[8] The oxygen saturation gap is the difference between the calculated theoretical hemoglobin saturation on blood gas analysis and that measured by pulse oximetry; an elevated gap is strongly suggestive of methemoglobinemia. CO-oximetry measurements should be ordered if carbon monoxide exposure or methemoglobinemia is suspected. Sulfhemoglobin is often reported as methemoglobin on CO-oximetry. If sulfhemoglobinemia is possible (exposure to sulfa-containing drugs), the sulfhemoglobin percentage should be specifically determined. Devices designed to measure methemoglobin levels noninvasively (e.g., pulse CO-oximetry) may be useful but have decreasing accuracy at lower Sao_2 levels (<95%) and higher methemoglobin levels (>14%).[5]

Imaging

A chest radiograph will evaluate lung fields for consolidation, infiltrates, effusions, and pulmonary edema. An abnormal cardiac silhouette and mediastinum may suggest congenital heart disease. If pulmonary embolus is suspected, a diagnostic strategy utilizing lower extremity venous Doppler ultrasound, computed tomography pulmonary angiography (CTPA), cardiac ultrasound, or, rarely, V/Q scanning should be pursued.

Electrocardiography and Echocardiography

An electrocardiogram should be obtained on all patients with a new presentation of cyanosis to assess for dysrhythmia and acute ischemic changes. Right axis deviation or right ventricular hypertrophy may be seen with significant cardiopulmonary disease (e.g., cor pulmonale, acute pulmonary hypertension). An echocardiogram may be useful in detecting septal defects in infants, valvular disease in infants and adults, and overall cardiac function.

DIAGNOSTIC ALGORITHM

Fig. 10.3 outlines an approach to the differential diagnosis of peripheral and central cyanosis. During the initial assessment, the emergency clinician should initiate oxygen therapy and follow steps to determine the cause of cyanosis. In peripheral cyanosis, improvement with oxygen suggests a low-flow state due to global under-perfusion such as with hypovolemia or cardiogenic shock. Lack of improvement with oxygen implies a focal vascular occlusion secondary to environmental exposures, arterial thrombosis/embolism, or Raynaud disease. In central cyanosis clinical improvement with oxygen suggests hypoxemia due to a diffusion impairment, hypoventilation, or V/Q mismatch resulting in increased dead space ventilation. Patients who do not respond to high-flow oxygen are more likely to have a right-to-left shunt such as from pulmonary consolidation or congenital heart disease.

The patient's respiratory status should be immediately assessed and tension pneumothorax, bronchospasm, or upper airway obstruction considered. Cardiac size and silhouette on a chest radiograph may suggest the presence of congenital heart disease or congestive heart failure. Acute cardiac dysfunction, such as from acute coronary syndrome can be assessed with an electrocardiogram. If heart size is normal, impaired pulmonary function, pulmonary embolus, or other noncardiac causes should be considered. If pulmonary embolus is suspected, CTPA is the diagnostic test of choice in the absence of contraindications. If a patient exhibits no respiratory distress and remains resistant to oxygen therapy, cardiac shunting or abnormal hemoglobin forms should be considered and treated accordingly.

Critical Diagnoses

Acute cardiovascular and respiratory compromise are considered in patients with cyanosis and symptoms or signs of shock. The differential diagnosis includes acute heart failure, acute coronary syndrome, and hypovolemic or cardiogenic shock. In addition, consider acute respiratory insufficiency or failure, upper airway obstruction, massive PE, decompensation in a patient with known congenital heart disease or pre-existing lung disease such as pulmonary fibrosis or COPD, or the first presentation of pediatric congenital heart disease.

Emergent Diagnoses

Methemoglobinemia is an infrequent cause of central cyanosis but should be considered in patients with no history or physical findings suggestive of cardiovascular or pulmonary disease.

Sulfhemoglobinemia is a rare cause of cyanosis, usually occurring after exposure to hydrogen sulfide from organic sources, medications

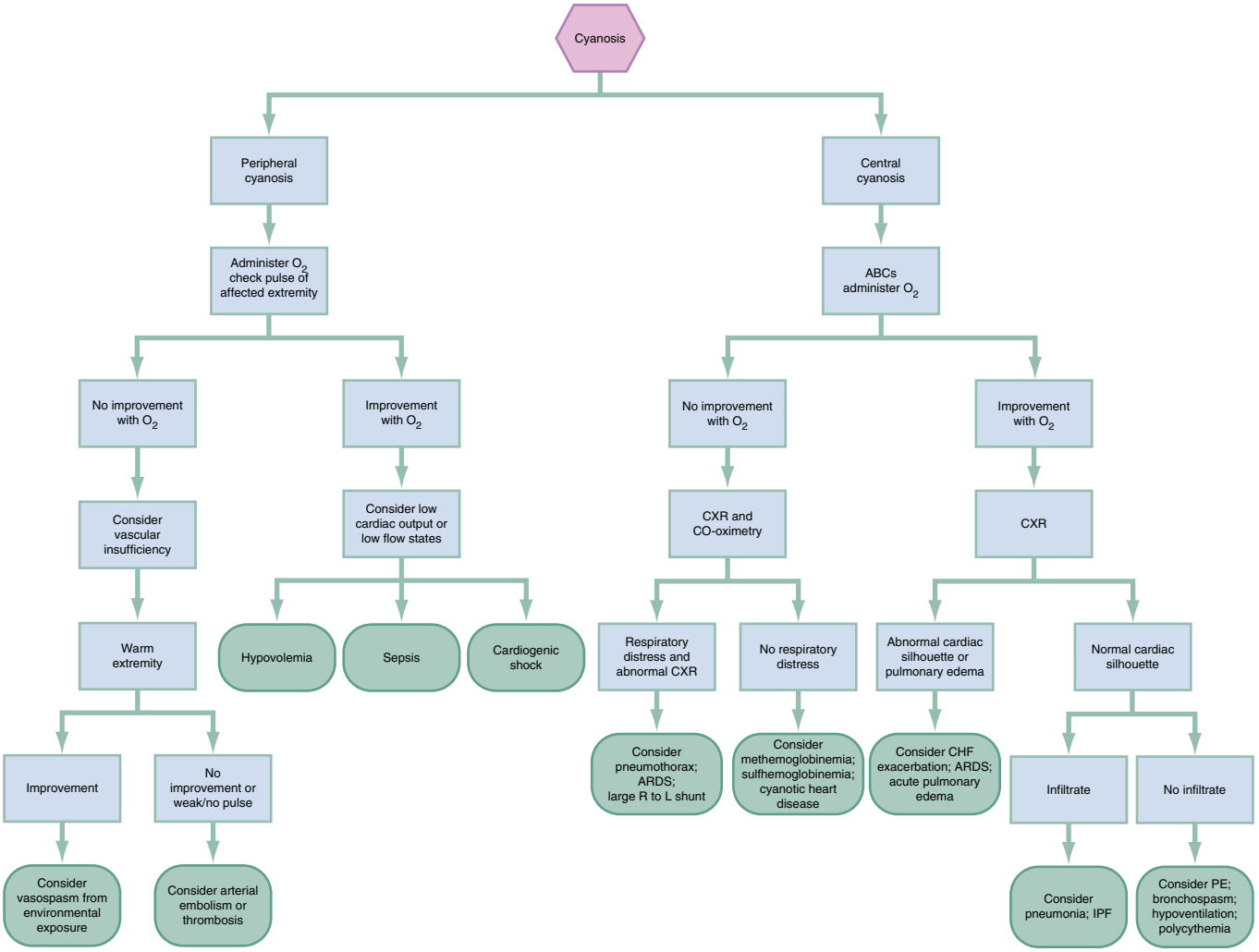

Fig. 10.3 Algorithmic Diagnostic Approach to Cyanosis. *ABCs,* Airway, breathing, circulation; *ARDS,* acute respiratory distress syndrome; *CHF,* congestive heart failure*; CXR,* chest radiograph; *IPF,* Interstitial Pulmonary Fibrosis; *IV,* intravenous; *O_2,* oxygen; *PE*, pulmonary embolism.

that are sulfonamide derivatives, or gastrointestinal sources (bacterial overgrowth). Sulfhemoglobinemia can cause cyanosis at levels as low as 0.5 mg/dL of blood, but the diagnosis may be challenging as some CO-oximeters will measure sulfhemoglobin as methemoglobin. Strong consideration should be given to sulfhemoglobin toxicity in patients with cyanotic findings and methemoglobin on CO-oximetry but who do not improve with methylene blue treatment, or when reported methemoglobin levels on CO-oximetry are not elevated enough to explain the low levels of oxyhemoglobin.[9,10]

Polycythemia is defined as an elevated RBC mass from one of three causes. Polycythemia vera is a disorder of bone marrow stem cells resulting in increased RBC mass, cyanosis predominately seen in the face and hands, and splenomegaly. Patients may demonstrate hyperviscosity syndrome. Secondary polycythemia occurs with an appropriate or inappropriate increase of erythropoietin, physiologic response to chronic hypoxemia (<92% oxygen saturation), cyanotic congenital heart disease, cigarette smoking, high-altitude exposures, or as a response to congenital methemoglobinemia.[11] Relative polycythemia is an increased RBC mass, often resulting from dehydration or reduced plasma volume.

Finally, vascular disease, such as Raynaud phenomenon, may cause peripheral cyanosis. Raynaud phenomenon occurs in 15% of the population, with a female predominance. Patients have an abnormal response to excessive cold or emotional stress, causing vasoconstriction, profound cold sensitivity, and recurrent events of sharply demarcated pallor or cyanosis of the digits (Fig. 10.4). Usually, the cutaneous arterial capillary beds of the fingers and toes are affected, but the tongue, ear, and other distal areas may also be affected.[12]

EMPIRIC MANAGEMENT

Fig. 10.5 outlines an approach to the management of peripheral and central cyanosis. Administration of high-flow oxygen is the first therapy for patients with central cyanosis; any clinical improvement, or lack thereof, should be noted. If the cyanosis improves with the administration of oxygen, consider arterial hypoxemia secondary to cardiopulmonary disease. If there is little to no improvement with oxygen, consider a right-to-left shunt causing hypoxemia or abnormal hemoglobin forms. In patients with cyanosis and concomitant respiratory distress or failure, airway management including positive pressure ventilation (PPV) and/or noninvasive PPV should be initiated.

Intravenous (IV) fluid resuscitation should be initiated in patients with hypovolemia. Treatment of congestive heart failure, arrhythmias, or poor cardiac output should occur as indicated. We recommend cardiology consultation for patients with congenital heart disease, who often have abnormal responses to oxygen and conventional fluid

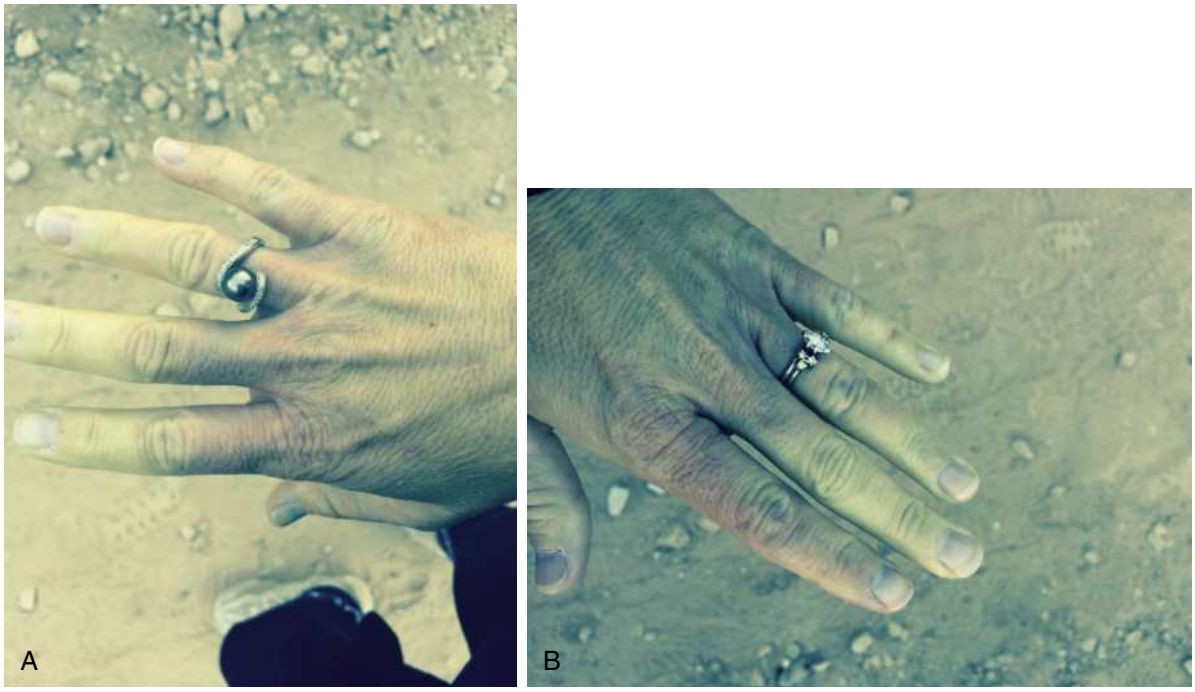

Fig. 10.4 (A and B) Raynaud phenomenon due to cold exposure.

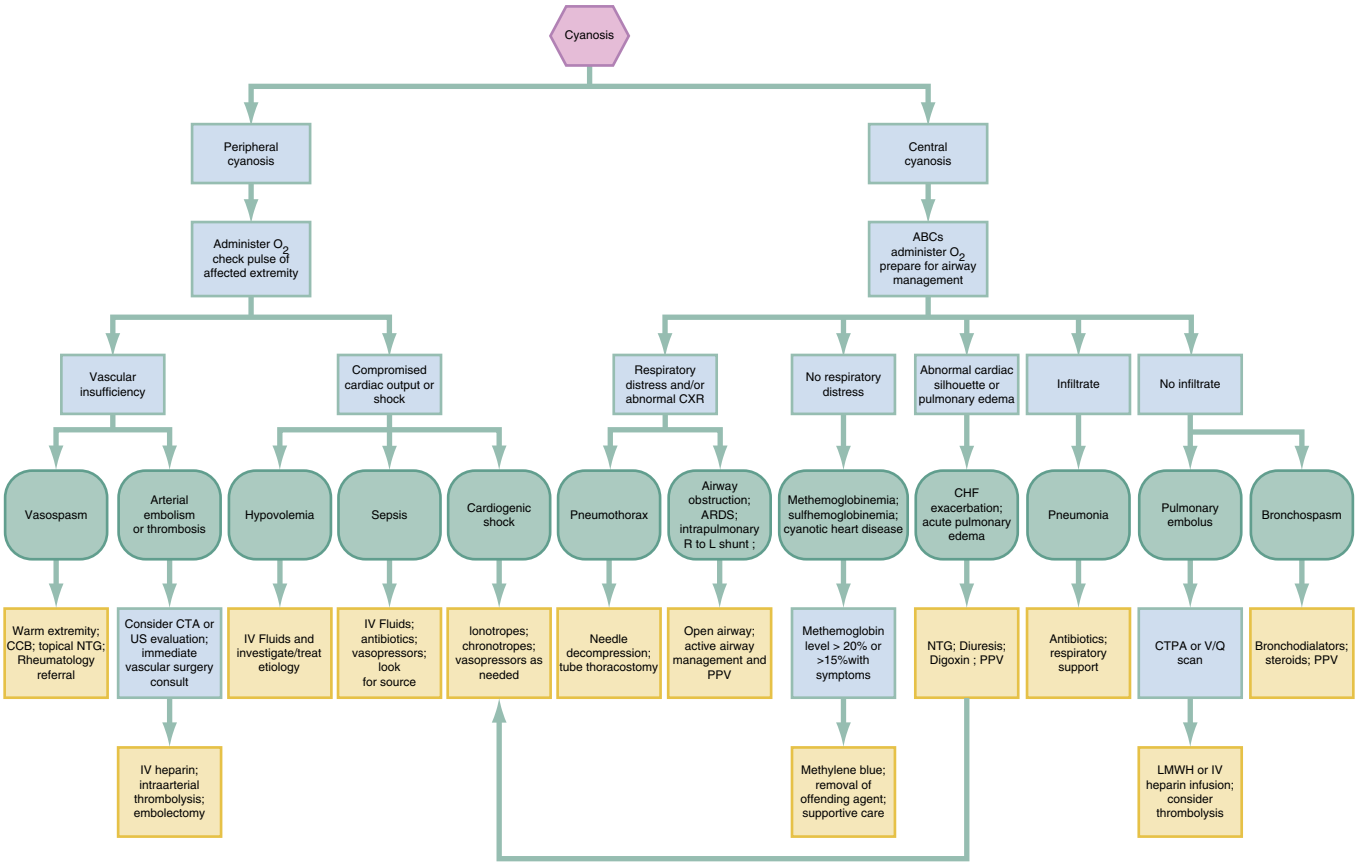

Fig. 10.5 Algorithmic Management Approach to Cyanosis. *ABCs,* Airway, breathing, circulation; *ARDS,* acute respiratory distress syndrome; *CCB,* calcium channel blocker; *CHF,* congestive heart failure; *CTA,* CT angiogram; *CTPA,* computed tomography pulmonary angiography; *CXR,* chest radiograph; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *NTG,* nitroglycerin; O_2, oxygen; *PE,* pulmonary embolus; *PPV,* positive pressure ventilation; *US,* ultrasound *V/Q,* ventilation-perfusion scan. Patients with chronic cyanotic heart disease may not require ICU care or even hospital admission. Disposition should be discussed with the patient's cardiologist. A V/Q scan may be obtained when CTPA is unavailable or contraindicated.

therapy. If oxygenation compromise is sufficient to cause ischemic chest pain, prompt correction of the underlying hemoglobin abnormality is undertaken simultaneously with conventional treatment of the ischemia. Although several specific treatments are discussed here, the cause of the cyanosis may be elusive, and hospitalization is required in all but chronic stable cases.

Methemoglobinemia and Sulfhemoglobinemia

If cutaneous exposure to an inciting agent (i.e., aniline dye) has recently occurred, surface decontamination with soap and water is recommended. Emergency personnel should use appropriate protective equipment. For asymptomatic patients with a methemoglobin level less than 20%, removal of the offending agent is usually the only necessary treatment; the methemoglobin level should return to normal within 24 to 36 hours, with a maximum of 100 mg. Urgent treatment with oxygen and methylene blue (1 to 2 mg/kg IV over 5 minutes) is indicated for patients with symptomatic hypoxia (e.g., dysrhythmias, angina, respiratory distress, seizures, coma) or methemoglobin levels greater than 30%. The response to treatment is usually rapid, within 15 minutes. In patients with continued symptoms or persistent methemoglobin levels greater than >30%, a repeat dose of 1 mg/kg can be administered.[13]

Methylene blue is relatively contraindicated in patients with known G6PD deficiency as it may result in massive hemolysis. In these patients, ascorbic acid may be used, however repeat doses are required with limited comparative effect.[14] Additionally, methylene blue is a potential teratogen and in pregnant patients, a risk-benefit analysis is warranted with consideration of supplemental therapies such as C-section delivery, hyperbaric oxygen, and exchange transfusion.[2] Consultation with the local poison control center may be of benefit.

Sulfhemoglobinemia is suggested when the laboratory reports an elevated methemoglobin level and the patient does not respond to methylene blue. Sulfhemoglobinemia is irreversible for the life of the erythrocyte and there is no known antidote. Treatment of sulfhemoglobinemia is supportive in addition to the removal of the causative agent. Exchange transfusion of RBCs has been described as a treatment,[15] but there are no controlled studies of this modality.

Other Causes of Cyanosis

Acute therapy for patients with symptomatic polycythemia with resultant hyperviscosity syndrome includes phlebotomy and volume expansion with isotonic crystalloid. The goal is to achieve a normal hematocrit (45%). Long-term therapy is focused on the underlying cause, and patients require referral to a hematologist.

Raynaud phenomenon is treated by warming the affected digits and extremities and protection from cold environments. Vasodilating agents (e.g., topical nitroglycerin, calcium channel blockers, endothelin receptor antagonists, phosphodiesterase inhibitors, botulinum toxin) may be useful in management.[12] If there is no improvement of localized peripheral cyanosis with warming and administration of 100% oxygen, arterial insufficiency or occlusion may be present. In cases of critical limb ischemia, IV heparin should be considered in consultation with a vascular surgeon. Vascular bypass, intraarterial thrombolysis, or stenting may be indicated. Embolic sources, such as endocarditis and abdominal aortic aneurysms, should also be considered.

PATIENT DISPOSITION

Admission

All patients with a first episode of cyanosis or an uncertain cause require hospitalization. Cardiology consultation and referral are recommended for children with a first episode of congestive heart failure and newly diagnosed or suspected congenital heart disease. Surgical consultation and intervention are indicated for acute arterial occlusion from embolic or thrombotic sources. Patients with symptomatic methemoglobinemia, a methemoglobin level over 15%, and those treated with methylene blue should be admitted for continued observation.

Discharge

Patients with peripheral cyanosis from vasospasm, those with asymptomatic methemoglobinemia less than 15% with removal of the offending agent, and stable patients with primary pulmonary disease may be treated as outpatients after several hours of monitoring in the ED. Follow-up should occur within 24 hours unless the patient has a previous diagnosis of chronic cyanosis. Instructions should clearly state that if the cyanosis worsens, or if dyspnea, altered mentation, or chest pain occurs after discharge, the patient should return immediately to the ED. Any identified precipitating agents should be removed.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 10: QUESTIONS AND ANSWERS

1. Which of the following statements regarding methemoglobin is true?

a. Methemoglobin begins to produce cyanosis when its concentration reaches 25% of total hemoglobin.
b. Methemoglobin changes from dark purple to light red when exposed to room air.
c. Methemoglobin normally accounts for 5% of total hemoglobin.
d. Methylene blue accelerates the reduction of methemoglobin to hemoglobin.
e. The primary method of reducing methemoglobin to hemoglobin is glucose-6-phosphate dehydrogenase (G6PD)–dependent.

Answer: d. Methemoglobin normally accounts for less than 1% of total hemoglobin. Cyanosis generally results when more than 10% to 15% of the total hemoglobin is methemoglobin (absolute level of 1.5 g/dL), which has a dark purple-brown color, even when exposed to room air. Methemoglobin is reduced to ferrous hemoglobin primarily by nicotinamide adenine dinucleotide (NADH)–cytochrome b5 reductase, an enzyme system present in red blood cells. A secondary nicotinamide adenine dinucleotide phosphate (NADPH)–dependent system uses glutathione and G6PD to reduce methemoglobin to hemoglobin. This secondary pathway normally plays a minor role but is accelerated by methylene blue.

2. Which of the following conditions produces central cyanosis?

a. Hypothermia
b. Raynaud phenomenon
c. Shock
d. Venous insufficiency
e. Ventricular septal defect

Answer: e. Central cyanosis is caused by decreased arterial oxygen saturation, often secondary to shunting of venous unsaturated hemoglobin into the arterial circulation, or the presence of abnormal hemoglobin. A ventricular septal defect causes shunting of deoxygenated blood from the right side of the heart to the left, with resultant decreased arterial oxygen saturation and central cyanosis. The remaining options would cause peripheral cyanosis.

3. In the cyanotic patient, clinical improvement with supplemental oxygen is most suggestive of which of the following underlying processes?

a. Arterial emboli
b. Congenital heart disease with right-to-left shunting
c. Hyperventilation
d. COPD
e. Methemoglobinemia

Answer: d. Clinical improvement with oxygen suggests diffusion impairment, hypoventilation, or an increased V/Q ratio due to mismatch. Patients who do not respond to oxygen are more likely to have decreased V/Q ratio abnormalities, such as shunting from pulmonary consolidation or congenital heart disease with right-to-left shunting, or abnormal hemoglobin. Arterial emboli will generally not be affected by supplemental oxygen.

4. Soon after receiving topical upper airway anesthesia with benzocaine, a patient becomes tachypneic and complains of chest pain. The patient is noted to be cyanotic. Supportive measures are initiated, and CO-oximetry reveals a methemoglobin level of 40%. Which of the following should be administered?

a. Benadryl
b. Hyperbaric oxygen
c. Methylene blue
d. Nitroglycerin
e. Thrombolytics

Answer: c. Local anesthetics such as benzocaine, lidocaine, and prilocaine can cause an acquired methemoglobinemia. Urgent treatment with oxygen and methylene blue is indicated in such patients, especially when accompanied by symptomatic hypoxia (e.g., dysrhythmias, angina, respiratory distress, seizures, coma) and methemoglobin levels greater than 20%.

5. An otherwise healthy 35-year-old woman presents with headache, mild shortness of breath, and central cyanosis. She is currently taking trimethoprim-sulfamethoxazole and phenazopyridine for

CHAPTER 10: QUESTIONS AND ANSWERS—cont'd

a urinary tract infection. She does not improve with supplemental oxygen. Her chest radiograph is normal. CO-oximetry shows a methemoglobin level of 28%. Her medications are withheld. The patient shows no improvement after 2 mg/kg of methylene blue is administered. Ongoing management should include which of the following treatments?

a. Calcium channel blockers
b. Hydroxocobalamin
c. Phlebotomy
d. Sodium thiosulfate
e. Supportive care

Answer: e. This patient likely has sulfhemoglobinemia, a rare complication of the medication phenazopyridine (Pyridium), as well as sulfa-containing drugs such as trimethoprim-sulfamethoxazole. Standard CO-oximetry will often report sulfhemoglobin as methemoglobin. Both sulfamethoxazole and phenazopyridine can also cause methemoglobinemia. Patients with an elevated methemoglobin level and no response to methylene blue likely have sulfhemoglobinemia, which is less severe than methemoglobinemia and only requires supportive care and removal of the offending agent. Phlebotomy is the treatment for polycythemia. Sodium thiosulfate and hydroxocobalamin are both used to treat cyanide toxicity, and calcium channel blockers may be used to treat peripheral cyanosis resulting from vasospasm (Raynaud phenomenon).

11

Syncope

Marc Probst

KEY CONCEPTS

- Syncope is defined as a sudden, spontaneous loss of consciousness and postural tone with rapid, complete, and spontaneous recovery. This loss of consciousness typically lasts seconds to minutes and is not followed by a persistent alteration in mental status.
- Syncope is caused by a transient global cerebral hypoperfusion. It is the final common pathway for a wide variety of underlying causes, and requires a systematic approach to diagnosis.
- Pre-syncope, or near-syncope, is defined as the sudden onset of a sense of impending or incomplete loss of consciousness.
- Most syncopal episodes have benign causes, but serious underlying conditions are possible. The causes of syncope can be organized into the following three categories: (i) cardiac, (ii) reflex (includes vasovagal syncope), (iii) orthostatic.
- National guidelines recommend a 12-lead electrocardiogram for all patients with syncope but most patients without serious underlying disease will have a normal or nondiagnostic electrocardiogram (ECG).
- National guidelines do not recommend routine laboratory testing or imaging (e.g., chest x-ray, neuroimaging, echocardiogram) and these tests should be obtained only when history or physical examination suggests such evaluation.
- Hospitalization or placement in an observation unit after emergency department (ED) evaluation for syncope is based on the specific, identified cause (e.g., gastrointestinal hemorrhage, malignant arrhythmia, pulmonary embolism).
- Patients with a clear description of reflex syncope (e.g., vasovagal syncope) without serious underlying disease are generally appropriately discharged directly from the ED.
- Several syncope clinical risk scores have been developed for ED use, but none have been definitively shown to outperform unaided clinical gestalt with respect to risk stratification and resource utilization.

FOUNDATIONS

Epidemiology

Syncope is a common clinical entity with a lifetime prevalence between 20% and 40%, and is slightly more common in women than in men.[1] The age distribution for syncope is bimodal, with a peak in early adulthood, around age 20 years, and a second peak in later adulthood, around and after age 60 years. Pre-syncope is a less common complaint than syncope for emergency department (ED) visits, perhaps because many patients with pre-syncope do not seek evaluation. Pre-syncope and syncope are associated with similar clinical outcomes at 30 days.[2]

Pathophysiology

Syncope is defined as a transient, spontaneous loss of consciousness and postural tone with rapid, complete, and spontaneous recovery, caused by global cerebral hypoperfusion, generally from a drop in cardiac output or systemic blood pressure. Loss of consciousness typically lasts seconds to minutes and is not followed by a persistent alteration in mental status. (For a discussion of the approach to altered mental status, see Chapter 12.) Approximately 8 to 10 seconds of hypoperfusion to both cerebral cortices and the brainstem reticular activating system will result in transient loss of consciousness and the inevitable loss of postural tone. Syncope is the final common pathway for a wide variety of underlying causes, (e.g., dehydration, hemorrhage, cardiac arrhythmia, structural heart disease) making for a broad differential diagnosis.

DIAGNOSTIC APPROACH

Differential Considerations

The causes of syncope can be organized into three broad categories:

(i) Reflex
(ii) Orthostatic
(iii) Cardiac (see Box 11.1).

Reflex syncope, also known as neurally mediated syncope, is the most common cause of syncope, particularly among younger patients. It is caused by inappropriate vasodilation, bradycardia, or both, and includes vasovagal syncope, carotid sinus syndrome, and situational syncope. Vasovagal syncope is commonly encountered in the ED and is typically characterized by a prodrome of some combination of the following associated symptoms: nausea, pallor, diaphoresis, lightheadedness, warmth, chills, and blurred or darkening vision. Common triggers include intense fear, emotion, anxiety, or pain; being in a warm, crowded place; prolonged standing; or other noxious stimuli, such as when a layperson encounters a traumatized traffic accident victim. Vasovagal syncope is a clinical diagnosis based on history, physical examination, and eyewitness accounts, if available. Carotid sinus syndrome is caused by carotid sinus hypersensitivity, which is defined as a pause of ≥3 seconds and/or a ≥50 mm Hg decrease in systolic blood pressure upon stimulation of the carotid sinus.[3] This entity is more common in older patients and in men. Situational syncope is defined by its close association with a specific action such as urination, defecation, recent or overeating, coughing, sneezing, swallowing, laughing, breath holding, or post-exercise. It can be preceded by the same prodromal symptoms as vasovagal syncope.

Orthostatic syncope, also known as postural hypotension, is defined by a decrease in blood pressure of at least 20 mm Hg systolic, and at least 10 mm Hg diastolic within 3 minutes of standing. This condition is associated with dehydration, blood loss, adverse medication effects, autonomic dysfunction, alcohol consumption, and older age. Syncope or pre-syncope will occur when the autonomic response is insufficient to counteract the drop in blood pressure associated with postural change. Measuring orthostatic vital signs in the ED setting is not generally useful since they do not appear to independently predict 30-day serious outcomes, nor do they reliably diagnose or exclude orthostatic

BOX 11.1 Cardiac Diagnoses Associated With Syncope

- Dysrhythmias: (See Box 11.2 for further detail)
  - Tachydysrhythmias
  - Bradydysrhythmias
- Structural causes:
  - Hypertrophic cardiomyopathy
  - Aortic stenosis
  - Severe pulmonic stenosis
  - Acute myocardial infarction/ischemia
  - Cardiac masses (e.g., atrial myxoma)
  - Pericardial tamponade
  - Prosthetic valve dysfunction
  - Ventricular assist device (VAD) dysfunction
- Cardiopulmonary causes:
  - Acute aortic dissection
  - Pulmonary embolism
  - Pulmonary hypertension

syncope, unless the vital sign changes upon standing reproduce the symptoms with which the patient presented.[4]

Cardiac syncope is divided into three general categories: Dysrhythmic, structural, and cardiopulmonary (see Box 11.1). This is the most serious form of syncope and must be distinguished from reflex or orthostatic syncope, when feasible. Cardiac dysrhythmias most often occur in patients with underlying structural heart disease, a prior diagnosis of a dysrhythmia syndrome, or a recent or acute myocardial infarction. Several dysrhythmias can lead to syncope or pre-syncope, including both brady- and tachydysrhythmias (see Box 11.2A). The symptoms caused by a given dysrhythmia will vary depending on the severity of the disruption of cardiac output and the patient's cardiovascular reserve. Patients with underlying heart disease, such as coronary artery disease (CAD), valvular disease, congenital heart disease, cardiomyopathy, or cardiac channelopathy (e.g., Brugada syndrome, long QT syndrome), are at higher risk for dysrhythmias. Various ECG findings are suggestive of such underlying heart disease (see Box 11.2B). Dysrhythmic syncope classically presents without a prodrome, although patients with tachydysrhythmias may report palpitations or chest discomfort prior to losing consciousness.

Structural heart disease has a significant morbidity and mortality without intervention, and also predisposes patients to serious dysrhythmia, making early diagnosis key to maximizing good outcomes. Structural causes of syncope include valvular disease (e.g., aortic stenosis), hypertrophic cardiomyopathy, pericardial tamponade, and atrial myxoma, among others (see Box 11.1).

Cardiopulmonary causes of syncope include conditions such as pulmonary embolism (PE), pulmonary hypertension, acute myocardial infarction (MI), and acute aortic dissection. Syncope is only a part of their presentation, and patients will have associated signs and symptoms of these conditions. Generally healthy patients with typical syncope and no findings suggestive of cardiopulmonary causes should not undergo specific testing, such as d-dimer assay or CT angiography. Routine testing of all ED syncope patients for PE, for example, with a d-dimer assay or CT pulmonary angiogram, is not indicated, and would lead to significant over-testing due to the low prevalence of this disease in this cohort.[5]

Cerebrovascular conditions associated with loss of consciousness should be considered, however, these will typically present with other cardinal signs and symptoms, and would generally not meet the strict definition of syncope. For example, a spontaneous subarachnoid hemorrhage (SAH) or basilar artery migraine could present with syncope

BOX 11.2A Dysrhythmias Potentially Associated With Syncope

- Atrioventricular (AV) Block
  - Mobitz type II second degree
  - Third degree (complete heart block)
- Sinus pause >3 s
- Sick sinus syndrome
- Persistent sinus bradycardia (<40 beats/min)
- Ventricular tachyarrhythmias
  - Monomorphic ventricular tachycardia
  - Polymorphic ventricular tachycardia (i.e., Torsades de pointes)
  - Ventricular fibrillation
- Supraventricular tachyarrhythmias
  - Atrial flutter/fibrillation
  - AV nodal reentry tachycardia
  - AV reentry tachycardia
- Alternating left and right bundle branch block
- Pacemaker or automatic implantable cardioverter-defibrillator malfunction with cardiac pauses

BOX 11.2B ECG Abnormalities Potentially Associated With Syncope

- Signs of acute myocardial ischemia (e.g., ST elevation/depression, T-wave inversions, new bundle branch block, new abnormal Q waves)
- Pre-excitation suggestive of Wolff-Parkinson-White syndrome
- Long QT interval suggestive of congenital or acquired form of the long QT syndrome (e.g., Jervell and Lange-Nielsen syndrome.)
- Short QT interval suggestive of short QT syndrome
- Right bundle branch block pattern with ST-elevation in leads V1–V3 suggestive of Brugada syndrome
- Inverted T waves in right precordial leads and epsilon waves suggestive of arrhythmogenic right ventricular cardiomyopathy
- Left ventricular hypertrophy, prominent abnormal Q waves, or deeply inverted T waves suggestive of hypertrophic cardiomyopathy
- Low voltages or electrical alternans suggestive of pericardial effusion
- Right ventricular strain pattern suggestive of pulmonary embolism

but would generally be preceded and accompanied by an acute headache, vertigo, or alteration in mental status. Acute stroke or transient ischemia attack does not cause syncope because it does not produce global hypoperfusion.

Syncope mimics are any of several conditions encountered in the ED that can mimic syncope, such as mechanical fall, intoxication, hypoglycemia, head trauma, and seizures (see Box 11.3). Differentiating these conditions from true syncope can be challenging, particularly without collateral history from witnesses. Seizures can be confused with syncope partly due to the fact that convulsions and incontinence, although classically associated with seizure, can also be seen with syncope as well. Rhythmic motor activity in the setting of syncope is often referred to as "convulsive syncope" and is usually brief (under 20 seconds). Unlike epileptic seizure, the motor activity and loss of consciousness of syncope are not associated with any post-ictal state.

Pivotal Findings

Taking a careful history is key to determining the etiology of the syncopal episode. In particular, the setting (e.g., bathroom after voiding, restaurant after a large meal, blood draw, crowded place), body position (e.g., seated, prone, standing, changing position), and context (e.g., exertion, emotional event, painful stimulus, fasting state) should

BOX 11.3 Syncope Mimics

- Seizure/epilepsy
- Hypoglycemia
- Hypoxemia
- Fall
- Concussion
- Intoxication (e.g., ethanol, opiates, carbon monoxide)
- Vertebrobasilar transient ischemic attack
- Cataplexy
- Drop attacks
- Psychogenic pseudo-syncope

BOX 11.4 Medications Associated With Orthostatic Hypotension

Vasodilators:
- Beta blockers, calcium channel blockers, nitrates, hydralazine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, phenothiazines, phosphodiesterase inhibitors (e.g., sildenafil, tadalafil)
- Diuretics (e.g., hydrochlorothiazide, furosemide)
- Central antihypertensives (e.g., clonidine, methyldopa)
- QT-prolonging agents (e.g., amiodarone, flecainide, procainamide, quinidine, sotalol)

Psychoactive agents:
- Anticonvulsants (e.g., carbamazepine, phenytoin)
- Antipsychotic drugs (e.g., olanzapine, risperidone)
- Antiparkinsonian agents (e.g., levodopa, pramipexole)
- Central nervous system depressants (e.g., barbiturates, benzodiazepines)
- Antidepressants (e.g., monoamine oxidase inhibitors, Selective serotonin receptor reuptake inhibitors, trazodone, tricyclic antidepressants)
- Opiates analgesics (e.g., morphine)
- Sedating antihistamines (e.g., diphenhydramine)
- Cholinesterase inhibitors (e.g., donepezil, tacrine, galantamine)
- Alcohol
- Digitalis
- Neuropathic agents (e.g., vincristine)
- Bromocriptine

be established. Age, current medications, personal history of prior syncope, family history, and past medical history are important, as with any cardiopulmonary compliant. The risk of adverse events increases gradually with age, and is low under age 45 years. A careful medication history can also lead to a diagnosis of drug-related orthostatic hypotension (see Box 11.4). Any family history of sudden cardiac death, recurrent syncope, significant dysrhythmia, or early CAD should raise concern for cardiac syncope. Many comorbidities can place a patient at higher risk for adverse events, particularly a history of heart failure, CAD, dysrhythmia, or structural heart disease. Risk factors for PE should also be explored.

These clinical variables, along with associated signs or symptoms (see the following sections) can inform the pretest probability of cardiac, orthostatic, situational, or vasovagal syncope. For example, syncope occurring after quickly rising from supine to a standing position may indicate orthostatic hypotension. Syncope occurring during a blood draw likely represents a vasovagal episode. Syncope during or immediately after urination (micturition syncope), defecation (defecation syncope), eating a large meal (post-prandial syncope), coughing or swallowing may indicate a situational syncope. Syncope during exercise may prompt concern for cardiac outflow obstruction such as hypertrophic cardiomyopathy or aortic stenosis or inability to increase cardiac rate in response to exercise (e.g., heart block).

Any prior episodes and relevant previous testing (e.g., recent echocardiography, stress test) should be explored in an attempt to reduce low-value repeat testing. The clinical approach to pre-syncope is the same as for syncope—pre-syncope exists on a continuum with syncope, with similar rates of adverse events. Thorough ED evaluation fails to identify the etiology of syncope/pre-syncope roughly 50% of the time.

Symptoms

Several symptoms should be explored during the history-taking process including chest pain, dyspnea, palpitations, abdominal or back pain, vaginal bleeding, headache, and any associated neurologic symptoms. Chest pain could suggest a diagnosis of acute coronary syndrome with dysrhythmia, PE, or aortic dissection, while dyspnea could suggest PE or underlying heart failure. Palpitations may suggest a dysrhythmia. Abdominal or back pain could suggest a rupturing aortic aneurysm. Vaginal bleeding suggests possible ectopic pregnancy; severe headache may indicate SAH. Prodromal symptoms such as lightheadedness, warmth, nausea or vomiting, and pallor help make the diagnosis of vasovagal syncope.

Other symptoms may suggest the presence of a syncope mimic. A preceding aura or prolonged confusion/somnolence could indicate a seizure with a post-ictal state. Convulsions can occur with either syncope or seizure, but epileptic convulsions generally last longer (>20 myoclonic jerks).[6] A mechanical fall leading to blunt head trauma and loss of consciousness could represent a mild traumatic brain injury, and not syncope, although differentiating between the two can be difficult in practice, especially in older patients with cognitive deficits or in those whose head trauma induces retrograde amnesia.

Signs

The physical examination, which usually is normal, is generally not helpful in the evaluation of syncope. Hypotension may indicate volume loss from dehydration or hemorrhage. Otherwise, unexplained tachypnea, tachycardia, or hypoxia should prompt consideration of PE. Orthostatic blood pressure measurement is not helpful unless the patient's symptoms are reproduced in synchrony with the fall in blood pressure. Orthostatic hypotension has a sensitivity for hypovolemia of only approximately 70%.[6]

The cardiovascular examination may reveal cardiac murmurs indicative of structural heart disease (e.g., aortic stenosis) or reveal signs of new-onset heart failure (e.g., elevated jugular pressure, bilateral lower extremity edema, third heart sound, rales or wheezes on lung auscultation). A pulse deficit, in the correct context, may raise suspicion for aortic dissection. We do not recommend performing diagnostic carotid sinus massage in the ED due to the lack of high-quality evidence supporting its diagnostic utility in this setting. Carotid sinus massage (CSM) may be considered as part of an inpatient or observation unit evaluation of older patients (>40 years) with syncope associated with abrupt neck movement or neck pressure, and no identified underlying cause on detailed evaluation.

A neurologic examination, including a cognitive assessment, should be performed, and based on the definition of syncope, the patient should be neurologically at their baseline. Any sign of a new neurologic deficit should prompt consideration of an acute neurologic condition.

Examination of the head, neck, and extremities should be done to assess for signs of trauma, since syncope is often associated with fall. Rectal examination for gross blood or melena is recommended if gastrointestinal hemorrhage is suspected and the patient is not able to report recent stool characteristics.

Ancillary Testing

Electrocardiogram

The 12-lead ECG is the most commonly ordered test in the ED evaluation of syncope. Although it is rarely diagnostic, this test is safe, noninvasive, and relatively inexpensive. We recommend a 12-lead ECG in all cases of syncope except in otherwise healthy patients under age 40 with no significant conditions identified by careful history or physical examination, and with a history clearly consistent with vasovagal syncope. If there is uncertainty, we recommend obtaining a 12-lead ECG to evaluate for underlying conduction disturbance or occult myocardial injury. Dysrhythmias, preexcitation, and a shortened PR or prolonged corrected QT interval may be identified on the 12-lead ECG. Certain ECG abnormalities are considered highly likely to be casually related to the syncope, such as sinus bradycardia less than 40 beats/min or sinus pauses greater than 3 seconds, third-degree (complete) heart block, Mobitz II second-degree AV block, and others (see Box 11.2A). Other ECG abnormalities may raise concern for other serious underlying conditions (see Box 11.2B). For example, a pseudo-right bundle branch block in association with ST elevation in leads V_1 through V_3 suggests Brugada syndrome. Acute myocardial ischemia or cardiac hypertrophy may be revealed. An ECG showing a right ventricular strain pattern may suggest PE, whereas diffuse ST-elevation can help diagnose pericarditis, which may be accompanied by myocarditis. In patients over 40 years of age without a clear causative finding for syncope, continuous cardiac monitoring in the ED for 4 to 6 hours, both at rest and during light exertion, may be helpful in identifying dysrhythmias not evident on the initial ECG.[7]

Laboratory Testing

Routine laboratory testing, although often done for patients with syncope, is not supported by evidence and is not recommended in national guidelines. In patients with suspected anemia or blood loss from heavy menses or gastrointestinal hemorrhage, a complete blood count (CBC) may be useful. Electrolytes are not useful as a screening test in healthy patients but should be obtained when there is concern for elevated or low potassium, based on dietary habits (e.g., excessive consumption of black licorice causing hypokalemia) or medications (excessive or inadequate potassium supplementation in a patient taking a diuretic). Hyponatremia may arise in the context of polydipsia, particularly in patients on certain psychotropic medications, but is usually accompanied by some alteration of mental status.

Cardiac biomarkers are often obtained in the context of syncope, particularly in older adults. Troponin testing is indicated if acute MI is suspected though acute MI rarely presents with isolated syncope without other cardiopulmonary symptoms, particularly chest pain or shortness of breath.[8] Natriuretic peptide levels appear to have prognostic utility for predicting 30-day serious cardiac outcomes in adults with syncope.[9] A d-dimer assay should be reserved only for adult patients who have either signs and symptoms of PE (beyond isolated syncope), or significant risk factors for venous thromboembolism.

Urine Testing

All females of child-bearing age with irregular menses, abdominal pain or tenderness, or a suspicion of pregnancy should undergo urine testing for pregnancy. Ectopic pregnancy can present with syncope, which will be accompanied by abdominal findings suggesting the diagnosis and is easily excluded if the pregnancy test is negative.

Imaging

Chest Imaging

We do not recommend routine chest x-radiography for syncope patients, absent an indication on history or physical examination.

BOX 11.5 Critical Diagnoses Associated With Syncope

- Myocardial infarction
- Life-threatening dysrhythmias
- Acute aortic dissection
- Critical aortic stenosis
- Hypertrophic cardiomyopathy
- Pericardial tamponade
- Abdominal aortic aneurysm (ruptured)
- Massive pulmonary embolism
- Subarachnoid hemorrhage
- Toxic-metabolic derangements
- Severe hypovolemia or hemorrhage
- Ruptured ectopic pregnancy
- Sepsis

Absent these indications, the test is of low diagnostic yield, exposes the patient to unnecessary radiation, and is wasteful of time and resources. In patients with suggestive symptoms or findings, a chest x-ray may reveal an infectious process, cardiomegaly, or signs of heart failure, which may inform the diagnosis. Patients with associated signs and symptoms concerning for PE (e.g., tachycardia, hypoxia, tachypnea, chest pain, dyspnea) may require a CT pulmonary angiogram if the d-dimer is elevated or if they are sufficiently high-risk (see Chapter 74).

Neuroimaging

Patients with head trauma after syncope may require a CT scan of the head to assess for traumatic injury. Patients with altered mental status or new neurologic deficits would also require neuroimaging; however these would not be classified as syncope, by definition. Despite being of extremely low diagnostic yield, the head CT continues to be a costly and commonly ordered test.

Echocardiography

Bedside echocardiography is not routinely indicated for evaluation of syncope. In patients with known or suspected structural heart disease, bedside ultrasound can assess for right ventricular strain, pericardial effusion with tamponade, valvular disease, and other relevant structural findings. Similarly, echocardiography performed by a cardiologist may be indicated in select cases where the pre-test probability of structural heart disease is high based on past medical history, ECG, or cardiac biomarkers, but is otherwise of low diagnostic yield.[10] Clinicians in the ED should also consider assessing the abdominal aorta with bedside ultrasound in older patients with vascular risk factors, particularly those with abdominal or flank pain, given that a ruptured abdominal aortic aneurysm can present with syncope.

DIAGNOSTIC AND MANAGEMENT ALGORITHM

Patients presenting with syncope generally do not require immediate intervention or resuscitation. With these stable patients, the next consideration is whether ancillary testing beyond an ECG is indicated. In certain scenarios, such as clear vasovagal syncope, confirmed by history, in an otherwise healthy patient, there is no need for further testing (e.g., laboratory or radiology). Ancillary testing may be required to evaluate for serious diagnoses in certain patients with suggestive history or findings (see Boxes 11.5 and 11.6 for a list of serious diagnoses). Once ED testing is complete, either a diagnosis will be evident, or the episode will remain unexplained. There are numerous possible critical and emergent diagnoses that can present with syncope. For

BOX 11.6 Emergent Diagnoses Associated With Syncope

Systemic Hypoperfusion Resulting in Central Nervous System Dysfunction

Cardiovascular System–Mediated

Outflow Obstruction

Mitral, aortic, or pulmonic stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Pulmonary embolism
Pulmonary hypertension
Cardiac tamponade
Congenital heart disease

Reduced Cardiac Output

Tachycardia
- Supraventricular tachycardia
- Ventricular tachycardia
- Ventricular fibrillation
- Wolff-Parkinson-White syndrome
- Torsades de pointes

Bradycardia
- Sinus node disease
- Second-degree and third-degree atrioventricular block
- Prolonged QT syndrome
- Brugada syndrome
- Pacemaker malfunction
- Implanted cardioverter-defibrillator malfunction

Other Cardiovascular Disease

Aortic dissection
Myocardial infarction
Cardiomyopathy

Neurally Mediated (Neurocardiogenic)

Reflex syncope (vasovagal)
- Emotion
- Pain
- Instrumentation
- Valsalva—elevated intrathoracic pressure, weightlifting; tussive, sneeze

Situational
- Carotid sinus sensitivity (necktie, shaving syncope)
- Post-exercise
- Gastrointestinal—swallowing, vomiting, defecation
- Post-micturition

Orthostatic Mediated

Volume depletion
- Anemia—hemorrhage

Primary autonomic failure
Secondary autonomic failure
Medication-induced (see Box 11.4)

Focal Hypoperfusion of Central Nervous System Structures

Cerebrovascular disease
Hyperventilation
Subclavian steal
Subarachnoid hemorrhage
Basilar artery migraine
Cerebral syncope

Central Nervous System Dysfunction With Normal Cerebral Perfusion
Hypoglycemia
Hypoxemia—asphyxiation
Seizure
Narcolepsy
Psychogenic
- Anxiety disorder
- Conversion disorder
- Somatization disorder
- Panic disorder
- Breath-holding spells

Intoxication
- Medications
- Carbon monoxide
- Undetermined causes

unexplained syncope, the clinician should risk-stratify the patient using best clinical judgment regarding the constellation of findings from history, physical examination, and any ancillary testing, alone, or in combination with a risk-stratification tool, also known as a clinical risk score (see **Risk-stratification** in the following section). The disposition decision for patients with unexplained syncope has two to three general options: direct discharge from the ED, admission to the hospital, and in some settings, observation care. This decision should be based on the results of the clinical risk-stratification, as well as on the particular health and living circumstances, values, and preferences of the patient. When more than one reasonable management option exits, shared decision making should be employed with appropriate patients, that is, those willing and able to participate in the clinical decision-making process. See Figs. 11.1 and 11.2 for diagrams of diagnostic and management algorithms for syncope in the ED.

RISK-STRATIFICATION

Syncope risk-stratification has been an area of active research for over 20 years. Numerous risk-stratification tools have been published in an attempt to guide the management and disposition of patients with syncope. Examples of these include the San Francisco Syncope Rule, the OESIL Risk Score, the STePS Score, the Canadian Syncope Risk Score, and, more recently, the FAINT Score, among others. Although derivation studies have been quite promising, there is no clear evidence that these risk scores are superior to thoughtful clinical judgment with regard to predictive accuracy and optimization of resource utilization. While often displaying a high sensitivity for predicting adverse events, many of these risk scores have suffered from low specificity. Nonetheless, risk scores provide a useful, objective framework for estimating short- and medium-term risk, and can inform clinical decision making. See Box 11.7 for a list of clinical variables included in three risk scores designed for ED use and other commonly used short-term risk factors. At this time, they are best used in conjunction with clinical gestalt but cannot be recommended as a stand-alone tool. Lacking clear evidence of efficacy or superiority, these scores are best used as part of a consensus approach to syncope within a particular ED.

EMPIRIC MANAGEMENT

The ED management of syncope is driven largely by the presumed or confirmed diagnosis. Since syncope is a symptom, or chief complaint,

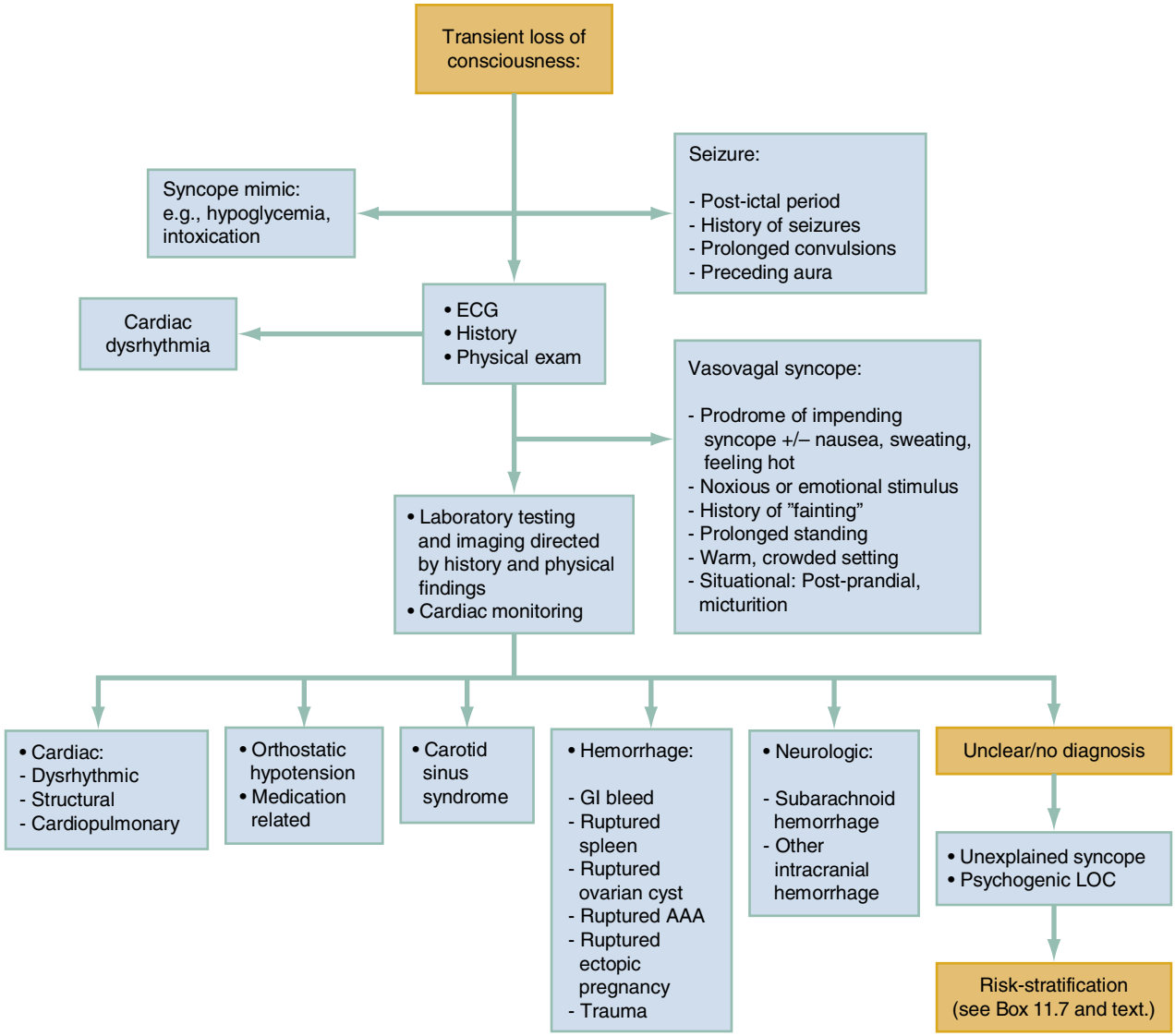

Fig. 11.1 Management Algorithm for Syncope in the Emergency Department. *AAA,* Abdominal aortic aneurysm; *LOC,* loss of consciousness.

it is not, per se, a treatable condition. Many syncope-related diagnoses require emergent treatment in the ED, for example, life-threatening dysrhythmias, gastrointestinal hemorrhage, ectopic pregnancy, MI, PE. For those patients in whom diagnostic uncertainty remains, disposition will be driven by the risk profile and circumstances of the patient, as described previously. In practice, factors that influence the decision to admit or discharge the patient include access to follow-up care, as well as the living situation, reliability, values, and preferences of the patient.

The references for this chapter can be found online at ExpertConsult.com.

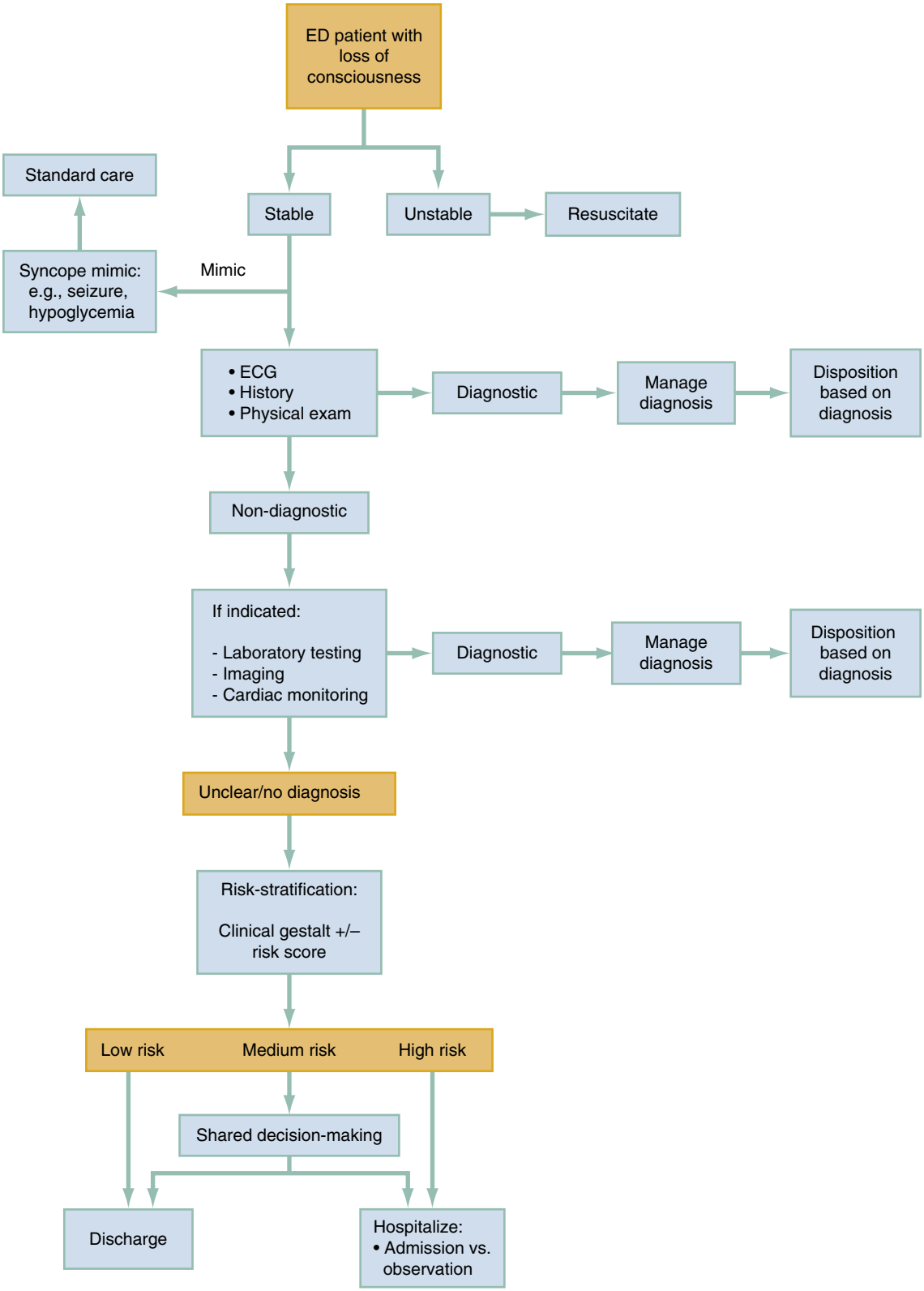

Fig. 11.2 Diagnostic Algorithm for Syncope in the Emergency Department.
ED, Emergency department.

BOX 11.7 Clinical Variables From Syncope Clinical Risk Scores With Point Values

Canadian Syncope Risk Score

1. Predisposition to vasovagal syncope –1
2. History of heart disease +1
3. Any systolic pressure reading in the emergency department <90 or >180 mm Hg +2
4. Troponin level >99th percentile for normal population +2
5. Abnormal QRS axis (<–30 degrees or >110 degrees) +1
6. Prolonged QRS interval >130 ms +1
7. Prolonged corrected QT interval >.480 ms +2
8. Emergency department diagnosis of vasovagal syncope –2
9. Emergency department diagnosis of cardiac syncope +2

Score of –2 is very low risk, –1 or 0 is low risk, 1–3 is medium risk, and >3 is high risk

FAINT Score[a]

1. History of heart failure +1
2. History of cardiac arrhythmia +1
3. Initial abnormal 12-lead ECG result +1
4. Elevated N-terminal pro b-type natriuretic peptide (NT proBNP) >125 pg/mL +2
5. Elevated high-sensitivity troponin T >19 ng/L +1

San Francisco Syncope Risk Score[a]

1. History of congestive heart failure
2. Hematocrit <30%
3. Abnormal findings on 12-lead ECG or cardiac monitoring
4. History of shortness of breath
5. Systolic blood pressure <90 mm Hg at triage

Other Short-term Risk Factors

1. Older age
2. Male gender
3. Family history of early sudden death (under 50 years old)
4. Syncope without prodrome
5. Exertional syncope
6. Syncope while in supine position
7. Palpitations before syncope

[a] Absence of all of the clinical variables corresponds to "low-risk."

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CHAPTER 11: QUESTIONS AND ANSWERS

1. Which of the following statements regarding the epidemiology of syncope is true?

a. Of athletes who die during exercise, the vast majority have had a prior episode of syncope.
b. People younger than 65 years account for 50% of all patients admitted for syncope from the emergency department.
c. Syncope in young adults is typically secondary to significant pathology.
d. Syncope is responsible for approximately 5% to 6% of all emergency department (ED) visits.
e. There is a slight female predominance among ED patients presenting with syncope.

Answer: e. Syncope accounts for approximately 1% to 2% of ED visits in the United States. There is a slight female predominance among ED patients with syncope. Approximately 32% of these patients are hospitalized, and people aged 65 years or older account for the majority of such hospitalizations. Benign causes of syncope predominate in adolescents and young adults. Approximately 30% of athletes who die during exercise have had a prior episode of syncope as a sentinel event.

2. Syncope resulting from serious pathology is usually caused by which of the following?

a. Transient ischemic attack (TIA)
b. Cardiac dysrhythmias
c. Pulmonary embolism
d. Atrial myxoma
e. Toxic-metabolic abnormalities

Answer: b. The principal serious causes of syncope are cardiac dysrhythmias. TIA is less frequently encountered but equally serious. Stroke generally does not cause isolated syncope. Toxic-metabolic abnormalities may induce syncope through alterations in blood pressure or cardiac rhythm. Structural cardiac lesions, such as atrial myxoma, and sudden interruption of right ventricular outflow by pulmonary embolism, can also cause sudden loss of consciousness but are less common.

3. Which of the following findings most strongly suggest that a patient presenting with syncope can be safely discharged from the emergency department (ED)?

a. Age under 85 years and a normal chemistry panel
b. A normal chest x-ray and CT scan of the head
c. Normal heart rate and temperature in the ED
d. Normal ECG findings and no past medical history
e. Absence of abdominal pain and absence of headache

Answer: d. A normal electrocardiogram in a patient without other significant risk factors (e.g., advanced age, preexisting heart disease) may be considered for outpatient disposition. The chemistry panel, chest x-rays, and CT head scan are commonly ordered but are of low diagnostic and prognostic utility. Abdominal pain, fever, and headache are important associated signs and symptoms to assess for, but their absence has little prognostic utility.

12

Depressed Consciousness and Coma

Charles Lei and Clay Smith

KEY CONCEPTS

- Coma is a state of depressed consciousness in which a patient is not aware, is not awake, and does not respond to vigorous stimulation. Consciousness consists of arousal (subcortical) and awareness (cortical).
- Damage to the dorsal brainstem, thalamus, axonal projections to the cortex, or extensive injury to bilateral cortices may result in depressed consciousness or coma.
- Toxicologic, metabolic, infectious, and other disorders causing diffuse brain injury cause 65% of coma cases; of these, toxins are the most common. Structural brain diseases account for most of the remaining cases.
- A patient with depressed consciousness is unlikely to provide a reliable history. Historical information should be elicited from other available sources, such as emergency medical services personnel, family members, the patient's belongings, or medical records.
- An abrupt onset of coma suggests a stroke, seizure, or cardiac event.
- The neurologic examination should include an evaluation of level of consciousness, cranial nerves, brainstem reflexes, and motor responses.
- Pinpoint pupils may represent a pontine infarct or intoxication from opioids, clonidine, or cholinergic substances.
- Nonconvulsive status epilepticus should be suspected in cases of coma of undetermined cause and is diagnosed by electroencephalography.
- Hypoglycemia and hypoxia are two easily identified and reversible causes of coma.
- An empiric trial of naloxone will lead to rapid reversal of opioid toxicity and other select medication overdoses.
- Targeted temperature management is recommended in comatose adult patients with return of spontaneous circulation after cardiac arrest from either a shockable or nonshockable rhythm, with a goal temperature range of 32°C to 36°C. In children who are comatose post arrest, it is reasonable to target a temperature range of 36°C to 37.5°C. Hyperthermia should be strictly avoided for all comatose postarrest patients.
- Most patients with coma will require intensive care monitoring. If the cause of coma is not treatable in the initial facility and the patient needs a higher level of specialty care (e.g., structural lesion requiring neurosurgery), then a coordinated transfer should be facilitated.

FOUNDATIONS

Coma is a state of depressed consciousness in which a patient is not aware, is not awake, and does not respond to vigorous stimulation. This stands in contrast to stuporous or lethargic patients, who also may have a decreased level of awareness or consciousness but can be aroused with external stimuli.

Epidemiology

Most cases of depressed consciousness or coma are the result of a metabolic derangement, usually a glucose disorder, drug overdose, or adverse drug effect, but other common causes include traumatic brain injury, systemic or central nervous system (CNS) infection, ischemic or hemorrhagic stroke, intracranial mass, and, less commonly, a psychiatric illness. Patients with depressed consciousness represent true emergencies because the potential causes are often life-threatening and must be rapidly diagnosed and reversed whenever possible. A review of relevant neuroanatomy and pathophysiology facilitates our understanding of how consciousness is affected in the setting of disease (Fig. 12.1).

Pathophysiology

To maintain normal consciousness, the brain requires a constant flow of sensory input and the ability to process this information. Visual, auditory, olfactory, gustatory, visceral, and somatosensory inputs are all synthesized and interpreted by the brain simultaneously. Disruption in this flow of information or inability to process it may lead to depressed consciousness.

Consciousness consists of two domains: arousal and awareness. Arousal ranges from fully awake, to arousable with verbal or tactile stimulation, to unarousable. Anatomically, arousal is maintained by the subcortical structures, including the brainstem nuclei, thalamus, basal forebrain, hypothalamus and, most notably, the ascending reticular activating system (ARAS). ARAS neurons are located predominately in the pons and midbrain, connect to the thalamus, and project to the cortex. Awareness consists of the content of consciousness, ranging from self-aware and coherent to confused, inattentive, or perhaps delusional. Awareness is generated by the bilateral cerebral cortices, which control the processing and understanding of sensory input. A patient's level of arousal may be low enough that the domain of awareness is difficult to assess.

Consequently, damage to the dorsal brainstem, thalamus, axonal projections to the cortex, or extensive injury to bilateral cortices may result in depressed consciousness or coma. The clinical presentation may vary considerably depending on the location of the insult.

DIAGNOSTIC APPROACH

Differential Considerations

Differential diagnoses of depressed consciousness and coma are broad (Table 12.1) and potentially involve dysfunction in any area of the brain, from the cortex to the brainstem. It may be the result of a global insult causing massive cortical neuronal dysfunction or a small injury to a critical area of the brainstem responsible for arousal. Toxicologic, metabolic, infectious, and other disorders causing diffuse brain injury or neuronal dysfunction cause 65% of coma cases; of these, toxins are the most common. Worldwide, the prevalence of unintentional drug overdose, particularly opioid overdose, is increasing.[1,2] Structural brain diseases account for most of the remaining cases. Common, largely reversible causes of depressed consciousness and coma, along with their clinical findings and emergency treatment, are listed in Table 12.1.

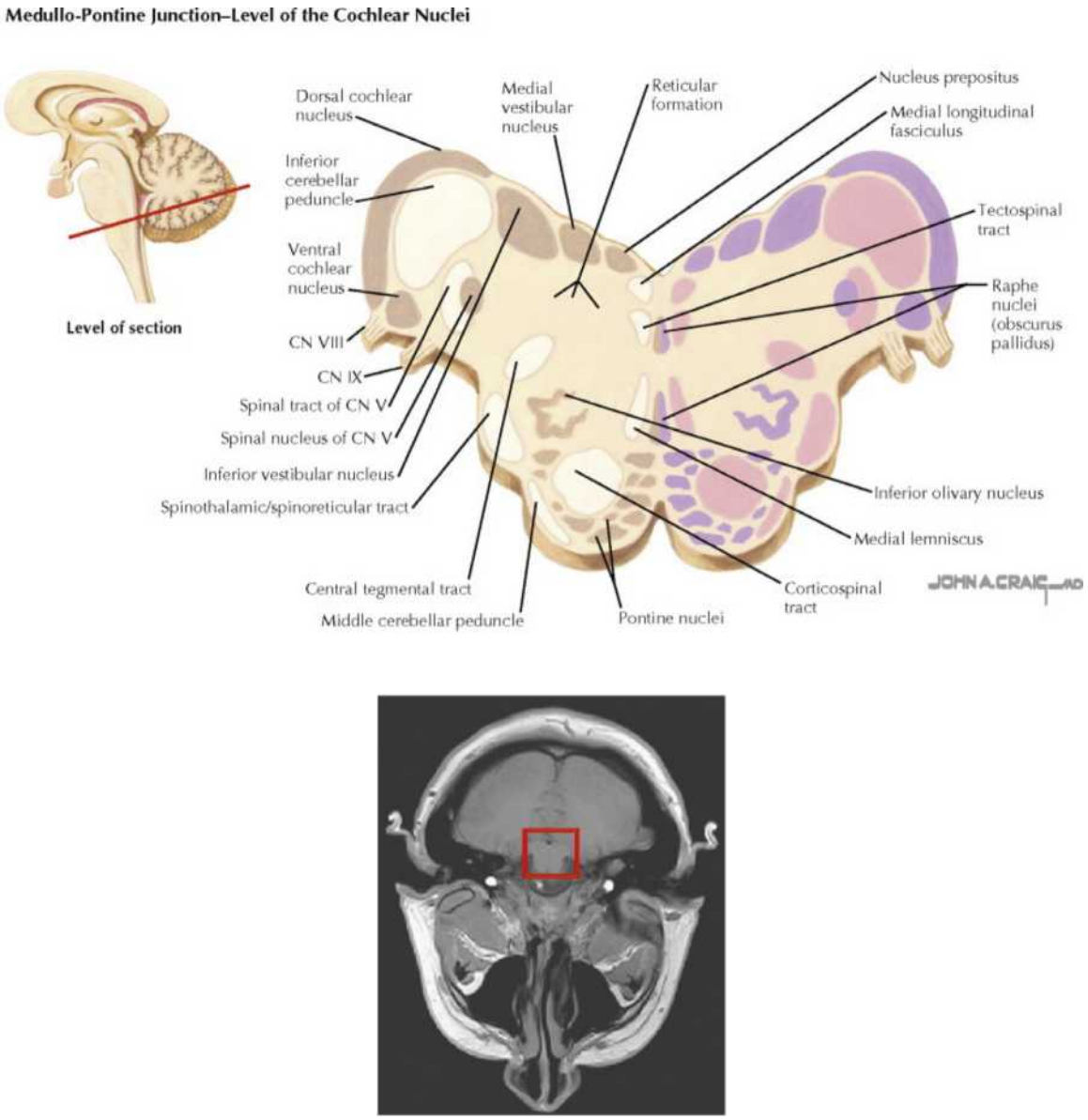

Fig. 12.1 Relevant anatomy showing the ascending reticular activating system and adjacent structures important for arousal. The *red box* denotes area of interest. *CN,* cranial nerve. (From www.netterimages.com. © 2018 Elsevier Inc. All rights reserved.)

Special consideration is needed for specific populations of patients. Older patients are often prescribed multiple medications and are at risk for accidental overdose, drug-drug interactions, and adverse drug reactions. Seemingly minor infections such as a urinary tract infection, upper respiratory infection, or viral gastroenteritis with dehydration may cause depressed consciousness or coma. In addition, immunocompromised patients are susceptible to opportunistic infections that are less common in the general patient population. Immunocompromise may result from acquired immunodeficiency syndrome (AIDS) or may be seen in patients receiving chemotherapy, immunosuppressive medications related to organ transplantation, or biologic agents (e.g., for rheumatologic illness or inflammatory bowel disease). Psychogenic causes of coma are uncommon, and caution is advised when making this definitive diagnosis.

In the evaluation of an undifferentiated comatose patient, keeping a broad initial differential diagnosis may prevent premature clinical fixation that could lead to diagnostic error. A careful history and clues from the physical examination will often shorten the list of possibilities, allowing a focused evaluation and rapid initiation of treatment.

Pivotal Findings

Symptoms

A patient with depressed consciousness is unlikely to provide a reliable history. Historical information elicited from alternate sources, such as emergency medical services (EMS) personnel, family members, or witnesses, usually guides the diagnostic evaluation. The time course of the patient's alteration in consciousness should be established. An abrupt onset of coma suggests a stroke, seizure, or cardiac event, whereas a more gradual onset of symptoms suggests an infectious or inflammatory process, metabolic disorder, or enlarging intracranial mass. Coma from poisoning may occur in minutes if the patient was exposed to a fast-acting agent or large dose of toxin. Conversely, substances with sustained or extended release can cause delayed toxicity resulting in depressed consciousness over the course of hours.

EMS personnel are trained to gather information at the scene and often provide valuable details about the circumstances surrounding the discovery of the patient, such as the presence of a suicide note

TABLE 12.1 Critical and Emergent Diagnoses of Coma

Diagnosis	Cause	Findings	Treatment (Adult Dosage)	Comments
Metabolic				
Critical diagnoses	Hypoglycemia	Diaphoresis, insulin pump	$D_{50}W$ 50 mL IV	
	Hyperglycemia (DKA, HHS)	Tachypnea, nausea, vomiting, abdominal pain, dehydration	Isotonic fluid; insulin	
	Adrenal crisis	Weakness, weight loss, hypotension, hyperpigmentation	D_5NS volume repletion; correct hypoglycemia; hydrocortisone 100 mg IV	Expect hyperkalemia as well
	Pituitary apoplexy	Sudden headache, visual impairment, multihormonal dysfunction	Treat electrolyte abnormalities; hydrocortisone 100 mg IV	May have pituitary adenoma; consult neurosurgery
	Sepsis	Fever, hypotension, poor end-organ perfusion	Isotonic fluid; appropriate antibiotics; source control	
Emergent diagnoses	Wernicke encephalopathy	CN III or CN VI palsy, nystagmus, sluggish pupillary response, anisocoria, gait instability, peripheral neuropathy	Thiamine 500 mg IV	Often seen in alcoholic or severely malnourished patients, seldom in hyperemesis gravidarum
	Hyponatremia	Progressive confusion, headache, anorexia, seizure	Free water restriction; hypertonic saline for seizures	Side effect of many medications
	Hyperammonemia	Lethargy, irritability, vomiting, seizure, poor feeding	Monitor protein intake; hemodialysis; levocarnitine for valproic acid toxicity	Seen in liver disease, inborn errors of metabolism, or as side effect of valproic acid or bariatric surgery
	Hypercalcemia	Lethargy, polyuria, AKI, constipation	Isotonic fluid; bisphosphonates IV; calcitonin	Causes nephrogenic DI; suspect malignancy
	Uremia	Nausea, vomiting, anorexia, fatigue, uremic fetor	Treat hyperkalemia; hemodialysis	Check ECG for hyperkalemia changes
	Hepatic encephalopathy	Fetor hepaticus, asterixis, ascites, stigmata of cirrhosis	Lactulose or rifaximin	Evaluate for sepsis, GI bleeding, SBP
	Thyrotoxic crisis	Fever, tachycardia, diaphoresis, diarrhea	Isotonic fluid; propranolol 1 mg IV, PO; propylthiouracil 600 mg PO starting dose (variable)	May also need to treat adrenal insufficiency
	Myxedema coma	Sluggishness, weight gain, edema, depression, hair loss, constipation	Levothyroxine or liothyronine; hydrocortisone 100 mg IV (variable)	May be precipitated by acute illness
	Heat stroke	Hyperpyrexia (>41.1°C), flushing, exertion in heat, dehydration	Isotonic fluid; evaporative cooling	Classic in older adults with comorbidities unable to seek cool environment
	High altitude cerebral edema	Rapid ascent, headache, confusion, psychosis	Rapid descent from altitude; hyperbaric oxygen; dexamethasone 10 mg IV	More common >3500 m
Toxic				
Critical diagnoses	Hypoglycemic agents	Older adult with worsening renal function, intentional overdose	Dextrose; octreotide if refractory hypoglycemia due to sulfonylurea toxicity	Sulfonylureas can be lethal with only one pill in children
	Opioids	Stupor, apnea, miosis, needle tracks	Naloxone IV, IN, or IM	Check skin for fentanyl patches
	Simple asphyxiants	Sudden lightheadedness, collapse, syncope	100% oxygen	Leaking CO_2 tank in enclosed space (e.g., walk-in freezer); also nitrogen, helium, argon, or methane gas
	Carbon monoxide	Combustion of fuel in enclosed space, headache, confusion, malaise, nausea	100% oxygen; hyperbaric oxygen per toxicology	Multiple people may be affected simultaneously; consider hyperbaric oxygen, especially during pregnancy
	Histotoxic hypoxia	Confusion, seizure, collapse, hydrogen sulfide smells like rotten eggs, cyanide (bitter almond smell) may result from combustion of plastics	100% oxygen; hydroxocobalamin 70 mg/kg (or 5 g) IV for cyanide	Consider cyanide in any house or car fire
	Methemoglobinemia	Use of medications, such as topical anesthetics or dapsone, cyanosis, pulse oximeter 85%	100% oxygen; methylene blue 1–2 mg/kg IV	Also may result from severe diarrhea in infants

Continued

TABLE 12.1 Critical and Emergent Diagnoses of Coma—cont'd

Diagnosis	Cause	Findings	Treatment (Adult Dosage)	Comments
Emergent diagnoses	Sedatives	Alcohol, benzodiazepines, and many others may be the culprit	Supportive; flumazenil for benzodiazepine toxicity	Avoid flumazenil in chronic benzodiazepine users, patients with proconvulsant drugs (cyclic antidepressants, isoniazid)
	Toxic alcohols	Nausea, vomiting, intoxication, vision changes, early osmolar gap then anion gap acidosis, renal failure	Fomepizole 15 mg/kg IV load; correct electrolyte abnormalities; isotonic fluid 500 mL/h	Consult nephrology and toxicology to consider hemodialysis for elevated levels and metabolic acidosis
	Inhalants	Often young, paint on hands or face, diplopia, slurred speech, cardiac dysrhythmia	Check ECG and monitor on telemetry; definitive airway if lip or tongue edema	Inhalants may be cold, may cause frostbite and edema to mucous membranes and hands
	Psychiatric medications	Hypotension, wide QRS, seizures	High-dose IV sodium bicarbonate for tricyclic antidepressant overdose	
	Anticonvulsants	Confusion, slurred speech, elevated drug levels	Supportive measures	Hyperammonemia may occur with valproic acid use
	Anticholinergics	Hyperpyrexia, pupillary dilation, urinary retention, visual hallucinations	Physostigmine; benzodiazepines may help in severe agitation	Consider physostigmine in severe anticholinergic toxicity; avoid if seizure, bradycardia, or abnormal QRS or QTc on ECG ; administer via slow IV push over 5 minutes
	Clonidine	Bradycardia, hypotension, somnolence	Isotonic fluids; vasopressors	Discuss naloxone with toxicology
	Beta blockers	Bradycardia, hypotension, hypoglycemia, seizure	Isotonic fluid; glucagon IV (5 mg); atropine IV (0.5 mg); vasopressors IV; high dose insulin infusion; transcutaneous or transvenous pacing	High doses of vasopressors may be needed. Discuss lipid rescue therapy and ECMO with toxicology and perfusionist, respectively
	Salicylates	Nausea, vomiting, tinnitus, delirium, hyperpnea, anion gap metabolic acidosis with mixed respiratory alkalosis	Isotonic fluids; urinary alkalinization with sodium bicarbonate; correct hypokalemia; consider hemodialysis	May come from oil of wintergreen or other non-aspirin source
	Neuroleptic malignant syndrome	Hyperpyrexia, muscular rigidity, delirium, autonomic instability, elevated CPK	Cooling, isotonic fluid; benzodiazepines, bromocriptine	Pharmacologic paralysis with nondepolarizing agent if severe
	Serotonin syndrome	Multiple serotonergic agents, hypertension, tachycardia, hyperreflexia, muscular rigidity, tremor, nausea, diarrhea, clonus	Isotonic fluid; check CPK; benzodiazepines; cooling, hydration, cyproheptadine	Pharmacologic paralysis with nondepolarizing agent if severe
Structural				
Critical diagnoses	Intracranial hemorrhage	Sudden onset headache, hypertension, neurologic deficits	CT without contrast; reversal of anticoagulation ; blood pressure control, antihypertensives and/or hyperosmolar agents	Early neurosurgical consultation for possible evacuation
	Cortical infarct	Sudden unilateral neurologic deficits	CT without contrast to evaluate for hemorrhage; neurology consultation; consider tPA and intraarterial clot retrieval; blood pressure control or antihypertensives	tPA contraindications must be excluded; tPA 0.9 mg/kg IV, not to exceed 90 mg total dose; administer 10% of total dose as initial IV bolus over 1 min and remainder infused over 60 min
	Cerebellar infarct	Sudden vertigo, nausea, ataxia, dysarthria	Consider tPA as above	Neurosurgery consultation if severe edema to consider decompressive craniectomy
	Basilar artery occlusion	Hemiparesis or quadriparesis, abnormal spontaneous movements, facial weakness, dysarthria, dysphagia	Consider tPA as above	May develop locked-in syndrome (loss of all voluntary movements except for eyes)

AKI, acute kidney injury; *CN*, cranial nerve; CO_2, carbon dioxide; *CPK*, creatine phosphokinase; *CT*, computed tomography; D_5NS, 5% dextrose in normal saline; D_5W, 5% dextrose in water; $D_{50}W$, 50% dextrose in water; *DI*, diabetes insipidus; *DKA*, diabetic ketoacidosis; *ECG*, electrocardiogram; *GI*, gastrointestinal; *HHS*, hyperosmolar hyperglycemic state; *IV*, intravenous; *PO*, per os (orally); *SBP*, spontaneous bacterial peritonitis; *tPA*, tissue plasminogen activator.

empty pill bottles, syringes, or medicinal (transdermal) patches. In addition, the possibility of trauma, seizure activity or the possibility of traumatic exposures. Family members or caregivers may have information regarding the patient's recent symptoms, which can offer important diagnostic clues. For example, a preceding, severe, sudden-onset headache suggests intracranial hemorrhage, cerebral venous sinus thrombosis, or cervical artery dissection; preceding fever may suggest meningitis or encephalitis; and a history of depression may suggest a drug overdose or adverse effects of psychotropic medications. The patient's medication history should be carefully reviewed for any recent changes to the medication regimen or dosages. A history of taking over-the-counter or alternative "herbal" medications should also be obtained.

The patient may be carrying additional pieces of information, such as a medical alert bracelet or medication list in the wallet. The patient's own mobile device may be used to retrieve supplemental data, review recent text messages, or contact next of kin.[3] If the patient can be reliably identified by a family member or photo identification card, the medical record may be accessed for additional medical history. In addition, the patient's pharmacy may be contacted to obtain an accurate prescription medication list.

Signs

After necessary stabilization measures have been instituted, the patient should be evaluated systematically, starting with an assessment of vital signs. Alterations in temperature are most commonly seen in infections, environmental exposures, metabolic disorders, and poisonings. Hypotension with depressed consciousness indicates shock with resultant cerebral hypoperfusion. Hypertension may be a sign of intoxication (e.g., sympathomimetic agents, amphetamines, cocaine, phencyclidine) or withdrawal (e.g., from alcohol, benzodiazepines, or opioids), cerebral or brainstem infarction, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome (PRES), or elevated intracranial pressure (ICP). The combination of hypertension and bradycardia, known as the *Cushing reflex*, suggests severe ICP elevation. Bradycardia may also be the result of a myocardial conduction abnormality, cardiac ischemia, or overdose from medications such as beta blockers, calcium channel antagonists, cardiac glycosides, or clonidine. Many medical conditions cause tachycardia and depressed consciousness, including sepsis, medications with stimulant or anticholinergic effects, severe anemia, hypovolemia, thyrotoxicosis, and acute structural brain injury. Alterations in respiratory rate, pattern, or depth are usually caused by primary CNS abnormalities and toxic or metabolic disorders. *Kussmaul breathing* consists of deep labored respirations and may be seen in patients with severe metabolic acidosis, particularly diabetic ketoacidosis (DKA). *Cheyne-Stokes respiration* is a cyclic breathing pattern in which episodes of gradually increasing and then decreasing respirations are separated by brief apneic periods and is associated with stroke and heart failure.

After an assessment of the patient's vital signs, a complete physical examination should be performed. The head should be inspected for signs of trauma, such as a scalp laceration or hematoma. Periorbital ecchymosis ("raccoon eyes"), retroauricular ecchymosis *(Battle sign),* hemotympanum, and cerebrospinal fluid (CSF) otorrhea or rhinorrhea are signs of a basilar skull fracture. The hydration of the oral mucous membranes and quantity of salivary secretions provide information regarding the patient's volume status and may indicate a specific toxidrome (e.g., dry mucosal membranes from anticholinergic toxicity or excessive salivation from cholinergic crisis). Laceration or contusion of the tongue suggests a recent seizure.

The patient's cervical spine should be immobilized if there is suspicion for a neck injury. The presence of meningismus raises suspicion for meningoencephalitis or subarachnoid hemorrhage. Stridor indicates obstruction of the large airways and is usually caused by infection, anaphylaxis, angioedema, trauma, or foreign body aspiration. Goiter in a patient with depressed consciousness suggests underlying myxedema coma or thyroid storm.

The cardiovascular system should be evaluated for rate or rhythm disturbances, murmurs, and signs of volume depletion or overload. Abnormal lung sounds, retractions, and impairments in chest wall excursion indicate a pulmonary cause of depressed consciousness. Examination of the abdomen may reveal hepatomegaly or ascites, suggesting a hepatic cause of coma. Diminished bowel sounds and bladder distension suggest an anticholinergic toxidrome. A rectal examination should be performed to assess for gastrointestinal bleeding, retained foreign bodies, and neurologic sphincter tone.

The patient should be fully undressed to evaluate the skin for needle track marks, medicinal patches, rashes, and signs of trauma or infection. The presence of jaundice, palmar erythema, spider angiomata, or caput medusa in a patient with depressed consciousness should raise concern for hepatic encephalopathy. Petechiae or purpura can be seen in patients with meningococcemia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and vasculitis. Diaphoresis may be present in sympathomimetic poisoning, whereas excessively dry, flushed skin is associated with anticholinergic toxicity. Unusual odors emanating from the patient may provide additional diagnostic clues, such as ethanol, isopropanol, uremic fetor, fetor hepaticus, melenic stools, or the "fruity," acetone-like breath odor in some patients with DKA.

The main objectives of the neurologic examination are to determine the depth of coma, identify lateralizing deficits, and assess for brainstem dysfunction. The examination should proceed systematically and include an evaluation of the patient's level of consciousness, cranial nerves, brainstem reflexes, and motor responses. The patient's level of consciousness should be assessed with stimuli of increasing intensity. Auditory stimuli, such as a verbal cue or loud noise, may be used first. If the patient does not exhibit a response to auditory stimuli, noxious stimuli may be applied, such as a sternal rub, nail bed compression, trapezius squeeze, or pressure on the medial aspect of the supraorbital ridge or posterior aspect of the mandibular ramus. These maneuvers should be applied gently in pediatric and elderly patients.

Level of consciousness may also be evaluated using a coma scale. The two most widely used scales are the Glasgow Coma Scale (GCS; Table 12.2) and Full Outline of UnResponsiveness (FOUR) score (Table 12.3). Both grading systems can be performed rapidly and have high interrater reliability. Although originally developed as a prognostic indicator in patients with traumatic brain injury, the GCS is commonly applied to all patients presenting with depressed consciousness. The GCS has considerable limitations because it does not account for abnormalities in brainstem function and may not detect subtle changes in the neurologic examination. In addition, the score may widely vary in individual patients (e.g., a patient with an opioid overdose may initially present with a GCS of 3 but may rapidly improve to a score of 15 after administration of naloxone). The FOUR score has been validated in a variety of clinical settings, incorporates a more detailed assessment of brainstem reflexes and breathing patterns, and may have greater predictive value than the GCS in intubated patients and those with very low GCS scores.[4] The utility of both coma scales can be maximized by reporting the scores of each element in addition to the total score.

The cranial nerves should be tested, with particular attention to the eye exam. The size, reactivity, and symmetry of the pupils can provide important diagnostic clues. Pinpoint pupils that are minimally reactive or unreactive to light may be a result of damage to the pons, usually from hemorrhage or infarction. Pupillary dilation with loss of pupillary reactivity in a comatose patient should raise concern for an expanding intracranial mass with transtentorial herniation, resulting

TABLE 12.2 Glasgow Coma Scale

Parameter	Rating	Score
Eye Opening		
Open before stimulus	Spontaneous	4
Open after spoken or shouted request	To voice	3
Open after fingertip stimulus	To pain	2
No opening at any time, no interfering factor	No response	1
Closed by local factor	Not testable (NT)	NT
Best Verbal Response		
Correctly gives name, place, and date	Oriented	5
Not oriented but communicates coherently	Confused	4
Intelligible single words	Inappropriate words	3
Only moans or groans	Incomprehensible sounds	2
No audible response, no interfering factor	No response	1
Factor interfering with communication	NT	NT
Best Motor Response		
Obeys two-part request	Obeys commands	6
Moves hand across body or above clavicle to stimulus	Localizes pain	5
Bends arm at elbow rapidly, features not predominantly abnormal	Withdraws from pain	4
Bends arm at elbow, features clearly predominantly abnormal	Flexion to pain	3
Extends arm at elbow	Extension to pain	2
No movement in arms or legs, no interfering factor	No response	1
Paralyzed or other limiting factor	NT	NT

Modified from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2:81–84.

TABLE 12.3 Full Outline of UnResponsiveness Score

Response	Score
Eye Response	
Eyelids open or opened, tracking, or blinking to command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids remain closed with pain	0
Motor Response	
Thumbs-up, fist, or peace sign	4
Localizing to pain	3
Flexion response to pain	2
Extension response to pain	1
No response to pain or generalized myoclonus status	0
Brainstem Reflexes	
Pupil and corneal reflexes present	4
One pupil wide and fixed	3
Pupil or corneal reflexes absent	2
Pupil and corneal reflexes absent	1
Absent pupil, corneal, and cough reflex	0
Respiration	
Not intubated, regular breathing pattern	4
Not intubated, Cheyne-Stokes breathing pattern	3
Not intubated, irregular breathing	2
Breathes above ventilator rate	1
Breathes at ventilator rate or apnea	0

in compression of the oculomotor nerve or injury to the midbrain. Drugs and other toxins can also cause miosis (e.g., opioids, clonidine, organophosphates) or mydriasis (e.g., cocaine, amphetamines, anticholinergics, tricyclic antidepressants). Fixed, midsize pupils can be seen in severe midbrain injury and may be the first sign of brain death.

Eye position and movement should also be assessed. Forced deviation of the eyes, usually in the horizontal plane, may indicate an ipsilateral hemispheric or contralateral pontine lesion. Seizures can also cause horizontal eye deviation, typically away from the cerebral lobe generating the epileptiform activity. Horizontal disconjugate gaze can be seen in patients who are sedated, drowsy, or intoxicated and those with metabolic disorders. Disconjugate gaze in the vertical plane, also known as skew deviation, strongly suggests a cerebellar or brainstem lesion. Spontaneous conjugate "roving" eye movements indicate bihemispheric dysfunction with a relatively intact brainstem. Nystagmus in an unresponsive patient may be a sign of nonconvulsive status epilepticus (NCSE), brainstem dysfunction, drug overdose (e.g., anticonvulsants, lithium, ketamine, ethanol, phencyclidine), or envenomation (scorpion sting).

A funduscopic examination may yield additional diagnostic information. The presence of a subhyaloid hemorrhage should raise suspicion for aneurysmal subarachnoid hemorrhage. Papilledema and retinal hemorrhages are associated with increased ICP and malignant hypertension. Optic disc hyperemia is a finding associated with severe methanol poisoning.

Brainstem function is evaluated through the various brainstem reflexes, including the *oculocephalic reflex* (doll's eyes), oculovestibular reflex (cold caloric testing), corneal reflex, and gag reflex. Provided that there are no airway issues or suspicion for cervical spine injury, the oculocephalic reflex is tested by rotating the head from side to side in the horizontal plane. In a patient with a normally functioning brainstem, the eyes will move in a direction opposite the head movement and appear to maintain visual fixation on a single point in space. Brainstem dysfunction should be suspected if the eyes remain in midposition with respect to the bony orbits and move in unison with the head. Conscious patients can usually suppress the oculocephalic reflex.

The *oculovestibular reflex* is a more sensitive test for brainstem dysfunction and cannot be resisted voluntarily. After cerumen impaction and tympanic membrane perforation have been excluded, the patient's head is elevated to 30 degrees up from the horizontal and ice water is infused into the external auditory canal. In a comatose patient with an intact brainstem, the stimulus results in sustained conjugate deviation of the eyes toward the ear being irrigated. Absence of a response to the irrigation should raise suspicion for brainstem dysfunction. In response to cold water caloric testing, conscious patients experience not only tonic deviation of the eyes toward the stimulated ear but also nystagmus (with the fast phase away from the side of irrigation), vertigo, nausea, and vomiting. The presence of nystagmus is suggestive of wakefulness and psychogenic unresponsiveness.

The corneal reflex is tested by gently touching the edge of the cornea with a wisp of cotton or small drop of saline and observing for blinking of the eyes. Elderly and diabetic patients may have a diminished or absent corneal reflex at baseline. The gag reflex is elicited by gently stimulating the posterior pharynx and observing for brisk elevation of the soft palate and bilateral contraction of the pharyngeal muscles. Because the gag reflex is symmetrically reduced or absent in a subset of normal individuals, the test is most informative when the response is asymmetric.

Motor function is assessed by observing any spontaneous movements and testing the motor responses to verbal commands and noxious stimuli. Purposeful movements should be distinguished from reflex activity. Examples of purposeful movements include following commands and localizing painful stimuli. Reflexive responses include withdrawal from pain, decorticate posturing (adduction of the shoulders and flexion of the elbows, wrists, and fingers), and decerebrate posturing (shoulder adduction, elbow extension, and forearm pronation). Although usually associated with focal brain lesions, posturing reflexes can also be seen in systemic conditions affecting the CNS, such as toxic and metabolic disorders.

Muscle tone, assessed by passive manipulation of the extremities, is usually decreased in structural brain disease but not affected in most metabolic conditions. Generalized muscle rigidity occurs in patients with neuroleptic malignant syndrome and malignant hyperthermia. Myoclonus may be a sign of NCSE, hepatic or renal dysfunction, serotonin syndrome, or hypercarbic respiratory failure. Myoclonic jerks can be seen with hypocalcemia and potassium imbalance. Tremors are classically noted with Parkinson disease, lithium toxicity, and withdrawal from alcohol and benzodiazepines.

Ancillary Testing

Diagnostic laboratory evaluation of a patient with depressed consciousness should begin with point of care measurement of the serum glucose level to confirm or exclude hypoglycemia. A comprehensive metabolic panel should be analyzed to identify metabolic acidosis, renal or hepatic dysfunction, and any electrolyte derangements, such as hyponatremia or hypercalcemia. In a patient with metabolic acidosis, a widened anion gap suggests possible ketosis (e.g., from diabetes, heavy alcohol use, or starvation), lactic acidosis (e.g., from sepsis, hypoperfusion, metformin or cyanide toxicity), uremia, or poisoning (e.g., with methanol, ethylene glycol, or salicylates). Anion gap acidosis in the context of poisoning is discussed in Chapter 135.

A complete blood count may identify profound anemia or thrombocytopenia and reveal a potential cause of severe hypotension or intracranial hemorrhage. Although an elevated white blood cell count can be a marker of infection, it is nonspecific and rarely helpful in discerning the cause of depressed consciousness. However, an abnormally low white blood cell count suggests an immunocompromised state and should raise suspicion for infection or malignancy. An elevated prothrombin or partial thromboplastin time can be seen in blood dyscrasias, disseminated intravascular coagulation, liver disease, and anticoagulant use.

Urinalysis can provide valuable diagnostic information. A high urine specific gravity suggests dehydration. Glucosuria can be seen in DKA and hyperosmolar hyperglycemic state. Detection of white blood cells, leukocyte esterase, or nitrites in the urine indicates a urinary tract infection. The presence of calcium oxalate crystals is associated with ethylene glycol ingestion.

Serum salicylate and acetaminophen levels should be determined if toxicity is suspected, such as in a case of an unexplained anion gap acidosis or hepatic failure. Other toxicologic tests, such as the serum ethanol level and urine drug screen, are less likely to significantly affect the acute management of a patient with depressed consciousness.

Oxygenation and ventilation may be rapidly and noninvasively assessed using pulse oximetry and end-tidal carbon dioxide monitoring. Blood gas analysis can be used to confirm acid-base balance and more accurately quantify the degree of hypoxia or hypercarbia. Co-oximetry should be included if carbon monoxide poisoning or methemoglobinemia is suspected. Due to its poor sensitivity and specificity, the serum ammonia level has little utility in the evaluation of comatose patients. Ammonia concentrations can be elevated in a variety of nonhepatic conditions, such as valproic acid toxicity and inborn errors of metabolism and may be normal or elevated in patients with hepatic encephalopathy. Thyroid function studies can help to confirm myxedema coma or thyrotoxicosis. Blood and urine cultures should be obtained if there is concern for infection. CSF analysis should be performed if CNS pathology such as infection or hemorrhage is suspected. Neuroimaging should be considered prior to lumbar puncture to exclude an intracranial mass lesion.

Noncontrast computed tomography (CT) of the brain, because of its wide availability and rapid acquisition, is the imaging modality of choice for the initial evaluation of a patient with depressed consciousness. It should be obtained in patients with preceding head trauma, those with suspected structural brain disease, and those in whom the diagnosis is not identified by other diagnostic means. Noncontrast cranial CT may identify intracranial hemorrhage, hydrocephalus, cerebral edema, mass lesion, or may reveal signs of ischemic stroke or elevated ICP. Other more subtle CT findings include putaminal necrosis or hemorrhage with methanol toxicity and low attenuation in the globus pallidus region associated with carbon monoxide poisoning.

CT angiography (CTA) of the head and neck should be performed if brainstem dysfunction is suspected on neurologic examination. It can provide valuable information regarding the cerebral vasculature and aid in the diagnosis of an intracranial aneurysm, arteriovenous malformation, cerebral venous thrombosis, and basilar or vertebral artery stenosis, dissection, or occlusion.

Due to bone artifact, CT has limited utility in the visualization of the posterior fossa. In comparison, magnetic resonance imaging (MRI) of the brain is better for identifying structural lesions in this region. MRI also provides greater anatomic differentiation of cortical and brainstem structures and is superior to CT imaging for detecting early ischemic stroke and identifying infectious, inflammatory, and neoplastic processes. However, MRI is less practical than CT because of cost, accessibility, and the length of time needed to acquire each study, which limits the ability to monitor and access a critically ill patient.

Electroencephalography (EEG) should be performed to evaluate for NCSE, which can manifest de novo and present with coma or persist after cessation of convulsive seizures. An EEG is also indicated in seizure patients who have received sedative or paralytic medications to assess for ongoing seizure activity (see Chapter 14).

An electrocardiogram may diagnose cardiac ischemia, conduction block, or other dysrrhythmias. It may also provide supporting evidence for an electrolyte abnormality (e.g., potassium, calcium), drug ingestion (e.g., tricyclic antidepressant, digoxin), or structural brain injury.

DIAGNOSTIC ALGORITHM

Critical and emergent diagnoses that require immediate consideration, evaluation, and treatment are listed in Table 12.1. Information from the history, physical examination, and initial battery of tests guides the direction of imaging and additional diagnostic testing. Advanced neuroimaging is performed next but not before treating emergent causes, such as hypoglycemia or opioid toxicity. An algorithmic approach to

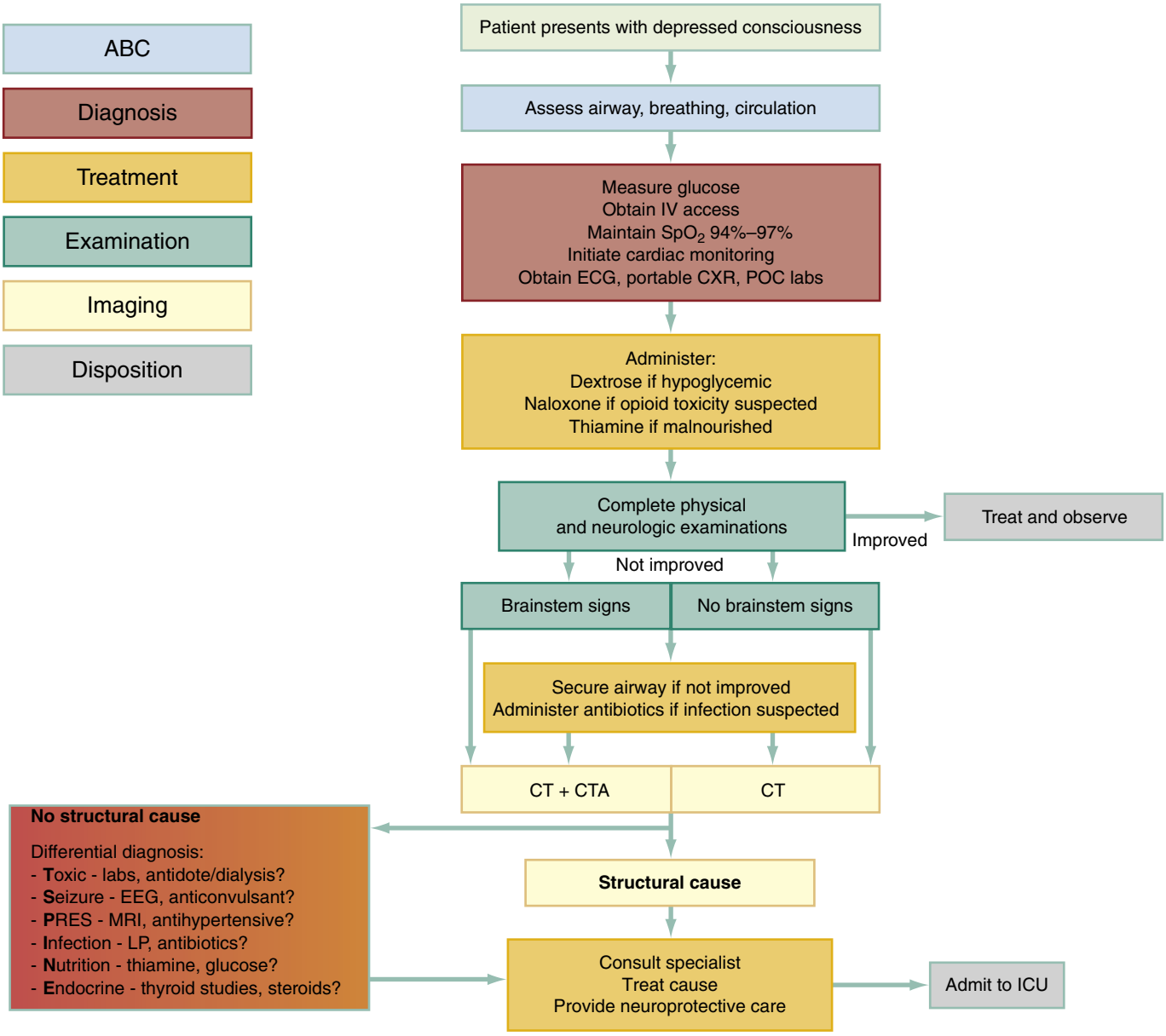

Fig. 12.2 Algorithm for Diagnostic and Management Approach to Depressed Consciousness and Coma. *ABC*, airway, breathing, circulation; *CT*, computed tomography; *CTA*, computed tomography angiography; *CXR*, chest x-ray; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *ICU*, intensive care unit; *IV*, intravenous; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *POC*, point of care; *PRES*, posterior reversible encephalopathy syndrome; SpO_2, oxygen saturation.

the diagnosis and management of patients with depressed consciousness is presented in Fig. 12.2. This approach allows diagnostic assessment and therapeutic intervention to proceed in parallel.

EMPIRICAL MANAGEMENT

The management of comatose patients should begin immediately on arrival to the emergency department, before a definitive diagnosis is established. Management prioritizes oxygenation and perfusion while the diagnostic evaluation is initiated. Care should be taken to avoid hypoxia and hyperoxia because both are deleterious.[5] A goal oxygen saturation of 94% to 97% is acceptable and avoids both extremes. Intravenous (IV) access should be established and cardiac monitoring initiated. A rapid bedside glucose level should be measured and, if hypoglycemic, treated immediately with dextrose administration. Rapid treatment of hypoglycemia will lead to reversal of coma due to neuroglycopenia. An empirical trial of naloxone (0.4 to 2.0 mg) will rapidly reverse opioid toxicity, as well as several other medication overdoses (see Chapter 151). We recommend administering an initial naloxone dose of 0.4 mg IV and increasing up to 10 mg IV if necessary. For patients with difficult IV access, especially in the prehospital setting, intranasal naloxone is also highly effective.[6] Effective reversal with naloxone may obviate the need for endotracheal intubation in these patients. In cachectic malnourished patients, women with severe hyperemesis gravidarum, chronic alcoholics, or other patients with suspected thiamine deficiency, empirical administration of thiamine 500 mg IV is recommended.

If initial management efforts do not promptly result in improvement, the patient's ability to protect and maintain a patent airway should be reassessed. Failure to oxygenate, ventilate, or protect the airway is an

indication for endotracheal intubation. GCS scores inversely correlate with aspiration risk, but GCS alone does not accurately predict which patients will maintain protective airway reflexes. Patients with a GCS score higher than 8 cannot be considered safe or not at risk for aspiration. We recommend endotracheal intubation in most trauma patients with coma and a GCS score less than or equal to 8 and for any patient thought to be incapable of sustained airway self-maintenance and protection. However, not all patients with GCS of 8 or less require endotracheal intubation.[7,8] It is best to consider the history, examination, expected clinical course, and ability of future critical care providers caring for the patient to perform an airway intervention successfully, should it become necessary, when making the decision to intubate. For example, patients with altered consciousness due to ingestion of a depressant or sedative hypnotic substance may not require endotracheal intubation. The expected clinical course for most of these ingestions is to closely observe the patient in a monitored setting and allow time for metabolism. The majority of such patients recover without need for airway intervention.

Prior to intubation, a detailed neurologic examination should be performed, with particular attention to assessing brainstem function. Once the airway has been reassessed and secured as needed, we recommend treating patients with undifferentiated coma and clinical suspicion for meningitis (e.g., fever, other signs of infection, sepsis, rash) empirically with ceftriaxone 2000 mg IV prior to CT imaging. Additional antibiotics may be added based on suspected infection source, local antibiogram, and patient-specific risk factors. If encephalitis is suspected, empirical acyclovir dosed at 10 mg/kg IV in adults and 20 mg/kg IV in pediatrics is also recommended.

If the head CT or CTA is diagnostic, notify the appropriate consultant (neurosurgery or neurology) and arrange for definitive management. In all patients with brain injury of any type, especially those with signs of herniation, general principles of neuroprotective care are recommended (Box 12.1; see Chapter 33).

If the head CT or CTA is nondiagnostic, determine if there are any other emergent conditions that could be treated and potentially reversed. Differential diagnoses are listed in Fig. 12.2 and may be easily recalled using the mnemonic shown.

Special consideration should be given to patients who present comatose following resuscitation from cardiac arrest. In addition to following the principles of neuroprotective care, which include simple avoidance of hyperthermia, adult patients should undergo targeted temperature management (TTM), with a goal temperature between 32°C and 36°C.[5,9] This applies to all comatose patients who have return of spontaneous circulation (ROSC) after cardiac arrest, including those with shockable and nonshockable rhythms as the cause of arrest.[10,11] Efficacy of a lower temperature target of 33°C (vs. 36.8°C) was not as convincing in children for both out-of-hospital and in-hospital cardiac arrest.[12,13] However, TTM has been recommended as a reasonable option in the 2019 Pediatric Advanced Life Support update, with an initial target temperature of 32°C to 34°C followed by 36°C to 37.5°C, or to simply target a temperature range of 36°C to 37.5°C.[14] Prehospital cooling using an infusion of cold saline was shown to be ineffective and is not recommended.[15] The most important principles in both adults and children with ROSC after cardiac arrest who remain comatose are rapid initiation of mild cooling and strict avoidance of hyperthermia.

BOX 12.1 Principles of Neuroprotective Resuscitation

- Elevate head of bed to 30 degrees if there is no suspicion for thoracic spine injury.
- Avoid constricting ties or collars around neck.
- Avoid hypoxia and hyperoxia.
- Maintain end-tidal CO_2 at 35 cm H_2O.
- Avoid hypotension.
- Avoid hyperthermia.
- Prevent and treat seizure activity.

CO_2, Carbon dioxide; *H_2O*, water.

Once the initial diagnostic evaluation has been completed and initial management is underway, most patients will require definitive treatment in an intensive care unit. The disposition will depend on what is discovered during the evaluation. Patients found to have a structural abnormality on neuroimaging potentially requiring neurosurgical intervention should be rapidly transferred to a facility with neurosurgical capabilities, if not available at the initial medical facility.

Many patients with toxic or metabolic causes (e.g., opioid overdose, hypoglycemia) of depressed consciousness may be rapidly treated and stabilized in the emergency department and some may be safely discharged home after a period of observation. Patients with alcohol or recreational drug intoxication and no other discernible cause of depressed consciousness may be discharged when clinically sober. Most patients with depressed consciousness of unclear etiology will require admission to the hospital or observation unit even if the level of consciousness markedly improves with initial treatment.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 12: QUESTIONS AND ANSWERS

1. In infants, what is the most common cause of a depressed level of consciousness?

a. Accidental toxic ingestion
b. Inborn error of metabolism
c. Infection
d. Physical abuse

Answer: c. The most common causes of depressed consciousness vary with patient age. In infants, infectious causes are most common; however, trauma secondary to physical abuse and metabolic derangements from inborn errors of metabolism can also be seen. Accidental toxic ingestions are often seen in younger children but are very uncommon in infants. Young adults and adolescents are more likely to present with depressed consciousness after recreational drug use or trauma. Older adults are particularly vulnerable to infectious causes, medication effects, and alterations in their living environments.

2. What Glasgow Coma Scale (GCS) score would be given to an adult patient who opens the eyes to painful stimuli, speaks in an incomprehensible manner, and withdraws from pain?

a. 7
b. 8
c. 9
d. 10

Answer: b. Using the GCS, this adult patient would receive 2 points for eye opening to pain, 2 points for a verbal response consisting of incomprehensible sounds, and 4 points for withdrawing from painful stimuli.

3. What Glasgow Coma Scale (GCS) score would be given to a pediatric patient who opens the eyes and flexes the extremities to painful stimuli and who is irritable and continually cries?

a. 6
b. 7
c. 8
d. 9

Answer: d. Using the GCS, this pediatric patient would receive 2 points for eye opening to pain, 4 points for persistently being irritable, and 3 points for flexion in response to painful stimuli. The pediatric GCS takes into account that younger children might not yet be verbal.

4. Awareness of one's self and surroundings defines which of the following?

a. Cognition
b. Consciousness
c. Judgment
d. Orientation

Answer: b. Consciousness is defined as the awareness of one's self and surroundings; it is made up of both arousal and awareness. Cognition involves knowing and understanding, especially through the perception of what is experienced by the senses; judgment is the ability to process input data to generate more meaningful information; and orientation is the ability to determine the relative position of oneself in relation to one's person, place, time, and situation.

5. In the evaluation of a comatose patient, which of the following responses most clearly indicates brainstem dysfunction?

a. A drop of saline on the cornea of one eye causes both eyes to blink
b. Infusion of cold water into the right ear causes rightward deviation of the eyes
c. Stimulation of the posterior pharynx has no effect on the soft palate of pharyngeal muscles
d. When the head is rotated from side to side in the horizontal plane, the eyes remain in midposition and move in unison with the head.

Answer: d. Brainstem function is evaluated through the various brainstem reflexes. The oculocephalic reflex is tested by rotating the head from side to side in the horizontal plane. In patients with normal brainstem function, the eyes should move in a direction opposite of head movement and appear to maintain visual fixation on a single point in space. The corneal reflex is tested by touching the edge of the cornea with a wisp of cotton or drop of water and observing for blinking of the eyes. The oculovestibular reflex is tested by infusing cold water into the external auditory canal. In patients with an intact brainstem, the stimulus causes sustained conjugate deviation of the eyes toward the ear being irrigated. The gag reflex is tested by stimulating the posterior pharynx and observing for brisk elevation of the soft palate and contraction of the pharyngeal muscles. Because the gag reflex is symmetrically reduced or absent in a subset of normal individuals, the utility of this brainstem reflex is limited.

13

Confusion

Patrick J. Maher

KEY CONCEPTS

- Confusion and delirium are symptoms, not a diagnosis.
- Focal cortical dysfunction, such as from tumor or stroke, typically does not cause confusion.
- Any underlying clinical process that disrupts optimal central nervous system (CNS) functioning can result in confusion.
- Emergent causes of confusion that need immediate detection and treatment include hypoglycemia, hypoxemia, hypotension, sepsis, and toxic ingestions.
- Assessment of attention is fundamental for the assessment of patients with confusion as disturbances in attention are consistent with delirium versus psychiatric illness or dementia.
- Recommended tools for identifying patients with delirium in the emergency department are the Delirium Triage Screen (DTS) and brief Confusion Assessment Method (bCAM), if indicated.
- Delirium often goes unrecognized unless a structured assessment tool is used.
- Sedatives, including antipsychotics, are useful for managing undifferentiated agitation while the diagnostic evaluation is in progress.

FOUNDATIONS

The term *confusion* indicates an acute impairment in higher cerebral functions, such as memory, attention, or awareness. The disorder has multiple synonyms, some of which imply causative mechanisms, and always represents a symptom of another underlying disease process. Confusion ranges in severity from mild disturbances of short-term memory to a global inability to relate to the environment and process sensory input. Along this spectrum, the disorder overlaps with the term *delirium* (see Chapter 90), and the two terms are often used interchangeably. The degree of confusion may fluctuate over time, as may the patient's level of consciousness.

Delirium implicitly develops over a short period of time, typically hours or days, although it may persist for weeks. Although patients with preexisting dementia are at higher risk for developing delirium, the acute changes of delirium are distinct from and cannot be better explained diagnostically by a newly diagnosed or evolving dementia. The same pathophysiologic processes causing confusion and delirium may manifest with altered mentation and diminished alertness along the coma spectrum.

Confusion has many causes, and an orderly approach is helpful to discover the causative diagnosis. The assessment of mental status and cognitive impairment, with a focus on changes from baseline function, is an important part of the evaluation in older emergency department (ED) patients. Altered mental status may be a frequent finding even without a chief complaint of confusion. Collateral history from family or caregivers, a structured physical examination, and the use of a specific assessment tool may be needed to detect the presence of confusion.

Epidemiology

Emergency clinicians underestimate the incidence of confusion in patients. Because confusion is often accepted as an incidental or secondary component of another condition, it may be overshadowed by the primary condition being treated. When confusion exists as an isolated or unexplained finding, it is more likely to receive full and immediate consideration by the emergency clinician. Confusion occurs in a high percentage of hospitalized patients, with highest risk in frail, elderly, and critically ill populations.[1] An estimate of ED prevalence of delirium in elderly patients is 8% to 17%, and delirium in the ED often persists into the hospitalization.[2] Presence of delirium carries important negative prognostic implications for patients. In hospitalized patients, delirium is associated with higher mortality, worse functional and cognitive outcomes, and decreased rates of home discharge.

Pathophysiology

Conceptually, consciousness is divided into elements of alertness, or arousal, and elements constituting the content of consciousness. Although arousal may be abnormal, the characteristic disturbance in confusion is to the content portion of consciousness, resulting in abnormalities of attention and awareness. Any underlying clinical process that disrupts optimal central nervous system (CNS) functioning can result in confusion. Global CNS dysfunction usually results from substrate deficiencies (e.g., hypoglycemia, hypoxemia), neurotransmitter dysfunction, intoxication with or withdrawal from neuroactive drugs, or circulatory dysfunction. Individuals with a preexisting impairment are more sensitive to these factors and may become confused after even minor changes in their normal physiologic state.

DIAGNOSTIC APPROACH

Differential Considerations

Four major groups of disorders encompass most causes of confusion: (1) systemic diseases secondarily affecting the CNS; (2) primary intracranial disease; (3) exogenous toxins; and (4) drug withdrawal states (Box 13.1). Within these groups, certain causes, such as hypoxia and hypoglycemia, require immediate evaluation and treatment. A more general mnemonic for causes of altered mental status, many of which can present with acute confusion, is presented in (Table 13.1).

Schizophrenia and mood disorders, such as bipolar and major depressive disorder, do not generally cause acute confusion, but similarities in presentation can lead to diagnostic difficulty. Many inpatients evaluated for new depression are eventually diagnosed with acute delirium. Likewise, the diagnosis of a psychiatric disorder requires exclusion of organic causes. Attention in patients with primary psychiatric

BOX 13.1 Critical and Emergent Causes of Confusion[a]

- Critical
  - Hypoxia
  - Hypoventilation
  - Hypoglycemia
  - Delirium tremens
- Emergent
  - Primary intracranial disease
    - Seizure/nonconvulsive status epilepticus
    - Traumatic brain injury
    - Hypertensive encephalopathy
  - Systemic diseases secondarily affecting the central nervous system
    - Sepsis
    - Hepatic encephalopathy
    - Uremia/renal failure
    - Hyperthermia/hypothermia
    - Endocrinopathy
    - Nutritional deficiency
  - Exogenous toxins
    - Sedatives/hallucinogens
    - Ethanol/toxic alcohols
    - Narcotics
    - Antihistamines
  - Drug withdrawal
    - Alcohol
    - Drugs of abuse

[a]This list is not meant to serve as a comprehensive catalog of all causes of acute confusional state.

disorders is typically normal unless psychosis or agitation is severe. A careful evaluation is required to differentiate between psychiatric and medical origins of thought disturbances (Table 13.2).

CNS causes of confusion include stroke, seizure, and infection. Focal cortical dysfunction, such as from tumor or stroke, may present as confusion when receptive or expressive dysphasia is present. Occasionally, other neurologic abnormalities may mimic a confusional state when involving bilateral lobar structures. Subcortical or brainstem dysfunction usually results in a diminished level of alertness, rather than confusion. Frontal lobe dysfunction from stroke, trauma, or tumor may result in personality changes and the report of confusion by family or friends. Postictal state or nonconvulsive or petit mal status epilepticus may present with acute confusion. Atypical migraines or migraine variants may present with confusion alone. Meningitis and encephalitis cause alterations of consciousness, often with other signs of infection. Neuroimaging or other diagnostic studies may be required to narrow the differential in these cases.

Pivotal Findings

A patient with confusion is evaluated through a focused history, physical examination, and rapid bedside screening assessment tools. Response to specific therapies (e.g., dextrose, naloxone) may identify critical causes. Additional evaluation may include laboratory testing and diagnostic imaging, which are usually confirmatory of one of a number of suspected conditions. Examples of pivotal historical findings that provide the key to the diagnosis include new medications, infection symptoms, history of head trauma, history of seizures, history of migraines, and time course of symptom onset. Examples of pivotal physical findings include vital sign abnormalities, evidence of trauma, focal neurologic deficits, loss of attention, preservation of orientation, and presence of a toxic syndrome ("toxidrome").

TABLE 13.1 Mnemonic for Altered Mental Status

A	Alcohol or Drug Intoxication; Atypical migraine (confusional migraine)
E	Electrolytes, Environment (hyper/hypothermia), Endocrinopathy, Encephalopathy (Wernicke), Epilepsy
I	Infection (meningitis, encephalitis, sepsis)
O	Overdose, Oxygen (hypoxia, pulmonary embolism)
U	Uremia
T	Trauma, Tumor
I	Insulin (hypoglycemia, DKA, HHS)
P	Poisons, Psychosis
S	Stroke, Status epilepticus (petit mal)

DKA, Diabetic ketoacidosis; *HHS,* hyperosmolar hyperglycemic state.

Symptoms

Confusion is frequently reported by caregivers and family members, rather than by the patient. Families may articulate the complaint as confusion but also may describe incoherent speech, disorientation, hallucinations, visuospatial disturbances, or simply "not being right." Increased anxiety and ill-defined delusions of harmful intent may be present. An essential goal of the history is to determine the baseline level of neurologic function for the particular patient, and when the patient last exhibited their baseline thinking and behavior.

The initial task in evaluating the patient is to define the symptoms and severity of confusion. The specific behaviors that are of concern to the patient or caregivers should be delineated. Often, the family is the most valuable source for information; a physician or other caregiver with an established relationship with the patient also may be helpful. The duration of the confusion, recent changes in medications, and recent illnesses are important points in the clinical history. A history of previous episodes that have resolved spontaneous may be a clue to petit mal status or confusional migraine. Hallucinations may occur in delirium and are classically visual, unlike the auditory hallucinations associated with schizophrenia. A history of medication or substance abuse and any recent changes, especially cessation of benzodiazepines or ethanol, should be sought.

Signs

The general physical examination may suggest a cause of confusion or altered mental status, such as asterixis and jaundice in liver dysfunction, fever and dysuria in urinary tract infection, or injection marks from illicit drug use. New focal neurologic findings suggest a possible mass lesion or stroke, but these would manifest with confusion only if global cortical dysfunction were caused by surrounding cerebral edema or elevated intracranial pressure by severe mass effect. Aphasia, fluent or nonfluent, is a focal sign suggesting a lesion in the dominant cerebral hemisphere. In confusional states, speech may be abnormal and is often incoherent, and the rate of speech may be rapid or slowed. Identification of the elements of a "toxidrome," such as serotonin syndrome, may assist in the identification of a drug effect as the cause of confusion, prompting intervention or consultation. A careful inspection of the skin, including the sacrum and lower leg, may reveal a culprit skin infection.

In some patients, confusion may be subtle, and an informal assessment of mental status and cognitive abilities may fail to detect

TABLE 13.2 Findings to Help Differentiate Between Delirium and Primary Psychiatric Disturbance

Delirium	Psychiatric	Dementia
History		
Acute onset	Onset usually over weeks to months	Onset over months to years
Any age	Onset usually age, 12–40 years	Usually >65, unless early-onset
Mental Status Examination		
Fluctuating level of consciousness	Alert	Usually alert
Disoriented	Oriented	Often disoriented
Attention disturbances	Agitated, anxious	Memory impairment
Hallucinations—visual, tactile	Hallucinations - auditory	Usually absent, except in dementia with Lewy bodies
Cognitive changes	Delusions, illusions	Word-finding difficulties
Physical Examination		
Abnormal vital signs	Normal vital signs	Normal vital signs
Nystagmus	No nystagmus	Neurologic deficits present in vascular dementia
Focal neurologic signs	Purposeful movement	Can show parkinsonism
Signs of trauma	No signs of trauma	No signs of trauma

abnormalities. In contrast to the agitated confused patient, delirium with hypoactive features may be both more common and more easily missed by clinicians. Studies have shown that delirium in older adults often goes unrecognized unless a structured assessment is performed. Casual conversation and basic questions about orientation will not detect confusion or delirium in all patients. A screening test for delirium must go beyond questions of orientation and the apparent ability to carry on a normal conversation.

Simple, rapid tests for diagnosing delirium in the ED have been derived. The algorithm recommended in current guidelines includes screening with a highly sensitive test, such as the Delirium Triage Screen (DTS) performed by emergency personnel, followed by confirmation using a specific test such as the brief Confusion Assessment Method (bCAM) (Fig. 13.1).[3] The DTS assesses level of consciousness using the Richmond Agitation and Sedation Scale (RASS) and assesses attention by a simple question (backward spelling of five-letter word, such as "LUNCH" or "WORLD" with positive result for more than one error). The screening test can be performed in less than 20 seconds, and the bCAM can be performed in less than 2 minutes (Fig. 13.2). Although other tests, including the Quick Confusion Scale (QCS) and the Mini-Mental State Exam (MMSE), have been used to rule out a diagnosis of confusion and delirium in the ED, both of these exams take longer to perform than the combination of the DTS and bCAM, without appreciable gains in accuracy of diagnosis. In comparison with the DTS with RASS and test of attention, a modified RASS scale alone does not have similar sensitivity for delirium.[4]

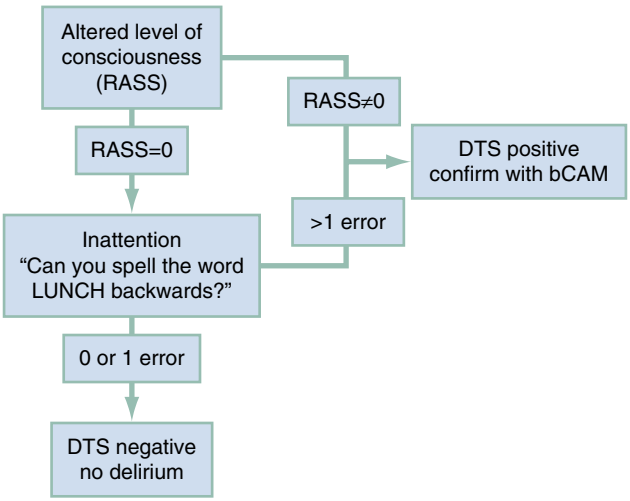

Fig. 13.1 Delirium Triage Screen *(DTS). bCAM,* Brief Confusion Assessment Method; *RASS,* Richmond Agitation and Sedation Scale.

Ancillary Testing

Synthesis of information from the history and physical examination guide the emergency clinician in the choice of laboratory tests most likely to yield valuable diagnostic information. Pulse oximetry may reveal hypoxia, or bedside glucose testing may reveal hypoglycemia or hyperglycemia. In the presence of fever, chest radiography and urinalysis often reveal the source of the infection causing the altered mentation. Serum chemistry tests for liver function may support a clinical diagnosis of hepatic encephalopathy, which does not require elevated serum ammonia level to be present. If there are clinical findings or a history suggestive of thyroid disease, thyroid-stimulating hormone (TSH) testing is indicated. Electrolyte testing can reveal either elevated or decreased sodium and calcium levels. Creatinine level and blood urea nitrogen levels may be elevated in renal failure and uremic encephalopathy.

Electrocardiography is indicated in older patients because myocardial infarction may manifest atypically as confusion. A complete blood count is unlikely to provide useful diagnostic clues unless profound anemia is suspected. White blood cell counts may be elevated, normal, or low, without specificity as to the presence or nature of a disorder. Blood gas testing may demonstrate acid-base disturbance or hypercarbia, although arterial, rather than venous, samples are rarely required unless pulse oximetry is not reliable.

If common and simple tests do not identify a cause, advanced diagnostic testing may be indicated. Selected drug and toxicologic testing may be ordered in this second tier of evaluation, although false-positive and false-negative results can occur. Caution should be applied before attributing mental status changes entirely to substance use in unclear cases. Blood and urine cultures are obtained in the febrile patient when hospital admission is anticipated and a clear infectious source is not evident. Paracentesis or thoracentesis may be appropriate if ascites or a new pleural effusion is present. Cranial computed tomography (CT)

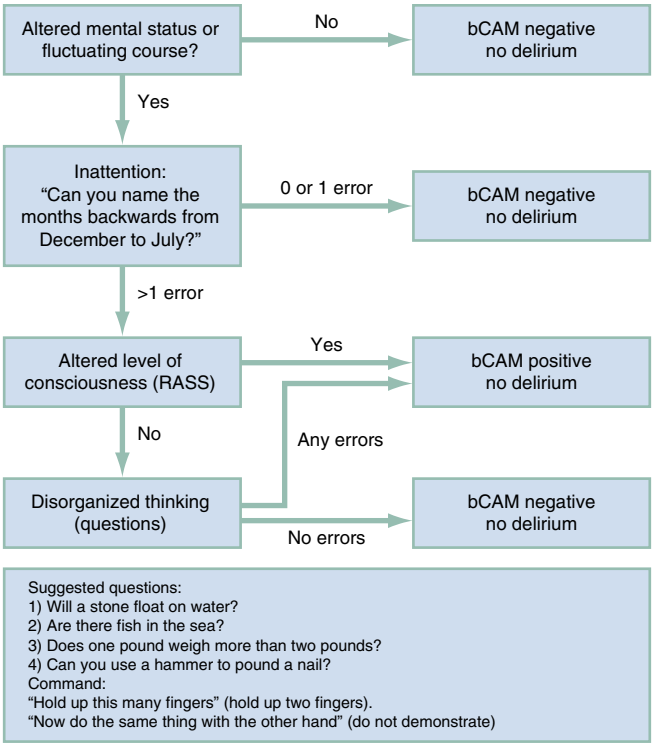

Fig. 13.2 Brief Confusion Assessment Method *(bCAM)*. *RASS,* Richmond Agitation and Sedation Scale.

scanning is often done to screen for CNS lesions in the absence of another identified source of the confusion and in patients with focal neurologic findings on examination. Lumbar puncture may allow discovery or exclusion of CNS infection if no other source has been identified. Cerebrospinal fluid examination may clarify a diagnosis of meningitis, encephalitis, or subarachnoid hemorrhage.

Additional evaluation with magnetic resonance imaging (MRI) or electroencephalography (EEG) can be considered, but the yield of these tests in unselected patients with delirium is unknown. In patients for whom stroke remains a possibility, MRI shows lesions with higher sensitivity than CT, whereas EEG effectively rules out ongoing seizures, but the results are nondiagnostic in many patients.

DIAGNOSTIC ALGORITHM

Certain critical and emergent diagnoses require prompt recognition to reduce morbidity or mortality (see Box 13.1). The diagnosis of confusion relies heavily on the history and physical examination, supplemented by indicated laboratory and imaging tests, for exclusion of common causes (Fig. 13.3).

Concurrent with the ongoing work-up of a patient with confusion, early steps of the management algorithm can be taken to ensure patient and provider safety, facilitate testing, and reverse critical causes (e.g., hypoxia, hypercarbia, hypoglycemia; Fig. 13.4). A complete set of vital signs, including temperature and oxyhemoglobin saturation, and a bedside blood glucose level should be determined promptly. Next, an assessment for delirium is performed using the DTS and bCAM if indicated. If the patient's bCAM score is negative, and if an underlying organic disorder can be ruled out as the cause of presentation, then a more comprehensive cognitive and mental status assessment can be performed, looking for evidence of an underlying dementia or psychiatric disorder.

The history and physical examination search for precipitating factors underlying the onset of the confusional state. Investigations continue until the patient is stabilized, a likely diagnosis is discovered, or consultation and admission are deemed necessary. Focal neurologic findings suggesting stroke, tumor, or some other mass lesion prompt immediate neuroimaging. If the examination is nonfocal, the presence of fever with other abnormal vital signs may lead to the discovery of an infectious cause of the confusion.

Postictal confusion is common in patients with seizures, usually improving within 20 to 30 minutes but lasting several hours in certain cases. If the patient remains unconscious or confused after a seizure, the possibility of ongoing or intermittent seizure activity should be entertained, and neurologic consultation and EEG should be considered. Nonconvulsive status epilepticus (NCSE) and convulsive subtle status epilepticus can present on a spectrum from confusion and abnormal behavior to deep coma, and these diagnoses carry significant morbidity if not diagnosed promptly.

Atypical migraine presentations, specifically confusional migraine, may or may not present with associated headache. If the cause of confusion remains unclear, or if the patient is unable to function safely in their current environment, admission is recommended for observation. Ideally, care is promptly coordinated with consultants and admitting physicians.

EMPIRICAL MANAGEMENT

Oral or intravenous (IV) glucose therapy is indicated if an abnormally low blood glucose level is discovered. In adults, one IV dose of dextrose (commonly 25 g as either a "D50" ampoule of 50 mL of 50% dextrose, or a prepared solution of 250 mL of 10% dextrose or similar product) is commonly administered, and the bedside glucose level is checked again. Thiamine, 100 mg IV, can be given at the time of dextrose administration if Wernicke encephalopathy is a concern. A "banana bag," which may include thiamine, folate, magnesium, and multivitamin for infusion within 1 L of normal saline, probably does not confer additional benefit over IV thiamine alone. Hypoxia and hypercarbia are addressed with noninvasive or invasive ventilation strategies tailored to the patient's presentation. If a "toxidrome" is present, treatment is directed toward the specific toxin.

Confused or agitated patients should be protected from harming themselves or others. Close observation may need to be supplemented by medications or physical restraint. Family members may offer valuable assistance in observing and comforting the patient. Environmental manipulations such as dim lighting or providing a quiet environment may be helpful. Confinement or physical restraint may be necessary at times but should be used with careful adherence to institutional guidelines. Use of physical restraints and bladder catheterization have been associated with prolonged duration of delirium.[5]

No medications are US Food and Drug Administration (FDA) approved for the treatment of delirium. Benzodiazepines can be used for acutely agitated patients requiring sedation for safety, but these agents can prolong delirium in hospitalized patients.

Antipsychotics have been studied extensively for chemical sedation of delirium in acutely ill patients, with conflicting data on efficacy.[6] Given a relatively rapid onset, availability of IV and intramuscular (IM) formulations, and some positive data from intensive care unit (ICU) populations, haloperidol may be the treatment of choice for acute confusion with agitation, at a dose of 1 to 5 mg, repeated up to every 15 minutes IV or every 30 minutes IM as needed to a maximum of 10 to 20 mg/day. Adverse events including QT prolongation, acute dystonic reactions, and tardive dyskinesia, with chronic use, may occur. Haloperidol administration is associated with an increased risk of death in patients with Parkinson's disease, which is why it is contraindicated in this patient population. Atypical antipsychotics, including quetiapine, dosed as 25 to 50 mg per os (PO) 1 to 4 times daily, and olanzapine, dosed 5 to 10 mg IM every 2 to 4 hours to a maximum of 30 mg/day based

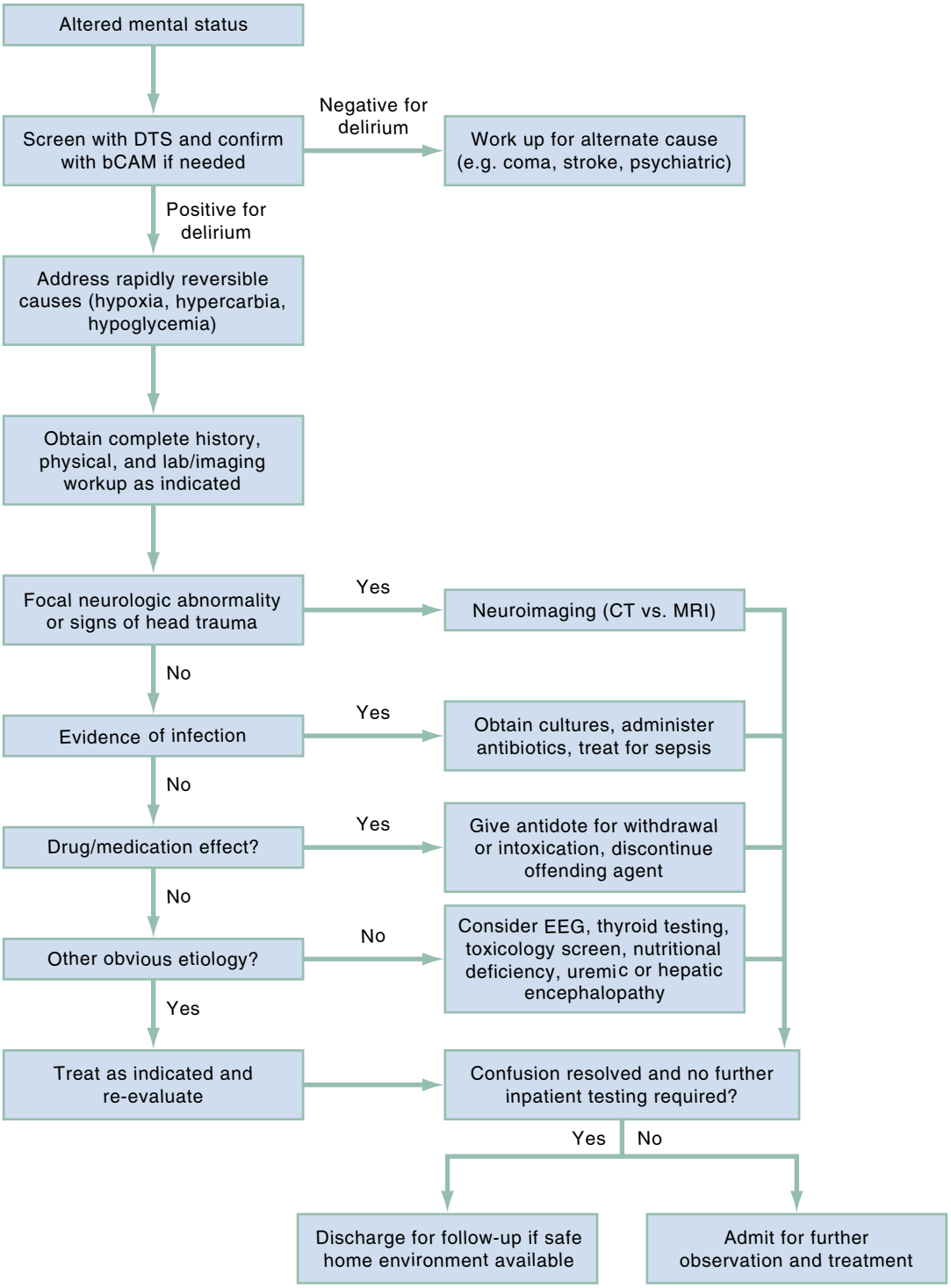

Fig. 13.3 Diagnostic Algorithm for Confusion. *bCAM,* Brief Confusion Assessment Method; *CT,* computed tomography; *DTS,* Delirium Triage Screen; *EEG,* electroencephalography; *MRI,* magnetic resonance imaging.

on patient tolerability, have been studied for treatment of agitation as well, and may be effective in some cases.

Age-appropriate antibiotic treatment for coverage of causes of sepsis tailored to the patient's comorbidities may be considered in ill febrile patients while a definitive evaluation is in progress. If a CNS infection is suspected, age-guided empirical antibiotic treatment without delay for lumbar puncture is recommended.

In patients with history of epilepsy who have uncontrolled seizures or are suspected of being in nonconvulsive status epilepticus, empirical treatment with benzodiazepines may be considered, although this may cause increased somnolence. Other antiepileptics, such as levetiracetam IV, may be considered as well to rapidly achieve therapeutic plasma levels and prevent recurrence of seizures.

Prochlorperazine or other medications to treat migraine headache may be administered if confusional migraine is suspected.

The references for this chapter can be found online at ExpertConsult.com.

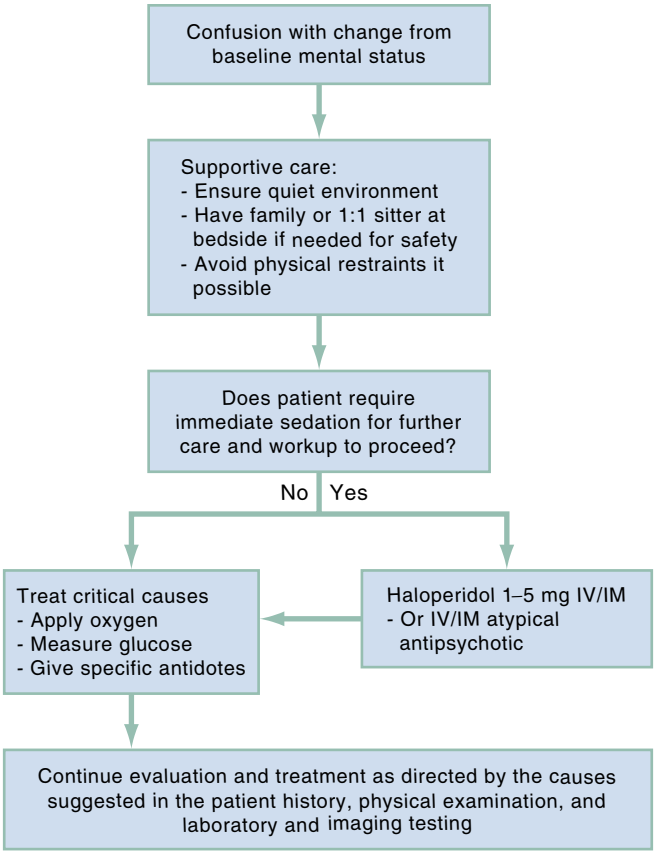

Fig. 13.4 Management Algorithm for Confusion.

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CHAPTER 13: QUESTIONS AND ANSWERS

1. A 70-year-old man with a chief complaint of confusion is brought to the emergency department by his family. Which of the following initial assessments should be included?

a. Blood pressure
b. Pulse oximetry
c. Temperature
d. All of these

Answer: d. Confusion may result from shock states, hypoglycemia, and hypoxia. Evaluation for these conditions is a priority. Confusion is a symptom rather than a medical condition, and reversible causes should be investigated.

2. A variety of brief screening tools may aid in the detection of confusion. All of these tests focus on which cardinal finding of confusion?

a. Attention impairment
b. Decreased level of arousal
c. Disorientation
d. Long-term memory impairment

Answer: a. Inattention is the critical finding for diagnosis of confusion and delirium. All of the screening tools (brief Confusion Assessment Method [bCAM], Mini-Mental State Exam [MMSE], Quick Confusion Scale [QCS]) evaluate this abnormality, although other components of consciousness are tested in some models.

3. A 30-year-old patient is brought to the emergency department for evaluation of odd behavior. Which of the following characteristics might suggest a psychiatric cause for the behavior?

a. Auditory hallucinations
b. Disorientation
c. Fever
d. Visual hallucinations

Answer: a. Auditory hallucinations are common in psychiatric illness. If hallucinations are present in organic causes of delirium, they are usually visual, tactile, or olfactory. Orientation is generally preserved with primary psychiatric disorders unless psychosis or severe impairment is present.

4. Postictal confusion is common in patients with seizures, but if improvement in consciousness does not occur within 20 to 30 minutes after seizure cessation, which of the following conditions should be considered?

a. Electrolyte abnormalities
b. Hypoglycemia
c. Nonconvulsive or subtle status epilepticus
d. All of these

Answer: d. For a patient with a generalized convulsive seizure, termination of the seizure activity is usually **followed** by improvement of mental status within a short period of time. For the patient with persistently altered consciousness or prolonged confusion, consider causes of provoked seizures with prolonged altered mental status or persistence of subtle seizures.

14

Seizures

Carolina Barbosa Maciel and Marie-Carmelle Elie-Turenne

KEY CONCEPTS

- Lifetime seizure incidence reaches up to 10% in the US population and depends upon multiple factors including age, history of epilepsy, structural brain or neurodegenerative disease, genetic predisposition, acuity and severity of metabolic derangements.
- Seizures are the result of an imbalance in the excitation and inhibitory neuronal synapses in the cerebral cortex or limbic system.
- Epilepsy is a condition associated with a lower seizure threshold and an inherently higher risk of recurrent seizures in a lifetime.
- Acute symptomatic seizures occur at, or in close temporal relationship with, a distinct provoked event, and may occur with any toxic or metabolic, structural, ischemic, inflammatory, or infectious insult.
- The initial evaluation of seizure includes the identification of seizure characteristics, duration, and etiology of possible inciting events. Recognizing the occurrence of similar events in the past is key in determining triggers and distinguishing the management priorities between patients with epilepsy or with acute symptomatic seizures.
- The majority of seizures will cease spontaneously within 5 minutes; however, when physiologic seizure termination pathways are overwhelmed resulting in status epilepticus, characterized by the persistent and exponential refractory response to abortive seizure therapies. The magnitude of treatment refractoriness is time dependent; therefore a prompt stepwise escalation of therapies aiming at seizure termination is warranted.
- Prompt identification and, whenever possible, reversal of seizure triggers are priorities. In particular, assessing for and correcting hypoglycemia should occur as early as possible.
- Initial nonpharmacologic interventions include ensuring physical safety of patients with seizures to prevent traumatic injuries and aspiration. During convulsions, focusing on lateral decubitus positioning and suctioning of oral cavity are important to prevent aspiration; the use of intraoral devices may lead to trauma without additional benefit.
- Pharmacologic interventions center on the timely and dose-appropriate administration of parenteral benzodiazepines, which are first-line therapy (i.e., lorazepam intravenous [IV] up to 0.1 mg/kg in divided doses, or midazolam IV/intramuscular [IM]/intranasal [IN] 5 to 10 mg).
- In pregnant patients, eclampsia should be considered the underlying etiology of de novo seizures after 20 weeks of gestational age and up to 8 weeks postpartum. Clinical evaluation should focus on evaluating for associated symptoms (e.g., headache, visual abnormalities and confusion), as well as focal neurologic deficits. Neuroimaging should be considered if neurologic deficits persist, prolonged loss of consciousness or encephalopathy. IV magnesium 4 to 6 g is first-line therapy in the pregnant patient experiencing new-onset seizures.
- During the postictal state, key priorities in management include ensuring airway patency with optimal positioning in those with alteration of consciousness, evaluation for nonconvulsive seizures and acute brain injuries or inciting factors that warrant further definitive treatment.
- Nonconvulsive status epilepticus can only be diagnosed with electroencephalography (EEG) monitoring and should be considered in any patient with prolonged, unexplained altered mental status. Patients at higher risk include those with poorly controlled epilepsy, acute brain injury, sepsis, and intoxication.
- A patient with new-onset seizures with a normal neurologic examination who returns to baseline mental status and does not have comorbid disease does not require diagnostic testing beyond, serum glucose and sodium levels, a pregnancy test (in women), and a noncontrast head computed tomography (CT); a toxicologic screen is considered in select patients.

FOUNDATIONS

Epidemiology

Seizures represent distressful and physically traumatic events that have the potential for lifelong social consequences and challenges to quality of life. The risk for an unprovoked or acute symptomatic seizure is approximately 8% to 10%; however, only 3%, or 1 in 26 Americans, will ultimately be diagnosed with epilepsy at some point in their lifetime. Up to one in four seizures evaluated in the emergency department (ED) represent first-time seizures.[1]

The incidence and risk of seizures are influenced by many factors, including age; history and type of epilepsy, structural brain disease, neurodegenerative diseases; presence of renal or hepatic disease; metabolic derangements; and exposure to triggers. Patients presenting to the ED with seizures have a bimodal distribution in terms of age, with the highest incidence among infants and individuals older than 75 years old. This is explained by the high prevalence of febrile seizures in infants and structural brain damage in elders.

Up to 45% of adults presenting with a first unprovoked seizure will experience another within 2 years, most occurring in the first year.[2] The risk is higher with known brain lesions, neuroimaging or electroencephalography (EEG) abnormalities, or nocturnal seizures[2]; the latter are associated with epilepsy syndromes. Up to 50% of patients with epilepsy have recurrent seizures despite initiation of therapy. Human immunodeficiency virus (HIV)-positive patients have an increased risk of seizures, and two-thirds of those who present with new-onset seizures experience recurrence.[3]

Etiologies underlying seizure events are diverse; importantly, the etiology plays a role in the risk for seizure recurrence and the progression to status epilepticus. For a comprehensive list of etiologies of

seizures and status epilepticus according to type of insult and neurologic process refer to Chapter 88 (Box 88.1), and for pediatric considerations, refer to Chapter 169.

Pathophysiology

Seizures are the clinical manifestation of increased excitation or impaired inhibition of neurons that result in the abnormal firing and synchronization of neighboring neurons. This *recruitment* is complex and follows neural networks that may be deep and cross the midline of the brain. Marked alteration of consciousness ensues when seizures propagate diffusely to the bilateral cortex or diencephalon or to deeper structures involving the reticular activating system in the brainstem. Increased inhibition, effect of medications, and neuronal exhaustion mediate postictal states, which reflect transient neurologic deficits that may include alteration of consciousness, language, sensory, motor deficits (Todd paralysis), and/or abnormal emotional states. The duration of a postictal state ranges from minutes to a few hours, with the majority lasting less than 1 hour. Longer postictal states are associated with generalized convulsive seizures, duration of the seizure, and older age.[4]

Seizures are typically self-limited. A combination of mechanisms ultimately leads to their termination including reflex inhibition, neuronal exhaustion, or alteration of the local balance of neurotransmitters between the excitatory acetylcholine and glutamate with the inhibitory γ-aminobutyric acid (GABA). However, when these mechanisms fail, progression to status epilepticus ensues, leading to a cascade of changes within the brain: a decrease in $GABA_A$ receptor subunits as these migrate inside cells and a parallel increase in the excitatory *N*-methyl-D-aspartic acid (NMDA) receptors occur; these events are time sensitive and underscore the pathophysiology of treatment refractoriness and benzodiazepine resistance ($GABA_A$ mediated). The International League Against Epilepsy put forth operational time definitions of status epilepticus according to different seizure types that reflect: (1) likelihood of continued seizure activity due to failure of abortive mechanisms and (2) likelihood of secondary long-term sequelae (Table 14.1).[5] This time distinction originated from the notion that different seizure types may have different consequences and distinct pathophysiologic mechanisms. The understanding that seizure types may have different presentations and associated sequelae lays the foundation for individualized therapeutic algorithms according to the type of status epilepticus. For example, the clinical threshold for escalating antiseizure therapies should be lower in seizure patterns associated with high morbidity: much lower in convulsive generalized status epilepticus than in focal nonconvulsive status epilepticus.

TABLE 14.1 Classification of Status Epilepticus According to Time Domains.[5]

Type of Status Epilepticus	Duration of Time (Further Seizure Activity Likely)	Duration of Time (Long-term Sequelae Likely)
Tonic-clonic	5 min	30 min
Focal with impaired awareness	10 min	>60 min
Absence	10–15 min	Unknown

DIAGNOSTIC APPROACH

Pivotal Findings

History and physical findings assist in differentiating seizure from other acute medical conditions. They help identify triggers, which will heavily influence decisions on the need for secondary prophylaxis and guide the selection of antiseizure drug according to the specific seizure type.

Clinical manifestations of seizures vary widely depending upon the region of the brain affected; they may range from subtle cognitive and/or mental status changes to coma, apneic spells, sensory and motor manifestations, and dysautonomia. Seizures can be classified according to their semiology into types, duration, refractoriness to treatment, and etiology. The classification of seizure types has therapeutic implications and facilitate communication between providers.

A revised classification of seizure types by the International League Against Epilepsy provides an operational framework that relies on the clinical manifestations of seizures (Fig. 14.1).[6] The first classification branch underscores the importance of the seizure onset: focal which include those with secondary generalization (i.e., focal to bilateral tonic-clonic), generalized, or unknown; the latter is reserved for cases when the onset is not witnessed. The terms "complex seizures" or "focal dyscognitive seizures" traditionally used to reflect impairment of consciousness have been replaced by the term "focal seizures with impaired awareness." Note that patients may be immobile during a focal aware seizure, so long as they retain awareness of self and the environment. Further specification of motor onset or nonmotor onset centers on the descriptive assessment of the first prominent sign or symptom in the seizure. Automatisms usually include oral or finger stereotypic movements such as lip smacking, yawning, repetitive vocalizations, or picking at sheets or clothing; these automatisms can be complex and often arise from a frontal seizure focus. Seizures impairing distinct cognitive domains such as language (e.g., aphasia) or abnormal thoughts and perceptions (e.g., dèjá vu, hallucinations, illusions, or perceptual distortions)—often referred to as "auras"—are now termed "cognitive seizures." These cognitive seizures commonly arise from the orbital frontal region manifesting as olfactory hallucinations, or from the temporal lobe, which classically manifests as epigastric rising sensation, auditory hallucinations, and increased fear or impending doom.

The time criteria for status epilepticus are based on duration of seizures and depend on seizure type (see Table 14.1). Other classifications of status epilepticus, which include several different categorizations according to semiology, etiology, age, and EEG correlates, are reported in Chapter 88 (Table 88.1 and Box 88.2).

History Taking and Physical Exam

The ramifications of a seizure diagnosis have important direct consequences for patients, which include restriction of certain activities (e.g., driving, swimming unsupervised, and operation of heavy machinery) and therapeutic implications. The first diagnostic task in the ED is to determine whether the patient has actually experienced an epileptic event and if similar events have occurred in the past. Obtaining a detailed description of the sequence of events leading to the seizure-like activity and the semiology of the episode is paramount.

In general, ictal events have five properties:

1. *Abrupt onset.* Identify immediate preceding events and whether auras, which are focal seizures, were present (e.g., perception alterations: visual, smell, tactile, auditory, gastric heave, impending doom, anxiety, and irrational fear). Check for immediate triggers, such as sleep deprivation, missed medications, new medications, alcohol or substance use, infections, or other inciting events.
2. *Brief duration.* Seizures rarely last longer than 60 to 120 seconds (except in status epilepticus), although bystanders may overestimate their duration.
3. *Alteration of consciousness.* Generalized seizures are characterized by loss of consciousness, whereas focal seizures may be accompanied by an alteration in consciousness.

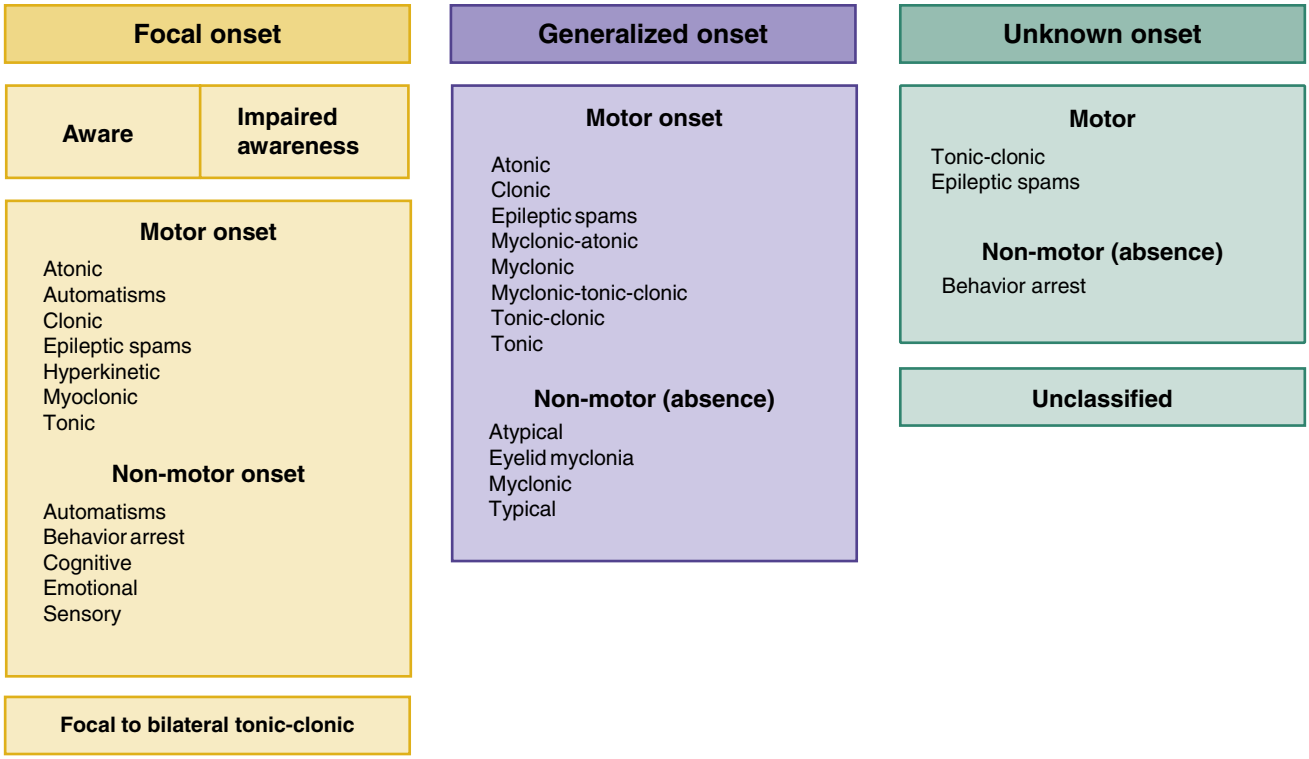

Fig. 14.1 Classification of Seizure Types (Extended Version).[6]

4. *Purposeless, stereotypic, and nonsuppressible.* Automatisms and undirected tonic-clonic movements are common in ictal events; if witnessed, a gentle attempt to suppress clonic activity (i.e., brief careful restraint of a convulsing limb in an attempt to extinguish movement) helps differentiate tremors and other nonepileptic convulsive events from seizures. Tonic-clonic movements are often rhythmic and if involving other body parts, synchronous. Dystonic posturing in tonic seizures is also common; they are usually asymmetric when bilateral and distinct from extensor or flexor posturing associated with neurologic emergencies.
5. *A postictal state of variable duration, which correlates with the duration of the preceding seizure.* The transient neurologic deficit may be sensory, motor, visual, cognitive, emotional, or related to consciousness. In general, the postictal state occurs with all seizure types, except absence. Postictal periods following seizures are typically transient (length-dependent according to seizure duration); the acute encephalopathic state may include lethargy, confusion, and impaired recollection of events.

Seizures may also be accompanied by transient cardinal systemic signs of sympathetic stimulation, such as tachycardia, hypertension, or tachypnea. Autonomic discharges and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with aspiration risk), lateral tongue biting, and airway compromise in the peri-ictal period. All of these signs are helpful discriminators in the differential evaluation of seizure-like episodes, although the presence or absence of these findings neither confirms nor excludes seizure occurrence. Evidence of physical injury should be thoroughly investigated because these may be occult in the altered patient.

Once a seizure is suspected, determining the underlying trigger is imperative. This should be followed by an inquiry regarding prior seizure history. New-onset seizures or a change in seizure patterns in those with known epilepsy may be the primary manifestation of serious underlying diseases and should prompt a thorough evaluation. If there is a documented history of seizures, ED evaluation may be limited to identifying precipitants and obtaining an antiseizure drug level, when applicable/available as the most common etiology is poor compliance or adjustment in regimen leading to subtherapeutic levels. The history should focus on clinical factors known to decrease the seizure threshold, such as recent illness or trauma, drug or alcohol use, sleep deprivation, potential adverse drug-drug interactions with antiseizure drugs, medication noncompliance, recent change in dosing regimens, or change in ictal pattern or characteristics. In women of reproductive age with epilepsy, catamenial exacerbation of seizures is extremely common. Furthermore, pregnancy can affect clearance of antiseizure drugs, leading to subtherapeutic levels. In pregnant women with and without a history of epilepsy, eclampsia must be considered.

After the seizure activity has ceased, resting vital signs are evaluated. Fever and underlying infection can cause seizures, although there may be a low-grade temperature elevation immediately after a generalized convulsive seizure. Tachypnea, tachycardia, fever, or an abnormal blood pressure that persists beyond the immediate postictal period may indicate toxic exposure, hypoxia, infection, or an acute central nervous system lesion. Pertinent physical findings may include nuchal rigidity, stigmata of substance abuse, lymphadenopathy suggestive of HIV disease or malignancy, dysmorphic features, or skin lesions. The examination should also focus on potential adverse sequelae of convulsive seizures, such as head trauma, oral and tongue injury, posterior shoulder dislocation, or back pain. (See Table 88.3.)

Finally, a complete neurologic examination is performed. A persistent focal deficit after a seizure (e.g., Todd paralysis) often indicates the focal origin of the event but also may suggest underlying structural injury, such as ischemic or hemorrhagic strokes. Approximately half of patients with convulsive generalized status epilepticus have subsequent nonconvulsive seizures when placed on continuous EEG monitoring, and more than 15% will be in nonconvulsive status epilepticus. The patient with persistent altered consciousness should be carefully examined for signs of ongoing subtle convulsive or nonconvulsive seizures, such as abnormal eye movements and facial myoclonus. The

higher-risk population for ongoing nonconvulsive status epilepticus include those with acute or remote brain injury (including prior violations of the intracranial cavity with craniotomies), toxic exposure, sepsis, or renal or liver failure.

ANCILLARY TESTING

Laboratory Testing

Women of reproductive age should be tested for pregnancy.

The serum glucose level should be determined in every seizing or postictal patient because hypoglycemia is a common metabolic cause of provoked seizures. Ictal activity of any semiology can occur at a plasma glucose level less than 45 mg/dL, although some patients may have a seizure at higher levels. Prolonged seizures can also *cause* hypoglycemia. Seizures that do not cease after correction of low blood glucose deserve further evaluation and treatment for alternative causes.

Patients with prolonged generalized convulsions (e.g., >2 minutes) should have creatine kinase and lactic acid tested to assess for rhabdomyolysis and acute metabolic acidosis, respectively; prolonged convulsions or tonic posturing without increased lactic acid are less likely to be epileptic in nature. Presence of a lactic acidosis that resolves on subsequent ED testing supports a seizure diagnosis. In epilepsy patients with unexplained increase in seizure frequency and a stable antiseizure regimen, infections such as common viral illness should be considered as precipitating events. Patients with a dramatic increase in the severity of seizures or those with an abnormal neurologic examination should undergo a more thorough laboratory assessment.

In patients with advanced age or comorbidities or who are ill in appearance, the diagnostic evaluation should be expanded to include a basic or comprehensive metabolic panel to assess metabolic derangements that may trigger seizures. Sodium, calcium, and magnesium are all associated with cell membrane stabilization; most commonly, hyponatremia and hypocalcemia are triggers of seizures. Because magnesium helps stabilize the neuronal cell membrane, hypomagnesemia is a common finding in adult and children presenting with seizures in several settings. Keep in mind that total body magnesium levels may not be reflected by serum levels. Hypomagnesemia must be considered and may warrant empiric treatment in cases of malnutrition or chronic alcoholism, for example. Patients with lower serum bicarbonate on basic metabolic panel may benefit from blood gas analysis and lactic acid testing. Anion gap metabolic acidosis is commonly secondary to lactic acidosis in convulsive seizures; acidosis is typically transient with lactic acid levels declining within the first hour after convulsions cease. Patients with prolonged nonepileptic convulsions often have normal lactic acid levels and white blood cell count. Persistent lactic acidosis or other anion gap acidosis suggests an underlying process, including sepsis, ketosis (alcoholic or diabetic), or poisoning (methanol, iron, isoniazid, ethylene glycol, salicylates, carbon monoxide, or cyanide). Liver enzyme (i.e., AST and ALT) abnormalities may indicate the presence of chronic disease or underlying hepatic-mediated metabolic derangements. Patients with known or suspected history of liver disease or those that take valproic acid should have ammonia tested given the heightened risk for hyperammonemia, which further increases the risk for seizures and will impact therapeutic decisions on antiseizure regimen. Routine testing of prolactin is not indicated given its relative lack of sensitivity and specificity for seizures.

Proposed cutoff laboratory values for acute symptomatic seizures and those values that can be interpreted as thresholds of metabolic derangements for lowering the seizure threshold can be found in Chapter 88 (Box 88.3).

Patients with or without history of epilepsy who are on antiseizure medications for any indication (i.e., seizure prophylaxis, mood stabilization, anxiety, and/or adjunctive psychiatric treatment) should have levels obtained, as available. The turnaround time for antiseizure drug level results varies widely; phenytoin, phenobarbital, valproic acid, and carbamazepine are the most commonly available levels with the fastest turnaround times and well-established therapeutic ranges. Lamotrigine, topiramate, and oxcarbazepine have therapeutic ranges established, but prolonged turnaround times reaching several days makes their assessment impractical in the emergent setting. Levetiracetam level has a broad therapeutic range with unclear ideal targets and variable turnaround times based on institution but may still prove instrumental in confirming compliance, particularly when patients have repeated visits to the ED with similar presentations who report not missing doses. Free levels of antiseizure drugs that are highly protein bound (e.g., valproic acid and phenytoin) are more accurate, and widely available online calculators provide a correction of total levels according to albumin.

Patients who are on medications that have epileptogenic potential (e.g., lithium) should have the levels of these drugs tested, whenever available. Directed toxicology screens with blood or urine samples should be performed if substance abuse (particularly cocaine, amphetamines, and other sympathomimetic agents) or overdose of aspirin or acetaminophen is suspected. However, many drugs of abuse (e.g., synthetic marijuana) and medications (e.g., baclofen, bupropion) that may be implicated in the etiology of seizures do not have a widely available testing method, and so, negative routine toxicology screens should be interpreted with caution. Furthermore, positive urine toxicologic screen for sympathomimetic agents are not confirmatory of the etiology of seizures in all cases because these substances can be detected in specimens for several days to weeks after the exposure. However, the screen may suggest a possible etiology and may help with future medical and psychiatric disposition.

Reactive leukocytosis of varying magnitude is very common after convulsive seizures; there are no thresholds of elevated white blood cell count that may definitively suggest a concomitant infectious process. Febrile patients should be evaluated for the source of the fever, including consideration of lumbar puncture and respiratory viral testing (i.e., influenza, respiratory syncytial virus). Lumbar puncture should also be considered in immunocompromised patients and in those presenting with acute headache concerning for subarachnoid hemorrhage, meningismus, or persistent altered mental status. Pleocytosis in cerebrospinal fluid may indicate infectious or autoimmune etiologies.

Imaging Studies

Neuroimaging is recommended by the American Academy of Neurology in adults presenting with new-onset seizures; it can be performed in the ED or at a follow-up in those who are back to a normal neurologic baseline and do not have headache. Most patients with a history of epilepsy, particularly in those who return to baseline, do not require neuroimaging. Box 14.1 summarizes characteristics of patients presenting with seizures that should prompt consideration for neuroimaging.

Headache is occasionally a postictal symptom. There are no specific characteristics pertaining to the quality of postictal headaches. Severe headache, thunderclap nature (reaching maximum severity from onset within seconds), associated neurologic deficits, altered mental status, meningismus, and/or fever should prompt additional evaluation with computed tomography (CT) of head. If there is clinical suspicion for meningoencephalitis or subarachnoid hemorrhage, after a nondiagnostic CT, lumbar puncture must be considered as part of the diagnostic management. Patients with a history of malignancy, immunosuppression, use of systemic anticoagulation, or history of prior intracranial hemorrhage; who are older than 40 years; or in whom trauma is suspected should have consideration for CT in the ED.

BOX 14.1 Characteristics Prompting Consideration of Neuroimaging in a Patient With Seizures

Age >40 years
Coma
Immunocompromised state
Clot disorder (hypercoagulability or hypocoagulability)
History of intracranial hemorrhage
History of malignancy
Severe, thunderclap headache
Status epilepticus, convulsive and nonconvulsive, of unclear etiology
Stigmata of neurocutaneous syndromes
Suspected trauma

CT perfusion, a contrast-enhanced modality with arterial phase and postsignal processing of imaging, can be particularly helpful in the evaluation of transient neurologic deficits consistent with Todd paralysis; in these cases, acute ischemic stroke is high in the differential and can be reliably detected by this modality.[7] However, there are no specific CT perfusion findings in seizure patients because their perfusion status is dependent on the temporal relationship of seizure and time of imaging acquisition. If magnetic resonance imaging (MRI) is readily available, it can be used instead of CT in most patients as long as the patient is stable to lay flat for a prolonged period: It has increased sensitivity for subtle structural lesions and adds to the diagnostic yield in patients with recurrent seizures and in those with focal abnormal EEG. When MRI is obtained in the work-up of seizures, the addition of gadolinium, T2 thin coronal views through hippocampus and limbic structures increases its diagnostic yield. Reversible cortical restricted diffusion is the typical signature of prolonged seizures on MRI (see Chapter 88, Fig. 88.1). For pediatric considerations, refer to Chapter 169); in brief, emergent neuroimaging in children presenting with seizures is indicated in the setting of an abnormal neurologic exam or medical or surgical comorbidities and in those younger than 3 years with focal or prolonged seizures.

Electroencephalography

EEG is useful to diagnose nonconvulsive status epilepticus, monitor seizure activity, guide third-line therapies after intubation and neuromuscular blockade, and help differentiate seizures from other nonepileptic presentations. ED-based EEG may assist with the prompt diagnosis of epilepsy in patients with new-onset seizures and decision making on the initiation of secondary seizure prophylaxis; however, studies demonstrating its cost-effectiveness are lacking.[1] New devices with limited montage or assembly that can be performed at the point of care in select cases may be of value and expedite EEG in the emergent setting but are not routinely recommended.

Cardiac Monitoring

Patients with a history of cardiac disease, with preceding or ongoing cardiac symptoms, and who continue to seize may benefit from cardiac monitoring. The same is true of patients suspected of overdose. An electrocardiogram (ECG) is also an early screen for drug toxicity. Tricyclic cardiotoxicity may manifest as a QRS complex lasting more than 0.1 second or a rightward shift of the terminal 40 ms of the frontal plane QRS complex (a prominent R wave in lead aV_R). The ECG can also identify a prolonged QT, a delta wave, Brugada pattern, or heart block, which might contribute further clues to the seizure etiology. Electrocardiographic changes are common in the peri-ictal period and range from sinus tachycardia to more concerning features such as ST segment depression and T wave inversion. Prolongation of intervals on ECG is common in the peri-ictal period, which may challenge differentiating seizures from a primary cardiac related etiology of syncope.[8]

BOX 14.2 Differential Diagnoses for Seizures

The following are diagnoses with presentations that can be difficult to differentiate from seizure activity.

Cardiac
Vasodepressive (vagal) syncope
Orthostatic syncope
Cardiogenic syncope

Neurologic
Stroke, transient ischemic attack (in particular, limb shaking TIA)
Complicated migraine
Movement disorders: chorea, dystonia, subcortical myoclonus, tremors
Parasomnias
Extensor or flexor posturing from herniation syndromes

Toxicologic
Intoxication, inebriation
Over sedation, over analgesia
Extrapyramidal symptoms

Metabolic
Hypoglycemia, hyperglycemia
Thyrotoxicosis
Delirium tremens

Infectious
Meningoencephalitis
Tetanus

Psychiatric
Nonepileptic spells
Conversion disorder
Panic attacks
Cataplexy

DIFFERENTIAL DIAGNOSES

The differential diagnoses to consider when evaluating for seizure are listed in Box 14.2. In all of these conditions, clarification of associated signs and symptoms (e.g., loss of sphincter control, postictal state, tongue biting, inability to suppress movements), exam (e.g., nystagmus, delayed pupillary response, hyperreflexia, abnormal plantar reflex), and the circumstances of the event (i.e., when and where the event occurred, the precipitating events, positioning, type of movements) are instrumental in discerning whether the event is epileptic or not in nature. In addition, several of these conditions may overlap with seizures because they are associated with seizure triggers, or even represent precipitating events themselves. Transient cerebral ischemia (focal or global) can be associated with nonepileptic convulsive symptoms such as convulsive syncope or limb-shaking transient ischemic attacks. A variety of movement disorders, including those that are transient and associated with toxins, can lead to tonic, myoclonic, or clonic symptoms that may be hard to differentiate from seizures. Migraine with an aura can be confused with nonconvulsive seizures given the positive visual phenomenon. However,

migraine has a gradual or protracted temporal evolution prior to developing a peak of symptoms over several minutes followed by gradual resolution; these are key distinctive features from occipital seizures, in which such evolution is much faster in the order of seconds to a few minutes. Furthermore, these patients will almost always have a history of migraine, often with similar presentation.

Nonepileptic spells, or pseudoseizures/psychogenic spells, are events that mimic seizures and status epilepticus, commonly reaching 5 minutes or longer.[9] Patients inadvertently medicated with high doses of benzodiazepine in an attempt to treat these seizure mimics must be monitored for respiratory failure and need for support of ventilation.[10] In fact, in the Established Status Epilepticus Treatment Trial (ESETT) trial that investigated second-line therapies for convulsive status epilepticus, more than 10% of enrolled patients were ultimately diagnosed with nonepileptic spells.[11] To complicate matters further, up to one-third of patients who have known epilepsy may also have nonepileptic spells. Features consistent with nonepileptic etiology of convulsions include prolonged duration of spells (at times reaching well over 20 minutes), a higher prevalence of "stop-and-go" pattern of convulsions, forward pelvic thrusting, horizontal head shaking and bilateral asynchronous convulsions while maintaining eyes closed, disproportionally shorter postictal period to duration of spells, avoidance of noxious stimuli, and preserved recollection of events. On laboratory testing, patients with psychogenic nonepileptic spells often lack reactive leukocytosis and lactic acidosis, which are nearly universal in those with prolonged generalized convulsive seizures or status epilepticus.

DIAGNOSTIC ALGORITHM

In patients suspected of having had a seizure, the first step is to determine whether the history from the patient or bystander(s) supports the diagnosis. Critical causes of seizures with specialized treatments include eclampsia, toxic ingestion (e.g., isoniazid, lithium, tricyclic antidepressants), hypoglycemia, hyponatremia, and increased intracranial pressure. Box 14.3 presents the critical and emergent diagnoses that must be considered.

Fig. 14.2 presents a practical framework for the approach of patients with seizures. Regardless of prior history of seizures, directed questions should be made to characterize event. In those with history of epilepsy, information should be gathered on the seizure disorder and typical events. Information regarding the onset, presence of aura, type of seizure, and duration of ictal and postictal periods is key to determining whether the seizure is similar to previous seizures. If the seizure appears typical for the patient, the emergency clinician should identify the antiseizure drug regimen and inquire about potential triggers that can lower the seizure threshold, such as sleep deprivation, infections, and new or modified medications. If the patient is taking an antiseizure drug for which a serum level can be measured (e.g., phenytoin, carbamazepine, valproic acid) and found to be subtherapeutic, then additional medication can be given via the intravenous (IV) or oral (PO) route as a bridge. The patient can then be discharged once recovered to their previous neurologic baseline, with outpatient evaluation by a neurologist or primary care physician.

In the absence of prior seizure history, the diagnostic approach is directed to assess for potential precipitants, such as toxic ingestions, and history or physical exam findings of a process that warrants further evaluation and specific treatment, such as immunosuppression, pregnancy, or head trauma.

Patients who arrive at the ED with ongoing seizure activity or who experience recurrent seizures without returning to baseline are in status epilepticus and require antiseizure therapy and cardiac monitoring. There should be a low threshold for obtaining a bedside EEG, especially if the postictal period is prolonged or automatisms are noted.

BOX 14.3 Critical and Emergent Diagnoses to Consider in a Patient With Seizures

Critical Diagnoses

Status epilepticus, convulsive and nonconvulsive, regardless of cause

Seizures with specialized treatments

- Eclampsia
- Toxic ingestion (e.g., isoniazid, lithium, tricyclic antidepressants)
- Hypoglycemia
- Hyponatremia, hypocalcemia
- Increased intracranial pressure

Emergent Diagnoses

Infection

Acute brain injury: ischemic or hemorrhagic strokes, traumatic brain injury, cerebral venous thrombosis

Serious mimics of seizure activity (e.g., cardiogenic syncope)

EMPIRIC MANAGEMENT

The initial priorities in the management of the actively seizing patient include the prompt recognition and treatment of hypoxia, hypotension, and hypoglycemia and the initiation of pharmacologic treatment when indicated (Fig. 14.3); there is overlap between prehospital and ED settings in these interventions.

The patient should be placed in a monitored setting, and airway should be assessed and secured if respiratory failure ensues and cannot be supported by cessation of seizure and bag-mask ventilation. The patient should be protected from injury related to uncontrollable convulsions and, if possible, placed in a lateral decubitus position to reduce aspiration risk. Intermittent suctioning of oral secretions must be performed with caution. Nasopharyngeal airway devices may help with transient obstruction that may occur in the peri-ictal period, but oropharyngeal devices should be avoided because they may induce gagging and vomiting and may damage the teeth or tongue. Oxygen may be administered to supplement immediate oxygenation and in preparation for possible rapid sequence intubation.

The majority of seizures will cease spontaneously, and thus abortive treatments are recommended for seizures lasting greater than 5 minutes or when airway or hemodynamic compromise is noted. In the prehospital and emergent setting, it may be difficult to ascertain the exact duration of seizure events; patients who are still seizing by the time of evaluation should be suspected to be in status epilepticus, and the management priority should be the rapid administration of a benzodiazepine. Well-designed trials have shown the efficacy and safety of early administration of benzodiazepines during prehospital care. Studies, specifically in children, have demonstrated that delays in first-line benzodiazepine treatment have been associated with increased mortality, longer seizure duration, and hemodynamic compromise.[12] Intramuscular (IM) midazolam can be quickly administered; there is evidence that it is superior to IV lorazepam in adults and noninferior in children. Based on ease of administration and comparable outcome to IV lorazepam, we recommend IM midazolam 0.2 mg/kg as the first-line intervention in field management of status epilepticus and IV lorazepam 0.1 mg/kg whenever access is established. We do not recommend the use of rectal diazepam in managing status epilepticus because absorption is erratic and not as dependable as other routes. Intranasal formulations of both midazolam and diazepam have recently been approved by the US Food and Drug Administration (FDA); however, available data are insufficient to make

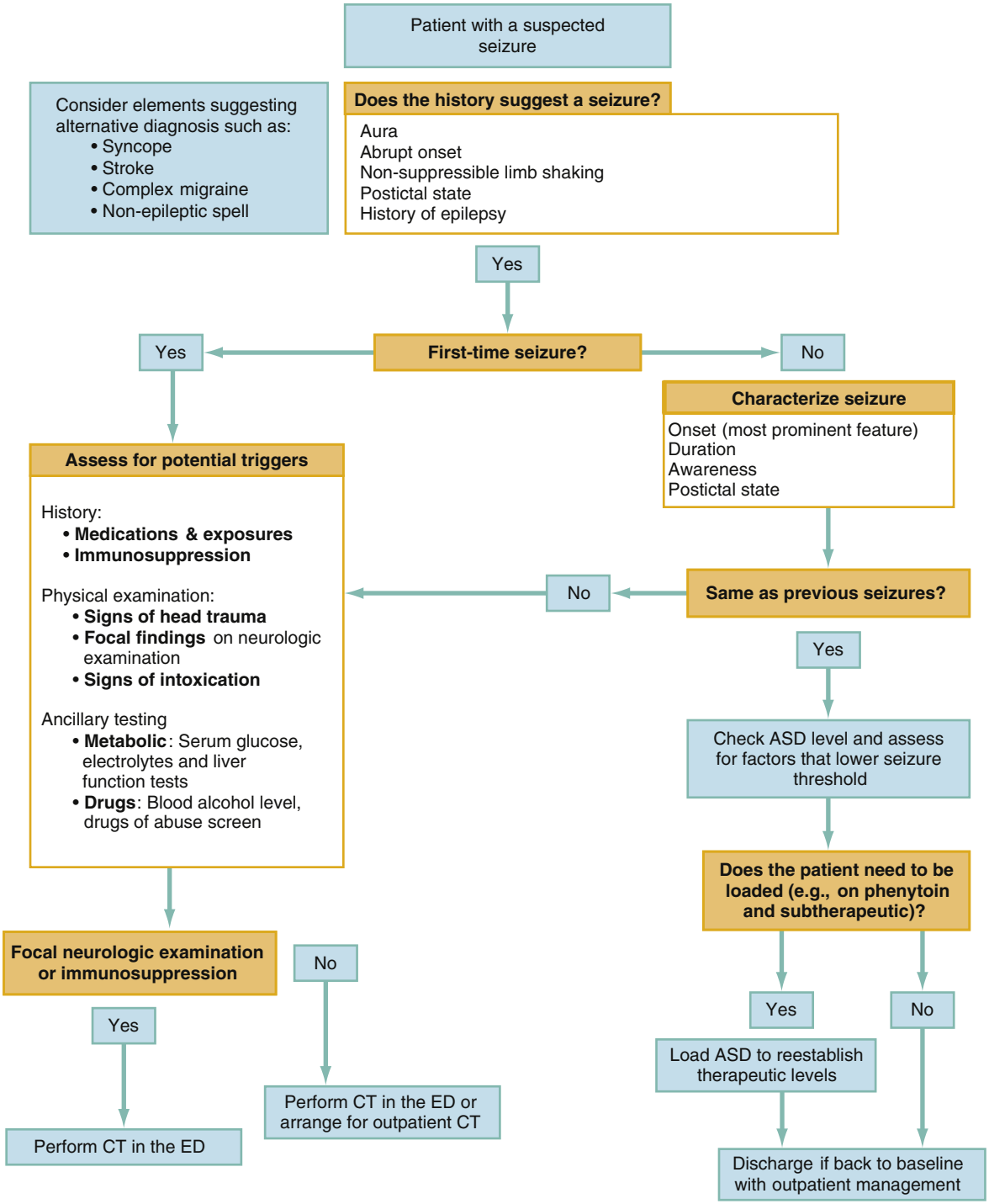

Fig. 14.2 Initial Approach to Patients With Suspected Seizure. *ASD*, Antiseizure drug; *CT*, computed tomography; *ED*, emergency department.

recommendations regarding their use in the ED. We recommend to repeat dosing of first-line therapy (i.e., midazolam or lorazepam) prior to moving on to second-line therapies.[13,14]

Among second-line therapies for convulsive status epilepticus, the best studied so far include valproic acid, phenytoin, and levetiracetam; when appropriately dosed, they have similar efficacy.[11] Table 14.2 provides details on dosing and pharmacologic considerations on the most commonly used medications according to the tier of intervention (medications are listed in alphabetic order; agent selection of second- and third-line therapy should be individualized). If seizures persist, endotracheal intubation and the consideration of third-line therapies are indicated. In patients at risk for hemodynamic compromise, the maintenance of cerebrovascular perfusion is paramount; and so the administration of fluid resuscitation and vasoactive support should be considered in the setting of administering parenteral antiepileptic medications that may compound the risk of hypotension in the setting of rapid sequence intubation (i.e., propofol, pentobarbital, ketamine, midazolam).

Refractory seizures require careful reassessment to ascertain underlying or occult processes, such as acute brain injury, drug overdose, and

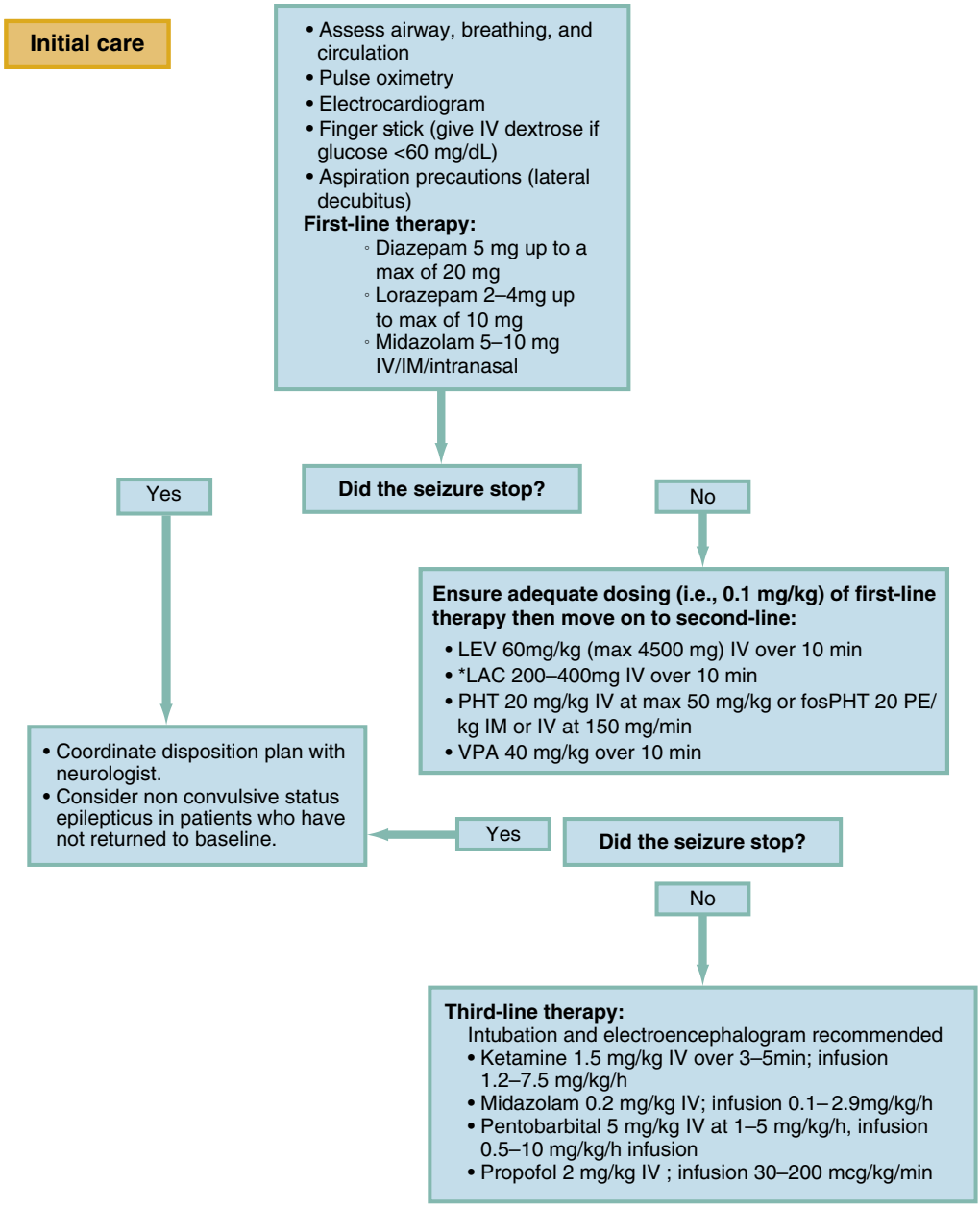

Fig. 14.3 Empiric Management of Patients With Seizures and Status Epilepticus.[14] Medications were listed in alphabetic order; agent selection of second- and third-line therapy should be individualized). *Limited high-quality data comparing efficacy of lacosamide with levetiracetam, phenytoin, fosphenytoin, and valproic acid in status epilepticus. *IM*, Intramuscular; *IV*, intravenous; *fosPHT*, fosphenytoin; *LAC*, lacosamide; *LEV*, levetiracetam; *PHT*, phenytoin; *PE*, phenytoin sodium equivalents; *VPA*, valproic acid.

metabolic abnormalities. Specific seizure syndromes should also be considered in patients at risk. For example, isoniazid overdose can cause prolonged seizures refractory to benzodiazepines and requires pyridoxine to terminate the seizures. In seizing female patients of childbearing age, eclampsia may be the cause, and IV magnesium is the treatment of choice. Eclamptic seizures refractory to magnesium may respond to benzodiazepines or barbiturates, with or without second-line therapy. Children and psychiatric patients at risk for water intoxication may be hyponatremic and require hypertonic saline therapy. See Chapter 88 (Table 88.4 for specific management strategies of these conditions and Table 88.5 for suggested loading doses to resume therapy in epilepsy patients).

Recurrence of seizures following first-time unprovoked seizures is highest in the first 2 years.[2] The consideration of secondary seizure prophylaxis—in collaboration with consulting neurologist—should include a risk stratification for recurrence (higher risk in those with prior brain insult, with abnormal EEG, brain imaging abnormality, and those with nocturnal seizures) and potential antiseizure drug related adverse effects.[2] Immediate antiseizure regimen initiation is associated with reduced recurrence risk in the initial 2 years and may positively influence quality of life,[15] but it is unlikely to change prognosis in the long term.[2]

Disposition

The disposition of a patient presenting to the ED with a seizure or history of a recent seizure must be individualized according to the underlying illness, likelihood of recurrence, indications for maintenance

TABLE 14.2 Commonly Used Parenteral Antiseizure Agents, Dosing, and Pharmacologic Considerations for Status Epilepticus

Medication	Adult Dose	Comments
First Line		
Diazepam	0.15–0.2 mg/kg IV over 1–2 min max 10 mg per dose, 10– 20 mg PR	Repeat doses every 5 min to a maximum of 30 mg; monitor respiratory status. Rapid redistribution. IV formulation contains propylene glycol. Preferred benzodiazepine for rectal route when IM midazolam and IV lorazepam are not available
Lorazepam	0.1 mg/kg IV over 1–2 min (maximum 4 mg per dose)	Repeat doses every 5 min to a maximum of 12 mg (adults); monitor respiratory status. Rapid redistribution. IV formulation contains propylene glycol. Preferred IV benzodiazepine; do NOT administer IM.
Midazolam	0.2 mg/kg IV over 1–2 min, IM, IN (max of 10 mg per dose)	Repeat doses may be administered every 5 min; monitor respiratory status. Half-life ~7 h. Rapid redistribution. Active metabolites. Preferred IM benzodiazepine.
Second Line		
Levetiracetam	1000–4500 mg over 10–15 mins (40-60 mg/kg for status epilepticus; maximum of 4500 mg)	Renally cleared.
Fosphenytoin	10–20 mg PE/kg IV (max 150 mg PE/min), IM	May give an additional 5 PE/kg 10 min after loading dose. May cause hypotension and dysrhythmia but less profound than phenytoin. May be administered IM if no IV access. Compatible in saline, dextrose and lactated Ringers.
Lacosamide	200–400 mg IV over 10 min	May give an additional 5 mg/kg over 5 min (max 250 mg IV). May cause arrhythmias (prolonged PR and QTc intervals, or tachyarrhythmias). Renally cleared.
Phenobarbital	15–20 mg/kg at 50–100 mg/min	May give additional 5–10 mg /kg. Monitor respiratory status. Strong cytochrome P450 (CYP) inducer. IV formulation contains propylene glycol.
Phenytoin	15–20 mg/kg IV infusion maximum at 50 mg/min (25 mg/min in patients with cardiac history)	May give an additional 5–10 mg/kg 10 min after the load, up to 30 mg/kg total. May cause hypotension and dysrhythmia. Potent CYP inducer. May cause rash, fever. IV formulation contain propylene glycol. Only compatible in saline. Severe tissue injury risk with extravasation.
Valproic acid	20–40 mg/kg IV over 5–10 min; max 3000 mg.	May give additional 20 mg/kg (max 2000 mg) over 5 min. Potent CYP inhibitor. May cause hyperammonemia, hepatotoxicity, and platelet dysfunction.
Third Line—Require Intubation, Mechanical Ventilation, and Hemodynamic Support		
Ketamine	Loading: 1.5 mg/kg IV over 3–5 min May repeat 0.5 mg/kg every 3–5 mins as needed Maintenance: starting dose 0.1-4 mg/kg/hr, max 15 mg/kg/hr	NMDA antagonist, which provides an alternative treatment to GABAergic mediated anesthetics. May cause hypotension when shock index ≥0.9. Higher infusion rates associated with large volumes due to dilution.
Midazolam	Loading: 0.2 mg/kg IV, followed by 0.2 mg/kg every 3–5 min (max 2 mg/kg) May repeat 0.2–0.4 mg/kg (max 40 mg bolus) max 2 mg/kg Maintenance: 0.05–2 mg/kg/h	May cause hypotension with higher doses.
Pentobarbital	Loading: 5–15 mg/kg at 50 mg/min, may administer an additional 5–10 mg/kg if needed, max 25 mg/kg Maintenance: 0.5–5 mg/kg/h	Half-life 22 h (up to 50 h as it is dose dependent). May cause hypotension, ileus, myocardial suppression, immunosuppression, and thrombocytopenia. Contains propylene glycol.
Propofol infusion	Loading: 1–2 mg/kg, may repeat 0.5–2 mg/kg every 3–5 mins up to max of 10 mg/kg total Maintenance: normal range 20–80 mcg/kg/min, max 200 mcg/kg/min	Half-life 0.6 h (extended with prolonged infusions). May cause hypotension, respiratory depression, hypertriglyceridemia, pancreatitis, propofol infusion syndrome

Medications are in alphabetic order. The selection of the second- and third-line agents should hinge upon consideration of potential side effects, interactions with other medications, severity of seizures, and their response to other types of medications and comorbidities.
GABA, γ-Aminobutyric acid; *IN*, intranasal; *IM*, intramuscular; *IV*, intravenous; *NMDA*, *N*-methyl-D-aspartic acid; *PE*, phenytoin sodium equivalents.

pharmacologic therapy, psychosocial considerations, and state reporting regulations.

Patients may be discharged home with early referral to a neurologist if they have a normal neurologic examination, no significant medical comorbidities, and no known structural brain disease, did not require more than one dose of a benzodiazepine in the ED, and are thought to have sufficient resources to comply reliably with follow-up instructions. When the diagnosis is uncertain, history of neurologic disease or other comorbidities exist or close follow-up is unlikely, neurologic consultation, longer observation, or admission for observation should be considered.

Patients discharged home from the ED should receive state-specific guidance regarding driver's license privileges, warning about potentially dangerous activities (e.g., swimming, climbing ladders and heights, operating machinery), and information for prompt follow-up with a neurologist.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 14: QUESTIONS AND ANSWERS

1. A 63-year-old woman with end-stage renal disease on hemodialysis, diabetes, and hypertension is brought to the emergency department after losing consciousness during hemodialysis. The episode occurred towards the end of the hemodialysis section approximately 45 minutes ago and was associated with foaming at the mouth, cyanosis, and bilateral tonic-clonic movements of upper extremities lasting nearly 3 minutes. On examination, T 36.6°C, HR 89 bpm, SBP 195 mm Hg, RR 11, pulse oximetry 94%, Glasgow Coma Score (GCS) is 10 with subtle nystagmus, and no meningismus. Computed tomography of the head (CTH) demonstrated hypodensities in bilateral parieto-occipital regions.

What is the leading diagnosis and required work up?

- **a.** Nonconvulsive status epilepticus from hypertensive emergency; electroencephalography (EEG)
- **b.** Cortical blindness from bilateral posterior cerebral artery stroke; computed tomography angiogram
- **c.** Coma from meningoencephalitis; lumbar puncture
- **d.** Coma from uremia; blood urea nitrogen (BUN)

Answer: a. The description of the episode of loss of consciousness with associated cyanosis, and tonic-clonic convulsions is highly suspicious for a generalized tonic-clonic seizure. The patient has not returned to baseline mentation as demonstrated by GCS of 10 and is displaying subtle signs of potentially ongoing seizures (nystagmus); thus the most likely diagnosis is nonconvulsive status epilepticus, which can be diagnosed only with an electroencephalogram. The elevated blood pressure along with hypodensities in the posterior cortical region on CTH are highly suggestive of posterior reversible encephalopathy syndrome, a form of hypertensive emergency. The patient has acute encephalopathy and the stem of the question does not display findings suggestive of cortical blindness (preserved pupillary light reflex with complete binocular vision loss). Lack of prodrome of headache and confusion, fever, and meningismus make meningoencephalitis less likely. The episode happened towards the end of hemodialysis section, so profound uremia is unlikely.

2. You suspected posterior reversible encephalopathy syndrome (PRES) and order a STAT electroencephalography (EEG) while lowering the blood pressure in a stepwise approach. While the patient is waiting to be admitted to the neurology intensive care unit and connected to EEG, the bedside registered nurse reports new left gaze deviation, fine eyelid twitching, and more prominent nystagmus that was refractory to 1 mg of lorazepam. Your index of suspicion for nonconvulsive status epilepticus is high and you decide to treat empirically. The patient weighs 52 kg.

What is the first-line therapy for status epilepticus treatment?

- **a.** Fosphenytoin 1000 mg intravenous (IV)
- **b.** Lorazepam 5 mg IV
- **c.** Levetiracetam 3000 mg IV
- **d.** Lacosamide 300 mg IV

Answer: b. The first-line therapy for seizures and status epilepticus is benzodiazepines. In the hospital setting, lorazepam IV is most commonly used. Although all the other choices are reasonable second-line antiseizure drugs, the patient has received only 1 mg of lorazepam at this point, and a total of 5mg of lorazepam (0.1 mg/kg) is considered appropriate first-line therapy.

3. According to the best evidence available from randomized controlled trials, which second-line antiseizure regimen is recommended for benzodiazepine-resistant convulsive status epilepticus?

- **a.** Fosphenytoin 20 mg phenytoin equivalent (PE)/kg
- **b.** Valproic acid 40 mg/kg
- **c.** Levetiracetam 60 mg/kg
- **d.** All of the above

Answer: d. According to the Established Status Epilepticus Treatment Trial (ESETT) fosphenytoin 20 mg PE/kg (max 1500 mg), valproic acid 40 mg/kg (max 3000 mg), and levetiracetam 60 mg kg (max 4500 mg) were equally effective in terminating convulsive status epilepticus in nearly half of randomized patients (fosphenytoin 45%, valproic acid 46%, levetiracetam 47%). The ESETT trial has provided the best

evidence to date on the second-line treatment of convulsive status epilepticus.

4. A 37-year-old woman with remote history of head trauma from a motor vehicle collision presents to the emergency department with ongoing bilateral convulsions. The patient's significant other witnessed the onset of convulsions 45 minutes ago following an argument. She received a total of 10 mg of intramuscular (IM) midazolam while being transported by the emergency medical services. On examination, T 36.3°C, HR 120 bpm, SBP 115 mm Hg, RR 22, pulse oximetry 100% on a nonrebreather mask; she has her eyes closed and resists passive eye opening of the examiner, does not respond otherwise to the examiner and has ongoing asynchronous, nonstereotypic, and suppressible convulsions of both upper extremities with associated pelvic thrust.

   What are the most important nonpharmacologic initial interventions in patients with suspected generalized convulsive status epilepticus?

   a. Placing an oropharyngeal airway device, lateral decubitus positioning, establishing an intravenous (IV) line
   b. Checking glucose fingerstick, establishing an IV line, lateral decubitus positioning
   c. Suctioning oral cavity, placing oropharyngeal airway device, lateral decubitus positioning patient
   d. Checking glucose fingerstick, placing nasopharyngeal airway device, supine positioning

Answer: b. Initial nonpharmacologic interventions include ensuring physical safety of patients with seizures to prevent traumatic injuries and aspiration. During convulsions, focusing on lateral decubitus positioning and suctioning of oral cavity are important to prevent aspiration; the use of intraoral devices may lead to trauma without additional benefit. Nasopharyngeal airway devices may help with transient obstruction that may occur in the peri-ictal period, but oropharyngeal devices should be avoided as they may induce gagging and vomiting and may damage the teeth or tongue. The serum glucose level should be determined in every seizing or postictal patient as hypoglycemia is a common metabolic cause of provoked seizures. Although some first-line seizure abortive medications can be given IM, intraosseous (IO), per rectum (PR), intranasal (IN), establishing an IV line is a helpful initial step to facilitate timely pharmacologic interventions.

5. An additional 6 mg of lorazepam IV (0.1 mg/kg) slows down the movements but does not abort them completely. What is the most common differential diagnosis for generalized convulsive status epilepticus?

   a. Nonepileptic spells
   b. Neuroleptic malignant syndrome
   c. Complex migraine
   d. Cardiogenic syncope

Answer: a. Although all the answers reflect conditions that can be considered seizure mimics, nonepileptic spells, or pseudoseizures, represent the most common differential diagnosis for generalized convulsive status epilepticus with an incidence of approximately 10% of subjects enrolled in clinical trials. Nonepileptic spells tend to last greater than 5 minutes, thus meeting criteria for convulsive status epilepticus by duration of events, and be resistant to high doses of benzodiazepines. Neuroleptic malignant syndrome is also associated with prolonged spells of abnormal movement, but the type of involuntary movement (typically tonic extension of all extremities, opisthotonos and rigors) and associated hyperthermia, tachycardia, and diaphoresis can distinguish these disorders. Complex migraine typically manifests as lateralizing dysesthesia in association with severe throbbing headache with phono/photophobia, and not with prolonged convulsions. Convulsions associated with cardiogenic syncope usually occur in the setting of hypoperfusion and are brief, unlike this case.

6. Which additional features may assist in the diagnosis of nonepileptic spells?

   a. Disproportionally short postictal confusional state
   b. Normal lactic acid and creatine kinase
   c. Lack of reactive leukocytosis
   d. All of the above

Answer: d. Although the only reliable way to diagnose nonepileptic spells is by characterizing the lack of an underlying seizure rhythm on electroencephalography (EEG) during spells, clinicians should be attentive to clues in the presentation and work-up that suggest a pseudoseizure diagnosis. Prolonged tonic-clonic convulsions (i.e., generalized convulsive status epilepticus) is invariably associated with some degree of rhabdomyolysis and elevation of lactic acid. The complete blood count often displays reactive leukocytosis. Postictal-related confusion or acute encephalopathy is one of the hallmarks of generalized tonic-clonic seizures and carries a direct relationship with the duration of seizures. Short periods of confusion following prolonged bilateral convulsions is suggestive of a nonepileptic spell diagnosis.

7. A 23-year-old woman currently 34 weeks' pregnant with her first baby presents to the emergency department with headache and fatigue. On exam, T 36.2°C, HR 89 bpm, SBP 145 mm Hg, RR 27, pulse oximetry 96%; she is fully oriented, complains of subjective blurry vision and has 2+ pitting edema of lower extremities. You suspect preeclampsia and initiate the work-up.

   What is the typical period for the development of preeclampsia and eclampsia?

   a. 16–37 weeks of gestational age
   b. 20 weeks of gestational age until 8 weeks postpartum
   c. 20 weeks of gestational age until delivery
   d. None of the above

Answer: b. In pregnant patients, the risk of eclampsia is highest from 20 weeks of gestational age up to 8 weeks postpartum. Clinical evaluation should focus on evaluating for associated symptoms (e.g., headache, visual abnormalities and confusion), as well as focal neurologic deficits.

8. What are the red flags that prompt neuroimaging in patients presenting with eclamptic seizures?

   a. No red flags needed, all patients should get a noncontrast computed tomography of the head with abdominal shielding
   b. If persistent neurologic deficits, including prolonged loss of consciousness or encephalopathy
   c. If more than two seizures are observed within 24 hours
   d. If seizures are refractory to benzodiazepines

Answer**: b.** Neuroimaging should be considered if neurologic deficits persist, prolonged loss of consciousness, or encephalopathy. Intravenous magnesium 4 to 6 g is first-line therapy in the pregnant patient experiencing new-onset seizures. Benzodiazepines and nonteratogenic antiseizure medications are reasonable alternatives in magnesium-refractory cases.

9. A 61-year-old previously healthy man presents to the emergency department with a first seizure. The episode consisted of left arm and face clonic movements with secondary generalization and postictal lethargy and left hemiparesis lasting 10 minutes. On examination, T 37.1°C, HR 79 bpm, SBP 105 mm Hg, RR 17, pulse oximetry 96%, GCS is 15 with no focal deficits. Given the focality of seizure onset and the patient age, you obtained a noncontrast computed tomography of the head, which was unremarkable. Which of the following factors should be considered when counseling patients on recurrent seizure risk after a first-time seizure?

a. Presence of focal abnormalities on electroencephalography (EEG)
b. Presence of focal abnormalities on neuroimaging
c. Identification of seizure triggers
d. All of the above

Answer: c. Up to 45% of adults presenting with a first unprovoked seizure will experience another within 2 years, most occurring in the first year 2. The risk is higher with known brain lesions, neuroimaging or EEG abnormalities, or nocturnal seizures 2; the latter are associated with epilepsy syndromes.

10. A 71-year-old man with advanced dementia from multiple prior strokes, atrial fibrillation on warfarin, localization related epilepsy on levetiracetam presents to the emergency department with a breakthrough seizure. The episode consisted of speech arrest and clonic movements of right face and arm. There was no postictal state identified. On examination, T 36.1°C, HR 109 bpm, SBP 115 mm Hg, RR 15, pulse oximetry 97%, GCS is 15 with no focal deficits. Which of the following factors should be considered when deciding on the need for neuroimaging after a breakthrough seizure?
a. No red flags needed, all patients should get a noncontrast CTH
b. Young age, specifically in the pediatric population
c. Use of vitamin K antagonist
d. Lack of identifiable triggers

Answer: c. Neuroimaging should be considered if neurologic deficits persist, prolonged loss of consciousness or coma, advanced age, immunocompromised state, coagulopathy (including anticoagulant drugs) or hypercoagulability, history of malignancy, preceding severe thunderclap headache, status epilepticus, in patients with stigmata of neurocutaneous syndromes, and suspected trauma.

11. What is the most common metabolic cause of seizure activity?
a. Hypercalcemia
b. Hyperglycemia
c. Hypermagnesemia
d. Hypocalcemia
e. Hypoglycemia

Answer: e. Seizure activity secondary to metabolic derangements is most commonly caused by hypoglycemia. The only treatment required in this situation may be intravenous (IV) glucose. Prolonged seizure activity may also cause hypoglycemia so that the cause-and-effect relationship may sometimes be reversed, and further therapy may be required.

12. A 15-year-old girl is brought to the emergency department for evaluation of a recent seizure. While awaiting laboratory results, she begins to have further seizure activity. Which of the following is the optimal first-line agent to terminate her seizure activity?
a. Fosphenytoin
b. Lorazepam
c. Phenobarbital
d. Phenytoin
e. Valproic acid

Answer: b. Benzodiazepines are the optimal first-line agents for stopping seizure activity in patients of all ages. Available agents include lorazepam, diazepam, and midazolam. Phenytoin is recommended as second-line therapy for adults with persistent seizure activity. The prodrug, fosphenytoin, can be administered more quickly, can be given intramuscularly, and has less of a tendency to cause hypotension. Second-line therapy for children is phenobarbital. Third-line therapy is pentobarbital, propofol, or a benzodiazepine infusion. Valproic acid should be considered for patients who are on chronic valproic therapy and whose levels are subtherapeutic.

13. A 24-year-old man is brought to the emergency department by emergency medical services (EMS). The patient's mother reports that she found her son seizing on the floor of her living room approximately 30 minutes before arrival at the hospital. Two months ago, the patient returned from Mexico, where he had been incarcerated for 6 months. The mother reports that during the past 2 months she has seen her son consistently take his seizure medicine and several other pills for a "bad lung infection" he got in Mexico. She cannot remember the names of any of the medications. Several doses of intravenous (IV) lorazepam have been administered, with no effect on the patient's seizure activity. Which of the following medications would be the most effective in aborting his seizure activity?
a. Diazepam
b. Magnesium sulfate
c. Phenytoin
d. Pyridoxine
e. Valproic acid

Answer: d. Several historical clues in this scenario point to tuberculosis being the "bad lung infection" in this patient. In patients with seizures that are refractory to benzodiazepines, isoniazid (a common medication for tuberculosis) overdose is a possibility and should be considered. Pyridoxine is the only fully effective pharmacologic treatment for toxic isoniazid seizures, although benzodiazepines have been shown to suppress seizure activity in some cases.

14. A mother arrives with her 10-year-old daughter (41 kg) who has been seizing for at least 10 minutes. The patient has a history of epilepsy, and a home dose of rectal diazepam has been ineffective. The mother states that the child has been in her usual state of good health until the seizure began, and there has been no history of trauma. Which of the following is the most appropriate initial action?
a. Administer 10 mg midazolam intramuscularly.
b. Consult neurology to obtain a bedside electroencephalogram.
c. Endotracheal intubation with vecuronium and etomidate.
d. Establish vascular access and administer 2 mg of lorazepam.
e. Obtain an immediate computed tomography scan of the head.

Answer: a. Early, aggressive benzodiazepine administration is associated with decreased morbidity and mortality in status epilepticus. Intramuscular midazolam is superior to intravenous lorazepam; in addition, the dose of lorazepam is inadequate. Endotracheal intubation may ultimately be required but is a secondary priority; use of a long-acting neuromuscular blockade agent, such as vecuronium, should be avoided. Cranial computed tomography may or may not be needed in this patient, depending on the response to benzodiazepine therapy. Bedside electroencephalograms are most useful in diagnosing nonconvulsive status epilepticus.

15. Paramedics present with a 24-year-old woman with a history of epilepsy after a seizure. She is somnolent but easily arousable and oriented to self and year. Her vital signs are normal, there are no signs of trauma, and an empty expired bottle of phenytoin is found in her purse. Her prehospital finger stick blood glucose level is 163 mg/dL. Which of the following treatment options is most correct?
a. Administer 20 mg/kg fosphenytoin intramuscularly and observe the patient until she returns to baseline.
b. Establish vascular access, and administer 4 mg lorazepam intravenously (IV).
c. Establish vascular access, obtain a phenytoin level, and administer 1 to 2 mg lorazepam IV if the patient begins to seize.
d. Place the patient in a monitored setting, establish vascular access, and withhold diagnostic tests and treatments unless patient's condition changes.

Answer: c. Medication noncompliance is a frequent cause of seizures in adults with epilepsy. It is recommended to check phenytoin levels before administering additional drug. Because the patient is not in status epilepticus, a low dose of benzodiazepines can be considered for patients who begin to seize while undergoing a period of observation.

16. Which of the following is not part of the routine emergency department evaluation and treatment of a 21-year-old healthy woman with a first seizure?

a. Discharge, with early outpatient neurology follow-up
b. Evaluation of serum electrolyte levels
c. Initiation of antiepileptic drug therapy
d. Performance of cranial computed tomography

Answer: c. Adults presenting with a first seizure should undergo cranial computed tomography and evaluation of serum electrolyte and glucose levels because abnormalities would likely influence disposition while identifying potentially life-threatening conditions. For otherwise healthy adults with normal findings after evaluation, early outpatient follow-up can be considered. In some cases, initiation of antiepileptic drugs can be considered after a first seizure; however, this should be done in consultation with the neurologist responsible for outpatient follow-up.

15

Dizziness and Vertigo

Andrew K. Chang

KEY CONCEPTS

- Neurologic complaints, such as imbalance, dysarthria, or numbness in patients with dizziness/vertigo raise the likelihood of transient ischemic attack (TIA) or stroke as the cause.
- Benign paroxysmal positional vertigo (BPPV) requires head movement to elicit symptoms. Consequently, the Hallpike test should *not* be performed if the patient is actively symptomatic during history taking (and the patient's head has not been recently moved) because such a history is inconsistent with BPPV.
- When performing the Hallpike test, the head should be turned to the side 45 degrees prior to laying the patient back into the head-hanging position.
- A positive Hallpike test should elicit upbeating (fast phase towards eyebrows) nystagmus.
- The Epley maneuver is used to treat posterior semicircular canal BPPV, which is the most common subtype of BPPV.
- Central causes of nystagmus are more likely when the pattern of nystagmus is purely vertical, downbeating (fast phase beating toward the nose), nonfatigable, direction changing with gaze, or spontaneous pure torsional.
- The presence of auditory symptoms (e.g., hearing loss, tinnitus) suggests a peripheral cause of the vertigo.
- Acute vestibular syndrome is diagnosed when dizziness develops acutely; is constant; is accompanied by nausea or vomiting, unsteady gait, nystagmus, and intolerance to head motion; and persists for longer than a day.
- Neck injury resulting in a vertebral artery dissection causes posterior circulation ischemia presenting with vertigo.
- Nystagmus is the cardinal sign of inner ear disease and the principal objective evidence of vestibular dysfunction.
- *HINTS* (Head Impulse test, Nystagmus, Test of Skew) is a bedside oculomotor examination test that helps to differentiate central from peripheral vertigo in symptomatic patients with a first ever onset of constant vertigo from acute vestibular syndrome.
- Meclizine (Antivert) has a time of onset of approximately 1 hour.
- Benzodiazepines are not recommended for the treatment of vestibular neuritis or labyrinthitis in patients who are discharged home, because they can interfere with the process of vestibular rehabilitation.

FOUNDATIONS

Epidemiology

Dizziness is an extremely common yet complex neurologic symptom that reflects a disturbance of normal balance perception and spatial orientation. Patients use the term *dizziness* to describe a variety of experiences, including sensations of motion, weakness, lightheadedness, unsteadiness, emotional upset, and depression. Dizziness has historically been categorized in a symptom-based approach into one of four categories though the validity of this categorization has recently been called into question.[1] The historical categories include vertigo, which is an illusion of motion and typically described as the room spinning; near syncope, which is a sensation of feeling faint or lightheaded; disequilibrium, which is a sense of unsteadiness when walking; and nonspecific dizziness, which is generally thought to be related to a polysensory disorder with an anxiety component.

Acute vestibular syndrome (AVS) is used to describe a clinical condition in which dizziness develops acutely, is constant, persists longer than a day, and is accompanied by nausea or vomiting, unsteady gait, nystagmus, and intolerance to head motion.[2] The major differential diagnosis in acute vestibular syndrome is vestibular neuritis versus posterior circulation stroke.[3] Some recommend subdividing this into acute vestibular syndrome with nystagmus and acute vestibular syndrome without nystagmus because the diagnostic approach differs between them.[3]

Approximately 4% of ED visits are from dizziness, and strokes are the underlying cause in approximately 5% of those visits.[4] Although common causes of dizziness (e.g., benign paroxysmal positional vertigo [BPPV] and vestibular neuritis) can often be readily diagnosed via history and specific diagnostic tests, a precise diagnosis is not always possible even after imaging and neurology consultation. Thus the challenge for the emergency clinician is to identify the patient with a dangerous underlying disorder from the many others who have benign causes.

Pathophysiology

The maintenance of equilibrium and awareness of the body in relationship to its surroundings depend on the interaction of the visual, proprioceptive, and vestibular systems. Input from these three systems is connected to the cerebellum by way of the vestibular nuclei in the brainstem. Any disease that causes a mismatch of information from any two of these three systems may give rise to symptoms of vertigo.

The vestibular apparatus helps maintain head position and stabilize head movement. It is housed in the inner ear, or labyrinth, which lies embedded in the petrous portion of the temporal bone. The vestibular apparatus consists of three semicircular canals and two otolithic structures (the utricle and the saccule). The semicircular canals and the utricle are connected to each other and contain endolymph. The semicircular canals provide information about movement and angular momentum, whereas the utricle (via otoliths, which are calcium carbonate particles attached to hair cells) provides information about head tilt and vertical linear acceleration.

The semicircular canals are paired (left and right ears) structures that normally respond to motion in a symmetrical manner. With

inner ear disease, the resting discharge or the discharge stimulated by motion can be altered in one ear. This alteration produces asymmetric responses and results in the perception of vertigo. For example, freely moving otoliths that are inappropriately located within the semicircular canals, as in BPPV, can produce positional vertigo even when the head is currently still if the head had been recently moved. This is because the recent head movement causes the otoliths to move under the influence of gravity and inappropriately signal the brain.

Impulses leave the vestibular apparatus by the vestibular part of the acoustic nerve (cranial nerve [CN] VIII), enter the brainstem just below the pons and anterior to the cerebellum, and proceed to the four vestibular nuclei of the brainstem and to the cerebellum. From there, impulses travel along two pathways that contribute to the clinical manifestations of vertigo: (1) the medial longitudinal fasciculus (MLF) and (2) the vestibulospinal tract, which connect to the motor neurons that supply the muscles of the extremities. In individuals with healthy vestibular systems, these connections allow the eyes to compensate for body movement in different directions and to maintain a visual axis that is stable with respect to the environment. However, patients with a defective vestibular apparatus may experience false steps or other body movements, which is different from true ataxia, because they attempt to correct for an imagined change in position. Connections between the vestibular nuclei and the autonomic system account for the perspiration, nausea, and vomiting that commonly accompany an attack of vertigo. Connections between the vestibular nuclei and the cerebellum account for the modulating influence of this organ on motor activity.

Nystagmus occurs when the synchronized vestibular information becomes unbalanced. Typically, it results from unilateral vestibular disease, which causes asymmetric stimulation of the medial and lateral rectus muscles of the eye. This unopposed activity causes a slow movement of the eyes toward the side of the stimulus, regardless of the direction of deviation of the eyes. The cerebral cortex then corrects for these eye movements and rapidly brings the eyes back to the midline, only to have the process repeated. By convention, the direction of nystagmus is denoted by the direction of the fast "cortical" component.

Vertebrobasilar insufficiency (VBI) describes a temporary set of symptoms due to ischemia in the posterior circulation of the brain, which supplies the medulla, pons, midbrain, and cerebellum. Major arteries of the posterior circulation include the posterior inferior cerebellar artery (PICA), which is a branch of the vertebral artery, and the anterior inferior cerebellar artery (AICA), which is a branch of the basilar artery.

Table 15.1 lists the pathophysiology for selected causes of peripheral vertigo.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis for peripheral and central vertigo is summarized in Box 15.1. More detailed information is given on selected causes in Table 15.2. Peripheral disorders are generally benign, whereas central disorders usually have serious consequences. Table 15.3 summarizes the different characteristics of peripheral and central vertigo.

The symptom-based approach to categorizing dizziness into four categories (vertigo, near syncope, disequilibrium, and nonspecific dizziness) has been criticized as being imprecise,[5] and new categorization systems have been recently proposed. One system uses three general categories: (1) acute severe dizziness (e.g., vestibular neuritis, stroke), (2) recurrent attacks of dizziness (e.g., Ménière disease, TIA), and (3) recurrent positional dizziness (e.g., BPPV, cerebellar tumor, multiple sclerosis). Another system uses a "timing and triggers" approach, resulting in three categories: (1) acute vestibular syndrome (e.g., vestibular neuritis, cerebellar stroke), (2) spontaneous episodic vestibular syndrome (e.g., Ménière disease, VBI), and (3) triggered episodic vestibular syndrome (e.g., BPPV).[5] Neither of these approaches has been prospectively validated or systematically studied as a diagnostic paradigm, but they may provide a superior way to differentiate among the many causes of dizziness and vertigo.

Pivotal Findings

Symptoms

Vertigo is described as the environment spinning; however, any sensation of disorientation (subjective or objective) in space or sensation of motion can qualify as vertigo. Vertigo is generally associated with some degree of nausea, vomiting, pallor, and perspiration. Peripheral vertigo is not associated with a change in mentation or syncope. A sensation of imbalance often accompanies vertigo but dissipates when the attack is over. This can distinguish more serious causes of true instability, disequilibrium, or ataxia, findings of which indicate a higher likelihood of a central process.

The time of onset and the duration of vertigo are important clues to the cause. For example, episodic vertigo produced primarily by a change in head position and lasting less than a minute suggests BPPV. It is important to tease out how long each *individual* episode of vertigo lasts because patients with BPPV often think their vertigo is constant because any time they move their head they get another episode of vertigo. Acute vestibular syndrome has an arbitrary cutoff of continuous vertigo for at least 1 day, in part to help differentiate acute vestibular syndrome from attacks of Ménière disease or prolonged migrainous vertigo.

The presence of auditory symptoms suggests a peripheral cause of the vertigo, usually on the side of end-organ disturbance. Acoustic neuroma, which can rarely cause vertigo, is usually associated with progressive unilateral hearing loss, typically of several months' duration. Hearing loss, vertigo, and tinnitus form the characteristic triad of Ménière disease. Labyrinthitis is differentiated from vestibular neuritis in that the former is associated with hearing loss due to inflammation of both the vestibular and cochlear components of the eighth CN.

Head injury can cause vertigo occasionally from intracerebral injury and more commonly from labyrinth concussion, as well as from displacement of otoliths resulting in BPPV. Neck injury can cause vertigo from vertebral artery dissection, resulting in posterior circulation ischemia.

TABLE 15.1 Pathophysiology of Selected Causes of Peripheral Vertigo.

Diagnosis	Pathophysiology
Benign paroxysmal positional vertigo (BPPV)	Otoliths inappropriately displaced from utricle into semicircular canals (posterior > horizontal > anterior)
Vestibular neuritis and labyrinthitis	Inflammation (possibly viral) of the vestibular nerve
Ménière disease	Endolymphatic hydrops (excessive endolymph in the inner ear)
Perilymph fistula	Abnormal opening between the middle and inner ear

BOX 15.1 Causes of Vertigo

Peripheral Causes

Benign paroxysmal positional vertigo (BPPV)
Vestibular neuritis (or neuronitis)/labyrinthitis
Ménière disease
Foreign body in ear canal
Acute otitis media
Perilymphatic fistula
Trauma (labyrinth concussion)
Motion sickness
Acoustic neuroma

Central Causes

Vertebral basilar artery insufficiency
Cerebellar hemorrhage or infarction
Tumor
Migrainous vertigo
Multiple sclerosis
Posttraumatic injury (temporal bone fracture, postconcussive syndrome)
Infection (encephalitis, meningitis, brain abscess)
Temporal lobe epilepsy
Subclavian steal syndrome

Associated neurologic symptoms such as imbalance, dysarthria, or numbness are concerning for posterior circulation TIA and stroke. Although the vast majority of patients with isolated dizziness/vertigo do not have TIA or stroke, dizziness and vertigo can be the only initial symptoms of cerebellar and other posterior circulation hemorrhage, TIAs, and infarction. In these cases, diagnostic testing is directed by history and physical examination risk assessment. Older age, male sex, hypertension, coronary heart disease, diabetes, prior stroke, and atrial fibrillation put patients at higher risk for TIA and stroke. Many medications (e.g., aminoglycosides, anticonvulsants, alcohols, quinine, quinidine, and minocycline) have direct vestibulotoxicity and can also be the cause of the patient's symptoms.

Physical Examination

Vital signs. The vital signs, including orthostatic changes, may be the key to identifying a cardiovascular etiology or drug effect as the cause of dizziness. When subclavian steal syndrome is suspected, which also can cause VBI, the pulse and blood pressure should be checked in both extremities. A difference in blood pressure of greater than 40 mm Hg from one arm to the other is concerning for subclavian steal syndrome, and the patient will likely have arm fatigue or other symptoms on the affected side.

TABLE 15.2 Selected Causes of Peripheral and Central Vertigo.

Cause	History	Associated Symptoms	Physical
Peripheral			
1. Benign paroxysmal positional vertigo (BPPV)	Short-lived (typically <30 s), positional, fatigable episodes; more often in older adults.	Nausea, vomiting	Certain positions can precipitate vertigo. Positive result on Hallpike test (posterior semicircular canal) or supine roll test (horizontal canal).
2. Vestibular neuritis/labyrinthitis	Vertigo may develop suddenly or evolve over several hours, usually increasing in intensity for hours, then gradually subsiding over several days but can last weeks. Can be worsened with positional change. Sometimes history of viral infection precedes initial attack. Highest incidence is found in third and fifth decades.	Nausea, vomiting	Spontaneous nystagmus beating away from the side of the lesion may be present in the first few hours. Positive head impulse test. Hearing is normal in vestibular neuritis; hearing loss for labyrinthitis.
3. Ménière disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions.	Nausea, vomiting, tinnitus, hearing loss (hearing loss required for formal diagnosis)	Positional nystagmus is not present; hearing loss
Central			
1. Vascular disorders			
A. Vertebrobasilar insufficiency (VBI)	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Can occur with neck trauma. May be preceded by an episode usually lasting minutes.	Often headache; usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision; tinnitus and hearing loss uncommon but possible	Neurologic deficits usually present, but initially neurologic examination can be normal.

TABLE 15.2 Selected Causes of Peripheral and Central Vertigo—cont'd

Cause	History	Associated Symptoms	Physical
B. Cerebellar hemorrhage	Sudden onset of severe symptoms.	Headache, vomiting, ataxia	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present.
C. Occlusion of posterior inferior cerebellar artery (Wallenberg syndrome)	Vertigo associated with significant neurologic complaints.	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner syndrome (ipsilateral ptosis, miosis, and decreased facial sweating).
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months.	Usually mild nausea	Occasionally, basilar skull fracture.
3. Migrainous vertigo	Vertigo attacks can occur during the headache (in one study of 33 patients, 24% always had headache with vertigo and 67% had headache sometimes with vertigo) but often occur during the headache-free interval. Most patients have a family history of migraine. Syndrome usually begins in adolescence.	Imbalance, head motion intolerance, photophobia, phonophobia, oscillopsia	No residual neurologic or otologic signs are present after attack.
4. Multiple sclerosis	Vertigo presenting symptom in 7%–10% and appears in the course of the disease in a third. Onset may be severe. Disease onset usually between ages of 20 and 40. Often history of other attacks with varying neurologic signs or symptoms.	Nausea and vomiting, which may be severe	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Internuclear ophthalmoplegia (INO) highly suggestive for multiple sclerosis. INO is diagnosed when, on eye movement, the adducting eye shows little to no movement while the abducting eye moves normally.

TABLE 15.3 Characteristics of Peripheral and Central Vertigo.

Characteristic	Peripheral	Central
Onset	Sudden	Gradual or sudden
Intensity	Severe initially, often decreasing over time	Mild in most but can be severe in stroke and multiple sclerosis
Duration	Intermittent episodes lasting seconds to less than a minute for BPPV; continuous and lasting hours to days for vestibular neuritis	Usually weeks, months (continuous) but can be seconds or minutes with vascular causes, such as with posterior circulation TIA
Direction of nystagmus	Usually torsional and upbeat (fast phase beating toward forehead) in classic posterior canal BPPV; horizontal in horizontal canal BPPV; horizontal-torsional in vestibular neuritis/labyrinthitis	Purely vertical, spontaneous and purely torsional, direction-changing on lateral gaze, downbeating (fast phase beats toward nose)
Effect of head position	Induces vertigo (BPPV); worsens vertigo (vestibular neuritis)	Usually little change but can worsen with head position change
Associated neurologic findings	None	Usually present
Associated auditory findings	May be present, including tinnitus (Ménière disease) and hearing loss (labyrinthitis)	Rarely

BPPV, Benign paroxysmal positional vertigo; *TIA,* transient ischemic attack.

Head and neck. Carotid or vertebral artery bruits suggest atherosclerosis and risk for TIA or stroke. The vertebral artery can be auscultated in the supraclavicular region.

Fluid in the middle ear as a result of a middle ear infection may cause mild vertigo, as can occlusion of the eustachian tubes associated with an upper respiratory tract infection or descent barotrauma. A perforated or scarred eardrum may indicate a perilymphatic fistula, especially if the history includes previous trauma.

Examination of the eyes is critical in assessing a patient with vertigo. Pupillary abnormalities may indicate third CN or descending sympathetic tract involvement. Papilledema suggests increased intracranial pressure. Relatively subtle extraocular movement abnormalities can be the only clue to a cerebellar hemorrhage. A sixth CN palsy ipsilateral to the hemorrhage may result from early brainstem compression by the expanding hematoma. Internuclear ophthalmoplegia, which indicates brainstem pathology, is recognized when the eyes are in a normal position on straight-ahead gaze, but on eye movement the adducting eye (CN III) is weak or shows no movement while the abducting eye (CN VI) moves normally (although often displaying a coarse nystagmus). This finding indicates an interruption of the MLF on the side that demonstrates third CN weakness and is virtually pathognomonic of multiple sclerosis.

Abnormal nystagmus is the cardinal sign of inner ear disease and the principal objective evidence of abnormal vestibular function. Positional nystagmus, induced by changing the position of the head, strongly suggests an organic vestibular disorder, typically BPPV. Noting the characteristics of the nystagmus can help to differentiate benign peripheral causes from serious central causes (see Table 15.3). Central causes of nystagmus are more likely when the pattern of nystagmus is purely vertical, downbeating (fast phase beating toward the nose), nonfatigable, direction changing with gaze, or spontaneous pure torsional. Severity of nystagmus is directly related to the degree of acute vestibular hypofunction that occurs. Spontaneous nystagmus usually occurs in severe cases. In mild cases, vestibular asymmetry is less prominent, so spontaneous nystagmus may be subtle or present only for the first few hours. After that it may be only detectable when the patient looks away from the damaged ear or if the examiner performs a head impulse test.

Neurologic examination. The presence of CN deficits suggests a space-occupying lesion in the brainstem or cerebellopontine angle, such as an acoustic neuroma, which can rarely manifest with vertigo.

Cerebellar function is tested several ways: Dysmetria is the inability to arrest a muscular movement at the desired point and should be assessed with finger-to-finger or finger-to-nose pointing. Dysdiadochokinesia (an inability to perform coordinated muscular movement smoothly) is assessed with rapid alternating movements.

Gait assesses ataxia, which, when of recent and relatively sudden onset, suggests cerebellar hemorrhage or infarction in the distribution of the PICA or the superior cerebellar artery. Ataxia that is slowly progressive suggests chronic cerebellar disorders. True ataxia may be difficult to discern from the unsteadiness that occurs when a patient with vertigo attempts to walk, although other findings (e.g., nystagmus and dysmetria) can help narrow the differential diagnosis. This examination is performed when the patient is both sitting and standing, because truncal ataxia, which is seen in midline cerebellar lesions, may become obvious only when the patient has to sit, stand, or walk unaided. Any marked abnormality (e.g., consistent falling or a grossly abnormal gait) should suggest a central lesion, especially in a patient whose vertiginous symptoms have subsided. Patients with an acute peripheral vestibular lesion typically can stand, although they will likely veer toward the side of the lesion. Patients with central vertigo often cannot stand without support. The main features of a cerebellar gait are a wide base, unsteadiness, irregularity of steps, tremor of the trunk, and lurching from side to side. The unsteadiness is most prominent on arising quickly from a sitting position, turning quickly, or stopping suddenly while walking. Patients with gait ataxia also cannot perform heel-to-toe walking.

Positional testing. Positional testing confirms the diagnosis of BPPV. The Hallpike test, also known as the *Dix-Hallpike test* or the *Nylen-Barany test,* confirms the diagnosis of posterior canal BPPV, which is the most common variant of BPPV.[6] This test should be reserved for those patients suspected of triggered vertigo from head position change, and caution should be exercised in performing it in patients with acute vestibular syndrome (acute and constant dizziness, nausea or vomiting, unsteady gait, nystagmus, and intolerance to head motion lasting more than a day) whose main differential diagnosis include vestibular neuritis and posterior circulation stroke. Some evidence indicates that provocative testing may lead to a nonspecific worsening of symptoms in these patients, which could be misinterpreted as diagnostic of a peripheral disorder before stroke has been adequately excluded. Thus, if a patient is actively experiencing vertigo during history taking and there has been no immediate prior head movement, then the Hallpike test should not be performed because this history is inconsistent with BPPV, which requires head movement to elicit symptoms.

The Hallpike test is performed with the patient sitting up. The examiner turns the patient's head 45 degrees to one side and then moves the patient from the upright seated position to a supine position with the head overhanging the edge of the gurney (Fig. 15.1). The patient is queried for the occurrence of vertigo, and the eyes are observed for nystagmus after a latency period of a few seconds. In a patient with classic posterior canal BPPV, the nystagmus usually lasts 5 to 30 seconds and is combined upbeating (the fast phase beats toward the forehead) and ipsilateral torsional (the top pole beating toward the downward ear). The patient is then brought back up to the seated position, and the test is repeated with the head turned 45 degrees to the other side. Findings are summarized in Box 15.2.

In general, if the patient has posterior canal BPPV, only one side should be positive during the Hallpike test, although it is theoretically possible to have otoliths inappropriately located in both right and left posterior semicircular canals. Assuming unilateral involvement, the downward ear indicates the involved side, which is the side to start with when treating with the curative bedside Epley maneuver. If the

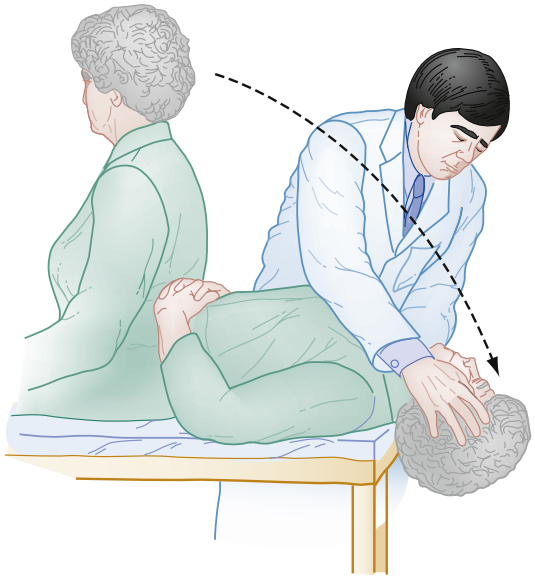

Fig. 15.1 Testing for Positional Vertigo and Nystagmus.

BOX 15.2 Classic Findings During Hallpike Test in Posterior Canal Benign Paroxysmal Positional Vertigo

- Latency (delay in nystagmus and vertigo once in head-hanging position) of approximately 3–10 s, although delay can take up to 30 s on rare occasions
- Reproduction of vertigo symptoms in head-hanging position
- Upbeat (fast phase toward forehead) and torsional nystagmus (usually toward the downward ear)
- Vertigo and nystagmus escalate in head-hanging position, then slowly resolve over 5–30 s
- Nystagmus and vertigo may reverse direction when patient returns to sitting position
- Nystagmus and vertigo decrease with repeated testing (fatigability)

patient pre-identifies the side that causes the symptoms, we test the opposite side first, and this should result in a negative Hallpike test. We then test the other side and, if positive, continue on to complete the Epley maneuver. (The first step of the Epley maneuver is the first part of the Hallpike test, which involves turning the head 45 degrees to the involved side and then laying the patient with the head hanging over the edge of the gurney.)

If the Hallpike test is negative or seems to be positive bilaterally, one can use the supine roll test to evaluate for the horizontal canal variant of BPPV. The patient starts in the supine position, although the head does not need to overhang the edge of the gurney as it would during the Hallpike test. The head is then turned 90 degrees to each side. With a positive test, the patient will have reproduction of symptoms and horizontal nystagmus with the head turned in either direction. The side that is involved is the side with the more intense symptoms and more dramatic nystagmus. Note that the nystagmus will change direction, but this is due to a change in head position and not from a change in gaze direction and so is not concerning for a central cause of vertigo. A video of a case involving failed attempts at the barbecue roll to treat horizontal BPPV, followed by conversion to posterior canal BPPV after a Gufoni maneuver[7] (with resultant cure using the Epley maneuver), can be found at www.youtube.com/watch?v=iOJOArGmepM.

The head impulse, or head-thrust test, is used to diagnose vestibular neuritis and labyrinthitis. The physician stands face to face with the patient and places both hands on the sides of the patient's head. The patient stares at the examiner's nose while the examiner rapidly turns the patient's head approximately 10 degrees to one side. Normally the patient's eyes should keep focusing on the examiner's nose. However, if there is a problem with the vestibular nerve, the eyes will temporarily move along with the head. A corrective saccade will then occur, in which the eyes jerk back toward the midline. If a saccade is seen, this denotes a positive head-thrust test result and indicates vestibular nerve dysfunction. In general, eliciting a positive head impulse test indicates a benign peripheral cause of vertigo, such as vestibular neuritis: The head must be turned rapidly to avoid concluding a false-negative which suggests a central cause.

Head Impulse Test, Nystagmus, Test of Skew. HINTS (*H*ead *I*mpulse test, *N*ystagmus, *T*est of *S*kew) is a bedside oculomotor examination test that has been proposed as a way to differentiate central from peripheral vertigo in patients with acute vestibular syndrome.[2]

The first part of HINTS is the head impulse test, and, as described earlier, a corrective saccade indicates a positive test and is more reassuring for vestibular neuritis, which is a benign cause of vertigo. The second part (nystagmus) refers to a direction change of nystagmus on eccentric gaze. Normally the fast phase is always directed to the same side regardless of gaze. But with direction changing nystagmus, when the patient looks to the left, the fast component beats to the left; and when the patient looks to the right, the fast component beats to the right. This direction-changing nystagmus may indicate a stroke in a patient with acute vestibular syndrome. The third part (test of skew) refers to vertical ocular misalignment during alternate cover testing, and its presence is suggestive of brainstem strokes.

Although the HINTS examination was initially thought to be possibly helpful to identify the smaller numbers of patients who are suffering from stroke or other central causes of vertigo, a recent systematic review and meta-analysis concluded that the HINTS examination, when used in isolation by emergency physicians, has not been shown to be sufficiently accurate to rule out stroke in those presenting with acute vestibular syndrome.[8] This is in large part because using HINTS requires experience and practice, and it should be used only in patients with a first ever episode of constant vertigo from acute vestibular syndrome, because this was the inclusion criteria in the majority of clinical studies involving the HINTS examination. For example, applying the head impulse test in a patient who is dizzy from BPPV would result in a negative test and may cause the emergency physician to incorrectly conclude that the patient's dizziness could be from a central cause of vertigo and lead to additional unnecessary testing. In general, performing both the Hallpike test and the HINTS examination on the same patient should not be routine. Instead, BPPV and acute vestibular syndrome should be distinguished from each other by history and by the presence of spontaneous nystagmus. Thus, if the patient does not have constant vertigo, then the patient does not have an acute vestibular syndrome and the HINTS examination should not be used. Overall the lack of evidence supporting the use of the HINTS examination by emergency clinicians is not evidence that it should not be performed by emergency physicians but rather that emergency clinicians should have a low threshold for referral and/or magnetic resonance imaging (MRI) in those presenting with AVS and one or more stroke risk factors.[8]

Ancillary Testing

Most routine laboratory testing is not helpful in the evaluation of a vertiginous patient except for a finger-stick blood glucose test. Blood counts and blood chemistries are helpful if the dizziness is thought to be due to anemia or dehydration. An electrocardiogram can evaluate for myocardial ischemia or dysrhythmia as a potential cause.

Radiologic imaging. Acute vertigo by itself does not warrant urgent computed tomography (CT) or MRI in all patients, particularly patients in whom a clear picture of peripheral vertigo emerges, such as with BPPV. Risk factor assessment can be helpful in deciding which patients warrant imaging: older age, male sex, hypertension, prior stroke, coronary artery disease, diabetes, and atrial fibrillation put patients at higher risk for more serious causes of dizziness and vertigo.

If cerebellar hemorrhage, cerebellar infarction, or other central lesions are suspected, emergent CT or MRI of the brain is indicated. MRI, when available, has become the diagnostic modality of choice for posterior fossa (cerebellum, medulla, and pons) lesions, as well as for rare causes of vertigo, including acoustic neuroma and multiple sclerosis.

DIAGNOSTIC ALGORITHM

Fig. 15.2 shows a diagnostic algorithm for dizziness and vertigo. Critical diagnoses include posterior circulation strokes. Emergent diagnoses include VBI, which should be considered in any patient of advanced age or at high risk of cerebrovascular disease who presents with isolated, new-onset vertigo without an obvious cause. Because of the possibility of progression of new-onset VBI in the first 24 to 72 hours,

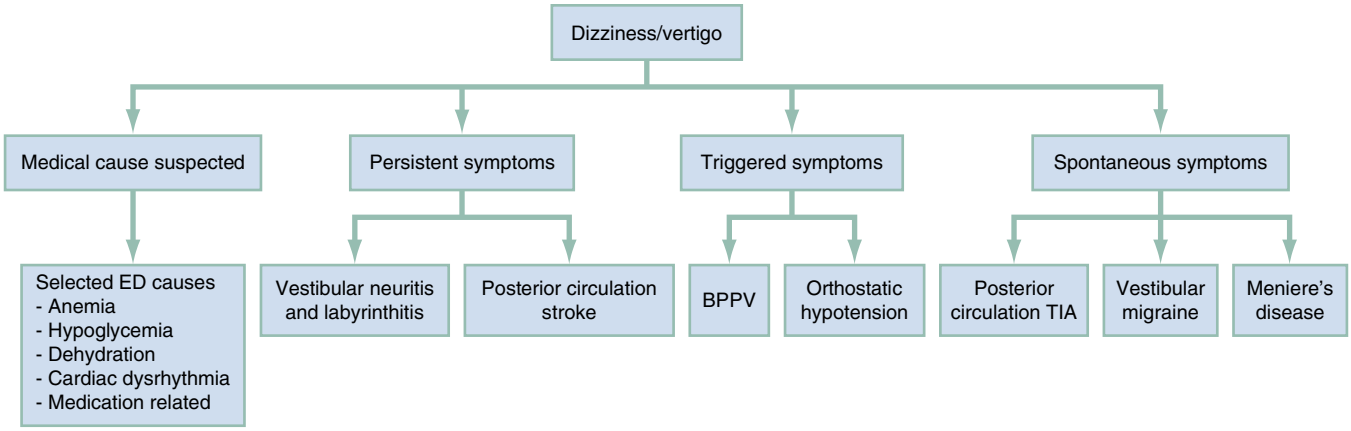

Fig. 15.2 Diagnostic Algorithm for Dizziness and Vertigo. *BPPV,* Benign paroxysmal positional vertigo; *TIA,* transient ischemic attack.

TABLE 15.4 Differentiating Benign Paroxysmal Positional Vertigo From Vestibular Neuritis/Labyrinthitis.

	Benign Paroxysmal Positional Vertigo	Vestibular Neuritis/Labyrinthitis
Age	More common in older adults	More common in younger patients
Hearing loss	None	None in vestibular neuritis; hearing loss in labyrinthitis
Frequency of symptoms	Episodic (occurs with certain movements of the head)	Constant
Hallpike test	Positive usually on one side only with upbeat and torsional nystagmus and reproduction of vertigo symptoms	Symptoms may be worsened in head-hanging position (*Note:* It is advised not to administer Hallpike test in a patient with a clinical history consistent with vestibular neuritis or labyrinthitis.)
Head impulse test	Negative (*Note:* It is advised not to administer head impulse test in a patient with a clinical history consistent with BPPV.)	Positive (corrective saccade seen)
Epley maneuver	Highly effective	Ineffective
Recurrence	Frequent	Rare (2%–11%)

BPPV, Benign paroxysmal positional vertigo.

hospital or observation unit admission and consideration of early magnetic resonance angiography (MRA) are reasonable, even in a stable patient. Changing or rapidly progressive symptoms suggest impending posterior circulation occlusion. If CT or MRI excludes hemorrhage as the source of the patient's rapidly progressive symptoms, an immediate neurologic consultation, further imaging (such as, angiography), and possible anticoagulation are indicated.

Most cases of vertigo are of peripheral origin and are not usually life-threatening. BPPV and vestibular neuritis are likely the most common peripheral causes of vertigo encountered in the ED. However, they are diagnosed and treated very differently. Table 15.4 helps to differentiate between these two diagnoses.

EMPIRICAL MANAGEMENT

Fig. 15.3 shows a general management algorithm in approaching patients with dizziness and vertigo. The Epley maneuver, which is the main canalith-repositioning maneuver used to treat posterior semicircular canal BPPV, involves four to five sequential rotations of the head, holding each position for approximately 30 seconds or until the nystagmus and vertigo resolves, as demonstrated in Fig. 15.4. Failure of the Epley maneuver is usually due to one of two problems: First, the head is lifted too high during the third step of the Epley maneuver, in which the patient rolls onto his or her side and looks toward the ground. Second, the Epley maneuver is often inappropriately applied to a patient who does not have BBPV but rather some other cause, such as vestibular neuritis (see Table 15.4).

The "barbecue roll" is a simple maneuver that can be used to treat the horizontal canal variant of BPPV, which is diagnosed by the supine roll test. The patient lies flat on the gurney with the head turned 90 degrees to the involved side. The head is then rotated in 45-degree intervals away from the involved side (each turn is held approximately 30 seconds or until nystagmus and vertigo resolve). Eventually the patient needs to turn over into the prone position. The maneuver is completed once the head has returned to the original starting position. The Gufoni maneuver is an alternative treatment for the horizontal canal variant (see http://careguides-videos.med.umich.edu/media/Gufoni+Left+Horizontal-Geotropic/1_3sii1rw8/20345631).

A practice guideline that was recently updated maintains that clinicians should not routinely treat BPPV with vestibular suppressant medications.[6] However, this guideline is from a specialty society whose patients often have chronic and likely milder forms of BPPV than patients who develop acute BPPV and come to the ED. For ED patients who are actively vomiting or cannot tolerate canalith-repositioning maneuvers and for those with other causes of acute vertigo (e.g., vestibular neuritis), it is reasonable to administer vestibular suppressants.

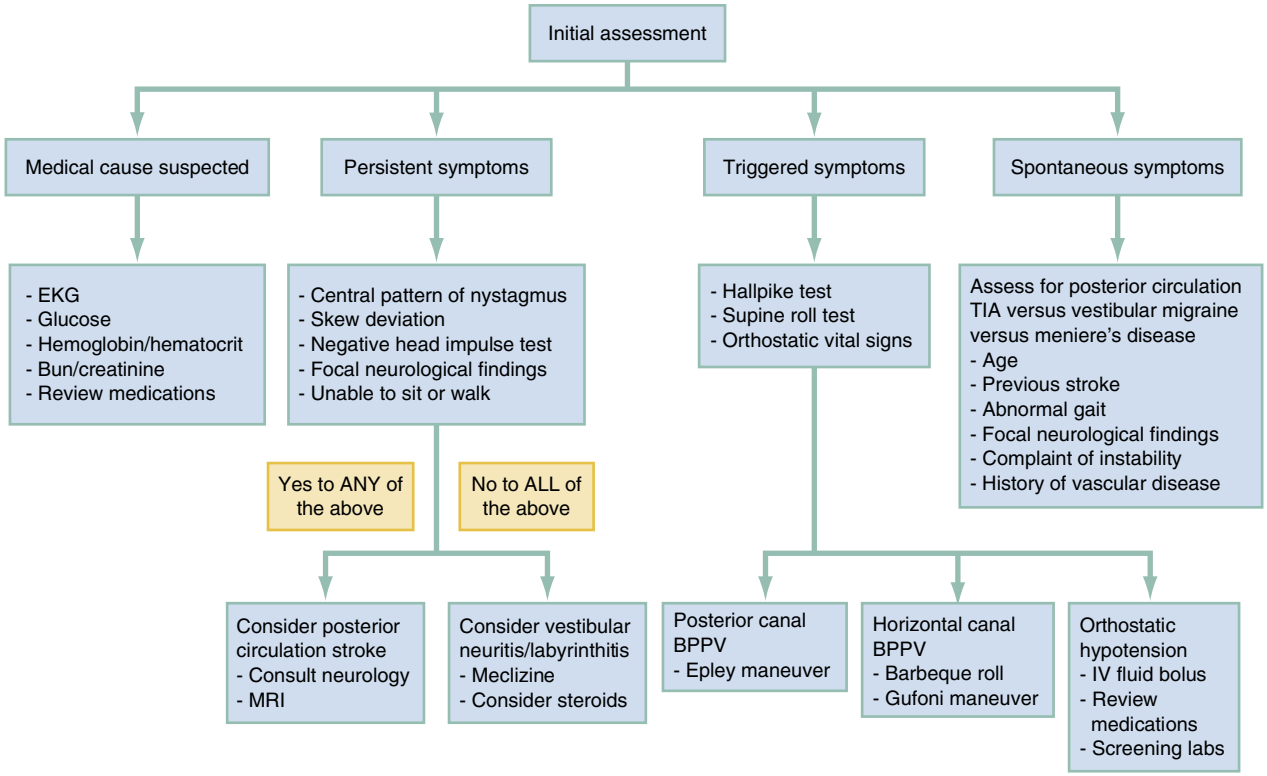

Fig. 15.3 Management Algorithm for Dizziness and Vertigo. *BPPV,* Benign paroxysmal positional vertigo; *ECG,* electrocardiogram; *IV,* intravenous; *MRI,* magnetic resonance imaging; *TIA,* transient ischemic attack.

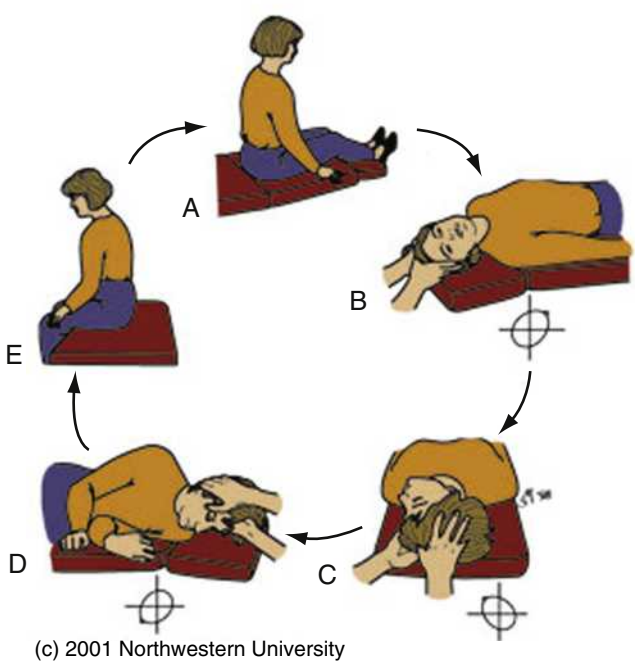

Fig. 15.4 (A to E) The Epley maneuver for benign paroxysmal peripheral vertigo, also known as the *particle-repositioning* or *canalith-repositioning procedure.* (Image used with permission of Timothy C. Hain, Professor of Neurology, Feinberg School of Medicine, Northwestern University, www.dizziness-and-balance.com/disorders/bppv/bppv.html.)

Most vestibular suppressants are antiemetic medications (Table 15.5), which not only suppress nausea and vomiting but also decrease the sensation of vertigo. Although promethazine (Phenergan) is likely the most effective parenteral vestibular suppressant, the US Food and Drug Administration (FDA) has given intravenous use of promethazine a boxed warning, and the use of the IM or oral routes are preferred. Trials using various agents including dimenhydrinate, lorazepam, and droperidol have given mixed results. We recommend intravenous ondansetron 4 mg as the first line intravenous medication for symptomatic vertigo, and a recent randomized clinical trial comparing intramuscular promethazine to intravenous ondansetron in patients with acute peripheral vertigo showed excellent improvement in both groups with fewer side effects in the ondansetron group.[9] Patients with intractable vertigo and vomiting who are unresponsive to antiemetics can be given an intravenous benzodiazepine, such as 1 to 2 mg of intravenous lorazepam. However, it is generally not recommended to discharge patients with oral benzodiazepines, especially in patients with vestibular neuritis and labyrinthitis, because these patients undergo a process of vestibular habituation, in which the vestibular system learns to adapt to the mismatch of information it is receiving, and benzodiazepines can interfere with this process.

Meclizine (Antivert) 12.5–50 mg every 4 to 6 hours can be given in the ED, although its time of onset is approximately 1 hour. Because it can exacerbate symptoms in patients with nonvertiginous types of dizziness, it should be reserved for patients with BPPV who have failed the Epley maneuver or for patients who have an alternative diagnosis of peripheral vertigo, such as vestibular neuritis. Transdermal scopolamine has shown disappointing results for treatment of peripheral vertigo but may be considered a third line option.

Vestibular neuritis results from inflammation of the eighth CN. Patients typically have severe vertigo for 1 to 2 days with gradual resolution over weeks to months. Nystagmus may be spontaneous during the first several hours of symptoms, and patients will have a positive head impulse test. Although vestibular neuritis is thought to be of viral origin[10] in a similar way to Bell palsy, antivirals, such as valacyclovir, are

TABLE 15.5 Medications for Acute Vertigo.

Drug	Usual Starting Dosage	Antiemetic Action
Promethazine (Phenergan)	12.5–25 mg IM, PO, PR (FDA boxed warning recommends IM over IV given risks of extravasation)	Moderate
Ondansetron (Zofran)	4 mg IV, SL/PO, IM	Prominent
Dimenhydrinate (Dramamine)	50–100 mg IM, IV, PO	Moderate
Prochlorperazine (Compazine)	5–10 mg IV, IM, PO, PR	Prominent
Droperidol (Inapsine)	0.625–2.5 mg IM	Prominent
Metoclopramide (Reglan)	5–10 mg IV, IM, PO	Prominent
Lorazepam (Ativan)	1–2 mg IV, IM, PO	Mild
Diazepam (Valium)	1 mg IV, IM, PO	Mild
Meclizine (Antivert)	12.5–50 mg PO	Mild
Scopolamine (Transderm-Scop)	0.2 mg transdermal patch	Moderate

IM, Intramuscular; *IV,* intravenous; *PO, per os* (by mouth); *PR,* per rectum; *SL,* sublingual.

not helpful in the treatment of vestibular neuritis. Corticosteroid use remains controversial, with four out of five studies in a recent review showing short-term benefits.[11] Until certainty is reached, we recommend steroid treatment with prednisone (or methylprednisolone) with a gradual taper over 2 to 3 weeks starting at 60 mg and decreasing to 10 mg before discontinuing the medication. However, shared decision making with the patient is an acceptable alternative.

Some cases of Ménière disease have been treated successfully with vasodilation and diuretic therapy. Diets low in sodium and caffeine and cessation of smoking also have been helpful. However, the diagnosis of Ménière disease requires documentation of hearing loss, so this is not a diagnosis that can be typically made during an ED visit, and the patient should be referred to otolaryngologist for further evaluation including audiology.

DISPOSITION

Documented or suspected VBI or cerebellar hemorrhage or infarction require diagnostic evaluation, treatment, and, usually, hospitalization. In patients older than age 55 with vascular risk factors, admission for observation and imaging of cerebral vasculature should be considered if the diagnosis is not certain. Most younger patients with peripheral causes of vertigo can be discharged from the ED after symptoms have been controlled. Some patients with peripheral vertigo may have such severe symptoms (e.g., intractable vomiting, inability to walk) despite medications that they require hospital admission for intravenous hydration, vestibular suppressants, and antiemetics. Reassessment of neurologic examination findings and assessment of response to therapy are encouraged to help ensure that symptoms are not of central origin. Discharged patients should receive primary care, neurology, or otolaryngology follow-up, particularly if symptoms are not significantly improved within 72 hours or are worsening despite symptomatic treatment.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 15: QUESTIONS & ANSWERS

1. A patient presents to the emergency department with dizziness and is diagnosed with horizontal canal benign paroxysmal positional vertigo (BPPV). What maneuver can be used to treat the patient?
   - **a.** Barbecue roll
   - **b.** Epley maneuver
   - **c.** Hallpike test
   - **d.** Head impulse test

Answer: a. The supine roll test, in which the patient lies flat on the gurney and the head is turned to each side, is used to diagnose horizontal canal BPPV, whereas the barbecue roll maneuver is used to treat the horizontal variant of BPPV. The Epley maneuver is used to treat posterior canal BPPV. The Hallpike test is used to diagnose posterior canal BPPV. The head impulse test is used to diagnose vestibular neuritis and labyrinthitis.

2. A 70-year-old woman presents with a first ever episode of severe vertigo. Which of the following examination findings should prompt the physician to order imaging tests and/or consultation with a neurologist?
   - **a.** Direction changing nystagmus on change in head position
   - **b.** Direction changing nystagmus on change in lateral gaze
   - **c.** Positive head impulse test
   - **d.** Torsional upbeat nystagmus during Hallpike test

Answer: b. Direction changing nystagmus on change in gaze is concerning for a central cause of vertigo and makes up part of the HINTS test. Direction changing nystagmus with changes in head position is expected in a patient with horizontal canal benign paroxysmal positional vertigo (BPPV) and is a benign finding. A positive head impulse test is expected in vestibular neuritis, while torsional upbeat nystagmus is expected in posterior canal BPPV.

3. Internuclear ophthalmoplegia most often suggests a diagnosis of which of the following conditions?
   - **a.** Horizontal canal benign paroxysmal positional vertigo (BPPV)
   - **b.** Labyrinthitis
   - **c.** Multiple sclerosis
   - **d.** Vestibular neuritis

Answer: c. Internuclear ophthalmoplegia is diagnosed when, on eye movement, the adducting eye shows little to no movement while the abducting eye moves normally. In a patient presenting with vertigo, this finding is virtually pathognomonic for multiple sclerosis.

4. Which of the following is a central cause of vertigo?
   - **a.** Labyrinthitis
   - **b.** Ménière disease
   - **c.** Vertebrobasilar insufficiency
   - **d.** Vestibular neuritis

Answer: c. All the other causes are peripheral.

5. Continuous vertigo of what duration is used to define acute vestibular syndrome?
   - **a.** 1 hour
   - **b.** 8 hours
   - **c.** 24 hours
   - **d.** 1 week

Answer**: c.** Acute vestibular syndrome has an arbitrary cutoff of continuous vertigo for at least 1 day in part to help differentiate acute vestibular syndrome from attacks of Ménière disease or prolonged migrainous vertigo.

16

Headache

Laura E. Walker

KEY CONCEPTS

- Patients with a known headache disorder who present with a change in the character of the headache should be evaluated for potential serious causes.
- The physical examination in the headache patient focuses primarily on mental status, funduscopic exam, meningeal signs, and neurologic examination, particularly cranial nerves (CNVs) II, III, IV, and VI, as well as specific cerebral territories.
- Mild to moderate primary and nonspecific headaches are treated with nonsteroidal analgesic drugs (NSAIDs). Severe headaches can be managed parenterally with dopamine antagonists (metoclopramide or prochlorperazine), migraine-specific agents (triptans), or NSAIDS (Ketorolac). Opioid pain medications are not indicated for the treatment of primary headaches.
- Most patients with headache do not require neuroimaging. When obtained, neuroimaging is tailored to the specific elements of concern in the differential diagnosis.
- The differential diagnosis of sudden severe headache includes subarachnoid hemorrhage (SAH) or other intracranial hemorrhage (ICH), cerebral venous thrombosis, and cervical artery dissection (Box 16.1).
- In patients suspected for SAH, a stepwise application of Ottawa SAH Rule, computed tomography (CT) imaging, followed by lumbar puncture (LP) and/or CT angiography (CTA) is appropriate.
- Antibiotics should be administered prior to performing a LP when bacterial meningitis is suspected.

FOUNDATIONS

Background and Importance

Headache is consistently among the top reasons for visits to the emergency department (ED). The vast majority of patients who have a primary complaint of headache do not have a serious medical cause for the problem. Most common primary headache etiologies are benign, such as tension headache and migraine. A minority of headaches are caused by underlying medical or surgical conditions that warrant prompt diagnosis and treatment. The low incidence of serious disease can create a "needle in the haystack" phenomenon, and headache is disproportionately represented in emergency medicine malpractice claims despite widespread overuse of imaging for benign headache conditions. Although representing only a small proportion of patients presenting with acute headache to the ED, the most important and commonly encountered life-threatening cause of severe sudden head pain is SAH.[1] Unfortunately, this is a diagnosis that is also missed on first presentation more than 25% of the time.[2] The other significant, potentially life-threatening causes of headache occur even less frequently. As is the case for SAH, these other serious disorders (i.e., meningitis, carbon monoxide poisoning, temporal arteritis, acute angle-closure glaucoma, ICH, cerebral venous sinus thrombosis, and increased intracranial pressure from space-occupying lesions or idiopathic intracranial hypertension [IIH]) can often be linked with specific historical elements and physical findings that facilitate their diagnosis.

Pathophysiology

The brain parenchyma is insensitive to pain. The pain-sensitive areas of the head include the meninges, the arteries and veins supplying the brain, and the various tissues lining the cavities within the skull. The ability of the patient to specifically localize head pain is often poor. Much of the pain associated with headache, particularly with vascular headache and migraines, is mediated through the fifth CNV. Such pain may proceed back to the nucleus and is then referred through various branches of CNV to areas not directly involved. Inflammation in a specific structure (e.g., periapical abscess, sinusitis, or trigeminal neuralgia) is much easier to localize than the relatively diffuse pain that may be generated by tension or traction headaches. Pain in the head and neck regions may easily overlap and should therefore be thought of as a single unit when complaints of headache are considered.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of headache is complex due to the large number of potential disease entities and the diffuse nature of many types of pain in the head and neck region (Table 16.1). In evaluating the patient with a primary complaint of headache, the top priority is to exclude the causes with significant morbidity and mortality: SAH, ICH, meningitis, encephalitis, temporal arteritis, preeclampsia, central venous sinus thrombosis, and mass lesions. Carbon monoxide is an exogenous toxin, the effects of which may be reversible by removing the patient from the source and administering oxygen. Carbon monoxide poisoning is a rare example of a headache in which relatively simple interventions may quickly improve a critical situation; however, returning the patient to the poisoned environment without a diagnosis could be lethal (see Chapter 148).

Pivotal Findings

Symptoms

Physical findings may be minimal or nonspecific, even in serious causes of headache, so the clinical history is extremely important (Table 16.2).

1. Determine the *pattern and the onset* of the pain. Patients may remember having had frequent and recurrent headaches similar to their current headache; a marked variation in the headache pattern can signal a new or serious problem. A rapid and severe onset of pain ("thunderclap") has been associated with serious causes of headache. Thunderclap headache alone cannot indicate if there is a serious underlying cause of headache, such as SAH, but is used in

BOX 16.1 Emergent Causes of Headache and Associated Risk Factors

1. Carbon monoxide poisoning
   a. Breathing in enclosed or confined spaces with engine exhaust or ventilation of heating equipment
   b. Multiple household members with the same symptoms
   c. Wintertime and working around machinery or equipment producing carbon monoxide (e.g., furnaces, heaters)
2. Meningitis, encephalitis, abscess
   a. History of sinus or ear infection or recent surgical procedure
   b. Immunocompromised state
   c. General debilitation with decreased immunologic system function
   d. Acute febrile illness—any type
   e. Extremes of age
   f. Impacted living conditions (e.g., military barracks, college dormitories)
   g. Lack of primary immunization
3. Temporal arteritis
   a. Age >50
   b. Females more often than males (4:1)
   c. History of other collagen vascular diseases (e.g., systemic lupus)
   d. Previous chronic meningitis
   e. Previous chronic illness, such as tuberculosis, parasitic or fungal infection
4. Glaucoma—acute angle closure
   a. Not associated with any usual or customary headache patterns
   b. History of previous glaucoma
   c. Age >30
   d. History of pain increasing in a dark environment
5. Increased intracranial pressure
   a. History of previous benign intracranial hypertension
   b. Presence of cerebrospinal fluid (CSF) shunt
   c. History of congenital brain or skull abnormalities
   d. Female gender
   e. Obesity
6. Cerebral venous sinus thrombosis
   a. Female gender
   b. Pregnancy, peripartum, hormone replacement therapy or oral contraceptive use
   c. Prothrombotic conditions
7. Reversible cerebral vasoconstriction syndrome
   a. Episodic sudden severe pain, with or without focal neurological findings or seizure
   b. Recurrent episodes over a period up to several weeks
   c. Exposure to adrenergic or serotonergic drugs
   d. Postpartum state
8. Intracranial hemorrhage (ICH)
   a. Subarachnoid hemorrhage (SAH)
      i. Sudden and severe pain; "worst headache of life"
      ii. Acute severe pain after sexual intercourse or exertion
      iii. History of SAH or cerebral aneurysm
      iv. History of polycystic kidney disease
      v. Family history of SAH
      vi. Hypertension—severe
      vii. Previous vascular lesions in other areas of the body
      viii. Young and middle-aged
   b. Subdural hematoma
      i. History of alcohol dependency with or without trauma
      ii. Current use of anticoagulation
   c. Epidural hematoma
      i. Traumatic injury
      ii. Lucid mentation followed by acute altered mentation or somnolence
      iii. Anisocoria

TABLE 16.1 Headache Etiologies and Associated Spectrum of Severity of Disease by System

Organ System	Critical	Emergent	Nonemergent
CNS, neurologic, vessels	SAH	Shunt failure	Migraine, various types
	Carotid dissection	Traction headaches	Vascular headache, various types
	Venous sinus thrombosis	Tumor or mass	Trigeminal neuralgia
		Subdural hematoma	Post-traumatic (concussion)
		Reversible cerebral vasoconstriction syndrome	Post LP headache
Toxic/metabolic, environmental	Carbon monoxide poisoning	Mountain sickness	
Collagen vascular disease	Temporal arteritis		
Ocular/ENT		Glaucoma	Sinusitis
			Dental problems
			TMJ disease
Musculoskeletal			Tension headache
			Cervical strain
Allergy			Cluster or histamine headaches
Infectious disease	Bacterial meningitis	Brain abscess	Febrile headaches, non-neurologic source
	Encephalitis		
Pulmonary or oxygen		Anoxic headache	
Cardiovascular		Hypertensive crisis	Hypertension (rare)
Unspecified		Preeclampsia	Effort-dependent or coital headaches
		IIH	Medication overuse/rebound

CNS, Central nervous system; *ENT,* ear, nose, and throat; *IIH,* idiopathic intracranial hypertension; *LP,* lumbar puncture; *SAH,* subarachnoid hemorrhage; *TMJ,* temporomandibular joint.

TABLE 16.2 Signs and Symptoms of Various Headache Etiologies

Symptom	Finding	Possible Diagnosis
Sudden onset of pain	"Thunderclap" with any decreased mentation, any positive focal finding, meningismus or intractable pain	SAH, cervical artery dissection, cerebral venous thrombosis, acute angle closure glaucoma
Sudden onset of pain	Recurrent thunderclap episodes, may be associated with stroke-like symptoms	Reversible cerebral vasoconstriction syndrome
"Worst headache of my life"	Associated with sudden onset	SAH, cervical artery dissection, cerebral venous thrombosis
Near syncope or syncope	Associated with sudden onset	SAH, cervical artery dissection, cerebral venous thrombosis
Increased with jaw movement	Clicking or snapping; pain with jaw movement	TMJ disease
Facial pain	Fulminant pain of the forehead and area of maxillary sinus; nasal congestion	Sinus pressure or dental infection
Jaw, forehead and/or temporal area pain	Tender temporal arteries	Temporal arteritis
Periorbital or retro-orbital pain	Sudden onset with tearing	Temporal arteritis or acute angle closure glaucoma

SAH, Subarachnoid hemorrhage; *TMJ,* temporomandibular joint.

conjunction with other signs and symptoms.[3] Similarly, slow onset of headache cannot be solely relied on to rule out a potentially life-threatening cause, and the nature of the onset usually is not possible to ascertain if the headache came on during sleep.

Almost all studies dealing with subarachnoid bleeding report that patients move from the pain-free state to severe pain within seconds to minutes. The thunderclap headache is common in acute presentations of SAH but is not highly specific. If the patient with moderate or severe headache can indicate the precise activity in which he or she was engaging at the time of the onset of the headache, the suddenness of onset warrants consideration of SAH. Careful questioning about the onset of headache may lead to the correct diagnosis of SAH, even if the pain is improving at the time of evaluation.

2. The patient's *activity at the onset of the pain* may be helpful. Headaches that come on during exertion raise concern for vascular events. Additionally, although the syndrome of postcoital headache is well known, coitus is also recognized as an activity associated with SAH, so a pattern of previous postcoital headache is key, as is understanding whether the current headache fits that pattern. Postcoital headaches require the same evaluation on initial presentation as any other exertion-related head pain.
3. If there is a *history of head trauma*, the differential diagnosis shifts markedly toward epidural and subdural hematoma, traumatic SAH or intraparenchymal hemorrhage, skull fracture and closed head injuries, such as concussion and diffuse axonal injury.
4. The *intensity of head pain* is difficult to quantify objectively. Almost all patients who come to the ED consider their headaches to be severe. Use of a pain scale with appropriate explanation may help differentiate patients initially but has more value in monitoring their response to therapy. Rapid resolution of pain in the ED, either from time or therapy, should not be relied on to rule out serious causes of headache.
5. The *character of the pain* (e.g., throbbing, pressure), although sometimes helpful, may not be adequate to differentiate one type of headache from another.
6. The *location of pain* at onset (and as the pain progresses) is helpful when the patient can identify a specific area. It is certainly useful to direct the examination to evaluate for externally visible contributing factors, such as an infectious process or trauma. Unilateral pain is more suggestive of migraine or localized inflammatory process in the skull (e.g., sinus) or soft tissue. Muscle tension headache often starts at the base of the skull and can extend over the entire head, following the occipital-frontal aponeurosis. Temporal arteritis, temporomandibular joint (TMJ) disease, dental infections, and sinus infections frequently have a highly localized area of discomfort. Meningitis, encephalitis, SAH, and even severe migraine, although intense in nature, are usually more diffuse in their localization.
7. *Exacerbating or alleviating factors* may be important. Patients whose headaches rapidly improve when they are removed from their environment or recur each time they are exposed to a particular environment (e.g., basement workshop) may have carbon monoxide poisoning. Most other severe causes of head pain are not rapidly relieved or improved when patients get to the ED. Intracranial infections, dental infections, and other regional causes of head pain tend not to be improved or alleviated before therapy is given.
8. *Associated symptoms and risk factors* may relate to the severity of headache but rarely point to the specific causes (see Box 16.1). Nausea and vomiting are nonspecific symptoms seen in both primary and secondary headaches, but they are rare in simple muscle tension headache. Migraine headaches, increased intracranial pressure, temporal arteritis, and glaucoma can all manifest with severe nausea and vomiting, as can some systemic viral infections with headache. Such factors may point toward the intensity of the discomfort but are not specific in establishing the diagnosis. Immunocompromised patients are at risk for unusual infectious causes of headache, which may present with deceptively low-grade symptomatology. Toxoplasmosis, cryptococcal meningitis, and abscess are very rare but may be seen in patients with a history of human immunodeficiency virus (HIV) or other immunocompromised state. This subset of patients may have a serious central nervous system infection without typical signs or symptoms of systemic illness (e.g., fever and meningismus).

Another special population to consider is the pregnant and peripartum woman. In addition to the typical causes of secondary headache, this population may have headache resulting from preeclampsia, and is more likely to have headache caused by idiopathic IIH and reversible cerebral vascular syndrome. Additionally, the more serious vascular causes of headache, including venous sinus thrombosis, pituitary apoplexy, arterial dissection, and stroke, are important considerations.[4] Symptomatic treatment and diagnostic assessment of pregnant patients is undertaken with consideration of potential teratogenic effects of medications, and of the effects of radiation and contrast exposure to the fetus.

TABLE 16.3 Signs and Symptoms Associated With Different Headache Etiologies

Sign	Finding	Possible Diagnoses
General appearance	Nonfocal mental status changes	Meningitis, encephalitis, SAH, subdural hematoma, anoxia, increased intracranial pressure, carbon monoxide poisoning
	Mental status changes with focal findings	Intraparenchymal bleed, tentorial herniation, stroke
	Severe nausea, vomiting	Increased intracranial pressure, acute-angle closure glaucoma, SAH, carbon monoxide poisoning
Vital signs	Hypertension with normal heart rate or bradycardia	Increased intracranial pressure, SAH, tentorial herniation, intraparenchymal bleed, preeclampsia, reversible cerebral vasoconstriction syndrome
	Tachycardia	Anoxia, anemia, febrile headache, exertional or coital headache
	Fever	Febrile headache, meningitis, encephalitis
HEENT	Tender temporal arteries	Temporal arteritis
	Increased intraocular pressure	Acute angle closure glaucoma
	Loss of venous pulsations on fundoscopy or papilledema	Increased intracranial pressure, mass lesions, subhyaloid hemorrhage, SAH, cerebral venous thrombosis
	Acute red eye (severe ciliary flushing) and poorly reactive pupils	Acute angle closure glaucoma
Neurologic	Enlarged pupil with third nerve palsy	Tentorial pressure cone, mass effect (aneurysm, bleed, abscess, or tumor)
	Lateralized motor or sensory deficit	Stroke, subdural hematoma, epidural hematoma, hemiplegic or anesthetic migraine (rare), reversible cerebral vasoconstriction syndrome, central venous thrombosis
	Balance and coordination deficits	Cervical artery dissection, acute cerebellar hemorrhage, acute cerebellitis (mostly children),[9] chemical intoxication of various types
	Extraocular movement deficits (CN III, IV, and VI)	Mass lesion, neurapraxia (post-traumatic headache), IIH

CN, Cranial nerve; *HEENT,* head, eyes, ears, nose, and throat; *IIH,* idiopathic intracranial hypertension; *SAH,* subarachnoid hemorrhage.

Patients on medications containing estrogen are also at higher risk for thrombotic events, such as cavernous venous thrombosis, and this is considered in the formulation of the differential diagnosis.

7. A *prior history* of headache, although helpful, does not rule out current serious problems. One important consideration is the association of migraine headaches and stroke, with particular consideration of carotid dissection.[5] Previous testing for serious disease can be useful to guide the current evaluation. Prior visits to an ED or outpatient setting, CT, magnetic resonance imaging (MRI), and other forms of testing can provide support for, or help rule out, a specific diagnosis. Patients with migraine, cluster, and tension headaches tend to have stereotypical recurrent patterns. Concordance of current symptoms with prior episodes can help inform the decision to pursue additional testing versus a strategy of symptom control. A typical recurrent episode can warrant symptom control alone, whereas an atypical presentation will prompt consideration of a broader differential and care pathway.
8. Additionally, risk of a secondary medication overuse headache is an important consideration in patients taking medications for headaches more than 10 to 15 times per month, and should be considered after the presence of underlying emergent conditions is eliminated.[6]

Signs

Vital signs may be normal in headache, despite significant discomfort. There are signs that may be elicited on physical examination that can be particularly high yield. For example, deficits of extraocular movements localizing to cranial nerves (CNs) III, IV, and VI, or papilledema noted on CN II assessment, may indicate the presence of increased intracranial pressure due to a mass lesion or IIH. When headache is associated with an acutely red eye, consideration of acute angle closure glaucoma should prompt testing of intraocular pressure. Signs of meningeal irritation (nuchal rigidity, jolt accentuation, or Kernig and Brudzinski signs) are concerning for SAH or meningitis. Any focal neurological deficit found on examination, regardless of subtlety, warrants further investigation. Not all signs associated with headache contribute greatly to final determination of diagnosis, but they may serve as cues to trigger further consideration of a serious intracranial process. Presence of fever raises the suspicion of a primary infectious etiology. Nausea and vomiting are often associated with migraine, but they are also associated with intracranial mass, acute angle closure glaucoma, intracranial bleeding, and carbon monoxide poisoning. Alteration of mental status may indicate serious underlying causes of headache, including hemorrhage and infection. Additional physical examination findings associated with various forms of headache are listed in Table 16.3.

Ancillary Testing

The vast majority of headache patients do not require additional testing (Table 16.4). Advanced imaging is directed toward the specific disease of concern in the differential diagnosis, and not as a default process in the investigation of headache in general. For example, a head CT scan is not indicated for muscle tension headache or recurrent migraine, and it may not be sufficient to assess for cerebral venous thrombosis or for a posterior circulation stroke. Instead, use of CT venogram (CTV) or magnetic resonance venogram (MRV) for cavernous thrombosis, or MRI for posterior circulation disorders, are more appropriate.

A CT scan performed within 6 hours of onset of headache has been shown to be sufficiently sensitive to exclude the diagnosis of SAH when using a third-generation CT scanner.[7] Outside this window, sensitivity declines, and additional testing must be undertaken for appropriate evaluation for SAH.[8] However, there are other causes of sudden severe headache beyond SAH that must be considered in select patients. Overall, judicious use of imaging and selection of an advanced imaging study that will answer a specific question is the optimal approach.

LP with measurement of the opening pressure and cerebrospinal fluid (CSF) analysis is indicated when assessing for an infectious process, IIH, or SAH. In evaluation for SAH outside the 6-hour window, utilization

TABLE 16.4 Diagnostic Findings in Emergent Causes of Headache

Diagnosis	Test	Finding
Temporal arteritis	Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)	ESR greater than 50 mm/H Elevated CRP
SAH Increased intracranial pressure	Electrocardiogram (ECG)	Nonspecific ST/T wave changes
Anoxia	Complete blood count (CBC)	Severe anemia
Increased intracranial pressure	Computed tomography (CT) scan: Head	Increased ventricular size
SAH		Blood in subarachnoid space
Epidural or subdural hematoma		Blood in epidural or subdural space
Intraparenchymal hemorrhage		Bleeding into parenchyma of brain
Pale infarct		Areas of poor vascular flow
Traction headache secondary to mass effect		Structural, mass lesion
IIH Mass lesion Shunt failure Cryptococcal meningitis	Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis	Increased opening pressure
Tumor or other structural lesions, infection		Increased protein
SAH		Increased RBCs
Infection		Increased WBCs
Infection		Positive Gram's stain
Infection		Decreased glucose

IIH, Idiopathic intracranial hypertension; *RBC,* red blood cell; *SAH,* subarachnoid hemorrhage; *WBC,* white blood cell.

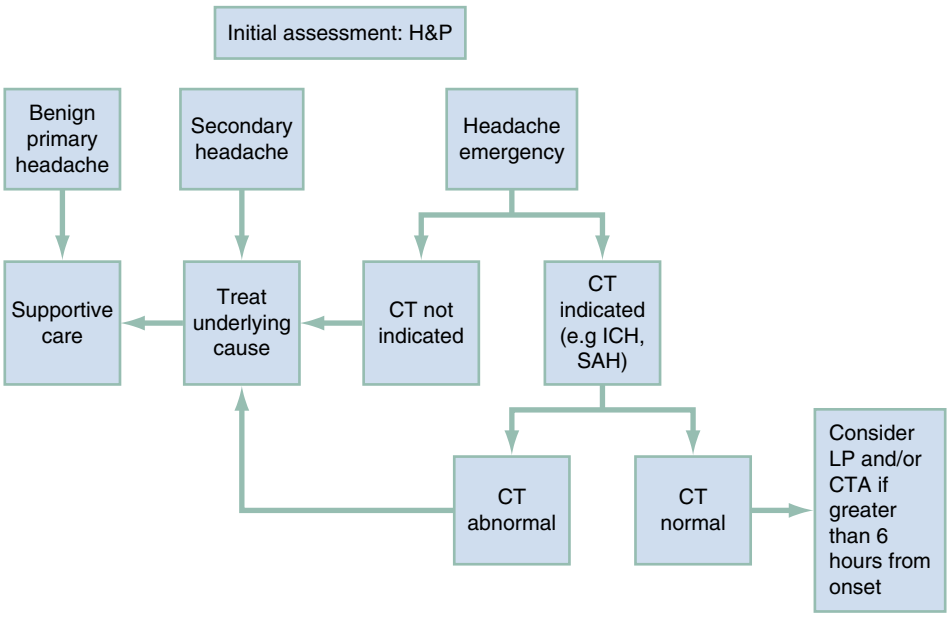

Fig. 16.1 Evaluation Algorithm for Presentation of Headache. *CO,* Carbon monoxide; *CT,* computed tomography; *CTA,* computed tomography angiography; *HA,* headache; *H&P,* history and physical examination; *ICH,* intracranial hemorrhage; *LP,* lumbar puncture; *SAH,* subarachnoid hemorrhage.

of CTA in lieu of LP has been proposed, but there is not yet sufficient evidence to definitively advocate this diagnostic pathway to confirm or rule out SAH.[3] It is widely believed that LP may increase the likelihood of herniation in certain cases with elevated intracranial pressure caused by a mass lesion, though supportive evidence is scant. This belief is the genesis of the common dictum of "CT before LP" when a mass lesion or abscess is a consideration. In reality, this concern is likely misguided, and the compelling reason to obtain a CT scan first in such patients is that it may provide the diagnosis and make the LP unnecessary.

DIAGNOSTIC ALGORITHM

Key elements of the history of present illness, past medical history, and examination are used to narrow the differential diagnosis and choose the appropriate diagnostic pathway. Fig. 16.1 outlines a diagnostic algorithm for assessment of headache patients.

When a primary headache disorder is clinically suspected, or when the etiology of a headache is uncertain but there are no signs or symptoms suggestive of a significant underlying cause (minor severity,

gradual onset, absence of meningeal signs, and normal funduscopic and neurological examination), then symptomatic treatment is provided without need for further diagnostic evaluation.

When a particular etiology of concern is identified based on the clinical history or physical examination, additional directed testing to confirm or exclude the diagnosis is warranted. Examples include intraocular pressure determination for acute glaucoma and LP for meningitis.

In considering the potential diagnosis of SAH, utilization of the Ottawa Subarachnoid Hemorrhage Rule is recommended to help guide evaluation. This decision rule has been shown to have a high sensitivity and low specificity, allowing for decreased unnecessary testing when appropriately applied (Box 16.2).[8]

Cases in which there are highly concerning elements of history but no definitive diagnosis are the most challenging in terms of choosing the appropriate evaluation. Signs and symptoms that indicate patients are at higher risk for serious causes of headache and therefore candidates for more comprehensive evaluation include: (1) sudden onset of headache, (2) patient description of the headache as "the worst ever," (3) altered mental status, (4) meningismus, (5) unexplained fever, (6) focal neurological deficit on examination, (7) symptoms refractory to appropriate treatment or worsening despite treatment, (8) onset of headache during exertion, (9) history of immunosuppression, or (10) pregnancy or peripartum state.

Sequential evaluation of the patient's condition and assessment of ancillary data will confirm a working diagnosis or trigger a reconsideration of alternatives, including more serious conditions (Table 16.5).

BOX 16.2 Ottawa Subarachnoid Hemorrhage Rule

Inclusion: patients age 15 and over, nontraumatic headache, peak intensity within 1 h of onset

Exclusion: New neurological deficits, prior aneurysm, prior SAH, known intracranial mass, chronic recurrent headaches

If none of the following are present, SAH can be reasonably ruled out:

a. Age >40 years
b. Neck pain or stiffness
c. Witnessed loss of consciousness
d. Headache onset during exertion
e. Thunderclap headache (immediate peak pain)
f. Limited neck flexion

EMPIRICAL MANAGEMENT

Headache, although a frequent chief complaint, is a nonspecific symptom. The speed and intensity of the initial evaluation and treatment are guided by the presentation and the patient's mental status. Fig. 16.2 represents a treatment algorithm with recommendations for immediate management pending completion of a full diagnostic evaluation.

Pain is treated as soon as possible. The pain medication of choice depends on the working diagnosis of a patient's headache. For primary headache and nonspecific mild to moderate headache, oral NSAIDs are appropriate in analgesic doses (e.g., 500 mg of naproxen). Primary headaches that are severe or not responsive to NSAIDS can be treated with parenteral nonnarcotic medications. Recommended options include three classes of medication: intravenous (IV) antiemetic dopamine antagonists, such as metoclopramide (10 mg) or prochlorperazine (10 mg); subcutaneous (SC) migraine-specific agents, such as Sumatriptan (6 mg); and an intramuscular (IM) or IV NSAID, such as Ketorolac (15 mg). Opioids are not considered first-line management for any type of primary or nonspecific headache. Secondary headaches, including those caused by infection, hemorrhage, or intracranial mass, may warrant use of opioids as initial therapy.

There is no contraindication to immediate and appropriate treatment of headache while initiating evaluation. Additionally, if bacterial meningitis is under consideration as a possible cause, empiric

TABLE 16.5 Causes and Differentiation of Potentially Catastrophic Illness Manifesting With Nontraumatic Headache

Disease Entities	Pain History	Associated Symptoms	Support History	Prevalence
Carbon monoxide poisoning	Usually gradual, subtle, dull, nonfocal throbbing pain	May wax and wane as individual leaves and enters the involved area of carbon monoxide; throbbing may vary considerably	Exposure to engine exhaust, old or defective heating systems, most common in winter months	Rare
Subarachnoid hemorrhage (SAH)	Sudden onset, "thunderclap," severe throbbing	Symptoms variable; may present from relatively asymptomatic to altered mental status or focal neurological deficit	History of polycystic kidney disease; history of HTN	Uncommon
Meningitis, encephalitis, abscess	Gradual; as general symptoms increase, headache increases. Nonfocal pain	Decreased mentation prominent, irritability prominent. With abscess, focal neurologic findings may be present	Recent infection, recent facial or dental surgery or other ENT surgery, unimmunized state	Uncommon
Temporal arteritis	Pain often develops over a few hours from mild to severe, almost always localized to temporal area(s)	Decreased vision, nausea, vomiting may be intense and confound diagnosis	Age over 50; other collagen vascular diseases or inflammatory diseases	Uncommon
Acute angle closure glaucoma	Sudden in onset	Nausea, vomiting, decreased vision	History of glaucoma; history of pain increasing in dark areas	Rare
Increased intracranial pressure syndromes	Gradual, dull, nonfocal	Vomiting, decreased mentation	History of CSF shunt or congenital brain or skull abnormality	Uncommon

CSF, Cerebrospinal fluid; *ENT,* ear, nose, and throat; *HTN,* hypertension.

antibiotic therapy should be provided as soon as possible, as the treatment is time-sensitive. It is appropriate to begin treatment of potential bacterial meningitis prior to completion of confirmatory CSF testing.

Patients who are thought to have a benign cause for their head pain not requiring hospitalization, but who are without a specific diagnosis, should be provided with appropriate return precautions and recommendations for follow-up care. Some patients may benefit from beginning a headache journal to facilitate further outpatient evaluation.

The references for this chapter can be found online at ExpertConsult.com.

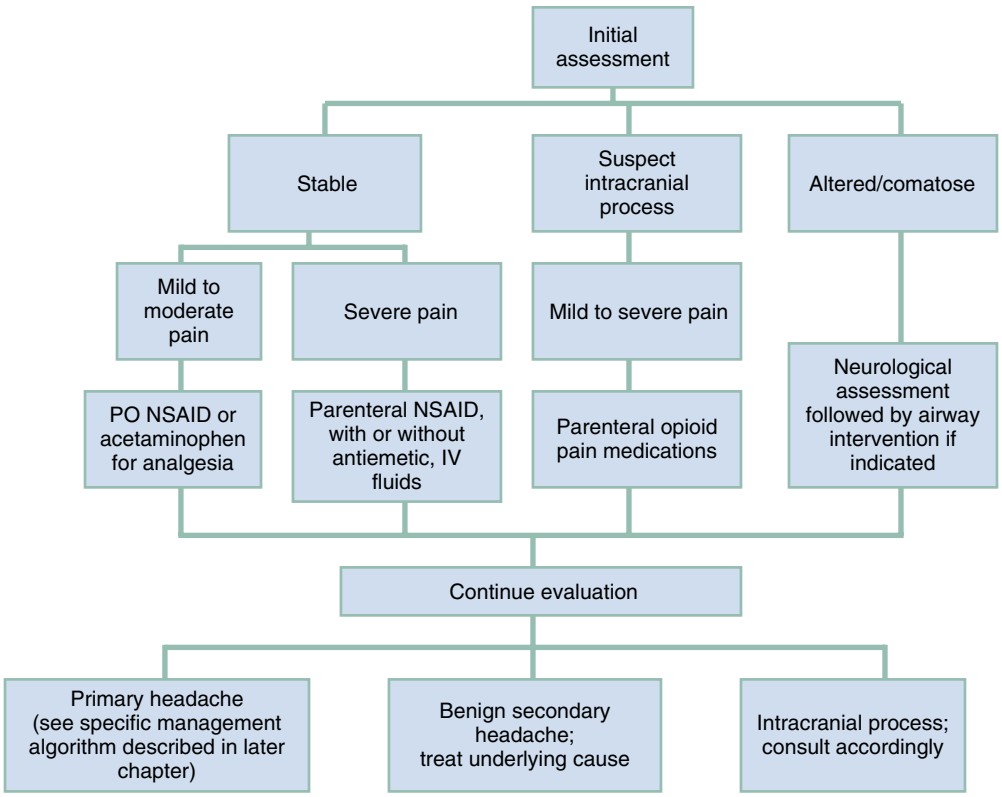

Fig. 16.2 Management Algorithm. *IV,* Intravenous; *NSAID,* nonsteroidal antiinflammatory drug; *PO, per os* (by mouth).

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CHAPTER 16: QUESTIONS AND ANSWERS

1. Of the following, which is most appropriate in the initial evaluation of a patient with nontraumatic headache?
- **a.** Computed tomography (CT) scan of brain
- **b.** Electroencephalogram (EEG)
- **c.** Magnetic resonance imaging scan of brain
- **d.** Thorough neurological evaluation

Answer: d. A thorough neurological examination may reveal deficits not seen on gross evaluation, prompting expansion of the differential diagnosis to include more concerning etiologies. Depending on the history and remainder of the physical, a normal neurological examination may be reassuring and obviate need for advanced imaging studies.

2. In the setting of headache, the presence of nausea and vomiting are diagnostic of which of the following underlying causes?
- **a.** Glaucoma
- **b.** Increased intracranial pressure
- **c.** Migraine
- **d.** None of the above

Answer: d. Nausea and vomiting are completely nonspecific. Migraine headaches, increased intracranial pressure, temporal arteritis, and glaucoma can all be manifested by severe nausea and vomiting, as can some systemic viral infections with headache. Such factors may point toward the intensity of the discomfort but are not specific in establishing the diagnosis.

3. Which of the following is the most appropriate initial diagnostic study for a pregnant woman with normal vital signs and a presentation concerning for a headache emergency?
- **a.** Computed tomography (CT)
- **b.** Inflammatory markers (e.g. erythrocyte sedimentation rate [ESR], C-reactive protein [CRP])
- **c.** Magnetic resonance angiography (MRA)/magnetic resonance venogram (MRV)
- **d.** No studies are indicated

Answer: a. CT studies with and without contrast are able to identify many vascular causes of headache, for which pregnancy is a risk factor. Iodinated contrast is safe in pregnancy. Magnetic resonance imaging (MRI) without contrast is another option; however, MRA and MRV are relatively contraindicated due to use of gadolinium contrast, which has not been shown to be safe in pregnancy. Inflammatory markers are nonspecific and will not confirm or rule out important emergency headaches in this population. For emergency headaches in pregnancy deferral of additional studies is not appropriate.

4. A 42-year-old male patient presents with the sudden onset of severe headache that worsened over the 30 minutes while at rest 4 hours prior to arriving in the emergency department (ED). His examination reveals only mild distress, no neck stiffness or meningismus, and normal funduscopic and neurological examinations. What is the most appropriate diagnostic test?
- **a.** Intraocular pressure determination
- **b.** Sphenopalatine block
- **c.** Computed tomography
- **d.** Lumbar puncture

Answer: c. The patient has a sudden onset severe headache and Ottawa Subarachnoid Hemorrhage Rule can be applied. However, his age being greater than 40, the rule is unable to exclude subarachnoid hemorrhage (SAH). Next step is computed tomography (CT) because he is within the 6-hour window. Lumbar puncture and or/ CT angiography can be considered if initial noncontrast CT is normal.

17

Diplopia

Ashley Booth Norse

KEY CONCEPTS

- The diagnostic approach to diplopia is aimed at determining (1) if the diplopia is monocular, (2) if there is a restrictive or mechanical issue in the orbit or orbital structures, (3) if there is a palsy of one or more of the oculomotor cranial nerves, (4) if there is a neuroaxial process involving the brainstem and related cranial nerves, or (5) if there is a systemic neuromuscular process.
- Monocular diplopia is most commonly caused by an ophthalmologic problem related to refractory distortions or retinal buckling.
- Binocular diplopia resolves when either eye is closed and is the result of a misalignment in the visual axes.
- Important historical features in assessing diplopia includes onset, directionality and orientation of the diplopia; presence of pain, and the presence of other associated symptoms.
- An isolated CN III palsy presents with diplopia in all directions of gaze, except on lateral gaze to the affected side; the eye is deviated down and out; ptosis and a dilated pupil may also be present.
- A CN IV palsy results in vertical or torsional diplopia that worsens on looking down and toward the nose.
- A CN VI palsy will cause the affected eye to turn inward and results in diplopia that worsens on lateral gaze toward the affected side.
- Cavernous sinus or posterior orbit disease (orbital apex syndrome) may present with ipsilateral diplopia involving CN III, IV and or VI; associated symptoms may include pain, exophthalmos, chemosis, and possibly ipsilateral periorbital facial numbness or dysesthesia.
- Multiple sclerosis or localized pathology in the brainstem, such as tumor, lacunar infarct, basilar artery thrombosis, vertebral artery dissection or ophthalmoplegic migraine, may present with focal lesions presenting as diplopia.
- The diplopia caused by myasthenia gravis is associated with ptosis, gets worse as the patient fatigues, and improves with rest or on placing ice over the eye.
- Initial treatment for diplopia is directed toward imminent threats to airway and ventilation (e.g., with botulism and myasthenia gravis) and immediate or rapidly evolving threats to the central nervous system (CNS) (e.g., stroke, meningoencephalitis or Wernicke encephalopathy).

FOUNDATIONS

Diplopia (double vision) can be either monocular or binocular. Although life-threatening diagnoses are rare, ED patients have a higher incidence of harboring a serious neurological process than patients presenting in the ambulatory setting. Most ED cases are binocular, with cranial nerve palsies being the most common cause.[1]

Pathophysiology

Double vision or diplopia is seeing two or more images. The etiology can be from systemic disease or pathology in the eye or brain. Monocular diplopia does not correct when one eye is closed and is usually caused by intraocular pathology, for example, lens subluxation, retinal abnormalities, or a refractive error, in which case the diplopia should resolve with pinhole testing.

Binocular diplopia is double vision that resolves when one eye is closed. It is caused by misalignment of the visual axes, and has an extensive differential diagnosis: see Table 17.1. Approximately one-third of patients presenting to the ED with binocular diplopia have a secondary cause, such as stroke, multiple sclerosis, brain tumors, and cerebral aneurysms.

Cerebral diplopia, or polyopia, is seeing many images and can be monocular or binocular. It is rare and associated with stroke, vascular spasm, tumor, multiple sclerosis, trauma, infections, or seizures, primarily involving the occipital or temporal lobes.

DIAGNOSTIC APPROACH

Differential Considerations

Monocular diplopia is an ophthalmologic problem related to distortions in the light path from dry eyes, a corneal irregularity, cataract, lens dislocation, or retinal wrinkles involving the macula. In rare cases, monocular diplopia may be the presenting complaint in conversion disorder, but this is a diagnosis of exclusion. Box 17.1 outlines some key causes of monocular diplopia.[2]

Binocular diplopia may be due to a mechanical or restrictive process in the orbit or structures of the orbit, a palsy of one or more of the oculomotor cranial nerves, a proximal neuroaxial process involving the brainstem and related cranial nerves, a systemic neuromuscular process, or trauma. Table 17.1 outlines some key causes of binocular diplopia.

The clinical approach in the ED entails narrowing the differential diagnosis to those diagnoses that may result in rapid and profound morbidity, in distinction from those that are less acute. In most cases a systematic history and physical exam will elicit the underlying etiology.

Pivotal Findings

History. The history begins by determining if the diplopia is monocular or binocular. Additional information helpful in formulating the differential diagnosis in diplopia includes: (1) the timing of onset and symptoms; (2) directionality and orientation of the diplopia (horizontal, vertical, or torsional); (3) presence of pain; and (4) presence of other associated symptoms. In terms of the timing, sudden onset suggests an ischemic, cerebrovascular, or microvascular cause, especially if the intensity or degree of diplopia is maximal at onset. A fluctuation of symptoms over time may suggest transient ischemic attacks or an impending stroke, but more generally implies a neuromuscular disease.

The directionality of the diplopia is as important as the type of diplopia. The directions of gaze that elicit or worsen the diplopia and the

TABLE 17.1 Differential for Binocular Diplopia

Structural Orbitopathy:	Trauma Infection/abscess Craniofacial masses
Orbital Myositis:	Thyroid eye disease Wegener granulomatosis Giant cell arteritis Systemic lupus erythematosus Dermatomyositis Sarcoidosis Rheumatoid arthritis Idiopathic orbital inflammatory syndrome (orbital pseudotumor)
Isolated Oculomotor Nerve Palsy: Cranial nerve III Cranial nerve IV Cranial nerve VI	Multiple sclerosis Hypertensive vasculopathy Diabetic vasculopathy Idiopathic intracranial hypertension Compression Trauma
Multiple Oculomotor Nerve Palsies:	Cavernous sinus infection, mass, vasculitis or thrombosis Orbital apex syndrome
Neuroaxial Process Involving the Brainstem and Related Cranial Nerves:	Focal: • Multiple sclerosis Localized brainstem process: • Tumor • Stroke • Hemorrhage • Basilar artery thrombosis • Vertebral artery dissection • Ophthalmoplegic migraine Diffuse (involving the brainstem and/or CNs III, IV, and VI) • Infectious: basilar meningoencephalitis • Autoimmune: Miller-Fisher or Guillain-Barré syndrome • Metabolic: Wernicke encephalopathy
Neuromuscular Disorder:	Myasthenia gravis Botulism

CN, Cranial nerve.

general orientation of that diplopia—horizontal, vertical, torsional—should be carefully determined to localize the problem. Diplopia can be horizontal with the images side by side, vertical with the images above and below each other, or torsional. Horizontal diplopia, without vertical separation, is often indicative of medial or lateral rectus muscle pathology, whereas torsional diplopia is more commonly caused by superior or inferior oblique muscle dysfunction or lateral medullary syndrome. Vertical diplopia is most commonly associated with brain or brainstem pathology but can been seen with CN IV palsy.

Important associated symptoms include vision changes, periorbital pain, pain with eye movement, ptosis, and systemic symptoms such as headache, nausea, vomiting, generalized weakness, and neurological deficits. In the absence of trauma, the presence of pain suggests an inflammatory or infectious process and narrows the differential significantly. Associated neurological symptoms concerning for cerebrovascular disease include vertigo, dizziness, ataxia, or aphasia.[3]

BOX 17.1 Key Causes of Monocular Diplopia

Dry eyes
Corneal irregularity
Cataract
Lens dislocation
Retinal wrinkles
Conversion disorder

Other critical components of the history include: progression of the symptoms, relieving or exacerbating symptoms, trauma, and past medical and family history. A history of progressive symptoms raises concern for a compressive lesion, whereas intermittent diplopia, especially if associated with ptosis, raises concerns for a neuromuscular junction disorder such as myasthenia gravis. In addition, a history of worsening symptoms throughout the day that improve with rest also raises concerns for myasthenia gravis. Past medical history should focus on immune system compromise and vascular risk factors such as hypertension, diabetes, coronary artery disease, and smoking. Family history should include questions about multiple sclerosis, lupus, and vascular diseases.

Physical Exam

The physical exam includes a complete neurological exam with particular attention on the cranial nerves. The provider should focus on any subtle findings, including head positioning, facial asymmetry, cranial nerve abnormalities, extremity weakness, and sensory deficits. Binocular diplopia, due to cranial nerve pathology on one side of the body, with neurological deficits involving the contralateral side of the body, raises the suspicion for brainstem pathology.

The eye exam should include the external eye exam, a visual acuity and visual field exam, a pupil exam, the extraocular muscle exam, a funduscopic exam, and a slit lamp exam to look at the anterior chamber as well as intraocular pressure measurements. If there is concern for increased intracranial pressure, a bedside ultrasound can be done to look for papilledema.

The external eye exam. The external eye exam includes an exam of the orbital and periorbital structures. The conjunctiva is examined for signs of injection, inflammation, chemosis, or hemorrhage. Document head positioning, proptosis, ptosis, and lid lag, as well as evidence of trauma. A patient presenting after trauma to the eye may have orbital fractures causing entrapment of the extraocular muscles, most commonly the inferior rectus muscle, which prevents the affected eye from tracking with the nonaffected eye on upwards gaze, resulting in diplopia, or a proptotic eye secondary to a retrobulbar hematoma. In addition, space-occupying lesions of the orbit can cause unilateral proptosis, and systemic diseases—for example, thyroid disease—can cause bilateral proptosis or myopathy resulting in diplopia.

Pupil exam. The patient should undergo a careful pupillary examination, looking for signs of asymmetry. Patients with a CN III palsy may have pupil dilation due to ischemia or a compressive lesion, most commonly an aneurysm at the junction of the posterior communicating artery and the internal carotid artery.[4]

Extraocular muscle exam. The extraocular muscles of the eye include the lateral rectus, which is innervated by the abducens nerve (cranial nerve VI), the superior oblique, which is innervated by the trochlear nerve (cranial nerve IV), and the inferior, superior, and medial rectus muscles, all innervated by the oculomotor nerve (cranial nerve III). An extraocular muscle injury or cranial nerve palsy in one eye will prevent both eyes from moving and tracking together. Examination of the extraocular muscles should be performed in the "H pattern"

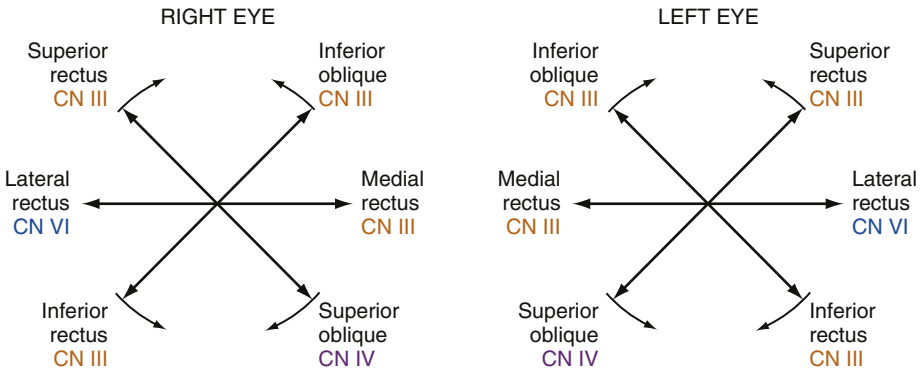


Fig. 17.1 Cardinal movements of the eyes, with the oculomotor muscles that create them and the nerves that supply those muscles. *Small curved arrows* denote intorsion or extorsion of the eye by the muscle indicated. *CN,* Cranial nerve.

(Fig. 17.1) while holding the head steady, with close observation of both eyes through the full range of motion.

Injury to the lateral rectus muscle or a palsy of CN VI will cause the affected eye to turn inward and patients will have limited abduction of the affected eye with horizontal diplopia that is worse when looking toward the affected side. Injury to the superior oblique or palsy of CN IV will cause the affected eye to be displaced slightly upwards and have vertical or torsional diplopia. Patients may compensate with a head tilt to the side of the palsy, making an isolated CN IV palsy difficult to diagnosis. Palsy of CN III results in the affected eye turning down and outwards. Patients are unable to supraduct, infraduct, or adduct the affected eye. Patients with a complete CN III palsy will also have ptosis and may have a dilated pupil.

The diplopia from a cranial nerve palsy is different from that resulting from a myositis or structural process involving the orbit and orbital structures. It can be identified during range of motion testing. Ocular myositis abruptly restricts eye movement away from the muscle, whereas a cranial nerve palsy smoothly and progressively impairs movement toward the weakened muscle. Entrapment of the inferior rectus muscle after trauma to the eye prevents the affected eye from tracking with the nonaffected eye, especially on upward gaze.

Funduscopic exam (posterior chamber exam). Structures of the posterior chamber include the retina, the optic nerve, the optic disk, the central retinal artery, the retinal veins, and the vitreous. A funduscopic exam should be performed on patients presenting with diplopia to look for signs of retinal pathology and papilledema.

Slit lamp exam (anterior chamber exam). Structures of the anterior chamber include the sclera, conjunctiva, cornea, iris, lens and the aqueous humor. Examination includes an assessment for irregularities of the pupil, inflammatory changes in the anterior chamber and abnormalities in the lens such as opacification (cataract) and positional changes. Subluxation of the lens can occur spontaneously or after trauma and the displaced lens can cause monocular diplopia. The abnormal lens is apparent on direct visualization or ultrasonography.

Signs and Symptoms

Monocular diplopia. Monocular diplopia is present only if the patient complains that the diplopia persists in the affected eye with the normal eye closed. Monocular diplopia is most commonly due to abnormal refraction, in which case it will resolve with having the patient look through a pinhole; diplopia due to a retinal abnormality or lens dislocation will not resolve with pinhole testing.

Binocular diplopia

Structural orbitopathy or myositis. An orbitopathy refers to any disease that affects the orbit and its contents. A structural orbitopathy can be caused by orbital myositis, trauma, infection/abscess, or craniofacial masses, any of which can directly restrict movement of the eye. A structural restriction of motion of a single eye, typically gradual in onset, may cause diplopia in a single direction of gaze or in multiple directions, depending on the type and extent of muscular involvement. A sensation of mass effect, discomfort, or pain in the culprit eye are characteristic symptoms. If the cause is infectious, the patient may have a history of a fever. Patients with orbital myositis due to giant cell arteritis will classically have a headache as well. Giant cell arteritis should be suspected in older patients presenting with any combination of headache, scalp tenderness, jaw claudication, or vision changes.

Signs of a structural orbitopathy or myositis include proptosis, periorbital swelling, edema, conjunctival or scleral hyperemia, and palpebral swelling involving a single eye. Diplopia due to a mass in the orbit may appear as a mechanical diplopia, in which having the patient attempt to look in the direction of the problem induces the most diplopia. This can also be seen in patients with significant periorbital swelling from trauma. In contrast, diplopia due to a process in any of the individual extraocular muscles, except for the lateral or medial recti muscles, may present with a torsional diplopia, based on the direction of pull and therefore restriction by each muscle (see Fig. 17.1). There is a mismatch between the primary direction of diplopia and primary direction of movement, possibly improved by head tilt. Although findings may mimic a neurogenic palsy to some extent, the signs induced on testing extraocular eye movements will not reflect the stereotyped deficits typical of palsies of the oculomotor cranial nerves.

Thyroid related eye disease results from the enlargement or fibrosis of the extraocular muscles and is most commonly seen in Graves disease; however, it can also be seen in other autoimmune thyroid conditions. Patients may present with isolated diplopia prior to the onset of systemic symptoms. Stigmata of thyroid eye disease includes proptosis, eyelid retraction, diffuse conjunctival edema, and vascular injection. Thyroid eye disease typically affects the inferior and medial recti muscles, first causing restriction of elevation and abduction of the eye leading to diplopia.

Isolated oculomotor nerve palsy. There are multiple causes of an isolated oculomotor nerve palsy including hypertensive or diabetic vasculopathy, a demyelinating process (multiple sclerosis), idiopathic intracranial hypertension, trauma, or compression. Isolated oculomotor nerve palsies present with typical findings as outlined in Fig. 17.2. The patient with a CN III palsy typically reports diplopia in all directions of gaze, except on lateral gaze to the affected side, and an eye that is deviated down and out. Patients may also have a dilated pupil and ptosis since CN III also innervates the levator palpebrae superioris muscle, which lifts the upper eyelid and provides parasympathetic innervation to two intrinsic ocular muscles, the ciliary and constrictor pupillae muscles. In patients

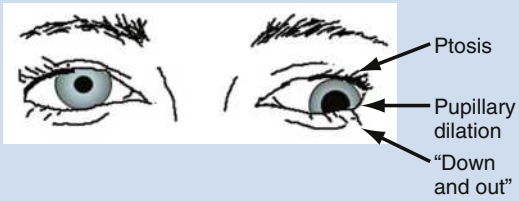
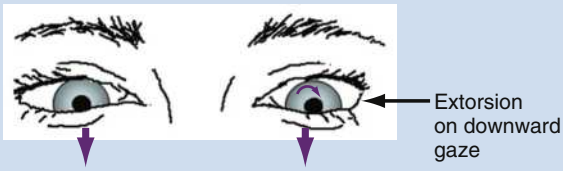
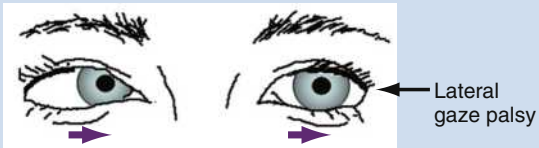
NERVE PALSY	MUSCLE(S) "OFF"	SYMPTOMS	EXAMINATION FINDINGS
Normal	N/A	N/A	
Oculomotor (CN III)	Medial, inferior, and superior rectii muscles • Inferior oblique muscle • Levator palpebrae (eyelid) • Ciliary and constrictor pupillae muscles (pupil)	Multidirectional horizontal and vertical diplopia, except on lateral gaze to the affected side • Eyelid "droop"	
Trochlear (CN IV)	Superior oblique muscle	Rotational diplopia that worsens on looking down and toward the nose	
Abducens (CN VI)	Lateral rectus muscle	Horizontal diplopia on gaze toward the affected side	

Fig. 17.2 Corresponding muscle dysfunction, symptoms, and examination findings for each oculomotor cranial nerve palsy. *CN,* Cranial nerve.

with microvascular ischemia to CN III due to hypertension and diabetes, the pupil may be spared but patients presenting with a compressive lesion, such as an aneurysm, will often have pupillary mydriasis due to the compression of pupillomotor parasympathetic fibers in the exterior of the nerve. However, this is not a hard and fast rule and should not be solely used to rule out a compressive lesion such as an aneurysm, as there are rare reports of patients with a compressive third nerve palsy having pupil sparing.[4]

A vertical or sometimes torsional diplopia that worsens on looking down and toward the nose implies a superior oblique (CN IV) palsy. A CN IV palsy makes descending stairs, reading, and watching television in bed difficult. CN IV is more susceptible to trauma because it sits against the tentorium. Diplopia that worsens on lateral gaze to one direction implies an issue with the abducens nerve (CN VI). Due to the length of the nerve, CN VI is the most common cranial nerve palsy, accounting for 50% of all CN palsies. In addition, a CN VI palsy may present with bilateral findings due to its susceptibility to increased intracranial pressure.

A patient with diplopia from an isolated palsy of CN III, IV, or VI should not have other associated symptoms. Pain and speed of onset are differentiators. A sudden isolated CN III, CN IV, or CN VI palsy associated with orbital discomfort in a patient with chronic diabetes or hypertension strongly suggests microvascular ischemia as the cause, with a caveat that a headache or eye pain may also be present in a CN III palsy caused by an aneurysmal compression. An isolated VI palsy associated with a change in vision, headaches, nausea and vomiting, with papilledema on physical exam, point to idiopathic intracranial hypertension as the diagnosis.

In contrast to an isolated cranial nerve palsy, the combination of ipsilateral palsies of CN III, IV, and VI raises a concern for cavernous sinus or orbital apex pathology, since the nerves run in close proximity in those areas. The orbital apex is the posterior part of the orbit and houses the extraocular rectus muscles, CN III, CN IV, CN V, and CN VI as well as the optic nerve. The cavernous sinuses are located in the base of the skull with CN III, CN IV, CN V, and CN VI plus the internal carotid artery traversing the cavernous sinus on each side. Trauma, infection, tumor/mass, vasculitis, and thyroid disease can all cause pathology in the orbital apex or cavernous sinus. There will typically be associated findings of exophthalmos, chemosis, and injection. Since the V1 and V2 branches of the trigeminal nerve travel though these structures, the patient may also have associated ipsilateral periorbital facial numbness or dysesthesia. An orbital apex syndrome can be differentiated from cavernous sinus pathology by decreased visual acuity since the optic nerve passes through the orbital apex.[5] Herpes zoster ophthalmicus is a well-described cause of orbital apex syndrome.

Cavernous sinus pathology may present initially with isolated CN VI involvement because it traverses through the cavernous sinus, as opposed to CN's III and IV, which are located within its wall. In addition, bilateral eye findings may be present in cases of cavernous sinus thrombosis because the cavernous sinuses directly communicate. A complex palsy in the cavernous sinus may also be iatrogenic due to intravascular injection from an intraoral dental anesthetic nerve block.

Neuroaxial process involving the brainstem and related cranial nerves. A focal brainstem lesion, seen in multiple sclerosis, may result in isolated diplopia. However, localized brainstem lesions usually present with other signs and symptoms from anatomically contiguous involvement. Additional symptoms of nausea, vertigo, or slurred speech are concerning for an impending basilar artery occlusion, especially if symptoms are sudden in onset, painless, and fluctuate. Gradual and progressive symptoms point more toward a brainstem mass. A young person with an ophthalmoplegic migraine may present in a similar fashion to someone with a brainstem stroke but will typically develop an associated ipsilateral headache.

Diplopia from a more diffuse neurologic syndrome involving the brainstem is usually gradual in onset and manifests with various other discordant symptoms. A gradually evolving combination of double vision, slurred speech, and problems swallowing suggests foodborne botulism. These patients have a descending flaccid paralysis that begins with multiple cranial nerve palsies. There may also be autonomic signs such as dry mouth, ileus, postural hypotension, respiratory muscle weakness, and pupillary abnormalities.

Nystagmus, ataxia, and altered mentation in a patient with chronic alcoholism, malnutrition, or history of bariatric surgery should raise the possibility of Wernicke encephalopathy. Most patients with Wernicke encephalopathy have ocular abnormalities, including nystagmus and ophthalmoplegia, usually from a CN VI palsy, due to metabolically induced lesions in the pontine tegmentum, abducens nucleus, and oculomotor nucleus.

In multiple sclerosis, diplopia may present as a clinically isolated syndrome or may be associated with additional neurologic findings, for example, optic neuritis with blurred vision and eye pain, focal motor findings, or sensory abnormalities. An internuclear ophthalmoplegia (INO), suggested by an inability to adduct the eye on one side in the contralateral direction during lateral gaze that resolves during convergence, implicates a lesion in the medial longitudinal fasciculus (MLF) and is typically found in patients with multiple sclerosis.

Diplopia and other cranial nerve symptoms, together with headache, photophobia, stiff neck, and fever are suspicious for a basilar meningoencephalitis. A brainstem lacunar stroke may present as any of a number of identifiable syndromes but usually presents with "crossed finding"—neurological deficits on the contralateral side of the body.

Patients with Miller-Fisher syndrome may present with an isolated ophthalmoplegia, but more typically have the classic triad of ophthalmoplegia, ataxia, and areflexia. Muscle weakness should not be present. If muscle weakness is present, the case is better classified as Guillain-Barré syndrome with ophthalmoplegia.

Neuromuscular disorder. Diplopia that is variably triggered in multiple directions, without a distinct structural or neuropathic cause, implies a neuromuscular cause such as myasthenia gravis. However, a mild neuromuscular manifestation of myasthenia may present with a diplopia isolated to one direction. In myasthenia gravis, the diplopia generally fluctuates over time, worsens with fatigue, and improves with rest. Patients with myasthenia gravis may have unilateral or bilateral ptosis, weakness on forced eyelid closure, and proximal or generalized muscle weakness, but with normal reflexes and no sensory abnormalities. There may be associated symptoms of shortness of breath or difficulty swallowing; however, approximately 50% of patients with myasthenia present with purely ocular symptoms. The diplopia may represent a myasthenic crisis, possibly associated with occult respiratory muscle weakness and ventilatory insufficiency.

Ancillary Testing

In addition to a thorough history and physical examination, additional testing may be needed in patients presenting with binocular diplopia. Patients presenting with a suspicion for systemic pathology such as hypertension, diabetes mellitus, myasthenia gravis, multiple sclerosis, thyroid disease, vascular disorders, or stroke should have lab work ordered. If thyroid disease is suspected, labs should include a thyroid panel. The inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific but should be considered in patients over 50 years old presenting with new onset binocular diplopia to rule out vasculitis and other inflammatory conditions. Patients with an ESR greater than 50, a CRP greater than 20, and other systemic symptoms of vasculitis or giant cell arteritis may need a temporal artery biopsy as well.[6,7]

If myasthenia gravis is suspected in a patient with diplopia or ptosis, a bedside ice test may be diagnostic. The test is performed by applying an ice-filled glove or bag to the patient's closed eye for 5 minutes; a positive test is an improvement in the ptosis (typically ≈5 mm) or diplopia. Cold temperatures mitigate the effect of myasthenia-related acetylcholine receptor blockade by decreasing cholinesterase activity and promoting the efficacy of acetylcholine at the endplate. The ice test has a sensitivity of 80% and specificity of 25%; another bedside test for ocular myasthenia gravis is testing for fatigability on sustained upward gaze, which has a sensitivity of 80%, and a specificity of 63%.[8] An edrophonium (Tensilon) challenge is no longer performed as the drug is not available.

Most patients presenting with binocular diplopia will undergo computed tomography (CT) or magnetic resonance imaging (MRI) imaging. Imaging will be directed by the history and physical examination; however, patients presenting to the ED with diplopia are more likely to have pathology that is better visualized by MRI, making MRI more definitive imaging and the study of choice in most cases. Patients with a history of trauma and diplopia should undergo CT and/or MRI imaging.

For an isolated neuropathy of CN III, IV, or VI presenting without evidence of an aneurysm, the optimal study is MRI of the brain and orbits with fat-suppressed orbital imaging to assess for inflammation, neoplasm, or demyelination along the course of the nerves. Isolated CN IV and VI palsy in adults, especially in adults over 50, are most commonly caused by microischemia (hypertensive or diabetic) and imaging may be deferred in patients presenting with vascular risk, absent other red flags, and only performed if symptoms persist past 3 months. However, younger patients, or those without vascular risk factors, may require initial neuroimaging and should undergo evaluation for undiagnosed hypertension and diabetes, as isolated cranial nerve palsy can be the initial clinical presentation of underlying disease. Children presenting with new onset diplopia and cranial nerve IV or VI palsy should undergo emergent MRI since compression is the most common cause of pathology in the pediatric population.

There is some controversy as to whether patients presenting to the ED with an isolated cranial nerve III palsy, with vascular risk factors and no associated signs and symptoms of compression, need emergent imaging. Patients presenting with a complete CN III palsy (complete ptosis and no adduction, depression, or elevation) and a normal reactive isocoric pupil may not need emergent imaging, as a complete CN III palsy with pupil sparing essentially excludes the diagnosis of aneurysm. However, one study found that other compressive lesions presented with pupil sparing in a small number of cases.[4] Patients without vascular risk factors and patients with an incomplete CN III palsy, regardless of pupil involvement, should undergo magnetic resonance angiography (MRA) or CT angiography to rule out a mass lesion. Patients that do not undergo emergent imaging should have close follow-up to monitor for delayed pupil involvement and progression of symptoms.[4,9]

Orbital infectious processes are readily visualized on contrasted CT of the orbits; however, extraocular muscles are best imaged by MRI of the orbits with gadolinium and high-resolution cuts through the brainstem. If MRI of the orbits is not available, a contrast-enhanced cranial CT scan with fine cuts through the orbit can be used as a second-line option. The same imaging paradigm applies to localization of the process within the cavernous sinus or orbital apex, because an MRI will highlight infiltrative, inflammatory, or compressive pathology. A CT and CT venogram of the brain and orbits should be ordered if MRI is not available. An MRI should be ordered when symptoms suggest a demyelinating process.

Lumbar puncture is diagnostic for CNS infections involving the eye and useful for inflammatory conditions that extend to the CNS. Lumbar puncture is also indicated in cases of suspected idiopathic intracranial hypertension.

DIAGNOSTIC ALGORITHM

The critical, emergent, and urgent diagnoses applicable to each of the differential considerations noted are outlined in Table 17.2. Narrowing the differential diagnosis for the ED patient with diplopia involves determining the nature of the diplopia and finding the secondary or underlying cause. Most of this diagnostic evaluation is done via the history and physical, followed by targeted imaging, as indicated. A diagnostic algorithm is presented in Fig. 17.3, using a systematic approach that incorporates the following queries, taking into consideration the symptoms and signs described earlier (see Signs and Symptoms section):

1. Is the diplopia monocular?
2. Is the diplopia due to a structural orbitopathy or orbital myositis?
3. Is the diplopia due to a palsy of the oculomotor cranial nerves (CN III, IV, VI) in a single eye?
4. Is the diplopia due to a neuroaxial process involving the brainstem and related cranial nerves?
5. Is the diplopia due to a neuromuscular disorder?

The first step is to determine if diplopia is purely monocular. In the absence of trauma, the evaluation of monocular diplopia that corrects with a pinhole essentially ends with a referral to ophthalmology. However, lens dislocation or retinal pathology diagnosed on physical examination may prompt an Ophthalmology consult.

In contrast, if the diplopia is determined to be binocular, the next question is whether or not there is an orbital myositis or structural orbitopathy, from an inflammatory, traumatic, neoplastic, or infectious cause directly restricting the movement of a single eye. If both eyes are involved, thyroid disease (Graves orbitopathy) should be considered. If an orbital mechanical problem is clearly apparent, with no neuroophthalmologic findings (including ptosis, pupillary abnormality, and anisocoria) or

TABLE 17.2 Important Causes of Diplopia

Diplopia-Causing Entity	Mechanism and Mortality	Distinguishing Features
Tier 1—Critical		
Basilar artery thrombosis	Impending thrombosis of the basilar artery with brainstem ischemia; untreated mortality, 70%–90%	Vertigo, dysarthria, other cranial nerve involvement; risk factors for stroke
Botulism	Toxin inhibits release of acetylcholine at cholinergic synapses and presynaptic myoneural junctions; untreated mortality, 60%	Dysarthria, dysphagia, autonomic dysreflexia, pupillary dysfunction
Basilar meningitis	Infection; untreated mortality, close to 100% if bacterial (15%–20% if treated)	Headache, meningismus, fever
Aneurysm	Enlarging aneurysm directly compresses cranial nerve; mortality, 26%–67% with rupture	CN III palsy with pupillary involvement
Tier 2—Emergent		
Vertebral artery dissection	Dissection causes vertebrobasilar ischemia; acute untreated mortality, 28% (2%–5% if neurologically asymptomatic)	Neck pain, vertigo; risk factors for vertebral dissection
Myasthenia gravis	Autoantibodies develop against acetylcholine (ACh) nicotinic postsynaptic receptors; untreated crisis mortality, 42% (5% if treated)	Fluctuating muscle weakness, ptosis, and diplopia worsen with activity, improve with rest
Wernicke encephalopathy	Thiamine-dependent metabolic failure and tissue injury; untreated mortality, 20%	Nystagmus, ataxia, altered mental status, ophthalmoplegia; alcoholism and nutritional deficiency
Orbital apex syndrome, cavernous sinus process	Inflammation or infection in the orbital apex or cavernous sinus directly affects oculomotor cranial nerves; acute mortality low unless infectious and complicated by meningitis	Combination of palsies of CN III, IV, or VI, with retro-orbital pain, conjunctival injection, possible periorbital, facial numbness
Tier 3—Urgent		
Brainstem tumor	Tumor involvement at the supranuclear level; acute mortality low (long-term mortality variable)	Skew deviation—vertical diplopia, internuclear ophthalmoplegia
Miller-Fisher syndrome	Autoantibodies develop to a cranial nerve ganglioside, GQ1b; acute mortality low (if fully differentiated from Guillain-Barre Syndrome (GBS);	Ophthalmoplegia, ataxia, areflexia
Multiple sclerosis	Demyelinating lesions; acute mortality low	Internuclear ophthalmoplegia
Thyroid myopathy (Graves disease)	Autoimmune myopathy; acute mortality low in regard to ocular complaints	Proptosis, restriction of elevation and abduction of the eye, signs of Graves disease
Ophthalmoplegic migraine	Inflammatory cranial neuropathy; low mortality, self-limited disease	Ipsilateral headache, CN (usually III) palsy
Ischemic neuropathy	Microvascular ischemia; mortality low, self-limited disease	Isolated CN palsy (pupil-sparing if CN III)
Orbital myositis, pseudotumor	Autoimmune or idiopathic myositis; acute mortality low in regard to ocular complaints	Eye pain, restriction of movement, periorbital edema; exophthalmos and chemosis when more severe
Orbital apex mass	Tumor, infiltration, or mass effect in orbital apex or cavernous sinus directly compresses oculomotor cranial nerves; acute mortality low	A combination of palsies of CN III, IV, or VI and possible periorbital, facial numbness, with retro-orbital pain, proptosis, signs of venous congestion

CN, Cranial nerve.

neurologic findings (including cranial nerve abnormalities), a contrast-enhanced MRI (or CT) is indicated.[9]

If the diplopia does not appear to be strictly mechanical or structural, the next question is whether there is unilateral oculomotor cranial nerve palsy in the oculomotor (CN III), trochlear (CN IV), or abducens (CN VI) nerve, from trauma, compression, or microvascular ischemia. An older patient, with vascular risk factors (hypertension, diabetes, smoking) and a classic presentation of CN IV, CN VI, or a complete CN III palsy with pupil sparing due to microvascular ischemia, does not need emergent neuroimaging if specialty follow-up is arranged. If there is

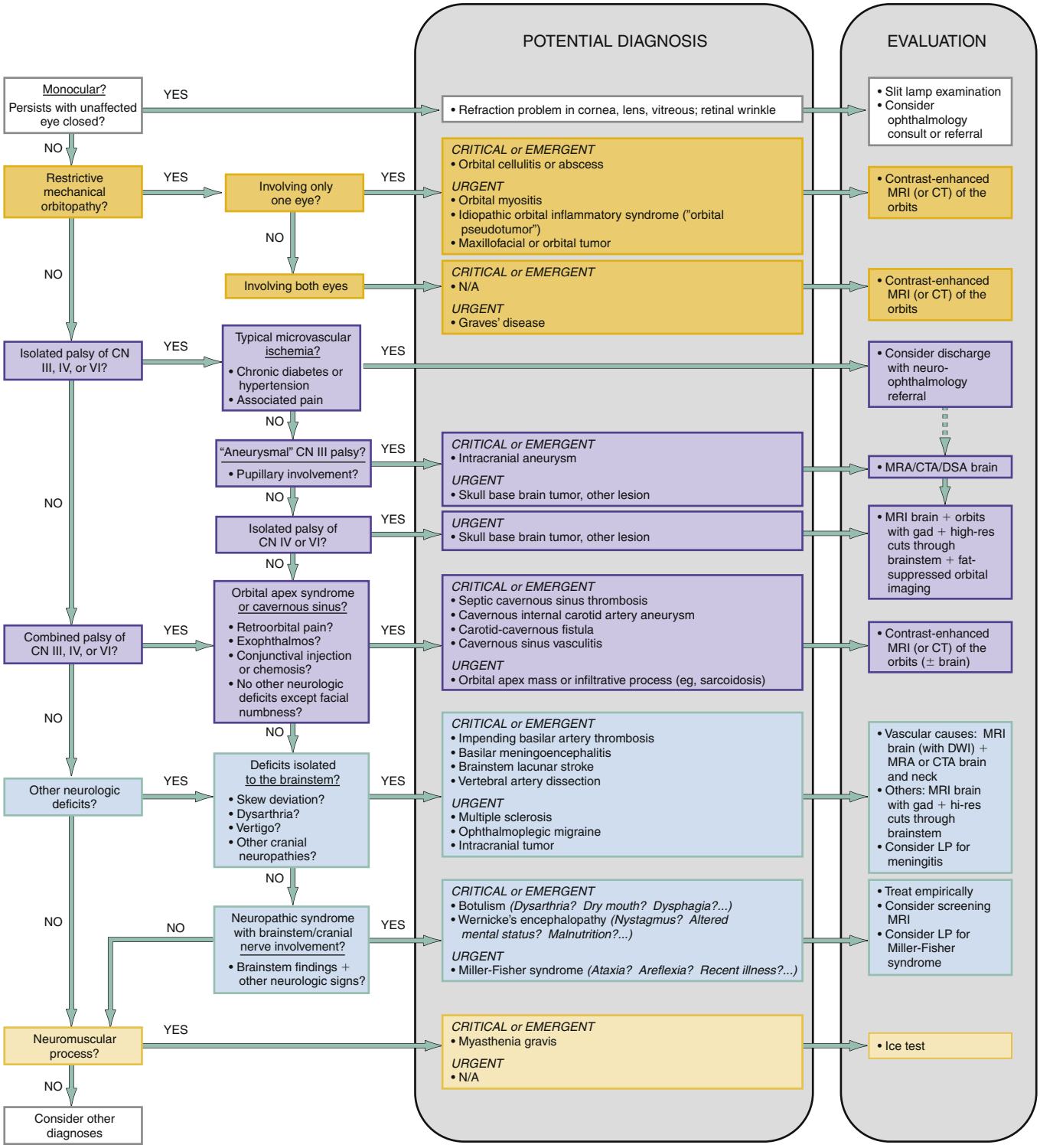


Fig. 17.3 Algorithm for the diagnostic approach to diplopia in the emergency department, a guideline. *CN,* Cranial nerve; *CNS,* central nervous system; *CT,* computed tomography; *CTA,* computed tomography angiography; *DSA,* digital subtraction angiography (conventional angiography); *DWI,* diffusion-weighted imaging; *gad,* gadolinium; *High-res,* high-resolution; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging.

any equivocation, imaging should be obtained in the ED since there is a small percentage of patients with risk factors who have a cause other than microvascular ischemia. Pediatric patients with a new-onset CN III, CN IV, or CN VI palsy and patients with ipsilateral involvement of more than one oculomotor nerve should undergo emergent imaging.

Assuming that a unilateral process, limited exclusively to the orbit or oculomotor cranial nerves, is not clearly identifiable, a neuroaxial process involving the brainstem and related cranial nerves should be considered. Brainstem lesions from multiple sclerosis, brainstem tumor, brainstem lacunar stroke, impending basilar artery thrombosis, vertebral artery dissection, or ophthalmoplegic migraine prompts an MRI of the brain plus MRA or CTA of the brain and neck. More diffuse neurologic syndromes involving the brainstem and/or CNs III, IV, and VI due an infectious, autoimmune, neurotoxic, or metabolic process (e.g., basilar meningoencephalitis, botulism, Miller-Fisher or Guillain-Barré syndrome, Wernicke encephalopathy) should be treated empirically based on signs and symptoms while the workup is obtained. Diplopia may be the first, primary, or only symptom of these diseases, and neurological signs suggesting a focal brainstem process may actually be a mild or an early presentation of a diffuse neurologic syndrome.

Finally, if the presentation of the diplopia does not fit into an anatomically congruent process, a neuromuscular cause such as myasthenia gravis or other diseases such as botulism or multiple sclerosis should be considered.

EMPIRICAL MANAGEMENT

Because the treatment of diplopia depends entirely on the cause, there are few primary treatments for diplopia in the ED. Treatment is aimed at addressing the secondary cause of the diplopia. Such approaches are outlined elsewhere in this text.

Management Algorithm

The management of diplopia centers on the diagnosis of the underlying cause. Certain emergent therapeutic measures may be indicated in the context of potentially serious underlying causes, as outlined in the algorithm in Fig. 17.4. The priority is to assess for any airway or

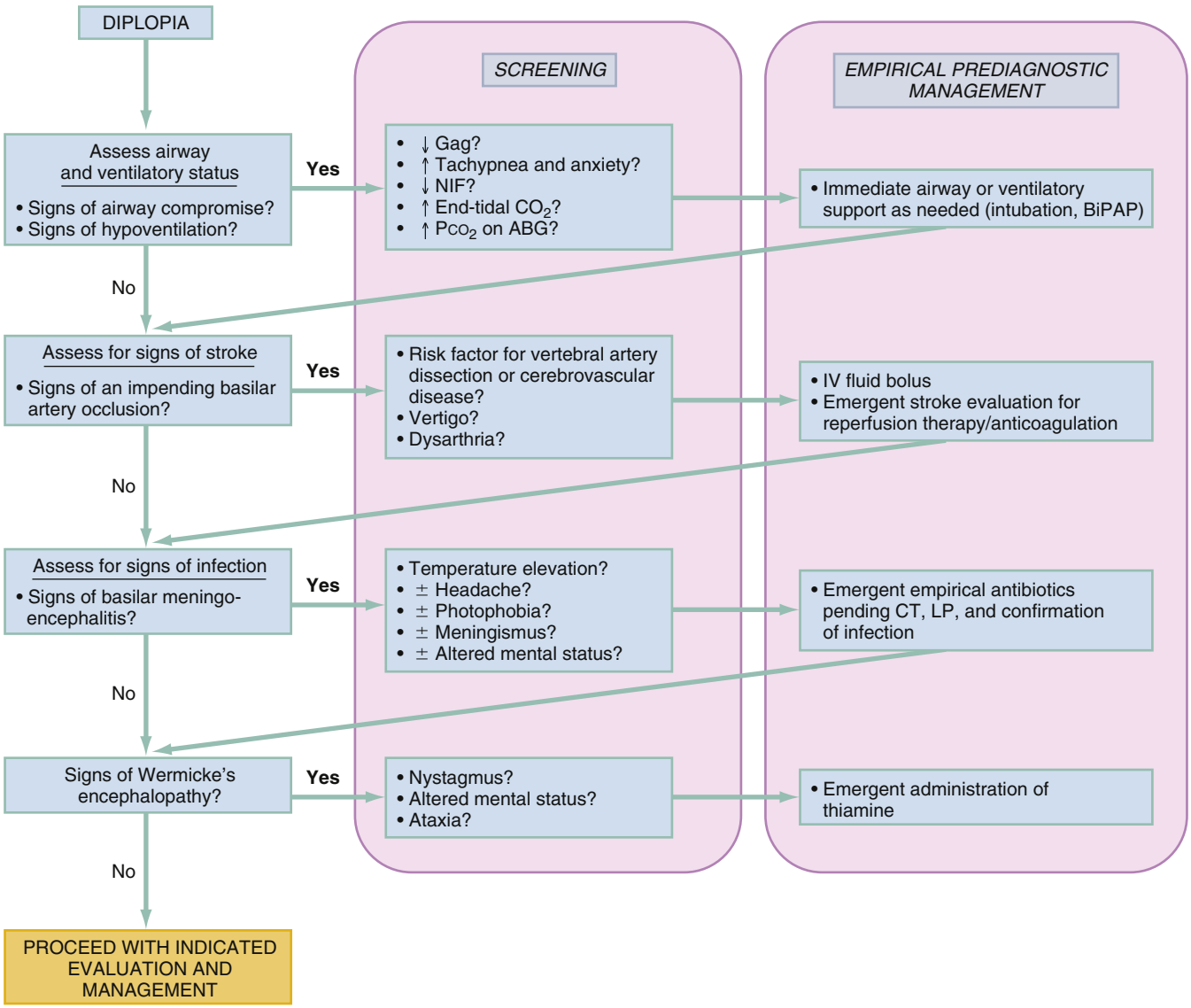


Fig. 17.4 Algorithm for the initial stabilization of the patient with diplopia in the emergency department, a guideline. *ABG,* Arterial blood gas; *BiPAP,* biphasic positive airway pressure; CO_2, carbon dioxide; Pco_2, partial pressure of carbon dioxide; *CT,* computed tomography (of the cranium); *LP,* lumbar puncture; *NIF,* negative inspiratory force.

ventilatory compromise that may be present. If the patient's airway and breathing are not compromised, the next consideration should be imminent threats to CNS tissue viability, such as an impending basilar artery thrombosis, and rapidly evolving threats to CNS tissue viability, such as botulism, meningoencephalitis, or Wernicke encephalopathy. Appropriate treatments should be started empirically either before or as the evaluation gets underway. Monitoring and frequent reassessment are indicated in patients at risk of respiratory and neurologic deterioration, for example, botulism, Guillain-Barré syndrome, brainstem strokes or intracranial hemorrhage. Patients with any suspicion for infection should be treated with antibiotics. Patients with a history of alcohol abuse or bariatric surgery should be given thiamine empirically.

The patient with binocular diplopia will typically require admission for further evaluation and treatment of the underlying disorder, unless diagnosed with a low-acuity condition such as microvascular ischemia. A CN III, IV, or VI palsy from microvascular ischemia is generally self-limited; the pain usually resolves after a few days, and complete spontaneous resolution is the norm, occurring in up to 95% of patients. These patients can typically be discharged home, with close outpatient follow-up.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 17: QUESTIONS AND ANSWERS

1. A 65-year-old man with a longstanding history of diabetes and hypertension presents with sudden onset of persistent diplopia that began a few hours before arrival. He describes left retro-orbital discomfort, and his examination is notable for a left eye that is deviated laterally and downward, with a palsy of movement medially and upward. He also has a left-sided ptosis but no conjunctival injection, chemosis, or proptosis. His pupils are equal in size at 4 mm, round, and equally reactive to light in both a direct and consensual reflex, and his examination is otherwise unremarkable. What is the most likely cause of the diplopia?

a. Brain tumor
b. Cerebral aneurysm
c. Microvascular ischemia
d. Orbital apex syndrome

Answer: c. Based on examination, this is a patient who has a pupil-sparing complete CN III (third nerve) palsy. Because his pupillary examination is normal, with an otherwise complete CN III palsy, the palsy is very unlikely to be due to external compression from a brain tumor, aneurysm, or orbital apex process. It is a typical presentation of microvascular ischemia, to which the patient is predisposed, given his history of diabetes and hypertension.

2. A 56-year-old woman presents with recurrent episodes of diplopia that have been ongoing for a week. She describes double vision that gradually comes and goes, typically worse at the end of the day, with no particular direction or orientation to the diplopia. The patient's coworker, who is present in the emergency department (ED) with her, states that the patient's eyes "looked droopy" during an animated staff meeting they attended that afternoon but look normal now. The patient also describes waxing and waning general muscular weakness that has also been present this past week but denies any other symptoms and states that when she rests, she feels better. With which entity are her symptoms most consistent?

a. Botulism
b. Hypothyroidism
c. Miller-Fisher syndrome
d. Myasthenia gravis

Answer: d. The patient and coworker are describing what appears to be an activity-related diplopia, with generalized muscle weakness and lack of other focal symptoms, all very suggestive of a possible neuromuscular process (myasthenia gravis). Miller-Fisher syndrome would not be associated with muscle weakness and would not wax and wane. Botulism would typically have a more progressive course, with other associated bulbar symptoms. Diplopia may be associated with hypothyroidism if it is a presentation of or treatment complication of Graves disease but would not change so markedly with activity.

3. A 76-year-old man with hypertension, hypercholesterolemia, and diet-controlled diabetes presents with a sudden onset of diplopia that developed 30 minutes before arrival. Paramedics state that the patient's wife reported that he suddenly began staggering around the room, unable to bear weight on his left side. On examination, the patient has normal vital signs except for mild hypertension and has a right CN III palsy, with left arm and leg weakness. He has no airway complaints and denies any pain. What is the most appropriate initial response?

a. Checking blood gas levels and assessing the patient's negative inspiratory force
b. Emergent treatment with botulinum antitoxin
c. Initiating broad-spectrum antibiotics to cover upper respiratory pathogens
d. Initiating clinical measures to address an acute ischemic stroke

Answer: d. The paroxysmal onset of the patient's symptoms, with focal neurologic symptoms and signs, suggests an ischemic event. His crossed deficits and discrete CN III palsy suggest localization in the brainstem.

4. Which constellation of symptoms is most concerning for foodborne botulism?

a. Double vision, headache, and right leg weakness
b. Double vision, left eye discomfort, and periorbital swelling
c. Double vision, nystagmus, and confusion
d. Double vision, slurred speech, difficulty swallowing, and dry mouth

Answer: d. Double vision, slurred speech, difficulty swallowing, and dry mouth would be present with foodborne botulism.

5. A 45-year-old woman presents with progressively worsening double vision and the inability to adduct the eye on one side in the contralateral direction during lateral gaze that resolves during convergence on physical examination. What disease should be suspected with these findings?

a. Multiple sclerosis
b. Botulism
c. Myasthenia gravis
d. Idiopathic intracranial hypertension

Answer: a. An internuclear ophthalmoplegia (INO), suggested by an inability to adduct the eye on one side in the contralateral direction during lateral gaze that resolves during convergence, implicates a lesion in the medial longitudinal fasciculus (MLF) and is typically found in patients with multiple sclerosis.

18

Red and Painful Eye

Alan A. Dupré and Leslie R. Vojta

KEY CONCEPTS

- Critical diagnoses, such as caustic injury, orbital compartment syndrome, and narrow angle (acute angle closure) glaucoma, require immediate treatment and ophthalmology consultation.
- Prompt and prolonged irrigation is essential for patients who experience caustic injury to the eye.
- Headache and nausea may be prominent symptoms in patients with narrow angle glaucoma.
- Complete abolition of a foreign body sensation after instillation of local anesthetic solution indicates a high likelihood of a superficial corneal lesion.
- Keratitis, inflammation of the cornea, is most commonly caused by a viral infection, but may also be caused by recent ultraviolet light exposure, chemical injury, or hypoxic injury from contact lens use.
- A localized corneal defect with edematous, inflammatory changes may signal corneal ulceration.
- A corneal dendritic pattern may signal a herpetic infection, which can progress to corneal opacification and visual loss.
- Pain, consensual photophobia, perilimbic conjunctival injection, and a miotic pupil could signal iritis or uveitis. The cause may be trauma or an underlying autoimmune disease. The presence of cell and flare in the anterior chamber can help identify these conditions.
- Conjunctivitis is usually self-limited and rarely requires antibiotic treatment.

FOUNDATIONS

Epidemiology and Pathophysiology

Most eye complaints are not immediately sight-threatening and can be managed by an emergency clinician; however, some require immediate recognition, emergent intervention, and consultation. In the United States from 2006 to 2011, the three most prevalent emergency department (ED) ocular complaints were conjunctivitis, corneal abrasion, and corneal foreign body.[1] As more outpatient ophthalmological surgeries are performed, more patients with postoperative complications can be expected to present to the ED. Nontraumatic diseases, such as glaucoma and peripheral vascular disease leading to retinal ischemia, are more common with advancing age.

The external and internal anatomy of the eye is depicted in Fig. 18.1. The globe has a complex layer of blood vessels in the conjunctiva, sclera, and retina. Redness reflects vascular dilation and occurs with processes that produce inflammation of the eye or surrounding tissues. Eye pain may originate from the cornea, conjunctiva, iris, vasculature, or optic nerve. Each is sensitive to processes causing irritation or inflammation.

DIAGNOSTIC APPROACH

Rapid and accurate triage is the most critical consideration in the approach to the red and painful eye. Critical conditions are time sensitive and can rapidly lead to progressive visual loss without immediate intervention in the ED. Urgent conditions are managed in the ED before discharge. The remainder of conditions require supportive management, such as conjunctivitis and spontaneous subconjunctival hemorrhage. Even low-acuity ocular complaints can benefit from evaluation and management by the emergency physician.

Visual acuity is the vital sign of the eye. Rare situations preclude early and accurate visual acuity testing. Patients with complaints of contamination with an acid, alkali, or other caustic substance; sudden visual loss, especially if unilateral and painless; and significant trauma, especially with retrobulbar hematoma causing orbital compartment syndrome, should have only a gross visual acuity examination performed as interventions are simultaneously prepared. When not being actively examined or treated, injured eyes with concern for globe rupture should be protected with a rigid shield to prevent inadvertent external pressure that could cause additional damage.

Differential Considerations

The diagnostic approach to the red or painful eye typically begins with categorization into traumatic and nontraumatic causes. Patients almost always can report whether or not their eye was injured—even indirectly, such as injury from reflected sunlight.

Traumatic pain and redness can be caused by caustic fluids and solid materials, low-velocity contact with a host of materials that can fall or be rubbed into the eye, higher velocity blunt-force impacts to the orbit or globe, or potentially penetrating injuries. Caustic contamination is discussed under critical diagnoses. Other traumatic complications that must be considered early in the course of care include retrobulbar hematoma, abscess, or emphysema with orbital compartment syndrome and suspicion of an open globe from either blunt or penetrating trauma.

The first triage question for any eye complaint should be, "Did anything get in your eye?" If so, attempt to identify the nature of the substance or foreign body. Specifically, this question seeks to quickly identify eyes that may have been exposed to a caustic substance. Patients exposed to acids, alkalis, and other caustic substances require rapid decontamination before additional evaluation to potentially prevent permanent loss of visual acuity.

The possibility of an open globe must be considered following any traumatic injury, regardless of the mechanism. Findings may be obvious, subtle, or occult. Blunt trauma may rupture the globe. Penetrating trauma can result from obvious causes identified through determining the events leading to injury, but it can also be unknown to the victim,

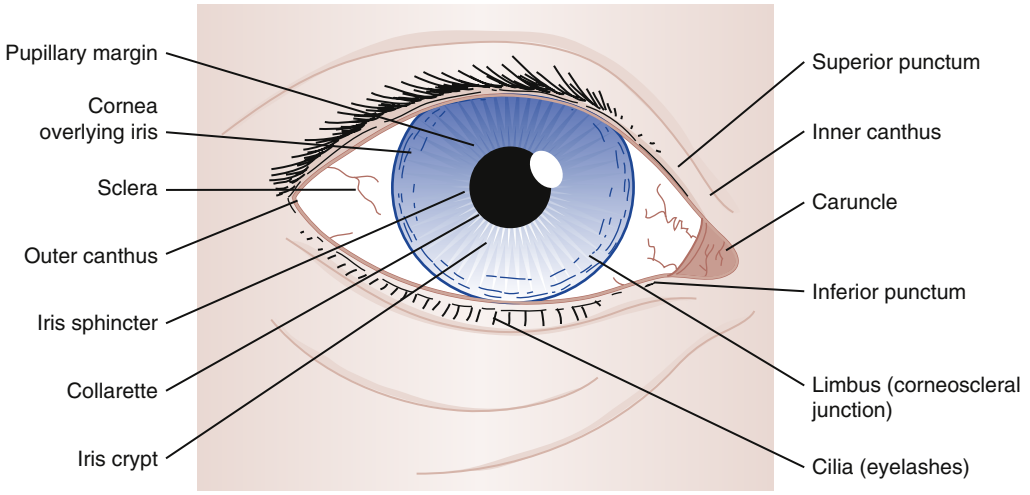

Fig. 18.1 External (A) and internal (B) anatomy. (From Ragge NK, Easty DL. *Immediate Eye Care*. St Louis, MO: Mosby-Year Book; 1990.)

such as if the patient did not realize a tiny ballistic metal fragment may have penetrated the eye while walking near a person hammering metal or using a high-speed grinder.

Causes of nontraumatic pain and redness are diverse but are mostly infectious and inflammatory, although these may be due to processes intrinsic to the globe and adjacent structures, neurologic conditions, or be due to ocular manifestations of systemic illness (e.g., giant-cell arteritis). Exposure history and review of systems are helpful when infection is suspected (e.g., concomitant upper respiratory tract infections making a viral etiology of conjunctivitis more likely). Questions related to recent surgery and contact lens wear and cleaning practices must be asked. Therefore, nontraumatic eye complaints require a more detailed history than would be necessary following a known traumatic etiology.

Not all visual disturbances are due to conditions that cause ocular inflammation resulting in pain or redness. Two conditions that are essential to consider are retinal detachment and central or branch retinal artery occlusion. Only rapid diagnosis by funduscopic or ultrasound examination and immediate intervention offer the possibility to restore sight. Retinal artery occlusion is readily apparent as a diffusely pale retina with indistinct or unseen retinal arteries (Fig. 18.2). Because these conditions do not typically present with either pain or external signs such as redness, diagnosis and treatment of retinal artery occlusion and retinal detachment are detailed in Chapter 57. Diplopia is covered in Chapter 17.

Pivotal Findings

Measurement of the patient's best corrected visual acuity (with glasses on if available) with each eye individually provides vital information when evaluating eye complaints and may be prognostic in some situations. Only a few situations, discussed earlier, preclude obtaining visual acuity using a chart. Decreased visual acuity caused by abnormal refraction (e.g., chronic myopia) can be detected by using a pinhole device during acuity testing, because central vision remains intact despite refractive errors. If there is nonrefractive pathology, such as retinal edema or aqueous hemorrhage, causing the acuity deficit, pinhole testing will show no improvement in the (poor) visual acuity.

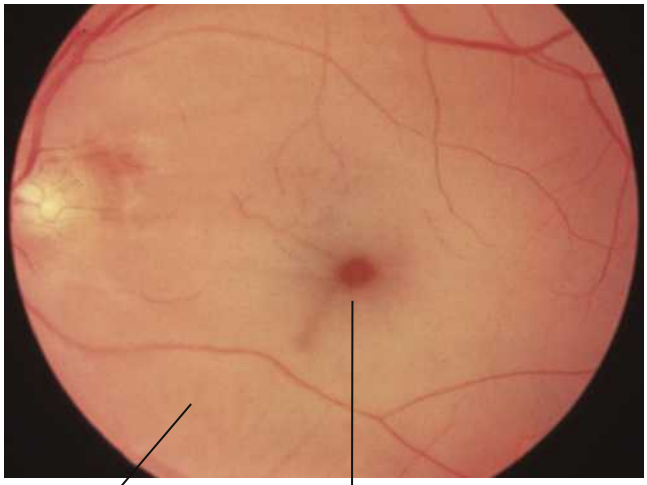

Fig. 18.2 Key funduscopic findings in acute central retinal artery occlusion include general pallor of the retina (except for a characteristic cherry-red spot where the perfused choroid shows through the thinner fovea) and attenuation of retinal arteries (possibly with retinal veins preserved as in the photograph). (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004:297.)

Symptoms and signs that are more likely to be associated with a serious diagnosis in patients with a red or painful eye are listed in Box 18.1.

Symptoms

When the presenting complaint is pain, the first step is to characterize it: itching, burning, dull pain, sharp pain, diffuse, or localized. Two factors of the history are particularly important: suddenness of onset and perception of a foreign body. A foreign-body sensation, particularly when it can be localized, is a strong indicator of corneal origin to the pain (foreign body, corneal abrasion, ulcer, or viral or ultraviolet keratitis). Itching is more often due to irritation by blepharitis, conjunctivitis, or dry eye syndrome. Burning is associated with these conditions and with other superficial problems, such as irritation of a pterygium or pinguecula, episcleritis, or limbic keratoconjunctivitis. Sharp pain generally results from abnormalities of the anterior eye, such as the cornea and uvea. Dull pain, which may be severe, is usually generalized throughout the eye (and may be reported as "headache"). It is typically a manifestation of increased intraocular pressure (IOP) (such as with narrow angle glaucoma), vitreous infection (e.g., endophthalmitis), or referred pain from an extra-orbital process (such as sinusitis, migraine headache, or temporal arteritis). Acute orbital compartment syndrome, caused by retro-orbital hematoma, presents with intense pain and progressive visual loss. These patients often present with head trauma that precludes them from reporting pain, emphasizing the importance of physical examination.

Rarely is there a chief complaint of redness that is not accompanied by pain, itching, irritation, or foreign body sensation. Completely asymptomatic "red eye" is almost always a spontaneous subconjunctival hemorrhage, which is benign but often alarming to the patient. Spontaneous subconjunctival hemorrhage may follow coughing or straining, but it most often occurs without any identifiable precipitating event and is simply noticed by the patient when looking in a mirror.

Symptomatic red eye commonly causes bulbar or limbal injection of the conjunctiva. Free blood noted behind the bulbar conjunctiva (i.e., subconjunctival hemorrhage) or in the anterior chamber (i.e., hyphema) may be spontaneous or post-traumatic. Spontaneous subconjunctival hemorrhage is painless, and the presence of pain raises concern for a more serious cause of the hemorrhage, such as direct globe injury or a retrobulbar process. Hyphema of sufficient size to be noted by the patient or bystander usually presents with pain and blurred vision.

Other symptoms include lid swelling, tearing, discharge, crusting, discomfort on blinking, or sensitivity to light. Lid swelling can be caused by inflammatory and noninflammatory processes. Concurrent erythema and tenderness of the lid favors the former. In the absence of trauma or other external irritant (e.g., contact dermatitis from eye makeup), inflammatory processes include primary lid problems, such as hordeolum (i.e., stye) or blepharitis, as well as extension from concomitant conjunctivitis or cellulitis in orbital or periorbital structures. When pain is present, tearing is usually secondary. Discharge and crusting are most commonly associated with conjunctivitis, whether allergic, chemical, viral, or bacterial. Blepharitis, dacryocystitis, and canaliculitis are other inflammatory processes that may create a discharge and subsequent crusting.

There is considerable debate within the published literature about the importance of eyelid matting as a predictor of a bacterial conjunctivitis. While some studies show that morning eyelid matting is predictive of positive bacterial cultures of ocular discharge,[2] the clinical significance of these cultures are unclear. The hazards of equating lid sticking with bacterial infection are underscored by the fact that viral conjunctivitis, particularly caused by subtypes of adenovirus, can cause dramatic symptoms with mucopurulent discharge, lid sticking, keratitis symptoms, and lid inflammation. There is a decreased likelihood of positive bacterial cultures if the redness is not observed at 20 feet, absence of morning eyelid matting, or presentation during the summer.[2] Even in the setting of a presumed bacterial conjunctivitis, most ophthalmology literature does not support the use of antibiotics in acute, mild conjunctivitis in patients who do not wear contact lenses, have a traumatic injury, and are immunocompetent.[3] Additional past ocular history questions are listed in Box 18.2.

Signs

A complete eye examination includes eight components, although many patients require only a limited or directed eye examination, depending on the presentation. The mnemonic *VVEEPP* (pronounced "veep") plus slit-lamp and funduscopic examinations represent these components (Box 18.3). We recommend slit-lamp examination for any complaint involving trauma, foreign-body sensation, or alteration of vision. Funduscopic examination is pursued if there is vision loss, visual alteration including clouding of vision, or suggestion of serious systemic pathology in the history and initial physical examination. A thorough

BOX 18.1 Pivotal Findings More Likely Associated With a Serious Diagnosis in Patients With a Red or Painful Eye

Severe ocular pain
Persistently blurred vision
Exophthalmos (proptosis)
Reduced ocular light reflection
Corneal epithelial defect or opacity
Limbal injection (also known as *ciliary flush*)
Pupil unreactive to a direct light stimulus

Adapted and reprinted with permission from Trobe JD. *The Physician's Guide to Eye Care*. San Francisco, CA: Foundation of the American Academy of Ophthalmology; 2001.

BOX 18.2 Past Ocular History Questions

1. Do you wear contact lenses? If so, what type, how are they cleaned, and how old are the lenses? How often is the lens solution changed?
2. Do you wear glasses? If so, when was your last evaluation for your glasses prescription? Do you have any changes in your vision?
3. Have you had previous eye injury or surgery?
4. What is your past medical history? Do you have any systemic diseases that may affect the eye? Do you have a weakened immune system?
5. What medications do you take?
6. Do you have any allergies?

BOX 18.3 Complete Eye Examination

*V*isual acuity (best possible using correction)
*V*isual fields (tested by confrontation)
*E*xternal examination
  Globe position in orbit
  Conjugate gaze
  Periorbital soft tissues, bones, and sensation
*E*xtraocular muscle movement
*P*upillary evaluation (absolute and relative)
*P*ressure determination (tonometry)
Slit-lamp examination
Funduscopic examination

Adapted from Wightman JM, Hurley LD. Emergency department management of eye injuries. *Crit Decis Emerg Med.* 1998;12:1–11.

physical examination can be conducted in the following order: *V*isual acuity, *v*isual field testing, *e*xternal examination, *e*xtraocular muscle movement, *p*upillary evaluation, and *p*ressure determination.

Visual Acuity

A patient's initial visual acuity provides a baseline from which deterioration or improvement may be followed. It is also predictive of functional outcome after ocular trauma. Visual acuity is quantitatively assessed by use of a Snellen chart at a distance of 20 feet (6 m) or a Rosenbaum chart at a distance of 14 inches. Young patients who cannot yet read letters and numbers should be tested with an Allen chart that depicts easily recognizable shapes. Each eye is tested separately with the opposite eye carefully covered. Patients who present without their prescribed corrective lenses are evaluated by having them view the chart through a pinhole eye cover, which improves most refractive errors in vision.

If the patient cannot distinguish letters or shapes on a chart, visual acuity must be determined qualitatively. Any printed material suffices. The result may be recorded as, for example, "patient able to read newsprint at 3 feet." If this is not possible, visual acuity is recorded as:

- Unable/able to count fingers (CF)
- Unable/able to perceive hand motion (HM)
- Unable/able to perceive light (LP)

Visual Field Testing

Confrontation is the most common method of testing visual fields in the ED, but it is unreliable for detecting anything short of an extensive field deficit. Thus, visual field examination rarely adds useful information in the evaluation of the acutely red and painful eye. Detection of a scotoma usually represents a retinal problem. However, glaucoma may cause scotomata that can be crescent-shaped, involve just the binasal visual fields, or affect all peripheral vision. Hemi- or quadrantanopia is more commonly a problem of the neural pathways to the brain.

External Examination

Gross abnormalities are assessed by a visual inspection of both eyes simultaneously. Findings are more apparent if compared with the opposite side.

Globe position is part of the external examination. Subtle exophthalmos and enophthalmos are rare and best detected by looking inferiorly, tangentially across the forehead, from over the patient's scalp. Exophthalmos may have traumatic or nontraumatic causes but may be due to increased pressure or a space-occupying lesion within the orbit, which may manifest as pain. Medical causes of exophthalmos include orbital cellulitis and intraorbital or lacrimal tumors. Hyperthyroidism may also cause enlargement of the extraocular muscles and fatty tissue within the orbit leading to exophthalmos. Orbital emphysema and inflammation caused by a retained foreign body behind the eye are other causes of exophthalmos.

The most important cause of exophthalmos in the ED is orbital compartment syndrome, which pushes the globe forward, stretching the optic nerve and retinal artery and increasing IOP. The resulting microvascular ischemia is sight-threatening if sufficiently severe and persistent. Other signs of orbital compartment syndrome include limited eye movement and a relative afferent pupillary defect (RAPD) described under ancillary testing. If retrobulbar hemorrhage is the cause, blood often dissects anteriorly to fill the subconjunctival potential spaces.

The discovery of exophthalmos should prompt ocular tonometry measurements to determine the urgency of intervention. Trauma, particularly penetrating globe injury with extrusion of vitreous, can cause the globe to recede into the orbit, but the most common cause of enophthalmos is actually pseudo-enophthalmos, when the contralateral globe is proptotic.

Inspection also involves examination of the upper and lower palpebral sulci for foreign bodies or other abnormalities. The lower sulcus is easily viewed after manual retraction of the lower lid toward the cheek and having the patient gaze upward. The upper sulcus is inspected by pulling its lashes directly forward and looking under the lid with a white light. The lid can then be everted by pressing a cotton-tipped applicator in the external lid crease and folding the lid margin over the applicator.

Conjunctivitis, with conjunctival injection and discharge, is a common diagnosis following evaluation of patients with red and painful eyes. The presence of punctate "follicles" (i.e., hypertrophy of lymphoid tissue in Bruch's glands) along the conjunctival surfaces of one or both lower lids has been touted to be relatively specific for a viral etiology (Fig.18.3). Trachoma, a chronic keratoconjunctivitis caused by *Chlamydia trachomatis,* is one notable nonviral cause of this follicular hypertrophy.

Any discharge present is assessed as serous, mucoid, or purulent. Both viral and bacterial infections can cause mucoid or purulent discharge, so it is not possible to clinically distinguish viral from bacterial conjunctivitis on this basis alone.

A red eye in a neonate or infant is always abnormal. It is usually caused by corneal abrasion or infection. Corneal abrasions can also be a cause of inconsolable crying in an infant. Fluorescein examination helps to identify traumatic abrasions and herpes keratitis acquired from the birth canal or transmitted from a caregiver's fingers. In the absence of a corneal abrasion, consider chemical conjunctivitis in the first 24 to 36 hours after birth, then consider conjunctivitis caused by *Neisseria gonorrhoeae* (2 to 5 days after birth), *C. trachomatis* (5 to 12 days after birth), and other bacterial or viral causes.[4] Early treatment is required to prevent longterm sequelae.

Extraocular Muscle Function

Limitation of ocular movement in one eye may be detected by having the patient follow the examiner's finger or a bright light through the

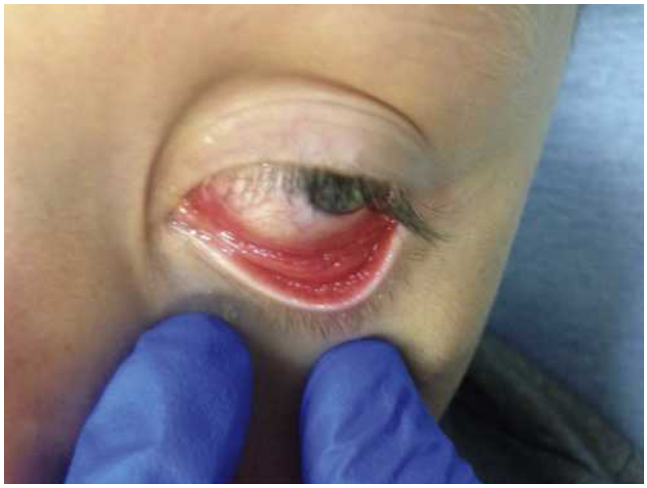

Fig. 18.3 Injection of the palpebral and bulbar conjunctiva plus hypertrophy of Bruch's glands in the lower eyelid. (Photograph courtesy Dr. John Wightman.)

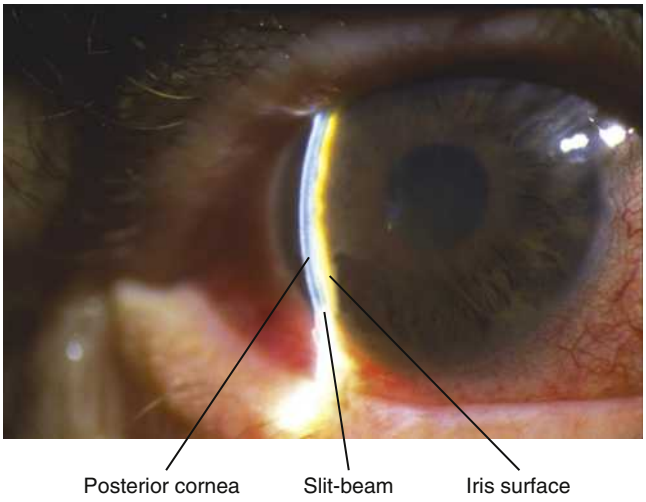

Fig. 18.4 Narrow angle-closure glaucoma with very shallow anterior chamber and iridocorneal touch (no space between slit-beam views of cornea and iris). (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004.)

cardinal movements of gaze. The eyes may move in a disconjugate fashion, or the patient may admit to diplopia if asked. Diplopia on extreme gaze in one direction may indicate entrapment of one of the extraocular muscles within a fracture site, but it is more often caused simply by edema or hemorrhage related to the injury and is functional rather than actual entrapment. In the absence of trauma, diplopia is rarely associated with redness or pain.

Pupillary Evaluation

The pupils are inspected for abnormalities of shape, size, and reactivity. These examinations are conducted with light specifically directed into the pupil and by means of the swinging flashlight test.

Blunt or penetrating trauma, previous surgery (e.g., iridotomy for cataract extraction), and synechiae from prior iritis or other inflammatory conditions are the most common causes of irregularly shaped pupils.

Asymmetrically sized pupils may represent normal or pathologic conditions. Physiological anisocoria is a slight difference in pupil size that occurs in up to 10% of the population. Topical or systemic medications, drugs, and toxins may cause abnormal pupillary constriction or dilation.

Pathologic reasons for failure of one pupil to constrict with a direct light stimulus include globe injury, abnormalities of afferent or efferent nerves, and paralysis of the ciliaris or sphincter pupillae muscles in the iris. Potentially serious problems, which also cause pain and redness, include uveitis and narrow angle glaucoma.

While examining the pupils, the anterior chambers can be visually inspected for hyphema or hypopyon. Blood in the anterior chamber is usually the result of direct ocular trauma and may be associated with traumatic mydriasis or an obvious tear of the iris. If penetration and rupture can be reasonably excluded, the hyphema should be graded and IOP determined. Inability to view posterior structures through the anterior blood may necessitate radiologic or ultrasonographic imaging. Point of care ultrasound is discussed below in the Imaging section.

Pressure Determination

Ocular tonometry is usually the last examination performed in the ED. Common methods of determining the IOP in the ED include use of electronic, manual (e.g., Schiøtz), or applanation tonometers. IOPs in the 10 to 20 mm Hg range are considered normal. Causes of intraocular hypertension include glaucoma in its many forms, suprachoroidal hemorrhage, and space-occupying retrobulbar pathology. Narrow angle glaucoma is a relatively rare but an important critical diagnosis to make in the ED. Patients present with pain, the onset of which is often sudden in low-light conditions causing pupillary dilation through contraction and thickening of the iris peripherally. The iris becomes immobile and often irregular, and the pupil is commonly fixed at 5 to 6 mm in diameter. Inability of the pupil to constrict may result in photophobia, and accommodation may be affected. These reactions and the increased IOP can lead to frontal headache, nausea, and vomiting. As inflammation progresses, limbal injection of the conjunctiva is almost universally seen. Fig. 18.4 demonstrates many of these findings. Patients presenting with IOPs exceeding 20 mm Hg should have ophthalmological consultation. Rapid treatment is usually not necessary unless the pressure exceeds 30 mm Hg.

Ancillary Testing

Physical examination can be augmented by a number of additional tests to assess the relative amount of light reaching the retina or being converted into neural signals, determine the IOP, and visually inspect the anterior and posterior globe with magnification. Imaging of internal anatomy and pathology can be accomplished at the bedside or in the radiology suite.

Swinging Flashlight Test

The swinging flashlight test is used to determine whether an RAPD exists (see https://youtu.be/soiKbngQxgw). An RAPD may be partial or complete and due to inhibition of light transmission to the retina because of vitreous hemorrhage, loss of some or all of the retinal surface for light contact because of ischemia or detachment, or the presence of lesions affecting the pre-chiasmal optic nerve (e.g., optic neuritis).

Slit-Lamp Examination

The slit lamp is used in the ED to examine anterior eye structures. It permits a magnified, binocular view of the conjunctivae and anterior globe for diagnostic purposes and to facilitate delicate procedures. It allows depth perception in otherwise clear structures, such as the cornea, aqueous humor, and lens. Fig. 18.5 shows the typical appearance of an angled slit beam reflecting from and passing through the cornea. Components of the slit-lamp examination are found in Box 18.4.

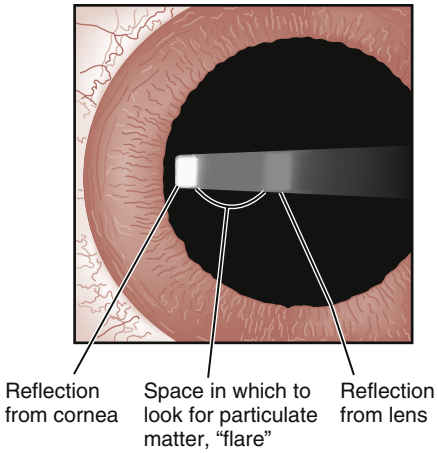

Fig. 18.5 Technique of slit-lamp examination with a short, narrow light beam projected from an extreme temporal angle across the contrasting black pupil to better find cells or "flare" indicative of acute anterior uveitis. (From Ragge NK, Easty DL. *Immediate Eye Care*. St Louis, MO: Mosby-Year Book; 1990.)

BOX 18.4 Slit-Lamp Examination

1. **Lids and lashes** inspected for blepharitis, lid abscess (i.e., hordeolum) and internal or external pointing, and dacryocystitis.
2. **Conjunctiva and sclera** inspected for punctures, lacerations, and inflammatory patterns.
3. **Cornea** (with fluorescein in some cases) evaluated for abrasions, ulcers, edema, foreign bodies, or other abnormalities.
4. **Anterior chamber** evaluated for the presence of cells (e.g., red and white blood cells) and "flare" (diffuse haziness related to cells and proteins suspended in aqueous humor), representing deep inflammation. Hyphema from surgery or trauma, hypopyon, or foreign bodies may also be noted.
5. **Iris** inspected for tears or spiraling muscle fibers noted in acute angle-closure glaucoma.
6. **Lens** examined for position, general clarity, opacities, and foreign bodies.

Fluorescein examination with cobalt blue light from the slit lamp identifies corneal defects. Fluorescein is not taken up by intact corneal epithelium but concentrates in areas where corneal epithelium is breached by an abrasion, foreign body, or ulcer (Fig. 18.6). If the patient cannot sit in front of a slit lamp, a Wood's lamp may be used for magnification and an alternative cobalt blue light source. When corneal perforation is suggested, the Seidel's test can be used to visualize anterior chamber leakage (see https://www.youtube.com/watch?v=GlFcAv0DR4c).

Ulcers can be large and easy to visualize (Fig. 18.7) or small and difficult to detect. They are best identified under slit-lamp examination by noting a denuding of epithelium with surrounding edema. Edema, in the form of increased interstitial water, is seen as whitish clouding of the normally clear tissue in the base of and adjacent to the lesion. This is best identified without fluorescein staining.

Direct Funduscopic Examination

Funduscopy is used to examine posterior eye structures. Emergency clinicians most commonly perform a nondilated funduscopic examination, because there are several eye conditions in which dilation may be harmful (e.g., narrow angle glaucoma). Iridodialysis, lens dislocation, and conditions requiring early intervention are usually identifiable along the visual axis. Inability to obtain a red reflex or visualize the fundus of the eye can be due to the causes listed in Box 18.5.

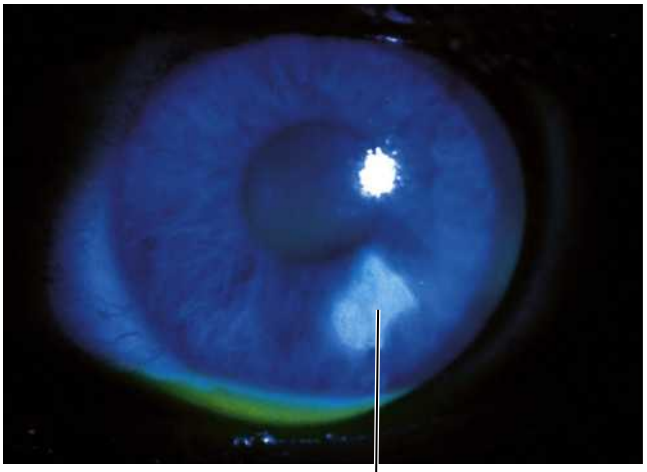

Fig. 18.6 Corneal abrasion demonstrating fluorescein pooling of a small inferior epithelial defect. (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004.)

In the absence of trauma, few posterior findings are associated with chief complaints of external redness. Findings associated with visual loss include pallor of the retina indicating ischemia, "cupping" of the optic disk indicating glaucoma, indistinctness of disk margins indicating papilledema or optic neuritis or neuropathy, air or plaque emboli in retinal arteries, and a host of other signs indicating more chronic ocular or systemic pathology not normally amenable to management in the ED.

Topical Anesthetics

Relief of discomfort after instillation of a topical anesthetic can be used as a diagnostic test for a superficial source of pain. In general, abolition of pain by local anesthetic drops indicates pain of corneal origin. Modest but incomplete relief suggests a conjunctival process. Intraocular pain, including pain associated with uveitis, is not diminished by local anesthetic solution.

Imaging

A penetrating wound that violates the sclera may be immediately obvious. In other cases, the penetration may have occurred elsewhere in the head or neck, then reach the orbit posterior to the orbital septum to injure the globe. In these cases, computed tomography (CT) or plain radiography is used to determine the presence of an intraocular or intraorbital foreign body.

Ultrasonography can be used in the ED when the patient condition precludes movement to the radiology suite, and it can be highly accurate in identifying ocular foreign bodies. In experienced hands, ultrasonography is an excellent bedside modality for evaluating pathology of the globe. Ultrasonography can be used to evaluate abnormalities of the anterior chamber, iris, ciliary body, lens, vitreous, retina, choroid, posterior wall, and optic nerve.

When used in traumatically injured patients, ultrasound can be successfully used to diagnose retinal detachment, lens dislocation, intraocular foreign body, globe rupture, retrobulbar hematoma, and vitreous hemorrhage.[5]

CT is the preferred modality for evaluating orbital trauma. Magnetic resonance imaging (MRI) clearly delineates orbital and retroorbital structures but is less rapidly obtained, with no advantages over

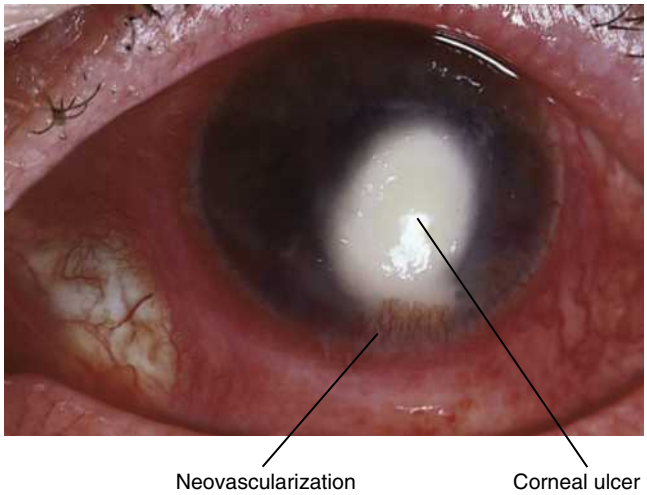

Fig. 18.7 Bacterial keratitis demonstrating a large, central *Streptococcus pneumoniae* corneal ulcer. Note the dense, white corneal infiltrate and the extreme conjunctival injection. (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004.)

BOX 18.5 Causes of Inability to Visualize a Red Reflex or the Otic Fundus

1. Opacification of the cornea, most commonly by edema secondary to injury or infection
2. Hyphema or hypopyon within the anterior chamber
3. Extremely miotic pupil
4. Cataract of the lens
5. Blood in the vitreous or posterior eye wall
6. Retinal detachment
7. Intraocular mass (e.g., retinoblastoma)

CT in trauma. MRI is contraindicated in cases of suspected metallic foreign body, and is reserved for ocular issues felt to be of neurological origin.

Laboratory Testing

Laboratory tests, such as a complete blood count, are generally not necessary in the evaluation of the red and painful eye. One notable exception is the evaluation of temporal arteritis. Temporal arteritis may present with eye pain and decreased visual acuity, but there may be no injection or other physical alteration of the eye. An erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are generally elevated in the acute phase, although one or both may be normal in up to 5% of biopsy-proven cases of temporal arteritis.[6] We recommend obtaining CRP and ESR in cases of suspected temporal arteritis.

Microbiologic cultures are rarely ordered in the ED, but an ophthalmologist may request them in select circumstances.

DIAGNOSTIC ALGORITHM

A recommended algorithmic approach to the patient with an acutely red or painful eye is provided in Fig. 18.8.

Critical Diagnoses

Critical diagnoses require immediate intervention in the ED. Ophthalmological consultation is mandatory but should not delay potentially sight-saving procedures. Critical ophthalmologic diagnoses that do not present with redness or pain are discussed in Chapter 57. Because of its prognostic value, a quick visual acuity should be obtained while the patient is being triaged and subsequently managed.

Caustic injury to the eye can rapidly lead to a destructive keratoconjunctivitis if the agent is not removed immediately (Fig. 18.9). Intervention is initiated on history alone, before any other examination is performed. Early and copious irrigation is indicated. Many patients have already undergone extensive irrigation at the job site, but when the exposure has occurred at home, adequate irrigation prior to arrival in the ED is uncommon. Alkaline caustic agents cause a liquefactive necrosis of the cornea by progressively reacting with the corneal layers, and destruction is severe and relentless. Acid injury causes coagulation necrosis, which tends to limit the depth of injury. Both types require copious irrigation with any clean, relatively neutral fluid (e.g., tap water, normal saline). Continuous irrigation until the pH of the tears is neutral is the only effective method to terminate these chemical reactions. Irrigation should be performed for a minimum of 30 minutes, using 1 to 3 L of irrigation fluid. Ideally, a physiologic buffered irrigation fluid (i.e., lactated Ringers solution) should be used to prevent further corneal edema, increase the rate of neutralization, and improve patient tolerance of the irrigation procedure, but it is more essential to rapidly irrigate the eye than to delay in search of the ideal irrigation fluid.[7] If post-irrigation examination reveals any abnormalities (except expected conjunctival injection) or if a normal pH cannot be reached, an ophthalmologist must evaluate the patient emergently. Orbital compartment syndrome can occur whenever intraorbital pressure increases to the point of causing dysfunction of the optic nerve. IOP can be used as a surrogate measure of intraorbital pressure, but this should only be safely measured when penetrating trauma is not suspected. Retrobulbar hematoma is usually caused by orbital trauma, but it can also occur spontaneously in patients with coagulopathy. Retrobulbar abscess or emphysema can also occur and increase intraorbital pressure. Elevated IOP in any of these conditions implies an orbital compartment syndrome and constitutes a surgical emergency. Intervention in the ED requires decompressing the orbit by performing lateral canthotomy and cantholysis (see https://youtu.be/bUAagMd_Q8A) to relieve the pressure on the optic nerve, and should be performed within 60 to 90 minutes of injury for the best chance of sight recovery.[8] These patients should be examined by an ophthalmologist as soon as possible afterward.

Patients with narrow angle glaucoma (see earlier) require prompt medical intervention to decrease IOP in the ED and urgent ophthalmologic consultation. Follow-up can be decided based on the patient's response to therapy and discussion with the ophthalmologist.

Emergent Diagnoses

Most emergent diagnoses involve inflammation secondary to trauma, infection, or systemic disease. These include keratitis, anterior uveitis, scleritis, and endophthalmitis. Any of these may be complications of surgical procedures, and an appropriate ophthalmological history must be obtained. Consultation with an ophthalmologist is appropriate for all emergent diagnoses.

If penetrating ocular trauma is suspected, a CT scan of the orbits should be obtained. If penetrating ocular trauma is confirmed, or if the possibility persists after evaluation, an ophthalmological consultation is indicated. The injured globe should be protected with a rigid eye shield.

Keratitis is treated with topical anesthesia, which provides immediate (but temporary) relief of pain, thus reinforcing the corneal origin of the process and facilitating examination and definitive diagnosis.

Following thorough irrigation, thermal and chemical burns must receive a careful slit-lamp examination for potential full-thickness

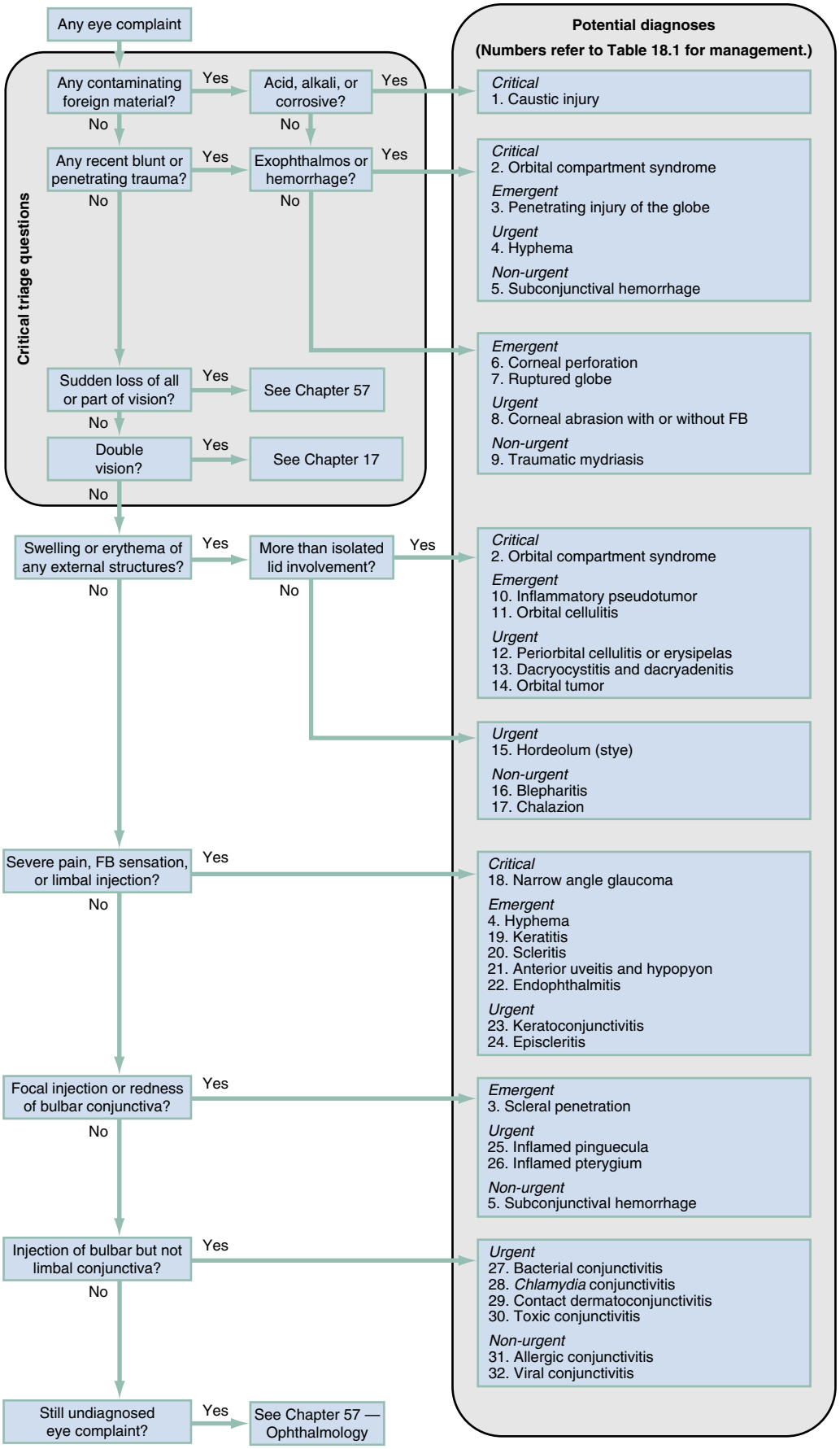

Fig. 18.8 Diagnostic Algorithm for Red and Painful Eyes. Numbers next to diagnoses correspond to Table 18.1 for management of each condition. *FB,* Foreign body.

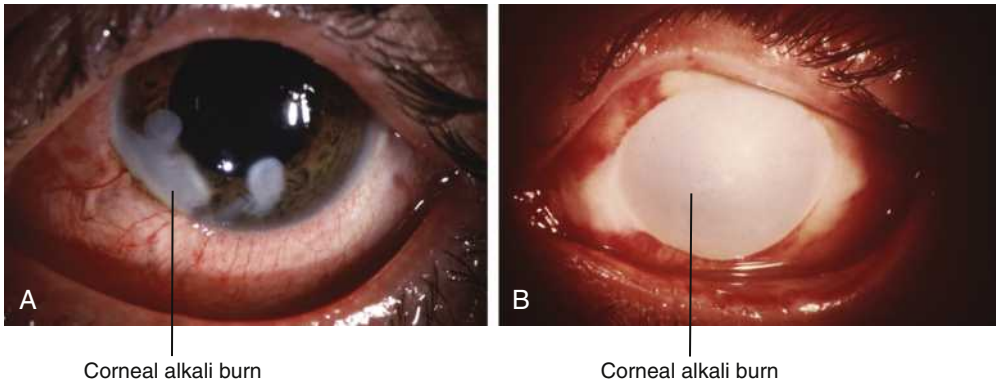

Fig. 18.9 (A) Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. (B) Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004.)

injury. If this is not found, superficial corneal burns may be treated similarly to abrasions. If full-thickness injury is identified, immediate ophthalmological consultation is indicated.

Corneal ulcerations caused by overuse of contact lenses are treated with prophylactic antibiotics and avoidance of the lenses for at least 72 hours. We recommend follow-up with an ophthalmologist or optometrist before contact lens use is resumed.

Infections of the cornea with herpes simplex virus can rapidly lead to opacification and significant visual loss. It is most commonly recognized by a characteristic dendritic pattern of fluorescein pooling under blue light (Fig. 18.10). Anterior uveitis, which includes iritis and iridocyclitis, often occurs secondary to a traumatic injury or infectious process or can be associated with serious systemic immune diseases, such as adult and juvenile rheumatoid arthritis, sarcoidosis, and ankylosing spondylitis. For these conditions, we recommend urgent ophthalmologic evaluation, either in the ED or by immediate evaluation in an ophthalmological clinic.

Scleritis is commonly idiopathic, but may be associated with a systemic inflammatory process, such as a connective tissue disease, gout, or infection (e.g., rheumatoid arthritis and granulomatosis with polyangiitis, Lyme disease, syphilis, tuberculosis). Scleritis can be divided into anterior scleritis (either diffuse, nodular, or necrotizing) or posterior scleritis and is distinguished from other causes of ocular redness by recognition of inflamed vasculature in the deeper sclera, sometimes appearing violaceous. Posterior scleritis is more difficult to diagnose because some patients do not have anterior signs of inflammation to accompany their history of dull, ocular pain. Diagnosis can be made using point of care ultrasound to visualize thickening of the posterior wall of the globe.[9] Often presenting without pain, episcleritis is a more common, superficial, and benign inflammatory process and less often associated with an underlying systemic infectious or inflammatory disease.

Endophthalmitis usually results from an infection of structures inside the globe. It is most common following penetrating trauma or after intraocular surgical procedures but may begin after hematogenous seeding from a remote or systemic infection, particularly in immunocompromised hosts. Unless it is detected early and is responsive to antimicrobial therapy, endophthalmitis is a devastating process that frequently requires enucleation.

Urgent Diagnoses

Foreign bodies on the cornea or under the lid are removed, as described in Chapter 57.

Fig. 18.10 Fluorescein pooling in the dendritic-shaped lesions of herpes simplex keratitis. (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004.)

Superficial corneal abrasions, once universally patched, are now known to heal spontaneously without patching, prophylactic antibiotics, or prophylactic tetanus immunization.

Patients with hyphema are placed with the head of the bed elevated to 30 degrees, and they receive systemic analgesia and, if required, antiemetics, with emergent ophthalmologic consultation (see Chapter 57). Medications affecting platelet function should be avoided. If the iris is not injured, a long-acting cycloplegic agent (e.g., topical homatropine) may be recommended to prevent repetitive motion of the iris. After consultation by ophthalmology, outpatient therapy and follow-up are often sufficient for management with simple analgesia (e.g., acetaminophen) for pain. Though outpatient therapy is appropriate for most patients, some will require hospitalization, including patients with large hyphemas (>50%), increased IOP, history of sickle cell trait or disease, history of coagulopathy, or those who may have difficulty adhering to the treatment plan as an outpatient.[10] We recommend a rigid shield to protect the eye during sleep, but this should not be worn during the day. The patient should see the ophthalmologist or return to the ED if the patient experiences an increase in pain or decrease in visual acuity.

EMPIRIC MANAGEMENT

Management of the specific entities listed in the diagnostic algorithm presented in Fig. 18.8 is presented in Table 18.1. Specific management of ophthalmologic conditions is also discussed in Chapter 57.

Critical and emergent conditions are treated as described earlier. All other ocular emergencies are generally diagnosable in the ED, and treatment is initiated based on the diagnosis. Caustic exposures receive copious irrigation, but all chemical or liquid exposures should undergo irrigation unless 1 hour has passed since exposure and the patient is completely asymptomatic at the time of evaluation.

Foreign bodies should be removed, along with all fine particulate matter. Irrigation is advisable after foreign body removal if there is suspicion of remaining, very fine, foreign substance. After irrigation,

TABLE 18.1 Management Algorithm for Red Eyes Extended From Diagnostic Algorithm in Fig. 18.8[a]

Potential Diagnosis	Key Findings	Management	Consultation	Disposition
1. Caustic injury		Immediate and copious irrigation with tap water or sterile normal saline until tear-film pH = 7. Solids: Lift particles out with dry swab before irrigation Acids: Minimum of 2 L and 20 min Alkalis: Minimum of 4 L and 40 min	Ophthalmologist must come to ED if there is any abnormal visual acuity or objective finding on examination after sufficient irrigation, with exception of expected injection of conjunctiva secondary to treatment.	Discharge only if tear film pH = 7 and no abnormal findings on examination except conjunctival injection; then ophthalmologist can reevaluate next day.
2. Orbital compartment syndrome	Exophthalmos (proptosis), decreased visual acuity, painful or limited ocular mobility, and increased IOP	Measure IOP, unless the possibility of a ruptured globe. IOP >30 mm Hg may necessitate lateral canthotomy and cantholysis in ED.	IOP >20 mm Hg may be surgical emergency, may add medications used in glaucoma #18 to decrease IOP before decompression in ED. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses. Consider POCUS	Admit all cases of retrobulbar pathology causing increased IOP. Others might be candidates for discharge depending on the cause of the problem.
Retrobulbar hematoma	Occurs due to trauma, coagulopathy, or thrombocytopenia and associated with possible dissection of blood to potential space under bulbar conjunctiva	Correct any coagulopathy or thrombocytopenia. Consider performing lateral canthotomy and cantholysis in the ED.		
Retrobulbar emphysema	Occurs with forceful sneeze or occasionally happens spontaneously and associated with possible dissection of air to potential space under bulbar conjunctiva	Antibiotic prophylaxis to cover sinus flora.		
Retrobulbar abscess	Occurs with contiguous or occasionally hematogenously disseminated infection and associated with possible dissection of pus to potential space under bulbar conjunctiva	Antibiotics as in orbital cellulitis (see #11).		
3. Penetrating injury of the globe	Localized redness at site of entry plus possible teardrop pupil, blood in anterior chamber or loss of red reflex	Protect the eye from further pressure, provide pain relief, and prevent vomiting. Parenteral antibiotic and tetanus prophylaxis.	Ophthalmologist must come to ED if there is any concern for globe penetration.	Admit for continuation of antibiotics and possible procedural intervention.
4. Hyphema	Pain, decreased visual acuity, gross or microscopic blood in anterior chamber, may be associated with dilated and fixed pupil following blunt trauma Graded by amount of blood: • Percentage of vertical diameter of anterior chamber when blood layers with patient in upright position • Microhyphema shows no layering and only suspended red blood cells	First, rule out open globe. May require POCUS if cannot visualize posterior structures. Measure IOP unless the possibility of a ruptured globe. IOP >30 mm Hg may require acute treatment as in glaucoma (see #18). If IOP >20 mm Hg and no iridodialysis, may use cycloplegic to prevent iris motion.	Discuss findings and use of antifibrinolytics and steroids, other medical therapy, best disposition, and follow-up examination by ophthalmologist within 2 days. Some patients (e.g., those with sickle cell disease/trait, coagulopathy) may be admitted for observation, bed rest, head elevation, and frequent medication administration.	Most patients can be discharged with careful instructions to return for any increased pain or change in vision. Patients should decrease physical activity and sleep with an eye shield in place. Eyes should be left open while awake so that any change in vision can be immediately recognized. PO NSAIDs or narcotics should be given for analgesia.

TABLE 18.1 Management Algorithm for Red Eyes Extended From Diagnostic Algorithm in Fig. 18.8[a]—cont'd

5. Subconjunctival hemorrhage	Red blood beneath clear conjunctival membrane	Exclude coagulopathy or thrombocytopenia, if indicated by history.	None required if no concerns for underlying ocular pathology and no acute complications.	Reassure patient that discoloration should resolve over 2–3 weeks.
6. Corneal perforation	Direct visualization of full-thickness injury or positive Seidel's test	Protect eye from further pressure, provide pain relief, and prevent vomiting. Administer parenteral antibiotic and tetanus prophylaxis.	Ophthalmologist must come to ED to evaluate.	Admit for continuation of antibiotics and procedural intervention.
7. Ruptured globe	Misshapen cornea or globe following trauma	Protect eye from further pressure, provide pain relief, and prevent vomiting. Parenteral antibiotic and tetanus prophylaxis.	Ophthalmologist must come to ED to evaluate.	Admit for continuation of antibiotics and procedural intervention.
8. Corneal abrasion	History of direct trauma or foreign body plus direct visualization of defect in the corneal epithelium using white light, or fluorescein and blue light; any surrounding corneal edema indicates a concomitant keratitis (see #19)	Antibiotic prophylaxis with polymyxin-B/trimethoprim solution 1 drop every 3 h while awake and erythromycin ointment while sleeping. If contact lens wearer, consider fluoroquinolone	Discuss plan for follow-up in 1–3 days.	May discharge if no other findings. No patch.
9. Traumatic mydriasis	Nonreactive dilated pupil without any other identifiable eye abnormalities following blunt trauma	None once other abnormalities of the eye, cranial nerves, and brain have been reasonably excluded.	Discuss plan for follow-up evaluation of slowly developing hyphema and ensure resolution.	May discharge if no other findings.
10. Inflammatory pseudotumor	Nonspecific idiopathic retrobulbar inflammation with eyelid swelling, palpebral injection of conjunctiva, chemosis, proptosis, blurred vision, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina	Measure IOP. Evaluate for infection, diabetes mellitus, and vasculitis with CBC, BMP, UA, and CRP or ESR. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP >20 mm Hg may be surgical emergency, may add medications used in glaucoma #18 to decrease IOP before decompression in ED.	May discharge if no systemic problems, no findings of particular concern on CT, and IOP ≤20 mm Hg. Start high-dose PO steroids after discussion with ophthalmologist, and ensure reevaluation in 2–3 days.
11. Orbital cellulitis	Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone; palpebral injection of conjunctiva, and chemosis; differentiated from periorbital cellulitis by presence of any finding of fever, ill appearance, blurred vision, proptosis, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina	Measure IOP and rule out orbital compartment syndrome. Start parenteral antibiotics targeted at suspected infection source with vancomycin, ceftriaxone/cefotaxime and metronidazole (if need to cover anaerobes)	IOP >20 mm Hg may be surgical emergency, may add medications used in glaucoma #18 to decrease IOP before decompression in ED. Obtain blood cultures and start antibiotics. Axial and coronal CT of orbits and sinuses to rule out FB, retrobulbar abscess, orbital gas, subperiosteal abscess, osteomyelitis, and changes in cavernous sinus. Consider LP.	Admit all cases of orbital cellulitis.
12. Periorbital cellulitis or erysipelas	Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone, palpebral injection of conjunctiva, and chemosis; differentiated from orbital cellulitis by absence of any other finding listed in #11	First rule out orbital cellulitis (see #11). PO antibiotics for sinus and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient.	May discharge mild cases with PO antibiotics. Ophthalmologist must reevaluate next day to ensure no orbital extension.

Continued

TABLE 18.1 Management Algorithm for Red Eyes Extended From Diagnostic Algorithm in Fig. 18.8[a]—cont'd

13. Dacryocystitis and dacryoadenitis	Eye tearing and inflammation of lower eyelid inferior to lacrimal punctum finding redness and tenderness over nasal aspect of lower lid and adjacent periorbital skin	First rule out orbital cellulitis (see #11) and periorbital cellulitis (see #12). Inspect for obstruction of punctum by SLE, may express pus by pressing on sac, PO antibiotics for nasal and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient. Ask about culturing before prescribing medications if admitting, and then may add medications used in glaucoma #18 to decrease IOP before decompression.	May discharge mild cases with PO analgesics and antibiotics (e.g., amoxicillin/clavulanate), and instructions to apply warm compresses to eyelids for 15 min and gently massage inner canthal area four times a day.
14. Orbital tumor	Blurred vision, proptosis or other displacement of globe, painful or limited ocular mobility, or binocular diplopia (but can be asymptomatic)	Measure IOP. Evaluate for extraocular signs of malignancy. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP >20 mm Hg may be surgical emergency, prescribe to decrease IOP in ED. Ophthalmologist may want MRI, MRA, or orbital ultrasonography.	Based on findings and discussion with consultant.
15. Hordeolum (stye)	Abscess in eyelash follicle or modified sebaceous gland at lid margin: external or internal based on side of lid margin that abscess is pointing	External: Warm compresses often all that is needed, may prescribe anti-*Staphylococcus* ointment twice daily. Internal: PO antibiotics for β-lactamase–positive *Staphylococcus* such as amoxicillin/clavulanate	Outpatient referral only for treatment failure after 2 weeks.	Discharge with instructions to apply warm compresses to eyelids for 15 min and gently massage abscess four times a day.
16. Blepharitis	Inflammation of eyelid margins often associated with crusts on awakening, FB sensation, and tearing	Artificial tears, as needed for dry eye.	Outpatient referral only for treatment failure after 2 weeks.	Discharge with instructions to apply warm compresses to eyelids for 15 min four times a day and scrub lid margins and lashes with mild shampoo on washcloth twice daily.
17. Chalazion	Inflammation of meibomian gland causing subcutaneous nodule within the eyelid	None.	Outpatient referral only for treatment failure after 2 weeks.	Discharge with instructions to apply warm compresses to eyelids for 15 min and gently massage nodule four times a day.
18. Narrow angle glaucoma	Sudden-onset eye pain and blurred vision that may be associated with frontal headache, nausea, and vomiting; anterior eye may manifest shallow or closed angle between iris and cornea, pupil fixed at midsize, or limbal injection of conjunctiva	Administer medications below in ED if IOP >30 mm Hg Decrease production of aqueous humor: • Timolol 0.5% 1 drop • Apraclonidine 1% 1 drop • Dorzolamide 2% 1 drops or if sickle cell disease or trait, then methazolamide 50 mg PO Decrease inflammation: • Prednisolone 1% 1 drop every 15 min four times Constrict pupil: • Pilocarpine 1%–2% 1 drop after IOP <50, then repeat in 15 min Consider establishing osmotic gradient: • Mannitol 2 g/kg IV	Discuss any IOP >20 mm Hg with ophthalmologist.	Based on findings and discussion with consultant, which primarily depends on speed of onset and response to treatment.

TABLE 18.1 Management Algorithm for Red Eyes Extended From Diagnostic Algorithm in Fig. 18.8[a]—cont'd

19. Keratitis (abrasion or UV injury)	Pain, FB sensation, blepharospasm, tearing, photophobia, epithelial disruption on inspection under white light, or fluorescein pooling under blue light; SPK appears as stippling of corneal surface (often lower two-thirds of cornea if due to light exposure); if neglected for a time, may have surrounding edema appearing as white "cloudiness" in clear tissue	First, rule out corneal penetration employing Seidel's test. Relieve pain and blepharospasm with topical anesthetic. Inspect all conjunctival recesses and superficial cornea for any foreign material that can be removed by irrigation or manually lifted from surface.	Ophthalmologist must come to ED if there is any concern for globe penetration. Otherwise consult for follow-up examination in 1–2 days.	May discharge cases not infected or ulcerated. May provide topical antibiotic prophylaxis using polymyxin B combinations with bacitracin (ointment) or trimethoprim (solution). Erythromycin, gentamicin, and sulfacetamide are less desirable single-agent alternatives. PO NSAIDs or narcotics for analgesia. No patch.
Keratitis (ulceration)	Symptoms and signs as described previously; ulceration from complications of contact wear has "scooped out" epithelium with surrounding edema appearing as white "cloudiness" in clear tissue	Relieve pain and blepharospasm with topical anesthetic. *Staphylococcus* and *Streptococcus* species still most common organisms, but *Pseudomonas* greater percentage in existing infections (especially contact lens wearer), so prescription with topical fluoroquinolone is preferred.	Discuss with ophthalmologist any potential need to débride or culture before starting antibiotic.	Based on findings and discussion with consultant. Typically prescribe fluoroquinolone. For large ulcerations or ulcers near the visual axis, a fortified antibiotic, such as tobramycin, may be added.
Keratitis (herpetic infection):	Symptoms and signs as described previously Look for other signs of herpes, varicella, zoster (or CMV infection in immunocompromised patient) Look for "dendritic" defects of cornea with fluorescein under blue light	Relieve pain and blepharospasm with topical anesthetic. Prescribe acyclovir 5% ointment or trifluridine 1% solution Varicella-zoster and CMV not normally given antivirals if immunocompetent.	Discuss with ophthalmologist any potential need to débride or culture before starting antiviral.	Based on findings and discussion with consultant. Typical acyclovir dosing is five times a day for 7 days, then taper over 2 more weeks. Typical trifluridine dosing is 1 drop every 2 h for 7 days, then taper over 2 more weeks. PO NSAIDs or narcotics for analgesia. No patch.
20. Scleritis	Progressively increasing eye pain with radiation to ipsilateral face and decreasing vision, photophobia, tearing, and possible pain with eye motion	Decrease inflammation with PO NSAIDs.	Discuss findings and use of topical or PO steroids.	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2–3 days.
21. Anterior uveitis and hypopyon	Eye pain, photophobia, tearing, limbal injection of conjunctiva, and cells or flare in anterior chamber; hypopyon is layering of white cells (pus) in anterior chamber	First, rule out glaucoma with IOP measurement. Prescribe in ED if IOP >20 mm Hg. Otherwise okay to dilate pupil with 2 drops of cyclopentolate 1%.	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist but range is every 1–6 h).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2–3 days. Patients with hypopyon are generally admitted.
22. Endophthalmitis	Progressively increasing eye pain and decreasing vision, diminished red reflex, cells and flare (and possibly hypopyon) in anterior chamber, chemosis, and eyelid swelling	Empirical parenteral antibiotic administration with vancomycin and ceftazidime to cover *Bacillus, enterococcus*, and *Staphylococcus* spp. Ciprofloxacin or levofloxacin are used when others contraindicated.	Ophthalmologist must admit for parenteral and possibly intravitreal antibiotics.	Admit all cases of endophthalmitis.

Continued

TABLE 18.1 Management Algorithm for Red Eyes Extended From Diagnostic Algorithm in Fig. 18.8[a]—cont'd

23. Keratoconjunctivitis	Conjunctivitis with subepithelial infiltrates in cornea causing pain and decreased vision, possibly with halos reported	Treat for conjunctivitis by likely etiologic category (see #25 to #30).	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2–3 days.
24. Episcleritis	Rapid onset of localized pain, injection of episcleral vessels, and localized tenderness	Relieve irritation with artificial tears.	Outpatient referral only for treatment failure after 2 weeks.	Discharge patient with PO NSAIDs
25. Inflamed pinguecula	Inflammation of soft yellow patches in temporal and nasal edges of limbal margin	Decrease inflammation with naphazoline or ketorolac drops.	Outpatient referral only for treatment failure after 2 weeks.	Discharge to follow-up with ophthalmologist for possible steroid therapy or surgical removal.
26. Inflamed pterygium	Inflammation of firmer white nodules extending from limbal conjunctiva onto cornea			
27. Bacterial conjunctivitis	Hyperpurulent discharge not typical of common "pink eye" and more commonly unilateral in adults; inflammation of eyelid margins associated with lid edema, chemosis, and possibly subconjunctival hemorrhage, but usually little or no follicular "cobblestoning"	Topical polymyxin-B/trimethoprim in infants and children, because more *Staphylococcus* spp. Topical sulfacetamide or gentamicin clinically effective in 90% of uncomplicated adult cases. Use topical fluoroquinolone if Pseudomonas possible.	Culture drainage and ophthalmology consult in all neonates and those at risk for vision loss or systemic sepsis. *Neisseria gonorrhoeae* can be rapidly sight threatening.	Discharge uncomplicated cases with 10 days of topical antibiotics in both eyes, regardless of laterality of apparent infection. Use ointments in infants and drops in others.
28. Chlamydia conjunctivitis	Often bilateral palpebral injection of conjunctiva in neonate or other individual at risk for sexually transmitted disease	Empirical PO azithromycin for Chlamydia. Consider empirical parenteral ceftriaxone for concurrent *N. gonorrhoeae*.	Culture drainage and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Discharge uncomplicated cases on 3 days of PO azithromycin.
29. Contact dermatoconjunctivitis	Localized lid and conjunctival redness and swelling	Irrigation with tap water or sterile normal saline. Decrease irritation with naphazoline drops.	Outpatient referral only for severe cases or treatment failure after 2 weeks.	Identify offending agent and avoid subsequent exposure. Discharge uncomplicated cases on continued naphazoline.
30. Toxic conjunctivitis	Diffuse conjunctival injection, chemosis, and lid edema	Irrigation with tap water or sterile normal saline. Decrease irritation with naphazoline drops.	Outpatient referral only for severe cases or treatment failure after 2 weeks.	Identify offending agent and avoid subsequent exposure. Discharge uncomplicated cases on continued naphazoline.
31. Allergic conjunctivitis	Often bilateral palpebral injection of conjunctiva and chemosis that may be seasonal and associated with other allergic symptoms, such as rhinitis	Decrease irritation with naphazoline drops or consider ophthalmic antihistamine	Outpatient referral only for treatment failure after 2 weeks.	Identify antigen if possible. Consider treating other allergic symptoms with PO antihistamines.
32. Viral conjunctivitis	Often bilateral palpebral injection of conjunctiva and follicular cobblestoning of inner surface of lower lid; inflammation of eyelid margins often associated with crusts on awakening, FB sensation, and tearing	Decrease irritation with artificial tears, naphazoline, or ketorolac drops.	Culture drainage, and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Ask about pregnant mothers, infants, and immunocompromised individuals in close contact. Discharge uncomplicated cases with instructions on respiratory and direct-contact contagion for 2 weeks.

BMP, Basic metabolic profile (includes electrolytes, glucose, and renal function tests); *CBC*, complete blood count; *CMV*, cytomegalovirus; *CRP*, C-reactive protein; *CT*, computed tomography; *ED*, emergency department; *ESR*, erythrocyte sedimentation rate; *FB*, foreign body; *IOP*, intraocular pressure; *IV*, intravenous; *LP*, lumbar puncture; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *NSAID*, nonsteroidal antiinflammatory drug; *PO*, per os (by mouth); *POCUS*, point of care ultrasound; *SLE*, slit-lamp examination; *SPK*, superficial punctate keratitis; *spp.*, species; *UA*; urinalysis; *UV*, ultraviolet.

[a]Antibiotic choices should be based on current practice.

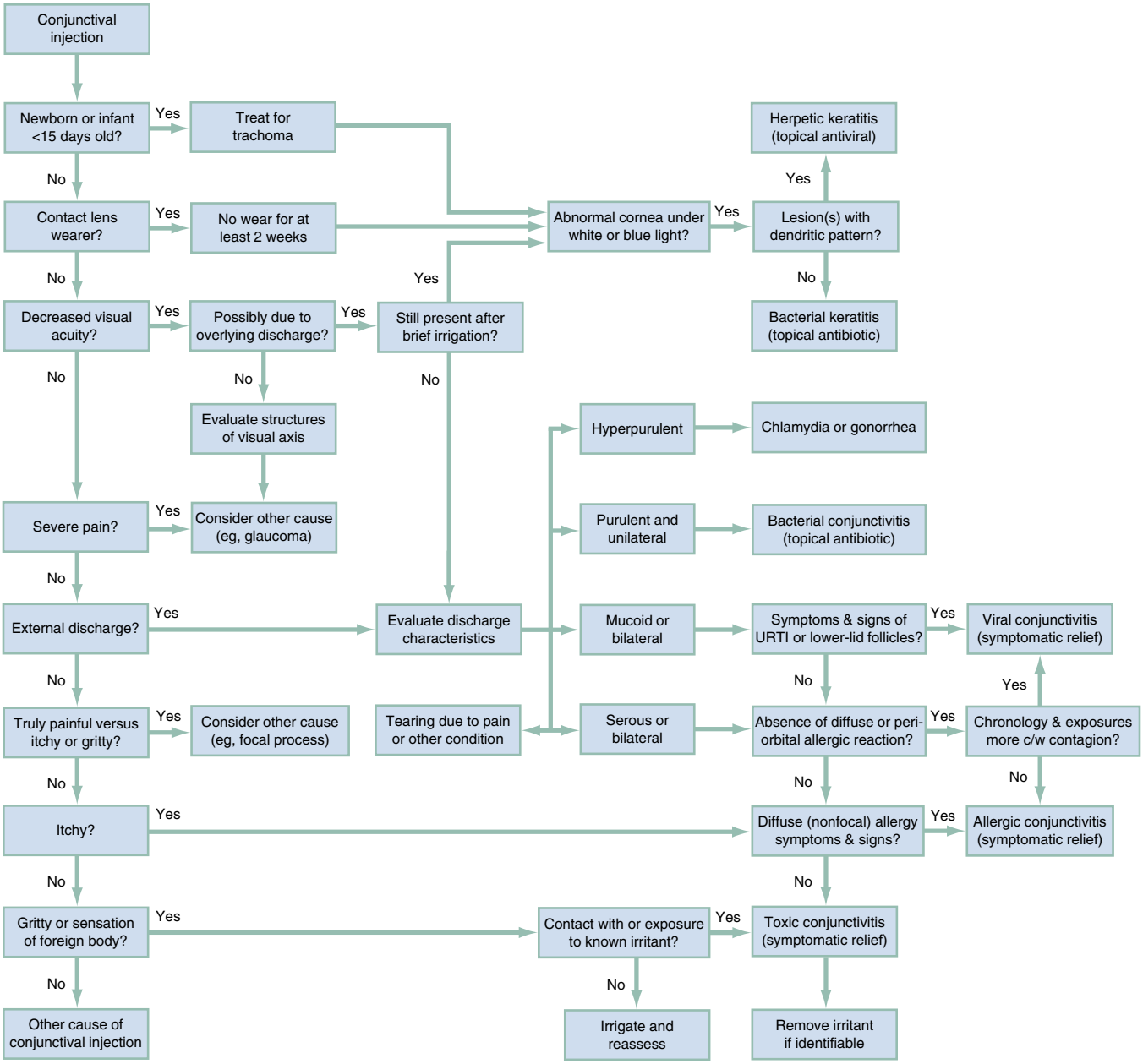

Fig. 18.11 Diagnostic Algorithm for Suspected Acute conjunctivitis. *c/w,* Consistent with; *URTI,* upper respiratory tract infection.

re-examine the eye to evaluate for iatrogenic injuries. Conjunctival injection is common, but symptoms are expected to be mild. Patching is not indicated. Topical nonsteroidal antiinflammatory analgesic solutions might play a role in decreasing pain, but studies do not provide strong evidence for their utility.[11] Topical anesthetics should be given sparingly and only to patients with simple corneal abrasions.[12] While studies performed in the ED show lack of poor outcome when limited to the appropriate use of topical anesthetics in simple corneal abrasions, there is not yet enough data to encourage home use of topical anesthetics as routine practice.[13] This practice is discouraged by many ophthalmologists. Since controversy remains about prescribing topical anesthetics for home use, we do not recommend this practice unless the topical anesthetics are prescribed in conjunction with ophthalmologic consultation.[14]

An algorithm for the treatment of acute conjunctivitis is presented in Fig. 18.11. We do not recommend topical antimicrobial or corticosteroid treatment for conjunctivitis or keratoconjunctivitis. This is an area in which antibiotic misuse is widespread. There is no good medical evidence to support the requirements of most daycare and school facilities to mandate antibiotic treatment for acute conjunctivitis before returning to activities with other children. First, some causes of "pink eye" are not infectious. Second, in patients enrolled in clinical trials for acute infectious conjunctivitis, bacteria continue to be cultured many days after treatment is started, and viruses continue to be shed for 2 weeks or more, with or without antibiotics. Unless a patient with conjunctivitis might potentially expose an immunocompromised individual, there is no medical reason not to return to daycare or school with or without treatment. If bacterial,

only direct eye-to-hand-to-eye exposure will result in transmission. If viral, others have likely already been exposed. In immunocompetent patients, bacterial conjunctivitis is likely to be self-limited and does not require antibiotic therapy.[3] Topical corticosteroids should be avoided because they can prolong viral infection.[15] Because many schools and daycares mandate antibiotic treatment of conjunctivitis before children are allowed to return to school, in practice, antibiotics are frequently prescribed contrary to antibiotic stewardship best practices.

Topical acyclovir, 5% ointment, is indicated for herpes keratitis, in conjunction with ophthalmologic or infectious disease consultation. Azithromycin is indicated for trachoma, again with consultation.

Topical antimicrobial prophylaxis is similarly not indicated for superficial epithelial defects of the cornea, although this also is common practice despite an absence of supporting evidence. There is also no evidence supporting the practice of administering tetanus immunization to patients with superficial corneal abrasions, other than as a general public health measure. However, true open wounds of the adnexa or globe do require tetanus prophylaxis if the patient's immunization status is not up to date.

Mydriatic and cycloplegic agents are also commonly prescribed but rarely are indicated. Mydriatic agents are contraindicated in patients with narrow-angle glaucoma. Larger corneal lesions sometimes require a cycloplegic agent for pain relief, but this should be prescribed only for the few patients experiencing refractory iris spasm and not prophylactically. Treatment of bacterial keratitis and endophthalmitis is described in Chapter 57.

Most ED patients with eye complaints are candidates for discharge and, if indicated, follow-up in the ED or with an ophthalmologist in 1 to 2 days. Others may require referral only if there is lack of resolution or treatment fails. A few patients require admission for procedural intervention, parenteral antibiotic regimens, management of intractable pain, or further diagnostic evaluation. General consultation and disposition considerations for the most important entities are outlined in Table 18.1.

The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 18: QUESTIONS AND ANSWERS

1. A patient who normally wears contact lenses is diagnosed with bacterial conjunctivitis. Which of the following is the preferred treatment in this patient?
   a. Bacitracin
   b. Chloramphenicol
   c. Erythromycin
   d. Moxifloxacin

Answer: d. Patients who wear contact lenses are at increased risk for infections with *Pseudomonas* and, in the setting of bacterial conjunctivitis, should be prescribed a quinolone, barring any contraindications.

2. A 15-year-old boy presents to the emergency department (ED) after having been shot in the face with a BB gun. He has a solitary penetrating wound just inferior to his left eye. His visual acuity in the left eye is limited to light perception, but he reports having normal vision prior to the injury. He has significant proptosis of his left eye, and his fundus is clearly seen with direct ophthalmoscopy. Intraocular pressure (IOP) of the affected eye is 50 mm Hg. His mental status is normal. What is the most appropriate next step in the management of this patient?
   a. CT scan of the head and face
   b. ED observation with repeated neurologic examinations
   c. Lateral canthotomy and inferior cantholysis
   d. Plain radiography of the face

Answer: c. The described patient likely has a retrobulbar hematoma with visual acuity changes and an elevated IOP. The elevated IOP with a clear fundoscopy are findings consistent with no penetration into the globe. Although CT scan of the head and face is indicated to further delineate specific injuries, lateral canthotomy and inferior cantholysis is emergently necessary for orbital decompression in an attempt to salvage vision. This sight-saving procedure should not be delayed more than 90 minutes after injury when severe findings (decreased visual acuity and significantly increased IOP) are present. Ophthalmology consultation would be indicated emergently.

3. A collection of pus in the anterior chamber of the eye is known as which of the following?
   a. Cotton wool spot
   b. Dacryocystitis
   c. Hyphema
   d. Hypopyon

Answer: c. A collection of layered pus in the dependent portion of the anterior chamber is called a hypopyon.

4. Which of the following results from inflammation of a meibomian gland?
   a. Blepharitis
   b. Chalazion
   c. Dacryocystitis
   d. Hordeolum

Answer: b. Inflammation of a meibomian gland with the subsequent formation of a subcutaneous nodule within the eyelid is known as a chalazion. This condition typically resolves spontaneously over several days. Authorities often recommend warm compress application and gentle massage of the nodule several times a day, although there is no evidence supporting this. If complete resolution does not occur within 2 weeks, the patient should be referred to an ophthalmologist.

5. A neonate presents 7 days after birth with a unilateral red eye. Further examination reveals inflamed conjunctiva, purulent discharge and negative uptake on fluorescein examination. The child was born full term after a pregnancy complicated by poor prenatal care. Which of the following diagnoses is most likely in this patient?
   a. Chemical conjunctivitis
   b. *Chlamydia trachomatis*
   c. Corneal abrasion
   d. *Neisseria gonorrhoeae*

Answer: b. Neonates are at high risk for serious ophthalmologic diseases. Typically, they present with chemical conjunctivitis from antibacterial prophylaxis (i.e., erythromycin ointment) at birth within 2 days. Gonococcal conjunctivitis is seen 2 to 5 days after birth. Chlamydial conjunctivitis is seen 5 to 12 days after birth. Corneal abrasions, while common in this age group, will most likely be evident on fluorescein examination of the cornea.

19

Sore Throat

Elizabeth P.D. Pontius and Kevin C. Reed

KEY CONCEPTS

- Sore throat can indicate a range of pathology, from simple pharyngitis to deep space infection, with or without airway compromise.
- Physical examination, supplemented by nasopharyngoscopy when appropriate, is key to determining threats to the airway and establishing a diagnosis.
- If oropharyngeal examination reveals minimal findings, lower or deeper structures may be involved, and endoscopic examination of the upper airway is recommended.
- The modified Centor criteria can help identify adult patients with a higher likelihood of Group A Streptococcus (GAS) infection. Patients with a score of –1 to 1 are unlikely to have GAS infection (10% to 15% likelihood, 95% confidence interval 5% to 25%), while a score of 4 or 5 corresponds to a 40% to 50% likelihood of GAS infection (95% confidence interval 31% to 51%).
- Viral pharyngitis, the most common cause of pharyngitis, is self-limiting and antibiotics are more harmful than helpful in its management.
- For GAS-positive pharyngitis, a single injection of penicillin or a 10-day course of oral penicillin may decrease the duration of symptoms, transmission to close contacts, and prevent rare suppurative and nonsuppurative complications.

FOUNDATIONS

Epidemiology

Patients of all ages present to the emergency department (ED) and outpatient settings with sore throat and throat-related complaints. While the vast majority of simple pharyngitis is caused by viruses, approximately 15% have an alternate cause.[1] Certain pathogens affect children and adolescents more commonly than infants or older adults. For example, Group A Streptococcus primarily affects those between the ages of 5 and 15 years and is rarely seen in children under the age of 3 years.[2]

Pathophysiology

Sore throat, or pharyngitis, results from inflammation of the soft tissue of the pharynx. The pharynx has three distinct regions: the nasopharynx, oropharynx, and hypopharynx (Fig. 19.1). Though these regions are distinct, they are contiguous, and inflammation can affect more than one region. Inflammation in any region can cause a sore throat. The nasopharynx includes the area superior to the oral cavity from the base of the skull to the soft palate and includes the opening of the eustachian tubes. The oropharynx is the area immediately visible when a patient opens their mouth, behind the oral cavity. Its borders are the uvula superiorly, the hyoid inferiorly, and the tonsillar pillars laterally. The oropharynx includes the vallecula and epiglottis. The hypopharynx lies inferior to the epiglottis and terminates at the vocal cords. When viewing a patient, the hypopharynx is posterior and slightly superior to the thyroid cartilage. The retropharyngeal and submandibular spaces surround the pharynx, and disease in these areas may cause pain and possible airway compromise.

Pharyngitis and *tonsillitis* are often used interchangeably; however, they are two distinct processes, with pharyngitis affecting the pharyngeal tissues, and tonsillitis affecting the tonsillar tissues. The pharyngeal tonsillar ring is composed of distinct areas of lymph tissue located throughout the pharynx, including the pharyngeal (adenoid), tubal, palatine, and lingual tonsils. The palatine tonsils are located on either side of the oropharynx, and infection here, whether viral or bacterial, can trigger inflammation which can also cause a sore throat. Cranial nerves IX and X supply sensory innervation to the region.

Sore throat with associated dysphagia and odynophagia may also result from mass lesions. These patients can present with hoarseness, weight loss, and lymphadenopathy. Inflammatory or mechanical complications from other neck structures, such as thyroiditis or an aortic ring, can also present with sore throat. Patients with referred throat pain from acute coronary syndrome may also have chest pain, diaphoresis, dizziness, or shortness of breath.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of a sore throat is quite broad (Box 19.1). Three major categories to consider as the cause of a sore throat are infectious, noninfectious (neoplastic, inflammatory, traumatic), and referred pain from the chest, such as acute coronary syndrome, pericarditis, and myocarditis.

Pivotal Findings

Symptoms and Signs

The first priority is to simultaneously assess the patient's airway and overall appearance. Patients with impending airway compromise can present sitting upright or leaning forward, with neck extension and the jaw thrust forward, and may often appear restless and agitated. The patient may be unable to swallow oral secretions secondary to inflammation in the oropharynx or hypopharynx, leading to drooling. Drooling is indicative of an advanced airway process and should prompt emergent airway evaluation and possible intervention. Patients with a muffled voice should be evaluated for a supraglottic process, including visualization of the floor of the mouth and palpation of the submental region. Induration and tenderness in this region are associated with Ludwig angina, typically the result of odontogenic extension.[3] Inflammation in the glottic or infraglottic structures causing a partial obstruction leads to stridor, a high-pitched inspiratory noise. Unless the patient is a child less than 10 years presenting with suspected croup,

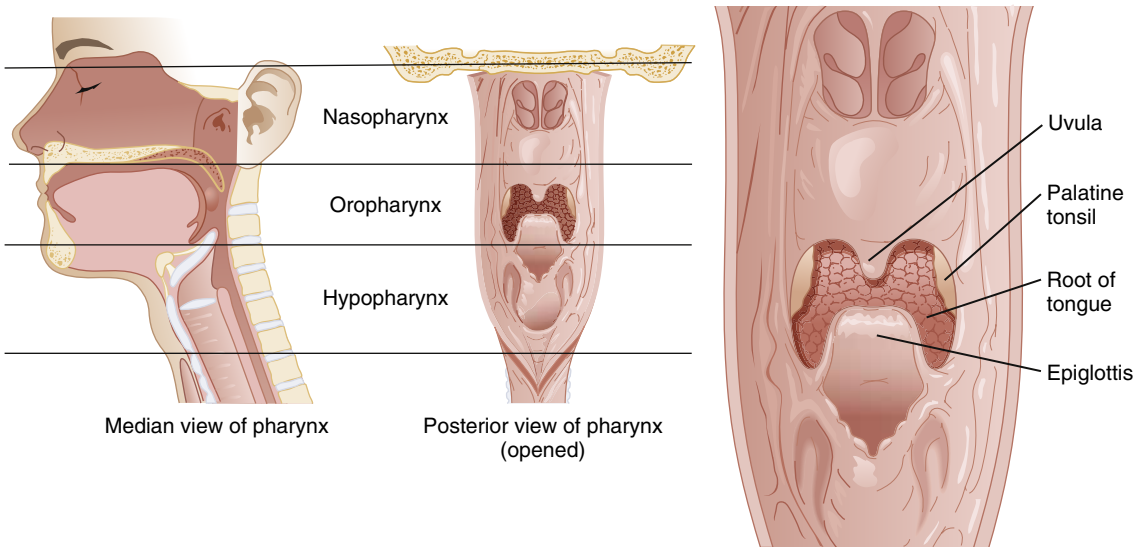

Fig. 19.1 Anatomy of the Nasopharynx, Oropharynx, and Hypopharynx.

BOX 19.1 Differential Diagnosis in Patients Presenting With Sore Throat

Critical
Trauma causing an expanding neck hematoma
Epiglottitis causing airway compromise
Retropharyngeal or parapharyngeal abscess causing airway compromise
Peritonsillar abscess causing airway compromise
Ludwig angina
Angioedema
Croup causing stridor at rest
Lemierre syndrome from septic internal jugular thrombophlebitis
Acute coronary syndrome presenting with referred throat pain

Emergent
Trauma causing a nonexpanding neck hematoma
Mass lesion in the neck causing sore throat (tongue, larynx, thyroid, leukemia)
Epiglottitis, retropharyngeal, parapharyngeal, or peritonsillar abscess not causing airway compromise
Stevens-Johnson syndrome

Urgent
Group A streptococcal pharyngitis
Retained foreign body
Kawasaki disease
Thyroiditis
Laryngeal fracture
Pericarditis or myocarditis presenting with referred throat pain

stridor is a sign of a true airway emergency. Critical conditions such as epiglottitis, retropharyngeal abscess, and angioedema can present with stridor. It is important to determine the severity, rate of onset, and progression of symptoms, as this may guide the urgency of intervention.

While evaluating the patient's overall appearance, emphasis should be placed on the patient's hydration status and signs of systemic toxicity. Pain from even simple uncomplicated pharyngitis may impede a patient's ability to tolerate oral intake, particularly in children, leading to dehydration. Fever and mild tachycardia are common vital sign abnormalities, and do not typically indicate serious pathology.

TABLE 19.1 Modified Centor Criteria (McIsaac Score) and Likelihood of Streptococcal Infection

Criteria (1 Point Each)	# of Criteria Present	GABHS
History of fever (>38°C)	0 or –1	7%
Tonsillar exudates	1	13%
Tender cervical LAD	2	22%
Absence of cough	3	38%
Age 3–14: +1, Age >45: –1	4–5	>50%

GABHS, Group A beta-hemolytic streptococci; *LAD* lymphadenopathy. Data from Nadeau N, Kimia A, Fine AM. Impact of viral symptoms on the performance of the modified Centor score to predict pediatric group A streptococcal pharyngitis. *Am J Emerg Med*. 2019. https://doi.org/10.1016/j.ajem.2019.10.026[published Online First: Epub Date].

It is imperative to visualize the pharyngeal structures. Patients with lingual resistance may require coaching to help minimize the gag reflex, and those with trismus should receive analgesia to allow complete visualization. If examination reveals tonsillar erythema or exudates in a symmetric fashion, without signs of airway compromise, acute tonsillitis is present and generally no further investigation is warranted. Various scoring systems exist to estimate the likelihood of Group A Streptococcal infection (GAS) based on elements of the history and physical exam; the most common of these is the Centor criteria (Table 19.1).[1] The four Centor criteria are a history of fever, tonsillar exudates, tender anterior cervical lymphadenopathy, and absence of a cough; a later modification (the McIsaac score) added a fifth criterion (add one point for age 3 to 14 years, subtract 1 point for age >45 years). Recent studies report the prevalence of GAS as greater than 50% in patients with a score of 4 or higher, 33% with a score of 3, 20% to 30% with a score of 2, 10% to 15% with a score of 1, and 5% to 10% with a score of 0 or −1. This prevalence of GAS at low scores is higher than originally reported by Centor or McIsaac.[4] If ulcerations are visualized, or if rhinorrhea, sneezing, cough, hoarseness or conjunctivitis are present, a viral etiology is more likely.[5] The vast majority of pharyngitis is due to either viral or streptococcal causes, though less common causes such as gonococcal infection and mononucleosis should be considered (Table 19.2).

TABLE 19.2 Differential Diagnosis for Infectious Pharyngitis

	AEROBIC BACTERIA			
Viral	**Common**	**Uncommon**	**Anaerobic Bacteria**	**Fungal**
Rhinovirus	*Streptococcus pyogenes* (GABHS)	*Haemophilus influenzae*	*Bacteroides* spp.	*Candida* spp.
Adenovirus	GABHS	*Haemophilus parainfluenzae*	*Peptococcus* spp.	
Coronavirus	*Coccidioides* spp.	*Corynebacterium diphtheriae*	*Clostridium* spp.	
Herpes simplex virus 1, 2	Non–group A streptococcus	*Streptococcus pneumoniae*	*Fusobacterium* spp.	
Influenza A, B	*Neisseria gonorrhoeae*	*Yersinia enterocolitica*	*Prevotella* spp.	
Parainfluenza	*Neisseria meningitides*	*Treponema pallidum*	*Peptostreptococcus* spp.	
Cytomegalovirus	*Mycoplasma pneumoniae*	*Francisella tularensis*		
Epstein-Barr virus	*Arcanobacterium haemolyticum*	*Legionella pneumophila*		
Varicella-zoster virus	*Chlamydia trachomatis*	*Mycobacterium* spp.		
Hepatitis virus	*Staphylococcus aureus*			

GABHS, Group A beta-hemolytic streptococci.

A prolonged fever of more than 5 to 7 days in children may indicate Kawasaki disease; cervical lymphadenopathy is seen in approximately 50% of patients.[6] Periodic episodes of fevers, aphthous lesions, and cervical lymphadenitis are consistent with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome; episodes typically occur every 3 to 6 weeks.[7] Unilateral swelling and contralateral uvular deviation suggest peritonsillar abscess; typically no exudates are present. If the patient has significant symptoms and examination of the oropharynx reveals minimal pathology, direct or indirect visualization of the hypopharynx, particularly the epiglottis, is indicated. Retropharyngeal and parapharyngeal abscesses may also present with significant symptoms and a relatively normal oropharyngeal exam. Lemierre syndrome, or septic thrombophlebitis, can complicate an episode of acute pharyngitis or a peritonsillar abscess, and affects the ipsilateral internal jugular vein. In addition to sore throat, fever, and neck pain, patients can present with arthralgias and pulmonary symptoms from septic emboli.

Ancillary Testing

A rapid antigen detection test (RADT) or culture can distinguish patients with GAS from non-GAS pharyngitis. In the setting of acute pharyngitis, this can help select patients for whom antibiotic treatment is beneficial. If the patient presents with a clear viral etiology (oral ulcers, cough, rhinorrhea, hoarseness), then no testing or treatment is indicated. GAS and rheumatic fever are rare in children under the age of three years, so testing and treatment for GAS are not indicated in this age group, unless the child has an older sibling with a recent GAS infection.[5] In most patients, it is difficult for the clinician to distinguish between GAS and viral pharyngitis, even with the use of the Centor criteria, which can lead to overtreatment. It is important to make an accurate diagnosis, as overtreating for GAS pharyngitis can lead to overprescribing of antibiotics for viral pharyngitis, leading to undesirable adverse effects and antimicrobial resistance. However, undertreatment can lead to both suppurative complications (peritonsillar abscess, cervical lymphadenitis, mastoiditis, internal jugular septic thrombophlebitis) and non-suppurative complications (acute rheumatic fever).[1,8] The Infectious Disease Society of America (IDSA) does not recommend RADT testing or initiating antimicrobial treatment in children or adults with clinical features strongly suggesting a viral etiology, such as rhinorrhea, cough, oral ulcers and hoarseness. If the clinical picture is not clearly viral, the IDSA recommends RADT testing for all patients, regardless of the Centor criteria. The Centers for Disease Control and Prevention (CDC) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend using the Centor score to determine which patients should be tested, with the recommendation that adult patients with a Centor score of 0 to 2 should not be tested, because the risks of testing and treatment outweigh the benefits. Testing is recommended over empiric treatment by all organizations.[1,5,9] The IDSA recommends that a negative RADT should be followed with a throat culture in children and adolescents, as the sensitivity of the RADT is only 70% to 90%, but that this is not necessary in adults as the incidence of GAS and the risk of subsequent rheumatic fever is much lower.[5] In contrast, the ESCMID does not recommend following a negative RADT with throat culture in any age group.[9] We recommend RADT testing in all children greater than 3 and adolescents with fever and pharyngitis, and in adult patients with a Centor score of ≥3, with follow-up throat culture testing only in children and adolescents who have a negative RADT. The specificity of the RADT is 95%, so a positive RADT requires no additional testing.[5] A number of newer nucleic acid amplification tests (NAATs) are commercially available and can be used in place of RADT and throat culture. These tests take between 15 minutes and 2 hours to result and have higher sensitivity and specificity than both RADT and throat culture, though their cost is higher. The use of NAATs to diagnose GAS is rising, and although they are not yet part of formal guidelines, their use may reduce inappropriate antimicrobial administration, as there is no need for follow-up culture testing in the setting of a negative NAAT.[10–12]

Clinicians can consider heterophile antibody testing for mononucleosis, testing for acute retroviral syndrome, or additional tests in patients with a prolonged course, unusual features, or treatment failure, in order to exclude other causes and guide advice regarding contagiousness and activity limitation.

Imaging

Direct visualization of pharyngeal structures is recommended, as it can provide a definitive diagnosis, assessment of potential threats to the patient's airway, and the ability to secure the airway by endotracheal intubation. However, radiographs can assist in assessment of the epiglottis and structures of the hypopharynx. If epiglottitis is suspected, in adult patients, examination either by nasopharyngoscopy at the bedside or direct visualization with laryngoscopy in the operating room is recommended. Before visualization, preparation for an emergent airway intervention, typically cricothyroidotomy, should occur—the

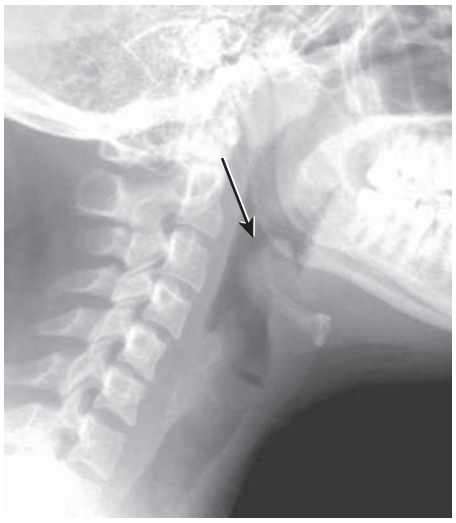

Fig. 19.2 Soft tissue lateral neck x-ray demonstrating thumb sign or widening of the epiglottis silhouette *(arrow)*.

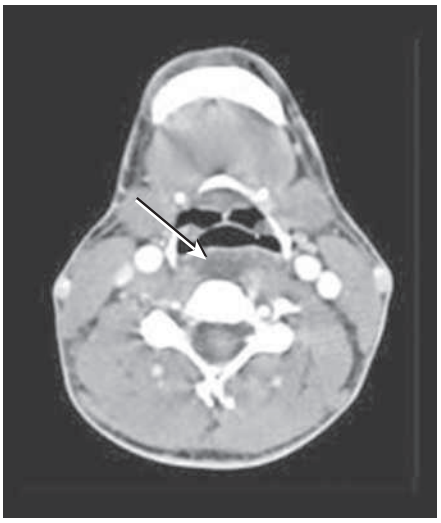

Fig. 19.3 Computed Tomography Scan of Retropharyngeal Abscess *(arrow)*.

so-called double setup—as manipulation of the upper airway tissues may lead to laryngospasm and obstruction. Endoscopic examination is preferred over plain radiographs, as endoscopic examination can also identify other life-threatening causes of airway obstruction, such as foreign bodies and angioedema, and is more sensitive for the diagnosis. If, however, endoscopy is not available or feasible, and the patient has a stable airway, plain film radiography can assist in the diagnosis of epiglottitis, as widening of the epiglottis silhouette, or thumb sign, may be appreciated (Fig. 19.2).[13]

Computed tomography (CT) provides the most detailed information regarding deep infections of the neck in both adult and pediatric patients. It is important to ensure that the patient's airway is either patent or secure before sending a patient to CT, as lying the patient flat may compromise the airway. CT is highly accurate for detecting infection in the deep tissues and is the definitive test for evaluation of deep neck infection (Fig. 19.3).[14] In addition, CT can provide additional information regarding alternate diagnoses, such as tumors or hemorrhage, and can delineate invasion of nearby structures.

Ultrasound is emerging as a useful tool to evaluate oropharyngeal and hypopharyngeal disease, and using ultrasound in place of CT can reduce both radiation exposure to patients and overall cost.[15] In peritonsillar and parapharyngeal abscesses, ultrasound can not only identify the abscess, but can also guide needle aspiration or incision and drainage if indicated (Fig. 19.4).[16,17] Ultrasound is also useful not only for evaluation of parapharyngeal and peritonsillar abscess, but also to evaluate a visible neck mass, as well.

DIAGNOSTIC ALGORITHM

Critical and Emergent Diagnoses

In patients with a sore throat, airway compromise can result from a number of critical and emergent conditions (see Box 19.1). During the diagnostic evaluation, the clinician must assess whether or not an emergent airway needs to be established. The immediate examination should focus on identifying edema, masses, an abscess, or foreign body (Fig. 19.5).

In patients without impending airway compromise, a more deliberate evaluation is warranted. One important question is whether or not signs of pharyngitis exist. Findings consistent with pharyngitis include exudates, erythema and cobblestoning of the posterior pharyngeal wall. In the absence of features pointing to an unusual cause, management should focus on viral or streptococcal causes.[1]

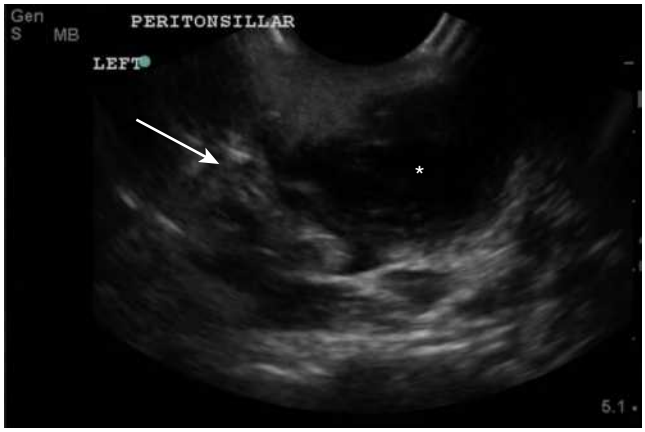

Fig. 19.4 Ultrasound image of peritonsillar abscess (*), a fluid collection adjacent to the tonsil *(arrow)*.

EMPIRIC MANAGEMENT

Fig. 19.5 describes a management algorithm for the patient with a sore throat. First and foremost, airway compromise and impending airway compromise must be identified and managed. Patients should be evaluated for signs of severe infection or sepsis and managed accordingly. In patients who have no signs of airway compromise or invasive disease, management should treat the underlying presumptive cause.

The most common cause of sore throat is a viral pharyngitis, and symptomatic treatment with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) is the only recommended treatment. For all causes of pharyngitis, patients can take these medications around-the-clock, rather than on an as-needed basis, to help keep symptoms at bay.[9,18] Overuse of antibiotics for self-limited, often viral, upper respiratory infections is a common practice across many outpatient settings despite messaging on antibacterial stewardship. This leads to increased antibiotic resistance and higher rates of adverse events, often resulting in return ED visits.[1,19–21] In summary, antibiotics for viral pharyngitis should be avoided to reduce individual adverse effects as well as for public health reasons.

A common perception is that patients expect or desire antibiotics. Because of this, patient education is a crucial component of sore throat management. Education should include both positive and negative

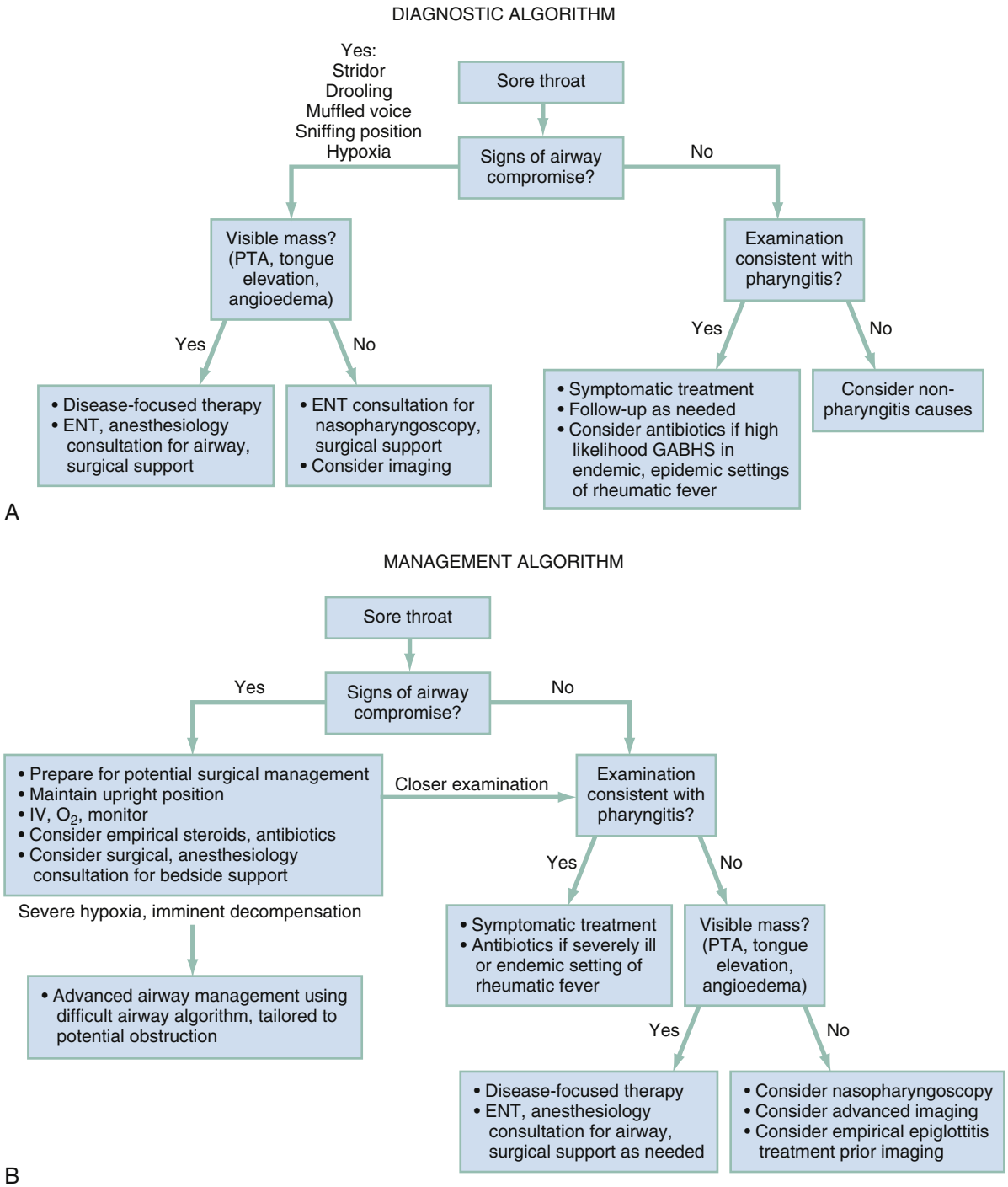

Fig. 19.5 Approach to the Patient With Sore Throat, Diagnostic and Management Algorithms. *ENT,* Ear-nose-throat; *GABHS,* Group A beta-hemolytic streptococci; *IV,* intravenous; *PTA,* peritonsillar abscess.

recommendations: explanation of both what the patient can do to improve symptoms (positive recommendations) and explanation of why antibiotics are inappropriate (negative recommendations), including the lack of symptomatic benefit with antibiotics and the potential harm of antibiotics (for example, gastrointestinal side effects, rashes, fungal infections in women, increased antibiotic resistance, and potentially dangerous allergic reactions). Emphasis on symptomatic treatment and reduction in pain, with NSAIDs or acetaminophen, is the most important educational aspect, reducing antibiotic prescribing by half.[22] Corticosteroid therapy may reduce pain and duration of pain in patients greater than 5 years of age with severe pharyngitis causing difficulty swallowing; most studies use 0.6 mg/kg (maximum dose, 10 mg) of dexamethasone, either orally or parenterally, in a one-time dose.[23] While not routinely recommended by the IDSA or ESCMID for cases of routine pharyngitis, we recommend consideration of corticosteroids for patients greater than 5 years of age with significant swelling or dysphagia, in line with the ESCMID guidelines.[5,9,23] The presence of pain necessitating opioid therapy should prompt evaluation for a more severe cause, such as an abscess or epiglottitis. Achieving pain control allows patients to resume oral intake, maintain hydration, and take additional medications that may be necessary to treat the underlying condition.

In patients who test positive for GAS by RADT, NAAT, or throat culture, we recommend treatment with intramuscular penicillin G or a 10-day course of oral penicillin VK, due to penicillin's proven efficacy and low cost. Alternative regimens, and options for patients allergic to penicillin, can be found in Box 19.2. Antimicrobial treatment may also decrease the duration and severity of illness and reduce the risk of transmission to close contacts.[1]

A fluctuant, unilateral peritonsillar mass should be drained whenever possible, as drainage is the definitive treatment. Peritonsillar cellulitis, or unilateral swelling and redness that is not fluctuant, can be treated with the same antibiotics as those used for GAS pharyngitis, though there are few data to support this practice.[24] For patients with signs of severe, systemic illness or airway compromise, antibiotic treatment for streptococcal and anaerobic bacteria may be helpful; we recommend parenteral clindamycin (10 mg/kg/dose or 900 mg tid) and a third-generation cephalosporin such as ceftriaxone (50 mg/kg or 1000 mg q24h), though there is very little evidence to support or refute this practice.[25,26] Unusual or severe presentations may require additional diagnostic studies, specialty consultation, or other empiric antibiotic treatment.

Signs of airway compromise, or impending airway compromise, should prompt preparation for emergent advanced airway management, as well as otolaryngology and surgical services consultations if available (see Chapter 1). Airway compromise can result from epiglottitis, retropharyngeal or parapharyngeal abscess, Ludwig angina, angioedema, and expanding hematomas. After securing the airway, disease-specific treatment can be initiated.

Since the introduction of the *Haemophilus influenzae* type B vaccine, epiglottitis is predominantly caused by *Streptococcus*, *Staphylococcus,* and nontypeable *Haemophilus* species, and we recommend parenteral treatment with ceftriaxone (50 mg/kg or 1000 mg qd), ampicillin/sulbactam (50 mg/kg of ampicillin component or 3000 mg q6h), or levofloxacin (750 mg qd) in penicillin-allergic patients. For the treatment of retropharyngeal or parapharyngeal abscess and Ludwig angina, we recommend broad antibiotic coverage, such as ampicillin/sulbactam (50 mg/kg or 3000 mg q6h of penicillin G (4 million units or 50,000 units/kg qid) and metronidazole (500 mg or 7.5 mg/kg qid), until culture results are available. For Lemierre syndrome, preferred agents include piperacillin/tazobactam (3.375 gm qid) or the combination of ceftriaxone 1000 mg q24h and metronidazole 500 mg q8h.

It is important to review local antibiotic resistance patterns to ensure appropriate antibiotic selection. Medical treatment of angioedema depends on the underlying cause. Treatment of anaphylaxis or allergen-induced angioedema includes epinephrine, antihistamines, and glucocorticoids; treatment of angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema includes discontinuing the causal medication and supportive care; treatment of hereditary angioedema can include purified C1 inhibitor concentrate, fresh frozen plasma, and either ecallantide or icatibant, if available. Because the cause of angioedema in the emergency setting is often unknown, we recommend treatment with antihistamines and glucocorticoids in all patients, and intramuscular epinephrine if impending airway compromise exists. (See Chapter 106.)

Sore throat caused by an expanding neck hematoma or an aortic ring should prompt surgical consultation, as patients may require definitive surgical treatment.

The vast majority of patients with sore throat will be able to manage their illness as an outpatient. Patients with airway compromise or impending airway compromise are typically managed in the intensive care unit for close monitoring of the patient's airway. In these cases, as well as in cases of deep space infections, surgical consultation for possible operative intervention or for nasopharyngoscopy can be helpful. Patients with pharyngitis who are unable to tolerate oral medication or nutrition, or who have signs of systemic illness, may benefit from inpatient management.

The references for this chapter can be found online at ExpertConsult.com.

BOX 19.2 Antibiotic Regimens for Proven Group A Streptococcus

Benzathine penicillin G, intramuscular, 600,000 U for <27 kg and 1.2 million U for >27 kg

Penicillin V, oral, children <27 kg 250 mg 2 to 3 times daily; children ≥27 kg 500 mg 2 times daily; adolescents and adults 250 mg 4 times daily or 500 mg twice daily × 10 days

Amoxicillin, oral, 50 mg/kg once daily (max = 1000 mg); or 25 mg/kg (max = 500 mg) twice daily × 10 days

If penicillin-allergic:

Clindamycin, oral, 7 mg/kg/dose 3 times daily (maximum, 300 mg/dose) × 10 days

Cephalexin, oral, 20 mg/kg/dose twice daily (maximum, 500 mg/dose) × 10 days

Azithromycin, oral, 12 mg/kg/day × 5 days

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CHAPTER 19: QUESTIONS AND ANSWERS

1. A 20-year-old female presents to the emergency department complaining of a sore throat. She has a temperature of 39°C, tender cervical lymphadenopathy, exudates on exam and denies any history of cough, rhinorrhea, nausea, vomiting or diarrhea. Her modified Centor score is which of the following?
   a. 2
   b. 3
   c. 4
   d. 5

Answer: c. This patient meets four Centor criteria: fever, tender cervical lymphadenopathy, exudates, and absence of a cough. The age criteria is +1 point for age 3 to 14 years, and −1 point for age greater than 45 years.

2. A 39-year-old male presents to the emergency department complaining of a sore throat. He is sitting forward on the stretcher, drooling, with inspiratory stridor. His oropharynx exam shows minimal erythema and no exudate. Which of the following conditions is the likely diagnosis?
   a. Epiglottitis
   b. Group A streptococcal pharyngitis
   c. Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome
   d. Viral pharyngitis

Answer: a. Simple pharyngitis, either bacterial or viral, and PFAPA syndrome do not cause airway compromise. Drooling and inspiratory stridor are symptoms of airway compromise, and epiglottitis is the only diagnosis on this list that results in airway compromise.

3. In adult patients who test positive for Group A streptococcal (GAS) pharyngitis who have no allergies, which of the following is the most appropriate antibiotic choice?
   a. Azithromycin 12 mg/kg/day (max dose, 500 mg) × 5 days
   b. Clindamycin 7 mg/kg/dose (max dose, 300 mg) TID × 10 days
   c. Metronidazole 30 mg/kg/day divided TID × 10 days
   d. Penicillin VK 50 mg/kg/day divided QID × 10 days

Answer: d. Penicillin VK is the first-line treatment for GAS pharyngitis in patients without allergies. Clindamycin and azithromycin are options in penicillin allergic patients. Metronidazole is not a treatment of GAS pharyngitis.

4. A 24-year-old female presents for sore throat, difficulty swallowing, and a muffled voice. On examination, she has fullness, swelling and induration of the left posterior peritonsillar area with uvular deviation to the right. What is the next step in the management of this patient?
   a. Computed tomography imaging
   b. Discharge with antibiotics, clindamycin 300 mg TID × 10 days
   c. Drainage either by needle aspiration or incision and drainage
   d. Rapid Antigen Detection Test for Group A Streptococcus

Answer: c. This patient has a peritonsillar abscess. In a clear-cut case such as this, no imaging is needed. Definitive treatment is with either needle aspiration or incision and drainage.

5. In which age group is Group A streptococcal infection most common?
   a. Age <3 years
   b. Age 5–15 years
   c. Age 15–45 years
   d. Age >45 years

Answer: b. GAS pharyngitis is most common in children aged 5 to 15 years. It is less common in young adults, and rare in children less than three, or adults over the age of 45.

20

Hemoptysis

Calvin A. Brown III

KEY CONCEPTS

- Hemoptysis is caused by infection, trauma, cancer, or coagulopathy or as a complication of invasive pulmonary procedures.
- "Massive hemoptysis" is defined as greater than 100 mL of blood loss or approximately ½ cup of blood in a 24-hour period or a bleeding rate ≥100 mL/h.
- Plain radiographs are the initial screening test in most cases of massive hemoptysis, although high-resolution chest computed tomography scans are more sensitive and can supplant plain chest x-rays as the initial diagnostic test.
- Bronchial artery embolization is highly effective, with hemostasis rates ranging from 85% to 95%.
- With massive hemoptysis, hypoxia is the more immediate concern rather than volume resuscitation, and early intubation to ensure adequate oxygenation is paramount. Most causes of mortality are a result of asphyxiation.
- If a tracheo-innominate artery fistula (TIF) is suspected, then overinflation of the tracheostomy balloon or digital pressure at the site of bleeding should be performed for immediate hemorrhage control.

FOUNDATIONS

Epidemiology

Hemoptysis is defined as the expectoration of blood from the respiratory tract below the vocal cords. Most cases seen in the emergency department (ED) are minor episodes of small-volume hemoptysis, typically consisting of either blood-tinged sputum or minute amounts of frank blood, most often associated with bronchitis. Although hemoptysis is commonly seen in the ED, only 1% to 5% of hemoptysis patients have massive or life-threatening hemorrhage. Many definitions exist, but *massive hemoptysis* is generally accepted as greater than 100 mL or greater than ½ cup of blood loss in any 24-hour period or a bleeding rate ≥100 mL/h, which may result in hemodynamic instability, shock, or impaired alveolar gas exchange and has a mortality rate approaching 80%. The average blood volume of the tracheopulmonary tree is 150 mL; therefore what might be considered small-volume bleeding from another location could be lethal when it occurs in the lungs. In patients admitted with hemoptysis to an intensive care unit (ICU), overall mortality is approximately 6.5%. Highest short-term mortality is found in patients with alcoholism, active cancer, aspergillosis, pulmonary artery involvement, multifocal pulmonary infiltrates, and need for mechanical ventilation at the time of admission.

Large, contemporary series of patients with massive hemoptysis are lacking. Previously, tuberculosis (TB), bronchiectasis, and lung abscesses were responsible for the majority of cases. Contemporary causes of hemoptysis, especially in developed nations, include cancer, cystic fibrosis, arteriovenous malformations, pneumonia, anticoagulant use, and postprocedural complications. Pediatric hemoptysis is rare but can be caused by infection, congenital heart disease, cystic fibrosis, or bleeding from a preexisting tracheostomy. Major causes of hemoptysis are listed in Box 20.1.

Pathophysiology

Minor hemoptysis typically originates from tracheobronchial capillaries that are disrupted by vigorous coughing or minor bronchial infections. Conversely, massive hemoptysis nearly always involves disruption of bronchial or pulmonary arteries, which are the two sets of vessels that constitute the lung's dual blood supply. Bronchial arteries, which are direct branches from the thoracic aorta, are responsible for supplying oxygenated blood to lung parenchyma, and disruption of these vessels from arteritis, trauma, bronchiectasis, or malignant erosion can result in sudden and profound hemorrhage. Although small in caliber, the bronchial circulation is a high-pressure system and the culprit in nearly 90% of the cases of massive hemoptysis requiring embolization. Pulmonary arteries, although transmitting large volumes of blood, do so at much lower pressures and, unless affected centrally, are less likely to cause massive hemoptysis.

Nearly all causes of hemoptysis have a common mechanism—vascular disruption within the trachea, bronchi, small-caliber airways, or lung parenchyma. Modes of vessel injury include acute and chronic inflammation (from bronchitis and arteritis), local infection (especially lung abscesses, TB, and aspergillosis), trauma, malignant invasion, infarction following a pulmonary embolus, and fistula formation (specifically aortobronchial fistulae).

Bronchiectasis, a chronic necrotizing infection resulting in bronchial wall inflammation and dilation, is one of the most common causes of massive hemoptysis worldwide. As tissue destruction and remodeling occur, rupture of nearby bronchial vessels can result in bleeding. Bronchiectasis can complicate chronic airway obstruction, necrotizing pneumonia, TB, or cystic fibrosis. Broncholithiasis, the formation of calcified endobronchial lesions following a wide array of granulomatous infections, is an uncommon problem with a similar propensity to erode nearby vessels. Hemorrhage control often requires surgical intervention.

Iatrogenic hemoptysis complicates 2% to 10% of all endobronchial procedures, especially percutaneous lung biopsies. Right (pulmonary artery) heart catheterization using a Swan-Ganz catheter can cause iatrogenic pulmonary artery perforation especially in patients with pulmonary hypertension. Although this complication is rare, the mortality is between 50% to 70%. Diffuse alveolar hemorrhage can be seen with autoimmune vasculitides, such as Wegener's granulomatosis, systemic lupus erythematosus (SLE), and Goodpasture syndrome. An uncommon cause of hemoptysis occurs when ectopic endometrial tissue within the lung results in monthly catamenial episodes of bleeding. Less common causes include pulmonary hereditary telangiectasias

BOX 20.1 Differential Diagnosis of Hemoptysis

Airway Disease
Bronchitis (acute or chronic)
Bronchiectasis
Neoplasm (primary and metastatic)
Trauma
Foreign body

Parenchymal Disease
Tuberculosis (TB)
Pneumonia, lung abscess
Fungal infection
Neoplasm

Vascular Disease
Pulmonary embolism
Arteriovenous malformation
Aortic aneurysm
Pulmonary hypertension
Vasculitis (Wegener's granulomatosis, systemic lupus erythematosus [SLE], Goodpasture syndrome)

Hematologic Disease
Coagulopathy (cirrhosis or warfarin therapy)
Disseminated intravascular coagulation (DIC)
Platelet dysfunction
Thrombocytopenia

Cardiac Disease
Congenital heart disease (especially in children)
Valvular heart disease
Endocarditis

Miscellaneous
Cocaine
Postprocedural injury
Tracheal-arterial fistula
SLE

and hydatidiform infections. Any episode of hemoptysis can be exacerbated by intrinsic or acquired coagulopathy and thrombocytopenia.

DIAGNOSTIC APPROACH

Differential Considerations

First, the clinician should be convinced that the source of the bleeding is pulmonary. Distinguishing hemoptysis from hematemesis is accomplished by the clinician working with the patient to clarify details of the history, particularly differentiation between coughing and vomiting or spitting. Nasal, oral, or hypopharyngeal bleeding may contaminate the tracheobronchial tree, mimicking true hemoptysis. The clinician should closely inspect the nasopharynx and oral cavity to exclude this possibility. Gastric or proximal duodenal bleeding can similarly mimic hemoptysis, and differentiating a gastrointestinal (GI) source of bleeding is especially important because further evaluation and management of these two pathologies follow divergent pathways. In unclear cases, inspection and pH testing may help to distinguish GI from tracheobronchial hemorrhage. Unless an active, brisk upper GI hemorrhage is present, the acidification of blood in the stomach results in fragmentation and darkening, producing specks of brown or black material often referred to as *coffee-ground emesis*. Pulmonary blood appears bright red or as only slightly darker clots and is alkaline.

Inflammatory disorders that secondarily involve the lungs or pulmonary vasculature include Wegener's granulomatosis, Goodpasture syndrome, and SLE, and a history of these should be elicited. Any risk factors for platelet dysfunction, thrombocytopenia, and coagulopathy should be noted, as should any hypercoagulable states that might contribute to venous thromboembolic disease.

Primary or metastatic cancer can cause hemoptysis by erosion into pulmonary and bronchial vessels. Recent percutaneous or transbronchial procedures can cause immediate or delayed postprocedural bleeding, and any recent history of trauma should also be noted. A pertinent travel history to areas in which TB or pulmonary *paragonimiasis* is endemic is crucial.

A history of chronic alcoholism, cancer, and pulmonary fungal infections are other critical historical elements because these independently predict increased in-hospital mortality.[1]

Pivotal Findings

Symptoms

Although patient reports of bleeding severity can be inaccurate, an estimate of the rate, volume, and appearance of expectorated blood should be obtained. Additional pertinent history includes prior episodes of hemoptysis or parenchymal pulmonary disorders, including bronchiectasis, recurrent pneumonia, chronic obstructive pulmonary disease, bronchitis, TB, fungal infection, and travel history.

Signs

A targeted examination may suggest the location and cause of bleeding but does so in less than 50% of cases. Focal adventitious breath sounds in a febrile patient may indicate pneumonia or pulmonary abscess. A new heart murmur, especially in a febrile patient, may reflect endocarditis causing septic pulmonary emboli. A rash might hint at underlying rheumatologic disorders, such as SLE or vasculitis. Symptoms and signs of deep venous thrombosis suggest pulmonary embolism. Ecchymoses and petechiae can indicate coagulopathy and thrombocytopenia, respectively.

Ancillary Testing

In patients with massive hemoptysis, a diagnostic work-up should begin after resuscitation and stabilization. Initial laboratory studies include a complete blood count, coagulation tests, and a type and crossmatch for packed red blood cells. Renal function tests should be performed if vasculitis is suggested. Plain chest radiography plays a limited role in evaluating patients with minor hemoptysis. Although chest x-rays are easy to obtain and can screen for causes of hemoptysis (including infection and malignancy), their sensitivity is poor and often cannot identify the source of bleeding, a critical step in triage and management (see the Empirical Management section). Up to half of hemoptysis patients with a normal chest radiograph will have positive findings on chest computed tomography (CT).

When there is massive hemoptysis, plain films can localize the side of hemorrhage in approximately half of patients and suggest an etiology in only a third. High-resolution CT (HRCT) of the chest is the principle diagnostic test for investigating both bronchial and nonbronchial causes of massive hemoptysis and is able to determine the site and cause of bleeding in 70% to 80%.[2] Advantages of HRCT include highly detailed parenchymal images due to thin slices and no requirement for intravenous (IV) contrast given the high intrinsic contrast between air and lung tissue. When compared with bronchoscopy, HRCT is nearly twice as likely to determine the cause of bleeding.[3] A chest HRCT scan should be obtained in the high-risk patient (i.e., smokers, oncology

patients) or in any patient with moderate to severe bleeding, even if the initial chest radiograph is normal. HRCT localization of hemorrhage can expedite bronchoscopic evaluation and guide subsequent interventional procedures.

HRCT is diagnostically comparable to conventional angiography but less invasive and more rapidly available. Angiography is the first line study when the cause of the hemoptysis is known (e.g., malignancy), when bronchial artery hemorrhage is suspected, or when angiography-assisted embolization therapy is to be performed. Successful embolization rates are as high as 95%.

DIAGNOSTIC ALGORITHM

Critical Diagnoses

Box 20.2 shows critical and emergent diagnoses. Proper management hinges not only on standard resuscitative measures but also specific therapies, such as reversal of coagulopathy or emergent surgical intervention. For example, in patients with preexisting tracheostomies, new hemoptysis (especially within 3 to 4 weeks of surgery) often represents a tracheo-innominate artery fistula (TIF) for which the need for hemorrhage control is immediate and can often be accomplished in the ED.

BOX 20.2 Critical and Emergent Diagnoses in Patients Presenting With Hemoptysis

Critical Diagnoses
Disseminated intravascular coagulopathy (DIC)
Tracheo-innominate artery fistula (TIF)
Aortobronchial fistula
Iatrogenic (postprocedural) hemoptysis
Pulmonary embolism

Emergent Diagnoses
Trauma
Bronchiectasis
Pneumonia
Abscess/fungal infection
Oral anticoagulant overdose
Endocarditis

Congestive Heart Failure
Acute Pulmonary Edema

Although management decisions hinge on the volume and rate of bleeding, the initial diagnostic strategy is the same for all patients with hemoptysis (Fig. 20.1). Patients with trace hemoptysis or blood-tinged sputum only and a classic story for viral bronchitis may not require laboratory or radiology investigation of any type. In a recent single-center ED study of patients presenting with submassive hemoptysis, those with normal blood pressure, lack of a cancer history, and a single episode of blood-tinged sputum could safely be discharged after a normal chest x-ray.[1] For all others, the initial screening test obtained in the ED is a chest x-ray. Since the advent of HRCT, radiologic evaluation has had an integral role in the evaluation and treatment of patients with hemoptysis. Unless the initial chest radiograph is diagnostic or the patient is hemodynamically unstable, a chest HRCT should be obtained. Further management decisions should be guided by the HRCT results and made in conjunction with pulmonary and thoracic surgery consultants.

Bronchoscopy

Early bronchoscopy may be the right option because it facilitates both localization of bleeding and therapeutic intervention. HRCT may be diagnostically more accurate than bronchoscopy in locating bleeding peripheral vessels, not accessible by a flexible bronchoscope. HRCT of the chest can be used to identify the site of bleeding to determine whether angiography is indicated. There may be little added benefit of bronchoscopy before interventional angiography if the bleeding source has already been accurately identified on HRCT.

EMPIRICAL MANAGEMENT

Fig. 20.2 outlines the management algorithm for patients with hemoptysis. Although hemodynamic instability can occur as a result of hemorrhage, the most lethal sequela of massive hemoptysis is hypoxia,

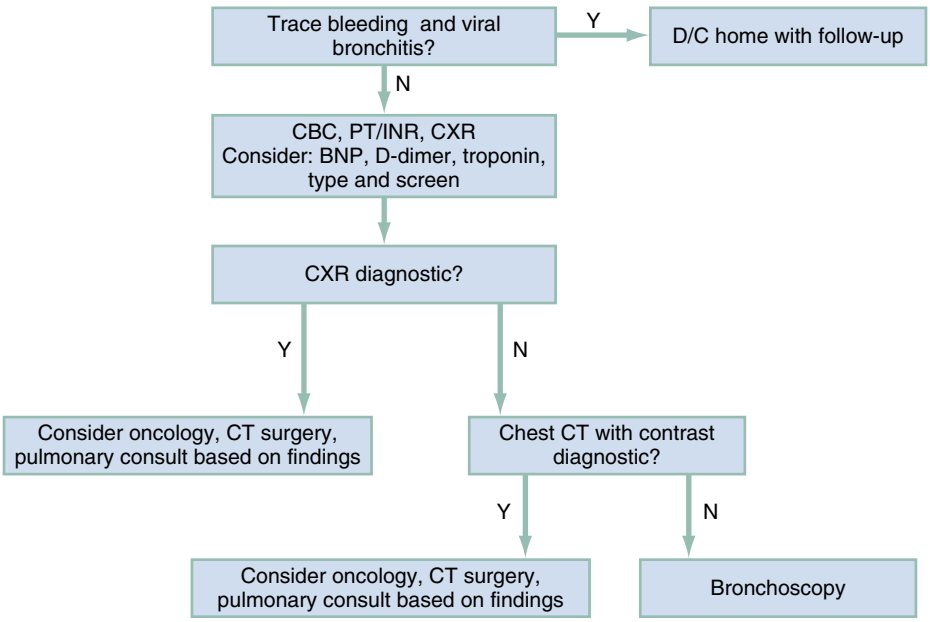

Fig. 20.1 The Emergency Department Diagnostic Approach to Hemoptysis. *BNP,* B-type natriuretic peptide; *CBC,* complete blood count; *CXR,* chest x-ray; *D/C,* discharge; *HRCT,* high-resolution computed tomography; *INR,* international normalized ratio; *PT,* prothrombin time.

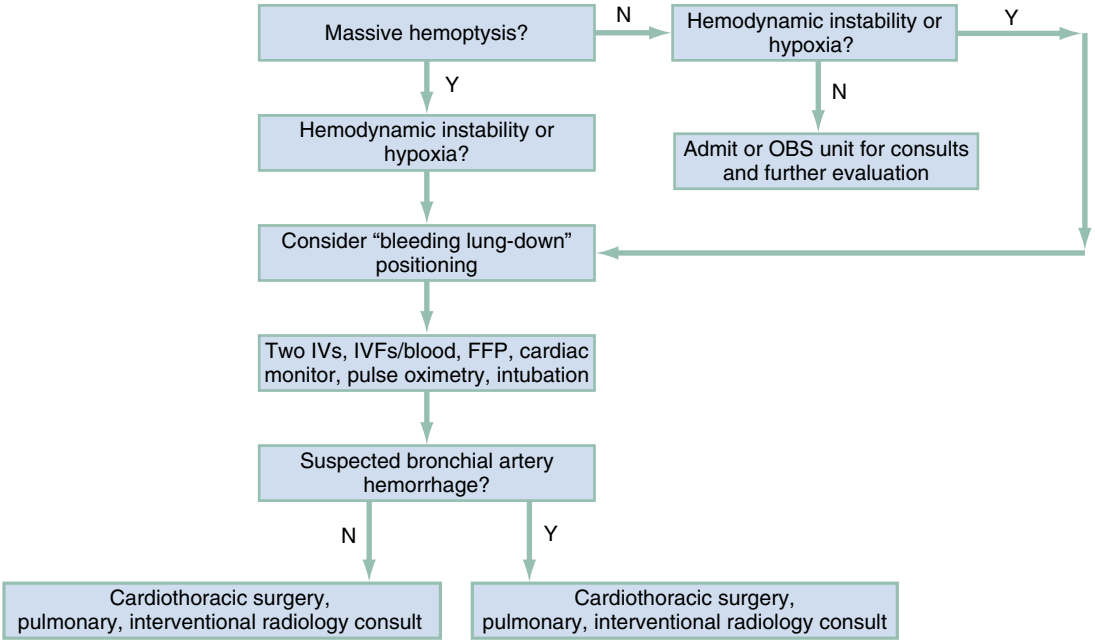

Fig. 20.2 The Emergency Department Management Approach to Hemoptysis. *IV,* Intravenous; *IVF,* intravenous fluid; *FFP,* fresh frozen plasma; *OBS,* observation.

which results from the ventilation-perfusion mismatch that follows submersion of the small airways and alveoli with blood.

All patients with massive hemoptysis should have multiple large-bore peripheral IV lines placed. Volume resuscitation should begin immediately for patients with ongoing bleeding or shock. Coagulopathy, in the setting of severe bleeding, should be reversed by infusing 2 to 4 units of fresh frozen plasma (FFP) and 10 mg of IV vitamin K. Prothrombin complex concentrates (PCCs) have been successful in reversing warfarin-induced intracranial hemorrhage, but there is no information to guide the use of PCC in patients with severe hemoptysis. In a recent single-center randomized controlled pilot study of patients presenting with submassive hemoptysis, tranexamic acid (TXA) reduced the severity of bleeding compared with placebo.[4] Case reports of bleeding cessation have been reported after use of inhaled, nebulized TXA.[5] Patients with thrombocytopenia should have a platelet transfusion with a goal platelet count of 50,000 to 60,000.

If a TIF is suspected, the emergency clinician should immediately attempt to overinflate the tracheostomy balloon in an effort to tamponade the bleeding. If this fails, the tracheostomy tube should be removed, the patient should be orally intubated, and the operator's index finger should be placed through the tracheostomy hole with pressure applied at the sight of bleeding (Fig. 20.3).

Aortobronchial artery fistulae are highly lethal, but if caught early, general resuscitative measures should be undertaken in addition to immediate consultation with or transfer to an endovascular surgeon. Pulmonary embolus is only rarely associated with massive hemoptysis. When trace hemoptysis accompanies pulmonary embolism, usual care with anticoagulation is standard treatment.

Hemoptysis as a complication of disseminated intravascular coagulation (DIC) should be treated following the general management guidelines for DIC. Treatment of DIC remains controversial; however, when bleeding is present with platelet counts less than 50,000, transfusion is indicated. FFP and cryoprecipitate have also been advocated to replace factors lost due to consumptive coagulopathy.

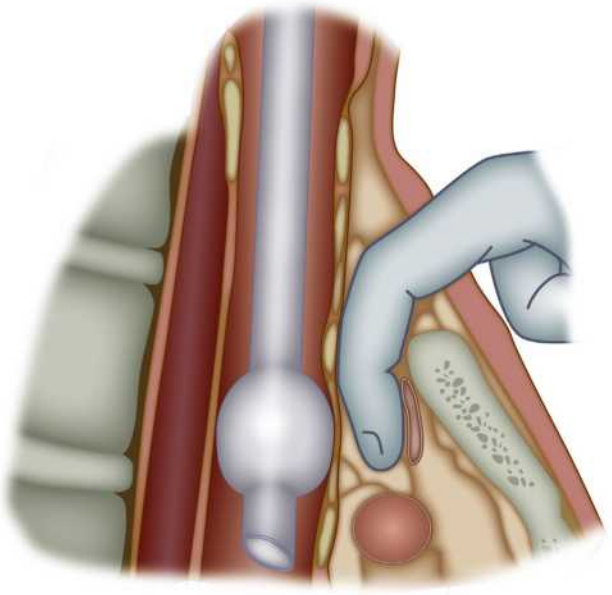

Fig. 20.3 Pressure placed by the clinician's finger through the tracheostomy hole occluding the tracheo-innominate artery.

Patients with a known or suspected lateralizing source of bleeding should be placed in the "bleeding lung-down" position such that the bleeding lung is more dependent, promoting continued protection and ventilation of the unaffected lung and improved oxygenation. If intubation is required, a large-diameter (8.0) endotracheal tube should be used to facilitate emergent flexible bronchoscopy.

If the patient has marginal hemodynamic status, the intubation should proceed with a "shock-sensitive" strategy focusing on preload maximization with isotonic fluids or blood, reduced dose induction agents, and peri-intubation pressors, such as norepinephrine (see Chapter 1). In selected cases of confirmed left-sided bleeding, a single-lumen right-mainstem intubation often can be successfully performed

through advancement of the tube in the neutral position or use of a 90-degree rotational technique, during which the tube is rotated 90 degrees in the direction of desired placement and advanced until resistance is met. Left-mainstem intubations are more difficult but may be attempted when the bleeding site is the right lung and simple lung-down positioning is not sufficient to stabilize the patient's airway and oxygenation.

When these measures fail or the hemoptysis is life threatening, anesthesia consultation is sought for consideration of placement of double-lumen endotracheal tubes for lung isolation. The correct positioning of blindly placed double-lumen tubes is difficult and requires confirmation by auscultation and fiberoptic bronchoscopy, both of which are severely impaired by massive hemoptysis. Complications of double-lumen tubes include unilateral and bilateral pneumothoraces, pneumomediastinum, carinal rupture, lobar collapse, and tube malposition.

Fiberoptic bronchoscopy, in addition to being one of the first diagnostic maneuvers, is a first line therapeutic option as well. Balloon and topical hemostatic tamponade, thermocoagulation, and injection of vasoactive agents can all effectively control arterial bleeding. Optimal timing for bronchoscopy remains conjectural. Although stable patients with mild to moderate bleeding may benefit from early bronchoscopy, in unstable patients or those with brisk hemorrhage, bronchoscopy may facilitate airway management but is less likely to control bleeding.

Bronchial arterial embolization is an effective first line therapy for massive hemoptysis and is the procedure of choice for patients either unable to tolerate surgery or in whom bronchoscopy has been unsuccessful. Hemostatic rates range from 85% to 98%, but as many as 20% to 50% of patients have early episodes of recurrent bleeding. The risk of bleeding may exist for up to 36 months. To guide therapy, initial localization of bleeding by bronchoscopy or HRCT is preferred. Rare complications include arterial perforation and dissection.

Emergency thoracotomy, in the operating room, is reserved for life-threatening hemoptysis that is uncontrolled by bronchoscopy and percutaneous embolization. Although lung resection for massive hemoptysis carries with it high morbidity and mortality, it is a permanent solution to ongoing life-threatening hemoptysis. Pulmonary arterial hemorrhage from tumor necrosis represents a surgical emergency.

Healthy patients with blood-streaked sputum or intermittent small-volume hemoptysis in the context of an acute or subacute respiratory infection with resolved hemoptysis and normal vital signs do not require imaging beyond plain chest radiography and can be discharged. High-risk patients (e.g., those with known lung cancer, pulmonary vascular abnormalities, or coagulopathy with minor hemoptysis) and all patients with moderate or large amounts of hemoptysis should undergo emergent HRCT scan. In these situations, there is little value in first obtaining a plain chest radiograph and a plain x-ray film should not be obtained if HRCT is planned regardless of the findings on the plain film. Brief hospitalization or admission to an observation unit for bronchoscopy should be considered. All patients with massive hemoptysis require admission to an ICU and expedited multidisciplinary treatment involving the emergency physician, pulmonologist, interventional radiologist, and thoracic surgeon.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 20: QUESTIONS AND ANSWERS

1. What is the most common cause of trace hemoptysis (blood-tinged sputum)?
   - **a.** Bronchiectasis
   - **b.** Bronchitis
   - **c.** Cancer
   - **d.** Congestive heart failure
   - **e.** Pulmonary embolism

Answer: b. The most common cause of small-volume hemoptysis is bronchitis.

2. Disruption of which of the following vessels is responsible for the vast majority of cases of massive hemoptysis?
   - **a.** Aorta
   - **b.** Bronchial arteries
   - **c.** Pulmonary arteries
   - **d.** Pulmonary veins
   - **e.** Tracheobronchial capillaries

Answer: b. Massive hemoptysis almost exclusively involves one of the two sets of vessels that constitute the lung's dual blood supply. Bronchial arteries, direct branches from the thoracic aorta, are responsible for supplying oxygenated blood to the lung parenchyma. Disruption of these vessels can result in sudden and profound hemorrhage. Although small in caliber, the bronchial circulation is a high-pressure system and the cause in nearly 90% of the cases of massive hemoptysis requiring embolization. Although they transmit large volumes of blood, pulmonary arteries are at much lower pressure and, unless affected at a very central location, are less likely to cause massive hemoptysis. Trace hemoptysis typically originates from tracheobronchial capillaries that become disrupted with vigorous coughing or minor bronchial infections.

3. Which of the following statements regarding the evaluation of hemoptysis is true?
   - **a.** Chest x-ray localizes the site of bleeding in nearly 90% of cases of patients with large volume hemoptysis.
   - **b.** Conventional angiography is the preferred diagnostic test to detect both bronchial and nonbronchial arterial causes of massive hemoptysis.
   - **c.** High-resolution CT, even with recent advances in technology, remains diagnostically inferior to angiography.
   - **d.** Patients with fever, cough, and blood-tinged sputum should receive a chest x-ray even if the vital signs are normal.

Answer: b. In patients with massive hemoptysis, plain films may localize the site of hemorrhage in approximately 50% of patients. However, high-resolution multidetector CT of the chest is the principal diagnostic test to detect both bronchial and nonbronchial arterial causes of massive hemoptysis. CT is diagnostically comparable with, but less invasive than, conventional angiography, which currently is done as a combined diagnostic/therapeutic modality. A chest CT scan should be obtained in high-risk patients (smokers and oncology patients) or in any patient with moderate-to-severe bleeding even if the initial chest radiograph is normal. CT localization of hemorrhage can expedite bronchoscopic evaluation or guide subsequent interventional procedures. Patients with "garden variety" bronchitis, normal oxygenation, and a normal exam do not require imaging in the emergency department.

4. A 50-year-old man presents after an episode of hemoptysis. He describes coughing up several large clots of dark blood. During his evaluation, he coughs and expectorates approximately 5 mL of clotted blood. The patient's vital signs are normal, and no abnormalities are noted on physical examination. His chest radiograph is normal. Which of the following is the most appropriate next step in the management of this patient?
   - **a.** Admission to an observation unit
   - **b.** Consultation for bronchoscopy
   - **c.** Consultation for percutaneous embolization
   - **d.** Discharge home with follow-up in 24 hours
   - **e.** Obtain chest high-resolution computed tomography (HRCT) scan

Answer: e. Since the advent of HRCT, radiologic evaluation has had an integral role in the evaluation and management of patients with hemoptysis. Unless the initial chest radiograph is diagnostic or the patient is hemodynamically unstable, an HRCT scan should be obtained in most cases. Further management strategy should occur in conjunction with pulmonary and thoracic surgery consultants, guided by the HRCT results.

5. A 58-year-old man with a single lung transplant presents to the emergency department (ED) with what appears to be large-volume hemoptysis. He was just discharged from the endoscopy suite, where he had a number of surveillance biopsies performed. He looks pale and diaphoretic with an initial oxygen saturation of 71%. After placement of an intravenous line and supplemental oxygen, the next most appropriate step is:
   - **a.** Blood transfusion
   - **b.** High-resolution computed tomography scan of the chest
   - **c.** Intubation
   - **d.** Thoracic surgery consultation

Answer: c. This patient is profoundly hypoxic and will need imaging outside of the ED and invasive procedures. The primary cause of mortality in patients with hemoptysis is asphyxiation. All resuscitative and procedural efforts will be futile without intubation and adequate oxygenation.

21

Dyspnea

Sabina A. Braithwaite and Amanda L. Wessel

KEY CONCEPTS

- Dyspnea results from a variety of conditions, ranging from nonurgent to life-threatening. Neither the clinical severity nor the patient's perception correlates well with the seriousness of underlying pathology.
- Dyspnea is subjective and the differential diagnosis can be divided into acute, acute on chronic, and chronic causes, of which the majority are cardiopulmonary. Other causes include metabolic, infectious, neuromuscular, traumatic, psychiatric, and hematologic conditions.
- Chronic or progressive dyspnea usually denotes primary cardiac or pulmonary disease. Acute dyspneic spells may result from asthma exacerbation, infection, pulmonary embolism, cardiac dysfunction, or psychogenic causes.
- All patients experiencing dyspnea, regardless of etiology, should be promptly evaluated. Bedside pulse oximetry readings should be obtained, and the patient placed on a cardiac monitor.
- If the pulse oximetry is less than 92% on room air, the patient should be placed on supplemental oxygen either by nasal cannula or mask, depending on the degree of desaturation.
- If altered level of consciousness, or hypoxia cannot be improved with suctioning, supplemental oxygen, or airway adjuncts then breathing should be assisted with manual or mechanical ventilation, either noninvasively for the short term, or with intubation for prolonged ventilation.
- Unstable patients or patients with critical diagnoses must be stabilized and may require an emergent procedure and admission to an intensive care unit. Urgent patients who improve with emergency department management may be admitted to an intermediate care unit. Patients diagnosed with urgent conditions in danger of deterioration without proper treatment or patients with severe comorbidities, such as diabetes, immunosuppression, or cancer, may also require admission for observation and treatment.

FOUNDATIONS

Dyspnea is the term applied to the uncomfortable sensation of breathlessness. It is described by patients in various ways, such as shortness of breath, chest tightness, or difficulty breathing. Dyspnea results from a variety of conditions, ranging from non-urgent to life-threatening. Neither the clinical severity nor the patient's perception correlates well with the seriousness of underlying pathology and may be affected by emotions, behavioral and cultural influences, and external stimuli.

The following terms may be used in the assessment of the dyspneic patient:

Tachypnea: Greater than normal respiratory rate. Normal rates range from 44 cycles/min in a newborn to 14 to 18 cycles/min in adults.

Hyperventilation: A minute ventilation that exceeds metabolic demand.

Dyspnea on exertion: Dyspnea provoked by physical effort. It often is quantified simply as the number of stairs or number of blocks tolerated before symptom onset.

Orthopnea: Dyspnea in a recumbent position. It is commonly described as the number of pillows the patient uses to rest comfortably in bed (e.g., two-pillow orthopnea).

Paroxysmal nocturnal dyspnea: Sudden onset of dyspnea occurring while reclining at night.

Epidemiology

Dyspnea is a very common presenting complaint among emergency department (ED) patients of every age. Causes vary widely, and range from benign, self-limited conditions to life-threatening events. The symptom of dyspnea itself is an independent predictor of mortality.[1] As chronic conditions become more prevalent, especially in the elderly, multiple etiologies may contribute to an individual's symptoms.[2,3]

Pathophysiology

Normal breathing is controlled both centrally by the respiratory control center in the medulla oblongata and peripherally by chemoreceptors located near the carotid bodies, but there are numerous sensory inputs that affect the feeling of dyspnea, including pulmonary stretch receptors and mechanoreceptors in the diaphragm and skeletal muscles. Imbalances among these inputs can be perceived as dyspnea and may manifest as increased work of breathing due to increased lung resistance, or decreased compliance in asthma or chronic obstructive pulmonary disease (COPD).[4]

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

The differential diagnosis for dyspnea can be divided into acute, acute on chronic, and chronic causes. It spans a wide range of systems including cardiac, metabolic, infectious, neuromuscular, traumatic, hematologic, and psychiatric conditions (Table 21.1).

Pivotal Findings

Symptoms

Patient descriptions of dyspnea vary significantly and frequently correlate poorly with the healthcare provider's perception of the patient's presentation.[5] One example is patients presenting with severe acute respiratory syndrome-2 coronavirus (COVID-19) who present with profound hypoxia without signs of respiratory distress (i.e., "the happy hypoxic") (see Chapter 119).

Quality of symptoms. The description of symptoms may provide clues to a diagnosis. For example, chest tightness is fairly specific to bronchoconstriction and the stimulation of airway receptors.[6]

Duration and onset of dyspnea. Chronic or progressive dyspnea usually denotes primary cardiac, pulmonary, or, less commonly, neuromuscular disease. Many of these processes such as COPD or heart failure are prone to acute exacerbations. Sudden onset of dyspnea should lead to consideration of pulmonary embolism (PE), spontaneous

TABLE 21.1 Differential Diagnoses for Acute Dyspnea

Organ System	Critical Diagnoses	Emergent Diagnoses	Nonemergent Diagnoses
Pulmonary	Airway obstruction	Spontaneous pneumothorax	Pleural effusion
	Pulmonary embolus	Asthma	Neoplasm
	Noncardiogenic pulmonary edema	Cor pulmonale	Pneumonia (CAP score ≤70)
	Anaphylaxis	Aspiration	COPD
	Ventilatory failure	Pneumonia (CAP score >70)	
Cardiac	Pulmonary edema	Pericarditis	Congenital heart disease
	Myocardial infarction		Valvular heart disease
	Cardiac tamponade		Cardiomyopathy
PRIMARILY ASSOCIATED WITH NORMAL OR INCREASED RESPIRATORY EFFORT			
Abdominal		Mechanical interference	Pregnancy
		Hypotension, sepsis from ruptured viscus, bowel obstruction, inflammatory or infectious process	Ascites, obesity
Psychogenic			Hyperventilation syndrome
			Somatization disorder
			Panic attack
Metabolic or endocrine	Toxic ingestion	Renal failure	Fever
	DKA	Electrolyte abnormalities	Thyroid disease
		Metabolic acidosis	
Infectious	Epiglottitis	Pneumonia (CAP score >70)	Pneumonia (CAP score ≤70)
Traumatic	Tension pneumothorax	Simple pneumothorax, hemothorax	Rib fractures
	Cardiac tamponade	Diaphragmatic rupture	
	Flail chest	Neurologic injury	
Hematologic	Carbon monoxide or cyanide poisoning	Anemia	
	Acute chest syndrome		
PRIMARILY ASSOCIATED WITH DECREASED RESPIRATORY EFFORT			
Neuromuscular	CVA, intracranial insult	Multiple sclerosis	ALS
	Organophosphate poisoning	Guillain-Barré syndrome	Polymyositis
		Tick paralysis	Porphyria

ALS, Amyotrophic lateral sclerosis; *CAP,* community-acquired pneumonia; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *DKA,* diabetic ketoacidosis.

pneumothorax, myocardial infarction, acute environmental exposure, or foreign body. Worsening of new symptoms over several days may indicate a more gradual process such as pneumonia.

***Positional changes.*.** Orthopnea can result from left-sided heart failure, COPD, or neuromuscular disorders.[4] It can be one of the earliest symptoms in patients with diaphragmatic weakness from neuromuscular disease. Paroxysmal nocturnal dyspnea is most common in patients with left-sided heart failure but also occurs in COPD. Exertional dyspnea is commonly associated with COPD but also can be seen with poor cardiac reserve and abdominal loading. Abdominal loading, caused by ascites, obesity, or pregnancy, leads to elevation of the diaphragm, resulting in less effective ventilation and dyspnea.[7]

***Associated symptoms.*.** Anxiety or overwhelming fear, particularly if it precedes the onset of dyspnea, may point to panic attack or psychogenic dyspnea. Organic causes should be considered first as the sensation of dyspnea can itself provoke anxiety, but it is also frequently noted with hypoxia or inadequate ventilation. PE or myocardial infarction may or may not be associated with chest pain, particularly pain that is constant, dull, or visceral. Pain that is sharp and worsened by deep breathing but not by movement may indicate pleural effusion, pleurisy, or pleural irritation from pneumonia or PE.

Signs

Physical signs in dyspneic patients may be consistent with specific illnesses (Table 21.2). For example, fever suggests an infectious cause, somnolence or obtundation may indicate hypercarbia, agitation can be associated with hypoxia, and trauma may produce dyspnea through various injuries. Drooling or a tripod position may indicate upper airway obstruction.[8] Physical findings found in specific diseases also can be grouped by presenting patterns (Table 21.3). Some findings have improved predictive value for specific pathologies when combined with laboratory testing in validated risk stratification tools.[9–11]

Ancillary Testing

Specific findings obtained from the history and physical examination should drive which ancillary studies are needed to focus the differential diagnosis (Table 21.4). Bedside oxygen saturation is useful in assessing the degree of hypoxia and typically correlates well with arterial blood gases (ABG), which are invasive and painful. Venous blood gas (VBG)

TABLE 21.2 Pivotal Findings in Physical Examination

Sign	Physical Finding	Diagnoses to Consider
Vital signs	Tachypnea	Pneumonia, pneumothorax, metabolic acidosis
	Hypopnea	Intracranial insult, drug or toxin ingestion
	Tachycardia	PE, traumatic chest injury, sepsis, anxiety
	Hypotension	Tension pneumothorax, cardiac tamponade, sepsis
	Fever	Pneumonia, PE
General appearance	Cachexia, weight loss	Malignancy, acquired immune disorder, mycobacterial infection, COPD
	Obesity	Hypoventilation, sleep apnea, PE
	Pregnancy	PE
	Barrel chest	COPD
	"Sniffing" position	Epiglottitis
	"Tripoding" position	COPD or asthma with severe exacerbation
	Traumatic injury	Pneumothorax (simple, tension), rib fractures, diaphragmatic injury, flail chest, hemothorax, pulmonary contusion
Skin and nails	Tobacco stains or odor	COPD, malignancy, infection
	Clubbing	Chronic hypoxia, intracardiac shunts, or pulmonary vascular anomalies
	Pallid skin or conjunctivae	Anemia
	Muscle wasting	Neuromuscular disease, malignancy, COPD
	Bruising	Chest wall: Rib fractures, pneumothorax
	Diffuse: Thrombocytopenia, chronic steroid use, anticoagulation	
	Subcutaneous emphysema	Rib fractures, pneumothorax, tracheobronchial disruption
	Hives, rash	Allergic reaction, infection, tick-borne illness
Neck	Stridor	Upper airway edema or infection, foreign body, traumatic injury, anaphylaxis, vocal cord dysfunction
	JVD	Tension pneumothorax, fluid overload or CHF, cardiac tamponade
Lung examination	Wheezes	bronchospasm due to asthma, COPD, or anaphylaxis; CHF
	Rales	CHF, pneumonia
	Unilateral decrease	Pneumothorax, pleural effusion, consolidation, rib fractures or contusion, pulmonary contusion
	Hemoptysis	Malignancy, infection, PE, bleeding disorder, CHF
	Sputum production	Infection (viral, bacterial), CHF
	Friction rub	Pleurisy
	Abnormal respiratory pattern (e.g., Cheyne-Stokes)	Intracranial insult
Chest examination	Pain on palpation	Rib or sternal fractures
	Subcutaneous emphysema or crepitus	Pneumothorax, tracheobronchial rupture
	Thoracoabdominal dyssynchrony	Diaphragmatic injury with herniation; cervical spinal cord trauma
	Flail segment	Flail chest, pulmonary contusion
Cardiac examination	Murmur	Valvular dysfunction/CHF
	S_3 or S_4 gallop	PE, CHF
	S_2 accentuation	PE
	Muffled heart sounds	Cardiac tamponade, pericardial effusion
Extremities	Unilateral edema or pain	VTE
	Bilateral Edema	CHF
Neurologic examination	Focal deficits (motor, sensory, cognitive)	Stroke, intracranial hemorrhage causing central abnormal respiratory drive; if long-standing, risk of aspiration pneumonia
	Symmetrical deficits	Neuromuscular disease
	Diffuse weakness	Metabolic or electrolyte abnormality (hypocalcemia, hypomagnesemia, hypophosphatemia), anemia
	Hyporeflexia	Hypermagnesemia
	Ascending weakness	Guillain-Barré syndrome

CHF, Congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *JVD,* jugular venous distention; *PE,* pulmonary embolism.

TABLE 21.3 Diagnostic Table: Patterns of Diseases Often Resulting in Dyspnea

Disease	History (Dyspnea)	Associated Symptoms	Signs and Physical Findings	Tests
Pulmonary embolism	HPI: Abrupt onset, pleuritic pain, immobility (travel, recent surgery) PMH: Malignancy, DVT, PE, hypercoagulability, hormonal therapy, obesity, tobacco use, pregnancy	Pleuritic chest pain, unilateral lower extremity pain or swelling	Tachycardia, tachypnea, low-grade fever	Pulse oximetry, ABG (A-a gradient), D-dimer ECG (dysrhythmia, right-sided heart strain) CXR (Westermark sign, Hampton's hump), CTA, MRV Pulmonary angiogram Ultrasound positive for DVT
Pneumonia	Fever, productive cough, chest pain	Anorexia, chills, nausea, vomiting, cough	Fever, tachycardia, tachypnea, rales or decreased breath sounds	CXR, CBC, sputum and blood cultures
Bacterial	SH: Tobacco use			Pulse oximetry Waveform capnography if altered mental status; ABG if capnography unavailable and acid-base derangement or hypercarbia suspected
Viral	Exposure (e.g., influenza, varicella)			Viral polymerase chain reaction
Opportunistic	Immune disorder, chemotherapy			
Fungal or parasitic	Exposure (e.g., birds), indolent onset	Episodic fever, nonproductive cough		Fungal sputum culture
Pneumothorax	Abrupt onset: Trauma, chest pain, thin males more likely to have spontaneous pneumothorax	Localized chest pain	Decreased breath sounds, subcutaneous emphysema, chest wall wounds or instability	CXR: Pneumothorax, rib fractures, hemothorax Ultrasound: Pneumothorax, pleural effusion
Simple				Ultrasound positive for pneumothorax
Tension	Decompensation of simple pneumothorax	Diaphoresis, lightheadedness	JVD, tracheal deviation, muffled heart sounds, cardiovascular collapse due to obstructive shock	Clinical diagnosis: Requires immediate decompression. May verify via bedside ultrasound
COPD or asthma	Tobacco use, medication noncompliance, URI symptoms, sudden weather change PMH: Environmental allergies FH: Asthma	Air hunger, chest tightness	Retractions, accessory muscle use, tripoding, cyanosis "Shark fin" capnograph	CXR: Rule out infiltrate, pneumothorax, atelectasis (mucus plug) Ultrasound: Distinguish from heart failure Waveform capnography
Malignancy	Weight loss, tobacco, or other occupational exposure	Dysphagia, generalized weakness	Hemoptysis	CXR, chest CT: Mass, hilar adenopathy, focal atelectasis
Fluid overload	Gradual onset, dietary indiscretion or medication noncompliance, chest pain PMH: Recent MI, diabetes, CHF	Worsening orthopnea, PND	JVD, peripheral edema, S_3 or S_4 gallop, new cardiac dysrhythmia, hepatojugular reflux	CXR and/or ultrasound: Pleural effusion, interstitial edema, Kerley B lines, cardiomegaly ECG: Ischemia, dysrhythmia BNP
Anaphylaxis	Abrupt onset, exposure to allergen	Dysphagia, nausea/vomiting, abdominal pain, pruritis	Oral swelling, stridor, wheezing, hives	

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *BNP,* B-type natriuretic peptide; *CBC,* complete blood count; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *CTA,* CT angiography; *CXR,* chest x-ray examination; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *FH,* family history; *HPI,* history of present illness; *JVD,* jugular venous distention; *MI,* myocardial infarction; *MRV,* magnetic resonance venography; *PE,* pulmonary embolism; *PMH,* past medical history; *PND,* paroxysmal nocturnal dyspnea; *SH,* social history; *URI,* upper respiratory infection.

TABLE 21.4 Ancillary Testing in the Dyspneic Patient

Category	Test	Findings and Potential Diagnoses
Laboratory	Pulse oximetry, VBG, selective ABG use	Hypoxia, hypercarbia, hyperventilation (muscular weakness, intracranial event)
	Waveform capnography	CO_2 retention (COPD, sleep apnea), obstructive or restrictive pulmonary pattern
		Metabolic versus respiratory acidosis (DKA, ingestions)
		A-a gradient (PE)
		Elevated carboxyhemoglobin (inhalation injury or CO poisoning)
	Complete blood count	WBC
		Increase: Infection, stress demargination, hematologic malignancy
		Decrease: Neutropenia, sepsis
		Hgb, Hct: Anemia, polycythemia
		Smear: Abnormal Hgb (i.e., sickling), inclusions
		Platelets: Thrombocytopenia (marrow toxicity)
		Electrolytes
		BUN, Cr: Acute or chronic renal failure
		K, Mg, PO_4: Low levels resulting in muscular weakness
		Glucose: DKA
		D-dimer: Abnormal clotting activity
		BNP: Heart failure, PE
		Troponin: Cardiac ischemia or infarct
Cardiac	ECG	Ischemia, dysrhythmia, $S_1Q_3T_3$ (PE), right-sided heart strain
	Echocardiogram	Pulmonary hypertension, valvular disorders
		Wall motion abnormalities related to ischemia, intracardiac shunts
Radiologic	Chest radiograph	Bony structures: Fractures, lytic lesions, pectus, kyphoscoliosis
		Mass: Malignancy, cavitary lesion, infiltrate, foreign body
		Diaphragm: Eventration, elevation of hemidiaphragm, bowel herniation
		Mediastinum: Adenopathy (infection, sarcoid), air
		Cardiac silhouette: Enlarged (cardiomyopathy, fluid overload)
		Soft tissue: Subcutaneous air
		Lung parenchyma: Blebs, pneumothorax, effusions (blood, infectious), interstitial edema, local consolidation, air bronchograms, Hampton's hump, Westermark sign
	Ventilation perfusion scan	PE
	Pulmonary angiogram	PE, intervention (thrombolysis)
	CTA	Mass lesion, adenopathy, trauma, PE
	MRI	PE, bony and soft tissue lesions, vascular abnormality
	Soft tissue neck radiograph	Epiglottitis, foreign body
	Ultrasound	Pneumothorax, pleural effusion, impaired cardiac function or pericardial effusion
Fiberoptic	Bronchoscopy	Mass lesion, foreign body
		Intervention (stenting, biopsy)
	Laryngoscopy	Mass lesion, edema, epiglottitis, foreign body

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *BNP,* B-type natriuretic peptide; *BUN,* blood urea nitrogen; *CO,* carbon monoxide; *CO_2,* carbon dioxide; *COPD,* chronic obstructive pulmonary disease; *Cr,* creatinine; *CT,* computed tomography; *CTA,* CT angiography; *DKA,* diabetic ketoacidosis; *ECG,* electrocardiogram; *Hct,* hematocrit; *Hgb,* hemoglobin; *K,* potassium; *Mg,* magnesium; *MRI,* magnetic resonance imaging; *PE,* pulmonary embolism; Phos, phosphate; *VBG,* venous blood gas; *WBC,* white blood cell.

is a less painful alternative while still useful in determining pH and pCO_2.[12,13] An additional noninvasive resource for quickly assessing ventilatory status is waveform capnography. End-tidal carbon dioxide ($ETco_2$) measurement and waveform can be helpful in assessing the adequacy of ventilation, and also can provide clues to the underlying cause of dyspnea (see Chapter 5).[14–16] An electrocardiogram may be useful if history or physical examination findings suggest heart failure, ischemic cardiac disease, dysrhythmia, or right heart strain. Bedside ultrasound can quickly visualize pleural effusion, pulmonary edema, pneumothorax, and cardiovascular anomalies such as regional wall motion abnormalities or global dysfunction, right heart strain, pericardial effusion or tamponade, inferior vena cava size and collapsibility, and lower extremity deep venous thrombosis[17,18] (see Chapter e3) Procalcitonin correlates well with community acquired pneumonia pathogens in admitted patients, but its usefulness in EDs to guide antibiotic therapy has not yet been shown, therefore routine use is not recommended.[19,20]

Serum electrolytes may confirm metabolic acidosis or a less common cause, such as hypokalemia, hypophosphatemia, or hypocalcemia. A complete blood count may identify severe anemia or thrombocytopenia associated with sepsis. The white blood cell count is not sufficiently sensitive or specific to be of discriminatory value.

Expanded availability of specific blood biomarkers relevant to emergent evaluation of dyspnea provides improved immediate decision support, and in some situations, prognostication. These biomarkers include cardiac markers in cardiac ischemia and D-dimer assay in venous thromboembolic disease. B-type natriuretic peptide (BNP) analysis adds both diagnostic and prognostic value for several causes of dyspnea, including heart failure, PE, and ischemic cardiac disease.[21]

If venous thromboembolism is suspected, the use of D-dimer testing, chest computed tomographic angiography (CTA), duplex venous ultrasonography, or, rarely, ventilation-perfusion scanning, is performed on patients identified using clinical decision rules. If dyspnea is believed to be of upper airway origin, direct or fiberoptic laryngoscopy or a soft tissue lateral radiograph of the neck may be useful.

DIAGNOSTIC ALGORITHM

The range and diversity of pathophysiologic conditions that produce dyspnea render a simple algorithmic approach difficult. The primary branch point is the determination of acuity of illness. After initial assessment, stabilization, and symptom relief in critical patients, findings from the history, physical examination, and ancillary testing are collated to match illness scripts related to dyspnea.[22,23] Table 21.3 presents recognizable patterns of disease for common dyspnea-producing conditions, along with specific associated symptoms.

Critical Diagnoses

Several critical diagnoses should be promptly considered to determine the best treatment options for immediate stabilization. The presence of hypotension and dyspnea should raise suspicion for tension pneumothorax and cardiac tamponade, two immediately life-threatening causes of obstructive shock that can quickly be confirmed with bedside ultrasonography (see Chapter e3). Jugular venous distension may or may not be apparent and its absence does not rule out these conditions. Tension pneumothorax is differentiated by asymmetric breath sounds with signs of poor perfusion, and requires prompt decompression via needle thoracostomy. Dyspnea and stridor can indicate upper airway obstruction, which at its worst can require complex maneuvers including emergent consultation by anesthesia, or head and neck surgery, to secure a definitive airway. Complete obstruction by a foreign body warrants abdominal thrusts in adult patients until the obstruction is relieved or the patient is unconscious, followed rapidly by direct laryngoscopy for foreign body removal. ST elevation myocardial infarction requires prompt activation of a cardiac catheterization lab. Hypoxic or hypercarbic respiratory failure may require any of a range of interventions ranging from nasal cannula and non-rebreather mask to noninvasive positive pressure ventilation via mask or endotracheal intubation.[24] Significant dyspnea and wheezing in anaphylaxis requires immediate use of intramuscular epinephrine in addition to supportive airway measures. Bronchospastic exacerbations of asthma at any age may lead rapidly to respiratory failure and arrest and should receive continuous or frequent administration of a beta-agonist aerosol, early steroid and magnesium therapy, and in severe cases intramuscular epinephrine. Presumptive anticoagulation or even thrombolytics, even prior to diagnostic testing or confirmation, may be appropriate in patients presenting with severe symptoms consistent with PE.

Emergent Diagnoses

Asthma and COPD exacerbations can result in marked dyspnea with bronchospasm and decreased ventilatory volumes. Sudden onset of dyspnea with a decreased oxygen saturation on room air accompanied by sharp chest pain may represent PE or pneumothorax. Dyspnea associated with decreased respiratory effort and negative inspiratory force may represent progression of a neuromuscular process, such as multiple sclerosis, Guillain-Barré syndrome, or myasthenia gravis. Unilateral rales, cough, fever, and dyspnea usually indicate pneumonia.

Fig. 21.1 provides an algorithm for assessment and stabilization of a dyspneic patient. The initial division is based on the degree of breathing effort associated with the symptoms. The most critical diagnoses are considered first, and appropriate intervention undertaken.

All patients experiencing dyspnea, regardless of possible cause, should be promptly evaluated. Bedside pulse oximetry readings should be obtained, and the patient placed on a cardiac monitor. If the pulse oximetry is less than 92% on room air, supplemental oxygen either by nasal cannula or mask should be administered, depending on the degree of desaturation. In patients with somnolence or obtundation, hypercarbia and respiratory failure should be considered as possible etiologies and waveform capnography used for confirmation. Ventilation should be assisted manually or mechanically, either noninvasively for the short term, or with endotracheal intubation for prolonged ventilation.

Decreased mental alertness, inability to speak in full sentences, or certain types of body positioning (tripod) signal the presence of significant respiratory distress and the need for rapid intervention.

Empirical Management

The management algorithm for dyspnea (Fig. 21.2) outlines the approach to treatment for most identifiable diseases. Empiric treatments are typically directed at optimizing oxygenation, ventilation, and overall work of breathing. There are few other treatments directed at the symptom itself, rather than the underlying diagnosis. Opiate medications and sedatives help to relieve the sensation of air hunger and anxiety, but their use is generally reserved for the palliative care setting due to their respiratory depressant effects.

Unstable patients or patients with critical diagnoses must be stabilized and may require admission to an intensive care unit or an emergent procedure. Urgent patients who improve with ED management may be admitted to an intermediate care unit. Patients diagnosed with urgent conditions in danger of deterioration without proper treatment or patients with severe comorbidities, such as diabetes, immunosuppression, or cancer, may also require admission for observation and treatment.

Most patients in the nonurgent category can be treated as outpatients if medical follow-up can be arranged. If dyspnea persists despite therapy and no definitive cause has been delineated, the preferred course of action is hospitalization for observation and further evaluation. If no definitive diagnosis can be obtained and the symptoms have abated, the patient may be discharged with medical follow-up and instructions to return if symptoms recur.

The references for this chapter can be found online at Expert Consult.com.

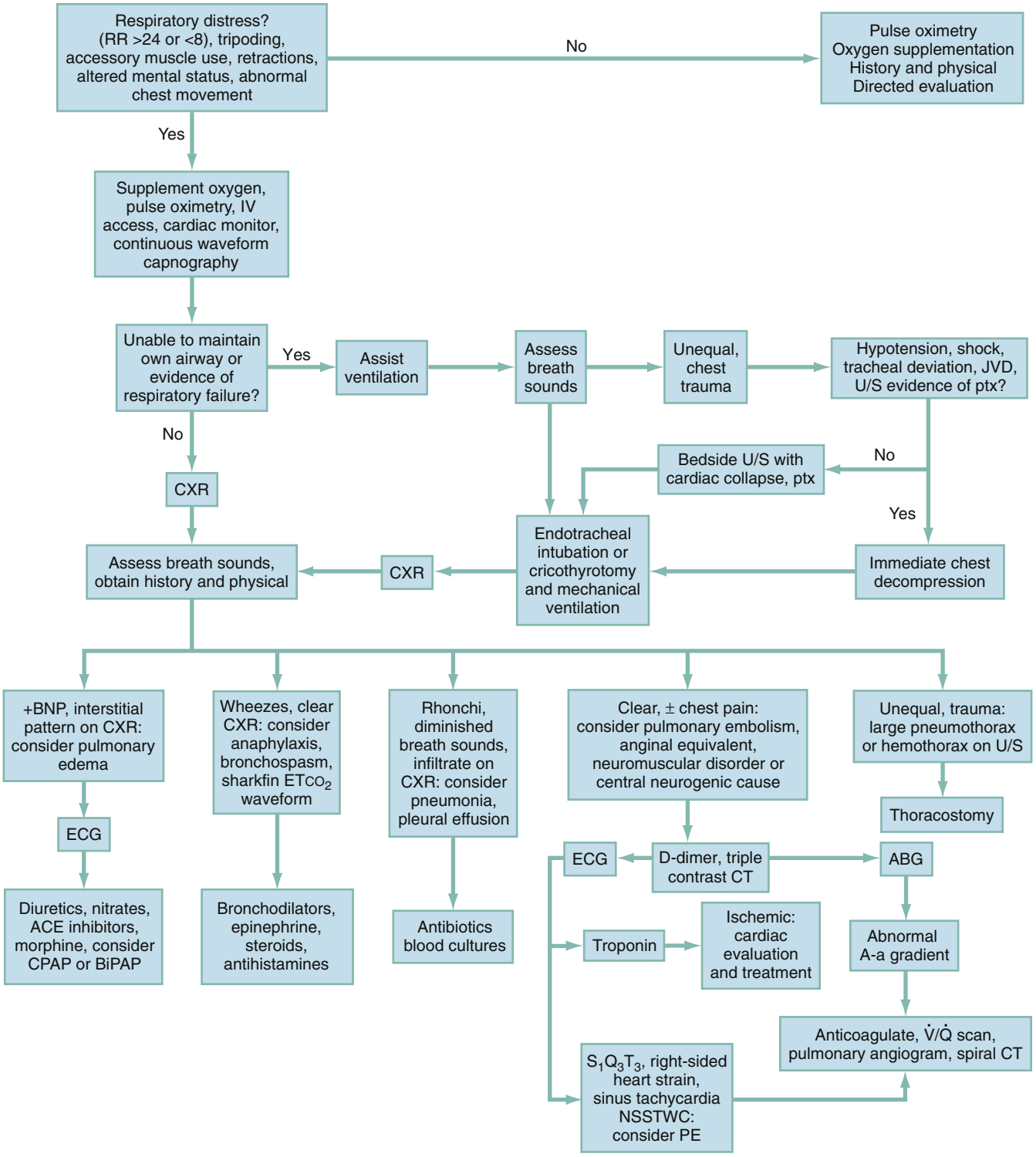

Fig. 21.1 Rapid Assessment and Stabilization of a Dyspneic Patient. *A-a,* Arterial-alveolar; *ABG,* arterial blood gas; *ACE,* angiotensin-converting enzyme; *BiPAP,* biphasic positive airway pressure; *BNP,* B-type natriuretic peptide; *CPAP,* continuous positive airway pressure; *CT,* computed tomography; *CXR,* chest x-ray; *ECG,* electrocardiogram; *ET_{CO_2},* end-tidal carbon dioxide; *IV,* intravenous; *JVD,* jugular venous distention; *NSSTWC,* nonspecific ST wave changes (on ECG); *PE,* pulmonary embolism; *ptx,* pneumothorax; *RR,* respiratory rate; *V/Q,* ventilation-perfusion ratio; *U/S,* ultrasound.

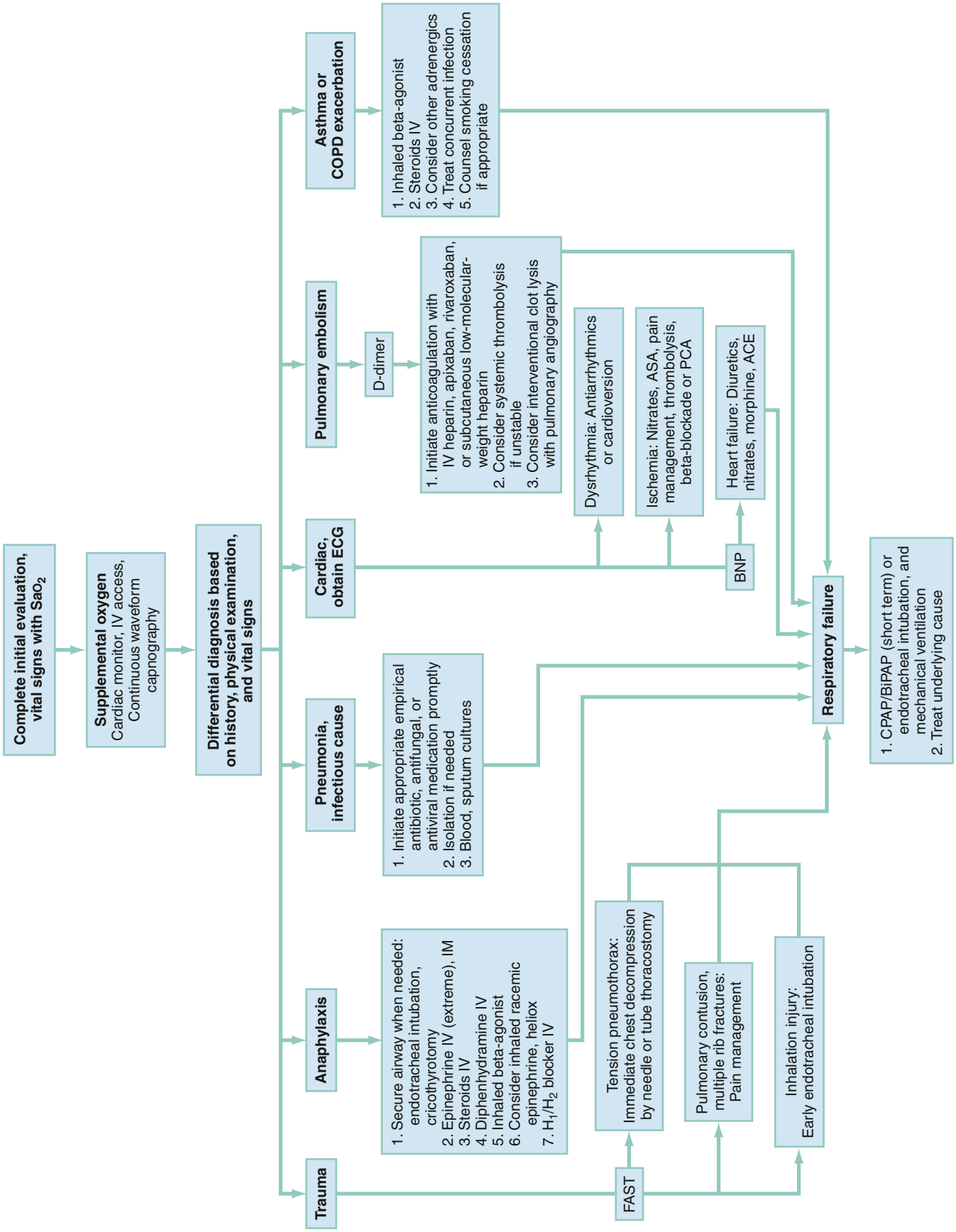

Fig. 21.2 Clinical Guidelines for Emergency Department Management of Dyspnea. *ACE,* Angiotensin-converting enzyme; *ASA,* acetylsalicylic acid; *BNP,* B-type natriuretic peptide; *COPD,* chronic obstructive pulmonary disease; *CPAP/BiPAP,* continuous positive airway pressure/biphasic positive airway pressure; *ECG,* electrocardiogram; *FAST,* focused assessment with sonography in trauma; *IV,* intravenous; *PCA,* patient-controlled analgesia; *Sao_2,* arterial oxygen saturation; *SC,* subcutaneously.

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CHAPTER 21: QUESTIONS AND ANSWERS

1. Orthopnea is best defined by which of the following?
- **a.** A respiratory rate greater than normal
- **b.** A tidal volume that exceeds metabolic demands
- **c.** Decreased end-tidal carbon dioxide levels
- **d.** Dyspnea in a recumbent position

Answer: d. Dyspnea in a recumbent position, commonly described as the number of pillows the patient uses to rest comfortably in bed (e.g., two-pillow orthopnea).

2. Stridor is most likely due to which of the following conditions?
- **a.** Bronchospasm
- **b.** Guillain-Barré syndrome
- **c.** Laryngeal edema
- **d.** Malignancy

Answer: c. Stridor is an upper airway noise caused by airway narrowing. Of the given options, stridor is most likely due to laryngeal edema.

3. A 34-year-old male was struck repeatedly with a pipe in the right chest. He becomes acutely more dyspneic during emergency medical services (EMS) transport and becomes clammy, hypotensive, and more tachycardic on arrival to the emergency department (ED). Examination reveals tachypnea, right chest crepitus, and decreased breath sounds. Which of the following actions should be done next?
- **a.** Needle chest decompression of the right chest
- **b.** Perform portable chest radiograph
- **c.** Provide supplemental oxygen by non-rebreather mask
- **d.** Rapid sequence intubation (RSI) and endotracheal intubation

Answer: a. Needle chest decompression is indicated for management of a likely tension pneumothorax. If ultrasound is immediately available, it can be used to confirm pneumothorax, but in this patient, who is in cardiovascular collapse, immediate intervention is necessary.

4. Which of the following causes of acute respiratory distress is most likely to be associated with decreased respiratory effort?
- **a.** Pleural effusion
- **b.** Tension pneumothorax
- **c.** Cyanide poisoning
- **d.** Multiple sclerosis

Answer: d. multiple sclerosis. Several different neuromuscular diseases are associated with decreased respiratory effort in acute distress due largely to inadequate ability to create sufficient negative inspiratory force and generate adequate tidal volume and minute ventilation.

CHAPTER 21: QUESTIONS AND ANSWERS—Cont'd

5. When assessing a patient with acute respiratory distress, a shark fin waveform on capnography suggests which of the following conditions?

a. Cardiac ischemia
b. Pneumothorax
c. Pulmonary embolism
d. Pneumonia
e. Bronchospasm

Answer: e. Bronchospasm. The classic "shark fin" indicates bronchospasm such as with significant asthma exacerbation. See Fig. 21.1 for assessment paradigm considerations.

22

Chest Pain

James E. Brown

KEY CONCEPTS

- Tension pneumothorax is a clinical diagnosis, treated with needle decompression, followed by tube thoracostomy.
- Patients with suspected acute coronary syndrome (ACS) are risk-stratified by history, electrocardiogram (ECG), and troponin levels. Those with ST segment elevation myocardial infarction (STEMI) undergo revascularization via fibrinolysis or percutaneous coronary intervention (PCI). Those with non–ST segment elevation myocardial infarction (NSTEMI) do not require immediate PCI. Those with a nondiagnostic ECG and troponin level are managed with observation.
- Thoracic dissection is diagnosed with CT angiography. The initial management of dissection is with urgent control of heart rate, followed by lowering of blood pressure. Further management, medical or surgical, depends on the location of the dissection.
- Pulmonary embolism is diagnosed using a combination of history, serum D-dimer measurement, and imaging, usually CT angiography. Patients with a low pretest probability and normal D-dimer level do not have pulmonary embolism as the cause of their chest pain presentation.
- Patients with pericardial effusions undergo echocardiography to evaluate for cardiac tamponade. Those with signs of shock may require emergent pericardiocentesis.

FOUNDATIONS

Approximately 7.5 million patients visit the emergency department (ED) each year with complaints of chest pain, constituting 5% of all patients seen in EDs in the United States.[1] Chest pain is a symptom caused by several life-threatening as well as non–life-threatening diseases and has a broad differential diagnosis. It is complicated by a frequent disassociation between the intensity of symptoms and signs and the seriousness of underlying pathology.

Epidemiology

The epidemiology of the critical diagnoses causing chest pain varies widely. Acute coronary syndrome (ACS), aortic dissection, pulmonary embolism (PE), pneumothorax, pericarditis with tamponade, and esophageal rupture are potentially catastrophic causes of chest pain. These are discussed in the relevant chapters in this text. Chest pain that is atypical or of unclear cause is a daily presentation in virtually every ED—large or small, academic or community, urban, suburban, or rural.

Pathophysiology

Afferent fibers from the heart, lungs, great vessels, and esophagus enter the same thoracic dorsal ganglia. Through these visceral fibers, each organ produces the same indistinct quality and location of pain. The quality of visceral chest pain varies widely and is described as "burning," "aching," "stabbing," or "pressure." Because dorsal segments overlap three segments above and below a level, disease of a thoracic origin can produce pain anywhere from the jaw to the epigastrium. Radiation of pain is caused by somatic afferent fibers synapsing in the same dorsal root ganglia as the thoracic viscera. This stimulation can confuse the patient's central nervous system into misperceiving that the pain originates in the arms, shoulders, or neck.

DIAGNOSTIC APPROACH

Differential Considerations

Because of the indistinct nature of visceral pain, the differential diagnosis of chest pain is broad and includes many of the most critical diagnoses in medicine and many nonemergent conditions (Table 22.1).

All patients, except those with obvious benign causes of chest pain, undergo electrocardiography as soon as possible after reporting their pain. The electrocardiogram (ECG) should be read for acute myocardial infarction (MI) by the emergency clinician promptly after it is completed.[2] Patients with positive electrocardiographic findings and those considered at high risk are triaged directly to the treatment area and monitored.

In clinical evaluation of the patient, the initial questions are "Should I intervene now?" and "What are the life-threatening possibilities in this patient?" The answers are usually apparent within the first few minutes after assessment of the patient's appearance, ECG, and vital signs. If a patient has unilateral chest pain, respiratory distress, shock, and unilateral reduction or absence of breath sounds, emergent intervention with needle or tube thoracostomy is required. In addition, patients with severe derangements in vital signs require stabilizing treatment during a search for the precipitating cause. Patients with respiratory distress require prompt intervention and lead the emergency clinician to consider a more serious cause of the pain (Fig. 22.1).

Symptomatic derangements in vital signs are addressed. If vital signs are stable, a focused history and physical examination are performed. Many patients also require a chest radiograph to evaluate the chest pain. If myocardial ischemia is suspected, aspirin and nitroglycerin may be appropriate. Patients with pain, findings suggestive of aortic dissection, and significant hypertension are candidates for immediate reduction of blood pressure (see Chapter 71). Patients with low voltage on the ECG, diffuse ST segment elevation, elevated jugular venous pressure on examination, and signs of shock should undergo prompt bedside cardiac ultrasound to evaluate for pericardial tamponade.[3]

Pivotal Findings

The broad and complex nature of chest pain defies application of a simple algorithm. An organized approach to a patient with chest pain is essential, however, to ensure that all causes are evaluated appropriately. The history and physical examination are key to diagnosis. Information pertinent to the differential diagnosis is obtained through the directed history, physical examination, and ECG in 80% to 90% of patients.

TABLE 22.1 Differential Diagnosis of Chest Pain

Organ System	Critical Diagnoses	Emergent Diagnoses	Nonemergent Diagnoses
Cardiovascular	Acute myocardial infarction	Unstable angina	Valvular heart disease
	Acute coronary ischemia	Coronary spasm	Aortic stenosis
	Aortic dissection	Prinzmetal angina	Mitral valve prolapse
	Cardiac tamponade	Cocaine-induced pericarditis or myocarditis	Hypertrophic cardiomyopathy
Pulmonary	Pulmonary embolus	Pneumothorax	Pneumonia
	Tension pneumothorax	Mediastinitis	Pleuritis, tumor, pneumomediastinum
Gastrointestinal	Esophageal rupture (Boerhaave syndrome)	Esophageal tear (Mallory-Weiss)	Esophageal spasm
		Cholecystitis	Esophageal reflux
		Pancreatitis	Peptic ulcer, biliary colic
Musculoskeletal			Muscle strain, rib fracture, arthritis, tumor, costochondritis, nonspecific chest wall pain
Neurologic			Spinal root compression, thoracic outlet, herpes zoster, postherpetic neuralgia
Other			Psychological, hyperventilation

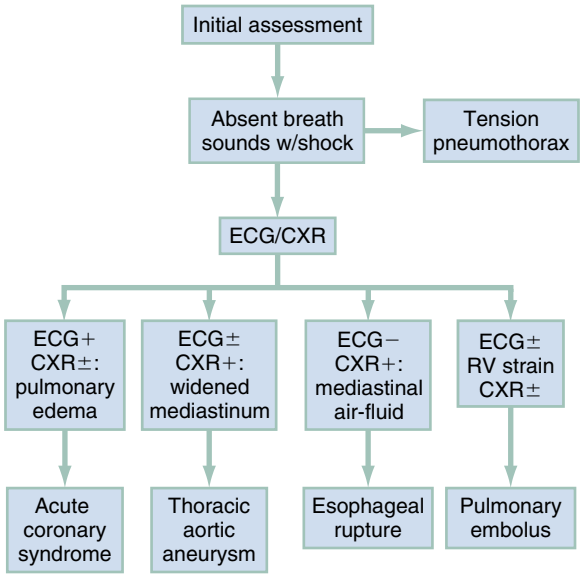

Fig. 22.1 Initial Assessment of Critical Diagnoses. *CXR,* Chest x-ray study; *ECG,* electrocardiogram; *RV,* right ventricular.

History

The patient is asked to describe the character of the pain or discomfort. Descriptions such as "squeezing," "crushing," or "pressure" lead the emergency clinician to suspect a cardiac ischemic syndrome, although cardiac ischemia can also be characterized by nonspecific discomfort, such as "bloating" or "indigestion." "Tearing" pain that may migrate from the front to back or back to front is the classic description in aortic dissection. "Sharp" or "stabbing" pain is seen more in pulmonary and musculoskeletal diagnoses. Patients reporting a "burning" or "indigestion" type of pain may initially be thought to have a gastrointestinal condition, but owing to the visceral nature of chest pain, patients with all causes of pain may report any of the preceding descriptions. Of note, descriptors may vary among ethnic groups; for example, "sharp" may mean "severe."

Additional history about the patient's activity at the onset of pain may be helpful. Pain occurring during exertion suggests an ischemic coronary syndrome, whereas progressive onset of pain at rest suggests an acute MI. Pain of sudden onset is more typical with aortic dissection, PE, or pneumothorax. Pain after meals is more indicative of a gastrointestinal cause.

The severity of pain is commonly quantified with a 1 to 10 pain scale. Alterations in pain severity are documented at times of onset, at peak, at present, and after intervention.

The location of the discomfort is described. Pain that is localized to a small area is more likely to be somatic versus visceral in origin. Pain localized at the periphery of the chest is more likely to have a pulmonary rather than cardiac cause. Lower chest or upper abdominal pain may be of cardiac or gastrointestinal origin.

Any description of radiation of pain should be noted. Transthoracic pain through to the back should suggest aortic dissection or gastrointestinal causes, especially pancreatitis, cholecystitis, or posterior ulcer. Inferoposterior myocardial ischemia may also manifest primarily as thoracic back pain. Radiation to the arms, neck, or jaw increases the likelihood of cardiac ischemia. Pain located primarily in the back, especially interscapular back pain that migrates to the base of the neck, suggests aortic dissection.

Duration of pain is another important historical factor. Pain that lasts a few seconds or minutes is rarely of cardiac origin. Pain that is exertional but abates with a few minutes of rest may be a manifestation of cardiac ischemia. Pain that is maximal at onset may be caused by aortic dissection.[4,5] Pain that is not severe and persists over the course of days is less likely to be of serious origin than pain that is severe or has a stuttering or fluctuating course.

The emergency clinician should consider aggravating or alleviating factors. Pain that worsens with exertion and improves with rest is more likely related to coronary ischemia. Pain related to meals is more suggestive of a gastrointestinal cause. Pain that worsens with respiration is seen more often with pulmonary, pulmonary vascular, pericardial, and musculoskeletal causes.

Other associated symptoms may suggest the visceral nature of the pain (Table 22.2). Diaphoresis is uncommonly associated with somatic pain unless it is severe, such as with rib fractures, so the presence of diaphoresis should prompt a search for a serious or visceral cause and points away from a chest wall origin. Hemoptysis, a classic PE sign, is rarely seen. Near-syncope and syncope suggest a higher likelihood of a cardiovascular cause or PE. Dyspnea is seen in cardiovascular and pulmonary disease. Nausea and vomiting may be seen in those with cardiovascular and gastrointestinal complaints.

TABLE 22.2 Significant Symptoms of Chest Pain

Symptom	Findings	Diagnosis
Pain	Severe, crushing, pressure, substernal, exertional, radiation to jaw, neck, shoulder, arm	Acute MI, coronary ischemia, unstable angina, coronary spasm
	Tearing, severe, radiating to or located in back, maximum at onset, may migrate to upper back or neck	Aortic dissection
	Pleuritic	Esophageal rupture, pneumothorax, cholecystitis, pericarditis, myocarditis
	Indigestion or burning	Acute MI, coronary ischemia, esophageal rupture, unstable angina, coronary spasm, esophageal tear, cholecystitis
Associated syncope or near-syncope		Aortic dissection, PE, acute MI, pericarditis, myocarditis
Associated dyspnea (SOB, DOE, PND, orthopnea)		Acute MI, coronary ischemia, PE, tension pneumothorax, pneumothorax, unstable angina, pericarditis
Associated hemoptysis		PE
Associated nausea, vomiting		Esophageal rupture, acute MI, coronary ischemia, unstable angina, coronary spasm, esophageal tear, cholecystitis

DOE, Dyspnea on exertion; *MI,* myocardial infarction; *PE,* pulmonary embolism; *PND,* paroxysmal nocturnal dyspnea; *SOB,* shortness of breath.

BOX 22.1 Risk Factors Associated With Potentially Catastrophic Causes of Chest Pain

Acute coronary syndromes
- Past or family history of coronary artery disease
- Age
  - Men >33 years
  - Women >40 years
- Diabetes mellitus
- Hypertension
- Cigarette use or possible passive exposure
- Elevated cholesterol (low-density lipoprotein [LDL]) or triglyceride levels
- Sedentary lifestyle
- Obesity
- Postmenopausal
- Left ventricular hypertrophy
- Cocaine abuse

Pulmonary embolism
- Malignancy
- Prolonged immobilization
- Surgery >30 min in last 3 months
- Prior deep vein thrombosis or pulmonary embolus
- Pregnancy or recent pregnancy
- Pelvic or lower extremity trauma
- Oral contraceptives with cigarette smoking
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Obesity
- Past medical or family history of hypercoagulability

Aortic dissection
- Hypertension
- Congenital disease of the aorta or aortic valve
- Inflammatory aortic disease
- Connective tissue disease
- Pregnancy
- Arteriosclerosis
- Cigarette use

Pericarditis or myocarditis
- Infection
- Autoimmune disease (e.g., systemic lupus erythematosus)
- Acute rheumatic fever
- Recent myocardial infarction or cardiac surgery
- Malignancy
- Radiation therapy to mediastinum
- Uremia
- Drugs
- Prior pericarditis

Pneumothorax
- Prior pneumothorax
- Valsalva maneuver
- Chronic lung disease
- Cigarette use

A history of prior pain and diagnosis of that episode may facilitate the diagnostic process, but the emergency clinician should not allow the prior diagnosis to form an anchoring bias and be misled. A prior history of cardiac testing, such as stress testing, echocardiography, or angiography, may be useful in determining if the current episode is suggestive of cardiac disease. Similarly, patients with previous spontaneous pneumothorax or PE are at increased risk of recurrence.

The presence of risk factors for a particular disease is primarily of value as an epidemiological marker for large population studies (Box 22.1). In the ED, presence of risk factors in an individual patient without established disease has minimal or no effect on the clinical likelihood (pretest probability) of a specific disease process.

Physical Examination

Specific findings may be found with a variety of causes (Table 22.3).

Ultrasound

Point-of-care ultrasonography (POCUS) is an emerging, important tool in the evaluation of chest pain.[6,7] It is a quick, economical, noninvasive way to evaluate the patient with chest pain in whom the diagnosis is not readily apparent.[8] POCUS has improved sensitivity over chest

TABLE 22.3 Pivotal Findings in Physical Examination

Sign	Finding	Diagnoses
Appearance	Acute respiratory distress	PE, tension pneumothorax, acute MI, pneumothorax
	Diaphoresis	Acute MI, aortic dissection, coronary ischemia, PE, esophageal rupture, unstable angina, cholecystitis, perforated peptic ulcer
Vital signs	Hypotension	Tension pneumothorax, PE, acute MI, aortic dissection (late), coronary ischemia, esophageal rupture, pericarditis, myocarditis
	Tachycardia	Acute MI, PE, aortic dissection, coronary ischemia, tension pneumothorax, esophageal rupture, coronary spasm, pericarditis, myocarditis, mediastinitis, cholecystitis, esophageal tear (Mallory-Weiss)
	Bradycardia	Acute MI, coronary ischemia, unstable angina
	Hypertension	Acute MI, coronary ischemia, aortic dissection (early)
	Fever	PE, esophageal rupture, pericarditis, myocarditis, mediastinitis, cholecystitis
	Hypoxemia	PE, tension pneumothorax, pneumothorax
Cardiovascular examination	Significant difference in upper extremity blood pressures	Aortic dissection
	Narrow pulse pressure	Pericarditis (with effusion)
	New murmur	Acute MI, aortic dissection, coronary ischemia
	S3–S4 gallop	Acute MI, coronary ischemia
	Pericardial rub	Pericarditis
	Audible systolic "crunch" on cardiac auscultation (Hamman's sign)	Esophageal rupture, mediastinitis
	JVD	Acute MI, coronary ischemia, tension pneumothorax, PE, pericarditis
Pulmonary examination	Unilateral diminished or absent breath sounds	Tension pneumothorax, pneumothorax
	Pleural rub	PE
	Subcutaneous emphysema	Tension pneumothorax, esophageal rupture, pneumothorax, mediastinitis
	Rales	Acute MI, coronary ischemia, unstable angina
Abdominal examination	Epigastric tenderness	Esophageal rupture, esophageal tear, cholecystitis, pancreatitis
	Left upper quadrant tenderness	Pancreatitis
	Right upper quadrant tenderness	Cholecystitis
Extremity examination	Unilateral leg swelling, warmth, pain, tenderness, or erythema	PE
Neurologic examination	Focal findings	Aortic dissection
	Stroke	Acute MI
	Coronary ischemia	Aortic dissection, coronary spasm

JVD, Jugular venous distention; *MI,* myocardial infarction; *PE,* pulmonary embolism.

radiography in many important diagnoses with improved sensitivity over all of these except pneumonia. POCUS is useful in the evaluation of the following conditions: pericardial effusion/tamponade, pneumothorax, pleural effusion, pulmonary edema, acute coronary syndrome, and PE.[9] Should an intimal flap be identified, it is useful in the diagnosis of thoracic dissection.[10,11]

Ancillary Studies

The two most commonly performed studies in patients with chest pain are chest radiography and 12-lead electrocardiography (Table 22.4). Electrocardiography should be performed as quickly as feasible and ideally within 10 minutes of arrival in all patients with chest pain or potential angina equivalent in whom myocardial ischemia is a possibility.[2,12] This generally includes all patients who report pain from the umbilicus to the mandible, unless a noncardiac cause is readily apparent. Rapid acquisition of the ECG facilitates the diagnosis of acute MI and expedites the recommended door to treatment times for PCI or fibrinolytic therapy in acute MI. Patients with a new injury pattern on the ECG (Table 22.5) or new ischemic electrocardiographic changes should have appropriate therapy instituted at this point (Fig. 22.2; see also Chapter 64). An ECG showing right ventricular strain pattern, in the appropriate setting, should raise the clinical suspicion for PE.[13,14] Diffuse ST segment elevation helps confirm the diagnosis of pericarditis.[15]

Chest radiography is performed for patients with a possibly serious cause of chest pain. Pneumothorax, pneumonia, empyema, and pleural effusion are definitively diagnosed at this point. A wide mediastinum or ill-defined aortic knob increases the clinical suspicion for acute aortic dissection. Pleural effusion, subcutaneous air, or mediastinal air-fluid level may be seen in esophageal rupture.[16] An increased cardiac silhouette may indicate pericarditis or cardiomyopathy. Pneumomediastinum is seen with esophageal rupture and mediastinitis.[16]

A serum D-dimer assay may help discriminate patients with PE from those with a possible gastrointestinal cause. A low serum D-dimer level in a patient without a high pretest probability of PE effectively excludes the diagnosis.[13,17,18] Patients with a low pretest probability who meet certain defined criteria do not require further testing (see Chapter 74).

Patients at high pretest probability for PE should undergo diagnostic imaging. High pretest probability warrants initiation of anticoagulation

TABLE 22.4 Ancillary Testing of Patients With Chest Pain

Test	Finding	Diagnosis
ECG	New injury	Acute MI, aortic dissection
	New ischemia	Coronary ischemia, coronary spasm
	RV strain	PE
	Diffuse ST segment elevation/Electrical Alternans	Pericarditis
CXR	Pneumothorax with mediastinal shift	Tension pneumothorax
	Wide mediastinum	Aortic dissection
	Pneumothorax	Esophageal rupture, pneumothorax
	Effusion	Esophageal rupture
	Increased cardiac silhouette	Pericarditis
	Pneumomediastinum	Esophageal rupture, mediastinitis
ABG	Hypoxemia, A-a gradient	PE
CT with contrast	Intimal tear in aorta	Aortic dissection
	Clot in pulmonary artery	Pulmonary embolism
	Esophageal wall edema, pneumomediastinum, periesophageal fluid, pleural effusion	Esophageal rupture
Bedside ultrasound	Pericardial fluid	Pericarditis/tamponade
	Loss of lung sliding	Pneumothorax
scan	High probability or any positive in patient with high clinical suspicion	PE

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *CT,* computed tomography; *CXR,* chest x-ray examination; *ECG,* electrocardiography; *MI,* myocardial infarction; *PE,* pulmonary embolism; *RV,* right ventricular; , ventilation-perfusion.

TABLE 22.5 Electrocardiographic Findings in Ischemic Chest Pain

	Findings
Classic myocardial infarction	ST segment elevation (>1 mm) in contiguous leads; new LBBB
	Q waves > 0.04-s duration
Subendocardial infarction	T wave inversion or ST segment depression in concordant leads
Unstable angina	Most often normal or nonspecific changes; may see T wave inversion
Pericarditis	Diffuse ST segment elevation; PR segment depression

LBBB, left bundle branch block.

(e.g., with heparin or low-molecular-weight heparin, DOAC [rivaroxaban or apixaban]) therapy in the ED before the imaging study in the absence of a contraindication.[13]

Patients with suspected thoracic aortic dissection may be evaluated by computed tomography (CT) angiography, transesophageal echocardiography, or magnetic resonance imaging. Selection of the imaging modality depends on the patient's clinical status and availability of the test modality.[5]

A high-resolution (>64 slice) CT scanner can be used to rule out all the life-threatening causes of chest pain. Although ACS, PE, and thoracic dissection (the so-called triple rule-out) are the causes most commonly discussed, pneumothorax, mediastinitis, and pericardial effusions are also diagnosed with CT.

Laboratory testing is useful in the evaluation of ACS. An elevated troponin level in the correct clinical setting is synonymous with acute MI and is embedded in the universal definition of MI.[19] Troponins (I and T), when elevated, identify patients with ACS who have the highest risk for an adverse outcome. Sensitivity for acute MI at 4 hours is approximately 50%, rising to nearly 100% by 12 hours. Creatine kinase (CK) and CK-MB are used only if determination of the troponin level is unavailable. [19]

DIAGNOSTIC ALGORITHM

After the patient is stabilized and assessment is completed, the findings are matched to the classical and atypical patterns of the seven potentially critical diseases causing chest pain. This matching process is continuous while the patient is evaluated and the response to therapy is monitored. Any inconsistency in findings with the primary working diagnoses necessitates a rapid review of the pivotal findings and the potential diagnoses (Table 22.6).

EMPIRICAL MANAGEMENT

The management of ACS is discussed in Chapter 64. Fig. 22.3 outlines the approach to treatment of critical noncardiac diagnoses. Patients with critical diagnoses generally are admitted to the intensive care unit. Patients with emergent diagnoses typically are admitted to the hospital, most often on telemetry units. Patients with nonemergent diagnoses are usually treated as outpatients. Hospitalization is required in certain cases, particularly when patients have other comorbid conditions.

Frequently, no definitive diagnosis is established. Any patient with almost any type of chest pain may be having coronary ischemia, PE, or aortic dissection. When a clear pattern does not emerge to allow the emergency clinician to make an alternative diagnosis confidently, or if the pattern of symptoms clearly is not compatible with a serious disorder, such as coronary ischemia, continued evaluation, hospitalization, or observation admission may be the best course.

The references for this chapter can be found online at ExpertConsult.com.

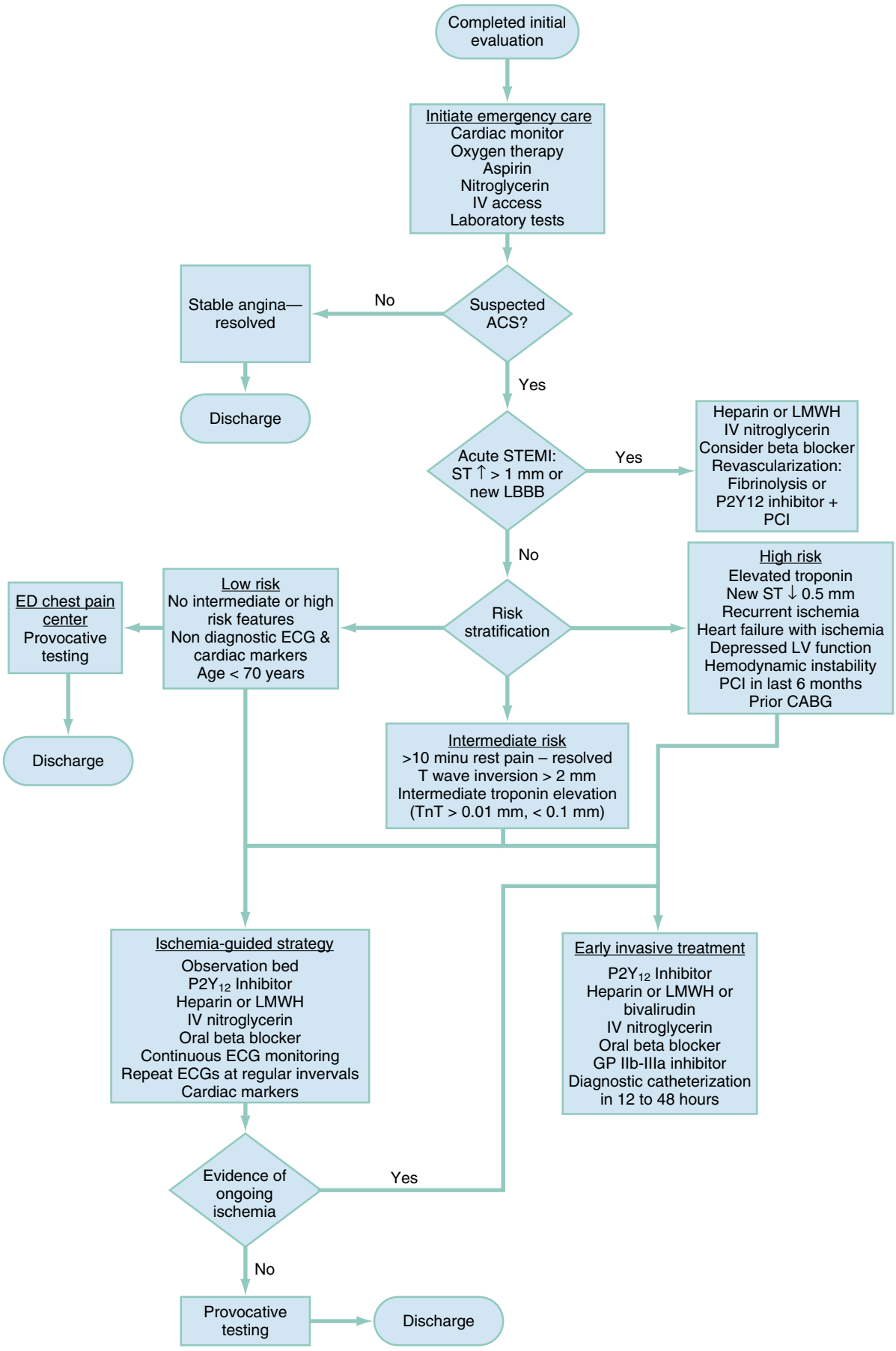

Fig. 22.2 Clinical guidelines for emergency department management of chest pain of myocardial ischemic origin. *ACS,* Acute coronary syndrome; *CABG,* coronary artery bypass graft; *ECG,* electrocardiogram; *ED,* emergency department; *GP,* glycoprotein; *IV,* intravenous; *LBBB,* left bundle branch block; *LMWH,* low-molecular-weight heparin; *LV,* left ventricular; *PCI,* percutaneous coronary intervention; *STEMI,* ST segment elevation myocardial infarction. (Adapted from Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: e344.)

TABLE 22.6 Causes and Differentiation of Potentially Catastrophic Illness Manifesting With Central Chest Pain or Discomfort

	Pain History	Associated Symptoms	Supporting History	Prevalence in Emergency Department	Physical Examination	Useful Tests	Atypical or Additional Aspects
Myocardial infarction	Discomfort is usually moderately severe to severe and rapid in onset. May be more "pressure" than pain. Usually retrosternal, may radiate to neck, jaw, both arms, upper back, epigastrium, and sides of chest (left more than right). Lasts more than 15–30 min and is unrelieved by NTG.	Diaphoresis, nausea, vomiting, dyspnea.	May be precipitated by emotional stress or exertion. Often comes on at rest. May come on in early awakening period. Prodromal pain pattern often elicited. Previous history of MI or angina. Age >40 years, positive risk factors, and male sex increase possibility.	Common.	Patients are anxious and uncomfortable. Blood pressure usually is elevated, but normotension and hypotension are seen. The heart rate is usually mildly increased, but bradycardia can be seen. Patients may be diaphoretic and show peripheral poor perfusion. There are no diagnostic examination findings for MI, although S3 and S4 heart sounds and new murmur are supportive.	ECG changes (new Q waves or ST segment–T wave changes) occur in 80% of patients. CK-MB and troponins are helpful if elevated, but may be normal.	Pain may be reported as "indigestion" or "unable to describe." Other atypical presentations include altered mental status, stroke, angina pattern without extended pain, severe fatigue, syncope. Elderly may have weakness, congestive heart failure, or chest tightness. 25% of nonfatal MIs are unrecognized by patient. The pain may have resolved by the time of evaluation.
Unstable angina	Changes in pattern of preexisting angina with more severe, prolonged, or frequent pain (crescendo angina). Pain usually lasts >10 min. Angina at rest lasting 15–20 min or new-onset angina (duration <2 months) with minimal exertion. Pattern of pain change important in gauging risk for AMI. Unpredictable responses to NTG and rest.	Often minimal. May have mild diaphoresis, nausea, dyspnea with pain. Increasing pattern of dyspnea on exertion.	Not clearly related to precipitating factors. May be a decrease in amount of physical activity that initiates pain. Previous history of MI or angina. Older than 40 years, presence of risk factors, and male sex increase probability.	Common.	Nonspecific findings of a transient nature; may have similar cardiac findings as in MI, especially intermittent diaphoresis.	Often no ECG or enzyme changes. Variant angina (Prinzmetal) has episodic pain, at rest, often severe, with prominent ST segment elevation.	May be pain-free at presentation. Full history is essential. Fewer than 15% of patients hospitalized for unstable angina go on to acute MI. May respond to NTG. May manifest similarly to non–Q wave infarction.
Aortic dissection	90% of patients have rapid-onset severe chest pain that is maximal at beginning. Radiates anteriorly in chest to the back interscapular area or into abdomen. Pain often has a "tearing" sensation and may migrate.	Neurologic complications of stroke, peripheral neuropathy, paresis or paraplegia, abdominal and extremity ischemia possible.	Median age, 59 years. History of hypertension in 70%–90% of patients. 3:1 ratio, males to females. Marfan syndrome and congenital bicuspid aortic valves have increased incidence.	Rare.	Often poorly perfused peripherally but with elevated BP. In 50%–60% of cases, there is asymmetric decrease or absence of peripheral pulses; 50% of proximal dissections cause aortic insufficiency. Other vascular occlusions—coronary (1%–2%), mesentery, renal, spinal cord. New-onset pericardial friction rub or aortic insufficiency murmur supportive of diagnosis.	ECG usually shows left ventricular hypertrophy, nonspecific changes. Chest film shows abnormal aortic silhouette (90%). Aortic angiography has diagnostic accuracy of 95%–99%. Transesophageal echocardiogram, CT, MRI most useful in screening.	Rare for patient to be pain-free. May have neurologic complications. Physical examination findings may be minimal. Dissection into coronary arteries can mimic MI. Ascending aortic aneurysms are more often approached surgically. Descending are generally managed medically.

Continued

TABLE 22.6 Causes and Differentiation of Potentially Catastrophic Illness Manifesting With Central Chest Pain or Discomfort—cont'd

	Pain History	Associated Symptoms	Supporting History	Prevalence in Emergency Department	Physical Examination	Useful Tests	Atypical or Additional Aspects
Pulmonary embolism	Pain is more often lateral pleuritic. Central pain is more consistent with massive embolus. Abrupt in onset and maximal at beginning. May be episodic or intermittent.	Dyspnea and apprehension play a prominent role, often more than pain. Cough accompanies about 50% of cases. Hemoptysis occurs in < 20%. Angina-like pain may occur in 5%.	Often some period of immobilization has occurred (e.g., postoperative). Pregnancy, oral contraceptives, heart disease, and cancer are all risk factors. Previous DVT or PE is the greatest risk factor.	Uncommon in ambulatory patients but common in departments with high volumes of older or medically complex patients.	Patients are anxious and often have respiratory rate >16 breaths/min. Tachycardia, inspiratory rales, and an increased pulmonic second sound are common. Fever, phlebitis, and diaphoresis are seen in 30%–40% of patients. Wheezes and peripheral cyanosis are less common.	Arterial blood gases show Po2 <80 mm Hg in 90%. Widened A-a gradient is helpful. Chest film is usually normal, although 40% show some volume loss, oligemia, or signs of consolidation caused by pulmonary infarction. Lung perfusion scan rules out, if truly negative.	Patients may have dyspnea, with or without bronchospasm. Acute mortality rate is 10%. Emboli usually from lower extremities above knee, prostate or pelvis venous plexus, right side of heart. May be subtle cause of COPD exacerbation.
Pneumothorax	Pain is usually acute and maximal at onset. Most often lateral pleuritic, but central pain can occur in large pneumothorax.	Dyspnea has a prominent role. Hypotension and altered mental states occur in tension pneumothorax.	Chest trauma, previous episode, or asthenic body type.	Infrequent.	Decreased breath sounds, increased resonance on percussion. Elevated pressure in neck veins occurs in tension pneumothorax.	Chest film definitive. Inspiratory and expiratory films may enhance contrast between air and lung parenchyma. Tension pneumothorax should be diagnosed on physical examination.	May be subtle in COPD, asthma, cystic fibrosis. Can be complicated by pneumomediastinum.
Esophageal rupture	Pain usually is preceded by vomiting and is abrupt in onset. Pain is persistent and unrelieved, localized along the esophagus, and increased by swallowing and neck flexion.	Diaphoresis, dyspnea (late), shock.	Older individual with known gastrointestinal problems. History of violent emesis, foreign body, caustic ingestion, blunt trauma, alcoholism, esophageal disease.	Rare.	Signs of lung consolidation, subcutaneous emphysema may be present.	Chest film usually has mediastinal air, a left-sided pleural effusion, pneumothorax, or a widened mediastinum. pH of pleural effusion <6.0. Diagnosis supported by water-soluble contrast esophagram or esophagoscopy.	Patient may be in shock state. This entity often considered late in differential diagnostic process.
Pericarditis	Dull, aching recurrent pain unrelated to exercises or meals, or it may be a sharp, stabbing, pleuritic-type pain that does not change with chest wall motion. May be severe. Not relieved by NTG.	Dyspnea, diaphoresis.	Pain is often worse when supine but improves sitting up. Often preceded by viral illness or underlying disease (SLE or uremia).	Rare. Tamponade even more rare complication.	Friction rub may be heard, often fleeting, position-dependent (50% of patients).	ECG pattern typical for ST segment elevation across the precordial leads. Erythrocyte sedimentation rate may be elevated.	More common in 20- to 50-year-olds. May have associated tachycardias, ventricular dysrhythmias. Idiopathic most common (80%). Treated with aspirin, NSAIDs.

A-a, Alveolar-arterial; *AMI,* acute myocardial infarction; *BP,* blood pressure; *CK-MB,* an isoform of creatine kinase; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *MI,* myocardial infarction; *MRI,* magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug; *NTG,* nitroglycerin; *PE,* pulmonary embolus; Po2, partial pressure of oxygen; *SLE,* systemic lupus erythematosus.

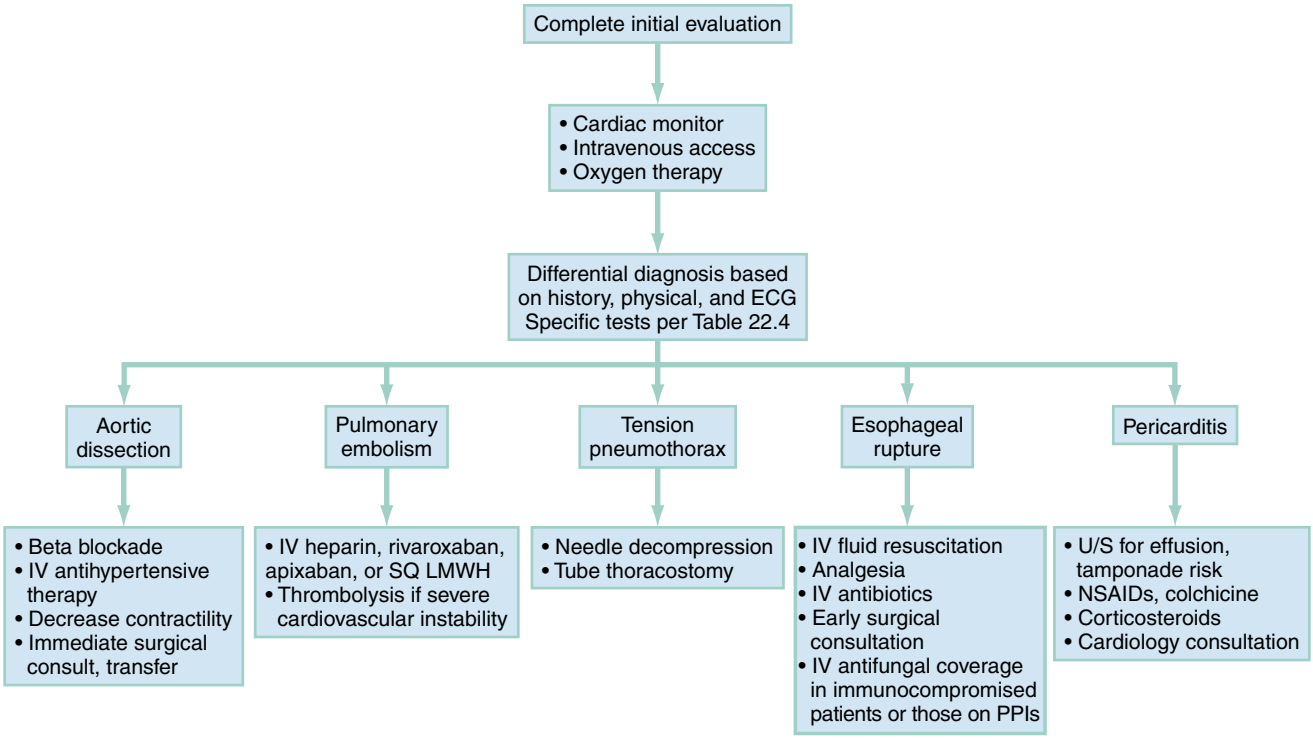

Fig. 22.3 Clinical guidelines for emergency department management of chest pain from potentially catastrophic nonmyocardial origins. *ECG,* Electrocardiogram; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *SQ,* subcutaneous; *U/S*, ultrasound.

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CHAPTER 22: QUESTIONS AND ANSWERS

1. A 25-year-old man presents with the sudden onset of unilateral chest pain, followed almost immediately by respiratory distress. He is noted to have a blood pressure of 75/45 mm Hg, pulse of 130 beats/min, and decreased breath sounds on the right side of his chest. What is the most appropriate initial step in the management of this patient?

a. Administer intravenous (IV) antibiotics.
b. Infuse a 2-L bolus of normal saline.
c. Obtain a chest radiograph.
d. Perform a tube thoracostomy.

Answer: d. Tension pneumothorax is a critical diagnosis that must be made and remedied, if present, in the first few moments of the rapid stabilization and assessment phase of any patient encounter. If a patient presents with chest pain, respiratory distress, shock, and unilateral reduction or absence of breath sounds, immediate intervention with needle or tube thoracostomy is required.

2. A 65-year-old man with a past medical history of prostate cancer presents with chest pain. His blood pressure is 60/40 mm Hg, and his pulse is 145 beats/min. The ECG shows diffuse ST segment elevation, and cardiomegaly is seen on his chest radiograph. What is the most appropriate first step in the management of this patient?

a. Administration of dobutamine
b. Thrombolysis
c. Cardiac catheterization
d. Cardiac ultrasonography

Answer: d. Prompt bedside cardiac ultrasonography would be the most appropriate next step in the management of this patient, who presents with symptoms and signs of pericardial effusion with tamponade. If confirmed by ultrasonography, immediate pericardiocentesis would logically follow in an effort to reverse the signs of shock in this patient. Other signs that could accompany the presentation are low voltage on the ECG and elevated jugular venous pressure on examination.

3. A "tearing" sensation is classically described for which of the following causes of chest pain?

a. Aortic dissection
b. Esophageal rupture
c. Mallory-Weiss tear
d. Pneumothorax

Answer: a. "Tearing" pain that may migrate from the front to back or back to front is classically described in aortic dissection. Descriptions such as "squeezing," "crushing," or "pressure" lead to the suspicion of a cardiac ischemic syndrome, although cardiac ischemia can be characterized by nonspecific discomfort, such as "bloating" or "indigestion." "Sharp" or "stabbing" pain is seen more in pulmonary and musculoskeletal diagnoses. Patients complaining of a burning- or indigestion-type of pain may initially be suspected of having a gastrointestinal cause; however, because of the visceral nature of chest pain, all causes of pain may present with any of the preceding descriptions.

4. Uremia is a risk factor associated with which of the following causes of chest pain?

a. Acute coronary syndrome
b. Aortic dissection
c. Pericarditis
d. Pneumothorax
e. Pulmonary embolism

Answer: c. Uremia is a risk factor for the development of pericarditis. Other risk factors associated with the development of pericarditis include infection, autoimmune disease, acute rheumatic fever, recent myocardial infarction or cardiac surgery, malignancy, radiation therapy to the mediastinum, and prior pericarditis.

5. A narrow pulse pressure is more closely associated with which of the following diagnoses?

a. Acute myocardial infarction
b. Aortic dissection
c. Pericarditis with effusion
d. Pulmonary embolism

Answer: c. A narrow pulse pressure is a pivotal finding in the diagnosis of pericarditis with associated pericardial effusion. Other characteristic, but less specific, potential findings in the patient with pericarditis include hypotension, tachycardia, fever, and jugular venous distention (JVD). The more specific finding of pericardial rub is also heard in some patients with pericarditis.

6. The finding of Hamman's sign is most consistent with which of the following?

a. Cholecystitis
b. Mediastinitis

c. Pericarditis
d. Pulmonary embolus

Answer: b. Hamman's sign is an audible systolic "crunch" heard on cardiac auscultation that is produced by the heart moving against air in the mediastinum. This can be heard in conditions such as esophageal rupture, mediastinitis, and pneumomediastinum.

7. Right ventricular strain on the ECG of a patient complaining of chest pain would be most consistent with which of the following diagnoses?
a. Acute myocardial infarction
b. Coronary ischemia
c. Coronary spasm
d. Pulmonary embolus

Answer: d. In the setting of chest pain, right ventricular strain as evidenced on the ECG is highly suspicious for pulmonary embolus.

8. The ECG finding of PR segment depression would be more commonly found in which of the following causes of chest pain?
a. Pericarditis
b. Pulmonary embolus
c. ST segment elevation myocardial infarction (STEMI)
d. Subendocardial infarction
e. Unstable angina

Answer: a. The electrocardiographic findings most commonly associated with pericarditis are diffuse ST segment elevation and PR segment depression. The ECG in patients with unstable angina is most often normal or nonspecific. T wave inversion may be seen in these patients. The characteristic ECG findings with subendocardial infarction are T wave inversion and/or ST segment depression in concordant leads. Classic STEMI is manifested electrocardiographically by ST segment elevation (>1 mm) in contiguous leads, a new left bundle branch block (LBBB), or Q waves 0.04 second or more in duration. Many possible electrocardiographic findings are associated with pulmonary embolus, usually manifestations of right ventricular strain.

23

Abdominal Pain

Joseph P. Martinez

KEY CONCEPTS

- While the etiology of abdominal pain is frequently benign, requiring little work-up or intervention, abdominal pain can also be the presenting symptom of catastrophic illness, requiring life-saving interventions to be implemented within minutes to hours (see Table 23.1).
- Patients who are pregnant, of advanced age, or immunocompromised are at higher risk for acute pathology and require expeditious evaluation, which generally includes imaging studies.
- Patients with prior surgery, especially bariatric surgery, have unique anatomic features that put them at risk for pathology not seen in patients that have never had abdominal surgery.
- Patients with hemodynamic instability require resuscitation in conjunction with diagnostic evaluation, and often surgical (or gynecologic) consultation. Bedside ultrasonography can be helpful in these patients.
- Pain medication while evaluating stable patients is appropriate and generally should not be withheld. We recommend the administration of IV morphine at a dose of 0.05 to 0.10 mg/kg (usually 2 to 5 mg in adults) every 15 to 20 minutes until pain is controlled (pain score <4).
- Intra-abdominal infections are often polymicrobial and require broad spectrum antibiotic coverage with regimens such as: piperacillin/tazobactam 3.375 g IV, ciprofloxacin 400 mg IV + metronidazole 500 mg IV, or cefepime 2 g IV + metronidazole 500 mg IV.
- Stable patients with unrevealing evaluations whose symptoms improve may be considered for disposition to home with close follow-up. High-risk patients without a clear diagnosis may require in-hospital observation.

FOUNDATIONS

Epidemiology

Abdominal pain is one of the most common emergency department (ED) presentations. Both the absolute number of patients and the overall percentage of patients presenting to U.S. EDs with abdominal pain is increasing.[1] Laboratory tests and imaging studies are being performed at high rates, but many patients ultimately are discharged home without a specific diagnosis.

The etiology of abdominal pain is frequently benign, requiring little work-up or intervention. However, abdominal pain can also be the presenting symptom of catastrophic illness, requiring life-saving interventions to be implemented within minutes to hours. Certain patient populations have a higher likelihood of acute pathology when they present with abdominal pain (Box 23.1). Patients with advanced age, pregnant women, and immunocompromised patients are high-risk populations. Adhesions from previous surgeries are the leading cause of small bowel obstruction in the U.S. Patients who have had bariatric surgery are also at high risk for internal hernias, anastomotic site breakdown, and bleeding. Elders have a higher prevalence of deadly conditions such as abdominal aortic aneurysm (AAA) or acute mesenteric ischemia (AMI). They often present atypically, even with conditions such as appendicitis, where they account for a disproportionate number of deaths.[2] Older patients with benign causes for their symptoms still often receive higher rates of testing compared to younger cohorts, as clinicians are appropriately cautious of being falsely reassured by stable appearance in this age group. Pregnant women with abdominal pain can have symptoms either related or unrelated to their pregnancy. Ruptured ectopic pregnancy can be rapidly fatal if not diagnosed and treated emergently. With increasing rates of assisted reproductive technology, heterotopic pregnancy (simultaneous intrauterine and extrauterine pregnancy) is being seen more frequently,[3] although still often underrecognized. Patients with immunosuppression have variable and often subtle presentations with laboratory values that may confound the clinical picture, such as derangements in liver function, or false elevations (or depressions) of white blood cell (WBC) counts.

Pathophysiology

The most common etiology of abdominal pain is pathology of the gastrointestinal tract, genitourinary tract, or reproductive organs (Fig. 23.1). However, abdominal pain may also be a manifestation of extra-abdominal causes, such as thoracic or spinal pathology, and may also be a symptom of systemic disease, such as diabetic ketoacidosis or Addisonian crisis. Abdominal pain can be perceived as visceral or somatic and may also be referred to a location distinct from its origin (Fig. 23.2).

Visceral pain results from stimulation of autonomic nerves in the walls of hollow organs or the capsules of solid organs. Visceral pain fibers enter the spinal cord bilaterally. The pain is usually poorly characterized, difficult to localize, and located in the midline of the abdominal region correlated to its embryonic development.

- Foregut structures (stomach, duodenum, liver, gallbladder, and pancreas) are associated with upper abdominal pain.
- Midgut derivatives (small bowel, proximal colon, and appendix) are associated with periumbilical pain.
- Hindgut structures (distal colon and genitourinary tract) are associated with lower abdominal pain.

Somatic pain arises from irritation of the parietal peritoneum. Stimuli are transmitted to the dorsal root ganglia ipsilaterally; therefore pain is often sharper and more well localized. The classic example of visceral followed by somatic pain is appendicitis. The typical periumbilical, dull, aching pain reflects visceral pain which classically then becomes a sharper, more well localized right lower quadrant pain as the inflammation of the appendix irritates the overlying parietal peritoneum.

Abdominal pain can also be referred to distant sites through shared central pathways for afferent neurons from disparate sites. Classic examples of referred pain include epigastric pain associated with an inferior myocardial infarction, shoulder pain associated with free peritoneal blood irritating the diaphragm from ruptured spleen or liver, or lower lobe pneumonia causing upper abdominal pain.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of abdominal pain is divided into abdominopelvic (intraperitoneal, retroperitoneal, pelvic) causes (e.g., appendicitis, cholecystitis, pancreatitis) and non-abdominopelvic processes (e.g., pneumonia, myocardial infarction, ketoacidosis, and toxicologic causes). Table 23.1 lists potentially life-threatening nontraumatic causes of abdominal pain, representing most major causative disorders likely to be associated with hemodynamic compromise and for which early therapeutic intervention is critical. More common emergent conditions that lead to abdominal pain are listed in Table 23.2.

BOX 23.1 Populations at Higher Risk When Presenting With Abdominal Pain

- Age greater than 60 years
- Pregnant women
- Patients with previous abdominal surgeries, particularly bariatric surgery
- Recent instrumentation of the gastrointestinal tract
- Immunocompromised patients, including low-dose steroid therapy or immune modulator use
- Patients with known vascular disease
- Patients with known abdominal/pelvic malignancy

Pivotal Findings

Symptoms

A careful and focused history is central to determining the source of abdominal pain. Language or cultural differences may influence accurate communication and mutual understanding; therefore, use of a medical interpreter is a key component of evaluation when the clinician doesn't speak the patient's language.

Abrupt onset, severe pain, especially if accompanied by nausea, vomiting, or diaphoresis, suggest a serious underlying cause. While dividing the abdomen into four quadrants and thinking anatomically about causes for pain is a useful starting point, it is helpful to remember that pain can be referred and that anatomic variations or changes due to pregnancy, weight loss, or previous surgery may alter both the site

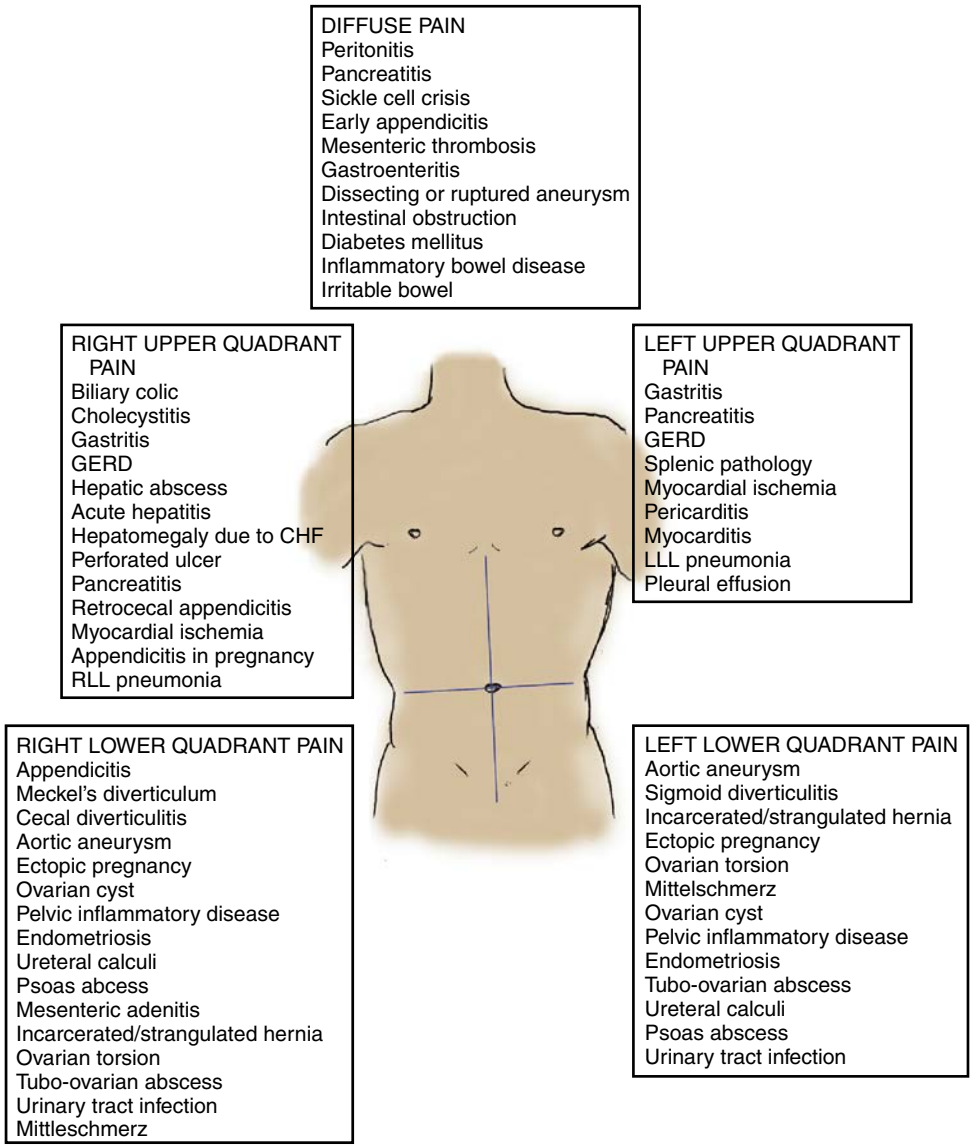

Fig. 23.1 Differential Diagnosis of Acute Abdominal Pain by Location. *CHF,* Congestive heart failure; *GERD,* gastroesophageal reflux disease; *LLL,* left lower lobe; *RLL,* right lower lobe.

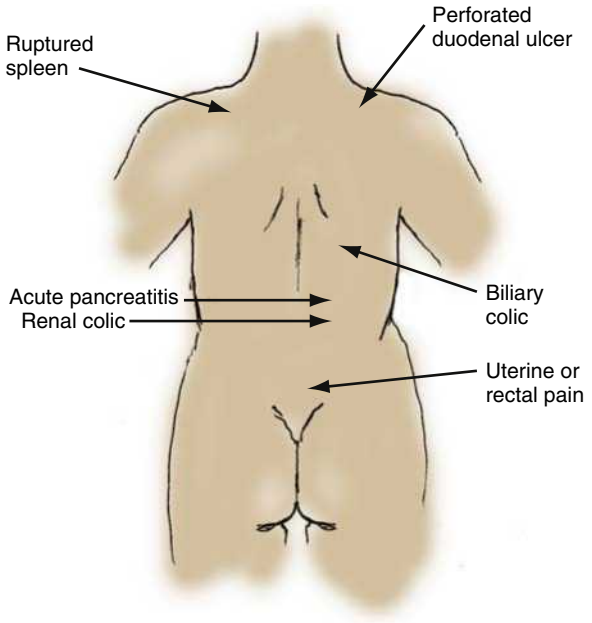

Fig. 23.2 Common Locations of Referred Pain from an Abdominal Cause.

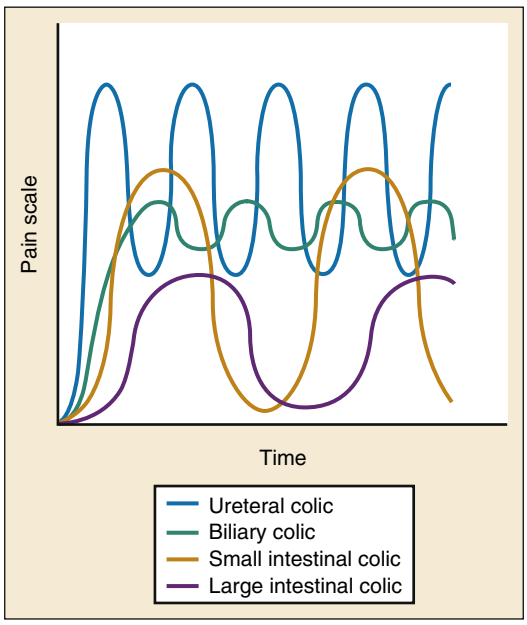

Fig. 23.3 The Characteristics of Colicky Abdominal Pain.

of organs and how their pain is perceived. Provoking factors such as movement or eating should be noted. Diffuse pain, particularly crampy pain that migrates and has periods of minimal or no symptoms, generally is nonsurgical, especially if the pain does not worsen during serial evaluations. Poorly localized pain may represent the early visceral component of a surgical process, however, so monitoring for progression of symptoms is important. Colicky pain is indicative of hollow viscus distention, and duration and timing of colic may give clues to the identity of the culprit organ (Fig. 23.3).

Character of pain is highly subjective, but certain patterns and descriptions emerge:

- The diffuse, severe, colicky pain, occurring at regular ("timeable") intervals associated with severe nausea in small bowel obstruction
- The "pain out of proportion to examination" (i.e., severe pain that is not readily reproduced with palpation) observed in patients with mesenteric ischemia
- The radiation of pain from the epigastrium straight through to the midback, almost invariably accompanied by nausea and vomiting, associated with acute pancreatitis
- The radiation of pain to the left shoulder, or independent pain in the left shoulder, associated with splenic pathology, diaphragmatic irritation, or free intraperitoneal fluid
- The onset of pain associated with syncope seen in ruptured aortic aneurysm or ruptured ectopic pregnancy

The patient's medical and surgical history is crucial, especially as many of the truly emergent conditions are vascular related. Medications can both cause or mask pathology in the abdomen. Social history, especially with respect to tobacco, alcohol, and illicit substance usage is important. Conditions such as perforated peptic ulcers and chronic mesenteric ischemia are much more common in smokers. Alcohol use can lead to gastritis, peptic ulcer disease, pancreatitis, and liver disease. Illicit substances such as cocaine can lead to vascular pathology or peptic ulcer disease, while opioids can lead to severe constipation. Family history of gastrointestinal diseases such as inflammatory bowel disease or colon cancer may also be helpful.

Signs

Physical examination begins with the patient's general appearance and vital signs. Position of the patient in bed and response to movement may point toward peritonitis. Pallor or jaundice may be appreciated. Mental status changes may accompany abdominal pathology, especially in elders. Examination of the patient's vital signs may show derangements consistent with severe hypovolemia or sepsis. Tachypnea may be a marker of metabolic acidosis from intra-abdominal pathology, sepsis, diabetic ketoacidosis, or simply from pain itself. While abnormal vital signs are important, seemingly normal vitals are not uniformly reassuring. Elders may not mount a fever even with a surgical cause of abdominal pain. Similarly, tachycardic response may be blunted, particularly by medications such as beta-adrenergic blockers. Paradoxical bradycardia resulting from reflex, parasympathetically-mediated vasomotor disturbance in response to peritoneal irritation is well described in cases of ruptured ectopic pregnancy.[4]

Head and neck examination may show pallor or scleral icterus. Pulmonary examination may reveal abnormalities such as lower lobe rales pointing to pneumonia or pulmonary edema with concomitant hepatic congestion. Cardiovascular examination may reveal signs of volume depletion or sepsis; show atrial fibrillation, pointing toward AMI; or offer signs of peripheral vascular disease, increasing the likelihood of either AMI or ruptured AAA.

A thorough abdominal examination is an essential component of evaluating abdominal pain. Inspection of the abdomen may reveal ecchymosis, visible peristalsis, or surgical scars. Auscultation has more limited utility though may reveal findings such as the pathognomonic "tinkles and rushes" of an early small bowel obstruction, the hypoactive bowel sounds of an ileus, or a constant bruit which may be the only clue to an aortocaval fistula. Palpation begins with asking the patient to identify the area of maximal tenderness then examining the remainder of the abdomen first, using initially soft then more firm pressure. Gentle shaking of the abdomen may elicit pain in patients with peritonitis. Tenderness in one quadrant often corresponds with the location of the diseased organ, which will direct the evaluation. Some disease processes may manifest with pain that is not exclusively within one specific quadrant, such as the suprapubic pain of a urinary tract infection or the midepigastric pain of a gastric ulcer. Although many patients with appendicitis have right lower quadrant abdominal tenderness, this may

be absent in elders, immunocompromised patients, or women with advanced pregnancy.

A tender, rigid abdomen indicates the presence of diffuse peritonitis. Localized peritoneal irritation is often revealed by the presence of rebound tenderness, where pressure sufficient to indent the peritoneum is applied to the abdomen, then abruptly withdrawn. Discomfort with releasing the peritoneum is visually noted, rather than asking the patient if their symptoms were worse with pressure or with release of pressure. A gentler method of eliciting the presence of peritoneal irritation is having patients perform maneuvers that cause the abdominal parietal and visceral peritoneal surfaces to rub against each other, such as coughing or having them drop their heels to the ground after standing on their toes. Studies of all tests used to elicit rebound tenderness show them to have limited sensitivity and specificity.

Rectal examination is of limited utility unless there are concerns for prostatitis, anorectal pathology, rectal foreign body, or fecal impaction. Pelvic examination in females may help differentiate pelvic source from abdominal source. This may change initial imaging strategy as pelvic organs are generally better imaged with ultrasound, while intraabdominal disorders are better evaluated with abdominal computerized tomography (CT). Findings in acute appendicitis and right adnexal or ovarian pathology can overlap and may require the use of both imaging modalities. Testicular pathology should be assessed for in male patients. Inguinal or femoral hernias can also cause abdominal symptoms. Fournier's gangrene is a time-sensitive entity that may be missed without a thorough physical examination of the perineum.

In view of the evolving nature of abdominal pain, documented serial examinations are useful. This is common practice with respect to suspected appendicitis and serves to improve the diagnostic accuracy in patients with atypical presentations.

Ancillary Testing

Laboratory Tests

Urinalysis and testing for pregnancy are perhaps the most time- and cost-effective laboratory tests available to evaluate acute abdominal pain. Urinalysis results should be interpreted within the context of the patient's clinical picture. Pyuria, with or without bacteriuria, often may confirm the diagnosis of urinary tract infection, but also is present in a variety of other conditions, such as appendicitis or pelvic inflammatory disease. Similarly, hematuria is present in the vast majority of patients with nephrolithiasis but also may be seen in conditions ranging from benign cystitis to ruptured AAA. Pregnancy testing, especially when performed as a point-of-care (POC) test, has the ability to rapidly alter a patient's evaluation and disposition. A POC fingerstick glucose can be helpful in pointing clinicians toward diabetic ketoacidosis as a cause for abdominal pain.

The utility of other laboratory tests is less clear. Although many clinicians will send a broad panel of laboratory studies in patients with undifferentiated abdominal pain, rarely do blood tests confirm or exclude diagnoses with sufficient sensitivity or specificity. The complete blood count and evaluation of the WBC count has been studied extensively with mixed results. The WBC count can be falsely normal, especially in patient populations that are already high risk, such as elders or immunocompromised patients. It may be falsely elevated in any acutely ill patient owing to stress demargination. Serum electrolytes and measurements of renal function are prudent in patients suspected of being significantly volume depleted. Serum lipase is useful when there is suspicion for acute pancreatitis and is preferred over serum amylase for its greater specificity. Lactate levels may be elevated in AMI. While this is the best laboratory test readily available, early in the course of the disease, serum lactate may be normal. Serial levels showing rising lactate or failure to clear despite fluid resuscitation is suspicious for mesenteric ischemia.

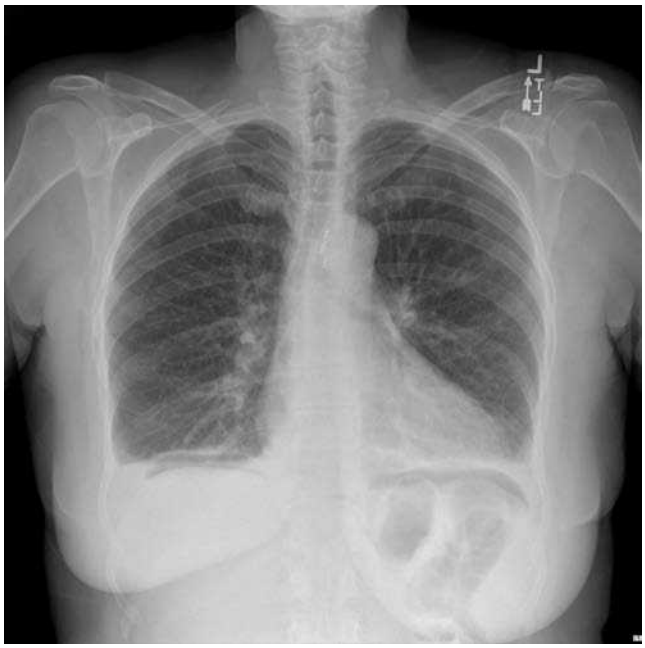

Fig. 23.4 Upright chest radiograph showing free intraperitoneal air under both hemidiaphragms.

Imaging Studies

Plain radiographs of the abdomen have limited utility and are generally only useful if there is clinical suspicion for bowel obstruction, perforation, or foreign body ingestion or rectal insertion. Chest radiographs may reveal a pulmonary cause or may show free air under the diaphragm in cases of perforated viscus (Fig. 23.4).

Ultrasonography can be performed at the bedside and may expeditiously reveal biliary pathology, small bowel obstruction, ovarian/testicular pathology, ectopic pregnancy, or AAA. Patients that are hemodynamically unstable and found to have free intraperitoneal fluid on ultrasound should be considered for emergent surgical (or gynecologic) consultation.

Abdominal CT has become the test of choice for undifferentiated abdominal pain when the clinician determines that advanced imaging is warranted. It has a high degree of accuracy, and has been shown to improve clinician confidence in both diagnosis and disposition. After many years of increased CT utilization, CT imaging has decreased in adults[1] and plateaued in children.[5] The utility of CT imaging in elders is well established and has been shown to change management or disposition in a significant number of patients.[6] Technologic advances have improved both image acquisition and resolution. With new generation CT scanners, the need for oral contrast has been greatly reduced.[7] Reducing the use of oral contrast can help decrease turnaround and throughput times, and improve patient satisfaction, without sacrificing diagnostic accuracy. Computed tomography angiography (CT-A) has also advanced to the point that it is the test of choice in most EDs when AMI is suspected. Institution-specific protocols should be developed accounting for the quality of the scanner and the comfort level of the radiologist. Individual patient presentations that fall outside of the usual protocols merit discussion with the interpreting radiologist to ensure that the optimal imaging protocol is performed.

Magnetic resonance imaging is rarely utilized in the evaluation of acute abdominal pain. Emerging evidence suggests that it has utility in pregnant patients, particularly when the specific clinical question relates to the possibility of acute appendicitis.[8,9]

DIAGNOSTIC ALGORITHM

Critical Diagnoses

The list of diagnoses that lead to abdominal pain is extensive and includes numerous conditions that may be rapidly fatal (see Table 23.1). These diagnoses should be entertained early in the evaluation of any patient with abdominal pain, especially if there is overt hemodynamic instability or a toxic appearance. A diagnostic algorithm for initial assessment is shown in Fig.23.5.

Rapid history, physical examination, and other initial diagnostic evaluations occur concurrently with resuscitative efforts. Intravenous (IV) access and fluid administration, as well as bedside tests such as electrocardiogram, POC laboratory sampling, or bedside ultrasound should be considered. Women of reproductive age with a positive pregnancy test and

TABLE 23.1 Critical Causes of Abdominal Pain

Cause	Epidemiology	Etiology	Presentation	Physical Examination	Useful Tool(S)	Pearls/Pitfalls
Ruptured ectopic pregnancy	Occurs in females of childbearing age. No method of contraception prevents ectopic pregnancy. Approximately 1 in every 100 pregnancies. Heterotopic pregnancy seen increasingly with ART.	Risk factors include nonwhite race, older gestational age, prior history of sexually transmitted diseases (STD) or pelvic inflammatory disease (PID), infertility treatment (ART), intrauterine contraceptive device (IUD) placed within the past year, tubal sterilization, or previous ectopic pregnancy.	Severe, sharp, constant pain often localized to the affected side. More diffuse abdominal pain with intraperitoneal hemorrhage. Signs of shock may be present.	Shock or evidence of peritonitis may be present. Lateralized abdominal tenderness. Localized adnexal tenderness or cervical motion tenderness increases the likelihood of ectopic pregnancy. Vaginal bleeding does not have to be present.	β-hCG testing should be considered in all females of childbearing age or reproductive capacity (10–55 years old); Pelvic ultrasonography is a critical diagnostic tool in evaluation. FAST examination is useful in evaluating for free fluid in patients with shock or peritonitis.	ART patients should not be considered to have an ectopic pregnancy ruled-out when intrauterine pregnancy is found given incidence of multiple gestations with ART.
Ruptured abdominal aortic aneurysm	Incidence increases with advancing age. More frequent in men. Risk factors include HTN, DM, smoking, COPD, and CAD.	Exact cause is undetermined. Contributing factors include atherosclerosis, genetic predisposition, HTN, connective tissue disease, trauma, or infection.	Patient is often asymptomatic until rupture. Acute epigastric and back pain is often associated with, or followed by, syncope or signs of shock. Pain may radiate to back, groin, or testes.	Vital signs may be normal (in 70%) to severely abnormal. Palpation of a pulsatile mass is possible in aneurysms 5 cm or greater. The physical examination may be nonspecific. Bruits or inequality of femoral pulses may be evident.	Abdominal plain films are abnormal in 80% of cases. Ultrasound can define diameter and length but can be limited by obesity or bowel gas. FAST examination can be helpful in evaluating for leak by looking for free fluid. CT-A test of choice in stable patients.	Endovascular repair possible, even in some complex cases. Permissive hypotension allowable.
Acute mesenteric ischemia	Occurs most commonly in elders with CV disease, CHF, cardiac dysrhythmias, DM, sepsis, dialysis, or dehydration. Mortality is 70%. MVT is associated with hypercoagulable states, hematologic inflammation, or trauma. MVT often presents less acute and in younger patients.	20%–30% of lesions are nonocclusive. The causes of ischemia are multifactorial, including transient hypotension in the presence of preexisting atherosclerotic lesion. The arterial occlusive causes (65%) are secondary to emboli (75%) or acute arterial thrombosis (25%).	Pain can be severe and colicky starting in the periumbilical region and then becomes diffuse. Often associated with vomiting and diarrhea. May be preceded by months of postprandial pain or "intestinal angina."	Early examination results can be remarkably benign in the presence of severe ischemia. Bowel sounds are often still present.	Often a pronounced leukocytosis is present. Metabolic acidosis caused by lactic acidemia is often seen with infarction. CT-A is now test of choice, but traditional angiography allows for therapy as well.	Needs multidisciplinary approach in most cases (general surgery, vascular surgery, interventional radiology, critical care). Interventional approaches can usually be pursued first, unless frank peritonitis.

Continued

TABLE 23.1 Critical Causes of Abdominal Pain—cont'd

Cause	Epidemiology	Etiology	Presentation	Physical Examination	Useful Tool(S)	Pearls/Pitfalls
Perforated viscus	Incidence increases with advancing age. History of peptic ulcer disease or diverticular disease common.	More often a duodenal ulcer that erodes through the serosa. Colonic diverticula, large bowel, and gallbladder perforations are rare. Spillage of bowel contents causes peritonitis.	Acute onset of epigastric pain is common. Vomiting in 50%. Fever may develop later. Pain may localize with omental walling off of peritonitis. Shock may be present with bleeding or sepsis.	Fever, usually of low grade, is common; worsens over time. Tachycardia is common. Abdominal examination reveals diffuse guarding and rebound. "Board-like" abdomen in later stages. Bowel sounds are decreased.	WBC count is usually elevated owing to peritonitis. Amylase may be elevated; LFT results are variable. The upright radiographic view reveals free air in 70%–80% of cases with perforated ulcers.	Elderly rarely have rigidity (absent in almost 90% of cases).
Massive gastrointestinal bleeding	More common in adults ages 40–70.	History of peptic ulcer disease, gastritis, or liver disease; prior GI bleeding history	Nausea and vomiting typically occur with upper GI bleeding with hallmark coffee-ground or hematemesis; slow transit can lead to melena; lower GI bleeds associated with poorly localized discomfort and bright red blood per rectum.	Non-focal abdominal tenderness; large bleeds may result in tachycardia or hypotension with significant blood loss. Hemoglobin/hematocrit may be falsely reassuring in acute, massive bleeding.	Stool guaiac if there is a question of bleeding; massive bleeds may require emergent consultation by gastroenterology, interventional radiology, or surgery to intervene.	Stigmata of liver disease should prompt consideration of esophageal varices.
Acute myocardial infarction	Elderly women in particular may present with GI symptoms.	Plaque rupture leads to coronary vessel occlusion.	Nausea, vomiting, or epigastric discomfort may be the sole presenting symptoms, particularly in inferior events or in elderly females.	Nonspecific. Bradycardia often seen with inferior myocardial infarction.	Rapid electrocardiogram in evaluation of abdominal pain if possibility of coronary ischemia is suspected.	Mortality increases with delays in care.

ART, Assisted reproductive technologies; *β-hCG*, beta-human chorionic gonadotropin; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *CT-A*, computed tomography angiography; *CV*, cardiovascular; *DM*, diabetes mellitus; *FAST*, focused assessment by sonography in trauma; *GI*, gastrointestinal; *HTN*, hypertension; *LFT*, liver function test; *MVT*, mesenteric venous thrombosis; *WBC*, white blood cell.

hemodynamic instability, especially if free intraperitoneal fluid is found on ultrasound, should be assumed to have a ruptured ectopic pregnancy. Gynecologic consultation should be obtained, and preparations made for operative intervention. Patients suspected of ruptured AAA, based on physical examination or ultrasound, should similarly have emergent surgical consultation pursued, often contemporaneously with further imaging. ST elevation myocardial infarction necessitates expeditious reperfusion. Patients with frank peritonitis on examination should receive early surgical consultation, even if the etiology is not initially apparent. Patients suspected of AMI should have emergent CT-angiography performed, and appropriate consultations initiated, as mortality decreases dramatically if reperfusion is accomplished before the onset of peritonitis. Patients with overt gastrointestinal bleeding, especially if known or suspected to have cirrhosis, should be considered for blood product administration and emergent gastroenterology consultation if upper source is suspected, with interventional radiology or surgery consultation if hemodynamically significant lower gastrointestinal bleeding is suspected.

Emergent Diagnoses

Common emergent diagnoses of abdominal pain are listed in Table 23.2. Despite the limitations, the approach to the differential diagnosis of abdominal pain generally is based on the location of maximum tenderness. Patients should have ancillary testing performed after initial evaluation, with the goal of identifying serious or life-threatening causes. Serial examinations should be performed. Deterioration should prompt surgical (or gynecologic) consultation.

Despite the significant variety of tests available, nearly half of the patients presenting to the ED with acute abdominal pain will have no conclusive diagnosis. Prior to arriving at the diagnosis of nonspecific abdominal pain, clinicians should pause to consider extra-abdominal or life-threatening causes, especially in elders or immunocompromised patients.

EMPIRIC MANAGEMENT

The main therapeutic goals in managing acute abdominal pain include physiologic stabilization, mitigation of symptoms (e.g., nausea or pain), and expeditious diagnosis to the extent feasible, with consultation if required. An algorithm for management is presented in Fig. 23.6. Analgesia should not be withheld from patients while they are undergoing further evaluation or awaiting consultation. There is no evidence that administration of

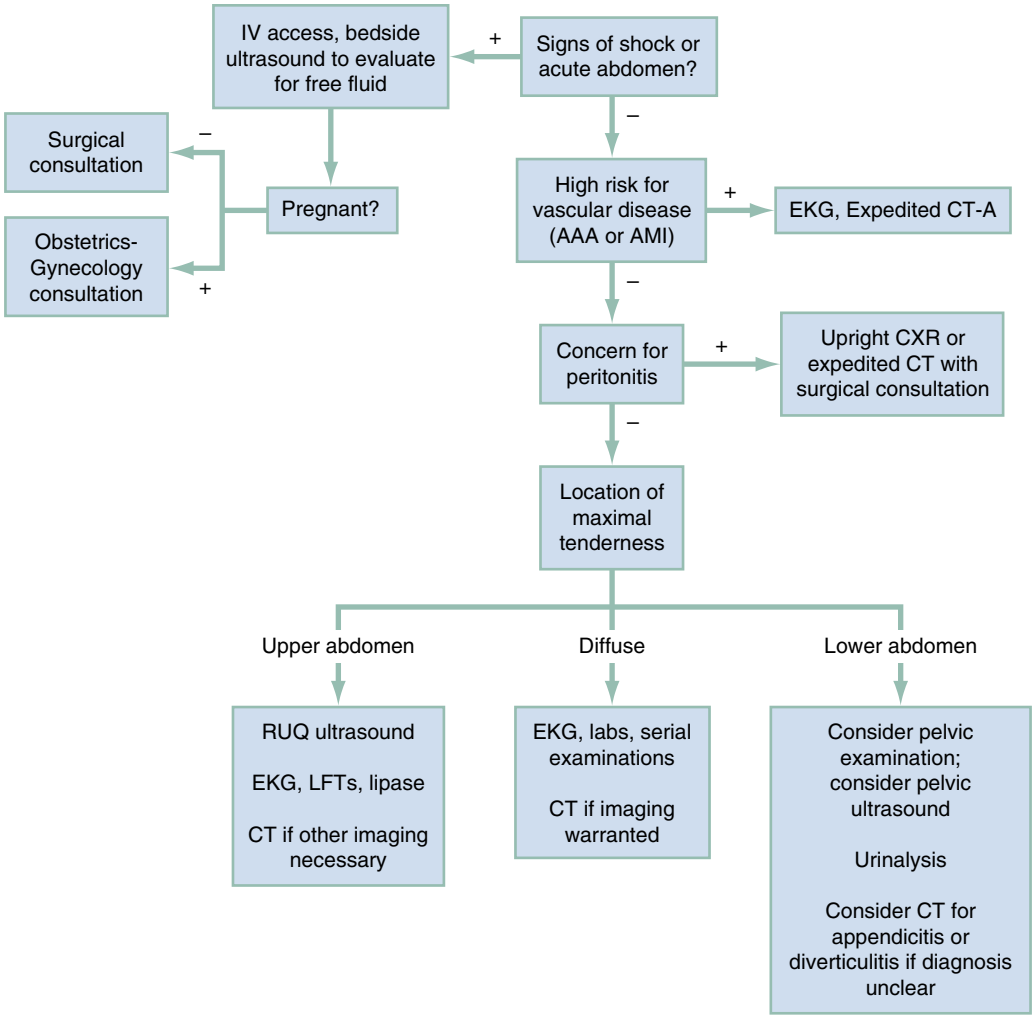

Fig. 23.5 Diagnostic Algorithm for Abdominal Pain. *AAA*, Abdominal aortic aneurysm; *AMI*, acute mesenteric ischemia; *CT*, computed tomography; *CT-A*, Computed tomography angiography; *CXR*, chest x-ray; *EKG*, electrocardiogram; *IV*, intravenous; *LFTs*, liver function tests; *RUQ*, right upper quadrant.

analgesia leads to an increase in diagnostic errors.[10] We recommend the administration of IV morphine at a dose of 0.05 to 0.10 mg/kg (usually 2 to 5 mg in adults) every 15 to 20 minutes until pain is controlled (pain score <4). Morphine is not preferred in patients with renal dysfunction. In the setting of renal insufficiency, fentanyl or hydromorphone are the preferred IV opioid analgesics. Patients with opioid dependence and those taking narcotics for chronic pain may require larger doses. The patient's mental and respiratory status should be monitored during treatment.

Other medications that may be commonly administered include antiemetics such as ondansetron, 4 or 8 mg, either IV or as an orally disintegrating tablet, or liquid antacids. Liquid antacids are most effective when the pain is suspected to arise from the esophageal or gastric mucosa. There are no scientific studies that show increased efficacy of a "GI cocktail" (which typically includes an antacid, an anesthetic agent such as viscous lidocaine, and an anticholinergic agent), when compared to liquid antacid alone.

If intra-abdominal infection is suspected, antibiotic therapy should be initiated promptly. Abdominal infections are often polymicrobial, and coverage for enteric gram-negative, gram-positive, and anaerobic bacteria is indicated. Considerations for antimicrobial selection include:

- Unless local antibiotic resistance dictates otherwise, in low-risk patients who have not recently been hospitalized, single agent therapy includes piperacillin-tazobactam 3.375 g IV or ertapenem 1 g IV. Combination therapy includes metronidazole 500 mg IV along with a cephalosporin, such as cefazolin 2 g IV, ceftriaxone 2 g IV, or cefotaxime 2 g IV, piperacillin-tazobactam 3.375g to 4.5g IV, or a quinolone such as ciprofloxacin 400 mg IV.
- Higher-risk patients (advanced age, significant comorbidities, immunosuppression, or evidence of severe disease) should be treated with meropenem 1g IV, or higher-dose piperacillin-tazobactam 4.5 g IV as single agent, or receive combination therapy with cefepime 2 g IV plus metronidazole 500 mg IV.
- It is unusual to require empiric antifungal therapy in the ED, but it may be considered in critically ill patients with immunosuppression.

For patients who do not have a clear diagnosis following ED evaluation, some may require observation or admission for continued evaluation, especially if they have high-risk features such as the following:

- Immunosuppression or advanced age[11, 12]
- Worsening abdominal examination or continued pain requiring potent analgesia
- Inability to tolerate oral hydration
- Unstable living situation with poor access to follow-up care

TABLE 23.2 Emergent Causes of Abdominal Pain

Causative Disorder or Condition	Epidemiology	Etiology	Presentation	Physical Examination	Useful Test(s)
Gastric, esophageal, or duodenal inflammation	Occurs in all age groups.	Caused by imbalance between digestive enzymes and mucoprotective barriers, infection, or exogenous sources.	Pain is epigastric, radiating or localized, associated with certain foods. Pain may be burning. In some cases, exacerbation in supine position.	Epigastric tenderness without rebound or guarding. Perforation or bleeding leads to more profound clinical findings.	Uncomplicated cases are treated with antacids or histamine H_2 blockers before invasive studies are contemplated. Gastroduodenoscopy is valuable in diagnosis and biopsy. Testing for *Helicobacter pylori* with blood or biopsy specimens. If perforation is suspected, an upright chest radiograph is obtained early to rule out free air. CT may be beneficial.
Acute appendicitis	Peak age in adolescence and young adulthood; less common in children and elders. Higher perforation rate in women, children, and elders, or in pregnancy. Mortality rate is 0.1% but increases to approximately 2% with perforation.[11]	Appendiceal lumen obstruction leads to swelling, ischemia, infection, and perforation.	Epigastric or periumbilical pain migrates (+LR 1.8 child/3.2 adult) to RLQ over 8–12 hours. RLQ pain common (+LR 1.4 in child/7.3–8.5 in adult).[12] Later presentations associated with higher perforation rates. Pain, low-grade fever (+LR 1.2 in child/1.9 in adult), and anorexia (80%) common; vomiting less common (50%–70%).	Mean temperature 38°C (100.5°F). Higher temperature associated with perforation. RLQ tenderness (90%–95%) with rebound (40%–70%) in majority of cases. Rectal tenderness in 30%.	Leukocyte count is nonspecific and may be normal or elevated. If elevated, may or may not show left shift. Urinalysis may show sterile pyuria. CT is sensitive and specific. US may have use in those with non-obese body habitus, women, pregnancy, and children with RLQ pain. MRI has excellent diagnostic accuracy in pregnant women.
Biliary tract disease	Peak age 35–60 years old; unlikely in patients younger than 20. Female-to-male ratio of 3:1. Risk factors include multiparity, obesity, alcohol intake, and use of birth control pills.	Presence of gallstones may cause biliary colic. Impaction of a stone in cystic duct or common duct may lead to cholecystitis or cholangitis, respectively.	Crampy RUQ pain radiates to right subscapular area. Prior history of pain is common. May have nausea or postprandial pain. Longer duration of pain favors diagnosis of cholecystitis or cholangitis.	Temperature is normal in biliary colic, may be elevated in cholecystitis or cholangitis. RUQ tenderness, rebound, or jaundice (less common) may be present.	WBC may be elevated in cholecystitis and cholangitis. US may demonstrate wall thickening, pericholecystic fluid, stones, or duct dilatation. Hepatobiliary scintigraphy (HIDA scan) evaluates gallbladder function.
Ureteral colic	Average age for first episode is 30–40 years, primarily in men. Prior history or family history of kidney stones is common.	Family history, gout, *Proteus* infection. Renal tubular acidosis or cystinuria lead to stone formation.	Acute onset of flank pain radiating to groin. Nausea, vomiting, and pallor are common. Patients are usually restless and unable to find position of comfort.	Vital signs are usually normal. Tenderness on CVA percussion with benign abdominal examination.	Urinalysis usually shows hematuria. Noncontrast CT is sensitive and specific. Ultrasound to evaluate for hydronephrosis may be sufficient if diagnosis previously established.
Diverticulitis	Incidence increases with advancing age, affects males more often than females. Recurrences are common.	Colonic diverticula may become infected, perforate, or cause local colitis. Obstruction, peritonitis, abscesses, fistulae result from infection or swelling.	Change in stool frequency or consistency commonly reported. LLQ pain is common. Associated with fever, nausea, and vomiting; rectal bleeding may be seen.	Fever usually low grade. LLQ pain without rebound is common. Stool may be heme positive.	Results on most tests usually normal. Plain radiographs not indicated. CT is diagnostic, but diagnosis can also be made clinically, without imaging, in selected lower-risk patients.

Continued

TABLE 23.2 Emergent Causes of Abdominal Pain—cont'd

Causative Disorder or Condition	Epidemiology	Etiology	Presentation	Physical Examination	Useful Test(s)
Acute gastroenteritis	Seasonal. Most common misdiagnosis of appendicitis and of acute mesenteric ischemia. May be seen in multiple family members. History of travel or immunocompromise. Most common GI disease in the United States.	Usually viral. Consider invasive bacterial or parasitic cause in prolonged cases, in travelers, or immunocompromised patients.	Pain usually poorly localized, intermittent, crampy, and diffuse. Diarrhea is key element in diagnosis; usually large volume, watery. Nausea and vomiting usually begin before pain.	Abdominal examination usually nonspecific without peritoneal signs. Watery diarrhea or no stool noted on rectal examination. Fever may be present.	Usually symptomatic care with antiemetics and volume repletion. Heme-positive stools may be a clue to invasive pathogens. Also consider more serious causes prior to concluding on diagnosis of acute gastroenteritis.
Constipation and obstipation	More common in females, elders, the very young, and patients on narcotics.	Idiopathic, or bowel hypokinesis secondary to disease states (low motility) or exogenous sources (diet, medications).	Abdominal pain; change in bowel habits.	Variable, nonspecific without peritoneal signs. Rectal examination may reveal hard stool or impaction.	Radiographs may show large amounts of stool. Constipation or obstipation are diagnoses of exclusion.
Intestinal obstruction	Peaks in infancy and in the elderly. More common with history of previous abdominal surgery.	Adhesions, carcinoma, hernias, abscesses, volvulus, or infarction. Obstruction leads to vomiting, extravascular fluid accumulation; strangulation and necrosis of bowel may occur.	Crampy diffuse abdominal pain associated with vomiting.	Vital signs are usually normal unless dehydration or bowel strangulation has occurred. Abdominal distention, hyperactive bowel sounds, and diffuse tenderness. Local peritoneal signs may indicate strangulation.	Elevated WBC count may suggest advanced disease or strangulation. Volume depletion may be severe. Electrolytes may be abnormal if associated with vomiting or prolonged symptoms. Abdominal radiographs, CT, and ultrasound are useful in diagnosis.
Acute pancreatitis	Peak age is adulthood; rare in children. Male preponderance. Alcohol abuse and biliary tract disease are risk factors.	Alcohol, gallstones, hyperlipidemia, hypercalcemia, or endoscopic retrograde pancreatography causing pancreatic damage, saponification, or necrosis. ARDS, sepsis, hemorrhage, or renal failure may be secondary complications.	Acute onset of epigastric pain radiating to the mid-back. Nausea and vomiting are common. Pain disproportionate to physical findings. Adequate volume repletion is important in the initial therapy.	Low-grade fever is common. Patient may be hypotensive or tachypneic. Some epigastric tenderness is usually present. Because the pancreas is a retroperitoneal organ, guarding or rebound not present unless condition is severe. Flank or periumbilical ecchymosis may be seen with hemorrhagic pancreatitis.	Serum lipase is the test of choice. Ultrasound examination may show edema, pseudocyst, or biliary tract disease. CT scan may show abscesses, necrosis, hemorrhage, or pseudocysts. Ultrasound is recommended to assess for gallstones while CT is recommended if severe acute pancreatitis is suspected.

ARDS, Acute respiratory distress syndrome; *CT*, computed tomography; *CVA*, costovertebral angle; *HIDA*, hepatobiliary scintigraphy; *LLQ*, left lower quadrant; *LR*, likelihood ratio; *RLQ*, right lower quadrant; *RUQ*, right upper quadrant; *US*, ultrasound; *WBC*, white blood cell.

Clinically stable patients may be discharged from the ED with appropriate follow-up care, which may include close follow-up for repeated physical examination, or additional diagnostic imaging if indicated. Clear discharge instructions should be provided, including specific symptoms that should prompt return to the ED, precise instructions regarding timing of follow-up, and an acknowledgment that the etiology of the patient's symptoms is unclear, and may declare itself in time. It is helpful to document a repeat abdominal examination around the time of discharge showing stability or improvement, as well as the ability to tolerate oral hydration.

The references for this chapter can be found online at ExpertConsult.com.

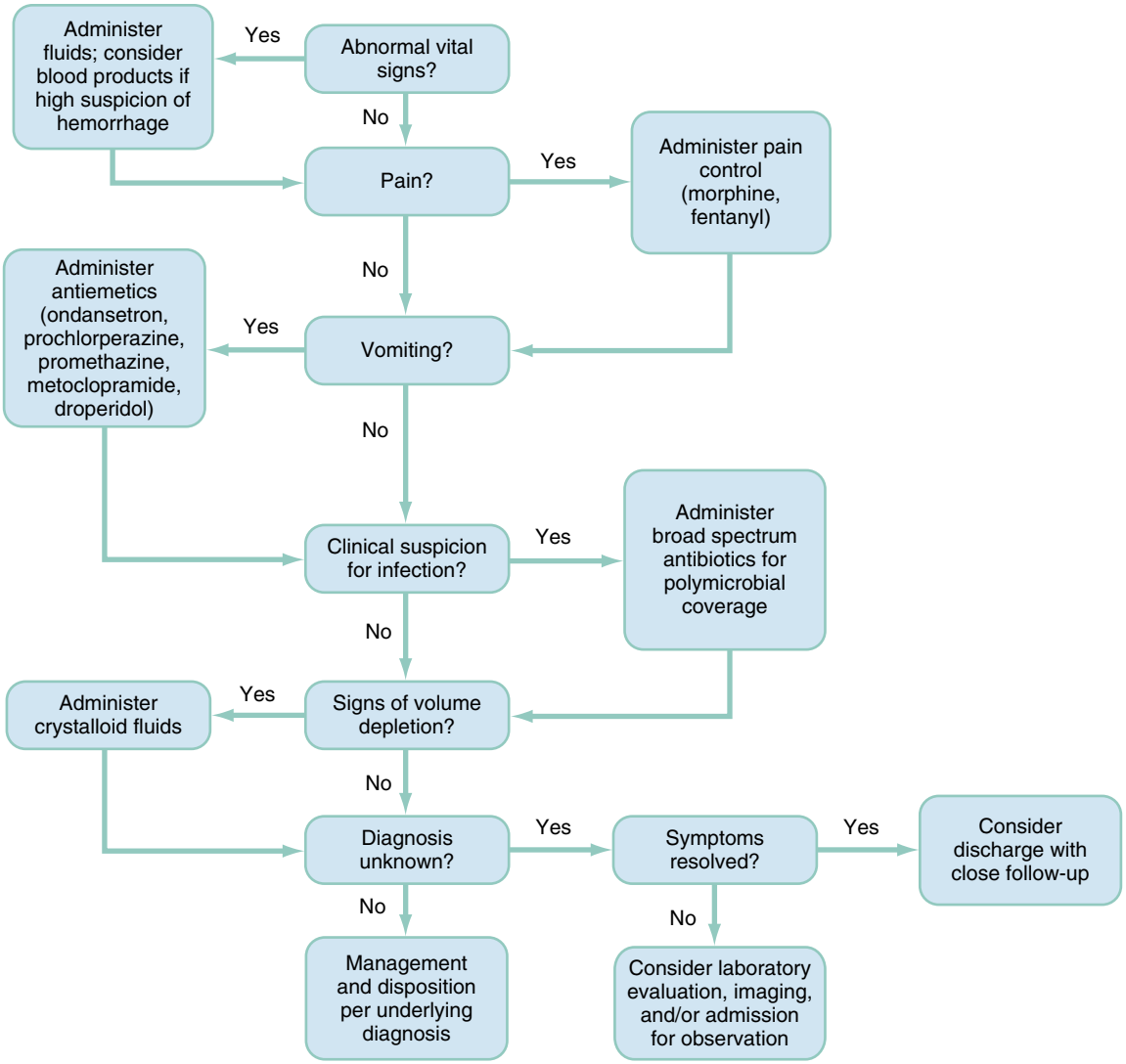

Fig. 23.6 Management Algorithm for Abdominal Pain.

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CHAPTER 23: QUESTIONS AND ANSWERS

1. A 65-year-old man presents with acute abdominal pain. He has a history of hypertension, diabetes, and an abdominal aortic aneurysm. On examination, he is hypotensive and tachycardic with a distended, rigid abdomen. Which of the following is the best method for diagnosis?

a. Computed tomography
b. Exploratory laparotomy
c. Plain radiograph
d. Right upper quadrant ultrasound

Answer: b. Exploratory laparotomy. Patients with known abdominal aortic aneurysm (AAA) and unstable vital signs must be assumed to have ruptured AAA and should be brought to the operating room without delay. If the patient were stable, CT would be indicated. Plain radiograph is not indicated in this patient, nor would right upper quadrant ultrasound be warranted.

2. A 25-year-old woman presents with abdominal pain. She has stable vitals. On pelvic examination, she has tenderness in the right adnexal region. Which of the following is the most appropriate initial imaging study?

a. Computed tomography
b. Magnetic resonance imaging
c. Plain radiograph
d. Pelvic ultrasound

Answer: d. Pelvic ultrasound. Women of child-bearing age with lower abdominal pain and adnexal tenderness on examination are best imaged with pelvic ultrasound. CT may be warranted if the ultrasound is inconclusive or suggestive of, but not diagnostic of, appendicitis. Plain radiographs are not helpful in undifferentiated lower abdominal pain. MRI could be a consideration if the patient were pregnant and there was concern for appendicitis.

3. A 70-year-old man presents with abdominal pain associated with one loose bowel movement and an episode of non-bloody emesis. He has a history of hypertension, diabetes, cigarette smoking, and atrial fibrillation. He rates his pain as "10/10." On examination, he has stable vitals. His abdomen is soft and nontender without signs of peritonitis. Which of the following is the most appropriate imaging study to confirm the suspected diagnosis?

a. Computed tomography angiography
b. Magnetic resonance imaging
c. Plain radiograph
d. Right upper quadrant ultrasound

Answer: a. Computed tomography angiography. The patient presents with "pain out of proportion" to examination, multiple vascular risk factors, and atrial fibrillation, which increases his risk for mesenteric ischemia. Computed tomography angiography would be the best screening test. Magnetic resonance imaging would be too time-consuming, plain radiographs have limited utility, and right upper quadrant ultrasound is not warranted in this patient with diffuse, non-localized symptoms.

4. A 30-year-old man presents with abdominal pain and fever. Which of the following would place him at higher risk for life-threatening pathology?

a. Drinking from a mountain spring
b. Prednisone therapy for systemic juvenile idiopathic arthritis
c. Recent cruise with norovirus outbreak
d. Use of metoprolol for essential hypertension

Answer: b. Prednisone therapy for systemic juvenile idiopathic arthritis. Low-dose steroid therapy places patients at higher risk when they present with abdominal pain. Drinking from a mountain spring increases risk for giardia. Neither this nor exposure to norovirus place the patient at increased risk for life-threatening pathology. Hypertension increases risk for vascular conditions such as abdominal aortic aneurysm, but this would be unlikely in a young patient controlled on metoprolol.

5. What is a characteristic of visceral abdominal pain?

a. Easily described
b. Midline
c. Sharp in nature
d. Well-localized

Answer: b. Midline. Visceral pain is classically midline, poorly localized, and less easily described than somatic pain, which is often referred to as "sharp."

Jaundice

Michael J. Zdradzinski and Todd Andrew Taylor

KEY CONCEPTS

- Jaundice is the clinical manifestation of elevated serum bilirubin, which arises through the metabolism of hemoglobin. Elevated bilirubin occurs when: (1) increased bilirubin is produced due to hemolysis, (2) liver dysfunction prevents conjugation of bilirubin, (3) an obstruction prevents secretion of bilirubin into the intestines.
- Jaundice is usually not evident on physical examination until the total serum bilirubin concentration rises above 2.5 mg/dL. Jaundice is first apparent in the conjunctiva, sublingually, or on the hard palate.
- Unconjugated bilirubin that is not bound to albumin can cross the blood-brain barrier, causing adverse neurologic effects; conjugated bilirubin is not neurotoxic.
- New-onset painless jaundice is the classic presentation for a neoplasm involving the head of the pancreas.
- In cases of unexplained hepatocellular injury, a quantitative acetaminophen level may be helpful.
- If the etiology of ascites is unknown, serum ascites albumin gradient (SAAG) determination will aid in distinguishing the cause as well as the presence of portal hypertension.
- Ultrasonography is the preferred initial imaging modality in evaluating for biliary obstruction, whereas CT is preferred if malignant obstruction is suspected or the full abdomen needs to be evaluated.
- Elevated direct bilirubin with transaminase elevation is indicative of hepatocellular inflammation or injury.
- Diagnosis of spontaneous bacterial peritonitis (SBP) is made by a peritoneal fluid neutrophil count of greater than 250. Treatment typically consists of cefotaxime 2 g IV and albumin 1.5 g/kg.

EPIDEMIOLOGY

Bilirubin is conjugated in the liver and secreted in the biliary system. If bilirubin cannot be processed adequately by the liver or secreted properly in the biliary system, it is deposited in the skin leading to jaundice. Therefore, many patients with jaundice will have a primary hepatic or biliary etiology. Jaundice can be caused by a variety of hepatic disorders including cirrhosis, hepatitis, toxin exposure, or infiltrative liver disease. Obstruction or infection of the biliary system can cause inadequate secretion of bilirubin. Recently, hepatitis A and B immunizations have significantly decreased the prevalence of these forms of hepatitis, and thus have altered the epidemiology of jaundice.

PATHOPHYSIOLOGY

Normal Bilirubin Metabolism

Bilirubin is generated from heme products, primarily red blood cells. A small portion is derived from myoglobin and maturing erythroid cells. Within the reticuloendothelial system, heme is oxidized to biliverdin, which is then converted to bilirubin. Unconjugated (i.e., indirect) bilirubin is passively taken into hepatocytes, where it undergoes glucuronidation and becomes conjugated (i.e., direct) bilirubin. This conjugated fraction is secreted into the biliary system and emptied into the gut. Colonic bacteria metabolize the majority of bilirubin to urobilinogen and stercobilin. Urobilinogen is reabsorbed and excreted in the urine and stercobilin is excreted in the stool, causing stool to turn brown. The remaining conjugated bilirubin is deconjugated and reenters the portal circulation to be taken up again by hepatocytes (enterohepatic circulation).

Abnormalities in Bilirubin Metabolism

Clinical jaundice is typically not evident until the total serum bilirubin concentration rises above 2.5 mg/dL. It is observed in tissues with high albumin concentrations including the skin and eyes. The physiology of bile metabolism may be altered in three principal areas: (1) overproduction of heme products, as occurs in hemolysis; (2) failure of the hepatocyte to take up, conjugate, and secrete bilirubin, as occurs in hepatocellular dysfunction; or (3) obstruction of biliary secretion into the intestine. The differential diagnosis of jaundice is broad, and understanding these components of bilirubin metabolism and excretion aids in narrowing the differential and streamlining the evaluation.

Unconjugated bilirubin that is not bound to albumin can cross the blood-brain barrier, potentially leading to adverse neurologic effects ranging from subtle developmental abnormalities to encephalopathy or death. Conditions that favor the unbound fraction of unconjugated bilirubin, including hemolysis, hypoalbuminemia, acidemia, or drugs that bind competitively to albumin, increase the risk of neurotoxicity. Conjugated bilirubin is not neurotoxic.

Diagnostic Approach

Differential Considerations

The three major diagnostic categories to consider in the patient with jaundice include:

1. Disorders of hemolysis (increased breakdown of heme products).
2. Liver injury, dysfunction, or cholestasis (failure to uptake, conjugate, or secrete bilirubin).
3. Biliary obstructive disorders.

Figs. 24.1 and 24.2 outline an approach to differentiating among these three broad categories.

Pivotal Findings

The pivotal findings related to history, physical examination, and ancillary testing are listed in Fig. 24.1.

Symptoms

Patients may be asymptomatic at presentation or have nonspecific symptoms, such as pruritus, malaise, or nausea. There are a few symptoms that can help narrow the differential diagnosis. Jaundice with

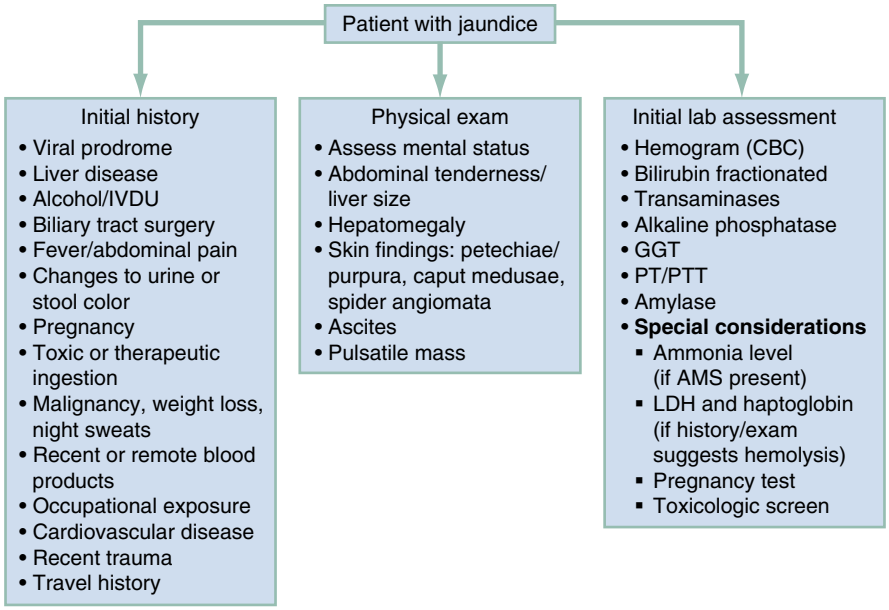


Fig. 24.1 Initial Approach to the Patient With Jaundice. *AMS,* Altered mental status; *CBC,* complete blood count; *GGT,* gamma-glutamyl transferase; *IVDU,* intravenous drug use; *LDH,* lactate dehydrogenase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

abdominal pain suggests biliary obstruction or significant hepatic inflammation. New-onset painless jaundice is the classic presentation for a neoplasm involving the head of the pancreas. These patients may complain of weight loss or increasing abdominal girth related to ascites. Patients with hepatic encephalopathy may present with subtle mental status changes, increasing confusion, or frank altered mental status.

Signs

Pertinent physical examination findings are summarized in Fig. 24.1. Examination of the skin and the abdomen is particularly helpful in narrowing the differential diagnosis.

Skin findings can point to acute or chronic liver disease. Jaundice is first apparent sublingually, in the conjunctiva, or on the hard palate. From there, it spreads caudally; however, the extent of cephalocaudal progression does not correlate with rising serum bilirubin levels. Cutaneous findings of chronic liver disease include angiomas, excoriations from pruritus, or caput medusae.

The abdominal examination should begin with a thorough visual inspection. A distended or protuberant abdomen can indicate the presence of ascites. On palpation, an enlarged, tender liver suggests hepatic inflammation or engorgement caused by biliary obstruction. An enlarged nontender liver is concerning for malignant infiltration. A nonpalpable liver can indicate fibrosis caused by cirrhosis. A palpable gallbladder, a rare finding, suggests chronic cholestasis or malignancy. The presence of splenomegaly suggests hemolysis, malignancy, or portal hypertension.

Neurologic examination of the jaundiced patient may show depressed mental status. In patients with jaundice, mental status changes can be caused by neurotoxic effects of unconjugated bilirubin, or in the setting of other conditions that may be associated with jaundice such as hepatic encephalopathy. In hepatic encephalopathy, mental status changes are not caused by bilirubin itself, but rather from other impacts of liver dysfunction such as elevated serum ammonia levels. Asterixis is a specific finding of hepatic encephalopathy. Table 24.1 addresses the clinical stages of hepatic encephalopathy.

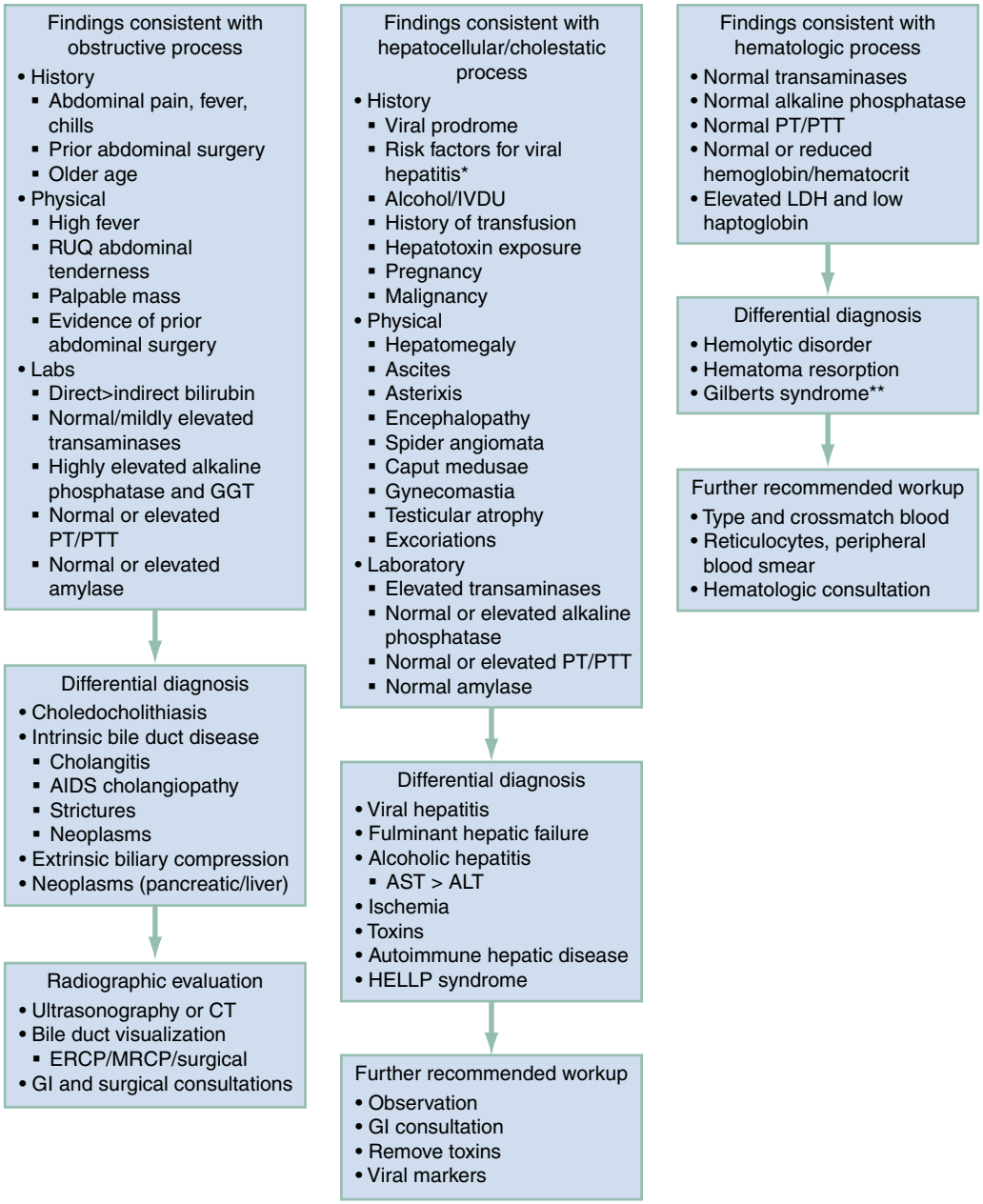
Laboratory Tests

Fig. 24.1 lists the laboratory tests that are helpful in the evaluation of a patient with jaundice.[1] Although there is some overlap, laboratory testing can be categorized in relation to presumed underlying etiology (hemolysis, liver dysfunction, or biliary obstructive disorders).

In hemolysis disorders, the most helpful laboratory tests include a reticulocyte count, evaluation of peripheral blood smear, haptoglobin, and lactate dehydrogenase (LDH). When the etiology is thought to be a primary liver dysfunction or cholestasis, the most helpful laboratory tests are serum gamma-glutamyl transpeptidase (GGT), hepatitis serologies, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, international normalized ratio [INR]), amylase, and an acetaminophen level in unexplained cases. Serum GGT rises in parallel with alkaline phosphatase in the setting of liver disease.[1] Although alkaline phosphatase also can be elevated in diseases affecting bone or placenta, the concomitant increase in serum GGT confirms a hepatic source. The evaluation for suspected biliary obstructive disorders includes testing for primary liver dysfunction with the addition of a lipase level.

Additional tests may be helpful in select patients. Both glucose and ammonia metabolism can be altered in the presence of hepatocellular injury, thus laboratory testing for blood glucose or ammonia levels may be important in the setting of altered mental status. The degree of elevation in serum ammonia does not correlate directly with the level of hepatic encephalopathy. Gastrointestinal bleeding can also cause an elevated ammonia level, secondary to the conversion of excess nitrogen load from blood into ammonia by intestinal bacteria, thus fecal guaiac testing may be helpful in select patients.

Ascitic fluid analysis should be considered in patients with new-onset ascites, or in those with established ascites but new complaints such as fever, worsening abdominal pain, gastrointestinal bleeding, hepatic encephalopathy, hypotension, or renal failure. Cell count and differential, as well as ascitic fluid albumin and total protein concentration, are typically sufficient initial screening tests. Gram stain and culture of ascitic fluid should be performed if spontaneous bacterial peritonitis (SBP) is suspected. The presence of more than 250 polymorphonuclear (PMN) cells per cubic millimeter of ascitic fluid is



* Risk factors for viral hepatitis include history of IVDU or intranasal drug use, tattoos, body piercings, blood transfusions, high risk sexual conduct or men who have sex with men, birth in HBV endemic area, known human immunodeficiency virus infection, birth between 1945 and 1965 (hepatitis C), dialysis patients (hepatitis B), recent travel (hepatitis A). (Kwo, 2017)

** A benign hereditary condition characterized by hyperbilirubinemia and jaundice due to inadequate hepatic conjugation of bilirubin.

Fig. 24.2 Differentiation and Further Evaluation of the Jaundiced Patient. *AIDS,* Acquired immunodeficiency syndrome; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *GGT,* gamma-glutamyl transferase; *GI,* gastrointestinal; *HELLP,* hemolysis, elevated liver enzymes, low platelet count; *IVDU,* intravenous drug use; *LDH,* lactate dehydrogenase; *MRCP,* magnetic resonance cholangiopancreatography; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RUQ,* right upper quadrant.

diagnostic for SBP. A negative ascitic fluid Gram stain is insufficiently sensitive to exclude SBP; treatment should be continued until ascitic fluid cultures result. If SBP is suspected, blood cultures should be considered. If the etiology of the ascites is unknown, determining the serum ascites albumin gradient (SAAG) may be helpful. The SAAG value is obtained by subtracting the albumin level of ascitic fluid from the serum albumin level. A SAAG value ≥1.1 g/dL, corresponding to relatively low albumin level in ascitic fluid and therefore transudative fluid, is often found in patients with portal hypertension. There are many causes of portal hypertension, including cirrhosis, liver failure, and heart failure. A SAAG value of less than 1.1 g/dL, corresponding to a comparatively higher albumin level in ascitic fluid and therefore

TABLE 24.1 Clinical Stages of Hepatic Encephalopathy

Clinical Stage	Intellectual Function	Neuromuscular Function
Subclinical	Normal examination findings, but work or driving may be impaired	Subtle changes in psychometric testing
Stage 1	Impaired attention, irritability, depression, or personality changes	Tremor, incoordination, apraxia
Stage 2	Drowsiness, behavioral changes, poor memory, disturbed sleep	Asterixis, slowed or slurred speech, ataxia
Stage 3	Confusion, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
Stage 4	Stupor and coma	Dilated pupils and decerebrate posturing; oculocephalic reflex

From Fitz G. Systemic complications of liver disease. In Feldman M, Sleisenger M, ed. *Gastrointestinal and liver disease*. Philadelphia, PA: WB Saunders; 1998.

exudative fluid, may be found in patients with conditions such as lupus or pancreatitis. Thus SAAG can assist in rapidly narrowing the differential diagnosis.

Imaging

When indicated, abdominal imaging can help narrow the differential diagnosis of jaundice, especially in patients for whom biliary obstruction is a concern. The primary role of imaging is in the characterization of obstructive biliary disease. The first choice of study depends on the clinical presentation. Ultrasonography is generally superior for visualization of the gallbladder and biliary ducts, and both ultrasonography and computed tomography (CT) are highly sensitive in diagnosing obstruction.[2] The choice of imaging modality depends on the pretest probability for biliary obstruction, and whether the obstruction may be malignant. For patients with painless, progressive jaundice without suspicion for hepatocellular injury, CT is the preferred imaging test. Unlike ultrasound, CT with IV contrast can evaluate for malignant obstruction by locating the site of the obstruction and can aid in determining resectability and assessing for disseminated disease. Patients with a high likelihood of non-malignant biliary disease and biliary obstruction are best screened initially with ultrasound. Ultrasonography is less expensive and less invasive than either magnetic resonance cholangiography or endoscopic ultrasound but has a lower sensitivity in identifying common bile duct stones. Ultrasonography with Doppler flow can detect obstruction in the hepatic, portal, and splenic veins. In patients with low or intermediate clinical likelihood of mechanical obstruction, ultrasonography is the preferred initial modality secondary to its low cost and absence of radiation exposure. CT is preferred if the entire abdomen needs to be evaluated.

Diagnostic Algorithm

The differential diagnostic considerations for jaundice are broad. There are critical and emergent causes that should be considered in the emergency department (ED) setting (Table 24.2). Particularly worrisome features are patients with jaundice and any of the following features: altered level of consciousness, hypotension, fever with abdominal pain, or active bleeding.

Further characterization of the cause of jaundice involves analysis of laboratory studies (see Fig. 24.2). Indirect bilirubinemia points to a hematologic cause, whereas direct bilirubinemia indicates hepatobiliary pathology. Elevated direct bilirubin with transaminase elevation is indicative of hepatocellular inflammation or injury. Prolongation of prothrombin time (PT) may indicate significant hepatocellular dysfunction. If hepatic dysfunction progresses, partial thromboplastin time (PTT) can also become elevated. Elevated alkaline phosphatase with elevated direct bilirubin suggests extrinsic biliary obstruction. As alkaline phosphatase elevation is not specific to liver disease, we recommend utilizing GGT as confirmatory biomarker evidence of biliary obstruction.[1]

Patients with suspected biliary obstruction should undergo ultrasonography or CT with IV contrast in the ED to determine the cause and site of the obstruction. Magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic ultrasound may be required to further characterize the obstruction, although these studies are usually performed following admission.[2] The most common causes of biliary obstruction are biliary stones and benign or malignant stenoses.

The identification of critical or emergent causes of jaundice is based on patterns of signs, symptoms, and ancillary testing. For instance, the triad of jaundice, encephalopathy, and coagulopathy (INR > 1.5) is usually indicative of acute hepatic failure. Fever, right upper quadrant abdominal pain, and jaundice can indicate biliary obstruction with infection (e.g., cholangitis, cholecystitis, or hepatitis). Ascites with abdominal tenderness raises suspicion for SBP. Rapid onset of hepatomegaly and ascites suggests portal vein thrombosis (Budd-Chiari syndrome). Mild or moderate transaminase elevations (up to 15× upper limit of normal) are often caused by viral hepatitis, alcoholic and nonalcoholic fatty liver disease, autoimmune hepatitis, or drug/supplement related injury. Severe elevations of transaminases (>15× upper limit of normal, or AST >1000 IU/L) are suggestive of acetaminophen toxicity or ischemic hepatopathy in particular.[1]

Empirical Management

Both general supportive and specific therapies are guided by the presumptive cause of jaundice (see Fig. 24.2). If coagulopathy is suspected or identified, compressible sites and ultrasound guidance should be considered for central venous access. Coagulopathy in the context of acute hemorrhage can be treated with fresh frozen plasma along with blood volume repletion with packed red blood cells.

In cases of SBP, the empirical antibiotic of choice is an IV third-generation cephalosporin (e.g., cefotaxime 2 g IV, ceftriaxone 2 g IV). Patients with SBP should receive an albumin infusion (initial dose 25% 1.5g/kg IV), as it has been shown to reduce the risk for mortality and hepatorenal syndrome.[3] Nonselective beta blocker use in patients with a history of cirrhosis should be discontinued, as beta-adrenergic blockers have been shown to increase mortality in patients with SBP.[3,4]

Jaundice and transaminitis out of proportion to the level of alkaline phosphatase elevation is consistent with a hepatocellular injury pattern. Patients with fulminant hepatic failure should be considered for admission to the intensive care setting. Strong consideration should be given to the possibility of transfer of acute hepatic failure patients to a facility with expertise in severe liver disease, when feasible.

Acetaminophen toxicity and indications for *N*-acetylcysteine (NAC) therapy are discussed in Chapter 138. There is evidence suggesting NAC offers a mortality benefit in non-acetaminophen induced acute liver failure, though the evidence is evolving and clear guidelines do not yet exist. Given the relative safety of NAC and the high morbidity of this disease, we recommend initiation of NAC therapy or discussion of NAC initiation with a hepatologist, depending on local practice patterns.[5,6]

In the absence of liver failure, patients with encephalopathy, coagulopathy, or unstable vital signs should be considered for admission.

TABLE 24.2 Jaundice: Differential Diagnosis of Critical and Emergent Diagnoses

System	Critical	Emergent	Nonemergent
Hepatic	Fulminant hepatic failure (toxin, virus, alcohol, ischemic insult, Reye syndrome)	Hepatitis of any cause with confusion, bleeding, or coagulopathy	Hepatitis with normal mental status, normal vital signs, and no active bleeding
		Wilson disease	
		Primary biliary cirrhosis	
		Autoimmune hepatitis	
		Liver transplant rejection	
		Infiltrative liver disease	
		Drug induced (isoniazid, phenytoin, acetaminophen, ritonavir, halothane, sulfonamides)	
		Toxin ingestion or exposure	
Biliary	Cholangitis	Bile duct obstruction (stone, inflammation, stricture, neoplasm)	
Systemic	Sepsis	Sarcoidosis	Post-traumatic hematoma resorption
	Heatstroke	Amyloidosis	Total parenteral nutrition
		Graft-versus-host disease	
Cardiovascular	Obstructing AAA	Right-sided congestive heart failure	
	Budd-Chiari syndrome	Veno-occlusive disease	
	Severe congestive heart failure		
Hematologic-oncologic	Transfusion reaction	Hemolytic anemia	Gilbert syndrome
		Massive malignant infiltration	Physiologic neonatal jaundice
		Inborn error of metabolism	
		Pancreatic head tumor	
		Metastatic disease	
Reproductive	Preeclampsia or HELLP syndrome	Hyperemesis gravidarum	
	Acute fatty liver of pregnancy		Cholestasis of pregnancy

AAA, Abdominal aortic aneurysm; *HELLP,* hemolysis, elevated liver enzymes, low platelets.

There are no comprehensive guidelines to indicate what level of hepatic or biliary dysfunction requires inpatient management. However, guidelines recommend consideration of immediate transfer to a liver specialist in cases of acute hepatitis with elevated INR or encephalopathy.[1] In addition, we recommend consideration of hospitalization for patients with new-onset jaundice and transaminase levels approaching 1000 IU/L, bilirubin approaching 10 mg/dL, or any evidence of coagulopathy, as these laboratory abnormalities suggest significant hepatic dysfunction. Patients with hepatitis or cholestatic jaundice may be managed in the outpatient setting, particularly patients with normal mental status, stable vital signs, ability to take oral fluids, no evidence of acute bleeding or significant coagulopathy, no complicating infectious process, and the ability to access follow-up care. Intravenous fluids and antiemetics may be necessary in the ED. Alcohol or medications with potential hepatotoxicity, particularly acetaminophen, should be avoided. In the setting of large volume paracentesis characterized by greater than 5 L of ascitic fluid removed, IV albumin repletion should be considered to prevent circulatory compromise with 6 to 8 g albumin administered IV for each liter of ascitic fluid removed.[3]

Management of biliary stone disease is discussed in Chapter 76. In general, patients with uncomplicated cholecystitis should receive intravenous fluids, antibiotics, parenteral analgesics, and antiemetics as needed, with subsequent hospitalization.[7] Ultrasound or CT with IV contrast, as well as consultation with a surgeon, should be considered.

Patients with confirmed or suspected choledocholithiasis, gallstones in the common bile duct, require admission for possible ERCP or cholecystectomy.[8] Neither CT nor ultrasonography is 100% sensitive in identifying a common bile duct stone, but they are reasonably sensitive in identifying a dilated common bile duct, which is highly suggestive of obstruction.

Fever, abdominal pain, and obstructive jaundice suggest ascending cholangitis (Fig. 24.3). Patients should receive antibiotics and intravenous fluids (see Chapter 76). As biliary excretion of most antibiotics is compromised in the setting of obstruction, patients often require biliary drainage.[8] This generally should be accomplished urgently but may be deferred 24 to 48 hours in stable patients. Drainage can be accomplished by endoscopic, percutaneous, or open surgical approaches. Prompt consultation with general surgery or gastroenterology, depending on local resources, is necessary to determine optimal timing and approach.

Patients with extrahepatic obstructive jaundice without cholangitis should also be considered for admission and drainage. ERCP is therapeutic for benign obstructions, such as gallstones or strictures. Patients with obstructive jaundice caused by malignancy may also benefit from biliary decompression, whether operative or endoscopic. Malignancy with jaundice heralds more advanced disease with increased morbidity and mortality.

In patients with anemia and jaundice, the management is based largely on the underlying etiology. Hematology consultation is often necessary to guide further management.

The references for this chapter can be found online at ExpertConsult.com.

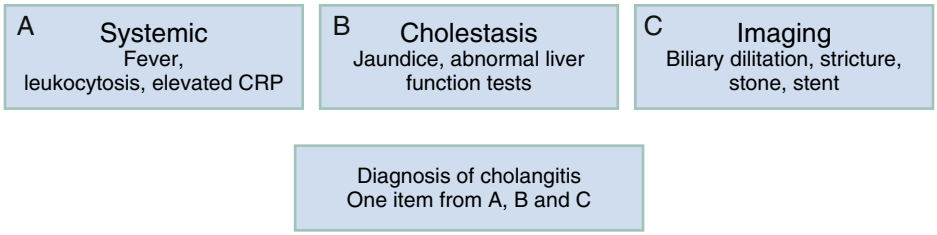


Fig. 24.3 Tokyo Guidelines for Diagnosis of Acute Cholangitis. *CRP,* C-reactive protein. (Redrawn from Kimura Y, Takada T, Kawarada Y, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines. *J Heptaobiliary Pancreat Surg*. 2007;14:15–26.)

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CHAPTER 24: QUESTIONS AND ANSWERS

1. A 56-year-old male presents with fever and abdominal distention. Bedside ultrasound reveals ascites and the results of paracentesis indicate possible spontaneous bacterial peritonitis (SBP). What daily medication should be stopped upon admission?

a. Amlodipine
b. Crestor
c. Lactulose
d. Nadolol

Answer: d. Beta blocker use in patients with cirrhosis with SBP should be discontinued as they have been shown to increase mortality.

2. A 43-year-old female presents with 1 month of painless abdominal swelling. On examination she has a diffusely swollen abdomen with a fluid wave. To help determine the etiology, you obtain the serum ascites albumin gradient (SAAG). Which value is consistent with cirrhosis?

a. 0.25 g/dL
b. 0.5 g/dL
c. 1 g/dL
d. 1.5 g/dL

Answer: d. A (SAAG) value of greater than or equal to 1.1 g/dL is found in patients with portal hypertension. There are many causes of portal hypertension, including cirrhosis, liver failure, or heart failure. A SAAG value of less than 1.1 g/dL may be found in patients with conditions such as lupus or pancreatitis.

3. A 48-year-old male with a history of cirrhosis presents with 3 days of abdominal pain and fever. Abdominal paracentesis suggests spontaneous bacterial peritonitis (SBP). Which of the following initial treatments is most appropriate?

a. Cefotaxime, albumin, and discontinue beta blockade
b. Ceftriaxone and dexamethasone
c. Ceftriaxone alone
d. Ciprofloxacin and metronidazole

Answer: a. The empirical antibiotic of choice is a third-generation cephalosporin (e.g., cefotaxime). Albumin administration has been shown to reduce risk for mortality and hepatorenal syndrome. If the patient has a history of cirrhosis and is taking a nonselective beta blocker, it should be discontinued because it has been shown to increase mortality in patients with SBP.

4. A 41-year-old male with a history of cirrhosis presents with fever, abdominal distension, and confusion. A paracentesis is performed in the evaluation of spontaneous bacterial peritonitis (SBP). What are the diagnostic criteria found in the ascitic fluid that confirms SBP?

a. Ascitic fluid neutrophil count >100
b. Ascitic fluid neutrophil count >250
c. Ascitic fluid total WBC count >100
d. Ascitic fluid total WBC >250

Answer: b. The presence of more than 250 polymorphonuclear cells per cubic millimeter of ascitic fluid is diagnostic for SBP.

5. A 55-year-old female presents with 1 month of diffuse abdominal swelling and pain. She reports a long history of alcohol use. In evaluating this patient for jaundice, at what bilirubin level does jaundice typically become clinically apparent?

a. 1 mg/dL
b. 2 mg/dL
c. 2.5 mg/dL
d. 4 mg/dL

Answer: d. Clinical jaundice is usually not evident until the total serum bilirubin concentration rises above 2.5 mg/dL. Jaundice is first apparent sublingually, in the conjunctiva or on the hard palate.

25

Nausea and Vomiting

Joshua Guttman

KEY CONCEPTS

- Nausea and vomiting can result from a primary problem in the gastrointestinal (GI) tract but can also result from problems in the neurological, vestibular, urogenital, cardiac, or other systems.
- In the acutely vomiting patient, associated symptoms and medication history are most helpful in narrowing the differential diagnosis.
- Laboratory studies are not necessary for all patients with vomiting. In patients with severe or protracted vomiting, consider checking electrolytes and renal function, particularly when intravenous (IV) rehydration is initiated.
- In patients with undifferentiated nausea or vomiting or vomiting due to non-obstructive GI disease, ondansetron is the first-line antiemetic due to its low side effect profile. However, no definitive evidence exists for the superiority of one antiemetic agent over others.
- Although evidence is limited, metoclopramide is the antiemetic of choice in hyperemesis gravidarum and vomiting associated with headache, and ondansetron is the drug of choice in chemotherapy-induced vomiting.
- Ondansetron is the first-line agent for children with vomiting due to acute gastroenteritis.
- Consider cannabinoid hyperemesis syndrome (CHS) in all patients with protracted vomiting. Emergency department (ED) treatment of CHS includes the use of capsaicin cream as well as haloperidol or lorazepam.

FOUNDATIONS

Epidemiology

The most common causes of nausea and vomiting are GI disorders. Nausea and vomiting may also represent disorders outside the GI tract, such as hyperemesis gravidarum, intracranial lesions and infections, myocardial infarction, diabetic ketoacidosis, and drug toxicities. With heightened access to marijuana, there has been an increased prevalence of cannabinoid hyperemesis syndrome (CHS). A cross-sectional study in the United States noted a near doubling of presentations for cyclical vomiting associated with marijuana use after legalization in one state.[1]

Pathophysiology

The act of vomiting occurs in three phases: nausea, retching, and actual vomiting. Nausea may occur without retching or vomiting, and retching may occur without vomiting. Similar pathways mediate them. In the *nausea* phase, increased tone in the musculature of the duodenum and jejunum, combined with a concomitant decrease in gastric tone, leads to the reflux of intestinal contents into the stomach. There is often associated hypersalivation, repetitive swallowing, and tachycardia.

Retching is the rhythmic, synchronous contraction of the diaphragm, abdominal muscles, and intercostal muscles against a closed glottis without the expulsion of gastric contents.

Vomiting is the forceful expulsion of gastric contents through the mouth. Contraction of the external oblique and abdominal rectus muscles, combined with relaxation of the hiatal portion of the diaphragm, increases the pressure in the abdominal and thoracic compartments. Simultaneously, there is relaxation of the gastric fundus, cardia, and upper esophageal sphincter as the vomitus is brought up and out of the mouth. The glottis closes to prevent aspiration.

Rumination may be confused with vomiting. Ruminating is when stomach contents dribble out of the mouth non-forcefully, which may be voluntary and is not associated with muscle contraction. Patients may swallow ruminated contents.

The complex act of vomiting is coordinated by the *vomiting center* located in the medulla. The vomiting center contains muscarinic receptors, which, when stimulated, trigger the vomiting reflex. The efferent pathways from the vomiting center are mainly through the vagus, phrenic, and spinal nerves (Fig. 25.1). These pathways are responsible for the integrated response of the diaphragm, intercostal muscles, abdominal muscles, stomach, and esophagus. The vomiting center is activated by afferent stimuli from a variety of sources. These include (1) visceral afferent impulses directly from the GI tract; (2) visceral afferent impulses from outside the GI tract, including the biliary system, peritoneum, pharynx, genitalia, and heart; (3) extramedullary central nervous system (CNS) afferents, including the vestibular system, thalamus, and cerebral cortex; and (4) the chemoreceptor trigger zone (CTZ) (Fig. 25.2), which is located in the area postrema in the floor of the fourth ventricle. Part of the CTZ is located outside of the blood-brain barrier, enabling it to respond to endogenous and exogenous substances that activate vomiting (see Fig. 25.2).

The discovery of various neurotransmitters and their receptor sites within the medulla has improved the understanding and development of therapeutic agents. The CTZ area is rich in dopamine D_2 and serotonin receptors, and the lateral vestibular nucleus is rich with cholinergic and histamine receptors. Serotonin receptors are also widely found in the GI tract. These receptor sites are targets for the various medications used to treat nausea and vomiting.

The pathophysiology of cannabinoid hyperemesis syndrome remains unknown, although downregulation of the cannabinoid receptor CB1 is speculated. While cannabinoid receptors typically inhibit vomiting, chronic cannabis use downregulates the receptors, predisposing to CHS. Other purported mechanisms include the pro-emetic properties of cannabis at higher and more sustained doses, as well as decreased gastric motility induced by cannabis.[2]

DIAGNOSTIC APPROACH

Differential Diagnosis Considerations

The differential diagnosis for nausea and vomiting is broad in scope; almost any organ system can be involved. *Acute* vomiting begins abruptly, generally lasts less than 1 week before presentation, and is

frequently associated with acute conditions. *Chronic* vomiting generally occurs longer than 1 month, is frequently associated with motility disorders, effects of systemic treatments (such as for cancer), neuropsychiatric conditions (e.g., bulimia), or neurologic conditions. *Persistent* vomiting has varying definitions and is not well defined in the literature.[3] *Cyclic* vomiting occurs in discrete episodes with intervening asymptomatic periods. Common causes of nausea and vomiting are outlined in Table 25.1, and a differential diagnosis is presented in Tables 25.2 and 25.3.

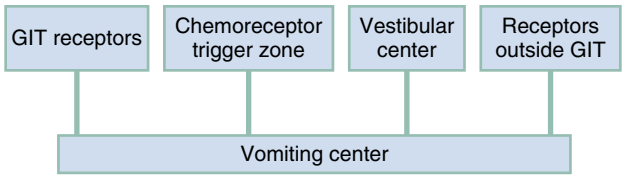


Fig. 25.1 Vomiting Process. *GIT,* Gastrointestinal tract.

Pivotal Findings

Symptoms

A thorough history, including past medical history, medications, and drug use, will generally elicit suspected etiologies of vomiting. The content and color of the vomitus may help determine its cause (Table 25.4). Although coffee ground emesis suggests a slower bleeding rate than bright red blood, this distinction is variable. The history is directed at assessing for both the causes of vomiting and its sequelae.

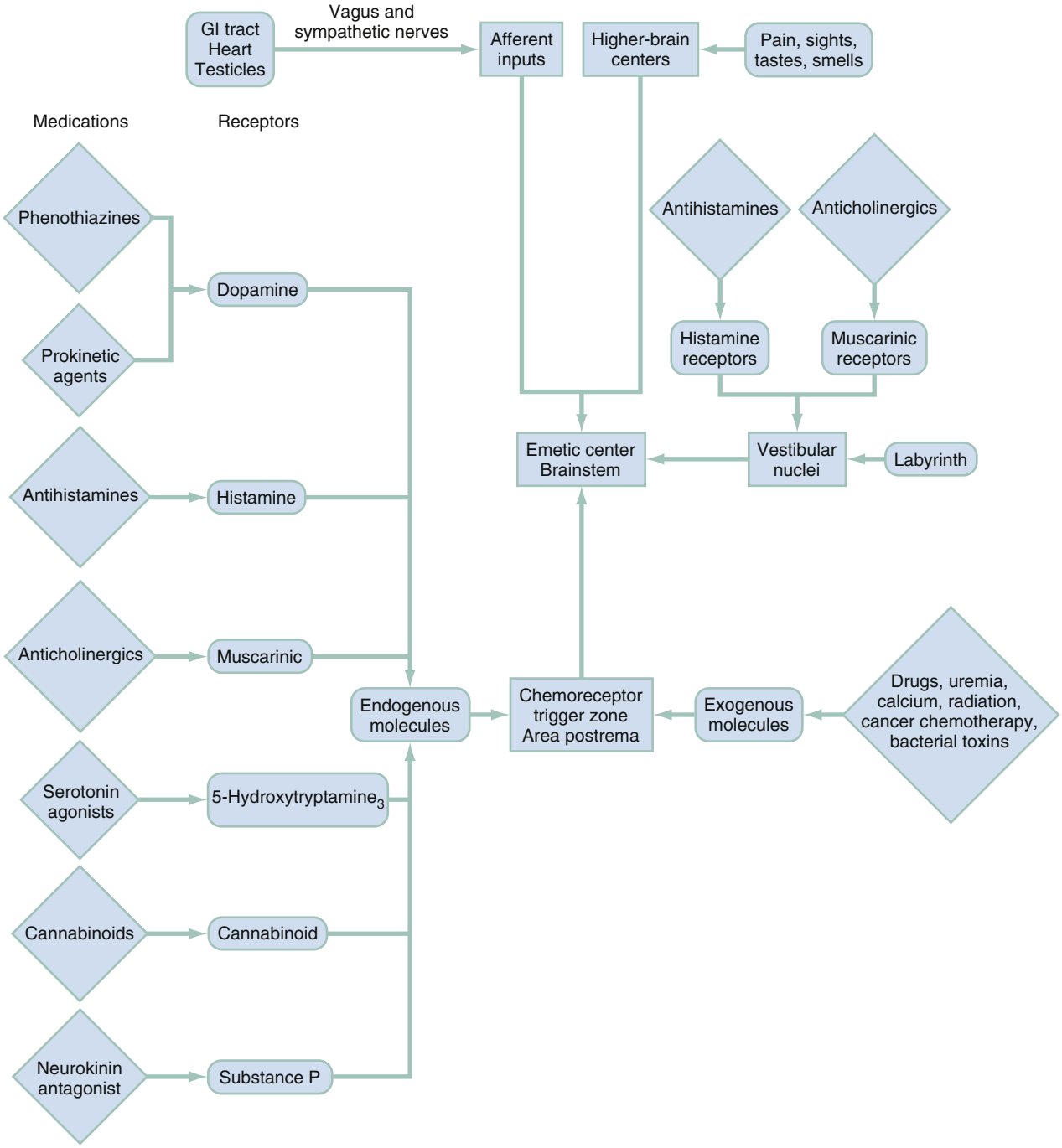


Fig. 25.2 Pathophysiology of Nausea and Vomiting. *GI,* Gastrointestinal.

TABLE 25.1 Disorders Commonly Associated With Vomiting.

Disorder	Class	History	Prevalence	Physical Examination	Useful Tests	Comments
Nausea and vomiting of pregnancy (NVP)	Acute	Vomiting may occur in the morning or throughout the day. Associated breast tenderness. NVP typically starts in weeks 4–7, peaks in weeks 10–16, and disappears by week 20. Vomiting that begins after week 12 or continues past week 20 should prompt a search for another cause.	Very common Affects 75% of all pregnancies	Benign abdomen	Urine pregnancy test Serum electrolytes, urine ketones to exclude hyperemesis gravidarum	Consider NVP in all females of childbearing capacity. Prognosis for mother and infant is excellent. NVP is associated with a decreased risk of miscarriage, fetal growth retardation, and fetal mortality.
Hyperemesis gravidarum	Acute	Severe, protracted form of NVP. No universally accepted definition of the disease. Generally accepted hallmarks include 5% weight loss, ketonuria, and electrolyte disturbance. Hyperemesis is associated with multiple gestation, molar pregnancy.	Affects 0.3%–3% of pregnancies	Signs of dehydration Benign abdomen	β-hCG Urinalysis for ketones (65% of patients) Serum electrolytes Ultrasound examination to exclude molar pregnancy or multiple gestations (if not already performed in current pregnancy)	Studies are conflicting on fetal outcomes. There may be an association with low fetal birth weight and maternal weight loss.
Gastroenteritis	Acute	Fever, diarrhea, and crampy abdominal pain. Vomiting and pain occur early, usually followed by diarrhea within 24 h.	Very common	Benign abdomen	Usually not necessary	Early gastroenteritis, when only vomiting and periumbilical pain are present, may be confused with early appendicitis. Diarrhea is usually in the diagnosis of gastroenteritis.
Gastritis	Acute	Epigastric pain, belching, bloating, fullness, heartburn, and food intolerance. Use of NSAIDs or alcohol is common.	Very common	Mild epigastric tenderness may be present.	Lipase, LFTs, and pregnancy test may be necessary to exclude other diagnoses	Removal of inciting agent along with antacid therapy will resolve symptoms in majority of patients.
Peptic ulcer disease (PUD)	Acute Chronic	Epigastric pain present in 90% of cases. Presence of severe pain should raise suspicion of perforation.	Very common	Mild epigastric tenderness	Hemoglobin and hemoccult testing if bleeding is suspected Upright chest film or CT scan if perforation is suspected	Three major causes of PUD are NSAIDs, *Helicobacter pylori* infection, and hypersecretory states.
Biliary disease		Abdominal pain may be midepigastric or RUQ. Onset frequently after a fatty meal. May have history of similar episodes in the past.	Very common	RUQ tenderness present in most cases. If instructed to breathe deeply during alpation in the RUQ, the patient experiences heightened tenderness and inspiratory arrest (Murphy sign).	WBCs Lipase Serum bilirubin LFTs RUQ ultrasound examination	Normal temperature, WBCs, and spontaneous resolution of symptoms suggest biliary colic. Fever, Murphy sign, elevated WBCs, and suggestive ultrasound indicate cholecystitis.
Myocardial infarction (MI)	Acute	Patients typically have substernal chest pain. Vomiting may be an associated symptom.	Common	Patients often are anxious and in distress from pain. No diagnostic examination findings.	ECG (new Q waves, ST segment changes, or T wave inversions) troponin	Not all patients have chest pain. Some patients, particularly women and diabetic patients, may not have chest pain. Consider an ECG and troponins for this subset of patients and patients with cardiac risk factors and isolated vomiting or vomiting with epigastric pain.

Continued

TABLE 25.1 Disorders Commonly Associated with Vomiting—cont'd.

Disorder	Class	History	Prevalence	Physical Examination	Useful Tests	Comments
Diabetic ketoacidosis (DKA)	Acute	Polydipsia and polyuria occur early. Without treatment, altered mental status and coma may develop. .	Common	"Fruity" breath odor results from serum acetone. Tachypnea Signs of dehydration may be present. Severe cases often manifest with altered mental status or coma.	Serum glucose Electrolytes serum beta hydroxybutyrate VBG	Any protracted vomiting, especially in children, should prompt measurement of a fingerstick glucose test.
Pancreatitis	Acute Chronic	Presenting symptom is epigastric pain, which often radiates to the back. Most cases are caused by gallstones or alcoholism.	Common	Epigastric tenderness is present. Associated paralytic ileus may cause abdominal distention and decreased bowel sounds. Frank shock may be present in severe cases.	Lipase WBC Serum glucose LDH AST Hematocrit BUN Calcium VBG	Early aggressive intravenous hydration is especially important in pancreatitis patients with severe vomiting.
Appendicitis	Acute	Abdominal pain classically begins in periumbilical region and later moves to right lower quadrant. Anorexia is common.	Common	Localized tenderness over right lower quadrant. Low-grade fever may be present.	WBC Ultrasound Abdominal CT	Early appendicitis can be a difficult diagnosis to make.
Bowel obstruction	Acute Chronic	Abdominal pain, vomiting, obstipation and constipation. Typically, patients will have a surgical history.	Common	Abdominal distention, mild diffuse tenderness, and high-pitched "tinkling" bowel sounds may be present. Thorough search for hernias should be performed.	Electrolytes Lactate POCUS Abdominal CT	Adhesions, hernias, and tumors account for 90% of bowel obstructions. NG tube placement can relieve the vomiting of obstructed gastrointestinal contents.
Carbon monoxide (CO) poisoning	Acute	Headache is usually present. CO poisoning often occurs during winter months when furnaces are turned on. Family members (or pets) may have similar symptoms if they also have been exposed.	Uncommon	No reliable signs of early CO poisoning.	CO level	Because CO is a tasteless, odorless gas, patients may not realize they have been exposed.
Boerhaave syndrome	Acute	Patients may have neck, chest, or epigastric pain. Forceful, protracted vomiting usually causes the tear. Most cases follow a bout of heavy eating and drinking. Other reported causes include childbirth, defecation, seizures, and heavy lifting.	Uncommon	Tachypnea, tachycardia, and hypotension may be present. Escaped air from the esophagus may produce subcutaneous emphysema. Air in the mediastinum produces a "crunching" sound as the heart beats (Hamman sign).	CXR showing mediastinal air is suggestive but CT is more sensitive. Esophagogram with water-soluble contrast is definitive.	The classic presentation includes forceful vomiting, severe chest pain, subcutaneous emphysema, and multiple CXR findings. There is a growing body of evidence that most cases do not have this "classic" picture. In more subtle presentations, the diagnosis can be difficult to make.
Cannabinoid hyperemesis syndrome	Cyclic	Severe retching and vomiting in the context of daily marijuana use. Relieved with hot showers.	Increasing	Severe distress from vomiting, dehydration. Occasional epigastric tenderness.	Electrolytes and renal function	Ask about marijuana use in all patients with intractable, recurrent, or episodic vomiting.

AST, Aspartate aminotransferase; *β-hCG,* beta-human chorionic gonadotropin; *BUN,* blood urea nitrogen; *CT,* computed tomography; *CXR,* chest radiography; *ECG,* electrocardiogram; *ETOH,* ethyl alcohol; *Hct,* hematocrit; *LDH,* lactate dehydrogenase; *LFT,* liver function test; *NSAID,* nonsteroidal anti-inflammatory drug; *Po2,* partial pressure of oxygen; *POCUS,* Point of Care Ultrasound; *RUQ,* right upper quadrant; *VBG,* venous blood gases; *WBC,* white blood cell.

TABLE 25.2 Causes of Nausea and Vomiting

Acute	Chronic	Episodic	Cyclical
Ischemic bowel	Chronic pancreatitis	Cholelithiasis	Cyclical vomiting syndrome
Ruptured viscus	Gastroparesis	IBD	Cannabinoid hyperemesis syndrome
Cholangitis	PUD	IBS	
Cholecystitis/ cholelithiasis	Gastritis	Gastritis	
Bowel obstruction	Gastric outlet obstruction	BPPV	
Appendicitis	CNS tumor	Motion sickness	
Peritonitis	Raised ICP	Chemotherapy	
Acute pancreatitis	Migraine	DKA	
PUD	Drug toxicity	Uremia	
Gastroenteritis	Bulimia	Pregnancy	
Hepatitis	Carbon monoxide		
Food poisoning	Pregnancy		
Intracerebral bleed			
Meningitis			
Cerebellar infarct			
Drug toxicity			
Drug withdrawal			
Renal colic			
Gonadal torsion			
Pyelonephritis			
Myocardial infarction			
Sepsis			
Carbon monoxide			
Alcohol intoxication			
Alcohol withdrawal			

BPPV, Benign paroxysmal peripheral vertigo; *CNS,* central nervous system; *DKA,* diabetic ketoacidosis; *IBD,* inflammatory bowel disease; *IBS,* inflammatory bowel syndrome; *ICP,* intracranial pressure; *PUD,* peptic ulcer disease.

The timing and duration of the vomiting may be important. Symptoms occurring primarily in the morning may suggest increased intracranial pressure. Vomiting occurring more than 1 hour after eating suggests gastric outlet obstruction or gastroparesis. Vomiting of material eaten more than 12 hours previously is pathognomonic for outlet obstruction.

Associated symptoms are helpful: Vomiting with diarrhea is generally due to infectious gastroenteritis but may also be present in mesenteric ischemia or other GI surgical emergencies. Vomiting associated with abdominal pain is generally caused by diseases of the GI system. Chronic headaches with nausea and vomiting should raise suspicion of elevated intracranial pressure. Vomiting without preceding nausea is also suspicious for CNS pathology.

The *social history* should include alcohol or other substance use. The *past medical history* should include GI diseases or prior surgery. Finally, a thorough *medication list,* including over-the-counter drugs and supplements, should be elicited.

A history of *similar episodes* should be elicited. A history of severe episodes of nausea and vomiting lasting hours to days with symptom-free

TABLE 25.3 Differential Diagnosis of Nausea and Vomiting

Etiologic Category	Critical Diagnoses	Emergent Diagnoses	Nonemergent Diagnoses
Gastrointestinal (GI)	Boerhaave syndrome Ischemic bowel GI bleeding Ruptured viscus Cholangitis Peritonitis	Gastric outlet obstruction Pancreatitis Cholecystitis Bowel obstruction or ileus Appendicitis Spontaneous bacterial peritonitis	Gastritis Gastroparesis Peptic ulcer disease Inflammatory bowel disease Biliary colic Hepatitis Gastroenteritis Food poisoning Inflammatory bowel syndrome
Neurologic	Intracerebral bleed Meningitis	Meningitis CNS tumor	Migraine
Vestibular	Cerebellar infarct	Raised ICP Suppurative labyrinthitis	BPPV
Endocrine	DKA	Adrenal insufficiency Uremia	Thyroid disorder
Pregnancy		Hyperemesis gravidarum	Nausea and vomiting of pregnancy
Drug toxicity	Acetaminophen Aspirin	Digoxin Theophylline Barbiturates Carbamazepine Valproic acid	
Therapeutic drug use			Aspirin Antibiotics cannabis Ibuprofen Chemotherapy
Drugs of abuse		Alcohol withdrawal	Opioid Opioid withdrawal Alcohol Cannabis
Genitourinary	Gonadal torsion		Urinary tract infection Nephrolithiasis
Miscellaneous	Myocardial infarction Sepsis Organophosphate poisoning	Carbon monoxide Electrolyte disorders	Motion sickness Labyrinthitis

BPPV, Benign paroxysmal peripheral vertigo; *CNS,* central nervous system; *DKA,* diabetic ketoacidosis; *ICP,* intracranial pressure.

TABLE 25.4 Differential Diagnosis Based on Content of Vomitus.

Color/Content of Vomitus	Diagnoses
Bright red blood	Peptic ulcer Gastritis Esophageal varices Aortoenteric fistula Esophageal rupture Duodenal or gastric tumors Mallory-Weiss syndrome Dieulafoy lesion Foreign body
Coffee grounds	Peptic ulcer Gastritis Esophageal varices Duodenal or gastric tumors Mallory-Weiss syndrome
Undigested food	Gastric outlet obstruction Achalasia Esophageal stricture Foreign body
Feces	Small bowel obstruction Large bowel obstruction
Bilious (adults)	Small bowel obstruction Large bowel obstruction

BOX 25.1 Rome IV Criteria for Cannabinoid Hyperemesis Syndrome.

Must include all of the following:

1. Stereotypical episodic vomiting resembling cyclical vomiting syndrome in terms of onset, duration, and frequency
2. Presentation after prolonged, excessive cannabis use
3. Relief of vomiting episodes by sustained cessation of cannabis use

Criteria fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis

Supportive remarks:

May be associated with pathologic bathing behaviors (prolonged hot baths or showers)

Rome IV criteria[5]

intervals may lead to a diagnosis of cyclical vomiting syndrome (CVS). In patients with a history of cyclical vomiting, chronic use of cannabis is essential to elicit, as it may lead to a diagnosis of cannabis hyperemesis syndrome.[1] Symptoms are similar to CVS, though patients will often note temporary relief with a hot shower.[1] The onset of the syndrome may occur following years of chronic marijuana use but can also occur with daily marijuana use of less than 1-year duration.[4] The Rome IV diagnostic criteria for CHS can be found in Box 25.1.[5]

Signs

The examination begins with an overall assessment of the patient's clinical status, including an assessment for volume depletion. The history will direct the examination to the appropriate organ systems (Table 25.5). The eye examination may reveal nystagmus, which may indicate cerebellar pathology, peripheral vertigo, or drug intoxication. Oral examination may reveal loss of dental enamel seen with bulimia or dry mucus membranes from dehydration. Abdominal examination may

TABLE 25.5 Physical Examination of the Patient with Nausea and Vomiting.

Organ System	Finding	Suggested Diagnoses
General	Poor skin turgor Dry mucous membranes	Dehydration
Vital signs	Fever	Gastroenteritis, cholecystitis, appendicitis, hepatitis Bowel perforation
	Tachycardia, orthostatic changes	Dehydration
HEENT	Nystagmus	Labyrinthitis Vertebrobasilar insufficiency Cerebellar infarct or bleed CPA tumor
	Papilledema	Increased ICP from CNS tumor or bleeding
Neck	Goiter	Thyroid disease
Lungs	Rales	Pneumonia
Heart	Arrhythmia Murmur	Acute myocardial infarction or other cardiac pathology
Abdomen	Abdominal distention Peristaltic waves High-pitched bowel sounds Decreased bowel sounds Hernias or surgical scars Peritoneal signs	Bowel obstruction, gastroparesis Gastric outlet obstruction Bowel obstruction Ileus Possible bowel obstruction Appendicitis, cholecystitis Perforated viscus
Neurologic	Abnormal mental status Cerebellar findings Cranial nerve findings	CNS pathology

CNS, Central nervous system; *CPA,* cerebellopontine angle; *HEENT,* head, eyes, ears, nose, throat; *ICP,* intracranial pressure.

reveal ascites, distention, hernias, abdominal tenderness and masses, hyperactive or hypoactive bowel sounds. Neurological examination (including funduscopic) is essential when considering a central cause. Provocative testing in patients with suspected benign paroxysmal positional vertigo may elicit vomiting or nystagmus (see Chapter 15). Symptoms of depression or anxiety may suggest a psychiatric origin, although this is a diagnosis of exclusion and rarely is made in the ED.

Ancillary Studies

The history and physical examination direct testing:

- Serum electrolytes and renal function: Measurement of serum electrolytes and renal function is not routinely required. It should be considered in patients with a history of prolonged or severe vomiting or clinical evidence of dehydration requiring volume replacement to assess for hypokalemia, hypochloremia, hypo- or hypernatremia, or contraction alkalosis. In the context of vomiting, acute renal dysfunction typically results from pre-renal azotemia.
- Serum lipase: Lipase determination is prudent in cases of suspected pancreatitis.
- Liver function and ammonia tests: Liver function tests are indicated in cases of suspected hepatic or biliary disease. Ammonia testing is appropriate when liver failure is suspected.
- Serum drug levels: Serum drug levels may be necessary for determining the cause of nausea and vomiting in patients on digoxin, salicylates, acetaminophen, valproic acid, carbamazepine, or phenobarbital,

especially in elders with cognitive or visual impairment who are taking medications without supervision. Specific serum drug levels are obtained when knowledge of the drug level would alter a patient's management.

- Serum betahydroxybutyrate or venous blood gas: These tests are obtained when diabetic ketoacidosis is suspected.
- Urine tests: A urine pregnancy test (or serum pregnancy test) should be performed in all women of childbearing capacity with nausea or vomiting. A urinalysis may show leukocyte esterase, nitrites, or bacteria as evidence of a urinary tract infection. Ketones support a diagnosis of diabetic ketoacidosis or prolonged starvation state. Hematuria indicates a possible renal calculus.
- Ultrasound: A point-of-care ultrasound (POCUS) or comprehensive abdominal ultrasound evaluates for cholelithiasis, cholecystitis, renal colic, or gonadal torsion. POCUS can also assess for small bowel obstruction (SBO). Additionally, a POCUS assessment of the inferior vena cava may help monitor patients with suspected dehydration. In pregnant patients, an ultrasound should be performed to confirm an intrauterine pregnancy. In pediatric patients, POCUS or comprehensive ultrasound can assess for appendicitis or intussusception.
- Abdominal computed tomography (CT): Abdominal CT scan is indicated in patients with a suspected SBO or surgical cause, such as appendicitis, when not diagnosed by ultrasound.
- Neuroimaging: Head CT evaluates intracranial etiologies of nausea and vomiting, while MRI is preferred for posterior fossa pathologies, such as cerebellar infarction.
- Chest imaging: A chest x-ray may reveal subdiaphragmatic air in a patient with a perforated viscus, but abdominal CT is far superior when perforation or other serious intra-abdominal pathologies are suspected. For patients with suspected Boerhaave syndrome, a chest radiograph can assess for a pneumomediastinum, though CT is the preferred modality.

DIAGNOSTIC ALGORITHM

Patients presenting with acute vomiting are rapidly assessed for critical conditions (see Table 25.4). A diagnostic algorithm is shown in Fig. 25.3. Vomiting may result in serious sequelae (Table 25.6).

If the patient is unstable or seriously ill, oxygenation is provided as needed, IV access and cardiac monitoring are established, and vital sign disturbances are addressed. A brief history and directed physical examination are performed concomitantly to determine the most likely causes, with evaluation and management prioritized to those causes.

If the patient is stable, a more thorough history and physical examination are performed. The history and physical examination direct ancillary testing and empiric therapy. Serum electrolyte and renal function determination is prudent in patients with significant volume depletion requiring IV replacement. IV analgesics and antiemetics are reasonable in patients with severe abdominal pain and vomiting, as are liver function tests and lipase. A serum lactate level can be helpful when evaluating possible sepsis. Many patients with severe pain and tenderness will require abdominal imaging. Patients with a history of abdominal surgery and decreased stool output are evaluated for SBO. Patients with severe headache or neurological deficits not thought to be due to a primary headache disorder should have neuroimaging performed, and patients with suspected myocardial infarction need an electrocardiogram (ECG) and troponin testing. Acetaminophen and aspirin levels, as well as the measurement of other serum drug levels, should be considered in patients with suspected medication overdose or drug toxicity.

If an emergent cause of nausea and vomiting is highly suspected or confirmed based on the initial evaluation and ancillary testing, then appropriate management is initiated to treat the underlying cause. Patients who are generally well-appearing and have a low likelihood of severe disease, whose symptoms are controllable, but for whom the diagnosis is still unclear, should have follow-up arranged within 24 to 48 hours for reevaluation if symptoms persist, or more urgently if symptoms worsen or a new, concerning symptom, such as blood in the stool or vomit, fever, or localized pain develops.

Patients who have a suspected or confirmed nonemergent diagnosis are treated with antiemetic medications, with specific management directed at the underlying cause. Patients with cyclical or recurrent vomiting syndromes do not generally require diagnostic testing in the ED and are managed in consultation with the patient's primary care physician. However, care should be taken to avoid anchoring on a previous diagnosis of CVS. Corroborative information from the patient, the medical record, family members, or the primary care physician can help ensure that the pattern of the presentation fits the patient's syndrome.

EMPIRICAL MANAGEMENT

Management is directed at simultaneous symptom relief and identification of the underlying cause. Symptomatic relief should proceed regardless, as the underlying cause may not be identified during the ED course. Decreased oral intake with concomitant fluid loss by vomiting or diarrhea causes dehydration. If the patient is mildly or moderately dehydrated and can take oral liquids, a solution containing sodium, carbohydrate, and water is administered. Many sports drinks contain the proper balance of these elements. Patients who are severely dehydrated or in whom intake of oral fluids is not feasible or contraindicated should receive an IV crystalloid solution, including the correction of electrolyte abnormalities as needed. Placement of a nasogastric tube is rarely indicated, except in patients with severe bowel obstruction.

The need for antiemetics and the response to therapy may be measured with scales similar to those used for pain assessment, such as a visual analog scale and the verbal categorical scale.

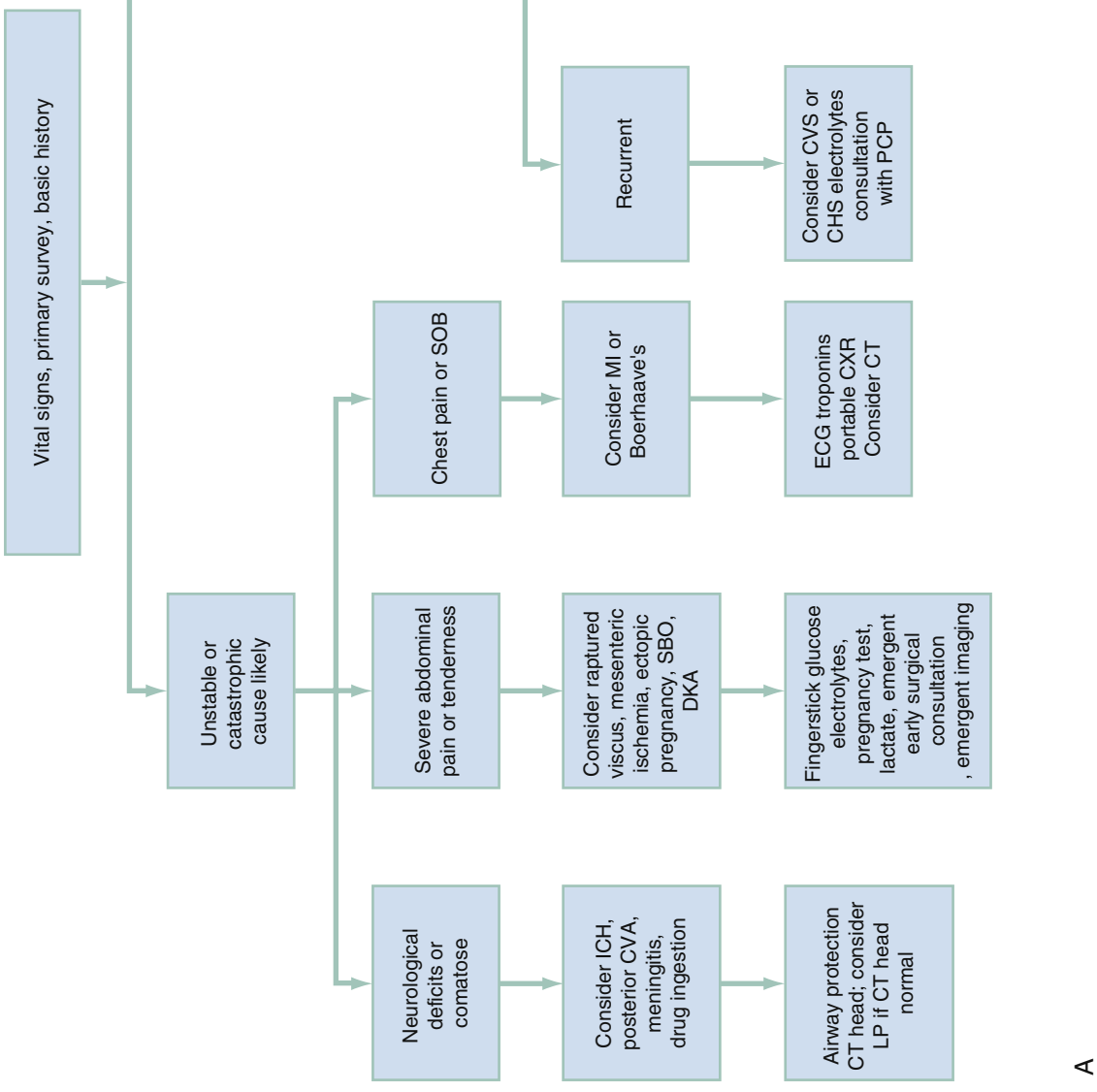
Patients presenting to the ED with nausea or vomiting may have a known etiology with specific treatment aimed toward treating the underlying cause. These are discussed in the Specific Situations section.

Adults

For the adult patient with non-obstructive GI causes or undifferentiated nausea and vomiting, there is limited evidence to support the use of one antiemetic agent over another. A 2015 Cochrane review did not demonstrate the superiority of any agent over placebo, other than droperidol, which demonstrated superiority in a single study.[6] Table 25.7 lists medications commonly used to treat nausea and vomiting, and My recommendations are shown in Fig. 25.4.

Pharmacologic therapies include serotonin antagonists, histamine antagonists, muscarinic antagonists, and dopamine antagonists.

The serotonin antagonists, particularly ondansetron, are considered first-line therapies for most cases of nausea and vomiting in the ED. The initial dose of ondansetron is 4 to 8 mg PO/IV. A single dose of up to 16 mg is considered safe in the non-elderly population. In elders, the initial dose should not exceed 8 mg infused over at least 15 minutes. For most patients, there are few or no side effects of the serotonin receptor antagonists and, if they occur, are mild. Ondansetron is known to cause QT prolongation with the resultant risk of Torsade de pointes. Patients at risk for having a prolonged QT should have an ECG before administration of ondansetron. QT prolongation occurs in a dose-dependent manner, with the risk occurring as the dose increases. The FDA recommends the correction of electrolytes, particularly potassium and magnesium, before administration.[7] Ondansetron has also been associated with serotonin toxicity when given concurrently with other serotonergic agents.



A

Fig. 25.3 (A and B) Approach to the patient with nausea and vomiting. *BMP*, Basic metabolic panel; *CT*, computed tomography; *CVA*, Cerebrovascular accident; *CVS*, cyclical vomiting syndrome; *CXR*, chest x-ray; *DKA*, diabetic ketoacidosis; *ECG*, electrocardiogram; *ICH*, intracranial hemorrhage; *LFT*, liver function test; *LP*, lumbar puncture; *MI*, myocardial infarction; *PCP*, phencyclidine; *SBO*, small bowel obstruction; *SOB*, shortness of breath; *US*, ultrasound; *VBG*, venous blood gas.

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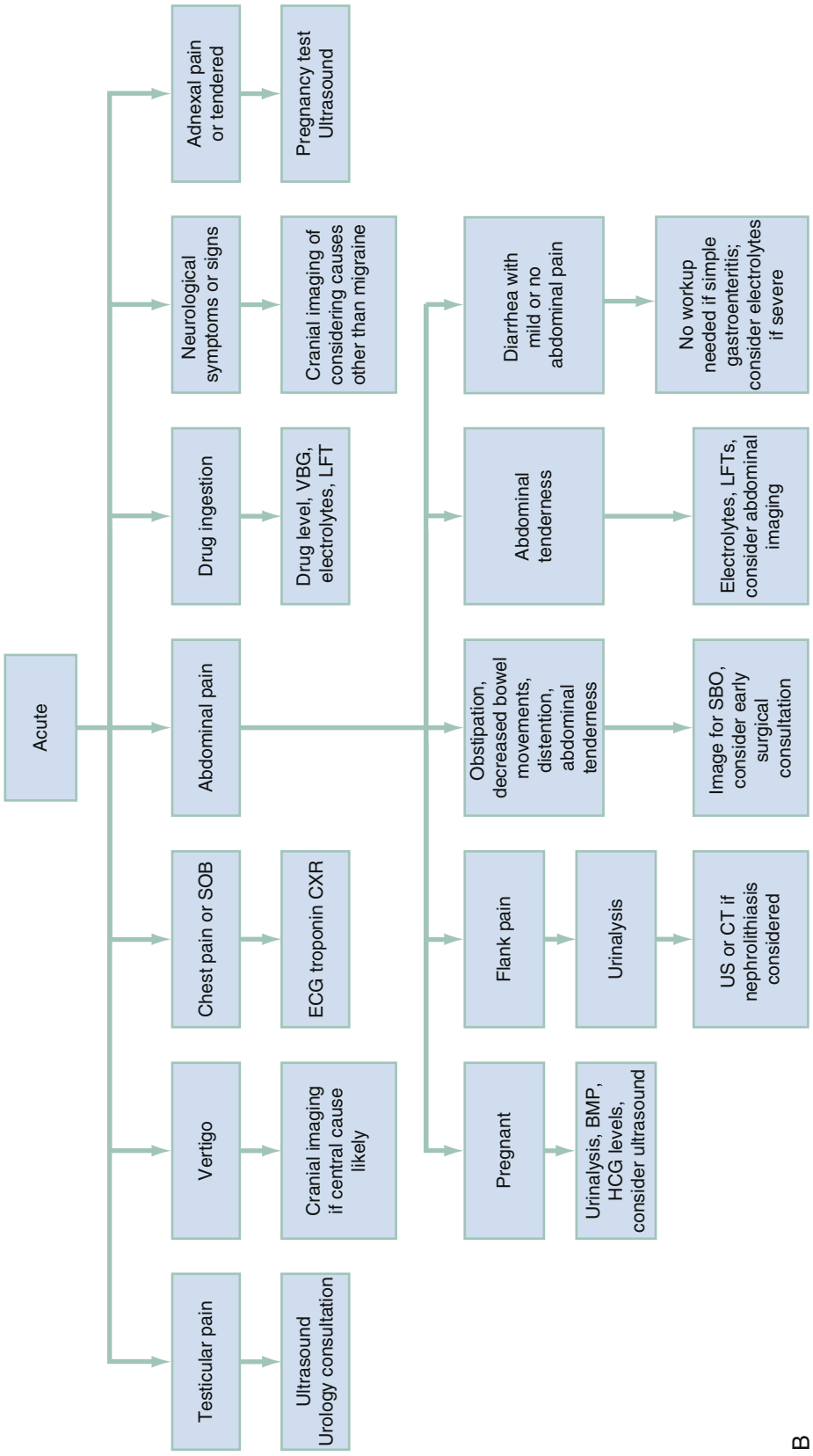

B

Fig. 25.3 cont'd.

Metoclopramide (Reglan) is another first-line agent for use in the ED as a general-purpose antiemetic. As a prokinetic agent, it is useful in patients with gastroparesis and other dysmotility syndromes. The initial dose of metoclopramide is 10 to 20 mg IV or intramuscular (IM).

The phenothiazines, prochlorperazine (Compazine, Stemetil) and promethazine (Phenergan), have historically been first-line agents and are still widely used as general-purpose antiemetics. Although both agents are sedating, promethazine is more sedating and is associated with more extrapyramidal effects. Due to increased side effects, these medications are considered third-line in the ED.

The antipsychotic medication, droperidol, is also considered useful in the treatment of nausea and vomiting. Droperidol had generally fallen out of favor due to the FDA black box warning regarding QT prolongation. Of note, none of the adverse events reviewed by the FDA were for the typical antiemetic doses of less than 2.5 mg. An ECG should be performed before administration to check for QT prolongation. A dose of 1.25 mg IV is sufficient in most patients. The dose may be repeated in 60 minutes if needed. Haloperidol, which is structurally similar to droperidol, may have similar antiemetic effects but has not been formally studied in patients with undifferentiated vomiting. It has no FDA black box warning and thus presents an alternative to droperidol, though similar precautions regarding QT prolongation remain.

Ondansetron 4 mg IV is an excellent first-line choice for patients with undifferentiated nausea and vomiting. It is inexpensive and generally well tolerated. IV crystalloid should also be given if the vomiting is severe. If needed, a repeat 4-mg IV dose can be given in 15 to 30 minutes. If there is an inadequate response, then metoclopramide 10 mg IV should be given, with a repeat dose of metoclopramide after 30 minutes, if needed. An inadequate response to these antiemetics should prompt the clinician to consider the possibility of an underlying mechanical GI obstruction.

If ondansetron and metoclopramide have not been effective and a mechanical obstruction is unlikely, consider using droperidol or haloperidol in a patient at a low risk of adverse effects. Begin with droperidol 1.25 mg IV or haloperidol 5 mg IV, with repeated dosing after 30 minutes, if needed.

If droperidol or haloperidol is not considered safe, then the next drug to consider is prochlorperazine 10 mg IV. If sedation is desired, promethazine may be given prior to trying prochlorperazine. For most patients, begin with promethazine 12.5 mg IM or IV, which may be repeated in 30 minutes if tolerated. If IV promethazine is used, it should be diluted in 10 to 20 mL 0.9% NaCl and administered over 10 to 15 minutes. Promethazine extravasation may cause severe tissue injury; thus, deep IM injection is preferred to the IV route. If the IV route is desired, then the IV should be confirmed to be patent and functioning appropriately prior to administration. In patients who may not tolerate sedation, such as elders, those with underlying respiratory diseases, or those using other sedating medications, begin at 6.25 mg IV or IM, then incrementally increase the dose as tolerated. Dimenhydrinate may be used instead of promethazine, but do not use them together due to their sedating effects.

For patients who remain highly symptomatic following repeated or escalating antiemetic medications, consider observation or hospitalization for continued management and evaluation for the etiology of the vomiting.

TABLE 25.6 Potential Sequelae of Vomiting

Sequelae	Etiology
Hypovolemia	Loss of water and sodium ions in vomitus
Metabolic alkalosis	Loss of hydrogen ions in vomitus
Hypokalemia	Loss of potassium in vomitus
Mallory-Weiss tears	Forceful retching or vomiting causing a 1-cm to 4-cm tear in the mucosa and submucosa; the cause of 3% of deaths from upper GI bleeds
Boerhaave syndrome	Perforation of the esophagus due to increased intraesophageal pressure during forceful retching or vomiting There is free passage of esophageal contents into the mediastinum, causing a chemical mediastinitis, leading to superinfection, sepsis, multiorgan failure, and death It is a surgical emergency The mortality rate is 50% if surgical repair is not performed within 24 h
Aspiration pneumonitis and pneumonia	A concern in patients with baseline poor mental status and pulmonary findings after an episode of vomiting

GI, Gastrointestinal.

TABLE 25.7 Commonly Used Medications for the Treatment of Nausea and Vomiting

Medication	Class	Site of Antiemetic Action	Dosage	Adverse Effects
Ondansetron (Zofran)	Serotonin antagonist	5-HT_3 receptor at CTZ and vagus nerve terminal in GIT	*Adult:* Usual: 4 to 8 mg IV/PO single dose, may go up to 16	May cause headache, dizziness, and musculoskeletal pain. Questionable teratogenic effects, discuss risks and benefits of this or any medication in pregnancy.
Metoclopramide (Reglan)	Dopamine and serotonin antagonist	D2 and 5-HT_3 receptors in CTZ. D2 in stomach and LES	*Adult:* 10 to 20 mg IM or IV, may repeat every 6 h	May cause dystonic reactions, tardive dyskinesia (black box warning), neuroleptic malignant syndrome, restlessness, drowsiness, diarrhea.
Prochlorperazine (Compazine)	Dopamine antagonist	D1 and D2 receptor in CTZ	*Adult:* 5 to 10 mg IM or PO; 2.5 to 10 mg IV every 4 h as needed; 25 mg by rectum every 12 h as needed	May cause lethargy, hypotension, extrapyramidal effects, dystonic reactions, sedation, and feelings of restlessness. Rarely neuroleptic malignant syndrome, blood dyscrasias, and cholestasis.
Promethazine (Phenergan)	Antihistamine	H1 receptor in CTZ, minimal D2	*Adult:* 12.5 to 25 mg IV, IM, PO, or by rectum every 4 h as needed	Extravasation may cause severe tissue injury (black box warning). May cause sedation, dry mouth, dizziness, blurred vision.
Dimenhydrinate (Dramamine, Gravol)	Antihistamine	H1 receptor in GIT and CTZ	25–50 mg IV, IM, or PO every 6 h as needed	Drowsiness, light-headedness.

CTZ, Chemoreceptor trigger zone; *GIT,* gastrointestinal tract; *IM,* intramuscularly; *IV,* intravenously; *LES,* lower esophageal sphincter; *PO,* per os (by mouth).

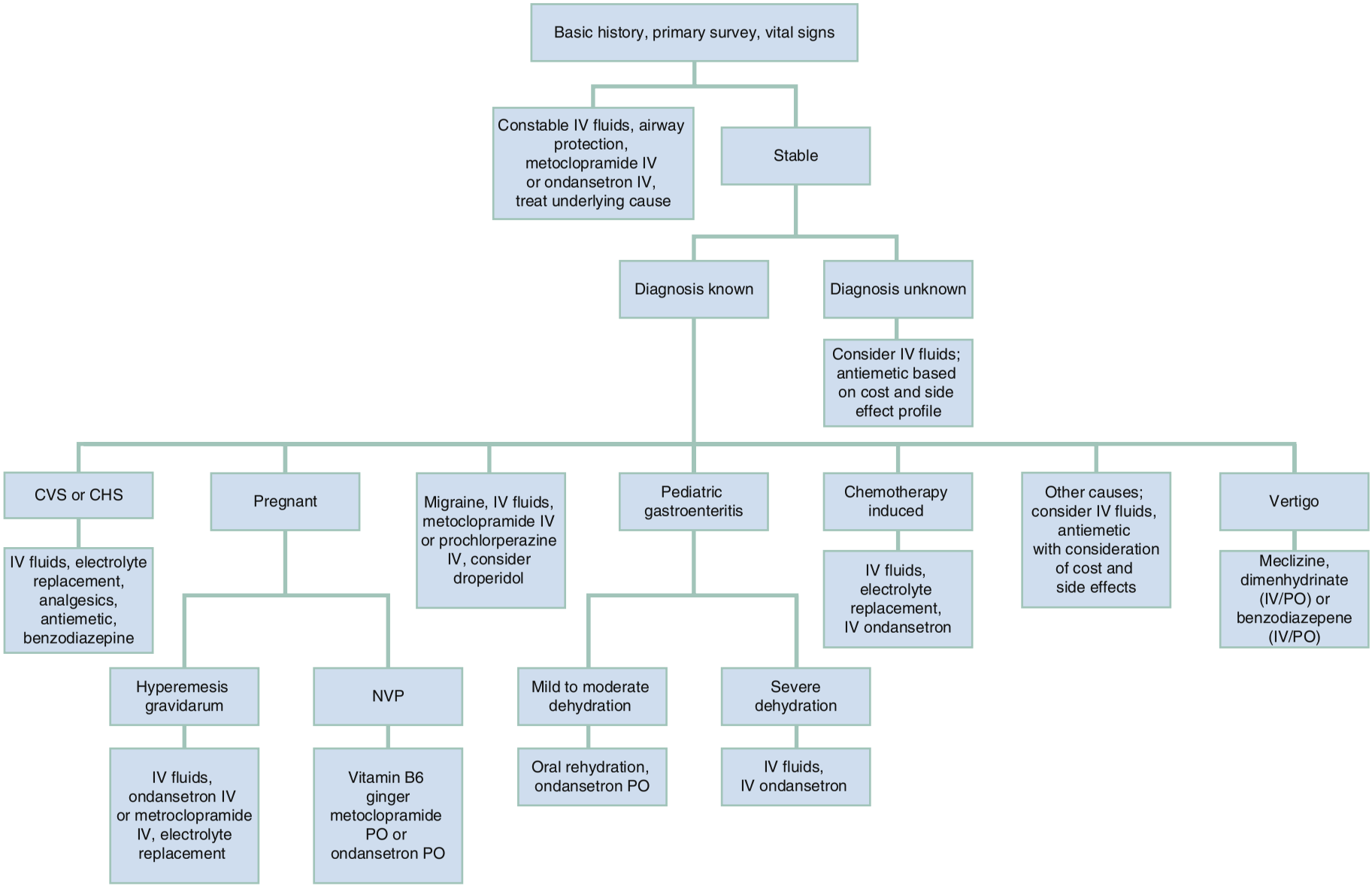

Fig. 25.4 Management Algorithm for the Patient with Nausea and Vomiting. *CHS,* cannabinoid hyperemesis syndrome; *CVS,* cyclical vomiting syndrome; *IV,* intravenous; *NVP,* nausea and vomiting of pregnancy; *PO, per os* (by mouth).

Pediatrics

Acute gastroenteritis is the most common cause of vomiting in the pediatric population (0.15 mg/kg IV or PO). Ondansetron is the first-line agent in children and has the most robust evidence. A 2016 meta-analysis found that ondansetron compared to placebo improved cessation of vomiting after 1 hour while reducing the failure of oral rehydration, the need for IV hydration, and hospitalization rate.[8] Several recent studies have shown the superiority of ondansetron as compared to domperidone or placebo.[9] Of note, all studies that showed benefit with administration of ondansetron were in children who had at least mild dehydration. A randomized control trial on pediatric patients with no dehydration showed no benefit to ondansetron over placebo.[10] All parents received education on appropriate methods of oral rehydration, so it is possible that in these low-risk children, rehydration alone adequately treats the vomiting. Ondansetron is available as an oral dissolve tablet (ODT) or oral solution. The ODT formulation may be superior to the oral solution; however, the evidence for this is weak.[11]

A recent study demonstrated the effectiveness of prochlorperazine in pediatric patients with acute gastroenteritis. A dose of 0.1 to 0.2 mg/kg IV or PO decreased the intensity of vomiting by 88% at 1 hour and 92% at 3 hours.[12] However, due to the relatively high incidence of adverse events (akathisia in 4% to 9% of patients), we recommend that prochlorperazine remain a second-line agent.[13] It is not recommended for children younger than 2 years. For older children, dose should not exceed 7.5 mg daily for patients <14 kg and 10 mg for patients >14 kg.

Special Situations

Opioid-Induced Vomiting

Antiemetic medications do not reduce the incidence of nausea and vomiting associated with the administration of opioid analgesics. Studies have demonstrated that the incidence of nausea and vomiting related to opioid administration is low, and these medications have little efficacy in preventing nausea and vomiting associated with opioids.

Headache

Patients with nausea or vomiting associated with a headache should be given metoclopramide as the first-line agent. Metoclopramide will treat the headache as well as nausea and vomiting. Ondansetron may cause headaches, and therefore is not a preferred first-line agent. Prochlorperazine is a useful second-line agent that is also effective in the treatment of headaches. Droperidol, which also treats headaches and GI symptoms, should be considered if the first two agents fail.

Pregnancy

Many pharmacologic and non-pharmacologic agents have been evaluated in the treatment of nausea and vomiting of pregnancy and hyperemesis gravidarum. A Cochrane review concluded that there was insufficient high-quality evidence to recommend one agent over another.[14] Agents that have shown to be more effective when compared to placebo include ginger, vitamin B6 (pyridoxine), vitamin B6 combination products (such as doxylamine with pyridoxine), ondansetron, phenothiazines, and metoclopramide.[15] A recent meta-analysis on the teratogenic effects of ondansetron showed no conclusive evidence for teratogenicity; however, sensitivity analyses showed a statistically significant increase in cardiac anomalies and cleft palate among fetuses exposed to ondansetron. Overall, the number of affected patients was meager.[16] Metoclopramide and phenothiazine do not have teratogenic effects.[17]

Pregnant patients presenting to the ED with nausea and vomiting may be unable to tolerate oral medication. First-line IV agents include metoclopramide, prochlorperazine, and dimenhydrinate (where available). Metoclopramide is preferred due to limited sedation. Should a first-line agent fail, then ondansetron should be offered. As with any medication in pregnancy, the risks should be discussed with the patient. The benefits frequently outweigh the risks of dehydration from continued vomiting. If these agents do not control the patient's symptoms, then observation or admission should be considered for continued management. Hospitalized patients are started on methylprednisolone 16 mg q8h IV continued for up to 3 days.[17] Methylprednisolone has been shown to decrease hospital readmission.[18]

Chemotherapy

Chemotherapy-induced nausea and vomiting may occur acutely (within the first 24 hours) or delayed (after 24 hours). Ondansetron is the first-line agent, given as repeated doses. Start with 4 mg IV and repeat every 30 minutes up to 16 mg IV. Ondansetron is effective for acute vomiting but is not useful beyond 24 hours. Palonosetron, a second-generation 5-HT_3 antagonist, decreases vomiting after 24 hours and should be given if available.[19] If dexamethasone was not given before chemotherapy then 10 mg IV may be added. Additionally, olanzapine 10 mg orally for 3 days has shown benefit in a randomized control trial.[20] It can be given intramuscularly for patients unable to tolerate oral medications.

Cyclical Vomiting Syndrome and Cannabinoid Hyperemesis Syndrome

Patients with CVS may be difficult to manage. They should receive IV hydration and may require high doses of antiemetic medications, none of which have been deemed superior to others for CVS. Benzodiazepines are recommended as inducing sleep often terminates the episode, especially if antiemetic therapy fails to abort the episode, and admission is considered.

CHS is likely a variant of CVS, and they are managed similarly.[2] Data on ED management of CHS stems from case reports and case series. Combinations of various first-line antiemetics such as ondansetron, metoclopramide, and prochlorperazine are frequently utilized, though none of these medications appears to be effective when given as a single agent. Benzodiazepines and haloperidol given IV have successfully terminated acute episodes. Capsaicin cream applied to the stomach is reported to be helpful in case series. The heating effect of the cream activates receptors that mediate vomiting in the CNS. This is also the purported mechanism for hot showers as a treatment for CHS. While patients with CHS often have severe abdominal pain, opioids should be used with caution as they may worsen vomiting and lead to addiction. Tricyclic antidepressants are used for long-term control of CVS and can be considered upon ED discharge in a reliable patient with close follow-up.

Patients with known or suspected CHS are usually dehydrated, so IV crystalloid fluids, 1 to 2 L, should be given. If the patient has responded well to a medication or combination of medications on previous visits, then those should be administered. Otherwise, it is reasonable to start with ondansetron 4 to 8 mg IV due to its low side effect profile. If there is no relief in 15 to 30 minutes, then a second-line agent should be given. Lorazepam 2 mg IV or haloperidol 5 mg IV can be given along with topical capsaicin cream placed topically over the periumbilical region. The patient may initially note a burning sensation or skin irritation, but both tend to be self-limited. If haloperidol is chosen, an ECG should be obtained prior to the administration to assess the QTc. If there is no relief with the haloperidol or lorazepam, then the other agent should be given. The capsaicin cream can be repeated every 4 hours. If additional agents are needed, then diphenhydramine, metoclopramide, prochlorperazine, and promethazine can be added. Adverse events such as QTc prolongation, extrapyramidal side effects, and sedation should be considered when choosing the combination of antiemetics. Patients who are successfully treated should be instructed to stop using marijuana.[21–23]

Vertigo

Antihistamines are useful in nausea and vomiting associated with motion sickness and vertigo. Agents such as dimenhydrinate (Gravol, Dramamine) and meclizine (Antivert) directly inhibit vestibular stimulation and vestibular-cerebellar pathways. Antihistamines have some role as general antiemetics but are better used in the prevention of motion sickness. The most common side effects of antihistamines are drowsiness, blurred vision, dry mouth, and hypotension. Benzodiazepines are effective as second-line agents. If vertigo is due to benign positional vertigo, the Epley maneuver can be attempted.

Gastroparesis

Gastroparesis is caused by impaired mobility of the stomach and most commonly associated with diabetes. Patients present with severe abdominal pain, nausea, and vomiting. Metoclopramide is the first-line agent due to its promotility effect.[24] Haloperidol has shown benefit in small studies and should be given in patients with refractory symptoms without contraindications.[25,26]

DISPOSITION

Hospital observation or admission is appropriate when the patient has a significant underlying disease, responds poorly to fluid or antiemetic therapy, or continues to experience uncontrolled emesis refractory to medication. Patients in whom the underlying diagnosis remains unclear are still often able to be safely discharged from the ED. Discharge may be considered if no serious underlying illness is identified, response to fluid and antiemetic therapy is adequate, the patient is able to tolerate clear liquids, and the prospects for follow-up are favorable.

Close follow-up often is advisable, preferably with the patient's primary care physician, in 24 to 48 hours. At discharge, the patient is prescribed medications as needed and is advised to restart oral intake with small feedings of a liquid diet, gradually returning to a regular diet. Instructions are given to return to the ED if there is a recurrence, change, or deterioration in symptoms.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 25: QUESTIONS AND ANSWERS

1. **A** 50-year-old male patient presents with a complaint of vomiting. He states the pancakes he ate 12 hours ago for breakfast came out undigested. He admits to several similar episodes in preceding weeks. He is otherwise asymptomatic and has normal vital signs. His physical examination is normal. Which of the following conditions is most likely?

a. Constipation
b. Gastric outlet obstruction
c. Hepatitis
d. Increased intracranial pressure

Answer: b. Vomiting intact food eaten over 12 hours earlier is considered pathognomonic for gastric outlet obstruction. None of the other choices have this as a feature.

2. Antihistamines would most effectively control the nausea and vomiting caused by which of the following conditions?

a. Chemotherapy administration b. Gastritis
c. Gastroparesis
d. Labyrinthitis

Answer: d. Antihistamines are particularly useful in nausea and vomiting associated with labyrinthitis, motion sickness, and vestibular disorders by directly inhibiting vestibular stimulation and vestibular-cerebellar pathways. The anticholinergic effect may also contribute to their effectiveness in vertigo and motion sickness.

3. Which of the following is the most effective for the treatment of cannabinoid hyperemesis syndrome?

a. Capsaicin cream
b. Cessation of marijuana use
c. Haloperidol
d. Lorazepam

Answer: b. Cessation of marijuana use has been demonstrated to decrease syndrome recurrence. The other choices are frequently utilized in the acute treatment of cannabinoid hyperemesis syndrome, and have only been described in case reports or series.

4. **A** 28-year-old female presents to the emergency department with severe vomiting. She is 7 weeks pregnant. She has experienced nausea during this pregnancy which she had controlled with oral ginger and a pyridoxine/doxylamine combination pill, but for the last 3 days she has been unable to tolerate anything by mouth. Her electrolytes and renal function are normal. Bedside ultrasound reveals a single live intrauterine pregnancy. Her urinalysis reveals large ketones. In addition to intravenous fluids, which of the following medications should be selected as the first line intravenous antiemetic agent?

a. Dexamethasone
b. Haloperidol
c. Metoclopramide
d. Ondansetron

Answer: c. Metoclopramide is a first-line agent due to its safety for the developing fetus. Ondansetron should be reserved for second line as there is some suggestion of the capacity for fetal harm. Olanzapine is indicated for chemotherapy-associated vomiting and haloperidol is best used for gastroparesis or cannabinoid hyperemesis syndrome. Dexamethasone is reserved for patients who fail first- and second-line therapies.

5. What is the most common cause of nausea and vomiting in the pediatric population?
a. Acute gastroenteritis
b. Drug side effects
c. Intussusception
d. Motion sickness

Answer: a. In pediatrics, acute gastroenteritis is the most common cause of vomiting. Studies on management of vomiting in this population focus on children with this condition.

26

Gastrointestinal Bleeding

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KEY CONCEPTS

- Routine placement of a nasogastric tube in patients with suspected upper gastrointestinal bleeding (UGIB) is not recommended, because this procedure fails to reliably provide useful data to guide management and is associated with unnecessary patient discomfort and potential complications.
- Patients older than 35 years with UGIB should have an electrocardiogram (ECG) performed early in their evaluation, because patients with UGIB and coronary disease (including occult coronary disease) may develop an acute coronary syndrome that presents with atypical symptoms, such as nausea and abdominal discomfort.
- A blood urea nitrogen (BUN) to creatinine (Cr) ratio of greater than 35 is 90% specific for UGIB. However, the BUN:Cr ratio is poorly sensitive and cannot be used to rule out UGIB.
- Patients with exsanguinating hemorrhage should receive an emergent transfusion of untyped packed red blood cells. For stable patients without known coronary artery disease, transfusion should be initiated when the hemoglobin level is less than 8 g/dL.
- Standard pharmacologic therapy for UGIB includes intravenous (IV) proton pump inhibitors and prokinetic agents. Patients with cirrhosis and suspected esophageal varices should receive octreotide and antibiotics.
- Based on available evidence, we do not recommend the routine use of tranexamic acid for patients with UGIB.
- Platelet transfusion is not indicated for patients on antiplatelet medications unless the platelet count is <50,000 per μL.
- Empirical administration of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) to patients with cirrhosis or anticoagulant use is not indicated.
- Stable patients with lower gastrointestinal bleeding (LGIB) who can tolerate bowel preparation are best managed through urgent gastroenterology consultation for colonoscopy, while unstable patients should be seen by an interventional radiologist for possible selective embolization.

FOUNDATIONS

Acute gastrointestinal (GI) bleeding is a potentially life-threatening condition that requires prompt recognition and treatment. Upper GI bleeding (UGIB) usually presents as hematemesis (blood or coffee-ground emesis) or melena (black, tarry stool). Lower GI bleeding (LGIB) most frequently presents as hematochezia (frank blood per rectum or red or maroon-colored stool). Inpatient mortality from UGIB and LGIB is estimated to be 10% and 4%, respectively.[1] The goals for evaluation and management of the patient with possible GI bleeding are to stabilize the patient, confirm that the gut is the origin of the bleeding, determine the likely site and nature of the bleeding, and provide appropriate therapy.

Hospitalizations for GI hemorrhage related to peptic ulcer disease (PUD) decreased by 66% in the United States between 2000 and 2011, attributed mainly to antimicrobial treatment for *Helicobacter pylori*.[2] Nonsteroidal antiinflammatory drug (NSAID) use remains a significant risk factor PUD-associated bleeds, although the use of proton pump inhibitors (PPIs) in vulnerable patients has mitigated the risk of severe NSAID-related hemorrhage.[3,4]

DIAGNOSTIC APPROACH

Differential Considerations

UGIB originates proximal to the ligament of Treitz, which anchors the small bowel at the duodenal-jejunal flexure, and most often presents as coffee-ground or frankly bloody emesis, melanotic stool, or a combination of these. The most common causes are PUD, erosive disease, and esophageal varices (Table 26.1).

Mallory-Weiss tears, ulcers, gastritis, and esophagitis are the most common causes of UGIB in children, although UGIB can also occur after a caustic ingestion. For neonates, coagulopathy or swallowed maternal blood should also be considered.

LGIB originates distal to the ligament of Treitz. Gastroenterologists subdivide LGIB into small intestinal versus colonic or rectal bleeds.[5,6] Bleeding from the small intestine often presents with a prolonged occult blood loss but also can cause melena if GI transit times are long, and makes up a relatively small proportion (approximately 5% to 10%) of all GI bleeds.[7] Such bleeds were previously considered obscure; however, advances in video capsule endoscopy, computed tomography angiography (CTA), and enteroscopy have greatly enhanced the ability to localize small intestinal hemorrhages. Younger patients (<40 years old) with small bowel bleeding often have underlying inflammatory bowel disease, malignancy, or a Meckel diverticulum, whereas older patients generally bleed from angiodysplasia, NSAID-induced ulcers, or malignancy.

Colonic or rectal bleeds often present with hematochezia. Diverticulosis is the most common cause of bleeding originating from the large bowel, followed by ischemic colitis, postpolypectomy bleeds, hemorrhoids, and malignancy (see Table 26.1).[8]

Common causes of pediatric LGIB include anal fissures, Meckel diverticulum, allergic colitis, enteric infections, and polyps. Necrotizing enterocolitis is a consideration in neonates.

Patients presenting with an apparent GI bleed should be evaluated for non-GI sources. Epistaxis can mimic or cause hematemesis, and vaginal bleeding can be mistaken for hematochezia. Some foods (e.g., beets) and medications (e.g., cefdinir) can discolor stools to appear red and bismuth (e.g., in Pepto-Bismol), or iron use can turn the stool black.

Pivotal Findings

Symptoms

UGIB usually presents as hematemesis (either bright red blood or coffee-ground emesis) or melena, whereas LGIB generally presents

TABLE 26.1 Common Causes of Gastrointestinal Bleeding in Adults and Children

Location	Adults	Children
Upper gastrointestinal	Peptic ulcer disease Erosive disease Esophageal and gastric varices Esophagitis Mallory-Weiss tears Malignancy	Mallory-Weiss tears Gastritis Esophagitis Foreign bodies Caustic ingestion Swallowed maternal blood (neonates) Coagulopathies (neonates)
Lower gastrointestinal	Diverticulosis Hemorrhoids Colitis (inflammatory, infectious, ischemic) Malignancy Postpolypectomy bleeding	Anorectal fissures Meckel diverticulum Allergic colitis Infectious colitis Polyps Angiodysplasia

with hematochezia but can present with melena if the origin is proximal in the small bowel. However, the character of stools is not entirely specific to the location of the hemorrhage. For example, small bowel or colonic bleeding with slow transit times can present with melena. Likewise, hematochezia is not limited to LGIB. It can be seen with a brisk UGIB, and upper GI origin should be considered in a hemodynamically unstable patient with hematochezia.

For patients vomiting blood, the character of the emesis does not reliably indicate the severity of hemorrhage. Bloody and coffee-ground emesis have similar rates of shock, anemia, and mortality.[9] Clinical indicators of shock are more reliable as a gauge of bleeding severity than is the color of the emesis.

Associated symptoms and the context of bleeding may provide important clues. Epigastric pain may indicate PUD. Hematemesis that occurs after vomiting or retching is seen with esophageal tears. Unexplained weight loss is suggestive of malignancy. Constipation or painful bowel movements may precede bleeding from hemorrhoids or an anal fissure, respectively. A recent colonoscopy may indicate postpolypectomy or biopsy bleeding.

Organ systems that may be impaired by significant blood loss should be assessed. Symptoms indicative of cerebral hypoperfusion, such as lightheadedness, are predictive of more severe hemorrhage.[10] Susceptible patients with significant blood loss may develop acute coronary syndrome (ACS).[11] Patients with significant blood loss should be queried for a history of coronary disease, but typical symptoms of ACS, such as chest pain or shortness of breath, may not be present in UGIB patients who instead may develop an ACS with atypical symptoms, such as nausea and abdominal discomfort.

Signs

Patients with acute GI bleeding should be assessed for signs of shock, which increases risk for death.[12] Tachycardia and hypotension are predictive of a severe bleed.[13] A shock index (heart rate divided by systolic blood pressure) can be used to guide resuscitation (see empiric treatment section later).[14]

On physical examination, patients with PUD or severe gastritis may have tenderness in the left upper quadrant. The presence of ascites may indicate portal hypertension, increasing the likelihood of esophageal varices. In such cases, rectal examination may identify varices or dense collateral veins around the anus and rectum. Significant, diffuse abdominal tenderness may indicate GI perforation or bowel ischemia. A digital rectal exam can help in elucidating the type or severity of bleeding. For example, hematochezia suggests either LGIB or brisk UGIB, whereas melena usually indicates an upper GI source. Hemorrhoids or anal fissures may be apparent on rectal exam. Bleeds from fissures are rarely severe and often associated with discomfort with bowel movements.

Ancillary Testing

Laboratory Testing

Laboratory testing is generally focused on risk stratification. Patients with hemodynamic instability require rapid resuscitation before laboratory results become available. Testing helps to guide the management of patients who appear stable on presentation. An initial lactate level greater than 2.5 mmol/L is associated with the development of in-hospital hypotension and increased 30-day mortality.[15] An initial international normalized ratio (INR) greater than 1.5 or a hemoglobin less than 10 g/dL is predictive of increased inpatient mortality and the need for intensive care unit (ICU) admission.[16] An INR is also potentially useful for patients taking antithrombotic medications such as warfarin, because reversal therapy may be required.

Laboratory testing can also provide clues to localize the source of bleeding. Isolated azotemia is often seen in patients with UGIB and results from the degradation of digested blood and reduced blood flow to the kidneys. A blood urea nitrogen to creatinine (BUN:Cr) ratio higher than 35 is 90% specific in identifying UGIB.[17] However, the BUN:Cr ratio is poorly sensitive and not useful in excluding an UGIB.

Blood is typed and screened for stable patients and crossmatched for unstable patients. Use uncrossmatched blood product transfusion for patients with ongoing brisk hemorrhage requiring rapid resuscitation, as detailed in the empiric treatment section later.

Electrocardiogram

The development of concomitant ACS may complicate GI bleeds and present with atypical symptoms. We recommend a screening electrocardiogram (ECG) for patients older than the age of 35 years and those with cardiac risk factors. A history of diabetes, tobacco use, liver cirrhosis, anemia (hemoglobin <9 g/dL), or prior episodes of ACS are risk factors for the development of ACS in patients with UGIB.[11]

Nasogastric Aspirate Testing

We do not recommend the routine placement of a nasogastric tube (NGT) for diagnostic or therapeutic purposes in patients with suspected UGIB. The procedure is both uncomfortable and potentially time-consuming, and it does not reliably predict the source of hemorrhage nor significantly affect patient outcomes.[18] Potential complications from NGT placement include pneumothorax, aspiration, and injury to nasopharyngeal or GI tract structures. Although NGT lavage performed before endoscopy may improve visualization by removing blood and clots, this decision should be left to the endoscopist and performed as part of that procedure.

Imaging

Radiographic imaging is rarely necessary for patients with acute UGIB and may detract from the care of hemodynamically unstable patients who require close monitoring. Bedside ultrasound can confirm the presence of ascites, increasing the likelihood that esophageal varices are the cause of UGIB. The American College of Radiology (ACR) Appropriateness Criteria state that endoscopy is preferred before radiologic imaging for patients with significant UGIB.[19]

In LGIB, emergent colonoscopy can be challenging due to insufficiently prepared bowel and the presence of blood and clots in the GI

lumen, making visualization of the source of bleeding difficult. The ACR recommends angiography as an appropriate alternative in unstable patients with suspected LGIB, because this modality can potentially be used to both localize and embolize bleeding sources.[20]

CTA is capable of detecting bleeding as slow as 0.3 mL/min. It is useful if endoscopic localization of the hemorrhage is not possible or unsuccessful. CTA should be considered, in consultation with gastroenterology, for stable patients with LGIB to assist in identifying the hemorrhage location.[21] This may guide management options, including endoscopy, surgery, or angiography. However, CTA is not optimal in hemodynamically unstable patients with suspected LGIB, because it may delay management. Immediate conventional angiography (with potential embolization) is the preferable strategy for these patients, with CTA reserved for stable patients without immediate access to conventional angiography and suspected LGIB in whom bleeding etiology is crucial prior to the ability to perform a bowel preparation for colonoscopy. For example, patients on anticoagulation (who are at risk for rapidly becoming hemodynamically unstable) may benefit from CTA to assess for bleeding location and etiology.

Nuclear scintigraphy with tagged red blood cell injection can detect bleeding as slow as 0.05 mL/min. However, this study takes up to 18 to 24 hours to obtain results (if delayed image acquisition is needed when initial images do not demonstrate bleeding) and does not explicitly locate the site of hemorrhage, owing to its two-dimensional nature. As such, nuclear scintigraphy is more useful for evaluating patients with possible occult bleeding and is not indicated in the setting of an acute GI bleeding in the emergency department (ED).

DIAGNOSTIC ALGORITHM

Patients with acute UGIB are managed with a stepwise approach aimed at preventing end-organ injury, limiting transfusion complications, averting rebleeding, and managing comorbidities. Fig. 26.1 depicts a combined diagnostic and management algorithm.

The first step is determining if the patient is having a massive GI bleed or not. We suggest defining patients as having a massive bleed if they present with an ongoing active bleed (hematemesis or hematochezia) and a shock index of 0.9 or greater, similar to hemorrhage thresholds for patients following trauma.[22,23] These critically unstable patients with a massive GI bleed require immediate volume resuscitation, which includes placement of at least two large-bore intravenous (IV) catheters, infusion of crystalloids, and transfusion of uncrossmatched blood. Rapid crystalloid infusion should be given as a bolus infusion of 2 L over 30 minutes with a balanced isotonic solution such normal saline or plasmalyte. The primary goal is the maintenance of adequate tissue perfusion, as evidenced by skin perfusion, urine output, and mental status.

The second step is attempting to localize the bleed as either UGIB or LGIB, which is based primarily on the history and physical examination.

The third step is risk stratification, which has important implications for the patient's management and ultimate disposition. High-risk patients have ongoing bleeding requiring interventions such as endoscopy, surgery, or continued blood transfusion. Patients who remain hemodynamically unstable with a shock index of 0.9 or greater despite receiving 2 L of crystalloid infusion and packed red blood cell (PRBC) transfusion require emergent subspecialty consultation (gastroenterology for UGIB; surgery and/or interventional radiology for LGIB) along with ICU admission.

Low-risk patients are generally younger, lack significant comorbidities, are hemodynamically stable, and have a minor source of bleeding identified. Low-risk patients who have access to follow-up care are appropriate for discharge and outpatient management.

Clinical prediction rules can assist in risk stratifying patients with GI bleeding. The Glasgow-Blatchford score (Table 26.2) was developed to assess the likelihood that a patient with UGIB will need an intervention but has also been used to predict the need for admission, blood transfusion, surgery, and mortality. A Glasgow-Blatchford score of 7 or greater is 80.4% sensitive in predicting the need for endoscopic treatment (negative predictive value [NPV] 92.4%), and a score of 5 or greater is 88.7% sensitive in predicting 30-day mortality (NPV 97.9%).[24] International consensus guidelines recommend using a Glasgow-Blatchford score of less than or equal to 1 to identify patients at low risk of rebleeding who may be appropriate for discharge and close outpatient follow-up.[25]

MANAGEMENT

Empiric Treatment

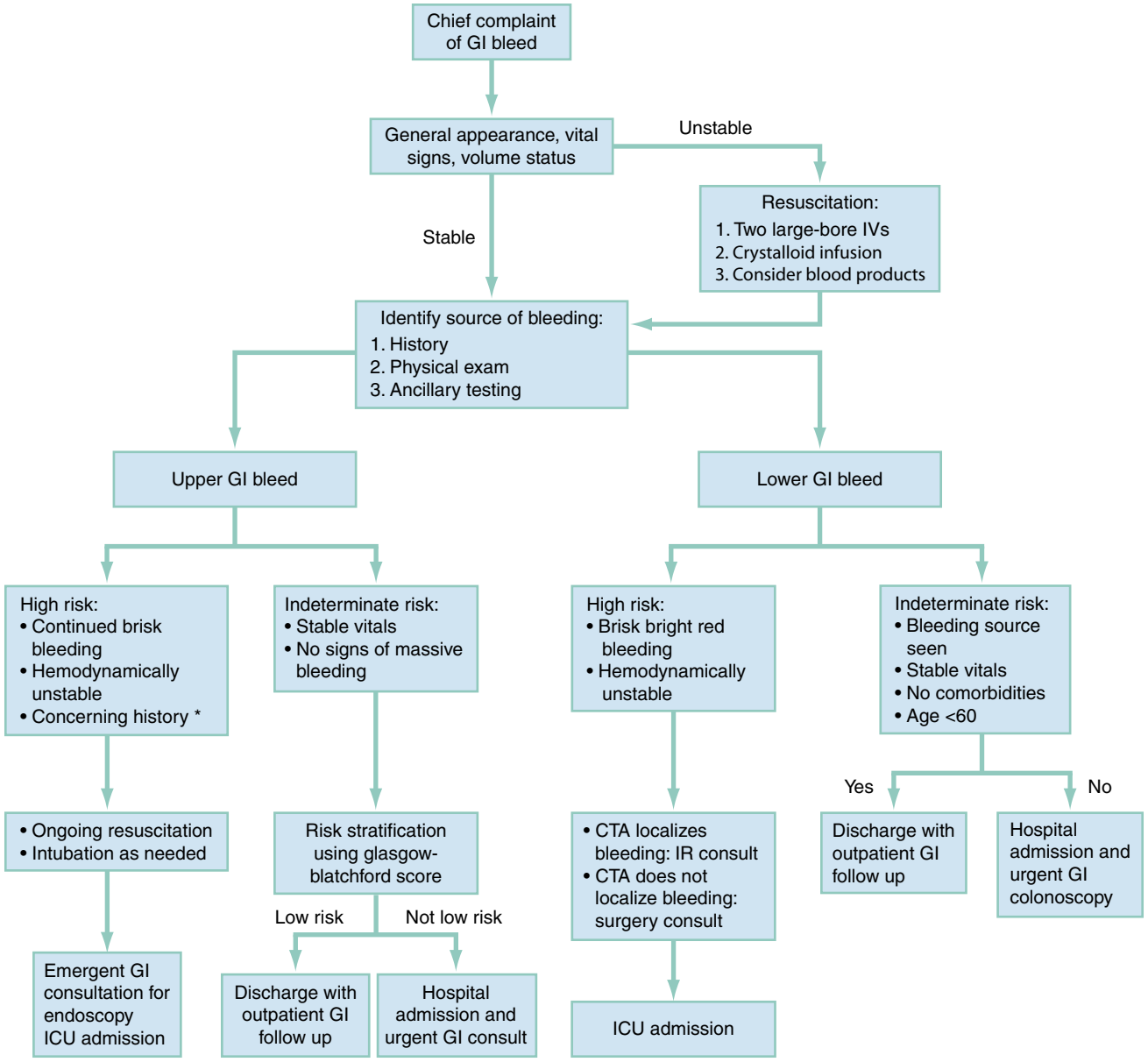
Patients with acute GI bleeding are at risk for rapid deterioration. Empiric treatment involves prompt resuscitation, consideration of blood or platelet transfusion, pharmacologic therapy, and early consultation with gastroenterology, interventional radiology, or surgery. For patients with massive UGIB, early attention to airway protection and intubation may be required.

Resuscitation

We recommend that all patients who present with an acute GI bleed have a minimum of two large bore IV catheters placed. Patients with signs of impending hemodynamic compromise (tachycardia, hypotension, diminished mental status) should have crystalloid fluids rapidly infused, with a goal of delivering 2 L over the first 30 minutes. We further suggest that patients with a massive bleed (active hematemesis or hematochezia with a shock index >0.9) should receive an immediate transfusion of PRBCs. Patients with massive UGIB with uncontrollable hematemesis, respiratory distress, or severe shock limiting their ability to protect the airway or cooperate with treatment should be intubated early in their resuscitative course, unless they respond rapidly to treatment. Optimizing hemodynamic status prior to administering intubation drugs and initiating positive pressure ventilation will mitigate the severe fall in cardiac output that can occur, sometimes leading to circulatory arrest. See Chapter 1 for details pertaining to intubation of the critically ill patient. The need for intubation also correlates with overall worse outcomes. One study found significantly higher rates of unexpected cardiopulmonary events in intubated patients with UGIBs compared with nonintubated patients (20% vs. 6%, $P = .008$) within 48 hours of endoscopy.[26]

Blood Product Transfusion

Rapid bleeding can result in significant loss of oxygen-binding capacity leading to organ ischemia, so patients with exsanguinating hemorrhage should receive an emergent transfusion of untyped PRBCs. Early use of blood products for resuscitation is explained earlier. Stable patients require a more thoughtful transfusion strategy. Although the optimal threshold for transfusion is not clearly established, stable patients with an UGIB without known coronary artery disease (CAD) should receive transfusion of red blood cells to restore their hemoglobin to at least 8 g/dL.[25] A higher hemoglobin target is appropriate for patients with known CAD who are at increased risk of adverse outcomes from anemia. International consensus guidelines do not recommend a specific cutoff, advocating instead to tailor targets based on the severity of both the patient's cardiovascular disease and UGIB.[25] However, we recommend transfusion to a minimum hemoglobin greater than 9 g/dL for patients with known or symptomatic CAD or to the level necessary to resolve cardiac ischemia.



* Concerning history includes:
- Estimated blood loss >500 mL as suggested by symptoms of hypovolemia: dizziness, lightheadedness, syncope, confusion, and weakness
- History of previous abdominal vascular surgeries
- Use of anti-coagulants
- Initial lactate >4
- Hemoglobin <10 or decrease >1 from baseline

Fig. 26.1 Diagnostic and management algorithm for acute gastrointestinal bleeding. *GI,* Gastrointestinal; *ICU,* intensive care unit; *IV,* intravenous; *CTA,* computed tomography angiogram; *IR,* interventional radiology

A systematic review of five randomized controlled trials found that a restrictive transfusion strategy using a hemoglobin threshold of 7 to 8 g/dL in patients with acute UGIB was associated with a lower risk of all-cause mortality and overall rebleeding.[27] For patients with suspected portal hypertension–related bleeding, transfusion response and hemodynamic parameters are closely monitored because overtransfusion may worsen portal hypertension and increase bleeding. Although there are limited data regarding the optimal hemoglobin target for patients with acute LGIB, we advocate for using the same transfusion threshold as discussed earlier for UGIB.

There is a paucity of data regarding the optimal threshold for platelet transfusion in patients with UGIB. We support the American College of Gastroenterology clinical guidelines, which recommend maintaining a platelet count of greater than 50,000 platelets/μL.[6] Empiric platelet transfusion for patients on antiplatelet medications who are not thrombocytopenic is unlikely to be of benefit and therefore not recommended.[28]

The use of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) in patients with liver disease, anticoagulant use, or otherwise elevated INR level is controversial. In patients requiring massive

TABLE 26.2 Glasgow-Blatchford Score

	Risk Factor	Score
Blood urea nitrogen, mg/dL	≥18.2 to <22.4	2
	≥22.4 to <28.0	3
	≥28.0 to <70.0	4
	≥70.0	6
Hemoglobin (men), g/dL	≥12.0 to <13.0	1
	≥10.0 to <12.0	3
	<10.0	6
Hemoglobin (women), g/dL	≥10.0 to <12.0	1
	<10.0	6
Systolic blood pressure, mm Hg	100–109	1
	90–99	2
	<90	3
Other markers	Pulse ≥100 beats/min	1
	Melena	1
	Syncope	2
	Hepatic disease	2
	Heart failure	2

transfusion (more than 4 units of PRBCs), we recommend a balanced transfusion approach of 1:1:1 PRBC:platelets:FFP. Coagulation studies such as partial thromboplastin time (PTT) or prothrombin time (PT)/INR in patients with liver failure are poorly representative of actual bleeding risk.[29] Empirically correcting an abnormal PTT or PT/INR with FFP or PCC has not been shown to reduce bleeding and may increase bleeding in UGIB by worsening portal hypertension. The administration of FFP and PCC may increase the rate of thrombotic events, so their routine use in patients with liver failure and acute GI bleeding is not recommended unless receiving massive transfusion.

For patients on vitamin K antagonists, such as warfarin, limited data suggest discontinuation of the medication and anticoagulation reversal to a target INR of 1.5 to 2.5. However, given the known benefits of early endoscopy for acute UGIB, endoscopy should generally not be postponed while awaiting correction of coagulopathy. Treatment options for reversal include FFP and PCC. Vitamin K has less of a role in emergent reversal for acute GI bleeding given its comparatively prolonged time to treatment effect, but it should still be administered to prevent rebound coagulopathy and bleeding due to the short duration of effect from PCC and FFP. The administration of vitamin K is a reasonable option for patients with hemodynamically stable GI bleeding. Although FFP rapidly corrects coagulopathies, its administration requires large infusion volumes, potentially limiting its use in patients at risk for volume overload. PCC allows for rapid correction of coagulopathy with lower volume administration. INR, PT, and PTT have less of a role in the management of GI bleeding in patients on direct oral anticoagulants such as dabigatran or factor Xa inhibitors (apixaban, rivaroxaban, edoxaban). Reversal agents may be used in unstable patients. Idarucizumab can be utilized to reverse dabigatran. PCC or coagulation factor Xa [recombinant], inactivated-zhzo may be used to reverse factor Xa inhibitors.

Pharmacologic Therapy

Several medications improve outcomes in patients with an acute GI hemorrhage. PPIs have long been a mainstay in the treatment of acute GI bleeding. Compared with placebo, treatment with a high-dose, continuous PPI infusion has been shown to decrease rebleeding, surgery, and mortality in patients with bleeding ulcers. As a result, treatment with omeprazole 80 mg IV followed by a continuous infusion of 8 mg/h has almost routinely been used. However, a meta-analysis showed intermittent PPI therapy to be equally effective as a continuous infusion in reducing bleeding.[30] We recommend a single dose of IV omeprazole 80 mg as a cost-effective and less time-consuming treatment option. This is followed by subsequent doses of 40 mg every 12 hours.

Splanchnic vasoconstrictors such as somatostatin and octreotide reduce portal hypertension and decrease risks of bleeding and transfusion requirements in patients with variceal bleeding. We recommend octreotide 50 μg IV bolus (or an equivalent agent), followed by 50 μg/h continuous infusion for patients with acute UGIB and known liver disease, variceal bleeding, alcoholism, or abnormal liver function tests.[31] There is no rationale for the routine administration of these agents in patients with presumed nonvariceal bleeding.

Prokinetic agents such as erythromycin administered prior to endoscopy improve visualization, limit the need for repeat esophagogastroduodenoscopy (EGD), decrease blood transfusion requirements, and decrease hospital length of stay for patients with severe or active UGIB.[32] For patients going directly for EGD from the ED, a single dose of erythromycin 250 mg IV should be administered 30 to120 minutes prior to EGD.

Tranexamic acid is an antifibrinolytic agent that improves outcomes in the settings of postpartum hemorrhage and trauma. However, its effectiveness in patients with acute GI bleeding remains uncertain.[33] There are currently insufficient clinical data to recommend the use of tranexamic acid in patients with GI bleeding.

For the specific subset of patients with UGIB and known or suspected cirrhosis, antibiotic prophylaxis is recommended. Antibiotics reduce the rate of bacterial infection and mortality.[34] Fluoroquinolones (e.g., ciprofloxacin 400 mg IV) or a third-generation cephalosporin (e.g., ceftriaxone 1 to 2 g IV) are appropriate prophylactic antibiotics in these patients.

Balloon Tamponade

For rapidly exsanguinating patients with a presumed variceal bleed, the placement of a balloon tamponade device is indicated when endoscopy is not promptly available. Commercially available devices include the Sengstaken-Blakemore tube and the Minnesota tube. There are significant complications associated with the use of these devices, so they should be used only as a temporizing measure for patients with ongoing, life-threatening bleeding.

Definitive Treatment

Patients with an acute GI bleed and hemodynamic instability warrant early consultation. Patients with significant UGIB need consultation with a gastroenterologist for consideration of endoscopy. Patients with stable LGIB who can tolerate proper bowel preparation may benefit from urgent but not emergent gastroenterology consultation for colonoscopy. For patients with a brisk LGIB, we recommend emergent consultation with an interventional radiologist for possible selective embolization. We also recommend simultaneous consultation with surgery. If a source of bleeding is not readily identified with CTA, unstable patients with brisk LGIB may require urgent surgical intervention.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 26: QUESTIONS AND ANSWERS

1. What is the most common cause of upper gastrointestinal (GI) hemorrhage in adults in the United States?
   - **a.** Esophagitis
   - **b.** Gastritis
   - **c.** Liver cirrhosis
   - **d.** Peptic ulcer disease

Answer: d. Despite a decreasing prevalence with the treatment of *Helicobacter pylori,* peptic ulcer disease (PUD) remains the most common cause of upper GI bleeds in adults in the United States.

2. Management of unstable patients with massive upper gastrointestinal bleeding (UGIB) should include which of the following?
   - **a.** Placement of at least two large-bore IVs.
   - **b.** Avoidance of rapid crystalloid infusion in effort to decrease rebleeding rates
   - **c.** Empiric treatment with fresh frozen plasma (FFP)
   - **d.** Routine intubation for airway protection

Answer: a. Initial resuscitation of unstable patients with massive GI bleeding should include placement of two large bore IV catheters and rapid crystalloid infusion with consideration of early blood transfusion. Intubation should be reserved for patients with altered mental status, respiratory distress, or high concern for aspiration. FFP should be given empirically only for patients receiving a massive transfusion protocol or in select patients with coagulopathy.

3. Which of the following statements is true regarding platelet administration for patients with acute gastrointestinal (GI) bleeding?
   - **a.** Patients requiring massive transfusion should receive a balanced transfusion approach of 1:1:1 packed red blood cells (PRBCs):platelets:FFP.
   - **b.** Platelets should be administered to a target level of >100,000 per μL
   - **c.** All patients with GI bleeding on antiplatelet medications such as aspirin should receive an empiric platelet transfusion
   - **d.** Antiplatelet medications do not increase the risk of acute GI bleeding

Answer: a. Despite a high risk of GI bleeding while taking antiplatelet medications, the routine use of platelet transfusion for patients on antiplatelet medications has not been shown to be beneficial. Platelet transfusion should be reserved for patients who are thrombocytopenic <50,000 per μL or those requiring massive transfusion protocol.

4. Elevations in which of the following serum markers in the setting of an acute gastrointestinal bleed is predictive of increased 30-day mortality?
   - **a.** C-reactive protein
   - **b.** Lactate
   - **c.** Serum osmolality
   - **d.** White blood cell count

Answer: b. An initial lactate greater than 2.5 mmol/L is associated with the development of in-hospital hypotension and an increased rate of 30-day mortality.

5. Appropriate pharmacologic therapy in the emergency department for most acute upper gastrointestinal bleeds (UGIB) includes which of the following agents?
   - **a.** Antibiotics
   - **b.** Erythromycin
   - **c.** Proton pump inhibitor (PPI)
   - **d.** Somatostatin

Answer: c. PPIs decrease rebleeding, surgery, and mortality in patients with an acute UGIB from an ulcer. Because peptic ulcer disease is the most common cause of UGIB, it is appropriate to administer PPIs for most acute UGIB.

27

Diarrhea

Michael Nitzberg and Janet Smereck

KEY CONCEPTS

- Hospital-acquired *Clostridioides difficile* and norovirus infection are the most prevalent causes of fatal illness from diarrhea in the United States.
- Key elements of the history in the patient with diarrhea include recent travel, hospitalization or antibiotic use, dietary factors, immunosuppression, fever, and presence of blood in stool.
- Acute diarrhea is most often viral and treated with supportive therapy.
- Fluids and foods with excess sugar, caffeine, or high fat content should be avoided in patients with diarrhea.
- In selected nontoxic patients, loperamide, initial dose of 4 mg by mouth and subsequent doses of 2 mg by mouth after each loose stool (not to exceed 16 mg in 24 hours), is typically safe and effective in providing symptom control.
- Empiric antibiotics are uncommonly indicated in patients well enough to go home. However, they should be considered in patients with fever or bloody diarrhea who are immunocompromised or in travelers diarrhea. Empiric antibiotics are prudent whenever sepsis is suspected.
- Fluoroquinolones (ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg by mouth daily for 3 to 5 days) or azithromycin (500 mg by mouth daily for 3 days) cover the majority of enteric pathogens if empiric antibiotics are required.
- A single dose of azithromycin, 1000 mg by mouth, is sufficient antibiotic treatment for travelers diarrhea.
- First line treatment for *C. difficile* is vancomycin 125 mg by mouth four times daily for 10 days. Second line treatment is fidaxomicin 200 mg by mouth for 10 days.
- The efficacy of probiotics in reducing stool frequency in acute infectious diarrhea is unclear.

FOUNDATIONS

Introduction

Acute diarrheal illness is defined as the passage of three or more liquid or watery stools in a 24-hour period, for a duration of up to 14 days, as per the updated definition by the World Health Organization (WHO).[1,2] The Greek origin of the word "diarrhea," *"to run or flow straight through,"* is descriptive and distinguishes true diarrhea from a patient complaint of producing more frequent but fully formed bowel movements. Hippocrates (450–380 BC) understood that diarrhea was a symptom of a number of diseases, both infectious and noninfectious, and could be caused by faulty food handling as well as acquired from travel or inadequate hygiene practices.

Diarrhea may be characterized as mild, moderate, or severe based on accompanying symptoms, presence of comorbidities, degree of incapacitating dehydration, and subsequent need for hospitalization.[2,3] A careful history may identify precipitating causes. Although most cases of acute diarrhea require only supportive care, a systematic approach to the patient presenting with acute diarrhea will lead to appropriate testing and treatment.

Epidemiology

Diarrheal illness is frequently associated with extremes of age (children younger than the age of 5 and adults older than 65 years) or immunocompromised status, including immune deficiency syndromes or use of immunosuppressant medications. Severe acute diarrhea, defined as an acute diarrheal episode requiring hospital admission, is associated with significant fluid losses and may be life threatening, particularly in young children, elders, or individuals with impaired immunity.[3] Acute human immunodeficiency virus (HIV) infection may present with acute diarrheal illness, due to impaired enteric defenses in intestinal mucosa resulting from lymphocyte depletion. HIV disease with CD4 counts less than 200 is associated with increased risk of both common and opportunistic viral, bacterial, or parasitic diarrheal enteric infections. In addition, all classes of antiretroviral drugs may cause diarrhea, which can affect more than 25% of individuals taking combined antiretroviral therapy.[4]

Diarrheal illness may be acquired through foods consumed (notably raw or undercooked fish, shellfish, meat, eggs and unpasteurized dairy products, or contaminated raw produce in sporadic outbreaks); occupational exposure including health care and recreational water sport settings; antibiotic use in the preceding 8 to 12 weeks; and international travel. Up to 60% of those traveling from developed to developing countries acquire acute diarrhea, with children at particular risk.[5] Diarrhea may also occur in travel between developed countries, presumably due to lack of immunity to local, low-level microbial contamination of food and water with enteric pathogens. Diarrhea associated with seafood consumption deserves special mention because fish and shellfish may be associated with acute diarrheal illness due to infectious agents (viral, bacterial, parasitic) as well as toxic factors resulting in scombroid, ciguatera, and paralytic shellfish poisonings.[6]

Pathophysiology

Diarrhea is a symptom rather than a diagnosis, and considerations regarding the mechanisms and causes of acute diarrhea assist in guiding management. Acute diarrhea, defined as the passage of three or more large-volume liquid stools in a 24-hour period for up to 14 days, should be distinguished from self-reported increase in frequency of formed stools, or severe constipation and fecal impaction with overflow leakage. Descriptions of what actually constitutes "diarrhea" are further defined by several clinical instruments, including the Bristol stool scale and modified Bristol score for children (Table 27.1).[7]

The evaluation and treatment of diarrhea must take into account comorbid conditions such as immunosuppression, as well as postsurgical complications including short gut syndrome, blind loop dysfunction following bariatric procedures, or peptic ulcer surgery. Incontinence of stool in the setting of profuse watery diarrhea is not necessarily indicative of acute neurologic impairment. Diarrhea is a symptom of a number of pathophysiologic entities: *osmotic diarrhea* due to the presence

TABLE 27.1 Summarized Descriptions, Bristol Stool Scales for Adults and Children

Adult Bristol Stool Scale
Type 1 Hard separate "lumps", hard to pass
Type 2 Sausage shaped, formed but hard and lumpy
Type 3 Sausage shaped with fissured surface
Type 4 Sausage shaped with smooth, soft texture
Type 5 Soft separate "lumps" passed easily
Type 6[a] Unformed, "mushy" stool
Type 7[a] Entirely liquid, watery, with no solid pieces

Modified Bristol Stool Scale for Children (ages 8–18 years)
Type 1 Hard separate small "lumps", hard to pass
Type 2 Sausage shaped, formed but hard and lumpy
Type 3 Sausage shaped with smooth, soft texture
Type 4[a] Unformed, "mushy" stool
Type 5[a] Entirely liquid, watery, with no solid pieces

[a]Bristol stool types 6 and 7 for adults, and 4 and 5 for children, when 3 or more passed in a 24-hour period, indicate diarrhea.

of poorly absorbed solutes within the gut, *secretory diarrhea* due to toxin-producing infectious agents, *exudative diarrhea* due to infectious or inflammatory conditions, *motility-related diarrhea* associated with diabetes mellitus or scleroderma as well as prokinetic medications, and *malabsorptive diarrhea* related to infectious agents, lactose intolerance, celiac disease, or pancreatic insufficiency. The term *dysentery* is used to describe infectious diarrhea in which enteropathogens and their toxic metabolites have invaded the intestinal mucosa, resulting in fever, abdominal pain, and visible blood mixed with stools.[8]

DIAGNOSTIC APPROACH

A thorough history should note onset and duration of symptoms; character of stools including estimated volume and presence of blood or purulent mucus; fever; abdominal pain; nausea and vomiting; and ability to maintain oral hydration. Key historical features include foods consumed prior to onset of symptoms, alcohol or substance use, travel history, antibiotic use within the preceding 8 to 12 weeks, ill contacts, medications and dietary supplements, and comorbid conditions such as diabetes mellitus, collagen vascular disease, immune deficiency, malignancies, or transplant status.

Differential Considerations

Broadly, diarrheal illness may be divided into two categories, infectious and noninfectious. In the acute care setting it is not always possible to reliably distinguish infectious from noninfectious causes. Although the etiology may not be precisely identified in the emergency department (ED) and most cases of infectious diarrhea have a self-limited course, some causative agents have specific presentations and may require targeted therapies. Acute diarrhea of infectious etiology is suggested by the presence of fever, abdominal cramps or pain, tenesmus, or presence of blood mixed with the stool.[2,9] A number of pathogens are associated with acute diarrhea; some enterotoxins can produce dangerous volume losses, and enteroinvasive pathogens may lead to septicemia.

Acute infectious diarrhea is associated with numerous viral and bacterial agents as well as some parasitic pathogens (Box 27.1). Viral agents most commonly identified in hospitalized patients with acute diarrhea include norovirus, rotavirus, and adenovirus.[3] Norovirus is frequently implicated in travelers diarrhea and large population-based outbreaks. Vaccination against rotavirus has made this a less common pathogen, particularly in children.[10,11] Gastrointestinal cytomegalovirus is associated with immunosuppression and advanced HIV infection (CD4+ counts less than 50) and can lead to severe hemorrhagic colitis.[4]

BOX 27.1 Common Causative Agents of Acute Infectious Diarrhea

Viral
Cytomegalovirus
Enteric adenovirus
Human immunodeficiency virus (HIV) enteropathy
Norovirus
Rotavirus

Bacterial
Invasive
Campylobacter species
Clostridioides difficile
Enteroinvasive *Escherichia coli*
Salmonella species
Shigella species
Vibrio vulnificus
Yersinia enterocolitica

Toxigenic
Food Poisoning With Preformed Toxins
Bacillus cereus
Staphylococcus aureus

Toxin Formation After Colonization
Shiga toxin–producing *E. coli* 0157:H7 (STEC) [also known as enterohemorrhagic *E. coli* (EHEC) or verocytotoxin-producing *E. coli* (VTEC)]
Enterotoxigenic *E. coli*
Shigella species
Vibrio cholerae

Protozoa
Cryptosporidium
Cyclospora
Entamoeba histolytica
Giardia

Most frequently identified bacterial pathogens include *Campylobacter* spp., *Clostridioides difficile*, various pathogenic *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Yersinia enterocolitica*.[3] *E. coli* O157:H7 is associated with hemolytic uremic syndrome, and enterotoxigenic *E. coli* (ETEC) is implicated in some cases of travelers diarrhea. The overall incidence of *C. difficile* is increasing. Although generally associated with antibiotic use or overnight hospital stay in the preceding 3 months, community-associated *C. difficile* is increasingly identified in patients without traditional risk factors, which may be due to gastric acid–suppressing medications, hypervirulent strains, or improved testing.[12,13] *Campylobacter* and *Yersinia* have been identified in cases of diarrhea with accompanying right lower quadrant pain mimicking appendicitis, presumably due to accompanying mesenteric adenitis.[11]

Vibrio cholera, associated with contaminated water or seafood from tropical and subtropical zones, is associated with secretory enteritis leading to profuse watery diarrhea with large fluid and electrolyte losses and may lead to shock, renal failure, and death. *Vibrio vulnificus*, associated with raw shellfish consumption, has been associated with septicemia and carries a high mortality rate, particularly in patients with liver disease.[6]

Most parasitic infections present as chronic diarrhea. *Giardia lamblia* may lead to acute as well as chronic malabsorptive diarrhea and

BOX 27.2 Selected Causes of Noninfectious Diarrhea

Pharmaceuticals
Antacids (magnesium)
Antimicrobials
Antiretrovirals
Chemotherapeutic agents
Cholinergic agents
Cholinesterase inhibitors
Colchicine
Lactulose
Laxatives/Cathartics
Prostaglandins

Dietetic supplements
Caffeine
Sorbitol
Xylitol

Seafood-Associated Toxins
Ciguatera
Paralytic shellfish poisoning
Scombroid

Plant and herbal preparations
Aloe vera juice
Senna
Pokeweed
Turmeric

Miscellaneous
Pesticides—organophosphates
Opiate withdrawal

Gastrointestinal Pathology
Celiac disease
Irritable bowel syndrome with diarrhea
Lactose intolerance
Malabsorption syndromes
Post vagotomy
Radiation enteritis
Short gut syndrome

Endocrine-Related Conditions
Carcinoid syndrome
Adrenal insufficiency
Diabetic enteropathy
Pancreatic insufficiency

Systemic Illness and Other Causes
Alcoholism
Connective tissue disease/scleroderma
Cystic fibrosis
Runners diarrhea

is associated with contaminated food and unprocessed water, including well water or unchlorinated water consumed by campers and backpackers.[5]

There are numerous noninfectious causes of diarrhea, including foods (osmotically active agents such as sorbitol and xylitol, seafood-associated toxins), pharmaceuticals (including prokinetic agents, laxatives, colchicine, chemotherapeutic agents, antimicrobials, immune checkpoint inhibitors, and all classes of antiretrovirals), and endocrinopathies (Box 27.2). Runners diarrhea has been described as an acute exercise-related diarrhea which may have multiple causes, including transient mesenteric ischemia as well as dietary factors, particularly intake of large quantities of carbohydrates and beverages containing monosaccharides and polysaccharides.[14]

Pivotal Findings

Signs and Symptoms

Initial assessment of the patient with a chief complaint of diarrhea begins with ensuring clinical stability with attention to volume status. Indications of hypovolemia and hypoperfusion include tachycardia, hypotension, dry mucosa, cool extremities, diaphoresis, poor skin turgor, decreased urine output, or mental status changes. Increased respiratory rate or Kussmaul respirations may indicate an associated acid-base disorder. Young, healthy adults and especially children may maintain a normal blood pressure and heart rate even in the setting of severe dehydration. The heart rate in patients taking antiarrhythmic medications or who are reliant on a pacemaker may be an unreliable indicator of volume status. Clinical signs of dehydration in the pediatric patient may include sunken eyes, depression of the fontanel, reduced number of wet diapers, or decrease in energy, alertness, or activity.

The secondary evaluation assesses the patient's overall health condition, including the presence of fever and the potential for an acute abdomen. Focal abdominal pain in the setting of diarrhea may mimic an acute surgical abdomen. Serial abdominal examinations may be helpful. Rectal examination can detect melena, hematochezia, or fecal impaction. Rectal examination may be beneficial for a patient who cannot describe his or her stools and therefore the presence/abscess of gross blood is unclear, or if fecal impaction is considered possible after obtaining the history. Gross blood may be indicative of invasive, infectious diarrhea, although there are other pathologic states that manifest with gastrointestinal bleeding, including inflammatory bowel disease. Parasitic infection, such as *Strongyloides stercoralis,* may be accompanied by histamine-induced changes, such as urticaria or bronchospasm. Systemic findings of jaundice or scleral icterus demonstrate associated liver pathology. In addition, clinical presentations of toxic syndromes (e.g., anticholinergic or sympathomimetic) may include diarrhea.

Ancillary Testing

In many cases of acute diarrhea, laboratory and further diagnostic testing is not necessary. Testing is guided by the clinical severity of the illness, including vital signs alterations, presence of comorbidities, or physical examination findings suggestive of serious intra-abdominal disease or diarrhea related to serious systemic illness. A toxic appearance with fever, moderate-to-severe volume depletion, blood- or mucus-containing stools, frequent voluminous stools, peritoneal findings, or serious comorbidities, especially immune suppression or chronic inflammatory gastrointestinal disease, should prompt consideration of further investigation to guide appropriate therapy.

Blood tests. Leukocytosis has been reported in *C. difficile* infections, although an isolated white blood cell count elevation is not sensitive or specific enough to aid in diagnostic decision making. Eosinophilia may be seen in parasitic infections with an extraintestinal migration phase. Hemoglobin levels may be assessed to screen for anemia secondary to blood loss or hemolytic uremic syndrome in the setting of *E. coli* O157:H7 infection. A basic metabolic panel to check electrolytes and renal function can be useful when moderate to severe hypovolemia is suspected, or if there has been voluminous diarrhea. Liver function tests including aspartate transaminase (AST), alanine transaminase (ALT), and coagulation times may be helpful when there is jaundice or other evidence of liver disease. Other laboratory studies are rarely indicated but may be obtained when there are particular findings on history or physical examination. For example, a lipase level may be helpful if the diarrhea is part of a syndrome that includes epigastric pain and tenderness accompanied by vomiting. An elevated lactate level may aid in identifying and directing therapy in patients with severe dehydration, sepsis, or causes of noninfectious diarrhea (e.g., mesenteric ischemia, gastrointestinal bleeding).

Stool studies. Fecal leukocytes are not sufficiently specific or sensitive as the sole criterion to determine which patients should be treated with antibiotics. Inflammatory diarrhea of varied causes, including bacterial or parasitic infection as well as noninfectious causes, may lead to red or white blood cells visualized on stool examination. A history of gross blood in the stool accompanying acute diarrhea is usually sufficient to guide consideration of antibiotic therapy; a positive stool guaiac should not be used in isolation. The assays for fecal calprotectin and fecal lactoferrin produced by leukocytes are not typically useful in guiding ED patient evaluation, treatment, or disposition.

Testing for specific pathogens. There are multiple tests available to identify the specific pathogen causing a patient's symptoms; however, the results are generally not available until after the ED encounter and thus are unable to assist in guiding initial therapy.

Testing for bacterial infection. Stool cultures are generally not indicated in the ED given their low sensitivity and delayed results. Stool culture panels for pathogenic enteric bacteria generally screen for *Campylobacter*, *Salmonella*, and *Shigella*. If available, polymerase chain reaction (PCR) testing can result in faster diagnosis but does not provide information regarding antibiotic sensitivities. However, bacterial testing is generally indicated for toxic patients being admitted to hospital, immunocompromised patients, or those with high clinical concern for bacterial source of illness (bloody diarrhea, fever). Bacterial testing is also indicated for patients with persistent or chronic diarrhea not previously tested for these pathogens, although this can be deferred for outpatient follow-up.

***Clostridioides difficile* assay.** Testing for *C. difficile* should be considered if the patient is immunocompromised or reports antibiotic use during the preceding 3 months, recent hospitalization, nursing home residence, employment in a health care setting, or significant diarrhea (>5/day) for several days (generally without vomiting). Diarrhea associated with *C. difficile* most commonly occurs during or closely following the completion of the antibiotic course. Cephalosporins, penicillins, fluoroquinolones, and clindamycin are most frequently implicated, but any antibiotic use potentially places a patient at risk for *C. difficile* infection. Quantitative PCR is the assay of choice for diagnosis of *C. difficile* infection. Reports suggest that rates of community-acquired *C. difficile* infection are increasing, even in patients without traditional risk factors.[12]

***Escherichia coli O157:H7* toxin assay (Shiga toxin).** This assay should be considered when there is a known outbreak or if the presentation occurs in an endemic area. It should also be considered for patients with suspected hemolytic uremic syndrome with associated anemia, thrombocytopenia, and renal dysfunction.

Stool examination for ova and parasites. These tests may be useful in patients with chronic diarrhea (*Entamoeba histolytica* and *Cryptosporidium*), patients with a history of travel or recent immigration from developing countries (*Cryptosporidium*, *Giardia*, and *Cyclospora*), or patients with HIV infection or other immunocompromised state (*E. histolytica* and *Giardia*).

***Giardia* antigen assay and serologic testing for amebiasis.** *Giardia* antigen assay and serologic testing for amebiasis should be considered in patients exposed to poor sanitation or those with immune compromise, a history of travel to developing countries, or recent camping with ingestion of stream or spring water.

Radiographic studies. Radiographic studies are not commonly used in the evaluation of acute diarrhea. Plain radiography is rarely indicated. If peritoneal signs are present or abdominal perforation is suspected, abdominal computed tomography (CT) scan with intravenous (IV) contrast is typically the imaging modality of choice. Abdominal CT is also useful in the diagnosis of fistula, mesenteric ischemia, inflammatory bowel disease, or other acute surgical conditions.

Gastrointestinal Referral

Patients with diarrhea concerning for inflammatory bowel disease or other chronic gastrointestinal conditions should be referred to their primary care provider or a gastroenterologist for further diagnostic testing, much of which is beyond the scope of the ED (including endoscopy, biopsy, or other stool studies).

DIAGNOSTIC ALGORITHM

Unlike many presenting symptoms and signs, critical and emergent diagnoses for patients with diarrhea depend much more on the effects of the diarrhea (hypovolemia, renal compromise) and patient comorbidity (immune compromise, advanced age, inflammatory bowel disease) than on the cause (Fig. 27.1).

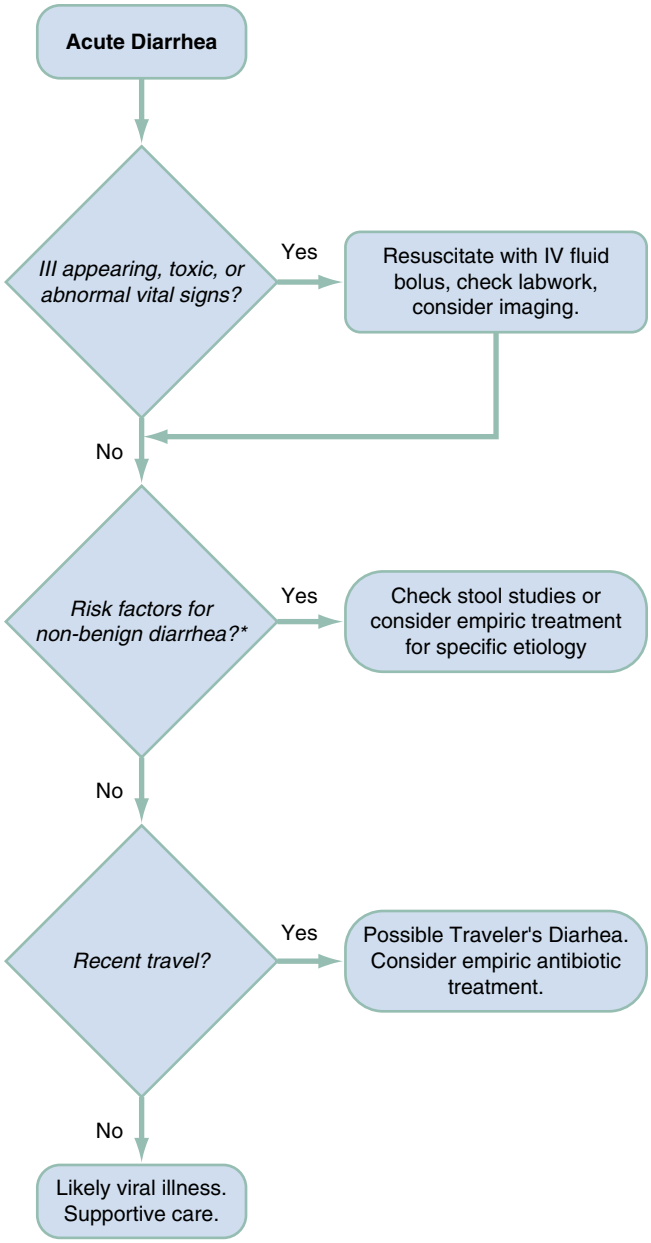


Fig. 27.1 Diagnostic Algorithm. *See Table 27.2.

Critical Diagnoses

Patients with diarrhea accompanied by abnormal vital signs are suspected of having a critical condition and are evaluated for shock. Resuscitation, including IV fluids, is prudent while the underlying etiology of shock is investigated, whether it be hypovolemic, septic, or hemorrhagic. In addition, consideration should be made for possible drug- (e.g., cholinergic poisoning) or food-related toxicity. Laboratory studies may include a creatinine to assess renal status, hemoglobin to assess for gastrointestinal bleeding or hemoconcentration, and a lactate to assess for organ perfusion. An elevated white blood cell count is nonspecific, although it can be associated with *C. difficile* infection, invasive causes of diarrhea, or simply the stress effects of the illness and volume loss. Even viral infectious diarrhea perceived as "self- limited" may result in life-threatening illness in patients presenting with

TABLE 27.2 Factors Increasing Probability of Nonbenign Diarrhea

Factor	Specific Pathogen(s) and Other Considerations
Travel history	Especially foreign travel or to endemic areas of dysenteric disease
Recent hospitalization	*Clostridioides difficile* from antibiotic exposure
Day care attendance	Rotavirus, *Shigella, Giardia*
Nursing home residence	*C. difficile,* medication side effects, tube feedings, ischemic colitis, or fecal impaction with overflow leakage
Wilderness or untreated water exposure	*Giardia* or *Cryptosporidium*
Antibiotic therapy	*C. difficile,* antibiotic-associated diarrhea
Raw shellfish, farm animals or fair livestock, pet reptiles or amphibians, petting zoos	*Salmonella* species, *Escherichia coli* O157:H7, and non-O157 Shiga toxin–producing *E. coli, Vibrio* species
Epidemic of multiple patients within a short time of onset	Norovirus, and less commonly *Campylobacter jejuni, Salmonella* species, or *Cryptosporidium*
Epidemic of severe gastroenteritis traced to eggs, poultry, meat, or dairy products	*C. jejuni*, *Salmonella* species
Abdominal pain, bloody stool, fever, rectal pain, tenesmus	Severe bacterial infections: *Salmonella, Campylobacter, Shigella,* EPEC, *Yersinia* or *Vibrio* species Also consider surgical abdomen, gastrointestinal bleeding, inflammatory bowel disease
Diarrhea (>7–14 days duration)	Protozoa or microsporidia, *C. difficile, Campylobacter,* Shiga toxin–producing *E. coli*
Chronic disease (e.g., cirrhosis, DM)	Complicated course expected with any form of diarrheal illness
Organ transplantation (immunosuppression)	Abnormally severe illness from rotavirus or adenovirus Increased frequency of *Cytomegalovirus* Severe illness from dysenteric diarrhea Spore-forming protozoa or microsporidia
HIV or other immunodeficiency	Severe illness from common bacteria, spore-forming protozoa, or microsporidia Increased frequency of *Cytomegalovirus* or *Mycobacterium avium* complex

DM, Diabetes mellitus; *EPEC,* enteropathogenic *E. coli*; *HIV,* human immunodeficiency virus.

severe dehydration. If vomiting accompanies diarrhea or if the patient appears jaundiced, liver function tests may help delineate other causes of diarrhea, including infectious hepatitis. At particular risk for shock are the elderly, pediatric populations, or the immunocompromised.

Emergent Diagnoses

In patients who have stable vital signs and are nontoxic appearing, it is important to consider risk factors for nonbenign illness (Table 27.2). Most cases of acute diarrhea will resolve on their own without specific medical intervention; however, patients with a history suggestive of a specific nonbenign cause require further investigation. In most well-appearing patients, determining the specific cause of diarrheal illness is not important, because treatment is supportive and the course is expected to be self-limited. In addition to consideration of the etiology of the diarrhea, it is important to assess for secondary complications of diarrhea, such as renal impairment (due to hypovolemia or hemolytic uremic syndrome), electrolyte disturbances, or anemia (see Fig. 27.1).

EMPIRIC MANAGEMENT

Rehydration

Oral rehydration is the treatment choice for mild fluid losses and can be accomplished with sports beverages, commercial rehydration solutions, or a balanced clear liquid diet at home. The WHO has outlined an oral rehydration solution (WHO-ORS) that can be made by dissolving the following in 1 L of clean water: 3.5 g of sodium chloride, 2.9 g of trisodium citrate or 2.5 g of sodium bicarbonate, 1.5 g of potassium chloride, and 20 g of glucose or 40 g of sucrose. In developing countries, 10 mg daily oral zinc supplementation has been shown to decrease the length of symptoms with a greater effect on children appearing chronically malnourished.[15]

The choice of rehydration fluids is dependent on the extent of dehydration and the underlying status of the patient. In otherwise healthy patients with mild dehydration, fluids including sports drinks and diluted fruit juices may be supplemented with soups, broths, or crackers. Diluted fruit juice may be preferred by children and can frequently prevent the need for IV hydration.[16] However, some "clear liquids" may contain excess sugars and insufficient sodium content, resulting in an osmotic diarrhea. Caffeine should be avoided because it increases cyclic adenosine monophosphate levels and may lead to a secretory diarrhea.

Pathogens responsible for acute diarrhea may cause a transient lactase deficiency causing malabsorption and osmotic diarrhea if lactose-containing milk products are subsequently ingested. Patients should be cautioned that, if persistent diarrhea appears to be related to dairy consumption, these products should be avoided for at least 2 weeks. Foods that have high-fat content delay gastric emptying. The BRAT (bananas, rice, apples, toast) diet is often recommended because it is relatively constipating and nonstimulating. Fruit pectin, such as is found in apple peel, was the "pectate" in the older formulation of Kaopectate (kaolinite and pectin), an over-the-counter antidiarrheal product; however, Kaopectate has been reformulated as bismuth subsalicylate. Bananas contain an insoluble fiber which helps to regulate stool consistency and also assists in replenishing potassium which is lost through excessive diarrhea.

Patients who are severely dehydrated should receive IV fluid replacement with normal saline or lactated Ringers solution, which generally is given by bolus (1 to 2 L in adults) followed by infusion at 300 to 500 mL/hour until the patient is well hydrated and passing

normal or dilute urine. Fluid replacement rates are reduced for patients with heart failure. Pediatric patients receive an initial bolus of 20 mL/kg of normal saline, which may be repeated. There is no significant clinical difference between normal saline or lactated Ringers solution, so either may be used in children.[17] In adults, the same conclusion can be extrapolated for low volumes of solution, although direct evidence in this exact clinical scenario is lacking. We generally prefer lactated Ringers solution for patients with diarrhea, because the composition of lactated Ringers solution more resembles the electrolyte composition lost in diarrhea, as compared with normal saline.

Antibiotics

Antibiotic therapy in the ED is often empirical because the specific pathogens causing infectious diarrhea are rarely identified (see Box 27.1). Viral and noninvasive bacterial gastroenteritis are most frequently self-limited, and thus symptomatic therapy and attention to hydration are all that is needed. Empiric antibiotics should be considered for patients who are immunocompromised or demonstrating signs of sepsis. Fluoroquinolones (ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg by mouth daily for 3 to 5 days) or azithromycin (500 mg by mouth daily for 3 days) cover the majority of enteric pathogens. Importantly, guidelines discourage empiric antibiotics for the majority of patients with bloody diarrhea, because their use may increase the risk of developing hemolytic uremic syndrome in patients with Shiga toxin–producing *E. coli*.[15] This is especially pertinent in pediatric patients, in whom the risk of hemolytic uremic syndrome is higher. Empirical antibiotic treatment can reduce the duration of symptoms of travelers diarrhea. A single dose of azithromycin 1000 mg by mouth will effectively reduce time to formed stool in travelers diarrhea.[8] IV antibiotics may be necessary for patients with significant illness or sepsis. Reasonable choices of IV antibiotics include ciprofloxacin 400 mg IV twice daily or ceftriaxone 1–2 gm IV daily.

Although the results of testing for *C. difficile* are unlikely to be available during the patient's visit in the ED, it is reasonable to start empiric treatment with targeted antibiotics if there is a high clinical suspicion. The 2021 guidelines on management of C. difficile infections recommends fidaxomicin (200 mg by mouth twice daily for 10 days) over vancomycin if resources allow, due to decreased episodes of recurrent infection and a narrower spectrum. Vancomycin (125 mg by mouth four times daily for 10 days) is still an acceptable first line option if fidaxomicin is not available. Metronidazole (500 mg by mouth three times daily) is now used only if oral vancomycin or fidaxomicin is not available and is acceptable only for nonsevere disease.[13] Although the initial antibiotic response rates are high, recurrence rates are approximately 35% in weeks 1 through 8; following retreatment, recurrence occurs in 50% to 65% of patients. The high recurrence rate has propelled the employment of a unique microbial replacement therapy, fecal microbiota transplant, in the treatment of patients with recurrent *C. difficile* infections.

Antimotility Agents

Nontoxic patients with acute watery diarrhea often obtain significant relief of symptoms with antimotility agents. In adults, an initial dose of loperamide 4 mg orally with subsequent doses of 2 mg (not to exceed 16 mg in 24 hours) is safe and effective with relief of symptoms. Adding simethicone (60 mg to 125 mg by mouth up to 4 times per day) to loperamide produces a synergistic effect and decreases time to formed stool. Loperamide is also safe and effective for travelers diarrhea when used in combination with antibiotics but can lead to toxic megacolon in patients with severe colonic inflammation.[18] For patients with more severe colitis in which loperamide may lead to significant complications, bismuth subsalicylate (525 mg every 30 mins to 1 hour orally up to maximum 4.2 gm [8 doses] per 24 hour period) is an acceptable alternative for symptomatic relief, although it is slightly less effective. Diphenoxylate with atropine is generally as effective as loperamide but with higher frequency of side effects, and as such is not our recommended choice of agent. In the pediatric population, the use of antimotility agents has been associated with the precipitation of obstruction and toxic megacolon and possibly hemolytic uremic syndrome; therefore it is not recommended. Antimotility agents are also used with caution in any patient at high risk for intestinal obstruction.

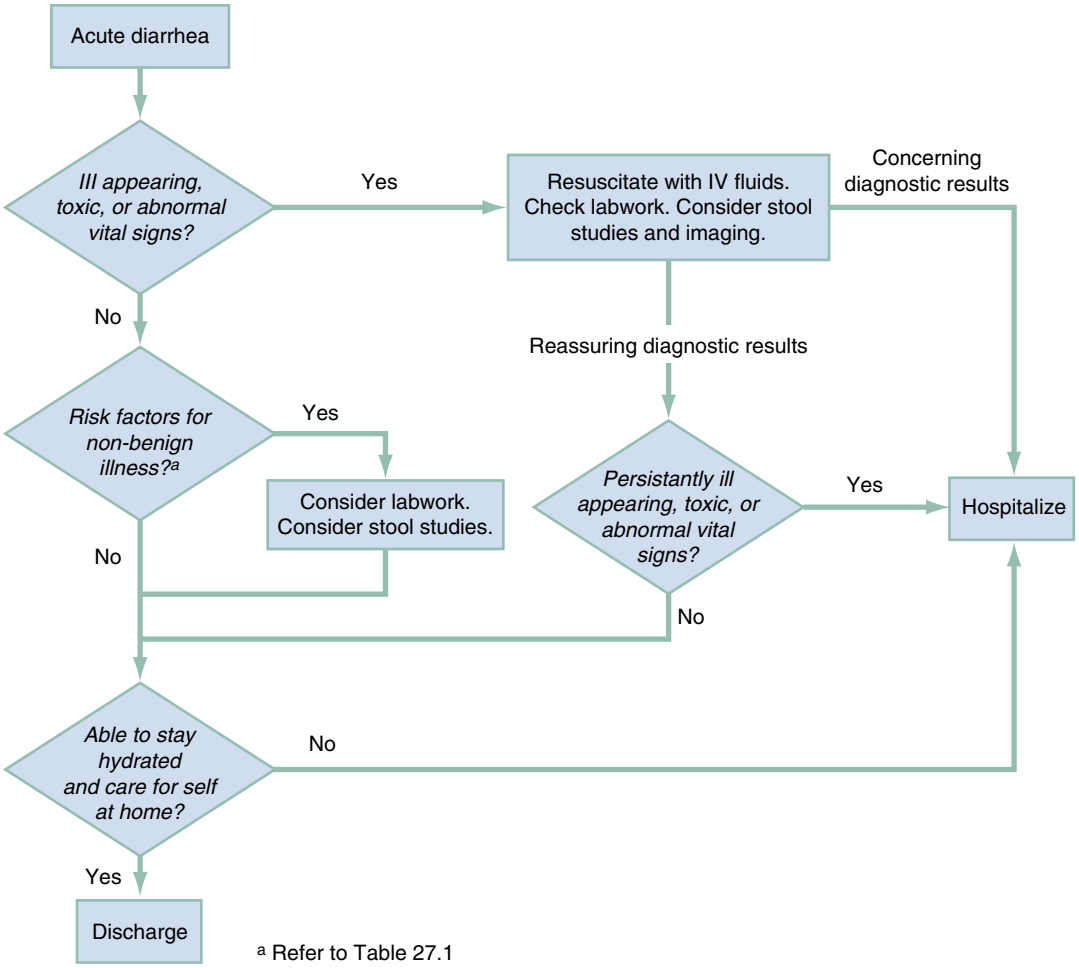
Probiotics

Probiotics have been proposed as an alternative to antibiotic therapy for diarrhea, although there is no consensus on dosage or frequency of specific products. Oral ingestion of lactobacillus or other "probiotic" bacteria may be effective in restoring the normal gastrointestinal flora that is disrupted during diarrhea illness, and is safe in immunocompetent patients. Studies are mixed as to the efficacy of probiotics in acute infectious diarrhea, with more recent studies failing to find a benefit.[19] There is moderate evidence demonstrating a protective effect of probiotics in preventing *C. difficile*–associated diarrhea when antibiotics are prescribed for another reason.[20] We do not routinely advise the use of probiotics in the context of acute diarrhea unless we believe the diarrhea to be associated with previously prescribed antibiotics.

DISPOSITION

Patients with uncomplicated, acute diarrhea are usually discharged following assessment and symptomatic treatment in the ED or observation unit. Hospitalization may be indicated for patients with hemodynamic instability, toxic appearance, or inability to maintain adequate oral hydration or in cases where the diagnosis is unclear and there is suspicion of significant underlying disease. For patients with multiple comorbidities who are being discharged home with likely uncomplicated diarrhea, it is prudent to arrange close outpatient follow-up. Even for otherwise healthy patients, outlining specific return precautions to the ED is essential prior to discharge (Fig. 27.2).

The references for this chapter can be found online at ExpertConsult.com.



[a] Refer to Table 27.1

Fig. 27.2 Approach to Disposition.

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CHAPTER 27: QUESTIONS AND ANSWERS

1. Which of the following is not a common cause of diarrhea in a patient with human immunodeficiency virus (HIV) disease?
   - **a.** Antiretroviral therapy
   - **b.** Cytomegalovirus
   - **c.** Giardia
   - **d.** Intestinal lymphocyte proliferation in acute HIV infection
   - **e.** Shigella

Answer: d. Acute HIV infection is associated with depletion (not proliferation) of intestinal lymphocytes from intestinal mucosa, which alters the gut microbiome leading to increased incidence of viral, bacterial, and protozoal causes of diarrhea. Gastrointestinal cytomegalovirus is associated with advanced HIV infection (CD4+ counts less than 50), which can lead to severe hemorrhagic colitis. In addition, all classes of antiretroviral drugs may cause diarrhea, which can affect more than 25% of individuals taking combined antiretroviral therapy.

2. In which of the following patients would *Clostridioides difficile* testing be least useful?
   - **a.** Patient with diarrhea who is taking omeprazole for known peptic ulcer disease.
   - **b.** Patient with diarrhea after recent tonsillitis treated with amoxicillin.
   - **c.** Patient with diarrhea who is a long-term resident of a skilled nursing facility.
   - **d.** Patient with acute vomiting and watery diarrhea following contact with a toddler with similar symptoms.
   - **e.** Patient with uncontrolled HIV and acute watery diarrhea.

Answer: d. Patient in answer D likely has a viral gastroenteritis, and C. difficile testing is more likely to result in false positive result or identify chronic colonization. Risk factors for C. difficile colitis include antibiotic or gastric acid suppressive therapy, skilled nursing facility residence, and chronic medical conditions.

3. Evaluation of stool for ova and parasites would prove least beneficial in which of the following subsets of patients presenting with diarrhea?
   - **a.** Patients concurrently taking clindamycin with diarrhea for 1 week
   - **b.** Patients recently returning from a backpacking trip
   - **c.** Patients returning from a trip to Nepal
   - **d.** Patients with chronic diarrhea
   - **e.** Patients with human immunodeficiency virus (HIV) infection

Answer: a. The assessment of stool for ova and parasites is not routinely recommended in most cases of diarrheal illness. This study is used in patients with chronic diarrhea (Entamoeba histolytica and Cryptosporidium); patients with a history of travel to developing countries, particularly to Nepal or areas of Russia (Cryptosporidium, Giardia, and Cyclospora); patients with exposure to infants in day-care centers (Cryptosporidium and Giardia); and patients with HIV infection (E. histolytica and Giardia). Acute diarrhea can last up to 2 weeks.

4. In which of the following patients is loperamide a safe treatment option?
   - **a.** Adult patient with acute watery diarrhea of unknown etiology
   - **b.** Adult patient with sepsis and bloody diarrhea
   - **c.** Elderly patient with a history of bowel obstruction with watery diarrhea
   - **d.** Pediatric patient with acute watery diarrhea from norovirus
   - **e.** Pediatric patient with travelers diarrhea

Answer: a. Loperamide, a bowel-selective opioid agonist, is an effective tool to reduce diarrhea severity. Although generally safe, it has been associated with toxic megacolon and obstruction in select groups, such as the elderly, pediatric patients (especially younger than age 3), and patients with a severe inflammatory colitis. Adult patients in which the risk of obstruction or severe inflammatory colitis is low are candidates for loperamide treatment.

5. In which of the following patients is empiric antibiotic treatment the most reasonable option?
   - **a.** Adult patient returning from Mexico with watery diarrhea.
   - **b.** Adult patient with bloody diarrhea during outbreak of *Escherichia coli O157:H7*
   - **c.** Pediatric patient returning from Thailand with bloody diarrhea.
   - **d.** Pediatric patient with fever and bloody diarrhea.
   - **e.** Well-appearing adult patient with suspected norovirus based on ill contacts.

Answer: a. Travelers diarrhea generally responds well to a single dose of azithromycin 1000 mg PO which can decrease time to resolution of symptoms with limited side effects. The choice to initiate antibiotics must be tailored to weigh potential benefits and harms of the treatment for the individual patient. Empiric antibiotics are generally contraindicated in children, as well as patients in which E. coli O157:H7 is a possibility, as antibiotics increase the risk of hemolytic uremic syndrome. In cases of suspected viral-mediated diarrhea, such as a clustered norovirus outbreak, antibiotics are generally not indicated.

28

Constipation

Jessica Palmer

KEY CONCEPTS

- Constipation is a variable term used by patients and may refer to straining with defecation, hard or infrequent stools, pain with a bowel movement, a sensation of incomplete evacuation, or abdominal bloating.
- Primary constipation is caused by functional abnormalities of the gastrointestinal tract.
- Secondary constipation is due to diet, related medical or psychiatric disorders, or medication side effects.
- The etiology of constipation can frequently be discovered through a thorough history.
- The physical examination of patients with constipation focuses on the patient's appearance, the presence of pain, and structural abnormalities identified on abdominal or rectal examination.
- Lab work to evaluate constipation is typically not indicated.
- Imaging to evaluate constipation is not typically indicated when the physical examination is normal.
- The treatment of constipation for most patients is empiric and focuses on lifestyle modifications in addition to laxatives.
- Patients with constipation should be referred for outpatient evaluation and testing when they fail empiric treatment.
- Opioid-induced constipation is common and may require peripherally acting μ-opioid receptor antagonists for management.

FOUNDATIONS

The term *constipation* refers to a symptom or complex of symptoms and not a specific diagnosis. Patients and health care providers may define constipation differently. Most health care providers define constipation based on stool frequency. Patients often use the term *constipation* to describe a broad set of complaints, including straining, hard or infrequent stools, pain during a bowel movement, a feeling of incomplete evacuation, or abdominal bloating. Constipation may be acute (new for the patient) or chronic. *Chronic constipation* is defined as the presence of symptoms for at least 3 months. In clinical practice, attempting to identify the cause of the symptoms often results in the best chance of effective treatment and helps determine disposition. A definitive diagnosis often is not possible in the emergency department (ED) setting, and appropriate follow-up evaluation should be arranged. When constipation becomes severe with constant pain, some clinicians use the term *obstipation*. Obstipation represents the progression of the symptom of constipation toward bowel obstruction.

ED visits for constipation have continued to increase over the past 10 years.[1] In adults, constipation is more common in women, the elderly, and those with high body mass index, sedentary lifestyle, or low socioeconomic status. A consistent trend of increasing prevalence of constipation is observed with age, with significant increases after the age of 70 years. The high prevalence among elders is multifactorial and related to a diet low in fiber (soft diets due to dysphagia or chewing difficulties), lack of adequate fluid intake, sedentary habits, multiple medications, and various disease processes that impair neurologic and motor control.[2]

Pathophysiology

Normally the gastrointestinal tract receives 9 to 10 L/day of secretions and ingested fluids, of which the small intestine routinely absorbs all but approximately 500 mL. The colon mixes the ileal effluent, ferments and salvages the unabsorbed carbohydrate residues, and desiccates the contents to form stool. The process of stool transport and evacuation is complex and is regulated by neurotransmitters, intrinsic colonic reflexes, and a multitude of learned and reflex mechanisms that are not fully understood. Constipation may result from structural, metabolic, mechanical, neurologic, or behavioral disorders that affect the colon or anorectum either directly or indirectly.

Constipation is either primary or secondary (Table 28.1). Primary constipation, or functional constipation, can be separated into three subtypes—normal transit constipation, slow transit constipation, and disorders of defecation. Patients may experience multiple subtypes at the same time. Normal transit constipation occurs when patients have bowel movements with regularity, but the bowel movements may be hard or require excessive straining. Slow transit constipation occurs due to neurologic changes in the bowels, which impact the colon's ability to contract.[3] Colorectal contraction is mediated by the cells of Cajal, which are responsible for both segmental contraction (used to mix colonic contents) and high-amplitude contractions (used to propel colonic contents). Patients with chronic constipation have been shown to have reduced numbers of cells of Cajal, which leads to reduced amplitude of contractions, a diminished gastrocolic reflex after meals and often retrograde propulsion. Disorders of defecation involve impaired smooth muscle contraction in the rectum or difficulty relaxing the muscles of defecation. Dyssynergistic defecation occurs when a patient has difficulty coordinating the pushing effort of the abdominal muscles along with the relaxation effort of the pelvic floor muscles necessary to have a bowel movement.[4] Finally, rectal sensorimotor dysfunction, common in elders, may blunt the patient's ability to sense the need to defecate when stool builds up in the rectal vault. This may result in significant stool buildup and rectal distension.[3] Irritable bowel syndrome, constipation-predominant (IBS-C), is also considered a functional gastrointestinal motility disorder, and although there is significant overlap with chronic constipation and its subtypes, it remains a separate entity.[5]

Secondary constipation is due to diet, medications, and certain medical or psychiatric conditions. Low-fiber diets or diets with decreased water and liquid consumption are associated with constipation. Fiber increases stool weight, which can lead to decreased colonic transit time in patients with normal colonic transport.[2]

TABLE 28.1 Causes of Constipation

Primary Constipation (Functional constipation)	Secondary Constipation	
Normal transit constipation	Congenital	Hirschsprung disease Imperforate anus Anorectal atresia Aganglionosis
Slow transit constipation	Neurologic	Chronic diseases (multiple sclerosis, Parkinson disease, diabetic neuropathy) Spinal cord injury Cerebrovascular accident
Disorders of defecation	Metabolic	Diabetes Hypercalcemia Hypokalemia Hypothyroidism Hypomagnesemia
Irritable bowel syndrome (predominant constipation)	Myopathies	Systemic sclerosis Amyloidosis
	Structural	Obstructing tumor or stricture Intussusception Rectocele Rectal prolapse Rectal abscess
	Medication side effect (Most common listed here)	Opiates Iron or calcium supplements Calcium channel blockers Antidepressants Diuretics Antipsychotics Anticholinergics Antiepileptics Antiparkinson drugs
	Psychological	Abuse (psychological, physical, sexual) Eating disorders (bulimia, anorexia nervosa) Affective disorders
	Others	Dehydration Immobility Pregnancy Postoperative pain Dietary factors

DIAGNOSTIC APPROACH

The etiology of constipation is usually discovered through thorough history. Start by having the patient define what is meant by "constipation." Patients may express varying definitions. Important features include the presence of fever, anorexia, nausea, vomiting, blood in the stool, anemia, significant weight loss, a family history of colon cancer, onset of constipation after the age of 50, or acute onset of constipation in an elderly patient.

Additional elements of the history are directed toward elucidating a possible cause. Symptoms that have evolved quickly and are worse with defecation may point toward acute rectal pathology such as a perirectal abscess, whereas consistent rectal pain and difficulty defecating over the course of a few years may be more consistent with a chronic rectal sensorimotor issue. Questions about the character of the stools may reveal a decrease in caliber of the stool, suggesting possible mass lesion, or diarrhea alternating with constipation, which may indicate irritable bowel provide important clues. A medication history should include any recent changes in dosage of any prescription medications, as well as the use of herbal agents or over-the-counter (OTC) medications. It is also important to ask about diet and dietary changes, given the relationship between constipation and diet.

Differential Considerations

In the ED, patients often present with acute constipation resulting from side effects of medications or avoidance of defecation secondary to presence of painful perianal lesions, such as fissures, hemorrhoids, or perirectal abscesses. Excluding emergent conditions related to constipation is the priority. Establishing a timeline and trajectory for a patient's symptoms will assist with diagnosis and subsequent management. Many patients experience constipation as a side effect of a medication or drug of abuse, with opioids commonly implicated. Elders in particular are at risk for constipation and are sometimes prescribed opioids for pain. Thus warnings about the potential for constipation and instructions for both prevention and treatment remain prudent. Other drugs that may cause constipation include iron supplements, calcium channel blockers, or antidepressants.

Pivotal Findings

The examination should begin with a general inspection of body habitus and nutritional status. Metabolic abnormalities related to a patient's nutrition and hydration status may play a significant role in the etiology of constipation. Focus should then shift to the abdominal and rectal examinations. The abdominal examination in patients with constipation is often normal, and abnormal findings (e.g., tenderness, mass, distention, or abnormal bowel sounds suggesting obstruction) prompt further directed evaluation.

Anorectal inspection may reveal fissures, hemorrhoids, abscess, or a rectal prolapse. The digital rectal examination should include palpation for impacted stool or mass, and the presence or absence of pain should be noted. Having the patient bear down may be helpful in assessing sphincter function and may reveal milder forms of prolapse. The quantity and the characteristics of the stool should be recorded. Testing the stool for occult blood may yield additional information, although straining with stooling can produce local anal lesions and bleeding. If results of occult blood testing are positive, diverticular disease, carcinoma, and local anal bleeding from repeated attempts at straining are possibilities.

Ancillary Testing

The majority of patients with a presenting complaint of constipation do not require any testing. Plain abdominal radiography is of significantly limited value, and patients whose history and examination suggest a need for imaging should undergo ultrasound or computed tomography (CT), depending on the working differential diagnosis. Plain radiographs documenting an increased stool load in the constipated patient should not be used to exclude more serious underlying causative disorders, especially if the patient has a significant amount of abdominal pain or tenderness on examination. Interpretation of abdominal films tends to be variable and can lead to misdiagnosis. In addition, a recent study showed that patients who received plain abdominal radiographs in the ED frequently required additional abdominal imaging, rendering the plain films unnecessary.[6]

Clinical laboratory studies are not routinely indicated in the evaluation of constipation. When blood is found in the stool, a hemoglobin level or complete blood count (CBC) may reveal an accompanying anemia, which may suggest an occult carcinoma or recurrent blood loss from localized colon disease, such as diverticulosis. The white blood cell count is nonspecific and of limited value.

Patients with acute constipation without an apparent emergent cause should receive symptomatic treatment, with referral for outpatient evaluation and reassessment as needed. The patient in the ED with chronic constipation and no alarming signs or symptoms should receive empirical treatment without any ancillary testing. Outpatient testing typically occurs after a patient has failed empirical treatment and may include blood tests to investigate metabolic or endocrine causes, or possibly specialized tests, such as colonic transit studies and anorectal manometry.[7]

Critical Diagnoses

The approach to the patient with constipation starts with assessing whether there is associated abdominal pain. If abdominal pain is present, the evaluation should be geared toward this symptom accordingly, which may ultimately reveal the cause of constipation. Constipation itself may cause abdominal pain; however, this should be a diagnosis of exclusion once other, more serious potential causative disorders have been excluded.

Fig. 28.1 is a diagnostic algorithm for the management of patients with constipation. Initially, history will be very helpful in differentiating among causes, such as medication side effect or possible neurologic disease. The presence of abnormalities on physical examination will dictate appropriate testing and management. For most patients with a normal examination, treatment will be empiric.

Emergent Diagnoses

Constipation is rarely associated with morbidity or mortality. Most negative outcomes are a result of missed diagnosis of bowel obstruction or perforation. These conditions are generally diagnosed through physical examination and appropriate imaging. Stercoral perforation, resulting from severe chronic constipation causing fecal impaction

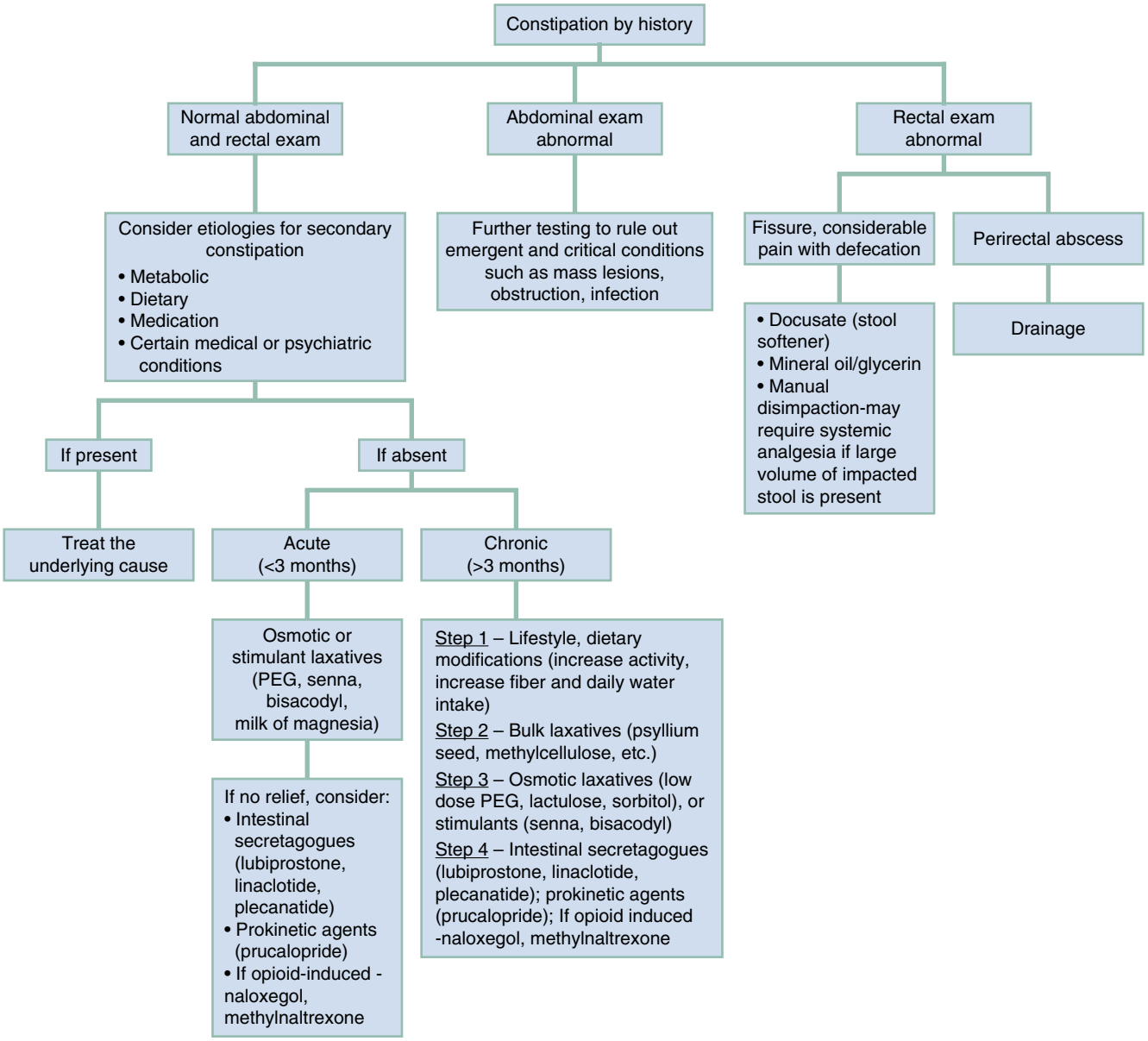

Fig 28.1 Algorithmic Approach to the Diagnosis of Constipation. *5HT$_4$,* 5-Hydroxytryptamine 4; *PEG,* polyethylene glycol.

in the large bowel and associated pressure necrosis and perforation, should be considered in patients with chronic fecal retention. This is typically diagnosed on CT imaging. Surgical consultation is necessary for suspected perforation or obstruction.

EMPIRICAL MANAGEMENT

Treatment of acute constipation is directed toward identifying the underlying cause and providing symptom relief. Prevention of further episodes may include recommending increased fluid intake, increased exercise, increased dietary fiber, and, if necessary, additional sources of bulk in the form of synthetic bulking agents. These interventions will not usually help the acutely constipated patient in the short term. Initial treatment for acute constipation without concern for structural abnormality should focus on the addition of osmotic or stimulant laxatives. If unsuccessful, treatment should be escalated including referral for outpatient testing. Therapeutic choices and recommendations for patients should be customized based on patient preferences, as well as prior personal history of efficacy with various treatments. Specific recommendations may also include withholding a causal medication, management of an anal fissure, or drainage of a perirectal abscess. Stool softeners (e.g., docusate sodium), although commonly recommended, should not be a first-line agent for most patients with constipation. Docusate has not been shown to be any more effective than placebo in relieving acute constipation, although it may be somewhat helpful in patients with anal fissures or hemorrhoids because it may make defecation less painful.

Specific agents for symptomatic treatment of constipation are listed in Table 28.2. There are seven main classes of commonly used laxatives. These include softeners, bulking agents (fiber), osmotic agents, stimulants, intestinal secretagogues, prokinetic agents, and peripherally acting μ-opioid receptor antagonists (PAMORAs). These agents aid defecation by decreasing stool consistency, stimulating colon motility, or both.

Intestinal secretagogues are a relatively new class of medications used to treat both chronic constipation and constipation predominant IBS. These drugs work by stimulating intestinal fluid secretion, increasing the amount of fluid in the stool and decreasing colonic transit time.[8] In recent studies, intestinal secretagogues performed better than placebo at reducing constipation and related symptoms, although direct comparison to laxatives has not yet been performed.[8,9] Diarrhea is the one major side effect of these medications, and their cost can be prohibitive as well.

TABLE 28.2 Preparations Used in the Symptomatic Treatment of Constipation

Medication	Maximal Recommended Dosage	Onset of Action	Comments
Bulk Laxatives			Indigestible fiber attracts water, which leads to larger, softer fecal mass.
Psyllium (Metamucil)	Titrate up to 21 g (females) to 30 g (males)	12–72 h	Natural fiber that undergoes bacterial degradation, which may contribute to bloating and flatus. Should be taken with plenty of water to avoid intestinal obstruction.
Methylcellulose (Citrucel)	Titrate up to 6 g per day		Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation.
Polycarbophil (Fibercon)	Titrate up to 5 g per day	12–72 hrs	Synthetic fiber of polymer of acrylic acid, resistant to bacterial degradation.
Osmotic Laxatives			Draw water into the intestines along osmotic gradient.
Magnesium or sodium salts			
Magnesium hydroxide (milk of magnesia)	4800 mg per day either at bedtime or in divided doses	1–6 h	A small percentage of magnesium is absorbed—use caution in patients with renal insufficiency or in children.
Magnesium citrate	300 mL per day	0.5–6 hr	
Sodium phosphate (Fleet Phospho-Soda)	15 mL per dose up to 45 mL/day	3–6 h	Hyperphosphatemia may result in setting of renal insufficiency. Commonly used before colonoscopy.
Poorly absorbed sugars			
Lactulose	60 mL by mouth per day	24–48 h	Synthetic disaccharide not absorbed by the small intestine. Gas and bloating common.
Sorbitol	45 mL by mouth per day (as 70% solution)	0.25–1 hr	Poorly absorbed by small intestine.
Polyethylene glycol and electrolytes (GoLYTELY, MiraLax)	34 g per day	24–96 h	Organic polymers that are poorly absorbed and not metabolized by bacteria; thus may cause less bloating and cramping. Can be mixed with noncarbonated beverages.
Stimulant Laxatives			Stimulate intestinal motility or secretion.
Senna (Senokot, Ex-Lax)	100 mg daily	6–12 h	Stimulates secretion and motility of small intestine and colon.
Bisacodyl (Dulcolax, Correctol)	15 mg by mouth daily	6–10 h	

TABLE 28.2 Preparations Used in the Symptomatic Treatment of Constipation—cont'd

Medication	Maximal Recommended Dosage	Onset of Action	Comments
Stool Softeners			Increase water penetration and soften stool.
Docusate sodium (Colace)	360 mg by mouth daily	12–72 h	In many studies, no better than placebo. Not recommended as first-line or solo therapy.
Mineral oil (Fleet mineral oil)	45 mL by mouth daily	6–8 h	Provides lubrication for the passage of stool. Long-term use is not recommended. Lipid pneumonia can occur in patients predisposed to aspiration.
Intestinal secretagogues			
Lubiprostone (Amitiza)	24 μg twice per day	1 h	Used in CIC.
Linaclotide (Linzess)	145 μg daily in CIC and 290 μg daily in IBS-C		Used in IBS-C and CIC.
Plecanatide (Trulance)	3 mg daily		Used in IBS-C and CIC.
5-HT$_4$ Agonists			
Prucalopride (Motegrity)	2 mg daily		Used in CIC.
Peripherally Acting μ-Opioid Receptor Antagonists			
Methylnaltrexone (Relistor)	450 mg orally daily or 12 mg SC daily	30–60 min	Used in opioid-induced constipation.
Naldemedine (Symproic)	0.2 mg daily		Used in opioid-induced constipation.
Naloxegol (Movantik)	25 mg unncessary daily		Used in opioid-induced constipation.

CIC, Chronic idiopathic constipation; *5HT$_4$,* 5-hydroxytryptamine 4; *IBS-C,* irritable bowel syndrome with constipation; *SC,* subcutaneously.

Prokinetic agents that target the serotonin receptor (5-hydroxytryptamine 4 [5-HT$_4$] receptor agonists) have been found to be effective as well for patients with chronic idiopathic constipation. When bound specifically to the 5-HT$_4$ receptor, they increase colonic propulsion without the cardiac side effects of older, less selective 5-HT agents.[10]

Constipation frequently occurs in patients who are taking medically necessary medications that cause constipation on a chronic basis (e.g., opioids in patients with chronic pain or cancer). Constipation is a nearly universal side effect of opioid pain medication due to the presence of opioid receptors in the gastrointestinal system.[11] Patients with chronic opioid use should be on bowel regimens designed to prevent constipation, which usually includes measures such as high levels of dietary fiber (e.g., added prunes or figs), as well as daily administration of stimulant laxatives. PAMORAs were developed to manage opioid-induced constipation in this class of patients who have failed other therapies. These drugs selectively block the gastrointestinal μ-opioid receptors without compromising the centrally mediated effects of opioid analgesia or precipitating withdrawal. There are three drugs in this category—methylnaltrexone (Relistor), which is administered both subcutaneously and orally, and naldemedine (Symproic) and naloxegol (Movantik), which are orally administered. All three medications have been shown to be more beneficial than placebo in patients with opioid-induced constipation.[11]

Enemas are sometimes necessary if laxatives have failed to provide relief or if the patient has a large volume of stool in the lower colon or rectum that cannot be expelled. Warm tap-water enemas are generally the safest choice. For immediate relief, manual disimpaction may be necessary in some patients, especially in elders with large amounts of stool present in the rectal vault. In rare cases, disimpaction may need to be performed with analgesia or even procedural sedation.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 28: QUESTIONS AND ANSWERS

1. A 48-year-old female with no known past medical history presents to the emergency department with the chief complaint of constipation. She states she has not had a bowel movement in the past 7 days. She has no history of similar symptoms. She denies taking any medications or any past surgical history. On examination, she has no abdominal tenderness with palpation or masses. Her rectal examination is unremarkable for fissures, and the patient does not have any blood or stool in her rectal vault. What is the next step in this patient's management?

a. A plain film abdominal x-ray
b. Discharge home with recommendation for laxatives and plan for lifestyle modification
c. Emergent outpatient gastroenterology follow-up
d. Trial of at home docusate and strict return precautions if plan fails

Answer: b. The patient in this question has acute constipation. Because her history and examination does not have any red flag concerns, this patient can be safely discharged home without any testing. This patient will require laxatives to help her acute constipation, but lifestyle management should help to prevent similar episodes in the future. There is no utility for plain film abdominal x-rays in the emergency department for the evaluation of constipation. Docusate has been shown to be ineffective as first line management for constipation unless the patient has a rectal abnormality or rectal pain that prevents the passage of stool. This patient is well-appearing on examination and therefore, she does not require intravenous (IV) hydration. Because this patient's constipation is acute and she has a benign examination, she does not require emergent gastroenterology follow-up.

2. A 96-year-old male from a nursing home presents with the chief complaint of constipation. He has a past medical history significant for cerebrovascular accident and now receives all of his medications, hydration, and feedings through a gastrostomy tube due to dysphagia. The patient has been on a bowel regimen of twice daily polyethylene glycol through his gastrostomy tube with minimal, watery stool output over the past week. The patient appears to be uncomfortable, but he is afebrile and hemodynamically stable. On examination, the patient's abdomen is soft and there is no focal tenderness. On rectal exam, you feel a large amount of firm stool in the rectal vault. What is the appropriate next step in this patient's management?

a. Admission for colonoscopy
b. Analgesia and disimpaction
c. Glycerin suppository
d. Oral milk of magnesia

Answer: b. This is an elderly male with chronic constipation for a multitude of reasons. Because of his age and possibly due to his cerebrovascular accident, he has denervation of his rectum preventing him from sensing rectal fullness. The large volume of stool in his rectum needs to be removed for his comfort, and disimpaction with analgesia will be necessary. The use of a glycerin suppository to lubricate the stool to be expelled is unlikely to be successful as this patient has lost the ability to expel stool on his own. Because this patient does not receive medications by mouth, milk of magnesia should not be given orally. Because his abdominal examination is benign and he is hemodynamically stable, the likelihood that he has a critical intra-abdominal process requiring imaging is low. Finally, this patient does not require admission to the hospital, nor does he require an emergent colonoscopy at this time.

3. A 32-year-old female with chronic pain followed closely by a pain management specialist presents with constipation. She normally takes a bowel regimen of bisacodyl daily in addition to consuming a high-fiber diet. Her physician recently increased her opioid medication dosage. Since then, she has had difficulty having more than one small, hard stool per week. She complains of abdominal discomfort but has not had any nausea or vomiting. On examination, her abdomen is soft without focal tenderness. Her rectal examination is normal. What is the appropriate next step in this patient's management?

a. A trial of a peripherally acting μ-opioid receptor antagonist and plan for close outpatient follow up with her care team
b. Consultation with her pain management specialist to decrease her medication dosage back to previous levels
c. Lab testing to rule out an electrolyte abnormality causing this patient's symptoms
d. Nonopioid pain medication for her discomfort while in the emergency department and plan for gastroenterology follow-up

Answer: a. This is a patient experiencing opioid-induced constipation. Her previous bowel regimen was sufficient until her medication doses increased. Because this patient has failed her bowel regimen, it is reasonable to try a peripherally acting μ-opioid receptor antagonist to block the effects of the opioids on the colonic μ receptor. Decreasing this patient's pain medications back to previous doses may lead to withdrawal. Lab testing is unlikely to be of benefit. Providing analgesia for discomfort will not relieve constipation.

4. Which of the following is true regarding constipation?
   - **a.** The diagnosis of constipation requires lab testing and imaging in the emergency department.
   - **b.** Most patients with constipation and a normal examination can be safely discharged home with empiric treatment.
   - **c.** Constipation is less common in the elderly due to low fiber, mechanical soft diets.
   - **d.** Chronic constipation occurs when a patient experiences decreased stool output for at least 1 year.

Answer: b. The term constipation refers to a multitude of symptoms, not a medical diagnosis. Patients often have different personal definitions for the term "constipation." Chronic constipation refers constipation symptoms for 3 or more months. Constipation is more common in the elderly due to sedentary lifestyles and low-fiber, mechanically soft diets. In the ED, lab testing and imaging is often unnecessary for patients with a normal physical exam. Most well-appearing patients with constipation and a normal examination can be discharged home with empiric management.

5. Which of the following is true regarding treatment options for constipation?
   - **a.** Bisacodyl works by increasing water penetration and thereby softens the stool.
   - **b.** Docusate sodium should be prescribed to all patients with chronic constipation given its effectiveness as a laxative.
   - **c.** Lifestyle modification is the first line treatment for patients with acute constipation.
   - **d.** Sodium phosphate and magnesium hydroxide should be avoided in patients with renal impairment.

Answer: d. The side effect profiles for many common treatments of constipation should be considered prior to prescribing to special patient populations. Both sodium phosphate and magnesium hydroxide can increase the levels of phosphorus and magnesium in the body, respectively, in patients with renal insufficiency/impairment. Bisacodyl is a laxative and works by stimulating intestinal motility. Docusate sodium is a stool softener, not a laxative, that should not be used as first line or solo therapy due to its marginal efficacy. Patients with acute constipation should be prescribed both a laxative for immediate treatment and lifestyle modification for longer-term management.

29

Acute Pelvic Pain

Ari M. Lipsky and Danielle Hart

KEY CONCEPTS

- Acute pelvic pain in women is often from a gynecologic source, but urinary and intra-abdominal sources are also common. Less frequently, the pain may arise from vascular, musculoskeletal, neurologic, or psychiatric disorders.
- Potentially lethal diagnoses associated with acute pelvic pain include ectopic pregnancy, ovarian cyst with significant hemorrhage, and domestic violence; highly morbid conditions presenting with acute pelvic pain include pelvic inflammatory disease and ovarian torsion.
- Nearly all women of childbearing age with pelvic pain should have a pregnancy test performed, and most should have a pelvic ultrasound examination.
- Ectopic pregnancy should be excluded in the pregnant patient with pelvic pain. Bedside ultrasound is an excellent test for confirming an intrauterine pregnancy (IUP); it excludes ectopic pregnancy with a high degree of certainty in patients who are not using assisted reproductive technology.
- Pregnant patients with acute pelvic pain may also have non–pregnancy-related disorders; appendicitis, nephrolithiasis, and ovarian torsion, among others, remain in the differential diagnosis.
- Many patients with acute pelvic pain require imaging as part of their assessment. If a gynecologic source is suspected, begin with an ultrasound and then progress to computed tomography (CT) or magnetic resonance imaging (MRI), if needed. The presence of an ovarian cyst on imaging does not necessarily explain the patient's pain, and further evaluation may be required. Ultrasound after normal CT is unlikely to be informative. Ovarian torsion may be radiographically occult.

FOUNDATIONS

Epidemiology

Acute pain caused by pelvic pathology is common, and the presenting complaint may be diffuse or lower abdominal pain, pelvic pain, or low back pain. A patient with chronic pelvic pain may also have an acute process related to the chronic condition or arising de novo.

More than one-third of reproductive age women will experience nonmenstrual pelvic pain. Among diagnoses for women with pain caused by gynecologic disorders in the emergency department (ED), pelvic inflammatory disease (PID) and lower genital tract infections (e.g., cervicitis, candidiasis, Bartholin abscess) account for almost 50%. Other common diagnoses are menstrual disorders, noninflammatory ovarian and tubal pathology (including cysts and torsion), and ectopic pregnancy. Ectopic pregnancy accounts for up to 20% of diagnoses among women presenting with vaginal bleeding or abdominal pain in the first trimester of pregnancy.

Younger patients and those with multiple sexual partners are more likely to have PID, and a previous episode increases the likelihood of a subsequent episode. The risk of ectopic pregnancy is higher in women who have had PID, pelvic surgery, prior ectopic pregnancy, or are using an intrauterine device (IUD). Heterotopic pregnancy is of special concern in women using assisted reproductive technology (ART). Although the rate of heterotopic pregnancy in spontaneous pregnancy is 1 in 30,000, this rate increases to as high as 1:1000 in patients undergoing ART.[1] Common nongynecologic diseases such as appendicitis, diverticulitis, urinary tract infection, and urolithiasis remain important considerations in the woman with acute pelvic pain. Box 29.1 lists conditions accounting for most cases of pelvic pain in women.

Some causes of pelvic pain may lead to serious sequelae. PID carries the short-term risk of tubo-ovarian abscess and the long-term risks of impaired fertility, chronic pelvic pain, and increased predisposition to ectopic pregnancy. Rupture of an ectopic pregnancy or hemorrhagic ovarian cyst may be life threatening. Unrecognized abuse may also have serious or even lethal consequences.

Pathophysiology

The female pelvis contains the vagina, uterus, fallopian tubes and ovaries, ureters and urinary bladder, and sigmoid colon and rectum, as well as components of the vascular and musculoskeletal systems. Although pelvic pain often originates from the reproductive organs, it may arise from any structures that lie adjacent to or course through the pelvis. Visceral pain afferents supplying the pelvic organs have common innervation with the appendix, ureters, and colon. Their significant overlap makes accurate localization difficult for both patient and emergency clinician. Pain may be initiated by inflammation, distention, or ischemia of an organ, or by spillage of blood, pus, or other material into the pelvis. Pain may become more localized when the afferent nerves in the parietal peritoneum adjacent to an affected organ are stimulated.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of pelvic pain is broad (see Box 29.1). Most causes of pelvic pain fit into three categories: (1) reproductive tract; (2) urinary tract; and (3) intestinal tract. Because a subset of pelvic pain is found only in pregnancy, the pregnancy test is a key branch point in the diagnostic process. Potential pregnancy-related disorders can be divided into complications of early pregnancy and complications that occur further along in pregnancy. Although the specific cause of pelvic pain cannot always be determined at the initial ED visit, an organized approach usually leads to the confirmation or exclusion of disorders most likely to result in significant morbidity or mortality.

Pivotal Findings

The pelvic examination may at times provide crucial information. However, some findings on bimanual examination are subjective and may be unreliable; they are perhaps most helpful in localizing the process to one side or the other or in helping to plan further work-up. There are not currently sufficient data to select reliably women in whom the pelvic examination need not be performed, although the

BOX 29.1 Causes of Pelvic Pain in Women

Reproductive Tract
Ovarian torsion
Ovarian cyst
Pelvic inflammatory disease
Salpingitis
Tubo-ovarian abscess
Endometritis
Endometriosis
Uterine perforation
Uterine fibroids
Dysmenorrhea
Vulvar/vaginal trauma
Neoplasm

Pregnancy Related
First Trimester
Ectopic pregnancy
Threatened abortion
Nonviable pregnancy
Ovarian hyperstimulation syndrome

Second and Third Trimesters
Placenta previa
Placental abruption
Round ligament pain
Labor or Braxton Hicks contractions
Uterine rupture

Intestinal Tract
Appendicitis
Diverticulitis
Ischemic bowel
Perforated viscus
Bowel obstruction
Incarcerated or strangulated hernia
Fecal impaction or constipation
Inflammatory bowel disease
Gastroenteritis/colitis
Irritable bowel syndrome

Urinary Tract
Pyelonephritis
Cystitis
Ureteral stone

Vascular
Septic pelvic thrombophlebitis
Ovarian vein thrombosis
Sickle cell disease
Pelvic congestion syndrome

Musculoskeletal
Muscular strain or sprain
Hernia
Abdominal wall hematoma
Pelvic fracture

Neurologic, Psychiatric, and Other
Depression
Domestic violence
Sexual abuse
Abdominal migraine
Herpes zoster

pelvic examination may be deferred in patients for whom immediate imaging is planned for a suspected critical condition such as ruptured ectopic pregnancy.[2–4] Depending on imaging results, a subsequent speculum or bimanual pelvic examination may still be necessary.

It is unlikely that any particular finding on history or physical examination, summarized in Table 29.1, is reliable enough to make or exclude a particular diagnosis conclusively, so ancillary testing beyond a pregnancy test is commonly needed in the evaluation of patients with acute pelvic pain. Focused pelvic ultrasound or computed tomography (CT) scan is often required, depending on the clinician's level of suspicion for reproductive tract versus intestinal tract pathology. Patients with severe pain or tenderness, or peritoneal signs should undergo expedited imaging: bedside ultrasound, if available, should be performed emergently to evaluate for pelvic or intra-abdominal free fluid.

Symptoms

The location of pain and pattern of radiation often are helpful in focusing the differential diagnosis toward a specific cause or group of causes. Lateral pelvic pain is often related to a process in the tube or ovary. However, with right-sided pain, appendicitis is considered, and in left-sided pain (especially in patients >40 years), the differential diagnosis includes diverticulitis and colitis. Urolithiasis may also manifest as lateral pelvic pain, especially when the stone is at the ureterovesicular junction, or as pain radiating to the labia or vaginal area. Central pelvic pain usually is caused by processes involving the uterus, bladder, or both adnexae. Pain radiating to the rectum may be secondary to pooling of fluid or blood in the cul-de-sac, or a rectosigmoid process. Diffuse pain may occur with a central or bilateral process such as PID or with diffuse peritonitis from infection or intra-abdominal hemorrhage.

Information regarding the onset and duration of pain may be useful. Patients with uncomplicated appendicitis (without perforation or abscess) typically are seen within 48 hours of symptom onset. Sudden-onset pain suggests acute intrapelvic hemorrhage, cystic rupture, ovarian torsion, or ureterolithiasis. Ovarian cyst pain may also fluctuate through several menstrual cycles before rupture. Gradual-onset pain is more consistent with inflammation such as in PID or appendicitis. Chronic or recurrent pain is consistent with endometriosis, recurrent ovarian cysts, or persistent ovarian mass. The quality of pain may differentiate the crampy, intermittent pattern of muscular contractions along a hollow viscus (arising from uterine, ureteral, or bowel pathology) from the steady progressive pain associated with inflammatory or neoplastic causes.

Fever and chills are more common with an infectious process. Nausea and vomiting occur more frequently when the process originates within the gastrointestinal tract but may accompany any pain of visceral origin such as ovarian torsion and ureteral colic, any severe pain, and normal pregnancy. Dysuria occurs in many local vulvar and vaginal processes such as herpesvirus infection, candidiasis, and other types of vulvovaginitis, but urinary urgency typically signals an irritated bladder or urethra and should focus attention on the urinary tract.

Information about the patient's last menstrual period, pattern of menses, and sexual activity pattern may be useful but does not necessarily exclude pregnancy. In a pregnant patient, the obstetric history may provide some helpful diagnostic clues. Recurrent spontaneous abortion or previous ectopic pregnancy increases the likelihood of these conditions, respectively. Patients who are actively undergoing infertility treatment are at increased risk for ectopic pregnancy, heterotopic pregnancy, ovarian torsion, and ovarian hyperstimulation syndrome. Round ligament pain is usually noted in the second trimester. Postpartum patients are at increased risk for endometritis.

The presence, quantity, and duration of associated vaginal bleeding should be ascertained (see Chapter 30). In a nonpregnant patient, bleeding may be associated with abnormal uterine bleeding (e.g., from PID, ovulatory dysfunction, cancer) or trauma (e.g., vaginal laceration due to pelvic fracture, direct vaginal irritation or trauma). In a pregnant patient, bleeding may also be associated with a subchorionic hemorrhage in an otherwise viable pregnancy, ectopic pregnancy, nonviable intrauterine pregnancy (IUP) (which may continue to cause bleeding after expulsion of the uterine contents, especially if any products of conception are retained), or later in pregnancy with placenta previa or abruption. In some cases, the amount of bleeding may be substantial enough to necessitate blood transfusion and surgical intervention. The presence of vaginal discharge (color, consistency, odor) should also be ascertained.

Sexual history is important, with emphasis on recent sexual contact and previous history of sexually transmitted disease. A history of any recent gynecologic procedures should be obtained because the onset of pelvic pain shortly after uterine instrumentation increases the possibility of uterine perforation or infection. Similarly, the presence of an IUD should be ascertained because of the risks of infection and perforation, as well as the increased prevalence of ectopic pregnancy among pregnant women with IUDs. All women should be interviewed in private to permit disclosure of sensitive information such as sexual history, pregnancy, recent abortion, and abuse.

Signs

The physical examination is directed toward the abdomen and pelvis. Pelvic examination is performed in almost all patients; exceptions will

TABLE 29.1 Differentiation of Common or Potentially Catastrophic Causes of Pelvic Pain

Causative Disorder or Condition	Pain History	Associated Symptoms	Supporting History	Prevalence in ED	Physical Examination	Useful Tests	Atypical or Additional Aspects
Ectopic pregnancy (critical if ruptured; otherwise emergent)	Classically severe, sharp, lateral pelvic pain, but severity, location, and quality highly variable	Vaginal bleeding (often mild, can be absent)	Missed period; history of previous ectopic pregnancy, infertility, pelvic surgery, PID, or IUD use	Common	Classically unilateral adnexal tenderness, adnexal mass, CMT	Pelvic US, quantitative β-hCG, T&C, laparoscopy	Cannot reliably exclude diagnosis based on history and physical examination; severe pain, hypotension, or peritonitis suggests rupture.
Ruptured ovarian cyst (emergent—critical with significant hemorrhage; otherwise, urgent)	Abrupt moderate to severe lateral pain	Light-headedness if bleeding is severe; rectal pain arises from fluid in cul-de-sac.		Rupture—common; significant hemorrhage—uncommon	Hypotension and tachycardia if blood loss is significant; possible peritonitis	Pelvic US, CBC, T&C	Physical examination findings often do not correlate with volume of blood in pelvis at US.
Ovarian torsion (emergent)	Acute onset of moderate to severe lateral pain	Nausea and vomiting	History of ovarian mass or cyst	Uncommon	Adnexal mass and tenderness, possible peritonitis	US with Doppler flow studies, laparoscopy	Torsion can be intermittent.
Appendicitis (emergent)	Duration often <48 h, generalized followed by localized RLQ pain	Low-grade fever, nausea, anorexia	Migration of pain to RLQ from center, abdominal pain before vomiting	Common	RLQ tenderness, possible peritonitis	US, CT, or MRI	Early in course, tenderness may be minimal or poorly localized.
PID, TOA (TOA: emergent; PID: urgent-emergent)	Without TOA, pain usually bilateral; may manifest acutely within 48 h, but PID may also be chronic.	Fever, vaginal discharge	Vaginal discharge, history of PID, history of unprotected intercourse or multiple partners	PID—common; TOA—uncommon	Pus from cervical os, CMT, adnexal tenderness; peritonitis suggests TOA or severe PID	CBC, ESR, CRP, pelvic US, laparoscopy, cervical cultures, cervical smear for WBCs	History and physical examination may be inaccurate for diagnosis, particularly in patients with subacute presentations.
UTI (urgent)	Pain with urination; patient may have flank pain from associated pyelonephritis.	Urinary urgency and frequency; fever and vomiting if patient has associated pyelonephritis	Prior history of UTI, recent urologic procedure	Common	Suprapubic tenderness; flank tenderness and fever with pyelonephritis	Urinalysis, urine culture (if recurrent or complicated)	WBCs can be present in urine with PID and appendicitis; RBCs present in urine with hemorrhagic cystitis.
Ureteral colic (urgent)	Acute onset, manifests within hours; pain is lateral, usually moderate to severe. Often radiates into the groin or costovertebral angle or flank	Nausea and vomiting	Prior history of stones	Common	Patient often appears uncomfortable, but physical examination can be otherwise unremarkable	Urinalysis—hematuria present in ≈80% of cases; renal ultrasound for hydronephrosis; abdominal CT	If stone is at ureterovesicular junction, patient may have localized pain that can mimic appendicitis or other acute pelvic pathology.
Unruptured ovarian cyst or tumor	Lateral ache, gradual onset	Often minimal	Prior history of similar pain	Common	Lateral pelvic tenderness, with or without a mass	Pelvic US	
Endometriosis	Unilateral or bilateral pelvic pain, often recurrent	Dysmenorrhea, dyspareunia.	Prior history of same type of pain in association with menstrual cycle	Common	Unilateral or bilateral adnexal tenderness, occasionally pelvic mass present, peritoneal findings uncommon	Pelvic US, laparoscopy	Symptoms can mimic other types of pelvic pathology; laparoscopy often is needed for confirmation.

CBC, Complete blood count; *CMT*, cervical motion tenderness; *CRP*, C-reactive protein; *CT*, computed tomography; *ED*, emergency department; *ESR*, erythrocyte sedimentation rate; *β-hCG*, β-human chorionic gonadotropin; *IUD*, intrauterine device; *MRI*, magnetic resonance imaging; *PID*, pelvic inflammatory disease; *RBC*, red blood cell; *RLQ*, right lower quadrant; *T&C*, type and crossmatch; *TOA*, tubo-ovarian abscess; *US*, ultrasonography; *UTI*, urinary tract infection; *WBC*, white blood cell.

be noted later in the discussion of the diagnostic algorithm. Pregnant patients beyond 20 weeks' gestation with complaints of vaginal bleeding should undergo transabdominal pelvic ultrasound for placental localization before the pelvic examination (see Chapter 173), should have a fetal heart rate measured and documented, and may need timely obstetric consultation.

Abnormal vaginal discharge may be seen in a variety of conditions, including vaginitis, cervicitis, endometritis, PID, and retained foreign body. Cervical motion tenderness usually indicates reproductive tract inflammation but can also occur with irritation of adjacent structures (e.g., cystitis, appendicitis). An open os is most consistent with an incomplete or inevitable abortion but does not definitively exclude an ectopic pregnancy. A large uterus in a nonpregnant patient may indicate fibroids. Fundal tenderness is often difficult to distinguish from cystitis but may suggest PID, endometritis, or necrotic fibroids. Unilateral adnexal masses and tenderness are suggestive of an ovarian cyst, ectopic pregnancy, tubo-ovarian abscess, or ovarian torsion.

The constellation of cervical motion tenderness, uterine tenderness, and adnexal tenderness is classically associated with PID, although only one sign is required to initiate treatment in certain clinical settings per the most recent Centers for Disease Control and Prevention (CDC) guidelines (2015).[5]

Ancillary Testing

Laboratory Tests

A pregnancy test is required in almost all patients of childbearing age with a complaint of abdominal or pelvic pain, irrespective of sexual history or reported contraception use, because pregnancy changes both the differential diagnosis and the management of many non–pregnancy-related conditions. Very few exceptions to the need for pregnancy testing exist, such as documented bilateral salpingo-oophorectomy or a woman who is known to be pregnant. A positive test result may indicate current or recent intrauterine or extrauterine pregnancy or, rarely, molar pregnancy or cancer.

Urinalysis of a clean-catch specimen may identify nitrites and pyuria from a urinary tract infection, or hematuria, consistent with urolithiasis or hemorrhagic cystitis. The absence of hematuria does not exclude the possibility of a ureteral stone, although it lowers the likelihood, and mild pyuria may be seen in extravesicular conditions such as appendicitis. Urinalysis should be performed in all pregnant patients with pelvic pain, even if their symptoms do not include urinary tract complaints, because urinary tract infection, including asymptomatic bacteriuria, is associated with morbidity for both mother and fetus.

Patients who may be hemorrhaging internally or externally should have their hemoglobin level checked, and type and crossmatching should be performed if the hemorrhage is substantial. Pregnant patients with concern for fetomaternal transfusion (e.g., vaginal bleeding) also require blood typing to identify Rh-negative patients who will require Rho(D) immune globulin.

Imaging

Bedside ultrasound is a core part of the evaluation of most women with pelvic pain and, along with the history and physical examination, should be considered as an integral part of the initial examination.[6] Patients with a positive pregnancy test result should undergo focused bedside ultrasound or formal (consultative) ultrasound examination to evaluate for ectopic pregnancy. Identification of a definite IUP by ultrasound imaging excludes ectopic pregnancy with a high degree of certainty in patients who are not undergoing assisted reproduction. Conversely, a patient with a positive pregnancy test in whom a definite IUP cannot be seen is presumed to have an ectopic pregnancy until further evaluation is completed. In addition, the presence of a gestational sac alone is not sufficient to confirm an IUP; experienced sonographers may use the double decidual sac sign, but it is recommended that less experienced sonographers visualize a yolk sac or embryo for definitive ultrasonographic confirmation of an IUP. A complex adnexal mass, tubal ring, extrauterine yolk sac or embryo, or free fluid is indicative of a probable ectopic pregnancy. The presence of free intraabdominal fluid on ultrasound with a negative urine pregnancy test is consistent with hemorrhage or a ruptured ovarian cyst. Regardless of cause, intra-abdominal free fluid is presumed to be blood and should be addressed expediently.

When the diagnosis of acute appendicitis is being considered, a CT scan (for nonpregnant patients) or magnetic resonance imaging (MRI) test (for pregnant patients) should be obtained.

DIAGNOSTIC ALGORITHM

The algorithm in Fig. 29.1 is designed to focus further testing and progress to a rational provisional diagnosis. However, it is not unusual to pursue evaluation of gynecologic and intra-abdominal causes of pain in parallel, when the initial history and physical examination do not provide clear direction. It is also possible for common diseases to manifest in uncommon ways, for more than one disease to be present, or for a positive finding not to explain the entirety of the patient's presentation. For example, patients with an abnormal urinalysis may have appendicitis, pregnant patients may also have ovarian torsion or appendicitis, and simple ovarian cysts seen on imaging may be asymptomatic. Tests are therefore interpreted in the context of the individual patient's presentation. With certain diseases such as endometriosis, definitive testing is not available in the ED and the patient's history may be the most important discriminator.

After an initial history and physical examination, the pregnancy test determines the subsequent priorities. Remember, however, that pregnant patients may also suffer from non–pregnancy-related conditions; for example, if a threatened abortion is most likely (i.e., there is an IUP on ultrasound imaging), unilateral pain may prompt further evaluation for torsion. An empty uterus on ultrasound imaging, or any ultrasound study that cannot confirm a definite IUP, could be consistent with an ectopic pregnancy, spontaneous abortion, or very early normal pregnancy. Patients past 20 weeks' gestation will likely require observation with fetal monitoring.

Nonpregnant patients with pain that seems to be gynecologic in nature should be assessed for hemorrhage from a ruptured or hemorrhagic ovarian cyst, for ovarian torsion, and for infection, including cervicitis, endometritis, PID, salpingitis, and tubo-ovarian abscess. Although the history and physical examination often are sufficient to diagnose infection, ultrasound assessment is helpful if torsion, tubo-ovarian abscess, or ruptured hemorrhagic cyst is suspected. Ultrasound findings also may support a diagnosis of PID if evidence of salpingitis is noted or a diagnosis of a simple ruptured cyst if a characteristic ovarian appearance is combined with the presence of a small amount of free fluid. Although not as reliable as CT, ultrasound may be able to identify appendicitis.

It is difficult to differentiate some gynecologic origins of pain from intra-abdominal causes (e.g., right ovarian pathology from appendicitis), so ancillary testing may require an ultrasound study, CT, or both. If the cause is most likely gynecologic, an ultrasound examination of the pelvis, and subsequently (if feasible) the appendix, is reasonable. These studies may be followed by CT if the ultrasound findings are unremarkable and the presentation remains consistent with appendicitis or other concerning diagnoses. Conversely, pelvic ultrasound performed after a normal CT is unlikely to yield additional useful information.[7] (Ovarian torsion may be radiographically occult, and if suspected, gynecologic consultation should be considered because a laparoscopy

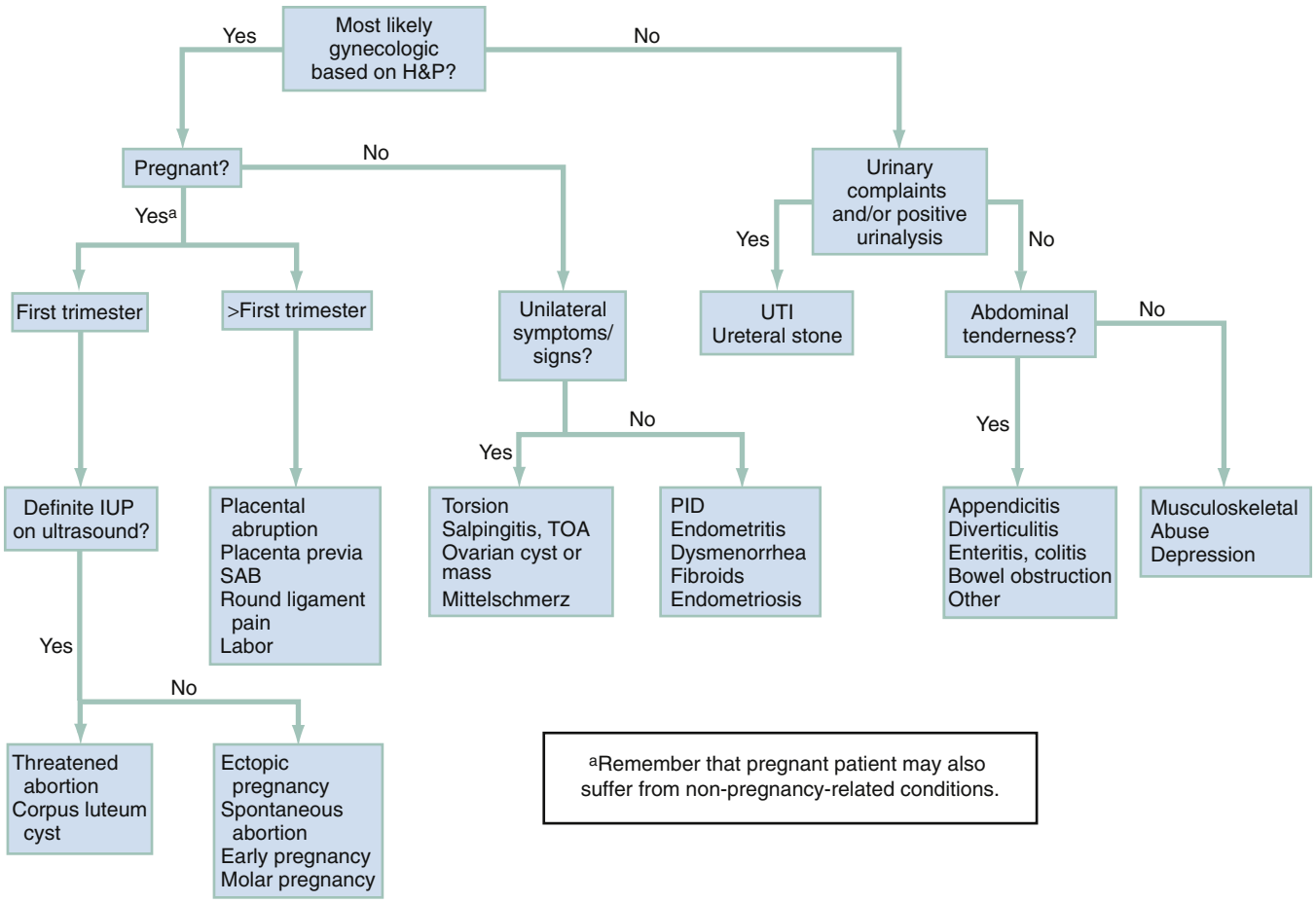

Fig. 29.1 Diagnostic algorithm for acute pelvic pain; see text for details. *H&P,* History and physical; *IUP,* intrauterine pregnancy; *PID,* pelvic inflammatory disease; *SAB,* spontaneous abortion; *TOA,* tubo-ovarian abscess; *UTI,* urinary tract infection.

may need to be performed to obtain a definitive diagnosis.) When ultrasound is nondiagnostic in a pregnant patient suspected of having appendicitis, we recommend MRI, which avoids the risk of disease progression during a prolonged observation period and obviates the need for ionizing radiation from CT. Patients whose pain does not seem to be from the reproductive tract often have urinary infections or stones, intra-abdominal sources of pain, musculoskeletal pathology, or may be victims of abuse or have depression. Vascular or neuropathic causes of pain are possible but less common.

If the available data do not make sense or conflict with clinical gestalt, the following three steps should be considered:

1. Ensure that emergent, life-threatening diagnoses have been addressed (e.g., ectopic pregnancy).
2. Reassess whether the presentation may be atypical (e.g., reconsider appendicitis).
3. If emergent causes are unlikely and sufficient consideration was given to less likely disorders without uncovering a cause, address the possibility of depression or abuse. Follow-up planning for all patients is recommended.

EMPIRICAL MANAGEMENT

An algorithm for the management of patients with acute pelvic pain is presented in Fig. 29.2. Patients in extremis are most likely hemorrhaging, although on occasion septic shock may be the cause. Ectopic pregnancy, placental abruption, and hemorrhagic ovarian cyst may cause life-threatening hemorrhage, with no or minimal vaginal bleeding. Patients with these disorders need rapid treatment with fluid and blood products and may require surgical intervention before stabilization can be achieved. A bedside ultrasound generally will help the clinician reach these presumptive diagnoses expediently. Septic shock may be a consequence of abdominal or pelvic processes and may require general surgical and gynecologic consultations, as well as admission to an intensive care setting.

We recommend early administration of analgesia for patients with significant pain, a practice that greatly improves patient comfort and the reliability of the physical examination, which is otherwise hampered by the patient's extreme pain, tenderness, or both. For severe pain, intravenous opioids such as morphine or hydromorphone are rapid and effective, titratable, and generally considered safe in pregnancy. After critical and emergent diagnoses have been excluded, well-appearing patients for whom a definitive or reasonable provisional diagnosis is reached may be discharged with close follow-up and appropriate treatment and precautions. Pregnant patients at a stage of fetal viability (20 weeks' gestation or as per institutional guidelines) should be referred to the obstetric service for fetal monitoring before discharge. Pregnant patients at a stage of fetal viability who have suffered abdominal trauma should undergo fetal monitoring before discharge.

The references for this chapter can be found online at ExpertConsult.com.

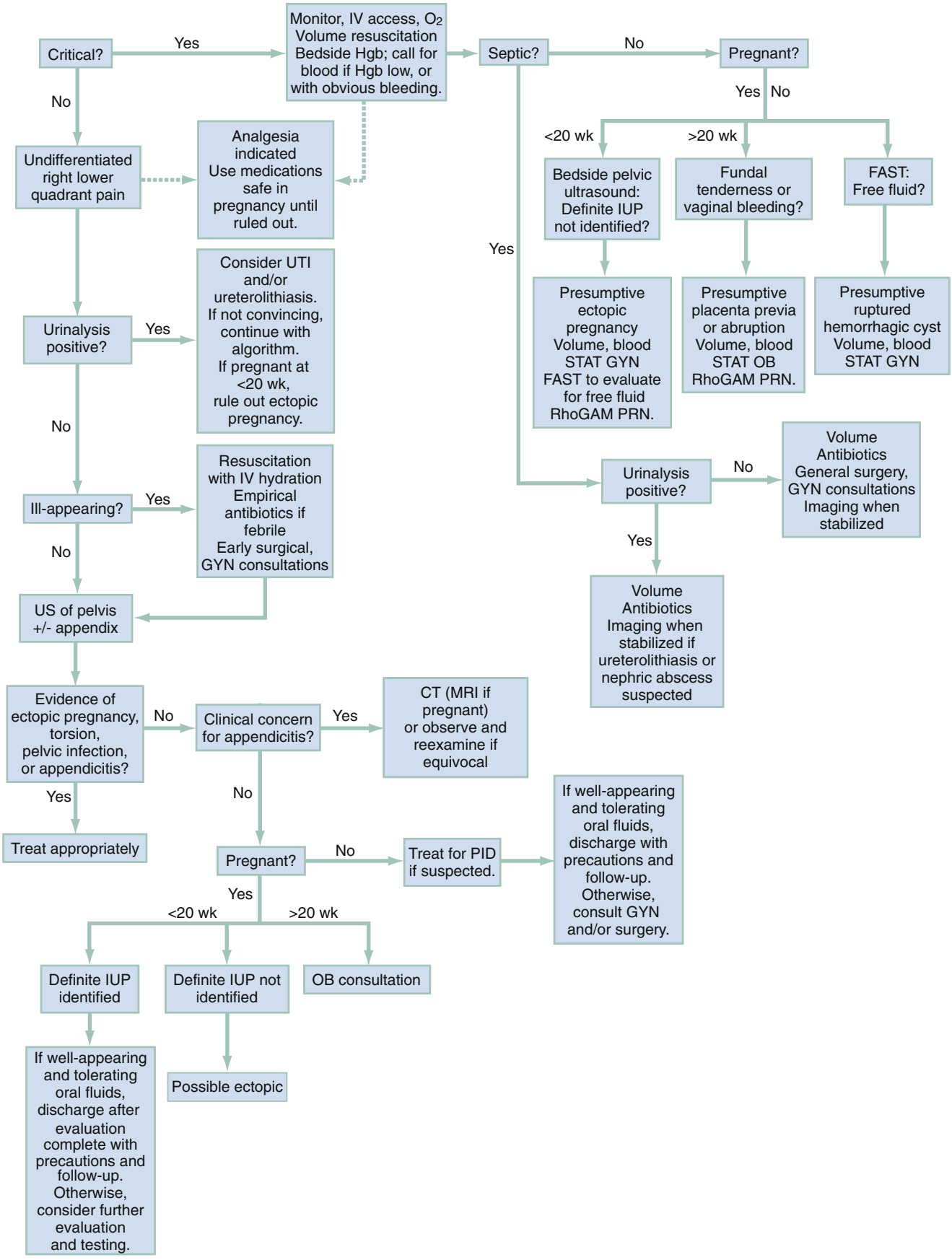

Fig. 29.2 Management algorithm for acute pelvic pain illustrating critical patients and right lower quadrant pain presentations. *CT,* Computed tomography; *FAST,* focused assessment with sonography for trauma; *GYN,* gynecology; *Hgb,* hemoglobin; *IUP,* intrauterine pregnancy; *IV,* intravenous; *MRI,* magnetic resonance imaging; *OB,* obstetric; *PID,* pelvic inflammatory disease; *STAT,* immediately; *US,* ultrasound; *UTI,* urinary tract infection.

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CHAPTER 29: QUESTIONS AND ANSWERS

1. Which of the following statements regarding the evaluation of patients with pelvic pain is true?

a. Ancillary testing can be limited to a urine pregnancy test in most patients.
b. Bimanual examinations have been shown to result in highly reliable findings, with substantial interobserver agreement.
c. Patients typically localize visceral pain with a high degree of accuracy.
d. Thorough history taking is adequate to exclude most life-threatening conditions.
e. None of the above.

Answer: e. It is rare that any particular finding on history or physical examination is reliable enough to make or exclude a particular diagnosis conclusively in patients presenting with pelvic pain, so ancillary testing (beyond a simple pregnancy test) is commonly required in the evaluation of these patients. Ultrasound is the most useful adjunct for most patients. The bimanual examination may, at times, provide important information. Unfortunately, however, findings on pelvic examination are somewhat subjective and unreliable and may serve more to localize the process to one side or the other rather than diagnose it or even limit it to the reproductive organs. Although pelvic pain often originates from the reproductive organs, it may arise from any structures that lie adjacent to or course through the pelvis. Visceral pain afferents supplying the pelvic organs have common innervation with the appendix, ureters, and colon. Their significant overlap makes accurate localization difficult for both patient and emergency clinician.

2. A 26-year-old female presents with right lower quadrant (RLQ) abdominal pain. She states her last menstrual period was 8 weeks ago. Bimanual pelvic examination reveals tenderness in the RLQ and right adnexal area. The patient's vital signs include a regular pulse of 120 beats/min and a blood pressure of 110/65 mm Hg. Urinalysis is unremarkable, and the urine pregnancy test is positive. What is the most appropriate next test?

a. Pelvic ultrasonography
b. Cervical cultures
c. Complete blood count (CBC)
d. Computed tomography (CT)
e. Magnetic resonance imaging (MRI)

Answer: a. This follows the algorithms in Figs. 29.1 and 29.2. The most life-threatening pathology requiring urgent or emergent intervention is hemorrhage from a ruptured ectopic pregnancy. Pelvic ultrasound scan is rapid and is the first step in an evaluation of a suspected ruptured ectopic pregnancy. In this case, bedside ultrasonography, if available, is strongly recommended.

3. A 30-year-old female presents with lower abdominal pain. She is not ill appearing and has lower abdominal, uterine, bilateral adnexal, and cervical motion tenderness on pelvic examination. She has a negative urine pregnancy test and urinalysis. What is the most appropriate next step in the patient's management?

a. Await cervical culture results.
b. Obtain a complete blood count.
c. Obtain a CT scan.
d. Obtain an erythrocyte sedimentation rate (ESR).
e. Treat with antibiotics.

Answer: e. The constellation of uterine tenderness, bilateral adnexal tenderness, and cervical motion tenderness is classically associated with pelvic inflammatory disease (PID), particularly when the pain onset is during or just after menstruation. However, the diagnosis may be made without the presence of all three signs, and treatment may be initiated with only one sign in an at-risk patient, as given in the 2015 Centers for Disease Control and Prevention (CDC) guidelines. Ultrasound is not strictly necessary in this case but should be performed if there is any concern for a complication, such as tubo-ovarian abscess.

4. A 35-year-old female using assisted reproductive technology presents with severe lower left quadrant (LLQ) abdominal pain and tenderness isolated to the left adnexal area on pelvic examination. The urine pregnancy test is positive, and the urinalysis is unremarkable. Rapid bedside ultrasonography reveals an intrauterine pregnancy with a gestational age of 6 weeks, 5 days, and moderate free pelvic fluid. Which diagnosis should be expediently further investigated?

a. Heterotopic pregnancy
b. Round ligament pain
c. Simple ovarian cyst
d. Tubo-ovarian abscess
e. None of the above

Answer: a. Women who are actively undergoing infertility treatment are at increased risk for ectopic pregnancy, heterotopic pregnancy, ovarian torsion, and ovarian hyperstimulation syndrome.

5. A 28-year-old female presents with sudden-onset, severe left adnexal pain that started 1 hour ago. The patient has left adnexal tenderness to palpation, but there is no vaginal discharge or bleeding, and no cervical motion tenderness. Urinalysis and urine pregnancy are negative. Pelvic ultrasound is unremarkable, and you do not suspect intra-abdominal pathology. The patient has required multiple doses of opiates for pain control in the emergency department (ED). What is the most appropriate next step in management?

a. Admit the patient for serial abdominal examinations.
b. Consult gynecology.
c. Discharge the patient with pain control and clinic follow-up.
d. Discharge the patient with treatment for PID and clinic follow-up.
e. Obtain a CT scan of the pelvis.

Answer b. Ovarian torsion should be suspected based on this patient's history and examination. Because torsion can be a radiographically occult diagnosis, gynecology should be consulted as laparoscopy may be needed for definitive diagnosis. Less emergent conditions, such as nephrolithiasis, could also be considered.

6. A 26-year-old female who is pregnant at 30-weeks' gestation presents with vaginal bleeding and pelvic cramping. She states the cramping and bleeding started 2 hours ago and she has filled one pad so far. She has not had any prenatal care. Which of the following should be initially avoided during this patient's evaluation?

a. Obstetrics consultation
b. Intravenous (IV) fluids
c. Pelvic examination
d. Type and Screen
e. Ultrasound

Answer c. Pregnant patients beyond 20-weeks' gestation with complaints of vaginal bleeding should undergo transabdominal pelvic ultrasound for placental localization before the pelvic examination. The concern is that placenta previa, which can be worsened by pelvic examination, may be the cause of the bleeding. Obstetrics will need to be involved in this patient's care, as two important potential diagnoses are placenta previa and placental abruption. In any case, the patient will need obstetric observation and fetal monitoring. A type and screen should be performed as Rho(D) immune globulin is indicated if the patient is Rh negative.

7. A 34-year-old female presents with severe abdominal pain. She does not allow for an abdominal examination and keeps pushing your hand away any time you attempt to even mildly palpate her abdomen. Her vital signs are stable. What is the most important and appropriate next step in this patient's care?

a. IV fluids
b. IV opiates
c. Oral (PO) opiates
d. PO acetaminophen
e. Do not give any medications at this time

Answer b. We recommend early administration of analgesia for patients with significant pain. Analgesia greatly improves patient comfort and the reliability of the physical examination, which is otherwise hampered by the patient's extreme pain, tenderness, or both. For severe pain, intravenous opioids such as morphine or hydromorphone are rapid and effective, titratable, and generally considered safe in pregnancy. In a patient who may require surgery, it is recommended to keep the patient nil per os (NPO).

Vaginal Bleeding

Joelle Borhart

KEY CONCEPTS

- Pregnancy status is the single most important determination to make in evaluating a patient with vaginal bleeding.
- The use of the term *dysfunctional uterine bleeding* is no longer recommended, and the term *abnormal uterine bleeding* is preferred.
- The etiologies of abnormal uterine bleeding can be divided into structural and nonstructural causes using the PALM-COEIN classification. Structural causes include ***p***olyps, ***a***denomyosis, ***l***eiomyomas, and ***m***alignancy (**PALM**). Nonstructural causes include ***c***oagulopathy, ***o***vulatory dysfunction, ***e***ndometrial, ***i***atrogenic, and ***n***ot yet classified causes (**COEIN**).
- For nonpregnant patients, the numerous causes of abnormal uterine bleeding are best categorized by patient age. The possibility of cancer should always be considered in postmenopausal women.
- Hormonal and nonhormonal treatments can be initiated in the emergency department to temporize an acute bleeding episode in a nonpregnant patient until they can follow up with their gynecologist.
- Vaginal bleeding is common in early pregnancy. Most patients will be diagnosed with threatened miscarriage, but ectopic pregnancy should always be considered at any level of serum β-hCG.
- Vaginal bleeding after the 20th week of pregnancy is less common and is often associated with significant morbidity and mortality for the mother and fetus. These patients should be managed in close consultation with an obstetrician.

FOUNDATIONS

Background and Importance

Abnormal uterine bleeding (AUB) occurs in women of all ages and can significantly impair quality of life. Abnormal vaginal bleeding in nonpregnant patients is rarely life threatening but may herald serious underlying pathology, such as cancer. Bleeding as a complication of pregnancy poses significant risk of morbidity and mortality to the fetus and mother.

Pathophysiology

Nonpregnant Patients

The mean time between menstrual periods is 28 days (±7 days), with menstruation generally lasting for 5 days. It is considered abnormal to bleed for more than 7 days. The average blood loss per menstruation is 35 mL; a loss of more than 80 mL is abnormal.

Since 2011, the American College of Obstetricians and Gynecologists (ACOG) has recommended the PALM-COEIN classification system, which uses the all-inclusive term *abnormal uterine bleeding* (AUB) and divides the causes of AUB into structural and nonstructural causes. Structural causes include ***p***olyps, ***a***denomyosis, ***l***eiomyomas, and ***m***alignancy (**PALM**). Nonstructural causes include ***c***oagulopathy, ***o***vulatory dysfunction, ***e***ndometrial, ***i***atrogenic, and ***n***ot yet classified causes (**COEIN**).[1] The use of the term *dysfunctional uterine bleeding* is no longer recommended.

Approximately 50% of cases of excessive menstruation fall under the nonstructural PALM-COEIN category of ovulatory dysfunction, which includes anovulatory bleeding. If a woman does not ovulate, there is no corpus luteum to produce progesterone, which results in estrogen being unopposed. Unopposed estrogen causes the endometrium to proliferate to the point at which it becomes unstable and begins to break down, causing irregular and unpredictable bleeding to occur. Cyclical heavy bleeding can also occur in the setting of regular ovulation (ovulatory bleeding).

Leiomyomas (fibroids) are benign tumors of the uterus that can be associated with significant morbidity including excessive menstrual bleeding.[2] Submucosal fibroids (fibroid that project into the uterine cavity) are especially prone to unpredictable and heavy uterine bleeding because they result in increased endometrial surface area that prevents uterine contractions from adequately compressing the vessels on the surface of the endometrium.[3] Fibroids are common and occur almost exclusively among reproductive-age women. The incidence increases with age and is highest for women ages 45 to 49 years. Black women are disproportionally affected (rates twofold to threefold higher).[4] Cervical polyps, which commonly occur in multiparous women in their 40s and 50s, are friable and prone to bleeding.

Pregnant Patients

Pregnant women may experience bleeding throughout their pregnancy. In early pregnancy, ectopic pregnancy causes hemorrhage into the fallopian tube by disrupting of the blood supply to the ectopic gestational sac. In addition, the size of the growing gestational sac can rupture through the tubal wall.

After the 20th week of pregnancy, vaginal bleeding can be caused by placenta previa, in which the placenta completely or partially covers the internal cervical os. As the lower part of the uterus becomes thinner during the third trimester in preparation for labor, bleeding can occur. Placental abruption causes bleeding when the placenta tears away from the uterine wall. This can occur spontaneously or secondary to abdominal trauma, with transmission of forces to the uterus. It is important to note that a large amount of concealed blood can be retained between the detached placenta and uterus, and the extent of the hemorrhage may not be fully appreciated until delivery. The most significant risk factor for abruption is a history of abruption in prior pregnancies (10-fold increased risk). An increased incidence is also seen in pregnancies complicated by hypertensive disorders, including preeclampsia, eclampsia, the HELLP (***h***emolysis, ***e***levated ***l***iver enzymes, and ***l***ow ***p***latelets) syndrome, and abnormal implantation of the placenta (e.g., placenta previa, accreta, increta, percreta). Smoking and cocaine use also increase the risk for abruption.

In the immediate postpartum period (first 24 hours), bleeding is usually the result of uterine atony if the uterus fails to contract. Atony is

BOX 30.1 Differential Diagnosis of Abnormal Uterine Bleeding in Nonpregnant Females

Structural Causes
Polyps
Fibroids
Malignancy
Hyperplasia
Endometriosis

Nonstructural Causes
Coagulopathies
von Willebrand disease
Factor XI deficiency
Thrombocytopenia
Idiopathic thrombocytopenic purpura
Endocrine
Polycystic ovarian syndrome
Hypothyroidism
Hyperprolactinemia
Adrenal hyperplasia
Cushing disease
Weight loss, extreme exercise
Stress
Obesity
Trauma
Sexual abuse
Infections
Sexually transmitted infection
Tubo-ovarian abscess
Vaginitis
Systemic disease
Liver disease
Kidney disease
Foreign bodies
Medications
Antiepileptics
Antipsychotics
Anticoagulants
Hormonal medications
Steroids
Intrauterine device

Note: Divide patients with vaginal bleeding into groups based on age when formulating a differential diagnosis.
From Borhart J. Emergency department management of vaginal bleeding in the nonpregnant patient. *Emerg Med Pract* 2013;15:1–20.

more likely to occur with conditions that overdistend the uterus, such as a large-for-gestational-age fetus, polyhydramnios, and multiparity. Prior history of postpartum hemorrhage, prolonged labor, induced labor, augmentation of labor with oxytocin, and instrumentation delivery also increase the risk of postpartum hemorrhage.[5] After 24 hours postpartum, retained products of conception (POCs) are the most common cause of bleeding.

DIAGNOSTIC APPROACH

Differential Considerations

Nonpregnant Patients

In nonpregnant women, there are numerous causes of AUB (Box 30.1), and it is helpful to categorize the differential diagnosis by the age of the patient. In *prepubescent girls*, causes of vaginal bleeding include vaginitis, foreign bodies, sexual abuse, tumors, and trauma. In *adolescent girls*, a common cause of abnormal vaginal bleeding is persistent anovulation due to immaturity of the hypothalamic-pituitary-ovarian axis.[6] Underlying bleeding disorders and coagulopathies, such as von Willebrand disease, may also first present in adolescence.[7] Sexually transmitted infections may also cause abnormal bleeding in this age group. For *women in their reproductive years*, structural lesions such as polyps and fibroids frequently cause abnormal bleeding. Black women are more likely to have fibroids, and they experience disproportionally more morbidity from heavy bleeding.[4] Endocrine causes, such as polycystic ovarian syndrome, should be considered in women with signs of androgen excess—obesity, acne, hirsutism. In *perimenopausal women*, anovulatory cycles become common as ovarian function declines. Endometrial atrophy is the most common cause of abnormal bleeding in *postmenopausal women*; however, the possibility of cancer should always be considered in this age group.

Regardless of age, review a patient's medication list for drugs that are known to cause abnormal bleeding (e.g., antiplatelet agents, anticoagulants), antiepileptic agents (especially valproic acid), and typical and atypical antipsychotics and steroids can cause AUB.

Pregnant Patients

For pregnant women with vaginal bleeding, the differential diagnosis is refined based on whether the bleeding occurs in early or late pregnancy or postpartum. For patients with vaginal bleeding in early pregnancy (before the 20th week of gestation and prior to fetal viability), common causes include miscarriage, ectopic pregnancy, implantation bleeding, molar pregnancy, and ruptured corpus luteum cyst. Bleeding in early pregnancy is common, affecting up to 20% of pregnancies. Miscarriage, defined as the spontaneous termination of pregnancy before the 20th week of gestation is also common; approximately 50% of women with early bleeding will miscarry. Miscarriages are described as threatened, missed, inevitable, incomplete, or complete depending on the status of the internal cervical os and if any POCs have been passed. The most concerning diagnosis in patients with bleeding in early pregnancy is ectopic pregnancy, a pregnancy implanted outside the uterus. Ectopic pregnancy is a leading cause of first-trimester maternal death, and the prevalence among emergency department (ED) patients presenting with pain or bleeding or both in the first trimester of pregnancy has been reported to be as high at 18%. Risk factors for ectopic pregnancy include pelvic inflammatory disease, previous ectopic pregnancy, prior tubal surgery, use of an intrauterine device, and endometriosis. However, half of women diagnosed with an ectopic pregnancy do not have any identifiable risk factors.

An important subgroup of patients are women undergoing assisted reproduction or in vitro fertilization (IVF). These patients are at increased risk for heterotopic pregnancy, which is a simultaneous intrauterine pregnancy (IUP) and ectopic pregnancy. Heterotopic pregnancies are rare in the general population.

Vaginal bleeding after the 20th week of pregnancy is less common, occurring in approximately 4% of pregnancies. Bleeding complications in late pregnancy generally occur in the third trimester and include placenta previa, placental abruption, and uterine rupture.

Pivotal Findings

Symptoms

Begin by eliciting the timing and duration of bleeding. Volume of blood loss is difficult to quantify because historical features, such as the frequency of changing a sanitary pad or tampon, have not been shown

to reliably predict blood loss; however, soaking more than one pad or tampon every 1 to 2 hours is suggestive of heavy bleeding.[6] Normal menstrual blood does not clot; therefore the presence of clots indicates heavy bleeding. A report of dizziness, syncope, or weakness could also indicate significant blood loss. Associated symptoms such as abdominal pain, fever, vaginal discharge or odor, and postcoital bleeding may indicate a possible sexually transmitted infection or pelvic inflammatory disease. Postcoital bleeding can also indicate a cervical lesion and occurs more commonly in pregnancy due to increased cervical blood flow.

A history of trauma should be noted. Vaginal injuries can be sustained in a number of ways and range in severity from minor contusions to deep lacerations. The most common mechanism of genital injury in adult women is coitus. In pregnancy, blunt trauma, such as falls, motor vehicle accidents, and interpersonal violence, is associated with a significantly increased risk of maternal and fetal morbidity and mortality.

Signs

For any patient presenting with vaginal bleeding, begin by determining the patient's hemodynamic status and performing a complete abdominal and pelvic examination. The pelvic examination may reveal the source of bleeding because masses, polyps, ulcers, foreign bodies, and evidence of trauma or inflammation may be visualized. After the 20th week of pregnancy, a pelvic examination should be deferred until after an ultrasound has been performed to exclude placenta previa as the cause of bleeding. In pregnant patients of sufficient gestational age, the fetal heart rate and fundal height should also be assessed. Fetal heart rate can be measured using the M mode on bedside ultrasound as opposed to Doppler because this is thought to transmit less acoustic energy to the fetus. Fetal cardiac activity may be measured as early as 6 weeks. Uterine size can be estimated by palpating the fundus. The uterus is palpable at the level of the umbilicus at 20 weeks. The fetal age is more than 24 weeks (i.e., viable) if the uterus can be felt at least four fingerbreadths above the umbilicus. This method may be less reliable in multiple pregnancies or other conditions that might affect the distention of the uterus or abdomen, such as large fibroids, polyhydramnios, oligohydramnios, intrauterine growth restriction, and obesity. Bedside ultrasound can also be used to estimate fetal age.

Ancillary Testing

Determination of pregnancy status is essential in the evaluation of any woman of reproductive age presenting with vaginal bleeding. Other critical laboratory tests in hemodynamically unstable patients include complete blood count, type and crossmatching of blood, coagulation studies, and, if pregnant, a quantitative β-human chorionic gonadotropin (β-hCG) level and Rh status determination.

Bedside ultrasound has become increasingly used in the ED evaluation of pregnant women with vaginal bleeding to determine whether an IUP is present. A yolk sac is the first sonographic evidence of a definite IUP and can be visualized using transvaginal ultrasound (TVUS), beginning around the 5th week of pregnancy. *Pregnancy of unknown location* (PUL) is the term used to categorize pregnancy in a patient with a positive pregnancy test when neither an IUP nor an ectopic pregnancy can be visualized using ultrasound.[8] In this case, the quantitative β-hCG level has traditionally been used to determine if the level is in the discriminatory zone. The discriminatory zone is the level of β-hCG in which an IUP, if present, should be seen consistently by ultrasound. For TVUS the discriminatory zone has traditionally been accepted to be around 2000 IU/mL. However, the value of the discriminatory zone has been called into question because it is not as reliable at excluding a viable pregnancy as previously thought.[9] Multiple studies have reported that a viable IUP not visualized on ultrasound is possible if β-hCG levels are greater than the traditional discriminatory zone.[10] ACOG now advises that if the concept of the discriminatory zone is to be used to help diagnose ectopic pregnancy, the value should be as high as 3500 IU/mL to avoid the potential for misdiagnosis and possible disruption of a desired IUP.[8]

Caution should be used when interpreting a single β-hCG measurement, because a single measurement alone cannot diagnose viability or location of a pregnancy; serial hCG measurements can be trended over days to help differentiate normal from abnormal pregnancies. It is appropriate to repeat TVUS and β-hCG measurements in hemodynamically stable patients instead of initiating medical or surgical intervention for possible ectopic pregnancy based on the discriminatory zone alone. There is no β-hCG level at which an ectopic pregnancy could be completely ruled out.

Additional testing for the stable, nonpregnant ED patient, such as thyroid and other hormonal studies, is usually performed on an outpatient basis. This also includes a complete pelvic ultrasound because the results will rarely change ED management.

DIAGNOSTIC ALGORITHM

Begin the evaluation by determining whether the patient is pregnant (Fig. 30.1). If the patient is not known to be pregnant or immediately postpartum, a urine pregnancy test should be performed. Next, determine the age of the pregnancy in weeks. The most critical diagnoses to consider in patients less than 20 weeks pregnant are ectopic and heterotopic pregnancies. Bedside ultrasound is useful to establish if an IUP is present. If the ultrasound is indeterminate, a quantitative β-hCG determination can help risk-stratify the patient further. Usually, the diagnosis will be threatened miscarriage.

For patients of more than 20 weeks' gestation, the crucial diagnoses to consider are placenta previa, placental abruption, uterine rupture, and arteriovenous malformation. Ultrasound should be performed before a pelvic examination in these patients.

For nonpregnant patients, the pelvic examination may reveal a cause of bleeding, but for most women in the ED, no cause will be identified. These patients will be diagnosed with AUB and should be referred for further gynecologic testing.

EMPIRIC MANAGEMENT

Patients with hemodynamic instability unresponsive to crystalloid fluid resuscitation require blood transfusion. For women of childbearing age, use Rh-negative blood if the Rh status of the patient is unknown. In addition to hemodynamic stabilization for severe bleeding in nonpregnant women, high-dose intravenous conjugated estrogen (Premarin) is considered first line treatment and may be administered every 4 to 6 hours for up to 24 hours (suggested dose, 25 mg). If bleeding continues, the vagina may be packed with long continuous gauze, which may be used with topical tranexamic acid (TXA). Alternatively, a Foley catheter or Bakri balloon may be inserted transvaginally into the uterus to tamponade bleeding. Vaginal packing, catheters, and balloon tamponade devices may be left in place for up to 24 hours.

Treatment of stable nonpregnant patients includes nonhormonal treatments such as nonsteroidal antiinflammatory drugs (NSAIDs) and antifibrinolytic medications such as tranexamic acid (TXA). Despite their varying degree of platelet activity inhibition, NSAIDs decrease blood loss by reducing endometrial prostaglandin levels and promoting vasoconstriction in the uterus. Different types of NSAIDs

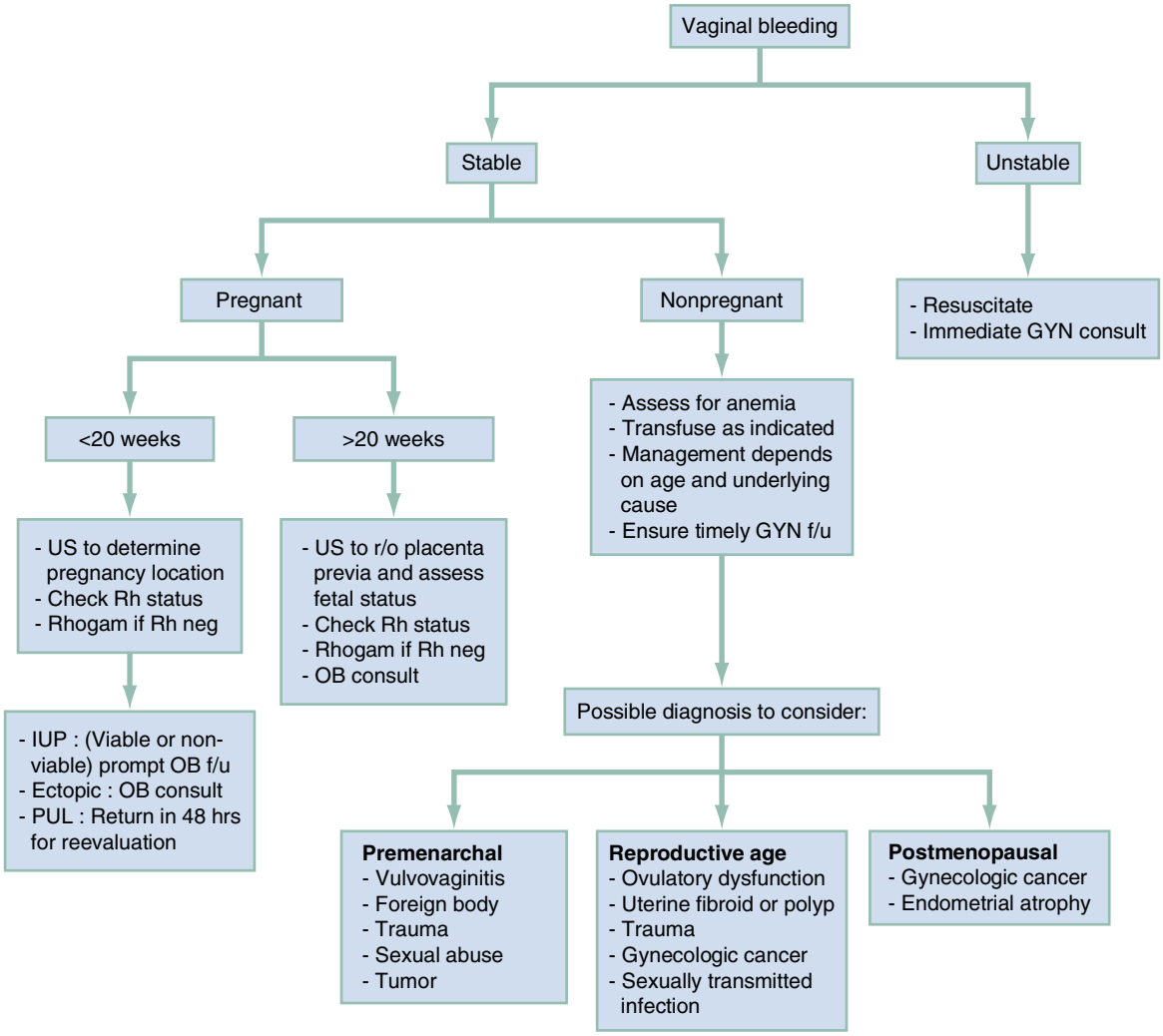

Fig. 30.1 Diagnostic Algorithm for Patient With Vaginal Bleeding. *GYN,* Gynecology; *IUP,* intrauterine pregnancy; *OB,* obstetrics; *PUL,* pregnancy of unknown location; *US,* ultrasonography.

appear to be equally effective at reducing bleeding.[11] TXA works by preventing clot degradation and has been shown to significantly decrease menstrual blood loss, especially for women with fibroids.[3,12] Hormonal treatments such as monophasic oral contraceptive pills are also frequently used to temporize a heavy bleeding episode and are typically prescribed as a taper. Hormonal treatment is likely to be most effective for women with suspected anovulatory bleeding. Any of the monophasic pills containing less than 35 µg of ethinyl estradiol can be used; a common low-dose regimen is one pill twice daily for 5 days and then one pill daily for the remainder of the pack.[13] Contraindications to the use of estrogen include a history of a thromboembolic event or stroke, pregnancy, active liver disease, severe uncontrolled hypertension, and women older than 35 years who smoke. High-dose, progestin-only treatment is a frequently used alternative therapy for women with contraindications to estrogen. A common regimen is medroxyprogesterone acetate (Provera) 10 mg, once daily, for 10 days (Table 30.1).

All unstable pregnant and postpartum patients should be managed in close consultation with an obstetrician. Patients with viable pregnancies may require emergency cesarean section. Unstable patients with confirmed or suspected ectopic pregnancies, heterotropic pregnancies, or previable IUPs may also require operative management. Stable patients with threatened, missed, incomplete, or inevitable miscarriages may be managed expectantly or medically with uterotonic medications such as misoprostol or may require dilation and evacuation or curettage. Rh status should be checked, and Rho(D) immune globulin treatment should be initiated in the ED for patients who are Rh negative. Management of the complications of pregnancy are discussed in detail in Chapter 173.

DISPOSITION

Most nonpregnant patients presenting to the ED with vaginal bleeding can be discharged home with timely gynecology follow-up. Adolescents with abnormal bleeding most likely have anovulatory cycles but should be evaluated for a possible underlying bleeding disorder. Perimenopausal and menopausal women with abnormal bleeding should have expedited follow-up for evaluation of possible malignancy. If sexual abuse is suspected in prepubertal girls, a safe environment for the patient must be ensured before considering discharge. Hospitalization

TABLE 30.1 Pharmacologic Treatment Regimens for Acute Abnormal Uterine Bleeding

Drug	Suggested Dose[a]	Contraindications and Cautions[b]
Hormonal treatments (conjugated equine estrogen)	25 mg IV every 4–6 h until bleeding stops, up to 24 h	• Contraindicated in patients with active or past thromboembolic disease, breast cancer, or liver disease • Use with caution in patients with cardiovascular or thromboembolic risk factors
Combination oral contraceptive pills	Monophasic oral contraceptive pills containing <35 μg ethinyl estradiol recommended: One pill tid PO for 7 days *or* One pill bid PO for 5 days, then one pill qd until pack is finished	• Contraindicated in women >35 years who smoke • Contraindicated in women who have a history of deep vein thrombosis or pulmonary embolism, breast cancer, liver disease, known thromboembolic disorders, pregnancy, ischemic heart disease, cerebrovascular disease, or uncontrolled hypertension
Progestin-only oral contraceptive pills (medroxyprogesterone acetate)	20 mg tid PO for 7 days	• Contraindicated in patients with active or past deep vein thrombosis or pulmonary embolism, liver disease, or breast cancer
NSAIDs		• NSAIDs contraindicated in patients with advanced renal disease • Use NSAIDs with caution in patients with history of GI ulcers or GI bleed and in patients with bleeding disorders
Ibuprofen	200–400 mg tid or qid PO for 5 days	
Mefenamic acid	500 mg tid PO for 4 or 5 days or until bleeding stops	
Naproxen	500 mg PO initially, then 250 mg tid or qid for 5 days	
Tranexamic acid	1.3 g PO every 6-8 hours up to 5 days	• Contraindicated in patients with current or past thromboembolic disease, acquired impaired color vision • Do not use with combined oral contraceptives

GI, Gastrointestinal*; IV,* intravenous; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PO,* by mouth.
[a]Other dosages and schedules also may be effective.
[b]Partial list of contraindications. The US Food and Drug Administration's labeling contains exhaustive lists of contraindications for each of these treatments. In making treatment decisions for women with abnormal uterine bleeding, emergency clinicians should consider the risks of treatment against the risk of continued bleeding on a case-by-case basis.
Adapted from Borhart J. Emergency department management of vaginal bleeding in the nonpregnant patient. *Emerg Med Pract* 2013;15:1–20.

should be considered for patients with significant or symptomatic bleeding.

Pregnant patients with ruptured ectopic or heterotopic pregnancies, placenta previa, placental abruption, or uterine rupture should be admitted to the hospital. Stable patients with threatened, inevitable, incomplete, or missed miscarriage can often be managed expectantly as outpatients, with close gynecology follow-up.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 30: QUESTIONS AND ANSWERS

1. To avoid the potential for misdiagnosis and possible disruption of a desired intrauterine pregnancy, American College of Obstetricians and Gynecologists (ACOG) recommends using which value of β-human chorionic gonadotropin (β-hCG) for the discriminatory zone?
   a. 1500 IU/mL
   b. 2000 IU/mL
   c. 3500 IU/mL
   d. 4500 IU/mL

Answer: c. The discriminatory zone has traditionally been accepted to be approximately 2000 IU/mL for transvaginal ultrasound (TVUS). However, viable intrauterine pregnancies may not yet be visualized on TVUS at β-hCG levels greater than 2000 IU/mL. Therefore ACOG currently advises that if the concept of the discriminatory zone is to be used to help diagnose ectopic pregnancy, the value should be as high as 3500 IU/mL to avoid the potential for misdiagnosis and possible disruption of a desired intrauterine pregnancy.

2. What is the most common cause of uterine bleeding in the immediate postpartum period?
   a. Uterine rupture
   b. Vaginal lacerations
   c. Retained products of conception
   d. Uterine atony

Answer: d. Postpartum hemorrhage is a leading cause of maternal mortality. Within the first 24 hours after delivery, this is usually caused by uterine atony. After 24 hours, the cause is frequently retained products of conception.

3. A 30-year-old woman with a history of polycystic ovarian syndrome (PCOS) and prior deep vein thrombosis (DVT) presents to the ED with 10 days of irregular, heavy uterine bleeding. Her vital signs are normal. What is the first step in her ED management?
   a. Check complete blood count (CBC).
   b. Order urine pregnancy test.
   c. Administer 25 mg intravenous conjugated estrogen.
   d. Prescribe a taper of oral contraceptive pills.

Answer: b. Pregnancy status is the single most important determination to make when evaluating a patient with vaginal bleeding and should be determined after assessing stability.

4. A 30-year-old woman with a history of polycystic ovarian syndrome (PCOS) and prior deep vein thrombosis (DVT) presents to the emergency department (ED) with 10 days of irregular, heavy uterine bleeding. Her vital signs are normal, and a urine pregnancy test is negative. She currently takes no medication. Which of the following is the most appropriate treatment?
   a. Oral contraceptive taper
   b. Medroxyprogesterone acetate
   c. Oral tranexamic acid
   d. Ibuprofen

Answer: d. Patients with PCOS may have anovulatory cycles and frequently benefit from hormonal treatment such as oral contraceptive pills. However, as the patient has a history of prior DVT she has a contraindication to hormonal treatments as well as oral tranexamic acid. Ibuprofen would therefore be the most appropriate treatment.

5. A 32-year-old woman who is 26 weeks pregnant describes a 1-hour history of painless vaginal bleeding after tripping and falling from a standing height. Her vital signs are normal, and physical examination of the abdomen reveals a nontender uterus with a fundal height 1 cm above the umbilicus. Of the following, which would be the most appropriate next step in evaluating this patient?
   a. Abdominal magnetic resonance imaging (MRI)
   b. Bimanual examination
   c. Sterile speculum examination
   d. Ultrasound

Answer: d. Painless vaginal bleeding after the 20th week of pregnancy is suggestive of placenta previa. Pelvic examination (speculum or bimanual) should be deferred until ultrasound has excluded placenta previa as the cause of bleeding.

31

Back Pain

Brian Niall Corwell and Natalie L. Davis

KEY CONCEPTS

- Acute low back pain is a common, costly, recurring and painful condition that often has no recognizable or dangerous cause.
- While most cases of back pain are non-specific and improve without laboratory evaluation or imaging, the aim of the emergency department (ED) assessment is to identify those serious and emergent pathologies that require urgent treatment.
- A thorough history and physical examination is performed with the goal of uncovering high-risk features predisposing the patient to an emergent or life-threatening etiology.
- The presence of multiple key clinical findings may increase the probability of disease and is often an indication for further investigation of patients with back pain. However, blindly allowing the presence or absence of these individual findings to guide diagnostic treatment will lead to potentially unnecessary, misleading, and costly investigations in most patients.
- Key clinical findings should supplement, not replace, clinical judgement when selecting appropriate laboratory and radiologic testing of patients with back pain. Imaging and laboratory studies are indicated only when there is evidence of neurologic deficit or multiple key clinical findings suggesting a dangerous or systemic pathologic cause.
- Patients who have low back pain emergencies are generally classified into five groups: (1) new onset back pain with neurologic findings in a patient with a malignancy history; (2) back pain and symptoms of epidural compression syndrome; (3) back pain with symptoms suggesting an infectious cause; (4) back pain with gross muscle weakness or paralysis; and (5) back pain with severe or progressive neurologic deficits.
- When a critical or emergent diagnosis is strongly suspected, MRI and spine surgery consultation should be undertaken emergently.
- Adherence to published guidelines will decrease improper laboratory studies and imaging, thereby lowering costs, improving ED throughput and improving overall patient care.
- Conservative therapies are recommended for most patients with nonemergent back pain given the high likelihood for recovery.

FOUNDATIONS

Background and Importance

Back pain is one of the most common chief complaints of emergency department (ED) patients in the United States.[1,2] It is an enormous source of health care expenditures and lost productivity, and causes more disability globally than any other condition. Most patients with acute back pain (defined as lasting less than 6 weeks) are ultimately diagnosed with mechanical or nonspecific back pain, or pain in the absence of a specific serious pathology. Patients with mechanical back pain generally have improvement in pain and disability in the first 6 weeks, though 65% report persistence of pain at least 1 week following an ED visit.[3] Those with chronic back pain (defined as lasting >3 months) will often experience persistence or a recurrence within 12 months. Three months after an ED visit for non-specific back pain, 30% to 40% report functional impairment and 16% report persistent moderate to severe pain.[3,4]

The goal of ED assessment is to separate the common benign causes of back pain from those that could result in significant morbidity or mortality if not promptly recognized. The key to accurate clinical decision-making in identifying the roughly 1% to 7% of ED patients with an emergent diagnosis is performance of a thorough history and physical examination with focus on identifying potential markers of serious disease that we will refer to as key clinical findings (Box 31.1).[5–10]

Pathophysiology

Back pain is a symptom rather than a disease. Just as headache or shortness of breath, it can have many causes both benign and serious. Back pain may be caused by a vascular, visceral, infectious, mechanical, or rheumatologic processes. Pain may originate from the spinal cord, nerve root, vertebral column, surrounding musculature, or an extraspinal origin (including thoracic, abdominal, or pelvic organs). The pathophysiology of non-radicular musculoskeletal back pain is frequently indeterminate; possible causes include muscle or ligament injuries, degenerative spinal disease, and disc herniation. Statistically significant modifiable risk factors for the diagnosis of back pain and sciatica include nicotine dependence (smoking), alcohol abuse, obesity, and depressive disorders.[7] Disc herniation occurs when the annulus fibrosis thins and tears, and the nucleus pulposus prolapses, usually laterally, compressing and inflaming a nerve root. Clinical symptoms are typically self-limited, with a high rate of spontaneous improvement and low likelihood of progression to a neurologic emergency. The natural history of disc herniation is that pain from pressure and nerve irritation improves as local inflammation subsides. The size of the disc protrusion may naturally decrease over time.

Although we commonly consider disc herniation and radiculopathy together, herniation is usually asymptomatic and likely only causes symptoms of sciatica occasionally. Radiculopathy is a clinical diagnosis of nerve root irritation and compression leading to symptoms in the distribution of the affected lumbar or sacral nerve root, such as pain, weakness, numbness or paresthesias. The most common causes are disc herniation and foraminal stenosis caused by spondylotic degeneration. The symptoms associated with disc disease resolve over time, while those associated with spinal stenosis tend to persist or worsen over time. Thickening of the ligamentum flavum and other degenerative changes with age contribute to spinal stenosis. The spinal cord ends at L1 in the adult, where it gives rise to the cauda equina. Compressive lesions above the cauda equina (i.e., the conus medullaris) cause upper motor neurologic signs. Compression of the cauda equina leads

BOX 31.1 Key Clinical Findings in the History and Physical Examination

Historical Information

Recent significant trauma
Sensation of ripping/tearing
Associated chest or abdominal pain
History of cancer
Anticoagulant use
Intravenous drug use
Immunocompromised status
History of prolonged glucocorticoid use
History of osteoporosis
History of abdominal aortic aneurysm
Patient >50 years
Unrelenting night or rest pain
Worsened with cough, Valsalva, sitting
Unexplained weight loss
Recent bacterial infection (skin/soft tissue, pneumonia, urinary tract infection)
Recent GI/GU procedure
Failure to improve after 6 weeks of conservative therapy
Bowel, bladder, and/or sexual dysfunction
Saddle anesthesia

Physical Examination

Abnormal vital signs—hypotension, hypertension, tachycardia, fever
Unequal blood pressure readings in the upper extremities
Murmur of aortic insufficiency
Pulse deficit or circulatory compromise of the lower extremities
Pulsatile abdominal mass
Urinary retention
Urinary or stool incontinence
Loss of rectal sphincter tone
Severe or progressive neurologic deficit
Focal lower extremity weakness
New ataxia or difficulty walking
Decreased perianal sensation

BOX 31.2 Differential Considerations in Acute Back Pain

Extraspinal Causes

Chest—aortic dissection, bacterial endocarditis, pulmonary embolism, pneumonia, pleural effusion, myocardial infarction
Abdominal—ruptured or expanding aortic aneurysm, esophageal disease, penetrating peptic ulcer disease, pancreatitis, pancreatic cancer, cholelithiasis (biliary colic), cholecystitis, cholangitis
Renal—nephrolithiasis (renal colic), perinephric abscess, pyelonephritis
Genitourinary—ovarian torsion or tumor, pelvic inflammatory disease, endometriosis, pregnancy, prostatitis
Musculoskeletal—acute muscle strain, acute ligamentous injury, osteoporosis, spinal curvature (lordosis, kyphosis), osteoid osteoma
Other—herpes zoster, retroperitoneal hemorrhage, psoas abscess, nonspecific low back pain

Spinal Causes

Cauda equina syndrome, spinal epidural abscess or hematoma, vertebral osteomyelitis, infectious discitis, fracture (traumatic, pathologic), malignancy (metastatic, leukemia/lymphoma, multiple myeloma, spinal cord tumor), transverse myelitis, spondylitis (ankylosing, psoriatic), spondylolysis or spondylolisthesis, disc herniation, degenerative disease (discs, facet joints), spondylosis (spinal osteoarthritis), isolated sciatica, spinal stenosis.

to lower motor neurologic findings. Cord compression can be caused by central disc herniation or other space occupying lesions such as abscesses, tumors, hematomas, or bone fragments.

Referred pain is perceived in a location other than that of the noxious stimulation. Irritation in a visceral organ frequently produces pain that may be perceived in somatic structures some distance away, such as a symptomatic abdominal aortic aneurysm (AAA) being felt as low back pain or ureteral colic being perceived as flank pain.

DIAGNOSTIC APPROACH

Differential Considerations

Following the history and physical examination, patients with acute back pain can be divided into three main categories: (1) those with serious extraspinal causes, such as abdominal aneurysm; (2) those with critical or emergent spinal pathology, such as epidural compression syndrome; and (3) those with musculoskeletal or nerve root pain. In the absence of radicular pain, the pain is classified as nonspecific low back pain (Box 31.2).

Myelopathy

Myelopathy is an injury of the spinal cord due to compression (from trauma, spinal stenosis, epidural tumor or abscess, degenerative disease or disc herniation), inflammation (such as transverse myelitis), or ischemia (from compression or embolization of the spinal blood supply). Depending upon the cause, its presentation may be acute or insidious with the gradual onset of lower extremity sensory deficits, loss of pain sensation, weakness, or gait disturbances that may be spastic and scissoring in quality. Upper motor neuron signs are present, such as hyperreflexia, hypertonia, Babinski sign as well as bladder dysfunction and multilevel neuropathic symptoms.

Radiculopathy

Radiculopathy is injury of the nerve root caused by irritation or compression resulting in pain, sensory abnormalities (in 90%) such as paresthesias, and less frequently weakness (in 15%) of the affected nerve root. The causes are similar to those for myelopathy. Differentiating myelopathy from radiculopathy is extremely important. Patients with evidence of acute myelopathy require urgent neuroimaging in the ED and appropriate consultation, while urgent imaging is generally not needed for radiculopathies unless progressive neurologic impairment exists.

Spondylosis

Spondylosis is a term for non-specific progressive degenerative changes (including spinal arthritis) of the vertebral bodies, facet joints, and central canal which typically affects patients greater than 60 years of age. This process can lead to neck or back pain due to nerve root compression and irritation (radiculopathy) or spinal cord compression (myelopathy) due to a variety of related processes including stenosis of the central spinal canal (spinal stenosis) and disc herniation.

With advancing age, spondylosis worsens, intervertebral discs lose height, the ligamentum flavum calcifies, and facet joints deteriorate, leading to narrowing of the vertebral column and foramina (spinal stenosis) and increasing risk of nerve and cord compression. This may be asymptomatic or present with classic symptoms of neurogenic claudication, or pain in the buttocks and/or legs provoked by standing and walking, which reduces canal size, and relieved by rest and bending forward (shopping cart sign), which increases canal size. Symptoms

may be unilateral but are more commonly bilateral and asymmetric. Poor correlation exists between symptom severity and degree of narrowing found on magnetic resonance imaging (MRI).[11] In the absence of acute myelopathy or progressive neurologic deficits, ED management is conservative.

Disc Herniation

Disc herniations occur when the annulus fibrosis thins and tears, and the nucleus pulposus prolapses. They may be asymptomatic or severely painful when they occur. The posterior longitudinal ligament does not extend laterally, so lateral herniation is most common. This can cause impingement and inflammation of the nerve root and radiculopathy symptoms. Clinical symptoms are typically self-limited, with a high rate of spontaneous improvement and low likelihood of progression to a neurologic emergency. The natural history of disc herniation is that pain from pressure and nerve irritation improves as local inflammation subsides. The size of the disc protrusion may naturally decrease over time. However, herniation of a large disc in the midline can cause cord compression and symptoms of myelopathy.

Spinal Infections

Bacterial spinal infections (epidural abscesses and vertebral osteomyelitis) are challenging but important diagnoses to make as they are life-threatening causes of back pain. These can occur due to contiguous spread from adjacent soft tissue infections, direct inoculation due to spinal procedures or trauma, or hematogenous spread. The presentation is often insidious with non-specific symptoms such as fatigue and nausea. Intraspinal abscess may be the most serious missed emergent condition in patients diagnosed with non-specific back pain.[12] No source is identified in one-third of epidural abscess cases. Symptoms may initially improve with conservative measures such as rest, making the diagnosis challenging and often leading initially to a non-infectious diagnosis such as musculoskeletal back pain. Almost half of patients are initially misdiagnosed and average two ED visits are made before diagnosis.

The most common symptom is diffuse spine pain and most common sign is severe local spinal tenderness. The classic triad of epidural abscess is fever, back pain, and focal neurologic deficits, but all three components are present in only 15% of cases. Fever is only present in 30% to 50% of patients at presentation and the neurological examination is normal in two-thirds of patients at first their ED visit. Suspect infectious etiology with new or progressive back pain in patients with recent intravenous drug use (IVDU). A recent study noted almost 40% of patients with a history of IVDU presenting to the ED with the onset of acute back pain had evidence of spinal infection on MRI performed within 24 hours.[13] Other risk factors include immunocompromised states, recent bacterial infection, chronic illnesses such as diabetes, and recent spinal procedures or trauma.

Staphylococcus aureus is the most common pathogen, though other gram positive and gram negative bacteria, as well as *Candida* species may cause infection as well.[9] The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests aid in risk stratification. If suspicion exists due to risk factors and examination findings, perform MRI with contrast, which is the gold standard for diagnosis of spinal infection.[14] The lumbar region is the most common site of infection but MRI of the entire spine is performed as extension to additional vertebral levels (average 3 to 5 cord segments) and non-contiguous skip lesions are common. Spinal infections are increasing in incidence due to more frequent invasive procedures as well as an aging population. Almost half of survivors are left with residual neurologic deficits and irreversible paralysis can occur if treatment is delayed.

Spinal Tumors

Neoplastic epidural spinal cord compression is a neurologic emergency that is caused by both benign and malignant tumors. The most common source is metastatic spread to the vertebrae from primary sources including lung, prostate, and breast cancers as well as multiple myeloma and lymphoma. Metastatic cord compression develops in 2.5% to 5% of patients with terminal cancer diagnoses and is the first sign of systemic cancer in 20% to 34%. The thoracic spine is involved most commonly and severe local back pain is the primary symptom in 80% to 95% of presentations. Infiltration leads to spine instability and risk of fractures and cord compression. Pain may precede weeks before neurologic symptoms and is described as dull, constant, not relieved by rest, and may be worse at night. Neurologic symptoms of myelopathy may include gait ataxia, bladder dysfunction, and weakness or paralysis. Suspect this diagnosis in patients with new onset back pain and new neurologic symptoms and a history of cancer. Timely diagnosis and treatment are important to reduce permanent injury. If neoplastic cord compression is suspected, obtain MRI with contrast of the full spine since pain and neurologic deficits may not correlate with the spinal level of the lesion.

Cauda Equina Syndrome

Cauda equina syndrome (CES) is a neurologic emergency caused by compression of the nerves of the cauda equina. CES is most often caused by disc herniation at L4/5 or L5/S1, as well as by other space occupying lesions such as abscesses, hematomas, fractures, lumbar spondylosis, and tumors. Compression in the lower region of the spinal cord (conus medullaris) can lead to both lower and upper motor deficits due to nerve root and spinal cord injury, while compression of the cauda equina leads to lower motor deficits only.

Clinical presentation is variable and no symptoms or signs are 100% sensitive or specific in isolation, which is why the time from first symptoms to diagnosis averages 11 days. This diagnostic difficulty was demonstrated in a study in which only 56% of patients with MRI positive for CES were accurately identified by senior neurosurgical residents based on history and physical examination. Classic features include bladder dysfunction (found in ~90%), bowel dysfunction (~50%), sexual dysfunction, saddle anesthesia (decreased perianal and genitourinary sensation, found in 80%), and unilateral or bilateral radiculopathy (progressively worsened back and lower extremity pain that is worse with recumbent positioning, weakness, and sensory abnormalities like paresthesias, found in ~96%).[15] Saddle anesthesia has the highest predictive value in diagnosing MRI-proven CES. However, these features are often late findings and signs and symptoms do not develop in a predictable manner. Further clouding this picture is that up to two-thirds of patients have preexisting chronic back pain. Because of the variable presentation, clinicians should have a low threshold for emergent imaging. Diagnosis is made by MRI of the lumbosacral spine.

CES is divided into two categories based on the effect on the bladder: CES-I (incomplete) and CES-R (retention). CES-I patients have urinary issues with reduced bladder sensation and difficulty voiding (decreased desire to void, strained micturition and decreased urinary stream). CES-R patients have complete urinary retention with overflow incontinence. This clinical characterization has important prognostic value. The functional status of patients at the time of presentation is predictive of prognosis. Variable deficits with micturition, defecation, and sexual function, are common residual symptoms irrespective of time to surgical decompression. Due to the nature of these lifelong complications, there is a strong association with CES and medico-legal litigation. Document a thorough history and physical examination, as well as attempts to obtain emergent imaging and consultation.

Acute Transverse Myelitis

Acute transverse myelitis is a rare disorder caused by spinal cord inflammation, rather than a compressive lesion, leading to motor, sensory, and autonomic dysfunction. It is most often idiopathic but can occur as an initial presentation of multiple sclerosis, autoimmune disorders (e.g., lupus), and vasculitis. Associations exist with preceding viral infections (e.g., varicella, herpes, cytomegalovirus) and bacterial infections (e.g., tuberculosis, Lyme disease, syphilis) either related directly to infection or due to post-infectious inflammation. Bimodal peaks exist between ages 10 and 19 years as well as 30 and 39 years. Presentation may be variable based on spinal segment involved, most commonly thoracic followed by lumbosacral, and is often bilateral. Presentation may be similar to other causes of myelopathy, including motor and sensory abnormalities, risk of progressive paralysis, and bladder, bowel, and sexual dysfunction. In an ED population eventually confirmed to have ATM, it was the initial diagnostic impression in fewer than 10% of cases. Diagnosis is made by full spine MRI with and without contrast. If multiple sclerosis is suspected, non-emergent brain MRI can be performed.

Mechanical Back Pain

Pain without a clear origin and not caused by a specific disease or spinal abnormality is defined as "non-specific" or mechanical back pain. This is the most common cause of back pain presenting to the ED but is a diagnosis of exclusion, after excluding other worrisome causes of back pain. Underlying causes are poorly understood and can include muscle strain, ligamentous strain, myofascial pain, facet joint arthritis, and disc disease. These patients report mild-to-moderate pain with an otherwise negative history and benign physical examination. There is an absence of radiculopathy and myelopathy symptoms. Pain is generally unilateral, often described as "aching," "throbbing" and "spasmodic," and is exacerbated by activity and improves with rest. Pain may radiate to the buttocks or posterior thigh but not past the knee. Because most patients with nonspecific back pain experience symptomatic improvement within 6 weeks, only conservative management is needed. No further diagnostic testing is required beyond the history and physical examination.

Chronic Back Pain

In the absence of new findings, chronic back pain (defined as pain lasting over 3 months) is often regarded as one of the most challenging clinical scenarios. One-third of ED patients will report functional impairment and pain three months after an ED visit for acute, non-traumatic, non-radicular back pain.[4] The underlying cause of chronic pain is complex and multifactorial, making proper assessment and treatment nearly impossible in the ED setting. These patients usually require a multidisciplinary treatment approach for the greatest chance for success. For some patients, chronic, recurrent back pain is a long-term issue, and they may visit the ED during an acute exacerbation. These patients still require a thorough examination and review of key clinical findings to stratify based on risk and to guide ED evaluation. Labelling these patients without performing a thorough investigation can have dangerous consequences. For example, CES is often seen in those with a prior history of back pain or sciatica.

Pivotal Findings

While most patients with back pain will be diagnosed with mechanical or non-specific causes, the emergency clinician must consider and confirm or exclude potentially life-threatening and disabling causes of back pain that require urgent treatment (seen in <1% in primary care, but 1% to 7% in the ED).[5] A thorough history and physical examination are invaluable. Technologically sophisticated radiologic and laboratory studies are not a substitute for a detailed history and physical examination. This approach will help separate patients into high- and low-risk groups. Specific findings will guide the additional evaluation of patients with neurologic deficits and more serious spinal or visceral sources (Table 31.1).

Symptoms

As with any patient who complains of pain, symptoms should be characterized by basic historical elements of the episode, such as the rate of onset, duration, severity, location, and quality (dull, aching, shooting, burning), exacerbating or alleviating factors, effects on activities of daily living and the presence of key clinical findings (see Box 31.1). Identify associated characteristics such as weakness, gait abnormalities, clumsiness, loss of fine motor skills, radiation, and/or paresthesias. Inquire specifically about bowel and bladder function, sexual dysfunction, or loss of sensation in the groin, as these indicate more serious pathology. Rather than asking about urinary incontinence, one should ask about difficulty passing urine and retention. Discussing issues related to sexual dysfunction are difficult for both clinicians and patients, but is important in the evaluation of epidural compression. Rather than asking if there are any issues with sexual function, a more direct and informative way would be to ask if the patient has a "change in ability to achieve an erection or ejaculate" or "loss of sensation in genitals during sexual intercourse."[8] Inquire about demographic features and comorbidities such as intravenous (IV) drug use, diabetes, age, immunocompromised states, osteoporosis, history of cancer, and constitutional symptoms (fever, chills and weight loss).

The different causes of acute back pain have distinguishing characteristics. Typical mechanical or non-specific back pain is unilateral, worsened with movement, alleviated with rest, and not associated with complaints of numbness, weakness, bowel or bladder dysfunction (see Table 31.1). Pain may radiate generally to the buttocks or posterior thigh areas, but not past the knee. Radicular (nerve root) pain occurs in a more focal dermatomal distribution, and often radiates distal to the knee toward the foot. There may also be associated numbness or weakness, relieved with recumbent positioning, exacerbated by Valsalva maneuvers (coughing, sneezing), and positions that produce increased pressure on annular fibers (prolonged sitting, standing, and bending postures).

Multi–nerve root pathology or the presence of bilateral symptoms is a potential indicator of a spinal mass lesion or large central disc herniation, which compresses multiple descending nerve roots within the spinal canal. Peripheral nerve pain may be described as "pins and needles" as opposed to nerve root pain (radiculopathy), which is transient and very sharp and "electrical."

Discogenic pain is typically worse with flexion, whereas pain from spondylolysis (defect or stress fracture in the pars interarticularis of the vertebral arch) is aggravated by facet loading, which occurs in extension. Inflammatory pain (spondyloarthritis) is insidious in onset, affects younger patients (under age 40), improves with exercise but not with rest, and causes pain at night with improvement upon arising.

Spinal stenosis is suggested by back pain with unilateral or bilateral radiculopathy that is worsened with back extension (walking and prolonged standing) since erect posture narrows the cross-sectional area of the central canal and neural foramina, most commonly in lumbar spine area. It is relieved by forward flexion (shopping cart sign), which increases spinal canal diameter, temporarily relieving the stenosis. Spinal stenosis can cause diffuse intermittent burning, cramping pain in the back, motor weakness, reflex changes, and pain radiating to the buttocks, thigh, and legs, with associated paresthesias. This symptom constellation is termed neurogenic claudication (also called pseudoclaudication) and is caused by neurologic compression, unlike vascular

TABLE 31.1 Classical Findings in Selected Serious Causes of Acute Back Pain

Findings	Diagnoses	History	Important Physical Examination Findings	Ancillary Testing	Comments
Critical					
Vascular	Aortic dissection	Often sudden-onset, tearing, severe chest and/or back pain; associated nausea, vomiting, acute anxiety common; syncope can occur.	Associated diaphoresis, unstable vital signs; hypertension common; unequal upper extremity blood pressure; new-onset aortic insufficiency murmur; central and peripheral neurologic deficits secondary to ischemia	Choice of CT, transesophageal ECHO, MRI; depends on patient stability and availability of equipment	More common as cause of thoracic back pain.
	AAA, Abdominal aortic aneurysm (ruptured, expanding)	Pain typically noted in the abdomen, but back, flank, or pelvic pain, or radiation to groin may occur; syncope may be present.	Pulsatile abdominal mass, abdominal bruits; hypoperfusion	Bedside US; if stable, abdominal CT with contrast; plain films may show calcified, enlarged, aortic contour	Can also mimic renal colic, GI bleeding, diverticulitis, myocardial infarction; 30% of signs are misdiagnosed.
Infectious	Spinal epidural abscess	At-risk population with diabetes, chronic renal failure, dialysis, IV drug use, HIV/AIDS, immunosuppression, steroid use, alcoholism, cancer, recent spinal surgery, trauma, recent bacterial infection, bacteremia	Fever (50%), back pain (75%); focal neurologic deficits are late findings (<50% of patients); all three (classic triad) present in 15%; localized body tenderness along spine; rare cauda equina–like syndrome	Elevated WBC (66%), ESR/CRP (80%–100%) sensitive but nonspecific; MRI with contrast is modality of choice; CT if MRI contraindicated; search for source of infection; obtain blood cultures; *Staphylococcus aureus* most common cause (>50%)	Manifests as mass- occupying lesion compressing spinal cord; may be mistaken for hematoma, malignancy, herniated disc; abscess drainage may be necessary; start IV antibiotics immediately as 5% will die from sepsis.
Mechanical	Epidural compression syndrome (e.g., cauda equina syndrome, neoplastic cord compression)	Usually history of back pain, cancer; symptoms may develop over hours; sciatica (96%), urinary dysfunction (89%), bowel dysfunction (47%)	Urinary retention, fecal incontinence; saddle anesthesia (81%), bilateral leg pain; lower extremity weakness with hyporeflexia	Evaluate postvoid residual; MRI makes the diagnosis, consider performing with contrast if infection or cancer highly suspected; if contra-indicated, then obtain CT	Emergent condition caused by compression of lumbosacral nerve roots; functional status at diagnosis highly predictive of longer term outcomes.
	Spinal fracture with cord impingement, or unstable fracture	Acute onset, localized pain; usually trauma history; older adults; chronic steroid use; osteoporosis	Bone tenderness, radiculopathy or myelopathy symptoms	Plain films initially, then CT or MRI	Symptoms, signs depend on level
	Epidural hematoma	Usually seen in patients with coagulation disorder, hereditary or acquired (e.g., anticoagulants); may occur after epidural anesthesia	Radiculopathy or myelopathy symptoms	MRI or CT	Can also occur in AV malformations
Emergent					
Infectious	Vertebral osteomyelitis	At-risk group similar to that for epidural abscess; onset may be insidious; back pain, tenderness, and stiffness may precede neurologic findings by significant time period.	May have fever (poorly sensitive or specific), other constitutional symptoms; localized tenderness of two adjacent vertebrae	CBC, blood cultures, generally low yield; ESR/CRP usually elevated but nonspecific; diagnose using MRI with contrast	Biopsy may be necessary for diagnosis; *S. aureus* most common, ideally hold antibiotics until bacteria isolated unless unstable patient; if cultures positive for GPC, consider endocarditis; can lead to pathologic fracture

Continued

TABLE 31.1 Classical Findings in Selected Serious Causes of Acute Back Pain—cont'd

Findings	Diagnoses	History	Important Physical Examination Findings	Ancillary Testing	Comments
Immune	Transverse myelitis	Back pain, neurologic deficits; Almost 50% of patients worsen maximally in 24 h	Presentation similar to other causes of myelopathy, including motor and sensory abnormalities, risk of progressive paralysis; bladder, bowel, sexual dysfunction; most common thoracic followed by lumbosacral; likely bilateral	Goal is to rule out mass lesion compressing the cord; thought to be autoimmune origin; MRI imaging modality of choice; contrast CT if MRI contra-indicated.	May be associated with multiple sclerosis, SLE, sarcoidosis; also associated with Lyme disease, Epstein-Barr virus, other viral (e.g., herpes, enterovirus) or bacterial (e.g., tuberculosis, syphilis) infections
Mechanical	Back pain with neurologic deficits; central disc herniation; spinal stenosis; spinal fractures without cord impingement; malignancy; sciatica with potential for nerve root compression	Search for key clinical findings (see Box 31.1) to rule out serious underlying disease.	Positive straight leg raise test; muscular weakness; sensory deficits; absent or diminished deep tendon reflexes	Plain films not indicated; Perform MRI or CT for complete assessment if infection, mass, cord hematoma, or cord compression is suspected	Perform complete neurologic examination including motor, sensory, reflex, and gait testing.

AV, Arteriovenous; *CBC*, complete blood count; *CRP*, C-reactive protein; *CT*, computed tomography; *ECHO*, echocardiogram; *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal; *GPC*, gram positive cocci; *MRI*, magnetic resonance imaging; *SLE*, systemic lupus erythematous; *US*, ultrasound; *WBC*, white blood cell.

claudication, which is caused by arterial insufficiency, may have abnormal pulses, and is relieved by rest.

Pain that is oncologic or infectious in origin is often severe, constant, may occur at night and is associated with constitutional symptoms. Epidural compression syndromes (spinal cord compression, CES) are associated with numbness, weakness, bilateral leg pain, incontinence and saddle anesthesia, or decreased perineal sensation. Ask patients about decreased sensation when wiping to assess for saddle anesthesia.

Back pain associated with pain in other locations should prompt consideration of an extraspinal cause. Association with chest or abdominal symptoms may indicate a visceral cause, such as vascular or solid organ pathology. Unilateral flank symptoms may have a renal or retroperitoneal origin, and thoracic level pain can emanate from the chest or pleura. Because most benign back pain is tolerable, worsened with activity, and improved with rest or lying still, symptoms such as severe night pain (especially deep bony pain) and severe unrelenting pain that is not relieved by rest, recumbency, or appropriate analgesic treatment are concerning for non-musculoskeletal causes, such as malignancy or infection. Other pertinent history considerations include past and present work history (a history of repeated loading would suggest a mechanical cause), medications (anticoagulants are associated with epidural and retroperitoneal hematomas, steroids are associated with infection and compression fractures), hematuria (nephrolithiasis, pyelonephritis, ruptured AAA), and colic (nephrolithiasis, cholelithiasis).

Although AAA as a cause is rare in the overall population of patients with back pain, isolated back pain is one of the classic presentations of a contained ruptured AAA. Vigilance is required to differentiate renal colic from AAA in older patients because both groups may present with back pain associated with nausea, diaphoresis, or syncope, and hematuria may be present in either condition. Previous atherosclerotic or vascular disease may suggest aortic disease, and sudden-onset, severe back pain suggests a vascular cause. Direct trauma may suggest contusion, strain, or fracture. Resulting splenic, hepatic, or retroperitoneal bleeding may lead to referred pain to the back.

Younger patients are at increased risk of spondylolysis and spondylolisthesis. Disc herniation is unusual in those younger than 18 years and is rare in the fibrotic discs of older adults. Prevalence of vertebral compression fractures increase with increasing patient age; they occur in almost a quarter of all postmenopausal women, and up to 30% of women by 80 years of age.

Increased risk of infectious etiology exists for patients with a history of IVDU, diabetes, hepatitis, recent spinal instrumentation, indwelling devices (e.g., epidural catheters, spinal stimulators, vascular access), and recent bacterial infection (e.g., pneumonia, urinary tract infection).[9]

Inquiring about risk factors for cancer is important since spinal epidural metastasis can be the initial presentation of malignancy or may occur in patients with a known primary malignancy. Spinal metastases usually arise in the posterior aspect of the vertebral body, with subsequent invasion of the epidural space.

It is important to note that the presence of an individual key clinical finding may raise suspicion but does not necessarily correspond to a specific pathology. These key clinical findings have traditionally been promoted as "red flags," or signs that predict increased risk of underlying serious spinal pathology. A wide variety of different "red flags" for back pain have been endorsed by many guidelines with a lack of consensus, poor consistency, and limited accuracy or evidence for their support. Examples of findings with poor diagnostic accuracy include night pain and age over 50 years increasing risk of cancer diagnosis.[6] The term "red flags" should be abandoned and we will instead refer to them as "key clinical findings." Many of these key clinical findings have poor or untested diagnostic accuracy and have meaning only in the context of the complete history and findings in an individual patient.[5,10] In addition, the absence of key clinical findings does not necessarily reduce the likelihood of a serious diagnosis.[6] Blindly allowing the presence or absence of these individual findings to guide diagnostic treatment will lead to potentially unnecessary, misleading, and costly investigations in most patients.

TABLE 31.2 Physical Examination for Lumbosacral Nerve Root Compromise

Disk Space	Nerve Root	Sensory Testing	Reflex	Strength and Motor Testing	Pain Location	Screening Exam
L3–4	L4	Test from the medial lower leg and foot down to the medial surface of the great toe (not including the first web space).	Patellar reflex	Test with knee extension (quadriceps), ankle inversion and dorsiflexion.	Back pain radiates to anterior thigh and to anterior leg.	Squat and rise
L4–5	L5	Test from the lateral lower leg, dorsum of the foot, and first web space (between great toe and second toe).	There is no reliable reflex to test L5.	Test with hip abduction, knee flexion, foot/ankle eversion/inversion, great toe dorsiflexion (extensor hallucis longus).	Back pain radiates to buttock, lateral thigh and calf, dorsum of foot, great toe.	Heel walking
L5–S1	S1	Test from the posterior lower leg, lateral/plantar foot and ankle.	Achilles reflex	Test with hip extension, knee flexion, and foot plantar flexion.	Back pain radiates to buttock, posterior-lateral thigh, posterior lower leg, lateral/plantar foot.	Toe walking

Presence of multiple key clinical findings may increase the probability of disease and is often an indication for further investigation, which may be initiated in the ED or on an ambulatory basis, depending on the individual patient. Key clinical findings should supplement (not replace) clinical judgment when selecting appropriate laboratory and radiologic testing. In an ED population, three of the important variables associated with serious outcomes include (1) new urinary retention, (2) disturbance of saddle sensation, and (3) use of anticoagulants.[5] A history of cancer predicts the greatest probability of back pain from bone metastasis. Prolonged use of corticosteroids, significant trauma, older age (>70 years), and presence of contusion or abrasion increase probability of fracture(s).

Signs

Begin by noting vital signs, as abnormal or unstable vital signs may indicate an extraspinal cause of the back pain (e.g., hypotension and tachycardia with ruptured AAA, hypertension with aortic dissection). Presence of a fever may indicate an infectious etiology, though its absence does not exclude diagnosis. Patients with back pain may prefer to lie relatively still as movement worsens pain. Extreme pain or writhing may have an underlying emergent etiology including spinal causes (epidural abscess and osteomyelitis) and extra-spinal causes (intraabdominal, retroperitoneal, or vascular) (See Table 31.1). Perform cardiac and pulmonary auscultation, abdominal examination (for tenderness, bladder distention, aneurysm, or masses), and palpate for symmetry of peripheral pulses. Examine the hips for musculoskeletal tenderness, deformity, or inflammatory focus other than the back.

The patient's neck and back should be fully exposed and inspected for signs of infection, trauma, paraspinal muscle spasm, edema, range of motion. Palpate midline spinous processes for tenderness suggesting fracture or infection. Pain during lumbar flexion suggests discogenic pain, whereas pain on lumbar extension suggests facet disease. Paraspinal muscle spasm should be noted but is not diagnostic of any particular condition. Superficial, non-anatomic, or variable tenderness suggests a non-organic cause.

Perform a complete neurologic examination, including strength, sensory, reflex and gait testing, and evaluation for upper motor deficits. Attempt to distinguish true neurologic weakness from pain-induced weakness. Early and effective treatment of pain will aid in obtaining an accurate physical examination. Lumbar spine pathology is frequently manifested in the lower extremities in the form of altered reflexes, sensation, and muscle strength. The distal neurologic examination targets the three most common locations for disc herniation—L4, L5, and S1. A vast majority of herniated discs affect the L4–5 or L5–S1 interspaces, causing impingement on the L5 (most common) and S1 nerve roots. At each spinal level, the corresponding muscle strength, sensation and reflex needs to be tested and documented (Table 31.2). Muscles may have innervation from multiple roots so patients may have preserved strength despite significant involvement of a single nerve root. True sensory loss is best tested with pinprick rather than light touch. Although the classic teaching is that sensory findings follow a dermatomal distribution, clinical experience suggests otherwise due to dermatomal overlap and individual variation in nerve root dermatomes. Owing to this sensory overlap, it is unusual to have a clearly demarcated sensory loss even in cases of severe radiculopathy due to a single root lesion. In contrast, a sharp line of demarcation is frequently seen in pure peripheral nerve lesions such as in carpal tunnel syndrome. Saddle anesthesia is defined as diminished to absent sensation over the buttocks, posterior-superior thighs and perianal regions and indicates neurologic compromise. Gait disturbance and unsteadiness are common early symptoms of myelopathy, characterized by a spastic, scissoring quality.

See Table 31.2 for nerve root levels and corresponding examination findings. Of note, ankle reflexes decrease with age, lost in nearly 50% of those older than 80 years. This loss is usually symmetric, so unilateral absence may signify pathology. Measurement of post void residual volume (PVR) may help to differentiate true overflow incontinence from urge or stress incontinence. Large PVR (>100 mL) indicates a denervated bladder with resultant overflow incontinence and suggest significant neurologic compromise.

Mid and upper lumbar nerve root impingement likely has a higher prevalence than previously reported and is found with increasing frequency in older adults with spinal stenosis. Pathology at the higher lumbar spine (L1, L2, L3) will cause acute back pain, with radiation to the groin or anterior thigh, weakness with hip flexion (iliopsoas), and anterior thigh sensory changes in the corresponding dermatome. A partial knee bend while bearing weight on one leg and then the other indicates normal hip, buttock, and thigh muscle strength. There are no individual reflexes for the L1–3 lumbar levels. Those with pathology at the lower sacral levels (S2–5) will have sacral or buttock pain that radiates down the posterior leg or into the perineum and can have difficulties with penile erection (S2–4), abnormal perianal sensation (S3–5), anal wink (S2–4), rectal tone (S2–5), and bladder function (S2–4). Assessment of perianal sensation is extremely important for the diagnosis and prognosis of epidural compression syndrome. Sensation changes can be unilateral, mild, or patchy. Specifically assess "pinprick"

sensation, which can be performed using a broken wooden cotton tip applicator, but warn the patient they may feel a sharp sensation. A digital rectal examination is not a routine part of the physical examination but can be performed in those with suspicion of progressive neurologic findings (e.g., epidural compression syndrome). Check the anal wink and bulbocavernosus reflex and perform a Babinski test in high-risk patients. A Babinski sign (positive plantar reflex) is extension of the great toe, with flexion and splaying of the other toes. The presence of clonus, hyperreflexia, or Babinski sign indicates an upper motor neuron lesion. These signs suggest myelopathy.

Straight leg raise (SLR) test for nerve root compression has a sensitivity of 72% to 97% and a specificity of 11% to 66%. In high-risk patients with sciatica or neurologic symptoms the test has a positive predictive value (PPV) of 67% to 89% and a negative predictive value (NPV) of 33% to 57%. To perform this test, the patient is positioned supine, with the legs fully extended. The clinician places one hand under the ankle and the other hand on the knee (to maintain leg extension). With the patient relaxed, the straightened leg is slowly lifted by flexing the leg at the hip until pain is elicited or end range is reached. Each leg is tested separately. A positive test causes or reproduces radicular pain below the knee of the affected leg when the leg is elevated between 30 and 70 degrees. Care should be taken that the patient is not actively helping in lifting the leg and that the knee remains straight throughout the examination.

A further positive finding occurs if radicular symptoms are elicited when the leg is then lowered until pain is eased and the ipsilateral ankle is dorsiflexed (Braggard sign). Pain at less than 30 degrees, more than 70 degrees, or with reproduction of pain only in the back, hamstring, or buttock region, does not constitute a positive test result. Pain referred to the affected leg when the opposite asymptomatic leg is tested, called a positive crossed-SLR, is highly indicative of nerve root irritation from a herniated disc (specificity, 85% to 100%; sensitivity, 29%). In cases where the patient is reluctant or unwilling to lie supine for SLR testing, the seated-SLR or slump test should be attempted. The patient sits at the edge of the examination table and slumps forward while flexing the neck and trunk. This is followed by knee extension and ankle dorsiflexion. A positive test reproduces radicular pain.

Waddell's examination findings can aid in distinguishing between true pathologic back pain and nonorganic back pain; it can be remembered by the mnemonic DORST—distraction, overreaction, regional disturbances, simulation tests, and tenderness). Waddell's signs, especially if three or more are present, correlate with malingering and functional complaints (physical findings without anatomic cause). Superficial, nonanatomic, or variable tenderness during the physical examination suggests a non-organic cause. Provocative maneuvers such as axial loading of the head or passive rotation of the shoulders and pelvis in the same plane should not elicit back pain. There may be a discrepancy between the symptoms reported during the supine and seated SLR tests. The seated version of the test, sometimes termed the distracted SLR, can be performed while distracting the patient or appearing to focus on the knee. Furthermore, radicular pain elicited at a leg elevation of less than 30 degrees is suspicious because the nerve root and surrounding dura do not move in the neural foramen until an elevation of more than 30 degrees is reached. Sensory and motor findings suggestive of a nonorganic cause include stocking, glove, or non-dermatomal sensory loss or weakness that can be characterized as "give-way," jerky, or cogwheel weakness. Finally, gross overreaction is suggested by exaggerated, inconsistent, painful responses to a stimulus. These signs can be used in the evaluation of selected patients and are merely a component of a comprehensive physical examination. They should never be used independently because they lack the sensitivity and specificity to rule out true organic pathology.

ANCILLARY TESTING

Ancillary testing is not indicated in the absence of concerning findings and should only be used to help guide specific management. Routine nonemergent use of laboratory testing, computed tomography (CT), MRI should be discouraged. Blind diagnostic testing may lead to false-positive results and further unnecessary evaluations and interventions.

Laboratory Tests

Laboratory studies are not often indicated in the early evaluation of low back pain. Complete blood counts (CBC) have poor sensitivity and specificity for infection. White blood cell (WBC) counts may be elevated and a left shift may be present and increase suspicion for infection, but lack of these does not rule out infection. Both the ESR and CRP tests are highly sensitive (84% to 100%) for spinal infections and are observed in greater than 80% with vertebral osteomyelitis and epidural abscesses. However, elevated CRP was found in 87% of patients with an epidural abscess as well as in 50% of patients with spinal pain not due to an epidural abscess, making it is not highly specific. CRP levels rise rapidly and decrease rapidly with improvement in disease and may be better used to follow response to treatment. ESR is the most sensitive and specific serum marker of infection. ESR is elevated in 94% to 100% of patients with an epidural abscess compared to only 33% of those without an epidural abscess. Infection is unlikely in patients with an ESR less than 20 mm/h. Although an elevated ESR (>20 mm/h) is the most specific serum test for infection, it also may indicate occult malignancy (sensitivity, 78%; specificity, 67%). Incorporating ESR and CRP values into an ED decision guideline may help identify patients that require imaging in the ED vs. non-emergent basis and decrease the rate of diagnostic delay. If infection is suspected, obtain two sets of blood cultures, as a causative pathogen may be identified in 50% of patients.

Imaging Studies

Imaging, like laboratory testing, is not indicated in the absence of concerns for malignancy, fracture, infection, or epidural compression syndrome. Acute back pain and radiculopathy are generally benign, self-limited conditions that do not warrant imaging studies from the ED. Although the added diagnostic value of modern neuroimaging is significant, unnecessary imaging increases the cost of the ED visit, length of stay and observation admissions, exposes patients to unnecessary radiation, and does not decrease return ED visits.[16]

Abdominal Ultrasound

Bedside ultrasound can aid in the rapid diagnosis of non-spinal conditions such as AAA.

Plain Film Radiographs

Radiographs are rarely helpful in diagnosing the causes of acute back pain or directing therapy in the acute setting. All emergent spine conditions with new or progressive neurologic symptoms presenting to the ED require evaluation with CT or MRI.

Computed Tomography Scan

CT scans are better than plain radiographs for the detection of bone pathology such as vertebral fractures, malalignment, and bony fragments within the spinal canal. CT is preferred in the setting of trauma, but without a trauma history should be performed only if MRI is contraindicated or unavailable. For example, CT with IV contrast is the next best imaging modality for epidural abscess. CT measurement of thecal sac effacement may correlate with MRI findings (98% sensitivity

and 86% specificity) for CES if MRI is contraindicated or not available. CT scanning is not without risks as CT of the lumbar spine carries a radiation level equivalent to 300 chest x-rays.

Magnetic Resonance Imaging

MRI is the imaging modality of choice for evaluating soft tissue, spinal cord, nerve roots, and intervertebral discs. MRI is indicated in the evaluation of progressive radiculopathy and myelopathy caused by malignancy (sensitivity and specificity >90%), infections (sensitivity and specificity >90%), and epidural compression syndromes (sensitivity and specificity >90%). If suspicion exists for metastatic disease, osteomyelitis, abscess, or inflammatory conditions, obtain MRI with contrast. However, the high sensitivity of MRI may identify asymptomatic diagnoses in the spine that may be incorrectly inferred as causative for pain. Disc disease is a component of normal aging and is a very nonspecific finding. In fact, one in four asymptomatic persons less than 60 years and one in three greater than 60 years will have MRI findings of a herniated disc. Similarly, spinal stenosis is seen in 21% of asymptomatic adults over age 60. In a recent study, 30% of MRIs ordered for back pain were inappropriate and ordered without indication, and 24% of the providers were responsible for 74% of inappropriate scans.[17] A primary goal of consensus-based guidelines and international campaigns such as Choosing Wisely has been to eliminate practice variation. MRI should be limited in the ED population to those with clinical concern for progressive or urgent neurologic deficits.

DIAGNOSTIC AND MANAGEMENT ALGORITHMS

Figs. 31.1 and 31.2 provide diagnostic and management algorithms which use key findings from the medical history and physical examination to risk stratify patients for further ancillary testing and subsequent management.

Critical Diagnoses

Back pain may be the major or even sole symptom of patients who present with a dissecting thoracic aneurysm or ruptured AAA. Other life-threatening disorders presenting with back pain are usually identified by their associated symptoms and signs.

Emergent Diagnoses

Spinal infections and tumors, CES, transverse myelitis and disc herniation causing severe neurologic impairment can result in significant morbidity if not recognized and treated appropriately.

EMPIRIC MANAGEMENT

Following the history and physical examination, the minority of patients who have multiple key clinical findings or a moderate to high probability of a critical or emergent condition will require further urgent evaluation and management aimed at identifying and treating the underlying cause. Those disorders are discussed in various chapters throughout the book.

One of the most important goals of treatment is provision of an acceptable level of analgesia until the underlying condition resolves or to ameliorate the suffering of those patients who await definitive therapy. Despite numerous studies and recommendations, few treatments have been proven effective for the management of low back pain. Patients' expectations are known to influence the outcome of treatment, and this process can begin in the ED. Reassurance and information about back pain, carefully selected and presented, can have a positive effect on patients' beliefs and clinical outcomes. Guidelines are shifting their focus from pain to functional status and from pharmacological to non-pharmacological management.[18] Setting a goal of pain improvement instead of complete resolution of pain may be beneficial. Avoid the medicalization of benign conditions by ordering unnecessary tests. This behavior, coupled with the over-prescription of analgesics, particularly opioids, fosters a belief on the part of the patient of the existence of serious pathology for an otherwise benign condition.

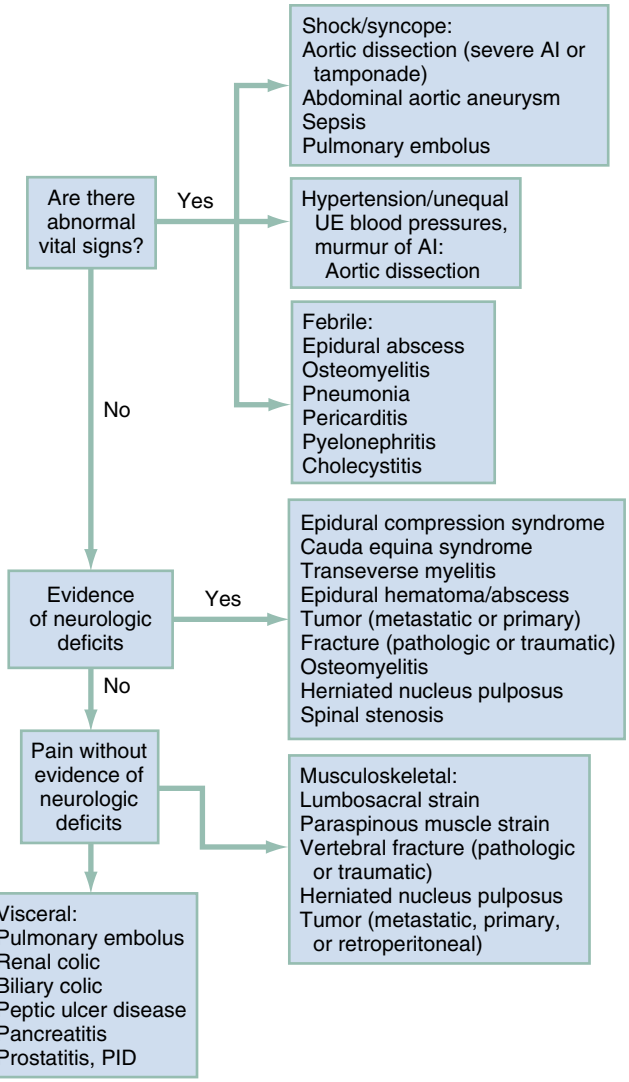

Fig. 31.1 Rapid Assessment of Acute Low Back Pain. *AI,* Aortic insufficiency; *PID,* pelvic inflammatory disease; *UE,* upper extremity.

Mild to Moderate Back Pain

For patients with mild to moderate pain, first-line pharmacologic therapy includes nonopioid analgesics. Enteral nonsteroidal antiinflammatory drugs (NSAIDs) are first line treatment for both acute and chronic back pain, unless contraindicated.[19] Parenteral NSAID analgesia is rarely indicated and is no more effective than an equivalent dose of an oral NSAID. No differences have been found between cyclooxygenase (COX)-2 selective and traditional NSAIDs. When considering NSAIDs, confine dosing to 1 to 2 weeks at most in carefully selected patients with a favorable renovascular and gastrointestinal risk profile. When used alone, acetaminophen has been shown to provide little benefit in the treatment of pain, disability, quality of life, and sleep quality outcomes for patients with back pain.[20] There is little to no benefit of adding acetaminophen to NSAID therapy.

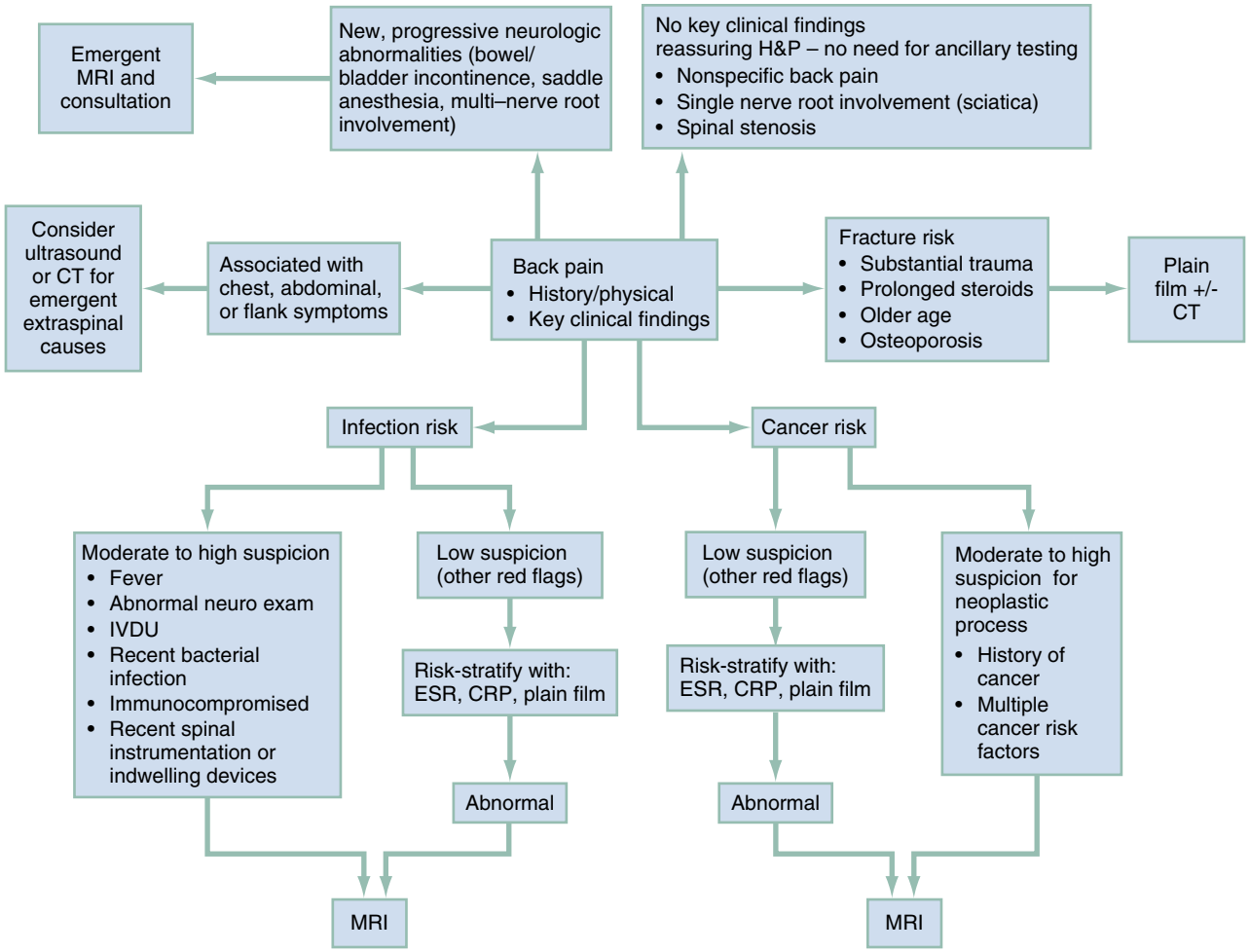

Fig. 31.2 Management of Acute Low Back Pain. *AAA,* Abdominal aortic aneurysm; *ADLs,* activities of daily living; *ASAP,* as soon as possible; *CBC,* complete blood count; *CRP,* C-reactive protein; *CT,* computed tomography; *ECG,* electrocardiogram; *echo,* echocardiogram; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *exam,* examination; *H&P,* history and physical examination; *IVDU,* intravenous drug use; *MRI,* magnetic resonance imaging; *neuro,* neurologic; *NSAIDs,* nonsteroidal antiinflammatory drugs.

Lidocaine transdermal patches are a safe, non-sedating, effective treatment option for acute and subacute back pain, especially in patients with paraspinal muscle involvement (spasm).

Muscle relaxants, such as cyclobenzaprine, may provide short term pain-relief for patients with acute low back pain compared to placebo, though results are controversial.[19,21] There is little difference in efficacy among the various muscle relaxants, and data are insufficient to support their use in the treatment of chronic back pain. Evidence for muscle relaxants for back pain is weak compared to NSAIDs, so limit use to patients who have contraindications to NSAIDS and who can tolerate the side effects of muscle relaxants, which include anticholinergic effects, dizziness, and sedation.

Caution and careful consideration should be used when deciding to prescribe muscle relaxants in elderly patients. Decision-making should weigh possible interactions with other medications and the potential for exaggerated adverse effects in this population, including drowsiness and dizziness, which may increase fall risk.

There is no evidence for the efficacy of benzodiazepines for back pain despite frequent prescriptions.[21] Among an ED population with acute back pain, addition of diazepam to naproxen does not improve functional outcome or pain compared to naproxen alone.[22] Their effect, if any, likely is based on their anxiolytic and sedative properties, which may promote sleep and synergize pain relief. Sleep quality is related to subsequent lower back pain intensity, so benzodiazepines may be beneficial, with limited side effects, when taken at bedtime.

Combination therapy with NSAIDs and the addition of muscle relaxants, benzodiazepines, or opiates for acute mechanical back pain does not improve pain or functional outcomes when compared to NSAID monotherapy.[22–25] Benzodiazepines and opioids should never be co-prescribed due to increased risk of overdose death.[26,27] Oral and intramuscular glucocorticoids have not been shown to provide benefit in regard to musculoskeletal low back pain (with or without sciatica), activity level, or ability to return to work for patients in the ED. ED providers' decision to prescribe multiple medications is often related to self-imposed pressure to escalate care or avoid inpatient admission, despite little supporting clinical evidence.[28]

Severe Back Pain

For patients with severe acute back pain, opioid analgesics or tramadol may be considered with caution. Opioids should be considered a second-line alternative and are best used for those experiencing severe or debilitating acute back pain with inadequate or refractory control with first-line non-opioid analgesics. When indicated, parenteral opioids such as morphine or hydromorphone are the preferred analgesic

for severe pain and should be given in a titrated fashion. When administering opioids, frequently reassess the patient until an adequate response is reached, and then transition to oral agents in preparation for discharge. Prescribe the smallest quantity possible for the shortest duration possible and ensure close outpatient follow up. Consider the known side effects of opioids (e.g., constipation, confusion, sedation). Even when accounting for patient clinical characteristics, large variability exists in ED opioid prescribing practices, which highlights the need for greater adherence to established treatment guidelines.[29] Although opioids are effective for relieving pain, they do not improve functional status or health-related quality of life.[30] Early opioid prescriptions in the ED for uncomplicated acute back pain increase long-term opioid use, increase medical costs, and prolong work disability.[31,32]

Chronic Back Pain

For patients with chronic back pain, opioid treatment efficacy is less clear and should be avoided in the ED. For such patients, NSAIDs are still indicated as first-line treatment, and opioids should be considered as an adjunct for short-term pain relief only and should be avoided whenever possible. They should be referred to a pain management center, where epidural glucocorticoid injections and other potential treatments may be provided. Practice guidelines recommend considering non-pharmacologic treatments such as heat, massage, acupuncture, yoga, and mindfulness-based stress reduction, and best coordinated by patients' PCPs.[19] Utilizing ED-based physical therapists for evaluation and treatment of patients with acute and chronic back pain may hold promise for improving clinical outcomes, but is not widely implemented.[33] Combination pharmacotherapy has not been shown to be effective for acute pain, but may be effective in chronic low back pain.[25]

DISPOSITION

Patients with back pain often present to the ED with high expectations of investigations (blood work and imaging) and analgesia making adherence to management guidelines challenging. Throughout the visit, focus on patient education and reassurance of the likely benign etiology of the pain. Educate patients regarding why they are not undergoing laboratory or radiographic studies. Most patients can be convinced by education and an explanation of radiation dosing and associated deleterious effects. This advice is best delivered by the physician and will help avoid misperceptions of substandard care as well as unnecessary return visits when symptoms persist for an expected amount of time. Reassure patients by acknowledging their pain and being supportive, provide reassurance that back pain is very common and that the pain does not indicate ongoing harm or serious pathology. Provide a full explanation of the diagnosis, evaluation, treatment plan, and expected time course for recovery in terms that the patient understands. Patients can be reassured that most will experience spontaneous improvement. Avoid language that may scare the medically naive patient by implying a serious abnormality when none exists (i.e., "ruptured disc"). Consider using the term "common" or "mechanical" back pain, and avoid the term "non-specific," as it may not engender patient confidence.

The final and perhaps most important aspect of ED management of acute back pain involves discharge instructions. All patients should be given clear discharge instructions with unambiguous indications on when to return to the ED. Although patients should avoid vigorous exercise and provocative activities, complete rest should be avoided. Bed rest has been proven to be deleterious to successful recuperation from back pain, leading to decreased functional recovery and slightly increased pain compared to those advised to remain ambulatory. Remaining active will also help with muscle spasm and atrophy. However, patients with severe pain may be able to do little beyond navigating between the bedroom, bathroom, and kitchen. The perception of activity as a trigger may predispose patients to experience additional disability. It should be made clear that ongoing pain does not imply ongoing harm. Recommend continuing daily activities and gradually increasing specific exercises, as tolerated. Clarify that back pain does not need to be totally alleviated before the patient can return to work. Returning to work should be based on consideration of the actual work duties of the patient. Those with jobs involving heavy manual labor may benefit from time away from work if no light duty options are available, and ED work notes should make this distinction clear. Lastly, patients should be told to return to the ED for symptoms such as new or progressive arm or leg weakness, bowel or bladder dysfunction, or saddle anesthesia, since these findings may be absent in early presentations of emergent pathologies.

ACKNOWLEDGMENTS

The authors would like to thank Roy Hatch for his invaluable assistance in preparing this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 31: QUESTIONS & ANSWERS

1. What is the most likely cause of back pain in a 48-year-old patient with bilateral leg pain and weakness, urinary retention, decreased rectal tone, and saddle anesthesia?
   a. Abdominal aortic aneurysm
   b. Bone metastasis
   c. Epidural abscess
   d. Herniated disk
   e. Primary bone tumor

Answer: d. The listed symptoms and signs describe cauda equina syndrome, which is usually caused by a large central herniated disk. Other less common causes include tumor and infection.

2. What percentage of asymptomatic persons less than 60 years old will have herniated disc findings on MRI?
   a. 10%
   b. 25%
   c. 50%
   d. 75%

Answer: b. Disc disease is a component of normal aging and is a very nonspecific finding. In fact, one in four asymptomatic persons <60 years and one in three >60 years will have MRI findings of a herniated disc.

3. A 35-year-old man presents with severe back pain that radiates down his right leg. He reports that while lifting a heavy box at work 2 weeks ago, he felt a "pop" in his lower back. He has not been able to return to work since the injury occurred. The patient spoke with his lawyer and was told to come directly to the emergency department to get an magnetic resonance imaging (MRI). He denies having any other symptoms and reports no significant past medical history. During the physical examination, the patient is asked to lie on his back, with his knees extended. His right leg is elevated and, at 50 degrees, he reports severe pain running down the lateral aspect of his right leg to his foot. The patient is then asked to sit with his knees flexed and legs hanging over the side of the bed. His legs are passively extended, with no production of pain. The remainder of the physical examination is normal. What is the most appropriate next step in managing this patient?
   a. Computed tomography (CT) of the lumbar spine
   b. Discharge home
   c. Emergent neurosurgical consultation
   d. MRI of the lumbar spine
   e. Radiography of the lumbar spine

Answer: b. Several aspects of this scenario point to malingering. The most convincing relates to the physical examination findings. The straight leg raise (SLR) is the classic test for sciatic nerve root irritation. The absence of a positive result generally rules out nerve root irritation. To perform the SLR, the patient is positioned supine, knee extended, and leg elevated until pain is elicited. A positive result is pain radiating down the leg below the knee in a dermatomal distribution when the leg is elevated between 30 and 70 degrees. In a patient who may be malingering, the SLR can be performed with the patient sitting on the side of the bed with knees flexed. Passively straightening the legs in this position should produce equally positive results if true nerve root irritation exists.

4. Disk herniation with involvement of the L5 nerve root will present with which of the following findings?
   a. Decreased or absent ankle jerk
   b. Decreased patellar reflex
   c. Diminished sensation of the lateral small toe
   d. Impaired plantar flexion
   e. Weakness with extension of the great toe

Answer: e. Involvement of the L5 nerve root presents with weakness, with extension of the great toe, decreased sensation in the first web space, and normal reflexes. An S1 radiculopathy is characterized by diminished sensation of the lateral small toe, impaired plantar flexion, and decreased or absent ankle jerk. The patellar reflex is associated with L2–4.

5. A history of IV drug use increases the risk for which of the following causes of acute back pain?
   a. Abdominal aortic aneurysm
   b. Epidural hematoma
   c. Malignancy
   d. Transverse myelitis
   e. Vertebral osteomyelitis

Answer: e. Vertebral osteomyelitis and spinal epidural abscess are diagnosed most frequently in an at-risk population that includes patients with a history of diabetes, chronic renal failure, IV drug use, alcoholism, cancer, AND recent surgery or trauma.

6. Spinal epidural abscess is most commonly caused by which of the following pathogens?
   a. *Mycobacterium tuberculosis*
   b. *Pseudomonas aeruginosa*
   c. *Staphylococcus aureus*
   d. *Staphylococcus epidermidis*
   e. *Streptococcus pyogenes*

Answer: c. *S. aureus* causes 70% of spinal epidural abscesses.

32

Multiple Trauma

Andrea C. Sharp and Leslie V. Simon

KEY CONCEPTS

- Immediately after a trauma patient arrives the emergency department (ED), the primary survey should be performed in a standardized fashion. The goal of the primary survey is to rapidly identify and initiate the treatment of critical, and life-threatening injuries.
- The extended Focused Assessment with Sonography for Trauma (eFAST) examination should be performed early in the evaluation of the trauma patient (ideally as part of the primary survey). Thoracic examination of the trauma patient by ultrasound is more accurate than plain radiography.
- Any patient with potentially life-threatening injuries should have blood typing and screening performed. When transfusion is indicated, blood products should be transfused in a 1:1:1 or 1:1:2 ratio of plasma to platelets to packed red blood cells.
- Tranexamic acid (TXA) is indicated for patients with evidence of significant hemorrhage or shock and is given as a 1-g intravenous bolus followed by a 1-g infusion over 8 h. Results are best if started within an hour of injury but benefit may occur when it is given within 3 h.
- Special consideration should be given to the elderly who demonstrate increased morbidity and mortality in settings where traumatic injury initially appear less concerning. Patients over the age 65 with one or more of the following comorbid conditions (coagulopathy, cirrhosis, COPD, CAD, or DM) have more than twice the mortality risk than younger patients.

FOUNDATIONS

Background and Importance

Unintentional injury remains the leading cause of death in persons 1 to 44 years of age.[1,2] Each day, approximately 9 people are killed and more than 1000 injured by distracted drivers that have led to new laws prohibiting texting while driving. Firearm-related deaths are a significant concern, especially in the United States.[1,3] The economic cost of traumatic injuries and death (medical costs and lost productivity) is estimated in the hundreds of billions of dollars.[1,4]

Stabilization, evaluation, and treatment of trauma patients are central to the practice of emergency medicine. Effective management of critically ill trauma patients requires decisiveness, technical skill, and effective leadership. A methodical, team-based approach is necessary, capitalizing on a strong clinical partnership between emergency medicine and surgery. Coordination with emergency medical services (EMS) providers, nursing, radiology, and other trauma-related specialties is needed to optimize outcomes. Prompt and safe transfer to the operating room requires collaboration and effective communication with other specialists such as surgeons, and anesthesiologists.

Anatomy, Physiology, and Pathophysiology

In blunt trauma victims, the mechanism of injury can be associated with particular injury patterns. These are listed in Table 32.1. Knowledge of these associations can help the clinician evaluate for injuries that may not be readily identified by initial examination.

Older patients commonly sustain extremity, craniofacial, and closed head injuries. Most of these occur as a result of a fall or motor vehicle collision (MVC). Thirty million older adults fall each year, resulting in about 30,000 deaths. Older trauma patients typically have comorbid illnesses, usually on medications (especially anticoagulants), and also have age-related changes in organ-system function. These factors can increase susceptibility to injury, morbidity, and mortality. Obese patients are also at risk for increased morbidity and mortality from trauma.[5]

In penetrating trauma from knife wounds or injuries from low-velocity sharp objects, tissue damage can be expected to occur primarily along the track of the object. However, the type and severity of injuries inflicted by gunshot wounds depend on several factors. The amount of tissue damage is related to the kinetic energy of the bullet, which is a factor of the bullet weight (caliber) and velocity. Gunshot wounds cause trauma to the surrounding tissue by direct laceration, crush injury, shock waves, and cavitation—the displacement of tissue forward and radially. Owing to these dynamic forces, high-velocity weapons, such as rifles, cause more widespread injuries than low-velocity weapons (handguns). Similar to knives, handgun bullets and shotgun pellets (from long range) generally cause injury based on direct laceration and crush generated by the missile along its track. Shotgun wounds from close range are characterized by massive tissue injury.

CLINICAL FEATURES

Primary Survey

A focused and methodical primary survey should be initiated immediately in the emergency department (ED). The goal of the primary survey is to diagnose critical, life-threatening injuries rapidly, and begin treatment at the time of diagnosis. Figs. 32.1, 32.2, and 32.3 show the recommended algorithms for the evaluation of airway, breathing, and circulation. Fig. 32.4 highlights special considerations between blunt

TABLE 32.1 Blunt Trauma Mechanisms and Associated Injuries

Mechanism of Injury	Additional Considerations	Potential Associated Injuries
Motor Vehicle Collisions		
Head-on collision		Facial injuries Lower extremity injuries Aortic injuries
Rear end collision		Hyperextension injuries of cervical spine Cervical spine fractures Central cord syndrome
Lateral (T-bone) collision		Thoracic injuries Abdominal injuries—spleen, liver Pelvic injuries Clavicle, humerus, rib fractures
Rollover	Greater chance of ejection Significant mechanism of injury	Crush injuries Compression fractures of spine
Ejected from vehicle	Likely unrestrained Significant mortality	Spinal injuries
Windshield damage	Likely unrestrained	Closed head injuries, coup and countercoup injuries Facial fractures Skull fractures Cervical spine fractures
Steering wheel damage	Likely unrestrained	Thoracic injuries Sternal and rib fractures, flail chest Cardiac contusion Aortic injuries Hemothorax, pneumothorax
Dashboard involvement or damage		Pelvic and acetabular injuries Dislocated hip
Restraint or seat belt use		
Proper three-point restraint • Lap belt only • Shoulder belt only	Decreased morbidity	Sternal and rib fractures, pulmonary contusions Chance fractures, abdominal injuries, head and facial injuries and fractures Cervical spine injuries and fractures, "submarine" out of restraint devices (possible ejection)
Air bag deployment	Front end collisions Less severe head and upper torso injuries Not effective for lateral impacts More severe injuries in children (improper front seat placement)	Upper extremity soft tissue injuries and fractures Lower extremity injuries and fractures
Pedestrian Versus Automobile		
Low speed (braking automobile)		Tibia and fibula fractures, knee injuries
High speed		Waddel's triad—tibia and fibula or femur fractures, truncal injuries, craniofacial injuries Thrown pedestrians at risk for multisystem injuries
Bicycle		
• Automobile-related		Closed head injuries Handlebar injuries • Spleen or liver lacerations • Additional intra-abdominal injuries • Consider penetrating injuries
• Non–automobile-related		Extremity injuries Handlebar injuries
Falls	LD_{50}, 36–60 ft.	
Vertical impact		Calcaneal and lower extremity fractures

Continued

TABLE 32.1 Blunt Trauma Mechanisms and Associated Injuries—cont'd

Mechanism of Injury	Additional Considerations	Potential Associated Injuries
		Pelvic fractures
		Closed head injuries
		Cervical spine fractures
		Renal and renal vascular injuries
Horizontal impact		Craniofacial fractures
		Hand and wrist fractures
		Abdominal and thoracic visceral injuries
		Aortic injuries

LD_{50}, Height of fall that would be fatal for 50% of those falling.

and penetrating mechanisms that should be considered during the primary survey.

In the absence of obvious direct trauma involving the airway, management decisions are based on the overall patient condition and potential for deterioration. Following initial airway assessment, decisions surrounding airway management should focus on the ability of the patient to protect their airway, adequacy of ventilation and oxygenation, and anticipated clinical course.

Inadequate ventilation, which may lead to respiratory acidosis, can be noted by the rate and quality of respirations and can be monitored using end-tidal carbon dioxide monitoring. Pulse oximetry will detect inadequate oxygenation, which may manifest clinically as agitation and restlessness, as opposed to hypercapnia which usually manifests as somnolence. Assessment of injuries that may compromise oxygenation or ventilation requires careful inspection and auscultation of the chest and may be augmented by use of point-of-care ultrasound. Signs of such compromising injury include increased work of breathing, tachypnea, penetrating wounds, subcutaneous emphysema, chest wall instability, flail segments, tracheal deviation, and distended neck veins. See Fig. 32.2.

Assessment of hemodynamic and circulatory status (see Fig. 32.3) follows evaluation of the airway and ventilation. Clinical indicators of adequate perfusion include normal mental status, skin color and temperature, heart rate, blood pressure, and capillary refill. However, a normal finding for any single sign does not rule out significant hemorrhage or even shock. Mental status changes associated with hypoperfusion can include anxiety, agitation, and depressed consciousness. Cool pale skin or extremities with delayed capillary refill suggest inadequate perfusion and shock. Vital signs can be misleading in well-conditioned athletes and children. Medications may also blunt expected physiologic responses. A normal heart rate, blood pressure, or both can be present, despite significant hemorrhage. Conversely, tachycardia could be seen without significant volume loss.

Traditionally, direct pressure to external bleeding sites was advocated, while the use of tourniquets was discouraged. While direct pressure remains first-line therapy, there is good evidence to support the early use of tourniquets for massive extremity hemorrhage that is not otherwise easily controlled.[6–9] Similarly, studies of newer hemostatic agents have shown potential application in combat and out-of-hospital settings.[6,10]

Early intravenous (IV) access is required in the assessment of circulation. Two short, large-bore (14- or 16-gauge) IV catheters are preferred. Routine IV access may be difficult or unobtainable in certain cases. Intraosseous (IO) vascular access can be obtained rapidly in pediatric and adult patients, and this allows the safe infusion of large amounts of fluid or blood products.[11,12] Battery operated drills are widely available and can facilitate IO placement. Ultrasound-guided peripheral venous access by nurses and emergency clinicians should be considered in patients with challenging peripheral vascular anatomy.[13] Central venous access may also be indicated in the appropriate clinical scenario or based on the emergency clinician's discretion. The use of ultrasound has been shown to increase successful vein cannulation and decrease complications in the placement of central venous lines.[14,15] A straight leg raise test or real-time ultrasound of the vena cava can be performed to determine adequacy or response to resuscitation.[16] An extended, focused, abdominal sonography in trauma (eFAST) examination should be performed on all patients during transition from the primary to secondary survey.[17–19]

Secondary Survey

The secondary survey begins once the primary survey is complete, immediate life threats have been addressed, and resuscitation efforts are in place. The goals of the secondary survey are to: (1) obtain pertinent historical data about the patient and injury; and (2) identify and manage all significant injuries by performing a systematic, complete examination. An AMPLE (***a***llergies, ***m***edications, ***p***ast medical history, ***l***ast meal, ***e***nvironments and events) history should be obtained. Trauma is a dynamic process, requiring frequent reassessment of level of consciousness, airway, circulatory, and pain status throughout the emergency phase of management. If deterioration occurs, a complete reevaluation of the primary survey should be initiated. Features of the secondary survey, with critical and emergent diagnoses, are listed in Table 32.2. Concurrently with the primary and secondary survey, oxygenation is enhanced as necessary, appropriate IV access is established, and volume resuscitation is initiated. On completion of the secondary survey, diagnostic laboratory and a more extensive radiographic evaluations commence.

DIFFERENTIAL DIAGNOSES

The differential diagnoses of injury to the airway or chest that might compromise ventilation or breathing is finite. Circulation problems have a variety of potential causes. Figs. 32.2 and 32.3 outline the approach to emergent diagnoses in the critically ill trauma patient. The early assessment of a trauma patient's circulatory status is crucial and includes hemorrhage control. An algorithmic approach is designed to localize the cause, as well as direct intervention. In victims of blunt trauma, the goal of management often focuses on localizing the injury to: (1) obvious external hemorrhage; (2) long bone fractures; (3) pelvic fractures; or (4) internal hemorrhage.

The goal of the initial assessment in the ED is to determine whether the patient is in shock. If so, the decision making process turns to an assessment of volume status. If the patient is hypovolemic, immediate

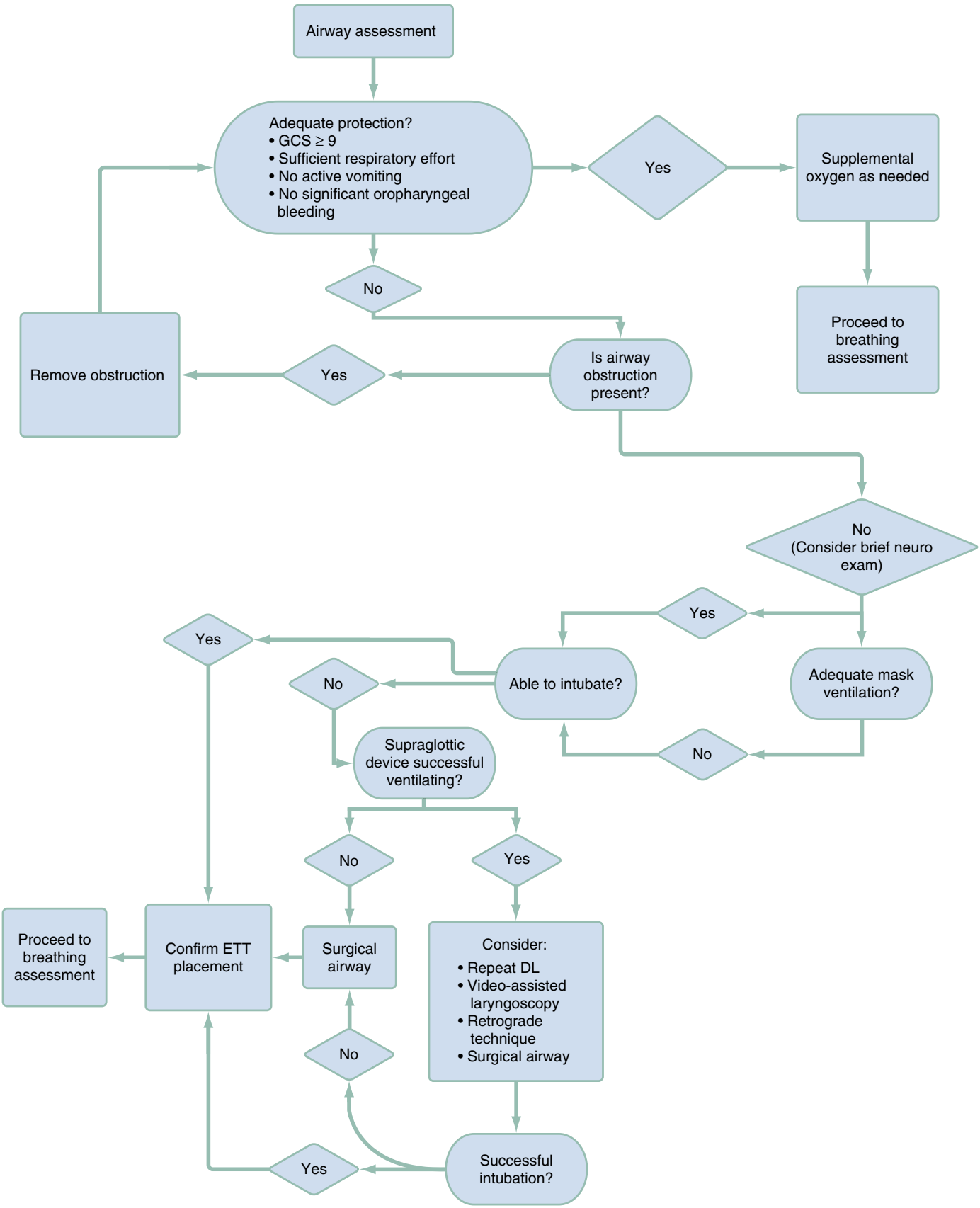

Fig. 32.1 Airway Assessment Algorithm. *DL,* Direct laryngoscopy; *ETT,* Endotracheal tube; *neuro,* neurologic.

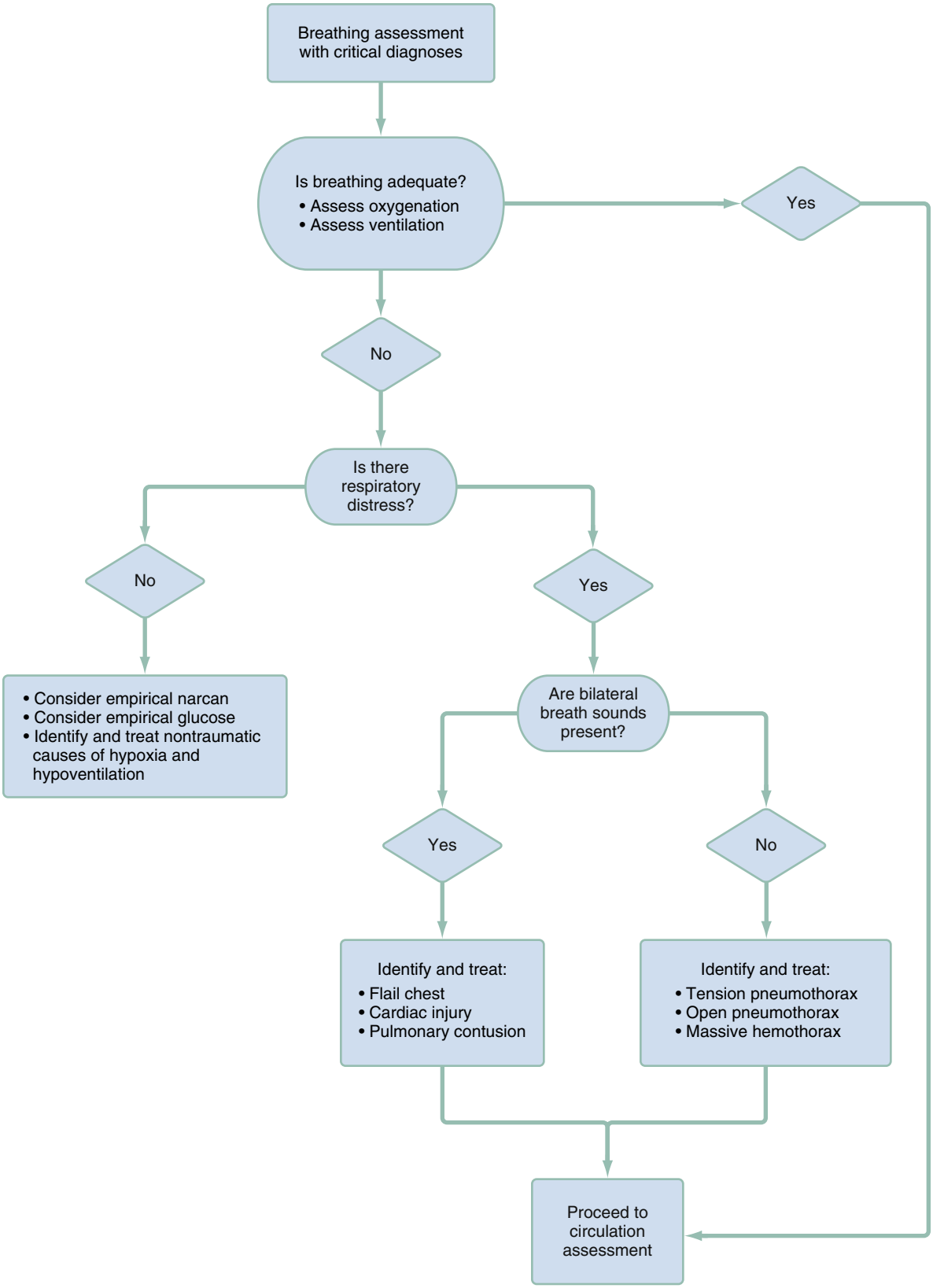

Fig. 32.2 Breathing Assessment Algorithm.

resuscitation is initiated. Hemorrhagic shock prompts the emergency clinician to rapidly locate the source of bleeding and target interventions, with ongoing reassessment.

Although mechanisms of injury alone cannot be relied on to predict all injuries caused by blunt major trauma,[18] common patterns of injuries can be anticipated and specifically assessed in ED patients (see Table 32.1). Although these injuries may be present, there is frequently significant overlap between mechanism and injury. In this section, the differential diagnoses of various presentations are discussed.

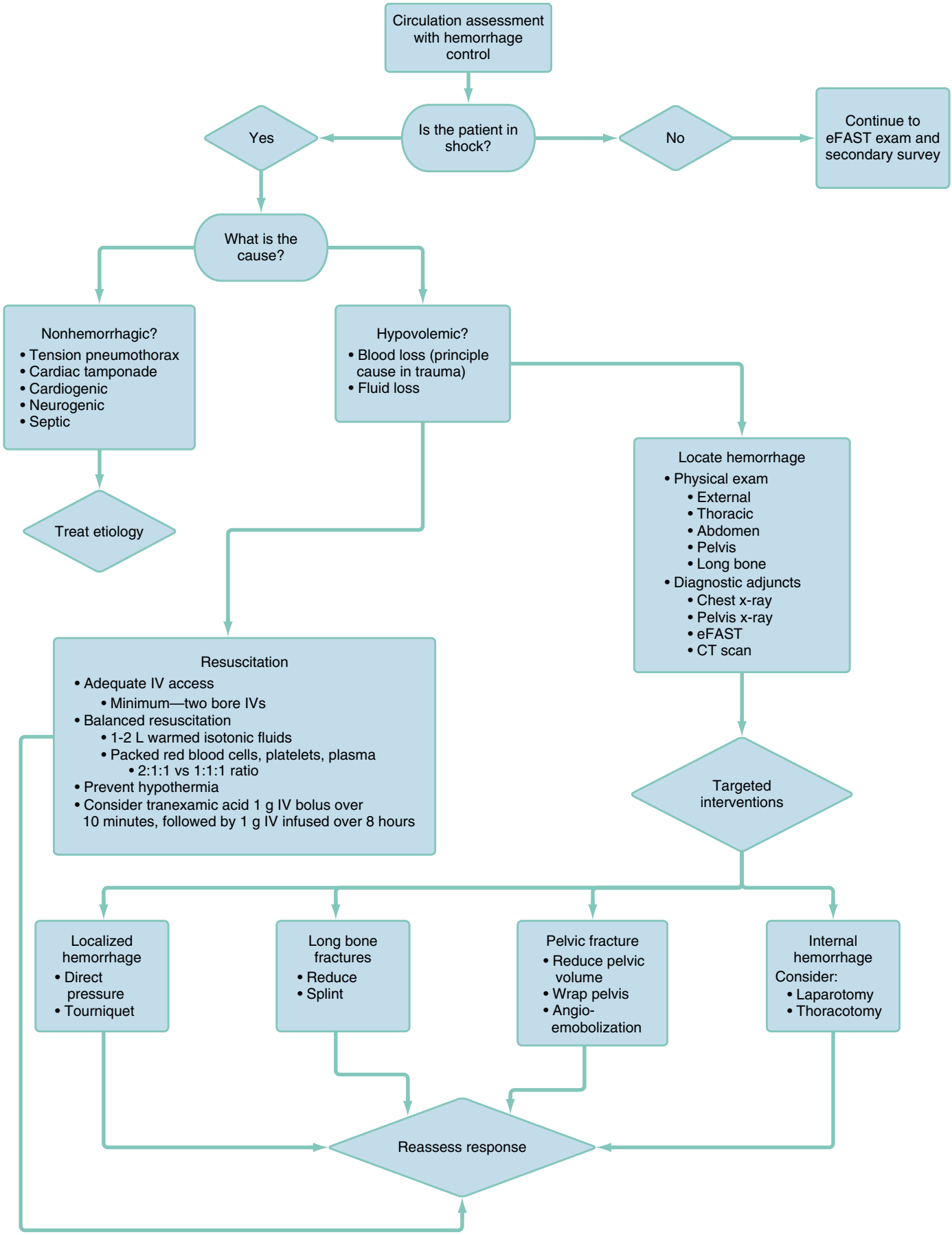

Fig. 32.3 Circulation With Hemorrhage Control Algorithm. *CT,* Computed tomography; *eFAST,* extended, focused, abdominal sonography in trauma; *exam,* examination.

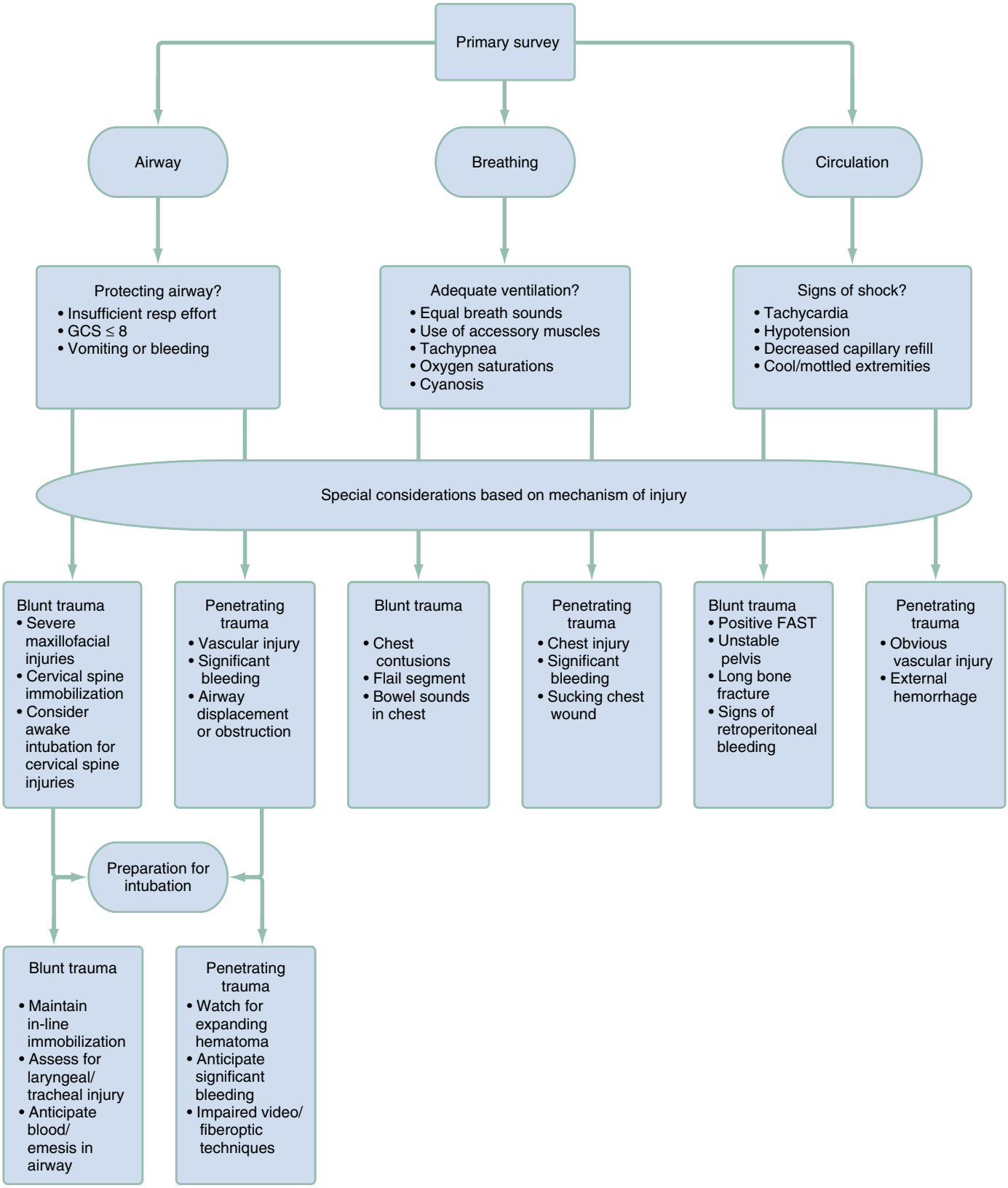

Fig. 32.4 Special Considerations of the Primary Survey. *FAST,* Focused, abdominal sonography in trauma; *GCS,* Glasgow Coma Scale.

TABLE 32.2 Secondary Survey of Trauma Patients

Region or System	Assessment or Examination	Critical Diagnoses	Emergent Diagnoses
General	Level of consciousness	GCS ≤8	
	Glasgow Coma Scale (GCS) score	Focal motor deficit	
	Specific complaints		
Head	Pupils (size, shape, reactivity, visual fields)	Herniation syndrome	Globe rupture
	Contusions		
	Lacerations		
	Evidence of skull fracture (hemotympanum, Battle's sign, raccoon eyes, palpable defects)		Open skull fracture Cerebrospinal fluid leak
Face	Contusions		
	Lacerations		
	Midface instability	Airway obstruction due to bleeding	Facial fractures
	Malocclusion		Mandible fracture
Neck (maintain cervical immobilization)	Penetrating injury, lacerations		
	Tracheal deviation	Carotid injury	
	Jugular venous distention	Pericardial tamponade	
	Subcutaneous emphysema	Tracheal, laryngeal fracture	
	Hematoma	Vascular injury	
	Midline cervical tenderness	Cervical fracture, dislocation	
Chest	Respiratory effort, excursion	Impending respiratory failure	
	Contusions		Cardiopulmonary injury
	Lacerations		Intrathoracic injury
	Focal tenderness, crepitus		Rib fractures
	Subcutaneous emphysema	Flail chest	Pneumothorax
	Heart tones (muffled)	Cardiac tamponade	
	Breath sounds (symmetric)	Tension pneumothorax	Pneumothorax Hemothorax
Abdomen, flank	Contusions		Solid, hollow viscous injury
	Penetrating injury, lacerations	Intra-abdominal hemorrhage	Solid, hollow viscous injury
	Tenderness	Intra-abdominal hemorrhage	Solid, hollow viscous injury
	Peritoneal signs	Abdominal catastrophe	
Pelvis, genitourinary	Contusions	Pelvic hemorrhage	
	Lacerations		Urogenital injury
	Stability, symphyseal tenderness	Unstable pelvic fracture Pelvic hemorrhage	
	Blood (urethral meatus, vaginal bleeding, hematuria)	Unstable pelvic fracture	Urethral injury
	Rectal examination	Colorectal injury (bleeding)	Urethral injury (high-riding prostate)
Neurologic, spinal cord	Midline bony spinal tenderness	Spinal fracture, dislocation	
	Mental status	Epidural hematoma Subdural hematoma	Cerebral contusions Shear injury
	Paresthesias		Spinal cord injury, contusion Nerve root injury
	Sensory level	Spinal fracture, dislocation	
	Motor function, including sphincter tone	Spinal fracture, dislocation	
Extremities	Contusions	Compartment syndrome	Rhabdomyolysis
	Lacerations	Vascular injury	
	Deformity	Neurovascular injury	Fracture
	Focal tenderness		Fracture
	Pulses	Arterial injury	
	Capillary refill	Hemorrhagic shock Arterial injury	
	Evaluation of compartments	Compartment syndrome	

Victims of trauma often present with altered mental status. Underlying medical issues may lead to traumatic injury. These include acute intoxication with pharmaceutical agents, drugs or alcohol, seizures, strokes, cardiac events, and behavioral/mental health conditions. Drug and alcohol testing can be misleading in the setting of altered mental status, and should not delay emergent head computed tomography (CT) when serious head trauma is suspected. Hypoglycemia causes depression of mental status and can be an inciting factor in major trauma. Point of care glucose testing should be assessed in the field and confirmed upon arrival in the ED. Minor mechanisms of injury with significant mental status changes may be a clue to a concomitant nontraumatic cause of altered mental status in these patients. Anticoagulants increase the risk of significant bleeding in patients with traumatic injuries. Therefore, patients on warfarin, other anticoagulants or antiplatelet agents should undergo neuroimaging with even minor mechanisms of injury.[20]

Hypotension is a significant finding in the acute trauma patient and requires a thorough evaluation for hemorrhagic shock. If hypotension persists and no clear source of hemorrhage is identified, other causes of hypotension must be considered. Obstructive shock due to tension pneumothorax, cardiac tamponade, or other causes can be quickly assessed using point of care ultrasound. Neurogenic shock, associated with a spinal cord injury, is less likely in the absence of paralysis but should be considered when other causes of shock have been excluded. If hypotension is present and no clear cause has been identified, diagnoses to be considered include: (1) acute myocardial infarction and cardiogenic shock due to severe myocardial contusion or underlying cardiac abnormalities, or (2) hypotension caused by preexisting sepsis or blood loss (e.g., gastrointestinal [GI] bleed). Multiple causes of shock may coexist simultaneously in the same patient and finding one etiology should not curtail the search for other causes.

Finally, a critical tenet of trauma management is to avoid distraction by what might appear as an obvious injury. Traumatic amputations, gaping wounds, complex open fracture dislocations, and combative patient behavior frequently distract providers from their structured trauma evaluation allowing occult but perhaps more lethal findings to be missed. Approaching every patient in a systematic way, using the primary and secondary surveys, will help prevent overlooking significant acute injuries. Similarly, complete exposure and a head-to-toe examination of the trauma patient will identify otherwise occult injuries, which may be concealed on the back, axilla or perineum of the patient.

DIAGNOSTIC TESTING

Laboratory Evaluation

Laboratory testing in the trauma patient should be guided by clinical assessment and the dynamic needs of the individual patient. Used wisely, these diagnostic studies may provide an objective measure of the adequacy of resuscitation, guide transfusion decisions, assess for coagulopathy, provide baseline information for ongoing assessment, and aid in the management of comorbid conditions, such as renal impairment and diabetes mellitus. Electrolyte levels, liver function studies, international normalized ratio (INR), urinalysis, blood typing and screening (or cross-matching, depending on severity of injury), lactate levels, and base deficit should be determined in all critically ill trauma patients. A pregnancy test should be performed in all female trauma patients of childbearing age. Serum β-human chorionic gonadotropin (β-hCG) testing can avoid the delays in obtaining a urine specimen.

Lactate level, base deficit, and anion gap determinations can help identify subclinical hypoperfusion and track the adequacy of resuscitation.[21,22] Serial serum lactate levels are useful in assessing resuscitative efforts in trauma patients with abnormal vital signs or other findings suggestive of hypovolemia (see Table 32.1).

A type and screen are indicated for those patients with abnormal vital signs thought to be due to injury or mechanisms with risk for occult injury. If transfusion is needed prior to cross-matched blood being available, the provider can temporize with type-specific blood or type O-negative in women of childbearing age or type O-positive in other patient groups.

An INR should be ordered in all patients with critical injuries, with ongoing hemorrhage requiring transfusion, and on anticoagulants. The INR, however, does not provide a rapid comprehensive picture of the clotting process.[23,24] In patients with extensive bleeding or undergoing massive transfusion, thromboelastography (TEG) or thromboelastometry (ROTEM) testing is used to aid the early diagnosis of trauma coagulopathies and direct blood and blood product transfusion.[25] These evaluations are most beneficial for patients undergoing massive transfusion therapy.[26]

Radiographic Evaluation

The initial approach to radiological evaluation of the trauma patient includes selective use of portable plain radiography, bedside ultrasound (eFAST), and CT scanning.

An eFAST examination should be performed on all patients with multisystem trauma or isolated trauma to the torso. Sonographic evidence of free intra-abdominal fluid, pelvic hemorrhage, hemo- or pneumothorax, and pericardial effusions or cardiac tamponade directs surgical management of the patient. An abdominal with relevant findings for free fluid in hypotensive patients can identify those in need of emergent laparotomy, with good sensitivity.[19] Of note, the absence of intraperitoneal fluid on bedside ultrasound does not rule out intra-abdominal or retroperitoneal injury.[27,28]

Cervical spine imaging by plain radiographs in the trauma bay is of limited value and has been largely supplanted by cervical spine imaging by CT. Patients with neurologic deficits are presumed to have spinal cord injury until proven otherwise, and a normal reading on a cervical spine radiograph is not sufficient to rule out injury. In these patients, vigilant spinal precautions should be continued.[29,30] Decision rules such as the Canadian or NEXUS (***N***ational ***E***mergency ***X***-Radiography ***U***tilization ***S***tudy) criteria may be used to reduce unnecessary imaging in selected patients. When a patient is not cleared using these criteria, a CT scan of the head and cervical spine should be obtained. If the neurologic examination is normal, a normal CT scan of the cervical spine is sufficient to exclude injury and further imaging is not necessary.[29]

Imaging of the chest early in the evaluation of the multiple trauma patient can provide important information concerning potentially life-threatening injuries. In the hands of a proficient user, ultrasound is superior to a supine portable chest x-ray as initial screening tool for pneumothorax and hemothorax.[27,31] Thoracic ultrasound should be used early in the evaluation of thoracic trauma; it can be supplemented with chest x-ray.[31] However, a normal chest x-ray does not exclude intrathoracic injury as sensitivity for intrathoracic injury is low.[32] Chest CT imaging should be performed in those with significant chest pain, dyspnea, sternal tenderness, or abnormal thoracic ultrasound or chest x-ray findings. Chest CT is not required in stable, asymptomatic blunt trauma victims with a normal chest x-ray.[33]

There is evidence that thoracic imaging can be avoided altogether in blunt trauma patients with very low risk of thoracic injury. The criteria for obtaining imaging in one large validation study are: (1) age above 60 years, (2) rapid deceleration mechanism, (3) chest pain, (4) drug or alcohol intoxication, (5) abnormal alertness and mental status,

(6) distracting painful injury, and (7) tenderness to chest wall palpation. This rule has a sensitivity of 99.8% and negative predictive value of 98.5%.[33]

In patients with a stab wound to the chest and an initial normal thoracic ultrasound or chest X-ray, routine use of chest CT is not indicated.[34] To exclude significant pathology, asymptomatic patients can undergo a repeat chest x-ray within an hour, rather than the traditional 6 hours after an initial normal chest x-ray.

Pelvic fractures can cause significant hemorrhage, and early recognition of fracture and closure of the pelvic space can mitigate hypotension in these patients. In hemodynamically unstable patients, a portable pelvic x-ray should be obtained in the trauma bay. The sensitivity for an anteroposterior pelvic x-ray to identify all possible fractures is not high; however, an abnormal x-ray showing an obvious open book fracture or vertical displacement of the posterior pelvis should alert the emergency clinician to the need for a pelvic binder and emergent embolization or surgical fixation to control ongoing pelvic hemorrhage. Hemodynamically stable patients with pelvic tenderness or a distracting injury, or those with severe mechanisms of injury and altered mental status, should have their pelvis imaged. If the patient is undergoing CT scanning of the abdomen and pelvis as part of the trauma assessment, we recommend using the bone windows of the CT scan rather than obtaining a pelvic x-ray. Hemodynamically stable patients who are awake, alert, and asymptomatic, with a normal pelvic physical examination, do not require pelvic imaging.[35]. Pelvic injuries in the elderly population presents particular challenges. Even stable injury patterns may require administration of blood products. Pelvic injuries in the elderly result in increased hospital lengths of stays, prolonged immobilization with associated complications, and increased rehabilitation needs. In patients greater than 65 years, a 30% 1-year mortality has been demonstrated with pelvic injuries and 40% after 3 years. This increases significantly to an over 80% 3-year mortality in patients greater that 85 years. Further discussion of pelvic trauma can be found in Chapter 46

In victims of blunt trauma, imaging with an abdominal-pelvic CT scan (AP-CT) is recommended for those with abdominal pain or tenderness, significant mechanism of injury (see Table 32.1), abnormal eFAST examination, gross hematuria, or an unreliable examination (e.g., altered mental status, distracting injury, or head injury). The presence of a seat-belt sign is associated with an internal abdominal injury (IAI) and should prompt CT imaging. Blunt multiple trauma victims who have a Glasgow Coma Scale (GCS) score of 15, normal abdominal physical examination, negative eFAST, and normal laboratory results can forego a CT scan; however, they should have a period of observation, with a repeat eFAST examination, and repeat hemoglobin level determination.

Indications for imaging of the head, spine, and extremities are covered in their respective chapters. Patients with moderate or severe head injury should have their head imaging completed as soon as possible after the primary survey, eFAST examination, and brief secondary survey. Imaging of the thoracic and lumbar spines and extremities can be delayed until other life-threatening injuries have been investigated and managed.

MANAGEMENT

Out-of-Hospital Management

Management of the trauma patient generally begins by first responders before arrival in the ED. The goals of out-of-hospital care include immediate intervention in life-threatening injuries, prevention of additional injury, and rapid transport to designated trauma centers for definitive care.

Most life-threatening injuries that require intervention by out-of-hospital providers are related to airway, breathing, and circulation stabilization. Endotracheal intubation or placement of an extraglottic device may be required for patients with severe trauma, particularly head trauma with coma, and for when transport times may be prolonged. Tension pneumothorax compromises ventilation and perfusion and requires emergent needle or other thoracostomy when suspected. Systemic hypotension with impaired end-organ perfusion necessitates restoration of intravascular volume to a level sufficient to provide perfusion, but not an attempt to restore normal blood pressure.

Preventing additional injury requires an awareness of both clinically evident abnormalities and potentially life-threatening injuries. Coordinated extrication and transport with cervical spine immobilization, spinal precautions, intensive hemodynamic monitoring, and stabilization of fractures to prevent neurovascular compromise are examples of assuming that serious injuries may exist in multiple trauma patients. First responders may treat the patient with IV analgesic medications of sedatives to aid in patient comfort or safety during transport.

Emergency Department Management

As victims of multiple trauma have a variety of injuries from varying mechanisms, the initial focus is directed at overall resuscitative care, with emphasis on performing interventions in a methodical and consistent sequence.

For level 1 trauma centers, the American College of Surgeons (ACS) requires the presence of a board-certified general surgeon to be present in the hospital 24 hours each day. The trauma surgeon is expected to be present in the ED no later than 15 minutes after arrival of trauma patients to the ED (Box 32.1).[4] Most trauma resuscitations in the community are performed by emergency clinicians, with consultation by a surgeon or surgical subspecialist based on specific identified injuries.

As for any other life-threatening condition, the first priorities in the treatment of trauma patients are: securing the airway, maintaining ventilation, controlling hemorrhage, and treating shock.

The goals of airway management are threefold—airway protection, adequate oxygenation, and adequate ventilation. The decision to intubate may go beyond these three tenets because of the potential for deterioration in clinical status. Patients may have an obvious need for early intubation identified during the primary survey. Others will have serious injuries detected later in their evaluation or will have deteriorated and require subsequent intubation and airway management. Still others will require intubation based on their overall clinical course and constellation of traumatic injuries, rather than for any one clear indication.

Airway protection is necessary for many trauma patients. Airway obstruction necessitates immediate intervention. Obstruction from debris, blood, or vomitus may be removed with suction. Neck or facial trauma may cause more complicated scenarios. Swelling, distorted

BOX 32.1 American College of Surgeons Requirements for the Presence of a Surgeon in Major Resuscitations

A surgeon should be present in the emergency department on trauma patient arrival or within 15 min if any of the following major criteria are found:

- Confirmed hypotension (systolic blood pressure <90 mm Hg)
- Gunshot wounds to the neck, chest, abdomen, or proximal extremities
- Intubated patients transferred from the scene
- Respiratory compromise requiring an emergent airway
- Penetrating gunshot wound to the neck, chest, abdomen, or pelvis
- Glasgow Coma Scale score <8 attributed to trauma
- At the discretion of the emergency clinician

anatomy, and hematoma formation may all contribute to impending airway obstruction. Early airway control is safest because these conditions may rapidly worsen. However, there is shift in emphasis from intubation first, to circulation first to prevent peri-intubation hypotension.[36,37] The inability to protect the airway adequately, such as in patients with depressed levels of consciousness, is another indication for intubation. Airway control is recommended for patients with depression of consciousness sufficient to compromise airway protection (usually associated with a GCS score <9).[34] Alcohol intoxication can be an important confounder in the early neurologic assessment of these patients. In patients who do not immediately require airway protection, close observation over time for neurologic recovery to a normal state is recommended.

An attempt to maximize resuscitative efforts should be made prior to administration of RSI medications when possible.

When oxygenation is compromised, face mask oxygen at a high flow rate is required. Restoring adequate oxygenation has a direct effect on the outcome of many trauma patients, particularly head-injured patients. The Brain Trauma Foundation has recommended maintenance of the arterial oxygen concentration (Pao_2) above 60 mm Hg. Certain ventilatory problems, such as pneumothorax or hemothorax, may require tube thoracostomy in addition to intubation. Placement of the chest tube before undertaking intubation, if possible, may improve the patient's hemodynamic status and decrease the risk of serious deterioration related to the use of rapid sequence intubation (RSI) agents and initiation of positive pressure ventilation.

If the patient tolerates, a detailed neurologic examination is important before administering neuromuscular blocking agents, which may confound serial clinical evaluations. Correlation of head CT scan findings with neurologic status is critical to making any decisions regarding operative intervention for intracranial hemorrhage. Also, documentation of neurologic function or deficit is essential in the setting of a potential spine injury. Most patients will not have been cleared of cervical spine injury before intubation, so in-line spine stabilization and video-visualized techniques are important. Videolaryngoscopy with RSI is recommended as the primary method to secure the airway in the severely traumatized patient.[34–39] Videolaryngoscopy has been shown to reduce spine movement, achieve superior laryngeal views and increase likelihood of first-pass success when compared with conventional direct laryngoscopy. When a potentially unstable spine injury has been identified, the use a flexible bronchoscope may be indicated for intubation. Overall, the choice of intubation technique will be based on the clinical scenario and emergency clinician's determination of what is most likely to stabilize the patient as time and expertise allows.

A surgical airway is indicated in cases of difficult airway control, failure to successfully intubate or if there are contraindications to intubation. Cricothyrotomy remains the preferred method, although it is performed in a small minority of all trauma cases requiring airway management. The incidence has been decreasing because of the availability of better alternative rescue devices when intubation fails.[34] When cricothyrotomy is required, we recommend the use of the open technique over the Seldinger technique as the latter may be associated with the creation on a false track. Use of a bougie device has been shown to enhance successful cricothyrotomy.[40]

Control of external hemorrhage and rapidly establishing IV access are essential early steps in the management of the acute trauma patient. This has been discussed earlier (see "Primary Survey"). Volume resuscitation is not a substitute for hemorrhage control. Hypothermia is associated with increased blood loss and IV fluids should be warmed prior to infusion. Current Advanced Trauma Life Support (ATLS) guidelines standardize the ratio of replacement fluids to loss and recommend 1 L of an isotonic solution be infused in all patients in shock. If an adult patient is unresponsive to the initial liter of crystalloid therapy, blood transfusion is indicated. O-positive blood should be used, except in women of childbearing age. Type-specific blood should be used when available, but emergent transfusion should not be delayed pending type and cross-match analysis. Massive transfusion protocols are commonly used for patients with severe hemorrhagic shock. Recent data have suggested that the use of a 1:1:1 ratio of plasma, platelets, and packed red blood cells which may result in earlier hemostasis, although no significant difference in mortality was documented.[6,41] We recommend the use of a 1:1:1 or 1:1:2 ratio of blood products based on specific institutional policies and procedures. Judicious use of fluids will prevent over resuscitation and its associated complications.[42] Calcium should be monitored or empirically administered in patients receiving multiple units of blood products or massive transfusion given risk for severe hypocalcemia, QT prolongation, and death.

The use of the antifibrinolytic agent, tranexamic acid (TXA), has been shown to decrease mortality in trauma patients at risk of major bleeding if given within the first hour following injury.[43,44] Any trauma patient with clinically significant hemorrhage, or those who present in shock, should receive 1 g of TXA intravenously over 10 minutes, followed by a 1-g infusion over 8 hours. TXA infusion should be separated from blood products either temporally or through a separate IV/IO line. Administering TXA up to 3 hours after trauma has shown mortality benefits, but an earlier administration (within one hour) is superior.

In the severely injured, hypotensive trauma patient, restoration of normal blood pressure may be undesirable. The concept of permissive hypotension is based on the premise that resuscitation to a normal blood pressure may increase bleeding from an uncontrolled hemorrhage site or even from a site that is tenuously contained and not actively hemorrhaging. In permissive hypotension, mean arterial pressure (MAP) is restored to a goal of approximately 50 mm Hg. Data have shown that this strategy leads to less blood product use, less bleeding, and lower incidence of coagulopathy.[6,10,45] Permissive hypotension is contraindicated in the management of traumatic brain injury because of the risk of hypoperfusion.[41,46] Rather than any particular MAP target, restoration of adequate tissue perfusion, with normal mentation or normalization of tissue oxygen saturation (Sto_2) monitoring, is the clinically relevant endpoint in the resuscitation of the trauma patient.[10,41,45]

The role of ED thoracotomy (EDT) has become more selective to limit futile resuscitation efforts and minimize risk to providers. Patients with penetrating trauma who undergo cardiac arrest during transportation or in the ED are most likely to benefit from EDT. In contrast, cardiac arrest patients with blunt trauma, prolonged cardiopulmonary resuscitation (CPR), or delayed transportation times generally have poor outcomes that are not altered by EDT.[47] Most institutions have protocols in place outlining criteria regarding when EDT should be performed. The National Association of EMS Physicians and ACS Committee on Trauma have published guidelines for withholding or terminating resuscitation efforts in out-of-hospital traumatic cardiac arrest patients. These guidelines prevent the transport of patients who would not likely benefit from EDT, including any blunt trauma patient without vital signs at the scene, apneic or pulseless penetrating trauma victims without other signs of life, patients undergoing more than 15 minutes of pre-hospital CPR, and patients with transport times of more than 15 minutes after arrest.[47] Suggested algorithms for the application of EDT are outlined in Figs. 32.5, 32.6, and 32.7. EDT is discussed further in Chapter 37. When EDT is performed, the goal is to rapidly manage correctable traumatic injuries and allow for rapid transfer to the operating room for definitive intervention.

To assess disability, a rapid assessment of the patient's neurologic status is necessary early in the ED course. If intubation is necessary early in the patient's treatment, perform a rapid neurologic examination,

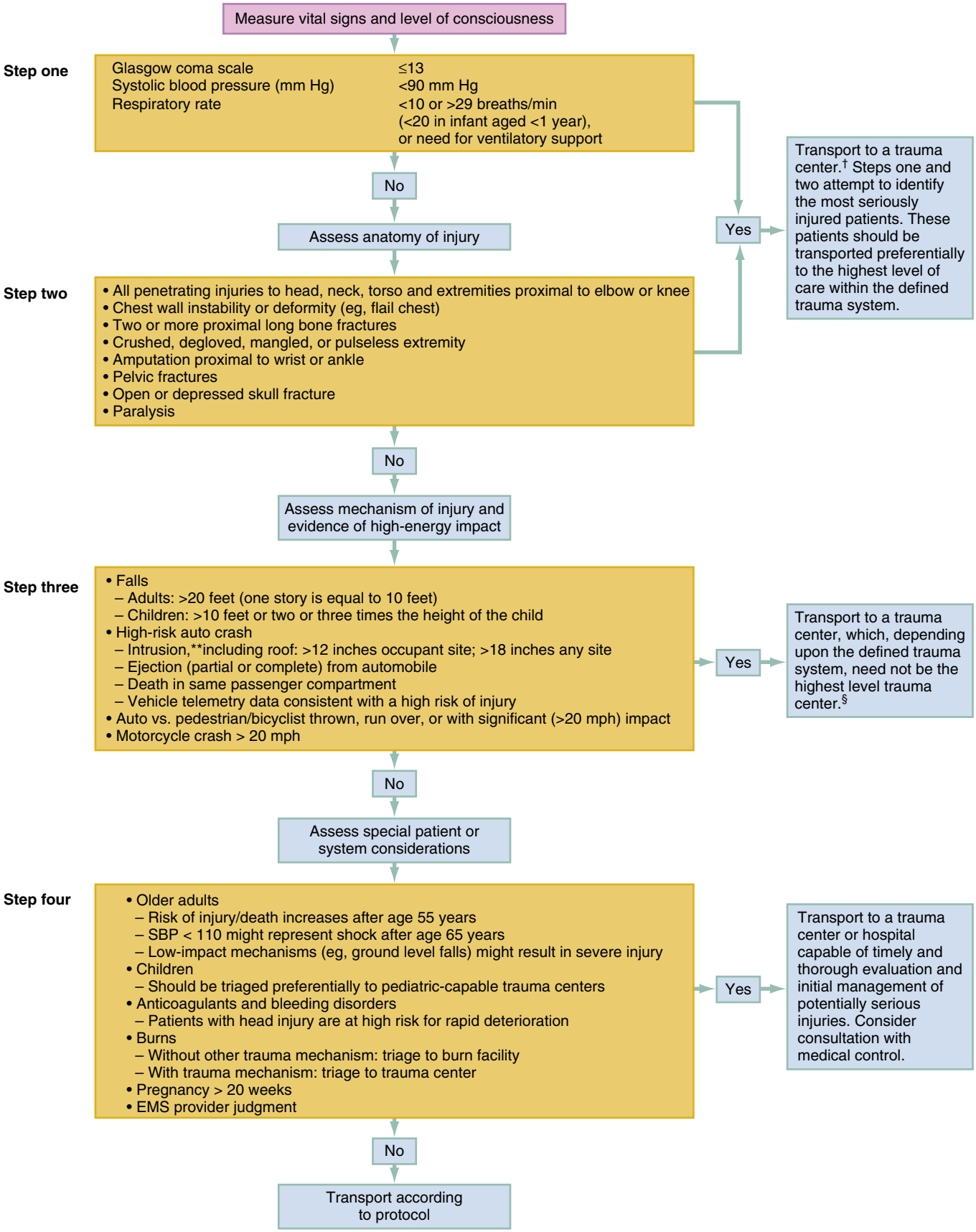

Fig. 32.5 Triage Decision Scheme. *EMS,* Emergency medical services. (Adapted from American College of Surgeons, Committee on Trauma: *Resources for the optimal care of the injured patient*, Chicago, 2012, American College of Surgeons.)

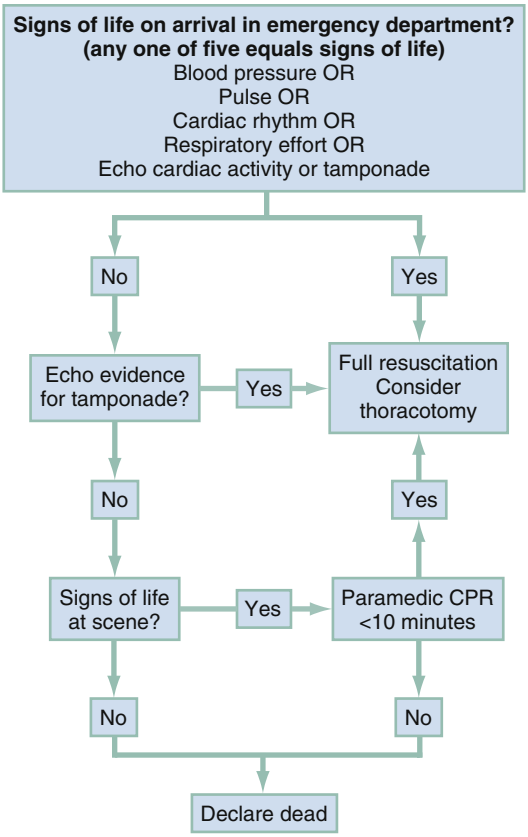

Fig. 32.6 Penetrating Chest Trauma—Emergency Department Thoracotomy Algorithm. *CPR,* Cardiopulmonary resuscitation; *ECHO,* echocardiographic.

including level of consciousness, tone and motor ability for all four extremities (e.g., spontaneous, purposeful, and withdrawal to pain), anal sphincter tone (if obtunded or evidence of paralysis), and any lateralizing signs, prior to administration of the paralytic and induction agent.

DISPOSITION

The decision to admit the patient or to transfer to a tertiary care facility should be coordinated based on available resources, consultation with the trauma surgeon, and consideration of institutional and regional guidelines. The ultimate disposition is dictated by a number of factors, including the patient's condition, nature of the injury, and availability of trauma surgeons, subspecialists, and anesthesiologists. Possible dispositions include transfer to the operating room, admission to the surgical service, observation in the ED, and transfer to another hospital for a more specialized care. The level of care and monitoring established in the ED should be maintained throughout transfer. All equipment and medications needed for resuscitation and maintenance of vital functions should be available during the transfer, as should qualified personnel (such as ALS trained paramedics) to oversee the patient's care.

In cases of interhospital transfers, emergency clinicians at the two institutions should carefully coordinate all arrangements and interventions. Stabilizing measures are begun before the transfer, but decompensation in transit should be anticipated. Qualified personnel and necessary resuscitative equipment should accompany the patient. The compelling reason for transferring a patient with life-threatening trauma is the lack of resources or personnel to care for particular injuries. Transfer should not be delayed for non-essential diagnostic procedures. All documentation and results of diagnostic testing and advanced imaging studies should accompany the patient in transfer.

In certain circumstances, the multiple trauma patient may not need admission or interhospital transfer. The decision to discharge these patients is evaluated carefully because many traumatic injuries may manifest in a delayed manner. When discharge from the ED is considered, thorough evaluation is necessary, with resources in place to ensure optimal surgical consultation (where radiologist image interpretation, and timely scheduled follow-up on an out-patient basis) is carried out.

The references for this chapter can be found online at ExpertConsult.com.

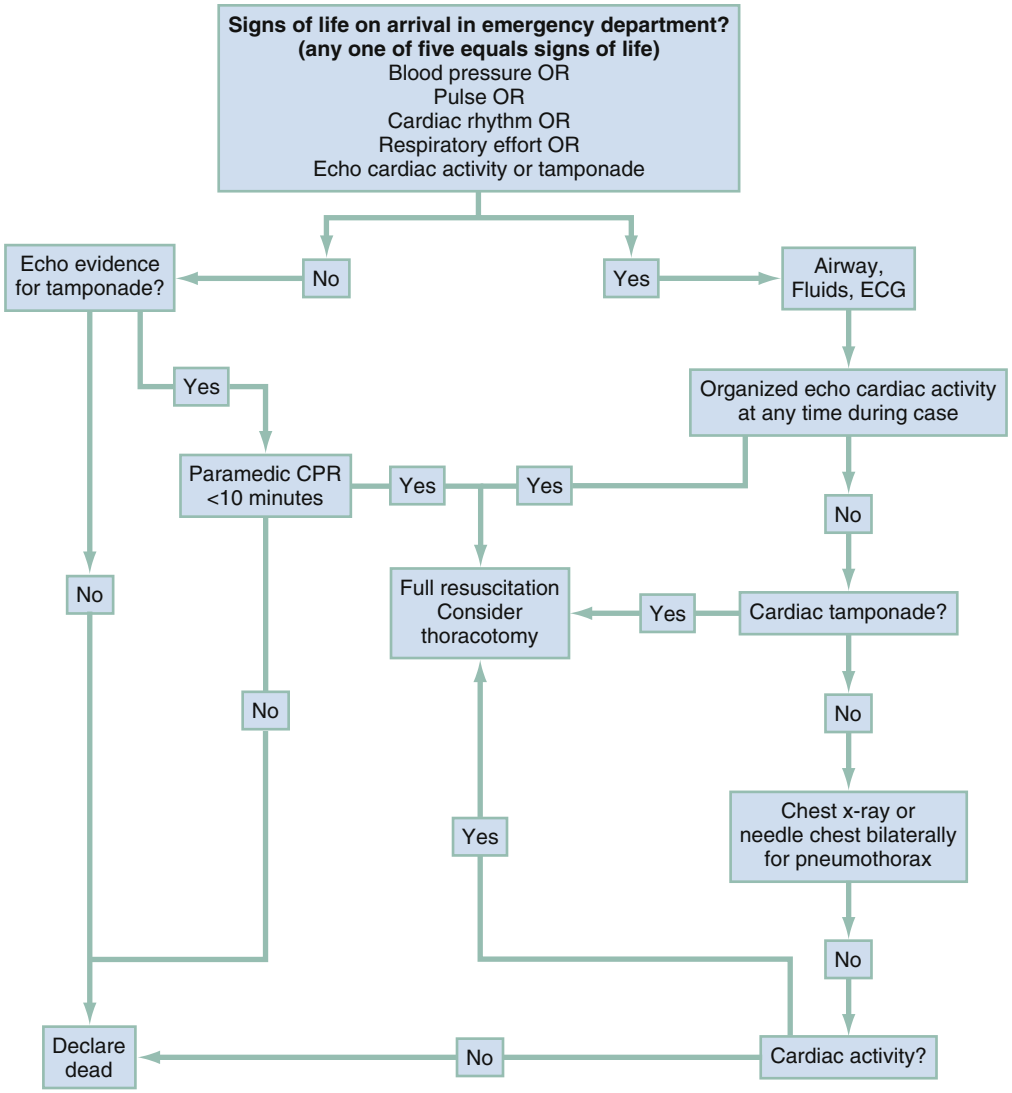

Fig. 32.7 Blunt Chest Trauma Emergency Department Thoracotomy Algorithm. *CPR,* Cardiopulmonary resuscitation; *ECG,* electrocardiogram; *ECHO,* echocardiographic.

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CHAPTER 32: QUESTIONS AND ANSWERS

1. A 33-year-old mother and her 2-year-old-son are brought in by paramedics after they were both hit by a car moving at 15 mph. Although mother and child had an identical mechanism of injury, the son would be at greater risk for all the following injuries, with the following exception:

a. Head injury
b. Hypothermia
c. Intra-abdominal injury
d. Multisystem injury
e. Posttraumatic stress disorder

Answer: e. Injury patterns can differ significantly between adults and children subjected to similar mechanisms of trauma. The major anatomic distinctions relate to the smaller size and surface area, larger head-to-body ratio, and less protected abdominal cavity of the child.

As a result, children are more vulnerable to multisystem injury in blunt trauma, including significant head and intra-abdominal injuries, as well as being at greater risk for hypothermia.

2. Which of the following is the goal of the primary survey?
   - **a.** Determine which consultations should be obtained.
   - **b.** Do an AMPLE (allergies, medications, past medical history, last meal, environments and events) history.
   - **c.** Obtain pertinent historical data from the paramedics.
   - **d.** Perform a radiographic evaluation.
   - **e.** Rapidly identify critical life-threatening diagnoses and begin treatment at the time of the diagnosis.

Answer: e. The emergency clinician should use a standardized approach to the initial evaluation of these patients. Following the Advanced Trauma Life Support (ATLS) algorithm of ABCs in the primary survey allows the timely identification of critical diagnoses and intervention without delay. The primary survey should be performed in a standardized fashion immediately after the patient arrives in the emergency department. The goal of the primary survey is to identify critical, life-threatening diagnoses rapidly and begin treatment at the time of diagnosis. The goals of the secondary survey are to obtain pertinent historical data about the patient and injury as well as evaluate and treat injuries not found on the primary survey. An AMPLE history should be obtained.

3. An 89-year-old man who was a restrained front seat passenger with a history of hypertension, anxiety disorder, and dementia is being evaluated after a head-on collision. His home medications include an angiotensin-converting enzyme (ACE) inhibitor for the hypertension, lorazepam for the anxiety, and olanzapine (Zyprexa) for the dementia. The patient does not have any complaints but is noted to have a blood pressure of 80/50 mm Hg and heart rate of 100 beats/min. In evaluating the patient, you should suspect that the asymptomatic hypotension is most likely due to which of the following?
   - **a.** Antihypertensive medication use
   - **b.** Antipsychotic medication use
   - **c.** Benzodiazepine use
   - **d.** Blood loss

Answer: d. Lower extremity weakness, gait disturbances, decreased visual acuity, and the use of psychotropics, antihypertensives, and sedatives have been associated with falls in older adults, resulting in major injury. The use of these medications, particularly antihypertensives, should not be considered causative in trauma patients with hypotension until acute hemorrhage has been ruled out. In addition, anticoagulants, antiplatelet drugs, and aspirin are commonly prescribed, and their effects should be suspected and reversed, if warranted.

4. A severely injured, hypotensive trauma patient is being considered for permissive hypotension because she has a contained retroperitoneal hematoma and is not actively hemorrhaging. In permissive hypotension, the mean arterial pressure is restored to a goal of 50 mm Hg. Which of the following should help you decide against using permissive hypotension?
   - **a.** Age >80 years
   - **b.** Age <10 years
   - **c.** Associated traumatic brain injury
   - **d.** Hemoglobin of 10 g/dL
   - **e.** Intoxication

Answer: c. In the severely injured, hypotensive trauma patient, restoration of normal blood pressure may be undesirable. The concept of permissive hypotension is based on the concern that resuscitation to normal blood pressures may increase bleeding from a site that is contained and not actively hemorrhaging. In permissive hypotension, the mean arterial pressure (MAP) is restored to a goal of about 50 mm Hg. Studies have shown that this strategy leads to less blood product use, less bleeding, and lower incidence of coagulopathy. However, the provider should be aware that permissive hypotension is contraindicated in the management of traumatic brain injury because of the risk of hypoperfusion.

5. An 87-year-old male with history of atrial fibrillation on anticoagulation, COPD, hypertension, and hyperlipidemia fell from a standing height sustaining a pelvic fracture requiring blood transfusion. Which of the following should raise concern for increased mortality in geriatric trauma patients?
   - **a.** Anticoagulation
   - **b.** Age >85
   - **c.** Isolated pelvic fracture
   - **d.** COPD
   - **e.** All of the above

Answer: e. All of the above can contribute to both morbidity and mortality of geriatric trauma patients. Often times with less severe injury patterns, this population will have increased transfusion needs, complications due to hospitalizations, immobilization, and prolonged rehabilitation times. Patients with one or more of: coagulopathy, cirrhosis, COPD, CAD, or DM have shown twice the risk of death in the setting of trauma. Additionally, elderly patients who sustain a pelvic ring injury are prone to increased mortality with those >85 years at highest risk.

6. A 52-year-old female involved in a motor vehicle collision (MVC) at 7 pm is transferred to a Level 1 trauma center. She arrives at 11 pm and despite appropriate isotonic resuscitation and remains hypotensive. Transfusion protocol is initiated. What is the next best intervention?
   - **a.** Administer tranexamic acid (TXA) 1 g over 10 minutes
   - **b.** Administer TXA 1 g over next 8 hours
   - **c.** Repeat primary survey
   - **d.** None of the above
   - **e.** All of the above

Answer: c. As with any transferred trauma patient any non-response or change in condition should prompt rapid re-evaluation. Additionally, TXA is indicated in patients with hemorrhagic shock ONLY if given within 3 hours of injury. TXA safely reduces the risk of death in bleeding trauma patients when administered up to 3 hours after trauma but earlier administration within 1 hour is considered superior. Many pre-hospital protocols allow for field use of TXA. Trauma patients with clinically significant hemorrhage, or who present in shock, should receive 1 g of T XA over 10 minutes, followed by 1 g infusion over 8 hours.

33

Head Trauma

Linda Papa and Scott A. Goldberg

KEY CONCEPTS

- *Head trauma* is a broad term describing an external trauma to the craniofacial area of the body from blunt, penetrating, blast, rotational, or acceleration-deceleration forces. The term *head injury* refers to a clinically evident injury on physical examination, and the term *brain injury* indicates an injury to the brain itself.
- Traumatic brain injury (TBI) is often categorized into mild (Glasgow Coma Scale score, 13–15), moderate (GCS score, 9–12), and severe (GCS score, 3–8), but this actually represents a spectrum of injury. Patients with a presentation GCS score of 13–15 who are stable or improving are unlikely to have CT scan findings that warrant intervention.
- The motor component of the GCS is the strongest predictor of outcome following TBI.
- Secondary systemic insults such as hypoxia and hypotension worsen neurologic outcome and should be corrected as soon as detected.
- A noncontrast head CT scan is the imaging modality of choice when TBI is suspected.
- Anticonvulsant prophylaxis with phenytoin or levetiracetam and broad-spectrum antibiotics should be given to patients with penetrating brain injuries for 7 days postinjury.
- Patients can deteriorate from an expanding intracranial hematoma after a mild traumatic brain injury (MTBI), and should undergo serial evaluations, including GCS scoring.
- An MTBI can be easily overlooked when an alert patient presents with distracting injuries. Specifically, assess for disorientation, confusion, amnesia, or disordered awareness (with or without loss of consciousness).
- Imaging of patients with MTBI should follow a validated guideline, such as the Canadian CT Head Rule and New Orleans Criteria. Emergency clinicians should select the system most applicable for their setting and patient population.
- Intoxicated individuals are high-risk patients. Alcohol and drug use affect the GCS score and may significantly obscure the neurologic examination.
- Most patients with MTBI can be discharged from the emergency department (ED) with a normal examination and after a reasonable period of observation (4–6 h) or following a negative CT scan of the head.
- Patients should be discharged with instructions describing the signs and symptoms of acute and delayed complications of MTBI. All discharge instructions should be relayed to a responsible third party.
- Athletes with a concussive head injury should be immediately removed from play and not return until they have been evaluated by a health care provider with expertise in concussion management. There should be a gradual stepwise increase in physical activity.
- Older adults (age greater than 60 years) may have significant intracranial injuries and not show signs of deterioration, especially if their baseline cognitive functioning is impaired; clinicians should therefore have a low threshold for obtaining CT scans with these patients.
- Falls in older adults, including low-mechanism falls, should prompt emergency clinicians to consider the possibility of brain injury.

FOUNDATIONS

Background and Importance

Head trauma accounts for approximately 2.5 million emergency department (ED) visits annually in the United States , representing an increase of more than 50% from approximately 1.6 million over the previous 6 years.[1] The most common principal mechanisms of injury for all age groups includes falls, being struck by or against an object, and motor-vehicle crashes in the civilian population.[1] Traumatic brain injury (TBI) caused by blasts has resulted in disproportionate morbidity to combatants in the recent wars in Iraq and Afghanistan.[2,3] As veterans return to the United States, the number of patients experiencing the consequences of TBI continues to increase.

Gunshot wounds (GSWs) to the head are particularly lethal; the overall mortality rate is estimated to be 90%, with 70% of deaths occurring at the scene.[4] Overall, TBI-related deaths account for 2.2% of all deaths in the United States.[1]

Head trauma is a broad term describing an external trauma to the craniofacial area of the body from blunt, penetrating, blast, rotational, or acceleration-deceleration forces. *Head injury* refers to a clinically evident injury on physical examination and is recognized by the presence of ecchymosis, lacerations, or deformities. The term *traumatic brain injury* indicates an injury to the brain itself.

The ultimate survival and neurologic outcome of the brain-injured patient depends on the extent of TBI occurring at the time of injury (primary injury) and the subsequent effects of systemic insults (secondary injuries), such as those caused by hypotension and hypoxia. Thus, clinical care of patients with TBI emphasizes early management to minimize the occurrence of secondary brain injury. Emergency clinicians can influence the incidence and severity of primary brain injury through injury prevention programs.

A number of terms describing *mild traumatic brain injury* (MTBI) have been used in the past, including minor, minimal, grade I, class I, and low risk. The term *concussion* is also used to describe a MTBI. However, the diagnosis of MTBI is based on symptoms and clinical assessment. One of the most commonly accepted criteria (from the American Congress of Rehabilitation Medicine together with the Centers for Disease Control and Prevention (CDC) and the World Health Organization) defines a patient with MTBI as one who has a Glasgow Coma Scale (GCS) score of 13 to 15 within 30 minutes of injury or at presentation to the ED, with traumatically induced physiologic disruption of brain function as manifested by at least one of the following: (1) any period of loss of consciousness (less than 30 minutes) or decreased level of consciousness (LOC); (2) any loss of memory for events immediately before or after the accident (posttraumatic amnesia should last <24 hours); (3) any alteration in mental state at the time of the accident (e.g., feeling, dazed, disoriented, foggy, "seeing stars," confused or slowed thinking); and (4) neurologic deficits (weakness,

loss of balance, change in vision, sensory loss) that may or may not be transient (Box 33.1).

Individuals with MTBI are acutely at risk for serious intracranial injuries. Up to 17% of patients with suspected MTBI in the ED have abnormal computed tomography (CT) scans of the head. Although the incidence of life-threatening lesions that require neurosurgical intervention in suspected MTBI is only about 1%, these patients have an important risk of subsequent deterioration from intracranial bleeding. If these cases are recognized and treated early, a full recovery is likely, otherwise, severe disability or death may ensue.

The GCS score was not originally intended for use in MTBI patients, and some authors have suggested that patients with a GCS score of 13 or 14 be excluded from the mild category and placed into the moderate-risk group due to the higher risk of neurosurgical intervention.[5,6] However, patients who may be under the influence of or intoxicated from the use of recreational drugs or alcohol can also present with a GCS score of 13 to 14. Mental status can also be affected by pain, certain medications, and post-traumatic shock. Nonetheless, over 10% of patients who become comatose start with a GCS score of 15. Patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be an MTBI. Among MTBI patients, those with GCS scores trending downward (worsening neurologic status) have a higher rate of neurosurgical interventions and have a less favorable outcome than those with GCS scores trending upward (improving neurologic status).[6,7]

BOX 33.1 Definition of Mild Traumatic Brain Injury

According to the American Congress of Rehabilitation Medicine, a person with mild traumatic brain injury (MTBI) is a patient with a Glasgow Coma Scale (GCS) of 13 to 15 who has had a traumatically induced physiologic disruption of brain function, as manifested by at least one of the following:

1. Any period of loss of consciousness less than 30 min
2. Any loss of memory for events immediately before or after the accident (posttraumatic amnesia should last <24 h)
3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)
4. Focal neurologic deficit(s) that may or may not be transient

Anatomy and Pathophysiology

Anatomy

Scalp and cranium. The scalp consists of five tissue layers (Fig. 33.1). The skull is comprised of the frontal, ethmoid, sphenoid, and occipital bones and two parietal and two temporal bones. Each bone consists of solid inner and outer layers separated by a layer of cancellous bone tissue (the diploe). In adults, the bones of the skull average 2 to 6 mm in thickness; the bones in the temporal region are usually the thinnest of the skull. The cranial bones form a smooth outer surface of the skull, but within the cranial vault are many bony protrusions and ridges. "*Contrecoup*" *brain injuries*, such as contusions, may occur on the opposite side of the head impact (coup) as the brain shifts to the uninjured side and strikes against uneven bone surfaces. After the first few months of life, the cranial bones begin to fuse, ultimately forming the rigid, nonexpandable cranial vault. The inner aspect of the skull is lined with the periosteal dura, which is a thick connective tissue layer that adheres closely to the bone surface. The inner meningeal layer of the dura is the outermost covering of the brain. This dural membrane reflects back on itself to make folds within the cranial space. These folds serve to protect and compartmentalize different components of the brain. The midline falx cerebri separates the two cerebral hemispheres

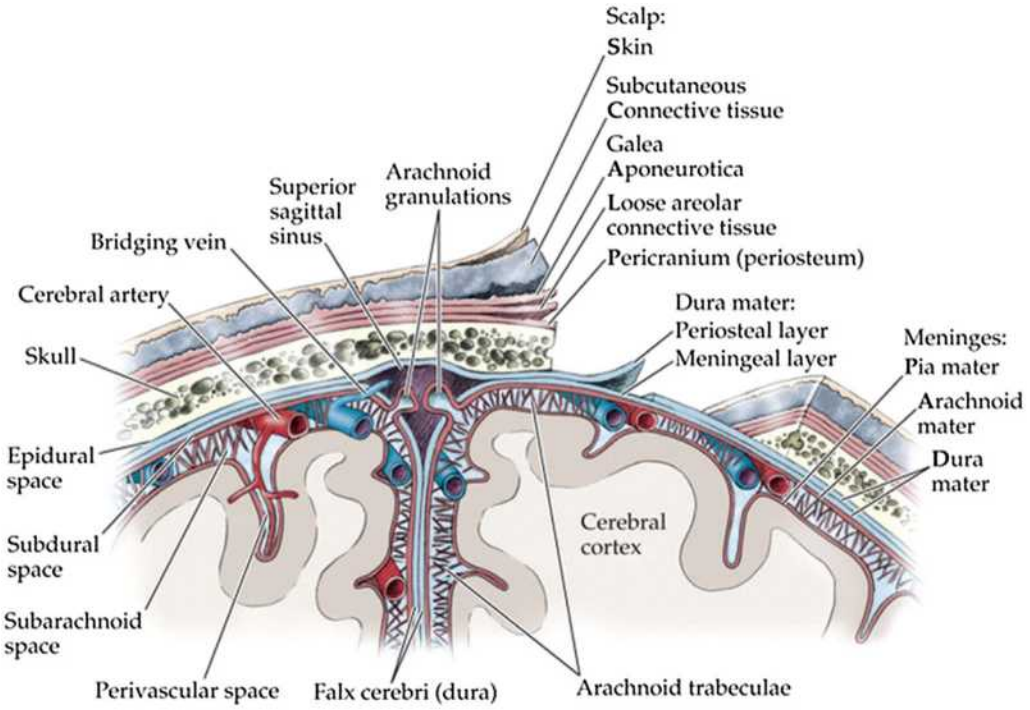

Fig. 33.1 Layers of the Soft Tissues, Skull, and Meninges. The dermis is the outermost layer and is among the thickest layers of skin on the body. The underlying subcutaneous tissue contains the hair follicles and rich blood supply of the scalp. The galea, made of tough fascial tissue, contains the occipitofrontalis and temporoparietalis muscles, which move the scalp backward and forward, elevate the eyebrows, and wrinkle the forehead. Under the galea is a loose areolar tissue layer. The deepest layer of the scalp, the pericranium, is firmly adhered to the skull. (From Blumenfeld H. *Neuroanatomy through clinical cases*. Sunderland: Sinauer Associates, Incorporated; 2002.)

Fig. 33.2 Diffuse axonal injury (DAI), otherwise known as traumatic axonal injury (TAI), is characterized by axonal stretching leading to axolemmal disruption, ionic flux, neurofilament compaction, and microtubule disassembly, resulting in axonal swelling and disconnection. Axonal swelling and disconnection can lead to axon death. **a,** Normal neuron, **b, c,** Axon reaction to increasing stretch. **d,** Retraction balls have formed, and aggregates of axonal material lie along the course of the axon. (From Peerless SJ, Rewcastle NB. Shear injuries of the brain. *CMAJ* 1967;96:577–582.)

from each other. The tentorium cerebelli partitions the cerebellum and brainstem from the cerebral hemispheres. The U-shaped free margin of this dural fold is important in the pathology of the transtentorial herniation syndromes. Within the margins of the dural reflections, the two dural layers separate to form large dural venous sinuses. Injury to the dural sinuses is associated with significant morbidity and mortality because of the potential for uncontrolled hemorrhage.

Brain and cerebrospinal fluid. The brain is a semisolid structure that weighs approximately 1400 g (3 lb.) and occupies approximately 80% of the cranial vault, with the remaining space occupied primarily by vasculature and cerebrospinal fluid (CSF). The brain is covered by three distinct membranes—the meningeal dura, arachnoid layer, and pia (Fig. 33.2). The location of traumatic hematomas relative to these membranes defines the pathologic condition and determines the consequences of the injury.

The brain is suspended in the CSF, which provides some physical buffering for the brain during trauma. CSF is produced by the choroid plexus, located primarily in the lateral ventricles of the brain. CSF passes from the ventricular system into the subarachnoid space that surrounds the brain and spinal cord. The normal pressure exerted by the CSF is 65 to 195 mm H_2O or 5 to 15 mm Hg.

The blood-brain barrier (BBB) maintains the microenvironment of the brain tissue and CSF. Extracellular ion and neurotransmitter concentrations are regulated by movement across this barrier. When the BBB is intact, the ability of neuroactive drugs to penetrate the brain tissue usually depends on their lipid solubility. However, the biomechanics of a brain injury or posttraumatic cerebral edema can cause a disruption of the BBB for up to several hours after the insult. In severe TBI, prolonged disruption of the BBB further contributes to the development of posttraumatic vasogenic cerebral edema and higher maximum intracranial pressure (ICP). Mild TBI patients exposed to repetitive biomechanical forces and those with post-concussive symptoms also appear to have higher BBB permeability on neuroimaging.[8,9]

Pathophysiology

Cerebral hemodynamics and increased intracranial pressure. The brain has an extremely high metabolic rate, accounting for approximately 20% of the entire oxygen consumption of the body and requiring approximately 15% of total cardiac output. In the normal brain, cerebral blood flow (CBF) is maintained at constant levels. Optimal regional CBF is maintained by the ability of the cerebral vessels to alter their diameter in response to changing physiologic conditions. This response protects the brain by increasing the delivery of oxygen to tissue, enhancing the removal of metabolic end products, and allowing nearly instantaneous adjustments to meet changing metabolic demands. Hypertension, alkalosis, and hypocarbia promote cerebral vasoconstriction, whereas hypotension, acidosis, and hypercarbia cause cerebral vasodilation.

Cerebral vasoactivity is also very sensitive to changes in the partial pressures of carbon dioxide and oxygen (P_{CO_2} and P_{O_2}, respectively). The response to changes in P_{CO_2} is nearly linear between P_{CO_2} values of 20 and 60 mm Hg. In this range, lowering P_{CO_2} by as little as 1 mm Hg decreases the diameter of cerebral vessels by 2% to 3%, corresponding to an overall change in CBF of 1.1 mL/100 g of tissue/min. This is the physiologic rationale for intentional hyperventilation in the setting of rapid and marked increases in ICP. Hyperventilation causes P_{CO_2} to fall, resulting in cerebral vasoconstriction. However, this is no longer recommended as a mechanism for reducing ICP.[10] The cerebral vessels also respond to changes in P_{O_2}. As P_{O_2} declines, cerebral vessels dilate to ensure adequate oxygen delivery to brain tissue. When brain injury occurs, increased CBF, vascular dilation, and a disrupted BBB promote vasogenic edema and can further increase ICP. Therefore, avoiding or reversing hypoxia is essential in managing the brain-injured patient.

CBF also depends on the cerebral perfusion pressure (CPP), which is the pressure gradient across the brain. CBF remains fairly constant when CPP is 50 to 160 mm Hg. This is referred to as autoregulation and occurs with a mean arterial pressure (MAP) of 60 to 150 mm Hg. The determinants of CPP are MAP and the resistance to CBF produced by the mean systemic venous pressure and ICP. Because ICP is higher than mean systemic venous pressure, ICP effects predominate, and CPP can be approximated as follows:

$$CPP = MAP - IC$$

If CPP falls below 40 mm Hg, autoregulation is lost and CBF declines, resulting in tissue ischemia and altered cerebral metabolism. Avoidance of hypotension or elevation in ICP in the head-injured patient helps ensure that CPP can be maintained.

The recommended target CPP value is between 60 and 70 mm Hg. However, the risks of aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors, including the risk of developing adult respiratory failure, should be considered.[10]

Increased intracranial pressure. Increased ICP is defined as a CSF pressure greater than 15 mm Hg (or 195 mm H_2O) and is a frequent consequence of a severe TBI. Initially, as ICP increases as a result of a traumatic mass lesion or edema, CSF is displaced from the cranial vault to the spinal canal, offsetting the increased blood or brain volume. When this compensatory mechanism is overwhelmed, the elastic properties of the brain substance allow tissue compression to provide buffering for the increasing pressure. Depending on the location and rate of mass expansion and edema formation, the intracranial compensatory mechanisms can accommodate an increased volume of 50 to 100 mL. Beyond that, even small changes in intracranial relationships, such as from vasodilation, CSF obstruction, or areas

of focal edema, may increase ICP. If ICP increases to the point at which CPP is compromised, vasoparalysis occurs and autoregulation is impaired. The CBF then depends directly on the systemic MAP. With the loss of autoregulation, massive cerebral vasodilation occurs. Systemic pressure is transmitted to the capillaries, contributes to vasogenic edema, and further increases ICP.

ICP above 22 mm Hg is associated with increased mortality requiring intervention and treatment.[10] If ICP is not controlled, herniation will occur, resulting in brainstem compression and cardiorespiratory arrest. Simple techniques to reduce ICP include head of bed elevation to 30 degrees and keeping the neck in a neutral position. Common therapies include use of osmotic and diuretic agents such as mannitol or hypertonic saline (HTS), and CSF drainage. Therapeutic hyperventilation, once almost universally used, is potentially harmful and is now recommended only as a temporizing measure for a select group of patients for whom other measures are not available or have failed.

Cushing reflex. Progressive hypertension associated with bradycardia and diminished respiratory effort is a specific response to acute, potentially lethal increases in ICP. This response is called Cushing reflex or Cushing phenomenon, and its occurrence indicates that the ICP has reached life-threatening levels. However, only one-third of cases of life-threatening increased ICP manifest the full triad of hypertension, bradycardia, and respiratory irregularity.

Altered Levels of Consciousness

Consciousness is the state of awareness of the self and environment, and it requires intact functioning of the cerebral cortices and reticular activating system (RAS) of the brainstem. With increasing ICP from brain swelling or an expanding mass lesion, brainstem compression and subsequent RAS compression can occur. A patient who has sustained TBI typically has an altered LOC, but reversible conditions that can alter mental status such as hypoxia, hypotension, or hypoglycemia should be corrected as soon as they are identified. Global suppression may result from an intoxicant consumed before the injury, posttraumatic seizure (PTS), or postictal period after a seizure from any cause.

Definitions and Patterns of Injury

Traumatic Brain Injuries: Severe, Moderate, and Mild

Traditionally, TBI has been separated into the three broad categories of mild, moderate, and severe, primarily based on the GCS score following resuscitation and stabilization. Severe brain injury is defined as a TBI with a post-resuscitation GCS score of 8 or lower, moderate as a GCS score of 9 to 12, and mild as a GCS score of 13 to 15. Overall, 80% of patients sustain MTBIs, 10% moderate brain injuries, and 10% severe brain injuries (Table 33.1). An MTBI is often referred to as a concussion.

The degree of brain injury following an MTBI or concussion also depends on the primary mechanism and magnitude of injury, secondary insults, and the patient's genetic and molecular response. Primary damage is caused by the initial impact or force that although not as evident as severe TBI, may lead to smaller contusions, hematomas, axonal damage, and microvascular injury. Following a MTBI without evidence of lesions on CT scans, there is a decrease in CBF over the ensuing hours and days after injury,[11] as well as cortical neurometabolic abnormalities.[12,13] Traumatic axonal injury (TAI) is also an important determinant of outcome.[14]

Increasing evidence has suggested that even a single MTBI can produce long-term gray and white matter atrophy, precipitate or accelerate age-related neurodegeneration, and increase the risk of developing Alzheimer, Parkinson, and motor neuron disease.[15,16] Repeated episodes of MTBI can provoke the development of chronic traumatic encephalopathy (CTE), a term used to describe clinical changes in cognition, mood, personality, behavior, or movement occurring years following concussion.[16,17] CTE has recently been found to occur after other causes of repeated head trauma, suggesting that any repeated blows to the head, such as those that occur in American football, hockey, soccer, and professional wrestling, as well as in military personnel, and in those victims of physical abuse, can also lead to neurodegenerative changes.[18,19]

Direct and Indirect Injuries

Direct injury. Direct head trauma occurs when the head is struck, or its motion is suddenly arrested, by an object. The resulting damage to the skull and brain depends on the consistency, mass, surface area, and velocity of the object striking the head. Direct injury can also be caused by compression of the head. External signs of trauma are frequently noted at the site of impact or compression force where the skull initially bends inward at the point of contact. If the force is sufficient, a skull fracture can occur. The cranium absorbs some of this applied energy, whereas some energy is transmitted to the brain by shock waves that travel distant to the site of impact or compression. With sufficient and prolonged application of a compression force, the ability of the skull to absorb the force is overcome, and multiple linear skull fractures occur. These resulting fractures can be depressed if a high-energy rapid compression force is applied to a small area of the skull. The extent of direct injury depends on the vasoelastic properties of the underlying region of brain tissue, duration of the force applied, magnitude of the force reaching the brain tissue, and surface area of the brain that is affected.

Indirect injury. In indirect brain injury, the cranial contents are set into motion by forces other than the direct contact of the skull with an object. A common example is an acceleration-deceleration injury

TABLE 33.1 Traumatic Brain Injury as a Portion of All Injuries and Emergency Department Visits

		ALL INJURIES		TRAUMATIC BRAIN INJURIES		
Parameter	All Visits	Number	Percent of All Visits	Number	Percent of All Injuries	Percent of All Visits
ED visits[a]	96,839,411	28,697,028	29.6	1,364,797	4.8	1.4
Hospitalizations[b]	36,693,646	1,826,548	5.0	275,146	15.1	0.7
Deaths	2,432,714	169,055	6.9	51,538[c]	30.5	2.1
Total	135,965,771	30,692,631	22.6	1,691,481	5.5	1.2

[a]Persons who were hospitalized, died, or were transferred to another facility were excluded.
[b]In-hospital deaths and patients who transferred from another hospital were excluded.
[c]28 mortality records (from 2002 to 2006) were omitted because of missing age information.
Adapted from Faul M XL, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002–2006. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010:1–74.

in which no direct mechanical impact is sustained, but the cranial contents are set into vigorous motion. As the bridging subdural vessels are strained, subdural hematomas (SDHs) may result.

In an indirect injury, differential acceleration of the cranial contents occurs, depending on the physical characteristics of the brain region. As one brain region slides past another, shear and strain occur. These movements result in diffuse injuries, such as a concussion or TAI. Additional injury occurs as the movement of the intracranial contents is abruptly arrested, and the brain strikes the skull or a dural structure. Contrecoup contusions are an example of such an injury. In a penetrating injury, the object produces pressure waves that can strike structures distal to the path of the missile.

Neurochemical Cascade

Following a brain injury, secondary insults may be mediated through physiologic events, which can decrease the supply of oxygen and energy to the brain tissue, or a cascade of cytotoxic events, mediated by many molecular and cellular processes. These events include activation of inflammatory responses, imbalances of ion concentrations (e.g., potassium, calcium), an increase in the presence of excitatory amino acids (e.g., glutamate), dysregulation of neurotransmitter synthesis and release, imbalance in mitochondrial functions and energy metabolism, and production of free radicals.[20]

Penetrating Head Trauma

The morbidity and mortality from missile injuries to the head depend on the intracranial path, speed of entry, and size and type of the penetrating object. Projectiles that cross the midline or geographic center of the brain, pass through the ventricles, or come to rest in the posterior fossa are associated with extremely high mortality. High-velocity wounds are associated with greater mortality than low-velocity injuries. Large missiles or missiles that fragment within the cranial vault are usually fatal. The design of the bullet and its fragmentation potential (capacity to deform or fragment) also contribute to final tissue destruction and patients' morbidity and mortality. Important clinical factors associated with mortality include increasing age, suicide attempt, lower GCS score, bilateral mydriasis, dural penetration, and bihemispheric and multi-lobar injury.[21]

Tangential wounds are caused by an impact that occurs at an oblique angle to the skull. If the missile has high velocity but low energy, it can travel around the skull, under the scalp, without passing through the skull. Intracranial damage, primarily cortical contusions, can occur at the initial site of impact secondary to pressure waves generated by the impact. Although many patients with tangential GSWs have a GCS score of 15 on presentation, many have underlying skull fractures and 25% have some degree of underlying intracranial hemorrhage.[22]

Most civilian penetrating brain injuries are penetrating missile wounds, which are produced by moderate- to high-velocity projectiles discharged at close range. The penetrating object may travel through the entire skull, bounce off the opposite inner table of the skull and ricochet within the brain, or stop somewhere within the cranial cavity.

As the bullet passes through the brain, a tissue cavity as much as 10 times the diameter of the missile is created. A percussion shock wave is also created, lasting 2 ms but causing little tissue destruction. The wounding capacity of a firearm is related to the kinetic energy of its missile on impact and how much energy is dissipated. Low-velocity missiles tend to be deflected by intracranial structures. The final track is therefore erratic and occasionally bears no relation to the exit or entrance site of the missile.

Scalp Wounds

The large blood vessels of the scalp do not fully constrict if they are lacerated and can be the source of substantial blood loss. Because the areolar attachments to the rest of the scalp are loose, scalp avulsions frequently occur through this layer. Subgaleal hematomas can become large because blood easily dissects through the loose areolar tissue. Hemostasis may be difficult to achieve, and blood loss may be significant to the point of causing hemodynamic compromise.

Skull Fractures

Skull fractures are local injuries caused by direct impact to the skull. Although the presence of a skull fracture does not always indicate underlying brain injury, the force required to fracture the skull is substantial, and all patients with skull fractures must be carefully evaluated to ensure that no additional injury is present. The pattern, extent, and type of skull fracture depend on the force of the impact applied and ratio of the impact force to the impact area. Clinically significant features of skull fractures include intracranial air, association with an overlying scalp laceration (open skull fracture), depression below the level of the skull's inner table, and location over a major dural venous sinus or middle meningeal artery.

Linear Fractures

A linear skull fracture is a single fracture that goes through the entire thickness of the skull. Linear skull fractures are clinically important if they cross the middle meningeal groove or major venous dural sinuses; they can disrupt these vascular structures and cause the formation of epidural hematomas (EDHs). Most other linear skull fractures are not clinically significant.

Sutural diastasis is the traumatic disruption of a cranial suture. In adults, sutural diastasis often involves the coronal or lambdoid sutures. Sutural diastasis usually occurs when a linear fracture extends into the suture line, and it is rare after sutures have undergone bone fusion. Comminuted skull fractures, which are multiple linear fractures that radiate from the impact site, usually suggest a more severe blow to the head than that producing a single linear fracture. A linear vault fracture substantially increases the risk of intracranial injury.

Depressed Fractures

Depressed skull fractures are usually caused by direct-impact injury with small blunt objects, such as a hammer or baseball bat. Most depressed skull fractures occur over the parietal or temporal regions. These fractures are clinically important because they predispose to significant underlying brain injury and to complications of head trauma, such as infection and seizures.

Basilar Fractures

Basilar fractures are linear fractures at the base of the skull, usually occurring through the temporal bone. Patients with basilar fractures are at risk for extra-axial hematomas because of the proximity of the fracture to the middle cerebral artery. Dural tears, resulting from a basilar skull fracture, may produce a communication among the subarachnoid space, paranasal sinuses, and middle ear. This offers a route for the introduction of infection into the cranial cavity and is suggested by a CSF leak. These fractures are the result of considerable impact force and are highly associated with an underlying brain injury.

Extra-Axial and Intra-Axial Intracranial Injuries

Extra-axial refers to injury or bleeding that occurs within the skull but outside of the brain tissue. Intra-axial injury or bleeding occurs within the brain tissue itself. Extra-axial intracranial lesions include EDH, SDH, traumatic subarachnoid hemorrhage (SAH), and subdural hygroma (SDHG). Intra-axial intracranial lesions include TAI, cerebral and cerebellar contusions, and cerebral and cerebellar hematomas.

Extra-Axial Injury

Epidural hematoma. An EDH is bleeding that occurs between the inner table of the skull and dura. Most EDHs result from a direct-impact injury that causes a forceful deformity of the skull. Often, a fracture occurs across the middle meningeal artery, or vein, or a dural sinus. The temporoparietal region is the most likely site for an EDH. The high arterial pressure of the bleeding vessel dissects the dura away from the skull, permitting hematoma formation. EDHs are rare in older adults and children younger than 2 years because of the close attachment of the dura to the skull in both patient populations.

Subdural hematoma. An SDH is a hemorrhage that occurs between the dura and brain and is usually caused by acceleration-deceleration injuries. SDH occurs most commonly in patients with brain atrophy, such as alcoholic or older patients, because bridging vessels traverse greater distances than in patients with no atrophy. As a result, the vessels are more likely to rupture with rapid movement of the head. Once they are ruptured, blood can fill the potential space between the dura and arachnoid. SDH is much more common than EDH, occurring in up to 30% of patients with severe head trauma. The slow bleeding of venous structures delays the development of clinical signs and symptoms. As a result, the hematoma compresses the underlying brain tissue for prolonged periods and can cause significant tissue ischemia and damage. Approximately 20% of patients will present with a bilateral SDH. The prognosis of SDH does not entirely depend on the size of the hematoma but rather on the degree of brain injury caused by the pressure of the expanding hematoma on underlying tissue or by other intracranial injuries. Mortality is highest in older adults, patients who have a GCS score of 8 or less, and those with signs of acute herniation syndrome on initial ED presentation. Posterior fossa SDHs make up less than 1% of all reported SDHs. They are caused by occipital trauma that tears bridging vessels or venous sinuses and have a very poor prognosis.

Traumatic subarachnoid hemorrhage. A traumatic SAH is blood within the CSF and meningeal intima and probably results from tears of small subarachnoid vessels. Traumatic SAH is detected on the first CT scan in up to one-third of patients with severe TBI and ultimately is identified in almost 50% of patients with severe head trauma. It is therefore the most common CT scan abnormality seen after head trauma. Traumatic intracranial hemorrhage is typically associated with significant morbidity and mortality.[23] Most patients with traumatic SAH and a normal GCS do not require neurosurgical intervention.[24]

Subdural hygroma. A SDHG is a collection of clear, xanthochromic blood-tinged fluid in the dural space. The pathogenesis of an SDHG is not certain. It may result from a tear in the arachnoid that permits CSF to escape into the dural space or effusions from injured vessels through areas of abnormal permeability in the meninges or in the underlying parenchyma. They may accumulate immediately after trauma or in a delayed manner.

Intra-Axial Injury

Diffuse axonal injury and traumatic axonal injury. Prolonged traumatic coma not caused by mass lesions or ischemic insult is thought to result from diffuse axonal injury (DAI). Although the term *diffuse axonal injury* has been widely adopted, the distribution of axonal injury is usually not diffuse but multifocal. Axonal injury occurs on a spectrum, with milder cases primarily localized. Furthermore, DAI has been used to describe axonal injury from nontraumatic causes in other neurologic conditions. Accordingly, the term *traumatic axonal injury* is preferred, particularly in milder cases. In more severe cases, when the axonal injury is more widespread, the term *diffuse traumatic axonal injury* more appropriately describes the condition.

In TAI, axons sustain a primary insult in which they are torn (axotomy) or stretched, resulting in the formation of axon retraction balls that interrupt synaptic connection and normal axonal function. Secondary insult including disruption of the extracellular brain matrix and influx of inflammatory mediators leads to axonal swelling and disconnection and can lead to axon death (see Fig. 33.2). Moreover, acute uncoupling of CBF, metabolism, and apoptosis are thought to be the important factors linked to axonal cell death after TAI.[11,25,26]

Most patients with TAI present with persistent traumatic coma that begins immediately at the time of trauma; however, some patients may recover consciousness briefly before lapsing into prolonged coma. Because diagnostic studies cannot predict the extent of the axonal damage, the severity of the injury is determined by the clinical course. Clinical grades of diffuse TAI have been based on length of coma: (1) grade I (mild)—coma for 6 to 24 hours; (2) grade II (moderate)—coma for longer than 24 hours but not decerebrate; (3) grade III (severe)—coma for longer than 24 hours and decerebrate or flaccid. Currently, no early clinical or biomarker predictor exists that differentiates patients with mild, moderate, or severe diffuse TAI.

Cerebral contusions. Contusions are bruises on the surface of the brain, usually caused by impact injury. Contusions are produced when parenchymal blood vessels are damaged, resulting in scattered areas of petechial hemorrhage and subsequent edema. Contusions develop in the gray matter on the surface of the brain and taper into the white matter. Subarachnoid blood is frequently found overlying the involved gyrus.

Most often, contusions occur at the poles and inferior surfaces of the frontal and temporal lobes, where the brain comes into contact with bone protuberances in the base of the skull. If the contusion occurs on the same side as the impact injury, it is a coup injury; if it occurs on the opposite side, the contusion is a contrecoup injury. Contusions can also develop in the brain tissue that underlies a skull fracture. Multiple areas of contused tissue may be produced with a single impact, often in association with other intracranial injuries. With time, the associated hemorrhages and edema of a contusion can become widespread and serve as a nidus for hemorrhage or swelling, thus producing a local mass effect. Compression of the underlying tissue can cause local areas of ischemia, and tissue infarction is possible if the compression is significant and unrelieved. Eventually, these ischemic areas become necrotic, and cystic cavities form within them.

Intracerebral hematoma. Intracerebral hematomas (ICHs) are formed deep within the brain tissue and are usually caused by shearing or tensile forces that mechanically stretch and tear deep small-caliber arterioles as the brain is propelled against irregular surfaces in the cranial vault. Resulting small petechial hemorrhages coalesce to form ICHs, with 85% in the frontal and temporal lobes. An ICH is often found in the presence of extra-axial hematomas and in many patients multiple ICHs are present. Isolated ICHs may be detected in as many as 12% of all patients with severe head trauma.

Intracerebellar hematoma. Primary traumatic intracerebellar hematomas are rare but can occur after a direct blow to the occipital area. Often, these patients have an associated skull fracture, posterior fossa EDH or SDH, or supratentorial contrecoup hematomas and contusions.

Primary and Secondary Brain Injuries

The acute clinical picture of the patient with TBI is dynamic and represents the sum of primary and secondary injury. A primary brain injury is mechanical damage that occurs at the time of head trauma and includes brain lacerations, hemorrhages, contusions, and tissue avulsions. On the microscopic level, primary injury causes permanent

mechanical cellular disruption and microvascular injury. Other than the evacuation of traumatic hematomas, no specific intervention exists to repair or reverse primary brain injury.

Following the primary injury, a cascade of events occurs at the cellular and molecular level that continues for hours to days and contributes to further brain injury. This secondary brain injury results from intracellular and extracellular derangements that lead to alterations in cell function and propagation of injury through processes such as depolarization, excitotoxicity, disruption of calcium homeostasis, free radical generation, BBB disruption, ischemic injury, edema formation, and intracranial hypertension.[27] Animal and human studies have revealed a complicated series of neurochemical, neuroanatomic, and neurophysiologic reactions after brain injury. The cell has compensatory mechanisms to protect itself from widespread damage, such as endogenous free radical scavengers and antioxidants. However, these systems are quickly overwhelmed, and the functional and structural integrity of the cell is threatened. Investigational agents aimed at specific steps in the destructive processes indicate that some aspects of secondary brain injury may be reversed or modified. Multiple ongoing brain injury trials have been performed with numerous investigational therapeutic interventions; to date, none have proved useful in the clinical setting.[27,28]

Secondary Systemic Insults

The ultimate neurologic outcome after head trauma is influenced by the extent and degree of secondary brain injury. In turn, the amount of secondary brain injury depends on certain premorbid and comorbid conditions, such as the age of the patient and trauma-related systemic events. A primary goal in the emergency care of a head trauma patient is prevention or reduction of systemic conditions that are known to worsen outcome after TBI, such as hypotension, hypoxia, anemia, and hyperpyrexia.[10]

Hypotension. Hypotension, defined as SBP less than 90 mm Hg, has been found to have a negative impact on severe brain injury outcome. Systemic hypotension reduces cerebral perfusion, thereby potentiating ischemia and infarction. Hypotension is associated with a near-doubling of the mortality from TBI and worse outcomes for patients who survive.[10,29]

Hypoxia. Hypoxia, defined as a Po_2 less than 60 mm Hg, is relatively common in the brain-injured patient. Causes include: (1) transient or prolonged apnea caused by brainstem compression or injury after the traumatic event; (2) partial airway obstruction caused by blood, vomitus, or other debris in the airway of the traumatized patient; (3) injury to the chest wall that interferes with normal respiratory excursion; (4) pulmonary injury that reduces effective oxygenation; and (5) ineffective airway management, such as the inability to bag-valve-mask or intubate the patient in an effective or timely manner. When hypoxia is documented, the overall mortality from severe TBI may double.[10,29,30] Significant hyperoxia with resultant oxygen toxicity is also associated with worse outcome after TBI, although this relationship is less clearly defined.[30–32] In TBI, normoxia should be maintained.

Hypocarbia and hypercarbia. $Paco_2$ is one of the most potent drivers of CBF. Hypocarbia ($Paco_2$ ≤35 mm Hg) results in vasodilation, while hypercarbia ($Paco_2$ ≥46 mm Hg) leads to cerebral vasoconstriction. In TBI, both hypocarbia and hypercarbia are associated with increased morbidity. Hypercarbia causes cerebral vasodilatation with a resultant increase in cerebral edema and ICP, and thus is associated with a worsened neurologic outcome.[33] Hypocarbia, generally secondary to hyperventilation, results in reduced CBF and a transient decrease in ICP. For patients with impending brain herniation brief therapeutic hyperventilation may be considered. However, in most patients, hyperventilation should be avoided in favor of maintenance of normal to slightly reduced $Paco_2$ levels.[10]

Anemia. Anemia caused by blood loss can be detrimental to the head-injured patient by reducing the oxygen-carrying capacity of the blood, thus reducing the amount of necessary substrate delivered to the injured brain tissue. When anemia (hematocrit, 30%) occurs in patients with severe brain injury, the mortality rate increases. However, transfusion of red blood cells also has adverse effects in TBI patients.[34–37] At this time, evidence is insufficient to recommend a restrictive or liberal approach to transfusion in the brain-injured patient and transfusion threshold should be tailored to the individual patient.

Hyperpyrexia. Hyperpyrexia (core body temperature >38.5°C [101.3°F]) is also correlated with worse outcomes after TBI, and its magnitude and duration are contributory factors. Pathophysiology likely involves increased metabolism in injured brain areas, thus recruiting blood flow, with a resultant increase in ICP.

Cerebral Herniation Syndromes

Cerebral herniation occurs when increasing cranial volume and ICP overwhelm the natural compensatory capacities of the central nervous system (CNS; Fig. 33.3). When the signs of herniation syndrome are present mortality approaches 100% without rapid implementation of temporizing measures and definitive neurosurgical intervention.

Uncal Herniation

The most common clinically significant traumatic herniation syndrome is *uncal herniation*, a form of transtentorial herniation. Uncal herniation is often associated with traumatic extra-axial hematomas in the lateral middle fossa or the temporal lobe. As compression of the uncus begins, the third cranial nerve (CN) is compressed, which may result in anisocoria, ptosis, impaired extraocular movements, or a sluggish pupillary light reflex on the side ipsilateral to the expanding mass lesion. As the herniation progresses, compression of the ipsilateral oculomotor nerve eventually causes ipsilateral pupillary dilation and nonreactivity.

Initial motor examination findings can be normal, but contralateral Babinski responses develop early. Contralateral hemiparesis develops as the ipsilateral peduncle is compressed against the tentorium. With continued progression of the herniation, bilateral decerebrate posturing eventually occurs; decorticate posturing is not universally seen with the uncal herniation syndrome.

In a certain percentage of TBI patients, the contralateral cerebral peduncle is forced against the opposite edge of the tentorial hiatus. Hemiparesis is then detected ipsilateral to the dilated pupil and mass lesion. This is termed *Kernohan notch syndrome* and causes false-localizing motor findings. As uncal herniation progresses, direct brainstem compression causes additional alterations in the LOC, respiratory pattern, and cardiovascular system. Mental status changes may initially be subtle, such as agitation, restlessness, or confusion, but soon lethargy occurs, with progression to coma. The patient's respiratory pattern may initially be normal, followed by sustained hyperventilation. With continued brainstem compression, an ataxic respiratory pattern develops. The patient's hemodynamic status may change, with rapid fluctuations in blood pressure and cardiac conduction. Herniation that is uncontrolled progresses rapidly to brainstem failure, cardiovascular collapse, and death.

Central Transtentorial Herniation

Less common than uncal transtentorial herniation, the central transtentorial herniation is demonstrated by rostrocaudal neurologic deterioration caused by an expanding lesion at the vertex or frontal

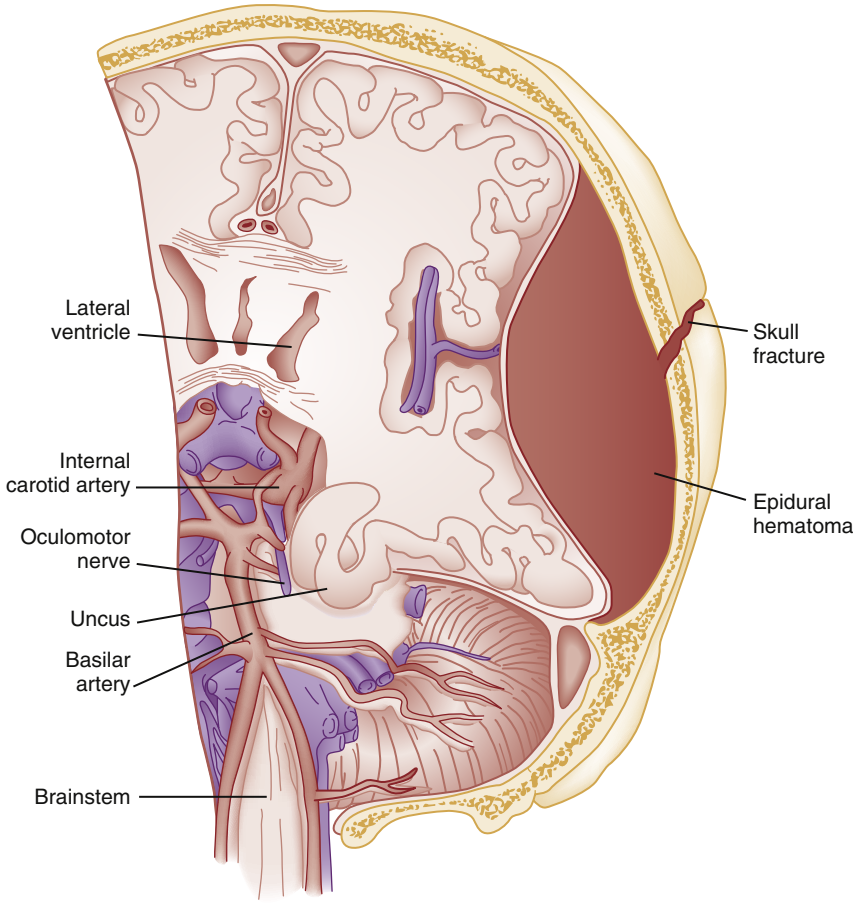

Fig. 33.3 Anterior view of transtentorial herniation caused by large epidural hematoma. A skull fracture overlies the hematoma. (From Rockswold GL. Head injury. In Tintinalli JE, et al., eds. *Emergency medicine*. New York: McGraw-Hill; 1992:915.)

or occipital pole of the brain. Clinical deterioration occurs as bilateral central pressure is exerted on the brain from above. The initial clinical manifestation may be a subtle change in mental status or decreased LOC, bilateral motor weakness, and pinpoint pupils (2 mm). Pupillary light reflexes are still present but are often difficult to detect. Muscle tone is increased bilaterally, and bilateral Babinski signs may be present. As central herniation progresses, both pupils become midpoint and lose light responsiveness. Respiratory patterns are affected, and sustained hyperventilation may occur. Decorticate posturing is elicited by noxious stimuli. This progresses to bilateral decorticate and then spontaneous decerebrate posturing. Respiratory patterns initially include yawns and sighs and progress to sustained tachypnea, followed by shallow slow and irregular breaths immediately before respiratory arrest.

Cerebellotonsillar Herniation

Cerebellotonsillar herniation occurs when the cerebellar tonsils herniate downward through the foramen magnum. This is usually the result of a cerebellar mass or large central vertex mass causing the rapid displacement of the entire brainstem. Clinically, patients demonstrate sudden respiratory and cardiovascular collapse as the medulla is compressed. Pinpoint pupils are noted. Flaccid quadriplegia is the most common motor presentation because of bilateral compression of the corticospinal tracts. Although mortality is high, timely neurointensive care and neurosurgical intervention results in recovery to a minimal or moderate level of disability in over 50% of patients.

Upward Transtentorial Herniation

Upward transtentorial herniation occasionally occurs as a result of an expanding posterior fossa lesion. The LOC declines rapidly. These patients may have pinpoint pupils from compression of the pons. Downward conjugate gaze is accompanied by the absence of vertical eye movements.

MODERATE AND SEVERE TRAUMATIC BRAIN INJURY

Clinical Features

Although the history may be delayed by the need for emergent resuscitation and stabilization, details regarding the mechanism of injury, circumstances surrounding the injury, and any concomitant drug or alcohol use should be solicited. The patient, prehospital providers, or any witnesses should be queried as to loss of consciousness or seizure activity. The patient should be asked about recall of the incident and the time periods and symptoms before including severe headache, nausea, vomiting, or amnesia. The patient's past medical history should be obtained, with particular attention to coagulopathies such as hemophilia. In addition, the patient's medications, particularly anticoagulant or antiplatelet agents, should be noted. If there has been a change in the patient's GCS score, this should also be noted.

The patient's current LOC, as well as that immediately before and after the injury and at the arrival of first responders, should be

noted. Worsening mental status or deteriorating GCS scores since the injury indicate the presence of moderate to severe injury. Witnessed seizures or apnea should be reported. If the patient is now awake but was unconscious at some point, the duration of loss of consciousness should be established, as well as if the patient has returned to baseline mental status.

Physical Examination

In the setting of head trauma and suspected brain injury, management should be guided by the principles of trauma resuscitation. A primary survey focusing on airway, breathing, and hemorrhage control should be performed expeditiously. After immediate life threats are adequately addressed, a secondary survey should evaluate for underlying head injury, brain injury, and neurologic compromise.

The head and neck should be carefully examined for external signs of trauma that may have also produced an underlying TBI. The signs and symptoms of a depressed skull fracture depend on the depth of depression of the free bone piece and the clinical exam may be misleading. A scalp laceration, contusion, abrasion, or avulsion may overlie a depressed skull fracture. The mobility of the scalp can result in nonalignment of the fracture with an overlying scalp laceration. As a result, the skull underlying the laceration may be normal, with the depressed area several centimeters away. Scalp swelling may interfere with physical examination findings and hide otherwise palpable bone defects. In the case of an impalement injury, the penetrating object should be left in place and removed during surgery.

Basilar skull fractures are often diagnosed by the clinical examination (Box 33.2), which should evaluate for hemotympanum, periauricular or periorbital ecchymoses, and clear otorrhea or rhinorrhea. Patients with basilar fractures are at risk for extra-axial hematomas because of the proximity of the fracture to the middle cerebral artery. Basilar fractures can compress and entrap the CNs that pass through the basal foramina, dislocate the bones of the auricular chain, and disrupt the otic canal or cavernous sinuses with subsequent injury to CNs III, IV, and V. Careful evaluation of the facial nerve is important. Fractures of the sphenoid bone can disrupt the intracavernous internal carotid artery, creating the potential for the formation of pseudoaneurysms or carotid venous fistulae.

The percentage of concurrent cervical spine injury in patients with severe head trauma ranges up to nearly 20%.[38] Often, other spinal regions are also injured. The neck should be evaluated for evidence of a cervical spine fracture. Carotid artery dissections caused by a hyperflexion-extension neck injury can occasionally be detected by auscultation of a carotid bruit. In these patients, a careful neurologic examination should assess for subtle asymmetry between the carotid arteries. Finally, all patients should undergo a thorough secondary evaluation after initial stabilization, evaluating for additional injuries, including an evaluation for spinal cord pathology.

Acute Neurologic Examination

General. The goals of the acute neurologic assessment of head trauma patients include detection of life-threatening injuries and identification of neurologic changes in the immediate post-trauma period. An accurate neurologic assessment in this period serves as a basis for comparison in subsequent examinations. An efficient neurologic examination in the emergency setting includes evaluation of mental status, GCS score, pupillary size and responsiveness, and motor strength and symmetry. If a formal GCS measure is not possible or is difficult because of comorbid confounders, the patient's mental status should be described in as much detail as possible. Declining mental status after head trauma suggests increasing ICP from an expanding mass lesion or worsening cerebral edema, which may rapidly become life-threatening. The strongest predictors of outcome following moderate and severe TBI are advanced age, pupillary reactivity, and GCS motor score. Additional predictors include the presence of extracranial injuries, CT characteristics including midline shift and subarachnoid bleeding, hypotension, hypoxia, and specific laboratory parameters (including glucose, hemoglobin, and coagulation profiles).[39,40]

Glasgow Coma Scale. The GCS is a 15-point scale used to quantify the patient's LOC and as an objective method of following the patient's neurologic status (Table 33.2). It was originally developed during a time when CT scanning was not available to communicate changes in neurologic status in comatose patients with TBI (Fig. 33.4). The score

BOX 33.2 Clinical Characteristics of Basilar Skull Fractures

Blood in ear canal
Hemotympanum
Rhinorrhea
Otorrhea
Battle's sign (retroauricular hematoma)
Raccoon sign (periorbital ecchymosis)
Cranial nerve deficits
Facial paralysis
Decreased auditory acuity
Dizziness
Tinnitus
Nystagmus

TABLE 33.2 Glasgow Coma Scale

Response	Score	Significance
Eye Opening		
Spontaneously	4	Reticular activating system intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
No eye opening	1	Does not open eyes to any stimuli
Verbal Stimuli		
Oriented, converses	5	Relatively intact CNS, aware of self and environment
Disoriented, converses	4	Well-articulated, organized, but disoriented
Inappropriate words	3	Random exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No verbal response	1	No response or intubated
Motor Response		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No motor response	1	Hypotonia, flaccid—suggests loss of medullary function or concomitant spinal cord injury

CNS, Central nervous system.

assigns points based on the patient's best eye opening (spontaneous opening = 4 to no response = 1), motor response (obeys commands = 6 to no response = 1), and verbal response (oriented = 5 to no response = 1). Recent literature has supported the integration of a pupillary component to the GCS score.[41] Due to its ease of use, it has been adopted in the routine assessment of all trauma patients, including those with MTBI who are not comatose. However, the GCS score can reflect impairment from conditions other than brain injury, such as distracting injuries, intoxication from drugs and alcohol, hypoxemia, and sedative medications. Furthermore, patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be a mild brain injury. Although TBI is often categorized into mild, moderate, and severe based on the GCS score, it actually represents a spectrum of injury and the trend in GCS score is more indicative of outcome than any one score in isolation.

Pupillary examination. An evaluation of the patient's pupil size and responsiveness is performed early in the initial assessment of the head-injured patient. Pupillary asymmetry, the loss of the light reflex, or a dilated pupil suggests herniation syndrome as increasing pressure on the CN III resulting in compromise of the parasympathetic fibers and pupillary dilation on the affected side. Of note, use of the pupillary examination for localization of an intracranial lesion is neither sensitive nor specific. Further, traumatic mydriasis, resulting from direct injury to the eye and periorbital structures, may confuse the assessment of the pupillary responsiveness. A pupillometer, though not commonly available, may be of some use in objectively determining pupillary reactivity.[42] As with the GCS score, a change in pupillary response is more indicative of intracranial pathology than the initial findings.

Motor examination. The patient's acute motor examination assesses for strength and symmetry. If the patient is not cooperative or is comatose, motor movement should be elicited by the application of humane external or noxious stimuli (such as a sternal rub). Any movement should be recorded, and voluntary purposeful movement must be distinguished from abnormal motor posturing. If RSI is to be performed, attempts should be made to perform the motor examination before paralytic agents are given as paralysis obscures involuntary reflexes.

Decorticate posturing implies injury above the midbrain and presents as abnormal flexion of the upper extremity and extension of the lower extremity. The arm, wrist, and elbow slowly flex, and the arm is adducted. The leg extends and rotates internally, with plantar flexion of the foot. Decerebrate posturing is the result of a more caudal injury, and therefore is associated with a worse prognosis. The arms extend abnormally and assume an adducted position. The wrist and fingers are flexed, and the entire arm is internally rotated at the shoulder. The neck undergoes abnormal extension, and the teeth may become clenched. The leg is internally rotated and extended, and the feet and toes are plantar-flexed.

Brainstem function. In the acute setting, brainstem activity is assessed by the patient's respiratory pattern, pupillary size, and eye movements. The oculocephalic response ("doll's eyes" maneuver) tests the integrity of the pontine gaze centers. The oculovestibular response (using cold water calorics) also permits assessment of the brainstem. Comatose patients no longer demonstrate nystagmus when cold water is placed in the ear canal; the only response is tonic deviation of the eyes toward the instilled cold water. This response is dampened by cerumen or blood in the patient's ear canal, and the tympanic membrane needs to be intact for this test to be performed. Neither maneuver should be attempted until cervical spine fractures have been ruled out. In patients who are awake and cooperative, a formal CN examination should be performed. In the severely head-injured patient, the CN examination is often limited to the pupillary responses (CN III), gag reflex (CNs IX and X), and corneal reflex (CNs V and VII). Facial symmetry (CN VII) can sometimes be assessed if the patient grimaces with noxious stimuli.

Common Presentations of Specific Lesions

Epidural Hematoma

The classic presentation of an EDH is head trauma producing a decreased LOC followed by a so-called *lucid interval.* Although the patient's LOC is generally normal or only slightly depressed, a completely normal mental status may not return before a second episode of decreased consciousness occurs. While nearly 50% of patients with EDHs present classically, the lucid interval is not pathognomonic for an EDH and may occur in patients with other expanding mass lesions. The development of symptoms and signs of EDH is entirely dependent on how quickly the EDH is developing within the cranial vault. Patients with an EDH often complain of a severe headache, sleepiness, dizziness, nausea, and vomiting. A small EDH may remain asymptomatic, but this is rare.

If the EDH is rapidly detected and evacuated, functional outcome is excellent. Because of their rapid formation, EDHs from arterial bleeding are usually detected within hours after injury and often earlier in children. EDHs that develop from a dural sinus tear develop more slowly, and clinical manifestations may be delayed, with resultant delays in detection.

The usual cause of a posterior fossa EDH is direct occipital trauma resulting in a skull fracture that disrupts a venous sinus, and most patients have external evidence of occipital injury. Most patients become symptomatic within 24 hours after injury, with complaints of headache, nausea, vomiting, and nuchal rigidity. Most patients eventually have a decreased LOC.

Subdural Hematoma

The patient's clinical presentation in SDH depends on the amount of brain injury sustained at the time of trauma and the rate of SDH expansion. If the patient with a SDH was rendered unconscious at the time of trauma, the prognosis is poor; these patients often have concurrent TAI. The signs and symptoms after injury that produce a SDH are initially related to the other intracranial injuries that may have been sustained and then to the slow expansion of the SDH. SDHs are classified by the time to clinical presentation. Acute SDHs are symptomatic within 24 hours after trauma. Patients with acute SDHs often have a decreased LOC and most patients with an acute SDH have a GCS score less than 8. Approximately 12% to 36% of patients will have a lucid period at some point in their presentation. The overall mortality of patients who have an SDH and require surgical intervention is 40% to 60%.

A chronic SDH becomes symptomatic 2 weeks or more after trauma. The signs and symptoms may be very subtle or nonspecific, but many patients demonstrate unilateral weakness or hemiparesis. Most report an altered LOC, but some patients are unable to recall the trauma or describe only a minor injury. A chronic SDH may have initially been a small asymptomatic SDH that eventually expanded owing to a combination of recurrent hemorrhage and escape of plasma into the hematoma. At some point, a critical mass is reached, and the chronic SDH becomes symptomatic.

Clinical manifestations of posterior SDH vary but usually include nausea, vomiting, headache, and decreased LOC. Occasionally, CN palsies may be found, as well as nuchal rigidity, cerebellar signs and symptoms, and papilledema.

Traumatic Subarachnoid Hemorrhage

An increased incidence of skull fractures and contusions is found in patients with a traumatic SAH (tSAH) compared with patients without tSAH. Patients may complain of headache and photophobia. The

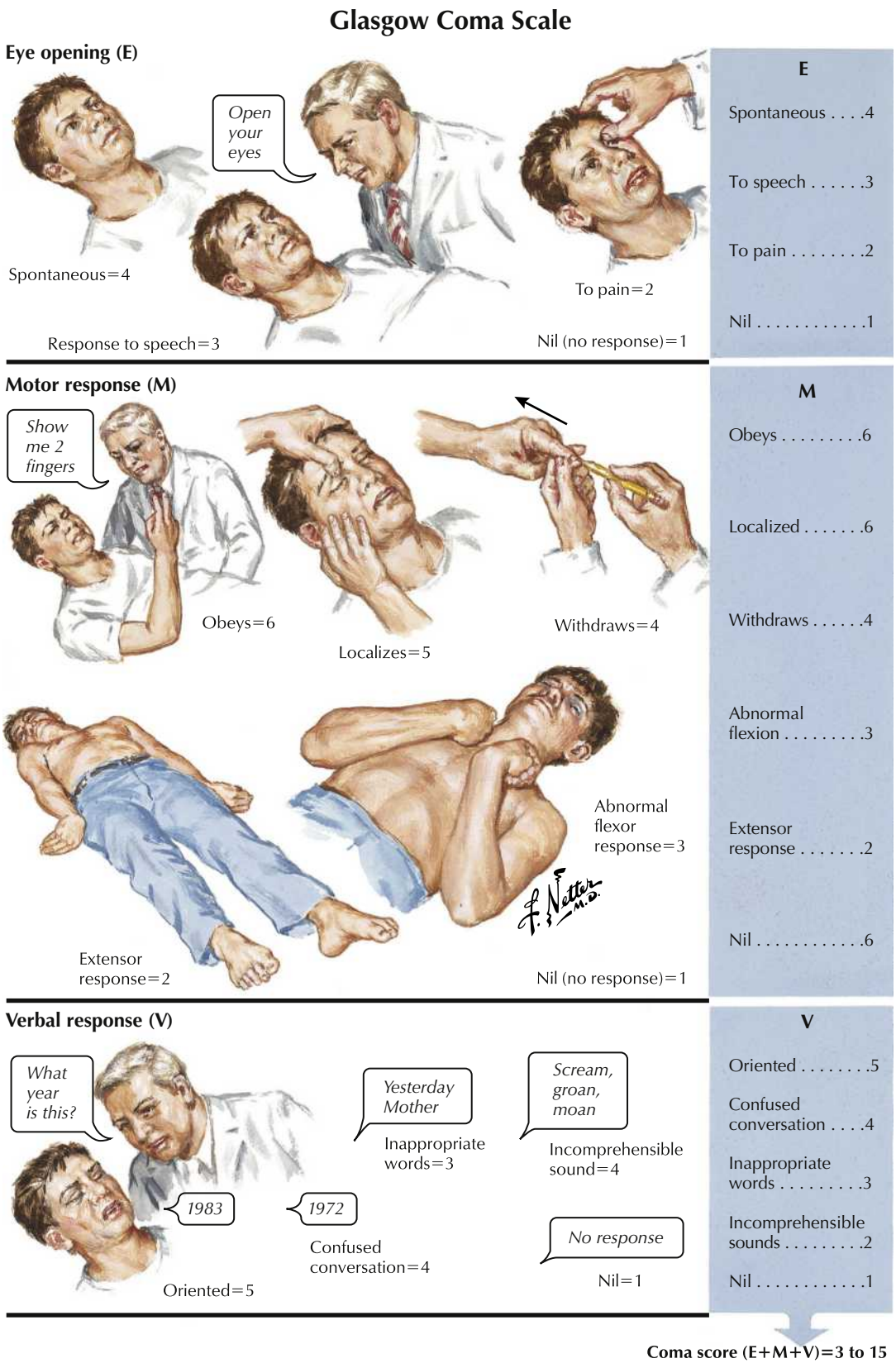

Fig. 33.4 How to calculate a Glasgow Coma Scale (GCS) score. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

amount of blood within the tSAH correlates directly with the outcome and inversely with the presenting GCS score.

Subdural Hygroma

Clinically, a SDHG cannot be distinguished from other mass lesions. Often, patients have a decreased LOC or focal motor deficits. They may complain of headaches, nausea, and vomiting. The ICP can increase because of the mass effect, and signs of increased ICP may be present.

Traumatic Axonal Injury

The duration of loss of consciousness or coma following injury is directly related to the extent of axonal pathology in the brainstem. Even with extensive axonal pathology in the white matter, there may be little or no loss of consciousness if the brainstem is relatively spared. Therefore, it appears that the distribution, rather than the overall extent, of axonal pathology is important in determining consciousness immediately following TBI.

Cerebral Contusion

The clinical presentation of patients with contusions is frequently delayed. They may have sustained only a brief loss of consciousness, but the duration of posttraumatic confusion and obtundation may be prolonged. If contusions occur near the sensorimotor cortex, focal neurologic deficits may be present. Many patients with significant contusions make uneventful recoveries, but contusions may cause significant neurologic problems, including increased ICP, PTSs, and focal neurologic deficits depending on the location of the contusion.

Intracerebral Hematoma

The clinical effects of ICHs depend on size and location and whether the bleeding is continuing. ICHs have been reported with all degrees of severity of head trauma. More than 50% of patients with ICH sustain loss of consciousness at the time of impact. The patient's subsequent LOC depends on the severity of the impact and coexisting lesions. Combined with contusions, other concurrent lesions, and subsequent perilesion edema, an ICH can produce substantial mass effects and precipitate a herniation syndrome (Fig. 33.5).

Traumatic Intracerebellar Hematoma

The clinical presentation of an isolated traumatic cerebellar hematoma is similar to that of other posterior lesions. When other traumatic lesions are present, the diagnosis may be difficult to make clinically.

Differential Diagnoses

In the context of trauma, conditions presenting with an altered LOC include seizures and associated postictal state, intoxication with alcohol or drugs, and systemic trauma resulting in hypoxemia or hypoperfusion. A patient's mental status may also be impaired by sedatives or motor function may be altered by neuromuscular blocking agents administered prior to ED arrival. Head trauma may result in confounding injuries to other parts of the head or neck, including skull or facial bone fractures, cervical spine or spinal cord injuries, eye injuries, otolaryngeal injuries, and damage to blood vessels within the neck. Although a GCS score of 15 does not exclude the possibility of brain injury, a decreasing GCS score suggests an expanding intracranial lesion. Signs of intracranial injury include worsening headache, focal neurologic signs, confusion, and lethargy, which may progress to coma. Presentation of a subdural hemorrhage may be acute, subacute, or chronic. Epidural or intracerebral hemorrhages have an acute presentation, which may be delayed by minutes to hours from the initial injury. Patients with an epidural hemorrhage may have a lucid interval following a brief loss of consciousness or period of confusion. A skull fracture may be accompanied by underlying traumatic pathology, including brain contusions, dural tears, and vascular trauma. Given the proximity of the middle meningeal artery to the temporal bones, consider extra-axial hematomas (especially EDH) if there are signs of a basilar skull fracture. Decorticate posturing implies injury above the midbrain, whereas decerebrate posturing is suggestive of a midbrain lesion. Pupil inequality and unilateral motor deficits may help localize a lesion. In vulnerable populations, consider nonaccidental trauma in all patients with brain injury. Furthermore, consider TBI in all patients with head trauma and advanced age or those on anticoagulant or antiplatelet agents, regardless of symptoms. With age, the brain atrophies and creates more space within the cranial vault for blood to accumulate, so older adults can have significant hemorrhage and not show signs of deterioration.

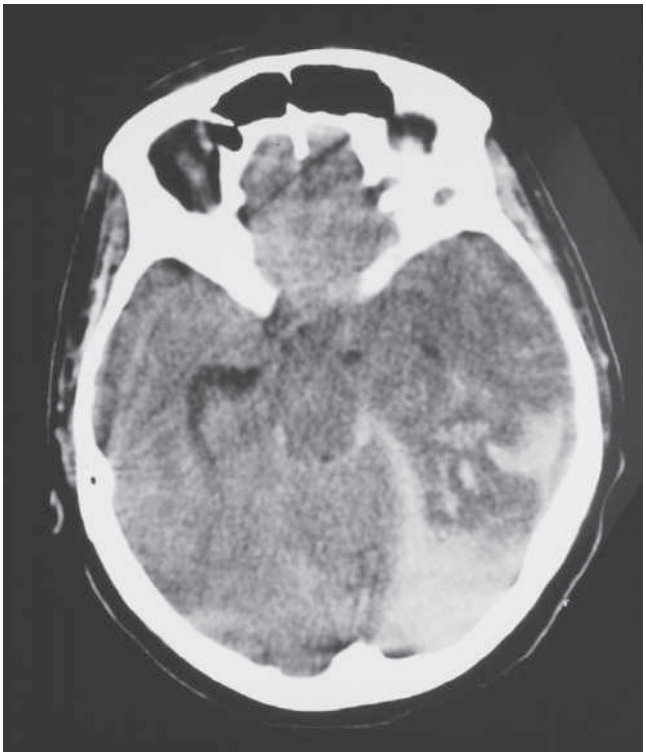

Fig. 33.5 Non–contrast-enhanced computed tomography (CT) scan of intracerebral hematoma and contusion in the left occipital region. The scan also shows layering of a tentorial subdural hematoma. Mass effect and early uncal herniation are visible as well.

Diagnostic Testing

Laboratory Tests

Routine laboratory tests are generally not needed for patients with isolated mild TBI in the acute setting, except for a bedside glucose test in patients with altered mental status and determination of the blood alcohol level in patients suspected of alcohol intoxication and head trauma. Suspicion of systemic pathology as the cause of the head trauma, such as when a diabetic patient sustains an MVC after losing consciousness from hypoglycemia, warrants directed testing for culprit conditions. Coagulation studies are indicated in patients with coagulopathies (e.g., hemophilia, Von Willebrand disease), suspected liver disease, and those on anticoagulants. Ancillary laboratory tests that may provide useful information in the subsequent management of the patient include a complete blood count and electrolyte levels. Routine laboratory testing has limited prognostic value.[43]

Neuroimaging

Skull radiography. Skull radiography after head trauma has long been replaced by cranial CT, which is the cornerstone of imaging for acute head trauma. The bone windows of a CT scan can better define skull pathology, including depressed and basilar fractures, than plain radiographs. Further, patients with clinical signs of skull fracture have a substantially increased incidence of intracranial lesions. When the clinical examination shows evidence of skull fractures, CT should be performed. Although plain skull radiographs were used in the past to localize missile fragments or ascertain penetration of the skull, CT is also the radiologic test of choice for penetrating head trauma. CT defines the precise location of the missile, its intracranial path, the presence of bone or missile fragments, extra-axial or intracerebral blood collections or other traumatic lesions, and pneumocephalus. Skull radiographs for adults with either mild or severe TBI are not recommended.

Computed tomography. Noncontrast CT of the head is the diagnostic standard for identifying intracranial injury in the ED. This scan delineates acute intra-axial and extra-axial bleeding, cerebral swelling, ischemic infarction caused by hypoxia after trauma, evidence of increased ICP, and pneumocephalus. It is sensitive for demonstrating mass effect, ventricular size and configuration, bone injuries, and acute hemorrhage, regardless of location (i.e., parenchymal, subarachnoid, subdural, or epidural spaces). The Rotterdam score was developed to determine the risk for mortality in TBI. It is based on initial noncontrast CT scan findings of basal cistern compression, midline shift, presence of an EDH, and the presence of intraventricular blood or traumatic SAH (Box 33.3). While initial CT scan is sensitive early in the patient's course, any clinical deterioration should prompt repeat scanning.

Pneumocephalus. This is often associated with missile wounds that penetrate the sinuses but can be caused by free air sucked into the penetration cavity behind the projectile. All tangential GSWs should be evaluated with a head CT scan secondary to the high incidence of associated intracranial injury.[25] Angiography may be indicated to better discern location referable to key vascular structures. Pneumocephalus in the setting of TBI should be considered an open fracture.

Epidural hematoma. On CT scan, an EDH appears hyperdense, biconvex, ovoid, and lenticular. The EDH does not usually extend beyond the dural attachments at the suture lines. The margins are sharply defined, and the hematoma usually bulges inward toward the brain (Fig. 33.6). EDHs of mixed density on CT may be actively bleeding. The temporoparietal region is the most likely site for an EDH. An EDH is usually unilateral, and 20% of patients have other intracranial lesions, usually SDHs or contusions. The deterioration of a patient who has an EDH from arterial bleeding can be rapid and dramatic.

A posterior fossa EDH is the most common traumatic mass lesion of the posterior fossa and accounts for 5% of EDHs. On CT scan, a posterior fossa EDH looks similar to other EDHs, but may cross the midline and extend above the tentorium to the supratentorial compartment (Fig. 33.7).

Subdural hematoma. Unlike EDHs, SDHs often extend beyond the suture lines (Fig. 33.8). An SDH may follow the contour of the tentorium and be detected within the interhemispheric fissure (Fig. 33.9). Many patients with an acute SDH also show CT evidence of intracerebral lesions contralateral to the SDH. A subacute SDH is symptomatic between 24 hours and 2 weeks after injury. It may appear hypodense or isodense on CT scans. Contrast increases the detection of isodense lesions. Patients complain of a headache, altered mental status, or focal deficits.

On a CT scan, a chronic SDH may appear isodense or hypodense to brain parenchyma. Indirect evidence of the lesion includes a midline shift, effacement of the ipsilateral cortical sulci, and ventricular compression. Contrast may increase the likelihood of identifying a chronic SDH that has become isodense. On a CT scan, blood of various ages is seen as a mixed-density lesion. On a magnetic resonance imaging (MRI) scan, a chronic SDH appears hyperdense.

Posterior fossa SDHs are caused by occipital trauma and, on a CT scan, they do not cross the midline or extend above the tentorium. The outcome of a posterior SDH is very poor.

BOX 33.3 Rotterdam Score of Initial Noncontrast Computed Tomography for Predicting 6-Month Mortality Following Traumatic Brain Injury[a]

1. Basal cistern effacement
0 = none
1 = partially effaced (compressed)
2 = completely effaced (compressed)
2. Midline shift
0 = no shift or ≥5 mm
1 = >5 mm
3. EDH (epidural hematoma)
0 = EDH present
1 = no EDH
4. IVH (intraventricular hemorrhage) or SAH (subarachnoid hemorrhage)
0 = neither present
1 = either present
2. Add 1 to score
Total score = 1–6 points

[a] Probability of mortality at 6 months postinjury based on score:
1 ≤ 0%
2 ≤ 7%
3 ≤ 16%
4 ≤ 26%
5 ≤ 53%
6 ≤ 61%

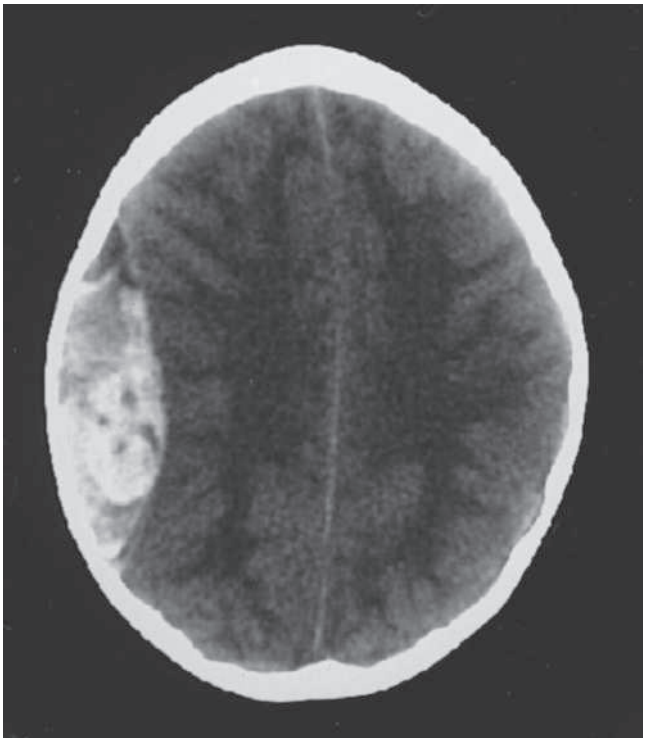

Fig. 33.6 Non–contrast-enhanced CT scan of acute epidural hematoma at the level of right midconvexity. There is an associated mass effect and moderate midline shift.

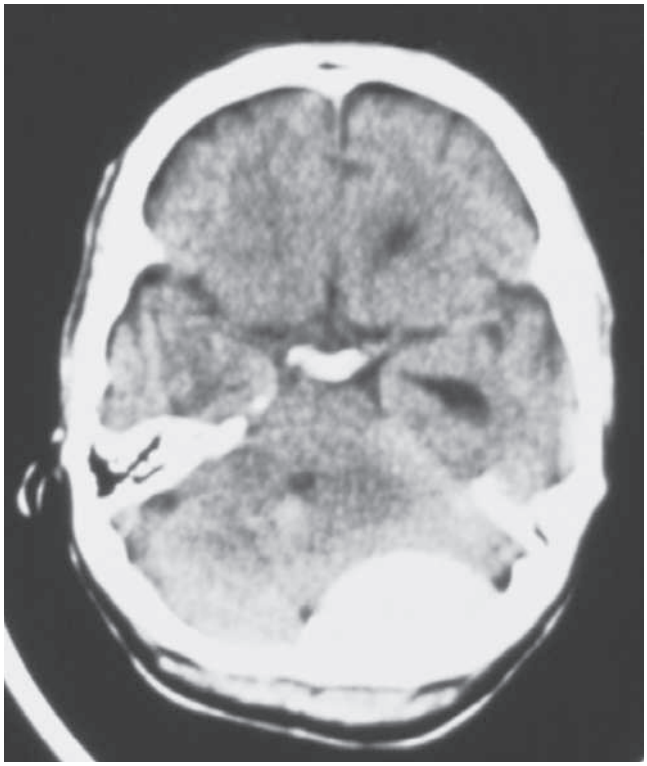

Fig. 33.7 Non–contrast-enhanced CT scan of large left posterior fossa, epidural hematoma. The size of the lesion at this high level suggests that it crosses into the supratentorial compartment. This lesion is often associated with occipital bone fracture that disrupts transverse sinus.

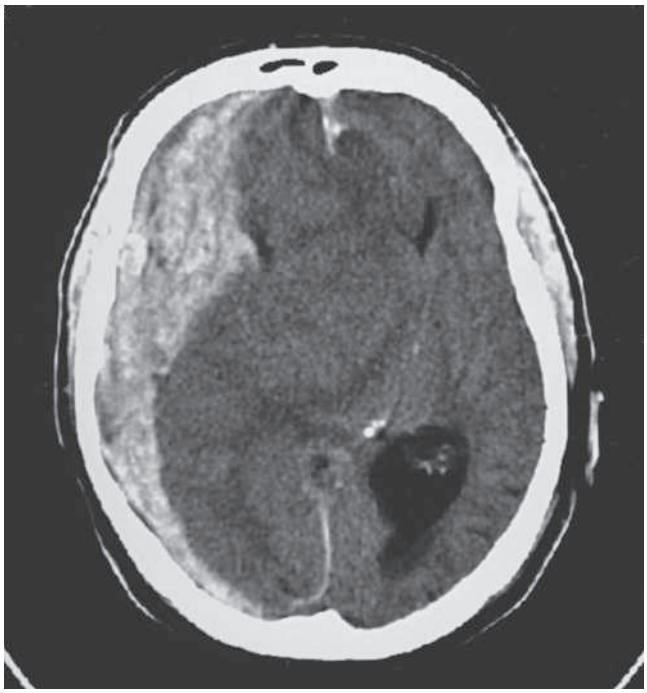

Fig. 33.8 Non–contrast-enhanced CT scan of acute right temporal subdural hematoma. There is acute bleeding and delayed bleeding, which explains the mixed density. Mass effect is large, with a midline shift measuring approximately 2.7 cm right to left. The right lateral ventricle has been obliterated.

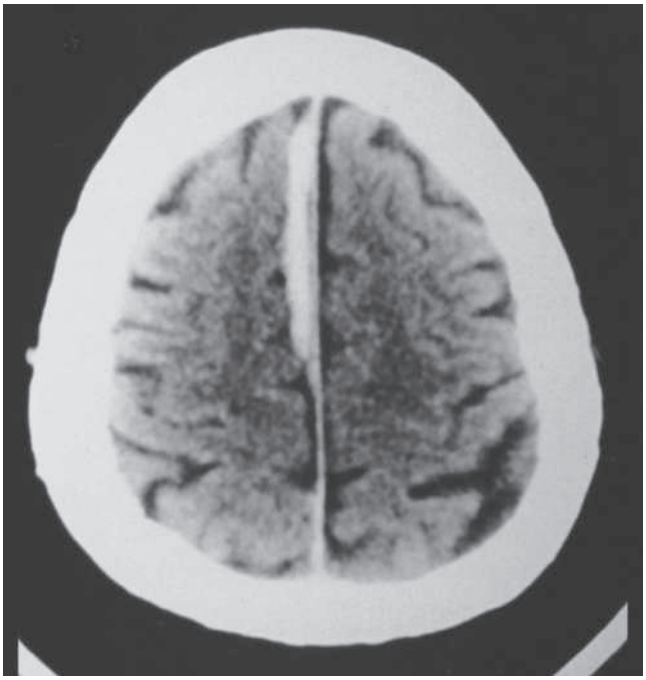

Fig. 33.9 Non–contrast-enhanced CT scan of interhemispheric acute subdural hematoma.

Traumatic subarachnoid hemorrhage. A noncontrast CT scan allows the diagnosis to be made, with increased density noted within the basilar cisterns. Blood can also be seen within the interhemispheric fissures and sulci. The amount of blood within the tSAH correlates directly with the outcome and inversely with the presenting GCS score.

Subdural hygroma. On CT, SDHGs appear crescent shaped in the extra-axial space; the density is the same as that of CSF. Bilateral SDHGs are common.

Traumatic axonal injury. Diffuse TAI is the most common CT finding after severe head trauma, estimated to occur in over 50% of all comatose head injured patients. However, in milder cases, there is no specific acute focal traumatic lesion noted on a head CT scan or on structural MRI scan. Occasionally, small petechial hemorrhages in proximity to the third ventricle and within the white matter of the corpus callosum or internal capsule of the brainstem are detected. Intraventricular hemorrhage and midline SAH have been reported to be an early predictor of TIA.[44,45] Although histopathologic examination of postmortem brain tissue is the gold standard for diagnosing TAI, advanced MRI neuroimaging techniques, such as diffusion tensor imaging (DTI), may help assess white matter integrity (Fig. 33.10).

Cerebral contusions. Non–contrast-enhanced CT is the best diagnostic test to discover contusions in the early posttraumatic period. These appear heterogeneous and irregular because of mixed regions of hemorrhage, necrosis, and infarction. Often, the surrounding edematous tissue appears hypodense. By post-trauma days 3 and 4, the blood located within the contusions has begun to degrade, and structural MRI becomes more diagnostic.

Intracerebral hematoma. An ICH may be detected on the first CT scan immediately after injury but often is not seen for several hours or days. Unlike contusions, ICHs are usually deep in the brain tissue and often become well demarcated over time. On CT scan, an ICH appears as a well-defined hyperdense homogeneous area of hemorrhage (Fig. 33.11).

Traumatic intracerebellar hematoma. Often, these patients have an associated skull fracture, posterior fossa EDH or SDH, or supratentorial contrecoup hematomas and contusions.

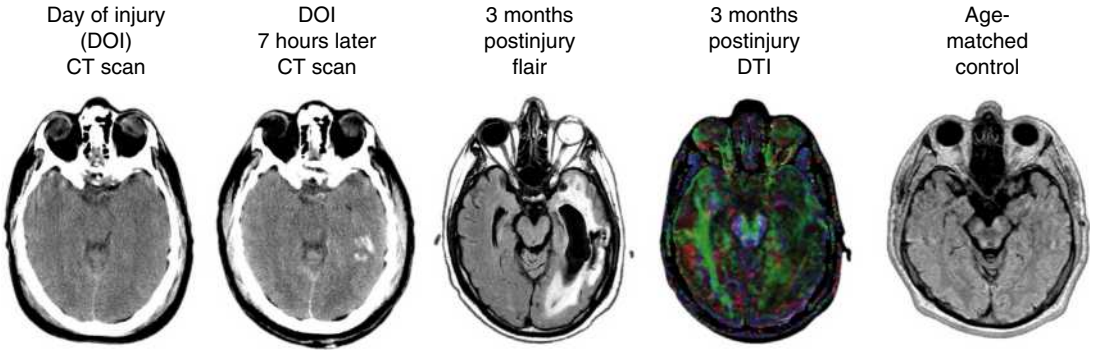

Fig. 33.10 Sequential scan findings in severe traumatic brain injury (TBI) with traumatic axonal injury (TAI). In the emergency department (ED), on initial day of injury (DOI) CT imaging, the scan on the *far left* shows primarily generalized edema but, by 7 hours, distinct intraparenchymal hemorrhages appear, particularly within the left temporal lobe. By 3 months postinjury, TAI and intraparenchymal hemorrhages result in massive degenerative effects, reflected in temporal horn dilation and markedly abnormal white matter signal differences throughout the temporal and occipital lobes on the fluid-attenuated inversion recovery (FLAIR) sequence. Temporal horn dilation is also evident in the right temporal lobe as well, reflective of the generalized atrophy. The loss of white matter integrity is more distinctly observed using diffusion tensor imaging (DTI), where there is no coherent direction noted in the left temporal region; even though the right temporal lobe exhibits atrophic changes, the inferior occipitotemporal fasciculus *(arrow)* is distinctly visible. The control MRI scan is a T1 image showing symmetric temporal lobe morphology with the normal slit-like appearance of the temporal horns. (Adapted from Bigler ED, Maxwell WL. Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. *Brain Imaging Behav.* 2012;6:108–136.)

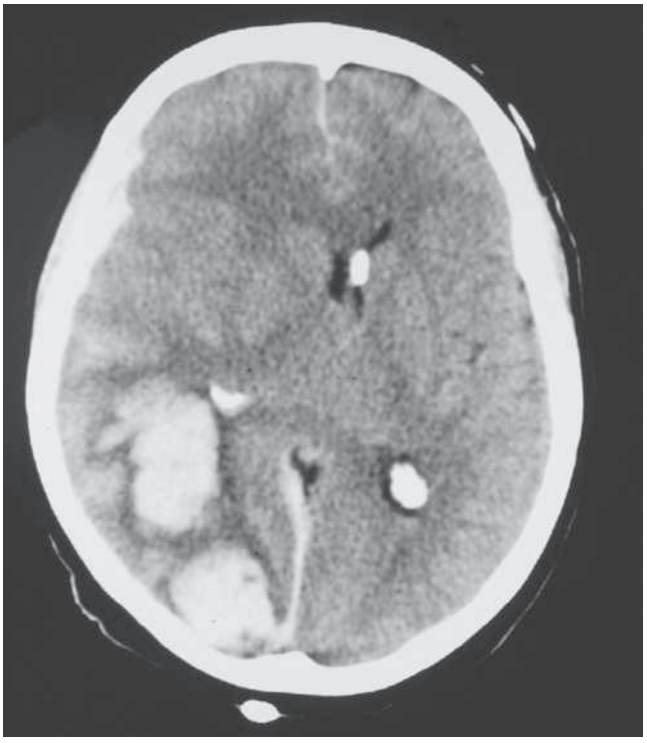

Fig. 33.11 Non–contrast-enhanced CT scan of right occipital and temporal intracerebral hematomas, surrounded by mild edema and hemorrhagic contusion. A small, interhemispheric, subdural hematoma is visible in the posterior interhemispheric fissure. Midline shift is obvious. A ventriculostomy has been placed and is visible as high-density image within the ventricles.

Cerebral edema. On CT scans, diffuse edema manifests as bilateral compression of the ventricles, loss of definition of the cortical sulci, or effacement of the basal cisterns (Fig. 33.12). Focal edema adjacent to traumatic mass lesions demonstrates decreased density on CT scans compared with normal tissue.

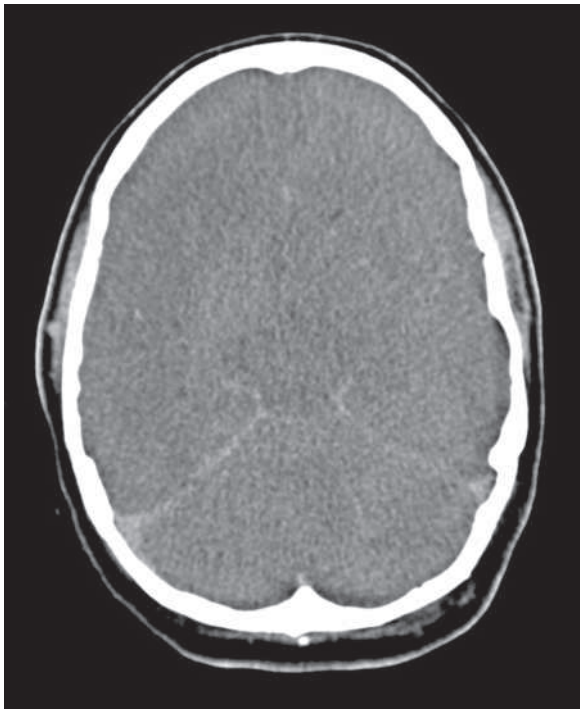

Fig. 33.12 Non–contrast-enhanced CT scan showing diffuse cerebral edema. Loss of gray-white differentiation in the brain parenchyma is present. Bilateral compression of the ventricles has occurred, with loss of cortical sulci.

Management

Out-of-Hospital Care

The out-of-hospital management of the head-injured patient should focus on preventing or minimizing secondary brain injury specifically on the major systemic insults of hypotension, hypoxia and hypocarbia. Interventions should be aimed at maintenance of oxygenation and

prevention of hypocarbia through appropriate airway management, supplemental oxygen as needed, and controlled ventilation. Hypotension should be avoided through directed fluid resuscitation and control of hemorrhage.

Airway. The ultimate goal in the field is to prevent or minimize hypoxia. Out-of-hospital airway protocols balance the risks of emergency intubation in an uncontrolled setting with the need to secure an at-risk airway and prevent hypoxia. Controversy exists regarding the benefits of out-of-hospital intubation in patients with brain injuries.[46] In systems with short transport times, and in patients in whom an oxygen saturation more than 90% can be maintained with supplemental oxygen, field intubation is of questionable benefit and may potentially lead to worse outcomes.[47] If oxygenation can be maintained and transport time is short, definitive airway management should be delayed until arrival in the ED.

If endotracheal intubation is undertaken in the field, it should be performed by skilled practitioners with a rigorous quality assurance program and continuous provider training.[48] All advanced airway placement should be confirmed with quantitative end-tidal capnography ($ETCO_2$), which dramatically improves the detection of improperly placed airway devices and inadvertent hyperventilation by field providers.[49] Prehospital endotracheal intubation is associated with poorer prognosis in children and if at all possible, should be avoided in this population (see Chapter 165).

Hypotension. Avoiding and managing hypotension are critical elements of the prehospital treatment of the head-injured patient.[50] The evaluation of the head-injured patient should include a search for external signs of head trauma. Scalp lacerations may bleed a large volume into a bulky dressing, and a less bulky dressing should be used with firm constant manual pressure applied to avoid excessive blood loss. Any other ongoing external hemorrhage should be expeditiously addressed and controlled. Although permissive hypotension may be beneficial in some trauma patients, it is detrimental in the setting of brain injury.[50,51]

Agitation. Many severely head-injured patients are initially combative or agitated. Transporting an agitated patient who is fighting against physical restraints may exacerbate physical injury, cause an increase in ICP, and interfere with appropriate stabilization and management. Management of agitation in the out-of-hospital setting mirrors that used in the ED, as described in the following.

Emergency Department Management

General. In the ED, management of patients with severe head trauma is in accordance with ATLS (Advanced Trauma Life Support) protocols. Monitoring of vital signs should be continuous including oxygenation (pulse oximetry) ventilation (capnography), heart rate, blood pressure, and temperature. Tetanus immunization status should be determined, and prophylaxis given, as appropriate. Pregnancy status in women of childbearing age should be verified.

Airway. Primary airway compromise in the setting of head trauma may result from craniofacial or neck trauma, bleeding, or vomiting. Secondary airway compromise may also result from brain injury, as in the case of loss of brainstem reflexes, patient agitation, severe systemic hypotension, or alterations in mental status. In such cases, the airway should be secured early to protect against aspiration and prevent secondary brain injury as a result of hypoxia or hypercarbia.

If possible, a rapid but detailed neurologic examination should be performed before the patient is given any sedative or neuromuscular blocking agent. This focused examination includes careful recording of the elements of the GCS, characterization of movement of all four extremities (to command, localization or withdrawal to pressure, posturing), tone, and pupillary reflexes. These elements are essential in correlating CT findings with clinical injury and are also useful in following the patient's clinical progression. The rapid sequence intubation (RSI) drug selection and technique of intubation for the head-injured patient is discussed in Chapter 1.

Hypotension. While hypotension can occasionally be attributed to isolated head injury, it is almost always secondary to another systemic insult such as hemorrhage or spinal cord injury. If hypotension is detected at any time in the emergent management of a potentially brain-injured patient, a cause other than the brain injury should be sought (see Chapter 33).

Systemic hypotension has profound implications for neurologic outcomes. As such, fluids or blood transfusion should be delivered to maintain a blood pressure as close to normal as possible, with a SBP of at least 110 mm Hg for those 15 to 49 and over 70 years of age, and at least 100 mm Hg for those 50 to 69 years old.[10] Blood pressure should be corrected early in the patient's course, as not only depth of hypotension but duration as well have an important effect on mortality.[29,50,52]

Brain-directed hyperosmolar therapy. Osmotic therapy should be guided by findings on ICP monitoring. Prior to initiation of such monitoring, brain-directed osmotic therapies should be reserved for patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.[10] If there are signs of impending herniation syndrome, such as deepening coma, a newly asymmetric pupil, or other substantially diminishing neurologic parameters, we recommend the use of osmotic diuretics, such as mannitol or HTS.

Osmolar therapy can draw water across an intact BBB and thereby lower ICP. Mannitol, 0.25 to 1 g/kg, is given every 6 hours up to a serum osmolality of 320 mOsm/kg. HTS (23.4%), 30 to 60 mL, can be given every 6 hours, up to a maximum serum sodium level of 160 mEq/L. Treatment with 30 mL of 23.4% HTS appears to be at least as effective as mannitol at lowering ICP rapidly and reversing herniation, although a central line is necessary for safe administration. Peripheral administration of 3% sodium chloride has a low complication rate and may be an acceptable alternative.[53,54] Peripheral administration of 250 mL of 3% sodium chloride (which is comparable to 23.4%) has a low complication rate and may be an acceptable alternative.

Mannitol is the time-honored mainstay for the control of elevated ICP in acute severe TBI effectively reducing cerebral edema by producing an osmotic gradient that reduces brain volume and provides increased space for an expanding hematoma or brain swelling. The osmotic effects of mannitol occur within minutes and peak approximately 60 minutes after bolus administration. The ICP-lowering effects of a single bolus may last for 6 to 8 hours. It also promotes CBF by reducing blood viscosity and microcirculatory resistance. It is an effective free radical scavenger, reducing the concentration of oxygen free radicals that may promote cell membrane lipid peroxidation. Proposed benefits of HTS include reducing secondary injury through effects on cellular modulation, decreasing cerebral edema, improving peripheral perfusion, decreasing ICP through vasoregulatory mechanisms, and upregulation of proinflammatory and prothrombotic mediators. Because it is a potent diuretic, mannitol is preferred in cases of fluid overload, whereas HTS can be used as a resuscitative fluid.

Mannitol can precipitate renal failure or hypotension if given in large doses. It may also induce a paradoxical effect of increased bleeding into a traumatic lesion by decompressing the tamponade effect of a hematoma. Potential adverse events associated with HTS include renal failure, central pontine myelinolysis, and rebound ICP elevation.

Few comparative data exist on brain-directed osmotic therapy.[55] Selection of mannitol versus HTS should be made on an institutional basis, so that providers across various specialties (e.g., emergency medicine, trauma surgery, neurosurgery, anesthesiology) provide consistent care.[10,56] Further, while guidelines highlight the utility of

hyperosmolar therapy in the care of patients with severe TBI,[10] there is limited high-quality evidence demonstrating improvements in mortality or functional outcomes.[57]

Hyperventilation. Under normal conditions, $Paco_2$ is the most powerful determinant of CBF and, between a range of 20 and 80 mm Hg, CBF is linearly responsive to $Paco_2$. Formerly, so-called therapeutic hyperventilation was recommended as a method to reduce ICP. However, this reduction in ICP is accomplished by reducing CBF, which is important in meeting the brain's metabolic demands. A low $Paco_2$, and the resulting lower CBF, may result in cerebral ischemia, whereas high $Paco_2$ levels can result in cerebral hyperemia and high ICP. Normal ventilation is currently the goal for severe TBI patients in the absence of cerebral herniation, and $Paco_2$ should be maintained in the normal range of 35 to 45 mm Hg.[10] Additional care should be taken to avoid hyperventilation during the first 24 hours after injury when CBF is often critically reduced.

In the case of life-threatening cerebral herniation or significant ICP elevation, therapeutic hyperventilation is appropriate only as a short-term intervention, bridging to more definitive therapy (such as craniectomy). If hyperventilation is to be used, jugular venous oxygen saturation (Sjo_2) or brain tissue O_2 partial pressure ($Btpo_2$) measurements are recommended to monitor oxygen delivery, although these modalities are not commonly available in the ED.[10,58] The neurologic effects of hypocapnia are illustrated in Fig. 33.13.

Cranial decompression. In patients with impending herniation who do not respond to first-line therapies, cranial decompression may temporarily reverse or arrest the herniation syndrome and emergency trephination may allow enough time for a patient to undergo a formal

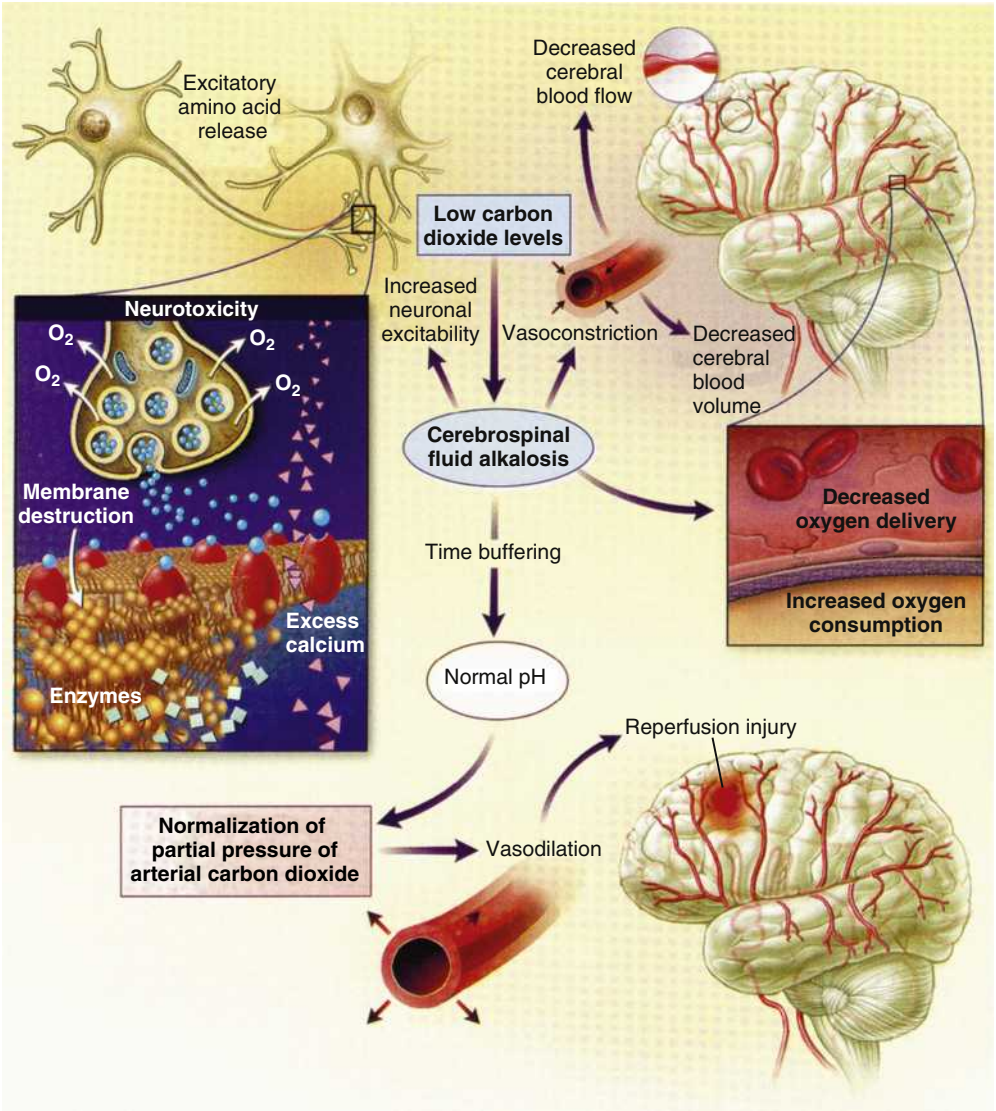

Fig. 33.13 **Neurologic Effects of Hypocapnia.** Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery and, to a lesser extent, cerebral blood volume. The reduction in intracranial pressure may be lifesaving in patients in whom the pressure is severely elevated. However, hypocapnia-induced brain ischemia may occur because of vasoconstriction (impairing cerebral perfusion), reduced oxygen release from hemoglobin, and increased neuronal excitability, with the possible release of excitotoxins, such as glutamate. Over time, cerebrospinal fluid pH and hence cerebral blood flow gradually return to normal. Subsequent normalization of the partial pressure of arterial carbon dioxide can then result in cerebral hyperemia, causing reperfusion injury to previously ischemic brain regions. (From Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med.* 2002;347:43–53.)

craniotomy in the operating room. However, most patients presenting unconscious have sustained diffuse massive brain injury, without focal lesion amenable to emergency decompression. Patients with erratic or absent respiratory effort, bilateral fixed and dilated pupils, no spontaneous eye movements, and decerebrate posturing do not benefit from emergent "burr holes." Outcomes in other patient populations are of questionable benefit.[59] Trephination should be undertaken only after confirmation of an extradural collection by neuroimaging and only by, or under the guidance of, an emergency clinician with specific training.

Decompressive craniectomy (DC) is the surgical removal of a portion of the skull bone and has been performed for the purpose of relieving elevated ICP. Bifrontal DC for severe TBI patients with diffuse injury (without mass lesions) who have ICP elevation refractory to first-tier therapies does not result in improved outcome, as measured by the Glasgow Outcome Scale-Extended (GOS-E) score, at 6 months postinjury.[10] DC for severe and refractory intracranial hypertension following brain injury results in improved mortality at the cost of worse neurologic outcomes at 6 months post injury.[60] As such, there is still ongoing debate as to the optimal timing, technique, and population for DC following TBI.[61,62]

Reversal of anticoagulation. Patients taking warfarin anticoagulants should have these medications reversed in the case of ongoing intracranial bleeding. Vitamin K antagonists may be managed with intravenous (IV) vitamin K, fresh frozen plasma, or 3-factor or 4-factor prothrombin complex concentrate (PCC). While specific international normalized ratio (INR) thresholds will vary depending on injury type and patient factors, a target of an INR less than 1.5 is recommended.[63] Vitamin K 10 mg IV administered slowly and 3-factor or 4-factor PCC is preferred over fresh-frozen plasma.[64] Reversal of warfarin-associated anticoagulation is discussed in Chapter 111.

Idarucizumab is a Fab fragment of a monoclonal antibody that binds to and inactivates dabigatran and serves as an emergency reversal agent for dabigatran.[65] The recommended dose for idarucizumab is 5 g (2.5 g/vial), administered as 2.5 g IV infusion or bolus injection. Each 2.5 g vial should be administered in a dedicated line over 5 to 10 minutes with the second vial administered in succession not more than 15 minutes after the first. If idarucizumab is not available, clotting factor products such as PCCs or fresh-frozen plasma can be used.[66] Idarucizumab should not be combined with other clotting factor products. Patients requiring emergent reversal of Factor Xa inhibitors (e.g. rivaroxaban, apixaban, and edoxaban) can be treated with andexanet alfa, 4-factor PCCs, or FFP.[67] Andexanet alfa is a class-specific antidote targeted to competitively inhibit Factor Xa inhibitors.[68] The initial dose depends on the dose of the Factor Xa inhibitor and the interval since the last dose. Andexanet should not be combined with other clotting factor products.[63] Data in this population are limited, and the decision to reverse the patient's anticoagulation must take into account the specific injury pattern and the risk of reversal.

Although common in practice, there is inadequate evidence to support the routine use of platelet transfusion for intracranial hemorrhage for patients taking preinjury antiplatelet medications (e.g., aspirin, clopidogrel).[69] The transfusion of platelets in patients on antiplatelet medications does not reduce mortality.[70,71] Likewise, while desmopressin has been proposed as a means to improve platelet adhesion in patients taking antiplatelet medications, the available data is insufficient to recommend its routine use.

Hemostatic agents. Recombinant factor VIIa (rFVIIa) is a hemostatic agent that was originally developed to treat bleeding in hemophiliacs. Limited military experience led to interest in the use of rFVIIa for traumatic intracerebral hemorrhage as well. However, results of clinical trials are mixed, and there has been no convincing evidence of benefit for this agent in traumatic intracranial hemorrhage in the absence of preexisting coagulopathy. The routine use of rFVIIa for patients with traumatic intracranial hemorrhage is not currently recommended.

When given early after injury (within 3 hours), tranexamic acid (TXA) has demonstrated benefit in trauma with hemorrhage without increasing the risk of adverse events.[72] The use of TXA is discussed in Chapter 32. While further studies are needed, recent studies have shown TXA to be promising in improving outcomes for TBI patients, particularly those with a less substantial injury burden.[73]

Induced hypothermia. Hyperpyrexia has been suggested to worsen outcomes after severe TBI. Induced therapeutic hypothermia decreases ICP and has been proposed to reduce proinflammatory cytokines and stabilize the BBB. Yet while induced hypothermia remains a significant area of research for patients with severe and moderate TBI, the available scientific evidence does not support its use to decrease morbidity or mortality. While early studies did demonstrate the potential for benefit, recent randomized trials have shown that therapeutic hypothermia for severe TBI does not improve the neurologic outcomes or risk of mortality compared with strict temperature control.[74,75] The routine use of therapeutic hypothermia for the treatment of TBI is not currently recommended.

Seizure prophylaxis. Though rare, acute symptomatic seizures may occur as a result of severe TBI.[76] Such posttraumatic seizures (PTSs) are classified as early when they occur within 7 days of injury or late when they occur after 7 days following injury. Posttraumatic epilepsy (PTE) is defined as recurrent seizures more than 7 days following injury. Up to 12% of all patients who sustain blunt head trauma and 50% of those with penetrating head trauma develop early PTSs. Although the occurrence of seizures in the immediate post-trauma period is not predictive of future epilepsy, early seizures can cause hypoxia, hypercarbia, release of excitatory neurotransmitters, and increased ICP, potentially worsening secondary brain injury.

Prophylactic use of antiepileptic medications is not recommended for preventing late PTS.[77] However, while early PTS have not been associated with worse outcomes, antiepileptics are recommended to decrease the incidence of early PTS (within 7 days of injury) when the overall benefit is thought to outweigh the risk of complications associated with such treatment.[10] Levetiracetam's use for early PTS is increasing, however, the evidence insufficiently demonstrates its effect is equal to phenytoin.[10]

If the patient is actively seizing, benzodiazepines are administered as effective, rapid-acting, first-line anticonvulsants. If an IV is available, administer lorazepam (0.05–0.1 mg/kg IV up to 4 mg at a maximum rate of 2 mg/minute; may repeat at 3 to 5 minutes if seizures continue). Lorazepam is the preferred agent for aborting seizures because of its high effectiveness and prolonged duration of action. An effective alternative is IV diazepam (0.15 mg/kg IV, up to 10 mg per dose at a maximum infusion rate of 5 mg/minute; may repeat at 3 to 5 minutes if seizures continue, up to a total dose of 30 mg). If an IV is not available, IM midazolam (0.2 mg/kg up to 10 mg) can be used.[77]

Antibiotic prophylaxis. Although the practice was once widespread, there is no evidence to support the use of antibiotic prophylaxis for the prevention of meningitis or other infection in patients with blunt basilar skull fractures, with or without evidence of CSF leakage.[78] In the case of penetrating brain injury, however, contamination with skin, bone, hair, and tissue occurs and may be widespread when there is cavitation caused by the missile as it passes through the brain. While evidence is mixed, guidelines support the use of IV prophylactic, broad-spectrum antibiotics to cover for staphylococci, gram-negative bacilli, and anaerobes for penetrating craniocerebral trauma. Although there are several potential antibiotic regimens, a combination of vancomycin, 1 g q12hr, gentamycin, 80 mg q8hr, and metronidazole, 500 mg q6hr, will provide adequate coverage.[79–81]

Patients undergoing ICP monitoring are reported to have related infection rates as high as 27%.[82] For external ventricular drains (EVDs), routine catheter exchanges have been replaced by attention to proper care during insertion, CSF sampling techniques and, in some cases, prophylactic IV antibiotics. We recommend training and situational awareness of best practices for infection control, assisted by protocol checklists. Antibiotic-impregnated EVDs should be considered for minimizing infection.[10]

Other therapies

Corticosteroids. Corticosteroids have no benefit for patients with head trauma, and in fact demonstrate an increase in adverse events, including infection, gastrointestinal bleeding, and mortality. In patients with severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated.[10]

Barbiturates. Barbiturate therapy has historically been used in severely brain-injured patients to reduce cerebral metabolic demands of the injured brain tissue and reduce elevated ICP. However, barbiturates also can cause a decrease in SBP. Compared with placebo, barbiturates offer no mortality benefit; furthermore, any benefit of decrease in ICP is offset by the risk of hypotension. The only remaining value of barbiturates in TBI is the use of high-dose barbiturate therapy to control elevated ICP refractory to maximum standard medical and surgical treatment.[10] Hemodynamic stability is essential before and during barbiturate therapy. Prophylactic administration of barbiturates to induce burst suppression measured by electroencephalography is not recommended. Decreasing the rate of administration for barbiturates may decrease the risk for hypotension.

Monitoring of intracranial pressure and cerebral spinal fluid drainage. Invasive ICP monitoring has been a mainstay of management for severe TBI, although its utility has recently been called into question. Nevertheless, ICP monitoring is recommended to reduce in-hospital and 2-week postinjury mortality.[10] An EVD in a closed position allows for monitoring of ICP, whereas in an open position drainage of CSF can occur. Practice patterns regarding whether the EVD should be maintained in a closed or open position vary widely based on a number of variables, including patient age, institutional resources, and neurosurgical preferences.[10]

Continuous CSF drainage is a relatively common practice in the pediatric population. In adults, there is more variability in practice. Guidelines state that the use of CSF drainage to lower ICP in patients with an initial GCS less than 6 during the first 12 hours after injury may be considered,[10] Further, an EVD system zeroed at the midbrain with continuous drainage of CSF may be more effective than intermittent drainage in lowering ICP burden.[10]

Erythropoietin. In randomized trials of patients with moderate to severe TBI, erythropoietin did not reduce severe neurologic dysfunction or improve mortality. While there may be some utility in an undefined population,[83–85] it is not recommended for use at this time.[86]

Progesterone. Progesterone has been shown to improve neurologic outcome in early-phase trials involving patients with TBI. In a double-blind, multicenter clinical trial, progesterone was administered to TBI patients with moderate to severe TBI within 4 hours of injury. Progesterone did not improve outcomes in patients with TBI over placebo. These findings are consistent with a recent meta-analysis.[87,88] Progesterone is not recommended for treatment of TBI.

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy following severe, acute TBI provides the injured brain with an increased partial pressure of oxygen and theoretically reduces cerebral edema. Although the pooled results of several small studies have suggested some benefit,[82] the clinical significance is questionable and the use of hyperbaric oxygen therapy for the treatment of TBI cannot be recommended.[89] Clinical trials are ongoing.

Management of Specific Injuries

Scalp wounds. For briskly bleeding scalp wounds, rapid hemostasis is a priority. Initially, hemostasis may be achieved by the application of a temporary, tight pressure dressing, allowing prompt attention to other priorities. Alternatively, a skin stapler may be used to rapidly staple the scalp laceration to control bleeding. The wound later can be reopened for proper irrigation and reclosure.

While the best approach is repair with sutures or staples because the closure will assist in tamponade, other methods to achieve hemostasis include direct digital compression of the bleeding vessel against the skull, infiltration of the wound edges with lidocaine plus epinephrine, and clamping or ligation of identified bleeding vessels.

Once hemostasis is obtained, the wound should be irrigated to rinse away any debris. The emissary vessels of the subgaleal layer of the scalp drain directly into the diploe veins of the skull which in turn drain into the venous sinuses. As such, contaminated or infected scalp wounds have the potential to cause serious intracranial infections. Blood clots and other debris should be removed and the galea and underlying cranium palpated to detect any remaining debris, disruptions, or bone step-offs, understanding that shear injuries to the scalp may deposit contaminants at sites distant from the apparent injury. The complexity of stellate lacerations often interferes with thorough inspection and debridement, making them particularly susceptible to infection. Digital exploration of a scalp wound should be performed gently; if done too vigorously, comminuted or depressed bone pieces may dislodge and be depressed further.

It is easy to confuse a disruption in the galea or tear in the periosteum with a skull fracture. The base of the laceration should therefore be directly visualized if at all possible. Clipping away a small area of hair parallel to the edges of the wound may facilitate this. Alternatively, an antibiotic ointment can be applied to the hair immediately surrounding the wound and used to plaster the hair away from the injury site. If hair is accidentally embedded within the repaired laceration, it can delay healing by producing an inflammatory reaction or by serving as a nidus of infection. If the laceration begins on the forehead and extends upward beyond the hairline, surrounding hair should not be removed as removal obliterates a useful landmark for cosmetic closure and may result in malalignment of the two laceration edges.

Several studies have evaluated the use of staples versus sutures to close scalp lacerations that do not involve the galea. For adult and pediatric scalp lacerations that begin beyond the hairline, staples have been shown to be cheaper, take less time, and have the same outcome as sutures if used in the appropriate manner. However, staples cannot be used to close the galea and may not be effective alone when hemostasis is a problem. Large lacerations of the galea are closed to prevent the edges of the wound from pulling apart as the muscles within the galea contract. The skin, dermis, and galea can usually be repaired in a single layer with interrupted or vertical mattress sutures of 3-0 nylon or polypropylene. An alternative method of scalp laceration closure, the "hair apposition technique," is to twist together bundles of the patient's hair on each side of the wound and then secure these with tissue glue. This may provide another method of effective repair and prevent the need to remove the closure material after the wound has healed, particularly in the pediatric population. Because of the rich blood supply of the scalp, even very large scalp avulsions may remain viable. If the avulsion remains attached to the rest of the scalp by a tissue bridge, it should be reattached to the surrounding tissue. If the avulsion is completely detached from the scalp, it should be treated as any other amputated part and reimplanted as soon as possible.

Scalp abrasions are often contaminated with pieces of dirt or other debris. The wound should be cleaned as thoroughly as possible and inspected for puncture wounds or other areas that penetrate beyond

the superficial layers of the skin to ensure the removal of unsuspected foreign bodies. A careful inspection often reveals a small scalp laceration within the abraded area.

Systemic antibiotics are not needed for carefully managed scalp wounds because rapid healing is facilitated by the rich blood supply of the scalp. However, special consideration may be given to large or highly contaminated wounds, bite wounds, and for immunocompromised patients.

Skull fractures. A noncontrast head CT scan with bone windows is the imaging modality of choice for patients with suspected skull fractures or to identify intracranial foreign bodies. Plain radiographs can be useful when CT scanning is not available.

Linear fractures. Linear skull fractures are clinically important if they cross the middle meningeal groove or major venous dural sinuses; they can disrupt these vascular structures and cause the formation of EDHs. No specific intervention is necessary for linear skull fractures if a noncontrast CT scan reveals no underlying brain injury. Patients with no evidence of intracranial injury on CT and no other significant extracranial injuries should be observed in the ED for 4 to 6 hours prior to discharge. If there is any suspicion or clinical evidence of brain injury, patients should be admitted for observation. Those with intracranial injuries should have an emergent neurosurgical consultation. Patients with simple linear skull fractures may demonstrate concussive symptoms or other evidence of mild TBI and should be provided appropriate discharge instructions (see later, "Mild Traumatic Brain Injury: Disposition").

Depressed fractures. When a depressed fracture occurs, traumatic impact drives the bone piece below the plane of the skull. The edges of the depressed portion of skull may become locked underneath the adjacent intact bone and fail to reduce into their anatomic position. As a result, the depressed piece of bone can penetrate tissue and lacerate the dura. Fractures in which the free piece of bone is depressed deeper than the adjacent inner table of the skull require surgical elevation.

Depressed skull fractures are usually open fractures with disruption of the galea, which can often be felt with palpation of the skull. However, this examination should be done cautiously to avoid driving a depressed bone fragment deeper into the cranium. The clinical examination for a depressed skull fracture may be misleading as the mobility of the scalp can result in nonalignment of the fracture with an overlying scalp laceration. As a result, the skull underlying laceration may be normal, with depressed area several centimeters away. Additionally, scalp swelling may interfere with the physical examination findings and hide any palpable bone defects.

CT scanning with bone windows is the imaging modality of choice, as depressed fractures may be difficult to visualize on plain skull radiographs. The free piece of bone demonstrates increased or double density because it often overlaps the nonfractured bone, or it is rotated from the rest of the adjacent cranium. Tangential views of the skull may increase the ability to visualize the fracture.

An open depressed skull fracture, as well as any type of penetrating skull injury, increases the risk for developing intracranial and meningeal infection. We suggest that prophylactic antibiotics be given for 5 to 7 days to prevent the risk of subsequent CNS infection. Suggested antibiotics are identical to those for penetrating head trauma. Development of seizures is also common after this type of injury and prophylaxis may be considered.[90] Patients with depressed skull fractures should be admitted for continued observation. Patients with open (compound) cranial fractures depressed greater than the thickness of the cranium may be treated nonoperatively if there is no clinical or radiographic evidence of dural penetration, significant intracranial hematoma, depression greater than 1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination.

Basilar skull fractures. Basilar fractures are the result of considerable impact force and are highly associated with underlying brain injury. Emergency clinicians should be suspicious of an EDH in patients with a temporal bone basilar skull fracture. All patients with basilar skull fractures should be admitted for observation, regardless of the need for surgical intervention. Routine prophylaxis is not supported by the available evidence, whether or not there is evidence of CSF leakage, unless the patient is immunocompromised.[78] Most CSF leaks resolve spontaneously within 1 week, with no complications. If the leak persists beyond 7 days, the incidence of bacterial meningitis increases significantly; prophylactic antibiotics should be given in such cases and surgical intervention may be warranted.[91] Antibiotic selection is identical to that for penetrating head trauma. If a patient with a previously diagnosed CSF leak returns to the ED later with fever, the diagnosis of meningitis should be strongly suspected and appropriate evaluation (i.e., lumbar puncture) and appropriate antibiotic treatment initiated immediately. Treatment of posttraumatic meningitis is discussed in Chapter 95.

Extra-axial lesions

Epidural hematoma. Consensus guidelines support rapid surgical evacuation for any patient who has mass effect on a CT scan or progressive neurologic deterioration. Indications for urgent surgical evacuation include EDHs larger than 30 cm^3, regardless of the patient's GCS score, as well as comatose patients with an acute EDH and anisocoria on pupillary examination. For patients with acute EDH who are awake and have no focal neurologic deficits, nonsurgical management is based on the size of the hematoma (<30 cm^3), thickness of the clot (<15 mm), and degree of midline shift (<5 mm). In those managed nonoperatively, close neurologic observation in a neurosurgical center is recommended, with a first repeat CT scan obtained within 6 to 8 hours postinjury.

Subdural hematoma. SDH is often associated with significant brain injury. Further, delays in clinical signs and symptoms and the older mean age of the at-risk population lead to a higher mortality rate than EDH. While a small SDH (only a few millimeters thick at its widest point on CT scan) often is amenable to serial observations of the patient's status and appearance of the SDH on CT scan, even a small SDH may be accompanied by extensive brain tissue damage that can cause an increase in ICP sufficient to precipitate a herniation syndrome. If the patient is deeply comatose at presentation, with flaccidity and without signs of brainstem activity, they may best be served by providing supportive care alone. Subsequent management and advanced directive decisions should be discussed with the patient's family and neurosurgeon.

Most patients with subacute SDH require surgical evacuation of the lesion. Indications for surgical evacuation include acute SDHs with a thickness more than 10 mm or a midline shift of more than 5 mm on a CT scan, regardless of the patient's GCS score. Other parameters for surgical evacuation include a worsening GCS score (≥2 points from the time of injury to hospital admission) in comatose patients, asymmetric or fixed and dilated pupils, and persistent elevation in ICP.

The treatment of chronic SDHs is controversial. Symptomatic chronic SDHs require surgical evacuation. Most patients have a good outcome after surgery. Overall, the mortality from surgically drained chronic SDH approaches 5%, with decreased survival in older adults.[92]

Traumatic subarachnoid hemorrhage. In the absence of other brain injury, tSAH generally carries a favorable prognosis. The most serious complication of tSAH is worsening of cerebral vasospasm, which may be severe enough to induce cerebral ischemia. Posttraumatic vasospasm is common, occurring approximately 48 hours after injury and persisting for up to 2 weeks. While commonly used to prevent or reduce cerebral vasospasm following aneurysmal SAH,

calcium channel blockers such as nimodipine and nicardipine are of questionable benefit in tSAH and are not routinely recommended.[93] Patients with severe TBI and large amounts of SAH may benefit from serial noninvasive monitoring and institution of therapy in the setting of radiographic or clinical deterioration.

Subdural hygroma. If SDHGs are asymptomatic, observation is a reasonable approach. Otherwise, they are surgically evacuated. Mortality approaches 20% and appears to depend on the severity of other intracranial injuries.

Intra-axial lesions

Cerebral contusion. Patients with brain contusions can often be treated conservatively, although almost half will have significant progression on CT and 20% will require surgical intervention. Patients with lower GCS scores and larger cerebral contusions are at higher risk for hemorrhagic progression and the need for delayed surgical decompression. Hemorrhagic progression of a contusion generally occurs within the first 12 hours but may occur as late as 3 to 4 days after head trauma.

Intracerebral hematoma. Many patients with an ICH require emergent intervention or surgery to lower elevated ICP. Mortality is low in patients who are conscious before surgery, whereas in unconscious patients, mortality approaches 45%. Bleeding into the ventricles or cerebellum carries a high mortality rate.

Intracerebellar hematoma. Mortality from isolated traumatic intracerebellar hematoma is very high. Emergent neurosurgical consultation is indicated.

Complications and Outcome

In the 24 to 48 hours after trauma, seizures are caused by worsening cerebral edema, small hemorrhages, or penetrating injuries. In patients with severe TBI, the rate of a clinical PTS may be as high as 12%, whereas that of subclinical seizures detected on electroencephalography may be as high as 20% to 25%.[10] Early PTS, within 24 hours of injury, are usually brief and are most likely caused by transient mechanical and neurochemical changes within the brain. PTSs are common in children and can be precipitated by MTBI but are more common in moderate and severe TBI.

Risk factors for early PTS include GCS score of 10 or lower, immediate seizures, posttraumatic amnesia lasting longer than 30 minutes, linear or depressed skull fracture, penetrating head injury, SDH, EDH, ICH, cortical contusion, age 65 years or younger, or chronic alcoholism. The risk factors for PTE include severe TBI, early PTS prior to discharge, acute ICH or cortical contusion, posttraumatic amnesia lasting longer than 24 hours, age older than 65 years, and premorbid history of depression. In addition, location of the lesion plays a role, with higher rates of PTE in patients with temporal lobe bleeding.[94]

Central Nervous System Infections

Meningitis after basilar fractures. Posttraumatic meningitis can be caused by a variety of microbes, depending on the portal of bacterial entry. Patients have typical signs and symptoms of meningitis, including fever, altered mental status, and occasional focal neurologic signs. In patients with a CSF leak after basilar fracture, early meningitis (i.e., within 3 days of injury) is usually caused by pneumococci. Treatment of posttraumatic meningitis is discussed in Chapter 95.

Brain abscess. Brain abscesses develop infrequently after penetrating missile injuries to the head. Abscesses can also develop after open depressed skull fractures if bone fragments are not removed or as a postoperative complication. Posttraumatic CSF fistulae and fractures that disrupt air-filled sinuses predispose to the formation of brain abscesses. Clinical manifestations include headaches, nausea, vomiting, declining mental status, signs of increased ICP, and new focal neurologic findings in patients who had been improving after trauma. Evaluation and treatment of brain abscess are discussed in Chapter 99.

Cranial osteomyelitis. Cranial osteomyelitis can occur after penetrating injury to the skull. The clinical manifestations include pain, tenderness, swelling, and warmth at the infected site. While more than 50% of cases are obvious on plain skull radiographs, plain radiographs lack sufficient sensitivity for routine use. Contrasted CT imaging has reasonable sensitivity, although MRI is the diagnostic test of choice for early identification of cranial osteomyelitis.[95] Patients with posttraumatic cranial osteomyelitis require surgical debridement and removal of the infected bone. Antibiotic choice is determined by culture results. If systemic symptoms are present, an underlying subdural or epidural empyema should be suspected.

Medical Complications

There are several systemic manifestations of TBI that can occur in the absence of any specific organ injury or systemic infection. The nature and severity of these manifestations depend mainly on the severity of the brain injury.

Disseminated intravascular coagulation. The injured brain is a source of tissue thromboplastin that activates the extrinsic clotting system. Disseminated intravascular coagulation (DIC) can develop within hours after any injury disrupting brain tissue. Cerebral intravascular coagulation is a universal response to TBI and is found in tissues from surgical specimens of human cerebral contusions. Coagulation abnormalities, including systemic DIC, are detected in over 50% of severe TBI patients and isolated severe TBI patients who develop coagulopathy have higher mortality rates than isolated severe TBI patients without coagulopathy.[96] DIC not only increases morbidity and mortality after severe TBI, it increases the risk of delayed intracranial hemorrhage. If a stable patient with DIC suddenly deteriorates, a repeat CT scan should be obtained to rule out hemorrhage.

The extent of tissue destruction determines the degree of DIC that develops. The diagnosis is based on abnormalities in the INR, prothrombin time (PT), partial thromboplastin time (PTT), platelets, plasma fibrinogen levels, and fibrin degradation products. Patients with coagulopathy or abnormal platelet function require interventions to correct these.

Patients with moderate or severe head trauma are at extremely high risk to experience venous thromboembolic events (VTEs) after admission to the hospital. The existing literature is insufficient to recommend a particular agent or dose, or timing of anticoagulation.[10] However, in those patients with stable CT scans after 24 to 72 hours, initiation of anticoagulation reduces the incidence of VTE without a corresponding exacerbation of intracranial hemorrhage.[97–99]

Respiratory complications. Pulmonary complications in the hours to days following TBI are common. Acute lung injury has been theorized to occur from a variety of pathologic processes, including a systemic inflammatory response, infection, induced hypertension in an effort to maintain cerebral perfusion, and neurogenic pulmonary edema.[100] Neurogenic pulmonary edema can develop minutes to days after head trauma, leading to extravascular fluid in the lungs, hypoxia, and decreased lung compliance. The catecholamine surge that often follows TBI can result in increased intravascular pressure, increased capillary permeability, and hydrostatic edema. Additionally, a systematic inflammatory reaction leads to endothelial damage and vasogenic edema. Treatment of acute lung injury in TBI is challenging because traditional treatment measures, including hypercapnia, fluid restriction, and prone ventilation (which raises ICP), are contraindicated in TBI.[100] Positive end-expiratory pressure (PEEP) may be beneficial, and although PEEP increases ICP by reducing

venous return, studies have shown that with adequate intravascular volume and MAP PEEP does not adversely affect ICP. Furthermore, controlling ICP also appears to reduce the neurogenic stimulation that may contribute to pulmonary edema. Close ICP and ventilator management are essential to improved outcomes in patients with acute lung injury secondary to TBI.

Cardiac dysfunction. Cushing noted a connection between cardiac dysrhythmias and intracranial bleeding in the early 20th century, and a variety of cardiac rhythm, rate, and conduction abnormalities may be detected after TBI. Catecholamine release following brain injury is common, which may lead to tachycardia, hypertension, or coronary vasoconstriction. Myocardial ischemia, particularly in patients with pre-existing coronary artery disease, results in the ECG changes frequently seen in the head-injured patient.[100] Further, cardiac rhythm abnormalities have been reported in up to 50% of all patients with traumatic intracranial hemorrhage and up to 70% of all patients with tSAH. The most common cardiac dysrhythmia after TBI is supraventricular tachycardia, but many other rhythms have been observed. Findings on the electrocardiogram include diffuse large upright or inverted T waves, prolonged QT intervals, ST segment depression or elevation, and U waves. The primary goal in the emergency management of cardiac dysfunction after head trauma is ensuring adequate tissue perfusion and avoiding hypoxia. Dysrhythmias in head-injured patients often resolve as ICP is reduced.

Disposition

All patients with moderate to severe head trauma require imaging to determine the extent and nature of the brain injury and necessity of neurosurgical intervention. Neurosurgical consultation should be obtained as soon as possible to help direct the patient's subsequent management. Moderate and severely head-injured patients require admission to an institution capable of intensive neurosurgical care and acute neurosurgical intervention. If this is not available at the receiving hospital, the patient should be transferred to an appropriate institution.

All patients with moderate TBI should be admitted for a period of observation, even with an initial, apparently normal CT scan. Frequent neurologic checks should be initiated, and a repeat CT scan is indicated if the patient's condition deteriorates or fails to improve over the first 48 hours after trauma. In patients with persistent symptoms of headache, confusion, or memory difficulties, delayed MRI may define lesions in the regions related to cognition that cannot be seen on CT. Although not useful in the emergency setting, MRI has prognostic value during subsequent care and assists in directing the future rehabilitation of these patients.

MILD TRAUMATIC BRAIN INJURY (ALSO KNOWN AS CONCUSSION)

Clinical Features

Signs and symptoms of MTBI can be subtle and easily overlooked, especially in the setting of polytrauma. A high index of suspicion and systematic diagnostic approach are necessary to ensure identification.[101] A two-question screen administered during triage could potentially improve identification by alerting the emergency clinician to the presence of an MTBI or concussion: (1) Did the patient sustain a blunt force mechanism or whiplash type acceleration-deceleration event, and, (2) At any point after injury, was there alteration in mental status, such as confusion or disordered awareness (feeling dazed, disoriented, foggy, "seeing stars," slowed thinking), amnesia (retrograde or anterograde), or loss of consciousness?[101,102] It is not uncommon for MTBI symptoms to dissipate by the time patients reach the ED. However, not having symptoms on arrival to the ED does not preclude diagnosis of a MTBI. If the answer to both screening questions is yes, a focused neurologic assessment for MTBI should follow.[102]

As with moderate and severe TBI, a comprehensive history includes information from the patient, prehospital personnel, family members, and witnesses about the mechanism of injury, including events before and after the injury. In addition, age, comorbidities, coagulopathies (e.g., hemophilia, Von Willebrand disease, hepatic insufficiency, use of anticoagulants), consumption of alcohol or drugs, changes in mental status or deteriorating GCS scores, previous TBI or concussion, symptoms of other potential injuries, and TBI symptoms (including postconcussive symptoms) should be taken into account. It is important to ask patients specifically about symptoms of disorientation, confusion, amnesia, or disordered awareness, with or without loss of consciousness. The majority of MTBI patients do not experience a loss of consciousness and, if they do, it is difficult to quantify unless there are witnesses.

MTBI symptoms fall into four broad domains: somatic, cognitive, sleep, and emotional.[103] Somatic symptoms include headache, dizziness, diminished balance, vertigo, tinnitus, sensitivity to light and noise, nausea, and vomiting. Cognitive symptoms include impaired memory or concentration, delayed language comprehension, and slowed or repetitive speech. Emotional disturbances include irritability, sadness, anxiety, and depression. Sleep-related disturbances include the spectrum between insomnia and fatigue. Using a validated concussion symptom checklist can facilitate quick determination of the current concussion symptom burden (e.g., Rivermead Post-Concussion Symptom Questionnaire, Post-Concussion Symptom Scale, SCAT5). The greater the number and severity of acute symptoms, the higher the risk of prolonged recovery.[104]

Physical Examination

As described earlier, the general trauma examination is as for the patient with moderate or severe head injury. A more detailed neurologic examination is often possible in MTBI patients who can cooperate with the examination. Although the physical examination for MTBI has not been standardized, it is important to assess MTBI patients consistently in the ED.[105] Recent ACEP guidelines suggests a framework for ED physicians to follow.[102]

Head and Neck

Alert patients are questioned regarding cervical spine pain. Immobilization is indicated until cervical spine injury is excluded. Validated decision guidelines such as the NEXUS or Canadian C-spine criteria may be applied in select alert patients to guide imaging.[106] Assess for scalp trauma, facial, skull, and basilar skull fractures and auscultate for bruits in the rare event of carotid or vertebral artery dissection.

Neck injuries, such as whiplash-induced neck injuries, can occur simultaneously with MTBI and have overlapping symptoms such as headaches, balance difficulties, dizziness, visual disturbances, and poor postural control.[105]

Mental Status and Alertness

Reassess the GCS score while the patient is in the ED and document changes. Patients with GCS scores trending downward (worsening neurologic status) are at higher risk of requiring neurosurgical intervention and having poor outcome.[107] Although the MTBI patient may be alert, they may exhibit signs of impairment, such as repetitive questions, intermittent bouts of confusion, and difficulty paying attention. Note if the patient displays a peculiar flat affect, appears devoid of emotion, and speaks in a slow monotone voice without inflection, which may indicate damage to the prefrontal cortex or frontal lobes.[108]

Cranial Nerves

CN injuries following MTBI are more common with fractures at the base of the skull.[109–111] Assess for anosmia and hyposmia, because the olfactory nerve (CN I) is one of the most common CNs affected after MTBI. This may be done by having the patient smell ground coffee or a citrus-scented beverage. The facial nerve (CN VII) and oculomotor nerves (CNs III, IV, and VI) are also frequently injured, so assess for facial paralysis, change in taste, or diplopia. In MTBI, CNs IV and VI are more commonly injured than CN III. CN VII palsy may indicate a fracture of the temporal bone, particularly if it occurs in association with decreased hearing (CN VIII). Hearing impairment can be one of the more subtle deficits seen after TBI. Facial pain (CN V) and occipital neuralgia may also occur in association with MTBI. CN IX and X palsies can present with dysphagia and may be associated with fractures of the occipital condyles.[110,111]

Cognitive Function (Attention, Memory, Concentration)

Performing a cognitive examination can be challenging in the ED setting. Brief assessment tools include the Mini-Mental State Exam (MMSE) and the Standardized Assessment of Concussion (SAC) can be used.[112] The SAC is embedded in the Sport Concussion Assessment Tool 5 (SCAT5) which can also be used.[113] Serial subtraction exercises, such as serial 7s beginning at 100, can be completed quickly and only require 4 or 5 rounds (down to 65) to ascertain if the patient can concentrate and adequately use working memory. Serial 3s from 100 can be used for adolescents ages 14 to 18 years, and serial 1s from 10 for children ages 7 to 14 years. Baseline cognitive status should be considered.

Vestibular Function (Balance, Gait, and Eye Movements)

A growing body of evidence suggests MTBI disrupts the vestibular system, including balance, gait, and eye movements.[114] Balance relies on visual, vestibular, and proprioception input from cortical networks. Balance is tested in a graduated way, with an initial test of simply standing with the examiner nearby for safety. Next, a formal Romberg test can be performed. Balance can also be quantified using the modified Balance Error Scoring System (mBESS) which counts errors with double leg, single leg, and tandem leg stances.

Gait is then assessed by having the patient walk several steps and then return back to the examiner. For younger individuals, tandem stance and tandem gait can be performed, initially with eyes open and then with eyes closed. Significant sway, missteps, arms extended for balance, and broad-based or abnormally slow gait are considered errors.

The vestibular system controls eye movements, such as smooth pursuits, saccades, and vestibulo-ocular reflex. These can be assessed using the Vestibular/Ocular-Motor Screening Exam (VOMS) screening tool. Although it is not currently routine practice to perform VOMS in the ED, it has been shown to be feasible following provider education along with the use of clinical support tools.[115] It should be considered for patients at high risk for ongoing symptoms.

MTBI disrupts neural pathways controlling ocular accommodation and convergence. Ocular near vision (accommodation and convergence) can also be assessed using the VOMS.[116] Moreover, MTBI patients often can have difficulty with the finger-nose-finger test and will use slow purposeful movements to complete the task.

Differential Diagnoses

MTBI (GCS score of 13 to 15) is characterized by symptoms of confusion and amnesia, with or without preceding loss of consciousness. The differential diagnosis, in the context of trauma, includes intoxication (drugs, alcohol, medications), PTSs and postictal state, hypoglycemia, and other injuries that may impair a patient's ability to communicate. These include facial bone fractures, hypoxemia or hypoperfusion (from extracranial injuries), cervical spine or spinal cord injuries, injuries to the eyes or tympanic membranes, laryngeal or vocal cord injuries, and vascular injuries of the neck. Patients can deteriorate from an expanding intracranial hematoma after what appears clinically to be an MTBI, even if the patient initially presents with a GCS score of 15. In such a case, the injury would be reclassified as moderate or severe TBI.

Prior to the trauma, patients may have experienced a syncopal episode, seizure, or cardiac event that produced a loss of consciousness that led to the subsequent trauma. For example, an MVC may have resulted from the driver becoming distracted or incapacitated by important symptoms suggestive of an unrelated disorder. Therefore, potential precipitants to the trauma should also be considered in the differential diagnoses.

An MTBI or concussion may go unrecognized in the ED, especially if symptoms are transient or if more visible injuries dominate the assessment. An underlying dementia or psychiatric illness make it challenging to distinguish an MTBI from baseline cognitive or mental dysfunction. Other conditions that could cofound the diagnosis include stroke, encephalopathies (e.g., hepatic, uremic), delirium from alcohol or drug withdrawal, neurologic conditions (e.g., Parkinson or Alzheimer disease, autism), and infection or sepsis. Even low-mechanism trauma should alert the emergency clinician to the possibility of brain injury in susceptible populations.

Diagnostic Testing

Neuroimaging in the Emergency Department with Computed Tomography

Traumatic intracranial injuries requiring prompt intervention occur in approximately 7% of patients with MTBI.[117] Intracranial injuries leading to death or requiring neurosurgical intervention is about 0.9%.[117] CT scan of the head is the diagnostic standard for acute evaluation of suspected traumatic intracranial injuries in the ED. However, CT is associated with exposure to ionizing radiation and higher health care costs. Several clinical decision rules have been prospectively derived and validated to reduce the need for CT scanning and identify MTBI patients at risk for intracranial lesions and neurosurgical intervention. These include the New Orleans Criteria (NOC), Canadian Computed Tomography Head Rule (CCHR), and National Emergency X-Radiography Utilization Study II (NEXUS-II; Box 33.4). Others have developed guidelines based on available evidence, including the American College of Emergency Physicians clinical policy on neuroimaging of adult ED patients with MTBI (ACEP), National Institute for Health and Clinical Excellence (NICE), Neurotraumatology Committee of the World Federation of Neurosurgical Societies (WFNS), Scandinavian Neurotrauma Committee, and Scottish Intercollegiate Guidelines Network (SIGN). Although most of the rules and guidelines produce high sensitivities for detecting neurosurgical intervention and intracranial lesions, the specificities are variable. Additional clinical decision rules have been developed for the pediatric population (see Chapter 160).

The most widely researched clinical decision rules for MTBI are the CCHR and NOC, with external validation studies in the United States and internationally. The CCHR was developed for use in patients with a GCS score of 13 to 15; it divides clinical variables into high- and medium-risk categories. The NOC was developed for use in patients with a GCS score of 15 only and is composed of seven clinical variables. For injuries requiring neurosurgical intervention, both the CCHR and NOC have a high sensitivity (99% to 100%) but the CCHR has a much higher specificity (CCHR, 48% to 77%; NOC, 3% to 31%). For identification of traumatic intracranial lesions on CT, the CCHR and NOC have a high sensitivity (CCHR, 80% to 100%; NOC, 95% to 100%)

BOX 33.4 Clinical Decision Rules for Neuroimaging in Adults with Mild Traumatic Brain Injury

Canadian Computed Tomography Head Rule (CCHR)

High-Risk Injury (May Require Neurologic Intervention)

1. GCS score <15 at 2 h after injury
2. Suspected open or depressed skull fracture
3. Any sign of basal skull fracture (hemotympanum, raccoon eyes, CSF otorrhea or rhinorrhea, Battle's sign)
4. Vomiting >2 episodes
5. Age >65 years

Medium-Risk Injury (May Have Important Brain Injury on CT)

6. Amnesia before impact ≤30 min
7. Dangerous mechanism (pedestrian struck by vehicle, occupant ejected from vehicle, fall from elevation >3 feet [five stairs])

New Orleans Criteria (NOC)

1. Headache
2. Vomiting
3. Age >60 years
4. Drug or alcohol intoxication
5. Persistent anterograde amnesia
6. Trauma above the clavicle
7. Seizure

NEXUS II Criteria

1. Evidence of significant skull fracture
2. Scalp hematoma
3. Neurologic deficit
4. Altered level of alertness
5. Abnormal behavior
6. Coagulopathy
7. Persistent vomiting
8. Age >65 years

CSF, Cerebrospinal fluid; *GCS,* Glasgow Coma Scale.

but specificity is higher with the CCHR. In terms of potential for CT reduction, adherence to the NOC results in an increase in head CT use; adherence to the CCHR results in a decrease in head CT use compared to current practice. Imaging of patients in this population should follow a validated guideline. Clinicians in emergency medicine, trauma surgery, neurosurgery, and neurology should review the relevant guidelines (CCHR, NOC) and select the system thought to be most applicable for their setting and patient population. Oversight should ensure that cases not following the adopted guidelines are reviewed and feedback is provided to emergency clinicians.

Of note, CT scanning detects the presence of intracranial bleeding but does not exclude the existence of underlying brain injury and is not diagnostic of an MTBI.

Other Neuroimaging Modalities

Structural magnetic resonance imaging. CT is the imaging modality of choice for initial screening to exclude serious traumatic intracranial lesions in MTBI. However, many patients who develop persistent symptoms and cognitive deficits have no detectable abnormalities on initial CT screening. About a quarter of concussion patients with normal CT scans have been shown on MRI to have traumatic abnormalities such as micro-hemorrhages.[118] MRI is better than CT in detecting posttraumatic ischemic infarctions, subacute nonhemorrhagic lesions and contusions, axonal shear injury, and lesions in the brainstem or posterior fossa. Structural MRI, particularly at a 3-T strength, improves structural sensitivity, can be performed when neurologic findings cannot be explained by CT, and is particularly valuable in assessing the brainstem, posterior fossa, and brain parenchyma adjacent to the calvaria. Structural MRI (without contrast) can also be used for the evaluation of TBI-related symptoms in the subacute and chronic phases of injury.

Susceptibility-weighted imaging. A significant advancement in the imaging of MTBI has been the development of susceptibility-weighted imaging (SWI). This technique is an imaging method that grew out of and is part of MRI. It uses differences in magnetic susceptibility between tissues and is particularly helpful for the evaluation of TAI and punctate hemorrhages (microhemorrhages) in the deep subcortical white matter not visible on CT or structural MRI scans. It takes about 4 minutes to image the entire brain and, in the ED, SWI detects additional lesions 30% of the time compared to CT and structural MRI.[118] The number and volume of SWI microhemorrhages correlate with clinical outcome.[119]

Diffusion tensor imaging. DTI uses MRI technology to analyze the movement of water molecules in the white matter of the brain and provides the opportunity to perform tractography—visualization of major white matter pathways—to assess damaged nerve fiber tracts. DTI can detect white matter abnormalities when conventional imaging is normal. These abnormalities may be a marker of TAI and are associated with cognitive dysfunction.[120] Continuing loss of structural integrity in certain tracts may contribute to persistent post-concussion symptoms and is associated with recovery.[121,122]

Computed tomography angiography and magnetic resonance angiography. Vascular imaging such as CT angiography and MR angiography are not recommended routinely for patients with MTBI unless there is suspicion of a traumatic vascular injury, such as pseudoaneurysm, dissection, or uncontrolled hemorrhage.[123] Typically, vascular injuries occur with penetrating trauma, skull base fractures, blunt neck trauma, or skull base or cervical spine fractures. Independent predictors of arterial injury in blunt trauma include cervical facet subluxation or dislocation, fracture lines approaching an artery, and high-impact injury mechanisms.

Ancillary Studies

Laboratory testing. Laboratory tests are not needed for patients with isolated MTBI except for a bedside glucose level in those with a GCS score less than 15. Coagulation parameters such as INR, PT, and PTT are indicated for those with inherent coagulopathies or suspected liver disease and those on anticoagulants.

Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin C-terminal hydrolase (UCH-L1) have been evaluated in several studies to determine the need for CT scan and neurosurgical intervention in adults with mild to moderate TBI[124–127]and more recently in children.[125,128–130] In early 2018, GFAP and UCH-L1 were FDA-approved for clinical use in adult patients with mild to moderate TBI to help determine need for CT scan within 12 hours of injury (Fig. 33.14).[131] The approval was based on the ability to find lesions on CT scan but was not approved to diagnose a concussion. Moreover, it was not approved for use in children.

Neuropsychological testing. Neuropsychological testing is used to assess cognitive function after MTBI and includes in-depth testing of memory, attention, and concentration that may reveal cognitive abnormalities not detected on the initial physical exam. Several studies have reported an association between cognitive deficits detected in the

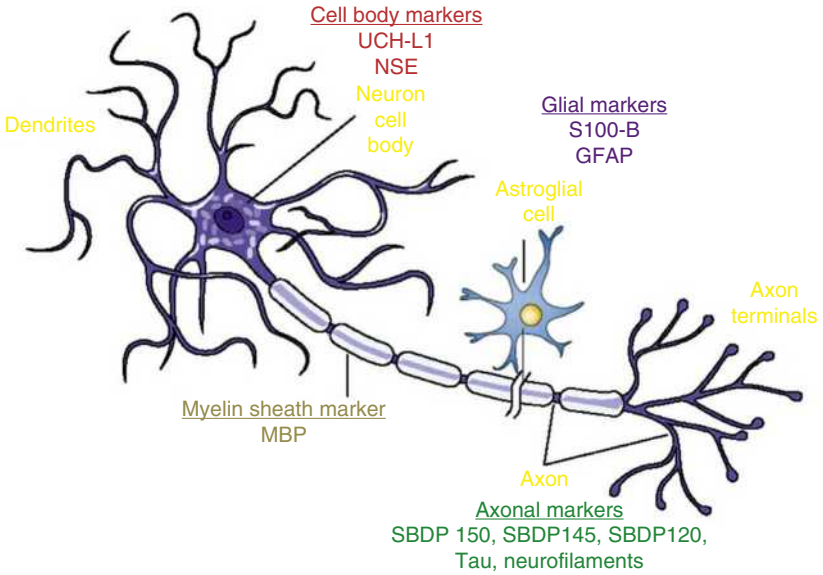

Fig. 33.14 Neuron and Neuroanatomic Locations of Potential Traumatic Brain Injury Biomarkers. S100β is the major low-affinity calcium binding protein in astrocytes that helps regulate intracellular levels of calcium. Glial fibrillary acidic protein (GFAP) is a monomeric intermediate protein found in the astroglial skeleton and in white and gray brain matter and is strongly upregulated during astrogliosis. Neuron-specific enolase (NSE) is one of the five isozymes of the glycolytic enzyme enolase found in central and peripheral neuronal cell bodies. UCH-L1 is highly abundant in neurons and was previously used as a histologic marker for neurons. Alpha II-spectrin is the major structural component of the cortical membrane cytoskeleton and is particularly abundant in axons and presynaptic terminals. Tau is an intracellular, microtubule-associated protein that is highly enriched in axons. Neurofilaments are heteropolymeric components of the neuron cytoskeleton. (From Papa L. Exploring serum biomarkers for mild traumatic brain injury. In Kobeissy F, ed. *Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects in brain injury models.* London: CRC Press; 2015: 303.)

ED and prolonged recovery.[104,132] Although commercially available computerized testing platforms can simplify and standardize test administration, testing still requires 20 to 25 minutes and the assistance of ancillary staff. Although not routinely done in the ED, referral to a neuropsychologist is warranted for patients having persistent symptoms following a concussion.

Disposition

Most patients with MTBI can be discharged from the ED with a normal examination and after a reasonable period of ED observation (4 to 6 hours) or following a negative head CT scan, except in the presence of therapeutic anticoagulation; in these cases, a more prolonged observation period of up to 24 hours, with repeat head CT scan, may be warranted.[63] If the emergency clinician decides that the patient with MTBI can be sent home, an appropriate early follow-up should be arranged. Providing patients and families with educational information about postconcussive syndrome and what to expect after injury helps improve outcome. Patients should also be given contact information for the brain injury association in their region. State brain injury associations can connect patients and families with support groups, programs, and professionals who understand the injury (www.biausa.org/mild-brain-injury.htm).

Patients should be discharged with instructions describing the signs and symptoms of acute and delayed complications of MTBI, have access to a telephone, and be monitored in the acute post-trauma period by a responsible adult. All discharge instructions should be printed and verbally described to a responsible third party. Warning signs for acute deterioration, such as inability to waken the patient, severe or worsening headaches, somnolence or confusion, restlessness, unsteadiness, or seizures, difficulties with vision, vomiting, fever, or stiff neck, urinary or bowel incontinence, and weakness or numbness involving any part of the body, should prompt the caregiver to seek immediate medical help. If any doubt exists regarding the safety of the discharged patient with MTBI, a brief inpatient observation period (12 to 24 hours) is advisable. Additionally, patients with persistent postconcussion symptoms, such as intractable headache or vomiting requiring parenteral medication, that are not amenable to outpatient treatment might require hospital admission.[102]

If resources allow, prolonged ED observation may be practical in some circumstances.[133] For example, intoxicated patients with MTBI who otherwise fulfill low-risk criteria should undergo serial evaluations in the ED until clinical sobriety is achieved. In these patients, a CT scan may be unnecessary, and ED observation is beneficial.

If a patient with MTBI returns to the ED because of persistent symptoms, delayed complications of injury should be sought. If a CT scan was not initially obtained, the intensity of symptoms may guide the decision to obtain a CT scan at the second ED visit. If a negative scan was initially obtained, the likelihood of the subsequent development of an intracranial lesion is exceedingly low. The decision to rescan is more complex in patients from certain subgroups who may be considered more likely to develop delayed complications. These include patients on anticoagulation therapy, those with preexisting neurologic injuries that may obscure an examination, and those with previous neurosurgical procedures (e.g., ventriculoperitoneal shunts). The literature about repeat CT scanning in MTBI suggests that patients who are unchanged or improving neurologically do not benefit from a repeat CT, but repeat imaging is indicated to assess a deteriorating patient.

Complications

In addition to being at risk for serious intracranial injuries, patients with a suspected MTBI can have elusive axonal injuries and microbleeds and over the long term, can suffer impairment of physical, cognitive,

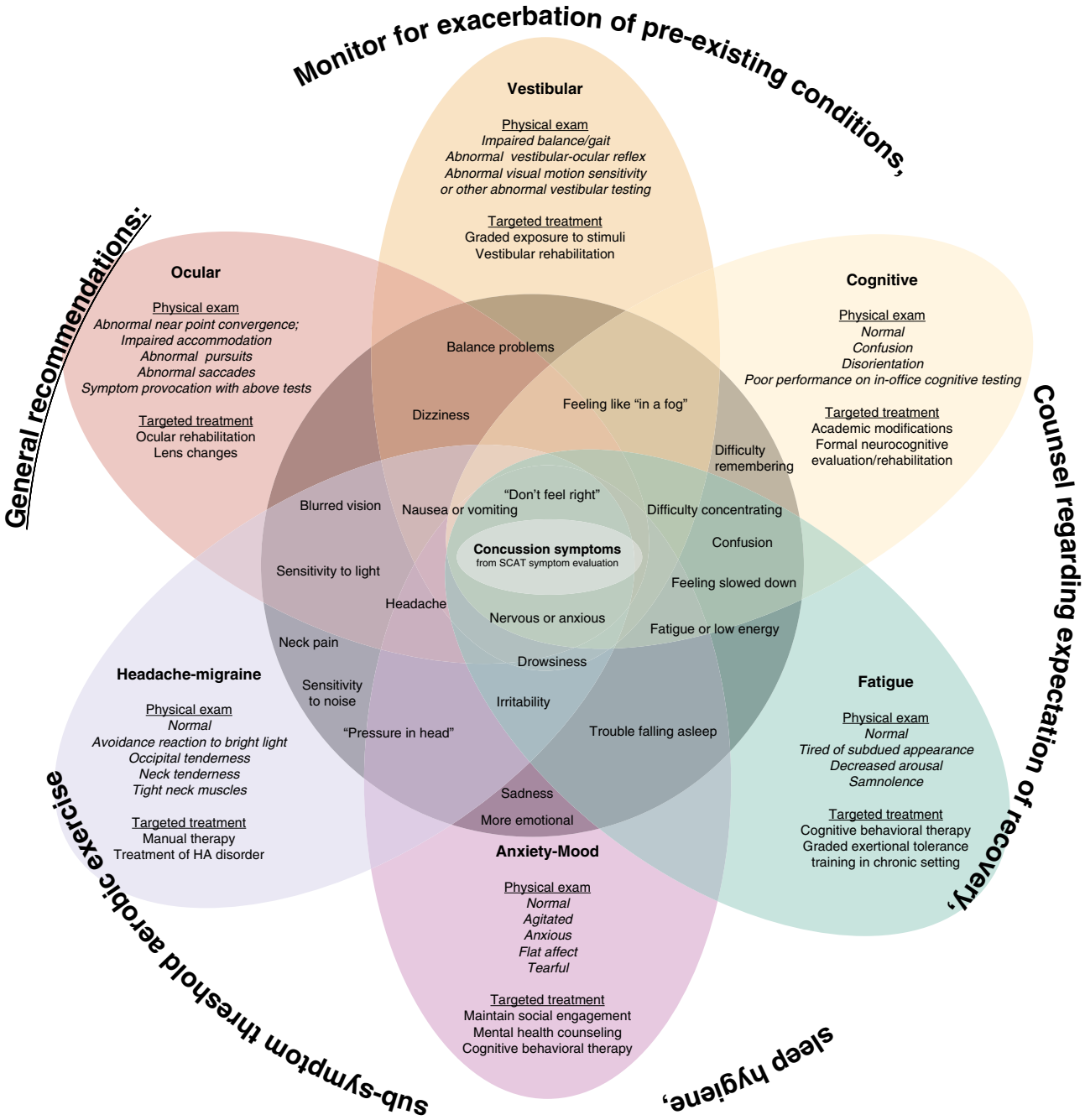

Fig. 33.15 Constellation of Symptoms Following Concussion. Overlapping clinical profiles is an emerging concept to facilitate individualized management after concussion. (From Harmon KG, Clugston JR, Dec K, et al. American Medical Society for Sports Medicine position statement on concussion in sport. *Br J Sports Med.* 2019;53(4):213–225.)

and psychosocial functioning (Fig. 33.15).[118,119] It has been reported that more than one-third of MTBI patients do not resume work until 1 to 3 months after their injury, and lingering cognitive complaints are reported by as many as 15% of patients 1 year postinjury.[134] Recovery can also be complicated by psychiatric or substance abuse problems, health problems, concurrent orthopedic or traumatic injuries, chronic pain, lack of family and social support, unemployment, and litigation.[135,136]

Postconcussive Syndrome

Postconcussive syndrome (PCS) refers to a constellation of symptoms that include somatic (headache, dizziness, vertigo, nausea, fatigue, sensitivity to noise and light), cognitive (difficulties with attention, concentration, and memory) and affective complaints (irritability, anxiety, depression, emotional lability) that occur following an MTBI or concussion and persist beyond the expected recovery period. Affected patients commonly report headache, dizziness, memory or concentration difficulties, irritability, sleep disturbances, dizziness, and depression. There appears to be psychological and structural components to postconcussive syndrome, because patients with a history of migraines, depression, or anxiety are more likely to experience postconcussive syndrome.[136] The severity and duration of postconcussive symptoms may correlate with the abnormalities found with early functional

imaging.[119] Studies of ED patients have indicated that as many as 30% of patients with a discharge diagnosis of MTBI will have symptoms at 3 months postinjury, and up to 15% will continue to be symptomatic at 1 year postinjury.[119] In the ED, patients with more severe symptoms, such as prolonged amnesia, dizziness, headache, anxiety, noise sensitivity, or trouble with verbal recall have been shown to be at a higher risk of developing postconcussive syndrome (see Fig. 33.15). Other factors that have been identified as conferring an increased risk for the development of PCS symptoms include prior MTBI, history of depression or anxiety, multiple injuries, forgetfulness or poor memory, noise or light sensitivity, and history of migraine.[137] There are a wide range of treatments being studied, including cognitive and behavioral therapies, medications, devices, dietary supplements, return to activity and rest.[138]

Seizures

PTSs occur in fewer than 1% of MTBI patients, and acute antiepileptic prophylaxis is not indicated. The cumulative incidence of PTE in the first 3 to 5 years after discharge is about 4% for patients with MTBI.[139] PTE usually develops within the first 2 years after injury. Prophylactic treatment with anticonvulsants does not prevent delayed-onset PTE and is not recommended.[140]

Posttraumatic Transient Cortical Blindness

Posttraumatic transient cortical blindness syndrome is characterized by transient visual loss, normal pupillary response, and normal funduscopic examination within hours following MTBI. This syndrome has been reported mainly in children. In most cases, vision returns to normal within minutes to hours (usually within 24 hours) following injury and leaves no neurologic sequelae. Headache, confusion, irritability, anxiety, nausea, and vomiting are common related symptoms. Although the mechanism for the transient blindness is unknown, it has been suggested that it is an abnormal vascular response to trauma, with resultant transient hypoxia and cerebral dysfunction.

Special Populations with Mild Traumatic Brain Injury

Mild Traumatic Brain Injury and Sports-Related Concussion

In the United States, the nearly 8 million students who currently participate in high school athletics and the greater than 480,000 who compete as National Collegiate Athletic Association (NCAA) athletes are at risk for concussion. Between 1.1 and 1.9 million concussions occur annually in children in the United States annually from organized and recreational sports.[141] Football, ice hockey, soccer, and lacrosse tend to have the highest concussion incidence rates when calculated by athlete exposure.[142] A concussion is mild TBI; the term sport-related concussion refers to the subset of concussive injuries occurring during sport activities.[102] It has been suggested that sports-related concussions are associated with less disability and more rapid recovery than concussions in nonathletes. However, neuroimaging has suggested similar patterns of neuronal disruption for sports- and nonsports-related MTBI.[143] Athletes are more vulnerable to the deleterious long-term effects of MTBI because they are often subjected to repetitive trauma and greater levels of physical exertion during recovery. Only recently has CTE come to public attention due to autopsy findings in high-profile athletes.[144] Originally identified in boxers, CTE has recently been found to occur after other organized sports, including US football, hockey, soccer, and professional wrestling.[18,145] Meta-analyses of neuropsychological outcomes following MTBI have suggested that recovery from impairments in the general population takes longer (weeks to months) than in athletes who tend to show recovery within 2 to 14 days following concussion. Among athletes there is a tremendous motivation to return to play. As a result, athletes often underreport symptoms, return to their regular activities prematurely, and may create the impression that they recover more quickly than they actually do.[146,147]

Second-impact syndrome is thought to be an exceedingly rare yet potentially fatal consequence of repeated MTBI in sports occurring within a short period of time (hours to days). It confers a mortality of 50% and permanent disability in the rest.[148] It is defined as occurring when an athlete who has sustained an initial head trauma, most often a concussion, sustains a second head trauma before symptoms associated with the first have fully cleared, leading to diffuse cerebral swelling.[148] The second impact could be smaller in magnitude and does not necessarily have to be a direct blow to the head.[149] Some debate whether a repeated head trauma is required or whether the brain swelling is the result of a single blow to the head or whether underreporting of symptoms could be a contributing factor.[149] Based on the published case studies, athletes at a highest risk include playing American football, male gender, and young age.[149] Accordingly, the CDC has developed the HEADS UP Concussion in Youth Sports initiative to offer information about preventing, recognizing, and responding to a concussion to coaches, parents, and athletes involved in youth sports.

Several new or updated clinical practice guidelines and position statements have been recently published on the diagnosis, treatment, and management of sports-related concussion including the American College of Emergency Physicians Sport-Related Head Injury Prevention Task Force,[102] the American Medical Society for Sports Medicine,[150] and the Zurich Consensus working group.[113] There is consensus that concussion is a clinical diagnosis that is ideally made by a licensed health care provider with experience in the evaluation and management of patients with a concussion. Any athlete suspected of having a concussion should be immediately removed from play. Graded symptom and clinical sign checklists can be useful, particularly if they can be compared to preseason data. The Sport Concussion Assessment Tool, fifth edition (SCAT5), is a standardized tool for evaluating injured athletes for concussion and can be used in athletes 13 years and older (https://bjsm.bmj.com/content/bjsports/51/11/851.full.pdf) and the Child SCAT5 can be used for children 5 to 12 years old (https://bjsm.bmj.com/content/bjsports/51/11/862.full.pdf).[151] The SCAT5 takes 15 to 20 minutes to complete and computes a composite score comprised of post-concussive symptoms, cognitive screening, and a screen of coordination, gait, and balance. The SCAT5 (Child and Adult versions) also includes a page of information to be given to the athlete and parents after discharge. This tool has been used successfully in the ED setting to evaluate sports-related concussion.[152]

When evaluating an athlete with sports-related concussion in the ED, follow the principles for MTBI evaluation including comprehensive history, details of injury mechanism, symptom trajectory, emphasis on mental status and alertness, head and neck, neurologic exam, vestibular exam (ocular, gait, and balance), and cognitive function.[102,150] As with all MTBI patients, monitoring of the injured athlete with serial assessments is crucial, because signs and symptoms may evolve over hours after injury. A head CT scans is not routinely recommended but should be considered if there is clinical suspicion of a traumatic intracranial lesion (see diagnostic imaging previously).

Before return to play, a gradual, stepwise increase in general physical activity, followed by sports-specific activities, is recommended. Progression to more strenuous steps is only recommended if the athlete is asymptomatic at the current level of activity (Table 33.3). Ideally, a multidisciplinary approach to assessment and management is used, with the inclusion of sports medicine specialists from various subspecialties, as appropriate for the athlete's symptoms and signs.[150] Because many

TABLE 33.3 Graduated Return to Play Protocol: Graduated Return-to-Sport (RTS) Strategy

Stage	Aim	Activity	Goal of Each Step
1	Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2	Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase heart rate
3	Sport-specific exercise	Running or skating drills. No head impact activities	Add movement
4	Non-contact training drills	Harder training drills, e.g., passing drills. May start progressive resistance training	Exercise, coordination, and increased thinking
5	Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6	Return to sport	Normal game play	

NOTE: An initial period of 24 to 48 hours of both relative physical rest and cognitive rest is recommended before beginning the RTS progression. There should be at least 24 hours (or longer) for each step of the progression. If any symptoms worsen during exercise, the athlete should go back to the previous step. Resistance training should be added only in the later stages (stage 3 or 4 at the earliest). If symptoms are persistent (e.g., more than 10 to 14 days in adults or more than 1 month in children), the athlete should be referred to a healthcare professional who is an expert in the management of concussion.

Adapted from McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport-the 5(th) international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med.* 2017;51(11):838–847.

states have passed laws regarding concussion management in organized youth sports, it is good practice for emergency clinicians to familiarize themselves with the laws of the state in which they are practicing.

Key recommendations of recent position statements have stated that any athlete suspected of having a concussion should not be allowed to return to play on the day of the injury. Athletes with concussion should not return to play until they have been evaluated by a licensed health care provider with expertise in concussion management. A head CT should only be considered if intracranial lesions are suspected. Furthermore, there should be a gradual stepwise increase in physical activity.[102,113,150]

Military Personnel and Blast Injury

Mild TBI is also a common injury among soldiers who have participated in combat. Explosive blast brain injury is becoming recognized as a distinct entity from the penetrating form of blast injury and closed brain injury.[153] In recent US conflicts in Iraq and Afghanistan, over 60% of combat casualties were from explosive blast, mostly from improvised explosive devices (IEDs).[154] Other mechanisms included falls, motor vehicle accidents, fragment shrapnel, and bullet wounds. In an explosive blast, the primary injury to the brain occurs when the physical forces emanating from a detonation impart loading on the head and consequently the brain. The definition of MTBI from the American Congress of Rehabilitation Medicine is currently being applied to explosive blast TBI (including loss of consciousness, amnesia, altered mental status, and focal neurologic deficit).[153] A soldier who has been exposed to a blast may lack overt evidence of a head injury, such as lacerations, bruising, or hematomas. Recognizing an MTBI acutely is important so that the soldier can receive appropriate medical attention and be removed from combat-related duty to avoid another TBI.[154] After the first blast exposure, many soldiers do not recognize that they may have been injured, and thus will not seek medical care. The first indication of injury may be persistent postconcussive symptoms, such as headaches, vertigo, short-term memory loss, and difficulty concentrating and multitasking.[154] The clinical presentation of explosive blast MTBI can be confounded by the considerable overlap between the symptoms of MTBI and posttraumatic stress disorder (PTSD), such as mood fluctuations, sleep disturbances, and difficulty concentrating.[155] Both may occur in the same individual. PTSD symptoms usually include bursts of anger, irritability, hypervigilance, and increased startle response.[153,155] Additionally, military service members are frequently subjected to subconcussive blast events during training and deployment that may also have long-term consequences on cognitive functioning.[156]

Anticoagulated Patients

Patients on anticoagulant medications. Most clinical decision guidelines for determining need for CT scan exclude patients who are taking anticoagulants such as warfarin (vitamin K antagonists), antiplatelet medications (aspirin, clopidogrel, prasugrel, ticagrelor), and non–vitamin K antagonists known as direct oral anticoagulants (DOACs) such as Factor IIa inhibitors (dabigatran) or Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, darexaban). Overall, there is a higher incidence of intracranial bleeding in TBI patients on anticoagulants following head trauma, with an incidence of up to 22% in patients with MTBI.[157,158] As a result, most practice guidelines propose that patients who sustain head trauma and are on anticoagulation treatment should undergo a CT scan without contrast.[63] For those on warfarin, an INR should be determined because an initial INR greater than 3 confers a much higher risk of intracranial bleeding.

Some guidelines advocate observation for the first 24 hours following MTBI, along with a second CT scan for those with an initially negative CT.[63,159] However, intracranial bleeding can be delayed beyond the first 24 hours in 1% to 3% of anticoagulated patients and can present as late as 6 weeks following injury.[160] This underscores the importance of detailed patient instructions on discharge from the hospital. In anticoagulated patients with a negative CT scan and a normal neurologic examination, routine admission is not required[160,161] but is recommended for patients at high risk for delayed bleeding (e.g., supratherapeutic INR), those with comorbidities, those who live alone or do not have adequate supervision for neurologic checks, and those who cannot return to the hospital in a timely manner should symptoms of delayed bleeding appear.[63,64]

Antiplatelet medications are more likely to lead to immediate traumatic intracranial hemorrhage (12%) compared with patients receiving warfarin (5%), who are more likely to have delayed bleeding.[162] Compared to warfarin, DOACs have a lower incidence of immediate intracranial bleeding after MTBI.[163–166]

Patients with therapeutic anticoagulation and a negative initial head CT scan do not need to have their anticoagulation reversed.[63,64,167] In patients on warfarin with traumatic intracranial lesions, reversal should be considered. PCCs or fresh-frozen plasma, together with vitamin K can be initiated in the ED.[63,64]

There is inadequate evidence to support the routine use of platelet transfusion for intracranial hemorrhage for patients taking preinjury antiplatelet medications as it does not impact mortality.[69–71] Likewise, while desmopressin has been proposed as a means to improve platelet adhesion in patients taking antiplatelet medications, the available data is insufficient to recommend its routine use.

Dabigatran can be reversed using idarucizumab, a Fab fragment of a monoclonal antibody that binds and inactivates it.[65] If idarucizumab is not available, clotting factor products such as PCCs or fresh-frozen plasma can be used.[66] Dabigatran can also be reversed with hemodialysis. Patients requiring emergent reversal of Factor Xa inhibitors can be treated with Andexanet alfa or 4-factor PCCs.[67,68] Idarucizumab and Andexanet should not be combined with other clotting factor products.

The decision to reverse the patient's anticoagulation must take into account the severity of the injury and the risk of reversal.

Patients with inherent bleeding disorders. The most serious site of bleeding for children and adults with inherent bleeding disorders, such as hemophilia, is the CNS. Intracranial hemorrhage in patients with hemophilia can occur spontaneously or following mild head trauma. Over 50% of hemophiliacs with MTBI who have intracranial bleeding are initially asymptomatic, with a normal neurologic examination. Therefore, patients with inherent bleeding disorders should undergo head CT following a MTBI.[168] There should be a low threshold for factor replacement (e.g., factor VIII or IX, cryoprecipitate, fresh-frozen plasma) in patients with severe hemophilia or in those with MTBI symptoms, even prior to performing head CT.[169]

Head Trauma in Older Adults

Older patients have increased morbidity and mortality from TBI and have higher rates of intracranial injuries following head trauma.[1] They also experience MTBI more frequently than severe TBI. Furthermore, frequent falls put them at risk for repetitive brain injury. Within 7 months following a mild or moderate TBI, older patients can show a decline in language, memory, executive function, activities of daily living, and mood compared with their preinjury functioning and compared to controls.[170] Accordingly, older adults with preinjury warfarin or clopidogrel use are at an increased risk for unfavorable long-term neurologic outcomes compared with similar patients without preinjury use of these medications.[162,171]

With age, the brain atrophies and creates more space within the cranial vault for blood to accumulate before symptoms appear. Moreover, with atrophy comes stretching of bridging veins that may tear and lead to SDHs more easily. Therefore, older adults can have significant hemorrhage into their brain and not show signs of deterioration, especially if their baseline cognitive functioning is impaired. Occult intracranial hemorrhages occur in over 2% of older patients with head trauma. Alcohol abuse is one of the most prevalent comorbid conditions found in older patients admitted to the hospital with TBI, so screening for alcohol abuse in older patients with head trauma is recommended.[172] Elder abuse is an important consideration in this population as well and should be assessed during the ED evaluation.

The presence of comorbid medical conditions, use of anticoagulants, preexisting cognitive deficits, polypharmacy, alcohol consumption, and unique physiology of the aging brain make it challenging for the emergency clinician to detect brain injury.[173] Even low-mechanism falls should prompt health care providers to consider the possibility of brain injury in older patients. Many clinical decision rules recommend CT for patients older than 60 to 65 years following any suspected MTBI. Reducing the risk of falls in older adults can reduce the risk of TBI. Particular attention needs to be given to polypharmacy, drug interactions, safety issues in the living environment, risk of elder abuse, and covert alcohol consumption.

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CHAPTER 33: QUESTIONS AND ANSWERS

1. The primary goal in the emergency care of a head trauma patient is prevention or reduction of secondary insults that are known to worsen outcome after traumatic brain injury (TBI). This includes acutely preventing:
   a. Hypotension
   b. Hypoxia
   c. Malnutrition
   d. All of the above
   e. Hypotension and hypoxia

Answer: e. Avoiding or reversing hypotension and hypoxia is essential in the acute management of TBI patients in the emergency department. Hypotension and hypoxia each double the risk of mortality following TBI.

2. Which of the following statements is true regarding cerebral blood flow (CBF), cerebral perfusion pressure (CPP), and intracranial pressure (ICP)?
   a. CBF autoregulation is lost below a CPP of 60 mm Hg.
   b. CPP closely parallels diastolic blood pressure.
   c. Normal ICP is 65 to 195 mm Hg.
   d. CPP = mean arterial pressure (MAP) – ICP.
   e. The only resistance to CBF is ICP.

Answer: d. CBF depends on CPP, which is the blood flow pressure gradient. CBF resistance is provided by mean systemic venous pressures and ICP, predominantly by the latter. CPP closely parallels MAP offset by ICP; thus, the formula CPP = MAP – ICP. ICP is estimated clinically by the central venous pressure unless a ventricular catheter is in place and ICP can be directly determined. CBF autoregulation is lost below a CPP of 40 mm Hg. Normal ICP is 5 to 15 mm Hg or 65 to 195 mm H_2O.

3. Which of the following parameters are associated with a worsened outcome after traumatic brain injury (TBI)?
   a. Hematocrit (Hct) <30%
   b. Temperature >38.5°C (101.3°F)
   c. Partial pressure of oxygen (Po_2) <60 mm Hg
   d. A and C
   e. All of the above

Answer: e. All of the above. The following are associated with worsened outcomes after TBI:
Hematocrit (Hct) <30%
Temperature >38.5°C (101.3°F)
Systemic blood pressure (SBP) <90 mm Hg
Po_2 <60 mm Hg

4. A 27-year-old man presents after a motor vehicle collision (MVC) with a severe closed head trauma. On examination, you calculate a Glasgow Coma Scale (GCS) score of 5 and a left dilated pupil, with a sluggish pupillary reflex compared with the right. What other finding will your examination likely reveal?
   a. Left carotid bruit
   b. Left foot weakness
   c. Loss of controlled pain/temperature sensation
   d. Right carotid bruit
   e. Right-sided hemiparesis

Answer: e. Uncal herniation is the most common posttraumatic herniation syndrome. The initial pressure compresses the third cranial nerve (CN III), causing ipsilateral pupillary sluggishness, ptosis, anisocoria, and impaired extraocular movements. Contralateral hemiparesis can develop early after an initial normal motor examination. In some cases, the contralateral uncus is compressed, resulting in ipsilateral weakness (Kernohan notch syndrome).

5. A 24-year-old man presents with a closed head injury after a motor vehicle collision (MVC). The physical examination is remarkable for a sluggish left pupil, right-sided hemiparesis, and a Glasgow Coma Scale (GCS) score of 12. What should be the most appropriate next step in this patient's management?
   a. 3% hypertonic saline IV
   b. Intubation and moderate hyperventilation
   c. Mannitol, 1 g/kg IV
   d. Methylprednisolone IV
   e. Pentobarbital IV

Answer: b. The most rapid effect on intracranial pressure (ICP) reduction is achieved via intubation and moderate hyperventilation to a Pco_2 of 30 to 35 mm Hg. The effect peaks within minutes and should be considered a short-term intervention, with an expected ICP reduction of 25%. Prolonged hyperventilation, however, is dangerous. Steroids may worsen outcome after traumatic brain injury (TBI). Mannitol is generally efficacious and exerts an effect within minutes and lasts hours. Other neuroprotective effects include volume expansion, viscosity reduction, cerebral blood flow (CBF) improvement, and free radical scavenging. Hypertonic saline data are encouraging but inconclusive; stronger data exist in the pediatric literature. Barbiturates exert a modest ICP-lowering effect because of their lowering of the cerebral metabolic rate and oxygen demand.

6. What is the minimum time after becoming asymptomatic that an individual should refrain from playing sports after a concussion if no loss of consciousness (LOC) or prolonged posttraumatic amnesia occurred at the time of injury?
   a. 24 hours
   b. 48 hours
   c. 1 week
   d. 2 weeks
   e. 1 month

Answer: c. All current recommendations for return to play after a sports-related concussion state that players with concussion should not return to play for at least 1 week after they have become asymptomatic. This is usually increased to at least a symptom-free month for an extended LOC or prolonged posttraumatic amnesia occurring at the time of the concussion.

7. A 15-year-old boy presents after being hit in the head with a baseball. He has a Glasgow Coma Scale (GCS) score of 7 and a large hematoma of his scalp, anterior and superior to his right ear. In addition, he is noted to have unequal pupils and a sluggish papillary light reflex of the right eye. Which of the following is most likely in this patient?
   a. Central transtentorial herniation
   b. Cerebellotonsillar herniation
   c. Downward transtentorial herniation
   d. Uncal herniation
   e. Upward transtentorial herniation

Answer: d. Uncal herniation is often associated with traumatic extra-axial hematomas in the lateral middle fossa of the temporal lobe. The classic signs and symptoms are caused by compression of the ipsilateral uncus of the temporal lobe on the U-shaped edge of the tentorium cerebelli as the brain is forced through the tentorial hiatus. As compression of the uncus begins, CN III is compressed; anisocoria, ptosis, impaired extraocular movements, and a sluggish pupillary light reflex develop on the side ipsilateral to the expanding mass lesion. This phase may last for minutes to hours, depending on how rapidly the expanding lesion is

changing. As the herniation progresses, compression of the ipsilateral oculomotor nerve eventually causes ipsilateral pupillary dilation and nonreactivity.

Initially, in the uncal herniation process, the motor examination can be normal, but contralateral Babinski responses develop early. Contralateral hemiparesis develops as the ipsilateral peduncle is compressed against the tentorium. With continued progression of the herniation, bilateral decerebrate posturing eventually occurs; decorticate posturing is not always seen with the uncal herniation syndrome. In some patients, the contralateral cerebral peduncle is forced against the opposite edge of the tentorial hiatus. Hemiparesis is then detected ipsilateral to the dilated pupil and mass lesion, termed *Kernohan notch syndrome,* and causes false-localizing motor findings. As uncal herniation progresses, direct brainstem compression causes additional alterations in the LOC, respiratory pattern, and cardiovascular system. Mental status changes may initially be subtle, such as agitation, restlessness, or confusion, but soon lethargy occurs, with progression to frank coma. The patient's respiratory pattern may initially be normal, followed by sustained hyperventilation. With continued brainstem compression, an ataxic respiratory pattern develops. The patient's hemodynamic status may change, with rapid fluctuations in blood pressure and cardiac conduction. Herniation that is uncontrolled progresses rapidly to brainstem failure, cardiovascular collapse, and death.

8. Central pontine myelinolysis is a potential adverse event associated with the administration of which of the following medications?
- **a.** Etomidate
- **b.** Hypertonic saline
- **c.** Mannitol
- **d.** Methylprednisolone
- **e.** Pentobarbital

Answer: b. Central pontine myelinolysis is a potentially adverse event associated with hypertonic saline administration.

9. What percentage of mild traumatic brain injury (MTBI) patients discharged from the emergency department (ED) will continue to have post concussive symptoms at 3 months and 1 year after injury?
- **a.** 5% at 3 months and 10% at 1 year
- **b.** 40% at 3 months and 50% at 1 year
- **c.** 30% at 3 months and 15% at 1 year
- **d.** 5% at 3 months and 5% at 1 year
- **e.** None of the above

Answer: c. Studies of ED patients have indicated that as many as 30% of patients with a discharge diagnosis of MTBI will have symptoms at 3 months postinjury, and up to 15% will continue to be symptomatic at 1-year postinjury.

10. Per the Canadian Computed Tomography Head Rule (CCHR) which criteria are NOT considered "High-Risk" for intracranial injury and possible neurologic intervention?
- **a.** A Glasgow Coma Scale (GCS) score that is persistently <15 after 2 hours
- **b.** Suspected open or depressed skull fracture
- **c.** Vomiting 2 or more times
- **d.** Age over 50 years
- **e.** Any sign of basal skull fracture

Answer: d. All are high risk except D. High-risk are patients age ≥65 years. Other criteria that suggest important brain injury on CT include amnesia before impact ≥30 min and dangerous mechanism (pedestrian struck by vehicle, occupant ejected from vehicle, fall from elevation >3 feet [five stairs]).

34

Facial Trauma

Ryanne J. Mayersak

KEY CONCEPTS

- The face is central to the patient's ability to breathe, eat, and communicate. Injuries to the face can have serious psychological and psychosocial consequences.
- Facial injuries may be prevented by the appropriate use of safety devices including motor vehicular seat belts, child restraints, air bags, helmets, and mouth and face guards.
- The epidemiology of facial injury is changing, with an increasing proportion of injuries occurring as a result of interpersonal violence. A careful history is required, and the possibility of abuse should be considered for every patient.
- Shock from facial trauma is rare and results only from obvious external bleeding. Facial injuries should not distract the emergency clinician from searching for other causes of shock.
- Assertive management of the airway is indicated in a patient with severe facial injuries. Surgical management (cricothyroidotomy) may be required, particularly with penetrating gunshot wounds.
- Directed facial CT scanning is the optimal imaging technique in patients with obvious injuries.
- Definitive facial treatment may be delayed, if necessary, to address other serious injuries.

FOUNDATIONS

Background and Importance

A complex structure vital to the function of the person, the face is comprised of airway openings, entry to the gastrointestinal tract, and special sensory organs, including the eyes, ears, and nose. Facial functioning is essential for eating, speaking, and effective nonverbal communication. The appearance and attractiveness of the face have significant implications for social interactions, sexual attraction, and self-esteem. Patients who have sustained facial trauma can experience long-term sequelae, including unemployment, drug and alcohol abuse, incarceration, marital difficulties, and negative body image.[1,2]

Apart from the immediate threat to the patient's airway and special sense organs, injuries to the face can have serious implications for the patient's mental health[3] and future functioning.[4] Posttraumatic patients with facial injuries often describe physical, financial, social, and psychological loss.[1,5] Multiple studies have demonstrated an association between facial trauma and psychological symptoms such as anxiety, depression, and posttraumatic stress disorder. Several screening tools exist which can be useful in assessing a facial trauma patient's psychological rehabilitation.[1] Some institutions are establishing multidisciplinary evaluations regarding interventions, as well as initiating support groups and online resources for facial trauma patients.[6,7]

Although the emergency clinician's first goal is to address life-threatening problems successfully, the care of facial injuries is aimed at optimizing the patient's function and cosmetic appearance. Four main specialties—ophthalmology, plastic and reconstructive surgery, otolaryngology, and oral and maxillofacial surgery—participate in the care of facial injuries. Early consultation with the appropriate specialist can expedite the care of facial injuries.

Anatomy, Physiology, and Pathophysiology

The face is a complex space encapsulated by a bony structure overlaid with muscle and skin. It includes several special sensory organs—the eyes, ears, nose, and mouth.

Bones

The posterior portions of the face form the anterior wall of the calvaria, placing the face and its features in close proximity with the structures of the central nervous system. The anterior facial skeleton is composed of the frontal bone, nasal bones, zygomata, maxillary bones, and mandible (Fig. 34.1). The sphenoid, ethmoid, lacrimal, vomer, and temporal bones lie deep within the facial structure, providing support and important sites for muscular attachments, including the muscles of mastication, speech, and deglutition. This musculature complex is innervated by cranial nerves IX and X.

Nerve Supply

The most anterior muscle layer includes the muscles of facial expression innervated by the seventh cranial nerve (CN), which lies just inferior to the external auditory canal. The trigeminal nerve (CN V) supplies sensation to the face through three major divisions (I–III). The ophthalmic division (CN V1) supplies the upper third of the face, including the eye and nose down to the tip. The maxillary division (CN V2) provides sensory innervation to the midface and includes the infraorbital nerve. The mandibular division (CN V3) supplies sensation to the lower third of the face.

Ears

The skeleton of the pinna is cartilage covered in closely apposed skin and rolled into a helical shape with a second ridge, the antihelix, defining the inner concha. The external auditory canal, middle ear, cochlea, semicircular canals, and superior origin of the eustachian tube all lie within the temporal bone.

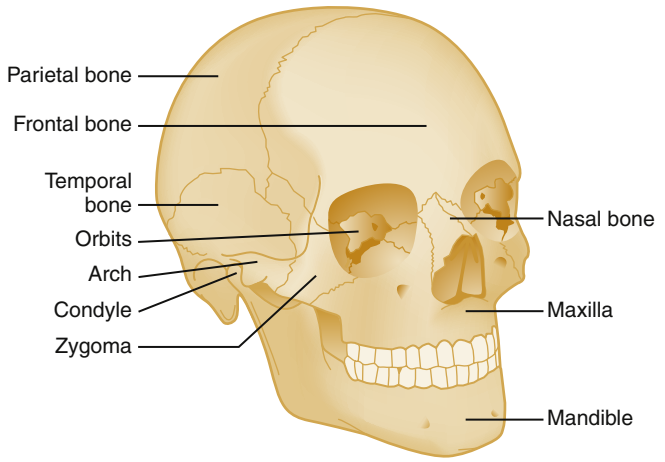


Fig. 34.1 Bones of the facial skeleton.

Eyes

The bony orbit is composed superiorly of the frontal bone. The zygoma forms the lateral wall and lateral floor of the orbit. The medial floor and anteromedial wall are formed by the maxilla. The lacrimal and ethmoid bones complete the medial wall, where the orbit is at its most delicate juncture and vulnerable to injury. The medial wall of the orbit forms the lateral walls of the intranasal space.

Nose

The nose serves as a major entryway for air and is composed of cartilage and bone covered by skin, with mucosa lining the internal surface. Alar cartilage arches over the entrances to the symmetric, mucosa-lined nares, separated by the anterior cartilage of the septum. Superiorly, the nasal bones create the bridge of the nose. With the head held in a neutral upright position, the floor of the nose is perpendicular to the ground and leads back into the nasopharynx, passing the turbinates laterally and bony septum medially. The ethmoid bone lies superiorly and crosses midline, behind the nasal bridge, to form the superior portion of the bony nasal septum and cribriform plate. The vomer makes up the inferior portion of the bony septum, and the palatine process of the maxillary bone forms the posterior floor of the nose and hard palate.

Air-containing sinuses are structural features unique to the facial skeleton. They warm and humidify inhaled air and form chambers that create the unique tone of the human voice. These sinuses develop over the period of human growth. At birth, only the ethmoid air cells and mastoid antrum are aerated. The sphenoid sinus and remainder of the mastoid air cells become aerated at approximately age 3 years. Frontal sinuses form at approximately age 6 years, and maxillary sinuses are not fully developed until age 10 years.

Mouth

The mouth serves as an entryway for the respiratory and gastrointestinal tracts. With the mouth in the closed position, the tongue fills the oral cavity. Single rows of teeth lie within the alveolar ridges of the maxilla and mandible. With the mouth closed, the teeth in normal individuals occlude, with the lower row lying just internal to the upper row. The "usual" occlusion for individuals varies widely; the patient's perception may be the best determinant of whether or not the teeth are meeting and approximating as usual. Anterior to the teeth is the vestibule, a fold of mucosa and flexible soft tissue that allows the lips to remain closed while various motor movements occur behind them. The mandible is a U-shaped bone that forms the chin and completes the lower facial skeleton. Containing the lower row of teeth, the body

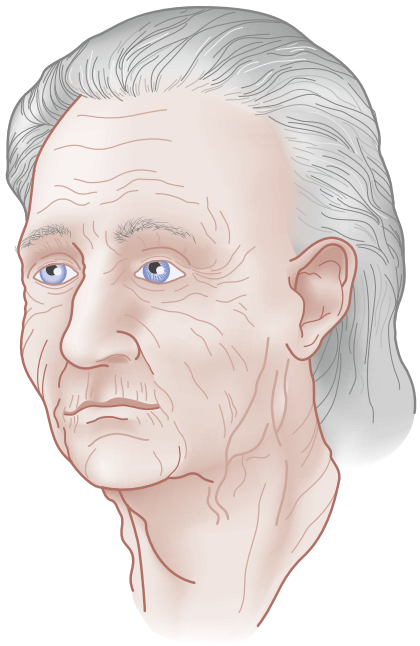


Fig. 34.2 Langer lines—lines of facial expression.

of the mandible meets in midline at the symphysis, which is completely fused by age 2 years. Posterior to the last molar, the bone turns to form the angle of the jaw and continues upward as the ramus of the mandible. At the most superior point of the ramus is the articular surface of the condyle, separated from the superior surface of the temporomandibular joint (TMJ) by an intervening meniscus of fibrocartilage. Anterior to the condyle lies a thin projection, the coronoid process, which provides the insertion point for the temporal muscle.

Temporomandibular Joint

The TMJ is complex, with the condyle of the mandible undergoing rotation and translation anteriorly during normal mouth opening (see Fig. 56.23). The function of the TMJ is preserved by a meniscus, which overlies the condyle. Essentially, the joint between the meniscus and condyle is a hinged joint, allowing rotation, and the joint between the meniscus and temporal bone is a sliding joint, allowing translation. A formal, thick joint capsule does not exist at the anteromedial portion of the joint; loose, relatively weak synovial tissue is positioned here to allow translation to occur.

Soft Tissue, Vasculature, and Specialized Glands

The skin of the face is among the thinnest of the body, draping over the underlying musculature. Facial skin falls visibly into predictable creases with age, following Langer's lines (Fig. 34.2). At the mouth, nares, and palpebral fissures, the skin is contiguous with the mucosa lining these structures. The skin of the lips is particularly thin and lined with vascular papillae, which give the lips their vermilion hue. Lips are particularly important as part of communication; understanding their movement can allow language without sound (such as lip reading).

The face is a highly vascular structure, which can have important implications for the treatment of facial injuries. With the exception of the ophthalmic artery, the superficial blood supply comes from the external carotid artery via the facial, superficial temporal, and maxillary arteries (Fig. 34.3). Soft tissue injuries and fractures that involve these vessels can lead to significant hematomas or exsanguinations. Because the face has extensive anastomotic connections across the midline and between arterial territories, however, ligation of major branches causes minimal ischemia.

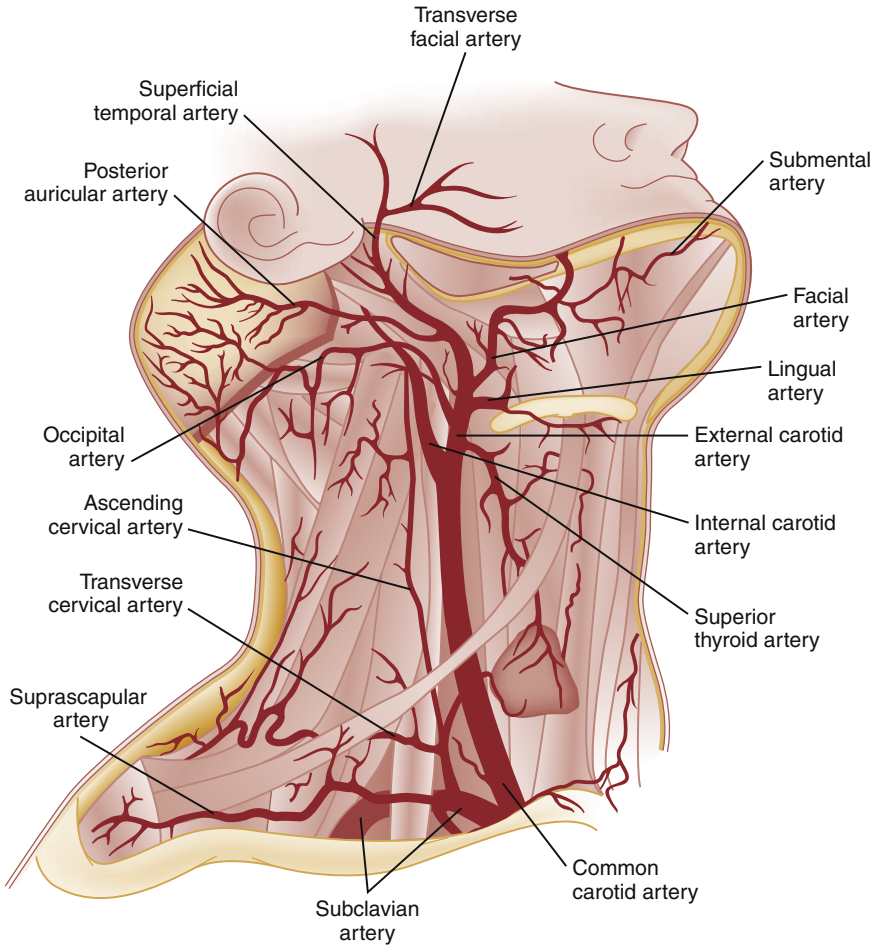


Fig. 34.3 Vessels of the face. (Adapted from Gray H. *Gray's anatomy*. Philadelphia: Lea & Febiger; 1918.)

Buried within the structure of the face are a series of glandular structures and ducts that are susceptible to injury. In the eye, the lacrimal glands lie within the orbits, superior and lateral to the globes, and secrete tears through ductules into the folds of the conjunctiva. The liquid flows medially into the puncta of the lacrimal canaliculi and drains into the lacrimal sac and then, via the nasolacrimal duct, into the nasopharynx.

The salivary system consists of the parotid, sublingual, and submandibular glands. The parotid is the largest of these glands, lying just anterior to the ear and wrapping around the mandible. The parotid is superficial to the masseter muscle and drains via the Stensen duct, a 5-cm tube that curves around the anterior edge of the masseter to enter the mouth opposite the second upper molar. In normal subjects, this duct is large enough to be palpated with the masseter clenched (Fig. 34.4). The sublingual glands lie entirely within the floor of the mouth and drain into the mouth via ductules. They surround the ducts draining the submandibular glands (Wharton ducts). The body of the submandibular gland is folded around the mylohyoid muscle so that a portion lies within the floor of the mouth and a portion lies external to it. The submandibular ducts run from the external portion of the gland to empty into the mouth on either side of the frenulum of the tongue.

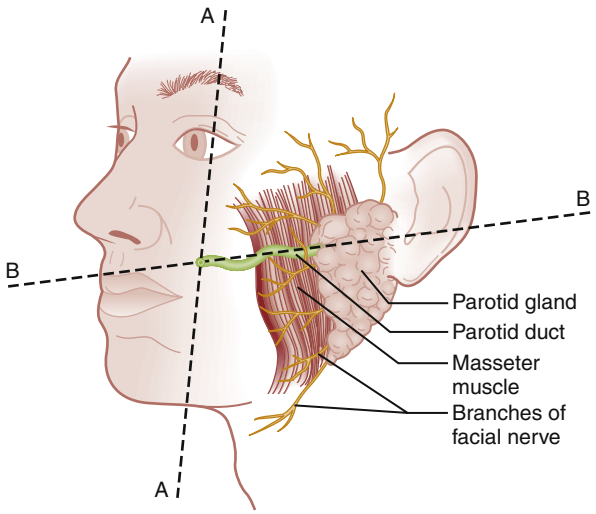


Fig. 34.4 Parotid gland and duct (Stensen), with the surrounding branches of the facial nerve. Line B approximates the course of the duct, which enters the mouth at the junction of lines A and B.

Pathophysiology

The basic mechanism of all injury is the transfer of energy, most often kinetic, to the structures of the body. When the energy overcomes the tolerance of the underlying tissue, injury results. Trauma traditionally has been classified as blunt or penetrating, but in many cases the effect is a combination of the two, such as the forehead injury (contusion and complex laceration) resulting from a child's fall against the sharp corner of a coffee table. The likelihood of injury is related to the amount of energy transferred and condition of the underlying tissue. Significant injury may result when an 80-year-old falls from standing to a carpeted floor, but it is more likely to result when the face strikes the steering wheel or dashboard in a high-speed motor vehicle collision (MVC).

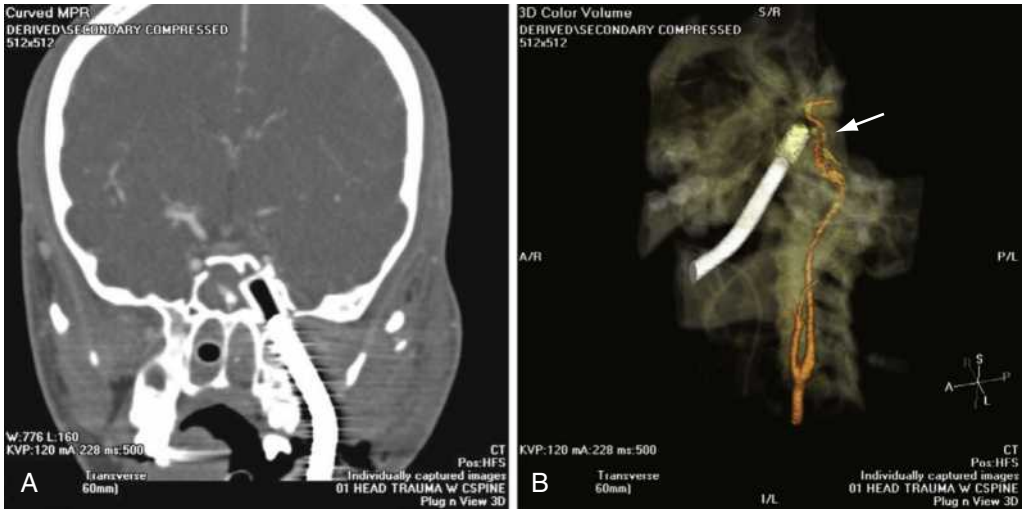


Fig. 34.5 Impalement by a turn signal lever. Computed tomography (CT) scan (A) and three-dimensional reconstruction (B) from a patient impaled through the face into the cranial cavity by the turn signal lever from his steering column when his vehicle rolled over in a single-car crash. The color three-dimensional reconstruction reveals a significant injury to the facial artery *(arrow)*.

The mechanism can be broken down into low-energy events, such as a fall from standing or walking into the corner of a piece of furniture, and high-energy events, such as an MVC. Understanding the mechanism of injury can help predict not only the severity of the facial injury but also the risk of associated cervical or brain injuries.[8] The face does little to protect the brain from traumatic injury. The incidence of traumatic brain injuries (TBI) in facial fractures has been reported to be anywhere between 11% to 80%.[9] Multiple studies have looked at predictive exam findings including Glasgow Coma Scale score less than 8 with loss of consciousness and fracture location site (upper versus midface) to demonstrate a positive correlation between TBI and facial fracture. Recent studies have suggested a significant increase in risk for brain injury among severe trauma patients with multiple facial fractures.[10-12] In addition, a recent review of over 20,000 trauma patients found that subjects with midface fractures are 2.4 times more likely to have a cervical spine injury (CSI) than patients without.[13,14] Cervical spine and brain injuries should be considered based on the trauma mechanism and presentation of the patient without allowing the presence or absence of a facial injury to change the level of suspicion.[15,16]

Penetrating trauma to the face from gunshots, stab wounds, blast debris, or impalement is often obvious and dramatic (Fig. 34.5). The emergency clinician should consider and search for associated intracranial, spinal, or vascular injuries, which are common in these cases.[17] Facial penetration from pellets (BBs) or small blast debris or shrapnel may be less obvious, and the face should be examined for these more subtle injuries. Nonlethal devices for recreation use or use by law enforcement with alternative ammunition (e.g., rubber bullets) can have substantial kinetic energy leading to significant facial and upper body trauma.[18]

Clinical Features

History

The history can provide information about the mechanism of the patient's facial injury. The history, however, may be limited in cases in which the patient's consciousness is altered by a head injury or intoxication, or under circumstances of secondary gain, involvement of law enforcement or suspicion of abuse. Patients with a clear sensorium are able to describe the events leading up to the injury and localize pain, deficits in motor or sensory function, and abnormalities of vision, hearing, taste, or smell. Although the association between facial trauma and brain or cervical spine injury has been debated, these possibilities should be considered, and the patient should be questioned regarding headache, peripheral weakness, numbness or paresthesias.

Physical Examination

Many facial injuries can be identified by simple inspection. During the primary assessment, an essential first step is attention to the patient's airway and inspection of the oropharynx. Airway compromise is often a result of intraoral trauma, and the examiner should note excessive bleeding, drooling, dysphonia, swelling of the tongue or posterior pharynx, and presence of avulsed teeth. When the patient is stabilized, a secondary survey should include a systematic examination of all facial structures and functions. Bony prominences should be palpated for abnormal motion, bony crepitus, tenderness, or step-off. Tenderness and massive swelling associated with facial trauma may preclude reliable palpation of a fracture. Consequently, areas of significant swelling should be imaged radiographically. Assessment of bony integrity includes testing for a possible Le Fort fracture. The upper incisors are grasped and pulled anteriorly. Movement of the upper alveolar ridge (LeFort type I), midface (type II), or entire face (type III) indicates a fracture (Fig. 34.6 and Fig. 34.7). Wounds may need to be palpated for underlying bony injury or foreign objects; anesthesia may be required for a thorough examination within the wound. Complex lacerations involving the cartilage of the nose or ear, eyelids, lacrimal apparatus, eyebrows, or vermilion border of the lips should be identified because their repair often requires advanced reconstructive surgical techniques.

Eyes and orbits. In addition to the examination of lacerations and contusions, the face should be evaluated for symmetry. The appearance of the zygomata may be evaluated by looking at the patient from above. This technique also draws attention to the relative position of the eyeballs. Orbital fractures may result in enophthalmos, and a large retrobulbar hematoma (Fig. 34.8) may cause exophthalmos. The anterior chamber of the globe should be inspected for hyphema or globe rupture. A complete examination of the eye requires specific testing. If the patient is able to cooperate, visual acuity should be documented. Contact lenses should be removed. In the event of a significant potential chemical exposure, the involved eye should be rapidly irrigated with saline or tap water and the pH of the residual eye fluid

measured. Fluorescein examination of the eye should be performed if there is any concern for a corneal abrasion. Victims of MVCs often have particles of glass in the conjunctiva or on the cornea, and these should be sought and removed. Extraocular motions should be tested. Blow-out fractures of the orbit may result in diplopia on upward gaze, secondary to entrapment of the inferior rectus muscle or anesthesia of the midface and upper lip in the distribution of the second division of the CN V. This often is secondary to neurapraxia resulting from a fracture through the infraorbital foramen or compression by a local hematoma (Fig. 34.9).

Oropharynx. The integrity of the mouth and nasal complex may be evaluated by listening to the patient's speech. A muffled or hoarse voice may indicate occlusion of the nose or nasopharynx, whereas dysarthria may indicate a mandibular fracture, tongue injury, or neurologic problem. Oral injury may result in progressive airway compromise, and dysphonia should alert the emergency clinician to the possible need for active airway management. The intraoral examination includes inspection of the palate, teeth, tongue, and gums and palpation with a gloved finger—the latter only if the patient is able to cooperate with the exam. The range of motion of the mandible should be determined. If the maximal incisor opening is less than 5 cm, a mandibular fracture may be present. Trismus is likely to indicate a fracture or significant hematoma within the face. If awake, the patient's impression about the normalcy of bite occlusion is a more sensitive determinant of a fracture of the mandible than the emergency clinician's clinical impression. Being able to perform a tongue blade test (grasping and holding a tongue blade between the teeth while the examiner pulls gently) is associated with a greatly reduced probability of mandibular fracture. If the patient is able to crack the tongue blade by biting on both sides of the mouth, studies have demonstrated the negative predictive value for a mandibular fracture is about 95%.[19] Injury to the parotid area should raise suspicion of disruption of the Stensen duct. The opening of the duct opposite the second upper molar should be examined for bleeding while the gland is compressed. If blood is expressed from the duct or the severed ends of the duct are identified within a facial wound, specialized repair over a stent is often required to prevent formation of a cutaneous fistula.

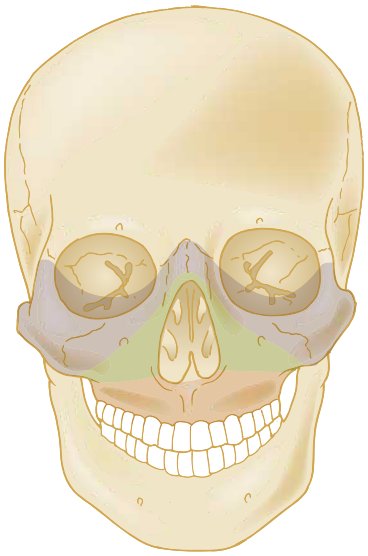


Fig. 34.6 Le Fort classification. Le Fort type 1 is shaded in *red*, Le Fort type II is shaded in *green*, and Le Fort type III is shaded in *blue*.

Ears. Otoscopy is performed to evaluate the integrity of the external canal, look for hemotympanum, and assess for otorrhea. Subcutaneous hematomas of the ear (Fig. 34.10) will require drainage. Clear fluid from the ear after trauma should raise the possibility of a cerebrospinal fluid (CSF) leak and basilar skull fracture. At the bedside, a drop of the fluid may be placed onto filter paper to demonstrate the halo or double ring sign where a rapidly advancing halo of clear fluid around red blood defines a positive test result (Fig. 34.11). This quick bedside test has a sensitivity above 85% when concentrations of blood products and other fluids are relatively equivalent, but does not differentiate between CSF and saline, saliva, or other clear fluids. Leaks can also be detected easily by β_2-transferrin electrophoretic examination, high-resolution computer tomography (HRCT), magnetic resonance cisternography

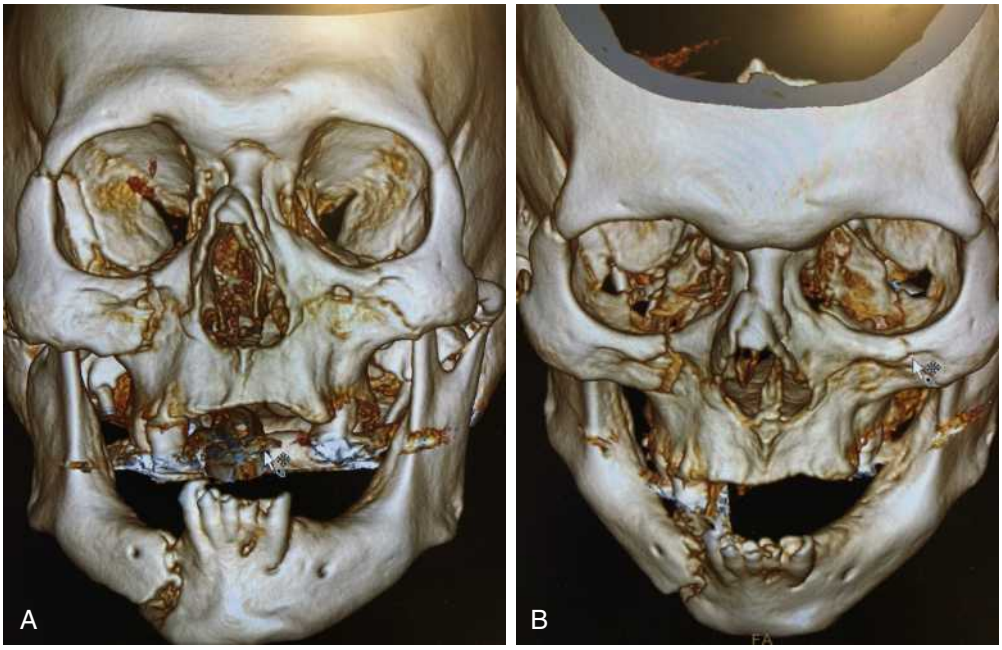


Fig. 34.7 3-D imaging of Le Fort injuries.

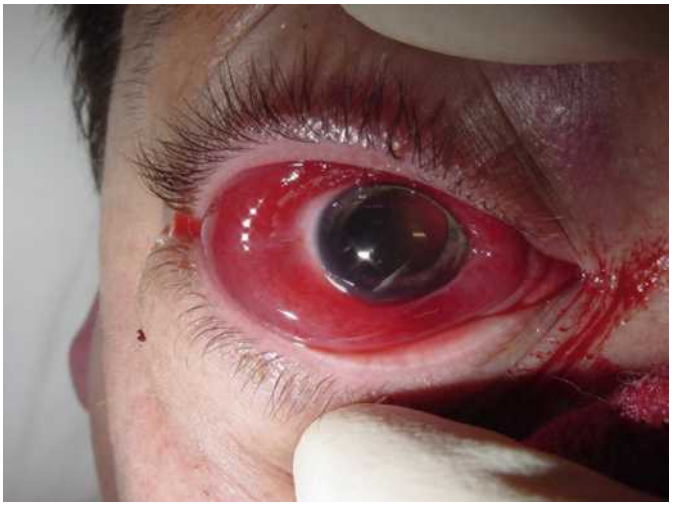
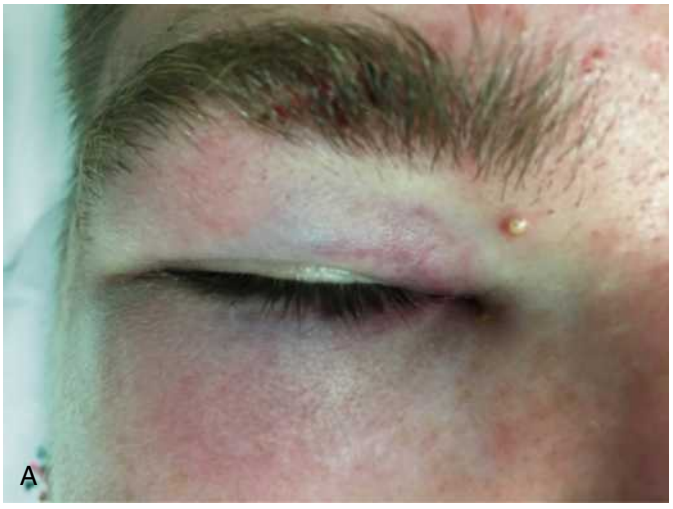


Fig. 34.8 Retrobulbar hematoma. (From Nickson C, Bashed, blind, and bulging. Available at: http://lifeinthefastlane.com/ophthalmology-befuddler-033-2.)



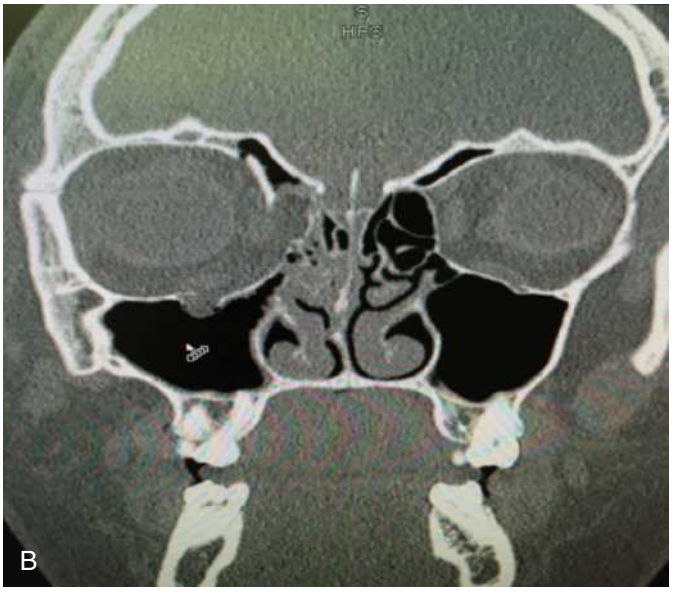


Fig. 34.9 Blow-out fracture. (A) Periorbital swelling and ecchymosis with an eyebrow laceration related to a blow-out fracture. (B) CT scan of a blow-out fracture.

Fig. 34.10 Auricular hematoma. (From Hanna P. Top 7 worst cauliflower ears in MMA history. Available at: www.fightofthenight.com/articles/top-5-worst-cauliflower-ears-in-mma-history.)

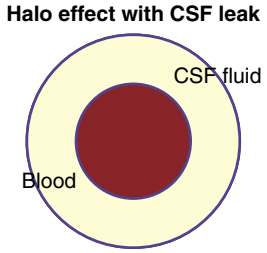


Fig. 34.11 Halo sign seen in CSF leak.

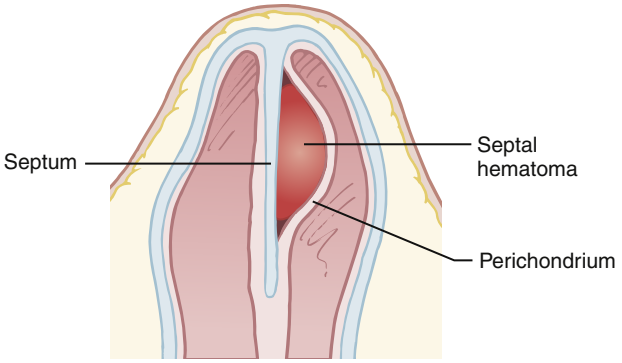


Fig. 34.12 Septal hematoma.

with contrast, and surgical exploration; however, these methods can be timely, costly, or invasive.[20,21]

Nose. The nose is palpated for tenderness, crepitus, or abnormal movement; then each naris is held closed in turn to ensure that the patient is able to breathe through either side. The septum should be examined visually for the presence of a septal hematoma (Fig. 34.12), which appears as a large purple mass extending from the septum. If there is any concern about CSF rhinorrhea, the aforementioned diagnostic filter test may be performed.

Neurologic Examination

Light touch should be tested for all three branches of CN V. Motor function (CN VII) can be examined by having the patient actively wrinkle the forehead, fully open and close the eyelids, smile widely, and bare teeth. Asymmetry of these movements indicates a potential nerve injury. Peripheral injuries to CN VII should cause discernible weakness in the forehead as well as the orbital and oral musculature, whereas central injuries will result in preserved forehead function because of crossing fibers distal in the course of the nerve. In an altered

Fig. 34.13 Facial Contusion. (A) Day 1 with small abrasion and ecchymosis. (B) Day 3 development of periorbital swelling and ecchymosis secondary to gravity. (C) Day 7 continued progression while healing.

or uncooperative patient, CN V (the ophthalmic branch of the trigeminal nerve) and CN VII can be quickly assessed by testing the corneal reflex.

DIFFERENTIAL DIAGNOSES BASED ON ANATOMIC SITES

Soft Tissue Injuries and Lacerations

Soft tissue injuries to the face present an acute cosmetic concern for the patient. Areas of injury may be contused, lacerated, or abraded. When cleaned of any debris, abrasions may be covered in a thin layer of antibiotic ointment and left exposed or covered. Patients with significant debris tattooing will benefit from topical lidocaine for anesthesia before vigorous scrubbing to remove embedded material. A delay in the removal of embedded material will result in further injury due to epithelialization. The patient should be cautioned to anticipate the development of periorbital swelling or ecchymosis over time, if contusions involve the brow, forehead, or bridge of the nose (Fig. 34.13). Head elevation and use of cold compresses may limit the degree of swelling and bruising.

Cosmesis is a priority for patients with facial lacerations and they may request facial specialty services for even minor wounds. Depending upon the size, shape, depth and location of the wound and the commitment of time dedicated to repair, consultation or referral to consultants (otolaryngology or plastic reconstructive surgery) may be appropriate if available. Children and patients with behavioral problems may require sedation to allow sufficient control for a cosmetic repair. Repair of facial wounds in uncooperative patients who are acutely intoxicated may be delayed until they are clinically sober enough to cooperate for the procedure.

The general principles and approach to wound management can be referred to in Chapter 50. Facial wounds should be explored for depth, foreign bodies, and underlying fractures, after appropriate anesthesia has been achieved. Field or facial nerve blocks can be used to minimize local distortion of wound edges. Irrigation may not be necessary in simple, clean facial wounds closed within 6 hours. For nongaping wounds smaller than 3 cm, a single-layer closure may be sufficient. For gaping wounds deeper than the dermis, subcuticular buried sutures of absorbable materials should be placed to close any potential space and relieve any tension on the skin. For simple skin closure, tissue adhesive is faster, less painful, results in equally effective cosmetic results in adults and children, and can be used to close the skin over deeper sutures. Tissue adhesive use is contraindicated to repair complicated wounds (stellate lacerations), animal bites, mucosal surfaces, or across mucocutaneous junctions or high tension areas. Compared with sutures, tissue adhesive has the additional benefit of not requiring later removal, but care must be taken not to glue the eye, nares, or mouth closed unintentionally.[22,23]

Antibiotic therapy use in the management of facial injuries continues to be debated and is highly variable in clinical practice. Given the increasing concerns for antibiotic resistance, minimizing infectious complications, and concern for rising health care expenses, attention has turned to appropriate antibiotic stewardship. Antibiotics are not required for simple facial wounds, which rarely become infected, and are best managed with copious irrigation and careful débridement. Bite wounds, wounds with any evidence of devascularization, wounds through and through the buccal mucosa, wounds involving the cartilage of the ear or nose, wounds with extensive contamination, and the immunocompromised patient are exceptions to this rule. Antibiotics should be selected on the normal bacterial flora that is associated with the affected area.[24-26]

Mouth

Lip lacerations are common and require special consideration to maintain the appearance of the lip edge or vermilion border and natural architecture of the philtrum. Because infiltration of even a small volume of local anesthetic may distort and blanch the soft tissue, marking the vermilion border (with nonpermanent ink) before anesthesia facilitates a cosmetic repair. To minimize any divots and maximize cosmesis and function, wounds that include the muscular layer should be closed in multiple layers. Skin may be closed with nylon or other nonabsorbable sutures; the lip and mucosa should be closed with absorbable sutures. Lip lacerations are not amenable to closure with wound adhesives.

Through-and-through lacerations of the mouth should be closed in layers, beginning with the intraoral mucosa and working outward in layers toward the skin. After closure of the mucosal layer, copious

irrigation of the external wound is indicated to remove lingering bacteria that otherwise might be incorporated into the wound. Prophylactic treatment with penicillin has been shown to decrease the risk of infection after significant through-and-through lacerations. Lacerations that approach the parotid (Stensen) or submandibular (Wharton) duct should be evaluated before intervention for ductal integrity. Saliva milked from the gland should be thin and clear and exit the duct readily. If a duct is involved or there is any doubt, a facial specialist should be consulted for evaluation and repair.[27]

Small lacerations of the tongue or oral mucosa do not require repair. Lacerations that gape (including deep tongue lacerations), collect food, and are likely to heal with a significant divot or thick scar that may hinder eating and speaking functions require repair. Deep or gaping lacerations of the tongue or oral mucosa should be closed (in layers, if necessary) with absorbable sutures that do not require removal. To facilitate repair, an assistant may be needed to expose the laceration by grasping the tongue between gauze and holding a segment outside the mouth. Some advocate placing a thick temporary suture through the distal tongue (after appropriate anesthesia) to facilitate this exposure. Discharge instructions for intraoral lacerations, whether or not they are repaired, should include gentle cleansing (swish and spit) with a mild antiseptic.

Cheeks

Contusions of the cheek should raise concern for an underlying zygomatic or maxillary fracture. Lacerations of the lateral cheek may involve the parotid gland or Stensen duct. Failure to identify and repair ductal injury results in retention of salivary fluid and enlargement of the gland or formation of a cutaneous fistula. Lacerations in the area anterior to the tragus may include injury to the facial nerve, and a careful neurologic examination should be carried out before closure. Langer lines change from mostly horizontal in the superior cheek to diagonal at the nasolabial fold, then curve convexly around the mouth; these changes should be taken into consideration when débridement is required as part of a complex laceration repair.

Nose

Because of its anterior position, soft tissue injuries to the nose are common. Almost any nasal trauma can result in epistaxis. In general, epistaxis is controllable by pinching the cartilaginous anterior nose closed between two fingers and holding compression for approximately 10 minutes. If it is not controlled, anterior packing is indicated. Intranasal inspection is required with nasal injuries to assess for a septal hematoma, which appears as a dark purple or bluish mass against the septum. Hematomas require drainage because they are associated with necrosis of the septum if left untreated. Simple incision and expression of the clot followed by anterior packing are sufficient. Traditional teaching has been that any patient with nasal packing should receive prophylactic antibiotics to cover *Staphylococcus* and *Streptococcus* spp. to prevent sinusitis and toxic shock syndrome. Toxic shock syndrome is a rare but measurable complication of postoperative nasal packing; however, the incidence with primary packing is unclear. There is no evidence that prophylactic antibiotics change this infectious risk. Although there is limited data, systemic prophylactic antibiotics have shown no benefit with nasal packing and are unnecessary.[28] A topical antibiotic, such as chlorhexidine-neomycin (Naseptin), can be used and is a more cost-effective alternative.

Because of the location and structure of the nasal bridge, fractures of the thin bones of this area are common. Patients with contusion or tenderness over the bridge of the nose may be assumed to have a fracture of the nasal bones. If the nose is acceptably straight on initial evaluation, there is no septal hematoma, epistaxis is controlled, and the patient is able to breathe out of each naris, no further evaluation is required emergently for isolated nasal injuries. Dedicated radiographs of nasal bones have little clinical value.

Swelling over the bridge often precludes determination of the acceptability of the appearance at the time of injury. The patient may be provided with a referral for outpatient specialty follow-up in 3 to 5 days if the appearance at that time, when the swelling has subsided, is still unacceptable. In a series of surgically repaired simple nasal bone fractures, septal fractures were present in more than 50% of cases. CT scanning does not provide any advantage in diagnosing septal fractures and should be reserved for evaluating patients suspected of having other, more complex fractures.[29]

Children with nasal fractures may have premature closure of sutures and uneven growth, particularly of the vomeroseptal line. In a child, no imaging studies are indicated for isolated nasal injuries, but a consultant should evaluate swelling and tenderness over the nose, preferably within 3 days with a repeat examination in 7 days once the area of swelling has decreased.[30,31]

Simple lacerations of the nasal skin may be closed with sutures or tissue adhesive. If needed, anesthesia may be achieved with a nerve block of the infraorbital or supratrochlear nerves. The large pores typically present in the area of the nasal ala increase the likelihood of stitch abscesses after laceration closure in this area. Closure with an absorbable running subcuticular suture may limit the risk of this outcome. If involved, the cartilaginous portions of the ala should be closed in a separate layer with absorbable 4-0 sutures. For lacerations through and through the nose, repair should be carried out from the mucosal layer outward, with copious saline solution irrigation between layers.

Ears

Blunt trauma to the ear may cause hematoma formation in the subperichondrial potential space. Such hematomas are the prelude to the development of a so-called "cauliflower ear" and should be drained by aspiration. Re-accumulation of the hematoma is prevented with a compressive dressing of the ear, but reexamination by a specialist is crucial, and re-aspiration should be performed as necessary.

Ear lacerations often involve the cartilage. The ear may be anesthetized with a field block; 1% lidocaine without epinephrine can be used as a local anesthetic for direct infiltration of the ear. 1% lidocaine with epinephrine can be utilized for a regional block. Simple skin wounds may be closed in a single layer. Lacerations to the underlying cartilage should be repaired with absorbable material. If there is significant degloving or loss of overlying tissue, a facial specialist should be consulted. Portions of aural cartilage may be saved temporarily in a distant dermal pocket for later reconstruction. Because cartilage is avascular, chondritis, when it occurs, requires extensive débridement and is disfiguring. No randomized trials have been performed, but when the cartilage of the pinna requires repair, antibiotic prophylaxis covering typical skin flora as well as *Pseudomonas* is recommended. Compressive ear dressings (splints) are indicated after any significant repair. Ear injuries occurring before age 1 year or injuries to both ears in children are less common and should raise the suspicion of abuse.[32]

Eyes

Simple eyelid lacerations may be repaired in a single layer. Wound adhesives should be used with caution anywhere near the eye; care must be taken not to glue the eyelids open or shut. Lacerations that involve deeper structures, loss of tissue, or the lid margin should be referred to a consultant. The integrity of the lacrimal apparatus can be assessed by instilling fluorescein into the eye and assessing for dye in the wound. A facial consultant should repair any injury to the sac or lacrimal duct.[33]

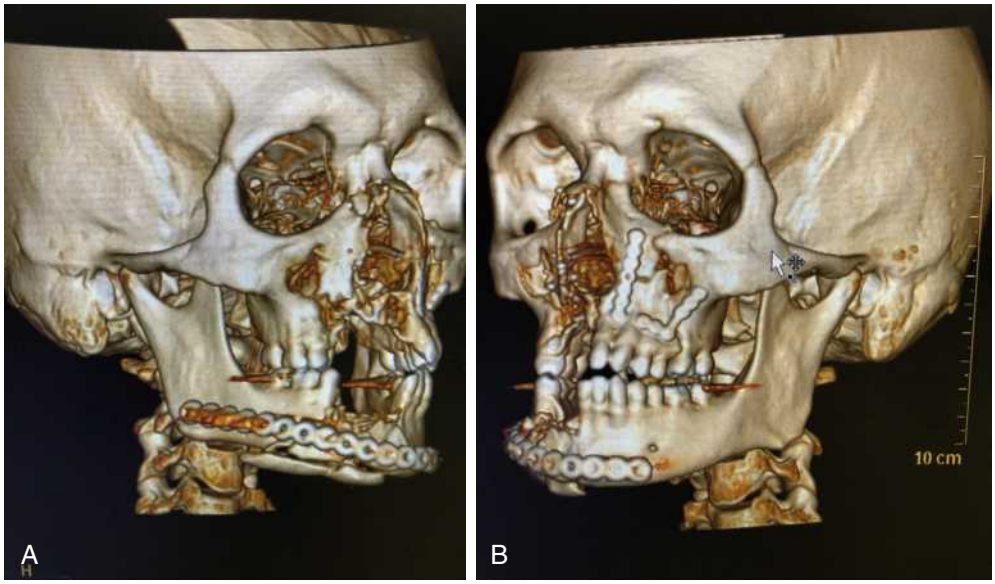


Fig. 34.14 3-D CT image of partial repair of a GSW with microplates.

Eyebrow lacerations are common because of the overhanging supraorbital ridge. Careful wound exploration should be performed to assess the integrity of the underlying bony structure. No shaving should be performed because the brow hairs may not regrow, and the hairs are necessary for realignment. If débridement is required, it should be done parallel to the hair follicles (skived) rather than perpendicular to the skin. This approach minimizes the bald area of the scar. Closing the deeper muscular layers preserves the normal expressive function of the brow. Injuries to the globe are further discussed in Chapter 57.

Fractures and Dislocations

For the emergency clinician, the key to facial fractures is accurate diagnosis and appropriate referral. Many nondisplaced or minimally displaced facial fractures may be managed on an outpatient basis, with definitive repair or fixation delayed several days. In adults, fractures develop firm fibrous union within approximately 10 to 14 days; however, definitive repair is performed most easily before day 7. Facial fractures in young children are relatively rare and may be incomplete or greenstick fractures. Fibrous union in these cases is rapid; early reduction (within 3 days) is recommended.

Broad-spectrum antibiotics treating sinus and nasal pathogens are indicated for open fractures and fractures that violate a sinus. Patients with fractures through the nasoethmoid (NOE) complex that violate the maxillary bones or floor of the orbit should be cautioned to avoid sneezing and blowing the nose because these activities force air out into the soft tissues of the face.

Surgical repair of simple nasal fractures may be performed closed and the nose splinted internally or packed. Repair of fractures of the floor of the orbit, when necessary, may require the placement of a silicone patch to occlude the opening into the maxillary sinus. Operative repair of most other fractures of the face is performed with the use of small metal plates (microplates), screws, or wires to stabilize fragments by attaching them to unbroken segments of bone and if possible, reconstructive efforts are made to preserve facial symmetry. Complex facial fractures may have to be repaired in a staged fashion, depending on the patient's degree of injury and amount and quality of the bone remaining (Fig. 34.14). Much of this surgery is best accomplished when the fragments are still freely mobile but initial swelling has been reduced, on postinjury days 3 to 5.

Forehead

Fractures through the superior forehead may occur above the level of the frontal sinus and represent skull fractures rather than facial fractures and should be addressed with special attention to risk of injury to the underlying brain. Unlike other skull fractures, frontal skull fractures often require repair for cosmesis alone. More often, fractures in this area involve the anterior portion of the frontal sinus. If even minimally displaced, these fractures require elevation for cosmesis. Fractures through the anterior wall of the frontal sinus are likely to continue through the posterior wall, and CT scanning should be performed to assess for this complication; if present, a CSF leak should be assumed until proved otherwise. CSF leaks into the frontal sinus may also manifest in a delayed manner, days or years after the initial injury. For many frontal sinus fractures, complex repair or surgical obliteration may be required to treat this complication.

Orbit

The most common simple fracture of the orbit is a blow-out fracture of the orbital floor, often caused by a fisted blow or ball striking the globe, increasing intraorbital pressure enough to force orbital contents through the floor. This injury may happen without other significant bony facial injury (Fig. 34.15). When displaced, the bony fragments are depressed and sag into the underlying maxillary sinus. If the inferior rectus muscle is entrapped in the defect, the patient is unable to elevate the globe on the affected side, resulting in diplopia on upward gaze. Stretching or compression of the infraorbital nerve, which passes through the floor, may cause anesthesia over the anteromedial cheek and upper lip. Because signs of entrapment may result from contusion and edema and be self-limited, immediate repair is not necessary, but follow-up evaluation is recommended. Repair typically is performed 1 or 2 weeks after the injury for persistent enophthalmos or diplopia. Because of the acute limitation in the visual field, discharge instructions for patients with acute diplopia should include patching for comfort and a request not to drive until the diplopia is resolved.

Fractures of the medial orbital wall, through the lamina papyracea, are often associated with nasal injury or a more general midface fracture, particularly with telescoping of the midfacial skeleton. Herniation of orbital contents into the ethmoids may occur. Patients with orbital fractures with a medial component are more likely to have ocular signs

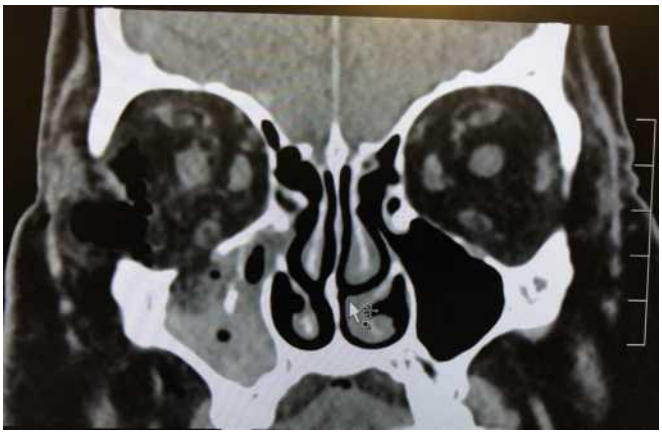


Fig. 34.15 CT imaging of a right orbital floor fracture with subtle downward herniation of the right inferior rectus muscle concerning for possible entrapment.

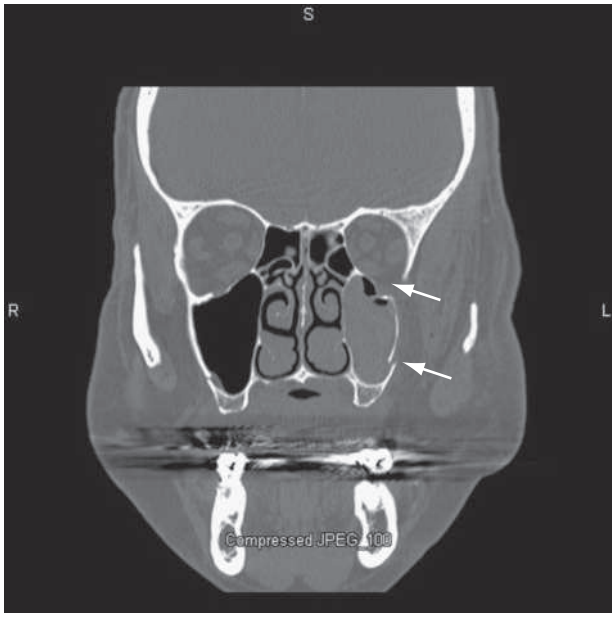


Fig. 34.16 CT scan of fractures of the left orbital floor *(top arrow)* and left lateral maxillary wall *(bottom arrow)*. There is streak artifact from dental devices.

of diplopia or exophthalmos than patients with fractures not involving the medial wall. Fractures involving the superior orbit and the base of the frontal sinus include issues described previously concerning anterior skull injuries. Herniation of orbital structures into the frontal sinus is rare.

Many orbital fractures involve more than one wall of the orbit and may be present in a constellation with complex midface fractures (Fig. 34.16). Several classification schemes aimed at improving communication among emergency clinicians, radiologists, and maxillofacial surgeons have been proposed, but no classification system has been generally accepted.

Injury to the orbit, particularly fractures, can cause a hematoma to form within the orbit, behind the globe. If significant in size, a retro-orbital hematoma can elevate retro-orbital pressure, causing acute exophthalmos and a compartment syndrome of the retro-orbital space. Stretching of the retinal artery limiting flow to the retina or neurapraxia of the retinal nerve may cause decreased visual acuity or blindness.

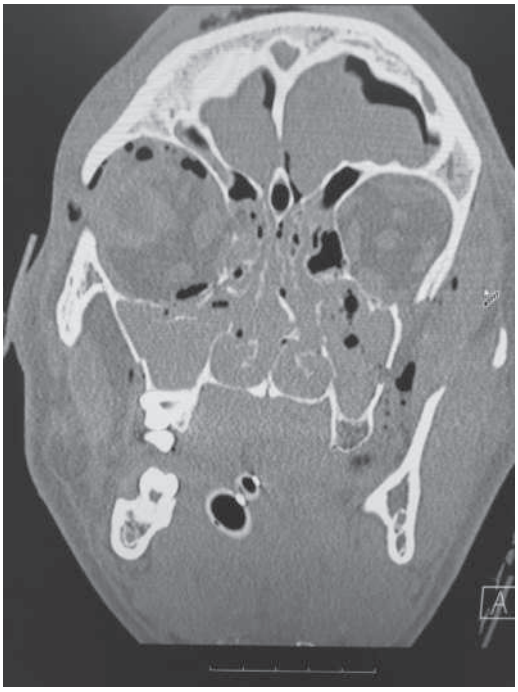


Fig. 34.17 Coronal slice from maxillofacial CT scan of a patient with blunt facial trauma. Acute comminuted fractures of the outer table of bilateral frontal bones, bilateral nasal bones, bony nasal septum, nasal spine, bilateral orbital floor, bilateral lateral and medial orbital walls, roof of the right orbit, posterior wall of the right sphenoid sinus, bilateral pterygoid plates, and anterior, medial, and posterolateral walls of the bilateral maxillary sinuses are noted. There is extraconal air bilaterally. There is near-complete opacification of bilateral maxillary sinuses and bilateral ethmoid air cells with hyperdensity within, suggestive of blood products. There is opacification of bilateral frontal and sphenoid sinuses with hyperdensity within, suggestive of blood products. Endotracheal and orogastric tubes are noted.

Orbital emphysema (Fig. 34.17) associated with fractures of the medial wall or floor rarely results in a space-filling lesion with the same effect. This is a true emergency and drainage of the air or blood via lateral canthotomy with cantholysis may be necessary to save the patient's vision. Needle aspiration of entrapped air may also be attempted, but this may be best left to an ophthalmology consultant, given the proximity of the globe.[34]

Midface

Tripod (or trimalar) fractures are among the simplest fractures of the midface and include fractures of three bones—the lateral orbit, zygoma, and maxilla (Fig. 34.18). Typically caused by a direct blow, these fractures are often displaced and require operative stabilization. If left untreated, the area may sink posteriorly and inferiorly, giving an unacceptable appearance of facial asymmetry emphasized by the inferior position of the orbit and malar flattening. On initial physical examination, there may be a large contusion over the cheekbone, enophthalmos, or malocclusion of the upper teeth. Fractures through the anterior wall of the maxillary sinus may denervate the maxillary teeth because the dentoalveolar nerves transverse through this area.

More complex fractures of the midface are classified with the Le Fort system, although many complex fractures defy this simple system. Other classification systems exist. One system has divided the face into a matrix of vertical and horizontal beams to describe the fracture patterns. Another system has utilized CT scan findings to describe low- and high-impact fractures. Despite the Le Fort system's

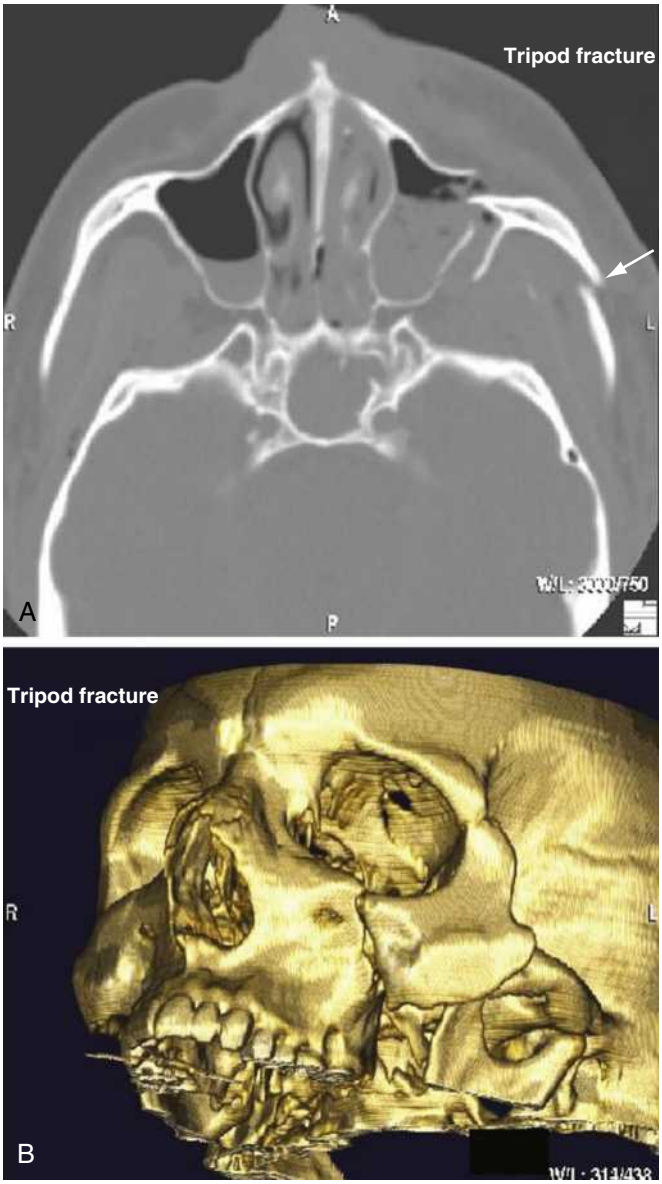


Fig. 34.18 Tripod fracture. (A) CT scan. (B) Three-dimensional reconstruction.

limitations in describing comminuted, complex fracture patterns, it is still the most accepted classification method used. All Le Fort fractures involve the pterygoid plate, and the injury pattern can be unilateral, bilateral, or a combination. A Le Fort I fracture involves a transverse fracture through the maxilla above the roots of the teeth and may be unilateral or bilateral. Patients may report malocclusion, and the maxilla may be mobile when the upper teeth are grasped and rocked. A Le Fort II fracture is typically bilateral and pyramidal in shape. It extends superiorly in the midface to include fractures of the nasal bridge, maxilla, lacrimal bones, orbital floor, and rim. In these cases, the nasal complex moves as a unit with the maxilla when the teeth are grasped and rocked. With CT scanning, the full extent of comminution can be appreciated. Simple Le Fort III fractures are rare and involve fracturing of the connections between the elements of the skull and face (craniofacial dysjunction). These fractures start at the bridge of the nose, extend posteriorly along the medial wall of the orbit (ethmoids), along the floor of the orbit (maxilla), and through the lateral orbital wall, and finally break through the zygomatic arch. Intranasally, they extend through all the lesser bones to the base of the sphenoid and frequently are associated with a CSF leak.[27]

Significant force to the bridge of the nose may fracture the deep naso-orbitoethmoid (NOE) complex without creating a formal Le Fort pattern. Fractures to the central portion of the ethmoid bone (cribriform plate) are likely to be associated with a CSF leak and commonly result in anosmia.

If possible, patients with a CSF leak should have the head elevated 40 to 60 degrees. Head elevation minimizes the intracranial pressure, with the idea of reducing CSF flow and allowing the leak to seal. Often, these patients are treated with antibiotics; however, this practice is controversial, and most of the studies supporting their use involve small, local case series. Although the evidence is equivocal, it is recommended that appropriate prophylactic antibiotics be used in patients who may be immunosuppressed, have an indwelling device, or have an open contaminated wound.[25,26] Neurosurgeons should be involved in the care of patients with CSF leaks, although many leaks will resolve spontaneously.[20]

Fractures involving the deeper structures of the midface may be associated with significant bleeding into the nose or oropharynx. Anterior nasal packing may be performed safely in the adult patient with multiple trauma. Even a 10-cm anterior pack should not reach the skull base in a skeletally mature person. Significant or massive bleeding into the posterior nasopharynx presents a complex problem and occurs in less than 1% of patients with midface fractures. It may be treated with nasal packing and immediate fracture reduction. The use of a long balloon catheter (or Foley catheter) for the control of posterior bleeding should be avoided unless a skull base fracture has been ruled out and the patient's anatomy well understood. The unintended positioning of these items within the intracranial or intraspinal space during blind nasal insertion has been well documented and, when the face is grossly distorted, preinsertion measurement or other methods of preventing this outcome have not been adequately tested. A recent case report documented an intracranial location on CT imaging of a 9-cm Rapid Rhino, placed in the field for epistaxis, secondary to the patient's extensive facial injuries.[35] An alternative method for containing posterior nasal bleeding is to provide compression by packing the area with gauze (soaked with tranexamic acid or TXA) by hand from the oropharynx after intubation.

Zygoma

Isolated fractures of the zygoma are relatively rare, usually the result of a direct blow, and often displaced. Because the condyle of the mandible may disturb zygomatic fragments while moving, fractures with significant displacement are likely to result in trismus or discomfort with mouth opening. Surgical repair is usually required to return the cheekbone to an acceptable position.

Mandible

Fractures of the mandible can result from any significant force applied to its U shape. Because of its shape, multiple fractures may result from a single blow, and the fracture sites may be distant from the site of impact.[36] Depending on the location of the fractures, the patient may have trismus (fractures of the coronoid process, neck, or rami), dental malocclusion, swelling, and tenderness intraorally or externally. Anesthesia of the lower lip may occur if there is damage to the inferior dental nerve.

Fractures of the symphysis, body, angle, or rami usually require early splinting, typically by the placement of arch bars to accomplish interdental fixation, commonly resulting in wiring the jaw shut. Fixation limits fracture motion, decreases the patient's discomfort and, if the fracture is minimally displaced, may provide complete fracture

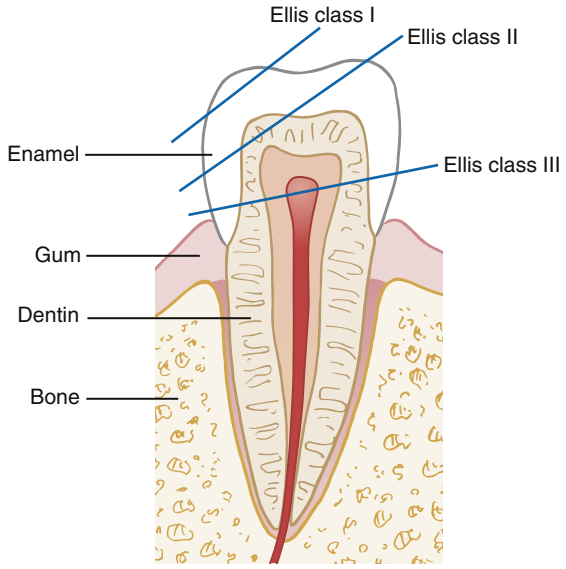


Fig. 34.19 Ellis classification of tooth fractures.

care. Impacted and nondisplaced fractures occasionally are treated with a soft diet and pain control, and fractures of the coronoid alone usually require no intervention, but these decisions should be made in consultation with an oral surgeon or other specialist. Arch bars may be placed in the ED or operating room, typically by an oral and maxillofacial surgery consultant. Fracture reduction may require the extraction of teeth adjacent to the fracture line. Patients with open fractures often require antibiotics and hospitalization. When the fractures are closed and adequate stabilization can be obtained, elective operative repair can be performed as an outpatient procedure in 3 to 5 days.[37]

Pediatric mandibular fracture management depends on the type of fracture (condylar is the most common injury site) and the dental and skeletal developmental phase. Conservative management with soft diet, pain control, and close observation is often utilized for non-displaced uncomplicated fractures. Early closed reduction and shorter immobilization times are usually favored when necessary secondary to the rapid healing time and high osteogenic potential of children compared to adults. Because of the frequency of growth disturbances, children in a mandibular growth phase, younger than 4 or older than 11, who have sustained a blow to the chin and who have any trismus or tenderness over the TMJ should be assessed with Panorex imaging for a condylar fracture and referred appropriately.[31]

Dental and Alveolar Trauma

Trauma to the teeth may occur with or without other facial injury. In the setting of caries, tooth fractures may occur with eating foods. Tooth fractures are classified by the Ellis system. Class I fractures involve only the enamel of the tooth, are not painful, and can await dental evaluation on an outpatient basis. Class II fractures expose the yellow dentin and may be painful. These also can await dental care but may be covered with a dressing of calcium hydroxide and aluminum foil. Class III fractures expose the dental pulp, seen as a red line or dot, and are exquisitely painful. These require early evaluation by a dentist or endodontist (Fig 34.19).

Sufficient energy to the area avulses teeth from their sockets. Multitrauma patients, particularly patients who are intoxicated, required to be supine for cervical spine immobilization, or neurologically impaired, should have avulsed or mostly avulsed teeth removed from the mouth and placed externally in saline to prevent aspiration of the tooth. In a

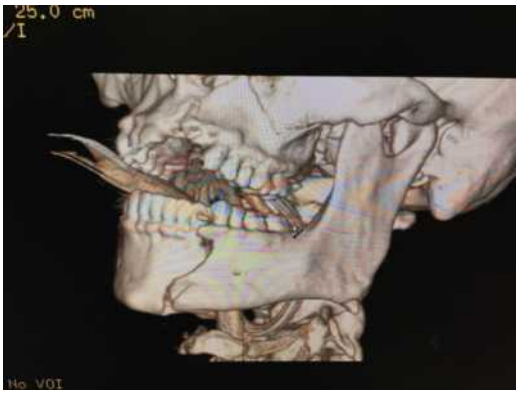


Fig. 34.20 Left comminuted fracture of the parasymphyseal mandible involving the alveolar ridge and extending to the root of the first mandibular molar. An endotracheal tube is also present.

critically ill multitrauma patient, avulsed teeth should be among the lowest priorities and are reimplanted only if the care of other injuries allows it, and there is little risk of aspiration if the teeth loosen.

To perform a reimplantation, the emergency clinician disturbs the socket as little as possible, gently rinses off the tooth (the root should not be wiped), and places it into the socket where it clicks into place. If the tooth is only partially avulsed, extruded, or laterally luxated, it should not be removed; it should be reimplanted or relocated. Intruded teeth should not be manipulated. Reimplantation can be painful and may require local anesthesia with a regional dental block. Alternatively, the area of a single socket may be anesthetized by placing approximately 0.5 mL of 1% lidocaine with epinephrine into the buccal sulcus and gum on the outer side of the alveolar ridge. After reimplantation, the tooth requires stabilization with acrylic splint or wiring to the adjacent teeth. Appropriate antibiotics such as penicillin and tetanus immunization prophylaxis should be given, as well as dental follow-up for possible root canal if the reimplantation does not take.

It may take weeks to assess the final success of reimplantation. The extra-alveolar time, periodontal state, and storage process are important factors in the initial success. Teeth that are successfully reimplanted within 20 to 30 minutes have fewer complications, including signs of inflammation and bone resorption. Studies also have shown that age is a factor in root resorption of teeth that have prolonged avulsion times.[38,39]

In children, the front maxillary incisors are frequently avulsed in facial injuries. After reimplantation, these teeth may ankylose and fail to grow normally, requiring later extraction or orthodontic intervention for cosmesis. This situation is most common in children aged 6 to 10 years with avulsed adult teeth.

Efforts should be made to ensure that the aspiration of avulsed teeth is ruled out after significant trauma, especially if the patient is intoxicated or is neurologically impaired. A chest x-ray examination may be used for screening for aspiration in an acute event. If the tooth is visualized below the diaphragm on radiograph, it does not require retrieval. Teeth lodged in a bronchus or the esophagus require bronchoscopic or endoscopic retrieval. Aspirated teeth result in pulmonary abscess formation unless removed.[36]

Fractures through the alveolar ridge may result in a group of teeth being dislodged and out of position, often leaning inward. These teeth require stabilization with wire or acrylic splinting after fracture reduction has returned the teeth to their correct location. The involved teeth may or may not survive after such a fracture, and follow-up with a dentist or oral surgeon is required (Fig. 34.20).

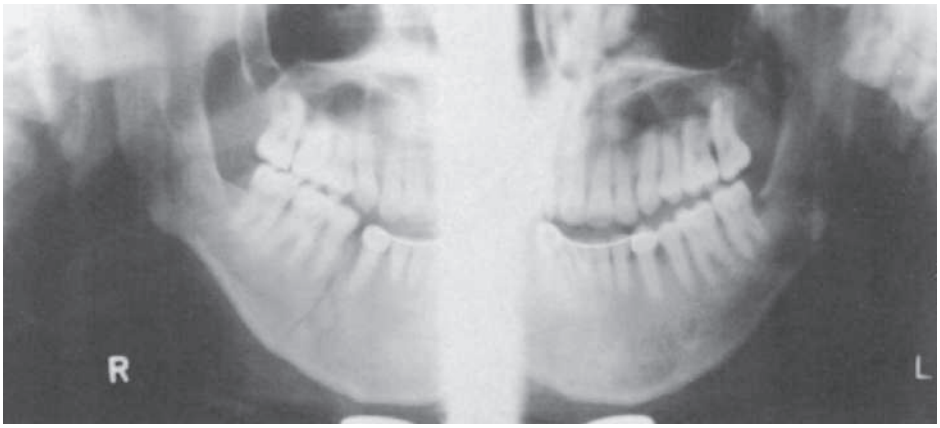


Fig. 34.21 Panoramic radiograph of the mandible shows fractures through the left angle and right body. A dental appliance is in place on the lower incisors.

Temporomandibular Joint

Trauma to the TMJ may tear the meniscus or injure the collateral ligaments holding it in a normal position. This injury can cause the meniscus to fail to translate normally, resulting in clicking or popping as it catches up to the condyle or inability to open the mouth fully because the meniscus fails to translate completely. Patients without fracture but with acute pain and difficulty with mouth opening should be placed on soft foods, asked not to yawn or struggle to open their mouths widely, and referred to an oral surgeon with expertise in TMJ pathology. Pediatric patients with posttraumatic internal derangements of the TMJ are prone to asymmetry of facial growth and retrognathia.

Anterior dislocation of the TMJ can occur after any activity that involves spontaneous wide opening of the mouth. When the condyle is out, spasm of the muscles of mastication prevents spontaneous reduction. Significant trauma is more likely to cause a fracture-dislocation. Simple dislocation may be unilateral or bilateral, and the patient may report being unable to close the mouth. In unilateral dislocation, the jaw is rotated laterally away from the affected joint; bilateral dislocation causes significant protrusion of the jaw. The jaws of these patients are often locked in an open position causing drooling and difficulty handling secretions. Speech is often garbled by the patient's inability to touch the tongue to the roof of the mouth or maxillary teeth. There is a depression in the area of the affected TMJ on inspection of the patient's facial contour.

If the mechanism of injury suggests a fracture, the area should be imaged with plain radiograph or Panorex examination before reduction is attempted. For reduction of a simple dislocation, the patient should be seated upright. For leverage to be maximized, the best position may be for the patient to be seated in a regular chair, with the operator standing in front of the patient. As in dislocations of other joints, adequate analgesia and sedation are required for success. With the thumb or index finger placed into the buccal sulcus on either side of the mouth, the angle of the jaw is pressed downward while the symphysis is rotated (chin) upward and backward. Care should be taken not to place fingers along the crowns of the teeth; when relocation occurs, spasm of the muscles of mastication snaps the mouth shut with force. If this is the only location possible for the emergency clinician's fingers, gauze wrappings should be placed to protect them from injury.

DIAGNOSTIC TESTING

Imaging

The choice of imaging for facial fractures depends on the patient's stability, patient's ability to cooperate, and availability of various options. The two main options are plain radiograph examination for isolated injuries and CT scan. Fractures are better visualized with CT than with magnetic resonance imaging (MRI), so MRI is not an optimal imaging choice. In patients in whom a fracture or penetrating injury is obvious from the physical examination, high-resolution CT (HRCT) is the imaging modality of choice. Head CT scans do include portions of the facial skeleton, but in 35% of trauma patients operative facial injuries are missed. A dedicated facial HRCT should be considered for patients with severe trauma, altered sensorium, and positive physical exam findings such as swelling, ecchymosis, wounds, lacerations, and bleeding. Technical components such as slice thickness, field of view, and reformatting capability available with dedicated facial CT imaging aids in treatment management including surgical planning.[40-43] For a complete evaluation, CT scans of the face should include axial, coronal, and sagittal reconstructions. The accurate interpretation of facial CT scans require attention to bones, sinuses, orbital contents, and soft tissue and should be reviewed by a radiology consultant.

CT imaging is the first choice for all patients in whom a midface fracture is suspected. However, when cross sectional imaging is not immediately available, patients with a low to moderate pretest probability of a midface or maxillary fracture and who are stable and able to cooperate, can be screened with a single facial radiograph (using a Waters or occipitomental view). CT imaging is indicated if the radiograph is positive for a fracture or air-fluid level is noted in any sinus.

The U shape of the mandible and presence of nearby bony structures make isolating the mandible on flat film difficult. Simple radiographs of the mandible are less sensitive than Panorex radiographs and particularly tend to miss fractures of the condyle (Fig. 34.21). If available, Panorex imaging is indicated for a first episode of TMJ dislocation, isolated mandibular fractures, dental fractures, or fractures of the alveolar ridge. In children, if fracture of the condyle is suspected, coronal CT is more sensitive and specific than Panorex studies. Although the traditional teaching has been that the mandible's shape results in "two fractures if it is fractured at all," a case series using CT evaluation found that 40% of mandibular fractures are unifocal.

For patients with complex fractures, new imaging techniques, such as 3D volume rendering, orbital volumetry, and cone beam CT, may help improve surgical planning and esthetic outcomes. In displaced orbital fractures, use of CT data to measure orbital volumes has shown that after repair, an orbital volume greater than 4% larger than on the unfractured side is associated with visible postoperative enophthalmos. This method is most useful in predicting which patients might benefit from operative repair. In conjunction with more standard two-dimensional facial CT scans, three-dimensional CT scans seem to

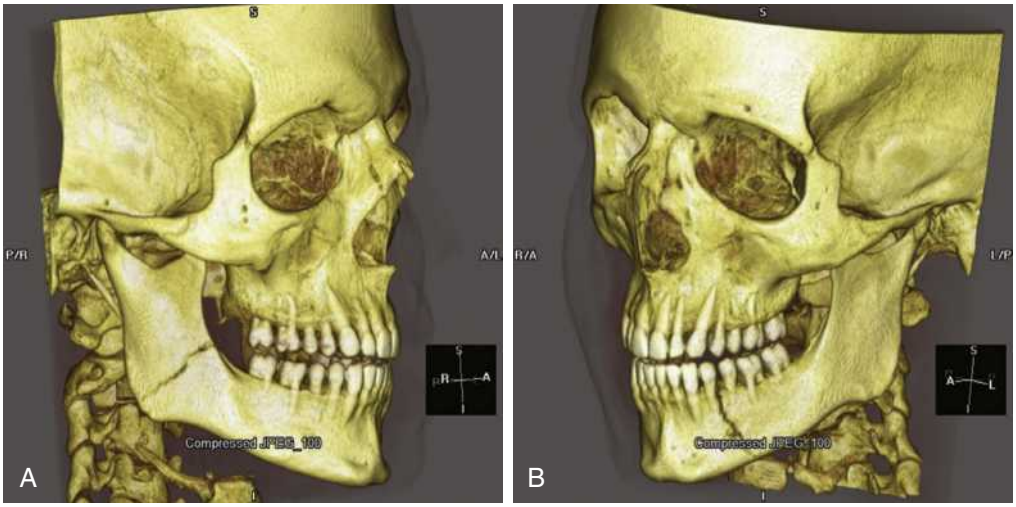


Fig. 34.22 (A–B) Three-dimensional CT reconstructions of minimally displaced mandibular fractures in the same patient as in Fig. 34.5.

TABLE 34.1 Blunt Cerebrovascular Injury (BCVI) Screening Criteria (The Denver Health Medical Center Criteria)

Risk Factors		Signs and Symptoms
High-energy traumatic mechanism	Severe facial fractures (LeFort II or III)	Arterial hemorrhage of neck, nose, or mouth
Complex skull fracture	Mandible fracture	Cervical bruit in patients <50 years of age
Severe traumatic brain injury (TBI) or GCS <6	Hanging or clothes-line neck injury	Expanding cervical hematoma
Seatbelt injury with abrasions, swelling, or pain	TBI with thoracic injuries	Neurologic deficits not consistent with CT examination
Thoracic injuries	Blunt cardiac rupture	Focal neurologic deficit
Scalp degloving	First rib fractures	Stroke on CT or MRI imaging

improve the diagnosis and aid preoperative planning for patients with complex fractures of the midface (Fig. 34.22).[44]

Blunt cerebrovascular injury (BCVI) incidence is still not fully known, with a reported 1% to 2% in the in-hospital trauma setting. CT angiography (CTA) should be used as a screening and diagnostic tool when evaluating for BCVI. This is an evolving area in which 20% of injuries are still missed until patients become symptomatic and are often outside the therapeutic window, with potentially devastating neurologic consequences. BCVI requires a high index of suspicion (Table 34.1) and should be considered in any patient with a cervical spine fracture, neurologic examination that does not fit the diagnostic picture, and patients with Horner syndrome. Additional considerations include LeFort II or III fractures (severe facial injuries), skull base fractures, or soft tissue injuries of the neck. The gold standard for diagnosis is angiography; however, CTA should be considered as part of the initial trauma evaluation protocol (Fig. 34.23).[45-47]

Patients with tenderness and swelling isolated to the bony bridge of the nose who do not have a septal hematoma, can breathe through each naris, and have a straight nose, do not require nasal bone radiography in the ED because imaging results would not alter treatment. If these criteria are not met, early reduction by a specialist or referral for surgical intervention may be indicated, and evaluation by plain films or ultrasonography (for truly isolated injuries) or CT scanning (if concern for other injuries exists) is indicated.[48] Plain radiograph examination may also be performed in the setting of legal concerns. If there is concern for a foreign body in a superficial wound, two standard x-ray

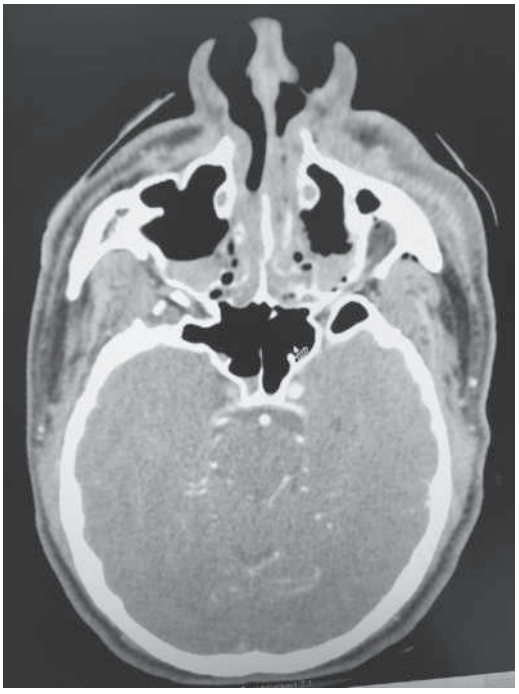


Fig. 34.23 CT angiography slice of the head and neck from a moped accident patient. There is no flow seen in the right internal carotid artery, suggestive of a blunt cerebrovascular injury.

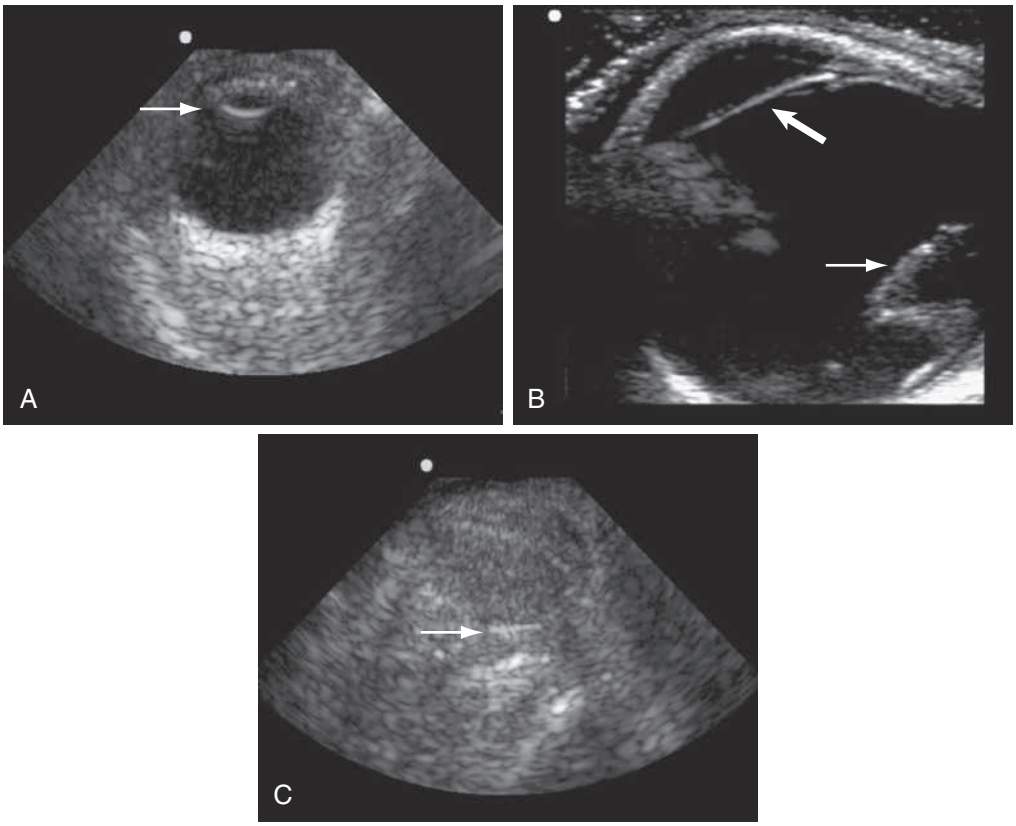


Fig. 34.24 Bedside sonograms of the eye. In each image, a small *white dot* is placed to identify the front of the eye, and *thin arrows* identify the lens. (A) Normal eye. (B) Detached retina. The large arrow is pointing to the lens of the eye, and the smaller arrow is pointing to the detachment. (C) Ruptured globe *(arrow)*. (Courtesy Dr. Keith Boniface.)

views (Waters and Caldwell, or occipitofrontal views) are indicated to triangulate the position of the observed foreign material.

Patients with suspected ocular injuries may benefit from bedside ultrasound as a noninvasive and cost-effective diagnostic tool, particularly if there is a need for urgent operative management of other injuries and no time for a dedicated facial CT scan. The different acoustic impedances of the orbit's anatomic structures make this modality operator-friendly, and an ultrasound of the eye can readily detect lens dislocation, vitreous hemorrhage, retinal detachment, and globe rupture (Figs. 34.24 and 34.25).[49] The operator should position the transducer in a transverse orientation, scanning in a cephalad to caudad direction, making sure to scan the entire anatomy of the eye, and using special care to minimize the pressure exerted over the eye, especially when evaluating for a specific ocular emergency. Prior findings have suggested that high-resolution ultrasound has a 94% correlation with axial and coronal CT imaging in the detection of orbital fractures and emphysema. A recent study demonstrated the high sensitivity and specificity of ultrasound in identifying traumatic ocular injuries including lens dislocation and retrobulbar hematoma compared to CT imaging.[50]

MANAGEMENT

Management of facial injuries occurs within the overall resuscitation of the patient (Table 34.2). Unless the airway is threatened or exsanguination is a concern, treatment of most facial injuries can be deferred until more life-threatening injuries have been stabilized. Care of the patient with penetrating trauma to the face should center on standard trauma care, with initial attention focused on maintenance of a patent airway, adequate ventilation, and systemic perfusion.

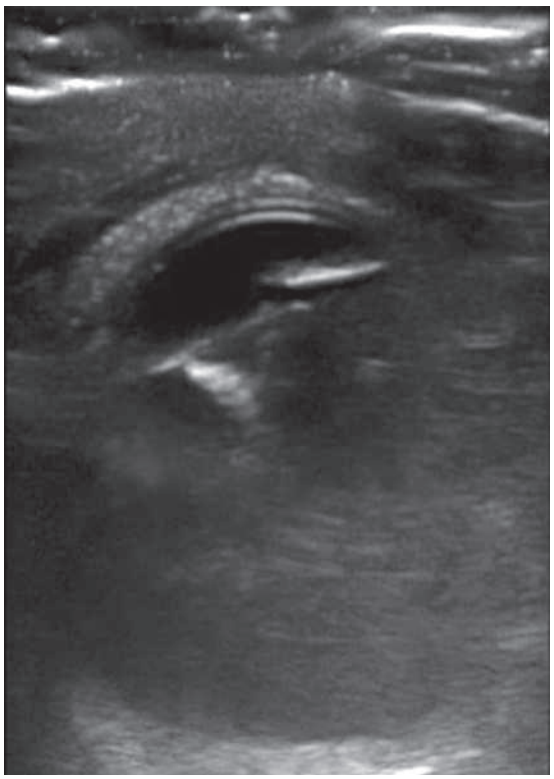


Fig. 34.25 Ultrasound image of a globe rupture with lens dislocation. At the top of the image, the cornea is visible, and just below that is the dislocation, with hemorrhage visible posteriorly.

TABLE 34.2 Key Concepts in the Clinical Approach to Facial Injuries

ASSESS ABCS AND INTERVENE APPROPRIATELY

HISTORY CAN HELP DIRECT YOUR EVALUATION (VISION LOSS, NUMBNESS, CHANGE IN BITE)

INSPECT AND EXAMINE

Injury Site	Presentation	Imaging	Management
Frontal Bone	1. Significant traumatic mechanism 2. AMS 3. Tenderness and edema over frontal bone, CSF rhinorrhea	CT scan imaging: head, C-spine, and max-face	1. ATLS protocol 2. Consultation with appropriate subspecialties
Orbital	1. Ocular deformity (exophthalmos) 2. Limited ocular movements 3. Visual symptoms	CT scan imaging of the orbits with thin-sliced helical cuts	1. Ophthalmologic evaluation 2. Follow up in 1 week 3. Avoid nose blowing or sneezing with a closed mouth
Nasal	Most commonly fractured facial bone 1. Deformity 2. Swelling and tenderness 3. Epistaxis	Imaging not necessary for isolated injury US is useful Complex and/or associated injuries require CT scan	1. Treat any septal hematoma and epistaxis 2. Closed reduction can be considered 3. Otolaryngology follow-up
Midface	1. Tenderness 2. Deformity 3. Bleeding 4. Malocclusion 5. Paresthesias	CT scan with 2-mm axial and coronal cuts, consider orbital imaging if needed	1. Control bleeding 2. Surgical consultation
Mandibular	Second most common injury 1. Trismus 2. Bleeding 3. Ecchymosis 4. Fractured or loose teeth, abnormal bite 5. Paresthesia	Panorex imaging for an isolated injury and in pediatric cases High clinical suspicion and concern for other injuries CT scan	1. Control bleeding 2. Dental involvement should be treated as an open fracture with appropriate antibiotics 3. Surgical consultation

Out-of-Hospital Care

The indications for airway management of a patient with a facial injury are the same as those for other patients. Does the patient have a currently patent airway and, if so, can the patient be expected to maintain an airway without intervention? If the answer to either question is "no," the patient needs to be intubated. If other injuries preclude the patient from ventilating appropriately, intubation is also required.

Patients with expanding hematomas after facial injury present a particular dilemma. Injuries to the facial vasculature may cause significant hematomas that can extend into the neck or down to the supraclavicular area. Such hematomas greatly distort the normal anatomy of the pharynx and neck, making intubation and cricothyroidotomy particularly difficult. If the patient has a patent airway, he or she can speak without difficulty, and the transport time is expected to be short, no intervention should be performed. The receiving institution should be notified so that planning and set-up can begin in anticipation of a difficult airway. If intubation must occur in the field, awake orotracheal intubation should be considered. If certified in its use, emergency medical services personnel should be ready to perform a surgical airway as needed. Gunshot wounds to the lower third of the face are particularly likely to require intubation for airway protection, and a significant proportion of these require a surgical airway.[51,52]

In the setting of significant facial trauma, active bleeding can obscure the view and make intubation considerably more challenging. Double suctioning may be required, which involves an assistant holding one suction catheter in the posterior oropharynx while the operator uses a second device more anteriorly or inferiorly, as needed during the procedure. Conversely, patients with fractures of the mandible may be easier to intubate because increased mobility of the mandible may allow wider opening of the mouth.

BOX 34.1 LEMON Criteria[1]

L = Look externally (facial trauma, large incisors, beard or mustache, large tongue)
E = Evaluate the 3-3-2 rule (incisor distance, 3 fingerbreadths; hyoid-mental distance, 3 fingerbreadths; thyroid to mouth distance, 2 fingerbreadths)
M = Mallampati (Mallampati score > 3)
O = Obstruction (presence of any condition such as epiglottitis, peritonsillar abscess, trauma)
N = Neck mobility (limited neck mobility)

[1] Patients in the difficult intubation group have higher LEMON scores.

Patients with multiple injuries should be resuscitated following Advanced Trauma Life Support (ATLS) protocol, and those who require intubation should have a LEMON assessment (Box 34.1) followed by rapid-sequence intubation, which has a higher success rate and fewer complications. Some alternative airway techniques may include submental or submandibular intubations or anesthesiology-assisted intubations with the use of adjuncts such as the C-Mac, GlideScope or lighted stylet.[53-57]

Control of local bleeding is the other significant out-of-hospital consideration in facial trauma. In many areas, external compression is sufficient to control bleeding during transport. Epistaxis and significant intraoral bleeding can be more difficult to manage. Even in the setting of significant nasal trauma, the soft portions of the nares can be

compressed to stop anterior nasal bleeding. In an awake alert patient with intraoral bleeding, 4- × 4-inch gauze packing may be placed into the buccal space to provide control. If these maneuvers are insufficient, and the patient's injuries require spinal immobilization, intubation may be a necessary first step to control intraoral or nasopharyngeal bleeding. After intubation, large amounts of gauze can be placed via the mouth into the oropharynx and nasopharynx to obtain control via direct pressure.

If out-of-hospital personnel suspect a ruptured globe, special protection against compression of the eye (shielding) should be provided in the field. Avulsed parts, including the ears, tip of the nose, teeth, or completely avulsed flaps, should be transported with the patient in saline-soaked gauze.

Completely avulsed teeth should be removed and carried with the patient during transport. Neurologically alert, unimpaired patients may be able to carry avulsed teeth in their mouths, held between the gum and buccal mucosa. Patients who are neurologically impaired, are intoxicated, require cervical spine immobilization, are nauseated, or cannot be transported upright should not be transported with avulsed teeth held in the mouth. In such cases, the risk of aspirating the teeth outweighs any other concerns, and the teeth should be transported in a container with sterile saline. Incompletely avulsed teeth should be left in place and not manipulated.

Emergency Department Treatment

The initial evaluation in the ED should focus on assessment and control of the airway. In the setting of significant distortion of the mouth, oropharynx, or upper neck by avulsion or hematoma, the awake fiberoptic method may optimize the chances of a successful intubation. When there is significant distortion of the oropharynx or larynx, a laryngeal mask airway may not achieve a sufficiently tight fit to allow ventilation. Emergent cricothyroidotomy is the procedure of choice if timely endotracheal intubation is not possible.

Unless there is life-threatening hemorrhage from the face, facial injuries can be safely left to the secondary survey after the airway has been secured. The emergency clinician should avoid being distracted by a facial injury and search instead for head, neck, chest, abdominal, pelvic, and extremity injuries. In-depth ocular examinations and other special testing should not be performed until other serious injuries have been managed emergently.

Significant bleeding can often be controlled by compression. If compression fails, hemostasis can be achieved in the ED by ligation of the relevant vessel. Great care should be taken, however, not to clamp or tie structures blindly deep within the face because serious iatrogenic injury of nerve or ductal structures could result. Massive uncontrollable bleeding from facial fractures occurs rarely and is best treated with arterial embolization, if available.[58] Intraarterial vasopressin has also been suggested as an option for hemostasis. Tranexamic acid may also be effective in controlling hemorrhage from facial trauma.[59,60]

In the rare case of acute exsanguination from a facial wound, the external carotid artery can be emergently ligated. This ligation is best accomplished with surgical assistance.[61]

Bite wounds, gross contamination, or significant tattooing from foreign bodies should be addressed definitively as soon as possible, given the needs of the patient's other injuries. Definitive treatment of simple soft tissue injuries can be left for 24 hours, if needed, after irrigation and temporary approximation. Ideally, facial fractures are treated early, before significant swelling occurs, or after several days, when return of more normal facial contours can aid in the repair. The need for tetanus prophylaxis should be considered for all open wounds. If the injury is an animal bite, the need for rabies prophylaxis should be considered. Because the rabies virus is transmitted to the brain along nerve axons, and symptomatic disease theoretically may occur sooner with wounds of the head, face, and neck, initiating rabies treatment within 5 days of the injury is recommended.[22]

Because lead poisoning has been reported from the ingestion of shotgun pellets in patients with primarily facial injuries, consideration should be given to looking for the presence of pellets in the gastrointestinal tracts of these victims. A plain radiograph of the abdomen will suffice. Early endoscopic removal of the pellets should limit future toxicity.

The final part of the physical examination when dealing with facial trauma is the importance of documentation. Facial injuries may be evidence of assault, domestic violence, or child abuse. Careful documentation of findings, including photographs, drawings, or both, not only communicates initial findings to other health care specialists but also can provide crucial legal evidence because many of these cases have forensic implications or result in litigation.

DISPOSITION

The decision to discharge or admit patients with facial trauma depends on their associated injuries, general injury severity, and plans for treatment. The emergency clinician has the expertise to manage the initial resuscitation and stabilization of patients with facial trauma. It is recommended that early consultation with the appropriate surgical specialists occur once the patient has been stabilized. Antibiotics should be considered in cases of severe facial trauma or open fractures. Telemedicine has opened the door for real-time discussions with appropriate surgical consultants, allowing the review of imaging and provision of treatment recommendations and potentially avoiding hospital-to-hospital transfers for isolated facial injuries.[62] Patients with isolated facial trauma who have been appropriately stabilized with no airway concerns can be discharged with close outpatient follow-up.

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CHAPTER 34: QUESTIONS AND ANSWERS

1. A nasal fracture complication that requires urgent treatment is:
- **A.** Periorbital swelling
- **B.** Septal hematoma
- **C.** Laceration
- **D.** Epistaxis
- **E.** Subcutaneous edema

Answer: B. A septal hematoma is a collection of blood within the nasal septum that can occur following trauma. A septal hematoma should be drained promptly to avoid the risk of developing a septal abscess or ischemia of the septal cartilage leading to a saddle nose deformity. With the use of an anesthetic, the hematoma can be aspirated or incised, drained, and packed to avoid reoccurrence.

2. A patient with a mandibular fracture may complain of:
- **A.** Trismus
- **B.** Epistaxis
- **C.** Paresthesias of the inferior eyelid, nose, and upper lip
- **D.** Ocular muscle entrapment
- **E.** Postnasal drip and sweet taste in the mouth

Answer: A. Individuals with mandibular fractures may report pain with chewing, abnormal bite, jaw malalignment, paresthesias of the lip and chin area, trismus, oral bleeding, and dental injuries. An orthopantomogram (Panorex) has 92% sensitivity in the diagnosis of a mandibular fracture; however, when there is high clinical suspicion or concern for associated traumatic injuries a facial CT scan should be obtained. Epistaxis can be seen with isolated nasal fractures as well as maxillary fractures. Postnasal drip and a sweet taste in the mouth could be related to a CSF leak, which can be seen in frontal and nasal bone fractures. Ocular muscle entrapment can be related to orbital and midface fractures.

3. A patient presents following a physical altercation complaining of eye pain, decreased vision, and swelling. On physical examination he is noted to have periorbital ecchymosis, swelling, and tenderness, an irregular, tear-shaped pupil, and a collection of blood in the anterior chamber of the eye. Which of the following diagnostic or treatment options should be avoided?
- **A.** CT imaging of the face
- **B.** Ophthalmologic consultation
- **C.** Prophylactic antibiotics
- **D.** Thorough eye examination including tonometry
- **E.** Medications for pain and nausea and place patient in semirecumbent position

Answer: D. The patient is presenting with a history of blunt trauma and examination findings consistent for a globe rupture. A thorough history including mechanism and anticoagulant use should be obtained. CT imaging should be performed to look for additional traumatic injuries. The patient should be medicated for pain and nausea to avoid any increase in intraocular pressures resulting in possible aqueous fluid loss. Prophylactic antibiotics are initiated to prevent secondary endophthalmitis. The affected eye should not be manipulated, a rigid shield should be used for protection, and ophthalmology should be emergently consulted.

4. Cribriform plate fractures can be associated with:
- **A.** LeFort I fracture
- **B.** CSF rhinorrhea
- **C.** Dental alveolar fractures
- **D.** Ageusia
- **E.** Tripod fractures

Answer: B. Cribriform plate fractures are commonly associated with severe traumatic injuries including TBI and CSI. Symptoms can include tenderness, swelling, bleeding, CSF rhinorrhea, and anosmia. More complex midface fractures, LeFort III, or significant nasal trauma affecting the NOE complex are associated with fractures of the cribriform plate. ATLS guidelines should be followed when evaluating this patient. CT imaging including head, C-spine, and face are obtained and a CTA to evaluate for blunt cerebrovascular injury is often performed. Appropriate specialists (neurosurgery) should be consulted and involved in the patient's care.

35

Spinal Trauma

Kian Preston-Suni and Amy H. Kaji

KEY CONCEPTS

- NEXUS or CCR decision rules may be used to determine the need for radiographic imaging in the awake, evaluable trauma patient.
- CT scanning is preferred over plain radiography in the evaluation of the trauma patient with potential spinal injury, especially if axial imaging is needed for evaluation of other injuries.
- Suspicion for an anterior cord syndrome warrants prompt neurosurgical consultation because it is a potentially surgically correctable lesion.
- Neurogenic hypotension is a diagnosis of exclusion in the trauma victim and should not be considered the cause of hypotension unless the presence of coexisting hemorrhagic shock, cardiac tamponade, or tension pneumothorax has been eliminated.
- Because neurogenic hypotension can lead to hypoperfusion and secondary spinal cord ischemia, prolonged, severe hypotension (systolic blood pressure < 70 mm Hg) should be prevented and treated.
- Methylprednisolone or any other corticosteroid is not beneficial in the treatment of acute spinal cord injury (SCI) and should not be used.
- Emergency department management of SCI includes care to prevent further cord injury, pressure ulcers, bladder distention, and gastric distention.

FOUNDATIONS

Background and Importance

According to the National Spinal Cord Injury Statistical Center, motor vehicle collisions (MVCs) account for 39% of all spinal injuries.[1] Speeding, alcohol intoxication, and failure to use restraints are major risk factors. The next most common cause of spinal cord injury (SCI) is falls, followed by acts of violence (primarily gunshot wounds) and sporting activities. Approximately 80% of victims are male, and the average age at injury is 43 years. The lifetime cost to care for SCI victims ranges from over $1 million if older than 50 years, with incomplete motor function, to over $5 million for those younger than 25 years, with complete paraplegia. The total cost to society from lifelong medical expenses and lost productivity for all ages and types of spinal injuries is estimated to be more than $5 billion. The devastating emotional and psychological impact is incalculable.

Injuries of the soft tissues supporting the cervical spine can result in chronic pain and disability. The term *whiplash-associated disorder* (WAD) has been used to describe these injuries because of the flexion-extension movement of the neck that results from rear-end MVCs, the most common cause of a WAD.[2] Due to the large number of people sustaining these injuries, the annual costs associated with a WAD exceed $230 billion, which is more than the combined costs associated with spinal cord and brain injuries caused by MVCs.

Anatomy and Physiology

The human spine consists of 33 bony vertebrae—7 cervical, 12 thoracic, 5 lumbar, 5 sacral (fused into one), and 4 coccygeal (usually fused into one; Fig. 35.1). These 26 individual units are separated from one another by flexible intervertebral disks and connected to form a single functioning unit by a complex network of ligaments (Fig. 35.2). The vertebral column protects the spinal cord, which extends from the midbrain to the level of the second lumbar vertebra.

Spinal injuries involve fractures in 85% of cases. In the remainder, 10% are ligamentous injuries without fracture, and 5% are SCIs without a radiographic abnormality (SCIWORA), in which the spinal cord is injured directly without radiographic evidence of bony or ligamentous injury. Stability of a spinal injury refers to the resistance to displacement of fracture fragments or, in the case of ligamentous injury, the entire vertebral unit. There are several classification systems for assessing the stability of subaxial spinal column injuries (Table 35.1), including the Allen Ferguson classification, AO Spine classification, Denis Classification and the Thoracolumbar Injury Classification and Severity Score (TLICS). According to a survey of the members of the Spine Trauma Study Group of the International Spinal Cord Society, practical implementation is evenly distributed among the classification systems, although the AO Spine classification has higher reliability than TLICS.[3,4]

Pathophysiology

Classification of Spinal Column Injuries

Acute spinal injuries are classified according to the mechanism of trauma—flexion, flexion-rotation, extension, and vertical compression (Table 35.2).

Flexion. Atlanto-occipital and atlantoaxial joint dislocation can occur with or without associated fractures of the odontoid (Fig. 35.3). The basion-axial interval (BAI) and basion-dens interval (BDI) are normally less than 12 mm, with larger values suggestive of atlantoaxial joint dislocation (Fig. 35.4). When the ratio of the distance from the basion to the midvertical portion of the posterior laminar line of the atlas over the distance from the opisthion to the midvertical portion of the posterior surface of the anterior ring of the atlas is greater than 1, subluxation is suggested (Fig. 35.5).

In pure flexion injuries below C2, a longitudinal pull is exerted on the strong nuchal ligament complex, which usually remains intact.

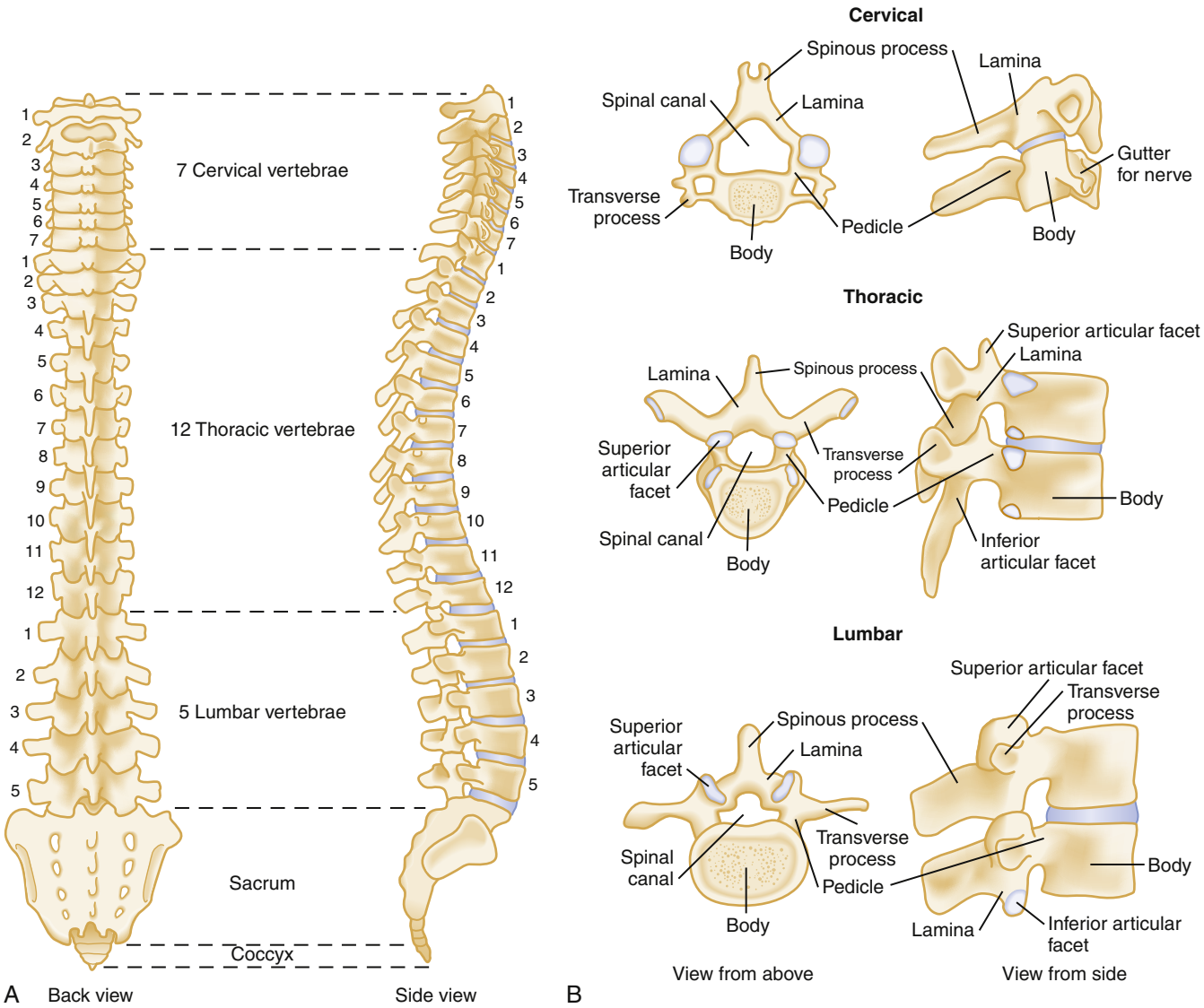


Fig. 35.1 (A) Vertebral column. (B) Typical vertebrae.

Most of the force is expended on the vertebral body anteriorly, causing a simple wedge fracture (Fig. 35.6).

Among the most unstable spinal injuries, the *flexion teardrop fracture* results from severe flexion forces causing subluxation and disruption of the longitudinal ligaments (Fig. 35.7).

The *clay shoveler's fracture* derives its name from an injury caused by the abrupt head flexion that clay miners experienced when tossing a heavy shovelful of clay and having the clay stick to the shovel. This force, transmitted through the supraspinous ligament, results in a stable avulsion fracture of the spinous process (Fig. 35.8).

Pure spinal subluxation begins posteriorly in the nuchal ligament and proceeds anteriorly to involve other ligaments (Fig. 35.9).

Bilateral facet dislocations occur when a greater force of flexion causes soft tissue disruption to continue anteriorly to the annulus fibrosis of the intervertebral disk and anterior longitudinal ligament, resulting in extreme instability (Fig. 35.10).

Chance fractures of the lumbar spine occur with a combination of distraction and flexion forces with an axis of rotation anterior to the vertebral body (Fig. 35.11).

Flexion-distraction injuries are similar to Chance fractures, but are characterized by an axis of rotation posterior to the anterior longitudinal ligament (Fig. 35.12). These injuries generally occur in the lumbar spine from forced deceleration in an MVC while restrained with a lap belt. As in Chance fractures, intra-abdominal injuries are common.[5]

Shear injury. Trauma to the head directed in an anteroposterior (AP) direction may result in fracture of the odontoid process above the transverse ligaments (type I) or, more commonly, at the base of the odontoid process where it attaches to C2 (type II; Fig. 35.13). Slight angulation of the force may result in extension of the fracture into the body of C2 (type III; Fig. 35.14).

Flexion-rotation. *Rotary atlantoaxial dislocation* is an unstable injury visualized best on open-mouth odontoid radiographs (Fig. 35.15) or computed tomography (CT) scan.

A *unilateral facet dislocation* is caused by both flexion and rotation. The rotational component of this injury occurs around one of the facet joints, which acts as a fulcrum. Simultaneous flexion and rotation cause the contralateral facet joint to dislocate, with the superior facet riding forward and over the tip of the inferior facet

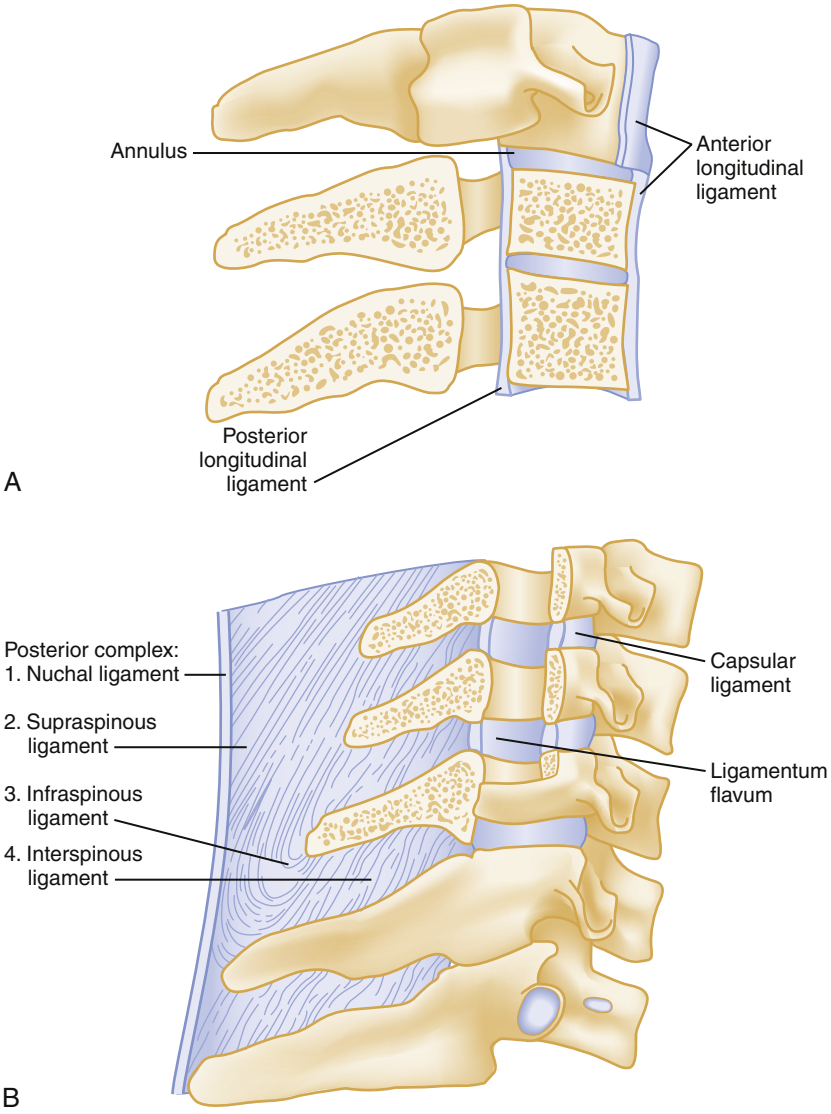


Fig. 35.2 (A) Ligaments of the anterior column. (B) Ligaments of the posterior column.

TABLE 35.1 Spinal Injury Classification Systems

Classification System	Characteristics
Allen Ferguson	Categorized by mechanism: compressive flexion, vertical compression, distractive flexion, compressive extension, distractive extension, lateral flexion
AO Spine	Classified by injury mechanism, segment of spine involved, severity of injury, associated neurologic deficit and complicating factors including instability, risk of nonunion, comorbidities, and vascular injury
Denis	Three-column model: injury to single column does not preclude SCI, injuries to two columns are unstable in one direction, and injuries to all three are highly unstable. • anterior column: anterior longitudinal ligament and anterior half of vertebral body and disk • middle column: posterior longitudinal ligament and posterior half of vertebral body and disk, spinal cord, laminae and pedicles, articulating facets, transverse processes, nerve roots, and vertebral arteries and veins • posterior column: spinous processes, nuchal ligament, interspinous and supraspinous ligaments, and ligamentum flavum
Thoracolumbar Injury Classification System (TLICS)	Characterized by injury mechanism, neurologic involvement and status of the posterior ligamentous complex

TABLE 35.2 Classification of Spinal Injuries

Mechanism of Spinal Injury	Stability	Radiographic Features	Other Features
Flexion			
Wedge fracture	Stable: posterior column intact. Unstable if > 50% vertebral body height or contiguous wedge fractures	Diminished height of anterior vertebral body with increased concavity, increased bony density, prevertebral swelling	
Flexion teardrop fracture	Extremely unstable: anterior and posterior ligaments disrupted	Wedge-shaped fragment of anteroinferior cervical vertebral body	Generally associated with neurologic injury
Clay shoveler's fracture	Stable: involves only spinous process	Oblique spinous process fracture, lower cervical spine	Seen in MVCs and direct blows to spinous process. Requires symptomatic care only
Subluxation	Potentially unstable if significant ligamentous injury	Ligamentous rupture without bony injury	Rarely associated with neurologic injury
Bilateral facet dislocation	Always unstable	Inferior facets of upper vertebra pass up and over superior facets of lower vertebra. Spine displaced anteriorly above injury	
Atlanto-occipital dislocation	Unstable: minimal muscle or ligamentous support	BAI or BDI > 12 mm Power's ratio > 1	
Anterior atlantoaxial dislocation with or without fracture	Unstable: minimal muscle or ligamentous support	Disruption of normal position of atlas on dens	
Odontoid fracture with lateral displacement	Unstable: associated ligamentous injury	Typically, oblique fracture	
Fracture of transverse process	Stable	Upper lumbar spine most common location	Cervical fractures are associated with vertebral artery injuries
Chance fracture	Usually stable: when involving only posterior column. May extend to middle column with high energy mechanism	Horizontal fracture through vertebral body, laminae, pedicles, transverse processes, and spinous process	Commonly associated with intra-abdominal injuries, cord injury rare
Flexion-distraction injury	Unstable: all three columns involved	Compression fracture of vertebral body with distraction of posterior elements	Also known as seatbelt injury
Shear			
Odontoid fracture	Type I: Usually stable unless apical and alar ligaments injured Type II: Generally unstable Type III: Unstable	Type I: Tip avulsion Type II: Fracture through base of odontoid Type III: Through odontoid, extends into lateral masses. Can extend laterally into articular facet	Type I: Uncommon Type II: Nonunion common Type III: Lowest rate of nonunion due to larger surface area
Flexion-Rotation			
Unilateral facet dislocation	Stable	Mild anterolisthesis, misaligned spinous processes	May have neurologic injury
Rotary atlantoaxial dislocation	Unstable: ligamentous injury	Asymmetry of lateral masses relative to odontoid	
Extension			
Posterior neural arch fracture (C1)	Unstable	Compression of posterior elements	
Hangman's fracture (C2)	Unstable	Bilateral pedicle fractures of axis	
Extension teardrop fracture	Usually stable in flexion as posterior elements intact; unstable in extension	Triangular fracture of anteroinferior corner of vertebral body	Appears similar to flexion teardrop
Posterior atlantoaxial dislocation, with or without fracture	Unstable	Odontoid process posterior to ring of atlas	Seen in high-velocity injuries
Vertical Compression			
Bursting fracture of vertebral body	Stable: all ligaments remain intact	Comminuted vertebral body on sagittal CT with typically > 40% compression, vertical fracture of vertebral body seen on coronal CT, bony fragments may enter canal	May be missed on plain radiography. Can cause anterior cord syndrome

Continued

TABLE 35.2 Classification of Spinal Injuries—cont'd

Mechanism of Spinal Injury	Stability	Radiographic Features	Other Features
Jefferson fracture (C1)	Extremely unstable: transverse ligament disrupted	Anterior and posterior arches of atlas fractured. Widened predental space. Lateral masses of C1 offset relative to C2, sum of distances >7 mm.	May be missed on plain radiography, especially with minimal displacement
Isolated fractures of articular pillar and vertebral body	Stable	Vertical and oblique fractures	Rare injuries

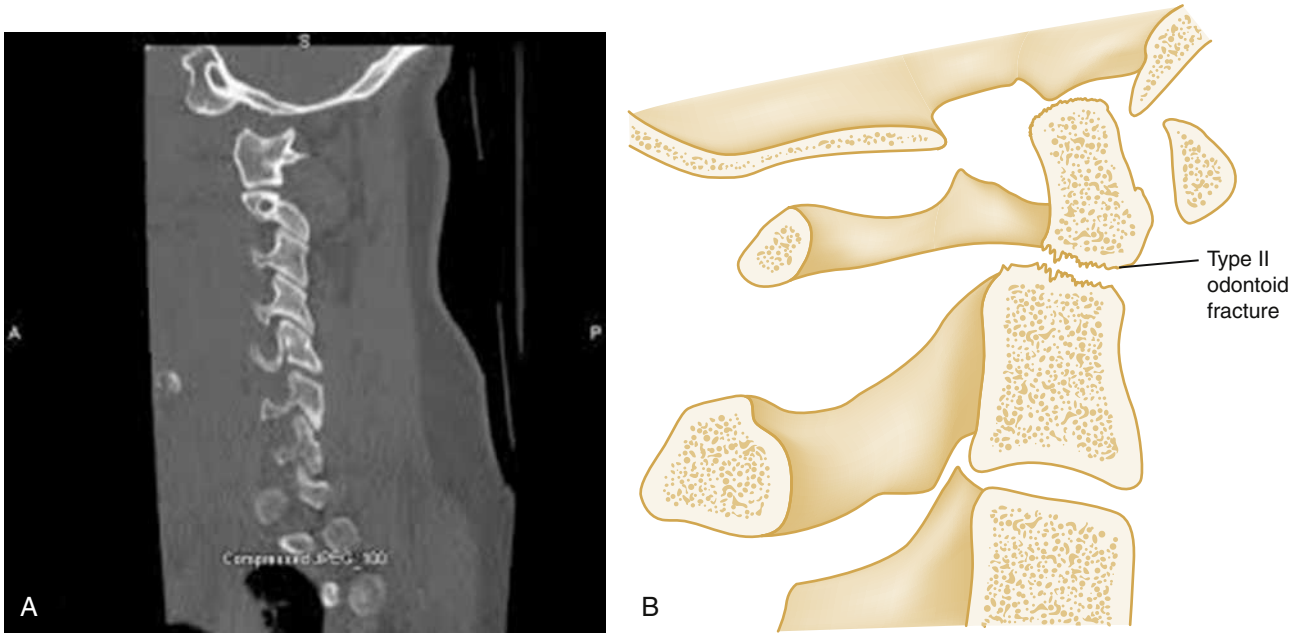


Fig. 35.3 (A–B) Odontoid fracture with anterior dislocation. Mechanism—flexion with shearing; stability—unstable.

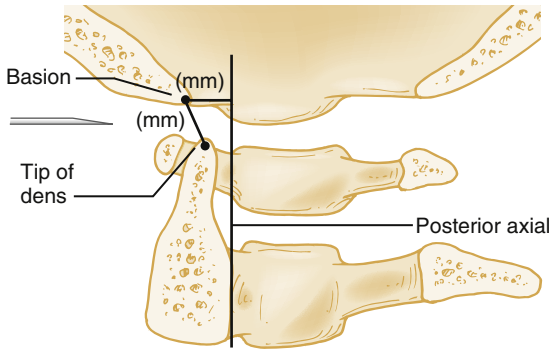


Fig. 35.4 The basion-axial interval (BAI) and basion-dens interval (BDI) are normally less than 12 mm.

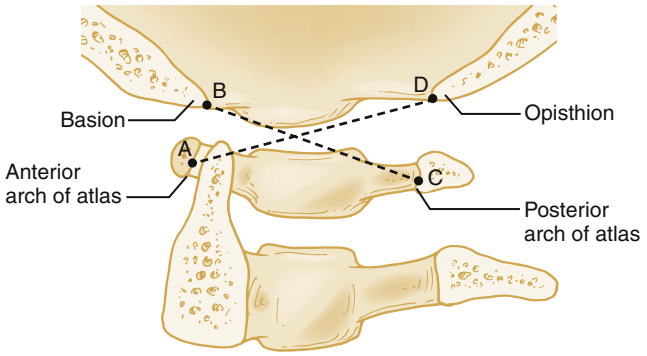


Fig. 35.5 The Power's ratio, BC:AD > 1 indicates subluxation.

and coming to rest within the intervertebral foramen. In this position, the dislocated articular mass is mechanically locked in place, making this a stable injury even though the posterior ligament complex is disrupted.

Any cervical fracture or dislocation may cause torticollis; however, torticollis may also be caused by a benign process such as a muscle spasm. It may be difficult to differentiate the two and in the setting of trauma, CT scan (Fig. 35.16) or oblique radiographs may be necessary to demonstrate the dislocated facet joint (Fig. 35.17).

Due to the varying shapes of the articular processes, different types of flexion-rotation injuries result. In the cervical region, where articular processes are small and almost horizontal, unilateral facet dislocations occur, whereas in the lumbar region, in which articular processes are large and nearly vertical, unilateral facet dislocation is rare. Instead,

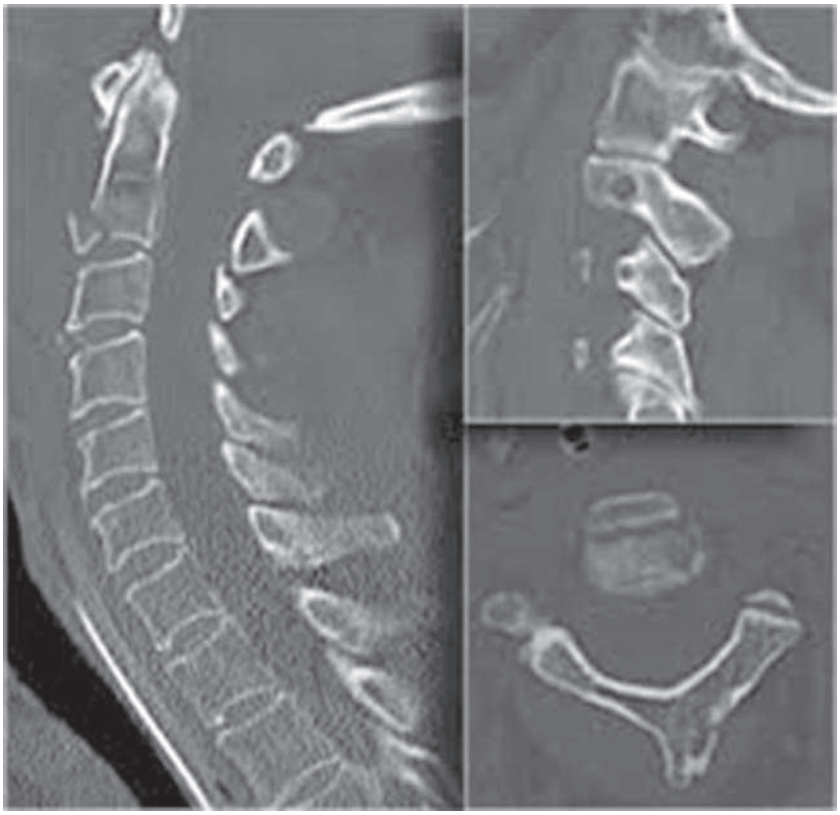
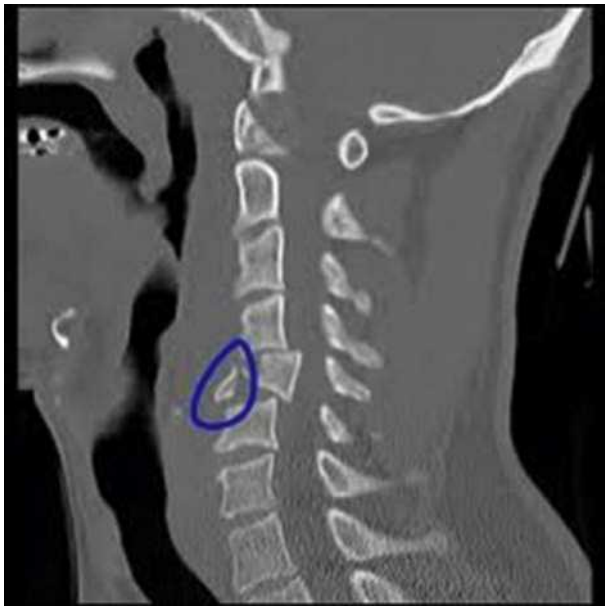


Fig. 35.6 (A) Lateral view of a wedge fracture of C5 with angulation. Mechanism—flexion; stability—mechanically stable. (B) Note the anterior wedging of the C4 vertebral body and angulation of C4 on C5.



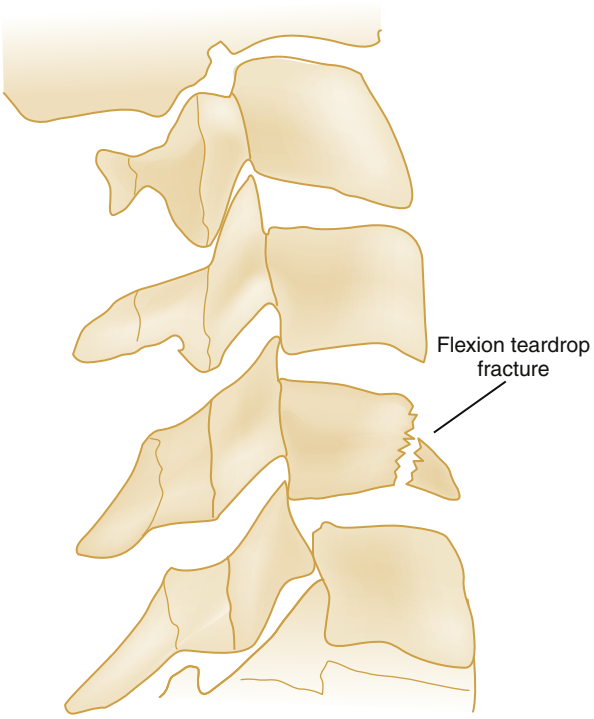


Fig. 35.7 (A–B) Lateral view of a teardrop fracture. Mechanism—flexion; stability—unstable. The fractured fragment off the C5 body resembles a teardrop.

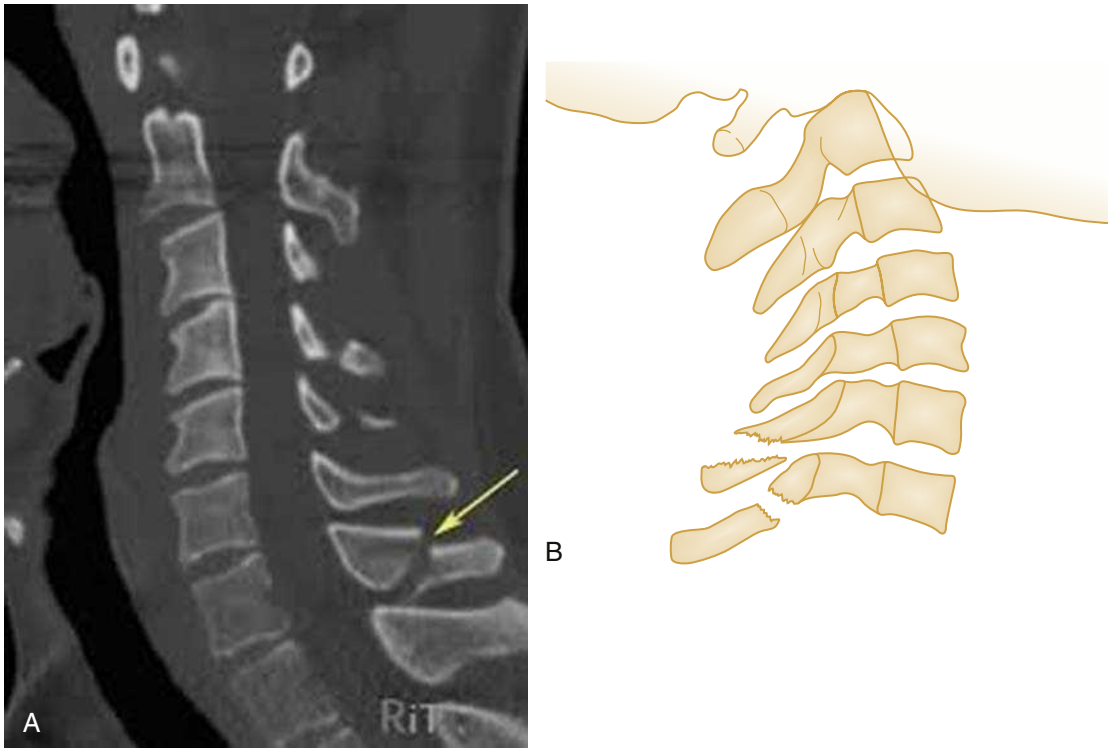


Fig. 35.8 (A–B) Clay shoveler's fracture. Mechanism—flexion; stability—mechanically stable. Note the avulsed fragment off the tip of the C7 spinous process in an underpenetrated lateral view (*arrow*).

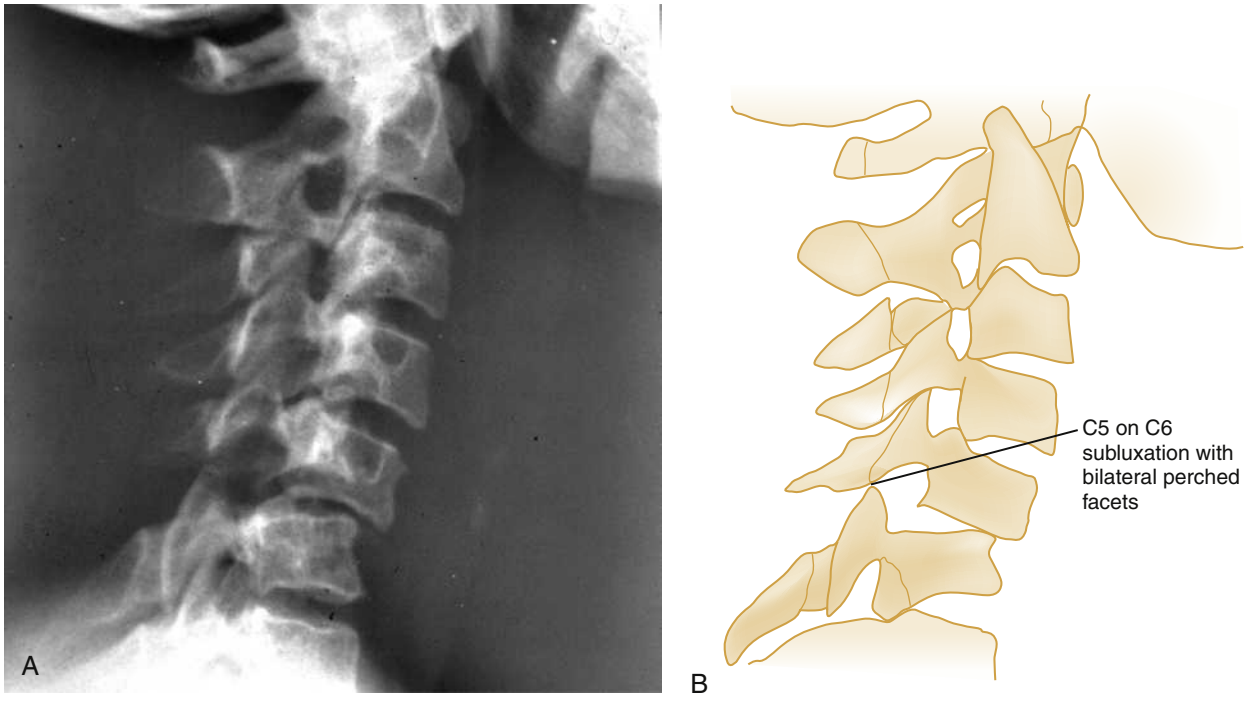


Fig. 35.9 (A–B) Subluxation with bilateral perched facets at C5 and C6. Mechanism—flexion; stability—unstable. Lateral view shows severe subluxation of C5 on C6.

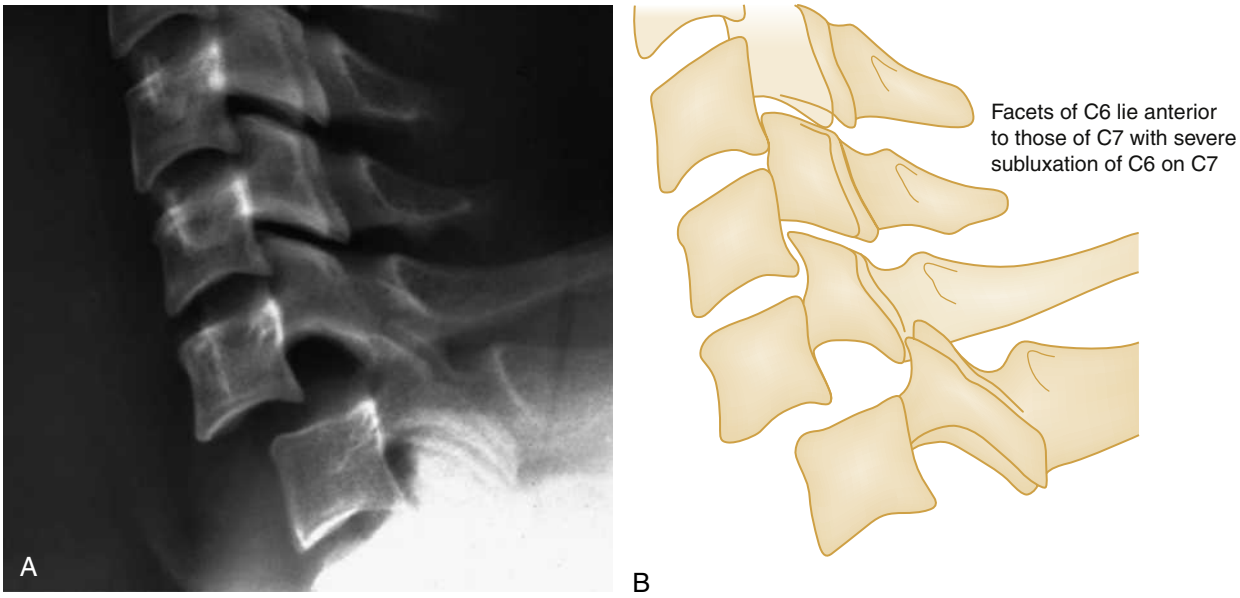


Fig. 35.10 (A–B) Bilateral facet dislocation. Facets of C6 lie anterior to those of C7, with severe subluxation of C6 on C7.

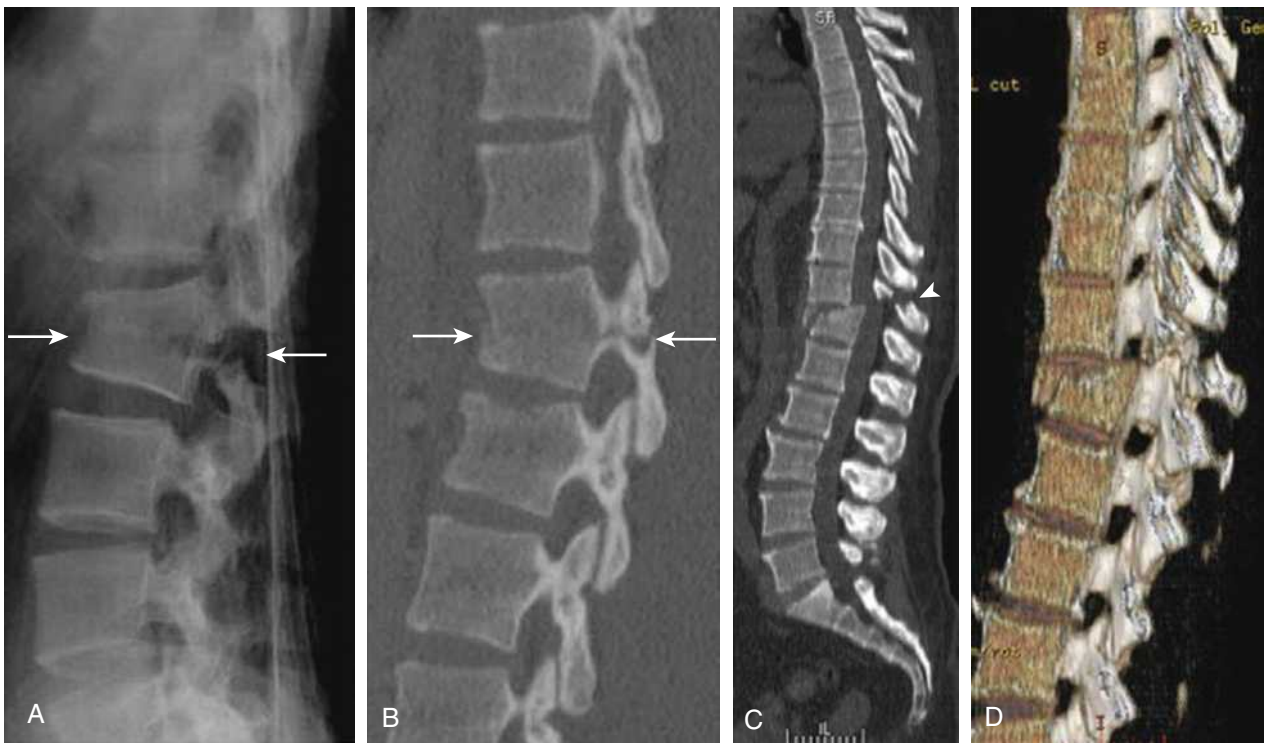


Fig. 35.11 (A–B) Chance fracture at thoracolumbar junction. Horizontal fracture in the axial plane. (From Cianfoni A, Colosimo C. Imaging of spine trauma. In: Law M, Som P, Naidich T, eds. *Problem Solving in Neuroradiology*. Philadelphia, PA: Saunders; 2011:473-495.)

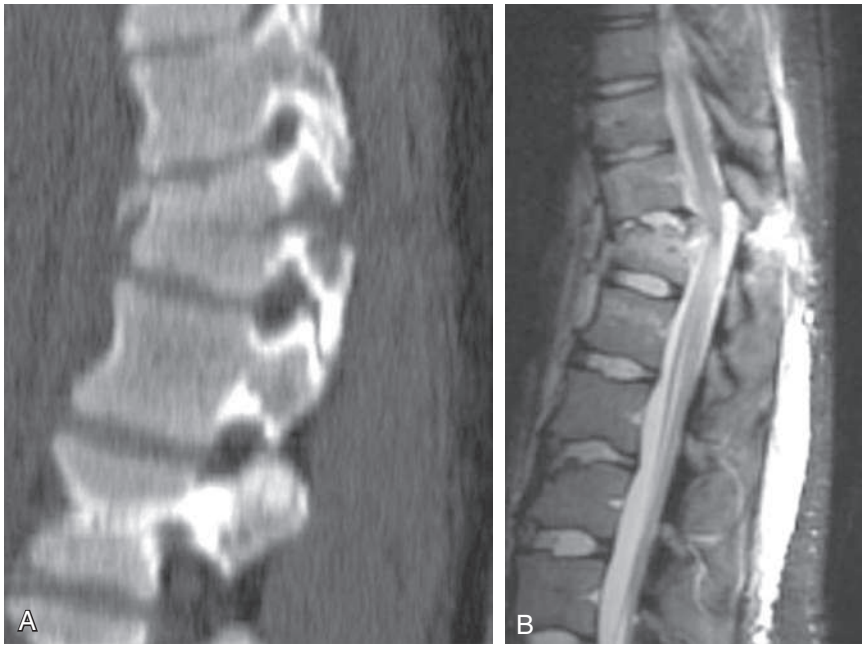


Fig. 35.12 (A) Sagittal CT reconstruction of T11 flexion-distraction injury extending through pedicle. B, MRI showing cord compression and marrow edema. (From Hart B, Hayek R. Imaging: Trauma. In: Steinmetz M, Benzel E, eds. *Benzel's Spine Surgery*. Philadelphia, PA: Elsevier; 2017:1663-1682.)

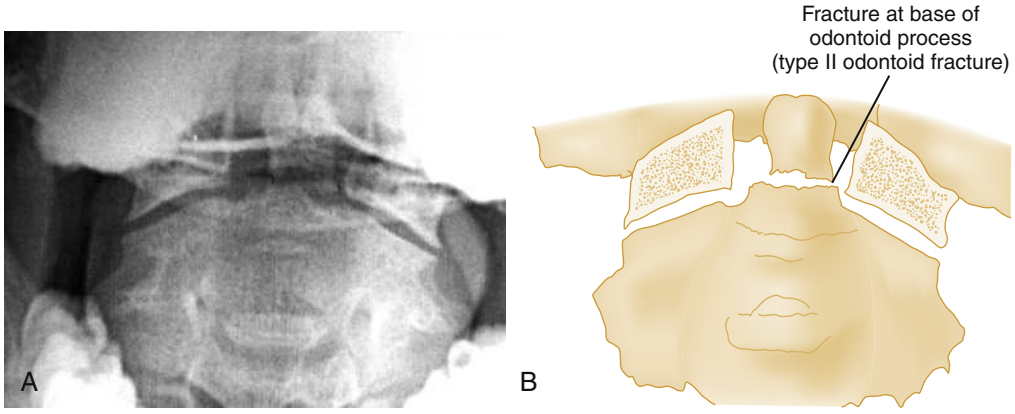


Fig. 35.13 (A and B) Odontoid fracture with lateral displacement. Mechanism—flexion; stability—unstable. The tip of the odontoid process is laterally displaced in this lateral flexion injury.

one or both articular processes fracture, and the upper vertebra swings forward. Commonly seen in the thoracolumbar and lumbar regions, this rotation fracture-dislocation is unstable (Fig. 35.18).

Extension. Fracture of the posterior neural arch of the atlas (C1) results from compression of the posterior elements between the occiput and spinous process of the axis (C2) during forced neck extension (Fig. 35.19). The injury is characterized by an intact anterior arch and transverse ligaments.

The *hangman's fracture*, or traumatic spondylolysis of C2, occurs when the cervicocranium—the skull, atlas, and axis functioning as a unit—is hyperextended as a result of abrupt deceleration (Fig. 35.20). Cord damage is usually minimal because the AP diameter of the neural canal is greatest at C2, and the bilateral pedicular fractures permit spinal canal decompression.

The *extension teardrop fracture* occurs when abrupt extension of the neck causes the anterior longitudinal ligament to pull the anteroinferior corner of a vertebral body away from the remainder of the vertebra. Often occurring in lower cervical vertebrae (C5–C7) from diving accidents, this injury may be associated with a central cord syndrome (see later) and is caused by the ligamentum flavum buckling into the spinal cord.

Vertical compression. Vertical compression injuries occur in the cervical and lumbar regions, which are capable of straightening at the time of impact. When forces are applied from above (skull) or below (pelvis or feet), one or more vertebral body endplates may fracture. The nucleus pulposus of the intervertebral disk is forced into the vertebral body, which is shattered outward, resulting in a burst fracture (Fig. 35.21). While often stable, fracture fragments may impinge on or penetrate the ventral surface of the spinal cord (Fig. 35.22).

The C1 *Jefferson fracture* occurs when a vertical compression force is transmitted through the occipital condyles to the superior articular surfaces of the lateral masses of the atlas, driving the lateral masses outward (Fig. 35.23).

Rarely, vertical compression fractures may result in isolated fractures of the articular pillar or vertebral body.

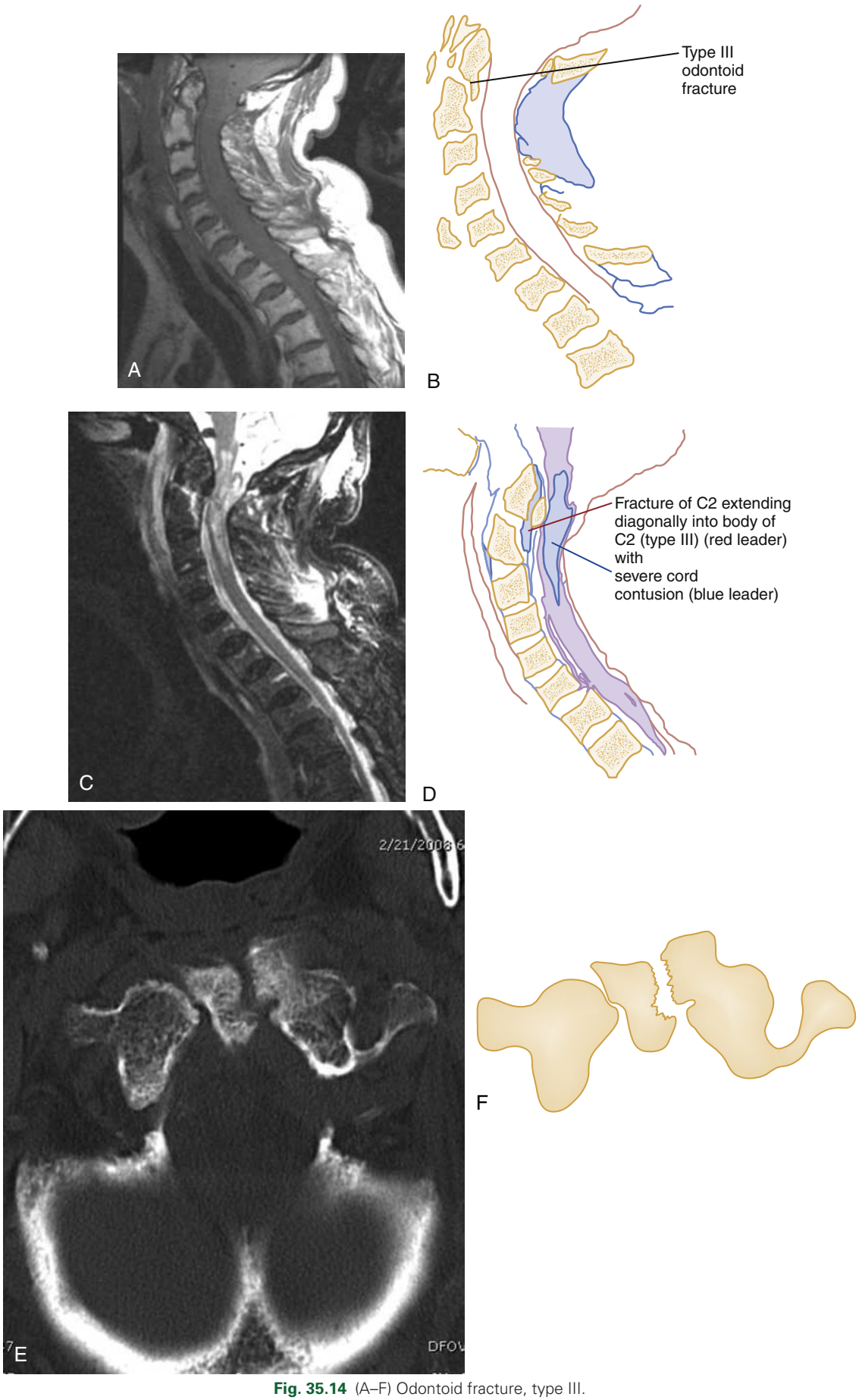


Fig. 35.14 (A–F) Odontoid fracture, type III.

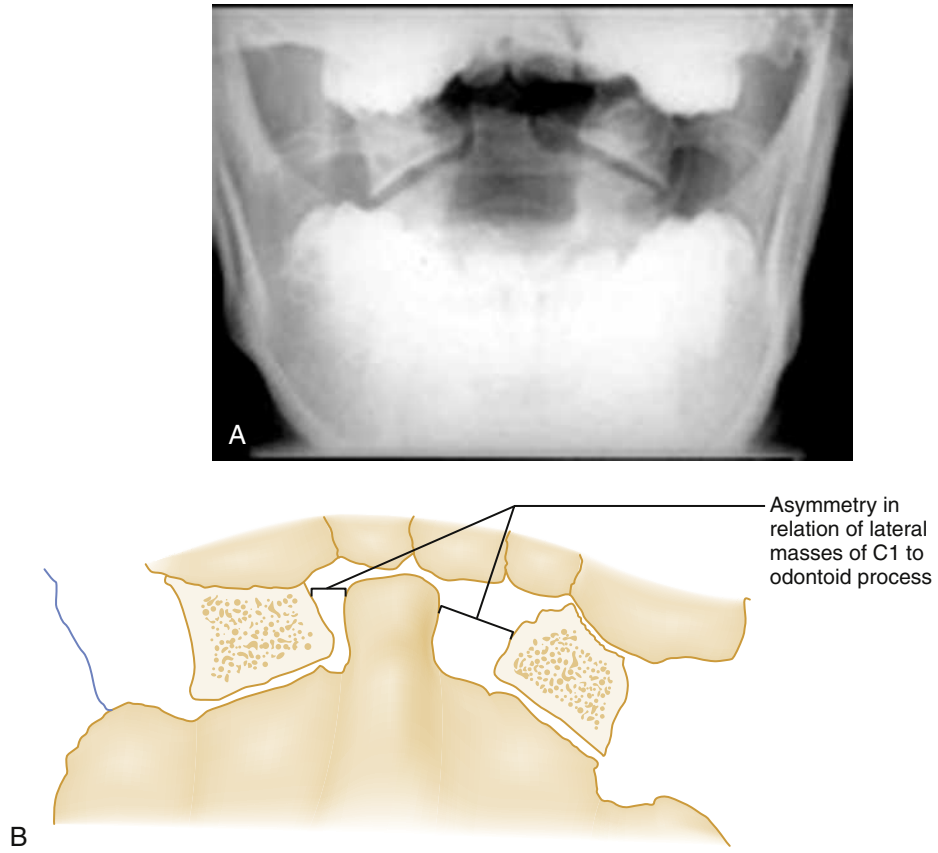


Fig. 35.15 (A–B) Rotatory subluxation of C1 on C2. Mechanism—rotation; stability—unstable. There is marked asymmetry in the relationship of the lateral masses of C1 to the odontoid process. Rotation causes the right lateral mass to appear slightly larger (farther from the x-ray film) than the left (closer to the x-ray film).

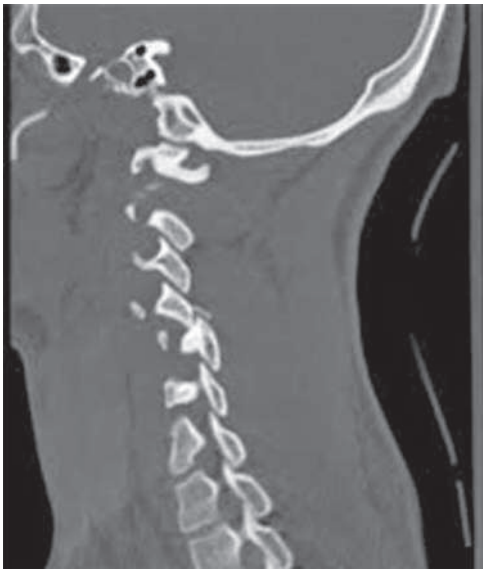


Fig. 35.16 Unilateral facet dislocation on CT.

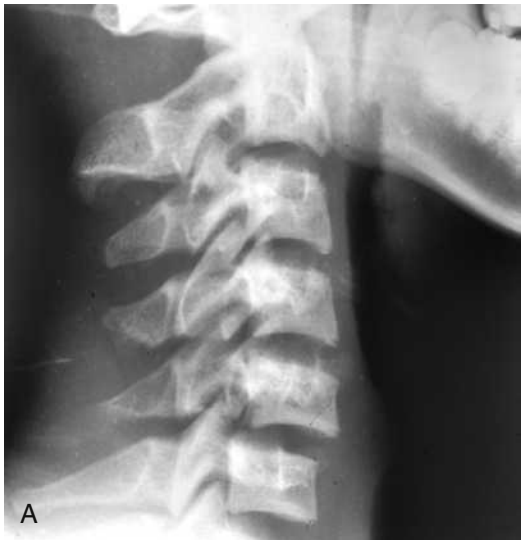
Classification of Spinal Cord Injuries

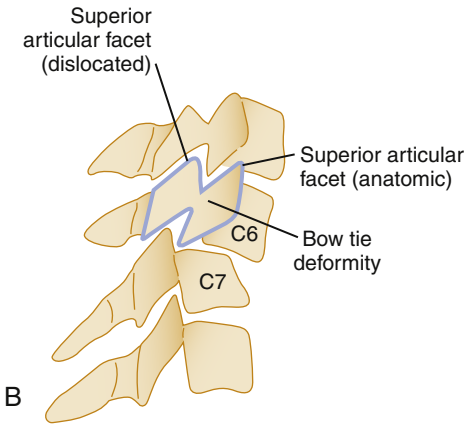
Primary spinal cord injury. The spinal cord may be injured by three broad categories of injury patterns. First, penetrating trauma or massive blunt trauma with disruption of the vertebral column causes transection of neural elements. Because spontaneous regeneration within the central nervous system following damage is poor, such injuries are irreversible. Less severe blunt trauma may have similar effects resulting from a displaced bony fragment or herniated disk injuring the cord.

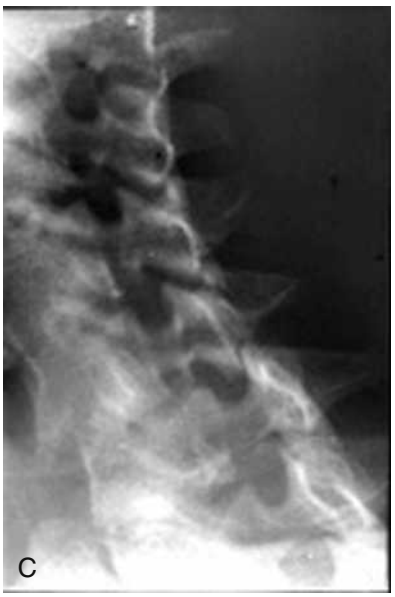
Second, when patients with cervical osteoarthritis and spondylosis, particularly older adults, are subjected to forcible cervical spine extension, the spinal cord may be injured secondary to compression between an arthritically enlarged anterior vertebral ridge and a posteriorly located hypertrophic ligamentum flavum (Fig. 35.24). This injury frequently results in a central cord syndrome.

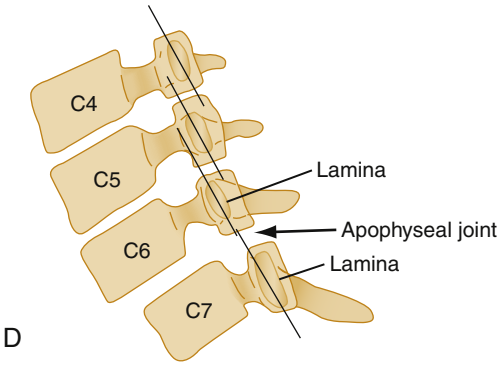
The third mechanism is primary vascular damage to the spinal cord. The spinal cord may be compressed by an extradural hematoma, particularly in patients who are on anticoagulants or have bleeding disorders. Vascular injuries should also be suspected when there is a discrepancy between the clinically apparent neurologic deficit and known level of spinal injury. For example, a lower cervical dislocation may compress the vertebral arteries as they travel within the spinal foramina of the vertebrae, resulting in thrombosis of the anterior spinal artery that originates from both vertebral arteries at C1 (Fig. 35.25). On physical examination, such an injury may erroneously appear to be localized to the level of C1 or C2. Also, the great radicular artery of Adamkiewicz, originating from the aorta and often entering the spinal canal at the level of L1, sends branches as cephalad as T4. Therefore, a lumbar fracture or dislocation can produce a neurologic deficit as high as T4.

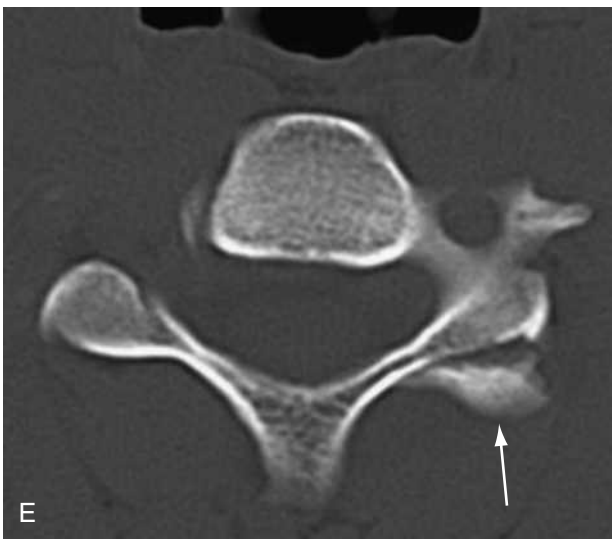
Secondary spinal cord injury. The maximum neurologic deficit after blunt spinal cord trauma is often not seen on initial examination and











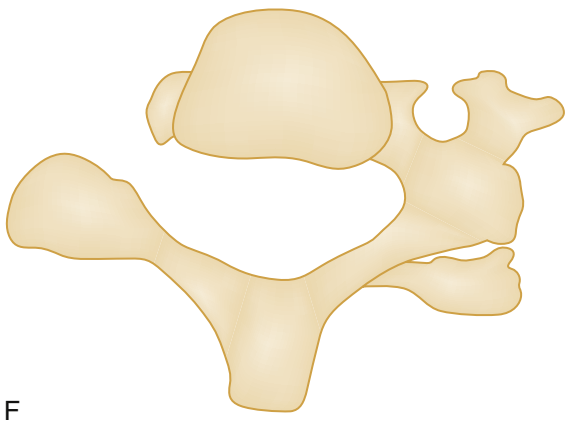


Fig. 35.17 Unilateral facet dislocation. Mechanism—flexion and rotation; stability—stable. (A–B) Lateral view showing one dislocated articular facet of C5 lying anterior to the corresponding facet of C6 and creating a bowtie deformity. The C5 vertebral body is subluxed anteriorly on C6. (C–D) Oblique view of unilateral facet dislocation with the lamina of C6 projecting into the neural foramen. (E–F) CT scan showing facet dislocation. The inferior facet (*arrow*) lies posterior to the superior facet.

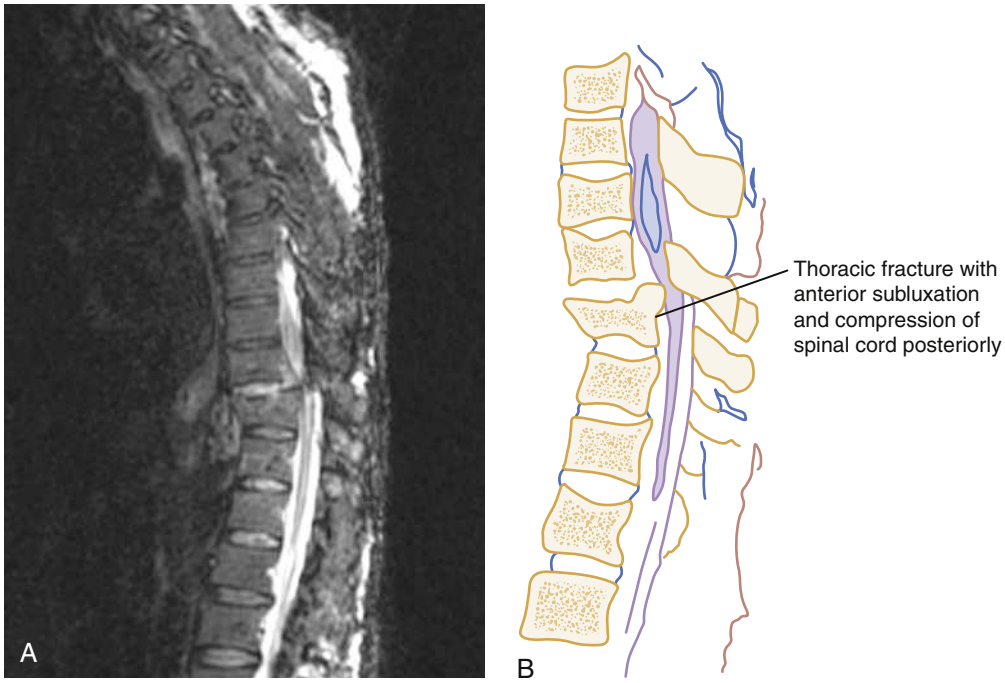


Fig. 35.18 (A–B) MRI scan showing fracture-dislocation of the thoracic spine.

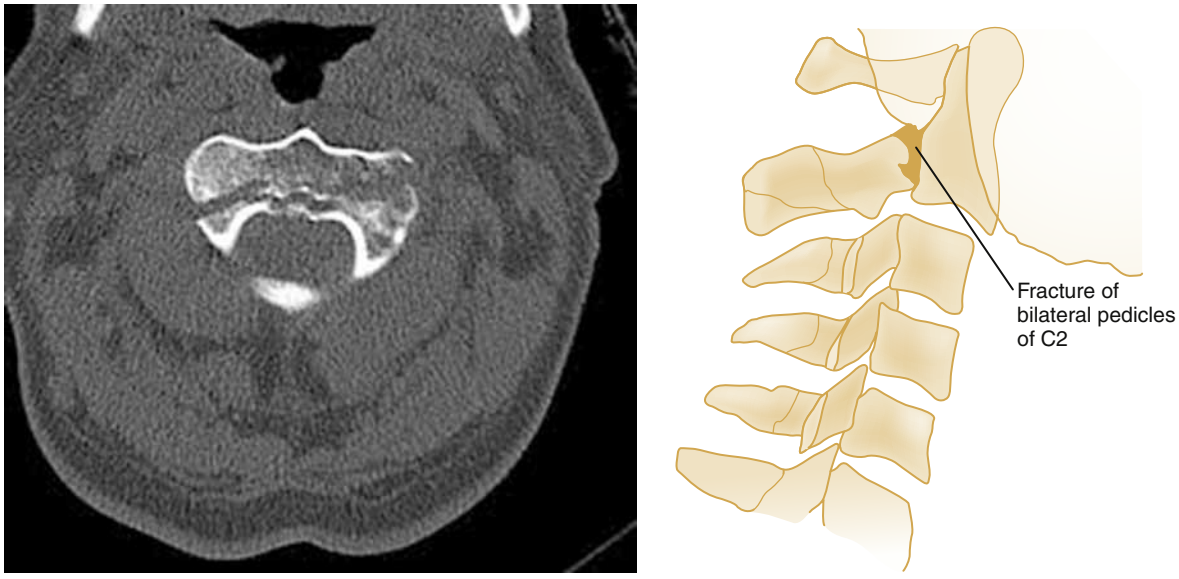


Fig. 35.19 (A–B) CT scan of posterior neural arch fracture of C1. Mechanism—extension; stability—unstable. The fracture line is well visualized.

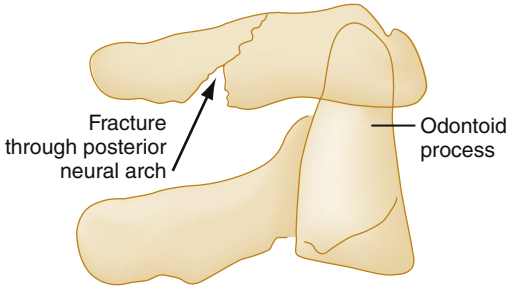


Fig. 35.20 Hangman's fracture. Mechanism—extension; stability—unstable. Fracture lines extending through the pedicles of C2 are well visualized. Retropharyngeal soft tissue swelling is apparent.

may, instead, progress over many hours. Studied extensively in animal models, the histopathology of secondary SCI is now thought to be due to a complex cascade of biochemical events that result in progressive ischemia of gray and white matter during the postinjury period (Fig. 35.26). Other factors, such as hypoxia, hypotension, hyperthermia, and hypoglycemia, also affect the ultimate extent of SCI.

Classification of Cervical Soft Tissue Injuries

Blunt force trauma can injure one or more of the soft tissues of the neck (see Chapter 36), including ligaments, muscles, intervertebral disks, zygapophysial facet joints, dorsal root ganglia and vertebral arteries. Although injuries of these tissues have been documented in biomechanical, animal, and human autopsy studies, a validated diagnostic

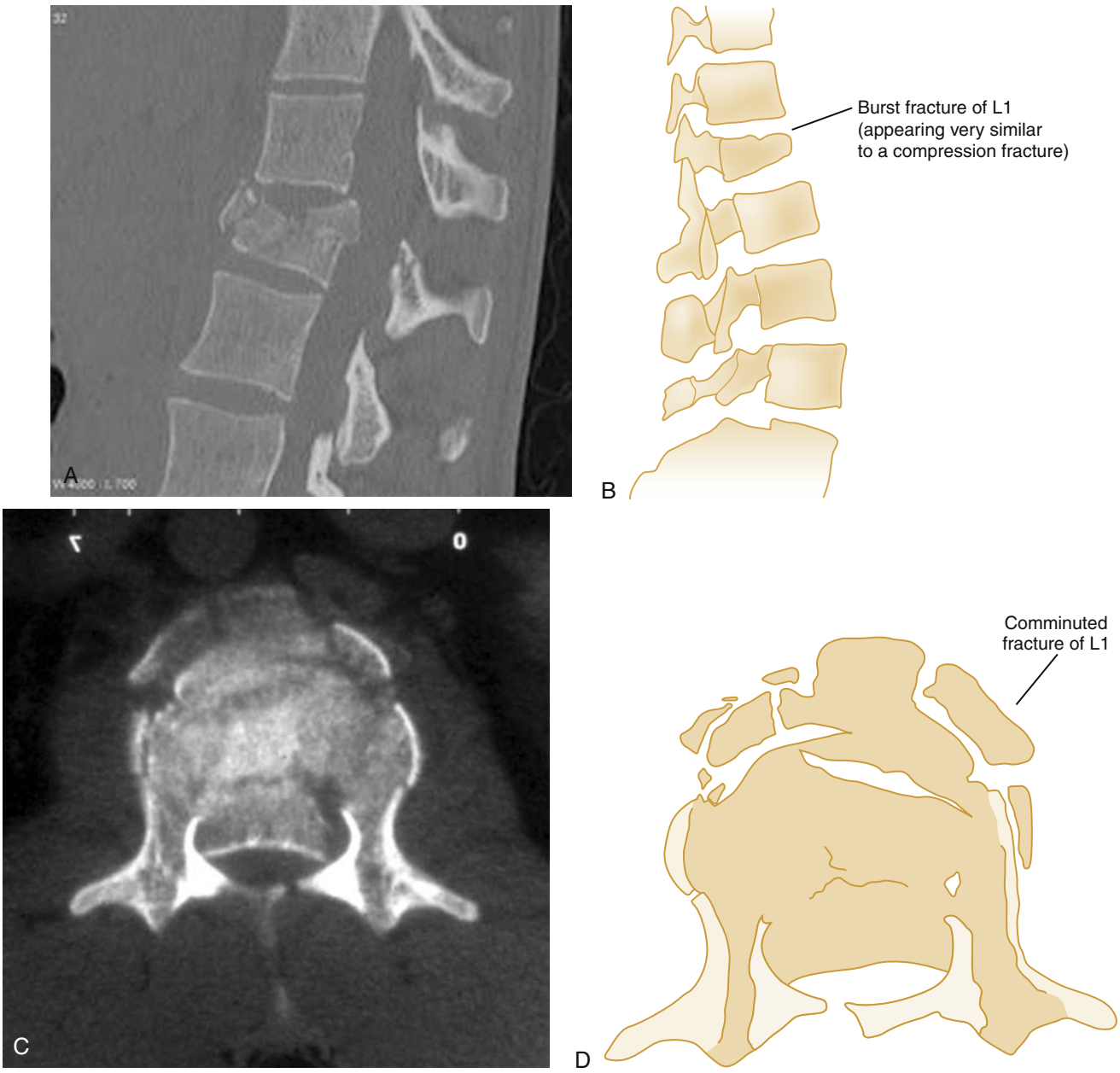


Fig. 35.21 Burst fracture of a vertebral body. Mechanism—vertical compression and flexion; stability—unstable. (A–B) Lateral CT scan showing a burst fracture of L1, appearing very similar to a compression fracture. Mechanism—flexion; stability—usually stable. (C–D) CT scan of L1 in the same patient showing comminution of the fracture and retropulsion of fragments into the spinal canal.

test is only available for facet injuries. The cardinal symptom of a WAD is neck pain but neck stiffness, neck and arm paresthesias, and dizziness are commonly reported. Table 35.3 shows the Quebec Task Force classification of WADs, the most common classification used worldwide.[2]

CLINICAL FEATURES

Neurologic Evaluation

Observation and careful inspection may reveal signs of possible spinal involvement of an injury. Significant head and facial trauma have a 5% to 10% incidence of associated cervical spine injuries. Scapular contusions suggest a rotation or flexion-rotation injury of the thoracic spine. Chest and neck abrasions from automobile shoulder belts and lower abdominal markings from lap belts indicate possible blunt carotid and vertebral injuries, as well as spinal, intrathoracic, and intra-abdominal injuries. As occurs with falls from considerable heights, injuries to the gluteal region, calcaneal fractures, and severe ankle fractures suggest a compression type of spinal injury.

Because the diaphragm is innervated by the phrenic nerve, which originates at C3–C4, an abdominal breathing pattern may provide an important clue to an upper cervical injury. The presence of *Horner syndrome*, characterized by unilateral ptosis, miosis, and anhidrosis, may result from disruption of the cervical sympathetic chain, usually between C7 and T2. Priapism may occur with severe SCI, and is often associated with spinal shock, a transient reflex depression of the spinal cord below the level of the injury.

Pain may be present in the sensory dermatome corresponding to the injured spinal level. For example, a C2 lesion may cause occipital

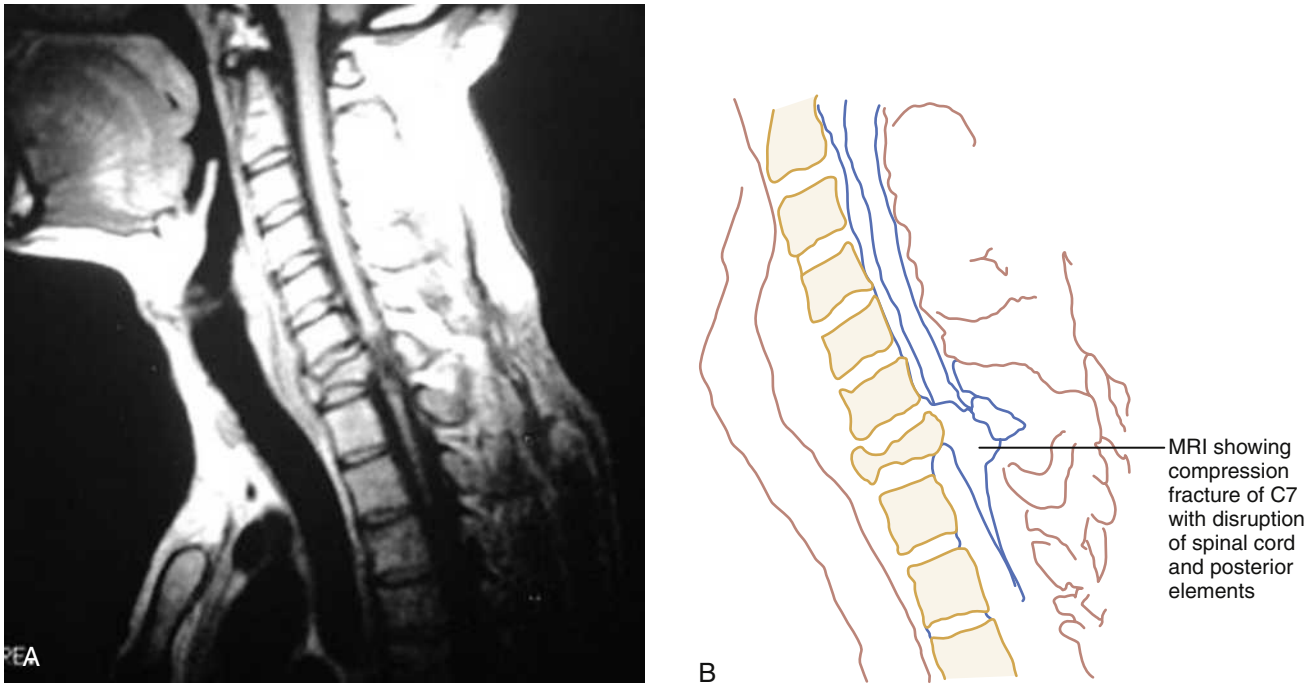


Fig. 35.22 (A–B) MRI scan showing a burst fracture of C7 with complete spinal cord disruption.

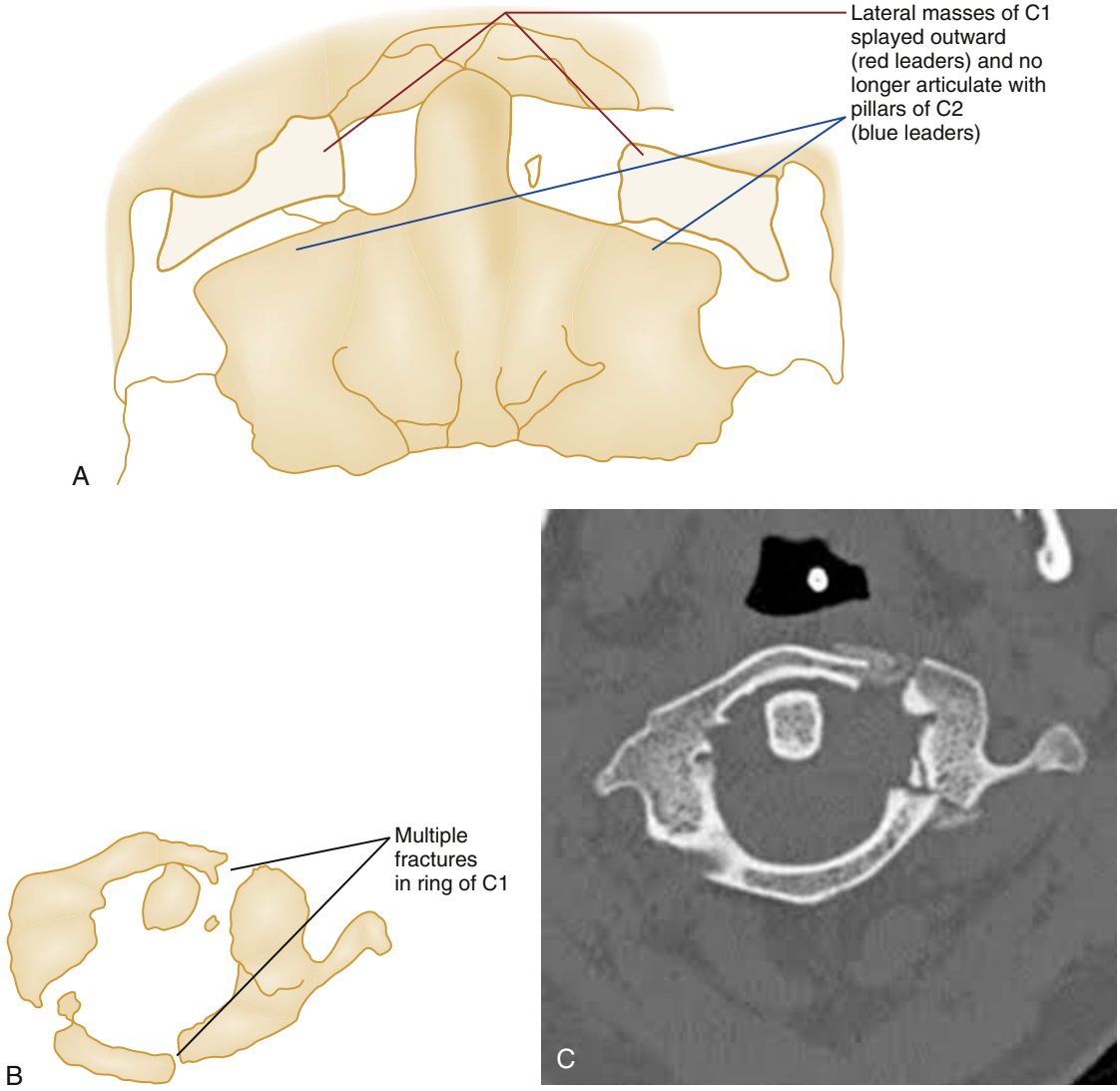


Fig. 35.23 Jefferson fracture. Mechanism—vertical compression; stability—unstable. (A–B) Bilateral lateral displacement of the lateral masses of C1 with respect to the articular pillars of C2 confirms a Jefferson fracture and differentiates it from fracture of the posterior neural arch of C1 on an anteroposterior view. (C) CT scan of C1 showing two fracture sites in the ring of C1, with lateral displacement of the lateral mass on the left.

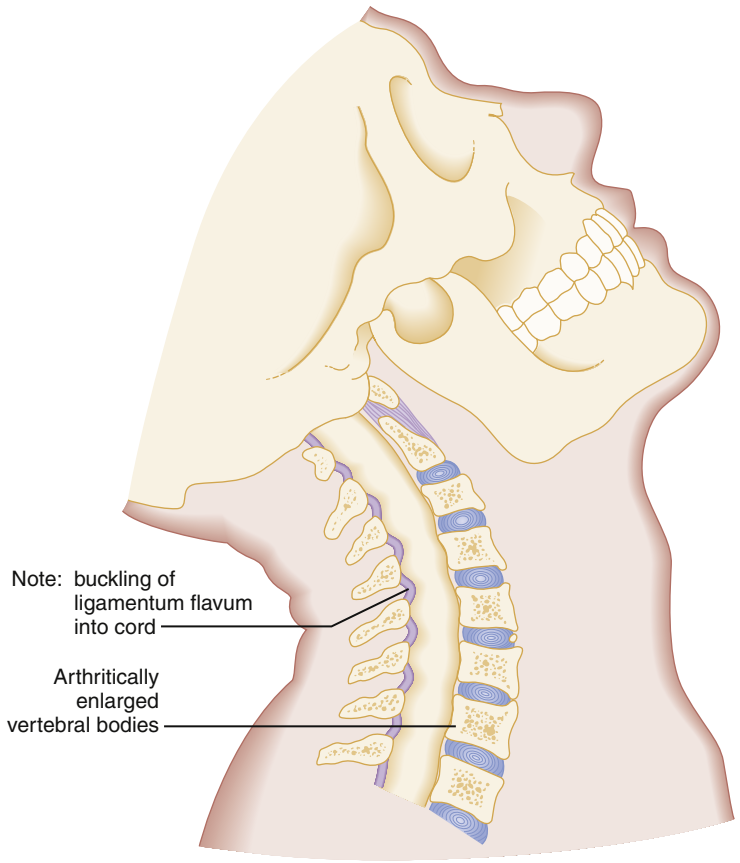


Fig. 35.24 Older patients subjected to extension forces can sustain cervical spinal cord injury as a result of compression of the spinal cord between the posterior hypertrophic ligamentum flavum and arthritically enlarged anterior vertebral bodies.

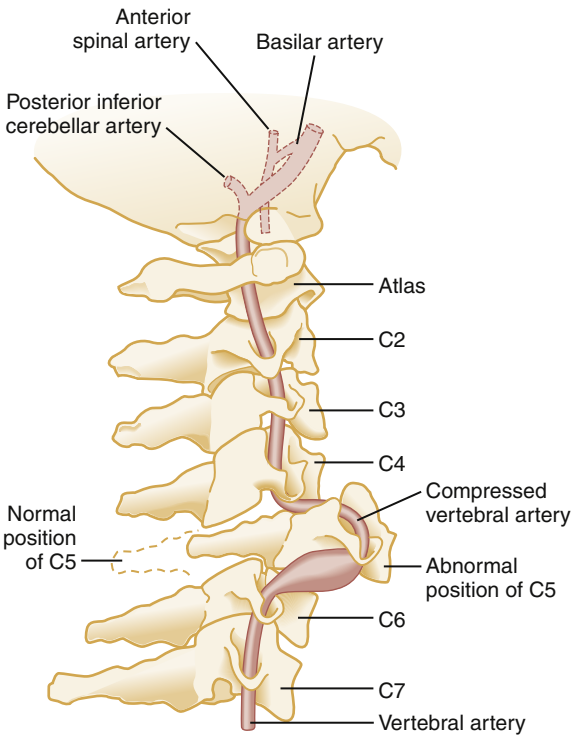


Fig. 35.25 Mechanism of vascular injury of the spinal cord resulting from cervical vertebral injury.

pain, whereas discomfort overlying the trapezius muscle, particularly in the absence of signs of local trauma, suggests a C5 injury. Certain medical conditions predispose patients to spinal injury. For example, patients with Down syndrome are predisposed to atlanto-occipital dislocation, whereas those with rheumatoid arthritis are prone to rupture of the C2 transverse ligament.

Palpation of the entire spine and paraspinal musculature may reveal areas of tenderness, deformity, or muscle spasm. A step-off may be appreciated with severe subluxation. Widening of an interspinous space indicates a tear in the posterior ligament complex and a potentially unstable spinal injury.

Because a single motion is often governed by muscles innervated by multiple spinal segments, localizing a spinal lesion based solely on motor function is extremely difficult. Testing the presence and strength of those motions outlined in Table 35.4, however, provides a rapid baseline assessment. When a deficit is noted, the motor and neurologic examination should be repeated because progression of dysfunction may occur. Even the most minimal of motor response should be elicited and documented, because any response improves prognosis. A slight toe flicker in an otherwise paralyzed individual indicates that the patient may again eventually walk unassisted.

The presence of cord-mediated deep tendon reflexes can be helpful as a localizing diagnostic aid (Table 35.5). Typically, muscle paralysis associated with intact deep tendon reflexes indicates an upper motor neuron (spinal cord) lesion, whereas paralysis associated with absent deep tendon reflexes indicates a lower motor neuron (nerve root or cauda equina) lesion. This differentiation is important because the

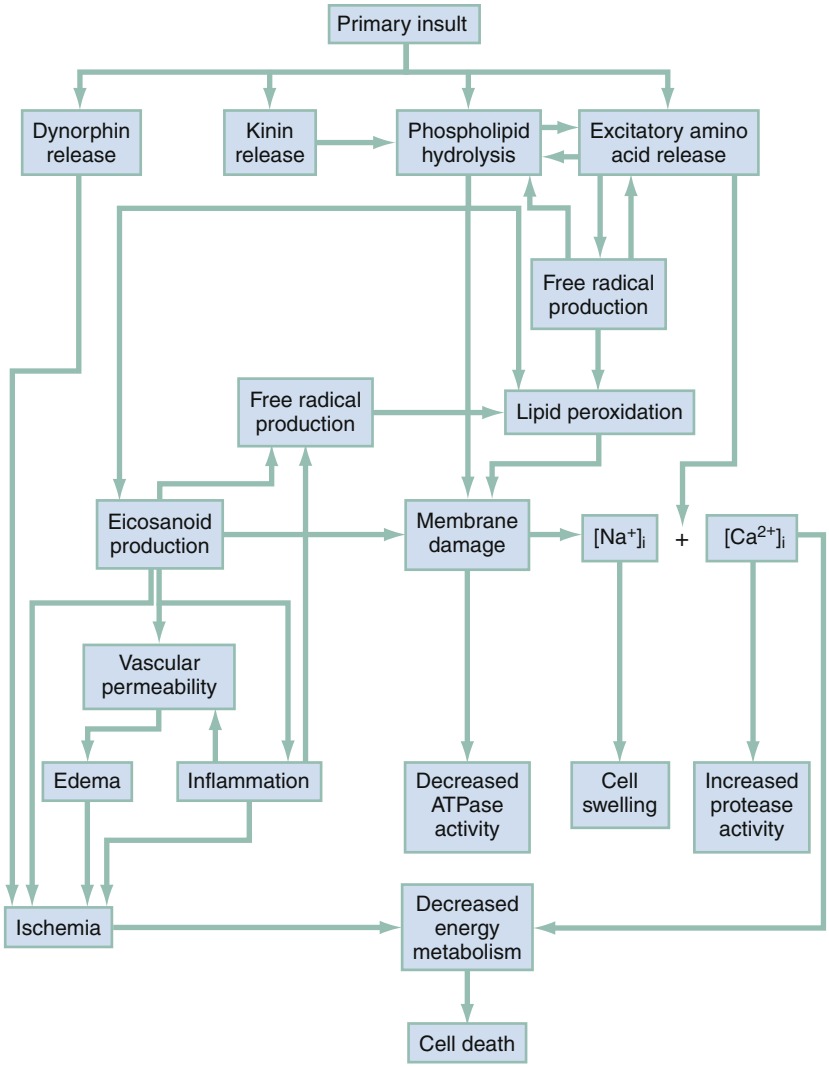


Fig. 35.26 Speculative paradigm of secondary pathophysiologic events after primary traumatic injury to the spinal cord. Ca^{2+}, Calcium ion; Na^{+}, sodium ion.

TABLE 35.3 Quebec Task Force Classification of Whiplash-Associated Disorders

Grade	Description
0	Whiplash injury but no pain, symptoms, or signs
1	Delayed neck pain, minor stiffness, nonfocal tenderness only, no physical signs
2	Early onset of neck pain, focal neck tenderness, spasm, stiffness, radiating symptoms
3	Early onset of neck pain, focal neck tenderness, spasm, stiffness, radiating symptoms, and signs of neurologic deficit
4	Neck complaint (grade 2 or 3 above) and fracture dislocation

(Adapted from Sterling S. Physiotherapy management of whiplash-associated disorders [WAD]. *J Physiother* 2014;60:5-12.)

latter condition may be caused by a surgically correctable lesion. After the initial period of areflexia, reflexes gradually return after 1 to 3 days and, after 1 to 4 weeks, patients with SCI will manifest characteristic hyperreflexia and spasticity. Reflexes are typically absent during the initial phase of spinal shock in the emergency department (ED).

TABLE 35.4 Spinal Motor Examination

Level of Lesion	Resulting Loss of Function
C4	Spontaneous breathing
C5	Shrugging of shoulders
C6	Flexion at elbow
C7	Extension at elbow
C8–T1	Flexion of fingers
T1–T12	Intercostal and abdominal muscles[1]
L1–L2	Flexion at hip
L3	Adduction at hip
L4	Abduction at hip
L5	Dorsiflexion of foot
S1–S2	Plantar flexion of foot
S2-S4	Rectal sphincter tone

[1]Localization of lesions in this area is best accomplished with the sensory examination.

Sensory function can be quickly evaluated through the use of a structured approach (Table 35.6) or graphic dermatome chart (Fig. 35.27).

TABLE 35.5 Spinal Reflex Examination

Level of Lesion (At or Above)	Resulting Loss of Reflex
C6	Biceps
C7	Triceps
L4	Patellar
S1	Achilles

TABLE 35.6 Spinal Sensory Examination

Level of Lesion	Resulting Level of Loss of Sensation
C2	Occiput
C3	Thyroid cartilage
C4	Suprasternal notch
C5	Below clavicle
C6	Thumb
C7	Index finger
C8	Small finger
T4	Nipple line
T10	Umbilicus
L1	Femoral pulse
L2–L3	Medial aspect of thigh
L4	Knee
L5	Lateral aspect of calf
S1	Lateral aspect of foot
S2–S4	Perianal region

After locating an area of hypesthesia, one should move the sensory stimulus from areas of decreased sensation upward, rather than the reverse, because patients are more sensitive to the appearance of sensation than to its disappearance. A cotton swab may be used to assess sensitivity to light touch, a posterior column function. A pin should be used to assess pain, which is an anterior spinothalamic tract function. Even in the presence of complete motor paralysis, the presence of islands of preserved sensation within an affected dermatome or below the level of dysfunction indicates potential for functional recovery. An accurate baseline sensory examination is imperative because cephalad progression of hypesthesia is the most sensitive indicator of deterioration. When this is observed in the cervical region, one should anticipate impending respiratory failure and preemptively secure the airway.

Spinal Cord Lesions

Complete Spinal Cord Lesions

A complete spinal cord lesion is defined as total loss of motor power and sensation distal to the site of an SCI. Functional motor recovery is rare with a complete cord syndrome that persists for longer than 24 hours. Before making the diagnosis of a complete cord syndrome, however, two points should be considered. First, any evidence of minimal cord function, such as sacral sparing, excludes the patient from this group. Signs of sacral sparing include perianal sensation, preserved rectal sphincter tone, and flexor toe movement. Any of these signs indicates a partial lesion, usually a central cord syndrome, and the patient ultimately may have substantial functional recovery, including bowel and bladder control and eventual ambulation.

Second, a complete spinal cord lesion may be mimicked by a condition termed *spinal shock,* which may persist for weeks. Spinal shock results from a concussive injury to the spinal cord that causes total neurologic dysfunction distal to the site of injury. The end of spinal shock is heralded by the return of the bulbocavernosus reflex, which is a normal cord-mediated reflex elicited by placing a gloved finger in the patient's rectum and then squeezing the glans penis or clitoris or by tugging gently on the Foley catheter. An intact reflex results in rectal sphincter contraction. Absence of this reflex indicates the presence of spinal shock, during which time the patient's prognosis cannot be accurately assessed.

Incomplete Spinal Cord Lesions

Approximately 90% of incomplete spinal injuries can be classified as one of three clinical syndromes—the *central cord syndrome*, *Brown-Séquard syndrome*, and *anterior cord syndrome* (Fig. 35.28). The most common is the central cord syndrome, often seen in patients with degenerative arthritis who suffer neck hyperextension (Table 35.7). Extreme hyperextension can also injure the vertebral artery causing a posterior inferior cerebellar artery syndrome resulting in ischemia to the lateral medulla (Fig. 35.29, and see Table 35.7).

DIFFERENTIAL DIAGNOSES

The differential diagnosis of spinal injuries includes peripheral nerve injuries that may mimic sensory or motor deficits from a central lesion. For example, compression of the superficial peroneal nerve from a fibular fracture may result in a foot drop, but impingement of a lumbar spinal nerve root from a lumbar vertebral fracture could also result in weakness in dorsiflexion. As noted, ligamentous injury in SCIWORA is also a consideration. Muscle contusions and strains around the neck, thorax, and lumbosacral regions would also be part of the differential diagnosis. Finally, a diagnosis of exclusion, conversion disorder, can result in apparent manifestations of sensory and motor deficits that may initially be confused and attributed to spinal injuries.

DIAGNOSTIC TESTING

Radiographic Evaluation

Indications

Emergency clinicians have historically taken a liberal approach to imaging the cervical spine in the setting of trauma because failure to recognize an SCI may result in devastating neurologic consequences. In an effort to standardize clinical practice and reduce avoidable radiographic imaging, two clinical decision rules were developed. The first rule to be developed, the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC), was based on a multicenter prospective observational study involving almost 35,000 trauma patients seen at 21 EDs in the United States. The decision instrument required patients to meet five criteria to be classified as having a low probability of injury (Box 35.1). The decision rule identified all but 8 of the 818 patients who had spinal injuries. Two of these patients had a clinically

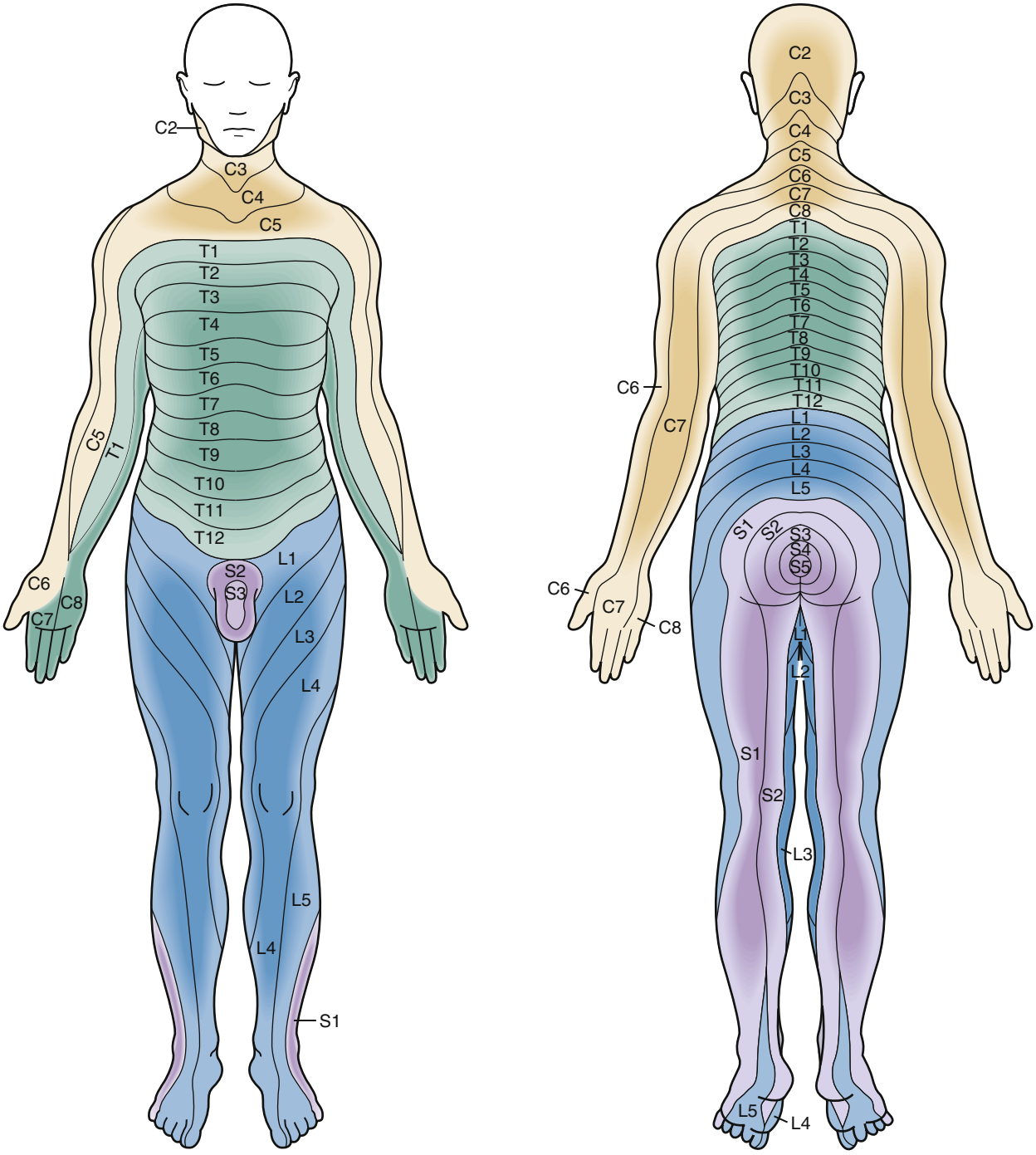


Fig. 35.27 Sensory dermatomes.

significant injury, only one of whom required surgical stabilization, and neither sustained a permanent neurologic injury. Sensitivity, specificity, and negative predictive value of the NLC were 99.6%, 12.9%, and 99.8%, respectively.

Owing to concerns about the low specificity of the NLC, the Canadian C-Spine Rule (CCR) was developed using 25 selected clinical predictor variables associated with spine injury. In 2003, the CCR was prospectively studied and compared with the NLC in nine Canadian tertiary care hospitals. Of 8283 patients, 162 were found to have clinically significant injuries, and the sensitivity, specificity, and negative predictive values of the CCR were, respectively, 99.4%, 45.1%, and 100%. The CCR is composed of the following three questions:

1. Are there any high-risk factors that mandate radiography?
2. Are there any low-risk factors that allow safe assessment of range of motion?
3. Is the patient able to rotate his or her neck actively 45 degrees to the left and to the right?

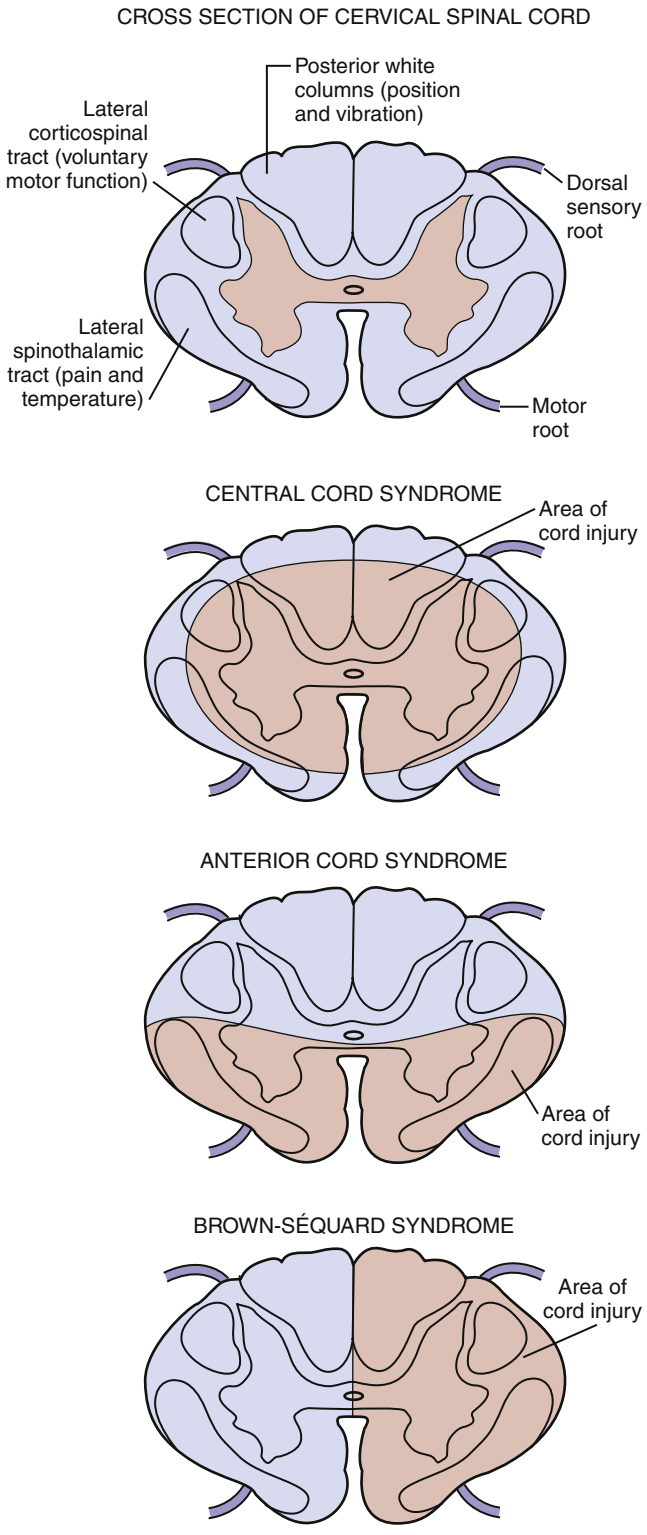


Fig. 35.28 Incomplete spinal cord syndromes.

According to the CCR, patients with no high-risk factors, any low-risk factor, and the ability to rotate the neck do not require radiographic evaluation (Box 35.2). Although the NEXUS criteria are more widely used in the United States, there is controversy regarding which of the two rules to implement; a systematic review demonstrated better diagnostic accuracy for the CCR. There are methodologic differences in the respective study designs, such as different inclusion and exclusion criteria. Nonetheless, both rules have been well-validated and are sensitive, and the use of either rule decreases the number of unnecessary radiographs while rarely missing clinically significant injuries.

A validated clinical decision rule for imaging in thoracolumbar spine (TLS) injuries does not yet exist, although it is recognized that the clinical examination alone is inadequate to exclude TLS injuries.[6] A prospectively derived rule found the absence of back pain, midline tenderness, and neurologic deficit in combination with age under 60 and low-risk mechanism were 98.9% sensitive for clinically significant TLS injuries, but validation of these findings is required before the rule is appropriate for clinical use.[7]

Cervical Plain Radiographs

Due to the widespread availability and superior test characteristics of CT imaging in the United States, spinal plain radiographs are now rarely obtained, especially when CT is ordered to visualize a different body part. Furthermore, plain radiographs have been shown to be inadequate to visualize the entire cervical spine in up to 72% of cases, thus necessitating CT scanning. However, plain radiographs are often used outside the United States, and there is concern regarding cost and exposure to medical radiation from CT. When compared to plain radiographs, CT respectively confers a 10- to 14-fold increase in radiation exposure to the skin and thyroid.

Thus, in light of the cost and radiation exposure, plain radiographs of the cervical spine may be obtained in patients who sustain a relatively minor mechanism of injury but fail the NLC and CCR criteria, and do not warrant CT of the head or other body parts. On plain radiographs, the C7–T1 vertebrae may be obscured in muscular or obese patients, as well as in patients with spinal lesions causing paralysis of the muscles that act to depress the shoulders. In this case, a swimmer's view of the lower cervical vertebrae, or CT scan, is often needed. The cross-table lateral view of the cervical spine is the most helpful x-ray, but its inadequacy as the sole view is well documented. The diagnostic yield is significantly increased when the AP and odontoid views are included. The NLC has shown that a technically adequate three-view trauma series will fail to diagnose significant spinal injury in only 0.07% of patients with injuries and in only 0.008% of patients with unstable injuries. Note that once a CT scan is performed, however, plain radiographs do not add any further clinically relevant information and should not be obtained.

Flexion-extension (F/E) views are rarely indicated in the acute evaluation of a patient presenting to the ED after acute trauma. F/E views have poor test characteristics for the detection of ligamentous cervical spine injuries and are inferior to MRI.

Thoracolumbar Plain Radiographs

Plain films of the thoracolumbar spine have inferior sensitivity for detection of fractures when compared with CT imaging and a higher dosage of radiation exposure. The posterior cortex is poorly visualized on plain film which causes some injuries to be inaccurately classified as stable, and causes some burst fractures to be misidentified as compression fractures.

Interpretation of spinal plain radiographs. The inspection of the lateral cervical spine film should be methodical and complete. It is helpful to remember the ABCs of interpreting the lateral film, where *A* stands for alignment, *B* for bony abnormalities, *C* for cartilage space assessment, and *s* for soft tissues (Figs. 35.30, 35.31,

TABLE 35.7 Incomplete Spinal Cord Injuries

Incomplete Cord Injury	Mechanism	Exam Findings	Prognosis
Central Cord Syndrome	Neck hyperextension buckles ligamentum flavum causing concussion of central cord. Spinothalamic and pyramidal tracts affected	Upper > lower extremity weakness and loss of pain and temperature sensation	>50% regain ambulation, bladder and bowel function. Hand function regained is variable.
Brown-Séquard Syndrome	Hemisection of cord usually from penetrating injury, more rarely from cervical spine lateral mass fracture	Ipsilateral loss of motor, position, and vibration sense. Contralateral loss of pain and temperature sensation	Contralateral motor, bladder and bowel function maintained. Most regain ambulation
Anterior Cord Syndrome	Hyperflexion causing cord contusion from bone fragment or herniated disk, or anterior spinal artery injury	Motor paralysis and hypalgesia below level of injury. Preservation of position, light touch, and vibratory sensation	Potentially surgically correctable, prompt neurosurgical consultation warranted. Variable recovery within 24 hours of surgery but minimal thereafter.
Cauda Equina Syndrome	Injury to nerve roots below the L2 level	Perineal or bilateral leg pain, bowel or bladder dysfunction, perianal anesthesia, urinary retention, diminished rectal sphincter tone, bilateral leg weakness	Variable recovery of bladder and bowel function
SCIWORA	Mechanism uncertain, but possibly ligamentous laxity allowing transient spinal subluxation, cord stretching and vascular compromise	Brief episode of upper extremity weakness or paresthesias followed by neurologic deficits appearing hours to days later[22]	Variable depending on severity of deficits present and rate of resolution[23]
Posterior Inferior Cerebellar Artery Syndrome	Vertebral artery injury from extreme hyperextension causing ischemia to lateral medulla (see Fig. 35.29)	Dysphagia and dysphonia from ipsilateral paralysis of pharynx and larynx, hiccups, nausea and vomiting, vertigo, cerebellar ataxia, contralateral loss of pain and temperature sensation	More favorable than other ischemic strokes, often recover ADLs despite persistent gait instability
Horner's Syndrome	Injury to sympathetic fibers in cervical spine	Ipsilateral ptosis, miosis, and anhidrosis	Dependent on other structures affected by injury
Spinal Trigeminal Tract Injury	Arterial injury from extreme hyperextension	Dejeuene onion skin analgesia of the face	Dependent on other structures affected by ischemia

and Table 35.8). Pseudosubluxation in infants and children is attributed to immature muscular development and a hypermobile spine. Thus, if a high cervical injury is suspected in a child, the posterior cervical line, which connects the points bisecting the bases of the spinous processes of C1 and C3, should be used (Fig. 35.32). If the base of C2 lies more than 2 mm anterior or posterior to the posterior cervical line, an injury at that level should be suspected. Odontoid and AP views should also be assessed for signs suggestive of fracture.

Advanced Imaging: Computed Tomography and Magnetic Resonance

The CT scan is the technique of choice for the evaluation of acute spine trauma because of its superior test characteristics and time efficiency in the radiology department when compared to plain radiography.[8] CT imaging permits examination without moving the patient from the supine position and is thus preferable in terms of fracture stabilization, airway control, and other life support measures. CT can also identify bony fragments, acute disk herniation, foreign body, paraspinal hematoma, or extramedullary hematoma. Thus, routine plain radiographs in many centers are reserved for the alert patient with minor trauma. In addition to those undergoing CT imaging of other body parts, CT is preferred when plain radiographs are difficult to interpret because of abnormal anatomy, such as in older adults with degenerative disease or the patient with rheumatoid arthritis. Additionally, rotational and distraction injuries resulting in atlanto-occipital dislocations may be missed on plain x-ray. For patients who have a severe mechanism of injury, unless CT is not available, we support the practice guidelines from the Eastern Association for the Surgery of Trauma, which recommend that CT imaging from the occiput to T1 be used as the primary screening. Because fractures in contiguous and noncontiguous vertebrae are fairly common, CT scans should be obtained to visualize the entire cervical spine.

Fractures involving the transverse foramina or C1–C3 are associated with vertebral artery dissection or thrombosis in up 22% of cases, as well as basilar artery stroke. When such fractures are identified, we recommend further study by magnetic resonance angiography (MRA), CT angiography (CTA), or four-vessel angiography to evaluate for blunt cerebrovascular injury (BCVI). Recognition of the risk factors for BCVI and dedicated vascular imaging allow for the early detection of these potentially occult injuries (Box 35.3). An in-depth discussion of BCVI is found in Chapter 36.

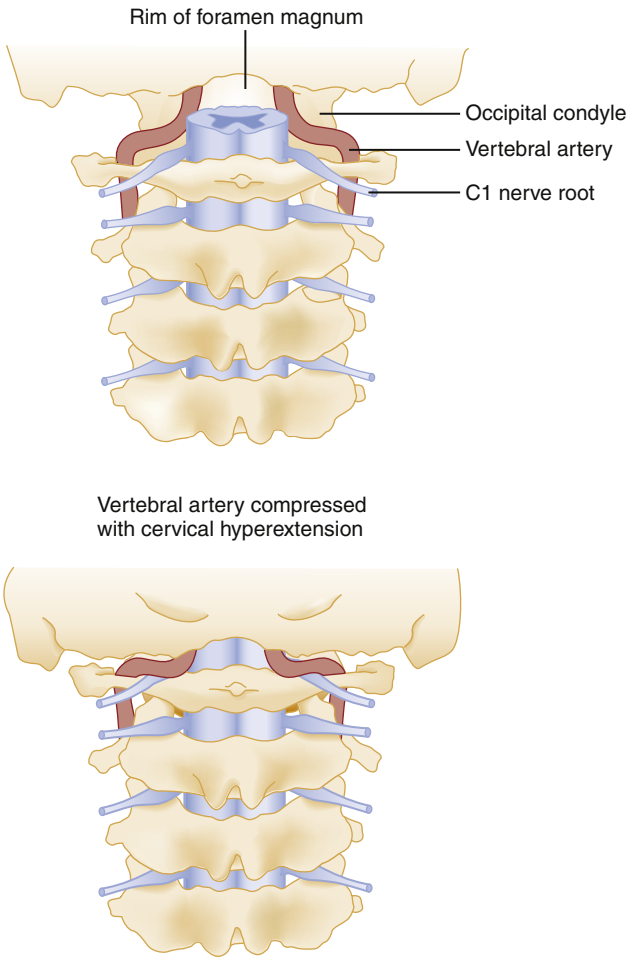


Fig. 35.29 Mechanism of vertebral artery injury in extension injuries of the cervical spine.

BOX 35.1 Nexus Criteria for C-Spine Imaging

- No midline spinal tenderness present
- No focal neurologic deficit present
- Normal alertness
- No intoxication present
- No painful distracting injury

BOX 35.2 Canadian C-Spine Rule

High Risk Mandating Radiography

Age > 65

Dangerous mechanism of injury or

Sensory deficit in extremities

Dangerous mechanisms include:

- Fall from ≥ 1 meter or five stairs
- Axial load (e.g., diving)
- MVA ≥ 100 km/hr, rollover or ejection from vehicle
- MVA involving recreational vehicle
- Bicycle collision

Low Risk Factors Allowing for Range of Motion Assessment

- Simple rear-end MVA
- Sitting position in the emergency department
- Ambulatory at the time
- Delayed onset of neck pain
- Absence of midline cervical spine tenderness and
- Able to rotate neck 45 degrees to L and R

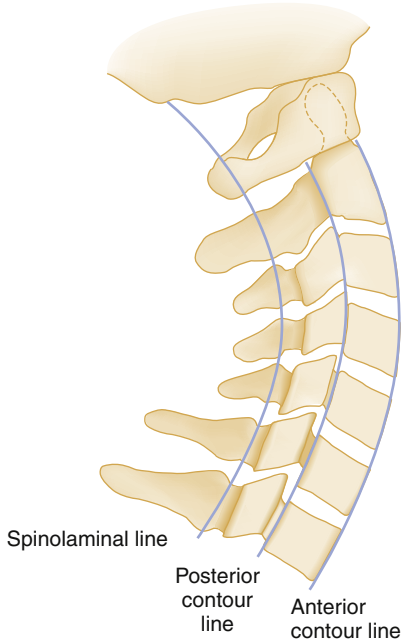


Fig. 35.30 Normal structural relationships of the lateral cervical spine.

Vertebral images reconstructed from CT scans of the abdomen and pelvis obtained for the evaluation of chest and abdominal injuries have sufficient sensitivity to detect fractures without additional dedicated CT imaging of the thoracolumbar spine.[9] CT is also thought to be adequate to clear cervical spines, even in the obtunded blunt trauma patient. The Eastern Association for the Surgery of Trauma issued a clinical practice guideline conditionally supporting the clearance of the cervical spine after negative CT imaging given a high negative predictive value, although the level of evidence was deemed low-quality.[10]

Although CT has a higher sensitivity than MRI to detect fractures and dislocations at the craniocervical junction, MRI provides superior visualization of nonosseous structures directly, including intramedullary and extramedullary spinal abnormalities that potentially cause neurologic deficit (Fig. 35.33). Its major impact has therefore been in demonstrating potentially surgically correctable lesions, including acute disk herniation, ligamentous injury, bony compression, epidural and subdural hemorrhages, and vertebral artery occlusion. MRI can identify three separate patterns of SCI, including acute cord hemorrhage, cord edema or contusion, and mixed cord injury. Patients with cord edema or contusion show significant neurologic improvement, whereas those with cord hemorrhage (Fig. 35.34) fare far worse. MRI can also diagnose a developing intramedullary (posttraumatic) syrinx or subarachnoid cystic changes (Fig. 35.35). Thus, a patient who demonstrates neurologic deficit or persistent neck pain suggesting ligamentous injury or an occult spine injury, should undergo an expedited MRI, even if the initial CT scan or plain radiographs are interpreted as normal (Fig. 35.36). In the obtunded or unreliable patient, MRI may

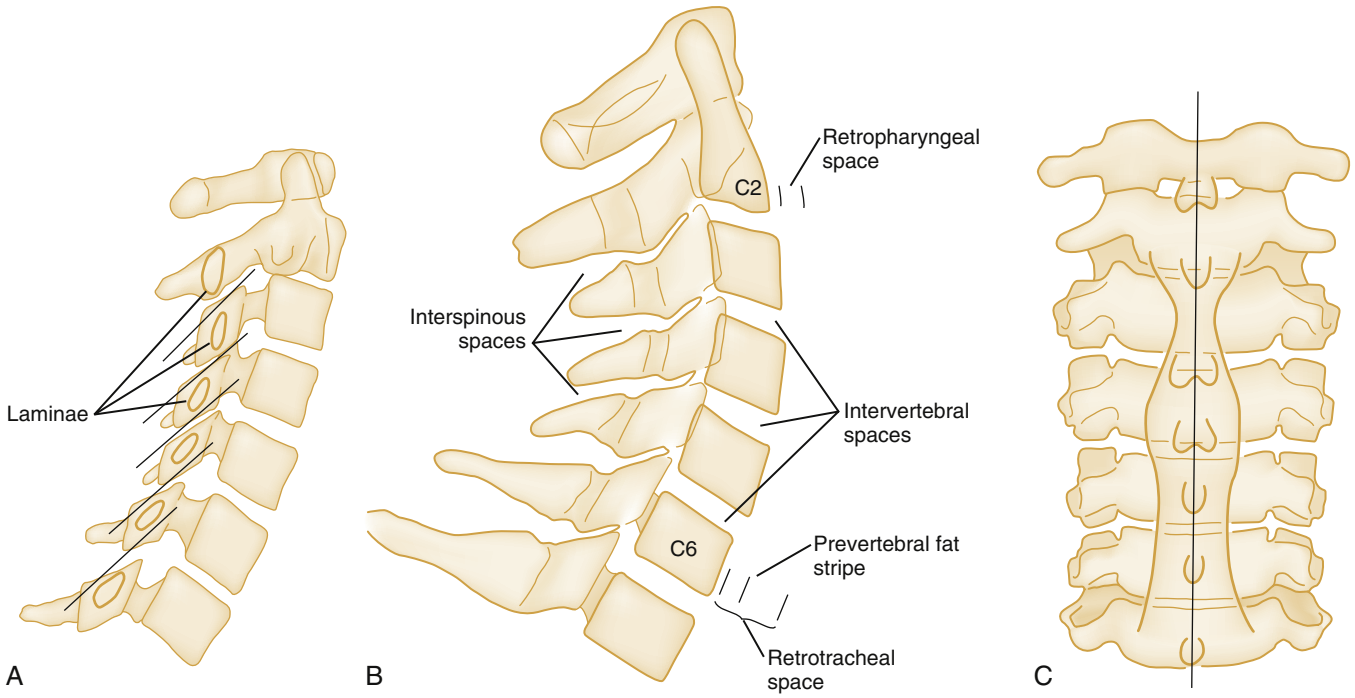


Fig. 35.31 (A) Normal structural relationships of the cervical spine laminae in an oblique view form a so-called shingles on a roof appearance. (B) In the lateral view, the intervertebral spaces and interspinous spaces should be compared with the spaces above and below for asymmetry. The retropharyngeal and retrotracheal soft tissues are measured at the C2 and C6 levels for swelling. (C) Normal relationship between soft tissues and bony structures of the cervical spine in the lateral and anteroposterior (AP) views. In the AP view, the tracheal and laryngeal air shadows should be within the midline. A straight line should connect points bisecting the spinous processes. If such is not the case, rotatory injuries are suspected.

TABLE 35.8 Interpretation of Spinal Plain Radiographs

Radiologic View	Normal Findings	Significant Findings
Cross-table lateral	Three continuous lines (see Fig. 35.30): • Anterior vertebral body margins • Posterior vertebral body margins • Spinolaminal line: spinous process bases Predental space: distance between anterior odontoid and posterior aspect of anterior C1 ring (see Fig. 35.32) • ≤3mm in adults • ≤5mm in children Cartilage spaces: Even width across each intervertebral and interspinous level Soft tissues: Retropharyngeal and retrotracheal spaces measured from anterior vertebral body to airspace (see Fig. 35.32) • C2: ≤6 mm in adults and children • C3–C4: ≤5 mm, or less than half width of vertebral body • C6: ≤22 mm in adults, ≤14 mm under age 15	Disruption of any line suggests bony or ligamentous injury Pseudosubluxation of C2 and C3 common in infants and children Widening of predental space may indicate Jefferson fracture of C1 Anterior or posterior widening of space may indicate unstable dislocation Prevertebral swelling may be only sign of hemorrhage and spinal injury Air in prevertebral space suggests aerodigestive tract injury Retropharynx may widen during expiration in children under 2 years, obtain inspiratory films
Odontoid	Open and closed mouth views of atlas and axis for diagnosing odontoid and Jefferson fractures	Fractures mimicked by nonfusion of odontoid in children, congenital odontoid anomalies in adults
Anteroposterior	Base of spinous processes should form straight line (see Fig. 35.32) Pedicles viewed end on Laryngeal and tracheal air shadows midline Regular outlines of lateral masses	Bulging mediastinal stripe from hemorrhage may be only evidence vertebral body fracture on chest X-ray Widened interpedicular distance suggests burst fracture

not be necessary to exclude unstable injuries if the CT scan is normal, according to the Eastern guidelines.[10]

MANAGEMENT

Spinal injury should be suspected in all trauma victims with an unknown or suggestive mechanism of injury associated with complaints of neck or back pain, evidence of significant head or facial trauma, spinal tenderness, signs of focal neurologic deficit, impaired consciousness, potentially distracting injuries, or unexplained hypotension.

Spinal Column Stabilization

Out-of-Hospital Care

Prehospital personnel are well versed in the care of the patient with a potentially traumatized spine, and all emergency medical services (EMS) incorporate these principles. Historically, the traditional approach to immobilization required the automatic and routine initiation at the scene of the use of a backboard, rigid cervical collar, and supportive blocks on both sides of the head with a concerning mechanism of injury. However, it has been noted that many trauma patients are unnecessarily immobilized by EMS, and immobilization can be detrimental. In addition to resulting in prolonged on-scene time and delayed transport to definitive care, the backboard can lead to pressure ulcers, increased pain, and decreased functional respiratory residual capacity. Also, cervical collars can hide other injuries, such as lacerations and hematomas, and have even been found to result in worsening vertebral distraction injuries. There is also ample evidence that EMS providers can safely apply spinal assessment guidelines, such as NEXUS.

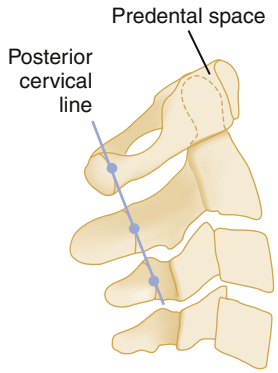


Fig. 35.32 Posterior cervical line of a normal lateral spine.

BOX 35.3 Expanded Denver Screening Criteria for Blunt Cerebrovascular Injury

Imaging Indicated if One or More Criteria Present

Signs/symptoms of BCVI:

- Arterial hemorrhage from neck/nose/mouth
- Cervical bruit in patients <50 years
- Expanding cervical hematoma
- Focal neurologic deficit
- Neurologic exam incongruous with head CT findings
- Stroke on secondary CT scan

Risk factors for BVCI (high-energy transfer mechanism):

- Le Fort II or III
- Mandible fracture
- Complex skull fracture/basilar skull fracture/occipital condyle fracture
- Severe traumatic brain injury (TBI) with GIsasgow Coma Score < 6
- Cervical spine fracture, subluxation or ligamentous injury at any level
- Near hanging with anoxic brain injury
- Seat belt abrasion with significant swelling, pain or altered mental status
- TBI with thoracic injury
- Scalp degloving
- Thoracic vascular injury
- Blunt cardiac rupture
- Upper rib fracture

Adapted from Geddes et al. Expanded screening criteria for blunt cerebrovascular injury: A bigger impact than anticipated. *Am J Surg* 2016;212(6):1167-1174.

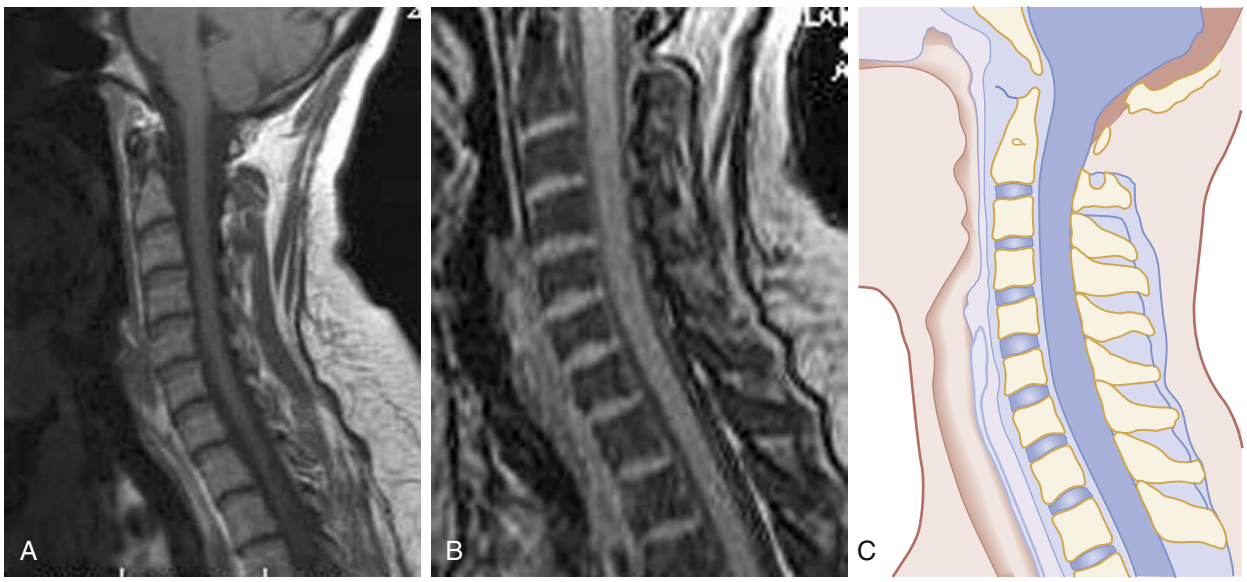
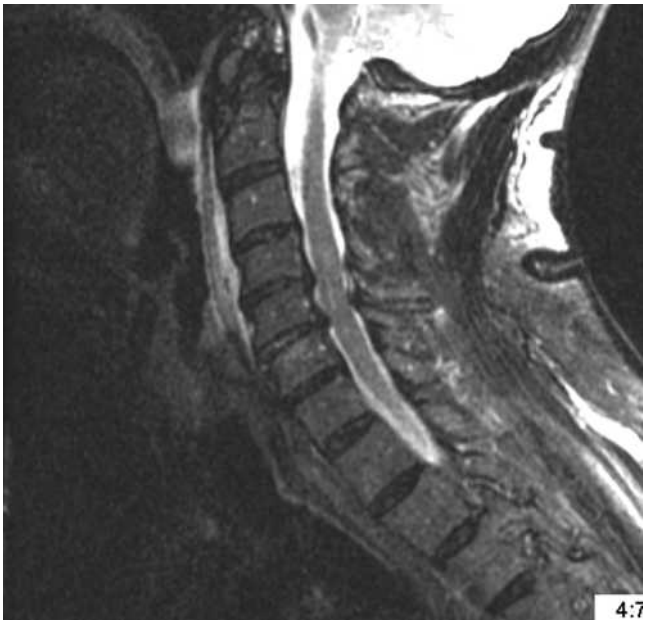


Fig. 35.33 Normal sagittal magnetic resonance images of the cervical spine. (A) T1-weighted and flip angle (B) scans. (C) Cervical spine.



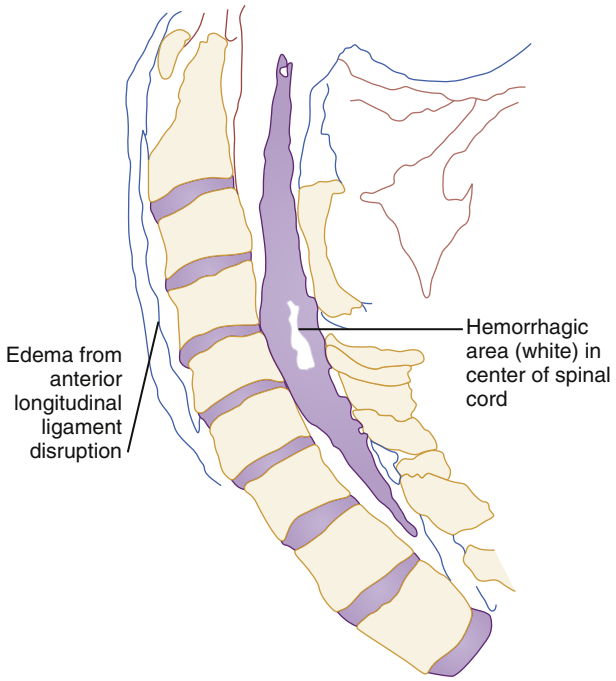


Fig. 35.34 MRI scan showing a small area of central cord hemorrhage and anterior and posterior ligamentous disruption.

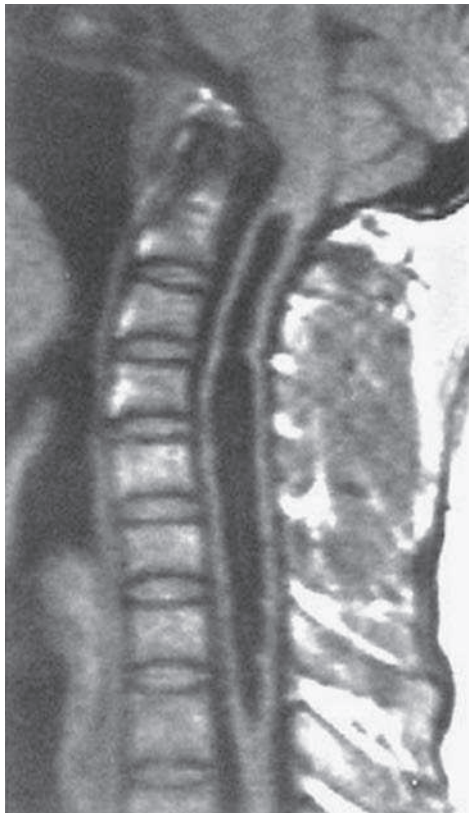


Fig. 35.35 MRI scan showing posttraumatic syrinx of the spinal cord.

Emergency Department

Trauma victims are assessed as described in Chapter 32 while maintaining immobilization. If the patient's spine can be clinically cleared by use of the NEXUS criteria or CCR, the immobilization device may be removed. If the trauma victim was wearing a helmet and the helmet was not removed in the field, the face mask, helmet, and any sports padding (e.g., shoulder pads on hockey or football players) may be carefully removed while immobilization is maintained. Ideally, at least two or three providers should be present to perform the task of helmet removal. Once the helmet and shoulder pads have been removed, a rigid collar should be placed if the patient's cervical spine cannot be cleared by use of the NEXUS criteria or CCR.

Patients with probable spinal injury who are conscious and cooperative should be immobilized until imaging has been performed. Patients who are uncooperative because of head injury, drug or alcohol intoxication, hypotension, or presence of multiple painful injuries require a deliberate approach, including the use of chemical and mechanical restraints. Suspected thoracic and lumbar spinal injuries are best managed by keeping the patient supine and immobile, using logroll precautions when needed. The goal of stabilization in cervical spine trauma is to immobilize the neck and body because any movement may extend the initial injury. If the patient is not already immobilized on a backboard, the torso should be firmly anchored to the examining table by straps or rolled sheets. Sedation, drug-induced paralysis, and intubation may be required for patients who pose a danger to themselves because of excessive movement and whose injuries otherwise will likely require intubation. Paralysis and intubation are not used simply to control patient movement or lack of cooperation. Spinal precautions should be maintained in patients with an altered sensorium until the presence of an injury can be excluded clinically or radiographically. Every effort, however, should be made to remove the patient as quickly as possible from the backboard to prevent aspiration and the development of pressure ulcers. Suctioning should be readily available to prevent aspiration. Vomiting patients should be placed on their side by logrolling while spinal alignment is maintained.

Airway Management

Cervical spine injuries often require early intubation as part of the resuscitation. Lesions above C3 may rapidly progress to respiratory paralysis, and the spread of edema from a lower injury may cause delayed phrenic nerve paralysis, as well as ascension of the neurologic injury above the level of C3. Cervical injuries may be associated with airway obstruction from retropharyngeal hemorrhage or edema or maxillofacial trauma. Medications for induction and post-intubation sedation should be chosen in order to reduce the risk of hypotension (e.g., propofol).

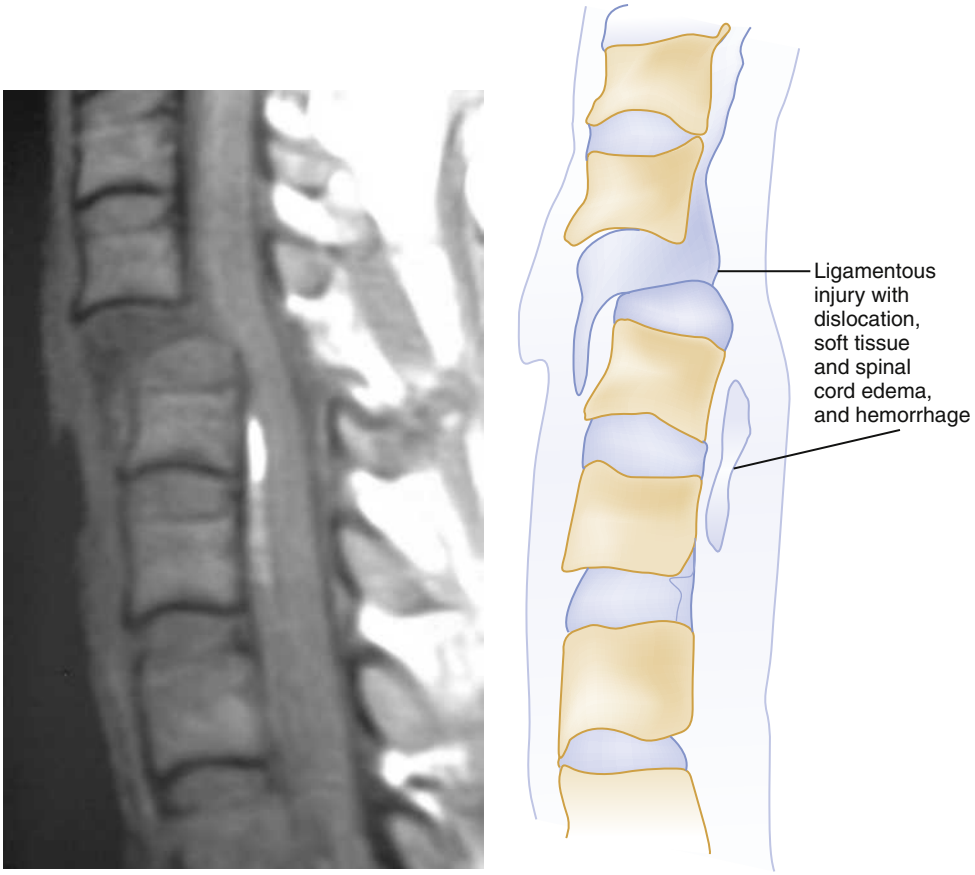


Fig. 35.36 Anteroposterior longitudinal ligament disruption. A sagittal MRI scan demonstrates ligamentous disruption between C4 and C5, with blood tracking in the anterior spinal canal.

Airway management of the trauma patient, including those with suspected spine injury, is discussed in Chapter 1.

Spinal Shock

Spinal shock is characterized by the temporary loss of neurologic function and autonomic tone below the level of an acute spinal cord lesion. Patients usually exhibit flaccid paralysis with loss of sensation, deep tendon reflexes, and urinary retention, along with bradycardia, hypotension, hypothermia, and intestinal ileus. Recovery from spinal shock, which may last from less than 24 hours to more than 2 weeks, is heralded by the return of the bulbocavernosus reflex.

Neurogenic hypotension, caused by loss of vasomotor tone and lack of reflex tachycardia, is a diagnosis of exclusion in the trauma victim. It should not be considered the cause of hypotension unless the patient is flaccid and areflexic, reflex tachycardia and peripheral vasoconstriction are absent and, most important, the possibilities of coexisting hemorrhagic shock, cardiac tamponade, or tension pneumothorax have been eliminated.

Although there is no high-quality evidence for an optimal mean arterial pressure (MAP), we recommend initiating the resuscitation of hypotensive trauma victims with a balanced crystalloid fluid infusion, as outlined in Chapter 32. Most cases of pure neurogenic hypotension are mild (e.g., systolic blood pressure > 90 mm Hg) and may not require fluid resuscitation or will respond to modest amounts of fluid.[11] Severe neurogenic hypotension (e.g., systolic blood pressure < 70 mm Hg), seen in 20% to 30% of cases, more often occurs with high cervical injuries associated with total or near-total loss of neurologic function.[12] Because hypotension can lead to hypoperfusion and secondary spinal cord ischemia, prolonged severe hypotension (systolic blood pressure < 70 mm Hg) should be prevented and treated. Fluid resuscitation is often ineffective in such patients and may result in fluid overload. Thus, when there is persistent hypotension despite fluids, we recommend vasopressor support with norepinephrine to be started at 0.05 μg/kg/min and titrated upward to a maximum dose of 1 μg/kg/min to achieve a MAP of 85 mm Hg.[13-15]

Pharmacologic Treatment for Incomplete Cord Injury

Delayed biochemical damage contributes to ongoing tissue loss and worsening neurologic function in SCI. Thus, numerous neuroprotective and neuroregenerative treatment strategies, including pharmacologic treatment, hypothermia, and decompression, have been investigated in laboratory animal studies and human clinical trials. Despite public interest and media attention on case reports of significant functional recovery after therapeutic hypothermia in SCI, evidence in support of therapeutic hypothermia is of low quality and limited to a number of case series.[16] To date, no randomized controlled trial of hypothermia in SCI has been performed, and it cannot be recommended for clinical use. Reported complications from hypothermia induction include pneumonia, thrombocytopenia, and atrial fibrillation.

Methylprednisolone, once widely recommended for use on the basis of extremely weak evidence, has been found to have no benefit and is likely, on balance, to be harmful. It is no longer recommended or used for acute spinal cord injury.[17]

Associated Injuries

Cardiopulmonary

Although cardiopulmonary deterioration in a trauma victim is usually the result of hemorrhagic shock or direct injury to the heart or lungs, pulmonary edema may also occur in response to brain injury and SCI.

Spinal cord trauma stimulates an intense sympathetic discharge with two subsequent effects. First, pulmonary capillary endothelial cells are disrupted, leading to the pulmonary capillary leak syndrome, in which pulmonary edema occurs in the presence of normal pulmonary artery pressures (<18 mm Hg). Second, marked increases in afterload may lead to pulmonary edema associated with high pulmonary artery pressures (>18 mm Hg) from ventricular dysfunction. Excessive fluid resuscitation can also contribute to pulmonary edema. Later in the recovery period, many SCI patients suffer from alternating episodes of low and high blood pressure, often with labile heart rates, termed *autonomic dysreflexia*.[18] The treatment for this is primarily supportive by addressing causative factors, such as bladder distention, pain, and hydration status.

Gastrointestinal and Genitourinary

If SCI renders the abdominal examination unreliable, an abdominal CT scan or ultrasound is often necessary. In the acute stages of SCI, the gastrointestinal tract and bladder become atonic. Thus, a nasogastric tube should be placed to prevent gastric distention and a Foley catheter inserted to prevent bladder distention and monitor fluid output. Because gastrointestinal bleeding from stress ulcers occurs in 2% to 20% of spinal trauma patients, ulcer prophylaxis with histamine H2 receptor antagonists or proton pump inhibitors should be initiated.

Skin

Denervated skin is extremely susceptible to pressure necrosis, and sores can develop in less than 1 hour on unpadded spinal carts. Therefore, backboards should be removed as soon as possible. Padding pressure areas with sheepskin or foam can help minimize decubitus ulcers.

Definitive Treatment and Prognosis

The role of prompt surgical intervention in the management of spinal injuries is currently limited to relieving spinal cord impingement caused by foreign bodies, herniated disks, bony fracture fragments, or epidural hematoma. Surgery may be necessary later to stabilize severe bony injuries or reduce spinal dislocations. The timing of surgical intervention remains controversial because there are no well-designed studies that have determined whether early (<12 hours) versus late decompression is beneficial.

Once almost uniformly fatal, major spinal injury caused death from pulmonary complications or sepsis from skin necrosis or urinary infection. The advent of antibiotic therapy made long-term survival not only possible but also expected. Today, patients with SCIs are best managed at a regional spine injury center, where a team of neurosurgeons, orthopedic surgeons, psychologists, and physical therapists can initiate rehabilitation. Specialized SCI treatment centers offer patients a chance to return to a productive life within the limits of their disability. With the exception of patients with high cervical lesions (above C5), most patients attain sufficient independence to live outside of high-level care environments.

Significant pain impacting quality of life is frequently reported after recovery from the initial injury. Pain after SCI may be nociceptive, or related to tissue injury, or neuropathic and can occur at the level of the SCI or below. Various pharmacologic agents have been investigated for the treatment of pain in SCI, with the strongest evidence supporting anticonvulsants including gabapentin and pregabalin.[19] Antidepressants may also be effective for those with co-occurring pain and depression. Opioids are effective for SCI-related pain, but caution should be exercised with their use given the often-chronic nature of pain after SCI. Nonopioid pharmacologic therapy is recommended prior to initiation of opioids in chronic pain. When given, opioids should be prescribed for a short duration at the lowest effective dose in an immediate release formulation,[20] because chronic opioid use and dependence are often preceded by an opioid prescription given for acute pain. Robotic powered exoskeleton devices have the ability to restore limited ambulatory function to survivors of SCI. Assisting patients with complete SCI with a thoracic or lower level after the initial recovery period, movements of the robotic limbs are coordinated using motion of the arms and trunk. Factors influencing function include software algorithms to generate smooth movements, and exoskeleton articulations analogous to human leg joints.[21]

BOX 35.4 Prognostic Indicators of Poor Functional Recovery Following Whiplash-Associated Disorders

Factors with Consistent Evidence for Being Prognostic Indicators for Poor Recovery

- Initial pain levels > 5.5/10
- Initial disability levels: NDI > 29%
- Symptoms of posttraumatic stress
- Negative expectations of recovery
- High pain catastrophizing
- Cold hyperalgesia

Factors with Consistent Evidence of Not Being Prognostic Indicators

- Accident-related features (e.g., collision awareness, position in vehicle, speed of accident)
- Findings on imaging
- Motor dysfunction

Factors with Inconsistent Evidence

- Older age
- Female gender
- Neck range of movement
- Compensation-related factors

NDI, Neurological Disability Index.
Adapted from Sterling S. Physiotherapy management of whiplash-associated disorders (WAD). *J Physiother* 2014;60:5-12.

DISPOSITION

Cervical Soft Tissue Injuries

Patients with cervical soft tissue injuries of the spine who have only mild to moderate discomfort without neurologic impairment or abnormal radiographic findings (WAD class 1 or 2) are best managed as outpatients. Discharge instructions should include educating the patient that pain often increases over the first 24 to 48 hours but that the symptoms will begin to dissipate thereafter. We recommend treatment with analgesics, such as acetaminophen, 650 to 1000 mg/dose, up to four times daily, not to exceed 4 gm. Although analgesic doses of a nonsteroidal antiinflammatory drug, such as ibuprofen, 400 to 600 mg/dose, is also reasonable, there is ample evidence that acetaminophen, which has fewer adverse effects on the gastrointestinal and renal systems, is equally effective, and there is no indication for antiinflammatory treatment. Additionally, we do not recommend medications with purported muscle relaxant properties, such as cyclobenzaprine, because they have not been found to provide additional benefit and have an adverse side effect profile (principally anticholinergic effects and drowsiness.). Finally, referral for follow-up with a primary care physician is indicated because up to 50% of patients experiencing neck pain after trauma will continue to have symptoms at 1 year. This is more likely in patients with WAD class 3 but can occur in patients with class 2 and rarely class 1. Box 35.4 lists the prognostic indicators of poor functional recovery in patients with a WAD.

Minor Fractures

Most patients with spinal fractures require hospitalization. Patients with isolated cervical vertebral body compression or spinous process fractures may be managed as outpatients if there is no evidence of neurologic impairment or associated ligamentous instability, and the degree of patient distress is not severe. Appropriate follow-up should be arranged for all patients because even minor spinal injuries may be associated with prolonged disability from chronic pain.

For patients with minor wedge fractures (<10% compression of the anterior vertebral body height) who do not have an associated ileus or neurologic deficit, outpatient management may be possible. However, most wedge fractures of the thoracic and lumbar spines are usually best managed in the hospital for several reasons. First, patients with these injuries usually have marked discomfort, often requiring parenteral opioid analgesia. Second, significant force is generally required to fracture thoracic or lumbar vertebrae, and associated intrathoracic or abdominal injuries are common.[5] Third, lower thoracic and lumbar fractures are associated with prolonged and occasionally delayed gastrointestinal ileus, requiring continuous nasogastric suction. Finally, older adults who have vertebral fractures and only minor associated injuries may require admission to facilitate assessment of fall risks and expedite rehabilitation.

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CHAPTER 35: QUESTIONS AND ANSWERS

1. Which of the following is a stable cervical spine fracture?
- **A.** Anterior atlantoaxial dislocation without fracture
- **B.** Bilateral facet dislocation
- **C.** Flexion teardrop
- **D.** Jefferson fracture
- **E.** Unilateral facet dislocation

Answer: E. See Table 35.1 for a classification of spinal injuries according to stability.

2. A 28-year-old man is brought to the emergency department (ED) after a rollover motor vehicle collision (MVC). He is moderately hypotensive, unable to flex his elbows, and has diffuse lower extremity paralysis. What is the likely site of the lesion?
- **A.** C4
- **B.** C5
- **C.** C6
- **D.** C7
- **E.** C8

Answer: C. See Table 35.2

3. Which of the following statements regarding high-dose methylprednisolone after spinal cord injury is true?
- **A.** Dexamethasone is superior to methylprednisolone if a concurrent closed head injury is present.
- **B.** High-dose methylprednisolone should not be used to treat spinal cord injury.
- **C.** It is efficacious after penetrating injury if given within 4 hours.
- **D.** It is efficacious in cases of spinal shock.
- **E.** It is more efficacious after thoracic than after lumbar injuries.

Answer: B. Evidence that high-dose methylprednisolone is a clinically efficacious intervention in the management of acute, blunt, partial spinal cord injury is lacking and, because of severe side effects, it should not be used.

4. A 27-year-old man presents after a high-speed rollover MVC. The physical examination is remarkable for T8 motor-sensory deficit and a moderately distended abdomen that is nontender. Vital signs are heart rate, 108 beats/min, blood pressure, 88/40 mm Hg, respiratory rate, 22 breaths/min, temperature, 35°C (95°F), and oxygen (O_2) saturation, 96%. Which of the following tests or treatments is indicated?
- **A.** Baseline laboratory tests and observation
- **B.** Computed tomography (CT) scan of the abdomen
- **C.** Intravenous phenylephrine infusion
- **D.** Packed red blood cell transfusion
- **E.** Thoracolumbar spine films

Answer: B. Spinal cord injury often renders the abdominal examination unremarkable. CT, ultrasonography, diagnostic peritoneal lavage, or some combination is necessary to rule out intra-abdominal injury.

5. A 23-year-old man presents after a rollover MVC. He is brought by emergency medical services (EMS) from the scene fully restrained on a backboard, with a cervical collar. The physical examination is remarkable for moderate symmetric numbness below the neck, symmetric arm and leg weakness, intact reflexes, and diminished rectal tone. Vital signs are heart rate, 94 beats/min, blood pressure, 80/46 mm Hg, respiratory rate, 24 breaths/min, and O_2 saturation, 96%. Which of the following treatment sequences is most indicated?
   A. Crystalloid to CT scan to phenylephrine
   B. Crystalloid to focused assessment with sonography for trauma (FAST) examination to transfusion
   C. Crystalloid to phenylephrine to transfusion
   D. Dopamine to crystalloid to CT scan
   E. Transfusion to phenylephrine

Answer: B. Spinal shock should not be considered the cause of hypotension unless the patient is flaccid and areflexic. Crystalloid is the first step regardless of the traumatic hypotensive cause. The possibilities of coexisting hemorrhagic shock, cardiac tamponade, tension pneumothorax, or other life-threatening injuries should first be addressed. The absence of vasomotor activity in patients with neurogenic hypotension may mask the usual presentation of these life-threatening injuries. In this case, the lack of flaccidity and presence of reflexes argues for a non-neurogenic cause for the hypotension.

6. Which of the following is not a characteristic of flexion-distraction injuries of the lumbar spine?
   A. Compression of the anterior vertebral body
   B. Associated intrabdominal injuries are common
   C. Axis of rotation anterior to the vertebral body
   D. Unstable fracture pattern

Answer: C. Flexion distraction injuries are characterized by an axis of rotation posterior to the anterior longitudinal ligament causing compression of the anterior vertebral body and distraction of the posterior elements with failure of all three columns. It is an unstable fracture pattern with a high rate of associated intra-abdominal injuries.

7. Presence of which of the following findings warrants imaging to evaluate for blunt cerebrovascular injury?
   A. Isolated seat belt abrasion
   B. LeFort I fracture
   C. Frontal scalp hematoma
   D. Cervical bruit in 40-year-old extricated after MVA

Answer: D. A cervical bruit auscultated in a patient under the age of 50 is a sign of possible blunt cerebrovascular injury and requires dedicated arterial imaging. A seat belt sign with significant swelling, pain or altered mental status is indication for screening for BCVI, but not an isolated seat belt abrasion. Midface fractures with instability, LeFort grades II and III, are associated with BCVI. Isolated scalp hematoma is not associated with an increased risk of BCVI.

36

Neck Trauma

Kim Newton and Ilene Claudius

KEY CONCEPTS

- Significant injuries to the cerebral vessels can occur as a result of blunt or penetrating trauma to the neck.
- Blunt trauma to the neck can lead to immediate or delayed ischemic strokes, and a low threshold for imaging vessels when neurologic findings or risk factors for cervical vessel injury exist is recommended.
- A no-zone approach to penetrating neck trauma is becoming widely accepted as opposed to a zone-based selective management algorithm.
- Multidetector CT angiogram is the initial imaging modality of choice in essentially all symptomatic cases of blunt or penetrating neck trauma.
- Both penetrating and blunt neck injuries can present with minimal to no initial signs of injury; a high index of suspicion is therefore required.
- Because of the paucity of neck trauma in children, many adult algorithms have been adopted for use in the pediatric population

FOUNDATIONS

Background and Importance

Penetrating neck injuries (PNIs) comprise 5% to 10% of all traumatic injuries, but represent less than 1% of admissions to the emergency department (ED).[1] Penetrating neck trauma carries a mortality rate of up to 10%.[2] This is primarily a condition of adults; penetrating neck trauma in the pediatric patient is fortunately an uncommon entity. Of all children entered in the 2008 to 2012 national trauma data bank, only 0.3% sustained PNI with an average age just under 8 years and a predominance of male victims (70%). In this study, 44% of the injuries were caused by knives and 24% by firearms. Aerodigestive injury is most common followed by vascular injury in children below age 11 years. In the 11 to 14-year group, this ratio reverses with vascular injuries being most common. Mortality rates are reported at 5.6%.[3]

Blunt neck trauma can injure the airway, pharyngoesophageal (PE) tract, nerves or glandular tissue, but the primary concern with blunt neck trauma involves blunt cerebrovascular injury (BCVI) to the carotid or vertebral artery. The incidence of BCVI in blunt trauma is 1%; however, 53-79% of patients are asymptomatic at presentation.[4] Therefore, asymptomatic patients with high-risk injuries require screening.

Anatomy and Physiology

The neck is defined as the area extending from the skull base to the T1 vertebral body and is separated by the superficial and deep (prevertebral) cervical fascia. The latter surrounds the perivertebral muscles and delineates the retropharyngeal space. The *superficial fascia* lies between the skin and platysma muscle. Immediately deep to the platysma is the *deep cervical fascia*, which comprises four separate layers: pretracheal, investing, and prevertebral layers as well the carotid sheath. The investing layer runs circumferentially around the entire neck just deep to the platysma. It splits to encase the trapezius and sternocleidomastoid muscles. The prevertebral fascia (deep to the investing layer) extends from the neck to the thorax, while encircling the cervical spine and prevertebral muscles. The pretracheal fascia completely surrounds the infrahyoid muscles, esophagus, trachea and thyroid gland. This layer inserts on the hyoid and thyroid cartilages above and the anterior pericardium below, while coursing deep to the sternum. It has clinical significance because it provides continuity from the neck to the mediastinum, meaning that spillage from neck wounds, in particular those involving the esophagus, can result in mediastinitis. The carotid sheath is comprised of all three layers of the deep cervical fascia. Within the sheath is found the internal or common carotid artery, the jugular vein, and vagus nerve.[5]

The neck has traditionally been divided into three zones. Zone 1 extends from the sternal notch to the cricoid cartilage, zone 2 from the cricoid cartilage to the angle of the mandible, and zone 3 from the angle of the mandible to the skull base (Fig. 36.1).[6] This distinction was largely predicated on the principal that zone 2 is the most commonly injured, has the highest mortality, and is most amenable to surgical exploration.[7] However, widespread use of computed tomography angiogram (CTA) has made evaluation of this area possible without surgical exploration, rendering these distinctions less relevant, although important for communication among consultants. Furthermore, particularly in the setting of penetrating trauma, injuries often span multiple zones, and the most significant injury may lie in a different zone than the point of entry.

The neck is also divided into an anterior and posterior triangle. The anterior triangle is densely packed with vital structures including neurovascular and aerodigestive tracts. It is bordered anteriorly by the midline, posteriorly by the sternocleidomastoid muscle, and superiorly by the lower edge of the mandible. The posterior triangle is bound by the sternocleidomastoid muscle anteriorly, the clavicle inferiorly, and the anterior border of the trapezius muscle posteriorly. Excluding spinal trauma, injury to the posterior triangle often has a more favorable prognosis because of the relative paucity of vital structures.

The left common carotid branches off the aortic arch and the right off the brachiocephalic trunk. The common carotids branch into the internal and external carotids just superior to the thyroid cartilage. The internal carotid passes through the carotid canal in the temporal bone before splitting into the anterior and middle cerebral arteries.[8] Blunt injuries to the carotids occur when hyperextension-rotation mechanisms stretch the carotid over the lateral processes of the upper spine, with hyperflexion, or with a direct blow to the vessel intraorally or externally.[9] Damage to proximal structures such as the petrous portion of the temporal bone around the carotid canal can also cause damage. The vertebral arteries run cephalad through the transverse foramina starting at C6, and through the foremen magnum. Injury occurs during

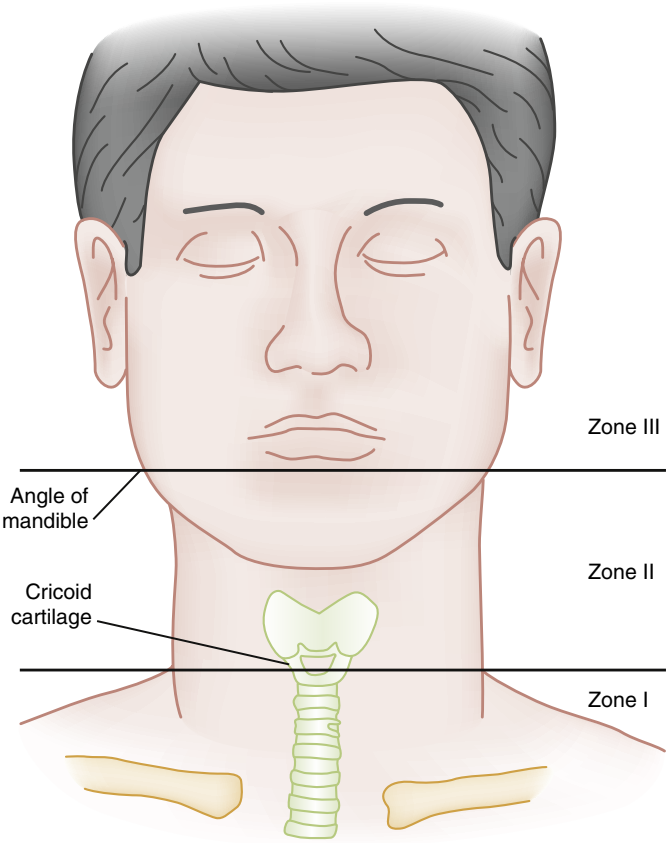

Fig. 36.1 Zones of the Neck.

damage to the transverse foramina, fractures or facet dislocations of the upper cervical vertebrae (C1 through C3), or from stretch and compression around the atlantoaxial and atlantooccipital joints.[9] Injuries to either vessel can predispose the patient to an ischemic stroke from obstruction of arterial flow.

The esophagus extends from the cricoid cartilage to the stomach (T11) and measures approximately 25 cm in the adult. It is anatomically divided into three sections: cervical, thoracic and abdominal. Physical examination alone is unreliable in diagnosing esophageal injury, and a normal examination does not exclude aerodigestive injury.

The larynx runs from the base of the tongue to the trachea, and contains the thyroid, cricoid, epiglottis and paired arytenoid, corniculate, and cuneiform cartilages. The low incidence of tracheal injury likely stems from its protected position sandwiched in-between the sternum, mandible and spine.

Pathophysiology

Vascular Injuries

The type of damage to the cervical vasculature differs according to the mechanism of injury. More than 90% of carotid injuries are caused by penetrating trauma, which can result in partial or complete vascular transection, puncture wounds, AV fistula or pseudoaneurysm[10] by direct transection or penetration injury. In addition, the concussive pressure effect resulting from the release of kinetic energy into small, contained deep neck spaces surrounding the carotid is seen with high velocity projectiles and tissue destruction remote to the projectile trajectory is expected.[4] Vascular wounds sustained from penetrating objects comprise anywhere from 10% to 25% of PNIs. The ratio of carotid to vertebral artery involvement is approximately 2:1. Carotid artery mortality rates range from 5% to 6% and it is the leading cause of immediate death in the setting of PNI due to exsanguination.[11] Extracranial vertebral artery injuries are less common with an overall incidence of 3%.[12]

Blunt trauma typically leads to vascular occlusion, dissection, and intimal flaps.[13] Up to 30% of BCVI can be bilateral.[14] Carotid injuries portend a 17% to 38% risk of mortality and 32% to 67% rate of morbidity. For vertebral injuries, these numbers are lower but still significant at 8% to 18% and 14% to 24%, respectively[8]. Two populations with distinct epidemiology are the pediatric and geriatric age groups. In one study looking at blunt injury, 23% of patients above 65 years of age with low energy falls who met screening criteria for vascular injury (detailed in the following) were diagnosed with BCVI. On the other hand, in pediatric patients, the rate of BCVI was lower than adults (0.2%),[15] but the rates of neurological morbidity (80%) and mortality (40%) were high if stroke occurs.[16] Most BCVI injury in the pediatric age group occur in teens, with only 9% impacting pre-school aged children.[17]

Pharyngoesophageal Injuries

Penetrating PE injuries are rare, and most often involve the cervical segment. Of all penetrating trauma, less than 1% results in injury to the pharynx or esophagus. Gunshot wounds comprise 54% and stab wounds 46%. Mortality rates for penetrating esophageal trauma have been reported from 4% to 8%.[18–21] Mortality rates climb significantly (exceeding 44%) when esophageal injuries occur in a trauma patient with multi-organ system involvement.[22] Diagnostic and/or therapeutic delays exceeding 24 hours are strongly associated with increased mortality.[23]

PE injuries are less common following blunt trauma, but still associated with high mortality. They occur in less than 1% of all blunt trauma and 5% of blunt neck trauma with a median age of 18 years.[24] Ten percent of laryngotracheal (LT) injuries are associated with a concurrent PE injury.[6] Falls followed by motor vehicle collisions (MVCs) are the most common mechanisms of injury, although assault is responsible for 12% of cases.[24] Mortality in patients who survive greater than 24 hours is similar regardless of whether the mechanism was penetrating or blunt.[21]

Laryngotracheal Injuries

Penetrating LT injuries most commonly result from bullets and knives. This type of injury is less common than blunt airway trauma. Penetrating LT occurs in 1% to 6% of all PNIs. These injuries can be subtle, and thus require a high index of suspicion.

In blunt neck trauma, the thyroid cartilage typically encounters forces to the neck first,[25] and is the most commonly injured, often due to direct compression or manual strangulation.[26] Laryngeal injury has been reported with sports-related neck trauma, mainly in young men.[27] Bicycle and scooter accidents are associated with posterior membranous tracheal wall injuries.[28] The cricoid cartilage is the only complete circumferential ring stenting the larynx open, leaving a patient with substantial damage to this structure at risk of airway collapse. Because the cricoid cartilage is a complete ring, there are often two fracture sites at the anterior and posterior aspects.[29] When LT separation occurs, typically, this is at the level of the cricothyroid membrane.

Hanging

Hanging is a specific type of blunt injury. Judicial hangings of the past resulted in death from cervical fractures and cord transection. Modern-day suicidal hangings rely on the external force of the ligature, which causes venous congestion and leads to unconsciousness with resultant tightening of the noose, arterial occlusion, and cerebral hypoxia. Vagal reflexes resulting from pressure on the carotid body may contribute to fatal dysrhythmias as well as increasing sympathetic

tone from pericarotid sinus pressure. Compression of the airway does not play as significant a role.

CLINICAL FEATURES

Vascular Injuries

Signs and symptoms suggesting penetrating vascular injury have been divided into two main categories: hard and soft signs of injury (Table 36.1). Differentiating between soft and hard signs in the setting of penetrating neck trauma is imperative. Hard signs are commonly seen with serious or life-threatening injuries and should prompt an immediate surgical consultation and operative intervention. Hard signs have been shown to have an 89.7% positive predictive value for the presence of vascular or aerodigestive injury.[30] Soft signs of injury are less specific but suggest the potential for a serious injury and warrant further workup. Soft signs are discovered during a thorough history and physical exam once airway stability is assured.[1] The majority of vertebral artery injuries will present without acute neurological symptoms, however any transient ischemic attack (TIA) or stroke symptoms, are specific to the vertebrobasilar artery territory.[12]

TABLE 36.1 Hard Versus Soft Signs of Penetrating Neck Injury

	Hard Signs	Soft Signs
Vascular injury	• Severe, uncontrolled hemorrhage • Refractory shock/hypotension • Large or expanding or pulsatile hematoma • Unilateral pulse deficit • Bruit or thrill (new or < 40 years old) • Neurologic deficit consistent with stroke	• Minor bleeding • Small, nonexpanding hematoma • Proximity wound
Aerodigestive injury	• Airway compromise/distress • Air bubbling through wound • Extensive subcutaneous emphysema • Stridor • Hoarse voice	• Mild hemoptysis • Mild hematemesis • Dysphonia • Dysphagia • Mild subcutaneous emphysema

Modified from Evans C, Chaplin T, Zelt D. Management of Major Vascular Injuries: Neck, Extremities, and Other Things that Bleed. *Emerg Med Clin North Am.* 2018;36:181.

The most concerning complication of BCVI is stroke. Because the development of neurologic symptoms from BCVI is frequently delayed, clinicians have both a challenge and opportunity to identify lesions prior to the development of an ischemic stroke. The untreated stroke risk following BCVI is 10% to 40% and is highest within the first 7 days.[31] When stroke occurs, it is seen on the first day following injury only one-quarter to half of the time.[32] Forty-three percent of patients will have a focal neurological finding at the time of diagnosis.[14] Strokes from blunt vertebral artery injuries occur less frequently (20% stroke risk) than those from carotid injuries, but tend to present in a slightly more delayed fashion.[9,7]

Potential presenting signs include ipsilateral headache (58% to 92%), neck pain (18% to 46%), pulsatile tinnitus, transient blindness, bruit (12% to 39%) and partial Horner syndrome (9% to 75%).[33,7] Because many patients are asymptomatic, several authors have developed screening criteria to identify patients at higher risk for BCVI, ideally prior to the development of stroke symptoms (see Table 36.2 for the two most commonly used criteria). The modified Denver and modified Memphis criteria are both well studied and commonly used to screen for BCVI. The modified Denver screening criteria include signs, symptoms and risk factors. The Eastern Society of Trauma has developed guidelines based on the Denver screening criteria.[34] In addition to the features included in these criteria, other authors have found Type 3 occipital condyle fractures[35] or mandible fractures[36] to increase the risk of BCVI. In fact, one retrospective study revealed that any facial fracture portends a three- to fourfold increased risk.[37] Risk seems to increase with increasing injury severity score, with BCVI seen in less than 3% of blunt trauma patients with ISS ≥16.[7] Some authors have found that substantial numbers of patients are missed using commonly accepted criteria. Using Denver, the probability of BCVI was 20% with no screening criteria met, 33% to 48% with one risk factor, 56% to 64% with two, 80% to 88% with three and 93% with four. Without any cervical spine fracture, there was a 3% risk of vertebral injury versus 33% with a fracture.[38] Approximately 20% to 30% of patients with BCVI have no identifiable risk factors at all.[39]

These guidelines perform poorly in children, causing both over- and under-utilization of CTA. Criteria can miss as many as two-thirds of children with brain ischemia as seen in some studies.[38] In children, injuries associated with BCVI are: basilar skull fracture (odds ratio; OR 2.21 to 3), cervical spine fracture (OR 3.6 to 3.85), jugular venous injury (OR 45.5), cranial nerve injury (OR 3.1),[9] injury severity score ≥16 (OR 2.65), brain infarct (OR 3.85), hanging (OR 8.71), LeFort fracture, facial fracture, and clavicle fracture. Seatbelt sign in isolation has

TABLE 36.2 Major Screening Criteria for Blunt Cerebrovascular Injury

MODIFIED DENVER CRITERIA		MODIFIED MEMPHIS CRITERIA
Signs/Symptoms	**Risk Factors[a]**	
• Arterial hemorrhage from neck, nose, or mouth • Cervical bruit (in patients <50 years) • Expanding cervical hematoma • Focal neurologic deficit: TIA, Horner syndrome, vertebrobasilar symptoms, hemiparesis • Stroke findings at CT or MRI • Neurologic deficit inconsistent with head CT findings	• LeFort II or III fracture • Basilar skull fracture involving the carotid canal • Cervical vertebral body or transverse foramen fracture • Cervical subluxation, or ligamentous injury at any level • Fracture at C1–C3 • Closed head injury consistent with DAI and GCS score <6 • Near-hanging with anoxia • Clothesline-type injury or seat belt abrasion with significant swelling, pain, or altered mental status	• Basilar skull fracture with involvement of the carotid canal • Basilar skull fracture with involvement of petrous bone • Cervical spine fracture • Neurologic examination not explained by brain imaging • Horner syndrome • LeFort II or III fracture pattern • Neck soft tissue injury (seatbelt sign or hanging or hematoma)

[a]Assuming high-energy mechanism.
DAI, Diffuse axonal injury; *GCS,* Glasgow coma scale.

not been associated with BCVI, but it is used in some screening criteria for BCVI.[17] A new score proposed for children (the McGovern score) was promising in an early trial, but still misclassified 19% of injured patients.

Pharyngoesophageal Injuries

Penetrating injury

In penetrating trauma, air leaking from the wound site, odynophagia, dysphagia, and gas in the deep soft tissues are the most compelling indicators of an underlying esophageal injury. Otherwise, there are no pathognomonic signs of esophageal injury based on history or physical exam. Soft signs of injury include hematemesis, odynophagia, dysphagia, subcutaneous emphysema, and blood in the saliva or nasogastric tube aspirate. Other associated findings include dyspnea, hoarseness, stridor, cough, pain and tenderness in the neck, and resistance to passive neck movement. Recent studies provide strong evidence that a normal examination coupled with CTA lacking proximity wounds while confirming the absence of deep tissue emphysema can safely exclude any surgically significant esophageal lesions.[19,40]

Blunt Injury

Blunt PE injuries are rare with little published data on clinical recognition. Signs and symptoms of penetrating PE injury may be useful in identifying patients with blunt PE injury. These injuries tend to be associated with facial fractures (16%) and traumatic brain injury (13%).[24]

Laryngotracheal Injuries

Signs and symptoms of penetrating and blunt LT injury overlap and one quarter of these patients ultimately requiring surgery will have no symptoms on arrival.[41] Delays in symptom onset can exceed 24 hours with some remaining asymptomatic.[41,42]

Penetrating injury

When symptoms exist, these can include dyspnea, dysphonia, dysphagia, hoarseness, laryngeal pain and tenderness, stridor, hemoptysis, subcutaneous emphysema, cyanosis, air escaping from the wound, significant air leaks or persistent pneumothorax following chest tube placement.[29] There is a high sensitivity for dysphonia, aphonia, stridor, hoarseness, and an irritating cough.[41]

Blunt injury

Blunt LT injuries tend to be more concerning than penetrating, with a short-term mortality of 15 to 40%.[26,42] LT injury can be associated with the following signs and symptoms: subcutaneous emphysema, air escape, external bleeding or bruising, dyspnea, hypopnea, stridor, cough, pain with phonation, dysphagia, hemoptysis, tracheal deviation, cyanosis, and nerve injury. Associated cervical spine injury occurs in up to half of patients.[42] Evaluation for hoarseness due to recurrent laryngeal nerve injury should be considered when a cricoid cartilage fracture is found because of proximity.[29]

Hanging

Patients who survive the initial hanging can suffer multi-system sequelae. Hypoxic-ischemic brain injury is the driving factor in the high mortality and neurologic morbidity. Pulmonary edema can occur from several mechanisms: centrally mediated neurogenic pulmonary edema with massive sympathetic discharge; post-obstructive from the marked negative intrapleural pressure generated by forceful inspiratory effort against an extrathoracic obstruction; and cardiogenic pulmonary edema, which is increasingly recognized as a result of hanging-associated Takotsubo cardiomyopathy. Tardieu spots, or punctate lesions left by the gravitational pressure causing capillary rupture, are helpful tipoffs to a hanging mechanism, if not already known.

Miscellaneous

Thyroid rupture can occur with blunt neck trauma and frequently involves a pre-existing goiter. This presents with painful swelling, dyspnea, or airway obstruction. The onset of symptoms can be delayed for up to 24 hours.[43]

DIFFERENTIAL DIAGNOSES

Penetrating neck trauma can result in injury to the carotid artery, vertebral artery, venous system (jugular vein), pharynx, esophagus, larynx and trachea, see Table 36.3 for mechanisms, signs and symptoms.

Blunt neck injuries can include carotid artery injury, vertebral artery injury, uncommonly venous injuries, LT injury, PE injury, injury to the thyroid gland, and nerve injuries. See Table 36.4 for mechanism, risk factors, and signs and symptoms of each.

DIAGNOSTIC TESTING

Laboratory testing in both penetrating and blunt neck trauma is largely unnecessary with the exception of serial hemoglobin testing with significant bleeding, platelet count and coagulation function testing. Faster clot formation and greater clot strength on thromboelastography is associated with a higher stroke risk in the setting of blunt trauma, but the clinical implication of this data is not yet defined.[44] In the presence of anticipated surgery or bleeding, type and cross-matched blood can be ordered from the ED. Screening radiographs of the chest and neck can be helpful to look for gas in the deep tissues or pneumothorax. An e-FAST exam can exclude pericardial effusion and pneumothorax.

Multidetector CT angiography (MDCTA) has changed the approach to blunt and PNI with CTA now the initial imaging modality of choice. This is based in part on greatly improved resolution, speed and availability, and is ultimately cost-effective.[17]

Vascular Injuries

Until the arrival of new generation scanners, digital subtraction angiography (DSA) was the gold standard for diagnosing vascular injury and in some clinical scenarios it is still useful. For example, the CTA may be normal despite a high suspicion for a vascular injury and in this instance, DSA would provide additional images for clarification. It is also possible to have an equivocal CTA in the setting of streak artifact from retained metallic foreign bodies. Further imaging would be warranted with four-vessel catheter angiography being a good follow up study. Catheter angiography can also be used when endovascular treatment is anticipated.[45] The disadvantage to DSA is that it is time-consuming, can lead to delays in definitive diagnosis, and is associated with a 0.5% of risk of stroke from the procedure itself.[33]

Penetrating Injury

Improved CTA capability has allowed better delineation of wound trajectory and proximity wounds in the setting of penetrating trauma, which has led to an evolvement in the diagnosis and management of these injuries. Despite decades of relying on a zone-based selective algorithm, current consensus supports a "no-zone" approach which uses clinical examination coupled with CTA, not the zone of injury, to arrive at the best diagnostic and therapeutic pathways.[46,47] A no-zone approach has been shown to reduce the rate of negative neck exploration and cost.[48] Patients who arrive and remain asymptomatic (no hard or soft signs of injury) with a negative CTA do not require further imaging or diagnostic testing, however a period of observation is

TABLE 36.3 Salient Features of Penetrating Neck Injuries

Injury	Mechanism	Signs/Symptoms
• Carotid/vertebral artery	• Stab wounds • Firearms • Bites, glass, other projectiles	Asymptomatic, minor bleeding, small, nonexpanding hematoma, proximity wound, severe, uncontrolled hemorrhage, refractory shock or hypotension, large or expanding or pulsatile hematoma, unilateral pulse deficit, bruit or thrill, neurologic deficit consistent with stroke. Vertebral artery specific: dizziness, vertigo, diminished coordination, disequilibrium, ataxia, nausea and/or vomiting, neck or head pain, altered sensorium, speech (dysarthria), visual deficits (double vision, nystagmus), lower cranial nerve palsies and medial or lateral medullary syndrome
Laryngotracheal injury	• Stab wounds • Firearms • Bites, glass, other projectiles	Asymptomatic, respiratory distress, dyspnea, dysphonia, aphonia, dysphagia, hoarseness, pain or tenderness over larynx, stridor, hemoptysis, subcutaneous emphysema, cyanosis, air escaping from wound, irritating cough
Pharyngoesophageal injury	• Stab wounds • Firearms • Bites, glass, other projectiles	Asymptomatic, air leaking from the wound site, odynophagia, dysphagia, hematemesis, subcutaneous emphysema, and blood in the saliva or nasogastric tube aspirate, dyspnea, hoarseness, stridor, cough, pain and tenderness in the neck, and resistance to passive neck movement

TABLE 36.4 Salient Features of Blunt Neck Injuries

Injury	Mechanism	Risk Factor	Signs/Symptoms
Carotid artery	MVC	LeFort fractures II or III, Carotid canal injury	Asymptomatic, neurologic findings, Horner syndrome, bruit, expanding hematoma
Vertebral artery	MVC	Cervical spine injury (C1–3 fracture or dislocation, any transverse foramina)	Asymptomatic, neurologic findings
Laryngotracheal injury	Direct trauma	Associated c-spine injury	Asymptomatic, subcutaneous emphysema, air escape, external bleeding or bruising, dyspnea, hypopnea, stridor, wheezing, cough, pain with phonation, dysphagia, hemoptysis, tracheal deviation, cyanosis, nerve injury
Pharyngoesophageal injury	Falls, MVC, strangulation	Facial fractures, traumatic brain injury	Extrapolated from penetrating trauma
Thyroid gland hematoma	Anterior neck trauma	Goiter	Painful swelling, dyspnea, or airway obstruction (can be delayed)
Nerve injuries	Bone fragment in facial canal	Temporal bone fracture	Facial paralysis

indicated with serial examination.[1] Regarding use of cervical spine collars with PNIs, practice management guidelines of the Eastern Association for the Surgery of Trauma do not endorse routine application for PNIs in patients lacking neurological findings.[49]

When hard signs of vascular injury, coupled with hemodynamic instability are identified, the patient is most often taken expeditiously to the operating room (OR) without imaging. In isolated instances, when hard signs of vascular injury are present in an otherwise stable patient, CTA may be indicated and beneficial prior to transfer to the operating room if delays will not be incurred.[50] Angiography can provide detailed information regarding vascular injury location and emergency surgical planning. If soft signs of vascular injury are identified, CTA is the initial imaging study of choice with a sensitivity of 90% to 100%, specificity of 98.6% to 100%, positive predictive value (PPV) of 92.8% to 100%, and an negative predictive value (NPV) of 98% to 100%.[51]

Blunt injury

For BCVI, the sensitivity of prior generation CT scan was 47% to 52%; therefore, DSA was considered the gold standard. Currently, CTA with 16-slice or better scanners have a sensitivity of 68% to 100%.[14]

Vessel wall magnetic resonance imaging (MRI) has been minimally studied but appears adequate, with agreement of 0.82 with verified BCVI.[51] MRA alone has had reported sensitivities and specificity of 50% to 75% and 67%.[52] EAST guidelines state that diagnostic ultrasound is not adequate to screen for BCVI.

Pharyngoesophageal Injuries

While CTA is a reasonable diagnostic test to begin evaluation of a patient suspected to have PE injury, both penetrating and blunt PE trauma often warrant confirmatory studies in the setting of an equivocal CTA. Esophageal barium swallow, also known as contrast swallow study or esophagogram, is a contrast enhanced X-ray modality used to better visualize the esophagus.

Typically, a water-soluble contrast agent such as diatrizoate meglumine or diatrizoate sodium (e.g., Gastrografin) is used. Barium, which has greater sensitivity than Gastrografin, is associated with risk of delayed mediastinal fibrosis in the event of contrast extravasation. In an attempt to avoid this complication while maintaining sensitivity, a thin barium swallow can follow a negative Gastrografin swallow. Most literature supports a confirmatory barium study in the setting of negative water-soluble imaging.[53]

Penetrating injury

Penetrating PE injuries are the leading cause of delayed morbidity in penetrating neck trauma.[2] Timely diagnosis and definitive treatment is

associated with decreased morbidity and mortality. Delays are defined as greater than 24 hours following injury. Morbidity includes increased use of percutaneous feeding and tracheostomy tubes, emphysema, pneumonia and sepsis.[19,54]

As the quality of CTA has improved, so has the ability to rely on this study in the context of PNI and specifically to detect esophageal injury. CTA has proven useful to delineate the wound track or bullet trajectory to determine if a proximity wound is present. Recently, literature has supported the use of CTA to search for gas in the deep fascial planes of the neck, a nonspecific finding that can be seen with pneumothorax, tracheobronchial and aerodigestive injury. This finding increases the suspicion for esophageal injury. If surgically insignificant wounds are excluded, the sensitivity and negative predictive value for deep surgical emphysema is 100% when searching for esophageal injury. Contemporary studies reveal that significant esophageal injury is essentially excluded in patients with low pre-test suspicion and in those who lack CTA proven deep surgical emphysema.[40]

CT esophagography has also been evaluated as a tool to diagnose upper digestive tract injuries including those located in the hypopharynx. A combination approach for penetrating neck trauma using both CTA and CT esophagography as a single diagnostic study, yields a sensitivity near or equal to 100% and does not interfere with a simultaneous search for vascular injury. In one study, radiologists felt confident in 65% of cervical PNI cases based solely on their CT esophagography read that further testing to exclude esophageal injury was not indicated. The sensitivity of radiology in this series was 95% with a specificity that ranged from 85% to 91%.[54] These studies require patient cooperation, which is not always possible in the acutely injured trauma patient.

When relying on esophagography, it is important to note that up to 22% of missed esophageal injuries following negative diatrizoate meglumine-diatrizoate sodium (Gastrografin) swallow studies were diagnosed with thin barium swallows.[54] Conversely, one study found that water-soluble swallow studies, when negative, are effective at excluding significant penetrating esophageal injuries.[19] This latter approach is not uniformly accepted.

Endoscopy is another modality used to diagnose esophageal injury. Both rigid and flexible scopes are available, but most operators prefer flexible endoscopy in the setting of penetrating trauma given its usefulness in both the ED and operating room as well in intubated patients or those who are unable to cooperate with oral contrast studies. Flexible endoscopy has a sensitivity of 100% and a specificity of 83% and should follow an equivocal contrast esophagography study or a CTA (deep surgical emphysema).[54] The combination of contrast studies and flexible endoscopy has an accuracy of essentially 100%.[55]

Blunt Injury

For PE injuries, CTA is typically the first study performed. Endoscopy can complement this with a sensitivity of 50% to 60% for perforation. A swallow study should be performed if there is subcutaneous air noted on CTA, but no clear injury identified.[4] Endoscopy is a reasonable option in equivocal cases as well. Alone, endoscopy has a sensitivity of 50% to 60% for perforation. However, it can be a useful adjunct when other studies are equivocal or when a negative study is obtained in a patient with a high pre-test probability of injury.

Laryngotracheal Injuries

Similar to the approach of any penetrating or blunt neck injury, the initial studies for a stable patient include laboratory testing, screening radiographs of the chest and neck, and CTA of the neck (see diagnostic vascular section).

The epiglottis, arytenoid vocal processes, and the cuneiform and corniculate cartilages never ossify because of their elastin fibrocartilage composition. The remaining airway cartilages are hyaline and will begin ossifying at 18 years and conclude by 65 years of age. When using CTA, thin cuts (1 to 2mm) are recommended to avoid missing subtle injury. There is controversy as to whether IV contrast further enhances visualization of these injuries.[56] MRI can provide additional information and is better for visualizing the airways of younger patients that lack calcification if a fracture is suspected but absent on CT scan. MRI does not have a role in the acute setting.[57]

Penetrating injury

CT plays a significant role in detecting LT injuries following penetrating injury; however, other diagnostic options exist in the setting of an inconclusive CTA. Direct laryngoscopy or flexible nasopharyngoscopy can be used initially not only for intubation, but also to directly visualize the airway. These procedures may be unsuccessful if significant airway edema, blood or debris is present. When CTA is nondiagnostic, rigid laryngoscopy can be performed in the operating room to glean further information about airway integrity.

Penetrating LT trauma can lead to acute complications including airway obstruction and death or long-term complications such as vocal cord dysfunction, voice changes, laryngeal or tracheal stenosis, chronic aspiration and tracheoesophageal fistulas.[41] Timely diagnosis and treatment are warranted in an attempt to mitigate these possibilities.

Blunt Injury

CTA is particularly useful when airway edema precludes passage of a laryngoscope.[4] However, some studies have shown a false negative CTA rate of up to 30%[28], therefore a high index of suspicion and a combination of laryngoscopy and CTA may be helpful in higher risk cases.

Hanging

CTA is adequate for the evaluation of the neck in hangings. However, cerebral anoxia or pulmonary edema may be the more significant pathology supporting additional imaging, specifically, brain MRI, chest imaging, and echocardiography, to detect the stress-induced characteristics of Takotsubo cardiomyopathy.

MANAGEMENT

Vascular Injuries

Penetrating injury

Vascular injury can present with life-threatening exsanguination. Direct manual pressure is the first line approach when a patient arrives with active bleeding, but in refractory instances, a 16- or 18-French Foley catheter placed and inflated in the wound may be required to tamponade the bleeding.[58] This is more likely in zone 3 injuries because the carotid artery lies deep into the mandible potentially precluding direct digital compression.[56]

Surgical access to vascular injury is dependent on the location with zone 2 wounds being the most accessible. Adequate surgical access to zone 3 may be partially obscured by the mandible and zone 1 by the sternum. Distal ICA injury at the base of the skull (zone 3) poses a unique challenge when attempting to gain vascular access for repair. Endovascular repair is the gold standard in this region. Open surgical options include primary surgical repair (such as end-to-end anastomosis, direct repair of defect, vein grafting, polytetrafluoroethylene patching, and transposition of the external carotid artery with the ICA) or ligation of the vessel.[11]

Primary repair or endovascular stent grafting are common approaches used for most penetrating carotid artery injuries with open repair being the gold standard.[11] Vertebral artery injuries are managed by surgical ligation, angiographic embolization, combined procedures or observation.[10,12] Unlike blunt carotid artery trauma where

TABLE 36.5 Biffl Scale Grading and Treatment of Blunt Cerebrovascular Injury

	Injuries	Management
Grade 1	Intimal injury or irregular intima	Anticoagulation or antiplatelet therapy (endovascular repair if not candidate)
Grade 2	Dissection with an intimal flap causing luminal narrowing of less than 25%	Endovascular repair if sx; o/w antiplatelet or anticoagulant
Grade 3	Pseudoaneurysm formation	Endovascular repair if symptoms; otherwise antiplatelet or anticoagulant
Grade 4	Vessel occlusion or thrombosis	Difficult to manage, as the injured vessel often thromboses and cannot be recanalized, endovascular repair if sx; o/w antiplatelet or anticoagulant
Grade 5	Vessel transection	Typically, lethal if left untreated; requires immediate endovascular intervention or surgical repair

antithrombotic therapy is widely accepted, data is lacking as to whether anticoagulation is warranted in penetrating carotid wounds.[59]

Blunt injury

Table 36.5 discusses decision making for medical versus surgical management. The Biffl scale dictates lesion grading, and largely management for BCVI. This is weighed against other injuries and risk of anti-thrombotic therapy.

Medical management of BCVI: Antithrombotic therapy is indicated in all grade I to IV injuries. For anticoagulation, the standard regimen includes a heparin infusion started at 10 units/kg/h and titrated to a PTT of 40 to 50 seconds. No heparin bolus is administered. If antiplatelet therapy is selected, 75 to 325 mg/day of aspirin (or 3 to 5 mg/kg in children) is recommended with some studies showing fewer bleeding-related complications and equivalency in stroke prevention in comparison to patients who are anticoagulated.[60] The Western Trauma association guidelines favor heparin in the acute phase, due to its short duration of action and the ability for it to be reversed,[61] while other guidelines support either therapy as reasonable. Typically, 3 to 6 months of antithrombotic treatment is recommended.[61] Treatment with either an anticoagulant or antiplatelet agent reduces stroke risk to somewhere between 1% and 7%.[39,62,63]

Surgical management of BCVI spans the spectrum from stenting to vessel sacrifice. One retrospective study indicated increased mortality with earlier intervention; however, this may have been biased toward sicker patients in the early intervention group.[64] Vascular occlusion of the external carotid does not usually necessitate treatment.[4]

Pharyngoesophageal Injuries

Regardless of the mechanism of injury, when esophageal injury is suspected, broad-spectrum antibiotics with anaerobic coverage (e.g., piperacillin and tazobactam IV or high-dose fluconazole IV) should be administered, and the patient made nil per os (NPO). Preoperative placement of an nasogastric tube (NGT) under endoscopic guidance may reduce the spillage of gastric contents into the wound.

Penetrating injury

Nonoperative management has been shown to be safe for hemodynamically stable patients with penetrating esophageal injuries, with no competing indications for exploration and no established sepsis. This approach is reinforced with a water-soluble swallow study showing either contained extravasation or none. Any uncontained perforation of the esophagus, signs of sepsis, or widespread contamination requires prompt surgery, whereas small, contained perforations may be candidates for observation and reimaging based on institution protocols.[65] Pharyngeal injuries if not recognized early and managed appropriately carry risks similar to esophageal injuries including sepsis. Most injuries to the caudal part of the cervical digestive tract mandate urgent exploration.[19] If the time to definitive repair is not excessively delayed, obtaining preoperative evaluation and diagnostic work-up of penetrating esophageal injury is associated with fewer hospital days as opposed to those patients who are taken directly to the operating room without preoperative definitive studies.[22]

Blunt Injury

About one quarter of those with blunt PE injury require surgical management. Some experts recommend repair of any injury greater than 2 cm in length. Observation, nothing per os, and prophylactic antibiotics are usually sufficient for smaller lesions.

Laryngotracheal Injuries

Early airway management can be challenging in LT injury. Up to 10% of neck wounds have associated respiratory compromise.[63] When approaching any neck injury, both airway integrity and the presence of active exsanguination will dictate early management. Assurance of a stable airway is the earliest priority and often represents a challenge. Airway integrity can be rendered unstable by several mechanisms including airway obstruction via blood or debris, partial or complete transection of the larynx or trachea, fractures of the cartilages, airway edema or compression secondary to a large hematoma or massive subcutaneous air.[66] Because these injuries are relatively uncommon, practice patterns vary regarding airway management, but most advocate for aggressive airway stabilization.[41]

Airway collapse in the setting of penetrating neck trauma can happen insidiously or in a delayed fashion, necessitating serial exams in the nonintubated patient. A pass at orotracheal intubation initially is warranted in an emergent situation. A one size smaller than anticipated endotracheal tube (ETT) in the setting of airway edema is prudent. A double set-up with a surgical airway option should be available during any intubation attempt.[42] In a semi-elective airway, fiberoptic intubation or an awake tracheostomy in the operating room are preferred. If such resources are not available, cricothyroidotomy in adults or needle cricothyroidotomy with jet ventilation in children under 12 years of age are reasonable back-up options. In the setting of a penetrating large partial or complete airway transection, localization of the distal airway with tracheal hooks and direct intubation through the wound may be required. Blind nasotracheal intubation or use of positive pressure supraglottic ventilation (e.g., bag-mask or laryngeal mask airway) is contraindicated in these injuries. Early intubation offers additional benefits including stenting a partially collapsed trachea as well air leak tamponade.[42] In a stable patient who appears to have a preserved airway, bedside laryngoscopy or fiberoptic nasopharyngoscopy can afford visualization of the upper airway proximal to the vocal cords. This quick look can help clarify the decision of whether intubation appears necessary in unclear cases. Both of these procedures can be challenging when significant amounts of blood, debris or airway edema are present. The majority of experts favor video laryngoscopy over direct laryngoscopy with these types of difficult airway trauma scenarios.

Definitive management for LT trauma is driven primarily by the grade of injury as defined by the Schaefer-Fuhrman classification. This grading system applies to both penetrating and blunt trauma. Table 36.6 lists the grades of injury according to this classification and typical treatment for each grade.[4] For mucosal lacerations less than 2 to 3

TABLE 36.6 Schaefer-Fuhrman Classification of Laryngeal Injury

	Injuries	Management
Grade 1	Endolaryngeal hematoma or laceration without detectable fracture; no airway compromise	Generally, medically managed and do not require surgical intervention. Helpful adjunctive medical treatments include steroids, antibiotics, humidification, voice rest
Grade 2	Moderately severe edema, hematoma, or laceration without exposed cartilage or nondisplaced fracture; partial airway compromise with varying degrees of severity	Serial examinations, since the injuries may worsen over time. These injuries infrequently require a tracheostomy. Helpful adjunctive medical treatments as described above
Grade 3	Massive laryngeal edema, large mucosal lacerations, exposed cartilage, displaced fracture, or vocal cord immobility, with associated airway compromise	Tracheostomy and surgical repair are often required. The following injuries of the larynx require surgical repair: disruption of the anterior commissure, major endolaryngeal lacerations, vocal cord tear, immobile vocal cord, cartilage exposure, displaced cartilage fractures
Grade 4	Grade III findings with more severe anterior laryngeal disruption, unstable fracture, two or more fracture lines, or severe mucosal injuries	Tracheostomy is always required Surgical repair requires stent placement to maintain the integrity of the larynx
Grade 5	Complete laryngotracheal separation	Disruption of the airway usually occurs above or below the cricoid cartilage, either at the cricothyroid membrane or cricotracheal junction. The airway is usually temporarily established using an endotracheal tube inserted through the neck directly into trachea distal to the site of transection. A complex laryngotracheal repair is then performed through a low cervical incision

Moonsamy P, Sachdeva U, Morse C. Management of laryngotracheal trauma. *Ann Cardiothorac Surg.* 2018;7(2):210–216.

cm in length, conservative management with analgesia, humidified air, elevation of the head of the bed, antibiotics, steroids, antireflux medications, vocal rest, and a clear diet is reasonable. For surgical lesions, prompt repair within 24 hours is important to minimize long-term disability from scar tissue and stenosis.[26] Long-term, about 20% will have a hoarse or breathy voice.[67] Aspiration, infection, air embolism, and recurrent laryngeal nerve injury can also complicate the course of these injuries.[42]

Hanging

Definitive studies providing guidelines for the management of hypoxic brain injury specifically related to near-hanging or strangulation injuries are lacking. Case series indicate a potential role for induced mild hypothermia in comatose survivors of strangulation. One study demonstrated a 43% rate of survival to discharge and 6% return of neurological function in hanging patients treated with hypothermia protocols after arrest. Case reports have suggested the use of thrombolysis for carotid injury-related stroke in survivors of near-hanging although confirmatory studies have not been conducted. Currently, there is insufficient data to recommend either for clinical practice.

Miscellaneous

Immediate surgical exploration is indicated when bony fragments are found in the facial canal or if facial paralysis is identified to prevent permanent loss of nerve function. Facial paralysis can result from direct nerve transection or from neuropraxia. In these settings, neuropraxia is often a result from a pressure effect related to local edema, hematoma or adjacent bone fragments.[4] For thyroid rupture, parenchymal hematoma should be observed for 24 hours in the intensive care unit (ICU) due to the risk of airway compression and thyroid storm.[43]

DISPOSITION

Penetrating Injury

Most penetrating injuries to the neck with platysma violation will be admitted to the hospital for ongoing definitive studies, management or observation. In the case of a penetrating wound in an asymptomatic or minimally symptomatic patient with no evidence of a viscerovascular injury and a negative CTA, serial examinations every 6 to 8 hours for 24 to 36 hours are recommended.[63]

Blunt Injury

BCVIs are high-risk injuries. For patients with CTA demonstrating vascular trauma not requiring surgery, admission is warranted.[68] Even grade 1 injuries have a risk of progression, with 5% converting to grade 3 while on heparin.[7] Upon discharge, patients should be asked to limit contact sports, neck manipulation, and estrogen-containing medications. Hypertension should be avoided, which may require additional prescriptions at discharge, or a discussion on the importance of compliance with prior prescriptions. In patients with stent placement, thrombosis of the stent has been reported and some providers discharge with anticoagulation, even in the face of a surgically managed lesion.

Since false positives can occur, a repeat CTA at 7 days to confirm diagnosis and at 3 months to confirm resolution is often prescribed.[61] If the injury is not seen at day 7, then antithrombotic therapy can be stopped. For patients at high risk but with a negative CTA, observation for 24 to 48 hours is recommended.[69]

Because CTA does not have perfect sensitivity for identifying LT fractures, a period of observation of 48 to 72 hours is recommended for patients suspected to have blunt LT injuries with a negative CTA who cannot also undergo laryngoscopy.[28] Patients with no identifiable injury beyond laryngeal tenderness, but who had a significant mechanism of injury can be observed for 12 hours in the ED or an observation unit. They can be subsequently discharged home if no additional symptoms or signs develop, voice and swallowing are normal, and discomfort is minimal and abating.

Since the mortality for PE injuries is up to 20%, these patients require admission.

Patients recovering from hanging with no identified injuries and no development of pulmonary edema after several hours of observation may be candidates for transfer to psychiatric care, as this most often represents an attempt at self-harm or suicide.

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CHAPTER 36: QUESTIONS AND ANSWERS

1. The presence of which of the following signs after penetrating neck trauma would indicate a likely benefit from surgical intervention?
   - **a.** Decreased or absent radial pulse
   - **b.** Small degree of hemoptysis
   - **c.** Horner syndrome
   - **d.** Muffled voice
   - **e.** Stable hematoma

Answer: a. "Hard" signs of penetrating neck trauma are the presence of an expanding hematoma, severe active bleeding, shock not responding to fluids, decreased/absent radial pulse, vascular bruit/thrill, cerebral ischemia, and airway obstruction. Most patients with hard signs benefit from surgical intervention.

2. Which of the following is true regarding pharyngoesophageal injuries?
   - **a.** Esophageal barium swallow is the best initial x-ray modality for evaluating esophageal injuries.
   - **b.** Gastrografin has greater sensitivity than barium and is therefore the preferred contrast agent in the initial evaluation of esophageal injuries.
   - **c.** Confirmatory barium study is not necessary after a negative Gastrografin swallow study.
   - **d.** Computed tomography angiogram (CTA) is the initial study of choice in evaluating pharyngoesophageal injuries and never requires additional confirmatory studies
   - **e.** None of the above is true.

Answer: e. CTA is a reasonable exam with which to begin evaluation of a patient suspected to have PE injury but confirmatory studies in the setting of an equivocal CTA are often required. Esophageal barium swallow has greater sensitivity than Gastrografin but is associated with risk of delayed mediastinal fibrosis in the event of contrast extravasation. Most literature supports a confirmatory barium study in the setting of negative water-soluble imaging.

3. The pathophysiology and sequelae of hanging include all of the following except
   - **a.** Pulmonary edema
   - **b.** Hypoxic –ischemic brain injury
   - **c.** Cardiogenic pulmonary edema as a result of Takotsubo cardiomyopathy
   - **d.** Neurogenic pulmonary edema from massive parasympathetic discharge
   - **e.** Presence of Tardieu spots

Answer: d. Pulmonary edema can occur from several mechanisms: neurogenic pulmonary edema from centrally mediated, massive *sympathetic* discharge; post-obstructive from relief of the marked negative intrapleural pressure generated by forceful inspiratory effort against an extrathoracic obstruction; and cardiogenic pulmonary edema, which is increasingly recognized as a result of hanging-associated Takotsubo cardiomyopathy.

4. Which of the following statements is true regarding zonal injuries to the neck?
   - **a.** Zone 2 is the most commonly injured, has the highest mortality and is most amenable to surgical exploration
   - **b.** Zone 1 extends from the sternal notch to the cricoid cartilage

c. Penetrating trauma injuries to the neck often span multiple zones, and the most significant injury may lie in a different zone than the point of entry
d. Current consensus supports a "no-zone" approach which uses clinical examination coupled with computed tomography angiogram (CTA) to arrive at the best diagnostic and therapeutic pathways
e. All of the above are true.

Answer: e. Despite decades of relying on a zone-based selective algorithm, current consensus supports a "no-zone" approach which uses clinical examination coupled with CTA, not the zone of injury, to arrive at the best diagnostic and therapeutic pathways

5. Which of the following statements regarding airway management after penetrating neck trauma is true?
a. Awake fiberoptic intubation is the first-line technique.
b. Bag-valve-mask ventilation should be high tidal volume, low rate.
c. Cervical spine immobilization is typically unnecessary.
d. Nasotracheal intubation is relatively contraindicated in neck trauma.
e. Preintubation nasogastric tube (NGT) placement may be lifesaving.

Answer: c. Unless there is concomitant blunt injury or evidence of spinal cord injury, cervical immobilization is not needed. Oral intubation after rapid sequence intubation (RSI) is the technique of choice and is successful in almost all cases. Although rarely a first line choice, nasotracheal intubation has been used successfully in these trauma patients. Gentle bag-valve-mask technique with low pressure is indicated to avoid venous air embolism (VAE) and subcutaneous emphysema. NGT placement, if done at all, should be gentle and placed after intubation.

37

Thoracic Trauma

Ali S. Raja

KEY CONCEPTS

- Even relatively minor chest wall injuries, such as rib fractures, may result in serious complications in elderly patients and patients with preexisting pulmonary disease if adequate analgesia and close follow-up care are not provided.
- Unless there are abnormalities on the electrocardiogram (ECG) or an elevated serum troponin level, there is no need to pursue the diagnosis of myocardial contusion with more sophisticated testing.
- Many patients with myocardial rupture or traumatic aortic rupture survive to reach the hospital and can be salvaged with rapid diagnosis and intervention.
- Pericardial tamponade can be diagnosed accurately before hemodynamic decompensation occurs by standard cardiac ultrasound performed by emergency clinicians.
- Chest computed tomography (CT) scan is the diagnostic test of choice for blunt aortic injury even in the presence of normal chest radiographs.
- The NEXUS-Chest CT criteria can be used to determine the need for chest CT in patients with blunt trauma.

Many causes of early deaths (within the first 30 to 180 minutes) resulting from thoracic trauma are preventable and include tension pneumothorax, cardiac tamponade, airway obstruction, and uncontrolled hemorrhage.

Approximately 75% of patients with thoracic trauma require only simple tube thoracostomy and volume resuscitation, and the initial care and disposition of these patients is usually performed by emergency clinicians. Care of severe thoracic trauma is multidisciplinary in nature, involving trauma surgeons, cardiothoracic surgeons, and intensivists. Improved understanding of underlying physiologic mechanisms, newer imaging modalities, minimally invasive approaches, and pharmacologic therapies have contributed to decreasing morbidity and mortality in patients with thoracic injuries.

Injury location and type dictates both assessment and management. This chapter is organized into sections highlighting chest wall, pulmonary, tracheobronchial, diaphragmatic, cardiovascular, and esophageal injuries.

CHEST WALL INJURY

RIB FRACTURE

Foundations

Background and Importance

The susceptibility to rib fracture increases with age. These injuries can be exquisitely painful, but their importance lies not in the fracture itself, which generally is self-limiting and will heal, but rather with associated complications, particularly pneumothorax, hemothorax, pulmonary contusions, and post-traumatic pneumonia. Rib fractures in children are discussed in Chapter 160.

Anatomy and Physiology

An intact chest wall, protected by its rib cage, is necessary for normal ventilation. Outward expansion of the thorax by the respiratory muscles with descent of the diaphragm creates negative intrathoracic pressure. This allows passive air entry into the lungs during inspiration. Chest trauma, particularly blunt trauma, can severely disturb the physiology of respiration. Fortunately, most individuals have substantial respiratory reserve and can tolerate chest wall injuries with adequate support.

Flail chest results when three or more adjacent ribs are fractured at two points, allowing a free segment of the chest wall to move in paradoxical motion (Fig. 37.1), with the flail segment moving inward with inspiration and outward with expiration. It can also occur with costochondral separation or vertical sternal fracture in combination with rib fractures. Underlying pulmonary contusion is considered to be the major cause of respiratory insufficiency with flail chest, and it is therefore one of the most serious chest wall injuries (Fig. 37.2). In addition, flail chest can be associated with a variety of other injuries, including hemopneumothorax, liver or spleen lacerations, and mediastinal injury.

Pathophysiology

Ribs usually break at the point of impact or at the posterior angle or posterolateral area, which is structurally the weakest area. Ribs 4 to 9 are the most commonly involved. Ribs 1 to 3 are short and relatively protected, and ribs 9 to 12 are longer and more mobile at the anterior end. This confers the relative resistance to fracture of the "high" and "low" ribs. Fractures occur more easily in older adults than younger adults or in children, due to the progressive inelasticity of the chest wall that develops through aging.

The true danger of rib fracture involves not the rib itself but the potential for penetrating injury to the pleura, lung, liver, or spleen. Fractures of ribs 9 to 11 are also associated with intra-abdominal injury. Right-sided rib fractures are associated with hepatic injury and left-sided rib fractures with splenic injury. Injury severity is indicated by the number of rib fractures. The presence of two or more rib fractures at any level is associated with a higher incidence of internal injuries than with a single, isolated fracture. Patients over 65 years old with multiple rib fractures have a greater incidence of pneumonia and a higher mortality compared their younger counterparts.

Clinical Features

Rib fracture is often a clinical diagnosis, with severe point tenderness, bony crepitus, ecchymosis, and muscle spasm over the rib being the

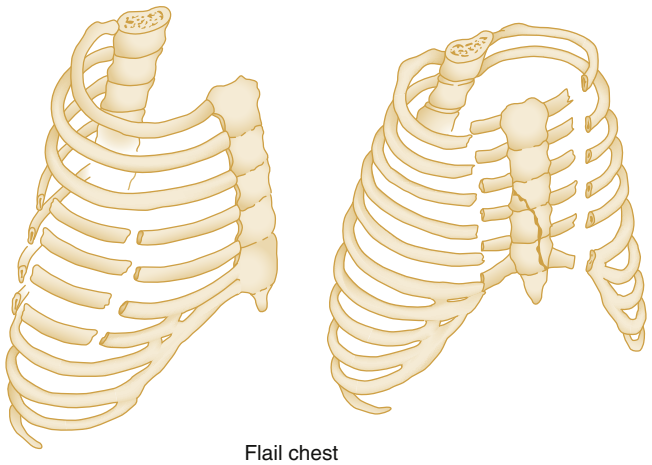

Fig. 37.1 Flail Chest. Fracture of several adjacent ribs in two places with lateral flail or central flail segments.

most common findings. Also, bimanual compression of the thoracic cage remote from the site of injury (barrel compression test) usually produces pain at the site of fracture. Injury to the parenchyma may be detected by assessing the respiratory rate, oxyhemoglobin saturation, respiratory effort, effectiveness of ventilation, and pulmonary breath sounds.

Flail chest is characterized by paradoxical motion of a portion of the chest wall during respiration and is usually obvious on physical examination. Unless the patient is unconscious, there will be severe pain, splinting, tenderness, and crepitus. Paradoxical chest wall motion is a product of negative intrathoracic pressure and is obscured if the patient has been intubated or is receiving positive-pressure ventilation. For such patients, the diagnosis is usually evident on examination of the integrity of the chest wall (compression and crepitus).

Differential Diagnoses

Patients with suspected rib fracture have always sustained trauma, thus focusing the evaluation. Patients with significant, potentially multisystem trauma require a thorough trauma evaluation (see Chapter 32). Rib fracture, costochondral separation, and rib contusion may present in similar fashion, and it is not critical to identify a single, isolated rib fracture. Patients with multiple suspected fractures are at higher risk for intrathoracic injury and also for later decompensation and complications. Important diagnoses to consider include chest wall or clavicle fracture (especially sternal fracture), pulmonary injuries (pulmonary contusion, laceration, pneumothorax, or hemothorax), tracheobronchial injury, diaphragmatic injury, cardiovascular injury (cardiac contusion or aortic injury), or esophageal injury. These broad differential diagnoses hold true for most patients with thoracic trauma, given the close proximity of the organs involved and the similar mechanisms behind most of the injuries described in this chapter.

Diagnostic Testing

Many patients with relatively minor thoracic trauma are evaluated and managed exclusively based on physical findings, and they do not require imaging. When the injury is significant enough to raise concern for underlying pulmonary injury, imaging is required. Because rib fractures are managed expectantly, imaging should be reserved for patients in whom multiple rib fractures, underlying pulmonary injury, or comorbid pulmonary status (e.g., chronic obstructive pulmonary disease [COPD]) is a concern. A plain chest radiograph will identify only about 50% of single-rib fractures; its greatest value is in identifying or excluding significant intrathoracic and mediastinal injuries. Rib series and expiratory, oblique, and cone-down views should not

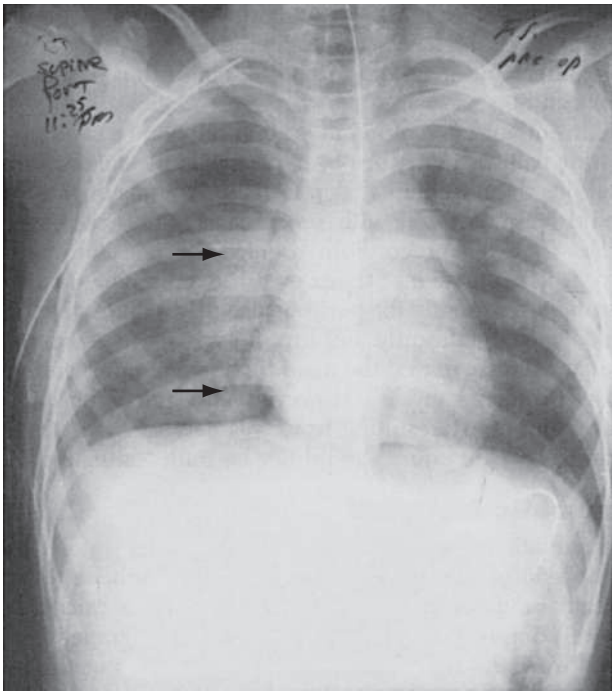

Fig. 37.2 Bilateral alveolar infiltrates *(arrows)* suggesting pulmonary contusion. Pneumopericardium and pneumomediastinum are also present.

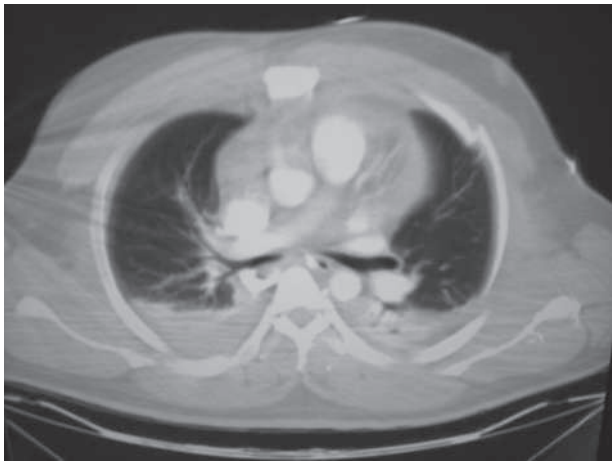

Fig. 37.3 Multiple rib fractures seen on chest computed tomography (CT) scan. (Also note presence of bilateral hemothoraces.)

be used routinely. If additional imaging is required beyond a standard upright posteroanterior and lateral chest x-ray, a computed tomography (CT) scan of the chest should be obtained (Fig. 37.3). A CT scan is not indicated to confirm suspected isolated rib fracture, but it will identify multiple-level fractures and associated pulmonary injury, such as pneumothorax or hemothorax, with much greater accuracy than additional chest x-ray views.

In an attempt to limit unnecessary use of diagnostic ionizing radiation, the National Emergency X-Radiography Utilization Study (NEXUS) group derived and validated a decision instrument to guide the use of chest CT in patients with blunt trauma.[1] The NEXUS-Chest CT derivation and validation studies, performed at eight trauma centers in the United States, enrolled 11,477 patients. In the validation phase, the decision instrument had a sensitivity of 95.4%, a negative predictive value of 93.9%, and a specificity of 25.5% for all thoracic

BOX 37.1 NEXUS-Chest CT Criteria for Chest Computed Tomography After Blunt Trauma

- Abnormal chest x-ray
- Rapid deceleration mechanism (defined as fall >20 feet or motor vehicle collision >40 mph)
- Distracting painful injury
- Chest wall tenderness
- Sternal tenderness
- Thoracic spine tenderness
- Scapular tenderness

From Rodriguez RM, Langdorf MI, Nishijima D, et al: Derivation and validation of two decision instruments for selective chest CT in blunt trauma: a multicenter prospective observational study (NEXUS Chest CT). *PLoS Med*. 2015;12(10):e1001883.

injuries. The results were even more impressive for major clinical injuries, with both sensitivity and negative predictive value approaching 100% (99.2% and 99.8%, respectively). We recommend that CT scan not be obtained for patients sustaining blunt trauma who do not meet any of the seven NEXUS-Chest CT criteria (Box 37.1).[1–3]

Management

Respiratory decompensation is the primary indication for endotracheal intubation and mechanical ventilation for patients with multiple rib fractures. Obvious problems, such as hemopneumothorax or severe pain, should be corrected before intubation and ventilation are presumed necessary. In the awake and cooperative patient, noninvasive continuous positive airway pressure (CPAP) by mask may obviate the need for intubation.[3] In general, the most conservative methods for maintaining adequate oxygenation and preventing complications should be used. Adequate analgesia is of paramount importance in patient recovery and may contribute to the return of normal respiratory mechanics.

Treatment of acute rib fractures is based on adequate pain relief and the maintenance of pulmonary function. Outdated management techniques involving stabilization of the flail segment by positioning the person with the injured side down or placing sandbags on the affected segments have been discredited. These interventions actually inhibit expansion of the chest and produce increased atelectasis of the injured lung. Instead, oxygen should be administered, cardiac and oximetry monitors applied, and the patient observed for signs of an associated injury, such as tension pneumothorax.

Otherwise well patients with single rib fractures are managed with opioid and non-opioid analgesia. These injuries can be severely painful, and regular opioid medication along with transdermal lidocaine patches (particularly at bedtime) is usually necessary for up to a week. Thereafter, simple analgesia with acetaminophen or a nonsteroidal anti-inflammatory analgesic generally will suffice. Continuing daily activities and deep breathing should be stressed to ensure ventilation and prevent atelectasis. It is helpful to advise patients to wait 30 to 45 minutes after taking their pain medications before performing deep breathing exercises, ideally with an incentive spirometer.

The greater the number of fractured ribs, the higher the mortality and morbidity rates. Hospitalization should be considered for patients with three or more fractured ribs, despite the lack of other identified injuries, to receive pulmonary therapy, repeated evaluation, and appropriate effective analgesia. Elderly patients with six or more fractured ribs should be treated in an intensive care unit owing to high morbidity and mortality.

Multiple rib fractures in trauma patients are associated with significant morbidity and mortality. Intercostal nerve blocks with a long-acting anesthetic, such as bupivacaine with epinephrine, may relieve symptoms up to 12 hours. Other alternatives for hospitalized patients include patient-controlled analgesia, parenteral opioids, and thoracic epidural analgesia.

For flail segments, consultation with a trauma or thoracic surgeon is essential to plan for surgical intervention. Early operative internal fixation of the flail segment results in a speedier recovery, decreased complications, and better cosmetic and functional results, and it is cost-effective.[4] Indications for open fixation for flail chest include patients who are unable to be weaned from the ventilator secondary to the mechanics of flail chest, persistent pain, severe chest wall instability, or a progressive decline in pulmonary function.

The patient with flail chest should be treated in the emergency department (ED) as if pulmonary contusion exists regardless of whether mechanical ventilation is used.

Disposition

Most rib fractures heal uneventfully within 3 to 6 weeks, and patients should expect a gradual decrease in their discomfort during this period. However, in addition to the complications of hemopneumothorax, atelectasis, pulmonary contusion, and pneumonia, rib fractures can result in post-traumatic neuroma, empyema, nonunion, or costochondral separation.[5] These rare complications are painful and heal slowly. Patients with blunt trauma and multiple rib fractures should be observed for 12 to 24 hours to ensure that occult vascular or intrapulmonary injuries are not present and then considered for discharge, with the full understanding that the rib fractures themselves will require a prolonged recovery period and close outpatient follow-up.

The outcome of flail chest is a function of associated injuries. Because many different physiologic mechanisms have been implicated in flail chest, there is no consensus about hospital treatment. The cornerstones of therapy include pulmonary physiotherapy, effective analgesia, selective use of endotracheal intubation and mechanical ventilation, and close observation for respiratory compromise.

STERNAL FRACTURE

Foundations

Background and Importance

Sternal fractures and dislocations are caused primarily by anterior blunt chest trauma (e.g., motor vehicle collisions [MVCs] or bicycle accidents when the chest strikes the steering wheel or handlebars). Risk factors for sternal fracture from blunt trauma include types of vehicular passenger restraint systems and patient age. Restrained passengers are more likely than unrestrained passengers to sustain sternal fracture, likely related to the central location of the shoulder portion of the restraint. Cardiac complications, such as myocardial contusion, occur rarely, and there is no association between sternal fracture and aortic rupture. Although sternal fractures may occur in the context of major blunt chest trauma, the presence of a sternal fracture itself does not imply other major life-threatening conditions.

Pathophysiology

During rapid deceleration from a frontal impact, the forward thrust of the body against the fixed seat belt across the sternum can result in a fracture. The location of the sternal fracture varies depending on the position of the belt, patient size, the magnitude of the impact, and the vector of the forces.

Clinical Features

Patients with sternal fractures typically present with a history compatible with the injury, and anterior chest pain, point tenderness over the sternum, ecchymosis, soft tissue swelling, or palpable deformity.

Diagnostic Testing

When sternal fracture is suspected after a relatively minor mechanism of injury (e.g., ground level fall or blow to the chest), posteroanterior and lateral chest radiography is sufficient to establish the diagnosis and for evaluation of the pulmonary structures. However, when more significant traumatic signs or symptoms are present (as per the NEXUS-Chest CT criteria)[1] or when plain radiography shows a displaced fracture or possible evidence of intrathoracic injury, we recommend obtaining a chest CT scan. Results will guide management of the sternal fracture and any associated mediastinal or other intrathoracic injuries.[6,7] Notably, there are also specific ultrasound views during evaluation by extended focused assessment with sonography in trauma (e-FAST) that may be more sensitive than plain radiography for sternal fracture.

Management

Treatment consists of providing adequate analgesia, as for rib fractures. In the absence of associated injuries, most patients with isolated sternal fractures who can achieve adequate pain control with oral medications can be safely discharged home. A small subset of patients with more severe sternal fractures may have severe pain and develop respiratory compromise or nonunion. These patients are best referred for operative fixation.

NONPENETRATING BALLISTIC INJURY

Foundations

Background and Importance

Injury caused by low-velocity projectiles against protective vests or the use of rubber bullets or beanbag shotgun shells represent high-frequency examples of nonpenetrating ballistic injuries. Composed of many different combinations of synthetic fibers such as Kevlar®, lightweight synthetic body armor is often used by law enforcement officers, emergency medical services personnel, and private security guards to protect against gunshot injury. These vests are "bullet resistant" rather than "bulletproof," depending on the weapon being used against them. Therefore, wearers who are shot often suffer nonpenetrating ballistic injuries rather than gunshot wounds. Rubber bullets have been used for many years by police agencies throughout the world for crowd dispersal and for nonlethal use of force. Beanbag shotgun shells are nylon bags filled with pellets, which are fired from a standard shotgun. Both of these projectiles have the potential to cause serious injury despite their classification of "nonmetal" or "less-than-lethal" use of force.

Pathophysiology

Bullet-resistant vests are usually capable of stopping penetration by the low-velocity projectiles from most handguns, but the kinetic energy of a bullet can be transmitted through the layers of protective cloth or armor and produce significant injury without penetration. The heart, liver, spleen, lung, and spinal cord are vulnerable to nonpenetrating ballistic injury that may occur despite benign-appearing skin lesions.

Clinical Features

Patients who have been shot with "less-than-lethal projectiles" or with standard bullets while wearing bullet-resistant vests usually have erythema, ecchymosis, and marked tenderness to palpation over the affected area. There may be a projectile, such as a beanbag, still located in the wound. The area of tenderness and surrounding structures should be carefully palpated to identify any subcutaneous emphysema, crepitus, or bony step-offs.

Diagnostic Testing

Most patients with nonpenetrating ballistic injury do not require testing beyond a thorough physical examination. Those in whom there is concern for retained foreign body or underlying injury may need ultrasound examination, chest x-ray, or CT scan (as they might with other blunt trauma). However, patients with only superficial ecchymoses without clinical signs or symptoms of rib fracture, pneumothorax, hemothorax, intrapleural or peritoneal penetration frequently require no additional testing.

Management

In patients in whom underlying injury has been excluded or determined to be of low clinical probability, management of nonpenetrating ballistic injury focuses on wound care, either of the ecchymotic area or of the superficial abrasion or laceration. Underlying injuries, when present, should be managed as noted elsewhere in this chapter.

Disposition

It is recommended that patients with all but the most superficial nonpenetrating ballistic injuries to the chest be observed for 4 to 6 hours to detect internal injuries that may manifest in a delayed manner.

PULMONARY INJURIES

PULMONARY CONTUSION AND LACERATION

Foundations

Background and Importance

Pulmonary contusion is present in up to 75% of patients with significant blunt chest trauma, most often from MVCs with rapid deceleration.[8] Pulmonary contusions can also be caused by high-velocity missile wounds and the high-energy shock waves of an explosion in air or water.

In addition to contusions, the lungs can also sustain lacerations. Although they are most often lacerated from penetrating injury, they may also be injured by the inward projection of a fractured rib or avulsion of a pleural adhesion.[4,8]

Pathophysiology

Pulmonary contusion is caused by an impact to the lung parenchyma followed by alveolar edema and hemorrhage but without an accompanying pulmonary laceration. The early diagnosis of pulmonary contusion is important if treatment is to be successful. Since its onset may be insidious, it should be suspected from a history of a high mechanism of injury (e.g., a fall from height, an MVC, and other forms of significant trauma) rather than the initial chest radiograph.

Clinical Features

The clinical manifestations include dyspnea, tachypnea, cyanosis, tachycardia, hypotension, and chest wall bruising. There are no specific signs for pulmonary contusion or laceration, but hemoptysis may be seen. Moist rales or absent breath sounds may be heard on auscultation. Palpation of the chest wall commonly reveals fractured ribs. If flail chest is discovered, pulmonary contusion is also likely present.

Of note, many of the worst contusions occur in patients without rib fractures. It has been theorized that the more elastic chest wall in younger individuals transmits increased force to the thorax. Although isolated pulmonary contusions can exist, they are associated with extrathoracic injuries in the majority of patients.

Diagnostic Testing

Laboratory

Hypoxemia frequently occurs with pulmonary contusions and is often detected by a decreasing pulse oximetry reading. In patients with thoracic injury and hypoxemia in whom other, more severe injuries (e.g., pneumothorax) have been excluded, a pulmonary contusion should be suspected. In these patients, arterial blood gas assessment is helpful in making the diagnosis, because a widening alveolar-arterial oxygen difference indicates a decreasing pulmonary diffusion capacity of the patient's contused lung, and it is one of the earliest and most accurate means of assessing the current status, progress, and prognosis.

Radiology

Typical radiographic findings can begin to appear within minutes of injury and range from patchy, irregular alveolar infiltrate to frank consolidation (Fig. 37.4). Although these changes may be present on the initial examination, they are almost always present within 6 hours. The rapidity of changes on chest x-ray visualization usually correlates with the severity of the contusion or laceration. Pulmonary contusion should be differentiated from acute respiratory distress syndrome (ARDS) because the radiographic appearance of the two conditions may be similar. Contusion usually manifests within minutes of the initial injury, is usually localized to a segment or a lobe, is often apparent on the initial chest study, and tends to last 48 to 72 hours. ARDS is diffuse, and its development is usually delayed, with onset typically between 24 and 72 hours after injury.

The increased frequency of CT scans for blunt trauma patients has resulted in a corresponding increase in the diagnosis of pulmonary contusions and lacerations. CT scans have been shown to detect at least twice as many pulmonary contusions as plain radiographs, and one recent study found that isolated pulmonary contusions seen on CT had a mortality of only 2.6% (compared to 4.7% for all patients with pulmonary contusion detected by plain radiography).[8]

Chest CT scan is particularly valuable to identify a pulmonary contusion in the acute phase after injury because plain chest x-ray films have a low sensitivity. Although CT scan may not be necessary to make the diagnosis of a pulmonary contusion that is evident on plain chest radiography, it may be helpful to further define the extent of the contusion and to identify other thoracic injuries. Occult pulmonary contusions are those that are initially visible only on CT scan, not plain radiographs, and usually involve less than 20% of the lung volume. These occult pulmonary contusions are not associated with a worse clinical outcome as compared with blunt trauma patients without pulmonary contusion.[8]

Management

Treatment for pulmonary contusions is primarily supportive. As with flail chest, intubation and mechanical ventilation should be avoided if possible, because they are associated with an increase in morbidity, including pneumonia, sepsis, pneumothorax, hypercoagulability, and longer hospitalization. In the rare case in which one lung has been severely contused and is causing significant hypoxemia, consideration should be given to intubating and ventilating each lung separately with a dual-lumen endotracheal tube and two ventilators. This allows for the difference in compliance between the injured and the normal lung and prevents hyperexpansion of one lung and gradual collapse of the other.

Management of patients with pulmonary contusions should include the restriction of intravenous (IV) fluids (to maintain intravascular volume within strict limits) and comprehensive supportive care consisting of tracheobronchial toilet, suctioning, and pain relief. These maneuvers may preclude the need for ventilator support and allow a more selective approach to both flail chest and pulmonary contusion.

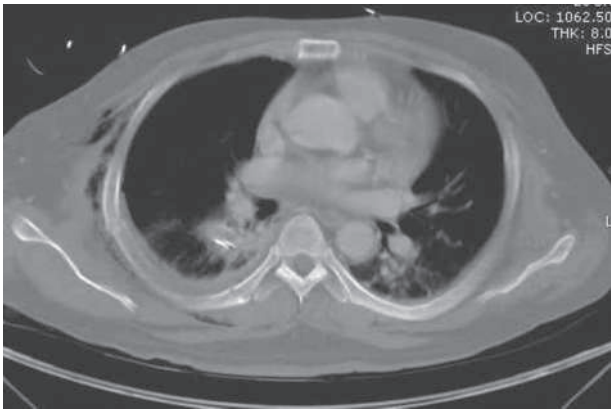

Fig. 37.4 Chest computed tomography (CT) scan showing bilateral alveolar infiltrates suggesting pulmonary contusion. There are also multiple rib fractures and subcutaneous emphysema.

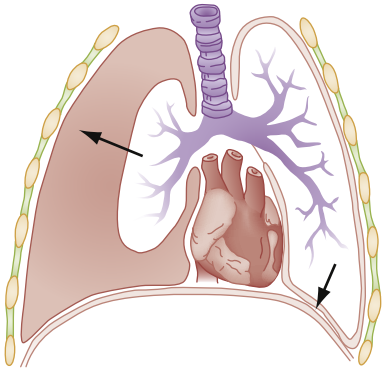

Fig. 37.5 **Closed Pneumothorax.** Simple pneumothorax is present in the right lung with air in the pleural cavity *(left arrow)* and collapse of the right lung *(right arrow)*.

Patients sustaining the force necessary to inflict a pulmonary contusion may also have pulmonary lacerations. Most of these are minor and rarely life-threatening, and they can usually be treated with continuous oxygen therapy, observation, or tube thoracostomy. Severe lacerations are associated with hemopneumothorax, multiple displaced rib fractures, and hemoptysis. Often, these life-threatening lacerations require thoracotomy with resection or tractotomy to control bleeding.

PNEUMOTHORAX

Foundations

Background and Importance

Pneumothorax, which is the accumulation of air in the pleural space, is a common complication of chest trauma. It is reported to be present in 15% to 50% of patients who sustain significant chest trauma and is invariably present in those with transpleural penetrating injuries.

Pathophysiology

Pneumothorax can be divided into three types depending on whether air has direct access to the pleural cavity: (1) simple, (2) communicating, and (3) tension.

Simple pneumothorax. A pneumothorax is considered simple or closed (Fig. 37.5) when there is no communication with the atmosphere or any shift of the mediastinum or hemidiaphragm resulting from the accumulation of air. Traumatic simple pneumothorax is most often caused by a fractured rib that is driven inward, lacerating the pleura. It may also occur without a fracture when the impact is delivered at full

inspiration with the glottis closed, leading to a tremendous increase in intra-alveolar pressure and the subsequent rupture of the alveoli. A penetrating injury, such as a gunshot or stab wound, may also produce a simple pneumothorax if there is no free communication with the atmosphere (Fig. 37.6).

Communicating pneumothorax. A communicating pneumothorax (Fig. 37.7) is associated with a defect in the chest wall and most commonly occurs in combat injuries. In the civilian sector, this injury is typically secondary to gunshot wounds. Air can sometimes be heard flowing sonorously in and out of the defect, prompting the term "sucking chest wound." The loss of chest wall integrity causes the involved lung to paradoxically collapse on inspiration and expand slightly on expiration, forcing air in and out of the wound. This results in a large functional dead space for the normal lung and, together with the loss of ventilation of the involved lung, produces a severe ventilatory disturbance.

Tension pneumothorax. The progressive accumulation of air under pressure within the pleural cavity, with shift of the mediastinum to the opposite hemithorax and compression of the contralateral lung and great vessels, is the constellations of findings in tension pneumothorax (Figs. 37.8 and 37.9). It occurs when the injury acts like a one-way valve, prevents free bilateral communication with the atmosphere, and leads to a progressive increase of intrapleural pressure. Air enters on inspiration but cannot exit with expiration. The resulting shift of mediastinal contents compresses the vena cava and distorts the cavoatrial junction, leading to decreased diastolic filling of the heart and subsequent decreased cardiac output. These changes result in the rapid onset of hypoxia, acidosis, and shock.

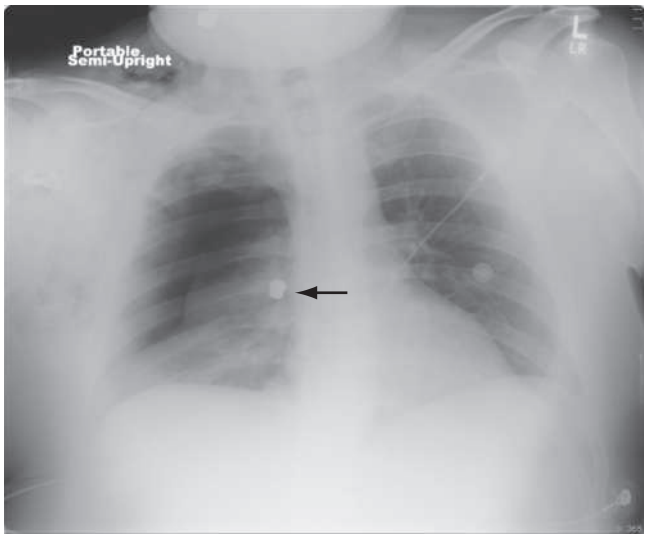

Fig. 37.6 Chest radiograph showing a moderate-sized right pneumothorax. A bullet *(arrow)* can be seen near the right mediastinum.

Clinical Features

Shortness of breath and chest pain are the most common presenting complaints of pneumothorax. The patient's appearance is highly variable, ranging from acutely ill with cyanosis and tachypnea to misleadingly healthy appearance. The signs and symptoms are not always correlated with the degree of pneumothorax. The physical examination may reveal decreased or absent breath sounds and hyper-resonance over the involved side as well as subcutaneous emphysema, but small pneumothoraces may not be detectable on physical examination.

Patients with tension pneumothorax become acutely ill within minutes and develop severe cardiovascular and respiratory distress. They are dyspneic, agitated, restless, cyanotic, tachycardic, and hypotensive and display altered mental status. The cardinal signs of tension pneumothorax are tachycardia, hypotension, oxyhemoglobin desaturation, jugular venous distention (JVD), and absent breath sounds on the ipsilateral side. However, JVD may not reliably be present with massive blood loss.

Diagnostic Testing

Because intrapleural air tends to collect at the apex of the lung, the initial chest radiograph should be an upright full inspiratory film if the patient's condition permits. An upright film will often reveal small pleural effusions that are not visible on supine films, and it also allows better visualization of the mediastinum. Although the chest radiograph has traditionally been the preferred initial study for diagnosing a simple pneumothorax, several studies have found that ultrasound has greater sensitivity for pneumothorax than chest radiography.[9,10] During the e-FAST examination, pneumothorax will be detected well before chest radiography is performed. This may be particularly critical in the hypotensive poly-trauma patient with oxyhemoglobin desaturation for whom tension pneumothorax is one of the considerations as

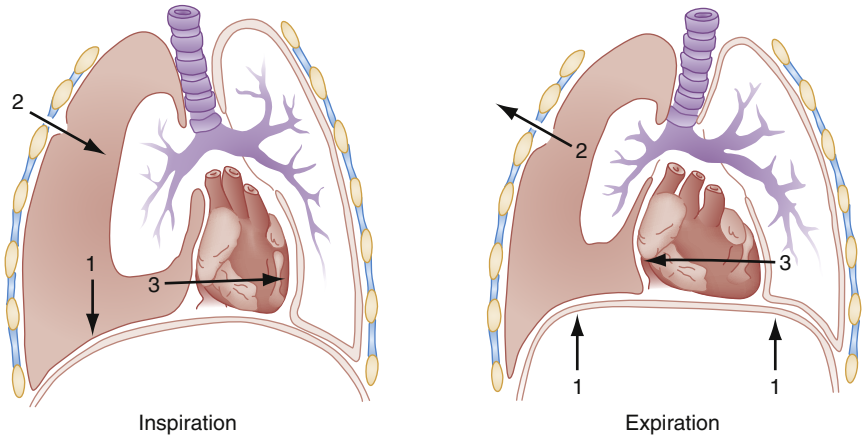

Fig. 37.7 Inspiration *(left):* The diaphragm contracts causing negative intrathoracic pressure *(arrow 1)* that draws air through the sucking chest wound in the pleural cavity *(arrow 2)* and causing the mediastinal structures to shift to the patient's left *(arrow 3)*. Expiration *(right):* The diaphragm recoils *(arrow 1)* causing air to exit the chest *(arrow 2)* and allowing the mediastinum to shift back to normal position *(arrow 3)*. The collapsed lung paradoxically shrinks on inspiration and expands on expiration.

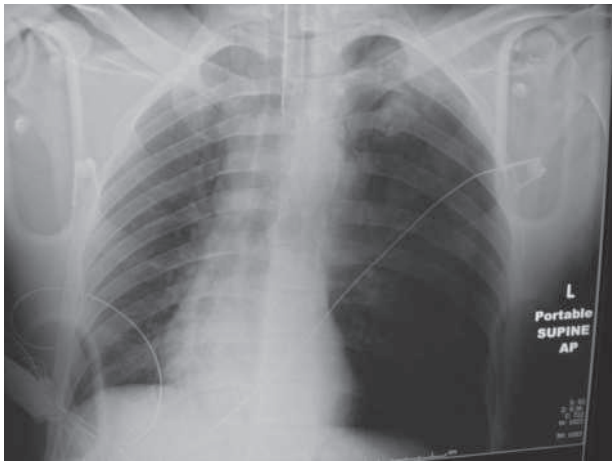

Fig. 37.8 Tension pneumothorax seen in intubated patient.

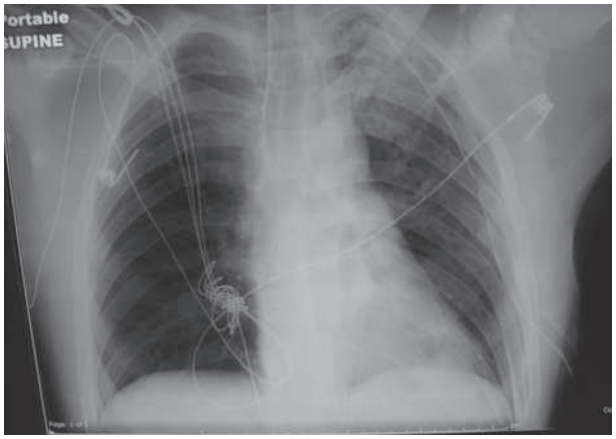

Fig. 37.9 Resolution of the tension pneumothorax shown in Fig. 37.8 with placement of a left-sided tube thoracostomy.

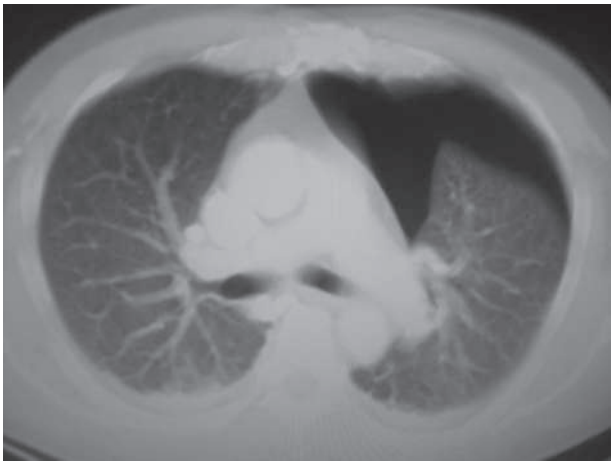

Fig. 37.10 Occult Pneumothorax. Large left-sided pneumothorax visible on chest computed tomography (CT) scan, which was not visible on chest x-ray film.

BOX 37.2 Indications for Tube Thoracostomy

- Traumatic cause of pneumothorax (except asymptomatic, apical pneumothorax)
- Moderate to large pneumothorax
- Respiratory symptoms regardless of size of pneumothorax
- Increasing size of pneumothorax after initial conservative therapy
- Recurrence of pneumothorax after removal of an initial chest tube
- Patient requires ventilator support
- Patient requires general anesthesia
- Associated hemothorax
- Bilateral pneumothorax regardless of size
- Tension pneumothorax

From Dougall AM, Paul ME, Finely RJ, et al. Chest trauma—current morbidity and mortality. *J Trauma* 1977;17:547.

the cause of the unstable state. Suspicion of tension pneumothorax on the basis of clinical findings is indication for immediate tube thoracostomy. Treatment should not be delayed pending a confirmatory chest radiograph. Ultrasound can confirm the presence of a pneumothorax within the first minutes of the patient's arrival, and identification of a pneumothorax in a patient with pulmonary and hemodynamic compromise is also considered confirmatory empirical evidence of tension pneumothorax requiring thoracostomy. Even without ultrasound confirmation, clinical suspicion of tension pneumothorax is justification for emergent tube thoracostomy, because delay can be detrimental.

Occult Pneumothorax

A pneumothorax that is absent on the initial chest radiograph but is identified on subsequent chest or abdominal CT is called an *occult pneumothorax.* Occult pneumothorax is being diagnosed more frequently given the increased use of CT scanning (Fig. 37.10).[11]

Management

An asymptomatic patient who suffers a low-velocity penetrating trauma (typically a stab wound) and who has negative initial imaging can be safely observed, typically for 6 hours. If the initial imaging was a CT scan, the patient may be safely discharged after the period of observation. If the initial imaging was via plain radiograph, a delayed chest x-ray should be performed prior to discharge.

Simple Pneumothorax

Treatment of a simple pneumothorax depends on its cause and size. Small, isolated apical pneumothoraces due to stab wounds may be observed without intervention. However, this conservative method seldom has application in multisystem trauma, and a chest tube should be inserted immediately upon any sign of deterioration.

Similarly, small occult pneumothoraces found only on CT scan in hemodynamically stable patients without symptoms can be managed with observation and do not need intervention, even if the patient is placed on positive-pressure ventilation.[11]

Any moderate to large pneumothorax should be treated with a chest tube. The indications for tube thoracostomy (chest tube insertion) are listed in Box 37.2. The preferred site for insertion is the fourth or fifth intercostal space at the midaxillary line. This lateral placement of the tube is preferred not only because it is more efficient, but also because it does not produce an easily visible cosmetic defect, compared to the anterior site at the second interspace at the midclavicular line. With multisystem trauma in which hemothorax is likely, a large chest tube (36-F to 40-F in adults and 16-F to 32-F in children) should be used. Conversely, spontaneous pneumothoraces or those due to minor or isolated injuries can be treated with smaller caliber chest tubes.

Care is taken to be certain the vent holes along the side of the tube are all inside the chest cavity. A radiopaque line along the side of the tube with interruptions at these drainage holes helps in radiographically

interpreting tube position. The tube should be attached to a water seal drainage system that allows re-expansion of the pneumothorax. If there is significant air leak or a large hemothorax, the tube may be connected to a source of constant vacuum at 20 to 30 cm H_2O for more rapid re-expansion.

Tube thoracostomy does have some potentially serious complications, including the formation of a hemothorax, pulmonary edema, bronchopleural fistula, pleural leaks, empyema, subcutaneous emphysema, infection, intercostal artery laceration, contralateral pneumothorax, and parenchymal injury.[12] A recent meta-analysis did not find sufficient evidence for or against the use of empirical antibiotics with all tube thoracostomy placements to prevent empyema or pneumonia, especially those needed for spontaneous pneumothoraces. However, for patients with multisystem trauma or hemothorax, the data was suggestive of a clinical benefit. We recommend routine intravenous antibiotic administration in these patients, specifically cefazolin 1 to 2 g given prior to, or within 1 hour of chest tube insertion. Vancomycin (1 g) or clindamycin (600 mg) are appropriate alternatives in patients with cephalosporin allergies.[13]

Communicating Pneumothorax

For a patient with a communicating pneumothorax in the out-of-hospital setting, the defect should be covered immediately, which helps convert the condition to a closed pneumothorax, eliminating the major physiologic abnormality. Either a partially occlusive dressing or a commercial vented chest seal can be applied; care should be taken to continually assess for conversion of the injury to a tension pneumothorax, especially in patients who are intubated and undergoing positive-pressure ventilation. The wound should never be packed, because the negative pressure during inspiration can suck the dressing into the chest cavity. These considerations are not as critical once the patient is in the ED, where formal tube thoracostomy can be performed. Positive-pressure ventilation can then be initiated, if needed, without the fear of producing a tension pneumothorax, and the patient can be prepared for definitive surgical repair.

Tension Pneumothorax

When the diagnosis of tension pneumothorax is suspected clinically, the pressure should be relieved immediately with needle thoracostomy, which is performed by inserting a large-bore (14-gauge or larger) catheter, at least 5 cm in length, through the fourth or fifth interspace laterally or the second or third interspace anteriorly on the involved side. However, some catheters may not be of sufficient length to penetrate the pleural space.[14] Therefore, we recommend the lateral approach if it is accessible. This method can be easily performed in the field, allowing vital signs to improve during transport or preparation for a tube thoracostomy.[15]

In the ED, it may be just as expeditious to insert a chest tube (or even perform a "finger thoracostomy," without actually inserting the chest tube) as it is to perform a needle thoracostomy, depending on the availability of equipment. Regardless, even if a needle thoracostomy is performed on a patient with suspected tension pneumothorax in the ED, a chest tube should emergently follow.

The intubated patient in the ED who is receiving positive-pressure ventilation and external cardiac compressions is at particular risk for developing tension pneumothorax. Fractured ribs from cardiopulmonary resuscitation (CPR) can penetrate lung parenchyma and cause pneumothorax. Positive-pressure ventilation then increases intrapleural pressure and produces a tension pneumothorax. The earliest sign of this complication is an increase in resistance to ventilation. If the patient has detectable vital signs, the blood pressure will fall and the central venous pressure (CVP) will rise. Misplacement of an endotracheal tube does not result in tension pneumothorax but, rather, asymmetry of breath sounds. If tension pneumothorax is suggested, the clinician should proceed with empirical emergent therapy.

HEMOTHORAX

Foundations

Background and Importance

Hemothorax, which is the accumulation of blood in the pleural space after blunt or penetrating chest trauma, is a common complication that may produce hypovolemic shock and rapidly reduce vital capacity. It is commonly associated with pneumothorax and extrathoracic injuries.

Pathophysiology

Hemorrhage from injured lung parenchyma is the most common cause of hemothorax, but this tends to be self-limited unless there is a major laceration. Specific vessels are less often the source of hemorrhage, with intercostal and internal mammary arteries causing hemothorax more often than hilar or great vessels. Bleeding from the intercostal arteries may be brisk, however, because they branch directly from the aorta.

Clinical Features

Depending on the rate and quantity of hemorrhage, varying degrees of hypovolemic shock will be manifested. Patients may present in respiratory distress and be tachycardic and hypoxemic. Breath sounds may be diminished. The diagnosis should also be recognized as a potential complication of central line placement and considered—along with pneumothorax—in patients who present with these symptoms after the procedure.

Diagnostic Testing

The *upright* chest radiograph remains the primary diagnostic study in the acute evaluation of hemothorax. A hemothorax is noted as meniscus of fluid blunting the costophrenic angle and tracking up the pleural margins of the chest wall when viewed on the upright chest x-ray film. Blunting of the costophrenic angles on upright chest radiograph requires at least 200 to 300 mL of fluid. The supine view chest film is less accurate but is often the only film available because of the patient's unstable condition. In the supine patient, blood layers posteriorly, creating a diffuse haziness that can be rather subtle (or appear to be a pulmonary contusion), depending on the volume of the hemothorax (Fig. 37.11). With massive hemothorax, the large volume of blood can create a tension hemothorax, with signs and symptoms of both obstructive and hemorrhagic shock (Fig. 37.12).

As is the case with pneumothoraces, ultrasound has greater sensitivity than supine chest radiography in the detection of hemothoraces.[10,16] Given this, early bedside ultrasonography should routinely be performed in patients with thoracic trauma, regardless of findings on supine radiography. Additional imaging via chest CT scan (Fig. 37.13) should be performed if indicated by the NEXUS-Chest CT criteria as discussed earlier,[1] because it may detect hemothorax or other associated injuries (Fig. 37.14).

Management

Treatment of hemothorax consists of restoring the circulating blood volume, controlling the airway as necessary, and evacuating the accumulated blood. Tube thoracostomy allows constant monitoring of the blood loss, and serial chest radiographs help monitor lung reexpansion.

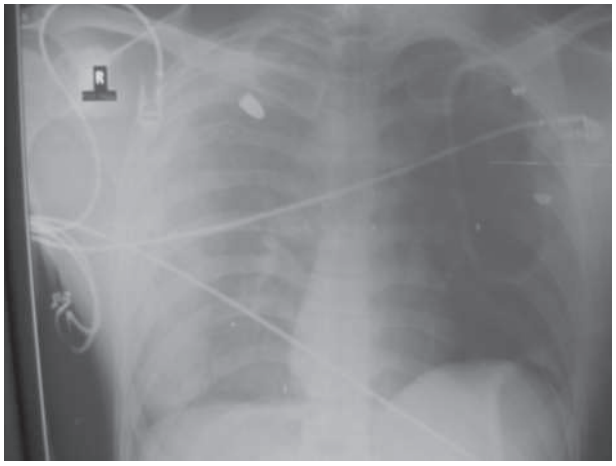

Fig. 37.11 Hemothorax Secondary to Gunshot Wound. Note haziness over right hemithorax with bullet seen in right upper lobe.

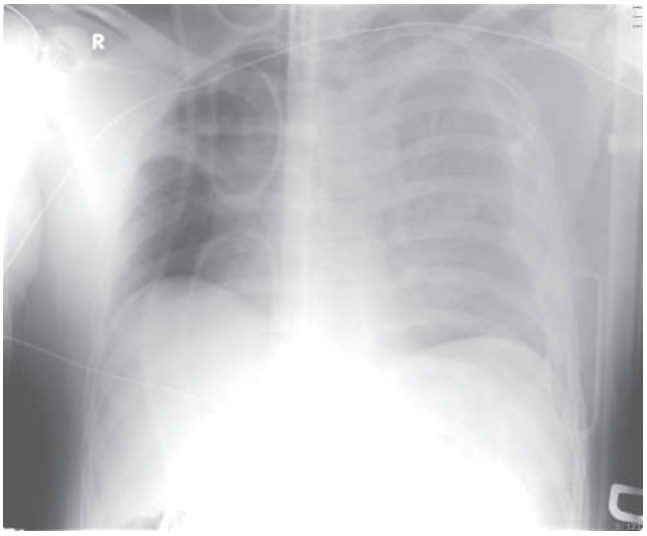

Fig. 37.12 Tension Hemothorax.

A large-bore tube (36-F to 40-F) should be inserted in the fifth interspace at the anterior axillary line and connected to underwater seal drainage and suction (20 to 30 mL H_2O).

Although small hemothoraces may be observed in stable patients, a moderate hemothorax or any hemothorax in an unstable or symptomatic patient requires tube thoracostomy. Severe or persistent hemorrhage requires thoracostomy or open thoracotomy. Further studies are required to better delineate the size of a hemothorax detected on CT scan that requires tube thoracostomy drainage.

Autotransfusion has been successfully used in tube thoracostomy. Autotransfusion also eliminates the risk of incompatibility reactions and transmission of certain diseases, such as hepatitis C. Because the majority of blood loss occurs immediately after tube thoracostomy placement, an autotransfusion apparatus should be immediately available in the ED.

Close monitoring of the initial and ongoing rate of blood loss should be performed. Immediate drainage of more than 1500 mL of blood from the pleural cavity is considered an indication for urgent thoracotomy, as is a continued output of at least 200 mL/h for 3 hours. General considerations for urgent thoracotomy are outlined in Box 37.3.

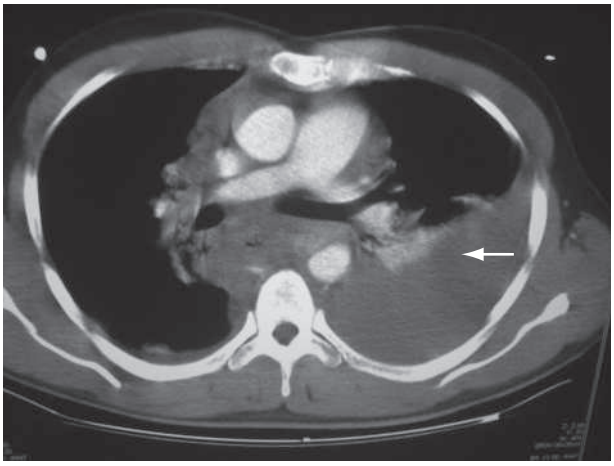

Fig. 37.13 Left-sided hemothorax visible on chest computed tomography (CT) scan *(arrow)*.

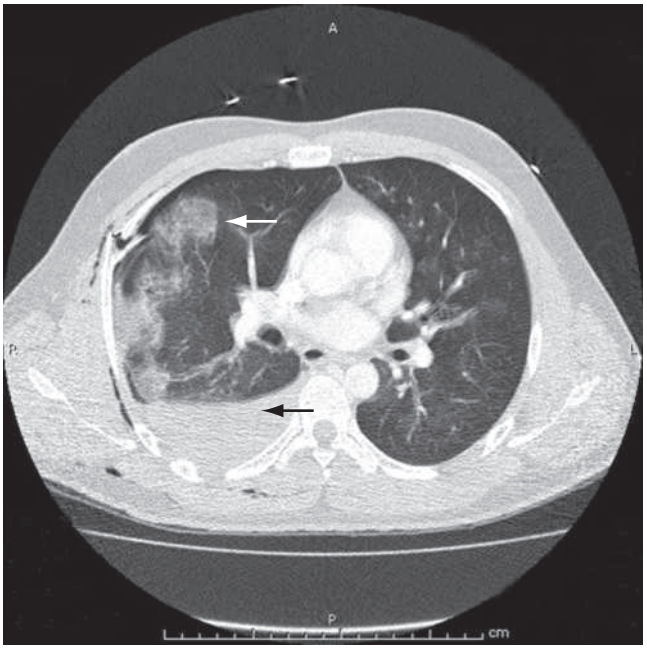

Fig. 37.14 Rib fracture resulting in pneumothorax, with associated hemothorax *(bottom arrow)* and pulmonary contusion *(top arrow)* seen on chest computed tomography (CT) scan.

BOX 37.3 Indications for Urgent Thoracotomy

- Initial thoracostomy tube drainage is more than 20 mL of blood per kilogram
- Persistent bleeding at a rate greater than 7 mL/kg/h is present
- Increasing hemothorax seen on chest x-ray films
- Patient remains hypotensive despite adequate blood replacement, and other sites of blood loss have been ruled out
- Patient decompensates after initial response to resuscitation

TRACHEOBRONCHIAL INJURY

Foundations

Background and Importance

Tracheobronchial injuries may occur with either blunt or penetrating injuries of the neck or chest. MVCs are the most frequent mechanism

causing tracheobronchial injury, accounting for more than half of all cases.

Although there has been an increase in the occurrence of tracheobronchial disruption, it is still a relatively rare injury, occurring in fewer than 3% of patients with significant chest injury. Its associated mortality rate is reported to be approximately 10%, although mortality rates are significantly affected by associated injuries and the timing of diagnosis and surgical repair.

Pathophysiology

Tracheobronchial injuries caused by knife wounds develop almost exclusively from wounds in the cervical trachea (see Chapter 36), whereas gunshot wounds may damage the tracheobronchial tree at any point. Intrathoracic injury to the tracheobronchial tree occurs most commonly from blunt trauma. These injuries may result from direct blows, shearing stresses, or burst injury. A direct blow to the neck may crush the cervical trachea against the vertebral bodies and transect the tracheal rings or cricoid cartilage. Shear forces on the trachea will produce injury at the carina and the cricoid cartilage, which are its relatively fixed points.

Sudden deceleration of the thoracic cage pulls the lungs away from the mediastinum, producing traction on the trachea at the carina. When the elasticity of the tracheobronchial tree is exceeded, it ruptures. It has also been suggested that if the glottis is closed at the time of impact, the sudden increase in intrabronchial pressure will rupture the tracheobronchial tree. Regardless of the mechanism, more than 80% of these injuries occur within 2 cm of the carina.

Clinical Features

Massive air leak through a chest tube, hemoptysis, and dramatic or increasing subcutaneous emphysema should suggest the diagnosis of major airway damage. Subcutaneous emphysema is typically the most common physical exam finding. Auscultation of the heart may reveal *Hamman's crunch* if air tracks into the mediastinum. Hamman's crunch is a crunching, rasping sound that is synchronous with the pulse and is best heard over the precordium. It is the result of the heart beating against air-filled tissues. Patients with tracheobronchial disruption have one of two distinct clinical pictures. In the first group of patients, the wound opens into the pleural space, producing a large pneumothorax. A chest tube fails to evacuate the space and reexpand the lung, and there is continuous bubbling of air (indicating a persistent leak) in the underwater seal device (Fig. 37.15).

In the second group of patients, there is complete transection of the tracheobronchial tree but little or no communication with the pleural space. A pneumothorax is usually not present. The peribronchial tissues support the airway enough to maintain respiration, but within 3 weeks, granulation tissue will obstruct the lumen and produce atelectasis. These patients are relatively free of symptoms at the time of injury, but weeks later they have unexplained atelectasis or pneumonia. Radiographic signs in either group of patients are pneumomediastinum, extensive subcutaneous emphysema (Fig. 37.16), pneumothorax, fracture of the upper ribs (first through fifth), air surrounding the bronchus, and obstruction in the course of an air-filled bronchus.

Diagnostic Testing

When tracheobronchial injury is suspected, bronchoscopy should be performed. Flexible endoscopic bronchoscopy is the most preferred and reliable means of establishing the diagnosis and determining the site and extent of the injury. However, CT scan has been shown to have high sensitivity in detecting tracheobronchial injury. Bronchopleural fistula (a communication between a bronchus and the lung parenchyma) can occur as a complication of tracheobronchial disruption and in some cases has been treated successfully via the fiberoptic bronchoscope. A mediastinal fluid collection, evidence of mediastinitis, or both may be noted on chest CT.

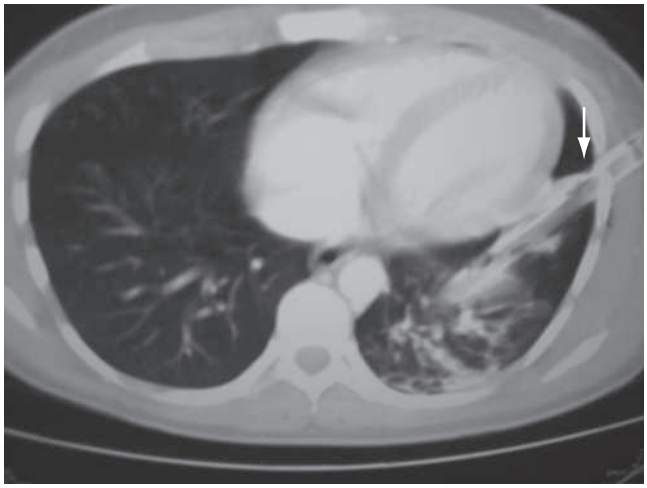

Fig. 37.15 Penetration of lung parenchyma by tube thoracostomy *(arrow)*, with large residual pneumothorax, visible on computed tomography (CT) scan.

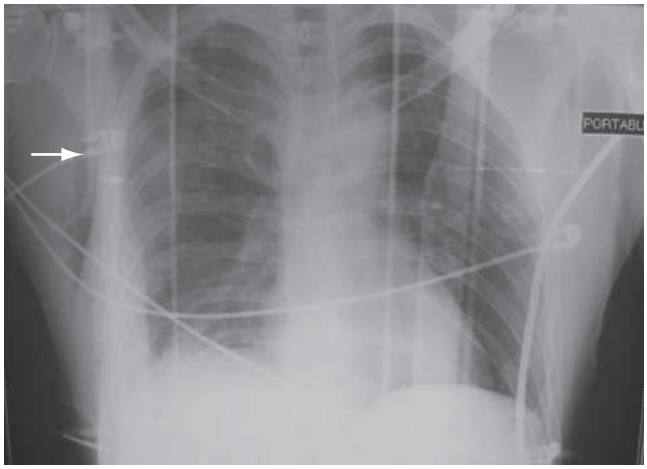

Fig. 37.16 Multiple rib fractures with extensive subcutaneous emphysema *(arrow)*, with no pneumothorax seen.

Management

If diagnostic bronchoscopy is performed, endotracheal intubation can be visualized over the bronchoscope to ensure that the tube passes safely beyond the site of injury. Blind intubation should not be attempted. If intubating using a video laryngoscope (or conventional laryngoscope), the tube is advanced slowly and gently to avoid creating a false passage or converting a partial tracheal tear to a complete tear.

The standard treatment for tracheobronchial injury has been thoracotomy with intraoperative tracheostomy and surgical repair of the disrupted airway. However, conservative medical treatment of such injuries can be considered for patients with tracheal tears less than 2 cm and without esophageal prolapse, mediastinitis, or massive air leakage.

DIAPHRAGMATIC INJURY

Foundations

Background and Importance

Diaphragmatic rupture is present in 1% to 6% of major thoracic injuries. Diaphragmatic rupture occurs most commonly after blunt

thoracoabdominal trauma, such as occurs in MVCs or falls from heights, but can also occur from penetrating trauma.

Pathophysiology

Diaphragmatic hernia is a herniation of abdominal structures into the thoracic cavity through a defect in the diaphragm, with a potential risk of strangulation of abdominal viscera, especially the small bowel. Signs and symptoms may not occur during the initial admission and may be delayed for as long as months to years, with a significant mortality rate.

Three-quarters of cases of diaphragmatic rupture secondary to blunt trauma occur on the left side, presumably due to the protective effect of the liver on the right side. Only about 5% of cases are bilateral. With penetrating injury, diaphragmatic injury occurs at the site of the penetration but may be occult.

In cases of blunt injury, the increased pressure within the abdominal cavity causes the diaphragmatic tear, and a pressure difference of generally 5 to 10 mm Hg forces the abdominal organs through the diaphragmatic defect. Because blunt trauma can cause multiple organ injuries, these coexisting injuries can mask the more silent diaphragmatic injuries, and diaphragmatic rupture may initially be overlooked. Over time, negative intrathoracic pressure generated by inspiration tends to draw abdominal contents into the thorax. This effect is minimized with the use of intubation and positive-pressure ventilation.

Clinical Features

Patients with diaphragmatic rupture can range from being completely asymptomatic to having vomiting; shortness of breath; abdominal, thoracic, or referred shoulder pain; or may have multiorgan failure that can result from visceral obstruction, strangulation, or perforation of hollow viscous. Delayed presentation up to years in patients with undiagnosed diaphragmatic tears without herniation can occur. As a result of the mechanism of injury and the force required to impart this injury, pelvic fractures as well as other significant intraabdominal and thoracic injuries are frequent, typically involving the lung, liver, and spleen. Rib and sternal fractures as well as cardiac contusions are also common.

Diagnostic Testing

Accurate diagnosis of traumatic diaphragmatic hernia is essential because prompt surgical repair is the treatment of choice. Plain chest radiography alone is poorly sensitive for diaphragm rupture. In patients with blunt trauma, CT examination of the abdomen and chest can be useful for the evaluation of diaphragmatic injury, although injury site and type affect its sensitivity. Nevertheless, CT can demonstrate findings consistent with diaphragmatic injury, including diaphragmatic discontinuity, intrathoracic herniation of abdominal contents, and waist-like constriction of abdominal viscera (known as the "collar sign").

In patients with penetrating left thoracoabdominal trauma, the incidence of herniation of abdominal contents is sufficiently high that thoracoscopy or laparoscopy is recommended for the diagnosis and repair of a diaphragmatic injury. Even in patients with right-sided penetrating lesions (which do not typically result in herniation because of the protective effect of the dome of the liver), evaluation of both sides of the diaphragm with laparoscopy or thoracoscopy is recommended.

Management

Diaphragmatic injuries may be markers of severity and predictors of serious associated injuries in trauma and should be surgically repaired. CT scan should identify the site and extent of herniation, herniated organs, complications, and damage to associated organs. Although they are not without complications, laparoscopy and thoracoscopy may be used for diaphragmatic hernia repair.

The incidence of diaphragmatic involvement after penetrating left sided thoracoabdominal injury is high, making nonoperative, expectant management of these patients potentially hazardous.

CARDIOVASCULAR TRAUMA

BLUNT CARDIAC TRAUMA

Blunt cardiac injury usually results from high-speed MVCs in which the chest wall strikes the steering wheel. Other causes, such as falls from heights, crushing injuries, blast injuries, and direct blows, are less common. The diagnosis of a blunt injury to the heart remains elusive because of the usual concomitant serious injuries to other body organs and, more important, because there is no accepted gold standard for making the diagnosis.

The importance of detecting blunt myocardial injury lies in the recognition of associated potentially fatal complications. Life-threatening dysrhythmias, conduction abnormalities, congestive heart failure, cardiogenic shock, hemopericardium with tamponade, cardiac rupture, valvular rupture, intraventricular thrombi, thromboembolic phenomena, coronary artery occlusion, ventricular aneurysms, and constrictive pericarditis have all been reported as complications.

Blunt cardiac trauma may be viewed as part of a continuous spectrum (i.e., myocardial concussion, contusion, infarction, and rupture). Myocardial concussion occurs when a blunt injury to the interior chest produces a "stun" response in the myocardium. No permanent cellular injury occurs, but transient clinical effects may result. Myocardial contusion is the least severe form of injury that can be demonstrated pathologically. Cellular injury occurs with extravasation of red blood cells into the muscle wall, along with localized myocardial cellular necrosis. Permanent myocardial damage is rare. Infarction typically occurs with traumatic occlusion or disruption of a coronary artery. Cardiac rupture is obviously the most severe form of blunt cardiac injury.

MYOCARDIAL CONCUSSION

Foundations

Background and Importance

The terms *myocardial concussion* or *commotio cordis* are used to describe an acute form of blunt cardiac trauma that is usually produced by a sharp, direct blow to the midanterior chest that stuns the myocardium and results in brief dysrhythmia, hypotension, and loss of consciousness. It is a rare event and primarily occurs in adolescents, especially those playing sports involving hard spherical objects (e.g., baseballs, hockey pucks).

Pathophysiology

Animal models of commotio cordis have determined that it is much more likely to occur if the impact occurs during early ventricular repolarization.[17] Additionally, flat objects and softer balls (e.g., tennis, soccer) are less likely to cause commotio cordis than other balls. Once this dysrhythmia occurs, it can result in a non-perfusing rhythm, such as asystole or ventricular fibrillation, and irreversible cardiac arrest. There are, however, a number of documented cases of successful resuscitation with both rapid provision of CPR and the use of an automated external defibrillator (AED).[18]

Clinical Features

Commotio cordis has a characteristic mechanism (blunt chest trauma) and presentation (sudden collapse). Notably, the condition itself is defined by a lack of structural cardiac damage, and so more severe

trauma (such as that necessary to cause cardiac contusion or rupture, as described later) is incongruent with the diagnosis.

Diagnostic Testing

Laboratory Tests and Electrocardiogram

Patients who present with the characteristic mechanism and presentation above and who have shockable rhythms on electrocardiogram (or who were defibrillated by an AED) can be presumed to have commotio cordis if there is no evidence of structural heart damage on echocardiography or CT. Laboratory evaluation of serum electrolyte and cardiac biomarker levels may identify additional contributors to their presentation, but these will typically be normal.

Management

The initial treatment of patients with commotio cordis should follow standard advanced cardiac life support (ACLS) algorithms, ideally with initiation of bystander CPR and early defibrillation (especially at sporting events). Barring any other more severe cardiac injuries (discussed later), commotion cordis does not require any specific interventions.

Disposition

In patients who survive the dysrhythmia of commotio cordis and are not found to have more severe traumatic cardiac injury, a short period of observation is appropriate. Although there is a paucity of evidence as to the duration of this observation period, we recommend 6 to 12 hours of telemetry monitoring. After this, patients may be discharged, although they should not return to sports play until additional outpatient cardiac testing (e.g., stress testing, cardiac magnetic resonance imaging [MRI], and pharmacologic testing for primary conductive disorders) is performed.[18]

MYOCARDIAL CONTUSION

Foundations

Background and Importance

Myocardial contusion is a very poorly understood and nebulous condition. Decades of research and widely varied clinical practice have failed to produce a consensus regarding its diagnosis, complication rate, and proper disposition.

Pathophysiology

Several mechanisms have been postulated by which the heart may be injured in cases of blunt trauma. A direct blow to the chest transmits energy through the ribs to the spine. When a large force is applied to the chest wall, the sternum is displaced posteriorly, and the heart is compressed between the sternum and vertebrae or an elevated diaphragm. Either can presumably result in cardiac injury. Increased intrathoracic pressure from a direct blow to the chest may contribute to the injury. In addition, compression of the abdomen and pelvis may displace abdominal viscera upward and result in cardiac injury.

Clinical Features

Myocardial contusion manifests clinically as a spectrum of injuries of varying severity. Although the majority of patients with myocardial contusion have external signs of thoracic trauma (e.g., contusions, abrasions, palpable crepitus, rib fractures, or visible flail segments), the absence of identifiable thoracic injury decreases the likelihood of myocardial contusion but does not exclude it. Virtually every known intrathoracic and chest wall injury has been associated with myocardial contusion. The most sensitive but least specific sign of myocardial contusion is sinus tachycardia, which is present in approximately 70% of patients with documented myocardial contusions. A reduction in cardiac output, which can be clinically insignificant or manifest as pronounced cardiogenic shock, may occur in patients with significant cardiac contusion.

Diagnostic Testing

There is no agreed upon gold standard diagnostic definition for myocardial contusion. Clinical evidence is often nonspecific, especially in the setting of multiple traumas. Many tests and definitions have been proposed over the years, but none has emerged as definitive.

Laboratory Tests and Electrocardiogram

Electrocardiogram. The right ventricle is far more likely to be injured than the left ventricle because of its anterior position in the thorax and proximity to the sternum. The standard 12-lead ECG is relatively insensitive to right ventricular damage, as demonstrated by pathologic evidence of cellular damage in patients with normal ECGs. A cardiac contusion usually results in moderate right ventricular damage with only minor electrical changes, which can easily be missed on ECG. Right-sided ECGs (the addition of V_4R) have not been found to be of diagnostic benefit.

The ECG for patients with myocardial contusion often shows evidence of dysrhythmia, conduction disturbance, or ischemia. Dysrhythmias or ECG changes also can be caused by significant hypoxia as a result of pulmonary injuries or blood loss, which resolve once the hypoxemia or blood loss has been corrected.

A few cases of delayed life-threatening dysrhythmia have been reported up to 12 hours after injury, and patients may develop less lethal dysrhythmias up to 72 hours after injury. The onset of ECG changes may be delayed up to 48 hours after injury, but all ECG changes usually resolve in 4 to 60 days. The presence of ECG abnormalities is neither specific enough to confirm the diagnosis of myocardial contusion nor reliable enough to predict subsequent complications, but a newly abnormal ECG (arrhythmia, heart block or ischemic changes) warrants admission for continuous ECG monitoring.[19]

Cardiac biomarkers. Creatine kinase (CK) is nonspecifically increased in trauma patients owing to associated skeletal muscle injury, and CK-MB levels have also been found to be falsely elevated in multitrauma patients. Therefore, the troponin assay is the preferred cardiac biomarker for testing.

The combination of a normal troponin level and a normal 12-lead ECG has a negative predictive value sufficient to "rule out" myocardial contusion, and these patients do not require any other evaluation or monitoring specific for myocardial contusion.[19]

Imaging

Although echocardiography provides a means to directly visualize cardiac structures and chambers and can be useful to rule out structurally significant myocardial injuries (e.g., wall motion or valvular abnormalities), it should not be routinely used as a primary screening modality for blunt cardiac injury. Rather, echocardiography should be reserved for patients in whom myocardial contusion is suspected (based on ECG or troponin level) and who have unexplained hypotension or arrhythmias.[19]

Management

Treatment of a suspected myocardial contusion is similar to that of a myocardial infarction (MI): cardiac monitoring, administration of oxygen if hypoxic, and analgesic agents. Dysrhythmias are typically transient and do not require treatment. Serious dysrhythmias, such as ventricular tachycardia or atrial flutter should be treated with appropriate medications as per current ACLS guidelines. No data exist to support prophylactic dysrhythmia suppression. Measures should be

taken to treat and prevent any conditions that increase myocardial irritability (e.g., metabolic acidosis). Thrombolytic agents and aspirin are contraindicated in the setting of acute trauma. In rare instances, there may be an acute MI associated with trauma, which can arise from lacerations or blunt injury to the coronary arteries. These cases should be managed by percutaneous coronary intervention (PCI), with cardiothoracic surgery for definitive repair as indicated.

In the setting of depressed cardiac output caused by suspected or confirmed myocardial contusion, judicious fluid administration to augment preload is warranted (e.g., 200 to 250 mL boluses every 15 minutes to a maximum of 1 to 2 L). A dobutamine infusion may be useful once preload has been optimized. While intra-aortic balloon counterpulsation has been used successfully in refractory cardiogenic shock, the priority is to ascertain that the decreased cardiac output is not the result of other undiagnosed traumatic injuries, particularly aortic rupture.

The prognosis of a patient with myocardial contusion depends on the character and magnitude of the initial trauma, the size and location of the contusion, the preexisting condition of the coronary arteries, and, most importantly, with the number of associated serious injuries. Recovery without complications is the usual course.

Disposition

Patients with suspected myocardial contusion who have normal serial troponin levels and a normal ECG do not have the diagnosis. Myocardial contusions resulting in ECG changes or troponin elevations necessitate telemetry observation or in-hospital monitoring, depending on the patients' other associated injuries. Markedly abnormal ECGs, troponin elevations, or hypotension warrant echocardiography and cardiology consultation.

MYOCARDIAL RUPTURE

Foundations

Background and Importance

High-speed MVCs are responsible for most cases of traumatic myocardial rupture, which is almost always fatal. Approximately one-third of these patients have multiple chamber rupture, and one-fourth have an associated ascending aortic rupture. Approximately 20% of patients survive at least 30 minutes, theoretically long enough to get them to operating room if the injury is recognized immediately and the center has the necessary cardiovascular surgical capabilities.

Anatomy and Physiology

Myocardial rupture refers to an acute traumatic perforation of the ventricles or atria, but it may also include a pericardial rupture or laceration or rupture of the interventricular septum, interatrial septum, chordae, papillary muscles, valves, and lacerated coronary arteries. A delayed rupture of the heart may also occur weeks after nonpenetrating trauma, most likely as a result of necrosis of a contused or infarcted area of myocardium.

The chambers most commonly involved in cardiac rupture are the ventricles, with right ventricular rupture being most common. Ruptures of the atria are less common, with right atrial rupture being more common than left. Multiple chamber involvement occurs in 20% of patients. Twenty percent of nonsurvivors have concomitant aortic rupture.

Pathophysiology

A rupture occurs during closure of the outflow tract when there is ventricular compression of blood-filled chambers by a pressure sufficient to tear the chamber wall, septum, or valve. This is the most likely mechanism for ventricular rupture when injury occurs in diastole or early systole concomitant with maximal ventricular distention. The atria are most susceptible to rupture by sudden compression in late systole when these chambers are maximally distended with venous blood and the atrial ventricular valves are closed. Other proposed mechanisms of rupture include: (1) deceleration shearing stresses acting on the "fixed" attachment of the inferior and superior vena cava at the right atrium; (2) upward displacement of blood and abdominal viscera from blunt abdominal injury that causes a sudden increase in intracardiac pressure; (3) direct compression of the heart between the sternum and vertebral bodies; (4) laceration from a fractured rib or sternum; and (5) complications of a myocardial contusion, necrosis, and subsequent cardiac rupture.

Because of the mechanisms involved in cardiac rupture, associated multisystem injuries are common. More than 70% of reported survivors of myocardial rupture have other major associated injuries, including pulmonary contusions, liver and spleen lacerations, closed head injuries, and major fractures.

The immediate ability of the patient to survive cardiac rupture depends on the integrity of the pericardium. Two-thirds of patients with cardiac rupture have an intact pericardium and are protected from immediate exsanguination. These patients may survive for a brief period but will then develop significant hemopericardium and pericardial tamponade. One-third of patients with cardiac rupture have associated pericardial tears and succumb promptly to exsanguination.

Clinical Features

The clinical presentation of a patient who has sustained a myocardial rupture is usually that of cardiac tamponade or severe hemorrhage. Rarely, a patient is seen with a large hemothorax, hypotension, and hypovolemia, obscuring the diagnosis by mimicking a serious pulmonary or other intrathoracic injury. A patient with an intact pericardial sac and developing tamponade displays physical findings of tamponade, usually with subsequent clinical deterioration. Initial inspection of the torso may reveal little more than a bruised area over the sternum or no external physical evidence. More often, however, signs of significant chest trauma or other associated injuries will be present, indicating a mechanism of injury that could result in myocardial rupture. Auscultation may reveal a harsh murmur, known as a *bruit de moulin,* which has been classically described as sounding like a "splashing mill wheel." This is caused by pneumopericardium.

Diagnostic Testing

Early use of ED ultrasound may facilitate the early diagnosis of cardiac rupture and pericardial tamponade. The combination of shock and JVD in a patient with blunt chest trauma should immediately suggest pericardial tamponade or tension pneumothorax, both conditions rapidly assessable by bedside ultrasound. In patients with coexistent hemorrhage from other injuries, JVD may be absent. Other considerations include myocardial contusion, superior vena cava obstruction, and ruptured tricuspid valve. Sonographic visualization of pericardial fluid in this setting should be followed by emergent thoracotomy (Fig. 37.17).

A portable chest radiograph may be helpful in patients suspected of having sustained trauma severe enough to cause myocardial rupture. Although this study usually does not help diagnose cases of myocardial rupture, it notes the presence of other intrathoracic injuries (e.g., hemothorax, pneumothorax, and signs of possible aortic dissection). An increase in the size of the cardiac silhouette more commonly reflects preexisting disease or valvular incompetence with chamber enlargement caused by increased filling pressures. ECG changes may occur with myocardial injury, but these are often nonspecific.

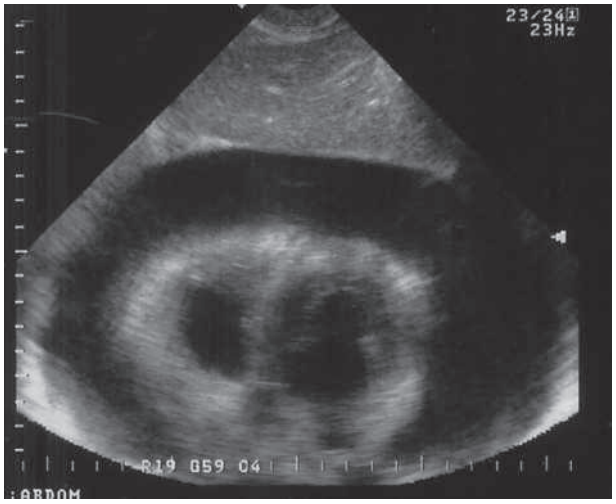

Fig. 37.17 Echocardiogram demonstrating pericardial fluid with cardiac tamponade.

Bedside echocardiography in the ED should be performed in any case of suspected cardiac rupture, pericardial tamponade, a previously undiagnosed murmur, or shock unexplained by other causes (e.g., exsanguination).

Management

When nonhospital medical personnel evaluate a patient who has sustained blunt chest trauma, they should concentrate on rapid transport and observe for any signs of pericardial tamponade. If examination is consistent with tension pneumothorax, this should be treated with needle decompression.

In the ED, treatment of patients with a myocardial rupture is directed toward immediate decompression of cardiac tamponade and control of hemorrhage. Pericardiocentesis may be effective in cases of a small rupture, but it is usually performed as a diagnostic or temporizing therapeutic procedure until surgical correction can be undertaken. Emergency thoracotomy and pericardiotomy may be required in the ED if the patient has rapidly deteriorating vital signs or a cardiac arrest. After emergency thoracotomy and pericardiotomy, the myocardial rupture should be controlled until the patient can be transported to the operating room for definitive repair. Hemorrhage from a ruptured atrium can often be controlled by finger occlusion or application of a vascular clamp. Insertion of a Foley catheter through the defect, followed by inflation of the balloon and traction on the catheter, may also help control the bleeding. Ventricular rupture can usually be controlled by direct digital pressure or by suturing with nonabsorbable vascular sutures.

Cardiopulmonary bypass is required in only 10% of successful repairs of myocardial rupture. Therefore, for patients with suspected myocardial rupture, it is appropriate to undertake emergency thoracotomy in institutions that have qualified surgeons but no immediate access to cardiopulmonary bypass.

PENETRATING CARDIAC TRAUMA

Penetrating cardiac injuries are one of the leading causes of death in the setting of urban violence. Improvements in emergency medical services, along with an emphasis on rapid transport, are responsible for an increasing number of cardiac injury patients arriving in impending or full cardiopulmonary arrest at high-volume urban trauma centers. The proportion of gunshot wounds versus stab wounds varies widely in reported case series, depending on the location of the trauma center.[20,21]

The right ventricle is affected more often than the left ventricle owing to its anterior anatomic location. One-third of penetrating cardiac wounds affect multiple chambers, and survival is much worse in these cases. In a minority of cases, a coronary artery is lacerated, although these injuries usually involve a distal segment of the artery and rarely produce significant acute MI when they are ligated. More proximal coronary artery lacerations require coronary bypass. Rarely, the interventricular septum, a valve, papillary muscle, or chordae tendineae are lacerated, producing an acute shunt or valvular insufficiency. These lesions are poorly tolerated and can quickly produce massive pulmonary edema and cardiogenic shock.

Two conditions may occur after penetrating heart injury: (1) exsanguinating hemorrhage if the cardiac lesion communicates freely with the pleural cavity, or (2) cardiac tamponade if the hemorrhage is contained within the pericardium. Patients with exsanguinating wounds frequently die before they reach medical attention, or they have rapidly progressive hemorrhagic shock on presentation, culminating in cardiac arrest. This presentation is most typically seen in patients sustaining gunshot wounds to the heart. Cardiac tamponade is a life-threatening condition but appears to offer some degree of protection and increased survival in patients with penetrating cardiac wounds. These patients often require immediate resuscitation by emergency department thoracotomy (EDT) if they meet those criteria listed in Box 37.4.

ACUTE PERICARDIAL TAMPONADE

Foundations

Background and Importance

The reported incidence of acute pericardial tamponade is approximately 2% in patients with penetrating trauma to the chest and upper abdomen; it is rarely seen after blunt chest trauma. It occurs more commonly with stab wounds than with gunshot wounds, and 60% to 80% of patients with stab wounds involving the heart develop tamponade. Patients with acute pericardial tamponade can deteriorate in minutes, but many can be saved if proper expediated steps are taken.

Pathophysiology

The primary feature of a pericardial tamponade is an increase in intrapericardial pressure and volume. As the volume of the pericardial fluid encroaches on the capacity of the atria and ventricles to fill adequately, ventricular filling is mechanically limited, and thus the stroke volume is reduced. This results in decreased cardiac output and ultimately diminished arterial systolic blood pressure and decreased pulse pressure. As little as 60 to 100 mL of pericardial blood may produce the clinical picture of tamponade. Concomitantly, CVP rises because of the mechanical backup of blood into the vena cava.

Several compensatory mechanisms then occur. The heart rate and total peripheral resistance rise in an attempt to maintain adequate cardiac output and blood pressure. A less effective compensatory response, resulting in a greater rise in CVP, is an increase in venomotor tone caused by contractions of the smooth muscles within the wall of the vena cava.

The diagnosis of pericardial tamponade should be suspected in any patient who has sustained a penetrating wound or blunt trauma to the thorax or upper abdomen. The trajectory of the bullet or the length, force, and direction of a knife thrust on initial evaluation may be difficult to ascertain. Wounds directly over the precordium and epigastrium are more likely to produce a cardiac injury resulting in tamponade than those in the posterior or lateral thorax. Nevertheless, it is assumed that a penetrating wound, particularly a gunshot wound, anywhere in the thorax or upper abdomen may have injured the heart. Rapid bedside echocardiography, performed as part of the standard e-FAST examination, easily detects a pericardial effusion causing cardiac tamponade.

BOX 37.4 Indications for Emergency Department Thoracotomy

Penetrating Traumatic Cardiac Arrest
Cardiac arrest at any point with initial signs of life in the field
Systolic blood pressure below 50 mm Hg after fluid resuscitation
Severe shock with clinical signs of cardiac tamponade

Blunt Trauma
Cardiac arrest in the emergency department (ED)

Clinical Features

Patients with cardiac tamponade may initially appear deceptively stable if the rate of bleeding into the pericardial space is slow or if the pericardial wound allows intermittent decompression. Some patients may complain primarily of difficulty breathing, which suggests pulmonary rather than cardiac pathology.

The physical findings of pericardial tamponade—hypotension, distended neck veins, and, rarely, distant or muffled heart tones (known as *Beck's triad*)—may be difficult to identify clinically, especially in the midst of a major resuscitation with concomitant hypovolemia, when the neck veins may be flat. Although the most reliable signs of pericardial tamponade are an elevated CVP (>15 cm H_2O) in association with hypotension and tachycardia, bedside echocardiography performed as part of the e-FAST examination rapidly diagnoses pericardial tamponade (by identifying pericardial fluid with concomitant tamponade physiology) and has largely replaced the use of CVP measurements to make the diagnosis. Echocardiography also distinguishes pericardial tamponade versus tension pneumothorax when the triad of elevated CVP, hypotension, and tachycardia is present.

Acute pericardial tamponade may be seen with three distinct clinical pictures. If the hemorrhage is confined to the pericardial space, the patient is initially normotensive but will have a tachycardia and elevated CVP. If untreated, most of these patients go on to develop hypotension. If significant hemorrhage has occurred outside the pericardial sac, either through a tear in the pericardium or from associated trauma, the clinical picture is that of hypovolemic shock with hypotension, tachycardia, and a low CVP. If the CVP rises to a level of 15 to 20 cm H_2O with volume replacement but hypotension and tachycardia persist, pericardial tamponade should be considered. The third clinical picture is that of an intermittently decompressing tamponade due to intermittent hemorrhage from the intrapericardial space, partially relieving the tamponade. The clinical picture may wax and wane depending on the intrapericardial pressure and volume and total blood loss. In general, this condition is compatible with a longer survival than are the first two clinical presentations.

Pulsus paradoxus is defined as an excessive drop in systolic blood pressure during the inspiratory phase of the normal respiratory cycle. This sign may be an additional clue to the presence of pericardial tamponade, but it is often difficult to measure during an intensive trauma resuscitation or in the presence of shock.

Diagnostic Testing

Radiology

Ultrasound. Ultrasound enables rapid, accurate, and noninvasive diagnosis of pericardial tamponade.[22] This study can be performed at the bedside in the ED during the initial resuscitation of the patient as part of the e-FAST examination. Although the sonographic definition of tamponade is the simultaneous presence of pericardial fluid and diastolic collapse of the right ventricle or atrium, the presence of pericardial fluid in a patient with chest trauma is highly suggestive of pericardial hemorrhage (see Fig. 37.17). An indirect sonographic sign of tamponade is the demonstration of a dilated inferior vena cava in a hypotensive patient. EDs in which cardiac ultrasonography is performed with subcostal and long parasternal views have reported a sensitivity and specificity of nearly 100% for the detection of pericardial effusion (see Chapter E3). Because ultrasound is noninvasive and extremely accurate, its immediate availability in the initial phase of major trauma resuscitation can help detect pericardial fluid before the patient deteriorates hemodynamically.

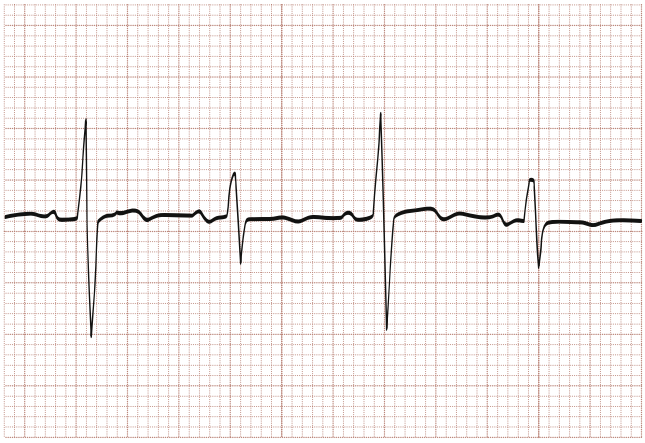

Fig. 37.18 Lewis (S5) lead electrocardiogram (ECG) revealing total electrical alternans of the QRS complexes. (From Sotolongo RP, Horton JD. Total electrical alternans in pericardial tamponade. *Am Heart J.* 101:853, 1981.)

Radiography. The radiographic evaluation of the cardiac silhouette in acute pericardial tamponade generally is not helpful, unless a traumatic pneumopericardium is present. Because small volumes of hemopericardium lead to tamponade in the acute setting, the heart will typically appear normal. This is in contrast to the "water-bottle" appearance of the heart with chronic pericardial effusion. Usually, the latter condition is tolerated for a long period of time.

Electrocardiography

Many ECG changes of pericardial tamponade have been described in the literature, but few are diagnostic, and each is more likely to be seen with chronic rather than acute tamponade. For example, electrical alternans (in which the morphology and amplitude of the P, QRS, and ST-T waves in any single lead alternate in every other beat [Fig. 37.18]) has been reported to be a highly specific marker of pericardial tamponade. The postulated cause is the mechanical oscillation of the heart in the pericardial fluid, which is called the *swinging heart phenomenon.* Echocardiographic studies have revealed that when fluid accumulates to a critical extent, the frequency of cardiac oscillation may abruptly decrease to half the heart rate. The cardiac position will alternate, with the heart returning to its original position with every other beat, and thus electrical alternans may be seen. Electrical alternans, when present, is pathognomonic for tamponade. However, it is much more common in chronic pericardial effusions that evolve into a tamponade, and it is rarely seen in acute pericardial tamponade. Notably, however, low amplitude of the QRS complexes may be seen as a result of the presence of pericardial effusion in both the acute and chronic settings.

Management

Field treatment for cases of pericardial tamponade is essentially the same as that outlined for any victim of major trauma. The diagnosis of tamponade should be suspected by the location of penetrating wounds or by the patient's poor response to vigorous volume resuscitation.

Tension pneumothorax, which is much more common, mimics certain aspects of acute pericardial tamponade. If the patient is in extremis or the clinical condition rapidly deteriorates, consideration should be given to performing a needle thoracostomy, which, if not therapeutic, suggests pericardial tamponade in the appropriate clinical presentation by virtue of a "diagnosis of exclusion." Expedient transport to the nearest trauma center should be paramount.

Upon ED arrival, volume expansion with crystalloid solution via two or three large-bore (14- or 16-gauge) catheters should be established immediately. The presence of a pneumothorax or hemothorax, which is often associated with penetrating cardiac trauma, is treated expeditiously with tube thoracostomy. Bedside echocardiography should be performed as quickly as possible to establish the diagnosis of pericardial tamponade, which then should be followed by emergent surgical repair.

There is increasing controversy regarding the role of pericardiocentesis. In the past, it was recommended that pericardiocentesis be performed for both diagnostic and therapeutic reasons. Aspiration of as little as 5 to 10 mL of blood may result in dramatic clinical improvement. However, it should be emphasized that pericardiocentesis is not a benign or invariably successful procedure. Blood in the pericardial space tends to be clotted, and aspiration may not be possible. Possible complications include the production of pericardial tamponade, the laceration of coronary artery or lung, and induction of cardiac dysrhythmias. Whenever possible, pericardiocentesis should be performed under sonographic guidance, because this approach will increase the success rate and decrease the incidence of complications. A pigtail catheter may be introduced into the pericardial space for repeated aspirations while preparations are underway to quickly transport the patient to the operating room for definitive management. If pericardiocentesis is unsuccessful or the clinical status deteriorates, and if acute pericardial tamponade remains important in the differential diagnosis, thoracotomy should be performed as quickly as possible.[23] Patients with penetrating cardiac injury invariably require surgical repair. The location (operating room vs. ED) and timing (immediate vs. urgent) depends on the patient's clinical status.

Emergency Department Thoracotomy

EDT is a drastic, dramatic, and potentially lifesaving procedure in which emergency clinicians should be proficient. Although the procedure is not described in detail here, a few technical points merit further description (see Chapter 32). A left lateral incision is preferred because it is rapidly accomplished; allows the best exposure of the heart, aorta, and left hilum; and facilitates open cardiac massage and internal defibrillation (Fig. 37.19). With right-sided or multiple injuries, it may be necessary to extend the incision across the sternum and right chest wall, creating a "clamshell" incision. The internal mammary arteries need to be ligated if this maneuver restores effective perfusion. After the heart is sufficiently exposed, the pericardium is vertically incised anterior to the phrenic nerve. Release of a tamponade may rapidly restore cardiac output. The heart is then delivered through the pericardium, and penetrating wounds are identified.

There are several alternatives for repairing cardiac wounds. Small wounds can be compressed by digital pressure to control bleeding en route to the operating room. If the injury is large, balloon tamponade can be achieved by applying gentle traction on a Foley catheter inserted into the wound with the balloon inflated with saline. This can temporarily stop the hemorrhage to allow suture repair of the injury (cardiorrhaphy) or to gain time while the patient is transferred to the operating room for a more definitive surgical procedure. Lacerations of the atria can be temporarily controlled with a vascular clamp.

Suture of cardiac wounds over pledgets is the time-honored and effective technique but is technically more difficult and time-consuming. The use of a monofilament suture, such as 2-0 Prolene, is recommended. Some trauma surgeons recommend stapling cardiac wounds with standard skin staplers because this technique may be much quicker and equally effective in closing these wounds.

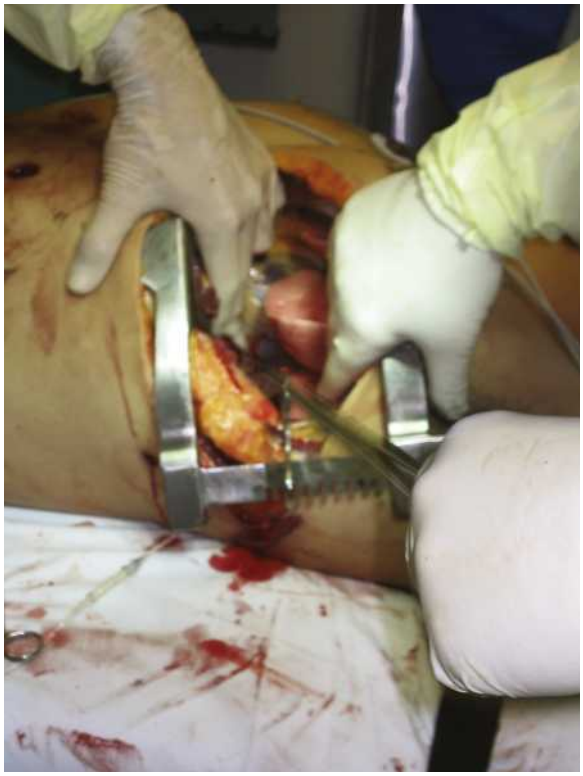

Fig. 37.19 Emergency Department Thoracotomy.

Care is taken to avoid ligating coronary arteries during the repair. Direct insertion of a large-bore catheter (e.g., a 5-French catheter) into the left atrial appendage provides a route for rapid infusion of fluids. If the heart is empty or the patient fails to respond to rapid fluid administration, the aorta is then cross-clamped to divert cardiac output to the brain and heart. Prolonged ischemia and severe acidosis often result in post-resuscitation myocardial depression with ineffective contraction and diminished cardiac output. Thus, the cross-clamp should be temporarily released every 30 to 45 minutes to minimize ischemic complications.

Indications for emergency department thoracotomy. Although it is tempting to perform "life-saving" EDT on all traumatic arrest victims in the ED, there are many cases in which patients have virtually no chance of survival. In addition, EDT is costly; requires the undivided attention of all personnel in the ED, diverting care from other, more salvageable patients in critical condition; and poses a risk to ED personnel for injury from needle sticks and other blood-contaminated exposures.

Evidence-based guidelines from the Eastern Association for the Surgery of Trauma recommend that EDT be performed on patients who lose pulses but who initially presented to the ED with signs of life after *penetrating* thoracic trauma (see Box 37.4). They conditionally recommend EDT for both patients who present to the ED without signs of life after *penetrating* thoracic trauma and patients who present to the ED with signs of life after *blunt* injury, and recommend against EDT in patients who sustain *blunt* injury and present to the ED pulseless.[23] It is worth emphasizing that EDT is a temporizing measure and should only be performed if definitive operative treatment is a viable option in the setting to which the patient presents.

BLUNT AORTIC INJURY

Foundation

Background and Importance

Blunt aortic injury is a life-threatening injury, usually resulting from sudden deceleration, frequently from MVCs. Other mechanisms of injury include high-velocity blunt trauma such as pedestrians struck by automobiles, motorcycle crashes, airplane crashes, and falls from heights. Despite the improvement in and increased use of restraint systems, the overall incidence of blunt aortic injury associated with fatal automobile crashes has remained unchanged over the past decade.

Blunt aortic injury includes a spectrum of lesions, ranging from a small intimal tear to frank rupture, which usually causes rapid lethal hemorrhage. The most common sites of injury are the aortic isthmus and the ascending aorta just proximal to the origin of the brachiocephalic vessels. Sixty percent to 90% of patients with blunt aortic injury die at the site of accident or within hours of hospital admission. However, an increasing number of patients arrive at a treatment facility because of improvements in out-of-hospital care, timely resuscitation in the field, and rapid transportation to a trauma center. The early survival rate of such patients depends on the initial resuscitation or the timeliness and correct choice of diagnostic procedures. A rapid and accurate diagnosis is thus mandatory to optimize treatment and maximize odds of survival.

Pathophysiology

The descending thoracic aorta is relatively fixed and immobile because of its tethering by intercostal arteries and the ligamentum arteriosum. With sudden deceleration, the more mobile aortic arch swings forward, producing a shearing force or "whiplash effect" on the aorta at the isthmus. A bending stress at the isthmus, created by sudden lateral oblique chest compression, may also result in rupture by causing flexion of the aortic arch on the left mainstem bronchus and the pulmonary artery. Forces created by the whiplash effect or lateral oblique compression may not be sufficient to provoke aortic tears. It is now postulated that those injuries may be caused by inferior and posterior rotation of anterior thoracic osseous structures (manubrium, first rib, and medial clavicles), pinching and shearing the interposed aorta as they strike the vertebral column.

Rupture of the ascending aorta just distal to the aortic valve likely occurs through a different mechanism. At the time of rapid deceleration and chest compression, the heart is displaced into the left posterior chest, which causes a shearing stress just above the aortic valve. A sudden increase in intra-aortic pressure, "the water hammer effect," may cause an explosive rupture of the aorta at this location. Involvement of the coronary ostia with coronary artery occlusion may occur in association with tears to the ascending arch. The intraluminal pressure tolerance of the aorta may be exceeded in a high-speed MVC.

A total of 80% to 90% of aortic tears occur in the descending aorta at the isthmus, just distal to the left subclavian artery (Fig. 37.20). Less common sites of involvement are the ascending aorta, the distal descending aorta at the level of the diaphragm, the midthoracic descending aorta, and the origin of the left subclavian artery. Although ruptures of the ascending aorta are much less common than those of the descending aorta, they have a 70% to 80% incidence of associated lethal cardiac injuries. This is in contrast to ruptures at the isthmus, which have a 25% incidence of associated cardiac injuries. Lethal cardiac injuries commonly include pericardial tamponade, aortic valve tears, myocardial contusion, or coronary artery injuries. Passenger ejection, pedestrian impact, severe falls, and crush injuries commonly result in ascending thoracic aortic ruptures. Survival long enough to be evaluated in the ED is rare among patients who sustain an ascending aortic rupture.

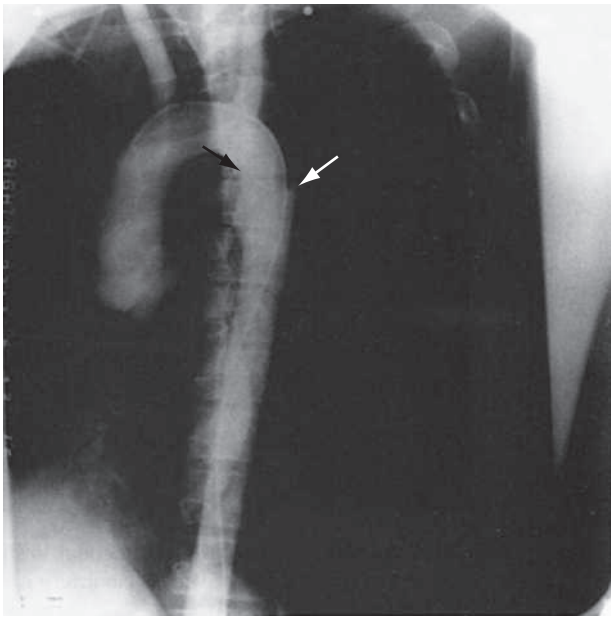

Fig. 37.20 Aortogram shows tear in aorta *(arrows)* at the most common location, at or just distal to takeoff point of left subclavian artery, which is not visualized.

Aortic rupture may occur from causes other than high-speed MVC deceleration. Rupture has been documented as a complication of external cardiac massage and has been known to occur after fracture-dislocations of the thoracic spine, presumably as a result of direct shearing force. Vertical deceleration injuries resulting from falls can cause a rupture of the ascending aorta by producing an acute lengthening of the ascending aorta. This is the likely mechanism responsible for aortic rupture in the setting of airplane and elevator accidents. Direct kicks by animals, crush injuries, sudden burial by landslide, and air bag deployment have also been reported as causes of aortic rupture. Direct compression of the compliant thorax has been postulated to contribute to aortic rupture in children. Displaced fractures of the sternum, ribs, and clavicle have also been shown to directly lacerate the aorta.

Clinical Features

The possibility of aortic disruption should be considered in every patient who sustains a severe deceleration injury, because approximately 30% of surviving patients with blunt aortic injury will die within the first 24 hours without treatment. This is especially true if the automobile was moving in excess of 45 mph or if there is evidence of severe blunt force to the chest (e.g., from a damaged steering wheel). In the case of any moderate- or high-speed MVC, it is imperative that paramedics carefully evaluate the extent of damage to the vehicle, the presentation of the victims, and the physical manifestations of blunt chest trauma. This information should be promptly relayed to the emergency clinician.

Despite the severe nature of the injury, the clinical manifestations of an aortic rupture are often subtle and deceptive. Associated pulmonary, neurologic, orthopedic, facial, and abdominal injuries are commonly present. Coexisting injuries can mask the signs and symptoms of an aortic injury or divert the clinician's attention away from the more lethal aortic rupture. The absence of any external evidence of a chest injury does not eliminate the possibility of an aortic tear. One-third to one-half of patients reported in the literature have no external signs of chest trauma.

The most common symptom is interscapular or retrosternal pain. It is often found in nontraumatic aortic dissection but is present in only

25% of patients with a traumatic aortic disruption. Other symptoms described in the literature but uncommonly present include dyspnea resulting from tracheal compression and deviation, stridor or hoarseness caused by compression of the laryngeal nerve, dysphagia caused by esophageal compression, and extremity pain caused by ischemia from decreased arterial flow.

Clinical signs are uncommon and nonspecific. Generalized hypertension, when present, may be an important clinical sign. Sympathetic afferent nerve fibers, located in the area of the aortic isthmus, are capable of causing reflex hypertension as a response to a stretching stimulus. The presence of a harsh systolic murmur over the precordium or posterior interscapular area may be auscultated in up to one-third of patients. The murmur is thought to result from the turbulent flow across the area of transection. A less commonly encountered physical finding is a swelling at the base of the neck caused by the extravasation of blood from the mediastinum, which results in an increased neck circumference or a pulsatile neck mass. Other clinical signs suggestive of aortic rupture include lower extremity pulse deficit and lower extremity paralysis. Initial chest tube placement output in excess of 750 mL is also suggestive of aortic rupture, especially if the hemothorax is left sided. However, the physical examination is neither sensitive nor specific for aortic injury.

Diagnostic Testing

Chest Radiography

Radiography of the chest can be a valuable tool when aortic rupture is suspected. An increase in the width of the superior mediastinum is the most sensitive sign and is found in the majority of aortic ruptures (Fig. 37.21).

However, specificity of this radiologic sign may be as low as 10%; mediastinal widening may be caused by venous bleeding from a clavicle, thoracic spine, or sternal fracture; or pulmonary contusions, a previous mediastinal mass, a misplaced CVP catheter, or magnification caused by the anteroposterior and supine position of a portable chest radiograph. Hence the sign is not pathognomonic for aortic rupture. Every effort should be made to obtain a standard upright inspiratory posteroanterior film, if clinically feasible, before a mediastinum is declared abnormal, to avoid false-positive interpretations. However, although mediastinal widening may be indicative of aortic rupture, its absence does not preclude the injury. Up to nearly half of patients with blunt aortic injury may have a normal mediastinum on chest radiography.[24] Given this, we recommend the use of chest CT scanning in patients with suspected aortic rupture, regardless of the chest x-ray findings.[24]

Chest Computed Tomography Scan

Chest CT scanning is the gold standard test for blunt aortic injury and has replaced aortography as the diagnostic test of choice. CT scans have almost 100% sensitivity and specificity for rapidly detecting aortic injury while requiring only IV contrast administration (Figs. 37.22 and 37.23). A normal aortic contour on CT, even in the presence of a mediastinal hematoma, has been shown to be highly accurate in excluding thoracic aortic disruption (Figs. 37.24 and 37.25).[24]

As a result of the improvements in CT scanning technology, more subtle aortic lesions are now being identified, which has led to the term "minimal aortic injury." A minimal aortic injury is defined as an aortic injury with an intimal flap less than 1 cm, and no or minimal periaortic mediastinal hematoma. Up to 10% of patients with blunt aortic injury diagnosed on CT scan may have a minimal aortic injury.[24] It is felt that minimal aortic injuries carry a relatively low risk of rupture, and we recommend following these patients with serial CT scans. If the injury is associated with significant thrombus, periaortic hematoma, lumen encroachment, or pseudoaneurysm, the patient can be treated via endograft.

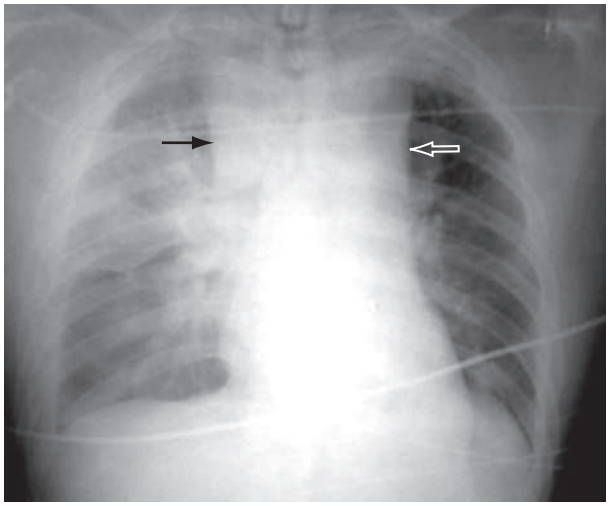

Fig. 37.21 Anteroposterior radiograph of the chest showing wide mediastinum *(arrows)*.

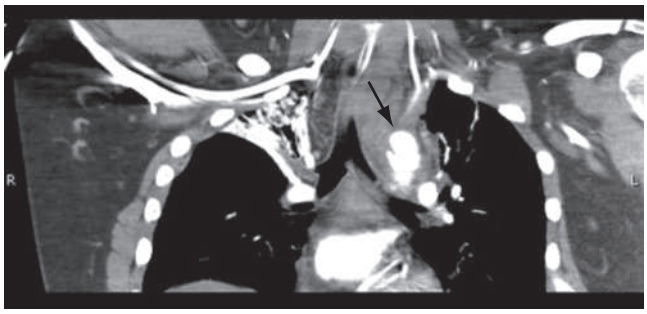

Fig. 37.22 Chest computed tomography (CT) scan showing aortic intimal tear with surrounding mediastinal hematoma *(arrow)*.

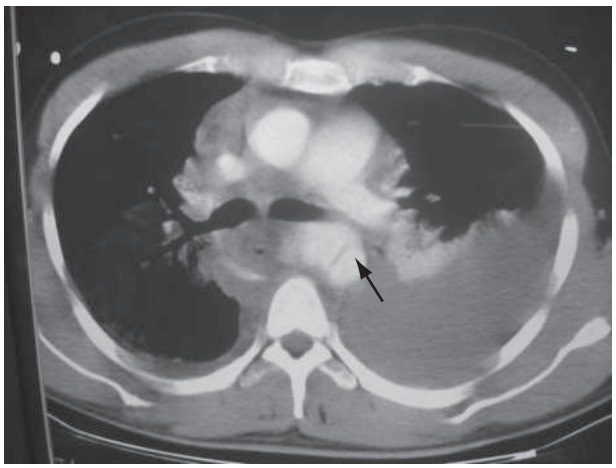

Fig. 37.23 Chest computed tomography (CT) scan demonstrating periaortic hemorrhage and an intimal flap *(arrow)*.

Management

Stabilization and Empirical Therapy

Due to the risk of sudden rupture and exsanguination, repair of the aortic injury should be performed as soon as the diagnosis is made. Management of the patient with multiple injuries who has documented

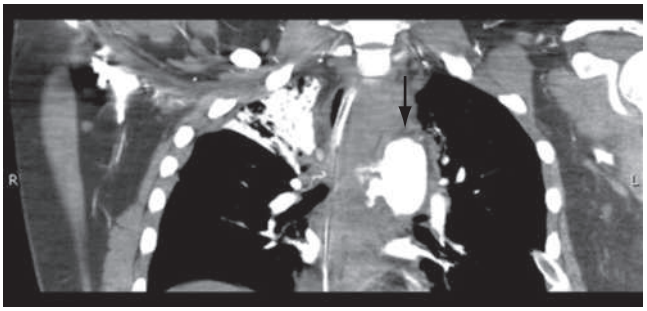

Fig. 37.24 Chest computed tomography (CT) scan showing aortic injury with active extravasation *(arrow).*

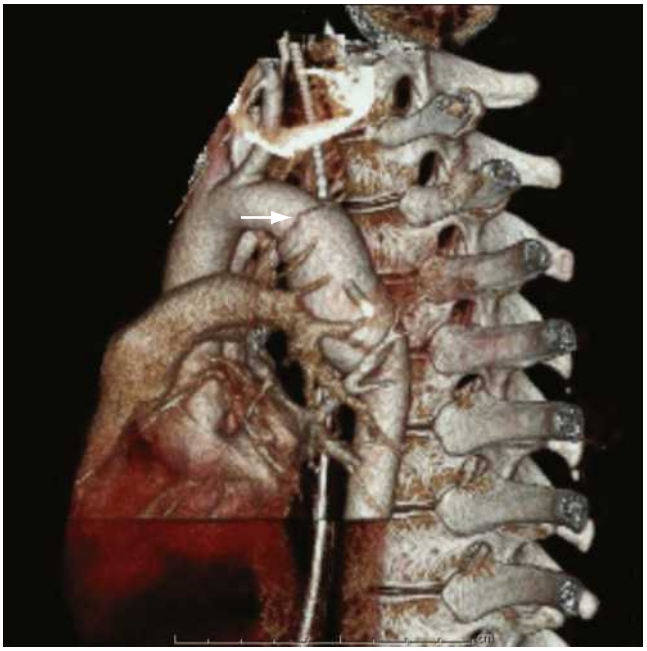

Fig. 37.25 Three-dimensional reconstruction of chest computed tomography (CT) scan showing aortic injury *(arrow).*

rupture of the thoracic aorta depends on the nature of associated injuries. Endovascular or surgical repair of the aortic rupture should be delayed in the presence of life-threatening intracranial or intra-abdominal injury or profuse retroperitoneal hemorrhage.[24] Consideration for delay of the procedure should be made for patients at high risk for infection (e.g., those who have extensive body surface burns, contaminated large open wounds, established sepsis, or severe respiratory insufficiency caused by thoracic trauma).

Careful regulation of blood pressure is mandatory until definitive surgical repair can be performed. If operative repair is delayed, the systolic blood pressure should be maintained between 100 and 120 mm Hg. The objective of lowering the blood pressure is to decrease the shearing jet effect of an elevated pulse pressure, thus decreasing the possibility of continued adventitial dissection and subsequent free rupture.

Esmolol, a short-acting titratable beta-blocker, is ideally suited for this purpose. Esmolol can be initiated with an intravenous bolus of 0.5 mg/kg over 1 minute, followed by an infusion of 0.05 mg/kg/min (titrated upward in 0.05 mg/kg/min increments to a maximum of 0.3 mg/kg/min). If blood pressure is not adequately controlled, nicardipine or clevidipine can be added as second agents.

Definitive Management

Many surgical techniques have been described since the first successful repair by Passaro and Pace in 1959. The pathologic condition found dictates the type of repair, and a synthetic graft is often required because of extensive tension on the vessel walls or jagged torn ends of the vessel. However, open repair can have associated complications of stroke, paraplegia, and renal failure due to aortic clamp time.

Endovascular repair. A number of studies indicate that success and complication rates are likely better than those of traditional open surgical repairs and that the risk of major surgery and subsequent paraplegia from prolonged aortic clamping is significantly reduced with endovascular repair. Current guidelines recommend endovascular treatment for patients without contraindications.[24]

ESOPHAGEAL PERFORATION

Foundations

Background and Importance

The classic description of esophageal perforation resulting from forceful vomiting was published in 1724 by Boerhaave, and from 1724 to 1941, the occurrence of Boerhaave syndrome was almost uniformly fatal. In 1941 the first successful surgical treatment, a drainage procedure, was reported, and in 1947 the first successful closure of a ruptured esophagus was described. Since then, improved surgical techniques, greater physician awareness leading to a prompt diagnosis, the availability of more effective antibiotics, and better supportive measures have reduced the mortality to approximately 20%. Mortality data cited for perforation are affected by several variables, such as location (with perforations of the thoracic segment having the highest mortality rate), mechanism of injury, time elapsed between injury and diagnosis, the presence of preexisting esophageal disease, and general health of the patient.

Pathophysiology

The anatomic feature responsible for the prolonged morbidity and high mortality associated with esophageal perforation is the lack of an esophageal serosal covering that allows perforation at any level with direct access to the mediastinum. Perforations in the upper or cervical esophagus enter the retropharyngeal space, where fascial planes extend from the base of the skull to the bifurcation of the trachea. Perforations in the midesophagus and lower esophagus enter directly into the mediastinum. Only the thin mediastinal pleura prevents free access to the entire pleural cavity, and this barrier is commonly overcome by continued drainage and the massive exudative inflammatory reaction induced by chemical and bacterial mediastinitis. When mediastinal pleura are penetrated, the negative pressure generated by respiratory efforts tends to increase contamination by promoting drainage from the gastrointestinal tract into the mediastinum and pleural space.

When esophageal rupture results from forceful emesis, as in cases of Boerhaave syndrome, the intrinsic weakness of the left posterior distal esophagus is important. Other areas (including cervical, midthoracic, and infradiaphragmatic sites) have been reported only rarely to rupture secondary to emesis. In addition, the esophagus has three areas of anatomic narrowing: (1) the cricopharyngeal muscle near the esophageal introitus, (2) the level at which the esophagus crosses the left mainstem bronchus and the aortic arch, and (3) the gastroesophageal junction. In the absence of a preexisting esophageal disease (such as carcinoma), it is unusual for a perforation caused by a foreign body to occur anywhere other than at these three sites. Foreign bodies may cause perforation by direct penetration, pressure, or chemical necrosis.

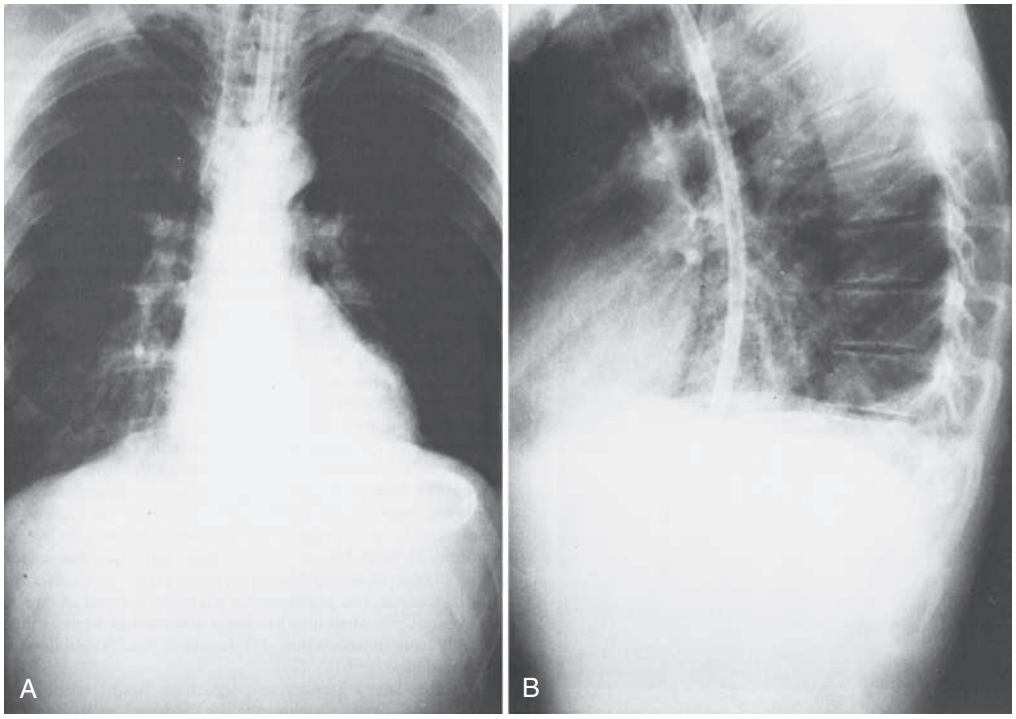

Fig. 37.26 (A) Chest radiograph of a 36-year-old man with acute onset of pleuritic chest pain after forceful vomiting. (B) Chest radiograph shows mediastinal and subcutaneous air typical of ruptured esophagus. Mediastinum is not yet widened, and there is no soilage of the pleural cavity.

Clinical Features

The most reliable symptom of an esophageal injury is pleuritic pain localized along the course of the esophagus that is exacerbated by swallowing or neck flexion (Fig. 37.26). Pain may be located in the epigastrium, substernal area, or back; usually worsens over time and tends to migrate from the upper abdomen to the chest. As the infectious process worsens, dyspnea usually ensues.

The early physical signs of an esophageal perforation are sparse. As air and caustic contaminated material move through the esophageal tear into the mediastinum and pleural space, and before any subcutaneous air is palpable at the root of the neck, the mediastinal air may impart a nasal quality to the voice. Mediastinal air may surround the heart and produce a systolic crunching sound (*Hamman's crunch*). As air and fluid move into the pleural space, signs of a hydropneumothorax or an empyema may develop. Eventually the air travels into the subcutaneous tissues, dissecting into the neck, where subcutaneous emphysema may first become evident. This classic sign is present in only approximately 60% of patients, however, and in the absence of a tracheal injury, it may occur in only 30%. The most common causes of an esophageal perforation are listed in Box 37.5.

Iatrogenic

Most esophageal perforations are iatrogenic, most commonly as a complication of instrumentation. The rigid endoscope is the most common offender, particularly when general anesthesia is used. Although use of the flexible endoscope has made this complication less likely, the total number of perforations has increased as more procedures are performed. Injuries tend to occur near the cervical esophagus as the endoscope is inserted. Endoscopic procedures that are too vigorous in the presence of a corrosive burn or carcinoma are also a common cause of iatrogenic esophageal injury. In the ED, nasotracheal or nasogastric intubations are the most common causes of iatrogenic perforation, with the perforation usually occurring in the pyriform sinus.

BOX 37.5 Most Common Causes of Esophageal Perforation

- Iatrogenic
- Foreign bodies
- Caustic burns
- Blunt or penetrating trauma
- Spontaneous rupture (post emetic or Boerhaave syndrome)
- Postoperative breakdown of anastomosis

Historically, the use of an esophageal obturator airway was also associated with occasional esophageal trauma, specifically midesophageal perforation. Use of newly designed esophageal obturator airways such as the laryngotracheal Combitube and the King airway, do not seem to be associated with trauma other than occasional esophageal abrasions or contusions.

Foreign Bodies

Foreign bodies can cause an esophageal injury by direct laceration, by pressure necrosis, or during endoscopic removal. Small perforations tend to seal without sequelae, but pressure necrosis or lacerating injuries provide ample access to the mediastinum. Foreign bodies usually lodge in the cervical esophagus. In children younger than 4 years old, the cricopharyngeal narrowing is the usual point of foreign body impaction. After 4 years old, most objects pass this region and traverse the remaining normal esophagus. In adults, a foreign body impaction, especially in cases of repeated episodes, raises the possibility of a stricture and warrants further diagnostic evaluation.

Caustic Burns

Caustic burns of the esophagus occur from intentional or accidental ingestion of acid or alkali. There are two peaks of incidence: (1) from 1 to 5 years old, which is when ingestion is accidental and with a small

amount of material, and (2) in the teens and 20s, when larger quantities are ingested during attempts of self-harm. Symptoms include hematemesis, respiratory distress, vomiting, drooling, or the presence of oropharyngeal lesions on physical examination.

The liquefaction necrosis classically resulting from strong alkali burns (pH >12) is more likely to cause esophageal perforation than the coagulation necrosis resulting from strong acid burns (pH <2). Individuals ingesting alkali substances with a pH less than 11.5 rarely sustain injuries more serious than superficial mucosal burns. Acid ingestions tend to cause damage more frequently in the stomach than in the esophagus.

Endoscopy within the first 6 to 18 hours may be used to determine the extent of the injury and guide therapy. Although admission after significant ingestion is the rule, some authors suggest that in the setting of accidental ingestion in children and in the absence of symptoms, endoscopy and admission may not be indicated. Esophagoscopy is commonly undertaken to ascertain the presence or absence of esophageal injury. Advancing the esophagoscope beyond the first burn in the esophagus increases the risk of perforation and is a common iatrogenic cause of esophageal perforation.

Penetrating and Blunt Trauma

Because of its well-protected position posteriorly, esophageal trauma is rare and usually not an isolated injury. Cervical esophageal injuries are the most common because of a lack of protection by the bony thorax, and the trachea is the most common associated site of injury. In some cases, the esophageal injury may be overlooked initially because of the dramatic presentation of a patient with a tracheal injury.

Typical symptoms seen in cervical esophageal injuries include neck pain, dysphagia, cough, voice changes, and hematemesis. Physical exam findings may include neck tenderness, resistance to flexion, crepitus, or stridor. In one large series, the most common life-threatening issue in the ED was compromise of the airway. Most of these cases were handled with rapid sequence intubation, but a significant number (12%) of patients required cricothyroidotomy.

If the patient's condition is stable, a preoperative esophagogram with a water-soluble agent should precede any endoscopy. Although chest and neck radiographs and CT scan also may be used to diagnose this injury, emergent bedside flexible endoscopy seems to be the diagnostic test of choice to confirm negative findings on esophagography (especially in the setting of penetrating trauma). Operative repair is indicated in most of these injuries (>90%) and should be done as quickly as possible to avoid the development of fistulae, mediastinitis, or abscess formation.

Spontaneous Rupture

Spontaneous esophageal rupture, post-emetic rupture, and Boerhaave syndrome are synonymous terms. This esophageal injury is associated with a poor prognosis because the forces required to rupture the esophagus result in almost instantaneous and massive mediastinal contamination. The distal esophagus is the usual site of injury, with a longitudinal tear occurring in the left posterolateral aspect. More than 80% of these injuries occur in middle-aged men who have ingested alcohol and large meals. Increases in intra-abdominal pressure resulting from blunt trauma, seizures, childbirth, laughing, straining at stool, and heavy lifting have also all been reported to cause this injury.

Diagnostic Testing

The diagnosis of esophageal perforation is aided by consideration of clinical circumstances. In patients with classic Boerhaave syndrome, emesis is followed by severe chest pain, subcutaneous emphysema, and cardiopulmonary collapse. Development of these signs and symptoms after instrumentation of the esophagus or removal of an esophageal foreign body is relatively straightforward. One-third of cases of perforated esophagus are atypical, however. A careful history and physical examination supplemented by appropriate imaging studies enable the clinician to diagnose a subtle case at an early stage. In considering any of the diagnoses listed in Box 37.6, a perforated esophagus should also be considered.

BOX 37.6 Clinical Conditions That May Mimic Esophageal Perforation

Spontaneous pneumomediastinum
Aortic aneurysm (thoracic)
Pulmonary embolus
Perforated peptic ulcer
Myocardial infarction (MI)
Pancreatitis
Mesenteric thrombosis
Cholecystitis
Pneumonia

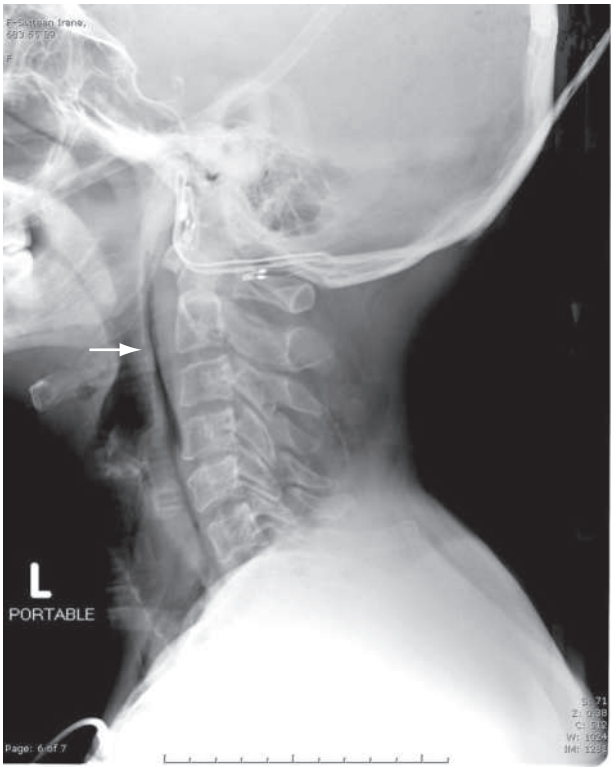

Fig. 37.27 Lateral view of the cervical spine revealing air in the retropharyngeal area *(arrow)*.

Radiology

The radiographic examination usually suggests the diagnosis of an esophageal perforation. The classic chest radiograph findings are mediastinal air (with or without subcutaneous emphysema), left-sided pleural effusion, pneumothorax, and widened mediastinum. Lateral views of the cervical spine may reveal air or fluid in the retropharyngeal area that is characteristic of a cervical esophageal perforation but also is found when perforations in the lower parts of the esophagus release air or fluid that dissects superiorly (Fig. 37.27). Water soluble diatrizoate meglumine (Gastrografin) is preferred for visualization in cases of suspected esophageal perforation. It does not obscure visualization during

subsequent endoscopy, and it produces less mediastinal contamination than barium. Then, if no leak is found, this can be followed by a barium study to better define the mucosal detail.

Endoscopy

Endoscopy, similar to contrast studies, is not an infallible aid in establishing the presence or absence of an esophageal perforation. The size and location of the perforation and the skill of the endoscopist are important factors in the low incidence of false-negative studies. If the accuracy of the endoscopy is in doubt, an esophagogram should be performed. Helical CT with dilute oral contrast has been reported as a safer, faster, and less personnel-intensive diagnostic examination. Some of the abnormalities that may be seen on CT scan include extraluminal air, periesophageal fluid, esophageal thickening, and extraluminal contrast. These CT findings may be the first clue to establishing the diagnosis of esophageal perforation.

Management

Early diagnosis can best be accomplished if one is cognizant of the pathophysiology and clinical settings in which esophageal perforations occur. Time is crucial in minimizing the mortality and morbidity of this condition. If the diagnosis is strongly suggested or confirmed, management should include broad-spectrum antibiotics (covering oral flora, as well as antifungal coverage in certain immunocompromised patients), volume replacement, and airway maintenance. An emergency surgical consultation should be obtained because prognosis worsens as time passes, with mortality almost doubling in the first 12 hours.

Although operative therapy is standard, nonoperative therapy is an option for patients with well-contained perforations, with minimal mediastinal involvement, and without evidence of sepsis. In such cases, the patient is placed on *nil per os* (NPO) status for at least 72 hours, broad-spectrum antibiotics are initiated, along with total parenteral nutrition management as indicated. The use of nasogastric tubes should be discouraged because they may increase gastroesophageal reflux and worsen the contamination of the mediastinum.

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CHAPTER 37: QUESTIONS AND ANSWERS

1. An 18-year-old man presents after a motor vehicle collision (MVC) in which he was ejected from the vehicle. The paramedics have been administering bag-valve-mask ventilation en route because of respiratory distress and now report increased resistance with ventilations. The patient has decreased breath sounds on the left. His blood pressure is 80/40 mm Hg, and his pulse is 145 beats per minute. His respirations are agonal, with a rate of 5 breaths per minute. Which of the following is the most appropriate next step in the management of this patient?

a. Anteroposterior chest radiograph
b. Emergency department thoracotomy (EDT)
c. Endotracheal intubation
d. Needle decompression
e. Tube thoracostomy

Answer: d. This clinical scenario depicts a patient with a tension pneumothorax. He has decreased blood pressure, decreased breath sounds, and, most important, an increased resistance to ventilation, which is the earliest sign of the development of a tension pneumothorax. Immediate decompression with a large-bore needle is the correct initial management in this condition.

2. Which of the following is the most sensitive electrocardiogram (ECG) manifestation of myocardial contusion?

a. Biphasic T wave
b. Left bundle branch block
c. Right bundle branch block
d. Sinus tachycardia
e. Transient ST segment elevation

Answer: d. Sinus tachycardia is present in approximately 70% of patients with documented myocardial contusion and is the most sensitive sign for this condition. It is, however, also the least specific.

3. A patient presenting with blunt thoracic trauma complains of shortness of breath and chest pain. On physical examination, he is tachypneic with chest wall bruising and moist rales on the right side on auscultation. Which of the following is the *least* likely finding?
- **a.** Consolidation within 6 hours of injury
- **b.** Diffuse patchy alveolar infiltrates on chest radiograph in 24 hours
- **c.** Low partial arterial pressure of oxygen (Pao_2) on arterial blood gas sampling
- **d.** Patchy alveolar infiltrate on chest radiograph within minutes of injury
- **e.** Rib fractures

Answer: b. This patient has physical findings consistent with pulmonary contusion. All answers are correct except B. Delayed onset of diffuse alveolar infiltrates is more consistent with acute respiratory disease syndrome (ARDS). The development of ARDS is diffuse and usually delayed, with onset typically between 24 and 72 hours after injury.

4. A 55-year-old man complains of chest wall pain after a high-speed motor vehicle collision (MVC). He has ecchymosis of the left lateral chest wall. You notice that there is outward movement of the left lateral chest wall on expiration. Which of the following statements regarding this patient's problem is *not true*?
- **a.** Chest radiograph likely demonstrates parenchymal contusions.
- **b.** Intubation splints the chest wall internally.
- **c.** Multiple rib fractures are likely.
- **d.** Positioning of patient with injured side down improves symptoms.
- **e.** The cornerstone of treatment is pulmonary physiotherapy.

Answer: d. This patient has a flail chest. Out-of-hospital or emergency department (ED) stabilization of the flail segment, by positioning the person with the injured side down or placing a sandbag on the affected segments, has been abandoned. Endotracheal intubation and positive-pressure ventilation will internally splint the chest wall, making the flail segment difficult to detect on physical examination. The cornerstones of therapy include pulmonary physiotherapy, effective analgesia, selective use of endotracheal intubation and mechanical ventilation, and close observation for respiratory compromise.

5. A 50-year-old woman is brought in by emergency medical services on a backboard after a motor vehicle collision (MVC), complaining of shortness of breath. She has decreased breath sounds on the right side of the chest. A chest tube is placed, with a return of 200 mL of blood in the first hour, 200 mL in the second hour, and 350 mL in the third hour. What is the next step in the management of this patient?
- **a.** Check coagulation profile
- **b.** Conservative management and transfusion as needed
- **c.** Emergency thoracotomy
- **d.** External fixation of rib fractures
- **e.** Insertion of a second thoracostomy tube

Answer: c. Immediate drainage of more than 1500 mL of blood from the pleural cavity is usually considered an indication for urgent thoracotomy. Perhaps even more predictive of the need for thoracotomy is a continued output of at least 200 mL/h for 3 hours.

6. A 37-year-old man presents with chest pain after a motor vehicle collision (MVC). He states that his chest hit the steering wheel. On initial evaluation, the patient is without fractures of the ribs or sternum, but there is a small chest wall contusion. The initial chest radiograph is negative, and the electrocardiogram (ECG) shows nonspecific ST-T wave changes. What is the next step in the emergency management of this patient?
- **a.** Admit to telemetry for 23-hour observation
- **b.** Discharge home after repeat ECG and troponin at 6 hours
- **c.** Discharge home after repeat ECG in 1 hour
- **d.** Discharge home if echocardiogram is negative
- **e.** Discharge home if initial troponin is negative

Answer: b. In patients who have minor injuries and are otherwise asymptomatic, elevated troponin levels and minor ECG abnormalities do not necessarily indicate a clinically significant myocardial contusion. Very few of these patients will develop complications. However, normal troponin level (4 to 6 hours after injury), along with normal (or unchanged) ECGs, correlate with minimal risk of cardiac complications. Echocardiography is rarely required in this low-risk subset of patients who have minor injuries and are otherwise asymptomatic.

7. A 30-year-old woman presents intubated by emergency medical services on a backboard with C-spine immobilization. She was found unresponsive and hypotensive after a front-end collision. She was the driver of the vehicle and unbelted. Despite fluid resuscitation, the patient continues to be tachycardic and hypotensive. On physical examination, you note jugular venous distention (JVD) and a harsh murmur that sounds like a splashing mill wheel. An electrocardiogram (ECG) reveals electrical alternans. Which of the following statements is true regarding the patient's underlying problem?
- **a.** Echocardiogram will reveal diastolic collapse of the right ventricle and fluid in the pericardium.
- **b.** Focused assessment with sonography in trauma (FAST) will demonstrate echogenicity in Morrison's pouch.
- **c.** Patchy consolidation will be seen on chest radiograph.
- **d.** Pericardiocentesis is not indicated.
- **e.** She will have a negative focused abdominal sonogram.

Answer: A. Early use of emergency department (ED) ultrasonography may facilitate the early diagnosis of cardiac rupture and pericardial tamponade. The combination of shock and JVD (or an elevated central venous pressure [CVP]) in a patient with blunt chest trauma should immediately suggest pericardial tamponade.

38

Abdominal Trauma

Megan L. Rischall and Michael A. Puskarich

KEY CONCEPTS

- The accuracy of a physical examination is limited in cases of abdominal trauma. It is rendered less reliable by distracting injury, altered sensorium (e.g., head trauma, alcohol or drug intoxication, developmental delay, psychiatric illness), and spinal cord injury.
- Stab and gunshot wounds frequently violate the lung parenchyma, diaphragm, mediastinum, intraperitoneal cavity, and retroperitoneum in some combination.
- Physical examination with extended focused assessment with sonography for trauma (e-FAST), followed by computed tomography (CT) scan when indicated, provides accurate diagnosis for the majority of blunt and penetrating abdominal trauma patients.
- Emergent laparotomy is indicated for patients sustaining a stab wound in the setting of hemodynamic compromise, peritoneal signs, evisceration, or left-sided diaphragmatic injury. Patients not meeting these criteria should undergo a combination of e-FAST, local wound exploration (LWE), CT scan, and serial examination, depending on the location of the wound
- Emergent laparotomy is indicated for patients sustaining a gunshot wound in the setting of hemodynamic compromise, peritoneal signs or evisceration. Patients not meeting these criteria should undergo a combination of e-FAST, CT scan, and serial examination, then proceed to laparotomy or admission for observation pending those results.
- The critical determinant in hemodynamically unstable patients with pelvic fracture is the existence of active intraperitoneal hemorrhage. Diagnosis of this by e-FAST, CT scan, or peritoneal aspiration is an indication for laparotomy, whereas its absence prompts diagnostic and potentially therapeutic angiography.

FOUNDATIONS

Background and Importance

The management of abdominal trauma relies on organization of key clinical features and the timely use of diagnostic procedures. Advancements in imaging have helped to decrease missed or delayed diagnoses, yet abdominal injuries can be notoriously occult, requiring vigilance to achieve the best clinical outcomes.

Penetrating Abdominal Trauma

Penetrating abdominal trauma is defined as any injury caused by an object that breaks the skin and enters the abdominal cavity. Whether by accident or intention, penetrating abdominal trauma can result from a wide variety of mechanisms of injury including weapons, sharp instruments, or other types of impalements. In general, the severity of injury is directly related to the velocity and depth of penetration, and approaches to management vary accordingly. Wounds from stabbing implements occur nearly as often as wounds from firearms, but the latter are responsible for approximately 90% of penetrating trauma mortality.[1] The small intestine, colon, and liver are the most likely organs to sustain injury after penetrating trauma.

The use of firearms in the United States contributes heavily to the morbidity and mortality of trauma. Firearm injuries are the third largest cause of trauma-related death in the United States, accounting for approximately 15% of trauma-related deaths. When compared with other mechanisms of trauma, firearm injuries have the highest case fatality rates across every age group.[1]

Blunt Abdominal Trauma

The majority of cases of blunt abdominal trauma are caused by motor vehicle collisions, whereas blows to the abdomen and falls from heights make up a minority of cases. Nevertheless, historical data may be incomplete, absent, or presumptive. The symptoms and signs can be unreliable and obfuscated by altered mental states due to trauma or other etiology or distracting injuries. The likelihood of extra-abdominal systems trauma adds further complexity, underscoring the need for a carefully organized diagnostic approach. Despite advances in imaging, blunt injuries can be difficult to diagnose and are commonly associated with severe trauma to multiple intraperitoneal organs and extra-abdominal systems.

The spleen is the organ most often injured; in nearly two-thirds of these cases, it is an isolated organ injury. The liver is the second most commonly injured intra-abdominal organ. Injury to any hollow viscus is uncommon by comparison, with the intestine the most likely hollow structure to be damaged.

Anatomy and Physiology

The abdominal cavity and its contents can be reached through the anterior abdominal wall and lower chest, as well as through the flank, back, and buttocks. Rarely, projectiles can lodge intraperitoneally after traversing the proximal extremities. The *anterior abdomen* is defined as that region between the anterior axillary lines from the costal margins to the groin creases. The *low chest* begins at the nipple line or fourth intercostal space anteriorly and the inferior scapular tip or seventh intercostal space posteriorly, and then extends down to the inferior costal margins. The *flank* is demarcated by the anterior and posterior axillary lines bilaterally from the inferior scapular tip to the iliac crest. The *back* is defined by the posterior axillary lines, beginning at the inferior scapular tip and extending down to the iliac crest. The intraperitoneal cavity is vulnerable to injury when penetration occurs as high as the fourth intercostal space anteriorly and the sixth laterally and posteriorly because the superior edge of the diaphragm can reach these levels during expiration. Simultaneous thoracic and abdominal penetration can be found in 20% to 40% of cases of abdominal thoracic trauma. Careful examination of entrance and exit sites, as well as wound tracts, is imperative.

Pathophysiology

Penetrating Abdominal Trauma

Penetrating abdominal injuries are predominantly caused by knives and firearms. Injuries caused by impalement from sharp objects such as fences, stakes, or similar objects should be treated as stab wounds. Projectiles from machinery or heavy equipment can be managed similarly to gunshot wounds, depending upon velocity of penetration. Fragmentation injuries produced by explosives are rare in the US civilian population, but industrial explosions can produce similar injuries, and blunt abdominal trauma from blast effect can coexist in this setting. Domestic terrorist acts may involve improvised bombs loaded with shrapnel, which can lead to penetrating abdominal trauma in the setting of more significant blast-related injuries.

The liver, followed by the small bowel, are most often injured from stab wounds, as a result of location and large surface area of these organs. Gunshot wounds typically result in multiple organ injuries, the greatest occurring in small bowel followed by the colon, and then the liver.

Stab wounds. Stab wounds occur most commonly in the upper quadrants and are caused by a variety of sharp implements besides knives. However, nearly one-quarter of cases have multiple wounds, and up to 10% of cases involve the chest. Most stab wounds do not cause an intraperitoneal injury, although the incidence varies with the implement used and the direction of entry. Anterior stab wounds penetrate the peritoneum in approximately 70% of cases but inflict a visceral injury in only half of these. Left lower chest wounds are associated with a 15% incidence of intraperitoneal damage in addition to the high rate of thoracic and diaphragmatic injuries, whereas right lower chest wounds have a much lower incidence of 0% to 5%. Abdominal entries from the flank and back have reported incidences of up to 45% and 15%, respectively. The liver and spleen are the viscera most commonly damaged in cases of back and flank stab wounds, but the injury pattern cannot be predicted by site of entry.

Gunshot wounds. The science of ballistics is complex, but a few basic principles are helpful in understanding the pathophysiologic processes. The magnitude of the injury is proportional to the amount of kinetic energy imparted by the bullet to the victim, according to the following equation:

$$E = \frac{7000\ mv^2}{2\ ga}$$

where E is the kinetic energy (in foot-pounds), m is the mass of the bullet, v is the velocity of the bullet (in ft/s), and ga is gravitational acceleration (in ft/s). The degree of injury depends on the mass of the bullet and the square of its velocity, although the resistance and viscoelastic properties of the tissue affect the resultant injury as well. Projectile velocities are categorized as low (slower than 1100 ft/s), medium (1100 to 2000 ft/s), and high (faster than 2000 to 2500 ft/s). Impact velocity is the most important determinant of extent of injury and depends on the distance between the firearm and the victim, the muzzle velocity, and characteristics of the projectile.

Although injury from low-velocity handguns occurs most often, injury due to higher-powered firearms is becoming more prevalent. At medium and high velocities, projectiles destroy tissue in its direct path; however, the shock wave of impact has an explosive effect and creates a temporary passage in the tissue along its course, directly proportional to the specific gravity of the penetrated tissue. The dissipating energy of impact displaces nearby organs and vascular structures, and bone and viscera may be fractured or torn without being directly struck by the projectile. Several cases of an intraperitoneal injury caused by a bullet that remained extraperitoneal throughout its entire course have been reported due to the secondary blast effect. Solid viscera, such as the liver and spleen, are more vulnerable to this effect. In addition, high-velocity missiles can drag external contaminants into the wound, fragment internally, and closure of the tract immediately after the bullet's passage may lead to an underestimation of tissue damage. A projectile at any velocity can fragment after contact with bone and cause additional multiple trajectories and injuries. Attempting to deduce the tracts of bullets in assessing patient injury is fraught with error and not recommended.

Shotgun wounds differ from other projectile injuries because the variation in tissue destruction is dependent upon type of shot (mass of pellets used), as well as distance of the victim from the firearm. Close-range, large buckshot wounds can be as lethal as high-velocity firearm injuries due to profound intra-abdominal tissue injury, whereas injuries sustained from greater distances or smaller pellets are associated with wider diameter clusters of injury, less tissue penetration (sometimes failing to penetrate the peritoneum), and lower mortality risk.

Blunt Abdominal Trauma

Sudden and pronounced rises in intra-abdominal pressures created by outward forces can cause rupture or burst injury of a hollow organ. Compression of abdominal viscera between the applied force to the anterior wall and the posterior thoracic cage or vertebral column produces a crushing effect. Liver and splenic injury are particularly susceptible to this type of injury. Individuals with reduced abdominal wall musculature are also more prone to these crush injuries. In addition, rapid acceleration and deceleration can cause a shearing affect, injuring organs and vascular pedicles by disruption of fixed points of attachment.

Seatbelt injuries. Unrestrained passengers are at an unequivocally greater risk of intra-abdominal injury than their restrained counterparts. The three-point shoulder-lap belt is the most effective restraining system in prevention of intra-abdominal injuries; however, abdominal injuries still occur with combined shoulder-lap belt systems. If seat belts are misused, particularly in the case of improper underarm use of the shoulder belt, the shoulder belt component can lead to rib fractures with potential for injury to underlying abdominal viscera. Injuries resulting from solitary lap belts are most often to the lower abdomen. The pathogenesis is usually the compression of bowel between the belt and the vertebral column, resulting in a contusion or perforation of the intestines or a tear of the mesentery. Approximately one-fourth of these patients develop evidence of a hemoperitoneum secondary to mesenteric lacerations. In the remainder, the intestinal injury most commonly involves the jejunum, and the initial signs and symptoms are often absent or considered insignificant. Subsequent delays in diagnosis of up to weeks later have rarely been reported. The "seatbelt sign," contusion or abrasion across the lower abdomen, is found in less than one-third of patients with abdominal injuries caused by lap belts. Its presence is highly correlated with intraperitoneal pathologic lesions. Rupture of the diaphragm can also occur in cases of high-speed frontal impact. Rare cases of acute abdominal aortic dissection with incomplete or complete occlusion have been described, and injuries to the lumbar spine are not uncommon. A patient with a seatbelt mark that suggests improper use of the restraint system (above the level of the iliac crests) is at particularly high risk of injury and clinical observation in addition to diagnostic imaging is recommended.[2]

Iatrogenic injuries. Abdominal injuries may be sequelae of various medical procedures. External cardiac compressions, manual chest thrusts to clear an airway obstruction, and the Heimlich maneuver can cause rib fractures and injury to abdominal viscera. Tube thoracostomy can cause injury to the liver or spleen because of unrecognized elevation of the diaphragm or improper technique or placement of the tube. Peritoneal lavage, paracentesis, and peritoneal dialysis can cause

vascular penetration or bowel perforation. A liver biopsy can lead to a hemoperitoneum or a biloma, whereas endoscopic procedures of the bowel may cause a hollow viscus perforation and peritonitis. Colonoscopy can cause splenic injury and hemoperitoneum, and although specific mechanisms and risk factors are less clear, it does not seem to be associated with the biopsy procedure.

Clinical Features

The patient's history may be unobtainable, elusive, or temporarily deferred while resuscitative measures are performed. The patient's ability to relate the course of events may be compromised by head or spinal cord injury, alcohol intoxication, developmental delay, psychiatric illness, and any number of toxins that will affect the clinician's assessment of the patient. In some cases, the trauma may have preceded the onset of symptoms by days or even weeks. When the situation permits and a reliable source is available, certain information such as the mechanism of injury, can prove valuable. Witnesses at the scene of injury, particularly paramedical personnel, often provide the most reliable data.

Appreciation of comorbid medical conditions, particularly cardiovascular disease and coagulopathies, will guide appropriate fluid and blood component therapy. When a prehospital care team or transferring hospital is involved, vital signs and physical exam assessment, prehospital course, and response to therapy should be obtained. Clinical records and laboratory and radiologic studies obtained at an outlying hospital should be carefully reviewed.

Abdominal pain is the most obvious symptom of abdominal trauma, as irritation of the peritoneum produces pain. The pain may be clearly present at the outset or delayed for hours to days. The communication of such pain may be impaired or ineffectual, or the perception of pain may be impaired by a spinal cord injury or underlying comorbidities. Occasionally, intense, competing pain at another body site dominates and distracts both the patient and clinician away from the abdomen. Abdominal pain can be localized (e.g., left upper quadrant with a splenic injury) or diffuse, such as in septic peritonitis secondary to bowel perforation.

Pain need not be localized to the abdomen, as irritation of the diaphragm by hemoperitoneum can cause referred pain to the right and left shoulder tips or neck, particularly when the patient has been in the Trendelenburg position. This most often is a marker of hepatic or splenic injury. Pain can also be referred to the inguinal region and testicles in the setting of retroperitoneal injury and is seen most commonly with urogenital and duodenal trauma.

A variety of other extra-abdominal symptoms may be present as well. If substantial enough, volume loss may cause dizziness, lightheadedness, confusion, and orthostasis. Nausea and vomiting can accompany peritoneal irritation or hypovolemia or can result from an obstruction, such as the development of a duodenal hematoma. Dyspnea sometimes occurs with gastric distention or diaphragmatic irritation or when abdominal contents herniate into the chest, impairing respiratory dynamics.

Specific Clinical Presentations

Penetrating Abdominal Trauma

Stab wounds. The number of stabs inflicted, type and size of the instrument, posture of the victim relative to the direction of assault, estimated blood loss at the scene, time of injury, and response to fluids help to gauge the nature and severity of injuries. Alteration in mental status due to any number of mechanisms, including drug or alcohol consumption, may make obtaining a useful history elusive and can compromise the clinical exam.

Gunshot wounds. Clinically helpful information for gunshot wound victims includes the weapon used, its distance from the victim when shot, the position of the victim in relationship to the weapon when fired, the suspected number of shots, the blood loss at the scene, the amount and type of field fluids administered, and vital signs assessment during the prehospital course.

Blunt Abdominal Trauma

Clinically relevant information for passengers in a motor vehicle crash includes the nature of the collision including the estimated velocity on impact, use of seatbelts, extent of damage to the car, presence or absence of intrusion, the victim's location within the car and evidence of internal impact such as steering wheel deformity, and airbag deployment. The magnitude of injury to pedestrians varies with the speed and size of the striking vehicle. A triad of injuries to the torso, cranium, and lower aspect of the lower extremity has been well described, and pathologic lesions discovered in two of these sites should prompt focused attention to the third. Motorcycle crashes can be placed in one of four categories: frontal, lateral, or angular ejection or "laying the bike down." Different pathologic lesions can be projected based on the mechanism of injury.

Physical Examination

Signs of abdominal trauma can range from subtle findings to severe shock and coma. Intraperitoneal injury can present as abdominal tenderness from peritoneal irritation, gastrointestinal hemorrhage, or hypovolemia not attributable to extra-abdominal causes. These signs may be initially absent or obscure but may emerge during serial examinations.

The physical examination of a hemodynamically unstable patient is performed coincident with resuscitation. When an obvious intracranial, thoracic, or orthopedic injury is present, abdominal symptoms or findings may remain undetected, and abdominal injury should be considered. Chest trauma is a risk factor for coincident intraperitoneal injury. This is particularly true in cases of suspected blunt trauma accompanied by a head injury, coma, or obtundation resulting from drugs or alcohol. An extended focused abdominal sonography for trauma (e-FAST) examination should be performed on all patients at the transition point from the primary to secondary survey (see Chapter 32). Acute hypotension resulting from hemorrhage is most often from a solid visceral or vascular injury. Traumatic pancreatitis may evolve to produce significant third-space fluid losses but is rarely the sole cause of acute shock. When unexplained hypotension accompanies significant blunt trauma, one should assume the presence of intraperitoneal hemorrhage until it is excluded. A known extra-abdominal source of hemorrhage does not mitigate the need to evaluate the peritoneal cavity. Solitary cranial or spinal injury should not be considered the sole cause of shock until an intra-peritoneal injury has been excluded.

In cases of penetrating trauma, inspecting the abdomen for entrance and exit wounds may help determine the path of injury. Distention can occur as a result of hemoperitoneum or pneumoperitoneum, gastric dilation, or ileus secondary to peritoneal irritation. An ecchymotic discoloration of the flanks *(Gray-Turner sign)* or umbilicus *(Cullen sign)* indicates retroperitoneal hemorrhage, but these findings can be delayed for 12 hours to several days. Abdominal contusions can result from several mechanisms; however, contusions from lap-seat belts result in intra-abdominal injuries in one-third of cases. Presence or absence of bowel sounds does not reliably identify or exclude the presence of intra-abdominal injury.

Although palpation elicits local or generalized tenderness in the vast majority of alert patients with an intra-abdominal visceral injury, it is less reliable in patients with an altered mental status. However, physical examination can be unreliable even in conscious and responsive patients. Local and generalized rebound tenderness and rigidity can be

signs of peritoneal irritation but occur less commonly. These signs lack specificity and can be found with lower rib fractures and contusions of the thoracoabdominal wall as well. Rarely, encapsulated bleeding into regions walled off by blood clots or adhesions can form palpable intra-abdominal masses, but these findings are usually delayed several hours after initial injury. Severe contusions of the abdominal wall can cause tenderness and voluntary guarding that is localized and usually exacerbated by use of the affected muscle. A palpable mass can represent a rectus ventral hernia or muscle hematoma, particularly in patients on anticoagulation therapy.

Rectal examination, once a routine part of the trauma assessment, rarely provides clinical useful information and is not indicated in the vast majority of trauma patients. This is particularly true in conscious patients of both sexes, for whom rectal examination is uncomfortable, unnecessary, and potentially humiliating. The sole remaining value of rectal examination is as part of the neurologic assessment (for anal sphincter tone) for patients with identified neurologic deficit believed to be caused by spinal cord injury.

Although the presence of physical findings makes intraperitoneal injury more likely, their absence does not preclude serious pathology. No finding is exclusively diagnostic of a specific injury. Extended observation, clinical imaging, and laboratory testing can reduce the chances of diagnostic error.

Penetrating Abdominal Trauma

Stab wounds. Serial physical examination performed by the same observer is useful in appropriately staffed and established trauma centers, particularly with patients who are alert, communicative, and neurologically intact. The presence of intoxicants does not necessarily preclude reliance on examination but may decrease its value until sobriety is regained. Even among patients with evidence of shock, peritonitis, or evisceration after penetrating trauma to the abdomen, exploratory laparotomy fails to reveal intraperitoneal organ injury in more than 10% of cases. In contrast, up to one-third of patients with significant intra-abdominal injuries have no suggestive physical signs, particularly when a retroperitoneal injury has occurred.

Gunshot wounds. As with blunt or other modes of penetrating trauma, there are limitations to physical examination of patients with abdominal gunshot wounds. Up to 20% of patients with a documented intraperitoneal injury have no peritoneal signs before exploration, whereas objective physical findings suggestive of intra-abdominal damage may be present in up to 15% of patients in whom laparotomy reveals no injury.

Blunt Abdominal Trauma

Overall, the accuracy of the physical examination in patients with blunt abdominal trauma is only 55% to 65% because the initial presentation may be deceptively benign. The most reliable symptoms and signs in alert patients are pain, tenderness, and peritoneal findings, particularly when risk factors for abdominal injury are present. When altered sensorium intercedes, the physical signs become less reliable. Frequent evaluations by the same examiner are indicated even in alert patients but especially in sensorium-altered patients, particularly as their mental status and sensorium normalize.

DIFFERENTIAL DIAGNOSES

The differential diagnosis in the setting of abdominal trauma is substantial and depends upon the mechanism of injury (blunt vs. penetrating) and the type of injuries that may occur. Both high-velocity blunt and penetrating abdominal trauma can cause lacerations or ruptures of intra-abdominal organs, whereas blunt injury can cause intra-abdominal solid or hollow viscous hematomas or isolated abdominal wall trauma and hematomas. The differential diagnosis includes solid or viscous organ injury, vascular injuries, intra-abdominal bleeding, abdominal compartment syndromes (ACSs) or retroperitoneal hematomas. Injury to the abdominal aorta can result in mortality up to 50% to 70%. Patients may present in profound shock and with altered mental status. Abdominal tenderness, although usually present, is largely unreliable depending upon presence of distracting injuries or altered mental status. Emergency clinicians should be vigilant for the effect of distracting injuries because isolated extremity injuries can, for instance, significantly suppress clinical signs of intra-abdominal injury.

Abdominal tenderness with rebound or guarding may suggest irritation of the peritoneum due to the presence of blood but will not detect the presence of a retroperitoneal injury. Rectal bleeding would suggest colonic laceration and the presence of blood at the urethral meatus would strongly suggest a genitourinal injury. "Open book" pelvic fractures and expanding hematomas can often present significant clinical challenges in combination with blunt abdominal trauma, resulting in extremely high rates of morbidity and mortality. The emergency clinician must be cognizant of the presence of this type of injury in the setting of high-velocity blunt force trauma (see Chapter 46). Traumatic diaphragmatic rupture, although present in less than 0.5% of all trauma cases, can be easily missed leading to high morbidity and mortality rates.

Medical and traumatic pathologic conditions can be coincident or can precipitate the other. The emergency clinician should be alert to instances in which medical conditions could portend traumatic events. For instance, hypoglycemia or a generalized convulsive seizure may precipitate a motor vehicle collision, and the patient's altered mental status may be incorrectly attributed to closed head injury, delaying the underlying diagnosis. Patients with infectious mononucleosis can experience splenic rupture after relatively trivial trauma, and the presentation of these injuries may be delayed. Patients with premorbid coagulopathy or who are on therapeutic anticoagulation may sustain serious intracranial or intra-abdominal hemorrhage from otherwise unimpressive traumatic injury (see Chapters 32 and 33).

DIAGNOSTIC TESTING

Ultrasonography

The e-FAST examination is indicated in all multiple-trauma patients and all patients with suspected abdominal injury, whether by blunt or penetrating mechanism. Ultrasonography's primary role is detecting free intraperitoneal blood after blunt trauma. This is accomplished by an examination of the *Morrison pouch*, splenorenal recess, and *pouch of Douglas*, which are dependent portions of the intraperitoneal cavity where blood is likely to accumulate (Fig 38.1). The thoracic portion of the examination detects pneumothorax, hemothorax, and pericardial effusion or tamponade (Fig. 38.2). Ultrasound applications in the trauma patient are discussed in Chapter e3. The e-FAST study is aimed precisely at the determinations described earlier and is most useful as a tool to rapidly rule-in the aforementioned conditions. The e-FAST exam is limited in the visualization of solid parenchymal damage, the retroperitoneum, or diaphragmatic defects and should not be used as a "rule-out" test for significant intra-abdominal trauma.[3,4]

Laboratory Testing

Metabolic and hematologic testing is of limited use in the initial management of the acutely traumatized patient and should be considered adjuncts to diagnosis and not substitutes for clinical assessment and

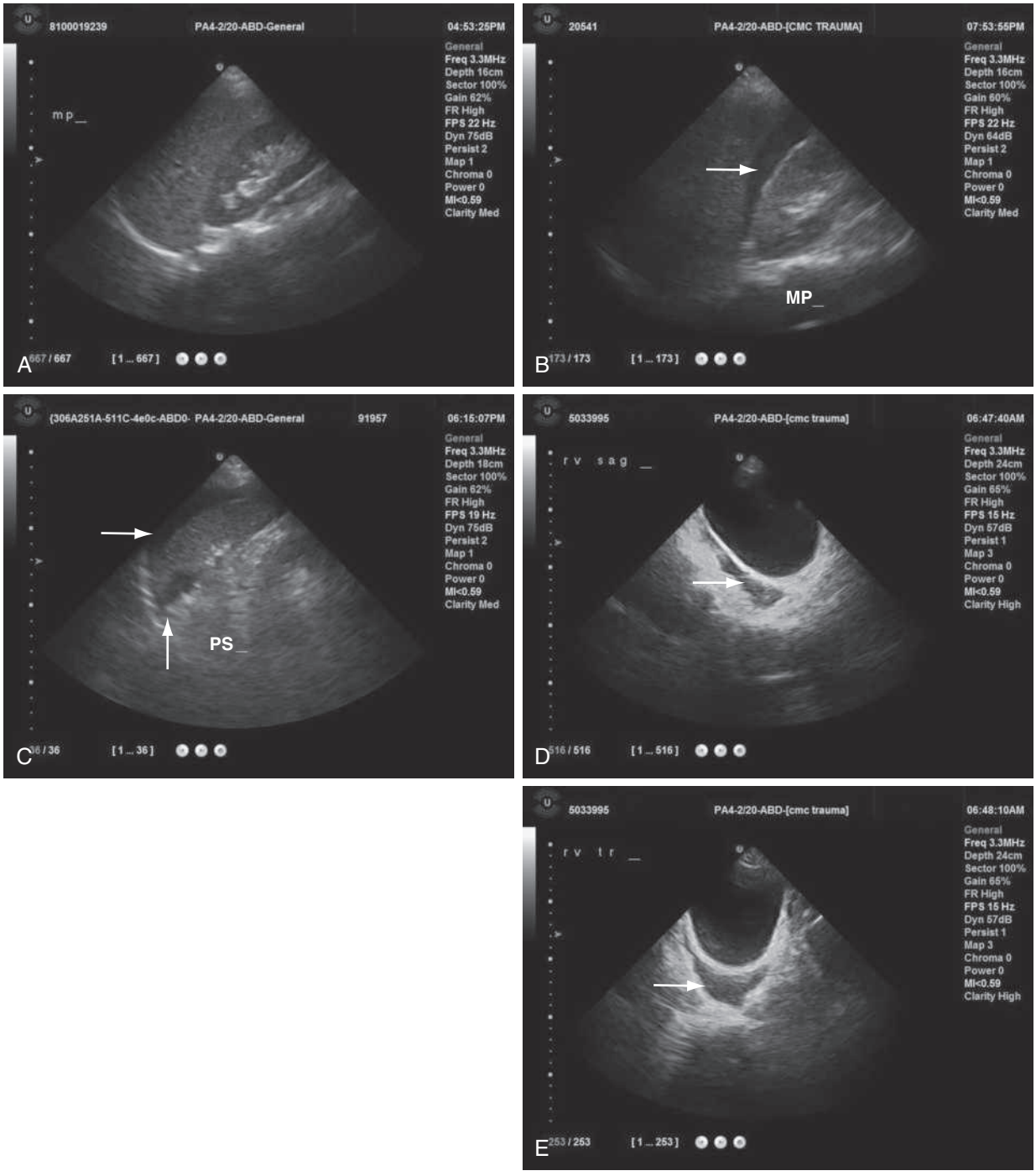

Fig. 38.1 (A) Normal Morrison pouch view. Note absence of an anechoic stripe, which would represent a fluid collection between the liver and kidney. (B) Positive Morrison pouch view. Note presence of an anechoic stripe representing a fluid collection between the liver and kidney *(arrow)*. (C) Positive perisplenic view. Note anechoic fluid around spleen *(arrows)*. (D) Positive fluid in the sagittal retrovesicular view *(arrow)*. Note anechoic stripe indicative of retroperitoneal fluid. (E) Positive transverse retrovesicular view. Note anechoic area indicative of retroperitoneal fluid *(arrow)*.

immediate interventions. However, targeted laboratory evaluation can provide significant guidance in the assessment and management of the traumatized patients that can be tailored to the severity of injury.

The hematocrit can represent a baseline value but is also a function of the extent of and time from hemorrhage, exogenous fluid administration, and endogenous plasma refill. Endogenous plasma refill is a physiologic compensatory shift of extracellular fluid into the intravascular space, the intent of which is to restore original blood volume. Based on a study of volunteers sustaining a 10% to 20% blood loss, this restoration can take more than 24 hours. Patients with hemorrhagic shock (at least 40%) demonstrate much faster plasma refill rates, with significant decreases in hematocrit within 90 minutes. Hematocrit values often represent a conundrum when viewed in isolation but are useful when measured serially.

The white blood cell (WBC) count has little discriminatory value in cases of abdominal trauma, particularly in its acute phase. The WBC

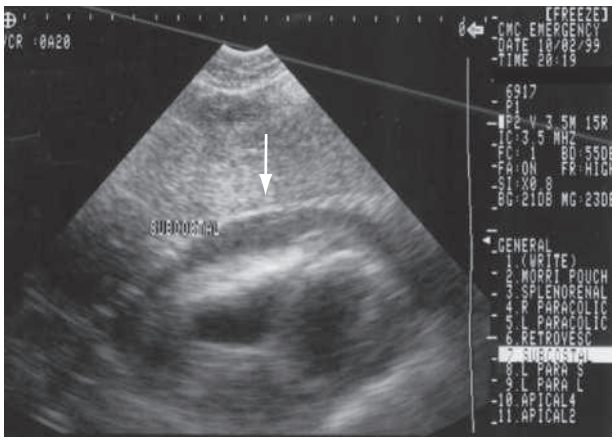

Fig. 38.2 Pericardial effusion seen on subcostal view *(arrow)*. The *white line* is the pericardium, and the anechoic space below represents a fluid collection in the pericardial space.

count may be normal or may show a modest leukocytosis (12,000 to 20,000/mm^3 with or without left shift), which can occur in the setting of multisystem trauma as a result of stress-induced demargination in the absence of any intra-abdominal process, or as a result of tissue injury, acute hemorrhage, or peritoneal irritation.

Metabolic acidosis in the setting of trauma can suggest the presence of hemorrhagic shock. This can be detected by a decreased serum bicarbonate level, increased base deficit, or elevated serum lactate level. Although normal values do not exclude abdominal injury, abnormalities, such as a base deficit greater than or equal to 6, elevated lactate greater than 4 mmol/L, or increase over time in either of these indices, suggest perfusion compromise or injury. These findings should be considered in clinical context because the cause of the abnormalities may be extra-abdominal and trending of laboratory findings may lag behind the clinical deterioration or stabilization of the patient.

Elevated serum transaminases can result from hepatic trauma but do not distinguish minor contusions from severe injury. Alternatively, these may be symptomatic of alcohol-induced liver damage. Elevated liver transaminase levels may be useful for screening pediatric patients for intentional trauma (see Chapter 172).

Screens for ethanol and drugs are often used in trauma centers. Their utility in the management of abdominal trauma has not been established, particularly in patients with a normal mental status. Positive study findings may prompt the emergency clinician to interdict and encourage the patient to decrease the use of ethanol or drugs, because physician intervention during these "teachable moments" has been shown to be effective. Although included in many "trauma panels," neither serum amylase nor lipase is useful in the evaluation of acute abdominal trauma. Normal levels do not exclude a major pancreatic injury, and elevated values may have other causes in addition to an injured pancreas, including chronic alcohol use or drug toxicity, systemic hypotension, and pancreatic hypoperfusion. Increasing levels may indicate but may not be conclusive of organ injury. In all cases, clinical examination, imaging, and vital signs assessment will direct further investigation.

Radiology

Resuscitation and initial stabilization measures precede abdominal radiographic studies. The purpose of diagnostic studies is twofold: to discern or eliminate the presence of hemoperitoneum in the patient whose condition is critical and unstable to properly sequence management and, in less urgent circumstances, to demonstrate organ injury that requires operative repair. Basic plain radiography of the abdomen in the trauma bay is not indicated, except for the location and identification of projectiles. Portable chest x-ray examination has been a staple to screen for significant hemothorax or pneumothorax before the patient is transferred to the computed tomography (CT) scanner, but this is largely being replaced by the chest portions of the e-FAST examination when equipment and sufficiently experienced personnel are available. The e-FAST is proven to be at least as sensitive and specific as a portable chest radiography for both conditions.

Hemodynamically stable patients who will undergo expedient abdominopelvic CT may forego portable pelvic radiographs during the initial trauma resuscitation. Indications for pelvic radiography are discussed in Chapters 32 and 46. In patients whose evaluation, including e-FAST results, demonstrates likely intra-peritoneal injury requiring laparotomy, delay in operative intervention to obtain further diagnostic radiology studies is permissible only when the patient has been stabilized and if these studies aid in determining management.

Plain Radiographs

The chest radiograph and anteroposterior pelvic films can be invaluable in some cases of penetrating and blunt trauma, depending on the presentation and results of initial evaluation. Chest radiographs can provide extra-peritoneal causes of hypotension in the unstable patient. Plain abdominal films can demonstrate the location or presumed track of projectiles in gunshot and shotgun injury but are of little value in blunt trauma or nonprojectile penetrating trauma, particularly if expedited CT imaging of the abdomen is anticipated. If plain radiography of the abdomen is obtained, the finding of rib, pelvic, vertebral body, or transverse spinous process fractures in the blunt trauma patient warrants special consideration for nearby visceral damage.

Although free intraperitoneal air can be detected on plain films, the small amounts and location of air associated with small bowel injuries are seen more readily on CT scan. Free intraperitoneal air uncommonly can be generated by mediastinal or pulmonary injury, as well as by barotrauma, and its presence is not pathognomonic of hollow viscus perforation. Intraperitoneal air is mobile; in upright x-rays, air is located under the diaphragm or the central tendon of the diaphragm anteriorly. In supine x-rays, air tracks under peritoneal attachments, such as the falciform ligament and urachus, up to the anterior abdominal wall. On radiographs in which the patient is in a lateral decubitus position, air is located in the superior flank and outlines the lateral liver edge. Extraperitoneal colonic perforations may extravasate air, which outlines the psoas muscle and perinephric region. All of these injuries are much more readily identified and localized on abdominal CT scan, which remains the imaging modality of choice.

Foreign bodies and projectiles are easily identified on abdominal images. Therefore their absence without a known exit wound warrants further search of other body cavities (e.g., the chest, upper thighs, buttocks). A ricochet off the spine or pelvis into the chest or proximal extremities can occur. An entry into the vascular system may carry the object toward and into the right side of the heart or peripherally into the arterial tree. It may also find migrate into the gastrointestinal tract and either produce obstruction or pass through unnoticed. Thus the location of a bullet and its fragments may provide its primary value in suggesting if extra-abdominal injuries are present.

Computed Tomography

CT scanning is the primary diagnostic imaging test for abdominal trauma because if its utility in defining the extent of intra-abdominal injury with detailed high-resolution images. It is most accurate for solid visceral lesions and discerns the presence, source, and approximate quantity of intraperitoneal hemorrhage (Fig 38.3). CT scanning can also demonstrate the presence or absence of active intra-abdominal

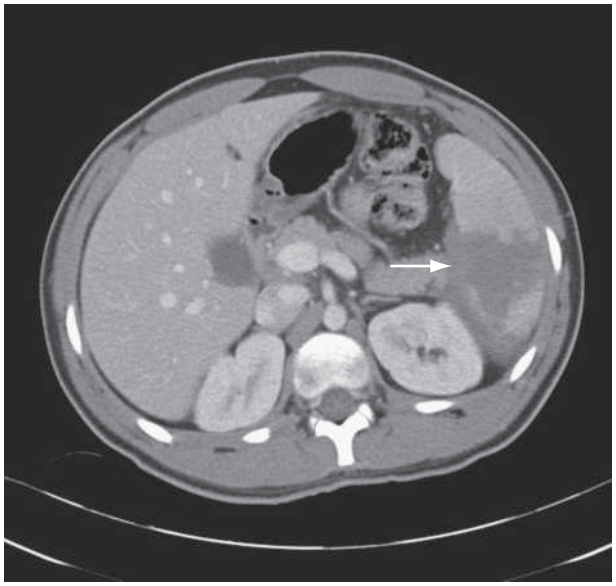

Fig. 38.3 Grade 4 splenic laceration *(arrow).*

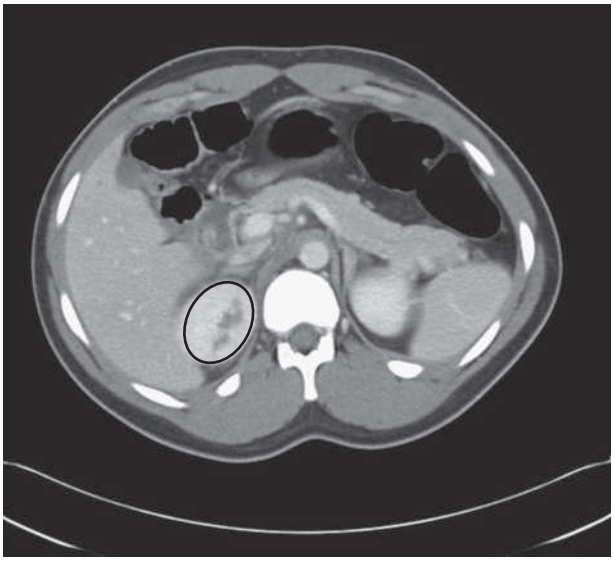

Fig. 38.4 Grade 3 right renal laceration *(encircled).*

bleeding and other vascular injury or hemorrhage, obviating the need for angiography in some patients. Imaging of the liver and spleen can support management decisions such as observation, therapeutic angiographic embolization, or open operative intervention. The minimization of nontherapeutic laparotomies for self-limited injury to the liver or spleen decreases morbidity and cost. CT scanning also can be used to definitively evaluate for genitourinary injury and can be used to evaluate the vertebral column and retroperitoneum (Fig. 38.4), areas not suitable for evaluation by ultrasound. The advantage of axial imaging is that the CT scanning and can be readily extended above or below the abdomen to visualize the thorax or pelvis for other associated injuries. The use of intravenous (IV) contrast alone is typically sufficient for most high-resolution imaging with little additional yield from the addition of oral contrast during initial scanning. When possible, protocols using high resolution (3 mm or less slice thickness values) with three-dimensional multiplanar reconstructions are ideal.[5]

CT imaging technology does have limitations. For example, injuries to the pancreas, diaphragm, small bowel, and mesentery can remain undetected, although higher-resolution technology is improving the diagnostic yield (Fig 38.5). Stab wounds can be particularly problematic. Sensitivity of detection of injury with axial imaging ranges from 50% to 100%, with 9% of patients with negative abdominal CT going on to require therapeutic laparotomy.[6,7] Given the risk of missed injuries, a negative CT scan should not be the sole determinant in the management and disposition of patients with abdominal stab wounds. In addition, coincidental hollow viscus injury in patients with blunt trauma is not rare, and increased morbidity and death can ensue if a diagnosis is missed or the condition goes undetected for a prolonged period. Findings on CT scans, such as suspected quantity of hemoperitoneum or the presence of isolated free fluid, are not sufficient to determine the need for operative intervention.

Use of CT scan is also not entirely risk free. Complications may result from IV contrast administration, including contrast-induced nephropathy, although recent data suggest the risk has been significantly overestimated.[8,9] In addition, there is increasing concern regarding the negative long-term effects from exposure to ionizing radiation resulting from medical imaging. Although direct evidence of increased cancer risk from CT scans has not yet been demonstrated, several techniques and parameters are used to reduce radiation exposure. These include patient positioning and scanning range, modulating the CT tube current and potential, reconstruction algorithms, and reconstructed slice thickness. Attempting to limit CT scanning only to a region of specific interest can be excessively insensitive for significant injury, and this practice is not recommended. Digital images should also accompany patients transferred between facilities, to avoid unnecessary repetition of the study and further radiation exposure.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is usually impractical and challenging to perform in the acute phase of patients with multiple blunt traumas. Currently, in acutely injured trauma patients, MRI should be reserved for the evaluation of spinal cord injuries and elusive diaphragmatic defects not amenable to laparoscopy or thoracoscopy in the fully stabilized patient.

MANAGEMENT

General principles: The field approach to multiple or serious trauma focuses on rapid transportation to a capable receiving emergency department (ED) and is discussed in Chapter 32. Although an emerging body of evidence has evolved around the concept of "permissive hypotension," in which a mild degree of hypotension (mean arterial pressure >50 mm Hg) is tolerated to decrease unnecessary fluid resuscitation during transport and initial stabilization, definitive clinical trial evidence mandating the practice is lacking, and current consensus recommend against this practice.[10]

Assessment of abdominal injury specifically is undertaken as part of the general management of the trauma patient (see Chapter 32). In patients who are intubated, have a massively distended abdomen, or in whom there is a high concern for stomach or duodenal injury, a nasogastric tube should be placed to decompress the abdomen, decrease the likelihood of aspiration, and determine whether blood is present, respectively. Placement of an orogastric tube is preferable in patients with midface or skull base fractures. Foley catheterization, once fairly routine, is reserved for unconscious patients, and those in shock, for whom urine output is an indicator of adequate end-organ perfusion. Thoracotomy and subsequent cross-clamping of the descending aorta have been used to stabilize patients with thoracoabdominal injuries and profound hypovolemic shock, but this is best undertaken as a temporizing rescue maneuver in the operating room when laparotomy identifies critical injuries not amenable to abdominal repair. In many

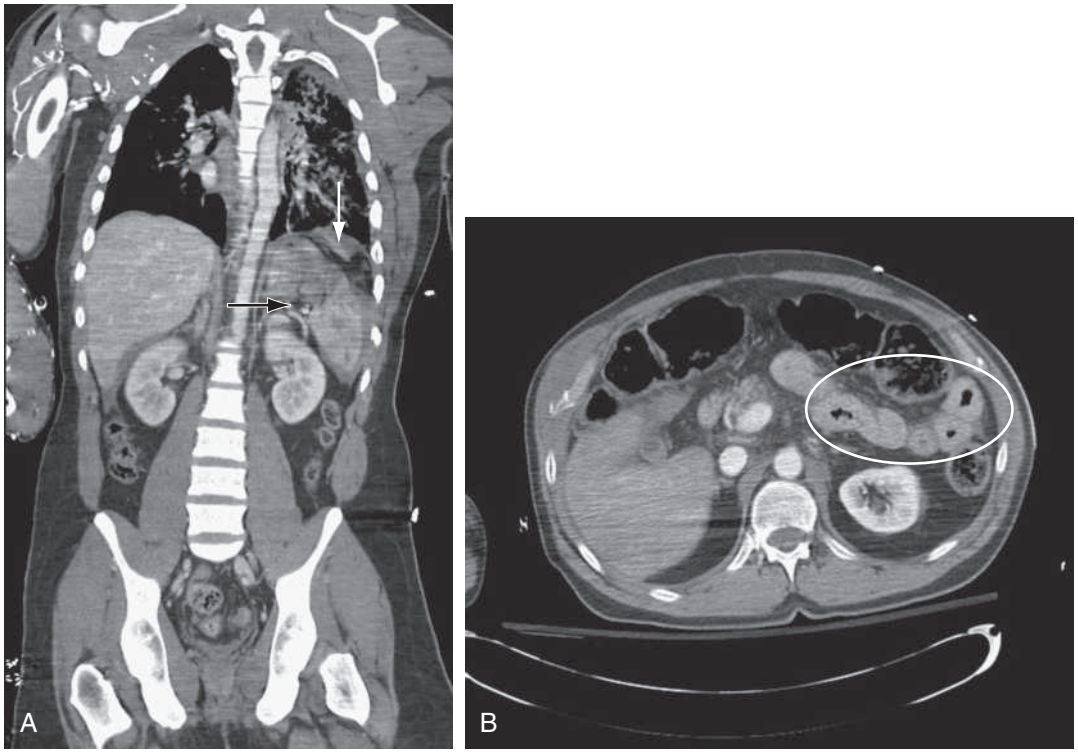

Fig. 38.5 (A) Grade 4 splenic laceration *(black arrow)* with diaphragmatic rupture *(white arrow).* (B) Small bowel edema concerning for hollow viscus injury *(encircled).*

trauma centers, resuscitative endovascular balloon occlusion of the aorta (REBOA) offers an emerging alternative to ED thoracotomy for management of exsanguinating intra-abdominal injuries in hypotensive patients who are not responding to initial resuscitation.[11]

Antibiotics, given prophylactically, are effective in decreasing the incidence of intra-abdominal sepsis. Intestinal perforation and soiling can occur with penetrating, and less commonly with blunt, trauma to the abdomen. A single preoperative dose of a broad-spectrum antibiotic or combination of antibiotics that covers both aerobic and anaerobic organisms, such as piperacillin-tazobactam 3.375 g intravenously, is recommended in the setting of perforated hollow viscus injuries.

Penetrating Abdominal Trauma

Stab Wounds

Selective management of abdominal stab wounds is currently well accepted because of the relatively low incidence of intraperitoneal injuries coupled with the success of various diagnostic strategies. This strategy is based on the site of penetration, the clinical status of the patient, and the experience of the hospital institution and its personnel. Compared with the former practice of mandatory laparotomy, selective management has resulted in a tremendous reduction in unnecessary laparotomies and associated morbidity, with minimal and acceptable loss in sensitivity for significant intraperitoneal injury. Overall, the nontherapeutic laparotomy rate should be less than 15%.

Anterior abdomen. In approaching the management of stab wounds to the anterior abdomen, the clinician is faced with three fundamental tasks. The first and most important is to determine whether clinical indications exist for emergent laparotomy. The presence of one or more of these indications, particularly in the context of an unstable patient, sets the course to expedited operative intervention. If none is found, the clinician may address the second issue of whether the peritoneal cavity has been violated. If it can be definitively demonstrated that it has not, no further diagnostic evaluation is required, and the patient can be discharged after appropriate wound care. If the cavity has been violated or if it cannot be determined whether the cavity has been violated, the third question is pursued: Does an intraperitoneal injury exist and, if so, is laparotomy required? One general approach to abdominal stab wounds founded on these three queries is summarized in Fig. 38.6. This algorithm is largely based on clinical indicators of injury, local wound exploration (LWE) as well as CT scanning, along with other radiologic modalities. Other strategies rely more heavily on other techniques, such as serial abdominal examinations or laparoscopy, and can be tailored to institutional expertise and resources.

Step I: Clinical indications for emergent laparotomy. Various clinical factors can be used to determine the need for emergent laparotomy (Table 38.1) based on the likelihood of associated intra-abdominal injuries requiring surgical repair. These clinical factors are summarized in the following list by reasons for immediate laparotomy, followed by clinical indications that require additional supportive evidence.

A: Emergent laparotomy immediately indicated

1. Hemodynamic compromise: This is the preeminent indication of the need for laparotomy in the setting of a stab wound and is the most likely reason that a patient will be taken urgently to the operating room without preliminary diagnostic studies.
2. Peritoneal signs: There is considerable debate over the reliability of peritoneal signs, particularly in the early postinjury period. Among physical examination findings, unequivocal peritoneal signs have the highest positive predictive value, whereas an entirely normal examination even in the presence of mild to moderate intoxication has the greatest negative predictive value for therapeutic laparotomy. In general, however, clear peritoneal signs indicate the need for laparotomy.
3. Evisceration: Patients with viscus evisceration sustain up to an 80% incidence of major intraperitoneal injury, and most trauma surgeons will take these patients for exploratory laparotomy. In rare cases, for isolated omental evisceration without

viscus evisceration and absence of free intraperitoneal blood on e-FAST examination, the surgeon may ligate, excise, and restore the omentum to the peritoneal cavity. This is done at the bedside in the ED trauma bay.

4. Left-sided diaphragmatic injury: Although rarely diagnosed acutely, left-sided diaphragmatic injury may be diagnosed through the observation of stomach or bowel in the left chest on bedside chest radiographs, and indicates the need for operative intervention.

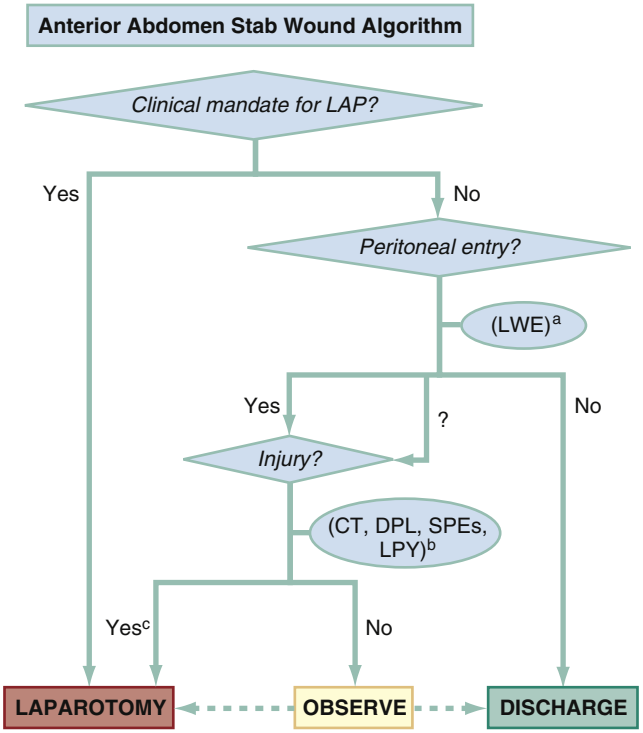

Fig. 38.6 Anterior Abdomen Stab Wound Algorithm. *LAP,* Laparotomy; *LWE,* local wound exploration. [a]Plain films, focused assessment with sonography for trauma, laparoscopy *(LPY),* and computed tomography *(CT)* can also assess peritoneal entry. [b]CT, diagnostic peritoneal lavage *(DPL),* serial physical examinations *(SPEs),* or LPY can be used in singular or complementary fashion, depending on the clinical scenario. [c]Expectant management of injuries is infrequently attempted.

B: Laparotomy only considered with additional clinical evidence

5. Gastrointestinal hemorrhage: Although rarely diagnosed because nasogastric tubes are rarely used in this clinical scenario, recovery of blood via a nasogastric tube or emesis may reflect a violation of the stomach or duodenum. However, blood without coincident peritoneal violation does not necessarily require surgical exploration.
6. Implements in situ: The conservative and widely held maxim is to remove implements in situ of the torso in the operating room. However, there is little evidence to support this practice and removal of such instruments in the ED under controlled circumstances and, in consultation with a surgeon, is reasonable.
7. Intraperitoneal air: See later.

Step II: Peritoneal violation. If clinical indications for laparotomy are absent, the logical next step is assessing the wound tract itself. The presence of peritoneal violation can be determined by a variety of means. There is great value in establishing that a wound tract is superficial to the peritoneal, retroperitoneal, intrathoracic, and pericardial cavities. In this event, the patient can be discharged from the ED after receiving appropriate wound care. If a study is inconclusive, it should be assumed that one or more of these cavities has been violated and further means of assessment are required. The five methods of assessing whether the peritoneum is intact are as follows:

1. Evisceration: Evisceration of bowel or omentum is clear evidence of peritoneal entry. Although typically mandating laparotomy, exceptions exist (see earlier).
2. Intraperitoneal air: Although a finding of intraperitoneal free air on an upright chest or a lateral decubitus abdominal radiograph may indicate bowel perforation, it may simply establish that the implement has entered the peritoneal cavity and drawn air in with it. Therefore, although intraperitoneal air is a strong indication of peritoneal violation, it does not necessarily imply bowel injury and is therefore should not determine the need for emergent laparotomy. Rarely, a false-positive determination of peritoneal entry can be made when the actual source of intraperitoneal free air is the pulmonary tract.
3. LWE: This has been demonstrated to be an effective tool in determining if the peritoneal cavity has been penetrated. Superficial wounds can be repaired if needed and the patient can be discharged from the ED. LWE is unreliable in small puncture type wounds, long tangential stab wound tracts, multiple stab wounds, or in obese

TABLE 38.1 Clinical Indications for Laparotomy Following Penetrating Trauma

Manifestation	Premise	Pitfall
Emergent Laparotomy Indicated		
Hemodynamic instability	Major solid visceral or vascular injury	Thorax, mediastinum, pelvic, or long bone sources; abdominal injuries causal or contributory
Peritoneal signs	Intraperitoneal injury	Unreliable, especially immediately post injury
Evisceration	Additional bowel or other injury	No injury in up to one third of stab wound cases
Diaphragmatic injury	Diaphragm	Rare clinical, radiographic findings unreliable
Laparotomy Requires Additional Clinical Evidence		
Gastrointestinal hemorrhage	Proximal gut	Uncommon, unknown accuracy
Implement in situ	Vascular impalement	Comorbid disease or pregnancy creates high operative risk
Intraperitoneal air	Hollow viscus perforation	Insensitive; may be caused by intraperitoneal entry only or may have cardiopulmonary source

Modified from Marx JA. Diagnostic peritoneal lavage. In Ivatury RR, Cayten CG, eds. *The textbook of penetrating trauma.* Baltimore: Williams & Wilkins; 1996.

patients with large subcutaneous fat layers.[5] In these cases, LWE alone should not be relied upon.

4. Ultrasonography: e-FAST examination demonstrating hemoperitoneum, pneumoperitoneum, or pericardial effusion (see Fig 38.2) identifies peritoneal penetration or injury. A negative e-FAST does not rule out peritoneal violation. Presence of intraperitoneal fluid on ultrasonography can preclude the need for LWE and suggests intra-abdominal injury.
5. Laparoscopy or thoracoscopy in the operating room: This has compared favorably with LWE in assessing the wound tract but requires a surgeon's expertise and carries a greater risk of iatrogenic complications. Benefits include the ability to detect organ injury (including diaphragmatic injury) and simultaneously repair some injuries, thus decreasing negative and nontherapeutic laparotomy rates. Thoracoscopy is primary used in evaluating for diaphragmatic violation in left anterior lower chest stab wounds.

Step III: Injury requiring laparotomy. In this algorithm, patients requiring an operation on clinical grounds have proceeded to laparotomy, and those in whom peritoneal violations have been excluded can be discharged home. The patients remaining have presumed or known peritoneal violation. The next consideration is whether injury exists that dictates operative repair, because organ injury is present in just over 60% of patients with peritoneal violation. In any case, patients who reach this stage of evaluation should be observed for 12 to 24 hours. Initial CT scanning coupled with serial e-FAST, and repeated physical examinations are used to identify significant wounds not initially obvious. Hollow viscus and occult diaphragmatic injuries remain the most frequently missed injuries on CT scan.

Historically, most patients with penetrating abdominal injuries and peritoneal violation underwent exploratory laparotomy, but selective nonoperative management (SNOM) of abdominal stab wounds is increasing. In examinable patients with no immediately identifiable operative injury, this approach includes close observation with serial vital signs, repeated abdominal examinations, and laboratory tests focused on identifying signs of new or ongoing hemorrhage or the development of peritonitis from hollow viscus injury. SNOM has been shown to decrease the incidence of nontherapeutic laparotomy, hospital length of stay, and cost without increasing morbidity or mortality.[12–14] Laparoscopy can also be performed when serial evaluation suggests possible, but not an obvious, need for laparotomy.

Thoracoabdominal penetration. Even a single stab wound to the low chest can violate the mediastinum, thoracic cavity, diaphragm, peritoneal cavity, and retroperitoneum. Nearly 20% of left thoracoabdominal stab wounds will be found to have diaphragmatic violation. When all thoracoabdominal wounds are considered, the risk of occult injury is 7%. Ultrasonography can be useful in permitting a quick assessment for hemopericardium and hemoperitoneum in the marginally stable patient, particularly if thoracotomy or laparotomy is not already clinically indicated. LWE of slash-type wounds may obviate the need for further evaluation, but the depth of investigation cannot be taken beyond the anterior rib margin to maximize safety and accuracy.

Diagnosis of diaphragmatic injury is particularly problematic in penetrating injuries, because many of the CT scan findings associated with blunt diaphragmatic injury are not present in penetrating injuries. Despite using multidetector CT, sensitivity for diaphragm injury in penetrating abdominal trauma can be as low as 47%. On retrospective review, the presence of a wound tract traversing the diaphragm is the most sensitive sign, occurring 92% of the time. Equivocal scans should be followed up with more definitive management, such as laparoscopy or thoracoscopy.[5]

Flank and back. The incidence of retroperitoneal injuries after stab wounds to the flank and back is greater than with injury to the anterior wall. However, risk of intraperitoneal organ injury also is significant, ranging up to 40%. LWE is less accurate than in anterior wounds because the paraspinal muscles are quite thick, so the procedure is only useful if the wound is obviously superficial (e.g., a slash wound). CT scanning with IV contrast is the method of choice for evaluating wounds not identified to be clearly superficial. A negative CT scan, followed by serial examination over a period of 24 hours, can effectively exclude the need for serious injury management of these patients.

Gunshot Wounds

Unlike stab wounds, almost all gunshot wounds penetrate the peritoneal cavity and typically produce multiple organ injuries and a high incidence of hollow visceral injury. Accordingly, the risk of mortality is significantly greater and increases with the velocity of the projectile. Penetration of the low chest commonly involves injuries to both intrathoracic and abdominal structures, including the diaphragm.

Anterior abdomen. Abdominal gunshot wounds enter the peritoneal cavity in approximately 80% of cases, and in more than 90% of those with penetration, there is intraperitoneal damage. If the patient is hemodynamically unstable, has peritonitis, or has an unreliable abdominal exam, the patient is taken for emergent laparotomy. In stable patients, a CT scan with IV contrast can be helpful in identifying the extent and severity of injuries and identifying active bleeding. If no peritoneal violation occurred or it is unclear, admission for serial examinations is indicated.

Previously, any patient with peritoneal violation from a gunshot wound was taken emergently to laparotomy, with very few exceptions. With advances in CT technology and increasing comfort with SNOM for other abdominal injuries, there is currently a growing trend towards SNOM of certain, isolated solid organ injuries secondary to gunshot wounds. This approach includes intensive monitoring and observation by an experienced trauma surgeon with or without adjunctive therapeutic angiography. Data from the National Trauma Data Bank suggest that SNOM is used in up to 35% of patients with renal injury and nearly 40% of patients with liver injury secondary to gunshot wound (GSW). Its use is independently associated with increased survival and decreased postoperative complications. Failure rate of SNOM is approximately 10% but use of SNOM is not associated with adverse outcomes. SNOM has been used across all grades of renal and liver injury.[15–18] Patient selection is critical, and a patient's hemodynamic status, mental status, abdominal exam, and CT scan findings should be considered. All patients not proceeding directly to the operating room should be admitted for monitoring and observation (Fig 38.7).

Thoracoabdominal. Fifty percent of patients with gunshot wounds to the low chest have intraperitoneal injuries. Clinical indications for emergent or urgent laparotomy are as for abdominal gunshot wounds. CT scanning is highly accurate for identification of both chest and abdominal injury and should be obtained before the patient is transferred to the operating room, unless the patient's instability will not allow this.

Flank and back. CT scan is highly accurate for identification of retroperitoneal injury and is the diagnostic test of choice in a stable patient. Most patients are then taken to the operating room. In some cases of low-velocity gunshot wounds to the flank, laparoscopy or observation alone can be used if the CT scan shows no evidence of injury and the bullet track does not traverse any anatomically important structures.

Blunt Abdominal Trauma

In cases of blunt trauma, laparotomy based on clinical findings alone is a rare exception. More typically, one or a complementary battery of diagnostic tests are performed. The choice of these tests is influenced

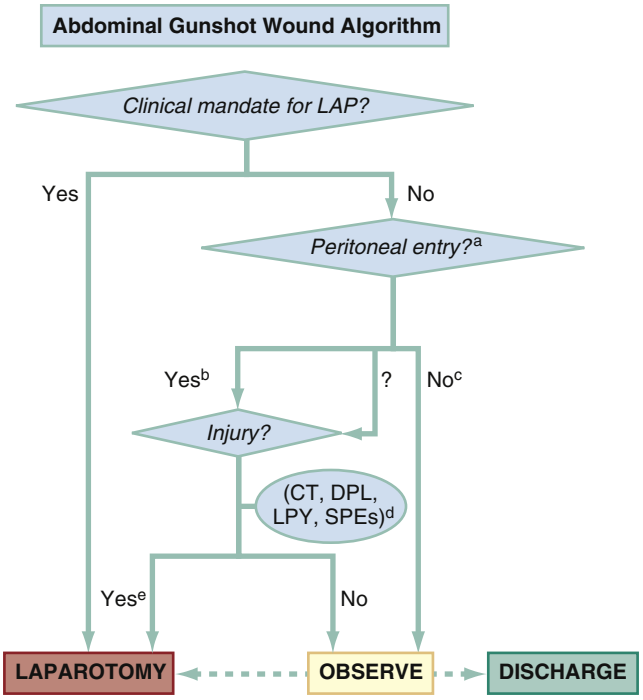

Fig. 38.7 Abdominal Gunshot Wound Algorithm. *LAP,* Laparotomy. [a]Can be assessed by missile path, plain films, local wound exploration, ultrasonography, and laparoscopy. [b]Most centers proceed to laparotomy if peritoneal entry is suspected. [c]Patients with documented superficial and low-velocity injuries can be discharged; unknown-depth or high-velocity injuries require further tests or observation. [d]Computed tomography *(CT),* diagnostic peritoneal lavage *(DPL),* laparoscopy *(LPY),* or serial physical examinations *(SPEs)* can be used in singular or complementary fashion, depending on the clinical scenario. [e]Expectant management of injuries caused by gunshot wounds is rarely attempted.

by the patient's hemodynamic status, the clinical scenario, and the institution's resources and preferences (Fig. 38.8).

The decision to perform immediate laparotomy after injury from a blunt mechanism is reserved for patients with the following findings (Table 38.2):

1. Refractory hypotension in a patient with positive e-FAST examination for hemoperitoneum and absence of an unstable pelvic fracture
2. Obvious peritonitis with positive e-FAST examination
3. Evidence on e-FAST of intra-abdominal injury in the context of other life-threatening injuries, such as uncontrollable chest hemorrhage, which require transfer to the operating room

In patients who are hemodynamically stable, CT scanning is the diagnostic modality of choice, as outlined earlier.

Operative Versus Nonoperative Management

Hemodynamically stable patients with solid organ injuries secondary to blunt trauma often can be managed without laparotomy. In patients with normal sensorium and without peritonitis or hemodynamic compromise, nonoperative management of blunt liver and spleen injuries has a success rate of 95%. [19–22] It is critical that an institution be adequately prepared to manage such patients, which includes having trauma surgeons, experienced nursing staff, adequate blood resources, and radiologists with the ability for rapid transfer to the OR for urgent laparotomy.

Several pitfalls in the expectant approach are noteworthy. First, hollow viscera injury, when present, requires operative management. The lack of sensitivity of CT scanning in the detection of hollow viscus injury is discussed earlier in this chapter. The patient with multisystem

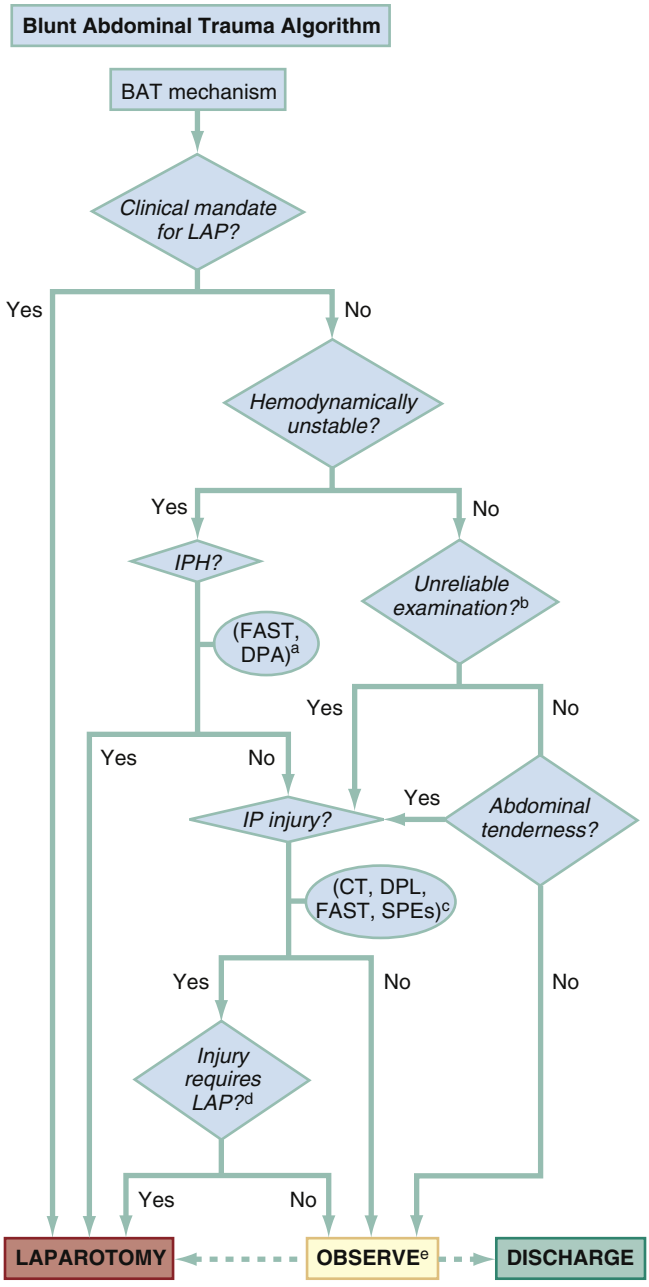

Fig. 38.8 Blunt Abdominal Trauma *(BAT)* Algorithm. *CT,* Computed tomography; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography for trauma; *IP,* intraperitoneal; *IPH,* intraperitoneal hemorrhage; *LAP,* laparotomy; *SPEs,* serial physical examinations. [a]Determined by unequivocal free intraperitoneal fluid on FAST or positive aspiration of blood on diagnostic peritoneal aspiration *(DPA).* [b]Can be unreliable because of closed head injury, intoxicants, distracting injury, or spinal cord injury. [c]One or more studies may be indicated. [d]Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources. [e]Duration of observation should be 6 to 24 hours depending on whether diagnostic tests have been performed, the results of the tests, and clinical circumstances, including the absence of factors rendering the examination unreliable.

injury and, specifically, closed head trauma is most vulnerable to having delayed diagnosis of perforated intestinal injury because of delayed development or impaired physical findings by abdominal examination. Second, expectant management may lead to increased use of blood products. Finally, this management approach will fail in those patients

TABLE 38.2 Clinical Indications for Laparotomy After Blunt Trauma

Manifestation	Pitfall
Unstable vital signs with strongly suspected abdominal injury	Alternate sources of shock
Unequivocal peritoneal irritation	Potentially unreliable
Pneumoperitoneum	Insensitive; may be caused by cardiopulmonary source or invasive procedures (diagnostic peritoneal lavage, laparoscopy)
Evidence of diaphragmatic injury	Nonspecific and insensitive, especially in penetrating trauma
Significant gastrointestinal bleeding	Uncommon, unknown accuracy

whose hemorrhage persists and is not amenable to therapeutic angiography and embolization. In such cases, the lag time from injury to an operative intervention may increase morbidity and mortality.

Pelvic Fracture

In the setting of pelvic fracture, the clinical triage determinant is the presence or absence of hemoperitoneum (Fig. 38.9). In a hemodynamically unstable patient with a pelvic fracture, the e-FAST exam is a reliable diagnostic bedside tool to identify clinically significant hemoperitoneum and guide further therapy.[23] If the e-FAST is negative and extra-abdominal sources of hypotension have been excluded, then the patient should proceed to therapeutic angiography with the presumed diagnosis of a life-threatening retroperitoneal bleed. In all patients, early mechanical pelvic stabilization is advised (see Chapter 46), and CT scan followed by pelvic angiography and embolization are undertaken as early as possible in the context of the multiple injuries.

Multiple System Injury

Complex trauma involving intraperitoneal hemorrhage in a patient with apparent closed head injury or suspected blunt aortic disruption or both is not uncommon. Operative intervention involving the abdomen usually takes precedence over that of the head and chest, given the key tenet that a patient with known hemoperitoneum whose vital signs cannot be stabilized should undergo laparotomy to avoid exsanguination. However, these situations are highly complex, and multispecialty decision making is influenced by numerous and dynamic variables. Approaches to two of these situations are summarized in Figs. 38.10 and 38.11.

Bedside Procedures

Diagnostic Peritoneal Lavage

Once the mainstay of evaluation of the abdominal trauma patient to determine the presence of injury and the need for laparotomy, diagnostic peritoneal lavage is currently largely of historic interest. Its remaining role in trauma is limited to centers where ultrasound equipment is not available or the clinician is not trained to perform ultrasound.

Local Wound Exploration

LWE is used to determine whether an anterior stab wound has penetrated into the peritoneal cavity in a nonobese patient. The wound is infiltrated with a local anesthetic containing epinephrine then carefully visualized through each successive layer of tissue. Blind probing with digits, instruments, or cotton-tipped swabs is unreliable, unless the peritoneal cavity is obviously freely entered. If LWE clearly indicates

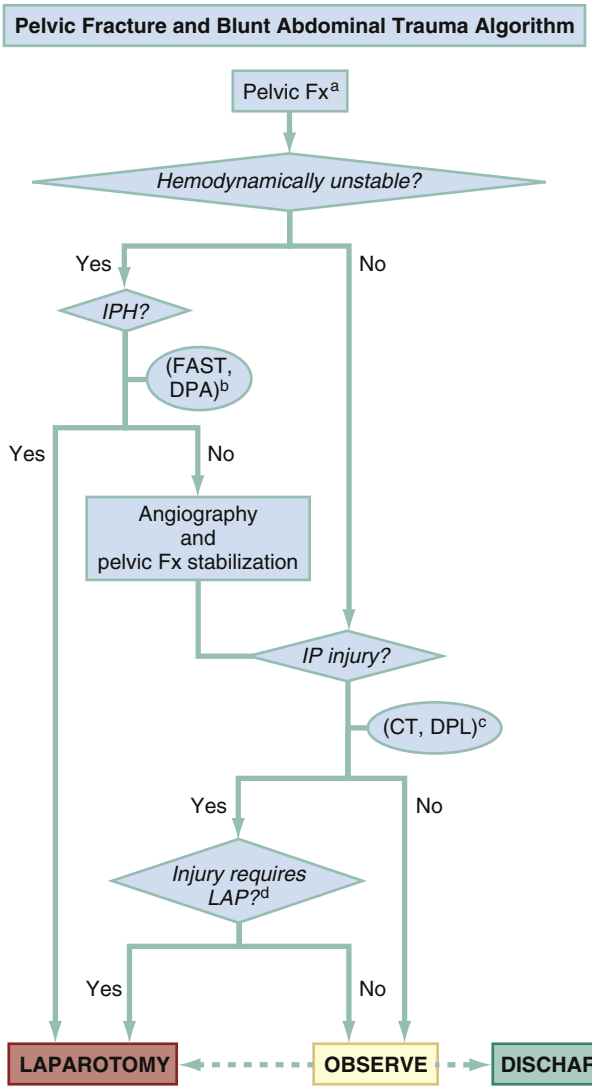

Fig. 38.9 Pelvic Fracture *(Fx)* and Blunt Abdominal Trauma Algorithm. *CT,* Computed tomography; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography for trauma; *IP,* intraperitoneal; *IPH,* intraperitoneal hemorrhage; *LAP,* laparotomy. [a]Certain pelvic fractures are more likely to cause pelvic vascular disruption and subsequent retroperitoneal hemorrhage. [b]Determined by unequivocal free intraperitoneal fluid on extended e-FAST or positive peritoneal aspiration on diagnostic peritoneal aspiration *(DPA).* [c]One or more studies may be indicated. Serial physical examinations are generally considered unreliable owing to the presence of pelvic fracture. [d]Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources. [e]Discharge from the perspective of need for further consideration for laparotomy.

that the peritoneum is not violated, the e-FAST is negative, and the patient is otherwise uninjured, the injury can be treated as a local abdominal wall injury, and the patient is treated and discharged. Indication of entry into the peritoneal cavity or inability to locate the end of the wound tract is an indication for ongoing observation or abdominal CT scan (see Management section).

Wound exploration in patients with multiple entrances is impractical, requiring extensive effort, and it may be prudent to assume peritoneal penetration. Deep exploration over the thoracic cage is precluded by attendant complications to neurovascular structures and pleura. However, careful inspection of superficial chest wounds (e.g., slash wound) is safe and can provide diagnostic data.

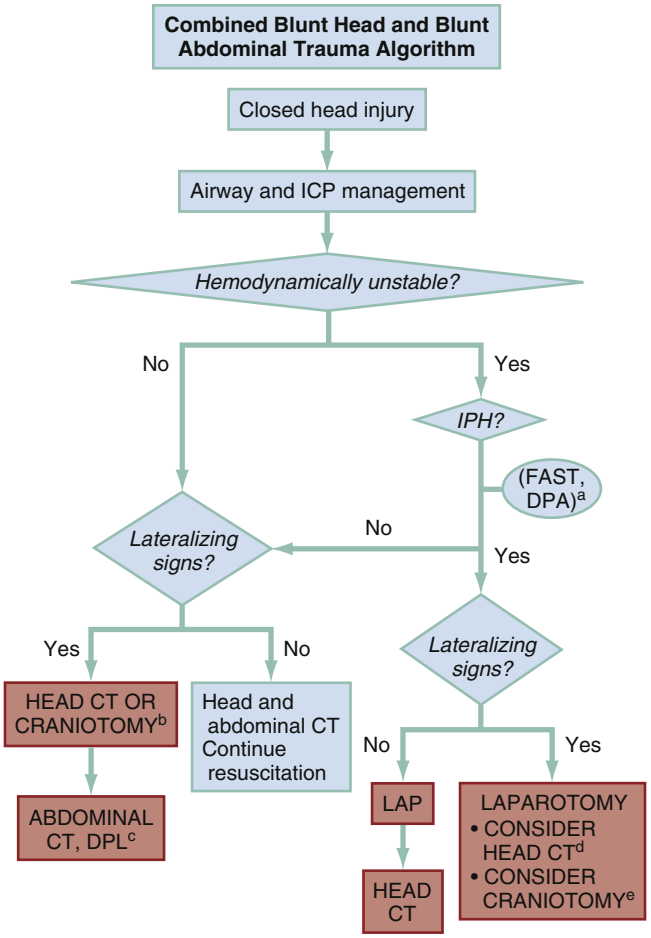

Fig. 38.10 Combined Blunt Head and Blunt Abdominal Trauma Algorithm. *CT,* Computed tomography; *ICP,* intracranial pressure; *IPH,* intraperitoneal hemorrhage. [a]Determined by unequivocal free intraperitoneal fluid on extended focused assessment with sonography for trauma *(e-FAST)* or positive peritoneal aspiration on diagnostic peritoneal aspiration *(DPA).* [b]Craniotomy or burr holes based on clinical picture and unavailability of computed tomography (CT). [c]Diagnostic peritoneal lavage *(DPL)* can be complementary to CT in determining hollow viscus injury. [d]Consider pre-laparotomy *(LAP)* head CT based on clinical picture and availability of CT. [e]Consider craniotomy or burr holes simultaneous with laparotomy.

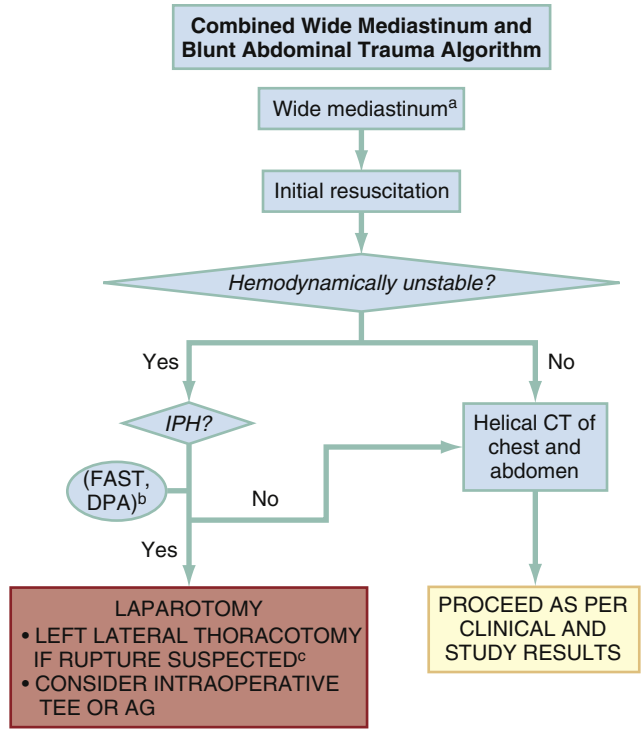

Fig. 38.11 Combined Wide Mediastinum and Blunt Abdominal Trauma Algorithm. *AG,* Aortogram; *CT,* computed tomography; *FAST,* focused assessment with sonography for trauma; *IPH,* intraperitoneal hemorrhage; *TEE,* transesophageal echocardiogram. [a]Preferably based on upright posteroanterior film and mechanism of injury; other radiographic signs or mechanism alone may signal need for evaluation. [b]Determined by unequivocal free intraperitoneal fluid on FAST or positive finding on diagnostic peritoneal aspiration *(DPA).* [c]Allows surgical access to majority of aortic disruption sites.

Resuscitative Endovascular Balloon Occlusion of the Aorta

REBOA is an endovascular procedure that can be performed at bedside to decrease ongoing intra-abdominal or pelvic exsanguination while increasing proximal (including cerebral) perfusion pressures. To place the device, access is obtained proximal to the bifurcation of the femoral artery, and the balloon is advanced and placed in the thorax distal to the subclavian for intra-abdominal bleeding or inferior to the renal arteries for pelvic bleeding. The balloon is partially inflated to increase proximal blood pressure while decreasing ongoing intra-abdominal bleeding. Indications for placement include life-threatening noncompressible hemorrhage unresponsive to resuscitation or traumatic arrest in place of resuscitative thoracotomy.[24,25] However, REBOA carries with it the risk of significant complications, including acute kidney injury, bowel ischemia, and lower extremity ischemia, particularly if the balloon is fully insufflated.[26] The optimal group to benefit from REBOA placement remains undefined. REBOA can be reliably learned within a formal training course and should be used only in the context of multidisciplinary protocols.[24] Should the device be placed, it should be considered a temporizing measure only as a bridge to definitive surgical management.

Therapeutic Angioembolization

Therapeutic angiography is usually reserved for the unstable patient with blunt trauma and pelvic fracture in whom it can be used to embolize bleeding vessels (Fig. 38.12). It can also be a means of stanching solid visceral hemorrhage from blunt trauma. Nonoperative management has become standard in management of splenic injuries but is associated with increasing failure rates in the setting of higher grades of injury. Successful nonoperative management increases significantly with the use of angioembolization. Angioembolization may have the added benefit over splenectomy of preserved splenic immunity, although further studies are needed. In both operative and nonoperative management of severe, isolated blunt liver injury, angiointervention is associated with increased survival despite increased systemic complications.[27] Angioembolization also has been used in rare cases for intraperitoneal and retroperitoneal hemorrhage after trauma by a penetrating mechanism.

DISPOSITION

Disposition will vary according to findings from the evaluation and the patient's clinical course. Stable patients without any identified injuries sustaining stab wounds (see Fig. 38.6) or blunt abdominal trauma (see Fig. 38.8) may be discharged home according to the algorithms provided. Patients sustaining penetrating wounds into the peritoneal cavity should

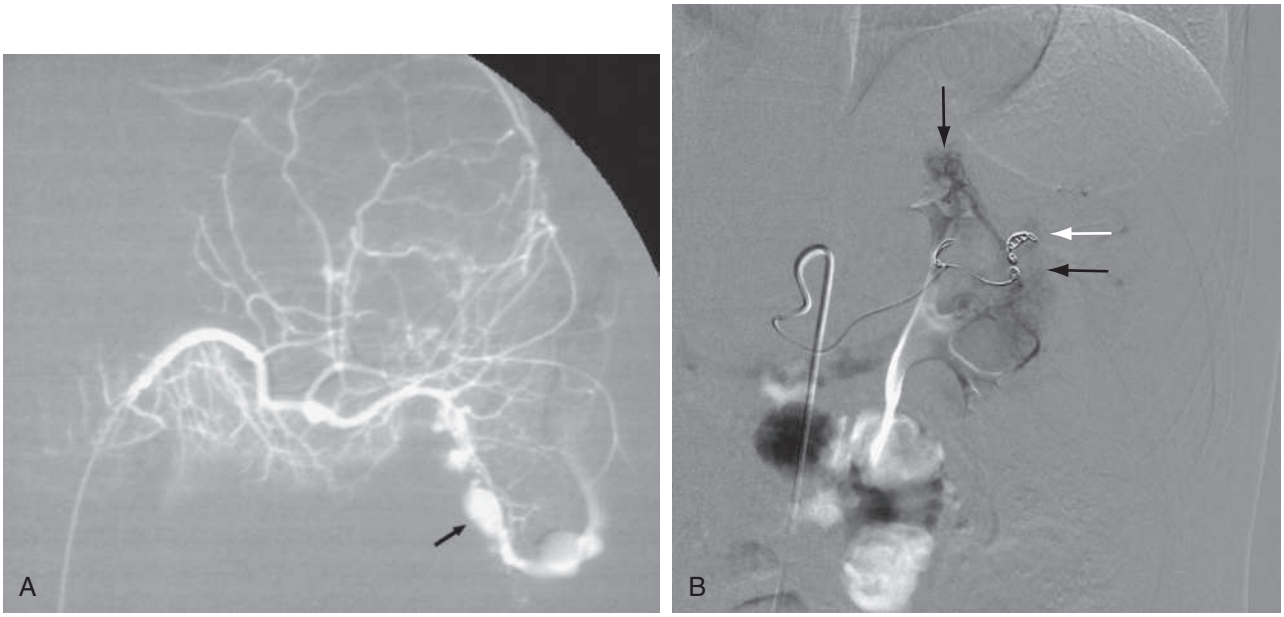

Fig. 38. 12 (A) Angiography of splenic laceration. Note the blush representing active hemorrhage *(arrow).* (B) Angioembolization of renal laceration. Note coil in the splenic artery *(white arrow)* and blush representing active hemorrhage stemming from two branches *(black arrows).* (A, From Mauro MA. *Image guided interventions.* Philadelphia: Elsevier; 2008:835)

either be admitted and followed with serial examinations or transferred immediately to the operating room (see Figs. 38.6 and 38.7). Patients sustaining blunt abdominal trauma should be taken to the operating room or angioembolization suite (see Figs 38.8, 38.9, 38.10 and 38.11), whereas stable patients with identified injuries can either be admitted for serial examinations or taken to the operating room, as necessary.

Consultation

Trauma is a multidisciplinary condition. Early consultation with a general or trauma surgeon or their involvement as part of a team response is a hallmark of an effective trauma center. Emergency clinicians provide care to the majority of abdominal trauma patients, but many injuries require operative intervention or prolonged observation on a surgical trauma service. Similarly, consultation with a radiologist may help to prioritize diagnostic studies, avoid unnecessary studies, or obtain the vital information with the minimum exposure of the patient to ionizing radiation or contrast material.

Transfer

Patients with significant abdominal trauma, whether blunt or penetrating, should be transferred to a trauma center as soon as possible after the threatening injury is identified and without delay for time-consuming imaging studies that will not alter the need for transfer. Trauma patients in nontrauma hospitals with significant transfer times may require a stabilizing "damage control" laparotomy by a general surgeon before being transferred to a trauma center for definitive care.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 38: QUESTIONS AND ANSWERS

1. The extended focused assessment with sonography for trauma (e-FAST) scan of a patient with blunt abdominal trauma shows a hypoechoic stripe in the pouch of Douglas. Which of the following is correct?

- **a.** In the presence of hemodynamic instability, this indicates a need for laparotomy.
- **b.** The patient needs to go for emergent laparotomy immediately.
- **c.** The patient requires repeat abdominal examinations and FAST examinations in the emergency department (ED).
- **d.** There is at least 500 mL free fluid in the abdomen.
- **e.** This indicates a ruptured bladder.

Answer: a. The pouch of Douglas is one of the areas of ultrasound inspection for an e-FAST examination. If free fluid is present and the patient is hemodynamically unstable, the patient should forego computed tomography (CT) scanning for the operating room. FAST examinations are effective in detecting as little as 100 mL of free fluid in the abdominal cavity.

2. An 18-year-old man presents after a high-velocity front-end vehicle collision. He has a blood pressure of 90/70 mm Hg, heart rate of 120 beats/min, respiratory rate of 17 breaths/min, and a Glasgow Coma Score (GCS) of 13. On physical examination, he has a tender abdomen and an unstable pelvis. An extended focused assessment with sonography for trauma (e-FAST) examination is positive for free fluid in the abdomen. What should be the patient's disposition?

- **a.** Admission to the trauma service for observation
- **b.** Emergency department (ED) observation for 12 hours with repeat FAST examinations
- **c.** Interventional radiology for pelvic angiography and embolization
- **d.** Operating room for emergency laparotomy

Answer: d. The e-FAST examination is an excellent bedside tool in guiding care in unstable patients with pelvic fractures. If the e-FAST exam shows intraperitoneal free fluid, the patient should be taken to the operating room emergently for laparotomy. If the e-FAST exam

CHAPTER 38: QUESTIONS AND ANSWERS—cont'd

is negative and no other readily identifiable source of hypotension is present, emergent pelvic angiography and embolization in interventional radiology (IR) is appropriate.

3. A 27-year-old male presents 4 hours after an isolated stab wound to the anterior abdomen. His vital signs are heart rate 84 beats/min and blood pressure 115/64, and the lactate level is 0.9 mg/dL. His extended focused assessment with sonography for trauma (e-FAST) examination is negative for free fluid. He denies alcohol and drug use and appears clinically sober. Which of the following statements regarding this patient's subsequent management is true?
   - **a.** A negative computed tomography (CT) scan rules out the need for further evaluation.
   - **b.** If local wound exploration (LWE) definitively demonstrates that the wound does not violate the peritoneum, the patient can be discharged from the emergency department (ED).
   - **c.** The negative e-FAST examination rules out intra-abdominal injury requiring operative intervention.
   - **d.** The patient meets criteria for emergent laparotomy.

Answer: b. Simple anterior abdominal stab wounds that do not violate the peritoneum can be discharged from the ED after appropriate wound care (see Fig. 38.6). CT scans poorly visualize both the small bowel and diaphragm and cannot be used in isolation to rule out injury in penetrating abdominal trauma. A negative e-FAST examination does not rule out significant intra-abdominal injury or even small-volume hemoperitoneum in either penetrating or blunt abdominal trauma. Not all anterior stab wounds meet indication for laparotomy, even in the presence of peritoneal penetration.

4. A 67-year-old female who is taking warfarin for atrial fibrillation presents after a high-mechanism motor vehicle collision. Her heart rate is 142 beats/min and blood pressure is 84/40 after 1 L of normal saline. Her Glasgow Coma Score (GCS) is 6, and her left pupil is 6 mm versus 3 mm on the right. Her physical examination is notable for a seat belt sign on the abdomen. Which of the following is *not* an acceptable approach to her initial assessment and treatment?
   - **a.** Perform an extended focused assessment with sonography for trauma (e-FAST) examination to evaluate for the presence of intra-abdominal fluid.
   - **b.** Perform chest and pelvic radiographs in the resuscitation bay.
   - **c.** Perform empirical craniotomy concurrently with laparotomy in the operating room after a positive diagnostic peritoneal aspiration.
   - **d.** Perform endotracheal intubation and begin mild hyperventilation.
   - **e.** Proceed to radiology for an emergent abdominal computed tomography (CT) scan.

Answer: e. The patient is hemodynamically unstable, with suspected intra-abdominal injuries in conjunction with signs of herniation. CT scanning of the abdomen would be inappropriate in this patient. Several concurrent management options to stabilize the patient and determine the source of her hypotension are desirable (see Fig. 38.10). Endotracheal intubation allows airway control and possible hyperventilation to delay impending herniation. Chest and pelvic radiographs rule out other sources of ongoing hemorrhage and may support emergent laparotomy. An e-FAST examination can confirm the presence of intra-abdominal free fluid, which in the setting of hemodynamic instability is an indication for laparotomy. Finally, after confirmation of intra-abdominal blood by e-FAST, proceeding to the operating room, with or without emergent CT scanning of the head, are management options. If the head CT is foregone because of instability, empirical craniotomy is an acceptable management option.

5. Which of the following statements regarding splenic injuries in blunt abdominal trauma is true?
   - **a.** A computed tomography (CT) scan with a grade IV splenic laceration indicates the need for laparotomy.
   - **b.** Angiographic embolization has no role in high-grade splenic lacerations.
   - **c.** Bedside extended focused assessment with sonography for trauma (e-FAST) can accurately rule-out splenic injury.
   - **d.** CT scanning followed by serial abdominal examinations and hematocrits is a reasonable management option for certain splenic injuries at experienced centers.
   - **e.** Mononucleosis increases the risk of splenic laceration from seemingly minor blunt abdominal trauma.

Answer: d. Serial abdominal examinations, laboratory tests, or repeat e-FAST examinations are reasonable management options at experienced centers. High-grade splenic lacerations, although having a higher rate of failed nonoperative or angiographic embolization management, do not represent a definitive indication for laparotomy. Angiographic embolization may preserve some of the immune function of the spleen, even in the setting of high-grade splenic lacerations. Bedside e-FAST, although sensitive for intra-abdominal fluid, is a relatively poor test for the evaluation of solid organ injury. Mononucleosis does increase the risk of splenic laceration. Trauma can be so minor that the patient may have little recollection of the remote trauma responsible.

39

Genitourinary Trauma

Spenser C. Lang and Sanjay N. Shewakramani

KEY CONCEPTS

- Microscopic or gross hematuria is suggestive of genitourinary trauma; however, the degree of hematuria does not correlate well with either the severity or anatomy location of injury.
- The kidney is the most frequently injured genitourinary organ, and imaging should be considered in patients with gross hematuria or microscopic hematuria with hemodynamic instability.
- Most noniatrogenic ureteral injuries are due to penetrating mechanisms and are unilateral; blunt ureteral trauma is rare. Delayed computed tomography (CT) images after intravenous (IV) contrast should be obtained in patients with mechanism or findings suggestive of ureteral trauma.
- CT scan with IV contrast is not sensitive for diagnosing bladder injury, and retrograde cystography should be obtained to allow proper distention of the bladder to allow for urinary extravasation.
- Pelvic fractures associated with hematuria strongly suggest bladder or urethral injury.
- Retrograde urethrography (RUG) should be performed in patients with pelvic fractures and hematuria, those with perineal ecchymosis or swelling, or those with blood at the urethral meatus, prior to attempting bladder catheterization, because blind passage of a Foley catheter in these scenarios can worsen a preexisting urethral injury.
- Genital injury is rarely life threatening but prompt diagnosis and evaluation are necessary to decrease the likelihood of future morbidity in these patients.

FOUNDATIONS

Background and Importance

Ten percent of trauma cases in the United States involve the genitourinary tract; however, most of these injuries are not life threatening. In fact, due to the anatomic protection of the kidneys, ureters, and bladder, as well as the mobile nature of the male external genitalia, isolated urologic injuries are uncommon in patients with major trauma. However, genitourinary trauma can cause significant, long-term morbidity, including renal insufficiency, chronic hypertension, incontinence, and sexual dysfunction. In addition, isolated traumatic renal injuries can be overlooked, due to the location of the kidneys and subtle presentation, with serious consequences for the patient.[1]

Approximately 5% of all trauma patients will have a concomitant renal injury, with a male predominance of 3:1.[2] Blunt mechanisms cause the vast majority of renal injuries. Although approximately half of all traumatic renal injuries are caused by motor vehicle collisions, it remains an uncommon injury that has continued to decrease with improvements in seat belts and airbags. Recent data show that less than 1% of all motor vehicle collisions result in any genitourinary trauma.[3] Although rare, 40% of patients with renal trauma also have a coexisting abdominal injury. Contrastingly, in urban or military settings, penetrating trauma accounts for 40% of renal injuries, and typically causes more tissue disruption and a higher severity of injury. Of the remaining blunt mechanisms, falls and direct blows (e.g., sports injuries or assaults) account for the majority of injuries.[4] Renal injuries from sports (e.g., skiing, snowboarding, and contact sports) tend to be isolated and can easily be overlooked.[5]

Pediatric renal injuries tend to be more common than in adults because children's kidneys are more mobile, are relatively larger, and have less perinephric adipose tissue. Blunt mechanisms are responsible for 90% of pediatric renal trauma.[6] Kidney injuries are more common than injuries to the spleen, liver, pancreas, and bowel in this population. However, due to more conservative approaches in management, even with high-grade injuries, pediatric renal trauma rarely leads to nephrectomy.[7]

Due to the long, tubular and mobile nature of the ureter and its location in the retroperitoneum (where it is well protected by the vertebrae and soft tissues), blunt traumatic injuries of the ureter are rare and virtually never occur in isolation. Most noniatrogenic ureteral injuries are due to penetrating mechanisms and are unilateral; the ureter is involved in up to 5% of penetrating injuries to the abdomen.[4]

After the kidney, the bladder is the most commonly injured genitourinary organ with blunt trauma. Bladder injuries occur in 1% to 2% of all blunt abdominal traumas and occur most frequently from motor vehicle collisions, which are responsible for approximately 50% of all bladder injuries.[1] Bladder injury most often occurs in the context of pelvic fractures or other intra-abdominal injuries. As a result, mortality rates in patients with blunt bladder trauma is as high as 22%, due mostly to the concomitant injuries.[8] The bladder also is subject to penetrating injury through the abdomen, rectum, or buttocks. Up to 80% of patients with penetrating bladder injuries also suffer bowel injuries.

Blunt trauma mechanisms, the majority of which are motor vehicle collisions, cause approximately 90% of urethral injuries. Males are five times more likely than women to suffer urethral injuries, due to the longer length and reduced mobility of the male urethra.[9] Similar to bladder injuries, significant blunt pelvic trauma is required to cause injuries to the urethra. As a result, concomitant injuries are often observed, particularly pelvic fractures or straddle-type injuries. Approximately 5% of pelvic fractures have an associated urethral injury.[10] Penetrating injuries to the urethra are rare (3% of all gunshot wounds) and are suspected on the basis of the nature and trajectory of the penetrating object.[11] Urethral trauma also can occur from misadventure during self-instrumentation, which is most often related to sexual activity. Urethral injury can cause significant morbidity, via stricture formation, incontinence, erectile dysfunction, and infertility. These injuries tend to occur in younger patients, and complications are common, even if urethral injuries are appropriately diagnosed and treated.[12]

The external genitalia, particularly the scrotal contents, are subjected to direct injury, which happens most frequently in sports-related trauma. Minor external trauma may occur with consumer products

(including zippers, sporting items, and moving furniture), and the large majority of these injuries are self-limited. Severe injuries, including penile fractures and testicular rupture, are rare but generally require emergent surgical management. These injuries also can lead to long-term reproductive, physiologic, and psychological consequences.[13]

The overall rates of external genital trauma are low in females, with the most common mechanism being childbirth-related injuries. However, blunt trauma, causing lacerations or hematomas, can occur. Unfortunately, in many parts of the world, female genital mutilation and sexual violence can lead to disfigurement, sexual dysfunction, and incontinence.[14]

Anatomy and Physiology

The genitourinary tract is divided into the upper tract (kidneys and ureters, including the renal pedicle), lower tract (bladder and urethra), and external genitalia (penis, scrotum, testicles, and vulva).

The kidneys are retroperitoneal organs that are encapsulated by fibrous tissue known as *Gerota fascia*. They lie against the psoas muscles, are surrounded by the ribs and spinal column, and are well-cushioned by perinephric fat, leaving them fairly well-protected (Fig. 39.1). This explains why isolated renal injury is rare in trauma, because it requires a significant mechanism to cause injury. However, the lower poles of the kidney do project inferior to the twelfth rib bilaterally, which makes them susceptible to trauma.[1] Due to their proportionately larger kidneys with less perirenal fat, weaker abdominal muscles, and a less rigid chest wall, children are at higher risk for renal injury.[6]

The renal pedicle—which includes the renal artery, renal vein, and the ureter—inserts into the kidney along the medial border, at the hilum. A longitudinal cross-section of the kidney reveals the outer renal cortex with inner medulla that compose the renal parenchyma (Fig. 39.2). These create and drain urine into the calyces, which flow into the renal pelvis, which then drains into the ureter.

The bladder is a muscular organ that lies in the abdomen at birth but descends into the pelvis at approximately 6 years old and is thus considered extraperitoneal. It is heavily protected by the bony pelvis, especially when it is not distended. However, when distended, the dome of the bladder rises into the abdomen (as high as the umbilicus), making it more prone to both blunt and penetrating trauma. Children are more prone to bladder injuries due to their underdeveloped pelvic structures.[15] Posteriorly, the bladder connects to the ureters on the superior aspect, and in males, it is adjacent to the seminal vesicle and vas deferens on the inferior side. Loose connective tissue surrounds the bladder laterally.

The male urethra is approximately 22 cm in length when measured from the bladder to the urethral meatus (Fig. 39.3). The urogenital diaphragm divides the posterior urethra (composed of the prostatic and membranous segments) from the anterior urethra (composed of the bulbous and penile segments). The fossa navicularis is the slightly dilated segment of the penile urethra contained within the glans. Although the anterior urethra is more mobile, the posterior urethra is anchored to the anterior pubic arch by the puboprostatic ligaments.[16] The female urethra is only approximately 5 cm long and is protected

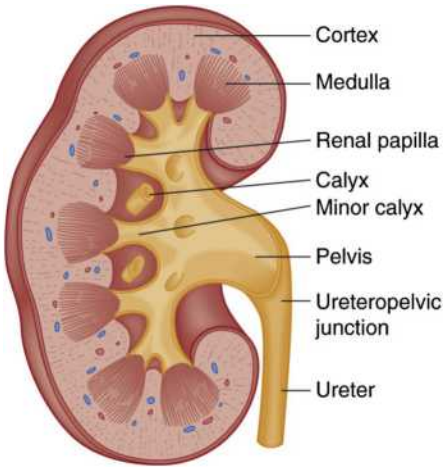


Fig. 39.2 Longitudinal Section of Kidney.

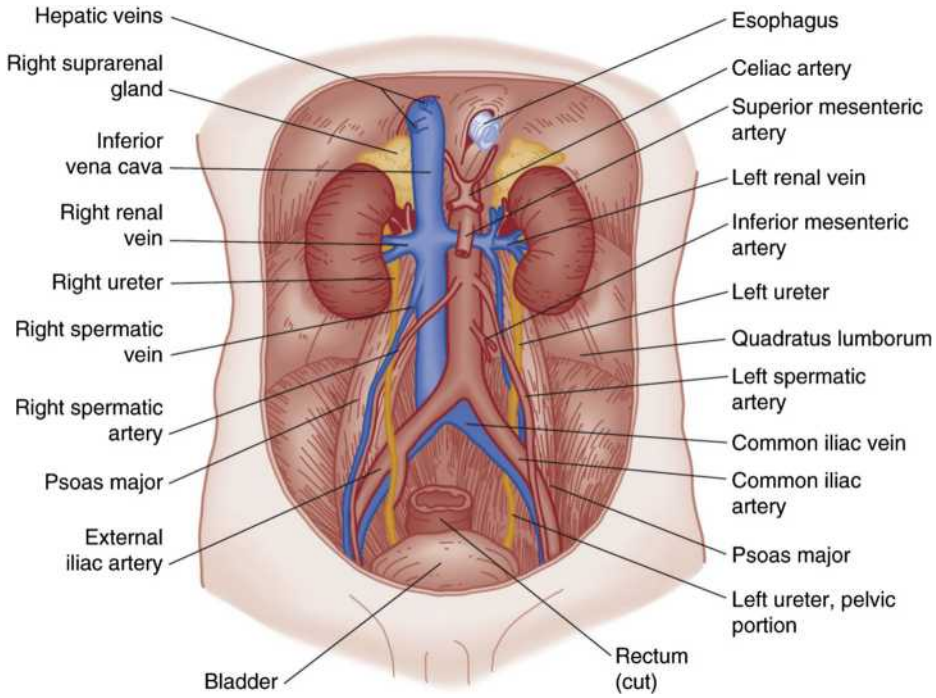


Fig. 39.1 Dissection of abdomen showing kidneys and ureters and their relationship to other anatomic features in the retroperitoneal space.

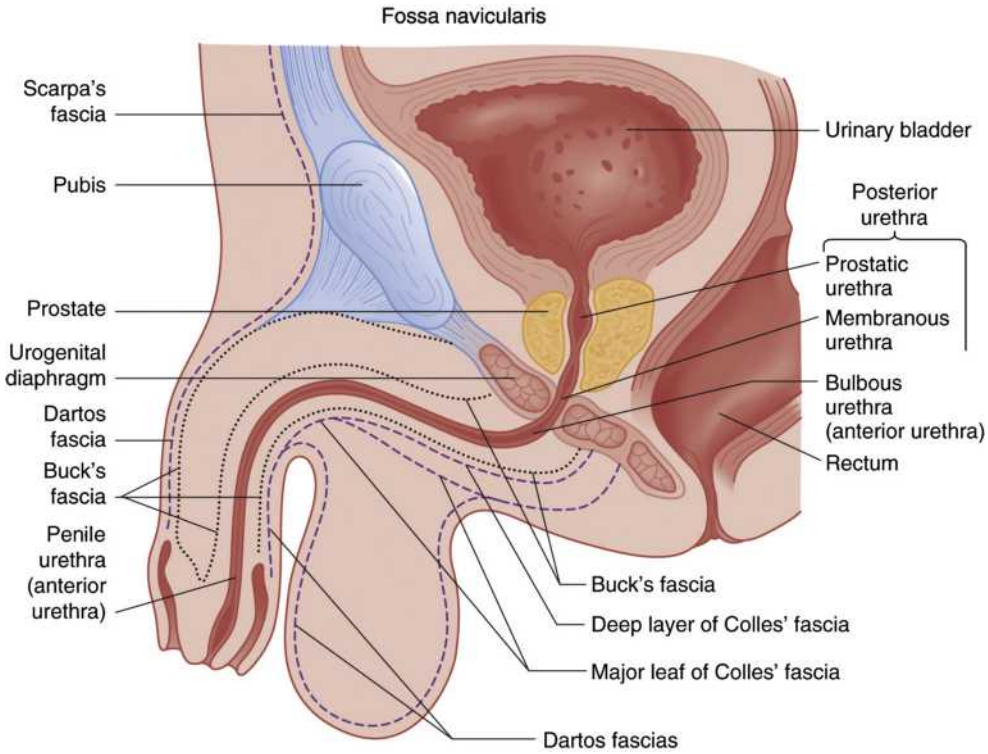


Fig. 39.3 Anatomy of Male Genitalia.

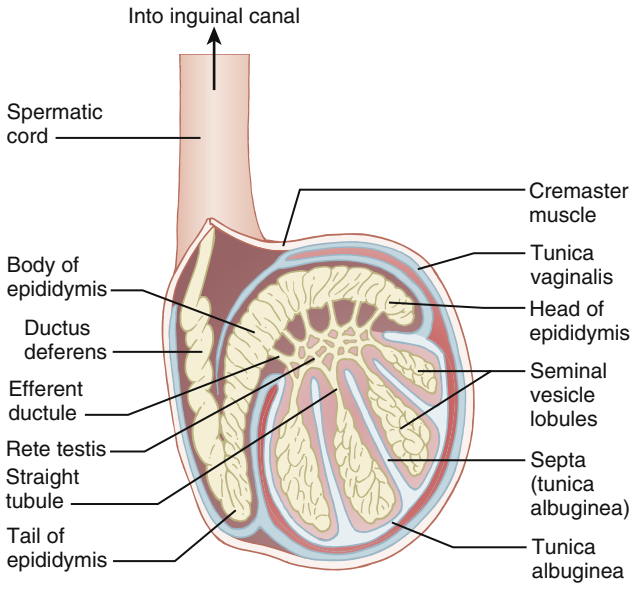


Fig. 39.4 Scrotal Anatomy.

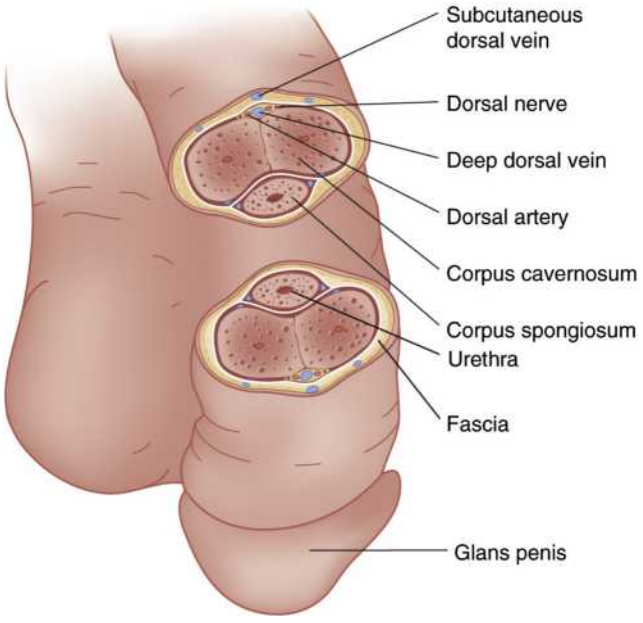


Fig. 39.5 Cross-sectional View of the Penis.

due to its close association with the vagina, which absorbs the majority of the force during trauma. In addition, the female urethra has no significant attachments, making it mobile, and reducing the likelihood of significant trauma.[17]

The testicles normally measure 5 × 3 × 2 cm each and are individually encapsulated by the fibrous tunica albuginea (Fig. 39.4). The encapsulated testicles are then surrounded by the tunica vaginalis, which has both a visceral and parietal surface. The potential space between these surfaces allows for hydroceles or hematoceles to form. Each half of the scrotum contains a separate testicle, spermatic cord, and epididymis.

The penis is composed of two paired corpora cavernosa along the dorsal aspect and a corpus spongiosum along the ventral surface (Fig. 39.5). Corpora cavernosa are filled with venous sinusoids that surround a central artery and engorge with blood during an erection, whereas the corpus spongiosum surrounds the urethra and forms the glans penis on its distal aspect. Each of the three is surrounded by a separate fascial sheath, which also is referred to as the *tunica albuginea.* Buck fascia, the deep fascia of the penis, immediately surrounds the three structures, and multiple other superficial fascial layers further surround Buck fascia. The superficial and deep dorsal veins provide most of the venous drainage

from the penis. The female external genitalia consist of the labia, vulva, and the vagina, as well as the clitoris. The thighs and groin provide relative protection, and isolated injuries to this area should raise suspicion for physical, sexual, or otherwise intentional abuse.[14]

Pathophysiology

Because it is fixed in space only by the renal pelvis and pedicle, the kidney is prone to acceleration and deceleration injuries from blunt trauma. The American Association for the Surgery of Trauma (AAST) guidelines for grading blunt renal trauma are essentially unchanged since their creation, with grades III, IV, and V defined as "high-grade" renal trauma (Table 39.1 and Fig. 39.6).[1] Higher-grade injuries not only require different treatments but are predictive of future morbidity, such as risk of chronic kidney disease and hypertension.[18] Lacerations and contusions typically occur from direct trauma, whereas renal artery avulsions can occur from deceleration mechanisms. Renal artery occlusion can occur when the renal artery is compressed between the anterior abdominal wall and vertebral bodies, or from arterial spasm due to surrounding contusions.[19] Penetrating injuries, typically due to gunshot and stab wounds, can cause similar patterns of injury as blunt injuries but tend to be more severe.

Blunt injuries can cause trauma to the ureter either directly from compression against fractured bony structures (e.g., transverse processes of lumbar vertebrae) or by deceleration mechanisms, which can cause a disruption at the ureteropelvic and the ureterovesical junctions.[4] Due to their hyperextensible vertebral columns, children are more prone to deceleration mechanisms. Penetrating injuries are almost exclusively unilateral, tend to occur in the distal third of the ureter, and carry a mortality rate of up to 6%. They are commonly associated with bowel and vascular injuries.[15]

Bladder injuries range from mural contusions (representing 20% of all injuries) to bladder ruptures, which are defined as lacerations through the entire wall of the bladder.[8] Ruptures are further classified into intraperitoneal bladder ruptures (IBRs) and extraperitoneal bladder ruptures (EBRs). Intraperitoneal injuries resulting from blunt trauma are typically caused by rupture of a distended bladder at its weakest point, which is the dome where it abuts the peritoneum. As a result, urine drains into the peritoneal cavity. Intraperitoneal ruptures tend to occur in high-impact injuries, such as motor vehicle collisions, but more recently up to 10% of bladder injuries have occurred from

TABLE 39.1 The American Association for the Surgery of Trauma Grading Scale for Classification of Renal Trauma

Grade	Type	Description
I	Contusion	Microscopic or gross hematuria
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma	Nonexpanding perirenal hematoma confirmed to renal retroperitoneum
	Laceration	<1 cm parenchymal depth of renal cortex without urinary extravasation
III	Laceration	>1 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation
IV	Laceration	Parenchymal laceration extending through the renal cortex, medulla, collecting system
	Vascular	Main renal artery or vein injury with contained hemorrhage
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of renal hilum that devascularizes kidney

From Harper K, Shah KH. Renal trauma after blunt abdominal injury. *J Emerg Med* 2013;45:400–404.

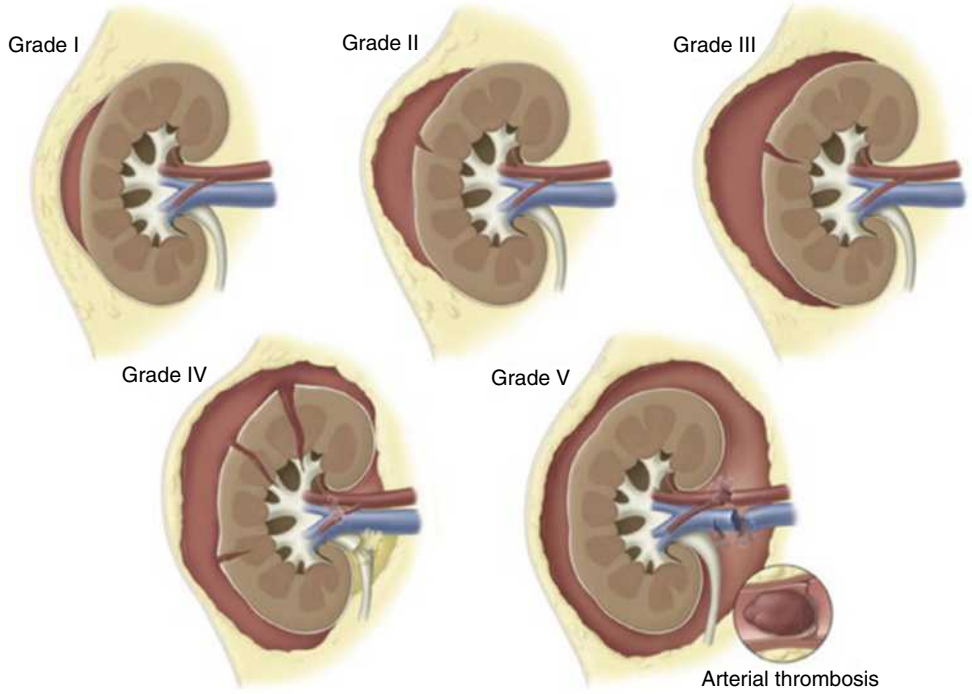


Fig. 39.6 Schematic of the American Association for the Surgery of Trauma (AAST) grading scale for renal trauma. (From Myers JB, Brant WO, Broghammer JA. High-grade renal injuries: radiographic findings correlated with intervention for renal hemorrhage. *Urol Clin North Am* 2013;40:335–341.)

sports-related abdominal trauma.[15] Case reports of nontraumatic IBRs have also been reported in patients with forceful vomiting.[20,21] EBRs, which account for the majority of bladder ruptures, occur as the result of direct compression, shear forces at the bladder base, or lacerations from bony spicules from pelvic fractures.[10] These ruptures result in urine draining into the pelvic cavity. Approximately 10% of bladder injuries are both intraperitoneal and extraperitoneal.[1,22]

With blunt trauma to the pelvis, shearing forces transmitted through the urogenital diaphragm create tension along the male urethra, most often between the anterior and posterior segments at the bulbomembranous junction. These forces occur commonly in unstable pelvic fractures, bilateral ischiopubic rami fractures, and symphysis pubis diastasis injuries. Injuries can range from stretching, to partial lacerations, to complete disruptions of the urethra; the latter of which accounts for 50% to 65% of urethral injuries. The majority of these injuries involve the posterior urethra, and the most severe injuries are complex posterior injuries involving the bladder neck or rectum.[1]

Blunt anterior urethral injuries, which are four times less common than posterior injuries, are often caused by straddle-type mechanisms, which result in crushing of the bulbar urethra against the inferior aspect of the pubic bone (Fig. 39.7).[23] These injuries occur more commonly in children and can be easily missed, potentially resulting in future strictures.[24] Gunshot wounds and other penetrating injuries more commonly involve the anterior urethra than the posterior urethra.[11] Urethral injuries in adult females are rare due to the urethra short course and relative mobility. However, female children are at higher risk, and urethral injuries in this population are associated with pelvic circle disruptions, multiple pelvic fractures, vaginal lacerations, hematomas, or sacral spine injuries.[25]

In addition to testicular rupture, which is caused by disruption of the testicular tunica albuginea, blunt trauma can also lead to scrotal hematomas, hematocele, spermatic cord injuries, testicular contusions, testicular fractures, testicular dislocation, and, rarely, traumatic testicular torsion or epididymitis.[26] Testicular hematomas form within the testicle and may be associated with testicular rupture, whereas testicular fractures are defined as linear avascular areas within the testicular parenchyma without rupture of the tunica albuginea. More than half of patients presenting to the emergency department (ED) with scrotal trauma may have a ruptured tunica albuginea (i.e., testicular rupture), although it is a rare injury.[1] Testicular dislocation occurs when blunt trauma forces the extrascrotal migration of one or both testicles, although bilateral dislocations are rare. They migrate along the course of the spermatic cord and typically are found in the superficial inguinal area, but they can even be found in the suprapubic region. Penetrating injuries violate the tunica albuginea in more than half of cases.[1]

Penile fractures, due to tears of the tunica albuginea, account for the majority of blunt penile injuries that present to the ED. Blunt trauma can also lead to rupture of the dorsal veins or artery, resulting in local ecchymosis that can be easily mistaken for a penile fracture, and is therefore termed a *false penile fracture*.[27] In these cases, the tunica albuginea is typically intact, and patients do not require immediate operative exploration.[28] Penetrating injuries to the penis involves the urethra in up to 29% of cases and can also result in penile amputation, which is more common in patients with a psychiatric history.[13]

Nonsexual genital injuries in females are most often due to straddle injuries in young girls, but other blunt and penetrating injuries do occur and are usually more severe. The labia are most frequently involved, as well as the perineum. Penetrating injuries can involve the rectum as well as urethra, and these deeper injuries can easily be missed in young girls if a thorough examination is not performed.[14]

The diagnostic and management approach to each organ varies, necessitating a basic understanding of the anatomy and traumatic pathophysiology of each individual organ. The majority of cases require early urologic consultation. The clinical features, diagnostic approach, and management guidelines for the specific organs are discussed in the following sections.

Renal Trauma

Clinical Features

The history for patients with renal trauma includes the mechanism of injury for blunt trauma and the type of projectile or weapon for penetrating injury. Any high-energy impact or direct blow to the flank or abdomen can lead to renal injuries. Various other traumatic injuries tend to accompany renal injuries due to the significant anatomic protections of the kidneys. Gross or microscopic hematuria warrants careful consideration for genitourinary injury, although the degree of hematuria does not necessarily correlate with the degree or grade of injury, and significant genitourinary trauma can occur without hematuria.[2] Importantly, hematuria can represent injury at any level of the genitourinary system and does not localize to the kidneys. Renal injury

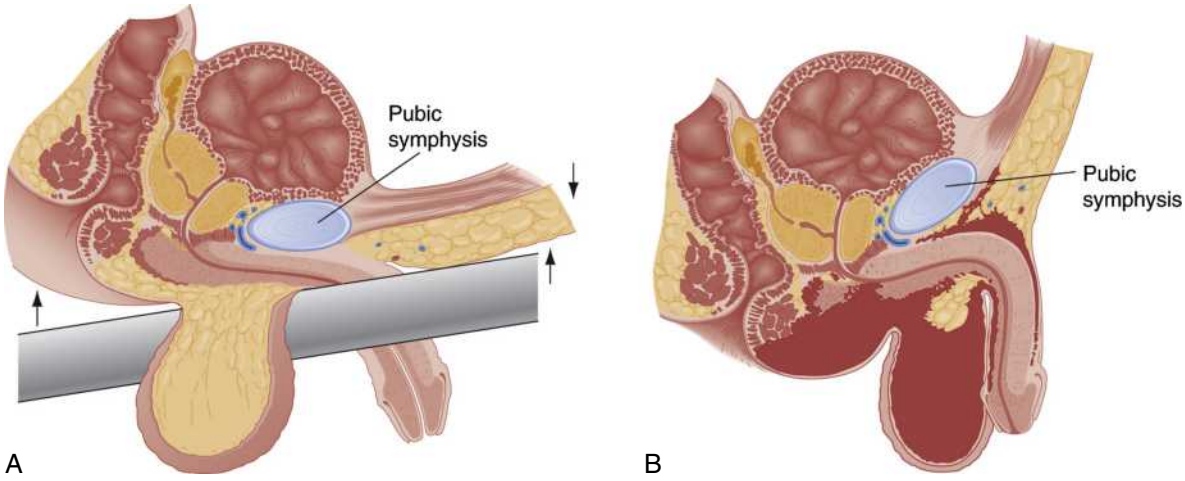


Fig. 39.7 Injury to the bulbous urethra due to straddle mechanism. (A) Mechanism: Usually a perineal blow or fall astride an object, crushing the urethra against inferior edge of pubic symphysis. (B) Extravasation of blood and urine enclosed within Colles fascia. (From McAninch JW. Injuries to the genitourinary tract. In: Tanagho EA, McAninch JW, eds. *Smith's general urology*. 14th ed. Norwalk, CT: Appleton & Lange; 1995.)

requiring intervention is rare in the absence of gross hematuria or shock. Examination of the patient with multisystem trauma may reveal shock; flank tenderness, fullness, or ecchymosis; loss of flank contour; obviously fractured ribs; abdominal tenderness or distention; or a palpable abdominal mass.[4]

Differential Diagnoses

Blunt or penetrating trauma can result in a range of injuries to the kidney and the vascular supply to the kidney, as shown in Table 39.1. Injuries to the renal parenchyma can cause contusions or lacerations within the kidney or hematomas surrounding the kidney. Vascular injuries can involve the renal artery or vein and vary in significance. Minor injuries to the vascular supply can lead to a contained hematoma, but hilar avulsion can result in complete devascularization of the kidney.[1]

Diagnostic Testing

Although significant renal injury can occur without causing hematuria, 95% of all patients with renal trauma have some hematuria on urinalysis, which is defined as more than five red blood cells per high-power field, or a positive urine dipstick. Patients with multisystem trauma, especially with evidence of blood loss, require a complete blood count and type and screen. Creatinine drawn within an hour of injury reflects renal function prior to the injury and thus serves as a baseline for future testing.[4]

Gross hematuria in a patient with a mechanism consistent with possible renal injury requires further investigation. Conversely, microscopic hematuria in a blunt trauma patient without shock is not a definite indication for renal imaging, even if there is evidence of mild local trauma, in the absence of other clinical signs. Although renal injuries may uncommonly be identified on imaging, the injuries are mild and patients typically do not require intervention. Imaging should be performed, with either gross or microscopic hematuria, in trauma patients with evidence of hemodynamic instability (systolic blood pressure less than 90 mm Hg), presence of lower rib fractures, significant flank ecchymosis, evidence of intraperitoneal injury, or specific mechanisms (e.g., rapid decelerations, significant blow to flank, or penetrating injuries). In addition, with gross hematuria, imaging should include the entire urinary tract or localized to the lower tract (bladder and urethra), depending on the mechanism and location of the injury.[1]

Multidetector computed tomography (CT) with intravenous (IV) contrast is the gold standard to evaluate for renal injury, with nearly 100% sensitivity and specificity.[22] CT can evaluate for renal lacerations, hematomas, extravasation of contrast, devascularized renal segments, and urinary extravasation and is used to provide a grade for the severity of renal trauma (Fig. 39.8). When renal injuries are highly suspected or visualized in real time, delayed images should be performed 10 minutes after administration of IV contrast to better evaluate the extent of injury,

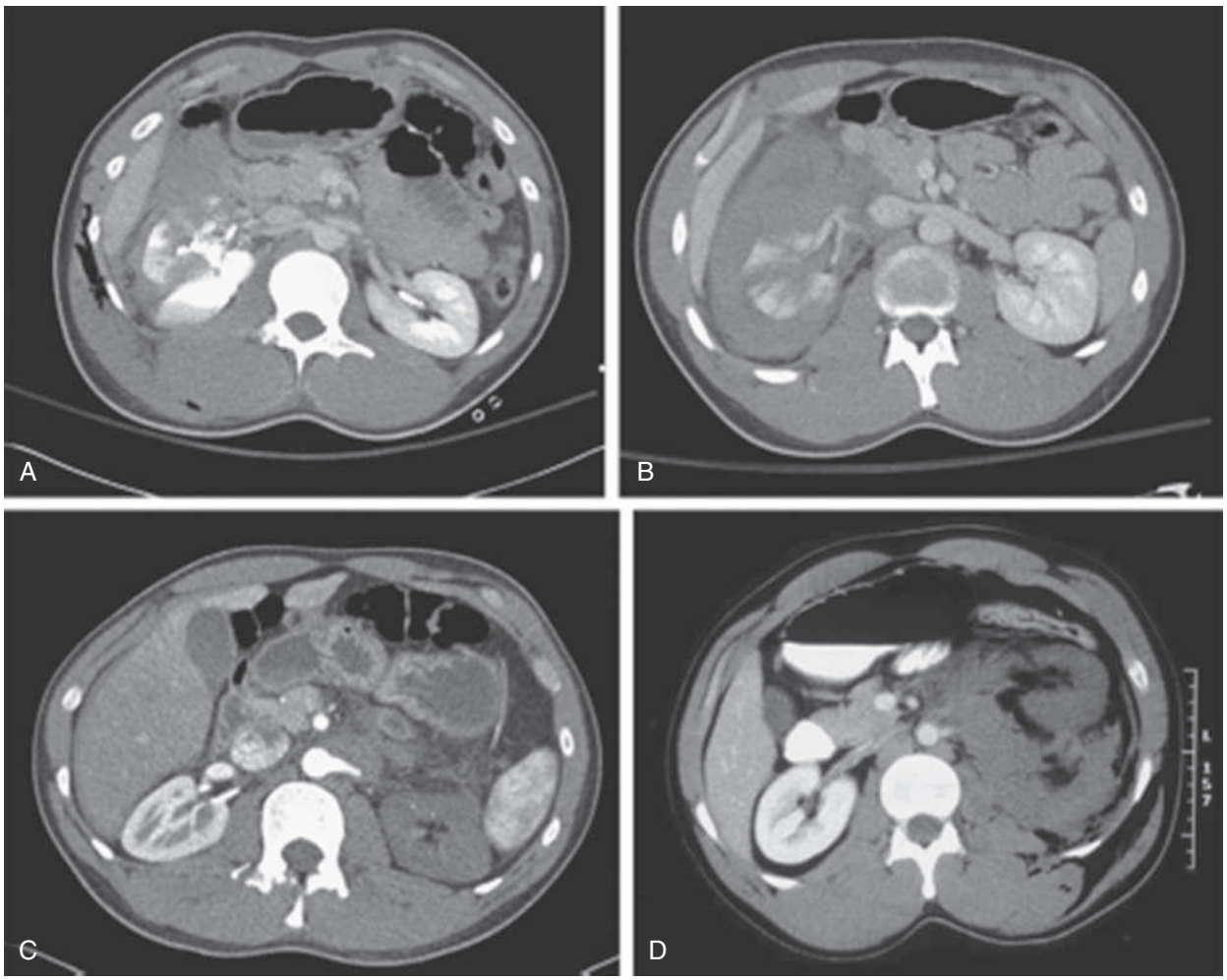


Fig. 39.8 High-grade Renal Injuries. (A) Grade IV injury with urinary extravasation. (B) Severe grade IV laceration, also referred to as *shattered kidney*. (C and D) Grade V injuries with devascularization of the affected kidney. (From Myers JB, Brant WO, Broghammer JA: High-grade renal injuries: radiographic findings correlated with intervention for renal hemorrhage. *Urol Clin North Am* 2013;40:335–341.)

as well as to assess for collecting system disruption, possible urinary extravasation, or accompanying ureteral damage. (Fig. 39.9).[1] In pediatrics, CT with IV contrast remains the gold standard, and obtaining initial delayed imaging can result in avoidance of repeated imaging later during the hospitalization, lowering the overall radiation to the child.[29]

Ultrasound can demonstrate renal injuries but has historically had lower sensitivity and specificity than CT, but the quality and predictability is operator dependent. It is also difficult to determine the depth and extent of renal lacerations, and it is often unclear if fluid seen surrounding the kidney on ultrasound represents urine or blood. However, unlike CT, ultrasound can be performed at the bedside if the patient is unstable and is often used in various other ways during an initial evaluation of a multisystem trauma patient because views of both kidneys are obtained during a focused assessment with sonography in trauma (FAST) examination. Recent studies have demonstrated comparable diagnostic accuracy with renal ultrasound in pediatric patients in both isolated renal injuries and multisystem trauma patients. Importantly, either radiologists or ultrasound technicians were performing the studies, and these data might not be applicable without those specialists present.[30]

Management

Multisystem trauma is managed in collaboration with a general or trauma surgeon, and prompt consultation with a urologic surgeon is indicated when there is injury to the urinary tract. Fig. 39.10 represents an algorithm for the management of blunt trauma to the kidneys. After renal trauma is identified on imaging, hemodynamic instability determines the next intervention. If the patient is unstable despite fluid resuscitation, they should undergo surgical exploration, with the extent of renal trauma determined intraoperatively. Hemodynamically stable patients found to have minor renal injuries (grade I to III) typically require only conservative management (including fluid resuscitation and observation). High-grade injuries (grade IV and V) are more likely to require operative intervention; however, over the past decade, even high-grade injuries (grade IV and V) are increasingly treated nonoperatively initially, with comparable outcomes.[31]

Therapeutic options for blunt renal trauma include nephrectomy, ureteric stenting, percutaneous drainage, and arterial embolization. Recent changes in management have increasingly focused on nonoperative therapy, leading to increased renal salvage in even high-grade injuries. Surgical practice has shifted away from early exploration due to the high number of nephrectomies performed with early exploration.[32] Both European and American urotrauma guidelines advocate for nonoperative initial management for all hemodynamically stable patients. The rates of renal salvage and decreased morbidity has improved alongside more advance endoscopic and transarterial embolization techniques.[33] This shift has been even more pronounced in the pediatric population, where the renal salvage rate now approaches 99%. In the past, penetrating renal injuries mandated urgent surgical exploration. More recently, urologists treat penetrating injuries with observation or embolization. Importantly, some injuries might require operative intervention, but morbidity and nephrectomies are decreased if operative management is performed in a delayed fashion.[1,34,35]

Although initial nonoperative management is preferred, certain factors do predict future need for operative management. Ten percent of grade IV injuries will require an open surgical procedure, and this number increases to approximately 50% for grade V injuries.[33] In addition, deceleration mechanisms, persistent hemorrhage, fevers, multiple comorbid injuries, and initial angioembolization all predict the need for surgical intervention.[7] The decision to obtain repeat CT imaging should be guided by individual patient characteristics and is not necessary for every patient with a renal injury.[36] Hemodynamic instability, decreased hemoglobin, and fevers are the most common reasons for obtaining repeat CT.

Early complications of renal trauma include persistent bleeding, infection (urinary tract infections, perinephric abscesses, and sepsis), persistent urinary extravasation and urinoma, and transient hypertension. In general, early antibiotics should be considered for all patients with renal trauma to potentially avoid future urinary tract infections and perinephric abscess formation. Long term, patients most commonly suffer from chronic kidney disease and hypertension and can develop urinary fistulae and arteriovenous malformations. The risk of chronic complications increases with the grade of the injury.[4] Grade III, IV, and V injuries are associated with a decrease in renal function of 15%, 30%, and 65%, respectively, after trauma. High-grade injuries are associated with increased rates of hypertension as well, because grades IV and V are associated with a 3.5-fold higher risk of being diagnosed with hypertension in the future.[18]

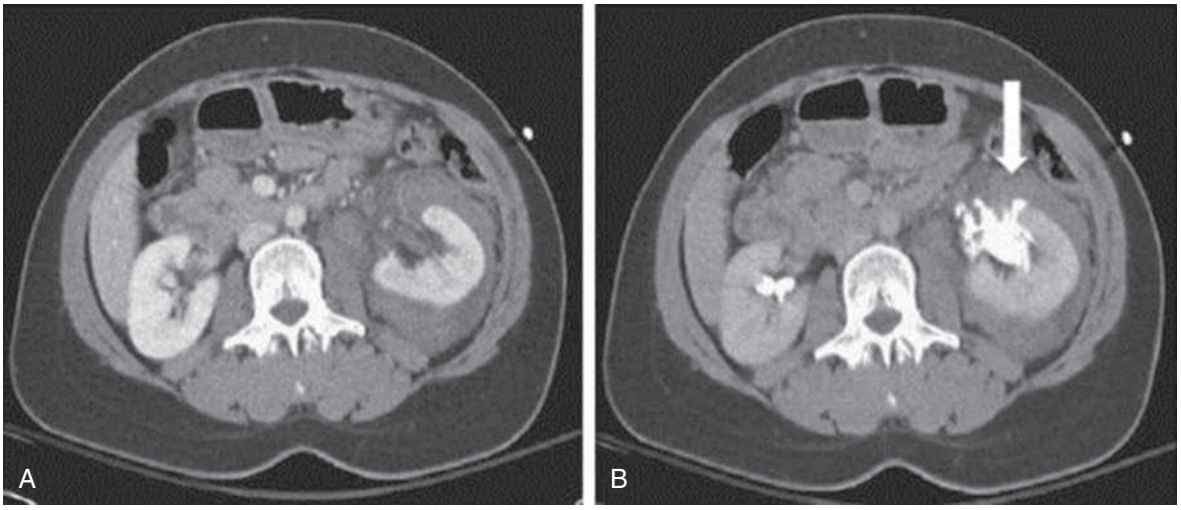
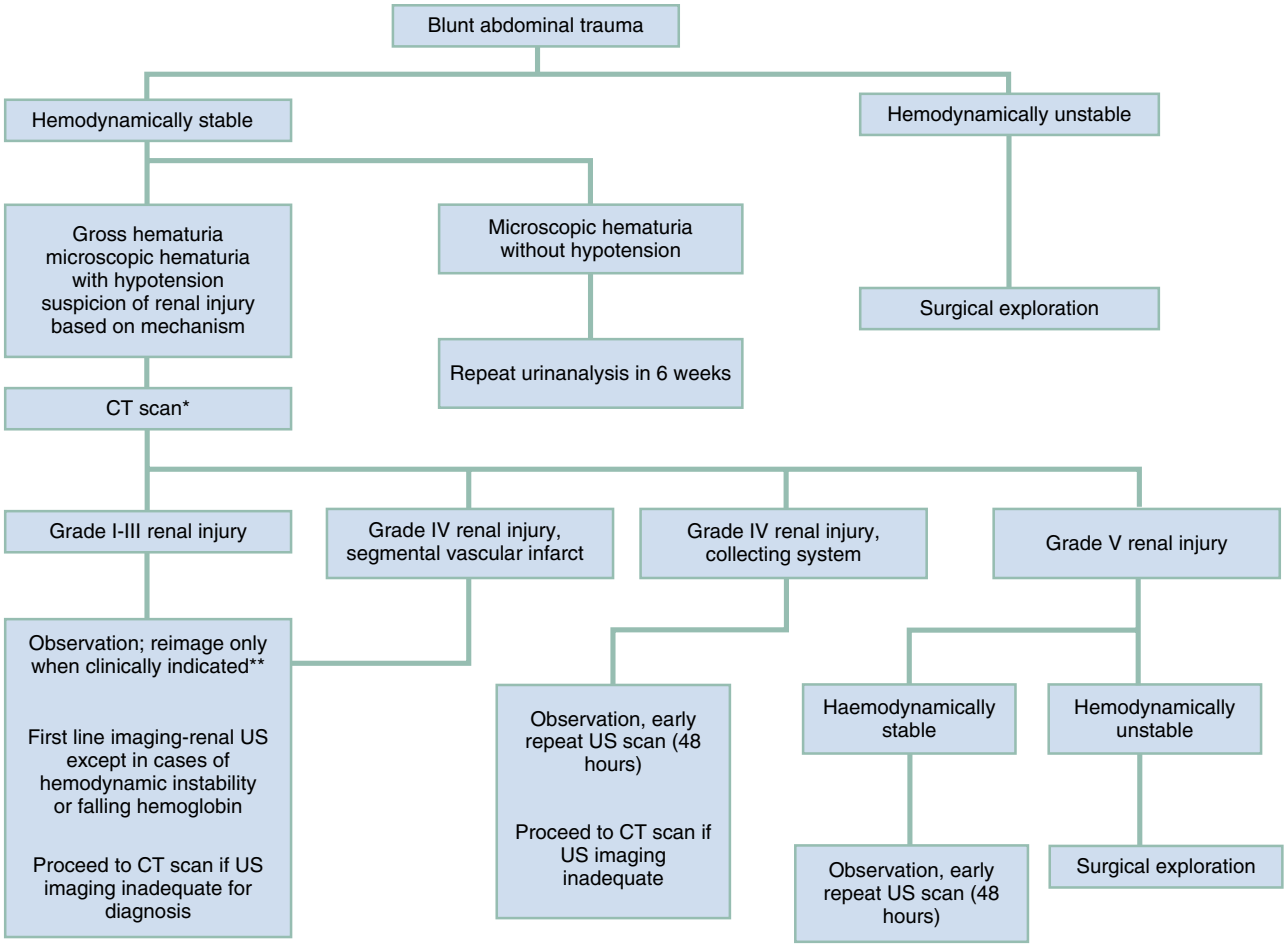


Fig. 39.9 (A) Left-sided perinephric fluid collection suggests a collecting system injury on computed tomography (CT) images. (B) Delayed images confirm a collecting system injury with contrast extravasation *(arrow)*. (From Hardee MJ, Lowrance W, Stevens MH, et al. Process improvement in trauma: compliance with recommended imaging evaluation in the diagnosis of high-grade renal injuries. *J Trauma Acute Care Surg.* 2013;74:558–562.)



* CT scan with and without IV contrast and delayed phase images

** Fever, progressive leukocytosis, hypertension, marked change in symptoms or physical exam

Fig. 39.10 Algorithm for Imaging and Management of Renal Trauma. *CT,* Computed tomography; *IV,* intravenous; *US,* ultrasound. (From Breen KJ, Sweeney P, Nicholson PJ, et al. Adult blunt renal trauma: routine follow-up imaging is excessive. *Urology*. 2014;84:62–67.)

Disposition

Patients with traumatic renal injury generally require urgent evaluation by a urologist. Despite low rates of early complications, it recommended that patients with renal injuries be at least observed for repeat examinations and serial diagnostic studies. Hospital length of stays tends to be of similar with conservative or operative management.[37] As with many traumatically injured patients, those with renal injuries tend to have better outcomes in high-volume tertiary care centers, where patients require fewer operations and have improved renal salvage rates.[38] Because the majority of patients with renal injuries have concomitant traumatic injuries, consultation with both trauma and urologic surgery services is important in determining the appropriate disposition for these patients.

Ureteral Trauma

Clinical Features

There are no pathognomonic clinical signs of ureteral injury, and suspicion must be based on mechanism and signs of other traumatic injuries on physical exam. These include signs of intra-abdominal or retroperitoneal injury, including flank ecchymosis, gross or microscopic hematuria, and abdominal distention or tenderness. However, hematuria is seen in less than half of patients and is usually microscopic. Associated injuries include fractures of the transverse process of lumbar vertebrae, pelvic fractures, bowel injuries, and vascular damage, particularly of the iliac vessels given their proximity to the ureters. Importantly, because the majority of these patients have multisystem traumatic injuries, they typically do not have complaints attributable to the ureter, despite having a significant injury. Given their subtle presentation, if not rapidly diagnosed by imaging or intraoperatively, ureteral injuries often do not declare themselves until days later when patients present with sepsis (from urinary extravasation), hydronephrosis from obstruction, or a urinary fistula.[15]

Differential Diagnoses

Blunt trauma affecting the ureter can lead to stretching and resultant hematomas or, if more severe, partial or complete disruption of the ureteral wall.[15] Penetrating injuries involving the ureter generally result in complete or partial transection.[11]

Diagnostic Testing

Hematuria is not a reliable indicator of ureteral trauma because it is present in less than 50% of patients. However, blunt ureteral injury is rare, and further diagnostic evaluation for ureteral injury is reserved for patients with unexplained persistent hematuria or evidence of injury adjacent to the ureter, such as retroperitoneal vascular injury,

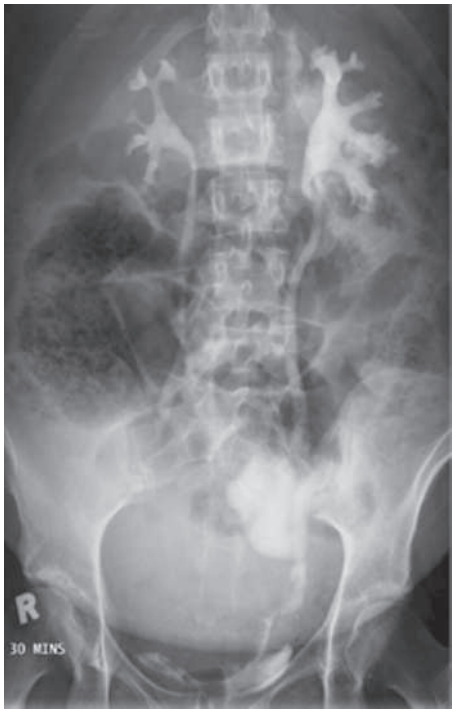


Fig. 39.11 Intravenous (IV) urography revealing an injury to the left distal ureter, resulting in contrast extravasation. (From Cutinha P, Venugopal S, Salim F. Genitourinary trauma. *Surgery [Oxford].* 2013;31:362–370.)

vertebral fractures, or pelvic fractures. Penetrating injuries in the location of the ureters should prompt imaging or operative exploration. The best modality for diagnosing ureteral injury is CT scan with IV contrast (CT urogram).[1]

IV pyelography/urography and retrograde pyelography (Fig. 39.11) were once used to diagnose ureteral injury, but they have been supplanted by CT scanning. A CT scan performed immediately after the administration of IV contrast can potentially miss ureteral injuries, and 10-minute delayed CT urogram imaging (allowing for contrast to opacify the collecting system and ureters) is recommended.[39] CT findings of ureteral injury include contrast extravasation, a delayed pyelogram, hydronephrosis, low-density retroperitoneal fluid (representing urinary extravasation), or lack of contrast distal to the ureteral injury.[15] Retrograde or anterograde urography is the gold standard for confirmation in stable patients with unclear or potentially delayed ureteral injury,[4] In unstable patients requiring surgical intervention, a single image intraoperative IV pyelogram can be performed to directly assess the ureters.[15]

Management

With minor injuries, including contusions and partial lacerations, ureteral stenting is typically sufficient. However, if enough tissue is devitalized, short-segment removal and primary anastomosis may be necessary. Additional options include percutaneous nephrostomy for unstable patients and ureteral reimplantation into the bladder. Rarely, severe injuries require nephrectomies, typically when renal function is less than 20% of baseline.[15]

Almost one-quarter of all patients develop a complication after ureteral injury, which are rarely life threatening but can occasionally lead to the loss of the affected kidney. Urinary leaks leading to sepsis or fistulas, as well as strictures, are among the most common complications. These complications are frequently seen when diagnosis of the initial injury is delayed. If suspicion is high, a repeat CT urogram or retrograde pyelogram should be performed.[15]

Disposition

As with most urogenital trauma, prompt consultation with a urologic surgeon is necessary for patients with ureteral injuries, because nearly all will require admission and some type of procedural or operative intervention.

Bladder Trauma

Clinical Features

In contrast to ureteral injuries, hematuria is the hallmark of a bladder injury, with gross hematuria noted in 72% of patients with blunt trauma to the bladder and up to 95% of patients with penetrating bladder trauma.[1] Other signs and symptoms include abdominal tenderness or distention, blood at the urethral meatus, the inability to void, ecchymosis, or entrance and exit wounds in the perineum, thigh, or abdomen.[23]

Differential Diagnoses

Differentiating IBR from EBR is of the utmost importance due to significant differences in management. Intraperitoneal injuries are most often caused by blunt force abdominal trauma in a patient with a distended bladder. Extraperitoneal injuries are usually associated with some form of pelvic trauma. Gross hematuria should also raise suspicion for other injuries in the genitourinary tract aside from bladder injuries.

Diagnostic Testing

Other than urinalysis, laboratory evaluation is not useful in diagnosis of acute bladder injury. Gross hematuria is present in the majority of cases; those without gross hematuria will have microscopic hematuria. Approximately 5% of bladder ruptures will not have gross hematuria; however, if there are less than 25 red blood cells per high-powered field on microscopic urine analysis, a rupture is extremely unlikely.[11] High-energy pelvic fractures, such as symphysis diastasis and displaced obturator ring fractures, should also raise the suspicion of bladder injury.[10]

All stable trauma patients with gross hematuria and pelvic fracture should undergo cystographic imaging, due to the high likelihood of bladder injury. Not all patients with microscopic hematuria and pelvic fracture require imaging for bladder injury; however, certain fracture patterns should raise suspicion and prompt investigation, as well as clinical signs of bladder rupture. These fractures include pubic symphysis diastasis as well as significantly displaced obturator ring or pubic rami fractures.[1] Gross or microscopic hematuria in patients with a penetrating injury suggesting a pelvic trajectory require further imaging.[11] CT scan performed with IV contrast alone does not sufficiently distend the bladder to evaluate for mural defects, leading to false-negatives, and thus retrograde "stress" cystography should be performed. This involves diluting 30 mL of water-soluble ionic contrast in a 500-mL bag of warmed saline. Approximately 300 to 400 mL of this solution is then introduced into the bladder via a Foley catheter using gravity.[22] Foley catheterization should not be performed unless the clinician is confident that a urethral injury is not present (see discussion following). By distending the bladder, thrombi that may have formed along the bladder wall are dislodged, allowing for urinary extravasation. Images are then acquired to assess for rupture, either by fluoroscopy or CT scan. Conventional fluoroscopic cystography can assess for urinary extravasation (Figs. 39.12 and 39.13). However, CT imaging is more sensitive (95%) and can evaluate for foreign body involvement from fractures or bladder neck injuries. An EBR may demonstrate a "molar tooth" appearance on cystography, which represents contrast tracking along the pelvic fascial planes (Fig. 39.14), whereas an IBR reveals contrast material outlining the intraperitoneal structures (Fig. 39.15).[39]

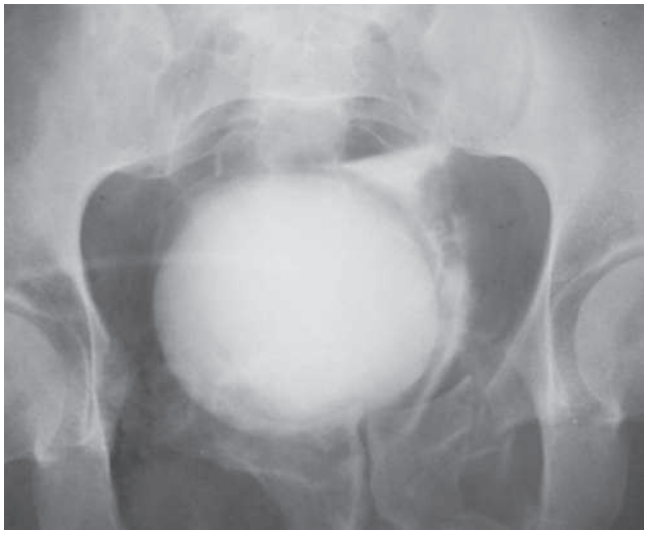


Fig. 39.12 Extraperitoneal Bladder Rupture on Retrograde Cystography. Contrast extravasation is limited to the pelvis. (From Cutinha P, Venugopal S, Salim F. Genitourinary trauma. *Surgery [Oxford].* 2013;31:362–370.)

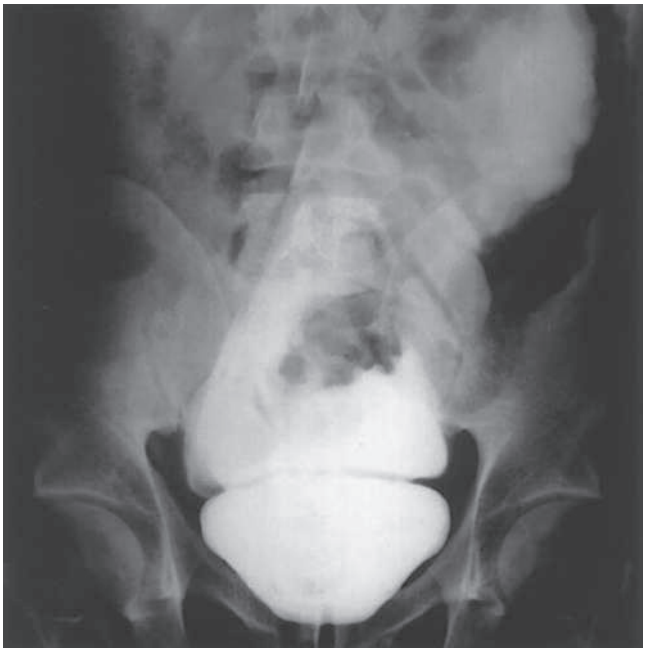


Fig. 39.13 Intraperitoneal Bladder Rupture on Retrograde Cystography. Extravasating contrast can be seen outlining bowel. (From Cutinha P, Venugopal S, Salim F. Genitourinary trauma. *Surgery [Oxford].* 2013;31:362–370.)

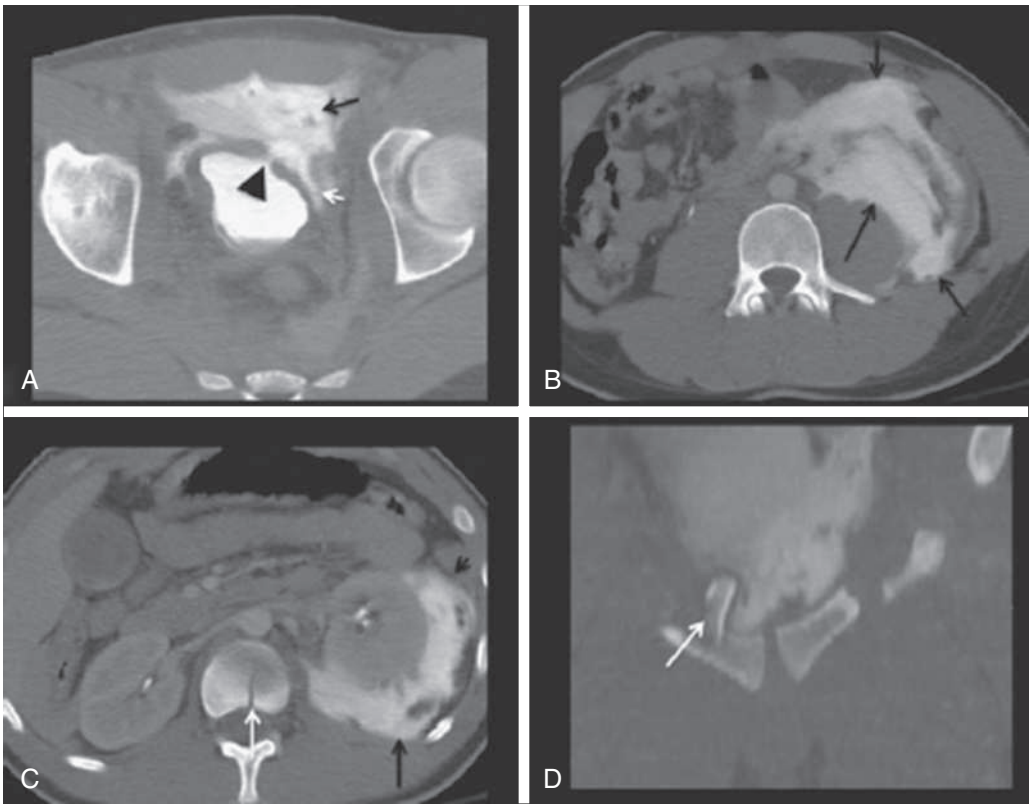


Fig. 39.14 Computed tomography (CT) cystography images from a complex extraperitoneal bladder rupture (EBR). (A) The *arrowhead* overlying the bladder points to the location of extravasation into the perivesicular spaces. (B and C) Contrast extravasation continues along the left retroperitoneum, extending into the perirenal space. (D) The rupture was likely caused by the displaced ramus fracture fragment which is seen violating the bladder wall. There is an associated lumbar spine fracture noted in (C). (From Avery LL, Scheinfeld MH. Imaging of male pelvic trauma. *Radiol Clin North Am.* 2012;50:1201–1217.)

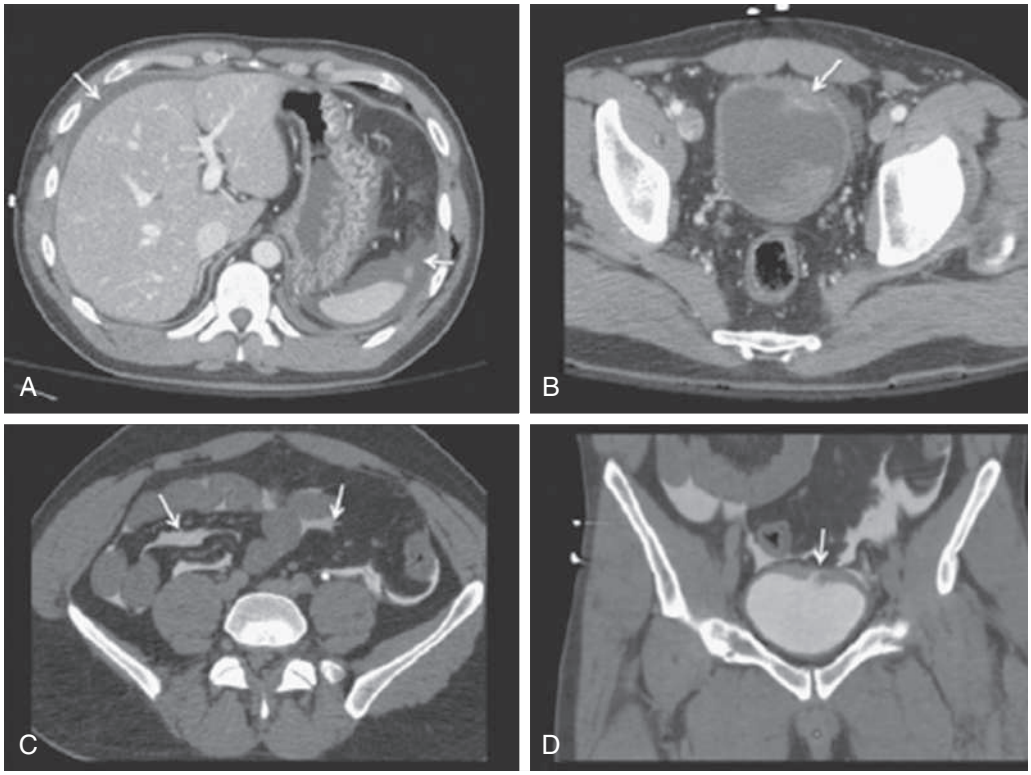


Fig. 39.15 Computed tomography (CT) images from a patient with intraperitoneal bladder rupture (IBR). (A and B) Images acquired immediately after intravenous (IV) contrast administration reveal fluid around the liver and spleen, as well as clot within the bladder and left anterior bladder wall. CT cystography reveals intraperitoneal extravasation of contrast (C) with a disruption of the dome of the bladder (D). (From Avery LL, Scheinfeld MH. Imaging of male pelvic trauma. *Radiol Clin North Am.* 2012;50:1201–1217.)

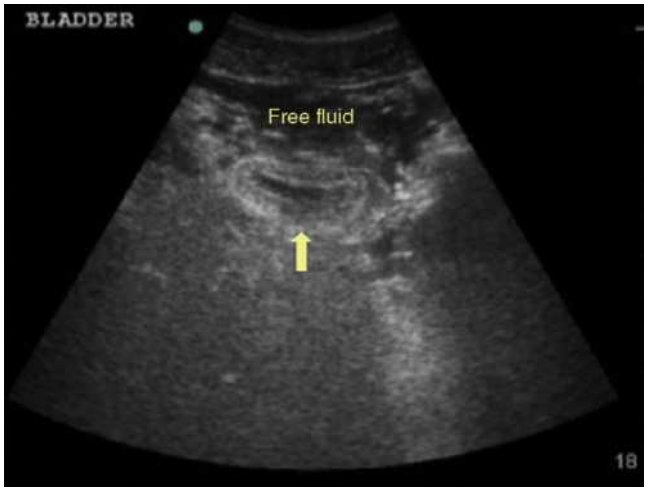


Fig. 39.16 Ultrasound Image of Bladder Rupture. The bladder is contracted, with an irregular bladder wall posteriorly *(arrow),* and free fluid anteriorly. (From Wu TS, Pearson TC, Meiners S, et al. Bedside ultrasound diagnosis of a traumatic bladder rupture. *J Emerg Med.* 2011;41:520–523.)

Bedside diagnostic ultrasonography can identify bladder rupture but has poor sensitivity (Fig. 39.16).[40] As with any evaluation using ultrasound, this technique is highly operator dependent.

Management

The distinction between EBR and IBR is important because the management differs. Contusions and extraperitoneal injuries due to blunt trauma are typically managed conservatively with Foley catheterization. Operative repair is indicated in a few situations, such as concomitant operative intra-abdominal injuries, bladder neck injuries, or bone fragments imbedded in the bladder wall, or if open reduction is performed on pelvic fractures.[1] Open repair of EBR results in improved outcomes and decreased hardware site infections in these cases.[41,42] In contrast, given the extremely low likelihood of IBR and penetrating injuries healing with conservative therapy, almost all patients with these types of injuries are taken to the operating room for exploration and direct repair.[1] Without surgery, there is an extremely high likelihood of complications, which include infections and fistula formation.

Compared with patients with pelvic fracture alone, a concomitant bladder injury is associated with a 75% increase in mortality. Due to the significant mechanism needed to cause an IBR, these injuries are associated with an approximate 20% mortality, which is 12 times more than is seen with isolated EBR. Operative repair decreases the mortality risk by nearly 60%.[37] Extraperitoneal injuries treated nonoperatively rarely lead to complications such as fistula formation or infections.[43] Penetrating rectal injuries leading to bladder involvement can result in abscess, bladder stones, urethral strictures, and fistulae. The high likelihood of potentially serious complications underscores the importance of performing retrograde cystography, when indicated, to diagnose all cases of bladder injury.

Disposition

As with other genitourinary injuries, bladder injuries should ultimately be managed by an experienced trauma surgeon or urologist. The vast majority of patients will be admitted, due to the need for either operative repair or transurethral bladder drainage and monitoring for complications.

Urethral Trauma

Clinical Features

The "classic" presentation of posterior urethral injury includes blood at the urethral meatus, urinary retention, and a "high-riding" prostate on digital rectal examination (DRE).[1] However, DRE lacks sensitivity because the prostate can be obscured by a pelvic hematoma, which is common after pelvic fractures. Therefore DRE should be focused on detecting rectal injuries, and it should not be used to diagnose urethral injury.[11] Similarly, a vaginal exam should be performed in females to evaluate for associated vaginal lacerations or hematomas, which are common with urethral injuries. Other findings include swelling or ecchymosis of the perineum or penis (including "butterfly bruising" seen with anterior injuries that violate Buck fascia; Fig. 39.17) and a distended bladder due to the inability to void.

Blood at the urethral meatus, although not entirely reliable, is the most common clinical sign and present in up to 90% of all urethral injuries. As a result, absence of blood at the meatus plus the lack of a genital hematoma, bruising, or swelling decrease the likelihood of urethral injury. Even without these signs, if patients with significant pelvic injury develop difficulty voiding, investigation for urethral injury is warranted. The degree of hematuria is not correlated with the degree of injury; in fact, a transection can cause a minimal amount of microscopic hematuria, whereas a contusion can induce copious bleeding.[1]

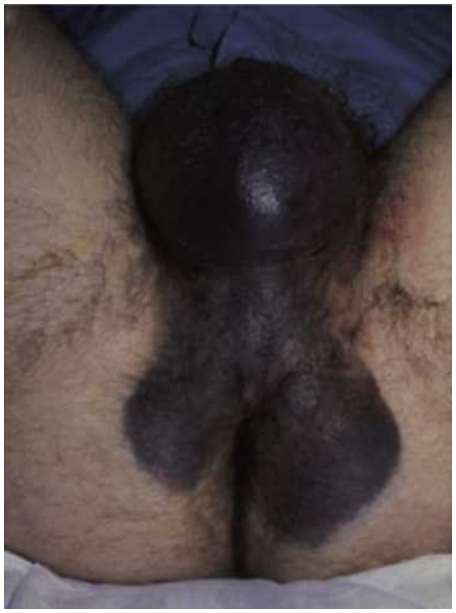


Fig. 39.17 "Butterfly Pattern" of Ecchymosis of the Scrotum and Perineum. (From Mundy AR, Andrich DE. Urethral trauma. Part I: introduction, history, anatomy, pathology, assessment and emergency management. *BJU Int.* 2011;108:310–327.)

Differential Diagnoses

Mild blunt-force injuries to the urethra can result in stretching of the urethra or a contusion of the wall. More severe injuries include partial or complete disruption of the wall. Penetrating injuries usually result in some sort of disruption of the lumen of the urethra. If complete disruption occurs, the amount of urethral separation is important because more than 2 cm of disruption carries a worse prognosis and may change the timing and approach of management.[23]

Diagnostic Testing

Retrograde urethrography (RUG) is the gold standard for diagnosing urethral injuries. RUG should be performed if there is blood at the urethral meatus, or other findings consistent with urethral injury (e.g., perineal or pelvic ecchymosis or swelling), prior to bladder catheterization (Fig. 39.18).[22] The technique for performing RUG is detailed in Box 39.1 and depicted in Fig. 39.19. A scout film that can demonstrate preexisting calcifications is important to avoid false-positive diagnoses, and then it can be compared with postcontrast images. Both anterior-posterior (AP) and lateral films should be obtained to avoid false-negatives in which the contrast extravasates directly posterior to the urethra. Urethrography can determine the location (anterior and posterior) and extent (partial versus complete) of the injury, and it has excellent sensitivity and specificity. Fig. 39.20 depicts a potential schematic of a urethral injury with the resultant RUG image. If a urinary catheter has already been placed prior to suspicion of a urethral injury, a pericatheter RUG can be performed by introducing a 3-Fr catheter into the fossa navicularis and then introducing a small amount of contrast.[1]

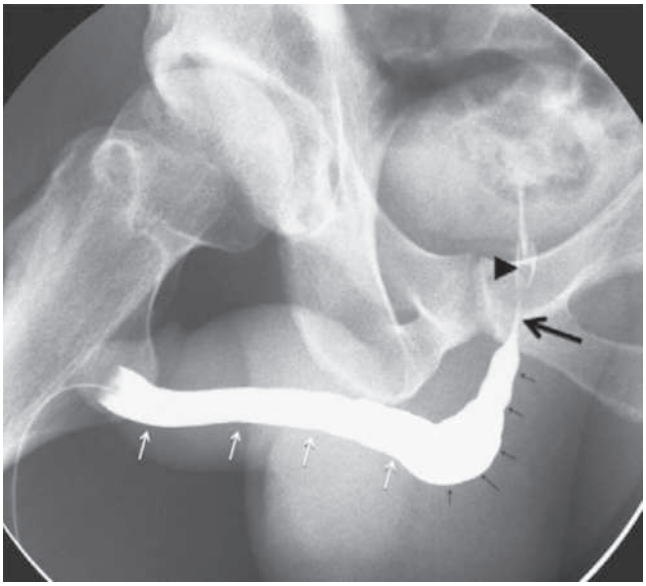


Fig. 39.18 Normal Retro Urethrogram. *White arrows* point to the penile urethra, and *black arrows* point to the bulbous urethra, which together form the anterior urethra. The posterior urethra is composed of the membranous urethra *(black arrow)* and the prostatic urethra *(black arrowhead)*. (From Avery LL, Scheinfeld MH. Imaging of male pelvic trauma. *Radiol Clin North Am.* 2012;50:1201–1217.)

Management

The immediate goal with urethral injury is to secure catheter drainage of the bladder. In addition, continued extravasation of urine through a urethral laceration can lead to infection. Therefore, if a urethral injury is diagnosed, a suprapubic catheter should be placed as soon as possible. Fig. 39.21 details this procedure, which should be performed under ultrasound guidance to avoid injury to the bowels. Alternatively, urethral catheterization can be attempted by experienced providers (typically urologic surgeons) in selected patients; however, repeated attempts, even by urologists, should still be avoided.[1]

After suprapubic drainage is established, the surgical management of urethral injuries can be delayed in favor of treating other life-threatening injuries, except in the case of penetrating injuries or concomitant bladder neck injuries, which should be explored and débrided immediately in the absence of other life-threats. There are multiple options regarding the timing of treatment depending on the location and extent of the urethral disruption, with some controversy

BOX 39.1 Technique for Performing Retrograde Urethrography

1. A 16- or 18-Fr Foley catheter or a hysterosalpingogram catheter is flushed with radiopaque contrast to avoid air bubbles.
2. The glans penis and urethral meatus are cleaned with antiseptic.
3. The catheter is inserted into the penis, and the balloon is partially inflated (1–2 mL) in the fossa navicularis.
4. The penis is then pulled laterally to straighten the urethra under moderate traction.
5. A precontrast "scout" image is obtained because prostatic calcifications may be confused for extravasated contrast.
6. Under fluoroscopic visualization, 20–30 mL of contrast is injected with the goal of filling the entire urethra.
7. If spasm of the external sphincter prevents posterior urethral filling, slow, gentle pressure may allow opacification.
8. Static images are obtained to demonstrate the identified pathologic condition.

From Avery LL, Scheinfeld MH. Imaging of male pelvic trauma. *Radiol Clin North Am.* 2012;50:1201–1217.

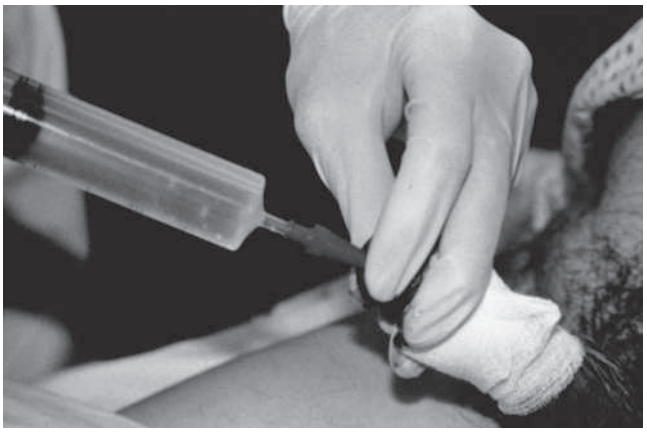


Fig. 39.19 Christmas tree adapter on the end of a 60-mL syringe has been gently placed inside the fossa navicularis in preparation for retrograde urethrography (RUG).

regarding primary repair versus delayed. However, delayed repair allows time for inflammation to decrease and is associated with lower rates of erectile dysfunction, urinary incontinence, and stricture formation.[23]

The complications from urethral disruptions are significant and can negatively impact future quality of life. Complications of urethral injury include urethral stricture, urinary incontinence, and erectile dysfunction, which effects up to 90% of men suffering urethral injuries.[12] Almost half of all children with pelvic fractures and associated urethral injury will exhibit erectile dysfunction at puberty. In children, a higher risk is seen with urethral gap lengths more than 2.5 cm and lateral prostatic displacement. Of note, this is thought to be due more to the accompanying pelvic fractures than the urethral injury or reconstruction. The cause of erectile dysfunction is thought to be neurogenic in most cases, but it can be vasogenic or mixed in some cases.[24] A higher rate of future stress incontinence is seen in women with urethral trauma.

Disposition

Patients with confirmed urethral injuries should be rapidly evaluated and treated by a urologic surgeon and thus either be admitted or transferred to an appropriate tertiary-care institution.

Genital Trauma

Clinical Features

Patients with scrotal injuries may present immediately with swelling and pain but often do not present acutely; in one study, patients had median presentation durations of 3 days.[44] On examination, there can be marked unilateral swelling, ecchymosis, and tenderness. Due to swelling, it is often difficult to distinguish between the different types of testicular injury on examination, and imaging is necessary. Blunt force of at least 50 kg is needed to cause a rupture of the tunica albuginea with extrusion of the seminiferous tubules, resulting in testicular fracture. Typically, the right testicle is more likely to be ruptured than the left, due to its larger relative size and more cranial position.[26]

Penile injuries result in pain, swelling, and ecchymosis. In the setting of blunt or penetrating injuries, blood at the urethral meatus, gross hematuria, or the inability to void suggests a concomitant urethral injury.[1] False penile fractures present with the swelling and ecchymosis

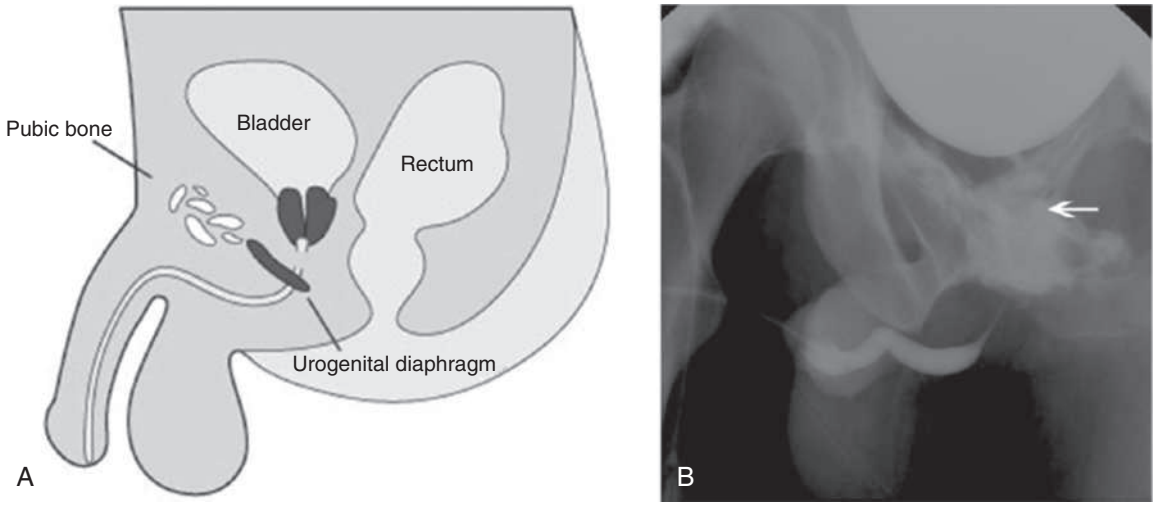


Fig. 39.20 Schematic representation of disruption of the membranous urethra (A) with retrograde urethrogram (B) revealing contrast extravasation above the urogenital diaphragm. (From Nicola R, Menias CO, Mellnick V, et al. Sports-related genitourinary trauma in the male athlete. *Emerg Radiol.* 2015;22[2]:157–168.)

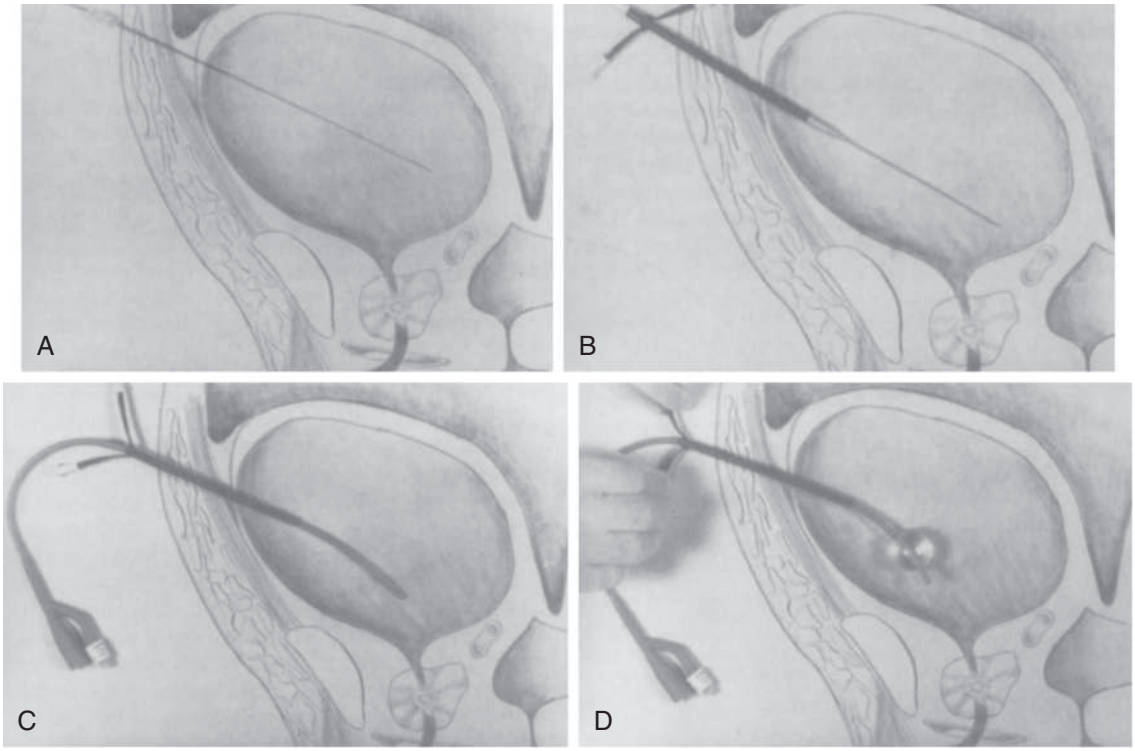


Fig. 39.21 Percutaneous Placement of a Suprapubic Tube with Peel-Away Sheath Introducer. (A) An 18-gauge needle is in the bladder. A guidewire is advanced through the needle. (B) A dilator and peel-away sheath are advanced over the guidewire. (C) The dilator and guidewire are removed. Through the peel-away sheath, an appropriately sized catheter can be introduced into the bladder. (D) The balloon is inflated, and the sheath is pulled back and peeled away. (From O'Brien WM. Percutaneous placement of suprapubic with peel away sheath introducer. *J Urol.* 1991;145:1015.)

that is seen with penile fractures, but patients more often experience a more gradual detumescence and do not typically notice the audible "popping" sound that accompanies most cases of penile fracture (Fig. 39.22). However, it is very difficult to make a clinical distinction between true and false penile fractures, and many of these cases still require imaging and possibly surgical exploration.[45]

True penile fractures are relatively uncommon but are also likely underreported. It is defined as a rupture of the tunica albuginea surrounding any of the three corpora of the penis. The tunica albuginea stretches when the penis is erect, making it thin and inflexible and thus more prone to rupture with lateral bending.[45] In the Western hemisphere, penile fracture most often occurs when the penis slips out of the vagina during intercourse and is accidentally thrust against the perineum or pubic symphysis. However, in the Mediterranean and Middle East, the most common cause is *taghaandan*—where the erect penis is forcibly pushed down to achieve detumescence.[45] Penile fractures are associated with urethral injuries in 20% to 50% of cases, and urethral injuries are more likely in cases of bilateral corporal fractures or when blood is noted at the urethral meatus (Fig. 39.23). Given the high rate of urethral coinjuries, RUG or cystoscopy should be considered for all patients with penile fracture.[13] Patients with penile fracture experience immediate pain, hear an audible "pop," and experience rapid detumescence with a resultant penile hematoma and swelling. Ecchymosis typically is present along the entire shaft of the penis; however, if Buck fascia is also torn, a "butterfly pattern" (see Fig. 39.17) of ecchymosis can be seen in the perineal region. The swelling and color caused by penile fractures can result in an "eggplant deformity," and

Fig. 39.22 Superficial Dorsal Vein Rupture Imitating Penile Fracture. (From Chang AJ, Brandes SB. Advances in diagnosis and management of genital injuries. *Urol Clin North Am.* 2013;40:427–438.)

Fig. 39.23 Penile fracture causing penile and scrotal ecchymosis and blood that has emanated from the urethral meatus, suggesting urethral injury. (From Hoag NA, Hennessey K, So A. Penile fracture with bilateral corporeal rupture and complete urethral disruption: case report and literature review. *Can Urol Assoc J.* 2011;5:E23–E26.)

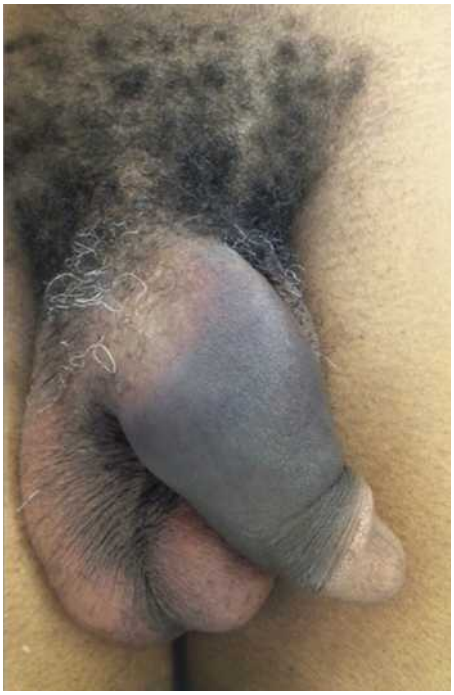


Fig. 39.24 Penile Fracture and Hematoma Causing an "Eggplant Deformity." (From Mundy AR, Andrich DE: Urethral trauma. Part II: types of injury and their management. *BJU Int.* 2011;108:630–650.)

the penis tends to deviate away from the damaged side (Fig. 39.24).[45] A defect in the tunica albuginea may be palpated along the shaft of the penis, which is known as the *Rolling sign*.

Injuries to the female genitalia can result in labial swelling or ecchymosis, but consideration should be given to performing procedural sedation or even general anesthesia to allow for adequate examination to assess the entire extent of their injuries, especially in young girls. An examination under anesthesia is suggested for female patients who are younger than 10 years old who present with perineal bleeding, hematoma, or swelling resulting from falls, assaults, or playground activities. Studies have shown that thorough examinations are underperformed in this population, resulting in missed diagnoses, which can lead to significant long-term morbidity.[14]

Differential Diagnoses

Blunt trauma to the scrotum can lead to testicular rupture, testicular dislocation, testicular fracture (parenchymal injury contained within the tunica albuginea), intraparenchymal contusions, hematoceles, or scrotal hematomas. Blunt trauma to the penis can cause penile fractures or false penile fractures, which can be difficult to distinguish based on examination alone. Urethral injury can sometimes occur as a result of blunt penile trauma and often accompanies penile fractures. Penetrating injuries to the male genitalia often cause a disruption to the tunica albuginea of the penis or scrotum, but they can lead to amputation as well.

Blunt trauma in females can cause labial and vaginal contusions, hematomas, and lacerations. Severe vulvar trauma, either from blunt or penetrating mechanisms, can lead to rectal injuries as well.[1] In children with genital burn injuries, consideration must be made for intentional abuse and other accompanying injuries.[46]

Diagnostic Testing

Due to the external nature of the genitalia, diagnoses of genital trauma can be made clinically, as opposed to other genitourinary trauma, which often require imaging studies. Scrotal injuries typically present with swelling, pain, bruising, lacerations, or skin loss. However, due to swelling, the examination can be limited, and imaging may be necessary to distinguish serious pathology in both penile and testicular injuries.

Imaging

Scrotal ultrasound is the imaging modality of choice when evaluating for testicular injury because of its accuracy, as well as its availability. The ability to evaluate flow using Doppler is extremely useful when determining viability and vulnerability of tissue. Along with testicular rupture, ultrasound can diagnose fractures, hematomas, hematoceles, and contusions. MRI can be used with accurate results but is less practical given its long acquisition time and the limited availability. For testicular rupture, the sensitivity of ultrasonography approaches 100% and should focus on testicular echotexture, as well as the contour of the testicle.[47] Irregularities of the contour or a discontinuity of the tunica albuginea suggest testicular rupture (Fig. 39.25). If there is concern for alternate pelvic injury or fracture, CT imaging can be considered.[48]

Ultrasound is also the preferred modality for penile imaging. It can diagnose penile fracture but can also be used to evaluate the blood flow in penile arteries and veins. However, unlike scrotal ultrasound, penile ultrasound is less often obtained because the diagnosis of penile fracture is usually made clinically. However, due to the extensive exploration required to evaluate for penile fracture, ultrasound is gaining more popularity because it can reveal a defect in the tunica albuginea with extruding hematoma, as well as assess blood flow in the arteries and veins (Fig. 39.26). Ultrasound is also useful to distinguish false from true penile fractures. Magnetic resonance imaging (MRI) provides similar diagnostic information but in a less timely and less cost-effective manner.[27]

RUG should be considered if there are concerns about concomitant urethral injury (Fig. 39.27).[27]

Management

Testicular and penile fractures require prompt urologic consultation and surgery. With any type of penetrating injury to the scrotum or

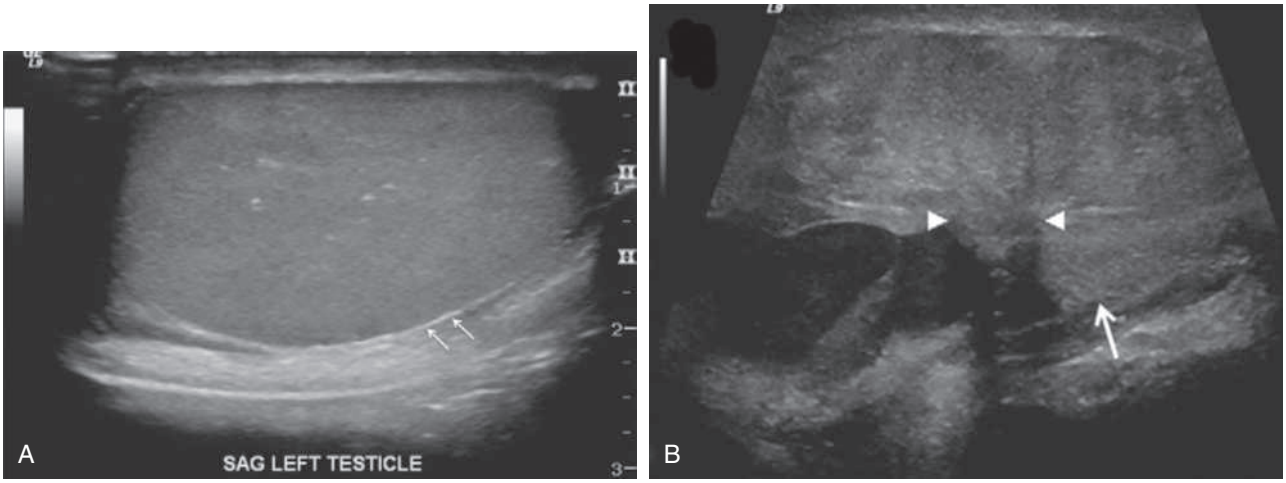


Fig. 39.25 (A) Normal testicular ultrasound. *Arrows* define the thin tunica albuginea. (B) Testicular rupture. *Arrowheads* point to a disruption in the tunica albuginea with extrusion of the seminiferous tubules. The *large arrow* indicates a hematocele. (From Avery LL, Scheinfeld MH. Imaging of male pelvic trauma. *Radiol Clin North Am.* 2012;50:1201–1217.)

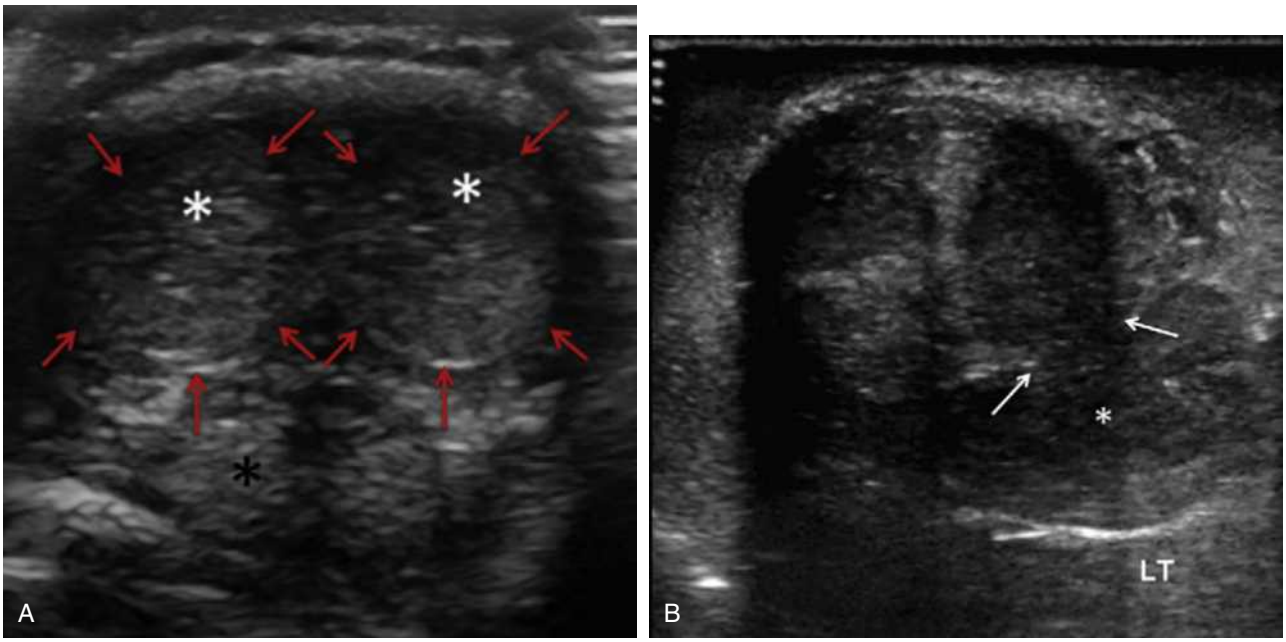


Fig. 39.26 (A) Normal penile ultrasound. *Arrows* outline the tunica albuginea, asterisks overlie the corpora cavernosa *(white asterisks)* and corpus spongiosum *(black asterisk).* (B) Disruption of the tunica albuginea *(arrows)* and extruded corpus cavernosum tissue *(asterisk)* suggest penile fracture. (From Avery LL, Scheinfeld MH. Imaging of male pelvic trauma. *Radiol Clin North Am.* 2012;50:1201–1217.)

penis, surgical exploration is typically indicated to evaluate for injuries to the urethra, corpus cavernosum, and tunica albuginea that could result in significant long-term morbidity[28] Prognosis after penile fractures is generally good, but cosmetic abnormalities can occur, even with prompt surgical repair.[45]

For testicular rupture, operative intervention focuses on débriding nonviable tissue and closing the tunica albuginea, although orchiectomy is performed if the testicle is deemed nonviable.[1] Operative management is best done immediately because testicular salvage rates drop from 90% to 45% after 72 hours.[26] Even with immediate surgery, penetrating testicular rupture results in a 35% rate of orchiectomy due to testicular necrosis or unhealthy parenchyma. If the testes or spermatic cord suffered complete amputation, microsurgery might be required at a specialized center.[13]

Typically, small scrotal hematomas respond well to rest and nonsteroidal antiinflammatory drug (NSAID) therapy. However, scrotal hematoceles and expanding or large scrotal hematomas may lead to testicular ischemia due to local pressure effects on blood vessels and thus may require surgical exploration. Reduction of testicular dislocations should be attempted by applying gentle caudad pressure following the course of the spermatic cord. After reduction of the testes, a repeat ultrasound should evaluate vascular supply. If vascular flow

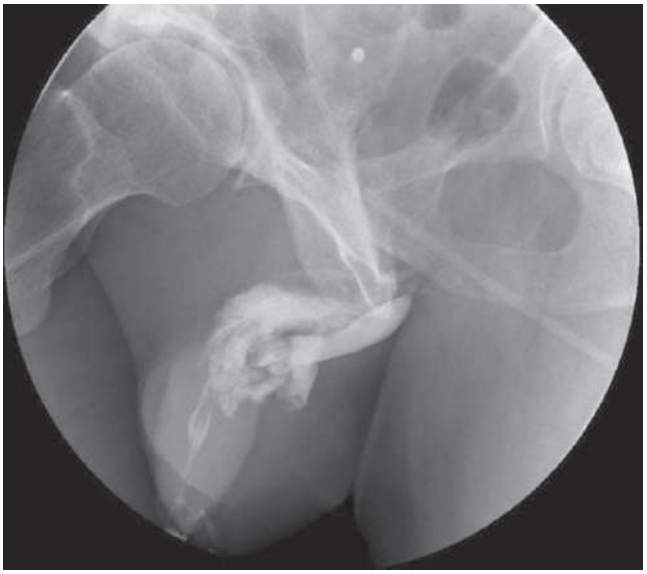


Fig. 39.27 Retrograde urethrogram revealing anterior urethral injury and contrast extravasation in the setting of a penile fracture. (From Cutinha P, Venugopal S, Salim F. Genitourinary trauma. *Surgery [Oxford].* 2013;31:362–370.)

is adequate, delayed operative fixation is usually recommended. If the reduction is unsuccessful, immediate orchiopexy is may be required.[44]

Amputations of either the testicles or penis require immediate surgical evaluation. In the interim, the amputated part should be wrapped in saline soaked gauze and then placed in a sealed bag, which can then be placed in another bag that is filled with ice.[13] The amputated part should never be placed directly on ice. Direct pressure is usually adequate to achieve hemostasis. Reimplantation is more successful within the first 24 hours and, counterintuitively, when the amputation is complete rather than partial.[49]

Injuries to the female genitalia may need the operative examination (and repair) under anesthesia for extensive lacerations involving the labia, perineum, and posterior fourchette. Again, the threshold for an examination under anesthesia should be extremely low, especially in the pediatric population.[14]

Zipper injuries should be evaluated thoroughly for underlying trauma to the penis (or scrotum when involved). If the zipper is stuck, the cloth between the interlocked dentition of the zipper can be cut. However, if the penis is caught in the buckle of the fastener, unzipping can be attempted, and mineral oil may help with removal. If this proves unsuccessful, the medial bar of the zipper can be cut with bone or wire cutters to separate the face plates. Occasionally, circumcision or an elliptical incision of the penile skin will need to be performed to achieve release.

Burns to the external genitalia are usually not seen in isolation, and the thin skin of the penis makes it quite vulnerable to full-thickness burns. Patients with significant partial- or full-thickness burns should be evaluated at a burn center as soon as possible. More than 10% of these patients will need surgical débridement, and most patients will require at least 24 hours of pain control. More commonly, burn centers are using enzymatic débridement successfully.[46]

Occasionally, patients will present with constricting rings that have created local ischemia and swelling, and attempts at removal should be made as quickly as possible to prevent tissue necrosis from ischemia. In this case, bolt cutters may be necessary, with proper analgesia and sedation if needed.

External genitalia injuries lead to complications both in cosmetics and function. Scrotal injuries leading to orchiectomy can be a source of infertility but can also alter hormonal function. Other complications include voiding dysfunction and erectile dysfunction. Many of the complications of penile injury are cosmetic in nature, including penile curvature and plaque or nodule formation superficially after penile fracture, but the likelihood is significantly decreased with surgery. Still, urethral injury can lead to stricture formation, penile abscess, permanent curvature, and painful erections, even if repair is successful.[45]

A delay in diagnosing female genital injury can lead to urinary or fecal incontinence, chronic fissures, rectovaginal fistula, or even vaginal stenosis, highlighting the importance of a thorough physical examination.[14]

Disposition

Most external genital traumatic injuries require prompt urologic consultation and management, and will require admission or transfer to a center with appropriate capabilities. Any full-thickness burns to the genitals should prompt transfer to a burn center.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 39: QUESTIONS AND ANSWERS

1. Which of the following scenarios associated with clinically significant blunt renal injuries in adult patients would the *least likely* to warrant further evaluation?
   - **a.** A sudden decelerating mechanism of injury in a patient without microhematuria
   - **b.** A sudden decelerating mechanism of injury in a patient without shock
   - **c.** Gross hematuria
   - **d.** Microscopic hematuria
   - **e.** Microscopic hematuria in a patient with shock

Answer: d. Renal injury requiring intervention is rare in the absence of gross hematuria or shock. Gross hematuria warrants careful evaluation for significant genitourinary injury, although the degree of hematuria does not necessarily correlate with the degree or grade of injury and significant genitourinary trauma can occur without hematuria. Microscopic hematuria in a blunt trauma patient without shock is not an indication for renal imaging, even if there is evidence of local trauma (e.g., costovertebral angle tenderness or localized ecchymosis). Although renal injury may uncommonly be identified on imaging for these patients, the injuries are mild and do not require intervention. Hemodynamic instability with evidence of intraperitoneal injury on abdominal examination, presence of pelvic fracture, a penetrating trauma mechanism, or presence of lower rib fractures, with or without hematuria, are indications for further investigation. In addition, imaging is advisable for patients with gross hematuria, targeted to the entire urinary tract or localized to the lower tract (bladder and urethra), depending on the mechanism and location of the trauma.

2. A 27-year-old male presents after a motor vehicle collision complaining of abdominal pain. He was the restrained driver of a car struck on the driver's side by a delivery truck. His vital signs are blood pressure 118/72, heart rate 70 beats/min, and respiratory rate 16 breaths/min. Physical examination reveals left upper quadrant abdominal tenderness without guarding or rebound tenderness. There is no blood at the urethral meatus or scrotal hematoma. A Foley catheter is placed without difficulty and drains gross blood. A radiograph of the pelvis reveals fractures of the left superior and inferior pubic rami, and a focused assessment with sonography in trauma (FAST) examination reveals free fluid in the splenorenal pouch. Which of the following diagnostic strategies is most appropriate?
   - **a.** Intravenous (IV) contrast-enhanced computed tomography (CT) of the abdomen and pelvis with delayed images of the bladder after clamping the Foley catheter to allow the IV contrast to collect in the bladder
   - **b.** IV contrast-enhanced CT of the abdomen and pelvis with delayed images of the renal collecting system
   - **c.** IV contrast-enhanced CT scan of the abdomen and pelvis and retrograde CT cystogram
   - **d.** IV contrast-enhanced CT of the abdomen and pelvis and retrograde urethrogram
   - **e.** Retrograde cystogram followed by IV pyelogram

Answer: c. This patient has clinical features concerning for several possible injuries, including a splenic laceration, renal injury, and bladder rupture. Significant urethral injury is less likely, given the examination findings and ease of Foley catheter placement. Because the patient is stable without apparent indication for laparotomy, the most appropriate diagnostic evaluation would be IV contrast-enhanced CT of the abdomen and pelvis and retrograde CT cystogram. The former will evaluate for solid organ injury and the latter for bladder rupture. It is essential that cystography not be obtained in an antegrade fashion, because such studies (e.g., injecting IV contrast material, clamping the Foley catheter, and allowing the examination to depend on antegrade filling of the bladder from renal excretion of progressively dilute contrast material) may produce incomplete and spurious findings because of inadequate distention of the bladder.

3. A 72-year-old male presents with flank and pelvis pain after he slipped and fell on an icy sidewalk. His examination reveals normal vital signs and abrasions over the left flank and left iliac crest and is otherwise unremarkable. He has grossly clear urine, but a urinalysis reveals 25 red blood cells per high-power field. Radiographs of the pelvis and hips reveal no fracture, and the patient is able to ambulate without difficulty. What is the most appropriate next step?
   - **a.** Obtain a renal ultrasound scan.
   - **b.** Obtain an IV contrast-enhanced CT of the abdomen and pelvis.
   - **c.** Perform a retrograde cystogram.
   - **d.** Perform a retrograde urethrogram.
   - **e.** Treat the patient's pain and discharge him home with outpatient urology follow-up in 1 week.

Answer: e. A significant genitourinary injury is unlikely, given the patient's history, physical examination, and urine findings. However, outpatient urology follow-up until microhematuria has cleared is advisable to be certain that it does not represent another more serious underlying (nontraumatic) condition.

4. A 35-year-old female presents after being stabbed with an ice pick during a robbery. Her examination is normal except for a 0.5-cm, hemostatic wound to the right flank at the level of the second lumbar vertebrae. Bedside ultrasonography reveals no free intra-abdominal fluid. Her urinalysis does not contain blood. What is the most appropriate next step?
   - **a.** Obtain a renal ultrasound scan.
   - **b.** Obtain an IV contrast-enhanced CT scan of the abdomen and pelvis, with additional images of the renal collecting system 10 minutes after contrast injection.
   - **c.** Perform a retrograde cystogram.
   - **d.** Perform a retrograde urethrogram.
   - **e.** Treat the patient's pain, counsel her on appropriate wound care, and discharge her home with outpatient urology follow-up in 1 week.

Answer: b. In cases of penetrating renal trauma, the presence or absence of hematuria is not a reliable predictor of upper urinary tract injury. The location of the penetrating injury in relation to the urinary tract is the most important determining factor in deciding the need for radiographic investigation. Therefore the absence of hematuria in a patient with a gunshot or stab wound in proximity to the urinary tract does not eliminate the need for IV contrast-enhanced CT as the initial diagnostic examination. Significant injuries to the kidney and ureter may occur in penetrating trauma without hematuria. Additional images obtained at 10 minutes after contrast injection are indicated to evaluate for delayed contrast extravasation and to maximize the sensitivity of the study.

5. A 25-year-old male presents after an unfortunate incident resulting in a scrotal injury and a left testicle that was traumatically amputated (the patient brings the amputated testicle with him in a towel). Which of the following would be *least* indicated?
   - **a.** Analgesics for the patient
   - **b.** Emergent urologic consultation

c. Place the amputated testicle directly on ice
d. Prepare the patient for possible operative exploration by the surgeon
e. Wrap the amputated testicle in saline soaked gauze

Answer: c. Amputations of either the testicles or penis require immediate surgical evaluation. In the interim, the amputated part should be wrapped in saline-soaked gauze, and then placed in a sealed bag, which can then be placed in another bag that is filled with ice. The amputated part should never be placed directly on ice. Direct pressure is usually adequate to achieve hemostasis.

6. A 30-year-old female presents after blunt abdominal trauma after a motor vehicle collision, and an ultrasound demonstrates free fluid. You suspect a bladder rupture. A true statement about this entity includes which of the following:
a. A bladder contusion may be successfully managed with Foley catheterization drainage.
b. Extraperitoneal bladder injuries are typically managed with surgical intervention.
c. It is less important to distinguish an intraperitoneal from an extraperitoneal bladder rupture (EBR) because the management options are essentially the same.
d. Most patients with an intraperitoneal bladder rupture (IBR) will resolve with Foley catheter drainage.
e. Most penetrating bladder injuries will resolve with Foley catheter drainage.

Answer: a. The distinction between EBR and IBR is important because the management differs. Contusions and extraperitoneal injuries due to blunt trauma are typically managed conservatively with Foley catheterization, unless they are complicated by other intra-abdominal injuries, bladder neck injuries, or bone fragments in the bladder wall or if open reduction is performed on an associated pelvic fracture. In contrast, given the extremely low likelihood of IBR and penetrating injuries healing with conservative therapy, almost all patients with these types of injuries are taken to the operating room for exploration and repair. Without surgery, there is an extremely high likelihood of complications, which include infections and fistula formation.

40

Peripheral Vascular Trauma

Ali S. Raja

KEY CONCEPTS

- The overall condition of the patient with an acute peripheral vascular injury determines the extent of emergency department (ED) evaluation and stabilization. Critically injured patients may require immediate surgery, which should not be delayed for confirmatory studies of obvious vascular injury.
- Arterial injury may be readily apparent or clinically occult. In patients with high-energy blunt mechanisms, computed tomography angiography (CTA) should be the initial diagnostic modality of choice. In patients with lower-energy mechanisms, serial physical examinations may be performed instead.
- Symptoms of arterial injury may be delayed by hours to months after the initial injury. Late onset of symptoms suggests delayed thrombosis, pseudoaneurysm or arteriovenous fistula (AVF) formation, compartment syndrome, or intermittent claudication, resulting from stenosis or reliance on small-caliber collateral vessels for arterial perfusion.
- Compartment syndrome frequently develops in extremities with arterial injury, particularly injuries of the lower leg, and fasciotomy is often required.
- Many vascular injuries are amenable to endovascular treatment with self-expanding stents. This results in fewer complications, lower cost, and earlier discharge from the hospital.

FOUNDATIONS

Background and Importance

Injury to the major peripheral arteries or veins may not always be life threatening, but it invariably poses a threat to the viability of the affected extremity. Historically, due to the rapidity of exsanguination, injury to major vessels was often fatal in the field, and most patients who survived to hospital arrival had relatively minor vascular injuries. However, with the advent of modern emergency medical service (EMS) systems with advanced extrication methods and rapid transport, more patients with major vascular injuries are reaching the emergency department (ED) alive. In addition, the incidence of both penetrating injuries from interpersonal violence and blunt injuries from motor vehicle–related trauma has increased dramatically over the past 50 years. Consequently, emergency clinicians are frequently confronted with critically ill patients harboring overt (or occult) peripheral vascular injuries.

Management of these vascular injuries has also evolved, with advances in diagnostic methods and surgical techniques. Treatment of vascular injuries before and during World War II resulted in limb amputation rates of 50% to 75%. Advances during the Korean and Vietnam wars reduced amputation rates to 5% to 15%, which approach the current rates of amputation for civilian injuries.

Tremendous progress has also been achieved in diagnostic and therapeutic techniques for dealing with peripheral vascular injuries, and several noninvasive diagnostic modalities have emerged as accurate alternatives to surgical exploration and angiography. These techniques are readily used in the ED setting, and the goal of timely detection and repair of serious vascular injuries is achievable in the majority of cases.

Peripheral vascular injuries are divided almost equally between blunt and penetrating mechanisms.[1] Major venous injuries are present in up to 50% of gunshot wound cases, and more than 80% of these have associated arterial injuries. In addition, due to the increased use of percutaneous endovascular diagnostic and therapeutic procedures, the incidence of iatrogenic vascular injuries has increased and accounts for up to one-third of all cases in some series.[2]

Anatomy and Physiology

The major vessels and their relevant anatomy are described in the following sections (Figs. 40.1 and 40.2).

Upper Extremity

The right subclavian artery arises from the brachiocephalic artery, and the left arises from the arch of the aorta. From their origin, they course posterior and inferior to the clavicles to the outer margins of the first ribs, where they become the axillary artery and vein. The left subclavian artery rises higher than the right and extends into the root of the neck.

The axillary artery courses from the lateral border of the first rib to the inferior border of the teres major muscle, where it becomes the brachial artery. The axillary vein runs medial to the artery. Due to the extensive anastomotic arterial connections around the shoulder joint, up to half of patients with axillary artery injuries will have palpable pulses as a result of collateral circulation. Because of the close proximity of the brachial plexus and the axillary vessels, significant denervation of the upper extremity can occur.

The brachial artery begins at the lower border of the teres major muscle and divides into the radial and ulnar arteries at the level of the proximal aspect of the radial head. The median and ulnar nerves and the basilic vein are in close proximity to the brachial artery. The profunda brachii artery is a major branch that arises slightly after the origin of the brachial artery and often contributes adequate collateral flow if the brachial artery is injured distal to this branch point.

The radial artery originates in the cubital fossa and runs superficially to the distal end of the radius, where it ultimately joins the deep branch of the ulnar artery to form the deep palmar arch of the hand. The ulnar artery begins in the cubital fossa and runs with the ulnar nerve anterior to the flexor retinaculum, at which point it joins the radial artery to form the superficial palmar arch of the hand.

Lower Extremity

The external iliac vessels become the common femoral vessels at the inguinal ligament. After bifurcation of the profunda femoris artery in the femoral triangle, the femoral artery continues as the superficial

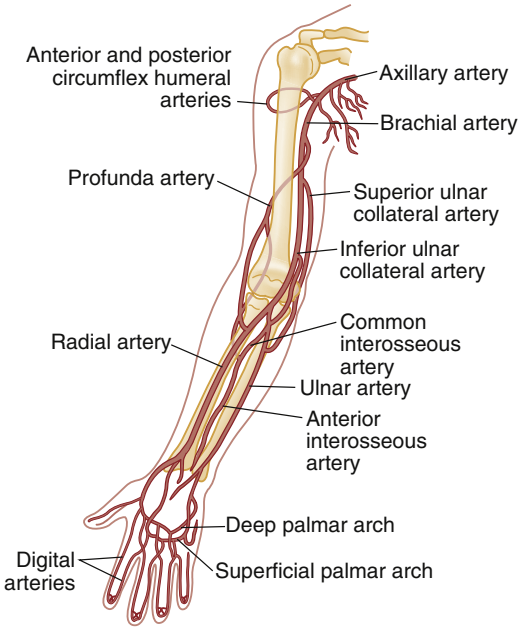

Fig. 40.1 Major Arteries of the Upper Limb. (From Snell R, Smith M, eds. *Clinical anatomy for emergency medicine*. St Louis: Mosby; 1993.)

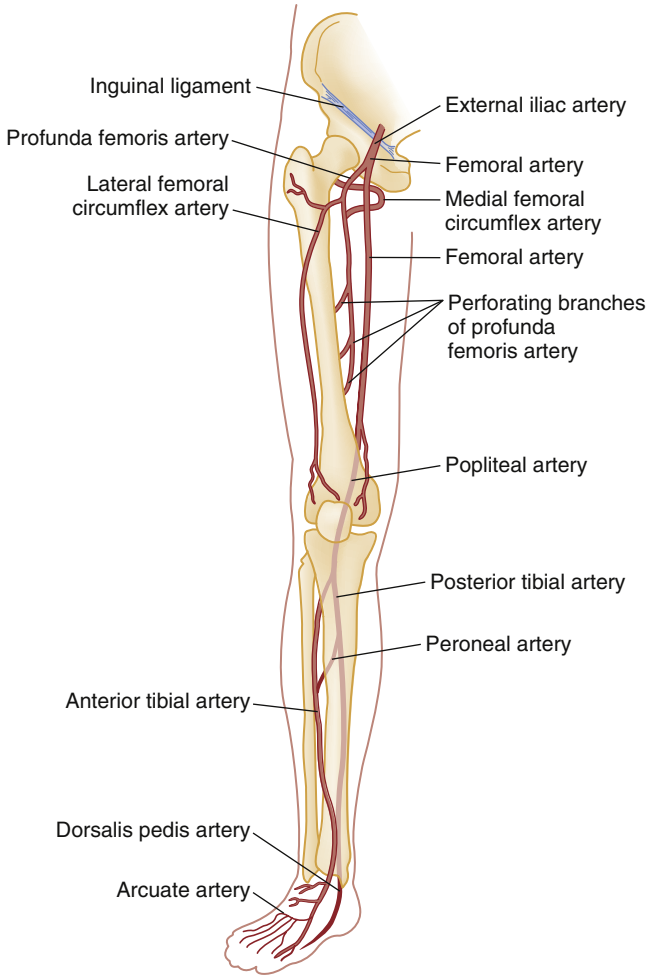

Fig. 40.2 Major Arteries of the Lower Limb. (From Snell R, Smith M, eds. *Clinical anatomy for emergency medicine*. St Louis: Mosby; 1993.)

femoral artery almost vertically to the adductor tubercle of the femur and enters the popliteal fossa as the popliteal artery. Extensive proximal collaterals are present around the hip joint, including the gluteal, obturator, and pudendal branches of the iliac artery.

The popliteal artery gives off the genicular branches in the popliteal fossa and then divides into the anterior and posterior tibial arteries at the lower border of the popliteus muscle. The peroneal artery arises from the posterior tibial artery slightly after its origin. The anterior and posterior tibial arteries and the peroneal artery form the trifurcation of the popliteal artery, and each run with a corresponding vein and nerve in different compartments of the leg.

The popliteal artery divides into three branches—the anterior and posterior tibial and the peroneal arteries—at the inferior margin of the popliteal fossa. Injuries below the trifurcation at the knee may require repair if classic "hard" findings of arterial injury are apparent in the foot or if two of the three arteries are occluded. The most common blunt trauma cause of popliteal artery injury is a posterior knee dislocation in which bony elements directly lacerate or cause thrombosis of the artery. Anterior knee dislocations may cause excessive stretch on the popliteal vessels resulting in arterial thrombosis, but this injury is relatively rare. Up to one-third of knee dislocations result in popliteal artery injury. Twenty-five percent of cases have an associated injury to the peroneal and posterior tibial nerves.

Pathophysiology

Blunt and penetrating types of trauma result in similar spectra of vascular injuries, although their mechanisms of injury differ. Although blunt vascular injuries are less common than penetrating injuries, they are often more severe and more commonly result in amputation because of associated injuries to nerves, bone, tendons, and soft tissue. Certain mechanisms of injury, such as animal bites that crush and lacerate vessels, can involve both penetrating and blunt mechanisms (See Chapter 52).

Penetrating Trauma

Gunshot wounds can cause direct arterial lacerations or transections, in addition to concussive injuries distal to the track of the bullet. These latter injuries tend to tear into the intima of an artery, with subsequent thromboses that may not become apparent for hours to months after the injury. Bullets may ricochet off bone, making predicting trajectories less accurate than with stab wounds.

Stab wounds cause vascular injuries by completely or partially transecting vessels. Partial laceration of an artery may produce few symptoms of arterial insufficiency on initial evaluation but result in delayed complications. The vascular structures at risk can be predicted more reliably with stab wounds than with gunshot wounds by taking into consideration the anatomic location, causative implement, depth, and direction of the wound.

Shotgun wounds are less common than gunshot or stab wounds, but they can cause injuries varying from minor soft tissue wounds to massive destruction of soft tissue and bone, depending primarily on the range from which the shotgun was fired. The presence of multiple missiles ranging from 9 or 10 (buckshot) to dozens (birdshot) also complicates the evaluation of these injuries because of the many potential sites of potential vascular injury. In addition, close-range shotgun wounds (<3 meters) can cause significant blunt trauma to blood vessels, as well as a higher rate of bone and nerve injury than might occur with gunshot wounds. Migration of pellets or bullets proximally through the venous system to the heart, or migration through an artery with subsequent distal occlusion, has been reported frequently as a delayed complication.[3]

Blunt Trauma

Blunt injury involves either avulsion forces that can stretch vessels beyond their capacities or direct crushing injuries that disrupt vessel walls. In addition, fracture fragments resulting from blunt extremity trauma can lacerate or entrap vessels. These vascular injuries can range from small intimal tears to complete avulsions of arteries and nerves. Open avulsion injury of an extremity is particularly severe because the skin, which is very pliable, is the final structure to tear. Once torn, it is inevitable that vessels and nerves will tear as well. Vascular injuries should also be suspected in patients with massive soft tissue avulsions or crush injuries, displaced long bone fractures, electrical or lightning injuries, and severe burns. In addition, compartment syndrome from trauma or prolonged immobilization as a result of stroke, coma, or drug overdose is another cause. Bites inflicted by large animals, such as dogs, are particularly prone to arterial injury and wound complications.[4] Collateral circulation may continue to perfuse the limb, but injuries that occur proximal to the collateral branch point—or that involve both the main trunk and collateral branches—will preclude adequate flow.

Distal ischemia results from the inability of tissues to continue aerobic metabolism. Eventually, anaerobic metabolism consumes all substrate, thereby resulting in the accumulation of lactic acid. As ischemia progresses, cellular integrity is compromised, and irreversible cell death occurs. A vicious cycle of tissue edema and further impairment of the blood supply occurs. When no specific measures are taken to cool the involved extremity, the limb essentially undergoes "warm ischemia" at ambient temperature. After 6 hours of complete warm ischemia, 10% of patients will have irreversible damage; by 12 hours, 90% will have irreversible damage. Artificially cooling the limb to near-freezing temperature ("cold ischemia") will reduce the metabolic demands and greatly prolong the tissue's tolerance of ischemia to 24 hours or more.

Vascular Injuries

Two main types of vascular injury can result from trauma: *occlusive injuries* (transections, thromboses, and reversible spasm), in which all perfusion distal to the occlusion is lost, and *nonocclusive injuries* (intimal flaps, dissections, arteriovenous fistulas [AVFs], and pseudoaneurysms), which include mechanical defects to vessel walls that may or may not lead to decreased distal blood flow.

Complete occlusive injury

Transection. The most common vascular injury is complete transection, in which distal flow is effectively eliminated. Cleanly transected arteries will often retract and undergo spasm to minimize blood loss. With longitudinal arterial lacerations and venous injuries, blood loss cannot be minimized by this physiologic response and therefore tends to result in greater blood loss. Pulsatile bleeding may quickly lead to exsanguinating hemorrhage and shock.

Thrombosis. Intraluminal thrombosis (Fig. 40.3) may occur in an injured artery acutely (within 24 hours) or may be delayed for many months. Acute thrombosis is initiated by stasis resulting from compression of the artery or from a disruption in the intima of an artery that becomes a nidus for thrombus formation. As the thrombus propagates, complete occlusion of the vessel can occur. Delayed thrombosis can occur months to years after injury if the injured vessel heals with stricture formation, resulting in decreased distal flow, followed by stasis and clot formation.

Reversible arterial spasm. The precise cause and incidence of significant reversible arterial spasm after trauma are unknown. In the case of arterial transection, arterial spasm is beneficial and limits hemorrhage. However, in other cases, the segmental arterial spasm occurs at some distance from the site of traumatic injury and can produce severe distal ischemia. Arterial spasm is particularly common in children. In many series, segmental arterial spasm is the most common arteriographic finding (Fig. 40.4). However, symptoms of ischemia should not be assumed to be a result of arterial spasm; that diagnosis is based on arteriographic results only.

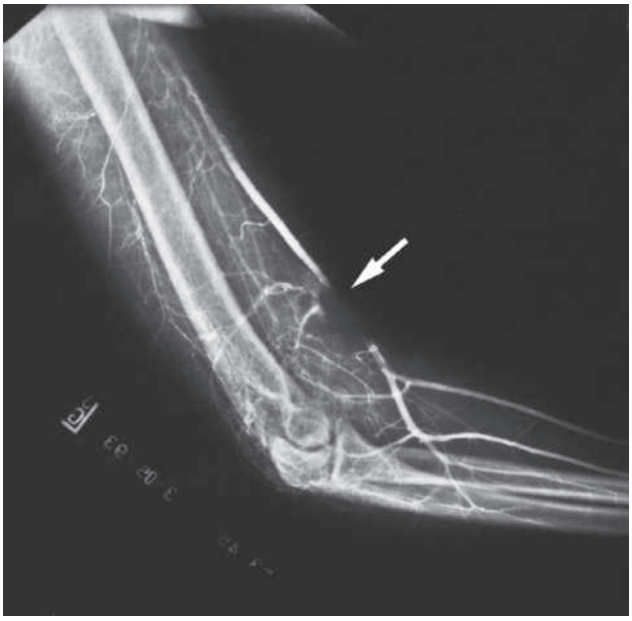

Fig. 40.3 Complete thrombosis *(arrow)* of the distal brachial artery after reduction of a posterior elbow dislocation. (Courtesy D. Demetreades, MD.)

Nonocclusive injuries

Intimal flap. An intimal flap occurs when there is a break in the vessel intima, generally from excessive stretch or concussive forces. Although flow is not altered by small flaps and the associated soft tissue wounds often appear benign initially, these intimal flaps may become a nidus for thrombosis that can occur hours to months after the initial injury.

Pseudoaneurysm. A true aneurysm contains all three layers of the vessel wall (intima, media, and adventitia) and is rarely caused by trauma. A pseudoaneurysm is formed following a tear in a vessel wherein the hemorrhage is contained by surrounding fascia and the resulting hematoma is gradually encased by a capsule of fibrous tissue, analogous in consistency to the adventitia of a normal vessel (Fig. 40.5). Because it is relatively thin walled, rupture of a pseudoaneurysm is a distinct possibility. In addition, because its diameter inevitably expands under arterial pressure over days to months, compression of adjacent tissue may result in neuropathy, venous obstruction with resultant peripheral edema and venous thrombosis, and even erosion into adjacent bone. The cavity of a pseudoaneurysm is in direct communication with the lumen of the vessel, so embolization of mural clots may produce distal arterial occlusion. Pseudoaneurysms may be diagnosed months to years after an injury when a patient manifests symptoms of compression neuropathy or peripheral arterial embolism or for investigation of a soft tissue "tumor" that represents the growing aneurysm.

Arteriovenous fistula. An AVF is formed when both an artery and an adjacent vein are injured. Higher-pressure arterial flow is directed into the lower-pressure vein, thereby diverting the blood supply to distal tissues and engorging the distal veins. Because the aperture of the fistula is often relatively narrow and thus results in turbulent flow, a bruit and palpable thrill are common bedside diagnostic findings. Symptoms are primarily those of distal ischemia, but rarely,

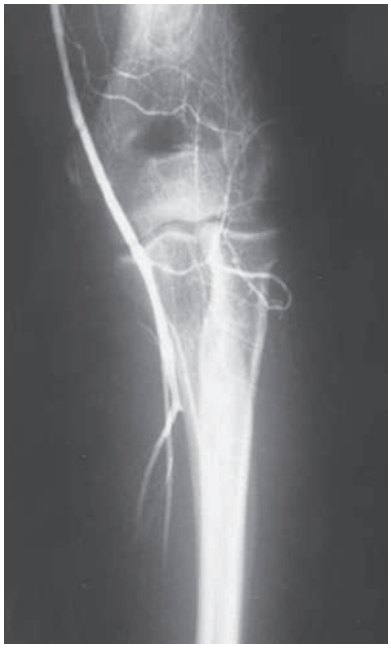

Fig. 40.4 Acute Arterial Spam of the Brachial Artery. (From Arquilla B, Gupta R, Gernshiemer J, et al: Acute arterial spasm in an extremity caused by inadvertent intra-arterial injection successfully treated in the emergency department. *J Emerg Med* 2000;19[2]:139–143.)

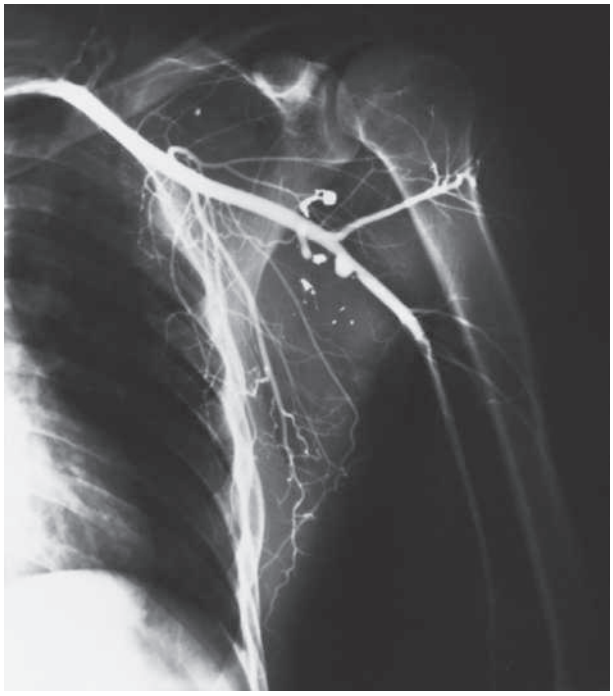

Fig. 40.5 Multiple small pseudoaneurysms of the axillary artery after penetrating injury. (Courtesy D. Demetreades, MD.)

high-output congestive heart failure may occur when large central vessels are involved. Symptoms are often delayed for months because it takes time for the fistula to mature.

Compartment Syndrome

Compartment syndrome is most common after crush injury or a long bone fracture but may also be seen after reperfusion of an ischemic limb. Initially, blood flow is diminished, and the injury is considered nonocclusive. Progressive edema elevates tissue pressure above capillary pressure, thus ending arterial perfusion and initiating a cascade of events that results in compartment syndrome. The risk for this complication is increased when ischemia time is prolonged; in the presence of combined arterial and venous injury; after ligation or repair of a major artery or vein; or in the presence of significant soft tissue injury, frequently concomitant with a long bone fracture. After restoration of arterial flow to a previously ischemic limb, a cascade of reperfusion injury results from release of oxygen free radicals, lipid peroxidation, and influx of intracellular calcium. These mediators give rise to progressive cellular damage, edema, and necrosis, thereby propagating the vicious cycle that increases compartment pressure. Consequently, frequent reexamination of the limb is indicated to assess compartment pressure after arterial repair or in the high-risk circumstances listed earlier. Compartment syndrome is discussed in more detail in Chapter 41.

CLINICAL FEATURES

Detection and treatment of vascular injuries take place within the context of the overall resuscitation of the patient according to established principles of trauma care.[5] If the source of bleeding is readily identifiable, it is compressed with digital pressure. Although control of active bleeding is being achieved in this manner, detection and treatment of other life-threatening injuries proceed concurrently. Peripheral vascular injury can occur coincident with other life-threatening trauma, which may take higher priority in resuscitation. In other cases, peripheral vascular injury may be the most serious or only injury, and evaluation and management of this type of injury can proceed directly. Many patients have no evidence of injury but are considered at risk for vascular injury because of penetrating wounds that traverse the course of major neurovascular bundles or because they have sustained high-risk injuries, such as posterior knee dislocation. In addition, patients without acute trauma but with symptoms of intermittent claudication or with unexplained peripheral embolization and a history of previous trauma to the extremity should be suspected of having occult arterial injury.

Peripheral vascular injury can be divided into three categories by physical examination: hard findings, soft findings, and asymptomatic high-risk wounds based on the mechanism of injury.

Hard Findings of Vascular Injury

Many patients have classic "hard" findings of arterial injury, listed in Table 40.1. The incidence of arterial injury in patients with any hard finding is consistently greater than 90%, and the presence of these findings requires further investigation by emergency angiography/computed tomography angiography (CTA) or, more commonly, immediate surgical intervention, depending on the duration of warm ischemia and the overall status of the patient.[6]

Soft Findings of Vascular Injury

An additional group of patients have "soft findings" of vascular injury (see Table 40.1). Up to 35% of patients with "soft" findings of vascular injury have positive angiographic studies, although only a small proportion of these injuries require emergency repair.

The significance of prolonged capillary refill (>2 seconds) is controversial; some experts find it to be a reliable sign of vascular injury (when combined with a pulse deficit) and consider delayed capillary refill to be a valid "soft sign" of vascular injury. However, capillary refill is age, gender, and temperature dependent. Of note, an arbitrary 2 second cutoff may result in a significant false-positive rate, especially in older patients.[7] Delayed capillary refill by itself is an unreliable predictor of arterial injury, but the presence of delayed capillary refill in

TABLE 40.1 Clinical Features of Vascular Injury

Hard Findings	Soft Findings
Pulsatile hemorrhage	History of significant hemorrhage at scene
Expanding hematoma	Nonexpanding hematoma
Absent distal pulses	Diminished pulse or ABI of injured extremity
Palpable thrill	Extremity peripheral nerve deficit
Audible bruit	Bony injury or proximate penetrating wound

ABI, Ankle-brachial index.

conjunction with a proximate penetrating injury or the presence of one or more soft signs warrants repeated hourly examinations.

Isolated penetrating injury to a peripheral nerve is commonly associated with vascular injury because of the close proximity of these structures within the neurovascular bundles. Vascular injury occurs in up to half of cases of penetrating peripheral nerve injury and vice versa.[8] It can be difficult to determine whether pain, paresthesias, or paralysis are caused by a primary nerve injury, an associated vascular injury causing compression of the nerve, or compartment syndrome. In general, primary nerve injury occurs immediately at the time of injury, whereas vascular neuropathy occurs over minutes to hours after the injury.

Asymptomatic High-Risk Wounds

Major neurovascular bundles include large limb arteries proximal to critical branch points (Table 40.2). Proximity of a penetrating wound to a neurovascular bundle is defined variably as within 1 cm, 1 inch, or 5 cm. This concept is useful in evaluating patients with penetrating injury but without evidence of vascular injury. We consider penetrating wounds that occur within 1 cm of a major neurovascular bundle or whose presumed trajectory has crossed such a bundle to be sufficiently likely to produce an occult vascular injury that they warrant frequent (every 30 to 60 minutes) evaluation for the first 4 to 6 hours to ensure that a developing vascular injury is not missed within the warm ischemia window. However, routine imaging is not indicated based on proximity alone.

In addition, a small minority of patients with high-risk injuries, such as bites from large dogs or other animals, displaced fractures, crush injuries, or major joint dislocations (especially knee dislocation), may have occult vascular injuries that are not initially detected on physical examination. The risk of missing such injuries is that the traditional 6-hour window of warm ischemia time will be exceeded, or the patient will experience delayed complications resulting in limb loss. Patients with intimal flaps may be completely asymptomatic initially but can subsequently develop arterial thrombosis. Similarly, pseudoaneurysms progressively enlarge to produce compression of adjacent structures but may be very small and undetectable on initial physical examination. Consequently, these patients also should undergo serial physical examinations.

Due to their noncompressible location, blunt subclavian injuries can be particularly challenging. These are often associated with clavicular fracture or dislocation. Isolated first rib fractures are rarely combined with vascular injury unless posterior displacement occurs. Shear injury of the subclavian artery can occur as a result of a loose shoulder restraint during a motor vehicle collision (MVC). Counterintuitively, penetrating subclavian vein injuries are even more lethal than those to the artery because, in addition to massive blood loss, there is a relatively high risk of massive air embolism, which is frequently fatal.

TABLE 40.2 Major Neurovascular Bundles

Major Artery	Proximate Plexus/Nerve
Axillary artery	Brachial plexus
Brachial artery	Median nerve
Radial artery	Median and radial nerves
Ulnar artery	Ulnar nerve
Femoral artery	Femoral nerve
Popliteal artery	Tibial nerve

Popliteal artery injuries can often be a result of knee dislocations, most of which will have spontaneously reduced. Patients showing complete ligamentous disruption of the knee on physical examination should be suspected of having a spontaneously reduced knee dislocation leaving little evidence of the original trauma, particularly in obtunded patients. Hemarthrosis may also be absent if the joint capsule is torn because blood can track into the fascial planes of the leg.

History

In patients who achieve and maintain hemodynamic stability, a more comprehensive history can be obtained. Important historical points to note include the exact time and mechanism of the injury. The time of injury is important because of the significant morbidity that results from prolonged warm ischemia time. The mechanism is of clinical and often forensic importance in that injuries are frequently inflicted during a criminal act or in the workplace. Various mechanisms of injury may mandate special reporting that can alter the patient's ultimate disposition. Certain types of injuries, such as crush or bite wounds, are particularly prone to complications. The occupation, avocation, and hand dominance of the patient are pertinent to determine the best approach to achieve maximum functionality. Comorbid medical conditions are also important. Patients who are immunocompromised because of diabetes mellitus, acquired immunodeficiency syndrome (AIDS), asplenia, cancer, or chronic steroid use are at increased risk for infection and impaired wound healing. Patients with preexisting vascular insufficiency have more tenuous perfusion, are more susceptible to ischemia from elevated compartment pressure, and have a higher incidence of complications. As with most aspects of trauma care, patients whose sensorium is altered by head injury or intoxication, patients with spinal cord injury who cannot perceive pain, and those with significant painful distracting injuries will not reliably be able to report pain or paresthesias suggesting vascular insufficiency, so extra vigilance should be exercised in these cases.

Evidence of abdominal injury raises concern for injury to the iliac vessels, and virtually all iliac artery and vein injuries have associated trauma to the small or large intestine, bladder, solid viscera, or bony pelvis. The common and external iliac arteries are injured with equal frequency and more often than the internal iliac vessels. Approximately 80% of iliac vessel injuries are caused by penetrating trauma, and the remainder are primarily associated with pelvic fractures. Trauma to the iliac veins is responsible for massive bleeding in displaced pelvic fractures and often requires angiographic embolization.

Physical Examination

Despite advances in technology, meticulous physical examination in combination with comparison of blood pressures in the affected and unaffected extremities remains the mainstay of diagnosis of vascular injury. Physical examination is directed at discovering evidence of local wound complications and distal ischemia suggestive of vascular injury. Pulses in the affected extremity are palpated to compare strength and

quality between the injured limb and its uninjured counterpart. Isolated detection of a diminished pulse distal to the site of injury merits further evaluation rather than immediate surgery because palpation of pulses is a relatively inaccurate means of predicting arterial injury. False-positive findings of a pulse deficit may occur because of shock, in which all pulses are diminished; congenital absence of a pulse in one extremity; preexisting vascular disease; operator technique; or arterial spasm or compression. False-negative findings can occur with transmission of the pulse through a "soft clot," past an intimal flap, or through collateral circulation. Distal pulses can persist despite significant arterial injury. Compression of an artery by casts, splints, or dressings may produce a pulseless extremity, and these should be removed if there is evidence of ischemia. Symptoms of limb ischemia may be apparent with absent radial and brachial pulses. However, pulses are only rarely completely absent, because collateral flow from the thyrocervical trunk may provide sufficient perfusion to avoid the symptoms and signs of ischemia. Finally, although the pulse may be absent, the extremity may be well perfused by collateral arterial supply, thus making immediate repair of the arterial injury less essential. Comparative palpation of the injured and unaffected limbs can also detect differences in skin temperature that may suggest hypoperfusion. Testing two-point discrimination on the injured and unaffected limbs may help to detect sensory deficits. Auscultation over the site of injury may reveal a bruit, which is present in more than half of patients with AVF. Repeated examination of any hematoma adjacent to a wound is indicated during the first 24 hours to determine whether it is expanding or pulsatile.

Neurologic deficits in the upper extremity occur in more than half of patients. The most severe of these injuries is damage to the brachial plexus, which occurs in nearly half of patients with blunt injury.

DIFFERENTIAL DIAGNOSES

In many cases, peripheral vascular injury will be readily apparent by external bleeding or hematoma formation. In other cases, vascular injury is suspected by the location or nature of the trauma the patient sustained. In all patients, vascular injury is a cue to search for associated injuries, such as bony injuries, injuries to proximate nerves, and soft tissue injuries due to either direct trauma or compression secondary to compartment syndrome. Conversely, some cases of vascular injury may not be obvious on initial examination and should be sought when evaluating patients with potential deep vein thromboses, crush injuries, and other presentations of acute extremity pain.

DIAGNOSTIC TESTING

Plain Radiography

Plain radiographs of the affected extremity are indicated to detect fractures, joint penetration, and foreign bodies. With gunshot wounds, the sum of the number of intact bullets seen on radiographs and the number of entrance and exit wounds in the body should be an even number. Rarely, bullets or shotgun pellets can deflect off bone and travel sufficiently far as to not be visible on the radiograph. Bullets or pellets can migrate distally and produce vascular occlusion or migrate proximally through the venous system to the heart. When there is concern for a missing projectile, broaden the radiographic search or consider a "through and through" penetrating injury in which the object passes through the extremity and exits the body.

Pulse Oximetry and Near-Infrared Spectroscopy

Pulse oximetry has been found to be a relatively insensitive means of identifying limb ischemia after trauma and should not be considered a discriminatory or useful test for vascular injury. However, measurement of tissue oxygenation by near-infrared spectroscopy (NIRS) to quantify muscle oxyhemoglobin has shown potential as a possible noninvasive and simple means of detecting diminished vascular perfusion; however, it is not yet used in common practice for this indication.[9]

Handheld Doppler

Absent or diminished pulses in an injured extremity should be evaluated using a handheld Doppler. Arterial injury is suggested by absent Doppler signal or by a change in the usual triphasic quality of the Doppler pulse to a biphasic or monophasic waveform, because the pulse is "damped" by partial occlusion.

Arterial Pressure Index and Ankle-Brachial Index

Measuring systolic blood pressure in the injured versus the uninjured extremity (arterial pressure index [API]) or measuring it in an injured leg at the ankle compared with brachial artery pressure (ankle-brachial index [ABI]) is an accurate means of screening for arterial injury. Systolic pressure is measured by inflating a standard blood pressure cuff proximal to the injury and recording handheld Doppler systolic pressure distal to the injury. The process is repeated on the uninjured limb (or the arm, if calculating an ABI), and a ratio of injured to uninjured systolic pressure is calculated. In general, a ratio less than 0.90 is considered abnormal and indicates need for further investigation. Clinical studies of API/ABI have shown promising results. In several studies, an API/ABI less than 0.90 yielded a sensitivity and specificity for the detection of vascular injury of more than 95%, with correspondingly high positive and negative predictive values.[10]

Patients with suspected vascular injury who have an API/ABI of 0.90 to 0.99 merit observation for 12 to 24 hours for repeated physical examination and API measurements to detect potentially evolving injury. Patients with normal physical examination findings and a completely normal (greater than or equal to 1.0) API/ABI can be safely discharged from the ED, provided that there are no other associated injuries requiring admission.

However, reliance on the API/ABI to screen for arterial injury is not always possible. Comparisons cannot be made when both limbs are injured or when severe soft tissue disruption precludes placement of a blood pressure tourniquet. Certain arteries (e.g., the profunda femoris, profunda brachii, and peroneal arteries) normally do not produce palpable pulses, and so API/ABI is of limited usefulness if injuries to these vessels are suspected. Shotgun wounds often are associated with normal API/ABI measurements despite multiple small arterial wounds; catheter-based angiography is the preferred diagnostic modality in this group.

Despite the limitations previously noted, API/ABI has proven effective in screening patients with proximity wounds in the ED setting. The vast majority of injuries missed by API/ABI heal spontaneously. Those that do not heal generally present within 3 months with signs of arterial injury and can be repaired electively.

Ultrasound

Bedside B-mode (real-time) ultrasound, particularly with color flow Doppler (see later), can reliably identify loss of arterial pulsation in major vessels (see also Chapter e3). However, B-mode ultrasound cannot visualize certain anatomic areas accurately (e.g., subclavian and iliac vessels) because of inadequate tissue windows, and it is unreliable in detecting a fresh, relatively nonechogenic thrombosis or hematoma. As blood liquefies within a hematoma, it becomes echolucent and more readily distinguishable from surrounding tissues.

Doppler ultrasound interprets sound moving toward or away from the transducer as flow. Venous flow is heard as a low-pitched hum, whereas arterial flow has a higher-pitched, triphasic quality. The

combination of B-mode and Doppler ultrasound is called *duplex ultrasound* and has enhanced accuracy in examining blood vessels. Duplex scans showing a focal increase in peak systolic velocity suggest partial obstruction of the vessel. However, duplex scanning is slightly less accurate for detecting injuries that do not decrease flow, such as small pseudoaneurysms, AVFs, and intimal flaps. In addition, it is technically limited in examining certain anatomic areas, such as the profunda femoris and profunda brachii arteries and the iliac and subclavian vessels. Duplex ultrasound findings may be subtle, and as with other applications of ultrasound, its accuracy is operator dependent. Despite these limitations, the sensitivity of duplex ultrasound in comparison with standard angiography ranges from 83% to 100%, with a specificity of 99% to 100% and an accuracy of 96% to 100%.[11]

Color flow Doppler converts Doppler echoes into quantitated visual signals. Flow toward the transducer is seen as red, and flow away from the transducer is seen as blue. The intensity of the color (the number of pixels on the screen) is proportional to flow through the vessel. Small prospective studies have indicated a high rate of accuracy in detecting arterial injury with color flow Doppler. Absence of flow is readily apparent, but subtle injuries, such as intimal flaps and small pseudoaneurysms, can be more difficult to identify than with CTA. The overall sensitivity of color flow Doppler in detecting arterial injury is 50% to 90%, with a specificity of 95% to 99%. The sensitivity for detecting injuries requiring surgical repair is greater than 90% (Figs. 40.6 and 40.7).[11]

Computed Tomography and Magnetic Resonance Imaging

With a few important exceptions, CTA has largely replaced catheter-based angiography for the detection of peripheral vascular injury in most trauma centers. Multidetector helical computed tomography (CT) scanners have proven very accurate for diagnosis of peripheral vascular injury in multiple series, with a sensitivity of 93% to 100% and specificity of 87% to 100% compared with catheter-based angiography.[12–14] The advantages of CTA over catheter-based angiography are that it is noninvasive, readily available, and less costly and provides information on other injuries in the region being studied. However, there are several

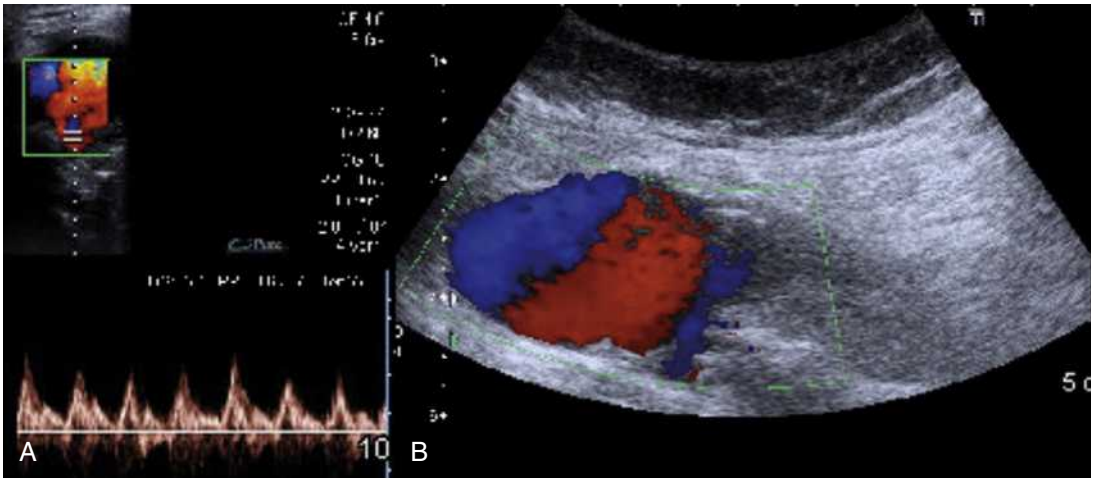

Fig. 40.6 Sonography of popliteal fossa with systolic bruit (A) and longitudinal color Doppler ultrasound (B) showing arterial blood. (From Tejero-Garcia S, Lirola Criado JF, Ast MP, et al: Popliteal pseudoaneurysm after unicompartmental knee replacement: a case report. *Knee.* 2014;21[2]:597–599.)

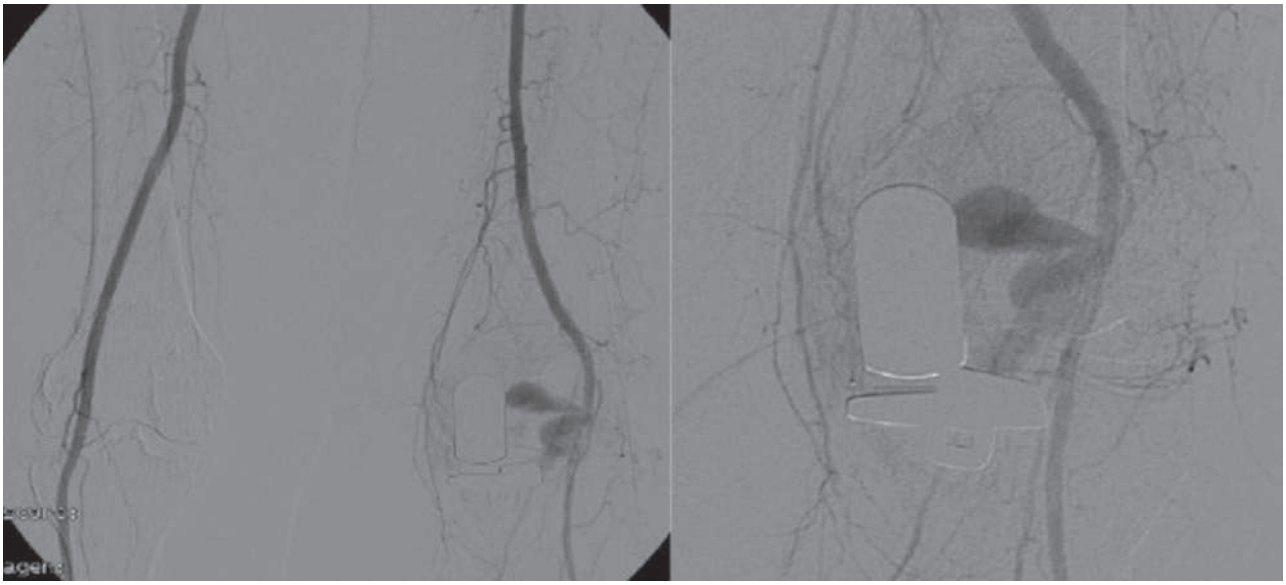

Fig. 40.7 Digital subtraction angiography of both popliteal arteries shows pseudoaneurysm on the *left (zoomed image on the right).* (From Tejero-Garcia S, Lirola Criado JF, Ast MP, et al: Popliteal pseudoaneurysm after unicompartmental knee replacement: a case report. *Knee.* 2014;21[2]:597–599.)

limitations to the use of CTA. Metallic artifact from bullets, orthopedic hardware, or other penetrating objects may obscure visualization of parts of a vessel, although with image reconstruction techniques, this problem can be largely overcome. Venous injuries may be missed depending on the phase of the contrast. The rapid image acquisition of current CT scanners makes timing of the contrast bolus more critical, and out-of-phase images may miss arterial injury. In practical terms, though, CTA is very useful in that it can be integrated into an overall plan for diagnostic imaging, including CT of the head and trunk, all of which can be accomplished rapidly.[12] Because of the enhanced detail, accuracy, and speed of image acquisition with 64 and greater slice CT scanners and the ability to perform three-dimensional reconstructions, this modality has become the standard imaging technique for suspected vascular injury. Magnetic resonance angiography (MRA) has been described and accurately detects vascular injuries but is not yet widely used. In most institutions, MRA is less readily available, more time consuming, and not appropriate for unstable patients.[12] MRI is also contraindicated in the presence of ferromagnetic foreign bodies.

Arteriography

Historically, catheter-based contrast angiography was used for diagnosing peripheral arterial injury. However, given the ready availability of CTA and additional steps necessary to obtain an angiography (transfer of the patient, activation of the angiography team, preparation of the angiography suite), CTA has replaced angiography as the initial diagnostic modality of choice in the ED.[12] Even those patients who may need intervention (embolization of pseudoaneurysms, endovascular stent insertion to bypass a dissection or AVF, and injection of thrombolytic agents to dissolve thrombus that are routinely performed via intra-arterial catheter) are best served by first obtaining a rapidly available CTA to establish the diagnosis.

Diagnosis of Specific Vascular Injuries

Although the aforementioned diagnostic strategies apply to vascular trauma overall, certain injuries bear particular mention.

For subclavian artery injury, the combination of physical examination and chest x-ray findings suggestive of subclavian injury (hemothorax, pneumothorax, apical pleural cap, or wide mediastinum) identifies nearly all injuries, and arteriography is not indicated in the absence of findings. When injury is suspected, and the patient is unstable, operative intervention is indicated. However, if the patient's clinical condition permits, angiography can confirm the diagnosis and can locate the injury precisely. APIs are not reliable with proximal thoracic outlet injuries because of collateral arterial flow. Ultrasound techniques are also relatively inaccurate in detecting subclavian injuries because of interference by overlying gas-filled lung tissue. Therefore, in cases in which the clinical diagnosis is equivocal (soft signs of injury or proximity wounds), arteriography (CTA or catheter based) is required to detect the injury.

No consensus has been reached on the diagnostic approach to detect popliteal artery injury resulting from documented or suspected knee dislocation. It is impractical to perform routine arteriography on every case of obvious or suspected knee dislocation. Although the exact diagnostic strategy is institution specific and dependent on available resources, our trauma center's approach is to perform a CTA in cases of high-energy mechanisms of blunt trauma (e.g., auto vs. pedestrian or MVC). For lower-energy blunt mechanisms, such as athletic injury, we perform serial clinical evaluations, including ABI. However, patients with *penetrating* trauma and more than one hard sign of popliteal artery injury can be taken directly to the operating room for repair, because delaying these cases to obtain a CTA is unnecessary for definitive care.

MANAGEMENT

Management of peripheral vascular injury is part of the total care of the trauma patient, including control of active hemorrhage by direct digital pressure. Blind clamping of a bleeding vessel is not recommended because of the risk of crushing adjacent nerves; however, clamping a clearly visible bleeding vessel can be effective. Tourniquet use for up to 6 hours is safe and effective, and it has been associated with increased survival in patients with major limb trauma. Tourniquets should be applied if direct pressure is insufficient to control bleeding and left in place until definitive surgical control can be achieved.[15] Few complications are associated with the use of tourniquets, and almost all of these are transient.[16] In cases in which proximal and distal control of large-vessel injuries cannot be readily achieved in the ED, insertion of a Foley catheter into the wound and inflation of the balloon with sterile water can temporarily tamponade the bleeding. Intravenous lines should not be started in the injured extremity, because they may be ineffective in delivering resuscitation fluid or medication and because extravasation from an injured vein may increase compartment pressure. Serial hemoglobin determinations may indicate unexpected blood loss from occult vascular injury. Patients with significant blood loss should have blood typed and crossmatched and may require immediate transfusion for stabilization. Patients with significant vascular injury often remain hypotensive despite crystalloid infusion and require further volume infusion or blood transfusion.

The issue of hypotensive resuscitation is controversial with regard to major vascular injuries. A tenuous clot can form in an injured artery and prevent further blood loss as long as the patient remains hypotensive. Once arterial pressure reaches a critical but variable point, the clot may be dislodged or expelled, and massive blood loss can ensue. Therefore, when an arterial injury is inaccessible for occlusion by direct pressure, the target blood pressure for resuscitation should be lowered to a systolic pressure of approximately 90 mm Hg. Overly rapid fluid administration in the field or in the ED can produce transient intravascular hypervolemia and may ultimately increase the rate of blood loss. Closely monitor vital signs and the total volume of fluid infused.

Once a vascular injury has been identified, a specific diagnostic and therapeutic strategy should be developed that is consistent with the severity of the injury, the presence of other injuries, and the resources available. In hospitals without the ability to perform vascular repair, transfer arrangements to a trauma center should be initiated early. In cases in which the transfer will involve a delay of several hours, cooling the ischemic limb will avoid exceeding the critical 6-hour cutoff for warm ischemia. To accomplish this, wrap the limb in towels, and apply ice in plastic bags around the limb, avoiding direct contact of the ice to the limb, which can result in frostbite.

Major Vascular Injuries

Major vascular injuries that compromise the viability of a limb should be repaired within 6 hours to avoid irreversible ischemic neuropathy and myonecrosis. Treatment of vascular injury has changed dramatically in the past 10 years. Endovascular treatment with self-expanding stents is currently the preferred technique for repair of these injuries in stable patients, and the majority of arterial repairs in the United States are now done with this technique.

Upper Extremity Arterial Injuries

For brachial artery injuries, limb salvage rates have improved to nearly 100% owing to efficient out-of-hospital transport, improved surgical techniques, and shorter time to first antibiotic dose. Repair is indicated in all cases because the amputation rate is high with ligation.

Injuries to forearm vessels detected by arteriography or ultrasound do not need to be repaired unless there are signs of ischemia in the hand; "hard signs" of arterial injury, such as an expanding hematoma, a pseudoaneurysm, or an AVF; or injury to both radial and ulnar arteries. However, some authors recommend repairing all these injuries because of the risk of intermittent claudication or cold intolerance in patients who have one artery ligated. Certain patients are almost exclusively dependent on the ulnar arterial supply to the hand because of an underdeveloped deep palmar arch. Clearly, ulnar artery injuries should be repaired in these patients. Ultimately, the decision to repair an arterial injury is in the domain of the vascular surgeon. Compartment syndrome in the forearm is common after repair of proximal arteries and veins and may require fasciotomy.[17]

Lower Extremity Arterial Injuries

In patients with severe injuries to the lower extremities, an initial "damage control" laparotomy with temporary vascular shunting of the iliac vessels is often necessary as resuscitation continues. Distal ischemic complications occur in approximately one-third of repaired iliac arteries, and subsequent amputations are required in up to 20% of cases.

Femoral artery injuries should be repaired as simple ligation of the common femoral artery and results in amputation of the lower extremity in 80% of cases.

Factors that place patients at higher risk of amputation include severe soft tissue injury of the extremity, the presence of multiple fractures, major venous repair, or delay in repair exceeding 6 hours of warm ischemia time. Because of the high incidence of compartment syndrome with lower leg injuries, fasciotomy is required in half of cases, and some centers routinely perform fasciotomy in all such cases.[17]

Late Complications of Arterial Injury

Despite timely optimal repair of arterial injuries, approximately one in five patients experiences delayed complications requiring further surgical intervention, including delayed amputation. The most common of such complications is delayed thrombosis, which often occurs after many months as stenosis at the repair site progresses. Other complications include intermittent claudication, chronic pain or edema of the limb, and aneurysm formation in the graft.

Venous Injuries

Venous injuries may be primarily ligated if the patient's condition makes them unable to tolerate a prolonged operative intervention. However, the current trend is to repair major venous injuries if possible, particularly in the lower extremity, because wound healing is improved and the incidence of compartment syndrome, venous thrombosis, pulmonary embolism, and chronic edema is decreased. Extensive venous collaterals in the upper extremity make surgical repair less compelling.

Minor Vascular Injuries

Increasingly, minor nonocclusive vascular injuries are being treated expectantly. Criteria for observation of vascular injuries include low-velocity missile wounds, intact distal circulation, absence of active hemorrhage, and minimal arterial wall disruption noted on angiography. Angiographic or CTA findings meeting these criteria include intimal flaps extending less than 5 mm and pseudoaneurysms smaller than 5 mm in diameter. Follow-up of these injuries with repeat angiography or ultrasound reveals that approximately 85% resolve spontaneously. Patients meeting these criteria can be monitored as outpatients for 3 months, with repeat physical examination and ultrasound to detect delayed complications. Most intimal flaps heal spontaneously, and asymptomatic injuries that do not disrupt perfusion of the limb can be treated conservatively with early administration of antiplatelet agents, such as clopidogrel or aspirin. However, almost all pseudoaneurysms ultimately require repair and, once discovered, should be repaired electively rather than undergoing continued observation. Failure to detect and repair occult arterial injuries in children often results in severe differential limb growth. Thus a more aggressive approach of repairing arterial injuries that cause a relatively minor decrease in blood flow to a child's growing limb may be justified.

Arterial Spasm

Isolated arterial spasm usually reverses with conservative treatment (topical warm saline or topical nitroglycerin paste), but prolonged spasm may require infusion of vasodilators, such as nitroglycerin, calcium channel blockers, alpha-blockers, nitroprusside, and specific prostaglandin inhibitors.

Antibiotics

Gram positive antibiotic coverage is needed for Type I and Type II fractures. Gram negative coverage is added for Type III open fractures. Appropriate antibiotic coverage (ideally administered within one hour of presentation) might include a first-generation cephalosporin (e.g., cefazolin 1 to 2 g intravenously preoperatively) and gentamicin 5 mg/kg. Alternative antibiotics include ceftriaxone and piperacillin/tazobactam.[18]

DISPOSITION

Patients with confirmed injury to major vessels, equivocal findings on diagnostic tests, or symptoms of limb ischemia should be admitted to the hospital or ED observation unit for further investigation and serial physical examinations. Frequent vascular and neurologic checks will be necessary in these patients, so step-down or intensive care unit levels of care may be necessary. Consultation with a vascular surgeon is indicated as soon as vascular injury is strongly suspected or the need for emergency operative repair established. Patients who are unstable because of vascular or other injuries may undergo further investigation or exploration in the operating room. If the treating hospital is incapable of performing vascular surgery or appropriate investigations, expedited transfer arrangements to a trauma center should be initiated. Obtaining angiograms for proximity wounds in centers that are incapable of acting on positive results is discouraged because this may delay definitive care beyond the safe limits of warm ischemia time.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 40: QUESTIONS AND ANSWERS

1. An 18-year-old man presents complaining of left lower leg pain. He was involved in a motor vehicle collision (MVC) 1 month earlier and required surgical repair of a left femur fracture. Which of the following is the *least* likely cause of the patient's symptoms?

a. Compartment syndrome
b. Intimal flap
c. Pseudoaneurysm
d. Thrombosis
e. Vessel stricture formation

Answer: a. Delayed thrombosis can occur months to years after injury if the injured vessel heals with stricture formation and decreased blood flow distally, followed by stasis and clot formation. Although flow is not altered by small intimal flaps and the associated soft tissue wounds often appear benign initially, they may become a nidus for thrombosis that can occur hours to months after the initial injury. The cavity of a pseudoaneurysm is in direct communication with the lumen of the vessel, so embolization of mural clots may produce distal arterial occlusion. Patients with pseudoaneurysm are commonly seen months to years later with symptoms of compression neuropathy or peripheral arterial embolism. The delayed presentation of this patient makes compartment syndrome the least likely cause of his leg pain.

2. A 45-year-old man complains of right leg pain and edema shortly after surgery for a midshaft femur fracture. Physical examination reveals decreased distal pulses in the extremity. What is the most important diagnosis to consider in this patient?

a. Anemia causing poor tissue oxygenation
b. Compartment syndrome
c. Intimal flap
d. Pseudoaneurysm
e. Vessel stricture

Answer: b. After restoration of arterial flow to a previously ischemic limb, a cascade of reperfusion injury has been identified that results from release of oxygen free radicals, lipid peroxidation, and influx of intracellular calcium. These mediators give rise to progressive cellular damage, edema, and necrosis, thereby propagating the vicious cycle that increases compartment pressure.

3. After vascular injury to an extremity, how many hours are generally required before irreversible damage occurs?

a. 2 hours
b. 6 hours
c. 10 hours
d. 12 hours
e. 24 hours

Answer: b. Although individuals may vary, 6 hours of complete warm ischemia is generally considered the point at which irreversible nerve and muscle damage begins to occur. After 6 hours of warm ischemia, 10% of patients will have irreversible damage; by 12 hours, 90% will have irreversible damage. Artificially cooling the limb to just higher than freezing temperature will reduce the metabolic demands of ischemic tissues and greatly prolong the tissue's tolerance of ischemia to 24 hours or more.

4. A 25-year-old man who sustained a gunshot wound to the right leg has an ankle-brachial index (ABI) of 0.9. What is the most appropriate next step in this patient's management?

a. Admit for observation and repeat examinations.
b. Discharge the patient home with surgical follow-up.

c. Obtain an emergent computed tomography (CT) angiogram.
d. Obtain immediate vascular consultation.
e. Perform a Doppler ultrasound scan.

Answer: a. Patients with an ABI of 0.90 to 0.99 merit observation for 12 to 24 hours for repeat examinations and ABI measurements to detect evolving injury. In general, a ratio of less than 0.90 is considered abnormal and is an indication for further investigation, such as computed tomography angiography (CTA).

5. Which of the following is *least* likely to cause vascular injury to an extremity?
a. Close-range shotgun wound
b. Crush injury
c. Electrical injury
d. Gunshot wound from a long distance
e. Massive tissue avulsion

Answer: d. Close-range shotgun wounds can cause significant blunt trauma to vessels, as well as a higher rate of bone and nerve damage than gunshot wounds. An open avulsion injury to a limb is particularly severe because the skin is the final structure to be disrupted, and there is inevitable injury to deeper vessels and nerves. Vascular injury must be suspected in patients with massive soft tissue avulsion or crush injury, displaced long bone fractures, and electrical or lightning injuries.

41

General Principles of Orthopedic Injuries

Joel M. Geiderman and Sam Torbati

KEY CONCEPTS

- Many orthopedic injuries can be stabilized and treated definitively by the emergency clinician. Consultation with an orthopedist should be sought for the treatment of some long bone fractures, open fractures, injuries with joint violation, tendon injuries, and injuries with neurovascular compromise.
- A careful history and physical examination can predict radiographic findings in orthopedic injuries with a high degree of accuracy.
- Open fracture management should focus on the early administration of antibiotics, tetanus prophylaxis, dressing coverage of the wound, and splinting. Suggested therapy for open fractures includes a first-generation cephalosporin, with the addition of an aminoglycoside for type II or III fractures.
- Compartment syndrome is associated most commonly with a closed long bone fracture of the tibia but also is well described in the thigh, forearm, arm, hand, and foot and can occur with isolated soft tissue trauma. Clinical examination remains the diagnostic cornerstone of acute compartment syndrome, which may then be confirmed by compartment pressure measurement.
- Because of the anatomic location and blood supply distribution, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, and capitate are particularly prone to this complication.
- Fat embolism syndrome is a serious consequence of fractures, occurring most commonly after long bone leg fractures in young adults and after hip fractures in older patients. Acute respiratory distress syndrome is the most serious manifestation. Neurologic involvement, manifesting as restlessness, confusion, and deteriorating mental status, as well as thrombocytopenia resulting in a petechial rash are early signs.
- Patients should be evaluated for the ability to ambulate safely prior to discharge. The use of a walker or other device, if it can be used safely, is acceptable. It also must be assured that the patient or a caregiver can carry out essential activities of daily living.

OVERALL FOUNDATIONS

Background and Importance

Orthopedic emergencies and musculoskeletal complaints and conditions comprise approximately 20% of all emergency department (ED) visits.[1] Although rarely life-threatening, orthopedic injuries may threaten a limb or its function, and accurate early diagnosis and treatment can avert long-term complications. Outcomes, including preventable complications, may affect a person's quality of life. Many orthopedic injuries can and should be treated definitively by the emergency clinician. Consultation with an orthopedist should be sought for the treatment of most long bone fractures, open fractures, injuries with joint violation, tendon injuries, and injuries with neurovascular compromise.

When evaluating a potential orthopedic injury, the following basic general principles should be considered:

1. Most orthopedic injuries can be predicted by considering the chief complaint, age of the patient, mechanism of injury, and estimate of the amount of energy transferred during the injury.
2. A careful history and physical examination can predict radiographic findings with a high degree of accuracy. A presumptive diagnosis before a radiographic study may prompt the emergency clinician to order special views necessary to diagnose an injury correctly. Many fractures were accurately described even before the advent of radiology (Table 41.1).
3. If a fracture is suggested clinically, but radiographic films appear negative, the patient should be treated with immobilization as though a fracture were present. Similarly, certain soft tissue injuries require prompt identification and follow-up and should be immobilized despite normal radiographic findings. Computerized tomography (CT) or magnetic resonance imaging (MRI) may be helpful to better define these injuries if available.
4. Inadequate or suboptimal radiographic images should not be accepted and should be repeated.
5. When a fracture is suspected, radiographic studies should be performed before reductions are attempted in most instances, except when a delay could potentially be harmful to the patient or in some prehospital settings, such as when neurovascular compromise or ischemic skin is present.
6. Neurovascular status should be assessed and recorded prior to and following all reductions and after splint or cast application.
7. Orthopedic injuries should be described precisely and according to established conventions.
8. In a patient with multiple trauma, noncritical orthopedic injuries should be diagnosed and treated only after more threatening injuries have been addressed and the patient stabilized. Complex pelvic fractures that may lead to exsanguination are an exception.
9. Patients should receive explicit aftercare instructions before leaving the ED, covering areas such as monitoring for signs of

TABLE 41.1 Common Fracture Names and Their Origins

Fracture Eponym or Name	Description	Comment
Aviator	Vertical fracture of the neck of the talus with subtalar dislocation and backward displacement of the body	First described in flyers during World War I; arises from forced dorsiflexion of the foot in flying accidents and in traffic accidents after a head-on collision
Barton	Intraarticular fracture-dislocation of the wrist	Considered complicated and unstable; requires surgical reduction in most cases; described by Barton in 1838 before the advent of radiography
Dorsal Barton	Oblique intraarticular fracture of the dorsal rim of the distal radius with displacement of the carpus along with the fracture fragment	Results from high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in dorsiflexion at the moment of impact
Volar Barton	Wedge-shaped articular fragment sheared off the volar surface of the radius (volar rim fracture), displaced volarly along with the carpus	Similar mechanism as dorsal Barton but with wrist in volar flexion at time of injury; also referred to as reverse Barton's fracture; much rarer than dorsal Barton fracture
Bennett	Oblique fracture through base of the first metacarpal, with dislocation of the radial portion of the articular surface	Usually produced by direct force applied to the end of the metacarpal; dorsal capsular structures disrupted by the dislocation; marked tenderness along medial base of thumb
Bosworth	Fracture-dislocation of the ankle resulting in the fibula being entrapped behind the tibia	Rare injury, produced by severe external rotation force applied to the foot; physical examination reveals foot severely externally rotated in relation to the tibia
Boxer	Fracture of the neck of the ring or small finger metacarpal	Results from striking a clenched fist into an unyielding object, usually during an altercation, or against a wall, out of frustration or anger
Chance	Vertebral fracture, usually lumbar, involving the posterior spinous process, pedicles, and vertebral body	Caused by simultaneous flexion and distraction forces on the spinal column, usually associated with use of lap seat belts; anterior column fails in tension, along with the middle and posterior columns; may be misdiagnosed as a compression fracture
Chauffeur	Solitary fracture of radial styloid	Occurs from tension forces sustained during ulnar deviation and supination of the wrist; name derived from occurrence in chauffeurs who suffered violent, direct blows to the radius incurred while turning the crank on a car, only to have it snap back, during previous eras
Clay shoveler	Fracture of the tip of the spinous process of the sixth or seventh cervical vertebra	First described in Australian clay shovelers who sustained a fracture of the spinous process by traction as they lifted heavy loads of clay
Colles	Fracture of the distal radius with dorsal displacement and volar angulation, with or without an ulnar styloid fracture	Most common wrist fracture in adults, especially in older adults; results from fall on an outstretched hand; also known as silver fork deformity, which accurately describes the gross appearance in the lateral view; first described by Colles in 1814, before the advent of radiography
Cotton	Trimalleolar fracture	Fracture of the lateral malleolus, fracture of the posterior malleolus, and either a fracture of the medial malleolus or disruption of the deltoid ligament, with visible widening of the mortise on ankle radiograph
Dashboard fracture	Fracture of the posterior rim of the acetabulum	Named for mechanism of injury—a seated passenger striking the knee on a dashboard, driving the head of the femur into the acetabulum
Dupuytren	Fracture-dislocation of the ankle	Results from a similar mechanism as the Maisonneuve fracture (i.e., external rotation of the ankle), resulting in deltoid ligament rupture or medial malleolus fracture, diastasis of the inferior tibiofibular joint, and indirect fracture of the fibular shaft; Maisonneuve was a student of Dupuytren
Essex-Lopresti	Fracture of radial head with dislocation of the distal radioulnar joint	Results from longitudinal (axial) compression of the forearm
Galeazzi	Fracture of the shaft of the radius with dislocation of the distal radioulnar joint; ligaments of inferior radioulnar joint ruptured, head of ulna displaced from ulnar notch of the radius	Results from fall on outstretched hand, with the wrist in extension and the forearm forcibly pronated; inherently unstable, with tendency to redisplace after reduction
Hangman	Fracture-dislocation of atlas and axis, specifically of pars interarticularis of C2 and disruption of C2–3 junction; separation occurs between second and third vertebral bodies from anterior to posterior side	Results from extreme hyperextension during abrupt deceleration; most common cause is the forehead striking the windshield of a car during a collision; a bit of a misnomer in that hanging usually produces death by strangulation rather than cord damage
Hume	Fracture of the proximal ulna associated with forward dislocation of the head of the radius	Essentially high Monteggia injury
Jefferson	Burst fracture of ring of C1, or atlas	Axial loading results in a shattering of the ring of the atlas; decompressive type of injury; associated with disruption of transverse ligament; unstable injury

Continued

TABLE 41.1 Common Fracture Names and Their Origins—cont'd

Fracture Eponym or Name	Description	Comment
Jones	Transverse fracture of the fifth metatarsal base, occurring at least 15 mm distal to the proximal end of the bone, distal to the insertion of the peroneus brevis	Should not be confused with the more common avulsion fracture of fifth metatarsal styloid, produced by avulsion at the insertion of the peroneus brevis; Jones described the fracture that bears his name in 1902, after sustaining the injury himself while dancing.
Le Fort	Maxillary fracture	Types I, II, and III (see Chapter 34)
Le Fort-Wagstaffe	Avulsion fracture of the anterior cortex of the lateral malleolus	Rare pull-off injury of the fibular attachment of the anterior tibiofibular ligament
Lisfranc	Fracture located around the tarsometatarsal (Lisfranc) joint, usually associated with dislocation of this joint	Lisfranc, a field surgeon in Napoleon's army, described an amputation performed through the tarsometatarsal joint in a soldier who caught his foot in a stirrup when he fell off his horse; since then, the joint has borne his name.
Maisonneuve	Fracture of proximal third of fibula associated with rupture of the deltoid ligament or fracture of the medial malleolus and disruption of the syndesmosis	Results from external rotation of the ankle with transmission of forces through syndesmosis; proximally, the force is relieved by fracture of the fibula; described experimentally in 1840, before radiography
Malgaigne	Fracture of the ilium near the sacroiliac joint with displacement of the symphysis, or a dislocation of the sacroiliac joint with fracture of both ipsilateral pubic rami	Resultant pelvic injury is unstable; described by Malgaigne, based on clinical findings, in 1847
March	Fatigue, or stress, fracture of the metatarsal	Arises from long marches or other repetitive use trauma (e.g., marathon running) or, less commonly, from single stumbling movements
Monteggia	Fracture of the junction of the proximal and middle thirds of the ulna associated with anterior dislocation of the radial head	Usually caused by fall on outstretched hand along with forced pronation of forearm or by a direct blow on the posterior aspect of the ulna; reported by Monteggia in 1814
Nightstick	Fracture of ulna, radius, or both	Name derived from a citizen's attempt to protect himself from a police officer's baton or "nightstick" by offering the forearm
Piedmont	Closed fracture of the radius at the middle third–distal third junction, without associated ulnar fracture	Named for a series of cases presented at the Piedmont Orthopaedic Society of Durham, North Carolina
Pott	Definitions vary (see comment); usually a bimalleolar fracture or fracture of the distal fibula, 4–7 cm above the lateral malleolus	The exact fracture Pott described in 1769 is uncertain; clearly, it referred to a fracture of the lower fibula, usually associated with other fractures or dislocations about the ankle.
Rolando	Intraarticular fracture at base of the first metacarpal; frequently Y- or T-shaped, or may be severely comminuted	Produced by an axial load with the metacarpal in partial flexion; worse prognosis than a Bennett fracture and, fortunately, rarer
Salter-Harris	Epiphyseal fracture occurring in children or adolescents	Graded I–V, depending on degree of involvement and/or displacement of epiphysis and metaphysis (see text dealing with Salter-Harris fractures and Table 41.2)
Smith	Extraarticular fracture of the distal radius with volar displacement of distal fragment	Reverse of the Colles fracture but much more uncommon; sometimes referred to as a garden spade deformity; usually results from fall with force to back of hand; first described by Smith in 1847
Stener	Avulsion of the ulnar corner of the base of the proximal phalanx of the thumb	Bony equivalent of rupture of the ulnar collateral ligament, or so-called gamekeeper's thumb
Teardrop	Wedge-shaped fracture of the anteroinferior portion of the vertebral body, displaced anteriorly	Commonly involves a ligamentous injury; may produce neurologic injury
Thurston Holland fragment	Triangular metaphyseal fragment that accompanies the epiphysis in Salter-Harris type II fractures	Described by Thurston Holland in 1929; the name is commonly hyphenated, although technically it should not be
Tillaux	Isolated avulsion fracture of the anterolateral aspect of the distal tibial epiphysis	Occurs in older adolescents (12–15 years) after the medial parts of the epiphyseal plates close but before the lateral part closes; external rotation force places stress on anterior talofibular ligament; described by Tillaux in 1872

neurovascular compromise, increasing compartment pressure, cast care, wound care, weightbearing, crutch use, the use of ice and elevation, and a plan and timing for follow-up.

10. Patients must be checked for the ability to ambulate safely before discharge from the ED and should not be discharged unless safe transportation and home care can be established. Also assure that they or a caregiver can carry out essential activities of daily living on their behalf.

FRACTURES

Foundations

Anatomic Location of a Fracture: Nomenclature

Describing orthopedic injuries with precise language according to established convention enables accurate and clear communication with other providers and consultants. Terms commonly used to describe a fracture are listed in Box 41.1. A fracture is a break in the continuity

BOX 41.1 Fracture Description

Identification
Open versus closed
Exact anatomic location
Direction of fracture line
Simple, comminuted
Position (displacement, alignment)

Additional Modifiers
Complete versus incomplete
Involvement of articular surface (%)
Avulsion
Impaction
  Depression
  Compression

Special Situations
Pathologic
Stress

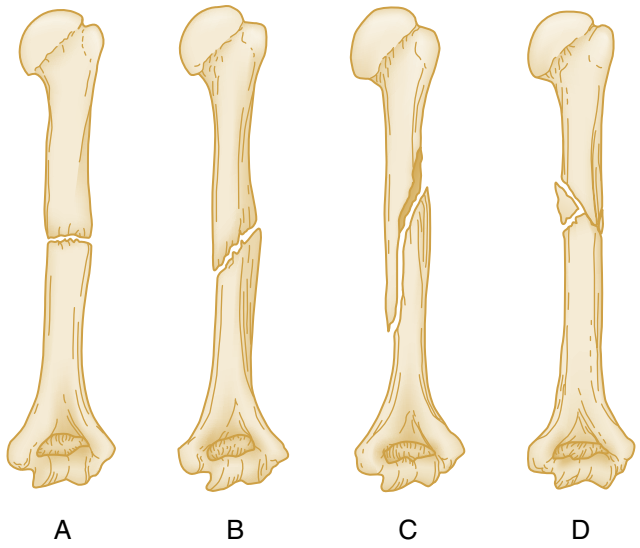


Fig. 41.1 Types of Fractures. (A) Transverse. (B) Oblique. (C) Spiral. (D) Comminuted.

of bone, which may be more subtle in children. Clinically, a history of trauma, loss of function, pain, tenderness, swelling, abnormal motion, and deformity all suggest a fracture.

Anatomic Descriptors

Description of a fracture should begin by stating whether the fracture is closed or open. In a closed fracture, the skin and soft tissue overlying the fracture site are intact. The fracture is considered open if it is, or has been, exposed to the outside environment in any manner, which may not be immediately obvious. Occasionally, it is difficult to determine whether a small wound in proximity to a fracture communicates with that fracture. Probing such a wound with a blunt sterile swab to establish a relationship may not be safe or accurate and should be avoided. If doubt exists, an open fracture should be assumed to be present and treated as such.

The exact anatomic location, including the name of the bone, left or right, and standard reference points along the bone (e.g., the humeral neck or posterior tibial tubercle) should be noted. Long bones can be divided into thirds—proximal, middle, or distal—and these thirds, or the junction of any two of them (e.g., the junction of the middle and distal thirds of the tibia), are often used to describe fractures. The most descriptive language possible should be used. It is better to say "closed fracture of the right ulnar styloid" than "closed fracture of the right distal ulna" because the former conveys more precise anatomic information and will help guide optimal treatment.

An additional modifier describes the direction of the fracture line in relation to the long axis of the bone in question. A *transverse* fracture occurs at a right angle to the long axis of the bone (Fig. 41.1A) whereas an *oblique* fracture runs oblique to the long axis of the bone (see Fig. 41.1B). A *spiral* fracture results from a rotational force, a torque, and encircles the shaft of a long bone in a spiral fashion (see Fig. 41C). The terms oblique and spiral are sometimes confused but can be important since the latter may have significance when child abuse is being considered as a mechanism of injury. A fracture with more than two fragments is termed *comminuted* (see Fig. 41.1D).

The position and alignment of the fracture fragments (i.e., their relationship to one another) should be described. Fragments are described relative to their normal position, and any deviation from normal is termed *displacement*. By convention, the position of the distal fragment is described relative to the proximal portion. Displacement may be described as a quantitative measurement (i.e., in millimeters) or as an approximate percentage of the bone width. It also may be described qualitatively as non, minimal, moderate, or severe. Fig. 41.2 shows dorsal displacement of the fractured radius, and Fig. 41.3 shows lateral, or *valgus*, displacement of the distal tibia and fibula.

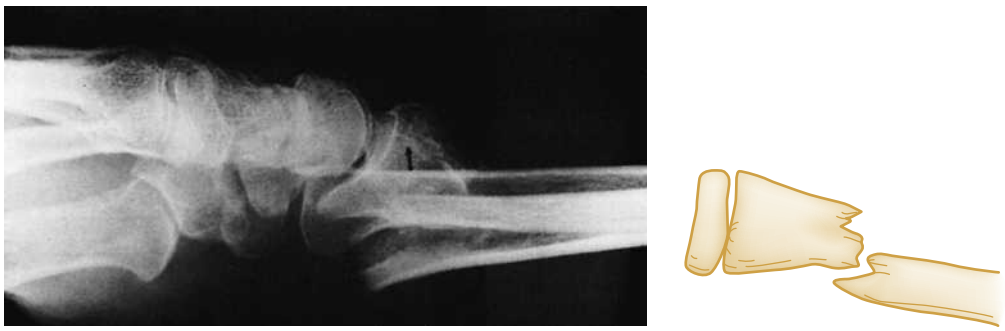


Fig. 41.2 Dorsal Displacement of Distal Radius.

Alignment refers to the relationship of the longitudinal axis of one fragment to another; deviation from the normal alignment is termed *angulation.* The direction of angulation is determined by the direction of the apex of an angle formed by the two fracture fragments (Fig 41.4). The term *valgus* denotes a deformity in which the apex of the deformity points toward the midline. Conversely, the term *varus* denotes a deformity in which the apex of the angulation points away from the midline. The relative position or angulation of the distal fragment of a fracture may also be described with terms such as *radial* or *ulnar, dorsal* or *volar, anterior* or *posterior,* and *lateral* or *medial.* For the forearms and hands, the anatomical position (palms up) should be used, along with radial and ulnar rather than medial and lateral to describe the direction of displacement. One should also be aware of rotational deformity, present when the distal fragment of a fracture is rotated to some degree along the axis of the bone itself. Especially in the digits of the hand, when the finger is flexed, clinically significant radial or ulnar deviation may be present that are not seen on radiographs (see Chapter 42).

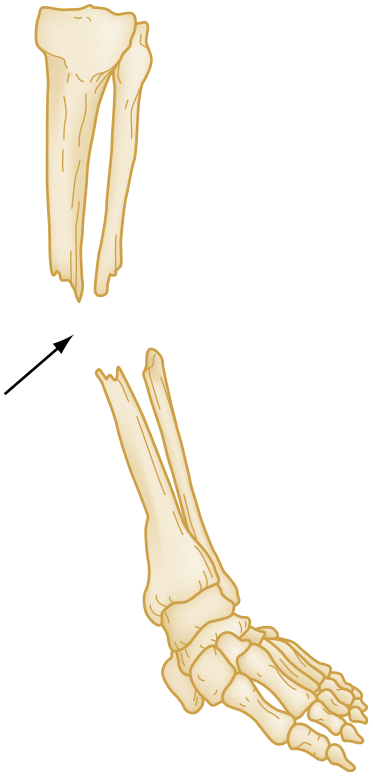


Fig. 41.3 Valgus Displacement of the Distal Tibia and Fibula. The distal segment is angled away from the midline of the body. The *arrow* shows the location of the fracture and the valgus displacement of the distal segment.

Descriptive Modifiers

A fracture is termed *complete* if it interrupts both cortices of the bone on orthogonal radiographic views and termed *incomplete* if one cortex remains intact. It should be noted whether a fracture extends into and involves an articular surface. Frequently, the percentage of articular surface involved can only be estimated; in some cases, the estimated percentage that is involved dictates the need to perform a surgical intervention. In general, it is important that the articular surface be restored to anatomic integrity to prevent consequent posttraumatic arthritis or disability.

The term *avulsion fracture* refers to a bone fragment that is pulled away from its normal position by the forceful contraction of a muscle (Fig. 41.5A) or the resistance of a tendon or ligament to a force in the opposite direction (see Fig. 41.5B). The term *impaction* refers to the forceful collapse of one fragment of bone into or onto another. In the proximal humerus, this collapse typically occurs in a telescoping manner, particularly in older patients, whose bones are osteoporotic and brittle. In the tibial plateau, impaction occurs frequently in the form of a depression (Fig. 41.6A and B) and, in the vertebral bodies, impaction frequently occurs in the form of compression resulting in a significant loss of bone height in some cases (see Fig. 41.6C).

A fracture that occurs through abnormal or diseased bone is termed *pathologic.* A pathologic fracture is suggested whenever a fracture occurs from seemingly trivial trauma. Diseases that cause structural weakness predisposing to injury include primary malignancy or malignant metastatic lesions, bone cysts, enchondromas, and giant cell tumors. In addition, metabolic and genetic disorders such as osteomalacia, scurvy, rickets, vitamin D deficiency, Paget disease, and osteogenesis imperfecta can alter bone density, making them susceptible to fracture. The term *pathologic* is also often applied to fractures through osteopenic bone when demineralization is a result of disuse, as in polio. In contrast, fractures through osteoporotic bone of older adults usually are not described as pathologic; these are more accurately referred to as geriatric or insufficiency fractures. When fractures occur in normal bones and a history of supposed trivial trauma or a suspicious mechanism is elicited, interpersonal violence or abuse should be suspected, and safety of the patient assured.

Repeated low-intensity forces may lead to resorption of normal bone, resulting in a stress fracture. Other terms for this condition are *fatigue fracture* and *march fracture* (see Table 41.1). Most stress fractures occur in the lower extremities and affect individuals involved in activities such as long-distance running, basketball, aerobics, and dancing. There is often a history of functional pain leading up to the fracture.

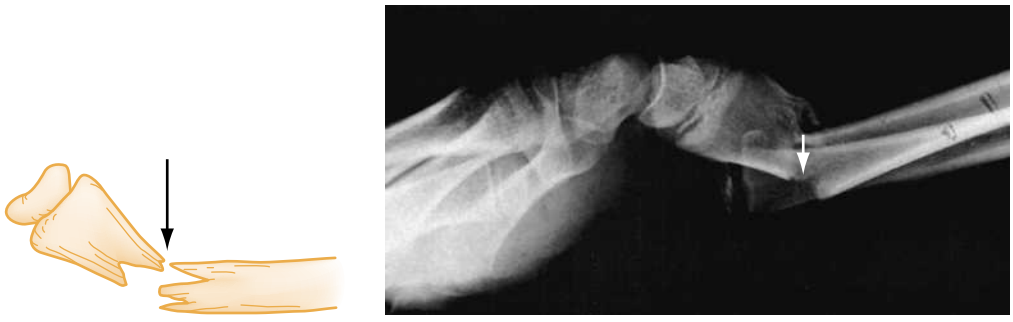


Fig. 41.4 Volar angulation of a fractured radius *(arrow).*

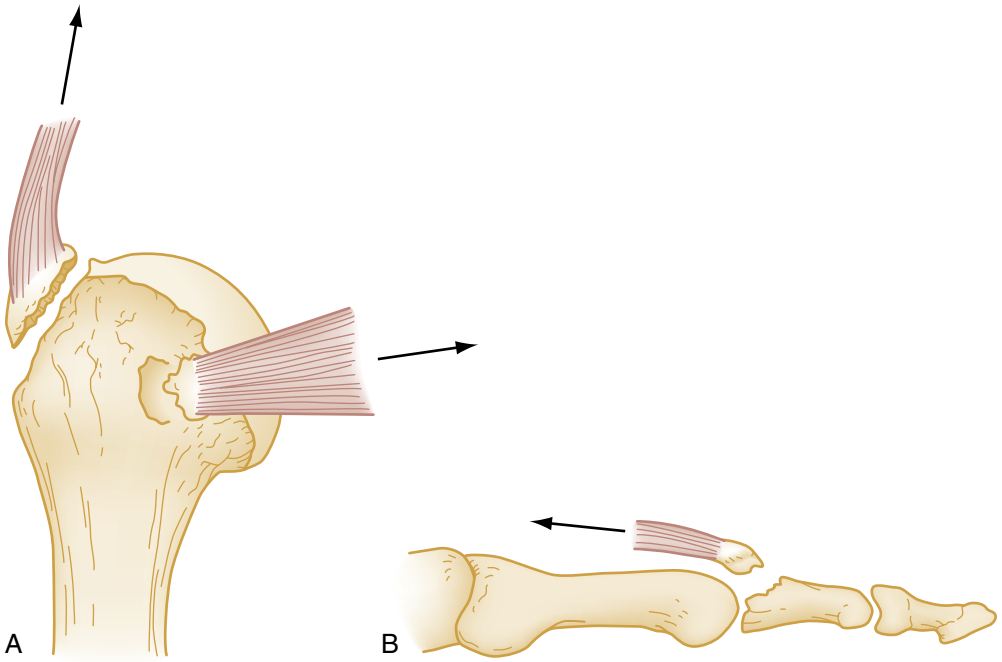


Fig. 41.5 Avulsion Fractures. (A) Musculotendinous avulsions of small bone fragments from the head of the humerus *(arrows)*. (B) Extensor tendon avulsion of bone from the base of the middle phalanx *(arrow)*.

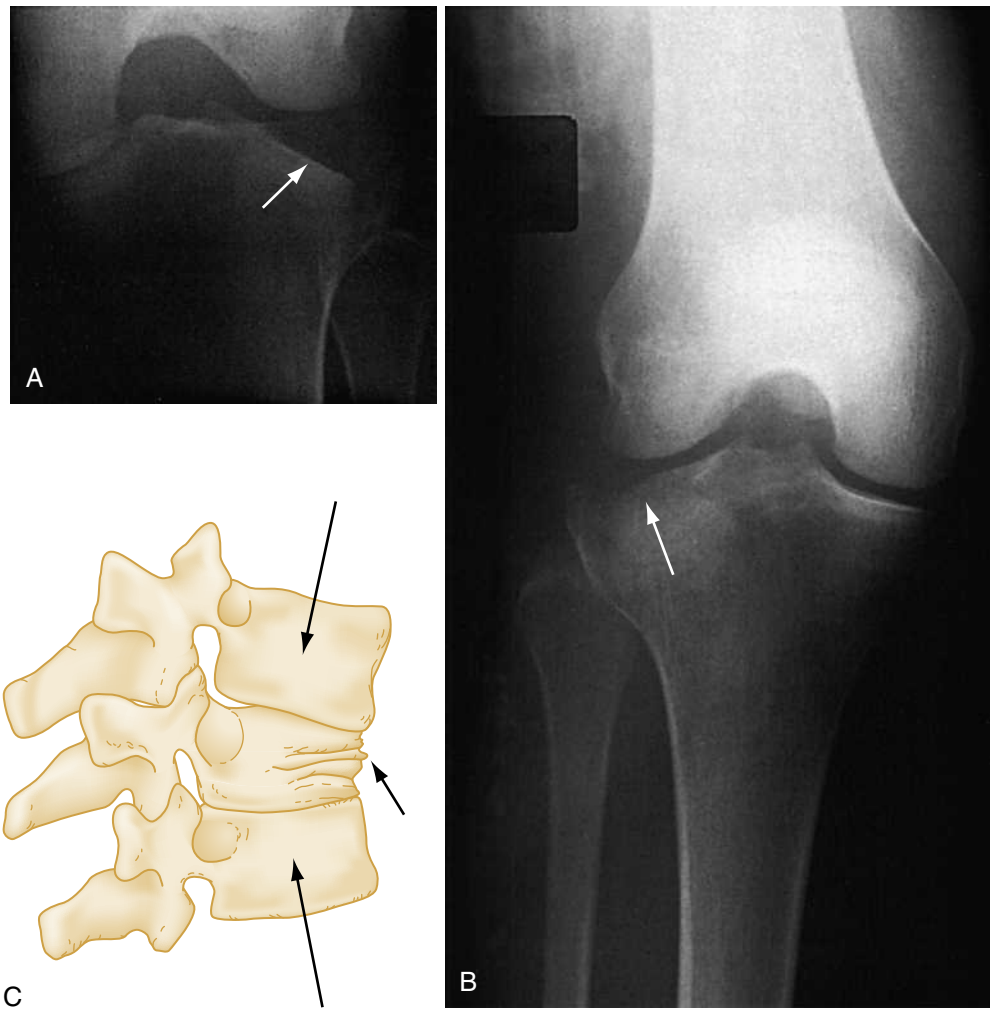
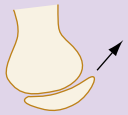
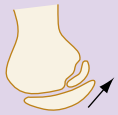
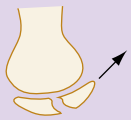
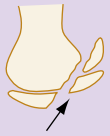
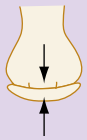


Fig. 41.6 (A and B) Tibial plateau fracture. (C) Vertebral body compression fracture *(arrows)*.

TABLE 41.2 Salter-Harris Classification

Type	Description	Diagram
I	Fracture extends through the epiphyseal plate, resulting in displacement of the epiphysis; this may appear merely as widening of the radiolucent area representing the growth plate.	
II	As above; in addition, a triangular segment of metaphysis is fractured.	
III	Fracture line runs from the joint surface through epiphyseal plate and epiphysis.	
IV	Fracture line occurs as in type III but also passes through adjacent metaphysis.	
V	This is a crush injury of the epiphysis; it may be difficult to determine by radiographic examination.	

Extrinsic factors such as training regimens, type of equipment used, nutrition habits, as well as intrinsic factors such as anatomic variation, muscle endurance, and hormonal factors, have all been associated with stress fractures. The tibia, fibula, metatarsals, navicular, cuneiform, calcaneus, femoral neck, or femoral shaft may be involved. These injuries may not be recognizable on initial plain films. Management therefore should be based on the clinical diagnosis.

Fracture Eponyms and Mechanistic Names

Many fractures were described before the advent of radiography and are described shorthand by an eponym or other name rather than by the exact bony injury. These eponyms and mechanistic names reflect the storied history of medicine and orthopedic care and are still commonly used to describe specific orthopedic injuries (see Table 41.1).

Epiphyseal Fractures

Fractures involving the epiphyses in children and adolescents are described according to the Salter-Harris classification (Table 41.2). The clinical features of fractures in children are further discussed in Chapter 170.

Clinical Features of Fractures

Fracture Healing

The goal of fracture reduction is to realign major bony fragments so that union can take place, and normal function is restored. In the initial stage of healing, a hematoma caused by the rupture of a vessel crossing the fracture line forms a hematoma. This hematoma eventually resorbs and provides the first continuity between the fragments. This *procallus* provides no structural rigidity for bearing stress but, with calcification and remodeling, callus is formed on the periosteal and endosteal surfaces of the bone, acting as a biologic splint. Over several months to a year, the callus normally completely ossifies, remodels, and becomes indistinguishable from mature bone.

Radiographic studies conducted 10 to 14 days after injury further reveal the fracture line as it becomes more visible due to localized bone resorption and hyperemia during the inflammatory phase. After 2 to 4 weeks, soft tissue swelling has regressed, and callus first becomes visible, initially in a mottled pattern and then taking on a dense appearance. Callus then undergoes organization, with peripheral margins becoming smooth as physically unstressed portions are resorbed.

In a healthy adult, the entire process from injury to consolidation takes approximately 2 months for the humerus and about 4 months for a large bone such as the femur. The rate of fracture healing is affected by the type of bone (cancellous bone heals faster than cortical bone), degree of fracture and opposition, systemic states, such as hyperthyroidism, use of corticosteroids, smoking, or illness requiring immobilization. Oblique fractures tend to heal more quickly than transverse fractures because of the greater amount of surface contact and a buttressing effect. Appropriately timed weightbearing can increase the rate of ossification of callus, whereas premature or excessive weightbearing can create a nonunion.

The presence of abundant bridging callus that is beginning to organize radiographically is usually associated with clinical union. If there is any suggestion of movement at the fracture site noted on clinical examination, union is regarded as inadequate. Several terms are used to denote abnormal healing. *Delayed union* is union that takes longer than usual for a particular fracture location; *malunion* occurs when a residual deformity exists; and *nonunion* is the failure of a fracture to unite. When nonunion results in a false joint, it is termed a *pseudarthrosis.*

If there is clinical evidence of stability, such as pain-free weightbearing, and radiographs demonstrate bridging bone at the cortices, a patient may resume activities of daily living with the injured extremity, even if the original fracture remains visible. The process of complete radiographic consolidation or healing can take several additional months.

Complications of Fractures

Infection (Osteomyelitis)

A fracture that communicates with the surface of the skin is termed an *open fracture.* Open fractures are treated as true, time-dependent orthopedic emergencies because of the risk of bone infection, or *osteomyelitis.* The high morbidity associated with osteomyelitis dictates that therapy be

BOX 41.2 Classification and Emergency Management of Open Fractures

Grades

Grade I: Wound less than 1 cm long, punctured from below

Grade II: Laceration 5 cm long; no contamination or crush; no excessive soft tissue loss, flaps, or avulsion

Grade III: Large laceration, associated contamination or crush; frequently includes a segmental fracture

- IIIA: Involves extensive soft tissue stripping of bone
- IIIB: Periosteal stripping has occurred
- IIIC: Major vascular injury present

Management

1. Control hemorrhage in field with sterile pressure dressing after carefully removing gross debris (e.g., wood, clothing, leaves).
2. Splint without reduction, unless vascular compromise is present.
3. Irrigate with saline, cover with saline-soaked sponges after arrival in the emergency department.
4. Begin IV antibiotic prophylaxis, usually a first-generation cephalosporin for grade I, with the addition of an aminoglycoside for grades II and III.
5. Administration of tetanus prophylaxis, including tetanus immune globulin, for large crush wounds.

initiated expeditiously, including parenteral administration of antibiotics as early as possible, coverage with a moist dressing, and emergent washout of debris. The Gustilo-Anderson classification is commonly used to describe the various types of open fractures (Box 41.2).

Suggested antibiotic therapy currently includes a first-generation cephalosporin, such as cefazolin, 2 g IV every 8 hours, for all open fractures, with the addition of an aminoglycoside, such as gentamicin, 5 mg/kg once daily, for type II or III fractures. Alternatively, a beta-lactam with both gram positive and negative coverage (e.g., ceftriaxone or piperacillin-tazobactam) may provide equivalent benefit. For patients with farm-related injuries or those with potential fecal contamination, ampicillin or penicillin should be added to the treatment regimen to empirically cover for clostridial contamination. Early versus delayed debridement of open fractures and the subsequent effect on rates of infection has been a source of debate.[2] Historic guidelines recommending debridement of open fracture wounds within 6 hours of injury were based on animal experiments conducted in the 1890s. The timing of debridement—less than 6 hours versus more than 6 hours after injury—has not been proven to change outcome, but general practice is to undertake debridement and irrigation of the wound within the first 24 hours of injury. Regardless, the goals of open fracture management in the ED should focus on early administration of antibiotics, tetanus prophylaxis, dressing coverage of the wound, and splinting of the extremity.

Open distal tuft fractures of the fingers and toes are a notable exception to the previous recommendation. These are common when the phalanx of a finger or toe is subject to crush injury (e.g., by a closing door) and there is a skin wound overlying a fractured bone. Treatment of these injuries can be provided by the emergency clinician without the need for immediate consultation. Vigorous irrigation and debridement are adequate primary treatment for these injuries, provided digital arteries are intact. Infections of the tuft region are rare.

Hemorrhage

Because of the rich blood supply to the skeleton, fractures can result in large amounts of blood loss, shock, and even death from exsanguination. In particular, certain pelvic fractures can cause major blood loss because adequate tamponade is not possible. In adults, blood loss can range from 100 mL from a forearm fracture to 3 L from a pelvic fracture (Table 41.3). Such hemorrhage can be controlled in part by early stabilization of the injured area through splinting, a binder, or skeletal traction. Definitive treatment options include embolization by an interventional radiologist or by emergent surgical intervention (see Chapter 46).

TABLE 41.3 Blood Loss Associated With Fracture in Adults

Fracture Site	Amount of Blood Loss (mL)
Radius and ulna	150–250
Humerus	250
Tibia and fibula	500
Femur	1000
Pelvis	1500–3000

Vascular Injuries

Vascular injuries are characteristically associated with certain fractures and may be limb threatening. Fractures and dislocations at the femorotibial articulation of the knee result from tremendous force, which may injure the popliteal artery and lead to the need for amputation (see Chapter 48). Fracture of the femoral neck requires emergent fixation regardless of the need for reduction to protect the blood supply to the femoral head and prevent aseptic necrosis. In the extremities, assessment of vascular injuries may be challenging. The initial survey should note the presence or absence of pulses and the state of capillary filling. If an end artery is completely disrupted, the tissue distal to the injury may exhibit the classic five Ps: pain and paresthesias (in the conscious patient), followed by pallor, pulselessness, and paralysis. Incomplete and subclinical injuries occasionally occur that initially may be asymptomatic and undetectable. In an unconscious, multiple trauma injured patient, major vascular injuries may not be obvious and may be overlooked. The mechanism of injury and anatomy dictate the need to assess the possibility of an injured vessel. If pulses cannot be palpated, a Doppler stethoscope should be used to detect blood flow. Even the presence of pulses may be misleading however, because pulses may be normal in some patients with significant arterial injuries. When pulses are present, but the mechanism of injury suggests the possibility of a vascular injury, additional diagnostic studies or surgical exploration may be necessary. If a limb is clearly not perfused, operative vascular exploration and repair should be undertaken promptly. Late complications of undiagnosed vascular injuries include thrombosis, arteriovenous fistulae, aneurysm, false aneurysm, and tissue ischemia with limb dysfunction. Delay of vascular injury repair is a risk factor for consequent amputation. The evaluation of peripheral vascular injuries is further discussed in Chapter 40.

Nerve Injuries

Nerves can be injured by blunt or penetrating orthopedic trauma:

- Neurapraxia is the contusion or traction injury of an otherwise intact nerve, with temporary disruption of the ability to transmit impulses. Paralysis, if present, is transient, and sensory loss is slight. Normal function usually returns to a neurapraxic nerve in weeks to months.
- Axonotmesis is the result of a crush or traction with more severe injury. There is complete interruption of the nerve axon and its myelin sheath, but the mesenchymal structures including perineurium and epineurium are either completely or partially intact. Because the Schwann tubes remain in continuity, spontaneous healing is possible, but delayed.
- Neurotmesis is the severing of a nerve along with its surrounding stroma, usually requiring surgical repair.

When the nerve is completely severed, all functions are absent, including superficial sensation to touch, pain, and temperature; deep sensation to muscle and joint movements; deep pressure, and vibration;

TABLE 41.4 Nerve Injuries Accompanying Orthopedic Injuries

Orthopedic Injury	Nerve Affected
Distal radius	Median nerve
Elbow injury	Median or ulnar nerve
Shoulder dislocation	Axillary nerve
Sacral fracture	Cauda equina nerve
Acetabulum fracture	Sciatic nerve
Hip dislocation	Femoral nerve
Femoral shaft fracture	Peroneal nerve
Knee dislocation	Tibial or peroneal nerve
Lateral tibial plateau fracture	Peroneal nerve

TABLE 41.5 Life-Threatening or Limb-Threatening Emergencies

Condition	Possible Adverse Outcome
Open fracture	Osteomyelitis
Fracture or dislocation with major vascular disruption (especially popliteal)	Amputation
Major pelvic fracture	Exsanguination
Hip dislocation	Avascular necrosis of femoral head
Compartment syndrome	Ischemic contracture; amputation; myoglobinuria, renal failure

motor supply and deep tendon reflexes to distally innervated muscle groups; and response to electrical stimulation. For less severe injuries, any subjective change in sensation should be noted. Light touch is a good screening test. Two-point discrimination is a more sensitive examination and should be used routinely in evaluating digital nerves. The discrimination on the injured digit is then compared with the uninjured ones. A normal two-point discrimination value at the fingertip of an adult is 4 mm, or discrimination may be compared to a non-injured digit. Evaluation of the innervation of the hand is further discussed in Chapter 42.

The injured nerve, patient age, site, and delay between injury and repair have all been shown to influence prognosis after microsurgical repair. Due to proximity, specific nerve injuries characteristically accompany certain fractures (Table 41.4). For example, in the upper extremity, a distal radius fracture caused by a high-energy insult can be associated with acute dysfunction of the median nerve. Deteriorating or lost neurologic function may necessitate temporary or definitive stabilization of a fracture.

Compartment Syndrome

Compartment syndrome is an acute, emergent complication that should be considered whenever significant pain and paresthesias occur in an extremity following a fracture or crush injury within an enclosed osseofascial space (Table 41.5). Pain is typically severe and out of proportion to the apparent underlying injury. A sense of tenseness may be detected on physical examination. The immediate threat is to the viability of nerve and muscle tissue within the involved compartment, but infection, gangrene, myoglobinuria, and renal failure also may ensue if the diagnosis is not made in a timely fashion. Compartment syndrome is usually associated with a closed long bone fracture of the tibia, but it also is well described in the thigh, forearm, arm, hand, and foot. In addition, compartment syndrome can occur with isolated soft tissue trauma and even with open fractures. It also has been described in a host of unusual situations, including prolonged procedures in the lithotomy position, the tuck position (knees tucked to the chest) for lumbar surgery, coma, spontaneous hemorrhage, extravasation of intravenous injections, and application of excessive traction in treatment of a fracture.

BOX 41.3 Causes of Compartment Syndrome

Increased Compartment Content

- Bleeding
  - Major vascular injury
  - Coagulation disorder
  - Anticoagulant therapy
- Increased capillary filtration
  - Reperfusion after ischemia
    - Arterial bypass grafting
    - Embolectomy
    - Ergotamine ingestion
    - Cardiac catheterization
    - Lying on limb
  - Trauma
    - Fracture
    - Convulsion
  - Intensive use of muscle
    - Exercise
    - Seizures
    - Eclampsia
    - Tetany
  - Burns
    - Thermal
    - Electrical
  - Intraarterial drug injection
  - Orthopedic surgery
    - Tibial osteotomy
    - Hauser procedure
    - Reduction and internal fixation of fractures
- Increased capillary pressure
  - Intensive use of muscles
  - Venous obstruction
    - Phlegmasia cerulea dolens (i.e., acute inflammation and edema of the legs)
    - Ill-fitting leg brace
    - Venous ligation
  - Diminished serum osmolarity (i.e., nephrotic syndrome)

Decreased Compartment Volume

- Closure of fascial defects
- Excessive traction on fractured limbs

Miscellaneous

- Infiltrated infusion
- Pressure transfusion
- Leaky dialysis cannula
- Muscle hypertrophy
- Popliteal cyst

External Pressure

- Tight casts, dressings, or air splints
- Lying on limb

Pathophysiology. Increased pressure in a closed, non-expandable compartment essentially represents a mismatch between the volume of that space and its contents. As such, it may arise from one of three circumstances: (1) increased compartment contents; (2) decreased compartment volume; or (3) external pressure (Box 41.3). As tissue

pressure increases, so does venous pressure, resulting in compromise of the local circulation and tissue hypoxia. This process is believed to occur at pressures that are above normal diastolic pressure but below systemic arterial pressure because of a reduced arteriovenous gradient at the tissue level. The body responds by releasing histamine in an attempt to dilate capillaries and increase blood flow to the affected area. Histamine also increases capillary membrane permeability, resulting in a leak of proteins and fluid into the surrounding tissue, further increasing compartment pressure in a vicious cycle.

As tissue pressure continues to increase, venous blood flow is impaired as capillary perfusion pressure is exceeded. Finally, arterial capillary blood flow falls to a point at which basic cellular metabolic needs are no longer met, leading to ischemic necrosis of muscles and nerves within the compartment and severe pain. An important concept in the management of compartment syndrome is that because local venous pressure cannot be significantly below local tissue pressure, and because elevation of a dependent limb decreases local arterial pressure by approximately 0.8 mm Hg for each 1 cm of limb elevation, elevation of a limb with resultant reduction in the local arteriovenous gradient is counterproductive and may actually exacerbate compartment syndrome. Vascular spasm seems to play a minimal role in the development of compartment syndrome.

Normal compartment pressure is 0 mm Hg. Microcirculation generally is impaired when tissue pressures reach 30 mm Hg or more; however, some patients can tolerate much higher compartment pressures without the development of compartment syndrome. Controversy exists over attempts to define compartment syndromes on the basis of specific tissue pressure. The tolerance to tissue ischemia varies among individuals because of shock, compensatory hypertension, altered tone in resistance vessels, and preexisting vascular disease. Inadequate perfusion and relative ischemia begin when tissue pressure within a closed compartment increases to within 20 mm Hg of a patient's diastolic pressure or, more accurately, within 30 mm Hg of the mean arterial pressure. When tissue pressure equals or exceeds the patient's diastolic blood pressure, tissue perfusion effectively ceases. The development of muscle ischemia depends not only on the magnitude but also on the duration of elevated pressure. Intra-compartmental pressures do not measure muscle and nerve ischemia but rather suggest the existence of the proper parameters needed for compartment syndrome. When establishing the diagnosis, clinical judgment should prevail.

Anatomic considerations and risk factors. Compartment syndrome theoretically can develop in any location where neuromuscular tissue is contained within a limited or confined space. The condition has been reported in the leg, thigh, buttock, arm, forearm, and hand (Box 41.4). By virtue of its location and higher likelihood of sustaining high-energy trauma, the leg, particularly the anterior compartment, is most commonly involved. Higher rates of compartment syndrome are seen with open fractures than with closed fractures, despite the fascial rents that accompany open fractures. The higher energy of injury observed with open fractures, with resultant tissue trauma, swelling, and bleeding, may account for this observation.

Most patients with compartment syndrome have an associated long bone fracture, and fractures of the tibial shaft are particularly likely to cause increased compartment pressure. Up to one-third of patients, however, have a crush or soft tissue injury without fracture. Compartment syndrome is more likely in patients with bleeding disorders or those on anticoagulation therapy.

Clinical presentation. Compartment syndrome is a clinical diagnosis. In a conscious and fully oriented patient, pain that is disproportionate to the apparent injury or physical findings is a hallmark finding in compartment syndrome.[3] Pain often is characterized as deep, burning, and unrelenting and is difficult to localize. The need for increasing amounts of analgesics should not lead the emergency clinician to the conclusion that the patient is drug-seeking; rather, it should serve as a prompt that compartment syndrome may be developing or is present.

BOX 41.4 Reported Anatomic Locations of Compartment Syndromes

Lower Extremity

Leg

Anterior compartment
Lateral compartment
Deep posterior compartment
Superficial posterior compartment

Thigh

Quadriceps compartment

Buttock

Gluteal compartment

Upper Extremity

Arm

Biceps compartment
Deltoid compartment

Forearm

Dorsal compartment
Volar compartment

Hand

Interosseous compartment

Pain on passive stretching of the muscle groups in the suggestive compartment is an important finding. In addition, active flexion of involved muscles may produce pain. Other reliable suggestive signs and symptoms are hypoesthesia and paresthesia in the distribution of nerves crossing the compartment or tenderness, tenseness, or sensation of tightness of the compartment.

Although it is classically taught that the five Ps—pain, pallor, pulselessness, paresthesias, and paralysis—are signs and symptoms of compartment syndrome, this is generally not true. Rather, these are the symptoms and signs of acute disruption of arterial flow. Skin color, temperature, capillary refill, and distal pulses *all* are unreliable monitors for compartment syndrome because the pressure necessary to produce compartment syndrome is well below arterial pressure. Pallor and loss of pulses are late and ominous signs. Diminished pulses suggest concomitant pathologic conditions responsible for reduced arterial flow. Subjective complaints are an important indicator of compartment syndrome. Patients who are not fully alert or cooperative should be fully assessed for clinical signs of compartment syndrome.

Diagnostic testing. Clinical examination remains the diagnostic cornerstone of acute compartment syndrome, which can then be confirmed by the measurement of compartment pressure. The two most common methods of measuring compartment pressures are the slit catheter techniques and side port needle. The Stryker Intra-Compartmental Pressure Monitor (Stryker, Kalamazoo, MI) system is a commercially available hand-held digital device that is easy to use with minimal training (Fig. 41.7). The monitor should be set at zero on the plane in which it will be inserted to account for the effects of gravity. It is paramount that the appropriate compartment be measured; consultation with an anatomy reference is recommended. Compartment pressures of less than 30 mm Hg generally do not produce compartment syndrome. When intra-compartmental pressures exceed 30 mm Hg, or when the difference between diastolic

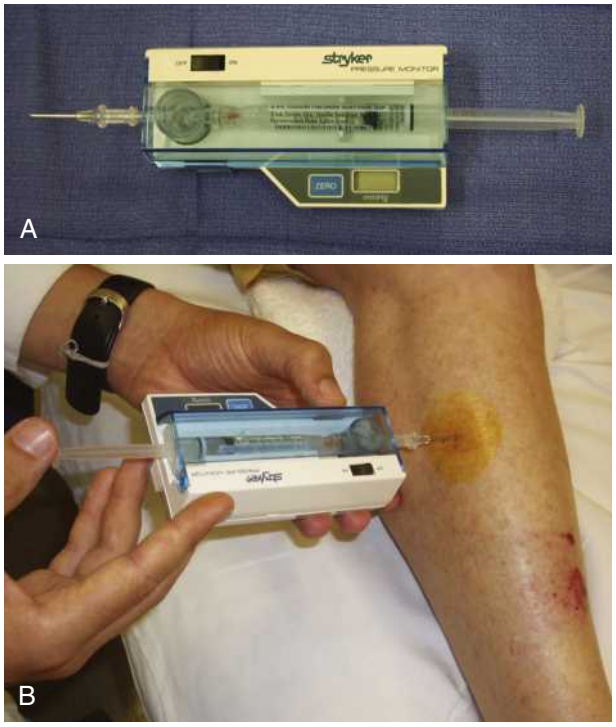


Fig. 41.7 (A) Hand-held device for measuring compartment pressure. (B) Device is inserted perpendicular to skin.

blood pressure and compartment pressure (perfusion pressure, also known as the ΔP) is less than 30 mm Hg, an emergent fasciotomy may be indicated. Serial or continuous pressure measurements should be performed in cases that are not clear-cut. A rising or sustained elevated compartment pressure is superior to a single measurement as an indicator of acute compartment syndrome or the need for fasciotomy. A hand-held Doppler stethoscope is not useful in evaluating these patients because arterial blood flow may still be detected, even in the presence of a significant compartment syndrome.

Treatment, complications, and disposition of compartment syndrome. Complete fasciotomy is the only treatment that can reliably normalize elevated compartment pressure. Surgery should be performed as quickly as possible. Delaying fasciotomy often results in irreversible myonecrosis and nerve damage. While the patient is awaiting definitive treatment, the affected part should not be elevated above the level of the heart because this maneuver does not improve venous outflow and reduces arterial inflow. Slight dependency (e.g., in reverse Trendelenburg position) has been suggested to maximize arterial flow to the extremity.

Because tissue compartments are more pliable soon after injury, the rate of extremity swelling is greater in the immediate postinjury period and tends to peak at 36 to 48 hours after injury. Although compartment syndrome usually appears within 36 hours of injury, cases have been reported more than 2 weeks following injury. Extremity swelling decreases over a similar duration. Rhabdomyolysis as demonstrated by elevated creatinine kinase, hyperkalemia, and myoglobinuria may occur and should be managed with fluid resuscitation to avoid subsequent renal failure. Lactic acid also is released from necrotic muscle tissue and its elevation in the serum may serve as a clue to the diagnosis.[4] Other complications include infection and tissue loss, necessitating amputation.

Short of amputation, delayed treatment often results in loss of nerve and muscle function and eventual contracture formation. The magnitude of these injuries is illustrated by the fact that in a 2017 national closed claims study, the mean indemnity award for compartment syndrome resulting from trauma was $987,716 USD. Delay in diagnosis was alleged 88% of the time. Thus, when the diagnosis of compartment syndrome is confirmed or highly suspected, surgical consultation and fasciotomy should be done without delay.[5]

Avascular Necrosis

Because of the anatomy of their limited blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, lunate, and capitate are particularly prone to this complication. These injuries are described in subsequent chapters.

Fat Embolism Syndrome

Fat embolism refers to the presence of fat globules in the lung parenchyma and peripheral circulation after a long bone fracture or major trauma. The phenomenon of fat embolization is probably more common than recognized as a subclinical event after long bone fracture.

Fat embolism syndrome (FES) is a serious manifestation of fat embolism, occurring most commonly after long bone fractures (usually tibia and femur) in young adults or after hip fractures in older patients. Symptoms usually appear 1 to 2 days after an acute injury or after intramedullary surgical nailing. Respiratory distress and hypoxemia are the earliest, most common manifestations. Acute respiratory distress syndrome (ARDS) may occur and is the usual cause of death. Neurologic involvement, presenting as restlessness, confusion, or deteriorating mental status, is an early sign, as are thrombocytopenia resulting in a petechial rash. Fever, tachycardia, jaundice, retinal changes, and renal involvement may occur. Fat is seen in the urine in 50% of patients within 3 days of injury. On computed tomography (CT) scan of the chest, common features are ground glass opacities and consolidation.[6] The incidence of full-blown FES varies from 1% to 2% in patients with isolated long bone fractures to 5% to 10% in patients with multiple fractures. Most patients with uncomplicated fat emboli recover without severe sequelae. Once FES appears however, the mortality rate is 10% to 20%. Management of FES is primarily supportive, usually in an intensive care unit often necessitating intubation and assisted mechanical ventilation.

Fracture Blisters

Fracture blisters are tense blisters or bullae that accompany high-energy injuries, with significant soft tissue swelling. They can occur anywhere but are most common in areas with thin soft tissue envelopes. The ankle, elbow, foot, and knee (in that order) are the most common sites; all these contain fewer hair follicles and sweat glands to anchor together the epidermal-dermal junction than other limb locations. Fracture blisters are believed, in many cases, to occur in the setting of increased underlying tissue pressure and may be a harbinger of compartment syndrome.

Early fracture reduction and splinting with expedited surgical intervention reduces the incidence of fracture blister formation. In addition, the presence of a fracture blister requires an alteration of the surgical approach or delay in surgery. We discourage incisions through a fracture blister because such incisions often lead to increased infection and skin breakdown. Early surgery after high-energy injuries might reduce the incidence of this complication. Once present, intact blisters should be covered with povidone-iodine solution and a sterile dressing. Unroofing the blister and applying coverage with silver sulfadiazine paste has been advocated by some to decrease the incidence of complications and to improve cosmesis but not in the presence of full thickness (blood-filled) blisters or diabetes mellitus.

BOX 41.5 Complications of Fractures

Avascular necrosis compartment syndrome
Complex regional pain syndrome
Fat embolism syndrome
Fracture blisters
Hemorrhage
Nerve injuries
Vascular injuries

Complications of Prolonged Immobility and Hospitalization

Contractures
Decubitus ulcers
Deep venous thrombosis
Delirium
Muscle atrophy
Pneumonia
Psychosis
Pulmonary embolism
Stress ulcers
Urinary tract infection
Wound infection

Complications of Immobilization and Hospitalization

Fractures frequently result in long periods of immobilization. Immobility may lead to multiple medical problems, especially in older patients, including pneumonia, deep venous thrombophlebitis, pulmonary embolism, catheter associated urinary tract infection, wound infection, nosocomial infection, decubitus ulcers, muscle atrophy, stress ulcers, gastrointestinal hemorrhage, and psychiatric disorders, especially psychosis or delirium (Box 41.5). In the geriatric population, surgery within 24 hours of admission has been shown to reduce delirium and improve 30-day mortality.[7] Early ambulation is a major goal of optimal orthopedic care.

Damage Control Orthopedic Surgery

Over the past few decades, the management of the multiply injured trauma patient has changed considerably. Historically, patients with multiple injuries were treated nonoperatively because it was believed they were too critically ill to tolerate surgery. In the 1970s, literature began to appear suggesting increased adverse outcomes as a result of prolonged bed rest. The notion of early total care of the polytrauma patient led to the advent of early fracture stabilization and subsequently, fixation techniques evolved. In 1993, the successful use of an abbreviated operation in patients with penetrating abdominal trauma to avoid the lethal triad of hypothermia, acidosis, and coagulopathy was reported, and the term *damage control* was introduced. In the polytrauma patient, similar principles were found to be applicable in the management of pelvic and long bone fractures.

The overall approach to all major fractures gradually shifted to early temporary fracture stabilization, resuscitation of the patient to a stable physiologic state, and definitive fixation at a later time once the patient is hemodynamically stable.[8] Temporary fracture stabilization is usually accomplished by the application of external fixation devices to aid in hemorrhage control and tissue oxygenation. The timing and optimal type of fracture surgery in the multiply injured trauma patient are still subjects of ongoing research. The role of the emergency medicine clinician is to facilitate stabilization, transfer to the operating room or angiography suite, or if necessary, to an outside tertiary care facility, and pre-operative preparation of the patient.

Differential Diagnoses

Pain and swelling of an extremity can occur after trauma with fracture as well subluxation, dislocation, sprain, strain, contusion, and thrombophlebitis. Severe pain alone or in combination with swelling may be present without trauma in arterial or venous occlusion, compartment syndrome, or with deep seated necrotizing fasciitis.

Diagnostic Testing

Plain Radiography

Conventional radiography is the mainstay for diagnosing fractures. In addition to confirming or excluding fractures, it can identify other pathologic conditions. Foreign bodies, air, and gas may also be detected. Conventional radiographic evaluation of long bones includes at least two orthogonal views (usually PA and lateral); an oblique view is part of the standard series in certain locations such as the phalanges and ankle. If fracture is suspected despite negative radiographs, additional oblique views should be obtained. A fracture line is most visible when it is parallel to the x-ray beam and is invisible when it is exactly 90 degrees to the beam. For this reason, for ribs, because of their curvature, multiple views must be obtained. To identify the extent of the fracture accurately, the entire bone should be visualized.

Each image should be examined to ensure that proper technique has been used and that no important area is omitted from the image. Emergency clinicians should review all films they order, even when the radiologist has already read it. Overexposed images may fail to reveal an abnormality. Although some fine detail is lost on portable images, these are acceptable if the patient is unstable or cannot tolerate transport to the x-ray suite and movement on and off the x-ray table, or for post-procedural films that are mainly concerned with acceptable positioning. Even with optimal technique, some fractures are not visible initially and do not appear until the margins of the fracture absorb. Absorption widens the radiolucent line, and a defect appears in 10 to 14 days. At that time, new bone produced beneath the periosteum at the margins of the fracture accentuates the fracture. Accordingly, if a fracture is suggested but is not visible at the initial visit, the injury should be treated as a fracture, reexamined clinically and radiographically in 10 to 14 days. The patient should be informed of the rationale for this regimen.

Comparison views with the contralateral bone may be useful in selected situations. It is reasonable to use comparison views in cases in which radiographs are inconclusive and when confusion arises specifically out of the need to distinguish between a possible fracture and normal developmental anatomy. Comparison views sometimes are helpful in adults when there is a question regarding the presence of accessory ossicles or non-fused bones (e.g., bipartite patella), because these anomalies are usually bilateral. They may at times be helpful in assessing fracture lines versus growth plates in pediatric patients (see Chapter 170). Consultation with orthopedic reference texts may be helpful. The bleeding that inevitably accompanies fractures may produce soft tissue swelling, which may impinge on or obliterate overlying muscle planes. Fat pads, such as in the elbow, may be displaced. Another useful sign is the fat-fluid level or *lipohemarthrosis* that results because fat is less dense than blood and layers out on top of it. This is most often seen in the knee joint and is only visible if the cross-table technique is used.

The bones themselves should be examined systematically. Normal adult bones possess a smooth contour. A distinct angle is highly suggestive of a fracture. In an adult, a lucent line that interrupts the smooth contour and usually extends to the opposite side represents a typical fracture. Nutrient arteries may be confused with fractures but have different radiographic characteristics: they are fine, sharply marginated, and extend obliquely through the cortex and are less radiolucent than

fractures. In addition, they do not extend to the opposite side of the bone. Pseudofractures can be created by soft tissue folds, bandages, monitor wires, or other overlying material or by a radiographic artifact called the "Mach effect," which occurs at the margin of areas of differing radiographic densities. If a lucency extends beyond the bone, the line is highly unlikely to represent a fracture.

Anomalous bones and calcified soft tissue likewise may be mistaken for fractures. Avulsions and small fracture fragments have an irregular surface that lacks well-corticated margins, with a defect in the adjacent bone, whereas anomalous ossification centers (accessory ossicles) and sesamoids are characterized by smooth cortical margins. Radiologic and orthopedic reference texts are useful in identifying and confirming these anomalies because they tend to occur in predictable locations. Compression fractures are suggested or represented by increased density rather than by a radiographic lucency (commonly occurring in the spine or proximal humerus). Finally, there is an adage that the most commonly missed fracture is the second fracture. One should be diligent in searching for additional fractures after discovering the first fracture in a patient. In particular, certain paired fractures should be sought, such as the distal tibia and proximal fibula, the *os calcis* and the lumbar spine, or in ring structures such as the mandible and pelvis.

Special Imaging Techniques

Computed tomography. Although conventional radiography remains the initial imaging study of choice for skeletal trauma, CT offers a more detailed and diagnostically sensitive evaluation of displacement, alignment, fragmentation of fractures, or joint penetration. CT should be considered when the clinical evidence does not correlate with the findings of routine radiography. Two-dimensional multiplanar reconstruction in any chosen plane, and three-dimensional surface rendering techniques provide images with higher quality, even in the presence of metallic implants or fixation devices which can be eliminated by advanced scanners equipped with special programs. Three-dimensional CT reconstructions are also sometimes useful for surgical planning.

CT is commonly used in blunt trauma to rule out a cervical spine fracture when plain films are equivocal, especially when there is underlying degenerative disease or in the elderly, and also in noncompressive vertebral fractures to assess the number of fragments and their spatial relationship to the spinal canal. CT is also used frequently to define the integrity of articular surfaces in the acetabulum, knee, wrist, or ankle and in certain Salter-Harris type fractures. In the multiple trauma patient requiring thoracic, abdominal, and pelvic CT imaging to rule out visceral injury, radiologic windows may be adjusted to also acquire diagnostic bone images of the thoracolumbar spine and bony pelvis structures.

Magnetic resonance imaging. MRI constitutes the most advanced noninvasive examination of orthopedic structures, delineating lesions of bone, cartilage, ligaments, and other structures, such as menisci, disks, and epiphyseal structures. It is rarely the test of choice for fractures, an exception being occult fracture of the hip.[9–11] MRI is expensive and time-consuming and should be reserved in the ED for cases in which the diagnosis is unclear, and specific findings would alter the treatment urgently. If not, it can be scheduled at a later time if deemed necessary.

Ultrasound imaging. Point of care ultrasound can be an effective tool for the diagnosis of fractures when conventional radiography is unavailable, such as in conflict settings or during mass casualty incidents.[12] Point of care ultrasonography can sometimes visualize fractures as an interruption of the linear bony cortex and may be clinically correlated during the physical examination of the affected area. The efficacy of ultrasound may be limited by the proficiency of the operator, the ability to control ambient light, and the quality of the machine. Plain radiography is the preferred initial diagnostic modality in the ED.

Laboratory Testing

Most fractures can be managed without the need for laboratory tests. C-reactive protein, sedimentation rate, and CBC may be useful in evaluating for complications such as osteomyelitis. A urinalysis and creatinine kinase may be useful in evaluation of compartment syndrome. When major bleeding is a concern, CBC and coagulation studies are indicated. Emergency clinicians should assure that patients in need of urgent surgery have routine pre-operative laboratory tests obtained so as not to contribute to a delay with surgical interventions.

Management

Field Care

Splinting and bandaging. Suspected fractures should be splinted in the field to limit damage to muscles, nerves, vessels, and skin and to prevent a closed injury from being converted to an open fracture during transport. In addition, splinting may relieve the pain associated with movement of the fracture. Numerous commercial devices are available, and most ambulances carry an assortment of immobilization devices (Fig. 41.8). Field personnel should splint suspected fractures before the patient is moved. Analgesics should be given according to need in keeping with local protocols. Severely angulated long bone fractures should be reduced in the field before they are splinted. Splints should be applied in such a way as to immobilize the joints above and below the fracture site to avoid motion of the involved bone. The skin should be padded to avoid local necrosis, and the splint should be secured by use of a circumferential wrapping material. This material should allow for some expansion and should not be applied in a constricting manner.

Standard ambulance equipment includes long and short backboards, cervical collars, sandbags, and extremity splints. A half-ring traction splint also is essential. Cardboard splints are acceptable and have the advantage of being able to be packed with ice packs. Inflatable air splints are favored by some because they are convenient, easy to apply, transparent, radiolucent and can tamponade low-pressure bleeding. If used, inflatable splints should be inflated only to the point that still permits splint indentation by gentle finger pressure.

Emergency Department Care

In the ED, the indications for initial splinting are the same as in the field. Splints applied in the field should be checked and, if properly applied, generally need not be changed. An exception to this rule is that if Hare traction was applied in the field and alternate traction is available, the former should be carefully removed in the ED because it may angulate femur fractures and result it decubitus ulcers over the ischium. Most splints can be left in place during initial clinical and radiographic evaluation. In some cases, a splint is all that is needed for definitive treatment. The following is an inventory of orthopedic devices available in most EDs.

Upper Extremity

Sling-and-swathe bandages. Sling-and-swathe bandages are useful in immobilizing the shoulder, humerus, and elbow. They are commonly used after reduction of dislocated shoulders and to treat impacted fractures of the humeral neck. The affected axilla should be padded and powdered with talc to avoid skin maceration. A commercial shoulder immobilizer also is available and is useful after reduction of a shoulder dislocation. Its advantages are ease of application and ease of removal and reapplication by the patient for bathing. Although they may aid

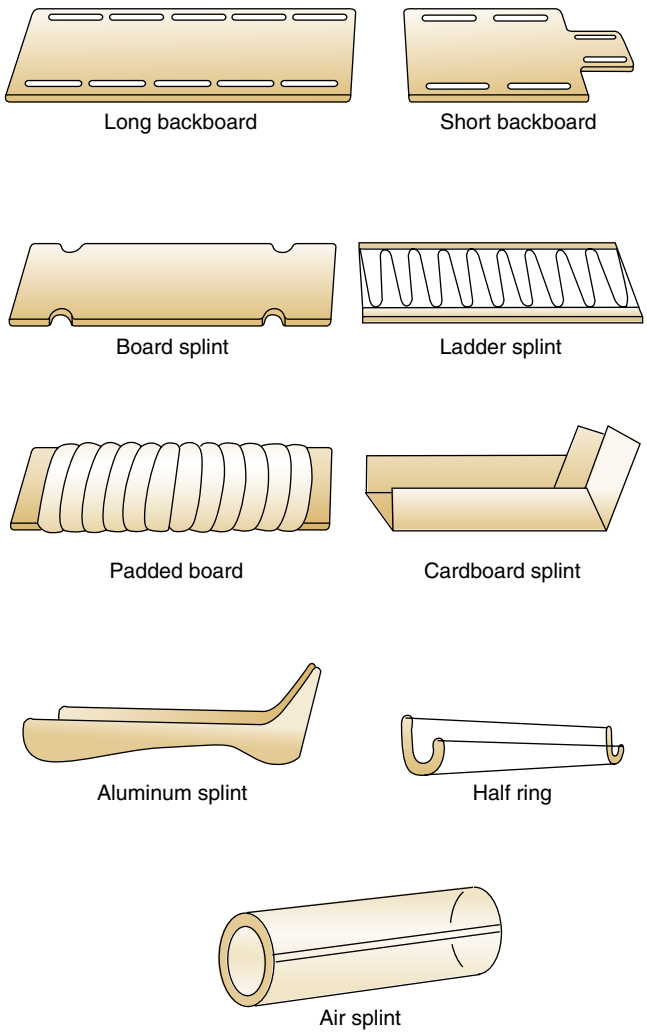


Fig. 41.8 Commercial Splints.

in healing, they are primarily placed for comfort and to decrease the incidence of recurrent injury.

Clavicle fractures. A simple sling of the arm on the affected side is sufficient to support the clavicle, improving healing immobilization and relieving pain. Figure-of-eight clavicular splints, once commonly used for clavicle fractures are no longer recommended because they are uncomfortable and provide no additional benefit.

Plaster and fiberglass splints. Well-fitting, customized plaster splints can be fashioned easily to immobilize the elbow, forearm, wrist, and hand. The advantage of these splints is the ability to mold them to a concise size and shape (e.g., along the ulnar side of the forearm and hand to immobilize a midshaft fourth or fifth metacarpal fracture, the so-called "gutter" splint). Several commercially available products consist of multiple layers of plaster or fiberglass strips, inside a covering of foam and flannel, on a continuous roll that can be applied to any length. The material is dipped in water and while the splint is still wet, a bandage is wrapped over it, and the splint is molded and held in the desired position as the plaster or fiberglass resin hardens. Cutting the fiberglass and plaster splints produces an exothermic reaction. To avoid burns, lukewarm water should be used to wet the splinting material and adequate skin padding applied.

Casts

Plaster casts perform a function similar to splints in that they provide stability and pain relief. Casts are not mandatory for all fractures and, in situations in which they are, application is usually not an immediate necessity. Because they are circumferential, casts provide more effective immobilization of a fracture, but they require more skill and time to apply. Swelling and subsequent pressure under the cast are highest during the first 24 hours after injury. Complications of casting include compartment syndrome, thermal injury, pressure sores, bacterial and fungal infections (especially if a wound is present under the casted area), and pruritic dermatitis. Plaster is applied as strips or rolls of cloth impregnated with a hemihydrate of calcium sulfate. When this cloth is dipped in lukewarm water, a creamy paste is formed that can be molded into a cast. As described previously, an exothermic reaction takes place that causes the plaster to harden and can burn the skin. Factors that have been shown experimentally to increase skin temperatures during plaster application are water temperatures greater than 24°C (75°F), cast thickness greater than eight sheets, and inadequate ventilation of the newly applied cast. Immersing the plaster in water for too short a time or squeezing too much water out can also lead to the generation of excess heat. To avoid pressure on the skin and over bony prominences, stockinette and layers of cotton sheet wadding are first snugly applied. Padding that migrates under a formed cast can be uncomfortable and result in pressure sores. Of note, padding alone does not prevent burns.

Variations of the basic cast exist. A window may be placed in the cast, and the cutout area may be used for access to skin wounds that require care or observation during immobilization. Walking heels may be worked onto a lower extremity cast and should be placed in the center of the foot. Synthetic fiberglass casts are lightweight, durable, and water-resistant. In addition, their setting temperatures are significantly lower, and they are less likely to produce burns. However, they are more expensive then plaster casting material, so may not be available in all settings.

Patients with casts may visit the ED for complaints related to their casts; these usually are pain, local irritation, swelling, or numbness of the distal part. A cast that is too tight results in swelling, pain, coolness, and change in skin color of the distal parts. Pain also may be caused by the initial orthopedic injury, by local pressure, a developing compartment syndrome, or wound infection. When a patient complains of pain, it is prudent to bivalve the cast and inspect the extremity. This is done by cutting the plaster and padding on each side and removing half the cast at a time, with the other half used as a mold to keep the extremity immobile. Afterward, the bivalved cast can be held together with bias-cut stockinette or elastic wrap until a new cast is applied. If relieving external pressure does not alleviate symptoms, the diagnosis of compartment syndrome should be considered. Casts may obscure open wounds, wound infections, and can be sources of sepsis or tetanus.

The need for a follow-up cast assessment 1 to 2 days after initial application is generally recommended depending on the location and type of fracture, the condition of the skin, reliability of the patient, and ease of access to alternative follow-up care.

Forearm and Wrist Splints

Numerous preformed Velcro splints are available for splinting fractures of the distal forearm and wrist. They are lightweight, form-fitting, and easy to apply and are easily removed by the patient (Fig. 41.9). Athletic taping can sometimes be used, such as in the management of a minor fifth metacarpal fracture.[13]

Lower Extremity

Splinting methods for various lower extremity fractures, including hip, femoral shaft, knee, and lower leg, are described in the respective chapters. Casts are applied as described previously. Commercially available knee immobilizers can be used after acute injuries to provide firm but nonrigid stabilization of the knee. The device is a foam cylinder with

medial and lateral aluminum stays, attached by Velcro straps, and spanning the upper thigh to upper ankle. This device is commonly used after trauma to allow the knee to rest until a more detailed physical examination or diagnostic study can be performed a few days later.

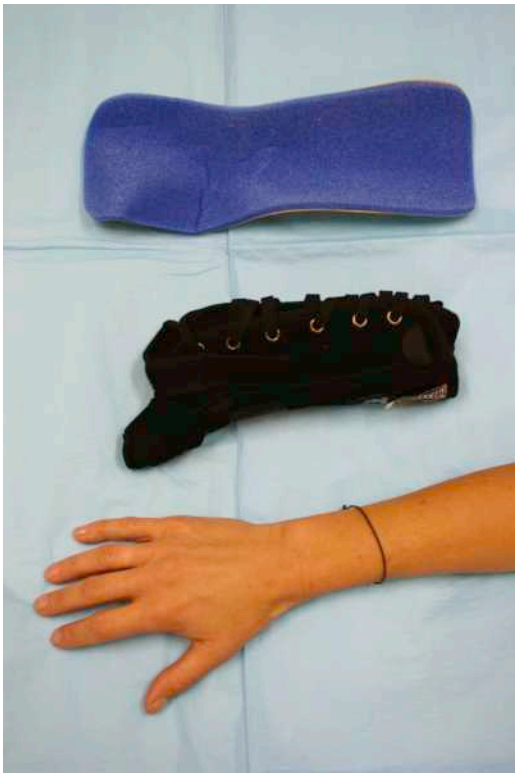


Fig. 41.9 Wrist Splints.

Ankle. Immobilization of the ankle can be accomplished by numerous methods. Plaster or fiberglass splints can be used temporarily for the treatment of nondisplaced ankle fractures or severe sprains. Plaster splints and casts are described previously. Most ankle injuries should be splinted with the patient's ankle in neutral position. Injuries to the Achilles tendon, plantaris muscle, or gastrocnemius muscle initially should be treated with the foot held in slight equinus (plantar flexion) for comfort. The toes should be free to move distal to the metatarsophalangeal joints, and the proximal border should end below the tibial tubercle to avoid pressure on the peroneal nerve.

Taping or adhesive strapping is an alternative method of ankle immobilization that provides good support and limitation of motion (Fig. 41.10). Taping tends to lose its protective properties with cyclic loading and sweating. This technique is commonly used by trainers in sports activities, who can reapply it as necessary. The method is lightweight and not bulky, and a shoe can be worn over the material. The use of tape is sometimes associated with dermatologic complications, including itching or contact dermatitis, owing to adhesion of the tape to the skin. For moderate to severe lateral ankle sprains, a commercial mechanical support composed of molded plastic with Velcro straps is more effective than elastic bandaging alone (Fig. 41.11). Another common commercially available device is the controlled ankle motion (CAM) boot. These boots are adjustable and removable and allow bathing but should not be used when strict weight bearing is needed.

The treatment of ankle sprains is further discussed in Chapter 49.

Thermal Therapy

Some confusion exists as to the role of cold versus heat therapy in the treatment of acute orthopedic injuries. Part of this confusion arises because heat may be more soothing to the patient. Icing or cooling is commonly recommended and used for acute orthopedic injuries to help reduce acute pain. In addition to a local anesthetic effect, cold

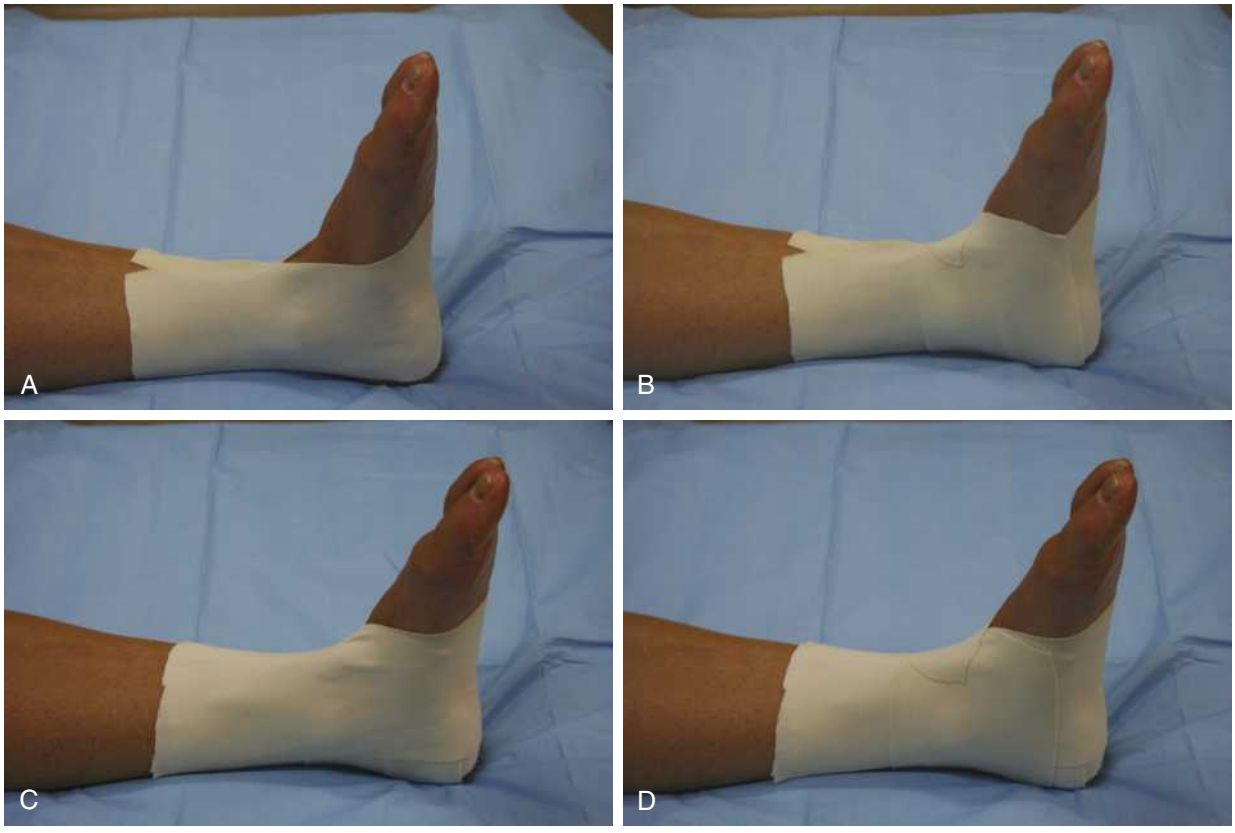


Fig. 41.10 (A–D) Application of adhesive strips to immobilize the ankle.

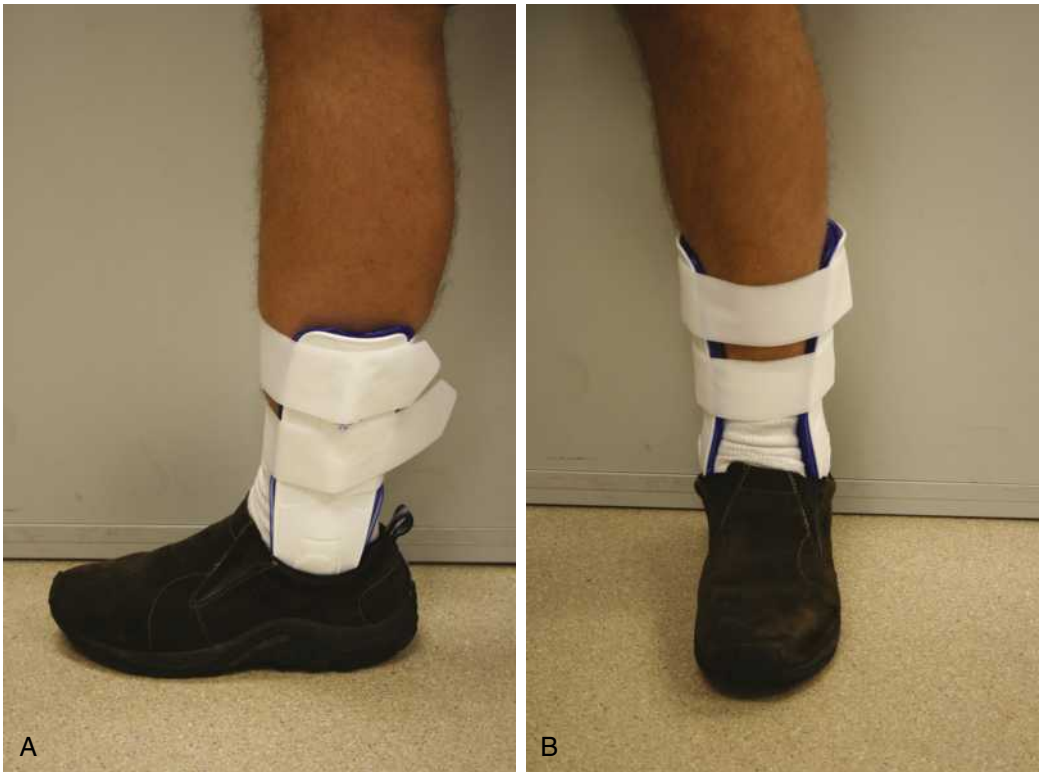


Fig. 41.11 Air Cast Ankle Support. (A) Lateral view. (B) Anterior view.

causes vasoconstriction, believed to limit blood flow and hemorrhage into the traumatized area. Metabolic requirements are reduced in cooled tissues, as is histamine, and less capillary breakdown occurs as a result. The sooner postinjury ice therapy is initiated, the more beneficial the reduction in metabolism will be. Reduced blood flow also should limit edema formation, and lower extravascular fluid pressure allows for better lymphatic drainage of injured areas. Generally, if ice is to be applied, it is recommended that an insulating layer be placed between the ice and skin, and that icing be continued for no longer than 30 minutes at a time, with the skin allowed to rewarm completely between applications. Ice therapy is most likely to be beneficial in the first 48 hours after injury.

Absolute contraindications to cold therapy include severe cold allergy (with hives and joint pain) and Raynaud disease. Relative contraindications include some rheumatoid conditions and paroxysmal cold hemoglobinuria, with renal dysfunction and secondary hypertension. Rare complications of cold therapy include skin burns and nerve damage, especially in athletic patients with more serious injuries. Anesthetic skin in a paralyzed or comatose patient is at greater risk with ice therapy.

Heat increases blood flow and initially increases the inflammatory response and edema. Warm tissues and cells have a higher metabolic rate and increased requirements for nutrients and oxygen. Patients seen 48 to 72 hours after injury with significant bruising may benefit from the application of heat in addition to elevation to help resolve the hematoma.

Disposition

Most fractures can be safely discharged for outpatient follow-up care, or surgery if indicated in the next 3 to 7 days. Significant fractures should be reduced to diminish pain and to avoid neurovascular compromise. Discharged patients should be given a short course of analgesics, as needed. Acute pain usually subsides in a few days as the fracture hematoma is absorbed and the swelling diminishes. It has been demonstrated that many patients can be managed with non-opioid medications.[14–17] Patients who are at risk for loss of function, who cannot ambulate safely, or whose analgesic needs cannot be met should be admitted. Patients who cannot perform activities of daily living (e.g., toileting and feeding) must have arrangements made for assistance with these activities, or else be admitted to a facility that can provide the care.

SUBLUXATION AND DISLOCATIONS

Foundations

Abnormal forces applied to joints may result in the loss of continuity between two articulating surfaces. Partial loss of continuity is termed *subluxation,* and complete loss is termed *dislocation*. In general, dislocations are named for the major joint involved, as in a dislocated shoulder or hip. In three-bone joints, the injury is named for the joint involved if the disturbance involves the two major bones or, if the lesser bone is involved, the disturbance is named for that bone. Separation of the femur from the tibia is termed *dislocation of the knee,* whereas displacement of the patella from its normal articulation is termed *dislocation of the patella* (Fig. 41.12). At the elbow, separation of the olecranon from the humerus is termed a *dislocation of the elbow,* whereas separation of the radius from the humerus is termed *radial head dislocation.*

Dislocations and subluxations should be described according to the direction of the distal segment relative to the proximal segment or of the displaced bone relative to the normal structures. The injury shown in Fig. 41.13 is termed *dorsal dislocation of the interphalangeal joint of the thumb.* Disruption of articulation also may occur in combination with a fracture. The term *fracture-dislocation* is used to describe this combination. If the overlying skin is broken in any way, dislocations, subluxations, or fracture-dislocations are described as open and constitute the same emergency treatment as an open fracture with contamination being a major concern.

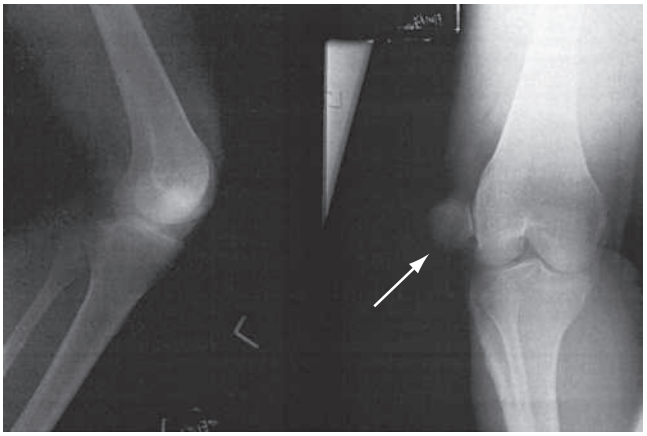


Fig. 41.12 Dislocation of the Patella. The *arrow* indicates the patella.

Clinical Features

In most cases of dislocation, severe to excruciating pain is present because the highly innervated joint capsule is stretched or torn. Attempted movement of the joint exacerbates the pain. This useful sign is lost in an obtunded, intoxicated, or unconscious patient and may result in a missed diagnosis if a careful examination is not performed. Some dislocations, such as anterior shoulder dislocation, cause an obvious deformity, whereas others, such as posterior shoulder dislocation, may be subtle. Swelling of soft tissues also may obscure the diagnosis, such as in the tarsal-metatarsal region. Gentle passive testing of range of motion should be performed but never forced. Assessment for neurovascular function is similar to that for fractures. Certain dislocations (e.g., the knee) are so commonly associated with vascular injuries that a meticulous assessment of blood flow is important in evaluating these injuries, including CT angiography.

Differential Diagnoses

Differential diagnoses of dislocation are usually comprised of an associated fracture (i.e., fracture/dislocation). In addition, acute neurovascular and tendon injuries may be mistakenly diagnosed as a dislocation or subluxation.

Diagnostic Testing

Plain radiographic studies detect most dislocations. In some locations, such as the shoulder, extra views are necessary to determine the type of dislocation (e.g., anterior versus posterior). Occasionally, when the diagnosis of dislocation is unclear, supplemental CT scanning can be helpful. Radiographs should be performed before and after attempts at reduction of first-time or complicated dislocations unless there is acute neurovascular compromise. This imaging not only confirms the diagnosis but ensures that associated fractures are documented before treatment is undertaken.

Management

Methods of reducing specific joints are reviewed in subsequent chapters, but a few basic principles apply. In general, a joint should be reduced as soon as possible. Over time, swelling and muscle spasm make reduction more difficult. Also, pain is not adequately relieved until the dislocation is reduced. In the hip, early reduction is mandatory to restore vascular supply and avert the complication of avascular necrosis. The general principle of reducing a dislocation is to stabilize the proximal bone and re-create and reverse the mechanism of injury, pulling the proximal end of the dislocated bone out and away from whatever is trapping it in its resting position. This technique helps prevent interposition of soft tissues in the joint that can preclude reduction. As this maneuver is accomplished, the disarticulated surface is manipulated back or may snap back spontaneously toward its normal anatomic position. Large joint relocation may require procedural sedation with parenteral analgesia. An ultrasound-guided regional nerve block can facilitate large joint relocations and is useful in some cases if available.[18] Smaller joints may require local anesthesia or, on occasion, no anesthesia. Some joints cannot be reduced in the ED because the opposing muscles are contracting too forcefully, and general anesthesia is necessary to overcome these forces. Mechanical obstruction by a bony fragment or torn piece of cartilage, tendon, or joint capsule usually requires surgical intervention for reduction to be accomplished.

Disposition

Most patients with dislocations that have been reduced can be discharged after a period of observation if sedation has been used. Patients should usually be referred for orthopedic follow up in 1 to 2 weeks. Patients with refractory unreduced joints should be admitted for surgery as should patients in whom vascular injury is suspected.

SOFT TISSUE INJURIES

Sprains

Foundations

Sprains are ligamentous injuries resulting from an abnormal motion of a joint with various degrees of tearing of the fibrous structure. While sprains may be graded according to the severity of pathologic findings, clinically, the grades may be less distinct but are classified as follows:

- A first-degree sprain is a minor tearing of ligamentous fibers, with resultant mild microscopic or obvious hemorrhage and swelling. Minimal point tenderness is usually elicited. Stressing the ligament produces some pain, but there is no opening or abnormal joint motion.
- A second-degree sprain is a partial tear of a ligament, i.e., more fibers are torn than in the first-degree injury. Clinical findings include tenderness, moderate hemorrhage and swelling, painful motion, abnormal motion, or loss of function. In some cases, there will be radiographic findings. In some joints there is a tendency toward persistent instability, loss of proprioception, and recurrence. Prevention of these complications is a major goal of treatment.
- A third-degree sprain denotes the complete tearing of a ligament. Signs include a further exaggeration of the signs mentioned for second-degree sprain. In addition, stressing the joint, when possible and not limited by pain or swelling, reveals grossly abnormal joint motion. In some cases, such as a third-degree acromioclavicular separation, there will be both clinical and radiographic findings.

Evacuation of a hemarthrosis and intraarticular analgesia may be used to allow a more complete diagnosis of some injuries. Chronic joint instability may result if severe ligamentous injuries are not properly treated.

Clinical Features

The clinical presentation of an extremity sprain may be indistinguishable from that of a fracture. The injury commonly occurs during vigorous athletic activity but may occur when there is other stress on the joint in an abnormal or exaggerated direction, such as stepping off the curb, or dancing. The patient may complain of hearing a snap at the moment of injury and conclude that a fracture is present. Patients may report "seeing stars" or "almost passing out" at the moment of injury and may still be in extreme pain, appearing pale and diaphoretic if seen shortly afterward. Analgesia should be provided promptly to these

patients. Evaluation should include a careful history of the sequence of events at the time of injury and attempting to ascertain the position of the extremity and the forces applied to it. Examination of the joint should include attempting to stress it to show abnormal motion. If radiographs are planned to rule out a fracture, or if excessive pain is produced by mild attempts to apply stress, it is probably better to delay stressing the joint until films have verified the absence of a significant fracture.

Differential Diagnoses

Fractures, sprains, and dislocations can present similarly. These injuries may be present concomitantly.

Diagnostic Testing

Plain radiography. Plain radiography is indicated in some, but not all, cases of suspected sprain to rule out a fracture. From a medical standpoint, validated clinical decision rules exclude the need for routine radiography in some situations. In these scenarios, shared decision making with the patient is a useful strategy to avoid unnecessary radiographic imaging.

Radiographic stress views of joints are occasionally used to evaluate the degree of ligamentous injury when other methods are not available.[1] The value of stress views is limited because pain may not allow sufficient stress to be applied, and there is a possibility of further injuring an already traumatized structure. Stress views should not be used until a fracture has been ruled out so as not to displace a fracture, especially if it involves an active growth plate in a pediatric patient.

Magnetic resonance imaging. MRI is generally not indicated acutely but may be indicated in follow up when significant ligamentous injuries that may require surgery are suspected. This is especially important in the knee when significant pain, hemarthrosis, and disability are present. Avulsion fractures may occur concomitantly with sprains. In children, epiphyseal fractures occur more commonly than ligamentous disruption because of the relative ligamentous strength compared with the ease of disrupting the epiphyses. MRI may be indicated in the follow-up evaluation of some of these injuries.

Management

Specific management of sprains varies depending on the location and severity of the injury. In general, initial measures should include the traditional recommendations of ice, elevation, and analgesia. Nonsteroidal antiinflammatory drugs (NSAIDs) are effective analgesics in many patients and may contribute to a more rapid decrease in swelling, increased exercise endurance, and earlier return to work and normal daily activities.

Immobilization provides protection and comfort in the initial management of most injuries. The method chosen depends on the location and specific recommendations are in the chapters that follow. Because the severity of injury is sometimes difficult to establish at the first visit, it is reasonable to immobilize the affected joint for the first 48 to 72 hours, after which the extent of injury can be better determined. At that time, early mobilization is often desirable, particularly in lateral ankle injuries, because this leads to earlier return to work and athletic activities and better preservation of proprioceptive and neuromuscular function. For lower extremity injuries, protected weightbearing with crutches provides patients with comfort and avoids motion of the impaired part. In older patients, safe ambulation sometimes cannot be accomplished, and a short hospitalization or respite in an acute rehabilitation or skilled nursing facility may be necessary. Surgical management is indicated for some specific injuries in certain patients. These are also addressed in the chapters that follow.

Disposition

Generally, for complete or nearly complete ligamentous disruption, urgent orthopedic consultation should be pursued within 5 to 7 days postinjury, when acute swelling has subsided, to determine whether surgical repair might be needed. When surgery is not indicated, physical therapy and rehabilitative exercises are sometimes prescribed at these visits and can be continued for several weeks. Because ligaments are relatively avascular, healing is slow, and patients with significant sprains should be informed of this. Sprains should be diagnosed as precisely as possible and should not be trivialized. If radiographs have ruled out fracture of an affected extremity, the patient should not be told that the injury "is only a sprain." This can be misleading, creating false expectations regarding recovery and may lead to missed occult fractures or epiphyseal injuries.

STRAINS

Foundations

A strain is an injury to a musculotendinous unit resulting from violent contraction or excessive forcible stretch. The term *pulled muscle* sometimes is used interchangeably with muscle strain. These injuries are graded in a manner similar to sprains.

- A first-degree strain is a minor tearing of the musculotendinous unit, characterized by minor swelling, local tenderness, and minimal restriction of movement.
- A second-degree strain increases fibrous tearing along a continuum but without complete disruption of the musculotendinous unit. Swelling, ecchymosis, and loss of strength are more marked.
- A third-degree strain is a complete disruption of the musculotendinous unit with resultant separation of muscle from muscle, muscle from tendon, or tendon from bone.

An accompanying avulsion fracture may be present on radiographs in second- or third-degree injuries.

Clinical Features

Signs and symptoms include pain, ecchymosis, swelling, and loss of function. A force applied to the muscle, passive stretching, or active contraction produces sharp pain at the site of injury, even as the injured muscle may be relatively comfortable at rest. A palpable defect sometimes is present at the site of a complete rupture, which usually involves the region of the muscle-tendon junction, or a bunching up of the muscle may be appreciated and is common with bicep tendon injuries.

In athletes, generation of tremendous contraction forces coupled with excessive forcible stretching (while the body may be accelerating or with sudden forced planting) results in severe strains. Involvement of almost any muscle group is possible, and the onset of such injuries is usually acute. Sudden generation of forces, of which the thighs are capable, results in second-degree strain of the hamstrings, quadriceps, or thigh abductor muscles. Rapid forcible contraction of the calf (e.g., in a tennis player) may result in a third-degree gastrocnemius or plantaris tear, whereas pushing off to jump is a common cause of Achilles tendon rupture in a basketball player. A sudden violent attempt at lifting by an older individual can result in a complete biceps brachii disruption.

Among nonathletes, strains commonly are seen in patients who have overstressed a muscle group or tried to generate repeated force in an unconditioned muscle. Examples are the weekend gardener or mover who experiences low back strain on Monday morning, the aerobics student who strains the rectus muscles, and the amateur weightlifter with pectoralis strain. These are usually first-degree injuries, and the onset is slow.

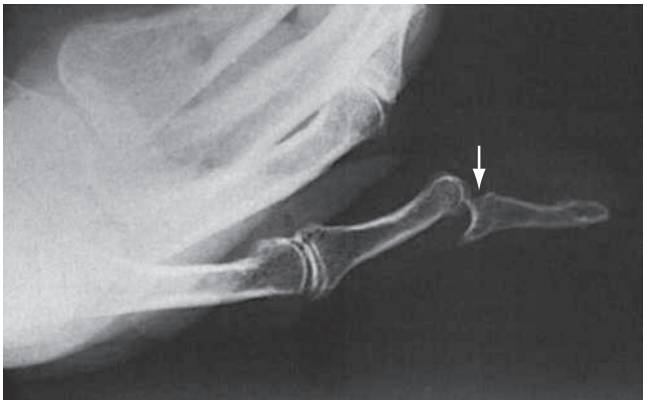


Fig. 41.13 Dorsal dislocation of the distal phalanx of the thumb *(arrow)*.

Differential Diagnosis

Fractures and sprains can mimic strains that occur in proximity to joints. These injuries may be present concomitantly.

Diagnostic Testing

Plain radiography is used in cases in which the possibility of a fracture is present, either by itself or in association with a strain. Ultrasound can be useful to diagnose complete tendon rupture. MRI is often used to diagnose rotator cuff tears, tendon ruptures, and muscle tears, but as mentioned, this modality often requires scheduling and is not always available or indicated in the ED. MRI can generally be safely delayed until a follow up visit outside of the ED.

Management

Treatment depends on location and the degrees of disruption and functional loss. Most first-degree injuries respond to rest, application of ice and, for some patients, analgesics for a few days post-injury. NSAIDs are commonly recommended. Second-degree strains are treated similarly, with protection against aggravating activity required for longer periods. Third-degree strains receive similar initial treatment in the ED plus early outpatient orthopedic consultation. Some of these injuries are amenable to surgical repair, whereas others may be treated with immobilization. The muscle affected, age, occupation, and activity level of the patient all are factors in deciding whether surgical intervention is appropriate. Early mobilization is an important tenet in the treatment of muscle strains; its timing may be based on the ability to stretch the injured muscle as much as the uninjured contralateral muscle and the use of the injured muscle without pain during basic movements.

Disposition

Strains can be referred and treated on an outpatient basis by either an orthopedist or at the direction of a primary care physician.

Tendinitis and Tendinosis

Foundations

Tendinitis is classically described as an inflammatory condition characterized by pain at tendinous insertions into bone, occurring in the setting of overuse. It is now believed that the pathophysiology of this condition is more complex than mere overuse, with the roles of load and use affecting the cell-matrix interaction. Contributing factors are those associated with aging, decreased blood supply and decreased tensile strength, muscle weakness and imbalance, insufficient flexibility as well as male gender, obesity (in weight-bearing joints), smoking, malalignments, training errors, and improper equipment. In addition, certain systemic diseases, including diabetes mellitus, chronic renal failure, rheumatoid arthritis, and systemic lupus erythematosus, steroid therapy, and fluoroquinolone use are associated with the development of tendinopathies.

The histopathology of tendinitis is characterized by the following: degeneration and disorganization of collagen fibers; infiltration by macrophages, plasma cells, and lymphocytes rather than leukocytes; and increased vascularity. Inflammatory changes are not a principal finding in tendinitis. This evolving understanding of tendinitis may allow for more logical treatment of these injuries aimed at the underlying pathophysiology. It also has led some to propose that chronic painful conditions of the tendon should be referred to as *tendinosis* rather than tendinitis or by other terms previously used to describe this condition, including the alternately spelled *tendonitis,* "degenerative changes of the tendon," and chronic tendinopathy. In this chapter, we use the terms tendinitis and tendinosis interchangeably.

Common sites for tendinitis are the rotator cuff of the shoulder, Achilles tendon, radial aspect of the wrist (de Quervain's tenosynovitis), and insertion of the hand extensors on the lateral humeral epicondyle (tennis elbow). Also commonly involved in athletes are the patellar tendon, particularly for those engaged in jumping sports; biceps femoris; semitendinosus and semimembranosus (hamstring syndrome); posterior tibial tendon (shin splint syndrome); and iliotibial band. It is also common in wrist flexors (e.g., medial epicondylar involvement is seen in little league pitchers and golfers). In some locations, most commonly the shoulder, calcium deposition occurs along the course of the tendon, resulting in a painful condition termed *calcific tendinitis.* This condition also may occur in the wrist, hand, neck, hip, knee, ankle, foot, and mandible.

Clinical Features

Physical examination reveals pain with motion and limitation of function and may include point tenderness and palpable crepitus over the involved tendon with motion. In general, a clinical test can be performed by forcible flexion of the involved muscle while keeping the point of insertion fixed or by operating the involved muscle against resistance. Either test should intensify the discomfort.

Differential Diagnosis

Avulsion fractures, sprains, and strains may mimic tendinitis.

Diagnostic testing

Radiographs are usually negative. A small fleck of bone suggests an avulsion, or the surface of the bone at the attachment may be irregular, indicating periostitis. Calcium deposits may occur along the course of the tendon due to calcific tendonitis and should not be confused with an avulsion fracture.

Management

Peritendinous local infiltration of anesthetics and corticosteroids may be useful in some anatomical locations but should not be repeated frequently because overuse may be associated with tendon rupture. Injection therapy is especially useful in calcific tendinitis demonstrated in the shoulder. Injection of steroids directly into the Achilles tendon should be avoided in the ED because of reports of partial or complete rupture after a single injection.

The classic approach to instances of tendinitis not amenable to injection therapy consists of rest, ice, and NSAIDs initially, followed by rehabilitation, physical therapy, training, and control of force loads (including weight loss), to prevent recurrences. NSAIDs may be useful

for a brief period as an analgesic but they have not been demonstrated to significantly alter the pathophysiology of this condition. They therefore should not be ordered for patients at significant risk for complications, including the elderly, diabetics, or those with or at risk for renal impairment. Arthroscopic or open surgery may be indicated in some cases of calcific tendinitis, not responsive to conservative therapy.

Disposition

Tendinitis is an outpatient condition. Persistent cases should be referred to the primary care clinician, a rheumatologist, or a musculoskeletal specialist.

Bursitis

Foundations

Bursitis is a painful inflammation of the bursa that may be traumatic, infectious, or related to systemic illness. Commonly involved sites include the olecranon, greater trochanter of the femur, and prepatellar or anserine bursae around the knee.

Clinical Features

Physical findings are tenderness and swelling over the involved bursa. In the olecranon, swelling will be prominent. Severe tenderness is a common feature and a hallmark over the greater trochanter of the femur. When accompanied by warmth and overlying erythema, common in the olecranon, an infection may or may not be present.

Diagnostic Modalities

Radiographs may rarely be useful in establishing the diagnosis, but their greatest usefulness is in ruling out other conditions. Advanced imaging is generally not indicated. If infection is suspected, aspiration of the bursa with gram stain and culture is indicated if the bursa is accessible and can be entered safely.

Management

Bursitis benefits from immobilization by resting the inflamed part and thus treating associated pain. If infection is suggested, aspiration of accessible bursal fluid, and Gram staining and culture are recommended, assuming aspiration can avoid any overlying cellulitis. If the bursa cannot be entered without avoiding an area of suspected cellulitis, it is usually better to wait. Otherwise, treatment is conservative and is similar to that for tendinitis, with rest, ice, NSAIDs, and the addition of antibiotics if there is a suggestion of cellulitis.

Disposition

Most patients can be treated as outpatients. When gross infection is present, especially when there is extension manifest by cellulitis, a short admission for intravenous antibiotics in addition to immobilization and elevation is indicated.

Other Soft Tissue Conditions

Other soft tissue injuries (e.g., inflammatory conditions, infections, bites, burns, repaired injuries of muscle bellies or tendons) may present to the ED as orthopedic conditions. Such complaints need to be carefully evaluated based on history and physical findings. Plain radiography may be helpful, along with specific blood tests or advanced imaging rarely. These conditions all generally benefit from immobilization. Splints also can be used to improve function, such as with wrist drop that accompanies radial nerve palsy. When an extremity is immobilized, it is important to stress elevation of the affected part to avoid edema formation and promote healing. The various immobilization devices are described previously.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 41: QUESTIONS AND ANSWERS

1. A 40-year-old diabetic woman is brought to the emergency department (ED) after crashing her car into a tree at moderate to high speed. She has a minimally displaced trimalleolar fracture and no other injuries after full body scanning and evaluation by the trauma team. While awaiting admission to the floor she develops blood-filled fracture blisters over the anterior ankle. What is the next step?

a. Debride blisters and apply silver sulfadiazine cream
b. Arrange for urgent surgery within 8 hours
c. Cover with sterile dressing and elevate foot and ankle
d. Measure the compartment pressure in the ankle

Answer: c. Fracture blisters sometimes follow high-energy injuries, especially when the overlying skin is thin and there are few hair follicles or sweat glands. Debridement and application of silver sulfadiazine is sometimes used when blood is not present. It is contraindicated in the presence of diabetes. Conservative treatment with a sterile dressing is recommended and surgery through the involved area should be delayed.

2. A patient presents with severe pain in the leg despite the removal of a cast 3 days after suffering a closed tibia fracture. Which of the following requires an emergent fasciotomy?

a. A high clinical suspicion based on extreme pain and tenseness in the compartment
b. The absence of pulses detected with a hand-held Doppler stethoscope
c. Tissue pressure less than the diastolic pressure
d. Tissue pressure of 20 mm Hg

Answer: a. Compartment syndrome cannot be diagnosed on the basis of specific tissue pressure. The tolerance to tissue ischemia varies among individuals because of shock, compensatory hypertension, altered tone in resistance vessels, and other unknown factors. Inadequate perfusion and relative ischemia begin when the tissue pressure within a closed compartment increases to within 20 mm Hg of a patient's diastolic pressure or, more accurately, within 30 mm Hg of the mean arterial pressure. When tissue pressure equals or exceeds the patient's diastolic pressure, tissue perfusion effectively ceases. Clinical judgment is paramount. Delayed diagnosis and fasciotomy frequently result in high damage claim awards.

3. An intoxicated alcoholic man is brought into the ED after being found on a bench and is found to have a wrist drop. Which is the likely cause of the wrist drop?

A. Axonotmesis
B. Neurotmesis
C. Neuropraxia
D. Increased compartment pressure

Answer: c. The patient likely has a contusion of the radial nerve; axonotmesis and neurotmesis involve more severe injury such as crushing or severing. Isolated neurologic dysfunction is not a feature of compartment syndrome.

41.4.)A 60-year-old woman presents to the emergency department (ED) with a closed deformity to the wrist as shown in the figure (show old figure 42.4 in text). In discussing this injury to a consultant, which is the best description?

a. Compound fracture of the wrist
b. Severely angulated fracture of the wrist
c. Fracture of the distal radius with dorsal displacement and volar angulation
d. Fracture of the distal radius with severe anterior displacement

Answer: c. Fractures should be described using the most precise language possible. The injury is a closed injury, so it is not compound. Fracture displacement in the forearm or wrist should be described as volar and dorsal, and occasionally as radial or ulnar (as the forearm is viewed in the anatomic position). Descriptions should convey as much information as possible.

5. A 50-year-old nonprofessional weightlifter presents after sudden pain in the upper arm described as a "pop." There is bunching up of the biceps muscle and bruising at its insertion. Which drug class is commonly associated with this condition?

a. Nonsteroidal antiinflammatory drugs (NSAIDs)
b. Angiotensin converting enzyme inhibitors
c. Fluoroquinolones
d. Statins

Answer: c. The patient appears to have rupture of the biceps brachialis tendon. Tendinopathy is associated with use of fluoroquinolones but not NSAID use, hypertension, or hyperlipidemia.

42

Hand Injuries

Benjamin Schoener and Mary Jo Wagner

KEY CONCEPTS

- For general testing of the motor nerve function of the hand, have the patient make an "OK" sign with their thumb and index finger (testing the median nerve), while spreading/abducting the third, fourth, and fifth fingers (ulnar nerve) and dorsiflexing the wrist (radial nerve).
- For general sensory exam, test two-point discrimination on the finger tufts of the index finger (median nerve), the little finger (ulnar nerve), and the dorsum of the first webspace (radial nerve).
- The most important treatment for the majority of hand injuries is applying an appropriate splint. The neutral position for general fractures of the hand or fingers is achieved by placing a volar splint ideally with the wrist at 20 to 30 degrees extension, MCP at 70 to 90 degrees flexion, and the PIP and DIP kept in extension. This is also known as intrinsic plus position.
- The most common extensor tendon injury is a terminal tendon disruption from sudden flexion of the extended DIP joint resulting in a *mallet injury.*
- A flexor tendon injury should be considered when an injured finger does not assume its naturally flexed position on *cascade sign* testing.
- Traditionally, patients with acute open wounds on the hand have been treated prophylactically with antibiotics, but there is little scientific data supporting the clinical efficacy of this practice.
- For a stable finger tuft with a subungual hematoma without external disruption of the nail plate, trephination without antibiotics is the only treatment needed.
- Small tuft avulsions defined as less than 1 cm^3 can be treated conservatively, while larger amputations should have emergent consultation with a hand surgeon for consideration for flap coverage or reimplantation. The presence of exposed bone or tendon indicates the need for surgical intervention.
- Most hand infections are based on skin flora; treatment for outpatient injuries are oral first-generation cephalosporins. With the growing emergence of community-acquired MRSA, antibiotics such as doxycycline, TMP-SMX, or clindamycin should be considered. For inpatient injuries, IV first-generation cephalosporins or vancomycin is recommended.
- The four classic Kanavel findings for infectious flexor tenosynovitis are fusiform swelling of the digit, tenderness along the tendon sheath, digit held in flexion at rest, and pain with passive extension of the digit.

FOUNDATIONS: A GENERAL APPROACH TO HAND INJURIES

Complaints regarding the hand present frequently to the emergency department with evaluation and management challenges due to the complex anatomy and function of the hand. Careful review of hand injuries is needed to identify simple wounds, injuries that can be initially managed but need further treatment, or time-sensitive emergencies. The disposition of the patient may involve simple follow-up or consideration for the need for specialized consultants.

The initial evaluation of a patient presenting with a hand injury should include a focused, but thorough, history and physical exam. The patient's age, mechanism of injury, time of injury, other acute or distracting injuries, hand dominance, occupation, and any prior hand injuries or impairments should be queried. For penetrating injuries, tetanus immunization status should be assessed, and for patients who may require surgical management, the timing of the last solid or liquid ingestion or nil per os (NPO) status should be assessed. For nontraumatic hand complaints, the presence of contracture, timing of symptoms, pain, aggravating or alleviating factors, presence of symptoms in other extremities, as well as functional impairment are additional key components of the history.

The hand should be completely exposed and examined, including all components as listed in Box 42.1. Inspection to identify deformity, discoloration, swelling, ecchymoses, laceration, or signs of open fracture should occur. Angular deformities are best evaluated with the fingers in full extension. Rotational deformities are best evaluated with the fingers in flexion. Severe hand injuries create the appearance of significant tissue loss or destruction which should not distract the provider from providing basic or advanced trauma care.

A neurovascular assessment should be performed and documented using the Allen test, capillary refill, and two-point discrimination. The point of maximal tenderness should be noted. Tendon, ligament, and joint capsule integrity should be examined with special testing performed where it is relevant to the patient's injury or complaint. Wound exploration may be necessary to assess for foreign bodies, gross contamination, or structural injury. Proper analgesia and regional blocks should be considered prior to wound exploration, which should be performed with sterile technique.

Radiographic imaging is the most widely available and used imaging modality for the hand. It is essential to obtain sufficient views to adequately assess the areas of injury. A standard x-ray series of the hand should include a posterior-anterior (PA), lateral (90 degrees to the PA), and generally, at least one oblique film. The ideal x-ray film should have no overlapping of bones, allowing for proper evaluation of each joint space, radiopaque foreign bodies, dislocations, and fractures. If possible, all rings, jewelry, and watches should be removed before imaging. Comparison of films performed on the uninjured side may assist in pediatric patients with developing growth plates.

Ultrasound imaging has also been shown to be a useful, though inferior, bedside modality for detecting fractures of the hand. A recent meta-analysis of 8 randomized control trials (RCTs) and prospective studies found a pooled sensitivity and specificity of 91% and 96% respectively in identifying fractures of the phalanx and metacarpals using x-ray as the gold standard.[1] Another blinded study looking at point-of-care ultrasound (POCUS) performed by emergency medicine

(EM) physicians, found a lower sensitivity of 79% and specificity of 90% for phalanx fractures.[2] Ultrasound is also helpful in evaluation of the soft tissue and for detection of foreign bodies.

CT and MRI are rarely used for evaluation in the acute setting, although they are occasionally used for evaluation of complex fractures or if there is a high clinical suspicion of fracture with negative x-ray imaging. MRI has the added ability to visualize the ligaments, tendons, and soft tissues. It is an effective imaging modality for investigating suspected osteomyelitis, avascular necrosis, and bone tumors.

BOX 42.1 General Hand Exam

I. Inspection
  A. Skin
    - Wounds
    - Erythema
    - Pallor (arterial compromise)
    - Cyanosis
  B. Edema
  C. Deformity
    - Rotation
    - Angulation
    - Cascade sign

II. Range of Motion
  A. Active
  B. Passive

III. Palpation
  A. Warmth
  B. Joint effusion
  C. Tenderness
  D. Masses (i.e., nodules, ganglions)

IV. Neurovascular Exam
  A. Motor
    - Median N.—Flexion of thumb and index finger ("OK sign")
    - Radial N.—Extension of thumb against resistance
    - Ulnar N.—Abduct fingers against resistance
  B. Sensation
    - Two-point discrimination
  C. Vascular
    - Allen test
    - Capillary refill at nail beds

Anatomy

Surface Anatomy and Skin

To understand the surface anatomy of the hand, it is important to be familiar with certain landmarks and associated terminology. The posterior surface of the hand is referred to as the dorsal surface, and the palmar surface of the hand is referred to as the volar surface. The radial border of the hand is that which borders the thumb, and the ulnar border of the hand is that which borders the little finger (Fig. 42.1).

The skin on the dorsal surface of the hand is generally thin and mobile compared to the volar surface. Unlike the volar surface, the dorsal surface is more prone to swelling. Also unique to the dorsal surface is the presence of hair follicles and the presence of the nail bed at the distal phalanges.

The volar surface of the hand is thick and stable. It is layered with subcutaneous fat and a thick dermis designed in a series of transverse folds or creases. This allows for sufficient padding and firmness with gripping. The folds are anchored directly to fascia in areas without underlying fatty tissue. This allows for easier flexion and limits the development of inflammation and edema. A collection of underlying muscles that respectively form the thenar eminence and the hypothenar eminence at the radial border and the ulnar border are also identifiable on the volar surface of the hand.

Fingertip and Nail. The fingertip is the area distal to the DIP and insertion of the flexor digitorum profundus (FDP) and extensor tendons. The volar surface is well-innervated, vascularized, and padded with adipose tissue. This area, which is anchored to the distal phalanx, is also known as the *pulp*.

The fingernails are specialized structures of keratinized epithelium that protect the distal phalanges. Underneath the nail, also known as the nail plate, is the nail bed which is comprised of skin (Fig. 42.2).

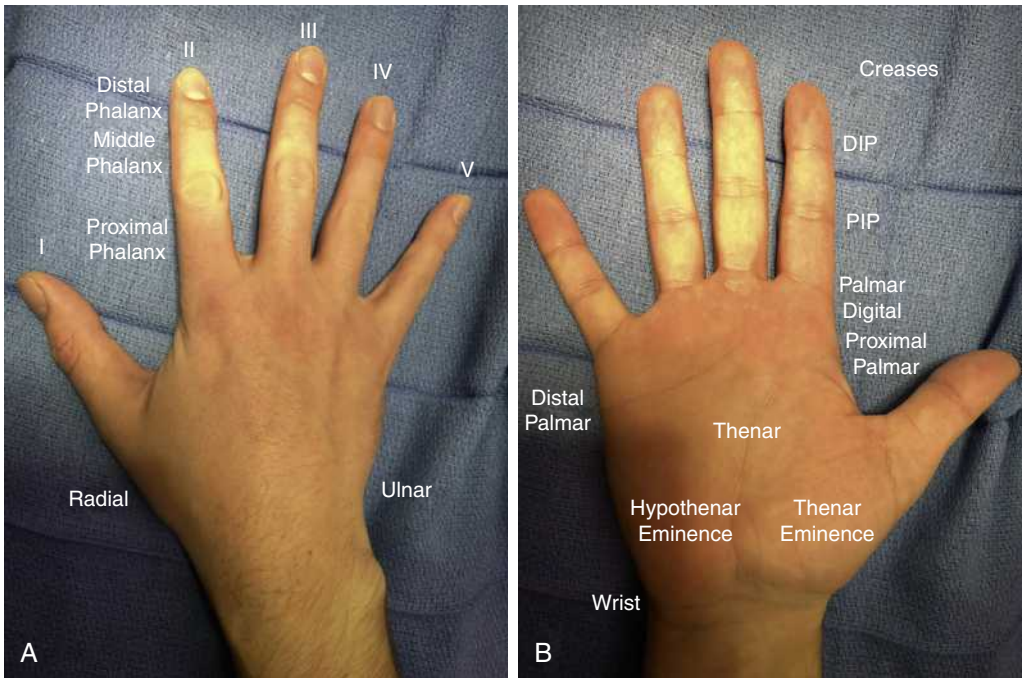

Fig. 42.1 (A) Dorsal and (B) volar views of the hand with digits I–V, palmar creases, and surface anatomy labeled (Courtesy of Benjamin Schoener, MD and Harrison Zeitler, MD; Central Michigan University COM)

The distal part of the nail is known as the nail body and the proximal portion of the nail is the nail root. The point of division is at the distal lunula, visible on exam as the white crescent-shaped area of the nail bed. The lunula represents the distal end of the germinal matrix, which is responsible for generation of the nail plate, which grows distally along the nail bed. Damage to the germinal matrix may lead to permanent damage of the nail plate. The insertion of the extensor tendons is found as distal as the lunula with a similar location for insertion of the flexor digitorum profundus (FDP), so damage to this area can result in tendon dysfunction. The small area of skin covering the proximal nail is known as the eponychium or cuticle. The hyponychium is skin underlying the distal nail plate. The paronychium refers to the skin overlying the lateral portions of the nail plate.

Examination of the nail bed by checking for capillary refill is important when assessing a patient's perfusion status. Additionally, the nail itself should be assessed for clubbing, spooning, splinter hemorrhages, discoloration, and thickness.

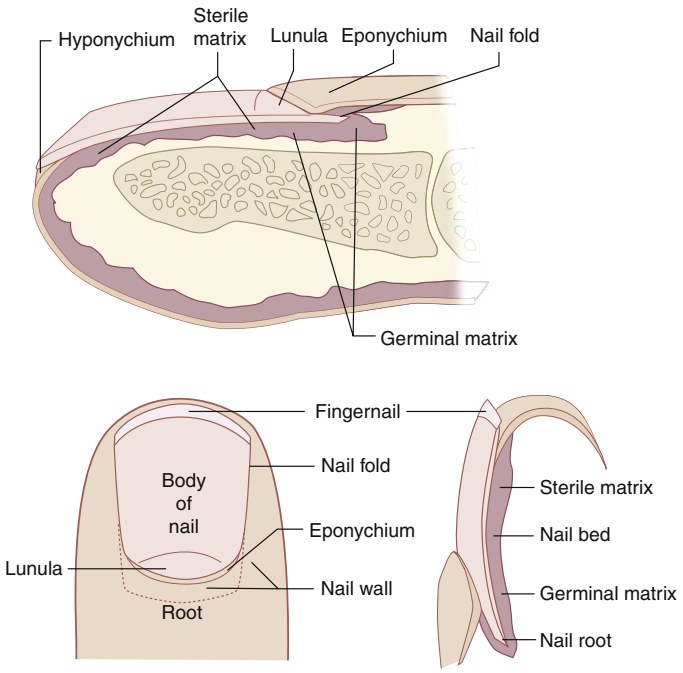

Fig. 42.2 Fingernail with labeled anatomy. (From: Buttaravoli P, Leffler, Stephen M. *Minor Emergencies*, ed 3. Philadelphia: Elsevier Saunders; 2012:535-538.)

Skeletal Anatomy and Ligaments

The hand is comprised of five digits: four fingers and one thumb. Each digit is numbered from I to V with digit I being the thumb and digit V being the little finger. The fingers contain a distal, middle, and proximal phalanx, while the thumb only has a proximal phalanx and a distal phalanx. The joints of the hand from proximal to distal include the carpometacarpal (CMC), metacarpophalangeal (MCP), proximal interphalangeal (PIP), and the distal interphalangeal joints (DIP) (Fig. 42.3). Proximal to the metacarpals are the 8 carpal bones which are tightly bound by ligaments which creates a concave formation on the volar surface. This is held together by the flexor retinaculum, a strong fibrous band, which forms the carpal tunnel, containing the median nerve and flexor tendons passing from the forearm. The boundaries of the carpal tunnel include the flexor retinaculum volarly and the carpal bones medially and laterally.

Bone development in the hand differs from other long bones. The thumb metacarpal epiphysis and phalangeal epiphyses are located at the proximal end. The finger metacarpal epiphyses are located at the distal end. The ossification centers of the phalanges and metacarpals appear at 10 to 36 months of age and usually fuse by age 14 to 16 years, with females having ossification earlier than males in general. The

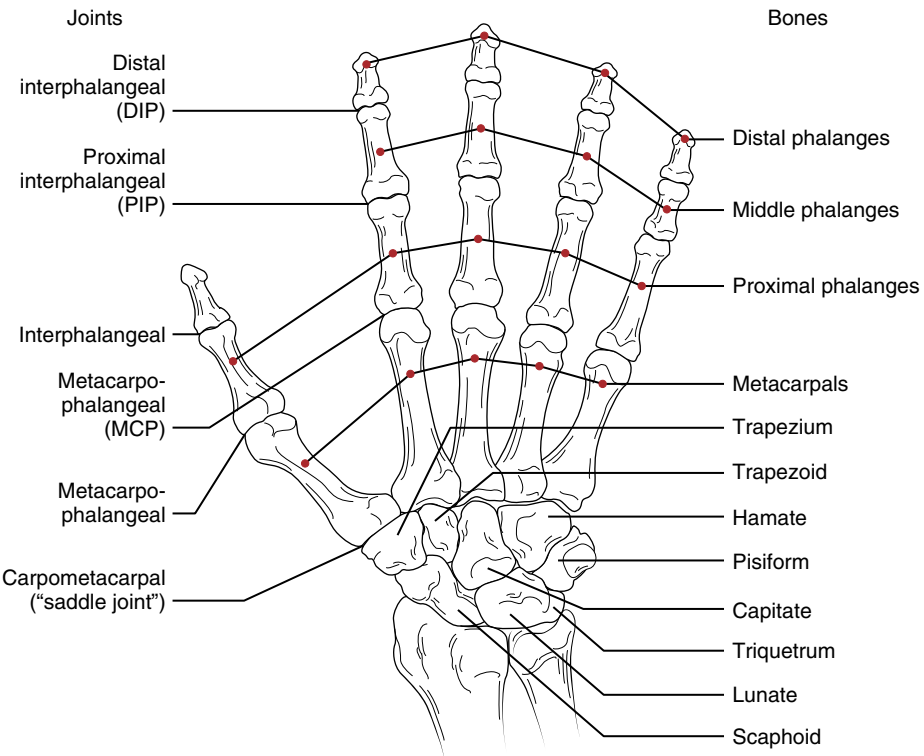

Fig. 42.3 Anatomy of the bones and joints of the hand. (Trott AT. *Wounds and Lacerations: Emergency Care and Closure*. Philadelphia: Elsevier Saunders; 2012:161-191.)

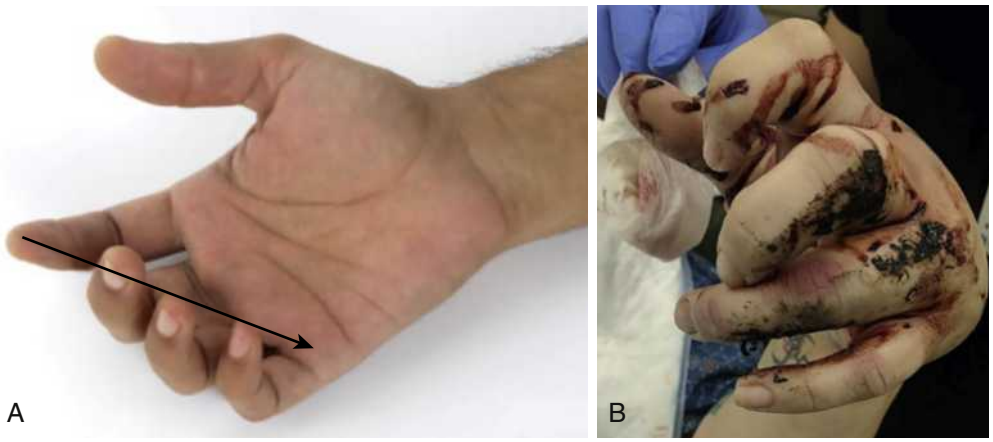

Fig. 42.4 Cascade of the hand. (A) Demonstration of cascade testing where the hand is positioned with the palm upward. Notice the gradual increase in flexion from radial to volar for joints of the hand. (B) Abnormal cascade in a patient following a crush injury. There is overlap of digits with a rotational deformity. (From: [A] Odak S, Bhalaik V. Assessment of the acutely injured hand. *Orthop Trauma.* 2014;28(4):199-204; [B] Courtesy of Tiffany Weiss-Feldkamp, DO and David Kramp, MD; Central Michigan University COM)

ossification center of the middle finger generally develops first and the fifth generally develops last.

The DIP and PIP joints of the fingers are uniaxial hinge joints that move along a sagittal plane. The DIP joint can flex to a maximum of 90 degrees whereas the PIP joint can flex up to 105 degrees from full extension. The DIP and PIP joints are structurally identical in that they both have a bicondylar configuration with a tongue-in-groove insertion of the distal phalanx. This configuration on both sides of the joint, in addition to collateral ligaments (also known as retinacular ligaments), is responsible for lateral stability and resisting of lateral, oblique, and rotatory forces. To provide additional stability, a fibrocartilaginous volar plate forms the anterior surface of the IP joint. The volar plate, along with a pair of check ligaments, serves to reinforce the joint capsule and limit hyperextension.

To evaluate any rotational deformities of the fingers in flexion, the *cascade sign* test may be used (Fig. 42.4). With the patient's elbow flexed to 90 degrees and the forearm supinated, the patient closes his or her hand with the thumb remaining open. Normally, the fingers should come together over the thenar and hypothenar eminences and point toward the scaphoid region. However, if there is overlap of the fingers or they are askew, this is a positive cascade sign, indicating rotational deformity often associated with metacarpal or phalangeal fractures.

In contrast to the IP joints, the MCP joints are less stable. They are formed by a rounded head of the metacarpal bone inserting into the concave surface of the proximal phalanx. This facilitates an efficient grasp by allowing for some rotational movement and side-to-side mobility. The MCP joints also contain a volar plate and collateral ligaments, though the volar plates of the MCP joints, unlike the IP joints, are interconnected by a deep transverse ligament. Additionally, the arc of rotation of the MCP joint depends on the degree of flexion of the proximal phalanx. As the MCP joint is flexed from 0 to 90 degrees, the collateral ligaments transition from a relaxed to a tight functional state. The integrity of the collateral ligaments should be tested when the MCP joint is fully flexed, where there should be no ability to abduct or adduct the phalanx. This is in contrast to the extended state, where limited side-to-side mobility is possible.

The functional anatomy of the MCP joint also illustrates the importance of splinting the joint in flexion to avoid shortening and subsequent stiffening of the collateral ligaments. Functional positioning is essential for proper splinting of the hand (Fig. 42.5).

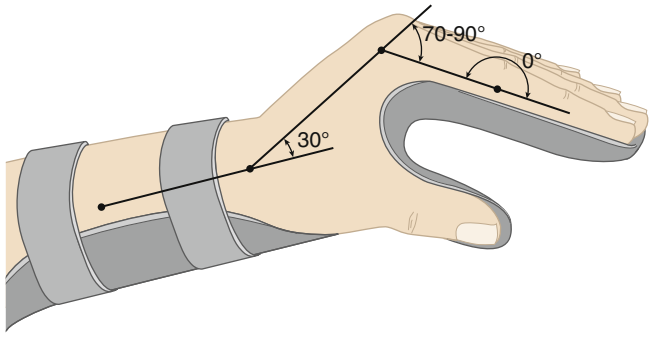

Fig. 42.5 Functional position of the hand with the wrist at 30 degrees extension, the MCP joint at 70-90 degrees flexion, and the PIP and DIP joints fully extended. (From: Yang G, McGlinn EP, Chung KC. Management of the stiff finger: evidence and outcomes. *Clin Plast Surg.* 2014;41(3):501-512.)

The arrangement of the metacarpals creates three arches: the proximal (carpal) and distal (metacarpal) transverse arches and the longitudinal arch (Fig. 42.6). The articulations between the carpal and metacarpals for the second and third digits are essentially fixed, making them relatively immobile in comparison to the articulations of the fourth and fifth digits, which have 15 and 25 degrees of movement, respectively. This variability creates a transverse and longitudinal concavity when the thumb is adducted against the index finger.

The joints of the hand should be properly examined for erythema, pallor, and swelling. They should also be examined for excessive warmth to assess for inflammatory arthritis. Cool or discolored digits may indicate vascular pathology or Raynaud phenomenon. Both passive and active range of motion of the joints should be assessed (Box 42.2). Crepitus may be present with a joint effusion or inflammatory arthritis. Clicking or snapping may indicate that tendonitis is present.

Musculature and Tendons

The muscles of the hand are divided into two groups: intrinsic and extrinsic. The intrinsic hand muscles contain origins and insertions within the hand itself, whereas the extrinsic hand muscles include origins proximal to the hand with tendon insertions within the hand.

Intrinsic Musculature. The intrinsic hand muscles include the muscles of the thenar and hypothenar eminences as well as the adductor

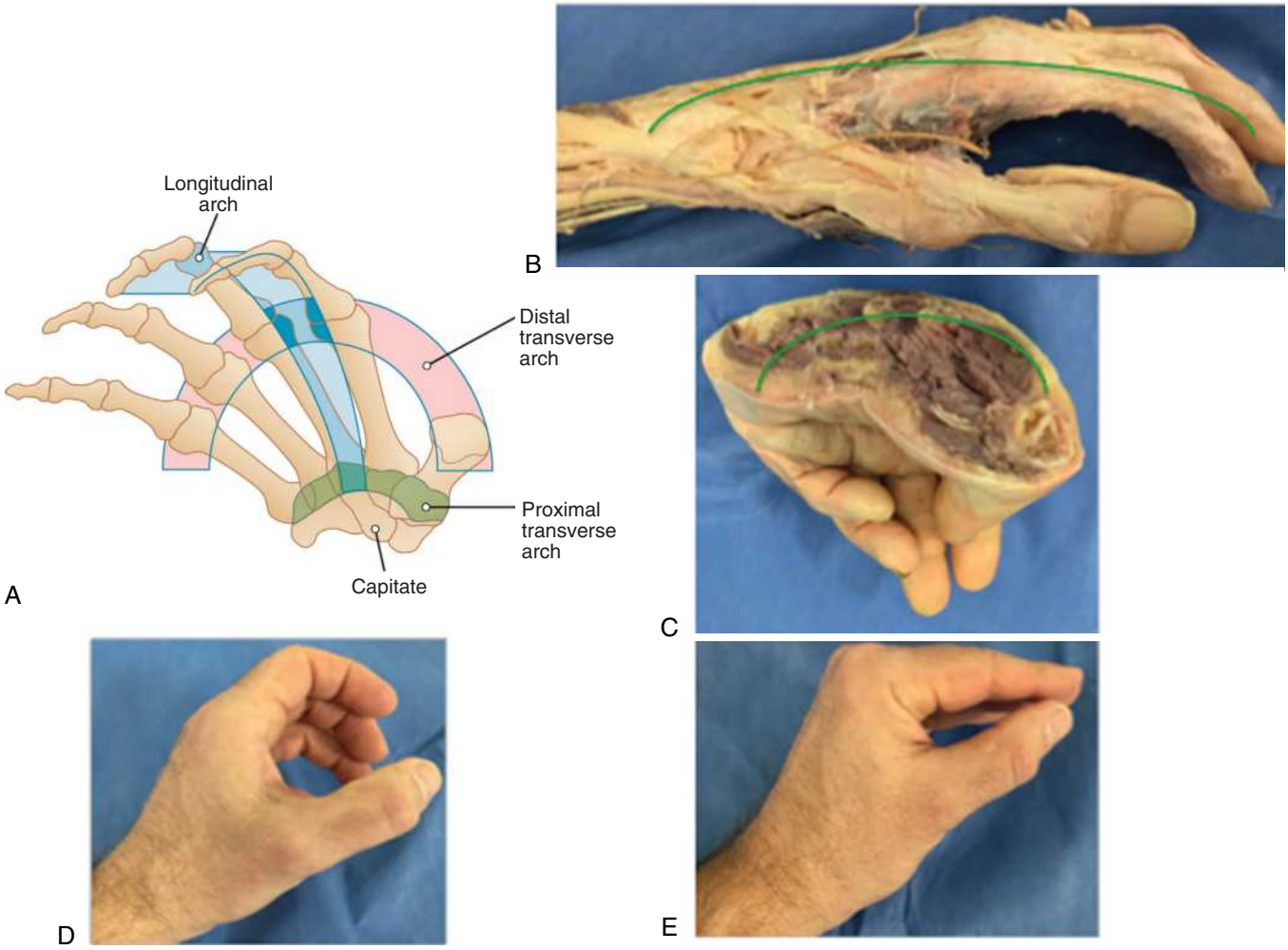

Fig. 42.6 (A) The longitudinal and transverse arches of the hand and their relationship to the metacarpals. (C) Proximal transverse arch. (D & E) Articulations of the thumb are unique and contribute to the intrinsic arches to create an array of grasp positions. (A from Erickson M, et al. Anatomy and kinesiology of the hand. In: *Rehabilitation of the Hand and Upper Extremity*. Jan 1, 2021. (c) 2021. Fig. 1.3; B–E courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

BOX 42.2 Maximum Joint Range of Motion

I. Fingers
- MCP: 0 to 90 degrees flexion
- PIP: 0 to 110 degrees flexion
- DIP: 0 to 85 degrees flexion

II. Thumb
- MCP: 10 degrees hyperextension to 70 degrees flexion
- IP: 15 degrees hyperextension to 90 degrees flexion

pollicis, lumbricals, and interossei. These muscles are innervated by the median and ulnar nerves.

The muscles of the thenar eminence cover the metacarpal of the thumb and include the abductor pollicis brevis, flexor pollicis brevis, and the opponens pollicis. The names of these muscles describe their function and they are controlled by the recurrent branch of the median nerve. The muscles are easily palpable over the volar surface of the hand proximal to the MCP joint of the thumb.

Another muscle in this location, the adductor pollicis, arises from the capitate and bases of the second and third metacarpals. Unlike other muscles in this location, it is innervated by the ulnar nerve and functions to adduct the thumb and rotate it medially. The adductor pollicis, as well as ulnar nerve function, can be tested by asking the patient to hold a piece of paper between the thumb and index finger. If when the examiner attempts to pull the paper out of the patient's hand, the patient is unable to hold on, or there is flexion of the thumb at the IP joint, this indicates weakness of the adductor pollicis muscle. This is also known as the *Froment paper sign* (Fig. 42.7). The patient flexes his or her thumb because the median nerve–innervated flexor pollicis longus tendon takes over to allow the thumb to grasp the paper when the adductor pollicis is weak.

The muscles of the hypothenar eminence include the opponens digiti minimi, flexor digiti minimi, and abductor digiti minimi. All three muscles aid in movement of the little finger and are innervated by the ulnar nerve. Strength of these muscles may be evaluated by having the patient hold a piece of paper between the thumb and little finger or by having the patient attempt to abduct the little finger against resistance.

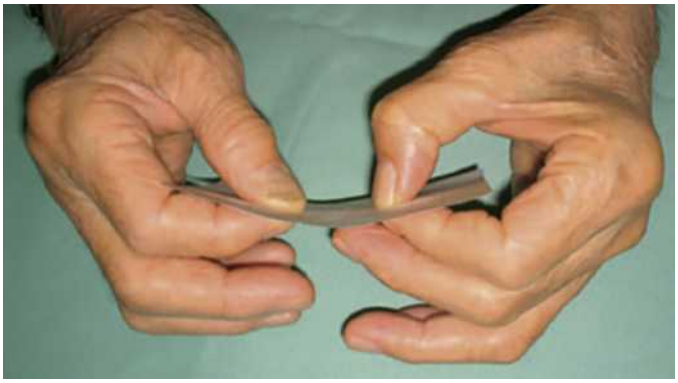

Fig. 42.7 Froment sign demonstrated in a patient with left ulnar nerve weakness. The patient attempts to hold onto the paper with the thumb IP joint in flexion and the MCP joint in hyperextension. (Kakinoki R. Examination of the upper extremity. In: *Plastic Surgery: Vol 6: Hand and Upper Extremity*, ed 4. London: Elsevier; 2017:49-70.)

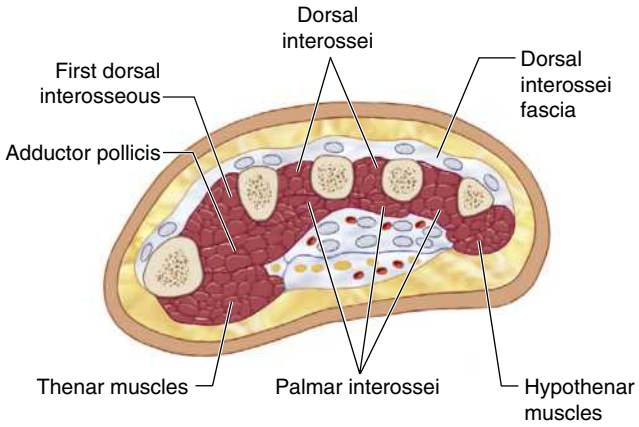

Fig. 42.8 Cross-sectional view of the compartments of the hand. (Lin PY, Sebastin SJ, Chung KC. Fasciotomy of the upper limb. In: Chung KC, ed. *Operative Techniques: Hand and Wrist Surgery*, ed 2. Philadelphia: Elsevier Saunders; 2012.)

The lumbricals originate from tendons of the flexor digitorum profundus (FDP) and insert at the extensor hood and the base of the proximal phalanx. They function to flex the MCP joints and extend the IP joints. The ulnar two lumbricals are innervated by the ulnar nerve and the radial two lumbricals are innervated by the median nerve.

The interossei muscles are divided into dorsal and palmar interossei. The four dorsal interossei are located in the intermetacarpal spaces and function to abduct the fingers. The three palmar interossei are also located in the intermetacarpal spaces and insert at the base of the second, fourth, and fifth proximal phalanx. They function to adduct the fingers. All interossei are innervated by the deep branch of the ulnar nerve.

Extrinsic Musculature. The extrinsic hand muscles are those that originate proximal to the wrist and insert within the hand. Most extrinsic hand muscles originate in the forearm. The dorsal forearm contains extensor muscles of the wrist and fingers as well as abductors of the thumb. The volar forearm contains flexor muscles of the wrist, thumb, and other fingers.

Extensor Muscles and Tendons. The extensors tendons pass through the dorsum of the wrist at 6 different compartments and are innervated by the radial nerve (Fig. 42.8). Compartment 1 is located most radial and contains the abductor pollicis longus and extensor pollicis brevis tendons which form the lateral border of the anatomical snuffbox. Both muscles are innervated by the posterior interosseus nerve, a branch of the radial nerve. Compartment 3 contains the extensor pollicis longus tendon, which forms the medial border of the anatomical snuffbox. The tendons forming the borders of the anatomical snuffbox are easily palpable and often visible when the thumb is held in abduction and extension. Compartment 2 contains the extensor carpi radialis longus and extensor carpi radialis brevis tendons, which insert at the base of the second and third metacarpals, respectively. Both muscles act to extend and abduct the hand at the wrist.

Compartment 4 contains the extensor indicis and extensor digitorum communis (EDC) tendons. The extensor indicis proprius (EIP) inserts into the extensor hood, which is a dorsal aponeurosis of the index finger. The EDC tendons similarly insert into the extensor hood of the middle and distal phalanges of the second, third, fourth, and fifth fingers. The muscles of compartment 4 function to extend the 4 digits and the hand, though primarily at the MCP joint. Extensions of tendons from the extrinsic and intrinsic muscles form an extensor complex on the dorsum of the fingers. Extensions from the lumbrical and interosseus muscles connect with extensions of the extensor digitorum tendons to form the extensor hood (expansion). The expansion divides into three bands—two lateral bands and a central tendon (central slip). The three bands are held together by the transverse retinacular ligament preventing volar displacement of the lateral bands which would result in PIP flexion as seen in the *boutonnière deformity* (Fig. 42.9).

Compartment 5 contains the extensor digiti minimi (EDM) tendon which inserts at the extensor expansion at the base of the fifth digit and extends it at all joints. Compartment 6 contains the extensor carpi ulnaris (ECU) tendon which inserts at the fifth metacarpal and functions to extend and adduct the wrist.

Of relevance to identifying and diagnosing an extensor tendon injury are the zones of the extensor tendons. This will be discussed in depth under extensor tendon injuries.

Flexor Muscles and Tendons. The anterior forearm contains muscles responsible for flexion of the wrist, hand, and digits and can be divided into an anterior compartment and posterior compartment.

The flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), and palmaris longus (PL) tendons are responsible for flexion of the hand at the wrist. The flexor carpi radialis (FCR) inserts at the base of the second and third metacarpals and is controlled by the median nerve. In addition to flexion of the wrist, it is responsible for abduction of the hand at the wrist. The flexor carpi ulnaris (FCU) inserts at the hook of the hamate and base of the fifth metacarpal. It is controlled by branches of the ulnar nerve and is responsible for flexion and adduction of the hand at the wrist. The palmaris longus muscle inserts at the palmar aponeurosis and flexor retinaculum. It is controlled by the median nerve and is responsible for wrist flexion. It can be visible and palpable when one flexes the wrist and touches the pads of the fourth finger and thumb together. Of note, it is innately absent in approximately 25% of patients.[3] Both the palmaris longus and flexor carpi ulnaris (FCU) partially insert at the flexor retinaculum, a fibrous band covering the carpal bones and forming the roof of the carpal tunnel.

The flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS), and flexor pollicis longus (FPL) are responsible for flexion of the digits and enter the hand via the carpal tunnel. All three muscles are innervated by the median nerve or one of its branches with the exception that movement of the fourth and fifth digits via the FDP is controlled by the ulnar nerve. The FDP originates over the proximal body of the ulna and fans out into 4 tendons which insert at the base of the distal phalanges. The FDP primarily functions to flex the fingers at both interphalangeal joints. The flexor digitorum superficialis (FDS) lies superficial to the FDP in the forearm and similarly fans into 4 tendons, though these insert at the base of the intermediate phalanges of digits 2 through 5. The FDS primarily functions to flex the PIP joints.

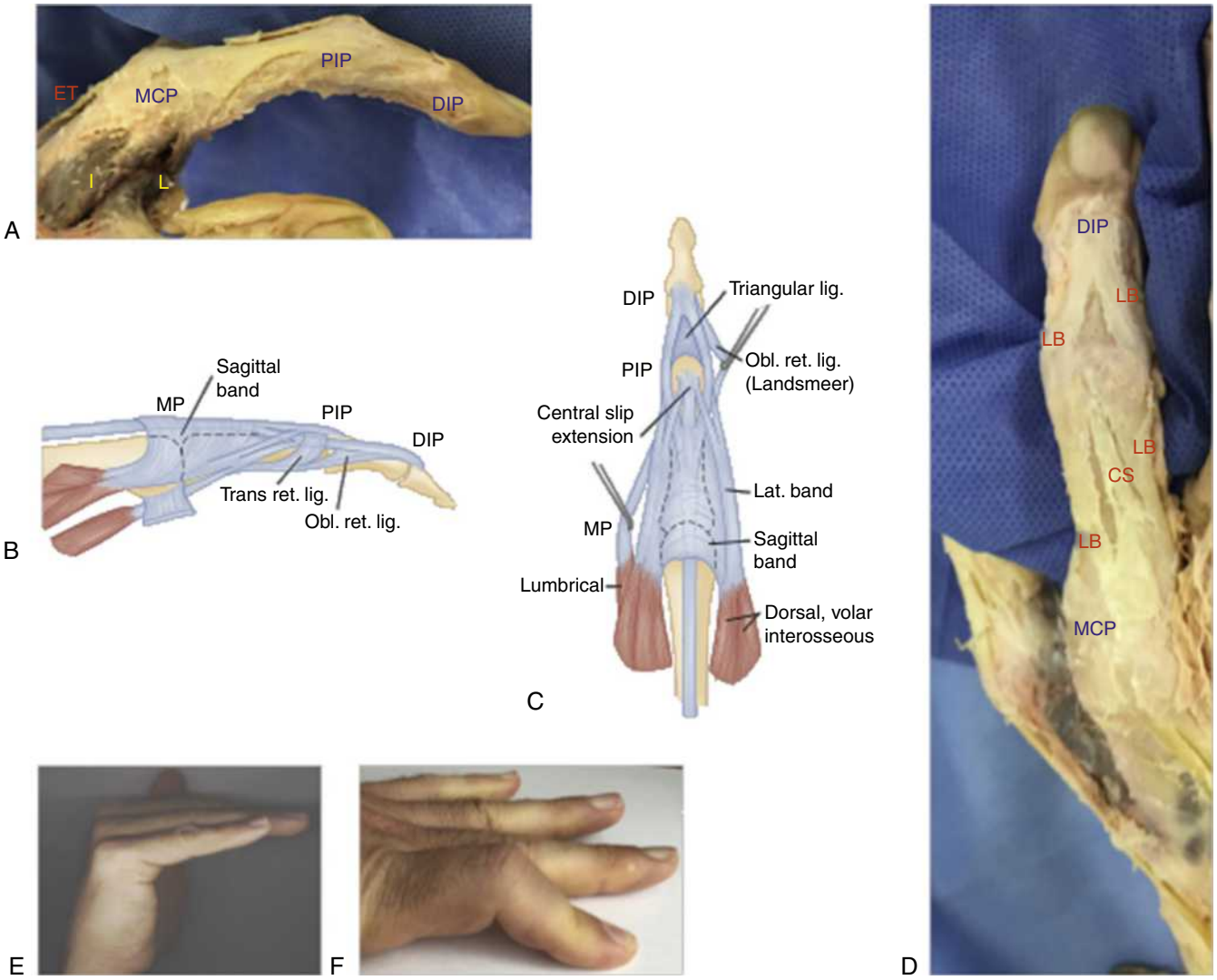

Fig. 42.9 Finger extensor complex. (A and B) The extensor hood is formed by a sagittal band originating from metacarpal ligaments and volar plate. The intrinsic tendons lumbrical (L) and interosseous (I) muscles insert into the extensor mechanism along the proximal dorsal phalanx. (C and D) The extension complex at the PIP joint contains a central slip (CS), which inserts on the dorsal base of the middle phalanx and two lateral bands (LB). The lateral bands insert at the dorsal base of the distal phalanx, extending beyond the distal interphalangeal (DIP) joint. (E and F) The PIP extension mechanism over the PIP joint is maintained by the transverse and triangular ligaments, preventing the lateral bands from migrating anteriorly, which would result in paradoxical PIP joint flexion. (F) Demonstration of boutonnière deformity where the PIP joint of the index finger is paradoxically flexed with DIP extension. (A, D–F: Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; B, C: from: Doyle JR. Extensor tendons—acute injuries. In Green DP, ed. *Operative Hand Surgery*. New York: Churchill Livingstone; 1998:1928.)

To test for FDS integrity, the examiner should flex the associated finger against resistance at the PIP while holding the other fingers in extension to control for FDP action (Fig. 42.10). The flexor pollicis longus functions to flex the thumb and inserts at the base of its distal phalanx (Table 42.1).

Digital Flexor Sheath. The digital flexor sheath of the hand is a closed system of synovial membranes that is divided into membranous and retinacular components. The membranous portion contains interdigitations between the retinacular tissue and tendons. Of note, the synovial sheaths of the flexor tendons are avascular systems and thus are more prone to infection. Extensor tendons, which do not have similar sheaths, are less likely to develop infectious tenosynovitis (Fig. 42.11).

The retinacular component is also described as the "pulley system" that overlies the synovial sheath which consists of the palmar aponeurosis (PA) pulley, 3 cruciform pulleys, and 5 annular pulleys. Of note, the thumb flexor tendon sheath has its own pulley system (Fig. 42.12). The overall function of the pulley system is to maintain tendons in axis with flexion of the MCP and ICPs, thereby preventing "bowstringing." The A2 and A4 pulleys are the most essential to preserve.

Blood Supply

Arterial Supply. The radial and ulnar arteries are primarily responsible for blood supply to the hand. The radial artery courses through the anatomical snuffbox where it branches into the deep palmar arch and the superficial palmar arch. The princeps pollicis

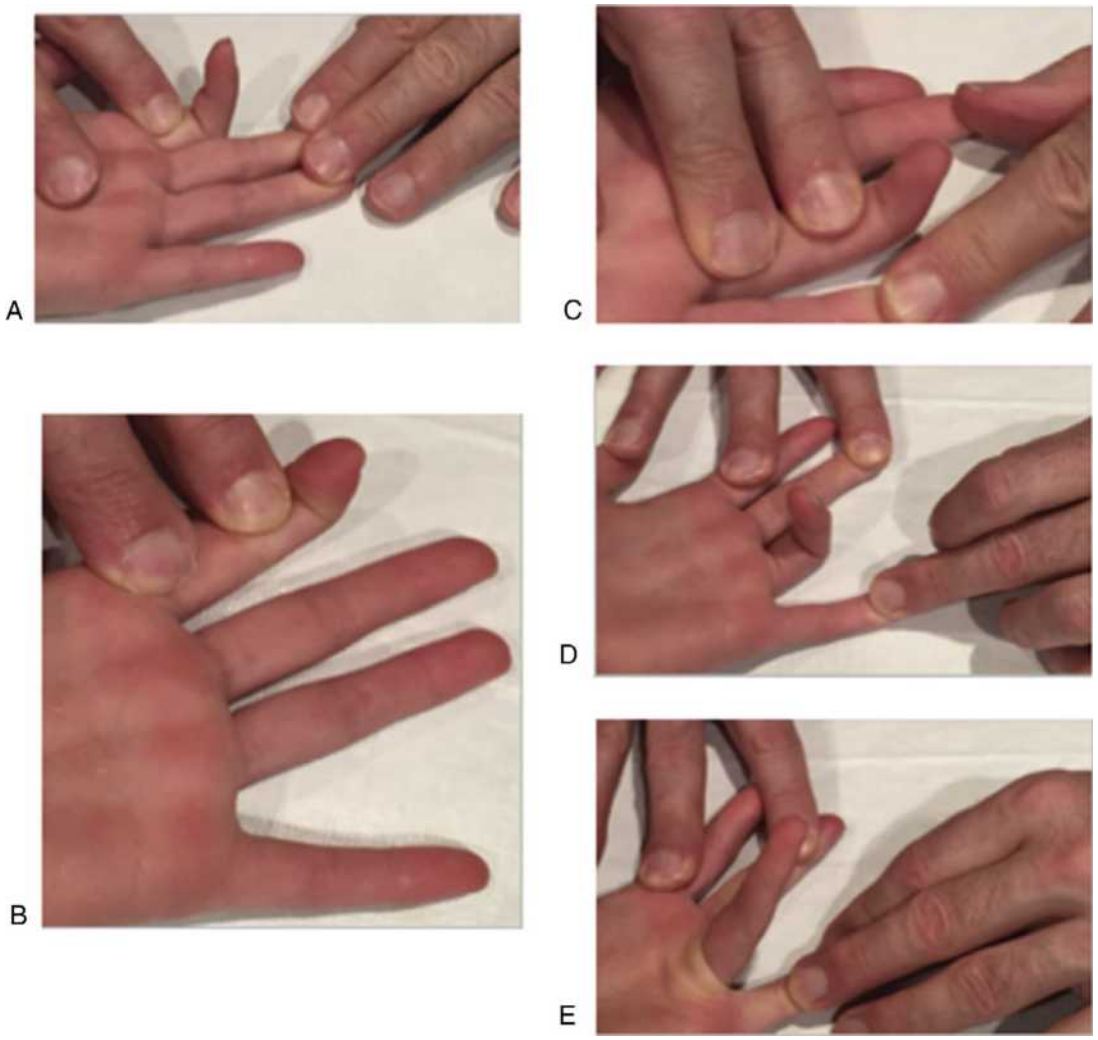

Fig. 42.10 Demonstration of individual testing of flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP) tendon integrity (A) The index finger FDS tendon is examined by asking the patient to flex the corresponding proximal interphalangeal (PIP) joint while the adjacent digits are held in extension by the examiner. (B) FDP integrity is assessed by asking the patient to flex the distal interphalangeal (DIP) joints of each digit individually while the corresponding PIP joints are stabilized in extension by the examiner. (C–E) The ring finger's flexor digitorum profundus (FDP), FDS, and lumbrical functions are tested individually. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

TABLE 42.1 Flexor Tendons of the Hand

Flexor Tendon	Insertion	Innervation	Function/Physical Examination
Flexor Carpi Radialis	Second and third metacarpal bases	Median N.	Flexion and radial deviation at the wrist
Flexor Carpi Ulnaris	Hook of hamate and base of fifth metacarpal	Ulnar N. Branches	Flexion and ulnar deviation at the wrist
Palmaris Longus	Palmar aponeurosis and flexor retinaculum	Median N.	Flexion at wrist, palpable tendon if present
Flexor Digitorum Profundus (FDP)	Base of distal phalanges	Median N. and Ulnar N.	Flexion of MCP, DIP, and PIP joints (Isolated examination by flexing DIP with other joints held in extension)
Flexor Digitorum Superficialis (FDS)	Base of proximal phalanges	Median N.	Flexion of MCP and PIP joints (Examine by flexing PIP with MCP held in neutral position)
Flexor Pollicis Longus	Base of distal phalanx of thumb	Median N.	Flexion at MCP and IP joints of thumb

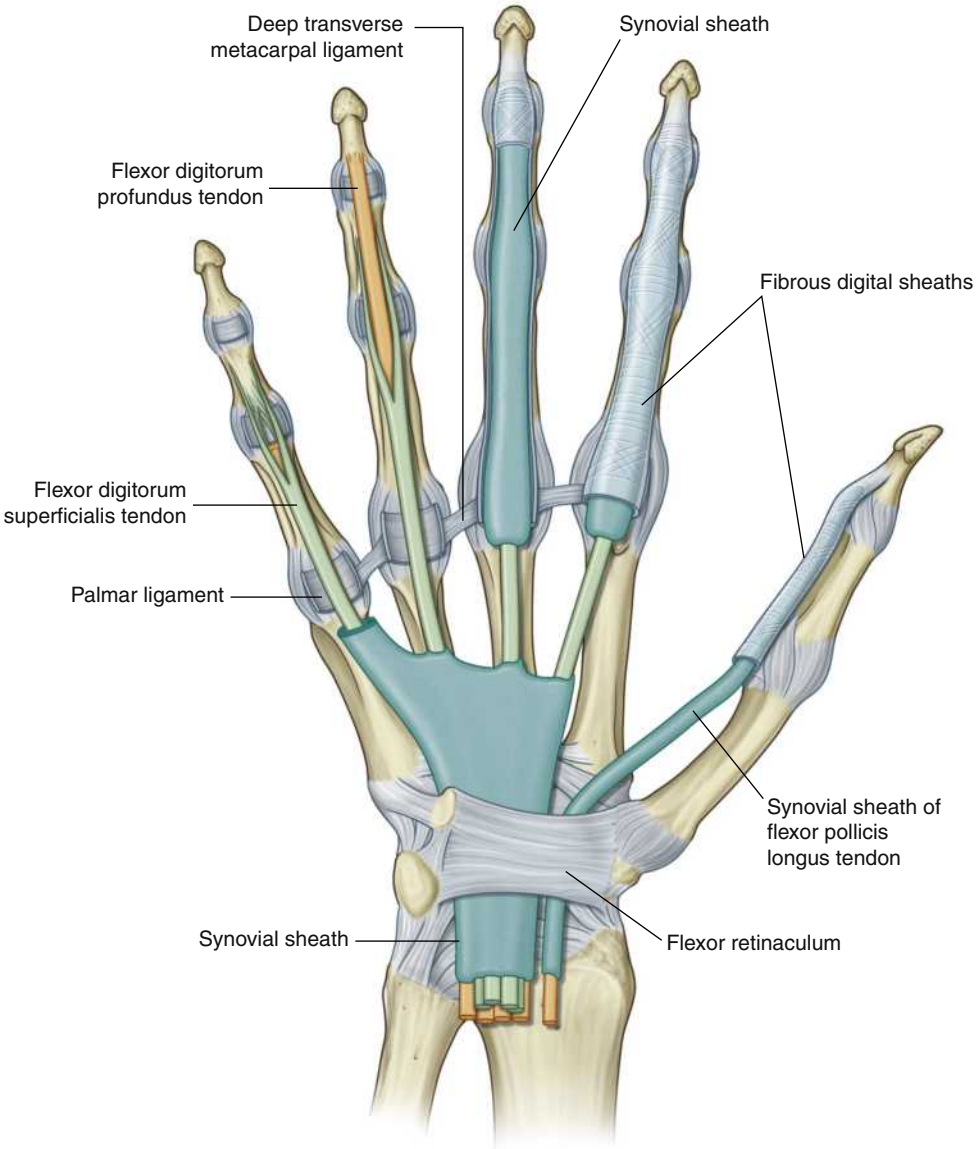

Fig. 42.11 The synovial sheaths of the hand and their relationship to the flexor tendons. (Drake RL, Vogl AW, Mitchell A. Upper limb. In: *Gray's Anatomy for Students,* ed 4. Philadelphia: Elsevier; 2020:671-821.)

artery and the radialis indicis artery arise from the deep palmar arch. The deep palmar arch of the radial artery continues to loop deep within the volar surface of the hand and anastomoses with the ulnar artery. The superficial palmar arch of the radial artery courses superficially over the metacarpals where it also anastomoses with the ulnar artery. In doing so, the superficial palmar arch gives rise to the palmar digital arteries which further branch to supply the fingers distally from the radial and ulnar aspects of each digit (Fig. 42.13).

The ulnar artery enters the hand superficial to the flexor retinaculum through the wrist via the Guyon canal, a space created by the pisiform and palmar carpal ligament. Immediately distal to the Guyon canal, the ulnar artery branches into the large superficial palmar arch. These arches form collaterals with the deep palmar arches of the radial artery and perfuse every digit in almost all patients. The collateral arterial system within the hand and digits allow for continued perfusion if either the radial or ulnar arterial flow is impaired. Testing for perfusion via the radial and ulnar arteries individually can be accomplished through the *Allen test* (Fig. 42.14).

There are times when an Allen test cannot be performed due to the patient's level of consciousness or due to other injuries. In those situations, simple palpation or use of Doppler ultrasound to assess blood flow to the hand through the radial and ulnar arteries at the wrist will suffice. It is important to make sure backflow through the palmar arch does not give the examiner a false-positive result of a patent artery. Thus, the ulnar artery should be compressed at the wrist when checking the patency of the radial artery when the Allen test cannot be done. Additionally, there may be significant arterial injury in the absence of heavy bleeding as the injured vessel may become compressed by surrounding edematous tissue.

Venous and Lymphatic System

The deep veins of the hand travel in a neurovascular bundle along with the arteries of the hand. The dorsum of the hand contains the lymphatic system within the loose subcutaneous tissue. The lymphatics eventually drain into the forearm via the cephalic and basilic veins. The presence of lymphatics and loose subcutaneous tissue results in greater swelling on the dorsum (versus volar) aspect of the hand with infections.

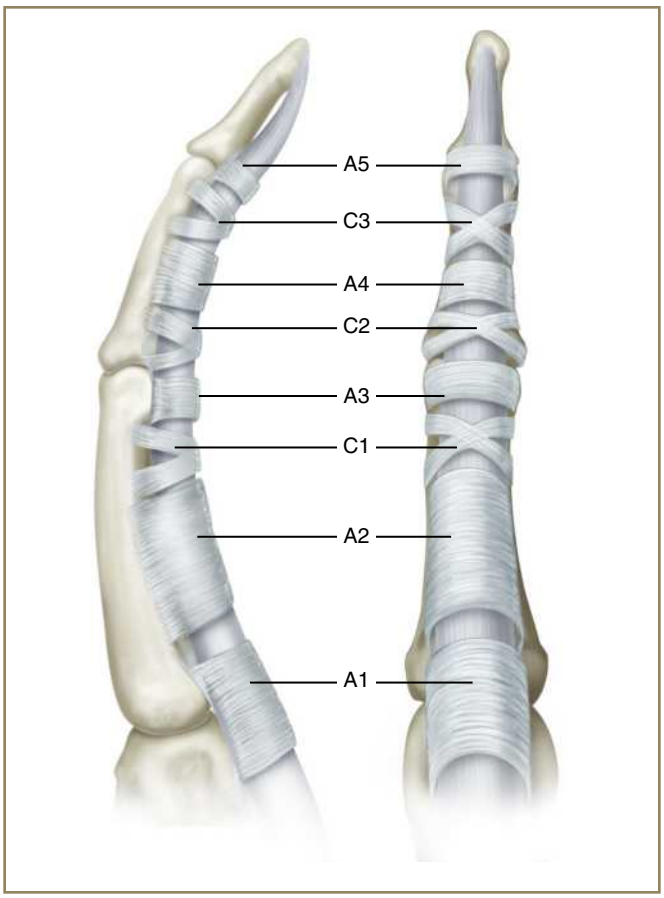

Fig. 42.12 Normal anatomy of the flexor pulley system with lateral and volar views. A2 and A4 are the narrowest points. (From: Morrison WB, Sanders TG. *Problem Solving in Musculoskeletal Imaging*. Philadelphia: Mosby; 2008:484.)

Innervation and Sensory Systems

The median nerve enters the hand via the carpal tunnel. It is responsible for sensation of the radial two-thirds of the volar surface of the hand as well as the flexor surface of fingers 1 through 3 and the radial half of the fourth (ring) finger (Fig. 42.15). The motor branch of the median nerve innervates five intrinsic muscles of the hand including the thenar muscles and two of the lumbricals. The extrinsic muscles of the hand innervated by the median nerve include the flexor tendons to the radial three digits and FCR.

The ulnar nerve supplies sensation to the ulnar one-third of the hand at both the volar and dorsal surfaces. It is also responsible for sensation of the fifth finger and the ulnar half of the fourth finger. The ulnar nerve is responsible for the extrinsic motor function of the flexor carpi ulnaris (FCU) and the flexor digitorum profundus (FDP) tendons of the fourth and fifth digits. It also innervates the remaining intrinsic muscles of the hand and divides into a volar and dorsal branch at the wrist. The volar branch, along with the ulnar artery, enters the palm through the Guyon canal. It is responsible for movement of muscles of the hypothenar eminence, interosseus muscles, and the lumbricals of the fourth and fifth fingers. The deep branch innervates the adductor pollicis. The ulnar nerve's motor innervation of the fourth and fifth digits is largely responsible for grip power and injury can significantly alter normal use of the hand.

The radial nerve contains superficial and deep branches and provides sensation to the radial two-thirds of the hand on the dorsal surface excluding the fingertips. There are no motor function branches for the radial nerve within the hand, though its innervation of the dorsal forearm leads to hand function including extension of the wrist (extensor carpi radialis longus) as well as other extensor tendons (extensor digitorum communis, extensor digiti quinti proprius, extensor pollicis longus and brevis).

The median, ulnar, and radial nerves each give rise to common digital nerves which further divide into lateral and medial branches on respective sides of each digit (Fig. 42.16). There are four individual digital nerves supplying sensation to each digit. The dorsal branch of these nerves run along the dorsal edge of the line made by the flexor crease to the tip of the finger.

Sensation of the hand should be tested in all hand injuries, particularly in patients with suspected nerve injury. Two-point discrimination is most precise in testing for sensation at the digits and may be tested by using the blunt ends of a paperclip (Fig. 42.17). Sensation is deemed intact if a patient is able to distinguish between one and two points to a distance of 5 mm.

For rapid examination of the motor and sensory functions of the hand, a few simple tests can be performed. One simple test for motor function of the radial, ulnar, and median nerve is to have the patient make an "OK" sign with their thumb and index finger (testing the median nerve), while dorsiflexing the wrist (radial nerve) and spreading/abducting the third, fourth, and fifth fingers (ulnar nerve). For general sensory examination, a clinician can test the finger tufts of the index finger (median nerve), the little finger (ulnar nerve), and the dorsum of the proximal phalanx of the thumb (radial nerve) with two-point discrimination. Simply being able to differentiate between sharp and dull is often enough to assess sensation. This can be done expeditiously at the bedside by using a broken tongue blade or 18-gauge needle.

If there is any concern about the function or sensation, more specific testing should be focused on a specific nerve and digit. It is important to identify where the nerves are injured. For example, if the ulnar nerve is severed in the forearm, the extrinsic muscles will not function and the fourth and fifth fingers will not flex. If tendons are lacerated in the hand, there may be similar dysfunctional results.

Regional Blocks

Digital Block

The digital block is commonly used for wound repair or incision and drainage of the affected finger. The volar and dorsal nerves of the finger course along the lateral edges of the fingers and allow for easy access to regional anesthesia (Fig. 42.18). Lidocaine 1% or 2% is commonly used for digital blocks, though bupivacaine may be used if a longer period of anesthesia is desired. Despite the lack of evidence, many people advocate against the use of epinephrine in anesthetic preparations given the theoretical potential for vascular compromise secondary to arterial constriction. However, a previous prospective study of over 3000 patients and a recent meta-analysis found no harm in the use of epinephrine for digital blocks in healthy patients.[4] Lidocaine with epinephrine has the added benefit of a longer period of anesthesia and potentiating hemostasis. Lidocaine with epinephrine should be used at the physician's discretion, though we uphold its safety in patients without severe vascular disease based on the current literature.

There are multiple ways to perform a digital block, though a common method is using the web spaces on each side of the digit being anesthetized. First, the skin at the locations of needle insertion should be adequately cleansed. The hand should be positioned with the palmar surface facing downward. A small needle is inserted into the skin at the distal webspace on the dorsal surface of the finger along the edge of the phalanx. The dorsal nerve runs under the skin alongside a

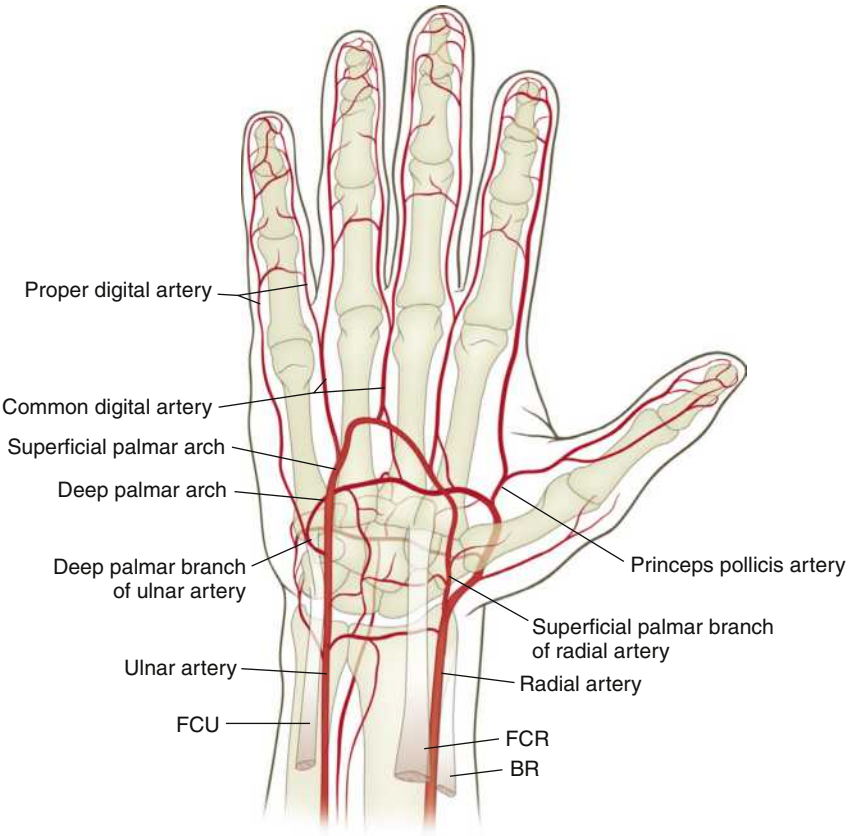

Fig. 42.13 Arterial anatomy of the hand. BR: brachioradialis; FCR: flexor carpi radialis; FCU: flexor carpi ulnaris. (From: Chhabra AB. Wrist and hand. In: Miller MD, Chhabra AB, Hurwitz S, et al,. eds. *Orthopaedic Surgical Approaches,* Philadelphia: Saunders; 2008:161.)

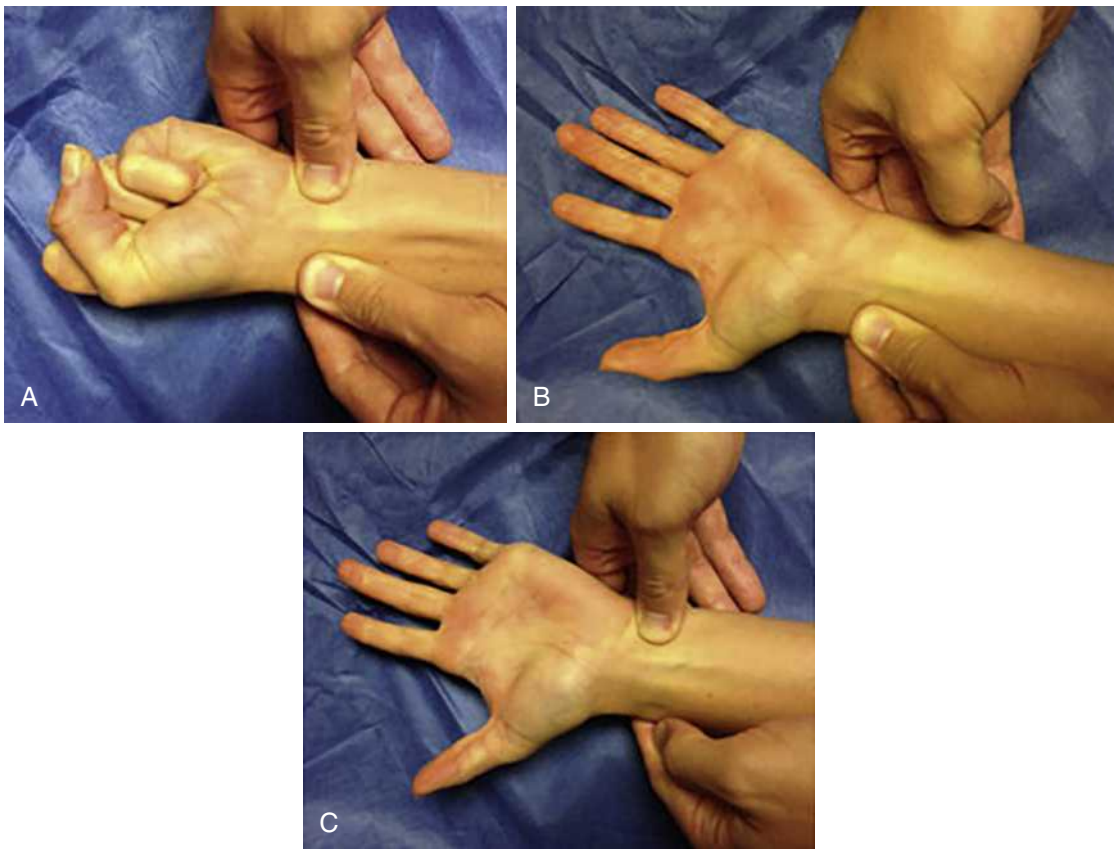

Fig. 42.14 Demonstration of the Allen test to individually evaluate ulnar and radial arterial flow. (A) Both arteries are compressed with the patient's hand in a fist. (B) Pressure over the ulnar artery is released while compression on the radial artery is maintained. (C) Capillary perfusion is assessed and then the test is repeated by reversing which vessel is compressed. (Grasau B, Jones CM, Murphy MS. Use of diagnostic modalities for assessing upper extremity vascular pathology. *Hand Clinic.* 2015;31(1):1-12.)

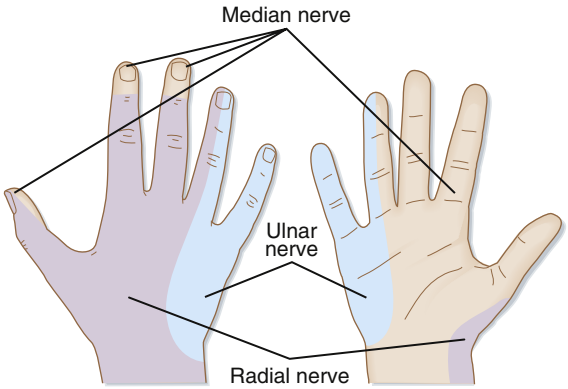

Fig. 42.15 Sensory distribution at the hand for radial, median, and ulnar nerves. (Murphy-Lavoie H, LeGros TL. Local and regional anesthesia. In: Adams JG, Barton ED, Collings, J, et al. *Emergency Medicine: Clinical Essentials*, ed 2. Philadelphia: Elsevier; 2013:1578-1586.)

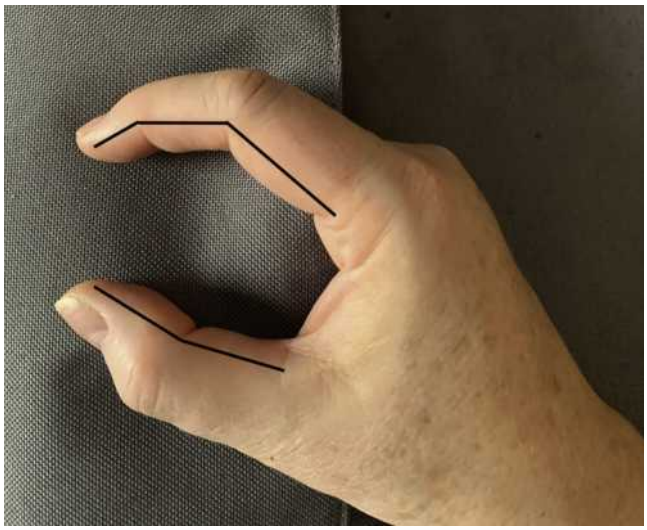

Fig. 42.16 The nerve, artery and vein bundle of the finger can be approximated on the skin by aligning the flexion creases of each joint. Avoiding this bundle when making an incision is desired. (Courtesy Clara Bihn, Butler University)

digital artery, so the operator should first aspirate to ensure there is no intravascular injection. A volume of 0.5 to 1 mL of local anesthetic is injected, and without withdrawing, the needle should be advanced into the volar side of the bony phalanx where an additional 0.5 to 1 mL of the anesthetic is injected. The same process should be repeated on the opposite side of the digit to ensure that all four nerves are anesthetized.

While it is possible to obtain appropriate anesthesia with local infiltration of anesthetic, there are several advantages of a digital block over local infiltration.[5] First, there are fewer injection sites, ideally resulting in less pain for the patient. Second, local infiltration creates edema along the wound margins leading to greater tissue distortion and greater difficulty in obtaining appropriate wound approximation, which can be avoided with a digital block. Third, less anesthetic is needed for most regional procedures.

Metacarpal and Transthecal Blocks

If more proximal anesthesia is desired, a metacarpal block may be performed. This block may be administered on either the dorsal or palmar side of the hand, though the dorsal approach is often preferred due to thicker skin on the volar surface as well as greater innervation, making penetration more difficult and less tolerable.

Fig. 42.17 Demonstration of two-point discrimination testing. (Jobe MT. Nerve injuries at the level of the hand and wrist. In: Azar F, Canale ST, Beaty J. *Campbell's Operative Orthopaedics*, ed 13. Philadelphia: Elsevier; 2016:3462-3477.)

For the palmar approach, the needle is inserted directly over the metacarpal head. When the needle is subcutaneous, it is directed to one side of the metacarpal. While advancing the needle approximately 1 cm, aspiration is performed to ensure the needle is not in a vessel, and approximately 3 mL of local anesthetic is injected. The needle is then partially withdrawn and redirected to the other side of the metacarpal and the procedure is repeated. With a transthecal digital block, the needle is similarly inserted into the palmar surface, though more proximally at the distal palmar crease. At a 45-degree angle, the needle is advanced directly into the flexor tendon sheath. If the sheath has been entered, there should be little to no resistance with injection of anesthetic. If there is significant resistance, the needle has likely entered the tendon and it should be gradually withdrawn.

The dorsal approach is similar to the traditional digital block. The needle is inserted along one side of the dorsal surface of the metacarpal approximately 1 cm proximal to the MCP joint. The needle is advanced until the palmar aponeurosis or the volar edge of the metacarpal where approximately 2 mL of anesthetic is injected. While withdrawing the needle, an additional 1 mL of anesthetic is injected along the tract. The procedure is then repeated on the dorsal surface of the opposite side of the same metacarpal.

Wrist Blocks

As discussed previously, the radial, median, and ulnar nerves supply sensation to the hand. Each nerve can be blocked individually to anesthetize its respective dermatome. Traditionally, these nerves have been blocked using anatomic landmarks at the wrist, though newer methods involve ultrasound-guided blocks at the forearm. These nerve blocks have the advantage of requiring less anesthetic volume and decreased need for opiate analgesia.[6] The goal is to inject around the nerve but not directly into the nerve. If the nerve is inadvertently injected the patient may feel an uncomfortable "shock-like" sensation.

Radial Nerve Block. The radial artery at the volar surface of the wrist is palpated. Immediately lateral (radial) to this region, after aspirating, approximately 2 to 5 mL of local anesthetic is injected.

Median Nerve Block. The tendon of the flexor carpi radialis at the volar surface of the wrist is palpated. The needle is inserted over the median nerve which is 1 cm ulnar from the flexor carpi radialis or between this tendon and the palmaris longus. The needle is advanced into the flexor retinaculum, where a "pop" may be felt, and the patient may complain of paresthesias. To avoid intraneural injection, the needle should be withdrawn a few millimeters where 3 to 5 mL of anesthetic agent is then injected. Due to baseline constriction at the flexor retinaculum, this procedure is a relative contraindication in patients with carpal tunnel syndrome.

Ulnar Nerve Block. The needle should be inserted between the ulnar artery and the flexor carpi ulnaris tendon and advanced approximately 1 cm. If the patient complains of paresthesia, the needle should be withdrawn a few millimeters with aspiration performed to ensure the needle is not in a blood vessel. Approximately 5 mL of anesthetic is then injected.

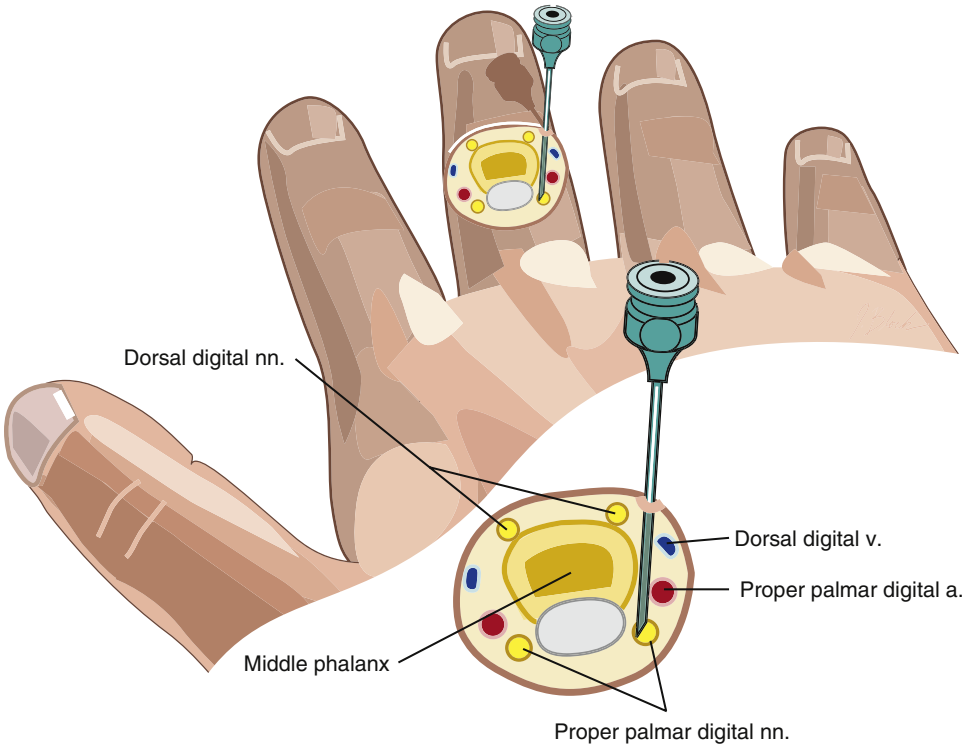

Fig. 42.18 Demonstration of digital and metacarpal nerve block with needle inserted at appropriate landmarks. (Waldman, SD. *Atlas of Interventional Pain Management*, ed 4. Philadelphia: Elsevier; 2015:275-278.)

Splinting

Splinting of hand injuries must take into account both the bony structures and the tendons that need to be protected. If a hand requires splinting for more than a day, the splint should maximize the length of the extensor tendons and the hand should be placed in a functional position. Specific positioning is needed for splints on patients with tendon or ligamentous injuries or certain fractures. The neutral position for general fractures of the hand or fingers is a volar splint with the wrist at 20 to 30 degrees extension, MCP at 70 to 90 degrees flexion, and the PIP and DIP kept in extension. This is also known as *intrinsic plus position* (Fig. 42.19). Appropriate positioning with splinting is critical because incorrect splinting is one the most common reasons for chronic hand stiffness after an injury.

Ring Removal

Early ring removal from an edematous finger is important because the ring acts as a tourniquet, causing further restriction of venous return and eventually arterial compromise if removal is delayed. Initial edema may occur secondary to a number of conditions such as infections, allergic reactions, fractures, arthritis, weight gain, or burns.

If the initial examination does not show signs of neurovascular compromise or severe constriction, the examiner may attempt removing the ring manually by lubricating the finger and then applying distal traction on the ring making twisting movements. The finger should be iced or elevated prior to this procedure to reduce swelling. If this is unsuccessful, there are other methods of ring removal.

In the absence of neurovascular compromise, deep ring erosion, or open wound, one may attempt less invasive methods such as the ring-wrap method, rubber-band method, or surgical glove method for ring removal. For the surgical glove method, the finger of a rubber or latex glove is cut off and placed over the patient's affected finger. The proximal end of the glove should be pulled underneath the ring (Fig. 42.20). Lubricant may be used to assist with this step. The proximal end of the glove should then be pulled back over the ring. Distal traction and twisting should be performed to advance the ring distally and assist in ring removal.

A similar technique has been described in the literature utilizing two rubber bands. These two rubber bands are advanced under the ring using a hemostat and are then used to pull distal traction on the ring for removal.[7]

In instances of deep ring erosion, an open wound, or obvious neurovascular compromise, prompt ring removal is essential. In these cases, we recommend use of a ring-cutting device if available (Fig. 42.21).[8] Most ring cutters have a circular blade and a hook or elevator. The hook should be slid under the ring. This serves as a barrier to the blade deep to the ring. The handle should be gripped, bringing the saw to the ring, where the grinding process through the ring can be performed. The ring may get hot during this process, and the patient may sustain a burn, so taking breaks approximately every 30 seconds is recommended. When the ring is cut, hemostats can aid in separating the two cut ends to remove the ring. Following ring removal, the patient should be monitored and examined for any signs of laceration or neurovascular compromise.

SPECIFIC HAND INJURIES

Phalanx and Metacarpal Fractures

Clinical Features

The hand is the most common location for fractures in the body. Specifically, phalanx and metacarpal fractures account for 10% of all fractures and the distal phalanx is the most common location.[9] These fractures are most common in young men and nearly a quarter occur during a sporting event. The type of fracture is classified based on

Fig. 42.19 Various types of splints for various hand injuries. Most hand injuries should be splinted in neutral (functional) position with the wrist slightly extended at 30 degrees, the MCP joints flexed to 90 degrees, and the PIP and DIP joints held in extension. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

Fig. 42.20 (A) The glove is pulled under the ring using hemostats. (B and C) The glove is moved over the ring, thereby removing it from the finger. (Haynes JH, Haynes AT, Hines TR. Ring removal from an edematous finger. In: Pfenninger JL, Fowler GC. *Pfenninger and Fowler's Procedures for Primary Care*, ed 3. Saunders; 2010:1320-1322)

location and stability. Common mechanisms of injury are with direct, crushing, penetrating, or blunt trauma.

Differential Diagnoses

The differential diagnoses for phalanx and metacarpal fractures are extensive and include tendon, joint-space, and ligamentous injuries (Table 42.2).

Diagnostic Testing

A standard x-ray series of the hand, including a PA, lateral, and oblique film, is sufficient imaging to detect most phalanx and metacarpal fractures. Ultrasound is another acute imaging modality, though it is inferior to x-ray imaging as previously described.

Fig. 42.21 Mechanical ring cutter. (Khodaee M, Tirabassi J. The hand-powered ring cutter: a useful tool in your wilderness medical bag. *Wilderness Environ Med*. 2015;26(3):441-442.)

Management

Transverse fractures are generally stable while oblique, intra-articular, comminuted fractures, and fractures associated with dislocations tend to be unstable. Most fractures can be managed with appropriate splinting (see Fig. 42.19), but there are certain situations which do require emergent surgical consultation, including open fractures, partial or complete amputations, displaced intra-articular fractures, and fractures that do not maintain reduction. Additionally, spiral, rotated, and oblique fractures tend to be unstable and require outpatient follow-up with a hand specialist for possible surgical fixation. Patients who have fractures that are amenable to closed reduction can generally tolerate the procedure with adequate anesthesia via hematoma block (metacarpal fractures) or digital block (phalanx fractures).

Although splinting varies based on individual clinical scenarios, there are certain principles for immobilization for fractures of the hand. For most phalangeal fractures, a long finger splint is sufficient, though in cases of instability and significant tendon and ligamentous injury, proximal immobilization at the wrist may be necessary. Further stabilization of phalanx fractures can be accomplished by dynamic splinting or "buddy-taping" the splinted injured finger to the adjacent uninjured finger. For metacarpal fractures and phalanx fractures with accompanying instability, a radial gutter splint may be used for fractures of the index and middle fingers. Similarly, an ulnar gutter splint may be used for fractures of the ring and little fingers. Fingers adjacent to the injured finger should be included in the splint. A thumb spica or radial gutter splint should be used for thumb fractures. We recommend a low threshold for splinting in skeletally immature pediatric patients if there is a high suspicion for fracture despite negative x-rays. Loss of motion, malunion, and nonunion are common complications for untreated fractures.

TABLE 42.2 Differential Diagnoses for Hand Injuries

Location of Injury	Differential Diagnosis
Distal phalanx/DIP joint	Tuft, shaft, or avulsion fracture Seymour fracture Crush injury Nail bed injury Subungual hematoma Mallet finger (dorsal) or jersey finger (volar) DIP dislocation or subluxation Collateral ligament injury Extensor digitorum communis injury FDP tendon injury
Middle phalanx/PIP joint	Head, neck, shaft, or base fracture Dorsal, volar, or lateral PIP dislocation or subluxation Volar plate or collateral ligament injury Central slip (extensor) injury FDP or FDS tendon injury
Proximal phalanx/MCP joint	Head, neck, shaft, or base fracture Dorsal, volar, or lateral MCP dislocation or subluxation Volar plate or collateral ligament injury Trigger finger Clenched fist ("fight bite") injury Extensor complex injury FDP or FDS tendon injury
Metacarpal/CMC joint	Head, neck, shaft, or base fracture Dorsal or volar CMC dislocation Ulnar nerve injury Extensor complex injury FDP or FDS tendon injury
Thumb distal phalanx/IP joint	Tuft, shaft, or avulsion fracture Crush injury Nail bed injury/subungual hematoma Mallet thumb IP joint dislocation or subluxation Volar plate or collateral ligament injury Extensor pollicis longus tendon injury
Thumb proximal phalanx/MCP joint	Head, neck, shaft, or avulsion fracture Ulnar collateral ligament injury (skier's or gamekeeper's thumb) Radial collateral ligament injury
Thumb metacarpal/CMC joint	Head, neck, or shaft fracture Base (Bennet or Rolando) fracture CMC joint dislocation or subluxation Oblique CMC ligament injury Abductor pollicis longus tendon injury

Phalanx Fractures

Distal Phalanx Fractures

Clinical Features

Distal phalanx fractures result from a direct blow to the dorsal surface of the finger or axial force to the extended fingertip. They are further classified into tuft, shaft, base, and intra-articular fractures (Fig. 42.22).

Tuft fractures generally occur secondary to a crush injury. These fractures are usually stable due to presence of the nail plate and pulp. They often involve injury to the distal phalanx with laceration to the nail bed or pulp and can be accompanied by subungual hematoma (see later).

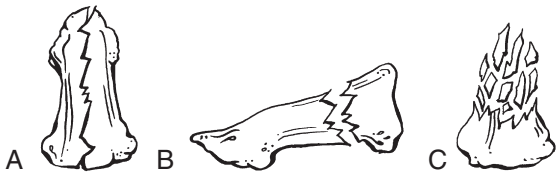

Fig. 42.22 Types of distal phalanx fractures. (A) Longitudinal, (B) transverse, and (C) comminuted. (Petering, RC. Finger fractures. In: Eiff MP, Hatch R, Higgins MK. *Fracture Management for Primary Care*. Ed 3 updated. Philadelphia: Elsevier Saunders; 2018:36-62.)

Fractures of the shaft are divided into transverse and longitudinal. Transverse fractures are generally stable and longitudinal fractures are unstable.

Fractures occurring at the base of the distal phalanx are usually unstable and intra-articular. These appear as avulsion fractures on x-ray and often are sports-related injuries. A common mechanism is an axial loading force on an extended distal phalanx resulting in forceful flexion or hyperextension at the DIP joint. Avulsion fractures at the base are further divided into dorsal injuries (e.g., mallet finger) and volar injuries (e.g., jersey finger). *Mallet finger* will present with inability to *extend* the distal phalanx at the DIP joint. Radiographs often show an avulsion fracture at the dorsal base of the DIP, though there may be an isolated distal extensor tendon rupture. In contrast, a *jersey finger* will present with inability to *flex* the distal phalanx at the DIP joint. X-rays may show an avulsion fracture at the volar base of the DIP, though there may be isolated rupture of the flexor digitorum profundus tendon.

The *Seymour fracture*, which is a transverse fracture of the distal phalanx involving the physis, occurs in the pediatric population.[10] This includes Salter-Harris type I and II fractures and typically involves a crush injury mechanism. It frequently occurs when a child gets a finger stuck in a door or folding chair. On exam, there will be exquisite tenderness at the distal phalanx and evidence of an associated nail bed injury, such as avulsion of the nail at the germinal matrix. This is considered an open fracture.

Differential Diagnoses

When considering a fracture of the distal phalanx, one should be mindful of other potential injuries or associated injuries to the distal phalanx. These include distal amputations, nail bed injuries, subungual hematomas, FDP tendon injuries, extensor mechanism injuries, collateral ligament injuries, and DIP dislocations or subluxations.

Diagnostic Testing

Standard x-ray imaging of the affected finger should be obtained if there is pain, swelling, tenderness, or loss of functional integrity following injury to the distal phalanx. Any separation, displacement, or angulation should be identified.

Management

Because most tuft fractures are stable and non-displaced, they are typically treated conservatively with analgesia and splinting. Splinting involves 2 to 4 weeks of protection with a finger cage splint or a molded aluminum splint that encloses the distal phalanx, though allowing for movement at the DIP. Hand specialist consultation is required for displaced fractures that are irreducible as well as for open fractures.

While antibiotics have traditionally been recommended for tuft fractures associated with nail bed or soft-tissue injuries, a recent meta-analysis involving 4 RCTs assessing rates of superficial infection and osteomyelitis in open distal phalanx fractures found no difference in rates of superficial infection and osteomyelitis in patients receiving antibiotics versus those who did not.[11] While there is strong evidence to support the use of antibiotics for open fractures elsewhere in the body, distal phalanx fractures are different in that most are secondary to deep lacerations or a crush injury where there is less periosteal stripping. The study suggests that the focus of treatment for open fractures should be on prompt irrigation and early débridement, rather than prophylactic antibiotics.

Transverse fractures at the shaft of the distal phalanx are usually non-displaced and require only protective splinting for 2 weeks. Reduction of displaced fractures should be attempted in the emergency department, though if closed manipulation is unsuccessful or if the fracture remains unstable, the distal phalanx should be splinted, and the patient referred to a hand specialist for pinning.

Longitudinal fractures should be splinted from the middle to distal phalanx, leaving the PIP joint mobile. Immobilization should be for 3 to 4 weeks followed by passive range-of-motion exercises until the finger is pain-free.

Almost all mallet finger injuries should be treated conservatively initially with splinting. The DIP joint is immobilized with splinting in neutral position or slight hyperextension continuously for 6 weeks. Compliance is critical. If the joint is flexed at any point during the 6-week splinting period, the course must be restarted. Stack splints or aluminum foam splints may be used (Fig. 42.23). Patients should be referred to a hand specialist as patients with a fracture involving one third or greater of the articular surface and those who fail conservative treatment are considered for surgical management by the hand specialist.

Avulsion fractures at the volar base of the distal phalanx may be treated conservatively with a dorsal or volar splint if there is some DIP joint flexion present. This is accomplished by immobilizing only the DIP joint in slight flexion (5–10 degrees) for at least 6 weeks. If there is no retained ability to flex the DIP joint, assume rupture of the FDP tendon (jersey finger) and refer the patient for surgical management. In the meantime, the finger should be immobilized in a splint that incorporates the wrist with the finger maintained in flexion.

Pediatric patients with Seymour fractures (Salter-Harris fracture of the finger in which the nail comes out from the nail fold) should ideally have repair performed in the emergency department. Irrigation, reduction, nail bed repair, and laceration repair may be performed by the emergency physician. If the fracture can be reduced and closed well, the patient can follow up in 7 to 10 days. If there is difficulty or instability to the injury after treatment in the ED, then the patient should be seen by a hand specialist within 24 hours. As these are open fractures, antibiotics (i.e., cephalexin 50 mg/kg/day divided q6 hours for 7–10 days) should be initiated. For repair of Seymour fracture injuries, it is important to save the fingernail, if possible, by carefully trimming a small amount of the proximal nail plate that is exposed and inserting it back underneath the eponychial fold with a mattress suture. With this, an acceptable reduction of the Salter-Harris fracture is obtained. One should avoid overdissection of nail bed from the nail plate as this may cause further damage. Repair of the nail bed with 6-0 or 7-0 chromic absorbable suture is done when the nail bed injury is visible. Careful reduction, nail bed repair, and fixation of the distal phalanx in slight hyperextension have been shown to improve outcomes and reduce the incidence of nail growth disturbance, growth plate damage, and long-term loss of flexor tendon function (Fig. 42.24 and 42.25).

Middle Phalanx Fractures

Clinical Features

Middle phalanx fractures are classified based on location, deformity, and stability. They may involve the head, neck, shaft, or base.

Fig. 42.23 Thumb stack splint immobilizing the IP joint as seen in (A) AP and (B) lateral views. (Courtesy of Mary Jo Wagner, MD, FACEP; Central Michigan University COM.)

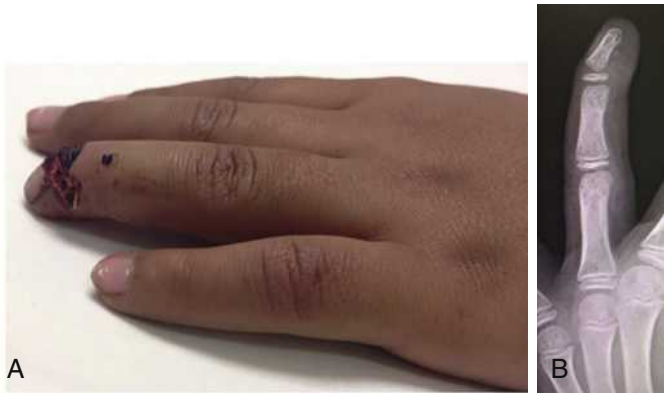

Fig. 42.24 Seymour fracture presentation. (A) Open fracture of the distal phalanx of the ring finger together with nail avulsion. (B) X-ray demonstrating open juxta-epiphyseal fracture of the distal phalanx. (Metcalfe D, Aquilina AL, Hedley HM. Prophylactic antibiotics in open distal phalanx fractures: systematic review and meta-analysis. *J Hand Surg (European vol)*. 2016;41(4):423-430.)

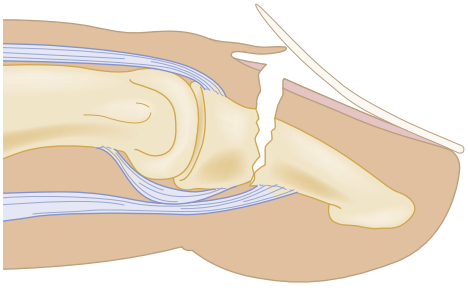

Fig. 42.25 Seymour fracture illustration demonstrating a lateral view with open avulsion fracture at the distal phalanx base and nail bed avulsion. (Modified from: Metcalfe D, Aquilina AL, Hedley HM. Prophylactic antibiotics in open distal phalanx fractures: systematic review and meta-analysis. *J Hand Surg (European vol)*. 2016;41(4):423-430.)

Deformity and displacement are dependent on the location of the fracture and result from the dynamic forces of the flexor and extensor tendons involved. The flexor digitorum superficialis divides and inserts along the volar surface while the extensor tendon (central slip) inserts at the proximal base (Fig. 42.26). As a result, fractures of the distal middle phalanx usually result in volar angulation, while proximal fractures near the base tend to result in dorsal angulation[9] (Fig. 42.27).

Fractures at the base include intra-articular types which appear on x-ray as avulsion fractures and are classified based on their location: *condylar, volar,* and *dorsal*. There is also the possibility of complete disruption of the articular surface (*pilon fracture*) in which multiple tendons are involved with instability in all directions.

Differential Diagnoses

One should consider volar plate, collateral ligament, central slip, FDP tendon, and FDS tendon injuries when assessing for a possible fracture. Associated IP joint dislocations or subluxations should also be considered.

Diagnostic Testing

Standard x-ray imaging of the digit is sufficient to identify most clinically significant fractures.

Management

Stable non-displaced transverse fractures can be treated with dynamic splinting (Fig. 42.28) and by buddy taping to an adjacent uninjured digit. Dynamic splinting offers the advantage of providing some degree of stability while preventing joint stiffness. Immobilization should be for 2 to 3 weeks followed by range-of-motion exercises.

Transverse shaft fractures that are angulated, shortened, or have rotational deformity require surgical referral. Displaced transverse fractures typically have volar angulation and require closed reduction which can be performed with longitudinal traction followed by flexion of the distal fragment to align with the proximal fragment. Oblique, spiral, and comminuted fractures, in addition to unstable transverse

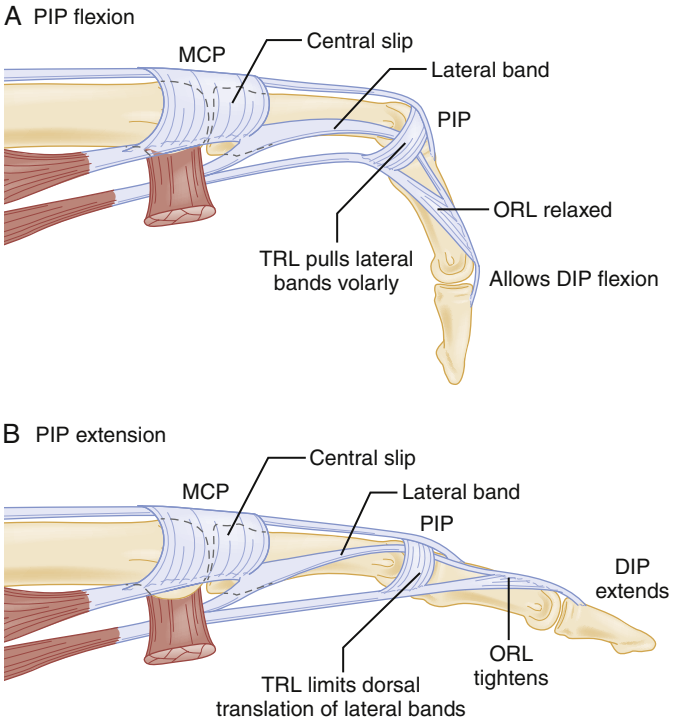

Fig. 42.26 (A) With PIP flexion, the transverse retinacular ligament (TRL) pulls the lateral bands into the volar position, while the oblique retinacular ligament (ORL) relaxes and helps coordinate DIP flexion. (B) With the PIP in extension, the TRL prevents PIP hyperextension by limiting the dorsal displacement of the lateral bands while the ORL tightens (permitting coordinated DIP extension). (From: Elzinga K, Chung KC. managing swan neck and boutonniere deformities. *Clin Plast Surg.* 2019;46(3):329-337.)

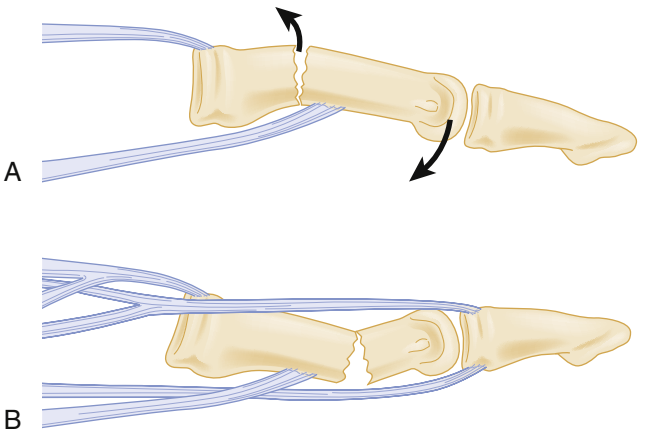

Fig. 42.27 Illustration of deforming forces acting on middle phalanx fractures (A) Transverse fractures proximal to the FDS insertion angulate dorsally. (B) Fractures distal to the FDS insertion angulate in the volar direction. (From: Capo JT, Hastings H II. Metacarpal and phalangeal fractures in athletes. *Clin Sports Med.* 1998;17(3):508. Fig. 15.)

fractures, should be immobilized to the level of the wrist with an ulnar or radial gutter splint to eliminate deforming tendon forces.

Fractures of the base that include 50% or greater of the articular surface or fractures requiring greater than 30 degrees of flexion to maintain reduction are almost always unstable and require surgical management.[12] Non-displaced stable fractures involving 20% or less of the articular surface may be managed by extension splinting.

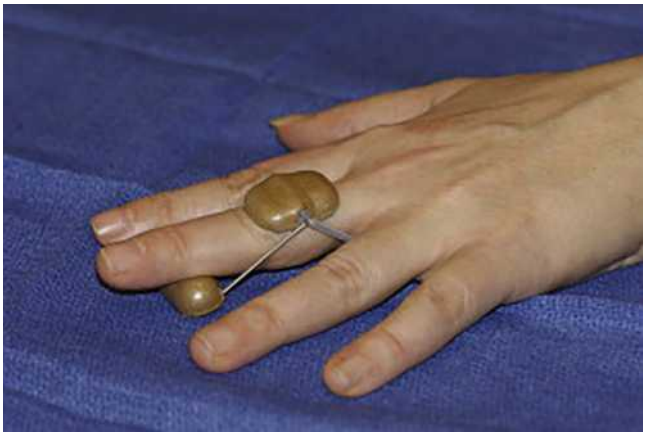

Fig. 42.28 Dynamic splint demonstrated in a patient. (Hays PL, Rozental TD. Rehabilitative strategies following hand fractures. *Hand Clin.* 2013;29(4):585-600. Fig. 7.)

Proximal Phalanx Fractures

Clinical Features

Fractures at the proximal phalanx may result from a direct blow, forcible hyperextension, or rotational forces and are classified based on location: *head*, *neck*, *shaft*, or *base*. Fractures of the head that are condylar or involve displacement are considered unstable. Similar to middle phalanx fractures, fractures at the shaft are prone to opposing tendon forces. Displaced fractures tend to have a visible apex volar deformity and involve the proximal fragment in flexion (interossei) and the distal fragment in extension (central slip)[9] (Fig. 42.29).

Differential Diagnoses

In addition to fractures, other injuries around the proximal phalanx should be considered including injuries to the volar plate, collateral ligaments, extensor mechanism, FDP tendon, and FDS tendon. For proximal injuries, the MCP joint should be assessed for evidence of clenched fist ("fight bite") injuries, trigger finger, and dislocations or subluxations of the MCP joint.

Diagnostic Testing

Standard x-ray imaging is sufficient to identify most proximal phalanx fractures.

Management

Non-displaced transverse fractures, and other stable fractures of the proximal phalanx, may be managed nonoperatively by splinting.[13] Splinting should be performed with a dorsal aluminum padded splint extending from the metacarpal to the middle phalanx with the MCP joint at 70 to 90 degrees of flexion and the PIP joint at 30 degrees of flexion. Displaced fractures should be reduced and splinted. Similar to stable non-displaced fractures, a dorsal splint should be placed with the MCP and PIP in slight flexion. Further stabilization at the wrist with a radial or ulnar gutter splint should be added. Oblique, spiral, angulated, and unstable intra-articular fractures should be splinted similarly, though they also require outpatient follow-up with a hand specialist for surgical repair to be performed within one week.

Unicondylar or bicondylar fractures of the head of the proximal phalanx are considered unstable even if nondisplaced. These types of fractures often require surgical management as displacement often occurs with splinting alone. The patient should have urgent outpatient follow-up with a hand specialist so that surgical fixation could occur within one week.

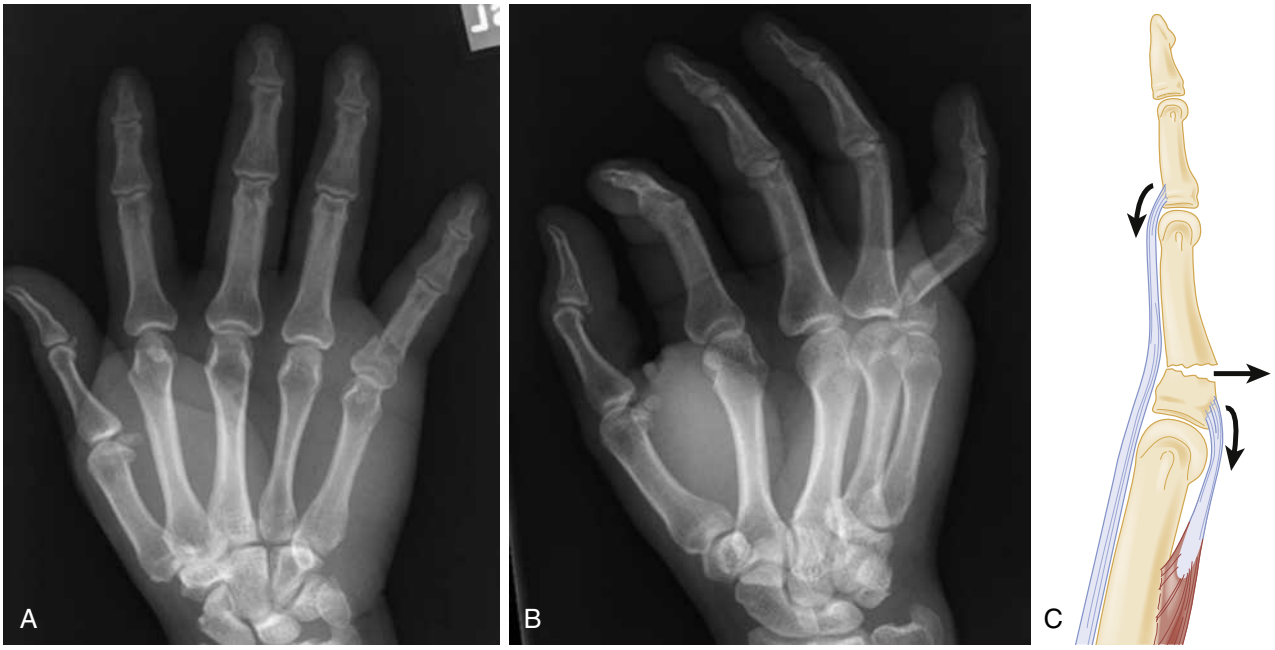

Fig. 42.29 (A) AP and (B) lateral x-rays of proximal phalanx fracture of the fifth finger, resulting in the typical angulation from apex volar deforming forces. (C) Illustration of the deforming forces acting on proximal phalanx fractures with the central slip pulling the distal fracture fragment into extension. (Cotterell IH, Richard MJ. Metacarpal and phalangeal fractures in athletes. *Clin Sports Med.* 2015;34:69-98.)

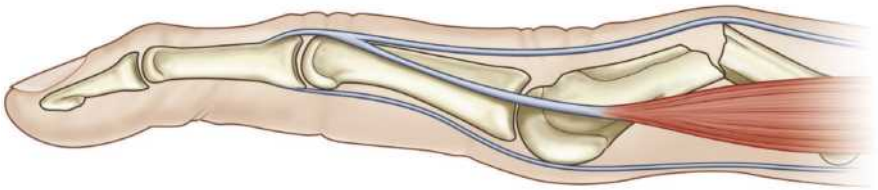

Fig. 42.30 Typical metacarpal fracture apex dorsal angulation occurring secondary to the location of the interosseous muscles. (Khouri JS, Hammert, WC. Hand fractures and joint injuries. *Plast Surg.* 2018;6:146-169.)

Metacarpal Fractures

Clinical Features

Patients with metacarpal fractures generally present after a direct blow to the dorsum of the hand or an axial loading force over the metacarpal head. The hand should be thoroughly examined for tendon integrity, deformity, and any evidence of open fracture or fight bite. Like phalanx fractures, metacarpal fractures are classified based on location: head, neck, shaft, and base.

Fractures of the metacarpal head are rare and usually occur secondary to a direct or crushing force. They often are intra-articular and accompanied by an extensor tendon injury.

The neck is the most common location for metacarpal fractures because the bone is weakest at this location. These fractures commonly occur secondary to punching a firm object, hence the term *boxer's fracture* given to fractures at the neck of the fifth metacarpal. Displacement is usually apex dorsal angulation owing to forces from the extrinsic flexor tendons which flex the distal fragment (Fig. 42.30). The carpometacarpal (CMC) joints inherently have greater stability and less range of motion at digits 2 and 3 relative to digits 4 and 5. Greater range of motion at the ulnar aspect of the hand, especially in flexion, enables a powerful grip. It also accounts for a greater degree of tolerable displacement in the ulnar metacarpals because the deformity can be more easily compensated (Table 42.3).

TABLE 42.3 Metacarpal Fracture Allowable Angulation

Digit	Acceptable Shaft Angulation (Degrees)	Acceptable Neck Angulation (Degrees)
II and III	10	10-15
IV	20	35
V	20–30	45[a]

[a]Various sources have quoted acceptable angulation of up to 70 degrees for the fifth digit

Metacarpal shaft fractures occur secondary to direct impact or an axial loading force. Like metacarpal neck fractures, they also present with apex dorsal angulation though they are comparatively less tolerant to angulation because more proximal fractures present with greater deformity given the same degree of angulation. While angulation is easily assessed from x-ray imaging, rotation is assessed more easily from physical exam. Malrotation will be noted with overlap of the digits when they are held in flexion (cascade sign) and are often associated with oblique or spiral fractures. As little at 10 degrees of malrotation in the fifth metacarpal may cause visible deformity. If there are adjacent metacarpal fractures, there is high risk for shortening and instability

due to loss of intermetacarpal ligament stabilization. Shortening is not well tolerated and may result in *pseudoclawing*, an extensor lag secondary to compensatory hyperextension at the MCP leading to inadequate extension at the PIP. Greater than 5 mm of shortening in any metacarpal is not acceptable because this results in an extensor lag that is no longer compensated by the MCP joint's natural hyperextension capability.

Fractures of the metacarpal base occur secondary to an axial loading force with the wrist in flexion. These fractures are often intra-articular and associated with CMC joint dislocations, which can be missed on standard x-ray imaging.

Intra-articular fractures at the base of the fifth metacarpal are also known as *reverse Bennet* fractures. The radial aspect of the fifth metacarpal base is stabilized by the intermetacarpal ligament while tension from the extensor carpi ulnaris causes ulnar and proximal displacement of the remainder of the base. The hypothenar muscles displace the shaft radially.

Differential Diagnosis

In addition to fractures, other injuries around the metacarpal should be considered including CMC joint dislocation, clenched fist injury, extensor mechanism injury, and FDP or FDS tendon injury. Compartment syndrome should also be considered if there is a crush injury mechanism, excessive swelling of the hand, pain out of proportion, or neurovascular compromise.

Diagnostic Imaging

Because CMC dislocations with metacarpal base fractures are often missed, in addition to standard hand x-rays, a 30-degree pronated lateral view for the index and middle fingers should be obtained for higher diagnostic sensitivity. Similarly, a supinated lateral view for the ring and little fingers should be performed. For metacarpal neck and shaft fractures, special attention should be paid to the degree of angulation to determine if reduction is needed (see Table 42.3).

Management

Because of the intra-articular predilection for metacarpal head fractures, patients should be referred to a hand specialist because they will likely require open reduction and internal fixation (ORIF). Special attention should be paid to the soft tissue surrounding the metacarpal head, as puncture wounds, lacerations, and particularly fight bite wounds require emergency consultation for surgical débridement and irrigation. Patients with closed fractures without signs of open soft tissue injury may be splinted in neutral position and referred for outpatient hand specialist follow-up within one week. The traditional method for splinting metacarpal fractures is in neutral position with the wrist at 20 to 30 degrees extension, MCP at 70 to 90 degrees flexion, and the PIP and DIP kept in extension.

Non-displaced or minimally angulated fractures of the metacarpal neck (below threshold for reduction) can be managed conservatively with immobilization for 3 to 4 weeks (see Table 42.2). These injuries that do not exceed the threshold are unlikely to cause functional impairment, so do not require anatomical reduction in the ED. The traditional recommendation is to immobilize the metacarpal in neutral position with a radial (digits 2 and 3) or ulnar gutter splint (digits 4 and 5). However, recent studies suggest that less immobilization may not be harmful and may actually yield benefits. A recent prospective study in patients with boxer's fractures found similar long-term clinical and radiologic results in patients treated with functional metacarpal splinting (FMS) compared to ulnar gutter splinting, though there was actually earlier return of grip strength at 2 months in the FMS group.[14] Similarly, a recent meta-analysis found that immobilization with a splint or cast was not superior to soft wrap in most cases.[15] Yet, given the importance of stability following an acute fracture, we recommend standard immobilization at least as a temporary measure if the patient is able to follow up with a hand specialist within one week.

Acute metacarpal neck fractures that exceed the threshold of acceptable angulation require reduction. This can be attempted in the emergency department via the Jahss manipulation technique for closed reduction. Using this method, the MCP joint and PIP joints are flexed to 90 degrees, upper (dorsal) pressure is applied through the proximal phalanx, and downward pressure is applied over the proximal metacarpal shaft (Fig. 42.31).

Metacarpal shaft fractures are managed similarly to metacarpal neck fractures, though with less acceptable angulation. The Jahss technique may be used for closed reduction. Patients with greater than 5

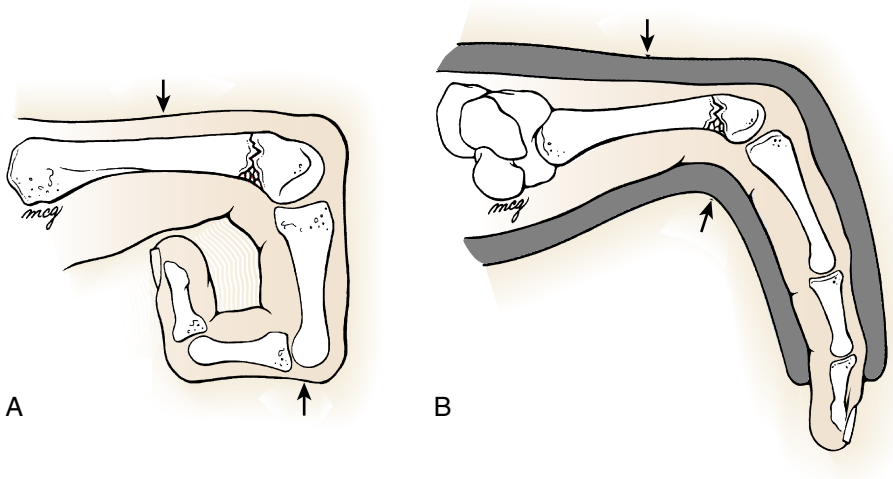

Fig. 42.31 Reduction of metacarpal fracture using the Jahss maneuver. (A) Arrows indicate direction of pressure for fracture reduction. (B) Fingers are held in intrinsic-plus (safe) position, after reduction, in ulnar gutter splint with molding pressure indicated by arrows. (Day CS. Fractures of the metacarpals and phalanges. In: Wolfe SW, Hitchkiss RN, Pederson WC, et al., eds. *Green's Operative Hand Surgery*. Philadelphia: Elsevier; 2017:231-277.)

mm of shortening, clinically significant rotation, and unstable fracture types should have prompt referral to a hand specialist for possible ORIF.

Intra-articular fractures at the base generally require surgical fixation to prevent posttraumatic arthritis.

Thumb Fractures

Clinical Features

Due to the highly mobile nature of the thumb, there is a lower frequency of fractures compared to the other phalanges. Similar to other distal phalanges, mallet injuries of the thumb may occur though they are rare and occur secondary to avulsion of the extensor pollicis longus tendon at its distal insertion point. Mallet injuries of the thumb, unlike mallet injuries of the fingers, are less likely to result in subluxation.[16] With a *skier's* or *gamekeeper's thumb*, there may be an associated avulsion fracture at the base of the proximal phalanx.

Most fractures of the thumb metacarpal occur at the base. There are strong ligamentous forces limiting abduction of the thumb (anterior oblique and first inter-metacarpal ligaments). An axial loading force on the partially flexed metacarpal creates an avulsion type fracture. The ligamentous forces are so strong that a fracture at the metacarpal base is actually far more common than a CMC joint dislocation. Two unique fractures at the metacarpal base are the Bennett fracture and the Rolando fracture.

The *Bennett fracture* is an oblique intra-articular fracture accompanied by a dislocation at the metacarpal base (Fig. 42.32A). The anterior oblique ligament holds the volar-ulnar base fragment in place while the remaining articular surface and shaft are displaced proximally and adducted by the abductor pollicis longus and adductor pollicis respectively.

The *Rolando fracture* is a comminuted complete intra-articular fracture at the metacarpal base that is T-shaped or Y-shaped on x-ray (see Fig. 42.32B).

Differential Diagnoses

When considering fractures of the thumb, other injuries including mallet injury, volar plate injury, collateral ligament injury, IP or CMC joint dislocation or subluxation, extensor pollicis longus tendon injury, or UCL or RCL injury should be considered.

Diagnostic Testing

Special x-ray views are necessary when evaluating potential thumb fractures or dislocations because the thumb is situated outside of the hand plane. One such view is the Robert view where the hand is hyperpronated with the dorsum of the thumb on the radiograph plate, creating a true AP view.

Management

There are no major differences in treatment for thumb phalangeal fractures compared to digits 2 through 5, though proximal fractures should be immobilized with a thumb spica splint for 4 weeks. Due to instability and associated deforming forces, both Bennett and Rolando fractures require urgent referral to a hand specialist for further management.

Joint Injuries

Clinical Features

The interphalangeal and metacarpophalangeal joints of the hand are stabilized by multiple tendons and ligaments. In particular, the collateral ligaments protect against radial and ulnar deviation of the IP joints. The volar plates are fibro-ligamentous structures that protect the joint capsule against hyperextension.

Mechanism predicts the injury. Forced hyperextension of the respective joint may result in volar plate tears and dorsal dislocations. Lateral forces may result in collateral ligament injury and lateral dislocation. Axial loading forces are responsible for intra-articular fractures. Injuries to ligaments generally accompany dislocations and range from small tears (grade I) to complete tears (grade III).

Inspection may show deformity and swelling. Active range of motion is the best test for joint functioning and stability. Sufficient local analgesia (i.e., digital block) is necessary for accuracy of this exam. Passive range of motion and ligament stressing are useful in identifying the location and severity of injuries, though this should be done gently to prevent further ligamentous injury.

Differential Diagnoses

The differential diagnoses for joint injuries are extensive and include associated fractures, dislocations, subluxations, tendon injuries, and ligamentous injuries (see Table 42.2).

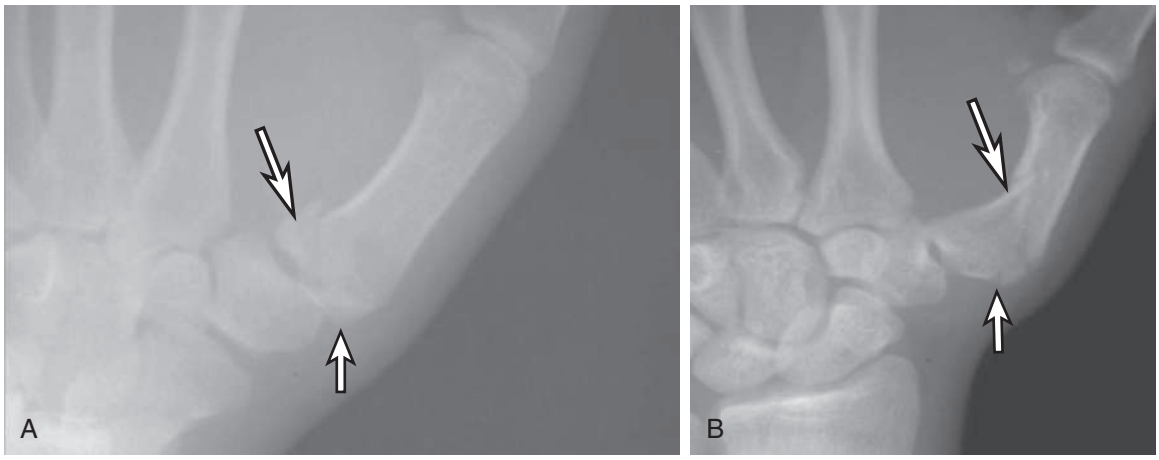

Fig. 42.32 Thumb metacarpal intra-articular fractures. (A) AP radiograph demonstrating a Bennett fracture. The long arrow points to the fracture site and the short arrow points to the fracture fragment that has minimal radial subluxation. Note the minimal subluxation. (B) AP view of a comminuted Rolando fracture. (Scanelli J, Deal N, Chhabra B, Sanders T. Hand fractures. In: Miller MD, Sanders TG, eds. *Presentation, Imaging and Treatment of Common Musculoskeletal Conditions*. Philadelphia: Elsevier Saunders; 2012:258-267. Fig 58-7.)

Diagnostic Testing

Standard x-ray imaging should include true lateral films of the affected digit to accurately identify dislocations and subtle subluxations. The classic "V sign" results from dorsal widening of the joint when there is minimal subluxation (Fig. 42.33).

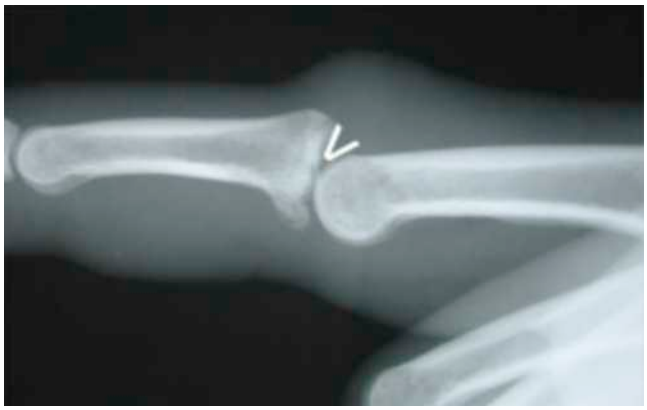

Fig. 42.33 Typical "V sign" seen on lateral view where there is a fracture at the volar base of the middle phalanx and dorsal subluxation of the PIP joint. (Chauhan A, Sikora-Klak J, Abrams R. Dynamic homemade digital external fixators for proximal interphalangeal joint injuries. *J Hand Surg.* 2018;43(9):875. Fig 5.)

Management

Most dislocations are amenable to closed reduction in the emergency department. Reduction should be performed immediately after identifying the injury because delays are associated with lower success rates and higher rates of neurovascular compromise. Following adequate analgesia, gentle longitudinal traction should be applied to the affected joint followed by hyperextension (if dislocation is dorsal) or hyperflexion (with volar dislocations) along with pressure at the base of the dislocated phalanx in the proper direction for realignment (Fig. 42.34). Active range of motion should be tested following reduction and a post-reduction film should be obtained.

Indications for emergent surgical management include neurovascular compromise after closed reduction, inability to reduce (often due to obstruction from soft tissue, volar plate, or osteochondral fragments), and contaminated open dislocations requiring extensive irrigation. Additionally, dislocations that remain unstable after reduction and those accompanied by displaced or sizeable intra-articular fractures require surgical intervention. Surgical referral for open reduction is also indicated in chronic dislocations, or those present for greater than 3 weeks.

Splinting principles are designed to prevent residual joint and flexion stiffness, which are common complications of immobilization. Uninvolved joints should have only minimal immobilization, if any. The MCP joint should be immobilized at 60 to 70 degrees flexion, whereas the IP joints should be flexed approximately 30 degrees. One

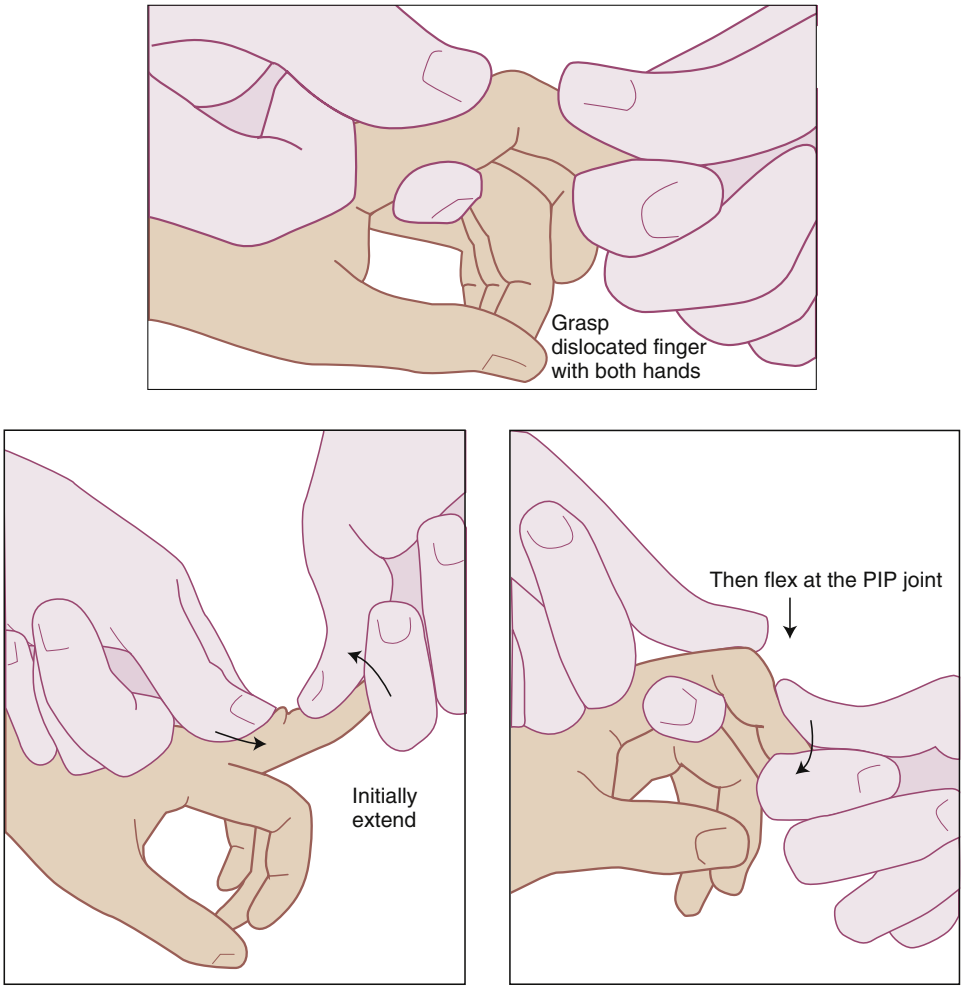

Fig. 42.34 Reduction technique for finger dislocation (PIP joint). (Buttaravoli P, Leffler, Stephen M. *Minor Emergencies*, ed 3. Philadelphia: Elsevier Saunders; 2012:419-422. Fig 109-1.)

exception to this principle is volar dislocations of the PIP which must initially be splinted in extension to avoid a boutonnière deformity. Simple sprains may be treated with buddy taping or dynamic splinting. Complete ligament tears require prolonged immobilization and surgical repair.

Interphalangeal Joint Injuries

Clinical Features

The distal interphalangeal joint is highly stable, and dislocations are rare. When dislocations do occur, they are almost always dorsal. Radiographs should be analyzed for dislocations complicated with mallet avulsion fractures. Uncomplicated dislocations of the DIP are generally stable after closed reduction, since the flexor and extensor tendons are attached to the distal phalanx.

The PIP joint is the most frequently injured joint in the hand. The collateral ligaments and accessory ligaments merge into the volar plate which is further anchored by the collateral ligaments proximally (see Fig. 42.9). This creates a three-dimensional hinge. Multiple supporting structures must be disrupted to cause joint instability. The PIP joint may be dislocated in any of three directions—dorsal, volar, or lateral.

Dorsal dislocations of the PIP joint are most common and frequently are associated with ball-handling sports. The mechanism is secondary to axial load and forced hyperextension resulting in rupture of the volar plate and tearing of collateral ligaments. This creates an easily recognizable bayonet-like dorsal displacement deformity seen on inspection (Fig. 42.35). Dorsal dislocations accompanied by fractures involving greater than one-third of the articular surface are considered unstable, because they are associated with greater detachment of the collateral ligament insertion at the middle phalanx.

Volar plate tears may also occur secondary to hyperextension and may be present without evidence of dislocation at the PIP joint. A volar horizontal skin laceration over the joint is often visible along with a hyperextension deformity. Pain and locking may be evident on active flexion of the PIP joint.

Volar dislocations of the PIP joint are rare and are frequently missed. Dislocations occur with disruption of the central slip. The head of the proximal phalanx ruptures through the retinacular fibers between the lateral band and central tendon (Fig. 42.36).

Lateral dislocations of the PIP joint occur from a lateral force with the PIP joint in extension, resulting in rupture of a collateral ligament. The patient may present with radial or ulnar deviation at the PIP joint, though these dislocations frequently reduce spontaneously. Collateral ligament integrity should be tested by providing lateral stress on the

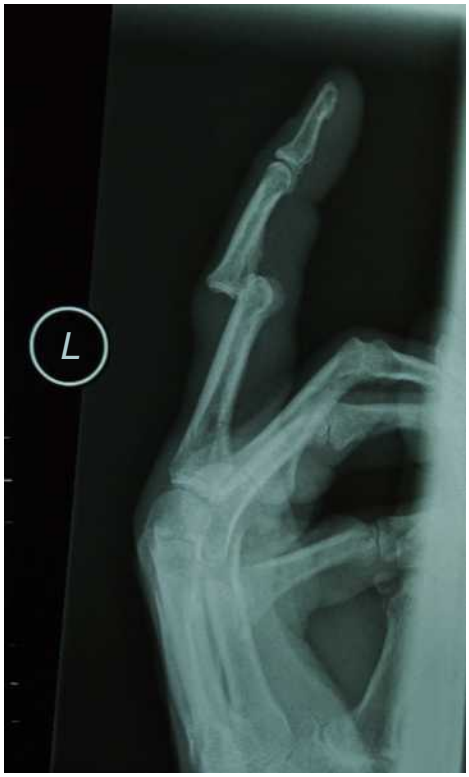

Fig. 42.35 Dorsal dislocation of the PIP joint on radiograph. (Courtesy of Timothy Kaufman, MD; Central Michigan University COM)

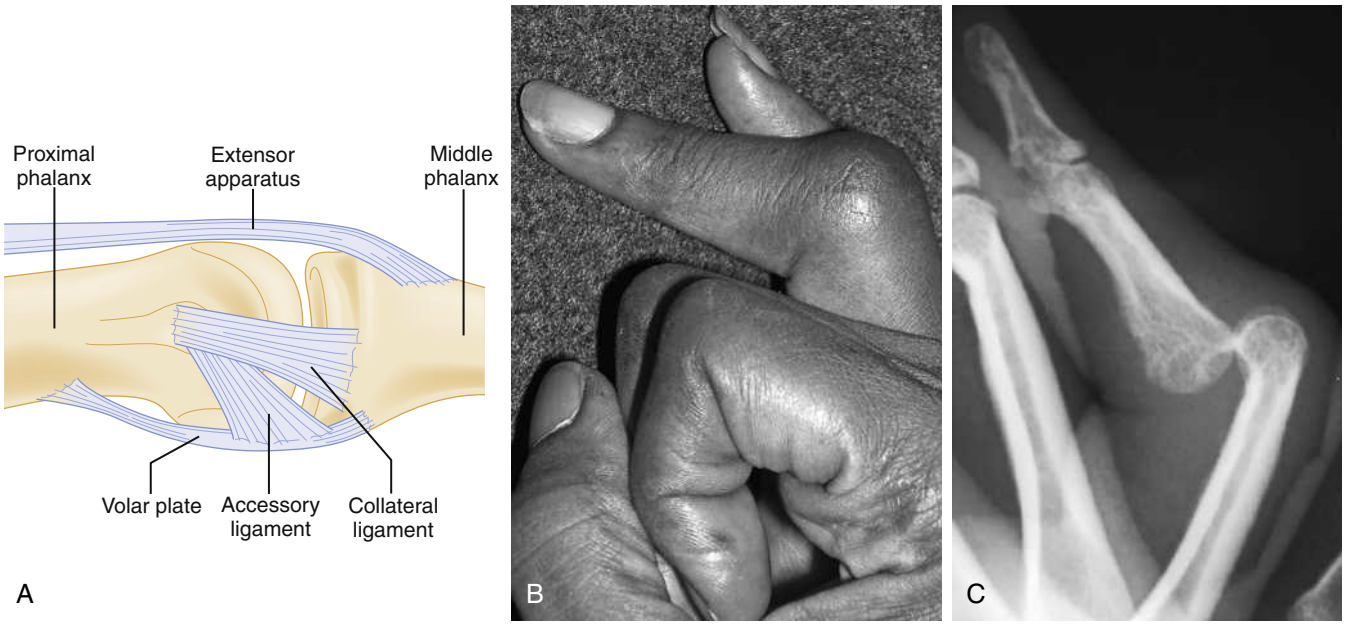

Fig. 42.36 (A) Key stabilizing forces surrounding the PIP joint. (B and C) Examination and radiograph of patient with volar PIP dislocation. (Bindra RR, Foster BJ. Management of proximal interphalangeal joint dislocations in athletes. *Hand Clinics*. 2009;25(3):423-435. Fig. 1 and 5.)

radial and ulnar sides of the joint. Ability to flex and extend the finger at the PIP joint is usually preserved.

Differential Diagnoses

When suspecting an interphalangeal joint injury, one must also consider associated fractures including open, closed, and avulsion fractures. Tearing of the volar plate, central slip, and collateral ligaments commonly accompanies dislocations and subluxations.

Diagnostic Testing

A standard 3-view x-ray of the affected digit is sufficient to identify subluxations and dislocations of the IP joints.

Management

Uncomplicated DIP joint dislocations that are functionally stable after closed reduction, as tested with active range of motion, should be immobilized for 2 to 3 weeks. Immobilization of reduced dislocations can be accomplished with an aluminum padded splint extending from the dorsal surface of the middle phalanx to the distal phalanx with the DIP slightly flexed to 30 degrees.

Closed reduction should be attempted for uncomplicated dorsal dislocations of the PIP joint. Functionally stable PIP dislocations and those not accompanied by intra-articular fractures can be managed with splinting for 2 weeks. Dorsal dislocations are splinted with the PIP in slight flexion (30 degrees). Fracture-dislocations of the PIP should have hand specialist referral following closed reduction, ideally within 3 days of presentation.

Patients with suspected isolated volar plate tears at the PIP joint should similarly be splinted in 30 degrees of flexion for at least 3 weeks.[17]

Reduction of volar dislocations can be challenging given obstruction from the lateral band. These dislocations often require open reduction by a hand specialist. We recommend discussing the case with a hand specialist prior to attempting closed reduction because many advocate for open reduction with central slip repair in all volar dislocations. If closed reduction is performed in the emergency department, the central slip integrity must be examined afterward. Inability to extend the PIP against resistance indicates significant central slip injury and the joint must be splinted appropriately in full extension (4 to 6 weeks) to avoid formation of a boutonnière deformity over time.

Lateral dislocations of the PIP that are deemed stable after reduction should be splinted with the PIP immobilized at 30 degrees of flexion for 2 to 3 weeks, though some advocate for simple buddy or dynamic taping. Joints that are unstable or associated with an avulsion fracture, require immobilization with prompt surgical referral, ideally within 3 days of presentation.

Metacarpophalangeal Joint Injuries

Clinical Features

The metacarpophalangeal joint should be taut in flexion, though it naturally has some laxity in extension allowing some lateral movement. Strong collateral ligaments, the transverse metacarpal ligament (volar plate), and intrinsic musculature provide significant dynamic stability to lateral forces. Thus, injuries to the lateral structures are rare. Injury to the collateral ligament should be suspected if there is pain or laxity at the MCP joint in extension when radial or ulnar stressing is applied.

In contrast, the shape of the MCP joint and lack of the collateral ligaments result in less stability for resisting hyperextension, responsible for dorsal dislocations of the MCP joint and hyperextension injuries.

With dorsal dislocations of the MCP joint, there is generally visible deformity with dorsal displacement of the proximal phalanx, hyperextension of the MCP joint, and slight flexion of the interphalangeal joints. There are two types of dorsal dislocations: simple and complex.

Simple dislocations of the MCP joint are technically subluxations because the articular surfaces remain in partial contact. Yet, examination may show significant deformity with the proximal phalanx locked in greater than 60 degrees of hyperextension.

Complex dislocations of the MCP joint occur when the metacarpal head ruptures through the volar plate, which becomes entrapped within the joint space. Examination may show less hyperextension compared to simple dislocations. Classically, there may be dimpling of the skin at the proximal palmar crease.

Differential Diagnoses

When assessing injuries at the MCP joint, also consider dislocations, subluxations, dorsal lacerations indicating fight bite injuries, associated metacarpal head and neck fractures, tears to the volar plate and collateral ligaments, trigger finger, and FDP or FDS tendon injuries.

Diagnostic Testing

Standard 3-view hand x-rays are sufficient in identifying most dislocations and subluxations. However, findings may be subtle for significant injuries. For example, complex dislocations of the MCP joint may show only mild widening of the joint space, sometimes with presence of a sesamoid. Physical examination should be relied upon to assess for ligamentous injury; MRI is rarely used for these types of injuries in the emergency setting.

Management

Treatment for collateral ligament injury at the MCP is splinting the joint in neutral position for 3 weeks. Unstable injuries and those with intra-articular fractures require surgical referral.

Simple dislocations of the MCP joint may be treated by closed reduction. With the wrist and MCP joint held in flexion, dorsal pressure over the proximal phalanx should be applied in a volar and distal direction. Special care should be taken to avoid longitudinal traction on the joint as this may entrap the volar plate into the joint, creating a complex dislocation. Following reduction, the MCP joint should be immobilized at 60 to 70 degrees flexion for 1 week followed by buddy or dynamic taping. Complex dislocations, due to entrapment of the volar plate, are irreducible by closed methods and require emergent surgical consultation for open reduction.

Carpometacarpal Joint Injuries

Clinical Features

The carpometacarpal joint is highly stable and requires significant force for injury. Dislocations are rare, though are frequently missed. Posterior dislocations (85%) are more common than volar dislocation.[18] The fifth CMC joint is most frequently involved, often occurring secondary to closed fist injury. Dislocations of the fifth CMC (metacarpohamate) joint may result in ulnar nerve injury resulting in claw-hand deformity in severe cases**.** Thorough ulnar nerve testing is required for fifth CMC joint dislocations. Examination often reveals no gross deformity, though there is usually significant dorsal swelling at the base of the metacarpal.

Differential Diagnoses

One should consider associated fractures of the carpal bones and metacarpal base, tendon, and ligamentous injuries when assessing injuries at the CMC joint.

Diagnostic Testing

All three radiographs of the hand—PA, lateral, and oblique—should be obtained if this injury is a concern. Special attention should be made to the lateral and oblique radiographs to identify CMC joint dislocations as well as any associated metacarpal fractures which frequently coexist. Due to the dorsal positioning of the dislocation, a cursory review of the PA film might lead to missing the diagnosis. The lateral film has significant bony overlap of the heads of the metatarsals so may also conceal a fracture or dislocation.

Management

Reduction of CMC joint dislocations should be performed in the emergency department, though hand specialist referral within 24 hours, where possible, is recommended because reduction is difficult to maintain. Immobilization alone is often inadequate, and surgical intervention is often necessary.

Thumb Dislocations and Ligamentous Injuries

Clinical Features

Interphalangeal joint dislocations of the thumb, similar to DIP joints of the other phalanges, are usually dorsal and occur secondary to hyperextension injury. The MCP joint of the thumb is the most mobile joint in the hand and is oriented obliquely, making it a common site of injury from radial forces. Dorsal dislocation may occur from volar plate disruption, while lateral dislocation may occur from a collateral ligament tear. The mechanism and morphology of the deformity is similar to that of other phalanges. Injuries to the collateral ligaments of the thumb are common, particularly ulnar collateral ligament injuries (ten times more common than radial).[19]

Ulnar collateral ligament injuries usually occur secondary to sudden radial deviation of the thumb while it is abducted. Classically, this occurs in skiers falling on an abducted thumb while holding onto a pole (skier's thumb). Less commonly, injuries to the UCL may occur chronically from repetitive valgus stress at the MCP joint. Radial collateral ligament injuries occur from sudden ulnar deviation of the thumb toward the fingers and palm.

With acute injuries of the collateral ligaments, there is usually pain and swelling at the MCP joint of the thumb. In UCL injuries, pain on the ulnar side of the thumb with radial stress indicates an injury. The classical round palpable mass is rarely noted along the ulnar side of the metacarpal neck with a complete tear of the UCL (Stener lesion). Stability of the MCP joint should be tested in full extension and 30 degrees flexion, assessing for UCL and RCL integrity. The examiner should stabilize the metacarpal with one hand and passively stress the proximal phalanx in the radial and ulnar direction with the other hand. If there is significant laxity at the MCP with radial deviation, assume there is a tear to the UCL. Likewise, if there is laxity with ulnar deviation, assume there is a tear to the RCL. RCL tears are much less common than UCL tears of the thumb. The thumb CMC joint is stabilized anteriorly and posteriorly by respective oblique ligaments. Isolated dislocations are rare, though associated fractures (e.g., Bennet fractures) are common.

Differential Diagnoses

Associated intra-articular fractures, volar plate, collateral ligament, extensor pollicis longus tendon, and abductor pollicis longus injuries should be considered.

Diagnostic Testing

X-rays should be performed in patients with suspected UCL or RCL injuries, looking for associated subluxation or avulsion fracture. A stress view is particularly useful. Greater than 30 degrees of lateral laxity compared to the opposite thumb at the MCP joint indicates complete disruption of the associated collateral ligament. As with other hand injuries, nonemergent MRI has been found to be reliable in identifying these types of tendinous and ligamentous injuries.[20]

Management

For IP joint dislocations, closed reduction should be performed followed by active range-of-motion testing. Most are stable after reduction, though integrity of the joint and flexor pollicis longus tendon should be examined. The IP joint should be immobilized in 30 degrees of flexion for 3 weeks. Irreducible dislocations and open dislocations require surgical management.

The same technique for closed reduction of other MCP joints should be used for the thumb, avoiding longitudinal traction and likewise avoiding entrapment of the volar plate. Stability, particularly of the collateral ligaments, should be assessed following reduction. Stable dislocations should be immobilized with the MCP joint in slight flexion for 4 to 6 weeks.

For collateral ligament injuries, most stable grade I and II injuries (less than 30 degrees of laxity) may be managed conservatively with immobilization of the MCP joint via thumb spica splinting for 4 weeks. Complete tears (grade III) should likewise be immobilized in a thumb spica splint, but also require prompt referral for surgical management.

If there is pain and tenderness at the CMC joint of the thumb, ligamentous injury or carpal injury should be assumed and thumb spica splinting should be performed. Dislocations should be reduced, though they are often unstable and require follow-up with a hand specialist.

Tendon Injuries

Lacerations, puncture wounds, forced extension or flexion, and crush injuries may result in a tendon injury ranging from strain to complete disruption. After a thorough neurovascular exam and identifying the point of maximal tenderness, a digital block should be considered prior to assessment of tendon integrity. Each digit should be examined individually to avoid a masking effect from adjacent tendons. Motor function should be assessed by having the patient flex and extend the fingers against resistance. Pain with preserved strength on active range of motion may indicate a partial tear, while weakness may indicate complete tendon disruption. X-rays should be obtained to assess for avulsion fractures which commonly occur with tendon disruptions.

Extensor Tendon Injuries

Clinical Features

The extensor mechanism includes muscles that originate proximal to the wrist whose tendons insert on the extensor surface of the fingers (extrinsic extensors). The extensor digitorum communis (EDC, digits II–V) connects with the lateral bands to form the central slip. The central slip inserts at the base of the middle phalanx and functions to extend the phalanx at the PIP joint. The lateral bands themselves arise from the intrinsic muscles (lumbricals and interossei) (see Fig. 42.9).

The extensor mechanism is divided into 9 zones. The classification is relevant to specific injuries and management of those injuries. The even numbered zones are located over bones while the odd numbered zones are located over joints. Zone VIII and IX are located proximal to the wrist (Fig. 42.37). The thumb has its own classification: TI for the interphalangeal joint, TII for the proximal phalanx, TIII for the MCP joint, TIV for the metacarpal, and TV for the carpus.

Thorough inspection should focus on evidence of lacerations, open wounds, and swelling. The extensor tendons should be palpated for tenderness, laxity, or step-off. This is best accomplished with the palm

down on a table. The most common extensor tendon injury is mallet finger in zone I.

Zone I Extensor Injuries. This zone includes the distal phalanx and DIP joint. Terminal tendon disruption from sudden flexion of the extended DIP joint results in the common mallet injury (Fig. 42.38). This injury is common in ball-handling sports from a jammed finger.

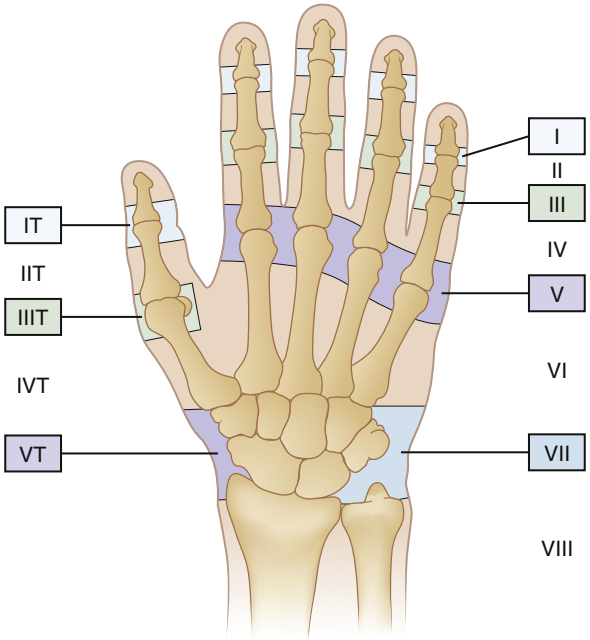

Fig. 42.37 Extensor tendon injury zones of the hand. Zones VIII and IX are located proximal to the wrist. (Rosenthal EA, Elhassan BT. The extensor tendons: evaluation and surgical management. In: Skirven TM, Osterman AL, Fedorczyk JM, Amadio PC. *Rehabilitation of the Hand and Upper Extremity*, ed 6. Philadelphia: Elsevier Mosby; 2011:487-520. Fig. 38-10.)

There is often pain and tenderness over the DIP joint, and extensor lag is associated with complete disruptions. X-rays should be evaluated for associated avulsion fractures, common with this injury.

Zone II Extensor Injuries. Injuries occur over the middle phalanx and are usually due to a laceration. Rarely, a mallet deformity will form from a laceration of the tendon's central and lateral bands.

Zone III Extensor Injuries. Injuries in this zone involve the PIP joint and the central slip. Boutonnière injury (flexion at the PIP joint with hyperextension at the DIP and MCP joints) occurs with central slip disruption (Fig. 42.39). Multiple mechanisms are responsible for these injuries including forced PIP flexion, deep laceration, blunt injury to the dorsum of the PIP joint, or volar PIP joint dislocation.

If there is disruption of the central slip and triangular ligament, there will be inability to extend the finger at the PIP joint. However, if the triangular ligament remains intact, there may be normal motion initially. Because deformities may not form until after the acute phase of injury, there should be a high index of suspicion and a low threshold for splinting.

Integrity of the central slip is best assessed with the *Elson test*. For this test, the PIP is held in maximum passive flexion. The examiner holds resistance against extension at the middle phalanx. If the central slip is intact, when attempted, the patient will not be able to extend the distal phalanx at the DIP due to distal slack at the lateral bands. Conversely, if there is a complete disruption of the central slip, there is increased tone at the DIP joint and there is extension or hyperextension at the PIP joint, indicating a positive test (Fig. 42.40).

The modified Elson test offers direct comparison of the injured to uninjured digit. The patient is asked to hold fingers against each other at the dorsal surface of the middle phalanx with the PIP joint at 90 degrees. The patient then attempts to extend each finger. If there is significant difference in the ability to extend the DIP in one digit compared to the digit in the other hand, assume a central slip injury (see Fig. 42.40).

The examiner should be aware of the *pseudo-boutonnière deformity* where PIP flexion contracture is present though there is no increased

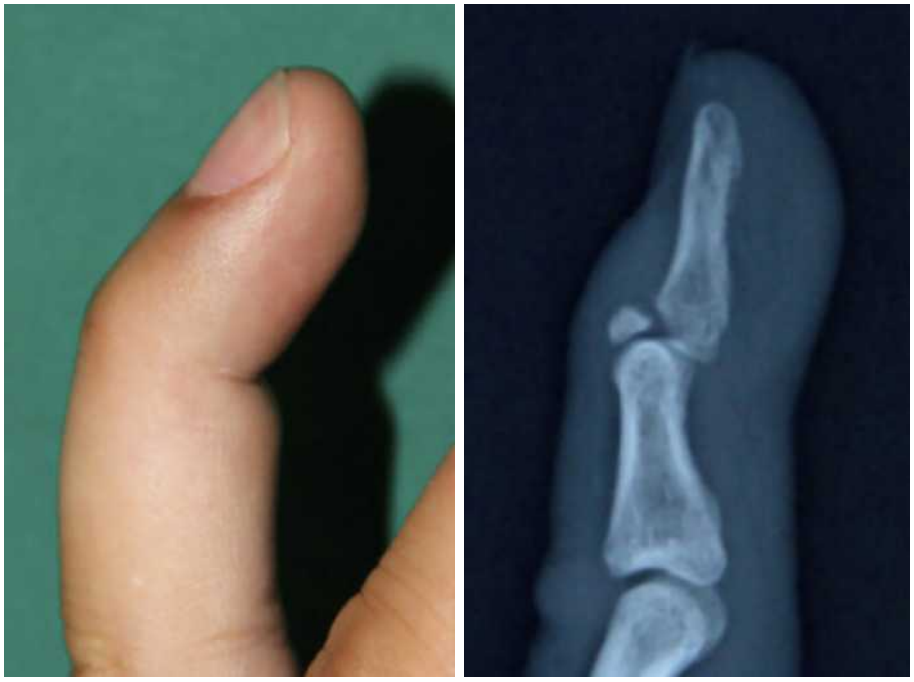

Fig. 42.38 Mallet finger deformity seen clinically with extensor lag and radiographically with an associated avulsion fracture. (Zhang W, Zhang X, Zhao G, Gao S, Yu Z. Pressing fixation of mallet finger fractures with the end of a K-wire. *Injury*. 2016;47(2):377-382. Fig. 3 and 7.)

extensor tone at the DIP (negative Elson test). Thus, the extensor mechanism is actually intact for patients with this deformity.

Zone IV Extensor Injuries. This zone includes injuries over the proximal phalanx. Like in zone II, injuries usually occur from lacerations. The tendon is wide and flat at this location, so most lacerations are partial.

Zone V Extensor Injuries. Injuries at this zone involve the sagittal band at the MCP joint. The most common injury is to the radial sagittal band of the middle finger. The common mechanism is forced flexion or direct blunt force. Swelling and tenderness over the dorsal MCP joint will generally be appreciated on exam. The patient can usually keep the joint in extension, though with active extension from the finger in flexion, there is a snapping relocation of the extensor mechanism. Human bite wounds should be considered with any laceration in this area (i.e., fight bite).

Injuries in zone V are classified based on whether there is no tendon instability (type I), tendon subluxation or snapping (type II), or complete tendon disruption (type III). One specific type of injury is boxer's knuckle. As the name implies, this injury usually occurs from punching an object, resulting in rupture of the sagittal band at the MCP joint.

Zone VI Extensor Injuries. Injuries at this zone occur over the metacarpals, most frequently secondary to lacerations. Complete lacerations are often missed as full extension may remain intact due to juncturae tendinum transmitting extension forces from adjacent tendons.

Zone VII Extensor Injuries. Lacerations over the carpals and extensor retinaculum account for most injuries at this zone, though injuries may also occur with a closed fracture. Wounds should be explored for tendon injury while the patient flexes and extends the fingers.

Differential Diagnoses

Patients with suspected extensor tendon injury often have associated avulsion fractures at the insertion points of the extensor mechanism (e.g., mallet finger). Patients with zone V extensor tendon injuries have a snapping relocation of the extensor mechanism with active extension, which is often mistaken for a trigger finger. With pain and swelling near joint spaces, there may be underlying ligamentous injury, fracture, dislocation, or subluxation. As there is difficulty extending the digit, one should also consider flexor tenosynovitis or Dupuytren contracture. To help with the differential diagnosis, note that Dupuytren contracture is a chronic condition and does not present as an acute injury.

Diagnostic Testing

Due to the strength of the tendon attachments to the bones of the hand, x-ray imaging should be done for symptomatic patients. In the ED, more advanced imaging is not generally used, though the

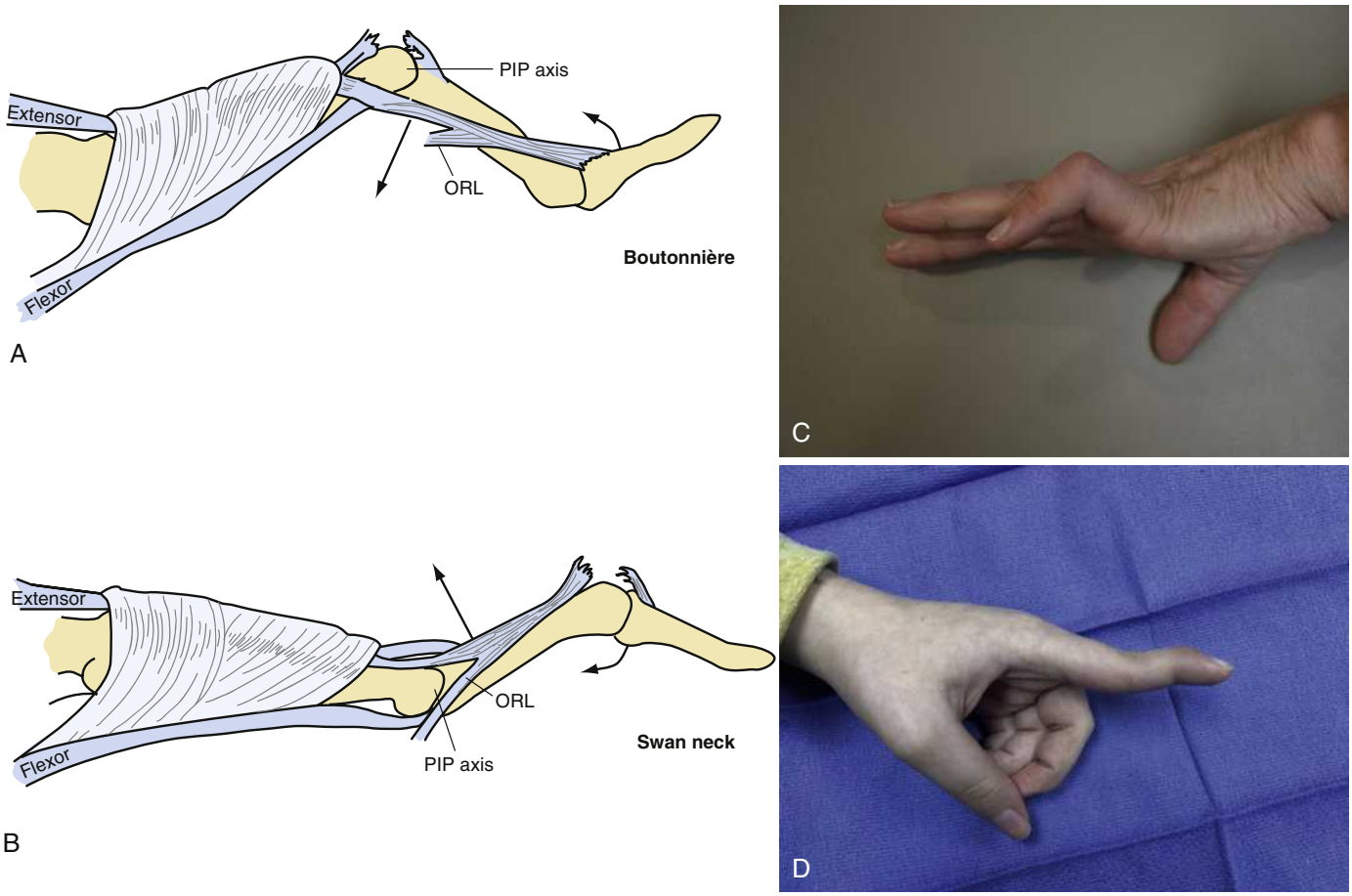

Fig. 42.39 (A) A Boutonnière injury (zone III injury) allows the ORL to subluxate volar to the axis of rotation at the PIP joint. (B) Mallet finger (zone I injury) that has resulted in a swan-neck deformity due to dorsal subluxation of the oblique retinacular ligament (ORL) (lateral bands). (C) Boutonnière deformity seen on physical examination. (D) Swan-neck deformity seen on physical examination. (A and B: Bortel DT. Extensor tendon repair. In: Pfenninger JL, Fowler GC. *Pfenninger and Fowler's Procedures for Primary Care*, ed 3. Saunders; 2020:1154-1159. Fig. 172.1; C: Courtesy of Anthony Zacharek, MD; D: Courtesy of Mary Jo Wagner, MD, FACEP and Thomas Ferreri, MD.)

utility of ultrasound for making the diagnosis of tendon injury is being investigated.[21-23]

Management

Closed extensor injuries are treated acutely with immobilization. Grossly contaminated open lacerations, including crush injuries and large open wounds, should have emergent consultation with a hand specialist for operative management. Irrigation, tetanus immunization, and IV prophylactic antibiotics covering skin flora (e.g., first-generation cephalosporin such as cefazolin 1 g IV q8 hours or for patients with penicillin allergy, vancomycin 1 gm IV with subsequent dosing calculated by pharmacy) should be initiated in the emergency department. Simple, noncontaminated extensor tendon lacerations may be repaired by the EM physician if properly trained with this procedure (see details later). Patients with open lacerations should have thorough irrigation and splinting. They should be discharged with prophylactic oral antibiotics covering skin flora (e.g., a first-generation cephalosporin such as cephalexin 500 mg q8 hours for 7 to 10 days or for penicillin allergic patients, doxycycline 100 mg po BID for 7 to 10 days).

Zone I Extensor Injuries Management. Most mallet finger injuries are successfully treated with immobilization, though injuries accompanied by fracture dislocations may require surgical fixation. For splinting, only the DIP joint should be immobilized, and it should be held in full extension for 6 to 8 weeks followed by nighttime only splinting. A premolded Stack splint is often placed due to its ease of use while performing normal activities. If this is not available, use of an AlumaFoam splint on the dorsal side of the finger is also appropriate. Some patients (15%) have residual extensor lag following splinting, which is considered an acceptable result.[24] We recommend hand specialist follow-up within one week of injury.

Patients with improperly treated mallet injuries may develop a swan-neck deformity where there is hyperflexion at the DIP joint with hyperextension at the PIP joint (see Fig. 42.39). Duck bill deformity may develop at the thumb.

Zone II Extensor Injuries Management. Incomplete lacerations can be managed with simple closure and splinting of the DIP in extension for 2 weeks. Complete lacerations require urgent surgical follow-up for repair and the splint will need to be maintained for 6 weeks. Similar to zone I injuries, if untreated, the patient may develop a swan-neck deformity.

Zone III Extensor Injuries Management. Central slip disruptions (boutonnière injuries) are treated by splinting the PIP joint in extension for 4 to 6 weeks followed by night splinting. DIP flexion exercises should also be performed multiple times each day to help correctly align the lateral bands.

Chronic boutonnière injuries should similarly be treated conservatively with splinting, though these patients often require surgical PIP joint release and should be referred to a hand specialist. Depending on the degree of flexor tendon contracture, complete extension may be unrealistic with initial splinting. Serial splinting, until complete extension is obtained, may be necessary.

Zone IV Extensor Injuries Management

If there is no loss of extension, conservative treatment with splinting is usually sufficient. Splinting, like for zone III injuries, should be performed with the PIP in extension and the DIP free to move. Tendon repair is indicated in patients with loss of active extension.

Zone V Extensor Injuries Management. Stable sagittal band injuries (type I) can be treated with buddy or dynamic taping for 3 to 4 weeks. Acute injuries with subluxation (type II) may be treated with an MCP

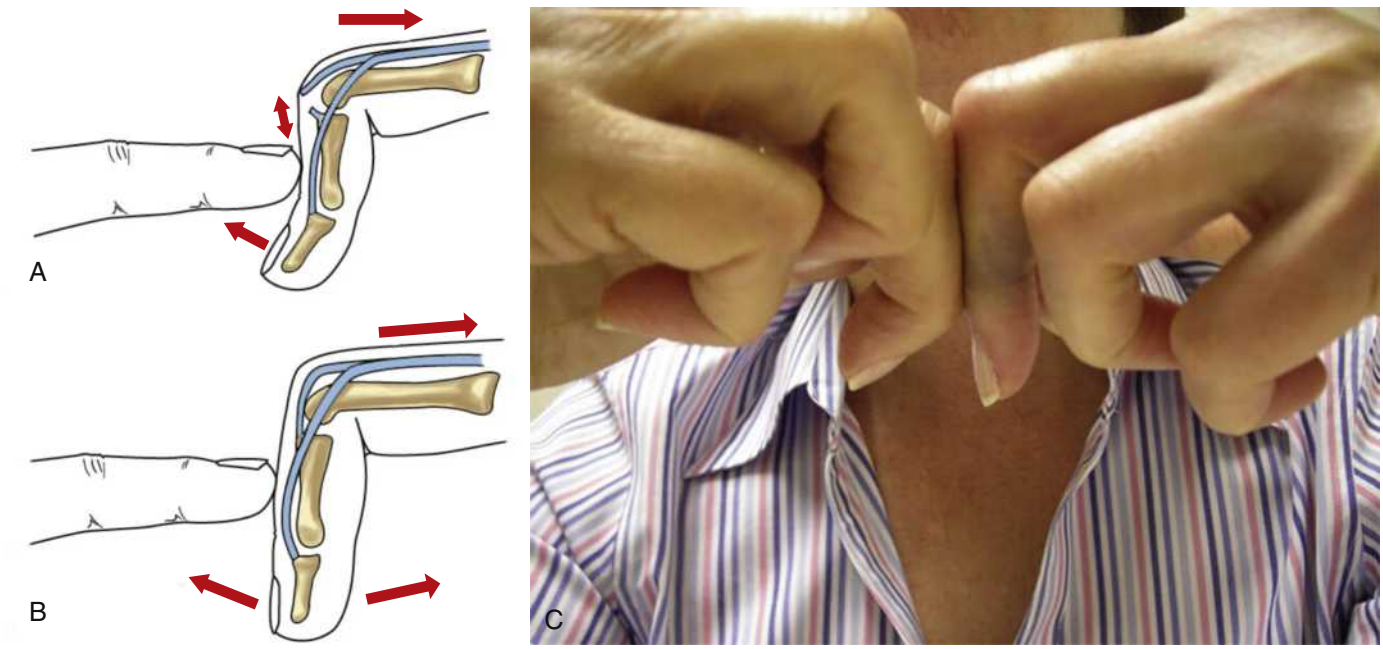

Fig. 42.40 The Elson test (A and B) and modified Elson test (C) are used for evaluation of central slip extensor injury. (A) With a disrupted central slip, the distal phalanx is held in extension as attempted active extension of the PIP joint against resistance allows proximal movement of the origin of the lateral bands. (B) With an intact central slip, attempted active extension of the PIP joint against resistance affects the middle phalanx but prevents extension of the distal phalanx. (C) Abnormal DIP extension of the injured left middle finger as demonstrated by modified Elson test. (A and B: From: Gause T. Boutonniere deformity. In: Miller MD, Hart JA, MacKnight JM. *Essential Orthopaedics*, ed 2. Philadelphia: Elsevier; 2020:327-329. Fig 84.3; C: Posner MA, Green SM. Diagnosis and treatment of finger deformities following injuries to the extensor tendon mechanism. *Hand Clinics*. 2013;29(2):269-281. Fig 13.)

flexion blocking splint (MCP joint in extension with the PIP and DIP joints free) for 8 weeks. Complete disruptions of the sagittal band (type III) should also be stabilized with an MCP flexion blocking splint, though patients with these injuries require referral to a hand specialist for surgical repair. Similarly, patients who have failed splinting and those with chronic injuries (>3 weeks) require hand specialist follow-up for surgical management.

Zone VI Extensor Injuries Management. Clean, complete tendon lacerations may be repaired by an EM physician, though we recommend discussion with a hand specialist first, if possible. Urgent follow-up with a hand specialist is indicated, ideally within one week. Initial splinting should immobilize the wrist at 30 degrees of extension, MCP joint in extension, and the PIP and DIP joints free to move.

Zone VII Extensor Injuries Management. If there is no need for immediate surgical intervention (such as gross contamination), wounds should be thoroughly irrigated followed by skin closure. The hand and wrist should be immobilized with a volar splint, keeping the wrist at 30 degrees of extension and the MCP joints at 15 to 20 degrees of flexion. Hand specialist follow-up is indicated, ideally within one week.

Disposition

In any case where there is concern for an extensor tendon injury, either open or closed, referral to a hand specialist is recommended from the ED. Due to risk of chronic functional impairment, patients with complete tendon lacerations should have urgent follow-up with a hand specialist so that surgery may occur within 2 to 3 weeks. Any delay that might come about by an initial referral to a primary care appointment should be avoided if possible, and patients should be instructed about this timeline. Loss of motion is the most common chronic complication of tendon injuries. This may be accompanied by extensor lag or joint contracture.

Flexor Tendon Injuries

Clinical Features

The majority of flexor tendon injuries are open injuries secondary to a deep laceration.

Closed flexor tendon injuries are less common in general and are less common than extensor tendon injuries. They tend to occur in athletes from having forced hyperextension of a digit that is in active flexion. The two most common flexor tendon injuries of the hand involve the flexor digitorum profundus (FDP) and the flexor digitorum superficialis (FDS) (Fig. 42.41). Most closed flexor tendon injuries occur at the fourth finger, involving the FDP. The FDS is generally spared. Patients will complain of a "pop" or "tear" with pain over the flexor surface, as well as loss of active flexion or weakness of the tendon. Bowstringing tends to occur only when multiple pulleys have been injured. This usually involves the two strongest pulleys A2 and A4 (see Fig. 42.12). A flexor tendon injury should be considered when an injured finger does not assume its naturally flexed position on cascade testing.

Specific tendon function testing should be performed (see Table 42.1). Recall that the FDP tendon inserts at the base of the distal phalanx and the FDS tendons insert at the base of the middle phalanx. The FDP tendon should be examined by holding the patient's MCP and PIP joints in extension and having him or her attempt to flex the DIP joint. The examiner should be sure not to impede the motion of the other digits when doing this or a false-positive test can occur. Inability to flex indicates a tendon laceration. Weakness or pain when flexing indicates that there is likely incomplete disruption or strain. To accurately assess FDS integrity, the FDP must be restrained. This is accomplished by holding all uninjured digits in full extension. Inability to flex at the PIP using this technique indicates FDS disruption. If there is partial or complete disruption of the FDS, the involved finger will rest with less flexion than normal and will be unable to flex at the PIP joint. With similar injury to the FDP, the PIP joint will be held in extension and the patient will be unable to flex at DIP joint or be able to pinch or grip with this finger.

Tendon avulsions are very rare in isolation for FDS injuries, though are far more common with the FDP tendons. There are three main types of FDP avulsion injuries. Type I involves a completely avulsed tendon migrating proximally through the flexor sheath into the palm. There is risk for compromised vascular supply to the tendon and surgery is recommended as soon as possible (no later than 7 to 10 days). Type II injuries involve a complete avulsion with proximal retraction to the level of the PIP joint. Similar to type I injuries, the patient may have

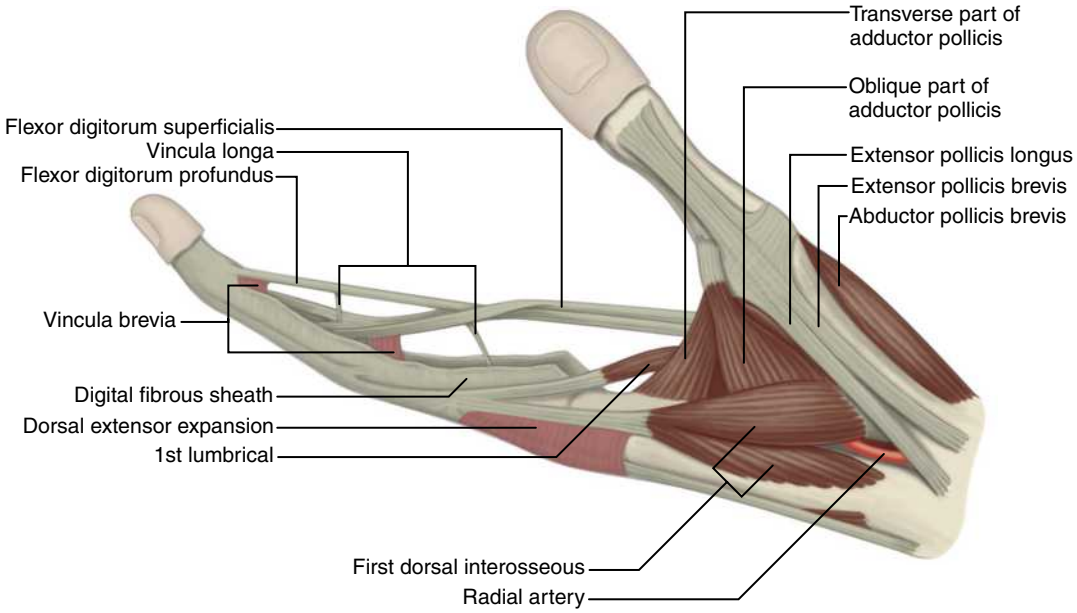

Fig. 42.41 Lateral view of the hand showing the flexor tendons of the finger. (From Standring S: *Gray's Anatomy: The Anatomical Basis of Clinical Practice*, ed 39. Edinburgh: Churchill Livingstone; 2005.)

compromised vascular supply and patient should have expedited surgical repair. For type III injuries, the avulsed tendon retracts only to the level of the A4 pulley. There is less concern for vascular compromise, though surgery is still recommended within 7 to 10 days.

The flexor tendons are divided into 5 anatomic zones (Fig, 42.42). Zone I extends from the insertion of the FDP at the distal phalanx to just distal to the insertion point of the FDS at the middle phalanx. FDP tendon avulsion from its insertion at the base of the distal phalanx is the most common (jersey finger) injury. With this specific injury, the patient is unable to flex the DIP. It classically occurs in football players who may grab onto an opponent's jersey to tackle or slow the runner and there is forced hyperextension with the digit in active flexion.

Zone II extends from the distal palmar crease to the proximal portion of the middle phalanx and includes both FDP and FDS tendons. Because the injured tendons and associated structures are within the tight space of the flexor sheath in this zone, repair is technically more demanding and results in a greater frequency of complications relative to other zones. As a result, it has been historically referred to as "no man's land." Advances in technique over the years have made primary repair of flexor tendons a standard option for treatment.

Zone III extends from immediately distal to the carpal tunnel to the proximal flexor sheath of the digits. Generally, injuries to this zone have good outcomes.

Zone IV includes the carpal tunnel. Damage to the median nerve is common, stressing the importance of a thorough neurovascular exam. Because of protection from the flexor retinaculum, other injuries in this zone are relatively rare.

Zone V is proximal to the carpal tunnel. Injuries in this zone usually occur from a deep laceration and involve multiple tendons.

Differential Diagnoses

Associated avulsion fractures are common with flexor tendon injuries (e.g., jersey finger). Other underlying fractures, ligamentous injuries, dislocations, and subluxations should also be considered.

Diagnostic Studies

X-rays may be obtained to rule out associated avulsion fractures. Ultrasound has also become increasingly popular as a dynamic bedside study.[21-23]

Management

Patients with flexor tendon injuries, both open and closed, should see a hand specialist given risk for chronic disability. Urgency depends on the injury, and any acute rupture or laceration is urgent. Emergency consultation is indicated in patients with associated open fractures or dislocations, grossly contaminated wounds, bites, arterial injury, or if the wound overlying the tendon cannot be closed in the ED. Follow-up within 3 days is indicated for most other patients with acute flexor tendon lacerations, because delay may result in retraction of the tendon ends, creating a more difficult repair and risk for worse outcome.

The tendon should also be immobilized with a blocking splint to prevent further retraction of the flexor tendons. Splinting should be performed with the wrist in neutral to slightly flexed position, the MCP joints flexed to 70 to 90 degrees, and the IP joints minimally flexed at 10 to 15 degrees. A thumb spica splint should be used for patients who have flexor tendon lacerations involving the thumb with the wrist, MCP, and IP joints in similar flexion.

Patients with any open wounds should be started on oral antibiotics covering skin flora for 5 to 7 days. Cephalexin 500 mg PO TID for 7 to 10 days or doxycycline 100 mg PO BID for 7 to 10 days (for penicillin-allergic patients) are appropriate regimens.

Disposition

Primary repair, or end-to-end repair, is defined as occurring within 24 hours of injury.[25] Referral for *delayed repair*, defined as occurring within 3 weeks of injury, may be considered if an experienced specialist is not available on the day of the injury and the wound has not been grossly contaminated. Direct communication with the hand specialist should occur to help ensure there is timely follow-up, since the success

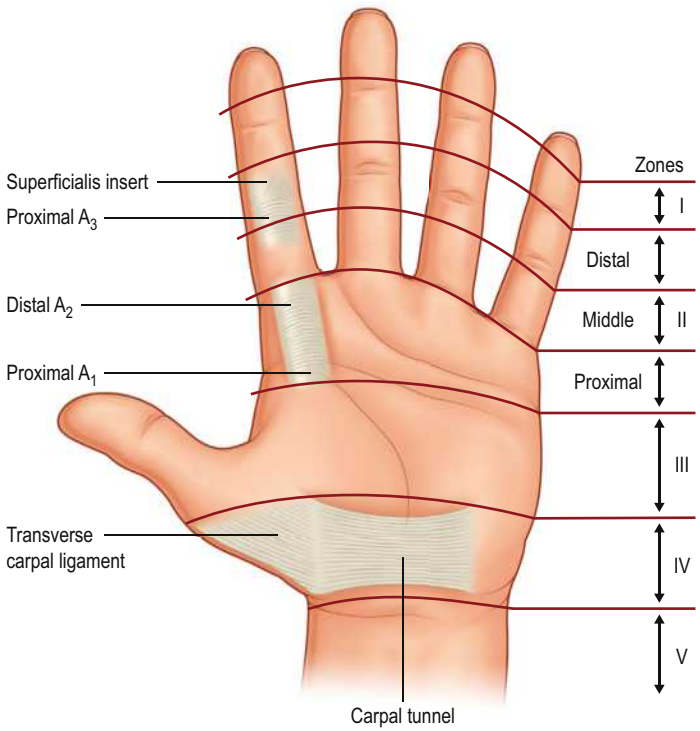

Fig. 42.42 Flexor tendon zones. (From: Chang J, Legrand A, Valero-Cuevas F. Anatomy and biomechanics of the hand. In: *Plastic Surgery: Vol 6: Hand and Upper Extremity*, ed 4. London: Elsevier; 2017:1-48. Fig. 1.39.)

and ease of the repair is improved with less delay than 3 weeks. If the patient will be undergoing delayed primary closure, the overlying wound should be thoroughly irrigated and closed with loose sutures and the hand splinted in the functional position.

Adhesions, infection, and tendon contracture are common complications. One rare complication following repair is recurrent rupture. This usually occurs within 5 weeks of repair. Patients will present to the ED complaining of feeling a "pop" or new acute pain with a sudden loss of function if the patient is in a dynamic splint. The diagnosis can often be made by noting an abnormal flexion cascade sign. The EM physician should avoid having the patient attempt any flexion activities that have not already been approved by the hand specialist or physical therapist and should not remove the splint. Referral back to the hand specialist within 3 days is appropriate.

Trigger Finger

Clinical Features

Trigger finger, often referred to as stenosing tenosynovitis, occurs from overuse. The common mechanism is repetitive forceful flexion. This leads to inflammation and narrowing at the A1 pulley, thereby inhibiting normal smooth tendon movement. The patient will usually complain of catching and pain with flexion and extension of the fingers (Fig. 42.43). Trigger finger is most common in patients with underlying inflammatory joint disease, diabetes mellitus (DM), and hypothyroidism. A snapping sensation is appreciated with examination of active and passive range of motion. In chronic cases, a nodule may be felt on the flexor surface of the MCP joint.

Differential Diagnoses

When considering trigger finger, one should consider underlying inflammatory joint disease, subluxation of the extensor tendon, or Dupuytren contracture. In the presence of preceding trauma, one should also consider underlying fracture, tendon injury, or ligamentous injury.

Diagnostic Testing

The diagnosis of trigger finger is made exclusively from history and exam, but if there is more to the clinical picture and there is concern for an underlying pathology such as DM, hypothyroidism, or inflammatory joint disease, then laboratory studies including blood glucose, HgbA1c, TSH, free T4, ESR, and CRP may be obtained in the ED. Hand radiographs are generally not needed, but if there is a history of acute trauma or concern for an avulsion injury, x-rays may be performed to rule out an underlying fracture.

Fig. 42.43 Trigger finger in a patient with the ring finger stuck in flexion. (Courtesy of Anthony Zacharek, MD)

Management

Initial treatment of trigger finger involves conservative measures including NSAIDs and splinting. Immobilization with an MCP blocking splint at slight flexion (10 to 15 degrees) for 6 to 10 weeks has been shown to improve symptoms.[26] Corticosteroid injections have also been shown to be effective in reducing symptoms though there is higher risk for recurrence (50% at 1 year). Injections may be performed by the EM physician, though we also recommend that injections be reserved for patients who have failed conservative measures. Following acute treatment, the patient should modify activity to limit overuse and recurrence.

Hand specialist referral for surgical management (A1 pulley release) is indicated in patients who fail conservative treatment. A Cochrane review of two RCTs comparing treatment with open surgery versus steroid injection (control) found that 92% of patients had resolution of symptoms without recurrence compared to 61% of patients in the control group. There is a lower risk of recurrence in patients with open surgery, though there are greater complaints of pain during the first week following treatment.[27]

Corticosteroid injections may be used in patients with trigger finger who have failed conservative measures such as splinting, icing, and NSAIDs. Corticosteroid injections have been shown to improve long-term pain in patients with trigger finger. In one study, greater than 68% of patients reported complete resolution in pain and snapping one month after the injection. In this same study, greater than 57% reported resolution of PIP flexion contracture.[28] There are two methods for corticosteroid injections in these patients: intra-sheath injection and extra-sheath injection. Ultrasound guidance is helpful in identifying landmarks. A linear-array transducer should be placed in the long-axis orientation along the volar side of the affected finger at the MCP joint.[29] The flexor digitorum superficialis and flexor digitorum profundus tendons as well as the A1 pulley should be identified (Fig. 42.44). For the intra-sheath technique, at approximately 45 degrees and using a distal to proximal long-axis approach, the needle should be advanced until the tip of the needle is between the FDS and FDP tendons. Approximately 0.5 mL of steroid such as triamcinolone acetonide 10 mg/mL suspension, mixed with a local anesthetic, is injected. The extra-sheath technique is similar, though the tip of the needle should rest at the distal end of the A1 pulley, superficial to the FDS and FDP, which is the site of injection. If there is resistance with injection or if the needle moves with flexion and extension of the digit, the needle is likely deep in the tendon and it should be withdrawn slightly. If, with flexion and extension of the digit, there is a sensation of the tendon rubbing against the needle point but no significant movement of the needle, it is likely in correct position in the tendon sheath.

Finger and Nail Bed Injuries

Nail Bed Injuries

Clinical Features. The nail bed is frequently injured in a manner that ranges from minimal to severe. Injury occurs after direct trauma to the fingertip with the nail compressed against the thin layer of skin (nail bed) and the bony tuft immediately underneath. A subungual hematoma or bleeding under the nail plate is described by the percentage of the nail bed that is covered by the blood with an unbroken fingernail and intact nail root. Pain results from the pressure caused by the blood within the closed space of the nail plate, nail bed, and nail fold. Identification of the extent and depth of any laceration of

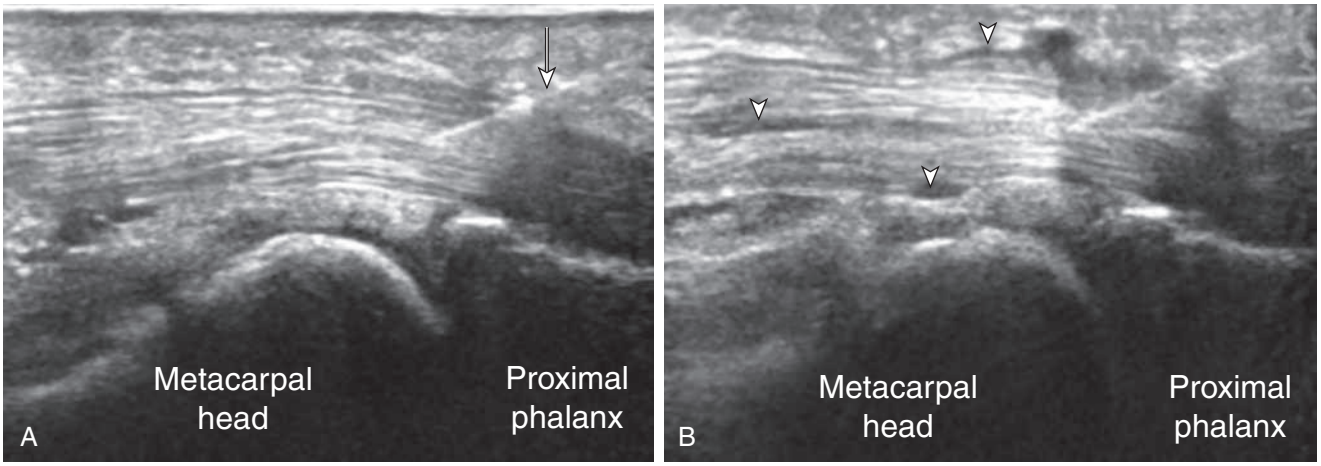

Fig. 42.44 Intra-sheath steroid injection technique using ultrasound guidance. (A) The needle tip is placed between the FDS and FDP tendons (*arrow*). (B) Expansion of material into the space between the FDS and FDP tendons or the margin of the flexor tendons (*arrowheads*). (Reprinted by permission of Elsevier, from Shinomiya R, Sunagawa T, Nakashima Y, Yoshizuka M, Adachi N. Impact of corticosteroid injection site on the treatment success rate of trigger finger: a prospective study comparing ultrasound-guided true intra-sheath and true extra-sheath injections. *Ultrasound Med Biol.* 2016;42(9):2203-2208.)

the nail bed or along the lateral or proximal nail folds will determine management options.

Differential Diagnoses. When evaluating a patient with a suspected nail bed injury, the EM clinician should also consider an underlying tuft fracture, open fracture, subungual hematoma, mallet injury, or FDP tendon injury.

Diagnostic Testing. Imaging is needed to determine if there is fracture of the finger tuft. PA, lateral, and oblique radiographs will identify a fracture and determine if surgical repair will be needed. Comminuted fractures are generally stable due to the fibrous septae of the pulp that are tightly adherent to the tuft. Transverse fractures of the distal phalanx and intra-articular fractures will need surgical referral, ideally within one week. If the only injury is a subungual hematoma, an x-ray is not needed if the mechanism or clinical findings do not indicate a fracture that would leave an unstable fingertip.

Management. For a subungual hematoma covering greater than 50% of the nail bed, the typical practice is to trephinate, or create an opening in the nail to release the blood. A hole to provide drainage of the hematoma can be created with a sterile 18-gauge needle or electrocautery. Several studies have shown that if the nail remains generally intact, trephination without nail bed repair achieves equal healing and cosmesis compared to the more invasive and painful removal of the nail and repairing the nail bed. If the fracture is only a parcellar (nondisplaced) fracture of the fingertip, no treatment with antibiotics is needed (Fig. 42.45).

If a finger tuft is unstable due to a fracture, surgical repair is needed to stabilize the bony support and use of the finger. Repair of the tissue injuries can be done during the surgical procedure, though some EM clinicians will primarily repair the laceration, as the bony damage can be stabilized at a later time. The decision whether or not to primarily repair the laceration in this situation is dependent on the local standard of care.

If there is disruption of the nail bed or root, then repair of these structures should be done (Fig. 42.46). Anesthesia using digital block in older children and adults is appropriate, though younger children may need procedural sedation to accomplish the repair. Use 6-0 absorbable suture to directly repair the laceration, or tension sutures to approximate the nail bed when the tissue is too disrupted. The goal is to cover the bony surface as well as possible. Some practitioners have used tissue adhesive to repair the nail bed, which may be appropriate instead of suturing if approximation is more easily achievable. Some practitioners use the tissue adhesive to repair the nail plate if it is cracked, so it can be used to cover the nail bed. Subsequent dressing with a nonadhesive covering is needed.[30]

Specific recommendations regarding the replacement of the nail plate after nail bed repair are rapidly changing. Historically, the practice has been to replace the nail plate after repairing nail bed lacerations, including putting the nail plate into the nail fold to prevent blocking the ability of a new nail to grow from the germinal matrix. However, no systematic trials have been done to determine if this is necessary or might decrease the infection rate (2% to 5%). In a recent large British study, one-third of specialists did not replace the nail plate and of those who did replace the nail plate, one-third did not secure the nail and 20% used tissue adhesive.[31] A more recent pilot study showed fewer infectious complications and less pain without replacement of the nail. A large prospective randomized trial is in progress to delineate a more definitive recommendation.[32,33] With the current debate in the literature, we recommend repositioning the nail after repair of the nail bed. The nail serves as the best source of a biologic splint for the injuries of the soft tissues and bone. If the nail is reinserted under the eponychial fold, the soft tissue can often be stabilized to it.

Most studies of antibiotic use in nail bed injuries with disruption of the nail plate included only patients that were referred to hand specialists, providing a selected population; no ED-based studies demonstrating appropriate treatment were found. In the survey of current practice for consultants caring for pediatric hand injuries in Britain, half of nail bed injuries were generally associated with fractures of the distal phalanx. Almost two-thirds used antibiotics even if there was no underlying fracture associated with a nail bed injury.[31] As previously noted, distal phalanx fractures have less periosteal stripping, so they do not have the infection rate of other open fractures in the body. A 2016 meta-analysis suggests that the focus of treatment should be on prompt irrigation and early débridement without the need for prophylactic antibiotics. Specifically speaking to fingertip entrapment (an injury generally from a finger being crushed in a door or window), the most recent Cochrane review indicates there are no well-designed studies to guide our practice for any specific repair or the need for antibiotics. Internationally, the practice variability ranges from giving

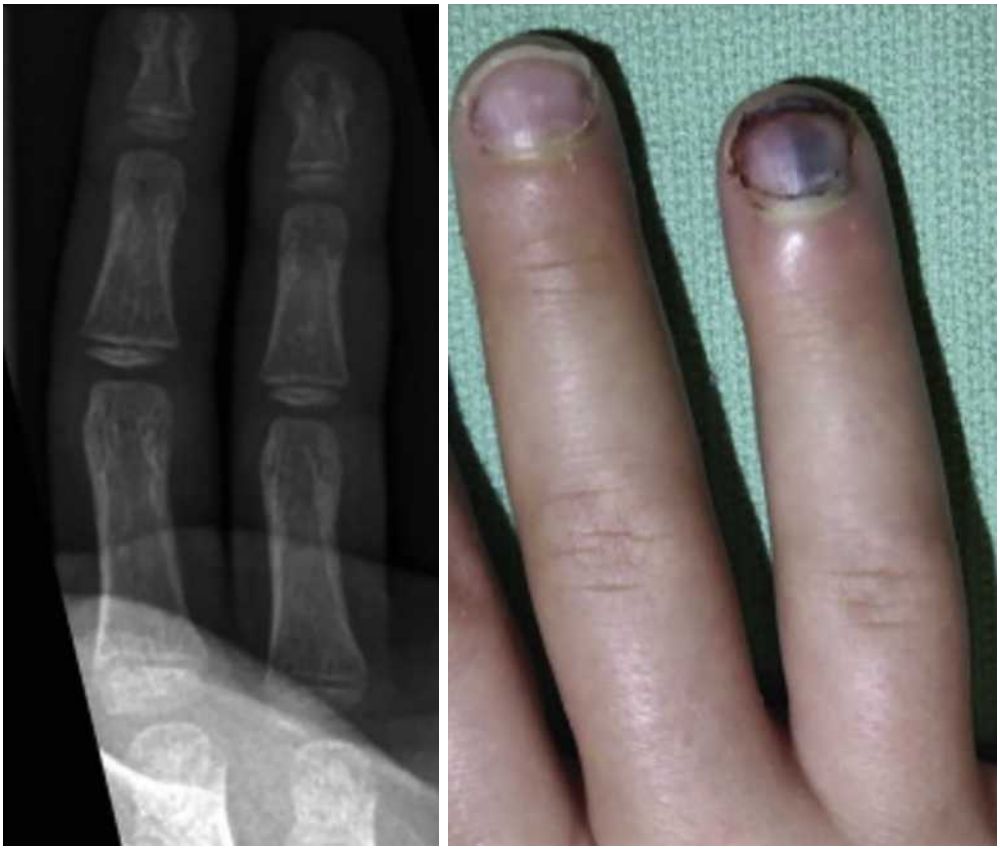

Fig. 42.45 Subungual hematoma in a 6-year-old boy with middle and ring fingertip crush injury. (Nellans, KW, Chung KC. Pediatric hand fractures. *Hand Clini.* 2013;29(4):569-578.)

a first dose of IV first-generation cephalosporin followed by 10 days of oral cephalosporin, to no antibiotics except for clearly contaminated wounds. Without clear evidence, following the recommendations of the local hand specialist that will ultimately care for the patient is most appropriate.

Disposition. The injuries resulting in subungual hematomas with non-displaced fractures can be followed up by primary care physicians as most do not need further treatment. Hand specialists should be consulted if primary care follow-up is not an option, and for injuries that are complex, including those with missing tissue, unstable fractures such as transverse fractures of the distal tuft or fractures that involve a joint.

Amputations

Fingertip Amputations

Clinical Features. Amputations of the fingertips are common, most often occurring in children. These injuries can result in macerated tissue, but any available amputated part should be initially preserved. With amputations of the fingertip, there are several different classification systems, based on the involved vascular structures or tissue structures. For EM physicians, the injuries have been classified by zones as shown in Figure 42.47. Zone I is distal to the bony distal phalanx, zone II is the area between the distal phalanx and the lunula, and zone III is proximal to the lunula. Practically, a functional description is more helpful to the hand specialist. The injuries in zone I and II allow for retention of the full function of the digit, even if there is some shortening of the digit. An injury more proximal than the lunula line generally indicates damage or loss of the flexor digitorum profunda (FDP) with the resultant loss of flexion and stiffness at both the DIP and PIP joints. The presence or absence of exposed bone will also determine management. In young children (less than 3 to 4 years old) with distal tip amputations, the tissue can be reattached as a composite graft if it measures typically 1.0 cm in size or less. Consultation with a hand surgeon is recommended in these situations.

With more proximal amputations, an accurate description or image of the injury will assist in the determination of where and which management would be appropriate. The hand specialist can help the EM physician determine if reimplantation is the proper course of action. Indications for reimplantation include amputation of the thumb, multiple adjacent digits, pediatric patients, and clean, sharp amputations. Relative contraindications include severely crushed or contaminated wounds, patients with significant comorbid conditions, and multilevel amputations of the same digit.

Differential Diagnoses. When caring for a patient with a digit amputation, one should consider associated foreign bodies, proximal fractures, ligamentous injuries, tendon injuries, and neurovascular injuries.

Diagnostic Testing. Standard 3-view x-rays of the affected digit should be performed.

Management. Initial management includes assessment of the wound, control of bleeding, and thorough irrigation of the injury without further disruption of the tissue. A methodical exploration of the injury to provide a detailed description to the hand specialist will allow for determination of the appropriate management. One of the most important objectives is to identify if there is disruption of the proximal portion of extensor or flexor tendon attachment to the distal phalanx. The work-up is assisted by appropriate radiographs, identifying any chip fractures. Coordination and possible transfer to a center with hand specialists that perform microsurgery may be needed. If reimplantation of finger or fingertip is to be attempted, the

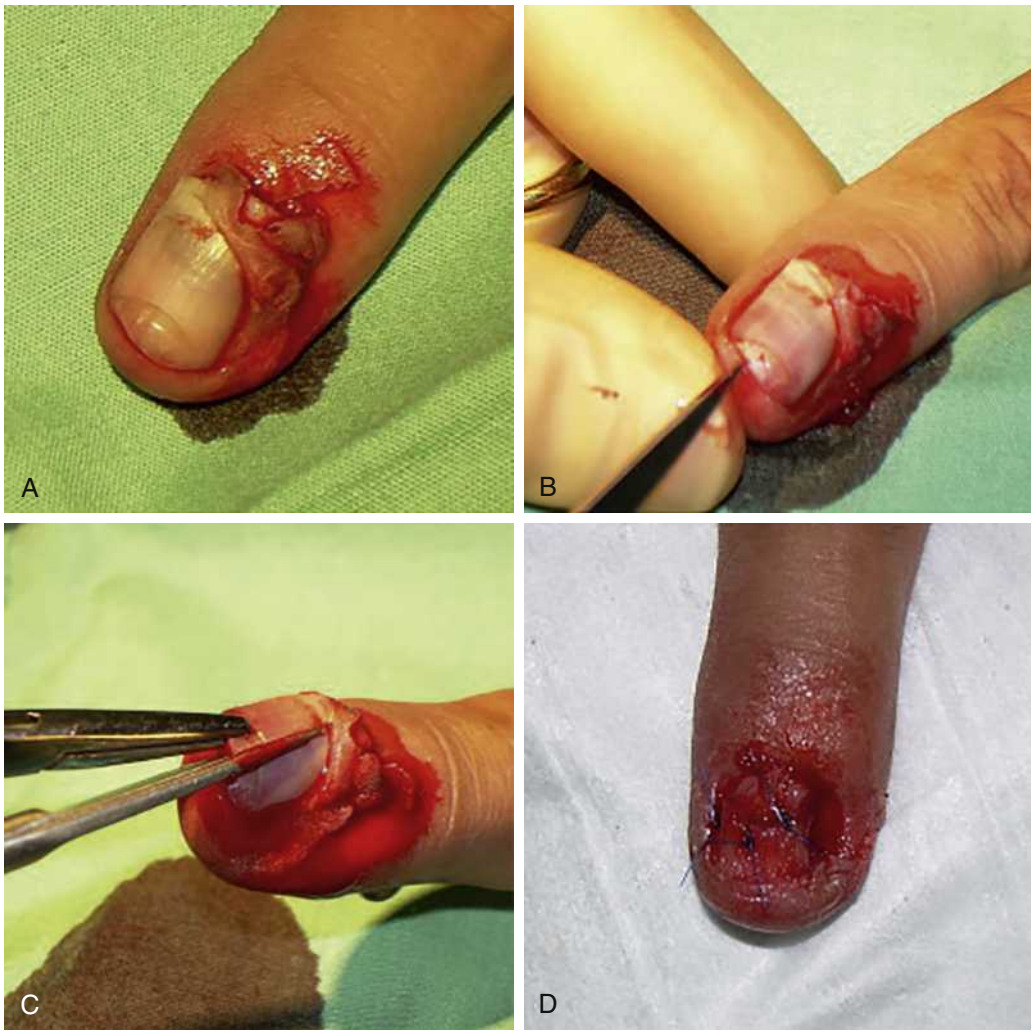

Fig. 42.46 Nail bed injury and repair. (A) Injury to eponychium prior to repair. (B) Separation of the nail plate from the sterile matrix with a fine scissor directly under the distal nail plate attachment. (C) The eponychium tissue is removed with scissor and the nail plate is removed with forceps traction. (D) Following nail bed repair. (Brown DJ, Jaffe JE, Henson JK. Advanced laceration management. *Emerg Med Clin N Am.* 2007;25(1):83-99. Fig. 1.)

amputated tissue should be placed in a normal saline-soaked gauze, in a clean plastic bag, and then this bag is placed in ice water to promote its viability over the next few hours.

In patients with small tuft avulsions (defined as less than 1 cm^3 loss of soft tissue with the nail intact and covered bone), healing by secondary intention is appropriate and does not seem to prolong pain or increase infection. The wound should be thoroughly irrigated and débrided of nonviable tissue, then loosely approximated if tissue allows. Patients generally report moderate discomfort for 7 to 10 days, with complete healing in 4 to 6 weeks, so appropriate counseling to set reasonable expectations should be provided to patients.[34] Even with a small tip of bony exposure, using a rongeur to trim the bone back and allowing it to heal with secondary intention has not been shown to change long-term outcome compared to other surgical options (Fig. 42.48). If coverage is needed for the tuft, then soft tissue from the pulp can be obtained with local tissue rearrangement or for a flap closure, such as a V-Y advancement flap (Fig. 42.49).

The majority of fingertip avulsion injuries of the distal tip in North America are managed nonoperatively, though in Asia and Europe, there is more focus on attempted reimplantation, with success rates of 70% to 90%.[35,36] This appears to be secondary to cultural concerns of missing digits, compared to a priority in the United States of rapid return to function. In the ED, optimizing the opportunity for a successful reimplantation in more significant injuries should be the goal as these patients have less pain and better functional outcome than those whose digit is amputated. The patients that should be referred immediately to a reimplantation specialist include those with loss of a thumb, multiple fingers, or the fingertip, and any child with loss of a digit.

If reimplantation is not an option, then a hand specialist may select several options for closing a larger wound. Free grafts, cross-flaps, advancement flaps, skin grafts, and healing by secondary intention are all possible treatment options for these injuries. If a patient who has previously undergone surgery for this injury such as a cross-finger flap presents to the ED, extreme care must be taken to avoid tension that may pull apart the graft site (Fig. 42.50). It may be of benefit to call the surgeon before removing the dressing.

The use of antibiotics has long been debated and, although prescribed for many patients with open tuft fractures with nail bed injuries, studies do not demonstrate that use of antibiotics reduces the risk of infection in a well-cleansed wound.[37] The consensus is that antibiotic prophylaxis (oral cephalexin 500 mg TID or oral doxycycline 100

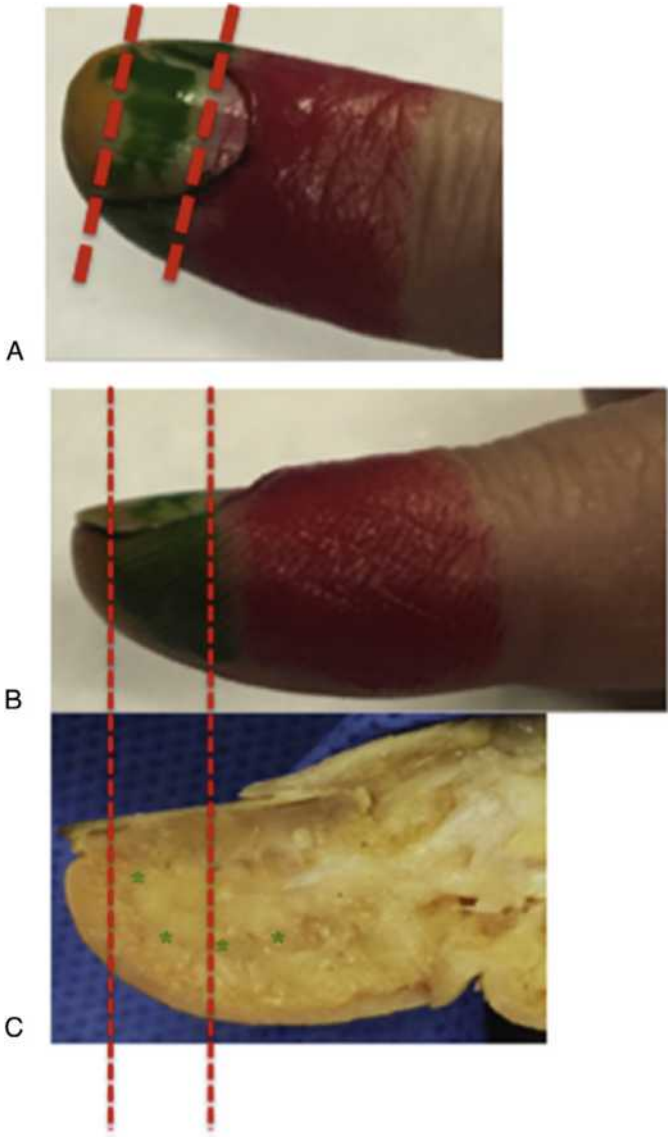

Fig. 42.47 Fingertip amputation zones: *Zone I* amputations include pulp and distal nail which generally heal by secondary intention. *Zone II,* Bone exposed—revision amputation soft tissue flap (e.g., V-Y advancement flap). *Zone III* involves the eponychium. Most require amputation of the distal phalanx at the DIP joint. (Courtesy Dr. D.A. Stearns, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.)

mg BID (for penicillin-allergic patients for 7 days) should be given for grossly contaminated wounds but is not necessary in clean wounds in immunocompetent patients.

Disposition. Immediate consultation with the hand specialist is needed for all but those with zone I and other minimal injuries. In the United States, it is rare that an isolated fingertip amputation will get reimplanted. If the emergency physician is not comfortable with the closure described, then the hand specialist should see that patient at the time of the initial ED visit. After the patient's fingertip avulsion has been treated with coverage of the bone and tendon, the patient should have follow-up with the hand specialist in 7 to 10 days.

Transfer to a reimplantation center may be necessary during the initial ED visit. The success of reimplantation from specialized centers is reported to be 90% or better. Many clinicians are concerned about

Fig. 42.48 Volar finger-tip amputation. (Courtesy of Ronald Barry, MD, FACS)

delay to reimplantation after amputation. Recent studies have shown that the success rate of reimplantation remains above 90% whether done immediately or even with an overnight delay from injury to surgery.[38] The most common residual subjective symptom reported is cold intolerance to the tip of the finger. Other undesirable outcomes include infection, insensitivity, abnormal cosmetic appearance, and decreased range of motion.

Degloving Injuries

Degloving injuries and ring avulsion injuries (traumatic removal of a ring from a digit) result from trauma of a digit or the hand that pulls off the tissue, involving a varying degree of skin, muscle, tendons, flexor pulleys, and the associated neurovascular bundles (Fig. 42.51). The Urbaniak classification for ring avulsion injuries (Box 42.3) is helpful to determine treatment and prognosis. The more severe the injury, the less likely hand specialists are to attempt repair rather than amputation and the more likely for complications of flap coverage, revascularization, and reimplantation. Patients with class I injury should be seen by a hand specialist for assessment and wound closure. Class II or III injuries needs microsurgery with immediate referral to a hand specialist and facility capable of performing this repair. The most important indication of success is the ability to restore adequate revascularization.[39]

Mutilating Hand Injuries

Severe mutilating injuries of the hand can occur from explosions, gunshots, crushing industrial accident, motor vehicle collision, home equipment or environmental activities. These dramatic wounds are generally associated with other traumatic injuries that can be life-threatening, so appropriate evaluation for trauma patients should be prioritized without being distracted by the injured hand. Controlling the bleeding from a major hand wound can generally been done with direct pressure, or if not successful, by the use of a pneumatic or blood pressure cuff. Though challenging, a physical examination should be done to document the remaining function and sensation, if possible. Assessment of the vascular system might be difficult, but evidence of

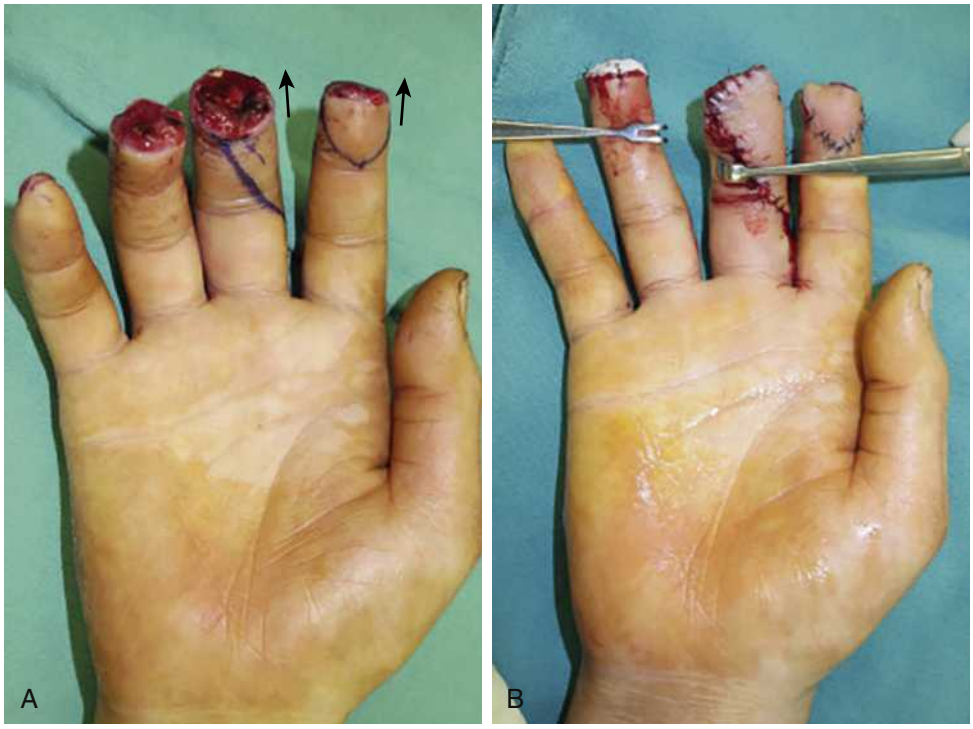

Fig. 42.49 Example of a V-Y advancement flap and an oblique triangular neurovascular island flap used for reconstruction of a small size pulp defect in the index and long fingers, respectively. (A) Flap design. (B) After advancement of flap. Direction of flap advancement as indicated by the black arrow. (Ono S, Sebastin SJ. Microsurgical flaps in repair and reconstruction of the hand. *Hand Clin*. 2017;33(3):425-441. Fig. 10.)

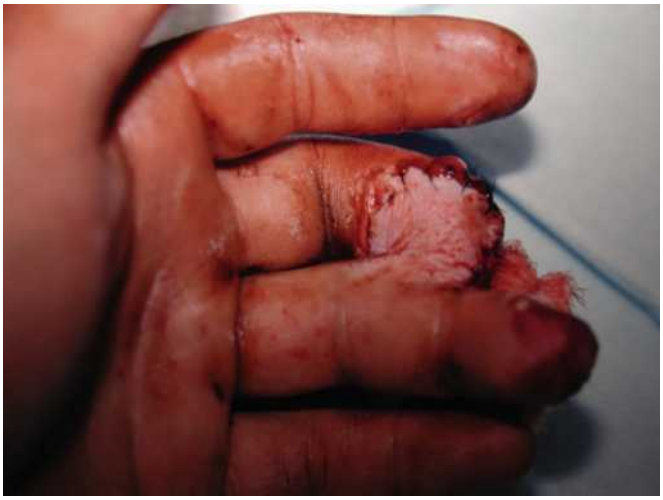

Fig. 42.50 Cross-finger flap. (Courtesy of Ronald Barry, MD, FACS.)

a pulse can be obtained through the use of a Doppler ultrasound or placement of a pulse oximeter. Immediate consultation with the hand specialist should be obtained after the patient is stabilized from other life-threatening injuries. In the ED, one dose of IV antibiotics (first-generation cephalosporin such as cefazolin 2 to 3 gm or vancomycin 10 to 15 mg/kg for adults) and appropriate tetanus prophylaxis are indicated prior to surgical stabilization. For the surgeon, the priorities are to have a stable thumb or a first digit post of at least the length of the IP joint, to have one or preferably two opposing digits, and to achieve coverage of tissue with sensation for the involved functioning extremity.

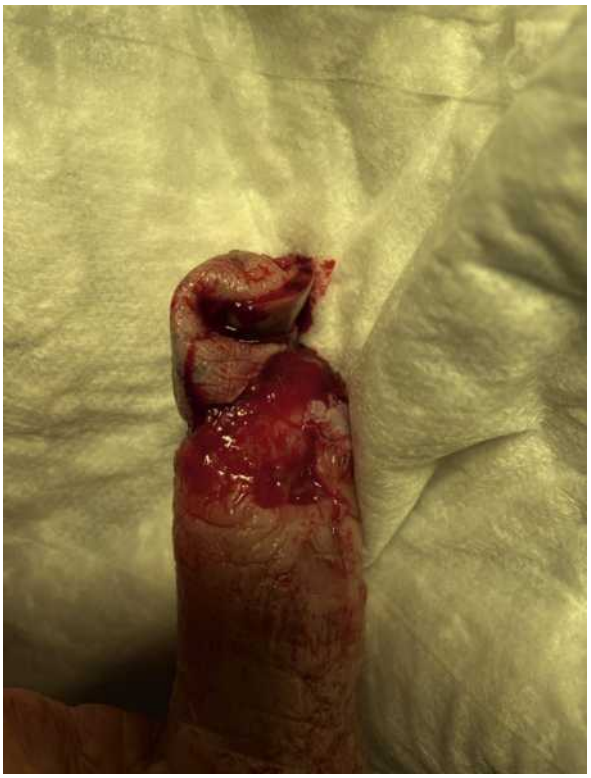

Fig. 42.51 Degloving injury in a patient who stuck her thumb in a wood splitter. (Courtesy Benjamin Schoener, MD. Central Michigan University COM.)

BOX 42.3 Urbaniak Classification for Ring Avulsion Injuries

- Class I: Circulation adequate
- Class II: Circulation inadequate
- Class III: Complete degloving injury or complete amputation

Skin and Soft Tissue Injuries

Clinical Features

Lacerations to the hand and fingers are approached with more care than those on the proximal extremities and torso due to the numerous structures covered by minimal tissue. Knowledge of hand anatomy will assist when performing careful exploration of each laceration to determine if any structures have been injured. A full examination of the function of surrounding tendons and muscles must be performed, and any abnormalities documented. Abnormal positioning of the hand or fingers may indicate a tendon injury or displaced fracture. Two-point sensation of each of the fingers should be tested distal to the laceration to identify possible nerve injury. Foreign bodies such as glass can easily be missed in the wounds, so identifying the risk and instructing patients accordingly is important. Finally, all rings or constricting material should be removed on the injured hand to avoid swelling with resulting vascular congestion.

Diagnostic Testing

X-rays of the hand or digit with the laceration may help if there is concern for a foreign body, or to determine if there is air in the joint from a laceration.

Management

Initial assessment of any laceration includes direct visualization and complete examination of the muscle, tendon, and neurovascular functions of the hand and fingers. Determination of tetanus vaccination status should be assessed, and immunization updated if appropriate.

Each laceration should be explored to assure there is no injury to the tendon, joint or neurovascular bundle. If there is a laceration near a joint, the wound should be explored to determine if there is intrusion into the joint space, which would require extensive washout to decrease the chance of infection. If the laceration is over any region with a tendon, it is advised that exploration should occur while carefully examining the tendon moving through the entire length of its range of motion. A commonly missed injury is a partial tendon injury undiscovered because the patient's function with formal testing may be normal. A partial tendon laceration could put the tendon at risk for further injury later.

Generally, bleeding from the digital arteries distal to the DIP joint can be controlled with local compression and closure of the skin. An artery could be tied off without complication due to the collateral circulation of each digit, but this is rarely needed. Care should be taken to avoid tying off the accompanying digital nerve if it is intact.

Most hand and finger skin lacerations can be closed with simple interrupted sutures, 4-0 or 5-0 nonabsorbable (nylon) sutures using the standard technique including everting the wound edges. Absorbable (Vicryl) 4-0 or 5-0 suture material is used for deep layers. Care must be taken to avoid other structures in the hand while closing simple wounds. For wounds in the palm or other gapping wounds, it is difficult to approximate the wound edges due to the tension of the skin, so horizontal mattress sutures may be more advantageous. Tissue adhesive can be used on wounds that have bleeding controlled in areas that lack tension and if no underlying structures would be exposed to the adhesive.

Laceration of the joint capsule should be discussed with the hand specialist in the ED because many are brought to the operating room for an extensive wash-out. After expert consultation, distal joints may be copiously irrigated and closed within the ED with close follow-up. A first dose of empirical antibiotics (cephalexin 500 mg BID for 7 days) can be discussed with the consultant. Similarly, lacerations of the flexor tendons should be discussed with and cared for by the hand specialist. If delayed primary repair is recommended by the consultant, the wound should be copiously irrigated, then the skin should be closed with 5-0 non-absorbable sutures. The hand should be splinted to minimize stretch on the flexor tendon. In a dorsal blocking splint, the splint is placed on the dorsal side of the extremity with the wrist flexed at a 30-degree angle, the MCP joints at 70 degrees of flexion, and the IP joints in extension, flexed at only 15 degrees. Follow-up with the hand specialist should be arranged within a few days to reduce contraction of the tendons more proximally.

Laceration of the Extensor Tendon. Evaluation of a laceration over the extensor tendon includes obtaining visualization of the underlying tendon throughout its entire range of motion. If a tendon is cut by less than 50%, functional testing, even against a force, might be normal. It has been shown that a laceration of less than 50% can heal with conservative treatment including overlying wound care and splinting. It is very important to trim any minimal tags to allow for the gliding mechanism of the extensor tendon. After discussion with the hand specialist, an emergency physician can repair a complete or near-complete extensor tendon laceration. A nonabsorbable suture material should be used, 4-0 in the finger and 3-0 in the hand to repair the tendon. In thin tendons, a figure-of-eight or mattress stitch can be used or modified Bunnell or Kessler stitch in larger tendons that have enough width to hold the tension of the suture (Fig. 42.52).

Disposition

All lacerations of the hand should be followed up by a provider to assess for possible infection. If there is any concern for an infection, appropriate antibiotics should be started, such as a first-generation cephalosporin (cephalexin 500 mg BID) or doxycycline (100 mg BID) for 7 days for patients with true penicillin anaphylaxis. Due to the close association between the tissue of the digits and the bony phalanxes, osteomyelitis is a risk for any patients with an infected wound in the tissue of the digits. All patients with a potential tendon or joint laceration need close follow-up with a hand specialist, ideally within 3 days.

Clenched Fist Injuries

Specific laceration injuries to the hand include the clenched fist injuries, tooth-knuckle injuries or fight bites in which a patient develops a laceration from the impact of hitting another human's mouth or teeth with a fist. This must be considered in any laceration on the dorsum of the hand and lead to a concern for intrusion into a joint, tendon sheath or even bone. The delay in treatment, deep wounds, and PIP joint injuries significantly increases the complication rate. In a meta-analysis of these wounds, greater than one-third of patients had tenosynovitis, joint infections or osteomyelitis.[40] Treatment should include coverage for *Staphylococcus*, *Streptococcus viridans*, and *Eikenella corrodens*. For patient with an infection who will be admitted, we recommend the use of broad-spectrum antibiotics such as ampicillin/sulbactam (3 g IV q6 hours) due to the aerobic and anaerobic, polymicrobial nature of these infections. For outpatient therapy, one can also use amoxicillin/clavulanate 875 BID or clindamycin 600 mg q8 hours for 7 days plus a fluroquinolone (i.e., levofloxacin 500 mg daily) in a patient with true penicillin anaphylaxis. In addition, exploration and surgical wash-out

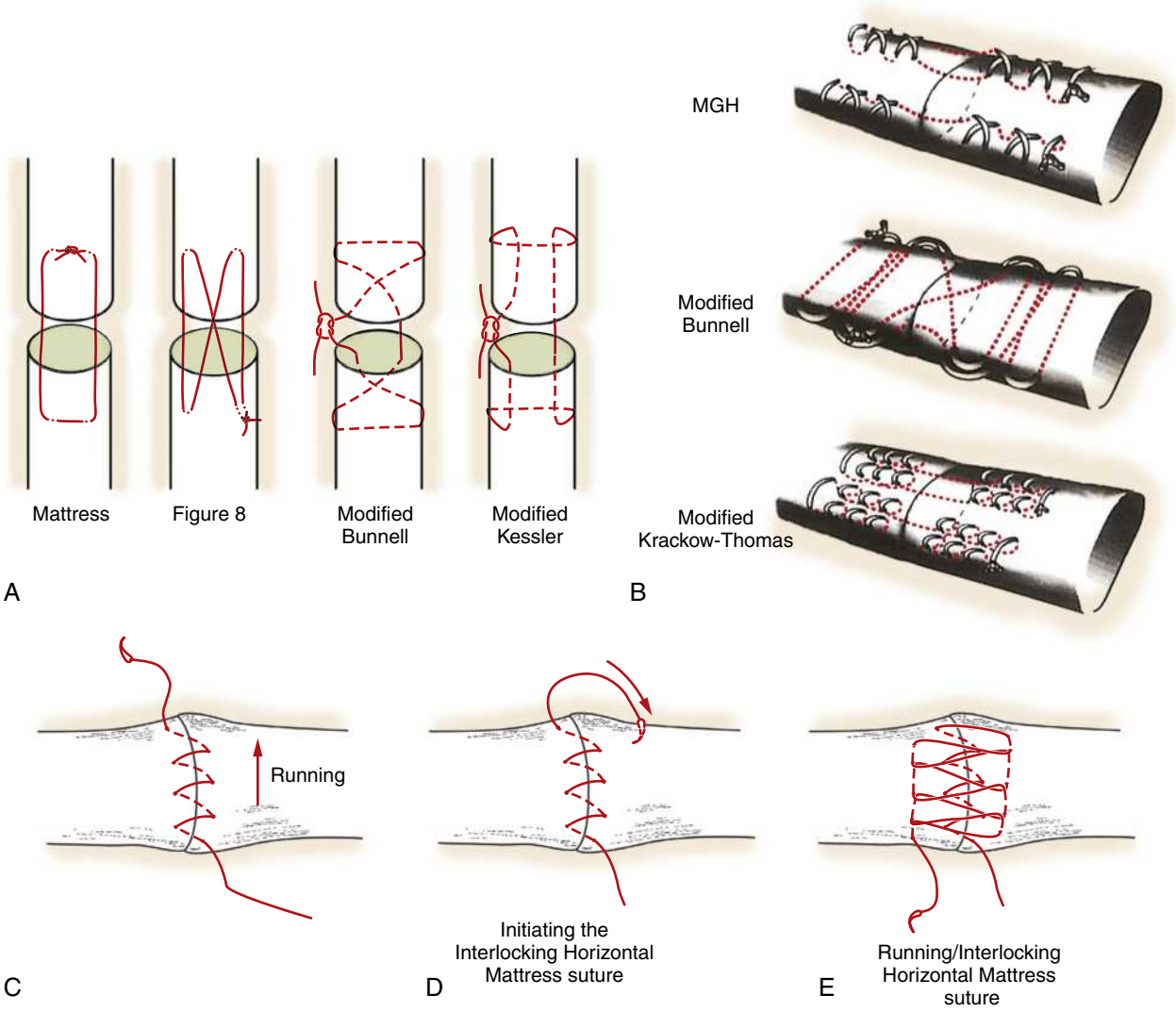

Fig. 42.52 (A–E) Demonstration of extensor tendon injury repair techniques. (A: From Newport ML, Williams CD: Biomechanical characteristics of extensor tendon suture techniques. *J Hand Surg Am.* 1992;17:111-119, with permission from The American Society for Surgery of the Hand; B: from Howard RF, Ondrovic L, Greenwald DP: Biomechanical analysis of four-strand extensor tendon repair techniques. *J Hand Surg Am.* 1997;22:838-842, with permission from The American Society for Surgery of the Hand; C–E: from Lee SK, Dubey A, Kim BH, et al. A biomechanical study of extensor tendon repair methods: introduction to the running-interlocking horizontal mattress extensor tendon repair. *J Hand Surg Am.* 35:19–23, 2010, with permission from The American Society for Surgery of the Hand.)

of the wound is indicated, due to the high incidence of joint or tendon sheath intrusion.[41]

INFECTIOUS DISORDERS OF THE HAND

General Hand Infections

Infections of the hand occur due to direct inoculation and open wounds. In one large study, almost 50% of infections in the hand had cultures positive for MRSA organisms, with increasing resistance to clindamycin and levofloxacin, especially in patients with intravenous drug abuse (IVDA) and patients with immunocompromised conditions such as diabetes mellitus.[42]

Paronychia

A paronychia is acute inflammatory changes or infectious changes in the skin in or under one of the nail folds that line the nail bed (Fig. 42.53). This is often due to trauma or a foreign body, such as a dry cuticle or open wounds from picking and pulling of skin in this region. Incision and drainage should be accomplished using general principles, including inspection for removal of any foreign body, opening of abscess to allow drainage, and avoiding damage to the nail bed or plate. The nail fold is elevated by blunt dissection or scalpel to release the purulent fluid while avoiding damage to the nail plate and nail matrix. On occasion, if the edge of the nail is the inciting irritant, a partial nail plate excision could be done to eliminate the cause and allow the nail to grow back in a corrected manner. With adequate incision, no treatment with postprocedural antibiotics is

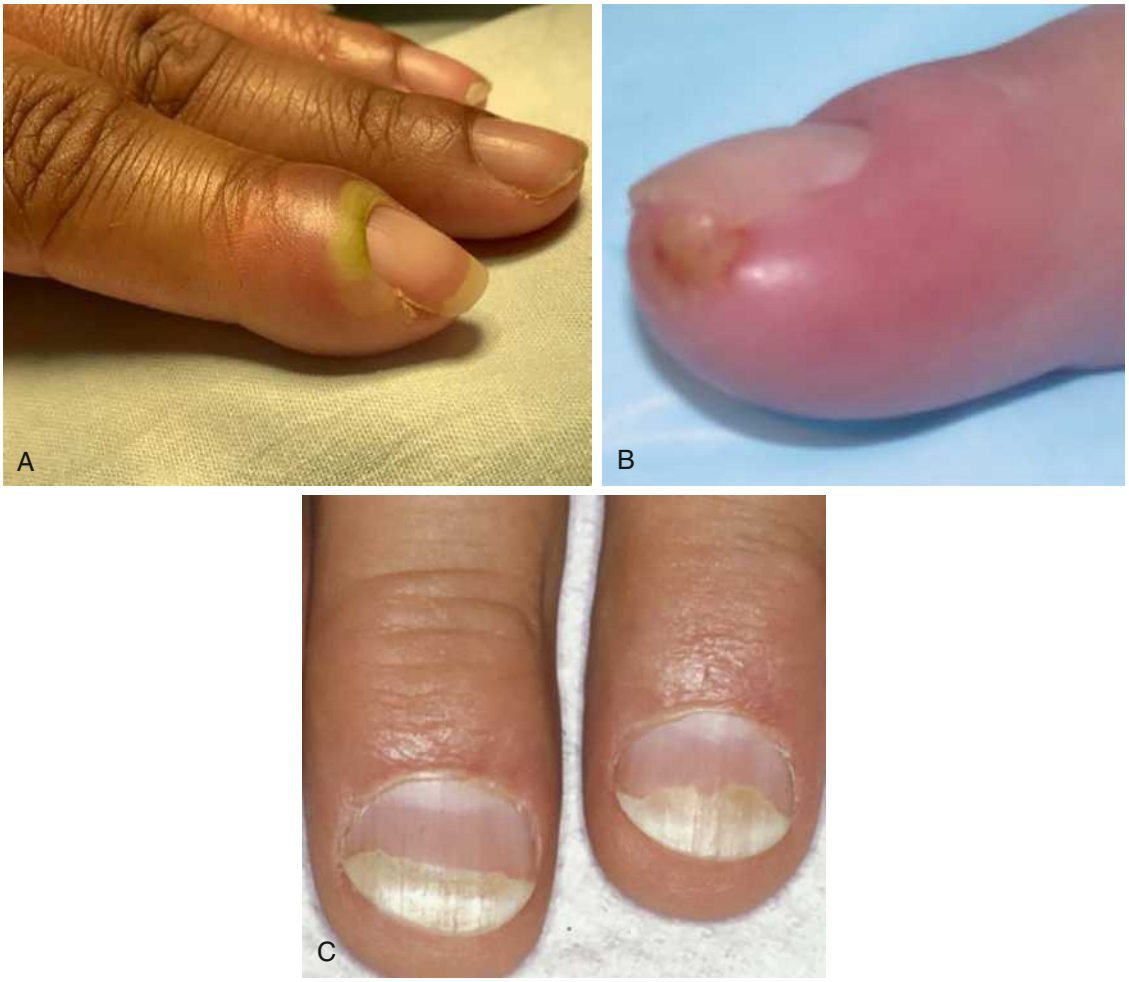

Fig. 42.53 (A) Paronychia of patient's index finger. (B) Felon. (C) Onycholysis. The detached nail plate is white in color. (A: Courtesy of Angela Gregory, MD and Ian Keck, DO. Central Michigan University COM); B: Rerucha, Caitlyn et al. Acute hand infections. Am Fam Phys. 99(4):228- 236, 2019; Fig 4.; C: Tosti A. Diseases of hair and nails. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, ed 26. Philadelphia: Elsevier; 2019:2655-2664. Fig. 413-15.)

appropriate.[43] If there is no abscess to incise, the digit can be soaked with 1% acetic acid and warm water for 15 minutes 2 to 4 times daily to decrease the bacterial count of *Pseudomonas aeruginosa* and other infectious agents.[44] Topical mupirocin daily for 7 to 10 days may also be used in combination with a topical steroid at night to decrease inflammation.

Chronic paronychia can be caused by topical irritation or hypersensitivity reaction. Treatment can include topical steroid medications such as triamcinolone cream once to twice per day for three months. If the patient indicates that the paronychia has been present for months, it is likely to be a fungal infection. Systemic medications for suspected fungal irritants are not useful because the irritation is topical and not due to an actual tissue infection. The patient should be informed to stop soaking it, keep it dry, and apply a topical antifungal (terbinafine 1% cream twice daily). A hand specialist could be consulted for marsupialization or other surgical treatments if necessary.

Onychomycosis

Onychomycosis is a mycotic infection within the nail rather than the nail folds and should be treated with antifungal medications for an extended period of time. The classic finding is thickening of the nail itself (hyperkeratosis) from invasion of the fungi. Though antifungal medication such as oral fluconazole 150 mg to 450 mg weekly could be started by the emergency clinician, the long-term nature of the therapy and possible systemic complications makes it more appropriate for a primary care provider to develop the treatment plan.

Felon

Felon is an infection of the pulp space of the fingertip, caused by penetrating trauma such as a diabetic lancet, though often no specific known source is identified (see Fig. 42.53). The fibrous septae of the fingertip create small compartments which restrict swelling, leading to increased pressure, nerve and vascular compression, and then necrosis of the tissue. This explains the severe pain associated with this infection and the increased risk of osteomyelitis and tenosynovitis. Oral antibiotics (cephalexin 500 mg TID for 7 days) and warm soaks can be used when this fingertip infection is at the stage of cellulitis, but when there is an abscess, incision and drainage is necessary. The incision should be along either the lateral side of the tuft, along the flexion crease, just below the nail edge dorsal to the neurovascular bundle and distal to

the DIP joint and pulley system, or midline on the dorsum of the tuft. Incisions to avoid include one around the edge to the tip of the finger and a double longitudinal incision pattern on the same side, because both will destabilize the fingertip.

Herpetic Whitlow

Clinical Features. Herpetic whitlow is a cutaneous herpes simplex virus (HSV) infection seen on the fingers from contact with oral lesions via self-inoculation (thumb sucking) or seen in health care workers such as respiratory therapists from oral care of intubated patients.

Differential Diagnoses. Herpetic whitlow is sometimes confused with a paronychia or felon. Special attention should be given to the presence of vesicular lesions which are not typically seen with a paronychia or felon.

Diagnostic Testing. Diagnosis is made through viral culture or PCR assay of the unroofed lesions.

Management. No antiviral therapy is indicated in immunocompetent patients because the disease is generally self-limited, though oral acyclovir (800 mg BID) or valacyclovir (500 mg BID) for 7 days may be used to decrease the infectivity of those whose infection may cause a risk to others, such as health care workers. If the patient has systemic infectious signs, IV acyclovir may be needed for treatment.[45]

Purulent Flexor Tenosynovitis

Clinical Features. The most common symptom of purulent flexor tenosynovitis is fusiform swelling of the digit, with direct tenderness over the flexor sheath as the most specific finding (Fig. 42.54). The findings described by Dr. Allen B. Kanavel a century ago remain the cardinal symptoms of patients with flexor tenosynovitis (Box 42.4). Diffuse swelling is often labeled the most common sign, however it is very nonspecific. Though both are independent predictors of infectious tenosynovitis, we find that pain with passive extension is a more specific sign compared to tenderness along the tendon sheath as the latter is found in most patients with cellulitis.[45] The EM physician should remain vigilant for patients with tenosynovitis because the initial presentation may be subtle and Kanavel findings are sensitive, but not very specific, for this infectious process. It has been found that direct inoculation is the primary infectious process. Less than 15% of all patients in one review had comorbid conditions, indicating this condition is generally found in immunocompetent hosts.[46]

Differential Diagnoses. One should also consider trigger finger (stenosing tenosynovitis), Dupuytren contracture, tendon injury, inflammatory arthritis, simple cellulitis, or underlying paronychia or felon when evaluating a patient with suspected infectious tenosynovitis.

Diagnostic Testing. Plain films do not appear to distinguish between tenosynovitis and other general hand infections, though they are used to assess for subcutaneous air in the tissue.[47] New studies are demonstrating the use of ultrasound for diagnosis of inflammatory and infectious tenosynovitis; though the specificity is low, the negative predictive value makes this modality useful.[48] The addition of an ESR may help guide the diagnosis as well, though other inflammatory markers were not found to be statistically sensitive.[45]

Management. Skin contaminants of gram-positive bacteria are typical in these infections, making early use of antibiotics appropriate. Initial treatment with vancomycin 10 to 15 mg/kg IV (with subsequent dosing per pharmacy adjusted for renal insufficiency) is appropriate in the emergency department, without waiting for surgical cultures, because early antibiotics use appears to decrease the serious complications associated with this disease. Definitive treatment remains surgical wash-out, so admission for operative management by a hand specialist is necessary. A systematic review showed that IV antibiotics and catheter wash-out, rather than open surgical drainage of the tendon sheath, improved outcomes. The most common outcome noted variable range of motion, which was clearly linked to how early the diagnosis was made in the course of the disease.[46]

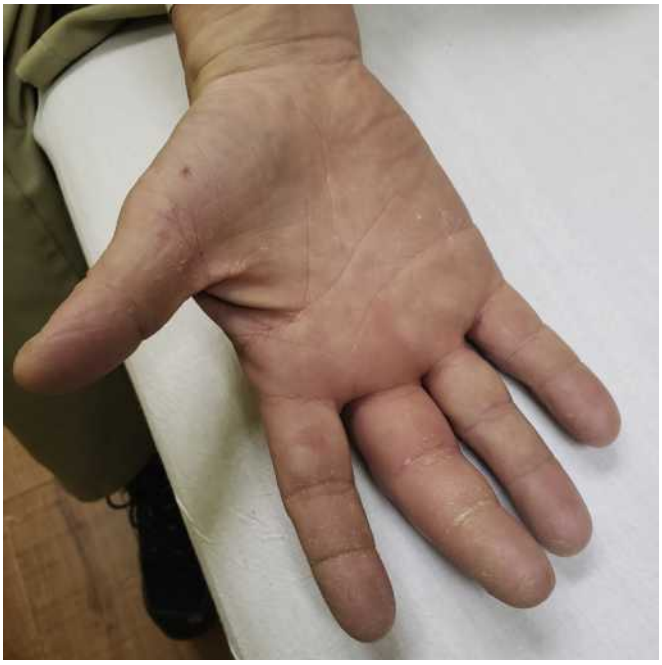

Fig. 42.54 Flexor tenosynovitis of the third digit. (Courtesy of Catherine Champagne, DO and Dan Coffey, DO; Central Michigan University COM.)

BOX 42.4 Kanavel Signs

1. Exquisite tenderness over the course of the sheath, limited to the sheath
2. Flexion of the finger
3. Exquisite pain on extending the finger, most marked at the proximal end
4. The whole of the involved finger is uniformly swollen (fusiform swelling)

Deep Space Infections

Clinical Features. Deep space infections of the volar side of the hand are found under the flexor tendons but above the interosseous muscles in the thenar, hypothenar, and mid-palmar spaces. The deep dorsal subaponeurotic space is between the aponeurosis of the extensor tendons and their attachment distally while the interdigital spaces are between the distal metacarpal heads of each digit. Each may present with distinctive complaints due to the involved tendons and muscles that course through and around the spaces. Given the variability of the components of the compartments, there are no classic descriptions of each. Initially, the patient will complain of aching pain and decreased movement of the digits without systemic symptoms.

Differential Diagnoses. Consider compartment syndrome in patients with exceptional swelling, disproportional pain, and neurovascular compromise.

Diagnostic Testing. Ultrasound and MRI are more sensitive than CT scan and often are needed to make the diagnosis early in the course of the disease.[49] For patients who are ill with systemic symptoms with signs such as fever, blood cultures should be obtained prior to antibiotic administration.

Management. The classic infectious organisms include *Staphylococcus aureus* and *Streptococcus* spp. Because there has been an increase in gram-negative and atypical organisms, the use of early broad-spectrum

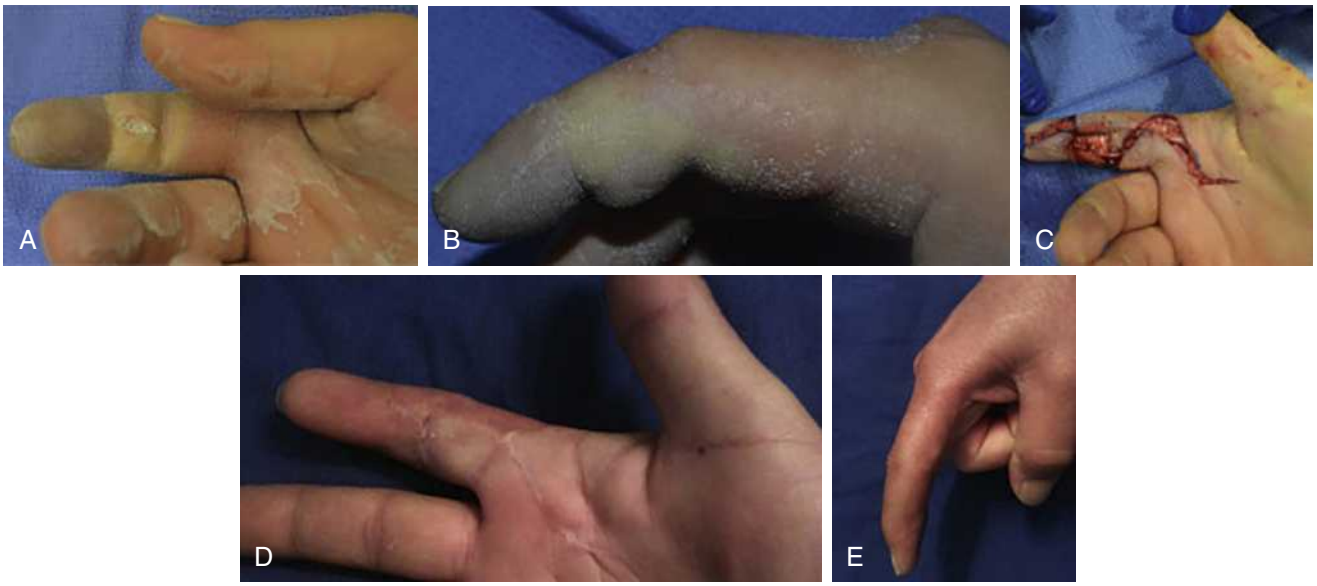

Fig. 42.55 High-pressure injection injury. (A and B) Index finger following injection of paint thinner. There is a small wound from the paint thinner and associated pallor throughout finger and swelling seen on the lateral view. (C) Following decompression and débridement of right index finger. Return of blood flow is demonstrated. The wound was left open without formal closure. (D and E) Follow-up postoperative pictures showing healed wound and functional range of motion. (Cannon TA. High-pressure injection injuries of the hand. *Ortho Clin N Am*. 2016;47(3):617-624. Fig. 2.)

antibiotics such as vancomycin (10 to 15 mg IV followed by pharmacy dosing) and piperacillin-tazobactam (3.375 g IV q6 hours) can decrease extension of the infection or complications. Early consultation with a hand specialist in the ED is imperative to assist with the decision on whether the patient requires surgical intervention.

Skin and Soft Tissue Disorders

Onycholysis

Onycholysis is the separation of the nail from the nail plate at the distal end and slowly separating more proximally (see Fig. 42.53). The etiology can be as simple as trauma or fungal infection, but consideration should be given to systemic diseases such as thyroid disease, psoriasis, and certain chemotherapeutic agents.[50]

High-Pressure Injury

High-pressure injection injuries occur when a finger is accidentally placed over the nozzle of a paint, oil, water or other high-pressure injector, often when it is being cleaned. Because the injection comes from a small pin, the entrance wound to this injection is unassuming and often the damage underestimated. The caustic chemical injected and the tissue destruction from the high pressure will cause increasing swelling, leading to ischemia. This creates a compartment syndrome, often within the flexor tendon sheath, which will require surgical decompression and wash-out (Fig. 42.55). High-pressure injections of air, water, and some medications do not seem to cause the same severe damage. Management recommendations for the patient in the ED include administering the first dose of IV antibiotics (first- or third-generation cephalosporin such as cefazolin 1 to 2 g IV or ceftriaxone 1 to 2 g IV) and pain control. Any injection injury should have emergent consultation in the ED by the hand specialist, who will determine if exploration of the wound is needed. Surgical débridement, if needed, has been found to decrease the rate of amputation if done within 6 hours.[51]

Ganglion Cysts

In the ED, patients present with cysts due to increased pain, often blamed on acute trauma. Typical ganglion cysts are mobile firm cysts filled with mucin that develop adjacent to joints and tendons, most commonly on the dorsal or volar surface of the wrist. Retinacular ganglion cysts are found on the volar finger at the proximal phalanx or MCP joint and are generally much smaller and less mobile, associated with the first two flexor tendon pulleys. Multiple theories have been formed to explain the development of ganglion cysts, but they do not seem to be related to direct trauma. The dorsal DIP joint ganglion cyst, known as a mucoid cyst, is often associated with osteoarthritis. Mucoid cyst walls are thinner and more likely to erode or rupture, which can lead to infection. These do not appear to connect directly to the joint, so the typical antibiotic treatment for skin infection is adequate.

Aspiration of the cyst may improve the patient's pain symptoms, but there is more than a 50% recurrence rate. Even with the use of ultrasound for guidance in the aspiration of the cyst, there is a high recurrence rate.[52] Surgical removal or excision has a much lower recurrence rate (average 6% noted in a meta-analysis).[53] Given the high recurrence rate and option for surgical removal, we recommend that most ganglion cysts not be aspirated in the emergency department. Injection of corticosteroids into the DIP joint space reduced ganglion cysts without complication but had a 50% recurrence rate[54] and other studies have shown that direct aspiration with injection of steroids had a slightly lower recurrence rate. Historically, these cysts were "popped" through direct compression from a "slap of the family bible." Based on an interesting study using internet videos with survey follow-up, direct blunt force successfully disrupted ganglion cysts and less than 50% had a recurrence at 2-year follow-up.[55]

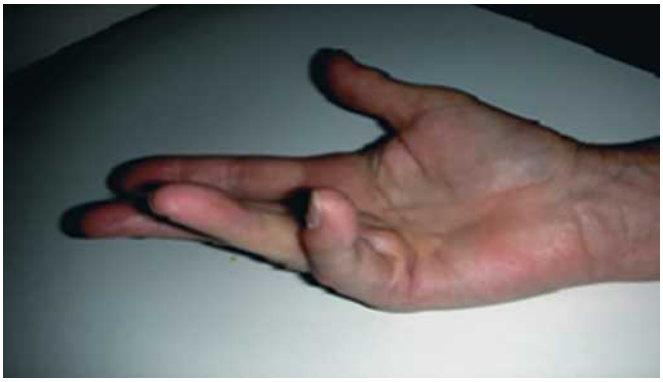

Fig. 42.56 Dupuytren contracture as demonstrated with typical nodule-like and cordlike changes in the ulnar digits resulting in the characteristic flexion contractures. (Kelly B Isaacs JE. Dupuytren contracture. In: Miller MD, Hart JA, MacKnight JM. *Essential Orthopaedics*, ed 2. Philadelphia: Elsevier; 2020:341-344. Fig 88.2. Courtesy of Bobby Chhabra, MD.)

Dupuytren Contracture

Dupuytren contracture is the result of fibrosis of the palmar fascia which causes the tightening of an area of fascia, creating a cord that limits the motion of a specific finger or area of the palm. In the ED, diagnosis can be made based on the clinical findings as shown in the Figure 42.56. Treatment is limited to appropriate referral to a hand specialist who may use percutaneous needle aponeurotomy, collagenase injections, or open surgery to treat this contracture.[56]

Acknowledgments

The authors would like to acknowledge the assistance of Ronald Barry, MD, FACS in the preparation of this chapter, including providing many of the images.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 42: QUESTIONS AND ANSWERS

1. Which of the following demonstrates the motor function of the median nerve?
   - **a.** Extending the hand at the wrist
   - **b.** Making an "OK" sign with the thumb and first finger
   - **c.** Pulling the thumb across the palm to touch the little finger
   - **d.** Spreading out the fingers of the hand

Answer: B. Making an "OK" sign with the thumb and first finger. The median nerve controls the flexors of the thumb and index finger that allow the hand to make the "OK" sign. The ulnar nerve innervates the adductor pollicis that pulls the thumb across the palm so it can touch the little finger and innervates the interosseous muscles to allow the hand to spread out or abduct the fingers. The radial nerve innervates the extensor carpi radialis longus and the other wrist extensors.

2. A 25-year old woman comes to the emergency department complaining of hitting the tip of her finger on a basketball. She has difficulty extending the tip of her ring finger. What is the most appropriate splinting technique for this injury?
   - **a.** Aluminium volar splint with finger in position of function
   - **b.** Dorsal blocking splint with DIP at 15 degrees of flexion
   - **c.** Stack splint with extension of distal phalanx
   - **d.** Ulnar gutter splint to include ring finger to the tip

Answer: C. Stack splint with extension of distal phalanx. The description of the injury is consistent with a mallet finger injury, where the distal extensor tendon has pulled off the proximal end of the distal phalanx. The premolded Stack splint keeps the distal phalanx in extension and can remain in place for 6 weeks for healing. The position of comfort for the finger in an aluminium volar splint is with the PIP and DIP at approximately 10 to 15 degrees of flexion, not complete extension as needed to allow the tendinous insertion to reattach. A straight aluminium splint could be used on the dorsal surface of the finger to keep the DIP joint straight. A dorsal blocking splint is used for flexor tendon lacerations or ruptures, preventing any extension in the digit and hand to decrease the contraction of the flexor tendon, which will increase the extensor tendon strain. The ulnar gutter splint provides much more extensive immobilization than is necessary for this injury.

3. After cutting her hand while washing a drinking glass, a patient complains of a laceration to her finger. In which location of the palmar hand surface is this laceration most likely to cause a lack of flexion to the index finger PIP joint?
   - **a.** Base of the thenar eminence
   - **b.** Distal end of the middle phalanx
   - **c.** Proximal end of the proximal phalanx
   - **d.** Volar crease of the MCP joint

Answer: D. Volar crease of the MCP joint. The flexor digitorum superficialis (FDS) functions to flex the finger at the PIP joint. It attaches at the proximal end of the middle phalanx as well as the distal end of the proximal phalanx. A laceration along the volar crease of the MCP joint will cut the FDS tendon when the fingers are in extension and reduce the flexion of the PIP joint. The flexor digitorum profundus (FDS) inserts at the proximal end of the distal phalanx. Cutting the finger from the mid aspect of the middle phalanx distally results in an injury to the FDP and an inability to flex at the DIP joint. There are no tendons running within the thenar webspace.

4. Which of the following is the most disease-distinguishing finding of a patient with pyogenic flexor tenosynovitis?
   - **a.** Involved finger is held in flexion
   - **b.** Pain on extension of the finger
   - **c.** Tenderness over the tendon sheath
   - **d.** Uniform swelling of the involved finger

Answer: B. Pain on extension of the finger. All of these findings are components of Kanavel's findings for infectious tenosynovitis. Even though uniform involved swelling has been listed as the most common sign in some studies, this is misleading as swelling is the most common sign in many hand problems and is very nonspecific. What most commonly separates purulent flexor tenosynovitis from other finger infections is pain with passive extension. Many patients with even just cellulitis have pain with palpation over the area of infection on the finger, so this does not distinguish it well. Only half of the patients diagnosed with pyogenic flexor tenosynovitis have all of Kanavel's findings.

5. A patient presents after a fist fight with a puncture wound to his hand. Which description of the presentation has the best prognosis?
   - **a.** Fingertip penetration
   - **b.** Delay in treatment
   - **c.** Depth of the wound
   - **d.** Involvement of joint

Answer: A. Fingertip penetration. The three factors that have been found to worsen the prognosis for a "fight bite" injury are delay in identification and treatment of the wound, an increase depth of the wound as it is more likely to include the tendon, and intrusion into the joint of the tooth. A puncture wound of the fingertip is much less likely to create a significant infection due to the close septae that decrease the likelihood of spreading bacteria in an open wound.

43

Wrist and Forearm Injuries

Vanessa S. Franco and Hyung T. Kim

KEY CONCEPTS

- On plain radiographs of the wrist, three distinct arcs, known as *Gilula's lines*, and equal spacing between carpus bones (1–2 mm), known as *parallelism*, assist in the radiographic diagnosis of carpal injuries.
- In the setting of trauma, there is a high incidence of occult fractures and soft tissue injuries of the wrist. Because of the associated risk of malunion, nonunion, posttraumatic arthritis, and avascular necrosis (AVN), splint immobilization is recommended if pain persists despite normal appearing radiographs.
- Routine wrist radiographs which include anteroposterior (AP), lateral, and oblique projections, may fail to detect scaphoid fractures.
- Thumb spica immobilization is recommended for suspected scaphoid and other carpal fractures. Expedited orthopedic follow-up for repeat assessment, radiographs, or advanced imaging (e.g., MRI, CT, or bone scan) is indicated.
- Triquetral dorsal chip fractures are best seen on the standard lateral view of the wrist as a small avulsion fracture fragment, although a more oblique pronated lateral view may be necessary to visualize these types of fractures.
- Hamate and pisiform fractures are best visualized with a carpal tunnel or reverse supinated oblique radiograph.
- Lunate dislocations result in a characteristic triangular appearance of the lunate on the posteroanterior (PA) view (commonly referred to as the "piece of pie" sign) owing to rotation of the lunate in a volar direction. This rotation also is visible on the lateral view of the wrist, where the lunate appears like a cup tipped forward, spilling its contents into the palm (referred to as the "spilled teacup" sign).
- A Colles fracture is a transverse fracture of the distal radial metaphysis, which is dorsally displaced and angulated. The Smith fracture is a transverse fracture of the metaphysis of the distal radius, with associated volar displacement and angulation.
- Ulna fractures associated with radial head dislocation are commonly known as Monteggia fractures. Galeazzi fractures refer to fractures of the middle to distal third of the radius associated with injury to and dislocation of the distal radial ulnar joint (DRUJ).

WRIST

FOUNDATIONS

Anatomy, Physiology, and Pathophysiology

The wrist joint is broadly defined as the anatomic area from the distal radius and ulna bones of the forearm to the carpometacarpal junctions of the hand. It is anatomically and biomechanically complex, allowing for diverse functional capabilities. The wrist is composed of many complex articulations, including the radiocarpal, midcarpal, and distal radial ulnar joints (DRUJs), allowing for flexion, extension, abduction (radial deviation), adduction (ulnar deviation), and circumduction movements. Pronation and supination of the hand are primarily movements of the forearm occurring at the proximal radial ulnar joint and DRUJ.

The wrist includes the distal radius, ulna, and eight carpal bones, which are arranged in two transverse rows and are commonly referred to as the carpus (Fig. 43.1). Each carpal row contains four bones. The more mobile, proximal row, listed radial to ulnar, consists of the scaphoid, lunate, triquetrum, and pisiform bones and the distal row consists of the trapezium, trapezoid, capitate, and hamate bones.

The radius has three articular surfaces at the wrist—radiocarpal joint, DRUJ, and an interface with the triangular fibrocartilage complex (TFCC), also known as the articular disk. The distal radius articulates directly with the carpus via the scaphoid and lunate bones, which forms the common wrist joint. The ulna is separated from direct articulation with the proximal carpal row by the TFCC. The articular disk binds the distal ends of the radius, ulna, lunate, and triquetrum together. The DRUJ is a synovial pivot where the distal radius articulates and rotates around the relatively fixed ulna, and this joint is primarily stabilized by the TFCC.

Aside from the pisiform, a sesamoid bone embedded within the flexor carpi ulnaris (FCU) tendon, the carpal bones are lined by synovium that creates a continuous capsule throughout the intercarpal joints, distally to the metacarpal articulations. The only muscular insertions that occur throughout the carpus are the origin of the abductor digiti minimi from the pisiform, and the point at which the FCU tendon inserts onto the hook of the hamate. As a result, nearly all carpal bone movements are passive, based on muscular insertions on the distal radius, ulna, and metacarpal bases.

The stabilizing ligaments of the wrist are divided into two major groups, the intrinsic and extrinsic ligaments. The intrinsic ligaments interconnect the individual carpal bones, and the extrinsic ligaments link the carpal bones to the distal radius, ulna, and metacarpals. The intrinsics are named for the adjacent bones to which they connect; the most important for maintaining carpal stability are the scapholunate and lunotriquetral ligaments. The extrinsics are divided into volar and dorsal groups. The volar extrinsic ligaments are thicker and stronger than the dorsal extrinsic ligaments and are the most important in providing stability to the wrist. Between two volar ligaments over the proximal capitate, there is an area relatively devoid of ligamentous support, called the *space of Poirier*. This space enlarges when the wrist is dorsiflexed, and an injury to the joint capsule in this region can result in significant carpal instability (Fig. 43.2).

Most structures that cross the wrist joint are contained within individual compartments formed by the deep fascia of the wrist. On the dorsal surface of the wrist, the extensor tendons are divided by the extensor retinaculum into six compartments, each having a separate

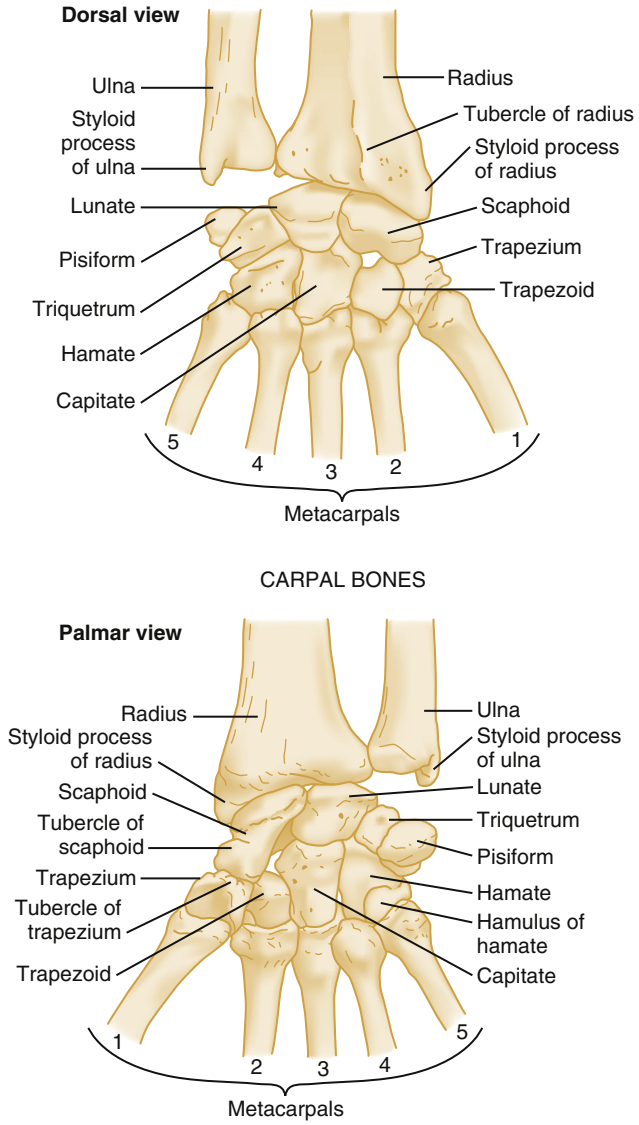

Fig. 43.1 Bones of the Wrist. The wrist joint includes the distal articular surfaces of the radius and ulna and the proximal and distal carpal rows. (Adapted from Netter FH. *Atlas of human anatomy*. 3rd ed. Teterboro, NJ: Icon; 2003.)

synovial sheath that extends proximally and distally to the retinaculum. On the volar surface of the wrist, the flexors of the digits and median nerve are contained within the carpal tunnel, which is formed by the flexor retinaculum superficially and its attachments to the carpal bones. Radially, the flexor retinaculum attaches to the scaphoid tubercle and ridge of the trapezium. On the ulnar side, it attaches to the pisiform and hook of the hamate. Both the trapezoid and capitate bones form the floor of the carpal tunnel. Radially and superficially to the carpal tunnel, the flexor carpi radialis tendon crosses the wrist joint in its own compartment.

The vascular supply to the wrist is provided by the radial and ulnar arteries, which join in a series of dorsal and palmar arches to supply the bones of the carpus. The intrinsic blood supply to most carpal bones enters the distal portion, leaving the proximal area, placing them at risk for devascularization and avascular necrosis (AVN) when fractured. This is particularly true for the scaphoid, capitate, and lunate bones, which receive their blood supply commonly from a single distal vessel (Fig. 43.3).

The wrist and hand are innervated by the radial, median, and ulnar nerves. The radial nerve and dorsal sensory branch of the ulnar nerve cross the dorsum of the wrist near the radial and ulnar styloids, respectively. The median nerve crosses within the carpal tunnel on the volar aspect of the wrist, just radial and deep to the palmaris longus tendon. The ulnar nerve is contained within *Guyon canal*, between the pisiform and hook of the hamate (see Fig. 43.3). In the setting of trauma, motor and sensory function of the radial, median, and ulnar nerves can be clinically assessed at the wrist and distally, based on their anatomical innervations (Table 43.1).

CLINICAL FEATURES

The clinical examination of the patient with a wrist injury begins with a history focusing on the mechanism of injury and location of pain. The physical examination begins with inspection of the wrist, with the opposite uninjured wrist used as the normal reference. The range of motion, and the presence of swelling, discoloration, or obvious deformity should be noted.

Several bony prominences serve as useful landmarks; their locations are best described in relation to the lateral and medial reference points in the wrist, the radial and ulnar styloids, respectively. Just distal to the radial styloid is the *anatomic snuffbox*, bordered radially by the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons, and ulnarly by the extensor pollicis longus (EPL) tendon. The body of the scaphoid is palpable within the snuffbox and is more prominent with ulnar deviation of the wrist. *Lister tubercle* can be palpated on the dorsum of the wrist, just ulnar to the radial styloid. The scapholunate joint lies just distal to the tubercle and is a common site of ligamentous injury in the wrist. With the wrist in a neutral position, the capitate is palpable in a small depression found midway between the base of the middle metacarpal and Lister tubercle. Bringing the wrist into flexion can bring the lunate forward into a palpable position at this same site. Lister tubercle divides the second and third dorsal extensor compartments of the wrist and is also used as a primary landmark for radiocarpal arthrocentesis. On the dorsal aspect of the wrist in the ulnar direction from Lister tubercle is the DRUJ. The triquetrum is palpable distal to the ulnar styloid in the proximal carpal row and is made more prominent with radial deviation of the wrist.

On the volar aspect of the wrist, the scaphoid tubercle is palpable just distal and palmar to the radial styloid. It is felt as a rounded prominence at the base of the thenar muscles and is more prominent when the wrist is extended. On the ulnar border of the wrist, the pisiform is palpable at the base of the hypothenar muscles, just distal to the wrist crease. In addition, approximately 1 cm distal and radial to this point, the prominence formed by the hook of the hamate can be palpated. Radial and ulnar pulses are easily palpable on the volar surface of the wrist, and the presence of adequate circulation should be assessed with all wrist injuries.

DIFFERENTIAL DIAGNOSES

Differential diagnoses for wrist pain depend on the mechanism of injury and the location of pain. A patient presenting with acute traumatic ulnar-sided wrist pain should raise suspicion for fracture of the distal ulna and the adjacent carpal bones (including the hamate, triquetrum, lunate, and pisiform). Pisiform or hamate fractures may cause ulnar artery or nerve damage, so ulnar artery pulse and ulnar nerve function should be tested. Extensor carpi ulnaris (ECU) tendinopathy is another cause of ulnar-sided wrist pain, and may be associated with substantial pain, erythema, and tenderness with range of motion. Tenderness over the TFCC and pain with axial loading of the TFCC suggests TFCC injury. DRUJ instability should also be considered in patients with ulnar-sided wrist pain as well as the

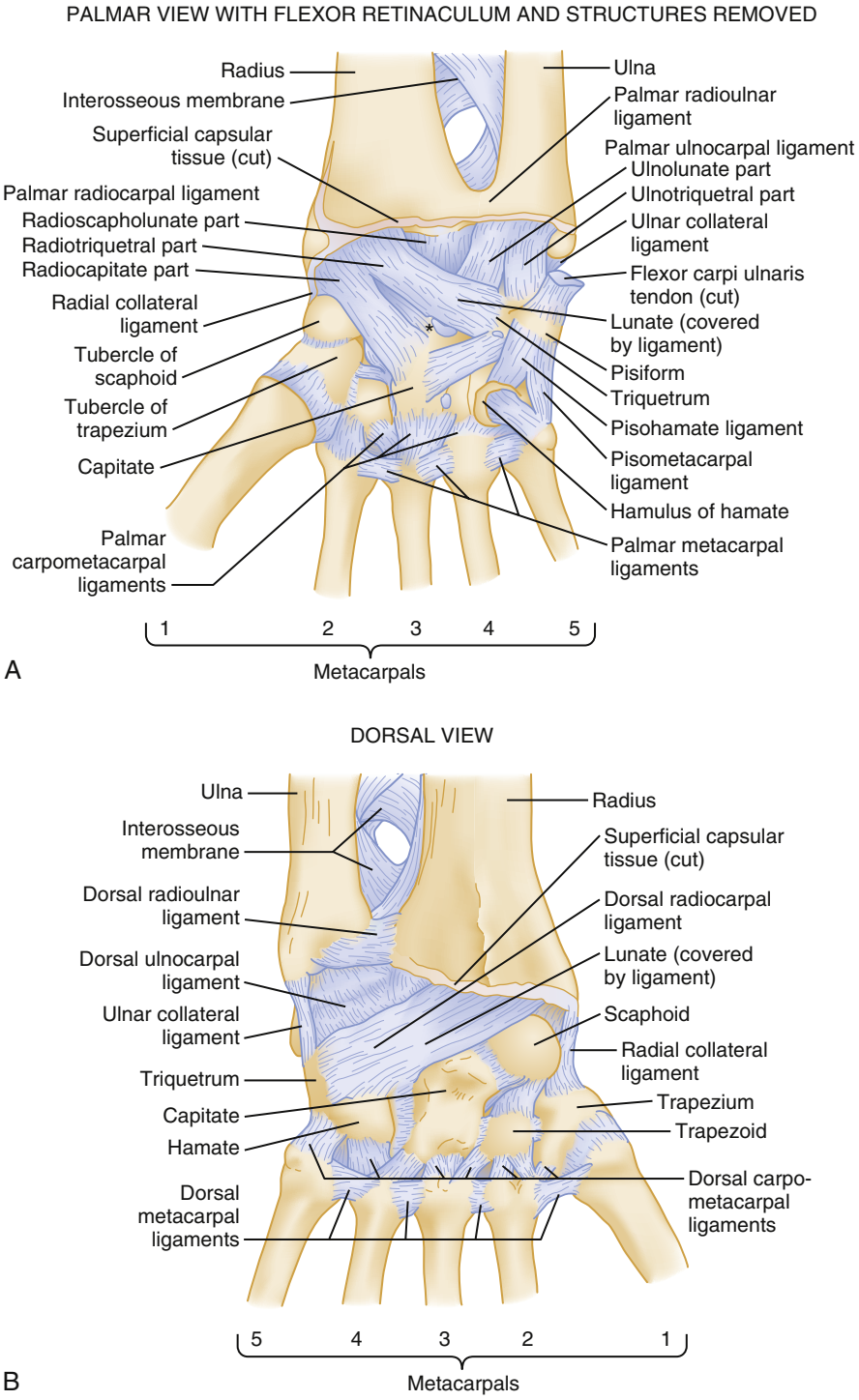

Fig. 43.2 Ligaments of the Wrist. (A) The volar extrinsic ligaments are most important in providing stability to the wrist. These include the radial collateral, radiocapitate, radioscaphoid, radiotriquetral, ulnotriquetral, capitotriquetral, and ulnar collateral ligaments. The space of Poirier (*) is a gap in the volar ligaments and the site of potential weakness. (B) The intrinsic (intercarpal) ligaments connect the individual carpal bones. The most important of these are the scapholunate and lunotriquetral ligaments. (Adapted from Netter FH. *Atlas of human anatomy*. 3rd ed. Teterboro, NJ: Icon; 2003.)

hypothenar hammer syndrome (caused by a single or repetitive blunt impact on the hypothenar eminence with injury to the hook of the hamate resulting in thrombosis of the superficial palmar arch of the ulnar artery).

Acute, traumatic radial-sided wrist pain is concerning for a scaphoid fracture, as suggested by tenderness over the scaphoid or anatomic snuffbox. Fractures of the distal radius and other adjacent carpal bones should also be considered (such as the trapezium and trapezoid). Patients with *de Quervain tenosynovitis* exhibit radial-sided wrist pain associated with overuse. Examination classically reveals tenderness over the radial styloid and a positive *Finkelstein test* (described later in the chapter). Tenderness to palpation more

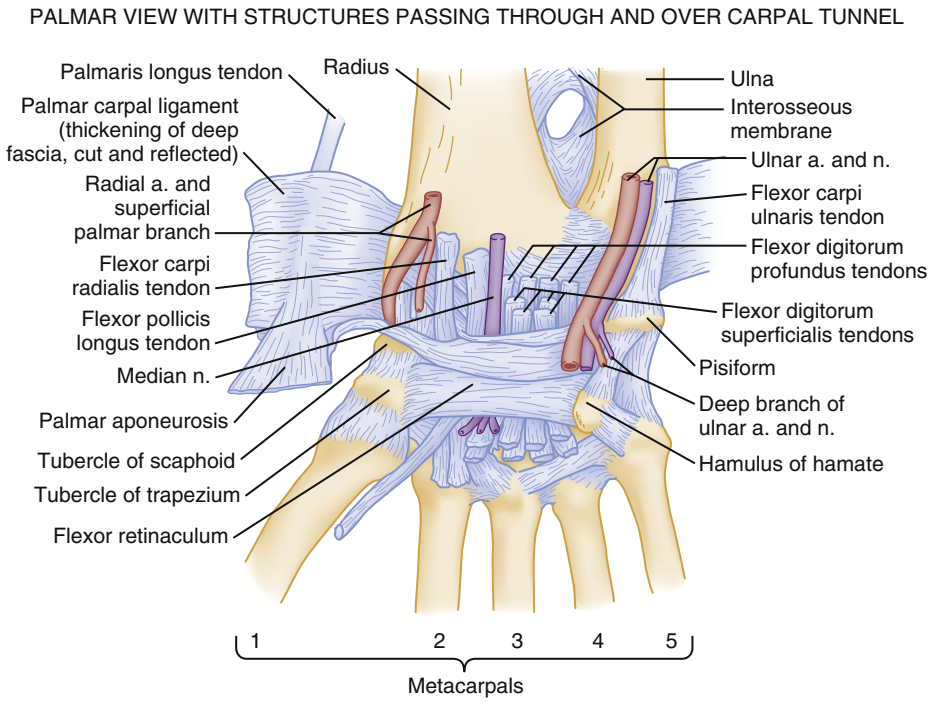

Fig. 43.3 Vascular Supply to the Wrist. Note the relationship of the ligaments to the neurovascular supply to the wrist. (Adapted from Netter FH. *Atlas of human anatomy*. 3rd ed. Teterboro, NJ: Icon; 2003.)

TABLE 43.1 Median, Radial, and Ulnar Nerve Innervations and Clinical Examination

Parameter	Median	Radial	Ulnar
Innervation	Pronator teres	Brachioradialis	Flexor carpi ulnaris
	Flexor carpi radialis	Extensor carpi radialis longus	Flexor digitorum profundus
	Palmaris longus	Extensor carpi radialis brevis supinator	Opponens digiti minimi
	Flexor digitorum superficialis	Extensor digitorum	Abductor digiti minimi flexor
	Flexor digitorum profundus	Extensor digiti minimi	Lumbricals 3 and 4
	Flexor pollicis longus	Extensor carpi ulnaris	Dorsal interossei
	Prone for quadrates	Abductor pollicis longus	Palmar interossei
	Opponens pollicis	Extensor pollicis longus	Adductor pollicis
	Adductor pollicis	Extensor pollicis brevis	Palmaris brevis
	Superficial head FPB	Extensor indicis	Superficial head FPB
Motor	Thumb opposition	Wrist extension	Finger abduction
	Pincer function (thumb, index finger)	Finger extension	Finger abduction
	Pronation	Supination	
	"A-OK" sign	"Thumbs-up" sign	
Sensory	*Sensation*	*Sensation*	*Sensation*
	Index finger, volar tip	First dorsal web space	Little finger, volar tip
	Volar	Dorsal	Volar dorsal

proximal to the radial styloid suggests intersection syndrome. Pain or instability with axial loading, manipulation, and palpation of the carpometacarpal (CMC) joint indicates CMC joint pathology such as arthritis or subluxation.

Many wrist injuries may cause pain in the dorsal or volar wrist. Fracture or dislocation of any of the carpal bones, the distal radius, or the distal ulna may cause dorsal-sided or volar-sided wrist pain. Perilunate or lunate dislocations may also present with dorsal- or volar-sided wrist pain and instability. Ganglion cysts often cause dorsal or volar wrist pain and may not always be visible or palpable on examination.

Traumatic isolated dorsal-sided wrist pain should raise concern for scapholunate dissociation, as this injury is often missed. The *Watson shift test* combined with dedicated clenched fist radiographs are useful in assessing for this injury. Triquetral fractures, dislocations, or even fractures to the base of the third metacarpal may also cause dorsal-sided wrist pain following trauma. *Kienbock disease*, or AVN of the lunate, is suggested by tenderness and swelling over the lunate. In the setting of overuse, intersection syndrome and wrist extensor tendinitis should be considered in patients with dorsal-sided wrist pain, while *carpal tunnel syndrome* and wrist flexor tendinitis would typically cause volar-sided wrist pain.

Gross deformity, swelling, and pain of the entire wrist should raise concern for radiocarpal dislocation. Arthritis and wrist sprains should be considered in differential diagnoses for patients presenting with

wrist pain in any location, but these conditions are largely a diagnosis of exclusion.

DIAGNOSTIC TESTING

Plain radiographs remain the cornerstone of emergent diagnosis of trauma to the wrist. Routine radiographic views include the posteroanterior (PA), lateral, and oblique projections each obtained with the wrist in neutral position.

On a correctly positioned PA view of the wrist, the ulnar styloid rises from the lateral aspect of the distal ulna; the ECU tendon groove should be visualized at, or radial to, its base. The radial styloid process extends beyond the end of the articular surface of the ulna by a normal distance of 9 to 12 mm. This normal difference in length is called the radial length measurement (Fig. 43.4). There may be some degree of ulnar variance that affects the radial length measurement on a PA radiograph. The distal articular surface of the ulna may terminate proximal or distal to the radiolunate articulation as a result of wrist rotation, flexion, extension, anatomic variation, or injury. Neutral ulnar variance (as seen in Fig. 43.4) is described when the distal ulnar and radiolunate articular surfaces terminate at the same point. A positive ulnar variance (ulnar articulation is more distal) or negative ulnar variance (ulnar articulation is more proximal) is independent of styloid size and may be associated with wrist pathology (e.g., ulnar impaction syndrome and Kienbock disease, respectively). The ulnar slant of the articular surface of the radius, referred to as radial inclination, is visible on the PA view and normally measures 15 to 25 degrees (see Fig. 43.4). Both of these measurements are important in assessing the degree of radial shortening seen in association with some fractures of the distal radius. The normal appearance of the carpus on the PA view shows an approximately equal distance (usually 1 to 2 mm) between each of the carpal bones, and opposing articular surfaces are parallel to one another (an arrangement known as *parallelism*). On radiographs, three smooth curves normally can be drawn along the carpal articular surfaces, known as carpal or *Gilula arcs* (Fig. 43.5). Disruption of these curves or widening of the carpal spaces is an indication of carpal ligament disruption, instability, or fracture.

The normal volar tilt of the distal radial articular surface is visible on the lateral view of the wrist and typically measures 10 to 25 degrees (Fig. 43.6). Adequacy of a lateral view of the wrist is assessed based on the relationship among the scaphoid, pisiform, and capitate (S-P-C) projections. The palmar cortex of the pisiform should project midway between the palmar margins of the distal pole of the scaphoid and capitate head, forming the S-P-C lateral (Fig. 43.7). The normal alignment of the distal radius with the lunate and capitate also is seen on the lateral view, which will show two concentric cups—the cup of the distal radius containing the lunate and the cup of the distal lunate containing the capitate. Ideally, the long axis of the radius, lunate, capitate, and third metacarpal should appear as a straight line on the lateral view, although the so-called normal alignment usually is within 10 degrees of this line (Fig. 43.8). The carpal alignment on the lateral view is defined further by the scapholunate angle, which should measure 30 to 60 degrees, and capitolunate angle, which is 0 to 30 degrees (Fig. 43.9). Abnormalities in these angles are seen in patients with carpal ligament injuries and instability.

The soft tissues of the wrist also offer valuable clues to the presence of underlying bony injuries. On most normal lateral radiographs of the wrist, the pronator quadratus line is visible as a linear, lucent, fat collection in the volar soft tissues just anterior to the distal radius (Fig. 43.10). Fractures of the distal radius or ulna result in a pronator quadratus sign representing volar displacement, anterior bowing, or complete obliteration of this line. This sign has a higher specificity than sensitivity for occult fracture, so its absence does not exclude a fracture.[1,2] A positive pronator quadratus sign has also been observed in soft tissue injuries and infectious and inflammatory conditions.

Many wrist injuries are occult and may not be identified or clearly characterized by routine wrist radiographs. Additional radiographic imaging of the wrist may assist the emergency clinician with diagnosis based on the mechanism of injury and physical examination

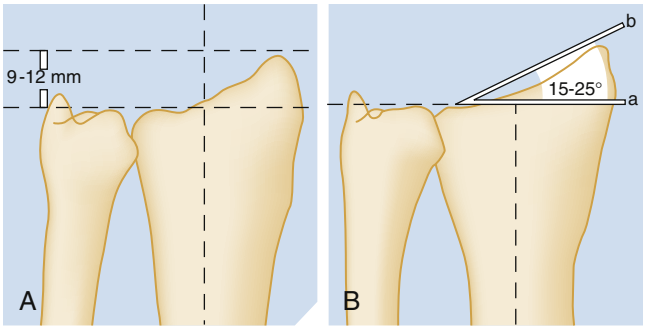

Fig. 43.4 Normal Radiographic Appearance of the Wrist on a Posteroanterior View. The ulnar styloid arises from the lateral aspect of the distal ulna, and the tendon groove for the extensor carpi ulnaris should be visualized at, or radial to, its base. (A) Radial length measurement with neutral ulnar variance. The radial styloid extends 9 to 12 mm beyond the articular surface of the distal ulna. The ulna may terminate distal, at, or proximal to, the radiolunate articulation affecting radial length measurement with a positive, neutral, or negative variance, respectively. (B) The ulnar slant of the distal radius (angle ab) normally measures 15 to 25 degrees. (From Greenspan A. *Orthopedic radiology: a practical approach.* 2nd ed. New York: Gower Medical; 1992.)

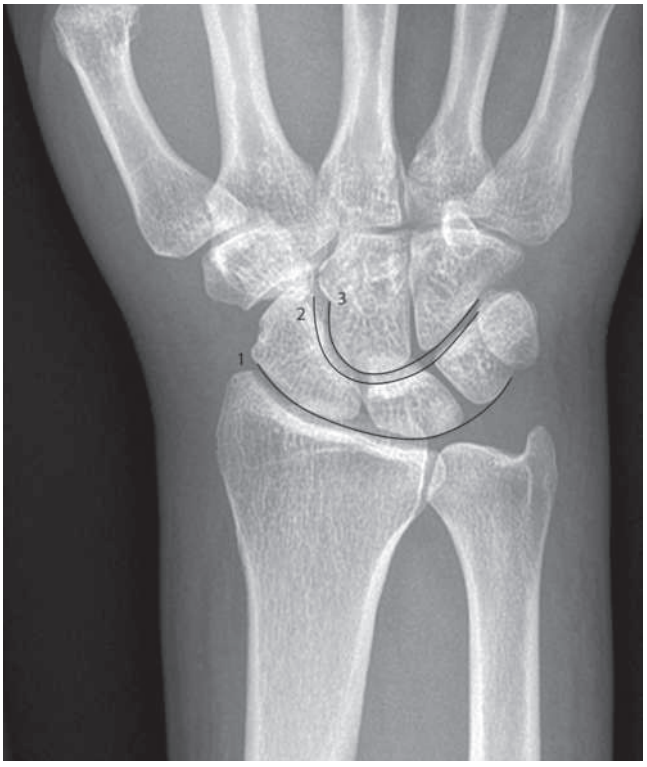

Fig. 43.5 Carpal *(Gilula's)* Arcs. On a posteroanterior radiograph of the wrist, three arcuate lines (1 to 3) can be drawn along the articular surfaces. Although small indentations at joint lines may occur, a step-off or broken arc suggests fracture, ligamentous instability, or disruption of the wrist.

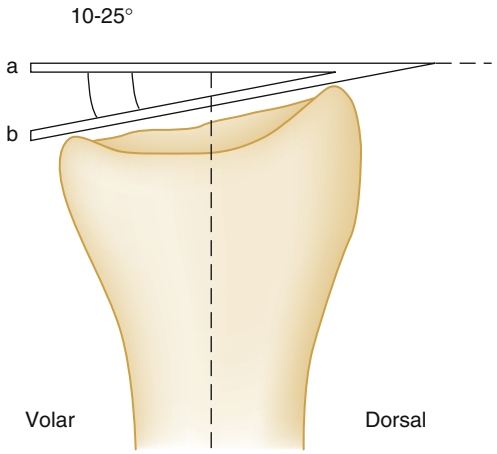

Fig. 43.6 Normal Radiographic Appearance of the Wrist on a Lateral View. The distal radius has a normal volar tilt (angle ab) of 10 to 25 degrees. (From Greenspan A. *Orthopedic radiology: a practical approach*. 2nd ed. New York: Gower Medical; 1992.)

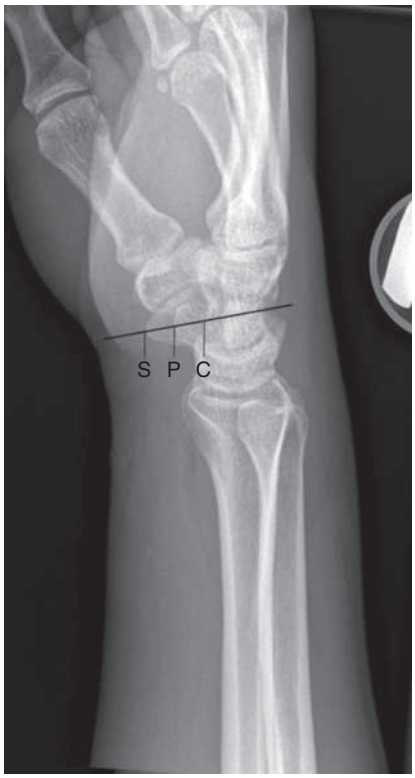

Fig. 43.7 Normal S-P-C (Scaphoid-Pisiform-Capitate) Lateral View of the Wrist. The palmar cortex of the pisiform *(P)* is shown bisecting the line between the palmar aspect of the scaphoid *(S)* and capitate *(C)* bones.

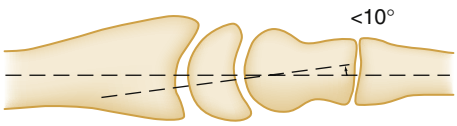

Fig. 43.8 Normal Relationship of Carpal Bones on a Lateral Radiographic View. The concavity of the radius and lunate and convexity of capitate form three C-shaped areas *(stippled)* along a straight line that runs through the central axis of these bones.

findings, including specific areas of tenderness. In addition to the standard PA, lateral, and oblique wrist radiographs, emergent patient-specific imaging helps delineate otherwise occult fractures or abnormal motion of the carpus resulting from ligamentous injuries. When a scaphoid fracture is suspected, a pronated ulnar deviated view of the wrist allows for better visualization of the bone along its long axis. The carpal tunnel view is performed with the wrist hyperextended and provides an axial volar image of bony margins. A hook of the hamate fracture is often radiographically occult and is better assessed with a dedicated carpal tunnel view. The carpal tunnel and reverse (supinated) oblique views help identify fractures involving the hook of the hamate and pisiform secondary to hypothenar wrist trauma. The clenched fist views drive the capitate proximally, causing diastasis within the scapholunate joint if ligamentous instability is present (Table 43.2).

MANAGEMENT AND DISPOSITION

There is a high incidence of radiographically occult wrist fractures. Thus, when radiographs are normal but significant localized pain persists, immobilization and a repeat examination should be arranged within 1 week. A thumb spica should be applied in the setting of suspected scaphoid fractures with orthopedic reassessment in 1 week. Occult fractures or soft tissue injuries may be diagnosed emergently, urgently, or on a routine basis with advanced computed tomography (CT) or magnetic resonance imaging (MRI) imaging protocols.[3,4] Although advanced imaging occasionally identifies an otherwise occult injury, emergent CT or MRI wrist imaging is rarely indicated in the emergency department (ED) in lieu of splinting and arranging for orthopedic follow-up, unless expedited outpatient orthopedic follow-up is not possible.

Carpal Injuries

Scaphoid Fractures

Foundations. Scaphoid fractures often occur after a fall on the outstretched hand, causing hyperextension of the wrist. These injuries are rare in skeletally immature patients because the carpus is composed entirely of cartilage at birth and remains predominantly cartilaginous until the adolescent years. Although the physis of the radius is more susceptible to injury, scaphoid fractures (with and without radial fracture) have been observed in pediatric patients. In older adults, a distal radius metaphysis fracture is more likely to occur. Scaphoid fractures are classified by their anatomic location and may be divided into three groups—fractures of the tuberosity and distal pole, waist, and proximal pole. Of these three patterns, fractures through the waist of the scaphoid are the most common (Fig. 43.11).

Clinical features. Patients typically report radial-sided wrist pain distal to the radial styloid with decreased range of motion of the wrist and thumb. The physical examination reveals tenderness with palpation of the scaphoid, often within the anatomic snuffbox. For scaphoid tenderness to be elicited, a combination of maneuvers can be performed, including ulnar deviation, palpation of the scaphoid tubercle volarly, a *Watson scaphoid shift test*, axial compression of the first metacarpal, resisted supination of the wrist, and a positive *clamp sign* (subjective radial pain caused by a thumb-index finger pinch on both sides of the wrist). Except for the absence of snuffbox tenderness, physical examination findings lack accuracy to effectively diagnose or exclude scaphoid fractures, and no validated clinical decision rules exist.

Diagnostic testing. Radiographic imaging remains the cornerstone for the evaluation of acute wrist trauma, but radiographic diagnosis of scaphoid fractures is challenging. An additional ulnar-deviated PA

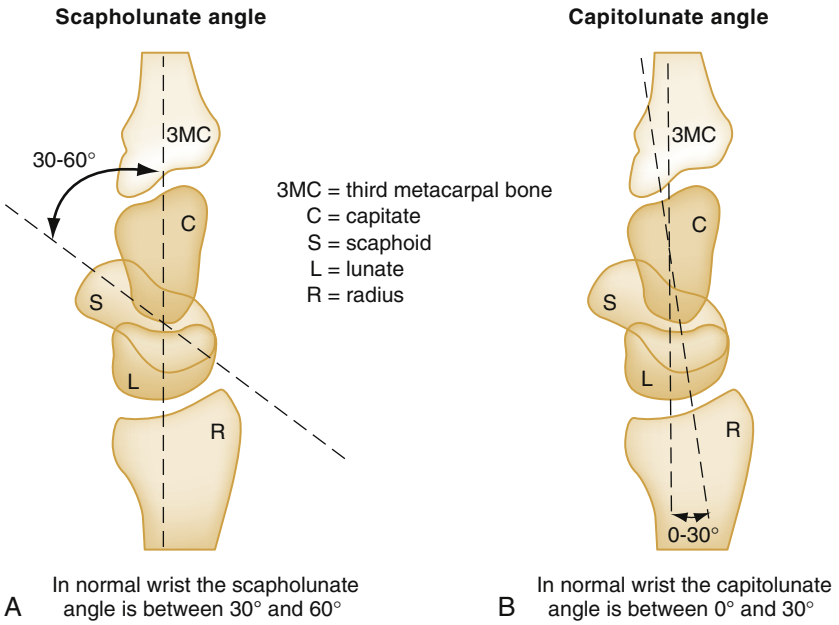

Fig. 43.9 (A) The normal scapholunate angle is formed by the intersection of the longitudinal axes of the scaphoid and lunate and normally measures 30 to 60 degrees. (B) The normal capitolunate angle is formed by the intersection of the capitate and lunate central long axes and normally measures 0 to 30 degrees. (From Greenspan A: Orthopedic radiology: a practical approach, ed 2, New York, 1992, Gower Medical.)

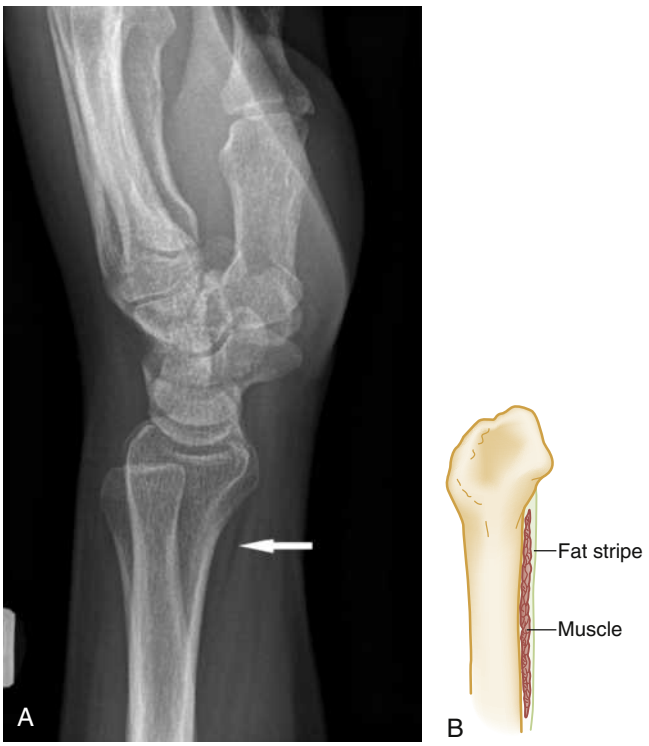

Fig. 43.10 The Pronator Quadratus Fat Pad. (A and B) A narrow fat stripe *(arrow)* located on the volar surface of the radius is seen on the lateral view of the wrist. Although not highly sensitive, volar displacements, anterior bowing, or complete obliteration of this line caused by hematoma in the setting of trauma is suggestive of wrist injury or fracture.

view of the wrist may assist with fracture visualization. A visible bony lucency or cortical disruption may be absent, and a more subtle change, such as bowing, obliteration, or displacement of the scaphoid fat pad may be the only visible clue that a wrist injury is present. However,

TABLE 43.2 Additional Radiographic Wrist Views

Radiographic View	Benefit
Clenched fist (AP or PA)	Exposes scapholunate ligament injury; pushes capitate into proximal carpal row
Scaphoid (PA with ulnar deviation)	Elongates scaphoid; exposes wrist fractures
Carpal tunnel and reverse supinated oblique	Identifies fractures involving hamate and pisiform; identifies bony encroachment onto carpal tunnel

AP, Anteroposterior; *PA,* posteroanterior.

these signs are not reliably present, and plain radiographs obtained soon after injury may fail to detect a distinct fracture.

While bone scintigraphy has the highest sensitivity for scaphoid fractures, this modality suffers from a lower specificity, resulting in a large number of false positives.[4] There is some evidence suggesting ultrasound may be more accurate in diagnosing scaphoid fractures than X-ray,[5] but other studies show mixed results.[6,7] Thus, ultrasonography may be a useful adjunct for the diagnosis of scaphoid fractures for those clinicians with sonographic proficiency, but this method still requires external validation. CT and MRI imaging permit the diagnosis of most radiographically occult scaphoid fractures. Despite its high cost and variable availability, MRI has greater sensitivity for diagnosing scaphoid fractures and soft tissue injuries than CT.[3] Despite extensive studies and multiple adjunct imaging modality options, emergent advanced CT or MRI protocols to rule out scaphoid fractures remain investigational and we do not recommend their routine use in the ED.

Management and disposition. To avoid complications associated with delayed diagnosis, such as occult fracture displacement and AVN, patients with suspected scaphoid fracture should have thumb spica immobilization placed in the ED with orthopedic follow-up within

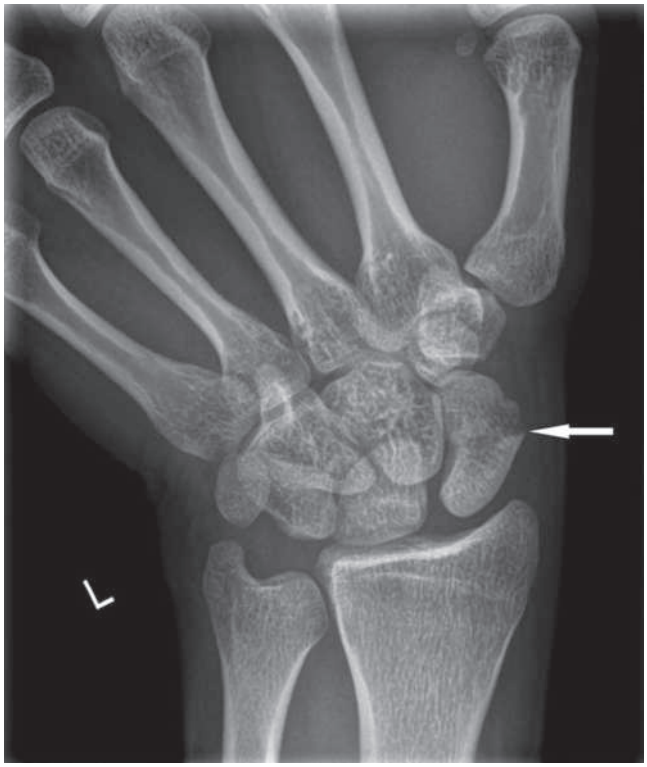

Fig. 43.11 Scaphoid Wrist Fracture. A posteroanterior view of the wrist in ulnar deviation (scaphoid view) illustrates a nondisplaced fracture of the scaphoid waist *(arrow)*.

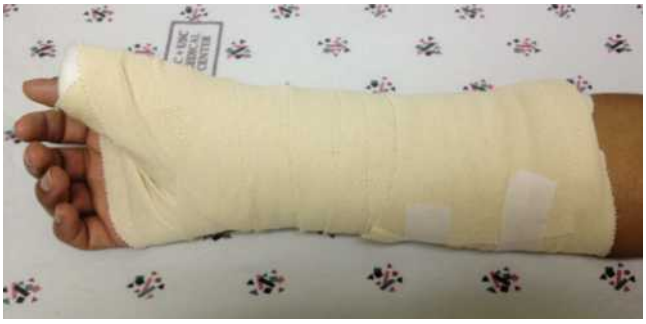

Fig. 43.12 Short Arm, Thumb Spica Splint. Common immobilization technique used for occult fractures of the scaphoid bone seen in a volar view. Note the optimal 10 degrees of wrist flexion and radial deviation, which assists in scaphoid immobilization.

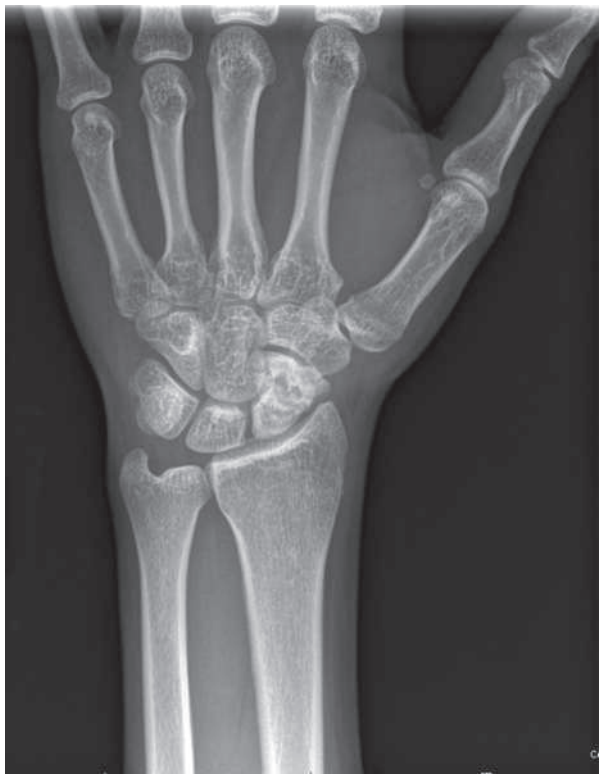

Fig. 43.13 Avascular Necrosis of the Scaphoid Bone. A common complication of scaphoid fractures is avascular necrosis as a result of the distal to proximal osseous blood supply, displacement, or nonunion, resulting in chronic wrist pain and arthritis.

1 week. Recent evidence has questioned the practice of immobilizing the wrist in all patients with suspected scaphoid fractures, instead suggesting that the emergent use of advanced imaging modalities is more accurate and cost-effective. The cost of time off work, serial casting, repeat physician evaluation, and office visits was found to exceed that of advanced imaging for definitive diagnosis when these imaging modalities are readily available.[8] A recent trial in the United Kingdom demonstrated improved cost savings, diagnostic accuracy, and patient satisfaction associated with immediate MRI in patients with clinically suspected scaphoid fracture with normal radiographic imaging.[9] Importantly, the outcomes of these trials vary depending on MRI cost and accessibility. At this time, we advise thumb spica immobilization with urgent orthopedic follow-up within 1 week for any patient with clinically suspected scaphoid fracture and normal radiographs.

The definitive treatment for uncomplicated, nondisplaced distal pole and nondisplaced waist scaphoid fractures depends on various factors, although screw fixation portends a faster recovery time.[10,11] There is no current consensus as to whether the thumb should be included in the splint, but clinical trials are ongoing. Most surgeons terminate the thumb spica at the interphalangeal joint line. Some specialists use a long arm (above the elbow) cast or splint, which prevents wrist pronation and supination for the first few weeks, while others prefer short arm immobilization. In addition to flexion and extension, pronation and supination may produce fracture displacement in the proximal carpal row. We advise immobilization in a thumb spica short arm splint with urgent follow-up with an orthopedic specialist within 1 week (Fig. 43.12). The duration of total immobilization will vary relative to the location of the fracture. More proximal fractures commonly require longer durations to ensure adequate healing. Variability in healing time is related directly to the pattern of blood supply to the scaphoid, which flows from the distal to proximal portion of the bone through the scaphoid tuberosity. This pattern of blood flow also accounts for the higher incidence of AVN and nonunion seen in more proximal fractures (Fig. 43.13). As a result of these complications, scaphoid fractures require urgent orthopedic referral.

Lunate fractures

Foundations. Fractures of the lunate are relatively uncommon. This injury tends to occur in persons with a congenitally short ulna.

Clinical features. Patients will experience pain over the dorsum of the wrist, exacerbated by axial loading of the long finger metacarpal. On physical examination, tenderness may be elicited by palpation over the dorsum of the wrist in the depression felt just distal to

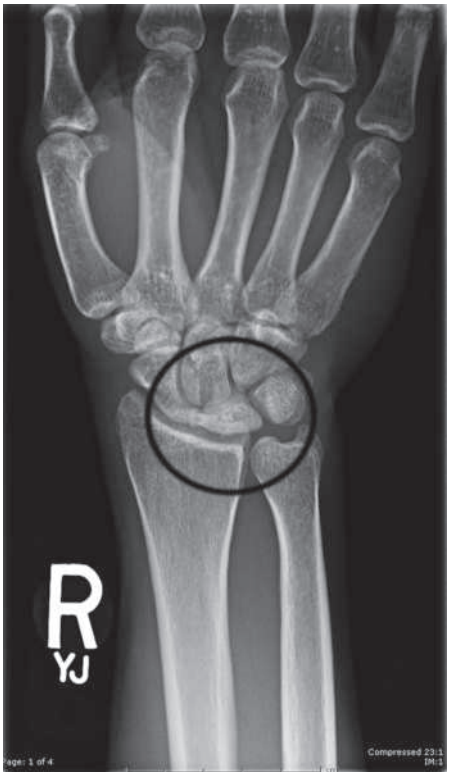

Fig. 43.14 Avascular necrosis of the lunate bone *(circle),* also known as *Kienbock disease.* Prevailing theories support fracture of the lunate bone or compromised circulation as the most likely cause of disease.

Lister tubercle. The usual mechanism of injury involves a fall on the outstretched hand causing extreme dorsiflexion, with transfer of the resultant force from the capitate to lunate. Complications of lunate fractures include progression to carpal instability, nonunion, and AVN. Kienbock disease, defined by AVN of the lunate, has a predictable pattern of bony collapse, carpal change, and degeneration. It results from a combination of vascular, anatomic, and traumatic mechanisms. In well-established cases of Kienbock disease, the lunate appears sclerotic and fragmented on radiographic examination, and ultimately the bone collapses, with resultant proximal migration of the capitate (Fig. 43.14). These changes cause secondary osteoarthritis of the radiocarpal joint, chronic wrist pain, and weakness at the wrist joint. Initial treatment involves a short arm cast, but patients may require operative intervention. In more severe cases, excision and prosthetic replacement of the lunate or arthrodesis may be necessary.

Diagnostic testing. In the ED, wrist radiographs are utilized to assess for lunate fractures; however, fractures of the lunate may be difficult to see on plain films because of overlap of the distal radius, ulna, and other carpal bones. CT or MRI can identify a fracture that is not visible on radiographic imaging. Arthroscopy remains the gold standard for assessing and diagnosing these injuries.

Management and disposition. To minimize the risk of AVN, clinically suspected lunate fractures should be immobilized due to the possibility of occult lunate injuries. Nondisplaced lunate fractures are treated with short arm immobilization with double sugar-tong splint or thumb spica splint with orthopedic follow-up in 5 to 7 days. Displaced injuries, open fractures, or those with neurovascular compromise require open reduction and internal fixation (ORIF) and warrant ED orthopedic consultation. Lunate and perilunate dislocations are discussed later, in the section on *Carpal Instability.*

Triquetral Fractures

Foundations. There are two main patterns of triquetral fractures that are observed: triquetral body and dorsal cortical chip fractures. An adequate blood supply to the triquetrum reduces the risk of AVN, but does not eliminate it.

Clinical features. Patients will experience local tenderness over the dorsal wrist (in the setting of dorsal cortical chips) or volar wrist (avulsion fracture). In addition, swelling and tenderness may be noted over the triquetrum on the ulnar aspect of the wrist. Triquetral body and volar avulsion fractures are commonly associated with perilunate and lunate dislocations, therefore, ligamentous injuries should be considered.

Diagnostic testing. A fracture to the triquetral body is best seen on the AP view. Dorsal triquetral chip fractures are best seen on the standard lateral view of the wrist as a small dorsal avulsion fragment, although a more oblique pronated view may be necessary for visualization (Fig. 43.15). CT or MRI can be used to identify a fracture not visible on radiographic imaging, but is generally not indicated in the ED.

Management and disposition. Treatment of triquetral fractures involves immobilization in a short arm volar splint. Urgent orthopedic referral within 5 to 7 days is suggested for non-displaced triquetral body fractures. Displaced triquetral body fractures will require ORIF and warrant ED consultation. Dorsal triquetral chips are avulsion-type fractures with a more benign clinical course, requiring routine orthopedic referral within 1 to 2 weeks. Neurovascular compromise and open fracture constitute additional indications for ED consultation.

Pisiform Fractures

Foundations. The pisiform is unique because it is the only sesamoid-like carpal bone and attaches to the FCU tendon, articulating on its dorsal surface with the triquetrum. Given the important role of forming the lateral wall of Guyon canal, ulnar arterial damage and neurapraxias may be associated with pisiform fractures.

Clinical features. Fractures of the pisiform usually occur from a fall on the outstretched hand but also may be seen after direct blows to the hypothenar eminence. This occurs from repetitive trauma when the palm of the hand is used in a hammer-like manner. On physical examination, there is tenderness over the ulnar aspect of the wrist, just distal to the volar crease. Paresthesias in the distribution of the ulnar nerve and hand "clumsiness" (or neurapraxia) from intrinsic muscle dysfunction can occur.

Diagnostic testing. Pisiform fractures are poorly seen on routine wrist radiographs and are likely underreported. A reverse (supinated) oblique and carpal tunnel view allow for better visualization (Fig. 43.16). CT scan or MRI can identify fractures that are radiographically occult.

Management and disposition. Nondisplaced fractures of the pisiform generally carry a good prognosis and are treated conservatively, with immobilization in a short arm splint in 30 degrees of wrist flexion with ulnar deviation and orthopedic referral within one week. Most pisiform fractures with evidence of ulnar neurapraxia will resolve, but orthopedic consultation for consideration of surgical decompression is warranted. Pisiform fractures complicated by displacement or nonunion may also require excision and orthopedic consultation in the ED.

Hamate Fractures

Foundations. The hook or hamulus is the most common site of hamate fracture, although articular surfaces and body fractures are also seen.

Clinical features. Fracture of the hook usually occurs from a fall on the outstretched hand or from a direct blow to the palm. A fracture

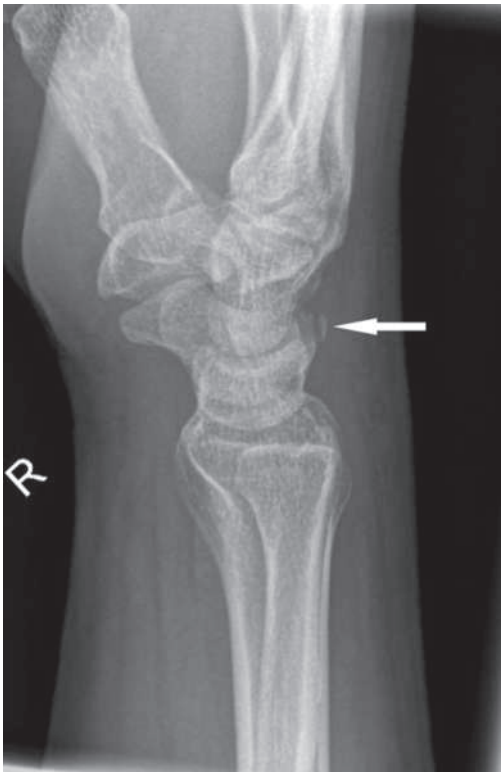

Fig. 43.15 Triquetral Avulsion Fracture. A minimally displaced triquetral avulsion or dorsal chip fracture *(arrow)* is seen on this lateral radiograph of the wrist.

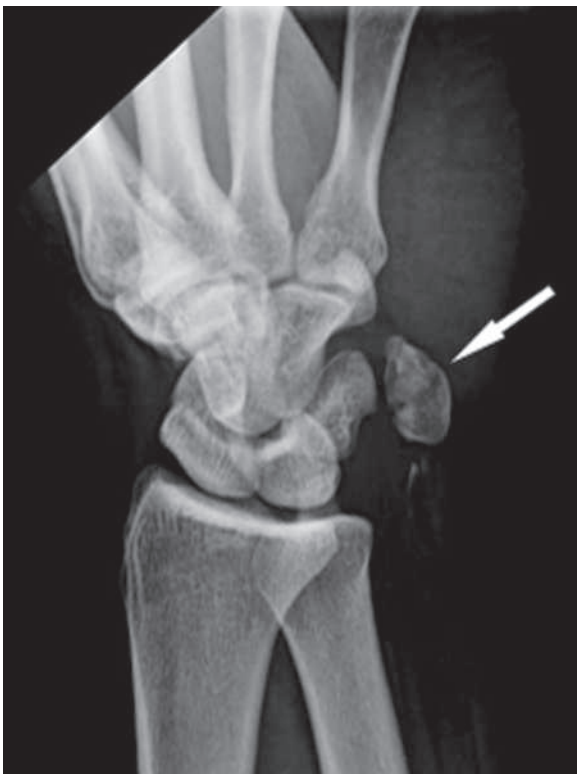

Fig. 43.16 Pisiform Fracture. A reverse supinated oblique radiograph of the wrist profiling the pisotriquetral joint demonstrates minimally displaced pisiform fracture *(arrow)* not typically seen on traditional posteroanterior, lateral, and oblique views.

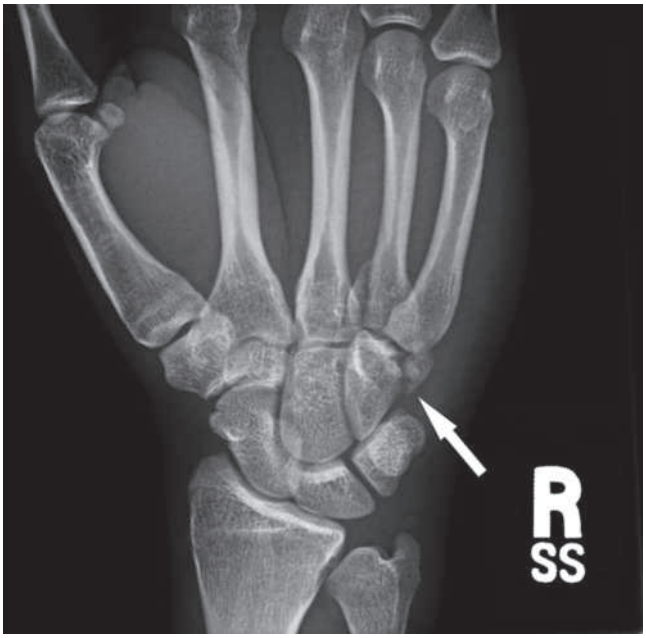

Fig. 43.17 Hamate Fracture. Fracture of the articular surface of the hamate bone *(arrow)* is seen on this posteroanterior radiograph of the wrist.

to the hook of the hamate typically occurs in patients participating in racket or club sports (e.g., tennis, golf, baseball). The repetitive use of hammers and vibration equipment (e.g., jack hammers) can predispose workers to hamate fractures and ulnar canal and hypothenar hammer syndrome. Patients may have isolated pain over the hypothenar eminence, decreased grip strength, or compromised distal perfusion. Pain may be localized directly on palpation of the hamate, 1 cm distal and radial to the pisiform. Hamate body and articular surface fractures are usually caused by increased load to the metacarpals of the ring and little fingers. Potential complications of hamate fractures include damage to the ulnar nerve, artery, and vein. Hook of hamate fractures may result in immediate or delayed ulnar arterial or nerve compromise, as well as flexor tendon rupture of the little finger.

Diagnostic testing. Hamate body and articular surface fractures are best seen on PA views of the wrist (Fig. 43.17). Standard wrist radiographs have poor sensitivity for hamate hook fractures, which are more readily seen on reverse, supinated oblique, and carpal tunnel views (Fig. 43.18). CT or MRI may be used to identify radiographically occult fractures. CT imaging may be slightly more accurate in identifying hook cortical fractures, but MRI is more accurate in identifying the integrity of the flexor digitorum profundus tendon as well as bone marrow edema and ulnar nerve injuries.

Management and disposition. Confirmed hook of hamate fractures should be immobilized in a volar splint that includes the fourth and fifth MCP joints in flexion to prevent tendon shortening. Displaced hook of the hamate fractures are frequently treated with operative resection, but immobilization has been successful for nondisplaced injuries. Vascular compromise, open fractures, or distal ischemia warrants emergent orthopedic consultation; otherwise, splinting and urgent orthopedic follow-up is recommended. Nondisplaced hamate body fractures can be treated with a short arm splint and orthopedic follow-up within one week. Displaced fractures or those associated with rupture of the flexor digiti minimi tendon should be referred to orthopedics urgently, within 3 to 5 days.

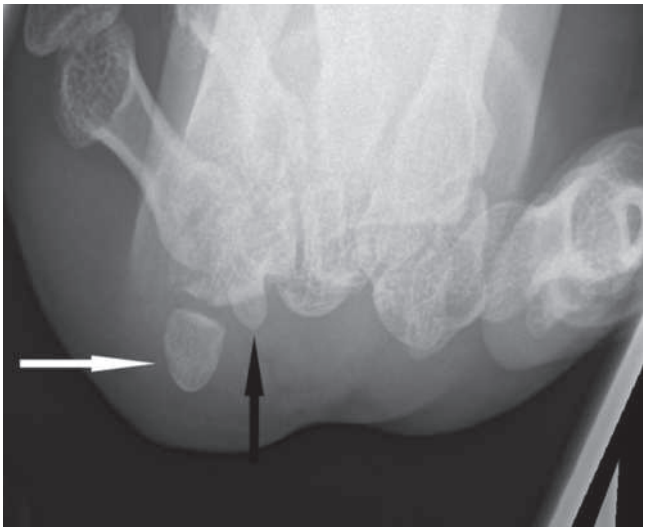

Fig. 43.18 Carpal Tunnel View of Wrist. The pisiform bone *(white arrow)* and hook of hamate or hamulus *(black arrow)* are better visualized on carpal tunnel views of the wrist when hypothenar palmar wrist pain is present, and a fracture is suspected.

Trapezium Fractures

Foundations. There are two main types of trapezium fractures, those involving the body and trapezial ridge.

Clinical features. A direct blow to the adducted thumb causes fracture through the body of the trapezium, with transmittal of the force by the base of the thumb metacarpal. Avulsion fractures of the trapezial ridge occur with forceful radial deviation or rotation of the wrist. On examination, patients report pain with movement of the thumb and on direct palpation of the trapezium, just distal to the scaphoid in the anatomic snuffbox. Complications of distal trapezium ridge fractures include nonunion, median nerve irritation, CMC arthritis, carpal tunnel syndrome, flexor carpi radialis tendinopathy, and loss of pinch strength.

Diagnostic testing. Although trapezium fractures may be seen on the AP view of the wrist, they are typically better visualized on oblique views (Fig. 43.19), a Bett view, and a carpal tunnel view to evaluate for ridge fractures. Trapezium fractures can be radiographically occult. CT scanning or MRI can be used to identify fractures that are not evident on X-ray.

Management and disposition. Nondisplaced trapezium fractures are treated with immobilization in a short arm thumb spica splint, with orthopedic referral within one week. Displaced fractures, comminuted fractures, intra-articular fractures, distal ridge fractures, and involvement of the carpometacarpal joint warrant urgent orthopedic consultation for ORIF within 2 to 3 days. Neurovascular compromise or open fractures warrant emergent consultation.

Capitate Fractures

Foundations. The capitate lies in a central position in the distal carpal row and, because of this protected location, it is rarely fractured.

Clinical features. The mechanism generally is a direct blow to the dorsum of the wrist. Fractures may also be seen in association with perilunate dislocations after a fall on the outstretched dorsiflexed hand. Clinical examination reveals dorsal wrist pain and swelling, with localized tenderness over the capitate. Complications of nonunion and AVN of the proximal fragment are rare but do occur because the capitate receives blood supply through its distal half.

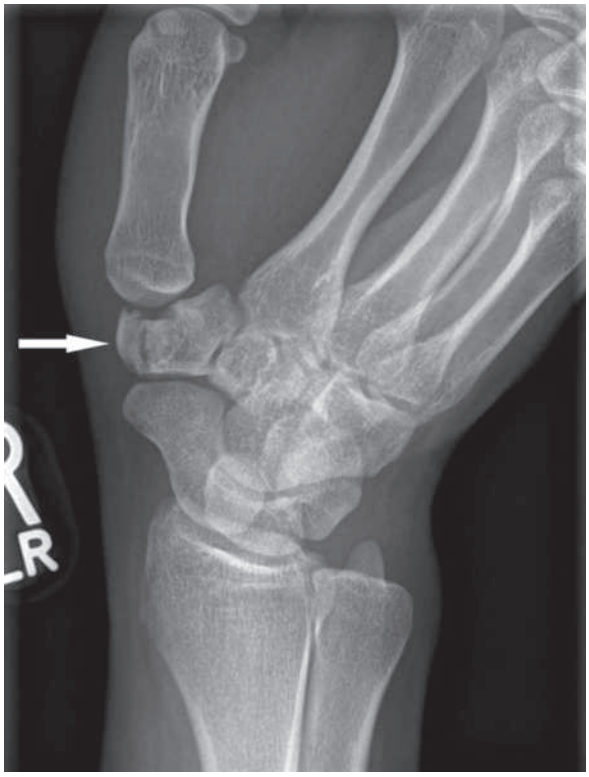

Fig. 43.19 Trapezium Fracture. An oblique view of the wrist shows an isolated, comminuted, intraarticular fracture of the trapezium body *(arrow)*.

Diagnostic testing. Fractures usually are visible on the standard PA view of the wrist, although the lateral and oblique views may be helpful in determining the presence of rotation or displacement of the fracture fragment. CT scan or MRI can be useful in identifying radiographically occult fractures.

Management and disposition. Identified or suspected nondisplaced fractures of the capitate should be managed with immobilization in a short arm thumb spica splint with routine orthopedic referral within one week. Urgent orthopedic referral within 2 to 3 days is recommended for fractures with displacement. ED consultation is indicated for associated carpal dislocation, open fractures, or neurovascular compromise.

Trapezoid Fractures

Foundations. Trapezoid fractures are rare, usually seen in association with other carpal injuries.

Clinical features. The typical mechanism of injury is a direct blow down the long axis of the index metacarpal, which may result in isolated fracture to the trapezoid or cause a dorsal fracture-dislocation. On clinical examination, pain and tenderness are localized over the dorsum of the wrist at the base of the second metacarpal.

Diagnostic testing. The fracture may be visible on routine PA views of the wrist; however, oblique views may be superior for visualization of the injury. CT scan or MRI can be used in identifying radiographically occult fractures.

Management and disposition. Confirmed or suspected nondisplaced trapezoid fractures should be immobilized with a short arm thumb spica splint with urgent orthopedic referral in 2 to 3 days. Displaced fractures or fracture dislocations warrant orthopedic consultation in the ED for reduction and fixation. Trapezoid fractures have a high rate of nonunion and AVN.

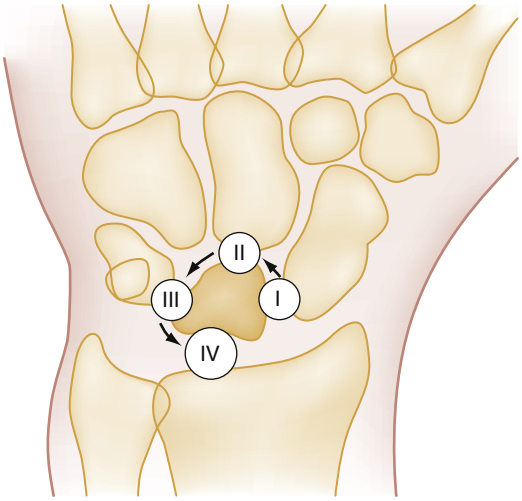

Fig. 43.20 Sequential stages of carpal dislocation. Each of four stages (I–IV) represents a sequential intercarpal ligament injury proceeding around the lunate. (From Greenspan A. *Orthopedic radiology: a practical approach*. 2nd ed. New York: Gower Medical; 1992.)

Carpal Instability

Foundations. The Mayfield classification of carpal instability is comprised of four distinct stages. Each stage represents a sequential intercarpal injury, beginning with scapholunate joint disruption and proceeding around the lunate, creating progressive carpal instability (Fig. 43.20). Each stage also may be associated with specific bony fractures, which, if present, should alert the emergency clinician to the possibility of an occult perilunate ligamentous injury. These associated injury patterns include fractures of the radial styloid, scaphoid, capitate, and triquetrum.

Clinical features. Carpal ligamentous injury is caused by wrist hyperextension, ulnar deviation, and intercarpal supination. Patients with these carpal dislocation injuries typically have a history of a fall on the outstretched hand. They complain of pain and swelling over the dorsum of the wrist, with limited range of motion. On physical examination, tenderness to palpation is noted over the dorsum of the wrist. Delayed scapholunate instability may be clinically elicited by a provocative maneuver, such as the *Watson scaphoid shift test*, which will increase pain and produce a clunk or snap. The test is performed by placing upward pressure on the scaphoid tuberosity while the hand is in ulnar deviation. In scapholunate instability, this action will cause the scaphoid to ride out of the radial fossa over the dorsal rim and, as the hand is moved back radially, a painful snap is produced. In the setting of acute trauma, this test is often too painful to perform. With perilunate and lunate dislocations, visible deformity of the wrist also is apparent, and two-point sensation in the median nerve distribution often is diminished. Complications of carpal dislocation injuries include median nerve injury and chronic carpal instability, with resultant degenerative arthritis.

Diagnostic testing. A stage I injury, or scapholunate dissociation, results in a characteristic widening of the scapholunate joint on the PA view, which has been called the *Terry Thomas sign* after the British comedian with a gap between his front teeth. This radiographic sign has been updated to reference more current celebrity figures and is also referred to as the *David Letterman sign*. This injury pattern may be associated with a rotary subluxation of the scaphoid. Radiographically, the scaphoid is seen end-on, with the cortex of the distal pole appearing as a ring shadow, referred to as the *signet ring sign* (Fig. 43.21). Scapholunate dissociation may not be demonstrated on routine radiographs, so when there is clinical suspicion for this injury, additional stress views could be considered. Radiographs taken with a clenched fist and with ulnar deviation (the clenched fist AP view) accentuate widening of the scapholunate joint and are suggestive of disease when a gap larger than 3 mm is measured.

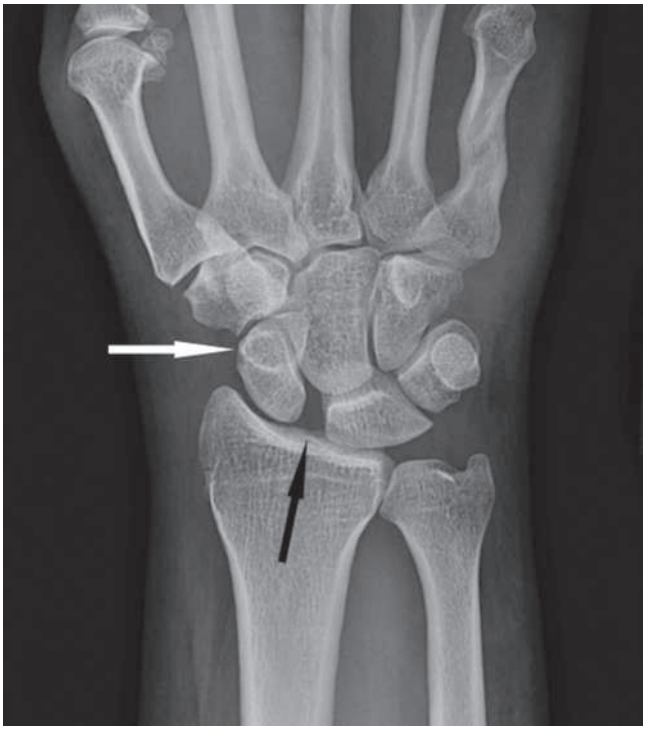

Fig. 43.21 Scapholunate Dissociation With Scaphoid Subluxation. Posteroanterior view of the wrist shows characteristic widening of the scapholunate joint *(black arrow)*, known as the *Terry Thomas sign*, and a ring shadow over the scaphoid *(white arrow)* secondary to subluxation, known as the *signet ring sign*.

A stage II injury, or perilunate dislocation, is seen best on the lateral view of the wrist. Although the lunate remains articulated to the distal radius, the capitate is dorsally dislocated. The PA view shows overlap of the distal and proximal carpal rows and also may show an associated scaphoid, radial styloid, or capitate fracture (Fig. 43.22).

A stage III injury appears identical to a stage II injury but includes a dislocation of the triquetrum that is seen best on the PA view, with overlap of the triquetrum on the lunate or hamate. This injury may be associated with a volar triquetral fracture.

A stage IV injury, or lunate dislocation, results in a characteristic triangular appearance of the lunate on the PA view caused by the rotation of the lunate in a volar direction. This triangular appearance is commonly referred to as the *piece of pie sign*. This rotation also is visible on the lateral view of the wrist, in which the lunate looks like a cup tipped forward and spilling its contents, referred to as the *spilled teacup sign*. On the lateral view, the capitate is seen to lie posterior to the lunate and often has migrated proximally to contact the distal radius (Fig. 43.23). MRI can identify these injuries in the setting of negative radiographs but is rarely indicated in the ED. Arthroscopy remains the gold standard for definitive diagnosis.

Management and disposition. Carpal dislocation injuries need emergent orthopedic consultation in the ED for reduction and stabilization. ED management of dissociations without evidence of dislocation or neurovascular injury consists of immobilization and urgent orthopedic follow up within one week.

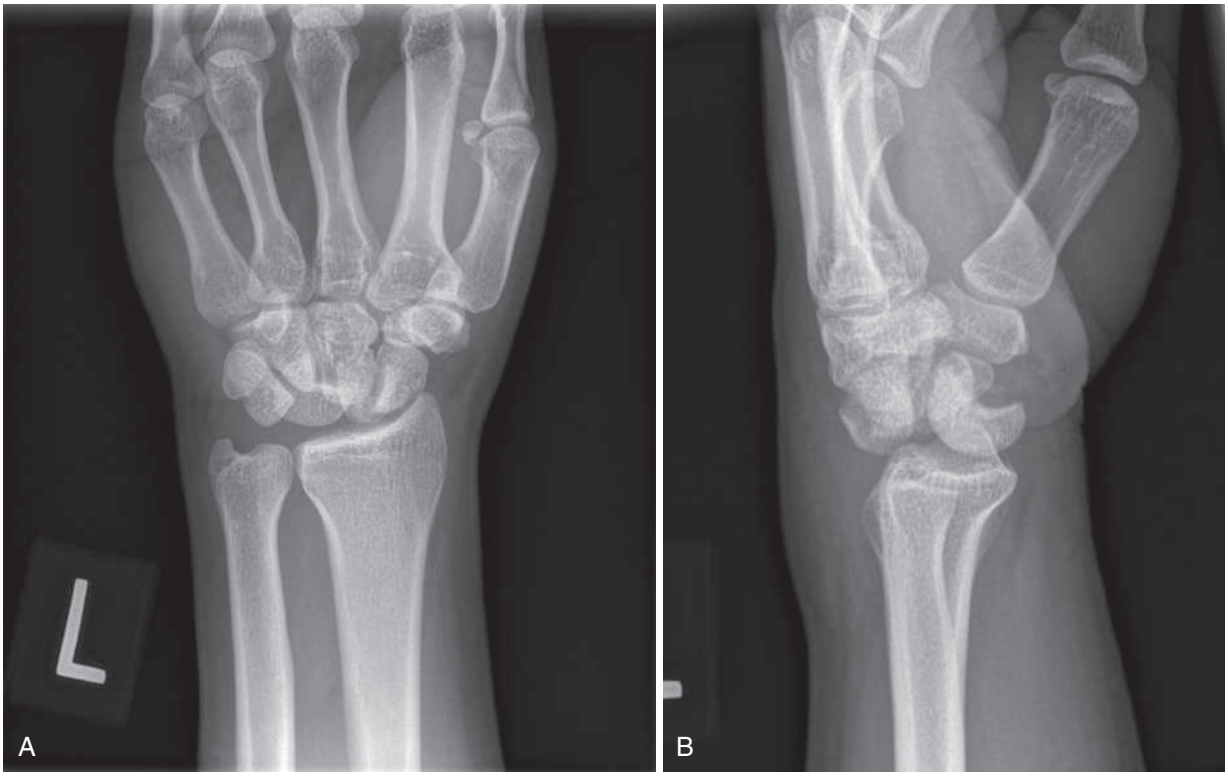

Fig. 43.22 Perilunate Dislocation. (A) This posteroanterior view of the wrist shows an abnormal-appearing lunate bone, obvious disruption of the normal carpal arcs, and commonly associated and, in this case, displaced scaphoid fracture. (B). Lateral view shows a dislocated and dorsally displaced capitate bone in relation to the lunate. Of note, the lunate maintains its articular connection and alignment with the radius, suggesting a perilunate dislocation.

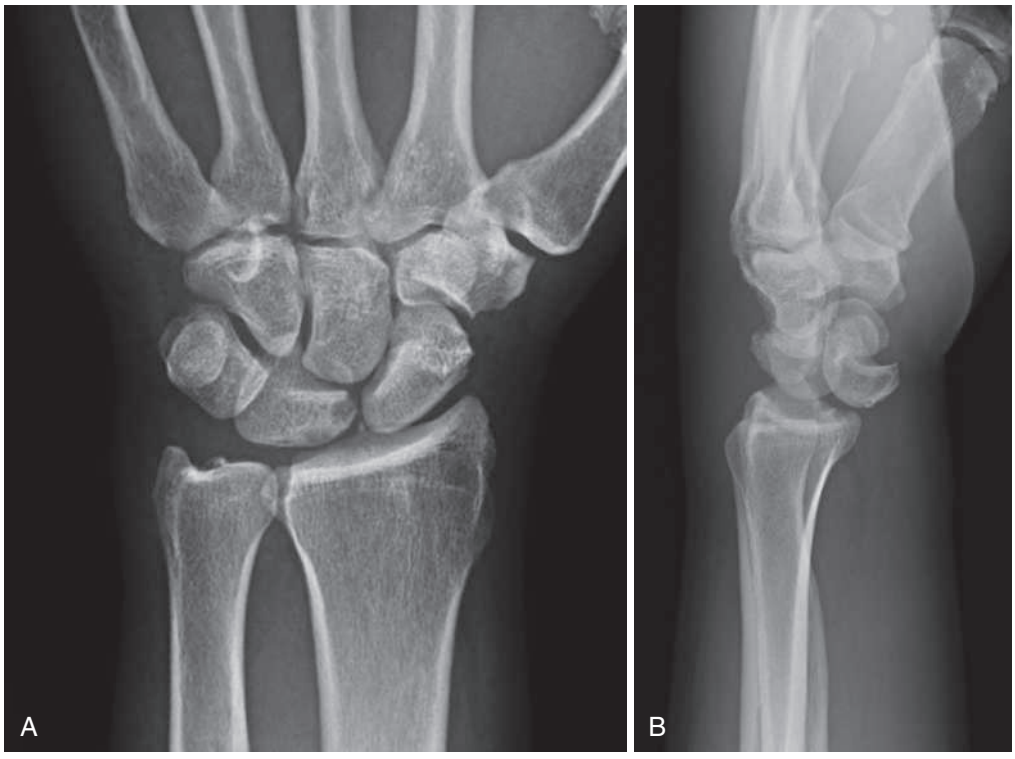

Fig. 43.23 Lunate Dislocation. (A). This posteroanterior view shows the characteristic triangular shape of the lunate bone during dislocation. (B) Volar displacement of the lunate resembles a spilled teacup on the lateral view. Note the disrupted articulation between the lunate and distal radius and realignment of the radius, capitate, and metacarpals, suggesting lunate dislocation.

Radiocarpal Dislocation

Foundations. Radiocarpal dislocations and fracture dislocations are considered extremely rare and are typically associated with high-energy trauma.

Clinical features. Patients are commonly involved in polytrauma scenarios. Dislocations may be volar or dorsal, although ulnar translation of the carpal bones is much more common than radial translation.

Diagnostic testing. Radiographs of the wrist are typically sufficient to identify radiocarpal dislocations.

Management and disposition. Emergent reduction of these injuries is paramount because of the extensive soft tissue damage and commonly associated neurovascular compromise. Reductions may be difficult to maintain in these complex and unstable injuries, which usually require ORIF. Emergent orthopedic consultation in the ED is indicated.

Distal Radius and Ulna Injuries

Distal radius and ulna fractures typically occur from a ground-level fall on the outstretched hand in older patients and from high-energy trauma in younger patients. These injuries are commonly closed and may have intraarticular involvement and displacement. They frequently require ED closed reduction, splinting, and orthopedic referral. Plain radiographs are generally adequate for the diagnosis and management of these injuries; rarely is advanced imaging indicated in the ED. A neurovascular examination should be performed to exclude any median, radial, or ulnar neurapraxia and radial or ulnar arterial compromise caused by the deformity or fracture fragments. Post-reduction radiography and a neurologic examination are also recommended. Open fractures, instability, or an acute carpal tunnel syndrome (ACTS) are indications for emergent orthopedic evaluation. Vascular compromise should prompt immediate reduction in conjunction with orthopedic consultation. Patients with open fractures should receive tetanus immunization prophylaxis and tetanus immune globulin (if unvaccinated), and 2 g of cefazolin intravenously, prior to surgical intervention. Numerous classification patterns have been devised, and the most commonly encountered fractures are discussed in the following sections.

Colles Fracture

Foundations. A Colles fracture refers to a transverse fracture of the distal radial metaphysis, which is dorsally displaced and angulated.

Clinical features. Patients classically present with a "*dinner fork deformity*" on physical examination. The fracture usually is located within 2 cm of the radial articular surface and may be associated with comminution and intraarticular extension into the radiocarpal or radioulnar joints. Carpal instability may also occur. Complications of Colles fractures are seen most often in older patients and those with comminution, displacement, and inadequate fracture reduction. Although radial and ulnar nerves may be compromised, median nerve injury is most common and may occur acutely from contusion, traction from displacement, transection from fracture fragments, nerve compression after closed reduction, overlying cast pressure, or secondary to ACTS. Thus, it is important to evaluate neurologic function before and after fracture reduction and splint application.

Diagnostic testing. The PA view may show extension of the fracture into the radioulnar or radiocarpal joints and the amount of intraarticular step-off and radial shortening present. The degree of dorsal displacement and angulation is best seen on the lateral view, with loss of the normal volar tilt of the distal radial articular surface (Fig. 43.24).

Management and disposition. Most Colles fractures require ED reduction for restoration of radial length, correction of dorsal angulation (especially when greater than 20 degrees), restoration of

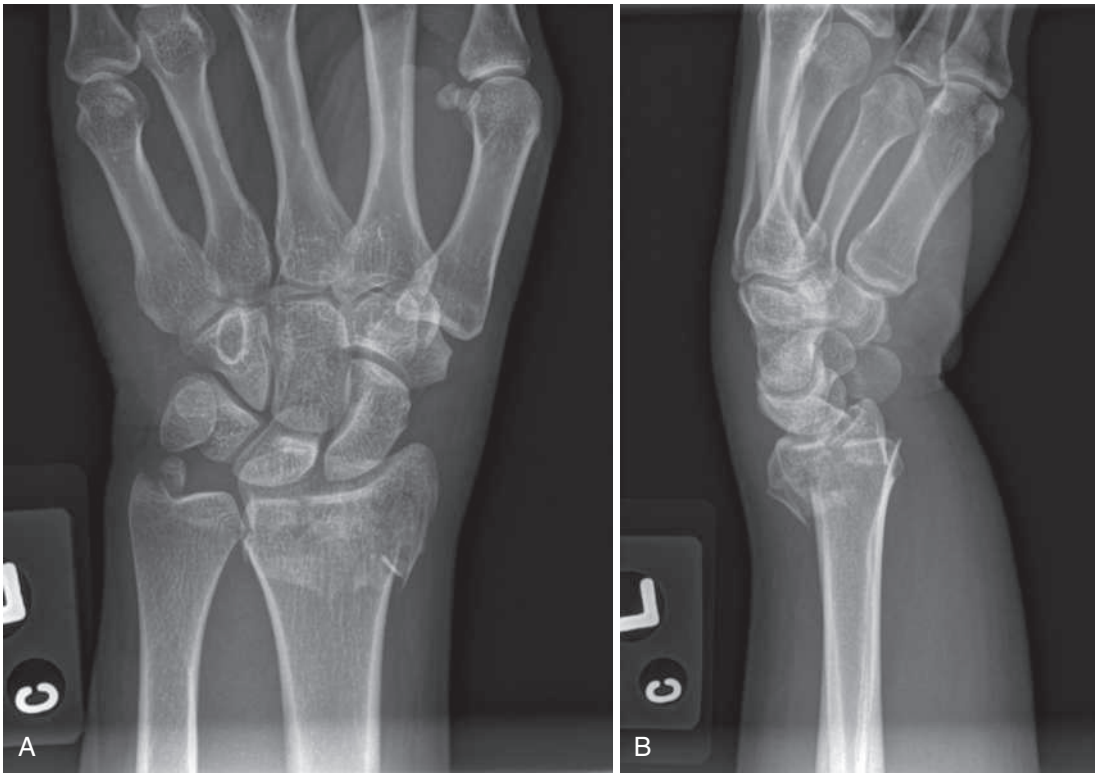

Fig. 43.24 Colles Fracture. (A) Posteroanterior view shows fracture and shortening of the radius, intraarticular extension, and associated ulnar styloid fracture. (B) Lateral view shows typical dorsal displacement and angulation of the radial fracture known as the *dinner fork deformity*.

anatomic volar tilt. Closed reductions should be performed under procedural sedation, local or regional anesthesia, or a combination of these options followed by immobilization in a double sugar tong splint. Splinting should immobilize the wrist but allow for finger movement. Immediate circumferential casting, as well as overly tight splinting, should be avoided for at least 24 hours because edema from this injury may induce subsequent pain or neurovascular compromise. Successful reduction allows for urgent outpatient orthopedic referral within 2 to 3 days in most cases.

Methods of local and regional anesthesia for distal radius fracture reduction include the classic hematoma block, IV regional anesthesia, known as the *Bier block*, and regional nerve blocks, including median, radial, ulnar, and brachial plexus approaches. The hematoma block remains an easy and effective method of anesthesia and may be performed by placing a 22-gauge needle in the dorsum of the distal radius, withdrawing until a fracture hematoma is encountered and then instilling 5 to 10 mL of 1% or 2% lidocaine, with or without the addition of a longer-acting agent such as bupivacaine (Fig. 43.25).[12] Hematoma blocks may avoid the requirement for procedural sedation and decrease ED length of stay. For pediatric distal radial fractures, local anesthesia should not be injected into the growth plate but is otherwise acceptable. Use of finger traps is another effective means of obtaining reduction to allow positioning for splinting (Fig. 43.26). The more comminuted and displaced the fracture, the higher the likelihood that operative reduction will be necessary.

Indications for emergent Colles fracture reductions include any neurovascular compromise, significant deformity, soft tissue tension, tenting of the skin, and loss of volar tilt, with significant dorsal angulation (>20 degrees). Loss of reduction will occur in many of these patients before orthopedic follow-up, especially intra-articular fractures, and in older adults, for whom the long-term benefits of anatomic restoration appear less beneficial. The American Academy of Orthopedic Surgeons has suggested surgical fixation of fractures with more than 3 mm of shortening, 10 degrees of dorsal tilt, and intra-articular step-off of more than 2 mm post-reduction. ED orthopedic consultation is recommended if a reduction is unable to be maintained, or if there is evidence of open fracture, severe comminution, neurovascular compromise, compartment syndrome, or skin tenting.

Smith Fracture

Foundations. Smith fracture is a transverse fracture of the metaphysis of the distal radius, with associated volar displacement and angulation. The fracture may extend into the radiocarpal joint.

Clinical features. The typical mechanism of injury involves a direct blow to the dorsum of the wrist or a fall onto the dorsum of the hand resulting in extreme palmar flexion. This fracture also may be seen after a backward fall on an outstretched hand, with the forearm in supination. The patient has a swollen painful wrist, which is deformed, with fullness visible on the volar aspect. On physical examination, a "*garden spade deformity*" will classically be observed. Because the displacement is opposite to that seen with a Colles fracture, Smith fractures are often called a "reverse Colles fracture."

Diagnostic testing. The fracture is visible on PA and lateral radiographs of the wrist, but the lateral view best shows the degree of volar displacement and angulation (Fig. 43.27).

Management and disposition. Treatment of this fracture involves closed reduction and immobilization in a splint if the fracture is extra-articular, as discussed for Colles fracture. Unlike Colles fracture, however, Smith fracture is more likely to be unstable and to require operative repair; it also has an increased tendency to cause neurovascular compromise, specifically median nerve compression. Urgent orthopedic referral within 2 to 3 days or emergent consultation is indicated based on the severity of angulation, neurovascular compromise, or associated soft tissue complications. Delayed tendon complications, including EPL entrapment and rupture, have been documented. Prognosis is most favorable in patients with successful reduction and restoration of the normal radial length and volar tilt. ED consultation is warranted for similar indications to the Colles fracture.

Barton Fracture

Foundations. Barton fracture is an oblique intraarticular fracture of the rim of the distal radius, with displacement and dislocation of the radiocarpal joint along with the fracture fragment.[13] The fracture may involve the dorsal rim of the radius with dorsal carpal subluxation (classic Barton fracture) or may involve the volar rim with volar carpal

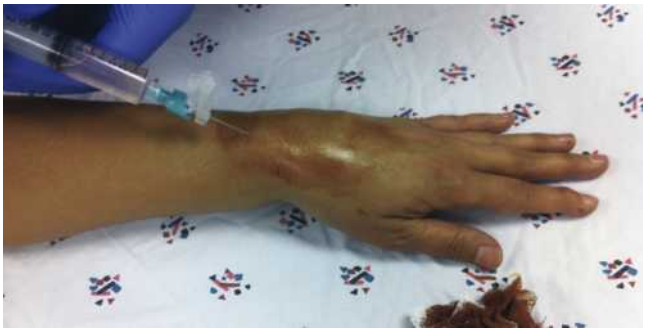

Fig. 43.25 Hematoma Block. Sterile preparation of the fracture area is performed, and local anesthetic is then introduced to the hematoma that surrounds the fracture site to assist with pain control during reduction.

Fig. 43.26 Finger Traps. The distal radius reduction method typically involves traction followed by manipulation facilitated by the finger traps. Ten pounds of weight are hung from the elbow at 90 degrees of flexion for approximately 10 minutes before the reduction attempt.

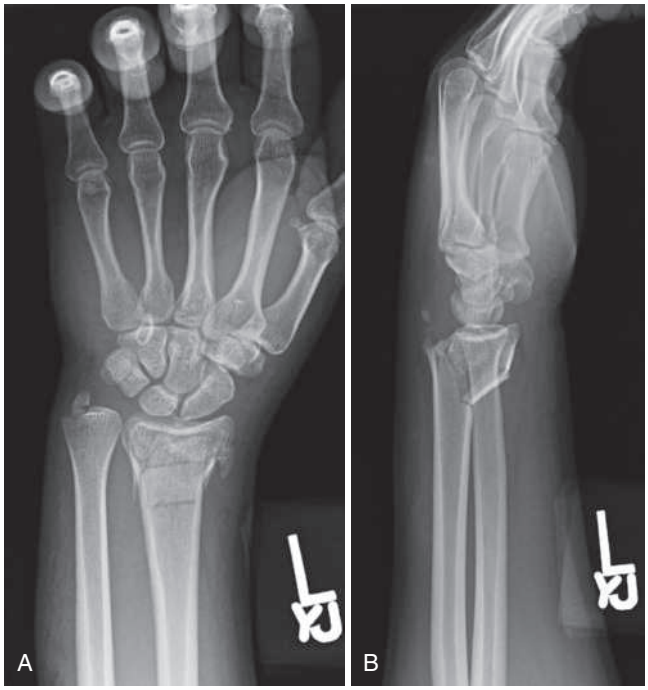

Fig. 43.27 Smith Fracture. (A) Posteroanterior view shows a metaphyseal fracture of the radius, with shortening and associated ulnar styloid base fracture. (B) Lateral view shows volar displacement of the distal fracture fragment along with the carpus.

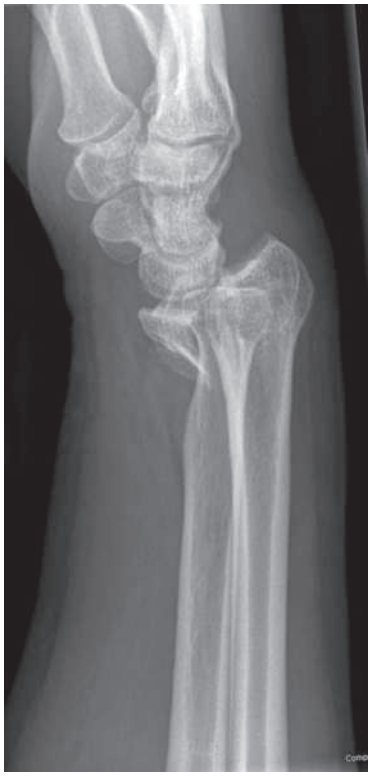

Fig. 43.28 Volar Barton Fracture. Lateral radiograph of the wrist shows typical oblique intraarticular fracture of the volar rim of the radius, with associated displacement of the distal radial fragment and carpus dislocation.

subluxation (volar Barton fracture). While these fractures are rare, the volar-anterior margin fracture is seen more often than the dorsal-posterior margin fracture.

Clinical features

The mechanism of injury for these fractures is a high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in volar flexion (causing a volar rim fracture) or dorsiflexion (causing a dorsal rim fracture). Complications include posttraumatic arthritis of the radiocarpal joint and delayed carpal instability. Both complications are seen more commonly when reduction fails to achieve or maintain anatomic realignment of the radiocarpal joint surface.

Diagnostic testing. Volar and dorsal rim fractures are visible on PA and lateral wrist radiographs; however, the lateral view best shows the degree of articular surface involvement and amount of associated fracture displacement (Fig. 43.28).

Management and disposition. Treatment of these unstable fractures requires emergent orthopedic consultation for reduction and fixation. Closed reduction may be successful when performed under fluoroscopy, although most fractures require percutaneous pinning or ORIF to restore the articular surface of the radius and stabilize the carpus.

Hutchinson Fracture

Foundations. Hutchinson fracture, or *chauffeur's fracture*, is an intra-articular fracture of the radial styloid.

Clinical features. The mechanism of injury is usually a direct blow or fall resulting in trauma to the radial side of the wrist. The term *chauffeur's fracture* originated in the era of hand-cranked automobiles, when this injury occurred because of direct trauma to the radial side of the wrist from the recoil of the motor crank. Posttraumatic arthritis is a common complication of radial styloid fractures and more common with displacement and scapholunate ligament disruption.

Diagnostic testing. The fracture is seen best on the PA view of the wrist as a transverse fracture of the radial metaphysis, with extension through the radial styloid into the radiocarpal joint.

Management and disposition. Nondisplaced fractures may be immobilized in a sugar tong splint, with the patient given urgent orthopedic referral within 2 to 3 days. Displaced fractures, which are frequently associated with scapholunate ligament disruption, require emergent open or closed reduction and fixation (Fig. 43.29). Because the radial styloid is the primary site of attachment for many of the ligaments of the wrist, accurate fracture reduction and union are crucial for proper wrist function.

Distal Radioulnar Joint Disruption

Foundations. Acute dislocation of the DRUJ can occur as an isolated injury, which is rare, or in association with a fracture to the distal radius *(Colles fracture)*, radial diaphysis *(Galeazzi fracture)*, or radial head *(Essex-Lopresti injury)*.

Clinical features. Certain characteristic findings on clinical examination may constitute the only clue to the presence of this injury. The typical mechanism of injury is a fall on the outstretched hand with hyperpronation, resulting in dorsal dislocation, or hypersupination, causing volar dislocation of the ulna. Dorsal ulna dislocations are more common than volar dislocations. Another mechanism known to cause DRUJ dislocation is the catching of the hand in rotating machinery, resulting in the same forcible hyperpronation or supination. This forcible rotation of the wrist causes disruption of the TFCC, the major stabilizer of the DRUJ, and may result in an associated avulsion fracture of the ulnar styloid.

Patients with this injury have a history of sudden onset of pain with a snapping sensation in the wrist, swelling, and limited range of

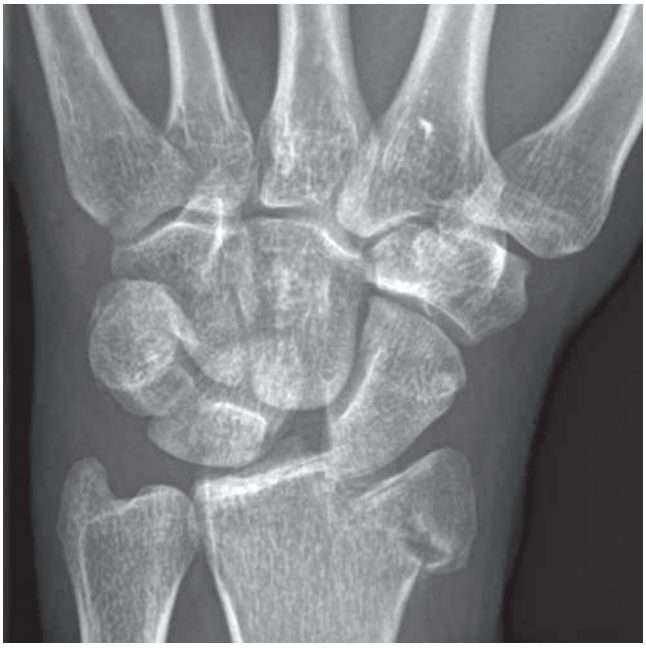

Fig. 43.29 Hutchinson Fracture. Posteroanterior radiographic view shows intraarticular fracture of the radial styloid with displacement and scapholunate dissociation, a common complication of untreated Hutchinson fracture.

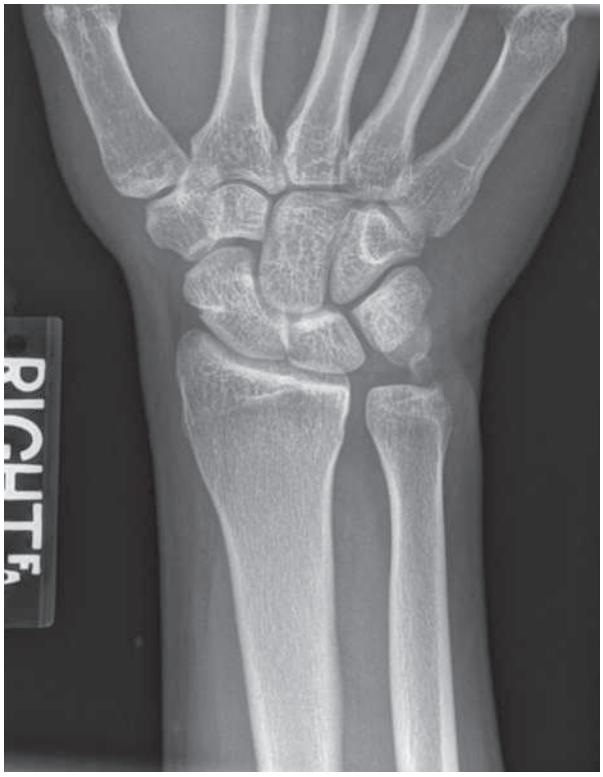

Fig. 43.30 Distal Radioulnar Joint Dislocation. Posteroanterior radiographic view shows an ulnar styloid base fracture suggestive of triangular fibrocartilage complex disruption and widening of the radius and ulna, consistent with distal radioulnar dislocation.

motion. On examination, tenderness is present over the ulnar aspect of the wrist, with palpable crepitus on supination and pronation. On examination, the *piano key test* may be used to assess for DRUJ instability. The test is positive when the ulnar head springs back like a piano key after being depressed volarly and then released. The *ballottement test* also evaluates stability of the DRUJ. With this test, the radius is grasped firmly by the examiner while the ulna is fixed between the examiner's other thumb and index finger. Pressure is then applied to the ulna in dorsal and volar directions with respect to the radius. Increased displacement relative to the contralateral wrist suggests instability.

With a dorsal dislocation of the ulna, the ulnar styloid appears more prominent than on the unaffected side, and significant pain and limitation of movement are noted on supination of the wrist. With a volar dislocation of the ulna, there is loss of the normal ulnar styloid prominence, with pain and limitation of movement on pronation. These characteristic clinical findings should alert the emergency clinician to the possibility of DRUJ disruption and prompt the appropriate imaging studies to confirm the presence or absence of injury.

Diagnostic testing. Diagnosis often is difficult because when the injury occurs in isolation or is not suspected, plain radiographs commonly are reported as normal. Well-positioned lateral radiographs of the wrist may show the presence of a DRUJ dislocation with more than 20 degrees of dorsal angulation or volar displacement, but pain and inability of the patient to rotate the wrist fully may cause a false-negative result because a true lateral view cannot be obtained. Fractures of the ulnar styloid base increase suspicion for a DRUJ disruption. It also is important to assess for radial head fractures because this injury is commonly associated with DRUJ disruption and interosseous membrane rupture (see below, "Essex-Lopresti Lesion"). A DRUJ dislocation may be seen on the PA view of the wrist radiograph showing significant overlap or widening of the distal radius and ulna (Fig. 43.30). If there is significant clinical suspicion of injury, and the radiographic appearance is normal, a CT scan or MRI may assist in the diagnosis.

Management and disposition. Treatment of DRUJ dislocations commonly requires emergent orthopedic consultation for reduction and stabilization. Closed reduction with the forearm in supination followed by application of a long arm splint is indicated. Alternatively, open reduction is often necessary with volar dislocations because the ulnar head may be locked on the distal radius. Operative reduction is also necessary in dorsal dislocations to repair the associated injury to the TFCC. Any associated bony injuries should be managed with immobilization as indicated.

SOFT TISSUE INJURIES OF THE WRIST

Carpal Tunnel and Acute Carpal Tunnel Syndrome

Foundations

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy; it occurs at the wrist and results in compression of the median nerve. CTS is typically a chronic, progressive, repetitive overuse syndrome with a female preponderance. The transverse carpal ligament and volar surfaces of the carpal bones form the carpal tunnel. It is a rigid compartment that contains nine flexor tendons (flexor pollicis longus, four flexor digitorum superficialis, and four flexor digitorum profundus tendons) and the median nerve.

Clinical Features

The classic symptoms include a gradual onset of numbness, paresthesia, and pain in the median nerve distribution (thumb, index, long and radial aspect of the ring finger; see Table 43.1). These symptoms often are bilateral and are worse during the night and after strenuous activities. Typically, patients report numbness and paresthesias on awakening that lessens when the hands are shaken or held in a dependent

position. Pain may actually radiate proximal to the carpal tunnel, and symptoms may progress to include decreased grip strength, hand clumsiness, thenar atrophy, and trophic ulceration of the fingertips.

Differential Diagnoses

CTS can be associated with numerous systemic conditions, such as rheumatoid arthritis, hypothyroidism, diabetes mellitus, renal failure, congestive heart failure, acromegaly, and collagen vascular diseases. Each of these systemic diseases is thought to produce an increase in pressure within the carpal tunnel from thickening of the flexor synovia or transverse carpal ligament. Hormonal changes associated with pregnancy and menopause also are known to be associated with CTS. Differential diagnoses also include cervical radiculopathy (especially the C6 or C7 nerve root) and Raynaud syndrome. The median nerve may also be compressed at other sites including the pronator teres. A brachial plexopathy may also produce similar symptoms.

Diagnostic Testing

The most common provocative test supporting the diagnosis of CTS is the wrist flexion or *Phalen test* (Fig. 43.31). This test is performed by asking the patient to flex the wrists fully for 60 seconds while holding the forearms in a vertical position. The test result is positive if paresthesia or numbness develops in the median nerve distribution. Other tests suggesting CTS are weakness observed on thumb abduction testing and *Tinel sign*, which demonstrates pain or paresthesias elicited by light tapping over the median nerve at the wrist. *Durkan test*, or the median nerve compression test, consists of the application of pressure directly over the median nerve at the carpal tunnel and may have the highest sensitivity and specificity for disease. However, no physical examination maneuver is completely reliable in making the diagnosis and is therefore more supportive when used in combination. Nerve conduction studies have traditionally been used to confirm the diagnosis. MRI and ultrasound are also being used for confirmation, but emergently the diagnosis of CTS is primarily clinical.

Management and Disposition

Conservative (nonoperative) treatment for CTS yields variable results. Specific measures include splinting the wrist in a neutral position and administering cortisone injections in the carpal tunnel as an outpatient in an orthopedic clinic. Splinting initially may be prescribed full time and then reduced to immobilization at night only. Five factors that lessen the likelihood of successful nonoperative treatment are (1) age older than 50 years, (2) symptom duration longer than 10 months, (3) constant paresthesias, (4) stenosing flexor tenosynovitis, and (5) positive Phalen test result at less than 30 seconds. Nonsteroidal antiinflammatory drugs (NSAIDs) have proved to be of little benefit. Open or endoscopic surgical release of the flexor retinaculum to unroof the carpal tunnel is indicated when medical management fails.

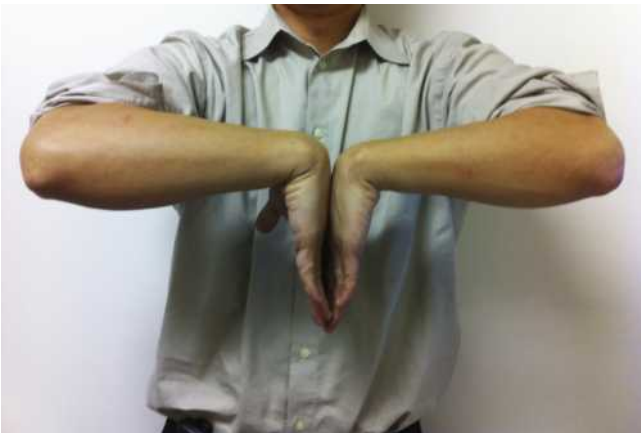

Fig. 43.31 Phalen Test.

ACTS, which occurs over hours rather than weeks or months, is much less common than the chronic, gradually progressive presentations of CTS. ACTS is more often directly related to fractures, fracture-dislocations, hemorrhagic conditions, infections, vascular disorders, and edema involving the wrist. Although the carpal tunnel is open at both ends, it has the physiologic properties of a closed compartment. Distal radius fractures are the most common cause of ACTS; however, lunate and perilunate dislocations are associated, and even isolated carpal fractures and rupture of the EPL tendon have been found to be associated with ACTS as well. Trauma resulting in an ACTS is typically relieved by closed reduction, and no reliable clinical method currently exists for differentiating acute median nerve compression in ACTS from concussive insult. In the absence of trauma, ACTS has occurred secondary to hemorrhagic, vascular, and bleeding disorders, and anticoagulant use. When ACTS has been diagnosed, ED orthopedic consultation is recommended for surgical decompression and release of the transverse carpal ligament.

De Quervain Disease

Foundations

De Quervain disease and intersection syndrome, like CTS, have been grouped into the overuse or repetitive strain injury pattern category, sometimes referred to as work-related cumulative trauma. The APL and EPB, both within the first dorsal extensor compartment of the wrist, are the tendons affected in de Quervain disease. Traditionally known as a stenosing tenosynovitis or tendinitis, de Quervain disease involves enlarged tendons, which may reach five times their original size, creating a stenosing tendinopathy.

Clinical Features

Clinically, patients report pain on the radial side of the wrist, with ulnar deviation, thumb movements, weakened grip strength, or a combination of these symptoms. Onset is gradual and typically the result of increased use. De Quervain disease is thought to be common, affecting women six times more frequently than men, typically at an age older than 40 years.

Diagnostic Testing

Radiographs are useful in ruling out bony pathology, but the diagnosis may be made with physical examination alone. *Finkelstein test* and radial styloid tenderness have long been considered to be a pathognomonic signs of de Quervain disease. Ultrasound reveals fluid in the first dorsal extensor tendon compartment tendon sheath with associated thickening of the APL and EPB tendons.

Management and Disposition

Conservative interventions of rest, splinting, and NSAIDs are the first-line treatments for mild to moderate disease. Thumb spica splints effectively immobilize the APL and EPB, but pain may return when the inciting activities are resumed. ED management should consist of rest, thumb spica splint immobilization, and nonsteroidal antiinflammatory agents. Orthopedic consultation is warranted within a few weeks. Injection of corticosteroid preparations into the dorsal extensor compartment of the wrist may be offered at follow-up with an orthopedic physician within 3 to 5 weeks. Patients with refractory or severe cases that interfere with activities of daily living may undergo surgical release of the first dorsal extensor compartment of the wrist, with decompression of the APL and EPB tendons.

Intersection Syndrome

Foundations

Intersection syndrome is another overuse tendinopathy that clinically manifests with pain on the radial side of the wrist, approximately 4 to 8 cm proximal to the site of de Quervain disease. Pathophysiologically, intersection syndrome occurs secondary to inflammation where the muscle bellies of the APL and EPB cross over the muscle bellies of the extensor carpi radialis longus and brevis, proximal to the retinaculum.

Clinical Features

The condition is also known as *crossover or oarsman syndrome*. The mechanism of injury is secondary to rowing, weightlifting, or a repetitive resistance pulling action.

Diagnostic Testing

Physical examination findings include significant pain, soft tissue swelling, and crepitus with movement in more severe cases. Ultrasound findings may include thickened tendons or effusion, and radiographs are generally negative for pathology.

Management and Disposition

The treatment for this disease is immobilization with a wrist splint and antiinflammatory medications. Although surgical treatments have been described, this syndrome is typically self-limited. Orthopedic follow-up is recommended within 3 to 5 weeks.

FOREARM

FOUNDATIONS

Forearm injuries are common encounters in the ED. There is a bimodal age distribution of patients who suffer forearm injuries—children aged 6 to 15 years and adults older than 50 years.[14] In children, forearm fractures account for nearly 50% of all pediatric fractures and are on the rise due to an increase in sporting activities and body mass index (BMI). Refer to pediatric fractures referenced in Chapter 160.

Anatomy, Physiology, and Pathophysiology

Mechanisms of injury for forearm fractures include falls on outstretched hands, direct blows to the area, or high-energy trauma, such as involvement in a motor vehicle collision. Evaluation of forearm injuries requires an understanding of the interdependent biomechanical relationship between the radius and ulna. These two bones articulate at the proximal and distal ends, which allows the radius to rotate around the ulna to provide pronation and supination. Because fractures of the radius or ulna can result in dislocation at the wrist or elbow, emergency clinicians should be vigilant when treating forearm fractures. Early diagnosis and prompt treatment of these injuries are critical to prevent loss of function.

The forearm is a unique two-bone structure with the radius and ulna being bound at both ends by a ligamento-capsular structure. The proximal radioulnar joint (PRUJ) consists of an articulation between the radial head and ulna. The radial head, the primary stabilizer of the forearm, combined with the annular, quadrate, radial, and ulnar ligaments, provides strong support at the PRUJ. At the DRUJ, the TFCC and anterior and posterior radioulnar ligaments support the articulation of the distal radius and ulna. The interosseous membrane further stabilizes the forearm by providing a strong interconnection between the radius and ulna. The ulna is relatively straight and provides the rotational axis for the bowed radius to rotate around through various planes of motion. The supinator, pronator teres, and pronator quadratus muscles insert along the shaft of the radius and ulna to provide their named function, but they also are responsible for the deforming forces in forearm fractures.

The forearm is typically divided into three compartments—volar, dorsal, and mobile wad of Henry. The interosseous membrane divides the volar and the dorsal compartments, and the mobile wad is located laterally (Fig. 43.32). The volar compartment, which can be further divided into superficial and deep layers, contains the pronators and flexor muscles of the hands. The radial, ulnar, and anterior interosseus arteries and median, ulnar, and superficial radial nerves are also contained within the volar compartment. The dorsal compartment consists of the extensor muscles of the hand and posterior interosseous artery and nerve. The mobile wad is located in the proximal lateral aspect of the forearm and contains the brachioradialis, extensor carpi radialis longus, and extensor carpi radialis brevis.

CLINICAL FEATURES

Obtaining the mechanism of injury is important in the initial assessment of a forearm injury. The most common mechanism of injury is an axial load applied to the forearm through the hand, which often leads to rotational displacement. Patients may present with obvious deformity and a significant amount of pain.

Physical examination of the forearm injury begins with visual inspection by evaluating for swelling along the injured area, obvious deformity, and evidence of lacerations. Gentle palpation can assist in localization of the injury, reveal crepitus in grossly unstable fractures, and allow assessment of skin turgor in the evaluation of compartment pressure. Significant swelling, as well as disproportionate pain, paresthesia, and paleness of skin, should alert emergency clinicians to the potential development of compartment syndrome. Neurologic evaluation should include careful examination of motor and sensory function of the radial, ulnar, and median nerves. Assessment of the brachial, radial, and ulnar arteries should be performed. See pediatric trauma and compartment syndromes referenced in Chapter 160.

DIFFERENTIAL DIAGNOSES

When approaching a patient with forearm pain, differential diagnoses will be determined by the mechanism of injury, location of pain, and chronicity of the symptoms. Acute trauma associated with inability to supinate will raise suspicion for acute fracture involving radius or ulna depending on the location. Other differential diagnoses include straining of the forearm muscles and tear of the ligaments stabilizing radius and ulna. For patients with chronic forearm pain without acute trauma, repetitive strain injury due to overuse and repetitive movement should be considered.

DIAGNOSTIC TESTING: RADIOLOGY

The radiologic evaluation of the forearm injury should begin with the AP and lateral views. It is necessary to include wrist and elbow in the x-ray examination of the forearm to exclude any concomitant injuries to the DRUJ or PRUJ.

On the normal AP view of the forearm, a medially pointing radial styloid and laterally projecting biceps tuberosity of the proximal radius are visible. On the lateral view, the coronoid process of the proximal ulna points volarly, and the ulnar styloid lies dorsally (Fig. 43.33). Any deviation suggests an abnormal rotational or axial deformity. The normal radiologic findings of the forearm, including radiocarpal articulation angle, relationship between radial styloid and ulnar styloid, and normal volar tilt of the radius, are described earlier in the *Radiology of the Wrist* section of this chapter.

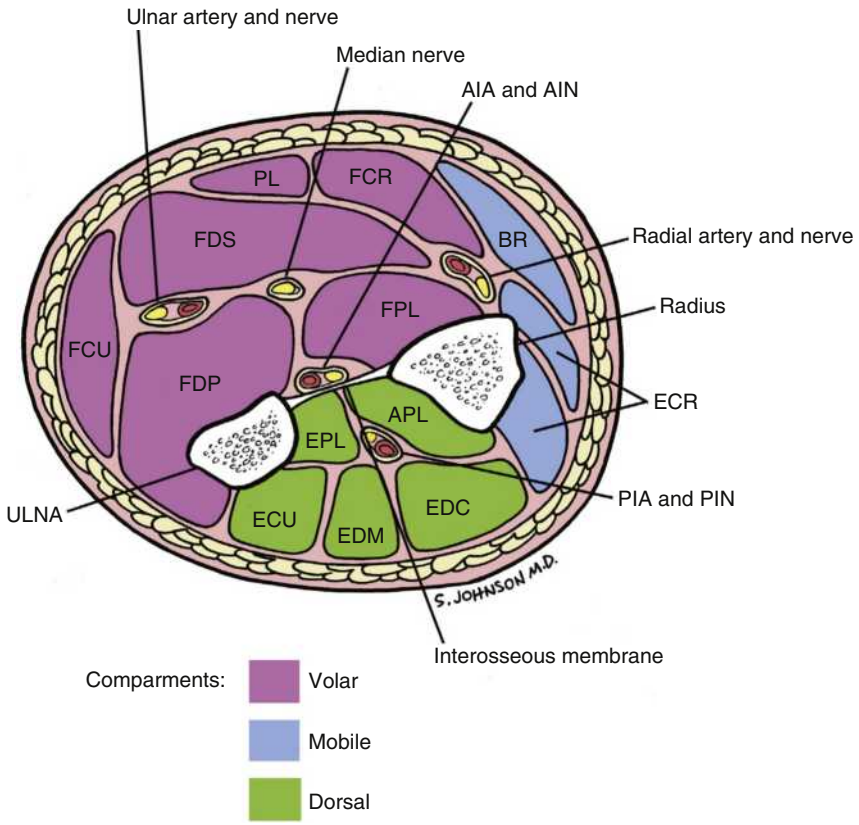

Fig. 43.32 Cross Section of the Forearm Demonstrating the Compartments and Neurovascular Structures. The volar compartment contains the flexors of hand and wrist, including the palmaris longus *(PL)*, flexor digitorum superficialis *(FDS)*, flexor carpi radialis *(FCR)*, flexor pollicis longus *(FPL)*, flexor digitorum profundus *(FDP)*, and flexor carpi ulnaris *(FCU)*, as well as the ulnar nerve, ulnar artery, median nerve, radial artery, superficial branch of the radial nerve, anterior interosseous artery *(AIA)*, and anterior interosseous nerve *(AIN)*. The dorsal and volar compartments are bordered by the interosseous membrane. The dorsal compartment contains finger extensors and long thumb abductor, as well as the posterior interosseous artery *(PIA)*, posterior interosseous nerve *(PIN)*, abductor pollicis longus *(APL)*, extensor digiti minimi *(EDM)*, extensor carpi ulnaris *(ECU)*, extensor pollicis longus *(EPL)*, and extensor digitorum communis *(EDC)*. The mobile wad, which is often considered to be a third compartment, is composed of the extensor carpi radialis brevis and longus muscles *(ECR)* and brachioradialis *(BR)*. (Courtesy Dr. S. Johnson.)

Injury to the radial head can be evaluated by drawing a midaxis line through the radial shaft, neck, and head. This radial midaxis line should intersect the center of capitellum of the elbow on any radiologic view. Any variance from this alignment should raise suspicion regarding radial head dislocation (Fig. 43.34).

CT scans can be useful when there is a suspicion of extension of the fracture into the DRUJ or PRUJ on plain radiography. MRI is the study of choice for evaluation of soft tissues (e.g., muscle, tendon, ligament) of the forearm, including the interosseous membrane. Ultrasound can also help with evaluation of interosseous membrane injury and to determine when pediatric forearm fractures have been adequately realigned after closed reduction.[15]

Shaft Fractures of Radius and Ulna

Foundations

Fractures involving both the radius and ulna, also known as both bone fractures, are common forearm injuries.

Clinical Features

Patients often have pain and obvious deformity of the forearm as a result of blunt trauma. Physical examination includes assessing for any associated neurovascular injury or open fracture. Compartment syndrome should be considered in all patients with these types of injury. Common complications of combined radius and ulna fractures are nonunion, malunion, infection, and neurovascular injury.

Diagnostic Testing

The initial radiologic evaluation should include the AP and lateral radiographs of the forearm, as well as dedicated wrist and elbow radiographs.

Management and Disposition

After initial evaluation, any open fractures should be irrigated with sterile water or saline to decrease contamination, and a sterile dressing should be applied, along with parenteral antibiotics, while awaiting emergent operative management. Any grossly displaced fracture-dislocation should be reduced to improve alignment and prevent impending or ongoing neurovascular injury. Application of a sugar tong forearm splint should be made with an urgent referral within 7 days to an orthopedist, as long as there is no evidence of open fracture or neurovascular compromise.

Nondisplaced concurrent radius and ulna fractures are uncommon and most both bone fractures of the forearm in adults generally require operative management as soon as possible to achieve the alignment.

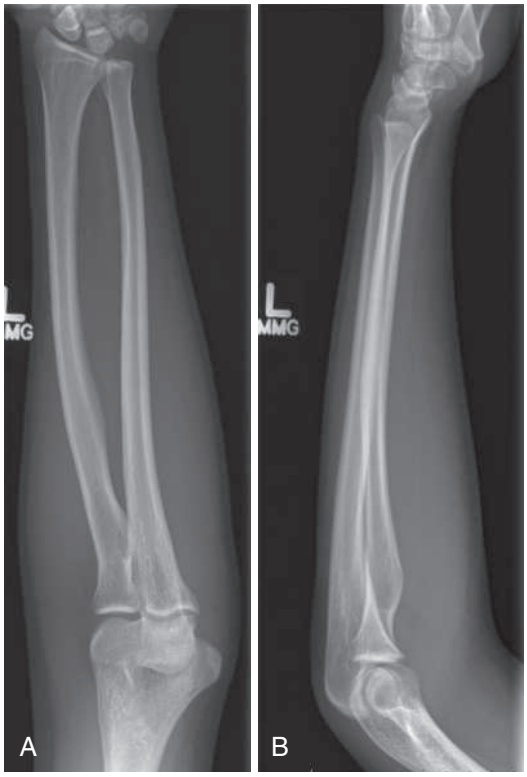

Fig. 43.33 Normal anteroposterior (A) and lateral (B) radiographic views of the forearm. Both bones should be visible for their entire length, and the radiograph should include the wrist and elbow joints.

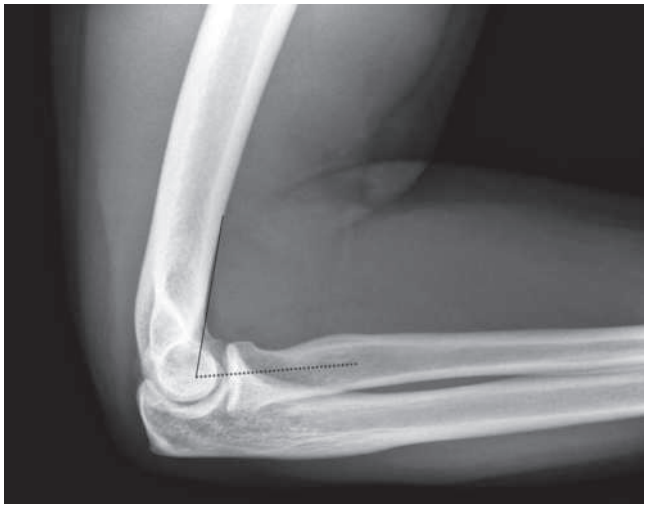

Fig. 43.34 Lateral Radiographic View of a Normal Elbow. A line bisecting the proximal radial shaft also bisects the capitellum *(dotted line)*.

Ulna Shaft Fractures

Foundations

Isolated fractures of the ulna shaft, known as nightstick fractures, are seen frequently in the ED.

Clinical Features

Patients often have pain and swelling over the medial aspect of the forearm, because the usual mechanism involves raising the arm overhead to protect it from a direct traumatic impact. Careful inspection

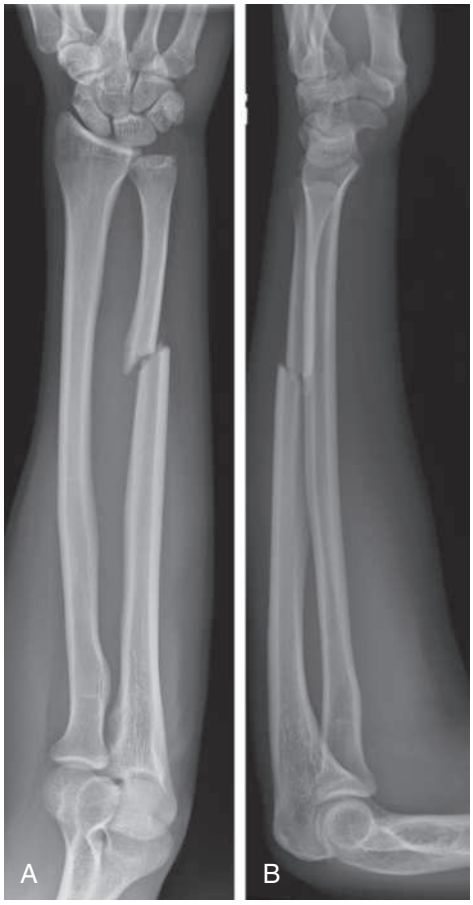

Fig. 43.35 Isolated Ulna Fracture *(Nightstick Fracture)*. Anteroposterior (A) and lateral (B) radiographic images show isolated ulnar fracture.

of the skin is necessary as many patients have open fractures, given the superficial position of the ulna directly under the subcutaneous skin. Examination should include wrist and elbow assessments to exclude any associated injuries involving the PRUJ or DRUJ. The emergency clinician should be aware of potential instability at either articulation associated with fractures involving the proximal or distal third of the ulna.

Diagnostic Testing

Diagnosis of an ulna fracture is made by obtaining AP and lateral radiographs of the full-length forearm (Fig. 43.35). Although most isolated ulna fractures are considered stable, those with more than 50% displacement, more than 8 degrees of angulation, involvement of the proximal third of the ulna, or instability at the DRUJ or PRUJ are considered unstable fractures.

Management and Disposition

There is a controversy regarding the indication for the operative management of isolated ulna shaft fracture; however, any unstable fractures should be referred to an orthopedist within 7 days for possible ORIF because they carry a high risk of function loss, nonunion, malunion, and radioulnar synostosis.[16]

Most stable ulna fractures heal without significant clinical sequelae. Stable fractures can be managed with 6 to 8 weeks of short arm, below-elbow immobilization with interosseous molding to limit radial angulation and prevent forearm rotation. Early mobilization with a removable forearm support achieves the earliest radiologic time to union and lowest rate of malunion. Above-elbow immobilization or long arm casting

may be detrimental to the healing process and have been associated with nonunion and delayed union.

Monteggia Fracture

Foundations

Ulna fractures associated with radial head dislocation are commonly known as Monteggia fractures. Monteggia originally described a traumatic lesion involving the fracture of the proximal third of the ulna and anterior dislocation of the radius. Bado later redefined the Monteggia fracture and classified it to encompass various ulna fractures with concomitant radial head dislocations. The Bado classification divides the injury into four types depending on the location and angulation of the ulna fracture, along with the direction of the radial head dislocation.

Clinical Features

Patients with a Monteggia fracture often have fallen on an outstretched hand, resulting in hyperpronation. Direct posterior force on the ulna or a fall on the flexed elbow has also been implicated in the mechanism of the injury. Typically, patients have swelling and tenderness along the fracture site accompanied by a limited range of motion at the elbow and pain with pronation of the forearm. A dislocated radial head may be appreciated on palpation. Initial assessment of a Monteggia fracture should include a focused neurologic examination because the posterior interosseous nerve (PIN), a deep branch of the radial nerve, can be injured. Because the PIN innervates the finger extensors along with the supinator, PIN injury is often manifested by weakness or paralysis of the thumb or finger extension. Complications of a Monteggia fracture include malunion, nonunion, synostosis, stiffness, and nerve palsy. Early diagnosis and treatment of a Monteggia fracture are crucial in achieving good outcomes.

Diagnostic Testing

The radiograph of the forearm reveals the obvious ulna fracture that often overshadows the subtle radial head dislocation (Fig. 43.36). A chronic, irreducible radial head dislocation can occur as a result of delay in diagnosis. Drawing the radiocapitellar line (RCL) through the head of the capitellum can prevent overlooking a proximal dislocation. The line should intersect the distal third of the capitellum on all views and confirm correct alignment. In young children however, an RCL may not reliably bisect the capitellum in normal pediatric patients. An abnormal RCL is suggestive of, but not pathognomonic for an injury.

Management and Disposition

Treatment of a Monteggia fracture depends on the age of the patient. Pediatric patients with this type of injury can be treated conservatively, with long arm casting in supination with acceptable reduction. Conversely, most adult patients with this type of fracture should have orthopedic evaluation to arrange for urgent ORIF.

Fig. 43.36 *Monteggia Fracture-Dislocation.* A fracture of the ulna diaphysis with anterior dislocation of the radial head *(arrow)* is shown in this lateral view of the forearm.

Galeazzi Fracture

Foundations

Galeazzi fracture refers to a fracture of the middle to distal third of the radius associated with injury to and dislocation of the DRUJ.

Clinical Features

Typically, a Galeazzi fracture results from a fall or motor vehicle collision as the patient attempts to brace for impact by stretching out the hand in hyperpronation. A direct blow to the dorsolateral aspect of the forearm is less common but also well recognized as a mechanism of injury for a Galeazzi fracture. Galeazzi fracture is often overlooked as a simple radius fracture, yet it often results in diminished forearm range of motion, loss of function, weakness, and chronic pain.

In addition to radiographic imaging, the mechanism of injury and focused examination play a critical role in the diagnosis of a Galeazzi fracture because injuries to the DRUJ may not be obvious. Patients with Galeazzi fracture have deformity at the site of the fracture associated with swelling and tenderness. The wrist should be meticulously examined to assess for stability of the DRUJ. Instability of the DRUJ can range from obvious prominence of the ulnar head (associated with the subluxation or dislocation) to tenderness elicited at the wrist, which can be a subtle sign of DRUJ ligament injury.

Diagnostic Testing

AP and lateral radiographs of the entire forearm and wrist are necessary to diagnose Galeazzi fracture. Besides the obvious fracture at the middle to distal third of the radius, there will be other subtle radiographic findings. On the AP view of the forearm, the space between the distal radius and ulna is widened (>2 mm) and the radius appears relatively shortened. In the lateral view, the dorsally angulated fracture of the radius can cause a dorsal displacement of the ulnar head. A fracture at the base of the ulnar styloid should raise the suspicion for DRUJ interruption (Fig. 43.37). Although not all radius shaft fractures are associated with DRUJ injury, previous studies have shown that at least 25% of all patients with radius fractures have DRUJ dislocation. Therefore, patients with radial shaft fractures should be referred to an orthopedist for further evaluation.

Management and Disposition

Conservative management of a Galeazzi fracture in adults has been associated with poor outcomes. Due to deforming forces from different forearm muscles and loss of stability at the DRUJ, displacement of the alignment in the cast occurs, despite successful initial reduction. A Galeazzi fracture has been termed a "*fracture of necessity*" to imply that surgical intervention is pivotal for achievement of an ideal anatomic position and acceptable functional outcomes. For any skeletally mature patients with this fracture, an orthopedist should be consulted emergently for ORIF of the radius and associated repair of the DRUJ to maintain the length and alignment. In contrast, conservative treatment with closed reduction and long arm casting has been successful in children and rarely necessitates surgical intervention. Along with the common complications associated with forearm fractures, such as malunion and nonunion, the occurrence of subluxation and dislocation of the DRUJ can result in limited motion and chronic pain.

Essex-Lopresti Lesion

Foundations

The Essex-Lopresti lesion, or longitudinal radioulnar disassociation, refers to an unstable forearm as a result of a triad of injuries to the radial head, disruption of the interosseous membrane, and violation of the DRUJ.

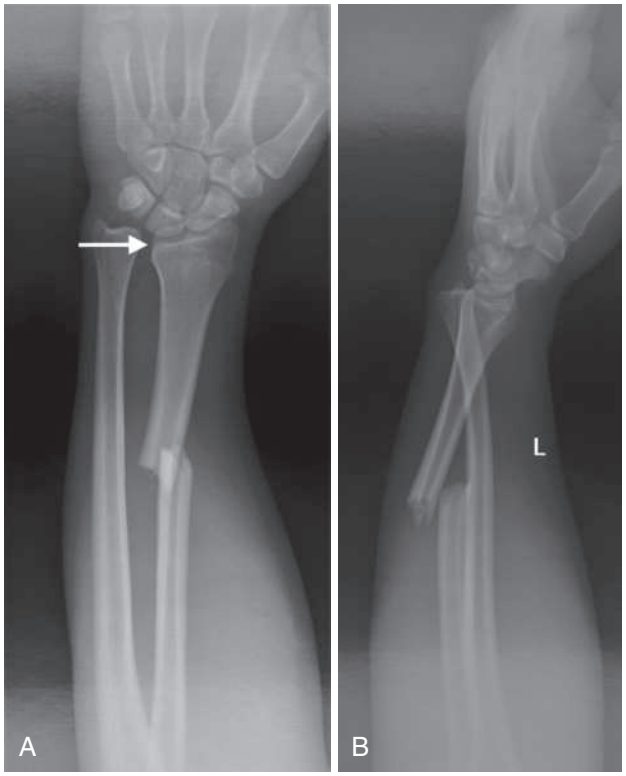

Fig. 43.37 Galeazzi Fracture-Dislocation. The anteroposterior (A) and lateral (B) views of the forearm show an obvious fracture of the distal third of the radius, with severe displacement and an associated dislocation of the distal radioulnar joint *(arrow)*.

Clinical Features

The patient often has fallen on an outstretched hand, resulting in transmission of a large axial loading force from the wrist to elbow. Consequently, the radial head, the primary forearm stabilizer, is fractured and displaced proximally. Disruption of the interosseous membrane and DRUJ also occurs and compromises the stability of the forearm. In addition to localized pain along the elbow from a radial head fracture, patients with the Essex-Lopresti lesion have wrist and forearm pain, along with grip and pronation weakness. Radioulnar synostosis and loss of forearm rotation can result from longitudinal disassociation. Early diagnosis of Essex-Lopresti injury and stabilization of DRUJ have been linked to favorable outcomes in comparison to delayed diagnosis.[17]

Diagnostic Testing

The diagnosis of an Essex-Lopresti lesion remains elusive because the standard AP and lateral views of the forearm often reveal an isolated radial head fracture. Thus, the incidence of the lesion may be higher than previously appreciated. The integrity of the interosseous membrane is difficult to assess based on a plain film. Subtle findings of positive ulna variance and a widened DRUJ are suggestive of longitudinal radioulnar dissociation. Obtaining a grip view and comparing the injured wrist with the contralateral wrist can be helpful in diagnosing an Essex-Lopresti lesion. MRI is the study of choice when clinical suspicion for an Essex-Lopresti lesion is high; however, ultrasound has recently been used more frequently to evaluate the integrity of the interosseous membrane. A CT scan (with three-dimensional reconstructions) of the elbow may be helpful in determining the degree of comminution and articular involvement of the radial head.

Management and Disposition

Once the diagnosis of an Essex-Lopresti lesion is confirmed, the patient should be referred to an orthopedic surgeon within 7 to 10 days for further surgical intervention. Many strategies have been proposed to repair Essex-Lopresti lesions, and the treatment option varies, depending on the chronicity of the injury.

ACKNOWLEDGMENT

We would like to thank David Williams, Karen G.H. Woolfrey, Michael Woolfrey, and Mary A. Eisenhauer for their contributions to previous versions of this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 43: QUESTIONS AND ANSWERS

1. In the setting of acute trauma and negative radiographs of the wrist, which clinical examination method(s) is (are) used to detect occult scaphoid fractures?
- **a.** Anatomic snuffbox tenderness
- **b.** Scaphoid tubercle tenderness
- **c.** Thumb metacarpal compression tenderness
- **d.** A positive Watson's scaphoid shift test
- **e.** All of the above

Answer: e. In the setting of acute trauma and negative radiographs, tenderness to palpation within the anatomic snuffbox, on the scaphoid tubercle, with thumb metacarpal compression, or a positive Watson's scaphoid shift test are all suggestive of occult scaphoid fracture.

2. A 45-year-old man complains of wrist pain after falling on an outstretched hand. What injury is shown in Figure 43.21 of the patient's wrist?
- **a.** Barton's fracture
- **b.** Lunate dislocation
- **c.** Perilunate dislocation
- **d.** Scaphoid fracture
- **e.** Scapholunate dissociation

Answer: e. The radiograph shows the signet ring, or cortical ring sign, which refers to the rotary subluxation of the scaphoid and oval appearance of the tubercle in the anteroposterior (AP) view of the wrist. On a properly positioned radiograph, this sign is typically associated with scapholunate widening, suggesting ligamentous laxity or dissociation. The signet ring sign is also used to describe pulmonary computed tomography (CT) imaging of bronchiectasis in relation to a dilated bronchus and associated pulmonary artery.

3. A 55-year-old man complains of wrist pain after a fall onto an outstretched arm. There is pain and swelling along the carpal bones. Also noted is decreased two-point sensation distally on the tips of the index and middle digits. Which structure is most likely injured?
- **a.** Median nerve
- **b.** Radial artery
- **c.** Radial nerve
- **d.** Ulnar artery
- **e.** Ulnar nerve

Answer: a. The median nerve courses through the carpal tunnel on the volar aspect of the wrist. It provides sensation to most of the palm and thumb, half of the ring finger and, specifically, the tips of the index and middle digits. The median nerve is the most common neurapraxia associated with Colles fractures.

4. Which nerve is commonly associated with a Monteggia fracture?
- **a.** Muscular branch of the radial nerve
- **b.** Posterior interosseous nerve
- **c.** Deep branch of the ulnar nerve
- **d.** Median nerve
- **e.** Ulnar nerve

Answer: b. Injury to the posterior interosseous nerve (PIN), a deep branch of the radial nerve, is commonly associated with a Monteggia fracture. Because the PIN innervates the finger extensors along with the supinator, associated injury is often manifested by weakness or paralysis of the thumb or finger extension.

5. A karate player presents with pain over the ulnar aspect of his hand. On physical examination, there is tenderness over the ulnar aspect of the wrist, distal to the volar crease. Paresthesias in the distribution of the ulnar nerve are present and the patient also complains of hand clumsiness. Standard X-rays are negative. What additional view might reveal the diagnosis?
- **a.** Clenched fist view
- **b.** Carpal tunnel view
- **c.** Scaphoid view
- **d.** External Oblique view
- **e.** Metacarpal view

Answer: b. Pisiform or hook of hamate fractures may cause the constellation of findings in the above scenario and are better appreciated on the carpal tunnel view. The clenched fist view is best for identifying scapholunate widening while the scaphoid view is optimal for identifying scaphoid fractures. The external oblique view would not optimize imaging of these two bones and the metacarpal view is not an actual view.

Humerus and Elbow Injuries

Matthew Salzberg and Kelly Bookman

KEY CONCEPTS

- Clinical decision rules for the elbow joint have not been validated. Radiographs should be obtained when there is limitation in range of motion, moderate to severe pain, obvious deformity, joint effusion, or significant tenderness or crepitus over any of the bony prominences or the radial head.
- The threshold for radiographic imaging should be lower in pediatric patients (with the exception of radial head subluxations), owing to the presence of open growth plates and limitations to the physical examination.
- Injuries that result in neurovascular compromise necessitate prompt intervention and consultation with an orthopedic specialist for reduction and potential operative intervention.
- In children with a traumatic wrist injury, normal radiographs should prompt consideration of an elbow injury causing referred pain to the wrist.
- On lateral elbow x-ray, a small anterior fat pad, parallel to the anterior surface of the humerus, can be a normal finding. Any convex ("sail sign") anterior fat pad and all posterior fat pads are pathological and indicate the presence of joint effusion.
- In the setting of trauma, patients with a radiological posterior fat pad sign of the elbow are assumed to have an intra-articular skeletal injury. In adults, a posterior fat pad sign is indicative of a radial head fracture, whereas in children, a supracondylar fracture is more likely. In the absence of trauma, inflammation and infection also cause effusions with positive fat pad signs.
- Radial nerve injury is the most common complication of humeral fractures. This is most often a benign neurapraxia that resolves spontaneously. Radial nerve injuries associated with penetrating trauma or open fractures are likely to represent anatomical disruption requiring operative exploration.
- The radius and ulna, bound together firmly by the annular ligament and interosseous membrane, typically displace as a unit and dislocate posteriorly following a traumatic injury.
- Biceps tendon rupture is more common in men, between ages 40 to 60, resulting from an unexpected extension force applied to the arm flexed at 90 degrees. Smoking, diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy may predispose to this injury.

FOUNDATIONS

Background and Importance

Injuries in the region of the elbow can be difficult to diagnose and have a high potential for complications and residual disability. Recognition of neurovascular and soft tissue complications improves the outcome in many of these injuries.

Anatomy, Physiology, and Pathophysiology

Knowledge of the relevant anatomy, mechanisms of injury, and appropriate management techniques, as well as knowing when to refer to or consult with orthopedic specialists will improve outcomes. The essential anatomy of the elbow region, as it relates to acute injury, is shown in Figs. 44.1–44.4.

GENERAL CLINICAL FEATURES

The history includes a description of the mechanisms of the traumatic event, pain characteristics including quality, duration, location, effects of movement, exacerbating or alleviating factors, severity, and radiation, in addition to concomitant injury or systemic complaint. Past medical history should include occupational factors and prior or chronic problems with the affected joint or other bones or joints. Numbness or weakness distal to the injury may indicate neurovascular injury. Pediatric orthopedic injuries, including those caused by abuse, are discussed in Chapters 160 and 172.

Examination begins with simple inspection and comparison with the contralateral limb. The position in which the extremity is held should be noted. Deformity may indicate fracture, dislocation, or hematoma. Range of motion may be evaluated, depending on the appearance of the extremity and suspicion of injury, but general manipulation of the acute injured extremity should be minimized. Bony prominences are palpated with notation of specific areas of tenderness. Crepitus, bony deformity, and pain in an acutely injured limb are virtually diagnostic of a fracture. The radial head specifically is palpated for tenderness. Intra-articular elbow fractures, including those of the radial head, are universally associated with effusion (hemarthrosis). Elbow effusions are notoriously difficult to discern on examination but are readily identified on lateral radiographs (Fig. 44.5). The extremity should be inspected for swelling, compromised circulation, or any wound that may indicate an open fracture.

In addition to the elbow region itself, focused examination incudes a thorough evaluation of the distal neurovascular status of the extremity. The presence of the brachial, radial, and ulnar pulses is confirmed by palpation. The ulnar pulse is more difficult to palpate than the radial pulse and may not be palpable in some normally healthy, uninjured patients. The radial, median, and ulnar nerve all transit the elbow in close proximity to major bony structures, so their motor and sensory functions require meticulous evaluation. The radial nerve can be tested by evaluating sensation to the dorsum of the hand and wrist extension. The median nerve should be tested for sensory function by assessing sensation at the lateral aspect of the thumb and for motor function by having the patient perform an "okay sign." The ulnar nerve provides sensation to the palmar aspect of the small digit and motor function to the medial interosseous muscles, which can be tested by having the patient abduct the small finger from the ring finger against pressure.

When movement of the elbow is possible without significant pain, the range of motion of the elbow in all planes (i.e., flexion-extension and pronation-supination) is determined. Inability to tolerate even

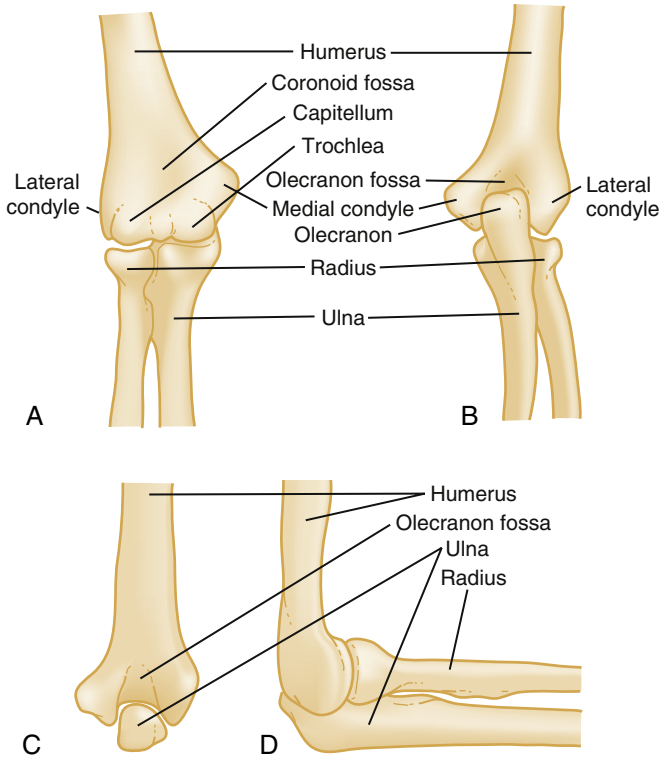


Fig. 44.1 Bony Anatomy of Distal Humerus and Elbow Region. (A) Anterior view. (B) Posterior view. (C) Posterior view, 90 degrees flexion. (D) Lateral view. Right elbow is shown. (Adapted from Connolly JF. *DePalma's management of fractures and dislocations*. Philadelphia, PA: WB Saunders; 1981.)

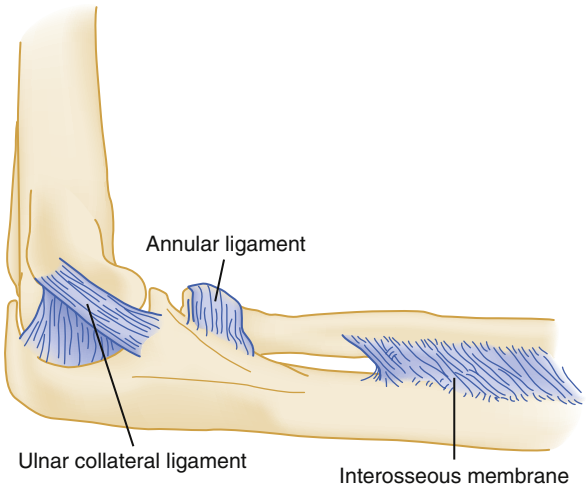
minimal passive movement often indicates dislocation or fracture. With the forearm supinated, the normal range of motion is 0 degrees in full extension to 150 degrees in full flexion. A mild degree of hyperextension is normal in some individuals and should be symmetric. With the elbow flexed at 90 degrees and the thumb facing up, the forearm normally supinates and pronates 90 degrees. Range-of-motion testing may be limited by pain and nearly impossible with severe injuries. These examination maneuvers can be delayed until after radiographic evaluation.

GENERAL DIFFERENTIAL DIAGNOSES

Injuries in the region of the shaft of the humerus and regions of the elbow fall into several categories including fractures, dislocations, subluxations, and soft tissue disorders (Table 44.1).

GENERAL DIAGNOSTIC TESTING

Most elbow and humerus injuries are evaluated radiographically, although on occasion, history and clinical examination alone are sufficient to make a diagnosis (e.g., minor mechanical fall with minimal pain, full range of motion, and no significant bony tenderness). There are no validated clinical decision rules for the elbow, so radiography should be performed when there is moderate to severe pain, significant limitation in range of motion, obvious deformity, swelling or effusion, or significant tenderness over any of the bony prominences or the radial head. With the exception of children with an apparent nursemaids' elbow (radial head subluxation), radiography should be used in virtually all pediatric elbow injuries with any bony tenderness on examination to assess for possible growth plate injury.



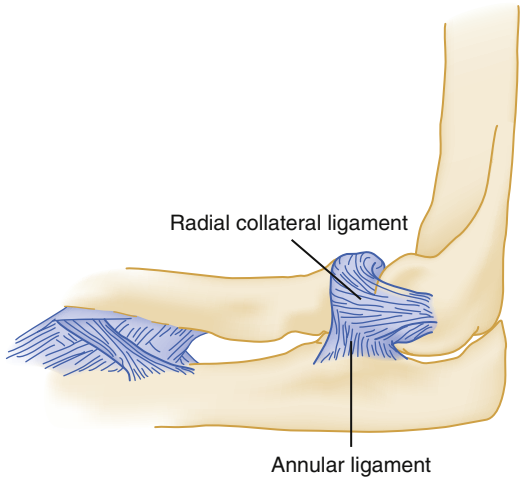


Fig. 44.2 Ligamentous Structures of Elbow. (From Simon R, Koenigsknecht S. *Emergency orthopaedics: the extremities*. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

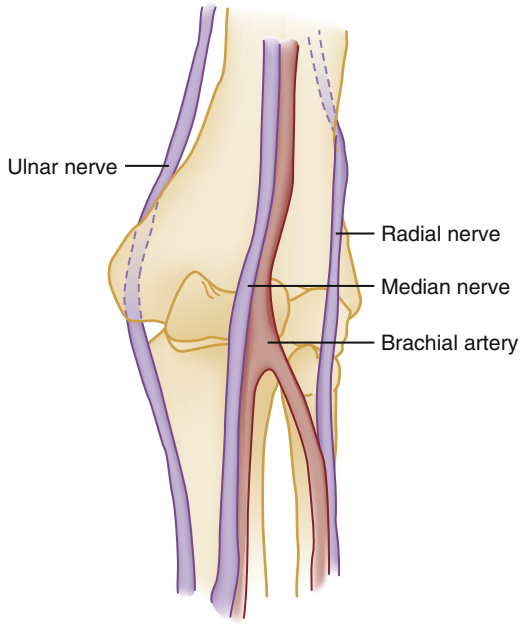


Fig. 44.3 Neurovascular Structures of Elbow Region. Volar surface of left elbow is shown.

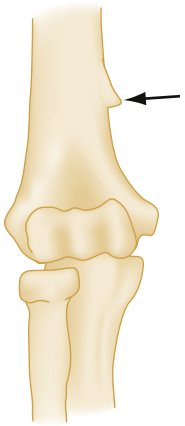
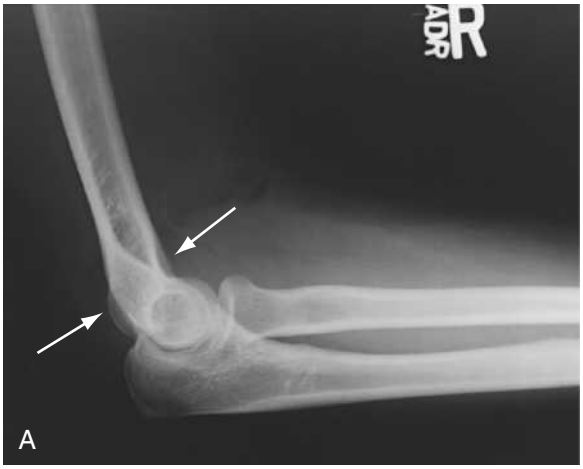


Fig. 44.4 Supracondylar process of the humerus *(arrow)* is present in approximately 2.5% of cases just proximal to the medial epicondyle. Volar surface of right elbow is shown.

Routine views of the elbow include at least the anteroposterior and lateral views, with oblique views when indicated. Anteroposterior and oblique views are taken with the elbow extended. The lateral view is taken with the elbow in 90 degrees of flexion and the thumb pointing upward. Positioning of the elbow is critical because anything other than a true lateral view makes accurate interpretation of soft tissue findings and alignment difficult.

Most fractures in the elbow region are identifiable on plain film, but radial head and subtle supracondylar fractures may be difficult to visualize. Radiographic examination of the elbow for the presence of fat pads secondary to traumatic effusion provides additional clues. The normal cortex of the radius is smooth and has a gentle continuous concave sweep. If consistent with history and physical findings, any disruption of this smooth arc is considered evidence of fracture. Abnormalities within the soft tissues on elbow films are particularly important and may be the only radiographic sign of a fracture. Normally, fat surrounding the proximal elbow joint is hidden in the concavity of the olecranon and coronoid fossae. The elbow normally has a narrow strip of lucency anteriorly, parallel to the anterior surface of the distal humerus (the anterior fat pad). The presence of a posterior fat pad is not considered a normal finding. Injuries that produce intra-articular hemorrhage cause distention of the synovium and displace the fat out of the fossa, making the posterior fat pad visible on lateral radiographic views. This intra-articular swelling displaces the anterior fat farther anteriorly, where it takes the shape of a main sail of a boat. Thus, this radiographic finding is commonly referred to as the "*sail sign*." Displacement of the posterior fat pad makes it visible on the lateral radiograph as a "posterior fat pad sign" (see Fig. 44.5). In the setting of trauma, more than 95% of patients with a posterior fat pad sign have an intra-articular skeletal injury. These soft tissue findings occur even with subtle fractures, and when present in the setting of trauma, an occult fracture should be suspected. In adults without an identifiable fracture on radiograph, fat pad signs most often indicate a radial head fracture, whereas in children a supracondylar fracture is the more likely. In the absence of trauma, the presence of a fat pad suggests other causes of effusion (e.g., inflammation or infection). Of note, the fat pad sign may be absent in fractures where the injury is severe enough to rupture the capsule.

Additional imaging modalities in the emergency department (ED), such as diagnostic ultrasound, computed tomography (CT) scanning, or magnetic resonance imaging (MRI) may be considered. Ultrasound may be considered as a quick bedside modality to assist in the diagnosis of fractures, most easily utilized on long bone injuries. This may



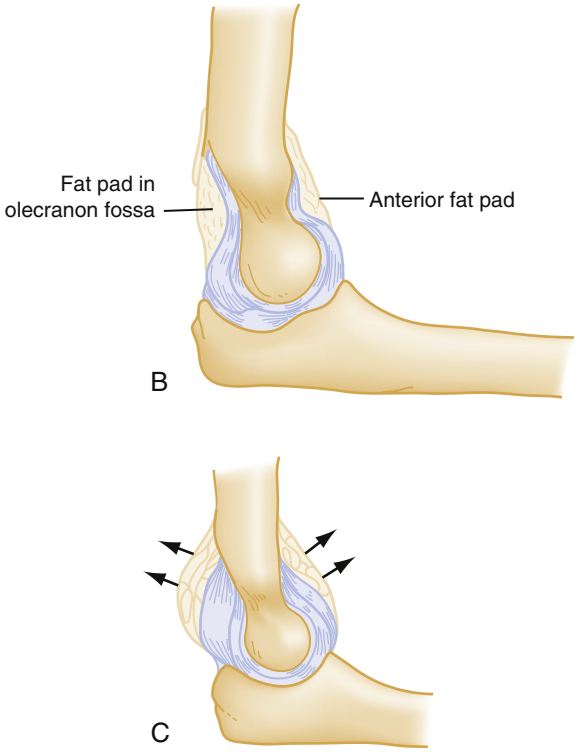


Fig. 44.5 (A) Anterior and posterior fat pads on lateral study *(arrows)*. (B) The anterior fat pad is normally a thin radiolucent stripe; the posterior fat pad is not visible. (C) An effusion displaces both fat pads. This posterior fat pad is now visible.

be especially useful in the hemodynamically unstable trauma patient during resuscitation.[1] MRI (or less commonly) CT imaging may be considered if there is high suspicion for a fracture on plain imaging that only reveals a traumatic effusion. Classically, this may be applied to pediatric elbow injuries to identify underlying fractures not visible on standard imaging.

GENERAL MANAGEMENT

General management should begin with an appropriate evaluation for additional traumatic injuries, pain control with appropriate analgesics, and attempt at providing patient comfort with support for the injured extremity. Once a potential fracture is identified, prompt neurovascular evaluation should be performed. Although a warm hand with

TABLE 44.1 Injuries to the Humerus and Elbow

Injury Site				Mechanism/Exam		Imaging
Humerus fractures	Shaft of the humerus fractures			Direct blow, severe twisting	Localized tenderness, may be shortened or rotated	Obvious fracture line
	Distal humerus fractures					
		Supracondylar (most common in children)				
			Extension	Fall on the outstretched hand when the elbow is either fully extended or hyperextended	Arm is held at the side and has a characteristic S-shaped configuration	Obvious fracture line or maybe the presence of a posterior fat pad or an abnormal anterior humeral line
			Flexion	Direct blow to the flexed elbow	Forearm is supported with the opposite hand with the elbow flexed to 90 degrees	Increase in the anterior angulation of the distal supracondylar fragment or gross displacement of the distal fragment proximal and anterior to the distal end of the proximal fragment
		Transcondylar (more common in elderly)		Mechanism of injury that is similar to that for supracondylar injuries	Localized tenderness	Fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface
			Extension	Mechanism of injury that is similar to that for supracondylar injuries	Localized tenderness	Fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface
			Flexion	Mechanism of injury that is similar to that for supracondylar injuries	Localized tenderness	Fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface
		Intercondylar		Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Nondisplaced	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Separated	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
			Separated and rotated	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment

Injury Site				Mechanism/Exam		Imaging
			Combination with articular surfaces	Direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end	Localized tenderness	T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment
		Condylar			Localized tenderness	Widening of the intercondylar distance
			Medial	Valgus force on the extended elbow	Localized tenderness	Widening of the intercondylar distance
			Lateral	Direct blow to the lateral aspect of the flexed elbow or a force that results in adduction and hyperextension with avulsion of the lateral condyle	Localized tenderness	Widening of the intercondylar distance
			Articular surface		Localized tenderness	Widening of the intercondylar distance
		Capitellum		Fall on outstretched hand	Localized tenderness, pain worse with flexion	Fragment lying anterior and proximal to the main portion of the capitellum
		Trochlea		Fall on outstretched hand	Localized tenderness with limited ROM	Fragment visible lying on the medial side of the joint, just distal to the medial epicondyle, signs of joint effusion
		Epicondylar		Fall on outstretched hand, repetitive valgus stress, direct blow	Elbow is held in flexion and any movement is resisted	A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation; evaluate for fracture fragments
			Medial	Fall on outstretched hand, repetitive valgus stress, direct blow	Elbow is held in flexion and any movement is resisted	A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation; evaluate for fracture fragments
			Lateral	Fall on outstretched hand, repetitive valgus stress, direct blow	Elbow is held in flexion and any movement is resisted	A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation; evaluate for fracture fragments
Radius/ulnar fractures	Radial head fracture			Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
		Nondisplaced		Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
		Displaced		Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign
		Comminuted		Fall on outstretched hand	Localized tenderness over radial head or pain with passive rotation of forearm	Range from subtle disruption of the gradual sweep of the radial neck and head surface to obvious displaced or comminuted fracture, positive fat pad sign

Continued

TABLE 44.1 Injuries to the Humerus and Elbow—cont'd

Injury Site				Mechanism/Exam		Imaging
	Ulnar fracture					
		Olecranon fracture		Direct blow, forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon	Localized tenderness, palpable separation at fracture site, inability to extend the elbow against force	Obvious fracture line
		Coronoid fracture		Direct blow, forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon	Localized tenderness, palpable separation at fracture site, inability to extend the elbow against force	Obvious fracture line
Subluxations/ dislocations	Elbow dislocation					Obvious dislocation, must assess for concurrent fractures
		Posterior		Fall on the outstretched hand or wrist, the elbow being either extended or hyperextended	Elbow in flexion at approximately 45 degrees and have marked prominence of the olecranon	Obvious dislocation, must assess for concurrent fractures
		Anterior		Blow from behind to the olecranon while the elbow is in the flexed position	Upper arm appears shortened, the forearm elongated and supinated, the elbow is fully extended and the olecranon fossa is palpable posteriorly	Obvious dislocation, must assess for concurrent fractures
		Medial/lateral		Mechanism similar to that in posterior dislocations, with a vector of force displacing the ulna and radius as a unit either medially or laterally	Obvious deformity either medially or laterally	Obvious dislocation, must assess for concurrent fractures
	Radial head subluxation			Forearm pulled while in pronation with the elbow extended, direct blow, twisting	Arm held in passive pronation, with slight flexion at the elbow; refuses to move the arm, localized tenderness, swelling, ecchymosis and deformity are absent	Radiographs are not necessary and are rarely positive
Soft tissue	Epicondylitis			Repetitive pronation and supination of the forearm	Dull pain over lateral aspect of elbow, the lateral epicondyle or radiohumeral joint, increased by grasping or twisting motions	Radiographs normal or may have calcifications
	Olecranon bursitis			Repetitive minor trauma, inflammatory	Progressive pain, tenderness, and swelling over olecranon	None
	Bicep tendon rupture					
			Proximal	Repetitive microtrauma to the tendon	Visible defect at top of bicipital groove with bunching of the muscle distally, flexion of elbow produces pain at proximal insertion but flexion remains intact	None
			Distal	Extension force applied to the arm flexed at 90 degrees	Pain and tearing in the antecubital region, visible deformity and palpable defect of the biceps muscle belly with weakness of elbow flexion and supination	None

normal color suggests adequate tissue perfusion, a handheld Doppler device is often required to evaluate major vessel flow if significant swelling is present or if the pulses are not palpable. Poor perfusion may be the result of a direct arterial injury, compression or kinking from a fracture or dislocation, or compartment syndrome. Identification of arterial compromise or injury warrants consultation with an orthopedic or vascular surgeon (see Chapter 40). Compartment syndrome is discussed in Chapter 41. Orthopedic consultation and measurement of compartment pressures is indicated for patients who are suspected of having a compartment syndrome.

GENERAL DISPOSITION

General disposition for patients with humerus or elbow fractures depends on several considerations. Common fracture factors include need for emergent operative intervention and need for neurovascular checks or compartment checks. Additionally, patient-centered factors may include pain control, ability to perform activities of daily life, and ability to follow instructions regarding fracture care. Given the previous factors, a large proportion of upper extremity, humerus, and elbow injuries can be discharged home with appropriate orthopedic specialty follow-up.

Specific Fractures

Shaft of the Humerus

Clinical features of humeral shaft fractures. Fractures of the humeral shaft commonly result from a direct blow to the arm, severe twisting, or a fall on an outstretched hand. Rarely, fractures may be caused by abrupt muscle contraction, such as occurs when a javelin or baseball is thrown. The shaft of the humerus most commonly fractures in the middle third in a transverse fashion. The patient reports localized pain, which is often severe in nature, and the arm is visibly swollen and cannot be used. When a fracture is complete, bony crepitus is felt in the shaft of the humerus with the slightest manipulation of the arm. The arm may be shortened or rotated, depending on the displacement of the fracture fragments. When the fracture is incomplete, there is bony tenderness and swelling without obvious deformity.

Diagnostic testing for humeral shaft fractures. Imaging studies should routinely include the shoulder and elbow joints. The humerus is a common site for benign tumors, unicameral cysts, and primary bone malignancies, as well as a common site for metastatic disease. Thinning of the cortex and abnormal osteoblastic or osteoclastic activity are evidence of a pathologic fracture (Fig. 44.6). Pathologic lesions may require orthopedic surgical intervention, though once a fracture occurs, a multidisciplinary approach with oncology should occur to determine the best course of surgical intervention. While these fractures may be stabilized with treatment such as plates, pins, intramedullary nails, cement, and joint replacement, these underlying fractures do not heal well without concomitant treatment of the underlying pathologic condition.[2]

Management of humeral shaft fractures. Isolated, closed fractures are treated with a high degree of success. Attempts at fracture reduction and external immobilization are generally unnecessary and may be detrimental to healing. Fractures that are nondisplaced or minimally displaced are immobilized by adding a coaptation, or "sugar-tong" splint, to the sling and swathe (Fig. 44.7). The coaptation splint is often replaced by a functional brace after the first 10 to 14 days. If the fracture is grossly displaced or comminuted, the hanging cast technique is preferable. This technique is especially effective with spiral fractures (Fig. 44.8). Care is taken not to make the cast too heavy because this would distract fracture fragments or too tight as this may compromise circulation. The hanging cast has the disadvantage of using gravity for traction and requires that the patient remain upright at all times, including during sleep, a situation that many patients find intolerable. Neurovascular examination should be repeated and documented before and after the application of any splint or cast because entrapment of the nerve between fragments can occur after these interventions. Open reduction and internal fixation (Fig. 44.9) are necessary for open fractures, presence of multiple injuries that preclude mobilization, bilateral fractures, poor reduction, poor patient compliance, failure of closed treatment, and fractures through pathologic bone. Although the success rate with nonoperative intervention is about 80%, patients should be included in treatment decisions regarding nonoperative versus operative intervention because operative intervention may decrease recovery time resulting in earlier return to work.[3]

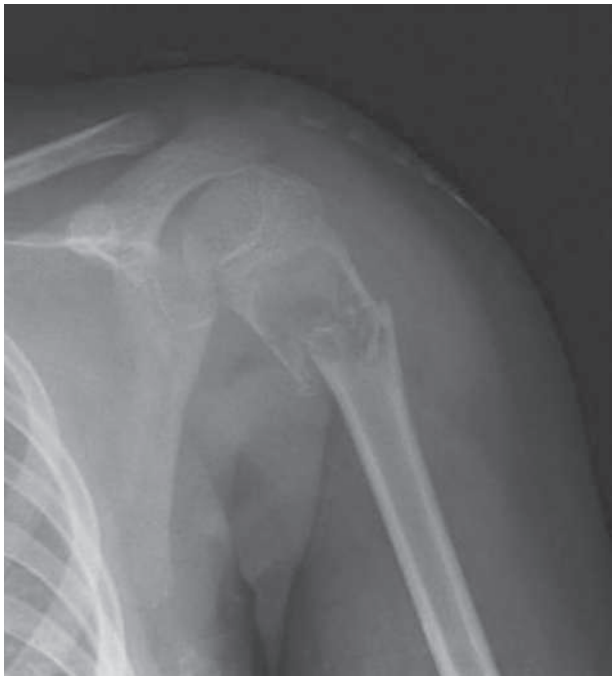


Fig. 44.6 Pathologic Fracture of Proximal Humerus.

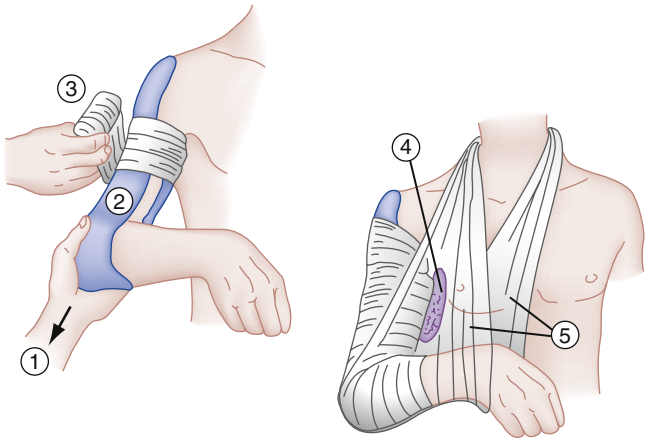


Fig. 44.7 Sugar-Tong Splint for Humeral Shaft Fractures. Gentle traction is applied (1) as the splint is placed (2) from over the deltoid laterally, under the elbow, and up into the axilla. An elastic wrap holds the splint in place (3). The axilla must be padded (4), and a sling is used (5). (Adapted from Connolly JF. *DePalma's management of fractures and dislocations.* Philadelphia, PA: WB Saunders; 1981.)

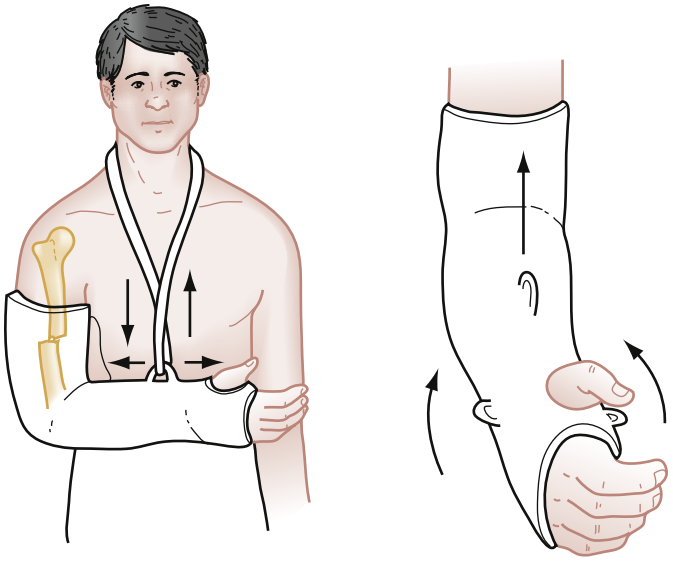


Fig. 44.8 Hanging Cast Technique.

For open fractures, the wound should be covered with normal saline soaked gauze. Splinting can be done for comfort during patient manipulation but should be limited. Cefazolin (2 g intravenously) is given, and consultation is obtained by orthopedic surgery for emergent operative washout. Additional antibiotics, such as an aminoglycoside or quinolone may be used as an alternate for gram negative coverage. For potential clostridial infection (e.g., contaminated farm injuries), clostridial coverage including clindamycin or metronidazole may also be indicated.[4]

The most common complication, radial nerve injury, occurs in up to 15% of humerus fractures.[5] Radial nerve injury causes wrist drop with loss of the ability to extend the fingers and thumb.[6] This nerve injury is most often a benign neurapraxia that resolves spontaneously in approximately 80% to 90% of cases without operative intervention, although recovery may take 6 to 9 months.[6] Of those with radial nerve palsy who fail conservative treatment, upwards of 90% of patients will recover.[5] Patients should be advised of this possible complication prior to discharge, and follow-up with an orthopedic surgeon should be arranged from the ED. Exploration and internal fixation are indicated if the radial nerve palsy develops after manipulation, because this is highly suggestive of nerve entrapment. Radial nerve injuries associated with penetrating trauma or open fractures are likely to be caused by anatomical nerve disruption and generally warrant operative exploration. Median and ulnar nerve injuries are rare and usually secondary to penetrating trauma. Injuries to the brachial artery occur rarely and, if suspected, vascular surgery consultation is indicated, often with angiography or other vascular studies.

Disposition of humeral shaft fractures. All patients with humeral shaft fractures should be referred to an orthopedic surgeon for further evaluation within 48 hours after treatment in the ED to ensure that the alignment has been maintained, no neurological deficits have emerged, and pain is adequately controlled. Emergent referral to an orthopedist is recommended for patients with evidence of radial nerve injury, severely displaced or comminuted fractures, open fractures, or fractures associated with forearm fractures in the same injured extremity.

Distal Humerus

Supracondylar fractures. Distal humerus fractures that occur proximal to the epicondyles are called supracondylar fractures. This type of fracture is almost exclusively an injury of the immature skeleton, with a peak incidence in children 5 to 10 years old.[7] This injury rarely occurs after age 15 and accounts for approximately one half of all elbow fractures and one third of pediatric limb fractures. In children, the tensile strength of the collateral ligaments and joint capsule of the elbow is greater than that of bone. In adults, the reverse is true, and a fall or accident that would result in a supracondylar fracture in children would likely result in a posterior elbow dislocation

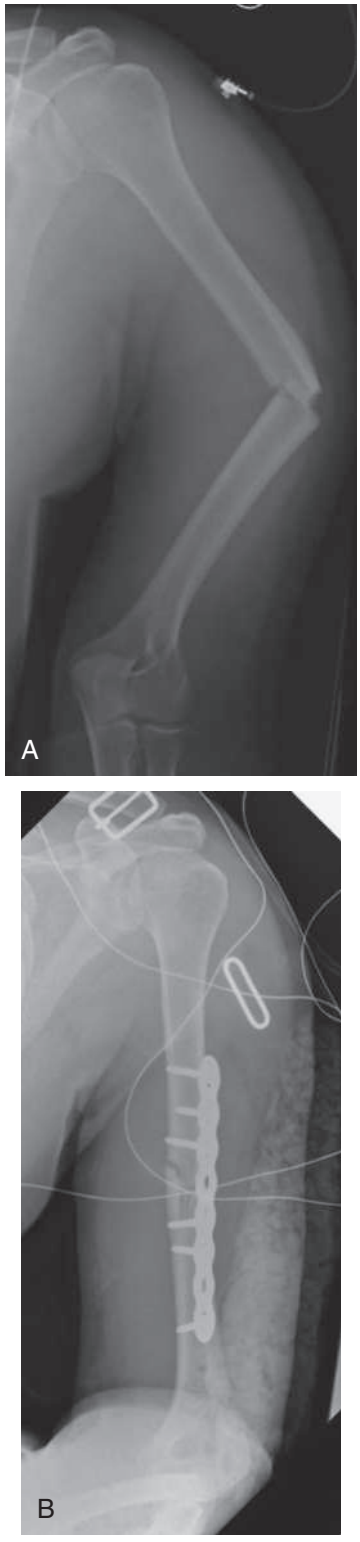


Fig. 44.9 Midshaft humerus fracture before (A) and after (B) open reduction and internal fixation.

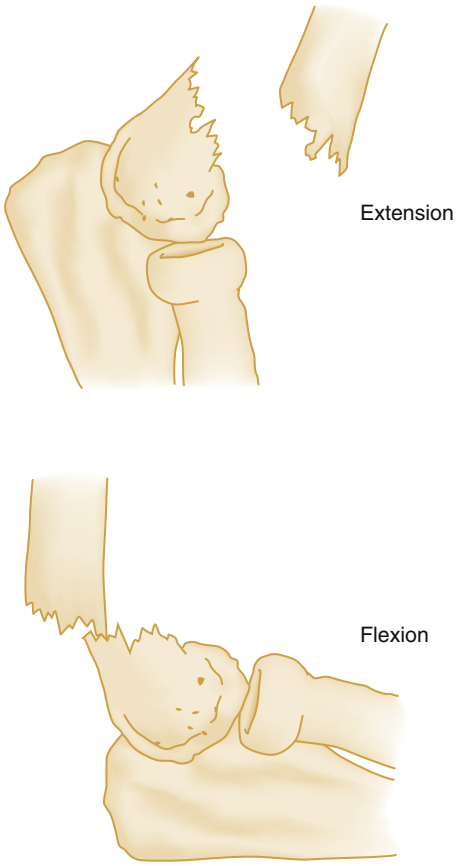


Fig. 44.10 Supracondylar Fractures, Extension and Flexion. (Adapted from Simon R, Koenigsknecht S. *Emergency orthopaedics: the extremities*. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

in an adult. Supracondylar fractures are classified as either extension or flexion fractures, depending on the mechanism of injury and the displacement of the distal fragment. Of these injuries, 98% are of the extension type.

Extension type supracondylar fractures.

Clinical features of extension type supracondylar fractures. Extension supracondylar fractures occur as a consequence of a fall on the outstretched hand when the elbow is either fully extended or hyperextended (e.g., a fall off the playground "monkey bars"). The strong action of the triceps tends to pull and displace the distal fragment in a posterior and proximal direction. In children with extension-type supracondylar fractures, the arm is held at the side and has a characteristic S-shaped configuration, whereas with flexion-type supracondylar fractures, the forearm is supported with the opposite hand with the elbow flexed to 90 degrees. There may be anterior angulation of the sharp distal end of the proximal fragment into the antecubital fossa, which could injure the brachial artery and median nerve (Fig. 44.10). In most cases, however, the brachialis muscle protects the anterior neurovascular structures from injury. Because this fracture primarily occurs in children, 25% of supracondylar fractures are of the greenstick variety, with the posterior cortex remaining intact. Subtle changes (e.g., the presence of a posterior fat pad or an abnormal anterior humeral line) may be the only radiographic clues to the presence of a fracture (Fig. 44.11). Ten percent of children lose the radial pulse temporarily, most often as a result of swelling and not direct brachial artery injury. Fracture reduction, avoiding flexing the elbow more than 90 degrees, and elevating the arm help prevent secondary obstruction to arterial flow. Nerve injuries occur in approximately 10% of these injuries,

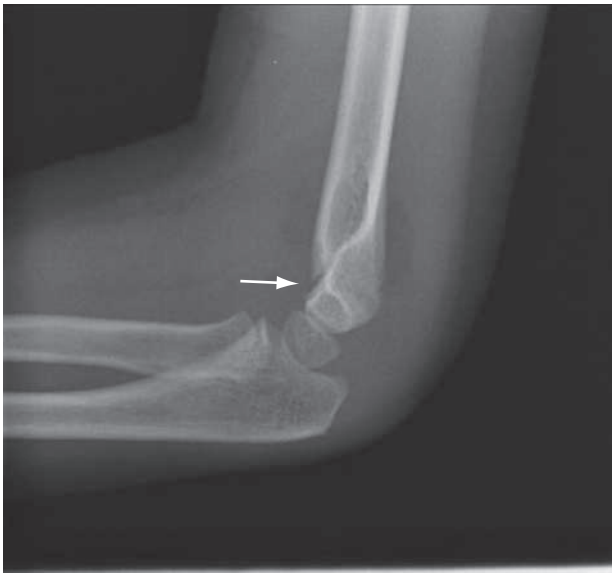


Fig. 44.11 Supracondylar fracture *(arrow)* with anterior and posterior fat pad.

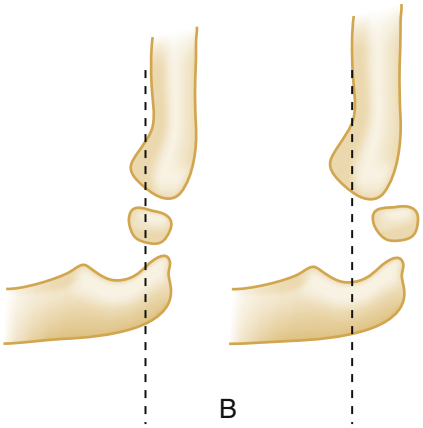


Fig. 44.12 (A) A line drawn down the anterior surface of the humerus on a lateral film should transect the middle third of the capitellum. (B) With an extension supracondylar fracture, the line passes more anteriorly. (From Simon R, Koenigsknecht S. *Emergency orthopaedics: the extremities*. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

but the incidence increases to a range of 20% to 50% with increasing severity of fracture displacement.[8,9] The anterior interosseous nerve is the most commonly injured, followed by the radial, median, and ulnar nerves. Most deficits seen at the time of injury are neurapraxias that resolve with rest and conservative management. Motor function returns within 7 to 12 weeks, whereas recovery of sensation may take over 6 months, though the recovery of injuries with multiple nerve injuries may take longer than that of isolated nerve injuries.[8,10]

Diagnostic testing of extension-type supracondylar fractures. Two diagnostic aids in evaluating for possible supracondylar fractures include using the anterior humeral line and evaluation of Baumann's angle. The *anterior humeral line* is a line drawn on a lateral radiograph along the anterior surface of the humerus through the elbow. Normally, this line transects the middle third of the capitellum (Fig. 44.12). With an extension supracondylar fracture, this line either transects the anterior third of the capitellum or passes entirely anterior to it. An abnormal relationship between the anterior-humeral line and capitellum may be the only radiographic evidence of a minimally displaced supracondylar fracture and is a presumptive finding of a

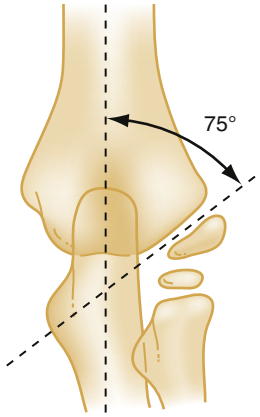


Fig. 44.13 Baumann's Angle as Measured on Anteroposterior Film. (From Worlock P. Supracondylar fractures of the humerus. *J Bone Joint Surg Br.* 1986;68:755.)

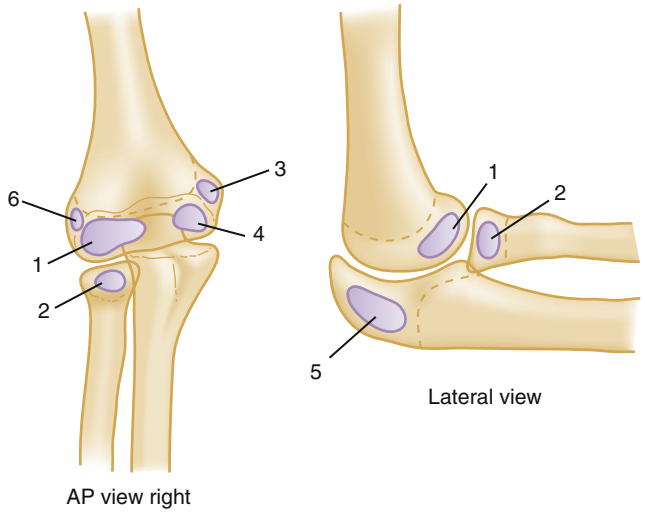


Fig. 44.14 Secondary Growth Centers of the Elbow. 1, Capitellum. 2, Radial head. 3, Medial epicondyle. 4, Trochlea. 5, Olecranon. 6, Lateral epicondyle. (From Townsend DJ, Bassett GS. Common elbow fractures in children. *Am Fam Physician.* 1996;53:2031.)

fracture. *Baumann's angle* is the intersection of a line drawn on the anteroposterior film through the midshaft of the humerus and the growth plate of the capitellum defines an angle of approximately 75 degrees (Fig. 44.13).[11] Radiographic evaluation of the elbow in children is challenging because of the presence of multiple ossification centers (Fig. 44.14). Comparison views of the uninjured elbow are often helpful in distinguishing fractures from the normal epiphyses and ossification centers. Table 44.2 lists the typical age of first appearance and fusion of ossification centers.

Based on radiographic findings, supracondylar fractures are classified into four types: type I, minimal or no displacement; type IIA, displaced fracture, posterior cortex intact with no rotational component; type IIB, displaced fracture, posterior cortex intact with a rotational component; type III, totally displaced fracture, anterior and posterior cortex disrupted; and type IV, multidirectionally unstable due to complete circumferential periosteal disruption.[12]

Management and disposition of extension type supracondylar fractures. Current treatment recommendations for supracondylar fractures from the American Academy of Orthopedic Surgeons remain based on the modified Gartland classification (Box 44.1). Nondisplaced extension supracondylar fractures (type I) are immobilized primarily

TABLE 44.2 Ossification Centers of the Elbow: CRITOE

Ossification Centers	Age of Appearance
Capitellum	1–2
Radial head	4–5
Internal (medial) epicondyle	4–5
Trochlea	8–10
Olecranon	8–9
External (lateral) epicondyle	10–11

BOX 44.1 Gartland Classification for Supracondylar Fractures in Children

Type I: Minimal or no displacement
Type II: Displacement of the fracture but with the posterior cortex intact
  Type IIA: No rotational component
  Type IIB: Some rotational component
Type III: Displaced, no cortical contact, periosteal contact
  Type IIIA: No rotation of the fracture
  Type IIIB: Rotation present
Type IV: Complete disruption/displacement

for comfort and protection, because they are inherently stable. They are treated in a splint or cast flexed to 75 to 80 degrees with the forearm in neutral rotation.[8] Protected active range of motion is begun in approximately 3 weeks. Even without definite radiographic findings, a child with localized tenderness consistent with a supracondylar fracture should be splinted and referred for follow-up examination within 24 to 48 hours. A plain radiograph performed a few weeks after the injury may reveal periosteal new bone formation in the supracondylar region. Patients with a type I fracture can be discharged safely from the ED with instructions to elevate the extremity, apply ice, and have a follow-up evaluation in 1 to 2 days. Fractures that require manipulation usually warrant admission to the hospital to ensure compliance and for neurovascular monitoring. Minimally displaced (type II) fractures that are stable after reduction can be treated with splinting or casting with the elbow flexed. We recommend flexion to 110 to 120 degrees for this injury.[7] This position uses the intact posterior periosteum as a tension band to hold the reduction; however, if swelling or circulatory obstruction prevents this amount of flexion, it should not be used. The greater the flexion at the elbow, the greater is the chance of vascular impairment. When swelling peaks at 24 to 48 hours, the risk of vascular obstruction and compartment syndrome is highest. Occasionally, these injuries require percutaneous pinning to maintain stability, especially if a significant rotational component is present.[8] Percutaneous pinning of fractures after reduction has grown in popularity in recent years and is recommended for type IIB fractures with some studies showing better outcomes with pinning than without.[8,13] Type III totally displaced fractures generally are the result of more severe injuries that produce more swelling than type I or type II injuries. Displacement necessitates the reestablishment of length, increases the chance of varus deformity, and increases the chances of interposed soft tissues and neurovascular injury. For all these reasons, patients with type III fractures require emergency orthopedic consultation in the ED and should be admitted to the hospital for frequent neurovascular checks and closed reduction and percutaneous pinning. Open reduction may be necessary if closed reduction is unsuccessful.[8] Reduction in the ED is indicated only when the displaced fracture is associated with vascular compromise

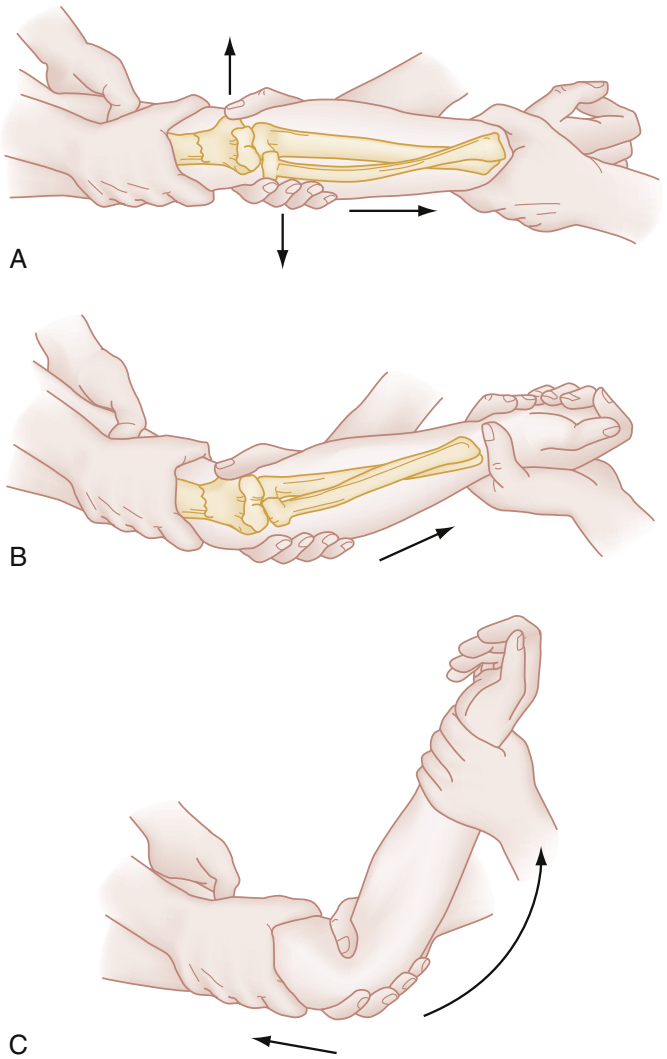


Fig. 44.15 (A) to (C) Steps in reduction of displaced supracondylar fracture.

that threatens the viability of the extremity. Under these conditions, closed reduction should be attempted. After appropriate procedural sedation, an assistant fixes the arm of the patient. The clinician grasps the patient's wrist and applies steady, firm traction in line with the long axis of the limb (Fig. 44.15A). The forearm is kept in the neutral, thumb-up position. While traction is maintained, correction of any medial or lateral displacement is accomplished with the other hand at the elbow (see Fig. 44.15B). If the distal fragment is displaced laterally, it is pushed inward; if it is displaced medially, it is pushed outward. After the length has been restored and the angular deformity has been corrected, the thumb of the free hand is placed over the anterior surface of the proximal fragment with the fingers behind the olecranon. While traction is maintained, the elbow is gently flexed to just beyond 90 degrees (see Fig. 44.15C). Angulation is corrected to a normal carrying angle. Only one attempt should be made at this manipulation technique. Multiple attempts increase the likelihood of neurovascular injury and swelling. If reduction is unsuccessful, simple traction on the extended elbow may restore vascular supply. When reduction is performed, follow-up radiographs are obtained to ensure adequate reduction and neurovascular function is checked at frequent (hourly) intervals. Cylinder casts are not applied initially because they increase the risk of forearm ischemia; a posterior plaster splint

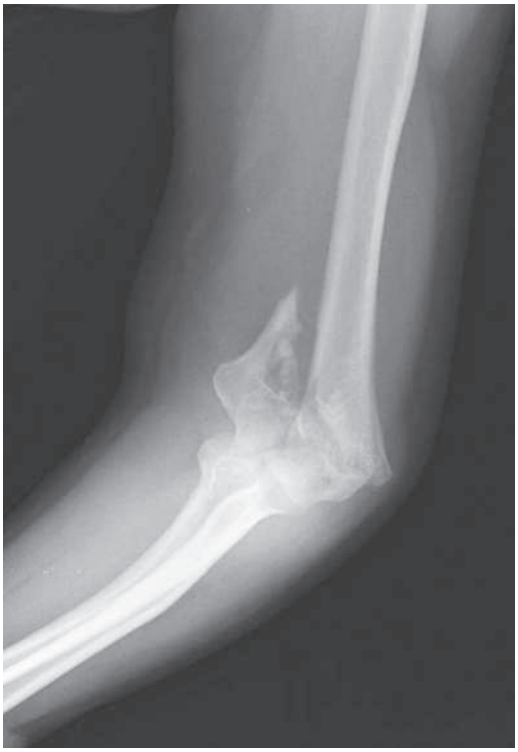


Fig. 44.16 Type III supracondylar fracture with significant displacement of distal fragment.

provides safe and adequate immobilization. Type IV injuries require emergent orthopedic consultation for operative intervention. These injuries represent a surgical challenge, but recent studies show that a satisfactory outcome can be achieved.[12]

Flexion type supracondylar fractures

Clinical features of flexion type supracondylar fractures. Flexion-type supracondylar injuries are much less common, with a reported frequency of about 2% of all supracondylar fractures. The mechanism of injury is a direct blow to the flexed elbow.

Diagnostic of flexion type supracondylar fractures. Plain films may reveal a simple increase in the anterior angulation of the distal supracondylar fragment or gross displacement of the distal fragment proximal and anterior to the distal end of the proximal fragment. In the latter case, the distal end of the proximal fragment protrudes posteriorly. A line drawn down the anterior humeral shaft (see earlier discussion in the extension type supracondylar fractures section) intersects the capitellum either normally or posteriorly in these fractures, depending on whether there is anterior displacement. The most common complication is nerve injury with injury to the ulnar nerve, occurring in over 90% of cases.[8] The radial and median nerves are rarely injured.

Management of flexion type supracondylar fractures. For flexion-type supracondylar injuries, when the posterior periosteum is torn, the anterior periosteum functions as a tension band with the arm in extension. In type I fracture, the periosteum is minimally displaced. These injuries do not need to be immobilized in extension. The elbow can be comfortably flexed and should be immobilized in a splint as with extension injuries. Type II and III injuries require emergent orthopedic consultation. Type II injuries are manipulated into extension and then either in a long arm cast or with percutaneous pins. Type III injuries are treated with closed reduction and percutaneous pinning but will require open reduction if closed reduction fails (Fig. 44.16).[8]

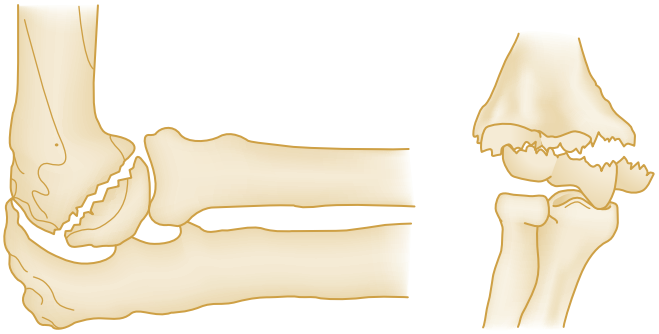


Fig. 44.17 Transcondylar Fracture of Distal Humerus. (*Left*, From Ruiz E, Cicero J. *Emergency management of skeletal injuries*. St Louis: Mosby; 1995. *Right*, Adapted from Simon R, Koenigsknecht S: *Emergency orthopaedics: the extremities*. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

Transcondylar Fractures

Clinical features of transcondylar fractures. Both extension and flexion types of transcondylar fractures have been described based on the position of the elbow when fractured. Extension types are the most common with a mechanism of injury that is similar to that for supracondylar injuries. In contrast to supracondylar fractures, however, the injury is more common in elderly individuals with fragile, osteoporotic bone.

Diagnostic testing of transcondylar fractures. Transcondylar (or dicondylar) fractures have a fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface (Fig. 44.17).

Management and disposition of transcondylar fractures. Transcondylar (or dicondylar) fractures are difficult to treat because the small distal fragment possesses little extra-articular bone, and only a small amount of bone contact is available for union. Orthopedic consultation in the ED should be obtained for these injuries. Both internal fixation and elbow arthroplasty are viable operative options, with internal fixation now supplanting primary elbow arthroplasty as the mainstay of treatment for most cases.

Intercondylar Fractures

Clinical features of intercondylar fractures. These injuries are rare and generally are seen in adults aged 50 to 70 years. The common mechanism of injury is direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end. Patients with intercondylar fractures complain of pain at the elbow, which on examination is tender to palpation. Neurovascular complications are not common with these injuries.

Diagnostic testing of intercondylar fractures. Good-quality anteroposterior and lateral radiographic views are essential in evaluating fracture displacement and comminution (Fig. 44.18). Intercondylar fractures are usually T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment (Fig. 44.19). The distal portion of the fracture extends to the articular surface of the distal humerus. CT may be used to delineate fracture patterns further.

Management and disposition of intercondylar fractures. Treatment of intercondylar fractures is challenging. The goal of treatment is to reestablish articular congruity and alignment and to begin active motion as soon as possible, most often through open reduction with rigid internal fixation. Closed treatment is typically restricted to elderly patients, patients with medical conditions that prohibit surgery, and certain patients with nondisplaced fractures; although recent literature

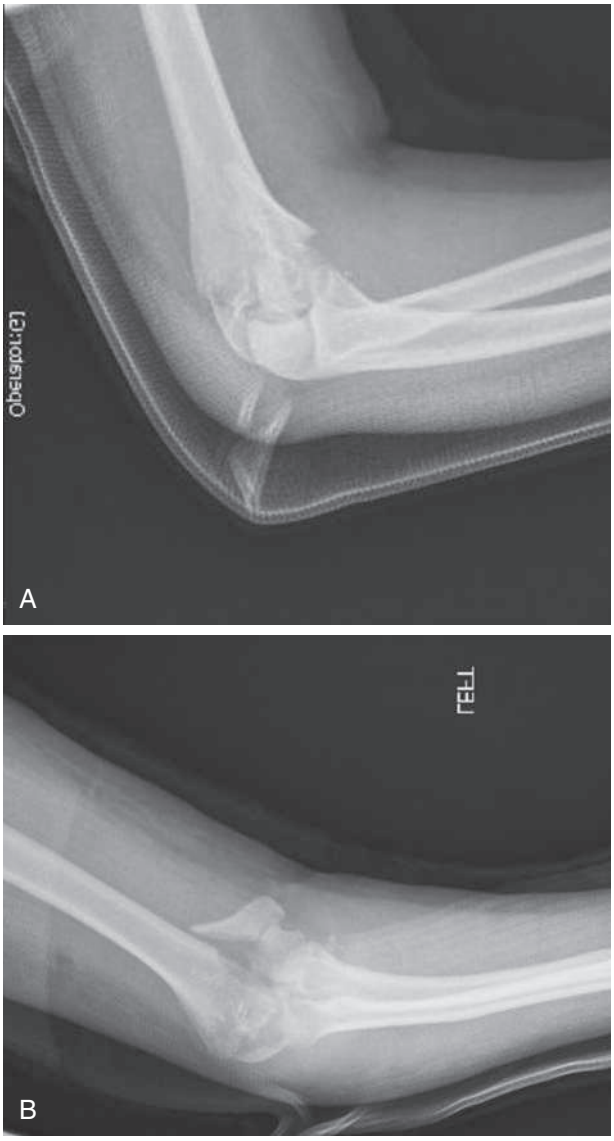


Fig. 44.18 Intercondylar fracture, type III. Lateral (A) and anteroposterior (B) views.

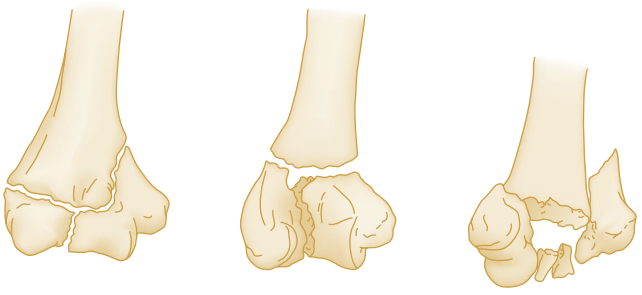


Fig. 44.19 Intercondylar T Fractures, Types I, II, and III. (From Connolly JF. *DePalma's management of fractures and dislocations*. Philadelphia, PA: WB Saunders; 1981.)

shows that both closed and open methods may have similar results in children.[14] These injuries require emergent orthopedic consultation. As with supracondylar fractures, manipulation should be avoided unless limb-threatening ischemia is present. Traction across the elbow

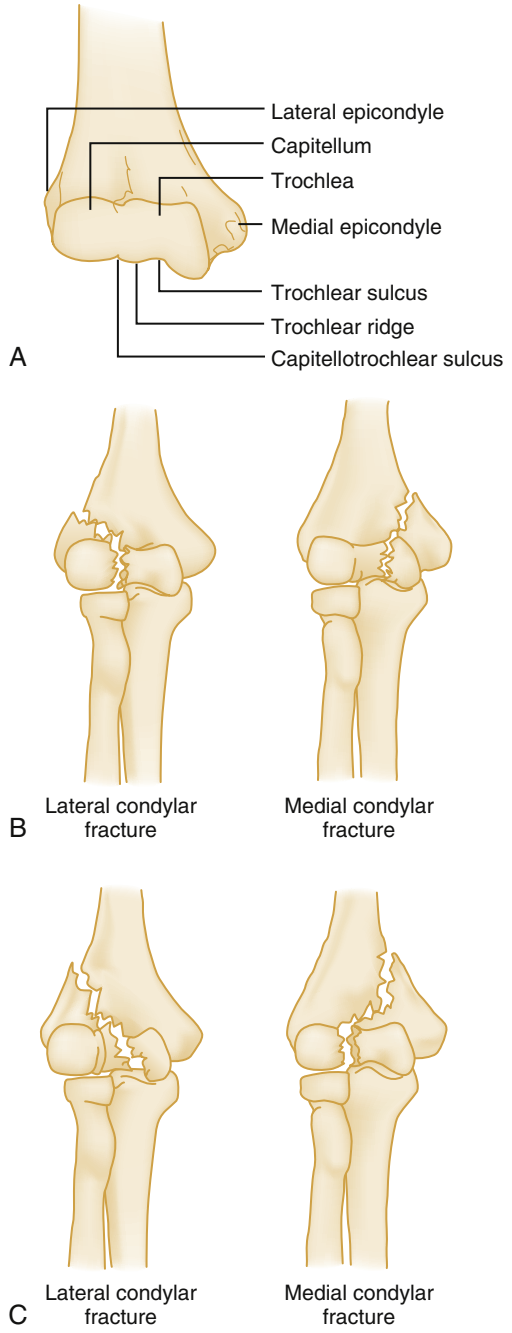


Fig. 44.20 Condylar Fractures. (A) Normal anatomy. (B) Lateral trochlear ridge not in fracture fragment (stable). (C) Lateral trochlear ridge included with fracture fragment (unstable). (Adapted from Simon R, Koenigsknecht S. *Emergency orthopaedics: the extremities.* 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

with the arm extended is helpful in restoring blood flow to an ischemic forearm.

Condylar Fractures

Clinical Features of condylar fractures. Condylar fractures are rare in adults and typically involve the articular surface and the nonarticular portion of the distal humerus, including the epicondyle (Fig. 44.20). Lateral condylar fractures are uncommon, although more frequent than fractures of the medial condyle. The mechanism of injury is either a direct blow to the lateral aspect of the flexed elbow or a force that results in adduction and hyperextension with avulsion of the lateral condyle. Medial condylar fractures are rare and result from either a direct blow to the apex of the flexed elbow or a fall on the outstretched hand with the elbow forced into a varus angulation. The presentation of condylar fractures is similar to that of other distal humerus fractures, with swelling, tenderness, and crepitus localized over either the medial or the lateral elbow. On palpation, independent motion of the involved condyle may be appreciated. In lateral condylar fractures, findings may be accentuated with movement of the radius. In children, lateral condyle fractures are the second most common fractures involving the elbow, after supracondylar fractures. The fracture has an age distribution similar to that of supracondylar fractures and occurs after a fall on the outstretched hand, with a varus stress applied to the extended arm. Tenderness and swelling are noted over the lateral aspect of the elbow. In general, children exhibit less swelling than with supracondylar fractures and neurovascular compromise is uncommon. Because of the location of the ulnar nerve, it is vitally important to test its function when this fracture is present. Medial condylar fractures are associated with tenderness over the medial condyle and pain with flexion of the wrist against resistance. Medial condyle fractures are rare in children, comprising 1% to 2% of pediatric elbow fractures.[15] When they do occur, medial condyle fractures are considered type IV Salter-Harris injuries, possibly a physeal injury. The mechanism of injury is believed to be a valgus force on the extended or overhead elbow.[14] The patient has tenderness and swelling over the medial aspect of the elbow.

Diagnostic testing of condylar fractures. Diagnosis is usually made on standard anteroposterior and lateral views, although an oblique view also may be helpful. These fractures are notoriously difficult to diagnose because fractures with minimal displacement are difficult to see radiographically and are often misdiagnosed as supracondylar humerus fractures. The status of the lateral trochlear ridge is the key to analyzing humeral condyle fractures. It may be involved with either medial or lateral condylar fractures and, when incorporated into the distal fragment, is far more likely to result in instability. On radiographic examination, lateral condylar fractures show a widening of the intercondylar distance. The distal fragment is often displaced, most commonly posteriorly and inferiorly. Displaced distal fragments tend to be anterior and inferior because of the pull of the forearm flexors. For medial condoyle fractures, anteroposterior, lateral, and oblique films may show the fracture in older children, but because the trochlea does not ossify until about age nine, plain films in younger children may not clearly demonstrate the fracture. MRI is often necessary to confirm the diagnosis in these patients.

Management and disposition of condylar fractures. For condylar fractures, treatment depends on radiographic findings, but controversy exists about the accuracy of these findings.[16] For nondisplaced or minimally displaced condylar fractures, immobilization of the flexed elbow in a long arm posterior plaster splint is sufficient. Surgical intervention is recommended for a fragment incarcerated within the elbow joint, open fracture, nerve injury, or gross elbow instability.[16] For fractures displaced more than 3 mm, surgical fixation is traditionally recommended, but there is some controversy around this with acceptable displacement ranging from more than 2 to 15 mm.[16] Due to the high rate of complications, we recommend orthopedic consultation be sought for all adult condylar fractures. For lateral condylar fractures, the forearm should be supinated and the wrist extended to relieve the tension on the extensor muscle attachments. For medial condylar fractures, the forearm should be pronated and the wrist flexed). Nondisplaced lateral condyle fractures are treated nonoperatively with a cast, whereas fractures with any displacement require closed or open reduction with percutaneous pin fixation for 3 to 4 weeks. For medial

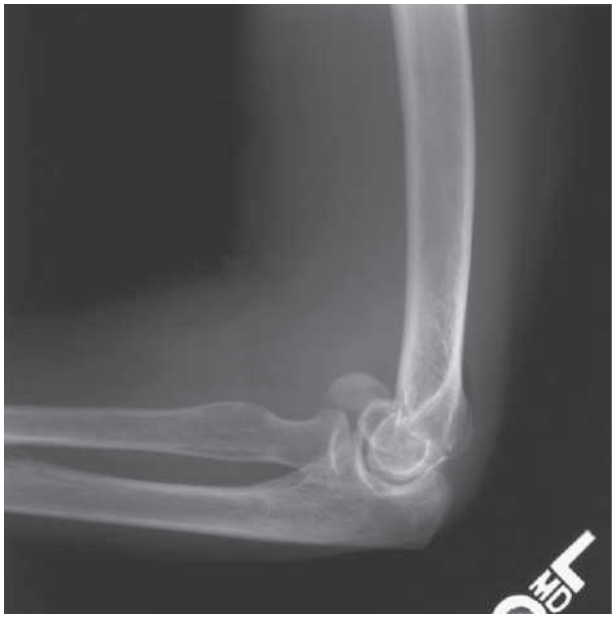


Fig. 44.21 Fracture of the Capitellum.

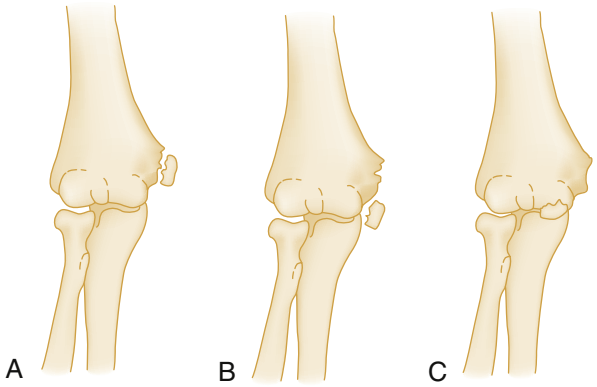


Fig. 44.22 Fractures of Medial Epicondyle. (A) Minimal displacement. (B) Marked displacement. (C) Displacement into joint. (From Connolly JF. *DePalma's management of fractures and dislocations*. Philadelphia, PA: WB Saunders; 1981.)

condyle fractures, operative treatment is indicated if displacement is greater than 2 mm; otherwise, conservative treatment is sufficient.

Capitellum and Trochlea Fractures

Clinical features of capitellum and trochlea fractures. Fractures of the capitellum and trochlea typically occur together, usually as a result of posterior dislocation of the elbow, with isolated fractures being less common. Injury to the capitellum occurs when the patient falls on an outstretched hand, forcing the radial head upward, similar to the motion of a piston, shearing off the capitellum into the radial fossa. Because the capitellum has no muscular attachments, the fragment may remain nondisplaced. More often, the fragment is displaced, usually anteriorly and occasionally posteriorly. A radial head fracture also may be present and should be clinically suspected because of this mechanism. The development of significant signs and symptoms may be delayed with capitellum fractures. Eventually, swelling within the capsule results in severe pain that manifests as well-localized tenderness on examination and flexion of the elbow. Isolated fractures of the trochlea are exceedingly rare because of the structure's protected position deep within the elbow joint. The shearing force of the ulna against the trochlea is associated more commonly with posterior elbow dislocation. The elbow is painful, with an effusion and limited range of motion because this is an intra-articular injury.

Diagnostic testing of capitellum and trochlea fractures. For capitellum fractures, a lateral plain film usually shows the fragment lying anterior and proximal to the main portion of the capitellum (Fig. 44.21). In an isolated trochlear fracture, the radiograph shows a fragment visibly lying on the medial side of the joint, just distal to the medial epicondyle, and signs of joint effusion are visible. The fracture may extend into the distal portion of the medial epicondyle.

Management and disposition of capitellum and trochlea fractures. Treatment of capitellum and trochlea fractures begins in the ED with a posterior splint, ice packs, elevation, compression, and analgesia. Accurate anatomic alignment, rigid internal fixation, and early mobilization are prerequisites for a good functional result.[17] Fractures of the articular surfaces can be treated non-surgically, but only if radiographs show perfect anatomic alignment. Nondisplaced trochlea fractures may be treated with a posterior splint for 3 weeks, followed by early range-of-motion exercises. Displaced fractures (> 2 mm) should be treated operatively; fragments that can be internally fixed are repaired, whereas small fragments are excised. Immobilization should be minimized to 10 to 14 days.

Epicondylar Fractures

Clinical features of epicondylar fractures. Most epicondylar fractures involve the medial epicondyle. Medial epicondyle fractures are most common in children and adolescents and often involve the apophysis, which is the last ossification center to fuse in the distal humerus, usually after age 15. Fractures through this ossification center usually occur in adolescence and constitute 10% of pediatric elbow fractures. These are not Salter-Harris injuries, because the apophysis is involved rather than the physis. The lateral epicondyle is almost level with the flattened outer surface of the lateral condyle giving it only minimal exposure to a direct blow and fracture is rare. Medial epicondyle injuries occur from a variety of mechanisms. First, avulsion fractures are associated with posterior elbow dislocations in patients younger than 20 years in up to 50% of cases. Avulsion fractures also may occur with severe or repeated stress, such as from arm wrestling or pitching (also known as "*Little Leaguer's elbow*"). Finally, a direct blow to the medial epicondyle can cause this injury. The elbow is held in flexion and any movement is resisted. Isolated fractures are associated with focal tenderness over the medial epicondyle. The use of the forearm flexors increases pain because their attachment is along the medial epicondyle. Ulnar nerve function should be evaluated as an associated ulnar nerve palsy may be present with an entrapped fragment.

Diagnostic testing of epicondylar fractures. Simple fractures of the medial epicondyle are extra-articular injuries with limited soft tissue injury.[18] They generally do not produce a fat pad sign on the lateral radiographic view of the elbow. A posterior fat pad or significant swelling of the joint suggests concurrent injuries, such as elbow dislocation. Meticulous radiographic evaluation is especially important because fracture fragments may migrate into the joint space. If the fragment is overlying the joint line on radiographic examination, it should be considered intra-articular (Fig. 44.22). Radiographic detection of the intra-articular fragment may be subtle.[14] Fragments are often difficult to see on radiographs and a true anteroposterior view is challenging to obtain because of severe pain on extension. In an adolescent patient, there is a tendency to confuse the normal radiolucent epiphyseal growth plate with a fracture. In addition, minimally displaced fractures may be difficult to appreciate with

radiographs and comparison films of the uninjured elbow may assist in making the diagnosis. If dislocation is present, repeat radiographs after reduction should be evaluated for fragment location.

Management and disposition of epicondylar fractures. For epicondylar fractures, if the fracture fragment is minimally displaced (< 5 mm), treatment with a posterior splint is appropriate. To minimize distraction of the fragment by the forearm flexors, the elbow and wrist are flexed with the forearm pronated. Treatment of displaced fractures is controversial. The degree of displacement will dictate the need for surgery but results of operative and nonoperative treatment are generally good regardless of the amount of displacement. Some experts advocate surgery for patients who participate in high-performance athletic activities that involve the injured extremity, but controlled studies are lacking. Intra-articular fragments that cannot be removed from the joint by manipulation are an indication for surgery. Emergent orthopedic consultation should be sought for these types of injuries. The rare lateral epicondylar fracture in adults was traditionally treated with immobilization; however, more recent experience indicates that operative management is more successful.

Olecranon

Clinical features of olecranon fractures. Fractures of the olecranon commonly occur from a direct blow as a result of a fall, a motor vehicle or motorcycle crash, or an assault. Less commonly, indirect force applied by forceful contraction of the triceps while the elbow is flexed causing a transverse or oblique fracture through the olecranon. Olecranon fractures are uncommon in children. The anatomic integrity of the olecranon is essential for triceps strength and normal function of the elbow. Physical findings may include tenderness and pain over the olecranon, a palpable separation at the fracture site or the inability to extend the elbow against force. This last finding indicates complete discontinuity of the pulling mechanism and the consequent failure of triceps function. The neurovascular status should be examined with special attention given to the ulnar nerve distribution. Loss of sensation over the palmar aspect of the fifth digit and hypothenar eminence or motor weakness in the interossei muscles of the hand suggests ulnar nerve injury. Symptoms of ulnar nerve injury occur in 10% of patients, and in most cases, the injury is an ulnar contusion that resolves spontaneously.

Diagnostic testing of olecranon fractures. Lateral radiographic views provide the most information. In addition to the fracture, the degree of comminution, the extent of articular surface disruption and the amount of displacement in the 90-degree flexion position should be noted.

Management and disposition of olecranon fractures. In olecranon fractures, non-displacement in the 90-degree flexion position indicates that the triceps aponeurosis tendon is still intact and prolonged immobilization is not indicated. Displacement of more than 2 mm is considered an indication for surgery (Fig. 44.23A). A fracture line that increases in separation with flexion of the elbow is also considered a displaced fracture. When this fracture is associated with elbow dislocation, the plane of instability is located through the fracture site and the radiohumeral joint. This results in posterior displacement of the proximal fragment of the ulna and anterior dislocation of the radius and ulna as a unit (see Fig. 44.23B). Nondisplaced fractures can be treated conservatively on an outpatient basis with ice, compression, immobilization in 45 to 90 degrees of flexion and analgesia. Follow-up radiographs should be performed to ensure that subsequent displacement does not occur. In many cases, range-of-motion exercises can be started within 3 weeks. Displaced fractures or fracture-dislocations require open reduction and internal fixation and patients should be referred urgently to an orthopedist. Displaced fractures in elderly patients can be treated conservatively but this should be left to the discretion of the consultant. Orthopedic referral is also necessary when ulnar nerve compromise is present.

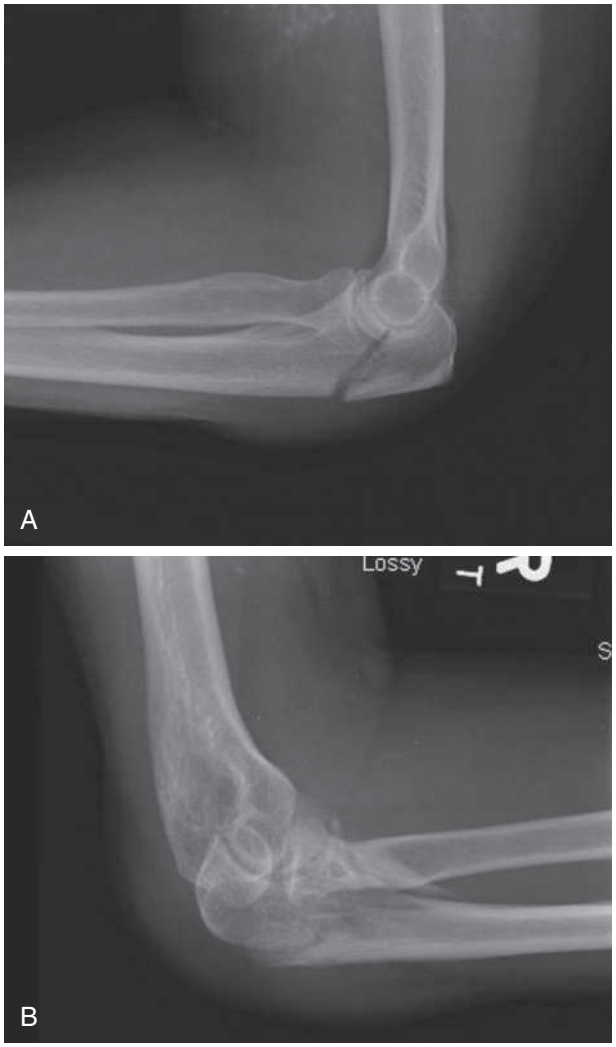


Fig. 44.23 (A) Olecranon fracture with displacement. (B) Fracture accompanied by radial head dislocation.

Radial Head and Neck

Clinical features of radial head and neck fractures. Radial head and neck fractures, in general, are produced by an indirect mechanism, typically a fall on an outstretched hand. The radius transmits the force upward, driving the radial head against the capitellum and resulting in fracture of the weaker radial head or neck. Although the fracture of the radial head may be the only radiographic finding, damage to the articular surface of the capitellum and injury to the collateral ligament may also occur. Displacement of the radial head fragment suggests considerable force and significant soft tissue injury. This injury is characterized by localized tenderness over the radial head or pain with passive rotation or supination and pronation of the forearm.

Diagnostic testing of radial head and neck fractures. Radiographic findings range from a subtle disruption of the usual gradual sweep of the radial neck and head surface to an obvious displaced or comminuted fracture (Fig. 44.24). Nondisplaced fractures are notoriously difficult to detect on radiographs. Tenderness coupled with a positive fat pad sign on the radiograph indicates that the injury should be treated as a radial head fracture even in the absence of a visible fracture.

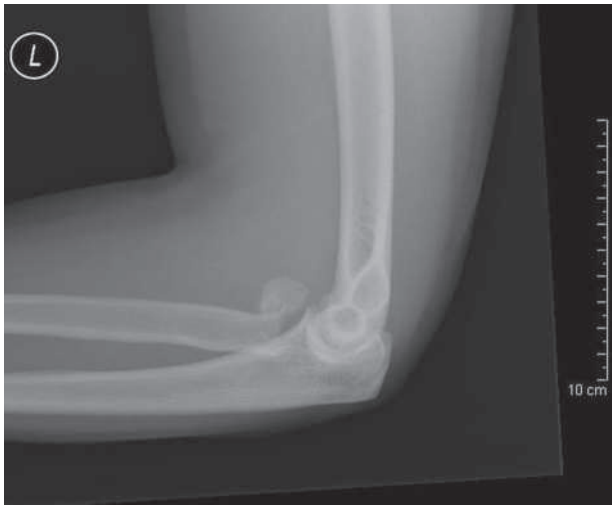


Fig. 44.24 Radial Head Fracture with Displacement.

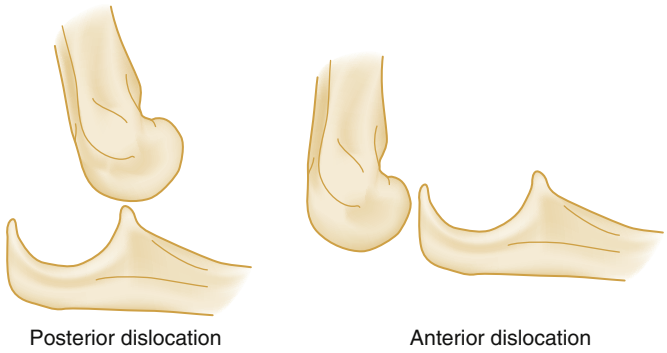


Fig. 44.25 Elbow Dislocation, Posterior and Anterior. (Adapted from Simon R, Koenigsknecht S. Emergency orthopaedics: the extremities. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

Radial head fractures are classified into four types: type I, nondisplaced fractures; type II, fractures involving less than 30% of the articular surface with more than 2 mm displacement, including impaction or angulation; type III, comminuted fractures of the entire radial head; and type IV, any of the previous types with elbow dislocation.[19]

Management and disposition of radial head and neck fractures. Radial head and neck fractures are classified by Manson criteria. Type I nondisplaced fractures are treated symptomatically with a brief period of sling support and early range-of-motion exercises (within 24 to 48 hours). Aspiration of the hemarthrosis from the joint space may give relief of pain and improve the range of motion, though this should be considered only as an adjunct to conservative splinting management.[19] Based on a prospective randomized study, which found no benefit to bupivacaine instillation compared with simple aspiration, we do not recommend injection of bupivacaine into the joint. Most patients with this injury recover well in 2 to 3 months. A few heal poorly however, with long-term pain, contracture, or inflammation. Type II injuries are usually treated similarly, with aspiration and immobilization in the ED, followed by a trial period of range-of-motion exercises. Radial head excision is sometimes performed later if the patient fails to improve. Early excision is advised for type II fractures when a mechanical block is present and for most type III fractures, though the management between excision, open reduction internal fixation, and arthroplasty remain controversial. Long-term functional results after radial head excision are acceptable in most patients with few having some functional disability after this procedure with up to 96% having good long-term outcomes.[19] Treatment of type IV injuries is directed at the elbow dislocation as described next and for specific radial head injuries.

Dislocations/Subluxations

Elbow

Clinical features of elbow dislocations/subluxations. The elbow is inherently subject to mechanical instability because of its anatomic structure and dislocations are common. *The elbow is second only to the shoulder as the most commonly dislocated large joint.* Elbow dislocation is a term usually used to describe a disruption of the relationship between the humerus and the olecranon. In general, the radius and ulna, bound together firmly by the annular ligament and interosseous membrane, displace as a unit. Most classifications refer to the abnormal position of the ulna relative to the humerus. The elbow most often dislocates posteriorly, although it may dislocate anteriorly, medially, or laterally (Fig. 44.25). Although rare, a divergent dislocation, which is a dislocation between the radius and ulna concurrently with the ulnohumeral type, can occur. Dislocation of the elbow requires considerable energy and is often associated with fractures of adjacent bony structures and a fracture-dislocation injury is referred to as a complex elbow dislocation.

The mechanism of injury of a posterior elbow dislocation is a fall on the outstretched hand or wrist, causing hyperextension of the elbow with a valgus stress at the time of impact. Patients hold the elbow in flexion at approximately 45 degrees and have marked prominence of the olecranon. Some elbow dislocations may reduce spontaneously prior to presentation in the ED where obvious swelling and tenderness may be the only findings. Because elbow dislocations are associated with brachial artery and median nerve injuries, neurovascular examination is important especially prior to any manipulation or reduction and should be documented and repeated after reduction. Radiographic evaluation is crucial before manipulation to rule out fractures that can mimic dislocation on examination. Several fractures, including fractures of the distal humerus, radial head, and coronoid process commonly occur in conjunction with dislocation, which need to be identified and treated when present. The most serious complication of elbow dislocation is vascular compromise. Severe disruption results in injury to the brachial artery in 5% to 15% of cases.[20] Vascular injury should be considered when a wide opening between the tip of the olecranon and the distal humerus is palpated or seen on a radiograph. Of note, the presence of distal pulses is not proof of an intact artery; and if a question of vascular compromise exists, emergent vascular studies and consultation is indicated. Median nerve traction injuries and entrapment have been reported. Unlike the shoulder, recurrent dislocation of the elbow is rare. Medial and lateral elbow dislocations are produced by a mechanism similar to that in posterior dislocations, with a vector of force displacing the ulna and radius as a unit either medially or laterally. Anterior dislocations are rare and occur as a result of a blow to the olecranon from behind while the elbow is in the flexed position. Severe associated soft tissue trauma is often present, including avulsion of the triceps mechanism or vascular disruption, and these dislocations are frequently open. On examination, the upper arm appears shortened, the forearm elongated and supinated, the elbow is fully extended, and the olecranon fossa is palpable posteriorly.

Diagnostic testing of elbow dislocations/subluxations. A radiographic example of posterior elbow dislocation before reduction is provided in Fig. 44.26. The anteroposterior view is important for visualization of either medial or lateral dislocations.

Management and disposition of elbow dislocations/subluxations. Rapid reduction of complete elbow dislocations is important to relieve pain and to prevent circulatory injury or cartilaginous damage.

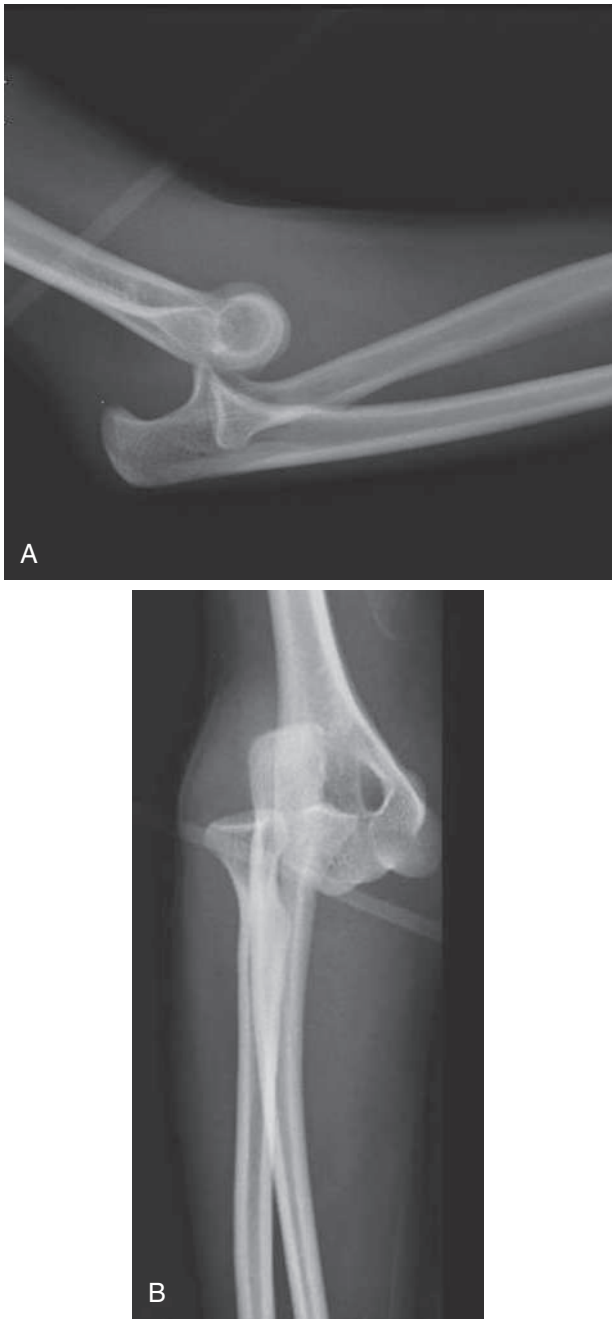


Fig. 44.26 Characteristic posterior dislocation of elbow, lateral (A) and anteroposterior (B) views.

Reduction should be attempted as soon as possible, especially if there is neurovascular compromise. Because of the time sensitivity, delayed orthopedic consultation should not be waited upon to proceed. Intra-articular injection of local anesthetic may provide adequate analgesia to allow for closed reduction, but procedural sedation is often required to facilitate reduction. Posterior dislocations are reduced with an assistant immobilizing the humerus and applying counter traction while traction is applied to the distal forearm. The ideal position is for the elbow to be flexed at 30 degrees with the forearm supinated while distal traction is applied. When the capitellum slides over the coronoid process, a coupling sound occurs as the articular surfaces mesh. If reduction is unsuccessful with this technique, the clinician should apply downward pressure at the proximal forearm and apply pressure behind the olecranon while maintaining in-line traction. This downward force may help "unlock" the coronoid process, which may be trapped in the olecranon fossa. The joint is gently moved through its normal range of motion to check stability. As with all reductions, neurovascular status should be checked before and after any reduction attempt. Post-reduction radiographs are required to access concomitant fractures of the coronoid process or radial head or, in children, separation of the medial epicondylar apophysis. Post reduction management includes immobilization in a posterior splint with the elbow in as much flexion as circulation allows along with a sling. Circular casting should initially be avoided in the ED. Patients can be discharged with instructions to apply ice, elevate, and watch for signs of vascular impairment. If the elbow is stable after reduction, gentle range-of-motion exercises may be initiated in 3 to 5 days. Unstable joints may require either prolonged immobilization in the presence of ligamentous instability or internal fixation if associated with fracture. For medial and lateral elbow dislocations, reduction is carried out with the arm in slight extension but otherwise is similar to that for posterior dislocation. Care should be taken not to convert these to posterior dislocations during reduction. Complications and aftercare are the same as for posterior dislocations. Reduction of closed anterior dislocations is performed with distal traction of the wrist and a backward pressure on the forearm while the distal humerus is grasped. A clicking sound usually indicates that reduction has been achieved. These injuries have a higher incidence of vascular impairment than the more common posterior dislocation although ulnar nerve injuries are unusual. Emergent orthopedic referral is standard for open injuries or when vascular disruption is suspected.

Radial Head Subluxation

Clinical features of radial head subluxation. Subluxation of the radial head (or "*nursemaids' elbow*") is a common injury, representing more than 20% of upper extremity injuries in children. Children 1 to 4 years old are most often affected, although cases have been reported in children 6 months to 15 years old. Girls are affected more commonly than boys, and the left arm is more commonly affected than the right. The classic history, which is present approximately half of the time, is that of the forearm being pulled while in pronation with the elbow extended with stretching of the annular ligament, allowing fibers to slip between the capitellum and the head of the radius, resulting in an inability of the child to supinate the arm.[21] By the age of 5, the annular ligament becomes thick and strong and thus is far less likely to tear or be displaced. Other mechanisms include direct trauma to the elbow or a twisting motion of the arm. In children younger than 6 months old, the mechanism of subluxation involves rolling over in bed that may trap the involved forearm under the body with resulting longitudinal traction on the joint. Clinically, the arm is held in passive pronation, with slight flexion at the elbow. The child is unable or unwilling to move the arm. Resistance to supination and tenderness on direct palpation over the head of the radius are present. Swelling, ecchymosis, and deformity are generally absent.

Diagnostic testing of radial head subluxation. When the history is suggestive of radial head subluxation, radiographs are not indicated and are rarely useful. If there is swelling or deformity, if there is an uncharacteristic history, if the child does not resume use of the arm after reduction, or if there is a possibility of nonaccidental trauma, appropriate radiographic studies are recommended. If palpation of the forearm, wrist, or humerus away from the elbow elicits reproducible tenderness, radiographs should be taken to exclude other diagnoses.

Management and disposition of radial head subluxation. Reduction may be attempted in children with typical presentations and is safe even when the classic history is absent. Although historically, supination-flexion has been the reduction technique most commonly used, hyper-

pronation has a significantly higher reported success rate of reduction on the first attempt and is the recommended method for reduction.[21] With the hyperpronation method, the child's elbow is supported with moderate pressure applied to the radial head. The examiner then grips the child's distal forearm and hyperpronates the forearm, resulting in a click felt over the radial head (Fig. 44.27). In the supination-flexion method, reduction is achieved either by supination or pronation of the forearm while applying direct pressure over the radial head. With the supination method, the forearm is supinated while slight pressure on the radial head is applied with the examiner's thumb. In one continuous motion, the elbow is supinated and flexed with gentle axial pressure applied. A click often, but not always, is felt as the radial head reduces (Fig. 44.28). Many patients are asymptomatic within 5 to 10 minutes; 90% of patients regain use of the arm within 30 minutes. Because a fearful child often does not use even the successfully reduced limb, it is a good idea for the physician to leave the room and for parents to distract the child to demonstrate a return of normal function. If function does not return within 24 hours, the patient should be reevaluated. After successful reduction, no additional treatment, immobilization, or activity reduction is necessary. Parents and caregivers should be instructed to avoid excessive traction on the child's forearm to prevent recurrent radial head subluxation. The recurrent radial head subluxation rate is approximately 20%.[22]

Soft Tissue Disorders

Epicondylitis

Clinical features of epicondylitis. Epicondylitis is a term first introduced to describe an inflammatory process that involves the radiohumeral joint or lateral epicondyle of the humerus. Commonly called "*tennis elbow*" to describe lateral epicondylitis or "*golfer's elbow*" for medial epicondylitis, it is a common exercise-related syndrome, and the mechanism is thought to be repetitive pronation and supination of the forearm. Radiohumeral bursitis or synovitis, tendinitis of the common extensor tendon, periostitis of the lateral epicondyle, and entrapment by scar tissue of the radial nerve all have been suggested as causes of this syndrome. Histologically, the abnormality has been described as angiofibroblastic hyperplasia, a term subsequently modified to angiofibroblastic tendinosis. It is thought to be a degenerative process because of the paucity of acute inflammatory cells seen histologically. Most cases are lateral (tennis elbow), but medial epicondylitis (golfer's elbow) and posterior epicondylitis have been reported; the former involving the pronator teres and flexor carpi radialis insertions and the latter involving the triceps tendon. Onset is usually gradual, and patients report dull pain over the lateral aspect of the elbow over the lateral epicondyle or radiohumeral joint, increased by grasping or twisting motions. Supination and pronation against resistance may be painful, and pain can be elicited by stretching the wrist extensors. To test this, the elbow is extended, the forearm pronated, and the wrist fully dorsiflexed.

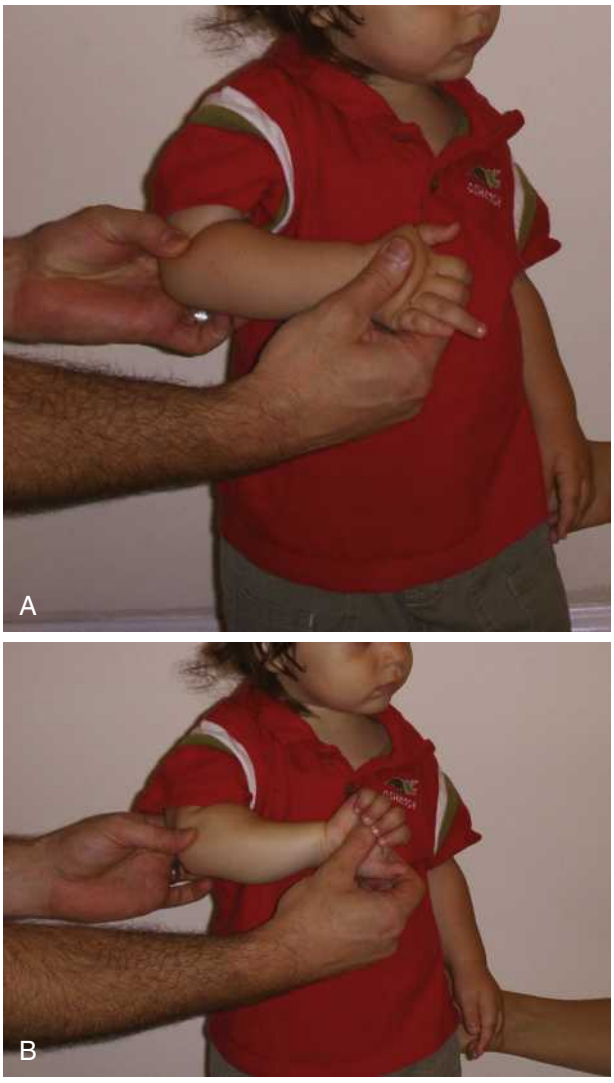


Fig. 44.27 Hyperpronation Method of Radial Head Subluxation Reduction. (A) Support elbow with pressure to radial head. (B) Then hyperpronate the arm distally.

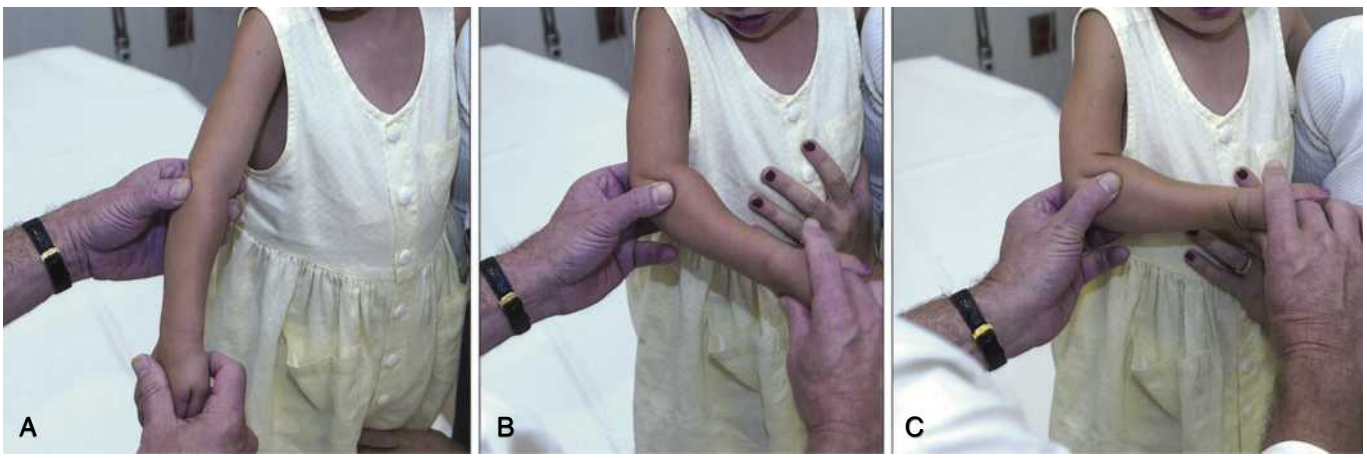


Fig. 44.28 Subluxation of the Radial Head. Method of reduction: Apply pressure to radial head (A) supinate the forearm (B) and flex elbow (C) in one continuous motion.

Diagnostic testing of epicondylitis. Radiographic findings may be normal, although with chronicity, calcifications may be present over the lateral epicondyle. Characteristic MRI findings also have been described, although MRI is not indicated emergently.

Management and disposition of epicondylitis. Treatment includes protection, rest, ice, compression, elevation, and analgesics. Initial therapy includes avoidance of the inciting activity and immobilization with a sling. Nonsteroidal antiinflammatory drugs (NSAIDs) are often used, but their efficacy is limited to their analgesic rather than their antiinflammatory properties. Injection of a corticosteroid at the point of tenderness provides some pain relief in most patients. Because corticosteroids weaken collagen, injection directly into the tendon and premature resumption of heavy loading of the tendon at the lesion should be avoided. Patients with pain that persists despite treatment and a rehabilitation program should be referred for possible surgery. Modification of athletic technique is recommended after the symptoms subside.

Olecranon Bursitis

Clinical features of olecranon bursitis. Olecranon bursitis is commonly caused by repetitive minor trauma, such as leaning on the elbow during work activities. It also may result from an inflammatory process, such as gout or an infectious process within the bursa (septic bursitis). Septic olecranon bursitis occurs most commonly in patients engaged in work that predisposes to repetitive trauma to the elbow, such as gardening or plumbing. Although several bursae are located in the elbow region, the olecranon bursa is the one most often involved in an isolated pathologic process. Patients usually have progressive pain, tenderness and swelling over the olecranon. Some patients with septic bursitis have an abrupt onset instead, with a rapid increase in pain over a few hours and on examination. The septic bursa is typically swollen, warm, erythematous, and tender. Flexion is limited by pain brought on by tightening of the skin over the inflamed bursa. Minor breaks in the skin, abrasions, or healing lacerations over the bursa may be present. Noninfectious bursitis usually manifests with less warmth and erythema. The skin is intact and swelling may be the only finding.

Diagnostic testing of olecranon bursitis. The most important aspect of evaluation is the differentiation of a septic process from a benign inflammatory one, and this differentiation may be difficult on clinical grounds because considerable overlap exists in the histories and physical findings. If suspicion exists, aspiration of the bursa should be performed and the fluid sent for crystals, white blood cell (WBC) count, Gram's stain, and cultures. Unless the aspirate is frankly bloody, traumatic non-septic olecranon bursitis usually has a leukocyte count lower than 1000 cells/mm^3, whereas septic bursal fluid usually has a count higher than 10,000 WBCs/mm^3.

Management and disposition of olecranon bursitis. Aspiration is diagnostic and therapeutic because relief of pressure relieves some of the pain. In cases of purulent bursitis, the bursa should be drained, and appropriate antibiotics to cover staph and streptococcal infections should be prescribed. Pending culture results, empirical antibiotics should include coverage for routine skin organisms, as well as methicillin-resistant *Staphylococcus aureus* (MRSA). Sulfamethoxazole/trimethoprim double-strength twice daily or doxycycline 100 mg should be used twice daily for 10 to 14 days. For patients with severe inflammation or who are immunocompromised, initial treatment with intravenous vancomycin at 15 to 20 mg/kg or intravenous or oral lineozlid 600 mg should be used. Bursitis refractory to aspiration and appropriate antibiotics may require incision and drainage. Noninfectious bursitis can be managed with a compression dressing, ice, NSAIDs, and avoidance of the inciting activity. Patients who have had their bursa aspirated should be rechecked within 24 to 48 hours to verify culture results and monitor their response to treatment.

Biceps Tendon Rupture

Clinical features of biceps tendon rupture. Biceps tendon rupture occurs most commonly in the proximal portion of the long head of the biceps. It is most common in middle-aged athletes or physical laborers who sustain repetitive microtrauma to the tendon. Patients experience a snapping sound and pain in the anterior shoulder during strenuous activities that produce rapid loading of the muscle. Rupture also occurs distally, usually as an avulsion from the insertion on the radial tuberosity, although ruptures at the musculotendinous junction occasionally occur. Rupture of the distal biceps tendon occurs almost exclusively in men, most commonly between the ages of 40 and 60, and most often involves the dominant arm.[23] The inciting event is usually an unexpected extension force applied to the arm flexed at 90 degrees. The pathophysiology of tendon rupture generally occurs in the setting of underlying tendinosis. Diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy all may result in tendinosis. Smoking has been shown to be strongly associated with distal biceps tendon rupture.[23,24] In proximal tendon rupture, the patient usually has a visible defect at the top of the bicipital groove with bunching of the muscle distally. Flexing of the elbow produces pain at the proximal insertion but flexion remains intact, because the short head of the biceps usually maintains its integrity. With distal ruptures, the patient reports pain and tearing in the antecubital region. Visible deformity and a palpable defect of the biceps muscle belly are present with weakness of elbow flexion and supination. If the tendon is completely ruptured, there is a bunching up of the muscle and this effect is accentuated when the patient attempts flexion.

Diagnostic testing for biceps tendon rupture. The patient's history and physical exam is often diagnostic of such an injury, and radiographs are not revealing and usually not necessary. MRI may be useful when a partial rupture is suspected but can be obtained in follow-up and is not indicated in the ED. The often-mentioned *Speed's and Yergason's tests*, while potentially useful, have poor diagnostic sensitivities and specificities for the diagnosis of biceps tendon rupture, and therefore should only be used in appropriate clinical contexts.

Management and disposition of biceps tendon rupture. All patients require referral to an orthopedist within 72 hours for evaluation for early anatomic repair of complete ruptures. Partial ruptures occasionally respond to conservative treatment but often require surgical repair. The upper extremity is splinted, and the patient advised to apply ice and take analgesics while awaiting orthopedic consultation.

ACKNOWLEDGMENTS

The authors would like to thank Thom Mayer, Joel M. Geiderman, and Sam S. Torbabi for their work on this chapter in previous editions.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 44: QUESTIONS AND ANSWERS

1. A 4-year-old boy is brought to the emergency department (ED) by his mother after falling from a swing set. He complains of right wrist pain and resists detailed examination of the arm. Radiographs are normal. What is the most appropriate next step in this patient's management?

a. Computed tomography (CT) scan of the wrist
b. Elbow radiograph
c. Reassurance
d. Splinting for 3 to 6 weeks
e. Triple-phase bone scan after 7 to 10 days

Answer: b. In children with wrist pain and traumatic mechanism of injury, the absence of a clear-cut explanation for the pain (e.g., normal radiograph) should prompt suspicion for an elbow injury producing referred pain.

2. A 3-year-old girl comes in from home with arm pain after being playfully swung by her parents. The child appears uncomfortable and refuses the move her arm. After manipulation and a palpable click, the child appears more comfortable however after 30 minutes will not range her arm for the provider. What is the most appropriate next step for this patient?

a. Obtain an XR to evaluate for fracture
b. Continue to observe the patient with frequent re-evaluations
c. Observe for neurovascular check
d. Discharge home with parents with strict return precautions
e. Consult Orthopedics

Answer: d. In children with radial head subluxation, the child, fearful for eliciting a pain response, may continue to hold their arm in protection while appearing more comfortable. Appropriate comfort and discharge may be appropriate with reliable caregivers and with instructions to return within 24 hours if the child does not return to normal.

3. A 67-year-old right-hand dominant man fell onto his right arm and suffered an injury to his upper arm, with crepitus, gross deformity, and is diagnosed with a midshaft humerus fracture. 30 minutes after placement in a sling begins having difficulty extending the thumb and first finger. Repeat radiography shows improvement in alignment of prior fracture. What is the appropriate action?

a. Adjust splint and discharge to home
b. Do not adjust splint and discharge to home
c. Adjust splint and admit for surgery
d. Do not adjust splint and admit for surgery
e. Admit for compartment checks

Answer: c. The patient is now presenting with a radial nerve injury and palsy, likely after movement of the fracture fragments. The offending manipulation should be undone to potentially improve nerve function, and the patient should then be admitted for operative repair.

4. A 57-year-old man presents with acute left upper extremity pain while suffering an injury doing pullups. The patient has visible deformity of his proximal upper extremity and is splinting his arm and unable to supinate and flex his forearm. The patient is neurovascularly intact. X-rays of the shoulder and humerus are unremarkable. An ultrasound diagnoses a torn biceps tendon. What is the most appropriate treatment plan?

a. Orthopedics consultation for emergent operative repair of the ruptured tendon
b. Splinting and urgent orthopedic follow-up within 48 to 72 hours for operative repair
c. Splinting and follow-up with PCP in 1 week
d. Splinting and discharge with instructions for physical therapy

Answer: b. Patients with a biceps tendon rupture should be evaluated for fractures with plain radiography. If negative, consultation with orthopedics for urgent follow-up with possible operative repair is the most appropriate follow-up plan.

5. A 46-year-old construction worker falls onto an extended arm and has a sudden injury to their elbow. The patient arrives with a gross deformity to the distal humerus/elbow. Radiography reveals a posterior elbow dislocation with a wide humerus-olecranon space. The patient as 1+ radial pulses on the affected arm but is otherwise neurovascularly intact. What is the most appropriate next step?
   a. Manual reduction of the elbow dislocation and discharge to follow up with orthopedics
   b. Manual reduction of the elbow and a CT angiography to evaluate for brachial artery injury
   c. Orthopedics consultation for emergent operative reduction
   d. Vascular surgery consultation for management of potential brachial artery injury

Answer: b. The patient likely has a brachial artery injury. These are more common in elbow dislocations with a wide separation between the olecranon and humerus. While there may be persistent pulses distally, the presence of pulses does not eliminate the risk for brachial artery injury. The injury should be reduced, and the patient should undergo CT angiography for evaluation of potential vascular injury.

45

Shoulder Injuries

Charles Craig Rudy and Mohamud R. Daya

KEY CONCEPTS

- Axillary nerve function is best evaluated by testing the motor function of the deltoid muscle.
- The three-view trauma series of the shoulder (true anteroposterior, scapular Y, and axillary views) leads to an accurate radiographic diagnosis of most fractures and dislocations, although specialized views are sometimes necessary. Consider the presence of unfused epiphyses in adolescents and young adults.
- Most shoulder girdle fractures can be treated with simple immobilization with good functional outcomes.
- The most important aspect of scapular fractures, scapulothoracic dissociation, and posterior sternoclavicular joint (SCJ) dislocations is the high incidence of associated injuries to the ipsilateral lung, chest wall, mediastinum, or shoulder girdle complex.
- Type III acromioclavicular joint (ACJ) dislocations can be treated conservatively (immobilization, range of motion exercises, and strengthening).
- Recurrence is a common complication after anterior dislocation, especially in male patients younger than 30 years old, and such patients likely benefit from arthroscopic surgical repair.
- Posterior dislocation should be included in the differential diagnosis of any shoulder injury, particularly in patients who report shoulder pain after a seizure.
- Ultrasound can be a useful technique for diagnosing tendon tears, selected soft tissue conditions, fractures, and dislocation, as well as for confirming successful reduction.
- Early initiation of passive shoulder range-of-motion exercises reduces the risk of adhesive capsulitis when the shoulder is immobilized for any reason.

FOUNDATIONS

Background and Importance

The shoulder joint is a unique and complex articulation unit. It has the largest range of motion of any appendicular joint in the body and can be moved through a space that exceeds a hemisphere.

Shoulder injuries are commonly encountered in emergency medicine and dislocations account for more than 50% of all major joint dislocations seen in the emergency department (ED). The shoulder can be injured by trauma (indirect or direct) or by overuse.

In general, children are vulnerable to the same injuries as those incurred by adults; however, the presence of the epiphysis and its growth plate changes the pattern of injuries. The strength of the joint capsule and its ligaments is two to five times greater than that of the epiphyseal growth plate. An injury that produces a sprain or dislocation in an adult often causes a fracture through the hypertrophic zone of the growth plate in a child. Most shoulder injuries in children can be treated conservatively, with a good prognosis for full return of function.

Anatomy, Physiology, and Pathophysiology

The shoulder girdle connects the upper extremity to the axial skeleton and the sternoclavicular joint (SCJ) represents the only true articulation point (Fig. 45.1). The SCJ participates in all movements of the upper extremity and is the most moved joint in the body (Fig. 45.2). The superior mediastinum containing the great vessels, trachea, esophagus, thoracic duct, lung apices, and other important structures is immediately posterior to the SCJ.

The clavicle is an S-shaped bone that acts as a strut to support the upper extremity and keep it away from the chest wall, also protecting the subclavian vessels and brachial plexus. The middle third, which is thin and untethered, is the most commonly fractured segment.

The acromioclavicular joint (ACJ) connects the lateral end of the clavicle with the medial aspect of the acromion process (Fig. 45.3). The ACJ has little or no bony stability and is dependent on associated ligaments and muscles for support.

The scapula is a flat triangular bone that forms the posterior aspect of the shoulder girdle. The thin body of the scapula lies flat against the posterior thorax and widens laterally to form the glenoid fossa. The scapula's thickened borders are the attachment sites for 18 muscle origins and insertions. The thick muscle coat and ability to recoil along the posterior chest wall protect the scapula from both direct and indirect trauma.

The glenohumeral articulation is a ball-and-socket–type joint that depends largely on associated capsule, muscles, and ligaments for stability (Fig. 45.4). The absence of bony stability permits a range of motion greater than any other joint.

The proximal humerus articulates with the glenoid fossa and is the site for the attachment of many important muscles. The rotator cuff stabilizes the glenohumeral joint (GHJ) and consists of the supraspinatus, infraspinatus, teres minor, and subscapularis muscles (Fig. 45.5). The long head of the biceps tendon originates from the supraglenoid tubercle and ascends over the humeral head to enter the arm via the bicipital groove (see Fig. 45.5).[1] Long muscles that cross the articulation are involved primarily in movements of the GHJ. The pectoralis major, latissimus dorsi, and teres major muscles all insert into the humeral intertubercular groove. Displacements encountered with fractures of the humerus usually reflect the pull of these attached muscle groups. The proximal humerus is composed primarily of trabecular bone with a thin cortical shell. Changes in bone density with age increase the risk of fractures.

The brachial plexus and subclavian vessels enter the shoulder girdle superiorly between the clavicle and the first rib, traverse under the coracoid process, and exit anterior to the inferior aspect of the GHJ as the median, ulnar, radial, musculocutaneous, and axillary nerves and axillary vessels. These nerves represent the final branches of the upper brachial plexus (nerve roots C5 to T1).

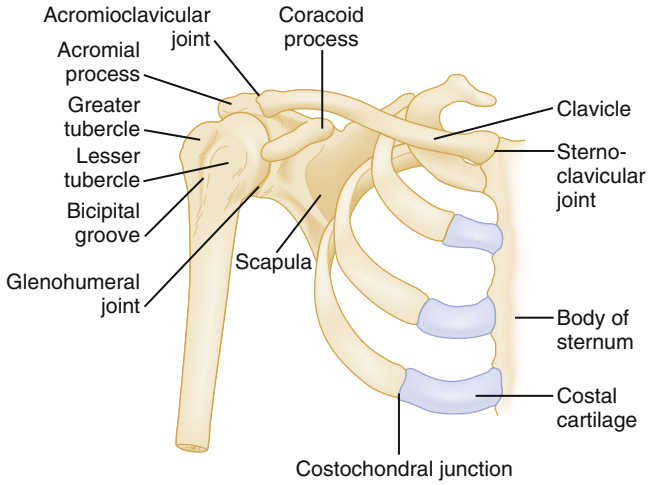

Fig. 45.1 Anatomy of the Shoulder Girdle. It consists of three bones: the clavicle, humerus, and scapula; three joints: the acromioclavicular, glenohumeral, and sternoclavicular joints; and one pseudoarticulation: the scapulothoracic pseudoarticulation. (From Roy S, Irwin R. *Sports medicine: prevention, evaluation, management and rehabilitation*. Englewood Cliffs, NJ: Prentice Hall; 1983.)

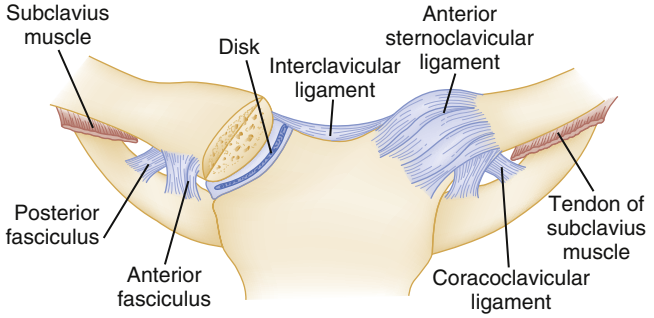

Fig. 45.2 The sternoclavicular joint is stabilized by several ligaments. (Redrawn from DePalma AF. *Surgery of the shoulder*. 3rd ed. Philadelphia: JB Lippincott; 1983.)

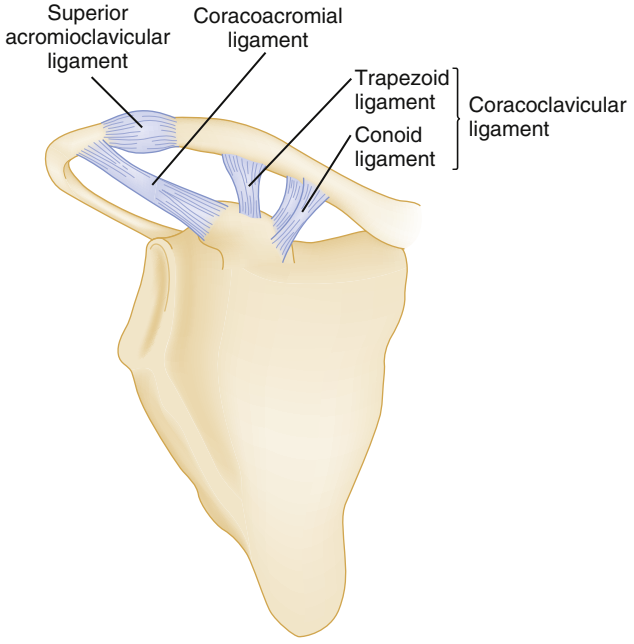

Fig. 45.3 Ligaments of the Acromioclavicular Joint. (Redrawn from DePalma AF. *Surgery of the shoulder*. 3rd ed. Philadelphia: JB Lippincott; 1983.)

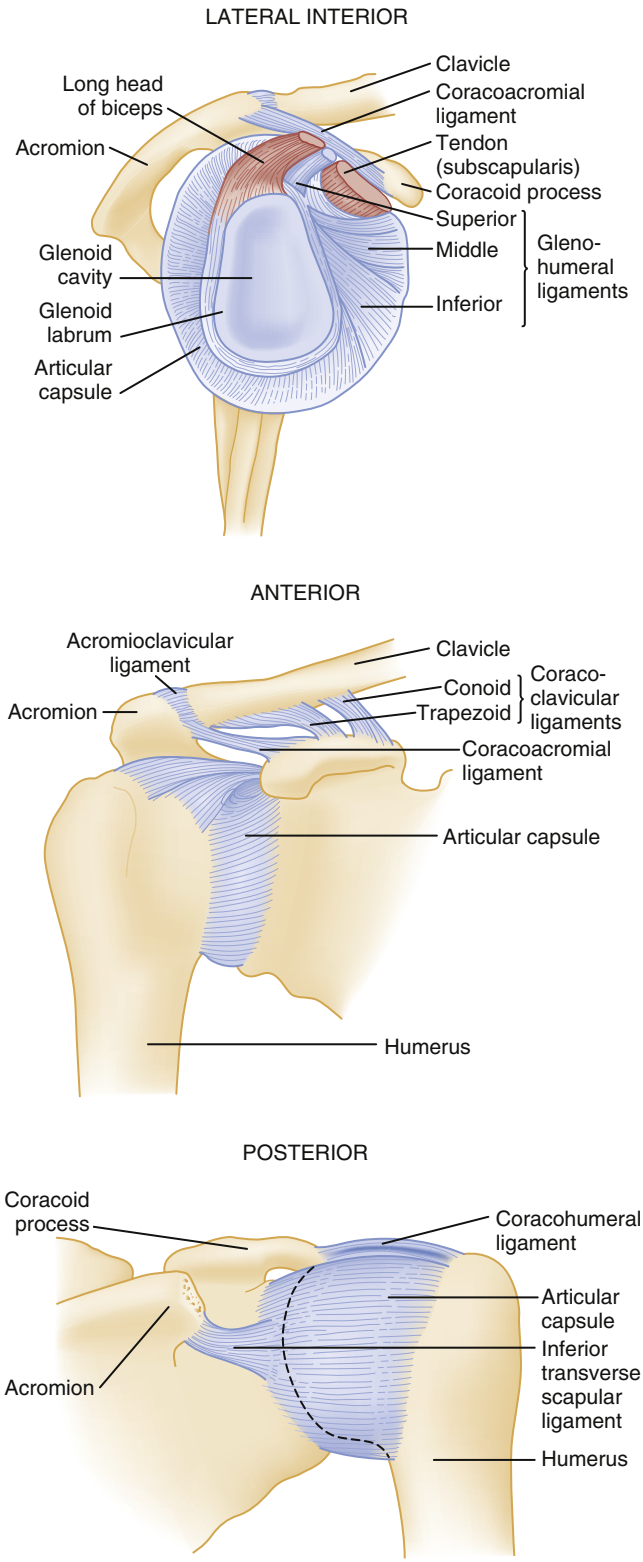

Fig. 45.4 Anatomy of the Glenohumeral Joint. Synovial membrane extends from the glenoid fossa to the humeral head. Overlying the synovial membrane is a loose and redundant fibrous capsule. Anteriorly, the capsule is thickened to form the superior, middle, and inferior glenohumeral ligaments. The anterior band of the inferior glenohumeral ligament is the most important restraint to anterior glenohumeral dislocations.

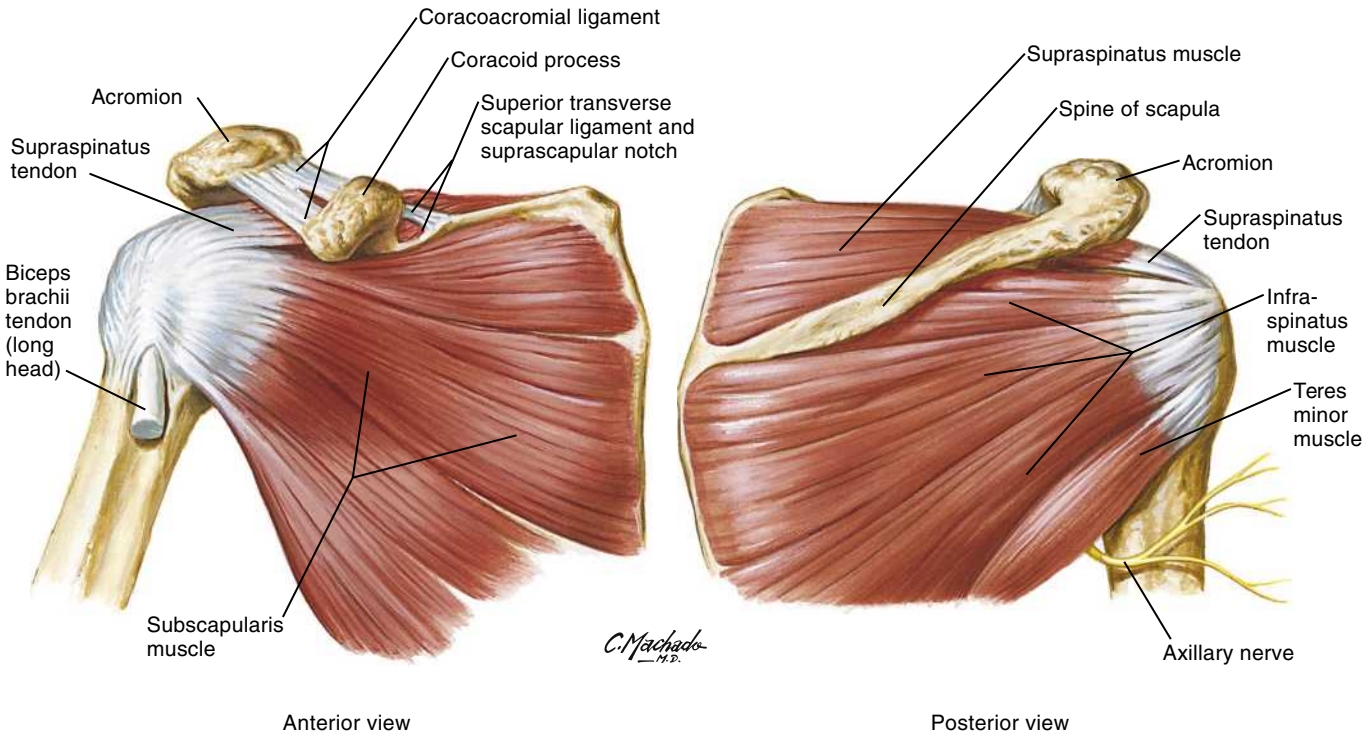

Fig. 45.5 The four rotator cuff muscles: anterior view (subscapularis) and posterior view (supraspinatus, infraspinatus, and teres minor). (Netter illustration from www.netterimages.com. Copyright 2016 Elsevier Inc. All rights reserved.)

CLINICAL FEATURES

History

Most complaints involve some combination of pain, stiffness, instability, or weakness. Pain can result from many different conditions extrinsic and intrinsic to the shoulder. Extrinsic sources of shoulder pain include disorders of the cervical spine, thoracic outlet, and myocardium, as well as symptoms referred from processes causing diaphragmatic irritation.

For intrinsic conditions, the most important factors to determine are the time and mechanism of injury (traumatic or overuse), location of the pain, and associated sensorimotor complaints. Shoulder pain also can manifest in an insidious manner, unrelated to any precipitating factor. In these instances, the duration, location, character, and aggravating and alleviating factors of the pain should be noted.

Stiffness usually manifests as a restricted range of motion resulting from an underlying painful condition of the shoulder. Instability can be chronic or acute and seen in the form of an obvious subluxation or dislocation or a sensation of the shoulder almost "going out of joint." Significant shoulder weakness is usually the result of an underlying nerve lesion or rotator cuff tear.

Physical Examination

The shoulder should be inspected from the anterior, posterior, and lateral positions, in addition to the axilla. Any obvious deformity, ecchymosis, laceration, swelling, or hematoma should be noted.

Palpation of the shoulder should be performed systematically, beginning at the SCJ and moving laterally to the ACJ. Next, the scapula, GHJ, and humerus are palpated. Any point tenderness, crepitus, swelling, or deformity should be noted.

Active and passive range of motion should be tested, although this may be limited due to pain. Active range of motion is best determined with the patient in the sitting position to eliminate the contributions of the lumbar spine and lower extremity joints. Passive range of motion is best evaluated in the supine position. The degrees of abduction, forward flexion, extension, and internal and external rotation should be compared with those of the unaffected extremity. In addition, observe the motion of the scapulothoracic articulation. After 45 degrees of abduction, the scapula moves approximately 1 degree for every 2 degrees of glenohumeral motion. Specific strength tests for the rotator cuff include resisted internal rotation (subscapularis), resisted external rotation (infraspinatus and teres minor), and the "empty can" test (supraspinatus). The empty can test is performed with the patient resisting downward pressure with their arm raised forward to 90 degrees, with arm extended and pronated, such that the thumb is down (as if pouring out a can of liquid).

The examination is completed with an assessment of neurovascular function. A complete neurologic examination of the brachial plexus includes sensory (light touch and pinprick) and motor assessment (Table 45.1). The radial pulse should be checked, although collateral circulation may preserve this, despite an underlying vascular injury.

TABLE 45.1 Sensory and Motor Components of the Brachial Plexus

Spinal Level	Sensory Area	Muscle
C2 to C4	—	Trapezius
C5	Lateral arm	Deltoid
C6	Lateral forearm and thumb	Biceps
C7	Tip of long finger	Thumb extensors
C8	Tip of little finger and medial forearm	Finger flexors
T1	Medial arm	Hand interossei

The presence of pallor, paresthesias, or a significant hematoma raises concern for a vascular injury. The neurovascular examination should be repeated and documented after any ED manipulation.

DIFFERENTIAL DIAGNOSES

Differential diagnoses for shoulder injuries are summarized in Table 45.2.

DIAGNOSTIC TESTING

Radiology

The initial assessment of traumatic injuries includes a three-view trauma series of radiographs consisting of true anteroposterior (45-degree lateral), trans-scapular lateral ("Y" view), and axillary lateral views. The true anteroposterior view is preferred over standard anteroposterior views, because it shows the GHJ without any bony overlap. Standard anteroposterior views obtained with the joint in internal and external rotation profile the lesser and greater tuberosity and are more useful in the evaluation of soft tissue conditions.

Orthogonal views include the axillary lateral, trans-scapular lateral, and apical oblique. The preferred view is the axillary lateral, which projects the GHJ in a cephalocaudal plane, helping to define the position of the humeral head with in the glenoid fossa and identify lesions of the coracoid process, humeral head, and glenoid rim. This view can be particularly helpful in identifying a posterior shoulder dislocation. If pain or post-reduction instability limits abduction, a modified axillary lateral view can be obtained by angling the central ray caudad with about 30 degrees of abduction. In the trans-scapular view, the scapula is projected as a Y, with the body forming the lower limb and the coracoid and acromion processes forming the upper limbs. The humeral head normally is superimposed over the glenoid, which is located at the junction of the three limbs. Advantages of this projection include its simplicity, reproducibility, and clear delineation of anatomic structures. Poor visualization of the glenoid is the primary disadvantage of the trans-scapular view. The apical oblique view (obtained by having the patient stand bending forward and angling the central ray 45 degrees caudally) shows the GHJ in a unique coronal projection. This view is useful in evaluating for Hill-Sachs lesions in shoulder dislocations, in addition to displacement and angulation of proximal humerus fractures.

Although plain radiographs suffice in most instances, additional bone and soft tissue details may be obtained via computed tomography (CT) or magnetic resonance imaging (MRI) in selected circumstances. Bedside point-of-care ultrasonography (POCUS) has emerged as a reliable screening and diagnostic imaging modality for selected conditions, in particular fractures of the clavicle, and soft tissue injuries, such as biceps tendon rupture and a rotator cuff tear.[2]

SPECIFIC INJURIES

Fractures

Clavicle

Foundations. The clavicle accounts for 3% to 5% of all fractures with a 2:1 male to female ratio. It is also the most commonly fractured bone in children. Clavicular fractures are classified anatomically and mechanistically into three groups. Fractures of the medial third are uncommon (5%) and occur as a result of a direct blow to the anterior chest. Fractures of the middle third are the most frequent (Figs. 45.6 and 45.9), accounting for 80% of all injuries. The usual mechanism of injury involves a direct force applied to the lateral aspect of the shoulder as a result of a fall, sporting injury, or motor vehicle collision (MVC). Fractures of the lateral third (15%) result from a direct blow to the top of the shoulder and are classified further into subtypes.[3] Type I fractures are stable and minimally displaced because the coracoclavicular ligament remains intact. Type II fractures are associated with a torn coracoclavicular ligament and have a tendency to displace because the proximal fragment lacks any stabilizing forces (Fig. 45.7). Type III injuries involve the articular surface.

Clinical features. The affected extremity is held close to the body as a result of the effect of gravity and the pull of the muscles

TABLE 45.2 Differential Diagnoses for Shoulder Injuries

Diagnosis	Differential Diagnoses
Clavicle fracture	Humerus fracture, AC joint injury, SC joint dislocation, soft tissue injury (contusion, sprain, strain)
Scapula fracture	Rib fracture, pneumothorax, hemothorax, glenohumeral dislocation, humerus fracture, and clavicle fracture
Humerus fracture	Glenohumeral dislocation, AC joint injury, rotator cuff tendon tear, soft tissue injury
Proximal humeral epiphysis	AC joint injury, humerus fracture, and glenohumeral dislocation
SC joint dislocation	Medial clavicle fracture, sternum fracture, rib fracture, mediastinal injury, and pneumothorax, soft tissue injury
AC joint dislocation	Distal clavicle fracture, acromion process fracture, coracoid process fracture, rotator cuff tear/strain, glenohumeral dislocation, soft tissue injury
Anterior glenohumeral dislocation	Proximal humerus fracture, proximal biceps tendon rupture
Posterior glenohumeral dislocation	Posterior glenohumeral subluxation, labral tear, glenoid fracture, proximal humerus fracture, scapula fracture
Inferior glenohumeral dislocation	Subglenoid anterior dislocation
Scapulothoracic dissociation	Glenohumeral dislocation, scapula fracture, proximal humerus fracture, and AC joint dislocation; brachial plexus injury
Impingement syndrome	Rotator cuff tendinopathy, rotator cuff tear, calcific tendinopathy, glenohumeral or acromio-clavicular osteoarthritis
Rotator cuff tear	Impingement syndrome, rotator cuff tendinopathy, biceps tendinopathy, AC joint osteoarthritis, GH or AC osteoarthritis
Biceps tendinitis	Proximal biceps tendon tear, rotator cuff tendon tear, rotator cuff tendinopathy, labrum tear, subluxing biceps tendon, and glenohumeral osteoarthritis
Biceps rupture	Subluxing bicep tendon, rotator cuff tendon tear, glenohumeral dislocation, and labrum tear
Calcific tendinitis	Rotator cuff tendinopathy, rotator cuff tear, impingement syndrome, and osteoarthritis
Adhesive capsulitis	Chronic dislocation, osteoarthritis, rotator cuff tendinopathy, calcific tendinitis, and rotator cuff tear

AC, Acromioclavicular; *GH*, glenohumeral; *SC*, sternoclavicular.

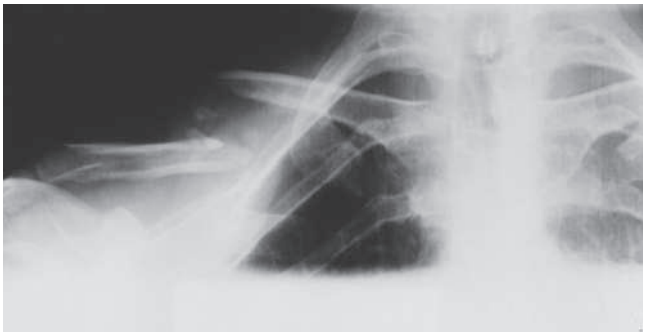

Fig. 45.6 Displaced Midclavicular Fracture.

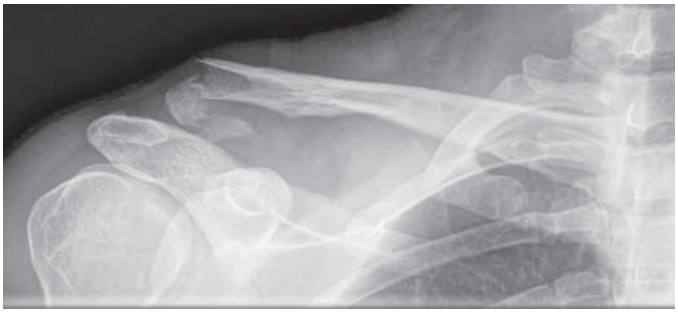

Fig. 45.7 Type II lateral clavicular fracture and torn coracoclavicular ligament. (Courtesy Erik Foss, MD.)

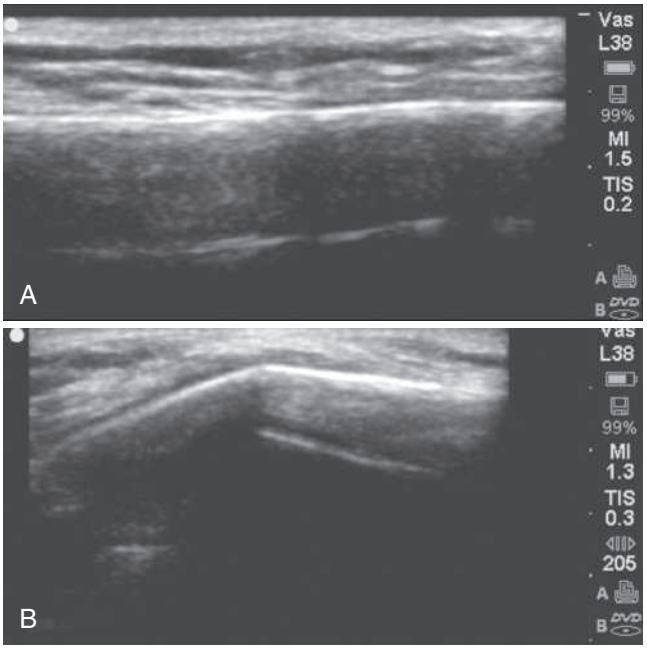

Fig. 45.8 Ultrasound images of the clavicle. (A) Normal. (B) Midclavicular fracture. (Courtesy Keith Cross, MD.)

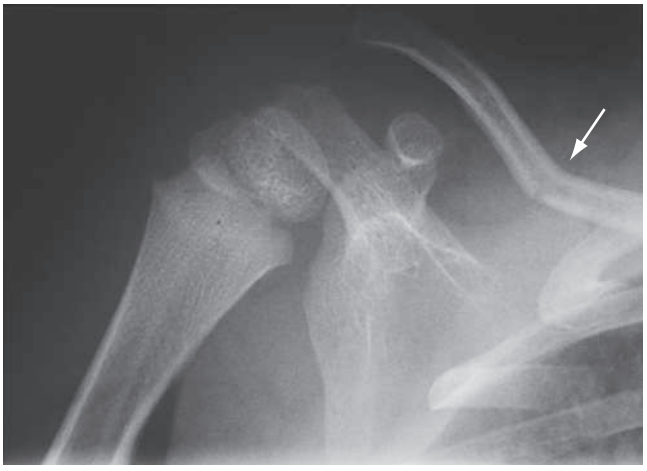

Fig. 45.9 Greenstick fracture of the clavicle *(arrow)*.

(pectoralis major, latissimus dorsi, sternocleidomastoid) on either side of the fracture site. The head is often tilted toward the injured side in an attempt to relax the effects of these displacing muscular forces. Tenderness, ecchymosis, crepitus, and a palpable or visible deformity may be present. Examine for any tenting of the skin, because this can cause progression to an open fracture. Furthermore, tenting of the skin is one of the indications for operative fixation and reduction. Although rare, it is prudent to evaluate for associated neurovascular and pulmonary injury due to close proximity of the subclavian vessels, brachial plexus, and lung apex. The most common complications are delayed union, nonunion, and symptomatic malunion. Displaced middle third fractures have a 15% to 20% rate of nonunion and up to 25% rate of symptomatic malunion.[4] Type III lateral clavicle fractures can lead to subsequent AC joint osteoarthritis.[3]

Differential diagnoses. In patients with direct fall onto lateral shoulder the differential diagnosis includes soft tissue injury (hematoma, contusion, strain, sprain), AC, GH, and SC joint injuries as well as rib, scapula, and humerus fractures.

Diagnostic testing. Clavicle-specific plain radiographs may be required to confirm the presence of a fracture, although most clinically significant fractures are diagnosed on chest or shoulder radiographs. Fractures in children can be reliably diagnosed or ruled out by POCUS, decreasing the exposure to radiation (Fig. 45.8).

Management. Principles of initial management for simple fractures include pain control, immobilization primarily for comfort, and proper follow-up care. In addition to oral analgesics, pain associated with clavicle fractures can also be managed with an ultrasound-guided superficial cervical plexus block in the ED.[5] Fractures of the clavicle are adequately immobilized with a simple sling since this results in similar functional outcomes and rates of union while providing greater pain relief than a figure-of-eight clavicular bandage.[6] Emergent orthopedic consultation should be sought for open fractures or fractures associated with neurovascular injuries, skin tenting, or interposition of soft tissues. More urgent orthopedic consultation (within 72 hours) is recommended for type II lateral clavicle fractures, because these fractures have up to a 30% incidence of nonunion and may require surgical repair.[3] Severely comminuted or displaced fractures of the middle third (defined as over 18 mm of initial shortening) are also associated with a higher incidence of nonunion and long-term functional deficits and deserve urgent orthopedic evaluation for consideration of operative reduction.[4,7]

Disposition. Most fractures of the clavicle heal uneventfully, and follow-up can be provided by a primary care physician. A sling should be worn until the patient is comfortable, which may precede radiographic evidence of callous formation. Early passive shoulder range-of-motion exercises (Fig. 45.10) are encouraged to reduce the risk of adhesive capsulitis (commonly referred to a "frozen shoulder"). Adolescents and adults generally require 4 to 8 weeks of immobilization. Contact sports should be avoided until the bone healing is solidified (6 to 8 weeks). Full range of motion of the shoulder and an absence of pain are two reliable clinical signs that the fracture has healed.

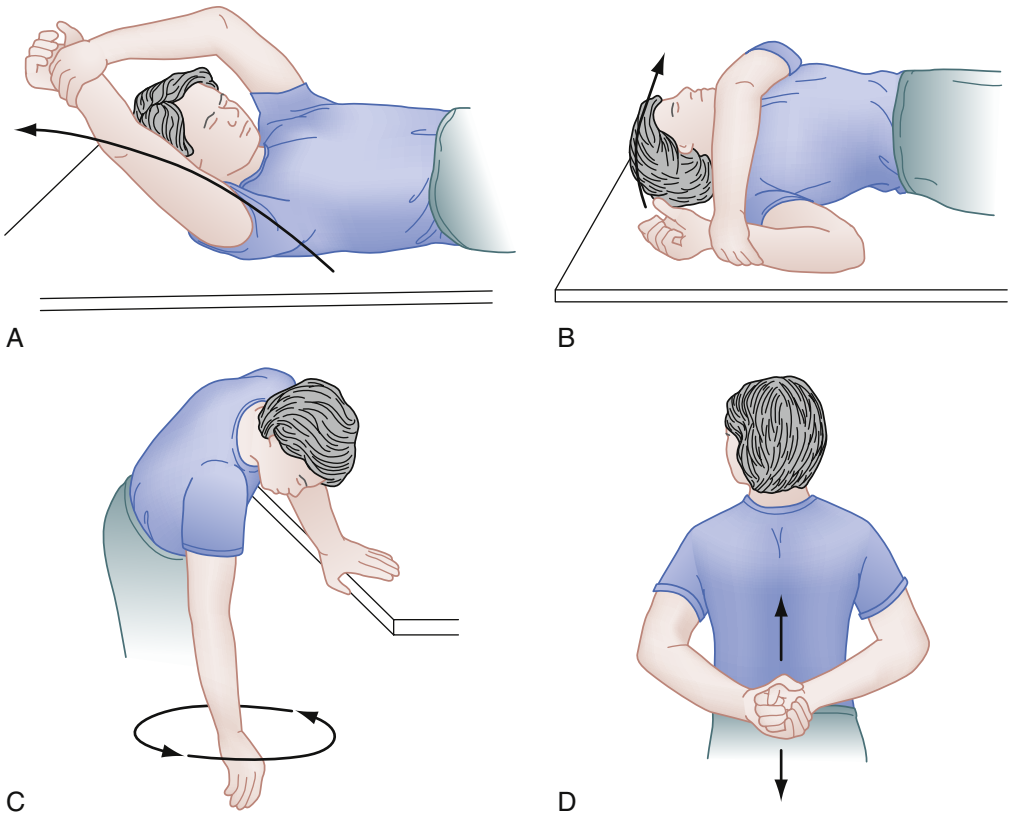

Fig. 45.10 Types of Active and Passive Shoulder Exercises. (A) Passive flexion. (B) Passive external rotation. (C) Pendular. (D) Passive internal rotation.

Scapula

Foundations. Fractures of the scapula are rare, accounting for approximately 1% of all shoulder fractures and caused by high-energy trauma, such as high-speed MVCs and falls from heights. Scapular fractures rarely require management but are associated with major injury (75% to 98%), specifically injuries to the ipsilateral lung, chest wall, and shoulder girdle complex. The most common associated orthopedic injuries are fractures of the ribs, proximal humerus, and clavicle. Associated lung injuries, including pneumothorax, hemothorax, and pulmonary contusion, usually occur acutely, but may manifest up to 2 to 3 days after the initial injury. Associated injuries of the head, spinal cord, brachial plexus, and subclavian or axillary vessels are less common.

Scapular fractures are divided into two main types: extra-articular (neck [Fig. 45.11], body, acromion process, coracoid process, spine) and intra-articular (with partial or total glenoid involvement).[8]

Clinical features. In a conscious patient, the shoulder is held in a position of most comfort, usually with the arm adducted and held close to the body. Any attempts at movement will result in significant pain. Tenderness, crepitus, or hematoma may be noted over the fracture site. The clinical findings occasionally mimic those seen with a rotator cuff tear. Associated injuries of the ipsilateral lung, chest wall, and shoulder girdle account for most complications. Neurovascular (e.g., brachial plexus, axillary artery, suprascapular nerve) injuries also have been reported with fractures of the acromial process, coracoid process, scapular neck, body, or spine fractures that extend into the suprascapular notch. Delayed complications include adhesive capsulitis and rotator cuff dysfunction.

Differential diagnoses. High energy trauma that can lead to a scapula fracture should also include the following on the differential diagnosis: rib fracture, pneumothorax, hemothorax, glenohumeral dislocation, humerus fracture, and clavicle fracture. The shoulder girdle is complex, so high-energy injury mechanisms to one part can affect any other associated part.

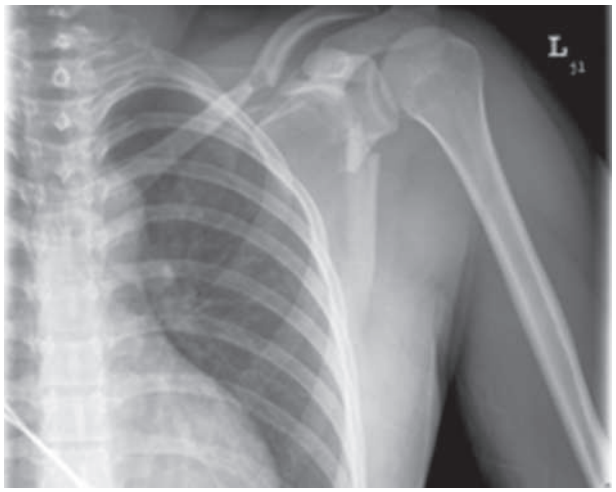

Fig. 45.11 Extra-Articular Fracture Involving the Neck of the Scapula. Note the associated midclavicular fracture.

Diagnostic testing

Radiology. The three-view trauma shoulder series will reveal most scapular fractures, as will careful examination of the scapula on the trauma chest radiograph. An os acromiale (unfused acromial process epiphysis) is present in 3% of the population, will not be tender to examination, and should not be confused with an acromion fracture.

A comparison film can be useful, because the abnormality is present bilaterally in 60% of cases. Although additional dedicated scapula views can be obtained in the ED, the presence and the extent of scapular injury is best determined by CT scan.[8] In the event that a trauma chest CT scan has been obtained to search for associated injuries, a three-dimensional reconstruction of the scapula should be requested to define the nature and extent of the injury.

Management. Presence of a scapular fracture should prompt a thorough search for associated thoracic, intracranial, orthopedic, and neurovascular injuries. Most fractures, including fractures with severe comminution heal rapidly with nonoperative therapy. Initial therapy consists of analgesia, immobilization in a sling for comfort to support the ipsilateral upper extremity, and passive range-of-motion exercises (see Fig. 45.10). Most patients require a sling for 2 to 4 weeks, physical therapy, and follow-up assessment for delayed displacement.

Nondisplaced fractures of the body, spine, and acromion process usually require no further therapy. Displaced acromial fractures that impinge on the GHJ require surgical management. Rarely, the acromion is fractured as part of a superior dislocation of the humeral head. In these instances, an accompanying tear of the rotator cuff which may require surgical repair is invariably present. If the coracoclavicular ligaments remain intact, fractures of the coracoid process respond well to conservative therapy. Severely displaced coracoid fractures with ruptured coracoclavicular ligaments usually require open reduction and internal fixation. Scapular neck and glenoid fossa fractures present the most difficult management issues. Although most of these injuries also do well with conservative therapy, open reduction and internal fixation may be necessary to improve long-term function.[9]

Proximal Humerus

Foundations. Fractures of the proximal humerus occur primarily in the older population, in whom structural changes (osteoporosis) weaken the proximal humerus, predisposing it to injury from low-energy falls. Although most of these injuries involve minimal displacement and are adequately managed with conservative therapy, significantly displaced fractures may require operative intervention. Displacements encountered with fractures of the humerus usually reflect the pull of the attached muscle groups.

Fractures of the proximal humerus separate along old epiphyseal lines, producing four distinct segments consisting of the articular surface (anatomic neck), greater tuberosity, lesser tuberosity, and humeral shaft (surgical neck). The Neer classification system is based on the relationship of these fracture fragments. In this system, a segment is considered displaced if it is angled more than 45 degrees or separated more than 1 cm from the neighboring segment. Because this classification system considers only displacement, the number of fracture lines is irrelevant. There are four major categories of fracture: (1) minimal displacement (Fig. 45.12), (2) two-part displacement (Fig. 45.13), (3) three-part displacement, and (4) four-part displacement. When present, anterior and posterior dislocations are included as part of the classification. Impaction and head-splitting fractures are classified separately.

The classic mechanism of injury involves a fall on an outstretched abducted arm. Concurrent pronation limits further abduction and levers the humerus against the acromial process; this produces a fracture or dislocation, depending on the tensile strengths of the bone and surrounding ligaments. Older patients are prone to fracture, whereas younger persons are apt to have dislocations. The combined injury (fracture and dislocation) may be seen in middle-aged patients. Proximal humerus fractures also may result from a direct blow to the lateral side of the arm or from an axial load transmitted through the elbow. High-energy mechanisms and polytrauma are more common in younger persons.

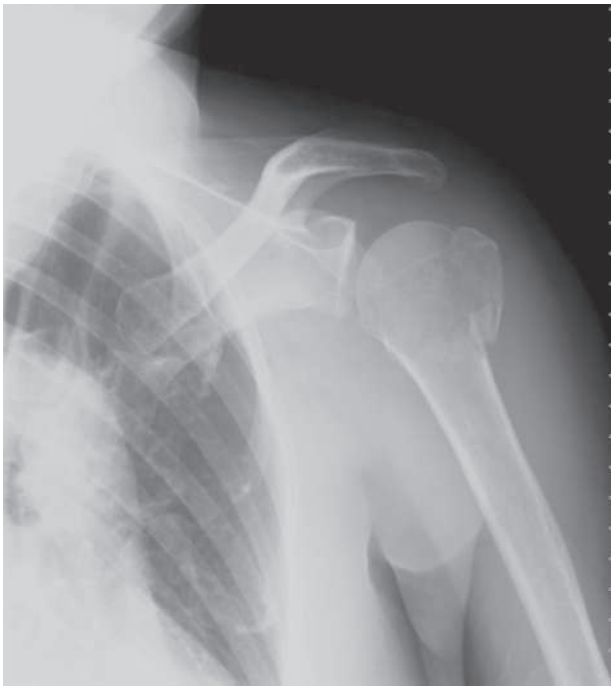

Fig. 45.12 Three-part minimally displaced fracture of the proximal humerus involving the greater and lesser tuberosities.

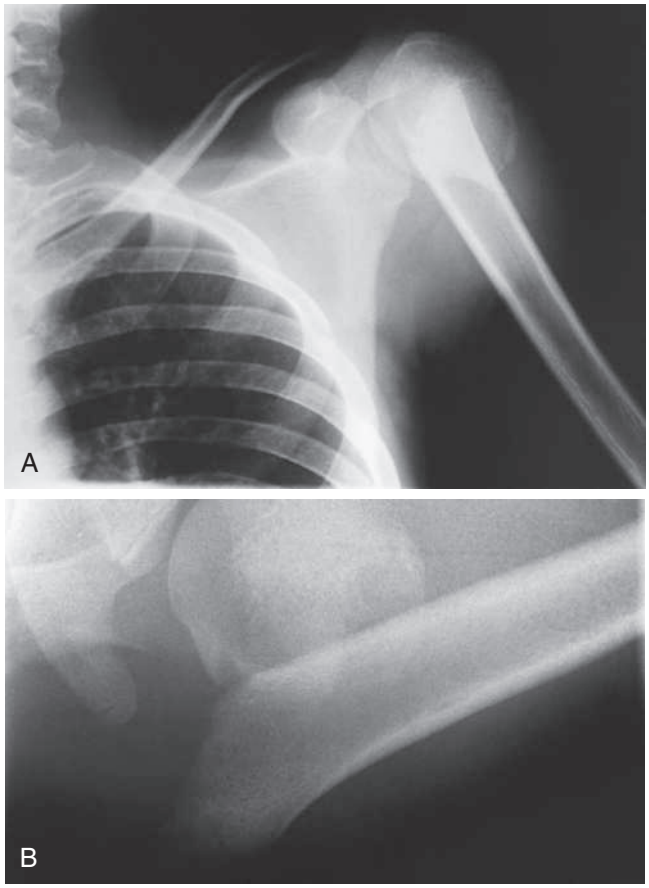

Fig. 45.13 Anteroposterior (A) and axillary (B) radiographic views of a two-part displaced fracture of the proximal humerus. The degree of displacement often is better visualized on the axillary view. (Courtesy David Nelson, MD.)

Clinical features. The affected arm is held close to the body, and movement is restricted by pain. Tenderness, hematoma, ecchymosis, deformity, or crepitus may be noted over the fracture site. A thorough neurovascular examination is essential to identify associated injuries of the axillary nerve, brachial plexus, or axillary artery (see Table 45.1). The most common complication of proximal humeral fractures is adhesive capsulitis. This complication can be prevented by the early initiation of pendular shoulder exercises, along with a thorough rehabilitation program. One of the most devastating complications is avascular necrosis (AVN), which is more common in multi-part fractures, and fracture-dislocations due to the disruption of the blood supply to the humeral head.[10] Repeated forceful attempts at reduction of fracture-dislocations may be associated with subsequent heterotopic bone formation (myositis ossificans). Neurovascular injuries (axillary nerve, brachial plexus, and axillary artery) may be encountered with displaced surgical neck fractures and fracture dislocations.

Differential diagnoses. The differential diagnosis of a proximal humerus fracture includes: glenohumeral dislocation, AC joint separation, rotator cuff tendon tear, or soft tissue injury including hematoma, contusion, and muscle strains.

Diagnostic testing. The three-view trauma series allows for assessment of the number of fracture fragments and degree of displacement or angulation. Cross-sectional imaging is usually not necessary in the ED; however, there may be certain situations where it is helpful, including making the diagnosis of an occult fracture, orthopedic surgery request for surgical planning, and further evaluation of neurovascular structures. If there is high concern for a vascular injury, a CT scan with contrast is the most appropriate study. If there is concern for a peripheral nerve injury, an MRI may be helpful, although a normal MRI does not rule out an associated nerve injury. In such instances, patients may require an outpatient electromyography (EMG) and orthopedic consultation.

Management. Minimally displaced fractures (see Fig. 45.12) constitute up to 80% to 85% of all cases. In these instances, limited displacement or angulation is present, and the fracture segments are held together by the capsule, periosteum, and surrounding muscles. Initial treatment consists of adequate analgesia and immobilization with a sling. A Cochrane review noted that rapid commencement of physiotherapy (within 1 week) resulted in less pain without compromising long-term outcomes.[11] Initial passive exercises (see Fig. 45.10) are gradually replaced by more active and resistive exercises. Most nondisplaced fractures heal over 4 to 6 weeks.

The management of displaced two-part, three-part, and four-part fractures remains controversial and an orthopedist should be consulted. A prospective randomized clinical trial failed to show a significant functional difference between operative and nonoperative treatment of displaced two-part, three-part and four-part fractures in elderly patients.[12,13] If operative treatment is selected, the procedures of choice for three-part and four-part fractures are reverse hemiarthroplasty or hemiathroplasty.[14,15]

Fracture-dislocation injuries are best managed in consultation with an orthopedic surgeon before attempts at reduction (except in cases of neurovascular compromise or unavailability of an orthopedic surgeon). Reductions of these injuries in the ED may be unsuccessful, and manipulation can cause separation of previously non-displaced segments. Closed reduction under fluoroscopic visualization and general anesthesia is preferable.

Pediatric Proximal Humeral Fracture

Foundations. Fractures of the proximal humeral physis and metaphysis are uncommon and account for a small proportion of pediatric fractures.[16] The injury can occur at any age while the physis remains open but is most common in adolescent boys. The most common mechanism of injury involves a fall onto the outstretched hand, and the fracture typically occurs through the zone of hypertrophy in the epiphyseal plate. Injuries can be classified according to their location (Salter system), stability, and degree of displacement.[16]

Clinical features. The patient typically holds the injured arm tightly against the body, using the opposite hand. The area over the proximal humerus is swollen and tender to palpation. Complications are rare and include malunion, growth plate disturbances, and injuries to the neurovascular bundle. Markedly displaced or angulated fractures can result in a residual loss of mobility.

Differential diagnoses. The differential diagnosis for pediatric proximal humeral fractures varies based on age and acuity of the injury. Differential diagnoses for acute traumatic injuries include osteochondral lesion in the GHJ (rare in the upper extremity), AC joint injury (more common in late teenage years as physis reaches maturity), and glenohumeral dislocation.

Diagnostic testing. Orthogonal radiographs help confirm the diagnosis. Comparison views may be helpful with minimally displaced fractures (Fig. 45.14). POCUS can also be used to identify these injuries.

Management. Fractures of the proximal humeral epiphysis can result in significant permanent injury and disability as the physis accounts for 80% of the longitudinal growth of the bone. Urgent orthopedic consultation should be obtained for all such injuries in the ED.

Dislocations

Sternoclavicular

Foundations. SCJ dislocations are infrequent and account for less than 1% of all dislocations.[17] Significant forces are required to disrupt the strong ligamentous stabilizers of this joint. The most common causes are MVCs and injuries sustained in high impact contact sports.

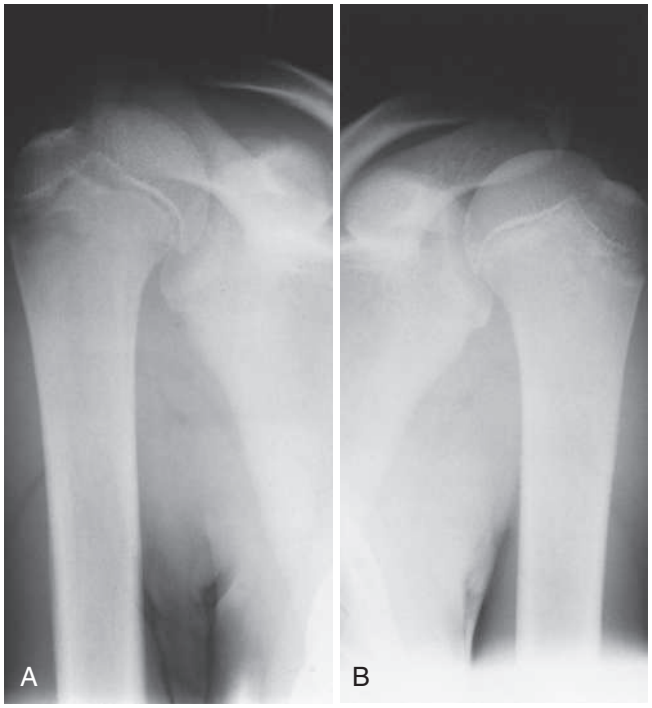

Fig. 45.14 (A) Salter I injury of the right proximal humeral epiphysis. (B), Normal left side is included for comparison.

The vast majority of dislocations are anterior. Posterior dislocations, although less common, can be associated with life-threatening injuries within the superior mediastinum.[18] The usual mechanism of injury for anterior and posterior dislocations is pictured in Fig. 45.15. Posterior dislocations can also result from a direct blow to the medial clavicle.

Injuries to the SCJ can be graded into three types.[17] A grade I injury is a mild sprain of the sternoclavicular and costoclavicular ligaments. A grade II injury is associated with subluxation of the joint (anterior or posterior) secondary to disruption of the sternoclavicular ligament and capsule. Complete rupture of the sternoclavicular and costoclavicular ligaments results in a grade III injury (true dislocation). In patients younger than 25 years old, these may represent Salter type I injuries if the medial clavicle epiphysis is unfused.[17]

Clinical features. Clinical suspicion based on mechanism and exam is the single most important factor in diagnosing these injuries. The injured extremity is flexed at the elbow and supported across the trunk by the opposite arm. Pain results from any movement of the upper extremity or lateral compression of the shoulders. The SCJ may be mildly swollen and tender to palpation. With an anterior dislocation, the displaced medial end of the clavicle may be palpable. Posterior dislocations are more painful and may be associated with complaints of hoarseness, dysphagia, dyspnea, and weakness or paresthesia in the ipsilateral upper extremity. The patient's neck is often flexed toward the injured side and the clavicular notch of the sternum may not be palpable. Hoarseness may be related to tracheal injury. Damage to the innominate vein may present as cyanosis and venous congestion of the neck, which should prompt vascular imaging and consultation. Complications of anterior injuries are primarily cosmetic. By contrast, 25% of posterior dislocations may be complicated by life-threatening injuries to intrathoracic and superior mediastinal structures.[18] These include compression or laceration of the great vessels, tracheoesophageal fistula, tracheal compression, pneumothorax, thoracic outlet syndrome, and brachial plexus injuries.

Differential diagnoses. The differential diagnosis for patients with traumatic SC joint pain include medial clavicle fracture, rib fracture, costochondral injury, sternum fracture, sternoclavicular dislocation, contusion, mediastinal injury, and pneumothorax.

Diagnostic testing. Although diagnosed clinically, sternoclavicular dislocation requires radiological confirmation. Findings on standard anteroposterior, oblique, and specialized (40-degree cephalic tilt) SCJ views are challenging to interpret. These dislocations and associated injuries are best visualized by a chest CT angiogram (Fig. 45.16). POCUS can be a useful bedside adjunctive test.[19]

Management. Treatment of grade I injuries includes sling immobilization for comfort and primary care follow-up. Immobilization generally is maintained until symptoms improve and full painless motion is restored. Grade II injuries should be immobilized with a sling and the patient referred for orthopedic follow-up care. Grade II injuries require a longer course of immobilization (4 to 6 weeks) and are more likely to be associated with persistent pain. Grade III injuries are generally managed by closed reduction and rarely with open reduction.

Anterior dislocations may be reduced in the ED with proper analgesia and on occasion may require general anesthesia. Patient positioning is optimized by a bolster between the scapulae (Fig. 45.17). Stable reductions should be maintained in a sling and referred for orthopedic follow-up care. Most reductions are unstable; and because the deformity is primarily cosmetic and not functional, the treatment of choice for recurrent anterior dislocations is benign neglect and pain control.

Posterior dislocations constitute true orthopedic emergencies and should be reduced expeditiously. Ideally, reduction of posterior dislocations should be attempted under general anesthesia due to the risk of injury to mediastinal structures and potential need for open reduction.[18] ED reduction may be required for patients with airway obstruction or vascular compromise. The patient is positioned as described previously (see Fig. 45.17). If traction alone does not reduce the dislocation, concurrent clavicular manipulation may be helpful. After sterile preparation of the skin and administration of local anesthesia, the clavicle shaft is grasped with a sterile towel clip and pulled out anterolaterally (Video 45.1).[18] Once reduced, these injuries generally are stable and can be immobilized with a sling. An alternate method of reduction involves traction to the adducted injured arm while both shoulders simultaneously are forced posteriorly with direct pressure. This technique levers the clavicle into place and requires far less force.

Acromioclavicular Joint

Foundations. Injuries of the ACJ occur primarily in young men as a result of MVCs, bicycle accidents, or participation in high impact contact sports. The most common mechanism of injury involves a fall or direct blow to the point of the shoulder with the arm adducted. The ACJ also can be injured after a fall onto the outstretched hand. The

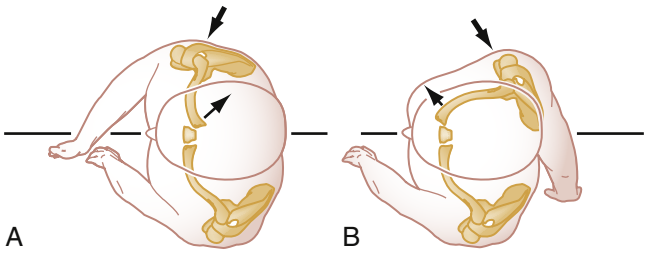

Fig. 45.15 Mechanisms That Produce Posterior and Anterior Displacements of the Sternoclavicular Joint. (A) When a compression force *(upper arrow)* is applied to the posterolateral aspect of the shoulder, the medial end of the clavicle is displaced posteriorly *(lower arrow)*. (B) When the lateral compression force *(upper arrow)* is directed from the anterior position, the medial end of the clavicle is dislocated anteriorly *(lower arrow)*. The same mechanism could apply with any type of lateral compression injury of the shoulder. (From Neer CS, Rockwood CA. Fractures and dislocations of the shoulder. In Rockwood CA, Green DP, eds. *Fractures in adults*. 4th ed. Philadelphia: JB Lippincott; 1984.)

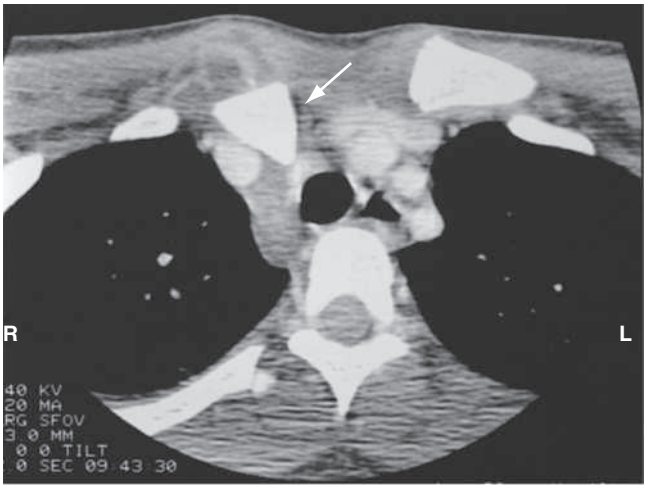

Fig. 45.16 This computed tomography (CT) scan shows posterior dislocation of the right sternoclavicular joint (SCJ; *arrow*) with compression of the superior mediastinum. (Courtesy Donald Sauser, MD.)

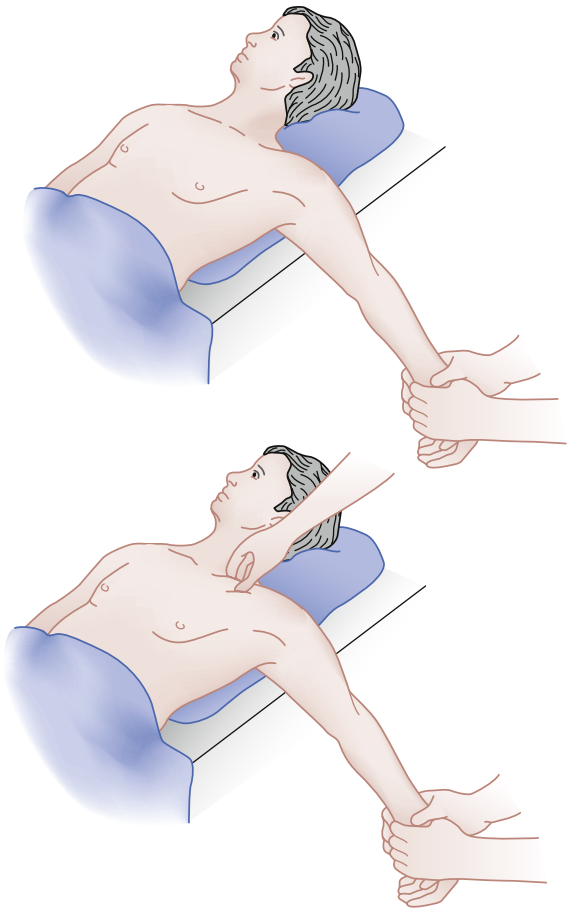

Fig. 45.17 Reduction of Dislocated Sternoclavicular Joints. A rolled sheet is placed posteriorly between the shoulder blades to elevate both shoulders approximately 5 cm above the table. Traction is applied to the arm in an extended (10- to 15-degree) and abducted (90-degree) position. If reduction does not occur, an assistant can add posterior pressure on the medial end of the clavicle for anterior dislocations (not pictured). (From Simon RR. *Emergency orthopedics: the extremities*. 7th ed. Norwalk, CT: McGraw-Hill; 2015.)

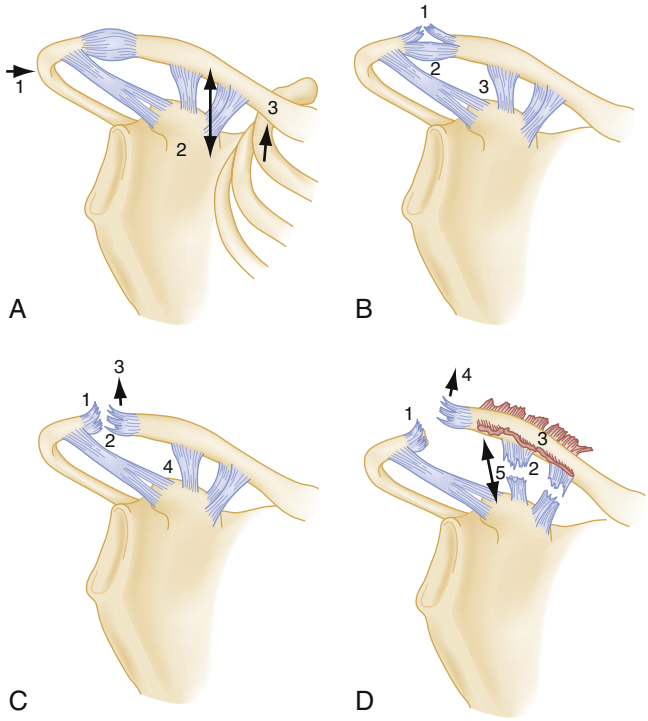

Fig. 45.18 Mechanism of Injury and Classification of Acromioclavicular Joint Injuries. *Arrows indicate direction of applied force and relevant movement.* (A) The direct force is applied to the point of the lateral shoulder (1); the scapula and attached clavicle are forced downward and medially; the clavicle approaches the first rib (2). If the force continues, the first rib abuts the clavicle, producing a counterforce (3). Depending on the magnitude of the force, a grade I, II, or III sprain may occur. (B) Grade I sprain. A few fibers of the acromioclavicular ligament stretch, and a few tear (1); the ACJ is stable (2); the coracoclavicular ligament is intact (3). (C) Grade II sprain (subluxation). The joint space widens but the coracoclavicular distance is maintained. The capsule and the acromioclavicular ligament rupture (1); the joint is lax and unstable (2); the end of the clavicle rides upward, with displacement usually less than half of the width of the end of the clavicle (3); the coracoclavicular ligament remains intact (4); the attachments to the trapezius and deltoid remain intact. (D) Grade III sprain (dislocation). The capsule and acromioclavicular ligaments rupture (1); the coracoclavicular ligament ruptures (2); the insertions of the trapezius and deltoid tear away (3); the clavicle rides upward (4); the interval between the clavicle and the coracoid process is greatly increased (5). *Not pictured:* In type IV and V injuries, the ligamentous and muscle disruptions are similar to the disruptions encountered in type III injuries, but the clavicle is displaced either posteriorly into the trapezius (type IV) or superiorly in an exaggerated fashion (coracoclavicular distance increased 100% to 300%; type V). In the rare type VI injury, the clavicle is displaced inferiorly. (From DePalma AF. *Surgery of the shoulder*. 3rd ed. Philadelphia: JB Lippincott; 1983.)

weak acromioclavicular ligaments rupture first. With increasing force, the coracoclavicular ligament ruptures, and the attachments of the deltoid and trapezius muscles are torn from the distal clavicle.

Classification is based on the degree of damage sustained by the acromioclavicular and coracoclavicular ligaments (Fig. 45.18) and the Rockwood 6-class grading system.[20]

Clinical features. Patients should be examined while they are upright, because the supine position can mask ACJ instability, and it is helpful to visualize both shoulders simultaneously to assess for symmetry. Type I and type II injuries are associated with mild tenderness and swelling over the ACJ margin, with minimal deformity and full range of motion (albeit painful). Patients with type III, IV, V, and VI injuries have severe pain and hold the arm tightly adducted to reduce traction stress across the joint. In type III injuries, the shoulder hangs downward and the clavicle rides high, producing a characteristic clinical deformity that can be reduced by an upward force under the elbow. In type IV injuries, the clavicle may be palpable posteriorly. In type V injuries, the clavicle is dramatically displaced superiorly and palpable subcutaneously above the acromion; however, unlike type III it is not reducible by elbow elevation. In type VI injuries, the clavicle displaces inferolaterally behind the biceps tendon and the shoulder assumes a flattened clinical appearance.

The most common concurrent injuries are associated fractures of the clavicle and coracoid process. The most common complications of ACJ injuries are residual symptomatic instability, cosmetic deformity, and joint tenderness due to secondary degenerative changes.[21]

Differential diagnoses. While a lateral blow to the shoulder can cause an AC joint dislocation, other important diagnostic considerations include distal clavicle, coracoid or acromion process fractures, rotator cuff injuries, and glenohumeral dislocation.

Diagnostic testing

Radiology. The recommended projections include routine anteroposterior and axillary lateral view to evaluate for vertical

migration of the clavicle and anteroposterior displacement, respectively. A Zanca view (an anteroposterior with 15-degree cephalic tilt view) can improve visualization by removing the scapula from behind the joint. Anteroposterior and Zanca views are ideally obtained with a view of both joints on a single-wide film. Standing radiographs help unmask a higher-grade injury. A difference of more than 25% between the injured and uninjured sides is diagnostic of a complete coracoclavicular disruption.[20] With type I injuries, the radiographic appearance is essentially normal. With type II injuries, radiographs show upward or posterior displacement of the clavicle less than half the height of the clavicle and less than 25% side to side difference of coracoclavicular distance.[20] With type III, IV, and V injuries, radiographic features include a widened joint, an increased coracoclavicular distance, and either superior or posterior displacement of the clavicle (Fig. 45.19) with the lower margin of the clavicle cephalad to the upper margin of the acromion. Advanced cross-sectional imaging is rarely indicated in the ED management of AC joint separations. Vascular injury is extremely unlikely with AC joint injuries; however, if there is suspicion, a CT scan with contrast can be obtained. Orthopedic surgeons may request a CT scan to help further characterize the anatomy and associated injury pattern for potential surgical patients. MRI may be helpful in the evaluation of soft tissues (e.g., rotator cuff, labrum, ligaments) but is rarely indicated in the ED.

Management. Type I and II injuries should be immobilized in a sling for comfort and to remove stress on injured ligaments. Patients with these injuries can be referred for follow-up with their primary care physician. When pain has subsided (1 to 2 weeks), gradual range-of-motion and strengthening exercises can begin, with a return to sporting activities when pain-free function has been achieved (usually 2 to 6 weeks).

The management of type III injuries is variable, although most favor initial nonoperative management.[22,23] Selected patients who are young, competitive athletes, or perform repetitive overhead activities may be candidates for surgical intervention. Treatment of type III injuries in the ED should consist of sling immobilization with sports medicine or orthopedic referral for follow-up in 1 to 2 weeks. Type IV and V injuries classically have been treated surgically; however, recent literature suggests that nonoperative treatment leads to similar functional outcomes.[21] Type VI injuries require early surgical treatment.

Glenohumeral Dislocations

Foundations. The GHJ is the most commonly dislocated major joint in the body. Dislocation follows a bimodal age distribution for men, age 20 to 30 and greater than 85 years old, however there is a unimodal age distribution for women in their 60s.[24] The GHJ can dislocate anteriorly, posteriorly, or inferiorly. Anterior dislocations account for 96% to 98% of all glenohumeral dislocations.[25] Posterior dislocations account for most of the remainder, whereas inferior (*luxatio erecta*) dislocation is rare.

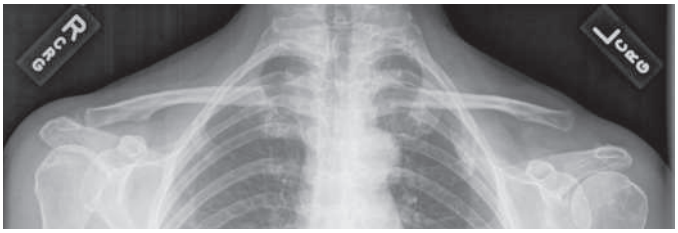

Fig. 45.19 Third-Degree Sprain of the Left Acromioclavicular Joint. The coracoclavicular distance is increased. Bilateral clavicle view (patient is standing) provides comparison to the unaffected side. (Courtesy Erik Foss, MD.)

Anterior Dislocations

Pathophysiology. Anterior dislocations can result from indirect or direct forces. In younger persons, the injury usually is sustained during athletic activities involving rapid movements with the arm elevated, abducted and externally rotated, or rarely by a direct posterolateral force. A characteristic pathologic feature is avulsion of the anteroinferior glenohumeral ligament with capsulolabral detachment (Bankart's lesion). In older patients, a fall onto the palm of an outstretched arm is the more common mechanism of injury.

Anterior dislocations can be classified according to their cause (traumatic or nontraumatic), frequency (primary or recurrent), and the anatomic position of the dislocated humeral head (Figs. 45.20 and 45.21). In most dislocations (99%) the humeral head will assume

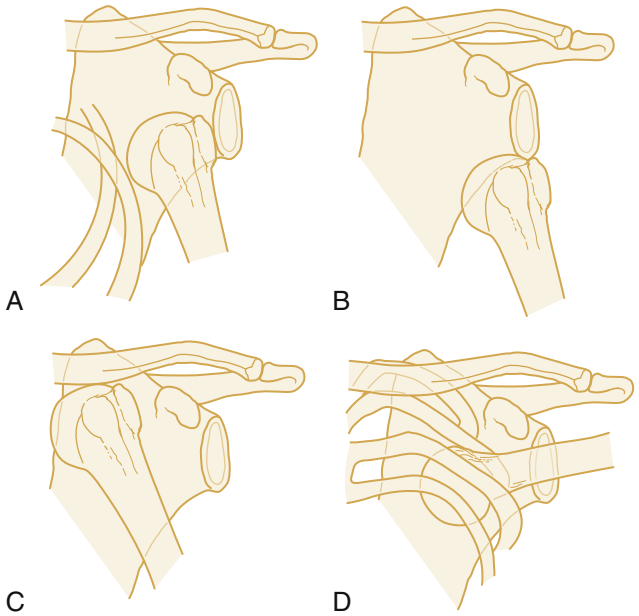

Fig. 45.20 Types of Anterior Dislocation. (A) Subcoracoid. (B) Subglenoid. (C) Subclavicular. (D) Intrathoracic. (From DePalma AF. *Surgery of the shoulder.* 3rd ed. Philadelphia: JB Lippincott; 1983.)

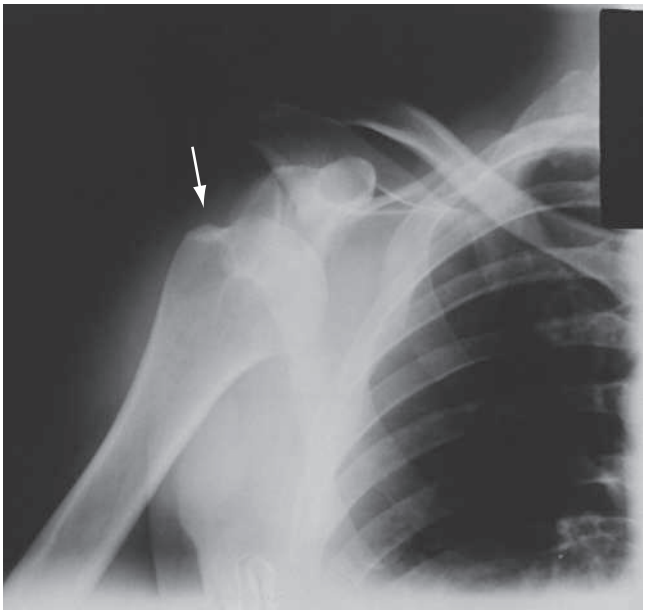

Fig. 45.21 Recurrent anterior subcoracoid dislocation with Hill-Sachs deformity of the humeral head *(arrow).*

a subcoracoid or subglenoid position. Of these, the subcoracoid is more common, and the head is displaced anteriorly and rests inferior to the coracoid process. Subclavicular and intrathoracic dislocations are extremely rare and involve the addition of strong lateral to medial forces.

Clinical features. The patient presents in severe pain often supporting the dislocated shoulder with the opposite extremity. The lateral edge of the acromion process is prominent, and the normally rounded shoulder assumes a "squared-off" appearance. The coracoid process is indistinct, and the anterior shoulder appears full.

Anterior dislocations can be associated with injuries of the brachial plexus, axillary nerve or artery. Axillary nerve injury occurs in less than 10% of patients.[24,26] Complications from the dislocation event include fractures, soft tissue trauma and neurovascular injuries. Most axillary nerve injuries are neurapraxic, management is expectant, and the prognosis for recovery of function is good. Rotator cuff tears are especially common in primary dislocations in patients older than 40 years old, increasing to 80% in patients over 60 years old. Supraspinatus tears resulting in failure to abduct the arm are commonly confused with an axillary nerve injury. Most of these patients require tendon and capsular repair to restore shoulder stability. Recurrence also is a common complication after anterior dislocation and there is an inverse relationship between age and stability.[27] Patients younger than 30 years old have recurrence rates of 79% to 100%. A large Hill-Sachs deformity, Bankart's lesion, or a glenoid rim fracture are associated with increased risk of recurrence. The traditional method of treatment (immobilization followed by physical therapy) is ineffective in preventing redislocation in young athletic patients. Bankart lesions are believed to be the primary predisposing factor for recurrence, and affected patients derive benefit from early arthroscopic repair of the lesion.[27] Recurrence rates decline with increasing age and in the presence of a greater tuberosity fracture.

Differential diagnoses. Patients presenting with shoulder pain and a full anterior shoulder on examination should be evaluated for glenohumeral dislocation, proximal humerus fracture, and proximal biceps tendon rupture. Less likely, but also worth considering, are muscular tears (pectoralis major, pectoralis minor, biceps brachii).

Diagnostic testing

Radiology. Radiographs including anterior-posterior, transscapular Y view, and axillary lateral will confirm the clinical diagnosis and identify the position of the humeral head. Radiographs are indicated in first-time dislocations but may be omitted in patients with a history of recurrent dislocations. POCUS may be useful as a diagnostic bedside test.[25] Some patients with a dislocation will have an associated fracture—most commonly, a compression fracture of the posterolateral aspect of the humeral head (Hill-Sachs deformity) caused by forceful impingement against the anterior rim of the glenoid fossa. Hill-Sachs fractures are not clinically significant unless they are large enough to cause recurrent shoulder instability or painful clicking or catching, in which case surgical repair may be necessary.

Management. Reduction of the dislocation should be accomplished expeditiously, because the incidence of neurovascular complications increases with time as does the reduction difficulty due to muscle spasm. For healthy patients with a history of recurrent dislocation, reduction may be attempted before imaging. A post-reduction film remains advisable to aid in the identification of glenoid rim fractures, as well as Hill-Sachs deformities, which when large can be associated with subsequent shoulder instability. POCUS can also be used to assess for successful relocation.

Procedural sedation is often used to facilitate reduction in the ED. Adequate analgesia often can also be provided through intra-articular injection of a local anesthetic agent. This technique is especially useful when intravenous procedural sedation is contraindicated or unable to be performed.[28] Longer acting local anesthetic agents (e.g. bupivacaine) may also offer continued post-reduction analgesia. Multiple studies have found that intra-articular lidocaine achieved similar reduction effectiveness (RR 0.92) when compared with procedural sedation with fewer complications. Depending on the duration of the dislocation, nature (primary vs. recurrent) and technique, reduction can also be attempted and accomplished successfully without the use of any analgesia or sedation, provided the examiner is prepared to stop the procedure if the patient experiences pain.

Reduction can be accomplished with various techniques, most of which involve traction, leverage, or scapular manipulation principles. The ideal method should be simple, quick, and effective; require little assistance; and cause no additional injury to the shoulder. It is important to be familiar with several techniques of reduction because none are uniformly successful. Several common techniques are described in Table 45.3. Clues to a successful reduction include feeling of a "clunk," relief of pain, normalization of anatomy, and improvement in range of motion. The neurovascular examination should be repeated and recorded after any reduction attempt. Most of these techniques are usually effective; however, approximately 5% to 10% of dislocations cannot be reduced in the ED and require reduction under anesthesia. After reduction, the affected extremity is immobilized with a sling and swathe bandage for comfort. Patients should be discharged with adequate analgesia and follow-up. Primary dislocations and complicated cases (associated fracture, rotator cuff tear, axillary nerve injury) should follow up with an orthopedist or sports medicine specialist in 1 to 2 weeks. Immobilization duration can be individualized according to age, dislocation type (initial vs. recurrent) and associated injury. General recommendation is sling immobilization until orthopedic follow-up in 1 to 2 weeks. Younger patients (under 30 years old and especially those with recurrent dislocations) can benefit from the capsular stiffness incurred by longer period of immobilization. Older patients (over 50 years old) are unlikely to have a recurrent dislocation and therefore benefit from early range of motion exercises to prevent adhesive capsulitis. The most important post-reduction therapy is a rehabilitation program aimed at restoring the static and dynamic stabilizers of the GHJ.

Posterior Dislocation

Pathophysiology. Posterior dislocations are uncommon, accounting for fewer than 5% of all glenohumeral dislocations.[24,26] The glenoid fossa acts as a partial buttress protecting against posterior dislocations. Posterior dislocations are easily missed on initial evaluation. Obtaining true orthogonal images (axillary lateral or scapular "Y" view) can prevent misdiagnosis. The axillary lateral if obtainable is preferable. If missed, posterior dislocations may remain unrecognized ("locked posterior dislocations") for weeks or months.

A posterior dislocation can result from several distinct mechanisms of injury. A posterior dislocation can occur after a fall onto the outstretched hand with the arm held in flexion, adduction, and internal rotation or after a direct blow to the anterior aspect of the shoulder.[26] Convulsive seizures (epileptic or after electrical shock) have been associated with unilateral or bilateral posterior dislocations. A seizure disorder should be suspected in cases of unexplained nocturnal posterior dislocations. Acute posterior dislocations are classified into three types—subacromial (most common), subglenoid, and subspinous—based on the final resting position of the humeral head.

Clinical features. Early diagnosis is essential to prevent long-term complications. The affected arm is held across the chest in adduction and internal rotation. The normal shoulder contour is replaced by a flat, squared-off appearance, and the coracoid process is prominent and easily palpated. Sometimes a dimple is apparent in the anterior

TABLE 45.3 Techniques to Reduce Anterior Shoulder Dislocations

Reduction Technique	Description
Stimson (hanging weight)[a]	Patient placed prone with the dislocated shoulder hanging over the edge of the examining table. Attach a 10- or 15-pound weight to the wrist or lower forearm providing traction in forward flexion. Reduction usually occurs over 20–30 min (see Fig. 45.22).
Traction/countertraction	Apply traction along the abducted arm while an assistant using a folded sheet wrapped across the chest applies countertraction. Although commonly used, this technique requires more force than others (see Fig. 45.23).
External rotation method	No traction involved. Patient seated or in supine, the involved arm is slowly and gently adducted to the side. The elbow is flexed to 90 degrees, and slow, gentle external rotation is applied to achieve reduction (see Fig. 45.24). Success rates with this method range from 80% to 97%.
Cunningham[a]	Patient sits without slouching in a hard-backed chair. Adduct the affected arm to the body and place elbow in full flexion resting against operator's shoulder. Operator then provides traction by placing their wrist on patient's forearm while asking the patient to shrug shoulders superiorly and posteriorly. The operator adds massage down through the trapezius, deltoid, and the biceps muscles. This technique is targeted to relax muscles causing a dynamic obstruction.
Milch technique[a]	Patient is placed supine and the head of the bed is elevated 20–30 degrees. The affected arm is held by the wrist and slowly abducted and externally rotated. The operator stops whenever resistance to motion is encountered and continues when the patient is relaxed. If the humerus has not reduced by the time 90 degrees of abduction and 90 degrees of external rotation have been reached, gentle longitudinal traction is applied along the humerus while the free hand is used to exert lateral and superior pressure on the humeral head to complete the maneuver. The effectiveness of this method has been attributed in part to more conical symmetry of the muscle forces acting across the glenohumeral joint (GHJ).
FARES[a]	A variation of the Milch technique called *FARES* (FAst, REliable, and Safe). FARES technique adds oscillation in a vertical direction while the affected arm is abducted. It is more effective, faster, and less painful than the traction/countertraction and Kocher methods.
Scapular manipulation[a]	Reduction is accomplished by repositioning the glenoid fossa rather than the humeral head. Manipulation can be combined with the other techniques, particularly Stimson or traction/countertraction. Apply traction (manual or hanging weights), and then manipulate the scapula by rotating the inferior tip medially and stabilizing the superior and medial edges with the opposite hand. This technique can also be used in a seated position in which a second operator applies traction in the forward horizontal position. Scapular manipulation can be difficult in obese patients, in whom it is difficult to palpate and grasp the inferior tip of the scapula (see Fig. 45.25).
Not recommended	Hippocratic method (traction with the foot in the axilla) and the Kocher maneuver (leverage, adduction, and internal rotation), are no longer recommended because of a high incidence of associated complications (axillary nerve injury, humeral shaft and neck fractures, capsular damage).

[a]This may also be attempted with minimal to no analgesia or sedation.

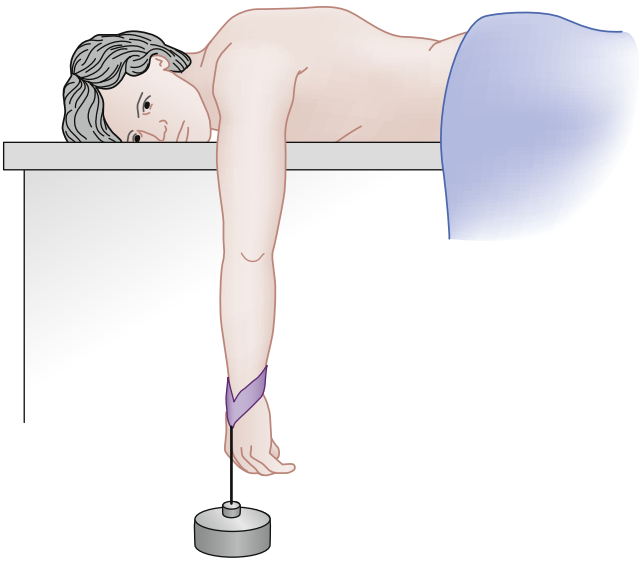

Fig. 45.22 Stimson or hanging weight method of reduction for anterior shoulder dislocations.

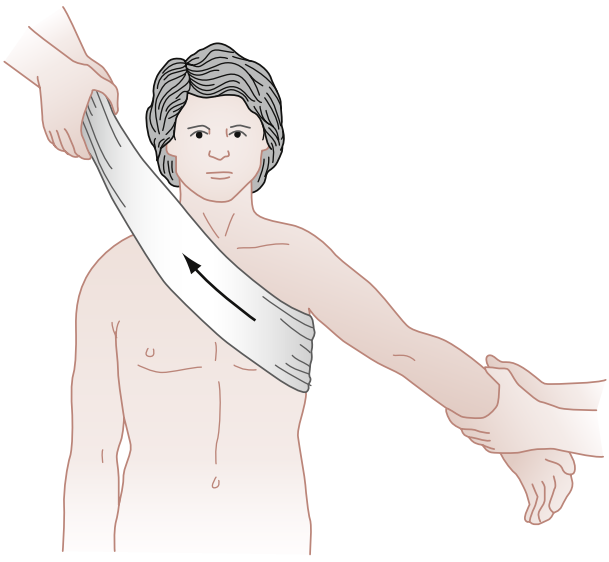

Fig. 45.23 Traction/countertraction method for reducing anterior shoulder dislocations.

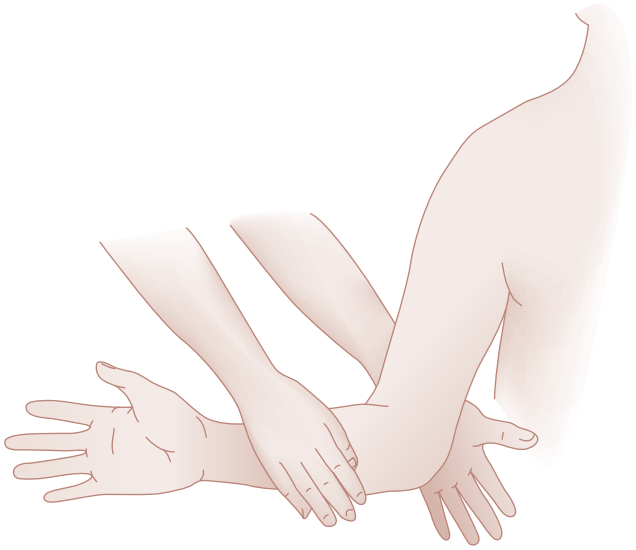

Fig. 45.24 External Rotation Technique for Reducing Anterior Shoulder Dislocations. The involved arm is slowly adducted to the patient's side, and the elbow is flexed 90 degrees. Gentle external rotation is applied to the forearm to achieve reduction. (From Simon RR, Koenigsknecht SJ. *Emergency orthopedics: the extremities*. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

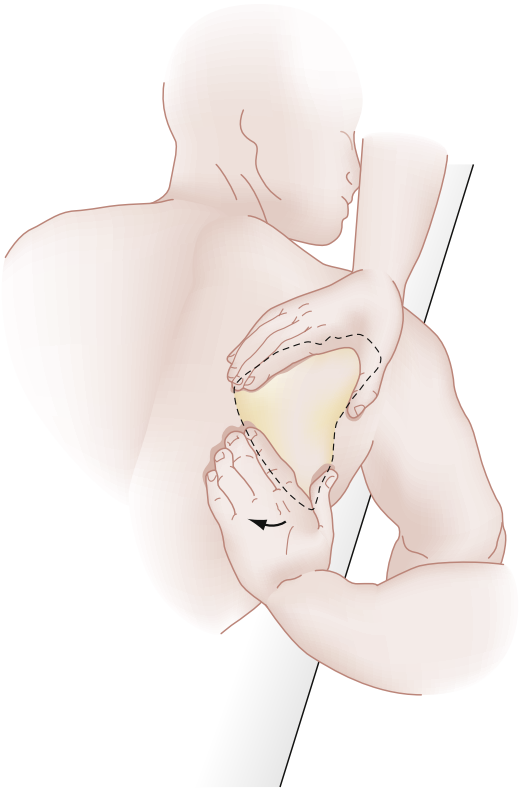

Fig. 45.25 Proper hand position and direction of rotation during shoulder relocation via the scapular manipulation technique. *Arrow indicates direction of applied force.* (From Kothari RU, Dronen SC. The scapular manipulation technique for the reduction of acute anterior shoulder dislocations. *J Emerg Med*. 1990;8:625.)

shoulder inferior to the acromion. The humeral head may be palpable posteriorly beneath the acromion process. Abduction is severely limited, external rotation is completely blocked, and restricted forearm supination may be present.

Posterior glenohumeral dislocations usually are associated with anteromedial impression fractures of the articular surface. A similar fracture of the posterolateral aspect of the humeral head is present with anterior dislocations (Hill-Sachs). Impression fractures involving more than 20% of the articular surface usually are unstable and require surgical repair post reduction.

Fractures of the glenoid rim, greater tuberosity, lesser tuberosity, and humeral head account for most associated injuries. The subscapularis muscle rarely may be avulsed from its insertion site on the lesser tuberosity. Neurovascular injuries are uncommon because the anterior location of the neurovascular bundle protects it from injury.

Differential diagnoses. Posterior glenohumeral subluxation is a much more common event than posterior glenohumeral dislocation and remains an important consideration in the evaluation of all patients. These patients are at risk of a posterior labral tear as a result of the trauma. Other important considerations include proximal humerus fracture, glenoid fracture, and rotator cuff strain or tear.

Diagnostic testing

Radiology. True or standard anteroposterior radiographs can appear deceptively normal with posterior dislocations. Radiographic features include loss of the half-moon elliptic overlap of the humeral head and glenoid fossa on a standard anteroposterior film. In addition, the distance between the anterior glenoid rim and the articular surface of the humeral head is increased (the *rim sign*). The humeral head is profiled in internal rotation and takes on a "lightbulb" or "drumstick" appearance (Fig. 45.26A). A true anteroposterior film shows abnormal overlap of the glenoid fossa with the humeral head (see Fig. 45.26B) and can be useful in visualizing an impaction fracture of the anteromedial humeral head (reverse Hill-Sachs deformity). This fracture may produce a curvilinear density on the frontal projection parallel to the articular cortex of the humeral head (the *trough sign*). An orthogonal view, such as a trans-scapular Y (see Fig. 45.26C), axillary lateral (see Fig. 45.26D), or apical oblique view, confirms the diagnosis. The axillary lateral view or apical oblique view also identifies associated fractures of the humeral head and posterior glenoid rim. If an adequate orthogonal view cannot be obtained, a shoulder CT scan should be considered. POCUS has also been used to diagnose posterior shoulder dislocations in the ED.

Management. Closed reduction may be attempted in the ED with procedural sedation. The technique incorporates internal rotation and lateral traction to dis-impact the humeral head from the glenoid rim. In the absence of humeral neck fracture or significantly engaged reverse Hill-Sachs lesion, the *Stimson technique* can also be used (see Table 45.3). If unsuccessful, reduction with the patient under general anesthesia is indicated. After reduction, the shoulder should be immobilized in a simple sling, or if available in an external rotation sling with slight abduction (with the use of a towel roll) until orthopedic follow-up in 1 to 2 weeks. Cases that were missed initially and manifest as chronic or "locked" posterior dislocations should be discussed with the orthopedist, because they often require semi-elective open reduction and internal fixation or arthroplasty.

Inferior Glenohumeral Dislocation (Luxatio Erecta)

Pathophysiology. *Luxatio erecta* is a rare type (<0.5%) of glenohumeral dislocation in which the superior aspect of the humeral head is forced

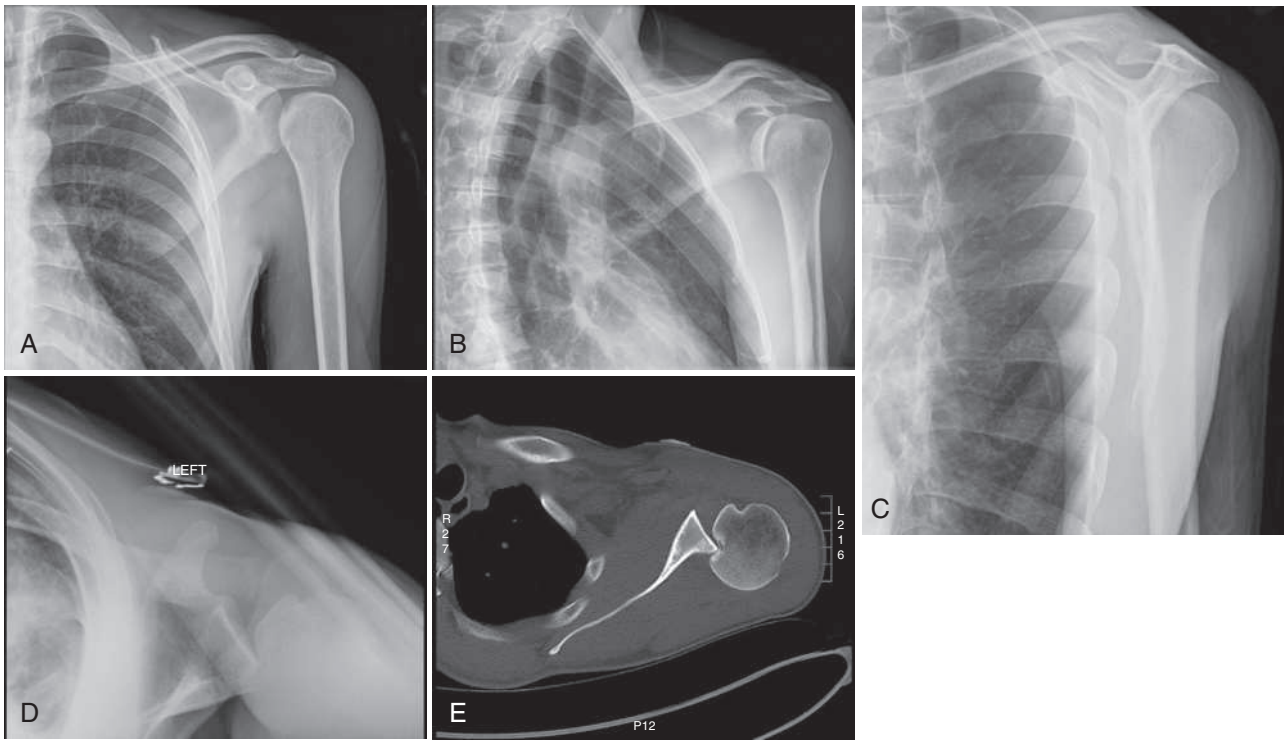

Fig. 45.26 Routine anteroposterior (A) radiograph of a posterior dislocation. Note the "lightbulb" or "drumstick" appearance of the humeral head while in internal rotation. True anteroposterior (Note the abnormal overlap of the glenoid rim and humeral head) (B) transscapular (C) and axillary (D) radiographic views of a posterior glenohumeral dislocation. Axial CT image showing locked posterior dislocation with reverse Hill-Sachs lesion (E).

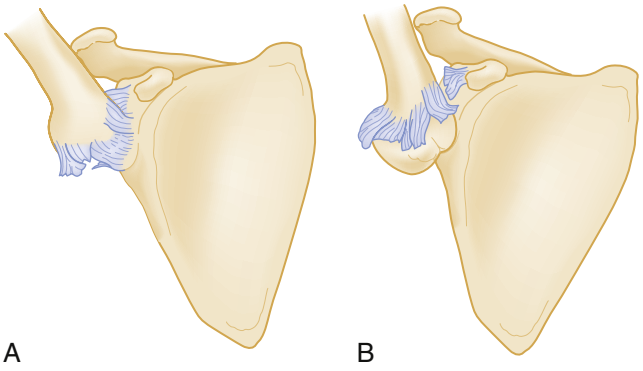

Fig. 45.27 Inferior Dislocation (Luxatio Erecta). (A) The mechanism by which this injury occurs in hyperabduction. (B) Leverage from impingement of the humeral shaft against the acromion ruptures the capsule and dislocates the head inferiorly. (From Simon RR, Koenigsknecht SJ. *Emergency orthopedics: the extremities*. 2nd ed. Norwalk, CT: Appleton & Lange; 1987.)

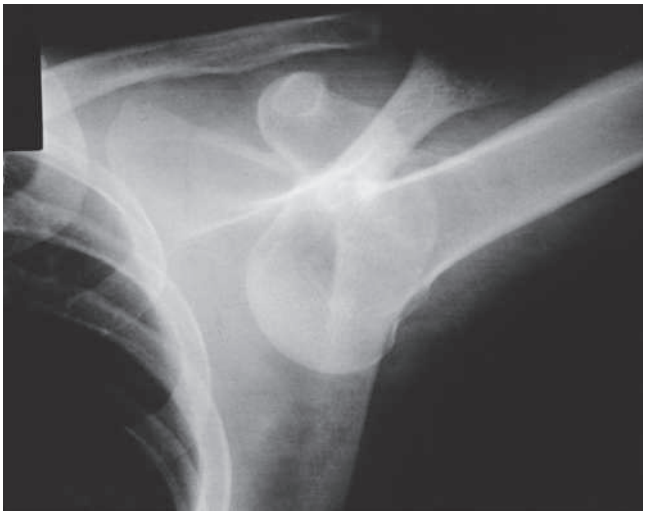

Fig. 45.28 Anteroposterior Radiographic View of an Inferior Glenohumeral Dislocation. The humeral shaft lies parallel to the spine of the scapula.

below the inferior rim of the glenoid fossa (Fig. 45.27). Application of a direct axial load to an abducted shoulder also can disrupt the weak inferior glenohumeral ligament and drive the humeral head downward.

Clinical features. Clinically, the patient has the arm locked overhead in 110 to 160 degrees of abduction. The elbow usually is flexed, and the forearm typically rests on top of the head. The shoulder is fixed in this position. The inferiorly displaced humeral head may be palpable along the lateral chest wall. A thorough neurovascular examination is essential to evaluate for associated injuries. Neurapraxic lesions of the brachial plexus are common, and thrombosis of the axillary artery has been reported. Other associated injuries include tears of the rotator cuff, damage to the glenoid labrum, and avulsion fractures of the greater tuberosity.[29]

Differential diagnoses. Luxatio erectae dislocations are easily mistaken, diagnosed, and treated as subglenoid anterior dislocations, because the radiographic features are remarkably similar.

Diagnostic testing

Radiology. Standard radiographs show the superior articular surface inferior to the glenoid fossa (Fig. 45.28). In addition, the

humeral shaft characteristically lies parallel to the spine of the scapula on the anteroposterior view. This radiographic feature is useful in distinguishing luxatio erecta from a subglenoid anterior dislocation; in the latter, the humeral shaft lies parallel to the chest wall. Associated fractures of the acromion, coracoid, clavicle, greater tuberosity, humeral head, and glenoid rim are common.

Management. Reduction usually can be accomplished by traction/countertraction maneuvers (Fig. 45.29) under procedural sedation. Regional anesthesia in the form of an ultrasound-guided interscalene block can also facilitate reduction. Multiple attempts may be necessary; occasionally, "buttonholing" of the capsule will prevent closed reduction, necessitating an orthopedic consultation for open reduction. An alternative approach is the two-step closed reduction maneuver in which the inferior dislocation is first converted into an anterior dislocation before being reduced.

Scapulothoracic Dissociation

Foundations. Scapulothoracic dissociation is a rare and severe injury characterized by complete disruption of the scapulothoracic articulation and may be thought of as a partial or complete closed internal forequarter amputation of the upper extremity. Mechanism of injury involves a sudden traction force to the body while the arm remains fixed or a high energy distracting force directed over the shoulder. Approximately half of the reported cases involve motorcycle accidents, with the injury occurring when the motorcyclist hangs onto the handlebars while the body is forced away.

Clinical features. Because most patients present with significant concomitant trauma, the dislocation may not be initially recognized. Massive local soft tissue swelling of the shoulder, clavicle distraction, and more than 1 cm of lateral displacement of the scapula on the anteroposterior chest radiograph is considered pathognomonic (Fig. 45.30). Clavicle distraction injuries include acromioclavicular separation, displaced fractures of the clavicle, and dislocations of the SCJ. Vascular lesions (subclavian, axillary, or brachial vessels) have been reported in 65% to 100% of patients and severe neurologic injuries in 95%. Acute limb ischemia is rare because of the extensive collateral network in the shoulder. Outcomes generally are poor, with death in 10% of cases and a flail anesthetic upper extremity in complete brachial plexus injuries often requiring above-elbow amputation.

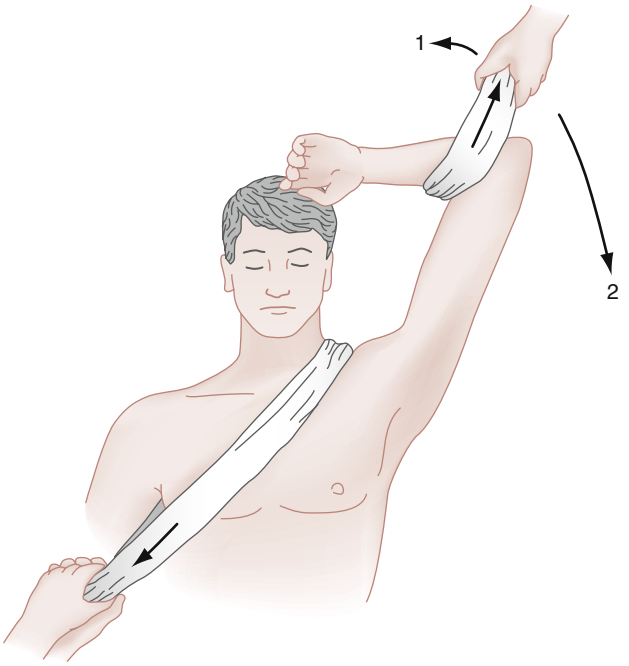

Fig. 45.29 Traction/Countertraction Method for Reduction of Luxatio Erecta Humeri. *Arrows indicate direction of applied force and relevant movement.* The initial maneuver (1) includes steady axial traction in line with the humeral shaft position, followed by gentle abduction. This reduces the glenohumeral dislocation. At this point (2), the arm is brought down to a position of adduction and internal rotation. (Redrawn from Davids JR, Talbott RD. Luxatio erecta humeri: a case report. *Clin Orthop Relat Res.* 1990;252:144.)

Differential diagnoses. Scapulothoracic disassociation is the result of a significant forceful movement and evaluation for concurrent neurovascular injuries is paramount to prevent secondary neurovascular complications. Alternative injuries that can result from a similar mechanism include brachial plexus injury, glenohumeral dislocation, scapular fracture, proximal humerus fracture, and AC joint dislocation.

Diagnostic testing. Vascular and neurologic injuries can be confirmed through emergent CT angiography and MRI.[30]

Management. Identification is a critical step in the management of this injury. Rarely occurring in isolation, these dislocations will typically require consultation with a trauma surgeon for ongoing management of multiple traumatic injuries. Additionally, in the case of a suspected vascular injury, early consultation with a vascular surgeon is necessary to prevent ischemic complications. There is no clear consensus regarding the timing of osseous stabilization or optimal management of nerve injuries. The complexity of the injury requires a decision tailored to the patient. It is recommended that early consultation with a trauma surgeon be initiated to help guide patient-specific decisions.

Soft Tissue Conditions

Impingement Syndrome

Foundations. Impingement syndrome of the subacromial space occurs across a wide spectrum of the population from the young adult overhead throwing athlete to the older adult performing repetitive daily activities. This exists as a pathophysiologic continuum from rotator cuff tendinopathy and subacromial bursitis to the endpoint of rotator cuff rupture. The subacromial space is the area between the coracoacromial arch and the greater tuberosity of the humerus. This space, which is only a few millimeters wide, contains the long head of the biceps, the rotator cuff, and the subacromial bursa. The bursa provides the gliding mechanism between the musculotendinous cuff and the coracoacromial arch. Impingement can occur during shoulder forward flexion, between 60 and 120 degrees of abduction and in the extremes of adduction. The critical wear from impingement is centered on the supraspinatus tendon, near its insertion on the greater tuberosity. Narrowing of the subacromial space (due to anatomic variants of anterior acromion) and occupations that require excessive overhead activity accelerate the entire process resulting in rotator cuff tendinitis. With time, the inflammatory reaction spreads to involve the adjacent bursa. This inflammation leads to edema, thickening, and fibrosis, further narrowing the subacromial space (secondary impingement) eventually followed by attritional changes within the rotator cuff. Because the rotator cuff is a primary humeral head depressor, loss of function worsens secondary impingement.

The impingement process also may involve the long head of the biceps. In such cases, bicipital tendinitis, degeneration, or rupture may also be present. Impingement in this context occurs at 120 to 180 degrees of abduction (Fig. 45.31).

Clinical features. The spectrum of illness is marked by a progression of symptoms. Initially patients report a dull ache around the deltoid area after strenuous activity. The inflammatory process within the bursa and tendons leads to the formation of minor adhesions. Disruption of these

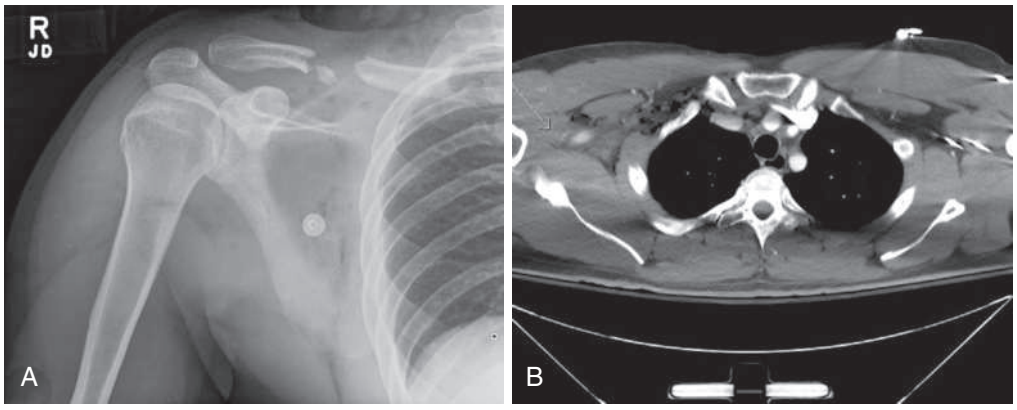

Fig. 45.30 Scapulothoracic dissociation with associated clavicle fracture (A) and computed tomography (CT) scan of associated axillary artery injury *(arrow)* (B).

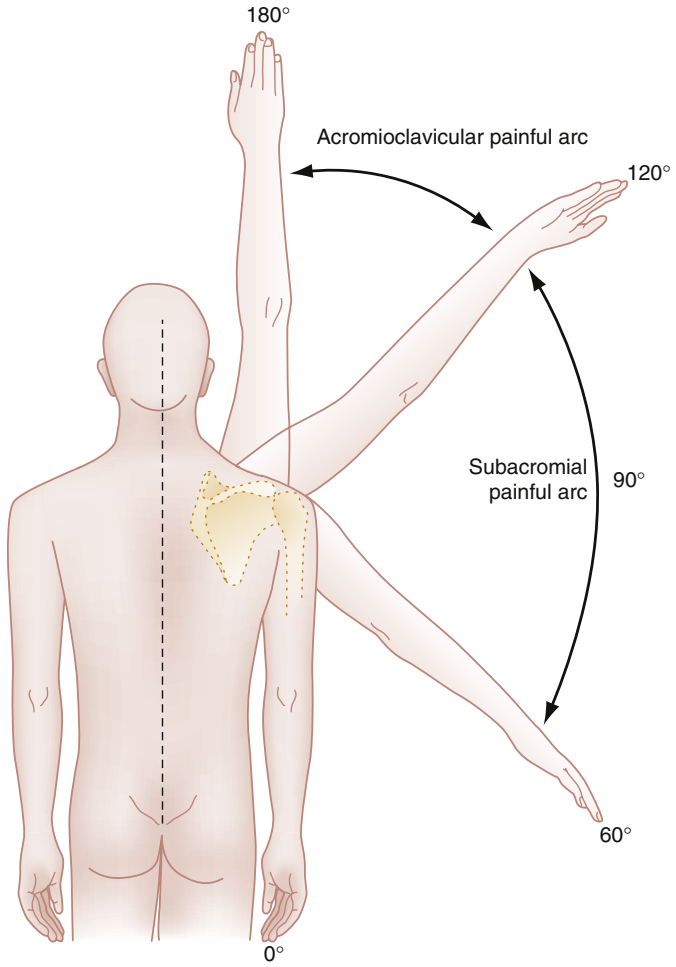

Fig. 45.31 Arcs of painful abduction: subacromial painful arc, 60 to 120 degrees; acromioclavicular painful arc, 120 to 180 degrees. (From DePalma AF. *Surgery of the shoulder*. 3rd ed. Philadelphia: JB Lippincott; 1983.)

adhesions is thought to account for the pain becoming more persistent and particularly severe at night. Significant tendon degeneration can lead to tears in the rotator cuff.

On examination, tenderness can be elicited over the supraspinatus and anterior acromion. A painful arc of abduction at 60 to 120 degrees (see Fig. 45.31) has a sensitivity and specificity of approximately 50% and 75%, respectively. The Hawkins-Kennedy impingement sign (arm placed into 90 degrees of forward flexion followed by internal rotation), has a sensitivity and specificity of 80% and 60%, respectively.

Differential diagnoses. People presenting with vague shoulder pain localizing to lateral shoulder that is worse with movement may have impingement syndrome; however, alternative diagnoses include: rotator cuff tendinopathy, RC tear, calcific tendinopathy, and glenohumeral osteoarthritis.

Diagnostic testing. POCUS can show thickening of the supraspinatus tendon and associated fluid in the subacromial bursa.[31]

Management. Initial treatment for impingement syndrome is conservative and consists of rest, simple analgesia using acetaminophen or analgesic doses of nonsteroidal antiinflammatory drugs (NSAIDs), and modification of activities that produce pain. Radiographs may help to evaluate for bony abnormality but are not necessary in the evaluation and management of impingement syndrome. Diagnostic ultrasound can confirm chronic changes in the supraspinatus as sequelae of this disease and may be performed in the hands of an experienced sonographer. Cross-sectional imaging is not indicated in the ED. Patients should be advised to seek primary care follow-up if not better within 1 to 2 weeks for consideration of physical therapy to maintain range of motion and strengthen the rotator cuff. Subacromial decompression for treatment refractory disease is controversial and may not provide additional benefit over physical therapy alone.[32]

Rotator Cuff Tears

Foundations. The rotator cuff acts as a dynamic stabilizer of the GHJ. Its primary function is to hold the humeral head in place throughout the full range of rotational motion (see Fig. 45.5). The infraspinatus and teres minor act as external rotators, whereas the subscapularis is an internal rotator. The supraspinatus assists initiation of shoulder abduction.

The tenuous blood supply of the rotator cuff, abusive tensile overload, and chronic wear of the supraspinatus under the coracoacromial arch predispose it to age-related degenerative changes and impingement. The advanced stage of this process is characterized by complete rupture.

Rotator cuff tears typically involve the dominant arm and occur in men over 40 years old. The occupational history is significant for strenuous overhead work activity.[33] Tears can be classified according to their chronicity, size, completeness, and pattern location. Acute tears (10%) usually are associated with a specific traumatic event. The most common mechanism of injury is forced abduction associated with significant resistance; this usually occurs when the patient attempts to break a fall with an outstretched hand.

Clinical features. With acute tears, patients report a sudden tearing sensation in the shoulder followed by severe pain that radiates into the lateral arm. Pain and muscle spasm limit shoulder motion in the acute setting. Physical findings depend on the completeness, size, and location of the tear. Point tenderness is usually present over the site of rupture (greater tuberosity). A discrepancy between active and passive range of motion is highly suggestive of a complete rotator cuff tear. Additionally, weakness or pain in the plane of motion of the affected rotator cuff tendon is suggestive of a tear. The acute pain resulting from hemorrhage and spasm subsides over a few days at which point a repeat exam will confirm the loss of function with significant tears.

Chronic tears account for approximately 90% of all lesions. Chronic tears are attritional and more insidious in their presentation. Early findings include the painful arc sign, as a result of secondary impingement of the supraspinatus in the subacromial space. The pain is often worse at night and interferes with sleep. Worsening pain is followed by the gradual onset of weakness in the arm. Flexion and abduction are affected with involvement of the supraspinatus. The patient attempts to initiate abduction with scapulothoracic movement. A tear in the subscapularis tendon causes pain or weakens internal rotation. A tear in the teres minor or infraspinatus compromises external rotation.

Differential diagnoses. Rotator cuff tears are rarely acute traumatic injuries. In the evaluation of a suspected chronic rotator cuff tear alternative considerations include impingement syndrome, rotator cuff tendinopathy, biceps tendinopathy, AC or GH joint osteoarthritis.

Diagnostic testing

Radiology. Plain radiographs likely will be normal in acute or chronic tears and are not generally indicated.[34] If obtained, they may show nonspecific degenerative changes within the GHJ and subacromial space. The hallmark of a complete tear is superior displacement of the humeral head best seen on an external rotation view. Outpatient ultrasound examination, MRI, or an MRI arthrogram can confirm the diagnosis. POCUS appears to be an excellent initial screening test for the detection of partial- and full-thickness rotator cuff tears (Fig. 45.32). When compared to MRI, POCUS by a trained clinician has similar diagnostic accuracy for full thickness tears.[35]

Management. Acute tears should be immobilized in a sling for comfort and the patient referred for orthopedic follow-up within 1 to 2 weeks. Early surgical repair (before 4 months) is preferred in young or active individuals.[36,37] The management of chronic tears includes pain control and a shoulder rehabilitation program. Orthopedic or sports medicine follow-up care may be needed as patients with persistent pain and weakness may require surgical management.

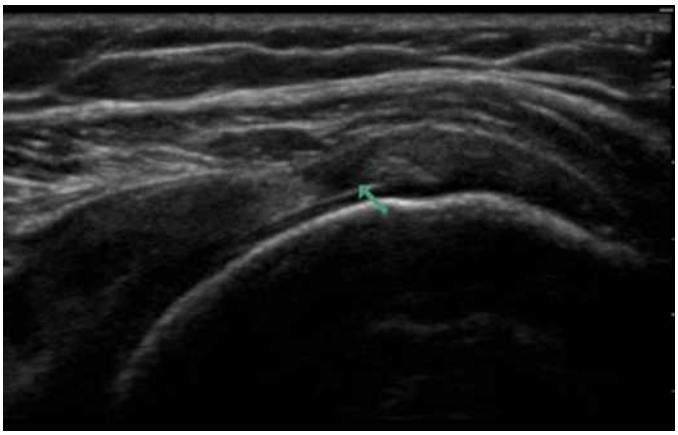

Fig. 45.32 Bedside ultrasound image of a rotator cuff a full-thickness rotator cuff tendon tear. The *arrow* points at the full thickness discontinuity of the tendon. Note the anechoic fluid that extends from the bursal to the articular surface. (Courtesy Ryan Petering, MD.)

Lesions of the Biceps Muscle

The biceps muscle is composed of two heads. The long head originates from the supraglenoid tubercle and glenoid labrum and ascends over the humeral head to enter the arm by way of the bicipital groove. The long head is covered by a synovial sheath and is held in place within the groove by the coracohumeral and transverse humeral ligaments.[1] The short head of the biceps originates from the coracoid process and inserts with the long head onto the radial tuberosity. The biceps muscle is responsible for flexion as well as supination at the elbow and serves as a stabilizer for the GHJ.

Bicipital Tendinitis

Pathophysiology. Anatomically, the long head of the biceps is subject to the same stresses as those incurred by the rotator cuff within the subacromial space. Irritation and microtrauma as a result of repetitive elevation or abduction of the shoulder produce an inflammatory reaction within the synovial sheath. Bicipital tendinitis is often associated with other impingement conditions.[38] Primary bicipital tendinitis (inflammation without other underlying pathology) is rare and affects younger individuals.

The typical patient is middle-aged and involved in an occupation or recreational activity that requires repetitive overhead movement. The pain localizes to the anterior part of the shoulder along the bicipital groove. There is usually no history of trauma. Abduction and external rotation in particular are painful. Pain is worse at night and may interfere with sleep.

Clinical features. On examination, point tenderness can be elicited over the biceps tendon as it passes through the bicipital groove. This is best shown with the arm in 10 degrees of internal rotation. Active range of motion is limited by pain, but the passive range remains intact. Supination against resistance *(Yergason test)* with the arm adducted and the elbow flexed to 90 degrees reproduces the pain in 50% of cases. Another provocative test is the biceps resistance test (*Speed's test*), in which forward flexion of the shoulder (elbow extended and forearm supinated) carried out against resistance produces pain in the bicipital groove. The specificity of these tests is limited in the presence of impingement and rotator cuff disease.

Differential diagnoses. The differential diagnosis of insidious onset anterior shoulder pain includes proximal biceps tendon tear, rotator cuff tear, rotator cuff tendinopathy, labrum tear, subluxing biceps tendon, and ACJ or GHJ osteoarthritis.

Diagnostic testing

Radiology. Radiographs are usually normal and not indicated unless fracture or dislocation is suspected. If obtained, they may show evidence of subacromial space impingement by associated acromioclavicular arthritis and osteophytic spurs. The preferred imaging modality is ultrasound or MRI. Ultrasound has been found to be excellent in diagnosing complete rupture, subluxation or dislocation, but is less sensitive for partial tears.

Management. Emergency treatment consists of rest (sling for comfort), ice, and oral analgesia. Gentle exercises are encouraged as symptoms subside. Although the bicipital sheath can be injected by landmarks with a corticosteroid preparation, the procedure is technically difficult, and inadvertent direct tendon injection can lead to tendon rupture. Referral to a sports medicine specialist in 1 to 2 weeks is appropriate if injection-based therapy is a consideration. Surgery may be necessary in patients who fail to respond to conservative therapy.

Ruptures of the Biceps Tendon

Foundations. Ruptures of the biceps tendon can be classified into proximal and distal types. Distal ruptures are rare (estimated to have an annual incidence of 2.55 per 100,000) and are not discussed here.[39]

Microtears and other age-related attritional changes within the long head predispose it to rupture. The rupture can be spontaneous or follow a traumatic event involving either forced extension or resisted supination and flexion.

Clinical features. The classic history of an acute rupture is that of a sudden snap or pop, followed by pain and ecchymosis along the arm. Recent fluoroquinolone or oral steroid use increases the risk of tendon rupture. With a complete rupture, distal retraction of the muscle results in a "Popeye" musculature appearance of the arm. A difference in muscle contour *(Ludington sign)* also may be seen when both arms are placed behind the head and the biceps muscles are contracted. Functionally, forearm supination is weakened, but elbow flexion stays strong because the coracobrachialis and short head of the biceps remain intact. Most bicep tendon ruptures are associated with rotator cuff disease.[40]

Differential diagnoses. Alternative differential considerations for anterior shoulder pain after an acute pop include: subluxing bicep tendon, rotator cuff tendon tear, glenohumeral dislocation, and labrum tear.

Diagnostic testing

Radiology. Radiographic findings usually are unremarkable, and the confirmatory test of choice is MRI. POCUS can be used to identify presence or absence of tendon in bicipital groove, and fluid collection within the sheath.

Management. The injured arm should be immobilized in a sling with the elbow in 90 degrees of flexion. The patient should be referred to an orthopedist or sports medicine specialist for further evaluation in one week. Surgical repair is a consideration in young, active persons. Conservative therapy (range-of-motion and strengthening exercise) is also an option as the intact short head of the bicep provides adequate function and strength. In older patients, this is preferred because the cosmetic deformity is minimal and functional loss minimal.

Calcific Tendinitis

Foundations. Shoulder calcific tendinitis affects up to 10% of the population and frequently is encountered in the ED. The condition affects people aged 40 to 60 years old and is painful in 65% of patients. Calcific deposits occur primarily in the supraspinatus tendon near its attachment to the greater tuberosity. Women are more often affected than men and 10% to 20% of the patients have bilateral deposits.

Clinical features. The clinical presentation can be divided into silent, subacute, and acute phases based on the physical characteristics of the calcific deposits and the nature of the inflammatory response. The *painful arc syndrome* (see Fig. 45.31) is a hallmark of the subacute phase of calcific tendinitis. Enlargement and softening of the deposit lead to narrowing of the subacromial space, resulting in impingement under the acromial arch.

A severe inflammatory reaction within and around the deposit produces the acute phase of calcific tendinitis. Often there is a precipitating history of atraumatic repetitive motion (e.g., swinging a tennis racket). The patient is in severe pain and holds the arm close to the chest. Active and passive range of motion is severely limited. Examination findings will be similar to those with shoulder impingement syndrome. Severe pain is related to increased intra-tendinous pressure, and spontaneous rupture of the deposit into the subacromial bursa may be associated with dramatic relief of symptoms.

Differential diagnoses. The clinical presentation of symptomatic calcific tendinopathy can be similar to that of rotator cuff tendinopathy, rotator cuff tendon tear, impingement syndrome, and osteoarthritis of the AC or GH joints.

Diagnostic testing

Radiology. Radiographs show calcific deposits in the involved tendon (Fig. 45.33). POCUS can identify and effectively localize calcific deposits (Fig. 45.34).

Management. The acute phase should be treated with a sling for comfort, NSAIDs, and avoidance of offending activities. Refer patients to primary care or sports medicine clinic in 1 to 2 weeks, because they may benefit from subacromial bursa steroid injections, or needle lavage procedures. The subacromial injection of anesthetic with corticosteroids for calcific tendinitis may give targeted relief (steroids take 1 to 3 days to take effect). With an experienced outpatient provider, patients may also be candidates for needle lavage (careful targeted puncturing of the calcific deposits to decrease intra-tendinous pressure) under ultrasound or fluoroscopy guidance. Minimally invasive surgical intervention may be helpful for refractory symptoms.[41] Early shoulder range-of-motion exercises are encouraged in all patients to minimize the risk of adhesive capsulitis.

Adhesive Capsulitis

Foundations. Adhesive capsulitis ("frozen shoulder") is a specific diagnostic entity characterized by an idiopathic inflammatory reaction within the capsule and synovium of the GHJ. Subsequent adhesion formation within the capsule leads to restricted active and passive range of motion. Adhesive capsulitis should be differentiated from other, more common causes of the painful stiff shoulder (e.g., calcific tendinitis, rotator cuff syndrome, osteoarthritis, or trauma), which also may be associated with decreased range of motion. Any condition associated with prolonged disuse of the arm can result in capsular contraction, including immobilization for painful intrinsic shoulder

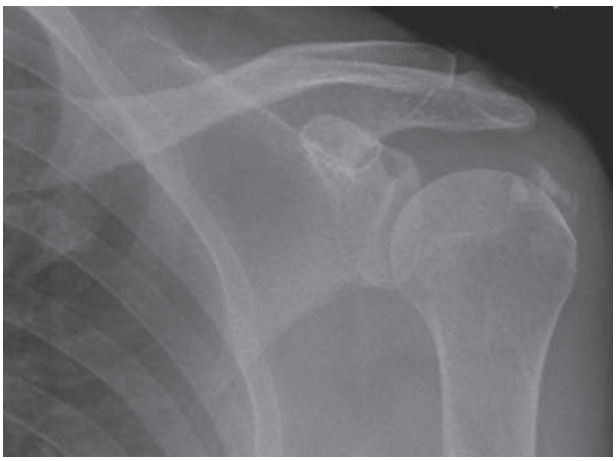

Fig. 45.33 Radiograph with Rotator Cuff Calcific Tendinitis. Note abnormal calcification near greater tuberosity.

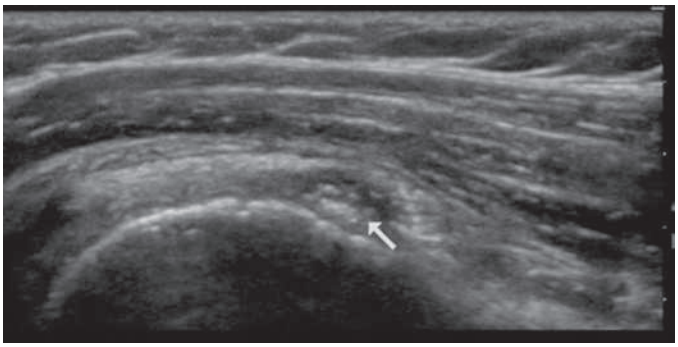

Fig. 45.34 Ultrasound image of rotator cuff calcific deposit *(arrow)* within subscapularis tendon. (Courtesy Ryan Petering, MD.)

conditions or use of a sling in healthy uninjured shoulders such as after a mastectomy or a distal upper extremity injury (e.g., Colles fracture).

Clinical features. Risk factors for developing adhesive capsulitis include female sex, age between 40 and 60 years old, thyroid disease, and diabetes mellitus.[42–44] The nondominant arm usually is affected and the patient has trouble with the activities of daily living. The pain is typically most severe at night and localized over the deltoid area. As the condition progresses, there is uniform limitation of all glenohumeral movement. On passive testing of external rotation, a sense of mechanical restriction of joint motion can be appreciated. Shoulder radiographs usually are normal in appearance if no associated pathologic condition is present.

Differential diagnoses. Asymmetric limitations in passive and active range of motion are hallmarks of adhesive capsulitis. Other causes of limited passive and active range of motion include chronic dislocations, in particular external rotation limitation is apparent in both adhesive capsulitis and chronic posterior glenohumeral dislocation. Other considerations include GH joint osteoarthritis and rotator cuff pathology.

Diagnostic testing. The diagnosis of adhesive capsulitis is typically made based on a clinical exam and history alone. Radiographs are helpful to evaluate for alternative diagnoses such as osteoarthritis or a missed dislocation. There are characteristic findings on MRI of adhesive capsulitis; however, this imaging modality is rarely needed to make the diagnosis and is not indicated in the ED setting.

Management. The best form of therapy is preventive in nature. Prolonged shoulder immobilization is to be avoided, and early motion encouraged (see Fig. 45.10). Treatment of adhesive capsulitis in the ED consists of NSAIDs and referral to a sports medicine provider or orthopedic surgeon within one to two weeks. Initial therapy is conservative and consists of a gentle assisted exercise program along with an intra-articular steroid injection.[45,46] Surgical treatment, including manipulation under anesthesia and arthroscopic capsular release, is reserved for patients who fail to improve with nonoperative treatment.

Injection Therapy

The local injection of corticosteroid preparations has long been used in many painful conditions that affect the shoulder, including rotator cuff tendinitis, subacromial bursitis, calcific tendonitis and adhesive capsulitis. Ultrasound guidance for subacromial injection has improved accuracy. Although advocated for relieving the inflammatory reaction, corticosteroid injections in general do not alter the underlying disease process, and there is no evidence that they are superior to short courses of antiinflammatory doses of NSAIDs. Systemic complications are rare after local injection therapy, although patients with diabetes mellitus may experience elevated glucose levels. Site-specific complications include articular cartilage damage, tendon weakening or rupture, and subcutaneous atrophy resulting in localized skin pigment changes. Direct tendon injection is particular hazardous and is associated with increased risk of tendon rupture. Corticosteroid injection treatments generally can be deferred to outpatient providers (primary care, sports medicine, or orthopedic specialists).

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 45: QUESTIONS AND ANSWERS

1. A 27-year-old male unrestrained driver is involved in a high speed motor vehicle collision (MVC) with direct impact of the steering wheel into his anterior chest wall. Which shoulder girdle injury represents a true orthopedic emergency?
- **a.** Anterior glenohumeral dislocation
- **b.** Anterior sternoclavicular dislocation
- **c.** Posterior glenohumeral dislocation
- **d.** Posterior sternoclavicular dislocation

Answer: d. Posterior sternoclavicular dislocations can be associated with life-threatening injuries within the superior mediastinum and intrathoracic cavity; therefore, they are considered true orthopedic emergencies and should be reduced expeditiously. Reported complications associated with posterior sternoclavicular dislocations include compression or lacerations of the great vessels, tracheal compression, pneumothorax, thoracic outlet syndrome, tracheoesophageal fistula, and injury to the brachial plexus.

2. A 30-year-old patient presents complaining of right shoulder pain and limited range of motion. On physical examination, you note that the shoulder has a "squared off" appearance and is held in abduction and external rotation. The patient is unable to adduct the arm or internally rotate without severe pain. What is the best way to manage this patient without the aid of other emergency department (ED) personnel?
- **a.** Hippocratic method
- **b.** Kocher maneuver
- **c.** Milch technique
- **d.** Traction/countertraction method

Answer: c. The ideal method for reduction of an anterior shoulder dislocation should be simple, quick, and effective; require little assistance; and cause no additional injury to the shoulder. It is wise to be familiar with several techniques of reduction because none is uniformly successful. The Milch technique (see Table 45.3) allows for reduction by a single practitioner, and it can be attempted without procedural sedation. Older techniques, such as the Hippocratic method (traction with the foot in the axilla) and the Kocher maneuver (leverage, adduction, and internal rotation), are no longer recommended because of a high incidence of associated complications (axillary nerve injury, humeral shaft and neck fractures, and capsular damage). Traction/countertraction requires two people to reduce the shoulder (see Table 45.3).

3. A 19-year-old skateboarder presents to the emergency department (ED) complaining of left shoulder pain with his left arm in adduction and supporting the elbow with his right hand. An obvious clavicular defect is palpable on exam. Urgent orthopedic consultation is recommended for which type of clavicle fracture?
- **a.** Minimally displaced midclavicular fracture
- **b.** Type I lateral clavicle fracture
- **c.** Type II lateral clavicle fracture
- **d.** Type III lateral clavicle fracture

Answer: c. Type I lateral clavicle fractures are stable and minimally displaced because the coracoclavicular ligaments are intact. Type II fractures are associated with a torn coracoclavicular ligament and have a tendency to displace because the proximal fragment lacks any stabilizing forces. Type III injuries involve the articular surface. More urgent orthopedic consultation (before 72 hours) is recommended for type II lateral clavicle fractures, because these fractures have up to a 30% incidence of nonunion and may benefit from surgical repair.

4. A 75-year-old right-handed woman presents to the emergency department (ED) after sustaining a ground level fall onto an outstretched right arm. She is holding her right arm in adduction and supporting the weight of the arm with her left hand. On examination she does not have an obvious palpable defect but there is significant pain in her shoulder with any attempt to move her arm. She has intact lateral deltoid sensation and full symmetric radial pulses. The x-ray demonstrates a proximal humerus fracture with minimal displacement. Which of the following is the most appropriate next step in care?
- **a.** Emergent orthopedic consultation for operative repair
- **b.** Pain control, immobilization, and discharge with outpatient follow-up with orthopedics
- **c.** Orthopedics consultation for outpatient surgical repair after resolution of swelling
- **d.** Emergent vascular surgery consult due to high risk of associated vascular injury

Answer: b. Proximal humerus fractures with minimal displacement respond well to conservative care. Patients may begin physical therapy as soon as one week after the fracture. Surgical repair is rarely indicated for minimally displaced fractures, hence answers (a) and (c) are incorrect. She has good radial pulses and these fractures are not commonly associated with secondary vascular injury.

5. A 30-year-old recreational basketball player presents after an awkward fall onto an outstretched left arm during a pickup basketball game with severe left shoulder pain. He is supporting his left elbow with his right hand and refuses to move his arm due to pain. There is a dimple inferior to the acromion and diffuse pain with palpation throughout his shoulder. There is no evidence of neurovascular injury. True and standard AP radiographs do not show any fracture or obvious dislocation. The technician was unable to obtain an axillary lateral due to significant pain with abduction. Which of the following is the next best step?
- **a.** Obtain modified axillary lateral or trans-scapular Y view radiograph
- **b.** Upper extremity CT with intravenous contrast
- **c.** Discharge with outpatient follow-up with primary care
- **d.** Refer to orthopedics for likely complete supraspinatus tear

Answer: a. Posterior dislocations glenohumeral dislocations are uncommon but cannot be excluded with a true orthogonal view. Options to consider in this patient include a modified axillary lateral, apical oblique, or transscapular Y view. A missed posterior dislocation can result in a locked posterior dislocation requiring orthopedic intervention under general anesthesia. If there is a high clinical suspicion, a non-contrast shoulder CT scan can reveal the diagnosis; however, the most appropriate next step would be to obtain orthogonal views. Contrast is only necessary if there is suspicion for an associated vascular injury which is uncommon with posterior GH dislocations. Although an acute rotator cuff tear can present similarly, this patient has had incomplete radiographic imaging and therefore a diagnosis of rotator cuff tear represents premature closure.

46

Pelvic Injuries

Michael C. Bond and Michael K. Abraham

KEY CONCEPTS

- The most serious pelvic ring injuries caused by high-energy impact are (1) anteroposterior compression fractures ("open-book" fracture), (2) vertical shear fractures, and (3) fractures involving significant displacement. These injuries are associated with major blood loss and transfusion requirements.
- Pelvic fractures are a marker for serious injury to other organ systems. The vast majority of patients who die after sustaining a pelvic fracture have multiple trauma.
- Careful examination of the perineum and buttocks, as well as digital rectal and vaginal examinations, are necessary to diagnose open fractures and expanding hematomas.
- Computed tomography (CT) is the imaging test of choice to diagnose pelvic fracture and concurrent intra-abdominal injuries for patients stable enough to undergo imaging. CT aids in establishing surgical priorities and planning of definitive orthopedic care.
- There is an increasing incidence of low-energy (e.g., fall from standing) pelvic fractures in older patients which often are managed medically due to multiple co-morbidities and poor bone quality that would make an anatomic reduction difficult to obtain.
- Fragility pelvic fractures in older patients often involve the anterior column of the acetabulum, are more comminuted, and result in severe impaction of the femur head.
- In the hemodynamically unstable patient who cannot undergo CT imaging, the anteroposterior radiograph usually reveals serious pelvic fractures that cause major pelvic bleeding, which is sufficient information to undertake pelvic stabilization.
- The combination of posterior arch fracture plus hypotension is associated with a mortality rate of approximately 50%.
- Early fluid resuscitation with blood products in a 1:1:1 ratio (packed red blood cells: platelets: fresh frozen plasma) is recommended for unstable patients suspected of having active pelvic bleeding.
- Trauma hospitals should have institutional guidelines and mechanisms to facilitate early decisions regarding treatment for pelvic hemorrhage. Treatment options include angiography and embolization, pelvic packing, invasive fixation, or a combination of these.
- Unstable patients with a positive focused assessment with sonography in trauma (FAST) and a pelvic fracture should be treated with laparotomy with pelvic stabilization and possible pelvic packing, followed by angiography.
- Unstable patients with a negative FAST and a pelvic fracture should be treated with pelvic stabilization (such as a pelvic binder) and angiography, and then a repeat FAST and laparotomy if they remain unstable.
- "Open-book" pelvis fractures should be internally compressed with a pelvic binder or sheet to reduce the size of the pelvis, unless the fracture forces have already internally rotated the hemi-pelvis. In this case, further internal compression may cause an increase in the pelvic diameter.
- Patients with pelvic fractures are at high risk for subsequent deep venous thrombosis (DVT), despite the use of mechanical and chemical thromboprophylaxis.

FOUNDATIONS

Background and Importance

Patients with traumatic **pelvic** ring injury are challenging for the emergency care provider. Pelvic ring **fracture**s present significant risk for exsanguinating pelvic **hemorrhage** caused by the extreme magnitude of force required to disrupt the pelvic ring. This frequently causes tearing of fragile pelvic veins and severe injuries to other organs. Prompt stabilization of pelvic fractures, rapid identification of other major injuries and sites of blood loss, and coordination of definitive angiographic and surgical treatments are the necessary steps to help avoid the development of hemorrhagic shock.

The majority of high-energy pelvic ring injuries are caused by motor vehicle collisions (MVCs), motorcycle crashes, pedestrians being struck by motor vehicles, and falls from a height. With the aging population, an increase in low-energy **fragility** fractures has also been noted. A nationwide inpatient sample from the United States showed a 24% increase in fragility pelvic fractures from 1993 to 2010.[1] A Finnish study showed a quadruple increase in the incidence of pelvic fractures in the elderly, typically from low energy trauma (such as a fall from standing) from 1970 to 2013.[2] Overall, the percentage of pelvic and **acetabular** fractures has been significantly increasing at U.S. level 1 trauma centers (1995 to 1999 32.7% of fractures; 2008 to 2012 39.9% of fractures).[3]

Mortality of patients with pelvic fracture ranges between 5% and 30% in studies of large cohorts of trauma patients. The presence of a pelvic fracture has been consistently shown to be an independent risk factor for death. In a study using multivariable analysis, however, pelvic factures were not associated with an increased 30-day mortality when it was adjusted for age, Injury Severity Score (ISS), American Society of Anesthesiologists (ASA) physical status classification score, Glasgow Coma Score (GCS), and shock.[4] Overall mortality rates appear to be improving. An investigation analyzing 22 years of pelvic registry data showed that hospital mortality decreased by one-third (from 9.3% to 3.8%) despite increasing median ISS scores.[5] Male patients showed a significantly higher mortality than female patients, as well as a higher median ISS, while the mortality rates of patients aged greater than 80 years did not significantly differ from those aged greater than 60 or 70 years.[5] Obesity has also been shown to be an independent risk factor of morbidity and mortality, and the incidence of pelvic fractures is higher in the obese when compared to those with a normal body habitus.[6]

Mortality rates for older patients with hip fractures, hip contusions and pelvic fractures were comparable during the hospital stay and at follow-up 4 and 12 months later. Retrospective studies of older patients with low-energy pelvic fractures demonstrate a mean one-year mortality of 16%.[7] Patients with pelvic fractures who present with shock on arrival to the hospital have mortality rates of up to 50%. Increased age, the presence of shock at the time of arrival, presence of multisystem injuries, and the need for transfusion increase the risk of death.

Despite advances in motor vehicle safety design, MVCs continue to be a major cause of pelvic fracture, with lateral impact collisions remaining the most prevalent mechanism. The widespread use of front impact airbags has had little protective effect on these lateral collisions. However, side-impact airbags reduce the risk of death in lateral impact MVC by 30% to 40%. Current research suggests that side impact airbags reduce the risk of head injuries by 30%, but they have minimal protective effect on thoracic or pelvic injuries. Newer technology, such as knee bolster airbags, has been claimed to reduce the risk of knee-thigh-hip injuries; however, there is not enough evidence to date to demonstrate their overall efficacy.

Anatomy, Physiology, and Pathophysiology

Bony and Ligamentous Anatomy

The right and left innominate bones and the sacrum together form the pelvic ring. The innominate bones consist of the pubis, ischium, and ilium (Fig. 46.1). The bony pelvis provides protection for its visceral contents, serves as attachment points for muscles, and transmits weight from the trunk to the lower limbs. The main weight-bearing forces are transmitted through the posterior wall of the pelvis, called the *posterior arch,* which is composed of thick bone and ligaments. The rich network of major arteries, veins, and nerves that course in front of the posterior arch can be injured concomitantly with forces responsible for bony injuries.

Knowledge of the ligamentous attachments of the pelvic ring is crucial to understanding stability derangements in pelvic injuries. Pelvic stability is maintained by soft tissue components including ligaments, muscles, and fascia that make up the pelvic floor. Anteriorly, the symphysis pubis provides the major mechanical stability. Posteriorly, a composite of strong ligaments—the sacrospinous, sacrotuberous, iliolumbar, and anterior and posterior sacroiliac ligaments—maintain the integrity of the posterior arch (Fig. 46.2). These ligaments are the primary stabilizing force of the posterior pelvis. Disruption of these ligaments is the primary cause of a mechanically unstable pelvic fracture.

Vascular Anatomy

Most of the blood supply to the pelvis comes from the left and right internal iliac arteries. The internal iliac arteries course at the level of the sacroiliac joints. The various arteries that derive from the internal iliac arteries initially run in close proximity to the posterior pelvic arch and eventually anastomose extensively with one another, forming a rich collateral network (Fig. 46.3). The superior gluteal artery is the largest branch and is commonly injured in fractures of the posterior pelvic arch. The obturator and internal pudendal branches are often injured in fractures involving the pubic rami.

Arranged in a plexus that adheres closely to the pelvic walls, the venous system has many collateral branches but does not have valves, which allows bidirectional flow. Because these veins are thin-walled, they do not have the ability to constrict in response to damage. This anatomic arrangement of the arteries and veins accounts for the hemorrhage often associated with pelvic fractures.

Neurologic Anatomy

The cauda equina travels through the sacral spinal canal and exits through the sacral neural foramina to form the lumbar and sacral plexus. Injury to the posterior bony pelvis and sacrum can result in neurologic deficits in the lower extremities and autonomic dysfunction involving the bowel, bladder, and genitalia.

Pathophysiology and Key Patterns of Pelvic Fracture

Numerous classification schemes for pelvic fractures have been created. The Tile classification stresses the biomechanical stability of the pelvic ring (Box 46.1). The Young-Burgess classification emphasizes the mechanisms of injury (Box 46.2). From a practical viewpoint, it is highly useful to consider both of these elements in the assessment of a pelvic ring fracture. Both classification systems delineate numerous subtypes of injuries. For the emergency clinician, however, a good understanding of the principles of pelvic stability and the mechanism of injury is more important than a detailed knowledge of injury subtypes. The broad distinction between mechanically stable and unstable fractures of the pelvic ring is clinically useful in assessing patients, as those with unstable injuries have a higher mortality rate and greater transfusion requirements.

The Rommens Classification System was developed to classify fragility fractures, which are low-energy injuries often seen in the elderly. The World Health Organization (WHO) defines a fragility fracture as a fracture caused by an injury that would be insufficient to fracture normal bone; it is the result of reduced compressive or torsional strength of bone.[1] Based on analysis of plain radiographs and computed tomography (CT) scans, four types of fragility fractures of the pelvis (FFP) have been described (see Fig 46.5 and Box 46.3).[1] Type I and II fractures

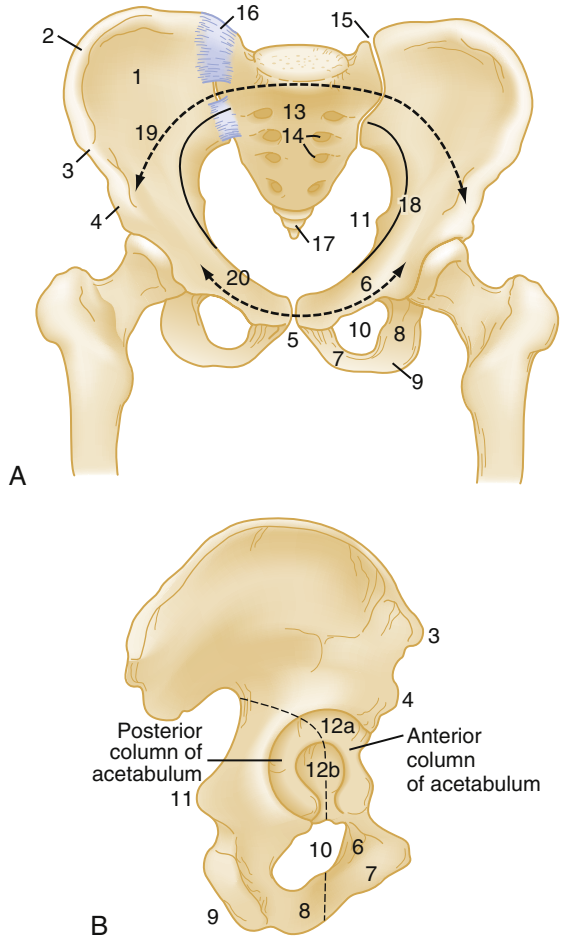

Fig. 46.1 Bony Pelvic Anatomy. (A) Anterior view of pelvis. (B) Lateral view of right innominate bone. *1,* Iliac fossa; *2,* iliac crest; *3,* anterior superior iliac spine; *4,* anterior inferior iliac spine; *5,* symphysis pubis; *6,* superior ramus of pubis; *7,* inferior ramus of pubis; *8,* ramus of ischium; *9,* ischial tuberosity; *10,* obturator foramen; *11,* ischial spine; *12,* acetabulum (*12a,* articular surface; *12b,* fossa); *13,* sacrum; *14,* anterior sacral foramina; *15,* sacroiliac joint; *16,* anterior sacroiliac ligament; *17,* coccyx; *18,* arcuate line; *19,* posterior or femorosacral arch, through which main weight-bearing forces are transmitted; *20,* anterior arch.

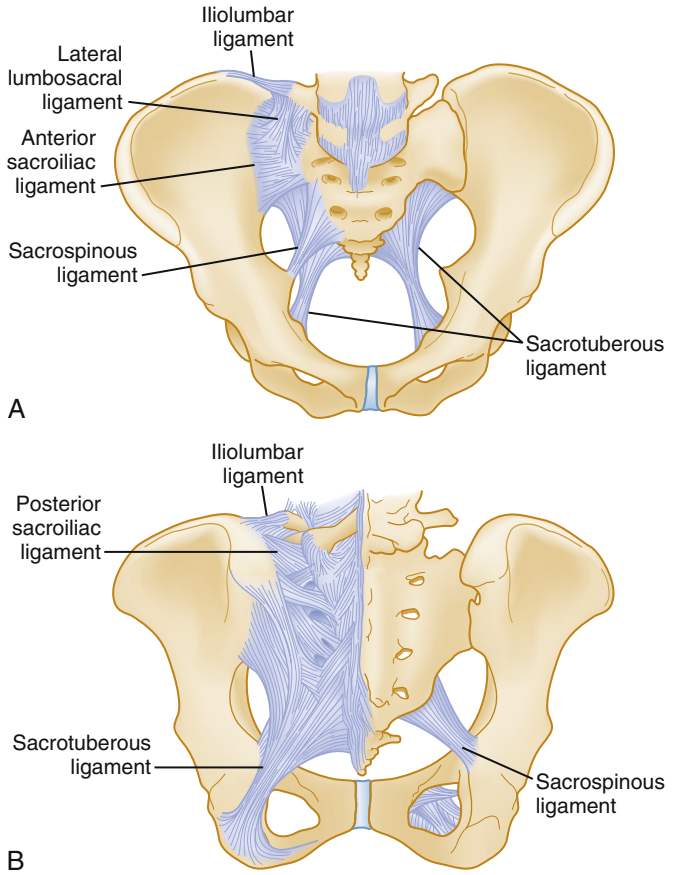

Fig. 46.2 (A) Anteroposterior view of the pelvis indicates that the sacrospinous ligament is a triangular strong ligament lying anterior to the sacrotuberous ligament, which is a strong broad band extending from the lateral portion of the dorsum of the sacrum to the ischial tuberosity. (B) The major posterior stabilizing structures of the pelvic ring, that is, the posterior tension band of the pelvis, include the iliolumbar ligament, posterior sacroiliac ligaments, sacrospinous ligaments, and sacrotuberous ligaments.

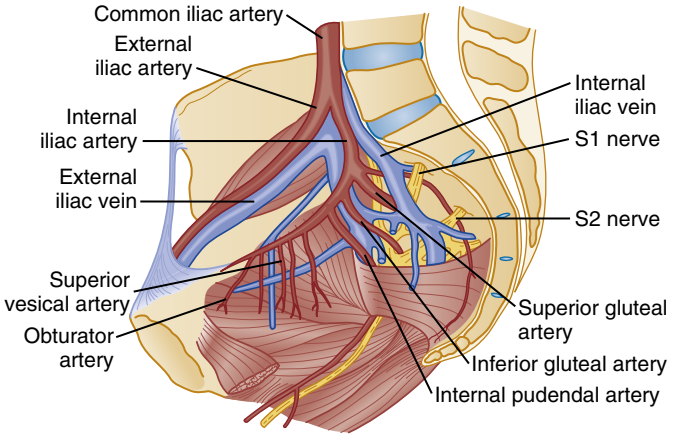

Fig. 46.3 The Internal Iliac Plexus of Arteries and Veins. (From Tile M. *Fractures of the Pelvis and Acetabulum*. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2003.)

are generally stable and treated nonoperatively, while type III and IV fractures require surgical fixation.

Overall inter-observer agreement has been shown to be fair in all three classification systems, and for Tile class B or C fractures, there was substantial agreement between experienced surgeons.[8]

BOX 46.1 Tile's Classification of Pelvic Fractures

Type A: Stable, posterior arch intact; includes avulsion fractures, isolated iliac wing fracture, pubic rami fractures, minimally displaced ring fracture, and transverse fractures of the sacrum or coccyx.

Type B: Partially stable, incomplete disruption of the posterior arch; includes anteroposterior injuries ("open-book" fracture) and lateral compression injuries; may be unilateral or bilateral; these injuries are rotationally unstable but vertically stable.

Type C: Unstable, complete disruption of the posterior arch; includes iliac, sacroiliac, and vertical sacral injuries that result from vertical shearing forces; may be unilateral or bilateral. These injuries are both rotationally and vertically unstable.

BOX 46.2 Young-Burgess Classification of Pelvic Fractures

Anteroposterior Compression

I. Symphysis diastasis <2.5 cm
II. Symphysis diastasis >2.5 cm, sacrospinous and anterior sacroiliac ligament disruption, results in rotational instability
III. Symphysis diastasis >2.5 cm, with complete disruption of the anterior and posterior sacroiliac ligament, results in complete rotational and vertical instability

Lateral Compression

I. Sacral crush injury on ipsilateral side
II. Sacral crush injury with disruption of posterior sacroiliac ligaments; iliac wing fracture may be present (crescent fracture); rotationally unstable
III. Severe internal rotation of ipsilateral hemipelvis with external rotation of contralateral side ("windswept" pelvis), rotationally unstable

Vertical Shear

Vertical displacement of symphysis and sacroiliac joints resulting in complete rotational and vertical instability

Combined Mechanisms

Any combination of the aforementioned mechanisms

BOX 46.3 Fragility Fracture of the Pelvis

Type I—Anterior pelvic ring fracture only (~17.5% incidence)
- Type IA—Unilateral fracture
- Type IB—Bilateral fractures

Type II—Nondisplaced posterior pelvic ring fracture (>50% incidence)
- Type IIA—Nondisplaced and isolated posterior fractures
- Type IIB—Sacral crush injuries with anterior disruption
- Type IIC—Nondisplaced sacral, sacroiliac, or iliac fractures with anterior disruption

Type III—Displaced but unilateral posterior pelvic ring fracture with an anterior pelvic ring fracture (11% incidence)
- Type IIIA—Displaced unilateral ilium fracture
- Type IIIB—Displaced unilateral sacroiliac fracture-dislocation
- Type IIIC—Displaced sacral fracture

Type IV—Displaced bilateral posterior fractures (~19% incidence)
- Type IVA—Bilateral iliac fractures or sacroiliac disruptions.
- Type IVB—Fracture is a spinopelvic dissociation associated with bilateral vertical fractures through the sacral ala with a horizontal component
- Type IVC—Fracture is a combination of different posterior instabilities

Stable Injuries (Tile Type A)

Fractures of individual bones without involvement of the pelvic ring represent one-third of all pelvic fractures. Most stable pelvic fractures heal well with rest and analgesia (Fig. 46.4).

Nondisplaced or minimally displaced fractures of the pelvic ring. The normal pelvis is not completely rigid, due to the slight mobility at the sacroiliac joints and symphysis pubis and the inherent elasticity of the bone. It is possible to sustain a single break in the pelvic ring; however, identification of a single break in the ring should prompt a thorough search for a second disruption.

The most common pelvic ring fracture is an isolated fracture of the superior or inferior pubic ramus. These fractures are stable and are generally categorized as an FFP type I (Fig 46.5) fracture. They are common in the elderly after a mechanical fall and should be given consideration in the evaluation of an acutely painful hip. Fracture of the body of the ischium is a rare injury that can result from a fall into the sitting position. Like all similarly classified fractures, fractures around the obturator foramen are managed conservatively with bed rest, analgesia, and early mobilization.

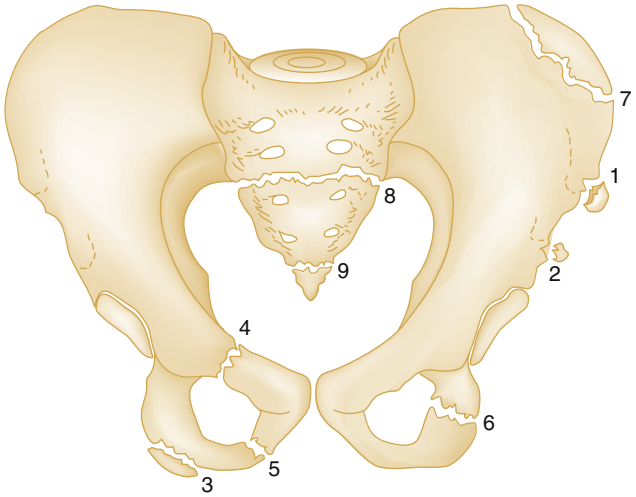

Fig. 46.4 Fractures of Individual Pelvic Bones. *1,* Avulsion of anterosuperior iliac spine; *2,* avulsion of anteroinferior iliac spine; *3,* avulsion of ischial tuberosity; *4,* fracture of superior pubic ramus; *5,* fracture of inferior pubic ramus; *6,* fracture of ischial ramus; *7,* fracture of iliac wing; *8,* transverse fracture of sacrum; *9,* fracture of coccyx. (From Tile M. *Fractures of the Pelvis and Acetabulum*. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2003.)

Fracture of the superior and inferior pubic rami on the same side is a commonly encountered injury after a fall or MVC. These are generally stable fractures and are treated conservatively. However, the presence of significant displacement at the fracture site indicates a second disruption elsewhere in the pelvic ring. Alternatively, fractures of both rami on the same side can be associated with an unrecognized impaction fracture of the posterior pelvis.

If the patient with a ramus fracture reports posterior pelvic pain, even if plain radiographs do not reveal a posterior injury, further investigations could reveal posterior fractures, such as occult bony or ligamentous injury of the acetabulum or sacroiliac joint. Up to 95% of elderly patients with isolated ramus fractures on plain films will have a sacral fracture detected by magnetic resonance imaging (MRI). This finding does not generally alter treatment, however, and an MRI is not indicated for most elderly patients with ramus fractures. Among the mechanically stable pelvic fractures, the lateral compression type I fracture described by Young and Burgess (Fig. 46.6), characterized by a pubic ramus fracture with ipsilateral sacral compression, bears special consideration. Although mechanically stable, this fracture has a mortality rate of nearly 10% and a high incidence of associated injuries.

A *straddle fracture* is a four-pillar injury involving fractures of both pubic rami on both sides of the symphysis pubis, creating a "butterfly segment" (Fig. 46.7), and is produced by a direct blow with a straddle mechanism. Although these fractures can occur without posterior arch disruption, four-pillar injuries are commonly associated with lateral compression or vertical shear forces, which can cause concomitant injuries to the posterior pelvic arch. CT of the pelvis is indicated in four-pillar injuries to detect and classify the posterior arch injury and to plan orthopedic treatment. The genitourinary tract is often injured with this type of pelvic fracture and should be evaluated meticulously (see Fig. 46.7).

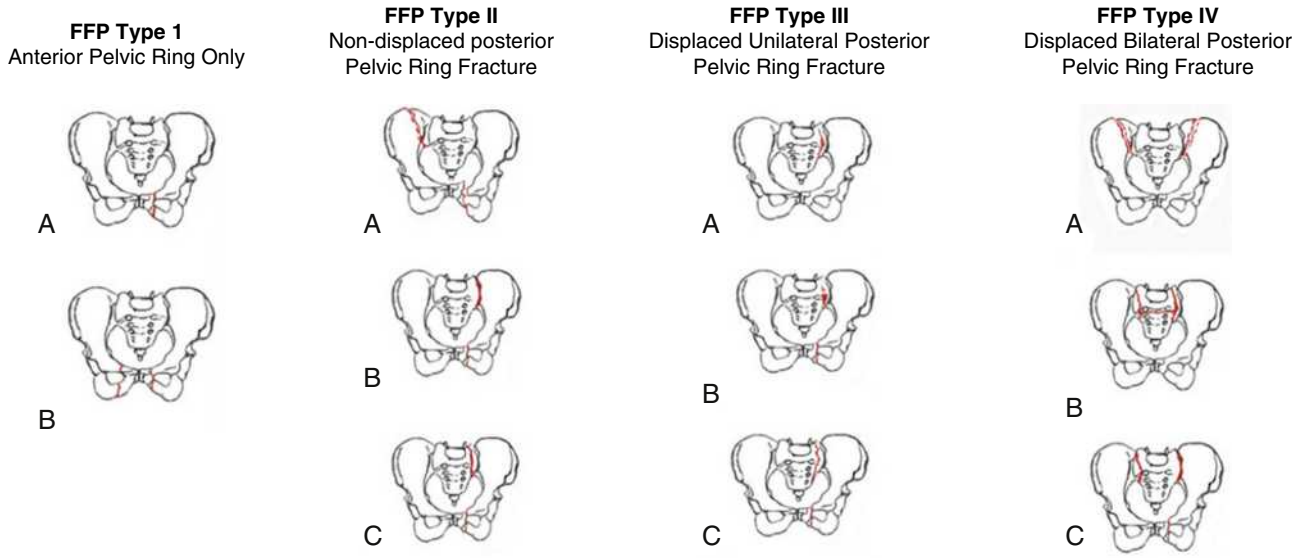

Fig. 46.5 Illustrations showing the four types of fragility fractures of the pelvis (FFP). The letters A, B, and C correspond with the subcategories of each fracture type as defined in the Box 46.3. (Modified with permission from Rommens PM, Wagner D, Hofmann A. Fragility fractures of the pelvis. *JBJS Rev.* 2017;5[3]:01874474-201703000-00004.)

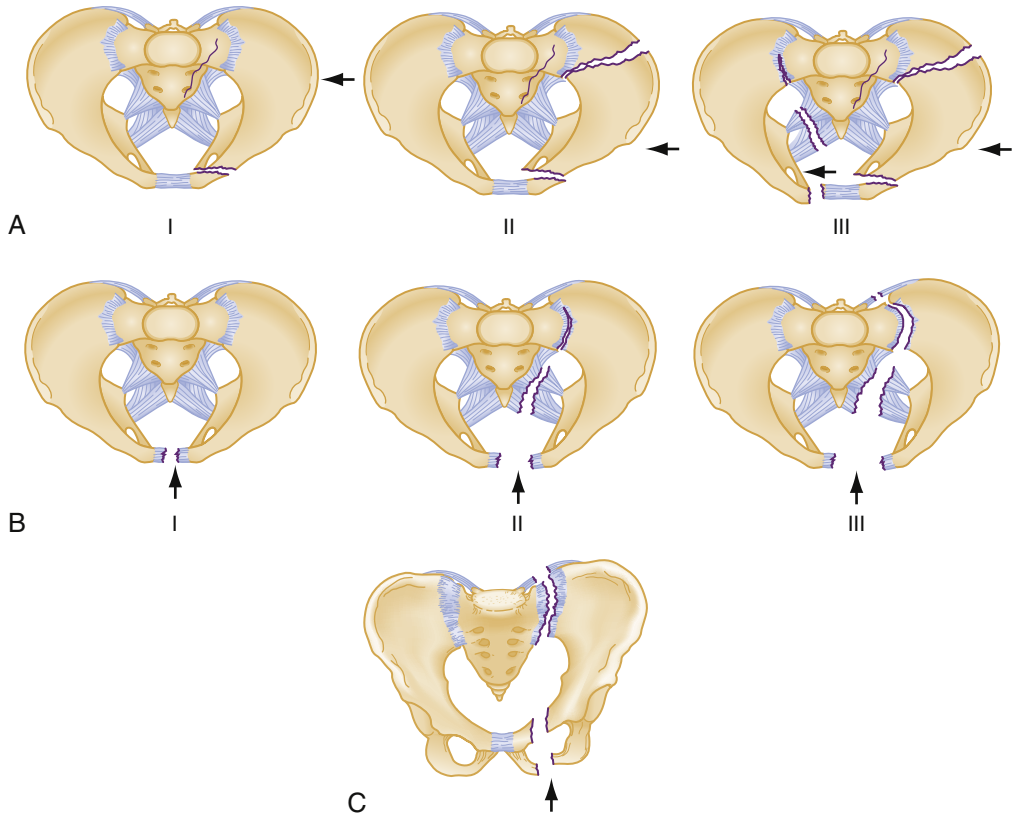

Fig. 46.6 Young-Burgess Classification. (A) Lateral compression. *Type I,* A posteriorly directed force causing a sacral crushing injury and horizontal pubic ramus fractures ipsilaterally. *Type II,* A more anteriorly directed force causing horizontal pubic ramus fractures with an anterior sacral crushing injury and either disruption of the posterior sacroiliac joints or fractures through the iliac wing. *Type III,* an anteriorly directed force that is continued, causing external rotation of the contralateral side; the sacroiliac joint is opened posteriorly, and the sacrotuberous and sacrospinous ligaments are disrupted. (B) Anteroposterior compression. *Type I,* Symphysis disrupted but with intact posterior ligamentous structures. *Type II,* Continuation of a type I fracture with disruption of the sacrospinous and potentially the sacrotuberous ligaments and an anterior sacroiliac joint opening. *Type III,* Continuation force disrupts the sacroiliac ligaments. (C) Vertical shear. Vertical fractures in the rami and disruption of all posterior ligaments. This injury is equivalent to an anteroposterior type III or a completely unstable and rotationally unstable fracture. *Arrow indicates the direction of force.* (Redrawn from Young JWR, Burgess AR. *Radiologic Management of Pelvic Ring Fractures.* Baltimore: Urban & Schwarzenberg; 1987. Browner BD. *Skeletal Trauma: Basic Science, Management, and Reconstruction.* 3rd ed. St Louis: Saunders/Elsevier; 2003.)

An isolated fracture of the iliac wing was first described by Duverney in 1751 and now bears his name. It is caused by direct trauma to the iliac crest, usually by lateral compression forces. Although there is usually minimal displacement because of the arrangement of the muscle attachments of the abdominal wall, orthopedic consultation in the emergency department (ED) is recommended. Extension of the fracture into the acetabulum alters treatment and prognosis. Severely displaced fractures of the iliac wing require open reduction and internal fixation (ORIF). A high incidence of major associated non-pelvic injuries has been reported among patients with isolated iliac wing fracture.

Transverse fractures of the sacrum. Transverse fractures of the sacrum do not compromise the pelvic ring. Transverse fractures at or below the S4 level are unlikely to be accompanied by neurologic injury. An upper sacral transverse fracture is the result of a flexion injury, such as being struck on the lower back by a heavy load while bending over, or by direct forces to the sacrum, as in a fall from a significant height. The patient often reports pain in the buttocks, perirectal area, and posterior thighs. There may be local pain, swelling, and bruising overlying the sacrum. Gentle bimanual rectal examination might elicit severe pain and abnormal motion and allow detection of a palpable hematoma. Radiographically, the fracture may be difficult to visualize on anteroposterior and lateral projections, in which case a pelvic outlet view may be diagnostic. Simple transverse fractures at or below S4 are treated conservatively. Above S4, neurologic injuries are common, necessitating careful clinical evaluation and surgery intervention when neurologic compromise is present.

Avulsion fractures. These usually occur during athletic activities and are the result of a sudden, forceful muscular contraction or excessive muscle stretch. They are seen more commonly in older children and teenagers before the corresponding physis matures and closes; adults can have the same symptoms from ligamentous injury at these sites, which may not be evident on a plain film or CT scan. The sites of ligamentous attachments on the pelvis are highlighted in Fig. 46.8.

The ischial tuberosity can be avulsed during strenuous contraction of the hamstrings. The result is pain on palpation of the involved tuberosity, which is increased by flexion of the hip with the knee in extension (hamstrings stretched), but not with the knee flexed (hamstrings relaxed). Ischial tuberosity avulsion can also cause chronic discomfort without a history of acute injury.

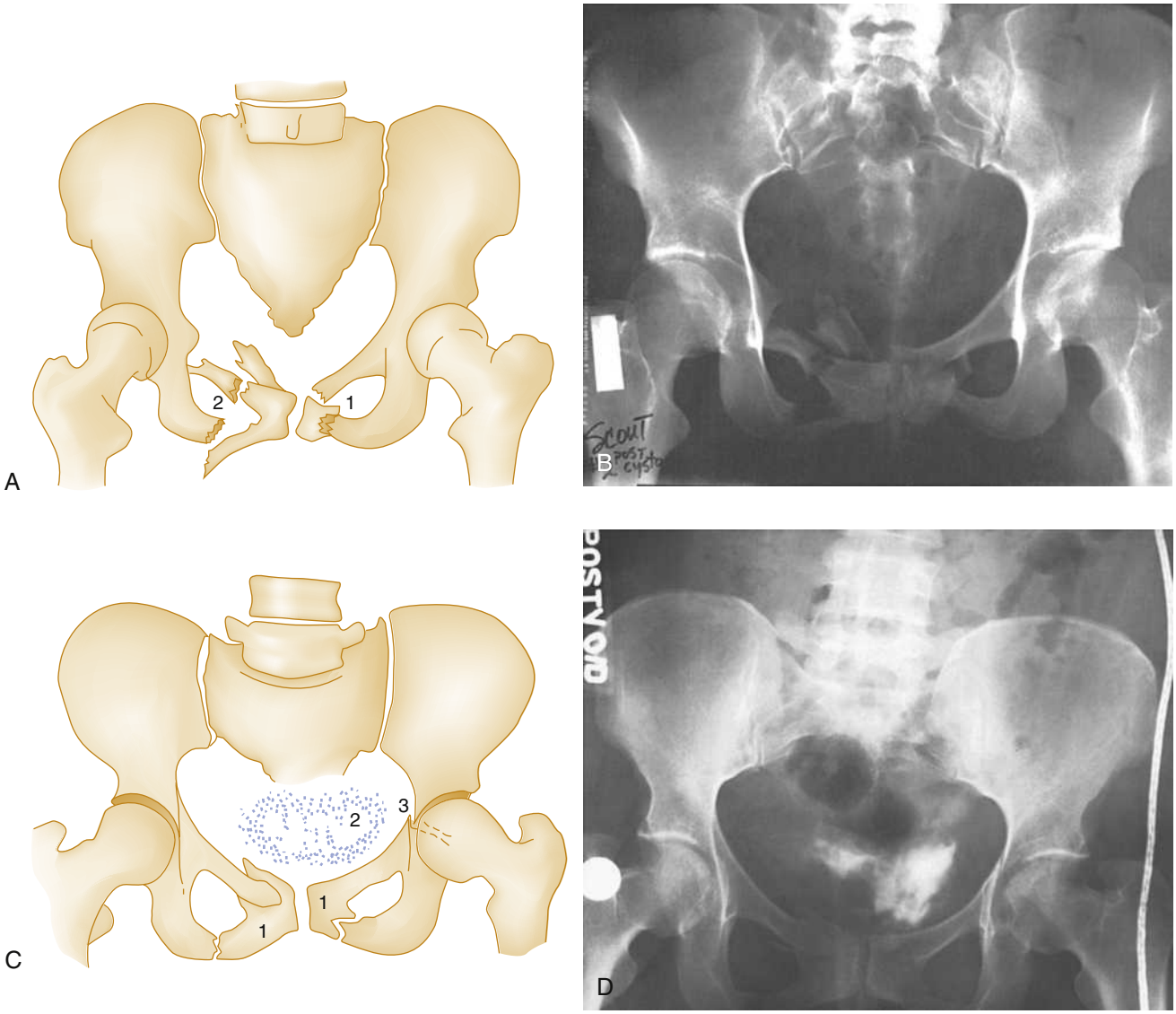

Fig. 46.7 Four-Pillar (Straddle) Fracture. (A and B) Partial inlet view of pelvis shows straddle fracture. *1* and *2,* Marked comminution of left pubic bone and comminuted right superior and inferior rami. This partial inlet projection shows displacement of fragments into the pelvis, which is not evident on the anteroposterior view of the same patient in C and D. A true inlet projection and computed tomography (CT) scan (not available) would provide further information about the posterior arch, which is injured frequently in straddle fractures and should be imaged (see text). (C and D) Post-void cystogram of the same patient with anteroposterior pelvis. *1,* Fractures of pubic rami are seen again but do not appear to be as displaced compared with A and B, because this projection is an anteroposterior view. Even minor degrees of angulation of the x-ray beam can change the appearance of pelvic fracture displacement. *2,* Extravascular contrast indicates bladder rupture. *3,* Left acetabular fracture is seen in this projection but not in B because of the difference in projection. The acetabular fracture disrupts the ilioischial line (see also Fig. 46.13) and is a posterior column fracture.

A portion of the iliac crest epiphysis can be avulsed by contraction of the abdominal muscles. Similarly, the anterior superior iliac spine can be avulsed by forcible contraction of the sartorius muscle. Forceful contraction of the rectus femoris (as in kicking a ball) can result in the less common injury of anterior inferior iliac spine avulsion; however, this radiographic finding should be distinguished from a normal variant, the *os acetabuli*, which is a secondary center of ossification at the superolateral margin of the acetabulum. Physical examination findings are similar in these injuries and reveal local pain, swelling, and limitation in the motion of the hip.

Conservative treatment, including analgesia and bed rest in a position that avoids tension on the affected muscles, is generally all that is required for avulsion injuries; surgical treatment is rarely necessary. Orthopedic consultation within a week is advised for follow-up care.

Stress fractures. Stress fractures can occur with vigorous athletic or military training or during the last trimester of pregnancy. The diagnosis of stress fractures is based on the clinical history and can be confirmed by radionuclide bone scan, although MRI has been shown to be a superior method for detecting these injuries.[9]

Pathologic and insufficiency fractures. Pathologic fracture related to neoplasm, Paget disease, or dietary osteomalacia should be included in the differential diagnosis of any pelvic fracture. Radiation therapy increases the risk of pelvic fracture.

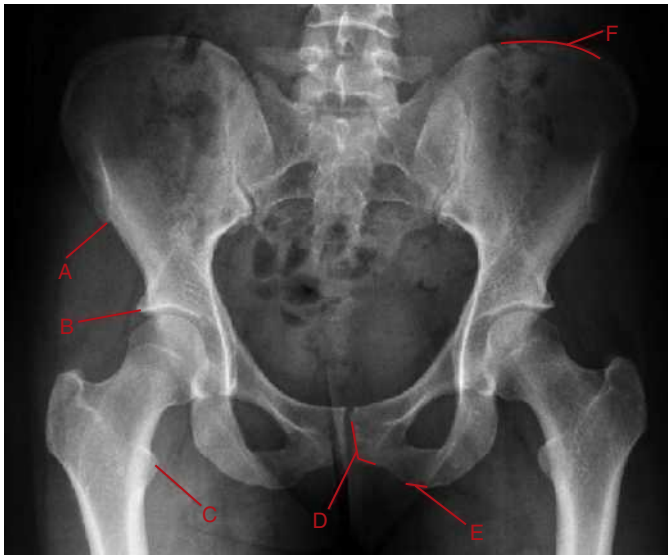

Fig. 46.8 Site of Tendon Insertion for Muscles Originating From the Pelvis. *A,* Sartorius (origin on the anterior superior iliac spine). *B,* Rectus femoris (origin on the anterior inferior iliac spine). *C,* Iliopsoas (inserts on lesser trochanter). *D,* Adductors and gracilis (origin on body of pubis or inferior pubic rami). *E,* Hamstrings (origin on the ischial tuberosity). *F,* Abdominal muscles (origin on the iliac crest).

Partially Stable and Unstable Injuries (Tile Types B and C)

Partially stable and unstable injuries are caused by high-energy impact. The forces applied to the pelvis determine the types of injuries that occur. Generally, forces can be applied to the pelvic ring in anteroposterior, lateral, or vertical directions, resulting in characteristic injury patterns; combinations of forces result in more complex injuries. The terms *unstable fracture* (referring to mechanical stability) and *unstable patient* (referring to hemodynamic status) should not be used interchangeably, although a cause-and-effect relationship often exists.

Anteroposterior compression. Severe anteroposterior compression forces cause disruption at or near the symphysis pubis. The symphysis is normally ≤0.5 cm in an adult but can increase 2 to 3 mm during or after pregnancy. Symphysis widening less than 2.5 cm is considered a stable injury; however, with continued force in the anteroposterior direction, the hemipelvis externally rotates, tearing the sacrospinous, sacrotuberous, and anterior sacroiliac ligaments. The sacroiliac joint opens and hinges on the intact posterior sacroiliac ligaments. The resulting injury is aptly described as an "open-book" fracture. The pelvis is rotationally unstable in the horizontal plane, but the intact posterior sacroiliac ligaments maintain vertical stability.

When diastasis of the pubic symphysis is greater than 2.5 cm on an anteroposterior radiograph, a resultant posterior injury is seen as widening of the sacroiliac joint and occasionally as a sacral or iliac fracture (see Fig. 46.6). If the injurious forces continue, they can separate the hemipelvis, and the sacroiliac joint is seen as widely separated on a plain anteroposterior radiograph (Fig. 46.9) and on CT. The anteroposterior radiograph can be misleading in suggesting a pure open-book fracture in cases with symphysis disruptions greater than 2.5 cm. Since these cases are commonly associated with vertical shear fractures, clinical and CT assessment for vertical instability is essential to classify the fracture properly and plan treatment accordingly. These same forces can also injure the neurologic and vascular structures at the posterior arch. The overall volume of the pelvis increases in the open-book injury, facilitating the expansion of a retroperitoneal hematoma. Several studies have demonstrated that patients with severe grades of anteroposterior compression injuries have the highest crystalloid and

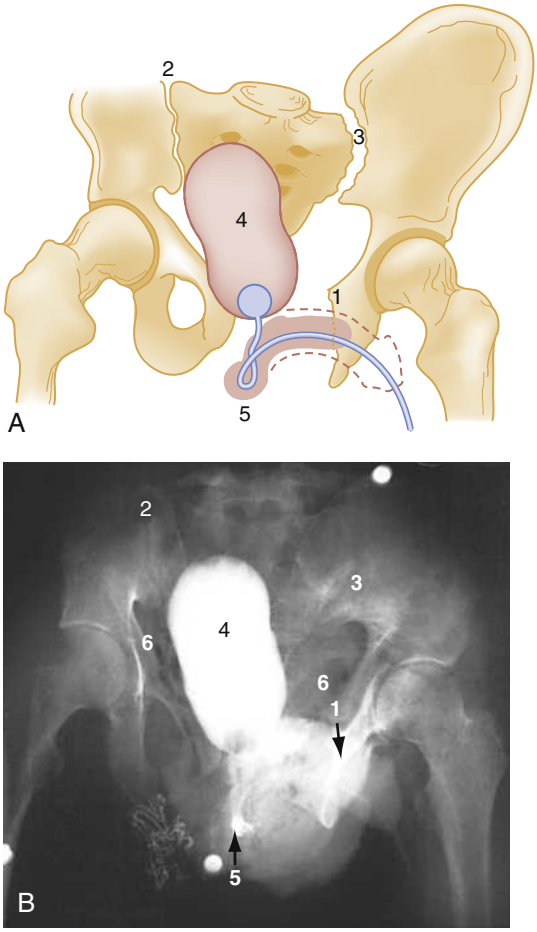

Fig. 46.9 Interpretive drawing (A) and radiograph (B). Severe unilateral "open-book" fracture from anteroposterior compression forces, which is also open (compound). *1,* Separated pubic symphysis with asymmetry of hemipelvis; *2,* normal sacroiliac joint; *3,* separated sacroiliac joint; *4,* cystogram with displacement and abnormally elongated shape of bladder caused by retroperitoneal hematoma associated with separated left sacroiliac joint, which has pushed the bladder to the right; *5,* extravasated contrast into perineum from urethral rupture; *6,* soft tissue air indicating an open fracture.

blood requirements. In addition, these injuries can be associated with non-pelvic injuries that contribute to significant blood loss.

Lateral compression. Lateral compression of the pelvic ring results in varying degrees of internal rotation of the affected hemipelvis. Initially, this causes buckling of the sacrum and horizontal pubic rami fractures. Rami fractures can occur on the ipsilateral or contralateral side, the latter being referred to as a "bucket-handle" fracture (Fig. 46.10).

As the magnitude of force increases, the symphysis can be disrupted, causing overlapping of the pubic bones. On plain radiographs, evidence of injury to the sacrum might be subtle; therefore, overlapping pubic bones with any significant displacement should prompt a search for a posterior injury.

Similar to the anteroposterior injury, as disruption of the posterior ligaments increases, so does rotational instability. In the most severe lateral compression trauma, the ipsilateral pelvis rotates internally to such a degree that the contralateral pelvis might externally rotate. This is referred to as a "windswept" pelvis. Lateral compressive injuries result in varying degrees of horizontal rotational instability; however, the vertical stability of the pelvis is maintained (see Fig. 46.10).

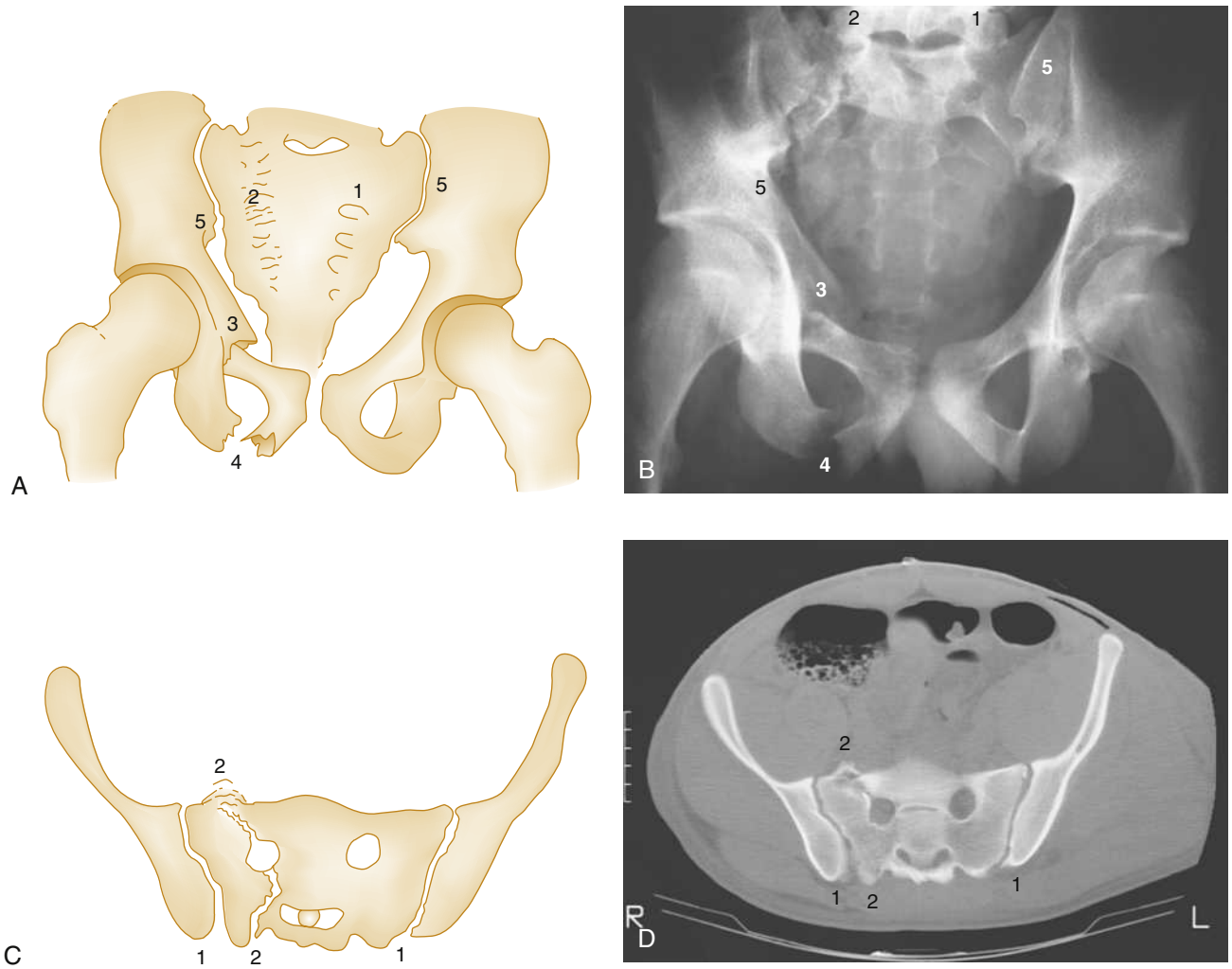

Fig. 46.10 Lateral Compression Fracture. (A and B) Anteroposterior view of the pelvis. *1,* Normal sacral foraminal lines on the left; *2,* sacral foraminal lines on the right are indistinct and do not mirror the normal side, indicating the subtle second break in the pelvic ring; *3* and *4,* fractures of the superior and inferior pubic rami are overriding and displaced, indicating the lateral compression forces (there must be a second break in the pelvic ring); *4,* the "bucket-handle" fracture; *5,* normal sacroiliac joints. (C and D) Computed tomography (CT) scan of the same pelvis. *1,* Normal sacroiliac joints; *2,* compression fracture of the sacrum through the foramen corresponding to the loss of definition of the foraminal lines in A and B.

Because internal rotation causes the pelvic volume to decrease, lateral compressive injuries are generally associated with lesser degrees of blood loss than are anteroposterior injuries.

Vertical shear. Vertical shear injuries are the most unstable injuries affecting the pelvic ring and are associated with violent axial loading of the hemipelvis (such as a fall from a height or "submarining" under a dashboard) that causes fractures in vertical planes. Anteriorly, the symphysis and rami could be disrupted. Posteriorly, gross displacement and instability in the rotational and vertical planes may be present through the sacrum, the sacroiliac joint, or the ilium such that the hemipelvis is displaced posteriorly and cephalad (Fig. 46.11).

Avulsion of the ischial spine, the lower lateral lip of the sacrum, and the transverse process of the fifth lumbar vertebra (sites of ligamentous insertion) (see Fig. 46.11 and Box 46.4) are important clues to the presence of vertical shear fractures. The vertical shearing forces transmitted through the bony pelvis are also transmitted through the rich vascular network and nerve plexus directly adjacent to the bone. This accounts for the major hemorrhage and neurologic injuries associated with vertical shear fractures.

Vertical sacral fractures. A crucial distinction in considering sacral fractures is that transverse fractures do not involve the pelvic ring, but vertical fractures do. Vertical sacral fractures are caused by high-energy injuries and were classified by Denis into three groups according to whether the fracture line extends (1) laterally to the sacral foramina, (2) through the foramina, or (3) medially to the foramina, involving the central spinal canal (Fig. 46.12). The radiographic diagnosis of this fracture hinges on examination of the symmetric cortical lines that are normally present at the superior margins of the sacral foramina on the anteroposterior view. Disruption, distortion, or asymmetry of these lines is an important marker of sacral fractures.

These injuries carry a high risk of neurologic complications: 6% when lateral to the foramina, 28% when through the foramina, and 58% when medial to the foramina. Neurologic dysfunction correlates with the nerve roots involved, but can also manifest as bowel, bladder, or sexual dysfunction. Urgent surgical correction (within 24 hours) is performed for fractures associated with neurologic dysfunction, with the goals of bony fixation of the sacrum and decompression of the affected nerve roots.

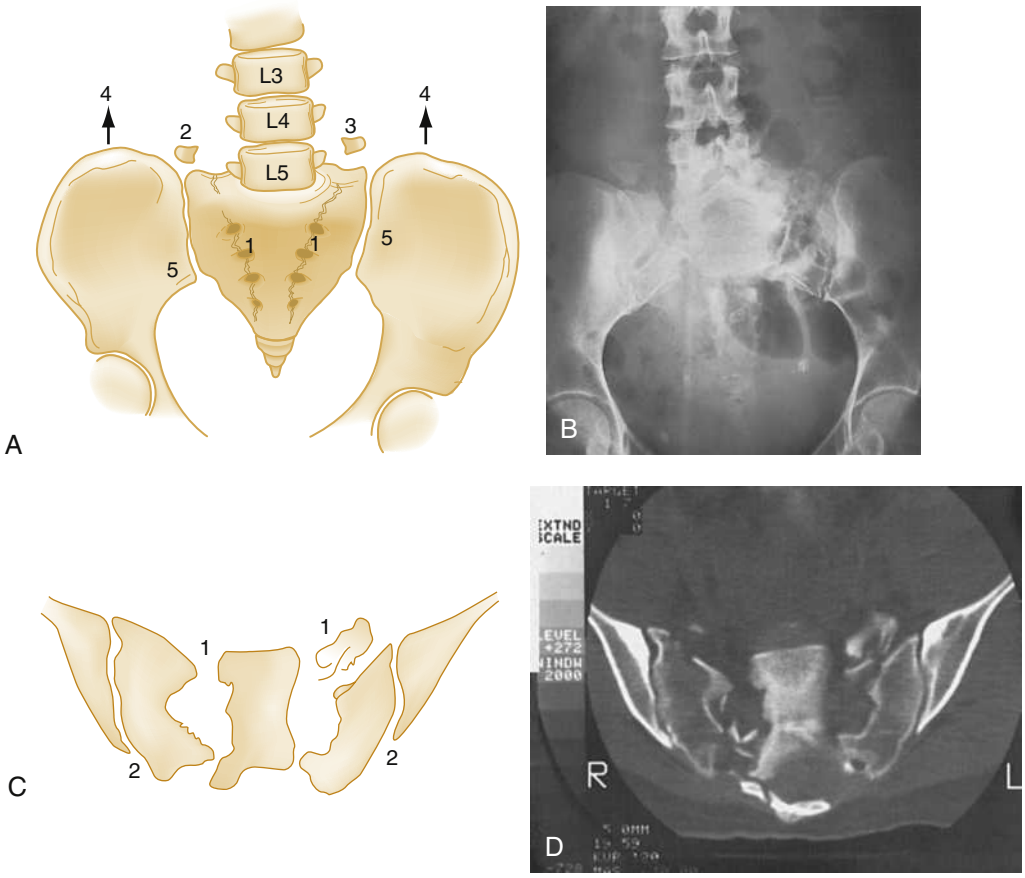

Fig. 46.11 (A and B) Vertical shear fractures bilaterally. At first glance the pelvis appears normal because of the smooth, uninterrupted arcuate line, but careful interpretation reveals the extremely critical nature of the injuries. *1,* Fractures through the sacrum—note loss of definition and symmetry of sacral foramina, indicating vertical fractures through both sides of the sacrum (see computed tomography [CT] scan in D). *2,* Transverse process fragment from right L5 (iliolumbar ligament attachment) is pathognomonic for a vertical shear fracture through the right sacrum. *3,* Transverse process fragment from left L5, pathognomonic for a vertical shear fracture through the left sacrum. *4,* Both hemipelves are dislocated cephalad because of the double-ring fractures through each side of the sacrum. This dislocation explains why the L5 transverse processes appear so close to the iliac crests. (The body of L5 is obscured because of rotational dislocation of the central free sacral fragment posteriorly and because of technique.) *5,* Normal sacroiliac joints. (C and D) CT scan of same pelvis. *1,* Bilateral comminuted fractures of sacrum with lateral displacement of both hemipelves; *2,* normal sacroiliac joints.

BOX 46.4 Radiographic Clues to Posterior Arch Fractures

- Avulsion of L5 transverse process[a]
- Avulsion of ischial spine[a]
- Avulsion of lower lateral lip of the sacrum (sacrotuberous ligament)*
- Displacement at the site of a pubic ramus fracture
- Asymmetry or lack of definition of bone cortex at superior aspect of the sacral foramina

[a] Indicates mechanical instability.

Open Pelvic Fractures

An open pelvic fracture is present when there is direct communication between the fracture site and a dermal, rectal, or vaginal wound. These are potentially lethal injuries, especially if not recognized early. Hemorrhage accounts for early mortality, and infection, sepsis, acute respiratory distress syndrome, and multisystem organ failure are causes of delayed death. The majority of older case series reported mortality rates greater than 50%; rates reported from more recent studies are generally less than 30%. A 2015 study of more than 30,000 patients reported in-hospital mortality of 2.7%, but this rate doubled for patients ages 55 to 70 years old and quadrupled for patients older than 70 years old.[10] Other predictors of mortality included injury severity, altered mental status, prolonged mechanical ventilation, or need for blood product administration.[10]

The skin over the posterior pelvis and gluteal area and perineum should be meticulously inspected for wounds. Some fractures are open only by virtue of a bone spicule penetrating the vagina or rectum, which can be identified by careful digital rectal examination (DRE) and vaginal examination. Hemorrhage from a large open laceration should be treated with direct manual pressure or pressure dressing. Traditionally, pelvic fractures communicating with the rectum have mandated a diverting colostomy; however, a systematic review of the literature on this topic found no difference in infection rates between patients treated with or without a colostomy.

Penetrating Pelvic Trauma

Because of the complex anatomy of the viscera, blood vessels, and nerves within the pelvis, penetrating trauma to this area presents another diagnostic challenge. Overall mortality in this group of patients is about 10%, but the mortality rate of patients who present in shock is

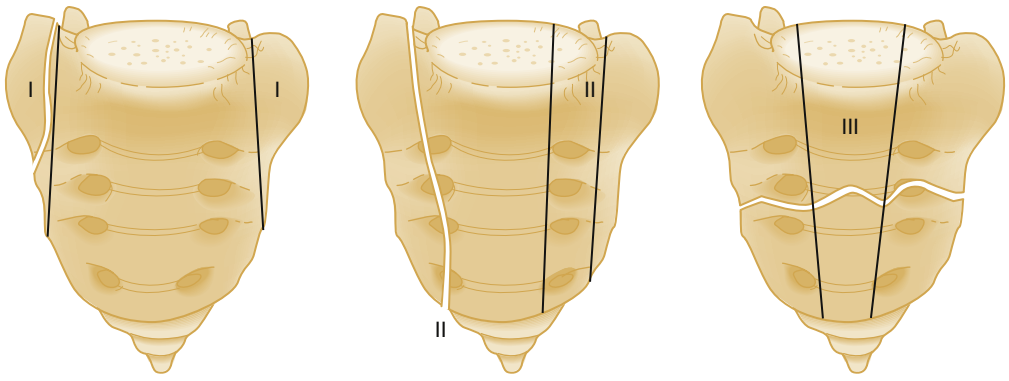

Fig. 46.12 The Denis Classification of Vertical Sacral Fracture. *Zone I* is lateral to the sacral foramina (known as the *sacral ala*). *Zone II* is transforaminal. *Zone III* is the central sacrum medial to the foramina.

BOX 46.5 Goldman Classification System for Pelvic Fracture Urethral Injury

I — Posterior urethra intact but stretched
II — Partial or complete pure posterior injury with tear of membranous urethra above the urogenital diaphragm
III — Partial or complete combined anterior/posterior urethral injury with disruption of the urogenital diaphragm
IV — Bladder neck injury with extension into the urethra
IVA — Injury of the base of the bladder with peri-urethral extravasation simulating a true type IV urethral injury
V — Partial or complete pure anterior urethral injury

TABLE 46.1 Neurologic Deficits of Pelvic Fractures as Expected by Nerve Root Level

Nerve Root	Expected Deficit
L5	Weakness—anterior tibial compartment Sensory deficit—dorsum of foot and lateral calf
S1 and S2	Weakness—hip extension, knee flexion, and plantar flexion Sensory deficit—posterior aspect of the leg, sole and lateral foot, genitalia
S2–S5	Sensory deficit to perineum, sexual dysfunction, bowel and bladder dysfunction

as high as 50%. Vascular injuries can involve the aorta; common iliac artery; external, internal, and common iliac veins; or a combination of vessels. Genitourinary structures and hollow viscera could be injured; fecal contamination from colorectal injury is a serious complication. The finding of blood on DRE is an important clue that a rectal injury has occurred. Emergent surgical consultation is recommended for all cases of penetrating pelvic trauma.

Associated Pelvic Injuries

Urologic Injury

The overall incidence of bladder or urethral disruption associated with any pelvic fracture is approximately 5% to 25%,[11] with increased risk among those with severe pelvic injuries. Because the urethra is far less exposed in women than in men, injury to the urethra in women with pelvic fracture is uncommon. MVCs are four times more likely to cause a pelvic fracture urethral injury (PFUI) than the second most common cause, falling from a height.[11] There are several classification systems for pelvic fracture urethral injuries. The Goldman Classification system is shown in Box 46.5.

Patients with fractures of the anterior arch of the pelvis were at greatest risk for bladder injury. Diastasis of the symphysis more than 1 cm and fracture around the obturator ring with displacement more than 1 cm are associated with a tenfold and threefold increased risk of bladder rupture, respectively.

The presence of gross hematuria indicates injury of the lower urinary tract. Other signs that suggest a urethral injury are scrotal or perineal hematomas, with a high riding prostrate on DRE. Bladder rupture is diagnosed in about 25% of patients with gross hematuria and pelvic fracture. Patients with blood at the urethral meatus in the context of pelvic fracture have up to a 90% incidence of urethral injury and indicate the need for a retrograde urethrogram followed by a cystogram (see Chapter 39). Gross hematuria is investigated with a combination of urethrography, intravenous pyelography, cystography, and CT. The sequence and types of examinations are individualized for each patient according to the capability of the heath care facility. Fracture of the inferomedial pubic ramus and widened symphyseal diastasis have both been shown to be predictive of a urethral injury. Retrograde urethrocystography done before CT of the pelvis might impair the ability of CT to detect extravasation of contrast, which would indicate active pelvic bleeding. Therefore, if CT is to be performed, it ideally is performed before retrograde urethrocystography.

Sexual dysfunction is a recognized complication of pelvic trauma, occurring in 44% of females and 50% of males. Even in the absence of a urethral injury, sexual dysfunction in men can occur secondary to neurovascular disruption associated with the pelvic fracture.

Neurologic Injury

The risk of neurologic injury correlates with instability of the pelvic injury, with a reported incidence of neurologic dysfunction of 2%, 4%, and 14% in Tile type A, B, and C fractures, respectively. Up to 10% of patients with acetabular fractures experience neurologic dysfunction. Neurologic injury occurs commonly in patients with vertical sacral fractures or transverse fractures above the S4 level. Up to 30% of patients with vertical fractures that involve the foramina have associated neurologic deficits. In patients with fractures medial to the foramina involving the spinal canal, almost two-thirds have neurologic deficits.

Pelvic injury can cause various plexopathies and radiculopathies, depending on the nerve root level of the injury (Table 46.1). In patients with sacral fractures, cauda equina syndrome may be fully or partially present. Hyperesthesia and subsequent anesthesia occur in a

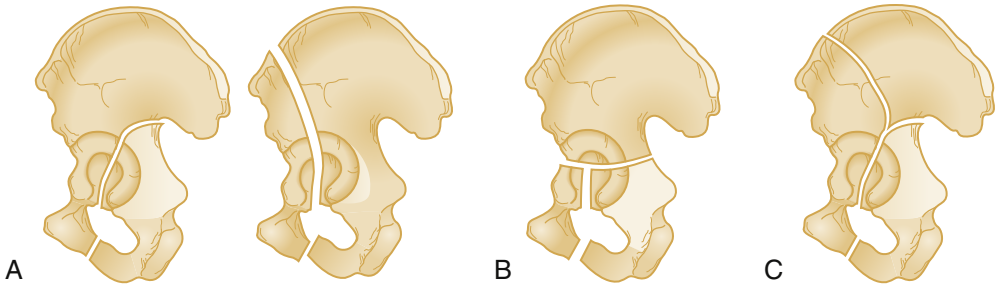

Fig. 46.13 Universal Classification of Acetabular Fractures. (A) Type A: Fractures of one column or one wall, for example, posterior column *(left)* and anterior *(right)* column. (B) Transverse (T-type) fractures involving both columns but, by definition, leaving a fragment of articular cartilage attached to the proximal ilium and thus to the axial skeleton. (C) Type C: Two-column fracture of the acetabulum. No portion of the articular surface remains attached to the axial skeleton because fracture of both columns of the ilium is proximal to the joint. (From Tile M. *Fractures of the Pelvis and Acetabulum*. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2003.)

saddle-shaped distribution in the groin, as well as weakness of ankle plantar flexion, hamstrings, and gluteus muscles and decreased or absent ankle jerk. If the lower sacral roots are affected, the patient might experience neurogenic bladder with overflow incontinence, motor and sensory deficits in the lower extremities, anal sphincter dysfunction, or sexual dysfunction. Patients with neurologic deficits from sacral fractures require urgent orthopedic or neurosurgical consultation.

Gynecologic Injury

Blood at the introitus may indicate a urethral injury, open pelvic fracture, or local laceration without communication with the bony pelvis. Delayed urologic or sexual dysfunction and complications with pregnancy are common after pelvic injury. Gynecologic consultation in the ED is recommended for any female who sustains an injury to the reproductive tract in association with a pelvic fracture and for all pregnant women who sustain a pelvic fracture of any kind.

Associated Non-Pelvic Injuries

The magnitude of force required to disrupt the pelvis commonly results in severe injuries to other organ systems. Among those patients who die as a result of these injuries, it is rare that the fracture is an isolated injury. Associated injuries in trauma patients with pelvic fracture can contribute more to the mortality risk than the pelvic injury itself.

Although patterns of non-pelvic injuries associated with certain patterns of pelvic fracture have been described, these findings have not been reproduced consistently in the literature. Severe injuries to the head, spine, thorax, aorta, and abdomen can occur in patients with both stable and unstable pelvic fractures and are associated with all major mechanisms of pelvic injury. Because of the forces involved, the diagnosis of a pelvic fracture should prompt a careful evaluation for other system injuries.

Acetabular Fractures

Pain and inability to bear weight are the hallmark complaints associated with acetabular fractures. On clinical examination, pain in the hip area with percussion of the heel of the foot or with medial pressure applied to the greater trochanter may indicate a potential acetabular fracture.

Acetabular fractures are broadly classified into three types (Fig. 46.13 and Box 46.6).

Type A fractures are subdivided into anterior and posterior column injuries. Posterior wall fractures are the most common acetabular injuries and are generally caused by a forceful impact to a flexed knee (such as a dashboard injury) where the force is transmitted up through the femur through the posterior acetabulum. As a result, concurrent fracture or **dislocation** of the patella are common. An associated posterior dislocation of the hip is frequently associated with posterior rim fracture of the acetabulum, which may result in an unstable hip joint, leading to recurrent dislocation. Posterior hip dislocation is commonly associated with secondary sciatic nerve injury. The anterior column of the acetabulum is commonly injured when a superior ramus fracture extends into the low anterior column.

BOX 46.6 Classification of Acetabular Fractures

Type A: Fractures of one column of the acetabulum (anterior or posterior column).
Type B: Transverse (T-type) fractures through both anterior and posterior columns; a portion of the acetabulum remains attached to the proximal ilium.
Type C: Transverse (T-type) fractures through both anterior and posterior columns; no portion of the acetabulum remains attached to the axial skeleton.

Type B fractures involve both anterior and posterior columns, but a portion of the acetabulum remains attached to the ilium. When the columns are split, the injury is referred to as a *transverse (T-type) fracture*. The T-type fracture is associated with the worst prognosis, due to the difficulty of obtaining an open anatomic reduction.

Type C fractures are two-column fractures of the acetabulum, with none of the articular surface remaining attached to the axial skeleton. These fractures are readily apparent on plain radiographs as a result of disruption of the ilium.

Assessment of an anteroposterior pelvic radiograph should focus on disruption of the ilioischial and iliopectineal lines, as well as the anterior and posterior lips of the acetabulum (Fig. 46.14). Ramus fractures should be evaluated for possible extension into the acetabulum. When plain radiographic films are used, oblique views of the acetabulum (Judet views) can aid in visualizing the anterior and posterior columns. CT is the imaging test of choice for visualizing acetabular fractures and, when deemed necessary, planning surgical repair. Fractures of the acetabulum often result from high energy mechanisms; thus, patients with isolated acetabular fractures might have significant hemorrhage necessitating blood transfusion. Patients with acetabular fractures require orthopedic consultation in the ED.

Acetabular fractures in older patients have different fracture patterns. In this population, the fracture often involves the anterior column, is more comminuted, and has a more severe articular impaction.[12] Most of these fractures are the result of low-energy trauma (fall

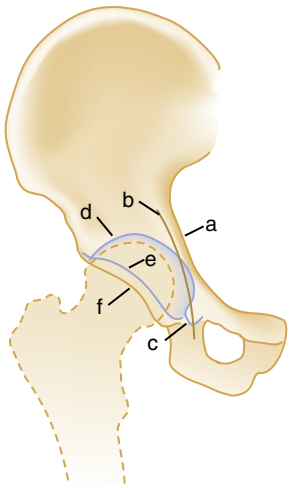

Fig. 46.14 Schematic Drawing of Radiographic Anatomy of Acetabulum in Anteroposterior Pelvis Projection. *a,* Arcuate (iliopubic) line; *b,* ilioischial line; *c,* radiographic U, or teardrop, caused by superimposition of parasagittal surface of ilium onto anteroinferior portion of acetabulum; *d,* acetabular roof; *e,* anterior lip of acetabulum; *f,* posterior lip of acetabulum. (Redrawn from Rogers LF, Novy SB, Harris NF. Occult central fractures of the acetabulum. *Am J Roentgenol.* 1975;124:98.)

from standing position) when the patient lands on the posterolateral hip in the region of the greater trochanter. The force vector drives the femoral head into the anterior column of the acetabulum. Management of older patients is further complicated by comorbid medical conditions and poor bone quality, osteoporosis, which limits the ability to obtain and stabilize an anatomic reduction.[12] Medical management is often the best treatment option. In one study, 56% of older patients who had low-energy fractures involving the anterior wall were treated nonoperatively.[13] In those patients that do undergo ORIF, approximately 25% of patients will ultimately need a total hip arthroplasty.[12] Factors that are associated with the need for total hip arthroplasty within 2 years of ORIF for acetabular fractures are shown in Box 46.7.[14]

Coccyx Fractures

Fractures of the coccyx are caused by a fall into the sitting position or being kicked in that area of the body. The bone can also be fractured during the birthing process. Physical examination reveals local tenderness to palpation in the gluteal crease cephalad to the anus. DRE may elicit pain and allow detection of abnormal motion of the coccyx. Normally, the tip of the coccyx moves 30 degrees anteriorly and 1 cm laterally. If displacement is detected during rectal examination, attempts at reduction are not recommended.

Radiographic confirmation of a coccygeal fracture is generally not necessary. Displaced fractures often are seen on the lateral view, but the diagnosis is evident on physical examination. Nondisplaced fractures can be difficult to identify radiographically. Rarely does the knowledge gleaned from radiographic studies alter the therapy to a degree that warrants radiation exposure to the pelvis, especially in women.

Treatment of coccygeal fracture consists of limited activity (as gaged by pain), stool softeners, non-opioid analgesia, and hot baths. As activity is increased, maneuvers that minimize discomfort include the use of an inflatable rubber donut cushion while sitting, alternately sitting on the side of each buttock, slouching to displace body weight more proximally, and sitting on a hard chair rather than a soft one, as sinking into a soft chair distributes weight onto the coccyx. Because of ongoing muscle forces on the bony fragment, healing is slow, and patients should be told that discomfort will persist for 4 to 8 weeks. If severe disability persists beyond that time frame, an orthopedic consultation is indicated for consideration of local steroid injection or possible coccygectomy.

BOX 46.7 Factors Predicting Need for Total Hip Arthroplasty Within 2 Years of Open Reduction Internal Fixation of Acetabular Fracture

- Age over 40 years
- Anterior dislocation
- Femoral head cartilage lesion
- Involvement of the posterior wall
- Marginal impaction
- Initial displacement of greater than 20 mm
- Nonanatomic reduction
- Postoperative incongruence of the acetabular roof
- Utilization of the extended iliofemoral approach

CLINICAL FEATURES

History

Understanding the mechanism of injury is an important means of determining a patient's risk of having a pelvic fracture and, if present, its pattern and severity. Low-energy injuries (such as ground-level falls) typically cause stable injuries to the pelvis; patients who have sustained high-energy injuries (MVCs and falls from heights) are at risk for unstable fractures of the pelvis, as well as associated injuries to other organ systems.

Determining the direction of forces applied to the pelvis can also give important clues to the types of injury sustained. Anteroposterior forces (such as head-on MVCs) can cause open-book injuries to the pelvis. Lateral forces from side-impact collisions can disrupt the posterior ligaments; however, the pelvic floor generally remains intact. Vertical shear injuries (such as falls from height) can disrupt the posterior ligaments and pelvic floor, causing instability of the pelvis.

Age is an important consideration in patients with pelvic fracture. When compared with their younger counterparts, elder patients have lower density bone, which fracture more easily, have an increased likelihood of hemorrhage, higher morbidity and mortality, greater number of comorbidities, and worse outcomes after acute resuscitation from hypotension. Pelvic fragility fractures in the elderly are nearly as severe as hip fractures in terms of loss of autonomy, mortality rates, and healthcare costs.[15]

Physical Examination

On inspection, rotation of the iliac crests indicates a serious pelvic fracture. Leg-length discrepancy suggests a hip injury or cephalad migration of an unstable hemipelvis. Thorough inspection of the skin and skin folds is necessary to identify open fractures. Perineal or genital ecchymosis or hematoma might be observed, and if many hours have elapsed since the injury, ecchymosis in the periumbilical region (Cullen sign), in the flank areas (Grey Turner sign), or over the inguinal ligament (Fox sign) may be present from retroperitoneal hemorrhage. Palpation along the pelvic ring, seeking the presence of point tenderness, is imperative; palpation starts at the symphysis anteriorly and proceeds to both pubic rami, the iliac spines and crests, and finally to the sacrum and sacroiliac joints posteriorly. The presence of tenderness in any of these locations is an important indicator of pelvic ring injury in alert patients without distracting injury.

Manipulation of the pelvis during physical examination is important to determine stability, but pressure should initially be applied gently and progressively increased, as long as the patient does not report pain. "Spring boarding" (i.e., vigorous downward pressure on the anterior superior iliac spines) to assess the rotational stability of the pelvic ring should be strictly avoided, because this maneuver has the potential to disrupt any tenuous blood clotting that may have occurred around a fracture site and can therefore worsen hemorrhage. Inward stability should be checked by bilateral compression of the iliac wings before outward stability to minimize the risk of opening the pelvis and causing more internal bleeding.

One recent study demonstrated the utility of the straight leg raise in the examination of patients with suspected pelvic fractures.[16] In their cohort of participants with a GCS of 15, all patients with a pelvic fracture, regardless of severity, were unable to SLR without pain (100% negative predictive value). The presence of pain was 100% sensitive in identifying patients with a pelvic fracture.[16]

The penis should be examined for blood at the meatus. DRE, once a fixture in assessment of pelvic trauma, is not sufficiently sensitive or specific to guide diagnosis of urethral or bladder injury (see Chapter 39). The DRE allows evaluation of sensation and sphincter tone for spinal cord injury, and the presence of frank blood, indicating possible mucosal disruption. A vaginal speculum examination should be performed to assess for an open fracture in women identified with fracture on imaging. If operative intervention is planned, this examination, which can be uncomfortable and distressing, is deferred to the operating room under anesthesia. Because it is possible to create an open fracture iatrogenically through the vaginal or rectal wall, the DRE and vaginal examination must be performed carefully, especially in unconscious patients who cannot localize pain. The examiner should be mindful when performing these examinations that bony spicules can lacerate the examining finger. Extravasated urine might be detected in the scrotum or the subcutaneous tissues of the penis, vulva, or abdominal wall. The presence and quality of pulses in the lower limb should be assessed, as should sensation, strength, and deep tendon reflexes.

DEEP VENOUS THROMBOSIS

Patients with pelvic fractures are at high risk for development of deep venous thrombosis (DVT) and pulmonary embolisms. The incidence of DVT and pulmonary embolism is almost 30% even with the patient on mechanical or chemical thromboprophylaxis.[17] The risk is higher in patients with complex acetabular fractures, associated injuries, when the time to surgery is longer that 2 weeks, and age greater than 60 years.[17] High index of suspicion for DVT is needed in these patients even if they are anticoagulants.

DIFFERENTIAL DIAGNOSIS

Pain can be referred from a multitude of areas. A detailed history and physical examination will often elicit the cause of a patient's pain. The causes of pelvic pain after trauma are outlined in Table 46.2. Thorough examinations of the back, abdomen, and lower extremities are necessary to exclude referred pain and associated injuries.

Coccydynia also can occur without fracture and is caused by trauma during parturition, faulty posture, and midline disk herniation (caused by nonsegmental referral of pain from irritation of the dura). Other causes include lumbar facet arthropathy, compression of the sacral roots, neuralgia from sacral plexopathy or sacrococcygeal neuropathy, infections, and local tumors.

TABLE 46.2 Differential Diagnoses of Pelvic Pain

Nontraumatic Causes	Traumatic Causes
• Appendicitis	• Acetabular fracture
• Colon cancer	• Back pain
• Constipation	• Femur fracture
• Cystitis	• Herniated disk
• Diverticulitis	• Hip fracture
• Ectopic pregnancy	• Muscle strain/sprain
• Endometriosis	• Pelvic fracture
• Fibroids	• Tendon/ligamentous strain
• Inflammatory bowel disease	• Vertebral fracture
• Intestinal obstruction	
• Miscarriage	
• Nephrolithiasis	
• Pelvic inflammatory disease	
• Prostatitis	
• Ruptured ovarian cyst	
• Testicular/ovarian torsion	

DIAGNOSTIC TESTING

Radiology

Plain Radiography

Routine radiographs of the pelvis are not necessary after blunt trauma if the patient is asymptomatic, awake, and alert and has normal findings on physical examination of the pelvis, including lack of tenderness to lateral and anteroposterior compression, direct pressure applied to the symphysis pubis, and a negative straight leg raise. However, routine anteroposterior plain radiography is indicated for patients with severe mechanisms of injury, such as MVC, pedestrian struck by motor vehicle, or fall greater than 10 feet, who are symptomatic or whose examination is compromised by either a decreased level of consciousness or distracting injuries.

On the anteroposterior radiograph, the symphysis pubis is normally no more than 0.5 cm wide, and a small (1- or 2-mm) vertical offset of the left and right pubic rami is normal. Overlapping at the symphysis pubis is abnormal and is the result of a crushing injury. Normally, the sacroiliac joint is approximately 2 to 4 mm wide.

On the anteroposterior view, the degree of pelvic rotation caused by technique and positioning can be judged by the presence of asymmetry in the size and shape of the left and right obturator foramina and iliac wings. Diastasis of the sacroiliac joint also causes an asymmetric appearance of the obturator foramina and the iliac wings. If there is displacement into external rotation, the affected iliac wing appears broader and the anterior iliac spine appears more prominent. Avulsion fractures of the fifth lumbar transverse process by the iliolumbar ligament often accompanies a sacroiliac joint disruption or a vertical sacral fracture and is a valuable clue to posterior arch injuries (see Fig. 46.11 and Box 46.4).

Several studies have shown that plain pelvic radiography has insufficient sensitivity and specificity to definitively identify or exclude pelvic fractures, and plain radiography is not generally necessary when abdominopelvic CT evaluation is obtained.[18] In particular, sacral fractures and sacroiliac joint disruptions are not well visualized on the anteroposterior view. However, the addition of inlet and outlet views of the pelvis increases the sensitivity and specificity of plain radiographs in detecting significant pelvic fracture (Fig. 46.15). Sacroiliac joint disruption should be considered in all patients with presumed stable

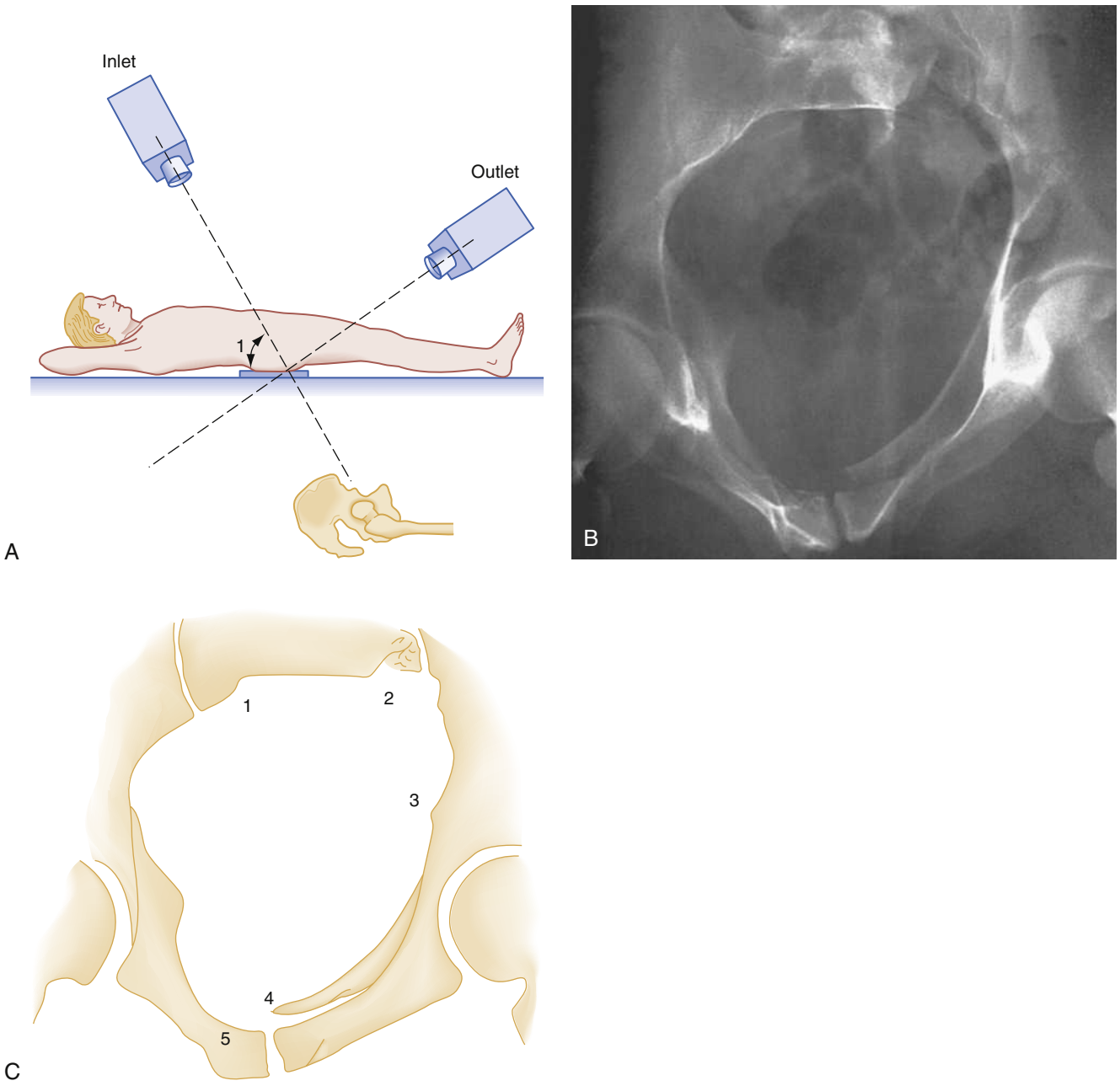

Fig. 46.15 (A) The inlet and outlet views. The inlet view is angled 60 degrees to the plate from head to feet; the outlet view is angled 30 degrees in the opposite direction. Both views can be obtained with a portable machine if necessary. Injuries to the sacrum and sacroiliac joint are commonly difficult to visualize with the anteroposterior view only. The combination of all three views allows the identification of virtually all significant injuries to the bony pelvis. (B) Inlet of pelvis is well demonstrated in this radiograph of a unilateral vertical shear fracture with cephalad and posterior displacement of the left hemipelvis. (C) Schematic of unilateral vertical shear fracture. *1,* Normal sacral ala on the right side; *2,* left sacral ala is indistinct because of a vertical fracture, and the cephalad and posterior displacement of this hemipelvis is shown by this inlet projection; *3,* ischial spine on the left is partially obscured by bowel gas, but it is located more cephalad compared with the right spine because of cephalad displacement of the left hemipelvis; *4,* fractured left superior pubic ramus with displacement cephalad; *5,* the inlet view is taken looking through the superior and inferior pubic rami, which are superimposed so that the obturator foramina are not seen.

anterior pelvic ring injuries with complaints of posterior pelvic pain for whom CT scanning is not anticipated.

When patients are too unstable to undergo CT investigation, or when significant hemorrhagic shock is present in the context of clinically suspected pelvic fracture, the anteroposterior pelvic radiograph is useful to screen for the pelvic injuries that are most often associated with major blood loss requiring urgent intervention. Findings that predict the need for a blood transfusion are highlighted in Box 46.8. Any of these signs could be associated with posterior pelvic injury. Therefore, plain radiography can be a vital test for patients who are unstable, those who are suspected to have unstable pelvic fracture on clinical examination, or those for whom CT cannot be immediately performed. These

BOX 46.8 Factors Predicting the Need for a Blood Transfusion in Patients With a Pelvic Fracture

- Displaced obturator ring fractures
- Displacement ≥0.5 cm of any fracture site in the pelvic ring in combination with a displaced symphysis pubis
- Obvious vertical displacement of the posterior pelvis
- Open-book fractures
- Shock index ≥0.9[36]

Tile C fractures as associated with the highest transfusion requirements.

studies may alert the clinician of the need for surgery, angiography, or other definitive management of pelvic hemorrhage.

Computed Tomography

CT is the imaging test of choice for evaluating the injured pelvis. If plain radiographs are negative and there is suspicion of an occult fracture, the sensitivity of clinical CT reports for detection of any type of fracture of the proximal femur, pelvis, or sacrum is 88%.[19] CT provides detailed visualization of the posterior arch and rotational deformities that indicate the relative stability of the pelvic ring. The acetabulum, which can be difficult to assess with plain radiographs, is well demarcated with CT. Furthermore, abdominopelvic CT provides detailed information about concomitant injury to abdominal organs, which aids in the planning of laparotomy, external fixation of the pelvis, angiography, and definitive orthopedic management. Controversy exists regarding whether all high-risk patients should undergo a "pan-scan," which is comprised of CT scanning of the head, neck, chest, abdomen, and pelvis, or whether a selective approach is better, using clinical indications to guide CT utilization. Proponents of pan-scanning argue that selective scanning of high-energy trauma patients leads to a high miss rate for important diagnoses that alter treatment plans. Although selective CT scanning misses some injuries, fewer than 5% of those missed injuries require a change in the treatment plan. CT imaging should be based on the evaluation of the patient, accounting for mechanism of injury, hemodynamic status, and suspicion of injury on physical examination. Some patients will require a pan-scan but obtaining this series of imaging on all patients meeting certain global criteria results in unnecessary radiation exposure, resource use, and expense. In general, CT scanning protocols are based on institutional preferences, guided by the literature. Imaging of the multiple-trauma patient is discussed in Chapter 32.

Unless a patient requires an immediate lifesaving surgical intervention, it is recommended that CT be used to evaluate patients with high-energy mechanisms of injury if pelvic fracture is suspected or has been confirmed by plain radiography; in order to better delineate the injury.

Evaluation of Hemorrhage

Hemorrhage is the most devastating complication of pelvic fracture. In the original series of high-energy pelvic injuries used to formulate their classification system, Burgess and colleagues found that an average of 14.8 units of blood were transfused in the anteroposterior compression group, 9.2 units in the vertical shear group, and 3.6 units in the lateral compression group. The correlation between transfusion requirements and type of pelvic fracture has been confirmed in other studies that demonstrate that unstable fracture patterns (including Tile class C and Young and Burgess lateral compression) increase the need for transfusion, interventional radiologic embolization, and risk of mortality.[20]

Major pelvic hemorrhage results from lacerations of the rich vascular network supplying the pelvis in the retroperitoneal space. Pelvic hemorrhage is commonly venous in origin; therefore, an intact peritoneum may help contain or tamponade a retroperitoneal hematoma. However, it is possible for bleeding to extend beyond the retroperitoneum and dissect into the anterior abdominal wall or through the peritoneum into the abdominal cavity. Bleeding can also occur from the marrow at the fracture sites. Finally, coagulopathies can lead to persistent retroperitoneal bleeding and should be considered when the patient does not respond to fluid and blood replacement.

BOX 46.9 Pelvic Fracture–Related Hemorrhage: Goals in the Emergency Department

1. Resuscitation: Recognize the patient who is in hemorrhagic shock and initiate blood transfusion early in the resuscitation.
2. Recognition: Realize that patients with posterior arch injuries are at higher risk for pelvic hemorrhage.
3. Evaluation: Identify associated non-pelvic injuries (especially head, chest, and intra-abdominal) that contribute immensely to an increase in mortality in patients with pelvic fracture.
4. Stabilization: Wrapping the pelvis in a sheet and towel clamps is the easiest way to immobilize the pelvis in the emergency department. Stabilization by external fixation or pelvic C-clamp should be performed by orthopedic surgeons.
5. Control of pelvic bleeding: Angiography is highly effective in treating pelvic arterial hemorrhage. Pelvic packing during laparotomy is another way of controlling bleeding. Institutional practices determine if one or both techniques are used.
6. Prevention: Avoid hypothermia and maintain body temperature above 36°C as this is associated with increased hemorrhage and decreased success if embolization is required.

The combination of pelvic and intra-abdominal bleeding is associated with life-threatening outcomes. Major pelvic injury is associated with intra-abdominal injuries in up to one-third of cases, particularly involving the liver and spleen. In the patient with pelvic fracture who is in shock, it is critical to establish early in the clinical course whether hemorrhage is occurring within the abdominal cavity and thus necessitating laparotomy. Diagnostic strategies for evaluation of hemorrhage resulting from pelvic fracture include diagnostic peritoneal lavage (DPL), bedside ultrasonography, and CT. Regardless of which is chosen, unnecessary laparotomy should be avoided at all costs, because a negative abdominal exploration is associated with a higher mortality rate for hemodynamically unstable patients with pelvic fractures.

Factors that have been associated with increased hemorrhage risk and need for hemorrhage control interventions are patients with Tile classification type B and C fracture patterns, hypothermia, and elevated serum lactate levels.[21] Box 46.8 lists factors that predict the need for a blood transfusion, and Box 46.9 summarizes goals for the ED treatment of pelvic fracture-related hemorrhage.

Diagnostic Peritoneal Lavage

DPL, once widely accepted as an accurate means of establishing the presence of intra-abdominal hemorrhage, has been largely supplanted by bedside ultrasound and CT imaging. When DPL is used, a supraumbilical peritoneal aspirate that is negative for blood indicates that the peritoneal cavity is not a major source of bleeding or a significant contributor to hemorrhagic shock. In the absence of another identified source of blood loss, a negative peritoneal aspirate in a patient with a major pelvic fracture and hypotension indicates pelvic hemorrhage.

Gross aspiration of blood suggests major intra-abdominal hemorrhage. Pelvic stabilization is indicated, with urgent laparotomy for hemodynamically unstable patients.

Ultrasound

Focused assessment with sonography in trauma (FAST) is the standard approach used to identify free intraperitoneal fluid in the trauma patient. An important caveat is that FAST is not helpful for evaluating the retroperitoneal space, where pelvic hemorrhage commonly occurs. However, FAST has essentially replaced DPL to identify whether intraperitoneal bleeding is the cause of the hypotension, leaving the pelvis as the probable source, when FAST is negative. Although a positive FAST study is widely used to decide whether to perform laparotomy in a hemodynamically unstable patient, its reliability in patients with major pelvic injury has been questioned. Historically, sensitivity has been reported at about 80% and specificity 95% for the detection of hemoperitoneum in patients with pelvic fracture. However, a recent case series of 81 patients in refractory shock showed that the FAST examination had a sensitivity of 96% and specificity of 96%.[22] The false-negative and -positive rates for FAST were 2% and 7%, respectively. The use of FAST in the evaluation of blunt abdominal trauma is discussed in Chapter 38.

Computed Tomography

CT is the diagnostic test of choice for detecting pelvic and intra-abdominal injuries. It reveals bleeding in the peritoneal and the retroperitoneal spaces. In many cases, CT of the pelvis with intravenous contrast can distinguish a stable hematoma from ongoing bleeding from pelvic arteries. The presence or absence of extravasated intravenous contrast material, indicated by a blush on CT, is useful in predicting which patients will require therapeutic angiography. However, absence of extravasation does not exclude the possibility of ongoing pelvic bleeding. Pelvic computed tomography angiography (CTA) can more accurately localize active pelvic bleeding and also distinguish bleeding from arterial and venous sources.[23] This distinction can have great impact on the decision to perform therapeutic angiography for active arterial bleeding.

MANAGEMENT

Resuscitation

Blunt trauma patients who have the combination of pelvic ring fractures and hemorrhagic shock have a mortality rate of approaching 50% and may require massive quantities of blood products. It is estimated that nearly 80% of deaths can be attributed to early uncontrolled hemorrhage and delays in hemostatis.[24] For patients in shock, resuscitation is described in Chapters 3 and 32.

For patients with pelvic fractures, achieving a normal pulse and blood pressure with fluid resuscitation alone in the ED may be an unrealistic goal. Such attempts may contribute to ongoing bleeding and may delay definitive treatment that can halt the hemorrhagic process.

Intravenous access in the lower limbs should be avoided in patients with severe pelvic fractures, because infused fluids and blood products might be lost through venous bleeding into the retroperitoneal space.

Box 46.9 details methods for controlling hemorrhage during the ED management of patients with pelvic fractures.

Control of Hemorrhage

In addition to blood transfusion, two important therapeutic modalities for control of hemorrhage are mechanical stabilization of the pelvis and angiographic embolization. There has been some debate as to which of these modalities should take precedence, and this has been predicated on institutional availability. As a general rule, angiography with therapeutic embolization of bleeding arteries is more effective than and takes precedence over invasive external fixation.

Stabilizing the Pelvis

Noninvasive techniques. The most readily available means to stabilize the pelvis quickly in the ED is a sheet and towel clamps. Wrapping the pelvis tightly with a sheet and securing it with towel clamps can reduce an open-book pelvic injury (Fig. 46.16) and the potential for volume and blood loss in the pelvis. We recommend early pelvic binder use, as this bedside maneuver is associated with improved survival and lower mean blood transfusion volume and mortality rates.[25]

Other commercial circumferential compression devices have been developed to facilitate noninvasive stabilization of the pelvis. Cadaveric studies suggest that these devices are effective at reducing an open-book pelvis. Patients with exsanguinating pelvic hemorrhage treated with a noninvasive splinting device appear to fare as well as those for whom formal external fixation was performed emergently.

Patients with open-book pelvic injuries are most likely to derive benefit from tight wrapping of the pelvis. This maneuver might not be desirable when lateral compression forces have already internally rotated the hemipelvis, where indiscriminate forceful wrapping could worsen the degree of displacement. Therefore, judgment is required to discern whether one is wrapping the pelvis to *reduce* the volume of an externally rotated pelvis or *splinting* a pelvis to minimize movement, especially when the patient is repositioned.

Formal external fixation. External fixation of the pelvis is performed by orthopedic surgeons to prevent movement at fracture sites and to control bleeding. Application of an external fixator does not appear to decrease morbidity or mortality rates but may improve clinical outcome by limiting hemorrhage and restoring mechanical integrity. Application of a fixator is a time-consuming process; it should not be attempted if it will delay more definitive treatment of pelvic bleeding by angiography or the treatment of other sources of severe blood loss. The timing of the application of the external fixator requires coordination among the emergency medicine physician, trauma surgeon, orthopedic surgeon, and interventional radiologist. Early surgical consultation is needed for efficient planning and prioritization of surgical management.

Many stable anteroposterior and lateral compression fractures can be treated definitively with an external fixator. When the pelvis is vertically displaced, traction combined with external fixation is necessary to reduce the pelvis, pending definitive open surgical repair. Most fixators can be constructed to allow convenient surgical access to the abdomen and pelvis. The specific mode of invasive fixation is specific to the institution and the orthopedic or trauma consultant.

Angiography and Embolization

Arteriography and venography have been evaluated for their utility in managing hemorrhage associated with pelvic fractures. Although pelvic bleeding is commonly venous in origin, venography is not useful in management. Extensive anastomoses and valveless bidirectional collateral flow make venous embolization impractical. In contrast, arteriography is superior at both diagnosing and managing arterial bleeding.

Angiography is indicated when hypovolemia persists in a patient with a major pelvic fracture despite attempts at controlling hemorrhage by other means. It is difficult to determine whether bleeding is venous or arterial in origin until angiography is performed. An inadequate response to initial resuscitation (defined as failure to maintain a systolic blood pressure above 90 mm Hg after the administration of 2 or more units of packed red cells) and the presence of contrast extravasation on admission CT are indicative of active arterial bleeding. Although the presence of contrast extravasation on CT is an indication for angiography, the absence of contrast blush on CT is not sufficient to rule out serious pelvic bleeding. Sacroiliac joint disruption, persistent systolic blood pressure below 100 mm Hg, hypothermia, elevated lactate levels,

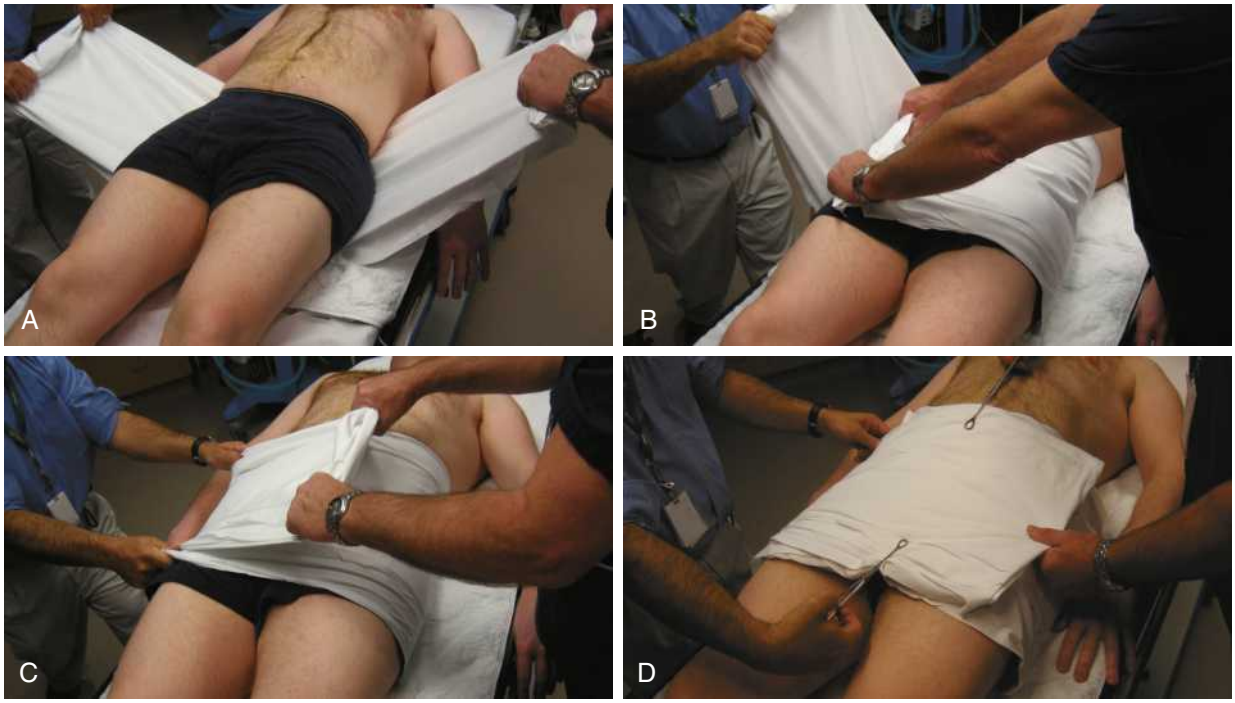

Fig. 46.16 (A) Circumferential pelvic anti-shock sheeting is applied in this example patient. The patient's clothing should be removed before application. The sheet is positioned beneath the patient's pelvis smoothly. The ends of the sheet are crossed in an overlapping manner anteriorly (B) and are pulled taut (C). D, Clamps secure the smooth and snug sheet.

and female gender have been shown to be predictors of the need for embolization at the time of angiography.[21]

The timing of angiography is individualized for each patient, depending on priorities for the treatment of concomitant injuries. Early access to angiography has been associated with reduced mortality, and delays in angiography greater than 60 to 90 minutes, or time to embolization greater than 3 hours, are associated with worse outcomes.[24,26,27] Posterior arch disruptions are associated with the most severe hemorrhage; angiography should be considered at an early stage for patients with this injury. Whether patients undergo angiography from the ED or immediately preceding laparotomy, it is important to be mindful of the logistical delay that occurs in mobilizing the angiography team, so this intervention should be anticipated as early as possible. Transfer to the angiography suite requires orchestrating the necessary personnel and equipment to care for a critically injured patient. The use of mobile angiography equipment in the ED to control pelvic hemorrhage has been reported. This option removes logistical delays while ensuring a greater degree of safety in monitoring patients during the procedure.

The contrast material for arteriography is injected through the femoral artery on the less-injured side or via the upper extremity. The examination starts above the level of the aortic bifurcation and proceeds to selective branches of the internal iliac (hypogastric) artery. Transcatheter embolization with thrombogenic coils, foam, or spherules is used to stop hemorrhage from the branches of the internal iliac artery.

Embolization is highly effective for controlling arterial bleeding, with fewer than 10% of patients requiring repeat procedures because of ongoing bleeding. The complications that can result from embolization include gluteal muscle necrosis, surgical wound breakdown, infections, acute renal failure, impotence, and bladder necrosis.[28] Transcatheter arterial embolization has been associated with a 13.6% complication rate; this rate increases if bilateral internal iliac artery embolization is needed to control bleeding.[28] Other complications that have been reported are femoral pseudoaneurysms, rhabdomyolysis, and post-angiography acute ischemia of the lower extremity.[28]

Initial factors on presentation that predict a successful transarterial embolization in patients with pelvic fractures are prevention of hypothermia with maintenance of body temperature greater than 36°C, maintenance of the respiratory rate at approximately 22 breaths/min, sustained systolic blood pressure approximately 90 mm Hg, maintenance of heart rate of approximately 100 beats/min, associated injuries limited to two organ systems, ISS less than 20, and minor head trauma with a GCS greater than 13.[29]

Hemodynamically Unstable Patients With Pelvic and Intra-Abdominal Hemorrhage

Patients who hemorrhage from both the pelvis and the abdomen have mortality rates above 40% and deserve special consideration. These patients may be too unstable to undergo CT imaging. Prioritizing the need for laparotomy versus angiography in these patients becomes challenging when the need for laparotomy is based on the detection of intra-abdominal fluid by FAST (or DPL). Unnecessary laparotomy performed in patients who are hemodynamically unstable with pelvic fracture further increases their already high mortality rate. In these cases, it is crucial that the general or trauma surgeon, orthopedic surgeon, and interventional radiologist coordinate their efforts to optimize the timing of necessary procedures.

If DPL is performed, gross aspiration of blood is a strong indicator for prompt laparotomy. A positive FAST examination indicates hemoperitoneum, and it is generally accepted that laparotomy should be pursued before angiography in such cases. Given the significant rate of false-negative FAST examinations in patients with pelvic trauma, a single negative FAST examination should not be considered definitive enough to exclude significant intraperitoneal hemorrhage. However, patients with hemorrhagic shock and a negative FAST examination

with adequate windows are more likely to be bleeding from the pelvis injury. When concurrent pelvic bleeding is highly suspected (as with patients with severe open-book pelvic injuries), it is advisable that angiography promptly follow the laparotomy. The use of hybrid operative suites and aortic balloon occlusion may improve outcomes in this subset of patients.[24]

At the time of laparotomy, the orthopedic surgeon will determine if it is appropriate to place an external fixator. Packing the pelvis at the time of laparotomy is a means of achieving hemostasis with pelvic hemorrhage.[30] This procedure has been a mainstay of treating pelvic hemorrhages in selected European centers; it has become much more widely accepted as studies have documented improved mortality rates with its use. Part of the rationale for packing rather than angiography is the fact that pelvic bleeding is more commonly venous in origin, for which arteriography and embolization have no benefit. In contrast, packing might provide tamponade of bleeding from the posterior venous plexus. It is recommended that the pelvis be stabilized before packing to provide solid structural support. Intraperitoneal, retroperitoneal, and extraperitoneal techniques of packing have been described; the retroperitoneal and extraperitoneal approaches have been used rapidly in the ED setting. A systematic review of pelvic packing concluded that, for patients with hemodynamic instability caused by pelvic hemorrhage, packing can be used as a temporizing measure for control of bleeding until more definitive treatments can be initiated.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is another option for control of bleeding from pelvic fractures.[31] Similar to cross clamping the aorta, this endovascular balloon can be placed in the infrarenal position using the Seldinger technique to occlude the aorta and prevent blood from entering the pelvis. This technique is amendable to out-of-hospital or bedside placement in the ED with ultrasound guidance of the final position of the balloon.[32] Several studies have shown improved mortality in patients with hemorrhagic shock from non-compressible torso and pelvic injuries.[33-35] REBOA is associated with a risk of vascular injury and limb ischemia, so it is restricted to patients in extremis, similar to what is seen with cross clamping of the aorta.[31,35] With appropriate training, REBOA can be a safe bridge to obtain hemodynamic stability until more definitive hemorrhage control can be obtained in the operating room or angiography suite.

DISPOSITION

Disposition of the patient depends on whether or not the fracture is considered stable, and whether there are other injuries or significant comorbidities. Most patients who have stable fractures (such as pubic ram or minor iliac wing fractures) can be discharged to home with adequate analgesics and with crutches or canes, as needed, to aid in weight bearing. Patients with stable coccyx and sacral fractures might benefit from a donut pillow that distributes their weight onto their buttocks and away from the fracture site when seated.

Patients with unstable fractures, hemodynamic compromise, or significant associated injuries require admission to the surgical intensive care unit or hospital equivalent for definitive care. ED management consists of temporarily stabilizing the fracture, addressing any life-threatening injuries, and arranging admission or transfer to a hospital or service that can provide definitive care.

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CHAPTER 46: QUESTIONS AND ANSWERS

1. While examining a patient with blunt abdominal trauma, you note blood at the urethral meatus. What is the most appropriate next step in the patient's management?
   a. Order a cystography
   b. Order a retrograde urethrogram
   c. Order a urinalysis
   d. Order an anterograde urethrogram
   e. Order an intravenous pyelography

Answer: b. Blood at the urethral meatus necessitates a retrograde urethrogram followed by a cystogram. Gross hematuria is investigated by a combination of urethrography, intravenous pyelography, cystography, and computed tomography (CT).

2. An avulsion fracture caused by the hamstring muscles most likely involves which of the following structures?
   a. Anterior inferior iliac spine
   b. Anterior superior iliac spine
   c. Iliac crest
   d. Ischial tuberosity
   e. Sacrum

Answer: d. Forceful contraction of the hamstrings can result in an injury of ischial tuberosity. The anterior inferior iliac spine may be avulsed during strenuous contraction of the rectus femoris muscle. A portion of the iliac crest epiphysis may be avulsed by contraction of the abdominal muscles. The anterior superior iliac spine may be avulsed by forcible contraction of the sartorius muscle.

3. A 25-year-old patient involved in a motor vehicle collision (MVC) presents with a suspected unstable pelvic fracture. The vital signs are blood pressure, 90/50 mm Hg; heart rate, 120 beats/min; and respiratory rate, 22 breaths/min. What is the most appropriate next step in this patient's management?
   a. Call trauma service for immediate laparotomy
   b. Call orthopedics for fixation
   c. Chest and pelvis radiographs
   d. Computed tomography (CT) scan of the abdomen and pelvis
   e. Perform serial abdominal and focused assessment with sonography in trauma (FAST) examinations

Answer: c. When patients are too unstable to undergo CT investigation, the anterior/posterior portable radiograph is useful in screening for pelvic injuries that are most associated with major blood loss. Findings with this technique that have been reported to predict the need for transfusion include "open-book" fracture, displacement of 0.5 cm or more at any fracture site in the pelvic ring, and displaced symphysis pubis or obturator ring fracture. Chest radiographs should be performed to rule out associated injuries that might be the cause of the patient's hypotension and tachycardia (e.g., hemothorax, tension pneumothorax, widened mediastinum).

4. Which of the following treatments can provide definitive control of hemorrhage from severe pelvic fracture?
   a. Blood transfusion
   b. Commercial circumferential pelvic compression devices
   c. External fixation
   d. Transfusion of concentrated clotting factors
   e. Wrapping pelvis with sheet

Answer: c. External fixation is an invasive strategy aimed at cessation of pelvic hemorrhage. Options A, B, and E are important for the emergency clinician to quickly stabilize a mechanically unstable pelvic fracture and hopefully minimize bleeding, but these options, per se, are not definitive treatments. Transfusion of blood products is important in overall resuscitation of the patient but does not stop bleeding from pelvic fractures.

5. Which of the following radiographic findings necessitates further evaluation of the pelvic ring?
   a. Asymmetry of the pelvis caused by rotation
   b. Duverney fracture
   c. Sacroiliac joint 4 mm wide on pelvic radiograph
   d. Symphysis pubis 7 mm wide
   e. Transverse fracture of the sacrum

Answer: d. On the anteroposterior radiograph, the symphysis pubis is normally no more than 5 mm wide, and a small (1 or 2 mm) vertical offset of the left and right pubic rami may be normal. Normally, the sacroiliac joint is approximately 2 to 4 mm wide. On the anteroposterior view, the physician may judge the degree of pelvic rotation caused by technique and positioning by the presence of asymmetry.

47

Femur and Hip Injuries

Michael K. Abraham and Michael C. Bond

KEY CONCEPTS

- A hip dislocation is an orthopedic emergency. The likelihood of avascular necrosis (AVN) is related to both the initial degree of trauma and the amount of time the femoral head remains out of joint. Reduction of the hip within 6 h after dislocation significantly decreases the incidence of AVN.
- When a painful hip makes ambulation difficult and plain radiographs do not reveal a fracture, computed tomography (CT) or magnetic resonance imaging (MRI) should be performed. MRI is the gold standard for diagnosis—although this does not need to be completed in the emergency department (ED).
- In patients with intertrochanteric fractures, hemodynamic instability can result from dehydration and blood loss. Up to 70% of patients with these injuries are under-resuscitated.
- It is important to identify acetabular fractures before closed reduction is attempted, because intra-articular bone fragments can interfere with effective reduction.
- In elderly patients, the use of femoral nerve blocks should be considered, due to the potential adverse effects of parenteral opioids.

GENERAL INFORMATION

Foundations

Background and importance—Injuries to the hip and femur are quite common in the emergency setting and are associated with significant morbidity and mortality. Hip and femur pathology, while considered a disease of the elderly, actually occurs among all age groups. While elderly patients are at risk for femoral neck **fracture**s, children can have Perthe disease and slipped capital femoral epiphysis (SCFE), among other pathologies. Women are at increased risk for both femoral neck fractures and intertrochanteric fractures, with a female-to-male ratio of 4:1. More than three-quarters of all hip fractures occur in postmenopausal women over 50 years of age. Perthe disease, or avascular necrosis (AVN) of the femoral head, occurs in children between 2 and 14 years old, with a peak age of onset of 5 years old. The incidence of SCFE peaks with the onset of puberty. While fractures show a female preponderance, both SCFE and Perthe disease have a higher incidence in males.

Anatomy of the Hip and Femur

Skeletal Anatomy

The femur is the longest and strongest bone in the human body and is routinely subjected to substantial forces during powerful muscle contraction and weight transmission. It consists of the femoral head, neck, and shaft. The femoral head is firmly seated in the **acetabulum**, reinforced by the labral cartilage. The well-developed capsule, overlying ligaments, and proximal musculature of the lower extremity add strength to the joint (Fig. 47.1). Structurally, the femoral neck serves as an oblique strut between the pelvis (the horizontal beam) and the shaft of the femur (the vertical beam) (Fig. 47.2). The length, angle, and narrow circumference of the femoral neck permit substantial range of motion at the hip, but these same characteristics subject the neck to significant shearing forces.

The type of bone in the femur changes depending on location, which affects fracture patterns. The bone in the femoral head, neck, and intertrochanteric region is predominantly cancellous, which is less resistant to torsional forces. Distal to the intertrochanteric region, including the subtrochanteric region and femoral shaft, the bone is cortical, which requires increased force to fracture. At the distal metaphysis, the femur widens as the cortical bone thins, lessening its resistance to stress.

Musculature

The musculature of the hip and thigh is the largest and most powerful in the human body. Grouped according to the primary action at the hip, the muscles in this region of the body are located within three compartments, each containing associated nerves and vessels (Table 47.1). Knowledge of the major muscle actions offers insight into common injury patterns and deformities (Fig. 47.3).

Arterial Supply

The arterial supply of the femoral head, neck, and shaft arises from different sources. The major arterial supply to the femoral head and neck comes from the medial and lateral circumflex arteries, which are branches of the femoral artery (Fig. 47.4). These branches form an extracapsular arterial ring around the femoral neck. Another blood supply source to the femoral head typically arises from the obturator artery and courses through the ligamentum teres.

As the external iliac artery passes beneath the inguinal ligament, it becomes the common femoral artery. At this point, the artery is located midway between the anterior superior iliac spine (ASIS) and the symphysis pubis. Approximately 3 to 4 cm distal to the inguinal ligament, the deep femoral artery branches off. The deep femoral artery is predominantly responsible for the vascular supply of the femur. It runs posterolaterally to the superficial femoral artery, supplies the hamstrings, and terminates in the distal third of the thigh as small branches supply the belly of the adductor magnus. The superficial femoral artery continues to pass along the anteromedial aspect of the thigh and terminates at the junction of the middle and lower thirds of the thigh. Here, the superficial femoral artery passes through the adductor hiatus and becomes the popliteal artery.

Venous System

In the proximal two-thirds of the thigh, the common and superficial femoral veins lie adjacent to the common and superficial femoral arteries. At the inguinal ligament, the common femoral vein is posterior and medial to the common femoral artery and moves to the lateral position as it passes distally. The deep femoral vein and the greater saphenous

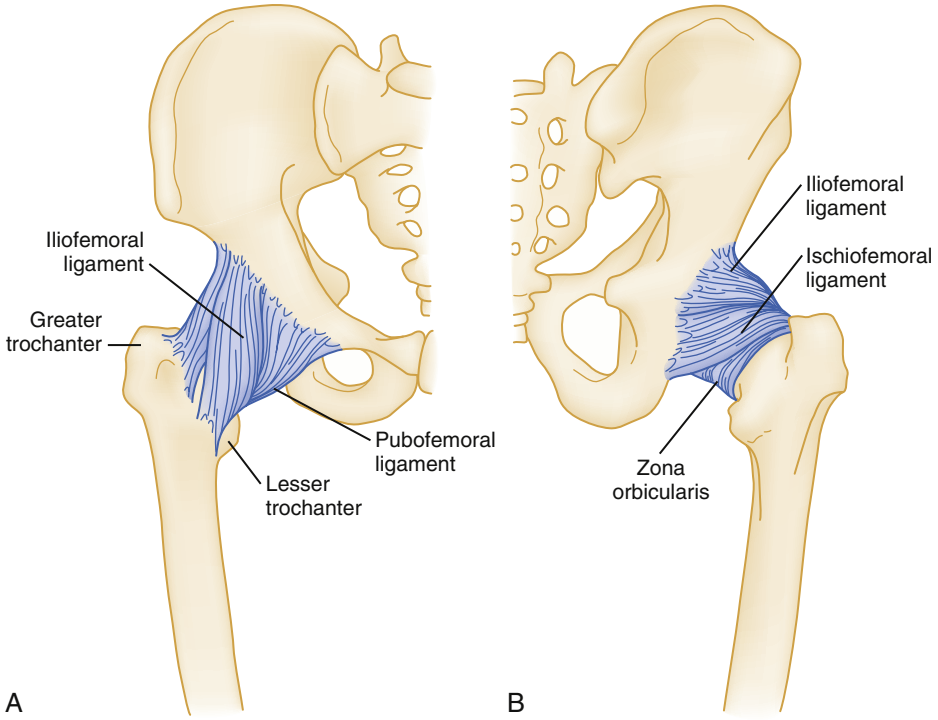

Fig. 47.1 The ligaments of the hip combine to form a tough joint capsule, as seen on both anterior (A) and posterior (B) views.

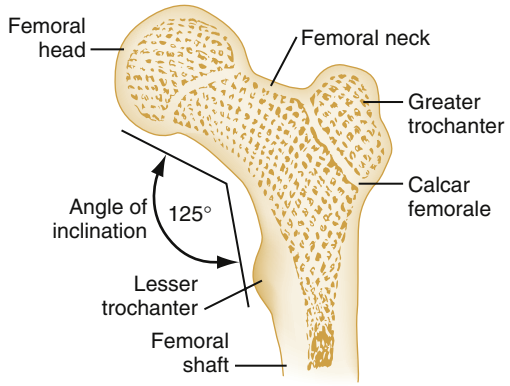

Fig. 47.2 Bony Architecture of the Proximal End of the Femur.

vein are the two main tributaries to the common and superficial femoral veins. The deep femoral vein and artery run in parallel as the vein joins the superficial femoral vein just distal to the inguinal ligament. The greater saphenous vein arises in the dorsum of the foot and ascends anterior to the medial malleolus. This vein is relatively superficial as it traverses up the medial aspect of the leg to join the common femoral vein distal to the inguinal ligament.

Nerves

The femoral and sciatic nerves are the major nerves within the thigh. The femoral nerve is the largest branch of the lumbar plexus; it passes under the inguinal ligament lateral to the femoral artery and divides into anterior and posterior branches soon after entering the thigh. The sensory divisions of the anterior branch, the intermediate and medial cutaneous nerves, supply sensation to the anteromedial aspect of the thigh. The motor division of the anterior branch innervates the pectineus and sartorius muscles. The posterior femoral branch gives off the saphenous nerve, which supplies sensation to the skin along the medial aspect of the lower part of the leg. The posterior branch also supplies motor function to the muscles of the quadriceps femoris group.

The sciatic nerve is the largest peripheral nerve in the body. It arises from the sacral plexus. The sciatic nerve exits the pelvis through the greater sciatic foramen and travels through the posterior thigh; it extends from the inferior border of the pyriformis muscle to the distal third of the thigh. The sciatic nerve gives off articular branches that supply the hip joint. In the thigh, muscular branches innervate the adductor magnus and hamstring muscles. Just proximal to the popliteal fossa, the sciatic nerve divides to form the tibial and common peroneal nerves.

Pathophysiology and Key Patterns of Injury

Fractures and Trauma of the Femur and Hip

The vast majority of hip fractures occur in elderly patients with preexisting bone disease who sustain low-energy trauma, usually a ground-level mechanical fall. In young, healthy individuals, high energy trauma, such as a motor vehicle collision (MVC) or a fall from a significant height, is responsible for most fractures.

Twenty percent of patients with hip fracture die during the first year after the injury, mostly from sequelae of the fracture rather than the fracture itself. One-third of patients require nursing home placement, and less than one-third regain their pre-fracture level of physical function. The economic impact of these fractures is significant.

Osteoporosis of the Femur

Osteoporosis is the leading cause of hip fracture. The pathophysiology of osteoporosis is not completely understood, but strong associations with hormonal changes related to aging, genetic predisposition, vitamin D deficiency, lack of physical activity, and smoking have been recognized. Severe osteoporosis and hip fractures are most common in elderly white women; however, a decrease in bone density after age 30 is seen across all demographic groups. The trabeculae of the femoral head and neck strengthen the bone and therefore support the large

TABLE 47.1 Structures Within Compartments of the Thigh

Compartment	Muscles	Nerves	Vessels
Anterior	Quadriceps femoris, sartorius, iliacus, psoas, pectineus	Lateral femoral cutaneous	Femoral artery and vein
Medial	Gracilis, adductor longus and magnus, obturator externus	Obturator	Profundus femoris artery, obturator artery and vein
Posterior	Biceps femoris, semitendinosus, semimembranosus, adductor magnus	Sciatic, posterior femoral cutaneous	Profundus femoris artery branches

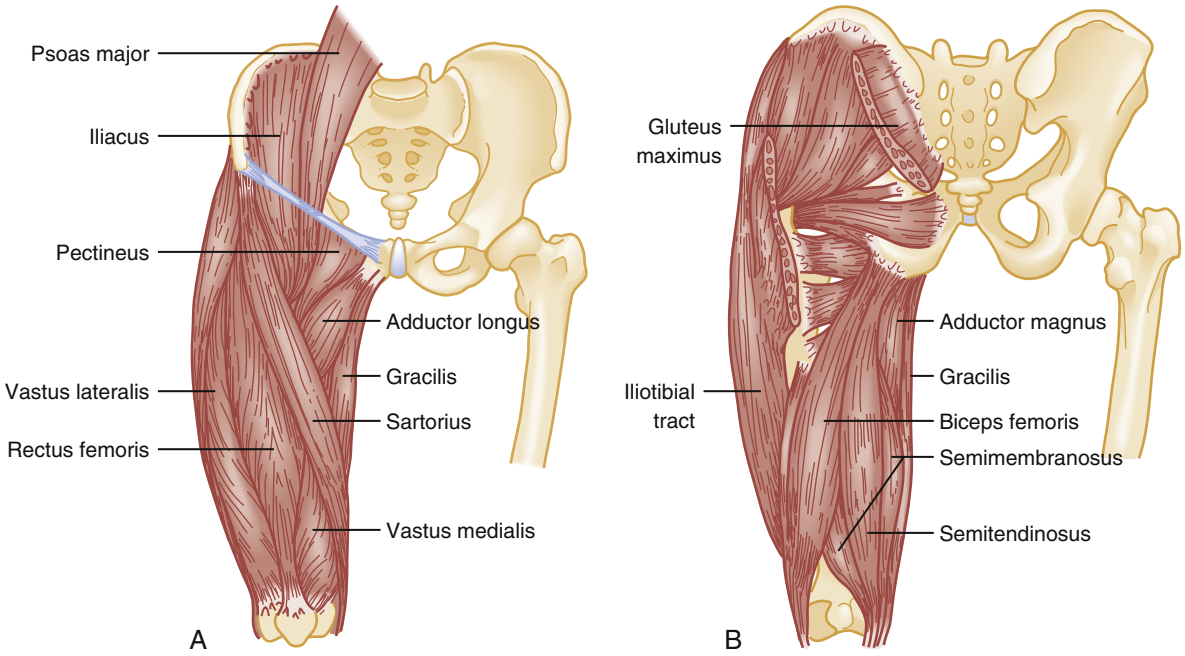

Fig. 47.3 (A and B) The major muscles acting about the hip and thigh.

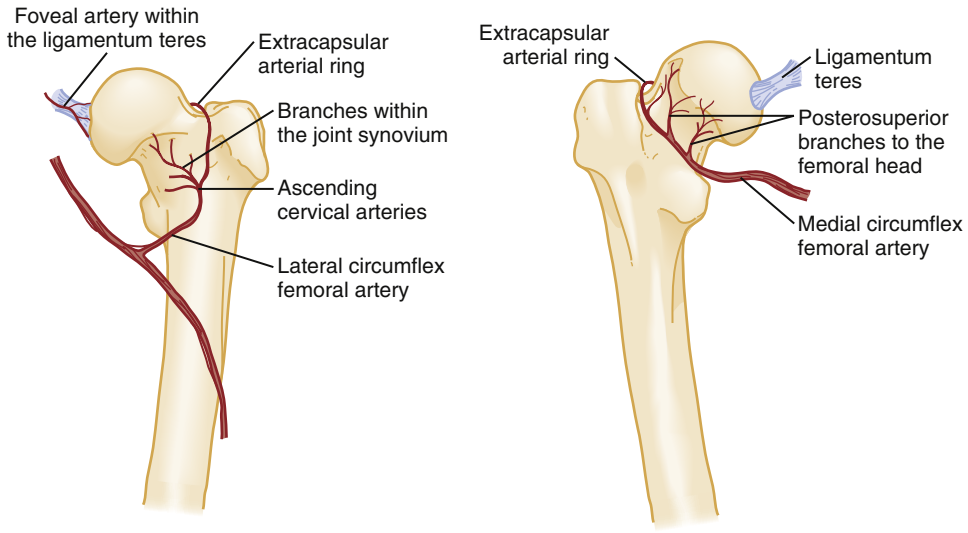

Fig. 47.4 The arterial blood supply of the femoral neck and head is provided to varying degrees by three sources: the ascending cervical arteries, the arterial branches within the marrow *(not illustrated),* and the foveal artery within the ligamentum teres.

mechanical forces produced across the hip joint. As osteoporosis progresses, the trabeculae disappear and increase the risk of fracture. Osteoporosis currently affects more than 10 million people in the United States and is projected to affect approximately 14 million adults older than 50 years by the year 2020. The number of hip fractures attributable to osteoporosis is expected to be more than 6 million by the year 2050, although the incidence in women has been decreasing in recent years. An important factor to consider is that while age standardized rates may be falling, the effects of an aging population significantly overcomes this decline, leading to an overall increase in incidence.[1,2]

Osteoarthritis of the hip. A large percentage of the American population experiences chronic pain from degenerative osteoarthritis

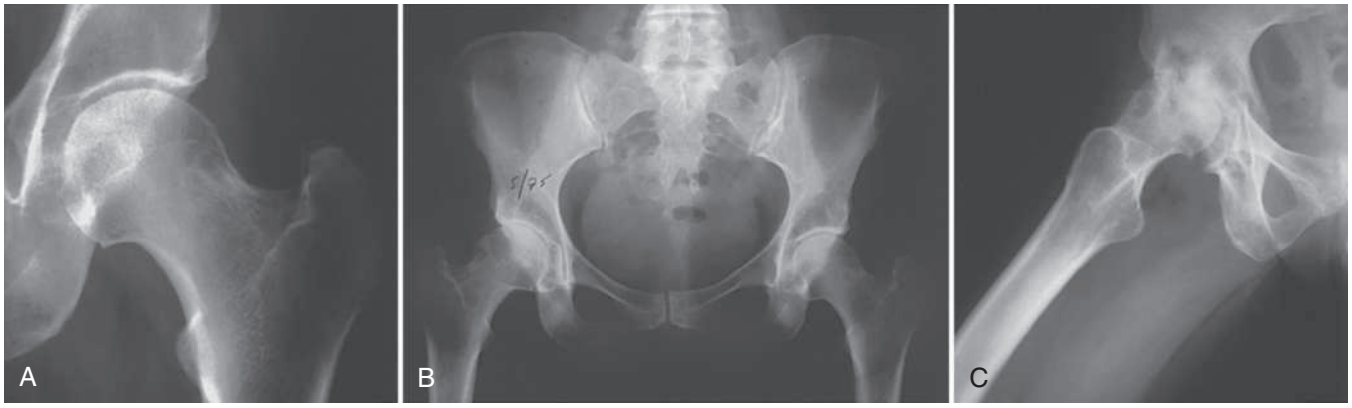

Fig. 47.5 Radiographic evidence of the development of osteoarthritis or degenerative joint disease of the hip is demonstrated with serial radiographs in the same patient over several years. (A) The initial symptoms are more dramatic than would be expected with the radiographic findings of increased sclerosis along the weight-bearing surface of the superior acetabulum. (B) The joint space is lost. (C) Erosion of the head and acetabular surfaces and reactive bony cystic changes are now evident.

of the hip. Disability often results from persistent pain, limited physical mobility, and sacrcopenia.[3] The progression of osteoarthritis can be demonstrated with serial radiographs of the affected hip (Fig. 47.5); however, radiographic findings do not necessarily correlate with symptoms.

Avascular Necrosis

When a patient has an increasingly painful hip, buttock, thigh, or knee and no history of recent trauma, AVN of the femoral head and sciatica should be considered. AVN has been referred to as *aseptic necrosis, ischemic necrosis,* and *osteonecrosis*. It is the result of ischemic bone death of the femoral head after compromise of its blood supply (Fig. 47.6). AVN is bilateral in 40% to 80% of patients. It is common in relatively young patients, the mean age at diagnosis being 38 years old. Although a specific causative disorder is not identified in 20% of cases, known atraumatic causes include chronic corticosteroid therapy, chronic alcoholism, hemoglobinopathy (e.g., sickle cell anemia), dysbarism, and chronic pancreatitis. AVN is an emerging complication associated with human immunodeficiency virus (HIV) infection. It is unclear whether the pathologic agent is the virus itself or an adverse side-effect of the treatment.

Traumatic AVN, a subacute manifestation after hip **dislocation** or femoral neck fracture, is a direct result of disruption of the blood supply to the femoral head. It is more common in males and African Americans. The incidence of AVN as a subacute complication is clearly related to both the initial degree of trauma and the amount of time the femoral head remains dislocated. Multiple studies have demonstrated a relationship between the length of time the hip is dislocated and the rates of AVN: it develops in about 5% of patients when **reduction** is performed within 6 hours and as many as 60% when reduction occurs after 12 hours. For this reason, *a hip dislocation is an orthopedic emergency*. The emergency clinician should perform reduction as soon as possible and definitely if orthopedic consultation will be delayed more than 6 hours.

Even with optimal treatment, owing to the tenuous blood supply to the area, femoral neck fractures can be complicated by AVN in up to 20% of cases. Immediately after fracture, bleeding may cause high intracapsular pressure and a tamponade effect on the femoral head, thereby impairing the blood supply. In contrast, intertrochanteric and subtrochanteric fractures are located in an area with a rich extracapsular arterial supply; therefore, AVN is a rare complication of these fractures.

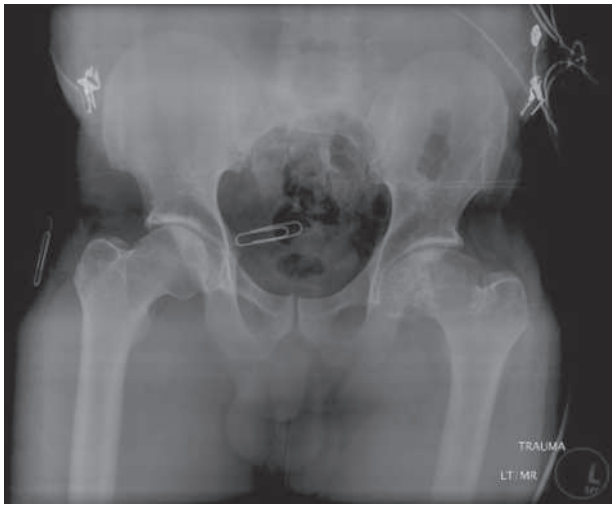

Fig. 47.6 Avascular Necrosis of the Left Femoral Head. Note the asymmetry of the joint and the collapse of the femoral head.

Myositis Ossificans

Myositis ossificans (or heterotrophic ossification) is pathologic bone formation at a site where bone is not normally found; the thigh and hip muscles are often involved. Traumatic myositis ossificans results most commonly from a direct blow to muscle or from repeated minor trauma. Bleeding into the muscle after trauma produces a local hematoma with subsequent new bone formation within it. Depending on its location, the ossific mass might be palpable, painful, and might limit range of motion.

Myositis ossificans occurs in up to 20% of patients undergoing medical evaluation for thigh contusions, likely related to the severity of the injury. The incidence of myositis ossificans after hip surgery is approximately 2%, and these lesions are clinically significant in 10% to 20% of cases. Increased susceptibility to myositis ossificans has been described in persons with hemophilia and other bleeding disorders in conjunction with soft tissue injury. Radiographically, myositis ossificans appears as irregularly shaped masses of heterogeneous bone in the soft tissues around the joint or along fascial planes (Fig. 47.7). It can be seen as early as 10 to 21 days after injury, but radiographic evidence typically lags behind the onset of symptoms by weeks. Its

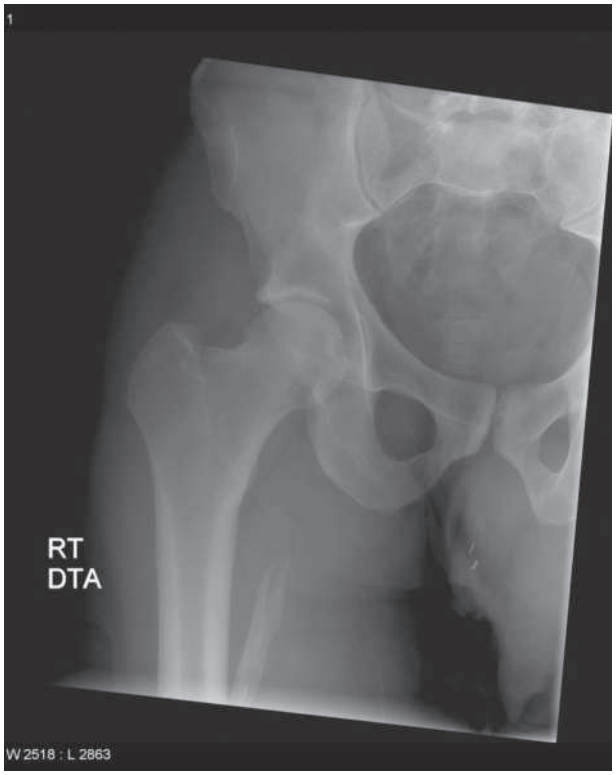

Fig. 47.7 Myositis Ossificans of the Proximal End of the Femur. Lesions can be immature or mature such as this one, with well-organized calcifications.

appearance might simulate primary bone neoplasm, especially when the periosteum is involved. Computed tomography (CT) can be helpful in distinguishing between neoplasm and myositis ossificans, because the lesions of myositis ossificans begin to calcify at the periphery and progress toward the center, and those of osteosarcoma begin to calcify at the center first.

Calcific Bursitis and Calcifying Peritendinitis

Calcification surrounding tendons and bursae or occurring in the joint capsule is referred to as *calcific bursitis* or *calcifying peritendinitis*. The cause of these lesions is unclear. No relationship has been documented between the radiographic findings and acute symptoms. Calcific bursitis of the hip is uncommon, but when it does occur, it most frequently affects the trochanteric bursa (Fig. 47.8). Other possible affected areas include the gluteal muscles and the hip flexors and adductors. The bursal calcification is seen on radiographs as an amorphous, poorly marginated line that is clearly separate from the cortex of the femur.

Neoplastic Disease in the Hip

The most common neoplastic disease of bone is metastatic, generally from breast, kidney, lung, thyroid, or prostate tumors.[4] Primary bone lesions also occur, *the most common being osteoid osteoma* (Fig. 47.9). Bone lesions can be osteoblastic or osteolytic. Patients present with significant bone pain or a large mass that has become irritated or painful (Fig. 47.10). Neoplasms place the patient at higher risk for pathologic fractures, especially if the lesions are large, lytic, or have eroded the cortex. Osteosarcoma and periosteal osteogenic sarcoma should be considered in the differential diagnoses of hip pain.

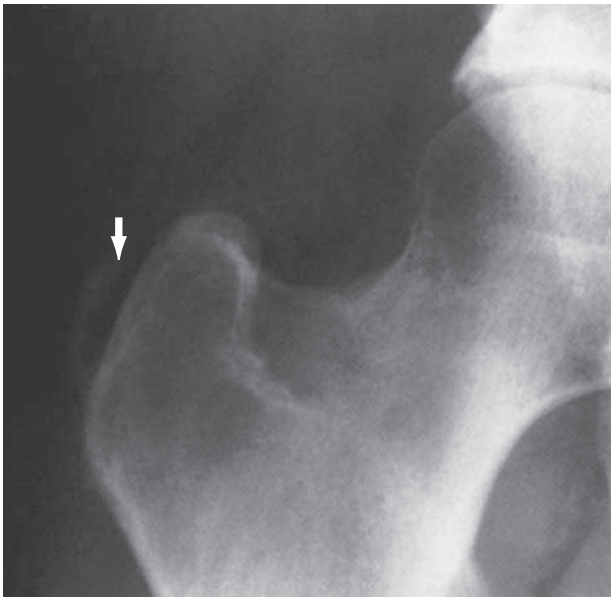

Fig. 47.8 Calcific Trochanteric Bursitis. Faint calcification *(arrow)* in the region of the trochanteric bursa is visible along the lateral cortex of the greater trochanter. (From Harris JH, Harris WH, Novelline RA. *The Radiology of Emergency Medicine*. 3rd ed. Baltimore: Williams & Wilkins; 1993.)

CLINICAL FEATURES OF HIP AND FEMUR PATHOLOGY

History

Injuries and pathologic conditions involving the femur are commonly dictated by age and gender. Pathology of the femur is commonly related to a traumatic incident because the femur is strong and can withstand normal use. Details of the mechanism of injury can aid in predicting an injury, and a detailed description of antecedent trauma or other precipitating events is helpful. Although direct trauma is a common cause of injuries, a thorough past medical history should be obtained, as certain disease entities are associated with hip pathology. Patients who recently altered their level of physical activity or exercise routine could indicate a stress reaction. Information about systemic illnesses or metabolic disorders should be elicited. A previous cancer diagnosis and its treatment with irradiation or chemotherapy could be a predisposing factor, providing clues to pathologic fractures. Any past steroid use, including inhaled steroids, is important to identify because it places patients at higher risk for osteonecrosis and changes in bone density. A linear relationship has been recognized between cumulative steroid dose and the incidence and severity of osteoporosis and hip fracture.

Determination of the location of the patient's pain is paramount, because hip pain can be referred to a number of anatomic locations. In adults, true hip joint pain can be perceived as groin pain, and children with hip pathology often have knee pain as the sole presenting complaint. The review of systems should include information that can help distinguish hip or femur pathology from another cause of the pain. Atypical causes of hip or groin pain include nephrolithiasis, pelvic inflammatory disease, osteomyelitis, malignancies, inguinal and femoral hernias, and lymphadenopathy. A history of low back pain suggests radiculopathy as the cause of the patient's pain.

The history should also focus on concomitant conditions and injuries. Elderly patients with a hip fracture sustained from a fall might be unable to summon help for hours to days. They often have associated dehydration, electrolyte abnormalities, rhabdomyolysis, and renal insufficiency. In addition, the reason for the fall should be determined,

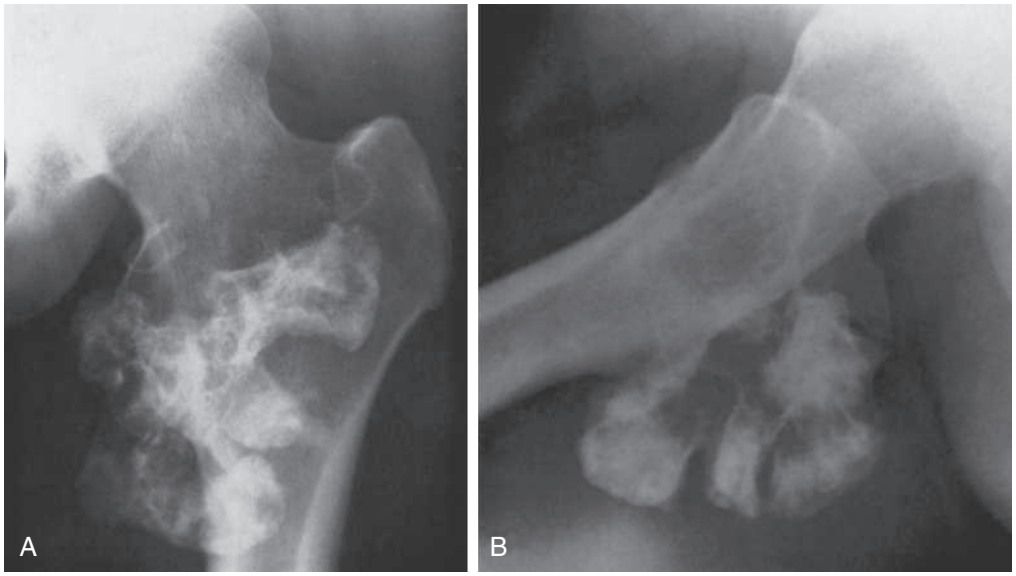

Fig. 47.9 Classic radiographic appearance of a solitary osteochondroma of the femur as seen in the antero-posterior (A) and frog leg lateral (B) views. This lesion is a cartilage-capped bony excrescence, typically arising from the cortex of long tubular bones. (From Harris JH, Harris WH, Novelline RA. *The Radiology of Emergency Medicine*. 3rd ed. Baltimore: Williams & Wilkins; 1993.)

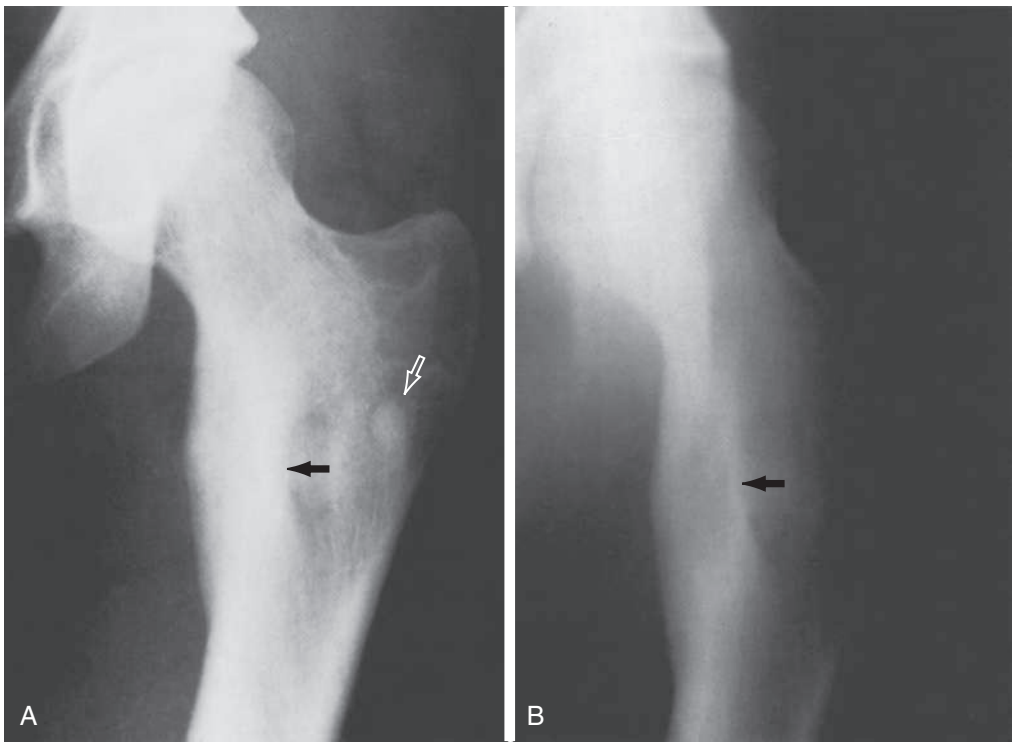

Fig. 47.10 Osteoid osteoma of the femur *(solid black arrow)*. (A) A large focal area of greater density than that of the surrounding femur represents both cortical and endosteal proliferation. The new cortical bone is smooth and sharply delineated, indicative of a nonaggressive process. The open arrow represents a bone island. (B) A frontal-view tomogram demonstrates an oval central radiolucent nidus *(solid black arrow)*. (From Harris JH, Harris WH, Novelline RA. *The Radiology of Emergency Medicine*. 3rd ed. Baltimore: Williams & Wilkins; 1993.)

as it may reveal other comorbid conditions (e.g., syncope, cardiac dysrhythmias, polypharmacy use, alcoholism). Sedative and antihypertensive medications predispose elderly patients to falling. With a fall, elderly patients might sustain additional injuries, most commonly, the fracture of a vertebral body or wrist. Cervical spine and intracranial injuries should also be considered, especially in patients taking oral anticoagulants. Forty to 75% of young patients with a hip fracture resulting from high-energy mechanisms have concomitant injuries.

Physical Examination

Patients with femoral pathology can have a multitude of presentations; therefore, a thorough physical examination is important. Due to the

major forces that are sustained in multisystem trauma, hypotension is a problem commonly encountered during the initial resuscitation. Hypotension, neurovascular compromise, or suspicion for multiple injuries are indications for transfer to a specialized trauma center.

After life-threatening conditions have been addressed, the injured extremity can be evaluated carefully. The position of the leg can offer a clue to radiographic findings. External rotation, abduction, and shortening suggest a displaced femoral neck fracture. External rotation with shortening suggests an intertrochanteric fracture. Visual inspection may reveal pallor, ecchymosis, asymmetry, or deformity. The presence of abrasions, lacerations, and open wounds may indicate forces that caused the injury and direct the evaluation for concomitant fractures. Nondisplaced fractures, including stress fractures, should not produce limb shortening or rotational deformities but will be painful on passive range of motion, particularly internal and external rotation. In patients with obvious deformities, testing range of motion should be deferred until after radiographs have been obtained and vascular integrity has been verified.

Systematic examination of the injured extremity may reveal focal tenderness or warmth suggesting injury or infection. Active and passive range of motion and assessment of muscle strength, though offering important information, are frequently limited by pain. A detailed neurovascular assessment is vital, as femoral nerve and arterial injuries often occur in conjunction with subtrochanteric and femoral shaft fractures or anterior hip dislocations. The sciatic nerve can be injured with a hip fracture or posterior hip dislocation. Neurologic examination includes evaluation of light touch, pinprick sensation, and proprioception. The examination should also assess for any signs of arterial injury indicating a rapidly expanding hematoma. Femoral, popliteal, dorsalis pedis, and posterior tibial pulses should all be assessed. Comparative blood pressures obtained by Doppler examination in the injured and uninjured extremities (arterial pressure index) are useful in diagnosing occult femoral arterial injuries. The ankle-brachial index (ABI) also can be determined by comparing the systolic pressures of the affected extremity and the ipsilateral arm. An index less than 0.9 necessitates further diagnostic studies. Although acute compartment syndrome of the thigh is rare, consideration should be given to this diagnosis if the patient sustained a severe mechanism of injury and has tense swelling in the thigh.

DIFFERENTIAL DIAGNOSES

A detailed history and physical examination often elicit the cause of the pain. Patients with hip and thigh pain can have pain referred from a multitude of other areas. If a fracture is not apparent, in patients who are experiencing hip or thigh pain, emergency clinicians should consider other causes. The differential diagnoses of hip pain without obvious fracture on radiographs are listed in Box 47.1.

In the setting of trauma, it is imperative that a thorough physical examination excludes referred pain and associated injuries. Most patients who arrive in the emergency department with hip or thigh pain can provide a clear history of a traumatic event. Hip or knee pain in the young, in athletes, and in the elderly deserves further investigation, even when minimal or no trauma has been reported. This elderly patient population commonly has an occult hip disruption, occasionally involving the femur. Senile osteoporosis is the leading cause of femoral neck fractures after minor trauma; pathologic fractures of the femur can result from metastatic, metabolic, or endocrine diseases.

BOX 47.1 Differential Diagnoses of a Painful Hip Without Obvious Fracture

- Referred pain (lumbar spine, hip, or knee)
- Avascular necrosis (AVN) of the femoral head
- Degenerative joint disease or osteoarthritis
- Herniation of a lumbar disk
- Diskitis
- Transient synovitis of the hip
- Septic arthritis
- Bursitis
- Tendonitis
- Ligamentous injuries of the knee or hip
- Occult fracture
- Slipped capital femoral epiphysis (SCFE)
- Perthes' disease
- Tumor (lymphoma)
- Deep venous thrombosis
- Arterial insufficiency
- Osteomyelitis
- Iliopsoas abscess
- Retroperitoneal hematoma
- Inguinal hernia
- Inguinal lymphadenopathy
- Genitourinary complaints
- Sports-related hernia

DIAGNOSTIC TESTING

Radiographic Evaluation

Plain radiographs, including true anteroposterior and lateral views of the femur, are usually adequate for the evaluation of potential fractures (Fig. 47.11). If possible, the femur should be internally rotated. Fracture lines can be subtle, particularly in the femoral neck. Three methods are useful for identifying these subtle fractures:

- First is the use of *Shenton line,* described in a subsequent section on hip dislocations.
- Second is a search for the normal "S" and reverse "S" curves seen on radiographs of non-fractured hips. In normal anatomic position, the convex outline of a normal femoral head smoothly joins the concave outline of the femoral neck. This produces an "S" curve and a reverse "S" curve, regardless of the orientation of the radiographic projection. In searching for a fracture of the femoral neck, the medial and lateral cortical margins of the femoral head and neck should be carefully examined for these curves (Fig. 47.12). A fracture produces a tangential or sharp angle, indicating disruption of the normal anatomic relationship.
- The third method, useful in the evaluation of unremarkable hip radiographs, is tracing the trabecular lines as they pass from the femoral shaft to the femoral head. Disruption of these lines as they pass through the fracture site is often the only subtle clue.

In impacted femoral neck fractures, the neck cortex is driven into the cancellous femoral head. Bone impaction lends a certain inherent stability (Fig. 47.13). If there is a femoral neck fracture, also obtain radiographs of the knee. *It is a basic orthopedic principle to image the joint above and below any fracture, because concomitant injuries are common.*

Occult Hip Fracture

If radiographs do not show an overt fracture or injury, the emergency clinician should assess the patient's gait. Inability to ambulate or difficulty in weight bearing suggests an occult fracture. Up to 10% of all hip fractures are radiographically "occult" on plain films. Failure to detect these injuries increases the risk of subsequent displacement of the fracture, the incidence of AVN, and the risk of death. When a painful hip prevents ambulation and plain radiographs do not reveal a fracture, advanced imaging (CT or magnetic resonance imaging [MRI])

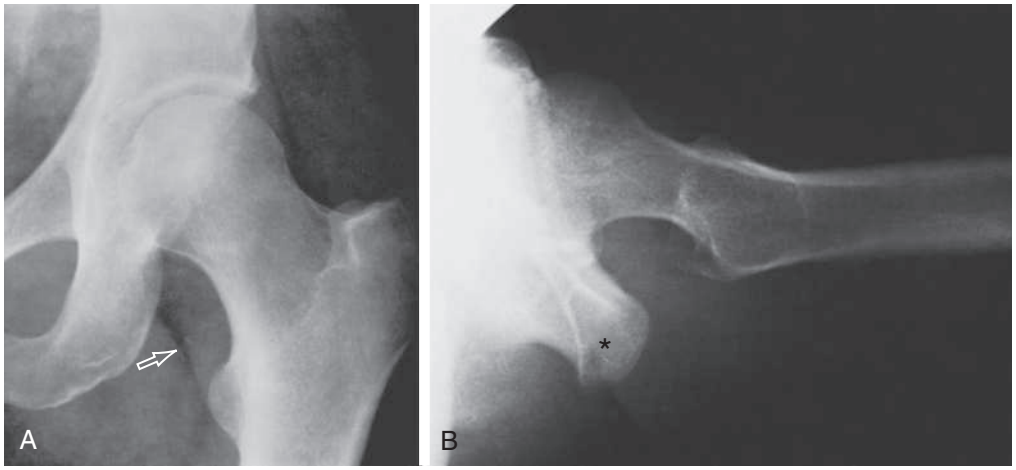

Fig. 47.11 Normal Radiographic Anatomy of the Hip. (A) Anteroposterior view of the normal adult hip. The open arrow indicates the edge of the iliopsoas muscle shadow. This muscle lies immediately on the capsule of the hip joint. The small concavity in the center of the femoral head is for the attachment of the ligamentum teres. (B) Cross-table lateral view of the hip demonstrating the normal relationship of the femoral head to the neck. *The asterisk indicates the ischial tuberosity.* (From Harris JH, Harris WH, Novelline RA. *The Radiology of Emergency Medicine*. 3rd ed. Baltimore: Williams & Wilkins; 1993.)

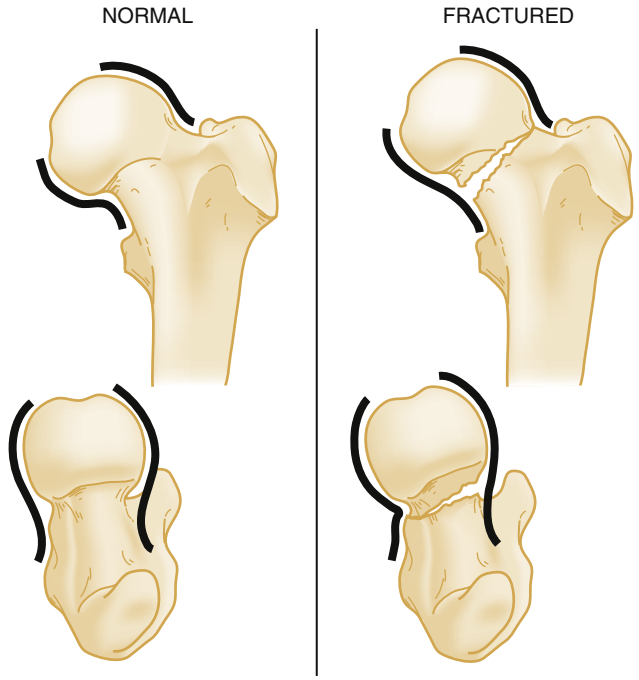

Fig. 47.12 The normal anatomic appearance of the femoral head as smooth S and reversed S lines is drawn above. The concave outline of the femoral neck meets the convex outline of the femoral head as shown here in various views. Any tangential angle suggests a fracture.

is indicated (Fig. 47.14). Elderly patients with unexplained hip pain lasting more than 3 weeks may be harboring an occult fracture even if they continue to walk. T1-weighted MRI will reveal a fracture that was imperceptible at the time of injury with nearly 100% accuracy and is cost-effective compared with other strategies. MRI is superior to CT and remains the "gold standard" for diagnosing occult hip fractures and helps guide treatment decisions (see Fig. 47.12).[5]

Bone scans have been useful in older patients with occult fractures, but they lack adequate sensitivity. To identify most occult fractures, this type of scan should be delayed for 72 hours after the injury, which limits its use in the ED setting.

Vascular assessment must be considered when there is any concern for any vascular injury including pallor, compartment syndrome, or rapidly expanding hematomas. This can include Doppler measurements including ABI. If the systolic pressure in the affected extremity is 90% or less (ratio less than 0.9) than that in the unaffected extremity, additional diagnostic studies should be performed. Vascular assessment studies include Doppler flow ultrasound imaging, computed tomography angiography (CTA), or angiography alone.

MANAGEMENT

Patients with femoral pathology often need hemodynamic stabilization. Because of the risk of blood loss—from both the injury and its subsequent operative repair—patients with traumatic fracture of the hip or femur should have a type and screen in case the necessity for transfusion arises. Original data suggested that transfusion confers a higher risk of morbidity and mortality. However, new data indicates that the need for transfusion was likely associated with injury severity, and once accounted for, the differences resolved. Hemodynamic instability can result in the loss of up to 3 units of blood into the fracture site. Elderly patients may be hypovolemic prior to the injury due to dehydration or comorbid illness, which can be exacerbated by further blood loss. Operative repair should be performed after the patient is resuscitated and in optimal preoperative condition. The preoperative stabilization of an elderly patient with a hip fracture may require a multidisciplinary approach from emergency medicine, orthopedics, internal medicine, cardiology, and anesthesiology. Comprehensive programs co-managed by geriatricians and orthopedic surgeons have been shown to improve short-term outcomes for the elderly with hip fractures and might even lower the mortality rate, highlighting the importance of the medical management of these complex patients.

Traction and Immobilization

If prehospital personnel suspect a femoral fracture, they often place a Hare splint, Sager splint, or similar device that applies traction to the leg before transporting the patient. This management strategy is popular because it provides pain relief, immobilization, and limits blood loss. However, great care should be taken to ensure the proper use of these devices as prolonged traction can cause or exacerbate neurologic

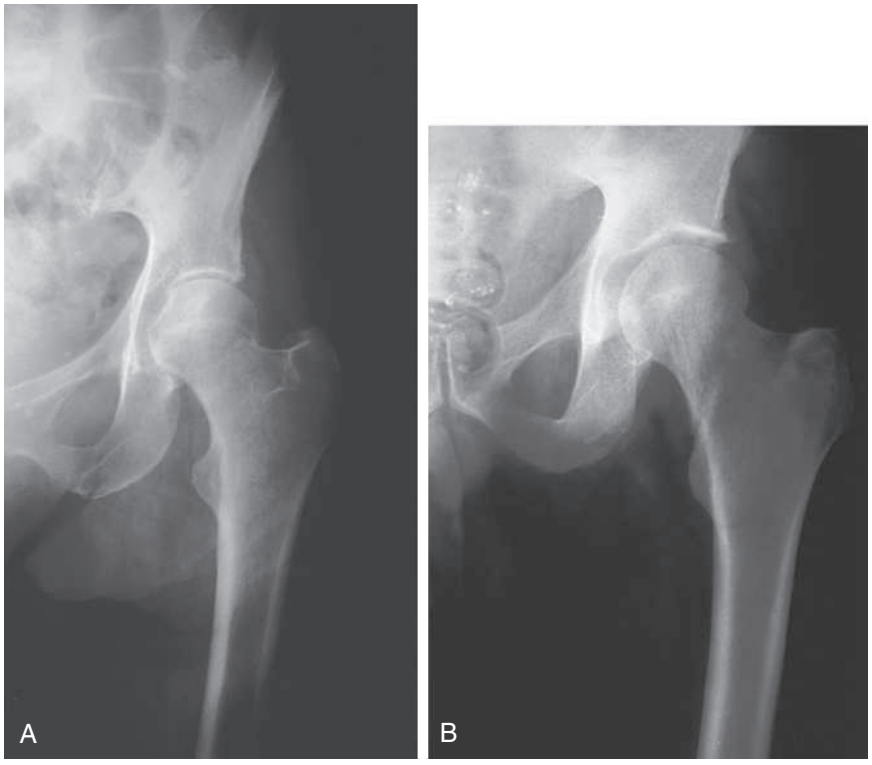

Fig. 47.13 (A) Subtle nondisplaced impacted femoral neck fracture. Use of S curves aids in identification. (B) A nondisplaced femoral neck fracture possesses no stability without impaction.

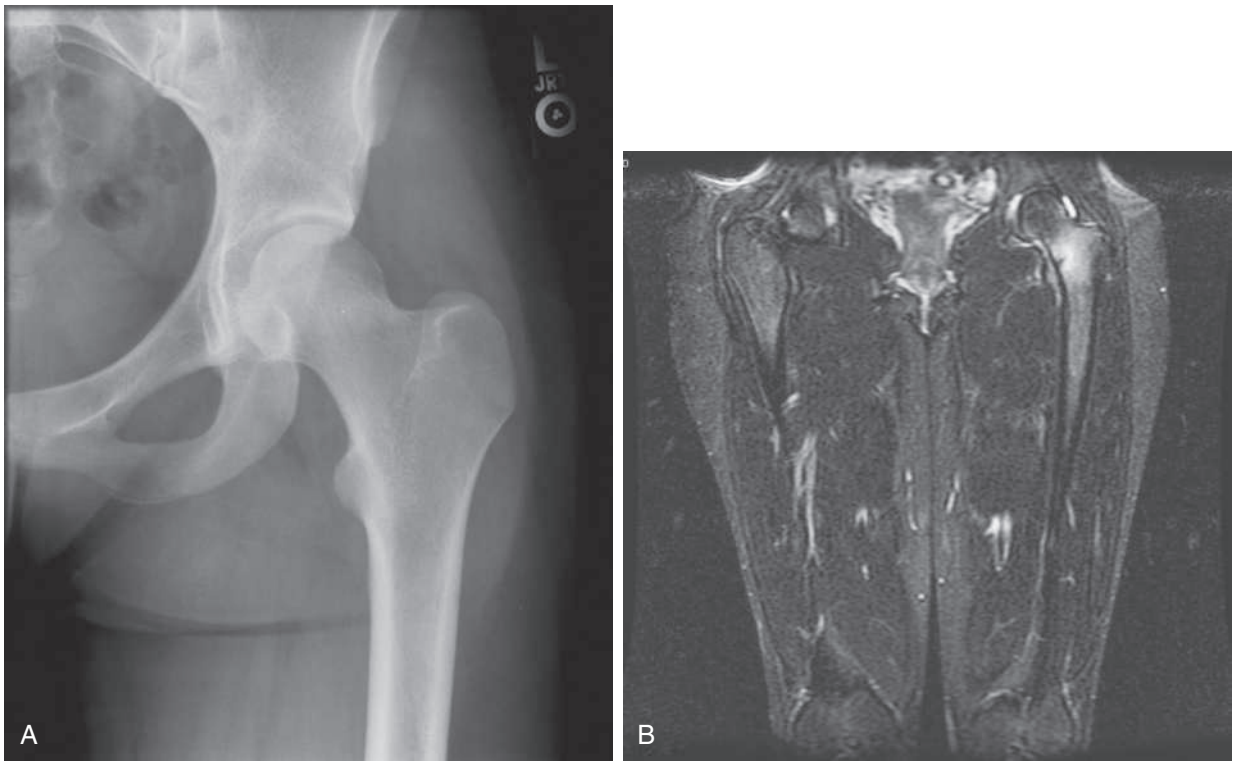

Fig. 47.14 The Patient Reported Hip Pain and Could Not Ambulate. (A) Initial radiographs failed to demonstrate a fracture. (B) A magnetic resonance image (MRI) revealed a femoral neck fracture through the compressive trabecular fibers.

injury. Traction used in the field for transport can cause skin breakdown at pressure points and might produce potentially damaging tension on the nerve. The femoral and sciatic nerves are more likely to be injured from traction or during surgery than from the femoral fracture itself.

Contraindications to the use of traction splints include suspected pelvic fractures, patellar fractures, ligamentous knee injuries, and tibia or fibula fractures. In the prehospital setting, traction should not be applied to any open fracture that has exposed bone. Such reduction pulls grossly contaminated bone fragments back into the wound before adequate irrigation. A study that evaluated patients with multisystem trauma in whom traction splints were placed in the field for femur fractures showed that nearly 40% had contraindications to the splints that were placed.

With or without traction, the injured extremity should be immobilized when the patient is moved to prevent further damage from mobile bone fragments. In the prehospital setting, this can be achieved with simple splinting. In the ED, maintaining the leg in slight flexion at the hip reduces intracapsular pressure, whereas extension of the leg increases pressure and the potential for ischemic necrosis of the femoral head. Therefore, traction for proximal femur fractures should be discontinued once the patient has arrived in the ED. The leg can be supported in a position of comfort with a pillow placed under the thigh. The theoretical advantages to continue traction in the ED are for improved pain control and facilitating fracture reduction and making operative management easier to perform. This is likely true for patients with femoral shaft fractures; however, a Cochrane systematic review found no evidence to support preoperative traction for fractures of the proximal femur in adults.

Open Fracture Care

By definition, an *open fracture* is any fracture in which a break in the integrity of the skin and soft tissue allows communication with the fracture and its hematoma. Any nearby wound or break in the skin must be considered to communicate with the fracture. The three categories of open fractures are described in Table 47.2. A bone piercing from the inside outward often causes only a small wound, after which the contaminated bone tip slips deceptively back into the soft tissue. Open wounds should be irrigated and then covered with sterile saline-moistened gauze.

For all type I open fractures, a first-generation cephalosporin (such as, cefazolin, 1–3 g IV) should be administered intravenously. Fracture types II and III might require additional gram-negative coverage depending on the amount of devitalized tissue and the extent of involvement of the groin and its gram-negative skin flora. This additional coverage could be provided by an aminoglycoside (such as, gentamicin 1.5–2 mg/kg IV). The use of perioperative first-generation cephalosporins reduces the risk of postoperative infection even in patients with closed fractures. Great care should be taken to identify tetanus-prone wounds so that patients can receive vaccination against tetanus when indicated. Immunization status should be verified in all patients and updated accordingly.

Compartment Syndrome

Because of the thigh's larger volume, compartment syndrome within the thigh is far less common than in the lower part of the leg. A large amount of bleeding into the thigh compartment is required before the pressure rises above capillary perfusion pressure. When compartment syndrome occurs in the thigh, only 50% of the cases are associated with a femur fracture. It is difficult to clinically differentiate the expected swelling after an injury from early compartment syndrome. Clinical examination and the use of direct pressure measurements can detect the development of compartment syndrome at an early stage.

TABLE 47.2 Classification of Open Fractures

Criterion	Type I	Type II	Type III
Wound size	<1 cm	1–10 cm	>10 cm
Soft tissue damage	Minimal, if any	Moderate, without nerve, arterial, or periosteal stripping	Extensive muscle devitalization; nerve and arterial involvement often classified as type IIIb
Mechanism of injury	Bone edge pierces outward	Variable	High-energy shotgun blast, high-velocity gunshots

Pain Management

Systemic Analgesia

Pain control in the ED is often inadequate. For patients with femoral fractures, opioid analgesia is often indicated in combination with other pain-relief strategies. In addition to parenteral medications, other pain-relieving strategies include immobilization of the injured extremity, placement of the injured extremity in a position of comfort, and the administration of local nerve blocks.

Pharmacologic Approaches

The classic pharmacologic treatment for pain management in patients with traumatic femoral injuries is opioid analgesics. Morphine, fentanyl, and hydromorphone are all acceptable options. Fentanyl and hydromorphone are the preferred IV opioid analgesics in patients with renal dysfunction. Due to the unpredictability of the supply chain and negative associations of opioids, many pre-hospital providers now use ketamine for pain relief. Meperidine should not be used because of unpredictable side effects, including seizures. Nonsteroidal antiinflammatory drugs (NSAIDs), while safe in younger populations, can be difficult to use, especially in the elderly, due to their renal and gastrointestinal side effects.

Femoral Nerve Block

The femoral nerve block is an excellent option as an adjunct or alternative to systemic analgesics in patients at risk for hypotension. Femoral nerve blocks significantly decrease the time to the lowest pain score compared with intravenous narcotics, and patients require significantly lower doses of narcotics. With the assistance of a peripheral nerve stimulator to localize the nerve or bedside ultrasound to directly visualize the nerve, the anesthetic is injected, safely, and under sterile conditions. The procedure can also be performed by emergency clinicians without the assistance of peripheral nerve stimulators or ultrasound.[4] If a long-acting anesthetic such as bupivacaine is used, the expected onset of analgesia is within 30 minutes and its duration (on average) is 6 to 8 hours. A Cochrane review demonstrated that regional blockade reduced pain on movement within 30 minutes after block placement, and there is moderate quality of evidence for reduced time to first mobilization, reduced cost of analgesic, and decreased risk of pneumonia.

A neurovascular examination should be performed and documented before the femoral nerve block is performed. After the nerve block, continued assessment of the femoral muscular compartments is advisable to check for the development of compartment syndrome. If an injury is considered to be at especially high risk for compartment syndrome, orthopedic surgery consultation should be obtained before the block, and measurement of compartment pressures after the block

should be considered. Because the sciatic nerve innervates the compartments of the lower limb, a femoral nerve block will not mask the clinical presentation of compartment syndrome in the lower leg.[6]

Specific Fractures of the Hip and Femur

Avulsion Fractures

Foundations. The incidence of avulsion fractures is increasing as a result of the growth of competitive sports and outdoor activities, especially in teenage athletes. The muscular origin of this type of injury commonly involves the pelvic apophyses, which might not fully ossify until age 25. Avulsion at the site of the growth plate is the result of sudden maximal muscular exertion. It can occur with rapid acceleration or sudden changes in speed or direction.

Clinical features. The athlete classically experiences a sudden piercing pain at the site of injury, along with a "snapping" or "popping" sound and frequently falls to the ground because of the intensity of the pain. The pain of avulsion injuries of the hip can manifest as referred pain to the thigh; these fractures are most common in adolescents and young adult athletes.

Differential diagnoses. The differential diagnoses of these avulsion fractures include muscle strain and tears, tendinopathy, and hip dislocations.

Management. As depicted in Fig. 47.15, avulsion at the ASIS involves the separation of a thin piece of bone as the sartorius muscle suddenly contracts (see Fig. 47.15A). The anterior inferior iliac spine (AIIS) is avulsed by the rectus femoris, and the hamstrings group can displace the ischial tuberosity (see Fig. 47.15B). Avulsion fractures of the ASIS and AIIS are managed nonoperatively. Treatment of avulsion fractures of the ischial tuberosity is more controversial. Most experts recommend conservative treatment for avulsion injuries with less than 2 cm of displacement. Fractures with more than 2 cm of displacement might benefit from operative fixation to prevent nonunion, as well as union achieved by exuberant callus formation.

Proximal Femur Fracture

Fractures of the proximal end of the femur are classified on the basis of their relationship to the hip capsule (intracapsular or extracapsular), anatomic location (neck, trochanteric, intertrochanteric, subtrochanteric, and shaft fractures), and degree of displacement.

Femoral Neck Fractures

Foundations. Femoral neck fractures are classified as either nondisplaced or displaced. Between 15% and 20% of all femoral neck fractures are nondisplaced fractures. The fracture line is often subtle. Techniques that allow detection of these fracture lines are useful for this reason. Evaluation of the continuity of the subcapital cortical lines, search for an indistinct broad band of increased subcapital density, and identification of the "S" and reverse "S" radiographic curves (see Fig. 47.12) lead to the diagnosis in most cases. With impacted femoral neck fractures, the neck cortex is driven into the cancellous femoral head. Bone impaction lends a certain inherent stability (see Fig. 47.13). Because of this stability, two management approaches have been advocated: internal fixation and early ambulation. Internal fixation reduces the length of hospitalization, improves rehabilitation, and is the preferred treatment modality. Without impaction, a nondisplaced femoral neck fracture is unstable and will become displaced without internal fixation.

Clinical presentation. On initial evaluation, a patient with a displaced fracture of the femoral neck lies with the limb externally rotated, abducted, and slightly shortened. To avoid further disruption of the blood supply to the femoral head, range-of-motion assessment should be deferred.

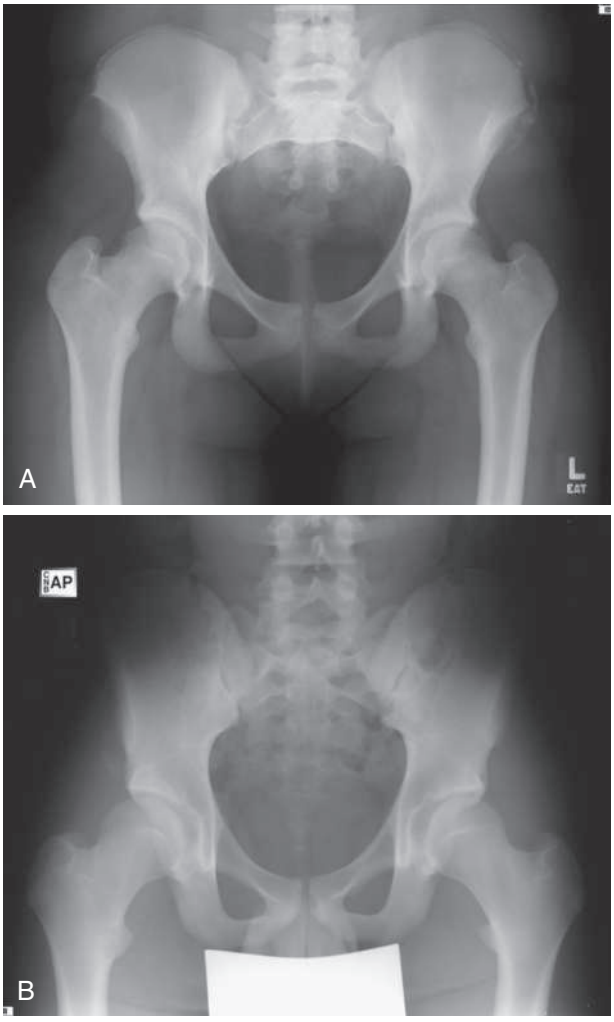

Fig. 47.15 (A) Avulsion fracture of the anterior superior iliac spine by the sartorius muscle. (B) Avulsion fracture of the anterior inferior iliac spine by the rectus femoris.

Diagnostic testing. Plain hip radiographs generally confirm the diagnosis of a femoral neck fracture.

Management. Treatment of these displaced fractures consists of open reduction and internal fixation (ORIF), hemiarthroplasty, or total hip arthroplasty (THA). In all displaced femoral neck fractures, the femoral head is rendered largely avascular, and signs of AVN and collapse might develop over the ensuing years. The mortality rate during the first year after a femoral neck fracture is 14%, compared with 9% for the control population. Factors affecting the mortality rate include age, male sex, psychiatric illness, end-stage renal disease, and congestive heart failure. Institutionalized patients have a death rate up to three times higher than noninstitutionalized patients. Complications can be minimized by early reduction, stable internal fixation, early ambulation, and close attention to medical comorbidities.

The two major complications of femoral neck fractures are AVN and nonunion. AVN is the most common complication, despite optimal treatment, because of the complex arterial anatomy. Deep infection in the form of osteomyelitis or septic arthritis is more common with femoral neck fractures, because the fracture line extends into the joint. The use of perioperative antibiotics reduces the rate of infection. Pulmonary embolism is another significant complication and is the leading cause of death 7 days after fracture. Venous thromboembolism

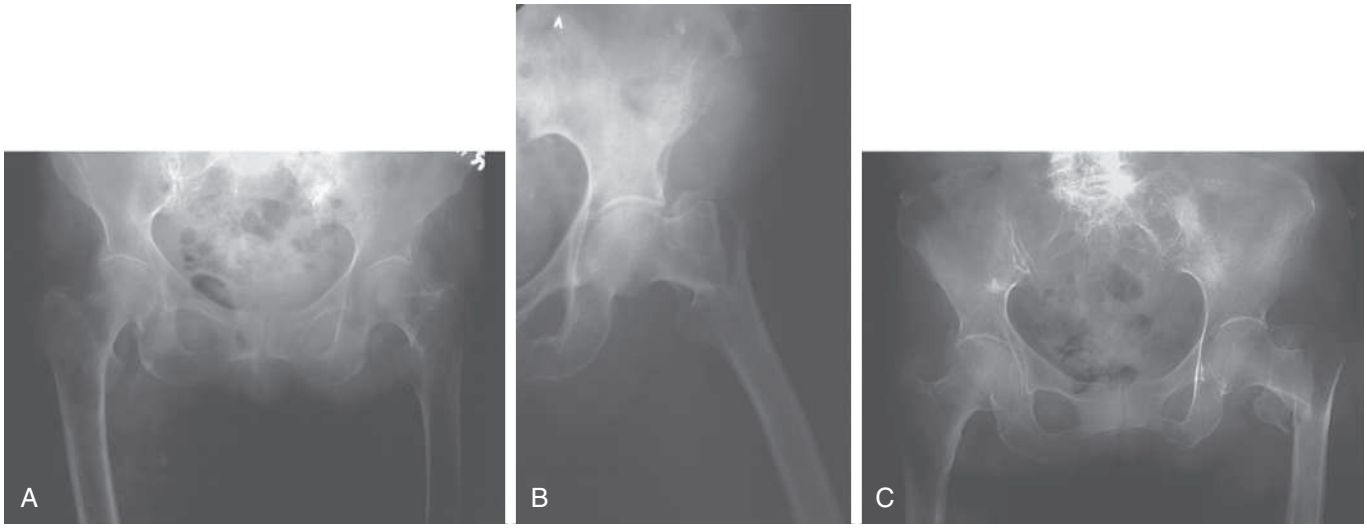

Fig. 47.16 The Number of Parts Produced by the Fracture Classifies Intertrochanteric Fractures. (A) Two-part fractures have one part connected to the femoral head and a second part attached to the shaft. (B) The greater or lesser trochanter also is fractured with three-part fractures. A greater degree of instability is produced because the attached muscles continue to act on the fractured trochanter. (C) Four-part intertrochanteric fractures involve both trochanters.

prophylaxis with anticoagulation therapy such as low molecular weight heparin or direct oral anticoagulants is recommended for 7 to 28 days, depending on the type of injury or surgical intervention.

Disposition. Patients with femoral neck fractures should be admitted for operative repair.

Intertrochanteric Fractures

Foundation. The fracture line of intertrochanteric fractures extends between the greater and lesser trochanters of the femur. These injuries are considered extracapsular fractures. The fracture line extends through cancellous bone, which has an ample blood supply. The hip's short external rotators remain attached to the distal fracture fragment, and the internal rotators are attached to the proximal fracture fragment.

A large number of classification systems for intertrochanteric fractures have been proposed to predict the likelihood of achieving and maintaining stable reduction. A useful system designates the fracture according to the number of bone fragments (Fig. 47.16).

Intertrochanteric fractures often are associated with other, distant fractures caused by the same trauma, such as a mechanical fall. Associated fractures of the distal radius, proximal humerus, ribs, and lumbar and thoracic spine are often overlooked because the femoral fracture distracts the attention of both patient and clinician. Nutrition status, chronic diuretic use, and decreased oral intake prior to the injury contribute to dehydration, and a greater requirement for resuscitative fluids.

Clinical presentation. The strong action of the iliopsoas muscle causes the leg to be shortened and externally rotated.

Diagnostic testing. Plain hip radiographs generally confirm the diagnosis of intertrochanteric fractures.

Management. A substantial majority of intertrochanteric fractures require internal fixation. Such fixation brings rapid mobilization, decreased hospital length of stay, reduced mortality, and improved function. The procedure should be performed on an urgent, rather than an emergent basis, because the patient should be fully resuscitated prior to operative repair. The risk of death increases when the patient is taken to the operating room on the day of injury; however, early repair within 24 to 48 hours improves the 1-year mortality rate. Preoperative medical optimization by multidisciplinary medical teams can decrease the 1-year mortality rate in these patients.[7]

Patients with intertrochanteric fractures have a mortality rate of up to 30% in the first year. Life expectancy returns to normal among patients who survive that year. Survival is most commonly related to the patient's age and preexisting medical conditions. Additional risks associated with operative treatment include mechanical failure, implant migration, and infection. Mechanical failures and nonunion are much more common in patients with unstable fractures and those whose fractures were not adequately reduced. Approximately half of patients who sustain these fractures are eventually able to regain their original level of ambulation. Outpatient yearly infusion of zoledronic acid (a bisphosphonate) beginning within 90 days after hip fracture repair reduces the incidence of new fractures and decreases the overall mortality rate.

Disposition. Patients with intertrochanteric fractures should be admitted for operative repair.

Isolated Fractures of the Greater or Lesser Trochanter

Foundations. Isolated fractures of the greater or lesser trochanter are rare. They occur in women more often than in men and are the result of a fall directly onto the trochanter or avulsion by the iliopsoas muscle. There may be a comminuted fracture involving only part of the greater trochanter or subtler impaction of the lateral cortex. If an avulsion is present, the fragments are displaced superiorly and posteriorly (Fig. 47.17).

Clinical presentation. Patients present with hip pain and tenderness over their trochanter.

Diagnostic testing. Plain hip radiographs generally confirm the diagnosis of these isolated fractures.

Management. Treatment consists of pain control and early mobilization with crutches; weight bearing is allowed as tolerated.

Disposition. Satisfactory outpatient management of this injury is possible because the healing process and prognosis is generally good.

Subtrochanteric Fractures

Foundations. Subtrochanteric fractures occur between the lesser trochanter and the proximal 5 cm of the femoral shaft. They may accompany intertrochanteric fractures. The subtrochanteric region is composed almost entirely of cortical bone, which lacks the vascularity needed for new bone growth and repair. When fractured, it is more

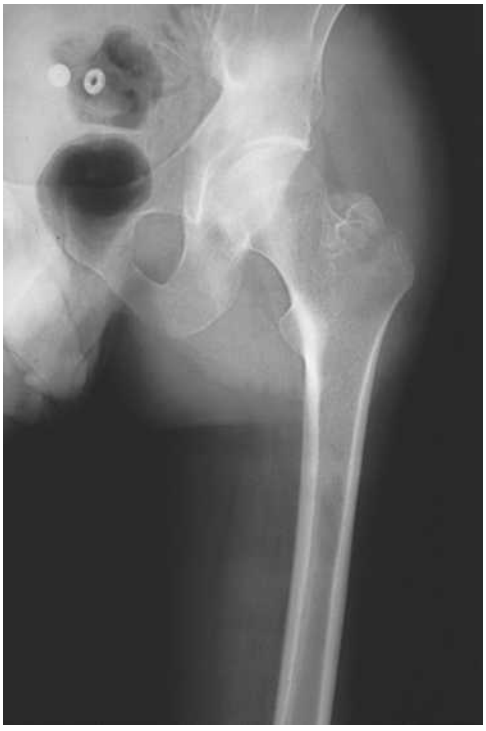

Fig. 47.17 Isolated Fracture of the Greater Trochanter. Note that the trochanter is displaced in the typical posterior and superior direction.

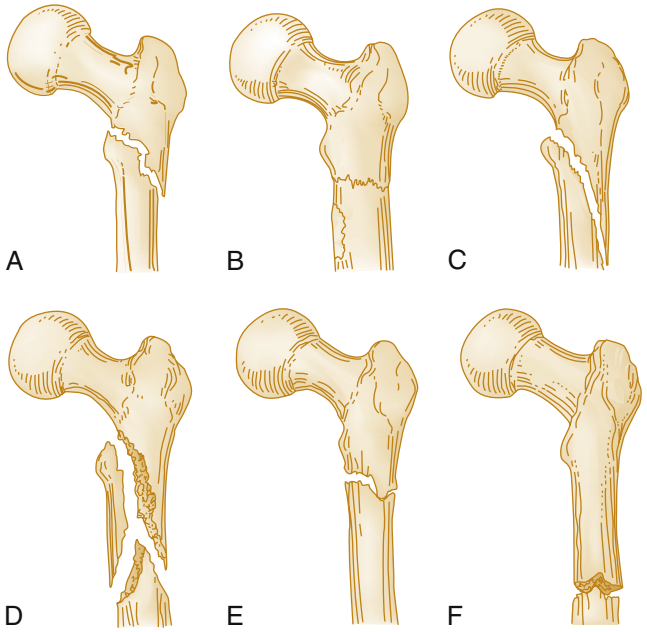

Fig. 47.18 Variants of Subtrochanteric Fractures. (A) Short oblique fracture. (B) Short oblique fracture with comminution. (C) Long oblique fracture. (D). Long oblique fracture with comminution. (E). High transverse fracture. (F) Low transverse fracture.

likely to be comminuted compared to bones with a higher cancellous content. In addition, the greater portion of the biomechanical forces of the femur is transmitted down the curved medial cortex of the femoral shaft. If this cortex is disrupted, the metal hardware undergoes the majority of the stress. This mechanism accounts for the increased incidence of hardware failure when the medial cortex is largely involved.[8]

These fractures characteristically are deformed because of the unbalanced muscle forces. In displaced fractures, the attachments of the iliopsoas, gluteal, and external rotator muscles consistently produce flexion, abduction, and external rotation of the proximal fragment.

Subtrochanteric fractures account for approximately 10% of all fractures of the proximal end of the femur. Although a small percentage of these fractures are caused by penetrating trauma, the usual mechanism of injury is direct blunt trauma. There is a bimodal distribution of injuries. The first group comprises victims of extreme high-energy trauma. In these patients, the subtrochanteric fracture is rarely an isolated injury because of the force required to produce it. Thirty to fifty percent of patients with subtrochanteric fractures have associated fractures of the pelvis, spine, or other long bones. The second group consists of elderly patients who experience a mechanical fall, in whom the fracture occurs through an area of weakened cortical bone. Pathologic fractures from metastatic lesions, Paget disease, renal osteodystrophy, osteogenesis imperfecta, and osteomalacia are well-recognized clinical entities in these patients. Stress fractures can occur in this region but are extremely uncommon. Various classification systems for these fractures have been proposed, although none is widely accepted. From a practical standpoint, it is best to define and describe these fractures by location (proximal or distal), angle (transverse or oblique), and the presence of comminution (Fig. 47.18).

Hemodynamic instability can result from blood loss at the fracture site. Although such blood loss can lead to hypovolemic shock, other causes of hypotension in a trauma patient need to be considered due to the forces required to obtain these injuries. Open fractures are rare and, when present, are accompanied by significant soft tissue injury. Vascular and neurologic injuries are also less common.

Diagnostic testing. Plain hip radiographs confirm the diagnosis of most subtrochanteric fractures.

Management. Definitive management of subtrochanteric fractures is complex. Maintaining limb length and controlling rotation are difficult. ORIF is the treatment of choice. However, in the rare case of a severely comminuted or an open, grossly contaminated fracture, nonoperative management may be preferable. Children younger than 10 years old also can be managed nonoperatively. The amount of remodeling and growth stimulation occurring in children of this age usually ensures good results without internal fixation.[8]

The bone in the subtrochanteric region is largely cortical and relatively avascular compared with the cancellous intertrochanteric region. As a result, healing is comparatively slow. Comminuted and distal subtrochanteric fractures carry a worse prognosis.

Complications include fat embolism in patients of all ages and the adverse effects of prolonged immobilization in the elderly. The mortality rate from subtrochanteric fractures is approximately 10%. The significant force and commonly associated traumatic injuries contribute to the high mortality among patients who sustain these fractures.

Disposition. Patient with subtrochanteric fractures should be admitted for operative repair.

Femoral Shaft Fractures

Foundation. Femoral shaft fractures are common injuries in young adults after high-energy trauma. As is the case with other femoral cortical fractures, considerable force is required to produce a fracture in a normal shaft. Automobile and motorcycle accidents, falls, and pedestrians being struck by vehicles account for a majority of femoral shaft fractures. The femoral shaft usually fails under tensile strain, resulting in a transverse fracture. Higher forces produce varying degrees of segmentation. Open fractures of the femoral shaft are less frequent and are often the result of a penetrating gunshot wound.

Pathologic fractures occur from a low-mechanism force that produces torsion and spiral fractures.

Depending on the age of the patient, if seemingly trivial trauma has resulted in a spiral femoral shaft fracture in a child, non-accidental trauma or pathologic fractures should be considered. Common causes of pathologic fracture include unicameral bone cysts, fibrous dysplasia, osteogenesis imperfecta, and malignancy.[9]

There is no commonly accepted or easily recalled classification system for femoral shaft fractures. The location and geometry of the fracture line should be used to describe them. Useful terms include transverse, oblique, spiral, wedge, and comminuted fractures.

Clinical presentation. Patients often arrive with the injured extremity immobilized by traction devices, which should be removed while immobilization of the limb is maintained. Neurovascular injuries are rarely associated with closed femoral shaft fractures. Significant hemorrhage into the thigh can occur with a femoral shaft fracture, just as with intertrochanteric and subtrochanteric fractures. Common concomitant injuries in patients with femoral shaft fractures include hip fractures, fracture-dislocations, femoral neck fractures, supracondylar femoral fractures, and patellar fractures. Almost half of femoral shaft fractures have associated ligamentous damage to the knee. If the patient has a femoral fracture, pain often prevents adequate evaluation of knee stability. Any attempt to evaluate the stability of the knee acutely will cause additional pain and hemorrhage without providing useful, diagnostic information.

Diagnostic testing. Plain hip radiographs including full length views of the femur confirm most femoral shaft fractures.

Management. Internal fixation with intramedullary rods has been demonstrated to shorten both hospitalization and total disability time after most femoral shaft fractures. The vast majority of femoral shaft fractures heal well in time, regardless of the mode of treatment. Severely comminuted fractures are more likely require closed reduction.[10]

Femoral shaft fractures have a union rate close to 100%, and most patients are able to return to work after approximately 6 months. Even a minor amount of limb shortening, or misalignment can result in arthritis of the hip or knee or chronic back pain. Refracture is a rare occurrence that is most likely to occur during early healing and callus formation. Refracture may also occur during the postoperative period after any hardware is removed. In this scenario, the unsupported bone is required to bear the entire weight of axial loading and is at risk for refracture.

Disposition. Patients with femoral shaft fractures should be admitted for operative repair.

Stress Fractures

Foundation. Femoral neck stress fractures or reactions occur when normal bone is subjected repeatedly to submaximal forces. This recurring stress stimulates the bones to remodel and strengthen. In a stress fracture, osteoblasts are unable to lay down new bone and remodel fast enough, so the bone fails. Stress fractures can also occur in diseased bone when it is subjected to repeated minimal stress.

Clinical presentation. The symptoms of a stress fracture of the femoral neck are often subtle and can be mistaken for a muscle strain or an overuse injury. Early symptoms frequently include morning stiffness and aching in the hip on the first steps after a period of rest. The pain gradually increases during prolonged exercise and may reach the point at which the patient is unable to bear weight. Pain typically radiates to the groin or along the medial aspect of the thigh toward the knee.

Patients with these stress fractures usually limp because of pain. Their antalgic gait is characterized by shortening of the stance phase of the injured extremity. No obvious external rotation or shortening of the leg is seen; the patient experiences minor discomfort with active or passive motion, except at the extremes of flexion and internal rotation. Tenderness is minimal because of the large amount of soft tissue coverage at the femoral neck.

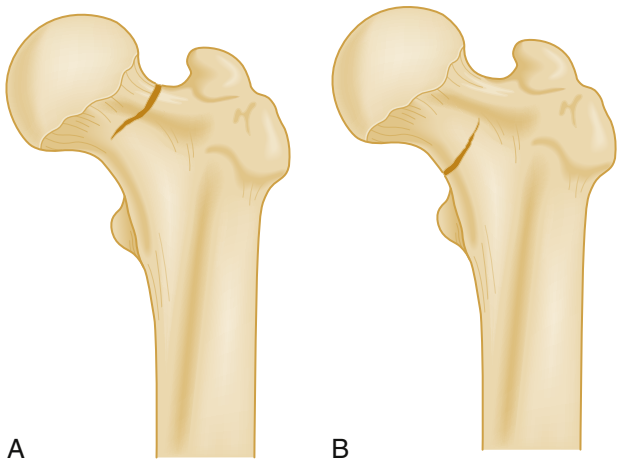

Fig. 47.19 Femoral neck fractures through the tensile (A) and compressive (B) trabecular fibers.

Diagnostic testing. Radiographs are helpful if they demonstrate a fracture, but findings are often negative until 10 to 14 days after the symptoms begin. Endosteal or subperiosteal callus develops at the fracture site during this period. In addition to the standard anteroposterior and lateral views of the hip, oblique views may delineate the fracture line. Particular attention should be paid to the trabecular fibers of the femoral neck. A stress fracture is often identified as an isolated disruption of the trabecular fibers on either the tensile (lateral aspect of the femoral neck) (Fig. 47.19A) or the compressive (medial aspect of the femoral neck) (Fig. 47.19B). If a fracture is suspected clinically but radiographic findings are negative, the next recommended diagnostic modality is MRI. If a fracture is found, the contralateral hip should be concomitantly evaluated because of the significant incidence of bilateral stress fractures.

Management. Treatment of stress fractures of the femoral neck is based on involvement of the compressive or tensile aspect. Compressive-side fractures involving less than half of the cortex are inherently stable and can be treated conservatively with partial weight bearing and crutches. Tension-side fractures and compressive-side fractures involving more than half the cortex are considered unstable and at risk for displacement. These fractures should be treated operatively with screw and hardware fixation.

Disposition. Urgent orthopedic consultation for decision of operative versus nonoperative treatment is recommended for these types of stress fractures.

Dislocations and Fracture-Dislocations of the Hip and Femur

Hip Dislocations

Foundations. Dislocations and fracture-dislocations of the hip are true orthopedic emergencies. The hip joint possesses impressive inherent strength and stability; therefore, considerable force is required to produce these injuries. With this understanding, a hip dislocation serves as a "red flag" for multisystem injury and should prompt a diligent search for other injuries. As many as 70% of patients with a dislocation have an associated acetabular fracture. Knee fractures, ligamentous injuries, and dislocations are present in up to 30% of patients who have sustained a hip dislocation. It is recommended that,

in the presence of this type of injury, patients be managed as major trauma victims. The incidence of hip fractures and dislocations are increasing in young patients, often as a result of high-energy trauma. Up to 50% of children with a hip dislocation have fractures elsewhere. In small children, dislocation of the hip is more common than femoral neck fractures. The force required to dislocate a pediatric hip is much less than that required in an adult because the acetabulum is less completely developed.[11] Seemingly negligible trauma, such as tripping or a minor fall, can dislocate the femoral head in a young child. In a school-age child, athletic injuries are the major cause of traumatic hip dislocation; in the teenage years, MVCs predominate.

Traumatic hip dislocations occur primarily in patients sustaining severe multisystem trauma, most often as a result of a high-speed MVC. Failure to use seat belts is a significant risk factor. Less common mechanisms include mechanical falls, sports injuries, and pedestrians struck by automobiles.

The vast majority of posterior dislocations are the result of MVCs. A seated vehicle occupant typically has the hip adducted, flexed, and internally rotated at the time of impact. As the knee strikes the dashboard, the force is transmitted through the femoral shaft to the femoral head. With sufficient force, the femoral head dislocates posteriorly. Anterior dislocations result from forceful extension, abduction, and external rotation of the femoral head. These forces lever the head up and out of the acetabular cup.

The relationship of the femoral head to the acetabulum is used to classify dislocations into anterior, posterior, central, and inferior types. A fracture-dislocation includes an associated fracture of the acetabulum or femoral head. Posterior dislocations (Fig. 47.20) account for 80% to 90% of dislocations. Anterior dislocations (Fig. 47.21) are seen in 10% to 15% of patients. In anterior dislocations, the femoral head can dislocate medially toward the obturator foramen (obturator dislocation) (Fig. 47.22) and laterally toward the pubis (pubic dislocation) or the iliac crest. Central dislocations, which occur in 2% to 4% of cases, are not true dislocations, since the entire femoral head is forced centrally through a comminuted fracture of the acetabulum. Inferior dislocation of the hip associated with inversion of the femoral shaft *(luxatio erecta femoris)* is a rare condition that occurs with or without associated trochanteric fracture.[11]

The precarious blood supply to the femoral head is particularly important with regard to the long-term consequence of hip dislocations. The development of AVN of the femoral head has been reported in up to 15% of dislocations. Other risk factors for the development of AVN include the total dislocation time, the severity of the injury, the number of reduction attempts, and the presence of comorbid conditions.

Clinical presentation. The position of the injured extremity might provide valuable clues in the evaluation of a hip dislocation. A patient with a posterior dislocation typically holds the hip flexed, adducted, and internally rotated. The knee of the affected extremity rests on the opposite thigh. The extremity generally is shortened, and the greater trochanter and buttock may be unusually prominent. In contrast, a patient with an anterior dislocation holds the hip in abduction, slight flexion, and external rotation, and the leg may appear lengthened. These physical findings might be absent in patients with an associated ipsilateral femoral shaft fracture.

The neurovascular examination should focus on the sciatic nerve and femoral vessels. Sciatic palsy is present in approximately 10% of patients with hip dislocation and most commonly involves the peroneal nerve branch. The most sensitive clinical sign of peroneal nerve palsy is weakness of the extensor hallucis longus; other signs include weakness of dorsiflexion and numbness or tingling over the dorsum of the foot. The femoral vessels and nerve are particularly prone to injury after an anterior dislocation.

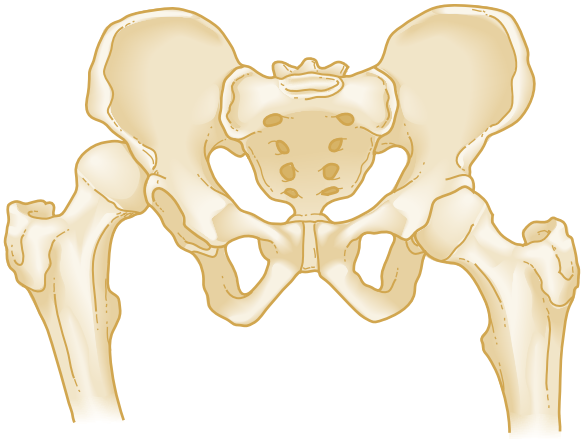

Fig. 47.20 In a posterior dislocation, the hip is internally rotated, and the lesser trochanter is superimposed on the femoral shaft. Failure to visualize the lesser trochanter on the anteroposterior projection identifies a posterior dislocation.

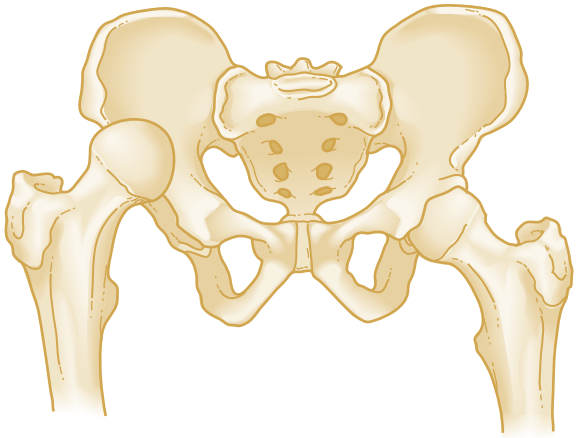

Fig. 47.21 In an anterior dislocation, the hip is externally rotated and the lesser trochanter appears in profile. The hip is farther from the x-ray cassette than the unaffected side and may appear larger because of the beam's projection.

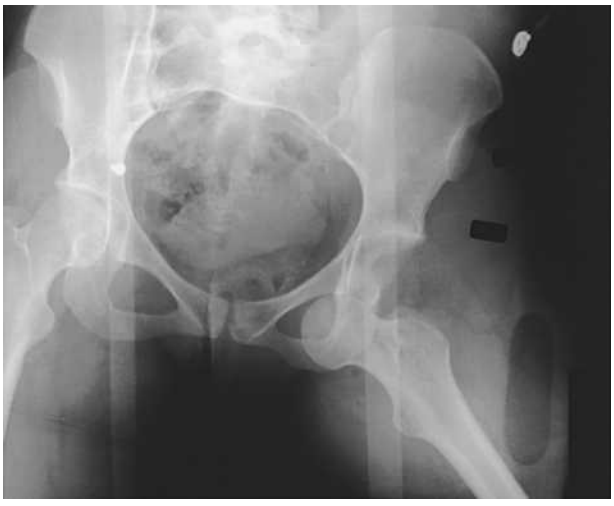

Fig. 47.22 Obturator Dislocation.

Diagnostic testing. Radiologic investigation begins with an anteroposterior view of the pelvis. This view alone will identify the majority of hip dislocations. An anteroposterior pelvis film should be obtained in all trauma patients with the aforementioned deformities. The anteroposterior radiograph should include the entire pelvis and the proximal third of the femur to allow comparison of both hips. When a dislocation is found or suspected, a lateral view of the hip will provide additional definition of the injury.

Although most hip dislocations are seen clearly with these two views, several key radiographic signs can assist emergency clinicians in making a diagnosis. The first indicator involves the position of the lesser trochanter. Because a posteriorly dislocated hip is internally rotated, the lesser trochanter is superimposed on the femoral shaft and is not seen on the anteroposterior projection. By contrast, an anteriorly dislocated hip is externally rotated, and the lesser trochanter appears in profile. The second clue is found in the size of the femoral head. Because a posteriorly dislocated hip is closer than the unaffected side to the x-ray cassette, it appears smaller. The converse is true in anterior dislocations, in which the hip is farther from the x-ray cassette than the contralateral side is and thus appears larger. The third finding relates to the integrity of *Shenton line* (Fig. 47.23), a smooth, curved line drawn on the radiograph along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion for a femoral neck fracture or hip dislocation.

An obvious dislocation might distract the clinician from a search for concomitant fractures. Examination of the trabecular pattern can identify associated fractures of the acetabulum and femoral head, neck, or shaft. It is important to identify acetabular fractures before closed reduction is attempted because intra-articular bone fragments could interfere with effective reduction. Although these fractures might make the reduction more difficult, their presence is not a contraindication to the procedure.

Management. *Hip dislocations constitute a true orthopedic emergency, and reduction should be performed within 6 hours.* The incidence of AVN, traumatic arthritis, permanent sciatic nerve palsy, and joint instability increases logarithmically with the length of time the hip remains dislocated.

The timing and method of reduction depend on the overall condition of the patient, the type of dislocation, and the presence or absence of associated fractures. In cases of simple dislocation, closed reduction should be attempted first. Although some clinicians recommend that this procedure be performed with the patient under general anesthesia, this delay, with its associated increase in the rate of AVN, is not warranted when timely procedural sedation in the ED is available. If the emergency clinician chooses to attempt closed reduction, the principles of procedural sedation and monitoring should be followed as described in Chapter 7. The primary relative contraindication to closed reduction is the presence of a femoral neck fracture. Another relative contraindication is the presence of fractures in the dislocated extremity, because such fractures preclude application of traction to the limb. Techniques of closed reduction are described next.

The Stimson and Allis techniques have been used most commonly for reduction of posterior hip dislocations (Fig. 47.24). *The Allis technique* usually is effective for both posterior and obturator dislocations (Fig. 47.25). It is the most commonly used method for hip reductions in the ED. On the negative side, it places the clinician at risk of slipping and falling off the bed, places strain on the lower back, and can be extremely difficult for smaller practitioners.

The Allis technique for reduction of posterior hip dislocations is performed by the following steps and technique:

1. To reduce harm to the clinicians, place the patient on a backboard that is lowered to the floor, instead of standing on the stretcher or bed.

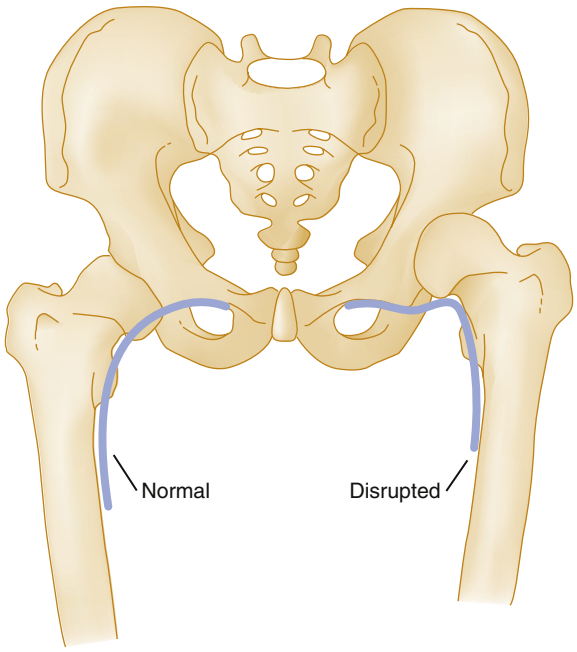

Fig. 47.23 Shenton line is a smooth curved line drawn along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion of a femoral neck fracture or hip dislocation.

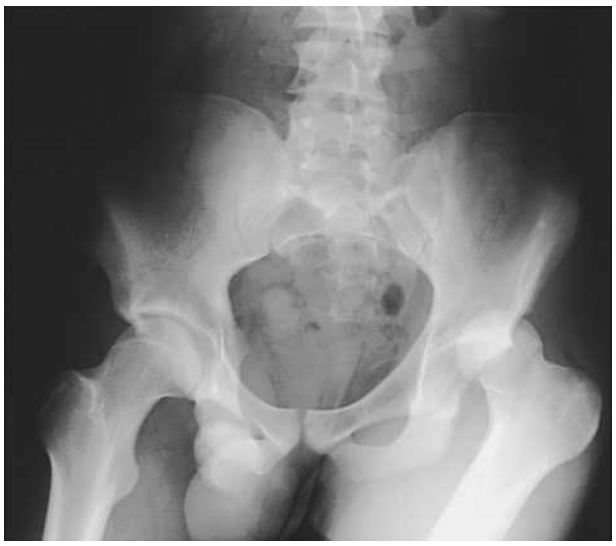

Fig. 47.24 Radiograph of posterior dislocation identified by loss of the lesser trochanter on the anteroposterior view.

2. Place the patient in the supine position, with the pelvis stabilized by an assistant. We suggest using a sheet or strap to secure the patient to the bed or backboard. Place the strap over the ischial wings and pubic symphysis.
3. With the knee flexed, apply steady traction in line with the deformity.
4. Slowly bring the hip to 90 degrees of flexion while applying steady upward traction and gentle rotation.
5. The assistant pushes the greater trochanter forward toward the acetabulum.
6. Once reduction has been achieved, bring the hip to the extended position while maintaining traction.

The Stimson technique (Fig. 47.26) uses the weight of the limb and the force of gravity to reduce the dislocation and is relatively atraumatic.

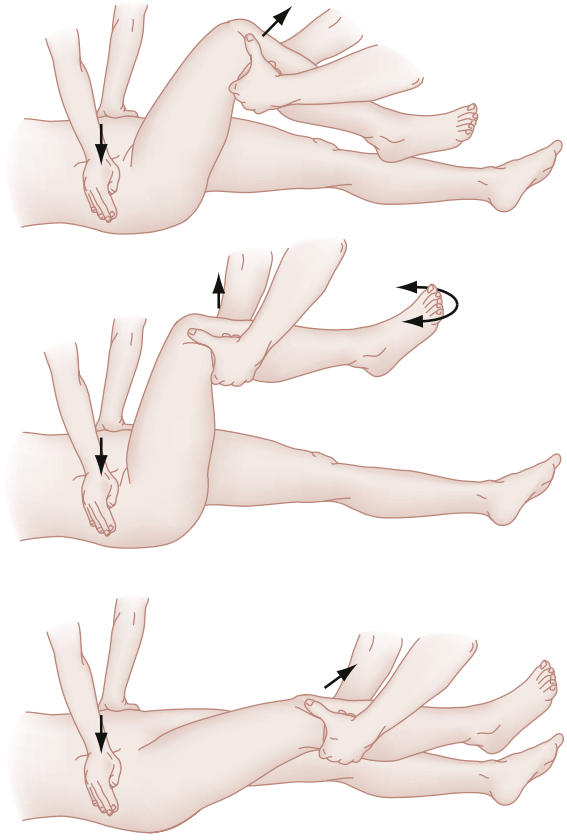

Fig. 47.25 The Allis Technique for Hip Reduction.

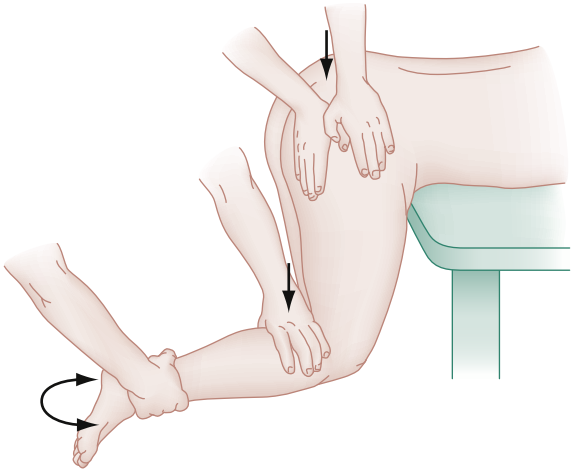

Fig. 47.26 Stimson's Technique for Hip Reduction.

Although Stimson's technique generally is effective, placing a patient with multiple traumatic injuries in the required prone position is not recommended. Radiographic clearance of the spine has not yet been accomplished, and the administration of sedatives and analgesics to a prone patient has potential adverse side effects.

To perform the Stimson technique for reduction of posterior hip dislocation:

1. Place the patient in a prone position, with the leg hanging over the edge of the bed. The hip and knee are flexed at 90 degrees.
2. Ask an assistant to stabilize the pelvis and secure the patient to the stretcher or bed with a sheet or strap. Place the strap over the ischial wings and pubic symphysis.

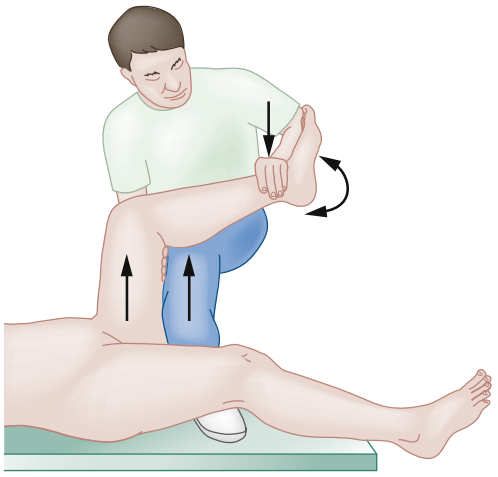

Fig. 47.27 Captain Morgan Technique for Hip Reduction. (Redrawn from Hendey GW, Avila A. The Captain Morgan technique for the reduction of the dislocated hip. *Ann Emerg Med.* 2011;58:536–540.)

3. Apply steady downward traction in line with the femur.
4. Gently rotate the femoral head while the assistant pushes the greater trochanter anteriorly toward the acetabulum.
5. Once reduction has been achieved, bring the hip to the extended position while maintaining traction.

The Stimson and Allis techniques are being replaced by newer methods of reduction that are considered safer and equally as effective. These include the Whistler and Captain Morgan methods.[12] These techniques use the power of the provider's leg muscles to reduce the hip, instead of relying on lower back and arm strength. The Captain Morgan and Whistler techniques use the provider's knee and arm, respectively, as a fulcrum to apply force and reduce the hip. The Captain Morgan technique has a success rate of 95%, but there are reports that excessive downward force on the ankle has caused ligamentous injuries in the knee.

To perform the *Captain Morgan technique* for reduction of posterior hip dislocation, the following steps are recommended: (Fig. 47.27):

1. With the patient supine on the stretcher in its lowest position, secure the pelvis to the stretcher with a bed sheet or strap. Place the strap over the ischial wings and pubic symphysis. This prevents the clinician from lifting the patient off the bed and is more effective than having an assistant try to secure the pelvis.
2. Stand at the side of the bed and place one foot up on the bed (like Captain Morgan standing on a rum barrel). If additional height is needed, consider using a stable cardiopulmonary resuscitation (CPR) stool.
3. Place the patient's ipsilateral leg over the clinician's leg so the knee is resting in the patient's popliteal fossa.
4. While holding the ankle in position with slight downward pressure (this is done only to lock the patient's leg onto the clinician's leg and is not meant to be a fulcrum), lift up with both legs to apply traction on the femur and reduce the hip.
5. If traction alone does not work, the clinician's hands are used to internally and externally rotate the leg to achieve the reduction.

The Whistler technique often works better for practitioners who are of shorter stature and have difficulty getting their leg in proper position for the Captain Morgan technique. In this method, the clinician uses their stabilized arm under the ipsilateral knee to lift the leg using the leg muscles.

To perform the Whistler technique for reduction of posterior hip dislocation (Fig. 47.28):

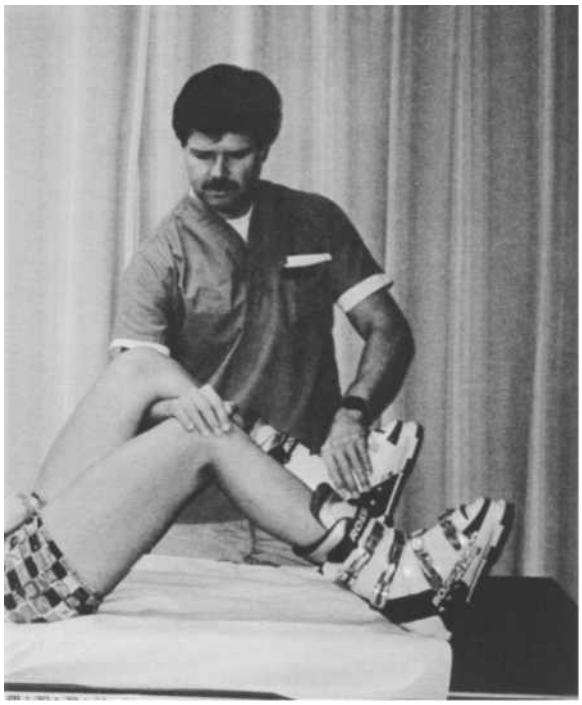

Fig. 47.28 Whistler Technique for Hip Reduction. (From Walden PD, Hamer JR. Whistler technique used to reduce traumatic dislocation of the hip in the emergency department setting. *J Emerg Med.* 1999;17:441–444. Used with permission.)

1. Start with the patient lying supine on the bed, and secure the patient's hips to the bed, as for the Captain Morgan technique.
2. Bend the contralateral leg so that the patient's knee is flexed 90 degrees and the foot is on the bed.
3. Bend the ipsilateral leg to the same position.
4. The clinician's arm is placed under the ipsilateral knee and rests on top of the contralateral knee.
5. The clinician's body is rotated perpendicular to the patient and looking at their feet. This causes the clinician to assume a squatting position.
6. While holding the patient's ipsilateral ankle with other hand, the clinician slowly lifts up with the legs, while keeping the arm straight and strong. This puts traction on the femur and should reduce the dislocation.
7. If reduction is not achieved with traction alone, the hand that is on the ankle can be used to internally or externally rotate the leg to achieve the reduction.

Other techniques for closed reduction of posterior hip dislocations include the Rochester method and the traction-countertraction technique.

Closed reduction of a pubic dislocation can be challenging. The anterior position of the femoral head will resist flexion, making the Allis maneuver technically impossible. The following sequence of maneuvers is recommended.

To perform the technique for reduction of pubic dislocation:

1. Place the patient in the supine position.
2. Apply longitudinal traction in line with the deformity.
3. Hyperextend and internally rotate the hip while an assistant applies downward pressure on the femoral head.

Although prompt anatomic reduction is clearly desirable, multiple attempts at reduction in the ED should be avoided because of potential damage to the articular surface. The incidence of osteonecrosis increases with the number of attempts at reduction, as well as the duration of the dislocation. Difficulty with reduction is usually the result of incarceration of a tendon, a capsular structure, or an osteochondral fragment that is blocking reduction. In the case of a nonreducible dislocation, closed reduction with the patient under general anesthesia or an open reduction procedure is often required.

After closed reduction, the hip should be tested for stability, which is accomplished by gently taking it through its full range of motion to see whether it will re-dislocate. After testing has ensured stability, the injured extremity should be placed in a knee immobilizer and an abduction pillow should be applied to prevent a repeat dislocation. An anteroposterior radiograph of the pelvis should be obtained to verify the adequacy of reduction. The radiograph should be inspected carefully to verify that the femoral head is in the acetabulum, the shaft of the femur is in neutral position, Shenton line is intact, and the profile of the lesser trochanter is well visualized. The intra-articular space should be symmetrical and when measured, at the same depth as in the unaffected joint. Asymmetry signals an entrapped intra-articular fragment and is an indication for CT imaging.

Disposition. Most patients with a native hip dislocation will require admission to the hospital and urgent orthopedic referral for serial examinations and to ensure that no additional injuries are present.

Fracture-Dislocation of the Femoral Head

Foundations. Hip dislocations can be associated with fractures of the femoral head (Fig. 47.29A). Femoral head fracture occurs in 35% to 55% of anterior hip dislocations and in 10% to 16% of posterior hip dislocations. These injuries are almost always the result of high-speed vehicular trauma. Because of the significant force required to produce this injury pattern, coexistent multisystem trauma is the rule.

Clinical presentation. When a femoral head fracture and hip dislocation coexist, patients assume the position typical for the dislocation. Hip mobility is markedly reduced, and pain is usually severe. After initial stabilization, the involved extremity should be examined for associated fractures of the femoral shaft and knee. The neurovascular examination should assess for femoral or sciatic nerve injury.

Diagnostic studies. Radiographs should be evaluated for any femoral head fracture in patients with hip dislocations. Evidence for fracture of the femoral head can be subtle. These fractures can be detected on radiographs by following the curve of the dislocated head and the acetabular cup to search for a small fragment that could otherwise be overlooked. Known or suspected injuries can be further defined by CT scanning or MRI.

Management. In most cases, satisfactory results can be obtained with closed reduction (see Fig. 47.29B). Several experts recommend obtaining a CT scan of the hip before closed reduction to further define the injury and locate fracture fragments. If the hip cannot be reduced by manipulation or if reduction of the femoral head fragment is unsatisfactory, open reduction will be indicated.

Disposition. Patient with fracture-dislocation of the femoral head should be admitted for operative management.

Dislocation of Hip Prosthetics

Foundations. An increasing number of patients have undergone hip arthroplasty. In addition to those procedures performed for treatment of femoral neck fractures, nearly 250,000 patients undergo elective primary THA each year. Postoperative dislocation occurs in 0.5% to 3% of patients with primary THA and in 5% to 25% of patients with a revised THA. Although most dislocations take place within 3 months of surgery, "late dislocations" have been reported up to 10 years after the operative procedure; such dislocations can result from major trauma or from trivial events (e.g., rising from a seated position). Posterior dislocations account for 75% to 90% of cases (see Fig. 47.30).

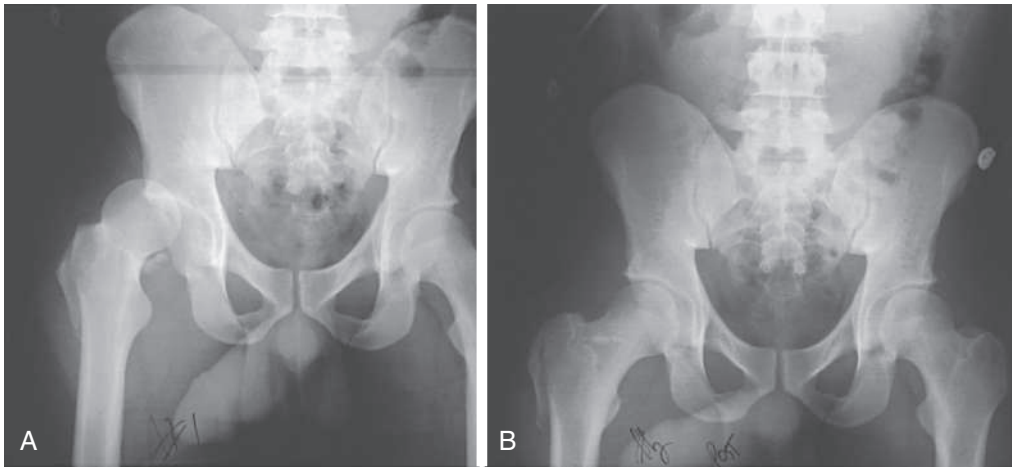

Fig. 47.29 (A) Anterior hip dislocation is identified as the lesser trochanter is brought into profile. Note the fracture of the lateral aspect of the greater trochanter. (B) A post-reduction radiograph demonstrates adequate reduction with symmetrical joint spaces.

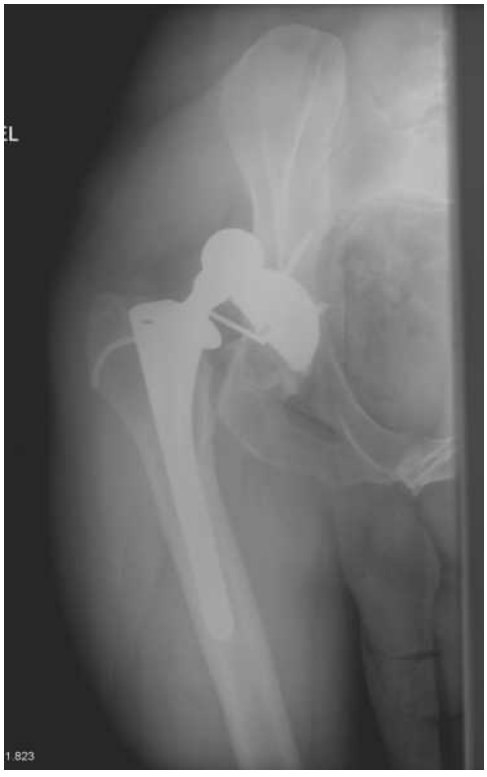

Fig. 47.30 Dislocation of the femoral prosthesis in a patient who had undergone total hip arthroplasty (THA). The femoral head often becomes caught on the rim of the acetabular cup, thereby preventing reduction. Reduction can disrupt or dislocate the acetabular cup.

Clinical presentation. Most patients will present with inability to bear weight with associated hip or groin pain. The affected leg with be externally rotated and shortened. They will have increased pain if the leg is internally rotated or flexed.

Diagnostic studies. Radiologic investigation begins with an anteroposterior view of the pelvis. See the Hip Dislocation section in this chapter for further details on diagnostic studies.

Management. Reduction techniques for prosthetic hip dislocations are identical to those described earlier but are not as time dependent as native hip dislocations. Most patients can be placed in a straight leg knee immobilizer, which will prevent them from re-dislocating their prosthetic hip.

Disposition. Consultation with an orthopedic surgeon is recommended for development of a long-term treatment plan for the patient as chronic dislocation may require operative repair. Reduction of the prosthesis does not carry the same urgency as for reduction of a dislocated native hip because there is no risk for the development of AVN once the femoral head has been replaced. Traction on the sciatic nerve can occur, however, making early reduction more compelling. In addition, the reduction itself carries the risk of loosening of the components, fracturing of the surrounding bone, and movement of the acetabular cup. Reduction is best performed in consultation with an orthopedic specialist.

Soft Tissue Injuries

Soft tissues can be subject to muscle or tendon strain or contusions from overuse or trauma. Rupture, hemorrhage, or myositis ossificans can develop in muscles.

Muscular Injuries

Foundations. Strenuous exercise by a poorly conditioned person, sudden exertion, and direct trauma all can injure soft tissues. Cold temperature, vascular or infectious disease, fatigue, and inadequate training are predisposing conditions for muscular injury.

Clinical features. Partial tears are reversible injuries that are aggravated by movement or tension. Mild spasm, swelling, ecchymosis, and tenderness cause minor loss of function and strength. Complete tears produce a palpable depression, and the torn muscle edge is often palpable. Other possible findings include severe spasm, swelling, ecchymosis, tenderness, and loss of muscle function. In significant muscle strains, radiographs are needed to evaluate for the possibility of an accompanying bone avulsion injury. Extremely strenuous exercise can lead to rhabdomyolysis and compartment syndrome in rare cases.

Differential diagnoses. Differential diagnoses of these soft tissue injuries include muscle strain, partial and complete muscle tears, ligamentous or tendon strains, avulsion injury, and compartment syndrome.

Diagnostic testing. In the ED, plain radiographs can be obtained to exclude any fractures. Bedside ultrasound is also helpful in evaluating for partial and complete ligamentous or tendon tears. Patients may eventually require an MRI to fully evaluate their injury. MRI has the best sensitivity and specificity for soft tissue injuries but does not need to be done emergently. If there is a concern for compartment syndrome, compartment pressures should be measured with orthopedic consultation.

Management. Initial management of incomplete tears traditionally includes the local application of ice for the first 48 hours, followed by heat. Compressive wraps can exacerbate distal venostasis, with the potential for distal venous clot formation, and do not significantly decrease recovery time. A regimen of nonsteroidal antiinflammatory agents to achieve sufficient analgesia is important for recovery and patient satisfaction. Muscle relaxants may be useful when the injury is accompanied by muscular spasm. In general, complete rest of the affected muscle should be maintained, with the recommendation of "weight bearing as tolerated." This progressive muscle loading can be started within 3 to 5 days once a sufficient scar has formed. To prevent reinjury, muscle loading should be limited by the patient's pain.

Disposition. Any patient with significant injury should be referred for physical therapy. A complete muscle tear requires follow-up care with an orthopedic surgeon or sports medicine specialist.

Some common specific muscular injuries are shown in Table 47.3

TABLE 47.3 Soft Tissue Injuries—Muscle Strains

Injury	Foundations	Clinical Features	DDx	Diagnostic Testing	Management	Disposition
Hamstrings	Common injury in athletes from accidents or overtraining. Common in sports involving running/ sudden acceleration (e.g., track and field or basketball.)	Sudden intense pain in the posterior aspect of the thigh. Active or passive motion at the hip is poorly tolerated due to pain	Ischial avulsion fractures	Pelvic radiographs should be obtained if the examination reveals bony tenderness	Crutches and toe-touch weight bearing are recommended until the patient is evaluated by a physician trained in sports medicine. Appropriate weight-training programs speed rehabilitation of this injury.	Complete recovery from a hamstring muscle strain can take weeks to months.
Quadriceps	Most common muscular group to sustain complete tears. This injury occurs when the muscles are contracted suddenly against the body's weight, as may occur when an athlete slips or stumbles and attempts to avoid a fall.	Ambulation is significantly affected. There is pain with active and passive knee extension. In significant tears, the patient might be unable to actively extend the knee or maintain its extension against gravity. A palpable depression just proximal to the superior pole of the patella suggests a complete tear.	Patellar Fracture can give similar issues with extension	Ultrasound can also be used to diagnose quadriceps tears.	Knee immobilizer and urgent surgical referral for operative repair	Refer to orthopedics or sports medicine.
Iliopsoas strain	Gymnasts and dancers are the athletes most likely to experience an injury to the iliopsoas as a result of sudden forceful hip flexion against resistance.	Severe pain often is experienced in the groin, thigh, or low back. Severe intra-abdominal pain is common at the muscle origin and might dominate the clinical picture. Examination reveals groin tenderness and pain with active hip flexion.	Pelvic fracture Sacroiliitis	Radiographs of the femur should be obtained to identify an avulsion fracture of the lesser trochanter. CT frequently demonstrates a large hematoma.	Bed rest with partial flexion at the knee and hip generally is required for 7–10 days.	Discharge with supportive care. Sports medicine vs. orthopedic follow up
Hip adductor strain	Injury to the hip adductors occurs as the thigh is forcefully abducted, as in a straddle injury.	Pain in the groin, the pubic region, and the medial proximal aspect of the thigh. Abduction and adduction often are limited because of pain. Swelling and skin discoloration may confirm presence of the tear. If the tear is complete, a defect in the muscle can be felt by the examiner along the medial aspect of the thigh near the groin.	Pelvic fracture Femoral avulsion fractures	Pelvic CT vs. MRI	Treatment is conservative, with patients initially benefiting from rest, with gradual progression in a stretching and strengthening program.	Discharge with PT, orthopedics, and/or sports medicine
Gluteus muscle strain	Vigorous or forced hip extension, as seen in track-and-field jumping events.	The pain typically is less severe. than that associated with injuries to other muscle groups. The hip is tender when extended or abducted.	Pelvic fractures	X-rays if indicated	Treatment is conservative, with patients initially. benefiting from rest, with gradual progression in a stretching and strengthening program.	Discharge with supportive care

Tendon Injuries

Foundations. Clinically, tendinopathies tend to have a more insidious onset than that typical for muscle strains. These strains occur at the attachment of the muscles to the superior or inferior pubic ramus, the pubic symphysis, the ischium, and the femur.

Clinical features. Local pain over the tendon, exacerbated by stretching of the tendon, is a common physical examination finding. Pain may radiate down the muscle and limb.

Adductor strains tend to be the most common groin injury in athletes, with 60% of the cases involving the adductor longus muscle. The adductor magnus and brevis and the pectineus often are involved as well. This injury commonly occurs in skaters and cross-country skiers when an accidental stress abducts the thigh during a powerful contraction of the adductors. These muscles also can be injured from overuse in an unconditioned patient. Local pain is noted at the inferior pubic ramus and the ischial tuberosity. Extension, abduction, and adduction of the hip are painful, with pain radiating to the back of the thigh.

Pain over the greater trochanter could represent tendon strain of the attachments of the gluteus medius, gluteus minimus, tensor fasciae latae, or piriformis. The pain is aggravated by resisted abduction. Tenderness in the groin and painful hip movement suggest a strain of the iliopsoas tendon at its attachment to the lesser trochanter.

Differential diagnoses. Differential diagnoses of these tendon injuries include avulsion fractures, partial or complete tears of the muscles or tendons, tendinopathies, peritendinitis, trochanteric bursitis, AVN, and oncological disorders.

Diagnostic studies. Ultrasound imaging may lend additional diagnostic information. MRI can provide a definitive diagnosis but is not indicated in the ED setting.

Management. Treatment of a tendon strain is similar to that for other soft tissue injuries. The use of crutches with weight bearing as tolerated is recommended for the first 2 weeks. Antiinflammatory agents or a short course of opioid analgesics may be given. Complete tendon disruption might require surgical repair.

Disposition. Most patients will require follow up with an orthopedic or sports medicine specialist within a week.

Osteitis Pubis

Foundation. Osteitis pubis is characterized by pubic symphysis pain and joint disruption and is most common in distance runners and soccer players. The adductor muscles act as a "compression strut," displacing forces across the hip. The most likely mechanism is repetitive pulling of the adductor muscles, causing increased shearing at the pubic symphysis.

Clinical features. Clinically, patients have groin pain of insidious onset, with most reporting pain at the symphysis and adductor muscles. Pain usually can be elicited on palpation of the symphysis and provoked by adduction of the hip or by doing sit-ups.

Differential diagnoses. Osteitis pubis has been associated with spontaneous cases of pubic symphysis osteomyelitis and should be considered in the differential diagnosis.

Diagnostic testing. Plain radiographs show widening of the symphysis, irregular contour of the articular surfaces, or periarticular sclerosis (a delayed finding) (Fig. 47.31). These features are not specific and in one study were seen in 75% of asymptomatic soccer players. MRI is the imaging study of choice and will show marrow edema on T2 images during the acute phase of the disease.

Management. Treatment is conservative since in most cases the process is self-limited. Patients benefit from activity modification, wearing supportive shoes, and from therapy addressing flexibility and strength of the pelvic and hip musculature. Average time to heal has been reported to be up to 9 months.

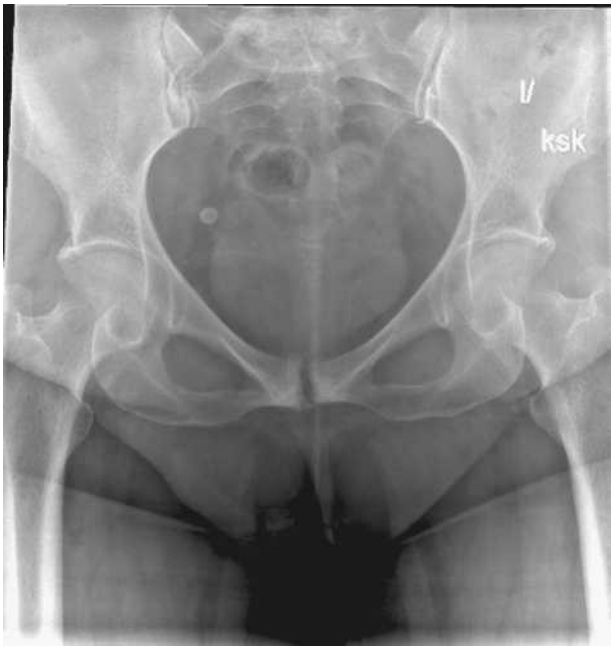

Fig. 47.31 Plain radiograph showing irregular articular surfaces and periarticular sclerosis consistent with osteitis pubis.

Disposition. Owing to the length of healing associated with these injuries, follow-up care should be arranged at the time of initial injury to an orthopedics or sports medicine specialist.

Vascular Injuries

Foundations. Hip dislocations and femoral fractures may have associated arterial injury. The vessel can be partially lacerated, dissected, completely severed, or thrombosed. A lack of distal arterial flow might also represent a stretched vessel in spasm. The superficial femoral artery is most commonly injured with trauma to the hip and thigh. The common and the deep femoral arteries are less frequently injured. In the acute setting, penetrating trauma is the usual mechanism of injury. Arterial injury with a femoral shaft fracture is rare. Anterior and superior dislocations can produce femoral artery injury.

Clinical features. Patients may have decreased pulses, poor capillary refill, cold extremities, paresthesias and increased pain.

Differential diagnoses. The differential diagnoses of these vascular injuries include arterial thrombus, arterial dissection, and complete or partial vascular tears.

Diagnostic testing. Ultrasound or CT angiogram are indicated for evaluating the vasculature.

Management. Orthopedic or vascular surgery consultation is recommended if any partial or complete vascular tear is found. Fracture reduction may restore blood flow if the vessel is being compressed.

Disposition. Most patients with these vascular injuries will require admission for their femoral fracture repair.

Neurologic Injuries

Foundation. Peripheral nerve injuries can be caused by trauma, external compression, infection, and degenerative disease. In trauma, nerves can be injured by a blunt object that causes a contusion, by a sharp penetrating object that produces a partial or complete tear, or by stretching. Nerves are particularly vulnerable to prolonged ischemia, which can lead to necrosis. Compression of the nerve

TABLE 47.4 Nerve Injuries

Nerve	Foundation	Clinical Features	Management	Disposition
Femoral nerve	The femoral nerve is most often traumatized in penetrating trauma of the pelvis, groin, or thigh. Femoral neuropathy occasionally results from compression by a hematoma within the abdominal wall or the iliopsoas as a complication of hemophilia, anticoagulant therapy, or severe trauma. When the femoral nerve is injured, the iliac and femoral arteries are commonly involved because of their anatomic proximity.	Marked weakness of knee extension. The patient is able to walk on level ground yet has extreme difficulty walking upstairs or an incline. Patients cannot rise from a sitting position because of significant proximal muscle weakness. The sensory deficit varies but is localized along the anterior aspect of the thigh and medial lower aspect of the leg. The most reliable spot for testing for a sensory deficit is just superior and medial to the patella. The deep tendon reflex of the knee is diminished or absent with such deficits.	Urgent orthopedics consultation. Reduce any fractures that may be compressing nerve. Control hemorrhage if due to a hematoma.	Urgent orthopedics consultation
Sciatic injury	Sciatic injury is rare with femur fractures, but occasionally it may be the result of traction used to stabilize the fracture during the initial management period. Complete traumatic injury can result from a deep penetrating wound in the hip, thigh, or buttock. Posterior hip dislocations and fracture-dislocations produce sciatic neurapraxia in 10% to 14% of patients with these injuries.	Patients with complete sciatic neuropathy have paralysis of the hamstring muscles and all muscles below the knee. With partial injury, a peroneal palsy with weakness of the extensor hallucis longus muscle is the most sensitive clinical sign. There is sensory loss below the knee and along the posterior aspect of the thigh. The deep tendon reflex at the ankle is absent or diminished. Sciatic nerve palsy from inadvertent injection into the nerve or secondary to intraneural or extraneural hemorrhage in patients taking anticoagulants has been described.	Urgent orthopedics consultation	The prognosis is poorest when the injury is proximal and complete. Even with optimal repair, recovery often is inadequate. Sciatic neuropathy is a disabling problem. Obvious atrophy of the lower part of the leg and foot develops, followed by ulceration of the sole of the foot and infection. A below-the-knee amputation frequently is necessary in these cases.

from a hematoma or a dislocated femoral head may also appear as a neurapraxia manifested by transient loss of conductivity.

Clinical features. Patients present with sensory loss or motor weakness. Mild cases may present with paresthesias.

Diagnostic testing. No specific testing in the emergency department is indicated other than a focused physical examination, though MRI may be able to identify injury to a larger nerve.

Management. Treatment of neurovascular compromise from a hip dislocation or a displaced femoral fracture consists of immediate reduction to ensure limb viability. Whenever possible, reduction should be accomplished before the patient is transferred to another treatment center.

If traumatic neuropathy is suspected, orthopedic consultation should be obtained. Nerve exploration and repair generally are indicated for penetrating trauma and for direct impingement on the nerve by bone fragments or hematoma. Surgical exploration may be required for drainage of a hematoma that is impinging on the femoral nerve.

Disposition. Most traumatic nerve injuries will be observed in the hospital or require urgent orthopedic consultation. Neurapraxia from compression often resolve with time and can be evaluated by orthopedics in 2 to 3 days.

For specific nerve injuries see Table 47.4.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 47: QUESTIONS AND ANSWERS

1. Which of the following fractures has the best outcome and lowest rate of complications?
- **a.** Femoral neck fracture
- **b.** Insufficiency fracture
- **c.** Intertrochanteric fracture
- **d.** Lesser trochanteric fracture
- **e.** Subtrochanteric fracture

Answer: d. Treatment of a lesser or greater trochanteric fracture consists of pain control and early mobilization with crutches; weight bearing is allowed as tolerated by pain. Outpatient management of this injury is possible with a satisfactory social situation. The prognosis is good, and healing is generally excellent. The mortality rate during the first year after a femoral neck (also known as an *insufficiency fracture*) fracture is 15%. Intertrochanteric fractures have an associated mortality rate of 10% to 30% in the first year. The reported mortality rate from subtrochanteric fractures ranges from 10% to 15%.

2. A 40-year-old man complains of persistent thigh pain that worsens over 2 weeks after an assault with a baseball bat. His pain is worse with knee extension. On physical examination, you note that there is a small palpable mass at the mid-anterior thigh. What should be your next confirmatory test?
- **a.** Bone scan for fracture
- **b.** Bone scan for stress fracture
- **c.** Computed tomography (CT) scan for tumor
- **d.** Magnetic resonance imaging (MRI) for evaluation of torn muscle
- **e.** Radiograph for heterotropic calcification

Answer: e. Myositis ossificans (heterotrophic ossification) is pathologic bone formation at a site where bone is not normally found. Traumatic myositis ossificans results most commonly from a direct blow to muscle. It should be suspected when symptoms persist past 10 to 14 days or if symptoms intensify several weeks after the trauma. The ossific mass is often palpable and may limit motion, depending on its location.

3. An 80-year-old woman presents complaining of pain in her right leg after a motor vehicle collision (MVC). Emergency medical services (EMS) noted a swelling and a deformity to her thigh, so they placed a traction device on her leg. Her blood pressure is 80/40 mm Hg; heart rate, 110 beats/min; and respiratory rate, 18 breaths/min. What is the most appropriate next step in the management of the patient's fracture?
- **a.** Femoral nerve block and leave the traction device in place
- **b.** Femoral nerve block and remove the traction device
- **c.** Intravenous morphine and leave the traction device in place
- **d.** Intravenous narcotic pain medication and remove the traction device
- **e.** Immediate orthopedic consult to take the patient to the operating room for an open reduction and internal fixation (ORIF)

Answer: b. Although the patient may ultimately need to go to the operating room, the patient is currently unstable and requires resuscitation and evaluation for other injuries. A femoral nerve block is a valuable adjunct or alternative to systemic analgesics in a patient at risk for hypotension and has been underused by emergency clinicians. Prolonged traction during the assessment and management of other injuries can cause or worsen serious neurologic injury in the thigh by producing potentially damaging tension on the sciatic or femoral nerves.

4. What is the most common complication of a proximal femur fracture?
- **a.** Avascular necrosis (AVN)
- **b.** Myositis ossificans
- **c.** Osteomyelitis
- **d.** Pulmonary embolism
- **e.** Septic arthritis

Answer: a. AVN is the most common complication of proximal femur fractures (despite optimal treatment) because of the complex arterial anatomy. Deep infection in the form of osteomyelitis or septic arthritis is more common with femoral neck fractures because the fracture line extends into the joint. Pulmonary embolism is another significant complication and is the leading cause of death 7 days after fracture in orthopedic patients.

5. A 60-year-old woman presents complaining of right hip pain after a trip and fall at home. The patient denies loss of consciousness or other symptoms. You note that the patient's right leg is internally rotated, and the thigh is adducted and flexed at the hip joint so that the ipsilateral knee is resting on the opposite thigh. Which is the correct maneuver?
- **a.** Apply traction and splint the leg in full extension.
- **b.** Apply traction to an extended knee and flexed hip at 90 degrees with a gentle rotational component.
- **c.** Consult orthopedics immediately to take the patient to the operating room.
- **d.** Provide analgesia and Holter monitor for discharge when ambulatory.
- **e.** Use the Allis maneuver and place the patient in a knee immobilizer.

Answer: e. A patient with a posterior dislocation typically holds the hip flexed, adducted, and internally rotated. The knee of the affected

extremity rests on the opposite thigh. The Allis technique is usually effective for both posterior and obturator dislocations. With the knee flexed, the operator applies steady traction in line with the deformity. The hip is slowly brought to 90 degrees of flexion while steady upward traction and gentle rotation are applied.

6. A mother brings her 11-year-old boy for evaluation of left knee pain that is worse after physical activity. Radiographs of the knee were negative. What is the most appropriate next step in the patient's management?
- **a.** Hip radiograph with frog-leg views
- **b.** Joint aspiration for evaluation of transient synovitis
- **c.** Place a knee immobilizer and ensure follow-up in 1 week
- **d.** Radiograph of right knee for comparison
- **e.** Rest, ice, compression, elevation, and orthopedic follow-up urgently

Answer: a. This patient may have a slipped capital femoral epiphysis (SCFE), which most commonly develops in boys 10 to 17 years old during their period of rapid growth. Referred pain to the knee is a classic manifestation, and patients frequently present with groin, thigh, or knee pain rather than hip pain. Initially, anteroposterior, lateral, and frog-leg lateral radiographs of the hip should be obtained. The frog-leg lateral projection shows the hip in a plane midway between the anteroposterior and lateral views.

7. A 75-year-old woman presents after a fall from standing. She has right hip pain and tenderness to palpation but no obvious deformity. Right knee and ankle examinations are normal, without tenderness, deformity, or external signs of trauma. Hip and pelvis radiographs are negative for fracture, but the patient is unable to bear weight on her right leg. The next appropriate step in management is:
- **a.** Admit to the hospital for bed rest.
- **b.** Discharge the patient home with analgesia and a walker.
- **c.** Obtain magnetic resonance imaging (MRI) of the hip to assess for fracture not identified by radiographs.
- **d.** Obtain radiographs of the rest of her right leg to ensure no occult fracture is present.

Answer: c. With hip injury, if radiographs do not show a fracture or suggestion of injury and the patient is unable to ambulate, further imaging studies should be obtained to evaluate for occult fracture. Two percent to 10% of all hip fractures are radiographically occult. Failure to detect these fractures results in increased morbidity and mortality.

8. Which of the following injuries is appropriate for traction splinting by prehospital providers?
- **a.** Femoral fracture with bone protrusion through the skin
- **b.** Posterior hip dislocation
- **c.** Severe crush injury of leg with obvious deformity of the knee
- **d.** Suspected closed mid shaft femoral fracture

Answer: d. Traction splints can provide pain relief, immobilization, and limit blood loss when applied correctly to a femoral fracture. However, contraindications to the use of traction splints include pelvic fractures, patellar fractures, ligamentous knee injuries, and tibia or fibula fractures. Traction in the prehospital setting should not be applied to any open fracture that has exposed bone. Such reduction pulls grossly contaminated bone fragments back into the wound before adequate débridement can be undertaken in the operating room.

9. A 15-year-old female gymnast presents after experiencing the sudden onset of severe groin pain during a dismount when she landed in a flexed-hip position. The pain radiates into her abdomen, and flexion of the hip produces pain, but there is no deformity noted. What is the most likely radiographic finding?
- **a.** Avascular necrosis (AVN) of the femoral head noted on magnetic resonance imaging (MRI) scan
- **b.** Diastasis of the pubic symphysis on anteroposterior pelvis radiographs
- **c.** Femoral neck fracture on dedicated anteroposterior hip radiograph
- **d.** Iliopsoas muscle with some associated hemorrhage on computed tomography (CT) scan

Answer: d. Gymnasts and dancers are the group of athletes most likely to experience an injury to the iliopsoas as a result of sudden forceful hip flexion against resistance. Severe pain often is experienced in the groin, thigh, or low back region. Severe intra-abdominal pain is common at the muscle origin and may dominate the clinical picture. Examination reveals groin tenderness and pain with active hip flexion. Radiographs of the femur should be obtained to identify an avulsion fracture of the lesser trochanter. CT scan frequently will demonstrate a large hematoma. Bed rest with partial flexion at the knee and hip generally is required for 7 to 10 days. With severe strains, symptoms may persist for 2 to 3 months. Referral to a sports medicine specialist is appropriate.

10. A 45-year-old male presents with a posterior hip dislocation after a motor vehicle crash (MVC) noted on radiographs. After sedation of the patient and reduction of the dislocated hip, what is the most appropriate next step in the patient's management?
- **a.** Have the patient ambulate to assess the stability of the joint.
- **b.** Measure the femoral compartment pressure.
- **c.** Obtain post-reduction hip radiographs to assess for additional injuries and adequate reduction.
- **d.** Place a traction splint.

Answer: c. Obtaining post-reduction radiographs to ensure adequate reduction and evaluate for associated injuries is essential. After closed reduction, the hip should be tested for stability, which is accomplished by gently taking it through a full range of motion to see whether it will re-dislocate. After testing has ensured stability, the injured extremity should be placed in a knee immobilizer, and an abduction pillow should be applied to prevent repeat dislocation.

48

Knee and Lower Leg Injuries

Moira Davenport and Vanessa S.Franco

KEY CONCEPTS

- Knee dislocation often causes vascular injury to the popliteal artery. Early revascularization is crucial. Hard signs of vascular injury include absent pedal pulses, cool mottled foot, expanding popliteal hematoma, or popliteal hemorrhage. When any of these are present, angiography or emergent surgical exploration is indicated.
- Soft signs of popliteal artery injury include asymmetric pedal pulses and foot or leg paresthesias. Computed tomography (CT) angiography or duplex ultrasound study is indicated when these are present.
- In the absence of signs of popliteal injury, the knee dislocation patient can be observed for 24 h, with measurement of the ankle-brachial index (ABI) every 3–4 h. An ABI >0.9 over a 24-h period effectively excludes significant popliteal artery injury.
- Tibial plateau fractures should be considered in patients with a traumatic knee injury and inability to bear weight. Fractures may be radiographically occult, so CT imaging should be considered if clinical suspicion is high. In general, if a patient is unable to bear weight after a knee injury but no acute fracture is identified in the emergency department (ED), advanced imaging should be considered.
- Extensor mechanism injuries such as patellar and quadriceps tendon injuries are important to recognize, as delayed diagnosis is associated with substantial morbidity. A palpable defect in the quadriceps tendon or patellar tendon or over the patella and an inability to perform a straight leg raise should raise suspicion for such injuries. Knee immobilization and urgent orthopedic follow-up are advised.
- A dislocated patella will be fixed in a position superolateral to its normal position. Reduction is performed by gentle knee extension with medially directed or valgus directed pressure on the displaced patella.
- Injuries to the cruciate and collateral ligaments may not be detectable on initial examination because of effusion and splinting. Emergent diagnosis is not necessary, but the patient should undergo a follow-up examination by an orthopedist within a week.
- Lipohemarthrosis is an uncommon and subtle sign of occult fracture but should be sought on radiographs of traumatized knees.
- Compartment syndrome is a serious complication of tibial shaft fracture, usually occurring 24–48 h after injury. Orthopedic consultation or measurement of compartment pressure should be obtained when the patient's pain is increasing despite immobilization and support of the fracture.

KNEE INJURIES—FOUNDATIONS

Background and Importance

The critical responsibility of the emergency physician in evaluating patients with knee pain includes identifying neurovascular injuries, reducing dislocations, stabilizing fractures, and administering antibiotics when indicated. Definitive treatment of less urgent problems can be referred to the outpatient setting.

Anatomy, Physiology, and Pathophysiology

The knee is a modified hinge, diarthrodial synovial joint that consists of the tibiofemoral and patellofemoral joints. The head of the fibula, although not part of this articulation, is closely approximated laterally and provides a site for the attachment of muscles and ligaments. Joint stability is provided primarily by ligaments, although surrounding muscles and the joint capsule contribute as well (Fig. 48.1). The capsule of the knee joint is reinforced at multiple sites—anteriorly, by the ligamentum patellae; medially and laterally, by the medial and lateral patellar retinacula; and posterolaterally, by a combination of structures termed the *posterolateral corner.*

Femur

The distal femur terminates in the medial and lateral condyles. A condyle is a rounded prominence at the end of a bone where it interfaces with another bone. An epicondyle is a prominence on a condyle where a ligament or tendon attaches. The femoral condyles protrude anteriorly, leaving a vertical groove between them, forming the femoral trochlea. *Trochlea* is the term for an anatomic structure that resembles a pulley. The patella slides up and down in the groove during knee extension and flexion. The femoral condyles articulate with the superior surface of the tibia and tibial condyles.

The Tibia

The proximal end of the tibia expands into the medial and lateral condyles. Together they make up approximately three-quarters of the proximal tibial surface, and their integrity is important for normal knee alignment, stability, and motion. The plateau normally slopes 10 degrees from anterior to posterior.

The intercondylar eminence, or tibial spine, is the central portion of the proximal tibial surface. The spine has two prominences, the medial tubercle and lateral tubercle. The medial tubercle is larger and more anterior. Two intercondylar fossae are present on the proximal tibial surface, one anterior and one posterior to the intercondylar eminence. The anterior cruciate ligament (ACL) and anterior horns of the medial and lateral menisci attach in the anterior intercondylar fossa. The posterior cruciate ligament (PCL) and posterior horns of the menisci attach in the posterior intercondylar fossa. The tibia is anchored to the femur by four strong ligaments, the ACL, PCL, medial collateral ligament (MCL), and lateral collateral ligament (LCL).

Cruciate Ligaments (ACL and PCL)

The cruciate ligaments are so named (Latin *crus,* meaning "cross") because they cross each other between their attachments. They are the primary stabilizers for anterior and posterior displacement of the tibia on the femur. The ACL arises from the medial surface of the lateral femoral condyle and inserts on the anterior surface of the tibial plateau within the tibial intercondylar notch. The ACL prevents excessive

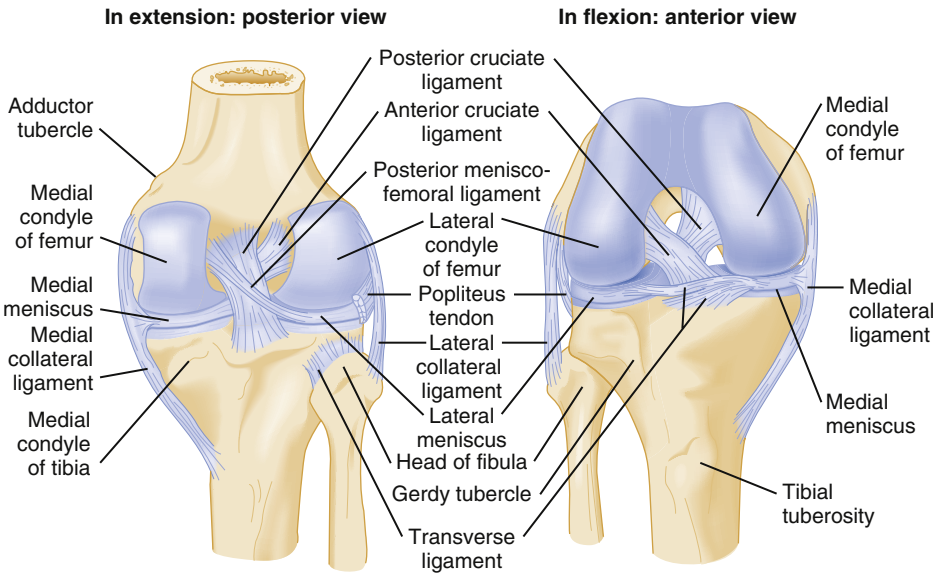

Fig. 48.1 Posterior and Anterior Views of the Right Knee.

anterior displacement of the tibia on the femur and helps to control rotation and hyperextension of the knee during twisting and turning activities. *It is the most commonly injured major ligament of the knee.*

The PCL originates from the medial femoral condyle and inserts on the posterior surface of the tibial plateau within the intercondylar notch. The PCL prevents excessive posterior displacement of the tibia on the femur, especially during flexion. The PCL is considerably stronger than its anterior counterpart and is thus less frequently injured than the ACL. The cruciate ligaments have a rich blood supply, and injury typically results in a hemorrhagic knee effusion.

Collateral Ligaments (MCL and LCL)

The medial stabilizers of the knee include the joint capsule, MCL, and the semimembranosus and pes anserinus. These structures resist valgus laxity and medial rotary instability. Like the ACL and PCL, the MCL is made up of two distinct entities, the long superficial fibers and the deep capsular fibers. The MCL originates from the medial femoral condyle and inserts onto the medial tibia. The deep capsular bundle inserts at the medial meniscus, further stabilizing this structure.

Lateral knee stability is anatomically similar to the medial aspect of the knee, with the LCL and the lateral joint capsule serving as the main restraints to varus deformity. The LCL originates from the lateral femoral condyle and inserts onto the fibula. Additional stability is provided by the iliotibial (IT) band, the biceps tendon, and portions of the posterolateral corner, particularly the popliteus tendon. Resistance to varus stress is provided mainly by the LCL. The lateral ligaments are under tension during standing and walking, when they are at or near maximal extension.

Knee Compartments

Functionally, the knee joint can be divided into three compartments—patellofemoral, medial tibiofemoral, and lateral tibiofemoral. These compartments, defined anatomically by the articulation of the bones, are contained within the same joint capsule. The patellofemoral compartment, located anteriorly, contains the quadriceps tendon, which envelops the patella, continues inferiorly as the patellar tendon, and inserts on the tibial tubercle. The fibers of the medial and lateral retinacula are found on either side of the patella, originating from the vastus medialis and vastus lateralis.

The medial tibiofemoral compartment is located on the medial aspect of the knee and consists of the medial femoral condyle, concave medial tibial condyle (plateau), medial meniscus, MCL, adductor tubercle, and pes anserinus.

The lateral tibiofemoral compartment encompasses the lateral half of the knee joint and includes the lateral femoral condyle and epicondyle, lateral tibial condyle (plateau), LCL, lateral meniscus, and popliteus tendon. The fibular head can be palpated posterolaterally and inferiorly to the joint line but is not usually considered a structure of the lateral tibiofemoral compartment.

Fabella

The fabella, present in some patients, is a sesamoid bone located in the lateral head of the gastrocnemius muscle and should not be mistaken for an intra-articular loose body or fracture fragment.

Popliteal Fossa

A hollow in the posterior aspect of the knee, the popliteal fossa is bound laterally by the biceps femoris tendon, medially by the semimembranosus and semitendinosus muscles, and inferiorly by the two heads of the gastrocnemius muscle. Found within the popliteal space are the popliteal artery, popliteal vein, and peroneal and tibial nerves.

Popliteal Artery

The popliteal artery is the continuation of the femoral artery beyond the adductor hiatus. It descends across the posterior aspect of the knee joint and terminates at the level of the tibial tubercle, where it divides into the anterior and posterior tibial arteries. The peroneal artery then branches from the posterior tibial artery. Together, the three arteries are termed the *trifurcation of the popliteal artery.* The popliteal artery is anchored firmly at the proximal and distal ends of the popliteal fossa, which explains the high incidence of arterial injury with knee dislocations. Blood supply to the knee joint comes from the popliteal artery by way of the geniculate arteries.

Tibial Nerve

The tibial nerve, along with one of its branches, the common peroneal nerve, is responsible for innervation of the knee. The tibial nerve joins the artery and vein in the popliteal fossa. The common peroneal nerve wraps around the head of the fibula and continues inferiorly as the deep and superficial peroneal nerves. Common peroneal nerve injury may occur in association with tibiofemoral dislocation

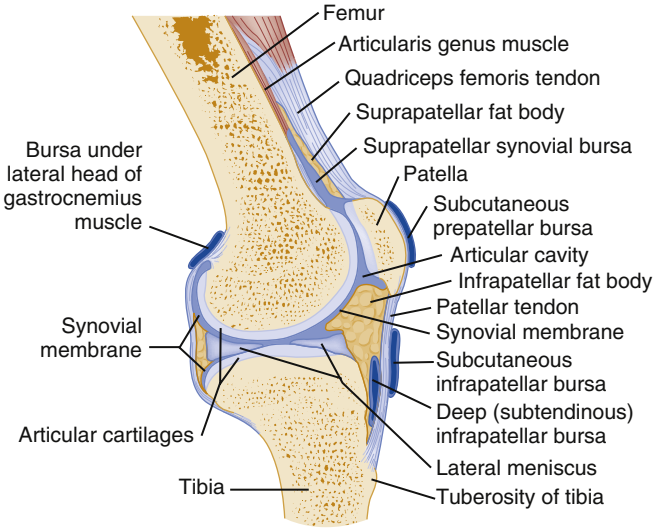

Fig. 48.2 Parasagittal section (lateral to midline) of the knee showing extensor mechanisms and relevant structures.

or injury to the head of the fibula or may be caused by prolonged compression.

Extensor Mechanism

The quadriceps muscles, quadriceps tendon, medial and lateral retinacula, patella, patellar tendon, and tibial tubercle comprise the extensor mechanism of the knee (Fig. 48.2). The patella is the largest sesamoid bone in the body. It is held in place by the quadriceps tendon, patellar tendon, and medial and lateral retinacula. As an integral part of the extensor mechanism, the patella increases the effective lever mechanism of the quadriceps by providing anterior displacement of the quadriceps tendon. The quadriceps tendon is a continuation of the quadriceps femoris muscle, which consists of the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius, which extend the knee.

Meniscus

The medial and lateral menisci are crescent-shaped fibrocartilaginous cushions that sit on the superior articular surface of the tibia and provide a gliding surface for the femoral condyles. They function as shock absorbers and aid in the distribution of stress across the joint surface by providing a larger area of contact. They also act as secondary stabilizers by deepening the tibial plateau. Normal tibiofemoral articulation and function depend on meniscal integrity. Meniscal damage or loss may lead to osteoarthritis. The medial meniscus is firmly attached anteriorly and posteriorly to the joint capsule. The lateral meniscus is less firmly attached to the capsule and more mobile. The menisci move slightly forward with extension and backward with flexion. Because of its greater mobility, the lateral meniscus is less vulnerable to injury. The meniscus is avascular except at the peripheral third, which has the greatest potential to heal after injury.

The Iliotibial band

The IT band is a fascial bundle that originates on the iliac crest and inserts on the lateral tibial tubercle. It connects the lateral femoral condyle and lateral tibia and stabilizes the knee joint in extension.

The Popliteus

The popliteus is a small flat muscle that originates on the lateral femoral condyle and inserts on the posteromedial tibia, capsule, and lateral meniscus. It passes beneath the lateral head of the gastrocnemius. Its tendon is surrounded by a bursa that separates it from the fibular collateral ligament, femoral condyle, and capsule. Functionally, it prevents external rotation of the tibia and withdraws the lateral meniscus during flexion to prevent impingement between the femur and tibia. A third function, along with the quadriceps and PCL, is to stabilize the knee by preventing forward displacement of the femur on the tibia.

Bursae

The knee has several bursae, which decrease friction between moving structures. They usually are thin but, with repeated stress, may become thickened and fluid filled. The prepatellar bursa is located between the patella and skin. The superficial infrapatellar bursa is located between the tibial tubercle and skin. The deep infrapatellar bursa is located between the posterior margin of the distal part of the patellar tendon and anterior aspect of the tibia. The suprapatellar bursa is not a true bursa but rather is an extension of the tibiofemoral joint capsule. Therefore it expands in conditions that cause knee effusion. The prepatellar bursa is anterior to the patella and does not communicate with the tibiofemoral joint.

The anserine bursa separates the pes anserinus from the distal portion of the MCL and medial tibial condyle. Pes anserinus means "goose foot" and anserine means "related to the pes anserinus." The term *pes anserinus* derives from the fact that the bursa underlies the anserine tendon, a three-forked structure constituting the insertion of the gracilis, sartorius, and semitendinosus muscles.

KNEE INJURIES—CLINICAL FEATURES

The initial assessment of a painful knee includes a history and physical examination. On history, immediate deformity noted by the patient, hemarthrosis, or instability after a traumatic injury suggests an intraarticular fracture, cruciate ligament injury, vascular injury, or dislocation. A complaint of giving way may indicate instability or involuntary muscle inhibition secondary to pain. This is a nonspecific symptom and may be reported in association with arthritis or patellofemoral disorders when inhibition of quadriceps function occurs in association with episodic pain.

The knee examination should be focused on specific locations of tenderness to palpation, visible deformity, abnormalities in range of motion (ROM), stability of the joint, and signs of external trauma such as effusion and ecchymosis, in addition to signs of infection such as warmth, swelling, erythema and purulent drainage. The femur, hip, and tibia should also be examined as pain from injuries to these regions may be referred to the knee. Patients with radiculopathy of the third, fourth, or fifth lumbar roots also may report knee pain. Children with a slipped capital femoral epiphysis, toxic tenosynovitis, toddler's fracture, or septic hip frequently complain of knee pain as well.

Physical Examination

Proper examination of the knee requires the patient to be supine, with both legs exposed. Examination of the knee begins with visual inspection (Box 48.1), followed by palpation. On initial inspection, localized swelling should be distinguished from the presence of a joint effusion. If a large joint effusion is present, the patella is elevated from the femur by fluid. Loss of the medial peripatellar concavity may be the only sign of a small knee effusion. Swelling in the prepatellar bursa or infrapatellar bursa, termed bursitis, is found just beneath the skin, superficial to or just inferior to the patella, respectively. Bursitis should not be confused with a knee effusion, because they have different etiologies and treatments.

Inspection should also include assessing for erythema of the joint, which may suggest an inflammatory or infectious process. Obvious deformities or open wounds should also be noted during visual

BOX 48.1 Examination of the Knee

1. Assess neurovascular integrity of the foot.
2. Determine whether a knee effusion is present, and assess for gross deformity or open wounds.
3. Identify signs of infection—redness, warmth, and effusion out of proportion to mechanism of injury.
4. Localize tenderness.
5. Assess for range of motion, stability, and the integrity of the extensor mechanism.

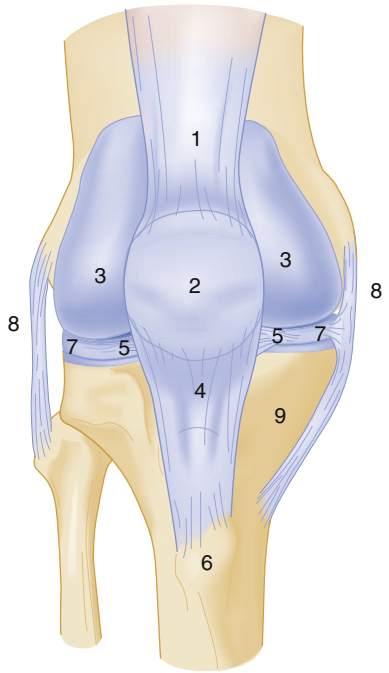

Fig. 48.3 Sites for Palpation of Tenderness in the Knee. *1,* Quadriceps tendon injury; *2,* prepatellar bursitis, patella pain; *3,* retinacular pain after patella subluxation; *4,* patella tendon injury; *5,* fat pad tenderness; *6,* tibial tubercle pain as in Osgood-Schlatter, but also consider tibial plateau fracture in the right setting; *7,* meniscus pain or arthritis; *8,* collateral ligament pain; *9,* pes anserine tendinitis-bursitis. (Adapted from Cailliet R. Knee pain. In *soft tissue pain and disability*. 3rd ed. Philadelphia: FA Davis; 1976:411.)

assessment. The posterior aspect of the knee should be examined for fullness.

After inspection, palpation of the knee should be performed (Fig. 48.3). The bony prominences of the knee (patella, tibia, fibula) should be palpated to assess for fracture or overuse injuries. The quadriceps tendon and the patellar tendon should be palpated for palpable defects that might suggest tendon rupture. The joint line should be palpated for tenderness. The posterior aspect of the knee should be palpated for tenderness or palpable defects. The vascular integrity of the knee should be assessed with the dorsalis pedis (DP) and posterior tibial (PT) pulses in the foot.

Accurate diagnosis of knee injuries based on examination alone is challenging in the acute phase because of pain and swelling. Thus the main goals are to relieve pain, ensure proper location and stability of the joint, assess for neurovascular injury, determine the need for radiography, and identify infections and inflammatory conditions.

A number of maneuvers have been developed to aid the emergency clinician in diagnosing ligamentous and meniscal injuries using only the physical examination (see later). However, interpretation of these maneuvers is limited by pain, splinting, or effusion and has been found to be variably accurate when compared with magnetic resonance imaging (MRI) or arthroscopy findings. Accuracy of these maneuvers is improved if they are done after pain and swelling have resolved. The primary goals in emergency care are to identify whether fracture, dislocation, or vascular injury is present, ensure weight-bearing status, and refer for reevaluation by a primary care provider or orthopedist in a timely manner.

TABLE 48.1 Differential Diagnoses for Various Knee Injuries

Injury	Differential Diagnostic Conditions
Knee dislocation	Patellar dislocation, distal femur fracture, tibial plateau fracture
Distal femur fracture	Tibial plateau fracture, knee dislocation, quadriceps tendon rupture
Tibial plateau fracture	Distal femur fracture, knee dislocation, patellar fracture, patellar dislocation, tibial spine fracture, patellar tendon rupture
Tibial spine fracture	Tibial plateau fracture, patellar tendon rupture, anterior cruciate ligament (ACL) injury
Osteochondritis dissecans	Distal femur fracture, tibial plateau fracture, meniscal injury
Osteoarthrosis	Distal femur fracture, tibial plateau fracture, meniscal injury, chronic ACL deficiency, osteochondritis dissecans
Injury	**Differential Diagnostic Conditions**
Quadriceps/patellar tendon injury	Patellar fracture, patellar dislocation, distal femur fracture, tibial spine fracture, tibial plateau fracture
Patellar fracture	Patellar dislocation, quadriceps/patellar tendon rupture
Patellar dislocation	Patellar fracture, quadriceps/patellar tendon rupture
Cruciate ligament injury	Meniscal injury, collateral ligament injury, distal femur fracture, tibial plateau fracture, tibial spine fracture
Collateral ligament injury	Posterolateral corner injury, meniscal injury, cruciate ligament injury, distal femur fracture, tibial plateau fracture
Meniscal injury	Collateral ligament injury, cruciate ligament injury, osteochondritis dissecans, distal femur fracture, tibial plateau fracture
Overuse syndromes	Cruciate ligament injury, collateral ligament injury, osteochondritis dissecans

KNEE INJURIES—DIFFERENTIAL DIAGNOSES

Differential diagnoses for patients presenting with knee pain is vast and varies depending on history as well as location of pain. Tenderness in specific regions can be suggestive of different etiologies (see Fig. 48.1 and Table 48.1). Focal bony tenderness in the absence of x-ray findings should raise suspicion for a stress fracture or occult traumatic fracture depending on history. Associated fractures of the femoral neck, hip dislocation, and acetabular fractures should always be considered in traumatic knee pain as well.

Dislocation

A patient presenting with a history of self-reduced knee "dislocation" may have suffered an actual knee dislocation or a patellar dislocation.

It is imperative to clarify both the mechanism of injury and what the patient observed to ascertain whether the patella or knee was dislocated, because these two diagnoses have very different management but may self-reduce prior to arrival.

Effusion

Differential diagnoses for patients presenting with a large effusion in the setting of trauma include a distal femur fracture, an ACL or a PCL injury, dislocation, and a tibial plateau or spine fracture. Examination in these patients is often difficult, so the mechanism of injury as well as the location of tenderness and x-ray findings may help the clinician to differentiate between these entities. An atraumatic knee effusion commonly results from osteoarthritis. A focused history and physical examination are important as the differential diagnoses includes insufficiency fracture, septic arthritis, inflammatory arthritis (e.g., gout), hemarthrosis or lipohemarthrosis from occult fracture, avascular necrosis, a ruptured Baker cyst, or possible malignancy. Arthrocentesis may be used for diagnosis.

Anterior Knee Pain

Patellofemoral pain is one of the most common causes of anterior knee pain in children and adults but is usually not associated with bony tenderness. Tenderness over the tibial tubercle in a pediatric patient may indicate Osgood-Schlatter disease, but underlying fracture should be considered in the setting of acute trauma. In an adolescent, pain along the femoral or tibial epiphysis after trauma may represent a Salter-Harris type I fracture, a fracture through the physis. Tibial tenderness in an adult may suggest a tibial plateau fracture.

Gradual-onset pain over the anterior femoral condyle in pediatric patients should raise suspicion for osteochondritis dissecans (OD). The anterior knee should also be inspected for any sign of septic or aseptic bursitis over the prepatellar bursa. Acute onset, traumatic pain over the anterior aspect of the knee should raise suspicion for an extensor mechanism injury, such as patellar tendon rupture, quadriceps tendon rupture, or patellar fracture. A straight leg raise is useful in assessing the integrity of the extensor mechanism. More insidious onset of pain over the patellar or quadriceps tendon may be more suggestive of tendinitis.

Medial and Lateral Pain

Acute-onset medial or lateral joint line pain after a twisting mechanism should raise suspicion for a meniscus injury. Differential diagnoses for meniscal tears are extensive and include loose bodies, osteochondrotic lesions, and tibial fractures. Medial knee pain is also seen with medial tibial stress fractures, proximal medial tibial stress syndrome (MTSS), pes anserine bursitis/tendinopathy, or MCL strain. Lateral knee pain is typically associated with LCL strain, IT band dysfunction, popliteal tendinitis, or proximal fibular stress fracture.

Posterior Knee Pain

Baker cysts are a common cause of posterior knee pain. However, differential diagnoses should include a deep vein thrombosis (DVT), hamstring injury, or popliteal artery pseudoaneurysm.

KNEE INJURIES—EXAMINATION MANEUVERS

Anterior Drawer/Lachman Test

The anterior drawer test seeks to identify tears of the ACL. The test is performed with the patient in a supine position, hip flexed at 45 degrees, and knee flexed at 90 degrees. While stabilizing the patient's foot, the examiner places his or her thumbs over the joint line while pulling the tibia forward. The thumbs are used to palpate for any translation of the tibia relative to the femur. A positive test result is defined as greater anterior translation of the tibia relative to the femur as compared with the other knee. The test is poorly sensitive but fairly specific. *The Lachman test* is a more accurate test for ACL injuries, with a high sensitivity and specificity. The Lachman test is done with the knee flexed 20 to 30 degrees while the examiner uses one hand to grasp and stabilize the femur. The tibia is then pulled anteriorly, and the examiner notes tibial excursion. The examiner records "firmness" or a "soft end point." The end point can be graded as 1+ (0 to 5 mm more displacement than on the normal side), 2+ (5 to 10 mm), or 3+ (>10 mm). The PCL must be intact for the test results to be valid.

Posterior Drawer Test

The posterior drawer test assesses for PCL injury. The posterior drawer test can be accomplished with the patient's knee flexed at 90 degrees and the foot stabilized by the examiner. A smooth backward force is applied to the tibia. Posterior displacement of the tibia more than 5 mm, or a soft end point, indicates injury to the PCL. The posterior drawer test result may be positive in only 85% of patients with PCL insufficiency documented operatively. The affected knee should be compared with the normal knee because patients may have increased laxity at baseline.

Posterior Sag Sign Test

The posterior sag sign test is a second method of determining PCL integrity. Sensitivity in the acute phase is 79%. To perform this test, the patient is placed in a supine position, and a pillow is placed under the distal thigh for support while the heel rests on the stretcher. The knee is flexed to 45 or 90 degrees. If the tibia sags backward, the test result is considered to be positive, indicating PCL insufficiency. It is possible to obtain a false-positive result on the anterior drawer test if the examiner fails to recognize the posterior sag sign, as the tibia will translate forward across the femur simply because its starting position is more posterior. Posterior sag also may be appreciated during passive elevation of the leg in a fully extended position, with the examiner applying the elevating force at the ankle. As the leg is elevated, the tibia may fall back on the femur if the PCL is ruptured.

Collateral Ligament Stress Test

The collateral ligament stress test is used to test the integrity of the MCL and LCL. With the patient lying supine, the examiner applies varus and valgus stress with the knee at 0 and 30 degrees of flexion. Joint line opening is the amount of movement produced between the tibia and femur; this can be palpated and estimated in millimeters. The normal knee should be subjected to the same amount of valgus and varus stress; the joint line opening is then compared with that in the injured knee. Isolated collateral ligament tears are detected only with the knee in slight flexion because, in extension, the cruciate ligaments, capsule, and lesser ligaments of the knee provide significant lateral stability. Laxity in full extension implies complete collateral ligament tear and also injury to the cruciate ligaments or other structures. Laxity may be graded as grade I (some laxity), grade II (marked laxity), and grade III (total laxity).

Assessing for Meniscal Tears

McMurray Test

The McMurray test is used to help identify meniscal tears. The patient is placed in a supine position with the knee hyperflexed. The examiner grasps the foot with one hand and the knee with the other. The

examiner flexes and extends the knee while simultaneously internally and externally rotating the tibia on the femur and providing slight varus and valgus stress. A positive test is the occurrence of clicking palpable along the joint line, pain, or locking of the knee.

Apley Test

This test also aids in diagnosing meniscal tears. With the patient prone, the knee is flexed to 90 degrees, and the leg is internally and externally rotated with pressure applied to the heel. Pain elicited by downward pressure suggests meniscal pathology. The pain should be relieved with distraction of the knee and rotation of the leg back to a neutral position. Although relatively specific, the Apley test is not sensitive.

KNEE INJURIES—DIAGNOSTIC TESTING

Radiologic Evaluation

X-rays can be used to assess for radiopaque foreign bodies, subluxation, dislocation, fracture, and joint space narrowing. Note that on a straight anteroposterior (AP) view, the anterior and posterior portions of the normal tibial plateau may not appear to be at the same level.

Some plain film findings may be suggestive of ligamentous injuries as well. An effusion can be seen as a radiolucent area (with density similar to that of fat) distending the joint capsule. The presence of a linear interface between two different densities within an effusion suggests *lipohemarthrosis* (Fig. 48.4), in which the effusion contains not only blood but also fat. This feature results from the entry of marrow fat into the joint cavity and is suggestive of fracture.

Clinical decision rules help to decrease unnecessary radiography. The Ottawa Knee Rules and the Pittsburgh Knee Rules are the most commonly used (see Table 48.2). Patients meeting any listed criteria should have knee x-rays performed. The Ottawa Knee Rules are meant to be applied only to acute injuries (<7 days old).

When the two rules are compared, both are more than 95% sensitive, but the Pittsburgh rule may be more specific, allowing fewer radiographs to be done without sacrificing sensitivity. Compliance with knee rules is poor in academic emergency departments (EDs) for various reasons. We recommend considering the use of either decision rule as support in evaluating patients with knee pain in the ED. However, neither rule is meant to supersede clinical judgment, because neither rule is 100% sensitive or specific for fracture.

In the evaluation of knee trauma, knee x-rays should include a standard AP, lateral, and "sunrise" view. Tunnel views, which image the intercondylar notch, are used to detect tibial spine fractures and loose bodies within the notch. Oblique views can be helpful in identifying tibial plateau fractures. Sunrise views are essential in evaluating for patellar fractures.

Because the sensitivity of radiographs for acute knee injuries is low, we recommend computed tomography (CT) or knee immobilization and urgent orthopedic referral reevaluation when fracture is suspected and plain films are negative. MRI may also be used to detect fractures and is the imaging gold standard (comparable with arthroscopy findings) for soft tissue injury but is rarely indicated in the evaluation of knee and leg trauma in the ED.

Vascular Imaging

CTA has largely replaced catheter-based angiography in assessing for popliteal artery injury after knee dislocations because it carries less risk without sacrificing a high sensitivity and specificity in detecting arterial injury. MR angiography and duplex ultrasonography can also be used for evaluation of the popliteal artery after tibiofemoral dislocation, but their roles in the ED setting are less well defined.

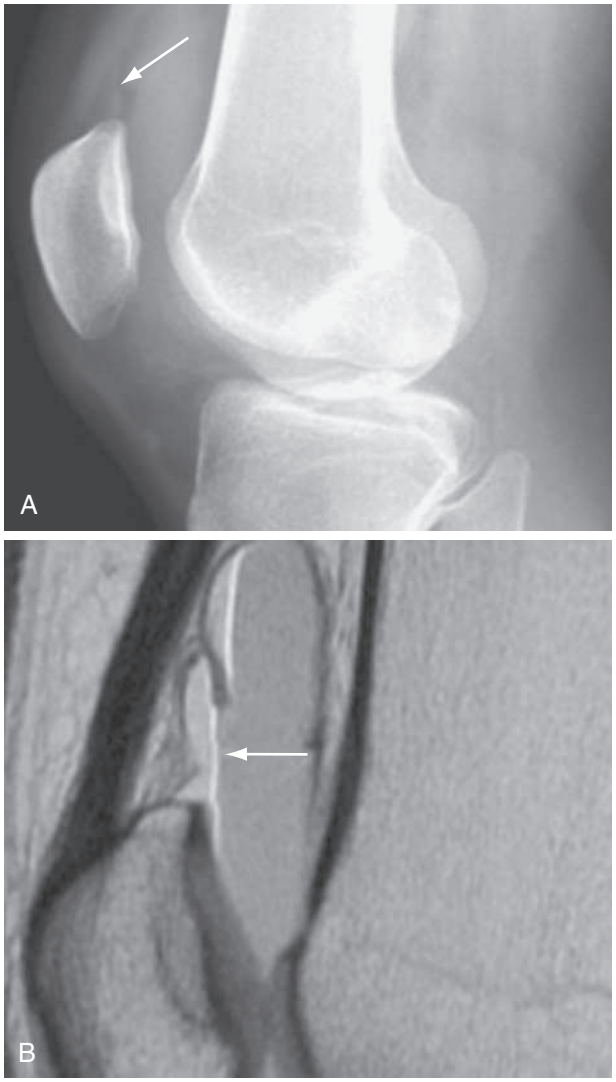

Fig. 48.4 Lipohemarthrosis. (A) Lateral plain film of the knee of a young woman with a nondisplaced patella fracture. The only radiographic abnormality is an effusion that contains a linear interface *(arrow)* between two soft tissue densities, suggesting lipohemarthrosis. (B) Magnetic resonance imaging scan from the same patient shows plainly the presence of blood and fat in the effusion *(arrow).* The nondisplaced patella fracture is not seen.

TABLE 48.2 Clinical Decision Rules for Knee Injury

Ottawa Knee Rules	Pittsburgh Knee Rules
Age >55	Age <12 or >50
Isolated patellar tenderness	Inability to walk 4 steps
Isolated fibular head tenderness	
Flexion <90 degrees	
Inability to weight bear 4 steps immediately after injury or in the emergency department	
98.5 sensitivity, 49% specificity	100% sensitivity, 79% specificity

Arthroscopy

Arthroscopy is a nonemergent but useful modality in the diagnosis and treatment of knee injuries, including injuries of the meniscus, cruciate

ligaments, articular cartilage, capsule, and synovium. Arthroscopy is superior to MRI for the diagnosis of meniscal tears and other soft tissue injuries, and the diagnosed problem can be repaired immediately. The need for arthroscopy need not be determined in the emergent setting as long as appropriate and timely referral to an orthopedist is made.

Joint Injection

An open joint is considered a surgical emergency. When violation of the joint capsule is suspected but not obvious, studies suggest that CT imaging performs better than the sterile saline load test in identifying traumatic knee arthrotomies. The sterile saline load test involves the injection of 200 mL of sterile saline into the joint capsule while observing the laceration to see if the saline emerges from the laceration. Methylene blue has not been shown to be more accurate than saline, can interfere with arthroscopy, and may cause an inflammatory reaction; therefore it is not advised. For open joints, we recommend orthopedic consultation, emergent antibiotics, and CT imaging to confirm diagnosis. Of note, there is mounting literature that CT imaging is sensitive for an open joint and less painful than infusing a saline load into the involved joint.

Arthrocentesis

Aspiration of fluid from the knee joint can be diagnostic as well as therapeutic by reducing pressure from an effusion. Arthrocentesis may be performed if the injured knee is greatly distended with a tight effusion and can be useful to perform if the cause of the joint effusion is unclear. Analysis of the aspirate can differentiate simple effusion, hemarthrosis, lipohemarthrosis, rheumatologic conditions, and septic arthritis and often provides significant relief of pain for the patient. *Arthrocentesis should be avoided in the setting of overlying cellulitis*.

SPECIFIC KNEE INJURIES

Knee Dislocations—Foundations

Knee dislocation refers to tibiofemoral dislocation and should not be confused with patellofemoral dislocation, a relatively minor injury. Knee dislocation is a limb-threatening emergency due to the risk of popliteal artery injury. Knee dislocations are always associated with significant ligamentous injury. The joint capsule is disrupted, with accompanying trauma to the muscles and tendons. Injury to the popliteal artery is the most severe complication and is the primary cause of morbidity and limb loss.

Knee dislocation is relatively uncommon but should be considered in the setting of an appropriate injury mechanism because many dislocations spontaneously reduce before the patient arrives in the ED. Importantly, reduction before ED arrival does not lessen the likelihood of vascular injury, and these patients should be evaluated for vascular injury, particularly if the patient is obese, has an associated distracting injury, or if the injury involved in a high-energy mechanism.

The neurovascular bundle, which is composed of the popliteal artery, popliteal vein, and common peroneal nerve, runs posteriorly behind all bony and ligamentous structures in the popliteal fossa. The popliteal artery is fixed in the fibrous tunnel of the adductor magnus hiatus proximally and traverses the fibrous arch of the soleus and interosseous membrane distally. In essence, it is tethered to the femur and tibia, and its inherent immobility renders it susceptible to injury during dislocation. Because of the parallel course of the popliteal vein and peroneal nerve, they are often injured simultaneously.

Anatomically, dislocations are described according to the displacement of the tibia relative to the femur. They are classified into five types—anterior, posterior, medial, lateral, and rotary. Most knee dislocations are anterior and result from hyperextension. Posterior dislocations are the second most common type and usually result from high-velocity direct trauma to the flexed knee, often in association with vehicular trauma (e.g., automobile dashboard impact).

Knee Dislocations—Clinical Features

The diagnosis of knee dislocation is based on the mechanism of injury and clinical and radiographic findings. When a dislocation is present and has not reduced spontaneously, it is usually clinically obvious. However, there may be no effusion after reduction because the ruptured capsule allows blood and joint fluid to escape into the thigh and leg.

Popliteal artery injury most commonly occurs with posterior dislocations. The collateral geniculate arteries around the knee also may be damaged directly or may be secondarily compressed by hematoma formation after the dislocation. Direct arterial injury, decreased collateral circulation, and elevated compartment pressures all may compromise limb perfusion.

Findings associated with peripheral vascular injury and management approaches are described in Chapter 40. The PT and DP pulses should be evaluated, but popliteal artery injury may still be present in some patients with palpable pulses.

Isolated intimal tears are not detectable on physical examination and are seen only angiographically or with duplex ultrasound. Although these tears are usually managed nonoperatively, a vascular surgeon should be consulted when identified. Injuries to small branches of the popliteal artery can be managed by observation and serial examinations.

As with all limb injuries, neurologic integrity should be assessed and documented. The peroneal nerve is at risk for injury, especially in posterolateral dislocations. Peroneal nerve function is evaluated by determining sensation of the dorsum of the foot and by having the patient dorsiflex the ankle. Less commonly, the posterior tibial nerve may be injured, which causes diminished plantar sensation and inability to flex the foot. Complete nerve palsy in the acute setting is associated with a poor prognosis for recovery.

Delayed complications associated with traumatic knee dislocations include DVT, compartment syndrome, pseudoaneurysm, and arterial thrombosis. Compartment syndrome may develop within 24 to 48 hours of the initial injury. Pseudoaneurysms are rare but may form several hours to months after popliteal artery injury. Heterotopic ossification is a poorly understood syndrome of calcification of the soft tissues of the knee. It has been observed in uninjured knees of patients who have sustained major trauma. In its most severe form, heterotopic ossification can cause severe decrease in knee mobility. Almost half of dislocated knees are found to have subsequent heterotopic ossification.

Knee Dislocations—Diagnostic Testing

The diagnostic evaluation begins with an understanding of two crucial facts. First, half of all tibiofemoral dislocations are reduced before presentation, and injury to the popliteal artery should be assumed with tibiofemoral dislocation regardless of spontaneous reduction. Therefore the diagnostic strategy is applied to all patients with known knee dislocation, multiligament knee injury, or high-force trauma to the knee. The intubated or unresponsive multitrauma patient with ecchymosis around the knee may harbor an occult popliteal injury.

Popliteal artery injury can be assessed by measurement of the ankle-brachial index (ABI) with serial physical examinations, CTA, and duplex ultrasonography. Formal angiography is rarely used. Of note, increased body mass index (BMI) is associated with a greater risk

of vascular injury after knee dislocations.[1] Serial palpation of the pedal pulses is not sufficiently sensitive for an injury with such potentially devastating consequences. Adding measurement of the ABI improves sensitivity. The ABI is the ratio of the systolic blood pressure measured in the standard humeral location relative to the systolic pressure measured at the ankle. An ABI more than 0.9 has a negative predictive value for popliteal artery injury, approaching 100% in knee dislocation. There is recent evidence that palpable dorsalis pedis and posterior tibial pulses combined with an ABI of 0.9 or greater is 100% sensitive in detecting clinically relevant popliteal artery injuries after knee dislocations[2]; however, the diagnostic strategy depends on the patient's presentation. In a patient with hard signs of vascular injury (see Table 48.3), emergent surgical exploration is warranted. If the patient has asymmetric pulses or distal pulses are present but ABI is less than 0.9, then CTA is warranted. If the distal pulses are both present and ABI is greater than 0.9, we advise admission for serial neurovascular examinations every 3 to 4 hours for at least 24 hours.[2] An algorithm for management is depicted in Fig. 48.5.

TABLE 48.3 Hard and Soft Signs of Vascular Injury

Hard Signs of Vascular Injury	Soft Signs of Vascular Injury
Lack of distal pulses	Decreased pulse relative to uninjured side
Palpable thrill	
Pulsatile hemorrhage	Significant hemorrhage at time of injury
Expanding hematoma	Nonexpanding hematoma
The classic 5 Ps (pain, pallor, paresthesia, poikliothermia, paralysis)	Peripheral nerve deficits

Knee Dislocations—Management and Disposition

The dislocated knee should be reduced at the earliest opportunity during the secondary survey. The neurovascular status documented before and after reduction. For patients being transferred from a nontrauma center to a trauma center, reduction should be attempted prior to transfer. Reductions usually can be accomplished with simple traction-countertraction, almost always requiring procedural sedation in the alert patient. Lateral pressure may be required. For an anterior dislocation, the femur can be pushed posteriorly while the tibia is pulled anteriorly, with special care taken not to apply undue pressure to the popliteal fossa. Posterolateral dislocations may not be reducible because the medial femoral condyle and MCL may secure the dislocated joint in place, in which case emergent open reduction in the operating room is indicated. Because many reductions are unstable, the limb should be immobilized in a long leg posterior splint with the knee in 15 to 20 degrees of flexion after reduction; serial neurovascular assessments will be necessary, warranting admission.

Disability is minimized by expedient revascularization and primary arterial repair, and thorough wound débridement. Open joints require prophylactic antibiotics, such as intravenous (IV) cefazolin 2 g. If the neurovascular structures remain intact after dislocation, the knee joint

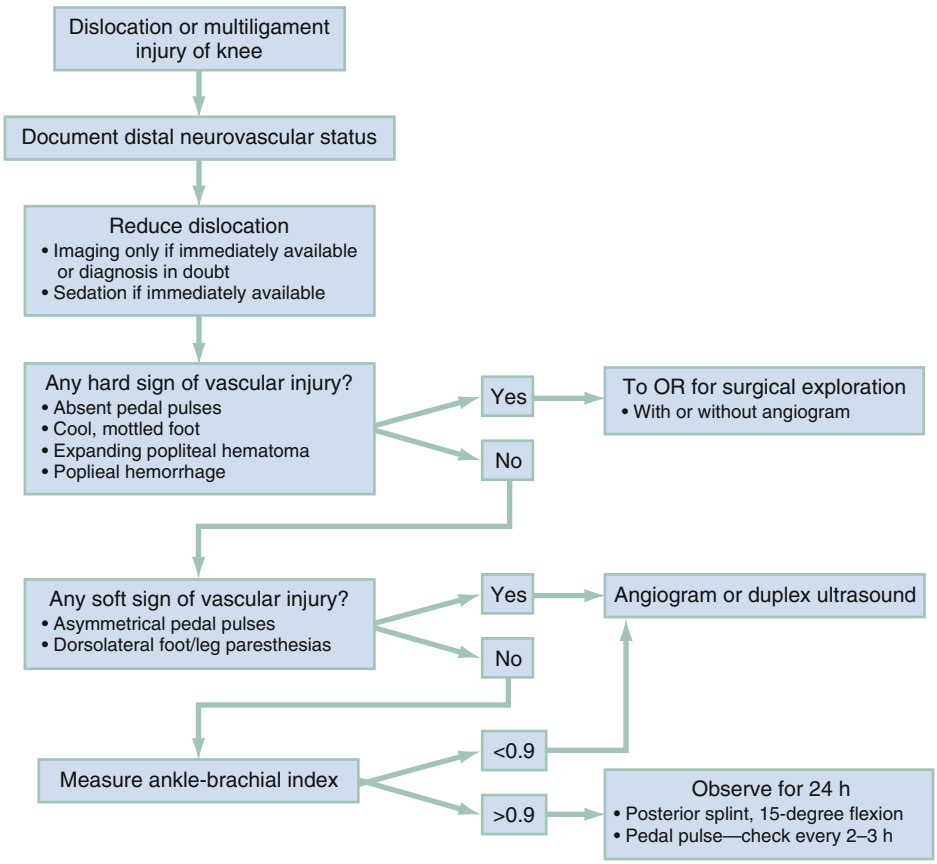

Fig. 48.5 Algorithm for the Management of Knee Dislocation. (From Nicandri GT, Dunbar RP, Wahl CJ. Are evidence-based protocols which identify vascular injury associated with knee dislocation underutilized? *Knee Surg Sports Traumatol Arthrosc.* 2010;18:1005–1012.)

is reduced, splinted, and allowed to rest for 2 to 3 days before reconstruction of the torn ligaments.

Distal Femur Fractures—Foundations

Distal femur fractures are uncommon and usually result from a high-energy mechanism. An isolated fracture of the femoral condyle may occur, or the fracture may extend in a T or Y pattern to include the intercondylar or supracondylar region of the femur. Condylar fractures are intraarticular and may result in disruption of the articular surface, with subsequent arthritis. See Chapter 47 for more detailed discussion of femoral shaft and proximal femur fractures.

Distal Femur Fractures—Clinical Features

Patients with condylar or intercondylar fractures have pain and swelling in the distal femur and suprapatellar region and often are unable to bear weight. Examination may reveal shortening, rotation, and angulation of the extremity and tenderness to palpation along the medial or lateral joint line. Acute hemarthrosis is common and may be caused by intra-articular extension of the fracture or associated ligamentous injury. Distal neurovascular status should be documented. Any laceration in the region of the fracture represents an open fracture until proven otherwise. Distal femur fractures may be associated with thrombophlebitis, fat embolus syndrome, delayed union or malunion if reduction is incomplete or not maintained. Intra-articular or quadriceps adhesions if the fracture is intraarticular, angulation deformities, and osteoarthritis, particularly in the patellofemoral articulation are some potential long-term complications.

Distal Femur Fracture—Diagnostic Testing

Routine AP and lateral views should be obtained and usually show the fracture pattern and any significant displacement of fragments. In high-energy injuries, radiographs of the ipsilateral hip and tibia are recommended to exclude associated fractures. Occasionally, CT imaging or MRI may be required to diagnose a nondisplaced fracture. If signs of vascular impairment are present, consultation for angiography or surgical exploration should be obtained emergently.

Distal Femur Fractures—Management and Disposition

Distal femur fractures are extremely painful. Ultrasound-guided femoral nerve blocks can be considered to reduce the need for opiates. After the initial examination, the leg should be splinted to prevent excessive motion and reduce pain at the fracture site. Emergent orthopedic consultation is advised. In a stable patient with an uncomplicated fracture dislocation, reduction may be done with skeletal traction, followed by immobilization. Intraarticular fractures generally are treated with open reduction and internal fixation. Virtually all patients with distal femur fracture require admission.

Tibial Plateau Fractures—Foundations

Tibial plateau fractures often are intra-articular. The most common mechanism of injury is a strong valgus force with axial loading. Severe high-energy tibial plateau fractures occur primarily in younger patients often after motor vehicle collisions (MVCs) or falls from heights. These fractures may be open and occur in concert with other associated injuries. Fatigue stress fractures of the tibial plateau occur mostly in older and obese adults. These low-energy fractures are the result of compression forces in osteoporotic bones.

The *Segond fracture* represents a bone avulsion of the lateral tibial plateau (Fig. 48.6). The avulsion occurs at the site of attachment of the lateral capsular ligament. On radiographs, an oval-shaped fragment can be seen adjacent to the lateral tibial plateau. Segond fractures are usually accompanied by ACL disruption. Most Segond fractures are caused by sports injuries; the mechanism is almost always knee flexion with excessive internal rotation and varus stress.

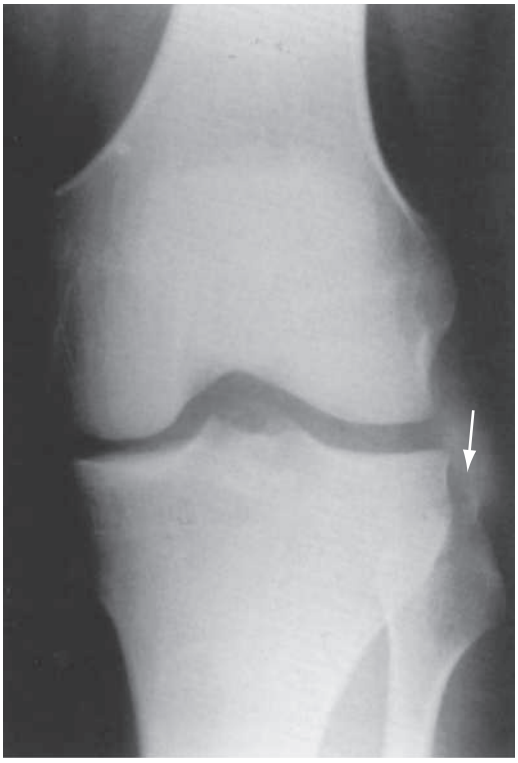

Fig. 48.6 Segond Fracture. Anteroposterior view of the left knee shows lateral curvilinear avulsion fracture *(arrow)* and joint effusion. (From Kerr HD. Segond fracture, hemarthrosis, and anterior cruciate ligament disruption. *J Emerg Med*. 1990;8:29–33.)

Tibial Plateau Fractures—Clinical Features

Tibial plateau fractures cause pain, tenderness, ecchymosis, soft tissue swelling, and hemarthrosis when intra-articular. A valgus or varus limb deformity may be present and usually indicates a depressed fracture or concomitant leg fracture. The most important aspect of the initial examination is assessment of neurovascular status. Many tibial plateau fractures cause vascular complications. The popliteal artery may be injured by fragments from bicondylar or comminuted fractures involving the subcondylar area. Displaced fractures of the lateral condyle may cause peroneal nerve paralysis or anterior tibial artery injury. Stretch of the peroneal nerve is the usual cause of injury. Ligamentous injuries frequently accompany tibial plateau fractures, most often involving the ACL and MCL. Of note, these patients are also at high risk for compartment syndromes.

Tibial Plateau Fractures—Diagnostic Testing

Lipohemarthrosis, seen as a fat-fluid level on a plain film, suggests an occult fracture and is caused by entry of marrow fat into the joint space (see Fig. 48.4). Lipohemarthrosis may also be detected on aspiration of a joint effusion. All knee radiographs should be examined closely for avulsion fragments from the fibular head, femoral condyles, and intercondylar eminence because these may indicate ligamentous injury. Widened joint spaces associated with a fracture of the opposite condyle also may indicate concomitant ligamentous injury.

CT imaging and MRI are more sensitive than plain radiography and quantify the amount of depression in displaced fractures and extent of articular surface involvement in comminuted fractures. In a patient with acute traumatic knee pain characterized by tibial tenderness to

palpation and inability to bear weight, a CT scan should be done to rule out fracture if x-rays are nondiagnostic.[3]

Tibial Plateau Fractures—Management and Disposition

All patients with a tibial plateau fracture should be referred for evaluation by an orthopedist, which often occurs with direct consultation in the ED. Absolute indications for emergent orthopedic consultation would include joint instability, open fracture, neurovascular compromise, and compartment syndrome. If orthopedic consultation is not obtained in the ED, acute fractures should be immobilized in a noncircumferential splint such as a knee immobilizer and the patient should not bear weight on the limb until evaluated by an orthopedist, preferably within the week. Patients should be given strict return precautions for compartment syndrome. Stable nondisplaced fractures may be treated with immobilization alone, but instability or significant depression or disruption of the joint surface requires surgical management. CT scanning is often required for surgical planning, even when indications for surgery are evident based on the clinical examination and x-ray.

Prolonged immobilization can result in DVT. Prophylactic treatment with low-molecular-weight heparin can reduce the risk of DVT but remains controversial. According to a Cochrane review,[4] there is moderate-quality evidence that low-molecular-weight heparin could reduce the incidence of DVT following immobilization of the leg. However, both the heparin and placebo groups exhibited a wide range of venous thromboembolism (VTE) across studies. A recent randomized controlled trial failed to show evidence that heparin reduced the incidence of VTE after casting of the lower leg.[5] Given the controversy surrounding this topic, we suggest that the decision to anticoagulate patients requiring lower limb immobilization be made on an individual basis after engaging in shared decision making with the patient and orthopedic specialist. Scoring systems have recently been developed to assist the physician in deciding whether to anticoagulate when immobilizing the lower extremity[6] but have not been externally validated.

Fractures of the Intercondylar Eminence (Tibial Spine)—Foundations

A fracture of the anterior tibial spine usually is associated with an ACL rupture. Tibial spine fractures are more common in children than in adults because the ligaments are stronger than the adjacent physeal plates in the immature skeleton. This fracture may be an isolated injury in the presence of open physes.

Most tibial spine fractures occur as a result of abrupt knee twisting, hyperflexion, hyperextension, or valgus-varus forces generated during MVCs or athletic activities. Tibial spine fractures occur by twisting knee movements, whereas hyperextension or hyperflexion forces may cause avulsion of the intercondylar eminence or cruciate ligaments from their tibial attachments.

Tibial Spine Fractures—Clinical Features

After a tibial spine fracture, the patient reports pain and swelling of the knee and may be unable to bear weight on the affected extremity. The examination confirms an acute hemarthrosis which may impair full knee extension. Tense effusion will limit ROM, hinder physical examination, and mask ligament disruption. ACL laxity is expected.

Tibial Spine Fractures—Diagnostic Testing

Radiographic evaluation should include standard AP and lateral views. A tunnel view provides a better look at the intercondylar area and may reveal the diagnosis. Joint margins should be examined closely for evidence of collateral ligament or capsular bone avulsions. CT scanning is sometimes required to show the location and displacement of the fracture.

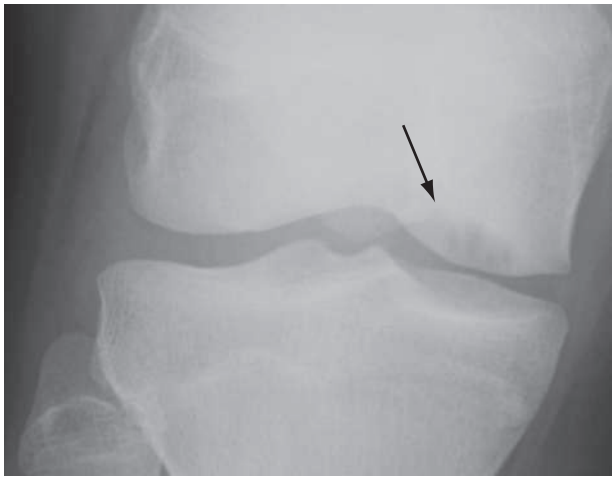

Fig. 48.7 Osteochondritis Dissecans. A subcortical radiolucency *(arrow)* is seen in the knee of an adolescent female with chronic medial knee pain.

Tibial Spine Fractures—Management and Disposition

The knee should be immobilized, and the patient should be given non–weight-bearing instructions and referred to an orthopedist within 3 to 7 days. Most patients are managed conservatively with good results, although some require surgical repair particularly when reduction cannot be achieved, or there is significant ligamentous disruption.

Osteochondritis Dissecans—Foundations

OD is a rare orthopedic disorder of unclear etiology (Fig. 48.7). The disorder is found mainly in adolescents. OD is characterized by a partial or total separation of a segment of articular cartilage and subchondral bone from the underlying bone. It is commonly unilateral, involving the non–weight-bearing lateral aspect of the medial femoral condyle and may be related to acute or chronic trauma, genetics, or ischemia.

Osteochondritis Dissecans—Clinical Features

Patients often have pain, swelling, and giving-way episodes.

Osteochondritis Dissecans—Diagnostic Testing

Routine radiographic views usually are diagnostic. A subcortical lucency (see Fig. 48.7) can be appreciated, and an osteochondral fragment may be seen separated from the underlying bone. Rarely indicated in the ED, CT or MRI may aid in determining the exact location and extent of the osteochondrotic lesion.

Osteochondritis Dissecans—Management and Disposition

ED patients with suspected OD should not bear weight on the affected extremity and should be instructed to limit their activity until seen by an orthopedist within 3 to 5 days.

Extensor Mechanism Injuries: Quadriceps and Patellar Tendon Ruptures—Foundations

Disruptions of the extensor mechanism may occur at any level, from the quadriceps muscle to the patellar tendon insertion on the tibial tubercle. Injury generally occurs as a result of sudden vigorous contraction of the quadriceps muscle with the knee in a flexed position, a laceration, or direct blow.

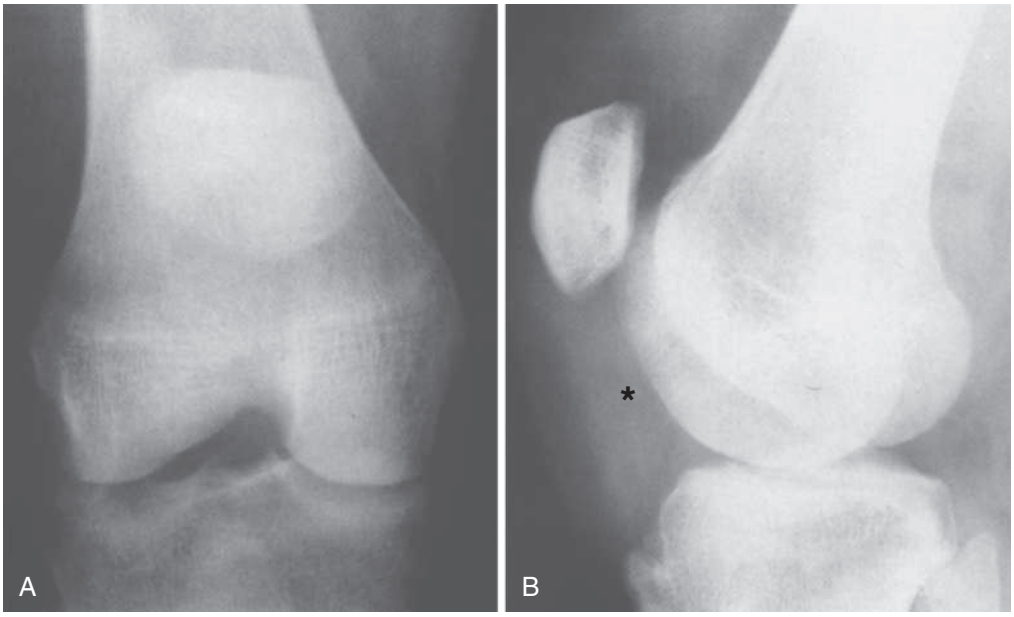

Fig. 48.8 Rupture of the patellar tendon, resulting in the high-riding patella in frontal (A) and lateral (B) projections. (B) The normally lucent infrapatellar portion of the joint space is dense *(asterisk),* representing blood within the anterior compartment. (From Harris JH Jr, Harris WH. *The radiology of emergency medicine.* 3rd ed. Baltimore: Williams & Wilkins; 1993.)

Chronic systemic conditions, including rheumatoid arthritis, gout, systemic lupus erythematosus, hyperparathyroidism, and iatrogenic immunosuppression in organ transplant recipients, may increase the risk of tendon rupture. Several studies have implicated the use of steroids or fluoroquinolones in tendon rupture. In children, quadriceps and patellar tendon ruptures are rare, and muscle tears are more common. In adolescents, patellofemoral dysplasia, chronic tendinitis, and use of steroids are predisposing factors. Dysplasia may cause extensor mechanism injury by repetitive tensile overloading. Corticosteroids seem to weaken collagen ultrastructure and impair the reparative process.

Quadriceps and Patellar Tendon Ruptures—Clinical Features

Clinical evaluation can elicit the correct diagnosis in most cases of complete disruption of the extensor mechanism. Patients with extensor disruption may have the following signs and symptoms: (1) acute onset of pain, and ecchymoses over the anterior aspect of the knee and a palpable defect in the patella, quadriceps tendon, or patella tendon; (2) loss or limitation of active leg extension with extension lag noted during the last 10 degrees of the maneuver; (3) high-riding patella *(patella alta),* with patellar tendon rupture and superior retraction; and (4) low-riding patella *(patella baja),* with quadriceps tendon rupture and inferior retraction. Partial disruptions may be difficult to diagnose on clinical examination and may require MRI for confirmation. Loss of active extension of the knee and inability to maintain a passively extended knee against gravity are the hallmarks of quadriceps and patellar tendon rupture, which otherwise may be clinically occult.

Quadriceps and Patellar Tendon Ruptures—Diagnostic Testing

Standard AP and lateral radiographs should be obtained and may reveal characteristic findings, including obliteration of the quadriceps or patella tendon, poorly defined suprapatellar or infrapatellar soft tissue mass, soft tissue calcific densities, or displaced patella (Fig. 48.8). Patella alta may be sought on the lateral radiograph with use of a ratio of patellar length to patellar tendon length (known as the Insall-Salvati ratio). If this ratio is less than 0.8, patella alta is present. The degree of flexion should not affect this ratio, which relies on the inelasticity of the patellar tendon. A soft tissue mass represents proximal or distal retraction of the torn tendon. Calcific densities may represent avulsed bone fragments of the patella or tibial tubercle or dystrophic calcifications in the substance of the tendons. The correct diagnosis is infrequently made by plain radiography in cases of incomplete quadriceps tendon rupture. MRI visualizes the entire extensor mechanism and is the best imaging modality.

Quadriceps and Patellar Tendon Ruptures—Management and Disposition

Treatment of acute extensor mechanism injuries produces a better clinical outcome if instituted early, within 2 to 6 weeks of the initial injury. All patients with acute partial or complete tears of the extensor mechanism should be placed in a knee immobilizer, made non-weight bearing, and referred for urgent orthopedic care within 1 week.

Patients with delayed diagnosis of patellar tendon rupture may experience significant retraction of the patella proximally and subsequent development of quadriceps contractures or adhesions. Surgical intervention is required for reattachment of complete tendon ruptures, and repair should be performed as soon as possible after injury for the best recovery.

Patellar Fractures—Foundations

Patellar fractures are classified as transverse, stellate, or comminuted, longitudinal or marginal, proximal pole or distal pole and, rarely, osteochondral. They may be displaced or nondisplaced and occur from direct or indirect forces or from dislocation. The most common fracture pattern is the transverse fracture (accounting for 50% to 80% of cases). This type often is seen in young adults and usually results from a powerful contractile force transmitted from the quadriceps tendon. This force may pull the superior portion of the patella upward, leading to wide displacement. In such cases the medial and lateral retinacula are usually disrupted, resulting in significant functional disability; active extension is impossible.

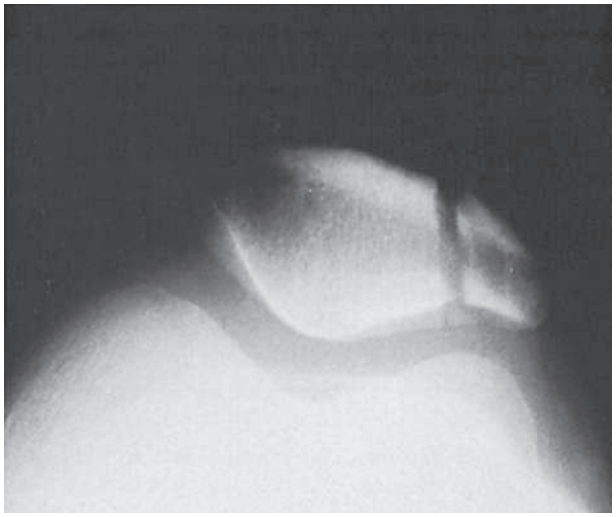

Fig. 48.9 Patellar Fracture, Sunrise View. The sharp nonsclerotic margins identify this as an acute fracture and not a congenital finding. (From Rosen P, et al. *Diagnostic radiology in emergency medicine*. St. Louis: Mosby; 1992:196.)

Nondisplaced transverse patellar fractures usually are caused by a direct blow to the anterior aspect of the patella (e.g., a fall on the knee or a direct blow sustained in vehicular trauma). The retinaculum and extensor mechanism usually remain intact, and the patient retains limited functional ability for active extension. Stellate and comminuted fractures often appear as separated fragments on plain radiographs but are held in place and supported by the medial and lateral retinacula and the overlying soft tissues. Small proximal fragments are at risk for avascular necrosis because the patellar blood supply is distributed centrally and inferiorly. Longitudinal or marginal vertical patellar fractures are less common and usually the result of direct blunt injury.

Patellar Fractures—Clinical Features

On physical examination, tenderness, swelling, and ecchymosis over the patella and prepatellar bursa may be noted. Active extension may be limited or absent, depending on the fracture pattern and amount of fragment displacement. Associated injuries may include fractures of the femoral neck, dislocation of the hip, and acetabulum fractures. Persistent patellofemoral pain and osteoarthritic symptoms may be late sequelae of patellar fractures.

Patellar Fractures—Diagnostic Testing

Radiologic evaluation of patellar fractures should include standard AP, lateral, and sunrise views. Most patellar fractures are obvious on plain radiographs, but vertical marginal fractures may be difficult to identify because they are obscured by the femur on the AP view and not visualized on the lateral view. Close examination of sunrise views may reveal an osteochondral avulsion fragment or marginal fracture (Fig. 48.9). Bipartite and multipartite patellae are common normal variants and should not be confused with fractures. Ossification centers are found at the upper outer quadrant of the patella and have smooth cortical margins, but differentiating physeal lines from fractures can be difficult. Comparison radiographs may be helpful because these anatomic anomalies are often bilateral. In some cases, MRI may be needed to identify occult marginal fractures or free osteochondral fragments.

Patellar Fractures—Management and Disposition

For initial management of nondisplaced fractures, a knee immobilizer may be used. Patients should be instructed to use crutches, with partial weight bearing as tolerated, and should be referred for orthopedic evaluation within 1 week. For widely displaced transverse fractures, open reduction and internal fixation are necessary for optimal results. A knee immobilizer can be used initially to stabilize the extremity before definitive care is provided. Treatment options for displaced comminuted fractures include open reduction, internal fixation, and partial or complete patellectomy.

Patellar Dislocation—Foundations

Patellar dislocations are commonly seen in both adult and pediatric patient populations, although they are more common in children. Most cases are lateral, and the mechanism of injury usually is a direct blow to the anterior or medial surface of the patella. The injury may also occur when a valgus stress is exerted on a flexed knee, resulting in external rotation of the leg. As these forces are dissipated, the medial retinaculum is typically torn, resulting in a lateral patella dislocation. Subluxation usually indicates a stretched medial retinaculum.

Patellar Dislocation—Clinical Features

Patients with patellar dislocations typically present to the ED with acute pain, noting difficulty ambulating and flexing the knee. There may be a history of previous dislocation. Physical examination typically reveals a defect anteriorly with the patella deviated laterally. A knee effusion may develop hours after the injury but may not be immediately evident. Effusions are typically more pronounced after the patellar dislocation has been reduced, which may occur spontaneously prior to the patient arriving in the ED. The forces that result in patellar dislocations may cause osteochondral fractures of the patella. These fractures are highly variable, sometimes involving only the cartilage (chondral fracture) and other times involving the underlying bone as well. Effusions, particularly hemarthroses, are more commonly seen with patellar dislocations with associated osteochondral fractures.

Patellar Dislocation—Diagnostic Testing

Standard AP and lateral x-ray views are usually sufficient to diagnose a patellar dislocation. Sunrise views are typically difficult to obtain prereduction due to pain and inability to flex the knee. Expected findings on x-ray include an empty trochlear groove, a displaced patella and an effusion. Radiographs should be examined for avulsion fracture. If a lipohemarthrosis is seen, it is important to look for fracture fragments.

Patellar Dislocation—Management and Disposition

Patellar dislocation is typically managed with closed reduction. To perform this reduction, the knee should be passively extended while an inferomedially directed pressure is applied to the patella. If the dislocation is difficult to reduce, gentle downward pressure may be applied to the lateral aspect of the patella in an effort to open the medial patellar facet. This procedure does not typically require conscious sedation and can be performed with analgesics only, depending on the patient's anxiety and pain level. As with every reduction, a neurovascular examination should be performed after the procedure. Postreduction knee x-rays, including a sunrise view, should be performed to confirm that the patella is in the trochlear groove. The clinician should also ensure that no osteochondral avulsion fragments are seen on x-ray, because these may require arthroscopy for removal.

Once the patella dislocation has been successfully reduced, patients should be placed in a knee immobilizer positioned in full extension. Patients should follow up with orthopedics within 1 to 2 weeks of the injury. Follow-up care is important due to the significant rate of recurrent patellar dislocation. Despite physical therapy, many patients will sustain another patellar dislocation. Recurrent dislocation or persistent

pain and laxity following dislocations may warrant surgical intervention. However, surgically and conservatively managed patients generally have similar functional long-term outcomes.[7,8]

Cruciate and Collateral Ligament Injuries—Foundations

Ligamentous injuries to the knee may range in severity from mild sprains to complete tears. Collateral ligament injury usually causes tenderness and pain along the joint line. Cruciate injuries pose more of a diagnostic dilemma because they are intra-articular.

Cruciate and Collateral Ligament Injuries—Clinical Features

The ACL is commonly injured in sports. Although direct contact with a flexed knee can result in an ACL tear, the injury is more common in noncontact sports, with the plant and pivot or stop and jump mechanisms predominating. A direct blow to the flexed knee, as may occur in MVCs (from the dashboard), and turf injuries with the knee flexed and the ankle plantar-flexed can also result in an ACL injury.

Given the force required to injure an ACL, it is common to see concurrent meniscal injuries. The traditional "unhappy triad" of ACL, MCL, and medial meniscal injury is actually less common than the combination of ACL, MCL and lateral meniscal injury. Patients with an acutely injured ACL will often report hearing a "pop" that is followed by pain. An effusion typically develops within the first 1 to 3 hours after the injury. Patients may also note knee instability with the sensation of the "giving out" or may be unable to bear weight on the injured leg. The anterior drawer test can be used to diagnose an ACL tear; however, the Lachman test is more sensitive and more specific.

The anatomic location of the PCL and its relative strength make isolated PCL injuries rare. The typical mechanism for PCL injury is a posterior force applied to a flexed knee, either from a fall or from contact with a dashboard. PCL injury can also occur when multidirectional forces are applied to a knee, resulting in a knee dislocation. Unlike ACL injuries, patients with PCL injuries do not typically report an audible pop and significant instability is not immediately appreciated. Later, the patient may complain of feeling the femur "fall off" the tibia. Knee pain and effusion are seen with PCL injuries. The posterior drawer test is still the clinically preferred diagnostic maneuver.

The MCL usually is injured by a direct blow or impact to the lateral aspect of the knee, which imposes a valgus stress. Despite the amount of force required to injure the MCL, these injuries are typically treated nonoperatively.

The LCL usually is injured by a mechanism of hyperextension with varus stress, commonly accompanied by a direct blow or rotation. LCL injuries are not as common as MCL injuries, because the contralateral leg provides significant protection against varus forces and the lateral compartment is inherently more stable than the medial compartment. If an LCL injury is suspected, a neurovascular assessment should be performed based on the proximity of the peroneal nerve to the LCL. The accuracy of the knee examination for ligamentous damage is enhanced if done immediately after injury before the onset of swelling and pain, but the patient may not tolerate the examination and muscle spasms may obscure findings. Ligamentous injuries are not emergencies and can be diagnosed definitively after the acute phase has subsided.

Cruciate and Collateral Ligament Injuries—Diagnostic Testing

A full knee x-ray series should be obtained, including AP, lateral, sunrise, and intracondylar notch views. X-rays should be evaluated for associated fractures, loose bodies, or avulsion injuries. The Segond fracture is an avulsion off the posterior aspect of the lateral tibial plateau and is classically seen with ACL tears (see Fig. 48.6). Ultrasonography can also be used to diagnose meniscal injuries, LCL injuries, and ACL injuries; however, the sensitivity and specificity of this modality vary greatly based on the type of probe used and the skill of the examiner. Although MRI is the preferred imaging modality to identify ligamentous injuries, it is not routinely necessary in the ED to evaluate for collateral and cruciate ligament injuries.

Cruciate and Collateral Ligament Injuries—Management and Disposition

All patients with suspected isolated ligamentous knee injuries should be placed in a fully unlocked, hinged knee brace with weight bearing as tolerated with orthopedic follow-up in 1 week. Crutches can be provided as needed. It is imperative not to place the patient in a knee immobilizer for isolated ligamentous injuries, because use of this brace significantly decreases quadriceps strength, which negatively affects surgical outcomes in ACL-injured patients. Orthopedic follow-up is needed to facilitate physical therapy, MRI imaging, and surgery, when needed.

Patients with isolated PCL injuries or isolated MCL injuries are typically treated conservatively with hinged knee brace, orthopedic follow-up, and physical therapy. If they are associated with multiligament or avulsion injuries, they may require surgery as an outpatient, so expedited orthopedic follow-up is advised. Isolated LCL injuries can be managed in the ED with a hinged knee brace and orthopedic follow-up. Operative intervention for patients with LCL injuries is usually not necessary but may be required if other structures within the posterolateral corner of the knee are involved or if there is substantial instability.

Definitive management of ACL tears depends on a combination of the patient's age, lifestyle, and the mechanism of injury. Younger, athletically active patients are more likely to undergo operative reconstruction, whereas older, less active patients may be managed with conservative measures. In the ED, a suspected ACL tear should be managed with a hinged knee brace, crutches, and urgent orthopedic follow-up.

Meniscal Injuries—Foundations

When a meniscal injury does occur, the posterior aspect is more commonly injured than the anterior portion due to the increased forces placed upon the posterior horn with knee flexion. Meniscal blood supply should also be considered when evaluating a potential meniscal injury. Branches of the inferior and middle geniculate arteries provide blood flow to the meniscus. These vessels enter the lateral aspect of the meniscus and then diffuse towards the medial aspect of the structure, effectively rendering the medial aspect of the meniscus avascular. Unfortunately, the medial aspect of the meniscus is the most commonly injured, and healing is impaired due to the lack of blood supply.

Meniscal Injuries—Clinical Features

An isolated meniscal tear should be suspected in a patient with a history of intermittent locking, effusion, giving way, and pain and physical examination findings of joint line tenderness. A torn meniscus more commonly is associated with delayed onset of swelling over 12 to 24 hours. Locking of the knee typically results from a meniscal tear or other loose body trapped within the joint, thereby preventing full extension. The cardinal sign of a meniscal tear is local pain and tenderness along the joint line. Joint line pain and tenderness are especially apparent with extremes of flexion and extension. Not all tears of the menisci are symptomatic. Degenerative lesions are relatively common in middle age and later and may be asymptomatic. Effusions are not typically seen based on the limited blood supply to the meniscus. Patients may note clicking or locking as the meniscus fragment slides or gets wedged between the tibia

and the femur. Acute and chronic injuries typically result from twisting on a flexed knee; however, minimal force may be required to convert a chronic degenerative tear into a complete tear.

Meniscal Injuries—Diagnostic Testing

With the exception of ultrasound, there are limited ED-based imaging options to assess a possible meniscal tear. Meniscal injury cannot be diagnosed by plain radiography or CT scanning. Arthroscopy is the gold standard for diagnosis; MRI is an alternative but may miss minor meniscal tears.

Meniscal Injuries—Management and Disposition

Patients with meniscal tears should be discharged from the ED similarly to those with ligamentous knee injuries with an unlocked hinged knee brace, crutches, and orthopedics follow-up. The patient should be weight bearing as tolerated. Patients with a locked knee due to a meniscal tear require further treatment prior to ED discharge. The emergency physician can attempt to unlock the knee by providing adequate analgesics (intra-articular lidocaine, intravenous analgesics, or conscious sedation) and then gently repeatedly performing the McMurray maneuver. An orthopedics consult can also be obtained to assist in unlocking the knee. In the absence of mechanical symptoms such as locking or catching, physical therapy is currently preferred to surgical management as definitive treatment for many meniscal injuries.[9–11]

OVERUSE SYNDROMES

Overuse syndromes result from repetitive motion and the subsequent inflammation that may result from repeated activity. The typical complaint is knee pain, often localized to one of three particular areas—the medial aspect, lateral aspect, or peripatellar region. The location of the pain varies based on the areas of inflammation associated with a given activity. Medial knee pain is commonly seen with medial tibial stress fractures, proximal MTSS, pes anserine bursitis, tendinopathy, or MCL strain. Lateral knee pain is typically associated with LCL strain, IT band dysfunction, popliteal tendinitis, or proximal fibular stress fracture. Anterior knee pain may be due to patellar tendinitis, bursitis, quadriceps tendinitis, or patellofemoral syndrome.

Patellofemoral Pain Syndrome—Foundations

The patellofemoral pain syndrome refers to the clinical presentation of anterior knee pain related to changes in the patellofemoral articulation. Chondromalacia patellae describes deterioration or softening of the articular cartilage. Correlating pathologic changes on the surface of the patella and clinical symptoms is difficult, and the pain mechanism has not been precisely defined.

Patellofemoral Pain Syndrome—Clinical Features

Patellofemoral pain syndrome is the most common cause of knee pain. Women are more commonly affected than men, and patients typically present in their 20s and 30s. The pain usually begins gradually and is not related to trauma. Unilateral symptoms are more common than bilateral involvement. The knee is more painful with prolonged flexion (e.g., from sitting in a movie theater), and the discomfort typically is accentuated by stair climbing and kneeling. The syndrome occurs in athletes and in older patients who have arthritis affecting the patellofemoral joint. Risk factors for patellofemoral pain syndrome include gluteal weakness, quadriceps weakness, patellar subluxation, prepatellar bursitis, arthritis, meniscal tears, and quadriceps/patellar tendinopathy.

Several physical examination findings may be seen in patients with patellofemoral pain syndrome. Gait abnormalities may be present. The medial and lateral aspects of the patella may be tender to palpation, particularly when the syndrome results from patellar subluxation or dislocation. Recreation of pain while performing a single leg squat on the affected leg may suggest patellofemoral pain syndrome.

Patellofemoral Pain Syndrome—Diagnostic Testing

Patellofemoral pain syndrome is a primarily clinical diagnosis. Standard knee x-rays should be obtained to evaluate the patellofemoral joint space integrity and to assess for osteoarthrosis.

Patellofemoral Pain Syndrome—Management and Disposition

Physical therapy is the cornerstone of management for those with patellofemoral pain syndrome. Literature suggests hip abductor strengthening in addition to traditional quadriceps strengthening improves symptoms.[12] Nonsteroidal antiinflammatory drugs (NSAIDs) may be used early in the course of treatment and can allow the patient to comfortably start a physical therapy program. Several taping techniques and bracing options are available to further assist the patellofemoral pain syndrome patient, although the efficacy of bracing has not been clearly established.[13] Orthopedic follow-up is recommended to facilitate the physical therapy program.

Iliotibial Band Syndrome—Foundations

Overuse can cause inflammation of a bursa underlying the IT band at the lateral femoral epicondyle, resulting in lateral knee pain.

Iliotibial Band Syndrome—Clinical Features

The syndrome is most common in long distance runners and is more likely in severe overpronators. Physical findings include localized tenderness of the lateral femoral epicondyle and IT tightness or pain, elicited by the *Ober test*. To perform the Ober test, the patient lies on his or her unaffected side with the uninjured leg down, flexed to 90 degrees at the hip and knee. The affected hip is abducted, the knee is extended, and then the hip is allowed to return to neutral adduction with gravity. Failure of the hip to adduct fully with gravity or reproduction of pain at the lateral knee indicates IT tightness or inflammation, respectively.

Iliotibial Band Syndrome—Diagnostic Testing

Standard knee x-rays should be done to exclude other causes of lateral knee pain.

Iliotibial Band Syndrome—Management and Disposition

Typical treatment for IT band syndrome should include relative rest, NSAIDs, and physical therapy. Bracing has not been shown to prevent IT band syndrome or help in the recovery process. Steroid injections or surgery may be helpful in refractory cases.

Patellar Tendinopathy—Foundations

Patellar tendinopathy refers to a range of cellular changes to the patellar tendon. These forces can result in microscopic tears. Over time, these microtears can initiate an inflammatory cascade, leading to long-term symptoms.

Patellar Tendinopathy—Clinical Features

Patellar tendinopathy typically results from chronic repetitive physical activity, particularly running and jumping. Patients will typically describe gradual onset pain over the patellar tendon and have tenderness when palpating the tendon. A traumatic mechanism, a palpable

defect over the tendon, or an inability to perform a straight leg raise should raise concern for patellar tendon rupture.

Patellar Tendinopathy—Diagnostic Testing

Standard knee x-rays can be done to evaluate for avulsion fractures or patella alta.

Patellar Tendinopathy—Management and Disposition

As with most overuse injuries, the mainstays of treatment include reducing inflammation, relative rest, and physical therapy in this case focused on eccentric exercises. There is no role for steroid injection in the treatment of patellar tendinopathy. In cases of recalcitrant patellar tendinopathy, surgical débridement may be required.

Plica Syndrome—Foundations

During embryonic development, synovial folds, or plicae, are present within the knee. Although most plicae are absorbed in the neonatal period, a small percentage of people have persistent plicae throughout adulthood. Relatively minor or repetitive knee trauma may result in thickening of this tissue, resulting in an intra-articular band-like structure.

Plica Syndrome—Clinical Presentation

Patients typically complain of pain over the region of the medial femoral condyle. Plicae-associated pain typically increases with repeated activity (especially running and biking) and may also be aggravated by prolonged sitting. Patients often note a snapping or popping sensation as the plica moves across the medial femoral condyle. A small effusion may be seen after significant periods of activity. If the plica continues to increase in size, it may also limit knee motion and lead to knee stiffness. The presence of plicae is difficult to detect clinically as the physical examination is relatively nonspecific. Effusions, medial femoral condyle tenderness, and a false-positive McMurray sign may all be seen on physical examination.

Plica Syndrome—Diagnostic Testing

Plain radiography may be necessary to exclude other causes of knee pain but is of no value in diagnosing plica syndrome. Plicae are often not detected on MRI, and thus nonurgent arthroscopy is the diagnostic study and intervention of choice.

Plica Syndrome—Management and Disposition

ED patients with a suspected plica should be discharged to follow up with orthopedics with weight bearing as tolerated. Physical therapy and NSAIDs may provide some symptomatic relief while awaiting definitive management.

Popliteus Tendinopathy—Foundations

Similar to patellar tendinopathy, popliteus tendinopathy results from cellular changes to the tendon that can cause chronic pain.

Popliteus Tendinopathy—Clinical Presentation

The classic presentation of a patient with popliteus tendinopathy is increasing posterior or posterolateral knee pain following a significant increase in downhill running or hiking. Mechanical symptoms and effusions are uncommon. Tenderness just medial to the lateral head of the gastrocnemius is the hallmark of the physical examination. Because of the close relationship of the popliteus to other soft tissue structures, a definitive diagnosis may be difficult. The *Webb test* may be performed to distinguish popliteus tendinopathy from biceps femoris tendinopathy, lateral meniscal injury and IT band dysfunction. This test is performed with the patient supine and the knee flexed to 90 degrees. The leg is rotated internally, and the patient is asked to resist the examiner's attempt to rotate the leg externally. Reproduction of symptoms suggests the diagnosis.

Popliteus Tendinopathy—Diagnostic Testing

X-rays should be considered to assess for other causes of knee pain but generally are not useful in diagnosing popliteal tendinopathy. As an outpatient, MRI may reveal this diagnosis.

Popliteus Tendinopathy—Management and Disposition

Patients with concern for popliteal tendinopathy should be managed with a period of relative rest, avoidance of hill or incline running, and physical therapy. NSAIDs may be used to decrease the associated inflammation.

Bursitis—Foundations

Bursitis is caused by repeated stress, infection, local trauma, crystal deposition, or systemic inflammatory arthropathy. It is important to differentiate bursitis from a joint effusion.

Bursitis—Clinical Features

Prepatellar bursitis is characterized by swelling of the superficial bursa overlying the lower pole of the patella. Usually, passive motion is fully preserved and the pain is mild. The disorder is often caused by pressure from repetitive kneeling on a firm surface (so-called housemaid's knee). The prepatellar bursa is also a common site of septic bursitis, and a common error is to confuse this entity with a septic knee (involving the tibiofemoral joint).

Anserine bursitis involves pain and tenderness at the proximal medial tibia, a few centimeters inferior to the medial joint line. It usually occurs in obese women in association with osteoarthritis of the knee but also may occur from overuse, especially in runners. It is characterized by localized tenderness and puffiness at the pes anserinus.

Bursitis—Diagnostic Testing

Bursitis is a clinical diagnosis. X-rays may be performed to help better determine if an effusion is intra- or extra-articular. Ultrasound may also be used to evaluate the location of the effusion. The definitive diagnosis of a septic bursa requires aspiration of the fluid in question; this can be done under ultrasound guidance or by using anatomic landmarks. The standard fluid studies should be ordered including protein count, glucose, Gram staining, culture, cell count, and crystal analysis. Additional studies (including gonorrhea and Lyme and tick-borne disease titers) may be added based on clinical suspicion.

Bursitis—Management and Disposition

Isolated septic (bacterial) bursitis without joint involvement requires antibiotic treatment, with operative drainage in refractory cases. Initial ED management includes outpatient antibiotics targeting skin flora with consideration of local resistance patterns and possible methicillin-resistant *Staphylococcus aureus* (MRSA) exposure for a minimum of 10 days with expediated orthopedic follow-up if the patient lacks systemic symptoms and is not immunocompromised. IV antibiotics and admission should be considered if the patient has systemic signs or is immunocompromised. Rarely, patients may fail antibiotic therapy and require operative débridement. Antibiotic choice should focus on skin flora while considering local resistance.

Aseptic (inflammatory) bursitis is treated with drainage, compression, ice, rest, antiinflammatory agents, and consideration of corticosteroid injection. In the ED, steroid injection of the anserine and prepatellar bursae is most common.

ARTHRITIS

Osteoarthritis—Foundations

Osteoarthritis describes degeneration of the articular cartilage, causing narrowing of the joint space and subsequent inflammation. Arthritis can occur at the tibiofemoral joint as well as the patella-femoral joint.

Osteoarthritis—Clinical Features

In the absence of a smooth articular surface, patients complain of pain and stiffness with ROM and activity. Examination may reveal an effusion and joint line tenderness over the affected compartment. Meniscal tears may also cause localized joint line tenderness but are frequently degenerative in nature when superimposed on a background of arthritis.

Osteoarthritis—Diagnostic Testing

Standard weight-bearing AP, lateral, and sunrise views will demonstrate joint space narrowing of the medial compartments, lateral compartments, or patellofemoral space. Osteophytes, subchondral cysts, and loose bodies may also be present.

Osteoarthritis—Management and Disposition

Patients with knee arthritis can be weight bearing as tolerated, but high-impact activities should be minimized. Physical therapy is the mainstay of treatment. NSAIDs and acetaminophen may be provided for pain control. Intra-articular steroid injections may also be used for symptomatic relief but should be used sparingly because evidence suggests they may accelerate arthritis.[14] Surgical treatment is typically limited to joint replacement.

Septic Arthritis—Foundations

Although direct trauma may cause knee joint infection, hematogenous seeding is the most common etiology. Bacterial spread usually affects the vascular synovial membrane and then extends into the joint. Skin flora, particularly *S. aureus,* is the most common causative agent of a traumatic septic joint. Different age groups and conditions may predispose patients to specific organisms. In young, sexually active patients, gonococcal arthritis should be considered.

Septic Arthritis—Clinical Features

Patients with septic arthritis of the knee present with an extremely painful joint that is difficult to elicit full ROM due to pain. The joint is often swollen, red, and warm. Patients often have an accompanying fever but can present with a normal temperature. Extreme pain with passive ROM should prompt the physician to consider this diagnosis even in the absence of erythema or fever.

Septic Arthritis—Diagnostic Testing

X-ray may be useful to rule out an underlying fracture. Most importantly, synovial fluid analysis should be performed. White blood cell count greater than 50,000 and 90% neutrophil predominance may suggest a bacterial source. Fluid should be sent for Gram stain and culture. Patients with early infection or a joint prosthesis may have a low synovial white blood cell count, highlighting the importance of fluid cultures. Orthopedic consultation should be performed if there is clinical suspicion for septic arthritis, regardless of synovial fluid cell count.

Septic Arthritis—Management and Disposition

Patients with septic arthritis should have emergent IV antibiotics initiated in parallel with orthopedic consultation for possible operative washout. Antibiotic selection for nongonococcal septic arthritis should target primarily skin flora. MRSA coverage should be considered. For gonococcal arthritis, IV ceftriaxone should be administered. To prevent septic arthritis in the ED, all open joint injuries should be treated with operative washout and antibiotics. Clinicians should avoid performing arthrocentesis through infected skin, which can seed the joint.

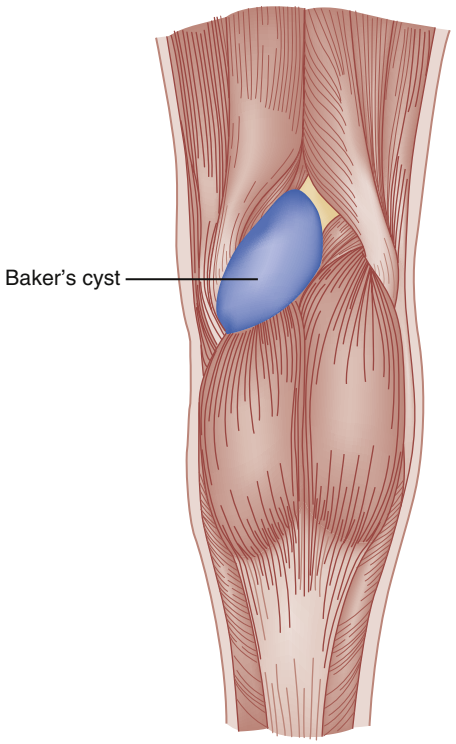

Fig. 48.10 Baker cyst is an extension of the semimembranosus bursa posteriorly. This bursa often is connected with a joint cavity.

BAKER CYST

Baker Cyst—Foundations

A Baker cyst (popliteal cyst) is a herniation of the synovial membrane through the posterior aspect of the capsule of the knee (Fig. 48.10). It results from a knee effusion of any cause.

Baker Cyst—Clinical Features

A mass is palpable in the posteromedial corner of the knee and often produces pressure, pain, and limitation of ROM. Rupture of the bursa, with resultant escape of fluid into the calf, may produce a clinical picture similar to that of DVT or compartment syndrome. Many Baker cysts go unnoticed until rupture, resulting in unilateral lower extremity edema.

Baker Cyst—Diagnostic Testing

A Baker cyst is a diagnosis of exclusion. In the ED, ultrasound should be done to rule out DVT if there is clinical suspicion. Venous duplex studies may identify cyst remnants and help to make the diagnosis as well. Nonemergent MRI can often confirm the diagnosis and help to identify the underlying cause of the cyst.

Baker Cyst—Management and Disposition

Treatment of the cyst focuses on symptomatic therapy (relative rest, compression, and NSAIDs) while also treating the underlying etiology of the cyst. Drainage can be considered on an outpatient basis but is not advised in the ED.

LEG

Foundations

Anatomy, Physiology, Pathophysiology

Anatomically, the leg is comprised of the tibia, fibula, and associated soft tissues, whereas the thigh is composed of the femur and its soft tissues.

Tibia and Fibula

Bearing the full weight of the body, the leg is subject to enormous stress, and *the tibia is the most commonly fractured long bone*. Moreover, the tibia is poorly covered by soft tissue anteriorly, making infection and delayed healing common. This is further compounded by the triangular shaped structure of the tibia, leaving the anteromedial aspect with less soft tissue and thus higher injury rates than other portions.

The distal aspect of the tibia fans out in a bell-bottom fashion to form the fibular notch, providing additional articulations and protection to the distal tibiofibular joint. The medial malleolus projects from the distal medial aspect of the tibia and has a posterior groove for the tibialis posterior tendon. The inferior surface of the distal tibia is covered with articular cartilage and forms the tibial plafond, the upper anterior surface of the ankle joint. The fibula, in contrast to the tibia, is covered by soft tissue except at the ankle, where it is subcutaneous and easily palpable. The fibula is composed of the head with its styloid process, neck, shaft, and lateral malleolus of the ankle. The proximal tibiofibular joint is a small synovial joint between a circular or oval facet on the head of the fibula and a similar facet on the inferior aspect of the lateral tibial condyle. The tibia and fibula are also connected by the superior and inferior tibiofibular ligaments as well as the syndesmotic ligaments. The syndesmosis ligament is a fibrous band that has particular importance at the distal portion of the lower leg, where it is responsible for keeping the tibia and fibula closely approximated to provide a stable ankle mortise.

Vascular Supply

The vascular supply of the lower leg is derived from the popliteal artery, which trifurcates to form three branches—the anterior tibial artery, posterior tibial artery, and peroneal artery. The anterior tibial artery can be assessed at the dorsum of the foot while the posterior tibial artery can be evaluated just posterior to the medial malleolus. The peroneal artery is the third branch of the popliteal to contribute to the vascular supply; however, it is not easily assessed clinically.

Fascial Compartments

The anatomy of the lower leg can be described in terms of four fascial compartments: the anterior, lateral, superficial posterior, and deep posterior compartments. Each compartment has a sensory nerve running through it, an anatomic feature that can be used to help diagnose compartment syndrome. The anterior compartment contains the tibialis anterior, long toe extensor muscles, anterior tibial artery, and deep peroneal nerve, which supplies sensation to the first web space of the foot. The lateral compartment contains two muscles that evert the foot, the peroneus longus and brevis, and the superficial peroneal nerve, which supplies sensation to the dorsum of the foot. The superficial posterior compartment contains the gastrocnemius, plantaris, and soleus muscles and sural nerve, which supplies the lateral side of the foot and distal calf. The deep posterior compartment contains the tibialis posterior muscle, long toe flexor muscles, posterior tibial and peroneal arteries, and tibial nerve, which supplies sensation to the plantar aspect of the foot.

TABLE 48.4 Differential Diagnoses of Leg Injuries

Injury	Differential Diagnostic Considerations
Subcondylar tibial fractures	Tibial plateau fracture, tibial shaft fracture, tibial tubercule fracture
Tibial tubercule fracture	Osgood-Schlatter syndrome, tibial plateau fracture, patellar tendinopathy/rupture
Tibial shaft fracture	Stress fracture, medial tibial stress syndrome (MTSS), tibial tubercule fracture, exertional compartment syndrome
Stress fracture	MTSS, tibial shaft fracture, exertional compartment syndrome, tibial tubercule fracture
MTSS	Stress fracture, tibial shaft fracture, exertional compartment syndrome
Proximal fibular fracture	Tibial plateau fracture, posterolateral corner injury, lateral collateral ligament injury, lateral meniscal injury, Maisonneuve injury
Proximal tibiofibular dislocation	Proximal fibular fracture, tibial plateau fracture, posterolateral corner injury

Leg Injuries Differential Diagnoses

The differential diagnosis for leg pain after a traumatic injury is broad (see Table 48.4). Pain over the tibia or fibula should always raise suspicion for any of a myriad of tibia and fibular fractures described later, depending on history and examination. In patients presenting with isolated proximal lateral leg pain, proximal tibiofibular joint dislocation should also be considered. Insidious-onset diffuse medial tibial pain may be due to MTSS or stress fracture. Focal pain and tenderness are more characteristic of a stress fracture. Sudden onset pain in the posterior lower leg should raise suspicion for gastrocnemius tear, rupture, or plantaris tendon injury. However, the clinician should also consider DVT, a Baker cyst, or even an Achilles tendon rupture (discussed elsewhere). Exercise-induced compartment syndrome, contusion, muscle strain, or tendinitis may also cause lower leg pain.

SPECIFIC LEG INJURIES

Proximal Extra-articular Tibial Fractures

Subcondylar Tibial Fractures—Foundations

Subcondylar tibial fractures are typically transverse or oblique fractures of the proximal tibal metaphysis. They are usually associated with tibial plateau fractures, especially bicondylar fractures.

Subcondylar Tibial Fractures—Clinical Features

The typical mechanism of injury is rotational stress with vertical compression. Patients with subcondylar tibial fractures will often have swelling and tenderness to palpation of this area.

Subcondylar Tibial Fractures—Diagnostic Testing

Standard knee x-rays will usually identify the fracture. If a hemarthrosis is seen on x-ray, the clinician should consider intra-articular extension of the fracture, an associated tibial plateau fracture, or ligamentous disruption. If clinical suspicion is high and x-rays are negative, CT scanning should be considered.

Subcondylar Tibial Fractures—Management and Disposition

Stable extra-articular nondisplaced transverse fractures are treated conservatively with a long leg splint with a sugar tong component.

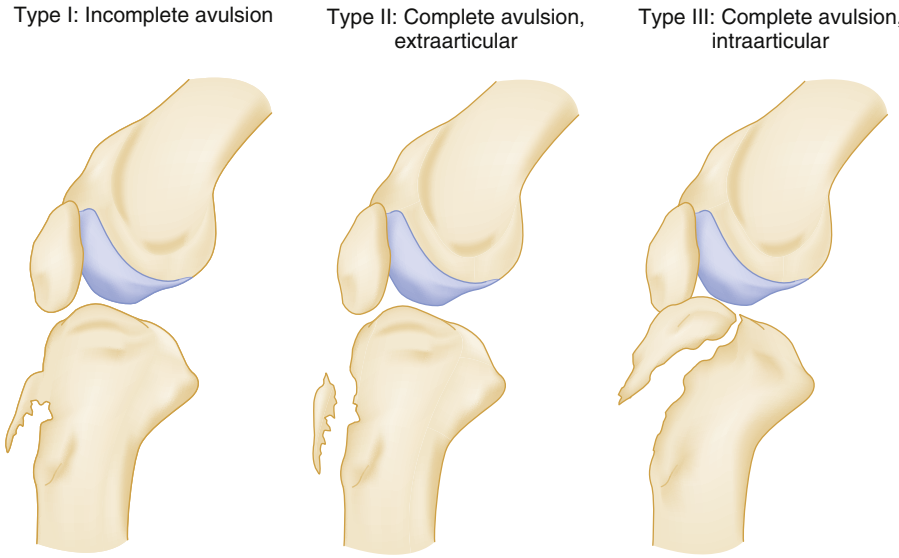

Fig. 48.11 Tibial Tuberosity Fractures.

BOX 48.2 Ogden Classification

Type 1: secondary ossification center fracture (near patellar tendon insertion)
Type 2: fracture extends between the primary and secondary ossification centers
Type 3: fracture extends to the primary center of ossification
Type 4: entire proximal tibial physis fractured
Type 5: sleeve avulsion fracture from the secondary ossification center
Tibial tuberosity fractures are further classified as follows:
Type A: nondisplaced
Type B: displaced

Orthopedic follow-up is recommended for transition to casting once swelling has decreased. Any supracondylar tibial fracture that is intra-articular, comminuted, or displaced has a higher risk for compartment syndrome and requires operative fixation. These patients are typically admitted to allow serial neurovascular examinations and to monitor swelling in the first 24 to 48 hours after injury.

Tibial Tubercle Fractures—Foundations

The tibial tubercle is located at the proximal anterior border of the tibial shaft and is the insertion point of the patellar tendon. The proximal tibial epiphysis and tibial tuberosity develop from two separate ossification centers that coalesce during adolescence. Epiphyseal ossification terminates in late adolescence.

Avulsion fractures of the tibial tubercle are uncommon. They occur predominantly in adolescent boys near the end of growth, when endochondral ossification of the physeal cartilage of the tibial tubercle occurs. Avulsion fractures mainly occur following an indirect injury during strenuous activity. The mechanism of injury has been described as an abrupt flexion of the knee against a tightly contracted quadriceps muscle, which also can cause patellar tendon rupture. The Ogden Classification of tibial tuberosity fractures expands the previously used Watson-Jones classification to better describe the injury pattern (Fig. 48.11; see Box 48.2). This fracture pattern is rarely seen in other age groups as this particular mechanism of injury typically results in patellar tendon rupture in the adult patient.

Tibial Tubercle Fractures—Clinical Features

Physical examination reveals acute tenderness and swelling at the anterior aspect of the knee and proximal tibia. Depending on the type of injury, functional disability may range in severity from extensor lag to complete loss of active extension. Hemarthrosis is evident if there is intra-articular fracture extension across the proximal epiphysis.

Tibial Tubercle Fractures—Diagnostic Testing

Standard knee x-rays should be obtained to evaluate for a tibial tubercle avulsion injury. The lateral view typically shows the avulsion fracture, number of fragments, and degree of displacement. Contralateral knee x-rays may be helpful to assess the patient's stage of ossification and better assess the injury.

Tibial Tubercle Fractures—Management and Disposition

Treatment depends on the degree of displacement and presence of joint involvement. Nondisplaced fractures are treated with a knee immobilizer and urgent orthopedic follow-up for casting. Displaced fractures are usually treated by open reduction and internal fixation. In the ED, orthopedic consultation is advised for these fractures.

Tibial Shaft Fractures—Foundations

The tibia and fibula are tightly bound to each other by the syndesmosis. This strong band of tissue can transmit energy so that the tibia and fibula may be fractured at nonadjacent sites. Tibial shaft fractures can be devastating, with a high rate of infection, delayed union, nonunion, malunion, and associated fibular fractures.

The type of tibial fracture seen varies based on the mechanism of injury. High-energy and direct trauma typically result in transverse fractures, whereas lower-energy, rotational, or compressive forces produce spiral or oblique fractures. Tibial fractures also may occur without trauma. Stress fractures usually occur in the tibial shaft. Pathologic fractures may be caused by metabolic bone disease, osteomalacia, and primary or metastatic neoplasms.

Tibial Shaft Fractures—Clinical Features

Patients with tibial shaft fractures can present with a significant amount of pain, edema, and deformity. Angulation of the foot is commonly seen in rotational injuries. The neurovascular exam should be the focus of the examination, particularly when foot angulation is present. Assessment of the DP and PT pulses should be performed as soon as possible, although

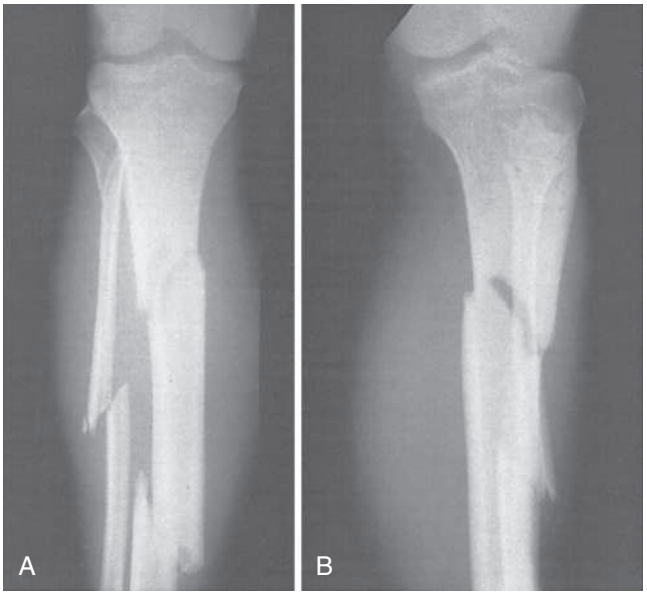

Fig. 48.12 Tibiofibular Fracture. (A) Anteroposterior view. Comminuted fractures of the tibial and fibular shafts are present. Note the obliteration of the normal soft tissue planes secondary to edema or hemorrhage. (B) Lateral view. (From Rosen P, et al. *Diagnostic radiology in emergency medicine.* St Louis: Mosby; 1992:198.)

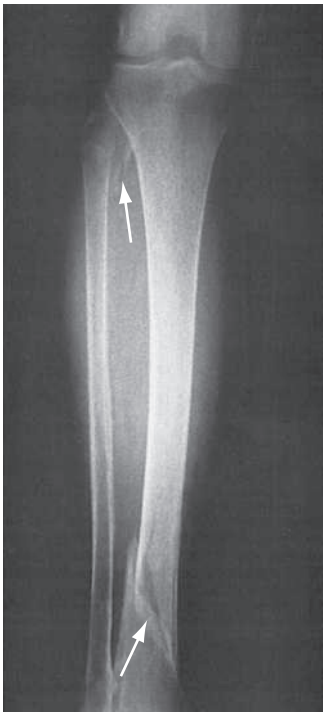

Fig. 48.13 Maisonneuve Fracture, Anteroposterior View. The rotatory force involved in this injury has caused fractures of the distal tibia and the proximal fibula *(arrows)*. (From Rosen P, et al. *Diagnostic radiology in emergency medicine.* St Louis: Mosby; 1992:197.)

vascular injury is a rare complication. Neurologic injury, by contrast, is common, particularly injury of the peroneal nerve. Motor function of the peroneal nerve is checked by testing active ankle and toe dorsiflexion (deep peroneal nerve) and active foot eversion (superficial peroneal nerve). Sensory function of the peroneal nerve is documented by testing sensation in the first dorsal web space of the foot (deep peroneal nerve distribution) and sensation of the dorsal lateral foot (superficial peroneal nerve distribution). Integrity of the posterior tibial nerve is assessed by checking for the presence or absence of plantar sensation. Compartment syndrome may be a complication of tibial fractures and usually develops within the first 24 to 48 hours.

In general, tibial fractures are slow to heal. A low-energy injury heals in 20 weeks, whereas high-energy injuries typically heal in 30 weeks. Delayed union describes fracture segments that have not united after 24 weeks or that show no radiographic evidence of callus formation for 3 consecutive months. Nonunion describes incomplete fracture healing. Fracture fragments have rounded, well-corticated edges (as compared with the jagged edges seen in the acute phase of injury). A variety of delayed vascular injuries can be seen with tibial fractures, including the development of pseudoaneurysms, arteriovenous fistulas, and DVT. Fat embolism syndrome may develop within the 24 to 48 hours following either the initial injury or operative application of intramedullary rods, nails, screws, or plates. This syndrome typically mimics pulmonary emboli, with sudden onset tachycardia, tachypnea, dyspnea, chest pain, and altered mental status.

Tibial Shaft Fractures—Diagnostic Testing

Standard AP and lateral x-rays of the tibia and fibula can be used to identify these fractures. Standard x-rays of the knee and ankle should be performed to assess the extent of injury. In cases of significant force, x-rays of the femur, hip, and pelvis may also be warranted (Fig. 48.12). Postreduction views should be taken after any manipulation of the extremity and should include the knee and ankle joints so that alignment of the proximal and distal joint surfaces can be determined.

Tibial Shaft Fractures—Management and Disposition

ED management of tibial shaft fractures varies based on the extent of injury. The majority of patients with an acute tibial shaft fracture are admitted for neurovascular monitoring while awaiting definitive operative management. Patients with a closed fracture should be placed in a long leg posterior splint while awaiting emergent orthopedic consultation. Circumferential casts are generally avoided in the acute setting due to the risk of compartment syndrome, although some orthopedists will cast pediatric fractures in the acute phase. In general, after fractures have been immobilized, pain decreases. Persistent pain after splinting should raise suspicion for impending compartment syndrome, nerve compression, or vascular compromise.

If an open fracture is noted on examination, a sterile dressing should be placed over the wound and the protruding bone. Ten days of antistaphylococcal antibiotic coverage (typically cefazolin, 2 g) should be given. Gentamicin (3 to 5 mg/kg daily) may be added for severely contaminated wounds. Penicillin G (2 million units IV q4h) should be added after farm-related injuries, while pseudomonas coverage should be provided for wounds contaminated by fresh or salt water. Gentamicin is also the first choice in penicillin-allergic patients. Tetanus vaccination status should be updated as indicated. A long leg posterior splint should be applied with a sugar tong component while awaiting emergent external fixator placement or operative intervention. Osteomyelitis is more likely with open fracture, significant soft tissue disruption, and delayed time from contamination to definitive surgical management.

Proximal Fibula Fractures—Foundations

The fibula is a non–weight-bearing bone, allowing most fibular fractures to be treated nonoperatively. Most fibular fractures result from a direct blow to the lateral aspect of the lower leg. Varus stress to the knee can also result in fibular head and neck fractures. An important exception is the *Maisonneuve fracture* (Fig. 48.13). This injury involves a medial ankle disruption (deltoid ligament tear or medial malleolar fracture), a complete tear of the syndesmosis, and a proximal fibula fracture. Consequently, the fibula floats freely relative to the tibia,

resulting in an unstable ankle mortise, for which surgical fixation is required. The possibility of this injury indicates the need for examination of the proximal fibula in all medial ankle injuries. A neurovascular examination should be performed on any patient with either a Maisonneuve fracture or an isolated proximal fibular fracture, as the peroneal nerve wraps around the proximal fibula.

Proximal Fibula Fractures—Clinical Features

Patients with isolated fibular shaft fractures typically note localized lateral leg pain that increases with ambulation. Localized swelling and tenderness to palpation can be seen on examination. A neurovascular examination should be performed with a particular focus on common peroneal nerve function. Proximal fibular fractures can be associated with both LCL and posterolateral corner injuries. Anterior tibial artery injury with thrombosis may also occur.

Proximal Fibula Fractures—Diagnostic Testing

If a fibular fracture is suspected, the patient should have standard knee, tibia, fibula, and ankle x-ray series performed.

Proximal Fibula Fractures—Management and Disposition

Isolated fibular shaft fractures are treated symptomatically with ice, analgesia, a stirrup splint, and non–weight bearing. Orthopedics follow-up is advised within 1 to 2 weeks to ensure healing and facilitate referral to physical therapy as needed.

For severely displaced fibular shaft fractures or fractures with associated peroneal nerve deficit (e.g., foot drop), or Maisonneuve fractures, ED orthopedic consultation is indicated. A Maisonneuve fracture results in an unstable ankle, and open reduction and internal fixation are usually required.

Proximal Tibiofibular Joint Dislocations—Foundations

The anterior and posterior tibiofibular ligaments and the joint capsule all contribute to the stability of the joint. This combination of structures makes joint dislocation relatively uncommon. Most proximal tibiofibular dislocations result from high-velocity injuries. When dislocation does occur, anterolateral displacement is most common and is typically seen after a fall onto a flexed, abducted leg. Posteromedial dislocation can be seen after direct force is applied to a flexed knee. A neurovascular examination should be performed in posteromedial proximal tibiofibular dislocations, because there is a high rate of peroneal nerve injury associated with the condition. Superior dislocation is associated with ankle diastasis and typically occurs simultaneously with an ankle fracture. This association highlights the need to examine the joints proximal to and distal to the area of primary injury.

Proximal Tibiofibular Joint Dislocations—Clinical Features

The patient may complain that the knee feels "out of joint" or report a sensation of instability. Physical examination reveals lateral knee pain, tenderness, and swelling over the proximal fibula and tibiofibular joint. In the absence of associated injury, findings on knee examination are otherwise normal, with full ROM and no joint line tenderness or effusion.

Proximal Tibiofibular Joint Dislocations—Diagnostic Testing

Standard knee x-rays may confirm the diagnosis, although CT scanning may be required to identify this injury. On the AP view, the fibular head is displaced laterally, and the interosseous space is widened. Comparison views of the uninjured knee may be necessary to appreciate these subtle findings.

Proximal Tibiofibular Joint Dislocations—Management and Disposition

Closed reduction is the first line treatment for acute proximal tibiofibular dislocations. If the patient seeks treatment acutely, reduction of an anterolateral dislocation can be accomplished in the ED by flexing the knee to 90 degrees, everting the ankle, and applying direct pressure to the head of the fibula. Orthopedic referral and immobilization of the knee are necessary after reduction. If closed reduction fails, the patient may require open reduction, with repair of the torn capsule ligaments and surgical pinning. For recurrent dislocations or injuries that do not respond to initial treatment, resection of the proximal fibula or arthrodesis may be effective. Patients with a delayed diagnosis and those with chronic subluxation of the proximal tibiofibular joint may require operative intervention. Orthopedics should evaluate this patient subgroup in the ED.

Stress Fractures—Foundations

Stress fractures, which occur as a result of excessive repetitive force to normal bone, are distinguished from pathologic fractures, which occur as a result of normal forces acting on abnormal bone (e.g., because of osteoporosis or tumor). Lower extremity stress fractures are more common than upper extremity injuries. The most common sites of stress fracture are the tibia, femur, fibula, navicular, and metatarsal bones. The orientation of the fracture (horizontal, oblique, or longitudinal) varies based on the bone involved and the patient's activities.

Stress Fractures—Clinical Features

Bone pain and tenderness without a history of direct trauma are characteristic for most stress fractures. The most important historical information includes a recent increase in physical activity, training on hard surfaces, and inadequate footwear. Most patients with stress fractures note a dull pain that has increased in intensity over time. Pain is initially noted only with activity but may progress to pain with walking and ultimately to pain at rest. Pinpoint tenderness is the hallmark examination finding in the stress fracture patient. In addition, determine if a patient has a previous history of stress fracture. If a female has a history of recurrent stress fractures, further information regarding menstrual irregularities and nutritional deficiencies should be obtained. ROM and muscle strength are preserved.

Stress Fractures—Diagnostic Testing

Stress fractures may be difficult to diagnose on x-ray. X-rays may not reveal the injury until up to 6 weeks after the onset of symptoms. Some stress fractures remain radiographically occult even after 6 weeks. Radiographic findings vary based on the location of the injury and the duration of symptoms, but may include a perpendicular lucency in the bone cortex, bony sclerosis, or new periosteal bone. MRI can be used to detect the injury within a week of symptom development.

If a stress fracture of the lower extremity is suspected and findings on initial plain radiography are unremarkable, follow-up evaluation within 2 weeks may detect radiographic signs of fracture after a period of inactivity. Evidence of healing (periosteal reaction) in response to treatment is sufficient to confirm the diagnosis.

Stress Fractures—Management and Disposition

Most tibial and fibula stress fractures can be treated nonoperatively. Activity should be decreased for 3 to 6 weeks to allow for healing, and serial radiographs should be obtained as an outpatient. If walking causes pain, splinting and non–weight-bearing status should be implemented. Rare cases of nonunion require surgery.

A small subset of stress fractures (including anterior tibia, navicular, fifth metatarsal, patella, sesamoid, and superior sided femoral neck)

are at high risk of progression to complete fracture and should be made non–weight bearing. They may require operative fixation.

Medial Tibial Stress Syndrome—Foundations

The term *shin splints* refers to anterior tibial pain occurring during or after exercise. Formally known as MTSS, the most common causes are a tibial stress reaction or periostitis. Tibial stress reactions are microfractures caused by stress placed on the tibia and are distinct from gross stress fractures, which predispose the bone to complete fracture.

Medial Tibial Stress Syndrome—Clinical Features

This condition is common among athletes, military recruits, and patients engaging in excessive amounts of running. The risk factors for MTSS are similar to those for stress fractures. MTSS is the result of periostitis or stress reaction and lacks a discrete fracture line. Patients with MTSS typically have more generalized tibial pain than patients with stress fractures.

Medial Tibial Stress Syndrome—Diagnostic Testing

Standard tibial/fibular x-rays are not necessary to make the diagnosis of MTSS but should be performed to rule out fracture.

Medial Tibial Stress Syndrome—Disposition and Management

Rest is a key component in the treatment of MTSS and should be done in conjunction with a review of the patient's training habits and footwear use. Orthopedic follow-up is advised.

Compartment Syndrome

Compartment syndrome is a true orthopedic emergency. Clinicians should have a high index of suspicion for the condition in any patient who has sustained a crush injury or an open fracture. Careful attention should be paid to the neurovascular examination in all patients with a concerning mechanism of injury. Compartment syndrome is caused by increased pressure within a fascial compartment, leading to necrosis of muscle and nerve. Diagnosis and management of compartment syndrome is further discussed in Chapter 47.

Soft Tissue Injuries Involving the Lower Leg

Gastrocnemius and plantaris injury—foundations. The gastrocnemius is composed of two distinct muscle bellies, the medial and lateral heads. The medial head is usually slightly larger and stronger than its lateral counterpart and is frequently injured during athletic activities.

The plantaris is a small muscle that originates at the lateral condyle of the femur and passes beneath the soleus to insert on the Achilles tendon. It is a relatively noncontributory flexor of the knee and plantar flexor of the ankle joint, with little functional significance. Rupture may occur at the myotendinous junction, with or without an associated partial tear of the medial head of the gastrocnemius muscle. A strain of the more proximal plantaris muscle also may occur as an isolated injury or in conjunction with injury to the ACL of the knee.

Gastrocnemius and plantaris injury—clinical features. Patients with gastrocnemius injury typically present to the ED with point tenderness and swelling in the calf. If the gastrocnemius has ruptured, a palpable defect may be appreciated on physical exam. Pain typically increases with passive and active ankle dorsiflexion. Patients with a DVT may present in a similar fashion but typically have more edema associated with the pain and are less likely to have been participating in athletic activities at the onset of symptoms. Patients with a ruptured Baker cyst may also present with generalized lower leg edema and pain about the gastrocnemius. Achilles tendon rupture may also be confused with gastrocnemius injury but can be differentiated by the palpable gap just proximal to the calcaneus and a positive *Thompson test*. Gastrocnemius tear can also present similarly to plantaris tendon rupture.

Patients with a plantaris tendon rupture often present with a pop sensation at the time of injury and may have ecchymosis at the proximal aspect of the lower leg. Tenderness is greatest just lateral to the midline of the posterior calf. Examination will show intact strength but pain with plantar flexion. Patients with Achilles tendon rupture may similarly note hearing "a loud pop" while running or jumping. In contrast, Achilles tendon rupture is associated with lower leg pain that is more distal to the pain associated with plantaris or gastrocnemius injury.

Gastrocnemius and plantaris injury—diagnostic testing. Venous duplex should be performed to rule out DVT and may help to differentiate between these conditions. Soft tissue defects can be seen on standard tibia/fibula x-rays, but this is not the preferred diagnostic modality. MRI is the optimal study for diagnosis because it permits the quantification of tendon retraction, but it is not indicated in the ED.

Gastrocnemius and plantaris injury—management and disposition. A small partial rupture of the medial head of the gastrocnemius can be treated with rest and non–weight bearing for several days. Extensive incomplete or complete gastrocnemius ruptures should be managed with splinting in plantar flexion with urgent orthopedic follow-up.

For plantaris injury, treatment is symptomatic, with a posterior splint in partial equinus position for the first few days if the pain is severe. The patient should be cautioned that significant posterior calf and posterior ankle ecchymosis often appears over the first few days. All patients with gastrocnemius injury or plantaris injury should be given strict precautions regarding the signs and symptoms of compartment syndrome and DVT.

Foreign bodies. Foreign bodies such as plant matter (e.g., thorns), glass, and metallic objects are commonly encountered in the leg. Missed retained foreign bodies in the lower leg can be the cause of cellulitis, abscess, necrotizing fasciitis, and gangrene. Plain films are a necessary part of the initial evaluation but will be unremarkable when the foreign body is radiolucent. Ultrasound may be used to assess for localized infection while helping to identify a foreign body. Ultrasound is more readily available than MRI and is the modality of choice in the ED, particularly if there is the possibility of metal fragments in the wound. If a retained foreign body is suspected, antibiotics should be initiated in the ED. Surgical exploration is sometimes necessary for deeper positioned foreign bodies. Extraction is difficult, and these types of foreign bodies should be removed by a surgeon, often in the operating room.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 48: QUESTIONS AND ANSWERS

1. A 45-year-old woman presents after a high-impact motor vehicle collision with pain in the left knee. She thinks her knee may have gone out of place but isn't sure. The distal neurovascular examination is intact. What is the most appropriate management?

a. Compression wrap and early range of motion exercises
b. Discharge if radiographs are negative with partial weight bearing
c. Knee immobilizer with orthopedic follow-up
d. Measure ankle-brachial index and perform duplex ultrasonography if less than 0.9
e. Orthopedic consultation

Answer: d. This patient had a knee dislocation. Knee dislocation is uncommon but should be considered in the setting of an appropriate injury mechanism because 50% of all knee dislocations are reduced spontaneously before emergency department (ED) arrival. Reduction before ED arrival does not lessen the likelihood of vascular injury, and vascular injury should be considered in patients with severe ligamentous injuries and injuries caused by high-energy mechanisms. Vascular injury to the popliteal artery is the most severe complication and is the major cause of morbidity and limb loss. Management of suspected knee dislocation involves an algorithm designed to be noninvasive but sensitive for arterial injury.

2. A 42-year-old man was at the gym performing squatting exercises. As he was coming to a stand, he had an immediate onset of pain in his right thigh. He presents with an inability to extend his knee. What is the most likely physical finding?

a. High-riding patella
b. Mid-quadriceps muscle tenderness and deformity
c. Popliteal swelling and tenderness
d. Positive Lachman test
e. Suprapatellar tenderness with patella baja

Answer: e. This is a quadriceps tendon rupture. Patients with extensor disruption may have signs and symptoms that include an acute onset of pain, swelling, ecchymoses over the anterior aspect of the knee, a palpable defect in the patella, quadriceps tendon, or patella tendon loss or limited ability for active leg extension; extension lag usually is seen when the last 10 degrees of extension are performed haltingly or with difficulty. With quadriceps rupture, a low-riding patella (patella baja) and inferior retraction may be seen.

3. A college football lineman presents complaining of left knee pain and inability to bear weight. He was on the scrimmage line when the ball was placed in motion and, as he lunged forward, he twisted his leg and heard an audible pop in his knee. He was immediately unable to bear weight. On physical examination, you find the left knee swollen, with a positive Lachman test. What is the most sensitive way to diagnose the injury accurately?

a. Arthroscopy of the knee
b. Computed tomography (CT) scan of the knee
c. History and physical examination
d. Magnetic resonance imaging (MRI) of the knee
e. Plain radiography of the knee

Answer: a. Clinical evaluation is moderately sensitive for anterior cruciate ligament (ACL) tears but, in the acute phase, is often inaccurate because of swelling and splinting. Acutely, only plain films are indicated as long as dislocation is not suspected. Tibial plateau fractures detected on plain film may require CT scanning to determine the need for admission for early operative repair. Arthroscopy is the gold standard for diagnosis of soft tissue injuries of the knee. MRI is useful but may miss small tears and anatomic abnormalities, and a normal study may still lead to arthroscopy if symptoms persist. MRI scanning of the knee is rarely indicated in the emergency setting.

4. A man presents with severe pain of his right lower leg. He was in the ED the previous night for splint placement for a tibial fracture. After removal of the splint, you see a lower leg with mild ecchymosis, healing abrasions, and palpable posterior tibial and dorsalis pedis pulses. He has severe pain on passive movement of his first toe and decreased sensation of the first toe web space. Which of the following should be the next step?

a. Admit for intravenous (IV) antibiotics and pain control.
b. Obtain venous Doppler scans.
c. Resplint the patient.

d. Test the anterior compartment pressures.
e. Test the superficial posterior compartment pressures.

Answer: d. The lower leg is divided into the following compartments by deep partitions of the investing crural fascia—anterior, lateral, superficial posterior, and deep posterior. The anterior compartment contains the tibialis anterior, long toe extensor muscles, anterior tibial artery, and deep peroneal nerve, which supplies sensation to the first web space of the foot.

5. A severe medial ankle sprain with no ankle fracture necessitates evaluation of which of the following?
a. Cervical spine
b. Femoral nerve
c. Lumbar spine
d. Popliteal artery
e. Proximal fibula

Answer: e. An important exception to fibular fractures being stable is a Maisonneuve fracture (see Fig. 48.13). This involves a medial ankle disruption (deltoid ligament tear or medial malleolar fracture), with complete tearing of the syndesmosis joining the tibia and fibula and fracture of the proximal fibula. This results in an unstable ankle mortise because the fibula now floats free relative to the tibia, and surgical fixation is required.

Ankle and Foot Injuries

Nicholas G.W. Rose and Thomas J. Green

KEY CONCEPTS

- The Ottawa Ankle and Foot Rules should be used to evaluate the need for x-rays in ankle and foot injuries.
- CT scans are indicated for negative x-rays of the ankle and foot when a high clinical concern of fracture exists.
- Ankle dislocations with obvious vascular compromise should be reduced promptly, before radiographs are obtained.
- The entire fibula should be examined if a medial malleolar fracture is present to rule out a proximal fibular (*Danis-Weber type C or Maisonneuve*) fracture.
- Osteochondral lesions of the talar dome, nondisplaced fractures of the lateral posterior process of the talus, and fracture of the anterior process of the calcaneus are important to include in the differential diagnoses of presumed ankle sprains.
- Patients discharged with a diagnosis of ankle sprain should be encouraged to seek outpatient follow-up should ankle pain and swelling persist for longer than 2 weeks.
- Patients with Achilles tendon rupture are still capable of weak plantar flexion. Ultrasound may be used to confirm the diagnosis if clinical uncertainty exists.
- A Lisfranc injury should be considered with any fracture or dislocation in the tarsometatarsal region, particularly with fractures of the second metatarsal base. When suspicion for a Lisfranc injury is high, even if plain radiographs and CT scans are negative, immobilization and orthopedic referral are indicated.
- Fifth metatarsal tuberosity (zone 1) fractures should be carefully differentiated from diaphyseal fractures. Orthopedic referral is indicated for zones 2 and 3 fractures.
- Stress fracture should be considered in patients with long-standing foot pain, particularly if symptoms are in the metatarsal region. This may be diagnosed by plain radiography, CT scanning, or radionuclide bone scanning.
- Compartment syndrome may occur in any of the four major compartments of the foot. Diagnosis is made by high clinical suspicion and measurement of the intracompartmental pressures.

ANKLE

FOUNDATIONS

Background and Importance

The ankle and foot are highly evolved structures designed to support the body's weight and facilitate locomotion over varied terrain. Pathology related to ankle and foot injuries is often subtle, and diagnoses may be delayed or missed, particularly in cases of multiple trauma.

The ankle and foot are best approached clinically as a single functional unit. Although they are discussed sequentially in this chapter, mechanisms of injury overlap, and a pathologic condition in one location may accompany an associated pathologic condition in another.

Anatomy

The ankle joint is the articulation of the tibia and fibula with the talus. The dome of the talus fits into the mortise formed by the medial malleolus, horizontal articular surface of the tibia (or plafond, French for "ceiling"), and lateral malleolus. Fundamentally, the stability of the ankle depends on the bony and ligamentous integrity of the mortise. The calcaneus is also important for the motion and stability of the ankle (Figs. 49.1 and 49.2).

The ankle is composed of three primary articulations—the inner surface of the medial malleolus with the medial surface of the talus, the distal tibial plafond with the talar dome, and medial surface of the lateral malleolus with the lateral process of the talus. These three articular surfaces are contiguous, lined with cartilage, and enclosed by a single joint capsule. The distal tibia also articulates with the distal fibula just proximal to the talus, forming the distal tibiofibular joint. Collectively, these articulations are termed the *talocrural joints*.

Three sets of ligaments—the syndesmotic ligament and lateral collateral ligaments (see Fig. 49.1), and medial collateral ligaments (see Fig. 49.2), together which make up the deltoid ligament—support the ankle joint and are essential to its stability.

Tendons course through the ankle in four anatomic groups (Fig. 49.3). The flexor retinaculum tethers the tendons of the tibialis posterior, flexor digitorum longus, and flexor hallucis muscles behind the medial malleolus. The peroneal retinaculum and tendon sheath tether the peroneus longus and brevis tendons behind the lateral malleolus. The extensor retinaculum tethers the tendons of the tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus tertius over the anterior aspect of the ankle. Posteriorly, in the midline, lie the Achilles and plantaris tendons.

Physiology and Pathophysiology

Ankle movements are multifaceted and often involve more than one joint. The ankle joint complex is made up of the talocrural joints and talocalcaneal (subtalar) joints, which allow movements along several axes of motion. Dorsiflexion (ankle flexed so the toes point cephalad) and plantar flexion (ankle extended so the toes point toward the floor) of the ankle joint occur primarily at the talocrural joints. Motions of the ankle joint in conjunction with the midtarsal joints include inversion (sole of the foot points to the midline), eversion (sole of the foot points away from the midline), abduction (external rotation of the foot), and adduction (internal rotation of the foot), which are rotational movements about the longitudinal axis of the tibia.

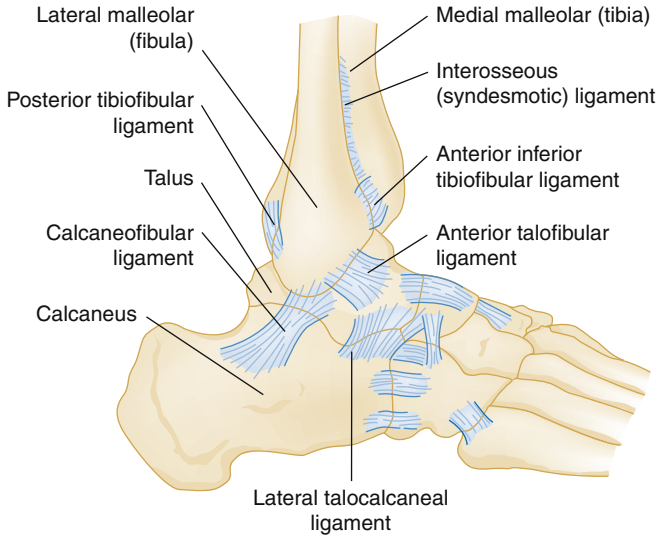

Fig. 49.1 Anatomy of the lateral collateral and syndesmotic ligaments of the ankle.

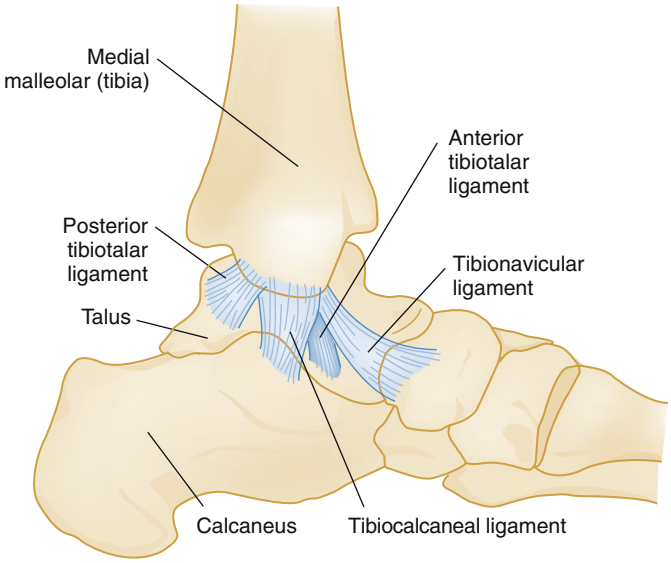

Fig. 49.2 Anatomy of the medial collateral ligaments of the ankle, which collectively constitute the deltoid ligament.

The components providing stability to the ankle are best conceptualized as a ring-like structure surrounding the talus (Fig. 49.4). Disruption of one element of this ring does not, by itself, induce instability. Injury to one ring element, however, should prompt careful scrutiny for a second injury. Any disruption of two or more elements causes ankle instability and can significantly affect joint function.

Fractures occur when a deforming force is sufficient to overcome the structural strength of a bone. A bone under tension fractures along the axis of the deforming force. Alternatively, ligamentous rupture or an avulsion fracture can occur at either end of a stressed ligament or tendon, and the mechanism of injury generally causes predictable fracture patterns (Fig. 49.5).

Clinical Features

Carefully eliciting the mechanism of injury can often provide clues to the injuries sustained. The presence of sudden swelling and severe pain in the ankle region suggests serious ligament disruption, hemarthrosis, or fracture, and rapid progression of symptoms may represent more severe injury. Inability to bear weight immediately after an injury often implies a significant pathologic condition. Patient recollection of a "popping" sound should prompt consideration of ligament, tendon, or retinacular rupture but does not necessarily increase the probability of a fracture. Finally, the inciting event causing the ankle injury should be determined and, when necessary, investigated further.

The physical examination of the ankle starts with an assessment of deformity, ecchymosis, edema, and perfusion, followed by active and passive range of motion. Assessment of point tenderness may help localize and differentiate between ligament, bone, or tendon injuries, particularly when the patient is seen soon after injury. Palpation should include the medial and lateral collateral ligaments, syndesmotic ligament, inferior and posterior edges of the medial and lateral malleoli, entire length of the fibula and tibia, anterior plafond, base of the fifth metatarsal, calcaneus, Achilles tendon, and tendons behind the medial and lateral malleoli. In addition, the medial and lateral dome of the talus is palpable with the ankle in plantar flexion. Stress testing of the ankle joint, discussed later, should not be performed until a fracture has been excluded. An evaluation of weightbearing ability should proceed only if clinical suspicion of a fracture is low, the location of tenderness does not indicate the need for plain radiography, or radiographs have ruled out a fracture.

Clinical findings specific to ankle fractures include ankle swelling, obvious deformity, skin abnormalities including lacerations and tenting and, if presenting in a delayed fashion, fracture blisters. Neurovascular compromise may occur, therefore performance of a neurovascular examination distal to the injury is necessary. If the fracture has occurred due to a fall from a height, the ankle injury can mask other injuries, such as lumbar compression fracture, fractures of the pelvis, tibial plateau, or other axial skeleton injuries. *Maisonneuve fractures* can also cause a neuropraxia to the peroneal nerve. Compartment syndrome is a rare complication following isolated ankle fracture and is usually associated with significant disruptive fracture patterns.

Early operative complications of closed and open ankle fractures include pin site infection, delayed skin necrosis, skin graft rejection, neuropraxia or neurotmesis, and osteomyelitis. Delayed complications of operative and nonoperative treatment include malunion, nonunion, osteopenia, traumatic arthritis, chronic instability, ossification of the interosseous membrane, avascular necrosis, and complex regional pain syndrome.

Differential Diagnoses

There is much overlap in the clinical presentation of skeletal, ligamentous, and tendinous pathologies of the ankle and foot due to the complex anatomy and hence differential diagnoses are broad, especially in subtler presentations (Box 49.1).

Diagnostic Testing

Radiology

The anteroposterior, lateral, and mortise views constitute the standard three-view radiographic series of the ankle. Subtle fractures can be easily overlooked on ankle radiographs, and a standardized approach to radiographic interpretation can reduce the likelihood of missing ankle fractures (Fig. 49.6). The lateral view is useful in identifying an ankle effusion, which appears as a teardrop-shaped density displacing the normal fat adjacent to the anterior or posterior margin of the joint capsule. The presence of an effusion suggests the possibility of a subtle intra-articular injury, such as an osteochondral lesion of the talar dome.

The mortise view, taken with the ankle in 15 to 25 degrees of internal rotation, and the lateral view are the most important for evaluating the congruity of the articular surface between the dome of the talus

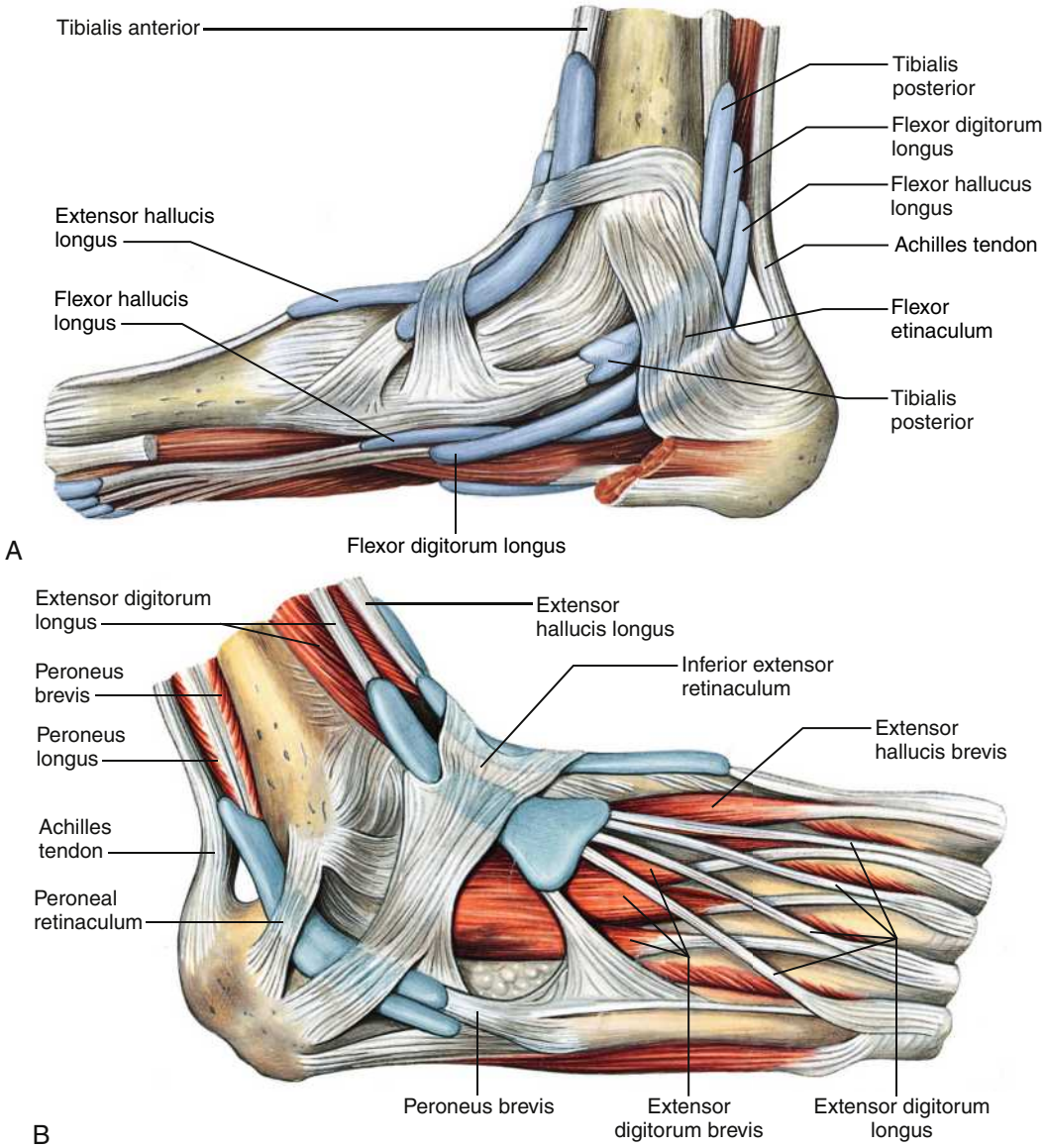

Fig. 49.3 Tendons of the ankle and foot. (A) Medial view. (B) Lateral view. (From Paulsen F, Waschke J. Lower limb. In: Paulsen F, Waschke J, eds. *Sobotta Atlas of Anatomy: General Anatomy and Musculoskeletal System*, ed. 16, vol. 1. Elsevier GmbH; 2018: Fig. 4.115a and b.)

and mortise. In the mortise view, the lines formed between the articular surfaces should be parallel, the joint space should appear uniform throughout the tibiotalar and talofibular components of the joint, and the medial clear space should not exceed 4 mm (see Fig. 49.6 and Fig. 49.7). On the lateral view, any incongruity of the articular space between the talar dome and distal tibia suggests ankle instability, particularly if narrowing of the anterior joint space is present.

Reproducible methods for the radiologic evaluation of syndesmotic diastasis have proven elusive.[1] Plain radiographs are the least reliable method for identifying syndesmotic instability. Rather than rely on standard measurements to evaluate for syndesmotic injury, comparison to the contralateral ankle may be valuable in identifying syndesmotic diastasis. The diagnosis of syndesmotic instability can be difficult in the emergency department (ED) and often relies on advanced imaging, which can be arranged at the time of specialist consultation.

In most cases of isolated blunt ankle trauma evaluated within 48 hours of injury, the Ottawa Ankle Rules (OAR) may be used by clinicians to determine whether ankle or foot radiographs are necessary. The OAR state that an ankle radiographic series is required if there is pain in the malleolar region with any of the following findings:

- Bone tenderness at the posterior edge of the distal 6 cm or tip of the lateral malleolus
- Bone tenderness at the posterior edge of the distal 6 cm or tip of the medial malleolus
- Inability to bear weight (defined as the ability to transfer weight onto each leg regardless of limping) for at least four steps immediately after the injury and at the time of ED evaluation

The OAR further state that a foot radiographic series is required if there is pain in the midfoot region with any of the following findings:

- Bone tenderness at the navicular bone
- Bone tenderness at the base of the fifth metatarsal
- Inability to bear weight for at least four steps immediately after the injury and at the time of ED evaluation

The OAR have a sensitivity approaching 100% for detecting acute malleolar zone ankle fractures and midfoot zone fractures but cannot be applied to subacute or chronic injuries. Although derived in an adult

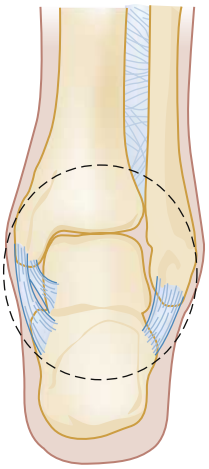

Fig. 49.4 The ring structure surrounding the talus is made up of the tibial plafond, medial malleolus, deltoid ligaments, calcaneus, lateral collateral ligaments, and syndesmotic ligaments. The integrity of this ring determines the stability of the ankle, and the degree of disruption determines the need for operative intervention.

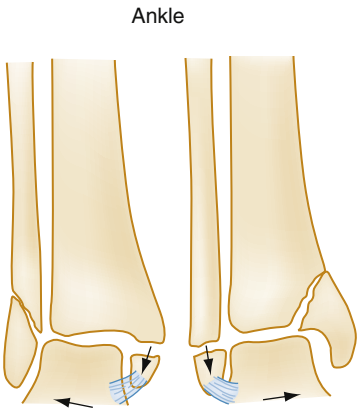

Fig. 49.5 The mechanics of bone failure in rotational tension and types of tension ankle fractures. *Arrows* indicate the direction of distracting forces.

population, the OAR appear to be clinically applicable in pediatric patients older than 5 years. In children younger than 5 years, alternative approaches can be used (see Chapter 170). Nurse initiated application of the OAR has proven to have similar sensitivity and reduce wait times in the ED.[2,3]

The decision rules for foot radiography, although applicable to blunt ankle trauma, apply only to the midfoot zone. The OAR were not designed to be general guidelines for foot radiography and do not apply to the hindfoot or forefoot. Finally, the OAR are not applicable to intoxicated patients or those who are difficult to assess because of head injuries, altered mental status, multiple injuries, or diminished sensation related to neurologic deficits.

Other Imaging Techniques

Although plain radiography is the initial imaging modality of choice for ankle injuries, it can miss subtle ankle fractures, osteochondral lesions, stress fractures, or ligamentous injuries. When unexplained symptoms persist after negative or inconclusive findings on plain radiographs, other imaging modalities or orthopedic consultation may be advisable. In situations where these are unobtainable, the ankle should be immobilized, the patient discharged with instructions to be nonweightbearing, given clear instructions that a fracture may be present despite the lack of conclusive evidence on x-ray, and instructed that repeat x-rays or additional imaging may be required on follow-up examination.

BOX 49.1 Differential Diagnoses for Presumed Ankle Fracture/Dislocation

Ankle sprain
Achilles tendon rupture
Syndesmosis injury ± proximal tibial fracture
Retinaculum rupture
Tendon dislocation
Monoarthropathies (gout/pseudogout/septic arthritis)
Charcot joint
Foot fracture
Pathologic fracture

Computed tomography (CT) imaging provides superior bone images and is an excellent modality to delineate abnormalities not identified or incompletely characterized by other imaging techniques. This is particularly relevant in the foot and ankle, where plain radiographs are complicated by overlying structures and complex articulations. In acute injuries, CT imaging of the foot or ankle is indicated, despite apparently normal radiographs when a fracture is highly suspected.[4] The emergency clinician can perform CT imaging in the ED or as part of outpatient follow-up, with the ankle immobilized and nonweightbearing in the interim. CT scan can detect small fractures, subtle stress fractures, intraarticular fractures, syndesmotic instability, and tendon entrapment or dislocation.[5,6] In certain cases, CT imaging plays an important role in surgical planning.

Radionuclide imaging (bone scanning) can detect soft tissue injuries such as distal syndesmotic disruptions, stress fractures, and osteochondral lesions. Bone scan abnormalities are present once a patient is symptomatic; for example, they typically appear 1 to 2 weeks before radiographic evidence of a stress fracture. Because of its high sensitivity, a negative bone scan effectively rules out the diagnosis. Bone scan abnormalities are nonspecific, however, because infections and tumors also can lead to positive results (see later discussion on stress fracture imaging of the foot). Bone scanning is not useful for follow-up because abnormalities can persist for up to 1 year after recovery. Radionuclide imaging should be ordered on an outpatient basis and has been largely supplanted by CT and magnetic resonance imaging (MRI).

Ultrasound has limited utility in the ED with the exception of the evaluation of tendons, and to some degree, ligamentous structures. Its relative simplicity and rapid availability have led to its increased utility in point-of-care settings in the ED. Ultrasound can easily identify tendinous disruption. The more technically difficult dynamic ultrasound can be used to identify tendinous subluxation or disruption.

MRI, although not typically performed emergently, provides unprecedented clarity in depicting soft tissue structures such as ligaments, tendons, and the syndesmosis, and can also delineate bone marrow changes associated with stress fractures before radiographic abnormalities appear. MRI can be helpful in guiding management decisions and following the patient's response to therapy.

MRI or CT arthrography can be useful in the evaluation of chronic ankle pain to detect loose bodies, ligamentous injuries, cartilaginous abnormalities, or osteochondral lesions. CT plus single-photon emission computed tomography (SPECT), which combines CT and radionuclide scanning, has been shown to increase the diagnostic ability of imaging significantly in osteochondral lesions, stress fractures, impingement syndromes, and osteomyelitis. The decision to perform specialized imaging of this nature is typically made through orthopedic

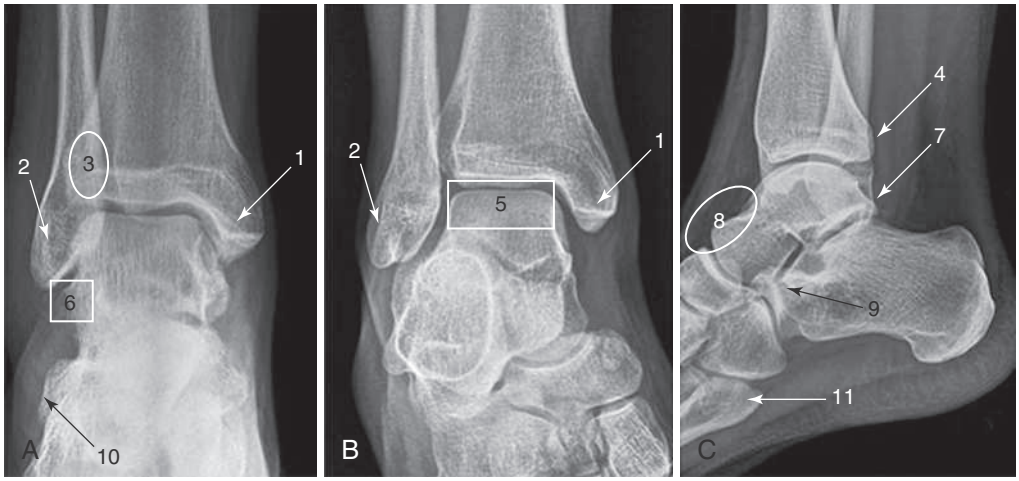

Fig. 49.6 Approach to reviewing ankle radiographs. (A–C) A standard radiographic series of the ankle has three views—an anteroposterior view (A), an internal rotation or mortise view (B), and a lateral view (C). The following 11 locations should be carefully scrutinized because they are areas where fractures frequently occur: medial (1) and lateral (2) malleoli, anterior tibial tubercle (3) and posterior tibial malleolus (4), talar dome (5), lateral talar process (6), tubercles of the posterior talus process (7), dorsal to the talonavicular joint (8), anterior calcaneus process (9), calcaneal insertion of the extensor digitorum brevis (10), and base of the fifth metatarsal bone (11). (From Yu JS, Cody ME. A template approach for detecting fractures in adults sustaining low-energy ankle trauma. *Emerg Radiol.* 2009;16:309.)

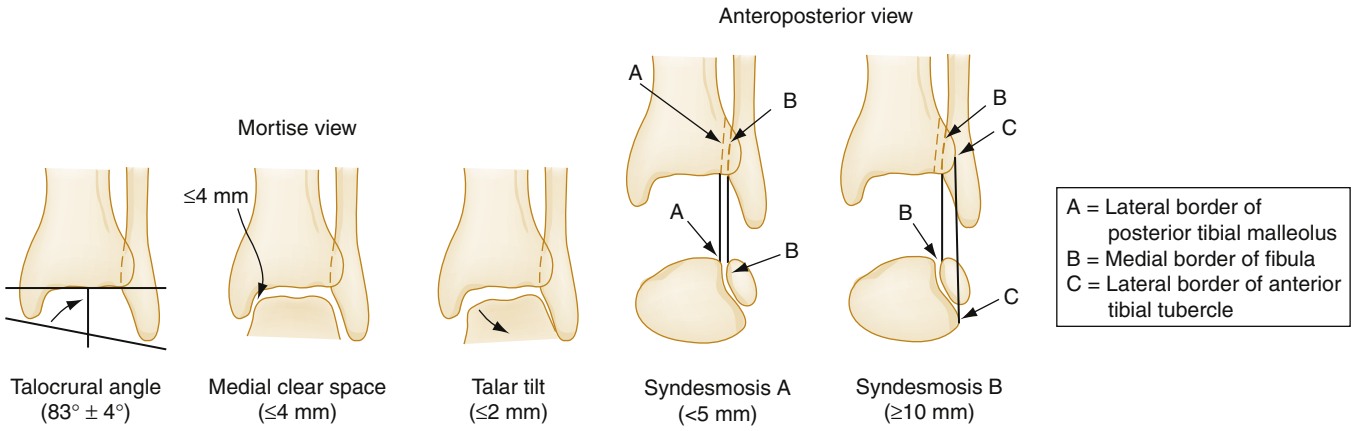

Fig. 49.7 Radiologic criteria for evaluating the stability of the ankle mortise.

or radiologic consultation; such studies are not routinely performed in the ED.

ANKLE FRACTURES AND DISLOCATIONS

General Considerations

The management of ankle fractures consists of identification and classification, emergent reduction of fracture-dislocations that threaten soft tissues or neurovascular status, and specific treatment and disposition. Most important, an evaluation of the stability of the ankle joint affects the decision for conservative versus operative repair.

To date, no ideal system has been developed for the classification of ankle fractures. The *Lauge-Hansen classification* and *Danis-Weber systems* are based on mechanism of injury and fracture location, respectively. The Lauge-Hansen classification was intended to characterize ligamentous injury patterns based on the radiographic appearance of ankle fractures but is complex and has been shown to have limitations in broad applicability. The Danis-Weber system (Fig. 49.8) has predictive value for operative repair in isolated lateral malleolar fractures because the location of the fibular fracture is related to the integrity of the syndesmosis. As such, it is more useful to emergency clinicians than the Lauge-Hansen classification. Both systems have limitations, however, and neither accurately predicts management or clinical outcome in all situations. Further details regarding how and when to apply the Danis-Weber system are provided in the following discussions of specific fractures.

The injured ankle should be promptly immobilized, elevated, and iced to minimize swelling and further soft tissue damage. The presence of gross deformity with neurovascular compromise or skin tenting necessitates prompt intervention. Plain radiography before reduction can be helpful but should not delay reduction in injuries with obvious vascular compromise.

In all cases, appropriate procedural sedation and analgesia techniques are required for reduction. The notion that some reductions are accomplished relatively quickly and easily (from the clinician's perspective) is not an excuse for failing to adequately manage the extreme pain that these orthopedic manipulations may cause for the patient. The fundamental principle of closed reduction is to reverse the deforming

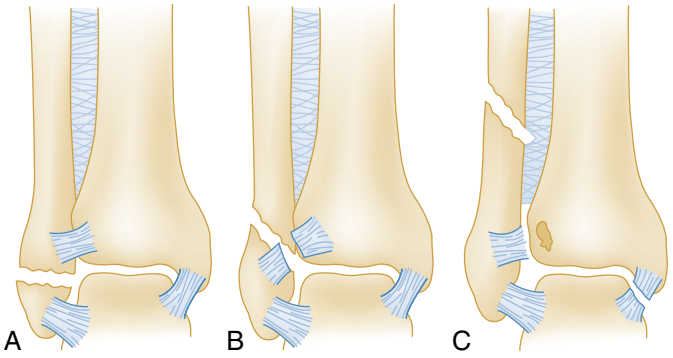

Fig. 49.8 The Danis-Weber classification of ankle fractures focuses on the location of the fibular fracture in relation to the tibiotalar joint and syndesmosis. Weber A fractures involve inversion-adduction forces. Weber B fractures involve abduction forces. Weber C fractures involve eversion-abduction forces. See text for further explanation.

forces. For example, reduction of a fracture-dislocation caused by an adduction injury might require an opposite abduction force. The initial application of a distracting force, sometimes combined with slightly increasing the deformity, is often helpful in achieving reduction. After reduction, neurovascular status should be reassessed, the leg immobilized and elevated, and postreduction radiographs obtained. The overarching goal in the definitive treatment of ankle fractures is to achieve anatomic reduction.

The outcome of ankle fractures depends on the extent of injuries, number of malleoli fractured, ankle stability, and patient age. All displaced or potentially unstable ankle fractures require orthopedic consultation. Traditionally, patients with displaced or unstable ankle fractures were admitted for operative repair, but it has been shown that delayed repair does not affect outcomes, and outpatient management where the emergency clinician immobilizes the patient's fracture, provides strict nonweightbearing instructions, and refers the patient to orthopedics on an urgent basis (within 24–48 hours) is acceptable.[7]

Extraarticular nondisplaced fractures that disrupt only one ring element generally can be treated with casting for 3 to 6 weeks.[8] Depending on the type of ankle fracture, and its stability, some fractures may be made weightbearing as tolerated, whereas others may be nonweightbearing, requiring the use of crutches. The presence of any abnormal measurement on the mortise view (Fig. 49.6) suggests instability and the need for orthopedic consultation, typically within 48 hours. Displaced fractures generally require reduction before immobilization and referral. Avulsion fractures, in which the avulsed fragment is smaller than 3 mm in diameter and minimally displaced, can be treated in a similar manner to an ankle sprain.

Unimalleolar Fractures

Lateral Malleolar Fractures

Lateral malleolar fractures are the most common ankle fracture. Stability of the ankle joint depends on the location of the fracture in relation to the level of the tibiotalar joint, which defines the distal portion of the syndesmotic ligament. The Danis-Weber classification (see Fig. 49.8) is useful and predictive of outcome in these types of unimalleolar fractures. This classification groups fractures into three types—A, B, and C. Subgroups exist but do not assist the emergency clinician in prognosticating the necessity of operative repair and are beyond the scope of this chapter.

Lateral malleolar fractures below the tibiotalar joint (Danis-Weber type A) rarely disrupt other bony or ligamentous structures and, in the absence of injury to medial structures, such fractures are unlikely to affect the dynamic congruity of the ankle joint. Uncomplicated Weber A lateral malleolar fractures may be considered part of the continuum of ligamentous ankle injuries and managed with functional bracing or walking boot and weightbearing as tolerated, with orthopedic follow-up within a week to ensure ongoing union. Concomitant tenderness over the deltoid ligament may suggest a biomechanical disruption of both malleoli, an associated fracture of the medial malleolus, or an associated fracture of the posterior malleolus. This injury warrants orthopedic consultation within 48 hours on an outpatient basis, especially if the medial clear space on the mortise view is widened (see Fig. 49.6). CT imaging can be useful in such situations because it may identify occult medial or posterior malleolar fractures.

Fibular fractures proximal to the tibiotalar joint line (Danis-Weber type C injury; see Fig. 49.8) frequently disrupt the distal tibiotalar syndesmosis and medial structures causing ankle instability. These commonly require orthopedic consultation in the ED, or within 48 hours on an outpatient basis (where the patient is immobilized and made nonweightbearing) for operative intervention.

Treatment of an isolated fibular fracture at the level of the tibiotalar joint (Danis-Weber type B injury; see Fig. 49.8) is controversial. Fifty percent of these injuries are accompanied by an injury to the distal tibiofibular syndesmosis causing ankle joint instability, and therefore may require operative intervention. Historically, Danis-Weber B fractures were all treated operatively, but the tendency more recently is to base the decision to operate on the stability of the joint, rather than purely on a radiologic classification system.[9,10] Tenderness on palpation of the syndesmotic ligament, a positive squeeze test (see soft tissue injury section), or widening of the medial joint space on the mortise x-ray view confirms the need for orthopedic consultation in the ED, or within 48 hours on an urgent outpatient basis (where the patient is immobilized and made nonweightbearing) for consideration of operative repair. Stress x-ray views, which include gravity or manual stressing of the fractured ankle, can identify ligamentous instability and clarify the need for operative intervention but are generally arranged by the orthopedic consultant. If discharged from the ED for urgent outpatient orthopedic follow-up, the patient is placed in a walking boot or noncircumferential splint and made nonweightbearing.

Medial Malleolar Fractures

Medial malleolar fractures are usually the result of eversion or external rotation. These two forces exert tension on the deltoid ligament, causing an avulsion of the tip of the medial malleolus or a rupture of the deltoid ligament. Although they can occur in isolation, medial malleolar fractures are commonly associated with lateral or posterior malleolar disruption. Because of this, identification of a medial malleolar fracture or deltoid ligament injury warrants a careful examination of the entire length of the fibula. Tenderness at any point warrants radiographic evaluation to rule out a proximal fibular fracture, known traditionally as a *Maisonneuve fracture* (Fig. 49.9). Any medial malleolar fracture requires orthopedic referral for assessment of joint and syndesmosis stability for operative syndesmotic stabilization. An isolated nondisplaced medial malleolar fracture can be treated with casting for 6 to 8 weeks, with nonweightbearing and close orthopedic follow-up on an urgent basis, usually within 48 hours. Any displacement or concurrent disruption of the lateral components of the ankle warrants orthopedic consultation in the ED or on an urgent outpatient basis for consideration of operative management. Rarely, stress fractures of the medial malleolus or distal fibula can be seen, particularly in athletes and runners. Plain radiographs may be nondiagnostic, but radionuclide bone scanning, CT imaging, or MRI—the choice is often influenced by local availability—can establish the diagnosis. These injuries can be treated nonoperatively with nonurgent outpatient orthopedic consultation.

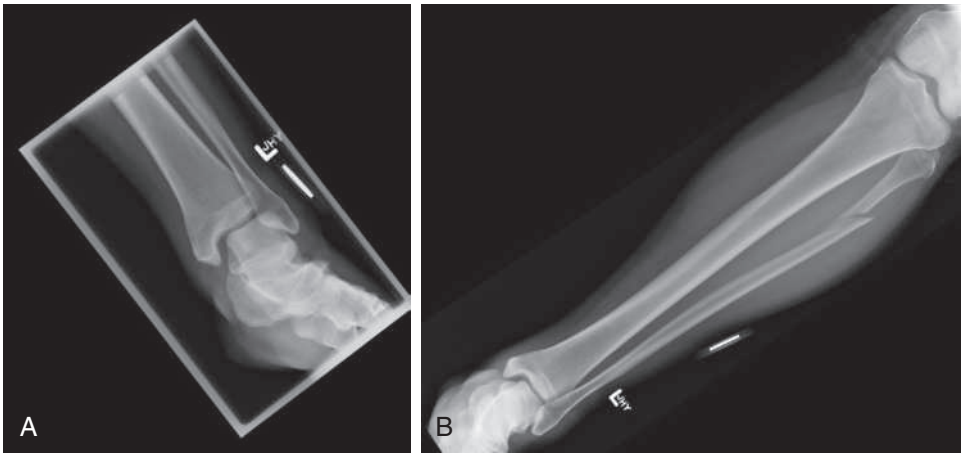

Fig. 49.9 Maisonneuve fracture. (A) Anteroposterior view shows a slight widening of the ankle mortise and the medial clear space. (B) Anteroposterior view shows an oblique fracture at the proximal shaft of the fibula. (Courtesy Dr. Nicholas G.W. Rose.)

Posterior Malleolar Fractures

Isolated fractures of the posterior malleolus are rare and imply an avulsion of the posterior tibiofibular ligament. These injuries can be associated with proximal fibular fractures and medial and lateral collateral ligament sprains. Treatment usually consists of casting for 6 weeks for nondisplaced fractures in which no associated injury or ankle instability is present. CT scanning is generally used to ensure anatomic reduction prior to conservative management. Fractures involving more than 25% of the tibial surface usually require open reduction and internal fixation (ORIF); however, this is an area of controversy, and displaced posterior malleolar fractures require orthopedics consultation within 48 hours on an urgent outpatient basis (where the patient is immobilized and made nonweightbearing).

Bimalleolar Fractures

Bimalleolar fractures involve the disruption of at least two elements of the ankle ring (see Fig. 49.4) and are therefore unstable. These fractures result from adduction or abduction forces, with the latter being more common. Rotational injuries also can cause bimalleolar fractures, as well as trimalleolar fractures, if the posterior malleolus is involved. Associated damage to other soft tissue structures (e.g., the syndesmosis) is common with bimalleolar fractures.

Controversy exists about whether nondisplaced bimalleolar fractures should be treated with surgical or closed reduction, and orthopedic consultation in the ED or within 48 hours on an urgent outpatient basis is warranted. The patient should be made nonweightbearing and placed in a walking boot or posterior splint until specialist follow-up.

Trimalleolar Fractures

Trimalleolar fractures involve fractures of the medial, lateral, and posterior malleoli and almost always require urgent surgical fixation due to their gross instability with orthopedic consultation in the ED.

Open Fractures

Open fractures require emergent orthopedic consult as most benefit from early surgical intervention for débridement and irrigation. After documentation of the neurovascular status and extent of soft tissue trauma, gross contaminants should be removed from the wound, saline-soaked sterile gauze should be applied, and the injured leg should be splinted. Swabbing an open wound for bacterial culture and sensitivity testing is unnecessary. If significant deformity is present, immediate reduction with appropriate analgesia before splinting is indicated. Tetanus immunoprophylaxis should be administered, as appropriate. Because open fractures are invariably contaminated with bacteria, patients with these injuries should receive intravenous (IV) antibiotics within the first hour in the ED. For low-energy injuries with mild to moderate contamination, a first-generation cephalosporin is usually sufficient. Heavily contaminated wounds require the addition of gram-negative bacterial coverage, typically an aminoglycoside. Adding penicillin G or clindamycin (if the patient is penicillin-allergic) as a third antibiotic is recommended for farm- or soil-related crush injuries, in which contamination with *Clostridium perfringens* can be present.

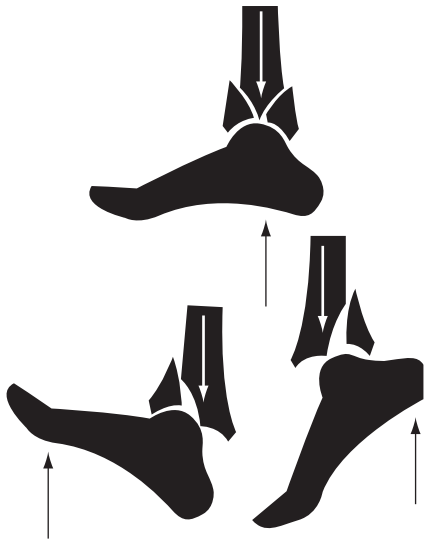

Fig. 49.10 Schematic diagram of the pathophysiology of pilon fractures. The position of the foot at the time of impact determines the fracture pattern.

Pilon Fractures

Clinical Features

Pilon fractures involve the distal tibial metaphysis and usually are the result of high-energy mechanisms with axial loading of the ankle joint, such as falls from a significant height (Fig. 49.10). Destot first coined

the term *hammer fracture* to describe how the head of the talus drives itself into the tibial plafond and causes a pilon fracture. The primary deforming force is one of axial compression, and the position of the foot at the time of injury determines the fracture location and pattern (see Fig. 49.10). Secondary rotational or shear forces may cause increased comminution and fragment displacement with more extensive soft tissue injuries. These injuries often are comminuted and thus associated with significant soft tissue trauma, tendon entrapment or dislocation, devastation of joint architecture, and leg shortening. Due to the high-energy mechanism of injury, patients with pilon fractures frequently have other significant injuries and patient assessments should take into account these mechanisms and include a full evaluation of the neurovascular status of the foot.

One-fourth of pilon fractures are open; associated injuries include fractures of the calcaneus, tibial plateau, fibula, femoral neck, acetabulum, and lumbar vertebrae, as well as trauma to other major systems. Complications of pilon fractures are common, particularly in more severe cases. Early complications include wound infection, skin sloughing, pin site infection, and wound dehiscence. Delayed and late complications include malunion, nonunion, leg shortening, posttraumatic arthritis, avascular necrosis, and protracted pain. Some patients with severe pilon fractures ultimately require arthrodesis of the ankle joint. Careful assessment of the affected bony anatomy and neurovascular status of the foot is necessary in a pilon fracture, and in the case of open fractures, management as outlined previously should occur.

Differential Diagnoses

Differential diagnoses of pilon fractures are relatively limited since the mechanism of injury and clinical presentation makes the diagnosis fairly obvious. However, it is important not to miss other associated injuries or complications such as compartment syndrome, ankle dislocation or other skeletal injuries.

Diagnostic Testing

Plain radiographs are the initial choice of imaging for the diagnosis of pilon fractures and should include the entire tibia and fibula, as well as the ankle. CT imaging is generally required by the orthopedic surgeon for operative planning.

Management

ED treatment involves restoration of the articular surface and fibular length with reduction if necessary, combined with meticulous management of soft tissue injuries. Difficulties in achieving reduction may occur if tendon entrapment has occurred, most often the posterior medial structures. Because surgical management is required, emergent orthopedic consultation is necessary. Pilon fractures with low-grade soft tissue damage are primarily managed with ORIF. In severe pilon fractures with extensive soft tissue damage, however, results are better with a two-stage approach involving initial length restoration and external fixation, followed by anatomic reduction and internal fixation after soft tissue swelling has subsided.

Dislocations

Anatomy, Physiology, and Pathophysiology

Ankle dislocations are described based on the direction of displacement of the talus and foot in relation to the tibia. Dislocation may be upward, posterior, medial, lateral, posteromedial, or anterior. Medial dislocation is the most common. Most dislocations involve associated ankle fractures; rarely, however, dislocations can occur without fracture. The mechanism in all dislocations begins with axial loading of a plantar-flexed foot, which forces the talus anteriorly or posteriorly from the ankle mortise. The eventual position of the dislocation depends on the position of the foot at the time of injury and direction of the displacing force. Ankle dislocations can be closed or open and usually result from significant falls, motor vehicle collisions (MVCs), or high-speed sports. The neurovascular supply to the foot usually is intact but may be compromised in open dislocations.

Clinical Features

The diagnosis is usually obvious due to gross deformity in the ankle joint although determining the orientation of the body of the talus, which must be reduced, can be challenging without imaging. A rapid assessment of neurovascular status is necessary.

Differential Diagnoses

Due to the deformity in the ankle joint that is observed in a traumatic setting, differential diagnoses are limited to evaluation for concurrent fracture at the site of dislocation.

Diagnostic Testing

Plain radiography remains the cornerstone of diagnosis of ankle dislocation and is helpful in clarifying the orientation of the talar body prior to reduction. However, attempts at reduction should not be delayed when vascular compromise or skin tenting is present.

Management

In order to achieve talar reduction, appropriate procedural sedation or an intraarticular hematoma block[11] is used, the patient is placed supine, and the knee is flexed to 90 degrees. Distraction of the foot, followed by a gentle force to reverse the direction of the dislocation, usually accomplishes the reduction. Difficulties in achieving reduction may be caused by entrapped posterior medial tendons. Postreduction reassessment of the neurovascular status, splint immobilization, ankle elevation, and radiography should follow. Open dislocations require the same management as previously discussed for open fractures. The prognosis for an ankle dislocation is generally good, although open fractures are associated with an increased incidence of complications. Isolated ankle dislocations once successfully reduced with documentation of intact neurovascular status, are immobilized and made nonweightbearing. These dislocations can be urgently followed by orthopedics on an outpatient basis within 48 hours.

Ligamentous Injuries

Foundations

Ankle sprains are frequently seen in EDs and are one of the most common injuries in an active patient population. Proper diagnosis and rehabilitation are important because 40% of patients experience dysfunction for up to 6 months post injury. The term *ankle sprain* refers to a multitude of ligamentous and nonligamentous injuries. Even when ligamentous injury is certain, the ideal treatment approach is controversial, and there is significant variation in clinical practice.[12]

Pathophysiology

Most ankle sprains occur from extreme inversion and plantar flexion that produce symptoms on the lateral aspect of the ankle. Usually, the anterior talofibular ligament is injured first, followed by the calcaneofibular ligament if the deforming forces are sufficiently strong (see Fig. 49.1). Approximately two-thirds of ankle sprains are isolated anterior talofibular ligament injuries, whereas 20% involve anterior talofibular and calcaneofibular ligament injuries. In addition, the lateral talocalcaneal ligament may be strained with an inversion injury, leading to avulsion fractures at either end of the attachment sites. Isolated calcaneofibular or posterior talofibular ligament injuries are rare.

TABLE 49.1 Ligamentous Injury Classification According to Functional and Presumed Pathologic Findings

Classification (Grade)	Physical Examination	Pathophysiology	Treatment
1	• Minimal lateral ATFL tenderness • Small effusion or no effusion • Weightbearing immediately or within 24 hr	• Microscopic tearing of ligamentous complex fibers	• PRICE • Weightbearing as tolerated • ROM, proprioceptive, and other functional exercises, as tolerated
2	• Moderate lateral ATFL tenderness and hematoma • Small to moderate effusion • Unable to bear weight for >24 hr	• Complete tear of some ligamentous fibers	• PRICE • Immobilization with air cast • ROM, proprioceptive, and other functional exercises, as tolerated
3	• Significant lateral ATFL tenderness ad hematoma • Large effusion • Unable to bear weight for >24 hr • Positive anterior draw, talar tilt test	• Complete tear of all ligamentous fibers within the ligamentous complex	• PRICE • Immobilization • Delayed ROM, proprioceptive, and other functional exercises, as tolerated • Prolonged rehabilitation phase ± delayed surgery

ATFL, Anterior talofibular ligament; *PRICE*, *p*rotection, *r*est, *i*ce, *c*ompression, *e*levation; *ROM*, range of motion.

Isolated injury of the medially located deltoid ligament occurs in less than 5% of ankle sprains and occurs during an eversion force. Rupture of this ligament usually occurs in conjunction with lateral malleolar fractures, especially when an external rotational force is involved.

Concurrent injury of the anterior talofibular and deltoid ligaments, determined by palpation and other physical signs such as ecchymosis, warrant investigation for instability of the ankle joint due to bimalleolar ligamentous injury

Injuries of the distal tibiofibular syndesmotic ligaments are uncommon in the general population because of the degree of force required but represent 10% to 20% of ankle sprain injuries in competitive athletes, the so-called "high" ankle sprain. Dorsiflexion and external rotation forces are usually responsible for this injury; their presence may significantly prolong the recovery time from concomitant lateral collateral ligament sprains.

Ligamentous injuries are classified into three grades based on functional and presumed pathologic findings, as outlined in Table 49.1. This classification system, although commonly used, fails to characterize ankle injuries involving two or more ligaments and does not address nonligamentous injuries.

Clinical Features

An accurate history of ankle position and injury mechanism is often unavailable. Inversion followed by external rotation of the ankle suggests the potential for deltoid or syndesmotic injury. Forced dorsiflexion with "snapping" may indicate peroneal tendon displacement. On physical examination, the presence of edema, ecchymosis, and point tenderness over the medial or lateral collateral ligaments or syndesmotic ligaments suggests a ligamentous injury. Inability to bear weight in the absence of a fracture suggests the presence of a grade II or III ankle sprain. Deltoid ligament tenderness necessitates palpation of the full length of the fibula to rule out a proximal fibular fracture—type C Danis-Weber or Maisonneuve fracture (see Figs. 49.8 and 49.9). Tenderness should prompt imaging of the entire tibia and fibula.

Differential Diagnoses

Many injuries can masquerade as ankle sprains. Box 49.2 lists conditions to be considered with the differential diagnoses.

BOX 49.2 Differential Diagnoses for Presumed Ankle Sprain or Ankle/Foot Tendon Injuries

Lateral collateral ligament sprain
Peroneal tendon dislocation
Osteochondral lesion of the talar dome
Fracture of the posterior process of the talus
Fracture of the lateral process of the talus
Fracture of the anterior process of the calcaneus
Midtarsal joint injury
Fracture of the base of the fifth metatarsal
Achilles tendon injury

Diagnostic Testing

The fibular compression test, or squeeze test, can be used to diagnose fibular and syndesmotic injuries. To perform this test, the examiner places the fingers over the fibula and the thumb over the tibia at midcalf and squeezes the two bones. Pain anywhere along the length of the fibula suggests a fibular fracture or syndesmotic ligament disruption at that location. Following this, the Achilles tendon should be assessed for rupture.

Stress testing is the application of a deforming force to assess joint motion beyond the physiologic range; its presence suggests ligament disruption or mechanical instability. Common ankle stress tests include the anterior drawer test, inversion stress test, and external rotation test. *The anterior drawer test* primarily assesses the integrity of the anterior talofibular ligament. To perform this test, the patient is seated with the knee in 90 degrees of flexion and the ankle in a neutral position or 10 degrees of plantar flexion, which is best achieved by allowing the foot to rest along the examiner's wrist and distal forearm, as the examiner cups the heel in his or her hand and gently flexes the ankle to the 90-degree position. The examiner then applies slow but firm traction on the heel with that hand and places the other hand on the anterior tibia to prevent the leg from moving anteriorly. Anterior displacement of the talus, the perception of a "clunk," and the induction of a sulcus

anteromedially over the joint indicate partial or complete tear of the anterior talofibular ligament.

The inversion stress test, or "talar tilt test," evaluates the anterior talofibular ligament and calcaneofibular ligament. It is performed by inverting the heel with the knee in 90 degrees of flexion and the ankle in neutral position. Palpation of the head of the talus laterally or a finding of increased laxity compared with the uninjured side suggests partial or complete tear of these ligaments.

The external rotation stress test is indicated when injury to the distal tibiofibular syndesmotic ligaments is suspected. It is performed by externally rotating the foot with the knee in 90 degrees of flexion and the ankle in a neutral position. Pain at the syndesmosis or the sensation of lateral talar motion suggests partial or complete tear of the ligaments.

Stress testing in the ED to identify acute ligamentous disruption is often limited by pain, so to be performed properly, the joint must be anesthetized with local anesthetic. Furthermore, a positive stress test suggesting ligamentous instability rarely alters management in the ED. If needed, this test can be deferred to orthopedic follow-up.

Standard ankle radiographic views exclude fractures and detect ligamentous instability by allowing the measurement of joint spaces (see earlier discussion and Fig. 49.6). Stress radiographs, accomplished by taking radiographs during stress testing of the ankle, including the use of gravity stress testing, generally do not influence the emergency management of ankle sprains and we do not recommend their routine use in the ED.

The presence of avulsion fractures constitutes an important clue to the location of ligamentous injuries. Common locations for avulsion fractures include the bases of the malleoli, lateral process of the talus, lateral aspect of the calcaneus, posterior malleolus, lateral aspect of the distal tibia, and base of the fifth metatarsal.

Management

Most ligament sprains, regardless of severity, heal well and result in a satisfactory outcome. To date, compelling evidence for a significant difference in outcomes between surgical and functional (nonsurgical) treatment is lacking. Most patients with acute sprains of the ankle should start with functional treatment. For the minority who fail to respond, delayed operative repair of ruptured ligaments, sometimes years after the injury, has been shown to yield results equivalent to those with primary repair.

Functional treatment, a form of therapy in which the ankle is not fully immobilized, allowing complete or partial joint function, starts in the ED with PRICE therapy (***p***rotection, ***r***est, ***i***ce, ***c***ompression, and ***e***levation). However, significant variability exists in how this combination is applied, and optimal methods for the rehabilitation of ankle sprains remain unclear.[13] Lace-up ankle splint support is more effective in short-term edema reduction than semirigid ankle support, elastic bandaging, and taping.

For grade I or II injuries, short-term protection with a compression bandage, taping, laced-up support, or commercial brace, with the optional use of crutches for a few days, is appropriate. For patients with first-time ankle sprains, treatment with a lace-up brace combined with elastic wrapping results in an earlier return to function compared with the use of a brace alone, elastic wrap alone, or walking cast.

For severe grade II or grade III injuries, there has been equipoise regarding the merits of immobilization compared with functional rehabilitation using a removable brace, with a paucity of high-quality evidence. We recommend use of a lace-up support or air cast that permits some ankle motion. These patients should also use crutches to avoid weightbearing until they can stand and walk a few steps on the injured ankle without pain. Crutch use varies significantly, ranging from a few days to 2 or 3 weeks. Functional therapy allows for the incorporation of earlier physical therapy rehabilitation and quicker recovery.

Discharge instructions are important in ankle sprains. The expected time for return to activity is generally 2 to 4 weeks, depending on the grade of the injury, with more severe injuries taking longer; however, patients are usually able to weight bear within 7–10 days. Patients who have not returned to a normal activity level beyond this time frame should be reevaluated for talar dome osteochondral lesions, syndesmotic injury, or occult fracture with advanced imaging. Follow-up with the patient's primary care physician or sports medicine specialist is appropriate.

Pain improves with immobilization, but additional analgesia is usually required. Appropriate pain relief can be provided by systemic nonsteroidal antiinflammatory drugs (NSAIDs), in analgesic doses, or with acetaminophen. A short course (2–3 days) of oral opioids is added when pain is severe, although this is generally not required or recommended.

Disposition

Acute ankle ligament sprains rarely require orthopedic consultation in the ED. Primary surgical repair of acute ligament rupture is controversial; possible indications include sprains with displaced osteochondral lesions, complete tears of the anterior talofibular and calcaneofibular ligaments in a young athlete, a ligament sprain associated with a fracture causing instability (e.g., a deltoid ligament rupture with a lateral malleolar fracture), and an acute severe sprain in a patient with a history of recurrent sprains. Failure of nonoperative treatment also constitutes an indication for surgical repair; however, a nonurgent referral on an outpatient basis at the discretion of the orthopedic specialist is an appropriate disposition from the ED.

Small avulsion fractures of the fibula or tibia with minimal or no displacement can be treated in the same manner as an ankle sprain. If the avulsed fragment is larger than 3 mm or significantly displaced, splinting and referral for orthopedic follow-up on a nonurgent outpatient basis within a week is justified.

Tendon Injuries

The tendons of the ankle and foot (see Fig. 49.3) are important for facilitating the complex motions of the foot. In general, chronic causes of tendinopathy are more common than acute injuries and occur with overuse type patterns of injury, although tendon entrapments and dislocation may occur in complex ankle and hindfoot fractures.[6] Nontraumatic causes of tendon injury may present to the ED with sudden worsening or debilitating pain causing an inability to bear weight. Acute nontraumatic injuries tend to occur in the sports settings or with sudden and forced motion, often against an opposing force. Table 49.2 outlines many of the tendinous injuries located around the ankle joint. Some of the more significant tendon injuries are discussed next in further detail.

Differential Diagnoses

Differential diagnoses of ankle tendon injuries is similar to that of ankle sprains and is included in Box 49.2.

Achilles Tendon Rupture

Background and Importance, Physiology, and Pathophysiology. Achilles tendon rupture is most common in middle-aged men, and its causes are multifactorial. This condition is easily misdiagnosed, leading to a delay in therapy, worse prognosis, and increased morbidity, including chronic weakness and loss of function. In the majority of cases, a complete transection of the tendon is present; however, partial tears of the Achilles tendon can occur and may be more prone to misdiagnosis.

TABLE 49.2 Tendon Injuries to the Ankle and Foot

Tendon and Function	Injury and Mechanism	Clinical Presentation	Management
Achilles • Ankle plantar flexion	Chronic tendinopathy > acute injury Tendon rupture • Direct trauma • Sudden or forced ankle hyperdorsiflexion	Rupture • Sudden pain, snap or pop, posterior ankle • Ankle plantar flexion weakness, inability • Palpable defect in Achilles tendon • Positive Thompson test	• Orthopedic referral for conservative vs. operative management • Heel lift with slight plantar flexion while in walking boot, posterior slab
Peroneal longus, brevis • Ankle plantar flexion • Ankle eversion	Chronic tendinopathy > acute injury (rupture vs. dislocation) Tendon rupture • Forced dorsiflexion while forced inversion	• With dislocation, snapping sensation while everting ankle ± dorsiflexion • Sudden pain, swelling, lateral (posterior groove) malleolus • Weakness with eversion	• Orthopedic referral for tendon rupture or dislocation • PRICE, physical therapy for tendinopathy
Tibialis posterior • Ankle plantar flexion • Ankle inversion	Chronic tendinopathy > acute injury Tendon rupture • Forced eversion • Disruption of flexor retinaculum, 2 degrees closed anterior ankle dislocation	• Medial ankle pain • Unopposed peroneal brevis action; exaggerated eversion causing pes planus • Inability to perform single leg heel raise	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy
Tibialis anterior • Ankle dorsiflexion	Traumatic laceration > acute rupture > chronic overuse injury	• Anterior mass 2 degrees tendon retraction with laceration • Visible recruitment of EDL, EHL to assist in dorsiflexion causes dorsiflexion of hallux	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy
Flexor hallucis longus • Ankle and hallux plantar flexion	Chronic tendinopathy > acute injury	• Pain posteromedial ankle • Pain with ankle and hallux plantar flexion	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy
Extensor hallucis longus • Ankle and hallux dorsiflexion	Chronic tendinopathy > acute injury	• Pain anterior ankle • Pain with ankle and hallux dorsiflexion	• Orthopedic referral for tendon rupture • PRICE, physical therapy for tendinopathy

EDL, Extensor digitorum longus; *EHL,* extensor hallucis longus; *PRICE, p*rotection, *r*est, *i*ce, *c*ompression, *e*levation; *ROM*, range of motion.

Clinical Features. Achilles tendon rupture results from direct trauma or indirectly transmitted forces, including sudden unexpected dorsiflexion, forced dorsiflexion of a plantar-flexed foot, and strong push-off of the foot with simultaneous knee extension and calf contraction, as in a runner accelerating from the starting position. Factors predisposing to Achilles tendon rupture include preexisting disease such as rheumatoid arthritis, systemic lupus erythematosus, gout, hyperparathyroidism, chronic renal failure, steroid use or injection, fluoroquinolone antibiotic therapy, and previous Achilles tendon rupture. The vast majority of ruptures, however, occur spontaneously during activity or trauma, without risk factors other than being a middle-aged male.

Diagnostic Testing. The diagnosis of Achilles tendon rupture is primarily clinical. Patients usually describe a sudden onset of pain at the back of the ankle associated with an audible "pop" or "snap." Although the pain can resolve rapidly, weakness in plantar flexion persists. On examination, a visible and palpable tendon defect may be noted 2 to 6 cm proximal to the calcaneal insertion in acute presentations but will be less apparent in delayed presentations because of hematoma or surrounding edema. Even in cases of complete Achilles tendon rupture, weak plantar flexion may still be possible because of the actions of the tibialis posterior, toe flexors, and peroneal muscles. This retained ability for plantar flexion leads to the misdiagnosis of complete ruptures as ankle strains or partial tears in as many as 25% of cases.

The classic maneuver to assess the integrity of the Achilles tendon is the *Thompson test*. This is performed with the patient prone and the knee flexed at 90 degrees or the feet hanging over the end of the stretcher. Alternatively, the patient kneels on a chair with both knees flexed at 90 degrees and the feet hanging over the edge. With an intact Achilles, squeezing the calf muscles in these two positions should cause passive plantar flexion of the foot. Absence of this motion, or a markedly weakened response compared with the uninjured side, suggests complete rupture. Lateral radiographic views of the ankle may suggest rupture by showing opacification of the fatty tissue–filled space anterior to the Achilles tendon (*Kager triangle*) or an irregular contour and thickening of the tendon. Ultrasonography or MRI can demonstrate partial or complete tendon ruptures, but these studies are indicated only when diagnostic uncertainty exists.

Management. A lack of consensus exists between operative and nonoperative management in the treatment of Achilles tendon rupture.[14] Surgical repair is routinely performed in active individuals owing to its lower incidence of rerupture. However, surgery carries higher rates of other complications, such as superficial or deep wound infections, in comparison with nonoperative management. In both types of management, early mobilization improves functional recovery without increasing rerupture rates. Achilles tendon rerupture after initial nonoperative treatment usually necessitates surgical repair. Urgent orthopedic referral of patients with Achilles tendon rupture is necessary to determine the appropriate management. Regardless, on discharge from the ED, for surgical or conservative management, the patient is placed in a walking boot with maximal heel lift, or in a posterior or anterior slab with the foot plantarflexed in a full equinus position.

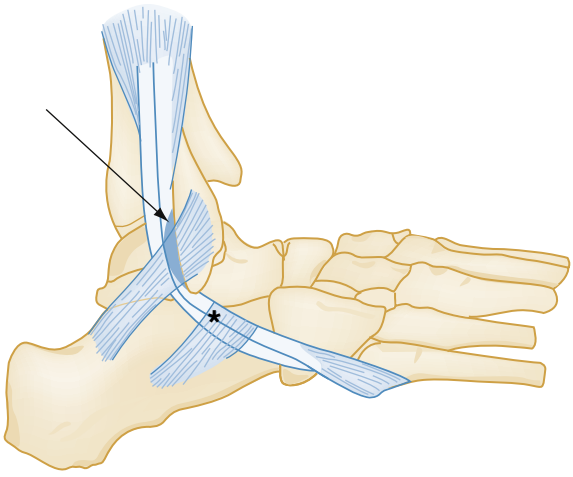

Fig. 49.11 Locations of the superior (*arrow*) and inferior peroneal retinaculum (*star*) in relation to the fibula and peroneal tendons.

Peroneal Tendon Dislocation or Rupture

Foundations and Clinical Features. The peroneal muscles are the primary evertors and pronators of the foot and also participate in plantar flexion. The peroneus longus and brevis tendons use the posterior peroneal sulcus (the fibular groove), located behind and underneath the lateral malleolus, as a pulley for their midfoot insertions. The peroneus brevis tendon inserts onto the tuberosity of the fifth metatarsal, and the peroneus longus tendon courses beneath the cuboid to insert onto the medial cuneiform and base of the first metatarsal. Injuries of the peroneal tendons include chronic overuse tendinopathy, tendon rupture, and tendon dislocation. The superior peroneal retinaculum (Fig. 49.11), a fibrous structure running from the distal fibula to the posterolateral aspect of the calcaneus, maintains the peroneal tendons against the fibular groove and, when ruptured, causes dislocation of the peroneal tendons.

Diagnostic Testing. Plain radiographs of the ankle may show the peroneal "fleck" sign, which can be confused for a simple avulsion fracture off the lateral aspect of the lateral malleolus but represents avulsion and tibial disruption of the superior peroneal retinaculum, considered pathognomonic for a superior peroneal retinaculum tear (Fig. 49.12).

Management. Peroneal tendon rupture, subluxation or dislocation should be clinically (see Table 49.2) or radiologically assessed and the patient referred to orthopedics on an urgent outpatient basis.

Tibialis Posterior Tendon Rupture

Foundations and Clinical Features. The tibialis posterior is primarily responsible for plantar flexion and inversion along the subtalar joint. Its tendon uses the posteroinferior surface of the medial malleolus as a pulley and inserts onto the navicular, medial cuneiforms, and bases of the second through fifth metatarsals. The peroneus brevis opposes the action of the tibialis posterior. With rupture of the tibialis posterior tendon, the peroneus brevis becomes unopposed, and the medial longitudinal arch loses its muscular support, leading to valgus deformity of the hindfoot and a unilateral flatfoot.

The mechanism of traumatic tibialis posterior rupture involves forced eversion. In addition to a unilateral flatfoot, pain and swelling on the medial aspect of the ankle are noted. Tenderness is present over the navicular, and the patient cannot perform a toe raise on the affected side. The patient with a tibialis posterior tendon rupture is also unable to invert the foot when it is in plantar flexion and eversion. With a unilateral flatfoot, an examiner standing behind the patient can see more toes on the lateral aspect of the affected side—a classic sign of tibial posterior rupture.

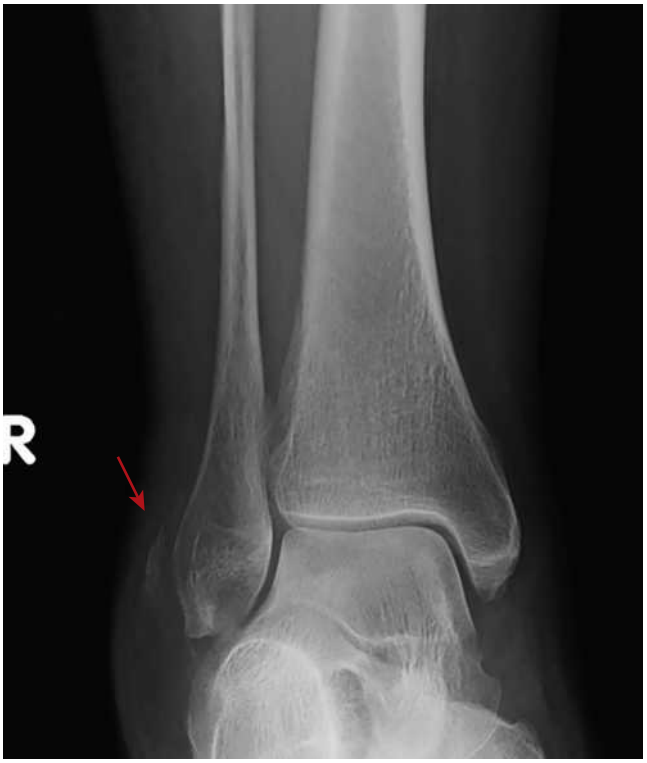

Fig. 49.12 Mortise x-ray view of the ankle showing a "fleck sign" (*arrow*) which represents an avulsion fracture and thus disruption of the superior peroneal retinaculum complex. (Courtesy Dr. Eric Giza.)

Diagnostic Testing. The diagnosis is generally made on a clinical basis. Plain radiographic films can exclude other bony pathology. Ultrasound can be used to confirm the diagnosis if clinical uncertainty exists.

Management. Urgent outpatient orthopedic consultation within a week is indicated for tibialis posterior tendon ruptures because surgical repair is often required.

Other Tendon Injuries

Injuries to the other tendons of the ankle are relatively rare and are outlined in Table 49.2. The tibialis anterior tendon is the primary dorsiflexor of the foot. It courses under the superior extensor retinaculum anterior to the medial malleolus and inserts onto the navicular, medial cuneiform, and base of the first metatarsal. The flexor hallucis longus tendon is responsible for flexion of the great toe and participates in plantar flexion of the foot. It courses behind the medial malleolus through a fibro-osseous canal and travels along the undersurface of the foot to insert onto the distal phalanx of the great toe. The extensor hallucis longus tendon travels anteriorly through the superior extensor retinaculum and inserts on the dorsal surface of the base of the distal phalanx of the hallux.

FOOT

FOUNDATIONS

Anatomy, Physiology, and Pathophysiology

The foot is composed of 28 bones and 57 articulations (Fig. 49.13), which can be divided into three anatomic and functional regions—the hindfoot (talus and calcaneus), the midfoot (navicular, cuboid, and cuneiforms),

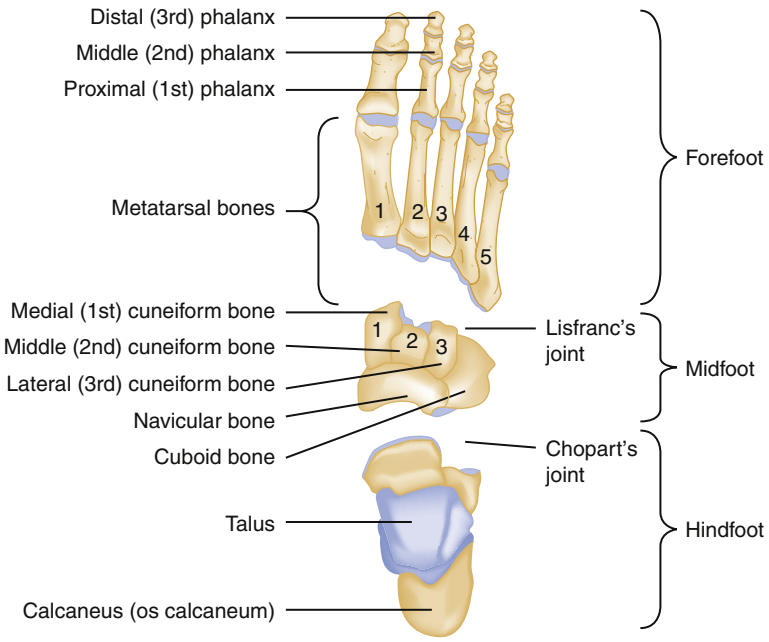

Fig. 49.13 Bones and joints of the foot.

and the forefoot (metatarsals, phalanges, and sesamoids). The midtarsal, or *Chopart joint*, connects the hindfoot to the midfoot. The tarsometatarsal, or *Lisfranc joint*, connects the midfoot and forefoot. The subtalar joint, comprised of three articulations between the talus and calcaneus, is another clinically important joint. Inversion and eversion of the hindfoot occur primarily through the subtalar joint, adduction and abduction of the forefoot through the midtarsal joints, and flexion and extension through the metatarsophalangeal (MTP) and interphalangeal (IP) joints.

The bones of the foot interlock to form a complex system of arches and beams tethered by ligaments and intrinsic muscles. Extrinsic muscles originating in the lower leg are responsible for most of the foot's movements. The course and insertion of these extrinsic muscles are important in their actions and association with specific avulsions and injuries. The arterial supply to the foot is from the anterior and posterior tibial arteries as well as the peroneal artery, a proximal branch of the posterior tibial artery. Motor and sensory innervation comes from branches of the deep and superficial peroneal, posterior tibial, saphenous, and sural nerves.

Clinical Features

In the setting of foot injury, an accurate history, including the mechanism of injury, timing, and duration of symptoms is important. The location of pain, along with a description of its quality, duration, and precipitants, focuses the differential diagnoses. A history of underlying medical conditions, medications, and previous foot problems provides additional key information.

The physical examination of the foot begins, if possible, with observation of gait and proceeds with assessment of the foot in its position of rest, normally one of slight plantar flexion and inversion. Swelling, deformity, ecchymosis, open wounds, color, and temperature should be noted. Precise localization of pain or crepitus, when not precluded by swelling, is valuable and guides further diagnostic testing when indicated. The entire foot should be methodically palpated, paying particular attention to commonly injured areas. Complete assessment includes a detailed neurovascular examination.

In some situations, evaluation of active and passive range of motion is indicated. Subtalar motion is evaluated by holding the lower leg with one hand and the heel with the other. Then, with the foot in a neutral position, the heel is inverted and everted. Normal range is 5 to 20 degrees of eversion and 5 to 40 degrees of inversion although there is substantial individual variability. Midtarsal motion is evaluated by stabilizing the heel while the other hand grasps the forefoot. There should be at least 20 degrees of adduction and 10 degrees of abduction.

Forefoot motion is evaluated by flexing and extending the MTP and IP joints individually. The first MTP joint has a particularly wide passive range of motion, with 45 degrees of flexion and 70 to 90 degrees of extension. Throughout the physical examination, findings can be compared with those of the opposite uninjured foot.

Differential Diagnoses

When formulating the differential diagnoses for injuries to the foot, it is useful to categorize these by anatomic location, mechanism of injury, and chronicity of symptoms. It should be noted that because the foot is an intricate anatomic structure with several interlocking bones and complex ligamentous attachments, it is important to consider a broad differential in the assessment. There is substantial overlap of the differential diagnoses both within, and between anatomic regions. Table 49.3 outlines differential diagnoses by anatomic region.

Diagnostic Testing

A complete plain radiographic evaluation of the foot consists of three standard views. The lateral view gives the best imaging of the hindfoot and soft tissues, whereas the anteroposterior and oblique projections allow assessment of the midfoot and forefoot. Certain specialized plain radiographic views may be considered when clinical concern exists in specific cases. Two commonly utilized "special views" include the Harris, or calcaneus, view when a calcaneus fracture is suspected, or weightbearing images in the case of suspected ligamentous Lisfranc injury. It should be noted that, in many cases, CT imaging has supplanted the utility of these special or focused views.

Accessory ossification centers are found in 30% of the population and may complicate interpretation of plain radiographs. On radiographs, these accessory bones are differentiated from fractures by their smooth corticated surfaces and with comparison radiographs of the

TABLE 49.3 Differential Diagnoses for Acute Traumatic Foot Injuries and Low Energy/Soft Tissue Injuries

Acute Traumatic/High Energy Injuries

Hindfoot		
Talus	Major fractures	Talar head fractures
		Talar neck fractures
		Talar body fractures
	Minor fractures	Talar head/neck dorsal avulsion fractures
		Talar body posterior process fractures
		Talar dome osteochondral injury
	Dislocations	Subtalar
		Pan talar
Calcaneus	Intraarticular fractures	
	Extraarticular fractures	Anterior process
		Sustentaculum tali
		Lateral process
		Medial process
		Peroneal tubercle
		Calcaneal tuberosity
Chopart joint	Dislocation	
	Fractures	
Midfoot		
Navicular	Fractures	Dorsal avulsion fractures
		Tuberosity fracture
		Body fracture
		Stress fracture
Cuboid	Fracture	
Cuneiform	Fractures	Medial fracture
		Intermediate/middle fracture
		Lateral fracture
Lisfranc joint injury	High energy (fracture)	
	Low energy (ligamentous)	
Forefoot		
Metatarsals	Fractures	First metatarsal fracture
		Middle metatarsal fracture
		5th metatarsal (shaft/base)
	Dislocations	Phalangeal fractures or dislocation
Sesamoid	Fractures	

Acute Traumatic/High Energy Injuries

Low-Energy and Soft Tissue Injuries

Hindfoot	
Distal Achilles	Achilles tendinopathy
Achilles insertion	Achilles enthesitis
Achilles insertion	Retrocalcaneal bursitis
Base of calcaneus	Fat pad atrophy syndrome
Inferior/posterior to lateral malleolus	Peroneal tendinopathy
Inferior/posterior to medial malleolus	Tibialis posterior tendinopathy
Inferior/anterior to lateral malleolus	Sinus tarsi syndrome
Base of foot, anterior/medial to calcaneus	Plantar fasciitis
Midfoot	
Base of foot, anterior/medial to calcaneus	Plantar fasciitis
Base of 5th, insertion of peroneus brevis	Peroneal enthesitis
Forefoot	
Usually distal ⅓ of metatarsals	Metatarsal stress fractures
Between the middle metatarsal heads	Morton neuroma
Base of 1st metatarsal head	Sesamoiditis
Base of affected metatarsal head	Metatarsalgia
1st MTP	Turf toe

Other Considerations	***Compartment syndrome***
	CRPS
	Peripheral vascular disease
	Neuropathies
	Cellulitis
	Neoplasm (sarcoma/soft tissue sarcoma)

opposite foot, although such variants are not inevitably bilateral. The most commonly seen accessory bones are the os trigonum, os tibiale externum (also called an accessory navicular bone), os peroneum, and os vesalianum. Accessory bones themselves can also fracture or cause pain syndromes which should be considered and assessed in the appropriate clinical context.

Plain radiography has limitations in the assessment of foot and ankle injuries. In the foot, overlapping bones and complex articulations can make images difficult to interpret. CT imaging is an invaluable tool for further assessment of many injuries to the foot, in particular to the midfoot, calcaneus, subtalar joint, and tarsometatarsal (Lisfranc) joint complex.

Advanced imaging, including MRI, ultrasound, and bone scanning, are useful for the diagnosis of certain foot injuries. However, these tests are rarely indicated in the emergent evaluation of foot injuries. As in the case of ankle injuries, such tests can be arranged following consultation with orthopedic, sports medicine, or radiology specialists.

MRI has a role in the diagnosis of ligamentous and soft tissue injury but also has value for identifying stress fractures and cartilaginous injury, such as talar dome osteochondral lesions. A common indication for MRI in foot injury would be in the assessment of suspected ligamentous Lisfranc injury, although weightbearing plain radiographs are advocated as an economical alternative when feasible.[15] In the case of stress fractures, MRI has comparable sensitivity and better specificity than bone scanning and has emerged as the imaging modality of choice.

Radionuclide imaging (bone scanning) can be useful for evaluating unexplained foot pain or pain in athletic injuries. CT-SPECT overlays bone scanning with more detailed anatomic information provided by CT imaging to improve localization of lesions. This specialized technique is useful in the diagnostic algorithm for a number of foot disorders, including osteochondral lesions, stress fractures, and osteomyelitis.

Ultrasonography also has utility in diagnosing soft tissue and tendinous injuries. In the foot, the assessment of plantar fascia pain is an example where ultrasound plays an important diagnostic role. Ultrasound has been studied in the assessment of Lisfranc injuries and foot fractures,[16] however, to date, has not been shown to supplant more conventional imaging.

SPECIFIC PATHOLOGIC CONDITIONS

This section covers the major fractures and dislocations seen in the foot, progressing anatomically from the hindfoot through to the forefoot.

Hindfoot Injuries

The hindfoot includes the talus and calcaneus. Injuries to the hindfoot can masquerade as other injuries, including ankle sprains. Attention to the history and physical exam as well as appropriate imaging, when indicated, is critical.

Differential Diagnoses

Differential diagnoses for acute, traumatic injuries to hindfoot structures include fractures to the talus and the calcaneus as well as fractures and ligamentous injuries affecting the midtarsal (or Chopart) joint (see Table 49.3). The calcaneus is the most commonly fractured of the tarsal bones, with fractures generally occurring following falls from height. Fractures to the talus can be differentiated by anatomic region of the talus, and most often occur from falls or forces resulting in dorsiflexion of the foot. In general, fractures to the calcaneus and talus should be considered high-energy fractures, although fractures do occasionally occur with less forceful mechanisms. The talus, in particular, is susceptible to a number of minor, lower-energy fractures such as a lateral process fractures, dorsal lip and talar dome fractures, which may result from mechanisms similar to those seen with ankle sprains. More subtle ligamentous injuries, such as those to the midtarsal (Chopart) joint should be considered in mechanisms of twisting, forced plantar flexion, or forced dorsiflexion.

The hindfoot is also prone to a number of nonacute conditions including stress fractures. A history suggestive of a more insidious pattern of pain should also make one consider other soft tissue pathology such as plantar fasciitis, fat pad syndrome, tarsal tunnel syndrome, Achilles tendinopathy, Achilles enthesitis, or retrocalcaneal bursitis.

Talar Fractures

Anatomy, Physiology, and Pathophysiology. The talus is a complex structure with articular cartilage covering 60% of its surface. It has no muscular attachments and is held in place with ligamentous attachment and by the medial and lateral malleoli. The talus can be divided anatomically into three regions—the head, which articulates with the navicular and calcaneus; the body, which articulates with the tibia, fibula, and calcaneus; and the neck, which connects the head and body. The neck is the only region that is predominantly extraarticular. The anterior width of the talus is greater than the posterior, causing it to be less stable and more prone to dislocation when the foot is plantarflexed.

The blood supply to the talus is from the anterior tibial artery, the posterior tibial artery, and a perforating branch of the peroneal artery. The talar head is supplied by branches of the dorsalis pedis and from the artery of the tarsal sinus. Vessels enter from three sites, all of which can be disrupted by fractures or dislocations, putting the talus at risk of avascular necrosis.

Clinical Features. Talar fractures range from obvious fractures to subtle injuries requiring special imaging for diagnosis. There is generally a history of a twisting injury, fall, or high-energy impact. Both dorsal swelling and tenderness over the talus are characteristic findings. Although ankle motion may be preserved, inversion and eversion of the hindfoot often are painful.

Talar fractures are described according to anatomic location into fractures of the neck, body, and the head. Talar fractures can also be divided into minor or major fractures.

Minor fractures of the talar body include fractures of the lateral and posterior processes, and osteochondral fractures of the talar dome. These fractures do not traverse the central portion of the talar body. Dorsal avulsion fractures of the talar neck and head are also classified as minor fractures.

Major fractures of the head, neck and talar body are fractures that traverse the central portion of the bone. These are often high energy fractures and care must be taken to exclude associated traumatic injuries.

Talar Neck Fractures. Talar neck fractures account for 50% of all talus fractures. With the exception of dorsal avulsion fractures, talar neck fractures are high-energy injuries that most commonly result from extreme dorsiflexion as generated in falls or MVCs. Associated fractures are common, usually an oblique or vertical fracture of the medial malleolus. Other associated injuries include calcaneal fractures and vertebral compression fractures which are common in other high energy, axial load type injury patterns.

Major fractures of the talar neck have a high incidence of complication, the most significant of which is avascular necrosis. Patient outcomes depend on the degree of anatomic reduction attained and preservation of the vascular supply. Other potential complications include skin infection, skin necrosis, posttraumatic arthritis, malunion, delayed union, nonunion, and predisposition to peroneal tendon dislocation.[17]

The *Hawkins classification* grades talar neck fractures by displacement and associated subluxations (Fig. 49.14):

- Type 1 fractures are nondisplaced.
- Type 2 fractures are displaced vertical fractures, with subtalar joint subluxation.
- Type 3 fractures, 50% of which are open, involve a vertical talar neck fracture, with subluxation of the subtalar and tibiotalar joints.
- Type 4 fractures, which are uncommon, involve distraction of the subtalar, tibiotalar, and talonavicular joints.

This classification system guides treatment and correlates with the incidence of osteonecrosis and subtalar arthritis. A recent meta-analysis reported osteonecrosis rates of 10%, 27%, 53%, and 48% for types I through IV respectively. The rate of subtalar arthritis approached 80% in studies with over two years of follow up.[17]

Talar Head Fractures. Talar head fractures make up 10% of all talar fractures. Their mechanism is an axial compressive force applied

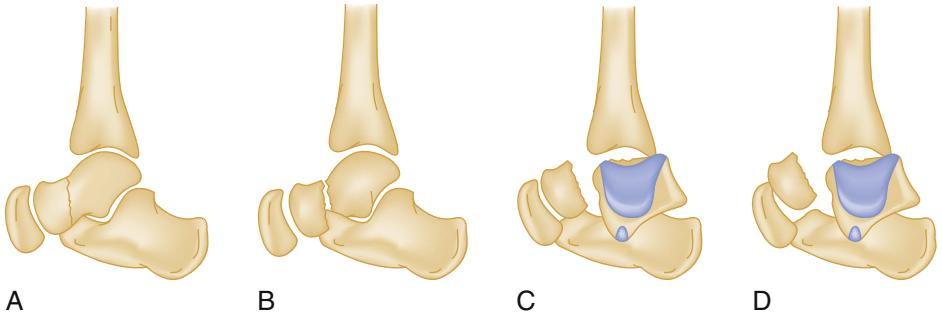

Fig. 49.14 Hawkins classification of talar neck fractures. (A–D) Hawkins tendons. *Shading* indicates the articular surface of the talar dome.

on a plantar-flexed foot and transmitted up through the talonavicular joint. Comminution is common and associated navicular fractures can occur, further disrupting the talonavicular articulation. Avulsion fractures of the dorsal talar head are rare and may extend into the talar body. These are minor fractures that occur from similar mechanisms to ankle sprains.

Talar Body Fractures. Major talar body fractures are uncommon and usually result from falls with axial compression of the talus, between the tibial plafond and calcaneus. These fractures traverse the central portion of the talar body and are typically intraarticular, involving the ankle and subtalar joints.

Minor talar body fractures include fractures of the lateral and posterior processes as well as osteochondral talar dome fractures. Lateral process fractures, sometimes referred to as "*snowboarder fractures*" result from forced dorsiflexion and inversion and have been described in other sports as well as from motor vehicle collisions and other high-energy mechanisms.

Up to 40% of lateral process fractures are missed on initial presentation, with ankle sprain being the most common alternative diagnosis, and hence other differential diagnoses are important to consider (Table 49.3). Posterior process fractures result from forced plantar flexion and present with pain and swelling in the hindfoot. Fractures of the posterior talar process need to be distinguished from an os trigonum, which is a normal accessory bone that can be found in 10% of the population. Osteochondral lesions of the talar dome, which are also considered minor fractures, can cause significant morbidity. These injuries result from the same mechanism as ankle sprains and often present in a delayed fashion as recurrent swelling and pain in the ankle joint.

Diagnostic Testing: Radiology. When talar fractures are clinically suspected, initial imaging should include standard foot and ankle radiographs. This series will usually identify fractures of the talar head, body, and neck (Fig. 49.15). The anterior and oblique ankle projections show talar alignment within the mortise, and the lateral projection shows the talar neck and alignment of the posterior aspect of the subtalar joint. Plain radiographs, however, have been shown to have a sensitivity of only 75%, although most missed fractures are minor. In addition, plain radiographs may underestimate fracture severity, particularly with respect to the degree of articular involvement. CT improves the reliability of classification and provides additional information in 90% of talar fractures. For this reason, a CT scan is recommended in addition to plain radiographs when a fracture is either identified or highly clinically suspected. Minor talar fractures may also be difficult to identify on plain radiographs. CT imaging may be considered when minor talar body fractures are clinically suspected and cannot be identified on carefully assessed plain radiographs.

Management. Talar neck fractures have a significant risk of long-term morbidity and require precise reduction. Type 1 fractures, which are nondisplaced, are the only talar neck fractures amenable

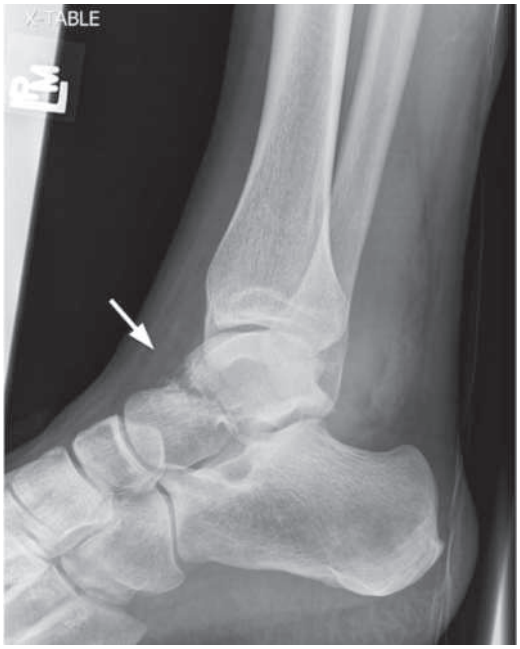

Fig. 49.15 Fracture of the talar neck (*arrow*). (Courtesy Dr. Thomas J. Green.)

to nonoperative treatment, with at least 6 weeks of nonweightbearing in a cast. Close outpatient orthopedic follow-up is required. Hawkins types 2 to 4 fractures, or talar neck fractures with any displacement, are managed surgically although often in a delayed fashion to allow for reduction of swelling. In the case of significantly displaced fractures, particularly if associated with neurovascular or cutaneous compromise, orthopedics should be consulted from the ED and emergent closed reduction should be attempted.

The treatment of talar head and body fractures is controversial and should be made by orthopedic consultants. Displaced fractures and fractures involving a significant degree of the articular surface are managed surgically. Nondisplaced fractures may be managed in a nonweightbearing cast, although some orthopedic surgeons advocate for operative repair due to the large articular surface requiring precise anatomic alignment. In the ED, assuming adequate control of pain and swelling, patients can be made nonweightbearing and immobilized in a well- padded, noncircumferential splint. Urgent, outpatient orthopedic consultation should be arranged for these types of fractures within 48 hours.

In general, minor talar fractures are treated conservatively. Treatment of lateral and posterior process fractures is dependent on the size, displacement, and comminution of the fragments. Displaced or comminuted lateral process fractures require operative fixation because of

their articular involvement. Minor fractures with fragments larger than 5 mm in diameter may require excision. The decisions for operative or conservative management are best made by orthopedic consultation. Depending on the amount of swelling, patients should be made nonweightbearing, and placed in a below-knee cast or posterior splint. Minor dorsal avulsion fractures of the head or neck are managed symptomatically and do not require immobilization.

Disposition. With the exception of minor dorsal avulsion fractures, all talar fractures should be managed by orthopedics. In the case of major fractures, with high-energy mechanisms, careful attention must be paid to rule out associated injuries. Nondisplaced talar neck fractures (type 1) are amenable to outpatient management. Patients in whom pain and swelling has been controlled should be nonweightbearing and immobilized in a padded noncircumferential short leg splint with orthopedic follow-up arranged in 24 to 48 hours. Patients with displaced talar neck fractures (types 2 to 4) should have orthopedic consultation in the ED. In cases where anatomic reduction has been achieved, outpatient follow-up can be arranged by orthopedics after consultation. In many cases, delayed operative repair is preferred.

Patients with talar head and body fractures as well as lateral process fractures require orthopedic consultation. If pain and swelling has been adequately controlled, outpatient referral is reasonable. Patients with these fractures can be splinted for urgent orthopedic evaluation within 48 hours. Minor avulsion fractures of the dorsal talar neck and head can be treated conservatively, similarly to ankle sprains, with weightbearing as tolerated and follow-up with primary care.

Osteochondral Lesions

Foundations. Osteochondral lesions of the talar dome warrant special mention. These talar body injuries are defects of the articular cartilage and often include subchondral bone. Although the incidence varies by study, osteochondral lesions are estimated to occur in 10% to 15% of ankle fractures using CT imaging to identify lesions[18,19] and in up to 40% of displaced fractures undergoing operative repair.[20] Using MRI following acute ankle sprain without fracture, osteochondral lesions were found in 8% of ankles, although older studies have suggested a much higher incidence.

Clinical Features. An osteochondral lesion should be considered in any patient with an acute ligamentous ankle injury with a joint effusion. Most lesions that result from ankle sprains are not diagnosed at the time of injury, but rather present with persistent pain and recurrent effusions (see Box 49.2). Physical findings usually are nonspecific, although tenderness over the posteromedial talus and increasing pain with exertion, weightbearing, or passive plantar flexion may be noted. Standard view radiographs are commonly normal in appearance or show subtle and easily overlooked abnormalities (Fig. 49.16).

Differential Diagnoses. Differential diagnoses of osteochondral lesions include those items outlined in Box 49.2.

Diagnostic Testing. Plain radiography can identify significant osteochondral defects, although CT is useful in identifying occult osteochondral lesions. However, more advanced imaging, most commonly MRI, is often necessary. Advanced imaging such as this can be arranged at the time of outpatient consultation.

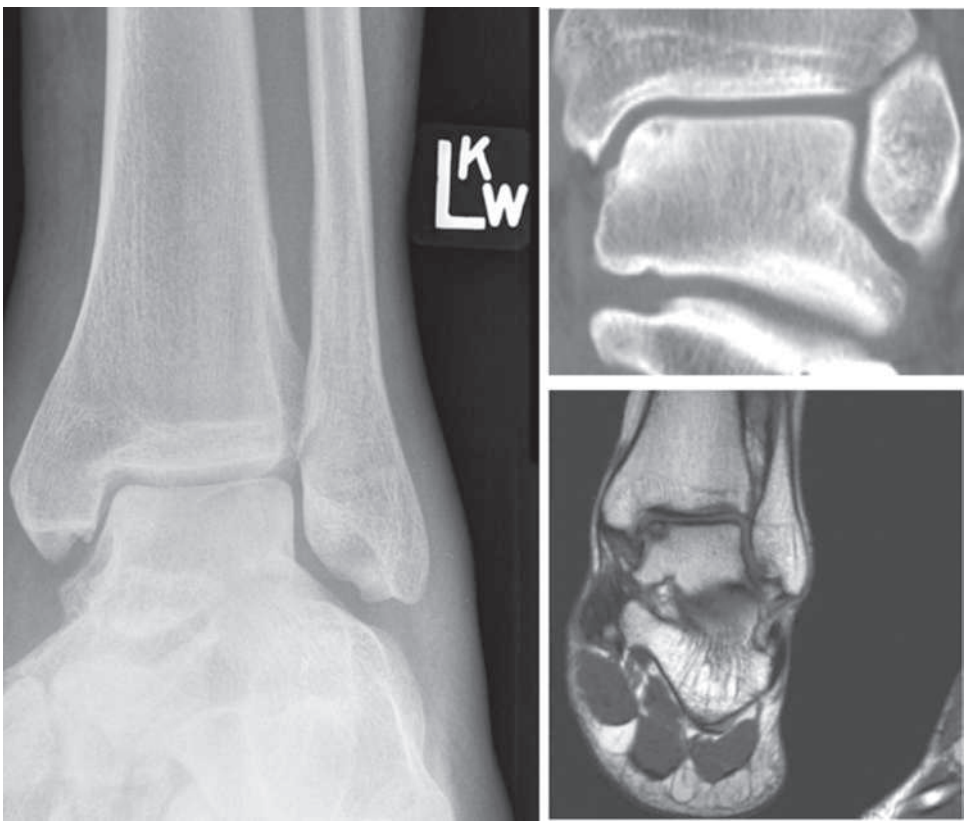

Fig. 49.16 (A) Mortise view of an ankle fails to identify an osteochondral lesion in a patient with recurrent effusions and ongoing pain following a sprain. (B) CT scanning identifies the suspected lesion. (C) Similar lesion in a different patient demonstrates the value of MRI in making the diagnosis. ((A & B) courtesy Dr. Thomas J. Green; (C) Adapted from Frost A, Roach R. Osteochondral injuries of the foot and ankle. *Sports Med Arthrosc Rev*. 2009;17:187.)

Management and Disposition. When an acute osteochondral lesion is confirmed or suspected, patients are best managed with outpatient orthopedic or sports medicine specialist consultation. The exception is with large, displaced fragments for which orthopedics should be consulted emergently.

Low-grade and minimally symptomatic osteochondral lesions are amenable to a trial of conservative therapy in a protective boot. Although there are many management options, higher grade lesions are often managed surgically. Patients with higher grade symptomatic lesions should be made nonweightbearing and can be placed in a splint for comfort.

This discussion underscores the importance of detailed discharge instructions following diagnosis of an ankle sprain. Patients with persistent swelling and pain or inability to return to function beyond the expected 2 to 4 weeks should be advised to seek follow-up with a primary care physician.

Subtalar Dislocations

Pathophysiology. Subtalar dislocation, also called peritalar dislocation, is the simultaneous disruption of the talocalcaneal and talonavicular joints, without disruption of the tibiotalar joint. This occurs when the talonavicular and talocalcaneal ligaments rupture while the stronger calcaneonavicular ligament remains intact. Subtalar dislocations are rare and are classified by the direction that the foot takes in relation to the talus. Medial dislocations are most common, with lateral, anterior or posterior occurring rarely. Ten percent of subtalar dislocations are open and associated fractures are present in 50% of cases. Isolated dislocation of the calcaneus is an exceptionally rare event distinct from subtalar dislocation; it involves disruption of the talocalcaneal and calcaneocuboid articulations.

Clinical Features. Obvious deformity is typically present, often with skin tension on the side opposite the direction of dislocation. Neurovascular status should be carefully assessed, although it is rarely compromised. Although serious complications, such as AVN, are uncommon in cases of closed subtalar dislocation, most patients have long-term limitation of subtalar motion, a sequela that can affect their gait.

Diagnostic Testing. Although standard foot radiographic views are diagnostic, properly positioning the patient for them may be difficult. The single most helpful radiograph is an anteroposterior view of the foot, which will demonstrate the talonavicular dislocation. Subtalar dislocations are frequently associated with fractures that may be difficult to detect on plain radiographs. Following reduction of the deformity, CT scanning should be considered.

Management. Subtalar dislocations require emergent reduction. Most closed subtalar dislocations can be treated with closed reduction with procedural sedation in the ED, although some patients require general anesthesia. Closed reduction is performed by flexing the knee and applying longitudinal traction to the foot with initial accentuation, followed by reversal of the deformity, using eversion for medial dislocations and inversion for lateral dislocations. Sometimes, direct pressure over the head of the talus aids in reduction. In some cases, buttonholing of the talus through the extensor retinaculum, entrapment in the peroneal tendons, or associated fractures can make closed reduction virtually impossible. After reduction, immobilization in a below-knee cast for 4 to 6 weeks is indicated. Orthopedics may elect to manage grossly unstable injuries that have been reduced with Kirschner (K) wire fixation.

Disposition. Emergent orthopedic consultation is indicated for subtalar dislocations.

Pantalar Dislocation

Pantalar or total talar dislocation is a rare and devastating injury requiring emergent orthopedic consultation in the ED. These injuries are the result of extreme forces that cause simultaneous disruption of the subtalar, tibiotalar, and talonavicular joints. Most are open fractures and infection and AVN are common complications.[20a]

Calcaneal Fractures

Anatomy and Pathophysiology. *The calcaneus is the largest and most commonly fractured tarsal bone*. It articulates superiorly with the talus (forming the subtalar joint) and anterolaterally with the cuboid.

Calcaneus fractures most often occur as a result of a fall from a height and from traffic accidents.[21,22] They are often high-energy injuries and frequently occur in association with other injuries, most importantly with vertebral fractures in up to 8% of cases.[22] Up to 5% of calcaneus fractures are open.[23] Calcaneus fractures can have serious short- and long-term sequelae. Compartment syndrome, historically thought to complicate up to 20% of fractures, has recently been identified in 5% of fractures. Unfortunately, the diagnosis of compartment syndrome is often made late, after development of sequelae, likely because the pain of the fracture itself masks early signs of compartment syndrome.[23] The degree of comminution is most predictive of risk of compartment syndrome. Other common complications include infection, chronic heel pain, posttraumatic arthritis, and hindfoot deformity. The inability to return to work or wear normal shoes are also common complications. Calcaneus fractures are classified as intraarticular, which involve the subtalar joint, or extraarticular.

Intraarticular Calcaneal Fractures. These are more serious and more common, accounting for up to 75% of calcaneal fractures. Classification systems used to describe intraarticular fractures are complex and more relevant to orthopedic consultants for guiding treatment planning and for prognosis. The commonly used classification systems have suffered poor interobserver reliability, although CT scanning has improved reliability.

Extraarticular Calcaneal Fractures. These include fractures of the anterior process, *sustentaculum tali*, lateral and medial calcaneal processes, peroneal tubercle, and tuberosity and extraarticular fractures of the calcaneal body. Isolated calcaneal tuberosity fractures are rare and occur as a result of avulsion by the Achilles tendons. However, these fractures deserve particular attention because displacement can compromise the skin overlying the Achilles tendon.

Clinical Features. Physical examination reveals pain, swelling, and tenderness over the heel. Weightbearing on the hindfoot is usually impossible. Ecchymosis may extend over the entire sole, and the heel may appear deformed, shortened, widened, or tilted. Particular attention should be given to the assessment for compartment syndrome, as well as to tension in overlying skin.

Differential Diagnoses. Please refer to Table 49.3 for differential diagnoses of extraarticular calcaneal fractures.

Diagnostic Testing. In the case of a suspected calcaneus fracture, initial radiographic imaging should include a foot series with the addition of an axial calcaneal view, also known as a *Harris view*. The anteroposterior view shows the calcaneocuboid joint and anterosuperior calcaneus, whereas the lateral view shows the posterior facet and can demonstrate compression of the calcaneal body. The Harris view is an additional axial projection of the calcaneal tuberosity, subtalar, and sustentaculotalar joints (Fig. 49.17).

The lateral X-ray allows for two important assessments: determination of involvement of the subtalar joint and evaluation of the degree of depression of the posterior facet by calculation of the *Boehler angle* (Fig. 49.18). Assessment of the Boehler angle can help identify

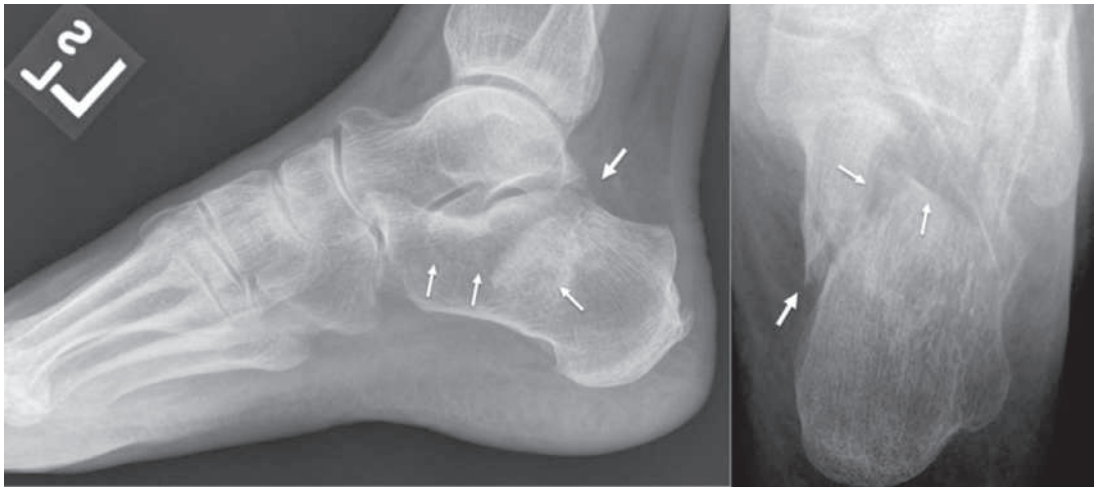

Fig. 49.17 (A) Lateral view of a comminuted fracture of the body of the calcaneus (*arrows*). (B) Axial or Harris view of the same fracture. (Courtesy Dr. Thomas J. Green.)

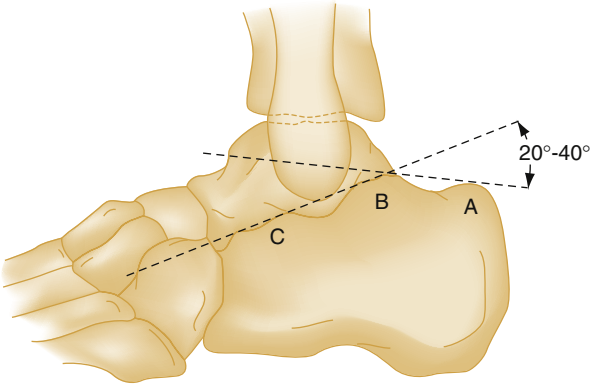

Fig. 49.18 Boehler angle is obtained by measuring the angle formed by two lines, one between the posterior tuberosity (A) and apex of the posterior facet (B) and the other between the apex of the posterior facet (B) and apex of the anterior process (C). Although several ranges for this measurement have been cited, an angle of 20 to 40 degrees gives the best diagnostic performance for fracture detection. An angle of less than 20 degrees suggests a compression fracture; comparison measurement of the uninjured side is helpful in questionable cases.

compression that may not be obvious, and is also prognostic of long-term functional outcome.[24]

Findings on plain radiographs can be subtle. CT imaging should be performed when fracture is highly suspected but is not identified on initial assessment. CT imaging also provides valuable information for classification, prognosis, and treatment planning. When an intra-articular fracture is identified on plain film, a CT scan should be performed.

Management. Emergency evaluation includes careful assessment for associated injuries, particularly vertebral fractures. Adequate pain control, splinting in a well-padded, compressive, noncircumferential splint, and careful clinical assessment for compartment syndrome are the mainstays of emergency care for calcaneus fractures. The decision to manage intraarticular or displaced calcaneal fractures operatively or conservatively must be made in consultation with an orthopedic surgeon and is frequently made on a case-by-case basis. In general, research does not support intervention for the majority of intraarticular fractures.[22,25,26] When operative repair is indicated for closed fractures, it is often best performed on a delayed basis, after resolution of swelling. In general, the goal of operative management is to reestablish both joint congruity and the Boehler angle by elevating depressed fractures. Operative repair is also indicated for open fractures, as well as those with neurovascular, skin, and soft tissue compromise. Emergent orthopedic consultation is indicated for patients in which compartment syndrome is a consideration.

Extraarticular fractures are most commonly treated nonoperatively. The emergency management of these fractures should include immobilization in a well-padded splint.

Calcaneal tuberosity, also known as tongue-type fractures, deserve special mention. These fractures, which may be intraarticular, are the result of avulsion at the Achilles insertion. Displacement may compromise overlying skin. In such cases, emergent orthopedic consultation is indicated. Nondisplaced tuberosity fractures may be placed in a nonweightbearing cast with the foot in slight plantar flexion.

Disposition. All patients with intraarticular calcaneal fractures, or fractures that compromise overlying skin or soft tissue, warrant orthopedic consultation in the ED. Compartment syndrome has been described as a complication to lower severity calcaneal fractures and as such orthopedics may decide to observe the patient for a period of time.[23] Conversely, in cases where pain and swelling is controlled and the risk of compartment syndrome is deemed unlikely, orthopedics may elect to discharge the patient for outpatient follow-up. In this case, the patient should be immobilized in a well-padded splint, made nonweightbearing, and given specific instructions on indications to return.

In general, nondisplaced extraarticular fractures have lower morbidity and benefit from symptomatic or conservative therapy. Outpatient orthopedic follow-up in the next 48 hours should be arranged, patients should be made nonweightbearing, and can be discharged with a compressive soft dressing or splint.

Midtarsal Joint Injuries

Foundations and Clinical Features. The midtarsal joint (*Chopart joint*) is comprised of the talonavicular and calcaneocuboid joints. Injury in this area is uncommon, occurring four times less frequently than injuries to the Lisfranc joint.[27] Falls, including those on stairs, and sports injuries are the most frequent causes of midtarsal joint injury.[27] Midtarsal joint injuries usually result from forced dorsiflexion and often are associated with other fractures. Pain, swelling, inability to bear weight, and tenderness over the midtarsal joint are usual findings. The possibility of a midtarsal joint injury should be

considered with any isolated midfoot fracture, particularly those of the navicular tuberosity. Complications of midtarsal (Chopart joint) injuries are common and include persistent pain, arthritis, and long-term disability.

Differential Diagnoses. Refer to Table 49.3 for a list of differential diagnoses of midtarsal joint injuries.

Diagnostic Testing. Although standard radiographs are often abnormal, the diagnosis frequently is overlooked or delayed, with symptoms ascribed to an ankle sprain (see Box 49.2). CT imaging is useful in identifying occult fractures around the midtarsal joint. In some cases, advanced imaging such as MRI may be helpful, although this can be arranged at the time of orthopedic follow-up.

Management and Disposition. Nondisplaced injuries may heal with casting, but operative fixation is often required. Orthopedic consultation in the outpatient setting is important when midtarsal injuries are identified or even when clinically suspected. Patients should be made nonweightbearing and follow-up arranged.

Nontraumatic Hindfoot Pain

Clinical Features

Hindfoot pain is a common complaint that more often is the result of overuse rather than trauma. History should elicit prior injury, with attention paid to patterns of activity and overuse, as well as a review of relevant medical history and whether pain is acute or chronic in onset. The plantar fascia is a tough layer of the sole that is functionally significant during foot strike and the early stance phase of walking. Plantar fasciitis typically presents with difficulty ambulating and pain with activity. Pain is classically felt on first weightbearing either in the morning or after prolonged sitting. Tenderness is noted at the calcaneal insertion.

Plantar fascial rupture is a tear of the origin of the plantar fascia at the calcaneus. This injury usually occurs during the push-off phase of gait. Swelling may be noted, and typically pain is elicited by passive dorsiflexion of the hallux.

Differential Diagnoses

See Table 49.3. Bone pain in the hindfoot necessitates consideration of calcaneal or talar stress fractures. A calcaneal stress fracture may be suspected when pain is elicited on squeezing the calcaneus mediolaterally.

With subcalcaneal heel pain, plantar fasciitis is the most common diagnosis. Differential diagnoses also include calcaneal fat pad atrophy, acute rupture of the plantar fascia, lateral plantar nerve compression, and tarsal tunnel syndrome.

Many tendons course through the hindfoot, particularly anteromedially, and tendinitis can occur (see Fig. 49.3 and Table 49.2). Other tendon pathologic conditions (e.g., ruptures, dislocations, retinacular injuries) should be considered because they can result in significant functional disability.

Diagnostic Testing

Plain radiographs are of limited diagnostic value for hindfoot pain although are usually necessary to rule out other bony pathology. Although MRI is the most useful diagnostic tool in the context of nontraumatic hindfoot pain, ultrasound (plantar fasciitis) and CT-SPECT (stress fractures) also have diagnostic utility. However, for many of these subacute nontraumatic hindfoot injuries, the diagnosis is clinical and the decision for advanced imaging may be at the discretion of the orthopedic consultant.

Management

Although there are several options for treatment of plantar fasciitis, the mainstays of management include activity and footwear modification, stretching, NSAIDs, and physiotherapy. Primary care follow-up is sufficient.

Treatment of plantar fascia rupture is generally nonsurgical, often with a period of cast immobilization for symptomatic relief. These patients generally benefit from referral to orthopedics or sports medicine on a nonurgent basis for guidance.

Midfoot Injuries

The midfoot (navicular, cuboid and cuneiforms) is an inherently stable region of the foot and is infrequently injured. Fractures and relationships of the midfoot tarsals are difficult to visualize on standard radiographic views. A compounding factor is that pain associated with midfoot injuries may be ill-defined and poorly localized. Although isolated fractures of the midfoot tarsals occur, associated injuries, including metatarsal fractures, subluxations, and spontaneously reduced tarsometatarsal dislocations, may be present.

Differential Diagnoses

The differential diagnoses of acute traumatic injuries of the midfoot includes fractures to the navicular, cuneiform bones, and the cuboid, as well as injuries to the Lisfranc joint (see Table 49.3). When considering the differential diagnoses, mechanism of injury is essential to narrow down the list of considerations. Specifically, one should consider whether the injury occurred from a high- or lower-energy trauma. This is particularly the case when Lisfranc injury is clinically suspected.

Midfoot bones, the navicular bone in particular, are prone to stress fractures, which should be considered in cases of insidious onset of pain. Soft tissue structures including the plantar fascia also traverse the midfoot and may be a cause of more chronic or nontraumatic pain.

Navicular Fractures

Anatomy. The navicular forms the supporting structure for the medial arch of the foot and bears most of the load within the tarsal complex during weightbearing. The navicular tuberosity is an insertion point for the tibialis posterior tendon. Because of the navicular's extensive articular surface, its blood supply enters only through a small waist of cortex, leaving the middle third relatively avascular and therefore at risk for avascular necrosis.

Pathophysiology. Navicular fractures are classified as dorsal avulsion fractures, tuberosity fractures, and body fractures. Fractures of the body are classified according to direction of the fracture line and disruption of surrounding joints, but classification to this detail is beyond the scope of this chapter. Stress fractures do occur in the navicular and although uncommon, carry a high risk of morbidity often related to misdiagnosis and subsequent fracture with nonunion.

Clinical Features. Navicular fractures cause localized tenderness over the dorsal and medial aspects of the midfoot. The navicular tuberosity is palpated anterior to the *sustentaculum tali*, a shelf of bone on the medial ankle approximately 2.5 cm below the tip of the medial malleolus. In the case of tuberosity fractures, pain may be exacerbated by passive eversion or active inversion of the foot. Navicular tuberosity fractures can be complicated by nonunion. Avascular necrosis and arthritis are potential late sequelae, particularly in displaced body fractures.

Differential Diagnoses. See Table 49.3. The *os tibiale externum* is an accessory bone present in approximately 10% of the population and it is not uncommon to confuse this with an acute fracture.

Diagnostic Testing: Radiology. Although standard foot radiographs usually identify navicular fractures, advanced imaging with CT may be necessary. This is particularly the case for patients with high-energy or complex foot injuries, for which the sensitivity of plain radiography is poor.

Management. Nondisplaced dorsal avulsion fractures can be treated symptomatically. Displaced dorsal avulsion fractures, or those involving more than 25% of the talonavicular joint surface may be

treated surgically. Navicular body and tuberosity fractures should be treated with the guidance of orthopedics. These fractures can have long-term complications and functional limitation. Nondisplaced fractures are amenable to treatment in a weightbearing cast, whereas displaced tuberosity and body fractures are managed surgically.

Disposition. The majority of navicular fractures are suitable for outpatient orthopedic referral. Nondisplaced dorsal avulsion fractures involving less than 25% of the articular surface are treated symptomatically with a compressive dressing. Nondisplaced body and tuberosity fractures should be splinted in a nonweightbearing splint, cast or boot with outpatient orthopedic follow-up within a week. Displaced tuberosity and body fractures as well as displaced or intraarticular avulsion fractures may be surgically managed. Assuming adequate pain control, these patients may be placed in a nonweightbearing splint and have orthopedic consultation arranged within 24 to 48 hours.

Cuboid Fractures

Cuboid fractures usually occur with other midfoot fractures, including Lisfranc injuries. Fractures are generally the result of avulsion or crush injury. The latter, known as a "*nutcracker fracture*," results from compression of the cuboid between the bases of the fourth and fifth metatarsals and calcaneus. These injuries may have associated with fractures of the posterior malleolus.

The cuboid is best evaluated by the oblique view of a standard foot radiographic series which demonstrates the calcaneocuboid and cuboid-metatarsal relationship. The possibility of Lisfranc injury should be considered with any cuboid fracture. Treatment of isolated injuries ranges from casting for minor nondisplaced fractures to operative fixation. Nondisplaced cuboid fractures are suitable for urgent outpatient orthopedic follow-up. A compressive dressing and splint are reasonable in the interim prior to consultation. Cuboid fractures associated with more significant injury or other fractures should have orthopedic consultation in the ED. Extraarticular cuboid fractures can be complicated by disruption of the peroneus longus tendon at the level of the peroneal groove.

Cuneiform Fractures

Fractures of the cuneiforms are extremely uncommon and usually result from direct trauma. As with cuboid fractures, the patient should be assessed carefully for the presence of a Lisfranc injury. Treatment usually is by casting; however, displaced fractures require orthopedic assessment.

Dislocations of the Navicular, Cuboid, and Cuneiforms

Isolated dislocations of each of the midfoot bones have been described. These uncommon injuries often require open reduction. Emergent orthopedic consultation is required for these injuries.

Lisfranc (Tarsometatarsal) Fractures and Dislocations

Anatomy. Lisfranc injuries refer to any fracture, dislocation, or ligamentous injury at the tarsometatarsal joint (*Lisfranc joint*). In concert, the tarsometatarsal joints act to allow supination and pronation of the forefoot. The Lisfranc joint is composed of the articulations of the bases of the first three metatarsals with their respective cuneiforms and bases of the fourth and fifth metatarsals with the cuboid. The stability of the Lisfranc joint is provided by the bony architecture and associated ligaments. The metatarsal bases form an arch, with the second metatarsal acting as the keystone. The Lisfranc ligament itself joins the medial cuneiform with the base of the second metatarsal and provides crucial structural support. Strong transverse intermetatarsal ligaments join the bases of the second through fifth metatarsals. The joint is further supported by dorsal and plantar ligaments, plantar fascia, and insertions of the tibialis anterior and peroneus longus tendons at the first metatarsal base (Fig. 49.19).

Physiology and Pathophysiology. Lisfranc injuries carry a significant risk of long-term disability resulting from arthritis, instability, foot deformity, and chronic pain. They arise from three mechanisms: rotational forces of the midfoot, axial loads of the foot, and crush injuries. Injuries to the Lisfranc joint complex can be thought of as high-energy injuries, such as occurring in MVCs, or low-energy injuries, such as those occurring in sports activities. Historically, these injuries were often described in equestrian riders who got their foot caught in the stirrup when falling from a horse.

High-energy injury usually results in fractures or fracture-dislocations, whereas low-energy injuries can result in isolated ligamentous injuries. Historically, low-energy mechanisms were thought to account for the minority of injuries but more recent evidence suggests that over 50% of injuries result from low-energy mechanisms.[27,28] Low-energy injuries are more likely to be primarily ligamentous, while high-energy injuries are much more likely to have associated foot, as well as non-foot, fractures.[29]

The most intuitive classification describes the direction of the dislocation in the horizontal plane (Fig. 49.19). In type A, or homolateral, injuries, all the metatarsals are displaced in one direction. In type B, or isolated, injuries, one or more metatarsals are displaced. In type C, or divergent, injuries, the metatarsals are splayed outward in the medial and lateral directions. Dorsal displacement is also commonly present in displaced Lisfranc injuries, whereas plantar displacement is uncommon because of the joint's bone architecture and strength of the plantar ligaments and fascia.

Low-energy Lisfranc injuries have been previously classified as stage 1 injuries, which are nondisplaced with low-grade strain, stage 2 injuries, in which a 2- to 5-mm diastasis exists between the first cuneiform and base of the second metatarsal, and stage 3 injuries, in which more than 5 mm of diastasis exists and there is loss of metatarsal arch height. Because of ligamentous attachments, Lisfranc injuries are frequently associated with metatarsal fractures, usually of the second metatarsal base. Fractures of the cuboid, cuneiforms, and navicular also are common, occurring in more than one-third of cases.

Clinical Features. The diagnosis of Lisfranc injury can be a challenge, particularly in the case of low-energy, isolated ligamentous injuries. Clinical and radiographic findings may be subtle, and the true extent of the pathologic condition can easily be missed or misdiagnosed. Seemingly trivial fractures, if viewed in isolation, may fail to reflect the extent of ligamentous disruption. Some have estimated the diagnosis is missed on initial presentation in up to 30% of cases, particularly for low-energy mechanisms.[29]

The clinical presentation varies with the extent of injury and displacement. Pain in the midfoot and inability to bear weight, particularly on the toes, are usual features. Typically, there is tenderness along the affected tarsometatarsal joints and pain with passive abduction and pronation of the forefoot, sometimes with pathologic mobility. Paresthesias are occasionally present, and examination may reveal edema and ecchymosis. The dorsalis pedis pulse can be absent, or evidence of vascular compromise of the forefoot may be present. It should be kept in mind that low-energy injuries may present with more subtle findings, such as chronic pain and limitation in activity. Lisfranc injuries may be complicated by vascular injury because a critical branch of the dorsalis pedis artery dives between the first and second metatarsals to form the plantar arch. Trauma to this vessel can cause significant hemorrhage and, uncommonly, vascular compromise.

Differential Diagnoses. See Table 49.3 for differential diagnoses of Lisfranc (tarsometatarsal) fractures and dislocations.

Diagnostic Testing: Radiology. Standard radiographic views of the foot are the initial investigation of choice for suspected Lisfranc injuries. However, plain radiographic findings can be subtle or even absent (Fig. 49.20). Abnormal radiographic findings are outlined

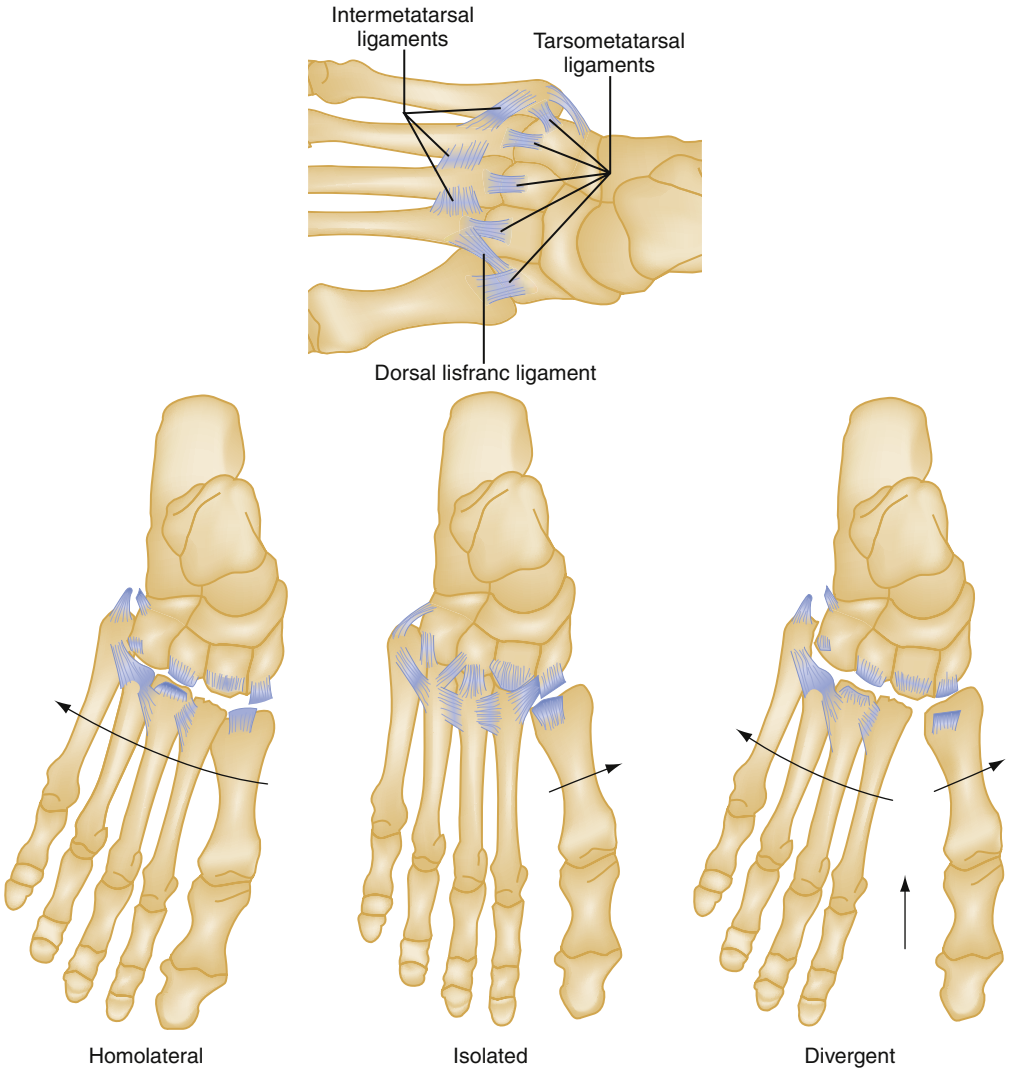

Fig. 49.19 Ligamentous anatomy of the Lisfranc joint and classification of Lisfranc injuries by direction of displacement of metatarsals with respect to the midfoot. Direction of displacement is indicated by arrows.

in Box 49.3.[30] In a recent retrospective study on nonweightbearing radiographs, the presence of an avulsion fracture ("*fleck sign*"), diastasis of greater than 2 mm between the medial cuneiform and base of the 2nd metatarsal, and diastasis of greater than 2 mm between the medial cuneiform and the middle cuneiform, were strong predictors of instability.[31]

When plain radiographs are normal, and Lisfranc injury is suspected, there are a number of alternative imaging options. Weightbearing films improve diagnostic accuracy for ligamentous injury.[30] Unfortunately, weightbearing radiographs are often impossible to obtain in the acutely injured foot, thus their utility in the ED is limited.

CT imaging detects subtle, or nondisplaced, fractures and avulsions that may be missed by plain films, but also fails to detect many isolated ligamentous injuries.[16] MRI is the most sensitive and specific for ligamentous injury, and there is a strong correlation with intraoperative instability, but the ability of MRI to detect subtle instability is unclear.[16] Ultrasound is a cost-effective and useful technique for many emergency medicine applications and can be used to evaluate the dorsal Lisfranc ligament,[32,33] however, the utility of ultrasound to diagnose instability is unproven.[16] Stress fluoroscopy is a technique that may be used in follow-up assessment, or under anesthesia by orthopedics, and may be a more definitive assessment of ligamentous injury.

BOX 49.3 Radiographic Findings Consistent with Lisfranc Injuries

Anteroposterior View

Fleck sign—bony fragment between medial cuneiform and second metatarsal
Lateral displacement of second metatarsal with respect to middle cuneiform
>2 mm widening between medial cuneiform and second metatarsal
>1 mm widening between first and second metatarsals or medial and middle cuneiforms and metatarsals

Lateral View

Dorsal subluxation of the metatarsals at the tarsometatarsal joint
Talometatarsal angle >15°
Reduced plantar distance between medial cuneiform and fifth metatarsal

Adapted from: Kennelly H, Klaassen K, Heitman D et al. Utility of weight-bearing radiographs compared to computed tomography scan for the diagnosis of subtle Lisfranc injuries in the emergency setting. *Emerg Med Australas*. 2019;31:741.

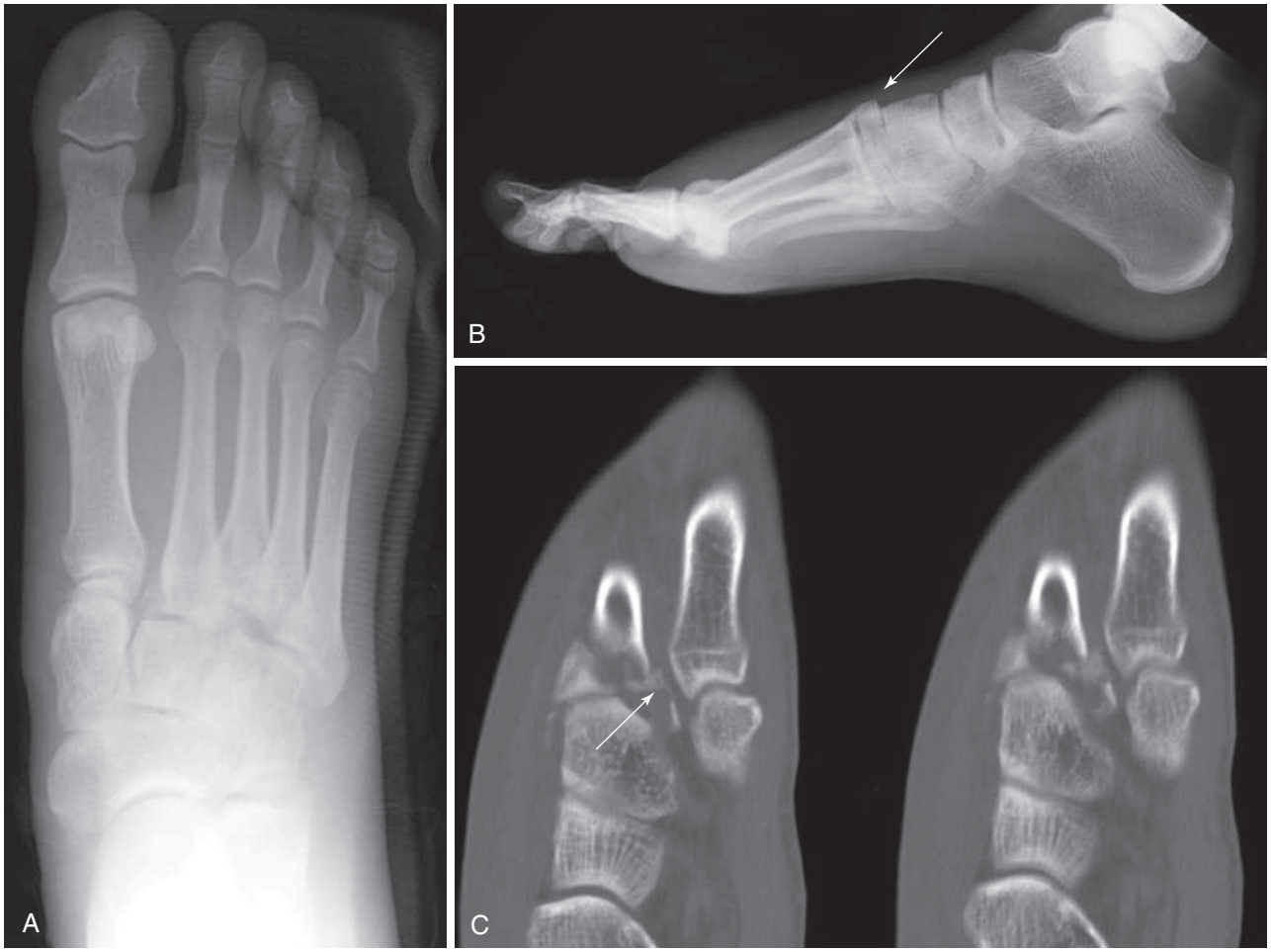

Fig. 49.20 (A) Anteroposterior radiograph showing a Lisfranc injury with fractures of the bases of the second through fourth metatarsals, including a fragment suspicious for an avulsion from the Lisfranc ligament at the second metatarsal base. (B) Lateral radiograph showing a step-off at the tarsometatarsal joints (*arrow*). (C) Computed tomography scan of the same patient showing increased detail, including lateral displacement of the first metatarsal relative to the first cuneiform (*arrow*). (From: Gupta RT, Wadhwa RP, Learch TJ, Herwick SM. Lisfranc injury: imaging findings for this important but often-missed diagnosis. *Curr Probl Diagn Radiol.* 2008;37:115.)

The American College of Radiology in their appropriateness criteria for acute trauma to the foot suggest the following approach.[15] Initial assessment of the Lisfranc joint should include standard three-view radiography. Weightbearing radiographs do provide additional diagnostic benefit and should be added, if possible. If weightbearing images are not possible, CT scanning or MRI may be considered on a case-by-case basis. In the case of a patient with normal plain radiographs, who cannot bear weight, the choice if advanced diagnostics and clinical assessment can be made at the time of consultation by the orthopedic specialist.

Management. High-energy Lisfranc injuries or ligamentous injuries with displacement, either on standard radiographs or stress imaging, are usually treated surgically. Following repair, patients are kept in a nonweightbearing cast for up to 12 weeks. Low-energy ligamentous injury without displacement can be treated with immobilization in a below-knee cast for 6 weeks. There is a significant rate of failure of nonoperative management of nondisplaced, ligamentous injuries. These patients may go on to have operative repair.[34]

Disposition. All proven or suspected Lisfranc injuries should be managed with orthopedic consultation. Delayed treatment or misdiagnosis can result in significant complications and poor functional outcome. When radiographic assessment in the ED is nondiagnostic, clinical suspicion of Lisfranc injury warrants further investigation and referral to an orthopedic surgeon.

Patients with high-energy or displaced Lisfranc injury are managed surgically. Orthopedic consultation, either in the ED or outpatient in 24 to 48 hours, is appropriate. Such patients can be immobilized in a well-padded lower leg splint and should be nonweightbearing. Patients with significant pain, swelling, or those with signs of compartment syndrome, require emergent orthopedic assessment.

Patients with nondisplaced but suspected ligamentous Lisfranc injury should have urgent outpatient orthopedic consultation within 48 hours arranged. These patients should be placed in a well-padded splint and should be nonweightbearing.

Nontraumatic Midfoot Pain

Isolated midfoot pain is less common than forefoot or hindfoot pain. Midfoot stress fractures, although uncommon, usually involve the navicular. Other causes of midfoot pain include symptomatic accessory bones, particularly the accessory navicular, os tibiale externum, and os peroneum.

Forefoot Injuries

Traumatic forefoot conditions are underdiagnosed and often consist of more than one fracture or dislocation occurring simultaneously. As occurs elsewhere in the foot, forefoot trauma may lead to prolonged disability and dysfunction.

Differential Diagnoses

The differential diagnoses for acute forefoot injuries include fractures of the metatarsal bones, phalanges and sesamoid bones in the forefoot (see Table 49.3). Dislocations of the interphalangeal and metatarsophalangeal joints should also be considered. The mechanism of injury is important to include when considering a broad differential. For example, an inversion injury may result in a ligamentous sprain, or in an acute avulsion fracture. The metatarsal bones are prone to stress fractures, in particular the base of the fifth metatarsal, the so called "*Jones and pseudo-Jones*" fractures. When pain is isolated to joints in the forefoot, common causes include inflammatory conditions such as gout, osteoarthritis, and a septic joint. When a more progressive or insidious history of pain is elicited, consideration of soft tissue pathology such as Morton neuroma and other causes of metatarsalgia should be considered.

Diagnostic Testing

Plain radiographs are generally adequate in diagnosing fractures to the forefoot. One potential exception may be when there is consideration of Lisfranc injury with metatarsal base fractures. In that circumstance, CT scanning provides an added diagnostic modality.

Metatarsal Fractures

Foundations. Metatarsal fractures are common and account for one-third of foot fractures. Management depends both on the specific location of the fracture, and on the metatarsals involved; first, middle (metatarsals two, three, four), and fifth. In assessing metatarsal fractures, it is important to consider and rule out associated injuries, particularly Lisfranc injury when there are fractures of the base of the first to fourth metatarsals.

Fractures of the First Metatarsal. The first metatarsal is the largest and strongest of the metatarsal bones and is rarely fractured. Injury to the first metatarsal occurs from both direct, and indirect trauma as well as from crush injuries. Patients will present with pain and swelling over the medial side of the foot along with pain or inability to bear weight. Axially loading the first phalanx will illicit pain. First metatarsal fractures are typically identified by a standard plain radiograph series of the foot.

Because of the forces acting through the first metatarsal, and its essential role in ambulation, maintenance of length and anatomic alignment is important. All first metatarsal fractures should be followed by orthopedics urgently within 48 hours. Nondisplaced fractures are treated with a nonweightbearing cast for up to 6 weeks. Displacement, shortening or comminution are indications for surgical repair, which can be arranged after outpatient orthopedics consultation in 24 to 48 hours. In the ED, care must be taken to rule out associated injuries, specifically Lisfranc injury. Assuming pain is adequately controlled, patients should be placed in a nonweightbearing cast or splint and outpatient orthopedic follow up should be arranged.

Fractures of the Middle Metatarsals (Two to Four). Middle metatarsal fractures often result from crush injuries but can occur from indirect trauma such as in twisting injuries. These metatarsals are also prone to stress fractures.

Clinical Features. Patients will present with pain, tenderness, and swelling in the midfoot and usually inability to bear weight.

Differential Diagnoses. See Table 49.3 for a list of differential diagnoses of metatarsal fractures.

Diagnostic Testing. Plain radiographs are generally adequate for diagnosis of acute fractures. CT imaging may better delineate the diagnosis, particularly in cases of fractures to middle metatarsal bases where Lisfranc injury is a concern.

Management and Disposition. The middle metatarsals are inherently stable with extensive soft tissue support from adjacent metatarsals. Nondisplaced fractures may be treated with weightbearing as tolerated usually in stiff soled footwear. If limited by pain, an initial period of nonweightbearing with application of a compressive dressing in the ED is a reasonable approach. Displacement, particularly in the sagittal plane, affects normal foot loading and can result in persistent pain. Fractures with greater than 3 mm of displacement, or greater than 10 degrees of angulation require reduction, which may be attempted using traction of the affected phalanx. Following reduction, patients with displaced fractures should be nonweightbearing and splinted.

Patients with nondisplaced or reduced middle metatarsal fractures can be referred to orthopedics for follow-up in 1 to 2 weeks. Patients with multiple fractures, or with persistently displaced fractures should be referred to orthopedics within 48 hours for consideration of operative repair.

Fractures of the Fifth Metatarsal. *The fifth metatarsal is the most commonly fractured metatarsal.* Fractures of the fifth metatarsal are divided anatomically into fractures of the base and fractures of the shaft and head. Fractures of the base are further divided into three types, based on anatomic zones. Zone 1 fractures are avulsion fractures of the tuberosity, zone 2 fractures or "*Jones fractures*" involve the metaphyseal diaphyseal junction, at the level of the intermetatarsal articulation of the fourth and fifth metatarsals. Zone 3 fractures occur in the proximal 1.5 cm of the diaphysis and are most commonly stress fractures (Fig. 49.21).

Fifth Metatarsal Shaft Fractures. Fractures of the shaft of the 5th metatarsal are often referred to as "*dancers' fractures.*" These injuries result from an inversion injury when the foot is in plantar flexion, as seen in dancers when up on demi-pointe. Fractures of the fifth metatarsal shaft present with localized tenderness and pain or inability to bear weight. These generally heal well and are treated nonoperatively with weightbearing as tolerated. The use of a walker boot or rigid support, although not strictly necessary, may be required in the initial phase due to pain. Routine follow-up with orthopedics is reasonable although these fractures could be safely managed in a primary care setting.

Fifth Metatarsal Base Fractures. Fractures in zone 1 of the fifth metatarsal base occur from avulsion of the tuberosity by the lateral band of the plantar aponeurosis. These fractures are extremely common and are the result of sudden inversion on a plantar flexed foot. They are usually extraarticular, although they may extend into the cubometatarsal joint. Often, these injuries masquerade as ankle sprains (see Box 49.2), making the fifth metatarsal base an important area to palpate following any twisting injury.

Differential Diagnoses. See Box 49.2 and Table 49.3 for a list of differential diagnoses of fifth metatarsal fractures.

Diagnostic Testing. Plain radiographs are generally adequate for diagnosis of acute fractures of the fifth metatarsal.

Management and Disposition. Historically, tuberosity fractures involving more than 30% of the articular surface or with more than 2 mm of displacement were managed operatively. Current evidence, however, suggests that all zone 1 fractures, regardless of articular involvement, can be managed symptomatically and functionally.[35,36] Often an elastic bandage and supportive footwear are adequate. If required due to pain, a short period in a walking boot is reasonable. These fractures can be managed in a primary care setting.

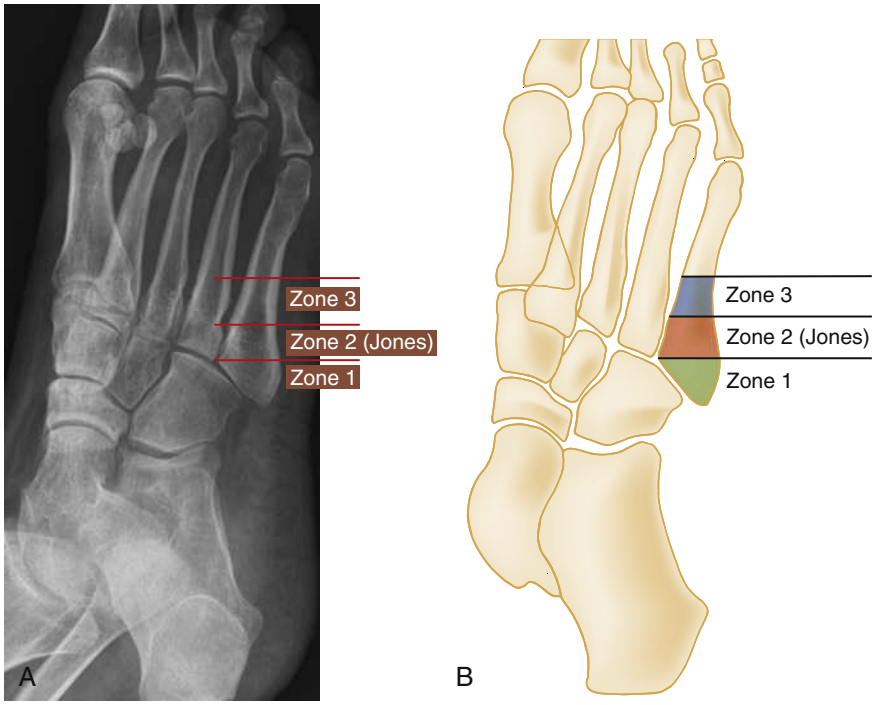

Fig. 49.21 Classification of fractures of the base of the fifth metatarsal. Zone 1 is a tuberosity avulsion fracture. Zone 2 (Jones fracture) occur through the fourth and fifth intermetatarsal articulation. Zone 3 fractures are distal to the articulation.

Zone 2 is a watershed area of blood supply and therefore fractures here are at a higher risk of nonunion. Historically, these fractures have been treated with prolonged immobilization, however, recent evidence questions this dogma, advocating for functional treatment with weightbearing as tolerated. In several studies the rate of symptomatic nonunion has been low, and the need for operative intervention approaches only 1%.[37,38] These studies show safe and effective nonoperative treatment at substantially lower health care cost.[37-39] Early operative intervention is still considered for certain populations, including athletes.[40] As management decisions are made on a case-by-case basis, routine referral to orthopedics is recommended for fractures in zone 2. In the ED, patients can be treated symptomatically in a compressive bandage and supportive footwear. In some cases, pain will necessitate provision of a walking boot, or even a period of nonweightbearing.

Fractures in Zone 3 are most commonly stress fractures resulting from repetitive trauma in a cavovarus (or high arched) foot. These fractures have a high rate of nonunion and may require prolonged immobilization and in some cases, operative management. In the ED, treatment of zone 3 fractures can be guided by symptoms. If there is pain upon weightbearing, patients should be made nonweightbearing and may benefit from the use of a walker boot. These fractures should be managed with the guidance of orthopedics or sports medicine specialists with routine referral in 2 weeks.

Phalangeal Fractures

Foundations. *Phalangeal fractures are the most common forefoot fracture.* The proximal phalanges are more commonly fractured than middle or distal phalanges and the proximal phalanx of the fifth toe is the most commonly injured of all. Fractures of the hallux often are displaced, whereas those of the lesser phalanges are often comminuted but are less commonly displaced.

Clinical Features. Although phalangeal fractures generally are considered minor injuries, they can lead to disabling sequelae. Patients present with acute pain and swelling of the affected toe, often with difficulty ambulating or wearing shoes. Examination will reveal tenderness and crepitus. A subungual hematoma is often present if the distal phalanx is involved, and open fractures are common. Complications of phalangeal fractures are uncommon. With intraarticular phalangeal fractures, particularly those involving the hallux, arthritis may be a late sequela. Symptomatic angular malunion and osseous deformity can occur with phalangeal fractures, and exostectomy is sometimes required.

Differential Diagnoses. See Table 49.3 listing differential diagnoses for phalangeal fractures.

Diagnostic Testing. As with metatarsal fractures, carefully assessed standard radiographic views are sufficient to demonstrate phalangeal fractures. Careful inspection will help to rule out associated dislocations.

Management. Most phalangeal fractures are easily managed and heal well. Large (greater than 50% of the nail bed) and symptomatic subungual hematomas should be trephinated and, on rare occasions, nail bed repair may be required. Nondisplaced lesser phalangeal fractures should be stabilized by dynamic buddy taping, with placement of gauze between the splinted toes to prevent skin maceration. Patients are advised to expect pain for 2 to 3 weeks until the fracture is stabilized by callus. Use of a stiff shoe is often beneficial.

If significant displacement or angulation is present, reduction should be performed with manual traction after digital anesthesia. Moderate persistent angulation or displacement is acceptable if the clinical appearance and function of the toe remain satisfactory. Rarely, operative fixation of lesser phalangeal fractures is indicated, particularly in cases with severe rotatory deformity or open fractures requiring débridement.

Nondisplaced phalangeal fractures involving the hallux are treated by buddy taping with a walking cast worn for 2 to 3 weeks if the toe is painful. Displaced hallux fractures require reduction. If the reduction is inadequate or unstable, operative fixation may be indicated. Unless

completely nondisplaced, most intraarticular fractures involving the hallux are treated with operative fixation.

Disposition. In general, primary care follow-up is appropriate for phalangeal fractures. If displacement persists or causes cosmetic or functional concern, nonurgent outpatient orthopedic referral is advised. Poorly reduced, or intraarticular hallux fractures should be splinted for urgent outpatient orthopedic follow-up within a week.

Sesamoid Fractures

The sesamoids are two flat oval bones found in the tendon of the flexor hallucis brevis, under the head of the first metatarsal and, rarely, under the second to fifth metatarsal heads. Sesamoid fractures are uncommon, usually resulting from direct trauma or hyperextension of the great toe, although they have been described in association with MTP joint dislocations. Stress fractures of the sesamoids also occur. A fracture should be differentiated from a bipartite sesamoid, which occurs in up to one-third of the population and also is more common on the medial aspect. Most sesamoid fractures heal without complication with symptomatic treatment only. A walker boot or below-knee cast may help function, although typically a supportive shoe is sufficient, possibly with a shaped pad to alleviate direct pressure. Orthopedic consultation is suggested only for patients with nonunion or chronic pain. This can be arranged by the primary care physician.

Metatarsophalangeal Dislocations

Foundations and Pathophysiology. MTP joint dislocations can occur in any joint and in any direction. First MTP joint dislocations require large forces and usually result from MVCs. These injuries, which are frequently open, are usually dorsal dislocations of the distal component caused by hyperextension of the MTP joint. Associated sesamoid fractures may be present. Complex dislocations, in which the sesamoids or local tendons prevent closed reduction, can occur. The most common MTP dislocation is a lateral dislocation of the fifth MTP joint.

Clinical Features. First MTP joint dislocations usually are obvious because the toe is angled upward, with dorsal and proximal displacement of the proximal phalanx. Rarely, the sesamoids are palpable dorsal to the metatarsal, indicating a complex dislocation. Dislocations of the lesser toes may be more subtle in presentation, and comparison with the uninjured foot may be helpful. Complications are rare after MTP dislocation but arthritis and reduced range of motion, particularly of the hallux, do occur. Dislocations for which the diagnosis is delayed for more than 3 weeks often are not amenable to closed reduction and may require metatarsal head excision.

Differential Diagnoses. See Table 49.3 describing differential diagnoses of metatarsophalangeal dislocations.

Diagnostic Testing: Radiology. Dislocations of the MTP joint are well-visualized on standard radiographic views of the foot. Radiographs should be scrutinized for signs of complex dislocation, such as the sesamoids lying between the articular surfaces or dorsal to the metatarsal head.

Management. Most MTP joint dislocations, particularly of the lesser toes, are easily reduced with longitudinal traction. Analgesia or local anesthesia may be required. Dorsal dislocations of the first MTP joint can be more challenging and may require initial accentuation of the deformity, in addition to longitudinal traction, for reduction. Joint stability should be assessed, and repeat radiographs obtained after reduction of an MTP joint dislocation. Joints that are stable after reduction can be treated with buddy taping and benefit from use of a hard soled, supportive shoe.

Disposition. Most MTP joint dislocations can be managed without orthopedic consultation. If crepitus or obvious instability is present, or postreduction radiographs show joint incongruity or an intraarticular fracture, outpatient orthopedic consultation should be obtained for possible fixation. First MTP joint dislocations that are open, are complex or do not easily reduce require emergent orthopedic consultation.

Interphalangeal Joint Dislocations

IP joint dislocations are much less common than MTP joint dislocations and are often overlooked. Most IP joint dislocations occur in the great toe and are a result of axial loading. IP joint dislocations usually involve dorsal displacement of the distal component. Reduction is performed with longitudinal traction after digital block anesthesia. If the dislocation involves the great toe, a walking cast with a toe plate for 3 weeks is indicated after reduction. Lesser toes require only buddy taping. As with the MTP joint, complex dislocations involving the first IP joint can occur, and orthopedic consultation in the ED for open reduction may be necessary. In rare cases, lesser toe IP closed reduction is not possible and open reduction is required.

Nontraumatic Forefoot Pain

Clinical Features. The forefoot is the site for a myriad of painful problems. Bunions, painful bursae, blisters, corns, calluses, hammertoes, and ingrown toenails all are diagnostically obvious but can pose therapeutic challenges. Many are the result of poor footwear or a biomechanical problem with the foot. These often respond to appropriate padding and avoidance of precipitants although in certain specific cases surgical intervention may help.

Metatarsalgia is an often used, loosely defined term referring to pain in the region of the metatarsal heads. This is a common presenting complaint, with many potential causes relating to biomechanics of the forefoot. Metatarsal stress fractures should be considered in the differential diagnoses for any unexplained forefoot pain. Flexor or extensor tendinitis also can produce metatarsal area pain. Arthritis, sesamoiditis, or a sesamoid stress fracture should be considered when pain occurs in the plantar area of the hallux. The term *turf toe* refers to MTP joint inflammation of the hallux resulting from repeated hyperextension. It usually responds to symptomatic measures but can be a debilitating injury in some athletes.

An important cause of unilateral metatarsalgia is a perineural fibrosis of the intermetatarsal plantar digital nerve, more commonly known as *Morton neuroma*. This neuropathy usually involves the second-third or third-fourth intermetatarsal space, causing lancinating pain with weightbearing that can radiate to the toes and may be associated with paresthesia. Pain is reproduced when structures of the affected interspace are pinched or when the metatarsal heads are compressed together. Hence, pain may occur with tight-fitting footwear. Crepitus or a nodule may be palpable.

Freiberg disease is an osteochondrosis of the metatarsal head, usually involving the second metatarsal, and is another cause of pain in this area. Ingrown toenails are a common affliction that can occur in any toe, usually the hallux. Often, the abnormality is perpetuated by short nail trimming, which affords the opportunity for a spicule of nail to grow under the nail fold.

Differential Diagnoses. Refer to Table 49.3 for differential diagnoses of nontraumatic forefoot pain.

Diagnostic Testing. Although the vast majority of nontraumatic forefoot pain is diagnosed clinically, plain radiography may be useful to rule out bony pathology. MRI may be helpful to clarify diagnostic challenges for entities such as Morton neuroma, tendinitis, stress fractures, and turf toe.

Management. Most diagnoses of nontraumatic forefoot pain may be managed on a nonurgent basis by a podiatrist or primary care physician. Morton neuroma treatment ranges from footwear

modification and physiotherapy to steroid injections and surgery for chronic and severe cases.

Ingrown toenails may be treated by allowing the nail to grow out and providing local care usually will lead to resolution, although chronic or recurring ingrowth necessitates partial or complete excision of the nail and germinal ablation. Antibiotics are indicated if infection is present.

SPECIAL CONSIDERATIONS

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a chronic pain condition in which pain is disproportionate in severity and duration to the expected course. CRPS is divided into types I and II, in which type II is associated with a nerve lesion, whereas type I is not. The International Association for Study of Pain (IASP) diagnostic criteria, also known as *the Budapest criteria*, were updated in 2010. These criteria require pain disproportionate to the inciting event, and without any alternative diagnosis. Signs and symptoms are categorized in four categories: sensory, vasomotor, sudomotor/edema, and motor/trophic. The diagnosis requires the report of one symptom in three out of four categories and manifestation of one sign in two of the four categories at the time of evaluation. Typically, pain is described as diffuse burning, aching, or searing in nature, together with evidence of vasomotor instability. The incidence of CRPS following foot and ankle injury has varied in the literature. CRPS has been reported in 5% of patients following foot and ankle surgery and in only 0.3% of patients with foot and ankle fractures.[41] Complex regional pain syndrome should always be considered in the differential diagnoses for chronic foot pain after trauma even after a relatively innocuous injury. The management of CRPS is multifaceted, often guided by a pain specialist. Although important to consider, the definitive diagnosis of CRPS is unlikely to be made in the ED. Emergent conditions on the differential include compartment syndrome, cellulitis, DVT, peripheral vascular disease, and ischemia. Other considerations on the differential include peripheral neuropathy, erythromelalgia, neoplastic diseases, and conversion and factitious disorders.

Stress Fractures

Foundations and Pathophysiology

Stress fractures can occur anywhere in the appendicular skeleton but are particularly common in the lower extremity. They can occur as a result of extrinsic factors (e.g., training volume, footwear, training surface) and intrinsic factors (e.g., metabolic state, fitness, muscle endurance, anatomic alignment). The syndrome of relative energy deficiency in sport, historically termed the *female athlete triad*, is a condition of disordered eating, menstrual disturbances, and low bone mineral density and is known to be associated with stress fractures.[42]

It is useful to categorize stress fractures as being high risk and low risk based on the rate of complications, including delayed union, nonunion, and persistent functional limitation. High-risk stress fractures often occur in bones with a vulnerable vascular supply. In the lower extremity, these stress fractures include the femoral neck, anterior tibia, medial malleolus, navicular, proximal fifth metatarsal, and sesamoid bones.

Clinical Features

Most stress fractures produce localized aching pain of insidious onset over several weeks. Initially, symptoms occur after athletic activities, but later they limit such activities. Often, a predisposing factor, such as a training regimen change, is present. Physical examination may reveal swelling, point tenderness, or percussion tenderness. However, in most patients, these findings are absent, and the diagnosis is suspected by history alone. A dietary history (e.g., restrictive diets or those low in vitamin D and calcium) may contribute as well. In addition, a menstrual history should be obtained in female patients because amenorrhea associated with overtraining is a marker of the syndrome of relative energy deficiency in sport.

Differential Diagnoses

See Table 49.3 for differential diagnoses of stress fractures.

Diagnostic Testing

Initial plain radiographs are commonly read as normal because bone reaction in stress fractures depends on the length of time from symptom onset. Radiographic abnormalities in the metaphysis can take up to 4 weeks to develop, and those in the diaphysis can take 6 weeks. Although plain radiographs have low sensitivity for stress fractures, their specificity is high. The three important findings are periosteal new bone formation, endosteal thickening, and a radiolucent line.

Because only 50% of patients develop plain radiographic abnormalities, the diagnosis of a stress fracture can be easily missed. Traditionally, plain radionuclide bone scanning was the imaging modality of choice for stress fractures. Bone scans are nonspecific but extremely sensitive, usually showing abnormal uptake within 24 hours of injury. More advanced imaging techniques such as CT-SPECT and MRI have gained value in diagnosing stress fractures.

Management

Low-risk foot and ankle stress fractures often resolve in 4 to 6 weeks with limitation of impact activities as guided by pain; most patients can remain weightbearing and do not require immobilization unless symptoms are severe. High-risk stress fractures, including the anterior tibia, medial malleolus, navicular, base of fifth metatarsal, and sesamoids, require treatment with immobilization and nonweightbearing under the guidance of a sports medicine or orthopedic surgery specialist as these are frequently are managed surgically, particularly stress fractures of the anterior tibia.

Disposition

Patients with confirmed low-risk stress fractures can be managed by primary care and can be weightbearing as tolerated, with activity modification. If required by symptoms, these patients may be placed in a short walker boot for comfort. Athletic stress fractures are overuse injuries that necessitate evaluation of training habits, equipment, and techniques. Patients with clinically suspected but unconfirmed stress fractures can be referred to sports medicine or orthopedic specialists to arrange further diagnostics, as indicated. All patients with high-risk stress fractures should be made nonweightbearing and immobilized, with arrangements made for outpatient orthopedic or sports medicine consultation within 2 weeks.

Tendon Injuries

Acute tendon ruptures in the foot, apart from the Achilles and posterior tibial tendons, are rare. Although isolated ruptures of the flexor hallucis longus and anterior tibial tendons have been described, most tendon transections are the result of lacerations (see Table 49.2).

Orthopedic or plastic surgery consultation is indicated for any patient known or suspected to have a tendon injury in the foot. It is clear that flexor and extensor hallucis longus tendons should be repaired primarily; however, the need to repair other tendons is controversial. In general, an attempt should be made to repair any tendon transection, because apparently minor injuries can lead to complications, such as *claw deformity*. Tendon injuries associated with innocuous lacerations

are easily missed if not carefully sought. Splinting for 2 to 6 weeks is required after tendon repair.

Compartment Syndrome of the Foot and Ankle

Foundations

Compartment syndrome is defined as an increase in pressure within a confined osseofascial space that impedes neurovascular function, resulting in tissue damage; it is discussed in detail in Chapter 41. Compartment syndrome related to ankle fractures may involve either the compartments of the lower limb (anterior, lateral, superficial posterior, deep posterior) or the compartments of the foot, which by convention are defined by four compartments (medial, central, lateral, and interosseous). However, as many as nine compartments have been identified in the foot. As elsewhere, compartment syndrome in the foot constitutes a surgical emergency.

Compartment syndrome in the lower limb secondary to ankle fractures is rare and is most often associated with significant force and hence disruptive fracture patterns.

Pedal compartment syndrome is most commonly caused by high-energy injuries, such as crush injuries, Lisfranc fractures, calcaneus fractures, and midfoot or forefoot trauma. Pedal compartment syndrome after an ankle sprain has also been reported. Damage is related to the duration and magnitude of compartment pressure increase and the arteriovenous gradient. Compartment syndrome can develop anywhere from 2 hours to 6 days after a traumatic injury, although the peak incidence is at 15 to 30 hours.

Clinical Features

Compartment syndrome typically causes pain out of proportion to that expected for the injury and is not decreased by immobilization. Physical examination may reveal tense swelling and sensory deficits. Pain is exacerbated by any movement (active or passive) that stretches the muscles of the involved compartment. Peripheral pulses and capillary refill usually are initially normal in compartment syndrome and thus offer no reassurance when present. The presence of an open wound does not guarantee that all compartments are decompressed. It should be noted that compartment syndrome is often missed in its early stages, perhaps masked by the pain of the acute injury. In calcaneus injury, for example, although compartment syndrome is known to complicate 4% of fractures, one-third of patients had the diagnosis missed on initial assessment.[23]

Differential Diagnoses

See Table 49.3 for differential diagnoses of compartment syndrome of the foot and ankle.

Diagnostic Testing: Special Procedures

Definitive diagnosis of compartment syndrome is by measurement of intracompartmental pressure. Pressure greater than 30 mm Hg is generally considered an indication for emergent decompression but compartment syndrome can occur at lower pressures in hypotensive patients. Because needle localization of foot compartments is challenging, and because of its importance in surgical decision making, measurement of pedal compartment pressures is optimally performed by the orthopedic specialist.

Management and Disposition

Early identification and prevention of further tissue damage are important considerations in any patient in which compartment syndrome is considered. Circumferential bandages and casts should be avoided during early management of foot and ankle injuries where swelling is expected. In diagnosed or suspected cases of compartment syndrome, the limb should be positioned at the level of the heart. Elevation beyond this is contraindicated because resultant decreased arterial flow narrows the arteriovenous pressure gradient. When compartment syndrome is identified or suspected, emergent orthopedic consultation is indicated for consideration of decompressive fasciotomy.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 49: QUESTIONS AND ANSWERS

1. A middle-aged farmer presents after an accident with a plow with a crushed open distal tibia fracture. What is the appropriate antibiotic choice?
   - **a.** Cefazolin
   - **b.** Cefazolin and gentamycin
   - **c.** Cefazolin, gentamycin, and penicillin G
   - **d.** Ciprofloxacin
   - **e.** Pen VK and cephalexin

Answer: C. Because the patient has a probable soil contaminant in his open fracture, he will need the addition of penicillin G to cover *Clostridium perfringens*. For low-energy injuries with mild to moderate contamination, a broad-spectrum cephalosporin is usually sufficient. Heavily contaminated wounds require the addition of gram-negative bacterial coverage, typically with an aminoglycoside. Adding penicillin G as a third antibiotic is necessary for farm- or soil-related crush injuries.

2. A 30-year-old woman complains of pain in the ankle and difficulty walking after attempting a jump shot while playing basketball. Her past medical history includes a recent urinary tract infection, for which she is taking ciprofloxacin. On physical examination, her ankle joint is not swollen, there is a palpable defect 4 cm proximal to the posterior ankle, and she has weakened plantar flexion. Which of the following is true concerning her condition?
   - **a.** The Boehler angle should be less than 20 degrees.
   - **b.** In a seated position, squeezing the calf causes foot dorsiflexion.
   - **c.** It requires a stress radiograph view.
   - **d.** On the radiograph, there may be an opacification at the Kager triangle.
   - **e.** Talofibular ligament laxity is present.

Answer: D. The patient has a ruptured Achilles tendon. On examination, a visible and palpable tendon defect 2 to 6 cm proximal to the calcaneal insertion may be present. In some cases of complete Achilles tendon rupture, weak plantar flexion may still be present because of the actions of the tibialis posterior, toe flexors, and peroneal muscles. When the Achilles tendon is intact, squeezing the calf muscles should cause passive plantar flexion of the foot (Thompson test). Lateral radiographs of the ankle may confirm rupture by showing opacification of the triangular fatty tissue–filled space anterior to the Achilles tendon (Kager triangle) or an irregular contour and thickening of the tendon.

3. A 24-year-old patient presents with pain in the left lateral ankle after a twisting injury. On physical examination, you find no point tenderness on the medial or lateral distal 6 cm of the malleoli, no proximal fibular tenderness, and no navicular tenderness. Which of the following physical findings would necessitate radiographs being taken in the emergency department?
   - **a.** Inability to ambulate to the car
   - **b.** Laxity on anterior drawer testing
   - **c.** Moderate swelling with ecchymosis
   - **d.** Tenderness at the base of the fifth metatarsal
   - **e.** Tenderness over the deltoid ligament

Answer: D. The Ottawa Ankle Rules advise ankle radiographs when any of the following are present: tenderness at the posterior edge of the distal 6 cm or tip of the lateral malleolus, tenderness at the posterior edge of the distal 6 cm or tip of the medial malleolus, or inability to bear weight for at least four steps immediately after the injury and at the time of evaluation. Foot radiographs in the setting of blunt ankle trauma are advised when any of the following are present: tenderness over the navicular, tenderness at the base of the fifth metatarsal, or inability to bear weight for at least four steps immediately after the injury and at the time of evaluation.

4. A 40-year-old female falls down some stairs and her ankle is forced into sudden dorsiflexion and eversion. She reports pain over the lateral aspect of the ankle and reports a "snapping" sensation with active ankle eversion, otherwise the rest of the examination is unremarkable. The plain radiograph of the ankle is negative with the exception of what appears to be a large avulsed fragment over the lateral malleolar region. The optimal management of this patient is:
   - **a.** Reassuring the patient that this is an avulsion fracture and make her weightbearing as tolerated.
   - **b.** Order a CT scan to evaluate the origin of the avulsed fragment.
   - **c.** Orthopedic evaluation in the emergency department.
   - **d.** Outpatient dynamic ultrasound and referral to orthopedics.
   - **e.** Splinting, nonweightbearing, and outpatient referral to orthopedics.

Answer: D. The patient's mechanism of injury, symptoms, and x-ray findings are consistent with a rupture of the superior peroneal retinaculum with peroneal tendon dislocation. If the diagnosis is in doubt, dynamic ultrasound can be used to evaluate the peroneal tendon because it will show dislocation of the tendon when the foot is dorsiflexed and everted. Rupture of the superior peroneal retinaculum invariably requires operative repair.

5. A 32-year-old male presents after a fall in which his foot was forced into dorsiflexion. He has severe pain and swelling on his dorsal foot just anterior to the ankle. In the ED, he is diagnosed with a nondisplaced talar neck fracture (Hawkins type 1). His pain is controlled, and he has no associated injuries. What is the disposition for this patient?
   - **a.** Place in a walking boot or a cast, weightbearing as tolerated, and follow up with orthopedics in 1 to 2 weeks.
   - **b.** Orthopedics consult in the emergency department is required and the patient should be admitted.
   - **c.** Immobilize in a padded, noncircumferential splint and arrange outpatient orthopedics within 48 hours.
   - **d.** Immobilize in a cast and nonweightbearing for 6 weeks, with outpatient orthopedics follow-up in 1 to 2 weeks.

Answer: C. Hawkins type 1 fractures are nondisplaced. These fractures are treated conservatively and are the only talar neck fractures that are appropriate for outpatient orthopedic follow-up. Follow-up, however, should be urgent in 24 to 48 hours, and the patient should certainly be immobilized in a well-padded and noncircumferential splint. Depending on local practice, orthopedic consultation in the ED is reasonable.

6. A 44-year-old male presents after a fall from a ladder in which he landed on his right foot. He has severe pain in his heel and is diagnosed with an intraarticular calcaneus fracture on plain x-rays. Which of the following is incorrect in the emergency management of this patient?
   - **a.** Assessment for other traumatic injuries, particularly spinal injury.
   - **b.** Once pain and swelling are controlled, the patient may be immobilized in a padded splint with orthopedic follow-up arranged for 48 hours.
   - **c.** The patient should get a CT scan of the foot, if available, in the emergency department.
   - **d.** Orthopedic surgery should be consulted to assess the patient in the emergency department.
   - **e.** Place the patient in a well-padded splint with the foot elevated.

Answer: B. Patients with intraarticular calcaneus fractures should have an orthopedics consultation in the ED. Treatment may be conservative, but even when operative repair is chosen, the repair may be done electively at a time when the swelling has decreased. It is important to

CHAPTER 49: QUESTIONS AND ANSWERS—cont'd

assess these patients for other associated injuries and for patients to be placed in a well-padded splint with the foot elevated to the level of the heart, to decrease swelling. CT imaging aids in classification and decisions about management.

7. A 22-year-old male football player presents with midfoot pain and difficulty weightbearing after being tackled in a college game. You are concerned about a Lisfranc injury, but his plain radiographs appear normal. What is the recommended next step in his management?
   - **a.** MRI in the emergency department
   - **b.** Attempt weightbearing x-rays or a CT scan, to assess for ligamentous disruption.
   - **c.** Immobilize in a nonweightbearing splint and refer for follow-up with orthopedic surgery.
   - **d.** Ultrasound to assess for disruption of the Lisfranc ligament
   - **e.** Orthopedics consultation for stress fluoroscopy

Answer: B. Diagnosing low-energy, ligamentous Lisfranc injuries is a challenge. The American College of Radiology guidelines recommend an attempt at weightbearing stress views to look for diastasis of greater than 2 mm between base of the first and second metatarsals, or a difference greater than 1 mm between the base of the first and second metatarsals comparing both feet. If weightbearing x-rays are not possible, a CT scan is recommended. If clinical concern persists, more advanced imaging with MRI or fluoroscopic stress views may be necessary, but these can be arranged at the time of specialist follow-up. Ultrasound has not yet demonstrated utility.

8. A 28-year-old female suffers a twisting injury to her foot during a fall. She is tender at the base of her fifth metatarsal. Plain radiographs reveal an acute, nondisplaced fracture at the level of the intermetatarsal articulation. Which of the following management options is incorrect?
   - **a.** She can be treated functionally in a supportive shoe and can bear weight as tolerated. Orthopedic follow-up should be arranged.
   - **b.** This type of injury may be managed surgically. She should be referred for orthopedic assessment as an outpatient.
   - **c.** She should be placed in a weightbearing cast or walker boot for 3 months with outpatient follow-up.
   - **d.** She can be provided with a walker boot but instructed to remove it when able. Orthopedic follow-up should be arranged.
   - **e.** She can be treated functionally in a supportive shoe if necessary. No follow-up is needed

Answer: E. This is a zone 2 fracture. The treatment of these fractures is evolving and varies according to patient factors. In high-level athletes, primary surgical management may be of benefit. Historically, these injuries were thought to have a high rate of nonunion and prolonged immobilization has been the standard approach in the average patient. More recent data, however, suggest that the rate of symptomatic nonunion is actually quite low, and there is evidence that treating these patients functionally in supportive footwear, perhaps with initial use of a protective boot, is efficacious and more economical. However, as there remains a risk of nonunion, orthopedic follow-up is recommended for these injuries. Fractures in zone 1 are the only base of fifth fractures that do not require orthopedic follow-up.

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Wound Management Principles

Barry C. Simon and H. Gene Hern Jr.

KEY CONCEPTS

- Risk factors for wound infection include crush mechanism; long (>5 cm) deep penetrating wounds; high-velocity missiles; diabetes; and contamination with saliva, feces, soil, or other foreign matter.
- Soaking wounds in povidone-iodine (Betadine) is toxic to healthy tissue. Prepare the skin with a chlorhexidine-alcohol solution.
- The most effective intervention to decrease wound bacterial counts and infection is thorough cleansing, with use of saline or tap water irrigation at approximately 8 psi. Attaching an 18-gauge needle to a 30-mL syringe creates an irrigant force of 7 or 8 psi.
- Bupivacaine is the preferred local anesthetic agent for the care of most wounds. In adults, the maximal reported safe dose is approximately 2 to 2.5 mg/kg without epinephrine and 3 to 3.5 mg/kg with epinephrine.
- The discomfort associated with the injection of bupivacaine into wounds can be reduced by warming the anesthetic and by adding sodium bicarbonate (0.1 mL of sodium bicarbonate to 10 mL of bupivacaine).
- High-risk wounds should not be sutured primarily but may be repaired in 4 or 5 days (i.e., delayed primary closure).
- Tissue adhesives offer several advantages compared to the suturing of simple wounds. However, the use of adhesives is not recommended for lacerations longer than 4 cm, for high-tension wounds, or in areas subject to frequent repetitive movements, such as joints and hands.
- Skin tears in elders are best treated with Steri-Strips, augmented with topical skin adhesives when tension exists.
- Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog and human bites, puncture injuries to the foot in high-risk individuals, open fractures, and wounds involving exposed tendons or joints.
- Tetanus immunization should be provided soon after injury but can be given days or weeks later as the incubation period for tetanus is 7 to 21 days (range, 3 to 56 days).
- Tdap is recommended for patients 65 years old or older requiring tetanus prophylaxis.

FOUNDATIONS

Background and Importance

The goals of emergency wound treatment are to restore function, repair tissue integrity with strength and optimal cosmetic appearance, and minimize risk of **infection**. Risk of infection depends on the location, mechanism, host factors, and wound care. The risk for a clean facial wound produced by incision is less than 1%, whereas a dirty crush injury to the lower extremity may have more than a 20% risk. Wound infection generally results in delayed healing, decreased strength, and a poor cosmetic result. These facts highlight the need for high-quality wound care. Understanding the biology of wound healing and the technical aspects of wound treatment facilitates emergency management of these patients.

Emergency clinicians must be aware of the medicolegal risk associated with soft tissue injuries. Including injuries to the hand, wound-related complaints are the fourth most common cause of malpractice claims against emergency clinicians with missed **foreign body**, wound infection, and missed tendon or nerve injury as the most common complications leading to claims.

Anatomy, Physiology, and Pathophysiology

An understanding of skin anatomy leads to better appreciation of wound closure concepts and techniques. The skin is a complex organ that protects the body against bacterial invasion, ensures thermoregulation, and helps to regulate water content and register sensory stimuli.

The skin and fascia vary in thickness from 1 to 4 mm, depending on the part of the body. The epidermis, the outermost layer, is several cell layers thick. The most important parts of the epidermis are the stratum germinativum (basal layer), where new cells originate, and the stratum corneum, the outermost cell layer that gives the skin its cosmetic appearance. The layer of skin directly beneath the epidermis is the dermis. It is a thicker, connective tissue layer and primarily responsible for ultimate wound healing. Removing debris and devitalized tissue from the dermis is key for optimal healing and minimal scar formation. The dermis also functions to anchor sutures placed percutaneously or subcutaneously.

The superficial fascia lies directly beneath the dermis and encloses the subcutaneous fat. This space must be irrigated and debrided to decrease the risk of infection. The deep fascia lies beneath the fat and is a strong, off-white sheath that covers and protects the underlying muscles and helps prevent superficial infection from spreading to deeper tissues. The deep fascia must be closed to maintain its protective and functional roles.

Normal wound healing is a well-choreographed sequence of biologic events.[1] (1) These include coagulation, inflammation, collagen metabolism, wound contraction, and epithelialization. Maintaining

the balance of these events is crucial for normal healing. Delaying any of the stages may result in a weak closure and dehiscence. Prolonging segments of the process may affect the ultimate scar appearance.

Soon after tissue integrity is altered, the process of coagulation begins. Platelets release factors that initiate and enhance a response from inflammatory cells. Capillary permeability increases to allow white blood cells to migrate into the wound. Neutrophils and monocytes act as scavengers to rid the wound of debris and bacteria. Monocytes transform into macrophages, which seem to have a major role in subsequent healing phenomena. In addition to providing wound defense, macrophages release chemotactic substances, signaling other monocytes to stimulate fibroblast replication and trigger neovascularization.

Collagen is the principal structural protein of most body tissues. Normal tissue repair depends on collagen synthesis, deposition, and cross-linking. Fibroblasts synthesize and deposit collagen compounds 48 hours after injury. Immature collagen is highly disorganized and has a gel-like consistency.

After a series of enzymatic processes, characteristic fibrils are produced followed by intermolecular cross-links that bolster their strength. The entire process depends on tissue lactate and ascorbic acid and is directly related to tissue arterial carbon dioxide partial pressure. In the absence of vitamin C, prolyl and lysyl hydroxylase do not activate, and oxygen is not transferred to proline or lysine. Under-hydroxylated collagen is produced, and characteristic collagen fibers are unable to form. As a result, wound healing is poor, and capillaries are fragile. Without oxygen to hydroxylate proline and lysine, a local condition resembling scurvy occurs.

Under normal conditions, collagen synthesis peaks by day 7, coincident with rapid increases in tensile strength. The healing wound has the greatest mass at 3 weeks but remodels itself during the next 6 to 12 months. However, the wound achieves less than 15% to 20% of its ultimate strength by 3 weeks and only 60% by 4 months.

Wound contraction is the movement of whole-thickness skin toward the center of the skin defect. Immediately after injury, the wound edges retract and increase the size of the defect. Normal skin tension along the lines of minimal tension produces this retraction (Figs. 50.1 and 50.2). Wounds perpendicular to these lines are under greater tension and result in a larger scar.

During the next 3 or 4 days, the wound size shrinks as its edges move toward the center. This phenomenon is independent of epithelialization, and the presence of collagen is not necessary for it to occur. This process is considered beneficial to healing and should not be confused with contracture that results from scar shortening.

Contracture becomes more apparent when the normal healing process is prolonged often producing a disfiguring hypertrophic scar. Optimizing the duration of the inflammatory phase and minimizing wound tension help to produce a more "appealing" scar.

Epithelialization is a process whereby epithelial cells migrate across the wound. Mitosis appears at the wound edge near the basal cell layer within hours of injury. Eschar or other debris impedes this process. Epithelialization proceeds most efficiently when a wound is properly cleansed, debrided, and kept moist and protected.

In a surgically repaired laceration, epithelialization bridges the defect by 48 hours. The new tissue proceeds to thicken and grow downward, beginning to resemble the layered structural characteristics of uninjured epidermis within 5 days. Simultaneously, keratin formation loosens the overlying scab.

Various forces (lines of tension) exist as a result of skin elasticity from collagen fibers. These static forces may vary more than fivefold with the respective area of body skin surface, but the static tension of a given area of skin remains constant. These static forces are shown clinically by the gaping of wounds after incision. The magnitude of static skin tension is directly related to ultimate scar width.

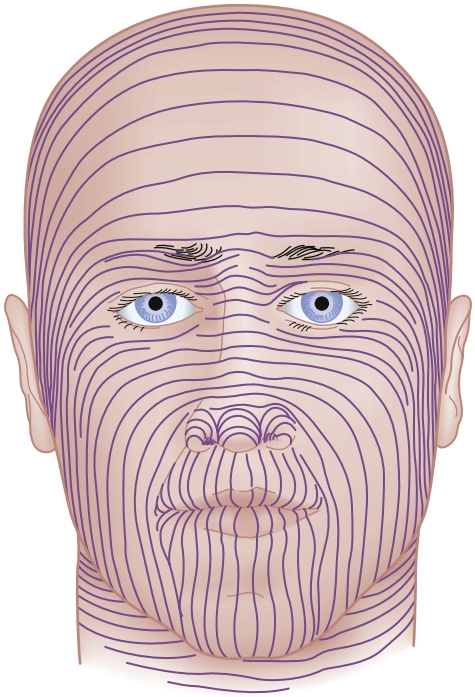

Fig. 50.1 Skin Tension Lines of the Face. Incisions or lacerations parallel to these lines are less likely to create widened scars than those that are perpendicular to these lines. (Adapted from Simon R, Brenner B. *Procedures and Techniques in Emergency Medicine*. Baltimore: Williams & Wilkins; 1982; as published in Trott A. *Wounds and Lacerations: Emergency Care and Closure*. 2nd ed. St Louis: Mosby; 1997.)

Uneven, jagged wounds have greater surface area than do linear lacerations. The skin tension distributed over a greater area is less per unit length of tissue. Meticulous reapproximation of the jagged edges results in a more appealing scar. Sharp debridement, converting a jagged wound to a linear laceration, is often unwise because it may result in too much tissue loss and produce a wider, more visible scar. Skin forces produced by muscular contraction and movements of flexion and extension influence healing and scar size. These dynamic forces are greatest where skin elasticity is necessary for function. Lacerations parallel to skin folds, lines of expression, and joints do not impair function or produce unattractive scars. Wounds that traverse the skin lines heal with conspicuous scars and may impair function. Knowledge of these lines and forces is necessary for optimal wound repair. In addition, the patient should be educated about wound healing and scarring potential.

CLINICAL FEATURES

History

A detailed history should be obtained as part of routine wound evaluation. Serious complications can result when basic information is not obtained. Wound care decisions may be changed if the patient has significant peripheral vascular disease, is immunocompromised, or has a high risk of a retained foreign body. Essential historical information includes past medical history, mechanism and setting of injury, and **tetanus** status.

Risk factors for wound morbidity include prolonged time since injury; crush mechanism; long (>5 cm) and deep wounds; patient age; high-velocity missiles; location on lower extremities; and contamination with saliva, feces, soil, or other foreign matter (Box 50.1).

Three hours after acute trauma, bacteria proliferate to a level that may result in infection. Standard wound care guidelines for routine

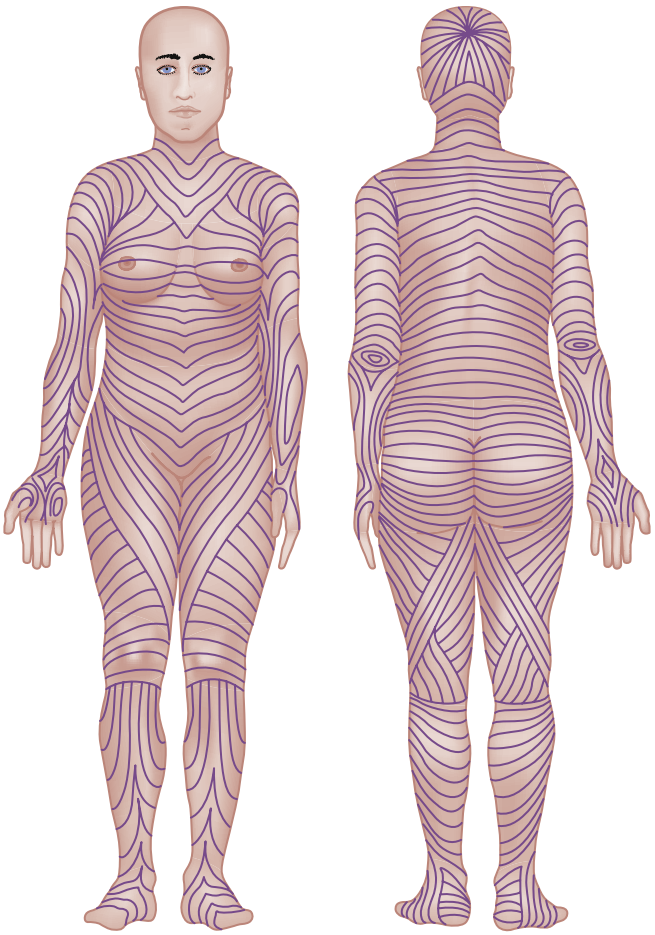

Fig. 50.2 Skin Tension Lines of the Body Surface. (Adapted from Simon R, Brenner B. *Procedures and Techniques in Emergency Medicine*. Baltimore: Williams & Wilkins; 1982; as published in Trott A. *Wounds and Lacerations: Emergency Care and Closure*. 2nd ed. St Louis: Mosby; 1997.)

wound care recommend closure within 8 to 12 hours of injury yet more recent data suggest that timing is less important than the other risk factors. All risk factors must be considered to optimize wound care, and flexibility is required. Lacerations produced by fine cutting forces resist infection better than crush injuries. Reduction of blood flow to wound edges in the latter may increase the infective concentration of bacteria by a hundredfold. High-velocity missile injuries produce damage remote from the missile tract. The extent of injury may not be apparent for several days. Clean, finely cut lacerations on the face may be safely closed in some patients 24 or more hours after injury, whereas blunt lacerations to the leg or thigh may be treated with delayed primary closure as early as 4 to 6 hours after injury. For sutured wounds, location has the strongest association with infection. Lacerations repaired on the leg and thigh may have an infection rate greater than 20%, those on the torso and other extremities greater than 10%, and those on the face and scalp less than 4%.

Optimal physical assessment of wounds requires patience, diligence, and an organized approach. Wound closure decisions involve an individualized approach for each laceration and patient. In addition to the history, host-specific data will influence management decisions: (1) immunocompetence of the host, (2) physical characteristics of the host (e.g., peripheral vascular disease), and (3) structural defects that invite bacterial seeding (e.g., damaged or prosthetic heart valves).

BOX 50.1 Risk Factors for Wound Infection

1. Location: Leg and thigh, then arms, then feet, then chest, then back, then face, then scalp
2. Contamination with devitalized tissue, foreign matter, saliva, or stool
3. Blunt (crush) mechanism
4. Presence of subcutaneous sutures
5. Type of repair: Risk greatest with sutures > staples > tape
6. Anesthesia with epinephrine
7. High-velocity missile injuries
8. Diabetes

Physical Examination

Physical examination errors are minimized with optimal visualization and anesthesia. When the injury occurs on an extremity, use of a sphygmomanometer may help to ensure a bloodless field. The blood pressure cuff is placed proximal to the injury, and the extremity is elevated above the heart for at least 1 minute. Exsanguinating the extremity may be hastened by wrapping the limb tightly with an elastic bandage, beginning distally and ending at the base of the cuff. The sphygmomanometer is inflated to a pressure greater than the systolic pressure of the patient. Although this process is uncomfortable at first, the cuff can safely remain inflated for 2 hours. Peripheral nerve blocks are often used if inflation is anticipated to be longer than several minutes.

Adequate anesthesia is required for a thorough wound examination. Subcutaneous tissues quickly reapproximate after injury, giving the appearance of a shallow wound. In addition, significant subcutaneous swelling lends to this appearance and renders examination of the laceration more difficult, as in wounds of the scalp and face. Careful probing and examination are needed to avoid missing damage to structures deep to the skin and subcutaneous tissue. This warning is more crucial for wounds on the distal aspects of upper and lower extremities. Finger lacerations are rarely gaping, but crucial structures (e.g., tendons, nerves, and vessels) are often damaged. The examiner must carefully pry the wound margins apart, ensure a blood-free field, and examine the tissues as the digit or extremity is placed through range of motion. The injured section of tendon may have been in a different state of tension and in a more proximal or distal location at the time of injury. Wounds that cannot be explored adequately and wounds with probable trauma to underlying tissues or with foreign matter require additional studies. A laceration can be extended if visualization of wound depth and extent is challenging.

Sterile gloves may not be a necessary part of wound closure. Although data are limited, one study found that the use of sterile gloves does not change infection rates. However, clean nonsterile gloves may be worn during wound assessment and closure to offer some protection for both the patient and the provider.

No single method can guarantee the identification and removal of all foreign matter from wounds. The key is to document all efforts and to explain to the patient the possibility of a foreign body. Physical examination with wound exploration will discover about 78% of foreign bodies; plain radiography will detect glass foreign bodies in about 75% of cases, metal in 99%, but wood in only 7%. Good documentation and follow-up can protect the patient as well as the health care provider.

DIFFERENTIAL DIAGNOSES

While a list of differential diagnoses is not required since the presence of soft tissue wound is self-evident, a differential list of causes is helpful as the mechanism can affect management decisions about closure technique, antibiosis and follow-up. Careful history-taking and visual

inspection are typically all that are required to differentiate high energy wounds from low energy injuries, determine whether contamination risk is high (e.g., cat bites) or low (e.g., laceration from a clean knife), or if foreign material is likely to be present.

DIAGNOSTIC TESTING

Standard radiography will not detect all foreign matter. The radiodensity of an object depends on the relative density of the matter and the adjacent tissue. Pieces of glass more than 1 mm thick are visible when appropriate views are ordered. Many organic substances, such as wood, are not visible on plain films, but specifically requested soft tissue views may increase the yield. A radiolucent shadow may be seen on close inspection because the foreign substance displaces tissue in its path. A computed tomography (CT) scan is excellent for identifying all foreign substances but is expensive and results in exposure to radiation. Ultrasonography is a good technique, but the small size of many foreign bodies and pockets of air, edema, pus, and some calcifications may produce confusing echoes, limiting its clinical usefulness. When simpler, standard methods fail to locate a foreign body that is likely or definitely present, we recommend that ultrasonography or a CT scan be performed.

MANAGEMENT

Anesthesia

After an appropriate neurovascular examination is documented, the involved tissue is anesthetized. Careful physical examination and thorough cleansing, irrigation, and debridement require that the patient be free of pain. Regional anesthesia may be preferable for wounds innervated by one superficial nerve. Injections along the wound margins produce swelling and further distortion of landmarks. With a regional block, more than one laceration may be repaired in the same nerve distribution without additional anesthesia. Lacerations on the face, hands, fingers, feet, and toes and in the mouth are often well suited for regional anesthesia.

Anesthetic Agents

Lidocaine and bupivacaine are the most common agents used for local and regional anesthesia. Both are safe and fast acting. For lidocaine, onset of action following direct infiltration occurs within seconds, and the effects last 20 to 60 minutes. When lidocaine is administered as a regional nerve block, onset occurs in 4 to 6 minutes and the effects generally last 75 minutes, although the block may remain effective for up to 120 minutes. A 1% lidocaine solution contains 10 mg/mL. It is safe to use 3 to 5 mg/kg, not exceeding 300 mg at a single injection. More volume can be added safely every 30 minutes. When epinephrine is added, the resulting vasoconstriction prolongs the effect for 2 to 6 hours, and the safe dose increases to 5 to 7 mg/kg. However, the addition of epinephrine has been shown to delay healing and lower resistance to infection. Lidocaine with epinephrine should be avoided in wounds with a high risk of infection and when tissue viability is of concern. Traditionally, epinephrine was not used in the fingers and toes because of the risk of vasoconstriction in small arterioles resulting in digital ischemia. However, literature from case studies in hand surgery suggests that with careful screening, epinephrine can be safely used in digital blocks. Digital artery vasospasm, accidentally induced by local injection of epinephrine, can be reversed successfully with a local injection of 0.5 to 2 mg of subcutaneous phentolamine or application of topical nitroglycerin.

Bupivacaine provides anesthesia that is equal to that of lidocaine. Onset of action is slightly slower than that of lidocaine, but the duration of anesthesia is four to eight times longer. These benefits suggest that bupivacaine is the preferred local **anesthetic** agent for the care of most wounds. In adults, the maximal reported safe dose is approximately 2 to 2.5 mg/kg without epinephrine and 3 to 3.5 mg/kg with epinephrine. The dose can be repeated every 3 hours, not exceeding a total of more than 400 mg in a 24-hour period. The maximal intraoral dose is 90 mg.

Local injection of lidocaine is best performed with a 27-gauge needle and slower injections are less painful. The rate of injection through a 30-gauge needle is too slow, and the thin needle is fragile and difficult to control. A 25-gauge needle is acceptable, but the more rapid injection can result in greater patient discomfort. The needle should be introduced through the cut margin to minimize the pain of the injection. Concerns of spreading bacteria into the adjacent uninvolved tissue and increasing the frequency and severity of wound infections are unfounded. Bicarbonate will buffer lidocaine and reduce the pain of injection. The shelf life of the lidocaine-bicarbonate mixture decreases, but it remains effective for 1 week at room temperature and for 2 weeks if refrigerated. Adding sodium bicarbonate in a 1:10 volume ratio to lidocaine (1 mL bicarbonate and 10 mL lidocaine) decreases the pain of injection without compromising the quality of anesthesia. A much smaller dose of bicarbonate is added to bupivacaine because the alkalinization results in precipitation. A 1:100 volume ratio (0.1 mL of bicarbonate and 10 mL of bupivacaine) has been found to be effective. Warming the anesthetic solution is also an effective means of decreasing the pain of injection.

Topical anesthesia can act synergistically with injectable agents. Studies show that a combination of lidocaine (4%), epinephrine (0.1%), and tetracaine (0.5%) (LET) can function effectively on skin lacerations, especially on the face and scalp. LET may be administered by soaking a cotton ball with 3 mL of the combined solution and applying it to the wound for 20 minutes. A gel formulation is available and may be preferred because it's easier to control and has less run-off which can inadvertently contact mucous membranes. The duration of action is 45 to 60 minutes following the removal of the gel from the wound. Toxicity is rare when the dose administered is less than 3 mL and mucous membranes are avoided. Potential toxic effects of lidocaine and tetracaine are related to the cardiovascular and central nervous systems. Cardiovascular effects may include dysrhythmias, decreased myocardial contractility, and cardiac arrest. Central nervous system toxicity may include headache, irritability, restlessness, blurred vision, and seizures. Topical anesthetics reduce repair time, preserve landmarks, and improve patient (and family) satisfaction. If additional anesthesia is required, the pain of the subsequent injection is lessened by the topical anesthesia.

Although LET has been found to be very safe, weight-based dosing has been recommended for children weighing less than 17 kg. Administering a maximum of 0.175 mL/kg of LET will prevent the application of more than 5 mg/kg of lidocaine. No cases of methemoglobinemia have been reported, but given the small risk associated with tetracaine extra caution is advised in neonates.

Tetracaine, adrenaline (epinephrine), and cocaine (TAC) was the original topical anesthetic solution. This combination is as effective as LET on the face and scalp and more effective elsewhere on the body, but the higher risk of complications and the complexities tied to handling cocaine limit its utility. Dripping 1% lidocaine into mucosal lacerations was demonstrated to be effective in one small case series, an interesting painless alternative that deserves further investigation.[2]

Eutectic mixture of local anesthetics (EMLA) is a cream used to produce anesthesia of wounds and intact skin. The active ingredients are lidocaine (2.5%) and prilocaine (2.5%). The micron-sized particles of the cream are designed to penetrate the skin and lessen the pain of needle penetration. Studies have demonstrated efficacy in venipuncture, immunization administration, lumbar puncture, and laceration

repair. Peak effect is seen at 1 hour and continues for 30 to 60 minutes after removal of the cream.

Allergy

Allergy to local anesthetics is uncommon. Two distinct groups of "caine" anesthetics exist. The esters include procaine, tetracaine, and benzocaine. The second group, including lidocaine and bupivacaine, belong to the amide family. Allergy to the esters is uncommon. True allergy to agents in the amide family is rare.

The subject of allergy is further complicated because multi-dose vials contain the preservative methylparaben, an ester structurally related to anesthetics in the ester family. Allergic reactions to lidocaine or bupivacaine may be a reaction to this preservative. Single-dose, preservative-free vials of lidocaine and bupivacaine should be standard stock in every emergency department (ED).

When allergy to a local anesthetic is known or strongly suspected, alternatives are available. No cross-reactivity occurs between the amide and ester families, so an agent from a different group may be chosen. If clarification is required, a test dose of 0.1 mL may be administered intradermally before proceeding. The patient is then observed for 30 minutes before proceeding. As with any allergy testing, the emergency clinician should be prepared to treat all complications. Injectable diphenhydramine (1%) has also been shown to provide effective local anesthesia.

Skin Preparation

Disinfection of the skin (not the wound itself) may be accomplished with several different agents. The ideal agent is fast acting and has a broad spectrum of antimicrobial activity and a long shelf life. Povidone-iodine (Betadine) and chlorhexidine (Hibiclens) have all three characteristics. Although excellent as skin disinfectants, both products are toxic to wound defenses and may increase the incidence of wound infection. Avoid spilling these substances into the wound. Povidone-iodine is effective against gram-positive and gram-negative bacteria, fungi, and viruses. Chlorhexidine is less effective against gram-negative bacteria and its efficacy against viruses is unknown. Eye exposure to these agents can be detrimental. Chlorhexidine has been shown experimentally and in case reports to produce serious permanent corneal opacification. Current data suggest that chlorhexidine-alcohol preparations are safe and more effective at limiting infection compared with povidone-iodine solutions.

Body, facial, and head hair is usually removed to clean and examine a wound, although this is not necessary to reduce the risk of wound infection. Hair removal makes it easier for the patient to keep the area clean and ultimately facilitates accurate suture placement and subsequent removal. Exceptions include parts of the body where hairlines provide important landmarks for the accurate reapproximation of tissue margins, most notably the eyebrow. Eyebrow hair should not be shaved since regrowth may be inconsistent or absent.

Surgical studies show that hair removal with a razor is three to nine times more likely to result in a wound infection than clipping the hair. The razor damages the infundibulum of the hair follicle and provides access for bacterial invasion and infection. For wounds at high risk of infection, clipping may be done with electric shears or scissors. Another option is application of a petroleum-based product to the hair adjacent to the wound margins, allowing the provider to keep the hair away from the surgical field.

Wound Preparation

Debridement

Debridement is the removal of foreign matter and devitalized tissue from the wound. With respect to ultimate wound healing and risk of infection, debridement remains the most important step in wound care. Devitalized wound tissue delays healing and significantly increases the risk of infection. The benefits of debridement, however, are weighed against the consequences of producing a larger tissue defect. Higher tension in the resultant closure may result in a wider scar. Skin edges that are clearly devitalized are debrided before wound closure. On the trunk, where there is little concern for specialized tissue, wide excision and debridement are feasible. On the face and hands, where as much tissue as possible must be saved, the process is more difficult. Meticulous sharp excision of small fragments of nonviable tissue is performed only by experienced clinicians. When the viability of large areas of skin or muscle is a significant concern, the wound should be prepared for delayed primary closure.

Wound Cleansing

An ideal wound cleanser has broad antimicrobial activity with a rapid onset. It is nontoxic to the tissue and does not reduce tissue resistance to infection, delay healing, or decrease the tensile strength of the healing wound. Many antiseptic solutions have been used clinically yet, despite multiple studies, there is still debate regarding which agent comes closest to possessing these qualities. Povidone-iodine in various concentrations, saline, and, more recently, tap water have received the most attention.

Evidence suggests that a 0.9% normal saline solution or tap water are effective irrigants when used with high-pressure syringe irrigation. While saline has been the traditional wound-**irrigating** fluid of choice, tap water has consistently shown equivalent rates of infection and cosmetic outcomes. Tap water irrigation allows a large volume of irrigation rapidly and inexpensively and is especially suited to upper extremity and scalp injuries.

Free iodine, although possessing broad, rapid antimicrobial activity, is too tissue toxic to have therapeutic value in the open wound. Iodophor is a complex of iodine with a carrier to increase its solubility and decrease the availability of free iodine. The most widely used iodophor is povidone-iodine, in which the carrier molecule is povidone (formerly polyvinylpyrrolidone). It is available in a 10% solution, which is 1% free iodine. It is well documented that even a 5% povidone-iodine solution is toxic to polymorphonuclear neutrophil leukocyte activity and may increase the infection rate. A 1% solution is safe and effective with little or no toxicity. Detergent-containing cleansers, such as povidone-iodine scrub, may be excellent for skin preparation but are toxic to tissue defenses and should never be allowed to contaminate open wounds.

Although many different irrigation solutions may be beneficial, the key to cleansing is high-pressure irrigation rather than the type of solution used. Tap water is the preferred wound irrigation solution, because it is safe, effective, requires no preparation, and is less expensive than other options.[3] Distilled water is preferred to tap water for nasal irrigation.

Irrigation

The quality of mechanical cleansing is one of the most important determinants of wound prognosis. The most effective form of wound cleansing is high-pressure irrigation. Irrigating with pressures greater than 7 pounds per square inch (psi) significantly decreases bacterial counts and the incidence of infection. Several commercial devices are available; however, one can be made by attaching an 18-gauge needle to a 30-mL syringe which will yield a force of 7 or 8 psi. High pressures of 50 to 70 psi may be obtained with a commercial water pick. These pressures may cause some tissue damage, but the beneficial effect of reduced bacterial load and debris outweighs this risk. Simply soaking the wound in an antiseptic solution is not beneficial and may be harmful. Scrubbing the wound with a sponge with large-pore cells inflicts tissue trauma and impairs the ability to resist infection. Using a sponge

with a fine pore cell size will decrease tissue damage. Adding a surfactant further minimizes mechanical trauma. Flooding the wound under low pressure via a bulb syringe or gravity alone does not reduce the incidence of infection, regardless of the agent used.

At least one study has shown little benefit to any irrigation in facial and scalp lacerations. This study prospectively compared outcomes of almost 2000 immunocompetent patients. Infection rates and cosmetic outcomes were similar in the irrigation and non-irrigation groups. We recommend irrigation only for scalp wounds more than 5 cm long and those with other high-risk features.

Wound Closure

Decision-Making

The first determination required is whether the wound should be treated open or closed. Each wound, patient, and clinical circumstance must be handled individually. Most wounds have a low risk of infection and can safely be closed primarily. A small study from Europe failed to show a difference in infection risk for wounds sutured greater than 6 hours after injury compared with those sutured in less than 6 hours. At the other end of the spectrum, some wounds must never be closed at the time of the initial ED visit. A large stellate laceration to the foot produced by blunt force and contaminated with dirt and grease must be cleaned and left open to be closed later. Human and animal bites to the hand are additional examples of wounds that should not be closed primarily given the high rate of infection. Physician judgment is often the best method for deciding when it is safe to close a wound. In one study in which hand wounds were described as dirty, 22% became infected. When the injury was documented to be clean, the incidence of infection was 7.1%.

Three wound closure options are available. The wound may be (1) closed primarily in traditional fashion, (2) closed in 4 or 5 days (delayed primary closure), or (3) left open and allowed to heal on its own. A safe alternative to traditional primary closure, delayed primary closure does not change overall healing time and the risk of infection is greatly decreased if proper technique is used. When a wound is slated for delayed primary closure, it is prepared, debrided, and irrigated in the same manner as for immediate closure. Initially, the wound is packed with sterile gauze to prevent it from closing on its own. If the wound is on an extremity, the injury is splinted and dressed, and appropriate wound care instructions are provided. The patient returns for a wound check and packing change in 24 hours and is instructed to follow up in another 72 hours for definitive repair, with wound closure undertaken 96 to 120 hours after injury. No studies offer guidelines for prophylactic antibiotic use when delayed primary closure is the treatment option. Extrapolation from other wound studies strongly suggests that **antibiotics** offer no benefit.

Individuals who do not seek medical care after an injury select the option of leaving a wound open to heal on its own. Most patients who visit an ED with a laceration undergo some form of wound closure. Yet one study that examined unsutured hand lacerations less than 2 cm long found that there was no significant difference in cosmetic appearance or time to resumption of activities of daily living after 3 months.

Closing a wound loosely is not a good choice although it is often discussed as an option in the treatment of contaminated wounds. This choice should rarely be considered. The loosely closed wound approximates the tissue margins enough to allow the wound to seal itself completely within 48 hours. The infection risk when this method is used is the same as when the wound is closed traditionally.

Wound Tension

The goal of wound closure is optimal anatomic and functional reapproximation of tissue with minimal risk of complications. Wounds with high static and dynamic tension that require meticulous closure cannot be closed with tape or staples. Delicate approximation of wound edges under tension can be accomplished only with suture.

Several techniques may be used to reduce wound tension. Deep sutures placed in subcutaneous tissue help bring the wound margins closer together. In this manner, forces on the skin are reduced and potential dead space can be closed. Avoid suturing adipose tissue because it may become necrotic, increasing the likelihood of infection. The number of dermal sutures depends on the characteristics of the wound. In general, the number should be kept to a minimum, because suture material acts as foreign matter in the wound and can increase the risk of infection. Subcutaneous sutures are rarely placed in the hand or foot because of the major structures that reside near the surface. Another method of ameliorating static tension from cut edges of the wound is to undermine at the lacerated margin. Undermining helps free the dermis from its deeper attachments, allowing the skin edges to be approximated with less force. It is crucial to preserve the blood supply to the wound margins and not increase dead space in the process.

Suture Technique

Careful surgical technique is important to optimize wound repair. Pickups, hemostats, and pointed or "rat tooth" forceps should not be used, especially on wound margins. Blind clamping in a wound can damage a nerve, artery, or tendon. Wound margins should be everted and the sutures tied just tightly enough to allow the edges to approximate lightly. The edges can be everted by ensuring that the needle enters and exits perpendicular to the skin. Wounds with opposing margins of different thickness can be difficult to close. If this difference is not considered and corrected, the ultimate scar has uneven margins that cast a shadow on the skin and is unsightly. In closing these wounds, the needle is pulled through the cut margin of one side before entering the opposite edge. This method gives the emergency clinician the best opportunity to take an equivalent amount of tissue on both sides of the wound. Viable edges of a jagged wound must be meticulously reapproximated. The greater surface area and the ultimate contraction of the wound preserves the jagged edges, resulting in a more "natural" scar.

Most lacerations are closed with running or interrupted percutaneous suture. The running technique is appropriate for linear lacerations under minimal tension when there is a low risk of infection. This technique is more rapid, requires less suture material, and yields equivalent cosmetic results. Curvilinear or jagged wounds are best closed with interrupted sutures to distribute tension properly. The tensile strength of interrupted sutures may be superior and wound edges subjected to higher levels of tension should be closed with this technique.

Simple sutures. Wound closure with simple interrupted sutures is the most common method of laceration repair in the ED and the majority of wounds can be closed with this technique. Simple interrupted sutures yield excellent cosmesis and a low infection rate.

Procedure. The needle is placed to one side of the laceration margin and enters the skin at approximately 90 degrees. To pass the needle through the tissue, the clinician supinates his or her wrist and guides the needle deep but parallel to the skin surface. Wrist supination is extended as the needle exits the skin on the opposite side perpendicular to the surface. The distance between the laceration margin and the entrance and exit sites of the needle needs to be equal to avoid asymmetric skin puckering. Proper technique produces wound edges that are slightly everted and are lightly touching. The art of the process takes into consideration swelling while being careful not to secure the suture too tightly, because necrosis of the wound margin tissue can seriously compromise healing.

Intradermal (buried) sutures. Placing cutaneous sutures in wounds under tension can lead to ischemia of the wound margin and an

unsightly scar. Proper placement of absorbable buried intradermal sutures helps to approximate dermal margins and reduce wound edge tension. Buried sutures should not be used in contaminated wounds because they increase the risk of wound infection. Sutures through adipose tissue also increase infection and do not relieve skin tension.

Procedure.. Placement of buried sutures differs from traditional suturing because of the need to bury the knot deep to the skin. Failure to do this can interfere with dermal healing and can leave a small lump under the surface of the skin. The needle is introduced deep in the wound in the subcutaneous tissue and emerges from the dermis below the skin surface. The needle is reintroduced in the dermis on the opposite wound margin and emerges from the subcutaneous tissue at the same level on the opposite side. The knot is secured and remains buried deep below the skin surface.

Scalp laceration repair. In contrast to small lacerations elsewhere on the body, most scalp lacerations require repair because of the propensity to bleed profusely. The dense connective tissue beneath the skin tends to hold vessels open and delay hemostasis. Frontal scalp lacerations just beyond the hairline should be considered cosmetically significant wounds, especially in men. Although the scalp laceration currently may be well hidden by hair, most men experience some balding. Explore the laceration thoroughly to look for a defect in the galea, an injury that requires repair with deep sutures. Staples may be ideal for the skin closure of simple linear scalp lacerations. Hair is less of a problem in placing staples; staples can be placed much more quickly than traditional sutures, are easier to see, can be removed 1 to 3 days earlier than traditional sutures, and yield cosmetically similar results (Fig. 50.3). Staples may produce artifact on CT scans, but useful information may still be obtained if CT is necessary. Staples may move during magnetic resonance imaging (MRI) and should not be placed if this imaging modality is being considered. Lightweight stapling devices are available. Most devices come preloaded with five or more staples and are easy to use. Hair apposition may also be an option for many scalp wounds. The technique involves grabbing a bundle of hair on both sides of the wound and then twisting the hair bundles with a hemostat. A small dab of cyanoacrylate glue is applied to the twisted hair to prevent unraveling. Patient satisfaction is high with this approach.

Traditional sutures are used to repair most scalp lacerations, usually with standard nylon suture. Absorbable chromic gut can be used in children and in adults who may not return for suture removal.

Procedure. Anesthesia with epinephrine is recommended to help control bleeding. Hair removal is necessary only if the hair makes closure difficult. A defect in the galea is closed first with 3-0 or 4-0 absorbable suture. Failure to repair the galea can lead to cosmetic deformity related to frontalis muscle function. Linear superficial scalp lacerations that do not require deep sutures can be closed with staples or with monofilament nylon sutures applied with a simple interrupted

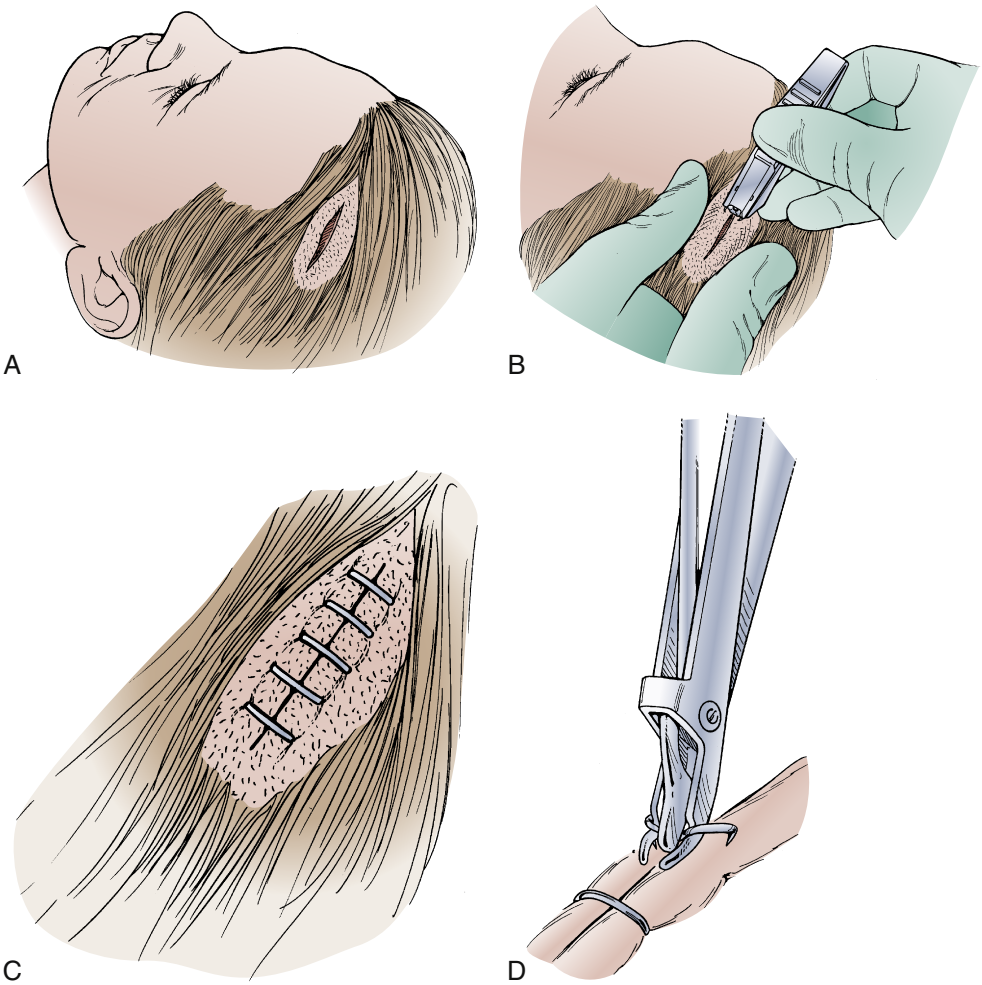

Fig. 50.3 (A–D) Scalp laceration repair. (Adapted from Simon BC. Skin and subcutaneous tissue. In: Rosen P, et al., eds. *Atlas of Emergency Procedures*. St Louis: Mosby; 2001.)

or running technique. Jagged or macerated lacerations may require some debridement and horizontal mattress sutures. To staple a scalp laceration, the adjacent skin margins are pinched together with forceps to evert wound margins. The "mouth" of the stapler is placed gently on the skin surface, taking care not to indent the skin. The handle of the stapler is squeezed carefully to eject the staple into the tissue. Ideally, the staple closely approximates the wound margins without indenting the surface of the skin. For release of the staple, the wrist is pulled back to disengage itself from the last staple.

Vigorously bleeding scalp lacerations often need temporizing measures to control bleeding while the patient is being evaluated and resuscitated. An anesthetic agent with epinephrine is typically used to help control bleeding. Blindly clamping in an attempt to control bleeding is unwise and not likely to be successful. Raney scalp clips can be rapidly applied to the wound margins to quickly gain control of the bleeding. An applicator is used to apply and remove the clips so that they can be replaced with sutures once the patient has been stabilized. The clips are plastic and will not interfere with CT or MRI.

Staple removal is simple, especially if the patient has kept the wound clean and free of dried secretions. The dual prongs on the disposable staple remover slide under the staple crossbar. As the handle is squeezed and the horizontal aspect of the staple is depressed, the sharp edges are eased out of the tissue for removal.

Skin tears. Most commonly seen in elders and the chronically ill, skin tears can be a treatment dilemma for emergency clinicians. These tears are caused by shearing forces that separate the epidermis from the underlying dermal layer of the skin. Often the result of minor trauma, these injuries range from minor tears to large gaping wounds with extensive loss of tissue. Approximating the wound margins by aligning thin, fragile tissue can be very difficult. Studies have confirmed that the use of Steri-Strips and or topical skin **adhesive**s (cyanoacrylate-based derivatives; see later) is the preferred option.[4] Either material may be used alone; however, when tension exists, placing the Steri-Strips first, then the adhesive, may be the optimal approach. Care must be taken in deciding what type of dressing to use. Transparent films can cause fluid to collect and delay healing. Additionally, adhesives are difficult to remove and can cause additional tearing. If the wound must be covered, then hydrogel sheets, hydrocolloid dressings, or both are recommended.

Vertical mattress sutures. Vertical mattress sutures improve wound edge eversion. They are also used to close gaping wounds and deep lacerations that may need more than simple sutures to limit dead space. Areas of lax skin tension, generally where maximal skin mobility is needed (e.g., over joint surfaces), may need assistance to ensure eversion of the wound margins. Vertical mattress sutures can accomplish both tasks.

Procedure. A vertical mattress suture technique is a combination of deep and superficial components. The needle is introduced at a 90-degree angle approximately 1 cm from the wound margin. The needle courses through the depth of the wound and emerges on the opposite side, 1 cm from the laceration margin at a 90-degree angle. The needle is reintroduced 1 or 2 mm from the epidermal edge at the depth used for simple sutures, then carried to the opposite side, introduced in a similar location and then tied for final approximation.

Horizontal mattress sutures. Horizontal mattress sutures are useful to help disperse excess skin tension and to evert wound edges. The scalp, which has minimal skin mobility, is one area where gaping lacerations may benefit from this method. Horizontal mattress sutures may also be beneficial in thin, fragile skin in elders and for lacerations that have lost tissue from the injury or debridement.

Procedure. The initial step is to pass the needle as for a simple interrupted stitch (Fig. 50.4). On exiting the skin, however, the needle is reintroduced approximately 0.5 cm adjacent to the exit point. This second "bite" reemerges 0.5 cm adjacent to the initial insertion point and is tied. Unlike with vertical mattress sutures, each bite is always the same distance from the wound margin.

Dog-ear deformity repair. Redundant tissue may be left on one side of the repair as the closure nears completion, especially with curvilinear lacerations. This redundant tissue generally can be avoided by placing the initial suture in the middle of a curvilinear wound. If the clinician has limited experience, excision and undermining of tissue are likely to result in complications and should not be attempted.

Procedure. The laceration repair begins in a traditional manner and continues to approximately the final 1 cm of the wound (Fig. 50.5). A short incision (approximately 1 cm) is made from the end of the laceration at a 45-degree angle. The angle is cut toward the side of the redundant, bunched tissue. In most cases, the subcutaneous tissue from the start of the dog-ear defect to the newly created end of the wound must be gently undermined to mobilize the skin. The next step, the final step before suturing, is the most important. The work that has just been completed leaves a small triangular piece of excess tissue. The redundant piece is gently lifted with the tissue forceps and excised in a line parallel to the incision made above. The wound can then be closed with simple interrupted suture technique.

Corner stitch (half-buried horizontal mattress sutures). Jagged and triangular wounds create corners that can be difficult to repair. The clinician must avoid placing the suture directly in the tip of the flap, as this practice may "stretch" the tissue and further compromise blood flow to the wound margin. The corner stitch allows optimal tissue approximation with minimal tension.

Procedure. The needle is introduced percutaneously through the non-flap side of the wound a few millimeters from the corner of the wound (Fig. 50.6). The needle is passed horizontally through the dermis of the flap. The final step is to pass the needle into the dermis of the non-flap aspect of the wound a few millimeters from the opposite side of the corner. The suture is led out through the epidermis and tied. This technique can also be used to encompass multiple flaps either individually or simultaneously if the tips are adjacent to one another. The most difficult, but crucial, aspect of the corner stitch is to take bites of equal depth with each pass of the needle. Failure to take equal bites of tissue results in a wound with opposing sides that do not lie flat; this leads to a more obvious scar. When the corner has been repaired, the remaining two sides of the wound may be closed with simple interrupted or running suture technique.

V-Y wound closure. The V-Y closure is indicated for the repair of V-shaped wounds with tissue loss or with nonviable margins that must be trimmed. The tissue loss is such that the adjacent mobile tissue is not sufficient to close the remaining defect.

Procedure. Nonviable tissue is trimmed with fine iris scissors (Fig. 50.7). The long V-shaped portion of the wound is sutured with simple interrupted percutaneous stitches. This first step brings the tip of the flap closer to the newly created corner of the wound. A corner stitch is used to secure the tip of the flap. The remaining limbs of the Y are repaired with simple interrupted stitches. Some degree of undermining is likely to be needed to mobilize tissue to close the defect. Debridement of too much tissue can make the final repair more difficult and distort adjacent anatomy.

Materials

In the Middle Ages and earlier, materials used to close wounds included flax, hemp, fascia, hair, linen strips, pigs' bristles, reeds, grasses, and even the mouth parts of the pincher ant. In the early 1900s, natural organic protein products, including silk, cotton, and catgut, were the only available substances. Polyester (Dacron) and nylon were the first

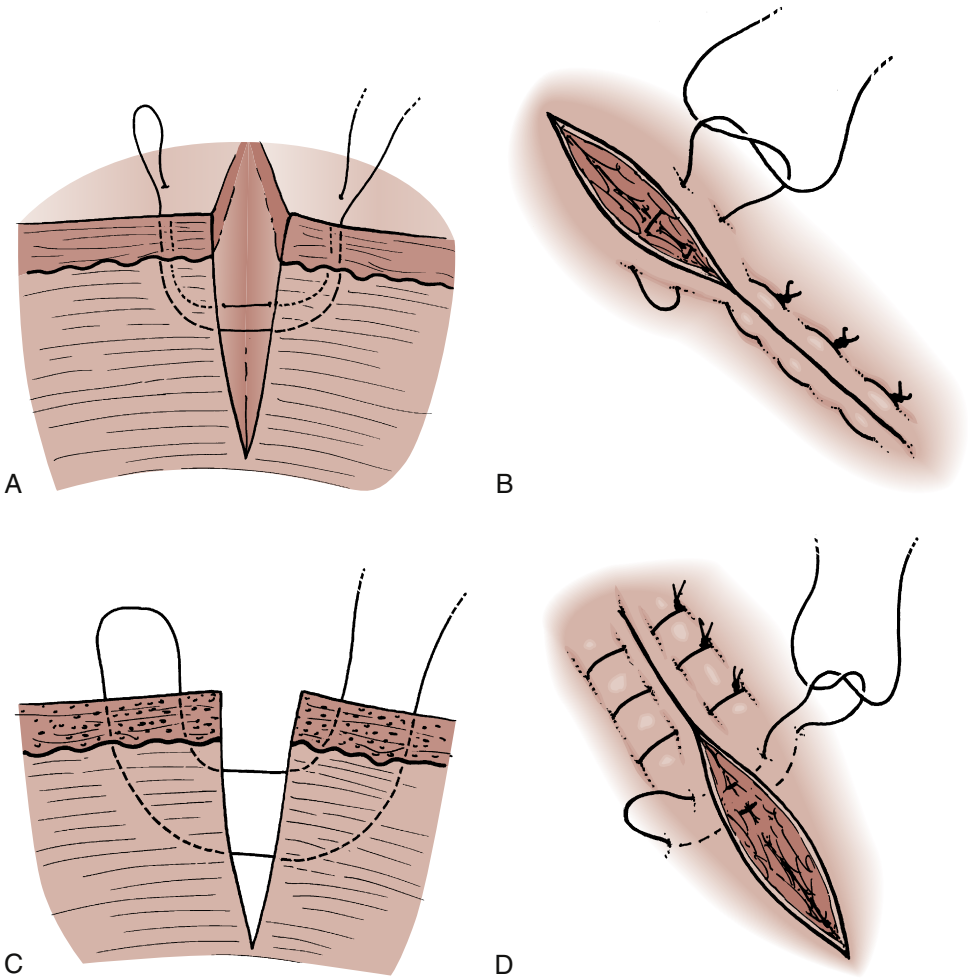

Fig. 50.4 (A–D) Mattress suture. (Adapted from Simon BC. Skin and subcutaneous tissue. In: Rosen P, et al., eds. *Atlas of Emergency Procedures.* St Louis: Mosby; 2001.)

synthetic materials, available in the 1940s. Since then, a host of other synthetic materials have become available.

Suture. The ideal suture is inert to metabolism, resistant to infection and inflammatory reactions, has great tensile strength, does not tear tissue, is easy to work with and tie, and is available in convenient colors with a variety of cutting and noncutting needles. A common classification of suture material relies on relative *absorbability.* In general, the materials that maintain their tensile strength for more than 60 days after implantation have been defined as *nonabsorbable.* Materials that undergo rapid degradation in tissue and lose their strength in less than 60 days are considered *absorbable.* A second classification considers the source and nature of the material. *Biologic* substances, which include catgut, collagen, silk, linen and cotton, generally produce the greatest tissue reaction (and scarring)and have the lowest relative tensile strength but the highest knot security. These characteristics are in contrast to *synthetic* materials, such as polyester (Dacron), polyamide (nylon), polypropylene (Prolene), polyglycolide and polylactide polymers (Dexon and Vicryl), polydioxanone (PDS), and steel, which usually have less tissue reactivity, greater strength, but less knot security.

Knotting properties and handling characteristics tend to vary inversely. Knot security is of particular importance in maintaining wound closure and the patient's confidence in the physician. Sutures with smooth or slippery surfaces produce little friction, glide effortlessly through tissue and are easy to tie. Smoother materials are more difficult to handle and more likely to untie spontaneously. Certain monofilament synthetic materials tend to return or spring back to their original shape. To overcome this suture memory, the first part of the tie should be a "double throw" pulled tightly enough to approximate the tissue, with care taken not to strangulate the margins. The second throw locks the tension of the first part into position. A third throw is used for added security. If this is done properly, additional knotting is not needed after the third throw.

The presence of any suture material in a wound increases the likelihood of infection. Subcutaneous sutures bear the greatest risk. The degree of risk depends on the characteristics of the substances used. Braided multifilament materials, such as the polyesters, polyamides, polyglycolides, and silk, yield the highest infection rates, whereas monofilament synthetic substances have the lowest risk of infection. There are several nonabsorbable monofilament synthetic sutures and one absorbable monofilament (PDS). The degree of infectivity of PDS compares well with the low rates of infectivity of similar materials.

Patient comfort in suture selection is important. Although silk is highly reactive, it ties well, is easy to handle, and is comfortable for the patient. It is an excellent choice for use in and around the lips, where comfort is a major concern. PDS is a comfortable absorbable suture and can be left in intraoral mucosa to be absorbed, with low risks of infection, or it can be removed in 5 to 7 days. Staples or metallic sutures are excellent when strength is needed, but they may be uncomfortable for the patient and thus better placed in less sensitive areas such as the

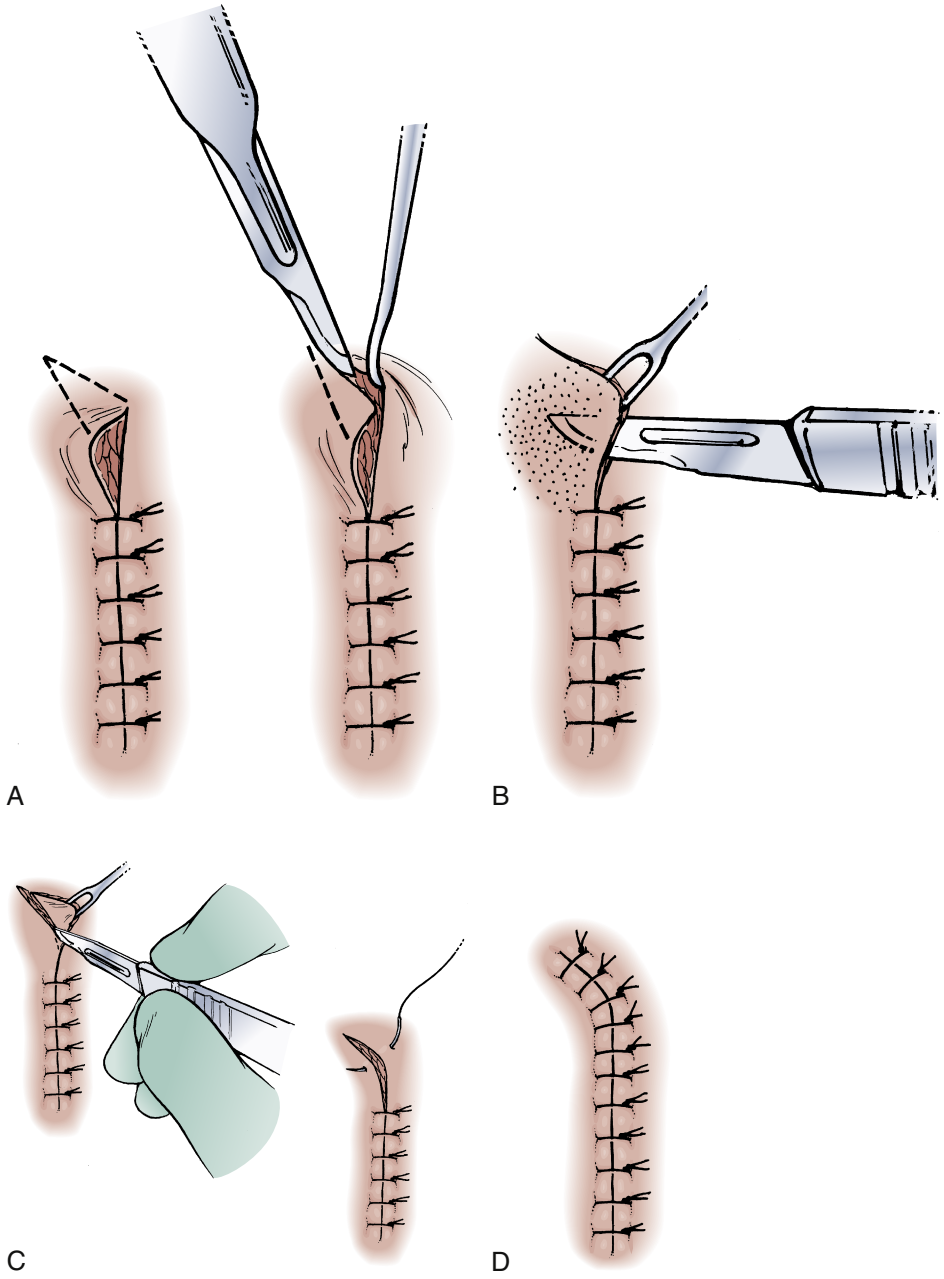

Fig. 50.5 (A–D) Dog-ear repair. (Adapted from Simon BC. Skin and subcutaneous tissue. In: Rosen P, et al., eds. *Atlas of Emergency Procedures.* St Louis: Mosby; 2001.)

scalp. Nylon and polypropylene, which are the most common sutures used on skin, produce little tissue reaction and offer good tensile strength. They tend to be stiff, produce discomfort near the lips, have poor knot security, and may be difficult to work with. A braided, coated polyester nonabsorbable material, such as Ethibond, is easier to work with and has better knot stability. Although Ethibond is more expensive than nylon, its characteristics and added patient comfort suggest that it may be preferable unless the laceration is in a cosmetically sensitive area, since braided suture incites a more vigorous inflammatory reaction compared to monofilament material. Absorbable sutures, such as polyglycolide and polylactide polymers (Dexon and Vicryl), have been used strictly for subcutaneous and mucosal closures. Their highly reactive nature allows them to be broken down and absorbed over weeks. Chromic catgut, another absorbable material, has been shown to be safe and effective for the closure of scalp wounds in children.

Needles. Surgical needles are available in a variety of sizes and shapes with myriad other characteristics. Cutting needles may be reverse cutting, conventional cutting, taper cut, or precision point. Most emergency wounds can be closed with a conventional cutting needle. In addition to its sharp point, it has two opposing cutting edges, with a third on the inside curve. Precision point needles are similarly shaped but are honed 24 extra times to maintain their sharpness longer. These needles are used for delicate plastic or cosmetic surgery. Noncutting needles are reserved for organ repair and subcutaneous suturing. Cutting needles may also be used to repair subcutaneous tissue. Needle nomenclature is confusing and varies by manufacturer.

Tape. Tape closure may be superior to closure with sutures and staples if applied in the appropriate circumstances. In general, the laceration should be linear and subjected to weak static and dynamic forces. Tape is not considered for wounds requiring meticulous

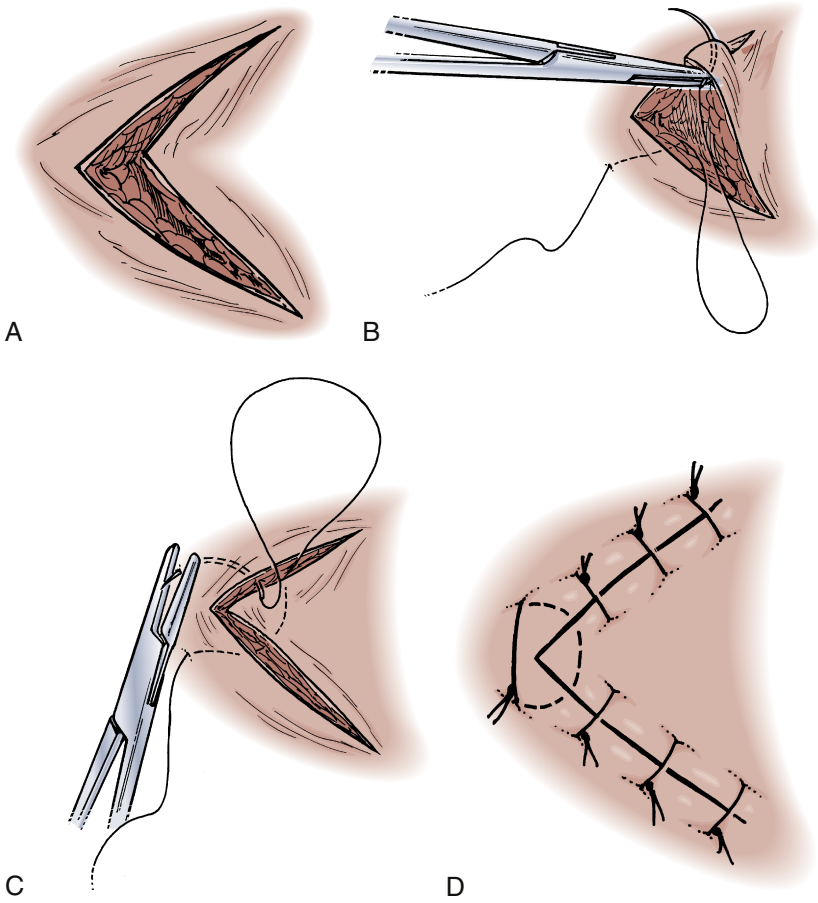

Fig. 50.6 (A–D) Corner stitch (half-buried horizontal mattress). (Adapted from Simon BC. Skin and subcutaneous tissue. In: Rosen P, et al., eds. *Atlas of Emergency Procedures*. St Louis: Mosby; 2001.)

tissue approximation. Compared with other closure materials, tape is associated with a lower risk of infection, less expense, and less physician time. In addition, injectable local anesthetics are not needed.

The ideal wound closure tape allows water and gas exchange and possesses elasticity, strength, and optimal adhesiveness. To maximize adhesiveness, tincture of benzoin is painted on the skin adjacent to the wound and care is taken to avoid introducing benzoin compound in the wound. A nonwoven, microporous tape, which is not reinforced, has been found to best meet these requirements.

Staples. Staples offer several advantages over sutures. Monofilament stainless steel staples offer less risk of infection than even the least reactive suture. The time necessary to accomplish closure may be significantly lessened. Acceptable wounds must be linear and subjected to weak skin forces. Wounds requiring accurate approximation of tissue are not candidates for staple closure. Staples are also uncomfortable while in situ and on removal. Stapled wounds gain tensile strength sooner, and the staples can be removed 1 to 3 days earlier than sutures. After removal, the staples should be replaced with wound closure tape for continued reinforcement.

Various stapling devices are available. The device must allow good visual access and flexible positioning for difficult angles. A pre-cocking mechanism is necessary to allow the physician to hold the staple securely during its placement. The angle of staple delivery is important. One brand releases the staple perpendicular to the wound with its crossbar flush with the skin; this can result in cross-hatching on the skin or tissue strangulation if placed too deeply. The device needs an ejector spring for smooth staple release and must be able to be handled without producing fatigue.

Tissue adhesives. European and Canadian physicians have used tissue adhesives (butyl-2-cyanoacrylates) for many years. In 1998, octyl-2-cyanoacrylates were approved for use in the United States. Tissue adhesives offer many advantages over traditional sutures. The adhesive can be applied quickly and easily with a minimum of patient discomfort. In addition, suture removal in 7 to 10 days is unnecessary because the adhesive sloughs off the skin in approximately the same amount of time. Adhesives not only provide their own dressing but also have antibacterial properties and may decrease the rate of wound infections. Closing wounds with adhesives is less expensive than traditional suturing and carries no risk of needle-stick injuries.

Tissue adhesives achieved cosmetic results similar to those of traditional sutures in randomized trials. Tissue adhesive may be applied in high-tension areas, but only if used in conjunction with subcutaneous or subcuticular sutures. If used alone, tissue adhesives are not recommended for lacerations longer than 4 cm or in areas of higher tension or frequent repetitive movements, such as joints or hands.

Other disadvantages of tissue adhesives include the inability to use antibacterial or other petroleum-based products on the wound; the recommendation not to swim and to limit forces that may prematurely remove the adhesive; and the greater risk of dehiscence. The tensile strength of tissue adhesives is significantly less than that of sutures. Despite these disadvantages, tissue adhesives represent a tremendous advance in the management of routine uncomplicated lacerations in non-tension areas. Patients routinely prefer tissue adhesives over traditional sutures.

Application of tissue adhesive begins with routine skin and wound preparation. The area must be dried and adequate hemostasis achieved

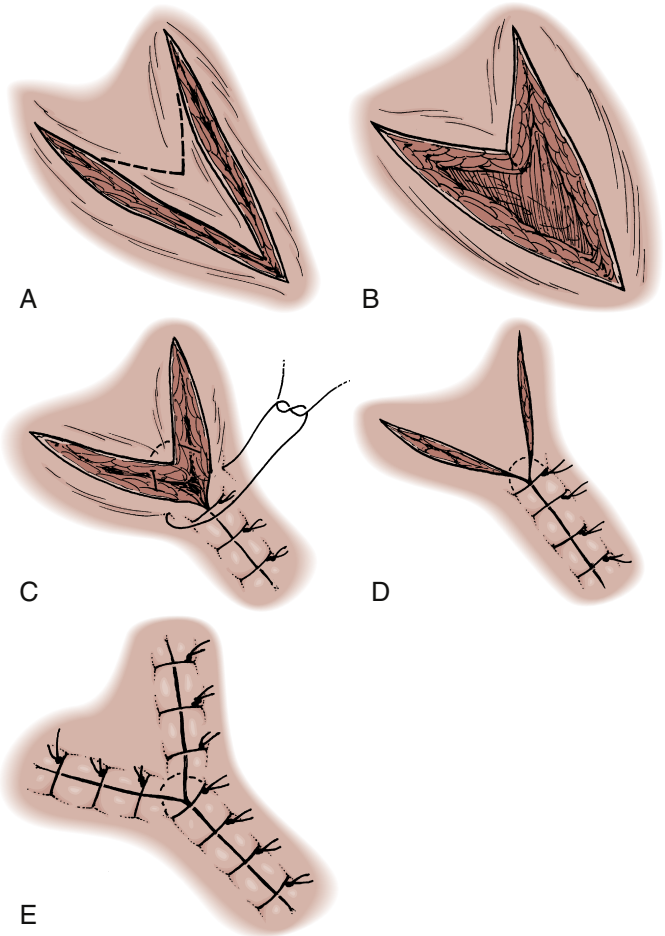

Fig. 50.7 (A–E) V-Y closure. (Adapted from Simon BC. Skin and subcutaneous tissue. In: Rosen P, et al., eds. *Atlas of Emergency Procedures*. St Louis: Mosby; 2001.)

before application. The wound margins are approximated as meticulously as possible in order to prevent the adhesive from getting between the wound margins. Applying tape (Steri-Strips) before application will facilitate wound margin approximation and make it easier to apply with similar results. Adhesive between the wound margins delays healing and increases the likelihood of wound dehiscence. The adhesive is applied to the entire length of the wound sufficient to cover 5 to 10 mm of skin adjacent to the margins. A single layer of adhesive is adequate. The adhesive sets in approximately 95 seconds. Special care is taken to ensure that the adhesive does not run off and disturb adjacent tissues. If the laceration is on the face, having the patient lie on the affected side will help prevent contamination of the eye near the wound and the opposing eye. Newer, high-viscosity formulations are now available that help limit this risk. Wounds may get wet but should not be immersed in water and should be blotted dry and not vigorously rubbed. An additional dressing may be desired by the patient but is not necessary.

Antibiotic Prophylaxis

Routine antibiotic prophylaxis for simple wounds has no scientific basis. A meta-analysis including more than 1700 patients compared the rates of infection in patients with simple non-bite wounds receiving antibiotics with those in control groups. Those treated with antibiotics had a slightly greater incidence of infection. The authors concluded that prophylactic antibiotics had no role in simple non-bite lacerations. Routine antibiotic use has obvious known complications, such as increasing resistance to antibiotics, gastrointestinal side effects (nausea, vomiting, *Clostridioides difficile* colitis), development of vaginal candidiasis, and allergic reactions that are common and may result in significant morbidity and unnecessary cost.

Although irrigation and debridement are the most important means of preventing wound infections, antibiotic prophylaxis is recommended in certain circumstances. Prophylaxis must be tailored to each patient. Some of the following recommendations are supported by scientific data, whereas others have few data to support their use and are based on established practice standards.

Contamination, crush, and host factors. Antibiotic prophylaxis with an antibiotic covering skin flora (e.g., cefazolin IV, cephalexin PO) is recommended for patients with wounds with gross contamination, patients with severe crush injuries, and immunocompromised patients. Some authors recommend not closing these wounds and instead using delayed primary closure. If circumstances require wound closure despite the infection risk, many emergency clinicians recommend prophylaxis despite scarce data.

Similarly, patients with significant crush injuries should receive antibiotics. Crush injuries are high-risk wounds because they produce more devitalized tissue and, despite a dearth of evidence, should be prophylactically treated.

Patients with certain risk factors have increased wound infection rates. Large prospective studies of patients with surgical wounds showed an increased rate of wound infection in patients with diabetes, obesity, malnutrition, chronic renal failure, advanced age, and chronic steroid use. No controlled studies of antibiotic prophylaxis in these patients exist, however, and clinicians should consider antibiotics based on individual circumstances. Finally, prophylaxis should be considered for other host factors, such as prosthetic joints or risk for endocarditis. Little evidence exists to support either recommendation.

Open fractures, joint wounds, and gunshot wounds. Wounds that involve joints or open fractures require prophylactic antibiotics. Prospective randomized controlled studies have documented decreased infection rates in patients receiving antibiotics compared with placebo. Indeed, the time to antibiotic administration in these wounds was found to be the most important factor in decreasing wound infection rates. Open fractures without evidence of significant soft tissue damage (avulsions and crushed or devitalized tissue) need antibiotics for 24 hours. Open comminuted fractures or fractures with significant tissue damage require 72 hours of antibiotics.

For gunshot wounds, which are classified as a type of open fracture, the recommendations vary with the type of missile wound. Low-velocity missile wounds not treated with antibiotics showed no increased infection rate in a randomized controlled trial of 67 patients with fractures treated with a closed technique. High-velocity wounds with fracture, on the other hand, are associated with an increased risk of infection, and antibiotic therapy should be initiated early and maintained for 48 to 72 hours. Patients with shotgun wounds with fracture should receive prophylaxis as well. Appropriate antibiotic therapy would be a cephalosporin (e.g., cefazolin 1 to 3 g IV) with or without an aminoglycoside (e.g., gentamicin 2 mg/kg IV). In patients with severe cephalosporin allergies, clindamycin 600 mg IV can be used instead of cefazolin.

For severely contaminated wounds, gentamicin 1.5 to 2 mg/kg IV is added. Some recent data have proposed limiting aminoglycoside use altogether and only using cefazolin for Gustilo grade I/II open fractures and ceftriaxone for grade III open fractures. A single institution study showed little difference in infection rates after limiting aminoglycoside administration for open fractures.

Bites and puncture wounds. Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, and some puncture injuries to the foot. Of all mammalian

bites, school age children account for almost half of all patients in this category, and 70% of animal bites are from pets or animals known to the victim (see Chapter 52).

Cat bites. Antibiotic prophylaxis is required for patients with cat bites, especially bites to the hand. These bites tend to be deep puncture wounds that do not require surface repair but are difficult to irrigate adequately. Cat bites have been reported to cause infections in 10% to 40% of all wounds. In one study, 13% of patients had signs of infection when they visited the ED, and 16% eventually developed infection. Other authors report that 80% of these bites become infected, although obvious selection bias limits this interpretation. Antibiotics seem to decrease the incidence of infection but a Cochrane review on mammalian bites suggested the limited literature on cat bites did not prove antibiotic efficacy, except in hand bites. At this time, we still advocate for antibiotic prophylaxis in all cat bites.

The organisms found in cat bites include *Staphylococcus* species, *Streptococcus* species, and, most often, *Pasteurella multocida*. *P. multocida* is usually found in infected cat bite wounds and is present in the normal oral flora of 70% of all cats. *P. multocida* is sensitive to penicillin, but the infection is often polymicrobial. *P. multocida* is resistant to dicloxacillin, cephalexin, and clindamycin, and there are many erythromycin-resistant strains. Amoxicillin with clavulanate (875 mg bid for 7 days) is the current recommendation for antibiotic prophylaxis for cat bites.

Dog bites. Antibiotic prophylaxis for dog bites is more controversial. The infection rate has been reported as 6% to 16% for patients not receiving antibiotics. Dog bites tend to involve more crush injuries with tearing and avulsions rather than puncture wounds. As such, dog bites are usually more amenable to irrigation and debridement. Seven of eight randomized trials of dog bite wounds showed no benefit with antibiotics. However, pooled data for meta-analysis did show a small but statistically significant benefit from antibiotics. On balance, we believe the use of prophylactic antibiotics should be limited to high-risk wounds, such as hand injuries, deep puncture wounds, bite in extremities with wounds with underlying venous or lymphatic compromise, wounds near or in a prosthetic joint, wounds in patients with diabetes, and wounds in older or immunocompromised patients.

Hand bites. In addition to the previous bite wound recommendations, antibiotic prophylaxis of injuries to the metacarpophalangeal joints is advised. These wounds are assumed to be human bites until proved otherwise. Known as "fight bites," these wounds have a high incidence of infection. Patients without signs of infection may be managed as outpatients. Close inspection, after anesthesia, is necessary to thoroughly evaluate the area for tendon involvement or penetration of the joint. If the joint is involved, irrigation is required. In some institutions, all of these patients are taken to the operating room for a thorough washout. Patients with early signs of infection are admitted for IV antibiotics, debridement and irrigation. The choice of antibiotics reflects the predominant organisms of hand bite infections. *Streptococcus* and *Staphylococcus* species are common, but *Eikenella corrodens* and *Bacteroides* species are also typical pathogens. *Eikenella* is often resistant to clindamycin, first-generation cephalosporins, and erythromycin. Amoxicillin with clavulanate (875 mg BID for 7 days) is the recommended initial therapy. Patients with later infection are treated with intravenous extended-spectrum antibiotics (e.g., ampicillin with sulbactam).

Intraoral lacerations. Lacerations of the oral mucosa involve bacteria-rich oral secretions and may become infected slightly more often (6% to 12%) than other wounds. Rates of infection for through-and-through lacerations may be twice the rates for simple mucosal lacerations. Although few data suggest a clear indication for prophylactic antibiotics, evidence suggests patients benefit from antibiotics if they are compliant with their regimen. Currently, we recommend antibiotic use in high-risk patients with through-and-through wounds. Penicillin (Pen VK) 500 mg bid for 5 days is an appropriate initial regimen.

Puncture wounds of the foot. Puncture wounds of the foot are seen frequently in the ED. These wounds are often caused by common carpentry nails, although other objects (e.g., glass, metal, and wood) must be considered. Despite their simple appearance, these wounds may produce significant morbidity. The infection rate for puncture wounds in the foot has been reported to be 15%. Most wounds occur on the plantar surface, from the neck of the metatarsal to the toes. Simple cellulitis accounts for half of these infections. More significant infections include septic arthritis, abscesses, and osteomyelitis. *Pseudomonas* organisms commonly cause osteomyelitis cases from puncture wounds. No data suggest a benefit from prophylactic antibiotics, but given the high risk of infection and serious complications, their use is recommended in high-risk puncture wounds. *Pseudomonas* organisms should be suspected when the puncture travels through a rubber-soled shoe. Patients with puncture wounds to the foot require early follow-up. Levofloxacin is the drug of choice to treat outpatients with suspected wound infection when *Pseudomonas* is of concern. Cephalexin or dicloxacillin is adequate for staphylococcal and streptococcal coverage unless methicillin-resistant *Staphylococcus aureus* (MRSA) is likely. In cases suspicious for MRSA, sulfamethoxazole-trimethoprim or doxycycline is recommended.

Drains, Dressings, and Immobilization

Drains. Drains have no role in ED wound care. In general, drains are placed when a collection of fluid exists or may develop. The presence of a drain reduces the wound's resistance to infection, regardless of the materials used in its construction, and the use of drains should be avoided. In wounds likely to collect fluid (e.g., around the elbow or knee), it is preferable to place the extremity at rest with a plaster splint or perform delayed primary closure.

Dressings. Various dressing materials are available. The microenvironment created by a dressing affects the biology of healing. The optimal wound climate must not interfere with the activity of fibroblasts and macrophages. The production of granulation tissue and migration of epithelial cells across the wound must be optimized.

Several factors should be considered in choosing the appropriate dressing. Dressings that prevent evaporation of water and keep tissues moist are helpful. A drying wound produces a thick, hardened scab that impedes the process of epithelialization. Excess fluid can lead to maceration of tissue and may be a potential culture medium for bacterial proliferation. Gaseous permeability is essential because epithelialization is accelerated greatly in the presence of oxygen. The wound-covering product should be impermeable to bacteria and other particulate matter that can contaminate the wound. It is important not to traumatize newly established tissue during dressing changes. The optimal dressing should have a nonadherent surface, be permeable to gases, and have a capacity to absorb some fluid but not allow desiccation. The outer barrier of the product should be impermeable to bacteria but permeable to water vapor. These products include films, hydrocolloids, foams, and hydrogels. The choice of dressing for ED wounds is primarily based on the amount of drainage that is expected.

Film dressings are thin membranes that are transparent, adhesive, and waterproof but are not absorptive. They are best reserved for wounds with low levels of drainage. Film dressings may be left in place for up to 7 days, as long as they do not leak or separate from the wound bed. For wounds with a moderate amount of drainage, moderately absorptive hydrocolloid dressings may be indicated. These dressings are thicker than films, semi-occlusive, waterproof, and very comfortable for the patient. Like films, they can be left on for up to 7 days. Foam dressings are more absorptive and made of a soft cushion sponge-like material. Some may require a secondary dressing for adhesion and need to be removed every 3 days. Hydrogel dressings are moisture-donating water-based gels that are available in sheets attached to a

semipermeable film. These dressings do not absorb fluids, so they must be used on relatively dry wounds. Patients often find these dressings to be the most comfortable, but they need to be changed every 1 to 3 days. The least expensive and simplest method of dressing a straightforward, uncomplicated laceration is to use petroleum-impregnated gauze or gauze on top of a thick layer of antibiotic ointment. These should be changed daily to prevent desiccation.

Immobilization. Wounds in proximity to joints must be immobilized as part of routine care. Splinting the injured body part places the injury at rest and hastens healing. Failure to splint appropriately exposes the healing tissue to the dynamic forces of muscular contractions, ultimately slowing the healing process and increasing scar size. In addition, immobilization decreases lymphatic flow and minimizes spread of microflora from the wound.

DISPOSITION

Wound Care Instructions

Discharge instructions must be clear, understandable, and reasonably comprehensive (Box 50.2). They should include daily care, observation for signs of infection, suture removal dates, and a follow-up source. Instruct the patient to elevate the injured extremity during the first 24 to 48 post-traumatic hours and explain that elevation lessens edema, hastens healing, and mollifies pain. The wound should be protected as described previously or cleaned daily to remove crust formations. It is safe for patients to bathe and get the wound wet 24 hours after injury. Daily swabbing with half-strength hydrogen peroxide rids the wound of debris and any blood clot that forms between the sutured edges. Hydrogen peroxide is not to be used after separation of the scab, because it is toxic to the epithelium and may produce bullae.

Wound infection is difficult for the untrained observer to distinguish from the inflammatory response of injury and subsequent healing. Patient education should be cautious and straightforward (e.g., return or seek follow-up for redness, swelling, increased pain, fever, pus, or red lines progressing up an extremity). A high-risk injury must be reexamined 48 hours after the trauma, regardless of its appearance. Highlight the possibility that a foreign body may be present despite efforts to remove it. Return precautions outlining signs of wound infection are essential.

Suture removal times vary, but generally they are 5 days for the face and 7 to 14 days for other body parts. Considerations include cosmetics, dynamic forces in proximity to the injury, static skin tension, blood supply, and anticipated healing rates.

Tetanus Immunization

The incidence of tetanus in the US is rare, with only 233 cases reported during the 2001 to 2008 surveillance period with a case fatality rate of 13.2%. Most tetanus patients in the United States are older than 50 years old. Immunization status is considered in all patients with wounds, regardless of severity. Forty percent of all cases of tetanus occur in individuals who have either minor wounds or no recollection of injury. These numbers raise serious questions regarding the validity of separating immunization recommendations according to clean and tetanus-prone wounds. Studies show that many people are inadequately immunized, especially patients older than 70 years, immigrants, and people with little education beyond grade school. In addition, patient immunization histories are often unreliable. Given the inability to predict which wounds are at high risk, all wounds are approached with suspicion.

The usual incubation period for tetanus is 7 to 21 days (range, 3 to 56 days). Immunization is given as soon as possible but can be given days or weeks after the injury. The dose of tetanus toxoid (T) or diphtheria, pertussis, and tetanus toxoids (DTaP) is 0.5 mL intramuscularly, regardless of the patient's age. Inadequately immunized patients need a dose of Tdap and tetanus immune globulin (TIG). The TIG dose is 250 IU for all ages 7 years old or older and 4 IU/kg IM up to 250 IU for ages younger than 7 years old (Table 50.1). A single injection of TIG provides protective levels of passive antibodies for at least 4 weeks. The immune globulin and toxoid may be given during the same visit but should be administered with a different syringe at separate sites. The literature suggests that emergency clinicians need to be more diligent administering TIG, because it is often not provided when indicated.

Because studies suggest that 10% to 40% of the population in the United States is inadequately immunized against pertussis, pertussis vaccination is recommended along with tetanus toxoid. Immunity to pertussis wanes approximately 5 to 10 years after vaccination. Since the 1980s, the number of reported pertussis cases has steadily increased,

BOX 50.2 Wound Care Instructions

I. Elevate the injured extremity above the level of the heart. Wear a sling when appropriate.
II. Cleanse daily in a gentle manner to remove debris and crusting that develops. Use dilute hydrogen peroxide.
III. Immobilization should be maintained at least until suture removal.
IV. Signs of infection
  A. Redness
  B. Increasing pain
  C. Swelling
  D. Fever
  E. Red streaks progressing up an extremity
V. Wound check
  A. As needed to check signs of infection
  B. Routine at 48 h for high-risk wounds
VI. Suture removal (*Note:* Suture may be removed earlier if Steri-Strips reinforce the wound.)
  A. Face: 5 days (always replace with Steri-Strips)
  B. Scalp: 7–10 days
  C. Trunk: 7–10 days
  D. Arms and legs: 10–14 days
  E. Joints: 14 days

TABLE 50.1 Tetanus Prophylaxis for All Patients With All Wounds[a,b]

Immunization History	DTaP (0.5 mL)	TIG (250 IU or 4 IU/kg)
Fully immunized, <10 years since booster	No	No
Fully immunized, >10 years since booster	Yes	No
Incomplete series (<3 injections)	Yes[c]	Yes

[a]All injections are intramuscular.
[b]Consider more frequent immunization for elderly patients. Tdap recommended for ages 11 to ≥65 years old (Adacel, Sanofi Pasteur and Boostrix, GalaxoSmithKlineBiologicals), although both products likely effective in the older than 65 age group.
[c]Refer these patients to complete their series; DTaP in 6 weeks and 12 months.
DTaP, Diphtheria, pertussis, tetanus toxoids; *TIG,* tetanus immune globulin.

BOX 50.3 Summary of Wound Care

I. Stabilize patient
II. History (include tetanus immunization and allergies)
III. Physical examination
  A. Neurovascular examination
  B. Anesthesia: Bupivacaine 0.5% without epinephrine, regional or local
  C. Bloodless field: Tourniquet or sphygmomanometer for extremities
  D. Thorough examination of anatomic structures, skin, nerves, tendons, blood vessels, bones, muscles, fascia, other (ducts, cartilage)
  E. Consultation if indicated
IV. X-ray films to detect injury to bone or the presence of foreign bodies (plain films, CT or ultrasound)
V. Wound preparation
  A. Cut—do not shave—surrounding hair
  B. Prepare surrounding skin with a chlorhexidine-alcohol solution
  C. Sharp debridement of foreign matter and devitalized tissue
  D. High-pressure irrigation with saline or a 1% povidone-iodine (Betadine) solution
VI. Wound closure
  A. Tape, staples, or suture
  B. Do not use subcutaneous sutures unless the wound is under high tension
VII. Antibiotics
  A. Apply topical antibiotics
  B. No systemic antibiotics unless wound is high risk
VIII. Dress and immobilize: Consider a transparent gas-permeable dressing
  A. Wound care instructions (see Box 50.2)
    Signs of infection
    Elevation
    Wound check if necessary
    Suture removal as soon as possible

especially among adolescents and adults. Children younger than 11 years old should receive the DTaP immunization. In 2005, a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap) product formulated for use in adults and adolescents was licensed in the United States for people 11 to 64 years old. Updated recommendations allow for Tdap (Boostrix, GlaxoSmithKline Biologicals) to be given to patients 65 years old and older, although it is likely that either Adacel or Boostrix vaccine will provide protection. When possible, it is recommended that this triple combined formulation be used in the ED for tetanus prophylaxis of adolescents and adults. Although all four injections (T, diphtheria and tetanus toxoids [DT], TIG, and Tdap) are considered safe and effective in pregnancy, because of limited experience during pregnancy the recommendation is to use DT. However, Tdap is recommended immediately postpartum, including for breast-feeding women.

Box 50.3 summarizes the principles of wound care management.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 50: QUESTIONS AND ANSWERS

1. Which of the following is associated with an increased risk of infection?
- **a.** Avoidance of epinephrine use in wound anesthesia
- **b.** High-pressure irrigation
- **c.** Use of clippers instead of razors for hair management near wound
- **d.** Use of silk suture material
- **e.** Use of tape over sutures for wound closure

Answer: d. Silk yields the highest infection rates, whereas monofilament synthetic substances have the lowest risk of infection. Other risk factors are listed in eBox 50.1

EBOX 50.1 Risk Factors for Wound Infection

1. Location: Leg and thigh, then arms, then feet, then chest, then back, then face, then scalp
2. Contamination with devitalized tissue, foreign matter, saliva, or stool
3. Blunt (crush) mechanism
4. Presence of subcutaneous sutures
5. Type of repair: Risk greatest with sutures > staples > tape
6. Anesthesia with epinephrine
7. High-velocity missile injuries
8. Diabetes

2. A 32-year-old man presents with 20 stab wounds to his arms and legs sustained in an assault. He weighs 80 kg. Which of the following is an appropriate dosage of wound anesthesia?
- **a.** 240 mg of 1% lidocaine
- **b.** 320 mg of 0.5% bupivacaine
- **c.** 400 mg of 0.5% bupivacaine with epinephrine
- **d.** 700 mg of 1% lidocaine with epinephrine

Answer: a. In adults, the maximal reported safe dose of bupivacaine is approximately 2.5 mg/kg without epinephrine and 3.5 mg/kg with epinephrine, assuming the injection is a wound infiltration technique and not one in a highly vascular area. General dose guidelines for lidocaine are 3 to 5 mg/kg without and 5 to 7 mg/kg with epinephrine, respectively. A 1% lidocaine solution contains 10 mg/mL. The actual percent solution does not matter; the total milligram dose does.

3. A 23-year-old female presents with a laceration to her thigh. As you begin to apply anesthetic, she tells you that when she went to the dentist she had an allergic reaction to procaine. Which of the following should you use?
- **a.** Benzocaine
- **b.** Benzocaine with epinephrine
- **c.** Bupivacaine
- **d.** Lidocaine from a multidose vial
- **e.** Tetracaine

Answer: c. Allergy to local anesthetics is uncommon. Two distinct groups of "caine" anesthetics exist. The esters include procaine, tetracaine, and benzocaine. The second group, including lidocaine and bupivacaine, belongs to the amide family. Allergy to the esters is uncommon. True allergy to agents in the amide family is rare. No cross-reactivity occurs between the amide and ester families, so an agent from a different group may be chosen. A "preservative-free" preparation should ideally be used because the para-aminobenzoic acid in multidose vials may cause an amine-like reaction that may be confused with an allergy to the primary agent.

4. Which of the following factors is most likely to require no antibiotic prophylaxis?
- **a.** Cat bite
- **b.** Diabetic with contaminated wound
- **c.** Dog bite
- **d.** Human bite
- **e.** Puncture wound through rubber sole

Answer: c. Antibiotic prophylaxis is often provided for patients with wounds with gross contamination, patients with severe crush injuries, and immunocompromised patients. Prophylaxis is also required for patients with cat bites. Seven of eight randomized trials of dog bite wounds showed no benefit with antibiotics. Human bites or lacerations to the metacarpophalangeal (MCP) joint are termed "fight bites," and these wounds have a high incidence of infection. Thus, of the choices given, dog bites have the lowest incidence of infection and therefore are the least likely to require prophylactic antibiotics.

5. Antibiotic coverage of a cat bite must target which of the following pathogens?
- **a.** Bacteroides species
- **b.** *Clostridium perfringens*
- **c.** *Eikenella corrodens*
- **d.** *Pasteurella multocida*
- **d.** Pseudomonas species

Answer: e. The organisms found in cat bites include *Staphylococcus* species, *Streptococcus* species, and, most often, *P. multocida*. *P. multocida* is usually found in infected cat bite wounds and is present in the normal oral flora of 70% of all cats. *P. multocida* is sensitive to penicillin, but the infection is often polymicrobial. *P. multocida* is resistant to dicloxacillin, cephalexin, and clindamycin, and there are many erythromycin-resistant strains. Amoxicillin with clavulanate is the current recommendation for antibiotic prophylaxis for cat bites.

6. A 74-year-old patient presents with a gaping wound from a dog bite, complaining of pain at the site. The dog belongs to a friend, has reportedly had "all his shots," and is in custody. The patient is from Central America but has lived in the US for more than 50 years; he does not recall his immunization history. Besides copious irrigation and wound dressing, which of the following should be included in the treatment of this patient?
- **a.** Diphtheria, pertussis, tetanus toxoids (Tdap) and tetanus immunoglobulin (TIG)
- **b.** Rabies immunization
- **c.** Tetanus toxoid
- **d.** Tetanus toxoid and immunoglobulin
- **e.** B and D

Answer: a. Studies show that many people are inadequately immunized, especially patients older than 70 years old, immigrants, and people with no education beyond grade school. Patient immunization histories are often unreliable. Given the inability to predict which wounds are high risk, all wounds should be approached with suspicion. Inadequately immunized patients need a dose of Tdap and TIG. Because studies suggest that 10% to 40% of the population in the United States is inadequately immunized against diphtheria, diphtheria vaccination should be given along with tetanus toxoid. Many adults are not immunized against pertussis, and the incidence of disease has been rising since the 1980s. In 2005, a new acellular form of the pertussis vaccine became available and is recommended for all adults.

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Foreign Bodies

Jeffrey M. Goodloe and Jaron Soulek

KEY CONCEPTS

- If the history and mechanism of injury are compatible with ocular penetration or if a small puncture wound of the globe is noted, anteroposterior and lateral radiographs of the orbit are an appropriate initial step when the foreign body is thought to be radiopaque. Computed tomography (CT) and ultrasound are complementary diagnostic studies.
- Although most otic and nasal foreign bodies are amenable to emergency department (ED) removal, instrumentation of these anatomical areas must be undertaken with great care because removal attempts can cause more injury than the foreign body itself.
- Most airway foreign bodies are seen in pediatric patients and may not be visible on plain films. A normal radiograph does not rule out an aspirated foreign body.
- The patient with critical airway obstruction and impending or actual respiratory arrest requires one of three options: (1) forced expulsion of the foreign body; (2) direct laryngoscopy with attempted manual removal with Magill forceps; or (3) cricothyroidotomy to bypass an obstruction, or intubation to push the foreign body distally into the right mainstem bronchus.
- Esophageal foreign bodies are typically found at one of the three constriction locations: (1) proximal esophagus at the level of the cricopharyngeal muscle and thoracic inlet—radiographically, the clavicular level; (2) midesophagus at the level of the aortic arch and carina; and (3) distal esophagus just proximal to the esophageal-gastric junction—radiographically, a level two to four vertebral bodies cephalad to the gastric bubble.
- Esophageal foreign bodies (e.g., coins) usually are oriented in the coronal plane, and airway objects usually are oriented in the sagittal plane.
- Unless caustic or sharp, foreign bodies in the stomach and bowel are increasingly managed with a conservative approach with watchful waiting and tracking of the object's progression through the gastrointestinal tract.
- In the perineal region, foreign body removal tends to be more difficult than anticipated by emergency clinicians and be physically and psychologically traumatic for patients. Consultation with appropriate specialists (e.g., urology or general surgery) is indicated.
- The most important determinant of successful soft tissue foreign body removal is an understanding of the object's precise location.

FOUNDATIONS

Patients often present to the emergency department (ED) with a complaint of a retained foreign body. The anatomical locations vary and determine the management, emergent removal, and need for subspecialty referral or surgical removal under general anesthesia. Patients may be forthright with a complaint of a foreign body, but in some cases, information may be withheld because of embarrassment.

Clinical Features

When people ingest or insert foreign bodies, often a brief history may be sufficient to establish the diagnosis, guide initial management decisions, and predict the process required for definitive removal. Those at higher risk of having a foreign body include neurologically impaired patients, edentulous individuals, patients with certain psychiatric diagnoses, incarcerated individuals, and individuals at the extremes of age. In these same groups, definitive history is often elusive, and the emergency clinician has to rely upon situational clues.

Depending on the location of the foreign body, the physical examination can provide direct or indirect evidence of the object. Specifics are described in the following sections, but there is a recurring theme, which is meticulous examination frequently establishes the correct diagnosis and suggests a successful extraction method.

Differential Diagnoses

Even when patients are fully cooperative, the diagnosis of a foreign body can be complicated by the fact that patients can be unaware of the object's presence. Although foreign body cases are usually not diagnostic dilemmas, the emergency clinician should keep in mind the possibility of foreign body mimics such as angioedema.

Diagnostic Testing

Plain radiography is classically the primary imaging modality that yields foreign body detection and characteristics of location, size, and number. Even when objects are not visualized, radiographs may show secondary changes (e.g., pulmonary air trapping) providing clues to foreign body presence.[1] To assist in the localization, two views—anteroposterior and lateral—are usually necessary. Metallic objects are usually easy to visualize on plain radiography. For non-metallic (e.g., organic) material with a density similar to that of human tissue, visualization requires alternative imaging, such as ultrasound, magnetic resonance imaging (MRI), or computed tomography (CT).[2,3]

Management

Extraction is indicated in most cases. A discussion with the patient (or appropriate surrogates) should outline the benefits and risks of the anticipated course for foreign body removal. Sometimes, a foreign body represents an immediate life threat, as is the case with an airway-obstructing foreign body, and the need for urgent extraction action takes precedence. Even without overt life threats, some foreign bodies require expeditious removal. For instance, illicit drug leakage can kill a body packer, an impacted button battery can cause fatal tissue perforation and hemorrhage, or an otic insect can cause intense pain and damage sensitive ear structures.[4-6] Foreign bodies may serve as a nidus for infection that is recurrent or refractory to antibiotic therapy; definitive

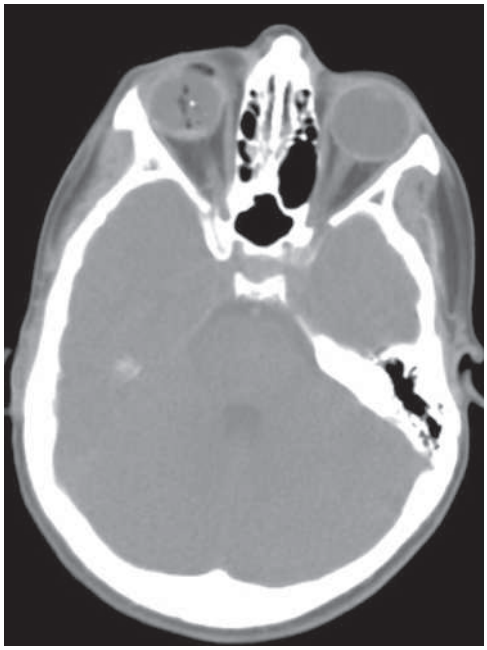

Fig. 51.1 Computed tomography (CT) scan shows right intraocular foreign body (BB pellet) in an intoxicated patient without known trauma history.

resolution only occurs with identification and removal. Specific recommendations for foreign body removal are presented in the following sections outlining management considerations by anatomic location.

Disposition

Most patients can be safely discharged home following uncomplicated foreign body removal. Retained foreign bodies may need surgical specialty follow-up. Depending on anatomic location and a patient's ability to cooperate, some retained foreign bodies require removal under sedation or surgical intervention under general anesthesia.

SPECIFIC DISORDERS

Eye

Foundations

The diagnosis usually is self-evident. Ocular trauma without proper eye protection is the most common history.[7] Foreign bodies are occasionally identified by abnormal ocular examination findings without a stated history of trauma. For example, the cause of reduced vision in an intoxicated patient may be a foreign body (Fig. 51.1). Early diagnosis, care, and follow-up minimize risks, such as endophthalmitis or sight-threatening siderosis bulbi.[7]

Clinical Features

Most patients report a foreign body sensation, even though they cannot see the foreign body. The patient may complain of frequent lacrimation and conjunctival injection. Foreign bodies that have created corneal injury and are no longer present may account for symptoms identical to those noted with a retained foreign body. Occasionally, patients with retained foreign bodies (e.g., malpositioned contact lenses) can present with recurrent conjunctivitis.

An important component of the history is whether radial keratotomy or similar ocular surgery has been performed. Historically, ophthalmologic procedures have been associated with the delayed diagnosis of foreign body entrapment. Although more current literature contains little or no mention of these procedures as foreign body risk factors, the potential for situational relevance (e.g., management of corneal foreign bodies) dictates a need for the emergency clinician to obtain a complete ocular surgical history.

The initial survey includes standard elements of the ED eye examination. Visual acuity at the time of presentation is a consistently reported predictor of ultimate visual outcome.[7] Slit-lamp examination allows the detection of a corneal foreign body by the shadow that it casts on the iris. The slit-lamp may also facilitate the identification of rust rings. Fluorescein can aid in detecting abraded corneal epithelium.

The inner aspects of both lids should be examined. The lower lid can be successfully exposed with gentle manual retraction outward and downward as the patient looks upward. The upper lid can be successfully exposed through eversion, instructing the patient to look downward while upward eyelash traction is applied. During this procedure, an applicator stick can be used to act as a fulcrum on the proximal edge of the tarsal plate. After location and removal of one foreign body, re-examination should occur to evaluate for other ocular foreign objects.

Differential Diagnoses

Selected differential diagnoses of ocular foreign bodies include corneal abrasions, conjunctivitis, iritis, glaucoma, allergic chemosis, and globe perforation.

Diagnostic Testing

If the history and mechanism of injury are compatible with ocular penetration by radiopaque material, or if a small wound of the globe is noted, anteroposterior and lateral radiography of the orbit is typically the initial step to evaluate for deeper penetration into the globe (see Fig. 51.1). However, given its advantages in depicting small ocular foreign bodies and complications such as globe rupture, CT is the best initial approach, especially when there is strong clinical suspicion of intraocular penetration. CT has the additional utility of imaging of the intracranial compartment, which is often indicated in cases in which ocular trauma has occurred.

When globe penetration is strongly suspected, fluorescein should be avoided because its application can obscure findings in subsequent physical examination. Fortunately, the incidence of intraocular perforation in the setting of low-velocity (non-explosive) exposures is very low. When perforation is judged unlikely and fluorescein is administered, the identification of rivulets of fluorescein tracking from a puncture (i.e., positive Seidel test) helps identify intraocular penetration.

Ultrasound is a useful adjunct to CT scanning in patients with foreign bodies that are difficult to localize. For patients in whom a foreign body is suspected despite negative ED evaluation, outpatient referral to ophthalmology is recommended because CT, ultrasound, and even MRI have all missed ocular foreign bodies in patients who subsequently developed complications. Given the paucity of reported case series and justifiable concerns about eye damage from the mobilization of ferromagnetic foreign objects, the use of MRI for ophthalmologic foreign body imaging remains controversial. When there is any chance of the presence of a metallic object in the eye, the emergency clinician should not order MRI without consulting both ophthalmology and radiology specialists.

Management

In nearly all cases, therapy is the removal of the ocular foreign body. If the object is located on the bulbar or palpebral conjunctiva (*not* the cornea), it often can be removed easily by sweeping the site with

a moist cotton-tipped applicator. For small corneal foreign bodies, after application of topical ocular anesthesia, it is often necessary to use an eye spur, small-gauge tuberculin syringe needle, or the edge of an IV catheter (needle removed) to move gently underneath one end of the object and flick or scoop it out. It is prudent for the emergency clinician to avoid significant corneal procedures in patients who have had corneal surgery, such as laser-assisted in situ keratomileusis (LASIK).

After the removal of a corneal foreign body that leaves no rust ring, treatment is essentially the same as for corneal abrasion. When there is a rust ring, ED management should be dictated by standing protocol (designed in collaboration with ophthalmologists) or referred to ophthalmology for removal.

Disposition

If attempts at foreign body removal are not indicated or are unsuccessful, the patient should be referred to ophthalmology for object removal within 24 to 48 hours. Ophthalmology referral should be initiated after removal of metallic foreign bodies because there may be subtle retained fragments or rust rings requiring removal.

Ear

Foundations

Otic foreign body extraction can prove problematic, and the difficulty is rarely diagnosis. Instead, with otic foreign bodies, the challenge usually lies in working in a sensitive anatomical region in a patient population that is often uncooperative.

Clinical Features

If the foreign body is an insect, the patient may report feeling motion or hearing buzzing. As compared to insect foreign bodies in the nose or throat, those in the ear are far more likely to be alive and moving.[4] Less specific complaints include itching, discharge, or otalgia. Similar secondary symptoms may be present when non-insect foreign bodies are within the ear canal. Nonspecific presentations are common in children, who can be fearful of reporting a foreign body. The child presents only when there are secondary problems (such as purulent discharge) from the affected ear.

If the ear canal foreign body erodes into the middle or inner ear, complications may range from malocclusion to eustachian tube dysfunction and serious infections (such as mastoiditis and meningitis). Although these situations are infrequent, recent literature outlines the risk entailed with impression material (e.g., silicone) used for indications, such as the molding of hearing aids.[8]

History should include home attempts at foreign body removal. Such efforts may have caused problems, such as ear canal trauma or tympanic membrane perforation.

The cylindrical external auditory canal has two anatomic points of narrowing (and, thus, foreign object lodging). The first point is near the inner end of the cartilaginous portion of the canal, and the second is at the point of bony narrowing called the *isthmus*.

Adequate lighting and an appropriately sized otoscope are essential to optimizing the visual search for otic foreign bodies. With any examination involving the external auditory canal, grasp the pinna of the ear and retract it in a posterosuperior direction to straighten the canal. This maneuver affords a more complete view of both the canal and the tympanic membrane.

If the tympanic membrane has been ruptured by the foreign object or by prior removal attempts, documentation should indicate the presence of rupture before ED attempts at foreign object removal. As in other body locations, the risk of multiple foreign objects warrants consideration.

Differential Diagnoses

The selected differential diagnoses of ear foreign bodies include otitis media, otitis externa, ear canal trauma, tympanic membrane perforation, Ménière's disease, and otologic tumors.

Diagnostic Testing

Diagnostic imaging is rarely required in otic foreign bodies. CT or MRI may be performed to characterize infectious or erosive sequelae.

Management

The treatment for otic foreign bodies is their removal, which should usually occur in the ED. Success rates for ED removal of ear canal foreign bodies vary with patient population and constituent foreign body types.

Even in a very young patient, the presence of a foreign body for more than 1 or 2 days does not constitute an independent risk factor for foreign body removal failure or complication. In the absence of clear contraindications (e.g., obvious tympanic membrane rupture), the emergency clinician should proceed with otic foreign body removal efforts, even in children with objects in the ear canal for a few days.

The patient should be informed about the extreme sensitivity of the auditory passage and the likely discomfort and potential for minor bleeding. Lidocaine instillation may aid in topical anesthesia; liquid 1% or 2% solution is preferred to gel preparations, which impair subsequent visualization.

Infrequently, foreign body removal requires local anesthesia of the external ear canal. The anesthesia instillation procedure may cause patient discomfort and iatrogenic injury if performed in an uncooperative patient. The procedure entails injecting all four quadrants of the canal with lidocaine via a tuberculin syringe inserted through an otic speculum. Given the complexity of local anesthesia to the canal, systemic procedural sedation and analgesia may be preferable.

When the ear canal is inhabited by an insect, it is important to kill or immobilize the creature to facilitate its removal. Any of a number of agents can be used to kill the insect. Topical anesthetics are recommended, and hydrogen peroxide should be avoided because of the risk of injury to the inner ear if there is tympanic membrane perforation. Efficacious formulations include lidocaine as a 10% spray or less concentrated liquid, 2% lidocaine gel, mineral oil with 2% or 4% lidocaine, and alcohol. Alternatively, a novel approach has been recently described in the literature in which a provider may remove a live insect by turning the lights off in the exam room, exert posterior and superior traction on the pinna while pulling forward on the tragus, and shine a bright light source into the ear canal.[9] The light may cause the insect to self-extricate as it tries to avoid illumination.

Several extrication methods may prove effective, and various instruments may be useful. With soft or irregularly shaped objects, it is often possible to grasp the foreign body with forceps (alligator forceps are usually best) and remove it either in one piece or in fragments. If the object cannot be grasped, it may be possible to remove it by passing a blunt-tipped right-angle hook or ear curette beyond the foreign body and gently coaxing it out. Alternatively, a balloon-tipped catheter can be passed distal to the object, with subsequent attempts to withdraw the (inflated) balloon, extracting the object. Any balloon-tipped catheter design may be used as long as its caliber is small enough (about 18-gauge or smaller) to allow comfortable introduction into the ear canal.

Irrigation techniques take advantage of the elliptic shape of the external ear canal. A stream of lukewarm or room-temperature water or saline should be directed at the foreign body's periphery via a 20-mL syringe and a 14- or 16-gauge catheter; this arrangement has been studied in the laboratory and demonstrated to generate pressures that are well below those required to perforate the tympanic membrane.

Irrigation should not be used if there is known history, clinical suspicion, or physical examination evidence of tympanic membrane perforation.

The removal of objects from the middle ear with cyanoacrylate adhesive-tipped swabs is not recommended and carries the risk of contaminating the ear canal with a substance that is difficult to remove and has been associated with ear canal and tympanic membrane injury. When cyanoacrylate has been instilled into the ear, acetone instillation is recommended to facilitate its safe removal.

The removal of otic foreign bodies must be undertaken with care and steadiness. Patient apprehension and sudden movements can risk untoward foreign body movement and avoidable damage to the ear canal.

Otic foreign body sequelae are usually not serious. There are sporadic reports usually related to missed diagnoses and persistent ear canal objects of serious complications ranging from chronic otitis to hearing loss, facial palsy, and deep-seated infections, such as mastoiditis.[8,10] The most common complications include external ear canal bleeding (10%), otitis externa, and (in about 2% of patients) tympanic membrane perforation.[11] Complications are more likely when the otic foreign body has been in place for prolonged periods, when patients are unable to be cooperative with removal attempts, and when practitioners are less experienced.[11]

After removal of the foreign body, the canal examination is repeated to ensure the lack of retained material and to evaluate otic anatomy. In cases in which the tympanic membrane is ruptured and the middle ear is at risk for infection, appropriate oral and topical antibiotics are recommended.

Disposition

If ED methods of removal are unsuccessful, the patient should be referred to an otolaryngologist within a week. More urgent referral is recommended for cases in which the tympanic membrane is ruptured or in cases where foreign body removal proves particularly traumatic (in such cases, the follow-up is aimed at assessing for external otitis).

Nose

Foundations

Although seen less frequently than otic foreign bodies, objects in the nasal passages are still commonly encountered in the ED. Compared with patients with otic foreign bodies, children with nasal foreign bodies tend to be younger, most commonly younger than 5 years old.[11]

ED removal is nearly always successful and with proper technique, serious sequelae are rare. Sedation with agents (such as ketamine) is often necessary. Although evidence is sparse, the overall risk of nasal foreign bodies' entering the bronchial tree is low. Cases of intranasal magnets or alkaline button batteries, which may cause electrical or chemical burns and tissue necrosis, are exceptions and could cause more serious complications.

Clinical Features

Most patients seek medical attention within 24 hours. Presentation delays are directly associated with secondary complications, such as infection.[11]

Patients seen in the ED with nasal foreign bodies usually have one of two histories. More commonly, the patient admits to having, or was seen placing, an intranasal object. The less common history is one of purulent or bloody discharge (usually unilaterally) suggestive of an unreported foreign object.[12] Unresolving rhinitis or sinusitis despite appropriate antibiotic therapy should raise suspicion for a nasal foreign body.

Preparing the patient for examination and subsequent removal attempts is advised. Because of the risks of iatrogenic movement of the foreign body further posteriorly, children may need to be restrained to permit the examination. The nasal mucosa is normally quite sensitive, and this sensitivity is increased by any infection or irritation. Examination is facilitated by the application of topical anesthesia and vasoconstrictors to the nasal mucosa. Examination should include both nares, with adequate lighting and visualization facilitated by the use of a nasal speculum. The presence of the foreign body and any secondary tissue damage should be documented. Necrosis of the nasal mucosa and septum may accompany button battery impaction.[13]

Differential Diagnoses

The select differential diagnoses of nasal foreign bodies include nasal polyps, septal hematomas, nasal tumors, infectious and allergic rhinitis, and anterior and posterior epistaxis.

Diagnostic Testing

Diagnostic imaging does not usually play a major role, although plain radiography is important when there is suspicion for a metallic foreign body, such as a button battery. When intrasinus foreign bodies are suspected, CT can be helpful. The potential risk of MRI for the detection of foreign bodies may become more relevant with an increasing frequency of foreign bodies related to magnetic jewelry (i.e., nose rings and studs).

Management

The emergency clinician is highly successful at the removal of nasal foreign bodies. Rarely, subspecialty consultation is required for removal in the operating room.[4] Foreign bodies that have eroded into the sinus space are an obvious exception to the rule of ED removal; admission for endoscopy in the operating room is recommended in such cases.

Occasionally, positive pressure applied to the patient's mouth by a parent or relative achieves rapid foreign body dislodgment while obviating the need for restraint, sedation, and other requirements attendant to more invasive removal techniques. The underlying principle is that a short burst of air blown into the mouth of a child with finger occlusion of the non-obstructed naris may force the foreign object out of the nose. Insufflation, preferably a mouth-to-mouth maneuver from a parent, can also be provided by a manual ventilation bag (with a pop-off valve to prevent pressure rising above 30 mm Hg) or a similar positive-pressure device.

Insufflation may be self-applied. Children can be instructed to take a deep breath and blow hard through their nose, as a parent closes the unaffected naris.

When insufflation is not warranted or is unsuccessful, ear, nose, and throat instruments and removal techniques may be required. Regardless of the method, the patient (usually a child) may benefit from some combination of restraint, sedation, and pretreatment with vasoconstrictive agents (e.g., nebulized racemic epinephrine) and anesthetic (e.g., benzocaine spray).[4] Adequate illumination is essential. Depending on the nature of the foreign object, necessary instruments include a blunt-tipped right-angle probe, suction catheter, and alligator forceps. The forceps are used when the foreign body is to be directly grasped, and the right-angle probe is used in an attempt to reach behind the foreign object and displace it forward.

Other useful instruments include Fogarty (vascular) and Foley catheters; commercially available "specialized balloon-tipped catheters can also be used. Magnets may be useful when the intranasal foreign body is metallic and appropriately constituted. In some cases, suction can be used to withdraw foreign bodies directly.

Cyanoacrylate-tipped swabs may be useful in certain circumstances, although there are obvious risks of inadvertent contact between the glue and nasal mucosa.

Antibiotics are rarely indicated for nasal foreign bodies. If the history or physical exam suggest prolonged impaction or obvious signs of infection, then oral antibiotic(s) to include coverage for streptococcal and staphylococcal species is appropriate.

Disposition

Patients with a simple foreign body presentation for whom the object is easily removed do not require special follow-up. In cases where the nasal foreign body was in place for an extended period of time, or in cases for which removal was difficult or traumatic, otolaryngology follow-up in 24 to 48 hours should occur to assess for post-extraction complications.

Airway

Foundations

Background and Importance. Children and the elderly are at high risk for foreign body aspiration. Most airway foreign body patients are younger than 9 years old, and there is a decline in incidence as mastication is facilitated by the emergence of permanent teeth. In adults, the elderly are at significant risk because of the presence of comorbidities such as neurological and dental conditions.

The most common airway foreign bodies vary with the particular case series, and the case report literature includes an array of respiratory tract objects ranging from dental appliances to turban pins and wall plugs.[14] In most series, food items are commonly aspirated as are medications.

Diagnostic delay is associated with increased complications in all patient age groups. One pediatric study identified a doubling of complication rates with presentations delayed beyond 48 hours. Patients with altered mental status from a variety of causes are at heightened risk for occult aspiration. Even in large-series reports of aspiration, the elusive nature of specific and reliable indicators of airway foreign body presence means that a concerning history should prompt a diligent foreign body search.

Anatomy and Pathophysiology. Foreign bodies can be located as proximally as the oropharynx, with retained objects having been found in the palatal and pharyngeal mucosal regions.[15] Foreign body impaction at the laryngeal or subglottic level often is caused by inappropriately executed attempts to finger sweep an oropharyngeal foreign body.

Airway foreign bodies that pass beyond the laryngeal inlet may cause complete obstruction. Foreign bodies passing beyond the carina are less likely to cause acute hypoxia because there is an unobstructed contralateral airway. Right-sided bronchial aspiration is the more common location because the carina is positioned right of the midtrachea in 40% of infants, and the proximal right bronchus is both wider and more steeply angled than the left.

Foreign objects can be bilateral, and the rule for airway foreign bodies mirrors that for other foreign bodies: when one object is identified, there should be a search for a second.

Clinical Features

Clinical presentation can range from chronic nonspecific respiratory complaints to acute airway obstruction.[16] In one series of ambulance-transported airway foreign body patients, 50% suffered cardiopulmonary arrest prior to ED arrival.[16] In most aspiration cases, foreign body presence can be suspected after a thorough history. Patients with airway foreign bodies may have noisy breathing, inspiratory stridor, rhonchi, vomiting, changes in voice, and hemoptysis.[12]

Some patients may give a history, known as the *penetration syndrome,* including a choking sensation accompanied by wheezing and coughing.[17] Coughing may not eject the foreign body completely but rather results in its impaction in the subglottic region. Therefore, coughing after suspected aspiration should prompt a search for a foreign body even if the symptoms improve.

In pediatric patients with suspected foreign body aspiration, the sudden onset of choking or intractable cough associated with wheezing and respiratory distress is present in more than 63% of cases. In addition to coughing and choking, stridor is frequent. The absence of early cough and choking is correlated with delayed diagnosis and chronic presentations (e.g., recurrent pneumonia).[12,18]

With the sudden onset of dyspnea and odynophagia, an impacted subglottic object may be present. If the object is known to be sharp and thin, the emergency clinician should suspect embedding between the vocal cords or in the subglottic region with resultant partial obstruction.

Other components of the history can help diagnose and characterize foreign bodies in patients with aspiration of nonfood objects. Many types of items may be aspirated by children who are exploring their environment. Another at-risk population comprises individuals who normally store small items in their mouths for quick access; examples of the latter include construction workers (nails) and seamstresses (pins).

Trauma patients with injured and loose teeth may have aspirated in the field or during emergency laryngoscopy for oral intubation. The incidence of airway aspiration of avulsed teeth or prosthetic dental appliances is low (0.5% of 1411 facial trauma patients), but both the initial trauma and subsequent airway management pose risks. In some cases of penetrating or blast trauma, the patient may be unaware of the potential for aspiration and not attribute symptoms to this entity. Patients aspirating objects that are long and thin (e.g., needles, hatpins) may have minimal or no symptoms other than a mild cough or chronic hemoptysis or odynophagia.

The child with respiratory difficulty after eating can represent a diagnostic dilemma. Children with stridor or other respiratory symptoms may have airway foreign body aspiration or esophageal bolus impaction with external compression of the trachea.[18] The pediatric trachea is soft, especially posteriorly, and may be compressed by a large esophageal body pressing anteriorly on the trachea. In addition, the trachea itself may be displaced anteriorly and kinked, causing a partial obstruction. Fever and localized infection may indicate bony aspiration (e.g., into the piriform fossa) that may occur when bone-containing foods are fed to very young children. Unfortunately, missed esophageal foreign bodies in children can result in wheezing and stridor from fistula formation; the result is long-term, yet mistaken, diagnosis and treatment for asthma.

The presentation of patients with a retained airway foreign object may include only infectious complications. A foreign object may cause retropharyngeal abscess. A patient with atypical or recurrent pneumonia may have pulmonary infection secondary to the persistence of a foreign object serving as a nidus of infection.

Physical findings depend on the degree of airway obstruction and the duration of the object's presence. Depending on the size and location of the foreign body, the examination may show a normal patient, one with cyanosis and respiratory arrest, or anything in between these two extremes.[19] There are some useful findings. Unilateral diminution of breath sounds, present in over a third of cases in one large pediatric series, may help diagnose an aspirated foreign body. Patients may be stridulous or hoarse with upper airway foreign objects, and intercostal or sternal retractions may be noted in patients with high-grade obstruction from tracheal foreign bodies. Hypoxemia may be present;

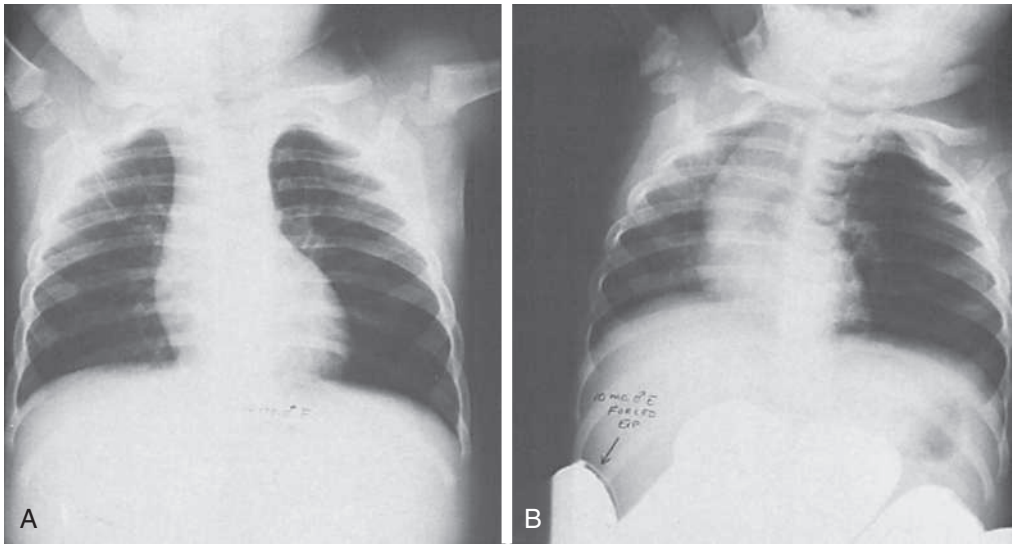

Fig. 51.2 (A) Normal inspiratory chest film in a child with a left mainstem bronchus foreign body. (B) Forced expiratory view shows expanded lung on the left with a shift of mediastinum to the uninvolved right side.

however, normoxia does not rule out a foreign body. Patients with secondary infection may have fever.

Oropharyngeal examination may reveal a foreign body posteriorly or donor sites of fractured teeth. The examination should include a search for fractured or missing dental prostheses. Oropharyngeal examination frequently can be augmented by indirect or direct laryngoscopy or nasopharyngoscopy, but these procedures should be performed only if the procedural stress does not pose an undue risk of airway compromise.

Coughing may result from local irritation caused by bronchial foreign bodies. Localized or apparently generalized wheezing is frequently auscultated in patients with lower respiratory tract foreign bodies.[1] Complete obstruction of a mainstem bronchus may be associated with absent ipsilateral breath sounds; however, breath sounds can be transmitted across the thorax, and the only physical abnormality may be asymmetric chest rise. Occasionally a foreign body acts as a one-way valve, allowing air into the lung during inspiration but permitting none to exit during expiration. The involved lung becomes hyperexpanded, and this finding may be detected as hyper-resonance to percussion.

Differential Diagnoses

The selected differential diagnoses of airway foreign bodies include anaphylactic reactions, acute pharyngitis, acute epiglottitis, retropharyngeal abscess, neck tumors, pulmonary carcinomas, pneumonia, bronchitis, bronchiolitis, and tuberculosis.

Diagnostic Testing

The main reason to characterize the type of airway foreign object is to determine the likelihood of radiopacity. Imaging decisions are informed by understanding whether a foreign body is likely to be radiopaque.

Most airway foreign bodies are not visible with plain films.[12,18] In 3,149 aspirated foreign body cases, 84% of airway foreign bodies consisted of organic material (usually nuts) difficult to see on x-rays.[20] Nearly half of fatal choking cases in children are a result of radiolucent food aspiration. In the stable patient, plain radiography of the neck and chest remains the mainstay of initial airway foreign body imaging. Air trapping may be visible when inspiratory and expiratory films are compared, but more recent literature casts doubt on the clinical necessity for adding expiratory views to plain radiography. Decubitus chest x-ray positioning does not offer significant benefits to standard radiographs of the chest.

A normal radiograph cannot rule out an aspirated foreign body in a patient with a suggestive history. Studies of series of patients who underwent endoscopy with confirmed foreign body aspiration demonstrate both low sensitivity and poor specificity.[12]

Specific findings on plain radiography are categorized as direct (i.e., identification of the foreign body itself) or indirect (e.g., hyperinflation). Radiographic findings are indirect in most cases, with hyperinflation and emphysema being far more common than pneumothorax.

If doubt exists as to the radiopacity of the suspected foreign body, and if the patient has brought a piece of the object, it may be tested for radiodensity by placing it over the shoulder while taking the radiographs. When subglottic foreign body impaction is suspected, plain soft tissue radiographs of the neck are the best initial step, provided that they are performed under the close supervision of a physician trained in airway management. Negative plain radiographs are not diagnostic, but clear identification of an airway foreign body can provide a rapid diagnosis, leading to admission for endoscopy.

Indirect or secondary signs, such as subglottic space narrowing (from an embedded foreign object), are an important aid in foreign body radiography. Air trapping and atelectasis are the most common early clues to airway foreign body presence, with bronchiectasis and pneumonia developing later. In air trapping, a comparison of inspiratory and expiratory films shows a flat, fixed diaphragm on the involved side and the heart and mediastinum shift to the uninvolved side during expiration (Fig. 51.2). In one pediatric series, air trapping was found in 90% of patients with lower airway foreign bodies, but subsequent years' clinical experiences confirm that the indirect signs of airway foreign body are easily missed on initial x-ray readings. If obstruction becomes complete, the involved lung becomes atelectatic and pneumonia can develop; patients with persistent atelectasis or pneumonia should have foreign objects considered as the explanation. An additional indirect radiographic sign of more proximal foreign bodies is prevertebral swelling or soft tissue emphysema seen on neck films.

In a stable patient when a foreign body is seen on the chest radiograph, but its airway-versus-esophageal location is in doubt, the anteroposterior orientation of the object may help (Fig. 51.3). Esophageal foreign bodies usually are oriented in the coronal plane, and airway objects, because they need to traverse the narrow vocal cord aperture,

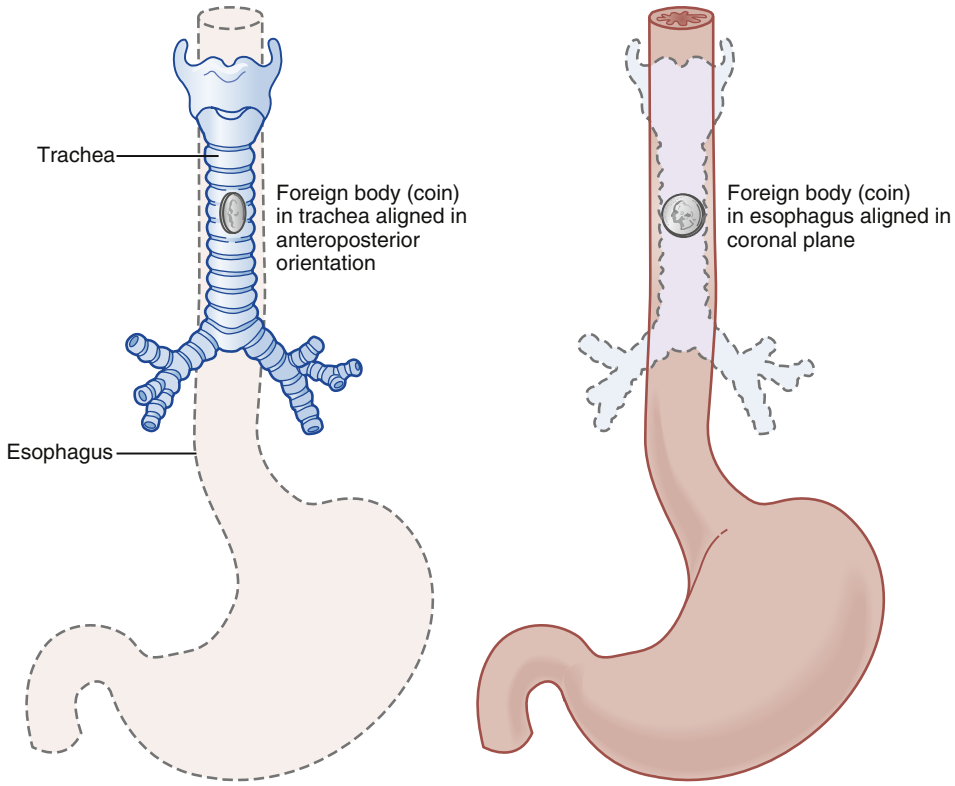

Fig. 51.3 Coronal Orientation of an Esophageal Foreign Object *(Left)* and Sagittal Orientation of a Tracheal Foreign Object *(Right).*

are oriented in the sagittal plane (Fig. 51.4). X-ray films also can provide useful information by showing whether the object is within or outside of the tracheal air column (Fig. 51.5).

Advanced imaging with CT or MRI is indicated when there is high clinical suspicion and plain radiography does not provide definitive results.[12] These imaging modalities usually require a more extended period outside of the ED, so patients must be sufficiently stable and able to lay supine to be considered for these studies.[19]

CT or MRI benefits include characterization of extra-airway anatomical complications, such as perforation or bleeding. Visualization of a foreign body by advanced imaging can also allow the elimination of diagnostic flexible bronchoscopy in favor of movement directly to therapeutic rigid bronchoscopy for foreign object retrieval.

In usual practice, CT tends to be more rapidly completed and widely accessible and therefore is the advanced imaging modality of choice for foreign body searches. The role of MRI tends to be in the diagnosis of foreign objects that are radiolucent (e.g., nuts with high-fat content).

CT (and less commonly, MRI) offers an additional utility—virtual bronchoscopy. Multidetector imaging provides a three-dimensional view of the tracheobronchial airway with proven utility in respiratory foreign body cases. CT virtual bronchoscopy has been shown to have very high (98%) positive predictive value in identifying tracheobronchial foreign bodies. CT virtual bronchoscopy should be considered when clinical suspicion is high and initial radiography is nondiagnostic.

Fluoroscopy was historically useful in airway foreign body evaluation. This modality has been supplanted by other advanced imaging techniques (e.g., CT, bronchoscopy).

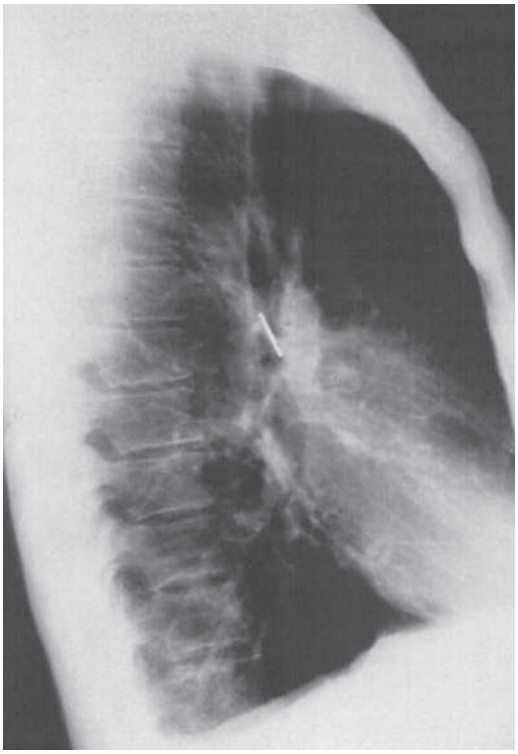

Fig. 51.4 Lateral X-Ray Study of a Chest Shows an Aspirated Coin in the Tracheal Air Column.

Management

Management of an airway tract foreign body is removal, which generally leads to rapid recovery of the patient. When the foreign object is distal to the oropharynx and the patient is minimally symptomatic, subspecialty consultation is the safest means for foreign body removal.

In rare cases, even oropharyngeal foreign bodies (e.g., small needles) may necessitate subspecialist consultation and operative removal. As a general rule, early consultation with an otolaryngologist to perform bronchoscopy in any patient with a suspected foreign body is key to

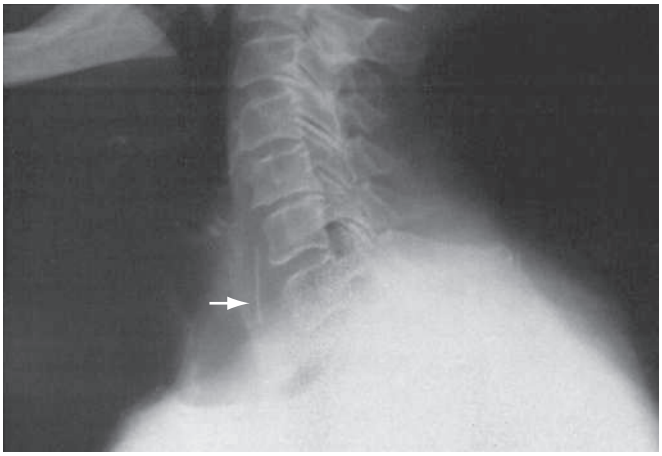

Fig. 51.5 Lateral X-Ray Study of a Neck Shows a Foreign Body (Chicken Bone) in the Esophageal Soft Tissue Shadow *(Arrow).*

reducing morbidity and mortality; the role of endoscopic management remains important given the limitations of other diagnostic methods.[20]

In a patient with critical airway obstruction and impending or actual respiratory arrest, the emergency clinician must act quickly to identify and remove the foreign body. There are generally three options: (1) attempt to extract the foreign body with maneuvers, (2) perform laryngoscopy or fiberoptic nasopharyngoscopy with attempts at removal under direct visualization, or (3) control the patient's airway. We recommend emergent consultation with other specialties who can assist in advanced airway management as resources and time allow (e.g., otolaryngology, anesthesiology, surgery).

Oropharyngeal foreign bodies may be removed with the use of pediatric or adult Magill forceps after visualizing the foreign body in the mouth. Blind finger sweeps should never be performed to remove a foreign body as it is more likely to push the foreign object deeper into the airway than result in retrieval.

The basic life support management of a choking infant (typically defined as up to 1 year of age) includes up to five back blows with the patient in a head-down position, followed by chest thrusts. In children, the Heimlich maneuver may be considered in the choking but conscious patient. In children who are unconscious, chest compressions are begun in cycles of five, and the oropharynx is visualized between cycles to see if the foreign body has been expelled into the mouth. If basic maneuvers fail to dislodge the foreign body allowing removal from the mouth, direct or video laryngoscopic visualization followed by removal of the object with Magill forceps should be performed. When a foreign body is not visualized on laryngoscopy but highly suspected, it is assumed to lie below the level of the vocal cords or is in the esophagus. If the patient is in extremis or is unresponsive and apneic, the emergency clinician should intubate the patient to establish an airway. Although it is indicated in these cases, the emergency clinician should be aware that intubation can change the position of the foreign body and the nature of the obstruction.

Intubation can force a tracheal foreign body distally into the right mainstem bronchus as long as the endotracheal tube tip is passed beyond the carina. If this is successful, the endotracheal tube can then be withdrawn back above the carina to facilitate left lung ventilation. It is important to have a stylet in place when advancing the tracheal tube as it will provide both the rigidity needed to move more stubborn foreign objects and a plug that will prevent the lumen of the tube from being occluded by softer objects. If the foreign body is in the esophagus, endotracheal intubation may provide necessary stenting of the trachea to keep the airway open.

In cases in which intubation fails because of the fixed positioning of a proximal foreign object (at or just above the vocal cords), surgical cricothyrotomy (needle cricothyrotomy in young children) is indicated. Cricothyrotomy may bypass such proximal obstruction and provide sufficient oxygenation to bridge the time gap to further definitive care by surgical subspecialists.

Patients who do not require immediate intubation or cricothyrotomy for complete airway obstruction may require airway management for other indications. These patients may have poor oxygenation, severe respiratory distress, and or hypoventilation. Especially in pediatric patients requiring bronchoscopy, the laryngeal mask airway may be an appropriate approach if ED airway management is necessary.

In noncritical situations, the only airway foreign objects generally amenable to emergency clinician removal are those in the oropharynx, which is best removed by forceps under direct or video laryngoscopic visualization performed after administration of topical anesthesia. Care should be taken when nonobstructing foreign objects appear to be impaled in the oropharynx because postremoval hemorrhage can occur. These should be removed in the operating room under general anesthesia. The removal of a laryngeal foreign object, even with general anesthesia, can be dangerous. Risks include hemorrhage, laryngeal trauma, and airway obstruction from the mobilized foreign object. Also, special care should be taken to prevent posterior displacement of oropharyngeal foreign objects or dropping of incompletely grasped proximal foreign bodies into the more distal airway.

The management decisions for endoscopic evaluation and treatment depend on the clinical presentation. When there is time-critical airway obstruction, rigid bronchoscopy is employed with flexible instrumentation used for diagnostic purposes in less acute patients.

At the other end of the clinical spectrum, patients may present with truly life-threatening cardiopulmonary distress because of airway foreign bodies. Future management strategies may increasingly take advantage of resources such as extracorporeal membrane oxygenation (ECMO), which has already appeared in published case series.[21]

Disposition

Pediatric data suggest that the performance of bronchoscopy within 24 hours of initial ED presentation reduces complications by half. Even after foreign body removal, sequelae may occur and can range from bleeding to infectious complications. Patients with a lower airway foreign body should be admitted for foreign body removal and observed for development of sequelae with post-discharge follow-up within a few days of removal of the foreign body.

Gastrointestinal Tract

Foundations

Most cases of gastrointestinal foreign bodies occur in pediatric patients, but adults are also at risk particularly if they are edentulous or if there are psychiatric conditions. Higher risk is present in cases in which chemical or electrical mucosal injury is likely (e.g., button battery or magnet ingestions). Perforation occurs in approximately 3% of cases and most frequently involves the esophagus or the ileocecal region. The duration of foreign body impaction and contour sharpness of the foreign body have been identified as the two major risk factors for complication development.[22]

Pharynx and Esophagus

Clinical Features

Foreign bodies lodged in the pharynx and esophagus are usually a sharp object (e.g., fishbone) that is impaled in the wall of the pharynx, hypopharynx, or esophagus or a larger bolus, usually a coin or food, that cannot pass beyond the anatomic points of esophageal constriction. In

pediatric patients, coins are the most common culprit, comprising well over half of ingested foreign bodies.

Esophageal constriction locations, where foreign objects tend to lodge, are (1) the proximal esophagus at the level of the cricopharyngeus muscle and thoracic inlet or, radiographically, the clavicular level; (2) the mid esophagus at the level of the aortic arch and carina; and (3) the distal esophagus just proximal to the esophagogastric junction or, radiographically, a level two to four vertebral bodies cephalad to the gastric bubble. In pediatric patients, as many as 90% of esophageal foreign bodies are impacted at the cricopharyngeal level. Foreign bodies may lodge at any level of the esophagus (or remainder of the gastrointestinal tract) with abnormal anatomy.

The complication rate for esophageal foreign body ingestion depends on the nature of the foreign body, the presence of impaction, and the duration of impaction. Overall, complications are rare, but there are important exceptions for perforating foreign bodies or those (e.g., button batteries) that mediate chemical damage. Complications become more likely with increasing impaction time and include esophageal erosion or perforation, tracheal compression, mediastinitis, esophagus-to-airway or esophagus-to-vascular fistulae, spondylodiskitis, extraluminal migration, abscess development, and formation of strictures or false esophageal diverticula.

In addition to coins, other common objects impacting the esophagus include but are not limited to food, toys, bones, batteries, wood, and glass. Esophageal rupture is a particular risk from the button (disk) battery. These batteries cause pathologic changes through pressure, electrical current, leakage of corrosives, or heavy metal poisoning. The identification of button batteries has both prognostic and therapeutic ramifications. Esophageal button battery impaction is considered an indication for prompt endoscopic intervention and removal. Although not as likely as button batteries or sharp foreign bodies to cause esophageal rupture, practically any ingested foreign body (e.g., meat) can cause rupture if patients vomit repeatedly after impaction.

Children usually are brought to the ED within 6 hours of foreign object ingestion. The most frequent presenting symptoms are dysphagia, drooling, retching, vomiting, and, occasionally, respiratory distress from extrinsic tracheal compression.[12] Pain, usually odynophagia, may be the major complaint. Anorexia, wheezing, or chest or neck pain also may be present.

Patients may complain that they can feel the object in the throat or chest, are unable to pass it, and are often able to localize the foreign body accurately. This presentation is particularly common if the foreign object is lodged in the upper esophagus. Drooling is consistent with high-grade obstruction.

Patients with suspected esophageal foreign body impaction rarely have complaints of shortness of breath or air hunger. When these findings are present, the emergency clinician should suspect a large esophageal foreign body impinging anteriorly and compressing the trachea. Infants and children may experience coughing, choking, croup-like symptoms, or significant respiratory compromise from foreign bodies lodged in the upper esophagus.

Patients may manifest late sequelae. Foreign bodies serving as a nidus for infection can result in fever. Signs of mediastinitis indicate esophageal perforation. Perforation of the esophagus with erosion into the vasculature or pulmonary tree can result in presentations ranging from hemoptysis to pulmonary abscess or life-threatening hemorrhage.

The history should include any known esophageal anatomic abnormality or prior instrumentation. A patient with a history of esophageal stenting should be considered to have stent migration when the history is dysphagia. Migration typically occurs within the first week of placement.

Examination begins with a careful inspection of the pharynx and hypopharynx. This search may reveal the foreign body or identify an oropharyngeal mucosal scratch that can cause foreign body symptoms even in the absence of an impacted object. Oropharyngeal examination also may provide indirect clues; for example, a missing dental plate on examination should lead the emergency clinician to suspect this item as a possible gastrointestinal tract foreign object. The base of the tongue, vallecula, supraglottic area, epiglottis, and piriform sinus should be examined. Topical anesthesia facilitates the examination. If adequate visualization is not obtained with the indirect laryngoscopy mirror, fiberoptic nasopharyngoscopy or direct laryngoscopy may be performed.

Subcutaneous emphysema found by neck palpation indicates probable esophageal perforation.

Differential Diagnoses

The selected differential diagnoses pharyngeal and esophageal foreign bodies include acute pharyngitis, acute epiglottitis, retropharyngeal abscess, esophagitis, strictures, esophageal webs, and oral cancers. When the history is unclear, the emergency clinician should consider an ingested foreign body in the differential diagnosis of atypical chest pain, wheezing, stridor, or signs of respiratory distress.

Diagnostic Testing

The fact that most foreign bodies (e.g., coins) are radiopaque accounts for reports that radiography contributes to diagnosis and management in most cases of esophageal impaction. The initial step is a posteroanterior and lateral chest radiograph and lateral cervical spine x-ray study using a soft tissue technique. The primary utility of plain radiography lies in the detection of radiopaque objects, with indirect findings (e.g., soft tissue swelling) more likely of utility in cases where there are chronic foreign bodies with complications.

Overall, the sensitivity of plain radiography for the detection of esophageal foreign bodies depends on the nature of the foreign body. In patients who are transferred to the ED from an outlying hospital, repeat radiography may be useful to assess whether the foreign object has passed into the stomach in the interval since prior films (Fig. 51.6). Additionally, cases have been described in which high-voltage radiographs can show visible markings on coins, thereby helping to differentiate from a disk battery.[23]

Esophageal foreign objects usually align themselves in the coronal plane and are posterior to the tracheal air column on lateral view. Coins in the esophagus lie in the coronal position in virtually all cases because the opening into the esophagus is much wider in this orientation (see Fig. 51.3).

Certain common foreign bodies are not radiopaque. Fish and chicken bones are frequently ingested, are difficult to visualize directly or radiographically, and often scratch the esophageal mucosa. Although some studies suggest that technique variation improves fish bone detection, plain x-ray examination remains insufficiently sensitive as a means to rule out these foreign bodies, and CT is recommended when initial imaging is negative.

When plain films fail to visualize foreign bodies and suspicion remains high, one option is contrast esophagography, which can be useful with radiopaque and sometimes with radiolucent foreign bodies. If perforation is not a concern, barium may be used as the contrast medium because it provides higher-quality images. If an esophageal leak is suspected, a water-soluble contrast solution should be used. When initial contrast films are not definitive, patients may be asked to swallow a contrast-soaked cotton ball, which may localize the foreign body by lodging proximal to the object.

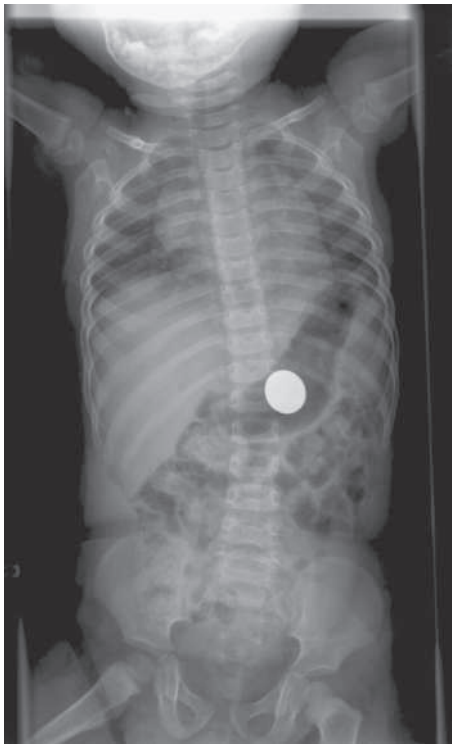

Fig. 51.6 Radiograph of a Child After Ingestion of a Coin, Located in the Stomach.

Contrast studies, even performed with barium, have limitations when the suspected object is an impacted bone. Barium swallow yields better results but risks aspiration and coats the object and esophagus, reducing the effectiveness of subsequent endoscopy.

CT scans with coronal and sagittal reconstructions are useful in identifying foreign bodies or more completely characterizing objects that are only vaguely appreciated on plain films. For some suspected foreign bodies that tend to be radiolucent, CT may be the primary diagnostic modality because it can give information about foreign body size, type, location, and orientation with respect to other anatomic structures. CT also can assist with the identification of complications because it can assess extra-esophageal anatomy.

One interesting modality reported in the detection of metal foreign bodies is the handheld metal detector. This modality does not involve risk or ionizing radiation, has no complications, and is quite useful with reported sensitivity approaching 90%. Especially when results are positive and indicate a foreign body below the diaphragm, or when the metal detector is used to track foreign body progress (e.g., coin passage) over time, this modality can obviate the need for radiography.

Management

Pharyngeal foreign bodies visualized by direct or video laryngoscopy usually can be removed with forceps or a clamp. The emergency clinician should guard against the possibility of inducing trauma or airway obstruction during extraction attempts.

With an esophageal food bolus or coin, the emergency clinician may be able to provide definitive management. With sharp objects, displaced esophageal stents, or impacted button batteries, more invasive and specialty consultation is necessary. Treatment strategy depends on the nature of the foreign body, length of time the object has been lodged, and expertise of the clinicians managing the case. In addition, the patient's age and prior medical and surgical history may be relevant. The overall success rate for endoscopic (i.e., nonsurgical) removal of esophageal objects is very high.

When the esophageal impaction is food, pharmacologic maneuvers are the first basic strategy for foreign body management. These steps are appropriate only if the object is known to be an impacted food bolus. The first medication that may be administered in an attempt to move a distal esophageal food bolus into the stomach is intravenous glucagon (0.5 to 2 mg), although its efficacy in causing the bolus to pass distally remains controversial. The drug appears to act by lowering the smooth muscle tone at the lower esophageal sphincter without inhibiting normal esophageal peristalsis and is effective in about one-third of cases. It should be noted that glucagon is less effective in esophageal eosinophilic infiltration, which the diagnosis may be increasingly reported by food-impaction patients presenting to the ED.[24]

Although it remains reasonable to try glucagon, the drug should be given slowly. If glucagon is given rapidly, there is theoretical risk that the induced vomiting could cause rupture of an obstructed esophagus.

Gas-forming agents have been historically used for the ED treatment of impacted esophageal food bolus, and this approach has poor evidentiary support. These medications also incur a known risk of mucosal injury and are not recommended.

Nitroglycerin, which had fallen out of favor for esophageal food bolus impaction management in the ED, has recently seen renewed interest. In one case report of steak bolus, a 0.4 mg nitroglycerin tablet was dissolved in 10 mL of water and swallowed and was effective in relieving obstruction.[25] The mechanism of nitroglycerin action is esophageal smooth muscle relaxation. A last approach, enzymatic degradation of an impacted meat bolus by use of the proteolytic enzyme papain, has fallen into disfavor because of the risks of esophageal perforation.

Early endoscopy is preferred when available and more effective as a first-line approach compared to medical therapies.[26] Endoscopic techniques can employ novel tools such as magnetic retrieval devices to aid in the removal of non-penetrating prone metallic foreign bodies (e.g., open safety pins).[27] Flexible endoscopy is the optimal approach for a variety of esophageal foreign bodies, including coins. The procedure does not require general anesthesia, can be performed in a sedated (nonintubated) patient, and may be diagnostic and therapeutic.[24]

The final strategy for foreign body removal, bougienage, involves pushing the foreign object into the stomach. The emergency clinician is generally not responsible for patient selection or actual performance of this procedure.

Expectant management, hoping for spontaneous foreign object passage into the stomach, is often successful. This approach is best suited for patients seen within 24 hours of ingestion who have a radiographically identified "safe" object (small and smooth-edged) in the distal esophagus.

Disposition

If a disk battery or magnetic object has been ingested, the location must be ascertained. If lodged in the esophagus, ED consultation for emergent removal by endoscopy is needed. If the object has passed distal to the esophagus, observation may be appropriate, but consultation with a gastroenterologist is suggested.

Regardless of the method used for esophageal foreign body therapy, there should be a follow-up evaluation of esophageal anatomy and patency after the removal of any esophageal object. Referral for such evaluation should be made by the emergency clinician.

Stomach and Bowel

Foundations

Foreign bodies that reach the stomach (Fig. 51.7) rarely cause major difficulties, although problems may occur, such as perforation and

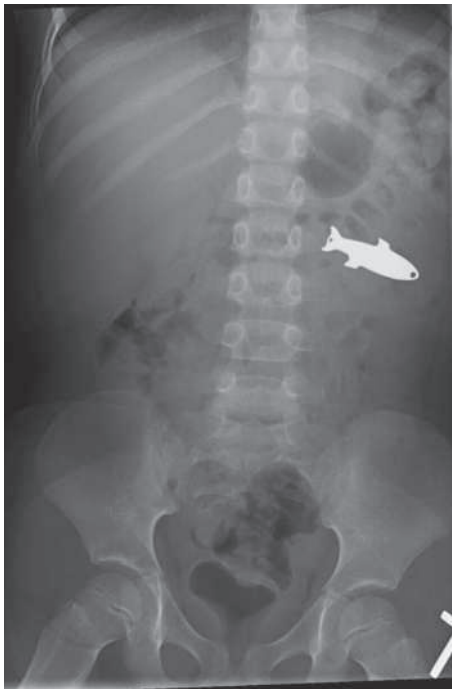

Fig. 51.7 Radiograph of a Child After Ingestion of a Fishing Lure Without Hooks.

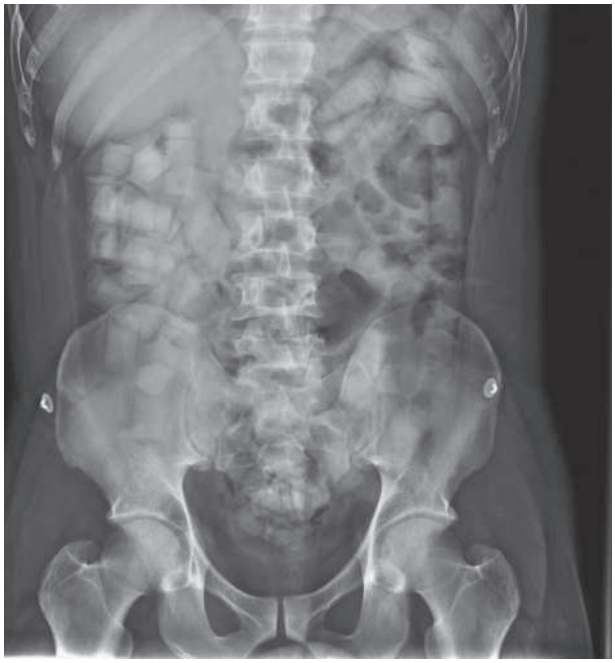

Fig. 51.8 Radiograph of a Patient After Body Packing. (Note the appearance of previously prepared drug packages.)

infection (e.g., after occult fish bone ingestion). Objects may still become impacted, most often at the gastric outlet or the ileocecal valve, although complications can arise at any point throughout the intestinal portion of the gastrointestinal tract. The increasing frequency of pediatric magnet ingestions contributes to an increasing complication rate seen with gastrointestinal foreign objects.[6]

Clinical Features

Symptoms of intraluminal objects range from none to vague abdominal pain to obstruction or perforation-associated peritonitis. Most patients have a specific history of ingested items.

The hiding of illicit drugs is a relatively frequent motivation for foreign body ingestion. Rupture of these drug-containing packages, especially when cocaine is involved, can result in rapid and lethal consequences.[28] Less often, such packages can cause bowel obstruction. Even when an obstruction is not present, vomiting may be reported. *Body packing,* which entails systematic gastrointestinal tract placement of previously prepared drug packages (Fig. 51.8), should be clinically differentiated from *body stuffing,* which denotes the hurried ingestion of hastily prepared packages in the face of imminent police presence. Because of the poorly organized wrapping of illicit drugs, body stuffers are more likely to experience toxicity and are less likely to have well-delineated findings on plain radiography. Drugs most often seen with body packing or body stuffing are cocaine and heroin.

Another important component of the history is medical implants in the gastrointestinal tract. Dental hardware and biliary stents are among the implants that can migrate and cause complications in the distal gastrointestinal tract.

Patients with gastrointestinal tract foreign bodies should be asked about history possibly related to bezoar presence. A habit of chewing hairs can result in trichobezoars, which infrequently extend from the stomach into the small intestine as a "tail" (Rapunzel syndrome). Phytobezoars (composed of vegetable matter) and lactobezoars (from milk curds) also have caused complications usually in the stomach. Other bezoars may be composed of infectious material (e.g., fungal bezoars) or inorganic substances (e.g., lithobezoars). Ingested toothpicks can lodge in the bowel wall, causing gastrointestinal complications and erosions or compression of nearby structures.

If the foreign body is a bezoar (a mass of indigestible food or nonfood material), there may be a palpable mass on abdominal examination. Physical findings may also include abdominal examination abnormalities typical of bowel obstruction or peritonitis.

Differential Diagnoses

The selected differential diagnoses of stomach and bowel foreign bodies include peptic ulcer disease, gastroesophageal reflux disease (GERD), gastric outlet obstruction, gastric tumors, bowel obstruction, intestinal polyps, and small and large bowel carcinomas.

Diagnostic Testing

Because most ingested foreign bodies are radiopaque, the initial imaging modality of plain radiography is often diagnostic (Fig. 51.9, see also Fig. 51.6).[29] Even when suspicion is low, radiography can identify foreign bodies as the explanation for symptoms. Two-view plain radiography has proved useful for situations ranging from coin ingestion to body packing (see Figs. 51.6 and 51.8).

The sensitivity of plain radiography varies widely depending on the nature of the foreign material. When plain films are nondiagnostic, CT is recommended. Contrast administration for some CT-delineated foreign bodies can identify the objects and assess for complications, such as perforation.

In the setting of body packing or body stuffing, oral contrast may confound identification of ingested packs so is most often done without oral contrast, but even this approach has been reported to have a sensitivity of well under 50% for either the detection or enumeration of packs.[30] Ultrasound is useful in drug packet cases in which plain radiography is nondiagnostic, when there is a need for an initial screening test, or when previously identified packets need to be tracked without ionizing radiation.[31] Negative ultrasound results are nondiagnostic.

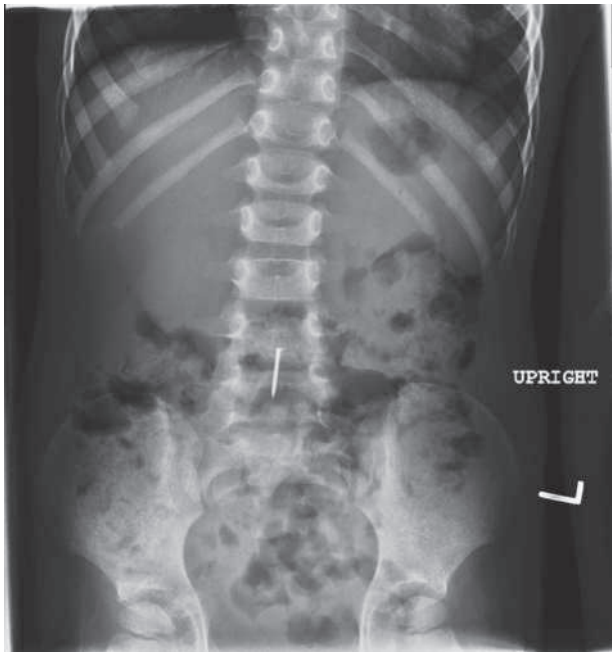

Fig. 51.9 Radiograph of a Child After Ingestion of a Nail (Which Ultimately Passed After Observation).

Management

The general rule for the management of gastric or intestinal foreign bodies is observation, with radiographic and stool follow-up to confirm passage. As is the case with esophageal impactions, early endoscopy is the preferred approach because of the modality's low risk and high efficacy.[32] However, for the routine cases that involve small, smooth-edged objects, most are expected to pass spontaneously if patients have normal anatomy.

Management decisions are based in part on the nature of the ingested object. Blunt objects can be expected to pass through the bowel with expulsion verifiable by stool collection and examination. If there is a particular concern, serial radiographs may be obtained after a week. Sharp objects (such as needles) are generally removed via endoscopy, but consultants (with whom all sharp gastrointestinal foreign bodies should be discussed) may decide to manage these cases expectantly. Early removal generally is required for objects wider than 2 cm because they do not pass the pylorus or longer than 5 to 6 cm because they do not clear the duodenal curvature. Overall, surgery is rarely required in intestinal foreign body cases, but there are cases (e.g., bowel obstruction) in which clinical circumstances prompt early operative intervention.

Button or disk battery ingestion has become increasingly common, garnering increased public awareness and media coverage. These batteries merit special considerations because of the possibility of the leakage of toxic substances and electrical mucosal burn.[12] The National Battery Ingestion Triage and Treatment Guideline advises oral honey administration followed plain radiography of the neck, esophagus, and abdomen. If an esophageal battery is identified, an aggressive endoscopic approach is recommended. However, batteries in the stomach and beyond can likely be monitored at home with a regular diet in the asymptomatic patient.[33]

When chosen, observation should be continued until (1) the object is found in the patient's stool; (2) the object becomes associated with bowel obstruction or perforation, necessitating immediate surgical intervention; or (3) the object shows no evidence of progression through the gastrointestinal tract on two radiographic examinations performed 24 hours apart, indicating impaction and the need for active removal.

In a body packer or body stuffer (see Chapters 135 and 144), regardless of law enforcement pressures, the emergency clinician should perform only interventions justified medically as reasonable steps to prevent injury from the ingested object or substance. If emergent drug package retrieval is medically unwarranted, the patient should be admitted for close observation for package passage or signs of toxicity. Monitoring drug metabolites in the urine may be helpful. Usually, the package passes through the gastrointestinal tract spontaneously. This passage can be facilitated with polyethylene glycol solution, laxatives, or both. Immediate removal of drug-containing packages should be considered if the patient develops intestinal obstruction or drug intoxication. Endoscopic removal of drug-containing packages is associated with theoretical risk because of package rupture and drug intoxication, but endoscopy remains a therapeutic mainstay in patients who are not passing ingested packets spontaneously.

Button batteries and magnets represent an additional group of foreign body types with specific management implications. Intact objects of this category that are ingested and pass into the stomach can be observed without the immediate removal necessary in cases of esophageal impaction. Administration of polyethylene glycol solution may speed distal movement. If the foreign body has not been passed after the first few clear-liquid stools, repeat radiography may identify objects in the rectum where they may be digitally evacuated. The emergency clinician should obtain early consultation (for endoscopy or surgery) when button batteries or magnets are encountered in the gastrointestinal tract because the complication rates with these objects are higher than for other foreign bodies. Available evidence is insufficient to confirm the usefulness of adjuvant medications (e.g., steroids, antireflux agents, prophylactic antibiotics) in cases of button battery ingestion.

Disposition

For button battery or magnet ingestions that are managed expectantly, repeat radiographs should be taken the next day to ensure movement of the object into the intestinal tract. X-rays should be repeated at least every 3 to 4 days thereafter to confirm continued distal movement. Management of other foreign bodies and bezoars depends on type and location. Infants with lactobezoars should be changed to elemental diets with close follow-up; most cases resolve without surgery.

Rectum

Foundations

Most anorectal foreign bodies result from retrograde introduction, typically as a result of sexual practices.[34] Prompt diagnosis is crucial because delay in definitive treatment is strongly associated with complications.

Clinical Features

Patients with anorectal foreign bodies are often hesitant to provide accurate histories. Studies have found that many patients with self-introduced anorectal foreign bodies do not freely admit to insertion but rather report anal pain or simply constipation. Other complaints include rectal pain, bleeding, or the inability to void when large objects impinge on the urethra.

It is possible for ingested food or objects (e.g., fish bones) to lodge in the rectum after passing through the proximal gastrointestinal tract. The duration for which the object has been in the anorectum has implications for mucosal failure and rupture.

Patients with anorectal perforation may have findings of peritonitis or abdominal tenderness. On digital rectal examination, the

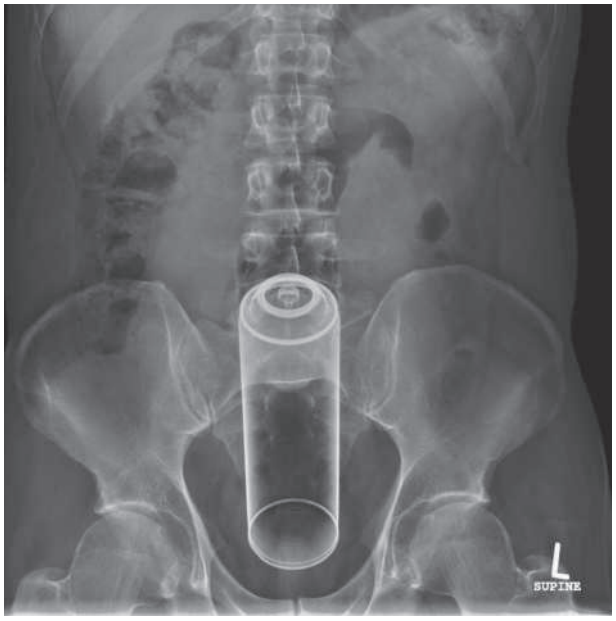

Fig. 51.10 Radiograph of a Patient Who Inserted an Aerosol Can Into the Rectum.

foreign body might be directly palpated; this is the method of diagnosis in a large number of cases. In the absence of direct foreign body palpation, digital rectal examination may reveal findings (e.g., bloody discharge, loose sphincter tone) that raise suspicion for anorectal foreign body.

When the digital rectal examination findings are negative or when better visualization is required, anoscopy is the next step. Although the anoscope's diameter limits the size of foreign bodies that may be extracted through the instrument, anoscopy affords an improved view of the object's nature and positioning. Rigid sigmoidoscopy may be performed, with special care taken to minimize pressure on possibly ischemic anorectal mucosa.

In many patients, especially patients in whom multiple examinations or removal attempts have been made, sedation and analgesia may be required to enable invasive examination techniques. When there is any doubt about the integrity of the anorectal mucosa, invasive examination is best done in the operating room with the use of general anesthesia.

Differential Diagnoses

The selected differential diagnoses of rectal foreign bodies include internal and external hemorrhoids, anal fissures, rectal and anal tumors, perirectal and anal abscess, and rectal vault stool impaction.

Diagnostic Testing

With rectal foreign bodies, the history usually renders imaging unnecessary unless there is a need to assess for complications, such as perforation or abscess. When diagnostic radiography is needed, plain films are recommended as the initial step and often demonstrate the foreign body (Fig. 51.10). An important secondary finding on plain films is free intra-abdominal air secondary to anorectal perforation. Foreign objects contained within the lower rectum or anal region may not show free air on plain radiography despite perforation because it resides below the peritoneal reflection. If the object is not visualized on plain x-ray studies, a contrast study can be performed, with care taken to minimize hydrostatic pressures on potentially compromised mucosa. Water-soluble contrast should be used if perforation is suspected. CT should be employed to provide defining detail when plain films are nondiagnostic or if complications (e.g., perforation) are suspected.

Management

With patience and judiciously administered procedural sedation and analgesia, the emergency clinician often can remove rectal foreign bodies. Surgical intervention may be necessary on occasion. Depending on the nature of the foreign body and the presence of damage or perforation of the rectal wall, transanal removal (with or without sedation and local anesthesia) is successful in roughly half of the patients. Some advocate early triage of patients for operating room removal if ED foreign body extraction carries undue risk of anal sphincter injury. The emergency clinician should not attempt to retrieve objects that pose a high risk for rectal injury (e.g., light bulbs).

Initial efforts at foreign body removal in the ED should begin with the examiner's digit. Small rectal objects occasionally can be hooked by the finger and withdrawn. The digits should be lubricated with lidocaine jelly, and gentle abdominal pressure may be applied posteriorly and inferiorly in an attempt to mobilize foreign objects distally.

When digital extraction fails, the emergency clinician should attempt to use an anoscope or small vaginal speculum to visualize the foreign body. Ring forceps are placed through the visualizing apparatus to grasp and remove small objects. Sometimes, the mucosa may become tightly adherent to the distal end of the foreign body, creating a vacuum that prevents object withdrawal. Passage of a Foley catheter beyond the foreign object (sometimes via a rigid sigmoidoscope) with proximal air inflation of the catheter balloon usually breaks the vacuum and permits retrieval. When the emergency clinician possesses the appropriate expertise and equipment or if consultants are available, the next step may be removal with a vacuum device that is well-suited for some foreign bodies or forceps; sigmoidoscopy may be a necessary adjunct to such an approach. As with other removal means, the physician should be careful to minimize the risk of anorectal perforation. Caution should be used when enemas or cathartics are administered to patients with known rectal foreign bodies, especially foreign bodies with sharp edges.

An assessment for rectal injury is indicated after removal of the foreign object. When foreign body retrieval has been simple and the patient does not show increased pain, tenderness, or rectal bleeding, further imaging or direct visual evaluation for rectal trauma is unnecessary. However, many cases have been described to result in complications before or during removal necessitating surgical intervention. Some clinicians have posited the benefits of post-retrieval imaging and colonoscopy to rule out inadvertent injury to the colorectum.[35] Appropriate antibiotics are indicated in all cases of suspected bowel wall perforation and peritonitis.

Disposition

If any signs or symptoms of pain or rectal bleeding are present, post-removal sigmoidoscopy may identify small abrasions requiring close follow-up with a gastrointestinal or colorectal specialist. In general, hospitalization is indicated if emergent surgery is needed or if a rectal laceration or perforation is found.

Genitourinary Tract

Foundations

The literature describes a wide variety of genitourinary tract foreign objects ranging from easily extracted tampons and condoms to penile rings removed with great difficulty. As is the case with other foreign body locations, the genitourinary tract has also been the site at which a variety of odd foreign objects have been reported (e.g., radio antennae, telephone wires, electric cables).

Clinical Features

The patient history has major value in the diagnosis of most genitourinary objects because these are often placed by the patient or the patient is aware of their placement (e.g., body piercing). However, in children who fear parental disapproval of foreign object placement, secondary signs are the more common presentation. They are brought to medical attention when parents note foul-smelling, purulent discharge or bleeding from the urethra, the vagina, or both. Another common presentation in infants is penile constriction caused by the inadvertent wrapping of hairs around the shaft, usually just proximal to the corona.

In children, intentional insertion is the more common cause as a way to explore anatomy or even stimulation. However, sexual abuse and psychiatric disorders should be assessed and explored. In adolescents and adults, metal objects are usually placed for autoerotic stimulation. Constricting bands may be placed proximal to the scrotum or more often on the penile shaft. These patients frequently have presentations delayed by 12 hours or more. The swelling that renders these constricting bands so difficult to remove also hinders the physical examination, emphasizing the need for an accurate history.

Occasionally, an object (e.g., tampon) is forgotten until it causes purulent discharge. Secondary symptoms also can bring foreign bodies to physicians' attention. The migration of both physician-placed intrauterine devices and patient-placed wires into the bladder has occurred with a diagnosis made because of symptoms of cystitis.

Genitourinary tract foreign bodies may be infectious. The term *bezoar,* traditionally considered to delineate indigestible material in the gastrointestinal tract, also has been used (along with *urobezoar*) to describe foreign material collections throughout the urinary tract.[36] One common urinary tract bezoar is the *Candida* bezoar. Fungal bezoars are usually, but not always, seen in immunosuppressed patients or in patients with diabetes mellitus, neurogenic bladder, antibiotic use, or an indwelling urinary catheter.

Patients of all ages require a careful, gentle examination because of frequent anxiety about the anatomic region being examined. In a pediatric patient, a nasal speculum may be used to help visualize a vaginal foreign body. Thorough vaginal examination is indicated in patients with symptoms of vaginitis, with the search directed for infectious agents and foreign bodies. A vaginal foreign body may be palpated during digital rectal examination.

In children and adults, the presence of blood or discharge at the urethral meatus or vagina should be noted. Patients with intraurethral foreign objects also may have perineal induration and a high incidence of associated infection, which may progress to sepsis. In males with penile shaft swelling, the emergency clinician should perform careful inspection for constricting objects. In any child (including an infant) with penile or labial swelling, a coronal constricting hair should be sought.

In patients with retained penile rings, especially in those cases presenting after some hours' delay, examination often will reveal a swollen penis with mottling, duskiness, and excoriation. The interruption of venous and lymphatic outflow results in increasing penile enlargement with risks of tissue damage. Damage is especially likely if there have been previous attempts—as is usually the case—by the patient at self-removal of the constricting device. Examination may reveal indirect evidence of other genitourinary objects as well (e.g., multiple abscesses from embedded metal objects).

Differential Diagnoses

The differential diagnoses of genital urinary tract foreign bodies include urethritis, urethral strictures, penile tumors, penile hematomas and priapism, vaginitis, cervicitis, Bartholin cysts, and retained products of conception.

Diagnostic Testing

Often, no imaging is necessary and the foreign body's contours and extent are evident on examination. Plain films may be used when urethral or bladder radiopaque foreign bodies are suspected. Plain radiography also has proved useful in unusual cases of embedded metallic objects that may be difficult to palpate because of regional swelling and tenderness on palpation.

Ultrasound is increasingly utilized to locate foreign bodies sensed in the genitourinary tract.[12,37,38] Ultrasound is also useful to investigate for hydronephrosis. Acoustic shadowing may not be seen depending on the nature of the foreign body; *Candida* bezoars lack acoustic shadowing. These bezoars and other genitourinary tract objects are generally identifiable on CT. Urethrocystography and cystourethroscopy may be useful tools for the urologist identifying and locating genitourinary tract foreign objects.

MRI is often the most sensitive in the detection of foreign bodies in the genitourinary tract because of its soft tissue differentiation capacity, but availability limits widespread use in most EDs including tertiary centers.[12]

Management

Vaginal foreign bodies usually are removed easily. If the object has been present for some time, there may be associated bacterial or fungal infection. This should be treated with appropriate antimicrobials (e.g., metronidazole 500 mg two times daily for a week for bacterial infection; fluconazole 150 mg in a single oral dose for candidal vaginitis).

In males or females, foreign bodies located just inside the urethral meatus usually can be grasped with a clamp and removed. After failure of one or two attempts at removal by the emergency clinician, the best course is early urology consultation. Objects located in the proximal urethra or bladder usually require cystoscopy for extrication. One exception is the *Candida* bezoar, which generally is treated with antifungal agents. Penile urethral foreign bodies may be associated with urinary retention and secondary infection; in these cases, early urology consultation for endoscopic intervention is necessary.

Constricting penile foreign bodies are removed as early as possible because progressive swelling makes removal more difficult. Sedation and analgesia may be necessary. Also, care should be taken when removing constricting objects with instruments such as ring cutters, because penile shaft lacerations may be easily caused because of the tautness of the thin underlying skin. Hair and string foreign bodies are removed relatively easily with forceps and scissors or scalpel.

Disposition

After penile ring removal and confirmation of ability to void, patients usually can be discharged with close follow-up. Consultation with a urological specialist should be obtained for patients with penile trauma. Vaginal tears secondary to foreign body insertion or extraction may require admission and emergent gynecological surgery.

Soft Tissues

Foundations

Soft tissue foreign bodies present unique diagnostic and management dilemmas. Foreign bodies may be present not only in patients with known wounds but also in patients with secondary symptoms who are unaware or uncertain of foreign body entry.

Clinical Features

All patients with wounds should be considered for soft tissue foreign body contamination. In straightforward cases, patients have symptoms such as pain or foreign body sensation and may specifically report a foreign body. Meticulous examination and use of diagnostic aids are

in order when the patient is certain of a foreign body not readily seen by the emergency clinician. Particularly for radiolucent objects, such as wood splinters, the history and patient sensation are used as a guide to exploration. In more difficult cases, patients have symptoms related to complications. Soft tissue infections, especially if recurrent, should suggest a foreign body serving as a nidus. A careful history in patients with soft tissue complaints should include a search for antecedent trauma, no matter how remote, that may have resulted in foreign body entry.

The diagnosis is frequently obvious on visual inspection or standard wound evaluation. For smaller objects, the use of magnification may be a significant aid in foreign body identification and removal. In addition to the location of the foreign body, the examination should address injuries collateral to the object's presence. Distal neurovascular function should be tested.

Differential Diagnoses

The selected differential diagnoses of soft tissue foreign bodies include skin infections, arthropod bites, lipomas, ganglion cysts, melanoma, and basal and squamous cell carcinomas.

Diagnostic Testing

Depending on the nature of the foreign object, anteroposterior and lateral radiographs of the involved area of the body can be diagnostic. Plain radiography has been shown to be more than 98% sensitive when the foreign body is metal or other radiopaque material, such as gravel. If silver nitrate sticks were used to achieve hemostasis before imaging, the deposited metal can be expected to appear on plain radiography.

One common foreign body is glass, which is usually radiopaque. The size of glass that can be seen on x-rays depends on composition and alignment, but most glass shards greater than 0.5 mm in cross-sectional diameter are visible on plain films. Not seen easily on plain radiographs are items such as vegetable material (e.g., wood) and plastic.

When plain radiographs are negative and suspicion for a foreign body remains, ultrasound or CT is the next step. Ultrasound is readily available in many EDs and has been the subject of intensive study, and the technique continues to evolve. With the use of a 10-MHz or 7.5-MHz probe for shallow depths and a 5-MHz probe for deeper searching, ultrasound is clearly useful when positive. The main imaging findings include hyperechoic foci (most common), posterior acoustic shadowing, and a halo sign indicating infection (fluid around the foreign body).

Overall, given the availability of ultrasound in the ED and the multiple case reports of its utility in foreign body localization and removal, it is reasonable to employ this technique with the understanding that a positive test result is much more useful than a negative one. In specific situations, ultrasound may even be the best available imaging modality. For example, B-scan ultrasound as performed by ophthalmologists is better than both CT and MRI for identifying wooden foreign bodies in the posterior segment of the eye.

Like organic matter, tiny glass foreign bodies can prove elusive during an initial diagnostic evaluation. Ultrasound can aid in detecting when traditional radiographs are nondiagnostic yet suspicion remains. In cases where glass remains hidden, despite magnification (Fig. 51.11), ultrasound performed in a water bath (Figs. 51.12 and 51.13) can help identify the foreign object. The use of ultrasound for foreign body detection and guided removal continues to evolve, although it seems to be most useful in objects embedded within subcutaneous soft tissues.

In addition to characterizing objects seen on plain films, CT can help identify items (e.g., plastic, wood) missed on plain radiographs. CT may also prove valuable in localizing small or deeply seated objects.

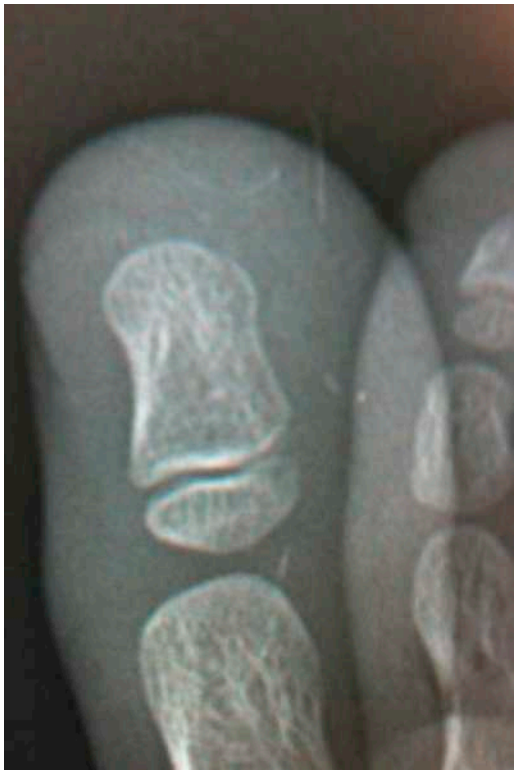

Fig. 51.11 Radiograph of a Finger With a Glass Foreign Body That Is Not Identifiable.

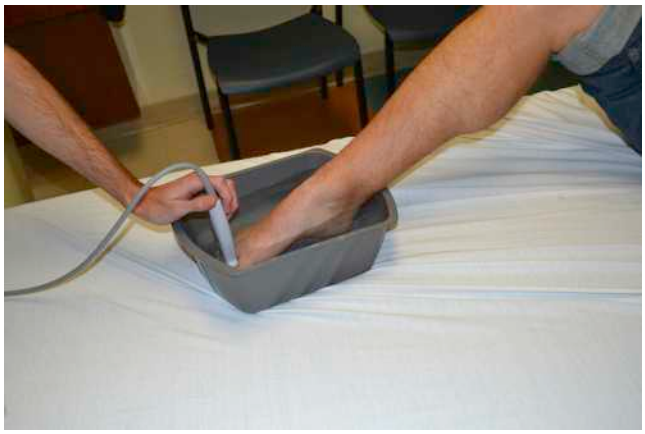

Fig. 51.12 Picture of the setup of a water bath to facilitate high-quality ultrasound images of soft tissue foreign body identification.

CT also is useful for identifying foreign body sequelae (e.g., abscess). For objects such as gravel, glass, and metals, MRI streaking can hamper image interpretation and CT is preferred.[39]

MRI can assist in identifying foreign body presence and complications in a variety of anatomical areas.[12,40-42] Soft tissue objects can induce a chronic inflammatory reaction and lytic or blastic osseous changes that allow MRI to locate foreign bodies. In other cases, MRI is less optimal. Wood, especially if rich in water (as is the case with chronic foreign bodies), is better imaged with CT than MRI.[39]

Management

The most important determinant of successful foreign body removal is knowledge of the object's precise location. Standard radiopaque markers can aid in wound localization. Fluoroscopy or ultrasound may

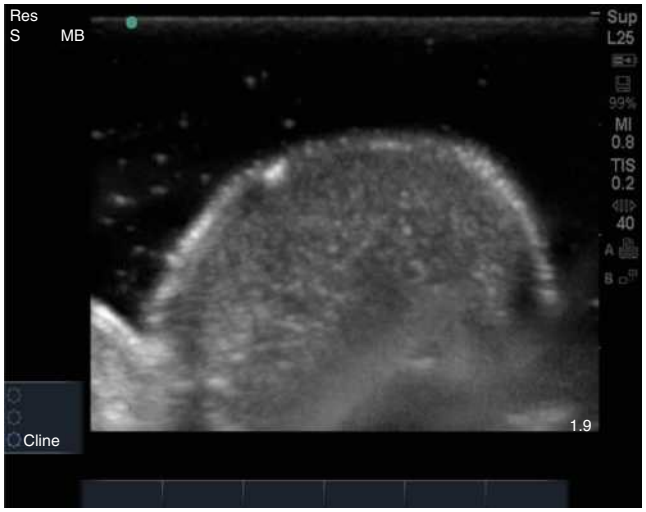

Fig. 51.13 Ultrasound Image of Glass Foreign Body Not Identifiable on a Radiograph. (Patient encounter case study archives. University of Oklahoma Department of Emergency Medicine. Lori J Whelan.)

allow simultaneous visualization and removal. When objects are not radiopaque, judicious probing of wounds with fine-gauge needles or forceps may allow tactile detection of the foreign body. For metallic foreign bodies, magnets may facilitate removal.

For removal of a foreign body, it may be necessary to extend the original wound or, if it is located away from the entrance site, to make a separate incision. The emergency clinician can perform limited wound extension or make separate incisions in regions where adequate analgesia and a relatively bloodless field can be achieved. Retrieval of foreign bodies, especially those linear in shape, is best achieved if the orientation of the foreign body is understood. The proximal end of the foreign body is grasped, and the object is gently removed following the plane of orientation.

In contrast to ingested fishbone foreign bodies, as previously discussed, an impaled fishhook in soft tissues is readily apparent without the aid of imaging. Many successful strategies for fishhook removal minimizing further soft tissue disruption have been described, including the "string-yank method" and the "advance and cut (the barb)" approaches. Both of these are demonstrated in videos on numerous online resources. Particularly, in the setting of "clean" fishhooks, routine prophylactic antibiotic use is not recommended.[43]

When inorganic objects are deeply embedded, it may be better to leave them in place than to create large surgical wounds to effect removal. Depending on foreign body location, operative intervention may be necessary for safe foreign body extraction. After foreign body removal, the emergency clinician should consider tetanus prophylaxis and empiric antibiotic treatment.

Disposition

Patients with suspected vascular or neurologic injuries require early evaluation by appropriate subspecialists. Soft tissue foreign bodies that are not suspected or undetected can lead to infectious sequelae. Therefore, careful discharge instructions and timely follow-up are crucial in these patients.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 51: QUESTIONS AND ANSWERS

1. A 33-year-old construction worker presents with left eye pain. On gross inspection, you note a watery discharge and moderate erythema. The patient tells you she was working with her coworker when she felt something hit her eye. She admits to not wearing protective goggles. Fluorescein examination of the eye reveals rivulets of dye tracking from a corneal defect. What is the next appropriate step in the patient's management?

a. Attempt ultrasound to find a foreign body
b. Check intraocular pressures
c. Obtain orbital computed tomography (CT) scan and consult ophthalmology
d. Obtain plain radiographs of the orbits
e. Topical antibiotics and ophthalmology follow-up in 24 hours

Answer: c. Rivulets of fluorescein tracking from the puncture (i.e., positive Seidel test) are helpful in identifying intraocular penetration. Ultrasound is, as always, operator dependent, and the pressure of the probe on the orbit may risk further injury to an open globe. Checking for intraocular pressures with an open globe is contraindicated. Compared with plain radiographs, CT delivers less radiation to the lens. Multiplanar reconstruction minimizes streak artifacts, affording better localization of intraorbital objects.

2. A 2-year-old presents with purulent drainage from the right naris and was brought to the ED by a parent concerned about sinusitis. The patient's vital signs are heart rate 110 beats/min, respiratory rate 15 breaths/min, and temperature 37.7°C. On physical examination, you see a small plastic ball in the naris surrounded by swelling and purulent discharge. What should be the next step?
   a. Attempt to displace the foreign body posteriorly
   b. Blow air into the contralateral naris to help dislodge the foreign body
   c. Consult the otolaryngologist for removal under anesthesia
   d. Make sure you have a right-angle probe, suction, and alligator forceps
   e. Treatment with topical vasodilators to facilitate removal

Answer: d. The emergency clinician can remove most nasal foreign bodies. Posterior movement of a nasal foreign body risks aspiration; objects should be removed anteriorly via suction or traction. In some circumstances, it may be prudent to place patients in lateral decubitus, perhaps with additional Trendelenburg positioning, to help prevent the aspiration of objects. Foreign bodies can sometimes be easily removed via positive pressure applied to the patient's mouth (not the contralateral naris, which should instead be clamped closed to increase pressure on the involved-side naris). Pretreatment with vasoconstrictive spray may improve chances of success. If positive-pressure techniques are not indicated or do not work, it is important to have necessary instruments close at hand to proceed with foreign body removal attempts. These instruments include a blunt-tipped right-angle probe (to maneuver posterior to the foreign body), suction equipment, and alligator forceps.

3. A 14-month-old girl presents in respiratory distress after eating a hot dog for lunch. Her mother states that she had stepped out of the kitchen, and when she came back, her daughter was sitting forward with noisy breathing and obvious distress. Which of the following management interventions is contraindicated?
   a. Back blows
   b. Blind finger sweep as the first step
   c. Chest thrusts
   d. Direct laryngoscopic visualization
   e. Intubate for respiratory distress

Answer: b. Blind finger sweeping has resulted in the conversion of partial to complete airway obstruction when objects are displaced into the subglottic space. For this reason, the technique has lost favor as an initial maneuver in pediatric and adult patients. It is recommended that up to five back blows be delivered (with the patient in a head-down position), followed by chest thrusts. Intubation or needle cricothyroidotomy may be performed if other maneuvers fail and circumstances dictate their need.

4. A 45-year-old man was at dinner when he had a choking episode. When he recovered, he experienced new-onset wheezing and presents with the following vital signs: blood pressure 140/90 mm Hg, heart rate 110 beats/min, respiratory rate 20 breaths/min, and arterial oxygen saturation (Sao_2) 92%. On chest radiograph, you see a flat, fixed diaphragm on the right with a mediastinal shift to the left and inadequate left-sided expansion. What is the next step in the management of this patient?
   a. Albuterol nebulizers and steroids intravenously
   b. Consult pulmonary for bronchoscopy
   c. CT scan of the chest with intravenous contrast
   d. Needle decompression of the left side
   e. Needle decompression of the right side

Answer: b. Air trapping and atelectasis are the most common early clues to airway foreign body presence, with bronchiectasis and bronchial stenosis developing later. In air trapping, a comparison of inspiratory and expiratory films shows a flat, fixed diaphragm on the involved side, and the heart and mediastinum shift to the uninvolved side during expiration. When the foreign object is distal to the oropharynx, however, subspecialty consultation is the safest and most expeditious means for foreign body removal. As a general rule, early bronchoscopy in any patient with a suspected foreign body is key to reducing morbidity and mortality.

5. A concerned father brings in his toddler, who has swallowed a button battery. Which of the following management strategies is most appropriate for this patient?
   a. Endoscopy is indicated if it is above the lower esophageal sphincter.
   b. Endoscopy is not indicated if it is found in the esophagus.
   c. Expectant management is appropriate.
   d. If it is in the small bowel, further surveillance is not indicated.

Answer: a. If a disk battery has been ingested, its location must be ascertained with immediate removal if it has lodged in the esophagus. If the button battery has passed distal to the esophagus, the patient can be observed, with follow-up radiography to confirm spontaneous passage through the gastrointestinal tract. Nifedipine is occasionally effective in managing food boluses but should not be used to manage nonorganic foreign bodies.

6. Which of the following is an initial management option for esophageal food bolus impactions in the ED?
   a. Glucagon
   b. Nifedipine
   c. Papain
   d. Sublingual nitroglycerine

Answer: a. Although none of the medical therapies are as good as endoscopy, Glucagon is likely more efficacious than nitroglycerin and nifedipine. Enzymatic degradation of an impacted meat bolus using the proteolytic enzyme papain, should not be performed because of risks of esophageal perforation. The gold standard intervention strategy for esophageal foreign body removal is endoscopy.

7. What do you expect to see on the chest radiograph of a child who has swallowed a coin?
   a. Foreign body anterior to tracheal air column
   b. Foreign body causing air trapping on the left side
   c. Visualized flat foreign body in the coronal plane
   d. Visualized round foreign body in the coronal plane
   e. Visualized round foreign body in the transverse plane

Answer: d. Esophageal foreign objects usually align themselves in the coronal plane and are posterior to the tracheal air column on lateral view. Coins in the esophagus lie in the coronal position in virtually all cases because the opening into the esophagus is much wider in this orientation.

52

Mammalian Bites

Wesley P. Eilbert

KEY CONCEPTS

- Mammalian bites require an evaluation for both trauma and their risk of infection.
- Cat and human bites are at higher risk for infection than dog bites.
- Most mammalian bite wound infections are polymicrobial. *Pasteurella* species are the most common pathogens in dog and cat bites.
- Preventing infection from mammalian bites relies more on vigilant cleaning, debridement, and irrigation than prophylactic antibiotics.
- Prophylactic antibiotics are most effective when started within 3 hours of the bite. The recommended duration of treatment is 5 days.
- Amoxicillin-clavulanate (Augmentin) is the prophylactic antibiotic of choice for dog, cat, and human bites.
- The decision to close mammalian bite wounds must weigh the benefit of improved cosmesis against the risk of wound infection.
- Given the risk of infection, mammalian bite wounds to the hand should not be closed primarily. Most facial bites can safely be closed if done so within 24 hours of the bite.
- Clenched-fist injuries or "fight bites" have high rates of damage to deep structures and infection.
- Mammalian bites to the hand should receive prophylactic antibiotics. Infected human bites to the hand are treated on an inpatient basis with intravenous antibiotics, operative debridement, and irrigation.

FOUNDATIONS

Background and Importance

It is estimated that 50% of individuals will sustain an animal bite during their lifetime, with more than 90% of these from a domestic animal.[1] Bite wounds account for 5% of all traumatic wounds evaluated in the emergency department and approximately 1% of all emergency department visits.[2] Dogs are responsible for more than 80% of animal bites in the United States, with cats accounting for 5% to 10%. Although few studies exist that have examined the incidence of wild mammalian bites, rodents are the most common offender in this group. Bites from other species include monkeys, ferrets, raccoons, foxes, bears, cougars, bats, livestock, and other wild mammals but comprise only a small percentage of reported bites.

Bites cause damage to skin and underlying structures including muscle, blood vessels, nerves, tendons, joint spaces, and bony structures. All bite wounds are contaminated with the oral flora of the biting animal and 10% to 20% of bite wounds become infected.[3] The potential for tetanus and rabies exposure must also be considered. Tetanus is discussed in Chapter 118 and rabies is covered in Chapter 119B.

DOG BITES

Foundations

Background and Importance

Of the nearly 4.5 million Americans bitten by dogs every year, approximately half are children.[4] Dog bites more often occur during summer months, with the dog being known to the victim in the majority of cases.[5] The arm and hand are most often bitten. Compared with adults, children are more likely to be bitten on the head and neck.[5] More than 30 dog bite fatalities occur in the United States each year, with American pit bull terriers responsible for the majority of these attacks.[6] Dog bites to the head and neck are of cosmetic concern and are at greater risk of life-threatening injury. The lips, cheek, and nose are the facial structures most likely to be bitten.[7] Young children are at greatest risk for mortality from a dog bite, with exsanguination after carotid trauma as the major cause of death. Craniofacial fractures and penetrating skull injuries have been reported in young children as a result of dog bites.[8,9]

Dog bite infection rates range from 1% to 30%, with hand bites at highest risk for infection.[1,10] Bites to the face and scalp are at lower risk for infection due to their rich blood supply. The type of wound appears to influence infection rates, with puncture wounds at higher risk for infection than superficial wounds, lacerations, or wounds limited to skin and soft tissue defects.[11] Cellulitis is the most common type of infection occurring after a dog bite, with tenosynovitis and septic joints more common after hand bites.[3,12]

Anatomy, Physiology, and Pathophysiology

Dog biting pressures exert forces estimated to be between 300 and 450 pounds per square inch, and dogs often shake the victim vigorously.[8] This causes a "hole and tear" effect resulting in complex lacerations and avulsions.

Clinical Features

Dog bite wounds may cause contusions or ecchymosis without a break in the skin, but more commonly are puncture wounds, lacerations, abrasions, and avulsions.[13] Most dog bite injuries are superficial, and the majority of patients are treated with medications, dressings, or suturing. Larger breeds cause more severe crush injuries due to the higher pressures exerted by their jaws and pose a greater risk of major organ or vessel injury than smaller breeds. Bites from pit bulls and dogs such as German shepherds used in law enforcement are at increased risk for associated orthopedic injuries when compared with other dog bites.[14]

Dog bites to the hand are often occlusive, with the crush injury component increasing the risk of infection. Hands are the most common

bite site to develop infection and long-term morbidity due to the number of bones and joints adjacent to the skin surface, small enclosed compartments and fascial planes, and small nerves that are present.[11] Tenosynovitis, septic arthritis, abscess formation, and traumatic digit amputation from dog bites have been reported.

Dog bite wound infections are usually polymicrobial, with an average of five bacterial isolates per wound culture. The responsible bacteria are a mixture of canine flora, environmental organisms, and the victim's skin flora. Approximately half of dog bite-related infections contain a mixture of aerobic and anaerobic bacteria, with anaerobes more likely to be present in abscesses and purulent wounds. *Pasteurella* species are the predominant organisms in infected dog bites, present in approximately 50% of cases. Other common anaerobic bacteria include *Fusobacterium, Bacteroides, Porphyromonas, Prevotella,* and *Propionibacterium* species. Common aerobic isolates from infected dog bites include streptococci, staphylococci, *Neisseria* species, *Corynebacterium* species, and *Moraxella* species.

Capnocytophaga canimorsus

C. canimorsus was first identified as a cause of systemic infection following dog bites. It is a slow-growing gram-negative rod found in the normal oral flora of both cats and dogs. *C. canimorsus* is a rare cause of systemic illness. Transmission is related to a bite in the majority of cases, although it has been documented from licks, scratches, and close animal contact. Most cases involve interaction with a dog, with only a small percentage occurring after contact with a cat.[15] In a small percentage of cases no animal source of infection is identified. The disease is more common in individuals over 50 years of age and affects men more than women. Approximately 50% of patients are immunocompromised by splenectomy, alcoholism, malignancy, or other condition.[15]

C. canimorsus may be associated with localized wound infection in a minority of cases but can cause systemic illness, sepsis, and disseminated intravascular coagulopathy (DIC) in immunocompromised individuals.[15–17] Symptoms of systemic illness typically begin within 10 days of the exposure with a mortality rate as high as 26%.[15]

Diagnostic Testing

Obtain radiographs if there is a likelihood of damage to underlying bones and joints. Bite penetration of joint capsules may be seen as air in the joint on plain radiographs. Scalp bites in children younger than 2 years old may require computed tomography (CT) imaging because intracranial penetration and injury may occur. Preemptive wound cultures sent from fresh bites are rarely of value and are generally not indicated.

C. canimorsus grows slowly and requires special media and growth conditions. In cases of sepsis without an obvious source following a dog or cat bite, *C. canimorsus* is a consideration and the laboratory should be notified to arrange for appropriate testing. Polymerase chain reaction (PCR) and detection of characteristic gene coding by molecular testing are the gold standard for detection of *C. canimorsus* infection.[17,18]

Differential Diagnoses

The differential diagnosis of dog bites includes bites from other domestic pets such as cats, and bites from wild canines including coyotes and wolves. The differential diagnosis for the patient with symptoms suggestive of *C. canimorsus* infection is extensive. Given its relative rarity and initial symptoms that are indistinguishable from other bacterial infections, *C. canimorsus* infections are likely to be misdiagnosed and treated as other more common infections initially. A history that includes mammalian bites may be the only diagnostic clue. Consider *Neisseria meningitidis* or *Streptococcus pneumoniae* in patients presenting with fever, headache, hypotension, and evidence of DIC.

Management

Management hinges on several historical elements that can be divided into three main parts: (1) the circumstances of the attack, (2) information about the biting animal, and (3) information about the bite victim. The timing of the bite should be determined. Untreated bites more than 6 hours old are at higher risk for infectious complications. When possible, it should be determined whether the bite was provoked or unprovoked, because this may influence the decision to administer rabies prophylaxis. Information about the biting animal should include ownership and immunization status, as well as the animal's current location. With dog bites, inquiring about the specific breed is important, because certain breeds (e.g., German shepherds, Rottweilers, and pit bulls) deliver more severe bites with a higher risk of damage to underlying structures. Information about the bite victim should include their medical history, current medications, and tetanus status.

The general principles of wound management apply to bite wound patients (see Chapter 50). Adequate analgesia is vital to allow for appropriate examination and wound care. Washing the wound with soap and water, ideally with gentle scrubbing with a fine pore sponge to minimize additional tissue trauma, should be performed. A virucidal agent such as povidone-iodine solution should be used on the skin surface surrounding the bite but can be toxic to exposed tissue beneath the skin. Irrigate wounds under pressure with saline or sterile water as this is the most effective method of reducing bacterial counts (see Chapter 50).

Examination of bite wounds should ideally take place in a bloodless field to allow for adequate visualization of deep structures. A blood pressure cuff inflated above the patient's systolic pressure for up to 20 minutes can be used for this purpose. Examine the wound for damage to tendons and possible joint capsule violations. Remove any retained teeth fragments. It is often helpful to extend the margins of puncture wounds in high-risk areas (e.g., overlying joints and tendons) to allow for better visualization. A neurovascular assessment is required in all extremity bites.

Primary closure of mammalian bites is controversial. Ultimately, the benefit of improved cosmesis of primary closure must be weighed against the increased risk of infection. Studies have found no significant difference in rates of infection between repaired dog bite wounds and those left open. Carefully selected dog bites closed primarily have an overall infection rate of 5%, similar to sutured non-bite wounds. When closing bite wounds, use subcutaneous sutures cautiously as the presence of additional foreign material increases the risk of infection. To optimize cosmetic outcome in those wounds deemed too high risk for infection for primary closure, loosely approximating the wound edges using adhesive strips may be performed. Another option is to reevaluate the wound in 48 to 72 hours and if no evidence of infection is present, perform a delayed primary closure.

Given the available data, we recommend the following guidelines summarized in Table 52.1. Bite wounds of the face and scalp from any species that are less than 6 hours old may be sutured after appropriate wound preparation. It is probably safe to suture most other uncomplicated dog bite wounds, although bites of the hands and feet are at high risk for infection and should rarely be sutured. Puncture wounds, wounds more than 12 hours old, and wounds infected at presentation should not be sutured.

Prophylactic antibiotics. The value of prophylactic antibiotics given for mammalian bites is secondary to the value of vigilant cleaning, debridement, and irrigation. Antibiotics should ideally be given within 3 hours of the bite to achieve a prophylactic effect

TABLE 52.1 Recommendations for Bite Wound Closure and Prophylactic Antibiotics

Species	Suturing	Prophylactic Antibiotics
Dogs, coyotes, wolves	The majority except hands and feet	Hand and foot wounds High-risk wounds[a]
Cat	Face only	All wounds extending through the epidermis
Human	Face only (up to 24 h after the bite)	All wounds extending through the epidermis
Monkey	Face only (up to 24 h after the bite)	All wounds extending through the epidermis
Rodent	All (but rarely needed)	No
Ferret, pig, horse, camel, bear, big cats	Face only	All wounds extending through the epidermis

[a]High-risk wounds: Deep puncture wounds, crush injury or damage to deep structures, delayed presentation (>6 h), wounds closed primarily, and high-risk patients (see Table 52.2).

TABLE 52.2 Risk Factors for Bite Wound Infections

Factor	High Risk	Low Risk
Species	Cat (domestic and wild) Human Monkey Pig Camel Bear	Dog (excluding hands and feet) Rodent
Location of wound	Hand (especially clenched-fist injuries [CFIs]) Foot	Face Scalp
Wound type	Puncture Crush injury or damage to deep structures Presence of devitalized tissue Delayed presentation (more than 6 hours) Closed primarily	Laceration Superficial
Patient characteristics	Age over 50 Diabetes Renal failure Liver disease Alcoholism Immune disorder Malnutrition Use of corticosteroids or other immunosuppressive medications Peripheral vascular disease Chronic edema of the bitten area	

and then continued for 5 days. Although there are mixed data on the efficacy of prophylactic antibiotics used for dog bites, they have consistently shown value when used in the treatment of hand bites. Ultimately, the use of prophylactic antibiotics should take into account the characteristics of the bite and the individual bitten. We advise giving prophylactic antibiotics to immune compromised patients and to those with dog bite wounds of the hand, foot, and other high-risk wounds (Table 52.2).

No clinical trials have reliably demonstrated the superiority of one antibiotic regimen over another, but a regimen that covers *Pasteurella* species is recommended. We recommend amoxicillin-clavulanate (Augmentin) for dog bite prophylaxis. Treatment failure of *Pasteurella* infections caused by dog and cat bites using monotherapy with erythromycin, clindamycin, penicillinase-resistant penicillins, and first-generation cephalosporins has been described. A fluoroquinolone, such as ciprofloxacin or moxifloxacin, or clindamycin combined with trimethoprim-sulfamethoxazole may be used in penicillin-allergic patients (Table 52.3). Empirical antibiotic options for those patients with established dog bite wound infections are similar to those used for prophylaxis. Parenteral antibiotic options for those patients requiring admission are listed in Table 52.3.

Although no clinical trials have evaluated antibiotic selection in *C. canimorsus* infections, most strains are susceptible to fluoroquinolones, macrolides, carbapenems, clindamycin, and third generation cephalosporins. *C. canimorsus* is typically resistant to trimethoprim-sulfamethoxazole and aminoglycosides.[15–17]

Disposition

Indications for admission after a dog bite are listed in Box 52.1. Reevaluate patients deemed appropriate for outpatient therapy in 24 to 48 hours.

CAT BITES

Foundations

Background and Importance

Females are twice as likely as males to be the victim of a cat bite, with a peak age incidence in the third decade. Approximately two thirds of cat bites are to the upper extremity, typically involving the hand and fingers.[19] More than 80% of cat bites are caused by a domestic pet that is owned by the victim. Most cat bites are perceived as minor injuries and often go unreported, with the majority of patients seeking medical care only after complications have developed.[19,20]

Anatomy, Physiology, and Pathophysiology

Cats possess narrow, sharp teeth that easily penetrate skin and the underlying soft tissues like a needle. This mechanism creates a small break in the skin that heals quickly, trapping the bacteria in the deeper structures, often resulting in invasive infection. Because of this, cat bites are more likely to become infected than dog bites, with a reported infection rate of more than 50%.[2] This increased rate of infection is multifactorial: the higher incidence of puncture wounds, a higher proportion of hand bites, an older average age of cat bite victims, and a higher likelihood of *Pasteurella* species in the feline flora.

Clinical Features

The majority of infected cat bites (90%) will manifest symptoms within 48 hours of the bite.[20] Although not as likely to cause damage by crush injury as dog bites, cat bites are more likely to cause infection in deeper structures, including osteomyelitis and soft tissue abscesses. Of infected cat bite wounds, over 50% present with cellulitis, 20% with tenosynovitis, 15% with osteomyelitis or septic arthritis, and 10% with an abscess. Mixed aerobic and anaerobic bacteria infections are the rule, being present in more than 60% of cases. One-third of cat bite infections are due to only aerobic bacteria. *Pasteurella* species are the most common pathogens, present in 70% to 75% of infected cat bites, with *Bacteroides, Fusobacterium, Porphyromonas, Propionibacterium*, and *Prevotella*

TABLE 52.3 Suggested Antibiotic Regimens for Bite Wound Prophylaxis and Inpatient Treatment of Establishing Infections

Species	Prophylaxis	Inpatient Treatment of Established Infection
Dog and cat	Amoxicillin/clavulanate (Augmentin) 875/125 mg q12h for 5 days Ciprofloxacin, 500 mg BID for 7 to 14 days Moxifloxacin 400 mg po qd for 7 to 14 days Clindamycin 300 mg QID plus trimethoprim- sulfamethoxazole 160/800 mg BID for 7 to 14 days	Ampicillin/sulbactam (Unasyn) 1.5 g (1 g ampicillin plus 0.5 g sulbactam) to 3 g (2 g ampicillin plus 1 g sulbactam) q6h for 7–14 days Piperacillin/tazobactam (Zosyn) 3.375 g (3 g piperacillin and 0.375 g tazobactam) IV QID for 7–14 days Imipenem 500 mg IV q6h or 1 g IV q8h Meropenem 500 mg IV q8h Ertapenem 1 g/day IV/IM Ciprofloxacin or moxifloxacin plus metronidazole (Flagyl) 250–500 mg QID Ciprofloxacin 600 mg BID or 400 mg IV BID or moxifloxacin 400 mg PO/IV qd plus clindamycin 300 mg QID
Human and monkey	Amoxicillin-clavulanate 875/125 mg q12h Ciprofloxacin 500 mg twice per day or trimethoprim sulfamethoxazole 160/800 mg BID plus clindamycin 300 mg QID	Ampicillin/sulbactam) 1.5 g (1 g ampicillin plus 0.5 g sulbactam) to 3 g (2 g ampicillin plus 1 g sulbactam) q6h Imipenem 500 mg IV q6h or 1 g IV q8h Meropenem 500 mg IV q8h Ertapenem 1 g/day IV/IM Ceftriaxone 1 g IVPB BID plus metronidazole 250 to 500 mg TID Clindamycin 600 mg QID plus ciprofloxacin 500 mg BID or 400 mg IV BID
Rodent	Not recommended	
Ferret, pig, horse, bear, big cats, coyotes, wolves	Same as for cats and dogs	Same as for cats and dogs
Camel	Ciprofloxacin 500 mg q12h Ofloxacin 400 mg po q12h	Same as for cats and dogs

BOX 52.1 Indications for Admission After an Animal Bite

Structural

Injury to deep structures (bones, joints, tendons, arteries, or nerves)
Injuries requiring reconstructive surgery
Injuries requiring general anesthesia for appropriate wound care

Infectious

Rapidly spreading cellulitis
Significant lymphangitis or lymphadenitis
Evidence of sepsis
Infection in patients at high risk for complications (see Table 52.2)
Infections involving bones, joints, tendons
Infection with failed outpatient therapy

species also common anaerobic pathogens. Common aerobes include streptococci, staphylococci, and *Moraxella* species.

Pasteurella multocida

An important factor contributing to the risk of infection after cat bites is the presence of *P. multocida,* a highly virulent, facultative anaerobic, gram-negative rod found in the normal oral flora of up to 90% of cats. It can also be found in the oral flora of the majority of dogs and several wild animals. Most human infections with *P. multocida* are caused by cat bites or scratches, dog bites, or open wounds that have been licked by a dog or cat.

The most common initial manifestation of *P. multocida* infection is a rapidly spreading cellulitis, usually presenting within 12 to 24 hours of the exposure. A low-grade fever and serosanguineous or purulent discharge at the site may be present. Regional lymphadenopathy is often present. Local infectious complications may occur if left untreated, most commonly subcutaneous abscesses and tenosynovitis. Less often, septic arthritis and osteomyelitis may occur. Systemic illnesses from *P. multocida* including bacteremia, pneumonia, endocarditis, and meningitis have been described in small case series. Up to 11% of patients with *Pasteurella* infections will have an associated bacteremia, which carries with it a 30% mortality.[21] The majority of patients with systemic illness have an underlying medical condition, with liver disease, malignancy, and chronic obstructive pulmonary disease being the most frequent comorbidities.

Differential Diagnoses

P. multocida cellulitis has a more rapid onset and progression than cellulitis caused by more common pathogens. Cat scratch disease, an infection caused by *Bartonella henselae* associated with a cat scratch or bite, presents with regional lymphadenopathy often with an associated fever. A preceding cat or dog bite may be the only initial clue that indicates *P. multocida* as the cause of a systemic illness, such as bacteremia.

Diagnostic Testing

As with dog bites, obtain radiographs if there is a likelihood of a retained tooth or damage to underlying bones and joints. Bite penetration of joint capsules may be seen as air in the joint on plain radiographs. Preemptive wound cultures sent from fresh bites are rarely of any value and are generally not indicated.

Management

P. multocida is not susceptible to many oral antibiotics typically given for skin and soft tissue infections, including dicloxacillin, cephalexin, vancomycin, and clindamycin. In most cases, treatment with

amoxicillin-clavulanate or a second- or third-generation cephalosporin is effective. Fluoroquinolones, azithromycin, doxycycline, and trimethoprim sulfamethoxazole may be used in penicillin allergic patients.[22]

Similar to dog bites, studies have demonstrated varying efficacy of prophylactic antibiotics used for cat bites, though they show consistent value when used in the treatment of hand bites. We advise giving prophylactic antibiotics to all cat bites that penetrate through the epidermis regardless of location, given the high-risk nature of these bites for infection. With similar common pathogens as dog bites, we recommend amoxicillin-clavulanate (Augmentin) for prophylaxis. (see Table 52.3)

Disposition

Indications for admission after an animal bite are listed in Box 52.1. Those patients deemed appropriate for outpatient therapy should be reevaluated in 24 to 48 hours.

OTHER MAMMALS

Monkeys

Foundations

Background and Importance. Monkey bites are rare in the United States, occurring primarily in laboratory workers involved in biomedical research. Monkey bites are more prevalent in other countries including India, where they are the second most commonly reported animal bite. Although not well studied, monkey bites are reported to have a high rate of infection and complications, such as osteomyelitis. The major concern with monkey bites is B virus (*herpesvirus simiae, herpesvirus B,* and *monkey B virus*) exposure. It causes disease in monkeys resembling that of human herpes viruses. Asymptomatic infected monkeys harbor the virus in their conjunctiva, buccal mucosa, and genital areas and may shed the virus, being more likely to do so when ill, under stress, immunocompromised, or breeding. The incidence of seropositivity for the B virus is widely variable in non-captive monkeys depending on geographic location and ranges from 80% to 100% in monkeys of the genus *Macaca* (macaques) used for biomedical research.[23] More than 50 cases of B virus infection in humans have been reported, with the vast majority of these in the United States being in laboratory workers.

Anatomy, physiology, and pathophysiology. Monkey bites may present with superficial bruising, puncture marks, or small, grouped lacerations. Superficial and deep soft tissue infections can occur. In contrast to human bites, preventing viral transmission and infection is the primary concern. In addition to bites, transmission via scratches, exposure to animal tissue, and needlestick injuries has been reported.

Clinical features. B virus disease in humans has an incubation period as short as 2 days but more commonly 2 to 5 weeks. The disease often starts with vesicular lesions at the site of exposure with concomitant influenza-like symptoms. Paresthesias and muscle weakness may develop and proceed proximally along the affected extremity. Signs of central nervous system dysfunction develop when the virus enters the brain and include altered mental status, cranial nerve palsies, ataxia, coma, and respiratory failure. Left untreated, the mortality rate of disseminated B virus infection is estimated to be 80%.

Differential diagnoses. The bacteria isolated from infected monkey bites is similar to that from infected human bites, with a predominance of *Staphylococcus* and *Streptococcus* species, *Eikenella corrodens,* and anaerobes including *Bacteroides* and *Fusobacterium* species.

Management. While under studied, monkey bites may also have a risk profile for bacterial infection similar to human bites and should receive similar antibiotic prophylaxis (see Table 52.3). The most critical period for the prevention of B virus infection is during the first few minutes after exposure. Scrub the area with soap, detergent, or iodine for 15 minutes and then irrigate with running water for 15 to 20 minutes.[24] Prophylaxis of high-risk bites with acyclovir or valacyclovir is recommended (Box 52.2). Postexposure prophylaxis is started as soon as possible after the bite and continues for 5 days. Treatment of suspected disseminated B virus infection involves intravenous acyclovir or ganciclovir.[24]

Disposition. The majority of monkey bites can be safely discharged home from the emergency department (ED) following local wound care, appropriate antibiotics, and reassurance of outpatient follow-up. Those patients with systemic symptoms of infection may require admission for intravenous antibiotics and antivirals if active B virus infection is suspected.

BOX 52.2 Prophylaxis for Monkey Virus B Exposure

Prophylaxis Recommended

Skin exposure (with loss of skin integrity) or mucosal exposure to a high-risk source (e.g., a macaque that is ill, immunocompromised, known to be shedding virus, or has lesions compatible with B virus disease)
Inadequately cleaned skin exposure (with loss of skin integrity) or mucosal exposure
Deep puncture bite
Laceration of the head, neck, or torso
Needlestick associated with tissue or fluid from the nervous system, eyelids, mucosa, or lesions suspicious for B virus
Puncture or laceration after exposure to objects contaminated with either fluid from monkey oral, genital, or nervous system tissues or any object known to be contaminated with B virus
A post cleaning wound culture is positive for B virus

Prophylaxis Considered

Laceration (with loss of skin integrity) that has been adequately cleaned
Needlestick involving blood from an ill or immunocompromised macaque
Puncture or laceration occurring after exposure to either objects contaminated with body fluid (other than from a lesion) or potentially infected cell culture
Drug of first choice: Valacyclovir 1 g by mouth every 8 hours for 14 days
Alternative drug: Acyclovir 800 mg by mouth five times/day for 14 days

Prophylaxis Not Recommended

Skin exposure in which the skin remains intact
Exposure associated with non-macaque species of nonhuman primates

Rodents

Foundations

Background and importance. As with monkey bites, laboratory workers are frequent rodent bite victims because these animals are commonly used in biomedical research. Rat bites tend to occur in urban areas and in patients of lower socioeconomic class. Children are more commonly bitten than adults. The majority of these bites occur while the victim is asleep, with the face and upper extremity most often affected. Squirrel bites occur almost exclusively on the hand, typically occurring while trying to feed the animal or rescue it from a dangerous situation.

Anatomy, physiology, and pathophysiology. Infection and systemic illness, "rat bite fever," is caused by bacteria from *Streptobacillus moniliformis* or *Spirillum minus*, organisms found in the nasopharyngeal flora of healthy rats.

Clinical features. Disease transmission may occur by bite, scratch, handling a rat, or by ingestion of contaminated food or water. The

incubation period ranges from 3 days to over three weeks but typically is less than 7 days. At disease onset, fever is prominent, followed by a migratory polyarthralgia. Nearly 75% of patients develop a maculopapular, petechial, or purpuric rash most prominent on the extensor surfaces of the extremities. Endocarditis is a well described complication. Untreated, rat bite fever has a mortality of approximately 10%.

Differential diagnoses

A number of systemic diseases may be transmitted by rodent bites including rat bite fever, leptospirosis, tularemia, sporotrichosis, murine typhus, and plague.

Management. Rodent bites are at low risk for local wound infection and require only appropriate wound care without antibiotic prophylaxis. Intravenous penicillin is the treatment of choice for proven or highly suspected cases of rat bite fever, with erythromycin, clindamycin, and tetracycline reasonable options for penicillin allergic patients.[25,26] Antibiotic prophylaxis for rat bite fever is not recommended given the low risk for infection after a bite.

Disposition. The vast majority of rodent bites can be safely discharged home from the ED with wound care instructions and outpatient follow-up.

UNCOMMON ANIMAL BITES

Ferrets

Ferrets *(Mustela putorius furo)* are in the same family as badgers, weasels, and skunks, and became increasingly popular as pets in the United States in the 1980s. Initially bred to hunt rats and rabbits, ferrets are known for their exceptionally vicious attacks, with infants and small children often their victims. Unlike dog and cat bites, many ferret bites are unprovoked and will frequently require plastic and reconstructive surgery. Although the oral flora of ferrets is known to contain *Pasteurella* and other aerobic species and *Fusobacterium* and other anaerobic species, no known reports exist that have examined the rates of infection or common pathogens with ferret bites.

DOMESTIC HERBIVORES

Sheep, Cattle, and Pigs

Bites from sheep and cattle are rarely reported in the medical literature. Pig bites are a common occupational hazard among farmers and slaughterhouse workers and most commonly occur on the posterior aspect of the thigh. Males have large, sharp tusks capable of deep penetrating wounds with injury to deeper structures. Bites from females are less damaging. Pig bite infections are often polymicrobial with organisms including *Pasteurella*, *Actinobacillus*, and *Streptococcus* species.[27] Methicillin-resistant *Staphylococcus aureus* has been a reported in infected pig bites.

Horses

Of all horse-related injuries, most are from falls and less than 5% are due to bites. Horse bite injuries range from superficial trauma to amputation of digits. Horse bite infections are typically polymicrobial with a mix of aerobic and anaerobic species. *Actinobacillus* species are gram-negative coccobacilli that are part of the normal oral flora of horses and common pathogens in infected bites. Other common pathogens include *Staphylococcus* and *Streptococcus* species, *Pasteurella* species, as well as *Fusobacterium* and *Bacteroides* species.[28]

Camels

Camel bites are commonly reported in Africa, the Middle East, and the Indian subcontinent. Camel bites are more likely to occur during their mating season from December through March, with most injuries occurring to the upper extremities. Camels have a strong jaw and canine teeth that may reach up to 4 cm in length, which result in serious injury and even death from their bites. Approximately one half of upper extremity bites have associated fractures, and bites to the head have been associated with skull fractures and intracranial injury.[29] Camel bites have a high infection rate with *Staphylococcus*, *Aeromonas*, *Pasteurella*, and *Actinobacillus* species as common pathogens.[30]

WILD ANIMALS

Bears

Bear attacks are rare in North America, occurring at a rate of 10 or fewer per year, with most occurring in the western United States and Canada. The incidence of bear attacks on humans appears to be increasing due to increasing human encroachment into bear habitat for living and recreation.[31] Bear attacks are more common in the warm weather months and have a reported mortality rate of up to 20%. Grizzly bears are responsible for an inordinate number of serious or fatal injuries caused by bears in North America. Most bear bites are to the head and face, often with underlying bony injury.[32] Although not well studied, bear bites have a reported infection rate of 44%. *Staphylococcus*, *Streptococcus*, and *Serratia* species are reported pathogens in bear bite infections.

Wild Cats

Most attacks by big cats (lions, tigers, leopards, jaguars, cougars, and cheetahs) now occur in captive conditions, such as zoos, animal farms, and circuses, although attacks in the wild are still reported with some frequency in Asia and Africa. Large cats target the neck of their prey, causing damage to the spine, trachea, and large blood vessels. As humans encroach on their natural habitat, cougars are responsible for the majority of big cat attacks in North America, with children and hikers the most common victims and the nape of the neck the most commonly bitten area. Common injuries from these attacks include neck lacerations and internal carotid, tracheal, and cervical spine injuries.[33] As is true for domestic cats, *Pasteurella multocida* is the most frequently isolated pathogen in wounds from large cats. Hyenas, which are related to cats, have been known to attack humans in the wild in Africa and Asia. Unlike the big cats, hyenas tend to bite the central face of their victims, causing damage to the cheeks, nose, and lips.

Coyotes and Wolves

Bites from coyotes and wolves are similar to dog bites and should be treated as such.

Management

As with all bite-related lacerations, location, type of wound, time to treatment, and patient factors all contribute to the risk of wound infection. Delay in wound cleaning and suboptimal cleaning techniques will increase infection risk. The animal responsible for the bite also is a factor in determining the risk of infection (see Table 52.2). Although there are no studies to firmly guide practice, antimicrobial prophylaxis for bites from other mammals is often provided. Ferrets, pigs, horses, bears, big cats, coyotes, and wolves have bite wound pathogens similar to those of dogs and cats, so in the absence of other data, prophylactic antibiotics given for these bites is similar. The unique mixture of camel bite wound pathogens is most adequately covered by fluoroquinolone antibiotics (see Table 52.3). Consider tetanus prophylaxis for all bite wounds. Rabies immunization should be considered following bites from bats, coyotes, wolves, foxes, raccoons, skunks, and stray dogs outside of the United States (see Chapter 119B). Bites from rodents,

squirrels, and lagomorphs (i.e., rabbits) do not require rabies prophylaxis. Indications for admission after an animal bite are listed in see Box 52.1. Those patients deemed appropriate for outpatient therapy should be reevaluated in 24 to 48 hours.

Human Bites

Foundations

Background and importance. Human bites tend to occur during summer months, typically on weekends, and most often involve acts of aggression. Sporting event altercations and sexual or physical abuse injuries are less common, but important causes. Males are more likely to be the victims of human bites, with a peak incidence in the 10- to 34-year-old age group.[19,34] The hands and upper extremities are the most commonly bitten location, followed by the head and neck. In victims of sexual crimes, the breast is the most commonly bitten area, and the arm is the most frequently bitten site in victims of child abuse. For various reasons, including embarrassing circumstances and possible legal repercussions, adult human bite victims may delay seeking medical care until a complication ensues. This is especially true for human bites of the hand.

Anatomy, physiology, and pathophysiology. Human bites can be divided into two categories: occlusive bites and clenched-fist injuries (CFIs). Occlusive bites are those caused by closure of the perpetrator's teeth onto the victim's skin. CFIs, or "fight bites," are injuries to the dorsum of the metacarpophalangeal joints of the fist as it strikes the teeth of an adversary. The overwhelming majority of CFIs occur in young adult males and frequently involve alcohol consumption.[35,36] Human bites have infection rates ranging from 5% to 50%, with hand bites and CFIs having the highest rates of infection. Children, in whom human bites are usually superficial, tend to have lower rates of infection (<10%) as compared with adults.

Clinical features. **Fight bites (clenched-fist injury).** Acute CFIs typically present as an innocuous appearing 3- to 8-mm laceration over the dorsal aspect of the second, third, fourth, or fifth metacarpophalangeal (MCP) joint (Fig. 52.1). Despite their initial benign appearance, CFIs often have extensive deep structure damage. Damage to underlying bones occurs in approximately half of all CFIs, and over half will have violation of a joint capsule.[35,37] Up to 20% of CFIs will have an associated tendon injury. Injury to the extensor tendons occurs with the fist clenched. When the fist is relaxed, the tendons retract carrying bacteria deeper into the hand and extending infection to other spaces. Retained tooth fragments in the wound may also occur.[38] CFIs have high rates of osteomyelitis (16%), septic arthritis (12%), and tenosynovitis (22%). Many patients will be reticent to discuss the details of their injury, and approximately one third of CFI patients will initially offer an alternative explanation for their hand laceration.

Other human bites. Human occlusive bites generally cause less tearing and crush injury than dog bites, and do not penetrate soft tissues as readily as cat bites. Occlusive human bites that are superficial, do not involve the hands or feet, and are not over joints or cartilaginous structures have a very low rate of infection. Intraoral and oral-cutaneous wounds caused by the patient's own teeth are usually a result of blunt facial trauma. These bite wounds are typically small and confined to the oral mucosa, requiring no specific intervention. Larger wounds and those that communicate with the overlying facial skin (i.e., "through and through" wounds) may require closure for functional or cosmetic reasons. Infection rates of these wounds range from 5% to 30%. Organisms cultured from these infected wounds include *Staphylococcus* and *Streptococcus* species, *Bacteroides*, and *Corynebacterium*. In the absence of any current clear evidence-based recommendation regarding the use of prophylactic antibiotics for these wounds, we advise prophylactic penicillin be used in those lacerations requiring primary closure and through-and-through injuries that communicate with the overlying skin.

Human saliva can contain up to 10^9 organisms per mL and may contain as many as 190 different species of bacteria. As with other mammalian bites, cultures sent from fresh, uninfected human bite wounds do not predict which patients will become infected, nor do they reveal the responsible pathogens in those who do. Information on the bacteriology of infected human bite wounds has come primarily from hand bites, with the majority being CFIs. Polymicrobial infections are the rule with human bites, with an average of four isolates per wound culture. Approximately half contain a mixture of aerobic and anaerobic species, with less than 5% containing only anaerobes. *Staphylococcus* and *Streptococcus* species, as well as *Corynebacterium* and *Fusobacterium* species, are common pathogens. *Eikenella corrodens,* a fastidious facultative anaerobe, is present in up to 30% of infected human bites. It is resistant to multiple antibiotics including erythromycin, antistaphylococcal penicillins, and first-generation cephalosporins.

Differential diagnoses. Human bites have resulted in transmission of tetanus, syphilis, actinomycosis, and herpes. Herpetic whitlow, an infection of the finger by HSV types 1 and 2, is an occupational hazard of nurses, physicians, dentists, and oral hygienists and classically described in sporting events like wrestling (Fig. 52.2). Although the presence of human immunodeficiency virus (HIV) inhibitors in saliva render the virus non-infective in most cases, there are several case reports of HIV transmission by human bites.[37] Infection with hepatitis B virus (HBV) has also been reported and carries a greater transmission risk than HIV.[38] The infectivity of the hepatitis C virus (HCV) from a bite is believed to be midway between that of HIV and HBV, and there are case reports of its transmission by human bites.[38] The risk of

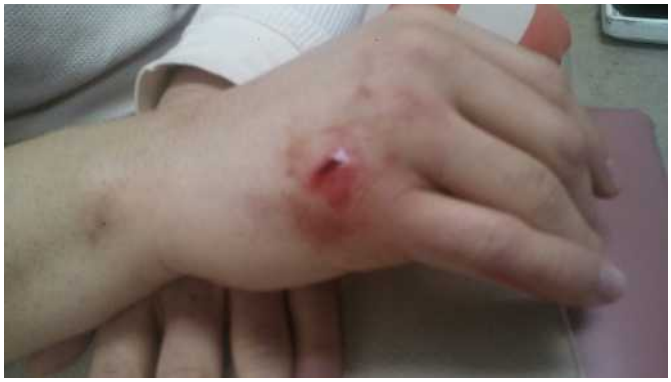

Fig. 52.1 Acute Clenched Fist Injury. (Courtesy Jeffrey E. Keller, MD.)

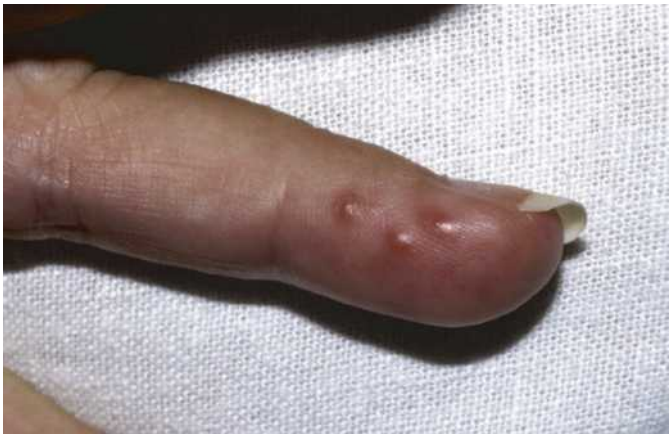

Fig. 52.2 Herpetic Whitlow. (Courtesy Gary M. White, MD.)

transmission of HIV, HBV, and HCV from a bite is more likely if blood was present in the mouth of the biter at the time of injury.[39,40]

Diagnostic testing. Due to their high incidence of deep structure injury and the possibility of retained tooth fragments, we advise obtaining radiographs in hand bites. A "skyline" view of the distal metacarpals may aid in the identification of vertical articular fractures of the metacarpal heads caused by CFIs.

Management. Treatment should focus on the mechanism of the bite (occlusive or CFI), the health of the bite victim including medical history and tetanus status, and the potential for transmission of viral hepatitis or HIV. If the biter is available for testing, local law enforcement may permit testing even without consent depending on the particular circumstances.

Treatment of occlusive human bites is generally similar to that of other mammalian bites. Although some authors have advocated surgical exploration of all CFIs in the operating room, nonoperative management in the ED for those patients presenting within 24 hours of injury has been proven sufficient.[36] Such an approach is predicated on thorough wound exploration in a bloodless field. The hand should be examined through its entire range of motion, including in the closed-fist position when the fingers are flexed, because extensor tendon injuries and cartilage damage may not be evident in any other position. Admit patients for operative debridement and irrigation in whom exploration shows signs of infection or injury to the joint or joint capsule, tendons, or bones. It is typical for patients with CFIs to present several days after the injury with evidence of an infected wound. These patients will also require surgical exploration and irrigation in the operating room.

Given their propensity for infection, only human bites to the face should be closed primarily. Case series of human facial bites closed primarily have reported infection rates of up to 10%, although all of these studies reported delays of treatment of up to several days. We recommend primary closure of human bites to the face for up to 24 hours after the bite has occurred (see Table 52.1). CFIs not requiring operative intervention should be cleaned, debrided, and irrigated, then left open with the hand splinted in a position of comfort.

HIV post-exposure prophylaxis is recommended for both the bite victim and the bite source if either party is known to be HIV-positive or at high risk and blood exposure has occurred. Postexposure prophylaxis is also indicated in all bites if either party is known to be HBV-positive or at high risk and blood or saliva exposure has occurred.

BOX 52.3 Indications for Admission for Human Bites of the Hand

- Infection present at the time of presentation
- Deep structure violation (tendon or tendon sheath, joint, or bone)
- Wounds requiring operative intervention for debridement of devitalized tissue or foreign body removal
- Patients at high risk for wound infection (see Table 52.2)
- Patients with likely social support or compliance issues

No current postexposure prophylaxis is recommended for HCV, so serologic testing with appropriate follow-up and counseling should be offered if the bite resulted in blood exposure, and either party is known HCV positive or at high risk.[41]

Prophylactic Antibiotics

Studies have consistently demonstrated the value of prophylactic antibiotics in the treatment of human bites. We recommend prophylactic antibiotics for any human bite that penetrates deeper than the epidermis regardless of body location, with the exception of those bites greater than 72 hours old without evidence of infection. We recommend beta-lactam/beta-lactamase inhibitor combination antibiotics, such as amoxicillin-clavulanate (Augmentin), or clindamycin combined with either trimethoprim sulfamethoxazole or ciprofloxacin (see Table 52.3). As with other prophylactic antibiotics, the first dose should be given ideally within 3 to 4 hours of the injury and continued for 5 days.

Disposition

Delay in presentation with human bites to the hand is strongly correlated with infection-related complications, and these patients should be admitted for parenteral antibiotics. Other indications for admission with human bites of the hand are listed in Box 52.3. Localized infections of human bites elsewhere on the body in immunocompetent patients can be treated as an outpatient. All patients with human bites discharged from the ED should have their wounds reevaluated in 24 to 48 hours. Patients with CFIs have notoriously high rates of noncompliance with follow-up care.[36] It is reasonable to admit patients who might predictably fall into this category.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 52: QUESTIONS AND ANSWERS

1. A 75-year-old woman presents with a puncture mark on her hand. She reports being bitten by her cat the previous night. Which of the following statements regarding this patient's injury is *true?*

a. *Capnocytophaga canimorsus* is the organism of concern.
b. Cats are very clean animals and do not carry any virulent strains.
c. Cats produce superficial infections because their teeth are not long enough to inoculate past the dermis.
d. Concern exists for a virulent gram-negative bacterium, which can produce a rapid cellulitis.
e. Irrigation and topical antibiotics are indicated.

Answer: d. Cats have long, slender, pointed teeth that can penetrate tendons, joints, and bone, inoculating bacteria deep into these tissues. Cat bites have a substantially higher risk of infection than dog bites do. Another important factor in the development of wound infection after cat bites involves the presence of *Pasteurella multocida,* a highly virulent, gram-negative, facultatively anaerobic rod found in the oral cavity or nasopharynx of 70% to 90% of healthy cats.

2. What is the most appropriate antibiotic prophylaxis for a cat bite?

a. Amoxicillin-clavulanate
b. Clindamycin

c. Erythromycin
d. First-generation cephalosporins
e. Vancomycin

Answer: a. In vitro, *P. multocida* is sensitive to penicillin, ampicillin, tetracycline, fluoroquinolones, amoxicillin-clavulanate, second- and third-generation cephalosporins, and trimethoprim-sulfamethoxazole.

3. A 19-year-old man presents 10 hours after sustaining a dog attack. He has multiple lacerations on his head and right hand. What is the appropriate management of this patient?
a. Repair the hand and the head lacerations
b. Repair the hand laceration but not the head laceration
c. Repair the head laceration but not the hand laceration
d. Use Steri-Strips on all and give him a prescription for amoxicillin-clavulanate (Augmentin)
e. Wound cleansing and bandaging

Answer: c. For dog bites, the infection rate of hand wounds is as high as 30%, regardless of suturing, whereas the infection rate of dog bites elsewhere averages 9%. Similarly, dog bites of the face and neck (including punctures) have lower infection rates of 0% to 5% even when they are sutured. Bite wounds of the face and scalp from any species that are less than 12 hours old may be cleansed well and sutured. Most other bite wounds that are going to be closed should have this done within 6 hours.

4. Selected monkey bites require postexposure prophylaxis with which of the following medications?
a. Amoxicillin clavulanate
b. Clindamycin
c. Flagyl
d. Tetracycline
e. Valacyclovir

Answer: e. Valacyclovir to prevent herpes B virus infection. Other terms for this virus include *herpesvirus simiae, herpesvirus B,* and *monkey B virus*. This virus has serologic cross-reactivity with herpes simplex virus (HSV) type 1 and type 2, which cause herpetic lesions in humans. Seventy-five to 100% of monkeys of the genus *Macaca* (macaques) used for biomedical research are seropositive for the B virus. Other antibacterials may be needed if cellulitis infection ensues.

53

Venomous Animal Injuries

Amelia M. Curtis and Timothy B. Erickson

KEY CONCEPTS

- Snake venom causes neurotoxicity and hematotoxicity, but one usually predominates, depending on the species of snake.
- Pit vipers have triangular or arrow-shaped heads, elliptical pupils, and characteristic pits found bilaterally midway between the eye and the nostril.
- The amount of crotalid antivenom given depends the severity of the bite. Currently, Crotalidae polyvalent immune Fab (CroFab) and F(ab′)2 (Anavip) are the antivenoms of choice for crotalid bites. Children require the same amount of antivenom as adults.
- Envenomation from exotic international snakes such as cobras, kraits, and mambas often require antivenom for life-threatening neurologic and hematologic toxicity.
- Arthropods such as hymenoptera account for more deaths from envenomation than snakes, usually as a result of allergic or anaphylactic reactions.
- Black widow spider bites are neurotoxic, causing severe pain and muscle spasms; an antivenom is available but used only in severe cases. Brown recluse spider bites cause necrotizing skin wounds.
- Nematocyst (jellyfish) stings should be neutralized with vinegar or hot water, and fish stings with hot water. Stings from venomous fish (e.g., lionfish and sting rays) are treated with circulating hot water to denature the toxin and cause vasodilation.
- Marine antivenoms are available for severe box jelly fish, stonefish, and sea snake envenomation.

FOUNDATIONS

Venomous animals account for considerable morbidity and mortality worldwide. Southeast Asia, India, Brazil, and areas of Africa lead the world in snakebite mortality. Snakes alone are estimated to inflict 2.5 million venomous bites annually, with approximately 150,000 deaths. The World Health Organization (WHO) estimates that up to 2 million people in Asia and 580,000 people in Africa are envenomated by snakes yearly. It is a challenge to estimate the worldwide morbidity and mortality resulting from other venomous animals, such as bees, wasps, ants, and spiders.

Approximately 45,000 snakebites occur annually in the United States; 7000 to 8000 are inflicted by venomous snakes, and fewer than 5 result in death. Worldwide, arthropods are responsible for 50% of venomous deaths, snakes for 30%, and spiders for 15%. Specifically, bees are responsible for the most fatalities, followed by rattlesnakes, wasps, and spiders.

The American Association of Poison Control Centers' 30-year experience shows a significant number of exposures by bite or sting but relatively few deaths. From 2012 to 2018, more than 370,000 total bites and envenomations, with 41 reported deaths, were reported to the American Association of Poison Control Centers. Although these data include most of the United States, there is no requirement that hospitals, emergency departments (EDs), coroners, or public health agencies report deaths or exposures to regional drug and poison information centers. This decline in deaths may be caused by an actual decrease in mortality or may be a result of inadequate reporting. Meaningful morbidity data, such as the number of amputations, hospitalizations, and disabilities, do not exist. The number of exposures and deaths from nonnative snakes seems to be increasing, possibly because of interest in collecting "exotic" or venomous varieties, such as cobras, mambas, and vipers.

An estimated 40,000 to 50,000 marine envenomation occur annually. In recent years, the number of injuries caused by these animals has increased dramatically because of the greater number of people living and vacationing near coastal waters, scuba divers, snorkelers, surfers, and others engaging in water sports.

In the northern hemisphere, most venomous exposures occur from April to October, which is when animals are most active and potential victims are outdoors and involved in activities that might increase their risk for envenomation. Many spider bites and exotic animal envenomation that occur indoors can take place at any time. Most deaths seem to occur in very young, elderly, or inappropriately treated patients.

Venom Delivery

Animals that have developed specific venom glands and venom delivery systems can be found in every class, including birds. The toxin and toxic apparatus vary from class to class. For example, the rattlesnake has modified salivary glands and maxillary teeth and uses this system primarily to obtain food. The bee has a modified ovipositor that is used mainly for defense. Poisonous and venomous animals are not the same and should be differentiated. Animals can be considered *poisonous* because of various toxins distributed in their tissues. For example, certain shellfish, toads, and barracuda have been known to cause death after ingestion. However, only animals with specific glands for producing venom connected to an apparatus for delivering that venom to another animal can be considered *venomous.*

VENOMOUS REPTILES

Snakes

Foundations

Of the 3000 species of snakes, approximately 800 are venomous. All venomous snakes belong to four of the 14 families of snakes—Viperidae, Elapidae, Colubridae, and Atractaspididae. Snakes are found throughout most of the earth's surface, including fresh and saltwater. The major exceptions are the Arctic and Antarctic zones, New Zealand, Malagasy, and many small islands. With recent trends in climate change, many of these geographic regions are in a state of flux and have altered snake biodiversity. The activity and native distribution of snakes

TABLE 53.1 Families of Venomous Snakes

Family	Subfamily	Examples
Viperidae	Viperinae (true vipers)	Gaboon viper, puff adder, saw-scaled viper, Russell viper
	Crotalinae (pit vipers)	Crotalus timber rattlesnake, eastern diamondback rattlesnake, western diamondback rattlesnake, sidewinder, Mojave rattlesnake
		Sistrusus pygmy rattlesnake, massasauga
		Agkistrodon copperhead, cottonmouth, bushmaster, cantil, fer-de-lance
Elapidae		Eastern coral snake, Texas coral snake, cobras, kraits, mambas
Hydrophiidae, Hydrophiianae		yellow-bellied sea snake
Colubridae		boomslang, bird snakes

are restricted to a fairly narrow range given they are poikilotherms; however, nonnative snakes, including venomous snakes, are popular pets worldwide and often transported out of their natural habitat illegally. All snakes are carnivorous, and their venom apparatus evolved for the purpose of obtaining food.

Approximately 5000 to 10,000 snakebites are reported to US poison centers every year. The incidence of reported venomous snakebites in the United States is greatest in the southern states, especially in Arizona and Texas. Within the United States, the vast majority of snakebites result from native pit vipers, although snakebites from coral snakes and nonnative species are also represented.[1]

Snakebites are often classified by the inflicting species, the age and gender of the victim, the location of the wound, and whether it followed intentional or unintentional contact with the snake. Men are more likely than women to have snakebites as a result of intentional contact, and snakebites following intentional contact are more likely to affect an upper extremity.[1] Overall, the majority of reported venomous snakebites in the United States result from unintentional contact with snakes and affect a lower extremity.[1]

In addition to native venomous snakes, imported venomous snakes are a problem throughout the United States and worldwide. In the past, only zoos, research centers, and herpetologists kept exotic venomous snakes. Today, private owners have easy access to a wide variety of exotic pets including venomous snakes through a 15 billion USD global industry in exotic animal trade. Emergency providers may lack experience treating exotic snakebites, and, depending on the species, may lack access to antivenoms crucial for patient management. In the United States, laws designed to limit exotic pet ownership have proven difficult to enforce. Approximately 30–50 snakebites from exotic venomous species are reported to US poison centers annually. Worldwide, venomous snakebites are an increasing public health threat with more than 150,000 estimated deaths annually, most occurring in tropical regions of Africa, the Middle East, Southeast Asia, and South America.

Classification and Characteristics

The four venomous families of snakes are the Colubridae, Elapidae, Viperidae, and Atractaspididae (Table 53.1). The Colubridae, although representing 70% of all species of snakes, have very few venomous members dangerous to humans; these include the boomslang and bird snake. They are rear-fanged snakes, and although many possess venom, they generally do not envenomate humans. The Elapidae are more common and include deadly cobras, kraits, mambas, and coral snakes. The Hydrophiidae are sea snakes and a subfamily of the Elapidae. The yellow-bellied sea snake, *Hydrophis platurus*, has been found off the coast of southern California, western Mexico, Japan, and the Korean peninsula, but bites from this snake are uncommon. The Viperidae, or true vipers, are represented by the Russell viper, puff adder, Gaboon viper, saw-scaled viper, and European viper. The Crotalidae, or pit vipers, are sometimes considered a separate family or subfamily (Crotalinae) of the Viperidae. Among the pit vipers are the most common American venomous snakes, such as rattlesnakes, water moccasins, copperheads, the bushmaster, cantil, and the fer-de-lance. The Atractaspididae are the mole vipers, which have side-positioned fangs; they rarely envenomate humans and are found only in Africa and the Middle East.

Pit vipers, the most prevalent venomous snakes in the United States, are native to every state except Maine, Alaska, and Hawaii. They are classified into three main groups: true rattlesnakes (genus *Crotalus*), copperheads and water moccasins (genus *Agkistrodon*), and pygmy or Massasauga rattlesnakes (genus *Sistrurus*). Pit vipers account for nearly all venomous snakebites in the United States.

The other major group of venomous snakes in the United States are the coral snakes. The eastern coral snake *(Micrurus fulvius)* is found in North Carolina, South Carolina, Florida, Louisiana, Mississippi, Georgia, and Texas. Envenomation from the eastern coral snake can be deadly. The Texas coral snake *(Micrurus tener)* and the western or Arizona coral snake *(Micruroides euryxanthus)* are found in the western United States and generally considered less dangerous than the eastern variety.

Anatomy and Identification

There are two key principles for identifying venomous snakes: only experts should handle live snakes, and even dead snakes can envenomate careless handlers.

It is not difficult to differentiate between pit vipers and harmless snakes found in the United States (Fig. 53.1). Pit vipers, as their name implies, have a characteristic pit midway between the eye and the nostril on both sides of the head. This pit is a heat-sensitive organ that enables the snake to locate warm-blooded prey. Pit vipers may be identified through other methods, but this characteristic is very consistent. The triangular shape of the head, the presence of an elliptical pupil, the tail structure, and the presence of fangs are useful characteristics but are inconsistent. The arrangement of subcaudal plates may be used for Crotalinae if the head has been damaged or is unavailable. An individual specimen may not fit the classic description, depending on the age of the snake, the time of the year, and the condition of the tail and mouthparts. Neither color nor skin pattern is a reliable method of identifying pit vipers.

Coral snakes can be readily identified by their color pattern. At first glance, they resemble one of several varieties of king snake found in the southern United States. The coral snake can be differentiated from the king snake by two characteristics: The nose of the coral snake is black, and the red and yellow bands are adjacent on the coral snake but separated by a black band on the king snake (Fig. 53.2). The popular rhyme is as follows:

Red on yellow, kill a fellow.

Red on black, venom lack.

This rhyme can be used only in the United States because there is significant color variation in coral snakes from other regions of the world.

Size is not an important factor in identifying venomous reptiles. Venomous snakes range in length from several inches to several feet. Although a 6-foot eastern diamondback rattlesnake is much more dangerous than a 10-inch copperhead, all venomous snakes are able to envenomate from birth and should be treated as though they are dangerous.

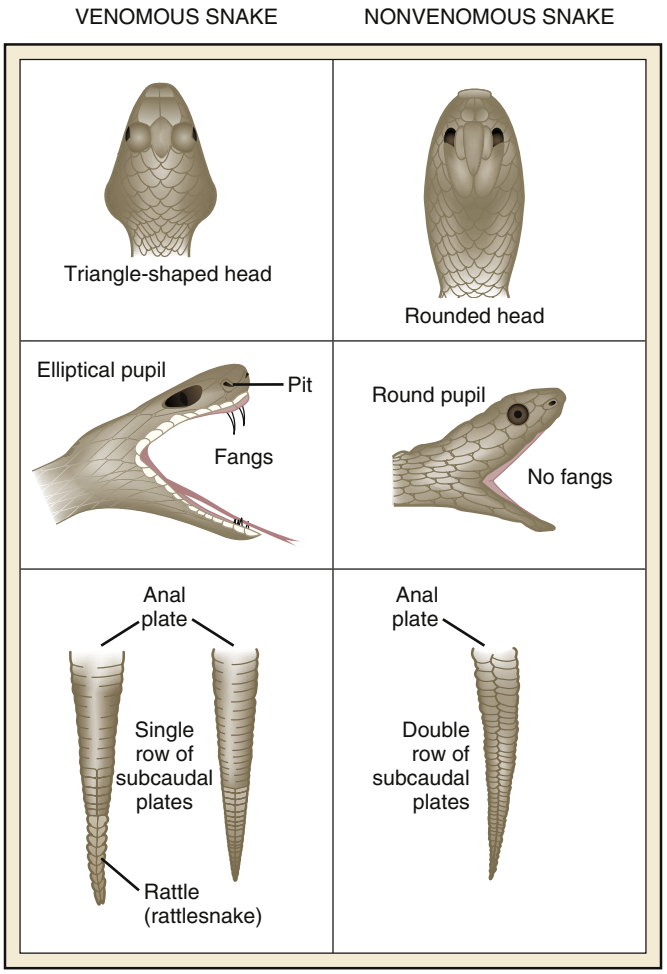

Fig. 53.1 Identification of Venomous and Nonvenomous North American Snakes.

Fig. 53.2 (A) The nose of the coral snake is black, with adjacent red and yellow body bands. (B) Body bands are separated by a black band on the scarlet king snake. (A, From Norris RL, Pfalzgraf RR, Laing G. Death following coral snake bite in the United States—first documented case (with ELISA confirmation of envenomation) in over 40 years. *Toxicon.* 2009;53(6):693–697.)

Exotic or international snakes that are *not* pit vipers are not as easily identified. If possible, rather than capturing and transporting an unidentified snake, a safe-distanced digital picture can be taken and electronically sent to an expert for positive identification. Local zoos, herpetologists, poison control centers, and universities often have resources to assist in identification of unknown snakes.

Other Reptiles

Only two venomous lizards are found in the world, both in the southwestern United States and Mexico. They are the Gila monster *(Heloderma suspectum)* and the Mexican beaded lizard *(Heloderma horridum)*. Fortunately, both of these lizards are nonaggressive and rarely encountered. Bites usually result from handling the animals in captivity and victims are usually male. The Gila monster and the Mexican beaded lizard are easily identifiable. Both have thick bodies, beaded scales, and either white and black or pink and black coloration (Fig. 53.3).

Fig. 53.3 Gila Monster *(Heloderma suspectum)*. (From Furman BL. The development of Byetta (exenatide) from the venom of the Gila monster as an anti-diabetic agent. *Toxicon.* 2012;59(4):464–471.)

Pathophysiology and Toxins

The two main factors influencing the pathophysiology of any venomous animal injury are the toxic properties of the venom and the victim's response to these toxins. In the past, snake venoms were classified as either neurotoxic or hematotoxic, depending on the observed response of the victim to the various venoms. Modern toxicologic investigation has shown that this classification is inadequate because most snake venoms contain compounds that have many toxic properties. However, it is true that the venom of a particular species of snake may cause a systemic clinical response that is predominantly neurotoxic or hematotoxic.

Between different species, the components of snake venom are variable. Between individual snakes of the same species, there is also

considerable variability of venom components depending on factors such as age, geographic location, and diet. The toxic components of snake venom include a mixture of small molecules and peptides. Peptides and proteins, which account for most of the toxic manifestations, make up to 90% to 95% of the venom. Common peptide/protein families include phospholipases A2, three-finger toxins, metalloproteases, and serine proteases.[8] Phospholipases A2 are a major component of elapid and viper venom.[2] The phospholipases A2 are a diverse group of enzymes whose activity is responsible for a wide variety of clinical effects, including neurotoxicity through inhibition of acetylcholine release from axon terminals as well as tissue damage through calcium dependent lipid hydrolysis. Metalloproteases are also major components of elapid and viper venom and have an important role in causing hemorrhage as well as local tissue damage.[2] The major component of elapid venom are the three-finger toxins.[2] The three-finger toxin family is extensive, with a wide variety of targets and resulting clinical effects including neurotoxicity and cardiotoxicity. Although there are many other protein families in snake venoms, the shared components of venoms across species have important medical implications regarding cross-neutralization by specific antivenoms and the possibility of a universal antivenom.[2]

Heloderma venom is perhaps most famous for its use in drug design. The identification of exedins in *Heloderma* venom led to the development of exanatide, a GLP-1 receptor agonist used in the treatment of diabetes. Exendins in venom functional similarly to stimulate glucose-dependent insulin release. Other components of *Heloderma* venom include phospholipases A2, helofensin, kallikrein, helofensin, and cysteine-rich secretory protein.

Venom Delivery

The mechanism for delivering venom is fairly standard among snakes. It consists of two venom glands, hollow or grooved fangs, and ducts connecting the glands to the fangs. The glands, which evolved from salivary glands, are located on each side of the head above the maxillae and behind the eyes. Each gland has an individual muscle and a separate nerve supply that allow the snake to vary the amount of venom injected. The venom duct leads from the anterior portion of the gland along the maxilla to the fangs. Pit vipers have fangs that are large anterior maxillary teeth. These teeth are hollow and rotate outward from a resting position to a striking position. The coral snake has fixed, hollow maxillary teeth that are much smaller than those of pit vipers. The fangs in most snakes are shed and replaced regularly, and it is not unusual to see a snake with double fangs on one or both sides of its mouth.

The snake can control the amount of venom injected. In biting a human, a prey much too large to swallow, the snake may inject little or no venom (a "dry" bite), especially if injured or surprised. It is estimated that up to one-third of potentially venomous bites to humans are actually "dry" bites. However, the snake may inject more than 90% of the contents of the gland for the same reasons.

Heloderma have venom glands located in the lower jaw that deliver venom through ducts into grooved lower teeth. *Heloderma* are known for prolonged, "chewing" bites.

Clinical Features

The signs and symptoms of a venomous snakebite vary considerably and depend on many factors. Clinical signs can include local tissue damage, myolysis, kidney injury, coagulopathy, cardiotoxicity, and neurotoxicity. Up to 50% of venomous snakebites result in little or no envenomation. A person with comorbidities including impaired cardiovascular, renal, or pulmonary function is less able to cope with even a moderately severe envenomation. The victim's autopharmacologic response to the envenomation must also be taken into account. An immunoglobulin E (IgE)-mediated anaphylactic-type reaction may develop in victims of a previous snakebite when reexposed to the venom or in individuals sensitized to snake proteins through frequent handling. Because of these multiple variables, the individual clinical response is the best judge of the severity of a venomous snakebite. Factors that influence the effects of a snakebite are the age, health, and size of the snake; the relative toxicity of the venom; the condition of the fangs; whether the snake has recently fed or is injured; the size, age, and medical problems of the victim; and the anatomic location of the bite. In the Americas, clinical features including time to presentation of greater than 6 hours, age 12 years of younger, bites from adult snakes, presence of ptosis, and evidence of coagulopathy on initial labs are associated with more severe envenomations.[3]

Elapidae and Hydrophiidae venoms have predominantly systemic effects, whereas Colubridae, Viperidae, and Crotalinae venoms have significant local effects. There are many exceptions to this general division. For example, the venom of the Mojave rattlesnake *(Crotalus scutulatus)* may show minimal local effects and significant systemic neurotoxic effects, whereas the venom of the Indian cobra *(Naja naja)* may cause extensive local tissue destruction.

Gila monster and beaded lizard bites are generally associated with pain, edema, and weakness. Hypotension is common with severe bites. There are no reported deaths from *Heloderma* bites, although myocardial infarctions have been reported.

Crotalids (Pit Vipers)

The most consistent symptom associated with pit viper bites is immediate burning pain in the area of the bite. Swelling typically develops minutes after envenomation and may progress for several hours to days; however, onset may be delayed. Ecchymosis, petechiae, blebs, and bullae may develop early at the site of envenomation (Fig. 53.4). The cytotoxic effects of envenomation including pain and paresthesias may suggest a developing compartment syndrome; however, a true compartment syndrome is rare in North American snakebites, even in the setting of severe edema, because most bites are subcutaneous in nature and not intramuscular. Systemic effects are generally less common but can include weakness, nausea, fever, vomiting, sweating, numbness and tingling around the mouth, metallic taste in the mouth, muscle fasciculations, and hypotension.

Hematotoxicity is especially common after North American rattlesnake envenomation. Laboratory abnormalities can include thrombocytopenia, hypofibrinogenemia, increased prothrombin time, and increased partial thromboplastin time. These laboratory abnormalities do not always correspond to clinical bleeding; however, the risk of bleeding increases with the presence of both thrombocytopenia and coagulopathy. Hypofibrinogenemia can occur for up to 2 weeks after treatment with Crotalidae polyvalent immune Fab (CroFab).

Neurotoxicity can be seen with several species of North American pit vipers including the Mojave rattlesnake *(C. scutulatus)* and Timber rattlesnake *(Crotalus horridus)*. There is significant geographic variation in Mojave rattlesnake venom; however, envenomation by snakes with venom type A (phospholipase A2 [PLA2] dependent neurotoxin [PLA2]-dependent neurotoxin) can result in cranial nerve dysfunction, skeletal muscle weakness, paralysis, and respiratory failure. Type A venom does not have significant hematotoxic effects, whereas type B venom contains a large component of fibrinogenolytic metalloproteinases responsible for hematotoxicity. Although most Mojave rattlesnakes carry one phenotype or the other, there are small populations of Mojave rattlesnakes with both type A and type B venom phenotypes. Similarly, the Timber rattlesnake has a largely neurotoxic type A venom and a proteolytic and hemorrhagic type B venom. There are small populations of Timber rattlesnakes with both type A and type B venom phenotypes.

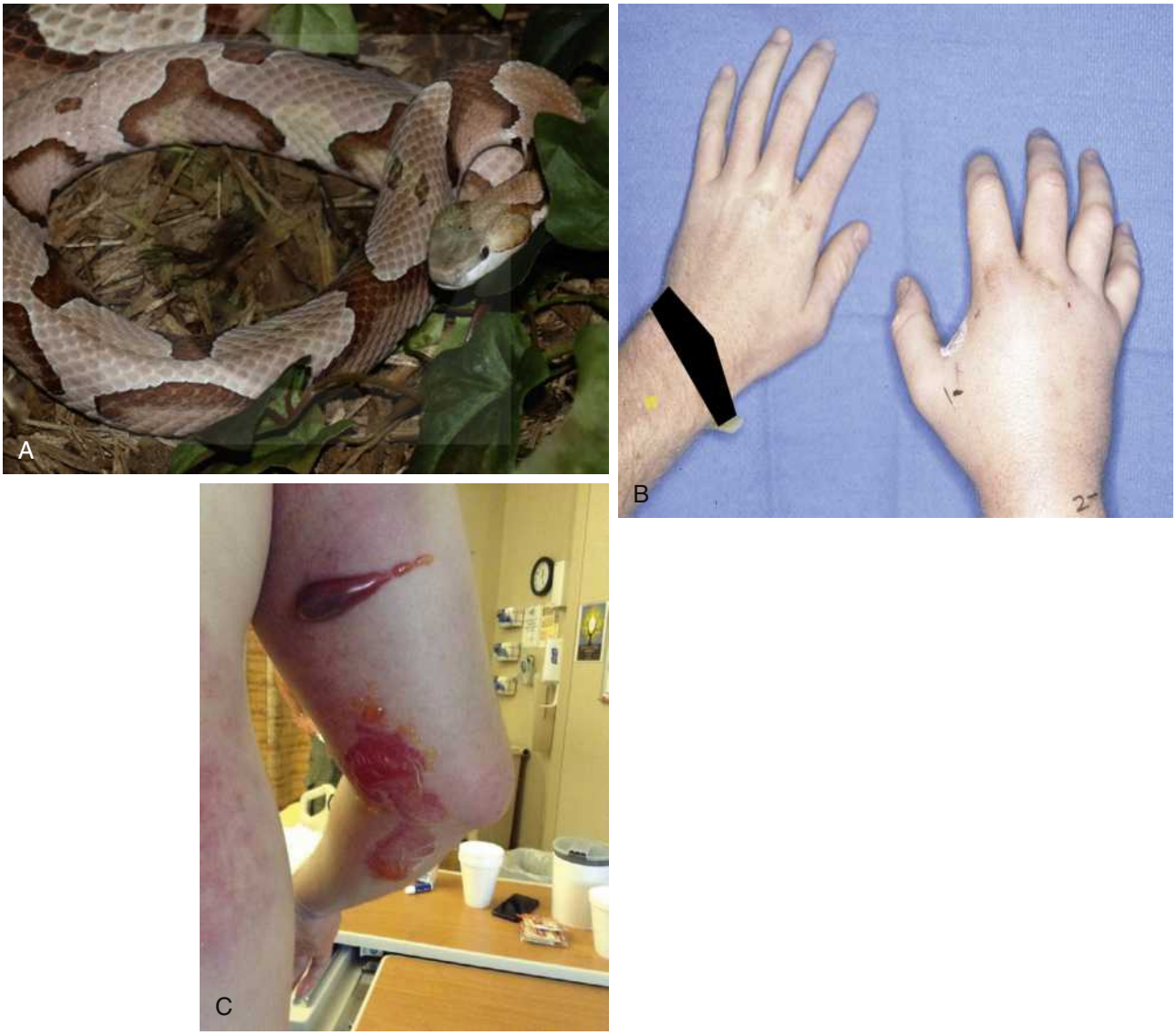

Fig. 53.4 (A and B) Northern copperhead *(Agkistrodon contortrix mokasen)* bite on right hand with normal left hand for comparison. (C) Northern Copperhead bite to upper extremity showing diffuse swelling, and hemorrhagic bullae formation.

Coral Snakes

Signs and symptoms can vary considerably with bites of coral snakes. Coral snakes are not aggressive, and a significant number of bites are "dry bites" that do not result in envenomation. Unlike many crotalid bites, envenomation by coral snakes typically causes minimal local pain and swelling. The neurotoxic effects of the eastern coral snake are often delayed for several hours but can progress rapidly after onset. Neurologic symptoms can include ptosis, vertigo, paresthesias, fasciculations, slurred speech, drowsiness, dysphagia, restlessness, increased salivation, nausea, and proximal muscle weakness. Although rare, the usual cause of death after coral snake envenomation is respiratory failure.

Infection

Although snakebite envenomation has been stressed here, any bite or puncture wound carries a risk for secondary bacterial contamination. There are significant geographic differences in rates of secondary infection, causative microorganisms, and standard use of prophylactic antibiotics following snakebites. In the United States, the rate of secondary infection after rattlesnake bite is less than 1%.[4] The majority of bacteria isolated from these infections were human skin flora and not rattlesnake oral flora.[4] This is in stark contrast to victims of viper bites in Costa Rica, where more than 20% of patients developed secondary infection, and isolated organisms were commonly snake oral flora.[5] Secondary infections may include osteomyelitis, cellulitis, or gas gangrene, and these infections may occur with or without associated envenomation. In the United States, routine prophylactic antibiotics are not recommended; however, it is reasonable to offer patients with deep puncture wounds from any mechanism antibiotic prophylaxis if they are at high risk for secondary infection. Risk factors may include immunodeficiency, delay to care, and heavily contaminated wounds. Antibiotics for infected wounds should include gram-negative coverage for snake oral flora and coverage for human skin flora.

Differential Diagnoses

The differential diagnosis of venomous snakebites includes dry bites, bites from nonpoisonous snakes, spider and tick bites, scorpion and

hymenoptera stings, dermatologic disorders such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, and methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Diagnostic Testing

Diagnosis of snakebite relies largely on clinical history and examination. Diagnostic testing following pit viper envenomation should include complete blood count, prothrombin time, partial thromboplastin time, and fibrinogen levels at presentation and repeated in 4 to 6 hours. Patients with evidence of systemic illness following snakebite should also have renal function, electrolytes, and electrocardiogram (ECG) assessed. Depending on clinical presentation, a creatinine kinase and urinalysis may also be indicated. Detection of venom in blood or urine by enzyme-linked immunosorbent assay is possible, although the results of these assays are too delayed to have any clinical impact in the ED. There are no standard laboratory or imaging diagnostics recommended in suspected *Heloderma* envenomation.

MANAGEMENT

Out-of-Hospital Care

All venomous snakebites are considered an emergency, and any victim should be medically evaluated. Out-of-hospital care should focus on safely separating the victim from the snake, addressing airway compromise and abnormal vital signs, and transportation to a medical facility. A stick, pole, or other object longer than the snake can be used to move the snake away from the victim or, if necessary, to kill the snake by striking it behind the head. Any constricting jewelry or clothing should be removed from an extremity to prevent a tourniquet effect proximal to the swelling. The affected limb can be immobilized. Identification or capture of a snake should not delay transport to a medical facility and may result in repeated bites to the victim or bystanders. First responders should be aware that even dead snakes can cause envenomation.

Multiple different techniques for neutralizing venom, removing venom, or limiting the rate of systemic venom absorption have been proposed, although none have been proven to be both effective and reliably feasible.[6] Tourniquets, wound incision or excision, suction, ice water immersion, and electrotherapy should be avoided. These techniques are either directly harmful or serve as unnecessary delays to proper treatment.

Pressure immobilization bandages are used in the prehospital care of suspected neurotoxic snake envenomation in Australia. When applied correctly, this technique slows the rate of systemic venom absorption. However, multiple studies have shown that, despite training, pressure immobilization is often incorrectly executed. Pressure immobilization is not recommended in the prehospital care of North American crotalid snakebites given the potential to worsen local effects of envenomation. Animal studies have shown possible survival benefit after eastern coral snake envenomation with use of pressure immobilization; however, significant local tissue damage including necrosis not typically seen in coral snake envenomation was attributed to the use of this technique.[7] We do not recommend pressure immobilization or tourniquet application for treatment after envenomation by native North American snakes.

Emergency Department Care

Emergency care of a snakebite focuses on supportive care and rapid treatment with the appropriate antivenom when indicated. By the time the emergency clinician examines a snakebite victim, the venom may have already caused significant damage, both locally and systemically. In this case, the emergency clinician must be prepared to support the victim's cardiovascular and respiratory systems.

Patient History

Specific historical information includes time elapsed since the bite, the number of bites, whether first aid was administered and what type, location of the bite, and symptoms (e.g., pain, numbness, nausea, tingling around the mouth, metallic taste in the mouth, muscle cramps, dyspnea, and dizziness). A brief medical history includes the last tetanus immunization, medications, and cardiovascular, hematologic, renal, and respiratory problems. An allergy history with emphasis on symptoms after exposure to horse or sheep products, previous injection of horse or sheep serum, and a history of asthma, hay fever, urticaria, or allergy to wool, papain, chymopapain, papaya, or pineapple should be obtained if antivenom treatment is being considered.

Patient Examination

The bite area is examined for signs of fang marks, scratches, or bleeding and local signs of envenomation (e.g., extremity edema, petechiae, ecchymosis, and bullae). The area distal to the bite is checked for pulses. A general physical examination is performed, with emphasis on the cardiorespiratory system and the neurologic examination, especially if a Mojave rattlesnake, coral snake, or exotic snake is suspected. The leading edge of local injury should be noted and marked. If the bite involves an extremity, the circumference of the extremity at the site of the bite and approximately 5 inches proximal to the bite should be measured and recorded.

Initial Medical Care

Initial medical management of snakebites should address the patient's airway, breathing, and circulation status. Snakebite victims with or without initial clinical evidence of envenomation should have an intravenous line with normal saline placed in an unaffected extremity as onset of systemic symptoms can be delayed but precipitous.

Following crotalid envenomation, the affected limb should be immobilized and elevated to prevent dependent edema. The leading edge of injury should be serially assessed. Intravenous opioids can be given for analgesia. Tetanus prophylaxis should be administered if the patient is not current on their immunization status. Labs including complete blood count, fibrinogen, and prothrombin time are obtained during initial evaluation. The emergency clinician should then determine if there is any evidence of envenomation by local signs (swelling, ecchymosis, blebs), laboratory abnormalities, or systemic signs (hypotension, neurotoxicity, abnormal bleeding). Bedside ultrasonography can be used by trained providers in conjunction with their physical exam to assess for underlying injury and edema.[8] If signs of envenomation are present, the need for antivenom is then assessed.

Pit Viper Envenomation Classification

Crotalid envenomation may be classified according to severity into five grades, from grade 0 (no sign of envenomation) to grade IV (very severe envenomation) (Table 53.2). Patient management, including the use of antivenom, can be correlated and guided with the grade of envenomation.

Antivenom

Any victim of a pit viper snakebite with moderate or severe envenomation is a candidate for antivenom. CroFab was approved by the US Food and Drug Administration (FDA) for treatment of North American pit viper envenomations. CroFab is derived from Fab fragments of immunoglobins from sheep immunized with one of four species of pit vipers in the United States: the western diamondback rattlesnake *(Crotalus atrox)*, eastern diamondback rattlesnake *(Crotalus adamanteus),* Mojave rattlesnake *(C. scutulatus),* and the cottonmouth *(Agkistrodon piscivorus).* In 2015, the FDA approved Anavip, an F(ab′)2

TABLE 53.2 Pit Viper Envenomation Classification

Grade	Clinical Features	Antivenom	Disposition
0 (None)	No evidence of envenomation. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 h after the bite. No laboratory changes occur.	No	Observe for 8–12 h. May be discharged if repeat labs are normal and no signs of envenomation develop.
I (Minimal)	Pain is moderate or throbbing and localized to the fang wound, surrounded by 1–5 inches of edema and erythema. No evidence of systemic involvement is present after 12 h of observation. No laboratory changes occur.	No	Admission for 12–24 h. Repeat labs every 6 h. May be discharged if repeat labs are normal and no signs of envenomation develop.
II (Moderate)	There is more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.	Yes	Admission to intensive care unit
III (Severe)	This may initially resemble a grade I or II, however within 12 h, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.	Yes	Admission to intensive care unit
IV (Very severe)	Sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 min of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.	Yes	Admission to intensive care unit

immunoglobulin derived from horses immunized against the fer-de-lance *(Bothrops asper)* and tropical rattlesnake *(Crotalus durissus)*. Anavip has a similar safety profile compared with CroFab and a longer half-life that results in lower rates of recurrent or late onset coagulopathy.[9] Anavip has a lower cost per vial than CroFab; however, it is unclear how many vials of Avavip will be needed for treatment of severe envenomation. Given the low rates of severe coagulopathies with copperhead envenomation, the efficacy of Anavip in treatment of copperhead envenomation is still yet to be determined. Avavip became commercially available in 2019.

A polyvalent, horse serum–derived antivenom was previously manufactured by Wyeth Laboratories for treatment of North American pit viper envenomation. Vials of this antivenom may still be found in zoos and hospitals, although most have been replaced with the ovine-derived Fab antivenom (CroFab).

The treatment of snakebites is expected to evolve as researchers discover new ways to create antivenoms. Currently, the process of creating antivenoms is highly labor intensive and antivenoms remain unavailable in many parts of the world with the most pressing need. Recently, researchers have discovered a method to culture snake venom glands from snake stem cells.[10] These cultured gland cells are functional and can secrete active toxins.[10] This breakthrough may allow for the creation of large banks of venoms for further study and also eliminate the need to "milk" venomous snakes for their venom. New research on the Indian cobra genome and transcriptome also raises the possibility of creating synthetic venom and, ultimately, a synthetic humanized recombinant antivenom.[11] At least one National Institutes of Health (NIH)-funded phase I trial is underway investigating monoclonal human-derived IgG as a potential source of a broad-spectrum, low immunogenicity antivenom (Project #1R43AI147898-01).

Dosage and Precautions

The CroFab package insert recommends an initial dose of four to six vials of CroFab intravenously (IV) as soon as possible after a rattlesnake or Crotalid bite in patients with systemic signs of envenomation or evidence of a coagulation abnormality (Table 53.3). Based on the severity of envenomation, the initial dose may be increased to a maximum dose of 12 vials. The patient should be observed for the next 1 hour to determine if initial control (defined as lack of progression in local signs of the leading wound edge, resolution in systemic symptoms, and normalization or near normalization of coagulation studies) has been achieved. If initial control is not achieved, an additional four to six vials can be administered repeatedly as needed. Once control is established, an additional two vials of CroFab are administered every 6 hours for 18 hours as maintenance. Given the high cost of antivenom, some experts will administer the maintenance vials on an as-needed basis only. This strategy can reduce intensive care unit (ICU) length of stay and the amount of antivenom administered without worsening patient outcomes; however, success rates rely on frequent bedside reevaluation by a clinician who is experienced in treating snake envenomation.[12]

The Anavip package insert recommends an initial dose of 10 vials given intravenously over 60 minutes as soon as possible after a rattlesnake or Crotalid bite in patients with signs of envenomation (see Table 53.3). A complete blood count, prothrombin time, partial thromboplastin time, serum fibrinogen, and chemistries should be obtained prior to the first dose. A repeat dose of 10 vials can be given as needed to establish initial control. Currently, there is no maximum known dose. Once initial control has been achieved, at least 18 hours of monitoring is recommended for observation of recurrence of symptoms. Initial control is demonstrated by lack of progression or improvement in local signs, resolution in systemic signs, and normalization (or near

TABLE 53.3 Antivenom Dosage for Pit Viper Envenomation

	CROFAB		ANAVIP	
Grade	**Initial**	**Maintenance**	**Initial**	**Maintenance[a]**
Moderate	4–6 vials (q1–2h until initial control achieved[b])	2 vials q6h ×3 doses	10 vials (q1–2h until initial control achieved)	4 vials (only for recurrence of symptoms)
Severe	8–12 vials (q1–2h until initial control achieved)	2 vials q6hr ×3 doses	10 vials (q1–2h until initial control achieved)	4 vials (only for recurrence of symptoms)

[a]Maintenance dosing is not required for patients who do not have recurrence of symptoms after 18 h of monitoring.
[b]Initial control is defined as lack of progression of local signs, resolution in systemic symptoms, normalization or near normalization of coagulation studies.
Anavip, crotalidae immune F(ab)$_2$ (equine); CroFab, crotalidae polyvalent immune Fab (ovine); q, every.

normalization) of coagulation studies. Return of symptoms can be treated with an additional four vials of Anavip IV.

Both CroFab and Anavip can cause severe allergic reactions. Patients who are allergic to papin, chymopapain, papaya extract, or bromelain (pineapple) may develop a hypersensitivity reaction to CroFab. Patient with allergies to sheep or horse proteins can develop anaphylactic reactions. Any evidence of hypersensitivity including wheezing, urticaria, and hypotension should be managed by immediate cessation of antivenom infusion and treatment with epinephrine, corticosteroids, and diphenhydramine as needed. Patients who are treated with a course of antivenom can become sensitized to it and should be cautiously monitored if the patient has a subsequent envenomation that requires antivenom.

The following are general guidelines to maximize patient care when antivenom is used:

1. Because anaphylaxis may occur whenever antivenom is administered, appropriate therapeutic agents (e.g., oxygen supply, airway support, epinephrine, diphenhydramine, corticosteroids, and other pressor agents such as norepinephrine) must be ready for immediate use. Any patient requiring antivenom should have two intravenous lines inserted. If an allergic reaction occurs, the line with the antivenom can be clamped and the other line used for resuscitation.
2. The pediatric antivenom dose is the same as the adult dose. A bitten child usually receives more venom in proportion to body weight and thus requires more antivenom to neutralize it. The smaller the body of the patient, the larger the relative initial dose that may be required. However, the total fluid requirements of children are lower, so the antivenom can be given in a more concentrated solution.
3. Pregnancy is not a contraindication to antivenom therapy.
4. Administration of antivenom at or around the site of the bite is not recommended.
5. The need for subsequent doses to achieve initial control is based on the patient's clinical response. The patient is monitored closely after the initial dose, and local and systemic symptoms, as well as laboratory findings, are determinants of the need for further antivenom. Additional injections of antivenom are administered every 1 or 2 hours if symptoms progress. Most hospital pharmacies do not stock large amounts of antivenom, and the pharmacy should be notified to obtain additional antivenom from surrounding hospitals or the regional poison control center for treating a severe bite.
6. Even with a history or signs of allergy, patients with severe envenomation are treated with a dilute form of antivenom and epinephrine to maximize antivenom administration but minimize allergic symptoms.
7. Consultation with an expert medical toxicologist or herpetologist should be obtained in cases of severe or complicated envenomation including allergic reactions to antivenom. Poison centers (1-800-222-1222) are an excellent resource for expert advice.

Coral and Exotic Snakes

Any patient bitten by an eastern coral snake is at risk for neurotoxicity that may not become evident for many hours. As a result, these patients require hospital admission, preferably to an ICU where they can be monitored closely for 24 hours for respiratory depression. Historically, it was recommended that all snakebite victims of the eastern coral snake *(M. fulvius)* be treated with antivenom even before any symptoms developed. North American coral snake antivenin (NACSA), a horse-derived IgG antibody, is currently in diminishing supply. Clinicians can still obtain the antivenom but might delay administration until the first signs of neurologic or respiratory compromise are observed. A local expert or certified poison center (1-800-222-1222) can help providers to determine the use of NACSA and aid in procuring it.

The stores of NACSA will eventually be depleted. Options for the future treatment of North American coral snake envenomation include prolonged supportive and respiratory care, the creation of a new antivenom, or relying on the cross-reactivity of a preexisting antivenom raised against another elapid species. Coralmyn antivenom is a polyclonal (Fab)2 fragment produced in Mexico that is obtained from horses inoculated with venom from the Black-banded coral snake *(Micrurus nigrocinctus nigrocinctus)*. Effective neutralization of both *M. fulvius* and *M. tener* venoms by Coralmyn antivenom has been demonstrated in a murine model. A murine model of *M. fulvius* envenomation was also successfully treated with an Australian tiger snake *(Notechis scutatus)* antivenom. The commercially available Australian polyvalent snake antivenom has effectively neutralized *M. fulvius* venom in another murine model.[13]

The challenges with managing bites of exotic or international snakes are threefold: Positive identification of the specimen is often difficult, even for experts; specific antivenom is not always readily available; and even if the antivenom is available, the instructions for reconstitution and dosage may not be described in English. Many zoos maintain a supply of antivenom for their exotic venomous snakes, and this may be the best source of antivenom for an exotic species. Some collectors keep appropriate antivenom on hand for the species that they collect. The Antivenom Index at the Arizona Poison Center (602-626-6016) can assist in identifying sources of exotic antivenom or in obtaining more pit viper antivenom. As with coral snakes, many patients do not show any early signs after envenomation by exotic neurotoxic snakes, so prolonged and intensive monitoring may be warranted.

Although exotic snake species are a source of concern in the United States, envenomation by these species in their native countries is a much more significant problem. The WHO estimates that up to 2 million people in Asia and 580,000 people in Africa are envenomated by snakes yearly. Many of these snakebite victims lack timely access to an

appropriate antivenom. In 2017, the WHO placed snakebites on the list of "Neglected Tropical Diseases."

Wound Care

The snakebite wound should be cleaned and examined for foreign bodies (e.g., retained fangs or teeth), the area immobilized, and proper analgesia administered. Elevation at or above heart level may relieve some of the pain. Local excision of the bitten area is not recommended. As with any puncture wound, one should ensure that tetanus immunization is current. The use of prophylactic antibiotics is previously discussed and not routinely administered with North America snakebites. Wounds should be cleansed daily with soap and water and a sterile dressing should be placed over any open wounds.

Surgical consultation may be required for management of necrotic wounds or in cases of true compartment syndrome refractory to adequate doses of antivenom. Superficial débridement of bullae allows for assessment of underlying tissue. Once necrotic tissue is identified, multiple surgeries may be needed for complete débridement of the nonviable tissue. In rattlesnake bites to the upper extremity, predictors of the development of necrosis include ecchymosis, initial cyanosis, and chronic alcohol use.[14] In the same study, cocaine use was associated with the need for surgical intervention.[14] Skin grafts are occasionally necessary after bites by pit vipers that produce large necrotic areas. Fasciotomy is rarely indicated unless compartment pressures are elevated greater than 30 mm Hg and signs of true compartment syndrome are present, which is uncommon because most snakebites involve subcutaneous layers and not deep into the musculature. Adequate doses of antivenom to lower intracompartmental pressures should be done prior to any consideration of fasciotomy in North American crotalid envenomation. Although not widely available in rural or remote settings, hyperbaric oxygen therapy is a potential adjunct to surgical management of severe snakebite wounds.[15]

Serum Sickness

Serum sickness can occur after administration of any animal protein derivative. The onset of serum sickness is typically 5 to 14 days after antivenom administration. Symptoms include fever, arthralgias, skin rash, and lymphadenopathy. Symptoms can be treated with oral antihistamines, nonsteroidal antiinflammatory drugs (NSAIDs), and corticosteroid taper. There is no role for prophylactic corticosteroids in the prevention of serum sickness.

Heloderma Envenomation

Gila monster and Mexican beaded lizard bites are treated similarly to pit viper bites with regards to first aid. No definitive medical treatment exists. Antivenom is currently not available. Local wound care, tetanus prophylaxis, use of antibiotics and analgesics, and supportive care are the extent of ED treatment for these types of envenomation.

DISPOSITION

If no envenomation is evident after a pit viper bite, the victim can be observed in the ED for 8 hours. If no sign of envenomation is seen after 8 hours and repeat diagnostic studies remain normal, the patient may be discharged home. These patients require wound care instructions as well as instructions on the types of delayed symptoms that may occur and when to return to the ED. Patients should seek medical care for worsening swelling, abnormal bleeding, signs of infection, and any development of serum sickness.

Following a minor pit viper envenomation that does not require antivenom, the patient should be monitored for 12 to 24 hours. Laboratory studies should be repeated every 4 to 6 hours. If the pain and swelling decrease and no systemic symptoms or laboratory abnormalities develop, the patient may be treated with the same precautions as a patient with no signs of envenomation. Antivenom should be considered and administered with any signs of a moderate or severe envenomation that develop during this period of observation.

Any patient with moderate or severe pit viper envenomation should be admitted for monitoring during antivenom therapy. Depending on the severity of the bite, blood products, vasopressors, and invasive monitoring may be necessary. Patients with recurrent hypofibrinogenemia following Crotalid envenomation can often be monitored in the outpatient setting; however, patients with other risk factors for bleeding may be treated with repeat doses of CroFab. Risk factors for clinically significant bleeding can include concurrent anticoagulant and antiplatelet medications, thrombocytopenia, and pregnancy.[16]

Once stable for discharge, patients who received CroFab antivenom need to be instructed to follow up for repeat laboratory testing given the risk of delayed coagulopathy. Patients should avoid high-risk activities such as contact sports and elective surgical or dental procedures. Patient treated with Anavip may not require routine follow-up testing given the longer half-life of the antivenom, but this requires further study.

Following suspected Mojave or eastern or Texas coral snake envenomation, the patient should be observed for 24 hours. Victims of unidentified exotic snakebites should also be observed for 24 hours for onset of symptoms or laboratory abnormalities. When the exotic species is identified, appropriate antivenom should be obtained if available. All patients receiving antivenom for hematotoxicity require close monitoring for recurrence of coagulopathy, which may occur several days after the initial envenomation.

VENOMOUS ARTHROPODS

Foundations

Arthropods are animals with segmented bodies and jointed appendages. The phylum Arthropoda contains approximately 80% of all known animals. The living members of this phylum are categorized into 12 classes, two of which, the Insecta and Arachnida, are of particular interest because they include numerous venomous species that are harmful to humans. The Insecta class includes wasps, bees, and ants. The Arachnida includes spiders, ticks, and scorpions. In general, arthropod species use venom as a mechanism to obtain prey or deter predators. With several exceptions, the venoms of the arthropods are largely unstudied. There is evidence that arthropod venoms evolved independently multiple times.[17]

Arthropods account for a higher percentage of deaths from envenomation than do snakes. They are found inside dwellings, as well as in deserts, forests, and lakes. Although most arthropods are more active during the warmer months, many are active throughout the entire year. Arthropods are also active 24 hours a day, and many can fly, thus increasing their range. This high level of contact results in millions of cases of envenomation annually. Most fatalities result from a hypersensitivity response by the victim rather than the toxicity of the venom. An individual stung by a bee may have a small amount of pain and local swelling or, in severe cases, an anaphylactic reaction and death.

Arthropods use three main methods of delivering venom: stinging, biting, and secreting venom through pores or hairs. Some arthropods combine multiple systems, one for offense and the other for defense. Human envenomation by arthropods is often defensive, accidental, or reflexive. Many venomous arthropods are omitted from this discussion because of their infrequent contact with humans or the relative impotence of their venom.

Fig. 53.5 Africanized Honeybee

Fig. 53.6 Female Black Widow Spider *(Latrodectus mactans)* With a Red Hourglass Marking.

Hymenoptera

Hymenoptera is a familiar order of arthropods that is composed of the families of bees, wasps, hornets, yellow jackets, and ants (Fig. 53.5). Many of these species are social insects, and their defense response is related to protection of the colony rather than the individual organism. Although most members of this order are stinging insects, several species of ants can bite and sting simultaneously. Of the more than 90,000 species of hymenoptera, less than 200 are known to envenomate humans. Of those, only honeybees, hornets, and yellow jackets are known to have killed humans through direct envenomation.[18]

Bees and wasps have similar mechanisms of delivering venom. Female insects of this type deliver venom from modified sex accessory glands through ovipositors that protrude from the abdomen. The barbed stinging apparatus of the bee is quite prominent. The stinging action pulls the stinger from the bee, thereby eviscerating the insect and killing it. The wasp, which has an unbarbed stinger, may inflict many stings without damaging itself or its stinging apparatus.

Ants can latch onto humans through a bite and then deliver a sting. In general, the stinging ants, including fire ants, cause greater symptoms in humans than those that spray noxious chemicals like formic acid. Fire ants typically sting 7 to 8 times once latched on at the bite site.

Hymenoptera venom is more widely studied than the venom of other arthropod groups. It is composed of several classes of substances varying in composition among different species. Components include enzymes such as phospholipase A and hyaluronidase, as well as biogenic amines, and peptides such as MCD-peptide and apamin. Many other antigenic substances have been identified in hymenoptera venom, and they account for the induction of hypersensitivity and anaphylaxis in humans. In the United States, 10% of all cases of anaphylaxis are attributed to hymenoptera. Purified venoms from honeybees, yellow jackets, and wasps are available to use in the diagnosis and treatment of hypersensitivity.

Spiders and Scorpions

The class Arachnida contains the largest number of venomous species known, with approximately 34,000 species of venomous spiders and 1400 species of venomous scorpions. Virtually all known species are venomous, but most are not harmful to humans. Only approximately 50 species of arachnids in the United States cause human illness, because most species do not have fangs or stingers sufficiently long to penetrate human skin. Humans commonly fear scorpions and spiders, a disorder known as arachnophobia. Ticks, which also belong to this class, are less feared but cause more morbidity because of transmission of infectious diseases, such as Rocky Mountain spotted fever and Lyme disease. Some spider bites are never diagnosed because of lack of significant symptoms and the fact that they occur while the victim is sleeping. Many nonspider bites are incorrectly diagnosed as spider bites because there is no gold standard for making an accurate diagnosis.

Black Widow Spider

The black widow spider, *Latrodectus mactans,* may be the most recognized venomous spider in the world. Several other closely related species of *Latrodectus,* or widow spiders, are found throughout the United States, including *Latrodectus hesperus, Latrodectus geometricus*, and *Latrodectus bishopi*. The diagnosis and treatment of the bites of all of these species are the same.

The black widow female is approximately twice as large as the male, and although both are venomous, only the female is able to envenomate humans. The female black widow spider is generally dark brown to glossy black, occasionally with red stripes, and has a bright red marking on the abdomen (Fig. 53.6). This marking may have an hourglass shape or may appear only as two spots. Abdominal markings may vary, and related *Latrodectus* species may be similar in appearance and toxicity. Female black widow spiders have a rounded body that is generally 8 to 10 mm in size. Window spider webs are generally in dark, protected places, such as under rocks, in woodpiles, and in outhouses and stables. The female is not aggressive except when guarding her eggs. Bites tend to occur when the web or spider is disturbed.

The venom apparatus of the black widow is a modified first appendage of the head known as the *chelicera.* The spider is able to control the amount of venom injected into its prey. Widow spider venom contains neurotoxins that effect insect and crustacean neurons, as well as one toxin, α-latrotoxin, that effects vertebrates. This toxin destabilizes neuronal membranes by opening ionic channels, causing massive exocytosis of acetylcholine, glutamate, dopamine, γ-aminobutyric acid (GABA), and norepinephrine from the mammalian presynaptic neuron.

Brown Recluse Spider

In the 1950s, several deaths were erroneously attributed to the brown recluse spider, *Loxosceles reclusa*, thus drawing the attention of the medical community. Many species of *Loxosceles*, or "brown spiders," are venomous to humans, and multiple species are found in the United States. These spiders are approximately 1 inch long, including leg span, and range in color from tan to dark brown. The most distinguishing mark is a violin-shaped darker area found on the dorsal cephalothorax (Fig. 53.7). Close examination may reveal that the brown recluse has three pairs of eyes rather than the usual four sets found in most spiders.

Fig. 53.7 Brown Recluse Spider *(Loxosceles reclusa).* (From Mullen GR. Chapter 22: Spiders *(Araneae).* In: *Medical and Veterinary Entomology.* Muller GR, Durden L (eds). 2002:427–448.)

As their name implies, these spiders are not aggressive and are usually found under rocks, in woodpiles, and occasionally in attics and closets. They do not bite unless provoked. As with widow spiders, the female *Loxosceles* spiders are more dangerous to humans than males. The typical range of the brown recluse spider is concentrated in the south-central United States, especially Missouri, Kansas, Arkansas, Louisiana, eastern Texas, and Oklahoma. However, with climate change, their geographic distribution is expanding.

The venom apparatus of the brown recluse is similar to that of most spiders, including the black widow. The composition of *Loxosceles* venom has not been completely determined; however, phospholipase D, metalloproteases, and insecticidal peptides are identified as significant components.[19,20] Toxins of the phospholipase D family (previously sphingomyelinase D) cause many of the feared complications of brown recluse envenomation, including dermonecrosis, hemolysis, and renal failure. Hyaluronidases, serine proteases, venom allergens, and serpins have also been identified, however at much lower rates of expression.[19,20]

Scorpions

Scorpions are arachnids that resemble crustaceans and are among the oldest terrestrial animals. Scorpions are found throughout the world, and several species are located in the southwestern United States. One species, *Centruroides sculpturatus*, is particularly dangerous to humans. Envenomations from *Centruroides* have been reported from several states including Arizona, Nevada, and Utah.[21] Globally, there are many other scorpion species that can cause severe envenomation in humans. Most scorpion species of medical importance belong to the Buthidae family, which in addition to *Centruroides* sp., includes several other dangerous scorpion genera including *Buthus, Parabuthus, Mesobuthus, Tityus,* and *Androctus.* Scorpions are nocturnal predatory animals that usually spend the day under rocks, logs, or floors and in crevices. *C. sculpturantus,* or the bark scorpion, is found on or near trees (Fig. 53.8).

The scorpion has a tail-like structure that is actually the last six segments of its abdomen. The last segment, or the *telson,* contains the two venom glands and stinger. The toxicity of scorpion venom varies greatly from species to species; however, the systemic symptoms from severe envenomation are generally autonomic neuroexcitatory

Fig. 53.8 Arizona Bark Scorpion (*Centruroides sculpturatus,* Formerly *Centruroides exilicauda*).

symptoms. One important component of scorpion venoms is the α-toxins, polypeptides that bind to voltage-gated sodium channels and inhibit inactivation. This prolonged depolarization results in neuronal excitation and activation of the autonomic nervous system.

CLINICAL FEATURES

Hymenoptera

The signs and symptoms of bee and wasp stings vary, depending on the degree, type, and location of envenomation, as well as the characteristics of the victim. Allergic reactions, not direct venom toxicity, are typically the major clinical concern following hymenoptera envenomation. However, it is important to note that bees and wasps can cause serious injury other than allergic types of reactions, depending on the number of stings, the species of insect, the size and previous health of the victim, and the anatomic area stung. Clinically significant envenomation, with the exception of those causing allergic reactions, often require a massive number of stings resulting in venom toxicity.[22] Certain species of honeybee release a pheromone, isoamyl acetate, when the ovipositor is pulled from the abdomen after stinging a victim. This pheromone attracts other bees to the victim and thus incites multiple stings.

The most consistent finding is immediate pain at the site of the sting, followed by local swelling, redness, and itching. A sensitized victim may experience swelling, urticaria, coughing, wheezing, coma, and respiratory arrest. Some large and especially venomous hornets have been known to cause muscle necrosis, rhabdomyolysis, and renal damage. In addition, cerebrovascular accidents, intracranial bleeds, and myocardial infarction have been described following hymenoptera envenomation.[23] Most serious reactions to bee stings occur in the first 30 minutes; however, the local effects of a sting may persist for 2 or 3 days. Delayed hypersensitivity may occur 7 to 10 days after the sting.

There is little antigenic overlap among hymenoptera species, which may explain the variability in reaction to stings reported by victims. For example, victims who are allergic to honeybees and who mistakenly identify a yellow jacket as a honeybee may not have a systemic reaction and thus may think that they are no longer allergic to honeybees.

Africanized Bees

Africanized bees, or "killer bees," are a hybrid species of the East African lowland honeybee *(apis m. scutellata)* and the western honeybee. Africanized bees were first bred in the 1950s in an effort to increase honey production. In the 1950s, multiple swarms of these hybrid bees were released from a facility in Brazil and have since spread rapidly

through the Americas. Africanized bees are not more toxic than the western, or European, varieties; however, they do display different behaviors. Africanized bees are more easily provoked and have a tendency to attack in massive numbers. Multiorgan system failure can result in the days following severe envenomation (hundreds of stings). Moderate envenomation (50 to 200 stings) typically causes nausea, vomiting, anxiety, tachycardia, hypertension, rhabdomyolysis, and kidney injury. Envenomation from Africanized bees is most dangerous to very young or elderly patients and those with comorbidities.

The Asian or Japanese giant hornet *(Vespa mandarinia)* is one of the world's largest hornet. It is native to tropical areas of east and southeast Asia in including the Russian Far East. In 2019, it was sighted in the Pacific Northwest of the United States and Canada as an invasive species. Popular media have coined the term "murder hornets" because it kills and feeds on other large insects and honeybee colonies. Although rare, human fatalities from multiple stings have been reported in Asia.

Fire Ants

Another venomous hymenoptera in the United States is the fire ant (Family Formicidae). Several species of fire ant are known, some native to North America and some imported. The species responsible for 95% of clinical cases, *Solenopsis invicta,* was imported from Brazil to Alabama in the 1930s. This ant is now found in nine southern states and is replacing many native species and inhabiting new niches. The limiting factor keeping *S. invicta* from progressive migration is cold winter temperatures, but with climate change, their ranges are increasing northward. This ant is small and light reddish brown to dark brown. Its venom is unique to the animal kingdom in that 95% of its components are alkaloids, mostly 2,6-disubstituted piperidines. The remaining fraction of venom is made of proteins which are immunogenic and can sensitize an individual to the venom. Properties of this venom include hemolysis, depolarization of membranes, activation of the alternative complement pathway, and general tissue destruction. A fire ant sting is produced when the ant bites the victim with its jaws and, while holding tight, pivots around and stings the victim with its ovipositor. The sting usually produces a sterile pustule within 24 hours. Other symptoms include local burning, redness, and itching. With victims of multiple stings and in sensitized individuals, urticaria, angioedema, dyspnea, nausea, vomiting, wheezing, dizziness, and respiratory arrest may occur. Approximately half of victims have some degree of hypersensitivity reaction, including late cutaneous allergic reactions. Although the invasive species of fire ants are most often implicated in clinically significant stings, envenomation by native species of the fire ant, including *Solenopsis aurea*, has resulted in severe systemic toxicity, including disseminated intravascular coagulation.[24]

Black Widow Spider

The classic symptomatology of the black widow bite is initially a pinprick sensation that may be followed by minimal local swelling and redness. Bites are most common on the extremities, especially the lower extremities, and rare on the trunk.[25] If the area is examined closely, two small fang marks may be noticed. Sometimes the bite is not felt, especially if the victim is working or active when the bite occurs. From 15 minutes to 1 hour later, dull crampy pain develops in the area of the bite and gradually spreads to include the entire body. Usually, the pain is concentrated in the chest after upper extremity bites or in the abdomen after lower extremity bites. The abdomen may become rigid, and the patient may complain of severe crampy pain. The abdominal manifestation may mimic pancreatitis, peptic ulcer disease, or acute appendicitis. Pregnant women may go into premature labor and precipitous delivery. Associated symptoms include dizziness, restlessness, ptosis, nausea, vomiting, headache, pruritus, dyspnea, conjunctivitis, facial swelling, sweating, weakness, difficulty speaking, anxiety, and cramping pain in all muscle groups. Priapism has been reported in children. Children with priapism are also affected by more common symptoms of latrodectism, including abdominal pain and tachycardia.[26] The patient is usually hypertensive, and cerebrospinal fluid pressure can be elevated. Although extraordinarily painful, death from latrodectism is rare.

The signs and symptoms of black widow envenomation typically begin to abate after several hours, and residual muscle cramping usually resolves in 2 or 3 days. Small children and adults with preexisting cardiovascular or cerebrovascular disease are at greater risk of complications.

Brown Recluse Spider

The symptoms of a brown recluse spider bite are both local and systemic. Initially, the victim may notice some burning pain in the area of the bite. Some victims do not notice the initial bite at all. In minor envenomation, a localized cytotoxic reaction may occur, and skin findings may be limited to a small papule or localized urticaria. The vast majority of brown recluse bites do not progress past this stage. With more significant envenomation, pain usually develops within 3 to 4 hours, and a white area of vasoconstriction begins to surround the bite. A bleb then forms in the center of this area, and an erythematous ring arises on the periphery. The lesion at this stage resembles a target or "bull's-eye." The bleb darkens, necroses over the next several hours to days, and continues to spread slowly and gravitationally, with involvement of skin and subcutaneous fat. Eschar formation typically occurs after 7 to 14 days. Systemic symptoms may develop and include fever, chills, rash, petechiae, nausea, vomiting, malaise, and weakness. Hemolysis, thrombocytopenia, shock, jaundice, renal failure, hemorrhage, and pulmonary edema are signs of severe envenomation. Skin findings do not predict systemic symptoms. Although rare, fatalities are more common in children, which are most often the result of severe intravascular hemolysis.

Scorpions

Scorpion envenomation causes severe and immediate pain at the sting site. Local edema and erythema may or may not be present, depending on the species. After envenomation by *C. sculpturatus,* the victim may have heightened sensitivity to touch in the area of the sting along with local numbness, weakness, and muscle fasciculations. Wound necrosis is not typical of most scorpion stings; however, delayed necrosis is common after envenomation by *Hemiscorpius lepturus* scorpion of Iran.

Systemic symptoms may then develop. Autonomic excitation includes both early cholinergic parasympathetic effects such as diaphoresis, lacrimation, and diarrhea, as well as the adrenergic sympathetic effects of tachycardia, hypertension, and restlessness that dominate the later course of toxicity. Peripheral nervous system excitation is especially common in *C. sculpturatus* envenomation and includes "roving eye movements" and thrashing of the extremities. Increased sympathetic tone results in tachydysrhythmias, ectopy, and ST and T wave changes on ECG. Direct cardiac toxicity is not a feature of *C. sculpturatus* envenomation.

Symptoms of *C. sculpturatus* envenomation typically peak within 5 hours of the sting and may persistent for 30 hours. Pediatric patients tend to have more severe symptoms and a more rapid onset of systemic systems.

DIFFERENTIAL DIAGNOSES

Hymenoptera

The differential diagnosis of hymenoptera envenomation include stings from honeybees, wasps, hornets, yellow jackets, fire ants, scorpions, centipedes, millipedes, caterpillars, spider bites, infectious causes such

as cellulitis, and other allergic reactions, including anaphylaxis and contact dermatitis.

Black Widow Spider

The manifestations following a black widow spider bite may mimic an acute surgical abdomen, renal colic, mesenteric ischemia, tetanus, scorpion stings, myocardial ischemia, or severe alcohol or opioid withdrawal.

Brown Recluse Spider

The differential diagnosis of a brown recluse spider bite includes pyoderma gangrenosum, furuncles, viral and fungal infections, and foreign body reactions. Cutaneous anthrax has been misdiagnosed as brown recluse envenomation. The most common mimic of *Loxosceles* or other necrotic spider bite are skin and soft tissue infections, including MRSA. Other spider species, such as the orb weaver, can also cause necrosis.

The mnemonic NOT RECLUSE has been proposed to avoid false diagnosis of brown recluse bites as is as follows[27]:

N—Numerous. Bites from the brown recluse are typically solitary.
O—Occurrence. Most brown recluse bites occur after the spider is disturbed from a quiet, covered place such as a box or unused clothing.
T—Timing. Most bites in North America occur between April and October.
R—Red Center. Envenomation results in destruction of the capillary bed. The center of a recluse bite will be pale, blue, or purple.
E—Elevated. Brown recluse bites are typically flat or sunken.
C—Chronic. Only the most severe and largest brown recluse bites will have not healed by 3 months.
L—Large. Necrosis from recluse bites very rarely extends past 10 cm.
U—Ulcerates too early. Brown recluse bites typically ulcerate between 7 and 14 days.
S—Swollen. Brown recluse bites do not cause significant swelling, except when the bite is to the face or feet.
E—Exudative. Brown recluse bites are typically dry.

Scorpions

The differential diagnosis of scorpion stings includes black widow spider bites, centipede stings, and hymenoptera stings, such as bees, wasps, and fire ants.

DIAGNOSTIC TESTING

Hymenoptera

Most cases of hymenoptera stings present with localized reactions and require no diagnostic studies. Severe reactions, infections, and anaphylaxis should have a complete blood count, serum electrolytes, and their acid-base status assessed. Those demonstrating severe allergic reactions should be referred for more comprehensive allergy skin testing.

Black Widow Spider

Routine testing is not recommended in black widow envenomation; however, patients with significant comorbid conditions may benefit from laboratory testing to assess for potential complications of latrodectism. These tests may include a complete blood count, electrolytes, blood urea nitrogen, creatinine, coagulation studies, urinalysis, and an ECG. There may be electrocardiographic changes similar to those produced by digitalis. Aside from advanced forensics analysis, there are no commercially available tests to diagnose black widow envenomation.

Brown Recluse Spider

Enzyme-linked immunosorbent assay (ELISA) for *Loxosceles* venom exists but is not commercially available for clinical use in the United States. The diagnosis of a brown recluse bite depends on a consistent clinical presentation, an observed spider bite, and identification of the spider as a brown recluse. In nonendemic areas, brown recluse envenomation should not be suspected absent an observed bite from an identified brown recluse spider. When significant wounds or systemic symptoms are present, a complete blood count, renal function tests, electrolytes, coagulation profile, hepatic function profile, creatine kinase, and urinalysis are recommended. With evidence of hemolysis, a type and screen, haptoglobin, fibrin split products, D-dimer, and fibrinogen should also be considered.

Scorpions

A serum Western blot test has been developed that can differentiate various scorpion venoms and thus help with diagnosis of *Centruroides* species, but it is not commercially available. Patients with minor, localized symptoms do not need routine laboratory testing. Laboratory testing for more severely symptomatic patients will depend on the envenoming species and may include a complete blood count, renal function test, serum electrolytes, liver function tests, urinalysis, lipase, troponin, and an ECG.

MANAGEMENT

Prehospital Care

Hymenoptera

First aid for Hymenoptera envenomation depends on the degree of reaction to the sting. For simple stings, an ice bag wrapped in a towel and applied to the sting area usually relieves the pain and swelling. In the event of an anaphylactic reaction, basic life support is administered until further medical help arrives. If available, epinephrine 1 mg/mL (1:1000) solution should be administered intramuscularly. Any patient who improves with epinephrine prehospital still requires emergency evaluation.

Black Widow Spider

First aid for a black widow spider bite consists of applying an ice pack to the bite area for relief of pain and transporting the victim to a hospital where supportive, symptomatic, and definitive treatment can be administered. The patient is monitored en route to the hospital, and basic life support is initiated if necessary. Bites in the neck or mouth area may cause airway compromise through muscle spasm.

Brown Recluse Spider

The specimen is secured or photographed for later identification, and the victim is transported to a medical facility. Because the lesion develops over a period of days, local treatment of the lesion in the acute setting is generally ineffective.

Scorpions

First aid for a scorpion sting consists of applying an ice bag to the area of the sting and transporting the victim to the hospital. History includes the circumstances surrounding the sting, any previous medical problems, and a description of the scorpion or digital image (if one can be safely obtained). It is relatively difficult for a layperson to differentiate the various scorpions. Capturing or attempting to identify a specimen should not delay transport to the hospital.

Emergency Department Care

Hymenoptera

No specific antivenom exists for Hymenoptera stings. Treatment consists of local wound care and general supportive measures. When possible, any retained stinging apparatus should be removed. A history

of previous allergic reactions to bee stings, hay fever, asthma, or drug reactions is obtained. The circumstances surrounding the sting and the number and location of stings are noted. In patients with a local reaction, an ice bag is typically sufficient treatment. Local reactions can extend a few centimeters from the site of the sting and typically improve over the course of hours to days. Larger local reactions are an exaggerated local response to envenomation. These reactions tend to worsen for the 2 days following the sting before gradually improving. Ice bags, steroid tapers, NSAIDs, and oral antihistamines can be used in the treatment of large local reactions. Standard treatment of anaphylaxis including epinephrine 0.3 mg (1 mg/mL) through intramuscular injection should be initiated in adults with evidence of a systemic reaction such as dyspnea, hypotension, generalized urticaria, flushing, or edema. Careful attention to the patient's airway and hemodynamic status is essential. In addition to epinephrine, patients with systemic reactions can be treated with H1 and H2 blockers. Bronchodilators should be given for bronchospasm. Glucocorticoids have traditionally been used in the treatment of anaphylaxis; however, their routine use is no longer recommended. Glucocorticoids do not address the initial symptoms of anaphylaxis and do not prevent biphasic reactions. Intravenous epinephrine is indicated when anaphylaxis is refractory.

Treatment of allergic reactions to fire ant stings is similar to bee stings. The skin lesions should be kept clean with soap and water and the patient should encouraged not to open any pustules. Ice bags may be applied initially to relieve burning and pain. Antihistamines are recommended for pruritis. Prophylactic antibiotics are not indicated.

Black Widow Spider

Emergency care consists of obtaining a history of the circumstances surrounding the bite, a description of the appearance of the spider, any significant past medical history, current medications, and allergies to insect bites, horses, or horse serum. The wound site is inspected for fang marks and cleansed with soap and water. As with any puncture wound, the patient's tetanus immunization status is assessed.

Symptomatic treatment involves controlling the muscle cramps responsible for most of the discomfort associated with the bite. Intravenous opioid analgesics and benzodiazepines are administered as needed for relief for severe symptoms. Calcium gluconate, dantrolene, and muscle relaxants are not recommended given the lack of supporting evidence. Antivenom should be considered in high-risk patients and in those with refractory symptoms despite adequate doses of benzodiazepines and opioids.

Latrodectus Antivenom

In general, young children, pregnant patients, the elderly, and those with persistent severe symptoms are candidates for *Latrodectus* antivenom. The available antivenom is an equine-derived IgG directed against *L. mactans*. Although most effective if used early in the clinical course, symptom resolution has occurred with administration up to 3 to 4 days after envenomation. The dose of antivenom is one 2.5-mL vial diluted in 10 to 50 mL of normal saline and administered IV over a period of 15 to 30 minutes. Intramuscular administration is not recommended.

Latrodectus antivenom IgG is composed of whole equine immunoglobulin and does carry a risk of anaphylaxis and serum sickness. It is also in short supply in the United States. Skin testing does not exclude a life-threatening allergic reaction and is therefore not recommended. Latrodectism itself is generally not life threatening, so the risks and benefits of giving the antivenom should be carefully considered. Consultation with a local expert or poison center (1-800-222-1222) is recommended prior to the use of *Latrodectus* antivenom.

The efficacy and safety of a highly purified equine F(ab′)2 antibody black widow spider antivenom is currently being investigated. Preliminary studies show promising results; however, further studies are needed to assess for safety and efficacy.[28]

Brown Recluse Spider

Emergent evaluation involves a history of the circumstances surrounding the bite; the time elapsed since the bite; past history of allergic reactions, medications, or medical problems; and an assessment for systemic toxicity. If the actual spider is available, identification may be facilitated by recruiting the expertise of a local entomologist. The wound is washed with soap and water. Ice, elevation, analgesia, and antihistamines may alleviate initial symptoms. If signs of systemic toxicity develop, an intravenous line is placed in an unaffected extremity. Vital signs and urine output are closely monitored. Excision of the lesion has not been shown to aid healing and may actually be detrimental to long-term healing. Although rare, lesions have been known to cause extensive scarring, infection, and necrosis. Bites that are in fatty areas, such as the thigh or buttocks, may cause more extensive necrosis. Surgical consultation should be obtained for evaluation of the wound; however, surgery is often delayed until clear wound demarcation has occurred.

Hyperbaric oxygen has been used successfully in humans to treat nonhealing wounds caused by brown spider bites.[29] Vacuum-assisted wound closure has also been used successfully for healing of necrotic wounds. Historically, dapsone, 50 to 200 mg/day, was thought to help prevent the local tissue effects of brown recluse venom. However, dapsone may cause methemoglobinemia and hemolysis (particularly in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency), and its effectiveness has never been clinically validated. As a result, we do not recommend routine use of dapsone in patients suffering brown recluse spider bites. There is no role of prophylactic antibiotics, and the use of antibiotics should be limited to treating any secondary infections. Patients who develop rhabdomyolysis should be treated with isotonic fluids to maintain adequate urine output, typically 200 to 300 mL/hr. As with the treatment of other etiologies of heme-associated renal injury, close monitoring for signs of fluid overload is essential during aggressive fluid administration. Although rare, hemodialysis may be necessary if acute renal failure develops. Hemolysis is generally self-limited; however, plasma exchange has successfully to treat refractory hemolysis after a brown recluse spider bite.[30] The Instituto Butantan in Sao Paulo, Brazil, and Instituto Bioclon, Mexico, both produce an antivenom for *Loxosceles* sp. bites, but they are not currently available in the United States.

Scorpions

Further management of North American *Centruroides* scorpion envenomation, including the use of antivenom, can be correlated with the grade of envenomation (Table 53.4). Grade 1 and 2 envenomations are treated with local wound care and analgesia. Tetanus prophylaxis should be given if the patient is not current on his or her immunization status. *Centruroides* antivenom is indicated for grade 3 and grade 4 envenomations. Anascorp (*Centruroides* [scorpion] immune F[ab]2 equine injection) is horse serum derived and has been shown to be effective and safe in both blinded and open clinical trials. Most studies investigating the effectiveness of antivenom (Anascorp) focus on children and young adults, which corresponds to the population more often severely affected by envenomation and more likely to require antivenom.[31] At 4 hours after Anascorp administration, a significantly greater number of patients have resolution of symptoms compared to those who are not treated with antivenom.[31] In general, Anascorp antivenom is not considered an essential life-saving intervention in adults, and supportive measures are typically sufficient. However, if Anascorp is indicated, the initial dose is 3 vials given intravenously as soon as possible after a scorpion envenomation. An additional vial may be administered every 30 to 60 minutes as needed.

TABLE 53.4 North American *Centruroides* Scorpion Envenomation Grading

Grade	Clinical Features	Antivenom[a]
1	Local effects only, including pain and paresthesias at the site of envenomation	No
2	Local and remote pain and paresthesias	No
3	Cranial nerve dysfunction OR skeletal somatic neuromuscular dysfunction. Cranial nerve dysfunction may include dysphagia, abnormal eye movements, drooling, dysphagia, slurred speech. Skeletal muscle dysfunction may present as jerking/writhing of extremities, opisthotonos, emprosthotonos, and restlessness. Autonomic dysfunction is common at this grade and includes tachycardia, bronchoconstriction, salivation, and diaphoresis	Yes
4	Cranial nerve dysfunction AND skeletal somatic neuromuscular dysfunction	Yes

[a]Anascorp (*Centruroides* [scorpion] immune F[ab]2 equine antivenom).

Supportive measures after any severe envenomation include adequate analgesia, cardiorespiratory support, and relief of neuromuscular hyperactivity. Acetaminophen and NSAIDs may be sufficient for minor symptoms; however, opioid analgesia (e.g., fentanyl) may be necessary for more severe symptoms. Benzodiazepines such as midazolam or diazepam should be used for severe anxiety and muscle hyperactivity if antivenom is not used. Nitroglycerin can help to reduce preload and afterload in patients who develop pulmonary edema. Ventilatory assistance may be necessary, especially in children. Prazosin has been effective, especially in addition to antivenom, for treatment of catecholamine excess and cardiovascular compromise in *Mesobuthus tamulus* stings.[31] This species of scorpion is found in India, Nepal, and Pakistan. Use of atropine is limited to specific species such as *Parabuthus transvaalicus,* which can cause acute cholinergic toxicity.

DISPOSITION

Hymenoptera

After a hymenoptera sting, the patient is monitored, and if no further reaction is observed, they may be discharged home with instructions to return to the ED if wheezing, dyspnea, hives, dizziness, or dysphagia occurs. Any patient requiring epinephrine should be watched for at least 6 hours and may require 24-hour observation if symptoms recur. There is a possibility of recurrence of the reaction up to 72 hours, and patients should be warned of this accordingly. Patients who present with systemic hypersensitivity symptoms after hymenoptera sting should be referred for allergy testing and possible immunotherapy. These patients should be prescribed an epinephrine autoinjector and educated regarding its proper use.

Black Widow Spider

A victim of a black widow spider bite is generally observed for approximately 6 hours. If symptoms do not develop, the patient may be discharged with instructions to return to the ED if any symptoms develop. Otherwise, healthy patients with only mild symptoms of envenomation after 6 hours can be managed as an outpatient with oral analgesia. Patients with moderate or severe symptoms are admitted to the hospital and treated until symptoms subside, usually within 24 hours. Fetal monitoring is initiated for pregnant women.

All patients should be educated on basic wound care and the signs of infection at the time of discharge. Patients who received antivenom should also be counseled to seek medical attention for any symptoms or serum sickness, such as fevers, arthralgias, or rash.

Brown Recluse Spider

Patients with expanding wounds or signs of systemic envenomation require hospital admission for wound care, monitoring, and serial laboratory testing to assess for hematotoxicity.

Scorpions

It is recommended that victims with systemic symptoms be observed for 24 hours and that young children be admitted to the hospital for monitoring. Patients with localized pain at the site of the sting can be given pain medications and discharged home with wound care instructions. All patients who have been treated with Anascorp are at risk of developing serum sickness and should be instructed to monitor for symptoms such as rash, arthralgias, and fevers.

Other Arthropods

More than 40 different species of ticks have been implicated in tick paralysis, a progressive ascending paralysis in humans and animals. The two species responsible in the United States are *Dermacentor andersoni* (wood tick) and *Dermacentor variabilis* (dog tick). The precise mechanism and structure of the *Dermacentor* toxins are unclear; however, neurotoxins appear to cause weakness through disruption of sodium flux across axonal membranes. The bite of the tick is usually painless, but the victim later has difficulty walking, weakness, flaccid paralysis, slurred speech, and visual disturbances. The victim is usually a child, often with a history of recent outdoor activity. Treatment is removal of the offending tick. Patients often start to improve within hours after removal of *Dermacentor* ticks; however, symptoms may continue to worsen for days after removal of *Ixodes holocyclus.* For further description of tick-borne illness, including Lyme disease (from *Ixodes scapularis* and *Ixodes pacificus*) see Chapter 123.

Several species of beetle, millipede, and caterpillar secrete irritating substances that cause severe burning pain, numbness, pustular contact dermatitis, edema, nausea, vomiting, and headache. Oropharyngeal exposure can cause mucosal edema and irritation. Deaths have rarely been reported. Treatment consists of washing the area thoroughly with soap and water and removing any spines or hairs present. Analgesics should be used as needed, and supportive therapy may be necessary for severe envenomation.

Centipedes can inflict bites that cause erythema and edema. Treatment is usually local soaks and the use of analgesics. Conenose bugs, or "kissing bugs," may cause severe local and systemic allergic reactions. Treatment with antihistamines and supportive care, depending on the degree of reaction, is generally all that is necessary. Many other arthropods can cause local skin reactions and severe allergic reactions, depending on the individual's sensitivity. Patients are treated symptomatically with local steroid creams, antihistamines, and other symptomatic supportive measures.

VENOMOUS MARINE ANIMALS

Foundations

Almost 2000 species of animals found in the ocean are either venomous or poisonous to humans. The majority of marine envenomation

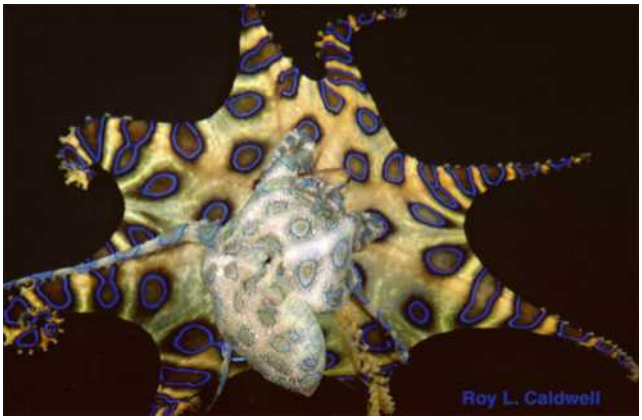

Fig. 53.9 Blue-Ringed Octopus (*Hapalochlaena maculosa*). (From Cheng MW, Caldwell RL. Sex identification and mating in the blue-ringed octopus, *Hapalochlaena lunulata*. *Animal Behavior*. 2000;60(1):27–33.)

are minor and do not require medical attention; however, many can produce severe illness or fatalities. An estimated 40,000 to 50,000 marine envenomations occur worldwide annually. In recent years, the number of injuries caused by these animals has increased dramatically because of the greater number of people living and vacationing near coastal waters, scuba divers, snorkelers, surfers, and others engaging in water sports. These animals are not typically aggressive, and many are completely immobile. Most of the venomous marine animals injure humans with defensive or food-procuring devices. Most venomous marine animals in the United States are found along the California, Gulf of Mexico, and southern Atlantic coasts. These creatures range in complexity from sponges to bony fishes and contain some of the most complex and toxic venoms known.

Pathophysiology and Venom Delivery

In general, venomous marine animals are divided into three main classes according to the mechanism of venom delivery: bites, nematocysts, and stings.

Bites

Biting animals include several species of cephalopods, most often octopuses. Several fatalities have been reported after a bite by the blue-ringed octopus, *Hapalochlaena maculosa*, a small octopus found in the shallow waters of the Indo-Pacific (Fig. 53.9). Most victims are bitten on the upper extremity because they disturb this normally nonaggressive creature. The octopus has a pair of modified salivary glands that secrete venom into puncture wounds produced by the animal's parrot-like beak. The venom contains tetrodotoxin, a potent sodium channel blocker, which causes neurologic symptoms within minutes of envenomation. No known antivenom exists, and treatment is largely supportive, with respiratory support being the most important lifesaving intervention.

Nematocyst

The second type of venom delivery is the nematocyst, a microscopic stinging organelle found in members of the phylum Cnidaria. This group of animals includes the Portuguese man o' war, true jellyfish, fire corals, stinging hydroids, sea wasps, sea nettle, and anemones. Most of these organisms are sessile, but some are free floating. Because of their large numbers, this group accounts for the greatest number of envenomations by marine animals.

Many different types of nematocyst are known, but the basic mechanism is a "spring-loaded" venom gland that can, on mechanical or chemical stimulation, suddenly evert and discharge a structure that penetrates the prey and delivers the venom through a connecting tube. Tentacular nematocysts can number in the thousands. Tentacles can be more than 100 feet long in giant species such as the Portuguese man o' war. Nematocysts can still function even if the animal is dead or if the tentacles are separated from the animal's body. These stinging organelles can remain active for weeks after an animal becomes beached. Nematocysts fire on initial contact but may also discharge later during attempted rescue and treatment. Certain marine species have evolved methods of using ingested nematocysts for their own secretory defense.

Toxicity

Nematocyst venom contains various peptides, phospholipase A, proteolytic enzymes, hemolytic enzymes, quaternary ammonium compounds, serotonin, and other toxic compounds. The severity of the envenomation can range from localized skin eruptions to life-threatening reactions. The severity of the reaction depends on multiple variables, including the envenoming species, the number of nematocysts discharged, the duration of exposure, the affected body part, and the victim's individual reaction to the envenomation.[32] Most envenomations produce minimal symptoms, and the danger is either drowning after being stung or an allergic reaction to the venom.

Clinical Features

Symptoms may range from simple isolated stings to respiratory paralysis, cardiovascular collapse, and death. The victim's autopharmacologic response to the venom may turn a relatively minor envenomation into a fatal anaphylactic reaction. Any clinician who regularly treats this type of injury should become acquainted with the common species indigenous to their region. The appearance of the wound is unlikely to aid in the clinical diagnosis.

Although potentially lethal jellyfish exist worldwide, the extremely toxic specimens are found in the Indo-Pacific waters and include the Australian box jellyfish or "sea wasp" *(Chironex flickeri)* and Irukandji *(Carukia barnesi)*. *C. flickeri* (Fig. 53.10) is responsible for several deaths along the Australian coast annually. Envenomation results in immediate severe pain with characteristic linear welts in a "frosted ladder" or crosshatched pattern. Skin ulceration and necrosis follows in 1 to 2 weeks. Systemic effects include muscle spasm, nausea, vomiting, malaise, pulmonary edema, and hemodynamic instability. Respiratory failure and cardiac arrest can occur within minutes of exposure. Envenomation by *C. barnesi* produces a devastating condition known as *Irukandji syndrome.* The initial sting is often not appreciated; however, symptoms typically become apparent after 30 minutes. Signs and symptoms are consistent with catecholamine excess and include back pain, muscle pain, difficulty breathing, nausea and vomiting, diaphoresis, and anxiety. Two known deaths have been attributed to Irukandji envenomation. Since initial description in the 1950s, Irukandji syndrome has been linked to multiple other jellyfish species globally.

Portuguese man o' war *(Physalia physalis)* are found along the southern coastline of the United States. The Portuguese man o' war is not a true jellyfish but a hydroid colony. Envenomation is usually limited to local pain, scarring, and paresthesias, but it may progress systemically to nausea, headache, chills, and even cardiopulmonary collapse. This organism has also been responsible for several deaths.

Stings

Some marine animals cause a "sting" that is produced by a specialized apparatus that punctures the victim's skin and then introduces venom. Common examples of this type of animal are sea urchins, cone shells, bristle worms, crown-of-thorns starfish, stingrays, lionfish, weever fish,

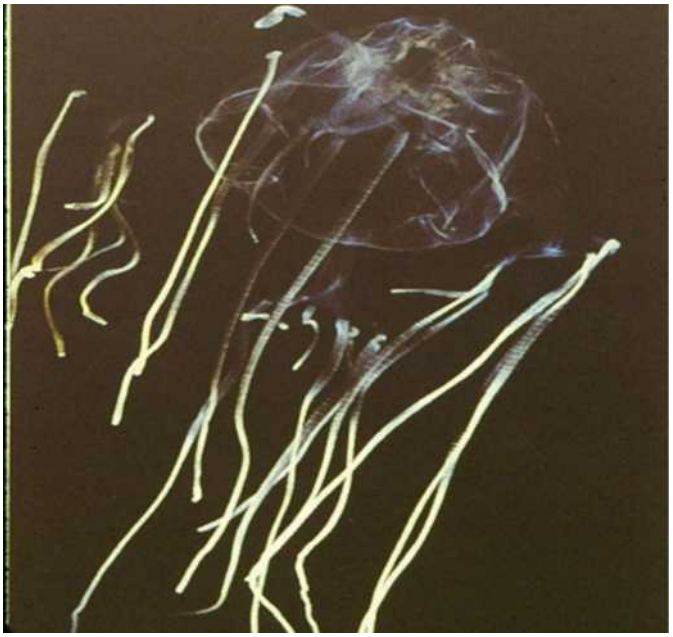

Fig. 53.10 Box Jellyfish or Sea Wasp *(Chironex fleckeri).*

catfish, stonefish, rabbit fish, and zebra fish. Deep injuries may be complicated by infection and retained foreign bodies.

Sea Urchins

Sea urchins belong to the Echinodermata phylum along with starfish and sea cucumbers. These animals produce injury and envenomation mostly through toxin-coated spines. These spines often break off and introduce calcareous material and debris into the wound, thereby potentiating infection. Symptoms often include severe local burning, pain, and discoloration, but they may progress systemically in some patients. The degree of envenomation is usually related to the number of spines involved and the species of animal encountered.

Cone Shells

Cone shells are much more toxic than sea urchins, and some species have been responsible for fatalities in the Indo-Pacific region. The venom apparatus is a tubular gland that connects to several teeth at the end of a retractable proboscis. All envenomations reported have occurred in people handling the shells. The venom typically contains hyalurondiase and multiple different toxic peptides known as conotoxins or conopeptides. Conotoxins have various different targets, including ion channels, ligand-gated channels, G-coupled proteins, and neurotransmitter transporters. Symptoms most often include pain on contact, depending on the species. Severe envenomation may cause diplopia, slurred speech, numbness, weakness, paralysis, and respiratory arrest. Onset and regression of symptoms may vary from minutes to days. No antivenom is currently available for cone shell envenomation. Airway control and supportive care are the mainstays of therapy for severe envenomation.

Stingrays

Stingrays are the most common cause of fish-related stings. The stingray is a broad, flat fish with a long, whip-like tail that contains between one and four barbed stingers that are used by the animal for self-defense. Stingrays vary in size from a few inches to several feet, and the stingers are proportional to the size of the fish. The spine has grooves lined with venom producing glandular cells and is encased in an integumentary sheath that breaks open on contact with the target. Stingrays are not aggressive and human envenomation typically occur when stingrays are mishandled or inadvertently stepped on after burying themselves in the sand of shallow water. Stingray venom contains serotonin, hyaluronidase, phosphodiesterase, and 5-nucleotidase. Following envenomation, the victim experiences an immediate, intense pain in the area of the wound, which may spread to the entire extremity. The local effects of stingray envenomation typically predominate; however, systemic symptoms can include salivation, nausea, vomiting, diarrhea, syncope, muscle cramps, fasciculations, dyspnea, cardiac dysrhythmias, and convulsions. The sheath and stinger are often broken or left in the wound. The presence of foreign material may impair healing and cause infection. In general, freshwater stingray envenomations are more severe than those caused by marine species, and tissue necrosis is nearly universal following these stings. Fatalities from marine stingrays are rare and are typically attributed to penetrating thoracic wounds.[33]

Bony Fishes

Venomous bony fish belong to the Scorpaenidae family of largely marine fishes. Bony fishes inflict their wounds through dorsal, pelvic, and anal spines. The spines and venom glands are encased in a sheath, and grooves along the spines act as channels for the venom. Venom can remain stable after the fish has died. Injuries from bony fish typically occur when the fish are stepped on in shallow water or when handled by fishermen and aquarium owners. The venom is made up of several classes of proteins, most of which are heat labile.

The family Scorpaenidae includes fishes of the genus *Pterois* (lionfish), *Scorpaena* (scorpionfish), and *Synanceja* (stonefish). Lionfish are native to the Indo-Pacific; however, since the 1990s, lionfish populations have expanded rapidly along the southern Atlantic coasts and throughout the Caribbean. The introduction of lionfish to Florida waters and its subsequent spread has been attributed to the aquarium trade.[34] Other theories include inadvertent transportation of these fish from the Indo-Pacific to the Atlantic Ocean when trapped in the ballast tanks of cargo ships.

Lionfish envenomation causes severe localized pain that increases for the first 2 hours after envenomation (Fig. 53.11). Systemic symptoms can include nausea, vomiting, diaphoresis, chest pain, abdominal pain, hypotension, and syncope. Although painful, the manifestations of lionfish stings are much less severe than the related stonefish.[35] Stonefish envenomation may cause serious and even life-threatening systemic illness, but manifestations such as cardiac and respiratory symptoms can be prevented by early administration of the appropriate antivenom. Following a stonefish sting, immediate pain and edema of the affected extremity can be followed by systemic effects of vomiting, headaches, seizures, hemodynamic instability, respiratory failure, and congestive heart failure. Wounds from stonefish envenomation can be complicated by infection, necrosis, compartment syndrome, and chronic tenosynovitis.[36,37]

DIFFERENTIAL DIAGNOSES

The differential diagnoses include nonvenomous stings, coral scrape, near drowning, diving barotrauma, shark and barracuda bites, and intoxication with water activities. In addition, skin wounds infected with MRSA or *Vibrio* sp. or those resulting in necrotizing fasciitis should be considered.

Diagnostic Testing

Diagnostic testing includes radiographs for detection of any foreign bodies. A radiograph of the involved area is recommended because many spines and sheaths are radiopaque.[38] Diagnostic ultrasound, focused computerized tomography, or magnetic resonance imaging (MRI) can be obtained for any nonhealing wounds from a marine sting.

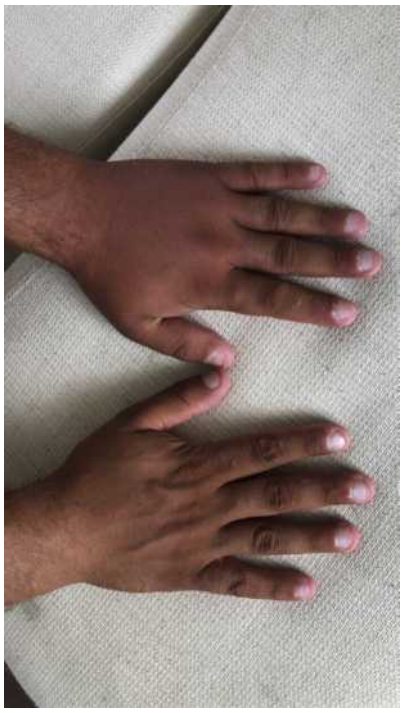

Fig. 55.11 Lionfish Sting on the Left Hand With Normal Right Hand for Comparison.

Management

Much of the venom from marine animals can be neutralized at the scene or in the prehospital setting, and most fatalities can be prevented with timely rescue. The most important first step after any marine envenomation is to remove the victim from the water. Drownings after minimal envenomation may account for more fatalities than the toxic effects of severe envenomation. The patient should be questioned about the circumstances of the bite, allergies, and systemic symptoms. If a severe allergic reaction has occurred, the victim should be treated for this emergency before the wound is addressed.

The type of wound care largely varies according to the type of venom apparatus involved. All marine stings from either bony fish or stingrays are treated with hot water immersion at the warmest bearable temperature (typically 40°C to 42°C) for 30 minutes or until the pain resolves.[36] Care should be taken to avoid burn injuries which can occur within minutes with exposure to water warmer than 49°C. For patients at sea, hot water can be carefully obtained from an outboard engine. The mechanism of hot water immersion in relieving pain is unclear; however, direct inactivation of heat labile marine toxins and modulation of human pain receptors resulting from vasodilation are two commonly proposed mechanisms. Hot water immersion therapy usually improves pain within minutes, but supplemental analgesics may be needed. As with all wounds encountered in the ED, appropriate cleansing, investigation for foreign bodies, débridement, and tetanus prophylaxis are paramount. Prophylactic antibiotics should be considered in deep puncture wounds, those with retained foreign bodies, and in immunocompromised patients. Specific antivenoms are available for some species, such as the box jellyfish, stonefish, and sea snake.

Bites

Bite injuries are treated with basic life-support measures and general wound care consisting of cleansing, débridement, and irrigation. Systemic signs and symptoms are treated as appropriate, with attention paid to the cardiac and respiratory systems.

Nematocysts

Supportive pharmacologic therapy (e.g., analgesics, antihistamines) is indicated for all but the most trivial envenomation. Delayed cutaneous reactions may persist despite optimal therapy.

Early cardiopulmonary resuscitation offers the best chance of recovery from severe envenomation, including *Chironex fleckeri* stings. Box jellyfish antivenom is also available, although its clinical efficacy and significant morbidity or mortality benefit have not been convincingly linked to its use. Suggested indications for use in victims suspected of *C. fleckeri* stings include coma, cardiovascular instability or collapse, respiratory compromise, and severe pain.[39] Antivenom can be given via intramuscular injection by first responders or by slow intravenous injection or intravenous infusion. Magnesium sulfate is also recommended as an intravenous bolus over 5 to 15 minutes at 0.05 g/kg (maximum dose 2.5 g) to victims of *C. fleckeri* stings with cardiovascular collapse.[39]

Care must be taken to prevent further nematocyst discharge when removing nematocysts from the victim. Various topical therapies including hot water immersion, vinegar, and sea water have been proposed for this purpose. As with most steps in management of jellyfish stings, the ideal treatment to prevent nematocyst discharge is not easily defined given the lack of randomized control studies and management differences between jellyfish species. Non–evidence-based recommendations dominate most treatment guidelines. In general, freshwater application should be avoided across species because the osmotic gradient can induce further nematocyst discharge.[39] Remaining tentacles are pulled off with a gloved hand or forceps. Scraping or rubbing off of residual tentacles leads to an increase in nematocyst discharge and should be avoided.[40] The specific topical agent applied to prevent nematocyst discharge depends on the suspected species. Vinegar (4% to 6% acetic acid) application for 30 seconds following suspected box jellyfish can prevent further nematocyst discharge but will not provide relief of pain from prior nematocyst stings. Application of vinegar is also recommended in cases of suspected *C. barnesi* (Irukandji) stings but should be avoided in cases of suspected *Physalia* (bluebottle) or *Chrysaora quinquecirrha* (man-of-war) envenomation because its application results in further nematocyst discharge. For suspected bluebottle and man-of-war stings, we recommend rinsing the wound with sea water followed by hot water immersion.

Initial treatment of severe pain from Irukandji syndrome requires intravenous analgesics such as fentanyl or morphine. Persistent hypertension despite control of pain can be treated with intravenous antihypertensives such as phentolamine or nitroglycerin. Because hypotension often develops in the later stages of envenomation, there is a theoretical advantage of using rapidly titratable agents such as nitroprusside for control of initial hypertension. Intravenous magnesium was previously recommended for treatment of refractory pain; however, the evidence for its use is largely anecdotal and is no longer recommended.

Stings

Broadly, treatment of fish and stingray stings focuses on adequate pain control and prevention of secondary complications such as infection. Fish and stingray venoms are generally heat labile, and significant analgesia can be achieved by immediate submersion of the wound in hot (40°C to 42°C) water for 30 to 90 minutes or until symptoms improve. Wounds should be copiously irrigated and investigated for foreign bodies. Retained spines and stingers are removed with forceps when possible. Wound care should include tetanus prophylaxis and prophylactic antibiotics for deep puncture wounds. Surgical exploration should be considered in deeply penetrating wounds and in cases of nonhealing injuries.[41] There is no role for steroids, tourniquets, or pressure

TABLE 53.5 Species-Specific Treatment Following Envenomation

Hot Water Immersion	Acetic Acid	Available Antivenom
Bony fish (includes lionfish, stonefish)	Box jellyfish *(Chironex fleckeri)*	Box jellyfish *(Chironex fleckeri)*
Stingray	Irukandji jellyfish (*Carukia barnesi*)	Ovine IgG Fab
Bluebottle[a] *(Physalia)*		Stonefish (Synanceia)
Portuguese man-of-war[a] *(Chrysaora quinquecirrha)*		Equine immunoglobulin G Fab
		Sea snakes (Hydrophiidae)
		Enhydrina schistose polyvalent antivenom

[a]Hot water immersion is recommended after sea water rinse.

immobilization bandaging in the standard treatment of marine stings. A specific antivenom for stonefish envenomation is available in Australia and is given in cases of severe systemic toxicity or refractory pain. As with other fish venoms, stonefish venom is heat labile and deactivated at temperatures greater than 39°C (Table 53.5).[42]

Disposition

Patients envenomated by unknown or unfamiliar organisms should be observed for systemic signs and symptoms. Careful discharge instructions are provided to the patient, warning them to return for increasing pain, numbness, difficulty breathing, and signs of infection. Patients with the potential for hemodynamic instability or airway compromise (e.g., Irukandji syndrome, box jellyfish envenomation, stonefish envenomation) or those treated with antivenom should be admitted or transferred to an ICU.

ACKNOWLEDGMENTS

We acknowledge the efforts and expertise of the previous chapter author for editions (1–9), Dr. Edward Joseph "Mel" Otten.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 53: QUESTIONS AND ANSWERS

1. Which of the following venomous snakes in the United States is a member of the neurotoxic Elapidae family?
   a. Copperheads
   b. Coral snakes
   c. Rattlesnakes
   d. Water moccasins

Answer: b. Pit vipers from the family Viperidae are the most prevalent venomous snakes in the United States. They are native to every state except Maine, Alaska, and Hawaii. They are classified into three main groups: true rattlesnakes (genus *Crotalus*), copperheads and water moccasins (genus *Agkistrodon*), and pygmy and Massasauga rattlesnakes (genus *Sistrurus*). Pit vipers account for 98% of all venomous snakebites in the United States. Other families include Colubridae, Hydrophiidae, Elapidae (to which the neurotoxic coral snake belongs), and Crotalidae.

2. A 30-year-old man complains of pain, burning, and swelling of his hand after gardening. Physical examination shows two puncture marks on his thenar eminence, as well as moderate localized swelling. When you inquire about it, he said that he did have some sudden burning pain while digging around in the ground by a bush, but he dismissed it as abrasions from sharp sticks. That was 2 hours ago. What should you do next?
   a. Apply a constricting band to impede venous and arterial flow.
   b. Discharge with instructions for rest, ice, immobilization, and use of oral antibiotics.
   c. Give tetanus and clindamycin for prophylaxis.
   d. Obtain baseline laboratory studies and observe the patient for increasing symptoms.
   e. Test compartment pressure and prepare for fasciotomy.

Answer: d. The symptoms are typical for a pit viper snakebite. The most consistent symptom associated with pit viper bites is immediate burning pain in the area of the bite, whereas pain may be minimal with bites of Elapidae and other exotic snakes. Tetanus prophylaxis may be indicated, but antibiotics are not. Fasciotomy is rarely if ever indicated for snakebite. A constricting band may be useful for first aid in the field with certain neurotoxic snakes, but not in North America. Immobilization may be helpful, but ice and antibiotics are not.

3. A 43-year-old woman sustained a snakebite while in her backyard in Florida. She was not able to secure the snake, but she remembered it to be colorful. She presents with ptosis, slurred speech, and nausea. What is true about the type of snake most likely involved in this case?
   a. Death usually occurs from coagulopathies.
   b. Eastern species are the most venomous.
   c. The snake has a heat-sensitive organ between eyes and nostrils on both sides of the head.
   d. The snake has a triangle-shaped head.
   e. The snake has elliptical pupils.

Answer: b. This woman sustained a bite from a coral snake. All of the above except B are related to pit vipers. The coral snake can be differentiated from the king or milk snake by two characteristics: the nose of the coral snake is black, and the red and yellow bands are adjacent on the coral snake. Eastern coral snake is considered more deadly as opposed to its western relative. There are no records of fatalities caused by the western species. Ptosis is common and often the first outward sign of envenomation. Other signs and symptoms include vertigo, paresthesias, fasciculations, slurred speech, drowsiness, dysphagia, increased salivation, nausea, and proximal muscle weakness.

4. Which of the following is true about snake antivenom?
   a. Antivenom may reverse symptoms of envenomation including laboratory abnormalities.
   b. Antivenom should be administered around the wound.
   c. Even mild envenomations require antivenom.
   d. Exotic snakebites require only antivenom if neurologic symptoms are present.
   e. Pregnancy is a contraindication to receive antivenom.

Answer: a. Pregnancy is not a contraindication to antivenom therapy. Any victim of a venomous snakebite with moderate or severe envenomation is a candidate for antivenom. Antivenom may reverse the local signs, systemic symptoms, and laboratory abnormalities associated with envenomation. As with coral snakes, many patients do not show any early signs after envenomation by exotic snakes. The antivenom should be administered before neurologic changes develop. All antivenom should be administered intravenously.

5. A 28-year-old man presents with a copperhead snakebite that occurred 1 hour ago. He complains of pain and moderate swelling of his right hand and wrist. He has no systemic symptoms and has a pulse of 80 bpm and a normal blood pressure. His initial coagulation studies are normal. What should be done?
   a. Admit for observation and antivenom
   b. Discharge with elevation, ice, and pain medications
   c. Give antivenom if swelling spreads to forearm
   d. Immediate antivenom, four vials intravenously
   e. Observe 12 hours for signs of increasing envenomation

Answer: e. The majority of copperhead bites do not require antivenom. Some toxicologists will administer antivenom if extremity swelling is progressive and may cause long-term disability. Copperhead bites generally cause a moderate amount of swelling that may peak 24 to 36 hours after the bite. All venomous snakebites should be observed for at least 12 hours if signs of envenomation are present. If systemic signs develop or the patient develops a coagulopathy, antivenom may be indicated.

6. Which of the following patients is most likely to be the first discharged home safely?
   a. A pregnant woman with black widow envenomation
   b. A 3-year-old child with a scorpion sting 1 hour before arrival
   c. A 55-year-old man with hypertension and coronary artery disease with black widow envenomation
   d. An 8-year-old with a coral snake bite
   e. An 18-year-old with an unknown snakebite 8 hours before arrival

Answer: e. A scorpion sting in a child should be observed for at least 6 hours. Symptomatic children with stings should be admitted. Most venomous snakes will show signs of envenomation with 6 hours. If this patient is asymptomatic, it is likely that the snake was nonvenomous or this was a "dry bite." All children with envenomation and coral snake bites should be admitted for observation. Pregnant patients and those with coexisting medical problems should be admitted after black widow envenomation.

7. While walking in shallow water, a patient accidentally steps on a stonefish. Which of the following is the least effective diagnostic and treatment intervention?
   a. Irrigating the wound with vinegar
   b. Obtaining radiographs for retained foreign body
   c. Observing for cardiovascular and respiratory symptoms
   d. Removing the spine with forceps
   e. Using hot water to relieve the pain

Answer: a. Stonefish, a type of bony fish, may cause serious cardiac and respiratory symptoms, which can be prevented by early administration of the appropriate antivenom. The fish spines of bony fish should be removed with forceps because they are thick and less likely to break off at the skin (like a bee stinger). In all cases, the wound should be copiously irrigated. Vinegar has been shown to be useful for some types of nematocyst injuries from jellyfish. Significant analgesia is achieved by submersion of the wound in hot water for 30 to 90 minutes or until improvement. There is a stonefish antivenom in limited supply for severe envenomation.

8. A patient presents with a necrotic lesion on his midthigh that started as a bleb while he was working in his woodshed 3 days ago. The wound has grown gravitationally. Her blood pressure is 110/80 mm Hg, respiratory rate 16 rpm, heart rate 110 bpm, and temperature 38.3°C. You suspect an envenomation of which of the following?

a. *Centruroides exilicauda*
b. *Hapalochlaena maculosa*
c. *Haplopelma lividum*
d. *Latrodectus mactans*
e. *Loxosceles reclusa*

Answer: e. The cobalt blue tarantula, *Haplopelma lividum,* is an aggressive spider with toxic venom. The black widow spider is *Latrodectus mactans*. *Centruroides exilicauda,* which is found in Arizona, is a particularly dangerous kind of scorpion. The blue-ringed octopus is *Hapalochlaena maculosa.* The brown recluse spider, *Loxosceles reclusa,* causes an initial white area of vasoconstriction at the site of the bite within 3 or 4 hours. A bleb then forms in the center of this area, and an erythematous ring arises on the periphery. The lesion at this stage resembles a bull's-eye. The bleb darkens, necroses during the next several hours to days, and continues to spread slowly and gravitationally.

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Thermal Injuries

Megan M. Rybarczyk and Sean M. Kivlehan

KEY CONCEPTS

- After removing the patient from the source of injury, burns should be cooled with room temperature water while avoiding hypothermia in patients with large burns.
- Clinical signs such as facial burns, hoarseness, drooling, carbonaceous sputum, and singed nasal hairs indicate inhalation injury; however, they are poor predictors of injury severity.
- Confirmation of inhalation injury is best accomplished by direct visualization of the glottic inlet via flexible or rigid video laryngoscopy augmented by topical anesthesia and judicious sedation, when necessary.
- Worsening hoarseness, edema, or soot in the supraglottic region necessitates immediate intubation.
- Supplemental oxygen should be given in patients with suspected inhalation injury and determination of carbon monoxide levels should be performed.
- Crystalloid resuscitation is required to support vital organ perfusion and is guided by urine output. Care should be taken to avoid over-resuscitation.
- Pain relief is required for larger burns and is accomplished through both pharmacological and non-pharmacological methods. Pain levels should be assessed frequently.
- Patients with large body surface area burns (>20% for adults and >10% for children and the elderly) or deep burns will require admission to a burn center. Most other patients presenting to the ED will have small and superficial burns that can be managed with over-the-counter or commercially available topical agents.

FOUNDATIONS

Background and Importance

Thermal injuries, which consist of fire or flame injuries, scald injuries, and contact with hot object injuries, are common in the emergency department (ED). Cooling, assessment of percent total body surface area (% TBSA), depth of tissue involvement, pain control and local wound care is generally all that is necessary for minor burns. For treatment of major burns, early management of airway, breathing, and circulation as well as continuous reassessment of burn depth are essential. Careful wound care to minimize the advancement of burns to greater thickness and prevent infection is imperative.

Burn injuries result in significant morbidity and mortality worldwide. According to the World Health Organization (WHO), burn injuries result in more than 10 million disability adjust life years (DALYs) lost and more than 150,000 deaths each year, 90% of which are in low- and middle-income countries.[1] In the United States alone, there were approximately 560,000 visits to EDs for injuries or burns related to fire or a hot object or substance in 2016.[2] Data from burn admissions in the United States between 2008 and 2017 show that more than 67% of burns were less than 10% TBSA. The overall mortality rate was 3.1%; however, flame and fire injuries had an overall mortality rate of 5.6%. Patients aged 1 to 15 years comprised more than 23% of the total burns, adults aged 20 to 59 years comprised 55% of burns, and patients age 60+ year comprised 15%. Fire and flame injuries, scalds, and contact injuries account for more than 85% of cases, with scalds being most common in children under five, and fire or flame most common in other age groups. Burn injuries occur most often in men (67%) and at home (74%). Only 13% are work related, and 95% are accidents. Patients are more commonly Caucasian/White (59%).[3]

Deaths from burn injury increase with increased burn size, presence of inhalation injury, and advanced age. Pneumonia is the most common complication and is more common in patients requiring four or more days of mechanical ventilation. The hospital length of stay (LOS) is estimated as just over 1 day per percent TBSA.[3] Overall, the burnt surface area associated with a 50% case fatality (LD-50) is 70% TBSA. However, this drops to 40% to 50% TBSA at age 55, 30% to 40% at age 60, and 20% to 30% at age 65 and older.[3,4]

Anatomy, Physiology, and Pathophysiology

The skin is the largest organ of the human body and serves as a barrier between the internal and external environments minimizing fluid losses and microbial invasion. It is comprised of seven layers: five in the epidermis (serving as the protective layer or barrier) and two in the dermis (containing structures that provide thermoregulation, water balance, immune surveillance, sensation, and most of the mechanical properties of the skin). The hypodermis, or subcutaneous tissues, are not a part of the skin, but contain subcutaneous fat and connective tissue that serve to connect the skin to the underlying structures. The thickness and resiliency of the skin depends on the location on the body (thickest on the sole of the foot, thinnest on the eyelid) as well as an individual's age, with peak skin thickness occurring in the middle age. Damage or loss to the skin can result in significant volume loss, thermo-dysregulation, and possible infection.

Pathophysiology of Burns

Thermal burns are the result of exposure of body surfaces to energy in the form of heat. The extent of injury is directly related to the integrity of the skin or epithelial surface, temperature of the offending agent, and duration of exposure. Higher temperatures (starting as low as 41°C) result in denaturing of cellular proteins and coagulative necrosis.[5,6]

Cutaneous Injury

The classical three zones of burn injury to the skin include the central zone of coagulation or irreversible necrosis, the intermediate and potentially reversible zone of stasis or ischemia, and the peripheral reversible zone of hyperemia or inflammation.[5]

The exact cellular-level of pathophysiology in the different zones is not entirely known, however it involves mechanisms of necrosis or necroptosis that result in significant inflammatory responses as well as autophagy—which, may have a protective effect—and either early or

delayed apoptosis, that results in cellular loss, but with less inflammatory response.[5,7,8] All of these mechanisms result in immediate loss of skin tissue and play a role in burn injury progression if not managed both in the ED and throughout the three phases of wound healing: the *inflammatory phase*, the *proliferative phase*, and the *remodeling phase*.[5]

Thermal injury not only sets into motion a cascade of local events, but also results in systemic responses, especially in larger burns. Local processes include inflammation, activation, and aggregation of immune cells. Additionally, this causes microthrombosis with ischemia as a result of endothelial damage, vasoconstriction, dilation, edema, and reperfusion with production of reactive oxygen species and toxic cytokines.[8] Systemic processes not only include inflammatory, cytokine, and immunologic responses, but also metabolic and endocrine responses.[9]

Burn shock is characterized by macro- and microcirculatory impairment and cellular damage, both at the site of injury and throughout the body. The initial resuscitation phase (hypodynamic or ebb phase) occurs within the first 24 to 72 hours and involves cytokine and inflammatory pathway activation as well as systemic circulation of reactive oxygen species, leading to diffuse alterations of transmembrane potentials, plasma extravasation, and edema. This process has either a biphasic pattern—most severe in the first hour and then again at 12 to 24 hours post-burn—or single peak with the most significant manifestations in the first eight hours followed by a slow but steady reduction over the following 16 hours. Subsequently, there is increased vascular resistance, reduced cardiac output, and diffuse end-organ damage.[5,6,9,10] Given the resulting hypoproteinemia and capillary leak, an imbalance between oncotic and hydrostatic forces develop, making resuscitation essential at this stage. The second phase is the hyperdynamic or hypermetabolic flow phase that begins 24 to 72 hours post-injury. As vascular permeability and systemic vascular resistance drop, heart rate and cardiac output increase and metabolic rates can rise two- to three-fold.[5,6] Additional systemic effects include impaired immunity, insulin resistance, renal and hepatic dysfunction, increased serum triglycerides and free fatty acids, muscle wasting, bowel mucosa degradation with reduced absorptive capacity, and hormonal changes, including reductions in growth hormone, TSH, T3, T4, and testosterone.[5,6,9–11]

Inhalation Injury

The incidence of inhalation injury with thermal burns is approximately 6%, however incidences range from 2% in smaller burn injuries to nearly 60% in larger burn injuries and burns to the face.[12,13] It can occur with or without cutaneous burns, and, after age and TBSA, it is the most important predictive factor of mortality and is associated with a nearly threefold increase in mortality and a decrease in the LD-50 by 25% in certain population groups.[12,13]

Inhalational injury is caused by thermal injury to the upper airway and chemical injury to the lower airway. Additionally, systemic toxicity occurs from inhalation of substances such as carbon monoxide and cyanide.[13] Heat can stimulate the glottic closure reflex resulting in rapid asphyxiation and death. At the cellular level, the effect of thermal injury on the upper airway is similar to the pathophysiologic cutaneous response with inflammation, including activation and aggregation of immune cells as well as ischemia, followed by edema and reperfusion injury. Progressive airway edema after significant thermal injury is predictable and may threaten airway patency within hours of initial presentation. Additional complications can occur in the first 24 to 48 hours such as bronchoconstriction, ulceration and hemorrhage, pseudomembrane formation, loss of surfactant, and impaired ciliary transport. These can lead to ventilation/perfusion (V/Q) mismatch, decreased lung compliance, obstruction, barotrauma, increased dead space ventilation, and infection.[13]

CLINICAL FEATURES

Classification and Diagnosis of Burns

Accurate estimates of burn depth and size are difficult given the dynamic nature of burn injury in the first hours and even days. While the physical examination is the fastest way to initially gauge burn severity, this has been shown to be inaccurate and inconsistent among clinicians.[14] Estimation of depth is particularly challenging as most burn injuries are not uniform in depth, can have varied appearances based on the thickness of the skin, and have a tendency to progress over time.[14] Adequate diagnosis, however, is imperative as it affects clinical decision-making and can affect the timing of critical interventions and the appropriate treatment protocols.

Depth

Cutaneous burns are classified according to depth as superficial (previously first-degree), superficial partial-thickness and deep partial-thickness (previously second-degree), full-thickness (third-degree), deep full-thickness (fourth-degree), and fifth-degree (such tissue destruction resulting in amputation).[15] This classification was developed for its implications regarding surgical intervention and healing potential. Furthermore, a category of "indeterminate-depth" burns, a partial-thickness burn of unknown healing potential, has also been described in the literature and is a current focus of study.[16]

Superficial burns involve only the epidermis and are painful, erythematous, and blanch with pressure. They are dry, and the epithelium peels away by day three or four after the pain and erythema resolve. A sunburn is a common example. These injuries often heal within a week without scarring.[15] Superficial partial-thickness burns involve the superficial portion of the dermis (papillary dermis) and result in separation of the epidermis and dermis with blister formation. They are painful, erythematous, and blanch with pressure. They are wet, take one to three weeks to heal, and rarely result in significant scarring.[15] Deep partial-thickness burns involve the deeper layers of the dermis (reticular dermis) and result in damage to dermal structures such as hair follicles. They can blister, are painful to pressure, can be erythematous, mottled, or white, and may be wet or dry. They heal in two to nine weeks and can cause hypertrophic scarring.[15] Full-thickness burns involve the entire dermis and often some underlying adipose tissue and result in an inelastic burn eschar that is waxy and white, gray, or black without blisters. A burn eschar can compromise underlying tissues. Full-thickness burns are insensate and heal over the course of weeks once the eschar falls off and the bed of granulation tissue contracts and epithelializes from the wound margins.[15]

Deep full-thickness burns involve muscle, tendon, ligament, or bone and may result in amputation.[15]

These categories are summarized in Table 54.1 and typical examples of the appearance of some of the different burn depths are presented in Fig. 54.1 to 54.3.

Several techniques to help improve the accuracy of burn depth estimation beyond clinical examination have been studied, including laser Doppler flowmetry, laser Doppler imaging, thermography or thermal imaging, photoacoustic imaging, spectrophotometric intracutaneous analysis, dermoscopy, near-infrared spectroscopy, videomicroscopy, ultrasonography, and spatial frequency domain imaging.[14] Only a few of these have been studied in human investigations, and some require biopsy of the wound. While potentially effective inpatient tools, these are unlikely to be useful in the ED evaluation of burn injury depth.

Size

Determining the size, or TBSA, of a burn injury predicts mortality and is used to guide management decisions, including fluid resuscitation

TABLE 54.1 Clinical Estimation of Burn Depth

Depth	Appearance	Blanches With Pressure	Sensitivity to Pinprick	Pliability	Time to Healing	Need for Excision and Grafting
Superficial	Red, no blisters	+	++	Soft	1 week	–
Superficial partial thickness	Red, blisters	+	++	Soft	1–2 weeks	–
Deep partial thickness	Red or white, possible blisters	±	±	Slightly tense	2–9 weeks	±
Full thickness	Leather like, charred	–	–	Stiff, leather like	Variable; weeks to months	+
Deep full thickness	Exposed muscle, tendon, and/or bone	Not applicable	Not applicable	Not applicable	Variable; weeks to months	+
Fifth degree	Requires amputation	Not applicable	Not applicable	Not applicable	Variable; weeks to months	+

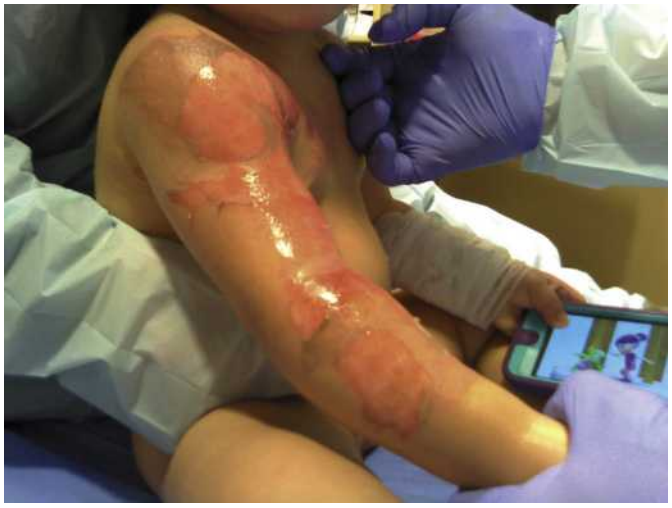


Fig. 54.1 Superficial Partial Thickness Burn, Which Is Pink and Glistening. Some of the blisters have sloughed off.

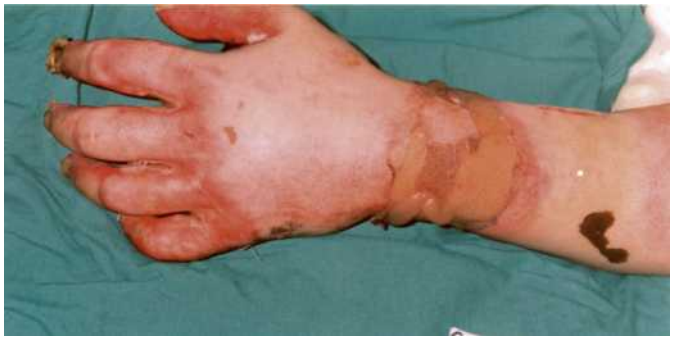


Fig. 54.2 Deep Partial Thickness Burn. The white appearing area over the dorsum of the hand is a deep partial thickness burn.

and burn center referral. TBSA does not include superficial burns. The Baux score, a sum of the patient's age and the percent TBSA burned, was originally described in the 1960s, but a revised score that includes inhalation injury that was published in 2010 is now more widely used, along with a simplified nomogram published in 2015.[17] Several other scores, including the Belgian Outcome in Burn Injury Score, Abbreviated Burn Severity Index, FLAMES Score, and the Ryan Score have also been used worldwide along with other mortality scores not specific to burn injuries (i.e., Sequential Organ Failure Assessment Score) to predict mortality.[18–22]

For larger (> 10% TBSA) burns in adults, the "Rule of Nines" is often used to estimate burn size. This method divides the body into areas

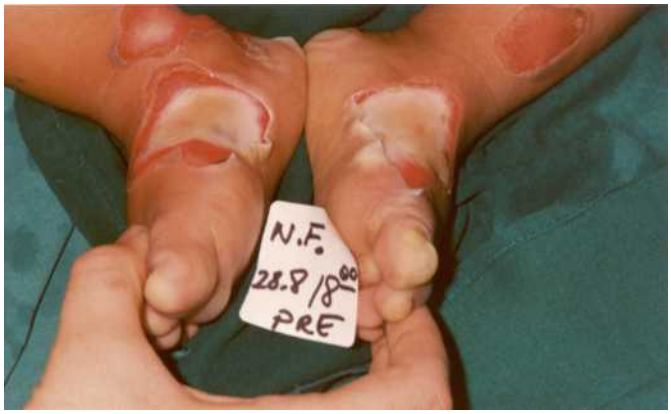


Fig. 54.3 Full-Thickness Burn Over Both Feet. The central area is depressed and has a yellowish color indicating it is a full-thickness burn.

that approximate 9% of the TBSA (Fig. 54.4).[21] In children, the Lund-Browder chart is recommended, which adjusts for age-related differences in the distribution of body parts and sizes (Fig. 54.5).[22] For small burns, the palmar surface area (PSA) of the entire palmar surface of the patient's hand and fingers can be used to estimate 1% of the TBSA, however studies have shown that PSA can represent 0.5% to 2.3% TBSA, depending on age, body habitus, and patient demographics.[21]

Given the increased incidence of obesity, the effect of bariatric-specific changes in body surface area (BSA) and physiological changes on burn care has yet to be fully explored. While it has been shown that these changes can affect treatment and outcomes, no reliable bariatric-specific BSA chart yet exists.[22,23]

Overestimation and underestimation of burn size is common, with ratios of overestimation to underestimation as high as 30:1 in the pre-hospital setting, and with variation as high as nearly 200% among clinicians, regardless of level of expertise.[21] Smaller burns are more likely to be overestimated than larger burns. A number of methods have been developed to increase the accuracy of burn size estimation. Computer software and other technologies can help improve burn size estimation.[21,24]

Inhalation Injury

Like burn size and depth, the diagnosis of inhalation injury is subjective and largely based on history and clinical findings. Pertinent historical features include exposure to flame, smoke, or super-heated air, presence in an enclosed space, duration of exposure, and loss of consciousness. Examination findings include facial burns; presence of carbonaceous material on the face, in the nose or oropharynx, or in sputum; singed facial or nasal hair; mucosal damage or edema; and

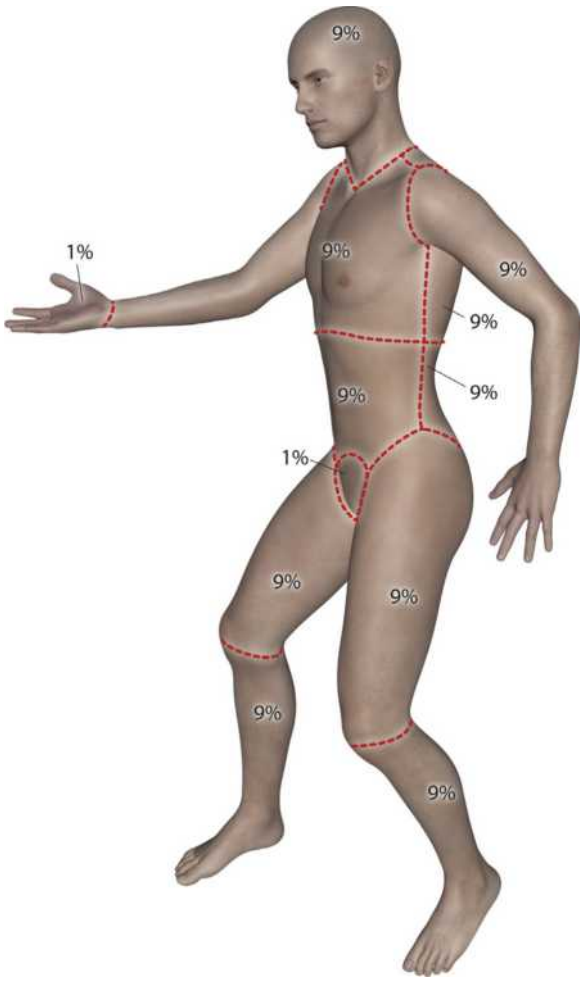
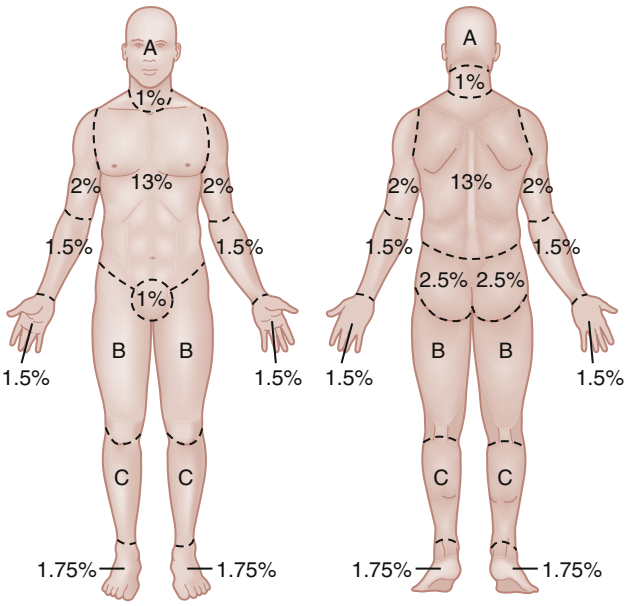


Fig. 54.4 The "Rule of Nines" for Estimating Burn Area in Adults.



Relative percentages of areas affected by growth

Age	Half of head (A)	Half of one thigh (B)	Half of one leg (C)
Infant	9.5	2.75	2.5
1 yr	8.5	3.25	2.5
5 yr	6.5	4	2.75
10 yr	5.5	4.25	3
15 yr	4.5	4.5	3.25
Adult	3.5	4.75	3.5

Fig. 54.5 Lund-Browder Chart.

signs or symptoms of airway obstruction or respiratory compromise such as dyspnea, tachypnea, stridor, hoarseness, drooling, wheezing, accessory muscle use, tripoding, nasal flaring, and hypoxia. When clinical signs or symptoms of airway injury are indeterminant, methods for confirming inhalation injury include visualization via flexible or rigid video laryngoscopy. Computed tomography (CT), carboxyhemoglobin measurement, radionuclide imaging with Xenon, and pulmonary function testing can all be performed to assess lower airway or pulmonary involvement but are not the initial diagnostic tests for evaluation of upper airway injury.[13,25] For now, the gold standard remains flexible laryngoscopy. The Abbreviated Injury Score is a commonly used grading system to augment interpretation of visualized damage. The score and ranges from zero (no trauma) to five (mucosal sloughing, necrosis, and airway obstruction).[13] There is no current comprehensive standardized or validated method for diagnosing or scoring inhalational injury severity in the ED setting.

DIFFERENTIAL DIAGNOSES

The diagnosis and etiology of burns is generally elicited on history and examination. In patients who are unable to provide a history, some diseases with dermatological manifestations, such as erythema multiforme, Stevens-Johnson syndrome, drug-induced hypersensitivity syndrome, toxic epidermal necrolysis, staphylococcal scalded skin syndrome, subacute cutaneous lupus, necrotizing fasciitis, pemphigoid, and pemphigus, may be mistaken as burns. In fact, the clinical features and management of Stevens-Johnson syndrome and toxic epidermal necrolysis, which can cause life-threatening mucocutaneous eruptions including sloughing of large areas of the skin, are very similar to those of large burns.

In patients who can provide a history, it is important to ask patients about the etiology of the burn, duration of contact, if it was in an enclosed space, if a blast or blunt trauma occurred, presence or absence of any protective clothing or equipment, whether it was an intentional injury or accidental, and any initial first aid measures used. Child or elderly abuse must always be considered, especially when the history and pattern of burns are inconsistent with the physical findings.

DIAGNOSTIC TESTING

Routine laboratory testing is generally of little value in evaluating and managing patients with burns in the ED. Patients with suspected inhalation injury should have a chest radiograph, lactic acid level, and blood gas determination, including a carboxyhemoglobin level. Moreover, pulse oximetry, capnometry, capnography, and peak expiratory flow rates, either continuous or with serial measurements may be useful in monitoring respiratory status. Patients with large burns requiring admission should have an electrocardiogram and baseline laboratory testing, including a complete blood count, electrolyte panel, blood type and cross, lactic acid, and coagulation studies. Clinicians should perform a standard trauma assessment for blunt and penetrating injury if the burns occurred as a result of a blast or explosive event.

MANAGEMENT

Initial First Aid

Patients should be removed from the source of injury and any clothing and jewelry removed from the affected areas and burns cooled with room temperature water.[26] Direct exposure to ice or iced water is to be avoided to prevent further injury. Cover the burns with a clean dressing to minimize further trauma and reduce pain.

During transport, patients with large burns (greater than 20% TBSA in adults and greater than 10% in children) should have two large bore intravenous catheters placed followed by fluid resuscitation. The American Burn Association (ABA) recommends starting 125 mL/h lactated Ringers solution (LR) for patients 5 years old and younger, 250 mL/h LR for patients 6 to 13 years old, and 500 mL/h LR for patients 14 years and older, with the plan to adjust fluid rates to estimated TBSA on arrival to the ED (see later for more details on fluid resuscitation).[27] Place patients on supplemental oxygen to maintain oxygen saturation greater than 92%. Pain management using intravenous opiates, such as morphine (2 to 4 mg IV in adults, 0.05 mg/kg for children <50 kg) every 5 to 10 minutes until pain control is achieved is also recommended as per local emergency medical service (EMS) protocols in hemodynamically stable patients (see later for more details on pain management).

Airway Management

One of the most critical decisions in managing burn victims is the need for and optimal timing of endotracheal intubation since thermal injury predictably results in swelling of glottic and supraglottic structures. The degree of swelling is related to temperature and length of exposure. Occasionally, patients present needing immediate intubation. However, patients may arrive initially with a "sore throat" or a mildly raspy voice. Edema may worsen over the first several hours, especially as patients receive fluid resuscitation, therefore it is essential to closely monitor for progression of clinical signs and symptoms that suggest developing airway obstruction or delayed-onset respiratory compromise. Patients with a history of exposure in an enclosed space, suspected smoke inhalation, moderate to severe facial or oropharyngeal burns, circumferential neck burns, visible injury on laryngoscopy or bronchoscopy, cognitive impairment, hemodynamic stability, dysphagia, hoarseness, oropharyngeal soot, singed nasal or facial hair, larger burns (≥ 40% TBSA), stridor, or signs and symptoms of impaired oxygenation or ventilation should be intubated early, if not immediately.[13,28] No single feature can adequately predict the need for intubation, but patients without these criteria should generally not be intubated and undergo close observation. There are currently no consistent validated criteria or scoring systems to diagnose inhalation injury or predict airway compromise. Even initial direct visualization of the airway may not always accurately predict the need for intubation. When in doubt, early intubation is still encouraged; however, in cases where symptoms are mild and history is inconclusive, a strategy incorporating flexible laryngoscopy in lieu of early intubation can be used and may improve outcomes.[29] Unnecessary intubation and mechanical ventilation may lead to complications such as injury to the upper airway, pneumonia, and acute respiratory distress syndrome (ARDS). At present, the best way to confirm inhalation injury and the need for endotracheal intubation is by directly visualizing the airways with flexible or rigid laryngoscopy using topical anesthesia augmented by mild to moderate sedation when necessary. Repeat laryngoscopy or intubation should be performed if symptoms change (Fig. 54.6).[29] Awake intubation with generous amounts of topical anesthetics with or without supplemental sedation is the preferred intubation method in patients with inhalational burns with a predicted difficult airway and partial airway obstruction, however, rapid sequence intubation with video laryngoscopy is a reasonable approach if intubation is performed early and

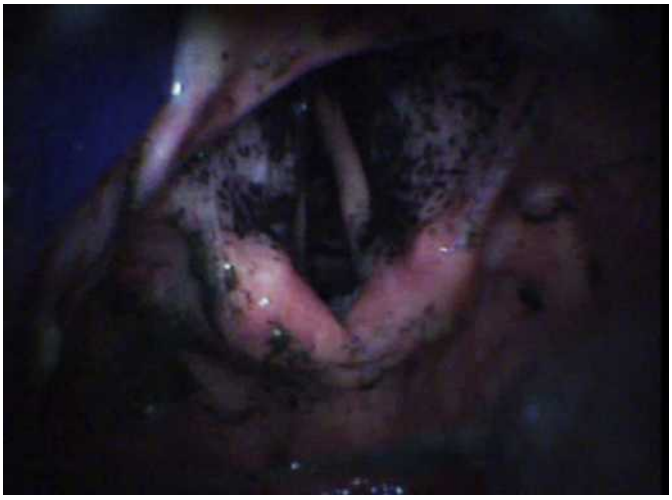


Fig. 54.6 Fiberoptic View of Inhalation Injury. (Courtesy Dr. Marvin Wayne.)

significant swelling is unlikely. If a "can't intubate and can't oxygenate" scenario develops during airway management, the failed airway algorithm (see Chapter 1) should be followed. Surgical airways are rarely needed but indicated if intubation is not successful and oxygenation cannot be maintained. The empirical use of corticosteroids in the management of inhalation injury is not recommended.[25]

Breathing Management

Although the chest radiograph and CT scans of the thorax may be helpful in some cases, there is no consensus as to the timing of these studies, and negative studies, especially in the initial period, should not be used to rule out inhalational injury.[25,30]

All patients with suspected inhalation injury should receive supplemental humidified oxygen to maintain oxygen saturation above 92%. Inhaled beta-agonists can be administered to reduce bronchoconstriction associated with inhalation injury. Non-invasive ventilation may be considered in awake, cooperative, spontaneously breathing, hemodynamically stable patients who can maintain their airway.[25]

For intubated patients, bronchoscopy is still the gold standard tool used to diagnose inhalation injury, determine severity, and remove airway debris and secretions that impede ventilation and enhance the inflammatory response. Furthermore, the presence of soluble urokinase plasminogen activator receptor (suPAR) in bronchial lavage fluid can help make the diagnosis and predict prognosis.[25]

It is well known that lung-protective ventilation strategies, including lower tidal volumes (6 mL/kg of predicted weight) and maintaining peak pressures below 35 mmHg, are imperative to avoid further lung injury during mechanical ventilation. This may lead to hypercapnia (permissive hypercapnia), which can be tolerated, especially in children. Addition of positive end-expiratory pressure (PEEP) may increase the functional residual capacity and improve oxygenation. Suggested initial ventilator settings are presented in Table 54.2. The best method of ventilation in patients with inhalation injury is subject to debate. In addition to traditional modalities (such as assist-control), some studies suggest that high frequency oscillatory ventilation or high frequency percussive ventilation may improve oxygenation in patients with inhalation injury when traditional methods are ineffective.[25,31] Prone positioning of the patient may also be considered in hypoxic patients. Extracorporeal membrane oxygenation (ECMO) has been studied for patients with burn injuries as they are prone to develop ARDS with or without inhalation injury. While initial results indicate good outcomes, more study is needed.[32]

TABLE 54.2 Recommended Initial Ventilator Settings

Tidal volume	6–8 mL/kg
Respiratory rate	8–12 in adults
	12–45 in children
Plateau pressures	<35 cm H_2O
I/E ratio	1 : 1 to 1 : 3
Flow rates	40–100 L/min
PEEP	8 cm H_2O

I/E, Inspiratory-expiratory; *PEEP,* positive end-expiratory pressure.

Nebulized heparin (5000 to 10,000 IU) in conjunction with beta agonists, n-acetylcysteine—an oxygen free radical scavenger and mucolytic—or other mucolytics have been shown to reduce the duration of mechanical ventilation.[25,33,34] Inhaled nitric oxide may also be helpful in some patients.[25] The empirical use of corticosteroids is not recommended. The use of exogenous surfactant may be helpful, but further study is required.[25]

Patients with smoke inhalation who are intubated are at high risk of developing pneumonia. Strategies such as use of silver-coated or hi-lo evac endotracheal tubes, restrictive blood transfusion, intensive insulin therapy, head elevation, frequent position changes, control of environmental infection (such as patient and staff cohorting, dedicated room equipment, contact barrier precautions, and hand hygiene), and good oral care should be used. Prophylactic antibiotics are not recommended. In the ICU, routine endotracheal surveillance cultures are performed to target early therapy in patients who develop pneumonia.[25,35]

Circulation Management and Fluid Resuscitation

Burn injuries result in significant fluids losses and shifts due to loss of the epidermal barrier and an increase in capillary permeability, respectively. Leakage of plasma proteins into the interstitial space during the early phases of a burn increases its oncotic pressure, further contributing to fluid shifts and tissue edema. As a result, a major focus of burn care is fluid resuscitation to restore tissue perfusion and prevent hypovolemic shock. Intravenous fluid resuscitation through large bore intravenous cannulas should be instituted for most burns greater than 20% TBSA in adults, and greater than 10% in children.[27] Avoid IV placement through burned tissue if at all possible. A number of formulas have been proposed for estimating the fluid requirements of burn patients (Table 54.3). The *Parkland formula* is the most common method used to calculate fluid requirements over the first 24 hours after injury and is based entirely on LR solution. Half of the fluids are given within the first 8 hours *from injury,* and the other half is given over the next 16 hours. However, patients managed with the **Parkland** formula have been shown to receive an average 4.6 to 6.3 mL/kg per percent of TBSA over the first 24 hours instead of the recommended 4 mL/kg per percent of TBSA, increasing the risk of over resuscitation.[36] The *Modified Brooke formula*, which calls for 2 mL/kg per percent of TBSA, may be a better starting point. The ABA recommends 3 mL/kg/% TBSA plus D5LR at maintenance for infants and young children ≤ 30 kg, 3 mL/kg/%TBSA for all other children < 14 years old and 2 mL/kg/%TBSA for all other individuals with thermal injuries.[27] The recommended fluid is LR for initial resuscitation. Studies evaluating other fluids, such as hypertonic saline, albumin, other colloids, and fresh frozen plasma (FFP), have shown conflicting results and any measured benefits were not noted in the initial stages of resuscitation.[27,36] Although these formulas are used as a general starting point, frequent readjustments based on patient response (such as monitoring vital signs, mental status, assessment of fluid status with ultrasound, and hourly urine output) are required to avoid both over and under resuscitation. A goal urine output of 0.5 to 1.0 mL/kg/h is recommended.[37]

TABLE 54.3 Burn Resuscitation Formulas

Formula	First 24 Hours
Parkland	LR solution 4 mL/kg per percent TBSA; half over the first 8 h
Modified Parkland	LR solution 3–4 mL/kg per percent TBSA; half over the first 8 h
Evans	Crystalloids in the amount of 1 mL/kg per percent TBSA and colloids at 1 mL/kg per percent TBSA; half over the first 8 h; plus 2000 mL glucose in water maintenance
Brooke	LR solution 1.5 mL/kg per percent TBSA and colloids at 0.5 mL/kg per percent TBSA; half over the first 8 h; plus 2000 mL glucose in water maintenance
Modified Brooke	LR solution 2 mL/kg per percent TBSA in adults and 3 mL/kg per percent TBSA in children; half over the first 8 h
Monafo	Solution containing 250 mEq Na, 150 mEq lactate, 100 mEq Cl; amount adjusted to urine output
Rule of Ten	LR solution at 10 mL per percent TBSA per hour for every 10 kg above 80 kg, 100 mL is added to this hourly rate
Cope and Moore	75 mL per percent TBSA oral electrolyte solution, 75 mL per percent TBSA FFP, 2000 mL fruit juice orally or 2000 mL 5% dextrose; half over the first 8 h
Gelin	Low molecular weight dextran: 2 mL/kg per percent TBSA for <30% TBSA; 2.5 mL/kg per percent TBSA for 30%–60% TBSA; 3 mL/kg per percent TBSA for >60% TBSA
Galveston (pediatric)	LR solution at 5000 mL/m^2 TBSA burned plus 2000 mL/m^2 TBSA, half over the first 8 h
Shriner's Cincinnati (pediatric)	Older children: LR 4 mL/kg per percent TBSA + 1500 mL/m^2 total; half over the first 8 h Younger children: 4 mL/kg per percent TBSA + 1500 mL/m^2 total; LR solution + 50 mEq $NaHCO_3$ in the first 8 h; LR solution in the second 8 h, and 5% albumin in LR in the third 8 h

LR, Lactated Ringers; *TBSA,* total body surface area; *Cl,* Chloride; *Na,* sodium; *FFP,* fresh frozen plasma; *$NaHCO_3$,* sodium bicarbonate.

Overly aggressive fluid resuscitation has been coined "fluid creep" and can have devastating results, including worsening local tissue edema with burn conversion, extremity compartment syndrome, abdominal compartment syndrome, and pulmonary edema.[36] Care should be taken to avoid hypothermia, which has been shown to worsen outcomes. Cold fluids as well as environmental and open-air exposure in the ED can inherently result in hypothermia, but patients with burns are particularly vulnerable given the impairment to their thermoregulatory function. Continuous monitoring of core temperature is recommended in patients with large burns.[38]

Escharotomy

With deep burns, a non-compliant and restrictive eschar forms, which, when circumferential or near-circumferential around an extremity or the abdomen, may compress the underlying tissues and structures

leading to a compartment syndrome. Similarly, an eschar involving the thorax may impede ventilation, eschar on the face may result in increased intraocular pressures, and eschar around the neck may compromise the airway. When this occurs, emergent release of the tissue pressure by making an incision through the eschar (escharotomy) is required. Escharotomy is rarely needed in the first few hours of burn injury, rather increased tissue edema as a result of resuscitation often leads to the need for the procedure at a later time.[39]

Specific indications for escharotomy include pain, pallor, paresthesia, paralysis, poikilothermia, pulselessness, decreased or absent oximetry signals, increased compartment pressures for eschar over limbs >30 mm Hg and increased intraocular pressures for peri-orbital eschar (>30 mmHg). Respiratory and hemodynamic dysfunction such as increased airway pressures, decreased tidal volumes, decreased preload, and tachycardia are indications for eschar over the chest. Poor respiratory compliance, hemodynamic instability, tube feed intolerance, decreased urine outpatient, or increased bladder pressure (>25 mm Hg) may indicate need for abdominal escharotomy.[39] Monitor bladder pressure in patients with concern for possible abdominal compartment syndrome.

Since the eschar is composed of necrotic tissue, escharotomy is generally associated with little pain or blood loss. The amount of blood loss can be further minimized by using electric cautery. To be effective, the incisions should be down to the subcutaneous level, allowing the stiff eschar to open. The incisions should also be slightly extended into normal tissue both proximally and distally. Along the extremities, the incisions are made over the medial and lateral aspects with care taken to avoid damage to underlying vital structures. With hand burns the incisions may need to be extended into the fingers. Proper escharotomy incisions are displayed in Fig. 54.7.[39]

Rarely, additional procedures, such as fasciotomy and nerve decompression may also be needed. Burns over the abdomen may require a decompressive laparotomy or a peritoneal catheter if escharotomy is not effective.[39]

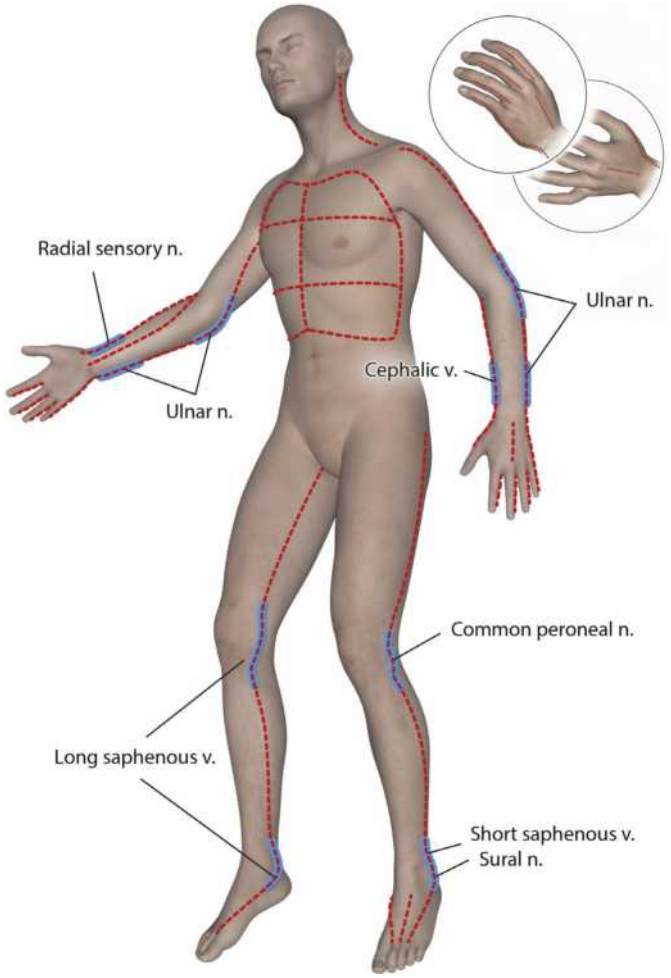


Fig. 54.7 Location of Escharotomy Incisions. Areas to avoid to prevent nerve injury are highlighted in blue.

Local Wound Therapies

Local wound therapies aimed at protecting the burn from further injury and infection and maintaining a moist wound environment that is most conducive to healing are paramount in burn injury care. Superficial burns do not require any local treatment. However, topical application of a nonsteroidal anti-inflammatory agent or aloe vera may reduce pain.

Burns should be cleaned gently with soap and water. Management of blisters is still a subject of debate. Intact blisters create a barrier, maintain a moist environment and contain some cells and signaling molecules that stimulate healing. On the other hand, they also contain substances that result in damage to the microcirculation, increased inflammatory response, and mechanical pressure over the wound. Practice varies by location, but in general, blisters should be left intact. Although there is no consensus, very large or tense blisters, as well as those located over joints, should be punctured to allow fluid to drain, but not fully deroofed.[40] Any already ruptured and non-adherent necrotic tissue should be gently removed manually or with topical agents. If a patient is to be transferred, wound therapy should generally be performed in the burn unit, and the burns should be covered with a clean, non-adherent dressing prior to transport.

Inpatient and outpatient dressings for patients who do not require skin grafting (partial-thickness burns, small full-thickness burns) is still a subject of considerable debate as evidenced by the large number of natural and synthetic agents and dressings available (Table 54.4). Dressing selection depends on depth and location of the injury; pain; condition of the wound and inherent amount of moisture, exudate, and drainage; risk of infection; ability for dressing changes; and cost. Dressings should prevent infection and contamination, maintain an appropriate amount of moisture but allow for gas exchange, provide comfort, and be cost-effective.[6,41,42]

Ointments are preferred over creams because they do not adhere to overlying dressings. Application of a topical generic antibacterial ointment is recommended. Petroleum jelly may also be used in wounds with low risk of contamination. Silver sulfadiazine cream was historically considered the standard therapy for the conservative management of burns. It has a wide antibacterial and antifungal spectrum and should be considered in heavily contaminated or infected burns however, it is no longer recommended for most other burns. Multiple systematic reviews have found that silver sulfadiazine was associated with poorer healing outcomes than other dressing types.[41,43] Moreover, other topical agents such as hyaluronic acid with or without zinc, or polyhexanide/betaine gel may also be effective.[44,45] Burn wounds should generally remain covered during the healing process.[46]

An alternative to topical agents is one of a number of commercially available occlusive dressings (see Table 54.4) in addition to other widely available dressings such as petrolatum gauze with or without other additives (such as tribromophenate). Although generally more expensive than topical agents and not as widely available, occlusive dressings require less frequent dressing changes and are associated with less pain and promote effective wound healing.[47–50] Many of the

TABLE 54.4 Representative Topical Agents and Dressings for Burns

Category	Examples	Advantages	Disadvantages
Non-Occlusive, Absorptive			
Gauze, nonadherent	Telfa (Kendall, Mansfield, MA)	Nonadherent, inexpensive	Requires daily dressing changes
Occlusive			
Foams	Mepilex (Mölnlycke, Gothenberg, Sweden); Curafoam (Kendall, Dublin, Ireland); Allevyn foam (Smith & Nephew, London, United Kingdom); Lyofoa (Molnycke, Gothenburg, Sweden)	Absorbs exudate, prevents surrounding maceration	Opaque, may dehydrate wounds with minimal exudate
Hydrocolloid	DuoDERM and Granuflex (ConvaTec, Bridgewater, NJ); Tegasorb (3M, St. Paul, MN)	Absorbs exudates, protective cushioning of wound	Opaque, no antimicrobial properties
Alginate	SeaSorb (Coloplast, Humlebaek, Denmark); Algiderm (Bard, Murray Hill, NJ); Melgisorb (Mölnlycke, Gothenberg, Sweden); Aquacel (ConvaTec, Bridgewater, NJ); Comfeel (Coloplast, Minneapolis, MN), or Sorbsan (Mylan, Morgantown, WV)	Absorptive	Frequent dressing changes
Nanocrystalline silver	Acticoat (Smith & Nephew, Largo, FL); Aquacel Ag (ConvaTec, Bridgewater, NJ); Silverlon (Argentum, Geneva, IL)	Antimicrobial, creates a moist environment, less frequent dressing changes	Need to keep dressing moist
Hydrogel	Curagel (Kendall, Mansfield, MA); Flexigel (Smith & Nephew, Largo, FL); Nu-Gel (Johnson & Johnson, Arlington, TX); Dermagel (Maximilian Zenho & Co, Brussels, Belgium), SilvaSorb (Medline, Mundelein, IL), or Skintegrity (Medline, Mundelein, IL)	Rehydrates dry wounds	Non-absorptive
Collagen	Fibracol (Johnson & Johnson, New Brunswick, NJ) or Puracol (Medline, Mundelein, IL)	Absorptive	Require secondary dressing
Transparent films	Tegaderm (3M, St. Paul, MN); OpSite (Smith & Nephew, Largo, FL)	Transparent, inexpensive	Non-absorptive

occlusive dressings may be left in place for up to one week unless obviously saturated or malodorous. Burns on the extremities should be elevated to reduce swelling and general care should be taken to avoid tight compressive dressings at any site. Emergency clinicians should know which products are available at their institution(s) and collaborate with clinicians in the inpatient and outpatient settings to determine the most appropriate and cost-effective protocols for burn wound treatment for patients at their institution.

For full thickness burns, the standard of care is early excision and grafting with autograft if possible. Patients with extensive burns may require temporary allograft, xenograft, skin substitutes, or dermal analogs, and, although beyond the scope of this chapter, there has been significant research in the surgical management of burns in the last couple of decades.[6]

A number of novel burn therapies have been investigated in preclinical and clinical studies but are not yet recommended in emergency settings. A systematic review of preclinical studies suggested that warm water, simvastatin, erythropoietin, or cerium nitrate may reduce the conversion of superficial to deep burns.[51] Ascorbic acid (vitamin C) is also being studied as a potential adjunctive therapy in burn resuscitation.[52,53] Finally, a systematic review and meta-analysis of growth factor use for partial thickness burns concluded that this therapy (fibroblast growth factor, epidermal growth factor, and granulocyte macrophage-colony stimulating factor) might be an effective and safe add-on to standard wound care for partial-thickness burns.[54] All patients with burn injuries should have their tetanus immunization status updated as appropriate.

Pain Management

Pain in patients who have sustained burn injuries is often undertreated, however routine monitoring of pain severity and the use of pain management protocols can improve pain management and avoid overuse of opioids. Pain in acute burn injury is predominantly due to three mechanisms: direct stimulation of nociceptors in the skin and the transmission of painful neural impulses via A-delta and C-fibers, inflammatory pain, and neuropathic pain (in chronic settings).

For pharmacological treatment, begin with acetaminophen (500 mg PO every 4 to 6 hours; 10–15 mg/kg/dose PO for children) or NSAIDs (such as ibuprofen 400 to 800 mg PO every 8 hours; 10 mg/kg/dose PO for children) for mild to moderate pain (although NSAIDs should be avoided in patients with severe burns or shock) and opioids (such as fentanyl at 1 to 2 mcg/kg IV for adults and children, morphine at 2 to 4 mg/kg IV for adults and 0.05 mg/kg IV for children <50 kg, and oxycodone 5–10 mg PO for adults and 0.1–0.2 mg/kg PO for children <50 kg) for more severe pain or breakthrough pain. Long-acting opioids, such as methadone, should be considered for patients suspected to need frequent or prolonged dosing of opioids. The addition of an anxiolytic, such as midazolam (1 to 2 mg IV for adults; 0.05–0.1 mg/kg IV depending on age for children) or lorazepam (0.5 to 1 mg IV for adults; 0.05 mg/kg IV for children), may be more effective than an opioid alone, particularly during wound management and procedures. Intravenous (0.15 to 0.3 mg/kg) ketamine has shown improvement in pain scores, particularly during debridement and dressing application, although more study is needed.[55,56] Ketamine infusion for background pain is used in some centers.[56] Intravenous lidocaine, dexmedetomidine, and nitrous oxide

may also be effective.[55,56] Finally, regional anesthesia may also be an effective substitute for systemic therapies when appropriate.[56] Avoid IM injections of medications (with the exception of tetanus immunization), particularly in large burns, given that changes in tissue fluid volume can make absorption less predictable.[27]

Although pharmacological agents are the cornerstone of burn pain management, non-pharmacological methods (such as cooling of the burn, covering the burn with a dressing) and cognitive-behavioral therapy (such as relaxation and distraction with mechanisms such as music, virtual reality, and aromatherapy) should be considered.[54,56]

DISPOSITION

Most superficial and small partial-thickness and even select small full thickness burns can be managed in the ED by an emergency clinician with close follow-up by a primary care physician comfortable handling burns (or a burn specialist for partial thickness and full-thickness burns) within the next 3 to 5 days. Patients with large or deep burns, burns involving sensitive areas, and those with significant comorbidities and trauma should be admitted. Criteria for referral and transfer to a burn center are presented in Box 54.1.[27]

The references for this chapter can be found online at ExpertConsult.com.

BOX 54.1 Criteria for Referral to a Burn Center

- Partial thickness burns greater than 10% TBSA
- Burns that involve the face, hands, genitalia, perineum, or major joints
- Full thickness burns in any age group
- Electrical burns, including lightning injury
- Chemical burns
- Inhalation injury
- Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
- Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality
- Burned children in hospitals without qualified personnel or equipment for the care of children
- Burn injury in patients who will require special social, emotional, or rehabilitative intervention

TBSA, Total body surface area.

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CHAPTER 54: QUESTIONS AND ANSWERS

1. A 30-year-old man presents with a burn to both anterior aspects of his forearms after being burned by a radiator. He has severe pain and has deep (reticular) dermis extension of the burn. You call the consultant and describe the burn as which of the following?
- **a.** Superficial burn of 4.5% body surface area
- **b.** Superficial partial thickness burn of 9% body surface area
- **c.** Deep partial thickness burn of 4.5% body surface area
- **d.** Full thickness burn of 2.5% body surface area
- **e.** Deep full thickness burn of 9% body surface area

Answer: c. Deep partial thickness burns extend through the epidermis into the deep (reticular) dermis. Body surface area is determined by the rule of nines. Nine percent for each upper extremity means that the forearm is approximately one fourth of 9%. Two forearms burns are half of 9%. Partial thickness burns are often more painful than full thickness burns, in which all of the nerve endings are destroyed.

2. A 3-year-old boy presents with circumferential burns involving both upper extremities, including his hands, from pulling a boiling pot of water off the stove. The burns are mixed partial thickness and full thickness burns. Which of the following best describes the body surface area burned and the most appropriate disposition?
- **a.** 9% and admit to pediatrics with surgery consultation
- **b.** 9% and transfer to burn unit
- **c.** 18% and transfer to burn unit
- **d.** 18% and admit to pediatric surgery
- **e.** 20% and admit to pediatric intensive care unit

Answer: c. Children with burns over 10% total body surface area (TBSA) should be transferred to a burn unit. In addition, hand burns should be treated at a burn unit. Circumferential burns are not consistent with a splash injury, and child abuse should be suspected and reported.

3. A 55-year-old, 80-kg man presents with partial thickness burns of both his legs, front torso, and groin. What is the initial fluid resuscitation according to the Parkland formula?
- **a.** 500 mL LR solution in the first 4 hours
- **b.** 1100 mL normal saline in the first hour
- **c.** 1100 mL of LR solution in the first hour
- **d.** 2400 mL normal saline in the first hour
- **e.** 4200 mL LR solution in the first 4 hours

Answer: c. The amount of LR solution required for the first hour can be rapidly estimated with the Parkland formula by multiplying the estimated total body surface area (TBSA) of the partial and full thickness burn (55%) by body weight in kilograms (80 kg) and dividing by 4.

4. A 25-year-old woman presents with a partial thickness burn to her right forearm after a grilling accident. You note areas of gray discoloration with decreased blanching in the erythematous region of the burn. In addition to irrigation, debridement, and dressing with a nonadherent dressing, which of the following would be the most appropriate treatment?
- **a.** Apply silver sulfadiazine and follow-up with plastic surgery in 1 week
- **b.** Calculate the Parkland formula and administer fluids before discharge
- **c.** Educate the patient about daily dressing changes and have her follow-up with plastic surgery in 24 to 48 hours
- **d.** Immerse her forearm in ice water for pain control
- **e.** Unroof soft blisters and have the patient follow-up with her primary care physician in 1 week

Answer: c. The distinction between superficial and deep partial thickness burns is important in that deep partial thickness burns often do not heal within 2 or 3 weeks and may result in severe scarring and contractures, especially in children. As a result, deep partial thickness burns that do not heal within 21 days may require excision and skin grafting to minimize scarring. Deep partial thickness burns may also progress to full thickness burns during the course of several days after injury. Burns less than 20% TBSA can be treated with oral hydration. Although there are little data to guide treatment, blisters are generally left intact initially if possible unless tense or over a joint. They may later require debridement.

5. Which of the following is an indication for intubating a patient who was found in a burning house and requires transfer 2 hours away to a burn center?
- **a.** Soot in the airway and singed nasal hair
- **b.** Dyspnea and hypoxia
- **c.** Patient unable to handle own secretions
- **d.** Altered mental status
- **e.** All of the above

Answer: e. Traditionally, inhalation injury was diagnosed on the basis of clinical findings, such as facial burns, singed nasal vibrissae, carbonaceous sputum, and a history of injury within a closed space. However, these findings are neither highly sensitive nor highly specific. If the patient is at a burn center and symptoms are mild, then an approach involving flexible laryngoscopy and close observation in an ICU is reasonable. However, if the patient requires prolonged transport to a tertiary care center then intubation is recommended if signs or symptoms or airway involvement are present.

6. What is the most appropriate management for a superficial partial thickness burn on the forearm?
- **a.** A clean dry dressing, such as gauze
- **b.** Petroleum gauze
- **c.** Systemic antibiotics and silver sulfadiazine
- **d.** Topical antibiotic ointment
- **e.** B and D

Answer: e. Superficial partial thickness burns may be treated with a topical antibiotic ointment, petroleum gauze or one of several commercially available burn dressings. Silver sulfadiazine, as well as dry dressings, will slow re-epithelialization. Silver sulfadiazine is appropriate for infected or heavily contaminated burns. Systemic antibiotics are *not* indicated for non-infected burns.

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Chemical Injuries

Michael D. Levine

KEY CONCEPTS

- For chemical injury, the degree of skin destruction is determined mainly by the properties of the toxic agent, its concentration, and the duration of its contact.
- Chemical injuries are commonly encountered after exposures to acids and alkalis.
- Hazardous materials (HazMat) are substances that can cause physical injury and damage the environment if improperly handled.
- In dealing with HazMat incidents, two distinct goals need to be achieved: (1) Containing the HazMat, extinguishing the fire and explosions, and eventually cleaning the site, and (2) evacuating victims exposed to the HazMat from the scene, decontaminating, and rapidly evaluating for treatment.
- Decontamination consists of removing contaminated clothing and hydrotherapy (i.e., washing of the skin) for the majority of exposures. For lithium, potassium, and sodium exposure, hydrotherapy is contraindicated because of the exothermic reaction upon contact with water.
- Alkali burns tend to penetrate deeper into tissue layers than acidic burns; and as a result, are associated with greater morbidity.
- Hydrofluoric acid burns can be associated with significant systemic hypocalcemia.
- Exposure to various toxic gases can occur from common industrial settings, and knowledge of these agents is necessary for proper treatment by the emergency clinician.
- Unconventional chemical weapons may be categorized into four major classifications: nerve agents, vesicants, choking agents, and cyanide agents.

GENERAL APPROACH TO A HAZMAT EVENT

Foundations

Background and Importance

During the past century, there has been a dramatic increase in the number of chemicals produced. Worldwide, there are more than 5 million known chemicals, with thousands of new chemicals developed annually. The chemical industry is a critical component to the US economy, producing more than 600,000 jobs. Large chemical incidents, such as the 1974 cyclohexane vapor leak and subsequent explosion in Flixborough, UK, and the 1984 methyl isocyanate release from a pesticide plant in Bhopal, India, have drawn large-scale media attention, and many smaller chemical spills occur daily.

It is estimated that 25,000 to 35,000 chemical incidents occur annually in the United States alone, with the majority resulting from either equipment failure or human error. Many individuals suffer injuries or deaths annually due to these chemical spills.[1] While these chemical incidents can occur in rural or urban environments, they are more common in rural areas.[1] Individuals living close to an industrial complex may be exposed to a chemical following inadvertent release from the industrial site. However, other individuals living far from any stored chemicals may be exposed due to accidents during transport.

It is estimated that half of all pesticide or agricultural chemical spills occur during transportation. The transport of hazardous materials occurs throughout the United States; it is estimated more than 1 million hazardous substances are shipped throughout the United States daily.[2] These chemicals, which include acids, alkalis, and other highly reactive substances, not only are found throughout industry but also are ingredients in many household products. Exposure to these substances can result in multi-system injuries.

A hazardous material (HazMat) is defined as a substance, including gases, solids, or liquids, that has the potential to cause harm to people or the environment. Historically, the Hazardous Substances Emergency Events Surveillance (HSEES) system collected information on chemical exposures, but this program concluded in 2009. The following year, the National Toxic Substances Incidents Program (NTSIP) was established, which compiles data from multiple sources to perform chemical surveillance. The most commonly released hazardous substances are volatile organic compounds, herbicides, acids, and ammonia. Various other products, such as cement, drain cleaners, and gasoline, are also hazardous, and exposure can result in severe disability or death.

Community Preparedness and HazMat Response

HazMats are found throughout society, including rural and urban settings. Furthermore, because these substances are often transported on highways and railroads, a HazMat exposure could potentially occur in any community. While industrial settings account for the largest percentage of chemical incidents, exposures in rural residential settings and agricultural settings occur.[3] First responders, paramedics, and members of the HazMat response team must work together to identify toxic chemicals and assess hazardous environments. Placards, shipping papers, United Nations chemical identification numbers, and markings on shipping containers help identify the offending agent. The Chemical Transportation Emergency Center (CHEMTREC) in Arlington, Virginia, maintains a 24-hour telephone hotline (Box 55.1) to assist in the rapid identification and management of hazards caused by chemical agents. Standardized placards have also been developed by the National Fire Protection Association (NFPA). These placards use four diamonds to identify specific hazards associated with this project. In addition, regional poison control centers (see Box 55.1) provide specific health information regarding individual chemicals.

Although placards can identify chemicals in the case of a known industrial exposure, it is not always clear an exposure has occurred. The challenges in identifying a HazMat scene are highlighted in Japan, where there has been an epidemic of chemical suicides with hydrogen sulfide gas inside locked cars. Following widespread internet awareness of this situation, there were a series of similar "copy-cat" incidents in the United States. Such exposures put first responders at particularly

BOX 55.1 Important Phone Numbers to Assist in the Identification and Management of Chemicals and Chemical Injuries

CHEMTREC: 1-800-424-9300
Poison Control: 1-800-222-1222

high risk of chemical injury, because they might have been unaware of any history of potential chemical exposure.

Contingency Plan

The contingency plan for HazMat management is comprised of two distinct parts: initiation of the site plan, and evacuation. Initiation of the site plan begins after the specific offending agent has been identified and the surrounding environment has been assessed. It is only after the substance has been identified that the risks to the public and the environment can be accurately identified. First responders should be trained to recognize the potential for a HazMat incident and establish a perimeter. During the evacuation phase, the HazMat technicians are specifically trained in the use of personal protective equipment (PPE), establishing entry into a HazMat scene, victim rescue, and determining the type and extent of a HazMat emergency. A central command post should be established in an area far enough from the incident to avoid direct contamination. Local geographic and environmental factors (e.g., wind direction and speed) may need to be considered when choosing a location for the command post, depending on the specific chemicals involved. The command post should coordinate the activities of the HazMat team with those of the emergency medical services personnel, firefighters, police officers, and other relevant personnel.

Anatomy, Physiology, and Pathophysiology

Most chemical agents cause skin damage by producing a chemical reaction rather than a hyperthermic injury. However, certain chemicals can generate significant heat production via an exothermic reaction after exposure to moisture. Nonetheless, the majority of dermal injuries result from direct damage to the skin rather than from a hyperthermic injury. The type of chemical reaction produced depends on the properties of the individual agent. In general, the degree of damage correlates directly with the toxic agent's concentration and duration of exposure. Several other factors contribute to the degree of injury—for example, areas of the body where the skin is particularly thin (e.g., face, scrotum) are more at risk than areas of the body where the skin is thicker (e.g., palms of hands and soles of feet). Skin that is thin or broken is at risk for more severe injury.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSES

Exposure to acidic compounds can produce protein denaturation and subsequent *coagulative necrosis*. In theory, the eschar limits the depth by which an acid can penetrate. Various acids produce eschars with characteristic colors. For example, nitric acid burns result in a yellow eschar, whereas sulfuric acid burns result in a black or brown eschar. Hydrochloric acid and phenol burns produce a white to gray-brown eschar. Despite the eschar formation, profound chemical burns can occur following exposure to an acid. Alkali agents, in contrast, produce a saponification and reactive *liquefactive necrosis*. Because there is no eschar to limit penetration, alkali burns tend to penetrate deeper into the tissues, which results in significant tissue damage.

Other infections (e.g., cutaneous anthrax), injury (e.g., full-thickness burn), or envenomation (e.g., Brown recluse spider bites or *Loxosceles* sp.) that result in eschar formation can be confused with chemical injury. However, history and physical findings differ, allowing for distinction from chemical injury. For example, a splash pattern may be seen following exposure to liquid chemicals. Ocular injection may be seen following exposure to chemical fumes that affect mucosal membranes. Wheezing may be heard following various inhalational injuries.

DIAGNOSTIC TESTING

Patients with significant burns or systemic toxicity are required to do a complete blood count, metabolic profile, including serum electrolytes, with hepatic and renal function tests. Monitor the urine output and check for infection or sepsis; an arterial or venous blood gas and serum lactic acid level is recommended. A chest radiograph is obtained following inhalational injuries.

MANAGEMENT

In dealing with a HazMat incident, two distinct processes occur simultaneously. First, the scene should be secured; this involves containing the substance, extinguishing fires, and controlling other environmental hazards. The second process involves treatment, which begins with decontamination. The exact decontamination depends on the specific agent and route of exposure. In general, all decontamination should be performed before arrival in the emergency department (ED). Individuals who are not exposed to the hazardous material are kept safely away from the scene to prevent subsequent exposure.

At the outset of any contamination event, the offending agent may not be known. Therefore, first responders and those having direct contact with exposed patients must wear appropriate PPE. Once the first responder is dressed appropriately, decontamination begins by removing the patient's contaminated clothes. It is critical that dry (anhydrous) chemicals can be brushed off the patient's skin, to the extent feasible, followed by copious irrigation with water delivered under low pressure. Ideally, the contaminated water will be contained on the scene for appropriate disposal. Liquid chemicals can be copiously irrigated directly. Decontaminate the patient before entering the ED if it was indicated but not performed on scene. The primary and secondary survey can occur simultaneously with decontamination.

Although the exact requirements for PPE among hospital personnel are somewhat controversial, at a minimum all personnel involved with decontamination should wear chemical-resistant clothing with a hood, boots, eyewear, at least two layers of gloves, and some form of respiratory protection.

The initial management of the chemically burned patient involves removing the individual from the hazardous environment. Because various chemicals will continue to destroy tissues until they are removed from the skin, the clothing should be removed, and prompt decontamination measures should be initiated at first chance.

Hydrotherapy involves the gentile irrigation of a large volume of water under low pressure for a prolonged time. Such therapy dilutes the toxic agent and washes it out of the skin. High-pressure irrigation should not be used, because it can drive the chemical deeper into the tissues, as well as produce splattering of the chemical into the eyes of the patient or rescuer.

Water should be used for irrigation after acid or alkali burns. Chemical neutralization may be more deleterious to victims with chemical burns. Additionally, it has been hypothesized that neutralizing agents produced additional heat, thereby augmenting the burn. Although the same effect may occur when certain chemicals come in

contact with water, large volumes of water tend to limit the exothermic reaction. More recently, scientists began to question the belief that neutralization of an alkaline burn of the skin with an acid increases tissue damage because of the exothermic nature of acid-base reactions. Nonetheless, at present, we recommend irrigation with water alone as the best method for decontamination. Not all agents are best decontaminated with irrigation or hydrotherapy. Dry chemical agents, such as lye or elemental metals (e.g., sodium), should be brushed away prior to instituting hydrotherapy. Elemental metals (e.g., sodium or potassium) may produce exothermic reactions when combined with water. To minimize the exothermic reaction from such compounds, mineral oil may be applied to the skin before water. However, copious irrigation should not be delayed while waiting for mineral oil. In addition to lye and elemental metals, some argue that phenol (carbolic acid) should not be irrigated with water owing to concern for enhanced skin penetration after exposure to water. The use of a substance that has both hydrophobic and hydrophilic properties for irrigation (i.e., polyethylene glycol [PEG]) has not been proven to exhibit clear benefit over water alone; therefore, hydrotherapy should not be delayed while waiting for PEG. If PEG solution is used for decontamination, a low-molecular-weight PEG solution (200 to 400 Da) is preferred. This solution is different than the PEG solution typically used for gastrointestinal procedures.

DISPOSITION

Treat patients in a similar manner as those with thermal burns, and criteria for transfer to a burn center are identical (see Chapter 54). Those with minor symptoms, in whom pain is controlled, and who lack systemic symptoms can be referred home. Admit patients with systemic toxicity, significant opioid analgesic requirements, and those requiring systemic administration of an antidote (e.g., intra-arterial calcium for hydrofluoric acid).

OCULAR INJURIES

Foundations

Background and Importance

Chemical burns to the eye require emergent management due to the potential for irreversible vision loss. Common causes include inadvertent handling of chemicals with resultant splash injury, exploding batteries, airbag deployment, and intentional assaults.

Anatomy, Physiology, and Pathophysiology

Alkali burns can initially appear trivial, but because of an interaction with lipids in the corneal epithelial cells, a liquefaction necrosis results, and deep penetration through the corneal stroma can ensue. The injury can occur rapidly; for example, anhydrous ammonia can penetrate the anterior chamber in less than 1 minute, resulting in complete blindness.

There are numerous grading systems that have been developed to describe ocular burns, including the Roper-Hall classification, which divides the injury into four grades based on the amount of corneal haze and perilimbal ischemia; and the Dua classification, which has six grades, and is based on the amount of limbal involvement (Table 55.1).[4] Exact classification systems are not particularly relevant for the emergency physician.

Clinical Features

Ocular chemical exposures can present with conjunctival injection, chemosis, cutaneous eyelid burns, subconjunctival hemorrhage and various degrees of vision impairment.

TABLE 55.1 Dua Classification

Grade	Prognosis	Clinical Findings	Conjunctival Involvement
I	Very good	0 clock hours of limbal involvement	0
II	Good	<3 clock hours of limbal involvement	<30%
III	Good	3 to 6 clock hours of limbal involvement	30%–50%
IV	Good to guarded	6 to 9 clock hours of limbal involvement	50%–75%
V	Guarded to poor	9 to 12 clock hours of limbal involvement	75%–100%
VI	Very poor	Complete limbal involvement	100%

Differential Diagnoses

The differential diagnosis for a red eye or vision loss is broad and is more fully discussed in Chapter 18. In the setting of trauma, the differential diagnosis includes subconjunctival hemorrhage, perforation, foreign body, and corneal abrasions. In the absence of trauma, the differential diagnosis includes benign etiologies (such as, subconjunctival hemorrhage or conjunctivitis) to more concerning etiologies (such as, iritis, uveitis, episcleritis, glaucoma, optic neuropathy, central retinal artery occlusion, or central retinal vein occlusion).

Diagnostic Testing

Perform a visual acuity test in all patients with ocular complaints. Check the ocular pH with litmus paper, ideally before and after irrigation. If the patient can tolerate the procedure, a comprehensive slit-lamp examination is preferred.

Management

The management of acute chemical burns to the eye involves several stages including removal of the offending substance, and administration of medications to decrease inflammation, avoid further tissue injury, and ultimately foster re-epithealization.[4] When a chemical injury to the eye is suspected, start copious irrigation immediately. In the pre-hospital setting, tap water irrigation is generally readily available and the ideal choice for irrigation. At the scene, it is recommended that the victim submerge the eyes in running tap water and continuously open and close the eyes with the head turned such that the affected eye is lower than the unaffected eye to minimize any contamination into the unaffected eye. In the ED, tap water irrigation can be continued in preparation for a more definitive irrigation system. However, because there is some concern for possible promotion of corneal edema, based on the hypotonicity of tap water, some advocate for use of other readily available solutions for ocular irrigation. Such solutions include either lactated Ringers, a balanced salt solution (BSS), or amphoteric solutions such as Diphoterine®.[4] The repeated application of topical anesthetics (such as, proparacaine) can decrease pain and facilitate irrigation. Hydrotherapy can also be accomplished by connecting intravenous tubing to a bag containing normal saline or lactated Ringers solution. The initial therapy consists of continual irrigation of the eye with 2 L of lactated Ringers during the first 30 minutes. A Morgan lens can be used for irrigation, although there is a theoretic risk of trapping the chemical between the conjunctiva and the Morgan lens, thereby increasing the burn. If a Morgan lens is used, we recommend replacing the lens between each liter. After 2 L has been infused, as described earlier, litmus paper is inserted into the conjunctiva

to determine the pH; irrigation is continued until the pH is at a near-physiologic level (pH of 7.4). Alkali burns are likely to require more irrigation than acidic burns. In either case, depending on the chemical's pH and amount of exposure, additional liters may be required to restore a near-neutral pH. Following irrigation, it is important that the emergency physician evert the upper eyelid and visually inspect the area for any lodged or hidden particulate matter. A slit-lamp examination with fluorescence staining is recommended to assess for any corneal abrasion. Although of undetermined benefit, ocular antibiotics are commonly used after appropriate decontamination if a corneal abrasion is present.

The use of topical or subconjunctival corticosteroids following alkali burns has been associated with reduced corneal opacity, vascularization, and inflammation. Topical corticosteroids, such as fluorometholone 1% or prednisolone 0.5% can reduce inflammation and should be continued for approximately 1 week. We recommend consulting an ophthalmologist prior to implementing corticosteroids.

Disposition

Emergent ophthalmologic consultation and close follow-up are indicated for all significant exposures. Most ocular burns, other than the mildest burns, are treated with a long-acting cycloplegic and a mydriatic. In addition, after consulting an ophthalmologist, a carbonic anhydrase inhibitor may be used for 2 weeks (or until the ocular pain subsides). These medications decrease the potential for pupillary constriction, increased intraocular pressure, and early glaucoma. Procedures such as amniotic membrane patching, anterior chamber paracentesis, and corneal transplant have been used for chemical injuries to the eye but should only be performed by an ophthalmologist.

Patients with lower grade ocular injuries can be managed as outpatients, but patients with higher-grade injuries should be admitted to the hospital for more intensive treatment.

SPECIFIC TOXINS

Hydrofluoric Acid

Foundations

Background and importance. Hydrofluoric acid is an acidic aqueous solution made from fluorine. It has a variety of industrial indications, including glass etching, the production of semiconductors, rust removal products, insecticides, tile-cleaning agents, and automobile wheel cleaning products.[5] It is available in many over-the-counter products in concentrations ranging from 6% to 12% but can be used in the industrial setting in concentrations exceeding 70%.

Anatomy, physiology, and pathophysiology. Absorption of hydrofluoric acid can occur upon exposure to the lung, skin, and eyes. In a 20-year review of all hydrofluoric acid deaths reported to the Taiwan Poison Control Center, dermal exposure accounted for 84% of all exposures, and the majority occurred in an occupational setting. Of these 324 subjects, the majority of subjects had mild toxicity. However, approximately 40% of subjects had moderate toxicity and 1% had severe toxicity. Two subjects died strictly from hydrofluoric acid-related dysrhythmias and shock. The timing of onset of pain after a hydrofluoric acid burn is inversely related to the concentration. For example, burns from a 20% hydrofluoric acid solution can have pain delayed for up to a day, whereas burns from a 50% hydrofluoric acid concentration will likely result in immediate pain.[5,6] Hydrofluoric acid is unique in its mechanism of action. Despite being an acid, it is capable of causing a liquefactive necrosis with subsequent deep tissue burn, similar to alkalis.[6] The free fluoride ion is responsible for most of the damage associated with hydrofluoric acid exposure. However, both the hydrogen ions as well as the fluoride ions cause tissue damage. In the setting of high concentrations of hydrofluoric acid (>50%), the hydrogen ion itself can cause damage to the skin, eyes, and mucosal membranes. Later, the fluoride ion causes both local and systemic toxicity, regardless of the concentration of hydrofluoric acid.[7] The free fluoride ion scavenges cations, such as calcium and magnesium, thereby resulting in systemic hypocalcemia and hypomagnesemia. In addition, free fluoride ions can inhibit sodium, potassium–ATPase (Na^+, K^+-ATPase), and the Krebs cycle. The combination of cellular destruction and inhibition of Na^+, K^+-ATPase can also result in hyperkalemia as a preterminal finding. As a result of the numerous electrolyte disturbances, QT prolongation, hypotension, and ventricular arrhythmias can occur. The severity of injury depends on the concentration of the substance and the duration of exposure.

Clinical Features

Inhalational Exposure

Inhalation of hydrofluoric acid is rare, and it almost always occurs in the industrial setting. Patient outcomes vary considerably depending on the concentration and duration of exposure to hydrofluoric acid. Inhalation and skin exposure to 70% hydrofluoric acid can result in pulmonary edema and death within hours. However, delayed pneumonitis and adult respiratory distress syndrome can occur, and the symptoms can be present for months. Pneumonitis can be severe and require ventilatory support.

Gastrointestinal Exposure

Gastrointestinal exposures are rare, except for cases of intentional ingestions. When such an exposure does occur, symptoms can include nausea, vomiting, and abdominal pain. Life-threatening fluoride toxicity can occur with large oral ingestions.

Ocular Exposure

Even though hydrofluoric acid is an acid, exposure of the eye to hydrofluoric acid can result in a severe burn with penetration and necrosis of the structures throughout the anterior chamber. As with other ocular injuries, immediate and copious irrigation of the eye is indicated. Systemic absorption is possible.

Dermal Exposure

Dermal exposure is the most common route of hydrofluoric acid injury. During handling of containers in which hydrofluoric acid is stored, contamination of inadequately protected fingers and hands often results in a chemical burn injury. The hydrofluoric acid skin burn has a distinct characteristic: the exposure causes progressive tissue destruction. Intense pain can occur; the onset of the pain is inversely related to the concentration of the hydrofluoric acid, such that the lower the concentration of hydrofluoric acid, the longer the time until symptoms may manifest. The pain may seem out of proportion the examination.[8] With larger exposures, the involved skin may develop a tough, coagulated appearance. If untreated, the burn can progress to an indurated, whitish appearance with vesicle formation. Within the digits, hydrofluoric acid has a predilection for subungual tissue. Severe untreated burns can progress to full thickness burns and can even result in loss of digits.

Differential Diagnoses

Because pain may seem out of proportion to the examination findings, shingles, neuropathy, and other chemical injuries are within the differential diagnosis. Numerous other gases causing respiratory compromise should also be included. In the presence of apparent burns, the differential diagnosis includes blistering disorders, toxic epidermal necrolysis, and infectious etiologies.

Diagnostic Testing

Test serum potassium, magnesium and ionized calcium levels in patients with hydrofluoric acid burns. With electrolyte abnormalities, an electrocardiogram (ECG) will assess for dysrhythmias or changes in the QTc or QRS intervals. Obtain a chest radiograph in individuals with inhalant or pulmonary symptoms. Finally, perform a detailed eye examination, including a slit-lamp examination, fluorescein staining, and visual acuities on individuals with ocular exposure.

Management

The initial treatment of hydrofluoric acid skin exposure is immediate irrigation with copious amounts of water for at least 15 to 30 minutes. Most exposures to dilute solutions of hydrofluoric acid respond favorably to immediate irrigation. Severe pain or any pain that persists after irrigation indicates a more severe burn that requires detoxification of the fluoride ion. Detoxification is accomplished when an insoluble calcium salt is formed. In the case of digital exposure, in which the fingertip is exposed, the fingernail should be removed.

In contrast to thermal burns, blisters are burst because necrotic tissue may harbor fluoride ions.[7] The fluoride ions can then be detoxified through topical treatment, local infiltrative therapy, or intra-arterial infusion of calcium. Calcium gluconate (2.5%) gel can be administered topically. Calcium chloride should not be used topically, as it is irritating to the dermis. Calcium gluconate gel is often not available in hospital pharmacies, but it can be made by mixing 3.5 g of calcium gluconate powder in 150 mL of a water-soluble lubricant (e.g., glycerin-hydroxyethyl cellulose lubricant [K-Y Jelly]). This gel is secured by an occlusive cover (e.g., powder-free latex glove). Because the skin is impermeable to calcium, topical treatment is effective only for mild, superficial burns.

Infiltration Therapy

Subcutaneous. Infiltrative therapy is necessary for treatment of deep, painful hydrofluoric acid burns. Calcium gluconate is the agent of choice and can be administered by either direct infiltration or intra-arterial injection. A common technique involves injecting 0.5 mL/cm^2 of 10% calcium gluconate subcutaneously through a 27- or 30-gauge needle. The use of an equal volume mixture of 5% calcium gluconate and 0.9% normal saline has been shown to reduce irritation of tissues and decrease subsequent scarring.

Despite its wide acceptance, the infiltration technique has disadvantages, especially in treating digits. A regional nerve block is recommended because the injections may be very painful. Removal of the nail to expose the nail bed is required if subungual tissue is involved. Vascular compromise can occur if excessive fluid is injected into the skin exposure sites, and unbound calcium ions have a direct toxic effect on tissue. Because of these disadvantages with subcutaneous infiltration in the hand, we recommend intra-arterial infusion in most instances.

Intravenous and intra-arterial. Patients with pain refractory to local or subcutaneous calcium administration may benefit from regional anesthesia, either intravenously (e.g., Bier block) or intra-arterially. Various dilute solutions of calcium have been used. Perhaps the simplest method involves the administration of a mixture of 10 mL of solution of 10% calcium gluconate in 40 to 50 mL of normal saline infused over 4 hours. Because of ease of administration, we recommend starting with this approach, although other approaches can be used in conjunction with this approach if pain persists. If more than 6 hours has elapsed since the time of hydrofluoric acid exposure, tissue necrosis cannot be prevented, even though pain relief can be achieved up to 24 hours after exposure. There is a direct correlation between the speed by which arterial infusion of calcium administration occurred and both the time of wound healing and the need for surgical intervention.

The intra-arterial infusion technique has potential disadvantages. Arterial spasm or thrombosis may result in significant skin loss. The intra-arterial procedure is more expensive, largely because it requires hospitalization for the use of the infusion pump and the monitoring of serum calcium concentrations if repeated infusions are used. Recently, the use of epidermal growth factor was found to be superior to saline, calcium gluconate, or magnesium sulfate.[9]

Respiratory Exposures

In the case of an inhalational exposure to hydrofluoric acid, prompt airway management is paramount, with endotracheal intubation occurring for the usual indications. Calcium gluconate can be nebulized as a 2.5% to 5% solution.[7] Racemic epinephrine or albuterol can be used for bronchospasm. Bronchoscopy can be performed to assess the degree of injury.

Ocular Exposures

The ocular use of calcium gluconate is somewhat controversial, because it has the potential to cause further damage to the eye. The use of ocular calcium gluconate is not routinely recommended. In the occupational setting, use of hexafluorine may be considered after copious irrigation of the eye with tap water or normal saline.[10]

Systemic Toxicity

Hydrofluoric acid binds calcium and magnesium ions with strong affinity. Systemic manifestations of fluoride toxicity are related to hypocalcemia and include abdominal pain, muscle fasciculations, nausea, seizures, ventricular dysrhythmias, and cardiovascular collapse. Burns as small as 2.5% of the total body surface area caused by concentrated hydrofluoric acid are fatal. Hypocalcemia can occur after significant exposure to hydrofluoric acid and is corrected with an intravenous 10% calcium gluconate infusion. Calcium chloride can be used, but its administration requires central venous access. In addition, fluoride ion toxicity has cardiac and neurotoxic effects.

Disposition

Patients treated with calcium therapy with continued refractory pain should be hospitalized for observation and should undergo a toxicological consultation. Patients with significant hydrofluoric acid exposure with systemic toxicity require hospitalization to monitor for cardiac dysrhythmias for 24 to 48 hours.

Formic Acid

Foundations

Background and importance. Formic acid is a caustic organic acid used in rubber, paper, tanning, agricultural, and electroplating industries. It has also been used to manufacture disinfectants and in various cosmetics.

Anatomy, physiology, and pathophysiology. Formic acid causes cutaneous injury by inducing a coagulative necrosis.

Clinical Features

Systemic toxicity occurs after absorption and is manifested by metabolic acidosis, gastrointestinal bleeding, bowel perforation, and aspiration. Because of its ability to induce oxidant stress, hemolysis may occur.

Differential Diagnoses

Similar to hydrofluoric acid, the differential diagnosis includes various other chemical burns, infectious etiologies, toxic epidermal necrolysis, and blistering disorders.

Diagnostic Testing

No specific diagnostic testing is indicated. If the patient shows any signs of systemic toxicity, obtain a complete blood count, serum electrolytes, and either an arterial or venous blood gas.

Management

Begin copious irrigation immediately. Acidosis (pH < 7.30) should be treated with sodium bicarbonate. Mannitol may be used to expand plasma volume and promote osmotic diuresis in patients with hemolysis. Folinic acid, which enhances the conversion of formic acid to carbon dioxide and water can be administered for severe toxicity. Hemodialysis may be required for patients with systemic toxicity, renal failure, and metabolic acidosis. Exchange transfusion may be indicated for those patients that are refractory to standard medical management, including hemodialysis.

Disposition

Treat patients according to local burn center referral guidelines and refer those who meet criteria for evaluation in a burn center. Other patients, including those without systemic manifestations and those not requiring significant doses of parenteral analgesics, can be discharged home with close outpatient follow-up. Specific treatment recommendations and disposition decisions can be discussed with a regional poison control center (see Box 55.1).

Anhydrous Ammonia

Foundation

Background and importance. Anhydrous ammonia is a colorless, pungent gas used extensively as a fertilizer in agriculture. It can also be used to manufacture explosives, petroleum, plastics, and synthetic fibers. In addition, the "dry cook" method of methamphetamine production uses anhydrous ammonia as an amphetamine precursor. This method was associated with numerous burns due to anhydrate ammonia. In recent years, due to changes in legislation, anhydrous ammonia has often been substituted with ammonium nitrate or ammonium sulfate-based products in a so-called "one pot" method. Nonetheless, it is used to produce methamphetamine. Anhydrous ammonia can be transported as a pressurized liquid. The sudden release of liquid ammonia can cause injury primarily through cutaneous (burn) and pulmonary injuries.

Anatomy, physiology, and pathophysiology. Anhydrous ammonia is generally stored at an extremely low temperature (−33°C). Consequently, exposure to liquid at this temperature can result in tissue necrosis and frost bite. The ammonia vapors readily dissolve in the moisture in skin, eyes, oropharynx, and lungs to form hydroxyl ions that cause chemical burns by liquefaction necrosis, which can result in full-tissue skin loss.

Clinical Features

Exposure to anhydrous ammonia results in dermal injury and chemical burns similar to other caustic agents. The severity of injury is directly related to the concentration and duration of ammonia exposure. In general, acute exposure to anhydrous ammonia produces the greatest injury to the proximal airway rather than the distal airway. However, following a recent large-scale release of anhydrous ammonia following an automotive accident, nearly 10% of the patients evaluated required intensive care unit admission. The majority of these patients required mechanical ventilation.[11]

Differential Diagnoses

The differential diagnosis includes chemical burns or frostbite injury from any other chemical (e.g., Freon), blistering disorder, infectious etiologies, and environmental exposures, such as frostbite and cold-related injuries.

Diagnostic Testing

Do a chest radiograph in patients with pulmonary complaints. Serum electrolytes and an arterial or venous blood gas are measured in symptomatic patients.

Management

Treatment consists of prompt irrigation of the eyes and skin with water and management of inhalation injury. If necessary, the airway should be secured through standard intubation methods with a large-diameter tube to prevent distal airway obstruction from sloughing of mucosa. After intubation, lower airway injury is managed with positive end-expiratory pressure ventilation.

Disposition

Patients with minor burns requiring admission or referral to a burn center, as per local guidelines can be discharged home, as long as there is no evidence of systemic toxicity or significant analgesic requirements. Patients with pulmonary complications should be admitted for further airway monitoring.

Cement

Cement is primarily composed of calcium oxide that combines with water to form calcium hydroxide. This compound is alkaline and can cause cutaneous injury following prolonged exposure.

There are three types of cement burns. The most common burn is a chemically abrasive form, and heat-related or blast-induced burns can also occur. Heat-related and blast-induced burns are more common in the industrial setting and are associated with severe burns, often involving the respiratory tract.

The treatment of cement burns attempts to eliminate the toxic component via copious irrigation, after all clothes have been removed. Early excision and grafting are often necessary, and referral to plastic surgery may be required for patients with extensive skin and degloving injuries.

Phenol and Derivatives

Foundations

Background and importance. Phenols are used industrially as starting materials for many organic polymers and plastics. They are widely used in the agricultural, cosmetic, and medical fields. Because of their antiseptic properties, they are also used in many commercial germicidal solutions. Dilute solutions of phenol have been used historically by plastic surgeons for chemical face peels. Phenols are usually mixed with water, soap, and croton oil. This solution can produce a partial thickness burn of a predictable depth in a controlled manner. The concentration is kept sufficiently low to reduce the occurrence of systemic complications. The physician performing phenol chemical peels should be concerned about the possibility of rapid phenol absorption. Even in a controlled setting, ventricular dysrhythmias occur as a result of the phenol application. A number of phenol derivatives (e.g., hexylresorcinol and resorcinol) are more bactericidal than phenol.

Anatomy, physiology, and pathophysiology. Phenol (carbolic acid) is an aromatic acidic alcohol with a characteristic odor. The concentration of phenol is inversely related to its depth of burn. Highly concentrated solutions result in coagulation of the keratin, thereby preventing deeper penetration. Histologic studies have demonstrated that 100% concentrations of phenol produce 35% to 50% less penetration than a 50% solution.

Both phenol and its derivatives are highly reactive, corrosive poisons that damage cells by inducing cell wall disruption, protein denaturation, and coagulative necrosis. After penetrating the dermis, phenols produce necrosis of the papillary dermis. This necrotic tissue may temporarily delay its absorption.

Clinical features. When the skin comes in contact with a phenol, treatment should be instituted immediately. The exposed area should be irrigated with large volumes of water delivered under low pressure. Because dilute phenol solutions are more rapidly absorbed through the skin than concentrated solutions, gentle swabbing of the skin surface with sponges soaked in water should be avoided. Any hair, including a beard or mustache, that has come in contact with a phenol should be removed as soon as possible, because the phenol can become trapped in the hair. Because of its lipophilic nature, it can easily penetrate the dermis, producing not only local findings, but systemic manifestations.

In animal studies, exposure to as little as 0.6 mg of phenol per kilogram can be lethal. Systemic toxicity of phenol primarily affects the central nervous system (CNS) and cardiovascular system. In the CNS, toxicity can manifest as stimulation, lethargy, seizures, or coma. Conduction disturbances can be either tachycardic or bradycardic in nature. Marked hypotension may occur as a result of central vasomotor depression, in addition to a direct toxic effect on the myocardial cells and small blood vessels. Hypothermia and metabolic acidosis can also occur.

Differential Diagnoses

The differential diagnosis includes burns from any other chemical or heat, blistering disorders, dermal infections, hydrofluoric acid exposure, methyl salicylate toxicity, and toxic epidermal necrolysis.

Diagnostic Testing

Perform an ECG, electrolytes and either an arterial or venous blood gas in patients with a phenol exposure.

Management

Experimental studies indicate that water alone is effective in reducing the severity of burns and preventing death in animals with skin exposed to phenol and its derivatives. The most effective treatment is undiluted PEG (molecular weight 200 to 400 Da) or isopropanol (isopropyl alcohol). Adequate supplies of either PEG or isopropanol should be stocked in hospitals located near areas where phenol is used and can often be found in the chemical section of hospital pharmacies. A quick wipe of the skin with PEG solutions reduces mortality and burn severity in experimental animals. These solutions can be used for facial phenol burns, because they are not irritating to the eyes. Decontamination with water should be performed until a PEG solution is obtained. Large amounts of water must be used, however, because small amounts enhance dermal absorption of phenols. Removal of phenol should be undertaken in a well-ventilated room so that the hospital personnel is not exposed to high concentrations of phenol fumes.

Treatment of Systemic Toxicity

The treatment of systemic symptoms is primarily supportive. Respiratory depression may require ventilatory support. Hypotension is best treated with an initial fluid bolus of 20 cc/kg of 0.9% normal saline or lactated Ringers solution. Vasopressors are recommended if shock and hypotension persist despite an adequate fluid challenge. Metabolic acidosis can be treated with sodium bicarbonate until the pH is near 7.40. The alkalization can also help prevent hemoglobin precipitation in the nephron as a result of hemolysis. Benzodiazepines, such as 2 mg intravenous lorazepam or 10 mg intravenous diazepam may be required to treat seizures caused by CNS stimulation. Intravenous lidocaine may be effective in treating ventricular dysrhythmia.

Disposition

Patients without systemic manifestations and not meeting local criteria for a burn center can be discharged after a period of 6 to 8 hours of cardiac monitoring, provided there are no arrhythmias or other manifestations of systemic toxicity. Admit patients with significant pain control requirements or vital sign abnormalities.

Phosphorus

Foundations

Background and importance. Phosphorus is a nonmetallic element that exists in three forms: elemental, white (yellow), and red. White phosphorus (also known as yellow phosphorus) is widely utilized for its explosive properties. It can be found in fireworks and munitions, but also in fertilizers and methamphetamine production. Historically, it has also been used as a rodenticide. The side of match boxes typically contains red phosphorus, a binder, and powdered glass. The heat generated by friction when the match is struck causes the red phosphorus to be converted to white phosphorus, which ignites spontaneously.

Anatomy, physiology, and pathophysiology. The autoignition temperature (the temperature at which spontaneous combustion can occur) is 30°C (86°F). When white phosphorus comes in contact with air at temperatures above the autoignition point, the phosphorus spontaneously oxidizes, forming phosphorus pentoxide. Phosphorus pentoxide can combine with small amounts of moisture in the air, forming phosphoric acid. In wounds, oxidation of phosphorus pentoxide will continue oxidizing until it is removed through debridement, neutralized, or consumed.

Clinical Features

Tissue injury from white phosphorus appears to have both thermal and chemical causes. The corrosive action of the phosphoric acid results in an exothermic reaction, thereby liberating heat and causing a thermal burn. The hygroscopic action of the phosphorus pentoxide is also responsible for causing a chemical burn, which may be partial or full thickness.

In cases of oral ingestion, white phosphorus toxicity classically occurs in three stages. The first stage can last 8 to 24 hours and is characterized by gastrointestinal tract irritation manifested as vomiting, diarrhea, abdominal pain, and gastrointestinal hemorrhage. The stool has a garlic-like odor and occasionally a luminescent or "smoking" appearance. Hypovolemic shock can result. Up to one third of patients who ingest significant quantities of white phosphorus will die during this stage. Following the first stage, a second, or latent phase ensues. During this period, which can last 1 to 3 days, symptoms appear to improve. However, the third stage is characterized by multisystem organ failure, including hepatic failure, renal failure, and CNS depression. Renal failure is usually present at days 1 to 4, whereas jaundice typically manifests at days 3 to 5. Red phosphorus can cause some gastrointestinal illness if consumed orally but is generally less toxic than white phosphorus.

Differential Diagnoses

The differential diagnosis depends on the type of phosphorous. For isolated burns, the differential diagnosis includes thermal or chemical burns (acids or alkali), infectious etiologies, and blistering disorders. For those with significant gastrointestinal illness, consider heavy metal toxicity (e.g., lead, mercury, thallium, arsenic, and iron), as well as ischemic bowel and common causes of gastrointestinal bleeding.

Diagnostic Testing

Regardless of the route of exposure, metabolic derangements including hypocalcemia and hyperphosphatemia can occur. Conduction system

disturbances, including bradycardia, QT prolongation, and ST and T wave abnormalities can occur and are partially explained by electrolyte derangements.[12] These ECG changes may explain the sudden early death that can occur in patients with relatively minor white phosphorus burns.

Management

The out-of-hospital management involves immediate removal of contaminated clothing, followed by submersion of the injured skin in cool water. Since white phosphorus becomes liquid at 44°C (111°F), avoid using warm or hot water. Remove visible phosphorus particles from the victim's skin and submerge in water. Cover burned skin with towels soaked in cool water during transport to the ED.

After the patient arrives the ED, the burned skin should be washed copiously with normal saline. In the past, some advocated for a suspension of 5% sodium bicarbonate, 3% copper sulfate, and 1% hydroxyethyl cellulose. Other similar solutions containing copper sulfate have also been described. The use of 0.9% normal saline solution, however, has demonstrated better effects than copper-containing solutions. Although there are some conflicting recommendations in the literature, given that saline is readily available and as efficacious as copper sulfate solutions with less associated toxicity, we recommend saline irrigation as the preferred irrigating solution.

Phosphorus particles can be identified with either ultraviolet light or copper-containing solutions. While the copper-containing solutions can convert phosphorus particles into cupric phosphide, which is black and thereby help facilitate removal, the use of copper solutions is associated with potential iatrogenic harm. Thus, we recommend a simple Wood's lamp be safely utilized, rather than copper solutions. Following copious irrigation with saline solution decontamination, and treatment of associated electrolyte disturbances, definitive management of the skin burns is accomplished as with any other burn wound. Monitor serum calcium and phosphate levels for 24 to 48 hours.

Disposition

Admit patients with significant phosphorus exposures to a monitored setting. As with all other caustic dermal burns, refer patients to a burn center as per local or regional guidelines.

Nitrates and Nitrites

Foundations

Background and importance. Both nitrates (NO_3^-) and nitrites (NO_2^-) are abundant in rural and industrial settings. Both sodium nitrate and sodium nitrite are used in food preservatives. Nitrites also have many medicinal uses secondary to their vasodilatory properties. Nitrates are commonly used in electroplating, engraving, and metal casting and as fertilizing agents. Exposure to either nitrates or nitrites has been associated with methemoglobinemia.

Anatomy, physiology, and pathophysiology. Reduced hemoglobin contains four heme groups, each with a ferrous (Fe^{2+}) ion. Methemoglobinemia results when the ferrous ion becomes oxidized to the ferric (Fe^{3+}) state. Under routine physiologic conditions, the body reduces the ferric valence back to the ferrous valence via cytochrome b5 reductase. At any given time, methemoglobin accounts for 1% to 2% of circulating hemoglobin. Cyanosis from methemoglobin occurs at concentrations above 1.5 g/dL.

Clinical Features

Methemoglobin toxicity exists along a spectrum. Many patients with low levels are asymptomatic. When methemoglobin concentrations in nonanemic individuals exceed 20%, headache, anxiety, dyspnea, and tachycardia can occur, although some individuals may be asymptomatic with levels exceeding 30%. Confusion, lethargy, and acidosis typically occur at methemoglobin levels approaching 40% to 50%. Coma, seizures, hypotension, dysrhythmias, and death occur when levels exceed 70%. Anemic patients may develop symptoms at lower levels. For example, a methemoglobin concentration of 1.5 g/dL in a patient with a baseline hemoglobin of 15 mg/dL will represent a methemoglobin level of 10%, whereas the presence of the same concentration of 1.5 g/dL of methemoglobin in an anemic patient with a baseline hemoglobin of 8 g/dL would represent a more concerning percentage of 18%. In addition, patients with profound methemoglobinemia and anemia (e.g., in the case of a drug-induced oxidant stress) may not develop cyanosis despite having a life-threatening methemoglobinemia.

Differential Diagnoses

The differential diagnosis includes exposure to any agent that can cause oxidant stress, including local anesthetics, phenazopyridine, dapsone, and arsine gas. In addition, hemolysis from non-oxidant stress should be included in the differential diagnosis. Consider other acquired hemoglobinopathies such as carboxyhemoglobinemia or sulfhemoglobinemia.

Diagnostic Testing

Consider the diagnosis of methemoglobinemia in any cyanotic patient whose pulse oximetry displays a saturation of 85% to 88% that is unresponsive to oxygen therapy and whose arterial blood appears "chocolate brown" in color. The methemoglobin level can be readily measured on a venous or arterial blood gas analyzed with standard co-oximetry.

Management

Asymptomatic patients are treated by rapidly removing the offending agent. For symptomatic patients without glucose-6-phosphate dehydrogenase (G6PD) deficiency, 1 to 2 mg/kg of a 1% methylene blue solution can be administered over 3 to 5 minutes. A repeat dose may be needed in cases of severe toxicity. Methylene blue acts via the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase, with which NADPH converts methylene blue to leukomethylene blue, which in turn donates an electron to reduce methemoglobin. For patients who fail to respond to methylene blue, or those with severe G6PD deficiency with concurrent severe toxicity from methemoglobinemia, exchange transfusion may be required.

Disposition

Patients without systemic toxicity and no evidence of methemoglobinemia can be discharged home after 6 hours, as long as the cutaneous burn is not too severe to warrant referral to a burn center as per local guidelines. Observe patients with methemoglobinemia in a monitored setting for 24 hours, even if the methemoglobinemia resolves after treatment with methylene blue.

Hydrocarbons

Foundations

Background and importance. Hydrocarbons are a heterogeneous group of organic compounds that are derived from carbon and hydrogen molecules. They are found in fuels, solvents, paints, paint and spot removers, dry cleaning solutions, lamp oil, rubber cement, and lubricants.

Hydrocarbons are primarily classified as aromatic or aliphatic, based on their shape. Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons in which one of the hydrogen molecules is substituted with a halogen (e.g., fluoride, chloride).

Anatomy, physiology, and pathophysiology. The toxicity from hydrocarbons can affect many different organs, but the lungs are the most commonly affected. The toxicity of hydrocarbons is directly related to their volatility and inversely related to the viscosity and surface tension. The primary cause of hydrocarbon toxicity is aspiration, especially agents with high volatility, low viscosity, and low surface tension are most likely to be aspirated.

Clinical Features

The principal manifestation of hydrocarbon exposure is a pulmonary injury secondary to risk of accidental aspiration following ingestion. A chemical pneumonitis ensues with tachypnea, wheezing, hypoxia and respiratory failure. Systemic toxicity from dermal exposure to a hydrocarbon is relatively rare. Significant dermal exposures can occasionally cause local tissue irritation. Chronic dermal exposure can result in a dermatitis with pyoderma around the nose or mouth. This so-called "huffer's rash" is primarily seen with recreational abuse. The hydrocarbon inhalant can dry the skin, thereby causing microscopic cracks and allowing bacteria to enter, causing a bacterial superinfection.

Differential Diagnoses

The differential diagnosis includes exposure to any agent that can cause a chemical pneumonitis, as well as infectious pneumonia, acute exacerbation of a reactive airway disease, or pulmonary edema.

Diagnostic Testing

We recommend obtaining a chest radiograph 6 hours after ingestion, although no randomized study has demonstrated this approach to be superior to observing the patient for clinical manifestations of aspiration (e.g., coughing, gagging, vomiting, wheezing, tachypnea, or hypoxia).

Management

Treatment involves removal of the patient from the source of exposure and removal of any contaminated clothing. Copious irrigation with warm water should be performed and burns managed as are other thermal injuries.

Significant toxicity from inhaled (non-aspiration) exposure to hydrocarbons is also unlikely to produce serious effects. Some patients may develop mild headache, dizziness, nausea, or wheezing. These symptoms resolve after removal of the patient from the source of exposure.

Ingestion of hydrocarbons can result in aspiration and systemic toxicity. After ingestion of hydrocarbons, it is recommended that patients be monitored for 6 hours. There is no need for gastric decontamination. Beta-agonists can be administered for bronchospasm, and supplemental oxygen administered for hypoxia as needed. Endotracheal intubation is occasionally required for severe hypoxia and aspiration pneumonitis. Neither corticosteroids nor empirical antibiotic administration are indicated. Corticosteroids may be beneficial in the select group of individuals with underlying reactive airway disease, if it is felt that the hydrocarbon aspiration triggered an asthma exacerbation. Antibiotics may be warranted later in the clinical course if a superimposed bacterial infection develops. Such superinfections would typically manifest at least 24 hours post exposure.

Disposition

A patient can be discharged home after a 6-hour observation period, assuming no symptoms develop during the observation period and a chest radiograph (if obtained) is negative. All other patients warrant admission to observe for progression of symptoms and treatment of hydrocarbon-induced pneumonitis.

Tar

Foundations

Background and importance. There are two types of hot tar: coal tar pitches and petroleum-derived asphalts. Both products are heated to maintain a liquid form. Roofing tar needs to be heated to temperatures of at least 232°C to achieve desirable viscosities. Deeper burn injuries are associated with burns from roofing asphalt.

Clinical Features

When hot, liquefied tar comes in contact with skin, heat is transferred, and thermal injury results. The tar cools and solidifies on the skin, making removal difficult.

Management

Burns from hot tar present a treatment challenge. When hot tar touches skin, it rapidly cools, solidifies, and becomes enmeshed in the hair. It is important to facilitate this cooling process by adding cold water to the tar at the scene of the accident. Cooling tar with cold water limits the amount of tissue damage and prevents the spread. The tar is continually washed with water until it has cooled and hardened. After cooling, the skin is dried with towels to prevent systemic hypothermia. Adherent tar should not be removed at the scene of the accident. In the ED, definitive care of the burn injury involves early removal of tar, because it occludes injured skin and encourages bacterial growth. Tar adheres to skin because it is enmeshed in the hair, not because of a direct bond between epidermis and tar.

Solvents used to remove tar ideally should have a close structural affinity to tar. Both petroleum-based aromatic hydrocarbon solvents and surface-active agents, such as polyoxyethylene sorbitan (Tween 80) and petroleum-based (De-Solv-it), have been used to facilitate tar removal. In addition, the use of topical neomycin can enhance removal. Use of these surface-active agents is an effective, safe, and inexpensive means of removing tar from skin. Sunflower oil, NISA baby oil, mayonnaise, and butter have also been used to remove adherent tar from the skin, requiring 30 to 90 minutes for complete removal. Sunflower oil has proved effective and safe in removing tar without causing further skin damage.

Asphalts are susceptible to both aromatic (e.g., naphthalene) and aliphatic (e.g., hexane) hydrocarbon solvents, whereas coal tars are susceptible only to aromatic hydrocarbons. Broad-spectrum antibiotic ointments (e.g., neomycin, polymyxin B, or bacitracin) can be used both to help with removal and to help prevent infection. The ointment should be removed and a new coating applied every hour until all the tar has been removed. This process typically takes 12 to 48 hours. Antibiotic ointment can also be used to remove tar layered over the cornea and conjunctiva.

Disposition

Admit patients with significant burns or refractory pain requiring multiple doses of parenteral analgesics. Those who meet criteria for referral to a burn center should be transferred as per local guidelines. Other individuals can be discharged home with close, expedited out-patient follow-up and detailed wound care instructions.

Elemental Metals

The elemental metals, such as lithium, sodium, and potassium, are harmless unless they come in contact with water. When this happens, a violent exothermic reaction occurs that produces heat, hydrogen gas, and hydroxide. Explosions are possible. The evolved heat is sufficient to ignite the hydrogen gas, which results in further heat production and thermal burns. The formation of the hydroxide compound may also result in significant chemical injury to tissue.

The reaction occurs more rapidly with elemental potassium than with sodium. These deleterious effects of potassium have been attributed to trace amounts of potassium superoxide released on exposure to room air. Water lavage is therefore contraindicated in these circumstances.

Chromium

Chromium burns can produce systemic toxicity. Death may occur with burn surface areas exceeding 10%. In addition to local wound effects, systemic toxicity can result including hemolysis and renal failure. It has been suggested that early excision may reduce systemic complications, although there is no experimental evidence to support such a practice. Medical management of chromium toxicity remains the mainstay of therapy. Chelation therapy has not proven to be of clinical benefit.

Miscellaneous

Chlorine, Chloramine, Phosgene, Nitrogen Oxide and Phosphide

Foundations

Background and importance. Chlorine and phosgene gases were used in World War I as part of chemical warfare. Today, exposure to chlorine exposures can result from industrial sites, railroad accidents in which trains are transporting large amounts of chlorine or following exposure to pool chemicals. Cases involving release of large amounts of chlorine gas may result in injuries remote from the exposure, depending on wind conditions.

Zinc or aluminum phosphide pellets are often used as rodenticides. When the phosphide pellets come in contact with water, phosphine (PH_3) gas is formed. In addition, PH_3 gas can also be formed during the production of methamphetamine from red phosphorus.

Nitrogen oxides include nitrogen dioxide (NO_2), nitric oxide (NO), and nitrous oxide (N_2O). NO_2 toxicity can occur from the burning of nitrocellulose, from use of hockey and ice-skating arena Zamboni machines in poorly ventilated areas, and from silo filler's disease, in which the gas accumulates within a silo of decomposing grain.

Anatomy, physiology, and pathophysiology. Chlorine is a heavy greenish-yellow gas or liquid with a characteristic odor. The combination of bleach (sodium hypochlorite) with an acid produces chlorine gas, and the combination of bleach and ammonia produces chloramine gas. Both chlorine and chloramine gas produce similar toxicities. The clinical effects observed after chlorine or chloramine exposure are directly related to the time and concentration of the gas.

Phosgene reacts with water to form carbon dioxide and hydrochloric acid. Given that phosgene is relatively water insoluble, high concentrations are needed before enough hydrochloric acid can be produced to cause mucosal membrane irritation. Phosphide toxicity occurs via several mechanisms, including free radical formation, inhibition of cytochrome oxidase, and increased lipid peroxidation.[13]

NO_2 fumes can often be easily recognized because of their reddish-brown color. The nitrogen oxides can cause respiratory tract irritation. Toxicity varies somewhat depending on the oxide, but severe toxicity can result in delayed pulmonary edema, hypotension, hemoptysis, and methemoglobinemia.

Clinical Features. Mild exposure to chlorine or chloramine may simply cause mucosal membrane irritation, whereas more severe exposure will induce edema of both the upper airway and the lung parenchyma. Large acute exposure can induce wheezing, cough, and dyspnea. Acute lung injury or adult respiratory distress syndrome can result in severe cases. Because these gases are primarily reactive only at a local level, absorbed systemic effects are not commonly observed. Following large exposure, fatalities can occur.

Phosgene undergoes acetylation to produce lung injury, which can manifest as delayed pulmonary edema. The timing of the pulmonary edema is inversely related to the degree of exposure. Inhalation of PH_3 gas produces near instantaneous symptoms. Both pulmonary toxicity and gastrointestinal toxicity can result after exposure to PH_3 gas. Common pulmonary symptoms include cough, chest tightness, and dyspnea, followed later by pulmonary edema and acute lung injury. Vomiting, diarrhea, and abdominal pain are also commonly encountered. Coma, hypotension, renal failure, and various dysrhythmias have been described.

Management. The first step in treating an exposure to chlorine, chloramine, or phosgene gas is removal of the individual from the environment. Rapidly assess the patient's cardiopulmonary status after significant exposure. Endotracheal intubation may be required. Bronchospasm is treated with beta-agonists, such as albuterol. Irritation of the eyes is managed with copious irrigation with water or saline, followed by an assessment for corneal abrasions if persistent eye irritation is noted. Nebulized sodium bicarbonate (2 cc of 8.4% sodium bicarbonate mixed with 2 cc of sterile water) can be used for treatment of chlorine or chloramine gas exposure. There is limited evidence of the use of nebulized acetylcysteine (1 to 2 g; 5 to 10 mL of a 20% solution) following phosgene exposure. The use of corticosteroids has not been proven to be beneficial in the treatment of chlorine, chloramine, or phosgene toxicity. With phosphine gas toxicity, treatment is largely supportive. However, there is limited evidence suggesting beneficial effects of intravenous *N*-acetylcysteine, melatonin, vitamin E, and magnesium.[13] Given the potential toxicity of aluminum or zinc phosphide and the relatively minimal harm and cost associated with these therapies, the risk/benefit ratio probably favors treatment with these agents.

Disposition. Phosgene, phosphene, NO_2, nickel carbonyl, diborane, as well as zinc-based smoke bombs can cause delayed-onset pulmonary edema even when patients are initially asymptomatic. Therefore, patients exposed to these chemicals are best admitted for 24 hours of observation to the hospital of observation unit, even if asymptomatic early on in the clinical course. Chlorine and chloramine gases can also cause delayed pulmonary edema, however, unlike the former group of gases, with which patients can be asymptomatic for hours and then develop pulmonary edema, delayed pulmonary edema is unlikely with chlorine or chloramine. Therefore, asymptomatic individuals who have been exposed to these chemicals do not require prolonged observation.

Chemical Terrorism

In recent years, the public has become increasingly aware of chemical terrorism. Despite being banned by the 1925 Geneva Convention, chemical weapons have been used in both the military and the civilian arenas for many years. In the 1980s, chemical weapons were employed against Iraqi civilians. In 1995, Aum Shinrikyo, a Japanese cult, released sarin nerve gas in the Tokyo subway, causing 12 deaths and more than 5000 casualties. In 2013, sarin nerve gas was used by military forces in the Syrian civil war. A more complete discussion of chemical and biological weapons is found in Chapter e15. As terrorist organizations continue to use unconventional weapons such as chemical and biologic agents, the civilian medical community needs to better understand their characteristics and pathophysiology.

Response During a Chemical Attack

Triage of patients with exposure to nonconventional weapons remains a critical component of appropriate care. Triage should be performed by specially trained emergency medical personnel who are familiar

TABLE 55.2 Common Gases That Can Be Encountered as Weapons of Mass Destruction

Class	Example[a]	Treatment
Nerve agents	Tabun (GA) Sarin (GB) Soman (GD) Cyclosarin (GF) VX	Atropine and pralidoxime
Vesicants	Mustard agents Mustard, sulfur mustard (H) Distilled mustard, sulfur mustard (HD) Nitrogen mustard (HN1, HN2, HN3) Organic arsenical agents (e.g., lewisite; L) Halogenated oxime agents (e.g., phosgene oxime; CX)	Hydrotherapy Moist dressing on blisters Supportive care
Choking agents	Phosgene (CG) Chlorine (CL) Military smoke (HC) Chloropicrin (PS)	Supportive care
Cyanide agents	Hydrogen cyanide	Cyanide kit Amyl nitrite Sodium nitrite Sodium thiosulfate Hydroxocobalamin

[a]Chemical or common name (military chemical symbol).

with these agents and with the use of PPE. The ED could be quickly overwhelmed with masses of noncritically injured survivors. Ideally, triage would be conducted both at the scene of the attack and again at a second point before ED arrival. The greatest challenge for EDs in caring for these individuals is the sudden increase in patients requiring treatment in addition to the day-to-day surge capacity of the hospital.

Chemical Agents

Chemical agents are classified as (1) nerve agents, (2) vesicants, (3) choking agents, or (4) cyanide and related toxins (Table 55.2). Tabun (military symbol GA), the first nerve agent documented, was synthesized by the German chemist Gerhard Schrader in 1937, while researching new insecticides. The following year, sarin (GB) was created. Other important nerve agents include soman (GD) and VX.

Vesicants, also known as *blistering agents,* are a class of drugs that produce blisters at the site of contact. Despite their discovery in the 1800s, its introduction to warfare did not occur until the 20th century. Since World War I, however, sulfur mustard (also known as *mustard gas, mustard,* or *CAS No. 505-60-2*) has remained a constant threat in modern warfare. Other vesicants include lewisite (dichloro-2-chlorovinylarsine), which is an organic arsenical, and phosgene (dichloroformoxime), which is a halogenated oxime. Although phosgene is often considered a vesicant, it technically is not, as the urticarial lesions that develop following contact are not fluid-filled.

Choking agents have been used in both military and civilian settings. Although there are many different agents and uses, the collective term *choking agent* refers to a chemical that can potentially induce pulmonary edema. Phosgene and chlorine are two agents that were used extensively in World War I. The use of chlorine gas attacks has also been widely documented in the recent Syrian conflict. Zinc-containing smoke is another choking agent that is used in conventional warfare. Other agents are used for riot control. These agents were discussed previously in the Miscellaneous Gases section.

Cyanide agents, such as hydrogen cyanide or sodium azide, are cellular toxins. Cyanide was discovered in the 18th century by the Swedish chemist Carl Wilhelm Scheele. Today, hydrogen cyanide remains one of the most toxic chemicals known.

Nerve Agents

Foundations

Background and importance. The nerve agents are classified as either "G" agents or "V" agents and most recently include the Russian-based novice or "Novichok" binary agents. The nerve agents are all derived from phosphoric acid and are volatile liquids at room temperature. As such, they must be aerosolized or evaporated to be used as inhalational weapons. Because the vapors are heavier than air, they tend to remain close to the ground and will travel downwind and downhill.

Anatomy, physiology, and pathophysiology. The nerve agents function by affecting acetylcholine (ACh). Acetylcholine receptors are found on the postsynaptic membranes of cholinergic synapses. These receptors can be either nicotinic or muscarinic. Activation of the nicotinic receptors results in depolarization of the postsynaptic neuron or skeletal muscle cell, whereas activation of the muscarinic receptor affects exocrine glands and smooth muscle, primarily in the CNS. Under normal conditions, ACh is inactivated by the enzyme acetylcholinesterase. The primary mechanism of action of the nerve agents is to prevent acetylcholinesterase from hydrolyzing ACh. Consequently, because ACh is not degraded, an excess quantity of ACh accumulates in the synapse. The effects at the muscarinic receptors include excess secretions and smooth muscle contractions.

Clinical Features

The mnemonics *DUMBBELS* (diarrhea, urination, miosis, bronchoconstriction, bronchorrhea, emesis, lacrimation, and salivation) and *SLUDGE* (salivation, lacrimation, urination, defecation, and gastrointestinal emesis) are often used to describe these effects. The nicotinic manifestations include muscle fasciculations and weakness. The primary lethal clinical effects are respiratory related and treatment should be aimed at correcting these effects.

Differential Diagnoses

The differential diagnosis of a nerve gas exposure includes gastroenteritis, ischemic bowel, ketoacidosis, pulmonary edema, and reactive airway disease. Other cholinergic agents such as carbamate insecticides and herbicides (e.g., paraquat and diquat) as well as neostigmine, physostigmine are differential diagnosis considerations.

Diagnostic Testing

Patients should undergo a chest radiograph, ECG, arterial blood gas, and electrolytes performed. Plasma or RBC cholinesterase levels are not available in real time and, along with significant intra-individual and interindividual variation, make checking levels impractical for the emergency physician.

Management

Victims of dermal exposure should be undressed and thoroughly decontaminated with large-volume, low-pressure irrigation with water. After decontamination, the initial treatment is aimed at maintaining an airway and restoring adequate oxygenation and ventilation. If rapid

sequence intubation is desired for airway management, the paralytic succinylcholine should be used with caution because the duration of action will be significantly prolonged as normal degradation will be inhibited by the nerve agent. Atropine is a direct-acting antagonist of the muscarinic receptor. Because atropine does not bind to the nicotinic receptors, all nicotinic effects, including weakness or paralysis, will not be reversed. The initial recommended dose is 2 mg of atropine for adults, although much larger doses will likely be required (2 mg every 5 minutes until desired clinical effect). The endpoint for stopping atropine administration is not improvement in heart rate but, rather, drying of bronchial secretions. The oxime agent pralidoxime is also administered to patients with suspected or known ingestion with significant symptoms. The traditional dosage of pralidoxime is 30 mg/kg (2 g maximum) intravenously over 30 minutes, followed by a maintenance infusion of 8 to 10 mg/kg/h (650 mg maximum). Standard doses of benzodiazepines (diazepam 5 to 10 mg intravenous push [IVP] or lorazepam 1 to 2 mg IVP) are recommended to prevent and to treat seizure activity.

For pediatric patients, if accurate weight-based dosage cannot be achieved, children younger than 1 year old can receive 0.5 mg atropine, whereas children older than 1 year can receive the standard adult dose of 2 mg atropine as a starting dose. As with adults, the subsequent doses should double (e.g., 0.5 mg followed by 1 mg, followed by 2 mg) until respiratory secretions are dried.

Disposition

Patients who do not develop any sign of toxicity after a 6-hour observation period can be discharged home. Those with any signs of cholinergic toxicity, respiratory distress, or seizures should be admitted to an intensive care unit.

Vesicants

Foundations

Background and importance. At temperatures below 14°C, mustard exists in the solid form. Once in the liquid or gaseous form, mustard gas can be recognized by its unique garlic or fishlike odor. Mustard vapor is also much heavier than air and, as a result, tends to remain close to the ground. When stored as an oil-based liquid, it can be readily aerosolized and attached to a bomb device or shell. Because vaporization occurs slowly, the risk of injury is much greater in cool environments and closed spaces. Several minutes of exposure can result in skin and eye injury, and exposure for more than 30 minutes can lead to respiratory injury and death.

Anatomy, physiology, and pathophysiology. Mustard gas can enter the body after inhalational, dermal, or oral exposures. After entering the body, it functions as an alkylating agent. The altered molecules then interact with proteins and nucleic acids, forming covalent bonds. Mustard is the only vesicant that does not cause immediate pain.

Clinical Features

Manifestations of exposure occur several hours after exposure. After exposure to aerosolized mustard gas, cutaneous manifestations appear after a latent period of up to 24 hours. Initial dermal symptoms include burning, itching, and erythema, followed by hyperpigmentation, vesicle formation, and, later, bullae. Electrolyte depletion and secondary bacterial infection can occur if the affected body surface area is large. In addition, inhaled mustard gas can lead to vomiting and diarrhea. Myelosuppression can occur within 3 to 5 days of exposure, resulting in leukopenia and thrombocytopenia. Direct mucosal damage in the respiratory tract can occur, resulting in bronchiolar damage and hemorrhage. The systemic manifestations can occur with any route of exposure.

Differential Diagnoses

The primary differential diagnosis includes blistering diseases and cutaneous infections, such as toxic epidermal necrolysis. Burns from any chemical or thermal agent may present with similar dermatological findings.

Diagnostic Testing

Obtain a complete blood count and reassess daily for several days to assess for the development of myelosuppression. Those with pulmonary exposure should have a chest radiograph performed. Check electrolytes in individuals with gastrointestinal illness.

Management

Treatment consists first of removing the patient from the environment and decontaminating the vesicant. If available, water can be used for decontamination but may not be the preferred agent. Currently, the United States military recommends using an alkaline hypochlorite solution (pH 10 or 11) as the decontamination method of choice; a 0.5% hypochlorite solution (diluted household bleach [1:9]) is another alternative. However, these solutions should not be used on open abdominal or chest wounds. No specific antidote exists. British antilewisite (BAL; 2,3-dimercapto-1-propanol; dimercaprol) was originally developed as an antidote for lewisite. Although BAL is currently available as a chelator for other heavy-metal poisonings (e.g., mercury, arsenic), we do not recommend its use for mustard gas poisonings.

Disposition

Patients with extensive exposure to mustard gas should be admitted to the hospital for monitoring, dermal care, fluid resuscitation, and serial assessment for pancytopenia.

Cyanide

Foundations

Background and importance. Cyanide salts and hydrocyanic acid are commonly used for metal cleaning, precious metal extraction, photographic processes, electroplating, laboratory assays, and jewelry cleaning. In addition, cyanide gas is often liberated from the combustion of plastic-containing compounds. Iatrogenic cyanide toxicity can result from exposure to cyanogens, including plant or herbal cyanogenic glycosides (e.g., peach and cherry pits), nitriles, and nitroprusside. There is growing concern that cyanide may be used as terrorist weapon of mass destruction.

Anatomy, physiology, and pathophysiology. Cyanide is a cellular toxin. It binds to both Fe^{3+} and cobalt. By binding and inactivating the enzyme cytochrome oxidase, which is part of cytochrome a3 on the electron transport chain, cyanide inhibits oxidative phosphorylation. This inhibition results in profound cellular hypoxia and death.

Clinical Features

After ingestion of cyanide, patients experience sudden cardiovascular collapse, coma, and profound metabolic acidosis. A characteristic odor of "bitter almonds" is frequently discussed but only rarely clinically noted.

Differential Diagnoses

The primary differential diagnosis is hydrogen sulfide and azide gas exposure. Carbon monoxide should be included on the differential diagnosis, and these two conditions may occur simultaneously particularly in house or industrial fires.

Diagnostic Testing

Although cyanide levels are confirmatory, they are rarely immediately available. However, most patients with significant cyanide exposure

will have a profound lactic acidosis, typically exceeding 10 mmol/L. In addition, because the cellular utilization of oxygen is blocked, venous blood is highly oxygenated. Therefore, an elevated mixed venous oxygen saturation, or an elevated peripheral venous partial pressure of oxygen (PO_2) may be observed. Typically, with cyanide toxicity, the difference between the PO_2 from an arterial blood gas and that from a venous blood gas, obtained simultaneously, will be under 10 mmHg. Cyanide toxicity commonly results in shortening of the QT interval, with subsequent "T-on-R" phenomena. The pulse oximeter reading may be near normal in cyanide toxicity, despite significant cellular hypoxia.

Management

The initial treatment focuses on maintaining adequate oxygenation and vascular perfusion. Standard antiarrhythmic medications are appropriate for the treatment of cyanide-induced cardiac arrhythmias. Vasopressors such as norepinephrine may be required.

First responders must wear PPE when rescuing a patient unresponsive after cyanide gas exposure. Patients with cyanide salts on their skin must have the particulate matter brushed off, followed by topical irrigation; decontamination from other routes of exposure is rarely indicated. Currently, two specific types of antidotes can be used to treat known or suspected cyanide intoxication. One historic method of treatment involves the administration of amyl nitrite, sodium nitrite, and sodium thiosulfate. With this combination of medications, amyl nitrite pearls are broken open, and the patient is allowed to breathe a pearl for 30 seconds of each minute. A new pearl is needed every 3 or 4 minutes. Once intravenous access has been established, 300 mg of sodium nitrite (one 10-mL ampule of 3% solution for adults and 0.12 to 0.33 mL/kg for children) can be administered. Because sodium nitrite is a potent vasodilator, hypotension can ensue. Therefore, the sodium nitrite is administered over a minimum of 5 minutes. After sodium nitrite administration, sodium thiosulfate is administered at a dose of 12.5 g (one 50-mL ampule of a 25% solution for adults and 1.65 mL/kg for children). The function of the nitrites is to induce methemoglobinemia. Thiosulfate enhances transulfuration of hydrogen cyanide to thiocyanate via rhodanese, which is renally excreted. We recommend avoiding nitrites if coexisting carbon monoxide toxicity is suspected, as can occur with smoke inhalation.

Hydroxocobalamin (Cyanokit) is the most recently introduced and preferred antidote for cyanide intoxication, given at 5 g initial, additional 5 g if needed, up to maximum cumulative dose of 10 g. Hydroxocobalamin binds to cyanide to form cyanocobalamin, which subsequently undergoes renal excretion. Hydroxocobalamin appears to be safe for use in both the hospital and the out-of-hospital settings. The administration may result in a red discoloration of the skin and a deep purple discoloration of the urine, which is not a true allergic reaction. Its use is also associated with alteration in laboratory measurements of magnesium, iron, aspartate aminotransferase, total bilirubin, and creatinine. In treating a patient for known or suspected cyanide toxicity (even if in combination with carbon monoxide poisoning), both sodium thiosulfate and hydroxocobalamin can be safely administered.

Disposition

Patients with a brief exposure without any manifestations of toxicity can be discharged home after an observation period of 6 hours. One notable exception includes those with exposure to agents that get metabolized to cyanide (e.g., acetonitrile); individuals with exposure to these agents should be admitted to an intensive care unit for 24 hours. Additionally, admit any patient with metabolic acidosis, coma, or seizures to an intensive care unit.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 55: QUESTIONS AND ANSWERS

1. A 34-year-old man presents with burning, erythema, and blurred vision after cleaning liquid is splashed in his eye. Which of the following should you do?

a. Be concerned about acidic burn.
b. Be concerned about alkali burn.
c. Postpone irrigation until confirmation of the type of cleaning liquid.
d. Use a miotic agent.
e. Use copious irrigation until a pH of 7.4.

Answer: e. When a chemical injury to the eye is suspected, regardless of the offending agent, copious irrigation should be started immediately. Irrigation with water or normal saline should continue until the pH is at a physiologic level (approximate pH of 7.4). All but the mildest burns should be treated with a long-acting cycloplegic and mydriatic.

2. A patient presents to the emergency department (ED) complaining of severe burning of both hands since leaving her building this morning. In her history, you find out that the metal doors of her housing complex had just been cleaned of all rust. She has small blisters on her palms and a white appearance to the skin. What is the next step?

a. Consult plastics for an alkali burn.
b. Leave blisters, cover with bacitracin and gauze.
c. Mix calcium gluconate with KY jelly, apply to hands, and cover with gloves.
d. Obtain pain control and prescribe oral clindamycin.
e. Administer intravenous magnesium.

Answer: C. The rust cleaning and physical findings are descriptive of a hydrofluoric acid burn. It is also commonly used in the production of microelectronics, etching glass, for removing rust, and for cleaning cement and bricks. Calcium gluconate (2.5%) gel is the preferred topical agent. However, this gel is often not available in hospital pharmacies, but it can be made by mixing 3.5 g calcium gluconate powder in 150 mL of a water-soluble lubricant. The gel should be secured by an occlusive cover, such as a latex glove.

3. In a hydrofluoric burn, what electrolyte abnormality causes systemic manifestations contributing to this chemical's significant morbidity and mortality?

a. Hypercalcemia
b. Hypermagnesemia
c. Hypocalcemia
d. Hypokalemia
e. Hyponatremia

Answer: C. Hydrofluoric acid binds calcium and magnesium ions with strong affinity. Systemic manifestations of fluoride toxicity are at least partly related to hypocalcemia and include abdominal pain, muscle fasciculations, nausea, seizures, ventricular dysrhythmias, and cardiovascular collapse. Of note, hyperkalemia is often a terminal finding in fatal cases.

4. A 30-year-old female presents by emergency medical services confused and hypoxic. She has a history of depression, and was found with an empty bottle of fluoxetine, which she takes for her depression, and cefalexin and phenazopyridine, which she is currently taking for a urinary tract infection. She is noted to be hypoxic with a saturation of 83%, which does not improve with oxygen administration. She is speaking full sentences but is confused. The nurse informs you the arterial blood sample blood has a "chocolate brown" appearance. Which of the following represents the best management strategy?

a. Obtain a carboxyhemoglobin level and consider hyperbaric oxygen
b. Obtain a methemoglobin level, and consider administration of methylene blue
c. Determine if acidosis is present, and if present, administer sodium thiosulfate
d. Determine if the urine fluoresces with a Wood's lamp
e. Examine the urine for presence of crystals.

Answer: B. The patient is suffering from methemoglobinemia. For those symptomatic patients without glucose-6-phosphate dehydrogenase (G6PD) deficiency, 2 mL/kg of 1% methylene blue can be administered over 3 to 5 minutes. Symptoms typically improve within 20 minutes, although repeat doses may be needed. Severe cases can be treated with exchange transfusion. Candidates for exchange transfusion include those with G6PD with significant toxicity from methemoglobinemia or those patients who fail to respond to methylene blue.

5. A 21-year-old man presents to the emergency department (ED) with chronic shortness of breath and a "huffer's rash." The patient has dry, cracked skin with perioral pyoderma. The cause of these symptoms is most likely which of the following?

a. Anhydrous ammonia
b. Cyanide

c. Hydrocarbons
d. Nitrites
e. White phosphorous

Answer: C. The toxicity from hydrocarbons can affect many different organs, but the lungs are the most commonly affected organ. The toxicity is directly related to the volatility and inversely related to the viscosity and surface tension. Chronic dermal exposure to hydrocarbons can result in perioral or perinasal dermatitis with pyoderma. This so-called "huffer's rash" is primarily seen with recreational abuse.

6. Nerve agent poisoning may be rapidly fatal. Besides appropriate decontamination and atropinization, which of the following should be administered?
a. British anti-Lewisite 2 mg/kg intramuscularly
b. Methylene blue 2 mg/kg intravenously
c. *N*-acetylcysteine 140 mg/kg orally
d. Pralidoxime 600 mg intramuscularly
e. Pyridostigmine 1 mg intravenously

Answer: D. Nerve agents work by affecting acetylcholine (ACh) levels via inhibition of acetylcholinesterase. ACh receptors are found on the postsynaptic receptor of cholinergic synapses. These receptors can be either nicotinic or muscarinic. The effects at the muscarinic receptors include excess secretions and smooth muscle contractions. The initial recommended treatment is 2 mg of atropine for adults, although much larger doses will likely be required. Pralidoxime should also be administered to patients with suspected or known ingestion with significant symptoms. This agent potentially helps prevent irreversible inhibition of the acetylcholinesterase enzyme.

7. A 31-year-old man was found in his apartment after an apparent suicide attempt. He smells of bitter almonds. He is obtunded with hypotension, tachypnea, and normal oxygen saturation. After decontamination and resuscitation, what is the next step?
a. Atropine
b. Hydroxocobalamin
c. Methylene blue
d. Naloxone
e. Sodium thiosulfate

Answer: B. This patient likely has cyanide poisoning. One older method of treatment involves the administration of amyl nitrite, sodium nitrite, and sodium thiosulfate. The U.S. Food and Drug Administration (FDA) approved, and we recommend hydroxocobalamin (Cyanokit) to treat cyanide intoxication. Hydroxocobalamin binds to cyanide to form cyanocobalamin, which subsequently undergoes renal excretion.

56

Oral Medicine

Ryan Anthony Pedigo

KEY CONCEPTS

- Antibiotics do not have a role in the management of pulpitis, whether reversible or irreversible.
- Missing teeth must be accounted for. They may be hidden, left at the scene, aspirated, swallowed, or traumatically impacted.
- Avulsed permanent teeth should be stored in milk, saline, or a commercially available solution and reimplanted at the earliest possible opportunity. Primary teeth are not reimplanted.
- A localized periapical abscess that is successfully drained in an immunocompetent patient does not require antibiotics.
- Cover dental fractures that involve the dentin or pulp with a calcium hydroxide paste then promptly refer to a dentist.
- Periodontal splinting material can stabilize reimplanted teeth or luxated teeth once they have been put in the appropriate position.
- Advanced imaging for localized periapical abscess is unnecessary; however, contrast-enhanced CT of the face is necessary if signs or symptoms of a **deep neck infection** are present.
- Supraperiosteal nerve blocks can anesthetize individual teeth but are less effective for adult mandibular teeth since the surrounding bone is thicker.

INTRODUCTION

Dental concerns are common in the emergency department (ED). The spectrum of oral disease ranges from bothersome to emergently life-threatening.[1] This chapter covers disorders of the **tooth**, **gingiva**, and periodontium, dental procedure-related issues, odontogenic and deep infections of the head and neck, traumatic dental emergencies, as well as temporomandibular joint disorder (TMD) and dislocation.

DISORDERS OF THE TOOTH

Foundations

Anatomy, Physiology, and Pathophysiology

Humans have 20 deciduous (primary) teeth and 32 permanent (secondary) teeth, which are supported and maintained in the maxilla (upper teeth) and mandible (lower teeth) by the periodontium. The portion of the tooth that is normally visible in the mouth above the gingival margin is called the crown, whereas the lower portion is the root (Fig. 56.1).

The crown of the tooth has three layers; from outside to inside they are the enamel, dentin, and pulp. The enamel is the only part of the tooth that is visible in the absence of pathology (e.g., **fracture**s, caries) and is a hard coating that protects the tooth. The outermost layer of the root of the tooth is the cementum, which allows for attachment of the periodontal ligament to the adjacent alveolar bone. The next layer deep to the enamel (for the crown) or the cementum (for the root) is the dentin, which is an intermediate layer that is yellow in appearance. The dentin is comprised of porous microtubules that support the enamel and act as a cushion during mastication. If the dentin is exposed by caries or trauma, the patient will have sensitive teeth or pain. The deepest layer is the pulp cavity, which houses the tooth's neurovascular supply.

The deciduous dentition ("baby teeth") consists of 10 mandibular and 10 maxillary teeth (Fig. 56.2). The lower central incisor is the first tooth to erupt at approximately 6 months of age; all primary teeth should be present by age 3. The permanent dentition begins to erupt at approximately 6 years of age with the appearance of the first molar followed by the second molars by age 13 and ending with the third molars ("wisdom teeth") by age 17 to 21.

The permanent dentition consists of 32 teeth; there are 8 teeth per quadrant (e.g., right upper, right lower, left upper, left lower). From the midline outward, the names of the teeth in each quadrant are the central incisor, lateral incisor, canine, two premolars (also called *bicuspids*), and three molars (also called *tricuspids*). The permanent dentition is numbered from 1 to 32, starting with the upper right third molar (1) and moving to the upper left third molar (16), to the lower left third molar (17), and to the lower right third molar (32). The starting point for this numbering system can be recalled by the mnemonic "upright." It is often easier to name the tooth or teeth involved; for instance, if tooth 8 is injured, the clinician could describe the tooth as the "right maxillary central incisor" or the "right upper central incisor." If multiple teeth are involved, numbering is more concise.

Specific terminologies are also used to describe the various tooth surfaces in the mouth. The facial (also referred to as labial or buccal) surface faces outside the oral cavity; the oral (also referred to as palatal for upper teeth, or lingual for lower teeth) surface faces the tongue; the mesial surface is toward the midline; and the distal surface is toward the ramus of the mandible. The interproximal surface refers to the contacting area of adjacent teeth, and the occlusal surface refers to the biting area. Finally, *apical* is in the direction of the root, whereas *coronal* is toward the crown of the tooth.

Tooth decay, or dental caries or cavities, is caused by the breakdown of the teeth secondary to bacteria. Bacteria generate acid as a byproduct from cellular metabolism of food left on the tooth surface, subsequently demineralizing the enamel. Once the enamel is breached,

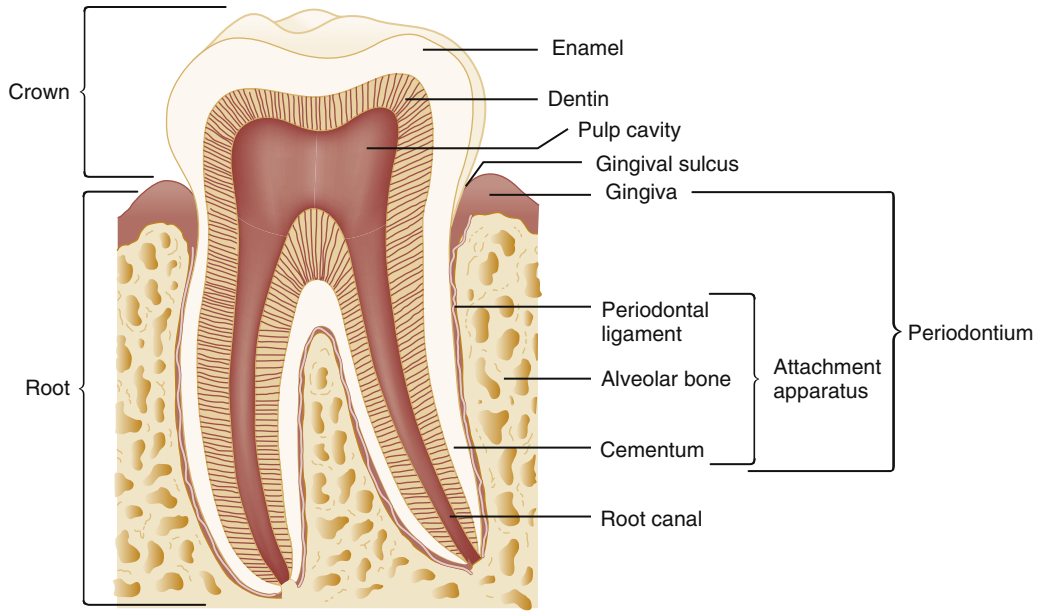


Fig. 56.1 The Anatomy of the Tooth and Associated Attachment Apparatus.

the microporous dentin can transmit saliva, byproducts of the bacteria, and the bacteria to the pulp. The pulp initially reacts with a hyperemic response, which proceeds to an inflammatory state termed pulpitis, which can be reversed. Untreated, pulpitis can further progress to total degeneration and necrosis (irreversible pulpitis).

Clinical Features

Dental caries are the most common cause of odontogenic pain. The patient may give a variable history of a sudden or gradual onset of a sharp to dull, throbbing pain. In most cases, the patient can indicate the specific tooth involved, but pain may be generalized. Early (reversible) pulpitis is sensitive to changes in temperature and pressure; irreversible pulpitis can show pain without any stimulus.

The physical examination described here is applicable to all sections of this chapter. Ideally the patient should be placed in a dental or ear, nose, and throat chair or on a bed at a 45-degree angle with adequate lighting. Pediatric patients often are examined while sitting on the parent's lap.

Pediatric patients may require distraction, familial assistance, anxiolysis, or sedation to permit adequate oral assessment and treatment of pain. Pediatric procedural sedation is described in Chapter 157.

A complete intraoral examination includes inspection of the oral cavity, gingiva, teeth, and surrounding structures (e.g., throat, neck, sinuses). Assess teeth for caries or fractures. Localization of the involved tooth may be accomplished by percussing the teeth or by having the patient bite on a tongue blade. Exquisite pain to percussion suggests an underlying periapical abscess (discussed in the section Odontogenic and Deep Neck Infections).

An extraoral examination includes evaluation of the nares and sinuses for discharge and pain, respectively, to evaluate for sinusitis. Facial asymmetry in the appropriate clinical context may indicate a deep neck infection. Palpate the temporomandibular joint (TMJ) with opening and closing of the jaw to assess for "clicks" or "pops," which may indicate the etiology of pain as TMJ disorder. In older individuals, palpate the temporal artery for tenderness and prominence.

Differential Diagnoses

Most dental pain is odontogenic, the most common cause being pulpitis due to caries. However, tooth pain is not always odontogenic. Unilateral upper tooth pain (usually the posterior teeth) can be related to maxillary sinusitis, dysbarism, or inflammation. Trigeminal neuralgia can present as tooth pain, but it is usually lancinating and may not be related to temperature changes or mastication. Atypical odontalgia is a centralized trigeminal neuropathy localized in a tooth or teeth. Frequently misdiagnosed, patients will often undergo multiple dental procedures with worsening of their pain. Atypical odontalgia causes persistent throbbing or burning pain that does not fulfill diagnostic criteria for another disorder and therefore is a diagnosis of exclusion. Elders with temporal (giant cell) arteritis may have pain with mastication because of jaw claudication.

Diagnostic Testing

Laboratory or radiographic testing are not routinely required. Panorex films, if available, can be obtained to assess for apical abscess if the diagnosis is not clinically apparent.

Management and Disposition

Management of dental caries with pulpitis consists in pain management and referral to a dentist for definitive care. Data are limited, but evidence suggests that antibiotics are not beneficial for the management of pulpitis, whether irreversible or not.[2]

Severe pain can be treated with supraperiosteal infiltration of local anesthetic to provide temporary relief (Fig. 56.3). To perform this, dry the area with gauze, apply a topical anesthetic to the gingiva (e.g., 20% benzocaine or 5% lidocaine) and allow it to sit for 5 minutes. Inject 1 to 2 mL of local anesthetic (e.g., 2% lidocaine) through the mucobuccal fold of the affected tooth with the bevel facing the tooth. Alternatively, an inferior alveolar nerve block may be used when multiple lower teeth are affected on one side. In adults, the supraperiosteal block is less effective for mandibular teeth due to the comparatively thicker bone surrounding the tooth compared to maxillary teeth.

The patient can be discharged with ibuprofen (400 to 600 mg every 6 to 8 hours). Nonsteroidal antiinflammatory drugs (NSAIDs) given at scheduled times (rather than as needed) are more effective than opioid analgesics.[3] However, for severe odontalgia, a short course of opioid analgesics in addition *to* scheduled NSAID administration is reasonable. Opioid analgesics should not be prescribed for long-standing dental problems, such as chronic caries. The patient with odontalgia from dental caries should follow-up with a dentist within one week.

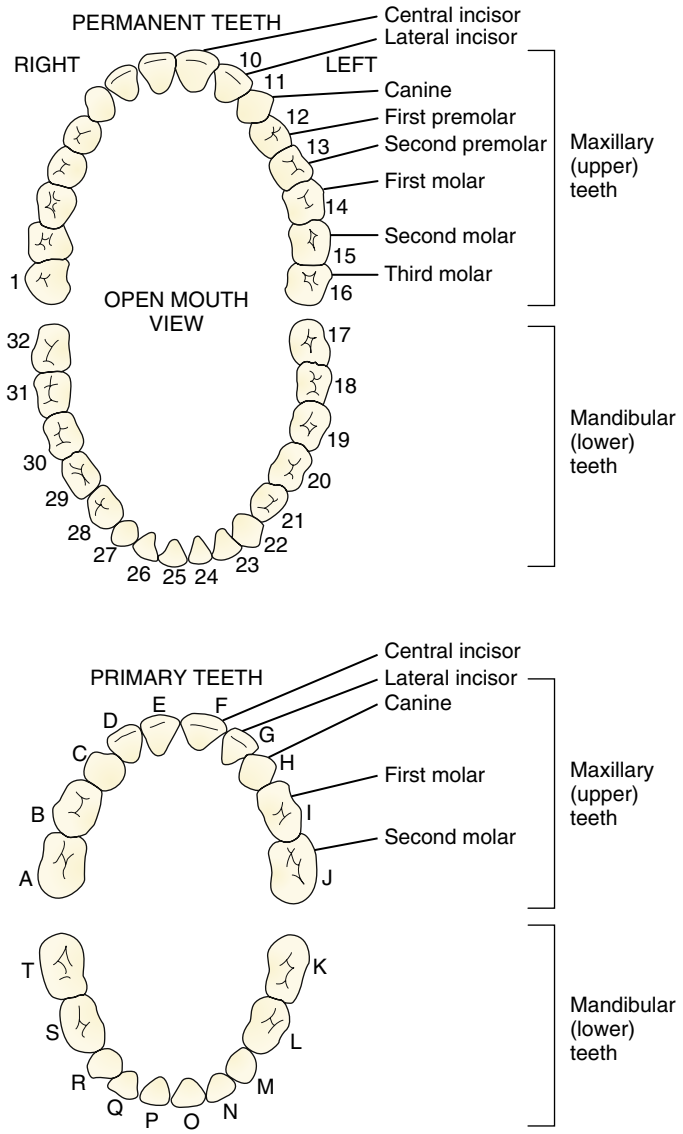


Fig. 56.2 **Identification of Teeth, Adult and Child.** Conventional numbering starts with the upper right third molar 1 to the upper left third molar 16; lower left third molar 17 to the lower right third molar 32. For the primary dentition, A to J and K to T. (Modified from Roberts J. *Roberts & Hedges' Clinical Procedures in Emergency Medicine*. 6th ed. Philadelphia, PA: Elsevier; 2014, Fig. 64.2, p. 1344.)

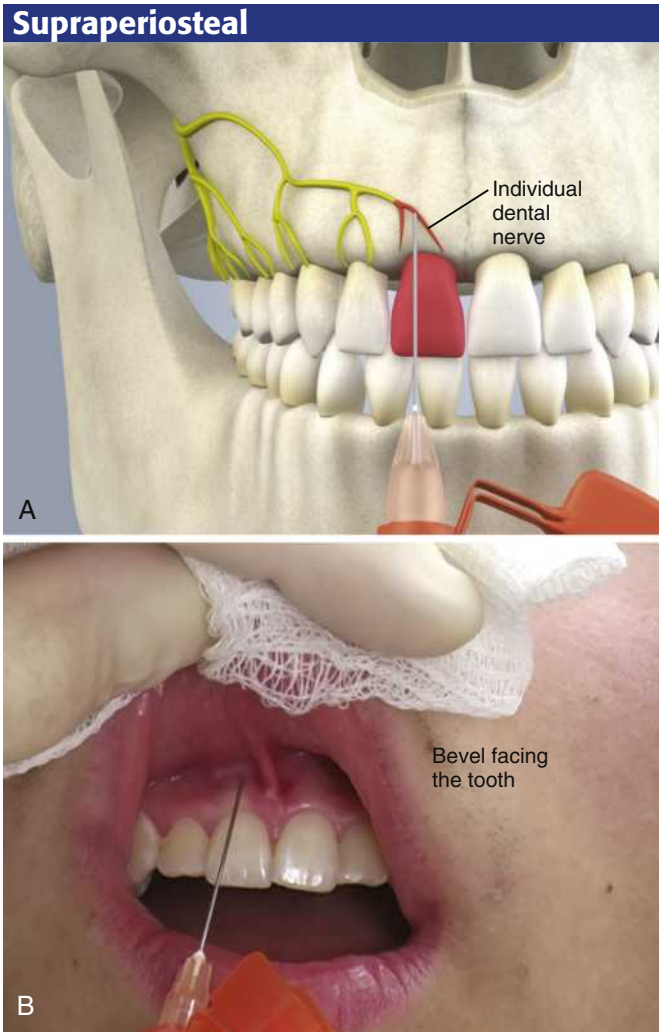


Fig. 56.3 (A and B) Supraperiosteal nerve block for anesthesia of individual teeth. (From Roberts J: Roberts J. *Roberts & Hedges' Clinical Procedures in Emergency Medicine*. 6th ed. Philadelphia, PA: Elsevier; 2014, Fig. 30.5.)

DISORDERS OF THE GINGIVA AND PERIODONTIUM

Foundations

Anatomy, Physiology, and Pathophysiology

The periodontium serves to hold the teeth in place and protect the root from bacteria. Collectively, the periodontal ligament, alveolar bone, and cementum comprise the attachment apparatus. The attachment apparatus plus the gingiva ("gums") is referred to as the *periodontium*. The gingiva consists of the mucosal tissue that overlies the mandible and maxilla inside the mouth and, in the normal state, acts as a barrier to infection and injury.

Gingivitis and Periodontitis. Periodontitis is inflammation of the supporting structures of the teeth (gingiva, alveolar bone, cementum, and periodontal ligament). Degradation of this support structure leads to loss of the alveolar bone and subsequent loosening or loss of teeth.

In necrotizing periodontal diseases, polymicrobial bacteria (with a predominance of *Fusobacterium* and spirochetes) invade the tissue and cause pain, bleeding, and destruction. These diseases include necrotizing gingivitis (acute necrotizing ulcerative gingivitis [ANUG], or "trench mouth") if the gingiva alone is involved, necrotizing periodontitis if the attachment apparatus in addition to the gingiva is involved, and necrotizing stomatitis if the disease extends to the surrounding oral mucosa (Fig. 56.4). Infection that further involves the tonsils and pharynx is termed *Vincent angina*. The most diffuse necrotizing disease is termed *noma* (cancrum oris, fusospirochetal gangrene) where the entire mouth is involved and is often fatal; this disease is most commonly encountered in young children in developing countries (Fig. 56.5).

Pericoronitis. The gingiva and surrounding tissue can also become inflamed leading to a condition known as *pericoronitis*. As teeth start to erupt, debris and bacteria can accumulate between the tooth and the surrounding soft tissue. The flap of gum overlying these teeth is called the operculum and is the source of pain and swelling during inflammation (Fig 56.6). This condition is exacerbated by trauma from mastication. The third molar ("wisdom tooth") is most commonly implicated, and symptoms typically occur in the second or third decade of life. This condition is more common with teeth that are malerupted or impacted.

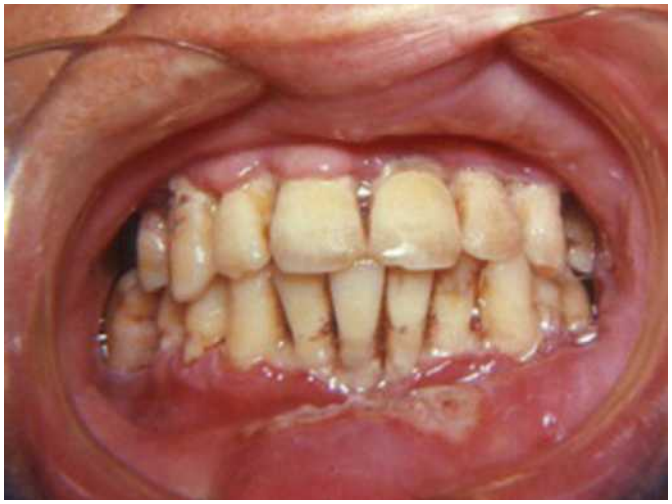


Fig. 56.4 Necrotizing Stomatitis. The gingiva has classic papilla necrosis but the oral mucosa is also involved, making this condition necrotizing stomatitis and not simply necrotizing gingivitis. (From Smith J. HIV and AIDS in the adolescent and adult: an updated for the oral and maxillofacial surgeon. *Oral Maxillofac Surg Clin North Am.* 2008;20[4]:535–565, Fig. 8.)

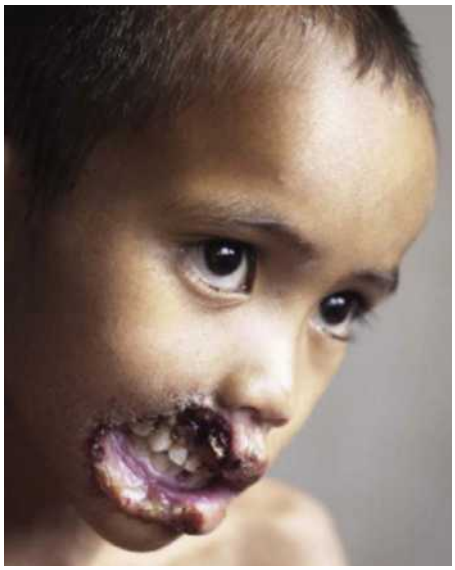


Fig. 56.5 Noma (cancrum oris, fusospirochetal gangrene) is usually found in children in developing countries and can be disfiguring or even fatal. Noma represents the most severe end of the necrotizing periodontal disease spectrum. (From Farrar J, Hotez PJ, Junghanss T, et al., eds. *Manson's tropical diseases*. 23rd ed. London: Saunders/Elsevier; 2014, Fig. 29.1.)

Gingival Hyperplasia. Gingival hyperplasia is an overgrowth of the gum tissue surrounding the teeth. It can occur secondary to poor oral hygiene, dental plaque build-up or as an adverse reaction to medications. The most commonly associated drug classes are anticonvulsants, calcium channel blockers, and immunosuppressants (Table 56.1).

Clinical Features

The presentation of periodontitis is variable, depending on the severity of the disease. Simple gingivitis presents with swollen or tender gingiva, gingival bleeding after manipulation (e.g., brushing teeth, flossing), and halitosis from bacterial overgrowth. Periodontitis involves

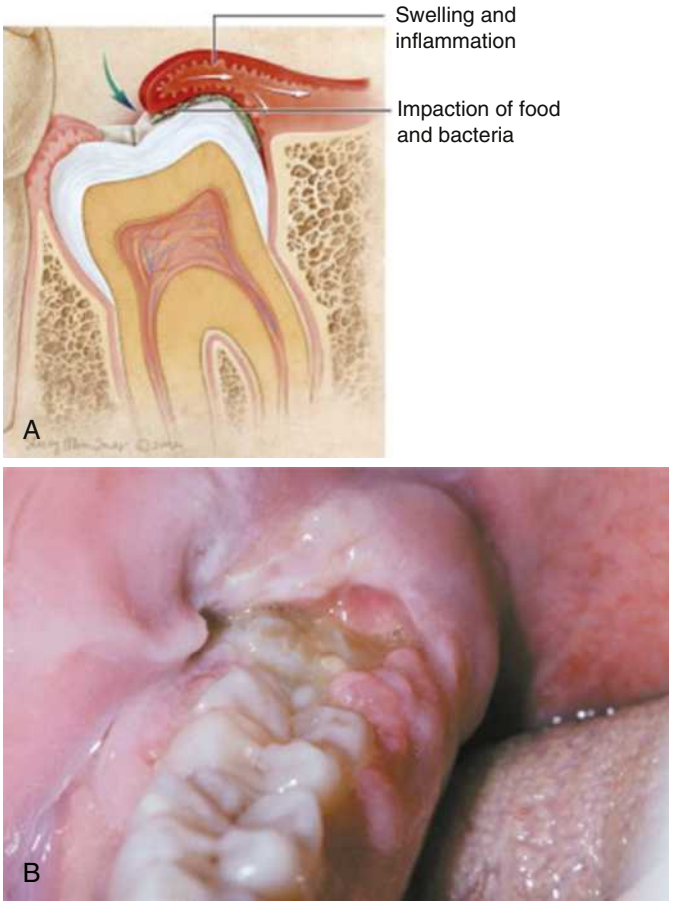


Fig. 56.6 Pericoronitis. (A) Illustration of pericoronitis with swollen and inflamed operculum. (B) Picture of pericoronitis of the third molar with erythema and inflammation of the surrounding tissue. (A, From Buttaravoli P, Leffler SM. *Minor Emergencies*. 3rd ed. St Louis: Elsevier; 2012, Fig. 46.1; B, From Neville BW, Damm DD, Allen CM, et al: *Oral and maxillofacial pathology*. 4th ed. St Louis, MO: Elsevier; 2016.)

the attachment apparatus as well and in more advanced cases, gingival recession from loss of alveolar bone and concomitant teeth loosening can be seen. Individuals with more severe periodontitis may also report fevers and malaise. Obtain a medication history to assess for drug-induced gingival overgrowth (see Table 56.1).

Inspect the gingiva for erythema, edema, and hyperplasia. The interdental papillae are normally pointed but, in necrotizing disease, the interdental papillae become blunted, "punched out," ulcerated, and covered with a whitish-yellow pseudomembrane of necrotic tissue and bacteria. The triad for necrotizing periodontal diseases includes papillary necrosis, gingival bleeding, and pain. More severe infection (e.g., necrotizing stomatitis) may also have an associated submandibular lymphadenopathy.

Mobile teeth suggest alveolar bone loss, where the disease has progressed deeper than the gingiva. Partially erupted teeth should be examined for evidence of pericoronitis. The overlying tissue (operculum) should be assessed for bleeding and inflammation.

Differential Diagnoses

Ulceration of the mucosa can be caused by necrotizing stomatitis and also by aphthous ulcers and other oral lesions. Aphthous ulcers are small (2 to 3 cm), superficial, and tender mucosal lesions that typically have a whitish center. They usually do not become infected. The neighboring gingiva should not be affected and appear healthy. Recurrent

TABLE 56.1 Medication Classes and Their Risk of Drug-Induced Gingival Overgrowth

Category	Pharmacologic Agent	Prevalence
Anticonvulsants	Phenytoin	50%
	Sodium valproate (valproic acid)	Rare
	Carbamazepine	None
Immunosuppressants	Cyclosporine	25%–30% (adults) 70% (children)
Calcium channel blockers	Nifedipine	6%–15%
	Felodipine	Rare
	Amlodipine	Rare
	Verapamil	<5%
	Diltiazem	5%–20%

From Song HJ. Periodontal considerations for children. *Dent Clin North Am.* 2013; 57(1):17–37, Table 1.

aphthous lesions can occur with Behçet disease and human immunodeficiency virus (HIV). Treatment is symptomatic with hydrogen peroxide rinses and topical anesthetics. Another consideration is acute herpetic gingivostomatitis, which is the most common manifestation of primary herpes simplex virus infection in children. In patients with gingival hyperplasia, an infiltrative process (such as leukemia) should be considered, especially if the patient has adequate oral hygiene or is not on medications associated with hyperplasia.

Diagnostic Testing

Gingivitis and Periodontitis

Necrotizing periodontal disease occurs most often in patients who are immunocompromised, such as patients with HIV, poorly controlled diabetes, or on long-term immunosuppressive therapy. Blood glucose and HIV testing may be initiated in the ED or as part of follow-up.

Pericoronitis

No laboratory or radiographic testing is routinely indicated for pericoronitis.

Management

Gingivitis and Periodontitis

Gingivitis responds to proper oral hygiene including twice daily flossing and brushing. Antibacterial mouth rinses, such as chlorhexidine rinses (preferred agent, 0.12% to 0.2%) or 3% hydrogen peroxide (diluted 1:1 with warm water) are recommended for more severe cases Necrotizing periodontal disease should be treated by a dentist, who will need to debride the necrotic tissue. Oral antimicrobials should be prescribed for patients with extensive disease, immunocompromise, or systemic symptoms; see Table 56.2 for more information.

All patients who smoke should be counseled on smoking cessation; this is the most common risk factor in HIV-negative patients. Analgesia using an NSAID such as ibuprofen (400 to 600 mg every 6 to 8 hours) or acetaminophen (650 mg every 6 hours) relieves pain and facilitates appropriate oral hygiene. Severe pain can be treated with opioid analgesic. Topical analgesics (e.g., viscous lidocaine) can also be effective but should be applied only to small areas to avoid ingestion or systemic toxicity.

Pericoronitis

Patients with pericoronitis should receive rinses as described previously; systemic antibiotics are not necessary unless the pericoronitis is severe. In such cases, penicillin 500 mg every 8 hours for 5 to 7 days is recommended. For patients with a penicillin allergy, clindamycin 150 to 300 mg every 6 hours is commonly used. Patients with pericoronitis should be referred to a dentist or an oral surgeon for local treatment of the operculum or, if impacted or malerupting, removal of the tooth. Adequate analgesia should be prescribed, as the pain in pericoronitis is often severe enough to affect the patients' quality of life.[4]

TABLE 56.2 Recommended Antibiotics for Severe Periodontal Disease, Severe Pericoronitis, and Simple Odontogenic Infections

Antibiotic	Dosage	Duration	Notes
Penicillin V	500 mg by mouth tid-qid	10 days	
Amoxicillin/clavulanate	500 mg/125 mg by mouth tid	10 days	875 mg/125 mg can be used
Metronidazole	500 mg by mouth bid	10 days	If allergic to penicillin
Clindamycin	300 mg by mouth qid	10 days	If allergic to penicillin
Nystatin	100,000 units/ml 5 ml swish/spit qid	10 days	If immunocompromised or suspect candidal infection

Disposition

Gingivitis and Periodontitis

Patients with gingivitis are discharged with dental follow-up in 1 to 2 weeks. Those with necrotizing gingivitis or mild necrotizing stomatitis should see a dentist within 24 to 72 hours, because they require frequent debridement until the infection is controlled. Patients with severe necrotizing gingivitis or stomatitis should have an emergency dental consultation (within 24 hours). Patients with significant systemic symptoms (especially fever or lymphadenopathy) or those who are immunocompromised with severe oral disease should receive antibiotic therapy and dental consultation.

Pericoronitis

Patients with pericoronitis should be referred for either extraction of the tooth or excision of the operculum.

DISORDERS INVOLING DENTAL PROCEDURES

Foundations

Anatomy, Physiology, and Pathophysiology

The most common dental procedures include fillings, crowns, root canals, and extractions. Fillings cover caries and protect the underlying tooth from further decay and infection. Crowns (or "caps") cover the portion of the tooth exposed above the gingiva and require an intact root for attachment. Root canals involve opening the pulp chamber, removing pulp tissue and root, sterilizing the canal, and sealing it to prevent ingress of saliva and contamination. Extractions are performed for non-salvageable teeth and involve removal of the entire tooth. All these procedures can have complications that may bring a patient to the ED.

Dislodgement of a filling or crown can expose the highly innervated pulp and lead to significant odontalgia. Similarly, the pulp can be irritated during procedures (e.g., root canal) because of residual gas bubbles that are inadvertently sealed into the cavity. In addition, any swelling that may elevate the tooth even minimally post-procedurally will cause premature and painful contact during mastication.

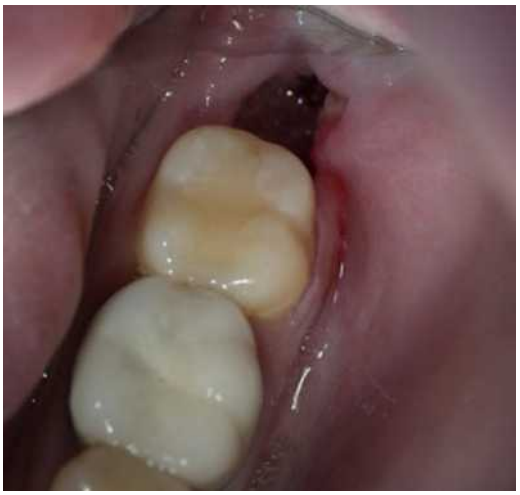


Fig. 56.7 Alveolar osteitis ("dry socket") with extraction site devoid of clot. (From Krakowiak PA. Alveolar osteitis and osteomyelitis of the jaws. *Oral Maxillofac Surg Clin North Am.* 2011;23[3]:401–413, Fig. 1.)

After an extraction, the patient will have an adherent clot in the fossa where the root of the tooth previously was. If this clot becomes dislodged (typically 3 to 4 days post-extraction) a condition called *alveolar osteitis* ("dry socket") can occur (Fig. 56.7). The incidence of alveolar osteitis is 2% after routine extraction but as high as 20% to 30% after removal of impacted mandibular third molars. The pain is secondary to localized inflammation of the exposed surrounding alveolar bone.

Clinical Features

Patients usually can provide the history of their dental procedures; dislodgement of a filling or crown can happen at any time but is more common early or after trauma. Post-root canal pain due to retained gas bubbles typically occurs immediately after the initial nerve block wears off.

Alveolar osteitis typically presents 3 to 4 days after an extraction with severe dull, aching pain at the site of extraction, often associated with halitosis and a foul taste in the mouth. Patients may have an antecedent of sucking through a straw or other activity that dislodged the clot.

Those with continued bleeding after an extraction should have their medical history and medications reviewed with specific attention to known or medication-associated coagulopathies and anti-platelet agents.

Patients with dislodged fillings or crowns will have an exposed dentin or pulp over the affected teeth. Post-extraction pain secondary to inflammation or retained gas bubbles may have a normal examination. Those with alveolar osteitis will have a tooth socket that has at least partial loss of the blood clot with exposed bone.

Differential Diagnoses

Differential diagnosis of alveolar osteitis after extraction includes a localized infection. In alveolar osteitis the extraction site is typically devoid of clot and should not have substantial surrounding edema, erythema or fluctuance, which is more typical of an infection.

Diagnostic Testing

An international normalized ratio (INR) is indicated for patients who are on warfarin and have post-extraction bleeding. A platelet count or hemoglobin may be helpful in selected cases where either thrombocytopenia or symptomatic anemia is considered.

Management

For teeth with exposed pulp, calcium hydroxide cement (Dycal) application to cover the exposed surface may provide symptomatic relief although analgesia with NSAIDs is generally enough. For those with severe pain, a short course (2 to 3 days) of an opioid (oxycodone 5 mg every 4 to 6 hours) is indicated. Patients with retained gas bubbles after a root canal have intense pressure-like pain, often refractory to analgesics and even nerve blocks, and they should be referred to an endodontist, preferably the clinician who performed the initial procedure.

Treat alveolar osteitis with NSAIDs and prompt (next working day) referral to their treating oral surgeon. If follow-up will be delayed, nerve block followed by gentle irrigation of the socket with sterile saline can be performed. The socket should not be curetted and the clot should not be removed if a residual clot exists, because this will expose more bone and lead to higher risk of continued pain and osteomyelitis. Medicated iodoform gauze with eugenol (an anesthetic) can be placed in the cavity and changed by the patient's surgeon within 24 to 48 hours with repeat irrigation. Chlorhexidine rinses have been shown to prevent alveolar osteitis yet its role in established alveolar osteitis is less clear.[5] No other treatment for alveolar osteitis has enough evidence to recommend use.

Extraction site bleeding should first be managed with direct pressure with the patient biting on dry gauze or gauze soaked with tranexamic acid.[6] If this fails, perform a supraperiosteal nerve block using lidocaine with epinephrine as this will decrease the blood supply and anesthetize the area so that more firm direct pressure can be applied. If bleeding continues after a second trial of pressure, the socket can be packed with absorbable gelatin sponge (Gelfoam) with or without topical thrombin. The gingiva can also be loosely closed with a 3-0 absorbable suture in a figure-of-eight fashion. With coagulopathy and significant ongoing hemorrhage, anticoagulation reversal may be required (see Chapter 111).

Disposition

In the absence of infection and with control of bleeding, patients with dental procedure-related complications can be discharged home with follow-up with the provider who performed the procedure.

ODONTOGENIC AND DEEP NECK INFECTIONS

Foundations

Anatomy, Physiology, and Pathophysiology

The anatomy of the neck is complex and comprises multiple true and potential spaces. There are fascial planes that normally act to contain infection. Aggressive organisms, an immunocompromised state, or surgical breech of these planes can result in deeper infections. For odontogenic infections, these spaces can be divided into those involved in maxillary infections and those involved in mandibular infections. More severe infections of the head and neck (such as those involving these spaces) are called deep neck infections (Fig. 56.8).

There are two primary spaces that can be involved in maxillary deep neck infections: the canine and buccal space. Infections of the root of the maxillary canine can lead to a canine space infection and often present with flattening of the ipsilateral nasolabial fold (Fig. 56.9). The major complication of this type of infection is cavernous sinus thrombosis. The buccal (buccinator) space can be involved with maxillary molars but also with mandibular molars (Fig. 56.10). Occasionally, the maxillary sinus itself can be involved.

The mandible has three associated primary spaces: submental, sublingual, and submandibular. The *submental* space is bound laterally by the digastric muscles and therefore causes a very discrete midline swelling when involved in a deep neck infection (Fig. 56.11); the mandibular incisors are the main culprits, because other teeth do not overly this space. The *sublingual* space is between the floor of the mouth and the mylohyoid muscle. It does not have a posterior border

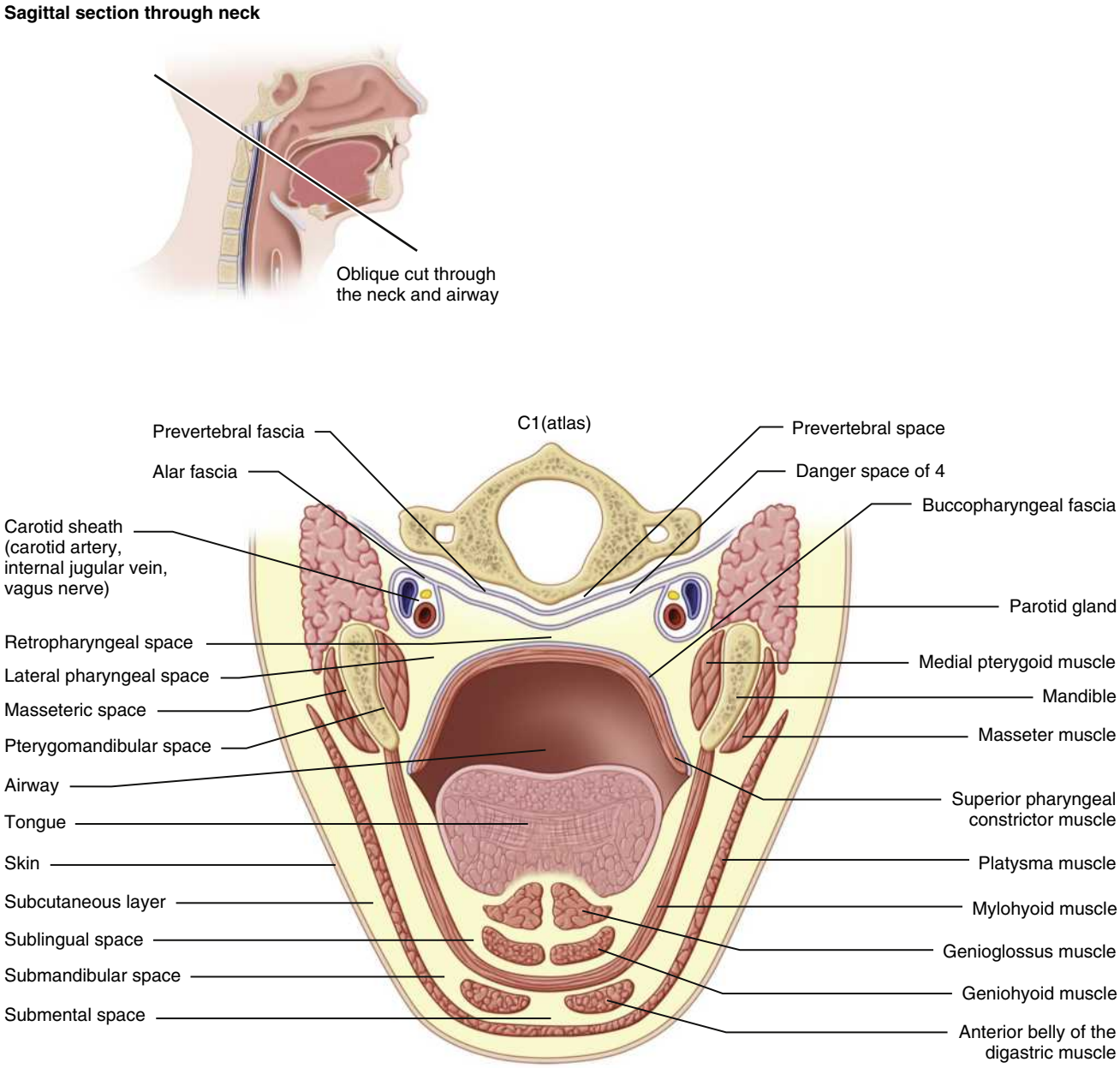


Fig. 56.8 Anatomy of Maxillofacial Space Infections. (From Bagheri SC. *Clinical Review of Oral and Maxillofacial Surgery*. 2nd ed. St Louis, MO: Elsevier/Mosby; 2013, Fig. 4.4.)

and therefore communicates with the submandibular space. Characteristically, infection of this space causes elevation of the tongue and firmness of the floor of the mouth (Fig. 56.12). Lastly, the *submandibular* space is usually involved as an extension of infection from a mandibular molar (Fig. 56.13). Although submandibular space infections have their medial border at the anterior belly of the digastric muscle, it can bypass this and enter the submental space and move to the contralateral submandibular space, and the sublingual space. This leads to infection of all three spaces termed *Ludwig angina.*

These primary space infections can progress to secondary spaces and lead to more wide-spread infection into the neck and mediastinum. A discussion of these spaces (e.g., retropharyngeal, parapharyngeal, prevertebral, and "danger" spaces) can be found in Chapter 58.

Oropharyngeal infections are the most common cause of deep neck infections in children (Fig. 56.14, Scenario 1 and 2). Acute tonsillitis can lead to peritonsillar abscesses and, if further invasion of the parapharyngeal space occurs, can spread into either the retropharyngeal (leading to a retropharyngeal abscess) or submandibular space (leading to Ludwig angina). Children can have retropharyngeal lymphadenopathy with pharyngeal and/or sinus infections, which may precipitate retropharyngeal cellulitis, lymphadenitis, or abscess. By age 4, there is spontaneous atrophy of these nodes; therefore, a retropharyngeal abscess in the absence of trauma (fish bone stuck in throat, etc.) in older children or adults is less common. Septic thrombophlebitis of the internal jugular vein, termed *Lemierre syndrome,* is caused by infection by *Fusobacterium necrophorum.*[7] Septic emboli dislodge from the internal jugular vein and lead to necrotic pleuropulmonary emboli, abscesses, and empyema. More distant embolic events can occur, leading to brain abscesses, meningitis, and septic joints.

Dental infections are the most common cause of deep neck infections in adults (see Fig. 56.14, Scenario 3). Pus leaks from the apex of an infected tooth root and forms a periapical abscess, confined within

the alveolar bone (Fig. 56.15). If the abscess erodes through the cortical plate of either the mandible or the maxilla, it can spread subperiosteally, extending into the previously described spaces. When the submental, submandibular, and sublingual spaces are involved in cellulitis with or without abscess, Ludwig angina occurs. Ludwig angina is a bilateral, board-like swelling involving the submandibular, submental, and sublingual spaces with elevation of the tongue (Fig. 56.16). The most serious sequela is airway obstruction. A characteristic brawny induration is present; there is often no fluctuance for incision and drainage. Hemolytic Streptococcus is usually responsible, although a mixed staphylococcal-streptococcal flora is common, and both may lead to an overgrowth of anaerobic gas-producing organisms, including *Bacteroides fragilis*.

Facial cellulitis is typically polymicrobial, which reflects the oropharyngeal flora. However, atypical organisms can also be present: *Actinomyces* can cause cervicofacial actinomycosis with draining sinus tracts, tuberculosis can cause cervical lymphadenopathy (scrofula) with secondary infection, and *Bartonella henselae* (the causative organism for cat scratch disease) can cause cervical lymphadenitis.

Clinical Features

Facial cellulitis and deep neck infections have many common historical features: in children, an antecedent of sinus or pharyngeal infection is common; in adults, a history of poor dentition is common. Frequently reported symptoms include pain at the affected site, fever, and malaise.

Recent dental work or trauma, recent upper airway manipulation or surgery, intravenous (IV) drug abuse, sinusitis, and otitis media are

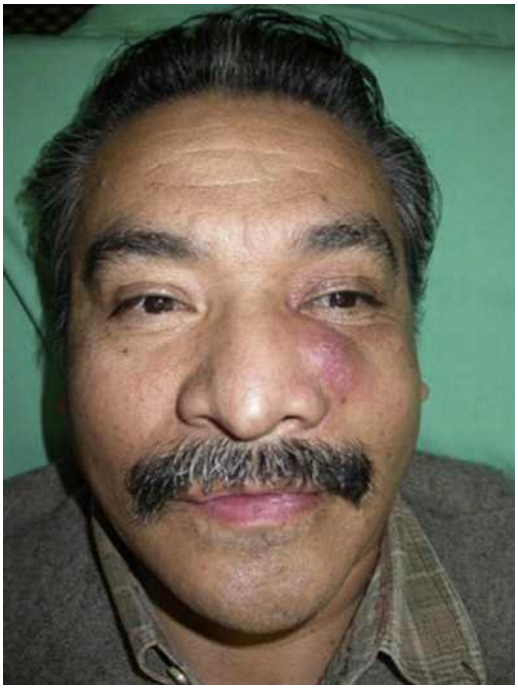


Fig. 56.9 Left Canine Space Infection. (From Lypka M, Hammoudeh J. Dentoalveolar infections. *Oral Maxillofac Surg Clin North Am.* 2011;23[3]:415–424.)

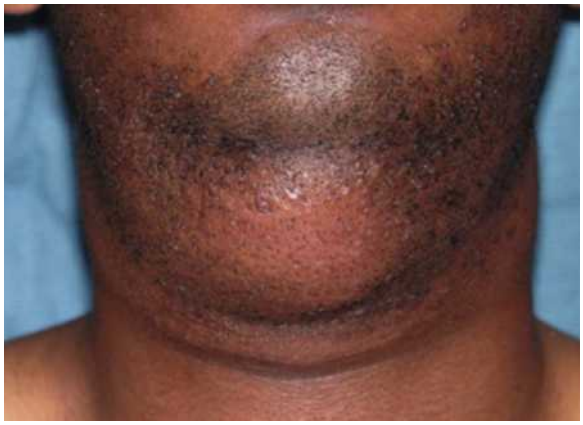


Fig. 56.11 Submental space infection with characteristic discrete midline swelling. (From Flynn TR. Complex odontogenic infections. In: Hupp JR, Ellis E, Tucker MR, ed. *Contemporary Oral and Maxillofacial Surgery*. 6th ed. St Louis, MO: Elsevier/Mosby; 2014, pp 319–338.)

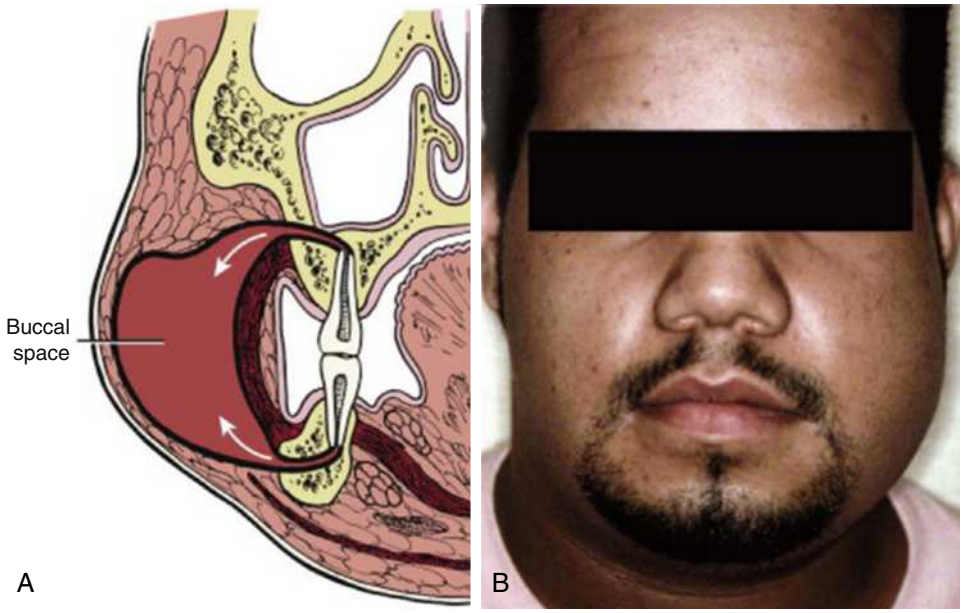


Fig. 56.10 Left Buccal Space Infection. (A) Schematic. (B) Photograph. (From Lypka M, Hammoudeh J. Dentoalveolar infections. *Oral Maxillofac Surg Clin North Am.* 2011;23[3]:415–424.)

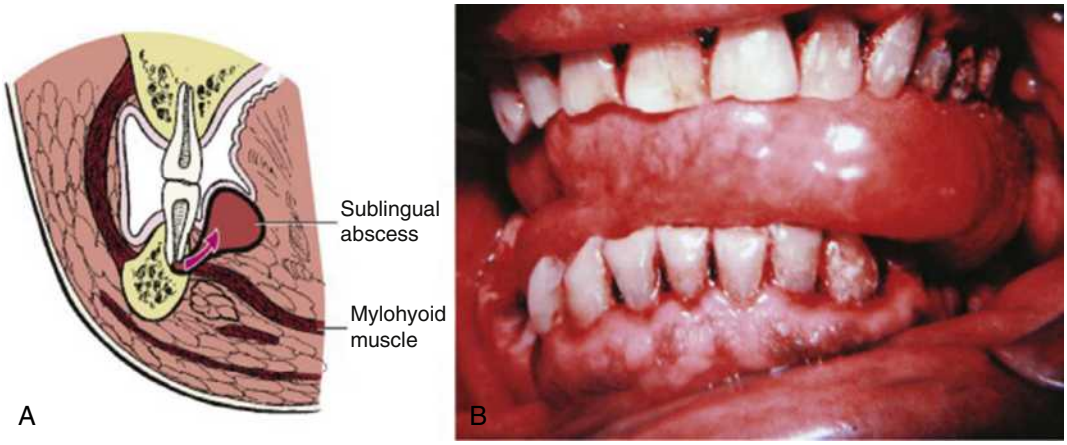


Fig. 56.12 (A) The sublingual space lies between the oral mucosa and the mylohyoid muscle. The space is primarily involved by infection from mandibular premolars and first molar. (B) Significant swelling causing elevation of the tongue. (From Flynn TR. Complex odontogenic infections. In: Hupp JR, Ellis E, Tucker MR, ed. *Contemporary Oral and Maxillofacial Surgery*. 6th ed. St Louis, MO: Elsevier/Mosby; 2014, pp 319–338.)

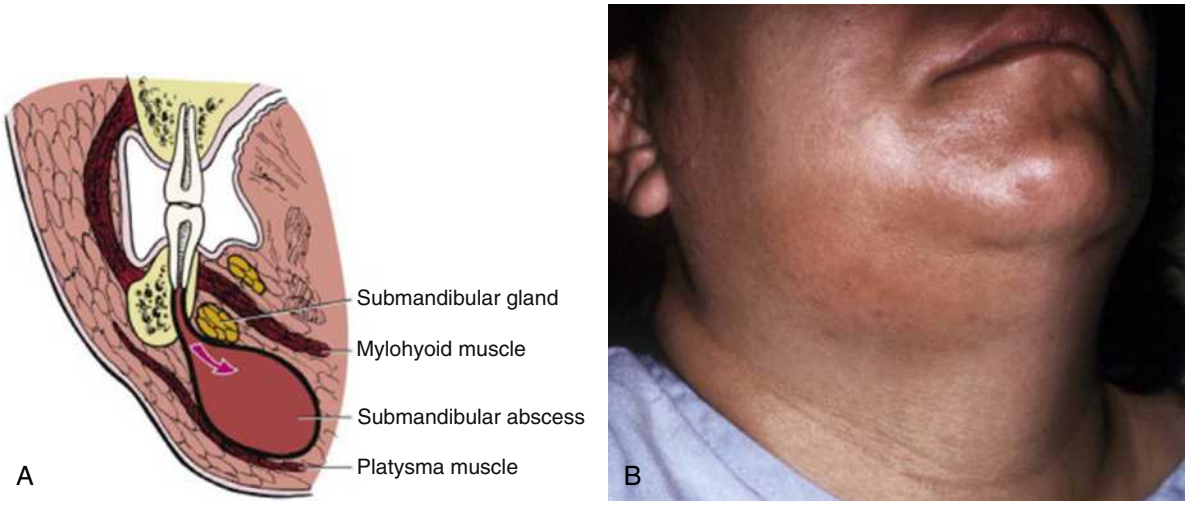


Fig. 56.13 (A) Schematic of the submandibular space. (B) Significant swelling that is bound medially by the digastric muscle. (From Flynn TR. Complex odontogenic infections. In: Hupp JR, Ellis E, Tucker MR, ed. *Contemporary Oral and Maxillofacial Surgery*. 6th ed. St Louis, MO: Elsevier/Mosby; 2014, Figs. 17.15 and 17.16.)

all risk factors for infection. Patients who are immunosuppressed from HIV/acquired immunodeficiency syndrome (AIDS), cirrhosis, diabetes, chemotherapy, and/or steroid use are all at higher risk and should raise suspicion.

A complete head and neck examination is required, keeping in mind the aforementioned anatomy. Extraoral palpation can help assess whether there is deep space involvement indicated by the presence of tenderness, warmth, fluctuance, or crepitus. Percuss teeth to assess for tenderness which may indicate a periapical abscess. Involvement of the sublingual space is assessed by palpating the floor of the mouth looking for edema and tongue elevation.

Irritation of the internal pterygoid or masseter muscles causes trismus, which is the inability to open the mouth because of involuntary muscle spasm. Incomplete mouth opening secondary to phlegmon or edema will make oral examination challenging and intubation difficult because it is not relieved by neuromuscular blockade. A "hot potato" voice or difficulty swallowing or handling secretions suggests partial airway obstruction due to retropharyngeal or parapharyngeal infection. Respiratory distress may be apparent when obstruction is near-complete and may proceed rapidly to complete occlusion.

Differential Diagnoses

The main differential consideration is whether the infection is limited to superficial head and neck spaces or whether a deep neck infection is present.

Diagnostic Testing

A complete blood count usually shows leukocytosis, but the absence of such does not rule out a deep neck infection or significant cellulitis. Patients with localized periapical abscesses and associated cellulitis do not require an advanced imaging.[8] However, when there is concern for a deep neck infection, the imaging modality of choice is a contrast-enhanced computed tomography (CT) of the face and soft-tissue neck. CT imaging is recommended when a deep space infection is suspected as indicated by facial swelling (resulting in blunting of the mandibular margin), restricted mouth opening, voice changes, floor of mouth elevation, dyspnea, or odynophagia.[9,10] Patients with HIV or diabetes have an increased risk of deep neck infections, and testing may be helpful.

Management

Well-appearing patients with simple odontogenic infections (localized infection, no recent antibiotics, and an immunocompetent patient)

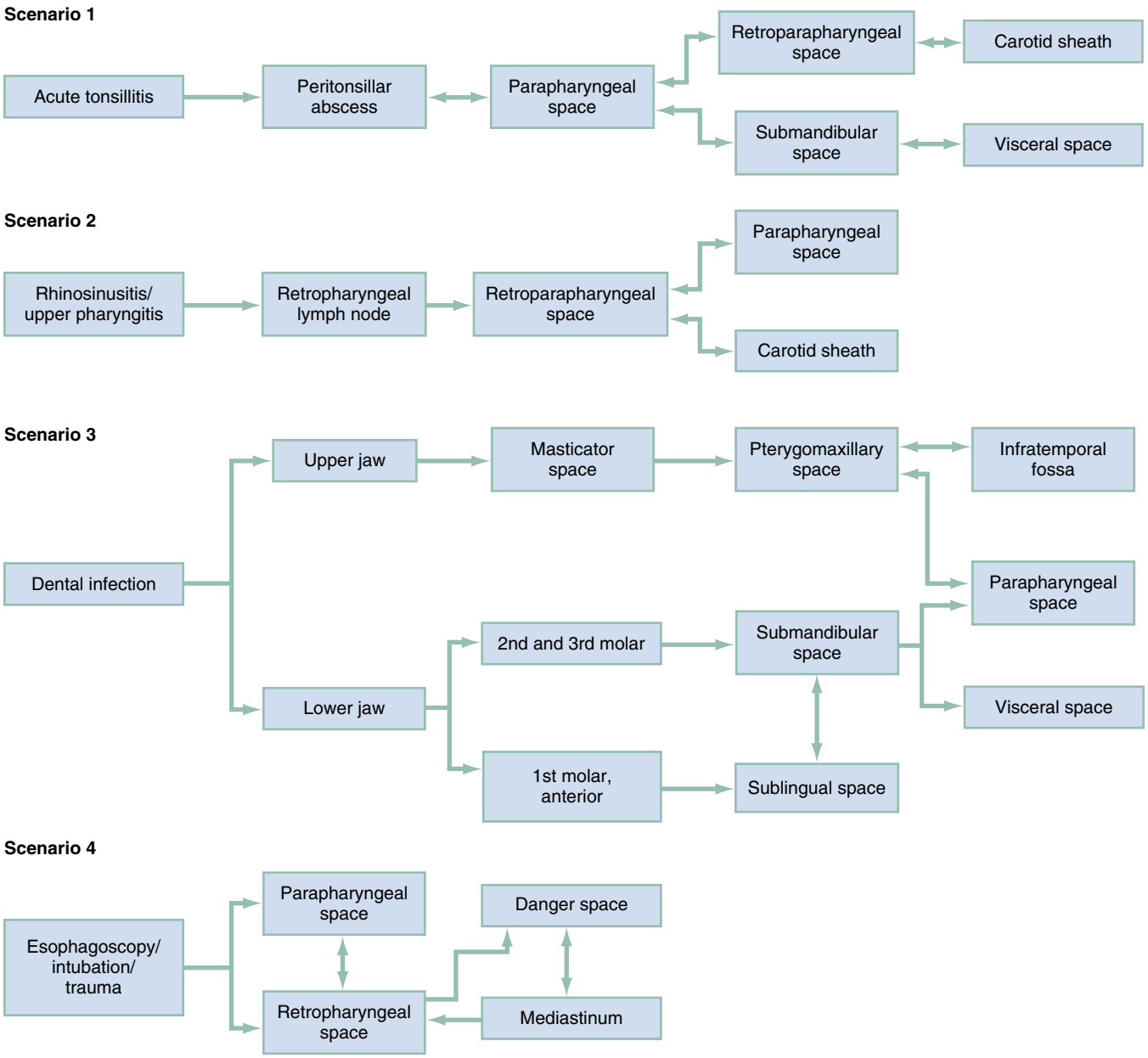


Fig. 56.14 Common Routes of Spread in Deep Neck Infections. (Modified from Cummings CW, Flint PW, Harker LA. *Cummings Otolaryngology Head & Neck Surgery*. 4th ed. St Louis, MO: Elsevier/Mosby; 2004, Fig. 10.2.)

can be managed with antibiotics as shown in Table 56.2. Simple tooth abscesses can be drained with local incision under local anesthesia if the clinician is skilled in the procedure. In the absence of systemic symptoms in the immunocompetent patient, routine antibiotics are unnecessary after successful drainage of a periapical abscess.[11,12]

Most deeper abscesses are drained by dentists or oral surgeons and tooth extraction may be required. Oral or oral maxillofacial surgery consultation is advisable before drainage of suspected deeply seated abscesses.

All serious deep neck infections should have broad-spectrum IV antibiotics administered. We recommend ampicillin-sulbactam with vancomycin or, if allergic to penicillin, clindamycin monotherapy in the immunocompetent host. See Table 56.3 for further details regarding antibiotic therapy in deep neck infection.

Ludwig angina management consists of antibiotics and airway management. Oral intubation may be difficult because of inability to displace the tongue with a laryngoscope. Intubation is not generally emergent and can be done in the operating room. Examination of the glottis and supraglottic airway by flexible endoscopy will ascertain the degree of airway compromise and, hence, the urgency of airway management. When emergent intubation is indicated, or a patient requires intubation before a prolonged transfer for care, we recommend use of a videolaryngoscope or flexible intubating endoscope (see Chapter 1). Consultation with an oral maxillofacial surgeon or otolaryngologist is indicated.

Disposition

Those with simple odontogenic infections can be discharged with close outpatient follow-up. Patients with severe odontogenic infections, deep neck infections, systemic toxicity, or immunocompromised patients should be hospitalized. Those with concern for airway compromise (e.g., Ludwig angina) or with extension into the neck or mediastinum should be admitted to the intensive care unit (ICU) after thorough evaluation of the airway by CT and flexible endoscopy.

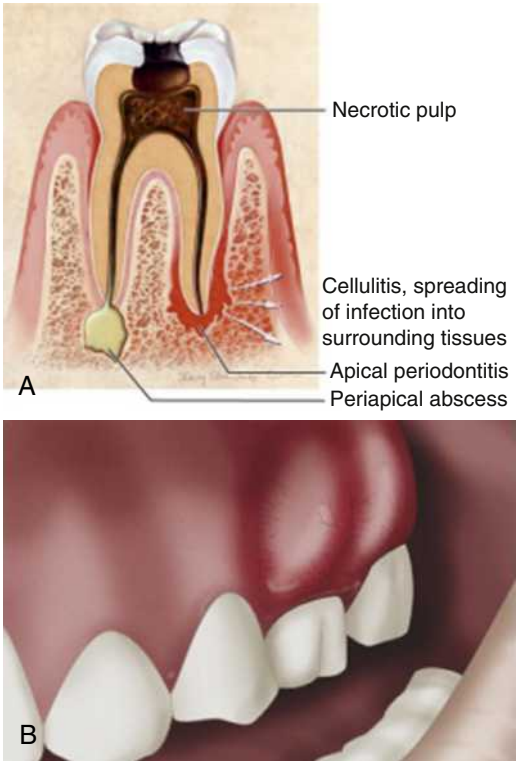


Fig. 56.15 (A) Periapical abscess diagram. (B) Physical examination findings of a periapical abscess. (From Buttaravoli P, Leffler SM. *Minor Emergencies*. 3rd ed. St Louis, MO: Elsevier; 2012, pp 178–180, Figs. 45.3 and 45.4.)

DENTOALVEOLAR TRAUMA

Foundations

Anatomy, Physiology, and Pathophysiology

Dentoalveolar trauma is common and can involve any tooth. The maxillary central incisors are commonly involved because many children have an anterior overbite, predisposing these teeth to injury. When teeth are subject to trauma, they can become concussed (with pain to percussion), subluxated (whereby teeth become more mobile, but are in their normal anatomic position), luxated (moved from their anatomic position), avulsed (out of the socket), have infraction (incomplete fracture of the enamel), or fractured. Refer to the first section of this chapter to review the relevant dental anatomy.

Forces that are applied to a tooth can lead to fractures. Classifying fractures is important because it guides management. Although some classification systems such as the Ellis system exist (Fig. 56.17), an anatomic description is always preferred. The following are types of fractures that can involve the crown of the tooth. An infraction is an incomplete fracture, or crack, of the enamel. An enamel fracture (Ellis I) is a complete fracture of the enamel, not involving any deeper layers. An enamel-dentin fracture (Ellis II) involves the dentin, which has a yellow tint. An enamel-dentin-pulp fracture (Ellis III) involves the pulp and will have a pinkish tinge or small amount of visible blood. In addition, fracture lines can extend into the root of the tooth which will often show tooth mobility. Fractures that extend into the root may additionally need stabilization as the attachment to the adjacent alveolar bone can be compromised.

Concussion occurs when the periodontal ligament sustains a mild injury, causing tooth pain but no mobility. More severe injuries include subluxation or luxation. If a tooth is mobile but is in the correct anatomic position, it is subluxated and will heal as long as no further trauma occurs. Luxation is where the tooth itself is moved in any direction that is no longer anatomic, and it can be further divided into four types: (1) extrusive luxation is where the tooth is forced partially out of the socket in an axial direction, (2) intrusive luxation occurs when a tooth moves apically (and can be mistaken for an avulsion if completely intrusively luxated), (3) laterally luxated, where the tooth is displaced laterally with potential surrounding alveolar bone injury, and (4) avulsion where the tooth is completely out of the socket (Fig. 56.18). A long-term sequela of blunt trauma or reimplantation of teeth is resorption of the root.

Dental trauma can also involve the surrounding alveolar bone. The alveolar bone usually breaks in segments, leading to malocclusion, pain, and a segment of teeth that are misaligned with respect to their uninvolved neighbors (Fig. 56.19). These injuries usually present in conjunction with injury to the tooth itself.

Clinical Features

Patients invariably will have a history of dentoalveolar trauma. Replantation of a pediatric tooth depends on whether the tooth is primary or secondary (Fig. 56.20) Primary dentition are not reimplanted as they will ankylose or fuse to the bone and interfere with the eruption of permanent teeth. Assessing the storage medium and timing of avulsion of a permanent tooth is important as it predicts success of reimplantation.

Inspect the teeth to evaluate for fractures, tenderness, and mobility. The diagnosis of subluxation can be made by gently tapping a tooth with two tongue blades: any perceptible mobility is evidence of subluxation. Mobility can also be seen when dental fractures extend into the root of the tooth.

Evaluate the oral mucosa and tongue for trauma. Small lacerations can usually be managed expectantly, but larger lacerations may require repair. Evaluate injuries for foreign bodies and to ensure injuries are not full thickness.

Differential Diagnoses

The extent of dentoalveolar trauma is typically apparent by the history and physical examination. The most important differential concerns the possible locations of missing teeth. If a tooth appears to be missing, ask the patient if the tooth was present before the trauma and, if so, whether any teeth were recovered at the scene. If no tooth is visualized, examine the socket to see if the tooth has been intrusively luxated. Evaluate surrounding soft tissue to ensure a tooth is not buried in in a mucosal laceration or other tissue defect. A tooth that cannot otherwise be accounted for may have been aspirated or swallowed.

Diagnostic Testing

Diagnosis of a tooth fracture or luxation is clinical, but CT of the face or Panorex x-rays can be ordered if CT is not available. Specialized views (e.g., maxillary anterior, periapical views) are used by dental professionals but are not regularly available in the ED. A chest or abdominal radiograph will help diagnose an aspirated or ingested tooth.

Management and Disposition

Prior to any manipulation of teeth, administer appropriate analgesia. Nerve blocks such as supraperiosteal nerve blocks (for isolated teeth) or inferior alveolar nerve blocks (for multiple traumatized mandibular teeth) are highly effective and easy to perform.

Check the patient's tetanus status and treat according to the standard for a non-tetanus-prone wound (10-year immunization update). Place all patients with dentoalveolar trauma (especially those who have splinting or calcium hydroxide paste applied) on a liquid diet for several days, advanced to a soft diet for 1 week.

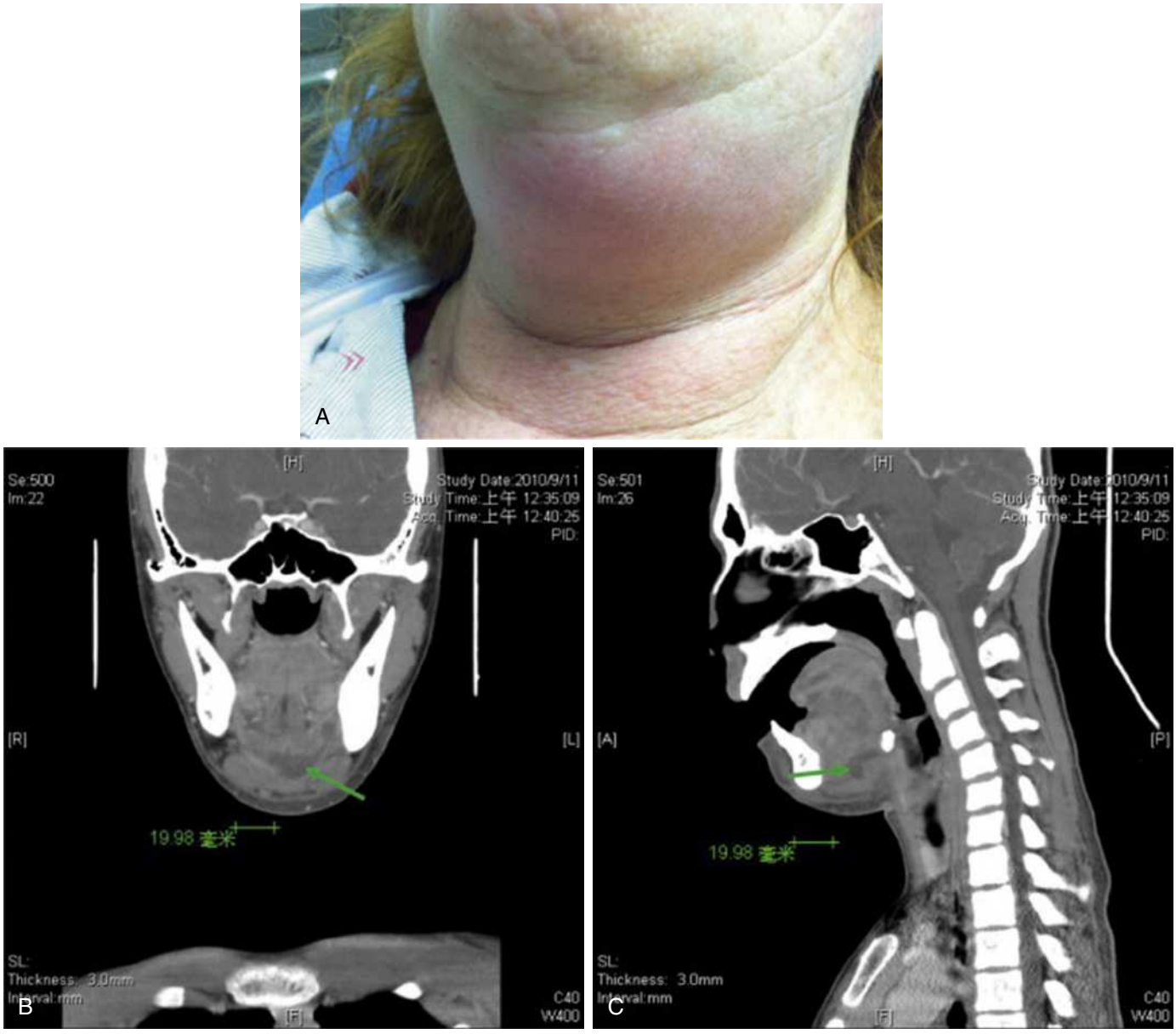


Fig. 56.16 **Ludwig Angina.** (A) Photograph. (B) Coronal computed tomography (CT) scan. (C) Sagittal CT scan. (A, From Hughes D, Holt S, Kman NE. Ludwig's angina triaged as an allergic reaction. *J Emerg Med*. 2013;45[5]:e175–176, Fig. 2. B and C, From Kao JK, Yang SC. Ludwig's angina in children. *J Acute Med*. 2011;1[1]:23–26, Fig. 3 [coronal] and 4 [sagittal].)

TABLE 56.3 Recommended Antibiotics for Deep Neck Infections

Antibiotic	Dosage	Notes
Ampicillin/sulbactam **plus** vancomycin	3 g IV every 6 h 15–20 mg/kg q8–12 hours (2 g maximum)	
Clindamycin	600 mg IV every 8 h	If allergic to penicillin
Meropenem **plus** vancomycin	1 g IV every 8 h 20 mg/kg (2 g maximum)	If immunocompromised

IV, Intravenous.

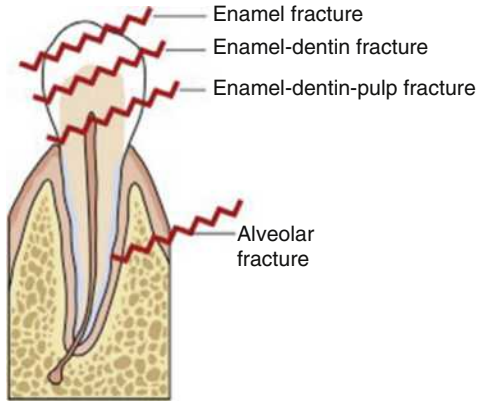


Fig. 56.17 **Ellis Fracture Classification.** *Ellis class I* fractures involve the enamel only; *Ellis class II* fractures involve the enamel and dentin; *Ellis class III* fractures involve the enamel, dentin, and pulp. (From Fowler GC. Management of dental injuries. In: Pfenninger JL, Fowler GC, ed. *Pfenniger and Fowler's Procedures for Primary Care*. Philadelphia, PA: Elsevier/Mosby; 2011:511–515, Fig. 81.2.)

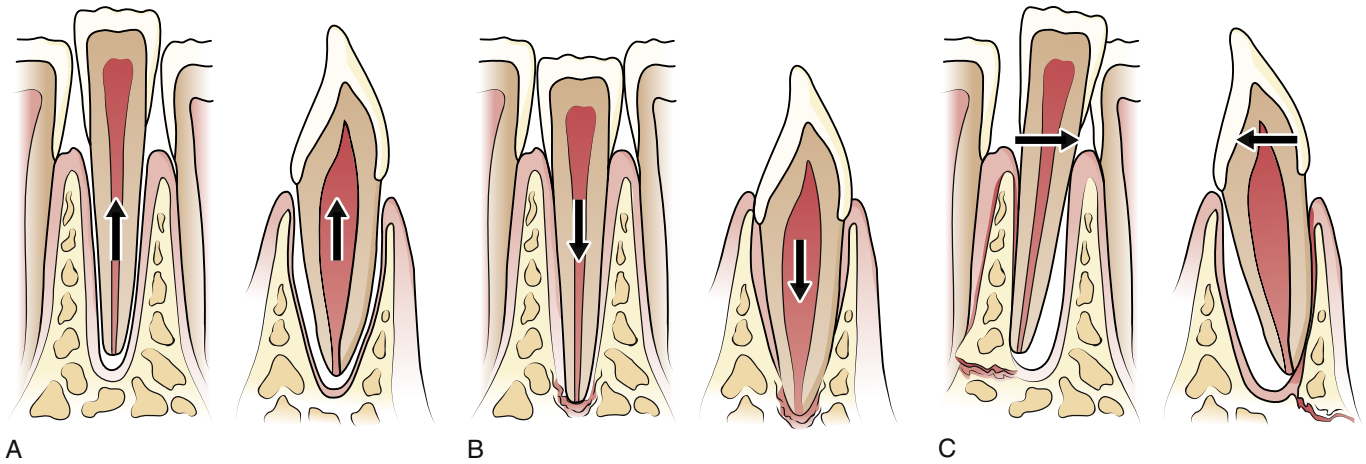


Fig. 56.18 Luxation of Teeth. (A) Extrusive luxation occurs when the tooth is forced partially out of the socket in an axial direction. (B) Intrusive luxation of a tooth compresses the periodontal ligament and vascular supply of the pulp. It may even crush the apical bone. (C) Lateral luxation occurs when the tooth is displaced in a lingual, mesial, distal, or facial direction. Fractures of the alveolar bone frequently accompany lateral luxation injuries. (From Roberts J. *Roberts & Hedges' Clinical Procedures in Emergency Medicine*. 6th ed. Philadelphia, PA: Elsevier; 2014, Fig. 64.9.)

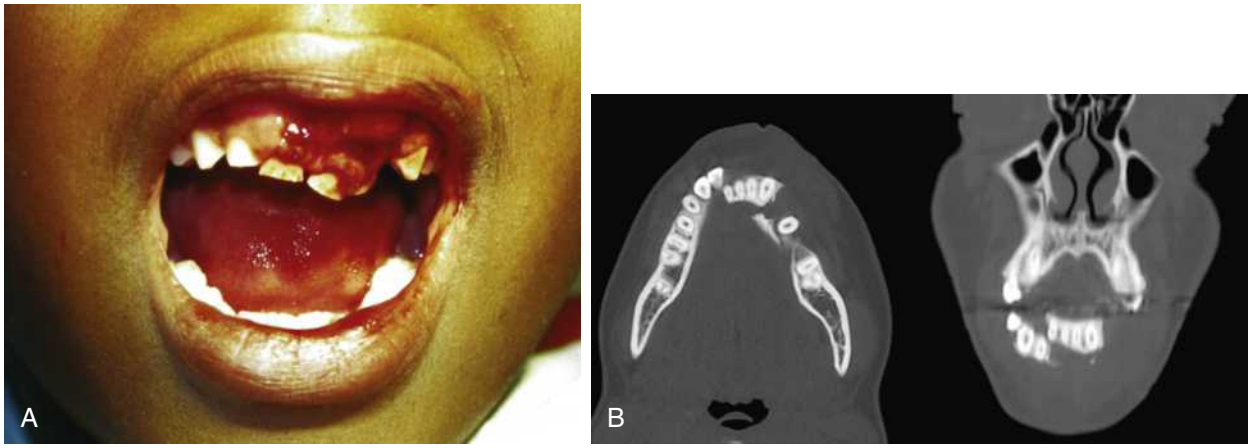


Fig. 56.19 (A) Alveolar ridge fracture involving the maxillary incisors with a segment of teeth misaligned with respect to their neighboring teeth. (B) Computed tomography (CT) demonstrating an alveolar ridge fracture in the axial and coronal planes, respectively. (From Roberts J. *Roberts & Hedges' Clinical Procedures in Emergency Medicine*. 6th ed. Philadelphia, PA: Elsevier; 2014, Figs. 64.14 and 64.15.)

Dental Fractures

Fractures of teeth involving the enamel only (Ellis I) need no emergent treatment. If available, an emery board can be used to file down any sharp edges to prevent intraoral trauma. Cover deeper fractures involving the dentin only (Ellis II) or both dentin and pulp (Ellis III) with a calcium hydroxide paste to protect the underlying structures from infection. Although dental trauma guidelines recommend sealing fractures involving the dentin with glass ionomer, this is not often available to the emergency clinician, so we believe it is reasonable to use calcium hydroxide paste instead. ED pulpotomy for enamel-dentin-pulp fractures to remove exposed pulp has been described, but it has a high complication rate and should not be attempted. We recommend follow up within 24 hours for all dental fractures that do not receive dental consultation in the ED, such as fractures involving the pulp or dentin.

To cover the tooth, first dry the affected tooth. Mix the catalyst and base of the calcium hydroxide product and directly apply it to the exposed tooth surface (Fig. 56.21). To keep the tooth dry, gauze rolls in the mucobuccal fold and a nasal cannula with air or oxygen directed at the anesthetized tooth surface is often helpful.

Tooth Avulsion

Avulsed *permanent* teeth should be reimplanted at the earliest opportunity as long as the tooth is still viable.[13,14] In general, teeth are likely to be nonviable if dry for over 60 minutes as the periodontal ligament cells die. There are some recommendations to reimplant the nonviable tooth to maintain contour of the alveolar bone, but the long-term viability of the tooth is unlikely as the periodontal ligament cells do not regenerate. Reimplantation of a nonviable tooth can be considered on a case-by-case basis and ideally in discussion with the provider that will follow the patient.

In the prehospital setting, the tooth can be reimplanted or stored in an appropriate medium to preserve periodontal ligament cell viability. Ideally, the tooth should be stored in either a commercially-available solution, such as Hank's balanced salt solution (e.g., Save-A-Tooth, EMT Toothsaver) or milk.[15] Saliva should only be used if no other storage media are available. Avoid water as its hypotonicity will cause the periodontal cells to swell and die. See Table 56.4 for the approximate length of viability of a tooth based on the solution in which it is stored. Do not soak the tooth in a doxycycline solution prior to reimplantation

Upper teeth	Primary erupt	Permanent erupt
Central incisor	8–12 months	7–8 years
Lateral incisor	9–13 months	8–9 years
Canine (cuspid)	16–22 months	11–12 years
First premolar		10–11 years
Second premolar		10–12 years
First molar	13–19 months	6–7 years
Second premolar	25–33 months	12–13 years
Third molar		17–21 years

Lower teeth	Primary erupt	Permanent erupt
Third molar		17–21 years
Second molar	23–31 months	11–13 years
First molar	14–18 months	6–7 years
Second premolar		11–12 years
First premolar		10–12 years
Canine (cuspid)	17–23 months	9–10 years
Lateral incisor	10–16 months	7–8 years
Central incisor	6–10 months	6–7 years

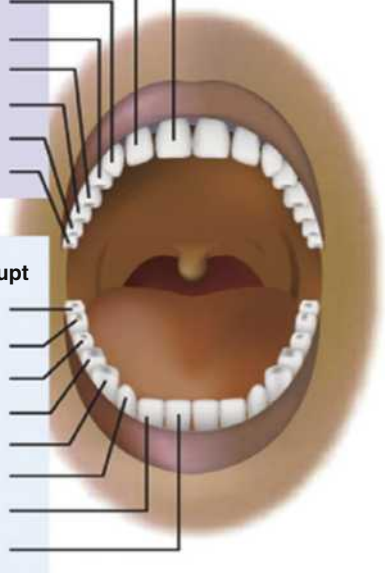
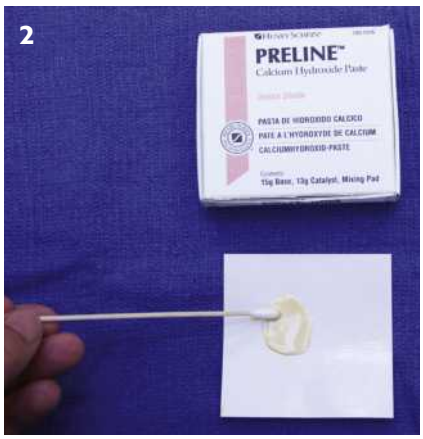


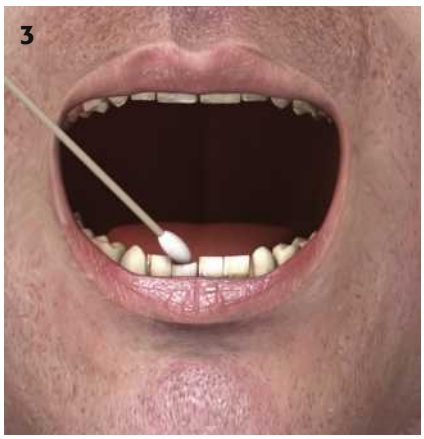
Fig. 56.20 Age of primary dentition and secondary (permanent) dentition of various teeth. (From Olynik CR, Gray A, Sinada GG. Dentoalveolar trauma. *Otolaryngol Clin North Am.* 2013;46[5]:807–823, Fig. 2.)

CALCIUM HYDROXIDE APPLICATION

Calcium hydroxide is used to treat dentin fractures and aids in prevention of infection and pain relief. It is supplied in separate tubes of catalyst and base.



Mix equal portions of catalyst and base on the mixing pad that is supplied with the product. A dental spatula is an ideal tool; however, a simple cotton applicator will suffice.



Dry the tooth surface prior to application by having the patient bite down on a gauze pad. Then place a small amount of the paste onto the exposed surface. It will dry within minutes.

Fig. 56.21 Calcium hydroxide application for the treatment of fractures involving the dentin (Ellis class II) and pulp (Ellis class III). (From Roberts J. *Roberts & Hedges' Clinical Procedures in Emergency Medicine.* 6th ed. Philadelphia PA,: Elsevier; 2014, Fig. 64.7.)

as there is no benefit to this practice.[16] There are no data to suggest other previously-proposed therapies such as hyperbaric oxygen and other specialized treatments provide benefit.[17] Implant-supported crowns have higher long-term success rates compared to reimplanted teeth, but it is still reasonable to attempt reimplantation as it is unclear which patients will have favorable outcomes with reimplantation and also unclear which patients would have access to implant-supported crowns.[18] Permanent teeth should be handled only by the crown to avoid injury to the periodontal ligament at the root.

In the awake patient not at risk for aspiration, provide analgesia (e.g., supraperiosteal nerve block), rinse the permanent tooth gently with saline while holding it by the crown if there are any visible debris, irrigate the socket to remove debris, and reimplant the tooth into the socket. Do not remove debris from the root that does not come off with saline,

because manual removal can damage the periodontal ligament cells. After replantation, a dental consultant can provide immobilization for the reimplanted tooth. If dental consultation is not available, use periodontal dressing material (Coe-Pak) to splint the tooth to the adjacent normal teeth to provide a 24- to 48-hour temporary splint. A resin and catalyst paste are mixed together in equal quantities to a firm consistency and molded over the anterior and posterior aspects of the involved tooth and two or three adjacent teeth on each side (Fig. 56.22). The gingiva and enamel must be completely dry; the provider's gloves should be wet or covered in lubricating jelly to allow for ease of handling of the paste. The positioning of the tooth does not need to be anatomically perfect, just approximate. Avoid getting the paste on the occlusal surface of the tooth. Advise the patient to have a soft diet (but avoid hot liquids that may soften the packing) and follow up with a dentist within 24 hours. Prescribe doxycycline 100 mg bid for 7 days for adults and penicillin 50 mg/kg/day divided qid (maximum 500 mg qid) for 7 days in children. Counsel patients about brushing gently with a soft toothbrush after each meal and utilizing chlorhexidine mouth rinses twice a day for 1 week.

TABLE 56.4 Periodontal Ligament Cell Viability by Storage Medium

Solution	Length of Preservation of Periodontal Ligament
None (dry)	Less than 60 min
Milk	3–8 h
HBSS	12–24 h
Oral rehydration solution	Similar to HBSS

HBSS, Hank's balanced salt solution.

Luxation and Alveolar Fractures

Teeth that are concussed or subluxated usually do not need specific treatment. Permanent teeth that have undergone extrusive or lateral luxation are gently placed into anatomic position and splinted in place.[20] Intrusive luxation does not have any ED-specific interventions

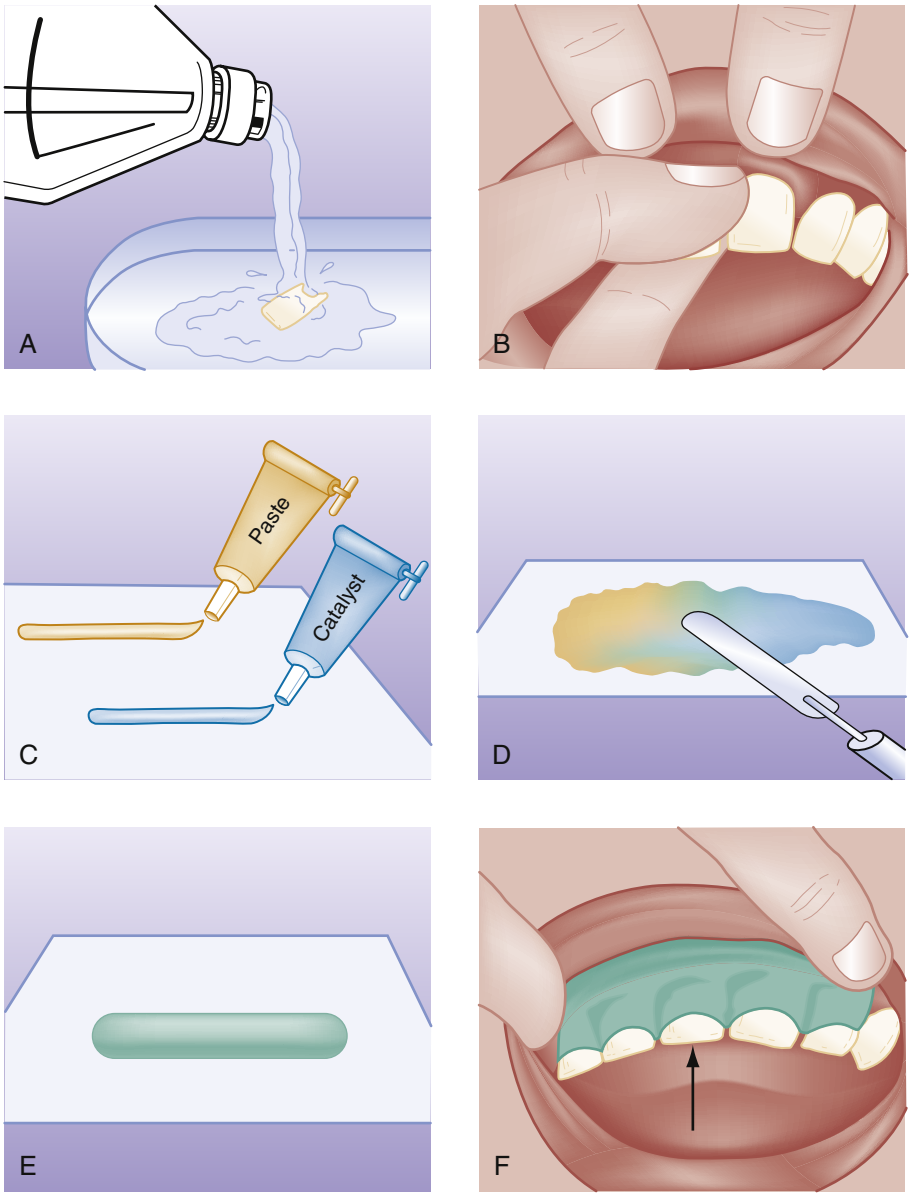


Fig. 56.22 Reimplantation and Stabilization of an Avulsed Tooth. (A) Tooth is rinsed. (B) Tooth is placed back into socket. (C and D) Periodontal pack is mixed. (E) Splint material is ready for application. (F) Packing is molded over reimplanted tooth and two adjacent teeth to either side.

except referral to a specialist, because the tooth cannot be easily retrieved. Pediatric teeth that have been extrusively luxated or laterally luxated and are close to shedding are gently removed.

Alveolar fractures may be apparent clinically from exposed pieces of bone or diagnosed radiographically. In massive facial trauma try to conserve as much of the alveolar bone as possible, unless there is a great danger of aspiration. Indiscriminate loss of alveolar bone results in tremendous cosmetic deformity that is difficult to restore with prosthetic devices or leaves no foundation for a dental implant, thus necessitating autologous bone grafting procedures. An alveolar fracture will eventually require 4 to 6 weeks of stabilization for adequate healing; if there is an associated subluxed or avulsed tooth, stabilization is maintained at the expense of possible ankylosis of the tooth.

Soft Tissue Injuries

Generally, lacerations to the buccal mucosa do not require repair if under 1 cm. A common rule is that if food can get stuck in the laceration, it should be considered for repair. In addition, lacerations to the gingiva that expose the base of the teeth should be repaired. This is a complex repair, however, and consultation or referral is indicated if the clinician is not experienced with the procedure. Frenulum injuries generally are not repaired but, in neonates and infants, should raise suspicion of child abuse.

Tongue lacerations usually heal well without intervention unless they are gaping, have a flap, involve the muscle, cause a bifid or grooved tongue, or if hemostasis cannot be achieved otherwise. After a lingual block or direct infiltration of anesthetic and irrigation, absorbable sutures such as 4-0 chromic, Vicryl, Dexon, or Vicryl Rapide can be used. Lacerations involving the muscular layer of the tongue are closed with one set of deep sutures that involve both the muscle and mucosa; a two-layer repair is not necessary. Full-thickness tongue lacerations can be closed either in three layers (e.g., mucosa inferiorly, muscle, mucosa superiorly) or one side of the mucosa can be repaired followed by a set of deep sutures that closes the muscular layer and opposing mucosa.

Disposition

Patients with dentoalveolar trauma usually do not need to be admitted, unless they have other concomitant trauma, uncontrolled pain, or have severe trismus preventing oral intake. All patients should have appropriate follow-up. Discharge includes adequate analgesia, antibiotics if indicated, and dental hygiene instructions.

TEMPOROMANDIBULAR JOINT DISORDER AND DISLOCATION

Foundations

Anatomy, Physiology, and Pathophysiology

The TMJ is the articulation between the squamous portion of the temporal bone and the condyle of the mandible. It is comprised of two types of synovial joints: hinge and sliding. The hinge joint action dominates during normal mouth opening, but with wide opening, translational movement occurs and the articular disc and condyle complex slide inferiorly (Fig. 56.23). When the condyle moves anterior to the articular eminence, dislocation occurs.

Temporomandibular Joint Disorder. The cause of TMD is debated, but jaw clenching and grinding associated with stress is thought to contribute. Tooth malocclusion was previously thought to be a common etiology, but this is rare unless there is an inciting event (e.g., if symptoms began after dental work with resultant malocclusion).

Temporomandibular Joint Dislocation. TMJ dislocation occurs when the condyle travels anteriorly along the eminence and becomes locked in the anterosuperior aspect of the eminence. The masseter, internal pterygoid, and temporalis go into spasm attempting to close the mandible; trismus results and the condyle cannot return to the temporal fossa. Mandibular dislocation is painful and frightening for the patient. Patients prone to mandibular dislocation include individuals with anatomic disharmonies between the fossa and articular eminence, weakness of the capsule and the temporomandibular ligaments, or torn ligaments. Dystonic reaction to drugs may result in mandibular dislocation. Patients who have had one episode of mandibular dislocation are predisposed to further dislocations. If a unilateral dislocation has occurred, the jaw deviates to the opposite side. More commonly, a symmetrical bilateral dislocation occurs.

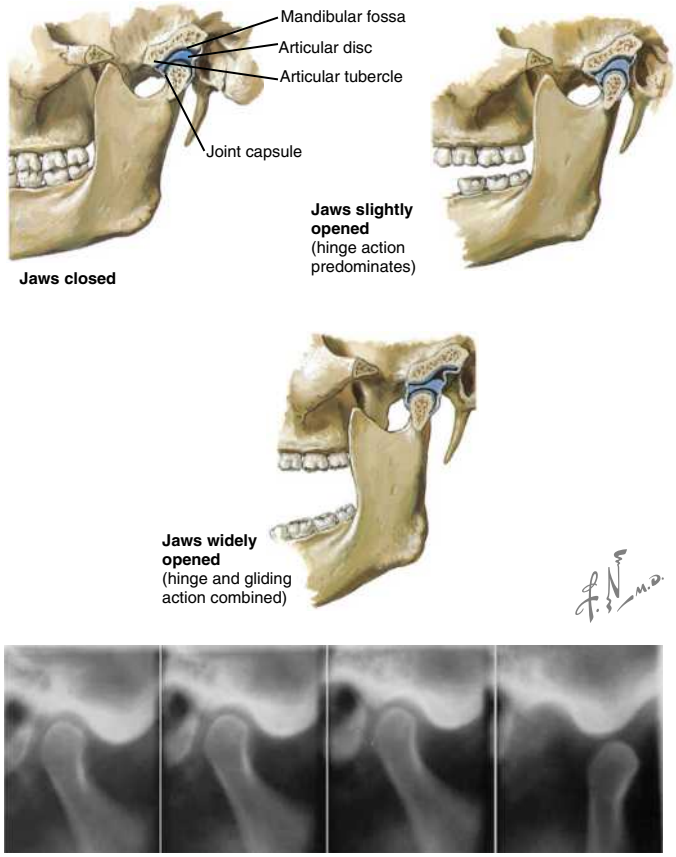


Fig. 56.23 The Temporomandibular Joint. With slight opening, the joint's function as a hinge predominates. With greater jaw opening, there is translational movement. (From Norton NS. Temporomandibular joint. In: *Netter's Head and Neck Anatomy for Dentistry*. 2nd ed. Philadelphia, PA: Elsevier/Saunders; 2012:2011.)

Clinical Features

Temporomandibular Joint Disorder

TMD is defined as "aching in the muscles of mastication, sometimes with occasional brief severe pain on chewing, often associated with restricted jaw movement and clicking or popping sounds." Patients may also report headache, facial pain, or even an earache. Pain is often precipitated by use of the muscles of mastication (e.g., chewing) or with increased ranging of the TMJ (e.g., laughing, yawning).

For TMDs, the main physical signs are related to three items: joint sounds, such as crepitus or a joint click upon range of motion; limitations of joint movements with pain during assisted maximum mouth opening; and muscle and joint pain and pain just anterior to the auricular canal. None of these findings alone has sufficient testing

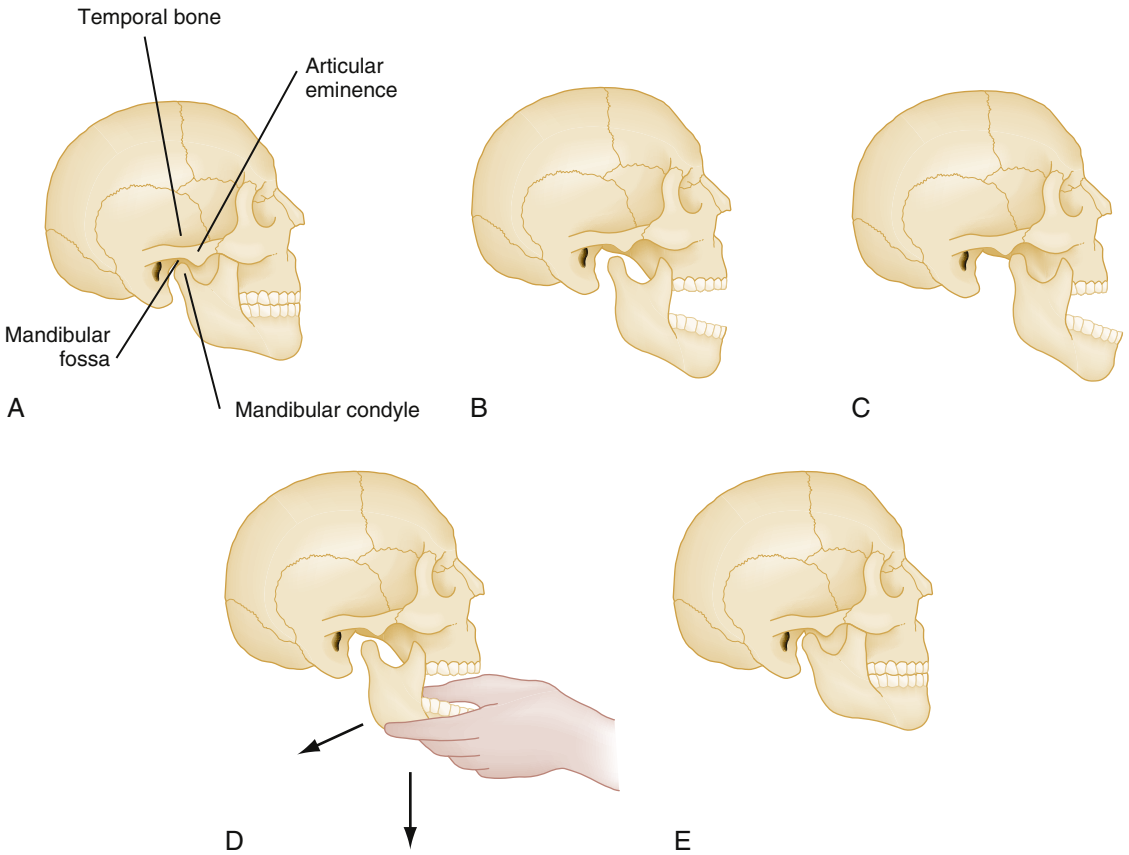


Fig. 56.24 Reduction of Temporomandibular Joint Dislocation. The temporomandibular joint is illustrated in normal and dislocated positions. (A) Closed position, with the mandibular condyle resting in the mandibular fossa behind the articular eminence. (B) In maximally open position, the mandibular condyle is just under and slightly behind the articular eminence. (C) In dislocated position, the mandibular condyle moves forward and upward slightly above the articular eminence; muscle spasm then occurs. (D) For reduction of dislocation, the thumbs are placed intraorally and lateral to the lower molars, and pressure is applied to the lower molar ridge area near the jaw angle in a downward and backward direction. (E) When the mandibular condyle has cleared the articular eminence, muscle contraction returns the jaw to a normal closed position. (Adapted from Rose LF, Hendler BH, Amsterdam JT. Temporomandibular disorders and odontic infections. *Consultant*. 1982;22:125.)

characteristics to rule TMD in or out, however. The diagnostic criteria of TMJ are outside the scope of this text.

Temporomandibular Joint Dislocation

The mandibular condyles may dislocate from trauma, but more often, dislocation follows extreme opening of the mandible, such as the case with yawning. Patients may have had prolonged jaw opening, such as in the case of dental procedures. They will report not being able to close the mouth. Recurrent dislocations are common, and patients may present knowing they have an anterior dislocation. Verbalization of their symptoms is often difficult because their mouth is stuck open.

On examination, jaw dislocations easy to recognize. The jaw will not be able to be closed, and a depression can be felt and seen in the preauricular area. There may be the appearance of an underbite as the mandible is anteriorly displaced. Asymmetry suggests a unilateral dislocation. If a traumatic mechanism is suspected, a secondary survey for trauma should be initiated.

Differential Diagnoses

The diagnosis of a TMJ dislocation is straightforward. However, TMD has many presenting complaints and therefore consideration for other etiologies is warranted. Pain can be secondary to pulpitis, an odontogenic infection, headache, otitis media, sinusitis, parotitis, and trigeminal neuralgia.

Diagnostic Testing

Radiographs are not indicated for straight-forward nontraumatic dislocation, unless the diagnosis is not certain. In cases of traumatic dislocation, obtain either a panoramic view of the mandible (Panorex) or CT scan of the facial to exclude fracture before manipulating.

Management

Temporomandibular Joint Disorder

Patients with TMD often have symptoms that fluctuate over time, and therefore initial therapy is conservative. NSAIDs, application of heat or cooling, and consideration of bite guards, if the patient has bruxism, are all reasonable first-line therapies. Heat therapy is typically 15 minutes at a time, four to six times daily. Refractory cases can also benefit from diazepam (2 to 5 mg by mouth every 8 hours as needed). If the symptoms are more severe, referral to a specialist is warranted because a multidisciplinary approach is often necessary to manage symptoms. Transcutaneous electrical nerve stimulation therapy or surgery may benefit patients with refractory cases.

Temporomandibular Joint Dislocation

Reduction of a dislocated mandible is often difficult, because masseter muscle contraction must be overcome. To relax the masseter, procedural sedation and analgesia is necessary. Either facing the patient or from behind, the emergency clinician grasps the mandible with both hands; the thumbs rest on the ridge of the mandible intraorally, posterior to the molars, and the fingers wrap around the outside of the jaw. It is best to have the patient sitting up, with a firm surface behind the head, so that posterior and inferior pressure can be exerted without accompanying movement of the patient's entire head. This method is effective and also prevents being inadvertently bitten by the patient since the reduction is extraoral.[19] Some physicians prefer an intraoral approach and place the thumbs on the occlusal surfaces of the teeth. In this case, the thumbs are wrapped with gauze and fortified with a piece of wooden tongue blade to protect them when reduction is accomplished, because the masseter muscles can contract with tremendous force.

Firm, progressive, downward pressure is applied on the mandible to free the condyles from the anterior aspect of the eminence; the mandible is guided caudally, then posteriorly and superiorly back into the temporal fossae (Fig. 56.24). If this maneuver is unsuccessful, both hands can be used on the affected side of the mandible. The patient is advised to avoid extreme opening of the mandible, such as occurs during laughing and yawning, to begin a soft diet for 1 week, and to apply warm compresses in the TMJ area. NSAIDs and muscle relaxants may be helpful. Patients with chronic dislocation may be helped initially with the application of a Barton bandage (elastic fabricated bandage that wraps around the top of the head and mandible).

A hands-free approach for reduction of acute nontraumatic TMJ dislocation using a "syringe" technique has also been described. With this technique, a 5- or 10-mL syringe is placed between the posterior upper and lower molars (or gums if edentulous) on the affected side. The patient then gently bites down and rolls the syringe back and forth; the syringe is a rolling fulcrum that helps the anteriorly-displaced condyle slip back into its normal position.

Disposition

Patients with TMD and with TMJ dislocation who have been relocated can be discharged home. Those with irreducible TMJ dislocation or those with TMJ dislocation in conjunction with a fracture are candidates for specialty consultation and may require admission for surgical reduction and fixation.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 56: QUESTIONS AND ANSWERS

1. A 27-year-old previously healthy man presents with dental pain, facial swelling, and a muffled voice. Physical examination is remarkable for trismus, poor dentition with diffuse periodontal disease, and an elevated floor of the mouth. You determine endotracheal intubation is necessary. Which of the following statements regarding the patient's management is *true?*

a. An awake intubation technique is indicated.
b. Pre-induction muscle relaxants will decrease the trismus.
c. Rapid sequence induction with rocuronium is indicated.
d. Succinylcholine will worsen the trismus.
e. Transtracheal retrograde wire intubation is indicated.

Answer: a. The trismus is mechanical (presence of a mass, abscess of phlegmon). Neuromuscular blockade, regardless of the choice between depolarizing or non-depolarizing agents, is not likely to help. Patients with anatomically difficult airway and symptoms of airway obstruction are optimally managed with an awake intubation, using a either a videolaryngoscope or flexible endoscope is indicated. Patients with limited oral access will be best managed with nasotracheal intubation over a flexible intubating bronchoscope. Transtracheal retrograde wire intubation is rarely, if ever, indicated in modern emergency practice. Traditional "muscle relaxants" are sedatives and have no direct muscle-relaxing properties.

2. A 21-year-old man presents with tooth pain. He underwent a left mandibular premolar extraction three days ago. Examination is remarkable for a painful but nonbleeding tooth socket. The face and mandible are not swollen. Which of the following statements regarding this patient's condition is *true?*

a. Analgesia is the main goal of emergency department (ED) therapy.
b. Antibiotics are indicated.
c. Dental consultation in the ED is indicated.
d. Opioids are the treatment of choice.
e. Provocation of socket bleeding is encouraged to form new clot.

Answer: a. A dry socket is an exquisitely painful post-extraction syndrome that typically occurs 3 or 4 days later. The pathophysiology is loss of the healing blood clot and localized bone infection. Treatment consists of pain control. Optionally, gentle irrigation, and packing with gauze soaked in eugenol can be performed. Opioids may be used, but this would be in addition to nonsteroidal antiinflammatory drugs (NSAIDs), which are excellent analgesics for dental pain and are preferred due to the inflammatory component.

3. A 2-year-old previously healthy toddler presents with an avulsed tooth after hitting his mouth on the ground after a trip and fall. Physical examination is remarkable for a non-toxic appearing child who is crying and has an open slightly oozing pocket at the maxillary central incisor. The mother has brought the tooth stored in milk and the event occurred one hour ago. Which of the following statements regarding the patient's management is *true?*

a. Set-up for conscious sedation should be arranged, because the replacement of the avulsed tooth may be painful.
b. The mother should store the tooth in the patient's mouth.
c. The tooth should be placed in Hank's balanced salt solution.
d. The tooth should be replaced in the socket as soon as possible.
e. The tooth should not be reimplanted.

Answer: e. Management of recovered avulsed teeth depends on the age of the patient and the length of time for which the tooth has been displaced. Avulsed primary teeth are not reimplanted. Reimplanted primary teeth ankylose or fuse to the bone, so although the dentofacial complex grows downward and forward, the reimplantation site does not. There also may be interference with the eruption of the permanent tooth. Cosmetic deformity results in either case. Thus, this patient should be referred to a specialist for consideration of a space maintainer or cosmetic appliance.

4. A 25-year-old previously healthy woman presents with recurrent pain from her temporomandibular joint disorder (TMD). The pain is described as being dull, and it worsens during the course of the day. Physical examination is remarkable for mild tenderness to palpation over the temporomandibular joint (TMJ) and some spasm noted over the masseter and internal pterygoid. Which of the following statements regarding the patient's management is *true?*
   a. A computed tomography (CT) scan of the face would be helpful.
   b. A Panorex should be obtained.
   c. Patient should be prescribed narcotic agents.
   d. Treatment consists of external application of heat for 15 minutes four to six times per day, soft diet, analgesics including nonsteroidal antiinflammatory drugs (NSAIDs).
   e. Ultrasound of the joint should be obtained.

Answer: d. TMJ radiographs are not helpful. Treatment consists of the external application of heat for 15 minutes four to six times per day, soft diet, analgesics including NSAIDs, and consideration of a muscle relaxant, such as diazepam (2 to 10 mg up to four times per day). Patients should be referred to a dentist specializing in TMD, such as a periodontist or a periodontal prosthodontist.

5. A 32-year-old previously healthy man presents with a fractured maxillary lateral incisor after a mechanical trip and fall. Physical examination is remarkable for a portion of the tooth that has an ivory-yellow appearance. You determine that he has a fractured tooth. Which of the following statements regarding the patient's management is *true?*
   a. A calcium hydroxide paste should be used to cover the exposed dentin.
   b. A dressing can be placed for comfort.
   c. An urgent pulpotomy is indicated.
   d. If this were a pediatric patient or an adolescent, it would be considered less serious, because children have more dentin than adults.
   e. The patient will likely need an emergent root canal.

Answer: a. This patient has a fracture involving the dentin, which has an ivory-yellow appearance. The pulp continually lays down dentin throughout the life of the tooth. In a child, the pulp is relatively large in size, and there is less dentin; the inverse is true in the adult. Because dentin is a microtubular tissue capable of preventing bacteria to percolate into the pulp chamber, fractures involving dentin are more serious in children and adolescents. In younger patients, the management of dentin fractures involves the immediate placement of a dressing of calcium hydroxide paste over the exposed dentin. Early intervention may prevent contamination of the pulp and avoid the need for subsequent root canal. In an adult, who has a greater thickness of dentin compared with pulpal tissue, there is less need for urgent referral to a dentist. A dressing can be placed on the tooth for comfort. Referral should be made to a dentist for the next working day.

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Ophthalmology

Kama Guluma and Jeffrey E. Lee

KEY CONCEPTS

- Prophylactic topical antibiotics are not indicated for the treatment of corneal abrasions, and eye patches are not recommended because they can mask a worsening infection.
- Eyelid lacerations that may require referral to a plastic or ophthalmic surgeon include those with lid margin lacerations, a canalicular laceration, or levator or canthal tendon injuries.
- Alkaline burns to the cornea and conjunctiva need to be irrigated until a neutral pH is attained because they produce a liquefactive necrosis that penetrates and dissolves tissue.
- Admit hyphema patients with sickle cell trait, uncontrolled elevations in intraocular pressures (IOPs), hyphema of greater than 50%, and when there is concern for rebleeding.
- Avoid manipulation, palpation, or tonometry on a suspected globe rupture pending an ophthalmology consult.
- Scleritis, an autoimmune inflammatory process involving the sclera, can be confused with episcleritis caused by inflammation in the more superficial episcleral layer of the eye.
- Episcleritis, unlike scleritis, is associated with much less discomfort, a pinker and more pronounced peri-limbal injection from superficial episcleral vessels that—unlike the deeper injected scleral vessels in scleritis—will vasoconstrict and blanch with 10% phenylephrine. Treatment of both involves topical corticosteroid drops.
- Endophthalmitis is an infection of the eye itself, typically following intraocular surgery, that is treated with intravitreal antibiotics.
- Herpes zoster keratoconjunctivitis can complicate herpes zoster ophthalmicus. Emergent ophthalmologic consultation and treatment with systemic antiviral agents are required.
- Treatment of acute angle-closure glaucoma requires both a reduction in the production and an increase in the outflow of aqueous humor (see Box 57.1).
- With anisocoria, the following considerations help in determining which pupil—the larger or the smaller—is the pathological one: (1) parasympathetic innervation constricts a pupil in bright light, whereas sympathetic stimulation helps dilate a pupil in the dark; (2) an abnormally small pupil may therefore be due to either a decrease in sympathetic stimulation or an augmentation of parasympathetic stimulation—but likely the former (e.g., Horner syndrome); (3) an abnormally large pupil may therefore be due to either a decrease in parasympathetic stimulation or an augmentation of sympathetic stimulation—but likely the former (e.g., partial third-nerve palsy from compression, Adie's pupil, pharmacological mydriasis); or (4) the abnormally small pupil will usually look worse in the dark, whereas the abnormally large pupil will usually look worse in the light.

OVERVIEW

The emergent conditions that affect the eye, its surrounding tissues, and the act of seeing itself are myriad and broad in scope and include trauma, inflammatory conditions, infections, hydrostatic issues (such as glaucoma), vascular events, structural issues, optical derangements, and neurological developments (visual field cuts, anisocoria, nystagmus, diplopia). The evaluation of a chief complaint of "eye problem" may take the clinician in a variety of directions. Fig. 57.1 represents a general orientation to non-neurological and nontraumatic ophthalmological emergencies based on the four cardinal symptoms of pain, redness, altered vision, and swelling.

TRAUMATIC CONDITIONS

Foundations

The evaluation of a traumatic injury to the eye is framed around anatomic involvement including superficial (eyelids, conjunctival, corneal, and anterior segment) structures to deep (including ocular, retrobulbar, and periorbital) structures, keeping in mind that deep injuries may be present with minimal superficial manifestations. With facial trauma, many extraocular structures are damaged along with the eye (traumatic facial injury is discussed in more detail in Chapter 34). A detailed examination for additional injury is therefore important.

Periorbital Contusions and Eyelid Lacerations

Clinical Features and Differential Diagnoses

Periorbital contusions and eyelid lacerations present very evidently, but it is important to determine whether additional ocular injury such as a globe perforation, an orbital septal injury (suggested by prolapsed fat), a canalicular laceration (suggested by laterally displaced puncta) (Fig. 57.2), a levator or canthal tendon laceration, or an intraorbital foreign body is present because all require consultation in the emergency department (ED) with an ophthalmic surgeon. An eyelid or periorbital injury should not be a distraction from less visible underlying injuries to the eye itself (see sections on injuries to the anterior segment, posterior segment, and retrobulbar space).

Diagnostic Testing

The emergency clinician should undertake best attempts to thoroughly examine all ocular structures, even those hidden by swollen eyelids and periorbital tissue, and evaluate visual function. With delay, swelling can increase and limit visualization. Early examination, gentle pressure to avoid excessive tissue manipulation, or use of ice can improve the ability to open the eyelids, whereupon an assessment for deeper injuries

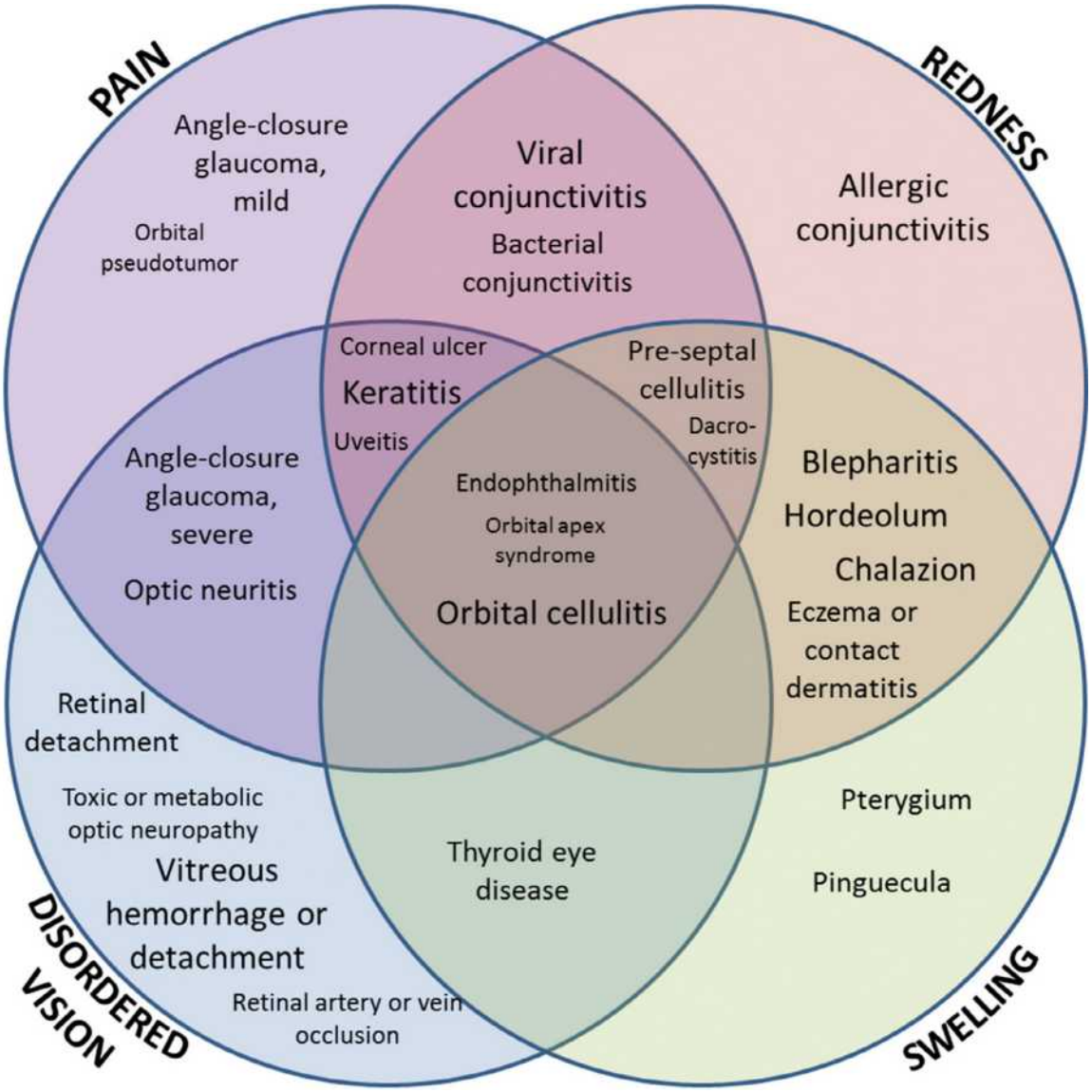


Fig. 57.1 An overview of nontraumatic, non-neurological ophthalmological conditions, arranged by primary presentation in the emergency department (ED). Relative text size is a general representation of the incidence or relatively likelihood of that entity in relation to others. (Note: The actual incidence or likelihood of the entity in any one ED will vary with the local disease patterns and patient population being treated in the department.)

can be made. The use of eyelid retractors, such as the Desmarres, can help avoid increasing intraocular pressure (IOP). However, if there is concern for a ruptured or perforated globe (with or without a foreign body present) and the globe cannot be safely and properly examined, computed tomography (CT) imaging, with or without consultation with an ophthalmologist, is advised (see Intraocular Foreign Bodies and Globe Rupture later in the chapter).

Management and Disposition

Isolated soft tissue injury to the eyelids and the surrounding area is treated with symptomatic management such as head elevation and cool compresses, as most will resolve. If there are no additional complications, one can manage simple lid lacerations that are parallel to relaxed skin tension lines (exceptions for damage to important structures noted earlier) with primary closure with 6-0 or 7-0 nylon or Prolene interrupted sutures, removed within a week. Patients are instructed to seek follow-up care for any increase in pain or swelling, decreased vision, double vision, or significant flashing lights or floaters, as these may be indications of retinal injury (see Posterior Segment/Ocular Injuries: Commotio Retinae, Retinal Detachment, Intraocular Foreign Body, and Perforated Globe later).

Conjunctival and Scleral Injuries: Subconjunctival Hemorrhage, Conjunctival Laceration, and Scleral Laceration

Clinical Features

Injuries to the conjunctiva include a subconjunctival hemorrhage (very common with blunt or penetrating injury) and conjunctival laceration. A subconjunctival hemorrhage develops when subconjunctival blood vessels bleed, either spontaneously or after a sudden acute venous congestion of the head, such as from a Valsalva maneuver or vigorous coughing. The hemorrhage smoothly and minimally raises the overlying conjunctiva, with no vessels visible behind the blood, and is

Fig. 57.2 Canalicular Laceration. (A) This patient experienced a laceration of the upper canaliculus. (B) Canalicular laceration extending from forehead and brow. (A, From Zitelli BJ, Davis HW, eds. *Atlas of Pediatric Physical diagnosis*. 5th ed. St Louis: Mosby; 2002. B, Courtesy Jeffrey Lee, MD, University of California San Diego.)

often discovered by the patient upon looking in the mirror (Fig. 57.3). Symptoms, if any are present, may include a very mild, diffuse foreign body sensation, due to the size and location of the hemorrhage, with no change in visual acuity. Subconjunctival hemorrhages from minor instigations are typically self-limited, but those from more direct trauma may be hiding an underlying injury. A 360-degree area of involvement associated with chemosis or pain, decreased visual acuity, or sensitivity to light should prompt an evaluation for globe perforation.

A conjunctival laceration will present with more discomfort than a subconjunctival hemorrhage, and if present, should prompt an evaluation for globe perforation and retained foreign body. A globe perforation from a related foreign body may present in an occult fashion, with only a mild-appearing conjunctival laceration or scleral "bruise," and should be suspected in the presence of a high-impact mechanism of injury (such as an injury from a compressed air tool or an object deflected by a hammer strike). A patient may also present with a scleral laceration, a laceration of the thick white envelope that provides the structural integrity of the globe, which should also prompt consideration of globe perforation.

Differential Diagnoses

Injury to the visible part of the anterior eye can be superficial or deep and largely can be distinguished based on the degree of pain, mechanism of injury, and depth of penetration on examination, as mentioned. The differential includes conjunctival abrasions or lacerations, scleral injury, and globe rupture. Inflammatory medical ocular conditions, such as scleritis or episcleritis, may have a similar appearance but will lack a history of trauma.

Diagnostic Testing

Examination for subconjunctival hemorrhage, conjunctival laceration, or scleral laceration is performed with a slit lamp and fluorescein dye. This is especially helpful in three ways: (1) identification of corneal abrasions, (2) screening for evidence of a globe perforation, and (3) identification of tarsal foreign bodies. A 10% fluorescein strip, applied using 2 to 3 drops of tetracaine or saline, will paint the conjunctival and corneal surface highlighting regions of lost or damaged epithelium with a bright greenish-yellow hue under a Wood's lamp. Intact epithelium will be spared. Fluorescein staining showing a pattern of repeated lines (Fig. 57.4) suggests the possibility of a retained tarsal foreign body hidden under the upper or lower lid. If the fluorescein

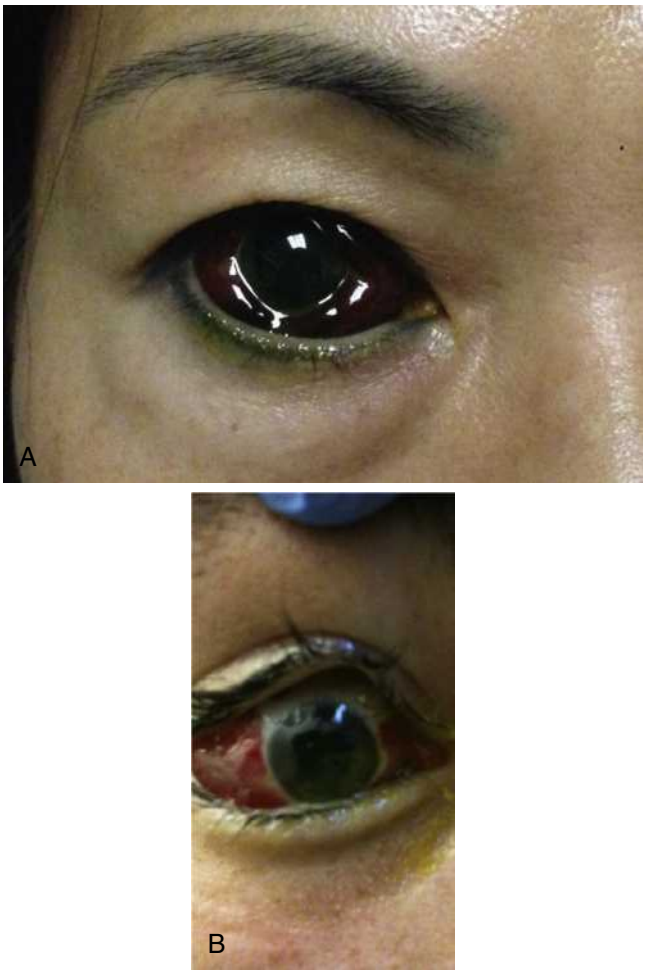


Fig. 57.3 (A and B) Subconjunctival hemorrhage. (Courtesy Jeffrey Lee, MD, University of California San Diego.)

dye on the conjunctival surface is focally displaced by leakage of nonfluorescent aqueous fluid (called a *positive Seidel's test*), or if there is brownish-black uveal tissue visible in the scleral wound (Fig. 57.5), a globe perforation is present (see Intraocular Foreign Bodies and Globe Rupture). If no globe perforation is suspected, evert the eyelids and

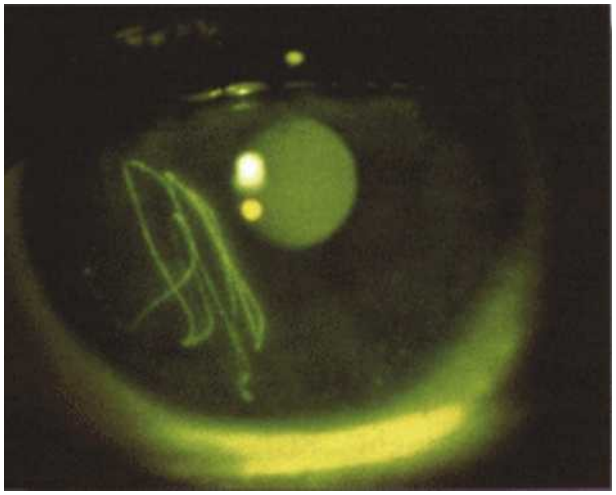


Fig. 57.4 Corneal Abrasion Demonstrated by Slit-Lamp Examination. (Courtesy www.perret-optic.ch/optometrie/symptomes_diagnostiques/symptomes/opto_symfor_gb.htm#abrasion.)

Fig. 57.5 Scleral Laceration With Penetrating Globe Injury. Note care being taken not to increase intraocular pressure with examiner's fingers.

inspect the conjunctival fornices for a hidden foreign body. In cases of spontaneous subconjunctival hemorrhage with no systemic signs of coagulopathy, the incidence of an underlying hemostatic disorder is low enough that a search for one is generally not warranted.[1]

Management and Disposition

Subconjunctival hemorrhages typically resolve spontaneously without treatment. Cool compresses are often recommended, but there is no evidence that they hasten recovery or improve outcome. There is no evidence to support the use of artificial tears or lubricants for treatment; however, it may help with normalizing the ocular surface and reduce any foreign body sensation the patient notices. Patients with simple subconjunctival hemorrhage are advised regarding the gradual resolution of their hemorrhage over 10 to 14 days, with the typical colorations associated with resolving hemorrhage. No follow-up is required unless the patient develops recurrent hemorrhages or new symptoms.

Although most conjunctival lacerations do not require repair, lacerations that are more than 1 cm need evaluation by an ophthalmologist in the ED for possible repair. Although there is no evidence to support the practice, topical antibiotic prophylaxis for 3 to 5 days (usually in ointment form; Table 57.1) is common practice. A deeper scleral

TABLE 57.1 Useful Topical Ophthalmic Medications and Their Dosages

Medication	Dosage
Topical Antibiotics	
Erythromycin 0.5% ointment	½-inch ribbon, four times per day for 7 days
Polymyxin B/trimethoprim solution	1 drop, four times per day for 7 days
Sulfacetamide 10% solution	1 to 2 drops, four times per day for 7 days
Azithromycin ophthalmic 1% solution	1 drop twice a day for 2 days, then daily for 5 days
Anti-Pseudomonal Topical Antibiotics	
Ciprofloxacin 0.3% ointment	½-inch ribbon, four times per day for 7 days
Ciprofloxacin 0.3% solution	1 to 2 drops, four times per day for 7 days
Moxifloxacin 0.5% solution	1 to 2 drops, three times per day for 7 days
Gentamicin 0.3% ointment	½-inch ribbon, two to three times per day for 7 days
Gentamicin 0.3% solution	1 to 2 drops, four times per day for 7 days
Ofloxacin 0.3% solution	1 to 2 drops, four times per day for 7 days
Topical Cycloplegics	
Cyclopentolate 1%	1 drop (may repeat in 5 min if needed), three times a day, for up to 4 days
Homatropine 5%	1 drop, four times per day, for up to 4 days
Topical Anesthetics[a]	
Tetracaine hydrochloride 0.5% or 1%	1 drop, every 30 min as needed, for 24 h only; up to 3 doses for minor procedures; up to 5 doses maximum for prolonged anesthesia
Proparacaine 0.05% (10 times dilution[b])	2–4 drops, every 30 min as needed, for 48 h only; up to 5 to 7 doses maximum
Topical Nonsteroidal Antiinflammatory Drugs	
Diclofenac 0.1%	1 drop, four times per day for 2–3 days
Ketorolac 0.4%	1 drop, four times per day for 2–3 days
Topical Antihistamines (Allergy)	
Azelastine 0.05%	1 drop twice a day
Emedastine 0.05%	1 drop up to four times per day
Topical Steroids	
Prednisolone acetate 1%	2 drops every 15–30 min four times, then four times per day for 2–3 days

[a]For corneal abrasions—use only in reliable patients who have been educated on use.
[b]Can use undiluted 0.5% for diagnostic purposes in emergency department (ED).

Azari AA, Barney NP: Conjunctivitis: a systematic review of diagnosis and treatment. *JAMA*. 2013;310(16):1721–1729; Varu DM, Rhee MK, Akpek EK, et al.; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. *Conjunctivitis Preferred Practice Pattern®*. *Ophthalmology*. 2019;126(1):P94–P169; Wipperman JL, Dorsch JN. Evaluation and management of corneal abrasions. *Am Fam Physician*. 2013;87(2):114–120.

laceration requires emergent consultation with an ophthalmologist and may predispose to endophthalmitis. A full-thickness scleral laceration should be treated as a globe perforation.

Corneal Injuries: Corneal Abrasions, Foreign Bodies, and Lacerations

Clinical Features

Traumatic corneal injuries come in three varieties: (1) abrasions, (2) foreign bodies, and (3) lacerations (which may also go into the sclera). A corneal abrasion is typically sustained when an object or part of an object is dragged across the eye, such as seen with a fingernail injury to the eye or an attempt to pull off an adherent contact lens. A corneal foreign body is typically sustained when a small dense object traveling at high velocity impacts the cornea and becomes embedded, commonly seen with debris ejected from a grinding tool. A corneal laceration is typically sustained from a direct lancinating injury to the surface of the eye. Corneal injuries present with more symptom intensity than a conjunctival or isolated scleral injury, with significant foreign body sensation, pain, tearing, and a decrease in visual acuity if the abrasion, object, or laceration infringes upon the visual axis. Reactive conjunctival injection is often seen with primary corneal injuries either as a result of the primary process or secondary to patient manipulation and rubbing.

Differential Diagnoses

A foreign body may actually be conjunctival and not embedded in the cornea, presenting with more diffuse irritation, or a sensation of "something under the eyelid." Symptoms of a corneal abrasion can occur when the foreign object travels across the surface of the cornea by blinking or rubbing. As with a conjunctival and scleral injury, consider a perforated globe with any corneal injury, suggested by symptoms and signs (e.g., deep eye pain, decreased visual acuity, or photophobia) and injury mechanism.

Diagnostic Testing

With corneal abrasions and foreign bodies, the use of topical anesthesia (see Table 57.1) facilitates patient cooperation and helps localize the extent of the injury. Focal pain that is completely abolished by topical anesthesia, with no signs of deeper injury present, suggests the injury is confined to the superficial layers of the cornea. This does not obviate the need for a detailed examination with a slit lamp and fluorescein staining, with diagnostic goals as outlined with conjunctival injuries earlier. A corneal foreign body should be readily evident on slit-lamp evaluation (Fig. 57.6). If the foreign body spans the full thickness of the cornea, it should be considered a globe perforation requiring emergent ophthalmology consultation.

A corneal laceration may be difficult to characterize (or may even be hidden) on slit-lamp examination. The primary diagnostic goal is identifying it and determining whether or not it is through-and-through (i.e., representing an open-globe injury). Signs suggesting the latter are loss of anterior chamber depth, prolapsed iris (Fig. 57.7A), an irregular or teardrop-shaped pupil (see Fig. 57.7B), blood in the anterior chamber (Fig. 57.8), and a 360-degree subconjunctival hemorrhage. Looking for a positive Seidel's test with fluorescein, as described for conjunctival injuries earlier, can be used to confirm (but not exclude) an open globe. A critical point is that corneal perforation is a form of an open globe, and once this is found, the examination ends (so as to prevent the additional extrusion of globe contents, worsening visual outcome) until the patient can be further examined under controlled conditions by an ophthalmologist (see Intraocular Foreign Bodies and Globe Rupture later).

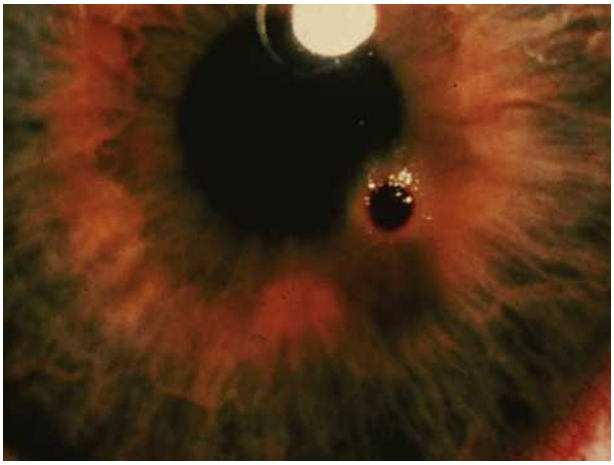
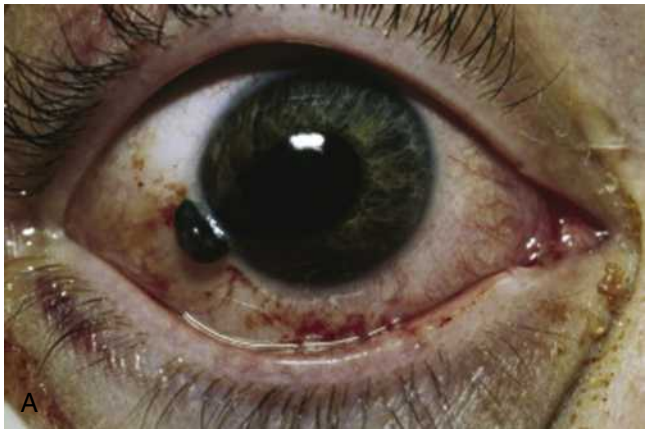


Fig. 57.6 Corneal Foreign Body Seen on Slit-Lamp Examination. (Courtesy www.tedmontgomery.com.)



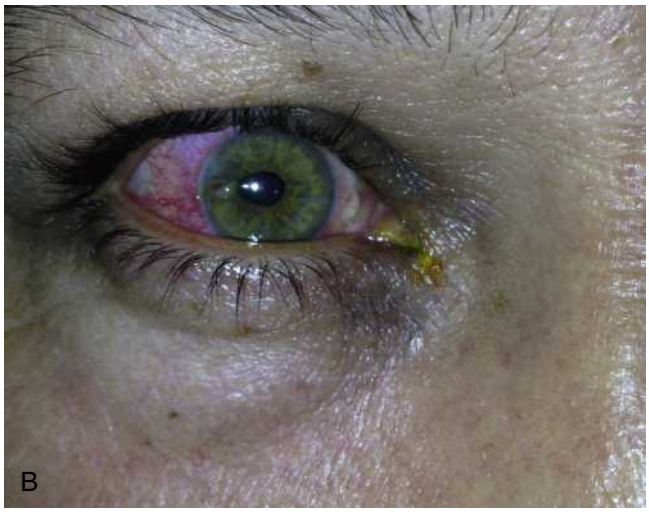


Fig. 57.7 Corneal Laceration With Prolapse of the Iris. (A) The pupil is irregular and teardrop-shaped, pointing toward the laceration. (B) Corneal laceration with teardrop pupil, pointing toward the laceration. (A, From Roberts JR, Hedges JR, eds. *Clinical Procedures in Emergency Medicine*. 5th ed. Philadelphia, PA: Saunders; 2010. B, Courtesy Jeffrey Lee MD, University of California San Diego.)

If the mechanism of injury involves a high-velocity projectile and no foreign body is seen on slit-lamp examination but is suspected, initiate an evaluation for an intraocular foreign body (see Intraocular Foreign Bodies and Globe Rupture).

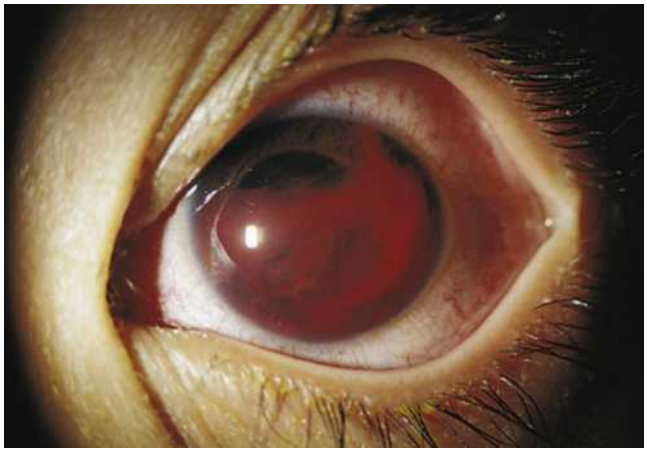


Fig. 57.8 Hyphema in the Anterior Chamber. (Courtesy Steve Chalfin, MD, University of Texas Health Science Center, San Antonio, TX.)

Management and Disposition

Corneal abrasions. There is no evidence that the treatment of corneal abrasions with topical antibiotics, as often recommended, has any beneficial effect. Furthermore, the infection rate of untreated corneal abrasions is low—at 0.7%—and prophylactic antibiotic use is not warranted. Indiscriminate use can introduce the risk of toxic and allergic reactions. We do not recommend routine topical antibiotics for uncomplicated, superficial corneal abrasions. They are reasonable to prescribe when abrasions are deep, caused by a heavily contaminated object, or present in a high-risk patient. Additionally, empiric treatment of a corneal abrasion with an anti-pseudomonal agent such as tobramycin, ciprofloxacin, or ofloxacin is warranted in a contact lens wearer or immunocompromised patient (see Table 57.1). Abrasions from organic material or any slowly healing abrasions may warrant additional treatment and ophthalmic consultation.

Pain control with a corneal abrasion is paramount. Topical nonsteroidal antiinflammatory drugs (NSAIDs), such as ketorolac or diclofenac (see Table 57.1), have been shown to decrease the need for rescue analgesia.[2] Prospective trials and observational studies suggest that topical anesthetics self-administered as needed for a short duration of time by ED patients for corneal abrasion pain provide significant pain relief without complications.[3] Meta-analyses incorporating these trials as well as postoperative ophthalmology literature support this finding.[4–6] Therefore, a patient with a corneal abrasion can be provided a limited 24- to 48-hour course of a topical anesthetic (see Table 57.1), as the most intense pain occurs in the first 24 hours.

Uninformed patients using over-the-counter topical anesthetics for otherwise simple corneal injuries can develop an erosive keratopathy, perhaps by masking the pain of an emerging infection or due to a direct toxic effect from a misused anesthetic. It is therefore important to counsel patients regarding the correct, limited use of these agents. Eye patches are not recommended as they can also mask a worsening infection. Urgent ophthalmologic consultation is warranted with signs of active infection, such as a corneal infiltrate (whitening of the cornea) or ulceration (see Corneal Ulcers and Infiltrates later); otherwise, the patient can follow-up with an ophthalmologist in 24 to 48 hours.

Corneal foreign bodies. Foreign bodies of the cornea and conjunctiva, especially those containing iron (given the risk of rust deposition over time), should be removed in the ED if possible, using a topical anesthetic for comfort (see Table 57.1). Corneal foreign bodies can be removed by a moist cotton-tipped applicator or, if needed, by using a 25-gauge or 27-gauge needle carefully applied in a plane tangential to the surface of the cornea, under slit-lamp visualization. Non-corneal conjunctival foreign bodies can be removed by irrigation, a wet cotton-tipped applicator, or fine forceps. For metallic foreign bodies, residual rust rings can be removed 24 to 48 hours later because the rust will migrate toward the corneal surface and be more accessible. Ophthalmologic consultation is recommended for deep and large corneal foreign bodies or if the central area of the visual axis is involved. Indications for topical antibiotic prophylaxis are the same as for corneal abrasions.

Corneal lacerations. Large but partial corneal lacerations should be evaluated by ophthalmology for potential closure in the operating room versus observation with medical therapy (topical cycloplegics and antibiotics; see Table 57.1), pressure patch, and possible tissue grafts. Smaller corneal lacerations can be evaluated and treated as corneal abrasions; however, topical antibiotics are routinely indicated given the depth of injury. A complication of a corneal laceration or abrasion is an infected corneal ulcer (see Corneal Ulcers and Infiltrates), which may develop days to weeks later.

Anterior Segment Injuries: Traumatic Hyphema, Iritis, Cyclodialysis, and Lens Dislocation

Clinical Features

Any blunt or penetrating injury of the eye may result in injury to the underlying anterior chamber, iris, lens, and associated anterior segment structures of the eye. A traumatic hyphema (blood in the anterior chamber from ruptured vessels in the ciliary body or iris) can present with a spectrum of severity, from microhyphema (where red blood cells suspended in the anterior chamber aqueous are only visible by slit-lamp examination), to a layered hyphema (where a layer of blood may be observed grossly in the lower anterior chamber), to a full or total hyphema (in which the entire anterior chamber is filled with blood). A microhyphema may not be visible to the naked eye but will be associated with peri-limbal conjunctival injection (ciliary flush) and either an abnormal or dilated pupil size, the latter known as traumatic mydriasis (Fig. 57.9). Patients may experience blurry vision and photophobia (ciliary spasm) from a simultaneous traumatic iritis (iridocyclitis). A traumatic hyphema from a blunt injury may also be associated with a cyclodialysis, a tear in which the ciliary muscle is avulsed from a scleral spur.[7]A blunt injury to the eye can also weaken the lens zonule complex, resulting in a lens dislocation (Fig. 57.10A). Predisposing factors for lens dislocation include Marfan's syndrome, homocystinuria, and myopia. Patients may complain of monocular diplopia, distorted images, and blurred vision, and have other signs related to the trauma, such as traumatic mydriasis, iridocyclitis, and hyphema.

Differential Diagnoses

Acute glaucoma may present with similar symptoms but only rarely occurs as a result of trauma. As with any eye injury, globe penetration is a concern and is best evaluated using fluorescein dye and a slit lamp examination.

Diagnostic Testing

A diagnosis of a traumatic hyphema can often be missed without the illumination and magnification with a slit lamp. One sequela is increased IOP and, as long there are no signs of globe rupture, the pressure should be measured. An elevated IOP occurs up to 3 days after the initial injury in approximately one-fourth of patients; it is typically self-limited, but in certain instances, it can persist and lead to optic nerve injury and vision loss. Photophobia in the injured eye, especially if occurring on the illumination of the opposite eye, strongly suggests traumatic iritis. A cyclodialysis will be evident on slit-lamp examination as a separation of the edge of the iris away from the limbal margin.

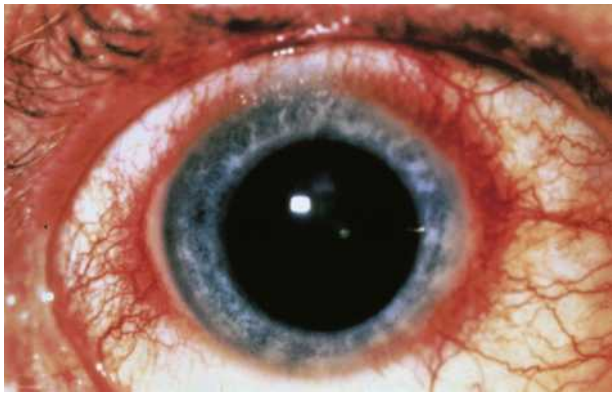


Fig. 57.9 Ciliary Flush. Note that conjunctival injection is most prominent immediately around the limbus. (Courtesy Douglas Brunette, MD.)

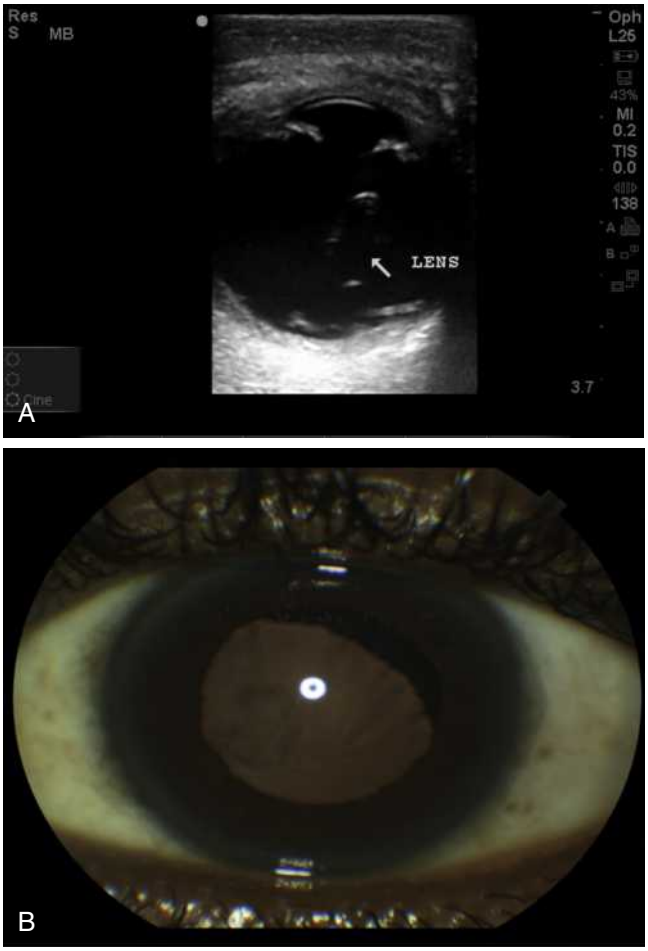


Fig. 57.10 (A) Ocular ultrasound showing lens dislocation. (B) Dislocated lens with edge visible. (A, Courtesy Douglas Brunette, MD. B, Courtesy Jeffrey Lee, MD, University of California San Diego.)

A lens dislocation may be evident on slit-lamp examination; one may see the edge of the natural lens (which is normally not visible whether or not the patient is dilated) (see Fig. 57.10B), phacodonesis (shimmering of the lens with eye movement), and iridodonesis (shimmering of the iris with eye movements), which are evidence that the lens zonules have been compromised. A displaced crystalline lens may also be visible on ultrasound (see Fig. 57.10A). Using a large amount of gel will minimize pressure from the higher resolution ultrasound probe on the eye.[8,9] Depending on the lens location, additional findings including increased IOP, corneal swelling, and intraocular inflammation may be present.

Management and Disposition

Traumatic iritis, hyphema, and cyclodialysis. With isolated traumatic iritis, the primary goals of treatment are minimizing scarring, decreasing inflammation, and pain relief. This is often best achieved with a paralytic agent for the iris and ciliary body (e.g., homatropine or cyclopentolate; see Table 57.1). Topical ophthalmic steroid drops (e.g., prednisolone acetate; see Table 57.1) are considered in cases where significant posttraumatic inflammation is present; however, use caution in cases of corneal abrasions. Close follow-up with ophthalmology within 48 hours is warranted to ensure the injury does not result in other ocular issues, such as glaucoma, corneal damage, and hypotony.

Both easily visible (see Fig. 57.8) and subtle traumatic hyphema deserve attention in follow-up to help minimize the likelihood of long-term complications. These complications include corneal staining and elevated IOP, which should be monitored to ensure proper resolution. In the past, recommended treatments for hyphema included strict bedrest with the head of the bed elevated at least 30 degrees, which presumably allows blood to settle and filter out inferiorly, and restriction of work requiring near-vision since accommodation may stress already injured blood vessels. However, there is no evidence that strict bedrest has any effect on outcome or that the head of the bed position affects resorption rate in a consistent manner, so a patient with an uncomplicated hyphema can be discharged home with gentle ambulation allowed, with the head of the bed elevation recommended with large hyphemas to prevent clotting in the visual axis and to help rehabilitate vision more effectively.[10,11] The recommendations for pediatric patients with small, uncomplicated traumatic hyphema are identical. In these cases, hospital admission is not warranted.[12] Admission is recommended, however, for patients with hyphema greater than 50% as large volumes of blood can lead to severely high IOP and permanent corneal damage. Additionally, patients with sickle cell trait, in whom sickling of red cells in the naturally hypoxic and acidotic anterior chamber prevents egress of aqueous humor and blood products, should also be observed in the hospital. Finally, patients who are poorly compliant, take anticoagulants, or likely to be lost to follow-up should initially be managed as inpatients. Topical and oral agents to lower IOP are appropriate, but carbonic anhydrase inhibitors should be avoided in sickle cell patients. Guidance on the use of antifibrinolytics is not clear. On the one hand, systemic or topical aminocaproic acid and tranexamic acid have been shown to reduce the rate of recurrent bleeding; however, they have not been shown to affect final visual acuity and may reduce the rate of clearance of the hyphema.[10] Initiation of these treatments is best done in consultation with an ophthalmologist.

For patients discharged with a traumatic hyphema, next-day follow-up with an ophthalmologist is recommended to assess IOP and to evaluate for indications for urgent paracentesis and washout of the anterior chamber or an emergent trabeculectomy or shunting surgery. Inability to clear the hyphema, uncontrolled IOP, or rebleeding (which occurs in 6% to 33% of patients within 2 to 5 days) typically require intervention.[10,13] Patients with 20/200 vision or less in whom a rebleed might go unnoticed or with elevated IOP should be followed for 3 days to identify these developments. Patents with underlying traumatic iritis may be prescribed cycloplegics (homatropine; see Table 57.1), but there is little evidence to support their use for hyphema alone. Eye patching is postulated to prevent photosensitization of the corneal endothelium by protoporphyrin, a blood product, but it has not been shown to improve outcome and is not routinely recommended.[10]

The patient with a cyclodialysis can be treated with topical cycloplegics (see Table 57.1) to relax the iris and ciliary body and be referred to an ophthalmologist for routine outpatient follow-up. Small tears tend to resolve spontaneously and can be managed conservatively, whereas large ones may be permanent or require surgery to correct.

Lens subluxation and dislocation. Lens subluxations or dislocations can be vision-threatening emergencies and should be evaluated by an ophthalmologist in the ED for potential medical or surgical treatment.

Posterior Segment/Ocular Injuries: Commotio Retinae, Retinal Detachment, Intraocular Foreign Body, and Perforated Globe

Clinical Features

A more significant mechanism increases the possibility of a deeper ocular injury including commotio retinae, a retinal or vitreous hemorrhage, a retinal detachment or tear, an intraocular foreign body, and a perforated globe.

Commotio retinae, also known as *Berlin's edema,* most often occurs after ocular trauma that results in bony injury to the orbit. In one series, it was diagnosed in approximately 6% to 13% of patients who had surgically treated orbital blowout fractures.[14] With a retinal or vitreous hemorrhage, patients can experience variable vision compromise ranging from dark floaters to vision blackout. A retinal detachment can present with floaters, flashes of light (photopsia), or both and may progress to a curtain-like blocking of the patient's vision as it evolves into a retinal detachment. The retina has no pain receptors and patients are usually pain-free.

An important evaluation after blunt trauma to the orbit is to determine if a globe perforation or intraocular foreign body is present. Besides pain and decrease in vision, other signs (loss of anterior chamber depth, irregular or tear drop-shaped pupil, blood in the anterior chamber, 360 degrees subconjunctival hemorrhage, or prolapse of uveal tissue) should be noted. When traumatic vector forces are not enough to blow out the orbit, they are typically re-directed to the globe itself. Muscle insertion sites and the limbus are the most common sites of scleral rupture because these are the thinnest areas (see Fig. 57.5). Significant collateral damage to adjacent structures such as the lens, retina, uvea, and optic nerve can also occur. The patient with a globe injury may develop sympathetic ophthalmia, a vision-threatening autoimmune response to the remaining healthy eye triggered by the exposure of the previously naïve immune system to intraocular contents from the ruptured eye.

Differential Diagnoses

In addition to retinal detachment, sudden painless alterations in vision or vision loss can stem from primary medical conditions such as central retinal artery and central retinal vein thrombosis. Embolic carotid artery disease and retinal arteritis, as seen with giant cell (temporal) arteritis, are additional considerations.

Diagnostic Testing

Test visual acuity in all patients with traumatic eye injuries. In some cases of retinal injury, visual acuity testing can be normal. Commotio retinae may appear as whitening of the retina on fundoscopy. The diagnostic approach to retinal detachment is discussed in more detail later in this chapter. In instances of a penetrating injury to the globe or orbit, careful evaluation for a retained foreign body is important. Initially, it may not be clear if a foreign body is intraocular or just intraorbital. If the suspicion for an intraocular foreign body or ruptured globe is high but the examination cannot be performed with minimal manipulation, an orbital CT scan can provide information about the structural integrity of the globe and orbit as well as the location of foreign bodies; however, because it has a sensitivity of between 56% to 75% for open-globe injury, CT cannot be relied upon alone, and formal surgical exploration may be needed.

Management and Disposition

Retinal injuries. A traumatic retinal detachment, if detected and treated early before the macula is involved, carries a good prognosis. Approximately 10% of all retinal detachments are caused by blunt trauma. The management of retinal detachment and vitreous hemorrhage is discussed in more detail later in this chapter. The decreased visual acuity from commotio retinae is self-limited and resolves in a few weeks. Evaluation by an ophthalmologist in the ED is recommended, however, because the commotio can mask a retinal tear.

Intraocular foreign bodies and globe rupture. For patients with a possible globe perforation (open globe) with or without an intraocular foreign body, examine the eye with as little manipulation as possible and, once diagnosed, stop the examination, cover the eye, and consult an ophthalmologist emergently. Any additional examination is only performed in the operating room. In anticipation of potential surgery, place a protective shield over the affected eye, administer a tetanus booster, and provide medications to control pain and nausea. The incidence of endophthalmitis (an infection of the globe; see Infectious Conditions later) following open-globe injury ranges from 2.6% to 30%. Administer systemic antibiotics that are active against *Staphylococcus aureus, Bacillus* species, *Pseudomonas* species, gram-negative organisms, and anaerobes, keeping in mind that *Staphylococcus* species are most common.[15] Cefazolin 1 g IV or vancomycin (dosed based on weight and renal function as per pharmaceutical guidelines) and a fourth-generation fluoroquinolone are good first-line agents. Foreign bodies, especially non-metallic foreign bodies, pose the highest risk of infection.[15]

In general, intraocular foreign bodies need to be removed. For intraorbital foreign bodies, the type and location of the material influence the necessity to remove them. Removal of inert plastic, glass, and metals may cause more damage than their permanent presence, whereas organic foreign bodies typically need to be removed because of their propensity to cause infection. Siderous oxidation of ocular tissues is a late complication of iron-containing intraocular foreign bodies and can lead to visual loss. Chalcosis, a sterile inflammatory reaction to copper-containing compounds, may occur, necessitating removal of the offending object.

It is controversial whether succinylcholine is contraindicated during rapid sequence intubation in a patient with a suspected open-globe injury because of the theoretical possibility of a rise in IOP from succinylcholine causing further extrusion of globe contents.[16,17] Where time and circumstances permit, we recommend rocuronium over succinylcholine for intubation of patients with open-globe injuries; however, there is no compelling evidence that succinylcholine causes harm.

Retrobulbar and Peribulbar Injuries: Orbital Wall Fracture, Retrobulbar Hemorrhage, and Optic Nerve Injury

Clinical Features

Trauma to the eye can result in disruption to tissue around the globe and should be suspected based on the mechanism and recognition of specific clinical features. Clinical signs that may indicate an acute orbital wall fracture include ecchymoses, tissue swelling, hypesthesia of the trigeminal nerve, double or blurry vision, enophthalmos (posterior displacement of the eyeball within the orbit), and ptosis. In an orbital floor fracture, a medially hinged bony "trapdoor" fragment may have transiently displaced inferiorly, allowing herniation of orbital contents

into the maxillary sinus. Associated globe injuries occur in 10% to 25% of patients with orbital floor fractures.

The triad of proptosis, ophthalmoplegia, and altered vision suggests a retrobulbar hemorrhage, which can threaten the patient's vision and be present without an orbital wall fracture. The orbit is essentially a continuous cone-shaped fascial envelope with rigid bony walls on all sides (except anteriorly where the orbital septum forms an inflexible boundary), in which there is little room to accommodate an increase in volume.[18] A retrobulbar hemorrhage from a ruptured infraorbital or ethmoidal artery occurring with intact orbit walls will increase intraorbital pressure and cause an orbital compartment syndrome, resulting in ischemia of the optic nerve and retina. Blunt trauma can also cause a direct optic nerve injury, causing decreased visual acuity or vision loss.

A rare complication of an orbital fracture or retrobulbar injury is an oculocardiac reflex from pressure exerted on the periorbital soft tissues. An afferent signal via the trigeminal nerve and efferent signal via the vagus nerve can trigger bradycardia, junctional rhythm, or even asystole, with nausea and vomiting, and is potentially fatal if unresolved.[19,20]

Differential Diagnoses

Orbital cellulitis, an infectious process involving the orbital compartment posterior to the septum may present in a similar fashion causing pain, swelling and pain with globe movement. Fever and lack of a blunt trauma will distinguish it from traumatic etiologies. An orbital CT scan, along with clinical features, can confirm the diagnosis.

Diagnostic Testing

The diagnostic evaluation of a possible retrobulbar or orbital injury requires a thorough examination, paying particular attention to extraocular eye movements, assessing for an afferent pupillary defect (APD; Fig. 57.11), and checking facial sensation. An orbital wall fracture is most readily diagnosed with an orbital CT scan with axial and coronal fine (minimum 1.5 mm) cuts (Fig. 57.12). Less sensitive diagnostic screening tools include plain x-ray, in which suggestive signs are a bulge extending from the orbit into the maxillary sinus ("teardrop" sign) and an air-fluid level in the maxillary sinus. Bedside ultrasound can suggest a retrobulbar process when bright acoustic shadowing or subcutaneous air is seen, although sensitivity is marginal between 56% and 92%).

Clinical signs strongly suggesting a retrobulbar hematoma include the presence of three or more of the following: pain, decreased vision, proptosis with resistance to retropulsion, chemosis, limited extraocular motility, diplopia, diffuse subconjunctival hemorrhage, increased IOP, and an APD.[18] fundoscopy may reveal edema of the optic disc or retina or retinal venous congestion. A CT scan of the orbit can provide

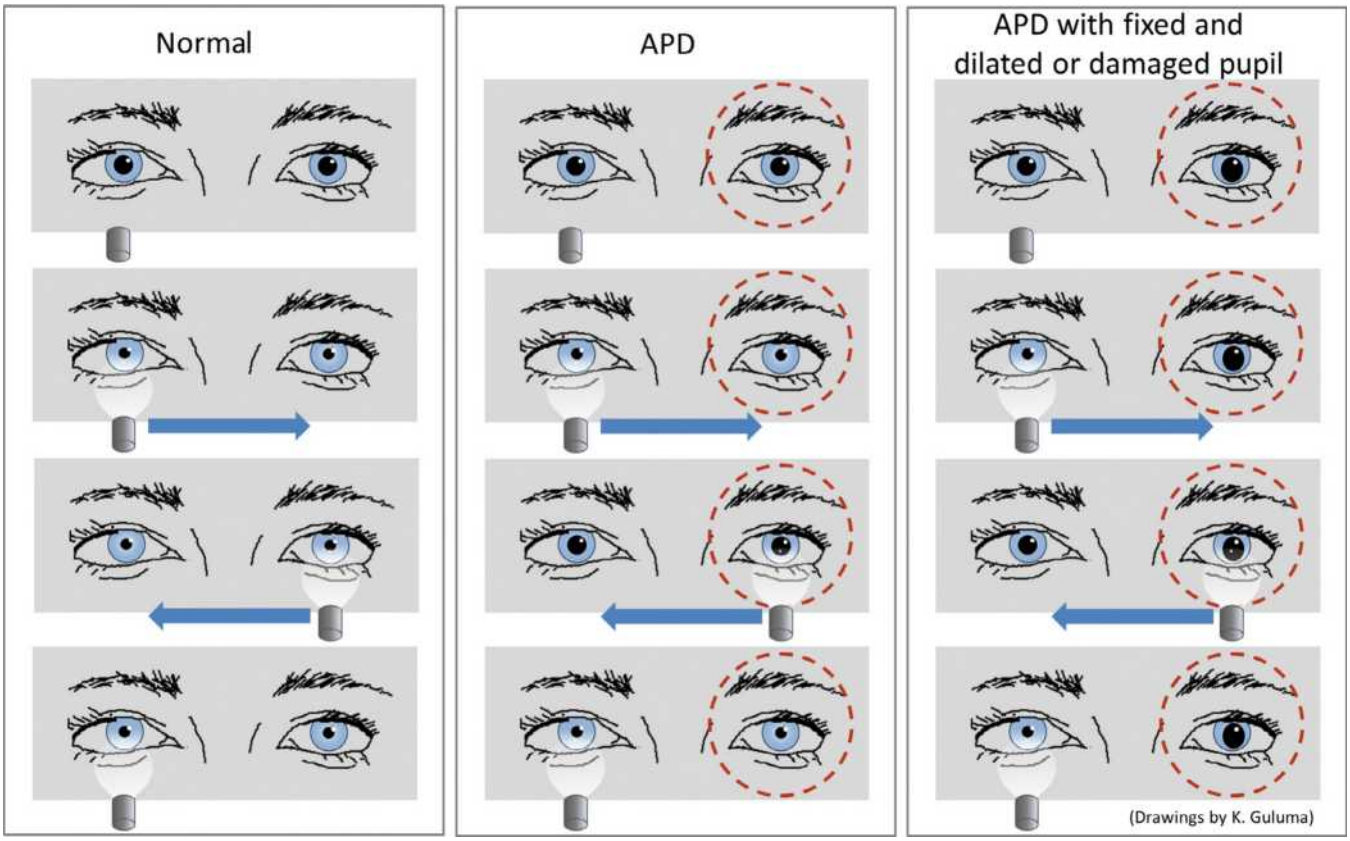


Fig. 57.11 The "swinging flashlight test" for an afferent pupillary defect *(APD),* which is otherwise known as a *Marcus Gunn pupil*. Normally *(panel on left),* both pupils constrict regardless of which eye is illuminated due to intact afferent stimulus into the direct and consensual pupillary light reflexes. With an APD *(panel in the middle),* the pupils dilate upon "swinging" the flashlight to the pathological eye with dysfunction in the retina or optic nerve *(dashed circle)* because of a sudden loss of afferent stimulus into light reflexes. With a fixed and dilated or damaged pupil *(panel on the right),* the same will hold true, except that the damaged pupil may not react due to an intrinsic problem, regardless of the presence of an APD. In each condition, whether normal or with an APD, the pupillary findings will reverse on swinging the flashlight back across to the other eye. The flashlight should be held over each eye for at least 3 seconds to ensure time for a response.

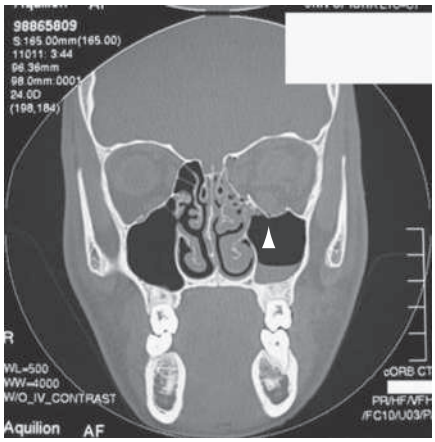


Fig. 57.12 Facial computed tomography (CT) scan showing left inferior orbital fracture with blood in the maxillary sinus. (Courtesy University of Iowa Department of Ophthalmology, http://webeye.ophth.uiowa.edu/eyeforum/Images/floorfx_08232004.jpg.)

additional evidence if clinical findings are inconclusive. However, if there is significant suspicion, treatment should not be delayed because vision loss can be permanent.

An optic nerve injury can coexist with a retrobulbar hematoma, and clinical findings may not necessarily differentiate whether there is compression or transection. Optic nerve injury may manifest as a decrease in visual acuity, visual field deficit, a relative APD (Marcus Gunn pupil), or a change in the appearance of the optic nerve. The optic disc can appear normal or swollen. A CT scan can help determine the nature and degree of optic nerve injury.

Management and Disposition

Orbital wall fractures. Prophylactic antibiotics are commonly administered for orbital wall fractures that extend into an adjacent sinus, although there is no scientific evidence supporting their use outside of intra-operative administration.[21] Antibiotic prophylaxis is warranted in patients with coincident sinusitis seen on CT scan because this increases the risk of developing orbital cellulitis. The patient should be instructed to avoid exerting Valsalva maneuvers and nose blowing and should be prescribed nasal decongestants, such as pseudoephedrine 30 mg every 6 hours, to decrease the risk of orbital emphysema. Lastly, to improve healing and decrease swelling, ice packs to the orbit for at least 48 hours is recommended.

Some ophthalmologists use steroids to reduce swelling; however, this is a case-by-case decision. Clinical findings that warrant urgent surgical exploration include pediatric trapdoor fractures, CT evidence of entrapment with associated diplopia, gaze restriction, or a non-resolving oculocardiac reflex. Early enophthalmos greater than 2 mm; large (>2 cm^2) defects of the orbital floor or medial wall may indicate urgent exploration, but recent evidence suggests delayed management is reasonable.[22] Outside of these indications, persistent diplopia and cosmetic concerns (such as, enophthalmos) are generally not addressed until the swelling subsides after 7 to 10 days. Patients can be discharged for reevaluation by an ophthalmologist in 1 to 2 weeks. Children with orbital wall fractures are a special consideration because they are more predisposed to buckling "green-stick" fractures of the orbital wall and develop fibrosis and shortening of the affected muscle within a couple of days, affecting ocular function; thus, refer children with orbital wall fractures to an ophthalmologist within 1 to 2 days.

Retrobulbar hemorrhage. The loss of vision associated with a retrobulbar hematoma is thought to be irreversible within 60 to 100 minutes after the onset of ischemia. Emergent ophthalmologic consultation for decompression is required. The time interval for decompression does not start with the injury but at the time at which the intraorbital compartment pressure from the hematoma reaches a pressure critical enough to start to cause vision loss. Use IOP-lowering agents to temporize compartment pressure until surgical decompression can occur. These include intravenous (IV) carbonic anhydrase inhibitors, topical beta-blockers, alpha agonists, and in some cases 1 to 2 g of IV mannitol per kilogram. Once ischemia and vision loss sets in, time is of the essence. A lateral canthotomy may need to be performed by the emergency clinician as a temporizing, vision-saving measure if definitive decompression is going to be delayed (Fig. 57.13).[23–26]

Optic nerve injury. Once the determination of the type and degree of optic neuropathy is determined, treatment options can be considered. There is not a clear benefit from surgical decompression of orbital canal fractures that impinge on the nerve, or from steroids for traumatic optic neuropathy. Both are options to consider in conjunction with an ophthalmologist.[27]

Chemical Exposures and Glues

Clinical Features and Differential Diagnoses

Chemical burns can lead to devastating vision loss. Alkaline burns are more severe because they produce a liquefactive necrosis in which damaged tissues secrete proteolytic enzymes as part of an inflammatory response leading to cataract formation, damage to the ciliary body and trabecular meshwork, and irreversible intraocular damage in as little as 5 to 15 minutes. Acid burns are usually less severe because they cause coagulative necrosis, in which the precipitation of tissue proteins limits the depth of the injury. The one exception to this is hydrofluoric acid, which may rapidly pass through cell membranes and enter the anterior chamber.

Superglue is another chemical exposure that may present in the ED. Cyanoacrylate is often used in ophthalmological surgical procedures and is relatively nontoxic to the eye.[28] The main issues arising from superglue exposure are adhesion of eyelashes, which is difficult to reverse, and concurrent conjunctival and corneal abrasion.

Certain substances, such as detergents and solvents, can lead to epithelial injury and anterior chamber inflammation, which are treated based on examination findings (e.g., abrasion or iritis). Signs of potent chemical exposure include periorbital edema and erythema, de-epithelialized skin, and loss of eyelashes and eyebrows, corneal and conjunctival epithelial defects, chemosis, corneal cloudiness, sterile ulceration, edema, and perforation. Elevated IOP may result from damage or inflammation of the trabecular meshwork. Although a determination of the pH of the solution involved is the most important consideration, other factors in the exposure, such as temperature, amount, impact force, concentration, osmolarity, and redox potential, can greatly influence the pathophysiology of chemical tissue damage. Accessing the material safety data sheet (MSDS) of the agent involved or consulting with a Poison Center can greatly facilitate identification of the offending agent and guide the appropriate treatment. If the exposure occurred as a result of an explosion, penetrating globe injury may also be present.

Diagnostic Testing

Treatment of a chemical exposure should begin as soon as possible with copious irrigation, even prior to arrival to the ED. During the initial ophthalmic examination pay attention to the inspection of the fornices to ensure that there is no remaining chemical gel or solid material. Screen for ocular trauma facilitated by a topical anesthetic for patient comfort. With known chemical exposures, irrigation should be

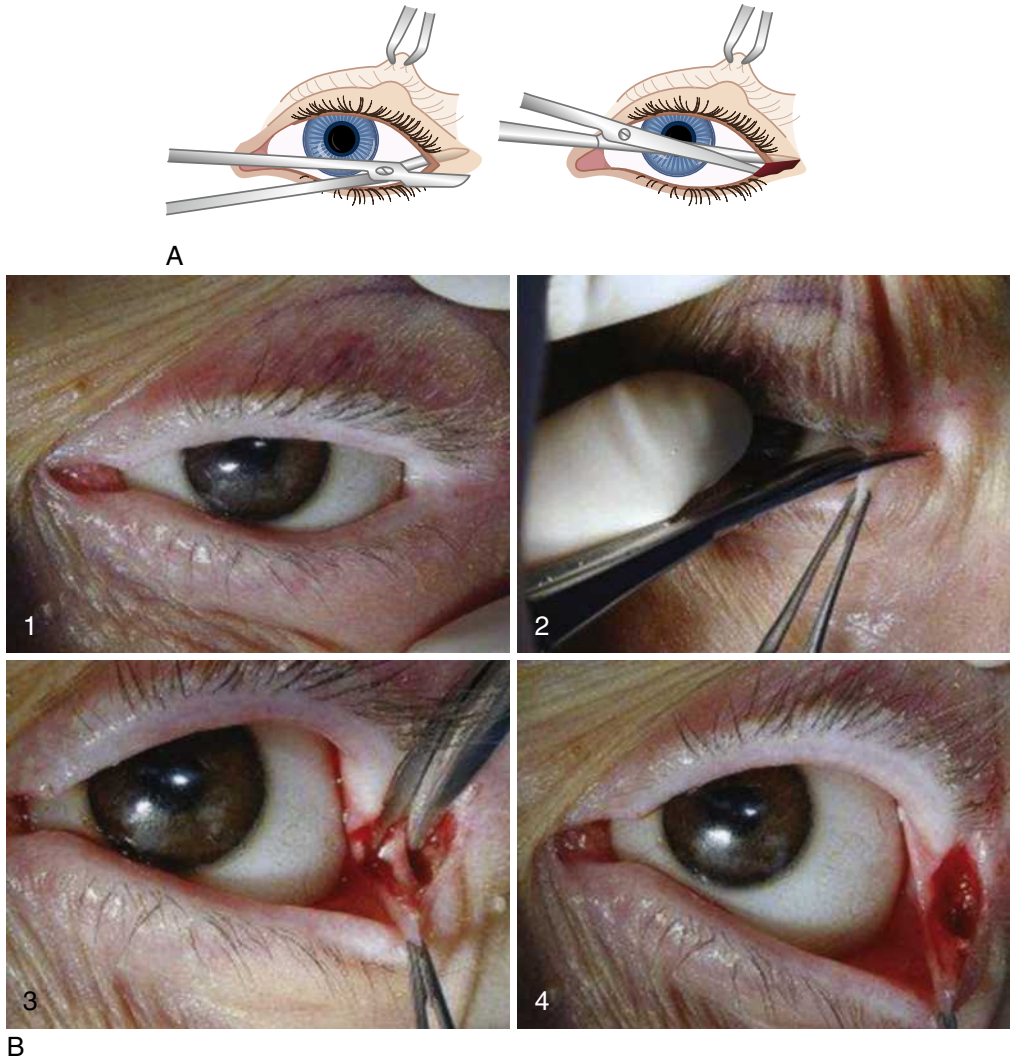


Fig. 57.13 (A) Lateral canthotomy. (B) *1,* Preoperative view of orbit. *2,* Incision for lateral canthotomy. *3,* Identification and incision of inferior canthal tendon, completing cantholysis. *4,* View after lateral canthotomy and inferior cantholysis, creating maximal immediate decompression by allowing eyeball and orbital contents to move anteriorly. (B, From Ramakrishnan VR, Palmer JN. Prevention and management of orbital hematoma. *Otolaryngol Clin North Am.* 2010;43:789–800.)

continued for a minimum of 10 minutes until a quick evaluation can be performed. This includes a pH measurement (Nitrazine paper dipped in lower lid fornix) to evaluate for acidity or alkalinity. Continue irrigation until the pH is in the neutral (7 to 7.5) range. Superglue exposure represents a special circumstance, and there are two main principles in the evaluation: (1) to separate the lids so that a detailed eye examination can be performed to remove residual superglue, and (2) to identify any corneal abrasion with fluorescein staining.

Management and Disposition

For acid or alkaline burns, perform immediate irrigation. The longer irrigation is delayed, the more irrigant will be required because the chemical can deposit within the tissue and be harder to wash away. It may take up to 20 L or more to change the pH to a physiologic level (a goal pH of 7 to 7.5). Based on animal studies, isotonic saline irrigation solutions may be ineffective at neutralizing a significant exposure to an alkaline agent (such as, sodium hydroxide) within the 20-minute time frame required to reduce injury, and buffered irrigation products specially designed for the task are significantly more effective.[29,30] This being said, initiation of irrigation with whatever solution is most readily available should not be delayed while such a solution is being obtained. Time to initiation of irrigation is the key determinant in patient outcome.[30] Ringer's lactate solution and tap water are options.[30] Tap water is more effective than saline at normalizing pH, specifically for alkali burns, and is also better tolerated than saline. It is therefore recommended in situations in which a buffered product is not available; however, since there is a concern for corneal edema due to the hypotonicity of water, Ringer's lactate is preferable if it is available.[30] The use of topical anesthesia (see Table 57.1) and assistive devices, such as a Morgan lens and an eyelid retractor, can aid in delivering the irrigation more effectively. Emergent ophthalmological consultation is warranted in significant acid burns and all alkaline burns. In chemical exposures deemed to have a low risk of significant injury (an assessment aided by contact with a local poison center) and with no signs of immediate ocular injury, the patient can be treated and referred for follow-up with an ophthalmologist in 24 to 48 hours.

For more significant chemical injuries, cycloplegics, antibiotic ointments, and occasionally steroid drops are indicated (see Table 57.1

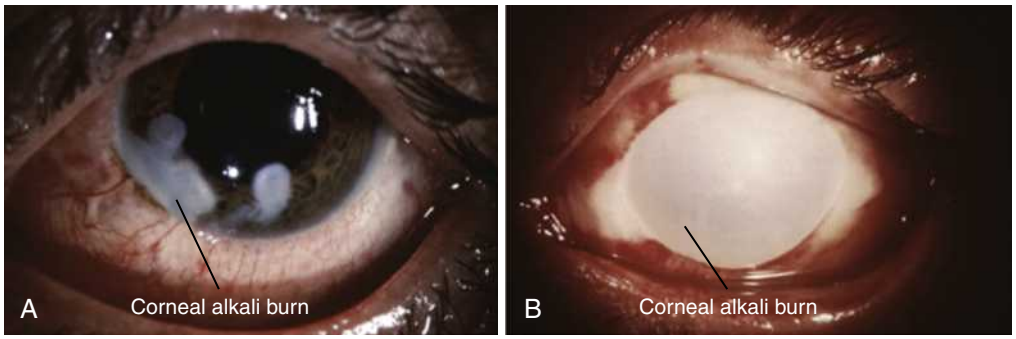


Fig. 57.14 (A) Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. (B) Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R II. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology*. 2nd ed. Philadelphia, PA: WB Saunders; 2004.)

for agents and dosing). After the acute treatment has been completed, obtaining additional history about the offending chemical can be useful in determining prognosis. Substances with a pH ranging from 2 to 12 with limited contact time tend to have a better prognosis. However, at the time of presentation, the severity and complications of the injury may not be completely known because the full extent of the injury has not yet occurred. These complications can include permanent corneal injury (Fig. 57.14), glaucoma, palpebral and conjunctival adhesions, cataracts, and retinal injury.

In the case of superglue, cyanoacrylate does not bond well to wet surfaces, and an exposure into the eye typically results in a forceful blink and extrusion of the glue onto the dry surfaces of the lid margins. Gentle traction will often separate glued eyelashes; if not, carefully trim them with Westcott scissors. Slit-lamp examination can help determine which lashes can be more readily separated. Time will help loosen the adhesions and allow for removal of the glue. If there is eyelid malposition, cutting the lashes can often allow for normalization of the eyelid position. Avoid attempts to dissolve the glue with other substances, such as acetone, because they may cause ocular damage. Ophthalmology consultation in the ED is recommended for cases in which the above measures fail to separate the lids to enable an examination, if there is residual eyelid mal-positioning, or if there is a suspected corneal abrasion from the hardened glue. If separating eyelids reveals no evidence of subsequent lid malalignment and no sign of conjunctival involvement or injury, the patient can be referred to an ophthalmologist for follow-up as an outpatient the next day.

INFLAMMATORY CONDITIONS

Foundations

Inflammatory conditions of the eye tend to present as a "red eye," which is a general term that encompasses a variety of etiologies in the conjunctiva, cornea, globe, and surrounding orbit. The clinical approach to the red eye in general, including inflammatory and infectious processes, is described in detail in Chapter 18.

The Conjunctiva and Cornea: Keratitis, Pterygium, and Pinguecula

Clinical Features

Conjunctival and corneal inflammatory conditions include allergic conjunctivitis, superficial punctate keratitis, ultraviolet (UV) keratitis (radiation keratitis), and pterygium and pinguecula. Allergic conjunctivitis, although technically an inflammatory process, is similar enough in presentation to infectious conjunctivitis that it is considered together with the infectious processes outlined later in this chapter.

Superficial punctate keratitis presents with pain or foreign body sensation, photophobia, and redness due to poor lubrication of the corneal surface from any one of several etiologies, including dry eyes, drug toxicity, and contact lens overuse. UV keratitis is a specific form of keratitis that presents when prolonged exposure to UV light results in a direct oxidative photodegradation injury to the corneal epithelium, at times severe enough to cause ulceration.[31] Sources of UV overexposure include tanning booths, reflection from snow or water, or a welder's arc. There is a latency of 6 to 10 hours before symptoms arise, at which point patients have a significant degree of pain and discomfort, photophobia, and mild conjunctival injection.

Another set of conjunctival inflammatory conditions, somewhat similar in appearance to one another, are pterygium and pinguecula. A *pterygium* is a chronic inflammatory fibrovascular hypertrophy of conjunctiva in the palpebral fissure triggered by chronic exposure to UV light. It typically grows temporally from the nasal side of the eye (or vice versa), eventually covering the cornea.[32] A pterygium can become acutely inflamed, whereupon patients experience foreign body sensation, dry eyes, and redness, but they typically do not have significant loss of vision unless the process starts to infringe upon the visual axis or becomes large enough to distort the shape of the cornea (both are very gradual and chronic processes). A *pinguecula* is of similar pathology and pathophysiology to a pterygium, resulting in similar symptoms, except that it stops at the limbus and does not enter the cornea or visual axis.

Differential Diagnoses

Squamous cell carcinoma of the conjunctiva can appear deceptively like hypertrophic conjunctiva and will be impossible to distinguish from more benign etiologies during an ED evaluation. While inflammatory conjunctival processes can occur in any age group, cancer tends to occur in elder Caucasian populations. Refer elders with new conjunctival growths to an ophthalmologist for definitive workup and management.

Diagnostic Testing

Slit-lamp examination is an integral part of the diagnostic evaluation of conjunctival and corneal inflammatory conditions. With superficial punctate keratitis and UV keratitis, multiple punctate epithelial erosions are seen upon fluorescein staining. A patient with a pterygium or pinguecula will have a visible, opaque conjunctival overgrowth on the conjunctiva of one or both eyes, typically triangular or pie-shaped, with the apex of the triangle pointing toward the pupil.

Management

Superficial punctate keratitis and radiation keratitis. Superficial punctate keratitis and UV keratitis are treated the same as corneal abrasions because all entail injury to the corneal epithelium and superficial cornea and include limited use of topical anesthetics and topical antibiotics administered for 3 to 5 days if infection is a concern (see Table 57.1). UV keratitis will typically resolve in about 24 hours or so, and given the nature of the injury, patients should be instructed to avoid damaging UV rays.[31]

Pterygium and pinguecula. Treatment of pterygium and pinguecula are similar, and it includes UV protection, lubrication, and treatment of acute inflammation with topical NSAIDs (see Table 57.1). The inflammation of a pterygium or pinguecula is usually self-limited, and encroachment into the visual axis from a pterygium is typically very gradual.

Disposition

For UV keratitis, ophthalmologic follow-up in 24 hours is recommended if symptoms have not resolved. With pterygium and pinguecula, non-emergent referral to an ophthalmologist is recommended for surgical treatment of severe cases and for evaluation of the rare coexistence of an ocular surface squamous neoplasia.

The Globe: Uveitis, Scleritis, and Episcleritis

Clinical Features

The globe can be afflicted by a variety of autoimmune conditions typically involving the uvea as a uveitis, sclera as a scleritis, or the superficial layers of the outer sclera, called episcleritis.

Uveitis is an autoimmune inflammation of the uvea, the part of the middle layer of the eye that includes the highly vascularized and pigmented iris, ciliary body, and choroid.[33] The iris and ciliary body are most commonly involved, a condition called *iritis* or *anterior uveitis,* but uveitis may rarely involve the intermediate and posterior chambers as a panuveitis. No cause is identified in 60% to 80% of people, although uveitis is one of the most frequent extra-articular features in seronegative arthritides (including ankylosing spondylitis, psoriatic arthropathy, arthritis from inflammatory bowel disease, and reactive arthritis). The typical patient with acute anterior uveitis will present with a very painful red eye, often with photophobia, and occasionally with decreased visual acuity.[34]

Scleritis is a similar autoimmune inflammatory process but involves the sclera (the tough connective tissue layer that begins at the limbus and surrounds the eye) instead of the uvea.[35] It is divided into anterior scleritis and the less frequent posterior scleritis, inflammation of the sclera posterior to the insertion of the rectus muscles. Scleritis can also be infectious but is difficult to treat and requires both systemic and local therapies.

Episcleritis, which can be confused with scleritis, is caused by inflammation in the episcleral layer of the eye rather than the deeper scleral layer. Episcleritis, unlike scleritis, is not vision-threatening and is not associated with as much discomfort.

Differential Diagnoses

Traumatic and infectious causes, specifically conjunctivitis, are the main differential considerations. Conjunctivitis has significant clinical overlap with more sinister inflammatory processes; however, more intense pain, photophobia and altered vision, as well as a history of autoimmune disease, will help distinguish a garden-variety conjunctival process from inflammation involving deeper ocular structures.

Diagnostic Testing

On slit-lamp examination, uveitis will typically reveal conjunctival injection, ciliary flush in the peri-limbal area, and cells and flare in the anterior chamber. Episcleritis can be distinguished from scleritis in that it is associated with more peri-limbal injection and has a redness that can be described as salmon pink, rather than the deeper purple hue seen in scleritis; instillation of 10% phenylephrine drops will constrict and blanch injected superficial episcleral vessels in episcleritis but will not do so to the injected deeper vessels involved in scleritis.[35] Scleritis is often more severe than episcleritis and has a much higher association with systemic diseases, such as Wegener granulomatosis, rheumatoid arthritis, and connective tissue disease. Further evaluation can be deferred to outpatient follow-up if there are no significant systemic findings.

Management

The treatment of uveitis and scleritis begins with topical corticosteroids and cycloplegics for symptoms of iridospasm (especially for anterior uveitis and scleritis; see Table 57.1). With treatment failures or severe cases, treatment is escalated to oral prednisone or IV corticosteroids followed by systemic immunomodulators (such as T-cell inhibitors or antimetabolites) and biologics (such as adalimumab or infliximab) in refractory cases.[33,34] Decisions about treatment are typically made in concert with an ophthalmologist.

Disposition

Patients with uveitis and scleritis should be referred to an ophthalmologist for close follow-up in 24 to 48 hours as scleritis has a strong association with ocular complications, including keratitis, increased IOP, and vision loss.

The Orbit: Orbital Pseudotumor, Orbital Apex Syndrome, and Thyroid Orbitopathy

Clinical Features

The orbit may be affected by idiopathic, noninfectious inflammatory processes that lead to diffuse eye pain, redness, swelling, and potentially disordered vision. These include orbital inflammatory pseudotumor and orbital apex syndrome (which are unilateral), as well as thyroid myopathy (which is usually bilateral but asymmetric).

Orbital inflammatory pseudotumor (also known as *idiopathic orbital inflammation syndrome, orbital pseudotumor,* or *orbital inflammatory syndrome*) presents as an acute to subacute tumor-like inflammation consisting of a pleomorphic cellular response and a fibrovascular tissue reaction. It is associated with various rheumatologic disorders, including Wegener granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis. In orbital apex syndrome, the apex of the orbit (through which the optic nerve, superior ophthalmic vein, and cranial nerves [CNs] III, IV, V, and VI travel) may be selectively affected similarly to cavernous sinus syndrome and superior orbital fissure syndrome. Etiologies include infection, carotid-cavernous fistula, inflammatory vasculitides (such as giant cell arteritis or Tolosa-Hunt syndrome), tumor, or infiltration as may be seen with sarcoidosis. Both orbital inflammatory pseudotumor and orbital apex syndrome may result in proptosis, chemosis, and/or conjunctival injection.[35] With orbital apex syndrome, there may be dysfunction of CNs II, III, IV, V, and VI (see Chapter 18).

Inflammatory thyroid orbitopathy from Graves disease is the most common cause of ocular myopathy in elders. It presents with oculomotor muscle swelling and restriction that is bilateral in 85% of cases. It classically affects the inferior and medial recti muscles first, leading to restriction of elevation and abduction of the eye with orbital muscle dysfunction and misalignment of the visual axes. The examination may reveal stigmata of the underlying disease process, such as lid lag or

periorbital swelling or proptosis, as well as diffuse conjunctival edema and vascular injection near the insertions of the rectus muscles.

Differential Diagnoses

Any visual disturbance coupled with periorbital pain and an ophthalmoplegia should raise concern about cavernous sinus thrombosis or an intracranial process. A history of hypercoagulable conditions, use of oral contraceptives, or any other focal neurologic finding will suggest one of these conditions. If suspected, a CT venogram is indicated, along with orbital imaging to better assess.

Diagnostic Testing

The diagnostic evaluation of a suspected orbital inflammatory process primarily involves imaging of the orbit. The optimal test is magnetic resonance imaging (MRI) of the orbits with gadolinium, which allows an assessment for enlargement or enhancement in extraocular muscles and orbital structures. Contrast-enhanced orbital CT, with fine cuts through the orbit, is a more readily available second-line option.[36]

Management

The mainstay of therapy (assuming infection is excluded) for orbital pseudotumor is systemic corticosteroid therapy, although there is increasing use of antimetabolites, cytotoxic agents, and other immunosuppressive agents.[37] Treatment of orbital apex syndrome includes management of underlying etiology (infection, neoplasm, or inflammation). These treatment choices will typically be made in concert with an ophthalmologist. For thyroid orbitopathy, the treatment of the underlying Graves disease will address many of the ophthalmological issues but may involve immunosuppressive medications, radiation, or even surgery (including orbital surgery).

Disposition

After consultation with an ophthalmologist, it is appropriate to discharge for outpatient follow-up in 24 to 48 hours.

INFECTIOUS CONDITIONS

Foundations

A critical determination in a patient with a red, irritated, or painful eye is whether or not there is an infectious process at play. This is based on clinical features, keeping in mind that the globe of the eye and the encompassing tissues of the orbit represent a pristinely organized and functional arrangement of tissue planes and glandular structures and that any disruption to these structures, whether from minor trauma, prior surgery, or inflammation, can present similarly and also predispose the patient to an infectious process.

The Conjunctiva: Allergic, Viral and Bacterial Conjunctivitis, and Ophthalmia Neonatorum

Clinical Features and Differential Diagnoses

Symptoms of conjunctivitis, whether it be allergic, toxic, or infectious, include redness, discharge, foreign body sensation, photophobia, and blurry vision.

The most common form of conjunctivitis is thought to be allergic conjunctivitis. This is not infectious per se, but it is considered in the differential diagnosis here because it often a challenge to distinguish it from a viral conjunctivitis. Allergic conjunctivitis is a type 1 histaminergic hypersensitivity reaction with red itchy eyes and clear discharge and is classically bilateral, associated with pollen and dust, and can be seasonal. In more severe cases, moderate-to-severe injection with glassy chemosis is observed. A toxic conjunctivitis, typically from topical ocular medications, may appear similar to allergic conjunctivitis; a contact dermatitis (from a trigger like eye makeup) should be suspected if there is an associated lichenified, eczematous periorbital dermatitis and edema.

Of the infectious etiologies, viral causes are most common. Viral conjunctivitis is classically preceded by a viral infection with upper respiratory symptoms, with sequential involvement of both eyes; however, many episodes of viral conjunctivitis have no preceding symptoms. Adenovirus is the most common cause and is highly infectious and easily spread by contact with fomites. The conjunctival discharge with viral infections tends to be watery and less purulent than that in bacterial conjunctivitis, although the quality of discharge cannot accurately separate viral from bacterial causes. Preauricular lymphadenopathy and follicular changes of the conjunctiva can be seen (Fig. 57.15). Viral conjunctivitis and keratoconjunctivitis can present with purulence, including having the eyelids stuck shut when awakening from sleep. Viral infections typically last 1 to 3 weeks. Epidemic keratoconjunctivitis is a highly contagious and more virulent viral conjunctivitis often presenting in epidemics, with which the patient may also complain of foreign body sensation and have mild keratitis.

Bacterial conjunctivitis is significantly less common than viral. The organisms involved include Staphylococcus species, as well as *Moraxella catarrhalis, Streptococcus pneumoniae, Haemophilus influenzae,* and rarely *Neisseria gonorrhoeae,* with an increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) conjunctivitis over the last decade. Conjunctivitis from gonorrhea classically presents with copious purulent discharge (Fig. 57.16) and carries a high risk for corneal involvement and subsequent corneal perforation.[38]

Distinguishing viral from bacterial conjunctivitis can sometimes be a challenge in the ED. A systematic review found that redness of the conjunctival membrane that is intense enough to obscure the tarsal vessels, physician-observed purulent discharge, and matting of both eyes in the morning increase the likelihood [LRs 3 to 4] of a bacterial cause, whereas inability to discern that the patient's eye is red from 20 feet away and absence of morning matting of either eye decrease the probability of a bacterial cause.[39]

What appears to be an infection of the conjunctiva may actually represent an infection of the cornea, and therefore, a slit-lamp examination is important; if signs of corneal involvement are present, a keratitis is likely (see Diagnostic Evaluation in The Conjunctiva and Cornea: Keratitis). Epidemic keratoconjunctivitis may have some mild punctate keratitis on fluorescein staining.

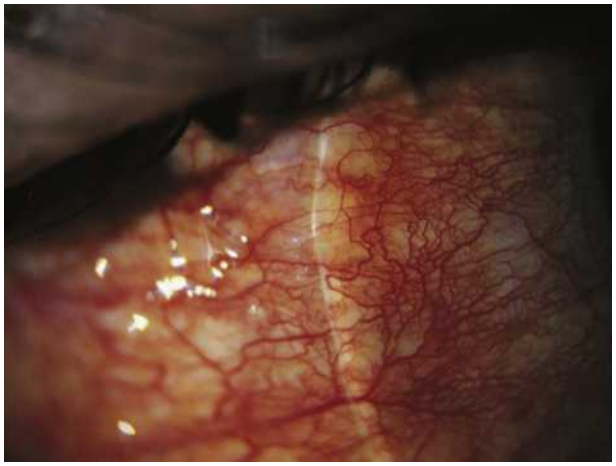


Fig. 57.15 Conjunctival Injection Resulting From Viral Conjunctivitis. (Courtesy www.tedmontgomery.com.)

Ophthalmia neonatorum is neonatal conjunctivitis that develops during the first 30 days of life. While it can be caused by allergy or chemicals, the most concerning causes are bacterial and viral infections, which present with tearing and discharge followed by scarring and blindness. The evaluation involves gram stain and cultures geared to infections such as *N. gonorrhoeae*, *Chlamydia,* and herpes simplex virus (HSV) that are transmitted from mother to infant through the birth canal. HSV may have associated corneal dendrites and lid edema. Infection with *N. gonorrhoeae* manifests within 2 to 4 days after birth (but may take up to 20 days). Examine the infant for evidence of systemic gonococcal infection.

Diagnostic Testing

Most cases of conjunctivitis are diagnosed clinically and do not require testing from the ED. In cases where *Neisseria* is highly suspected, a gram stain and culture (or a polymerase chain reaction [PCR] test as done for genital samples) can aid in the diagnosis.[40]

Management and Disposition

Allergic and viral conjunctivitis. Allergic conjunctivitis and viral conjunctivitis are usually self-limited and can be treated with supportive measures such as cool compresses. Topical antibiotics should be avoided unless there is concern for a bacterial superinfection; however, prescribe topical antibiotic ointment (erythromycin 0.5% applied two to three times daily until symptoms resolve) if there is diagnostic uncertainty. For allergic conjunctivitis, the patient should be counseled to avoid the offending agent and can be prescribed topical and systemic anti-allergy medications (see Table 57.1 for choices and dosing of topical options). Avoid medications with preservatives because they may exacerbate symptoms. Consider other etiologies if symptoms worsen after 2 to 3 days.

If inflammation is severe (with pseudomembranes or bleeding), then an ophthalmology evaluation in the ED for steroid treatment is recommended; otherwise, patients can be discharged with a referral to an ophthalmologist if they worsen or if they do not improve by 7 to 10 days. Keep children with viral conjunctivitis out of school until symptoms have resolved, which will be 3 to 5 days, keeping in mind that communicability can potentially last up to 10 to 14 days from onset of symptoms.[38]

Bacterial conjunctivitis. Although bacterial conjunctivitis is typically self-limited, most resolving in 1 to 2 weeks without treatment, topical antibiotics shorten the time to resolution.[38] Ointment is preferred given the smoothing effect on the eye and easy instillation. The prescribed antibiotics (see Table 57.1 for options) should cover the organisms mentioned previously and be taken for at least 1 week; those with the highest level of evidence for the treatment of bacterial conjunctivitis are tobramycin, ciprofloxacin, moxifloxacin, ofloxacin, azithromycin, and trimethoprim/polymixin B. Avoid gentamicin and neomycin due to toxicity. Prescribe ointment effective against *Pseudomonas* for contact lens wearers (see Table 57.1). For suspected *N. gonorrhoeae* conjunctivitis treatment involves ceftriaxone 1 g intramuscularly once or azithromycin 1 g orally if cephalosporin allergic. Saline irrigation of the affected eye(s), with concomitant empirical treatment for *Chlamydia trachomatis* infection is recommended (either doxycycline 100 mg orally bid for 7 days [preferred] or 1 gm of azithromycin orally once).[38]

Ophthalmia neonatorum. Hospitalization of neonates with blood and cerebrospinal fluid (CSF) examination may be indicated for ophthalmia neonatorum. *N. gonorrhoeae* conjunctivitis in a neonate is typically treated with a single dose of ceftriaxone 25 to 50 mg/kg up to a total dose of 250 mg intramuscularly (IM) or IV, topical erythromycin or polymyxin B–bacitracin ointment, and saline washes of the affected eye. Potential ocular chlamydial infection is simultaneously treated with topical erythromycin ointment and oral erythromycin syrup 50 mg/kg/day divided into four doses per day for 14 days. Treat suspected HSV with acyclovir IV 20 mg/kg every 8 hours plus vidarabine 3% ointment five times per day for 14 to 21 days. Evaluation for systemic involvement is indicated and ophthalmology consultation in the ED is warranted.

The Cornea: Corneal Ulcers, Herpes Simplex Keratitis, and Herpes Zoster Keratitis

Clinical Features

What appears to be conjunctivitis may actually represent an infection of the cornea. A *corneal ulcer*, also known as "ulcerative keratitis," (Fig. 57.17) is an infectious or inflammatory erosion of both the outer epithelial cell layer and the underlying stromal layer (which is the bulk of the cornea). Corneal ulcers present with pain and redness of the eye, tearing, sensitivity to light, and blurred, hazy, or otherwise decreased vision. There can also be a discharge or foreign body sensation. A corneal abrasion can become an ulcer if secondarily infected, which in turn can lead to corneal perforation if severe and untreated. Although corneal ulcers are due to infection, most of the resulting corneal injury is due to the secondary inflammation. The most common bacterial

Fig. 57.16 Purulent Discharge and Conjunctival Hyperemia Suggest Bacterial Conjunctivitis. (From Goldman L, Schaefer AI, eds. *Goldman's Cecil Medicine*. 24th ed. Philadelphia, PA: Saunders; 2012.)

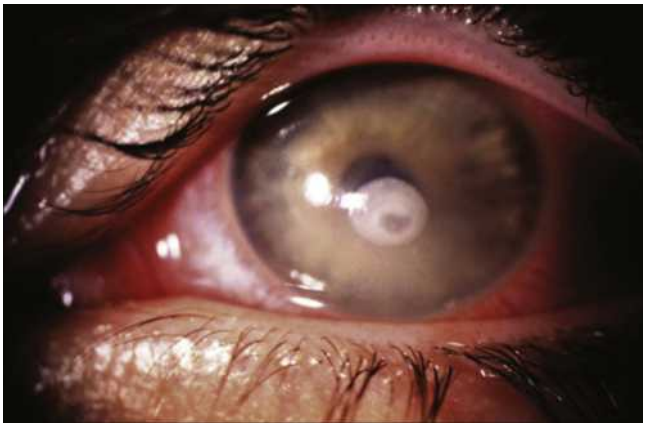


Fig. 57.17 This corneal ulcer caused by *Pseudomonas aeruginosa* occurred in a young man who wore decorative contact lenses without professional supervision. (From Yanoff M, Duker JS, eds. *Ophthalmology*. 3rd ed. Philadelphia, PA: Mosby; 2008.)

pathogens are *Staphylococcus, Streptococcus, Mycobacterium,* and *Pseudomonas*, with the latter associated with contact lens wear. Fungal pathogens are typically seen in users of corticosteroid drops and in agricultural workers who are at risk of contaminating their eyes with vegetable matter or soil.

The cornea can also be infected by viruses. Herpes simplex keratitis, one of the most common causes of viral keratitis, can produce recurrent corneal ulcers similar to herpes infections in other areas. Herpes simplex infection may be either primary or reactivation of preexisting disease. Symptoms are similar to corneal ulcers. Herpes zoster keratitis can occur in the setting of herpes zoster ophthalmicus. Herpes zoster is re-activated along the ophthalmic division of the trigeminal nerve, and eye involvement is possible. Patients will typically present with a dermatomal rash over the forehead and upper eyelid and sometimes along the nose (branch of the nasociliary nerve "*Hutchinson sign*") or even have a unilateral Horner syndrome.

Differential Diagnoses

Distinguishing a corneal from the conjunctival process is paramount but can be difficult based on symptoms alone, as both will present with pain, foreign body sensation, and conjunctival injection. Slit and Wood's lamp examinations, after fluorescein dye, will help reveal corneal defects suggestive of keratitis.

Diagnostic Testing

The foundation of the diagnostic evaluation of corneal lesions is a careful examination and biomicroscopy with the slit lamp and fluorescein staining to evaluate corneal epithelial surface disruptions. On slit-lamp examination, a corneal ulcer may appear to have more "heaped up" edges (seen with tangential lighting) than those seen with a corneal abrasion; this finding, combined with stromal edema or infiltration (whitening of the underlying or surrounding cornea), helps identify the process as an ulcer instead of an uncomplicated abrasion.

A corneal ulcer from herpes simplex keratitis may present with classic "dendritic" lesions on slit-lamp examination (Fig. 57.18), an amoeba-shaped ulceration, or have nonspecific findings such as punctate epithelial erosions, stromal whitening, and thinning of the cornea. Herpetic vesicles may be seen on the lids or conjunctiva. Herpes zoster keratitis can appear similar but will have signs of a dermatomal vesicular rash and is frequently associated with iritis, uveitis, and choroiditis. Viral cultures can help direct therapy.

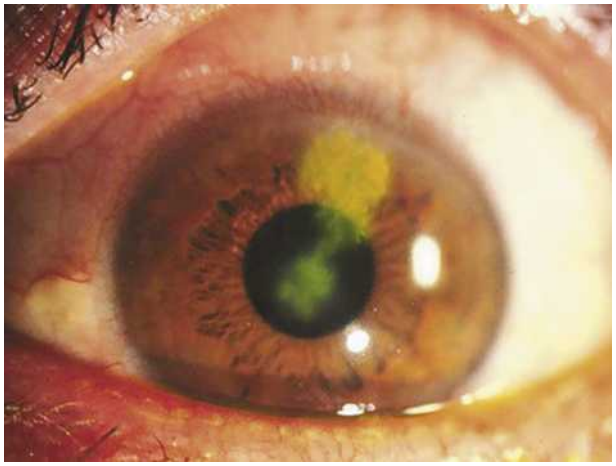


Fig. 57.18 Herpes Simplex Keratitis Infection. Note the typical dendritic pattern on the cornea. (Courtesy www.tedmontgomery.com.)

Management

Corneal ulcers and infiltrates. Topical anti-microbial therapy for corneal ulcers and infiltrates is appropriate initial therapy, although systemic antibiotics are warranted for severe infections. The fluoroquinolones (see Table 57.1) have particularly good ocular penetration; doxycycline and other tetracyclines have good anti-collagenase properties that help preserve corneal integrity. Steroids may be used to decrease inflammation but must be used with caution because they may exacerbate the clinical situation. Ophthalmology consultation in the ED is important for the management of corneal ulcers because they can rapidly progress to permanent vision loss.

Herpes simplex keratitis. Herpes simplex keratitis is the most common cause for corneal transplants in the United States. Emergent ophthalmologic consultation is recommended, and the severity of the disease will dictate treatment. Herpes simplex keratitis is treated with topical antiviral agents, such as topical acyclovir trifluridine 1% nine times a day for 14 days, ganciclovir 0.15% gel three to five times per day, or trifluridine 1% solution five to eight times per day for 14 days.[38] Topical prophylactic antibiotics, such as erythromycin ointment, and a cycloplegic agent are given if there are symptoms of iritis (see Table 57.1). Avoid topical steroids because they worsen infection. Consider systemic therapy (acyclovir 200 to 400 mg five times per day, valacyclovir 500 to 1000 mg two or three times per day, or famciclovir 250 mg twice a day for 7 to 10 days) if topical treatment is not available or if the process is severe.[38]

Herpes zoster keratitis. Herpes zoster ophthalmicus accounts for approximately 10% to 20% of all zoster cases and necessitates emergent ophthalmologic consultation. If not treated and recognized immediately, herpes zoster ophthalmicus may result in permanent vision loss. Systemic therapy is the standard of care (unlike HSV, topical antivirals have little effect). If retinal involvement occurs or the patient is immunocompromised, inpatient treatment is recommended. Higher dose antiviral agents (acyclovir 800 mg five times daily, valacyclovir 1000 mg three times daily, or famciclovir 500 mg three times daily, all for 7 to 10 days[38]) are used, and occasionally, topical steroid agents and systemic antibiotics may be added. Topical antibiotics are used to prevent bacterial superinfection of skin and lid lesions. Early treatment with antiviral therapy within 72 hours of the onset of the rash has been shown to reduce acute pain and ocular complications. Additional consideration for therapy includes pain management and aggressive lubrication to maintain a healthy ocular surface.

Disposition

Treatment of corneal infections is most often done as an outpatient with either topical or systemic anti-infective medications after consultation with ophthalmology. If ED consultation is unavailable, referral to be seen in 24 hours is recommended. Admission or transfer will typically not be needed but should be considered for severe symptoms or for patients with an inability to follow-up urgently.[41]

The Eyelids and Periorbital Area: Hordeolum, Chalazion, Dacryocystitis, Blepharitis, and Cellulitis

Clinical Features

The tissues of the eyelids and periorbital area are susceptible to any of a number of types of infections, which include those related to glandular or ductal structures, such as a hordeolum, chalazion, or dacryocystitis, or more diffuse involvement of tissue, such as blepharitis or periorbital cellulitis. Hordeola and chalazia, also known as *styes of the eyelid,* are inflamed oil glands of the eye. A *hordeolum* is caused by acute inflammation of an oil (Zeiss or meibomian) gland or hair follicle. It is typically painfully tender, erythematous, associated with swelling, and

can be infected. On the other hand, a *chalazion* is a chronic sterile, granulomatous inflammation of a meibomian gland (and may evolve from a hordeolum), which results in localized swelling that is usually not acutely painful (Fig. 57.19).

Dacryocystitis is an infection of the lacrimal sac, usually resulting from a nasolacrimal duct obstruction. It is more common in females. Symptoms and signs include pain, tenderness, swelling, and erythema over the lacrimal sac medial to the eye (Fig. 57.20). Pressure over the sac may express purulent material from the puncta. The lacrimal gland itself can also become infected, appearing as a focal area of periorbital erythema, swelling, and tenderness lateral to and above the upper eyelid.

Patients with blepharitis typically describe itching and burning of the eyelids with associated tearing and crusting. The eyelids become diffusely inflamed and thickened, with erythematous margins, and telangiectasias surrounding the eyelid margin. Blepharitis can be distinguished from a pre-septal cellulitis in that it is isolated to just the eyelid margin. Blepharitis has an association with atopic dermatitis, rosacea, and eczema.

Any one of the aforementioned focal infections, but especially dacryocystitis and blepharitis, may be complicated by a more diffuse cellulitis. Cellulitis frequently presents, however, as an individual entity, and it must be carefully distinguished as either pre-septal (also called *periorbital*) or post-septal (also called *orbital*). *Pre-septal* and *post-septal* are the most useful terms because they incorporate the most impactful clinical distinction in the ED and remove any chance of confusion as to what is being referred to in communications with consultants. Pre-septal cellulitis is limited to the tissue anterior to the orbital septum, whereas post-septal cellulitis implies the spread of the infection beyond the septum, which is concerning because it can lead to the involvement of valuable orbital structures. Pre-septal cellulitis will present with lid erythema, warmth, tenderness, swelling, and even a low-grade fever. Post-septal cellulitis will present similarly but will often have more sinister symptoms including proptosis, ophthalmoplegia, pain with eye movement, chemosis, and systemic signs of infection. In severe cases, visual loss can occur. In children, pre-septal cellulitis is often more difficult to differentiate from post-septal cellulitis because of an incompletely formed orbital septum.

Differential Diagnoses

The periorbital tissue can be swollen, erythematous, and even exhibit skin changes in a variety of conditions that are non-infectious. Renal disease leading to nephrotic syndrome may result in periorbital edema, although it is generally nontender and lacks erythema. Cutaneous allergic reactions and dermatitis commonly afflict the skin around the eyes as well as the eyelids. The skin will appear swollen and red, and the patient may even describe the areas as being painful. The most common offenders are makeup, facial moisturizers, and cleansers that are enriched with dye and perfumes.

Diagnostic Testing

For hordeolum, chalazion, dacryocystitis, blepharitis, and a cellulitis that is clearly pre-septal, the diagnosis is established on the clinical examination alone, and no additional diagnostic tests are needed. CT imaging is indicated in cases concerning an orbital abscess or when localization of an infection (pre-septal or post-septal) is difficult. In such cases, a complete blood count (CBC) may also be helpful. The primary diagnostic decision for the ED patient with a cellulitis around the eye is deciding who needs further evaluation with a CT scan. Proptosis, ophthalmoplegia, pain with eye movement, and chemosis suggest the possibility of post-septal cellulitis[42], but upward of 50% of confirmed cases may not exhibit these symptoms.[42] In these "no orbital symptom" cases, a peripheral absolute neutrophil count (ANC) of greater than 10 000 cells/μL, moderate-to-severe periorbital edema (extending beyond the eyelid margins), absence of conjunctivitis as the presenting symptom, age greater than 3 years, and recent antibiotic use have been shown to be predictors of an orbital abscess, specifically in the pediatric population. In addition, a sudden onset is more typical of post-septal orbital cellulitis. The absence or presence of a fever has little

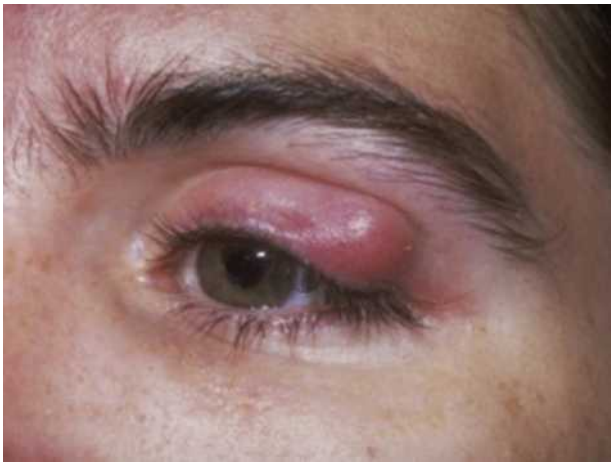


Fig. 57.19 Chalazion of the Upper Eyelid. (Courtesy www.tedmontgomery.com.)

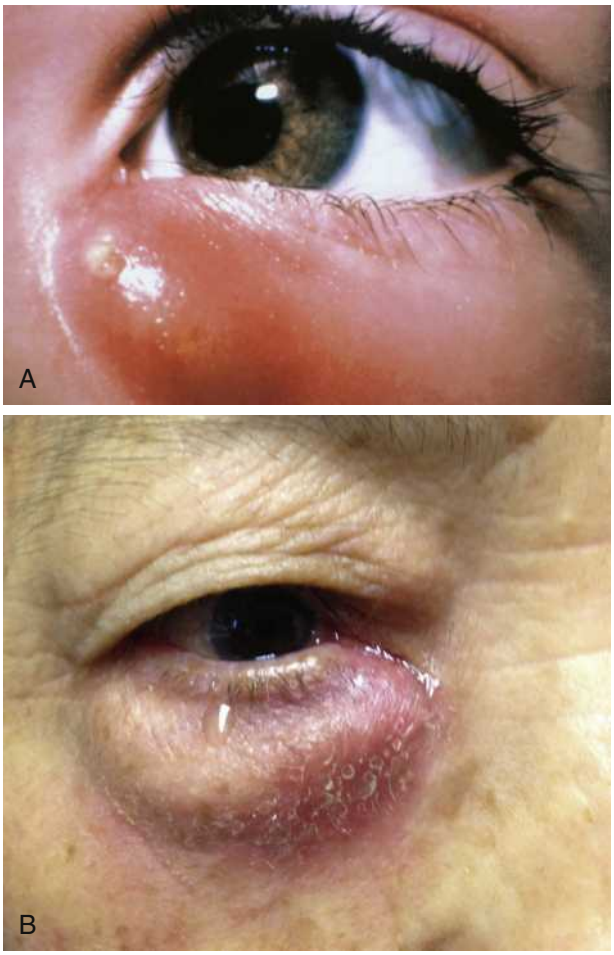


Fig. 57.20 (A and B) Dacryocystitis. (Courtesy Jeffrey Lee, MD, University of California San Diego.)

discriminatory utility. Cultures obtained from swabs of the eyes are discouraged due to the risk of misleading results from inoculation with commensal organisms, and blood cultures have little diagnostic utility.

Management

Hordeolum and chalazion. Hordeola and chalazia are typically self-limited and can resolve on their own when the glands become unobstructed. Conservative treatment to normalize the flow of the obstructed oil glands is the primary goal. This includes warm compresses for 10 to 15 minutes, three to five times a day. Treatment of an underlying blepharitis may be indicated. Referral to an ophthalmologist is recommended for incision and drainage or additional management and evaluation in nonresponsive cases. Progression to an infected oil gland may indicate the need for antibiotics, depending upon whether the process takes the form of a blepharitis or a cellulitis (see the treatment of each in the following sections).

Dacryocystitis. The most common causative organisms in dacryocystitis are *S. aureus, S. pneumoniae*, *H. influenzae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*, with an emerging prevalence of MRSA. Treatment consists of massage, warm compresses, and systemic antibiotics selected so as to include coverage of MRSA. Obtain a culture by applying gentle pressure to the nasal lacrimal duct and expressing fluid. In infants, acute dacryocystitis represents a medical emergency because it can lead to complications including orbital cellulitis. Admission is warranted for severe cases. Occasionally, drainage of the sac is required; however, this can lead to fistula formation. Dacryocystorhinostomy is the definitive treatment. The optimal time for surgery is when the infection is controlled, so arrange for patients to follow-up with an ophthalmologist in 24 to 48 hours.

Blepharitis. The initial treatment of blepharitis is conservative, designed to remove residual oils and scurf, and entails warm massage with a moist washcloth about for 10 to 15 minutes three to five times a day and cleaning the lid margins twice a day with a cotton swab soaked in mild baby shampoo. Because blepharitis arises as a result of an inflammatory process, there is potential for bacterial overgrowth and superinfection (*Staphylococcus epidermidis* primarily, but also *Propionibacterium acnes,* and corynebacteria), and—if there is a concern for infection—topical azithromycin, erythromycin, or levofloxacin (see Table 57.1) can be considered.

Periorbital cellulitis. If pre-septal cellulitis in a patient with no other underlying medical conditions is diagnosed with certainty, the patient can be discharged on oral antibiotics directed toward the most common organisms, *Streptococcus* and *Staphylococcus,* keeping in mind that orbital cellulitis tends to be polymicrobial. The incidence of MRSA, although still relatively low in children, is rising. It is prudent to tailor antibiotic therapy so it includes this species, especially in adults.[43,44] A treatment option is a beta-lactam antibiotic, such as oral amoxicillin-clavulanate, 875 mg two times daily for 10 to 14 days for adults (or 45 mg/kg/day divided in two doses for 10 to 14 days for children), and in considering MRSA, adding clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX). In children, the diagnostic uncertainty between pre-septal and orbital cellulitis dictates more aggressive management of any periorbital infection.[45] An IV second- or third-generation cephalosporin, such as cefuroxime or ceftriaxone, is recommended. Other IV antibiotic options include ampicillin/sulbactam (Unasyn) or a combination of a first-generation cephalosporin with metronidazole.

Disposition

Patients with hordeola and chalazia can be discharged to follow-up with an ophthalmologist if symptoms persist. Dacryocystitis, pre-septal cellulitis, and blepharitis are generally treated as outpatients with either referral to ophthalmology or an evaluation by the patient's primary care provider in 24 to 48 hours. In severe cases of pre-septal cellulitis, or with any concern of post-septal cellulitis, hospitalization with IV antibiotics is indicated to avoid complications, such as subperiosteal abscess, orbital abscess, meningitis, osteomyelitis, and cavernous sinus thrombosis.

The Globe: Endophthalmitis

Clinical Features

Endophthalmitis is an infection involving the globe itself. Pain and decreased vision are the primary symptoms. Examination findings include decreased visual acuity, chemosis, hyperemia of the conjunctiva, and intraocular inflammation (evidenced by hypopyon) (Fig. 57.21). The most common etiology of endophthalmitis is recent intraocular surgery. Other etiologies include previous perforated globe and endogenous infection. Early diagnosis and management are paramount to improve outcome.

Differential Diagnoses

Endophthalmitis and uveitis have significant clinical overlap. Recent ocular surgery or risk factors predisposing the patient to endocarditis suggest globe infection in contrast to autoimmune inflammation.

Diagnostic Testing

Endophthalmitis can be difficult to distinguish from uveitis, and the two have vastly different treatments and acuity. An ultrasound of the eye (done in much the same way as to evaluate for retinal detachment) can be performed. Endophthalmitis is suggested by numerous heterogeneous strands and membranes in a vitreous that would otherwise be uniformly hypoechoic.

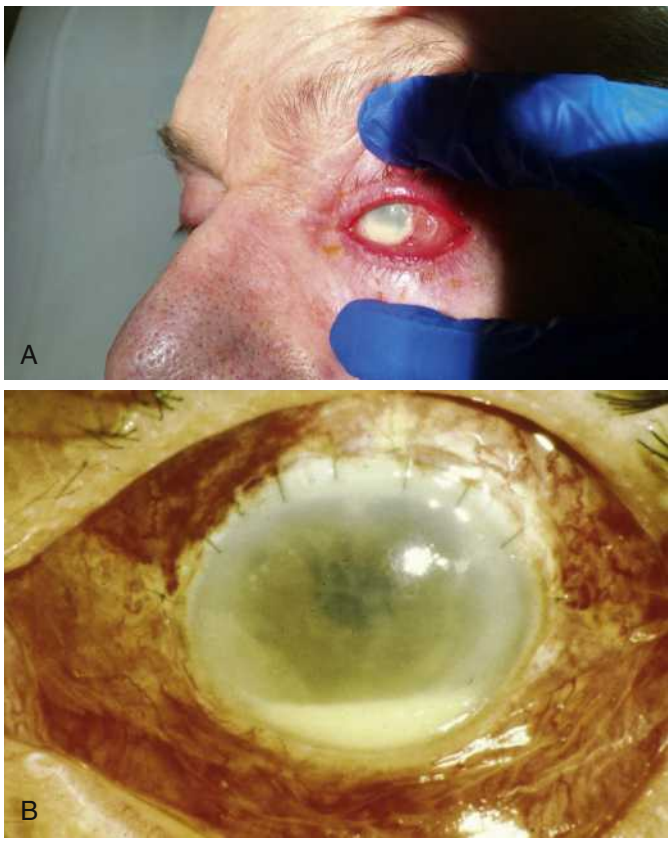


Fig. 57.21 Eye with endophthalmitis, illustrating a hypopyon (pus in the anterior chamber). (Courtesy Kama Guluma, MD, University of California San Diego.)

Management

Endophthalmitis is a medical emergency that must be promptly treated. Systemic antibiotics are not effective (although commonly administered), and intravitreal antibiotics should be given.[46] The evaluation and treatment should be done in consultation with an ophthalmologist who can administer the intravitreal antibiotics at the bedside and perform a vitrectomy (removal of infected vitreous akin to draining an abscess) in the operating room if needed. Gram-positive pathogens, especially coagulase-negative staphylococci, are most common in post-cataract endophthalmitis; *Candida* followed by streptococci and staphylococci are most common in post-keratoplasty cases; coagulase-negative staphylococci, Bacillus species, streptococci, gram-negative bacilli (e.g., Pseudomonas and Klebsiella) are prominent in post-traumatic endophthalmitis; and *S. aureus*, streptococci (viridans, *S. pneumoniae*, and group A and B streptococci), and gram-negative bacilli (*Escherichia coli* and *Klebsiella pneumoniae*) are found in endogenous endophthalmitis associated with endocarditis.[46]

Disposition

Patients with endophthalmitis should be admitted to the hospital for continued treatment, infectious disease consultation, and continued antibiotic therapy.

ACUTE ANGLE-CLOSURE GLAUCOMA

Foundations

Aqueous humor provides structural support to the eye and delivers oxygen and nutrients to the avascular lens and cornea. It is produced by the ciliary processes, passes from the posterior chamber to the anterior chamber through the pupillary aperture, and then is transported into the trabecular meshwork located at the anterior chamber angle formed by the junction of the root of the iris and the peripheral cornea. This trabecular meshwork serves as a one-way valve and filter for the aqueous humor as it enters into the canal of Schlemm, which in turn drains into episcleral veins. IOP is normally between 10 and 20 mmHg and is determined by the rate of aqueous humor production relative to its outflow and removal.

Clinical Features

Glaucoma is the most common optic neuropathy in adulthood. It is characterized by visual field loss and death of retinal nerve fibers. Glaucoma usually, but not always, is associated with elevated IOP. The two most common and important forms of glaucoma are primary open-angle glaucoma and acute angle-closure glaucoma.

Primary open-angle glaucoma is a chronic condition characterized by asymptomatic elevated IOP (but IOP may not always be elevated), and an enlarged ratio of the diameter of the optic cup to the diameter of the optic disc (termed *cupping*) and peripheral visual field loss. Patients may be on topical ophthalmic medications designed to improve aqueous outflow. It is not typically a condition that results in an ED visit, although it can lead to complete blindness over time.

Acute angle-closure glaucoma is an ocular emergency and may present in a patient with no prior knowledge or history of glaucoma. A variety of rare conditions, such as tumors or neovascular processes, can predispose a patient to this, but the more common etiology is an anatomically shallow anterior chamber that further narrows with aging as the lens enlarges. Acute symptoms are often precipitated by pupillary dilation from being in a low-light environment or taking an anticholinergic or sympathomimetic medication. This transient contraction of the iris crowds the angle ("pupillary block") and continued formation of aqueous without adequate drainage leads to a sudden increased IOP. This causes the iris to bulge forward, further inhibiting outflow, and eventually compromising arterial flow into the eye.

The patient with acute angle-closure glaucoma typically presents with severe unilateral eye pain, redness, and blurred vision with "halos," as well as nausea, vomiting, and headache. On examination, the pupil may be moderately dilated and unreactive to light. The anterior chamber is shallow, often visualized with illumination from the side by a penlight, the conjunctiva injected, and the cornea cloudy. (Fig. 57.22). The IOP is significantly elevated which can lead to ischemia of the optic nerve, retinal nerve fiber layer, and even the avascular anterior portion of the lens. Sustained elevation in IOP can cause permanent corneal and optic nerve damage and cause the peripheral iris to adhere to the trabecular meshwork, forming anterior synechiae and an irreversible occlusion that only can be corrected by surgery.

Differential Diagnoses

Cataracts will also result in corneal clouding and a multitude of traumatic and infectious conditions will result in a painful red eye, often with reduced vision. Cataracts are generally painless. The suddenness of symptom onset and the conditions under which the symptoms began will help distinguish acute angle-closure glaucoma from other conditions. Primary headache conditions such as paroxysmal hemicrania may present with autonomic symptoms and sometimes with eye symptoms, such as tearing. A thorough eye examination is required to ensure acute glaucoma is not missed.

Diagnostic Testing

IOP measurement, using a tonopen, can confirm the diagnosis. In acute angle-closure glaucoma, IOP is typically higher than 30 mm Hg, although patients may be symptomatic at lower pressures.

Management

Treatment of acute angle-closure glaucoma begins with medications used to lower the IOP by reducing the production and increasing the outflow of aqueous humor (Box 57.1) and then proceeds to definitive treatment of the anatomical abnormalities that predisposed the patient to elevated IOP. Emergent ophthalmology consultation is necessary.

Definitive treatment for anatomic abnormalities includes laser peripheral iridotomy. This is undertaken within 24 to 48 hours for persistent symptoms despite medical management.

Disposition

Obtain ophthalmology consultation for acute angle-closure glaucoma. Patients will often need to be observed in the ED or hospital in order to

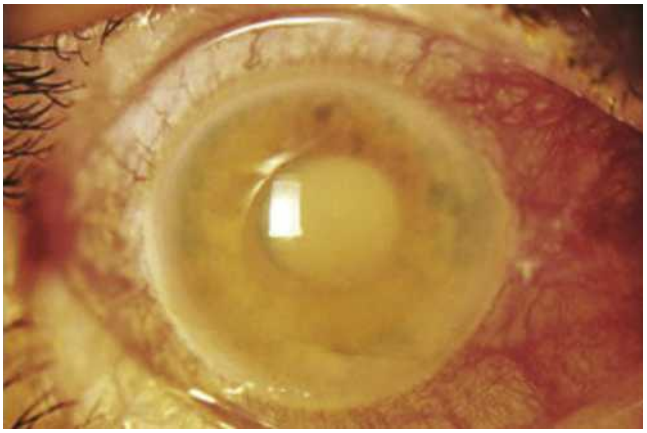


Fig. 57.22 Acute Angle-Closure Glaucoma. (From Yanoff M, Duker JS, eds. *Ophthalmology*. 3rd ed. Philadelphia, PA: Mosby; 2008.)

BOX 57.1 Drugs Used to Treat Acute Glaucoma

Drugs that reduce the production of aqueous humor
- Prostaglandins (latanoprost 0.005%—1 gtt)
- Topical beta-blocker (timolol 0.5%—1 to 2 gtt)
- Carbonic anhydrase inhibitor (acetazolamide 500 mg IV or orally)
- Systemic osmotic agent (mannitol 1–2 g/kg IV over 45 min, to minimize cerebral effects, and typically reserved if topical medications and acetazolamide do not work within 1 hour)

Drugs used to increase the outflow of aqueous humor
- Topical selective alpha agonists (like alphagan-alpha 2 specific-1 gtt)
- Miotics (pilocarpine 1%–2%)
- Topical steroid (prednisolone acetate 1%—1 gtt every 15–30 min four times, then every hour)

track IOPs. Final disposition is made in conjunction with an ophthalmology specialist.

PRIMARY DISORDERS OF VISION

Foundations

The process of visual perception is an orchestration of light refraction by the cornea and lens, signal transduction by the retina to generate electrical impulses, and transmission of those impulses through the optic nerve to be processed in each occipital cortex, being split and crossed at the chiasm along the way (Fig. 57.23). Primary disorders of vision can be caused by a derangement anywhere in this process and may present as blurred vision, a focal disturbance in the visual field (dark objects, floaters, flashing lights), a visual field cut, or frank vision loss. Double vision has a very distinct presentation and is addressed in Chapter 17.

The history enables a tailored approach to the evaluation of an atraumatic visual disturbance but may be fraught with challenges. It is

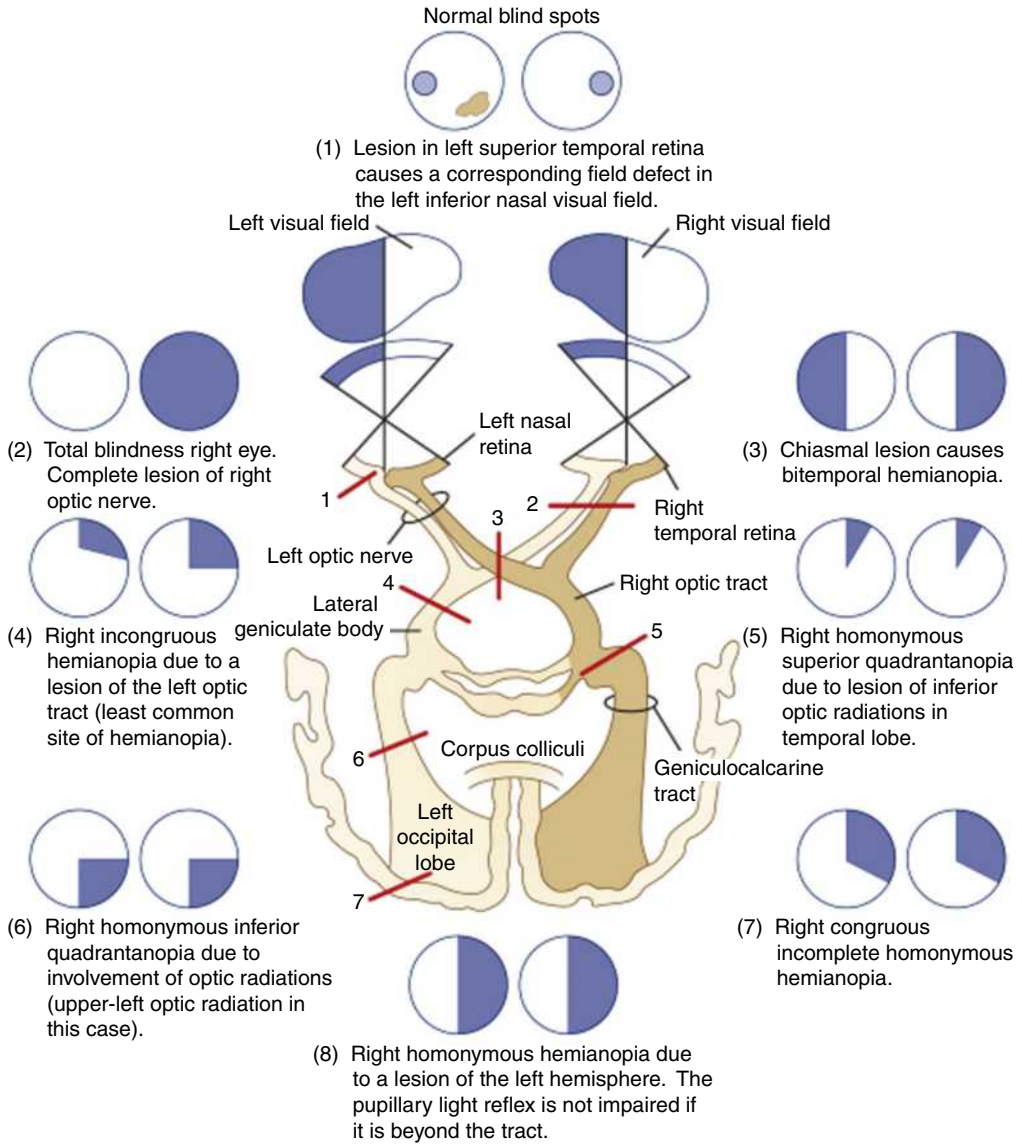


Fig. 57.23 Topographic Diagnosis of Visual Field Defects. (From Bradley WG, Duroff RB, Fenichel GM, et al: *Neurology in Clinical Practice*. 5th ed. Oxford: Butterworth-Heinemann; 2007.)

paramount to accurately catalog the symptoms. Patients may use the term *blurred vision* to actually describe double vision, and vice versa. A visual field deficit can be inadvertently ignored leading to a patient being "blind to the blind spot." In addition, a patient may not notice a chronic problem in one eye until it eventually develops in the remaining functioning eye. Finally, a patient may report what is actually a binocular defect of both visual fields on one side as a monocular issue in a single eye. This discrimination is lost if the visual disturbance was transient or not confirmed by checking both eyes.

Vision loss occurring beyond the retina can be considered *neuro-ophthalmologic* and divided, anatomically, into prechiasmal, chiasmal, and post-chiasmal (see Fig. 57.23). Patients with prechiasmal visual loss have monocular decreased visual acuity or visual field loss, typically from dysfunction of the optic nerve on that side, with an APD on the side involved in the swinging flashlight test (see Fig. 57.11). This finding will not cross the midline and involves only a single eye. Patients with chiasmal and post-chiasmal visual loss will typically have preserved visual acuity and a visual field loss in both eyes that respects the midline (see Fig. 57.23).

An ischemic event may occur anywhere from the retina to the occipital cortex depending on the vessel involved. The retina has a dual blood supply. The inner layers are supplied by a solitary central retinal artery, while the outer retinal layers are supplied by a choroidal circulation of ciliary arteries. The central fovea, within the macula, is also fed by choroidal vessels. In a central retinal artery occlusion (CRAO), the relative pallor of the surrounding retina, results in the pathognomonic "cherry-red spot" as the fovea continues to be perfused. About 15% to 30% of humans have a cilioretinal artery that also supplies the inner retina, which might preserve some residual blood flow to the macula in an acute CRAO. The blood supply to the optic nerve is complex and involves posterior ciliary and choroidal artery branches near the head and branches from the central retinal and ophthalmic arteries more proximally.

Blurred Vision: Optic Neuritis, Toxic and Metabolic Disturbances, and Papilledema

Clinical Features

Any disturbance in the refraction of light may cause blurred vision. These include corneal infiltrates (from infections), pupillary dilation (which results in an increase in the scatter of light rays reaching the lens), and changes in the refractive properties of the lens or vitreous, which can be seen with corneal edema from rapid osmotic changes. Blurred vision may also result from transductive dysfunction due to retinal or optic nerve inflammation or edema.

Typical optic neuritis is a primary, autoimmune inflammatory process of the optic nerve, affecting mostly young patients (range, 15 to 45 years old). It is the presenting symptom in 25% of cases of multiple sclerosis and may also be seen with other inflammatory, infectious, or autoimmune disorders.[47] The patient with optic neuritis typically presents with monocular blurring or fogginess of vision evolving over hours or days associated with variable degrees of pain with movement of the involved eye if the lesion is within the orbit. Patients may report fleeting flashes of light with eye movement, as well as worsening of vision with small increases in body temperature (from exercise, hot baths, or hot weather). Autoimmune optic neuritis often fluctuates with visual acuity reaching its poorest within 1 week and then slowly improving over the next several weeks. Approximately 30% of patients with acute optic neuritis develop multiple sclerosis within 5 years, and another 30% will have a recurrence within 10 years as the result of other causes. The natural history of atypical infectious and paraneoplastic etiologies of optic neuritis is concordant with the causative disease process.

Toxic visual disturbances are uncommon but may be seen with certain ingestions, such as methanol toxicity.[48] Orally ingested methanol is metabolized to formic acid, which accumulates in the optic nerve and leads to edema and compromised axoplasmic flow. In addition, it leads to widespread electrophysiological dysfunction that also affects photoreceptors in the retina, leading to visual loss. Other potential causes of a toxic visual disturbance are barbiturates, chloramphenicol, emetine, ethambutol, ethylene glycol, hypervitaminosis A, isoniazid, and heavy metals.

Metabolic visual disturbances, often from rapid osmolar shifts in the cornea, lens, or retina, have the potential to cause visual changes. This is most commonly seen with acute hyperglycemia. A rapid elevation in blood glucose (or a rapid correction of severe hyperglycemia), as seen in poorly controlled diabetics, may cause acute hyperopia (farsightedness), presumably due to changes in refraction in the lens.[49] It may alternatively cause acute myopia when the rise in intracellular glucose levels in the lens overwhelms the normal glucose metabolic pathway such that it is converted to less absorbable sorbitol and fructose, generating an acute hyperosmolar state and stromal swelling. This may be followed by acute bilateral cataract formation within a matter of hours to days. Metabolic visual disturbances can also result from a nutrition-related optic neuropathy from causes such as thiamine deficiency.

Papilledema may be seen on examination and refers to the changes in the optic disc from increased intracranial pressure. The subarachnoid space of the brain is continuous with the optic nerve sheath. Increases in the CSF pressure caused by idiopathic intracranial hypertension, cryptococcal meningitis in HIV/AIDS patients, hydrocephalus, or an intracranial mass can be transmitted to the optic nerve, resulting in swelling of the optic nerve head. Although visual symptoms may be isolated, patients often present to ED with a headache. A small percentage of patients with idiopathic intracranial hypertension present with isolated subjective visual loss, blurred vision, or enlargement of the physiologic blind spot as the initial presenting symptom of the disease, and rapid deterioration may occur over days in severe cases. Swelling of the optic disc and blurring of the disc margins, hyperemia, and loss of physiologic cupping are present (Fig. 57.24A). There may be the obliteration of spontaneous venous pulsations. Flame-shaped hemorrhages and yellow exudates may appear near the disc margins as the edema progresses (see Fig. 57.24B). Visual acuity will be affected as the swelling becomes severe. Papilledema is typically bilateral but may be asymmetrical. Conditions with optic nerve swelling (such as, ischemic optic neuropathy, optic disk vasculitis, and diabetic papillitis) may mimic papilledema.

Differential Diagnoses

As described, the differential diagnosis of "blurry vision" is broad and includes optic neuritis (which is usually monocular), toxic and metabolic visual disturbances (usually binocular), and papilledema from raised intracranial pressure (also usually binocular).

Diagnostic Testing

In the diagnostic evaluation of blurred vision, a standard ophthalmological assessment including visual acuity and a slit-lamp examination is important, but fundoscopy and an assessment of visual fields are critical.

Optic neuritis. With optic neuritis, visual acuity will usually be abnormal, and the patient may have variable visual field defects with central defects being most common. An APD is usually present, and direct ophthalmoscopic examination reveals a normal or swollen disk (Fig. 57.25). MRI of the optic nerves with gadolinium is used to confirm the diagnosis in most cases, as it reveals optic nerve lesions

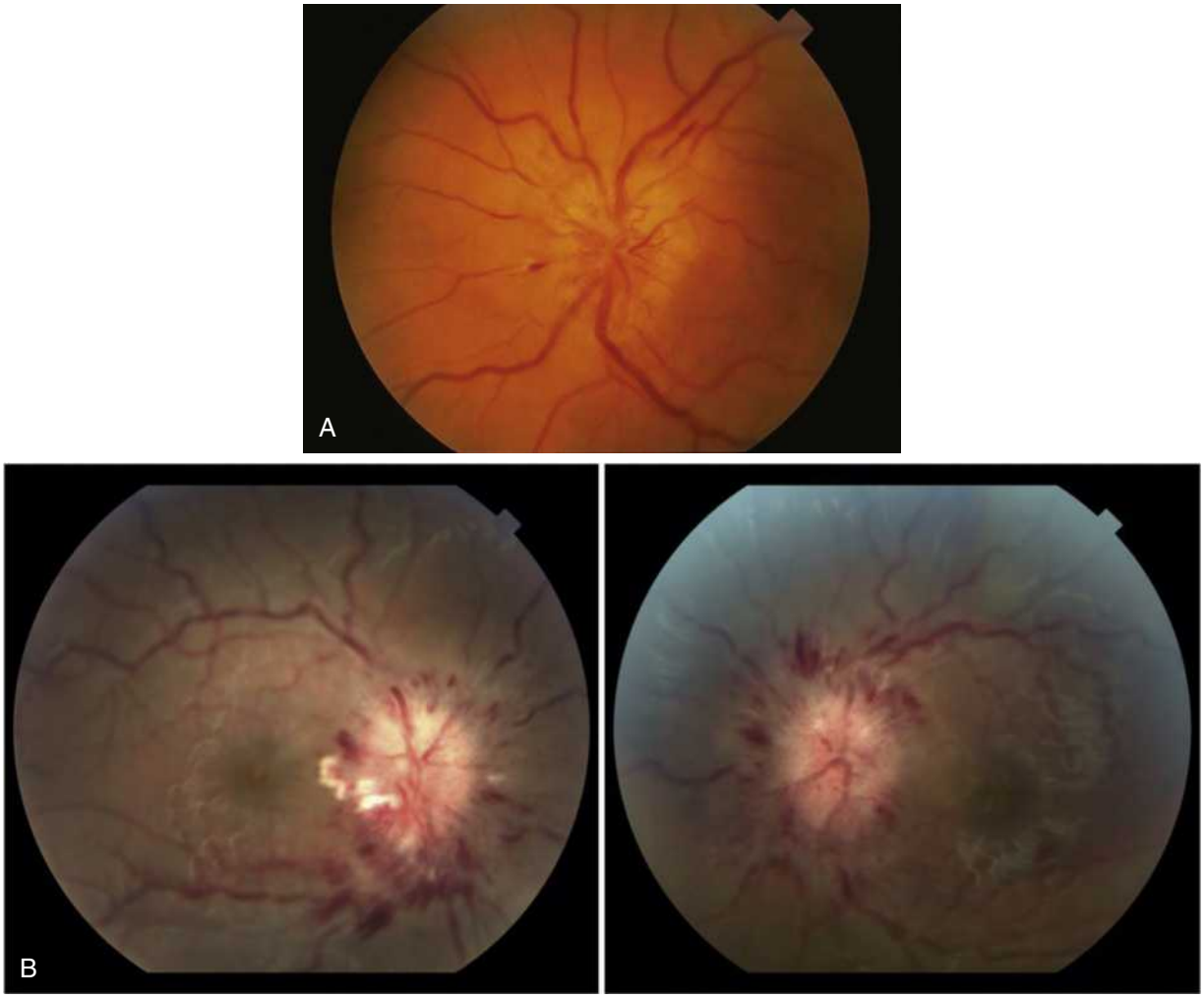


Fig. 57.24 (A) Papilledema. Note the blurred disk margins. (B) Papilledema. Note the blurred disk margins, exudates, and hemorrhages. (B, Courtesy Jeffrey Lee, MD.)

in the majority of cases.[50,51] CSF analysis from lumbar puncture, which may show pleocytosis and a raised protein concentration, can be performed if MRI is nondiagnostic or unavailable. Infectious and autoimmune serologies and optical coherence tomography may be utilized by consultants downstream in the workup.[52] Optic neuritis may be associated with autoimmune, infectious (syphilis, Lyme, HIV, varicella zoster virus, and cat-scratch disease) and non-infectious disorders such as sarcoidosis. The exact autoimmune etiology often requires antibody testing directed by specialists.[52,53] The ED workup for new-onset optic neuritis is to help exclude infectious causes that might need time-dependent antimicrobial therapy. Infectious etiologies of optic neuritis are frequently associated with uveitis, retinitis, and chorioretinitis; therefore, the presence of any of these features, or ocular inflammation, an optic nerve granuloma, or severe optic disc edema, should raise concern for infection.[52]

Toxic and metabolic visual disturbances. These processes are bilateral, progressive, and symmetrical and may manifest with a significant drop in visual acuity along with haziness in the lenses or retinal edema on fundoscopy. Blurred vision due to hyperglycemia typically reverses when hyperglycemia is treated, although cataracts may be permanent. Hyperglycemia and diabetic ketoacidosis have also been implicated in cortical blindness from posterior reversible encephalopathy syndrome lesions in the occipital lobes.[54,55]

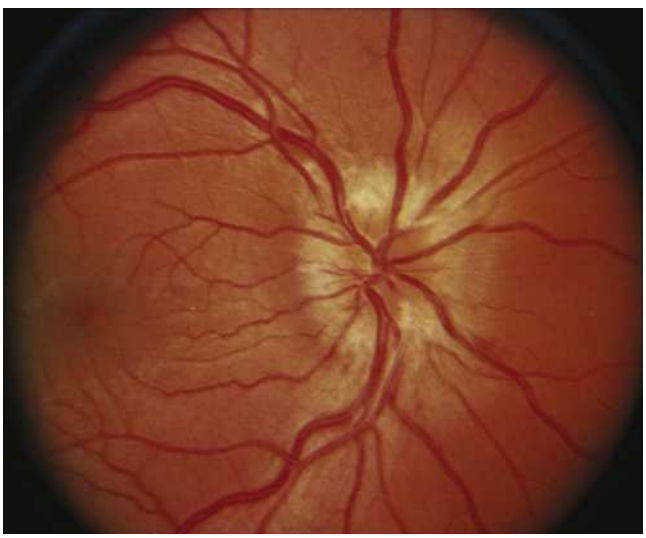


Fig. 57.25 Optic disk swelling (papillitis) associated with acute optic neuritis. (From Yanoff M, Duker JS, eds. *Ophthalmology*. 3rd ed. Philadelphia, PA: Mosby; 2008.)

Papilledema. Early or mild papilledema may be difficult to detect with the direct ophthalmoscope. When clinical suspicion is high, consultation with an ophthalmologist for stereoscopic viewing of the optic discs with indirect ophthalmoscopy is recommended. In cases in which idiopathic intracranial hypertension is suspected but there is still a question, patients can undergo neuroimaging with MRI.[56]

Management

For autoimmune optic neuritis, steroids are used for acute symptoms but lack proven benefit on long-term visual outcomes.[57] High-dose methylprednisolone, either 500 mg/day orally for 5 days, or 1 g/day IV for 3 days followed by oral prednisone (1 mg/kg/day for 11 days), is a common approach. Recent studies have shown no difference in efficacy between oral and IV administration.[58,59] Plasmapheresis, plasma exchange, and IV immunoglobulins are also options and are typically reserved for cases in which there is concern for a poor visual prognosis or a lack of response to steroids.[52,60] In toxic or metabolic causes, the treatment is aimed at the underlying toxin, metabolite, or deficiency involved. The management of papilledema is aimed at the underlying cause.

Disposition

Obtain neurology consultation for patients with presumed or diagnosed acute optic neuritis. Many patients will need admission for IV steroid treatment. Patients with toxic or metabolic visual disturbances will typically require admission for treatment of the underlying toxin or metabolic derangement. Patients with altered (but not loss of) vision due to simple hyperglycemia, without diabetic ketoacidosis, who have an improvement in symptoms after glycemic correction in the ED may be discharged with 24 to 48-hour follow-up.

Floaters, Flashes, and Field Deficits: Vitreous and Retinal Disorders

Clinical Features

Visual field disturbances may take the form of floaters, photopsia, or field deficits. Floaters are due to objects in the field of vision caused by material obstructing the light path. Photopsia (flashing lights) is from aberrant stimulation of the retina and can be unilateral or bilateral. The most common causes of unilateral photopsia are vitreous or retinal detachment (discussed later in this chapter), conditions in which abnormal mechanical stimulation of the retinal photoreceptors leads to a cascade of action potentials that the visual system interprets as flashes of light. A less common cause of unilateral photopsia is uveitis involving the choroid.

Vitreous hemorrhage results from bleeding into the pre-retinal space or the vitreous cavity. The most common causes are diabetic retinopathy and retinal tears. Additional causes include neovascularization associated with a variety of intraocular pathologies. Symptoms begin with dark floaters or "cobwebs" in one's vision that may progress over a few hours to painless visual loss. Floaters, described by the patient as dark or black dots or strands moving in the visual field in the direction of the preceding eye movement, are caused by vitreous blood.

Vitreous detachment is most common in patients older than 60 years. With aging, the vitreous gel desiccates, shrinks, and pulls away from the retina, leading to symptoms similar to those of vitreous hemorrhage and retinal detachment.

Three mechanisms cause retinal detachment: (1) rhegmatogenous, (2) exudative, and (3) tractional. The retina has two layers—the inner neuronal retina layer and the outer retinal pigment epithelial layer—that can be separated by fluid accumulation. A tear in the retinal membranes may lead to retinal detachment. A rhegmatogenous retinal detachment occurs as a result of a tear in the neuronal layer, allowing fluid from the vitreous cavity to leak between and separate the two retinal layers. It occurs in patients older than 45 years, is more common in men, and is associated with degenerative myopia. Trauma can cause this type of detachment at any age, with patients with severe myopia being at greater risk. An exudative retinal detachment occurs as a result of fluid or blood leakage from vessels within the retina and is associated with hypertension, pre-eclampsia, central retinal venous occlusion, glomerulonephritis, papilledema, vasculitis, and choroidal tumor. Finally, tractional retinal detachment is a consequence of contraction of a fibrous band that has formed in the vitreous. With retinal detachment, patients typically note flashes of light related to the traction on the retina, floaters from blood or pigmented debris in the vitreous, and visual loss. The visual loss is painless and commonly described as filmy, cloudy, or curtain-like in appearance.

If a visual field disturbance is binocular, then a chiasmal or cortical disorder should be considered. Chiasmal disease is most commonly caused by compression from nearby tumors. Visual loss is gradual and progressive. Post-chiasmal symptoms depend on the location of the tumor and can be located anywhere from the immediate post-chiasmal optic tract to the occipital cortex.

Differential Diagnoses

The differential diagnosis of visual field disturbances is broad and includes intraocular (monocular) entities such as vitreous hemorrhage, vitreous and retinal detachment, and extraocular (binocular) entities at the optic chiasm and beyond. The most common cause of bilateral (and homonymous) photopsia is migraines, although scintillating scotomas are much more frequent. Less common causes of bilateral homonymous photopsia include lesions of the visual cortex with release hallucinations or epileptic seizures. Perichiasmal disorders include pituitary tumors, craniopharyngiomas, and meningiomas. Beyond the chiasm, the list of culprits includes infarctions, tumors, arteriovenous malformations, and posterior reversible encephalopathy syndrome.

Diagnostic Testing

In the diagnostic evaluation of visual field disturbances, the history should be specific enough to ascertain if the problem is an issue of an absence of vision (i.e., a "blind spot,") or visual field deficit, or of an obstruction of vision (i.e., a "floater," as seen in vitreous detachment or hemorrhage, or retinal detachment). Perform a visual acuity assessment in all patients with a visual disturbance. In addition, complete a visual field examination to determine if the disturbance is monocular or binocular and whether it crosses the midline. Fundoscopy is especially important to enable an assessment of the vitreous and retina, and ocular ultrasound is a helpful adjunct. With this approach, the considerations outlined earlier can be differentiated and addressed.

Vitreous hemorrhage and detachment. With a vitreous hemorrhage, direct ophthalmoscopy reveals a reddish haze in mild cases and a black reflex in severe cases. Details of the fundus are usually difficult to visualize. There is a diminished red reflex and an inability to visualize the fundus clearly with the direct ophthalmoscope. Ocular ultrasound will reveal echogenic debris in the vitreous (Fig. 57.26A). A vitreous hemorrhage or detachment usually does not cause an APD by itself, and if an APD is present, an occult retinal detachment may be present. A hemorrhage may be evenly distributed throughout the vitreous, or—if trapped in the subhyaloid space as a pre-retinal hemorrhage—may be focal, with a boat shape (see Fig. 57.26B).

Retinal detachment. With a retinal detachment, visual acuity can range from minimally changed to severely decreased. Visual field

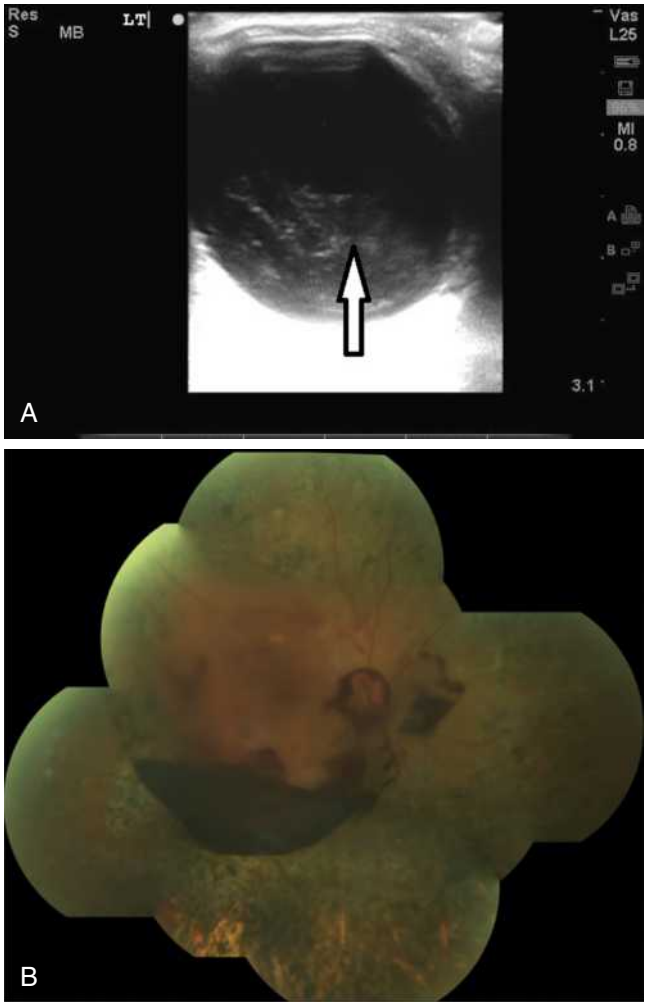


Fig. 57.26 (A) Ocular ultrasound showing vitreous hemorrhage *(white arrow).* (B) Boat-shaped pre-retinal vitreous hemorrhage. (A, Courtesy Douglas Brunette, MD. B, Courtesy Jeffrey Lee, MD.)

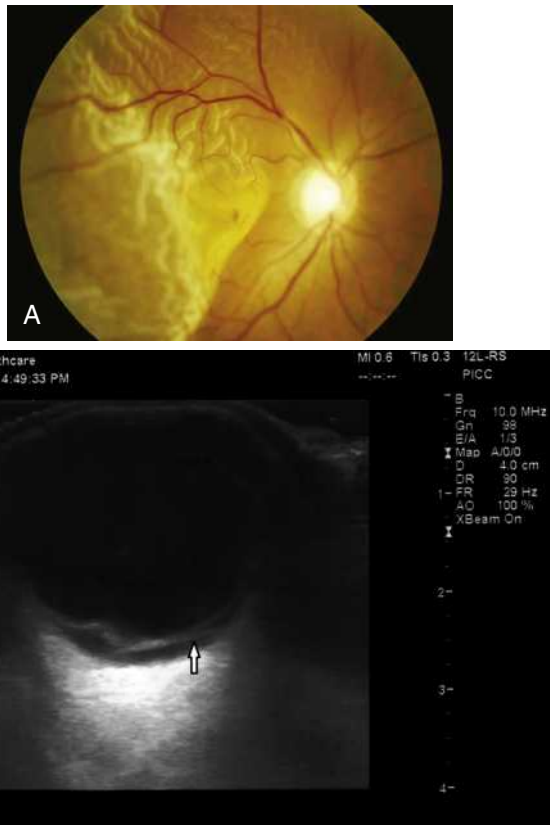


Fig. 57.27 (A) Retinal detachment. Note large portion of retina billowing forward. (B) Bedside emergency department (ED) ultrasound showing retinal detachment *(white arrow).* (A, Courtesy www.tedmontgomery.com. B, Courtesy Nicholas Connors, MD, and Sophia Lin, MD, New York Presbyterian-Weill Cornell Medical Center.)

deficits relate to the location of the retinal detachment, and an APD occurs if the detachment is large. When the detachment is visible on ophthalmoscopy, the retina appears out of focus at the site of the detachment. In large retinal detachments with large fluid accumulation, a bullous detachment with retinal folds can be seen (Fig. 57.27A). Retinal detachment cannot be ruled out by direct fundoscopy. Indirect ophthalmoscopy is needed to visualize the more anterior portions of the retina. Bedside ultrasonography can be a useful tool in screening for a retinal detachment (see Fig. 57.27B).[61] It will reveal a billowing hyperechoic line that may undulate with side-to-side movements of the eye and generally has very high sensitivity and specificity, both greater than 90%.[61] Point-of-care ultrasound is operator-dependent, however, and a recent study revealed that false negatives occurred when retinal detachment was mistaken for a vitreous detachment or hemorrhage, often due to improper technique or inadequate gain on ultrasound.[62] This being said, even though a retinal tear could still be present, the absence of any echogenicity in the posterior pole of the eye in a properly performed ultrasound scan makes a significant retinal detachment unlikely.

Chiasmal and cortical disturbances. A chiasmic or cortical cause of a visual field disturbance can usually be made by confrontation visual field testing. The classic defect for a lesion in or compression of the optic chiasm (chiasmal) is a bitemporal hemianopsia; however, tumors can compress the chiasm and optic nerves asymmetrically, resulting in combined central and temporal defects. When a visual field defect respects the vertical midline, the lesion is outside the globe and likely either chiasmal or post-chiasmal (see Fig. 57.23).

The classic visual field defect in post-chiasmal (cerebral or cortical) disease is a homonymous hemianopsia, a visual field loss on the same side of both eyes (see Fig. 57.23). Patients with such lesions need to be evaluated and treated based on underlying neurological conditions such as occipital infarction, neoplasm, an inflammatory or infectious process, or posterior reversible encephalopathy syndrome. The diagnostic workup involves imaging. Noncontrasted CT of the brain is easily and quickly obtained and the initial test of choice. CT angiography is obtained if intervenable cerebrovascular disease is possible. Obtain a brain MRI if initial CT imaging is normal or non-diagnostic.

Management

Ophthalmologic consultation in the ED, or a same-day evaluation by an ophthalmologist, is required to characterize the extent and complications of any suspected vitreous hemorrhage or detachment and to manage vision-threatening complications. Symptoms of photopsia with floaters are associated with a higher incidence of concurrent retinal tears.[63] The management of a vitreous hemorrhage is otherwise largely expectant, with limitation of activity, avoidance of anticoagulants, and sleeping with the head of the bed elevated to allow blood to settle and optimize visualization of the retina on subsequent examinations. Surgery is often required if there is an associated retinal detachment. The same consideration applies for a posterior vitreous detachment, for

which no specific emergent treatment is indicated unless accompanied by a retinal tear, vitreous hemorrhage, or retinal detachment.

For patients who are highly symptomatic from floaters, treatment options include laser vitreolysis (using laser energy to fragment the vitreous opacities) or vitrectomy which involves surgical replacement of the patient's vitreous with an inert and translucent balanced salt solution.[64] Any patient suspected of having a retinal tear or detachment requires immediate ophthalmologic consultation as treatment with tamponade or retinopexy can prevent a retinal detachment from progressing to involve the macula. Loss of central vision indicates macular involvement and the duration of macular detachment, measured from the reported time of the loss of central visual acuity, is inversely related to final visual acuity.

Disposition

Final disposition is determined in conjunction with an ophthalmologist. If a retinal disorder is likely, emergent consultation or transfer is required.

Sudden Monocular Vision Loss: Retinal Artery and Vein Occlusion, and Ischemic Optic Neuropathy

Clinical Features

Sudden onset of atraumatic, vision loss is usually due to a vascular process resulting in retinal ischemia or infarction. Binocular processes include a sudden homonymous hemianopia from an infarction of the visual pathways in the temporal, parietal, or occipital lobes; and sudden total blindness in both eyes due to a basilar artery territory infarction of both occipital lobes.

In a CRAO, acute retinal ischemia develops from a sudden embolic, thrombotic, vasculitic, or vasospastic occlusion of a branch of the retinal artery (a branch retinal artery occlusion [BRAO]) or the central retinal artery itself. The examination reveals a markedly reduced visual acuity with a prominent APD and an edematous with a pale gray-white retina with a cherry-red spot representing the fovea seen on fundoscopy (Fig. 57.28). A CRAO may be (1) non-arteritic and permanent (constituting over two-thirds of all CRAO cases), such as an ischemic stroke of the retina, (2) non-arteritic and transient, which may be seen with a transient ischemic attack [TIA] of the retina related to vasospasm, or (3) arteritic due to a systemic inflammatory condition like temporal arteritis.[65] CRAO has a poor prognosis with spontaneous resolution occurring in only 1% to 8% of cases. It most commonly occurs in patients 50 to 70 years old, with vascular risk factors or a history of collagen vascular disease, vasculitis, cardiac valvular abnormality, or sickle cell disease. Patients with increased orbital pressure from acute glaucoma, retrobulbar hemorrhage, and endocrine exophthalmos are also at risk.

A central retinal vein occlusion (CRVO) leads to congestion of venous blood and fluid in the intraretinal space that may lead to secondary retinal ischemia. A CRVO is differentiated from CRAO based on findings on funduscopic examination. Appearance can vary but classically includes dilated and tortuous veins, retinal hemorrhages, and disk edema (Fig. 57.29). Branch retinal vein occlusion is an incomplete CRVO and carries about better prognosis. Neovascular glaucoma and macular edema are the major complications of ischemic CRVO. It is characterized as either non-ischemic or ischemic; a non-ischemic CRVO is associated with dilatation of retinal vessels and edema only, whereas an ischemic CRVO presents with the sudden onset of painless vision loss in one eye. Predisposing factors include hypertension, hyperlipidemia, diabetes mellitus, vasculitides, hyperviscosity, and smoking.

Ischemic optic neuritis (ION) falls into two primary types, anterior ischemic optic neuropathy (AION; involving the optic nerve head) and posterior ischemic optic neuropathy (PION; involving the rest of the optic nerve). AION can further be divided into arteritic anterior ischemic optic neuropathy (A-AION) due to temporal arteritis and, more commonly, non-arteritic anterior ischemic optic neuropathy (NA-AION) from noninflammatory vascular causes.[66]

Examination findings are similar in A-AION and NA-AION and include a large APD, visual loss, and a visual field defect that may respect the horizontal (as opposed to vertical) midline, with a pale and swollen optic disc on fundoscopy. Patients with A-AION may have concurrent symptoms of temporal arteritis, such as weight loss, malaise, jaw pain,

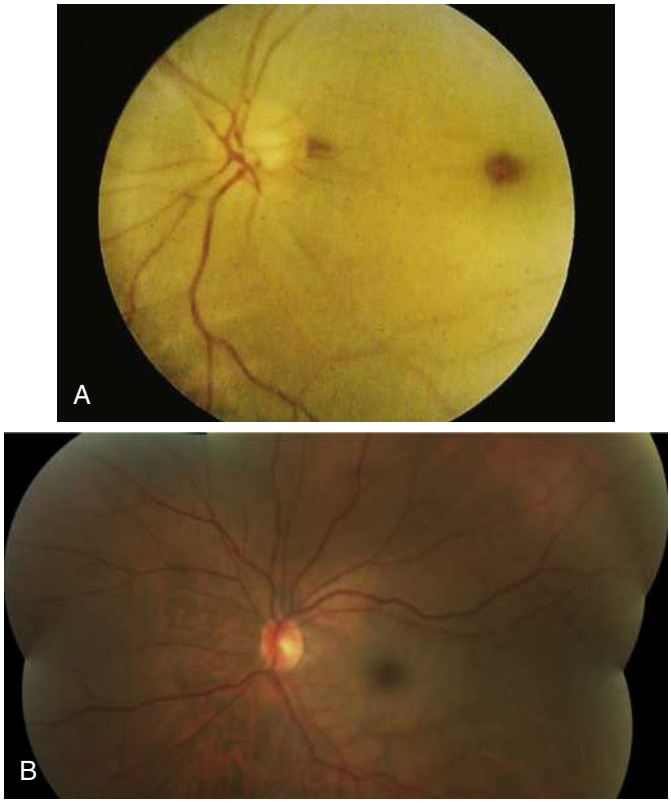


Fig. 57.28 Central retinal artery occlusion (CRAO). (A) Note the cherry-red spot representing the fovea. (B) Note whitening of the retina, with a less prominent cherry-red spot. (B) (Courtesy Jeffrey Lee, MD, University of California San Diego.)

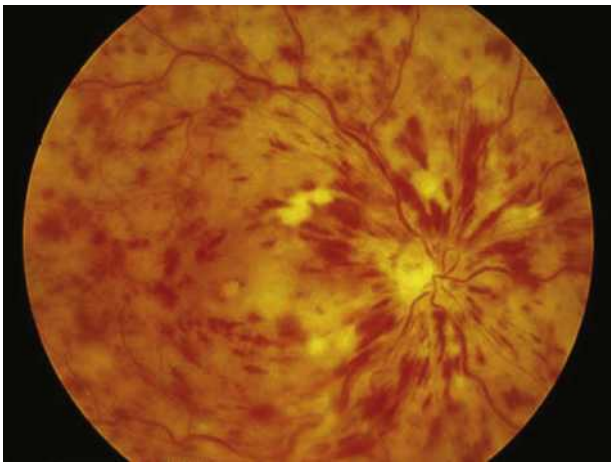


Fig. 57.29 Central Retinal Vein occlusion. Note the "blood and thunder" appearance. (Courtesy www.tedmontgomery.com.)

headache, scalp tenderness, polymyalgia rheumatica, and low-grade fever; in up to 25%, however, acute vision loss is the only symptom. Vision loss can be preceded by episodes of amaurosis fugax. Untreated, it may progress to involve both eyes. Temporal arteritis is extremely rare in people younger than 50 years, and the incidence rises with each subsequent decade. Vision loss is unilateral in 46%, sequential in 37%, and simultaneously bilateral in 17%.

Patients with the much more common NA-AION lack the classic symptoms of temporal arteritis and tend to be younger with systemic vascular disease, diabetes, or hypertension. This is an acute ischemic event affecting the anterior optic nerve that typically occurs in patients over the age of 50 years and may be precipitated by anemia, hypovolemia, dehydration, systemic hypotension, or fluctuations in blood pressure, especially in patients undergoing dialysis.[66]

A sudden complete monocular vision loss due to a vascular event can be transient *(amaurosis fugax)* and can herald a more significant or permanent loss of vision in any of the aforementioned processes. It has been reported in 2% of CRAO, 14% of BRAO, 5% of CRVO, just over 3% in NA-AION, and in 32% of patients with temporal arteritis who have ocular involvement.

Differential Diagnoses

Distinguishing cortical from retinal vascular causes of vision loss is accomplished by history alone in most cases. Cataracts and glaucoma typically cause gradual onset loss of vision, although sudden decreases in vision can occur. A cloudy or steamy lens will be visible. Acute angle-closure glaucoma can present with sudden monocular vision loss, but pain is universally present.

Diagnostic Testing

Diagnostic testing for monocular vision loss begins with a fundoscopic examination to look for the typical clinical features detailed previously. Along with the history, this is often enough to make a presumptive diagnosis. If there is diagnostic uncertainty, obtain CT or MRI to evaluate for structural causes. If inflammatory arteritis is a concern, check a sedimentation rate (ESR) or C-reactive protein (CRP) level.

Management

Central retinal artery occlusion. Like acute ischemic stroke, CRAO is a time-sensitive process. Animal models suggest that the retina will likely make a full recovery with an occlusion that lasts less than 90 minutes but will be irreversibly damaged with one lasting longer than 4 hours and will have variable degrees of recovery with times in between. A number of interventions have been proposed geared toward dislodgement of the embolus (via direct digital pressure through closed eyelids for 10 to 15 seconds and followed by a sudden release), dilation of the artery to promote forward blood flow (by increasing intra-arterial carbon dioxide level [pCO_2] with an inhaled mixture of 95% oxygen and 5% carbon dioxide [carbogen]), and reduction of IOP through anterior chamber paracentesis to increase the perfusion gradient.[67] Unfortunately, none of the presented therapies have been shown to improve visual acuity outcomes after CRAO.[65] A potential option is hyperbaric oxygen (HBO), which affords a theoretical benefit of direct oxygenation of the retina, but current evidence is limited to retrospective data.[68–71] There are no robust prospective, randomized controlled trials confirming the efficacy of HBO as a treatment for CRAO, likely because implementing such trials is limited by logistics.[68]

A non-arteritic CRAO may be amenable to the use of thrombolytic agents.[67] Available studies are heterogeneous, using different agents, dosing regimens, and time windows in largely retrospective case series with different findings, but it appears that intra-arterial thrombolytic therapy might be effective if given less than 6 hours from onset. IV thrombolysis might be effective if given less than 4.5 hours from the onset, with a post-thrombolysis major hemorrhage rate significantly lower than that seen with ischemic stroke.[72] Until a large randomized controlled trial of the safety and efficacy of thrombolysis for CRAO is performed, management should be tailored to individual patient circumstances in consultation with an ophthalmologist.

There are no national guidelines for the treatment of CRAO, and a survey of university-associated teaching hospitals offering vascular neurology, neuro-ophthalmology, or retina fellowships in the United States found significant heterogeneity in approaches.[73] Adding to the complexity of care is the variable time available for intervention. This depends on the extent of vascular disease and collateral flow from ciliary vessels.[74,75]

Begin a hypercoagulable workup in patients younger than 50 years. There is a strong association between non-arteritic retinal artery occlusion and subsequent risk of an acute ischemic stroke. An expedited workup for cerebrovascular disease and assessment of stroke risk is recommended.[76–80].

Central retinal vein occlusion. An ultimate visual acuity better than 20/200 is seen in over 80% of patients with a non-ischemic CRVO but in less than 10% of patients with ischemic CRVO. Treatment of CRVO includes treating the underlying etiology and monitoring for potential sequelae. Consult ophthalmology in the ED to secure timely initiation of therapy, which largely centers around treating the macular edema associated with the occlusion. Potential treatments include anti-vascular endothelial growth factor pharmacotherapies, intravitreal injections of corticosteroids or antiangiogenic monoclonal antibodies (ranibizumab, bevacizumab), retinal photocoagulation, and cyclocryotherapy.[81–83] The use of antithrombotic therapy, in particular, the use of low-molecular-weight heparin, has also shown promise.[84] Underlying medical disease should be managed; the prognosis depends on the degree of obstruction and resultant complications.

Ischemic optic neuropathy. Temporal arteritis with evolving vision loss or amaurosis fugax from A-AION represents a distinct clinical emergency. Untreated, vision loss becomes bilateral in days to weeks in at least 50% of cases.[66] Admit patients for high-dose IV methylprednisolone (typically 500 mg to 1 g daily for 3 days) before transitioning to oral medications. Patients treated with high-dose IV methylprednisolone are more likely to have visual improvement (a 34% chance of improvement) and are less likely to develop fellow eye involvement than those receiving oral prednisone.

The visual loss in NA-AION is less severe than with temporal arteritis, and improvement occurs in one-third of patients. There is no known treatment (intravitreal and systemic steroids have been tried without success, as have anti-VEGFs). Emergent ophthalmological consultation is warranted for any apparent ION to aid with differentiation of the type and extent of the process and management.

Disposition

All patients with sudden monocular vision loss require emergent ophthalmologic evaluation. Most will be admitted for further workup and management. Final disposition is done in conjunction with ophthalmology or neuro-ophthalmology specialists.

Functional Vision Loss

Functional (or factitious) vision loss may be due to a conversion reaction or malingering. Distinguishing organic from psychiatric causes of visual disturbances can be challenging and may require consultation with an ophthalmologist, a neurologist, and a psychiatrist. Some tests can be performed in the ED that will suggest a functional overlay, given that the most common presentation of functional vision loss is a decreased visual acuity. They include (1) rotating an optokinetic drum

or rocking a mirror slowly back and forth in front of the patient (which will induce nystagmus or eye movements in the functional patient, but not in the truly blind patient), (2) rapidly moving the examiner's hand toward the eye in question (which will induce a blink to a visual threat in the functional patient, but not in the truly blind patient), (3) checking for an APD as in Fig. 57.11 (which will be absent in the functional patient but not in the truly blind patient with an optic nerve problem), (4) having the patient raise his or her arms and touch both index fingers together. A functional patient will feign inability to approximate the fingers, but a truly blind patient will be able to do, given that the test is actually one of proprioception and not vision.

Another presentation of functional visual loss is a defect in the visual field, typically with a central scotoma. This can be identified as functional by having the patient sit in front of a picture and describe the extent of a visual field defect vis-à-vis what is missing and then moving him or her further away and asking for another description of what is missing. The functional patient may describe the same missing elements in the picture in an effort to convince the examiner that the defect is stable, whereas the patient will a real visual field deficit will notice that more elements in the picture are missing.

DIPLOPIA

Chapter 17 provides a comprehensive overview of the approach to diplopia. The approach is based on whether binocular diplopia is due to (1) a simple restrictive, mechanical orbitopathy from inflammatory or infectious mass-effect directly restricting of the movement of the eye, (2) a palsy of one or more of the oculomotor CNs, (3) a more proximal neuro-axial process involving the brainstem and related CNs, or (4) a systemic neuromuscular process.

ANISOCORIA

Foundations

Anisocoria, a difference in pupil size, is present normally in 20% of the population but can also result from a process affecting the nuclei or the innervation pathways or from pharmacological interference at the neural endplates in the pupillary muscles.

Dilation (mydriasis) of the pupil is controlled by the dilator muscle, innervated by sympathetic nerves that exit the spinal cord at the level of C8, T1, and T2, and then travel back up under the subclavian artery and over apices of the lungs, enter the superior cervical ganglion, then the internal carotid plexus, and finally the ophthalmic division of the trigeminal nerve (CN V), whereupon they reach the eye through the superior orbital fissure. This sympathetic innervation serves a largely inhibitory role, facilitating pupillary dilation in darkness.

Constriction (or miosis) of the pupil is controlled by the pupillary sphincter muscle, innervated by parasympathetic nerves that originate in the nuclei of CN III. This parasympathetic innervation is the primary means of regulating pupillary size in response to different intensities of light. Afferent input from the retina of each eye bifurcates to innervate the Edinger Westphal nuclei of each CN III, and each nucleus in turn provides efferent output to its pupillary constrictor muscle, underlying the direct and consensual pupillary light reflexes.

Clinical Features

Anisocoria may be a pupillary variant in neurologically normal patients. It can also be seen in pathologic conditions, as a post-surgical finding or after pharmacologic application. These include an Adie's or Argyll Robertson pupil, pharmacologic mydriasis and miosis, a third-nerve palsy, Horner syndrome, and a physiologic or headache-associated anisocoria.

Adie's and Argyll Robertson Pupils

An Adie's tonic pupil results from dysfunction or lesion of the ciliary ganglion or short ciliary nerves and may be idiopathic or the result of local ocular or orbital damage from surgery, trauma, procedures, infection, inflammation, or ischemia. An Adie's tonic pupil may also be part of a condition causing systemic autonomic dysfunction, such as diabetes, dysautonomia, neurosyphilis, amyloidosis, or sarcoidosis. These patients present with a large pupil on one side. They may be asymptomatic or report sensitivity to light in that eye and blurred vision when looking at things near them.

The Argyll Robertson pupil is typically smaller than an Adie's and similarly constricts poorly to direct light, but it briskly constricts when a target within reading distance is viewed. It is attributable to a dorsal midbrain lesion that interrupts the pupillary light reflex pathway but spares the more ventral pupillary near the reflex pathway.

Pharmacologic Mydriasis and Miosis

Anisocoria can be caused by a variety of accidental medication and plant exposures. Parasympathomimetic miosis may be induced by exposures to organophosphate esters, pilocarpine drops, or dust-containing cholinesterase inhibitors from a dog's flea collar. Parasympatholytic mydriasis may be seen with anticholinergic medications (such as, transdermal scopolamine), aerosolized ipratropium administered through nebulizer masks, cycloplegics (such as, homatropine, cyclopentolate, or tropicamide), and plants containing anticholinergic agents, such as Jimsonweed *(Datura stramonium)* and Angel's trumpet *(Datura suaveolens)*. *Sympathomimetic mydriasis* may occur from sprays containing phenylephrine (Neo-Synephrine), cocaine, and apraclonidine (a glaucoma medication).[85–87]

Third-Nerve Palsy

CN III innervates the medial, inferior, and superior recti muscles, the inferior oblique muscle, and the levator palpebrae superioris muscle, which lifts the upper eyelid. It also provides parasympathetic innervation to two intrinsic ocular muscles, the ciliary and constrictor pupillae muscles, which constrict the pupil. A CN III palsy, therefore, results in an eye that appears deviated "down and out" with a dilated pupil and ptosis. The parasympathetic fibers that affect pupillomotor constriction are located peripherally and on the superomedial surface of CN III, where compression from an aneurysm or other source may cause pupillary involvement before other oculomotor signs, such as ptosis or diplopia, develop.

Horner Syndrome

Horner syndrome presents with ptosis, miosis, and facial anhidrosis resulting from a disruption of sympathetic innervation anywhere along the chain of sympathetic innervation. The presence of associated symptoms may help localize the etiology, as outlined in Table 57.2.[88] In children, the most common cause of acquired Horner syndrome is a neuroblastoma of the paravertebral sympathetic chain, although it may be from a mediastinal tumor. Horner syndrome can also be congenital, suggested by heterochromia or hypopigmentation of the ipsilateral iris.

Physiologic and Headache-Associated Anisocoria

In physiological anisocoria, the difference in pupil size will typically be 1 mm or less. A more prominent transient mydriasis (benign episodic unilateral mydriasis) may occasionally accompany a migraine headache, either from sympathetic hyperactivity, or—with an ophthalmoplegic migraine—parasympathetic hypoactivity from CN III dysfunction.[89,90] A non-migrainous benign episodic unilateral mydriasis can occur without headache, ptosis, or ocular motility disorder, in episodes lasting minutes, hours, or even days and is also thought

TABLE 57.2 Potential Locations of Lesion Causing a Horner Syndrome, Based on Symptoms and Signs

Symptoms and Signs	Potential Lesion Location	Potential Lesion Type
Brainstem symptoms (vertigo, ataxia, diplopia, and focal sensory and motor deficits)	Pontine or midbrain	Infarction or neoplasm
Myelopathic symptoms (paraparesis, sensory deficit, bowel or bladder symptoms, or hyperreflexia)	High spinal cord	Neoplastic or demyelinating process
Arm pain, weakness or numbness, neck lymphadenopathy (especially with hoarseness from recurrent laryngeal nerve compression)	Brachial plexus or cupula of the lung	Neoplastic process, such as a Pancoast tumor
Ipsilateral ear or neck pain (especially with symptoms of phrenic or vagus nerve involvement)	Carotid sheath	Carotid dissection; inadvertent injection of an anesthetic into the sheath during dental or line-placement procedures
Hearing loss and ear pain; trigeminal nerve dysautonomia (ipsilateral facial pain, rhinorrhea, conjunctival injection, and tearing)	Skull base	Neoplasm; inflammatory or infectious mass effect

Flaherty PM, Flynn JM: Horner syndrome due to carotid dissection. *J Emerg Med* 2011; 41(1):43–46. Davagnanam I, Fraser CL, Miszkiel K, et al: Adult Horner's syndrome: a combined clinical, pharmacological, and imaging algorithm. *Eye (Lond)* 2013; 27(3):291–298. Kanagalingam S, Miller NR. Horner syndrome: clinical perspectives. *Eye Brain.* 2015;7:35–46.

to be caused by over-activity of sympathetic innervation to the pupil. Patients are typically young females, and episodes last a median duration of 12 hours.

Patients can also present with a "tadpole pupil," in which the pupil becomes distorted and pulled in one direction like the tail of a tadpole, possibly occurring several times a day for several days and then resolving. This is likely the result of a sectoral spasm of the dilator muscle, thought to be benign, and has been associated with strenuous exercise. If, on the other hand, the patient has a baseline anisocoria and the tadpole pupil manifests in the smaller of the pupils, testing for Horner syndrome is recommended.

Diagnostic Testing, Management, and Disposition

The evaluation of new anisocoria is outlined in Fig. 57.30. Assuming no damage to the iris (implying a purely structural problem) is evident on slit-lamp examination, the strategy is to differentiate a benign cause of anisocoria (e.g., physiological or pharmacological) from one that requires additional neuro-ophthalmological consultation (e.g., Horner syndrome) or emergent neuroimaging (e.g., CN III compression potentially due to an aneurysm). The first step is to determine which pupil—the larger or the smaller—is the pathological one, keeping in mind that that parasympathetic innervation constricts a pupil in bright light, whereas sympathetic stimulation helps dilate a pupil in the dark. The subsequent steps incorporate the principles that an abnormally large pupil may be due to either a decrease in parasympathetic stimulation or an augmentation of sympathetic stimulation, and an abnormally small pupil may be due to either a decrease in sympathetic stimulation or an augmentation of parasympathetic stimulation.

Medications such as hydroxyamphetamine (an indirect-acting adrenergic mydriatic that causes endogenous norepinephrine to be released from sympathetic nerve endings without directly stimulating the effector cells), as well as direct adrenergic agonists, such as a phenylephrine or 1% apraclonidine, can be used with ophthalmological consultation to perform a secondary evaluation of a Horner's pupil. Pilocarpine is a direct cholinergic receptor agonist and is used to differentiate hypo-parasympathetic conditions (see Fig. 57.30).

Once one of the typical presentations of anisocoria is identified, the evaluation progresses based on the clinical indications. Examination of an Adie's tonic pupil typically reveals poor reaction to light with sectoral palsy of the iris sphincter and a lack of (or slow) constriction with near accommodation. Slit-lamp examination may reveal sectoral palsies of the iris, and a weak cholinergic agent (pilocarpine 0.1%) causes an intense pupillary constriction (compared to the patient's normal pupil) as a result of the cholinergic supersensitivity in the affected pupil. These patients should be referred non-emergently to an ophthalmologist for further evaluation.

The Argyll Robertson pupil, like the Adie's pupil, will demonstrate segmental, slow, or little iris sphincter constriction with light, but normal constriction with near accommodation ("light-near dissociation," which distinguishes it from an acute Adie's pupil). Screen a patient with bilateral Argyll Robertson pupils for neurosyphilis (please refer to entries dedicated to syphilis elsewhere in this text).

Evaluate a patient with a new-onset Horner syndrome, based on associated signs and symptoms, as outlined in Table 57.2. An MRI is best for disorders of the brain, skull-base, and spinal cord lesions, while computed tomography angiography (CTA) is best for chest and neck/carotid pathology. The cadence of the evaluation (and which components are done in the ED) will be dictated by the acuity of the primary considerations in the differential diagnosis, with aneurysm, dissection, brainstem stroke, and a rapidly progressive myelopathic process evaluated emergently in the ED, and a more subacute or chronic process (such as a tumor) often worked up as an outpatient.

The diagnostic evaluation and management of a third-nerve palsy are covered in Chapter 17 and Chapter 91. With regards to pharmacologic mydriasis and miosis, most of the exposures and their effects will be self-limited and transient, and the specific management will be dictated by the severity of symptoms.

The first-time clinical presentation of physiological and headache-associated anisocoria (mydriasis) may provoke a neuro-imaging evaluation for the presence of aneurysmal or mass compression of CN III; although this is being excluded, treatment can be rendered along lines that are standard for migraine headache. Physiological and headache-associated anisocoria is otherwise self-limited and will not typically require urgent ophthalmology referral unless persistent.

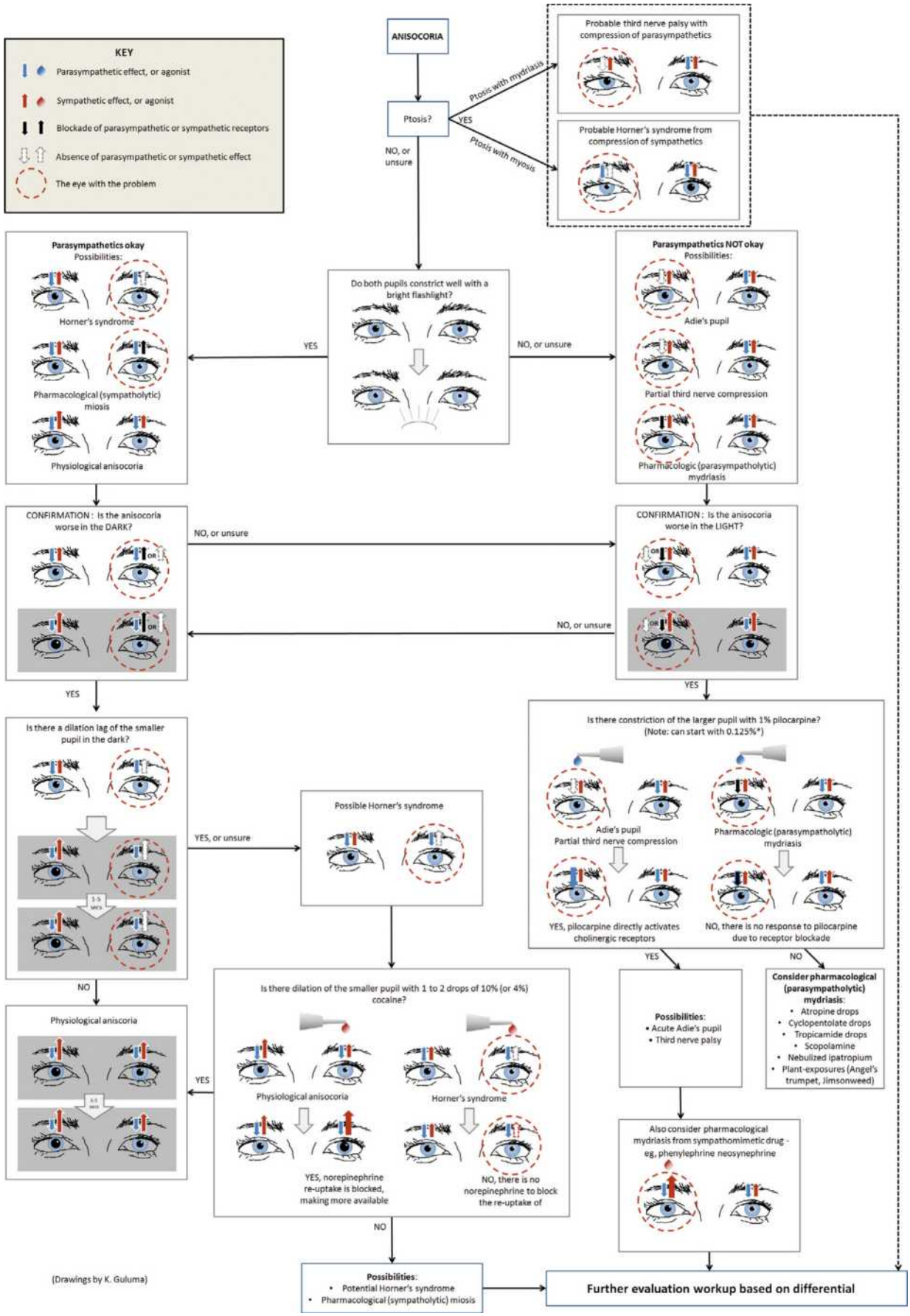


Fig. 57.30 The approach to anisocoria in the emergency department (ED), an explanatory algorithm. *Some authors advocate that a marked response to low concentration (0.1% or 0.125%) pilocarpine is more consistent with an Adie's pupil and can be used to differentiate it from an acute third-nerve palsy (which may require the more concentrated 1% to elicit a reaction). This approach may be impractical, however, as a sole means to rule out a third-nerve palsy from something like an aneurysm.

NYSTAGMUS

Foundations

Three specific mechanisms keep an object of visual interest on the fovea: (1) fixation, wherein the visual system detects retinal drifts and programs corrective eye movements; (2) the vestibulo-ocular reflex (VOR), which keeps the eyes on target despite head movements; and (3) eccentric gaze-holding, which requires ongoing signals from the brainstem and cerebellum to overcome the natural elastic pull of orbital tissues when the eyes are deviated away from the mid-position to fixate on a target.

Clinical Features

Dysfunction in any of these three mechanisms removes the visual target from the fovea and may result in nystagmus and oscillopsia (a subjective sense of movement of the visual field).[91,92] Nystagmus is a repetitive horizontal, vertical, or torsional back and forth movement of the eyes that may appear as an equal "to and fro" motion (pendular nystagmus) or demonstrate an alternating, slow phase followed by a corrective fast phase (jerk nystagmus). In jerk nystagmus, although the slow phase is the abnormal one, the directionality of the nystagmus is described as that of the fast phase. Gaze-evoked nystagmus is an inability to hold the eyes in a fixed position at the eccentric extremes of gaze. Drug-induced gaze-evoked nystagmus is symmetric with a larger amplitude and slower velocity and beats in the direction of the gaze (i.e., upbeat nystagmus with the patient looking up, rightward nystagmus with the patient looking to the right, and so on). GEN from a focal cerebellar or brainstem lesion may look similar to that which is drug-induced, but it is characterized by a sustained asymmetric and rebound nystagmus in which, although the slow phase is directed toward a primary position where the eyes deviate, a few slow phases may be directed toward the prior gaze direction after the eyes return to the primary position.

Nystagmus can be physiologic or pathologic and congenital or acquired. It may be a variety of characteristics that included differences in amplitude, sustainability, and direction and may present with or without cerebellar findings. A patient may also have congenital nystagmus, typically identified as chronic or present since birth. The focus in the ED is therefore on acquired pathological nystagmus, of which the etiologies can be classified as either (1) peripheral (such as, seen with benign peripheral vertigo or vestibular neuronitis), (2) central, indicating an ischemic stroke or CNS mass lesions, or (3) toxic and metabolic which can be seen with certain medications, alcohol, or illicit drugs. The key findings for these various forms of nystagmus are outlined in Table 57.3.

TABLE 57.3 Forms and Causes of Nystagmus

Type of Nystagmus	Presumed Area of Dysfunction	Character/ Primary Direction	Triggered by Head Movements?	Suppresses on Visual Fixation on an Object?	Changes Direction With Gaze?	Sustained?
Peripheral Nystagmus						
Labyrinthitis or vestibular neuronitis	Labyrinthine dysfunction or viral infection of the superior portion of the vestibular nerve trunk	Horizonto-rotatory, one direction only, slow phase toward dysfunctional nerve	Yes	Yes	No, just gets more pronounced the further the patient looks away from dysfunctional nerve	Yes
Benign paroxysmal positional vertigo (BPPV)	Otolithic, posterior canal (most common)	Torsional combined with vertical, one direction only	Yes, raising the head from horizontal to vertical	Yes	No	No
Benign paroxysmal positional vertigo (BPPV)	Otolithic, other canals	Horizonto-rotatory, one direction only, slow phase toward dysfunctional canal	Yes, turning head side-to-side	Yes	No, just gets more pronounced the further the patient looks away from dysfunctional canal	No
Central Nystagmus						
Downbeat nystagmus	Vestibulocerebellum Drugs: Lithium, phenytoin, carbamazepine, alcohol, toluene, felbamate, lamotrigine, phencyclidine (PCP), ketamine Nutritional deficiencies: magnesium, vitamin B_{12} or thiamine	Pure vertical, with fast component downward	No	No	No, just more pronounced on looking down	Yes
Upbeat nystagmus	Pontomesencephalic or pontomedullary junction, or the superior vestibular nucleus and tracts Nutritional deficiencies: Thiamine (Wernicke's)	Pure vertical, with fast component upward	No	No	No, just more pronounced on looking up	Yes
Torsional	Cerebellum or brainstem Drugs: PCP, ketamine	Pure rotary, with bi-directional fast component	No	No	Yes	Yes

TABLE 57.3 Forms and Causes of Nystagmus—cont'd.

Type of Nystagmus	Presumed Area of Dysfunction	Character/ Primary Direction	Triggered by Head Movements?	Suppresses on Visual Fixation on an Object?	Changes Direction With Gaze?	Sustained?
Horizontal	Cerebellum or brainstem Drugs: PCP, ketamine	Bi-directional	No	No	Yes, fast component beats in direction of gaze, and gets worse with more extreme deviation	Yes
Gaze-evoked nystagmus (GEN)	Cerebellum or brainstem Drugs: Phenytoin, alcohol	Multi-directional, but asymmetric intensity	No	No; in fact worsens on eccentric fixation	Yes, fast component beats in direction of gaze, and gets worse with more extreme deviation	Yes, specifically if vision is eccentrically fixated on an object
Other Miscellaneous Central Nystagmus Presentations						
Acquired pendular nystagmus	Paramedian pontine tract (seen in multiple sclerosis) Drugs: Phenytoin	Oblique or elliptical movements, can even be monocular	No	No	No	Yes
Periodic alternating nystagmus	Nodulus and ventral uvula of the vestibulocerebellum Drugs: Phenytoin	Horizontal nystagmus with a slow phase that changes direction every 1–2 min	No	No	No	Yes
Superior oblique myokymia	Possible cranial nerve (CN) disorder	Torsional oscillopsia, in one eye	No	No	No	Yes
See-saw nystagmus	Parasellar mass, or stroke to mesodiencephalic regions	Elevation with intorsion of one eye, with simultaneous depression and extorsion of the other eye	No	No	No	Yes
Oculopalatal myoclonus	Dentate, red, and inferior olivary nuclei in the brainstem	Vertical-torsional or pure vertical (with one eye being more prominent), associated with palatal myoclonus	No	No	No	Yes

From Baier B, Dieterich M. Incidence and anatomy of gaze-evoked nystagmus in patients with cerebellar lesions. *Neurology*. 2011;76:361–365; Ehrhardt D, Eggenberger E. Medical treatment of acquired nystagmus. *Curr Opin Ophthalmol*. 2012;23(6):510–516; Shaikh AG. Fosphenytoin induced transient pendular nystagmus. *J Neurol Sci*. 2013;330(1–2):121–122; Kang S, Shaikh AG. Acquired pendular nystagmus. *J Neurol Sci*. 2017;375:8–17.

Differential Diagnoses

Peripheral nystagmus may be seen in vertiginous middle ear disorders such as benign paroxysmal positional vertigo or viral vestibular neuritis. Central causes include stroke, vestibular schwannoma, and cerebellar pathology. Toxin-induced nystagmus can be seen with anticonvulsants, ethanol, lithium, ketamine, dextromethorphan, and recreational drugs such as phencyclidine and lysergic acid diethylamide (LSD).

Diagnostic Testing

Both peripheral and central nystagmus (e.g., from otoconia, vestibular neuronitis, posterior circulation stroke, brain tumor, and so on) present with prominent vertigo, and a detailed discussion of these entities is deferred to the entries on vertigo and dizziness in Chapter 15. The goal in the ED is differentiating more subtle presentations of central causes from benign peripheral ones. This can be determined by assessing (1) the direction of the nystagmus, (2) its intensity with extremes of gaze, and (3) how it is affected by visual fixation, as outlined in Table 57.3. Peripheral nystagmus, associated with vertigo and a presumed middle ear etiology, does not require an ED workup. For central causes or when the diagnosis is unclear, neuroimaging, typically MRI and MRA, is indicated. Nystagmus thought to be from medication or recreational drug toxicity is suggested by a concurrent toxidrome and lack of prominent vertigo or ataxia and will require toxicologic studies or specific drug levels to confirm the diagnosis may be suggested by a concurrent toxidrome and lack of prominent vertigo or ataxia.

Management

The management of nystagmus is targeted toward the underlying etiology. Peripheral nystagmus associated with vertigo and a peripheral etiology is symptomatic. Management of drug-induced nystagmus starts by holding the offending agent and targeted therapies for drug toxicity.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 57: QUESTIONS AND ANSWERS

1. A 23-year-old male presents with left periorbital pain after being struck with a fist. On examination, there are no globe injuries but marked periorbital swelling is noted. Computed tomography (CT) of the face reveals an orbital floor fracture. Which of the following would be the most likely physical findings?
   - **a.** Cheek anesthesia, enophthalmos, and limitation of upward gaze
   - **b.** Cheek anesthesia, ptosis, and limitation of inferior gaze
   - **c.** Forehead anesthesia and afferent papillary defect
   - **d.** Forehead anesthesia, diplopia, and limitation of lateral gaze
   - **e.** Ptosis, miosis, and ipsilateral anhydrosis

Answer: a. An orbital floor fracture may entrap the inferior rectus and inferior oblique muscles, resulting in diminished upward gaze. Other findings may include ptosis, enophthalmos, ipsilateral cheek/lip anesthesia, and orbital emphysema. As many as 25% of such patients have associated globe injuries. Option E describes Horner syndrome, which is not a typical finding.

2. A 20-year-old male presents with periorbital pain and swelling after a blow to the eye by a softball. Physical examination reveals proptosis with significant decline in vision and limitation of ocular motion in all planes. Tonometry reveals an intraocular pressure (IOP) of 45 mm Hg. Which of the following should be the first indicated maneuver?
   - **a.** Acetazolamide 500 mg IV, mannitol 20 g IV, and topical timolol
   - **b.** Computed tomography (CT) scan of the head and face
   - **c.** Endotracheal intubation and hyperventilation
   - **d.** Immediate lateral canthotomy and cantholysis
   - **e.** Ophthalmologic consultation

Answer: d. These findings should make one suspect retrobulbar hemorrhage. All of these interventions are likely indicated. Intraocular hypertension may compromise central retinal artery flow. Although immediate ophthalmologic consultation and pressure-lowering maneuvers are indicated, lateral canthotomy and cantholysis will provide the most rapid temporizing measure to preserve vision.

3. A 43-year-old male presents with acute ocular pain after a splash injury from drain cleaner. What should be the sequence of interventions?
   - **a.** Copious irrigation for 10 minutes, pH testing, cyclopentolate cycloplegia, topical antibiotics/intraocular pressure (IOP) measurement
   - **b.** Intravenous (IV) analgesia, cyclopentolate cycloplegia, IOP measurement, isotonic irrigation
   - **c.** IOP measurement, analgesia, head-up position, cycloplegia
   - **d.** Phenylephrine cycloplegia, isotonic irrigation for 10 minutes, pH testing, slit-lamp examination for foreign bodies
   - **e.** Phenylephrine cycloplegia, slit-lamp examination for foreign bodies, isotonic irrigation for 10 minutes, pH testing

Answer: a. Copious irrigation, ideally beginning at the scene, is the cornerstone of management. Nitrazine pH testing after 10 minutes should guide the need for continued irrigation. Cycloplegia, IOP measurement, and topical antibiotics come after pH normalization. Phenylephrine is contraindicated for cycloplegia in these cases because of its vasoconstrictive properties.

4. A 17-year-old girl who wears contact lenses presents with a 24-hour history of right eye pain. Physical examination reveals a right corneal abrasion at the 6-o'clock position of the limbus. Appropriate treatment consists of which of the following?
   - **a.** Cessation of contact lens wear, eye irrigation (qid) with isotonic saline solution, followed by instillation of undiluted topical tetracaine for 5 days
   - **b.** Emergent ophthalmology consultation
   - **c.** Tetanus prophylaxis, eye patching for 48 hours, antibiotic ointment, and a 24-hour recheck
   - **d.** Tetanus prophylaxis, topical nonsteroidal antiinflammatory drugs (NSAIDs), cessation of contact lens wear, and a 24-hour recheck
   - **e.** Topical nonsteroidal medications, topical anti-pseudomonal antibiotic, and a 24-hour recheck

Answer: e. Tetanus prophylaxis is not indicated for corneal abrasion unless there is corneal perforation or contamination with organic material. Topical NSAIDs reduce corneal abrasion pain. Antipseudomonas coverage with cessation of contact lens wear is appropriate. Eye patching is not indicated. Administration of undiluted topical anesthetics for more than 24 hours is untested and may be dangerous. Oral analgesics may be needed.

5. How do patients with subconjunctival hemorrhage most commonly present?
   - **a.** Asymptomatic blood in the eye, noticed in the mirror or by a friend
   - **b.** Decreased visual acuity
   - **c.** Foreign body sensation
   - **d.** Modest pain
   - **e.** Photophobia

Answer: a. Any significant symptoms, such as pain, decreased vision, foreign body sensation, or photophobia, should spark the search for more serious pathology. Bilateral hemorrhage in the absence of a clear cause (e.g., severe vomiting) should raise suspicion for coagulation issues.

6. A 38-year-old man presents with unilateral left-sided visual loss after a motor vehicle collision (MVC). The only clinical finding is a left-sided hyphema rising to 50% of the height of the anterior chamber. Intraocular pressure (IOP) is 17 mm Hg in the unaffected eye and 29 mm Hg in the affected eye. Appropriate management should include which of the following?
   - **a.** Cycloplegia, intravenous (IV) mannitol, ophthalmology consultation
   - **b.** IV analgesia and antibiotic, immediate ophthalmologic consultation for decompression resulting from intraocular hypertension
   - **c.** Oral acetazolamide, shield, antiemetics, 24-hour recheck
   - **d.** Topical beta-blocker, shield, modest analgesia, admission
   - **e.** Topical beta-blocker, topical nonsteroidal antiinflammatory drugs (NSAIDs) for pain, shield, 24-hour recheck

Answer: d. Significant hyphema is an indication for admission. The presence of elevated IOP requires urgent treatment (which might also include topical alpha agonists or IV acetazolamide, and so on), shield, elevation of the head, and cautious use of systemic analgesics. Any form of platelet inhibition would be contraindicated.

7. What is the major complication of hyphema?
   - **a.** Detached retina
   - **b.** Glaucoma
   - **c.** Horner syndrome
   - **d.** Rebleeding
   - **e.** Vitreous hemorrhage

Answer: d. Rebleeding typically occurs 2 to 5 days later as the clot retracts. It is most common in patients with elevated intraocular pressures (IOPs), hyphema greater than 30% of the anterior chamber, and with delayed presentation. Rebleeding may lead to glaucoma and synechia formation.

CHAPTER 57: QUESTIONS AND ANSWERS—cont'd

8. A 48-year-old woman presents with right eye pain, photophobia, and decreased vision after a motor vehicle collision (MVC). Physical examination reveals an irregularly shaped pupil and a small hyphema. Photophobia, decreased acuity, minimal pupil reactivity, and bloody chemosis are seen on examination. What is the most likely diagnosis?

a. Acute angle-closure glaucoma
b. Blunt ciliary injury
c. Iridodialysis
d. Scleral rupture
e. Traumatic miosis

Answer: d. Scleral rupture occurs either at the insertion of the extraocular muscles or at the limbus, where the sclera is the thinnest. A "teardrop" pupil is often seen and may be accompanied by bloody chemosis or severe subconjunctival hemorrhage. Brownish-black pigment prolapse may also be seen. Intraocular pressure (IOP) may be low, but tonometry is generally contraindicated in cases of suspected globe injury.

9. A 26-year-old man presents with a 3-day history of right eye pain, decreased vision, and photophobia. He reports a history of left eye trauma 6 weeks prior, with hyphema, traumatic iritis, and persistent decreased vision. He is otherwise healthy. Physical examination reveals photophobia in the right eye with bilateral decreased vision. Before the past 3 days, the vision in the right eye had been perfect. What is the most likely explanation for his right eye symptom?

a. Collagen vascular disease
b. Post-traumatic conjunctivitis
c. Post-traumatic retinal tear
d. Spontaneous vitreal hemorrhage
e. Sympathetic ophthalmia

Answer: e. Sympathetic ophthalmia is an autoimmune inflammatory response in the unaffected eye, days to months after uveal trauma in the opposite eye. Pain, photophobia, and decreased vision are common. This patient had no findings consistent with conjunctivitis or collagen vascular disease, and a retinal tear would not typically be painful.

10. Oral antibiotics are indicated for which of the following?

a. Blepharitis
b. Chalazion
c. Dacryocystitis
d. Endophthalmitis
e. Hordeolum

Answer: c. Dacryocystitis is an infection of the lacrimal sac from nasociliary duct obstruction. Warm compresses are also recommended and may be helpful, although evidence is lacking. Warm compresses and topical antibiotics are appropriate for the other conditions. Intravitreal antibiotics are indicated for endophthalmitis.

11. Bedside ocular ultrasonography can provide useful information for which of the following conditions?

a. Lens dislocation
b. Retinal detachment
c. Vitreous hemorrhage
d. All of the above

Answer: d. A displaced lens can be seen in the relatively hypoechoic vitreous. Vitreous hemorrhage and retinal detachment can both be diagnosed with emergency department bedside ultrasonography.

Otolaryngology

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KEY CONCEPTS

Otitis Media

- Otitis media is caused by eustachian tube inflammation and dysfunction leading to fluid accumulation in the middle ear and proliferation of nasopharyngeal bacteria, most commonly *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*
- Diagnosis of acute otitis media (AOM) is made based on the presence of a middle ear effusion and signs of inflammation, including ear pain, tympanic membrane erythema and bulging, and fever.
- Bullae may be seen in some cases of AOM. This is known as bullous myringitis and treatment for this condition does not differ from non-bullous AOM.
- Mastoiditis is the most common suppurative complication of AOM though is rare in the modern era.
- Most cases of AOM resolve spontaneously, and observation for 2 to 3 days may be offered instead of immediate antibiotics in appropriately selected pediatric patients. Observation strategies are not validated in adult patients.
- Amoxicillin is the recommended initial antibiotic treatment of choice for most patients with AOM. Recurrent otitis media or treatment failures warrant selection of an alternate antibiotic regimen.
- Antibiotics alone do not provide improvement in pain in the first 24 hours of AOM, and pain should be addressed with the use of over-the-counter analgesics, such as acetaminophen or ibuprofen.
- Otitis media with otorrhea from an acute perforation is treated in the same manner as AOM without perforation. These perforations are typically small and resolve spontaneously.
- In patients with tympanostomy tubes presenting with acutely increased otorrhea, treatment with ototopical fluoroquinolone drops is recommended.

Otitis Externa

- Otitis externa (OE) is most commonly seen in warm climates and summer months. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common causative pathogens.
- Patients with immunocompromised states (diabetes) and persistent OE despite treatment should be evaluated for necrotizing OE, a severe, life-threatening infection of the outer ear and surrounding structures.
- Topical antibiotic drops are effective for most cases of OE. Systemic antibiotics are not indicated in immunocompetent patients with infection limited to the external ear canal.
- Fluoroquinolone drops are effective in most cases of OE, and they may be used in patients with a non-intact tympanic membrane. Aminoglycoside ear drops are ototoxic and should not be used in patients with a tympanic membrane (TM) perforation.

Necrotizing (Malignant) External Otitis

- Necrotizing external otitis is an aggressive from of OE with high associated mortality. Patients with diabetes mellitus, immunocompromise, and advanced age are at particular risk.
- Necrotizing otitis media should be considered in at-risk patients with progressive OE unresponsive to treatment.
- CT scanning can aid in diagnosis of necrotizing otitis media by demonstrating bony erosion and characteristic soft-tissue abnormalities.
- Necrotizing otitis media is treated with systemic antibiotics with activity against *Pseudomonas aeruginosa.* Ciprofloxacin is an appropriate initial antibiotic treatment.
- Patients with necrotizing otitis media should be managed in coordination with an otolaryngologist. Surgical intervention may be needed in refractory cases.

Mastoiditis

- Mastoiditis is the most common suppurative complication of otitis media, though it is a relatively rare condition. It may occur in patients without known preceding otitis media.
- The most common physical findings with mastoiditis are postauricular erythema and tenderness, protrusion of the auricle, and an abnormal TM.
- CT scanning is indicated in patients with suspected intracranial involvement from mastoiditis.
- Mastoiditis is treated with vancomycin (15 mg/kg IV), and an agent active against *Pseudomonas aeruoginosa* is added in those who have previously received antibiotics.
- Consultation with an otolaryngologist is advised to assist in management of mastoiditis.

Sudden Hearing Loss

- Sudden sensorineural hearing loss (SSNHL) is defined as acute hearing loss over a period less than 3 days and is often misdiagnosed.
- SSNHL is idiopathic in 70% of cases. It may also be secondary to infection, otologic disease, trauma, vascular disease, hematologic disorders, or neoplasm.
- Imaging is not warranted in the ED for SSNHL unless a space-occupying lesion is suspected.
- SSNHL is treated with steroids (prednisone 1 mg/kg/day up to 60 mg, tapered over 10 to 14 days), and prompt surgical follow up for further evaluation.

Epistaxis

- Epistaxis is distressing to patients but rarely life-threatening. Most nosebleeds arise from an anterior locus.
- A causative link between hypertension and epistaxis has not been clearly established; however, patients are often hypertensive upon presentation, which may be associated with persistent bleeding.

Continued

KEY CONCEPTS—CONT'D

- Most cases of anterior epistaxis can be managed in the ED with a combination of direct pressure, topical vasoconstrictive drugs, chemical cautery and packing, as needed. Tranexamic acid is an effective adjunct to these treatments that decreases immediate and delayed bleeding.
- Posterior epistaxis requires specialized packing techniques and monitoring in an inpatient setting.
- Refractory cases of epistaxis may require embolization or surgical treatment
- Routine use of prophylactic antibiotics in patients treated with anterior packing for epistaxis is not recommended.

Sialolithiasis

- Sialolithiasis is most commonly seen in the submandibular salivary gland. Risk factors include dehydration, anticholinergic and diuretic medications and smoking.
- Sialolithiasis may be treated with manual massage of the gland, sialogogues and anti-inflammatory pain medications.
- CT scan is the preferred imaging modality for suspected sialolithiasis and can identify stones and evidence of infection.
- Sialadenitis is an associated infection of the salivary glands, and antibiotics such as amoxicillin/clavulanate or clindamycin should be added to the treatment regimen.

Neck Masses

- Neck masses in children are likely inflammatory or benign congenital abnormalities. In adults, neck masses commonly represent malignancies.
- Physical examination findings such as stridor, dysphagia, voice changes and referred pain can help localize symptoms and guide diagnostic approach.
- CT scan with contrast is the preferred initial imaging modality to characterize the neck mass and involvement of surrounding structures.
- Patients with airway compromise secondary to a neck mass warrant emergent airway management and ENT evaluation.
- Patients with hoarseness lasting greater than 2 weeks and patients with neck masses unresolved within 2 weeks should be evaluated in follow-up by an otolaryngologist.

OTITIS MEDIA

Foundations

Background and Importance

Otitis media is broadly defined as inflammation of the middle ear and is a continuum of disease. Acute otitis media (AOM) is characterized by the presence of a middle ear effusion with signs and symptoms of an acute infection. This has also been called acute suppurative or purulent otitis media. Otitis media with effusion (OME) describes a middle ear effusion without signs or symptoms of an acute infection. Chronic otitis media refers to prolonged discharge from the ear through perforation of the tympanic membrane (TM). Recurrent otitis media is defined by three or more episodes of AOM in 6 months or four episodes within 1 year.

AOM is one of the most common diseases affecting preschool children in the United States (US) and is the primary driver of pediatric antibiotic use in the outpatient setting.[1] The peak incidence is between 6 and 15 months of age.[2] Risk factors for the development of otitis media include male sex, non-Hispanic white race, daycare attendance and family history of recurrent otitis media.[3] Additional modifiable risk factors include parental smoking and pacifier and bottle use. Breastfeeding is shown to be protective.[4]

Children with anatomic abnormalities, such as cleft palate and Down syndrome, have a higher rate of OM, likely due to eustachian tube abnormalities. Pneumococcal vaccination in childhood has significantly decreased the incidence of both pneumococcal and non-pneumococcal cases of AOM.[4,5] AOM is less common in adults but the diagnostic and treatment approach is overall similar to that in children. OME is also less commonly seen in adults and is associated with head neck malignancy.

Anatomy and Pathophysiology

The eustachian tube, which lies between the middle ear cavity and nasopharynx, ventilates the middle ear to equilibrate pressure, allows for middle ear drainage, and provides protection from regurgitated nasopharyngeal secretions. The eustachian tube may become mechanically or functionally obstructed due to inflammation from an upper respiratory infection or due to anatomic factors, decreasing middle ear ventilation. This results in a negative middle ear cavity pressure, and fluid accumulates in the middle ear space. Colonized bacteria and respiratory viruses from the nasopharynx enter the middle ear cavity, leading to inflammation, further fluid accumulation and increased pressure; the signs and symptoms of AOM then follow.[6]

AOM is commonly a co-infection of viral and bacterial pathogens, and viruses have been isolated from middle ear aspirates in children in 70% of cases.[6] The most commonly isolated bacterial pathogens in AOM are *Streptococcus pneumoniae, Haemophilus influenzae* (primarily non-typeable), and *Moraxella catarrhalis*. The widespread use of the pneumococcal vaccination has changed the frequency of these common organisms, with *H. influenzae* increasing in frequency in some settings, particularly in persistent AOM and treatment failures. *H. influenzae* is also a common pathogen identified in cases of acute otitis media with TM perforation.[7] Rarer causative pathogens include *Streptococcus pyogenes, Staphylococcus aureus, Mycobacterium tuberculosis*, *Chlamydia trachomatis*, and gram-negative species.

In young infants with AOM, the associated bacterial pathogens are typically the same as in older children; however, in neonates, Group B *Streptococcus*, *S. aureus*, and gram-negative bacteria are also possible.[8]

Clinical Features

Ear pain, unilateral or bilateral, is the most important symptom for making the diagnosis of AOM. Patients with AOM may present with a multitude of symptoms, such as cough, upper respiratory tract symptoms, poor appetite, vomiting, fever, and pulling at the ears, all of which are nonspecific. In fact, there is no constellation of symptoms or scoring systems that reliably predict AOM, and examination of the tympanic membrane is essential to make the diagnosis.

During the physical examination, the auricle and external canal are inspected for signs of erythema, discharge, or tenderness. If the canal is occluded with cerumen, curettage or gentle irrigation may clear the canal to improve visibility. The TM in an uninfected ear may be pearly gray, pink, amber or blue. The presence of erythema, in itself, does not indicate infection since crying or fever may cause TM hyperemia. However, a TM that is distinctly or strongly erythematous suggests AOM. The presence of opacification, bubbles, air fluid levels, retraction of the TM, or lack of movement with pneumatic otoscopy are suggestive of a middle ear effusion. A moderate to severely bulging tympanic membrane is highly predictive of acute otitis media and represents the most important diagnostic characteristic.[4] A comparison examination of the other ear may help in confirming suspected infection.

Bullae may be seen on the TM in up to 5% of cases of AOM in children younger than 2 years. This condition is called bullous myringitis,

and while it was previously thought to be caused by *Mycoplasma pneumoniae,* cultures of middle ear aspirates in children with this condition generally yield the typical AOM pathogens. Thus, bullous myringitis is not treated differently than non-bullous cases of otitis media.

Children with purulent conjunctivitis may have concomitant AOM, a symptom complex known as otitis-conjunctivitis syndrome, which is predominantly caused by *H. influenza.*

In neonates, the TM is in a highly oblique position and normally appears thickened and opaque in the first few weeks of life. With tympanostomy tubes, even in the absence of infection, the TM may have decreased mobility, altered landmarks, opacity, or dullness. If the tube is patent, erythema and discharge indicate infection. If the tube is not patent, typical erythema, bulging of the TM, and immobility indicate AOM.

Severe complications of otitis media are categorized anatomically as intratemporal or intracranial, and they are both rare (less than 1% incidence) in the era of antibiotic treatment. Intratemporal complications include mastoiditis, facial nerve paralysis and conductive and perceptive hearing loss. Intracranial complications include meningitis and intracranial abscesses.[9] The development of each these complications may occur through direct extension of infection through diseased bone and blood vessels or extension of infection along existing pathways, such as the round or oval windows.

Spontaneous perforation of the tympanic membrane occurs in between 5% and 30% of cases of AOM and occurs more commonly in children with frequent episodes of OM and in those with a history of TM perforation. Perforation occurs most commonly anteriorly and inferiorly at the pars tensa and resolves rapidly and spontaneously, generally without residual clinical problems.[7] However, AOM with perforation can result in a persistent TM defect, chronic otitis media, or both.

Chronic otitis media (COM) refers to inflammation of the middle ear that persists for 6 weeks or longer, accompanied by discharge through a perforated membrane. Chronic TM perforation may allow keratin-producing squamous epithelium to migrate into and accumulate in the middle ear, resulting in cholesteatoma. More commonly, cholesteatoma results from chronic OME in which retraction of the TM results trapped pockets of keratin-producing epithelial cells behind the tympanic membrane. Cholesteatoma may result in hearing loss, temporal bone destruction and cranial invasion.[10]

Differential Diagnoses

AOM is uncommon in children younger than 6 months as a result of the protection of maternal antibodies. Other sources of infection should be investigated in a febrile, ill-appearing infant. In addition to AOM, other causes of otalgia include OME, trauma, foreign bodies, and complications of OM, such as mastoiditis and referred pain from the teeth, sinuses, throat, or temporomandibular joint (Box 58.1).

Diagnostic Testing

The primary diagnostic modality for AOM is direct visualization with pneumatic otoscopy to confirm bulging and immobility of the TM.

BOX 58.1 Differential Diagnosis of Acute Otitis Media

Otitis media with effusion
Trauma
Otic foreign bodies
Mastoiditis
Otitis externa
Referred pain from teeth, sinuses, throat or temporomandibular joint

Management

The American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) published updated guidelines for the diagnosis and management of AOM in children in 2013 and reaffirmed in 2019.[4] These guidelines address diagnosis, pain management, observation, and antibiotic recommendations and apply to healthy children, not those with anatomic conditions that put them at risk for infection. The guidelines were developed by a multispecialty panel, and we believe are both reasonable and applicable to emergency medicine practice.

AOM can cause substantial pain, which should be appropriately addressed. Antibiotic treatment does not reduce the patient's pain during the first 24 hours of treatment, so analgesics are usually required.[2,4] Acetaminophen and ibuprofen are safe and available over the counter and are first-line analgesics in most cases. Each agent has been shown to be more effective than placebo at reducing pain, and the adverse events do not appear to differ between these analgesics for this indication. There is insufficient evidence to recommend combination therapy with ibuprofen and acetaminophen over monotherapy.[11] Topical therapies, such as lidocaine drops have been shown to demonstrate a brief improvement in pain, however, the dose is not well-established.[4] Antiyprene-benzocaine and other benzocaine-containing topical otic analgesics used have been removed from the US market by the Food and Drug Administration (FDA), as many of these medications were not evaluated or approved by the FDA for efficacy or safety.[12]

Children younger than 2 years, those with bilateral disease, or those with associated otorrhea gain the greatest benefit from antibiotic treatment for AOM. However, approximately 80% of cases of AOM resolve spontaneously, and the use of observation in lieu of immediate antibiotics has been advocated.[2] In appropriate cases (see following), antibiotics can be deferred, and parents can be instructed to follow-up in 48 to 72 hours there is no improvement or if clinical worsening develops. Alternately, an antibiotic prescription may be given with the instruction to fill it if there is no improvement (or worsening) within 48 to 72 hours. This is sometimes referred to as the "wait-and-see" or "safety net" prescription. Observation for AOM has been demonstrated to reduce antibiotic exposure and healthcare costs, and has not been shown to increase the risk of complications.[2,13–15]

Observation in lieu of immediate antibiotics can be considered in healthy children older than 6 months if certain criteria are met. In children between 6 months to 2 years of age, observation can be offered as an alternative to antibiotics if the infection is unilateral and the patient is absent severe signs and symptoms or otorrhea. Severe signs and symptoms are defined as moderate-to-severe otalgia of greater than 48 hours duration and temperature greater than 39°C. In children older than 2 years, observation may be offered in the absence of severe illness or otorrhea. Observation decisions must also take into account the reliability of the caregivers and ability to ensure close follow-up, and shared decision with caregivers should be used. Table 58.1 summarizes the AAP recommendations.

Antibiotics are modestly more effective than placebo for AOM in reducing pain after 24 hours, but treatment benefits should be weighed against adverse effects from the treatment itself. Diarrhea and rash occur more commonly in patients treated with antibiotics compared to those treated with placebo or observation.[2,4,16] Rates of serious complications of AOM have not been shown to differ between antibiotic treatment and observation or placebo.[2,14] Observation in appropriately selected patients remains a safe practice, and we recommend the continued use of this strategy. It is important to note the lack of data supporting the use of observation in adult patients, and antibiotics are recommended as a first-line treatment for AOM in adults.

Amoxicillin is the most cost-effective treatment for AOM, has a favorable side effect profile, and is generally palatable to children.[17,18] We

TABLE 58.1 Recommendations for Initial Management for Uncomplicated Acute Otitis Media

Age	Otorrhea With AOM	Unilateral or Bilateral AOM With Severe Symptoms[a]	Bilateral AOM Without Otorrhea	Unilateral AOM Without Otorrhea
6 months to 2 years	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation[b]
≥2 years	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation [b]	Antibiotic therapy or additional observation [b]

[a]Toxic-appearing child, persistent otalgia >48 h, temperature >39°C (102.2°F) in the past 48 h, or if there is uncertain access to follow-up after the visit.
[b]Should be a shared decision with caregivers, and a mechanism must be in place to ensure follow-up and antibiotics if the child worsens or fails to improve within 48–72 h of AOM onset.
AOM, Acute otitis media.
Adapted from Lieberthal AS, Carroll AE, Chonmaitree T, et al. Clinical practice guideline: the diagnosis and management of acute otitis media. *Pediatrics.* 2013;131:e964–e999.

recommend amoxicillin as the first-line antibiotic in the non–penicillin-allergic pediatric patient. It is dosed at 80 to 90 mg/kg/day in two divided doses. This dose is preferred because it is effective against susceptible and intermediately resistant strains of *S. pneumonia*, and because only 15% to 20% of children have poor gastrointestinal absorption of amoxicillin.

In patients with reported penicillin allergies, it is important to ascertain the specifics and severity of prior reactions. There is only minimal cross-reactivity to cephalosporins for patients with a penicillin allergy, and the use of a second- or third-generation cephalosporin is generally considered safe in this setting, unless the child has a previous adverse reaction to cephalosporins or has a history of severe allergic reaction to penicillin. In patients with non-severe penicillin allergy history, alternate treatment options include cefdinir (14 mg/kg/day in one or two divided doses), cefuroxime (30 mg/kg/day in two divided doses), cefpodoxime (10 mg/kg per day in 2 divided doses), and ceftriaxone (50 mg/kg once daily for 3 days, max 1000 mg/day) IM or IV for 3 days.

In pediatric patients with cephalosporin allergy, or in those with history of severe penicillin allergy, alternate outpatient choices are limited, but macrolides and clindamycin are possible options. However, these agents have less favorable spectra of coverage for AOM pathogens. Macrolides have limited activity against *S. pneumoniae* and *H. influenzae*, and clindamycin has limited coverage of *H. influenzae*. Despite these limitations, these agents are preferred in patients with severe penicillin allergy. Clindamycin is dosed at 30 to 40 mg/kg/day divided TID, and azithromycin is given at 10 mg/kg for an initial dose, followed by 5 mg/kg for days 2 through 5.

Children who have taken amoxicillin in the previous 30 days, or those with concurrent conjunctivitis, or those in whom coverage of β-lactamase–positive *H. influenzae* and *M. catarrhalis* is desired should be initially treated with amoxicillin-clavulanic acid (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate, divided TID).

Patients should be reevaluated in 3 days if there is no improvement. Treatment failure is defined by a lack of improvement in signs and symptoms. The reasons for treatment failure may include an incorrect initial diagnosis or antibiotic resistance. In these cases, antibiotic agents effective against the β-lactamase–producing organisms *H. influenzae* and *M. catarrhalis* should be utilized. Recommended antibiotics include amoxicillin-clavulanate (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate) or IM or IV ceftriaxone (50 mg/kg IV or IM once daily for 3 days). Table 58.2 summarizes the AAP/AAFP guidelines for antibiotic treatment.

Patients with AOM for whom treatment with appropriate β-lactam antibiotics has failed, or in patients with cephalosporin or severe penicillin allergies for whom macrolide or clindamycin therapy has failed should be referred to a pediatric infectious disease specialist or otolaryngologist.

AOM treatment historically involved a 10-day course of oral antibiotics, but studies have demonstrated similar efficacy for shorter courses of treatment with less side effects for non-severe cases of AOM.[4,19] Patients younger than 2 years, those with TM perforations, or those with chronic or recurrent infections should be treated with a 10-day course. Children older than 2 years with a first-time infection, non-severe signs and symptoms and an intact TM can be treated with a 7-day course. Antibiotic treatment choices for AOM in adults mirror those used in children. The use of antihistamines, decongestants, or steroids are not recommended for the treatment of an acute episode of otitis media.

Patients with AOM associated with otorrhea secondary to acute TM perforation are treated with an oral antibiotic, following the same recommendations as for AOM with an intact membrane. There is no advantage to adding topical antibiotic therapy in this situation.

Tympanostomy tubes may be used in cases of recurrent or complicated AOM, and this represents one of the most common operative procedures for children in the United States. Such patients may present with otorrhea, and in general, increased drainage from a tympanostomy tube represents an acute infection. The organisms involved are usually the same that cause AOM, particularly in children younger than 2 years. *Pseudomonas aeruginosa, S. aureus, and Staphylococcus epidermidis* may also be seen. In the acute setting, topical antibiotic administration with ofloxacin (5 drops to the affected ear bid for 10 days) or ciprofloxacin-dexamethasone (four drops to affected ear bid for 7 days) is the preferred treatment, as these medications may be used in patients with a non-intact TM. Systemic treatment should be reserved for patients showing signs of complicated or invasive infections or signs of systemic disease.

Chronic suppurative otitis media is characterized by chronic middle ear inflammation and otorrhea associated with a TM perforation. It is one of the most common childhood infectious diseases worldwide and a leading cause of hearing impairment in resource limited settings. *P. aeruginosa and S. aureus* are common etiologic pathogens. Topical ofloxacin or ciprofloxacin are the recommended antibiotic treatments.

After a 10-day course of antibiotics, patients may demonstrate a middle ear effusion, but the majority of these cases resolve spontaneously. Patients with OME are generally observed with serial follow-up to reassess for significant hearing loss or structural abnormalities. Antibiotics, antihistamines, decongestants and steroids offer little or no benefit and are not recommended. Tympanostomy tubes may be beneficial in children with persistent OME with hearing loss, those with structural damage to the TM and middle ear, and in children at risk for speech, language, or hearing problems. Adenoidectomy may also be offered in specific cases.[20–22]

Disposition

Patients with acute otitis media should be seen in 48 to 72 hours if there is no improvement in symptoms. Children who improve can

TABLE 58.2 Recommended Antibiotics for Initial Treatment of Pediatric Patients With Acute Otitis Media and in Those Who Have Failed Initial Antibiotic Treatment

INITIAL ANTIBIOTIC TREATMENT		IF FAILURE OF INITIAL ANTIBIOTIC TREATMENT	
First Line	**Alternate[a]**	**First Line**	**Alternate**
Amoxicillin (80–90 mg/kg/day in two divided doses)	Cefdinir 14 mg/kg/day in one or two doses	Amoxicillin-clavulanate 90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate in 2 to 3 divided doses	Ceftriaxone 50 mg/kg IM or IV once daily for 3 days
Amoxicillin-clavulanate[b] (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate in 2 to 3 divided doses)	Cefuroxime 30 mg/kg/day in two divided doses	Ceftriaxone 50 mg/kg IM or IV once daily for 3 days	Clindamycin 30–40 mg/kg/day in three divided doses with third-generation cephalosporin[c]
	Cefpodoxime (10 mg/kg/day in two divided doses)		Tympanocentesis Consult specialist[d]
	Ceftriaxone 50 mg/kg IM or IV once daily for 1 or 3 days		

[a]Consider in penicillin allergy. Cefdinir, cefuroxime, and ceftriaxone are highly unlikely to be associated with cross-reactivity with penicillin allergy on the basis of their distinct chemical structures.
[b]May be considered initially for patients who have received amoxicillin in the previous 30 days or who have otitis-conjunctivitis syndrome.
[c]If failure of second antibiotic.
[d]Perform tympanocentesis and drainage if skilled in the procedure or seek a consultation from an otolaryngologist for tympanocentesis and drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek and infectious disease specialist consultation.
Adapted from Lieberthal AS, Carroll AE, Chonmaitree T, et al. Clinical practice guideline: the diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964–e999.

be followed up in 8 to 12 weeks to ensure resolution of any residual effusion. Children with complications of AOM warrant referral to an otolaryngologist. Adults who have persistent OME warrant otolaryngology referral to rule out nasopharyngeal carcinoma.

OTITIS EXTERNA

Foundations

Otitis externa (OE) is inflammation of the external auditory canal. The external auditory canal is lined with squamous epithelial cells and cerumen glands that provide a protective lipid layer. This protective layer may be disrupted by high humidity, increased temperature, maceration of the skin after prolonged exposure to moisture, and local trauma (cotton swabs or the use of hearing aids), resulting in the introduction of bacteria. Otitis externa (OE) is most commonly caused by *P. aeruginosa* and *S. aureus,* including methicillin-resistant *S. aureus*.[23,24] It occurs most often in the summer and in tropical climates and is also referred to as swimmer's ear or tropical ear.

Clinical Features

The diagnosis of OE is made clinically. The external auditory canal (EAC) may initially be pruritic and progress to ear pain. Additional symptoms include ear fullness, discharge, hearing loss or jaw pain. On otoscopy, the EAC will often appear erythematous and edematous. Manipulation of the auricle or tragus classically reproduces the discomfort. Debris or cerumen visible within the EAC may be yellow, brown, white, or gray. There may be associated lymphadenitis, TM erythema, or local cellulitis. Clinical assessment should include history related to immunocompromise, diabetes mellitus, TM tubes or non-intact TM, as these factors may modify management of OE.[25]

Differential Diagnoses

It may be difficult to distinguish OE from AOM with perforation and otorrhea, particularly in children. The TM may be erythematous in both conditions, and a TM perforation may be small and difficult to visualize in AOM with otorrhea. EAC edema may preclude a full view of the TM, and EAC discharge may appear similar in each condition. EAC pain with traction of the pinna and severe pain with otoscopy points more towards a primary external otitis. In equivocal cases, it is reasonable to treat for both conditions.

Otomycosis is a fungal infection of the ear canal and can occur as a primary or secondary infection and accounts for 10% of cases of OE. Itching is the prominent symptom, often with minimal pain or otorrhea. *Aspergillosis* and *Candida* are the causative organisms in most cases. Otomycosis usually affects individuals in tropical climates, those with diabetes, and immunocompromised patients.

Furunculosis is a small, erythematous, and well-circumscribed infection of the cartilaginous portions of the external canal, usually caused by *S. aureus.* Auricular cellulitis may cause erythema, induration, and other systemic infectious signs.

Skin conditions such as eczema, seborrhea, and contact dermatitis can all mimic OE. A careful dermatologic history, as well as medication and exposure history, should be elicited. Exposure to reactive metals from devices such as hearing aids, chemicals from cosmetics and shampoos are also differential considerations.

Herpes zoster oticus, also known as Ramsay-Hunt syndrome, is a manifestation of varicella zoster reactivation affecting the auricle, with resulting facial paralysis that may involve multiple cranial nerves. It initially causes pain, erythema, and swelling, with vesicles developing approximately 3 to 7 days later (Box 58.2).

Diagnostic Testing

OE is a clinical diagnosis. Generally, additional diagnostic testing is not indicated.

Management

Treating OE involves cleaning the canal and treating the infection. The external canal may be cleaned with a small cotton swab or combination of gentle suctioning and irrigation, depending on the degree of obstructing exudate and whether there is an intact TM.

BOX 58.2 Differential Diagnosis of Otitis Externa

Acute otitis media with otorrhea
Fungal infections of the ear canal
Auricular cellulitis
Furunculosis
Eczema
Seborrhea
Contact dermatitis
Herpes zoster oticus
Necrotizing external otitis

Topical antibiotics are highly effective for treatment of OE, and they remain the mainstay of therapy for uncomplicated cases, with clinical cure rates of 65% to 90% within 10 days. The addition of systemic antibiotics to topical therapy does not improve cure rate in uncomplicated OE and is not indicated in most immunocompetent hosts with infection localized to the EAC. Co-administration of topical and systemic antimicrobials are reserved for cases in which the infection extends beyond the ear canal, or in patients with significant immunocompromise, including those with poorly controlled diabetes.[25] In situations where systemic antibiotics are indicated, ciprofloxacin (adult dosage, 500 mg BID for 7 to 10 days) is recommended, in combination with topical antibiotic drops.

Many effective FDA-approved ototopical antibiotics are available, and cost and side-effect profile should be considered when choosing a drug. While there is not strong evidence for the superiority of any one agent, fluoroquinolone-containing drops may have a modest advantage in bacteriologic cure rates.[25] Otic corticosteroids can reduce inflammation and the duration of ear pain in OE, and several otic drops are available as a combination corticosteroid and antibiotic. However, the addition of a steroid formulation to antibiotics alone has not been shown to change clinical cure rate.

Fluoroquinolone otic drops are effective against common OE pathogens, including *P. aeruginosa* and *S. aureus*, and demonstrates adequate activity against MRSA at the high concentrations delivered by topical therapy.[26] Quinolone drops may also be used in the setting of a non-intact TM, in contrast to otic aminoglycosides, which are contraindicated in this situation due to their ototoxicity. We recommend ofloxacin otic at a dose of 5 drops in the affected ear(s) QD for 7 days in children less than 13 years and 10 drops in the affected ear(s) QD for 7 days in those older than 13 years. A reasonable alternative is ciprofloxacin plus dexamethasone (Ciprodex), at a dose of 4 drops in the affected ear(s) BID for 7 days.

Fluoroquinolone otic drops are relatively costly, and polymyxin B, neomycin, and hydrocortisone (Cortisporin) suspension is an effective and less expensive alternative, dosed as 3 drops to the affected ear TID or QID. This medication should not be given in patients with a TM perforation due to ototoxicity, and some patients to may develop cutaneous sensitivity to the neomycin component.

Having the patient lie down for 5 minutes after the otic solution has been placed can improve drug delivery. Commercially available wicks made of compressed cotton or hydroxycellulose can also be placed to facilitate medication delivery. If available, these should be inserted when EAC swelling is significant enough that drops could encounter difficulty entering the ear canal. The wick is inserted 10 to 12 mm into the canal, moistened with antibiotic drops, and left in place for 2 to 3 days pending follow-up. OE is often painful, and analgesia should be appropriately addressed.

Disposition

Patients with OE rarely require admission. Patients should be followed for symptom improvement within 2 to 3 days. If there is clinical worsening or no response to therapy, resistant organisms or other conditions such as necrotizing external otitis should be considered. Patients who have a wick placed should be evaluated in 2 to 3 days to reassess and to ensure removal of the wick.

NECROTIZING (MALIGNANT) EXTERNAL OTITIS

Foundations

Necrotizing external otitis (NEO) is an aggressive form of OE, also known as malignant OE, due to its relatively high rate of morbidity and mortality. This disease is most commonly seen in patients with advanced age, immunocompromise, and in particular, diabetes mellitus. In a recent national inpatient database review, diabetes was a comorbidity in 55% of cases of NEO.[27] *P. aeroginosa* is the predominant pathogen, identified in the majority of cases.[28–33] *S. aureus, S. epidermidis, Proteus mirabilis,* and *Aspergillus* have also been described as causative organisms. The infection begins in the external canal and progresses through the periauricular tissue and cartilaginous bony junction of the external auditory meatus. It may spread to the base of the skull at the temporal bone, with a resultant osteomyelitis of the skull base. The facial nerve is the first cranial nerve affected, but other nerves may also be involved.[34] The pathogenesis is uncertain but may be related to vascular insufficiency or immune dysfunction.

Clinical Features

Patients may have persistent otorrhea unresponsive to topical medications, severe otalgia, headache, and periauricular pain and swelling. The diagnosis should be considered for at-risk patients who have a prolonged course of OE. The characteristic clinical finding is granulation tissue on the floor of the ear canal at the bony cartilaginous junction. Cranial nerve VII is most commonly involved, and this manifests as facial paralysis. Further extension can result in involvement of the additional cranial nerves. Cranial nerve involvement is not associated with increased mortality from NEO.[31] Additional complications include meningitis, brain abscess, and thrombosis of the sigmoid sinus.

Differential Diagnoses

Differential considerations include severe OE, otitis media, mastoiditis, trauma, and referred pain from the teeth, sinuses, throat or temporal mandibular joint (Box 58.3).

Diagnostic Testing

There is no single diagnostic criterion for necrotizing external otitis. The diagnosis is made from a range of clinical, laboratory, and radiographic findings. The C-reactive protein level and erythrocyte sedimentation rate may be elevated, but they are nonspecific markers. In the ED, computed tomography is the initial study of choice and, in most cases, will identify bony erosion and soft tissue abnormalities. Magnetic resonance imaging can be helpful in determining the full extent of disease and evaluating for intracranial complications, and gallium nuclear medicine scans are helpful in evaluating treatment response.[35]

Management and Disposition

If NEO is suspected, systemic antibiotic therapy should be initiated, and consultation should be made with an otolaryngologist. Ciprofloxacin 400 mg IV every 12 hours can be given as monotherapy, or in combination with an antipseudomonal β-lactam depending on the severity of illness and local *Pseudomonas* resistance to fluoroquinolones. Piperacillin-tazobactam (4.5 g IV every 6 hours) or cefepime (2 g IV every 6 hours or 2 g extended infusion every 8 hours) are appropriate options for combination therapy with ciprofloxacin. Treatment may be required for 6 to 8 weeks. Although extensive surgical treatment was previously required, surgical intervention

BOX 58.3 Differential Diagnosis of Necrotizing External Otitis

Otitis externa
Otitis media
Mastoiditis
Trauma
Referred pain

BOX 58.4 Differential Diagnosis of Mastoiditis

Otitis media
Otitis externa
Necrotizing external otitis
Skull fracture
Lymphadenitis
Deep space neck infections

is now used in a minority of cases, particularly to obtain cultures, debride necrotic tissue or if medical management is failing.[27,31]

Patients are generally managed initially in an in-patient setting in consultation with an otolaryngologist.

MASTOIDITIS

Foundations

Mastoiditis is the most common suppurative complication of otitis media, although the incidence of acute and chronic mastoiditis has decreased significantly since the advent of antibiotics, and it is rare in the modern era.[36–38] Acute mastoiditis may occur with or without known preceding acute otitis media, and may occur as a complication of leukemia, mononucleosis, sarcoma of the temporal bone, and Kawasaki disease. It has also been described as a complication of cochlear implant placement.[39]

The middle ear and mastoid air cells are connected by the aditus ad antrum. If this narrow connection becomes obstructed, a closed space is formed with the potential for mastoid abscess development and bone destruction. Infection may spread from the mastoid air cells by venous channels, resulting in inflammation of the overlying periosteum. Progression results in the destruction of the mastoid bone trabeculae and coalescence of the cells, resulting in acute mastoid osteitis or coalescent mastoiditis.

Data are conflicting as to whether the incidence of mastoiditis has decreased in the post-pneumococcal vaccine era, and *S. pneumoniae* continues to be a leading cause of acute mastoiditis. Group A streptococcus is another commonly isolated pathogen. *P. aeruginosa*, *S. aureus* and *Fusobacterium necrophorum* are important emerging pathogens, particularly in patients who have recently received antibiotics.[37,40–42]

Clinical Features

Clinical findings in acute mastoiditis include fever, headache, otalgia, and erythema. Pain is nearly always present. There are no specific diagnostic criteria, but the most common physical findings are postauricular erythema and tenderness, protrusion of the auricle, and an abnormal TM. The TM is similar to that seen in AOM—erythema, bulging, and decreased mobility—but may be normal in 10% of cases. Suspicion should be heightened if symptoms of AOM have lasted longer than 2 weeks.

Differential Diagnoses

The differential diagnosis of mastoiditis includes severe otitis media, external otitis, skull fracture, posterior auricular lymphadenopathy or lymphadenitis, and deep space neck infections (Box 58.4).

Diagnostic Testing

Although the diagnosis of mastoiditis can be made clinically in patients with typical findings, a CT scan is indicated in patients with neurologic symptoms suggestive of intracranial extension or when there is failure to improve with conservative therapy.[43] Fig. 58.1 is a CT scan demonstrating acute mastoiditis.

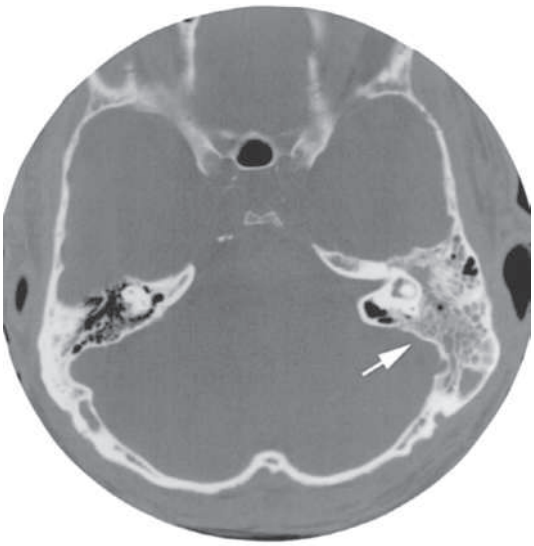


Fig. 58.1 CT Scan of Mastoiditis. (From McWhorter AJ, Limb CJ, Niparko JK. Otologic and skull base emergencies. In: Eisele DW, McQuone SJ, eds. *Emergencies of the Head and Neck*. St. Louis: Mosby; 2000:384.)

Management and Disposition

Parenteral antibiotics should be administered to patients with suspected mastoiditis. In patients without recurrent acute otitis media or recent antibiotic use, vancomycin at a dose of 15 mg/kg IV is recommended. In patients who have had an episode of acute otitis media within the past 6 months, or in patients with recent antibiotic use, we recommend the addition of an antibiotic with activity against *P. aeruginosa*, such as cefepime, at a dose of 50 mg/kg IV (max 2 g) in pediatric patients, or 2 g IV in adults. Patients may be managed with or without surgical procedures which may range from myringotomy and tympanostomy tube placement to mastoidectomy.[44]

Hospitalization is usually necessary for the administration of IV antibiotics. Early otolaryngologic referral is also advised for possible aspiration and drainage of the middle ear, as well as the management of any potential complications.

SUDDEN HEARING LOSS

Foundations

Sudden sensorineural hearing loss (SSNHL), defined as the idiopathic loss of hearing of 30 dB over at least three test frequencies, occurring over a period of less than 3 days, is considered an otolaryngologic emergency. Any age group can be affected, but the peak incidence occurs in the fifth or sixth decade of life, with an equal gender distribution. Its severity ranges from difficulty with conversation to complete hearing loss.

SSNHL is idiopathic in 70% of cases. It may also be secondary to infection, otologic disease, trauma, vascular disease, hematologic disorders, or neoplasm. A delay in diagnosis is common because the patient may report ear fullness that is often attributed to cerumen impaction or congestion from upper respiratory infections. Tinnitus is a common finding. The likelihood of recovery is related to the severity of the hearing loss, age of the patient, and associated vestibular symptoms.[45] A history should include the time of onset, history of trauma or recent illnesses, medications, and presence of otologic and neurologic symptoms.

Clinical Features

The physical examination includes a thorough inspection of the external canal and TM integrity. Weber's test for hearing and Rinne's test may help in distinguishing conductive versus sensorineural deficits. A comprehensive neurologic examination, including cranial nerve and cerebellar testing, may localize brainstem involvement.

Differential Diagnoses

The differential diagnosis for hearing loss is broad and can be differentiated into causes that involve the outer, middle, or inner ear. Outer ear causes include cerumen impaction and OE. Middle ear causes include otitis media and tympanic membrane perforation. Inner ear causes include medications, barotrauma, and autoimmune disease (Box 58.5).

Diagnostic Testing

Laboratory testing and imaging are not indicated in the ED evaluation unless the physical examination points to a space-occupying lesion (i.e., focal neurologic deficits not referable to the ear). MRI with gadolinium is the study of choice to identify retrocochlear pathology and is more likely diagnostic when the patient has associated vertigo.[46]

Management and Disposition

A tapered dose of oral steroids is the most common treatment, ideally given within the first 14 days but may have benefit up to weeks after the onset.[47] The usual dose and the one we recommend is prednisone 1 mg/kg/day, up to 60 mg, tapered over 10 to 14 days. Additional treatments include hyperbaric oxygen therapy and steroids, intratympanic steroids or a combination of both oral and intratympanic steroids by providers who can offer them.[48] Patients should be counselled on the limitations of these treatments and the possibility that the hearing may not recover, though some improvement is observed in 32% to 65% of patients.[49]

Patients should receive expeditious ENT referral on discharge from the ED.

EPISTAXIS

Foundations

Epistaxis is a common otolaryngologic problem, although only a minority of patients experiencing a nosebleed will require emergency care, and death from epistaxis is exceedingly rare. Epistaxis has a bimodal distribution, with peaks in childhood and in elders.[50] Incidence is higher in winter months and in colder geographic locations. This effect may be attributable to dry air from indoor heating, which desiccates nasal mucosa, and the effect of cold temperature on coagulation.[51] Epistaxis can be quite distressing to patients, and a thorough understanding of nasal anatomy, pathophysiology and treatment allow for prompt and efficient management of the disorder.

Anterior epistaxis accounts for 90% of all nosebleeds and usually involves Kiesselbach's plexus on the anteroinferior nasal septum. Anterior epistaxis is typically unilateral. Posterior epistaxis accounts for about 10% of cases and differs from anterior bleeding in that it is more severe and occurs mostly in older adults with multiple comorbidities.

Three arteries with anastomoses between them supply the nasal area (Fig. 58.2). The sphenopalatine artery supplies the turbinates and meatus laterally and the posterior and inferior septum medially. This artery is identified in a majority of cases of severe posterior epistaxis.[52] The anterior and posterior ethmoidal arteries from the ophthalmic branch of the internal carotid artery supply the superior mucosa medially and laterally. The superior labial branch of the facial artery provides circulation to the anterior mucosal septum and anterior lateral mucosa.

Clinical Features

Initial evaluation of epistaxis focuses on airway patency, tissue perfusion and hemodynamics, and abnormalities should be addressed immediately if identified. History should specify the timing, frequency, and severity of bleeding. Additional pertinent history with regard to trauma, comorbidities, and medications should be elicited. Bleeding disorders and use of anticoagulant and antiplatelet medications are a significant risk factor for epistaxis and are associated with bleeding recurrence.[53-58] Patients often are anxious, and an elevated blood pressure is commonly seen in individuals presenting with epistaxis; however, studies have not established a causal relationship between hypertension and epistaxis. When elevated blood pressure is present, however, it may be associated with persistent epistaxis.[59,60]

During physical examination, efforts should be made to identify the source of bleeding, as this allows for application of chemical cautery in appropriate patients, which decreases risk of recurrent bleeding. To optimize physical examination of the nares in an actively bleeding patient, instruct the patient to blow their nose, and then apply bilateral pressure on the nasal septum by compressing the cartilaginous part of the nose for 10 to 15 minutes.

A nose clip can be used, and this technique has been shown to be superior to manual pressure alone.[61] Administering two sprays of 0.05% oxymetazoline into the affected naris before applying pressure will optimize hemostasis and facilitate inspection after the pressure is released.

BOX 58.5 Differential Diagnosis of Sudden Sensorineural Hearing Loss

- Cerumen impaction
- Otitis externa
- Otitis media
- Tympanic membrane perforation
- Medication side effects or toxicity
- Barotrauma
- Autoimmune disease

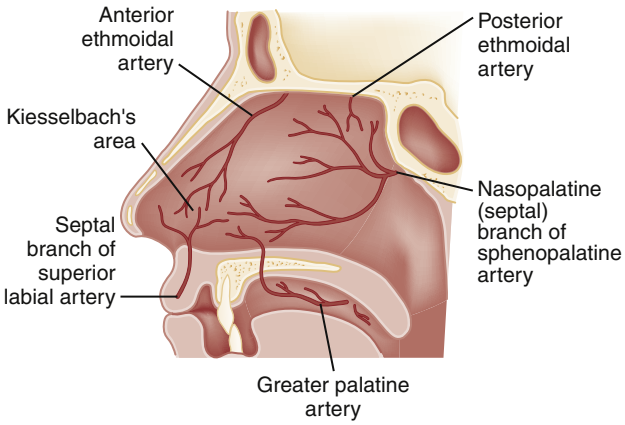


Fig. 58.2 Arterial Supply to the Medial Wall of the Nose.

This simple maneuver also educates the patient on how to self-manage further episodes. While pressure is being applied, materials for illumination, suction, visualization, and treatment should be assembled.

Upon examination, the floor of the nose should be parallel to the room floor. If the head is tilted, only the anterior and upper aspect of the nares can be visualized. A nasal speculum, if used, should be opened in a vertical direction rather than side to side in the nares, so as not to obscure the septum.

Differential Diagnoses

There are many etiologies of epistaxis, but the most common are an upper respiratory infection with associated mucosal vasodilation and trauma, either accidental or iatrogenic.

The differential diagnosis also includes nasal foreign bodies and clotting and vascular disorders. In children less than the age of 2, epistaxis is rare, and special consideration should be given to non-accidental trauma and bleeding disorders (Box 58.6).[62,63]

Diagnostic Testing

In most cases of epistaxis, diagnosis is made clinically, and diagnostic imaging and laboratory studies are not routinely indicated. Consideration of laboratory testing, including coagulation studies, should be reserved for patients on anticoagulant medications, those with severe hemorrhage or significant underlying medical conditions, such as advanced liver disease or hematologic malignancy that may contribute to coagulopathy or thrombocytopenia.

Management

Identifying and treating the source of epistaxis bleeding is important, as failure to identify the locus of hemorrhage is a significant risk factor for recurrent bleeding. Ahead of further intervention, a topical anesthetic agent, such as 2% aqueous lidocaine, should be applied via mucosal atomization or soaked gauze. When combined with a vasoconstrictive agent, this facilitates additional examination and hemostatic treatments.[64] If the bleeding site is identified, chemical cautery with silver nitrate should be considered, as it has been shown to be effective, with a low rate of re-bleeding compared with other treatment modalities.[58] Silver nitrate cautery is likely to be unsuccessful during active bleeding, so hemostasis is secured first. The area is cauterized from the periphery to the center and superiorly to inferiorly to avoid blood, which renders the silver nitrate sticks ineffective. Contact with mucosa should not be maintained longer than 15 seconds because septal damage may occur. Bilateral application of silver nitrate to the septum is not advised because it may deprive the septum of a blood supply and theoretically could lead to necrosis. If cautery is unsuccessful, apply topical thrombogenic agents, such as absorbable gelatin sponge (Gelfoam) and absorbable knitted fabric (Surgicel).

If bleeding persists, proceed to tamponade with an anterior nasal packing device. Options include polyvinyl acetal nasal tampons, such as the Merocel device (Medtronic, Inc, Minneapolis, MN) or inflatable nasal balloons, such as the Rapid Rhino device (Smith & Nephew, Austin, TX), which are coated in a procoagulant material. Such nasal balloon devices are self-lubricating once moistened; application of additional lubricant is unnecessary. They are inserted along the floor of the nose and inflated with air. For uncontrolled bleeding despite the presence of an adequately applied anterior tampon, a second anterior tampon should be inserted into the opposite naris.[65]

Topical tranexamic acid may also be used in the treatment of acute epistaxis, either as an adjunct to, or in place of packing or other hemostatic agents. Tranexamic acid functions by inhibiting fibrinolysis and has demonstrated effectiveness in a number of other clinical bleeding scenarios. A recent systematic review and meta-analysis evaluating topical tranexamic acid in the treatment of epistaxis found moderate quality evidence to support the benefit of topical tranexamic acid in reducing bleeding at 10 minutes and re-bleeding at 7 to 10 days when combined with standard care alone. There was no significant increase in adverse events among patients treated with tranexamic acid.[66-68] In one trial included in this meta-analysis, topical tranexamic acid was demonstrated to be superior to anterior nasal packing specifically in patients taking antiplatelet drugs.[69] While the dosing of topical tranexamic acid has not been standard across trials, several trials have used a dose of 500 mg of the intravenous tranexamic acid solution applied to a nasal pledget or atomized into the nose.[69–71]

Posterior epistaxis is suggested when bleeding persists in the setting of properly placed anterior nasal packing. In this case, placement of a posterior pack is necessary with a commercially available double balloon catheter device.[65] Double balloon catheters generally consist of a separately inflatable anterior and posterior portion. They are inserted along the floor of the nose after adequate topical anesthesia has been achieved. The posterior balloon is then inflated, and the device is gently seated by pulling anteriorly. The anterior balloon is then slowly inflated to a degree tolerable by the patient.

If a commercial double balloon catheter device is unavailable, a standard Foley catheter may be inserted into the nasopharynx, partially inflated with 5 to 7 mL of water, and then pulled anteriorly with an additional 5 to 7 mL of water added to the balloon if needed, but caution should be exercised to avoid pressure necrosis. Fig. 58.3 illustrates treatment of posterior epistaxis.

If these techniques do not provide successful hemorrhage control, otolaryngologic consultation is necessary. Surgical ligation has been the treatment of choice for intractable bleeding, but endovascular embolization has emerged as a treatment alternative and has a reported success rate of greater than 80%.[72] The decision to choose embolization over surgery is influenced by factors such as patient comorbidity, presence of anticoagulation, institutional experience, patient preference, and health care costs. Embolization is preferred in patients with chronic coagulation disorders and those being treated with antiplatelet/anticoagulation therapy that cannot be interrupted.[73,74]

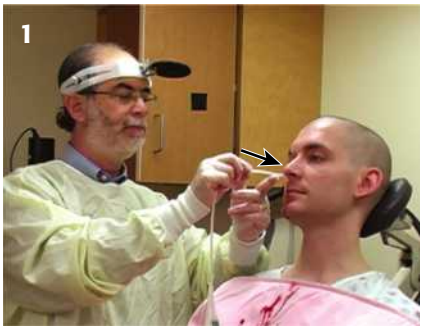
Prophylactic antibiotics remain in common use following nasal packing, given concerns for toxic shock syndrome from *S. aureus* as well as otitis media and sinusitis. However, there are no published reports

BOX 58.6 Causes of Epistaxis

- Nasal or facial trauma
- Upper respiratory tract infections
- Nose picking
- Allergies
- Low home humidity
- Nasal polyps
- Foreign body in the nose
- Environmental irritants
- Neoplasms
- Surgery (postoperative epistaxis)
- Anticoagulant or antiplatelet therapy
- Barotrauma
- Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)
- Blood dyscrasias
- Hepatic disease
- Alcoholism
- Vitamin K deficiency
- Folic acid deficiency
- Chemotherapy
- Chronic use of nasal vasoconstrictors
- Cocaine use

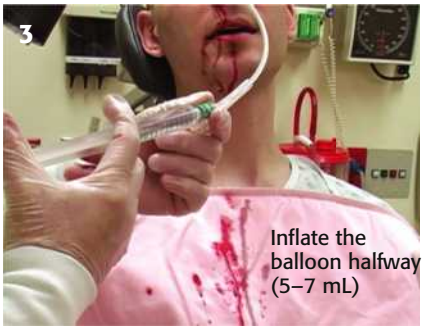
EPISTAXIS MANAGEMENT: POSTERIOR PACKING WITH INFLATABLE DEVICES

A



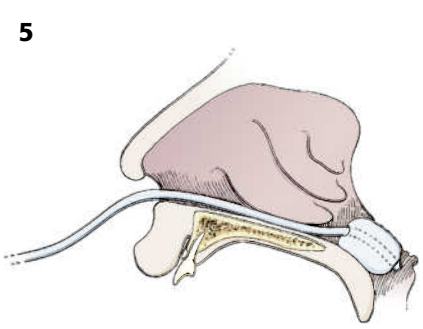
Insert a 12-Fr Foley catheter through the naris and into the posterior pharynx.

Look into the mouth to confirm that the catheter is properly positioned.



Inflate the balloon halfway with about 5–7 mL of water.

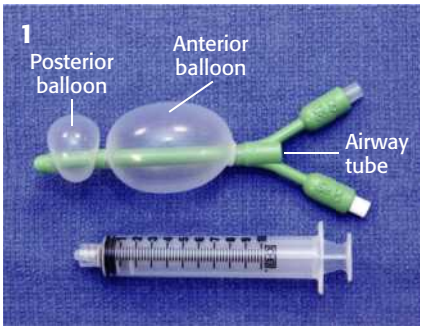
Slowly pull the catheter into the posterior nasopharynx up against the posterior aspect of the middle turbinate.



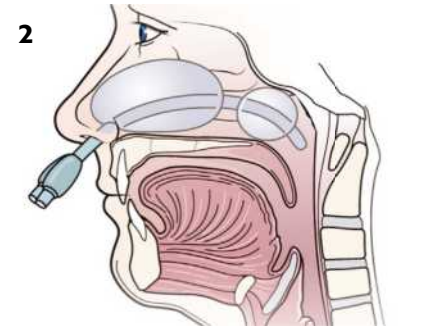
Foley catheter in proper position in the posterior nasopharynx. Inflate the balloon with another 5–7 mL of water.

While maintaining traction, place anterior packing with layered gauze. Packing of the opposite side may be required to prevent septal deviation. Place a piece of gauze on the exposed catheter and secure with an umbilical clamp.

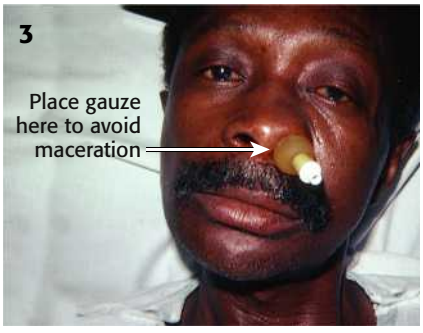
B



Double-balloon epistaxis catheters have both an anterior and posterior balloon, and some have an integral airway tube. These devices serve as an anterior and posterior pack. They are easily inserted and are often successful in the temporary control of posterior epistaxis in the ED.



Insert the lubricated device along the nasal floor as far back as possible. Inflate the posterior balloon halfway with air, apply traction to pull the balloon up against the middle turbinate, and then complete the inflation. Maintain the position of the balloon and then inflate the anterior balloon with 30 mL of air.



This patient with posterior epistaxis was successfully treated in the ED and discharged. Historically, most patients with posterior packs were admitted to the hospital; however, the ease and safety of balloon devices allow selected patients to be treated as outpatients. Consider admission for older adults and those with pulmonary or cardiovascular disease.

Fig. 58.3 Management of Epistaxis—Posterior Packing With Inflatable Devices. (A) Foley catheter technique. (B) Dual-balloon tamponade catheter. (Adapted from Riviello RJ. Otolaryngologic procedures. In: Roberts JR, ed. *Roberts and Hedges' Clinical Procedures in Emergency Medicine*. Philadelphia: Elsevier/Saunders; 2013:1330.)

of toxic shock syndrome associated with anterior nasal packing. Similarly, no studies have documented toxic shock syndrome, otitis media or sinusitis when patients were not given prophylactic antibiotics with nasal packing in place for less than 24 to 48 hours.[65,75,76] We do not recommend routine antibiotic prophylaxis after anterior nasal packing. However, antibiotics may be considered in patients with immune compromise or valvular disease, or in patients whose packing is left in place for greater than 48 hours.[65]

Disposition

Most patients with anterior epistaxis may be discharged with follow-up within 24 to 48 hours. Nasal packing is generally removed within 48 hours to avoid tissue necrosis associated with prolonged placement. Nasal packing is uncomfortable, and analgesia should be appropriately addressed at discharge.

Patients with posterior epistaxis and packing often warrant hospital admission. There has been concern that patients with posterior nasal packs may develop hypoxia as a result of a theoretical "nasopulmonary reflex." However, there is little evidence to support this theory. Adverse respiratory events are due to a combination of factors such as sedation, underlying cardiovascular or pulmonary disease, and obstructive sleep apnea. Most patients with posterior nasal packing can be admitted to a setting with continuous pulse oximetry, but patients with serious comorbidities such as heart disease or obstructive sleep apnea may require a higher level of care.

SIALOLITHIASIS

Foundations

Stones of the salivary glands occur in 1% of the population, most commonly in patients between 30 and 50 years of age. The most common gland affected is the submandibular (submaxillary) gland, accounting for 80% to 95% of cases. Stones are found less commonly in the parotid and sublingual glands. Sialolithiasis is uncommonly seen in children.

The exact causative mechanism is unclear, but sialolithiasis is thought to be due to increased viscosity of the saliva and the long upward curvature of the submandibular (Wharton's) duct. Stasis and inflammation result in precipitation of calcified stones after a nidus of a complex glycoprotein combines with calcium and phosphate. Risk factors include dehydration, diuretic or anticholinergic medications, trauma, gout, and a history of smoking.

Clinical Features

Pain from sialolith obstruction is usually associated with mealtime, when salivary secretion is increased. Patients generally present with pain, swelling, and tenderness of the gland. If the gland is infected, the patient may have systemic symptoms, such as fever or chills. The area may be erythematous, with purulence coming from the duct, a condition termed sialadenitis. *S. aureus, H. influenzae, Strep* species and anaerobes predominate in bacterial infections. Children differ in that they have a shorter duration of symptoms, and their stones present more distally in ducts than those found in adults.

Differential Diagnoses

The differential diagnosis of sialolithiasis includes other salivary gland pathology, lymph node disease, granulomatous processes, soft tissue masses, and neoplasms (Box 58.7).

BOX 58.7 Differential Diagnosis of Sialolithiasis

- Salivary gland pathology
- Lymph node disease
- Granulomatous process
- Soft tissue masses
- Neoplasms

Diagnostic Testing

CT scanning is very sensitive for salivary gland calculi of all sizes and remains the study of choice. Although there have been reports of ultrasonography recognizing up to 90% of stones larger than 2 mm, it does not allow reliable exclusion of small salivary calculi. Both modalities may help identify other causes of inflammation, such as an abscess or cellulitis.

Management and Disposition

If the salivary stone is palpable, gently massage the gland in an attempt to extract the stone. Additional measures include sialogogues (tart candies to promote glandular secretions) and analgesics. When infection is present, antibiotics with effective coverage of commonly implicated pathogens, such as amoxicillin/clavulanate (875/125 mg BID) or clindamycin (300 mg TID) are appropriate.

Stones larger than 5 mm and stones located within the gland or in the proximal duct are often resistant to conservative measures. These may require surgical or minimal invasive treatment by an otolaryngologist or oral surgeon.

NECK MASSES

Foundations

Neck masses are a relatively common clinical finding, with a multitude of causes. Children and young adults are more likely to have benign disorders, such as inflammatory or congenital abnormalities, including thyroglossal or branchial cleft cysts. Adult neck masses are more likely to be neoplastic. In general, 80% of non-thyroid neck masses in adults are neoplastic, of which 80% are malignant. In children, however, more than 80% of neck masses are benign. This is often referred to as the rule of 80, or the 80% rule. Risk factors that may predispose patients to ENT malignancies include alcohol and tobacco use, viruses such as herpes, genetics, diet, and excessive exposures to ultraviolet sunlight, dust, or chemicals.

Identifying the parotid and submandibular glands, thyroid cartilage, thyroid gland, and lymph nodes can help distinguish normal structures from other masses (Fig. 58.4). The neck is divided into cervical triangles, with the sternocleidomastoid muscle as the common boundary. The anterior portion is bordered by the midline of the neck, inferior aspect of the mandible superiorly, and anterior border of the neck posteriorly. Lesions of the skin, scalp, oral cavity, oropharynx, hypopharynx, larynx, and tongue may manifest here. The posterior triangle is bordered by the sternocleidomastoid anteriorly, posteriorly by the trapezius muscle, and inferiorly by the clavicle. Lesions in this area may include those from the nasopharynx and metastatic lesions from the lung, gastrointestinal, and genitourinary tracts.

Clinical Features

Important associated symptoms in patients with neck masses include dysphagia, odynophagia, otalgia, stridor, speech disorders, and globus phenomena. Dysphagia, or difficulty swallowing, may be caused by physical obstruction or neurologic disorders. Odynophagia is pain on swallowing and can have a number of causes, such as tonsillitis or carcinoma of the pharynx. In an adult, a sore throat that lasts for several weeks should raise the suspicion of a neoplastic process. Otalgia is pain felt in the ear that may be referred from the larynx, pharynx, or cranial

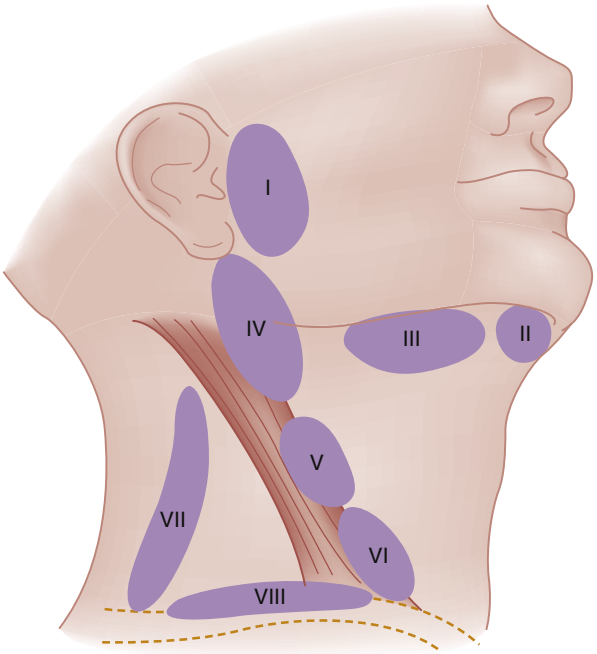


Fig. 58.4 Major Lymph Node Groups in the Head and Neck. *I,* Parotid nodes; *II,* submental nodes; *III,* submandibular nodes; *IV,* jugulodigastric nodes (superior jugular nodes); *V,* midjugular nodes; *VI,* lower jugular nodes; *VII,* spinal accessory nodes; *VIII,* subclavian nodes. Groups VI and VII are often termed *scalene nodes.* (Adapted from Moloy PJ. How to [and how not to] manage the patient with lump in the neck. In: American Academy of Otolaryngology–Head and Neck Surgery Foundation, ed. *Common Problems of the Head and Neck Region.* Philadelphia: WB Saunders; 1995:134.)

nerves V, IX, or X. Referred ear pain is an ominous sign in adults and should be presumed to be cancer until proved otherwise. Similarly, unilateral otitis media with effusion in adults should be considered nasopharyngeal carcinoma until proven otherwise.

Stridor, specifically inspiratory stridor, is diagnostic of upper airway obstruction. It localizes a lesion to above or at the level of the larynx. In adults, the presence of stridor with a neck mass increases the possibility of carcinoma. Speech disorders, particularly so-called hot potato speech, are suggestive of space-occupying lesions above the oropharynx, such as a peritonsillar abscess. Globus is the symptom of perceiving a lump in the throat. It is a commonly reported symptom, is often a functional complaint. Hoarseness is also a common complaint, with many varied descriptions, and causes range from viral pharyngitis to laryngeal cancer. Hoarseness lasting longer than 2 weeks should be investigated further. Additional history about alcohol or tobacco use, the location of the mass, rate of growth, presence of pain, and constitutional symptoms, such as fever, night sweats, and weight loss, are also helpful.

The head and neck examination may identify masses, lesions, mucosal ulcerations or discolorations, and cranial nerve abnormalities. The mass itself should be palpated for location, size, and consistency. Benign lymph nodes are generally mobile, soft, fleshy, and smaller than 1 to 1.5 cm, so any hard nodes larger than 1.5 cm with decreased mobility should be considered abnormal and as warning signs of malignancy.

Differential Diagnoses

The differential diagnosis of neck masses can generally be broken down into three categories—inflammatory, congenital, or neoplastic (Box 58.8).

Diagnostic Testing

The diagnostic strategy is tailored to findings elicited by history and physical examination. CT of the neck with contrast is the initial study of choice to evaluate the character of the mass and involvement of surrounding structures. Patients with hoarseness lasting longer than 2 weeks should be referred to an otolaryngologist for a flexible endoscopic examination unless they have developed acute stridor, dyspnea, or acute deterioration. These patients should have emergent otolaryngologic consultation for endoscopic examination of the upper airway.

BOX 58.8 Differential Diagnosis of Neck Masses

Inflammatory
Adenitis
Bacterial (*Streptococcus, Staphylococcus*)
Viral (HIV, EBV, HSV)
Fungal (coccidioidomycosis)
Parasitic (toxoplasmosis)
Cat scratch disease
Tularemia
Local cutaneous infections
Sialoadenitis (parotid and submaxillary glands)
Thyroiditis
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis

Congenital or Developmental
Brachial cleft cyst
Thyroglossal duct cyst
Dermoid cyst
Cystic hygromas
Torticollis
Thymic masses
Teratomas
Ranula
Lymphangioma
Laryngocele

Neoplastic
Benign
Mesenchymal tumors (e.g., lipoma, fibroma, neural tumor)
Salivary gland masses
Vascular abnormalities (e.g., hemangioma, AVM, lymphangioma, aneurysm)

Malignant
Primary tumors
Sarcoma
Salivary gland tumor
Thyroid or parathyroid tumors
Lymphoma

Metastasis
From primary head and neck tumors
From infraclavicular primary tumors (e.g., lung or esophageal cancer)

AVM, Arteriovenous malformation; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus.

Management and Disposition

Most masses in children are inflammatory, and it is reasonable to treat them with antibiotics. Amoxicillin/clavulanate or clindamycin are appropriate choices. Follow-up within 2 weeks should be advised. In adults, antibiotics should only be given if there is concern for a bacterial infection.[77] Adults warrant ENT referral if the mass does not resolve in 2 weeks, is enlarging or fixed, is associated with matted cervical lymph nodes, or if the masses are found in the parotid or thyroid gland.

DISCLAIMER

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The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 58: QUESTIONS AND ANSWERS

1. *Bullous myringitis* is most commonly caused by which of the following bacterial pathogens?
   - **a.** *Streptococcus pneumoniae*
   - **b.** *Pseudomonas aeruginosa*
   - **c.** *Mycoplasma pneumoniae*
   - **d.** *Staphylococcus aureus*

Answer: a. Bullae may be seen on the TM in up to 5% of cases of AOM in young children. While this finding has been historically associated with *M. Pneumoniae*, the bacterial pathogenesis of bullous myringitis is similar to that of non-bullous AOM and is treated similarly.

2. Which of the following patients with acute otitis media would be appropriate candidates for observation in lieu of immediate antibiotic treatment?
   - **a.** A 6-month-old female with bilateral middle ear effusions with red bulging tympanic membranes and fever to 103.5°F
   - **b.** A 6-year-old male with three days of ear pain, fever to 101.5°F and an erythematous, bulging TM with purulent material seen in the external ear canal
   - **c.** A 2-year-old male without significant medical history presenting with 1 day of right ear pain and fever to 100.5°F. His exam reveals an erythematous TM with a middle ear effusion. There is no otorrhea or TM perforation noted.
   - **d.** A 5-month-old female with fever to 101.2°F with an erythematous, bulging left TM seen on otoscopy.

Answer: c. Observation for 48 to 72 hours can be considered in lieu of immediate antibiotics in pediatric patients aged 6 months to 2 years with unilateral AOM of <48 hours duration, in the absence of severe symptoms (including temperature <102.2°F) or otorrhea. Patients older than 2 years with unilateral or bilateral AOM without otorrhea or severe symptoms can be appropriate for an observation strategy. Patients with otorrhea and those younger than 6 months should be treated with antibiotic therapy and are not appropriate for an observation approach. This decision should be made in conjunction with caregivers, and reliable follow-up must be in place. This approach is not validated in adult patients.

3. A 72-year-old female with a history of poorly controlled diabetes mellitus presents to the ED with severe left ear pain of 2 weeks duration. On ear examination, granulation tissue is noted in the external auditory canal. The patient has facial asymmetry, which her family states developed 2 days ago. What is the most appropriate imaging modality for this patient in the ED?
   - **a.** MRI with contrast
   - **b.** CT with contrast
   - **c.** Skull x-ray
   - **d.** Transcranial doppler ultrasound

Answer: b. This patient is presenting with findings consistent with necrotizing external otitis: granulation tissue in the EAC and facial paralysis. CT scan is the most appropriate choice for imaging in the ED and will demonstrate bony erosion and associated soft-tissue abnormalities. MRI and nuclear medicine studies may be helpful later in the patient's course.

4. Routine use of prophylactic antibiotics in patients treated with anterior packing for epistaxis has clearly demonstrated which of the following benefits?
   - **a.** Prevention of toxic shock syndrome
   - **b.** Reduction in incidence of acute otitis media
   - **c.** Prevention of acute sinusitis
   - **d.** None of the above

Answer: d. Administration of prophylactic antibiotics in patients discharged with anterior nasal packing has not been shown to prevent the listed infectious complications and is not recommended in patients without immunocompromise, valvular disorders, or in those whose packing will be left in place for less than 48 hours.

5. Neck masses in pediatric patients are more likely to represent an _____ process, while neck masses in adult patients are most likely secondary to a _____ process.
   - **a.** inflammatory, inflammatory
   - **b.** neoplastic, inflammatory
   - **c.** inflammatory, neoplastic
   - **d.** neoplastic, neoplastic

Answer: c. In adults, neck masses should raise concern for malignancy, as 80% of non-thyroid neck masses in adults are neoplastic in etiology. In children, the majority of neck masses are inflammatory in nature or secondary to benign congenital abnormalities.

59

Asthma

Taher T. Vohra and Richard M. Nowak

KEY CONCEPTS

- Inhaled and systemic steroid medications are effective in controlling airway inflammation and have important roles in the management of asthma exacerbations.
- Inhaled bronchodilators and systemic corticosteroids remain the mainstays of management for most acute asthma exacerbations.
- Acute severe asthma requires rapid identification. Treatment may use strategies not used in mild-to-moderate exacerbations, such as infusion of magnesium sulfate, use of non-invasive ventilation, and endotracheal intubation.
- Ventilator management in the intubated asthmatic is critical and includes lower tidal volumes (6 to 8 mL/kg) and low respiratory rates, often less than 10 per minute.
- A normal partial pressure of carbon dioxide (P_{CO_2}) in a pregnant patient represents hypercarbia.
- Elevated lactic acid levels are common in critically ill asthmatics and do not reflect deterioration or a poor prognosis.
- ED management of acute asthma is expanding (up to 24 hours) as more non-critically ill asthmatics are treated in observation units.
- Integration of discharged patients with acute asthma into chronic management strategies to prevent relapse requires physicians be familiar with controlling medications, such as inhaled corticosteroids and long-acting beta agonists.

FOUNDATIONS

Background and Importance

The word *asthma*, derived from the Greek ασυμα, signifies panting and was used initially as a synonym for "breathlessness." In 1698, Floyer published *A Treatise of the Asthma,* in which he attempted to differentiate asthma more clearly from other pulmonary disorders. Subsequent definitions of asthma highlight concepts of airway hyperresponsiveness, bronchospasm, reversible airway obstruction, and inflammation, emphasizing the many facets of this complex disease.

In 2017, it was estimated that 42.6 million Americans had been diagnosed with asthma by a health professional within their lifetime.[1] Asthma is more prevalent in children than adults, in females than males, and in African Americans and Puerto Ricans than whites or other Hispanics (Fig. 59.1). Asthma is also more prevalent in impoverished individuals and in the northeastern region of the United States (Fig 59.2).

African American adults had an ED visit rate for asthma nearly four times that of whites.[2] Over 3500 deaths due to asthma were reported in 2017 in the United States.[3,4] The female death rate from asthma was 1.3 times higher than males. African Americans were 2.5 to 3 times more likely to die from asthma than whites, Hispanics, and other races. Decreases in asthma death rates were noted from 2001 to 2007 but have remained steady from 2007 to 2017 (Fig. 59.3).[3] The highest death rate is reported among adults 65 years old and older, and the lowest among children 0 to 4 years old.

Industrialized nations have higher rates of asthma suggesting that urbanization and westernization correlate with increased asthma prevalence. Migrants who move from an area of low asthma prevalence to that of high prevalence assume increased asthma prevalence, suggesting that environmental factors play a role. Urban areas in the United States have high mortality rates associated with asthma, indicating that poverty and lack of access to medical care may also be major determinants of asthma complications.

Factors that contribute to asthma morbidity and mortality include under-treatment of acute episodes by emergency clinicians; overuse of prescribed or over-the-counter medications leading to delays in seeking treatment; failure of emergency clinicians to consider previous ED visits, hospitalizations, or life-threatening episodes of asthma; and failure to initiate corticosteroid therapy early in the course of an exacerbation. The cost of asthma care is a barrier to asthma management. African American and Hispanic adults identify costs related to seeking asthma care with a physician and the cost of asthma medications as significant impediments. Over-reliance on emergency facilities for all asthma care and lack of access or compliance with ongoing asthma care are other important factors contributing to morbidity and mortality from asthma.

Anatomy and Physiology

Asthma is a complex, immunologically mediated condition involving a variety of cellular and airway alterations. Airway inflammation and remodeling are the final common pathways that result in bronchospasm and limitation of airflow.

Asthma is a chronic respiratory disease characterized by periods of variable and recurring symptoms, airflow obstruction, and bronchial hyperresponsiveness that manifests clinically as attacks of impaired breathing. Asthma is an inflammatory disease. Repetitive episodes of acute superimposed on chronic airway inflammation are responsible for alterations in airway function and result in irreversible structural airway changes. Control of asthma symptoms ultimately depends on

ameliorating airway inflammation. Genetic, social, physiologic, and environmental factors influence the expression and control of asthma symptoms. Asthma is thus a complex interaction of the immune system, the environment, and genetic predispositions, which combine to alter airway structure and function. Successful emergency department (ED) management of asthma must address the multiple factors that result in airway dysfunction.

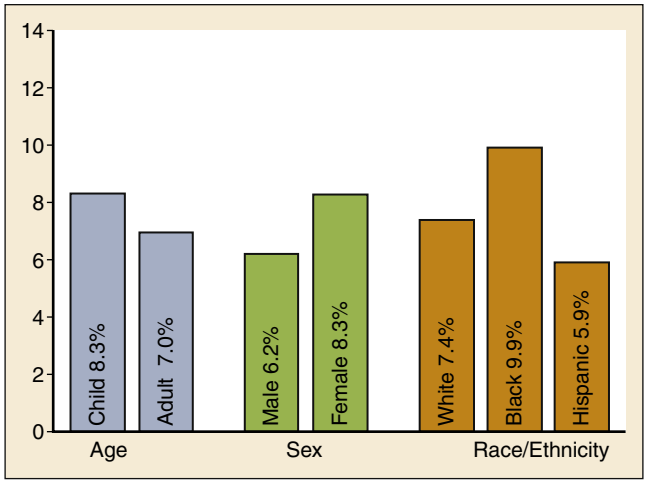

Fig. 59.1 Asthma Prevalence Percentages in 2017 by Age, Sex, and Race/Ethnicity in the United States. (From Centers for Disease Control and Prevention. Asthma: data, statistics, and surveillance. Available at: https://www.cdc.gov/asthma/data-visualizations/prevalence.htm.)

Compared with healthy individuals, patients with asthma show bronchial hyperreactivity (hyperresponsiveness) in response to various environmental and infectious stimuli (e.g., methacholine). Allergens (e.g., environmental, viruses, occupational) and non-allergic stimuli (e.g., exercise, aspirin-induced and menstrual-related asthma) induce bronchoconstriction via release of mediators and metabolites from inflammatory cells. Edema, inflammation, mucus production, and airway smooth muscle hypertrophy result in bronchoconstriction, airway obstruction, and airflow limitation. Recurrent episodes of airway inflammation result in permanent structural airway remodeling contributing to airway obstruction and hyperresponsiveness and decreases in response to therapy.

Autopsies of patients with fatal asthma reveal grossly inflated lungs that may fail to collapse on opening of the pleural cavities. Histologic examination reveals luminal plugs consisting of inflammatory cells, desquamated epithelial cells, and mucus. Marked thickening of the airway basement membrane, submucosal inflammatory cells, increased deposition of connective tissue, mucous gland hyperplasia, and hypertrophy of airway smooth muscle are also observed. Reports of slow-onset asthma fatalities reveal greater bronchial eosinophilia and basement membrane thickening when compared with rapid-onset fatal asthma. Reports of rapid-onset fatal asthma describe a greater number of degranulated mast cells and less mucus in the airway lumens, suggesting that terminal events may be dominated by bronchoconstriction without excessive luminal plugging.

Pathophysiology

Evidence that inflammation is a component of asthma physiology was initially derived from autopsy findings in patients with fatal asthma.

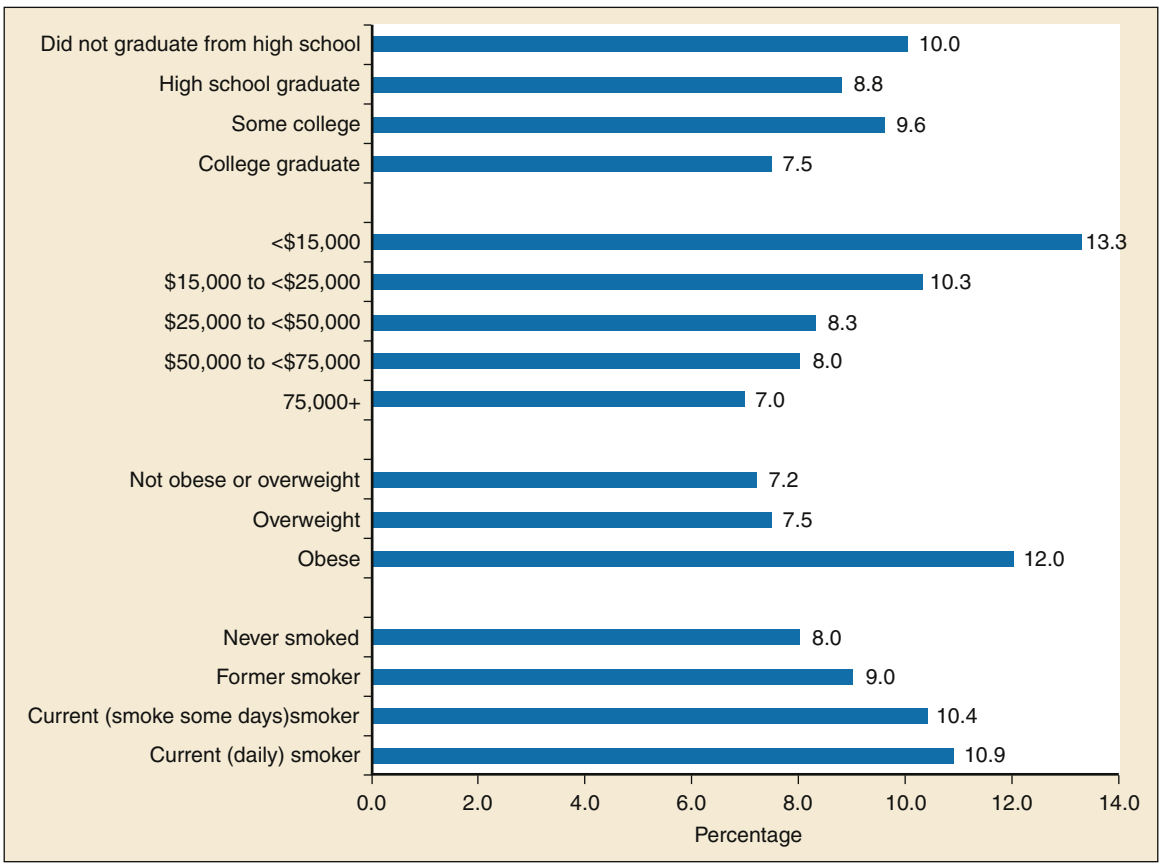

Fig. 59.2 Adult Asthma Prevalence Percent in 2017 by Education, Income, and Behavioral Risk Factors. (From Centers for Disease Control and Prevention. Asthma facts: CDC's National Asthma Control Program Grantees. Available at: https://www.cdc.gov/asthma/data-visualizations/prevalence.htm.)

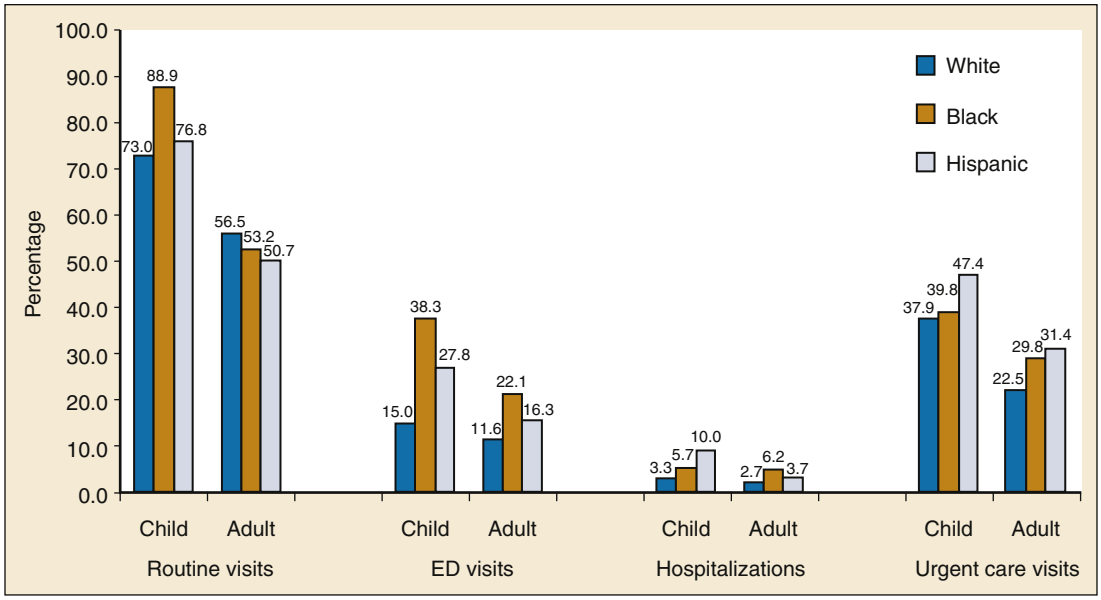

Fig. 59.3 Asthma Death Rates and Number of Deaths From 2007 to 2017. Thirty-five National Asthma Control Program (NACP) grantees. (Puerto Rico is excluded.) *Age-adjusted rate per million population. (From Centers for Disease Control and Prevention. Asthma facts: CDC's National Asthma Control Program Grantees. Available at: https://www.cdc.gov/asthma/data-visualizations/mortality-data.htm#anchor_1569599940376.)

The airways revealed infiltration by neutrophils, eosinophils, and mast cells and the presence of subbasement membrane thickening, loss of epithelial cell integrity, goblet cell hyperplasia, and mucous plugs. Bronchial biopsy findings in patients with even mild degrees of asthma also demonstrate inflammatory changes in the central and peripheral airways that correlate with disease severity. Inflammatory and chemotactic cytokines produced by both resident airway and recruited inflammatory cells are identified in bronchoalveolar lavage washings and pulmonary secretions.

Asthma has been divided into allergic and non-allergic types based on the presence or absence of immunoglobulin E (IgE) antibodies to common environmental antigens (pollen, dander, mites) and microbiologic antigens (bacteria, viruses). Exposure to microbes and allergens during childbirth, infancy, and childhood may confer a protective effect against atopy and suppress expression of the asthma phenotype later in life (known as the *hygiene hypothesis*). Regardless of the asthma type, a common feature is the presence of airway T-helper cells that release cytokines (e.g., interleukin [IL]-4, IL-5, and IL-13) that stimulate basophil, eosinophil, mast cell, and leukocyte migration to the airways and enhance IgE production. The result is amplification of the airway inflammatory response and, over time, irreversible airway remodeling. These complex cellular interactions clinically manifest as bronchospasm, mucus production, airway edema, and limitation of airflow.

Mast cells and eosinophils contain and release intracellular mediators and cytokines (histamine, prostaglandins, leukotrienes, tumor necrosis factor alpha [TNF-α]) that contribute to prolonged bronchial smooth muscle spasm, edema, and mucus production (Fig. 59.4). Airway epithelial cells are more than a passive barrier and produce pro-inflammatory mediators. Abnormal repair processes may further airway obstruction and contribute to airway remodeling.

Airway remodeling refers to the persistent structural changes in airways caused by repetitive or chronic airway inflammation. Microscopic remodeling features include epithelial thickening, subepithelial fibrosis, mucous gland metaplasia, increases in airway smooth muscle, angiogenesis, and loss of cartilage integrity. Airway remodeling occurs very early in asthma (childhood) and may precede clinical symptoms. Remodeling features are prominent in patients with severe asthma. Basement membrane thickening may be protective by preventing inflammatory cells and proteins from entering the airway submucosa through a damaged epithelium. Simultaneously, this process may be counterproductive by reducing the elasticity of the small airways. Airway remodeling induced by chronic inflammation may lead to the development of chronic irreversible airflow limitation and increased asthma mortality.

Genetics is playing an ever-increasing role in the understanding of asthma pathophysiology.[5] Heritability estimates vary between 35% and 95% for asthma and 30% and 66% for bronchial hyperresponsiveness. The first Genome Wide Association Study (GWAS) identified a novel asthma susceptibility locus on chromosome 17q21 and two large meta-analyses of asthma GWASs identified four gene loci considered robustly associated asthma susceptibility genes. Environmental influences (e.g., allergens, pollutants, tobacco, and occupational exposures) are associated with asthma, and the interaction of genetic variability and environmental factors may allow prediction of future disease risk, expression, and severity and response to therapies.[6]

CLINICAL FEATURES

Signs and Symptoms

Most patients with acute asthma have a constellation of symptoms, including cough, dyspnea, and wheezing. Slow-onset asthma with progressive deterioration over at least 6 hours (usually days) occurs in over 80% of cases. This type has a female predominance, is triggered by upper respiratory tract infections, and has an airflow inflammation mechanism that results in a slower response to treatment. Sudden-onset asthma with rapid deterioration in less than 6 hours occurs in less than 20% of cases. This type has a male predominance, is triggered by respiratory allergens, exercise, and psychosocial stress, and has a bronchospastic cause resulting in more severe airway obstruction with a faster response to therapy.

On initial history, questions should include possible triggers, onset of symptoms, and severity of symptoms, especially as compared with

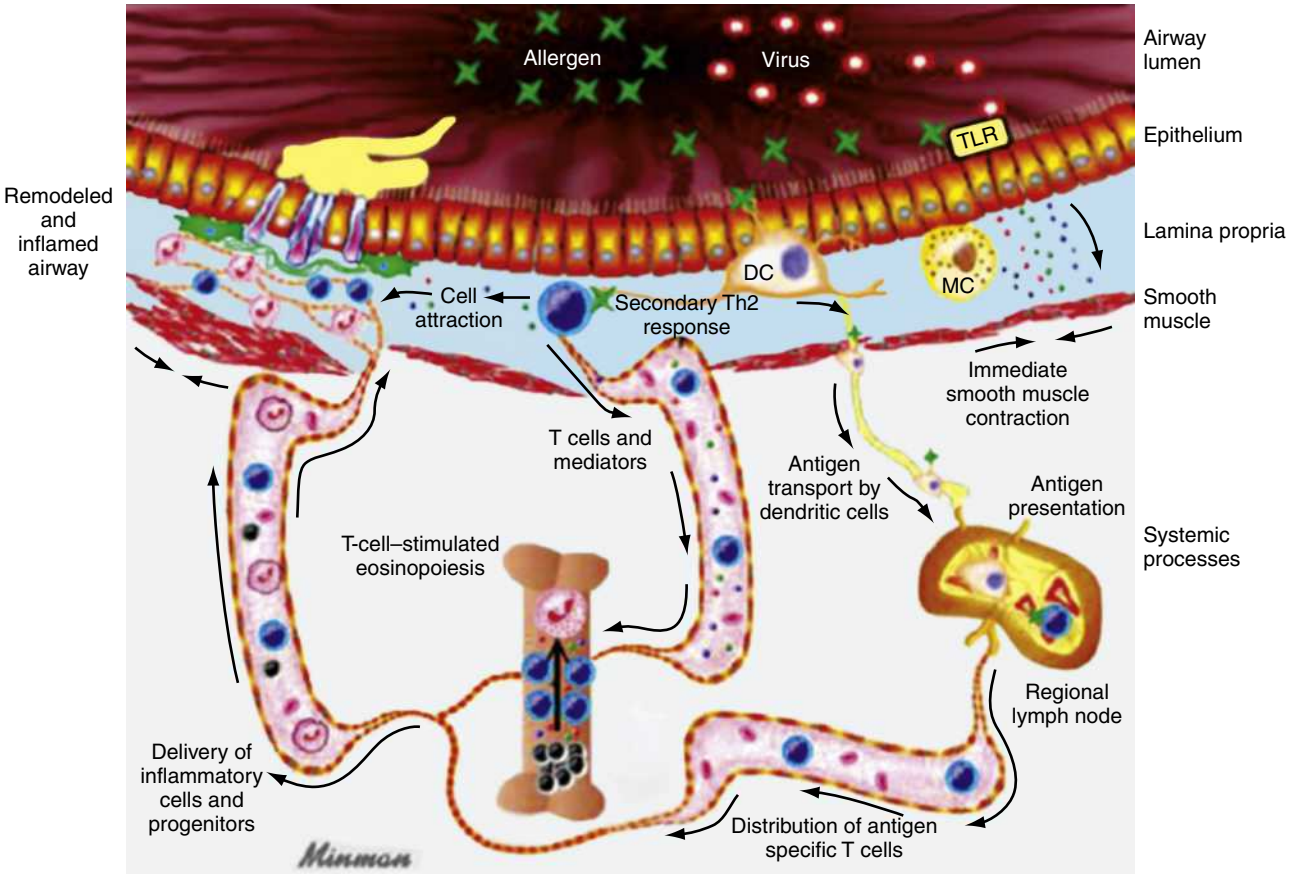

Fig. 59.4 The Physiologic Mechanism of Asthma. *DC,* Dendritic cell; *MC,* mast cell; *Th2,* T-helper 2; *TLR,* toll-like receptor. (From Murphy DM, O'Byrne PM. Recent advances in the pathophysiology of asthma. *Chest.* 2010;137:1417.)

previous exacerbations. Comorbidities should be identified, especially those that may be worsened by systemic corticosteroids such as diabetes, peptic ulcer disease, hypertension, and psychosis.[7] All current asthma medications should be noted, including times and amounts recently used, and any potential asthma aggravators, such as aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), beta-blockers (including topical agents used for glaucoma), and angiotensin-converting enzyme inhibitors. Cardioselective and nonselective beta-blocker use increases hospitalizations and ED visits. There are inter-individual differences in the dyspnea perceived by asthmatic patients for the same level of airway narrowing. Patients with a blunted perception of dyspnea ("poor perceivers") have more ED visits, hospitalizations, and near-fatal and fatal asthma attacks.

Patients with mild or moderate acute asthma usually speak in sentences or phrases and may have a normal or slightly elevated pulse and respiratory rates. They also will usually have a normal oxygen saturation. Patients with severe acute asthma typically speak only one to two words at a time, may be agitated or restless and hunched forward, may be tachypneic or tachycardic, and may be hypoxic. Patients with altered level of consciousness such as confusion or drowsiness, silent chest on exam, poor respiratory effort or elevated paCO2 have life-threatening or near-fatal asthma.[7,8]

Wheezing does not define the presence, severity, or duration of asthma. It correlates poorly with the degree of functional derangement and may be absent when maximal effort produces minimal airflow. Physical examination may help to identify such complications of asthma as pneumonia, pneumothorax, or pneumomediastinum.

BOX 59.1 Risk Factors for Death From Asthma

Asthma History

A history of near-fatal asthma requiring intubation and mechanical ventilation
Hospitalization or ED visit for asthma in the past year
Currently using of having recently stopped using oral corticosteroids (a marker of event severity)
Not currently using inhaled corticosteroids
Over-use of SABAs, especially use of more than one cannister monthly
Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan

Other Factors

Psychosocial problems
Psychiatric disease
Food allergy in a patient with asthma

Risk Factors

Asthma exacerbations are more common in females. Additionally, specific risk factors for exacerbations include a history of one or more exacerbations in the past year, poor adherence to a plan or uncontrolled symptoms, incorrect inhaler use, chronic sinusitis, or smoking. Ethnicity and socioeconomic status are also predictors of exacerbations with African Americans having higher rates of ED visits and hospitalizations than Caucasians or Hispanics.[2] Risk factors for death from asthma are also important to determine and are listed in Box 59.1.[7,8]

Specific Contexts

The following conditions are particularly challenging due to their overlap and contribution to asthma.

Cough Variant

Chronic cough may be the sole manifestation of the disease in cough-variant asthma. It is associated with airway hyperresponsiveness and may be present more often at night. Other conditions of chronic cough to consider would be angiotensin converting enzyme (ACE) inhibitors, gastroesophageal reflux disease (GERD), chronic sinusitis, postnasal drip, and inducible laryngeal obstruction.

Cigarette Smokers

One-third of patients who come to the ED with acute asthma are current cigarette smokers, and these patients have poorer asthma control and greater acute care needs than lifelong nonsmokers or former smokers. They may also have chronic obstructive pulmonary disease (COPD) which makes diagnosis and treatment more challenging. Ambiguity between COPD and asthma should prompt referral due to the worse outcomes of patients with asthma and COPD overlap.[8]

Athletes

Exercise-induced bronchoconstriction has been recognized since the first modern Olympic Games. The key stimulus is felt to be airway dehydration resulting from increased ventilation, increasing the osmolarity of the airway lining fluid. The increased osmolarity may trigger release of mediators (histamine, leukotrienes, prostaglandins) from airway inflammatory cells, resulting in smooth muscle contraction and airway edema.[9]

Prophylaxis for exercise-induced asthma includes environmental measures (face mask or nasal breathing to allow warming and humidification of cool dry air, pre-exercise warm-up, and avoidance of known allergens) and medications. Inhaled glucocorticoids are strongly recommended, and a short-acting inhaled beta-2 agonist used 5 to 10 minutes before exercise is effective in preventing exercise induced bronchoconstriction.[9] Long-acting beta agonists (LABAs) in combination with inhaled glucocorticoids are useful when low doses of inhaled glucocorticoids are ineffective. Pretreatment with cromolyn, leukotriene antagonists (montelukast), or an inhaled parasympatholytic (ipratropium) is also effective.

Perimenstrual Asthma

Perimenstrual asthma affects up to 40% of asthmatic women yet receives little emphasis in asthma treatment guidelines. The ratio of female-to-male asthma prevalence increases dramatically after puberty, and health care for asthma increases in the perimenstrual phase.

Elderly

Asthma can appear at any age, including the ninth decade, wheezing and dyspnea may be mis-ascribed by patients and physicians to heart failure, bronchitis, COPD, occupational lung disease, or poor exercise capacity. Older asthmatic patients (>55 years old) have higher morbidity and mortality.

Obesity

Due to respiratory symptoms associated with obesity overlapping with asthma, there may be misdiagnosis or underdiagnosis. Objective testing is important to diagnose asthma in this patient population accurately. Overweight (body mass index [BMI] of 25 kg/m^2 or more) asthmatics have poorer asthma control, higher admission rates, and a greater risk of complications, possibly secondary to a difference in the perception of dyspnea or response to asthma controller agents. However, obesity does not adversely influence the severity or the resolution of an acute exacerbation.

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD) was first described more than 100 years ago. Clinically, AERD includes the tetrad of nasal polyps, eosinophilic sinusitis, asthma, and sensitivity to cyclooxygenase (COX)-1 inhibitor drugs (e.g., aspirin). A detailed mechanism is shown in Fig. 59.5. NSAIDs also precipitate AERD. AERD is a common precipitant of life-threatening asthma; one survey notes that 25% of asthmatics who require mechanical ventilation have AERD. Patients with AERD should avoid aspirin and NSAIDs. ICS are the primary therapy in AERD. Oral corticosteroids may be needed, and leukotriene antagonists may be useful. Desensitization with aspirin can significantly improve symptoms. There is little evidence to justify managing patients with AERD differently than other patients with acute asthma except for avoidance of aspirin and NSAIDs.

DIFFERENTIAL DIAGNOSES

See Box 59.2.

Diagnostic Testing

Peak Expiratory Flow

The severity of airflow obstruction cannot be accurately assessed from symptoms and physical examination alone. Because physicians initially tend to underestimate the degree of airway obstruction in acute asthma, routine measurement of the peak expiratory flow (PEF) in liters per second should be part of ED assessment and monitoring. Any patient not able to perform peak flow measurement should be considered to have severe airway obstruction.

The same device should be used to assess an individual patient, and different portable meters should not be used interchangeably. PEF assessed as a percentage of previous personal best is the most useful measurement. PEF as a percentage of predicted values (available online) gives a reasonable estimate if personal best values are unknown. PEF < 50% is often used to categorize an acute severe asthma exacerbation, and less than 33% may signify life-threatening or near-fatal asthma.[7]

Pulse Oximetry

Oxygen saturation (SpO_2) should be measured using pulse oximetry to determine the efficacy of oxygen supplementation, especially in children that cannot perform PEF. SpO_2 should be maintained between 94% and 98%. If SpO_2 falls below 90%, it may signal the need for more aggressive therapy.[7]

Capnography

Capnography is an alternative technique to monitor for hypercapnia and respiratory failure and is effective in asthma. Capnographic waveform analysis can indicate improvements in airway diameter in acute asthma and has the advantage of being effort independent and providing continuous monitoring.

Blood Gas

Initially, in acute asthma exacerbations, stimulated hyperventilation leads to a fall in the partial pressure of carbon dioxide in arterial blood ($PaCO_2$). As airway obstruction increases, patients develop hypoventilation. With hypoventilation, the $PaCO_2$ normalizes and then increases with resulting hypercapnia and respiratory acidosis. Routine arterial blood gas (ABG) analysis is not indicated in acute asthma exacerbations. An ABG should be considered to identify hypercapnia if the SpO2 is <92% or the PEF is <50% of personal best or predicted value.

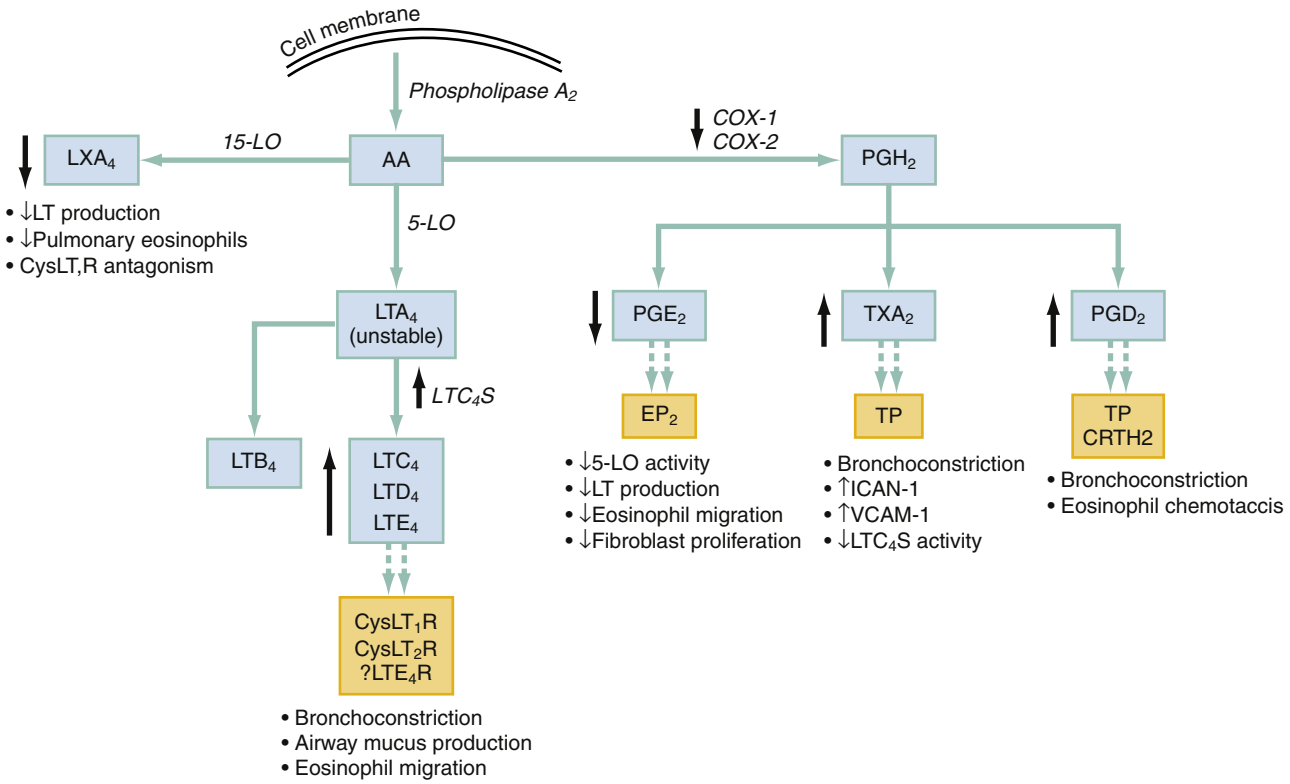

Fig. 59.5 Mechanism of aspirin-exacerbated respiratory disease (AERD). Inhibition of the enzyme cyclooxygenase *(COX)* decreases production of prostaglandin E_2 *(PGE_2).* PGE_2's inhibitory effect on 5-lipoxygenase *(5-LO)* is diminished resulting in increased production of leukotrienes (*LTC_4, LTD_4,* and *LTE_4)* causing bronchoconstriction, mucus production, and airway eosinophil migration. *5-LO,* 5 Lipoxygenase; *15-LO,* 15 lipoxygenase; *AA,* arachidonic acid; *COX-1,* cyclooxygenase 1; *COX-2,* cyclooxygenase 2; *CRTH2,* chemokine receptor-homologous Th2 lymphocytes; *$CysLT_1R$,* cysteinyl leukotriene T1R; *$CysLT_2R$,* cysteinyl leukotriene T2R; *EP_2,* E prostanoid 2 receptor; *LTA_4,* leukotriene A4; *LTB_4,* leukotriene B4; *LTC_4S,* leukotriene C4 synthetase; *LTC_4,* leukotriene C4; *LTD_4,* leukotriene D4; *LTE_4,* leukotriene E4; *LTE_4R,* leukotriene E4R; LXA_4, lipoxin A4; *PGD_2,* prostaglandin D2; *PGE_2,* prostaglandin E2; *PGH_2,* prostaglandin H2; *TP,* T prostanoid receptor; *TXA_2,* thromboxane A2. (From Laidlaw TM, Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. *Immunol Allergy Clin North Am.* 2013;33[2]:195.)

BOX 59.2 The Differential Diagnosis of Asthma

- Cardiac conditions
  - Valvular heart disease
  - Congestive heart failure
- COPD exacerbation
- Pulmonary infection
  - Pneumonia
  - Allergic bronchopulmonary aspergillosis
  - Löffler syndrome
  - Chronic eosinophilic pneumonia
- Upper airway obstruction
  - Laryngeal edema
  - Laryngeal neoplasm
  - Foreign body
  - Vocal cord dysfunction
- Endobronchial disease
  - Neoplasm
  - Foreign body
  - Bronchial stenosis
- Pulmonary embolus
- Cystic fibrosis
- Carcinoid tumor
- Allergic/anaphylactic reaction
- Adverse drug reaction (ACE inhibitors)
- Miscellaneous conditions
  - Churg-Strauss syndrome
  - GERD
  - Hyperventilation with panic attack
  - Noncardiogenic pulmonary edema
  - Addison's disease
  - Invasive worm infection

ACE, Angiotensin-converting enzyme; *COPD,* chronic obstructive pulmonary disease; *GERD,* gastroesophageal reflux disease.

This will help identify possible respiratory acidosis and the need for airway management and ventilatory support. A venous blood gas (VBG) may also be considered as a screening tool for hypercapnia. A $PaCO_2$ on a VBG of less than 40 mm Hg likely excludes hypercapnia, however for an accurate measurement, one should obtain an ABG.[10]

Other Blood Testing

Leukocytosis is common with acute asthma exacerbation and does not necessarily indicate an acute superimposed pulmonary infection. Corticosteroids and catecholamines demarginate polymorphonuclear leukocytes after 1 to 2 hours, and patients on chronic steroid therapy may have normal or significantly elevated white blood cell counts.

Serum electrolytes are not altered unless the patient takes corticosteroids or diuretics or has cardiovascular disease and is receiving beta-2 agonist therapy. Frequent albuterol treatments can cause transient hypokalemia, hypomagnesemia, and hypophosphatemia, but this is rarely of clinical significance. The rare asthmatic on chronic theophylline therapy should have a level measured for possible toxicity. In the older asthmatic with cardiovascular comorbidities, measurement of the B-type natriuretic peptide (BNP) level may reveal unrecognized congestive heart failure. Hyperlactatemia is common in acute asthma and is thought to be secondary to albuterol therapy or the increased work of breathing. It is not associated with worse pulmonary function tests,

more hospitalizations, or relapse at one week. Overall, routine testing of the blood in an acute asthma exacerbation is not recommended.

Radiology

A chest radiograph (CXR) is of little value in most acute asthma exacerbations and should be restricted to patients with a suspected complicating cardiopulmonary process, such as pneumonia, pneumothorax, pneumomediastinum, subcutaneous emphysema, or congestive heart failure. Patients who do not respond to optimal therapy and require hospital admission have a higher likelihood of radiographically identifiable, unsuspected, clinically significant pulmonary complications of asthma.

Point of Care Ultrasound

The finding of an ultrasound comet-tail sign has high diagnostic accuracy in differentiating acute heart failure from COPD/asthma-related causes of acute dyspnea.

Electrocardiogram

The electrocardiogram (ECG) is selectively helpful in assessing patients with chest pain or a history of significant cardiovascular disease, in whom the asthma attack may be a physiologic stress test. In patients with severe asthma, the ECG may show a right ventricular strain pattern that reverses with improvement in airflow. All patients with severe hypoxemia should also receive cardiac monitoring.

In summary, the severity of airflow obstruction cannot be accurately judged by patients' symptoms, physical examination findings, and laboratory test results. Serial measurements of airflow obstruction with PEF is key for disease assessment and response to therapy (Table 59.1).

MANAGEMENT

Subacute lack of asthma control, defined as more than four outpatient visits or more than five short-acting beta-2 agonist prescriptions per year, is associated with an increased risk of acute asthma exacerbation. The ability to gauge the severity of an attack and present to the ED promptly is important, because patients who wait longer have worse asthma on presentation, more functional limitations, and are more likely to be admitted. Emergency medical services providers should provide albuterol inhalation therapy by protocol, and basic emergency medical technicians can be authorized to administer the patient's own inhaler. Further studies are needed to determine whether paramedics should be trained to administer continuous positive airway pressure ventilation in asthmatics with severe respiratory failure to decrease tracheal intubation and mortality rates.

The rapidity of the reversal of the acute airflow obstruction is directly predictive of the outcome. Effective bronchodilation often results in a decreased need for hospitalization with significant cost savings. As outlined in Tables 59.2 and 59.3, the severity of an attack as measured by peak flow measurement determines the aggressiveness of the therapy.

TABLE 59.1 Objective Findings in Asthma Assessment

Factor	Severe Asthma
Pulse rate (beats/min)	≥120
Respiratory rate (breaths/min)	≥30
Use of accessory muscles of respiration	If present, may indicate severe asthma; if absent, may have equally severe asthma in 50% of cases
ABG analysis (mm Hg)	Pa_{O_2} ≤ 60 or Pa_{CO_2} ≥ 42 indicates severe asthma; all other values difficult to interpret unless PEF known
Pulmonary function studies	PEF measures the degree of airflow obstruction; most useful in assessing severity and guiding treatment decisions

ABG, Arterial blood gas; Pa_{CO_2}, partial pressure of carbon dioxide in arterial blood; Pa_{O_2}, partial pressure of oxygen in arterial blood; *PEF,* peak expiratory flow rate.

Oxygen Administration

All patients should receive supplemental oxygen titrated to maintain arterial oxygen saturation between 94% and 98%, as titrated oxygen is associated with better physiologic outcomes than empiric high flow 100% oxygen therapy.[7]

Adrenergic Medications

Inhaled Beta2 Agonists

Inhaled short-acting beta-2 agonist (SABA) such as albuterol should be used in patients that present with acute asthma exacerbations. For patients with mild to moderate asthma, albuterol can be administered with a pressurized metered-dose inhaler (pMDI) with a spacer and is

TABLE 59.2 Initial Severity Assessments and Therapies in the Emergency Department

	Mild to Moderate	Severe
PEF (percentage predicted/personal best)	≥40%	Unable or <40%
Oxygen therapy	Maintain Sa_{O_2} ≥90%	Maintain Sa_{O_2} ≥90%
Nebulized Albuterol Solution		
Albuterol	2.5 mg every 20 min for up to three doses	5.0 mg every 20 min for three doses Continuous for 1 h if severe
Albuterol Metered-Dose Inhaler With Spacer		
Albuterol (90 µg/puff)	6–12 puffs every 20 min for up to three doses with supervision	Same for three doses (if able to do) with supervision
Ipratropium Therapy		
Nebulized solution	0.5 mg every 20 min for three doses (may mix with albuterol solution)	0.5 mg every 20 min for three doses (may mix with albuterol solution)
MDI (18 µg/puff) with spacer	8 puffs every 20 min for three doses	8 puffs every 20 min for three doses
Systemic Corticosteroids		
Oral (preferred)	40–50 mg of prednisone or prednisolone per day if no immediate response to albuterol	40 to 50 mg of prednisone or prednisolone per day
IV (unable to take orally or absorb)	125 mg of methylprednisolone per day	125 mg of methylprednisolone per day
IV magnesium sulfate	Not indicated	2 g over 20 min (or at rates of up to 1 g/min) if PEF ≤ 25% predicted

IV, Intravenous; *MDI,* metered-dose inhaler; *PEF,* peak expiratory flow rate; Sa_{O_2}, oxygen saturation in arterial blood.

TABLE 59.3 Response After 1 Hour of Initial Treatment

	Moderate Exacerbation	Severe Exacerbation
PEF (percentage predicted)	40%–69%	<40%
Oxygen therapy	Maintain Sa_{O_2} ≥90%	Maintain Sa_{O_2} ≥90%
Albuterol Therapy		
Racemic albuterol	Every 1–3 h, admit decision in <4 h	Every 1 h or continuous
Ipratropium therapy	Every 1 h or continuous	Every 1 h or continuous
Corticosteroids	Every 6–8 h	Every 6–8 h

PEF, Peak expiratory flow rate; *Sa_{O_2},* oxygen saturation in arterial blood.

more efficient and cost-effective than nebulization. However, for severe or near-fatal asthma, nebulization of beta-agonist is recommended over pMDI to allow for continuous administration, although there is a paucity of data to guide this recommendation. (see Table 59.2).

Long-Acting Beta-2 Agonists

Inhaled long-acting beta-2 agonists are medications used as the initial additional therapy to manage symptoms not adequately controlled by ICS alone. Salmeterol is a LABA with an onset of action of 20 minutes and thus is not a rescue medication. Formoterol is also a LABA that has an onset of action within minutes (similar to albuterol) and maximal effect within 2 hours. There is no difference in the efficacy of combination LABA/ICS inhalers compared to both medications in separate inhalers with good adherence. Regular use of LABAs without concomitant use of ICSs results in greater hospitalizations and asthma-related deaths, resulting in a black box warning on the package insert. There is no role for the use of LABA without the concomitant use of ICS.[7] In practice, combination inhalers are preferred to ensure LABAs and ICS are taken together. Due to the rapid onset of the medication, combination formoterol and ICS inhalers may be used as both controller and rescue medications. However, the role of these medications in the ED is limited amidst other readily available options.

Intravenous Beta2 Agonists

There is no evidence to support the routine use of intravenous beta-2 agonists.[8] There may be a limited role in ventilated patients or those in extremis, however, there is little evidence to support this.[7]

Subcutaneous Beta2 Agents

Terbutaline is a beta-2 adrenergic receptor agonist, administered subcutaneously. While terbutaline was previously used regularly for severe asthma, no evidence supports the use of subcutaneous adrenergic agents over aerosol delivery. It may be considered in patients who cannot adequately inhale albuterol or with severe bronchospasm unresponsive to other treatments.

Epinephrine

Epinephrine 0.3 mg given intramuscularly in addition to standard asthma therapy is recommended for patients with anaphylaxis or angioedema.

Corticosteroids

Steroids are an important part of acute and chronic asthma management. They reduce mortality, relapses, subsequent hospitalization, and the requirement for beta-2 agonist therapy.[7] They should be given as early as possible in an acute asthma exacerbation. There is no benefit to adding ICS to systemic steroids.

Systemic Corticosteroids

Corticosteroids are indicated for all patients with an acute asthma exacerbation. Early systemic corticosteroids are particularly important for patients who fail to achieve lasting improvement with the initial administration of SABA, were taking OCS when they developed the exacerbation, or have required OCS with past exacerbations.[8] Steroid effects begin within hours in acute asthma and peak at about 24 hours.

As studies have demonstrated that oral corticosteroids are equivalent to IV therapy, oral steroids are preferred unless the patient is very ill, is unable to swallow or is vomiting, or is thought to have impaired gastrointestinal transit or absorption. The recommended initial oral dose is usually 50 mg of prednisone.[7,8] If IV methylprednisolone is used, the dose is 125 mg/day in one or two divided doses until the switch to oral therapy or until PEF reaches 70% of predicted or personal best. Oral dexamethasone can alternatively be prescribed at a dose of 16 mg per day for 2 days.[11] Side effects of short-term (hours or days) steroid use include reversible increases in serum glucose (important in diabetics) and decreases in potassium, fluid retention with weight gain, mood alterations including psychosis, hypertension, peptic ulcers, aseptic necrosis of the femur, and rare allergic reactions.

Inhaled Corticosteroids

Use of high-dose ICS within 1 hour of arrival for acute asthma without systemic steroids reduces the need for hospitalization.[8] However, there is conflicting evidence regarding the role of ICS in addition to OCS in the setting of an acute exacerbation, and there is no known benefit to using ICS instead of OCS. ICS have an additional cost and no established dose and duration of treatment for patients in the ED. Therefore, we do not recommend routinely adding ICS to systemic steroids for the ED treatment of acute asthma exacerbations.

Corticosteroids and Discharged Patients

Discharged patients who receive systemic corticosteroids should continue oral out-patient therapy to control disease and prevent relapse. Any need for additional steroids should be determined at follow-up. An acceptable regimen is 40 to 50 mg of prednisone (or equivalent) in single daily dose for 5 to 7 days. Dose tapering to prevent asthma rebound or adrenal suppression is unnecessary unless the patient was already receiving systemic steroids or a prolonged course of therapy of more than 2 weeks is necessary. An alternative approach, if compliance or inability to obtain oral corticosteroids is an issue, is to give a single intramuscular dose of dexamethasone 10 mg, triamcinolone diacetate 40 mg, or methylprednisolone 160 mg before discharge.[12]

Patients with acute exacerbations of asthma may be on insufficient chronic controller medications. If the patient is not taking oral corticosteroids or ICS, the addition of ICS to the patient's regular asthma medications on discharge as a controller medication significantly reduces the risk of asthma-related death or hospitalization.[8] Patients with a moderate or severe exacerbation not taking any ICS should be given a prescription for an ICS containing medication. Patients already on ICS therapy should continue this home medication in addition to the prescribed short course of oral steroids.

Anticholinergic Medications

Anticholinergic drugs available for inhalation therapy are bronchodilators that override the smooth muscle constrictor and secretory effects of the parasympathetic nervous system, blocking reflex bronchoconstriction and reversing acute airway obstruction. Ipratropium bromide,

a quaternary derivative of atropine, is the preferred anticholinergic agent for acute asthma exacerbations. The maximum effect with inhaled ipratropium is 30 to 120 minutes after administration, lasting up to 6 hours. Its bronchodilatory potency is lower and onset of action slower than those of the beta-2 agonists and should not be used alone for acute attacks. For patients with moderate to severe exacerbations, emergency department treatment with a SABA and ipratropium was associated with fewer hospitalizations and greater improvement in PEF compared with SABA alone.[13] Treatment recommendations (see Table 59.2) include adding ipratropium (0.5 mg) with the first three albuterol treatments in severe acute asthma (PEF < 40% predicted). The equivalent MDI dose is approximately eight puffs (18 μg/puff) every 20 minutes for three doses.

Inhaled tiotropium bromide is a long-acting (>24 hours) anticholinergic agent. There is inconclusive evidence about the benefit of adding tiotropium for patients not responding to ICS plus LABA therapy as an outpatient. It is also unclear if there is any benefit to adding tiotropium to ICS compared to increasing the dose of ICS. There is no clear role for use of tiotropium for patients presenting to the emergency department with acute asthma exacerbations.[7]

Magnesium

Magnesium relaxes bronchial smooth muscle and dilates asthmatic airways in vitro. Mechanisms include calcium channel-blocking properties, inhibition of cholinergic neuromuscular transmission, stabilization of mast cells and T-lymphocytes, and stimulation of nitric oxide and prostacyclin. Intracellular magnesium levels are lower in acute asthma, and the level correlates with airway reactivity in chronic disease.

For adults with severe asthma attacks (PEF < 25%, predicted), adults and children with persistent hypoxia after initial treatment, and children with PEF < 60% after 1 hour of care, the addition of magnesium decreases the need for hospital admission.[14] The optimal dose and rates of infusion are unclear, but it is reasonable to administer 2 g of IV magnesium sulfate over 20 minutes to adult patients with severe refractory asthma while continuing aggressive inhalation therapy. For pediatric patients, a dose of 40 mg/kg/day (max of 2 g) of IV magnesium sulfate is recommended. Studies that excluded patients with severe asthma showed no benefit with use of IV or nebulized magnesium. Side effects of magnesium infusion are dose-related and include warmth, flushing, sweating, nausea and emesis, muscle weakness, loss of deep tendon reflexes, hypotension, and respiratory depression.

Methylxanthines

Theophylline is the main oral methylxanthine used to treat asthma, and a small subset of ambulatory patients may benefit from its chronic administration. IV methylxanthines are not recommended for acute disease as there is no demonstrated efficacy and increased adverse events.[8] However, there may be a limited role in patients with near-fatal asthma with a poor response to initial therapy.[7]

Leukotriene Modifiers

The cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) are highly potent mediators of inflammation that play a large role in the pathogenesis of asthma. Leukotriene receptor antagonists (LTRAs) are used as controller medications. There is limited data regarding their efficacy in acute asthma management. Current recommendations do not support their use in the treatment of acute asthma in the emergency department.

Antibiotics

Bacterial, chlamydial, and mycoplasmal respiratory tract infections infrequently contribute to acute asthma. Antibiotics should generally be reserved for patients with clear objective evidence of infection. There may be a future role for procalcitonin to guide antibiotic use, but more studies are needed.[15]

Sedatives

Sedatives are contraindicated in acute disease because of their respiratory depression.

Ketamine

Ketamine is an IV dissociative anesthetic with potent bronchodilator effects. Studies suggest possible benefit when used in acute asthma, but no statistically significant findings have been reported. Further prospective work is needed. At present, ketamine is not recommended for acute asthma in the non-intubated patient.[7]

Heliox

Helium is an inert gas with one-eighth the density of nitrogen. When 60% to 80% helium is blended with 20% to 40% oxygen, the resulting gas mixture (heliox) has a threefold reduction in density compared with air. Heliox reduces the resistance associated with gas flow through airways with non-laminar flow and reduces respiratory muscle work; it also increases the diffusion of carbon dioxide and may improve alveolar ventilation. Heliox may decrease the work of breathing long enough to stop intubation by carrying bronchodilators to the distal airways and allowing anti-inflammatory agents time to achieve their effects. When heliox was compared to oxygen to drive nebulized delivery of beta-agonist therapies, an increase in PEF and a lower rate of hospitalization were observed. Patients with severe asthma receiving heliox nebulization of beta-2 agonists have more significant increases in PEF compared to those with mild to moderate asthma. Heliox has not been demonstrated to decrease the need for intubation in severe and resistant asthma, however. It is administered by nonrebreather mask and can also be used with mechanical ventilation. Emergency clinicians can consider heliox in cases of severe airflow obstruction (PEF < 30% predicted and a rapid onset of symptoms within 24 hours), a history of labile asthma or previous intubation, and inability to be adequately mechanically ventilated.

High-Flow Nasal Canula

Oxygen delivered via high-flow nasal canula (HFNC) can be used with hypoxemic patients. HFNC, with flow rates up to 60 L/min of warmed and humidified oxygen, provides high concentrations of oxygen, decreases respiratory work and may provide continuous positive airway pressure. The role in asthmatic adults is unknown, however, small studies have shown it reduces respiratory distress in children.[16] Further studies are warranted to determine overall efficacy.

Noninvasive Ventilation

Noninvasive ventilation (NIV) may benefit carefully selected patients with severe and resistant asthma. Continuous positive airway pressure improves oxygenation and reduces respiratory muscle fatigue by increasing functional residual capacity and lung compliance and supplying some of the inflating pressure required during inspiration. Biphasic positive airway pressure (BiPAP) provides continuous positive airway pressure but delivers higher pressure during inspiration than expiration. BiPAP allows speech and reduces the need for sedation as compared to intubation. Nebulized bronchodilators can be delivered through the BiPAP circuitry. BiPAP is well tolerated by children with status asthmaticus and may decrease the need for intubation and mechanical ventilation.[17] BiPAP may decrease the need for hospitalization, intubation, and ICU and hospital length of stay in adults with status asthmaticus.[18] There is limited evidence to routinely recommend NIV in patients with respiratory failure from severe asthma exacerbations.

NIV is not a substitute for endotracheal intubation and mechanical ventilation. A trial of NIV before intubation and mechanical ventilation can be considered in select patients by providers familiar with the use of NIV. Patients should have an alert mental status, intact airway reflexes, and ICU admission is mandatory. Intermittent ABG

monitoring to assess for worsening hypercapnia or respiratory acidosis during NIV identifies nonresponders that may need intubation.

Mechanical Ventilation

Endotracheal intubation and mechanical ventilation are required in 2% of all asthma exacerbations and 10% to 30% of those requiring ICU admission. Indications for intubation include coma, altered consciousness, cardiac or respiratory arrest, paradoxical breathing pattern, refractory hypoxemia, and failure of NIV. Some authors recommend threshold levels for intubation based on ABG results, but there is no evidence that ABG results provide better guidance regarding the need for intubation than overall clinical assessment.

Orotracheal rapid sequence intubation (RSI) with induction agents and muscle paralysis is preferred. A large endotracheal tube (≥8.0 mm for adults) facilitates airway suctioning, mucous plug removal, and bronchoscopy if needed later in the course. Ketamine (1 to 2 mg/kg) is the preferred agent for induction in RSI of the asthmatic patient because of its bronchodilatory and sympathetic stimulatory properties. Alternatively, propofol (1.5 to 2 mg/kg) offers rapid-onset deep sedation and possesses bronchodilatory properties, but its vasodilatory effects may cause hypotension, especially in the volume-depleted asthmatic. Succinylcholine (1.5 mg/kg) or a competitive neuromuscular blocking agent, such as rocuronium (1 mg/kg), can be used for intubation. Continued deep sedation with propofol, a long-acting benzodiazepine (e.g., lorazepam) or an opioid that does not release histamine (e.g., fentanyl) usually avoids the need for muscle paralysis. When bagging the patient after intubation, care must be taken to avoid hyperventilation.

A ventilator strategy providing adequate oxygenation and ventilation while minimizing hyperinflation, high airway pressure, barotrauma, and systemic hypotension must be instituted. Decreasing hyperinflation is the priority, rather than correcting hypercarbia and respiratory acidosis. Permissive hypercapnia is an appropriate technique. Low tidal volumes (6 to 8 mL/kg) keep airway pressures lower, thus reducing the risk of intrinsic positive end-expiratory pressure ("auto-PEEP"), stacking of ventilations, and barotrauma. Low ventilation rates (below 10 breaths/min) and high inspiratory flow rates (above 60 L/min) provide prolonged time for expiration. Oxygenation is maintained by titrating the fraction of inspired oxygen (Fio_2) as needed to maintain Spo_2 > 92%. Therapies such as IV hydration, inline beta-2 agonists and anticholinergics, IV corticosteroids, and magnesium to decrease airway pressure and airway obstruction are delivered simultaneously.

Continuous capnography is advisable. Moderate levels of hypercapnia are well tolerated and have few deleterious effects. Elevated carbon dioxide levels have vasodilatory effects on cerebral vessels. Cerebral blood flow reaches its maximum at a $Paco_2$ level of 120 mm Hg, which may increase intracranial pressure. Although there is no consensus on what constitutes a safe level of hypercapnia, $Paco_2$ levels above 100 mm Hg should be avoided.

Complications of mechanical ventilation in the asthmatic patient include hypoxemia, hypotension, nosocomial infections, and barotrauma. Hypotension is almost uniformly secondary to increased intrathoracic pressure with a subsequent decrease in venous return and cardiac output. Slowing the rate of mechanical ventilation or removing the patient from the ventilator for a short time (20 to 30 seconds) allows more time for expiration, thereby decreasing intrathoracic pressure. Volume depletion and medication effects (e.g., narcotic sedative agents) are other potential explanations for hypotension. Pneumothorax should be considered whenever sudden deterioration occurs or when hypotension is accompanied by a significant rise in peak inspiratory pressures on the ventilator. Although complications may occur, the use of mechanical ventilation in critically ill asthmatics is associated with low morbidity and mortality.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is an invasive therapy that uses an artificial membrane to oxygenate and remove carbon dioxide. ECMO allows for gas exchange while using lung-protective ventilation strategies. Currently, there are no studies showing a clear indication for the use of ECMO in the asthmatic patient, however, registry data and case reports suggest a role in treating near fatal asthma in ventilated patients. If available, ECMO may be considered in asthmatic patients that are refractory to conventional ventilator management.[7]

Other and Future Therapies

In patients without dehydration or hypovolemia, the administration of fluids does not clear airway secretions. Mucolytics may worsen cough or airflow obstruction, and chest physical therapy is not beneficial. Infused enoximone (a phosphodiesterase III inhibitor) can cause significant bronchodilation. Specific cytokine antagonists, agonists, inhibitors of T-cell function, selective inducible nitric oxide synthetase inhibitors, and possibly gene-directed therapies may become novel treatments. Dexmedetomidine is a unique sedative that induces sleep but preserves respiratory drive and does not cause respiratory depression or change in airway patency. There may be a future role for the use of intravenous or intranasal dexmedetomidine for anxiolysis in asthma. Further studies are needed.[19]

There are currently biologic therapies available for the management of chronic asthma. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, is indicated for the treatment of severe allergic asthma. It has been shown to control symptoms in severe chronic asthmatic and may be an alternative for patients with poor compliance to ICS therapy.[20,21] Benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, when given in the ED to severe nonresponding patients decreases future hospitalizations.[21]

SPECIAL SITUATIONS

Pregnancy

Asthma during pregnancy is extremely variable. During pregnancy, approximately one third of women have their asthma worsen, a third have their asthma improve, and a third have no change in their asthma symptoms. Approximately 11% to 18% of pregnant women will present to the emergency department with an asthma exacerbation and 62% of these will be admitted. Asthma exacerbation rates and hospitalizations are directly proportional to the degree of asthma control and baseline severity of disease. Maternal and neonatal outcome are excellent in patients with mild or moderate asthma. Severe asthma during pregnancy is associated with gestational diabetes and delivery before 37 weeks.[22]

The least amount of medication needed to maintain the pregnant asthmatic in the mild severity range is recommended. Acute exacerbations should be treated as in any nonpregnant patient. Pregnant asthmatics are less likely to receive systemic corticosteroids than nonpregnant asthmatics in the ED. Oral and IV steroids are safe during pregnancy and should be administered in a manner similar to nonpregnant patients. ICSs are not associated with adverse perinatal outcomes and are recommended for all pregnant patients with asthma (budesonide is preferred). Inhaled beta-2 agonists, ipratropium, magnesium sulfate, cromolyn, theophylline, and leukotriene antagonists are safe.[7] Acute asthma attacks are rare in labor likely due to endogenous steroid production. There are no contraindications to any asthma medication in the breast-feeding patient.

Near Fatal Asthma

Near fatal or life-threating asthma is used to describe acute severe asthma with clinical features such as altered consciousness level, exhaustion, poor respiratory effort, silent chest, hypotension, cyanosis,

a PEF <33% or hypoxia with a SpO_2 <92% or PaO_2 <60 mm Hg.[22a] Acute severe asthma does not require the patient to have severe asthma; rather it refers to acute episodes requiring immediate multimodal therapies to prevent progression to irreversible hypoxia and cardiopulmonary arrest. The terms status asthmaticus, near fatal asthma, and life-threatening asthma are all used to describe patients with different severity of acute severe asthma.

Risk factors for death from asthma have been identified (see Box 59.1). Other risk factors linked to near-fatal and fatal asthma include frequent use of inhaled beta-2 agonists, decreased use of corticosteroids, hospital admission for asthma treatment within the previous 12 months, low socioeconomic status, environmental exposures (air pollution, cigarette smoking), and psychosocial problems. Patients with near-fatal asthma are likely to depend on EDs for asthma management. Patients with fatal asthma commonly tend to be African American, live in inner-city areas, and are 15 to 34 years old. Less than 1% of asthmatics in the ICU die from their disease. Most deaths occur at home or on the way to the hospital, at night, and within 24 hours of the onset of symptoms.

Clinical Approach to Acute Severe Asthma

The patient with life-threatening or near fatal asthma appears agitated (hypoxemic), assumes an upright position, and appears to be in severe respiratory distress. Tachypnea, diaphoresis, and accessory muscle use are evident. Speech is fragmented into single or short bursts of syllables or words. Absence of wheezing indicates severe expiratory obstruction and minimal air movement. Peak expiratory testing is difficult for the patient to perform but when possible indicates severe expiratory obstruction. Alterations in consciousness and bradypnea indicate hypercarbia and impending respiratory arrest. No laboratory markers identify near fatal asthma.

Attempts to abort the episode include continuously nebulized beta-2 and anticholinergic agents (see Table 59.2). If parenteral adrenergic therapy is desired, terbutaline is preferred because of its beta-2 selectivity. IV magnesium sulfate may be of benefit. Oral prednisone 50 mg or IV methylprednisolone 125 mg should be administered. The use of additional therapies such as noninvasive or mechanical ventilation as described above may be necessary.

The American Heart Association recommendations for cardiopulmonary resuscitation in asthmatics indicate no difference from other cardiac arrest situations. Unrecognized barotrauma may cause cardiac arrest. Bedside ultrasound should be used to identify occult pneumothorax and to reveal nonpalpable cardiac contractions. Empirical bilateral tube thoracostomy should be performed if unexplained cardiac arrest occurs, especially in the context of dramatic increases in peak inspiratory pressure. ECMO may be indicated for severe asthma refractory to conventional therapies.

DISPOSITION

Asthmatic patients discharged from the ED have rates of relapse that vary from 11% over 3 days to 45% at 8 weeks. The relapse risk increases in those with numerous asthma-related ED visits within the previous year, more outpatient medications, and longer duration of symptoms before the ED visit. Other studies have also shown that insufficient improvement in peak flow measurements with hospital-based treatment is a risk factor for relapse.

Patients requiring extended care who are without life-threatening exacerbations, pregnancy, or complications of asthma can generally be treated in an observation unit with 8-week outcomes equal to those admitted to the hospital. Table 59.4 summarizes disposition guidelines based on PEF and other potential factors.

TABLE 59.4 Emergency Department Disposition Decision-Making Guidelines

	Good Response	Incomplete Response	Poor Response
PEF (% predicted/ personal best)	≥60%	40%–60%	<40%
Disposition Site			
Home	Yes	Consider based on risk factors (see Box 59.1)	No, continue therapy
Hospitalization	No	Consider based on risk factors (see Box 59.1)	Yes, if available and appropriate

Additional Factors With Increased Likelihood of Admission

- Female sex, older age, and non-white race
- Use of more than 8 beta agonist puffs in previous 24 h
- Severity of exacerbation (need for rapid medical intervention on arrival, respiratory rate >22, oxygen saturation <95%, final PEF <50% predicted
- Past history of intubations or asthma admissions
- Previous use of OCS

OCS, Oral corticosteroids; *PEF,* peak expiratory flow rate.

Asthma exacerbation does not end on discharge; airway inflammation and peripheral obstruction may take hours to days to resolve. Patients are likely to need continued beta-2 agonist therapy for a short time after the ED, and they should demonstrate the correct use of their inhalers. However, guidelines for the chronic use of inhaled beta-2 agonists recommend limited daily use only as a rescue therapy. A spacer should be used with any MDI. A patient using a portable, preloaded, multidose dry powder inhaler must be able to inhale from the mouthpiece in a rapid and forceful inhalation to total lung capacity.

Patients receiving systemic corticosteroids in the ED should continue these orally for 5 to 7 days. For patients with asthma symptoms less than twice per month, ED clinicians should consider discharging them with a low dose ICS-formoterol inhaler or having them take a low dose ICS whenever SABA is taken. If patients have asthma symptoms more than twice per month, they should be discharged with a low dose ICS-formoterol inhaler or taking a low dose ICS whenever SABA is taken. If the patient was not using controller medications before the acute visit and has characteristics of persistent asthma (symptoms or rescue therapy more than twice per week, interference with sleep more than twice per month, activity limitation caused by asthma or exacerbations requiring oral corticosteroids more than once in the past year), moderate-dose ICSs or a combination ICS and LABA should be started.[8]

Patients should contact their physician for asthma-related problems within the following 3 to 5 days and should make a follow-up medical appointment within 1 to 4 weeks. Interventions that include free medications, transportation vouchers, and appointment assistance significantly increase the likelihood that discharged asthma patients will obtain primary care follow-up. This assistance, however, may not affect long-term outcomes.

Patients managed by asthma specialists have fewer symptoms, less beta-agonist use, improved quality of life, reduced ED visits, and fewer hospitalizations than those managed by generalists. Patients

with severe persistent asthma or prior severe exacerbations should be referred to an asthma specialist.

The asthma patient should be provided with written education about discharge medications, medication adjustment if the condition is not improving (such action plans are not often created and when done are often inadequate), and a peak flow meter for daily measurements, especially for those who have difficulty perceiving airflow obstruction or who have symptoms of worsening asthma. At a minimum, focused education should address the difference between controller and rescue medications and the need for follow-up. Intervening in the ED during an acute asthma exacerbation with a web-based education tool may reduce future ED visits.[23] Smoking asthmatics have more respiratory symptoms, lower lung function, and more parenchymal abnormalities noted on chest computed tomography, so smoking cessation should be discussed.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 59: QUESTIONS AND ANSWERS

1. Which of the following is a risk factor for sudden death from asthma?

- **a.** A hospitalization for asthma in the past year but not within the past 30 days
- **b.** An emergency department (ED) visit for asthma in the past year but not within the past 30 days
- **c.** Current use of systemic corticosteroids
- **d.** Patient perception that the current exacerbation is very severe

Answer: c. Risk factors for sudden death are current or recent corticosteroid use, ED or hospitalization within the past 30 days, more than two hospitalizations for asthma in the past year, more than three ED visits for asthma in the past year, using more than two beta-agonist canisters per month, previous intubation or intensive care unit (ICU) visit, and difficulty perceiving symptoms or their severity.

2. A 23-year-old man with known severe asthma presents with an acute asthma flare over 2 hours. Physical examination reveals a well-developed man in marked respiratory distress. Heart rate is 120 beats/min, oxygen saturation is 90%, respiratory rate is 26 breaths/min, blood pressure is 140/92 mm Hg, and oral temperature is 98.7°F (37.2°C). Current medications are albuterol metered-dose inhaler (MDI) and fluticasone inhaler 500 µg twice daily. What therapy is recommended for this acute flare?

- **a.** Albuterol 2.5 mg nebulized, Ipratropium 0.5 mg, methylprednisolone 125 mg intravenously, and magnesium sulfate 2 g intravenously
- **b.** Epinephrine infusion at 5 µg/min
- **c.** Ipratropium 500 µg nebulized × three doses with methylprednisolone 125 mg intravenously
- **d.** Methylprednisolone 125 mg intravenously with salmeterol nebulized via continuous nebulization

Answer: a. Short-acting inhaled beta-agonists with ipratropium are the cornerstone of acute asthma management. Corticosteroids are indicated in any moderate or severe flare. Oral steroids are as efficacious as intravenous (IV) steroids if the patient can take oral medications. Magnesium sulfate may obviate the need for intubation or decrease hospital length of stay in severe cases. Salmeterol is a slow-onset, long-acting beta-2 agonist (LABA) not indicated in acute asthma management.

3. What is the medication combination of choice for the rapid sequence induction of an asthmatic?

- **a.** Etomidate/succinylcholine
- **b.** Ketamine/succinylcholine
- **c.** Midazolam/pancuronium
- **d.** Propofol/rocuronium

Answer: b. No choice is contraindicated. Ketamine is the sedative of choice because of its bronchodilatory effect. Propofol may have the same benefit, although less profoundly. Thiopental releases histamine, and etomidate does not bronchodilate. Succinylcholine releases trace amounts of histamine, but this is not known to cause any adverse effect. Rocuronium has an onset time similar to that of succinylcholine, no

histamine release, and a prolonged duration of action. Either succinylcholine or rocuronium is acceptable for rapid sequence intubation (RSI) in acute asthma.

4. Which of the following is a risk factor for death in patients presenting with an asthma attack?
   a. Currently taking theophylline
   b. Family history of asthma
   c. Presence of symptoms for 1 week
   d. Use of three albuterol metered-dose inhalers (MDIs) per month

Answer: d. The following are risk factors for death from asthma:

- Past history of sudden severe exacerbations
- Prior intubation for asthma
- Prior asthma admission to an intensive care unit (ICU)
- Two or more hospitalizations for asthma in the past year
- Three or more emergency department (ED) care visits for asthma in the past year
- Hospitalization or an ED care visit for asthma within the past month
- Use of more than two MDI short-acting beta-2 agonist canisters per month
- Current use of or recent withdrawal from systemic corticosteroids
- Difficulty perceiving severity of airflow obstruction
- Comorbidities such as cardiovascular diseases or other systemic problems
- Serious psychiatric disease or psychosocial problems
- Illicit drug use, especially inhaled cocaine and heroin

5. A 25-year-old woman presents with wheezing and shortness of breath from asthma. She was recently exposed to cigarette smoke. She denies cough and fever. You cannot get much more of a history from her at this time because she finds it difficult to speak in complete sentences. Her vital signs are blood pressure, 136/85 mm Hg; heart rate, 110 beats/min; respiratory rate, 32 breaths/min; and temperature, 99°F (37.2°C). Her oxygen saturation is 92%. Her PEF is 50% of predicted. On physical examination, you note bilateral wheezing, regular tachycardia, and accessory muscle use. The remainder of her examination is normal. Over the course of 1 hour, she receives supplemental oxygen, three doses of nebulized albuterol (5 mg) mixed with ipratropium (0.5 mg), and oral prednisone 50 mg. She now reports feeling somewhat better. She speaks in longer sentences but still cannot speak in complete sentences. A repeat peak flow measurement is now 60% of predicted. Otherwise, there are no changes on a repeat physical examination. You plan to admit her to your ED observation unit. What is an appropriate next step in the management of this patient?
   a. Additional nebulized albuterol
   b. Intravenous (IV) magnesium sulfate
   c. IV methylprednisolone (Solu-Medrol)
   d. Oral montelukast

Answer: a. This patient presents with a moderate-to-severe asthma exacerbation. She has responded to initial therapy but continues to have moderate symptoms. Additional adrenergic medications are indicated. Because she is tolerating nebulized medications and is responding, there is no need for IV or subcutaneous adrenergic agents, such as terbutaline. IV magnesium sulfate is a smooth muscle relaxant, but it is generally reserved for more severe asthma exacerbations. Oral and IV steroids have the same efficacy, and regardless of the route, only need to be administered every 6 to 8 hours. Montelukast is a leukotriene-modifying drug that is used in chronic management.

60

Chronic Obstructive Pulmonary Disease

Patricia Ruth Atchinson and Matthew A. Roginski

KEY CONCEPTS

- Chronic obstructive pulmonary disease (COPD) is "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."
- COPD exacerbation is a worsening of symptoms from baseline beyond day-to-day variation and requiring additional treatment. It is most commonly caused by viral infections, bacterial infections, environmental pollutants, particulate matter, thrombotic disease, or temperature changes.
- Dyspnea, cough, increased sputum production, and sputum purulence are the most common symptoms of COPD exacerbations. They are a result of airway inflammation, increased mucus production, and air trapping.
- Treatment includes nebulized short-acting beta-agonists such as albuterol, short-acting anticholinergics such as ipratropium, and glucocorticoids such as prednisone.
- Antibiotics should be given to patients with COPD exacerbations who have signs of lower respiratory tract infection, increased purulence of their sputum, or who have respiratory failure. Antibiotics should be provided empirically based on local resistance patterns to *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae* with common regimens including amoxicillin/clavulanate, macrolides, or tetracyclines.
- Patients with COPD are at increased risk for thromboembolic disease due to a sedentary lifestyle and chronic inflammation. Patients admitted for COPD exacerbation presenting a pleuritic chest pain or signs of heart failure without an infectious precipitant should be screened for pulmonary embolism.
- Patients with COPD exacerbations commonly present with tachyarrhythmias including atrial fibrillation, atrial flutter, and multifocal atrial tachycardia.
- Oxygen supplementation should be administered with a saturation goal of 88% to 92%.
- In severe exacerbations, patients develop a rapid, shallow breathing pattern which decreases the exhalation time, causes hyperinflation, increases the proportion of dead space ventilation, and causes respiratory muscle fatigue.
- Bi-level noninvasive ventilation is the first-line therapy for patients with hypercapnic respiratory failure and acute COPD exacerbations without hemodynamic instability, severe agitation, or respiratory arrest. Implementing noninvasive ventilation decreases the mortality, intubation rates, and hospital length of stay.
- If intubation is required, ventilation priorities are decreasing the patient work of breathing and limiting dynamic hyperinflation primarily using a low respiratory rate of 10 to 14 breaths/min and tidal volume of ≤8 mL/kg predicted by body weight. Respiratory acidosis with a pH greater than 7.2 should be tolerated without manipulating the minute ventilation.
- All patients being discharged from the emergency department should be counseled on smoking cessation, adequate inhaler techniques, and offered pneumococcal and influenza vaccination if not current.

FOUNDATIONS

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in the United States and worldwide[1] with a high financial burden to the healthcare system and frequent presentation to the emergency department (ED). The prevalence of COPD is likely underrecognized.[2,3] A large multinational collaboration called the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was created to develop guidelines worldwide to improve prevention and treatment of COPD. GOLD defines COPD as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1] COPD is caused by both environmental and genetic factors. Cigarette smoking is the most important risk factor for developing COPD, but fewer than half of smokers will develop COPD. Other risk factors include an age greater than 40 years, male gender, occupational exposures, indoor air pollution, and genetic factors such as alpha-1 antitrypsin deficiency.

Airflow limitation diagnosed by spirometry determines the disease severity. Symptom burden and exacerbation risk are also incorporated into the diagnostic criteria. Treatment recommendations of the stable patient incorporate both the airflow obstruction and symptom burden. Patients with COPD have a high prevalence of concomitant comorbid conditions, including ischemic heart disease, atrial fibrillation, heart failure, metabolic syndrome, musculoskeletal disease, anxiety, depression, and lung cancer.[4]

Anatomy/Physiology/Pathophysiology

The tracheobronchial tree is composed of large conducting airways that divide into smaller bronchi and bronchioles terminating in a functional lung unit called a pulmonary acinus. The acinus is supplied by a first order respiratory bronchiole and includes alveolar ducts and alveolar sacs (Fig. 60.1). The larger bronchi are in close proximity to pulmonary arteries and lymphatics and not directly connected to the lung parenchyma. They remain patent because of their cartilaginous structure and the pressure gradient from the alveolar to the intrathoracic space. Smaller bronchioles (<1 to 2 mm) are embedded in lung parenchyma and do not have a cartilaginous structure; they remain patent because of the elastic recoil of the lung parenchyma. Collectively, the total cross-sectional area of the bronchioles is approximately 100 times greater than that of the large proximal airways and, under normal circumstances, do not contribute to flow resistance. In COPD, progressive changes within the bronchial tree and the lung parenchyma cause airflow resistance.

Frequent exposure to noxious stimuli (e.g., cigarette smoke or small particles) induces inflammation in the airways and pulmonary parenchyma. Lymphocytes, macrophages, and neutrophils infiltrate inflamed tissues. Over time, a chronic inflammatory response leads

to remodeling and destruction of the normal tissue by oxidative stress and protease activity. Inflammation in the bronchi and bronchioles results in increased mucus production with submucosal gland enlargement and goblet cell metaplasia, decreased mucociliary clearance, and increased permeability of the airspace epithelial border. Sustained inflammation can result in the remodeling of smooth muscle and connective tissue, epithelial hypertrophy, and fixed obstruction in small airways from fibrosis.

Inflammation in the lung parenchyma destroys the connective tissue matrix of alveolar walls and septae. The balance of protease/antiprotease activity has an essential role in disease progression. Activated neutrophils are the primary producer of elastase in the lungs, and neutrophil elastase destroys the matrix of lung parenchyma. The action of neutrophil elastase is inhibited by alpha 1-antitrypsin. Patients who are deficient in alpha 1-antitrypsin, as well as patients who are chronically exposed to noxious stimuli, leading to the activation of neutrophils in the pulmonary parenchyma, have significant parenchymal damage.

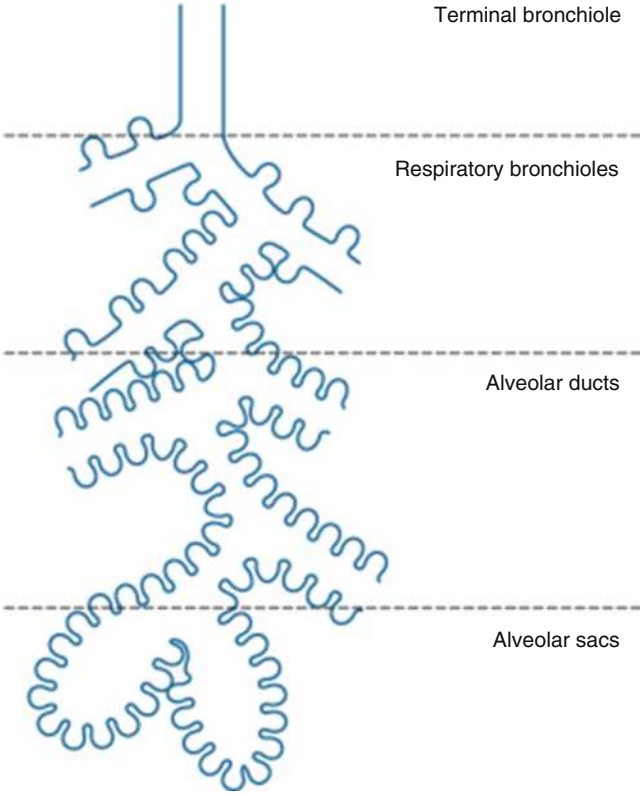

Fig. 60.1 Diagram of a single pulmonary acinus displaying the generations between terminal bronchiole and alveolar sacs. (From Nunn's Applied Respiratory Physiology. Lumb, Andrew B, MB BS FRCA. Published January 1, 2017. Pages 3–16.e1. © 2017. Figure 1.6.)

COPD is a multifactorial and heterogeneous disease with different aspects of the disease progressing independently of the another. Patients are no longer categorized as having primarily emphysematous or chronic bronchitis phenotypes because both often coexist. Emphysema is a pathological diagnosis referring to the destruction of the lung parenchyma. Pulmonary parenchymal destruction results in gas trapping and airflow obstruction. The pattern and location of damage can vary based on precipitating factors. Patients with alpha 1-antitrypsin deficiency usually have panacinar emphysema predominantly in the lower lung zones, whereas chronic smokers typically have central acinar emphysema predominantly in the upper lung zones (Fig. 60.2). Severity of airflow obstruction and air trapping are proportional to the amount of parenchymal destruction. Decreased and damaged lung parenchyma provide less traction on the small bronchioles (<1 to 2 mm) embedded in the parenchyma and requiring an intact architecture for patency. As airflow obstruction and parenchymal destruction worsen, the total number of terminal bronchioles is also reduced.[5] This combination of events leads to decreased gas exchange, decreased pressure gradient from the alveoli to the conducting airways during exhalation, and collapse of the bronchioles leading to gas trapping (Fig. 60.3). Fig. 60.4 shows evidence of parenchymal destruction in a patient with COPD and emphysema on contrast enhanced chest CT.

Chronic bronchitis is diagnosed in the presence of cough and sputum production for most days over 3 months for at least 2 consecutive years. These patients have increased mucus production, decreased ciliary clearance and chronic bronchial inflammation. They are likely to have central hypoxemia because of these changes. There are efforts to clarify different endotypes of COPD to develop targeted treatments. For example, alpha 1-antitrypsin deficiency and inflammation that has an eosinophilic predominance may be more amenable to steroids.[4] Asthma-COPD overlap syndrome has clinical features of both asthma and COPD regarding bronchial hyperresponsiveness and etiology of inflammation.[6] Differentiation is of limited clinical utility in the ED.

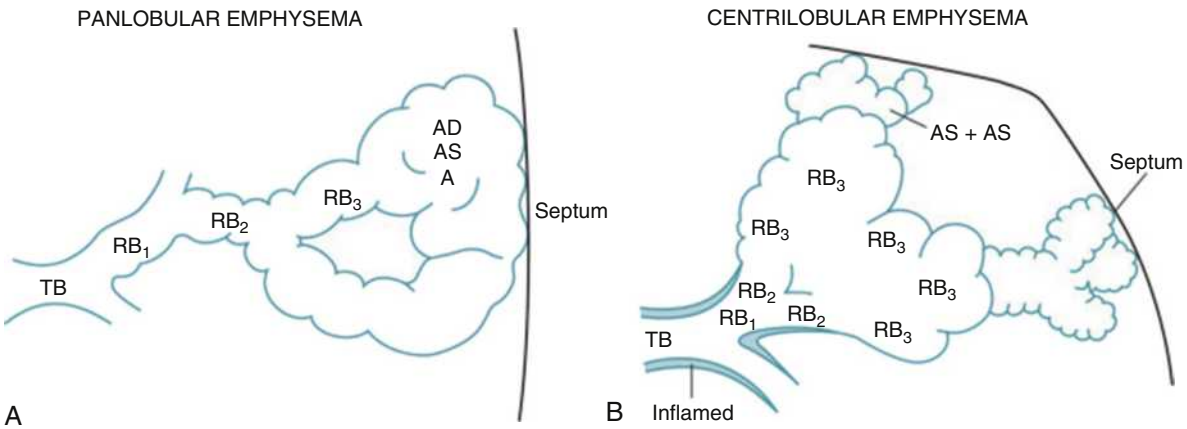

Fig. 60.2 Diagram of panacinar (A) and centriacinar (B) emphysema. Panacinar emphysema (A) has uniform enlargement of the acinus. Centriacinar emphysema the enlargement is primarily at the level of the respiratory bronchiole and not alveolar sacs. *A*, Alveolus; *AD*, alveolar duct; *AS*, alveolar sac; *RB 1, 2, 3*, three generations of respiratory bronchioles; *TB*, terminal bronchiole. (From Thurlbeck WM. Chronic obstructive lung disease. In: Sommers SC, ed. *Pathology Annual*, vol 3. New York, NY: Appleton-Century-Crofts; 1968.)

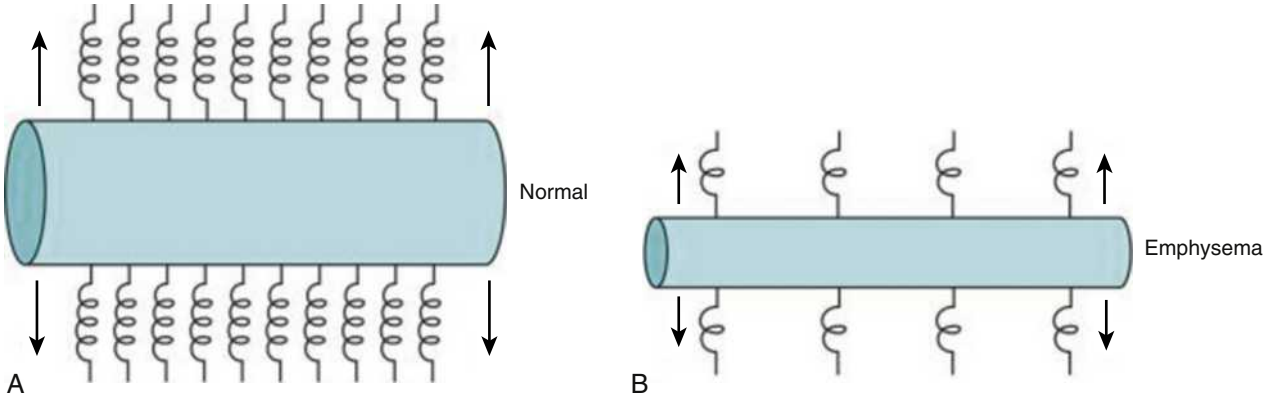

Fig. 60.3 Schematic diagram of traction exerted by alveolar walls (shown by springs), acting to keep the airways open. (A) Normal. (B) Loss of traction seen in emphysema. (From Weinberger, Steven E., MD, MACP, FRCP; Cockrill, Barbara A., MD; Mandel, Jess, MD, FACP. Published December 31, 2018. Pages 93–112. Copyright © 2019 by Elsevier, Inc.)

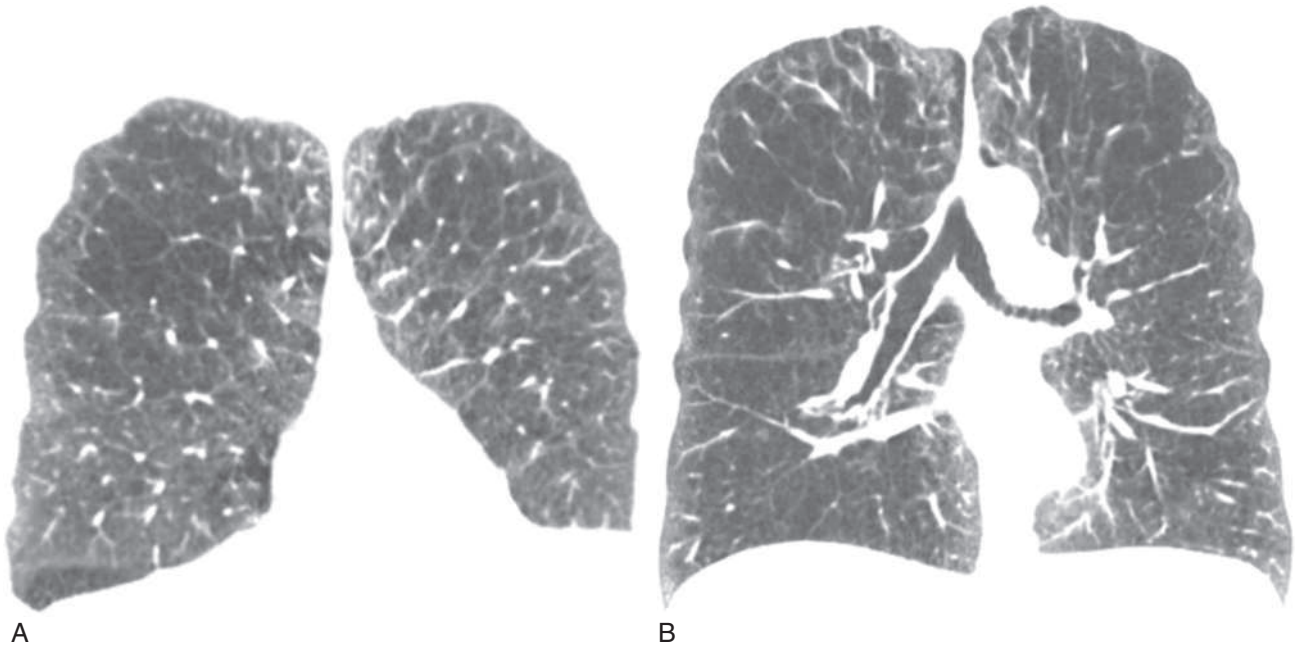

Fig. 60.4 (A and B) Coronal contrast enhanced CT images in a patient with emphysematous chronic obstructive pulmonary disease. Decreased attenuation in the right and left upper lung zones represents the parenchymal destruction and loss.

Pulmonary hypertension may be present in patients with severe COPD because of changes in the pulmonary vasculature and surrounding structures. Late in the course of COPD, there is often chronic hypoxia secondary to lung parenchyma destruction. Hypoxic vasoconstriction in the small vessels of the pulmonary arterial bed and loss of pulmonary capillaries result in vascular remodeling, intimal hyperplasia, smooth muscle hyperplasia, and hypertrophy. Hypoxic vasoconstriction may be reversible, but vascular remodeling may not be. As the disease progresses, pulmonary hypertension (cor pulmonale), and right ventricular remodeling may result. These progressive changes are also associated with a patient's clinical course. For example, a large pulmonary artery to aorta ratio on CT scan is associated with an increased risk of COPD exacerbation.

As airflow obstruction and increasing air trapping develop on the microscopic pulmonary acinus level, there are associated changes in the macroscopic lung physiology. COPD patients have increased residual volume, functional residual capacity (FRC), and total lung capacity due to hyperinflation. This contributes to the increase in dead space and decline of forced expiratory volume in one second (FEV_1) because of the loss of lung tissue and loss of elastic recoil of the lungs. Over time these changes cause the diaphragm to flatten with a decreased zone of opposition causing a decrease in mechanical efficiency. The rib cage also changes with an increase in the antero-posterior diameter (Fig. 60.5). These changes are associated with decreased respiratory efficiency and increased energy consumption to maintain an adequate minute ventilation. Patients with these underlying changes have a decreased respiratory reserve in the setting of a COPD exacerbation, pneumonia, or metabolic acidosis that requires respiratory compensation.

Clinical Features

The diagnosis of COPD should be considered in patients who have progressive dyspnea, chronic cough or sputum production, recurrent

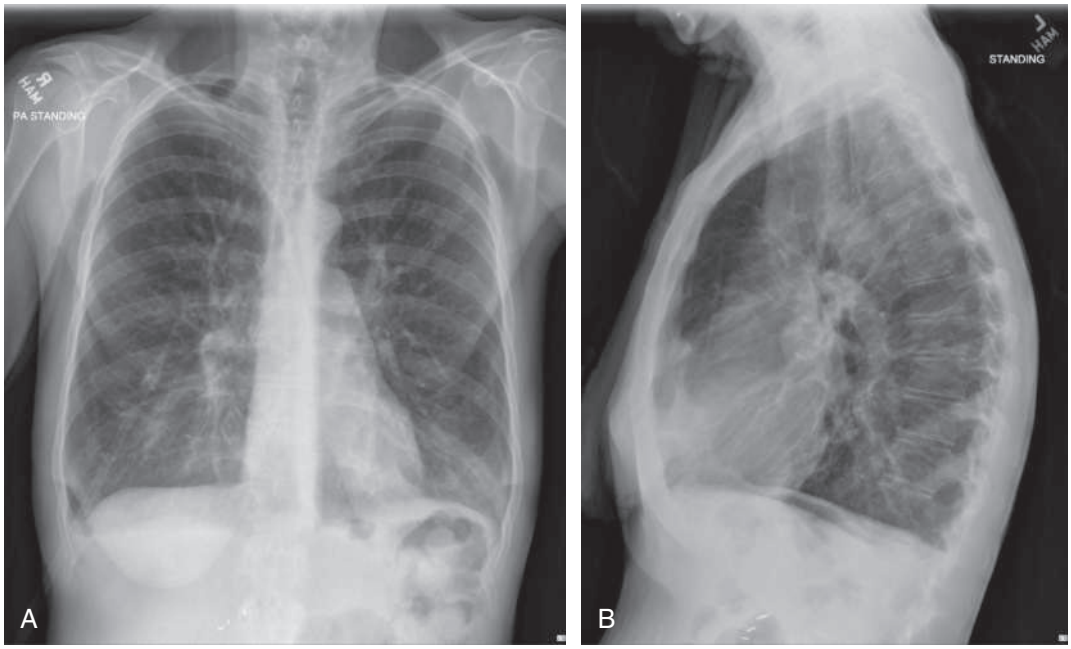

Fig. 60.5 (A and B) Chest x-rays displaying typical changes seen in chronic obstructive pulmonary disease. A is a posterior-anterior chest x-ray showing hyperinflated lungs and a flattened diaphragm. B is a lateral chest x-ray showing hyperinflated lungs and a flattened diaphragm and with an increased antero-posterior diameter.

lower respiratory tract infections or have multiple risk factors.[1] The diagnosis of COPD requires spirometry-proven airflow limitation defined as the ratio of FEV_1 divided by forced vital capacity (FVC) after bronchodilators of less than 0.7. Patients who have normal spirometry with chronic symptoms and possible emphysema on CT scan are not considered to have COPD.[7] Airflow limitation may worsen over time, especially in the setting of continued exposure to noxious stimuli, and is frequently associated with escalating patterns of worsening exacerbations. However, it is difficult to predict the progression of airflow limitation for an individual, because a small subset of patients get stable or improve over time.[8,9]

The GOLD classification of COPD incorporates the severity of spirometric abnormalities, nature and magnitude of the symptoms, history of moderate to severe exacerbations, and comorbid conditions because the health status and spirometric abnormalities have a weak correlation. The severity of COPD is graded by the degree of airflow obstruction (FEV_1) after bronchodilation (Table 60.1). In addition to the grade, the "ABCD" assessment tool incorporates symptomatic assessment and risk of exacerbations to better assess patients and guide therapy. The letter group is determined by the Modified British Medical Research Council (mMRC) Questionnaire[10] or COPD Assessment Test (CAT)[11] as well as the exacerbation history (Table 60.2). While emergency physicians are not tasked with diagnosing COPD, understanding the spirometric and letter grading provides a more complete understanding of the disease severity, symptom burden, medication regimen, and risk for hospitalization and decompensation.

Acute Exacerbations

A COPD exacerbation is an acute worsening of respiratory symptoms from baseline day-to-day variations that require additional therapy.[1,12] Exacerbations can be triggered by respiratory infection, environmental pollutants, particulate matter, thrombotic disease, or temperature changes. Respiratory infections are more commonly viral, with bacterial infections implicated in 30% to 50% of exacerbations. The most commonly implicated bacterial causes include *Haemophilus influenzae,*

TABLE 60.1 Severity Classification of Airflow Limitation in Patients With COPD (FEV_1/FVC <0.7)

GOLD Classification of Airflow Limitation Severity in COPD (based on post-bronchodilator FEV_1)		
GOLD 1	Mild	FEV_1 ≥80% predicted
GOLD 2	Moderate	50% ≤FEV_1 <80% predicted
GOLD 3	Severe	30% ≤FEV_1 <50% predicted
GOLD 4	Very Severe	FEV_1 <30% predicted

COPD, Chronic obstructive pulmonary disease; *FEV_1*, forced expiratory volume in one second; *FVC*, forced vital capacity; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease.
Adapted from GOLD 2020 guidelines. Gold Reports for Personal Use. *Global Initiative for Chronic Obstructive Lung Disease—GOLD*. https://goldcopd.org/gold-reports/. Accessed January 17, 2020.

TABLE 60.2 GOLD ABCD Assessment Tool

Moderate to Severe Exacerbation History	≥2 or ≥1 leading to hospital admission	C	D
	0 or 1 (not leading to hospital admission)	A	B
		Mild (mMRC or CAT)	Severe (mMRC or CAT)
		Symptoms burden	

The letter provides information about symptom burden and risk of exacerbation in addition to the airflow limitation severity classification that can be used to guide future therapy.
Adapted from GOLD 2020 guidelines. Gold Reports for Personal Use. *Global Initiative for Chronic Obstructive Lung Disease—GOLD*. https://goldcopd.org/gold-reports/. Accessed January 17, 2020. *CAT*, COPD Assessment TEST. This is an 8-item measure of health status impairment in COPD. *mMRC*, Modified British Medical Research Council Questionnaire.

Streptococcus pneumoniae, and *Moraxella catarrhalis*. The most commonly isolated virus is rhinovirus, and viral infections may have a longer and more severe course. Patients presenting with a COPD exacerbation without a clear exposure or infectious risk should be screened for pulmonary embolism, especially if pleuritic chest pain or signs of heart failure are present.[13,14]

Exacerbations are considered mild when only worsening of symptoms are reported, moderate when the patient receives antibiotics or systemic glucocorticoids, and severe when the patient requires an ED visit.[1,4,15] Exacerbations are commonly associated with dyspnea, cough, increased sputum production, and sputum purulence. Depending on the severity, dyspnea and respiratory symptoms may occur at rest or with exertion. Coughing spells may be associated with chest pain from irritation of the intercostal muscles or atraumatic rib fractures in severe cases. Severe coughing episodes may precipitate syncope because of the increase in intrathoracic pressure and decrease in cardiac preload. Inflammation and mucous production increase air trapping, combined with chronic changes to pulmonary mechanics and impaired ability to compensate; this ultimately leads to decreased respiratory efficiency, increased dead space ventilation, and dynamic hyperinflation. As the work of breathing increases, the proportion of cardiac output required by the respiratory musculature increases, further limiting the patient's ability to compensate, and predisposing the patient to progressive respiratory failure.

Respiratory Failure

Patients with a declining respiratory status have a breathing pattern marked by small, frequent breaths through pursed lips. This change in breathing pattern decreases the exhalation time, increases the proportion of dead space ventilation, and has a high energy cost. Many of these patients experience expiratory flow limitation (EFL), in which expiratory flow does not increase despite an increase in the gradient from alveolar pressure to ambient air pressure.[16] In patients with EFL, exhalation to passive FRC (complete exhalation) depends on the expiratory time and not the patient effort. Increased patient effort and pleural pressure do not result in faster expiratory airflow. EFL predisposes patients to dynamic hyperinflation and alveolar overdistension with tachypnea.

Dynamic hyperinflation occurs when inhalation occurs prior to complete exhalation because of truncated expiratory time. Dynamic hyperinflation increases the end-expiratory lung volume, with alveolar overdistension, increased intrathoracic pressure, and decreased lung compliance. These factors subsequently result in an elevated work of breathing, increased dead space ventilation, respiratory muscle fatigue, and hypercapnia culminating in respiratory failure. Clinical definitions of respiratory failure consider respiratory rate, accessory muscle use, increases in the arterial partial pressure of carbon dioxide ($PaCO_2$), and hypoxemia. Definitions of respiratory failure are displayed in Box 60.1.

Differential Diagnosis for the Emergency Presentation

The differential diagnosis for a COPD exacerbation, displayed in Box 60.2, includes pulmonary, cardiac, and metabolic conditions. Respiratory decompensation may be from pneumonia, bleb rupture and pneumothorax, or pleural fluid collection. Pulmonary embolism should be considered in patients without an infectious prodrome, unexplained pleuritic chest pain, signs of new heart failure, or in those whose vital sign abnormalities are out of proportion to the clinical exam. Traumatic or pathologic rib fractures from coughing can cause chest pain and dyspnea. Chest pain may also be related to hyperinflation and overdistention of the respiratory muscles causing discomfort. Patients with COPD have increased risk of coronary artery disease, arrhythmias, and heart failure. Acute cardiogenic pulmonary edema may also present as dyspnea and wheezing. Progressing pitting edema may represent cor pulmonale. Patients at risk for lung cancer may present with dyspnea in the setting of malignant pulmonary or pericardial effusions. Metabolic acidosis or sepsis may present as dyspnea and tachypnea because changes in the respiratory system in severe COPD limit respiratory compensation of a metabolic process.

BOX 60.1 Classification of Respiratory Failure in COPD Exacerbation

No respiratory failure
- Mild tachypnea with rate of 20–30 breaths per minute
- Normal work of breathing
- Baseline mental status
- Mild hypoxemia responsive to oxygen by nasal cannula
- No hypercapnia

Acute respiratory failure
- Significant tachypnea with rate >30 breaths per minute
- Increased work of breathing with accessory muscle use
- Baseline mental status
- Hypoxemia responsive to supplementation with <35% FiO_2
- Hypercapnia with $PaCO_2$ 50–60 mmHg and pH >7.25

Severe respiratory failure
- Altered mental status
- Hypoxemia requiring supplementation with >35% FiO_2
- $PaCO_2$ >60 mm Hg or pH ≤7.25

BOX 60.2 Differential Diagnosis of an Acute Chronic Obstructive Pulmonary Disease Exacerbation

Differential Diagnosis for COPD and COPD Exacerbation

Pneumonia
Pneumothorax
Pleural effusion
Pulmonary embolism
Pulmonary edema
Cardiac arrhythmia
Malignancy
Pericardial effusion
Heart failure
Metabolic acidosis with compensatory tachypnea

COPD, Chronic obstructive pulmonary disease.

Diagnostic Testing

In the outpatient setting, the diagnosis of COPD relies upon spirometry. Patients with symptoms and risk factors suggestive of COPD should be referred for formal evaluation. The diagnosis of COPD exacerbation is clinical and based on a worsening of the patient's baseline symptoms including increased dyspnea, changes in sputum production or increased sputum purulence, and cough.

Chest Radiography

A chest x-ray should be obtained for patients to evaluate a new alveolar process such as a lobar pneumonia, pneumothorax, pulmonary

edema, lobar atelectasis, effusion, or malignancy. Typical findings in a COPD exacerbation without the aforementioned pathology include hyperinflated lung fields, decreased vascular markings, increased antero-posterior diameter, and flattening of the diaphragms (see Fig. 60.5). Bullae may be present and can mimic pneumothorax on chest x-ray and pulmonary ultrasound. If there is diagnostic uncertainty for bullae versus pneumothorax, a CT scan should be performed given its greater sensitivity.

Pulse Oximetry

Continuous pulse oximetry should be used to identify hypoxemia and titrate oxygen therapy.

Blood Gas Analysis

We recommend an initial blood gas in patients presenting with acute respiratory failure. A venous blood gas provides an accurate determination of both pH and hypercapnia. A normal $PaCO_2$ on a venous blood gas can exclude hypercapnic respiratory failure.[17] If there is severe hypercapnia or hypoxia, correlation with an arterial blood gas is recommended. An arterial or venous $PaCO_2$ is recommended if end-tidal capnography is being used because of a possible $PaCO_2$ to end-tidal CO_2 discrepancy in the setting of an increased dead space fraction.

Electrocardiogram

An electrocardiogram should be performed in all patients presenting with acute dyspnea. Tachycardia and tachyarrhythmias, including atrial fibrillation, atrial flutter, multifocal atrial tachycardia, and ventricular arrhythmias, occur in up to 35% of patients presenting with COPD exacerbations.[17] Patients with COPD are at increased risk for ventricular tachycardia when compared to the general public, independent of their left ventricular ejection fraction.[18,19] Patients with COPD commonly exhibit P pulmonale, large (>2.5 mm) peaked P waves in leads II, III, and aVF, and >1.5 mm in V1 and V2, low QRS voltage (due to hyperinflated lung between the chest wall and the heart), and poor R wave progression (≤3 mm in V3) in the precordium.

Laboratory Tests

The utility of C-reactive protein (CRP) in COPD management is a developing area of research. Some studies describe that a low CRP decreases the prescription of antibiotics in COPD exacerbations without increasing the proportion of treatment failure.[20–22] We do not think there is sufficient evidence at this time to support using CRP to guide antibiotic prescribing.

Procalcitonin (PCT) has also been considered as a screening test to guide the use of antibiotics, with some studies suggesting that a low PCT can safely be used to decrease antibiotic prescriptions in COPD exacerbation.[23] However, in patients admitted to intensive care units, PCT-guided therapy was associated with worse mortality at 3 months, suggesting that in the critically ill, the prompt administration of antibiotics outweighs the need for judicious antibiotic prescribing.[24]

We also recommend a complete blood count to screen for anemia and a metabolic profile to screen for metabolic acidosis or hyperglycemia. A troponin should be obtained if there is concern for myocardial ischemia. A D-dimer should only be obtained to screen for an acute pulmonary embolism after prior appropriate risk stratification.

Management

Short-Acting Beta Agonists

Short-acting beta agonists (SABAs) with or without short-acting anticholinergics are the cornerstone of COPD exacerbation management. SABAs work through relaxing airway smooth muscle by stimulating beta-2 adrenergic receptors, increasing cyclic adenosine monophosphate (AMP) and producing a functional antagonism to bronchoconstriction. Short-acting anticholinergics prevent the bronchoconstrictive effects of acetylcholine on M2 muscarinic receptors expressed by smooth muscles. In an acute exacerbation, data do not support the use of nebulizers over metered dose inhalers to deliver these medications.[25,26] In the emergency setting, we recommend the use of nebulized medications instead of devices that require adequate inspiratory flow, breath holding, muscle coordination, and proper technique to promote adequate medication disbursement.[26,27] We recommend air-driven nebulizers rather than oxygen-driven nebulizers if available.[28] Patients may receive SABAs hourly for 1 to 3 hours then every 2 to 4 hours based on response. Continuous nebulization not indicated.

Glucocorticoids

Glucocorticoids act as potent anti-inflammatory mediators by inhibiting cytokine expression and eosinophils via induction of eosinophil apoptosis. They are recommended in COPD exacerbation because they decrease the recovery time, improve oxygenation, improve lung function, and decrease hospital length of stay. These benefits outweigh the risks, including infection, thromboembolism, osteoporosis, diabetes, and hypertension. Bioavailability is similar between oral and parenteral corticosteroids; thus we recommend oral glucocorticoids for patients able to tolerate oral medications or with enteral access. We recommend 40 mg oral prednisone for 5 days, because 5 day courses are as effective as longer courses.[29] Eosinophilia-guided therapy may be as effective as the standard 5-day course of steroids in patients ≥40 years old and hospitalized for COPD[30] but this is not part of the standard treatment recommendations at this time.

Antibiotics

The role of antibiotics in COPD exacerbation remains controversial. There is no clear mortality benefit of using antibiotics in patients who are to be discharged from the ED without signs of lower respiratory infection on chest imaging. The GOLD collaborators recommend the administration of antibiotics to patients with COPD exacerbation who note increased sputum purulence as well as increased dyspnea or increased sputum volume. Antibiotics should be provided empirically based on local resistance patterns to *S. pneumoniae, M. catarrhalis,* and *H. influenzae* with common regimens including amoxicillin/clavulanate, macrolides, and tetracyclines. Patients with chronic severe airflow limitations, known bronchiectasis, and or those that require mechanical ventilation should receive antibiotic coverage that includes pseudomonas. Data does not suggest a specific duration of treatment with antibiotics in those patients who are discharged from the ED. We recommend a 5-day course of macrolides or a 7-day course of amoxicillin/clavulanate or tetracyclines as initial antibiotic therapy, along with follow up with their primary care physician or pulmonologist within 10 days of discharge with attention to decreased sputum purulence as a marker of improvement. Any patient requiring ventilatory support via either noninvasive ventilation (NIV) or endotracheal intubation should receive antibiotics as there is a clear mortality benefit in these patients.

Adjunctive Treatments

All actively smoking patients who present a COPD exacerbation should be counseled on smoking cessation. Inhaler technique should be assessed, and counseling provided in case of inadequate techniques. Patients should be up to date on influenza and pneumococcal vaccinations unless contraindicated. There is no conclusive role for antitussive therapy. Patients being hospitalized should have vitamin D level checked and supplemented if below 25 nmol/L or above 10 ng/mL.[31]

Methylxanthines are not recommended. Heliox is not recommended as a treatment adjunct.[32–34]

Respiratory Support

Oxygenation

Hypoxemia is a common finding in patients with severe COPD and during a COPD exacerbation. The precipitating factors of hypoxemia are multifactorial, including changes in the ventilation and perfusion ratios because of hyperinflation and bronchospasm, mucous plugging, alveolar infiltration, disproportionate blood flow in under-ventilated areas, and increased oxygen consumption leading to decrease venous oxygen tension. Both hypoxemia and hyperoxemia should be avoided. Supplemental oxygen should be titrated to maintain an arterial partial pressure of oxygen (PaO_2) greater than 60 mm Hg and peripheral oxygen saturation between 88% and 92%. Prolonged exposure to high concentrations of inspired oxygen may result in increasing hypercapnia. The primary mechanism is thought to be from a change in the ventilation and perfusion ratios by altering hypoxic vasoconstriction to under-ventilated lung zones. The hypoxic respiratory drive does not appear to be a major contributor in most hypercapnic patients in respiratory distress, but there does appear to be a subset of patients in whom $PaCO_2$ increases in the setting of hyperoxia. The Haldane effect (high oxygen tension induces right shift in the CO_2 dissociation curve and increases the $PaCO_2$) may also contribute to hypercapnia. Normally, this is compensated for by an increase in minute ventilation, but if the patient cannot increase their minute ventilation, $PaCO_2$ will increase.

Non-Invasive Ventilation

Bi-level NIV is the first-line therapy for patients with an acute COPD exacerbation with respiratory failure (see Table 60.3 for indications and contraindications). NIV decreases the mortality, intubation rates, and hospital length of stay.[1,15,35,36] The inspiratory positive airway pressure (IPAP) of NIV helps offload respiratory muscles and aid in the work necessary to overcome the intrinsic positive end expiratory pressure (iPEEP). Initiating NIV changes the patient's breathing pattern; the respiratory rate decreases, allowing a more effective emptying of the lungs, and the patient can take breaths with larger tidal volumes, improving alveolar ventilation. If possible, a chest x-ray, blood gas, and respiratory assessment are recommended prior to the initiation of NIV to evaluate for pneumothorax, tachypnea, accessory muscle use, pH, and $PaCO_2$.

We recommend initial settings of an IPAP of 12 to 15 cm H_2O and an expiratory positive airway pressure (EPAP) of 5 cm H_2O through a facemask tightened to minimize air leaks. Inspired oxygen should be quickly titrated to an oxygen saturation of 88% to 92%. While fitting the mask on the patient, a nurse, respiratory therapist, or physician should explain the process to the patient because of the associated anxiety during mask placement while in respiratory distress. An adjunctive fan directed at the patient's face or adjunctive low dose morphine may relieve the sensation of breathlessness.[37–39] Should the patient have increased work of breathing on these initial settings, we recommend increasing the IPAP by increments of 2 to 3 cm H_2O every 2 to 3 minutes to a maximum IPAP of 25 cm H_2O. Improvement in pH and respiratory rate predict treatment success and are usually seen in the first 1 to 4 hours after initiation.[40]

Failure of NIV may occur because of the severity of the underlying disease, severity of comorbidities, or inability to tolerate therapy. The overall failure rate is approximately 10% to 15%[41] but increases with a lower presenting pH and severity of illness. In general, patients initiated on NIV should be reassessed for the same indications they were started on NIV (tachypnea, accessory muscle use, pH, and $PaCO_2$) and if there is no improvement after initiation of therapy, patients should have their NIV settings adjusted or be intubated.

TABLE 60.3 Indications and Contraindications for Noninvasive Positive Pressure Ventilation and Invasive Mechanical Ventilation

	RESPIRATORY SUPPORT INDICATIONS	
	Bi-Level Noninvasive Ventilation	**Invasive Mechanical Ventilation**
Indications	• Respiratory acidosis ($PaCO_2$ ≥45 mm Hg and pH ≤7.35) • Severe dyspnea with signs of respiratory muscle fatigue and accessory muscle use • Persistent hypoxemia despite supplemental oxygen therapy	• Unable to tolerate NIV • NIV failure • Persistent diminished consciousness • Respiratory or cardiac arrest • Persistent inability to remove secretions • Hemodynamic instability without response to fluids and vasoactive medications • Life-threatening hypoxemia not corrected by less invasive interventions
Contraindications	• Active vomiting/high-risk aspiration • Respiratory arrest • Facial trauma • Depressed mental status not related to high $PaCO_2$	• Appropriate for NIV • Patient wishes (e.g., advanced directive, do not resuscitate or do not intubate order)

NIV, Noninvasive ventilation.

High-Flow Nasal Cannula

While high-flow nasal cannula (HFNC) oxygen therapy is primarily used in hypoxic respiratory failure,[41] it is increasingly being used in patients with COPD. Multiple small studies show an increase in oxygenation, reduction in hypercapnia, and comfort in stable patients with COPD.[42–44] While NIV remains the first-line therapy in hypercapnic respiratory failure in COPD, HFNC is a viable support modality for patients with mild to moderate respiratory acidosis who do not tolerate or need breaks from NIV[45–47] and do not require intubation and invasive ventilation. The same monitoring parameters as NIV apply to HFNC.

Invasive Ventilation

The decision to intubate a patient during a COPD exacerbation depends on the patient's condition (not laboratory values), failure of first-line therapy, and patient's wish. Indications for intubation and mechanical ventilation are outlined in Table 60.4. The mortality rate of patients with respiratory failure secondary to COPD exacerbation is high, but it is important to note that the mortality rate in COPD exacerbation patients is lower than in all comers with respiratory failure to the intensive care unit. Treatment recommendations should be based on the patient's values and disease burden. We advise against prognostication in the very early phase of the resuscitation. An immediate response to intubation and continued treatment is often not seen in the ED. Inaccurate prognostication may have downstream repercussions in the care of the patient later in the hospital admission or subsequent admissions.

The goals of mechanical ventilation are to decrease the patient distress and work of breathing, minimize dynamic hyperinflation and intrinsic PEEP, and to lessen hypercapnia and hypoxemia without exposing the patient to iatrogenic complications. No mode of

ventilation is superior to achieve these goals. Focus during the initial ventilation phase should be directed towards maintaining normoxia and preventing dynamic hyperinflation. Severe respiratory acidosis is common, and hypercapnia should be tolerated without adjusting the minute ventilation if the pH is greater than 7.2.

After the patient is initially intubated and while still sedated and paralyzed, an assist control mode of ventilation is required. We recommend volume assist control with an initial respiratory rate of 10 to 14 breaths/min, tidal volume of ≤8 mL/kg of predicted body weight, a square flow inspiratory waveform, inspiratory time of 0.8 to 1 seconds, PEEP of 5, and titration of inspired oxygen to a saturation of 88% to 92%. These patients commonly have long time constants and EFL and require a longer exhalation time to reach FRC. Dynamic hyperinflation risk is proportionally related to a high minute ventilation. Setting a respiratory rate of 10 to 14 breaths/min is the most effective way to decrease the minute ventilation and duty cycle time to prevent dynamic hyperinflation. Respiratory rates less than 10 breaths/min are not recommended. They allow for longer emptying, but may decrease the minute ventilation to an undesirable level causing a severe hypercapnic respiratory acidosis without a significant benefit in lowering end-expiratory lung volumes and pressures (Fig. 60.6).[16] Soon after

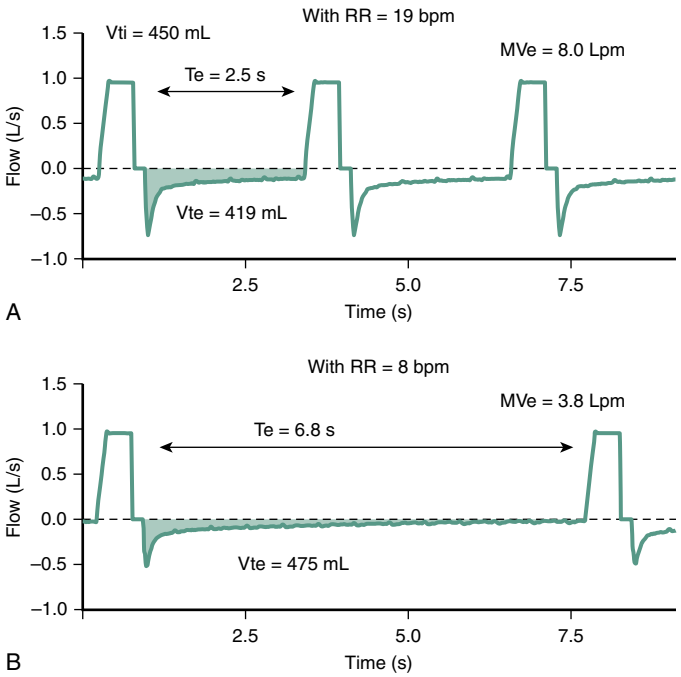

Fig. 60.6 Flow-time curves from a patient with chronic obstructive pulmonary disease with tidal expiratory flow limitation showing the result of prolonging expiration time. (A) Original ventilator settings in volume-controlled mode with a respiratory rate of 19 breaths/min, expiratory time *(Te)* of 2.5 seconds and the exhaled tidal volume *(Vte)* (area between the expiratory flow tracings and the x-axis) of 419 mL. This approach resulted in a total minute ventilation *(Mve)* of 8.0 liters per minute (Lpm) and the intrinsic positive end-expiratory pressure of 7.3 cm H_2O (not shown here). (B) The same patient with the respiratory rate reduced to 8 breaths/min while keeping the other parameters unchanged. This approach resulted in a Te of 6.8 seconds, more complete lung emptying (an end-expiratory flow virtually reached zero), and the intrinsic positive end-expiratory pressure decreased to less than 1 cm H_2O (not shown here). However, the additional Vte gained was less than 60 mL compared with the original settings, and the total MVe was decreased to 3.8 Lpm, which was clinically undesirable. (From Junhasavasdikul D, Telias I, Grieco DL, et al. Expiratory flow limitation during mechanical ventilation. *Chest*. 2018;154(4):948–962. https://doi.org/10.1016/j.chest.2018.01.046 https://doi.org/10.1016/j.chest.2018.01.046)

intubation, peak pressure, total PEEP, and plateau pressure should be measured. High peak pressures are expected because of high resistance in the airways. When there is an elevated peak pressure, greater than 40 to 45 cm H_2O, it is important to confirm that there are no quickly reversible causes of airway resistance such as a mucous plug, kinked or malpositioned endotracheal tube, or tension pneumothorax. Plateau pressures should also be measured at this time to evaluate pulmonary compliance, with a goal of less than 30 cm H_2O. High peak pressures and low plateau pressures reflect increased resistance with normal compliance of the respiratory system. In this scenario, peak pressures do not represent pressures at the alveoli. If the peak airway pressures are consistently above 40 to 45 cm H_2O without a reversible cause, and plateau pressures are low, we recommend adjusting the peak pressure alarm profile so the patient is not under-ventilated (if the peak pressure limit is reached, the flow will terminate resulting in a small tidal volume with a high dead space to alveolar ventilation ratio) and continue medical management while mechanically ventilated.

Dynamic hyperinflation occurs when the patient receives a breath before the respiratory system returns to FRC (i.e., completely exhales), which increases end-expiratory lung volumes and intrathoracic pressure. Signs of dynamic hyperinflation can be detected by evaluating the flow versus time waveform, the end-expiratory velocity, or measuring the total PEEP. The flow versus time waveform (Fig. 60.7) graphically displays inspiratory and expiratory flow throughout the respiratory cycle. If the expiratory flow limb does not reach zero prior to the next delivered breath, there will be dynamic hyperinflation because exhalation was not complete. Some ventilators display the end-expiratory velocity in liters/min, and a positive velocity at the end of the breath means they are exhaling at the time of the next breath.

Checking the total PEEP screens for dynamic hyperinflation and intrinsic or auto-PEEP (iPEEP). Total PEEP is measured after a 3 to 5-second end-expiratory hold on a passively breathing patient. The pressure reflects the externally applied (ventilator set) PEEP and the iPEEP (Fig. 60.8). For example, if the ventilator prescribed external PEEP is 5 cm H_2O and the total PEEP is 17 cm H_2O, the iPEEP or auto-PEEP is 12 cm H_2O. This increased pressure results from increased end-expiratory lung volumes and alveolar overdistension within the fixed thoracic space. Patients who are intubated during a COPD exacerbation without multiple pulmonary infiltrates should have a normal plateau pressure despite an increase in peak pressure. A high plateau pressure in the setting of an increase in iPEEP represents decreased compliance of an over distended lung. Increased expiratory lung volumes and iPEEP may cause hypotension from decreased preload. This

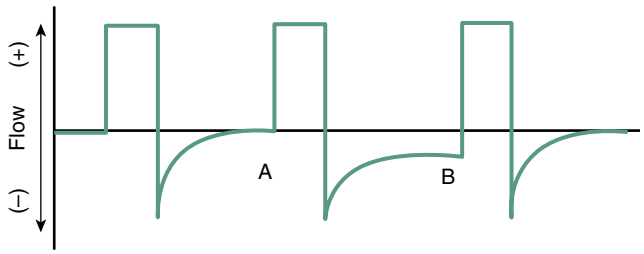

Fig. 60.7 **Flow Versus Time Ventilator Waveform.** Positive flow on the y-axis is the ventilator delivering a breath into the patient. Negative flow is the patient's passive exhalation. (A) depicts an expiratory flow limb returning to zero at the end of exhalation. The represents complete exhalation of the tidal volume and a return to the passive functional residual capacity. The curve and slope of the expiratory flow limb is determined by the passive recoil of the chest wall. (B) depicts an expiratory flow limb that does not return to zero prior to the next ventilator delivered breath. This represents the patient's continued and incomplete exhalation prior to the next delivered breath.

response is exaggerated in COPD because highly compliant lungs readily transmit the increased pulmonary pressures to the heart and great vessels. In the example above the total pressure in the chest transmitted to the great vessels is 17 cm H_2O (12.5 mm Hg).

Pressure assist control may also be used as an initial ventilator setting when a patient is sedated and paralyzed (also see Ventilatory Support, Chapter 2). We recommend starting with a pressure of 15 cm H_2O above PEEP and an inspiratory cycling time of 0.8 to 1 seconds. Inspiratory pressure and cycling time targets may be adjusted to deliver a tidal volume of approximately 8 mL/kg predicted body weight. Some patients may be more comfortable in a pressure-controlled mode because of an increased inspiratory flow, but there is no significant outcome difference among ventilation modes. When ventilating a patient in pressure assist control mode, it is essential to monitor tidal volumes to assure adequate ventilation because tidal volumes will vary depending on the resistance and compliance of the respiratory system.

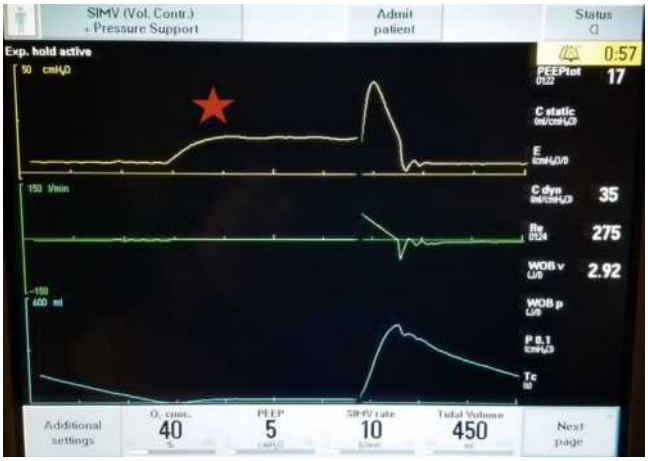

Fig. 60.8 Ventilator screen displaying an end expiratory hold with an elevated intrinsic positive end expiratory pressure (PEEP). The star marks an elevation in the pressure waveform with a corresponding total PEEP of 17 cm H_2O and set PEEP of 5 cm H_2O. The iPEEP in this case is 12 cm H_2O (total PEEP minus set PEEP). (Image courtesy of Dr. Skyler Lentz.)

Spontaneously breathing patients may be transitioned to pressure support ventilation. Many patients are comfortable in this mode of ventilation because they control inspiratory time and flow. We recommend an initial pressure support of 15 cm H_2O above PEEP titrated based on tidal volume and patient comfort. In any mode of ventilation, some patients may ineffectively trigger or cycle a mechanical breath causing ventilator dyssynchronies. If patients appear to be attempting to inhale or exhale in asynchrony with the ventilator, we recommend consulting an intensivist or pulmonologist. Ventilator troubleshooting steps are displayed in Table 60.4.

PEEP can be safely set to 5 cm H_2O for all patients with a COPD exacerbation. There is no significant benefit of decreasing the PEEP to 0 cm H_2O or increasing the PEEP in the early care of sedated and paralyzed patients. Further PEEP titration depends on individual patient's physiology. In most cases of patients with COPD who are intubated, EFL is present and PEEP may be increased to between 50% and 80% of the total PEEP. Increasing the PEEP does not decrease the expiratory flow because it is no longer determined by the absolute pressure

TABLE 60.4 Troubleshooting for Commonly Encountered Problems in Intubated Chronic Obstructive Pulmonary Disease Patients With Mechanical Ventilation

TROUBLESHOOTING VENTILATION DIFFICULTIES

Problem	Suggestion
Elevated end-tidal CO_2 or $PaCO_2$	Tolerate respiratory acidosis if the pH is >7.2 without adjusting the respiratory rate or tidal volume. Respiratory acidosis will improve with medical treatment and time while ventilated.
Elevated end-tidal CO_2 or $PaCO_2$ AND pH <7.2	1. If there is minimal iPEEP, increase the respiratory rate slowly and frequently check for iPEEP. 2. Should iPEEP develop, increase the tidal volume and keep the rate low. COPD does not require acute respiratory distress syndrome (ARDS) ventilation strategy. While the goal tidal volume is ≤8 mL/kg predicted body weight, if severe respiratory acidosis and obstructive shock from dynamic hyperinflation is a life threat start increasing the tidal volume.
High peak pressures	This is a reflection of increased airway resistance. Check a plateau pressure to evaluate compliance of the respiratory system. If the plateau pressure is low: 2. Evaluate for common causes of elevated peak pressures including kinked tubing, pneumothorax, mucous plugging, and mainstem intubation. 3. Continue bronchodilator therapy and tolerate high peak pressures. Increase peak pressure alarms to prevent hypoventilation.
High plateau pressures	If the patient does not have a reason to have a low compliance (e.g., multifocal pneumonia) this likely represents alveolar over distention from dynamic hyperinflation. Check a total PEEP and decrease the minute ventilation.
Elevated total PEEP or iPEEP	This represents dynamic hyperinflation. If hypotension is present remove the patient from the ventilator for approximately 10–15 s to allow adequate exhalation. Reduce the minute ventilation by decreasing the respiratory rate between 10 and 14 breaths/min.
Awakens from sedation or paralysis wears off	Clinical decision of transition to a pressure supported mode of breathing or increasing sedation. • If stable, patients will often tolerate pressure support ventilation with an initial setting of pressure support of 15 cm H_2O over a PEEP of 5 cm H_2O. The patient will determine their respiratory rate. Monitor for triggering or cycling dyssynchronies such as the patient trying to inhale or exhale and the ventilator not responding. • If a patient is unstable or has severe air trapping, increase sedation so the patient is synchronous with the ventilator. Reattempt sedation wean at a later time.

COPD, Chronic obstructive pulmonary disease; *iPEEP*, intrinsic positive end expiratory pressure.

gradient between the alveoli and ventilator and may improve expiratory flow by stenting open small collapsing airways. If any PEEP changes are made, it is important to follow the associated changes in peak pressure, total PEEP, and plateau pressure.

Disposition

Disposition decisions are based on a multitude of factors including severity of symptoms, presence of respiratory failure, response to treatment in the ED, presence of serious comorbidities, failure of outpatient treatment, and home resources/support. Patients who have significant symptom improvement in the ED with no signs of respiratory failure, no new oxygen needs, a normal laboratory evaluation, and no evidence of hemodynamic instability or cardiac ischemia, with adequate home support and a follow-up plan with a primary care or pulmonology provider are suitable for discharge home. We recommend education about inhaler or nebulizer use and close coordination with their primary care provider or pulmonologist. Patients with severe symptoms, including resting dyspnea, worsened hypoxia, tachypnea, drowsiness and confusion, or symptoms significantly worse than their baseline should be admitted to the hospital. If there are signs of respiratory failure and need for NIV, consultation with the intensive care unit is recommended (Box 60.3).

ED observation units (sometimes called short-stay units or clinical decision units) can provide short term care for COPD exacerbations in patients with non-severe symptoms who fail to improve significantly with initial treatment but are expected to improve within 48 hours. Observation units help decrease the number of patients requiring inpatient hospital admission.[48] Through protocolized care and the coordination of discharge services, observation unit stays can decrease the 30-day ED revisit rate without decreasing the number of patients discharged directly from the ED.[49] Patients with underlying severe disease, frequent recent hospitalizations, severe symptoms including new oxygen requirement, and abnormal chest x-ray findings suggestive of lobar pneumonia are unlikely to respond to treatment within a timeframe appropriate for an ED observation admission.[50]

BOX 60.3 General Guidelines for Admission of the Patient With Chronic Obstructive Pulmonary Disease

1. Significant worsening of symptoms from baseline
2. Inadequate response of symptoms to emergency department (ED) management
3. Significant comorbid conditions (e.g., pneumonia, heart failure)
4. Worsening hypoxia or hypercarbia (from baseline)
5. Inability to cope at home or insufficient home resources

Adapted from Vestbo J, Hurd SS, Agusti AG, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 187:351, 2013.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 60: QUESTIONS AND ANSWERS

1. A patient presents to the emergency department with 8 months of progressive dyspnea. There is no recent change in the patient's symptoms. On exam, there is a prolonged expiratory phase without wheezing, no rales, no pedal edema. The electrocardiogram is normal. The chest x-ray revealed hyperinflation with a flattened diaphragm. The diagnosis of chronic obstructive pulmonary disease (COPD):

a. Can be made clinically in this patient
b. Can be made radiographically with demonstration flattening of the diaphragms and hyperinflation on chest x-ray
c. Requires demonstration of spirometry-proven airflow limitation with the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) after bronchodilators less than or equal to 0.7
d. Requires genetic testing and historical features including increased cough, sputum production, noxious stimuli, and dyspnea

Answer: c. The diagnosis of COPD requires spirometry-proven airflow limitation defined as a ratio of FEV_1 divided by FVC after bronchodilators of less than 0.7. Patients who have normal spirometry with chronic symptoms and possible emphysema on CT scan are not considered to have COPD.

2. In a patient with a diagnosis of chronic obstructive pulmonary disease (COPD), increased dyspnea, sputum production, and sputum purulence worse than baseline day-to-day variations for the past three days requiring evaluation in the emergency department is defined as:

a. Chronic bronchitis
b. COPD exacerbation
c. Emphysema
d. Progression of underlying disease

Answer: b. COPD exacerbation can be defined as a worsening of symptoms from baseline day-to-day variations that requires treatment. The most common symptoms include increased dyspnea, cough, increased sputum production and increased sputum purulence.

3. A 64-year old male with a history of severe chronic obstructive pulmonary disease (COPD) with baseline 3 L/min oxygen requirement presents to the emergency department with complaint of dyspnea. On physical exam, he is taking rapid shallow breaths with a respiratory rate of 50, requiring 8 L/min by nasal cannula to maintain a SpO_2 of 88%, but is awake and following commands. A blood gas reveals a pH of 7.25 and a pCO_2 of 70 mm Hg. Chest x-ray reveals hyperinflated lungs without evidence of pneumothorax or infiltrate. Antibiotics, nebulized short-acting beta-agonists, and glucocorticoids are initiated. The next step in management is:

a. Continue medical management
b. Intubate the patient for anticipated clinical decline
c. Start noninvasive bi-level positive pressure ventilation
d. Trial high flow nasal cannula

Answer: c. This patient is presenting with respiratory failure without clear contraindications to noninvasive ventilation. The patient should be trialed on noninvasive ventilation and receive inhaled bronchodilators including albuterol and ipratropium, glucocorticoids, and antibiotics. Glucocorticoids have similar bioavailability and efficacy when given PO or IV, however in patients with respiratory distress we recommend avoiding oral medications.

CHAPTER 60: QUESTIONS AND ANSWERS—cont'd

4. The rapid, shallow breathing pattern that develops in a chronic obstructive pulmonary disease (COPD) exacerbation _____ exhalation time causing hyperinflation, and _____ the proportion of dead space ventilation causing hypercapnia and respiratory muscle fatigue.

a. Decreases, decreases
b. Decreases, increases
c. Increases, decreases
d. Increases, Increases

Answer: b. The rapid, shallow breathing pattern that develops in a COPD exacerbation decreases exhalation time causing hyperinflation and increases the proportion of dead space ventilation causing hypercapnia and respiratory muscle fatigue. If untreated, this will progress to respiratory failure.

5. When treating a patient with a chronic obstructive pulmonary disease (COPD) exacerbation who requires invasive mechanical ventilation, setting the initial tidal volume to 8 mL/kg predicted body weight and the respiratory rate to 10 to 14 breaths/min helps prevent the development of:

a. Acidosis
b. Dynamic hyperinflation
c. Hypercapnia
d. Expiratory flow limitation

Answer: b. Decreasing the respiratory rate in an intubated patient with COPD allows for complete emptying and return to FRC, decreasing the development of dynamic hyperinflation and auto-positive end expiratory pressure (PEEP).

61

Upper Respiratory Tract Infections

Matthew A. Roginski and Patricia Ruth Atchinson

KEY CONCEPTS

- Viral infections cause most cases of pharyngitis. Patients should not be treated with antibiotics based on symptoms and exam alone. Patients with a Centor criteria score of 0 or 1 do not require further testing or treatment. Those with a score of 2 or greater should undergo rapid antigen testing with treatment decisions based on results. Throat cultures are recommended in children but are not necessary in adults.
- Antibiotics for group A *Streptococcus* pharyngitis are aimed at symptom reduction, decreasing transmission, and decreasing suppurative complications. Rheumatic fever is very rare and likely from a shift in streptococcal M proteins rather than antibiotic use.
- Infectious pharyngitis presents with an acute onset and resolves within days. In subacute and chronic cases of pharyngitis, consider abscess formation, neoplastic causes, HIV, and autoimmune disease.
- In streptococcal pharyngitis, a single high dose of corticosteroids, such as 10 mg dexamethasone, is safe and reduces symptom severity.
- Consider deep space infection and epiglottitis in patients who present with neck pain, hoarseness, and have a benign oropharyngeal exam.
- Airway edema from palatine or lingual tonsillitis, epiglottitis, or deep space infection is rare, but life-threatening.
- Deep space infections such as retropharyngeal and parapharyngeal abscesses are difficult to diagnose clinically, and contrast-enhanced CT is recommended.
- Transcervical or intraoral ultrasound is useful in the diagnosis and treatment of peritonsillar abscess.
- Acute rhinosinusitis is likely viral and will resolve with supportive care, including nasal irrigation with hypertonic saline.
- Although rarely needed, first-line antibiotic treatment for acute rhinosinusitis is amoxicillin or amoxicillin-clavulanate for 5 days.

PHARYNGITIS

Foundations

Tonsillopharyngitis (pharyngitis) is generally a benign, self-limited inflammatory syndrome of the oropharynx. Although most cases are mild, severe cases may lead to airway swelling, dehydration from decreased oral intake, and suppurative complications, including peritonsillar abscess, deep space infection, and hematogenous spread. A majority of cases are viral and caused by common cold viruses. Bacterial infection is responsible for approximately 5% to 10% of adult and 20% to 30% of pediatric cases. Common bacterial causes of pharyngitis include group A beta-hemolytic *Streptococcus* (GAS), non–group A *Streptococcus*, *Fusobacterium*, and mixed aerobes and anaerobes (Table 61.1). Transmission occurs through direct person-to-person contact or via aerosolized respiratory secretions. Although fomite transmission is rare, crowded conditions such as in schools, daycare, and military training facilities increase transmission rates.

Tonsils are lymphoid tissue covered with respiratory epithelial tissue. Waldeyer ring refers to the lymphoid tissue in the pharynx consisting of the palatine tonsils (commonly referred to as tonsils), pharyngeal tonsils (adenoids), tubal tonsils (surrounding eustachian tubes), and lingual tonsils at the base of the tongue. Tonsillar infection, inflammation, and hypertrophy may occur in any of these locations (Fig. 61.1). Although rare, lingual tonsillitis predominantly occurs in patients who had their palatine tonsils removed.

Clinical Features

Symptom chronicity, associated complaints, patient comorbidities, and patient risk factors are important considerations. Acute presentations are more likely to be infectious, whereas more chronic presentations raise concern for noninfectious or neoplastic etiologies. Sore throat, odynophagia, fever, malaise, and tender anterior cervical adenopathy are the most common symptoms. Although presentation differs by the disease process, erythema, edema, and petechiae of the oropharynx (Fig. 61.2), as well as palatine tonsillar plaques (Fig. 61.3), are common findings.

Viruses that cause the common cold are responsible for 30% to 60% of pharyngitis cases (see Table 61.1). Symptoms may overlap with GAS but are unlikely to be as severe and are associated with rhinorrhea, cough, conjunctivitis, congestion, and headache. Viral symptoms usually precede symptoms of a sore throat. Inflammation and hypertrophy of tissue in the Waldeyer ring without exudate is common.

Infectious mononucleosis, caused by the Epstein-Barr virus (EBV), classically presents with the triad of fever, tonsillar pharyngitis, and posterior cervical lymphadenopathy. The incubation period is 3 to 7 weeks, and patients experience a prodrome of fever, chills, and malaise. Most patients have exudative pharyngitis with tonsillar hypertrophy (see Fig. 61.3). Petechiae are intermittently present at the junction of the hard and soft palate (see Fig. 61.2). In severe cases, upper airway swelling may lead to difficulty managing secretions, stridor, and dyspnea. Splenomegaly is present in approximately half the cases. A pruritic morbilliform rash may occur regardless of contact with beta-lactam antibiotics. Jaundice is rare.

Influenza may present with nonexudative pharyngitis and sore throat along with generalized fever, chills, myalgia, and headaches. Human immunodeficiency virus (HIV) and cytomegalovirus can present as a mononucleosis-like illness. Pharyngitis and hypertrophy of tissue in the Waldeyer ring may also occur. The acute retroviral syndrome of primary HIV infection includes fever, sore throat, nontender lymphadenopathy, diffuse maculopapular rash, arthralgias, mucocutaneous ulcerations, and diarrhea. Spread by sexual contact, herpes simplex pharyngitis presents with painful vesicles or ulcerations on an erythematous base on the lips, tongue, palate, or mucosa (Fig. 61.4). Patients with oropharyngeal herpes have palatal hyperemia with sore throat, odynophagia, stomatitis, and tender cervical adenopathy. Immunosuppressed patients with oropharyngeal herpes may present with large ulcerations, and bacterial superinfection is possible. Coxsackie virus may also cause herpangina

TABLE 61.1 Infectious and Noninfectious Causes of Pharyngitis

INFECTIOUS ETIOLOGIES				NONINFECTIOUS ETIOLOGIES
Bacterial	**Viral**	**Fungal**	**Adjacent Infections**	
Group A β-hemolytic strep	Rhinovirus	Candida	Retropharyngeal abscess	Tumor
Groups C and B β-hemolytic strep	Coronavirus		Parapharyngeal abscess	Autoimmune disease
Fusobacterium	Parainfluenza		Epiglottitis	Neurogenic pain
Neisseria gonorrhoeae	Adenovirus		Ludwig angina	Foreign body
Corynebacterium diphtheriae	Influenza			Trauma
Chlamydia	Human immunodeficiency virus			Medication induced
Mycoplasma pneumoniae	Epstein-Barr virus			Stevens-Johnson syndrome
Arcanobacterium haemolyticum	Herpes virus			Allergic reaction
	Cytomegalovirus			Esophageal reflux
				Environmental exposure

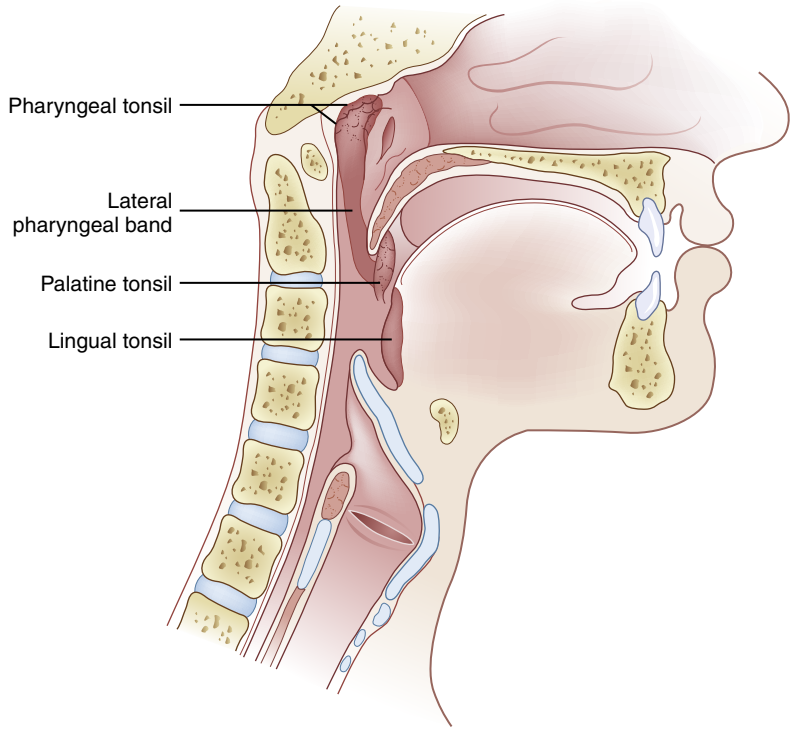

Fig. 61.1 Sagittal anatomic illustration of locations of tonsils in Waldeyer ring. Note the lingual tonsils on the posterior tongue. (From Embryology, anatomy, and histology of the pharynx. In: Wenig, BM. *Atlas of Head and Neck Pathology*. Philadelphia: Elsevier; 2016: 399-406. Fig. 8-2.)

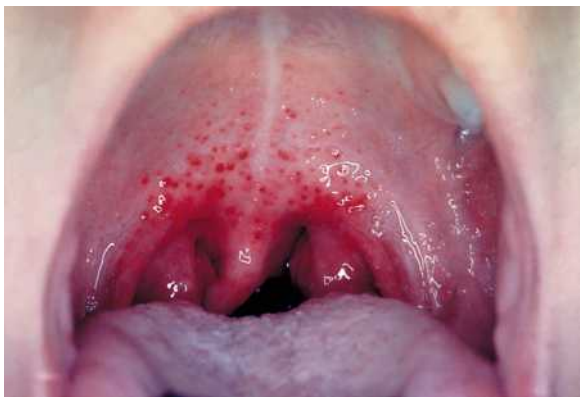

Fig. 61.2 Palatal petechiae. (Courtesy Centers for Disease Control and Prevention and Dr. Heinz F. Eichenwald.)

with oral and pharyngeal erythematous papulo-vascular ulcerations. Coxsackie virus also causes small tender, nonpruritic, cutaneous lesions on the palms, soles, and buttocks.

Group A beta-hemolytic *Streptococcus* is a gram-positive coccus that grows in chains and is the most frequent cause of bacterial pharyngitis, most commonly in children ages 5 to 15 years. Humans are the only carrier of GAS, and asymptomatic carrier status is uncommon. The incubation period is typically 2 to 5 days. Virulence factors of GAS include host inflammatory mediators, bacterial cell wall, and secreted enzymes and exotoxins. Infection is most common in the fall and winter. Untreated, symptoms last 3 to 7 days, and patients are contagious up to one week after symptom resolution. Treated, symptoms resolve approximately 16 hours sooner than in untreated patients, and the contagious period decreases to 24 hours after the start of antibiotics. Rapid onset of sore throat, odynophagia, cervical adenopathy, fevers, chills, and neck stiffness are characteristic. Headache, abdominal pain,

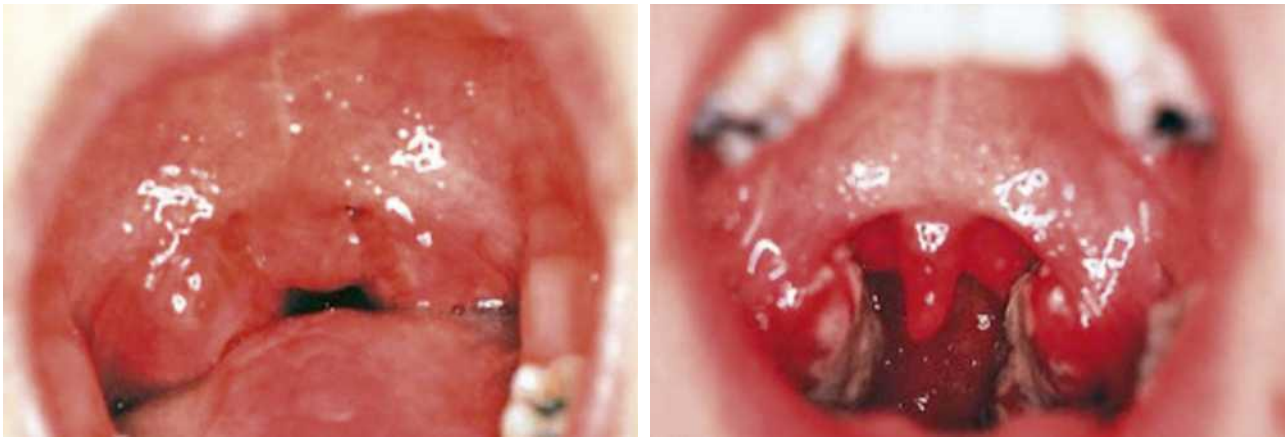

Fig. 61.3 Photograph of enlarged palatine tonsils. (A) shows nonexudative pharyngitis. The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens. (B) shows exudative pharyngitis with white plaques on the tonsils and hyperemia, most commonly seen in either group A streptococcal or Epstein-Barr virus infection. (From Wetmore RF. Tonsils and adenoids. In: *Nelson Textbook of Pediatrics*. 2019. Pages 2198-2202.e.1. 2020.)

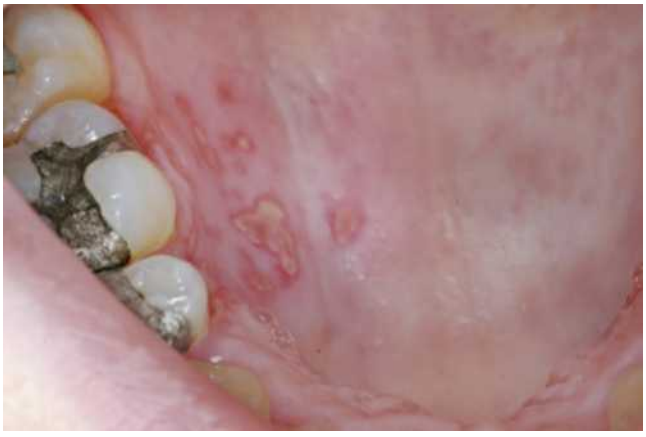

Fig. 61.4 Photograph of oral ulcerations from recurrent oropharyngeal herpes infection. (From Hellstein JW, Fielding CG, Castle JT. *Vesiculobullous Diseases. Oral and Maxillofacial Surgery*. Elsevier. Published January 1, 2018. Pages 550-574. © 2018. Figure 24-4 Recurrent herpes of palate.)

nausea, and vomiting may be present. GAS does not present with trismus, cough, conjunctivitis, diarrhea, rhinorrhea, or oral ulcerations.[1]

Exam findings include symmetric erythema and edema of the oropharynx, gray/white tonsillar exudates (see Fig. 61.3), palatal petechiae (see Fig. 61.2), and tender cervical adenopathy. GAS pharyngitis associated with a desquamating, fine, sandpaper-like rash is called *scarlet fever* and is related to an exotoxin-producing strain of GAS. Suppurative complications of GAS include acute otitis media, mastoiditis, meningitis, peritonsillar and retropharyngeal abscess, and rarely, necrotizing fasciitis or hematogenous spread to distant sites.[2] Acute rheumatic fever and post-streptococcal glomerulonephritis are rare in the general population. The decrease in the frequency of acute rheumatic fever is likely due to a shift in the streptococcal M protein types leading to decreased rheumatogenicity rather than due to the increased use of antibiotics.[2]

Non–group A *Streptococcus* also causes acute pharyngitis with a similar presentation to GAS, but acute infection is difficult to distinguish from normal upper respiratory flora on respiratory culture. *Fusobacterium necrophorum* is an anaerobic gram-negative rod that is part of the normal oral flora and causes pharyngitis in patients 15 to 45 years old with a similar presentation to GAS. *Fusobacterium* is the primary causative agent in septic jugular vein thrombophlebitis (Lemierre syndrome). The early identification and treatment (Table 61.2) of *Fusobacterium* in pharyngitis remains unclear; *Fusobacterium* should be considered in young adults with ongoing severe symptoms.[3-5]

Arcanobacterium haemolyticum is a nonmotile beta-hemolytic gram-positive bacillus that is not part of the upper respiratory flora and is associated with a minority of pharyngitis cases with peak prevalence in the late teens. It is associated with deep space infections such as retropharyngeal abscesses. Along with pharyngitis, patients may also experience an urticarial, maculopapular rash that spares the face, palms, and soles. *Francisella tularensis* is a zoonotic gram-negative bacillus that may cause a false-positive monospot test and has atypical lymphocytes on peripheral smear. It can present as pharyngitis and a flu-like illness in patients with a contaminated food or water source.[3,4] *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* pharyngitis may occur as part of an outbreak in crowded conditions. Lower respiratory tract infection and rhinosinusitis may occur.

Neisseria gonorrhoeae is an intracellular gram-negative diplococcus that is transmitted through sexual contact. Patients are usually symptomatic with tonsillitis and found to have enlarged tonsils with a white-yellow exudate in the tonsillar crypts. *Chlamydia trachomatis* pharyngitis has a similar presentation to gonococcal pharyngitis and is transmitted through sexual contact. *Treponema pallidum* is the spirochete that causes syphilis. Primary infection can present with painless oral ulceration. Secondary syphilis may have associated pharyngitis with localized adenopathy that can be mistaken for carcinoma. Patients with atypical presentations, risk factors for sexually transmitted infections, or no other apparent cause should have a focused sexual history and appropriate testing based on their response.

Diphtheria is caused by the gram-positive bacillus *Corynebacterium diphtheriae*. Although the incidence has decreased because of vaccination, diphtheria should be considered in patients who traveled to endemic areas or who are not vaccinated. The incubation period is 2 to 5 days. Early symptoms are typical of generalized pharyngitis with sore throat, cervical adenopathy, and fever. Toxin-producing strains may create a pseudomembrane that is grayish-green to black (if bleeding occurs) that tightly adheres to mucosal tissue and is friable. Severe forms may obstruct the airway and may be associated with extensive swelling of the tonsils, uvula, and anterior neck. Toxins produced can affect distant sites causing myocarditis, neuritis, and acute tubular necrosis. Non–toxin producing strains cause moderate to severe pharyngitis without pseudomembrane formation.

TABLE 61.2 Treatment Recommendations for Pharyngitis[a]

Organism	Treatment
Group A *Streptococcus*	Penicillin V, Oral • Children 250 mg two or three times daily for 10 days • Adolescents and adults 500 mg twice daily for 10 days Penicillin VK • Children <27 kg: 250 mg two or three times daily • Children ≥27 kg or adults: 500 mg two or three times daily Penicillin G, IM • <27 kg: 600,000 units; >27 kg 1.2 million U once Amoxicillin • 50 mg/kg once daily (max 1000 mg) or 25 mg/kg (max 500 mg) twice daily for 10 days Single-dose corticosteroids • Dexamethasone 0.6 mg/kg up to 10 mg PO Penicillin Allergic Cephalosporins • Cephalexin 20 mg/kg/dose (max 500 mg/dose) twice daily for 10 days Clindamycin • 7 mg/kg/dose (max 300 mg/dose) three times daily for 10 days Azithromycin • 12 mg/kg (max 500 mg/dose) for 5 days
Fusobacterium and anaerobic infections	Metronidazole • Adults 500 mg IV every 8 hours; children 10 to 15 mg/kg (max 500 mg/dose) IV every 8 hours AND Ceftriaxone • Adults 2 g IV every 24 hours; children 50 mg/kg (max 2 g/dose) IV every 24 hours OR Piperacillin-tazobactam • Adult 3.375 g IV every 6 hours, children 100 mg/kg of piperacillin (max 4.5 g/dose) IV every 6 to 8 hours
Diphtheria	Antitoxin (request from CDC) AND penicillin • Adults: Penicillin 2 to 3 million units/day IV in divided doses every 4 to 6 hours Children: Penicillin 150,000 to 250,000 units/kg/day IV in divided doses every 6 hours. The AAP recommends 14 days of treatment
Gonococcal	Ceftriaxone 500 mg IM ×1 (1g IM x1 if weight >150 kg) and doxycycline 100 mg twice daily for seven days (doxycycline is needed until chlamydia is ruled out)
Herpes	Acyclovir 200 mg 5 times/day for 7 days OR Valacyclovir 1 gm twice daily for 7 days OR Famciclovir 250 mg three times/day
Candida	Mild: Clotrimazole troches or nystatin swish/swallow Moderate to severe: adults, fluconazole 200 mg on day one and 100 to 200 mg once daily for 7 days; children, fluconazole 6 to 12 mg/kg (max 200 mg/dose) daily

[a]Renally dose antibiotics, antivirals, and antifungals.

Oral candidiasis presents with a white pseudomembrane over the tongue, buccal mucosa, palate, and oropharynx that can be scraped off with a tongue depressor. It occurs most commonly in immunocompromised patients, the elderly, patients with recent antibiotic exposure, and those on chronic steroids. Chronic hyperplastic candidiasis may present as elevated white plaques that cannot be scraped off of the buccal mucosa.

BOX 61.1 Centor Criteria for Determining Group A Beta-Hemolytic Streptococcal Pharyngitis

Swollen tonsils and exudates
Tender anterior cervical adenopathy
Absent cough
Fever

Differential Diagnosis for Emergency Presentation

A focused differential for pharyngitis is largely guided by the history and physical exam with attention to systemic signs and symptoms. Table 61.1 lists the infectious and noninfectious causes of pharyngitis.

Diagnostic Testing

Diagnostic testing is not required if features strongly suggest a viral etiology: associated with rhinorrhea, cough, conjunctivitis, congestion, and headache which usually precede symptoms of a sore throat. Testing for Epstein-Barr virus (EBV) can be considered in patients with splenomegaly, posterior cervical adenopathy, palatal petechiae, and those patients with persistent symptoms despite adequate treatment for GAS pharyngitis. The initial testing for infectious mononucleosis is a heterophile antibody test (Monospot). The Monospot has high specificity but variable sensitivity, with false-negative results in children and early in the infection. If the antibody test is negative and the patient remains symptomatic, we recommend follow-up with their primary care physician and retesting in 7 to 10 days or checking an EBV viral capsid antigen IgM. Viral load is not validated for infectious mononucleosis. Mononucleosis causes an absolute lymphocytosis with greater than 10% atypical lymphocyte count due to EBV's effect on B lymphocytes and the cytotoxic T-cell response. Influenza is tested with a PCR nasal or oral pharyngeal swab. Influenza testing should occur in patients with fevers, myalgia, headache, and sore throat occurring when influenza viruses are circulating in the community, when the patient is being admitted to the hospital, or when testing will influence management. HIV testing is performed with a fourth-generation combination assay. It should be performed in patients with risk factors and persistent pharyngitis symptoms without any other etiology. Herpes is diagnosed with PCR testing of a viral swab from an ulcer or unroofed vesicle or HSV IgG and IgM serology.

Rapid antigen testing is recommended as a first-line diagnostic test for GAS pharyngitis. These patients present with sore throat, fever, exudative pharyngitis, and cervical lymphadenopathy without associated cough or rhinorrhea. Scoring systems such as the Centor criteria (Box 61.1) should be used to identify adults who do not require further testing or treatment. The score should not be used in patients who are immunocompromised, have complicated comorbid conditions, or have symptoms for greater than 5 days. Patients with zero or one Centor criterion should not be tested or treated. Empiric treatment is not recommended for any patient.[1,5] Rapid antigen tests are highly sensitive and specific when performed correctly (swabbing the bilateral tonsils and the posterior pharynx, avoiding the buccal mucosa and tongue). A positive test indicates the presence of GAS and does not require follow-up testing. If the antigen testing is negative, a confirmatory culture on sheep blood agar is recommended in children, can be considered in adolescents, and is not necessary in adults. There is no role for antistreptolysin O titers.

Patients with persistent symptoms and unknown etiology should undergo throat culture. *Arcanobacterium haemolyticum* is performed on human blood agar. Diphtheria requires culture on Loeffler medium. The laboratory should be notified if there is concern for *Arcanobacterium* or diphtheria, which would be indicated in patients with severe pharyngitis or the appearance of gray pseudomembrane in the posterior oropharynx. Candida is diagnosed when budding yeast with or without pseudohyphae is seen on the Gram stain or potassium hydroxide stain. A throat swab with a nucleic acid amplification test is recommended for *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

Management

For a majority of cases, supportive care alone with nonsteroidal antiinflammatory medications or acetaminophen will be sufficient. There is no direct evidence of benefit from warm salt gargles, lozenges, soft or cold foods, or humidified topical analgesics. Viscous lidocaine should be avoided due to the potential for suppression of cough and gag and risk for aspiration. Treatment for infectious mononucleosis is supportive. Corticosteroids are not recommended for infectious mononucleosis,[6] except in the cases of significant oropharyngeal edema with stridor or change in phonation. Treatment of influenza should be started as soon as possible on documented or suspected influenza cases in hospitalized patients, children less than 2 years old, adults 65 years and older, pregnant women and within 2 weeks postpartum, patients with immunosuppression, and patients with chronic cardiac, pulmonary, hepatic, renal or hematologic disorders. Clinicians can consider antiviral treatment in patients not at high risk for complications and outpatients with symptom onset less than 2 days before presentation, and in those symptomatic with household contact with those at high risk for compilations of influenza, or health care workers with contact with those at high risk for complications.[7] Treatment consists of antiviral medication (oral oseltamivir, inhaled zanamivir, or intravenous peramivir.) HIV requires referral to appropriate providers for the initiation of antiretroviral medications.

The rationale for the treatment of GAS is to decrease the length of symptoms, suppurative complications, and the infectious period. Prophylactic antibiotics to close contacts of infected patients is not recommended. Retesting after treatment is not required unless there are recurrent symptoms. Treatment failures may be related to carrier status, lack of compliance, recurrent exposure, resistant bacteria, or eradication of protective flora. Treatments of pharyngitis are listed on Table 61.2. We recommend steroid administration for GAS. A single dose of corticosteroids such as dexamethasone appears to be safe and leads to a decrease in symptom duration.[8-10] Patients with recurrent episodes of GAS should be referred to an otolaryngologist for consideration of tonsillectomy.[11] Diphtheria is treated with diphtheria antitoxin (DAT) and penicillin or erythromycin. Mild candidal pharyngitis treatment is topical with clotrimazole troches or nystatin swish and swallow, whereas moderate to severe forms require systemic therapy with fluconazole.

Disposition

Patients with uncomplicated pharyngitis may be discharged and treated as outpatients. Patients with evidence of upper airway obstruction including stridor, difficulty managing secretions, and changes in phonation or severe systemic symptoms such as hypotension or altered mental status require consultation with an otolaryngologist and admission to the hospital.

LARYNGITIS

Foundations

Acute laryngitis is an inflammation of the larynx which is predominantly caused by viral infections. Chronic laryngitis is diagnosed after three weeks of continuous symptoms and may be due to gastroesophageal reflux, overuse of the voice, trauma, thermal and chemical burns, irritants, and allergic reactions.

Diffuse inflammation of the larynx caused predominantly by viral infection results in mucosal edema and laryngeal obstruction. It occurs most commonly in children ages 1 to 5 years and is more frequently seen in the winter and spring.[12] Immunocompromised patients can develop laryngitis caused by opportunistic fungal and viral infections. Patients with frequent use of inhaled corticosteroids are also at increased risk for fungal laryngitis.

Clinical Features

Laryngeal inflammation and edema cause sore throat, hoarse voice, inspiratory stridor, fever, and barking cough. Chronic laryngitis may additionally present with globus sensation and excessive throat clearing. Laryngitis may exist on its own or be part of a constellation of symptoms of upper airway infection including epiglottitis. Epiglottitis generally includes inflammation of the arytenoids and aryepiglottic folds and is sometimes referred to as supraglottitis. Inflammation of the glottis, arytenoids, and aryepiglottic folds increases the potential for acute upper airway obstruction, though the majority of cases of laryngitis are self-limited.

Differential Diagnosis for Emergency Presentation

The etiologies of laryngitis are similar to pharyngitis displayed in Table 61.1, with the majority being caused by the viruses that cause the common cold. The differential diagnosis includes infectious etiologies such as retropharyngeal abscess and noninfectious etiologies such as anaphylaxis, angioedema, tumor, thyroiditis, chemical or thermal injury, and foreign body.

Diagnostic Testing

There is no specific diagnostic testing for laryngitis, and the majority of cases will resolve within two weeks. Routine viral testing or bacterial cultures are not recommended.

Management

The majority of patients with laryngitis will improve without intervention. Systemic steroids have been shown to decrease symptom severity in pediatric patients; we recommend dexamethasone 0.6 mg/kg given via intramuscular, intravenous, or oral route depending on patient ability to tolerate oral intake and intravenous access availability with a maximum dose of 10 mg. Immunocompromised patients and patients with symptoms persisting for greater than two weeks should be referred to otolaryngology.

Disposition

Laryngitis can be treated on an outpatient basis. Exceptions occur when symptoms of laryngitis are occurring concomitantly with symptoms of supraglottitis/epiglottitis.

EPIGLOTTITIS

Foundations

Acute epiglottitis is an inflammation of the epiglottis and commonly the supraglottic region, including the arytenoids, base of the tongue, and vallecula. It is sometimes referred to as supraglottitis, but we will use the term epiglottitis. It is a rare but potentially life-threatening disease because of rapidly occurring airway obstruction and asphyxiation. Since the widespread adoption of the *Haemophilus influenzae* type B conjugate vaccine, epiglottitis is more common in adults than children.[13] Patients with diabetes, immunosuppression, and substance abuse issues, including tobacco and alcohol, are at increased risk for its

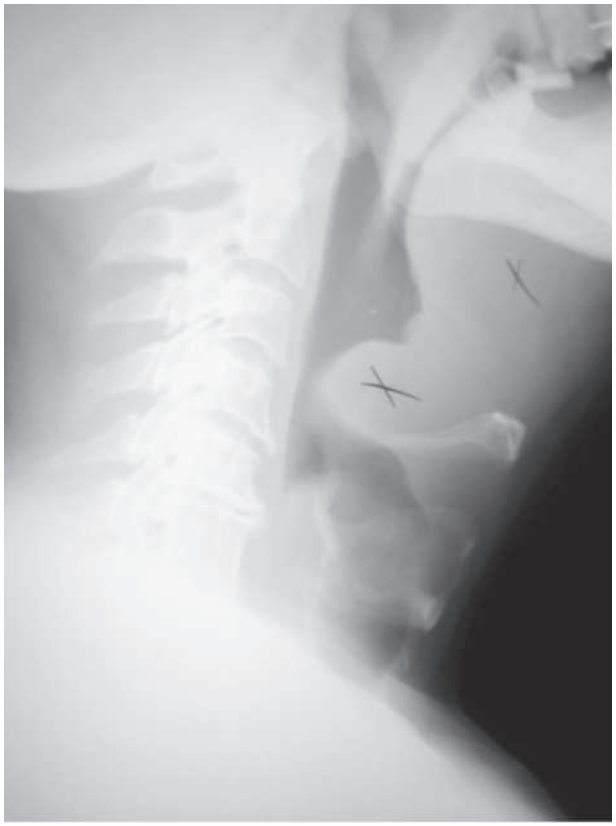

Fig. 61.5 Lateral neck x-ray with an edematous epiglottis: "thumb print sign."

development.[14,15] The majority of cases are caused by bacterial infection, including *Haemophilus influenzae* (type B and non-typeable), *Streptococcus pneumoniae,* and *Staphylococcus* subspecies. Noninfectious causes of epiglottitis include burns, trauma, and inhalational injury.[16]

Clinical Features

Symptoms are on a spectrum from sore throat, dysphagia, odynophagia, fever, hoarseness, and foreign body sensation in early stages to stridor, inability to manage secretions, and breathlessness with signs of airway compromise. Patients may sit forward in a sniffing position to maintain airway patency if there is sufficient swelling.

Differential Diagnosis

The differential diagnosis for epiglottitis includes infectious etiologies such as retropharyngeal abscess and noninfectious etiologies such as anaphylaxis, angioedema, tumor, thyroiditis, chemical or thermal injury, and foreign body.

Diagnostic Testing

Flexible laryngoscopy is the gold standard for diagnosis of epiglottitis and should be performed in patients presenting with symptoms of epiglottitis including sore throat, voice changes, and stridor. Lateral neck radiographs with an epiglottis width greater than 5.5 mm ("thumb sign" Fig. 61.5) have moderate sensitivity[17] but cannot be used to rule out epiglottitis.[18] We recommend against an initial diagnostic CT scan of the neck because of the need for supine positioning and potential for airway obstruction. Do not swab the posterior throat or use a tongue depressor because this may exacerbate the edema.

Management

All patients with epiglottitis should receive early airway evaluation assessing for voice changes, ability to manage secretions, position of comfort, and intravenous antibiotics. Antibiotic recommendations are outlined in Table 61.3. Corticosteroids can decrease supraglottic edema and may decrease the need for airway intervention we recommend dexamethasone 0.6 mg/kg with a maximum dose of 10 mg, though there is a paucity of randomized trials to guide steroid dosing.[10] Nebulized 2.25% racemic epinephrine diluted in normal saline and administered via jet nebulizer every 3 to 4 hours may decrease edema. Although oral or nasotracheal intubation is frequently unnecessary, the swelling typical of the epiglottitis (Fig. 61.6) can cause significant difficulty with intubation attempts and require an emergent surgical airway.[14] Given the high risk for failure to obtain an airway, we recommend early consultation with otolaryngology and anesthesia for intubation in the operating room. The need for emergency intubation increases in patients exhibiting dyspnea, stridor, drooling, tachypnea, and with the mouth held open or sitting forward in the sniffing position. If emergency intubation is required, we recommend awake fiberoptic intubation without the use of paralytics.

Disposition

Patients with epiglottitis require admission due to the risk for rapid airway obstruction. Patients who require emergency airway intervention or who are at high risk for deterioration should be admitted to the intensive care unit.

PERITONSILLITIS: PERITONSILLAR CELLULITIS AND ABSCESS

Foundations

Peritonsillar cellulitis is an infection of the peritonsillar tissue not associated with a collection of purulent material. Peritonsillar abscess is a collection of pus between the palatine tonsillar capsule and the superior constrictor muscle of the palatopharyngeus muscle. Fibrous septae in the peritonsillar space are responsible for directing the infection anteriorly and superiorly. Intratonsillar abscess refers to a collection of pus within the tonsillar parenchyma.

Peritonsillar abscess is most frequently seen in adults younger than 40 years old. Risk factors for developing a peritonsillar abscess include recent streptococcal tonsillitis, mononucleosis, obstruction or infection of the Weber glands, smoking, and dental or periodontal disease. There is an association with antiinflammatory medication use.[19,20] Infections are usually polymicrobial, but *Streptococcus pyogenes* is most frequently isolated. Recurrent peritonsillar abscesses have a high incidence of *Fusobacterium.*[21] Complications of peritonsillar abscess include abscess rupture into the airway and spread into the adjacent peritonsillar space.

Clinical Features

Symptoms include unilateral sore throat, odynophagia, dysphagia, fever, malaise, drooling, muffled voice, trismus, and ipsilateral otalgia. There is usually a delay between the time of symptom onset to abscess formation. Once an abscess has formed, the most common physical exam finding is a tense, erythematous, and edematous anterior tonsillar pillar with displacement of the infected tonsil and uvula towards the contralateral tonsil (Fig. 61.7). The tonsils and oral mucosa are usually erythematous with an exudate. Peritonsillar cellulitis may have a similar appearance without displacement of the tonsil and uvula. Associated findings are tonsillar edema, trismus, drooling, and tender cervical adenopathy. Peritonsillar abscess is usually unilateral, but bilateral abscesses occasionally occur.

TABLE 61.3 Microbiology[46] and Recommended Antimicrobials for Epiglottitis, Peritonsillar Abscess, Parapharyngeal Abscess, and Retropharyngeal Abscess

Condition	Organisms	Antimicrobial[a]
Epiglottitis/Supraglottitis	Normal Host: • Haemophilus influenzae • Streptococcus pneumoniae • Beta-hemolytic streptococci • Staphylococcus aureus • Neisseria meningitidis	• Ampicillin-sulbactam OR ceftriaxone AND • Vancomycin OR clindamycin (if low MRSA suspicion)
	Immunocompromised: • Above infection and • Pasteurella mul*tocida* • *Aspergillus* spp.	• Cefepime or piperacillin tazobactam AND Vancomycin
Parapharyngeal abscess Retropharyngeal abscess Peritonsillar abscess Ludwig angina	Community: • Streptococcus pyogenes • Staphylococcus aureus • Streptococcus milleri group • Arcanobacterium hemolyticum • Mixed oral flora	Ampicillin-sulbactam OR ceftriaxone and metronidazole OR Clindamycin and levofloxacin
	Immunocompromised	Cefepime and metronidazole OR Piperacillin tazobactam AND Vancomycin
	MRSA risk (eg, IVDA, diabetes)	Add vancomycin or linezolid

MRSA, methicillin-resistant *staphylococcus aureus*; *IVDA,* intravenous drug abuse.
[a]Renally dose antibiotics.

Differential Diagnosis for Emergency Presentation

The differential diagnosis for peritonsillitis is similar to retropharyngeal abscess displayed in Box 61.2. This includes infectious and noninfectious inflammation or infiltration of any of the surrounding structures including peritonsillar cellulitis, benign hypertrophy, lymphoma or tumor, pharyngitis, deep neck infection, carotid aneurysm, epiglottitis, and mononucleosis.

Diagnostic Testing

Although the diagnosis may be made clinically, ultrasound and contrast-enhanced CT aid in differentiation from cellulitis, characterization of the abscess, and identification of deep space infections. Transcervical ultrasound is useful in children.[22-24] While operator dependent,[25] a linear probe under the mandible can identify peritonsillar fluid collections. In pediatric patients, an ultrasound first approach can decrease the length of stay without increasing the frequency of return visits.[11,26-28] In older patients without trismus, intraoral ultrasound is a useful tool in the identification of an abscess (Fig. 61.8). In both transcervical and intraoral modalities the limitations of ultrasound include misinterpretation of a parapharyngeal abscess as a peritonsillar abscesses. Contrast-enhanced CT is recommended in patients in whom ultrasound is not technically possible or limited, swelling is significantly greater than anticipated in a patient with an otherwise mild presentation, or when there is a concern for a deep space infection (Fig. 61.9A and B).

Management

Peritonsillar cellulitis and intratonsillar abscess require medical therapy alone. Antibiotic options are listed in Table 61.3. Adjunctive treatment with a single dose of corticosteroids, such as dexamethasone 0.6 mg/kg with a maximum dose of 10 mg appears to be safe and effective, decreasing pain, edema, trismus, and leads to a faster recovery without deleterious effects.[11,26-28] In cases of a small peritonsillar abscess (<1 cm) antibiotics and steroids alone may be sufficient.

Larger abscesses benefit from drainage.[29] Needle aspiration or surgical incision and drainage can usually be accomplished in an awake patient with the use of topical lidocaine or benzocaine for anesthesia. Ultrasound guidance can increase diagnostic yield and identify the carotid artery during the procedure. Although needle aspiration is less painful and can be easier to perform, recurrence rates in needle aspiration may be higher compared with surgical incision and drainage.[30] Routine culture of purulent material is not indicated unless the patient is diabetic or immunocompromised, or if there are recurrent infections.

Disposition

Most patients are successfully managed as outpatients with a course of antibiotics after treatment in the emergency department. Hospital admission should be considered in patients who are toxic appearing, require intravenous hydration and analgesia, show signs of parapharyngeal extension on CT scan, or who are immunocompromised with multiple comorbidities.

LUDWIG ANGINA

Foundations

Ludwig angina is a rapidly progressive, bilateral, gangrenous cellulitis of all submandibular spaces that can rapidly lead to death within hours. Ludwig angina is a bilateral process because of the communication among the open posterior aspect of the submandibular spaces. Dental

origin from the mandibular molars is the most common cause of Ludwig angina. Mandibular molar roots insert below the mylohyoid muscle on the mandible, and the lingual aspect of the mandible is a thin osseous structure. Additional causes of Ludwig angina are mandibular fracture, oral trauma (tongue piercing, lingual laceration, iatrogenic lacerations from intubation), secondary infection of oral malignancy, suppurative parotitis, and adjacent head and neck infections. Infection may spread posteriorly between the submandibular and parapharyngeal spaces via the styloglossus muscle leading to deep neck infections. Ludwig angina occurs more frequently in immunocompromised and diabetic patients.

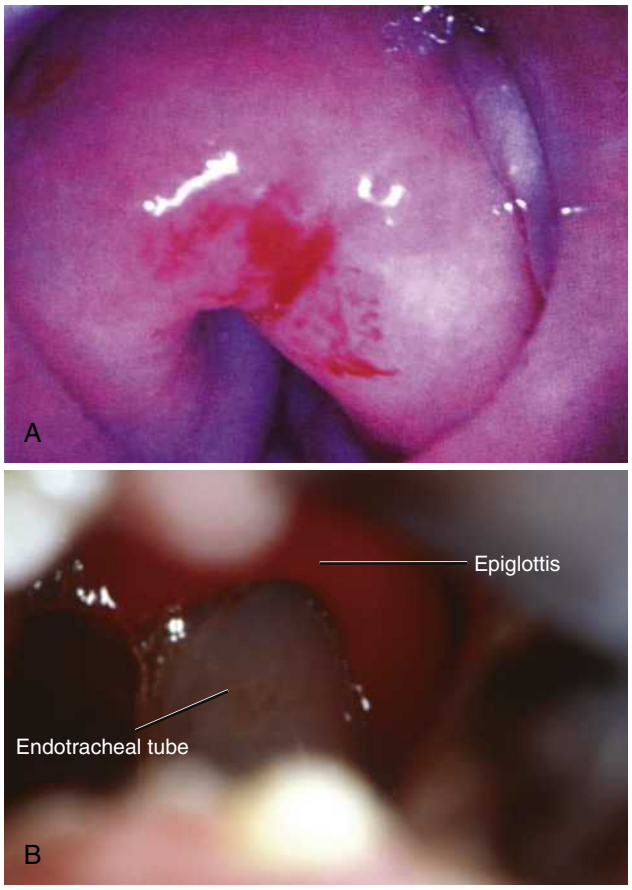

Fig. 61.6 Epiglottitis. Image A shows an enlarged and swollen epiglottis without visible vocal chords. Image B shows an enlarged epiglottis over an endotracheal tube. (From Hannallah RS, Brown KA, Verghese ST. Otorhinolaryngologic procedures. In: Coté CJ, Lerman J, Anderson BJ, eds. *A Practice of Anesthesia for Infants and Children*, 6th edition. Philadelphia: Elsevier; 2019: Figure 33.23)

Clinical Features

Patients may report recent dental infection, dental procedure, or dental caries with progressive pain and swelling. Patients present with dysphagia, odynophagia, drooling, swelling of the floor of the mouth, tongue displacement, muffled voice, fever, and neck stiffness. The most common physical exam findings are submental and submandibular swelling with protrusion of the tongue. There may be elevation of the floor of the mouth with a woody consistency on palpation. The patient's neck may have tense brawny edema from the submandibular region to the hyoid, commonly described as a bull neck. As the cellulitis progresses, the patient may have trismus, inability to manage secretions, dyspnea, a hoarse voice, and progressive anxiety secondary to airway impingement. Cervical adenopathy and palpable fluctuance are usually absent.

Differential Diagnosis for Emergency Presentation

The differential diagnosis includes viral and bacterial infections of the oropharyngeal region including deep space infections such as pharyngeal or retropharyngeal abscess, parotid or submandibular gland abscess, oropharyngeal tumors, sublingual hematomas, glossal and posterior oropharyngeal angioedema, and laryngeal diphtheria.

Diagnostic Testing

The diagnosis of Ludwig angina is made clinically. Contrast-enhanced CT scan may aid in the identification of deep neck structures involved and the extent of infection.

Management

Asphyxia from progressive edema is the leading cause of death in Ludwig's angina. Airway management is essential when there are any signs of airway compromise, including dyspnea, tachypnea, inability to manage secretions, agitation, stridor, and progressive edema. An awake fiberoptic nasal or oral intubation with a flexible bronchoscope after adequate topicalization is recommended. Oral laryngoscopy may be difficult because of edema and tongue displacement. Paralysis prior to securing the airway is not advised.

A surgical airway may be required if endotracheal intubation cannot be accomplished. Surgical airways can be more challenging

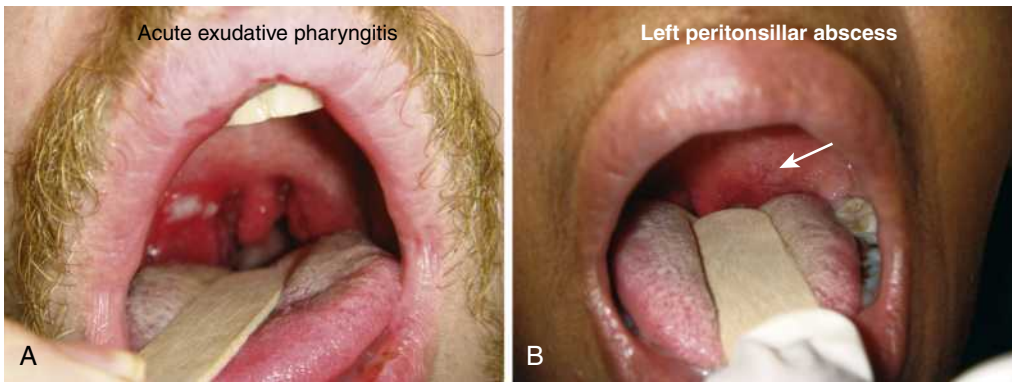

Fig. 61.7 Exudative pharyngitis versus peritonsillar abscess. Photograph A depicts acute exudative pharyngitis with tonsillar enlargement, erythema, and exudate. Photograph B shows left tonsillar bulging displacing the uvula to the right. (From Riviello RJ. Otolaryngologic procedures. In: Roberts JR, Custalow CB, Thomsen TW, eds. *Roberts and Hedges' Clinical Procedures in Emergency Medicine and Acute Care*, 7th edition. Philadelphia: Elsevier; 2019: Figure 63.7)

BOX 61.2 Differential Diagnosis of Suppurative Pharyngeal Infections

Retropharyngeal cellulitis and retropharyngeal abscess
Parapharyngeal abscess
Peritonsillar abscess
Retropharyngeal tumors
Tendinitis of the longus colli muscle
Meningitis
Hematoma secondary to trauma
Carotid artery aneurysm

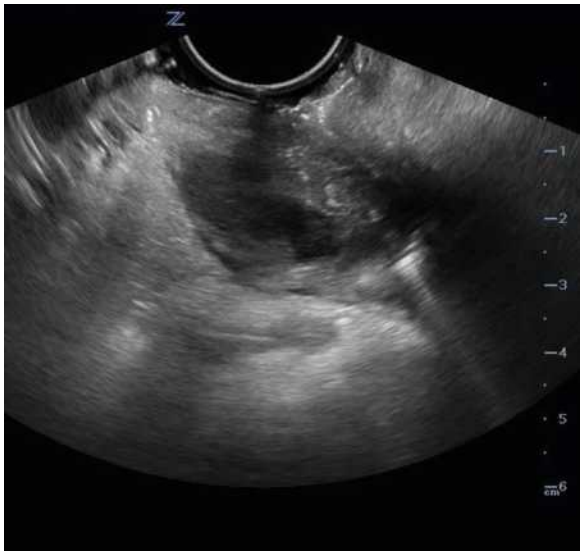

Fig. 61.8 Intraoral ultrasound with an endocavitary probe demonstrating a hypoechoic collection consistent with a peritonsillar abscess. (Image courtesy of Dr. Lindsay Reardon.)

in Ludwig angina due to anterior neck distortion from edema and the risk of spreading infection from dissecting tissue planes (Fig. 61.10). Intravenous antibiotics are of paramount importance once the patency of the airway is ensured (see Table 61.3.) There usually is not a role for surgical intervention with the exception of an infected tooth extraction, débridement of necrotizing infection, or drainage of purulent collections.

Disposition

Patients with Ludwig angina should be admitted to the intensive care unit.

RETROPHARYNGEAL ABSCESS

Foundations

Retropharyngeal abscess is an infection of the deep neck spaces that can lead to life-threatening complications, including airway compromise and mediastinal spread of infection. The retropharyngeal space is posterior to the hypopharynx and esophagus in the midline neck, immediately anterior to the danger and prevertebral spaces that extend to the diaphragm and coccyx, respectively (Fig. 61.11). It is bordered laterally by the carotid sheath/parapharyngeal space. Infections may spread from one deep space to another and involve the carotid sheath, mediastinum, and chest.

Retropharyngeal abscesses most commonly occur in children younger than 5 years old with a male predominance.[31] Children have lymph nodes present in the retropharyngeal space that are the lymphatic drainage of the nasal cavity, paranasal sinuses, oropharynx, hypopharyngeal space, middle ear, and eustachian tubes but atrophy prior to puberty. Upper respiratory tract infections, otitis media, and sinusitis can lead to suppurative lymphadenitis and abscess formation.[31] A minority of children with Kawasaki disease also have a deep neck infection.[32,33] In adults, retropharyngeal abscess formation can be caused by penetrating trauma, foreign body (fish or chicken bones) or iatrogenic instrumentation (feeding tube, laryngoscope, suctioning),

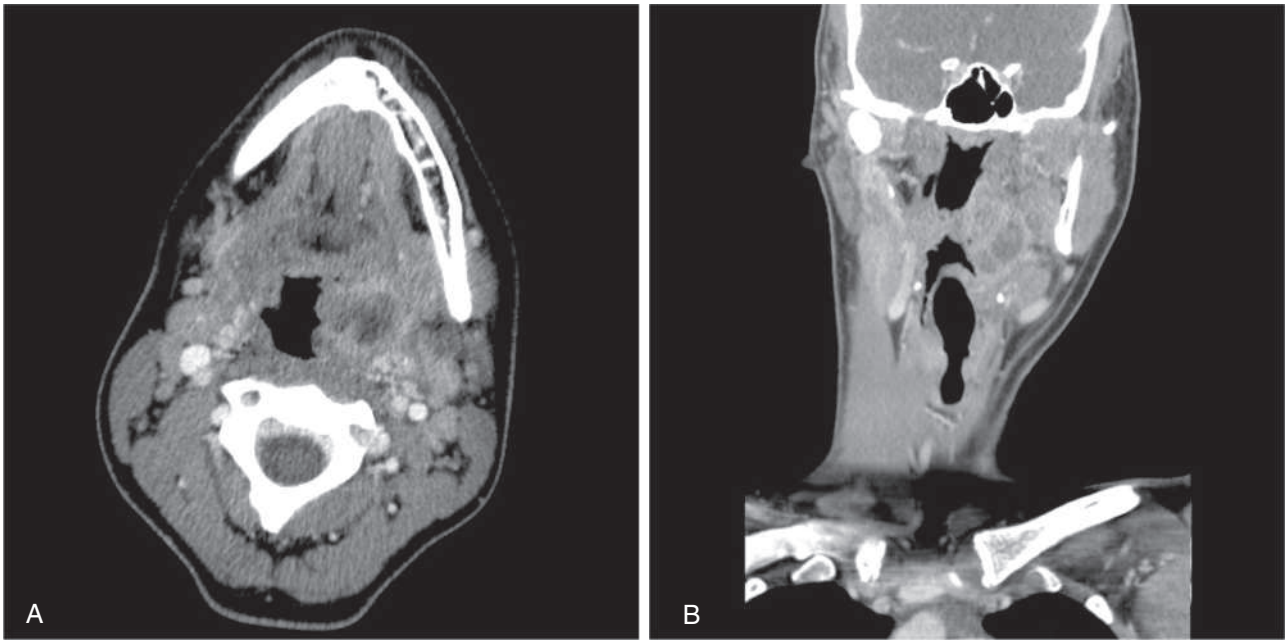

Fig. 61.9 Contrast-enhanced axial (A) and coronal (B) CT image of a left-sided peripherally enhancing and centrally hypoattenuating peritonsillar abscess. There is mild mass effect on the oropharyngeal airway and mild inflammation of the fat in the left parapharyngeal space.

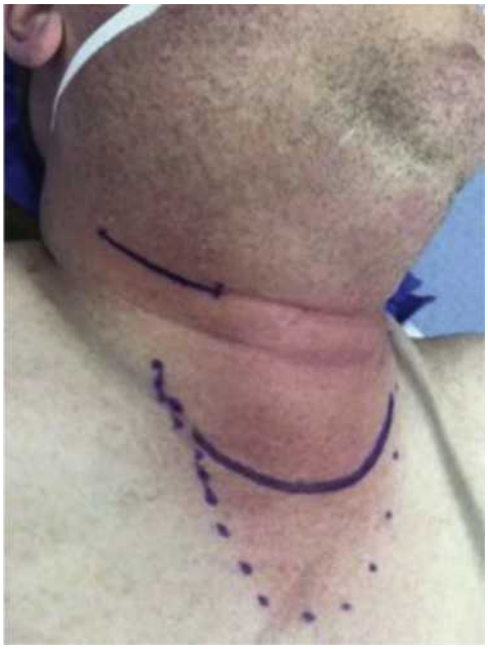

Fig. 61.10 Anterior neck swelling and erythema in Ludwig angina. (From Bernardoni B, Grosso R, Powell E, et al. Case study in critical care transport: a 51-year-old male with Ludwig angina. *Air Med J* 2017;36(2):45-48.)

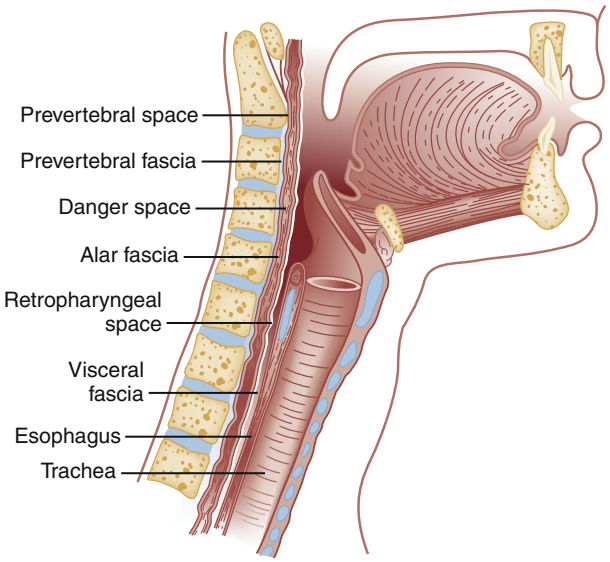

Fig. 61.11 Anatomic illustration of the lateral view of the neck showing of the prevertebral space, danger space, and retropharyngeal space.

spread from adjacent infections (dental or peritonsillar), hematologic spread of infections, and infections of the spine communicating with the prevertebral space. Risk factors include immunosuppression, chronic steroid use, diabetes, and human immunodeficiency virus. Diabetic patients have a higher prevalence of multispace spread of infection.[34] Adolescents and adults with a prior tonsillectomy also have an increased risk of deep neck infections.[35]

Microbiology of retropharyngeal abscesses is polymicrobial with a mixture of aerobes and anaerobes as described in Table 61.3. Intravenous drug abuse increases the frequency of methicillin-resistant *Staphylococcus aureus* infections.[36] A history of immunocompromise or prior nosocomial infection increases the risk of drug-resistant organisms as well as the risk for tuberculous or fungal infection. Complications from

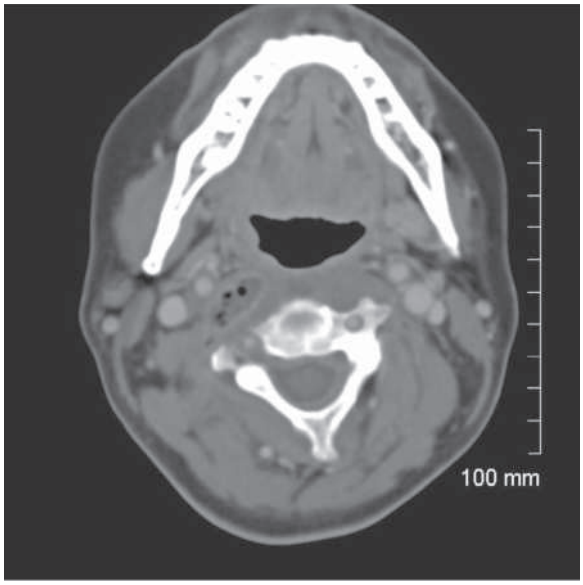

Fig. 61.12 Axial CT scan image demonstrating right sided retropharyngeal abscess.

retropharyngeal abscess include airway compromise, abscess rupture leading to aspiration of pus, and involvement of the carotid sheath. The carotid sheath is surrounded by deep fascia and includes the carotid artery, internal jugular vein, and vagus nerve, and thus infection can result in compromise of any of these structures including arterial erosion, aneurysm, Lemierre syndrome, palsy of cranial nerves IX–XII, and mediastinitis.

Clinical Features

Patients with a retropharyngeal abscess may present with fever, sore throat, dysphagia, odynophagia, drooling, pain, hoarseness, trismus, and neck stiffness. As the abscess and inflammation become more severe, patients may appear toxic and hold their heads in a sniffing position while sitting upright. Advanced cases can cause ligamentous and osseous destruction, resulting in torticollis and severe pain. The patient may experience referred pain to the posterior neck and shoulder when swallowing.

Physical examination findings of tender cervical lymphadenopathy, neck swelling, torticollis, and fever are common. Retropharyngeal cellulitis or early abscess present with diffuse edema and erythema of the posterior pharynx. Depending on the structures involved, patients may present with trismus, making intraoral physical examination difficult and not advised. Tenderness with external laryngeal and tracheal manipulation is commonly present.

Differential Diagnosis for Emergency Presentation

The differential diagnosis for retropharyngeal abscess is similar to peritonsillar abscess and parapharyngeal abscess displayed in Box 61.2.

Diagnostic Testing

Contrast-enhanced CT scan is the preferred diagnostic test for the identification of retropharyngeal abscess. CT findings are characterized by a fluid collection with central hypodensity and complete ring enhancement with scalloping (Figs. 61.12 and 61.13). Fat stranding and edema characterized by low-density thickening without peripheral enhancement may represent an early phase of infection before an abscess develops. If contrast-enhanced CT imaging is not possible, additional studies may include non-contrast-enhanced CT scan and ultrasound imaging. Lateral neck radiographs taken during inspiration

while the neck is extended will suggest a pathologic process if there is swelling but are unlikely to differentiate abscess from edema and the structures involved. On lateral neck radiographs, a retropharyngeal space measured from the anteroinferior aspect of the second vertebral body to the posterior pharyngeal wall that is wider than 7 mm (children and adults) or a retrotracheal space measured at the sixth vertebral body more than 14 mm in children and 22 mm in adults is abnormal and suggests an inflammatory process.

Management

Initial management should focus on airway stabilization and broad-spectrum intravenous antibiotics. Intravenous antibiotic selection is displayed in Table 61.3. Short-term, high-dose, adjunctive corticosteroids such as dexamethasone 0.6 mg/kg with maximum dose of 10 mg are often used with antibiotics and may be associated with a decreased need for surgical drainage.[11,34,37] In cases of a retropharyngeal abscess less than 2 cm, medical management alone may be sufficient. In immunosuppressed patients and those living in areas with high rates of tuberculosis with insidious onset of symptoms and a high suspicion for tuberculous or fungal infection, consultation with an infectious disease specialist along with an otolaryngologist is recommended. In cases with evidence of ligamentous and osseous destruction, neck immobilization and further dedicated cervical spine imaging may be required.

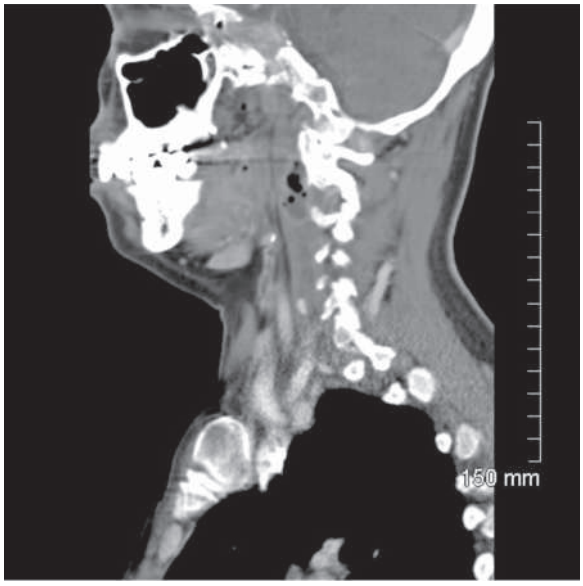

Fig. 61.13 Sagittal CT scan demonstrating right sided retropharyngeal abscess.

Disposition

Patients with a retropharyngeal abscess should be admitted to the hospital after otolaryngology consultation in the emergency department. In general, these patients are at high risk for airway compromise and should be admitted to an intensive care unit. If the patient has early, mild disease with a stable airway exam they may be suitable for admission to a floor bed.

PARAPHARYNGEAL ABSCESS

Foundations

Parapharyngeal abscess is a serious infection with close proximity to the airway, carotid sheath, and mediastinum. Seen in Figure 61.14, the parapharyngeal space is found on either side of the neck and extends from the skull base to the styloglossus muscle at the angle of the mandible. The posterior aspect of the parapharyngeal space is separated from the midline retropharyngeal space and danger space by a fascial plane. The carotid sheath is found in the retrostyloid compartment of the parapharyngeal space and contains the common carotid artery, internal jugular vein, the sympathetic plexus, cranial nerves IX through XII, and lymph nodes. Parapharyngeal space abscesses usually emanate from dental or peritonsillar infections with similar organisms. Spread from adjacent infections, suppurative lymphadenitis, iatrogenic via

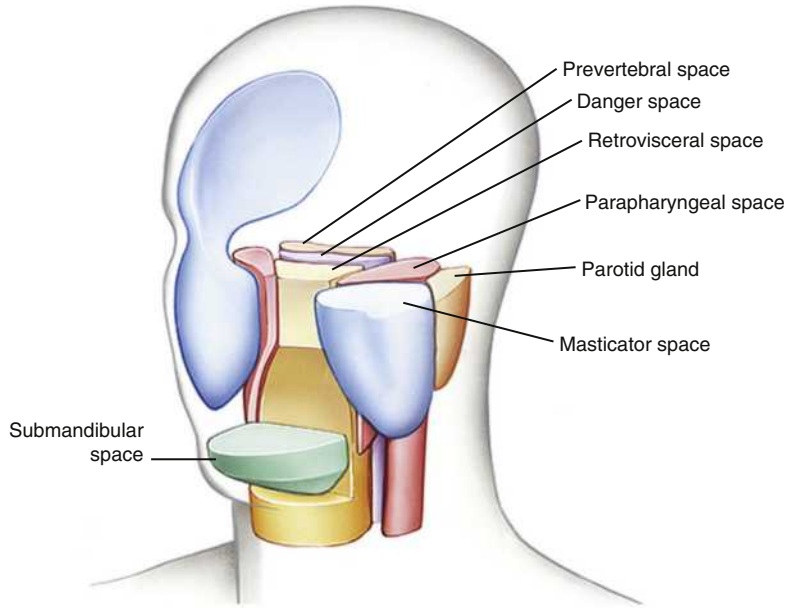

Fig. 61.14 Block diagram of the deep spaces in the neck showing the relationship of the parapharyngeal space, danger space, and prevertebral space. (From Som PM, Curtin HD. Parapharyngeal and masticator space lesions. In: Som PM, Curtin HD, eds. *Head and Neck Imaging*, 5th edition. St. Louis: Mosby, Inc.; 2011.)

local infiltration for surgical procedures or nerve blocks, infected neck tumors or cysts, parotitis, and sinusitis are rare causes.

Complications of a parapharyngeal abscess range from airway obstruction secondary to edema, neck or mediastinal spread, vascular involvement, and nerve compromise. Abscess rupture with pus into the airway can result in pneumonia, lung abscess or empyema. Mediastinal spread is possible through connection with the retropharyngeal space and danger space. Involvement of the carotid sheath has the potential to affect the sympathetic chain ganglia causing an ipsilateral Horner syndrome and neuropathies of cranial nerves IX–XII. Communication with the carotid artery may cause erosion, aneurysm, and rupture. Any signs of bleeding should be investigated with CT or MR angiography. Lemierre syndrome should be considered when sore throat or tonsillitis is followed by sepsis and multisystem involvement. Proptosis, impaired extraocular movement, or pupillary changes should prompt consideration of cavernous sinus thrombosis, a life-threatening complication with spread of infection through the ophthalmic venous system. Parapharyngeal abscess may have local spread causing mandibular osteonecrosis and parotid abscess.

Clinical Features

Symptoms include pain and swelling of the neck, odynophagia, pain with mastication, and torticollis if the sternocleidomastoid muscle is involved. Physical exam findings vary depending on the extent of the infection. The sternocleidomastoid muscle may obscure exam findings of an abscess. Fever, trismus, edema, and pain with movement of the sternocleidomastoid muscle may be observed. Patients with infection involving the anterior aspect of the parapharyngeal space may have medial tonsillar displacement and pharyngeal edema.

Differential Diagnosis for Emergency Presentation

The differential diagnosis for parapharyngeal abscess is similar to peritonsillar abscess and retropharyngeal abscess displayed in Box 61.2.

Diagnostic Testing

Contrast-enhanced CT is the preferred diagnostic study (Fig. 61.15). External ultrasound can provide useful information but may be limited in parapharyngeal abscess. Dedicated CT angiography or Doppler assessment are recommended if vascular complications are suspected.

Management

Initial management is focused on airway management, early treatment with broad-spectrum antibiotics listed in Table 61.3, dexamethasone 0.6 mg/kg intravenous or intramuscular with maximum dose 10 mg, and consultation with an otolaryngologist. Airway management is essential when there are any signs of airway compromise, including dyspnea, tachypnea, and inability to manage secretions, agitation, or stridor. An awake fiberoptic nasal or oral intubation with a flexible bronchoscope after adequate topicalization is recommended. Paralysis prior to securing the airway is not advised.

Disposition

Consultation with an otolaryngologist and admission to the hospital are recommended. Admission to the ICU is recommended should there be signs of airway or vascular compromise.

RHINOSINUSITIS

Foundations

Rhinosinusitis is inflammation of the upper airways and paranasal sinuses associated with nasal discharge, facial pain or pressure, nasal blockade, and a sense of fullness mostly associated with an infectious source (viral, bacterial, fungal.) Acute rhinosinusitis is classified as having symptoms for fewer than 4 weeks. Viral etiologies tend to have symptoms that peak and resolve in a few days, whereas bacterial etiologies tend to last longer than 10 days with persistent symptoms or will worsen after a period of improving symptoms. Rhinovirus, adenovirus, influenza or parainfluenza virus are the most common precipitants.[38] *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common bacterial causes of maxillary sinusitis.[32,39] *Staphylococcus aureus*, gram-negative bacilli, and *Streptococcus* spp. are associated with subacute, chronic, and health care–associated sinusitis.

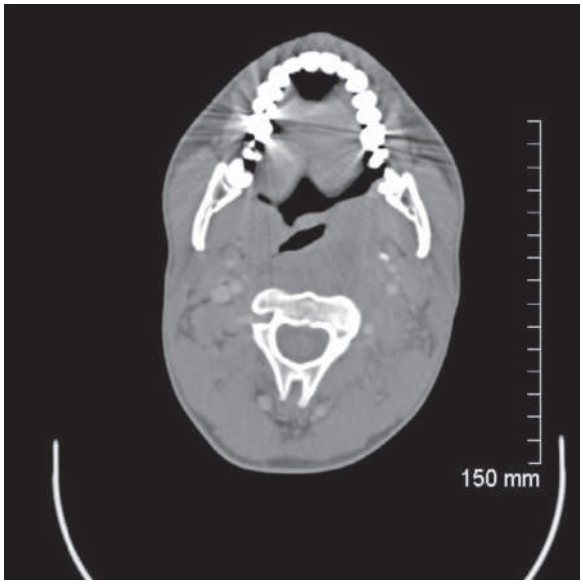

Fig. 61.15 CT scan showing a left-sided parapharyngeal abscess.

Structural abnormalities that predispose patients to acute rhinosinusitis include nasal septal deviation, infraorbital ethmoid air cells larger than 3 mm, accessory ostia in the common drainage pathway, conchae bullosa, oroantral fistula, and maxillary dental disease. Viral infection may be antecedent to bacterial infection because mucosal swelling and inflammation impair drainage and promote ciliary dyskinesia providing an environment for bacterial growth.[32] This may be the etiology of the double sickening phenomenon when patients report improvement of symptoms followed by worsening. It is impossible to differentiate between the viral and bacterial etiologies based on symptoms alone, and thus it is difficult to characterize the preponderance of antecedent infection. Rarely, acute rhinosinusitis may be attributed to periapical infection of the maxillary molars with direct extension into the sinus space.[38] Chronic rhinosinusitis causes symptoms for greater than twelve weeks. Chronic rhinosinusitis is not associated with structural abnormalities and is more commonly related to inflammatory disorders. Noninfectious etiologies of rhinosinusitis include allergic etiologies and vascular engorgement associated with pregnancy mimicking rhinosinusitis.

Complications from rhinosinusitis are extremely rare, but include cellulitis, meningitis, and orbital or intracranial abscess. Patients with poorly controlled diabetes and immunosuppression are at increased risk of invasive fungal species including *Aspergillus* spp., mucormycosis, and *Fusarium* spp.

Clinical Features

Symptoms of rhinosinusitis include purulent nasal discharge, facial pain or pressure, posterior nasal drip, and decreased sense of smell. These symptoms may be associated with sore throat, hoarseness,

cough, headache, fatigue, malaise, and fever. Differentiation between viral and bacterial rhinosinusitis is not possible based on any one symptom and relies mostly upon the time course of symptoms. Bacterial causes are more likely to be associated with prolonged symptoms lasting longer than 10 days, frequently with a worsening of symptoms after initial improvement, severe symptoms for greater than 3 to 4 days, and unilateral maxillary tooth or cheek pain. Allergic rhinosinusitis is more likely to be associated with watery rhinorrhea, ocular itching with watery discharge, and sneezing.[38,40] On exam, patients have purulent nasal discharge and may have pain with percussion of sinuses or maxillary teeth. High fever, nasal crusting or severe facial pain in immunocompromised patients is concerning for invasive infection.

Differential Diagnosis for Emergency Presentation

Differential diagnosis includes allergic rhinitis, dental infection, headache syndromes (including cluster headache, tension headache, and vascular headache), tumor, and intracranial abscess.

Diagnostic Testing

The diagnosis of acute rhinosinusitis is clinical. The diagnosis of bacterial rhinosinusitis requires one of the three criteria[5,41]: at least 10 days of persistent symptoms without improvement, three to four days of severe symptoms including a fever greater than 39 degrees Celsius with nasal discharge or facial pain without improvement, or onset of progressive symptoms with worsening symptoms after initial improvement. Visual examination of the nares directly or via nasal endoscopy may reveal swelling of the turbinates and purulent appearing discharge. Routine CT imaging is not indicated. However, if performed for other reasons, CT may reveal thickening of the walls of both nasal passages, engorgement of inferior turbinates, obstruction of the ethmoid infundibulum, and abnormalities of maxillary, sphenoid, and frontal sinuses.

The gold standard for diagnosis of bacterial rhinosinusitis is culture of secretions obtained via sinus puncture. This is not recommended in the emergency department. Culture taken via sinus puncture in patients with radiographic features of rhinosinusitis or with purulence of discharge has been found to correlate with positive cultures 50% of the time and the sinus puncture is painful and carries potential risks to the patient.[32]

Management

The vast majority of acute rhinosinusitis is self-resolving and management should focus on symptom management and patient education. We recommend symptom management with acetaminophen 650 mg (15 mg/kg for children) every 6 to 8 hours and ibuprofen 800 mg (10 mg/kg for children) every 8 hours, nasal irrigation with saline 1 to 2 sprays each nostril every 4 hours, and intranasal corticosteroids such as fluticasone propionate or mometasone furoate 2 sprays in each nostril once daily.[38,42,43] Data on the efficacy of decongestants and mucolytics are lacking and they are not recommended. Systemic corticosteroids for acute rhinosinusitis are not recommended. Routine use of antihistamines is not recommended unless there are additional allergic symptoms.

Given the risks and lack of benefit of routine antibiotic use in rhinosinusitis, antibiotics should only be used for patients who meet the definition of bacterial rhinosinusitis.[44] Overall, the use of antibiotics is contested, and the benefits are small, with cure rates at 7 to 15 days slightly higher in patients treated with antibiotics than in those treated with placebo.[38] In bacterial rhinosinusitis there is controversy as to when antibiotics should be initiated. Some guidelines propose initiation at the time of diagnosis[41] while others advocate for a watchful waiting approach for well appearing patients and initiation of antibiotics if symptoms do not improve within 7 days of diagnosis.[45] For ED patients we recommend starting the antibiotics at the time of ED presentation. Antibiotics should be given to patients with multiple comorbidities, immunosuppression, prior sinus surgery, or symptoms not isolated to the maxillary sinus. Amoxicillin 500 mg three times daily or amoxicillin-clavulanate 875 mg/125 mg twice daily for 5 days are first-line antibiotics. Amoxicillin-clavulanate should be used if the patient smokes, has diabetes, has had recent antibiotics, is older than 65 years, or is a health care worker. Doxycycline 100 mg twice daily may be given for penicillin allergic patients. Levofloxacin and moxifloxacin are also second-line agents but should be reserved for patients without other options because of the side effect profile. Avoid macrolides (azithromycin), trimethoprim-sulfamethoxazole, and second- and third-generation cephalosporins because of increasing *S. pneumoniae* resistance.

The length of antibiotic treatment is also controversial with ranges of 5 to 14 days. We recommend the initial treatment course of 5 days because there are similar treatment effects with reduced exposure to antibiotics. Children should be treated for 10 days. For adults with recurrent episodes of rhinosinusitis or prior antibiotic exposure the treatment course should be 10 days. Chronic sinusitis is not likely to be from an infectious etiology and should be managed with saline rinses and intranasal corticosteroids. If there is concern for an invasive fungal infection typified by severe rapidly progressive symptoms in patients with immunosuppression, patients should have emergent consultation with an otolaryngologist and begin empiric therapy with intravenous antifungal.

Disposition

Uncomplicated rhinosinusitis can be discharged home. Admission should be considered in patients presenting with systemic evidence of illness, immunosuppression, or complications. Referral to an otolaryngologist is indicated in patients presenting with recurrent acute rhinosinusitis (greater than 4 distinct episodes of rhinosinusitis within a calendar year).[46]

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CHAPTER 61: QUESTIONS AND ANSWERS

1. A previously well 18-year-old male presents with throat pain and fever to 39 °C for the past 2 days. He denies vomiting, diarrhea, cough, or rhinorrhea. He is not sexually active. Physical exam is notable for tender anterior cervical lymphadenopathy and symmetrically swollen and erythematous palatine tonsils with a gray-white tonsillar exudate. The remainder of his neck and physical exam is benign. What is the most appropriate next step?

a. Empirically prescribe amoxicillin for 10 days
b. Obtain a complete blood count with differential
c. Obtain an intraoral tonsillar ultrasound
d. Perform a rapid strep antigen test and prescribe antibiotics only if there is a positive result

Answer: D. This patient is presenting with pharyngitis, with sore throat, fever, exudative pharyngitis, and cervical lymphadenopathy without associated cough or rhinorrhea. A majority of cases are viral and caused by common cold viruses. Bacterial infection is only responsible for approximately 5% to 10% of adult and 20% to 30% of pediatric cases. Rapid antigen testing is recommended as a first-line diagnostic test for GAS pharyngitis, because it is highly sensitive and specific when performed correctly. A positive test indicates the presence of GAS and does not require follow up testing.

2. A 19-year-old female patient presents to the emergency department with vision changes and headaches. She reports a sore throat 10 days ago started to improve, but never completely resolved. For the past 3 days she noted increasing left-sided neck pain and fevers. On exam she appears uncomfortable with a fever and mild tachycardia. She is warm and diaphoretic with a dry forehead on the left. Her left eyelid is slightly lower than the right and her left pupil is 3 mm smaller than the right. Her extraocular movements are intact, and her intraoral exam shows symmetric tonsils with mild erythema and a midline uvula. She has mild trismus. What is most likely causing her symptoms?

a. Parapharyngeal abscess with invasion of the carotid sheath
b. Peritonsillar abscess with compression of the carotid sheath
c. Spread of infection into the cavernous sinus causing thrombosis and intracranial abscess
d. Submandibular space infection and spread into retropharynx

Answer: A. Complications from retropharyngeal or parapharyngeal abscess include airway compromise, abscess rupture leading to aspiration of pus, and involvement of the carotid sheath. The carotid sheath is surrounded by deep fascia and includes the carotid artery, internal jugular vein, and vagus nerve, and thus infection can result in compromise of any of these structures including arterial erosion, aneurysm, Lemierre syndrome, palsy of cranial nerves IX–XII, and mediastinitis.

3. A 34-year-old male presents with complaints of high fever, left-sided face pain, and purulent nasal discharge for 10 days. He has been attempting symptom management with nasal saline irrigation and intranasal corticosteroids, but after initial improvement reports worsening symptoms. What is the next step in treatment?

a. CT scan of his face to evaluate for complications of rhinosinusitis
b. Obtain bacterial culture via sinus puncture
c. Prescribe a 5-day course of amoxicillin
d. Supportive care with antiinflammatory medications, rest, and continued nasal saline irrigation

Answer: C. The diagnosis of acute rhinosinusitis is clinical. The diagnosis of bacterial rhinosinusitis requires one of the three criteria: at least 10 days of persistent symptoms without improvement, three to four days of severe symptoms including a fever greater than 39 degrees Celsius with nasal discharge or facial pain without improvement, or onset of progressive symptoms with worsening symptoms after initial improvement. Given the risks and lack of benefit of routine antibiotic use in rhinosinusitis, antibiotics should only be used for patients who meet the definition of bacterial rhinosinusitis with these criteria.

4. Patients presenting with symptoms concerning for a retropharyngeal abscess are best evaluated using what modality?

a. Contrast-enhanced CT
b. Intraoral ultrasound
c. Lateral neck x-ray
d. Visualization with a fiberoptic scope

Answer: A. Contrast-enhanced CT scan is the preferred diagnostic test for the identification of retropharyngeal abscess. CT findings are characterized by a fluid collection with central hypodensity and complete ring enhancement with scalloping. Fat stranding and edema characterized by low-density thickening without peripheral enhancement may represent an early phase of infection before an abscess develops.

CHAPTER 61: QUESTIONS AND ANSWERS—cont'd

5. This bacterium is frequently implicated in non-GAS pharyngitis and is also most commonly implicated in suppurative jugular thrombophlebitis:

a. *Arcanobacterium haemolyticum*
b. *Fusobacterium necrophorum*
c. *Haemophilus influenzae* type B
d. Methicillin-resistant *Staphylococcus aureus*

Answer: B. *Fusobacterium necrophorum* is an anaerobic gram-negative rod that is part of the normal oral flora and causes pharyngitis in patients 15 to 45 years old with a similar presentation to GAS. *Fusobacterium* is the primary causative agent in septic jugular vein thrombophlebitis (Lemierre syndrome). *Fusobacterium* should be considered in young adults with ongoing severe symptoms.

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Pneumonia

Matthew A. Waxman and Gregory J. Moran

KEY CONCEPTS

- Empirical antimicrobial therapy should be started in the emergency department (ED) for patients admitted with pneumonia.
- *Streptococcus pneumoniae* is the most commonly encountered pathogen in hospitalized patients, especially those requiring the intensive care unit.
- No characteristic radiographic pattern is pathognomonic for a specific pneumonia pathogen.
- *Legionella* should be suspected in patients with gastrointestinal or neurologic symptoms presenting with pneumonia.
- As part of the evaluation of patients with pneumonia, the patient's immune status should be considered. Patients with HIV and other immunosuppressive conditions are at risk for opportunistic infections, such as *Pneumocystis jiroveci.*
- Empirical therapy should treat the most likely pathogens for the clinical situation, such as *S. pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae,* and should be consistent with current national treatment guidelines, such as those from the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA).
- Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is an uncommon cause of community-acquired pneumonia (CAP), but empirical coverage of MRSA should be strongly considered for patients with severe pneumonia and sepsis, with concomitant influenza, contact with someone infected with MRSA, or radiographic evidence of necrotizing pneumonia.
- Patients with prior use of intravenous antibiotics, neutropenia, or underlying bronchiectasis are at increased risk of infection with *Pseudomonas aeruginosa.* Empirical therapy for high-risk or critically ill patients should cover for *P. aeruginosa.*
- Disposition is dictated by the patient's underlying medical conditions, severity of illness, likelihood of clinical deterioration, and feasibility of home care and outpatient follow-up.

PRINCIPLES

Background and Importance

Pneumonia is the leading infectious cause of death worldwide, with over 3.1 million deaths annually. In the United States, there are over 4 million adult cases of community-acquired pneumonia (CAP) annually. The economic burden associated with CAP annually in the United States is over 17 billion dollars. Most cases of CAP are managed in the outpatient setting, and the mortality is low. Pneumonia necessitating hospitalization is associated with a mortality rate as high as 20%. Pneumonia remains challenging because of an expanding spectrum of pathogens including SARS-CoV-2, changing antibiotic resistance patterns, continued introduction of newer antimicrobial agents, and increasing emphasis on cost-effectiveness and outpatient management.

As the percentage of the population older than 65 years continues to increase, the incidence of pneumonia is expected to increase. An increasing number of patients are taking immunosuppressive drugs related to the treatment of malignancy, transplantation, or autoimmune disease, resulting in more cases of pneumonia from opportunistic pathogens. *Streptococcus pneumoniae* is the most frequently identified pathogen and is also associated with increasing antimicrobial resistance. In addition, the threat exists of respiratory infections caused by biologic terrorism or newly recognized pathogens such as COVID-19 that have the potential to spread globally through international travel.

Anatomy and Physiology

Despite the constant presence of potential pathogens in the respiratory tract, the lungs are remarkably resistant to infection. The alveolar surface of the lungs covers an area of approximately 140 m^2, about 10,000 L of air passes through the respiratory tract each day, and typical ambient air can contain hundreds to thousands of microorganisms per cubic meter. Although the cough and laryngeal reflexes prevent most large particulate matter from entering the lower respiratory tract, aspiration of oropharyngeal contents may be a common occurrence during normal sleep. Despite these hazards, the lower airway tract is a virtually sterile environment.

Pathophysiology

The development of clinical pneumonia requires a defect in host defenses, presence of a particularly virulent organism, or introduction of a large inoculum of organisms. Pneumonia commonly results from microaspiration of upper respiratory pathogens into the sterile lower respiratory tract. If the challenge of invading organisms overwhelms host defenses, microbial proliferation leads to inflammation, an immune response, and clinical pneumonia. If host defenses are weak, a minimal challenge may lead to the development of pneumonia. The challenge with pneumonia is identifying the causative agent rather than making the diagnosis. A careful history, including foreign travel, recent antibiotic use, and exposure to the health care system, such as dialysis or living in a nursing home, can help inform empiric therapy. Empiric therapy should be chosen with activity against the spectrum of likely pathogens based on the patient's overall clinical presentation.

In the emergency department (ED), it is often difficult to determine the specific cause of pneumonia because routine microbiologic and serologic testing is not available in the time frame of ED evaluation, although rapid polymerase chain reaction (PCR) testing to determine the pathogen is increasingly available. Even in hospitalized patients, the specific microbiologic cause of pneumonia is usually not identified. When identified, *S. pneumoniae* is the most commonly encountered pathogen in hospitalized patients, with *Haemophilus influenzae* a distant second.[1,2] *Legionella, Mycoplasma,* and *Chlamydophila* spp., referred to as atypical pathogens, are also prevalent in hospitalized

patients. Improved molecular testing has shown that viral pathogens such as rhinoviruses, influenza, parainfluenza, and adenoviruses account for up to one-quarter of etiologies in hospitalized patients.[3,4]

Among adults requiring intensive care unit (ICU) admission, *S. pneumoniae* is the most common pathogen, with even higher prevalence among fatal cases. *Legionella* spp., *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), and aerobic gram-negative bacilli also appear to be relatively more common among adults with severe CAP.[4] Atypical organisms, such as *Mycoplasma* species or viruses, account for a higher proportion of pneumonia in patients with milder illness amenable to outpatient therapy. Atypical organisms can also occur with significant frequency in patients with severe illness requiring hospitalization, particularly because of *Legionella* infection. Coinfection, such as with *Chlamydophila pneumoniae* and *S. pneumoniae,* is also well recognized.

S. pneumoniae is a gram-positive coccus that colonizes the nasopharynx in 40% of healthy adults. Although this organism can cause pneumonia in healthy people, patients with a history of diabetes, cardiovascular disease, alcoholism, sickle cell disease, splenectomy, and malignancy or other immunosuppressive illness are at increased risk. A vaccine containing the capsular polysaccharides of 23 pneumococcal types most commonly associated with pneumonia reduces the likelihood of serious pneumococcal infection. It is recommended for adults at increased risk because of underlying illness or age older than 65 years and others who smoke or have comorbidities such as chronic lung disease.[5] Despite this recommendation, many ED patients have not received the pneumococcal vaccine, and vaccinating eligible patients in this setting seems to be feasible and effective. A 13-valent protein-conjugate pneumococcal vaccine effectively reduces invasive pneumococcal disease and pneumonia in infants and young children. Although underutilized in the adult population, the vaccine has resulted in a marked decrease in the incidence of pneumococcal pneumonia.[6]

H. influenzae, the second most frequently isolated organism in CAP among adults, is a pleomorphic gram-negative rod. It is a common pathogen in adults with chronic obstructive pulmonary disease (COPD), alcoholism, malnutrition, malignancy, or diabetes.

S. aureus may be emerging as a more common cause of CAP and has been found more frequently than *H. influenzae* in some series. Community-associated strains of methicillin-resistant *S. aureus* (CA-MRSA) are uncommon in CAP but are more likely to cause severe disease. Often associated with influenza, staphylococcal pneumonias are often necrotizing, with cavitation and pneumatocele formation. Intravenous (IV) drug users may develop hematogenous spread of *S. aureus* that involves both lungs, with multiple small infiltrates or abscesses (e.g., tricuspid endocarditis resulting in septic pulmonary emboli).

Klebsiella pneumoniae is a gram-negative rod that rarely causes disease in a normal host and accounts for a small percentage of cases of CAP. It may cause severe pneumonia in debilitated patients with alcoholism, diabetes, or other chronic illness. There is a high incidence of antibiotic resistance because the organism is often hospital-acquired.

Mycoplasma pneumoniae is one of the most common causes of CAP in previously healthy patients younger than 40 years. Another important organism in CAP is *C. pneumoniae,* an intracellular parasite transmitted between humans by respiratory secretions or aerosols. Seroprevalence studies have indicated that virtually everyone is infected with *C. pneumoniae* at some time and that reinfection is common, particularly in older adults. It accounts for at least 10% of outpatient CAP cases, although this is underestimated due to difficulty in diagnosing infection with this organism.

At least 30 species of *Legionella* have been isolated since the 1976 convention-related outbreak in Philadelphia, from which the organism derives its name. *Legionella* is an intracellular organism that lives in aquatic or soil environments. There is no person-to-person transmission. Although it is implicated in point outbreaks related to cooling towers and similar aquatic sources, the organism also lives in ordinary tap water and is underdiagnosed as a cause of CAP. *Legionella* prevalence seems to vary greatly by geographic region with a high prevalence in Australia.

Lower respiratory infections caused by anaerobic organisms generally result from the aspiration of oropharyngeal contents with large amounts of bacteria. These infections are typically polymicrobial with oral flora such as *Peptostreptococcus, Bacteroides, Fusobacterium,* and *Prevotella* spp. Presentation is often subacute or chronic and may be difficult to distinguish clinically from other causes of pneumonia. Clinical factors that suggest an anaerobic infection include risk factors for aspiration, such as central nervous system depression or swallowing dysfunction, severe periodontal disease, fetid sputum, and presence of a pulmonary abscess or empyema.

Viral pneumonias are common in infants and young children and are recognized as an important cause of pneumonia in adults. Respiratory syncytial virus and parainfluenza viruses are the most common causes of pneumonia in infants and small children, occurring mostly during autumn and winter. Influenza viruses are historically the most common cause of viral pneumonia in adults. Winter influenza outbreaks, usually of influenza type A, may cause up to 40,000 deaths annually in the United States. More than 90% occur in people aged 65 years or older. Updated influenza epidemiology is available from the United States Centers for Disease Control (CDC).[7] Metapneumovirus is a paramyxovirus that is an important cause of viral pneumonia in children and adults. SARS-CoV2 is now the most common viral pneumonia requiring hospitalization. During epidemics, clinicians should suspect a viral agent in patients with hypoxia, fever, and cough.

Fungal infections caused by organisms such as *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis* commonly manifest as pulmonary disease. These organisms are present in the soil in various US geographic areas—*H. capsulatum* in the Mississippi and Ohio River valleys, *C. immitis* in desert areas of the Southwest, and *B. dermatitidis* in a poorly defined area extending beyond that of *H. capsulatum*. These infections should be considered in people in appropriate geographic areas, especially in those who are near activities that disturb the soil, such as construction or dirt bike riding, and in patients who do not respond to antibacterial antibiotics. The clinical presentation varies from an acute or chronic pneumonia to asymptomatic granulomas and hilar adenopathy.

Pneumocystis pneumonia (PCP) occurs in immunocompromised hosts, principally those with acquired immunodeficiency syndrome (AIDS) or malignancy. *Pneumocystis jiroveci* is one of the most common opportunistic infections leading to a diagnosis of HIV infection (see Chapter 121). Patients with pulmonary complaints should be questioned about HIV risk factors, and emergency clinicians should search for signs of HIV-related immunosuppression, such as weight loss, lymphadenopathy, and oral thrush. PCP typically manifests subacutely with fatigue, exertional dyspnea, nonproductive cough, pleuritic chest pain, and fever.

Mycobacterium tuberculosis is a slow-growing bacterium transmitted between people by droplet nuclei produced from coughing and sneezing. *M. tuberculosis* survives within macrophages as a facultative intracellular parasite and may remain dormant in the body for many years. Active tuberculosis (TB) develops within 2 years of infection in approximately 5% of patients, and another 5% develop reactivation disease at some later time. Reactivation is more likely to occur in people with impaired cell-mediated immunity, such as patients with diabetes, renal failure, immunosuppressive therapy, malnutrition, or HIV. Approximately one-third of the world's population is infected with

M. tuberculosis. About 9 million new cases of active disease develop annually, resulting in 1.5 million deaths worldwide. Approximately 2.7 per 100,000 individuals in the United States develop TB each year.[8] Multidrug-resistant strains of *M. tuberculosis* have been found in increasing numbers, especially among patients with HIV and in immigrants from Southeast Asia.

Clinical Features

The ED evaluation should focus on establishing the diagnosis of pneumonia and determining the presence of epidemiologic and clinical features that would influence decisions regarding hospitalization and antibiotics. Fundamental components of the history include character of symptoms, setting in which the pneumonia is acquired, geographic or animal exposures, and host factors that predispose to certain types of infections.

Pneumonia generally manifests as a cough productive of purulent sputum, shortness of breath, and fever. In most healthy older children and adults, the diagnosis can be reasonably excluded on the basis of history and physical examination, with suspected cases confirmed by chest radiography. The absence of any abnormalities in vital signs or chest auscultation substantially reduces the likelihood of pneumonia as demonstrated by radiography. No single isolated clinical finding, however, is highly reliable in establishing or excluding a diagnosis of pneumonia.[6]

Older or debilitated patients with pneumonia often have nonspecific complaints, such as acute confusion or a deterioration of baseline function, without classic symptoms. Similarly, older patients may not present with a well-defined infiltrate on radiography. Older patients are more likely to have advanced illness at the time of presentation and may have sepsis in the absence of a previous syndrome suggestive of pneumonia. Occasionally, patients with lower lobe pneumonia have abdominal or back pain as a presenting symptom.

Classic teaching divides pneumonia based on clinical patterns into typical pneumonia caused by pyogenic bacteria, such as *S. pneumoniae* or *H. influenzae,* and atypical pneumonia caused by organisms such as *Mycoplasma* and *Chlamydophila* spp. This classic teaching is artificial, and a clear differentiation between these two types of pneumonia on clinical grounds alone is impossible. Clinical factors, including timing of onset, viral prodrome, absence of rigors, nonproductive cough, lower degree of fever, absence of pleurisy or consolidation, normal leukocyte count, and an ill-defined infiltrate on a chest radiograph, cannot reliably differentiate atypical pneumonias from those with pyogenic bacterial causes. Although it is impossible to determine the specific cause of pneumonia with certainty without microbiologic or serologic tests, certain clinical factors can suggest that a specific pathogen should be considered.

Clinical factors suggesting pneumococcal pneumonia include the abrupt onset of a single shaking chill, followed by fever, cough productive of rust-colored sputum, and pleuritic chest pain. Patients with a history of asplenia, sickle cell disease, HIV, multiple myeloma, or agammaglobulinemia are at increased risk of pneumococcal bacteremia and sepsis, with high mortality rates. Adults with chronic lung disease who develop pneumonia caused by *H. influenzae* typically demonstrate an insidious worsening of baseline cough and sputum production, and bacteremia is rare. *K. pneumoniae* may cause severe pneumonia in older or debilitated patients with so-called currant jelly sputum from the necrotizing nature of the infection. Abscess formation, empyema, and bacteremia are common with this organism, and mortality is high.

Mycoplasmal infection usually begins as a flulike illness with headache, malaise, fever, and nonproductive cough. Skin lesions, including maculopapular, vesicular, urticarial, or erythema multiforme–type rashes, are common, especially in younger patients. Although bullous myringitis is described as a classic finding, it is not specific for mycoplasmal infection and is seldom encountered. Patients generally do not have a toxic appearance, and most can be treated on an outpatient basis. Although mucopurulent sputum generally indicates the presence of pyogenic bacterial pneumonia or bronchitis, it may also be present with mycoplasmal or viral pneumonia. Viral pneumonia in adults is often preceded by symptoms of upper respiratory infection, such as rhinitis or sore throat. Most *C. pneumoniae* infections in young adults cause a minor, self-limited, upper respiratory illness that is subacute in onset. This organism is also associated with bronchitis, wheezing, sinusitis, and pharyngitis. Development of radiographically evident pneumonia is more common in older adults with C. *pneumoniae*. Some patients with *Legionella* infection have a mild, self-limited atypical pneumonia presentation. Older patients, smokers, and those with chronic disease or immunosuppression are more prone to develop the more acute and severe systemic illness of Legionnaires disease. Gastrointestinal symptoms, such as diarrhea and abdominal cramping, confusion, and muscle aches are sometimes prominent.

In addition to age, the presence of underlying illness, and presenting symptoms, the setting of acquisition of pneumonia may provide clues to likely causes. CAP that occurs in otherwise healthy individuals is likely to be caused by viruses, *Mycoplasma* spp., or *S. pneumoniae. S. aureus,* including MRSA, can cause severe pneumonia associated with influenza. Recently hospitalized and long-term care patients may develop pneumonia from agents that are uncommon in CAP, such as Enterobacteriaceae, *Pseudomonas aeruginosa,* and *S. aureus.* Healthy patients in an institutional setting, such as a dormitory or military barracks, are more likely to have pneumonia caused by *Mycoplasma* spp. or viruses.

Patients with underlying lung disease, especially COPD, constitute an important group likely to develop pneumonia. The lower respiratory tract of these patients is commonly colonized with organisms such as *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.* Cystic fibrosis patients are prone to pneumonia caused by *P. aeruginosa* or *S. aureus*. Defective mucociliary clearance in both these groups makes them highly susceptible to repeated episodes of pneumonia.

Patients with immunosuppression as a result of hematologic malignancy, patients receiving chemotherapy for malignancy, and transplant recipients are prone to pulmonary infections with a wide variety of organisms. In addition to the usual pathogens, these patients may develop pneumonia secondary to viruses such as cytomegalovirus (CMV), varicella, or herpes simplex virus. They are also more likely to develop pneumonia caused by aerobic gram-negative bacilli, *Aspergillus* and geographic fungi, and *P. jiroveci.*

Although the use of highly active antiretroviral therapy has decreased the incidence of opportunistic infections among HIV-infected patients, emergency physicians are likely to encounter patients presenting with opportunistic infections who are undiagnosed or not under regular HIV care. In addition to *P. jiroveci*, there is also an increased incidence of *M. tuberculosis* and common bacterial pathogens such as *S. pneumoniae. S. pneumoniae* and *S. aureus* pneumonia remain the most common pathogens in HIV-infected patients. Other less common causes of pneumonia in HIV-infected patients include *Mycobacterium avium* complex, CMV, aerobic gram-negative bacilli, and *Cryptococcus neoformans.* PCP usually has a gradual presentation characterized by malaise, nonproductive cough, exertional dyspnea, and weight loss. Hypoxemia, hypocapnia, and absence of pulmonary effusions are common with PCP pneumonia. PCP pneumonia often presents in the ED with a decreased oxygen saturation with ambulation in the setting of HIV disease or risk factors.

The potential for opportunistic pulmonary infection can be predicted by a recent absolute CD4 lymphocyte count less than 200/mm^3.

Patients with recognized HIV infection often know their CD4 count. A total lymphocyte count less than 1000/mm^3 on a complete blood count is also suggestive and can be used as a guide for patients in which a CD4 count is not known. In patients who do not know their HIV status, the presence of findings such as weight loss, oral hairy leukoplakia, oral candidiasis, and diffuse tinea infections strongly suggests immunosuppression.

SARS-CoV-2 is a novel beta-coronavirus that emerged in 2019 causing a pandemic (see Chapter 120). Patients with COVID-19, which refers to the disease, have a variable presentation with pulmonary symptoms predominating. COVID-19 causes a range of severity from asymptomatic or minimally symptomatic respiratory infection to severe pneumonia with hypoxemia in up to 20% of patients. The route of transmission is primarily respiratory droplets and is easily spread between close contacts. Risk factors for severe disease include obesity, advanced age, hypertension, and other comorbid conditions.[9]

Patients in nursing homes and extended-care facilities are at increased risk for infection with resistant organisms such as *P. aeruginosa, K. pneumoniae* (including strains producing extended-spectrum β-lactamases), *Acinetobacter* spp., and hospital-associated strains of MRSA. In 2019, the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) issued revised guidelines for the management of patients who may be at risk for multidrug resistance based on recent exposure to the health care system.[10] These guidelines for the treatment of CAP abandoned the use of a prior categorization of health care–associated pneumonia (HCAP) which indicated risk of drug resistant pathogens and suggested broad spectrum antibiotics. The guidelines now recommend using local data on resistance patterns and individual patient risk factors to decide when to cover for pathogens such as MRSA or *Pseudomonas*. Critical illness at time of presentation to the ED, living in a nursing home, and immunosuppression are risk factors for drug-resistant pathogens.

Differential Diagnoses

Differentiation between upper and lower respiratory tract infections may be difficult. A chest radiograph helps differentiate between upper respiratory tract infection or bronchitis and pneumonia. Many noninfectious conditions may result in inflammatory lung processes, including exposure to mineral dusts (e.g., silicosis), chemical fumes (e.g., chlorine and ammonia), toxic drugs (e.g., bleomycin), radiation, thermal injury, or oxygen toxicity. Immunologic disease (e.g., sarcoidosis, anti-glomerular basement membrane disease, and collagen vascular disease) or hypersensitivity to environmental agents (e.g., farmer's lung disease) may also result in pneumonia. Tumors may be confused radiographically with pneumonia or may appear initially as a postobstructive infection or adenopathy with peripheral infiltrates. The lymphangitic spread of lung malignancy may resemble that of interstitial pneumonia.

It is important to distinguish between the acute aspiration of gastric contents or other liquids and bacterial pneumonia that may develop later as a complication of aspiration. Aspiration of liquids into the lung disrupts surfactant and causes an inflammatory response that may lead to hypoxia and respiratory failure. The aspiration of acidic gastric contents is particularly damaging to the lungs and is common in patients who are unconscious from intoxication or anesthesia or who have neurologic deficits. Patients may initially have coughing or shortness of breath or may appear well initially and then develop respiratory dysfunction during the next several hours.

Acute aspiration of acidic fluid into the lungs causes a chemical pneumonitis. This may produce fever, leukocytosis, purulent sputum, and radiographic infiltrates that mimic those of bacterial pneumonia. Although some patients go on to develop bacterial pneumonia, prophylactic administration of antibiotics is not recommended, and anaerobic coverage should be avoided. Antibiotics should be initiated if the patient develops signs of bacterial pneumonia, including new fever, expanding infiltrate appearing more than 36 hours after aspiration, or unexplained deterioration.[11]

Diagnostic Testing

Although many chest radiographs are obtained unnecessarily for patients with upper respiratory tract infections or bronchitis, it is difficult to identify a set of specific criteria to direct test ordering that is better than the clinical judgment of an experienced physician. A routine chest radiograph for all patients with cough is not necessary. Computed tomography (CT) of the chest is more sensitive than plain radiography for detecting the presence of pulmonary consolidation, although the natural history of CT-positive, plain radiograph–negative pneumonia is not clear. CT of the chest should be considered in patients such as older adults or those with significant comorbidities, for whom identification of a subtle infiltrate would change management. Young healthy adults with a presumptive diagnosis of pneumonia who will be treated as outpatients may have a chest radiograph deferred unless there is a suspicion of immunocompromise or other unusual features of disease. A chest radiograph should be obtained subsequently if there is a poor initial response to treatment. Routine performance of chest radiography for patients with exacerbation of chronic bronchitis, asthma, or COPD is of low yield and may be limited to patients with other signs of infection or congestive heart failure.

Although the causative agent cannot be determined solely by the results of chest radiography, certain radiographic patterns may suggest the possibility of specific pathogens. In pyogenic bacterial pneumonias, radiographs usually show an area of segmental or subsegmental infiltration and air bronchograms (Fig. 62.1). Lobar consolidation is present in a few cases of bacterial pneumonia, often caused by pneumococci or *Klebsiella.* A dense lobar infiltrate with a bulging fissure appearance on a chest radiograph is often described with pneumonia caused by *Klebsiella,* but this finding is nonspecific, and most cases manifest as a more subtle bronchopneumonia. Pneumonia resulting from the spread of infection along the intralobular airway results in fluffy or patchy infiltrates in the involved areas of the lung. A wide variety of bacteria and agents such as *Chlamydophila*, *Mycoplasma*, and *Legionella* spp., viruses, and fungi may cause this pattern.

An interstitial pattern on a chest radiograph (Fig. 62.2) typically is caused by *Mycoplasma* spp., viruses, or *P. jiroveci*. The classic radiographic findings in PCP are bilateral interstitial infiltrates that begin in the perihilar region (Fig. 62.3). Radiographic manifestations of PCP can vary considerably, including normal appearance and lobar infiltrates, pleural effusions, hilar adenopathy, parenchymal nodules, and cavitary disease. Tiny nodules disseminated throughout both lungs represent a miliary pattern typical of granulomatous pneumonias, such as TB or fungal disease. The location of infiltrates may also suggest the cause. Aspiration pneumonia occurs in dependent areas of the lung, usually the superior segments of the lower lobes or posterior segments of the upper lobes. Infiltrates from pneumonias produced by hematogenous spread (e.g., *S. aureus*) tend to be multiple and peripheral. Apical infiltrates suggest TB.

The presence of additional radiographic features in association with infiltrates may suggest a specific cause. An infiltrate associated with hilar or mediastinal adenopathy suggests the presence of TB or fungal disease or may indicate pneumonia associated with a neoplasm. Bacteria most likely associated with cavitation (Fig. 62.4) are anaerobes, aerobic gram-negative bacilli, and *S. aureus.* Cavitation also may be

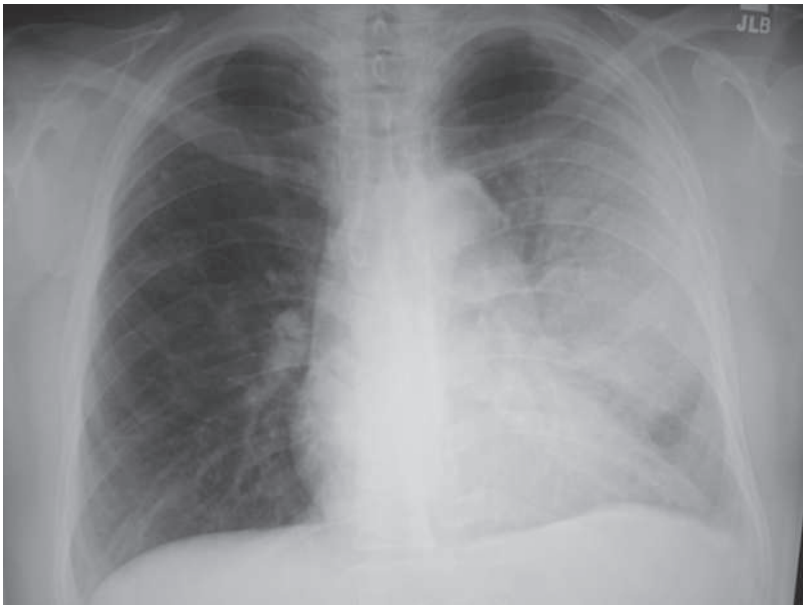

Fig. 62.1 Posteroanterior Chest Radiograph Reveals Left Upper Lobe Pneumonia. A variety of organisms can produce this pattern, usually *Streptococcus pneumoniae*, *Haemophilus influenzae*, or gram-negative bacilli, but also *Chlamydophila pneumoniae, Mycoplasma,* or *Legionella* spp.

present in fungal disease or TB and with noninfectious processes (e.g., malignancy and pulmonary vascular disease). Pneumatoceles or spontaneous pneumothorax may be seen in HIV patients with PCP. Pleural effusions occur with a wide variety of organisms, including many types of pyogenic bacterial pneumonias, *Chlamydophila* and *Legionella* spp., and TB. Anaerobic infections associated with an effusion are especially prone to the development of empyema. The diagnosis and aspiration of pleural effusions can be aided by bedside ultrasonography in the ED.

Lung ultrasonography is an emerging modality in the differentiation of respiratory complaints in the ED. The use of lung ultrasound has been shown to effectively differentiate pneumonia, congestive heart failure, and COPD/asthma in the acutely dyspneic patient.[12] Ultrasonography has been shown to be highly sensitive and specific for the diagnosis of pneumonia when compared to CT.[13] Normally air-filled alveoli in pneumonia are surrounded by fluid and on ultrasound appear as B lines which are a form of reverberation artifact. (Fig. 62.5)

Radiographic findings are nonspecific for predicting a specific infectious organism in pneumonia. *Mycoplasma* pneumonia may manifest as a dense infiltrate, or pneumococcal pneumonia may manifest as a diffuse interstitial infiltrate. Immunocompromised patients are particularly prone to having atypical radiographic appearances. Patients with a clinical picture strongly suggestive of pneumonia may have a normal initial chest radiograph and develop a radiographic infiltrate in the next 2 days. A chest radiograph is not required for the diagnosis of pneumonia. The absence of findings on a chest radiograph should not preclude the use of antimicrobial therapy in patients with clinical signs and symptoms of pneumonia. Immunocompromised patients, older adults, and patients with significant comorbidities may be treated with empirical antibiotics in the setting of signs and symptoms indicating pneumonia, even with a negative chest radiograph.

Laboratory studies also are nonspecific for identifying the cause of pneumonia. Although the finding of a white blood cell (WBC) count greater than 15,000/mm^3 increases the probability of the patient having a pyogenic bacterial cause rather than a viral or atypical cause, the predictive value of this finding depends on the stage of the illness and

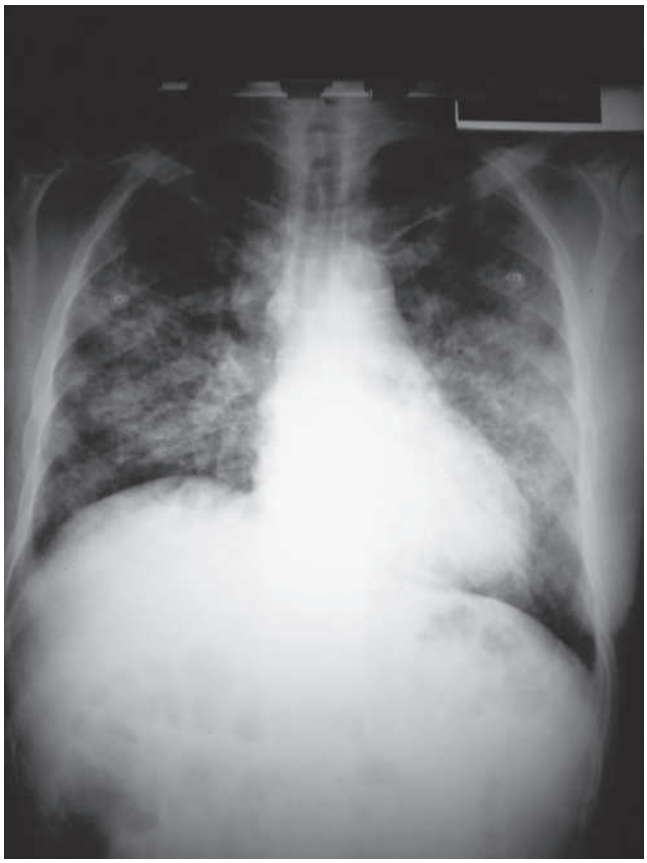

Fig. 62.2 Posteroanterior Chest Radiograph Reveals Patchy Interstitial Infiltrates. Viruses and *Mycoplasma* are the most likely causes in an otherwise healthy patient, but many bacterial organisms may also produce this pattern.

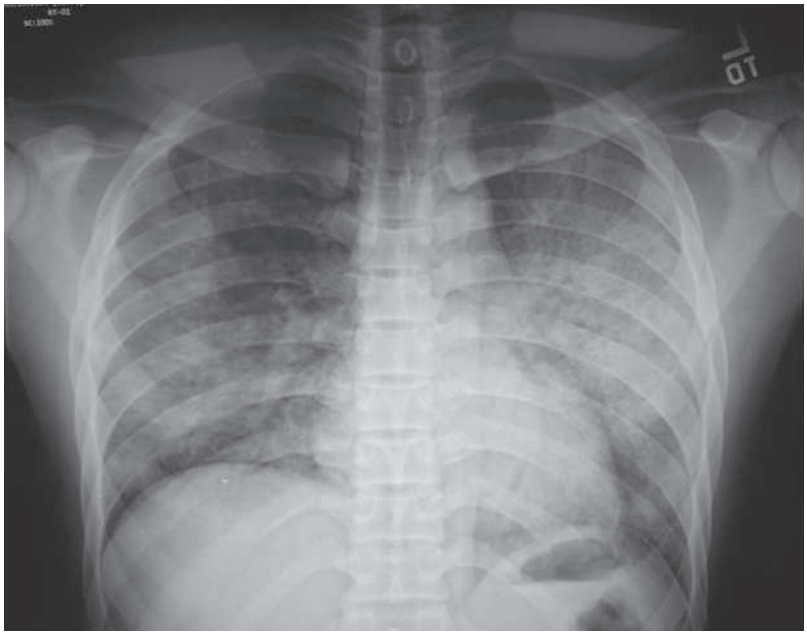

Fig. 62.3 Posteroanterior chest radiograph of a human immunodeficiency virus (HIV)–infected patient reveals interstitial disease mixed with patchy alveolar infiltrates. *Pneumocystis jiroveci* is the most common cause, but bacterial pathogens and tuberculosis also are considered.

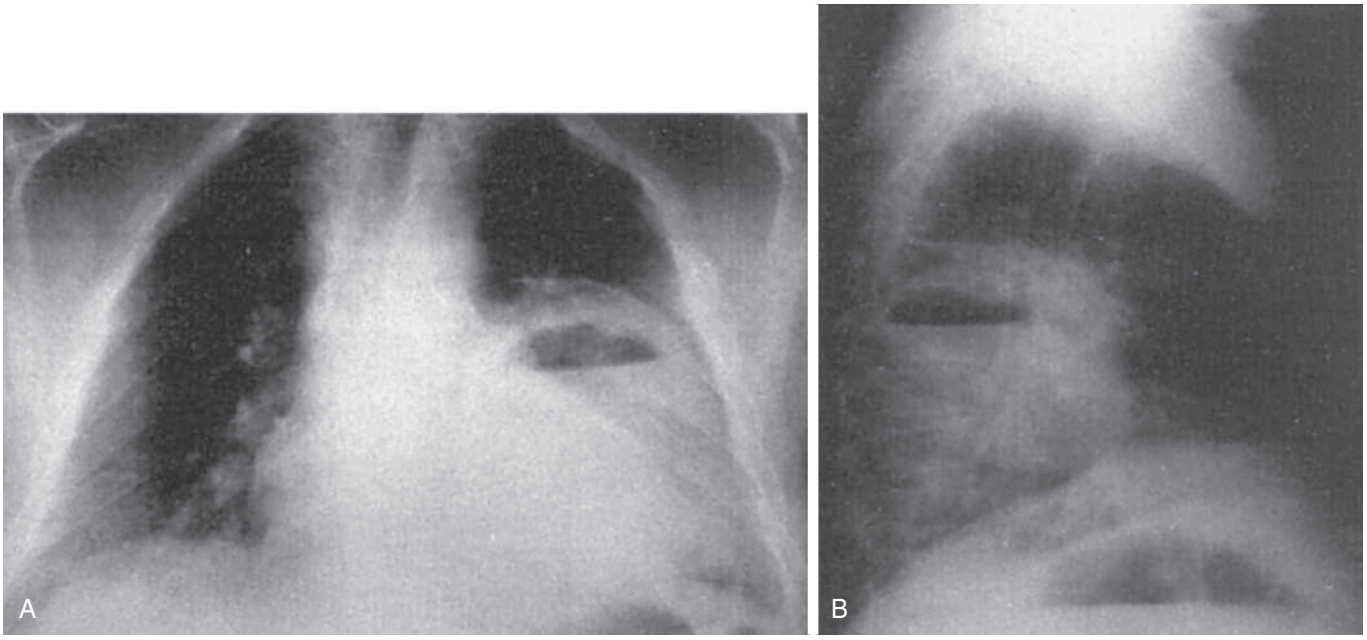

Fig. 62.4 Posteroanterior (A) and lateral (B) chest radiographs reveal a lung abscess in the left lower lobe, with a distinct air-fluid level.

likely prevalence of various causes. This is neither sensitive nor specific enough to aid decisions regarding therapy in an individual patient. A WBC count may be helpful if it yields evidence of immunosuppression, such as neutropenia, or if it reveals lymphopenia that may indicate immunosuppression from HIV. Basic metabolic panels may help identify patients with renal or hepatic dysfunction or metabolic acidosis associated with sepsis. These findings predict a complicated course and influence decisions regarding disposition, choice of antimicrobial agents, and dosages. The serum lactate dehydrogenase level is significantly elevated in patients with PCP compared with patients with non-PCP pneumonia. Inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein levels are not helpful in clinical decision making regarding pneumonia. The procalcitonin level has been suggested to assess the likelihood of a bacterial cause, response to antimicrobial therapy, and prognosis. A recent study of hospitalized patients with CAP failed to find a procalcitonin threshold that discriminated between viral and bacterial pathogens.[14] Empiric antibiotic therapy should be initiated in patients with suspected pneumonia regardless of procalcitonin level.[11]

Assessment of respiratory function with pulse oximetry is important in the evaluation of patients with pneumonia because the clinical assessment of oxygenation can be inaccurate. Pulse oximetry should be

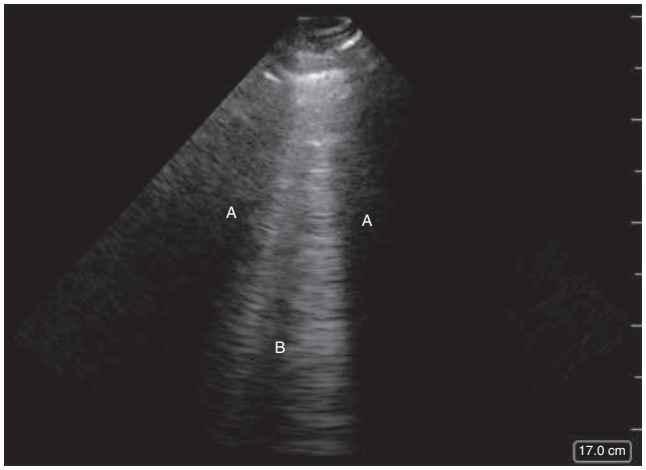

Fig. 62.5 Ultrasound image of the lung showing (A) hypoechoic rib shadows and (B) "comet tailing" or B-lines caused by reverberation artifact in lung tissue. B-lines when present anteriorly to posteriorly from the pleural line to the bottom of the image represent pneumonia or consolidation. (Image courtesy of Jackie Shibata and Alan Chiem.)

performed in any patient suspected to have pneumonia, and pneumonia should be considered in patients with low oxygen saturation.

Sputum gram staining rarely results in a change in therapy or outcome. Correlation between the identification of pneumococcus on Gram staining and sputum culture results is poor, even when commonly used criteria for an adequate sputum specimen are applied (<5 squamous epithelial cells and >25 WBCs/high-power field). Gram staining is even less likely to show gram-negative pathogens, such as *H. influenzae,* and should not be relied on to rule out a gram-negative cause. Empirical antimicrobial agents are usually highly clinically effective if chosen based on clinical information without sputum analysis. ATS/IDSA guidelines for the management of CAP support limiting sputum Gram staining and culture to patients with severe disease or risk factors for unusual pathogens.[10] Confirmation of the diagnosis of PCP requires sputum induction and staining and, in some cases, further invasive procedures, such as bronchoscopy with bronchoalveolar lavage or biopsy.

Routine blood cultures are of essentially no value in immunocompetent adults with pneumonia, in whom there is a very low prevalence of bacteremia, and management is rarely changed based on the results. Follow-up of false-positive blood cultures is costly and labor-intensive and may lead to the unnecessary use of antibiotics, such as vancomycin or linezolid, when contaminant growth is initially reported as gram-positive cocci. Blood samples for culturing should be obtained from immunocompromised patients, those with severe sepsis or requiring ICU admission, or those with risk factors for endovascular infection (e.g., prosthetic valves, IV drug use, cavitary infiltrates).[11] When culture specimens are drawn, they should ideally be obtained before the initiation of antibiotics, although antibiotics should not be delayed more than 60 minutes for this reason.

Patients with pneumonia and a large pleural effusion should undergo diagnostic thoracentesis. Fluid should be sent for cell count, differential, pH (pH <7.2 predicts the need for a thoracostomy tube), Gram staining, and culture. For most patients, thoracentesis can be safely deferred until after hospital admission. Patients in significant respiratory distress, or with evidence of tension and mediastinal shift, should undergo emergent diagnostic and therapeutic thoracentesis in the ED.

Serologic tests are widely available for the diagnosis of many organisms, including *C. pneumoniae, Legionella* spp., and fungi. The use of serologic tests to determine the cause of pneumonia may be helpful retrospectively, but these have traditionally required acute and convalescent serum titers and are of little use in the ED. Urine antigen tests for *S. pneumoniae* and *Legionella* are available and may be obtained within the time frame of an ED evaluation.

Rapid diagnostic testing using PCR such as the BioFire have increasingly become available for rapid identification of a wide variety of respiratory bacterial and viral pathogens. The use of a rapid diagnostic respiratory panel has been associated with a potential positive impact on hospital antibiotic stewardship.[15] The role and cost-effectiveness of rapid diagnostic respiratory pathogen testing in the ED is unclear. Rapid PCR testing may be especially useful in outbreak settings such as the SARS-CoV-2 pandemic to assist in isolating or cohorting patients with highly transmissible pathogens.

MANAGEMENT

The possibility of communicable disease should prompt consideration for early isolation. Patients with a history of TB exposure or suggestive symptoms (e.g., persistent cough, weight loss, night sweats, hemoptysis) or who belong to a group at high risk for TB (e.g., undomiciled, history of IV drug use or alcoholism, HIV risk, immigrant from high-risk area) should be given a mask and placed in respiratory isolation before evaluation, including chest radiography.[16] Because pulmonary TB cannot be distinguished reliably from other pulmonary infections at presentation in patients with advanced HIV, TB should be considered in all HIV-infected patients with respiratory complaints, and respiratory isolation should be initiated. The chest radiograph cannot exclude TB in this population because it may not have a typical appearance of TB. EDs that frequently care for patients at risk for TB should consider triage protocols to identify these individuals rapidly before patients, visitors, or staff are unnecessarily exposed. Suspected infection with organisms transmitted by respiratory droplet during seasonal transmission (e.g., influenza or SARS-CoV-2) should prompt infection control precautions, such as a mask being placed on the patient and proper personal protective equipment (PPE) worn by the provider.

Antimicrobials should be administered in the ED for patients who are being admitted to the hospital with suspected pneumonia. The timely administration of antimicrobials is associated with improved outcomes for hospitalized pneumonia patients, although confounding factors limit a full understanding of this relationship. Any presumed benefit of early antibiotic administration should be weighed against the risk of inappropriate use for patients in which the diagnosis is unclear. The antibiotics selected should cover the likely causes based on clinical, laboratory, radiologic, and epidemiologic information. The regimen should also be as selective as possible to avoid drug toxicity, emergence of resistance to broad-spectrum agents, and excessive cost.

The prevalence of drug-resistant *S. pneumoniae* (DRSP) has been increasing. In the United States more than 30% of isolates of *S. pneumoniae* are resistant to one or more antibiotic.[17] DRSP that is resistant to penicillin is usually resistant to other β-lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX). Extended-spectrum (or respiratory) fluoroquinolones, such as levofloxacin, are active against DRSP and other typical and atypical bacterial pathogens. Because the oral bioavailability of fluoroquinolones is high, oral therapy provides serum and tissue levels essentially equivalent to parenteral therapy. It is not clear, however, the extent to which in vitro resistance is related to adverse clinical outcome. Most cephalosporins achieve adequate levels in serum and tissues to treat *S. pneumoniae* respiratory tract infections successfully.

TABLE 62.1 Community-Acquired Pneumonia in Adolescents and Adults: Outpatient Treatment

Clinical Setting	Antibiotic Regimen[a]	Comments
Previously healthy, no antimicrobials in last 3 months	Doxycycline 100 mg PO bid for 7 days. or Centered between doxycyline and amoxicillin	Preferred for adolescent or young adult when likelihood of *Mycoplasma* is high; variable activity vs. *Streptococcus pneumoniae*
	Amoxicillin 1000 mg PO tid for 7 days.	Macrolide monotherapy no longer recommended unless local pneumococcal resistance is <25%.
Comorbidities or antimicrobials in last 3 months	Amoxicillin/clavulanate 875 mg/125 mg tid or Cefpodoxime 200 mg PO bid or Cefuroxime 500 mg PO bid for 7 days + azithromycin 500 mg PO on first day and then 250 mg daily for 4 days.	Especially preferable if fluoroquinolones recently received
	Levofloxacin 750 mg PO daily for 5 days	Can substitute moxifloxacin 400 mg daily for 7–14 days; active against DRSP; consider fluoroquinolone if recently received β-lactam.

DRSP, Drug-resistant Streptococcus pneumoniae; *PO,* orally.
[a]Renally dose antibiotics.

CA-MRSA remains an uncommon cause of CAP, but empirical coverage of MRSA should be strongly considered for patients with severe pneumonia associated with sepsis, especially in children or healthy young adults with likely influenza, contact with someone infected with MRSA, or radiographic evidence of necrotizing pneumonia. Antimicrobials with consistent in vitro activity against CA-MRSA isolates include vancomycin, TMP-SMX, tigecycline, linezolid, and ceftaroline. Although vancomycin is used most often for documented MRSA infections, vancomycin may be losing efficacy in light of increasing minimum inhibitory concentrations.[18]

Appropriate agents for the outpatient treatment of adults with CAP include amoxicillin, doxycycline, and fluoroquinolones with enhanced activity against *S. pneumoniae* (Table 62.1). Macrolide monotherapy is no longer routinely recommended for CAP unless local pneumococcal resistance is less than 25%.[11] Few places in the United States currently meet that criterion. In patients properly identified as being at low risk for complications with careful outpatient follow-up, use of amoxicillin 1 g PO three times daily or doxycycline 100 mg PO twice daily for 1 week is recommended. For patients at higher risk of DRSP because of recent antibiotic use or comorbidities such as chronic heart, lung, liver, or renal disease, treatment choices include monotherapy with a respiratory fluoroquinolone or combination therapy with amoxicillin/clavulanate and a macrolide, or a cephalosporin such as cefpodoxime and a macrolide. Patients who have received a fluoroquinolone in the past few months, or are at high risk of a fluoroquinolone adverse effect (e.g., QTc prolongation, tendon rupture, *Clostridioides difficile,* aortic dissection, aortic aneurysm, myasthenia gravis exacerbation), should be treated with a combination macrolide and beta lactam agent (see Table 62.1).

For patients whose illness is severe enough to require hospital admission and parenteral antibiotics, current guidelines use major and minor criteria to distinguish between non-severe and severe pneumonia (Box 62.1). For patients with a non-severe pneumonia needing admission to the hospital, a combination of a β-lactam agent such as ceftriaxone (or ceftaroline, ampicillin-sulbactam, or ertapenem) plus a macrolide such as azithromycin is the regimen recommended in ATS/IDSA guidelines (Table 62.2). Alternatively, an extended-spectrum fluoroquinolone (e.g., levofloxacin, moxifloxacin) can be given as monotherapy, but this regimen may be more likely to promote antimicrobial resistance and predispose the patient to adverse effects. These regimens treat the most common bacterial pathogens, such as *S. pneumoniae*, and *H. influenzae*, and atypical pathogens, such as *Mycoplasma, Chlamydophila,* and *Legionella* spp. β-Lactam monotherapy has been found to be noninferior to β-lactam–macrolide combination therapy or fluoroquinolone monotherapy in nonsevere CAP; it is a reasonable choice for patients without a specific reason to suspect atypical organisms.

Fluoroquinolones have some activity against TB and are important second-line agents. They should be avoided as a primary treatment for CAP in patients for whom TB is a possible diagnosis to avoid partial treatment and selecting for resistant strains. While anaerobic coverage should not be provided routinely for suspected aspiration pneumonia, if lung abscess or empyema is suspected, clindamycin or metronidazole

BOX 62.1 Criteria for Severe Community-Acquired Pneumonia

Minor Criteria[a]

- Respiratory rate ≥30 breaths/min
- Pao_2/Fio_2 ratio ≤250[b]
- Multilobar infiltrates
- Confusion, disorientation
- Uremia (BUN level ≥20 mg/dL)
- Leukopenia[c] (WBC count <4000 cells/mm^3)
- Thrombocytopenia (platelet count <100,000 cells/mm^3)
- Hypothermia (core temperature <36°C [96.8°F])
- Hypotension requiring aggressive fluid resuscitation

Major Criteria

- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

[a]Other criteria to consider include hypoglycemia (in patients who do not have diabetes), acute alcoholism or alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.
[b]A need for noninvasive ventilation can substitute for a respiratory rate higher than 30 breaths/min or a Pao_2/Fio_2 ratio below 250.
[c]As a result of infection alone.
BUN, Blood urea nitrogen; *Pao_2/Fio_2,* arterial oxygen pressure/fraction of inspired oxygen; *WBC,* white blood cell.
Adapted from Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:S27–S72.

TABLE 62.2 Community-Acquired Pneumonia in Older Children and Adults: Inpatient Antimicrobial Treatment[a]

Clinical Setting	Antibiotic Regimen	Comments
Community-acquired, immunocompetent patient	Ceftriaxone 1 g q24h ± azithromycin 500 mg q24h IV or PO	Can substitute ceftaroline, ampicillin-sulbactam, or ertapenem for ceftriaxone.
	Respiratory fluoroquinolone (levofloxacin 750 mg IV q24h, or moxifloxacin 400 mg IV q24h)	Treats most common bacterial and atypical pathogens; active against DRSP
Severe pneumonia (ICU)	Ceftriaxone 1 g IV q24h + levofloxacin 750 mg IV q24h + vancomycin 15 mg/kg IV q12h	Can substitute cefepime, ceftaroline, ertapenem, or β-lactam or β-lactamase inhibitor for ceftriaxone; can substitute moxifloxacin for levofloxacin; can substitute linezolid for vancomycin
Increased risk of resistant pathogens with IV antibiotics within the last 90 days or severe pneumonia with neutropenia, bronchiectasis (risk for MRSA, *Pseudomonas*)	Cefepime 2g IV q12h + levofloxacin 750 mg IV q24h + vancomycin 15 mg/kg IV q12h	Can substitute other antipseudomonal β-lactams, such as piperacillin-tazobactam, aztreonam, imipenem, meropenem, or doripenem, for cefepime; can substitute aminoglycoside plus macrolide for ciprofloxacin
Presumed PCP	TMP-SMX component 5 mg/kg	Add ceftriaxone to TMP-SMX if severe, until PCP confirmed; alternatives for sulfa allergy include clindamycin + primaquine

DRSP, Drug-resistant Streptococcus pneumoniae; *ICU*, intensive care unit; *IV*, intravenously; *PCP*, Pneumocystis pneumonia; *PO*, orally; *TMP-SMX*, trimethoprim-sulfamethoxazole.
[a]Renally dose antibiotics.

should be added, or the regimen can include an antibiotic with anaerobic activity, such as ertapenem, ampicillin-sulbactam, piperacillin-tazobactam, tigecycline, or moxifloxacin (see Table 62.2).

Severely ill and compromised patients are at relatively greater risk of infection with *S. pneumoniae,* aerobic gram-negative bacilli, *S. aureus* (including MRSA) and, in some areas, *Legionella* spp. For pneumonia patients admitted to an ICU, adequate activity against DRSP may be more important. Outcomes with severe pneumonia may be better with combination therapy.[11] A third-generation cephalosporin or β-lactam or β-lactamase inhibitor can be combined with a macrolide or fluoroquinolone, and addition of vancomycin or linezolid should be considered for MRSA activity.

Patients with prior use of IV antibiotics, neutropenia, or underlying bronchiectasis are at increased risk of infection with *P. aeruginosa.* Empirical therapy for high-risk patients or critically ill patients should include two agents with extended gram-negative activity, including *P. aeruginosa.* Empirical regimens include cefepime, imipenem, meropenem, doripenem, or piperacillin-tazobactam, plus ciprofloxacin (high dose) or an aztreonam and macrolide. For life-threatening pneumonia in populations at risk for MRSA, vancomycin or linezolid should be added to empiric coverage.

Because hospital-acquired pneumonia is associated with higher mortality and a greater likelihood of unusual pathogens, the use of broader spectrum empirical therapy is often appropriate, usually with a combination of antimicrobials to increase the chance that at least one antibiotic will be active against the causative pathogen. Patients admitted to the hospital for pneumonia should be tested for influenza in the appropriate season and treated with oseltamivir if positive. The use of corticosteroids to treat influenza pneumonia is associated with increased mortality, and only recommended for patients in refractory septic shock.[19]

For patients with HIV, it is important to treat *P. jiroveci* and bacterial pathogens such as *S. pneumoniae.* TMP-SMX is the treatment of choice; the usual regimen is 15 to 20 mg/kg of TMP to be continued for 21 days, in addition to a regimen to cover CAP organisms.[20] For patients allergic to sulfa, options include clindamycin 600 mg IV q6h, plus primaquine, 30 mg (base) PO daily. The addition of corticosteroids (prednisone 40 mg PO bid) reduces mortality and clinical deterioration in patients with hypoxemia. Traditionally, this has been defined as a PaO_2 less than 70 mm Hg or alveolar-arterial gradient greater than 35 mm Hg. In practice, pulse oximetry with an SaO_2 ≤92% on room air or desaturation with exercise should warrant the initiation of corticosteroids. *Mycoplasma, Legionella,* and *Chlamydophila* spp. are uncommon causes of severe pneumonia in HIV patients, so empirical therapy with erythromycin or doxycycline is not routinely recommended.

DISPOSITION

There is tremendous variability among emergency clinicians in deciding whom to admit for pneumonia. It is a common tendency to overestimate disease severity, leading to hospitalization of patients at low risk for death or serious complications. The decision to hospitalize a patient with pneumonia does not necessarily mean that a prolonged inpatient stay is required. Observation for 12 to 24 hours in the ED observation unit or hospital may allow the early discharge of certain moderate-risk patients and help support patients with complex social issues. Inpatient treatment of pneumonia is 15 to 20 times more expensive per patient than outpatient treatment, and most patients are more comfortable in a home environment.

Although no firm guidelines exist regarding hospital admission, scoring systems may assist with hospitalization decisions. One commonly used system is the Pneumonia Severity Index (PSI), a prospectively validated predictive rule for mortality among immunocompetent adults with CAP. This model suggests a two-step approach to assess risk. Patients are assessed as low risk for outpatient management if age is less than 50 years, have normal vital signs and lack of comorbid conditions. High-risk patients are stratified by a scoring system to determine if they need admission (Table 62.3). Hospitalization is recommended for patients with a score greater than 91, and brief admission or observation may be considered for patients with a score of 71 to 90. The PSI may underestimate disease severity in younger patients and oversimplify how clinicians interpret continuous variables such as blood pressure.[11] Clinical judgment should supersede a strict

TABLE 62.3 Scoring System for Pneumonia Mortality Prediction

Patient Characteristics	Points
Demographic Factor	
Age	
• Male	Age (yr)
• Female	Age (yr)—10
Nursing home resident	10
Comorbid Illness	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical Examination Findings	
Altered mental status	20
Respiratory rate >30 breaths/min	20
Systolic blood pressure <90 mm Hg	20
Temperature <35°C (95°F) or >40°C (104°F)	15
Pulse >125 beats/min	10
Laboratory or Radiographic Findings	
Arterial pH <7.35	30
Blood urea nitrogen >30 mg/dL	20
Sodium <130 mEq/L	20
Glucose >250 mg/dL	10
Hematocrit <30%	10
Arterial Po_2 <60 mm Hg	10
Pleural effusion	10

TABLE 62.4 SMART-COP Scoring System for Intensive Care Unit Admission

Hypotension	2 points
Multilobar chest radiograph	1 point
Hypoalbuminemia	1 point
Tachypnea	1 point
Tachycardia	1 point
Confusion	1 point
Hypoxia	2 points
Low arterial pH	2 points

interpretation of this scoring system. When emergency clinicians are provided with the patient's risk score, use of the decision rule results in a significantly lower overall admission rate, cost savings, and similar quality of life scores compared with those for patients conventionally managed by their physicians. The ability to take oral medications, access to follow-up, a stable living environment with adequate supportive services, and ambulatory pulse oximetry greater than 90% are important for successful discharge home from the ED.

A simpler tool is the CURB-65 rule. This mnemonic uses five simple criteria to determine patients at lower risk for adverse events—***c***onfusion, ***u***remia (blood urea nitrogen >20 mg/dL), ***r***espiratory rate greater than 30 breaths/min, ***b***lood pressure less than 90 systolic or less than 60 mm Hg diastolic, and age ***65*** years or older. The risk of 30-day mortality increases with more of these factors present: 0.7% with zero factors, 9.2% with two factors, and 57% with five factors. Patients with zero or one feature can receive outpatient care, those with two should be admitted, and ICU care should be considered for those with three or more factors. No randomized trials of hospital admission strategies have directly compared the PSI with the CURB-65 score. CURB-65 is the preferred clinical decision instrument given its simplicity and ability to risk stratify rapidly with readily available clinical information in the ED.

The decision to admit a patient to the ICU is straightforward when patients are intubated or require vasopressors. It is more difficult to identify patients who do not require these interventions initially but may be at greater risk for deterioration and require a level of monitoring beyond that available on the typical hospital ward. Objective criteria using the PSI (class V) and CURB-65 have been proposed but have not been prospectively validated for the ICU admission decision. When similar criteria were retrospectively studied in a cohort of CAP patients, they did not perform better than actual emergency clinician decisions. ATS/IDSA guidelines include criteria for defining severe CAP (see Box 62.1), but these have not been validated.[11] An ICU risk stratification score is abbreviated as SMART COP; intensive respiratory or vasodepressor support is predicted by clinical features such as hypoxia and hypotension (Table 62.4). A SMART-COP score above 3 points has identified 92% of patients who received intensive respiratory or vasodepressor support, including 84% of patients who did not need immediate admission to the ICU.[2] The decision to admit a patient to the hospital largely reflects the potential for acute deterioration, and some rate of floor to ICU transfer is inevitable. The Sequential Organ Assessment Score (SOFA) was found to be superior in identifying a severe state of disease compared to other CURB-65, PSI, and SMART-COP in patients admitted to the ICU with pneumonia.[21] The SOFA score is widely used in predicting mortality in patients admitted to the ICU. The SOFA score does not help differentiate lower-risk patients identified for discharge by the CURB-65 score.

Most patients with CAP do not need respiratory isolation. Patients who could pose a threat of transmission to other patients (e.g., influenza, varicella, TB, SARS-CoV-2) should be isolated. Neutropenic patients generally are placed in respiratory isolation. HIV-infected patients with pneumonia should be isolated until their TB status can be evaluated via sputum acid-fast bacilli smears; this is particularly true for patients with other risk factors for TB. Isolation should be strongly considered for others at high risk for TB.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 62: QUESTIONS AND ANSWERS

1. Which of the following statements is true regarding the treatment of community-acquired pneumonia (CAP)?

a. Amoxicillin monotherapy is not an option as it does not effectively cover atypical pneumonia.

b. Macrolide resistance almost always prohibits azithromycin monotherapy for CAP.

c. The most common atypical pneumonia in CAP is *Chlamydophila.*

d. Clinical history and prodrome often lead to the identification of the causative organism.

Answer: b. The 2020 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines no longer recommend macrolide monotherapy as *Streptococcus pneumoniae* resistance is greater than 30% in most settings in the United States. Amoxicillin is now recommended as a first-line agent in the treatment of CAP in healthy patients without comorbidities.

2. A 92-year-old male nursing home resident presents to the emergency department (ED) with a history of hypertension and nonproductive cough. He has a SaO_2 at triage of 82% but is speaking full sentences and with supplemental oxygen his saturation increases to 95%. Chest x-ray reveals diffuse infiltrates. Which of the following viral causes of pneumonia is this patient likely to have?

a. COVID-19

b. Respiratory syncytial virus (RSV)

c. Parainfluenza virus

d. Metapneumovirus

Answer: a. The novel coronavirus causing a worldwide pandemic is more likely to cause severe disease in patients with comorbidities and those living in nursing homes. SARS-CoV-2 often causes profound hypoxia that corrects with supplemental oxygen and causes diffuse infiltrates.

3. Which of the following causative organisms would be an indication for respiratory isolation?

a. *Histoplasma capsulatum*

b. *Herpes simplex virus* (HSV)

c. *Mycobacterium tuberculosis*

d. *Pneumocystis jiroveci*

Answer: c. Any patient with suspected tuberculosis (TB) infection should be placed in respiratory isolation and all staff should take appropriate personal protective precautions. None of the other causative agents require isolation.

4. A 60-year-old man with a past medical history of diabetes controlled with insulin and diagnosis of influenza 7 days prior presents with cough, weakness, and purulent sputum production. Vital signs are temperature 38.3°C (101°F) oral, heart rate, 130 beats/min, blood pressure, 80/50 mm Hg, respiratory rate, 30 breaths/min, and oxygen saturation, 92%. The chest radiograph reveals consolidation in the left lower lung (LLL). What is the most appropriate antibiotic therapy?

a. Ceftriaxone plus levofloxacin plus vancomycin

b. Ceftriaxone with a macrolide

c. Fluoroquinolone only

d. Trimethoprim-sulfamethoxazole (TMP-SMX)

e. Vancomycin only

Answer: a. In patients requiring hospitalization for community-acquired pneumonia (CAP), coverage for CAP would typically be with a combination of a macrolide with a β-lactam. Because this patient has signs of septic shock, consideration should be given to the addition of an agent for methicillin-resistant *Staphylococcus aureus* (MRSA; vancomycin) in addition to CAP coverage.

5. Which of the following is true regarding the use of procalcitonin in emergency department (ED) patients with pneumonia?

a. Procalcitonin is not useful in determining if a pneumonia is bacterial or viral.
b. Procalcitonin predicts mortality in ED patients.
c. It is helpful is predicting who can be discharged from the ED.
d. Procalcitonin is useful in guiding antimicrobial therapy.

Answer: a. While sometimes requested by hospitalist colleagues, the ED use of procalcitonin has not been shown to be useful in determining mortality, viral versus bacterial etiology, mortality, or prognosis.

63

Pleural Disease

Alysa S. Davis and Nicholas M. Mohr

KEY CONCEPTS

- Point of care thoracic ultrasound can be used to rule out pneumothorax with high sensitivity.
- For healthy young patients with a small primary spontaneous pneumothorax, observation with supplemental oxygen is an appropriate treatment option. For larger symptomatic primary spontaneous pneumothorax, simple aspiration with a catheter is often successful.
- In most cases of secondary pneumothorax, tube thoracostomy should be considered because less invasive approaches are associated with treatment failure.
- The most common causes of pleural effusion in the United States are congestive heart failure, malignancy, and bacterial pneumonia. Pulmonary embolism is an uncommon cause of pleural effusion.
- Thoracentesis should be performed under ultrasound guidance to minimize the risk of complications.
- On a frontal (anteroposterior or posteroanterior) projection, a volume of at least 200 mL of pleural fluid is required to detect a pleural effusion. Ultrasound can detect as little as 50 mL of pleural fluid and can be easily preformed at bedside.

INTRODUCTION

Emergent pleural disease presentations range in severity from asymptomatic pleural effusion to life-threatening tension pneumothorax. This chapter reviews the two most common nontraumatic pleural conditions: spontaneous pneumothorax and pleural effusion. Traumatic pleural diseases are covered in Chapter 37.

SPONTANEOUS PNEUMOTHORAX

Foundations

Background and Importance

Pneumothorax is defined as an abnormal collection of air in the pleural space between the parietal and visceral pleura and can range from benign to life-threatening. A spontaneous pneumothorax occurs in the absence of any precipitating external factors, such as trauma or thoracic procedures. A spontaneous pneumothorax can be either a primary spontaneous pneumothorax with no clinically apparent underlying pulmonary disease or a secondary spontaneous pneumothorax in patients with underlying pulmonary disease. Tension pneumothorax is a pneumothorax that leads to a life-threatening increase in pleural pressure associated with displacement of mediastinal structures and hemodynamic compromise.

Primary spontaneous pneumothorax most commonly occurs in healthy young men of above average height and is three times more likely to occur in men than in women. Marfan syndrome and mitral valve prolapse are associated with increased risk for primary spontaneous pneumothorax. Environmental risk factors include smoking and changes in ambient atmospheric pressure. Genetic factors also predispose to primary spontaneous pneumothorax, although this is a rare cause.

As with primary spontaneous pneumothorax, the incidence of secondary spontaneous pneumothorax is three times higher in men. Secondary spontaneous pneumothorax occurs in the setting of chronic pulmonary disease, with chronic obstructive pulmonary disease (COPD) being the most common cause in the United States (Box 63.1). Pneumothorax is also a known complication of *Pneumocystis jirovecci* pneumonia in patients with HIV. In developing countries, tuberculosis and lung abscess are the leading causes of secondary spontaneous pneumothorax.

Both primary and secondary spontaneous pneumothorax are relatively rare in children. Causes of secondary spontaneous pneumothorax include asthma, cystic fibrosis, foreign body aspiration, and connective tissue disease, such as juvenile idiopathic arthritis. The principles associated with the diagnosis, treatment, and surgical management of spontaneous pneumothorax in children are similar to those in adults.

Anatomy and Physiology

Anatomically, the visceral and parietal pleura lie in close approximation with only potential space between them. Normally, the intrapleural pressure remains negative during inspiration, meaning that it is slightly less than atmospheric pressure. The alveolar walls and visceral pleura form a barrier that separates the intrapleural and intraalveolar space and maintains the transpulmonary pressure gradient. When this barrier is disrupted, air enters the pleural space until either the pleural defect is sealed or until the intraalveolar and the intrapleural pressures equalize. In primary spontaneous pneumothorax, the alveolar-pleural barrier is disrupted when a subpleural bleb or bulla ruptures into the pleura space. Blebs are small subpleural thin-walled air-containing pockets that can easily rupture. Increased intrabronchial pressures and intraalveolar pressures generated by bronchospasm and intrinsic positive end expiratory pressure (PEEP) can play a role in the rupture of these blebs. In secondary spontaneous pneumothorax, underlying lung disease and chronic inflammation can also weaken the alveolar-pleural barrier and lead to rupture of blebs.

When negative intrapleural pressure is lost, the ipsilateral lung collapses. A large pneumothorax can result in a restrictive ventilation impairment with reduced vital capacity, functional residual capacity,

BOX 63.1 Causes of Secondary Spontaneous Pneumothorax

Airway Disease
Chronic obstructive pulmonary disease
Asthma
Cystic fibrosis

Infections
Necrotizing bacterial pneumonia, lung abscess
Pneumocystis jiroveci pneumonia
Tuberculosis

Lung Abscess

Interstitial Lung Disease
Sarcoidosis
Idiopathic pulmonary fibrosis
Lymphangiomyomatosis
Tuberous sclerosis
Pneumoconioses

Neoplasms
Primary lung cancers
Pulmonary or pleural metastases

Connective Tissue Diseases
Marfan syndrome
Ehlers-Danlos syndrome
Scleroderma
Rheumatoid arthritis

Miscellaneous
Pulmonary infarction
Endometriosis, catamenial pneumothorax

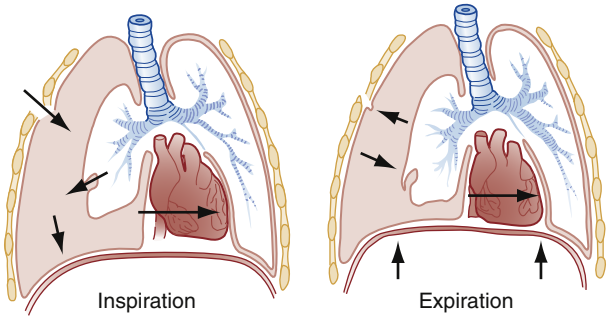

Fig. 63.1 Tension pneumothorax with total collapse of the right lung and shift of mediastinal structures to the left. Air is forced into the pleural space during inspiration and cannot escape during expiration.

and total lung capacity. Shunting of blood through poorly ventilated atelectatic lung tissue may lead to acute hypoxemia, but this effect is a late finding because it is mitigated by compensatory hypoxic vasoconstriction in the collapsed lung.

In tension pneumothorax, the alveolar-pleural defect acts as a one-way valve, allowing air to pass into the intrapleural space during inspiration and trapping the air in the pleural space during expiration (Fig. 63.1). This leads to progressive accumulation of intrapleural air and increasing intrapleural pressure, causing mediastinal shift and compression of the mediastinal venous structures and the contralateral lung. This leads to worsening hypoxemia and can impair venous return to the heart. Untreated, tension pneumothorax progresses to cardiovascular collapse and death.

Clinical Features

Symptoms of primary spontaneous pneumothorax are similar in adults and children. Symptoms often begin suddenly with ipsilateral pleuritic chest pain and dyspnea. Over time, the pain may evolve to a dull steady ache. Although dyspnea is common, it may not be severe in the absence of underlying lung disease or tension pneumothorax. Symptoms are often mild, and patients may wait several days before seeking medical attention. Without treatment, symptoms may spontaneously resolve within 24 to 72 hours, even though the pneumothorax may still be present.

Physical exam findings often correlate with the degree of symptoms. Sinus tachycardia is the most common early physical exam finding. With a large pneumothorax, hypoxia and decreased breath sounds with hyperresonance to percussion may be present. In children, breath sounds are distributed throughout the thorax, which makes unilateral breath sounds more challenging to identify. Other classic physical exam findings include unilateral hemithorax enlargement, unequal chest wall movement with exhalation, absent tactile fremitus, and inferior displacement of the liver or spleen (on the affected side). Absence of these findings does not exclude pneumothorax, and imaging should be obtained when pneumothorax is suspected. In children, routine chest radiography is not recommended in all cases of chest pain, but it should be performed if history or physical examination findings suggest that pneumothorax may be present.

Symptoms of tension pneumothorax include hypoxia, increased work of breathing, and tachycardia. Hypotension is a late finding. Distention of the jugular veins is common but may be difficult to detect. Displacement of the trachea is also a classically described sign but is usually a late finding. Absence of tracheal deviation does not rule out tension. Complete cardiovascular collapse, including cardiac arrest, may occur in tension pneumothorax if intervention is delayed.

In secondary spontaneous pneumothorax, the severity of signs and symptoms are related to both the size of the pneumothorax and the degree of underlying lung disease. Because of poor pulmonary reserve, dyspnea is nearly universal, even in the setting of a small pneumothorax. Symptoms are unlikely to resolve on their own. Physical exam findings such as hyperexpansion and distant breath sounds often overlap considerably with the findings of underlying lung disease, which makes clinical diagnosis difficult. The diagnosis of pneumothorax should be considered whenever a patient with COPD or other significant underlying lung disease has increasing dyspnea, and for this reason chest radiography is recommended in all patients with exacerbations of chronic lung disease.

Differential Diagnosis

The differential diagnosis of spontaneous pneumothorax includes many conditions that also manifest with chest pain and dyspnea. Among the most important is pulmonary embolism (PE), which has similar symptoms of pleuritic chest pain and dyspnea. Other pleural-based diseases such as pneumonia, tumor, and pleural effusion have characteristic radiographic findings that can help to make the diagnosis. Rarely, pneumothorax may mimic acute myocardial infarction or pericarditis with corresponding electrocardiographic changes. Pericardial effusion with or without tamponade can also present with chest pain, dyspnea, and tachycardia, but can be easily diagnosed with bedside ultrasound.

Spontaneous pneumomediastinum is a closely related clinical entity with similar symptoms, and it is diagnosed by the presence of subcutaneous or mediastinal emphysema on chest radiograph. Most cases of spontaneous pneumomediastinum occur in the absence of underlying disease and have a benign course. Secondary causes of pneumomediastinum (e.g., Boerhaave syndrome) are more serious, and treatment focuses on the underlying disorder.

Spontaneous hemopneumothorax is a rare but potentially serious condition that occurs when collapse of the lung is associated with the rupture of a vessel in a parieto-pleural adhesion. The clinical presentation is similar to spontaneous pneumothorax alone but may be accompanied by signs of hemorrhagic shock and effusion on chest imaging. Treatment entails tube thoracostomy to evacuate the pleural space, reexpand the lung, and limit ongoing bleeding.

Diagnostic Testing

Although the history and physical exam may suggest the diagnosis of spontaneous pneumothorax, the diagnosis is made with chest imaging, which may include chest radiography, ultrasound, or computed tomography (CT).[1] The classic radiographic finding is a thin visceral pleural line lying parallel to the chest wall, separated by a radiolucent band devoid of lung markings (Fig. 63.2). The average width of this band can be used to estimate the size of the pneumothorax, such as with the Rhea method which estimates the size of the pneumothorax by plotting the average of three different distances on a nomogram (Fig. 63.3). However, precise quantification is often inaccurate and, in general, it is more practical to characterize the pneumothorax using a semiquantitative approach as small, moderate, or large. The British Thoracic Society guidelines define size based on the measurement of the intrapleural distance at the level of the hilum: small, less than 1 cm; moderate, 1 to 2 cm; and large, more than 2 cm. The American College of Chest Physicians recommends measuring from the apex to the cupola with small being defined as less than 3 cm and large as greater than 3 cm. The estimated size, the patient's clinical status, and associated comorbidities are all useful in guiding management decisions.

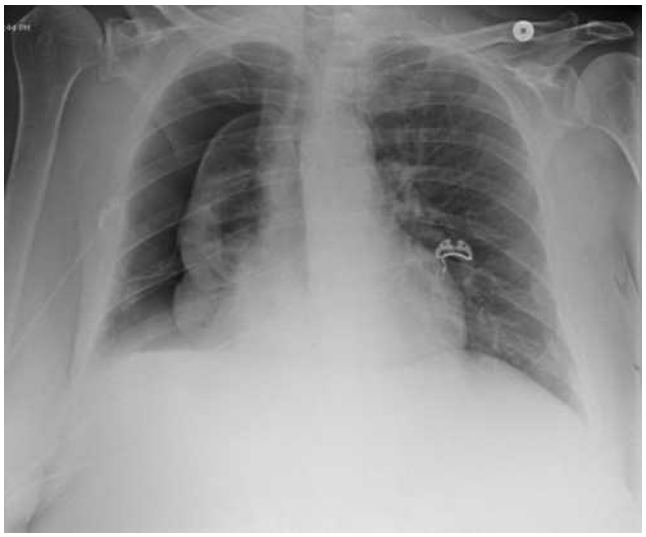

Fig. 63.2 Classic radiographic finding of a pneumothorax showing a thin visceral pleural line lying parallel to the chest wall, separated by a radiolucent band devoid of lung markings.

Tension pneumothorax is a clinical diagnosis, and there should be no delay in treatment for radiographic confirmation. When the diagnosis of tension pneumothorax is not clinically apparent and a chest x-ray is obtained, the classic appearance is one of complete lung collapse with gross distention of the thoracic cavity on the affected side and shift of the mediastinal structures across the midline. In critically ill patients for whom only a supine chest x-ray can be obtained, the finding of a deep sulcus (i.e., a deep lateral costophrenic angle) can suggest the presence of a pneumothorax on that side. Small to moderate pneumothoraces may be difficult to detect in the supine position.

Special care should be taken when viewing chest radiographs of patients with underlying lung disease, especially COPD. In patients with COPD, the relative paucity of lung markings throughout the lung makes pneumothorax more difficult to detect. In addition, large bullae may mimic the radiographic appearance of pneumothorax. A clue to differentiating pneumothorax from a giant bulla is that pneumothorax often shows a pleural line that runs parallel to the chest wall, whereas bullae usually have a more concave appearance. When the diagnosis is unclear, a CT scan can differentiate between the two and evaluate for underlying pathology. Chest CT should be obtained in patients with significant underlying lung disease who present with new-onset dyspnea or hypoxia with a nondiagnostic chest x-ray. Chest CT pulmonary angiography with intravenous contrast is necessary to rule out PE, but a noncontrast chest CT can identify occult pneumonia, pneumothorax, or progression of underlying chronic lung disease. CT can also be used in primary spontaneous pneumothorax to identify bullae, predict the likelihood of recurrence, and guide intervention decisions. Given the increasing use of CT, occult pneumothorax is an increasingly

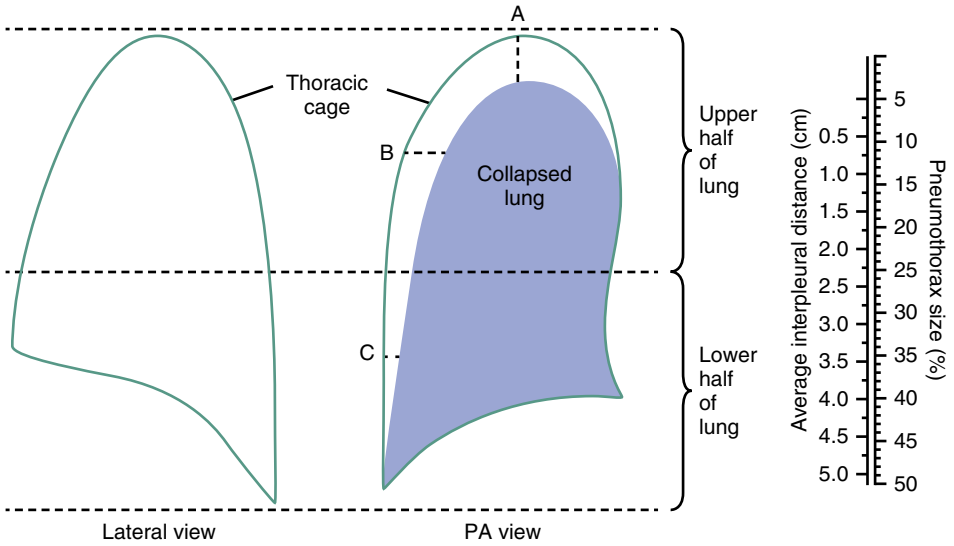

Fig. 63.3 Rhea method of calculating pneumothorax size involves taking the average of the maximal apical intrapleural distance (A), the intrapleural distance of the midpoint of the upper half of the lung (B), and the intrapleural distance of the midpoint of the lower half of the lung (C) and plotting that average distance on the nomogram to get the pneumothorax size (%).

common diagnosis. Typically, an occult pneumothorax not apparent on chest -ray can be managed conservatively in stable patients. Ventilated patients with an occult pneumothorax require close monitoring or early intervention due to the potential for expansion of the pneumothorax with positive-pressure ventilation.

Point of Care Ultrasound

Point of care ultrasound (POCUS) is increasingly being used to diagnose pneumothorax.[1] Bedside thoracic ultrasound is a very sensitive test for the diagnosis of pneumothorax. Sensitivity of chest radiographs in the diagnosis of pneumothorax is 28% to 52% whereas the sensitivity of ultrasound is 79% to 98%. The specificity of chest radiograph (99%) in the diagnosis of pneumothorax is similar to that of ultrasound (98%). In addition to using ultrasound for the diagnosis of spontaneous pneumothorax, it can also be used for screening of postprocedural pneumothorax (e.g., after central line placement). Ultrasound assessment for pneumothorax is best done with a high-frequency linear transducer. A phased array transducer or curvilinear transducer may also be used when set to a shallow depth. There are three features on two-dimensional ultrasound that have been described to be consistent with pneumothorax: lung sliding, B-lines, and a lung point. M-mode may also be used to clarify the ultrasound interpretation in the assessment of pneumothorax.[2]

In the absence of pneumothorax, the visceral and parietal pleura are closely approximated, and they create a characteristic shimmery or sliding appearance with respiratory variation (Fig. 63.4A). Visualization of lung sliding rules out pneumothorax in the area of examination. Visualization of lung sliding throughout the lung rules out pneumothorax, while absence of pleural sliding is suggestive of a pneumothorax. Because lung sliding only rules out pneumothorax in a local region, it is critical to obtain multiple views to rule out pneumothorax. Air generally goes to the most anterior portion in a supine patient and ultrasound should include the most nondependent portion of the patient when assessing for pneumothorax. Identification of a lung point, or the boundary between normal lung sliding and the absence of lung sliding, is highly specific for the detection of pneumothorax and can give clues about its size.

M-mode may be used to better capture the appearance of pneumothorax in a still image: normal lung sliding in M-mode creates a "seashore" sign while the absence of lung sliding creates a "barcode" appearance (Fig. 63.4B). Recent studies have shown that the addition of M-mode helps add to the diagnostic accuracy of lung sliding and is especially useful in less experienced sonographers.[2]

B-lines are long, wide bands of hyperechoic artifact of the visceral pleura that extend vertically through the entire image. If B-lines are present, the visceral pleura is visible by ultrasound, so no pneumothorax separates the two pleural layers. The presence of B-lines rules out pneumothorax in that area. The presence of B-lines can help rule out pneumothorax in patients with pleural disease that would otherwise cause poor lung sliding, such as blebs, fibrosis, or history of pleurodesis or pneumonectomy. In addition, mainstem intubation may lead to the absence of lung sliding in the contralateral hemithorax strictly because ventilation is not applied to the affected side, but B-lines will still be present.

Management

The management of spontaneous pneumothorax has two goals: (1) to evacuate air from the pleural space; and (2) to prevent recurrence. Therapeutic options for treatment of spontaneous pneumothorax include simple observation, aspiration with a catheter, tube thoracostomy, video-assisted thoracoscopic surgery, and thoracotomy. Treatment decisions should be individualized, with considerations for the size of the pneumothorax, severity of the signs/symptoms, presence of underlying pulmonary disease, other comorbidities, history of previous pneumothorax, patient reliability, availability of follow-up, and degree of persistent air leak.

Primary Spontaneous Pneumothorax

For young, healthy patients with a small primary spontaneous pneumothorax and minimal symptoms, supplement oxygen and observation are appropriate. The intrinsic resorption rate is 1-2% per day and the rate of absorption can be accelerated with the administration of 100% oxygen via nonrebreather mask. If observation is selected as the treatment of choice, the patient should be observed for at least 4 hours with supplemental oxygen in the emergency department (ED). Repeat chest radiography prior to discharge should confirm that there is no interval worsening. The patient should follow up with a primary care provider or return to the ED in 24 to 48 hours for reevaluation.

For a primary spontaneous pneumothorax that is larger in size (i.e., >2–3 cm) or a smaller pneumothorax that causes significant symptoms or expands during observation, therapeutic options include needle aspiration, placement of a small-bore (8–14 Fr) pleural catheter, or observation alone. Optimal treatment for those with a first episode of primary spontaneous pneumothorax has been controversial and no available treatment options have been demonstrated to be clearly superior. Advantages of a simple needle aspiration include low morbidity, less invasiveness than chest tube placement, fewer follow-up visits, and overall cost savings. Recent data suggest that conservative management (observation alone) in patients with uncomplicated moderate to large spontaneous pneumothorax is noninferior to drainage with a lower rate of serious adverse events.[3] Currently, either observation alone or simple aspiration is a reasonable approach, and symptoms and patient shared decision-making may be used to select an appropriate treatment option.

Needle aspiration is often performed with a thoracentesis kit, which typically contains an 8 French catheter over an 18-gauge needle and a three-way stopcock. In the needle aspiration technique, the small catheter is placed into either the second anterior intercostal space at the midclavicular line or laterally at the fourth or fifth intercostal space at the anterior axillary line after prepping and sterile draping of the patient and local anesthesia infiltration. A three-way stopcock is then attached, and a large syringe is used to aspirate aliquots of air until resistance is met. The catheter is then removed. If a repeat chest radiograph after the observation period shows no reaccumulation of the pneumothorax, the patient may be discharged home with return precautions and close follow-up. Success of a catheter aspiration is more likely when a patient is younger than 50 years or when the volume of air aspirated is less than 2.5 L. Aspiration of larger volumes of air suggests a continuing air leak. If aspiration fails to reexpand the lung fully, a small-bore chest tube (8–14 Fr) should be placed.

For most patients with primary spontaneous pneumothorax requiring ongoing pleural drainage, placement of a small-bore tube or pigtail catheter is sufficient, because air leak is usually minimal. Small-caliber tubes are easy to insert, are well tolerated by patients, and leave only a small scar after removal. Complications with small-caliber tubes include kinking, malposition, inadvertent removal, occlusion by pleural fluid or clotted blood, and failure due to large persistent air leak. Pigtail catheters have similar outcomes to small-bore chest tubes and are easily placed using the Seldinger technique. Traditionally, patients with indwelling chest tubes or catheters were managed in the hospital, but those with access to close outpatient follow-up can also be managed at home with a one-way Heimlich valve, which consists of a one-way flutter valve covered in transparent plastic.

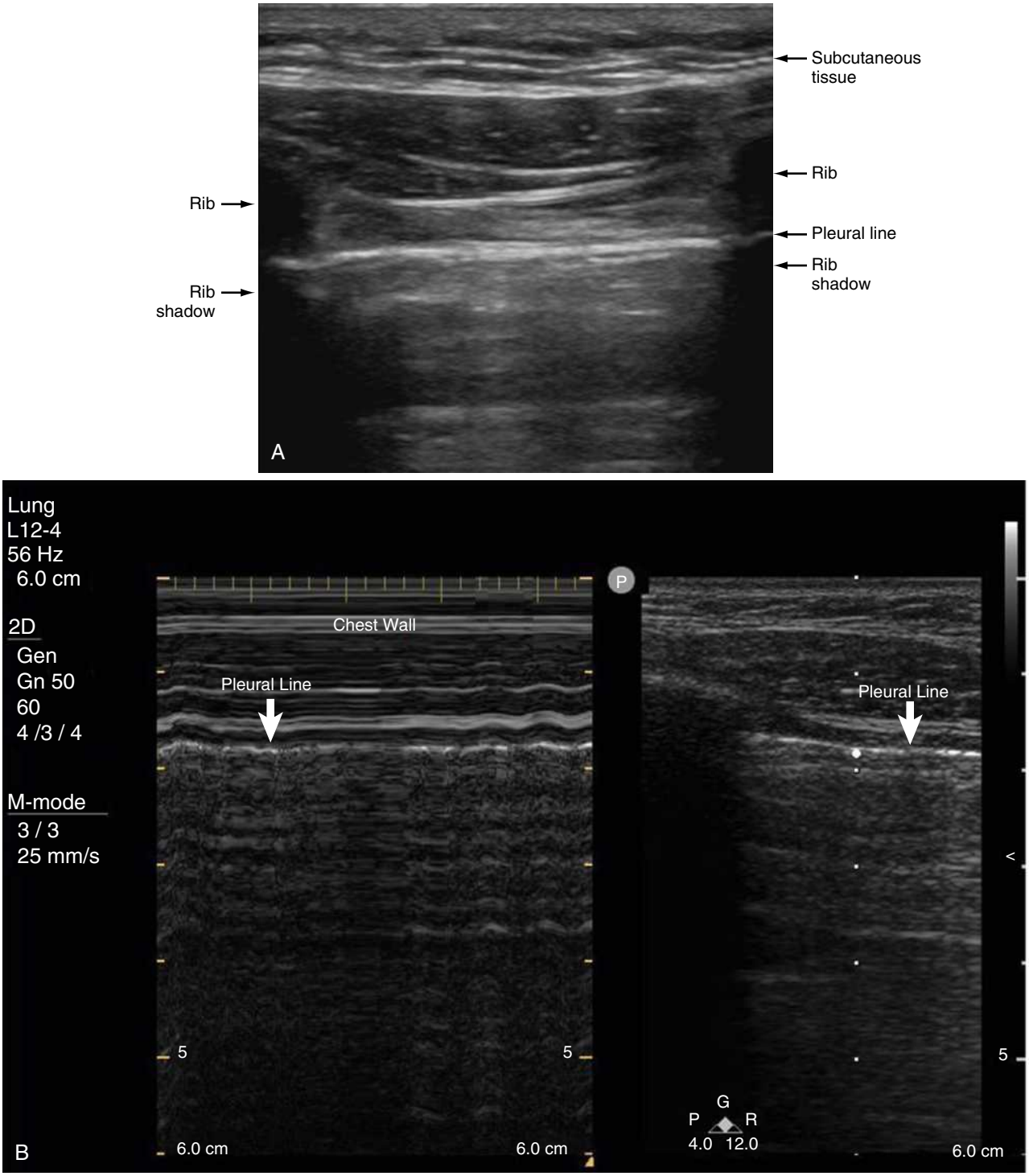

Fig. 63.4 (A) Ultrasound demonstrating location of pleural line. Lung sliding is dynamic and visualized in real time as shimmering or sliding of the pleural line. (B) The use of M-mode creates a "seashore" sign with normal lung sliding.

Secondary Spontaneous Pneumothorax

For patients with secondary spontaneous pneumothorax that is small (<1 cm), admission or placement in an ED observation unit for oxygen therapy and at least 24 hours of observation is appropriate. Secondary spontaneous pneumothorax has a higher likelihood of failing observation, which is why admission is recommended. In patients with secondary spontaneous pneumothoraces of moderate size (1–2 cm), a trial of simple needle aspiration is appropriate. If aspiration is successful and the pneumothorax is resolved or less than 1 cm in size, the patient should be admitted or placed in an ED observation unit for 24 hours of observation. If the pneumothorax is larger (>2 cm) or fails simple aspiration, then a tube thoracostomy is recommended with a small size chest tube or pigtail catheter (8–14 F).

Patients with respiratory distress, those with tension pneumothorax, those likely to require mechanical ventilation, and those with associated hemothorax or pleural effusion may require tube thoracostomy to definitively reexpand the lung with a moderate-sized chest tube (14–28 Fr). Larger-bore tubes (>28 Fr) may be required for patients with hemothorax or a large air leak, but typically are unnecessary in spontaneous pneumothorax.

After insertion, a chest tube is attached to a water seal device and left in place until the lung has fully reexpanded and the air leak has ceased. The routine use of suction neither increases the rate at which the lung reexpands nor improves patient outcomes and is no longer recommended. The use of suction (with a pressure of 20 cm H_20) is reserved for situations where the lung fails to reexpand after drainage through a water seal device or Heimlich valve for 24 to 48 hours.

Complications from chest tube placement include tube malposition, pleural space infection, and pain at the chest tube site. Reexpansion pulmonary edema and reexpansion hypotension are rare occurrences after evacuation of a large pneumothorax. Chest x-ray is routinely obtained after chest tube placement to assess for adequacy of placement and complications.

Tension Pneumothorax

If the clinical circumstances suggest a tension pneumothorax, treatment should be initiated prior to definitive diagnostic testing. Emergency management of tension pneumothorax includes rapid pleural decompression. This decompression may be accomplished by inserting a large bore intravenous catheter followed by tube thoracostomy or by immediate finger or tube thoracostomy. The determination of which procedure to perform should be guided by the setting, training of the care team, and available equipment.

Needle decompression is a temporizing procedure that releases high pressure air from the pleural space and restores hemodynamic stability. Definitive management is still required with a prompt tube thoracostomy. Needle decompression is completed by inserting a large bore IV catheter (14–16 gauge in adults, 18 gauge in children) of adequate length (at least 3–5 cm in adults) into the pleural space via the second intercostal space anteriorly at the midclavicular line or via the 4th/5th intercostal space at the midaxillary line. The diagnosis is confirmed by air escaping under positive pressure as the needle or chest tube enters the pleural space or by rapid hemodynamic improvement. The needle can then be removed, and the IV catheter remains in the chest wall open to air until definitive tube thoracostomy is completed. After tube thoracostomy, the catheter can be removed. In obese patients, a standard IV catheter may be of insufficient length to reach the pleural space and a longer needle or immediate finger or tube thoracostomy is required.

Disposition

Disposition decisions should consider the type and size of pneumothorax, underlying comorbidities, hemodynamic stability, and availability of follow-up. Admission to the hospital is generally not required for young, otherwise healthy patients with a small pneumothorax and no hypoxemia or hemodynamic abnormalities. After a period of observation (4–6 hours), these patients can be discharged home. Discharged patients should have the capability to return to an ED if their condition worsens and should undergo follow-up with a primary care provider or in the ED in 24 to 48 hours. Air travel and underwater diving must be strictly avoided until the pneumothorax has completely resolved, to prevent pressure-related pneumothorax expansion.

In most cases, chest tube management requires hospital admission although outpatient management of primary spontaneous pneumothorax with a small-caliber tube and Heimlich device is possible with good outpatient follow-up. Those with secondary spontaneous pneumothorax require either 24 hours of observation or admission for ongoing chest tube management.

Spontaneous pneumothorax usually resolves within 7 days of tube thoracostomy. Air leaks that persist beyond 2 days are less likely to resolve on their own. If the air leak persists beyond 4 to 7 days, tube thoracostomy is considered to have failed and surgical intervention is generally recommended. Failure of tube thoracostomy is more common in secondary spontaneous and recurrent pneumothorax because they tend to be associated with larger and more persistent air leaks.

Recurrence of spontaneous pneumothorax is common (approximately 30%). Younger age, lower weight/height ratio, and ongoing smoking are associated with increased risk of recurrence. There are a variety of operative and nonoperative interventions aimed at decreasing the rate of recurrence. Pleurodesis involves pleural instillation of a sclerosing agent or mechanical pleural abrasion to promote scarring of the parietal and visceral pleura, which obliterates the pleural potential space. Another strategy involves resection of apical bullae or other lesions at risk for causing recurrences. Often the two strategies are combined. Minimally invasive procedures, such as video-assisted thoracoscopic surgery (VATS), allow for resection of bullae and pleurodesis. Patients with extensive bullae may require thoracotomy for wider visualization of lesions.

Recurrence may be life-threatening for patients with serious underlying lung disease, and intervention may be used to prevent recurrence as part of the initial approach to secondary spontaneous pneumothorax. In contrast, for patients with primary spontaneous pneumothorax, interventions typically are not considered until after a second ipsilateral pneumothorax. However, those with a first episode of primary spontaneous pneumothorax with bullae greater than 2 cm have less recurrence when they undergo surgical resection after the first episode.[4] Preventive treatment is also recommended for patients who plan to continue activities that increase the risk of severe complications if a pneumothorax recurs, such as flying or diving.

PLEURAL EFFUSION

Foundations

Background and Importance

Pleural effusion is an abnormal collection of fluid in the pleural space. The most common causes of pleural effusion in the United States are congestive heart failure, malignancy, bacterial pneumonia, and pulmonary embolism. Tuberculosis remains a leading cause of pleural effusion in endemic areas. Other conditions commonly associated with pleural effusion include viral infections, cirrhosis, nephrotic syndrome, uremia, ovarian hyperstimulation syndrome, collagen vascular disease, myxedema, and intraabdominal inflammation. Esophageal perforation is a rare and uniquely morbid cause of pleural effusion (Box 63.2).

A pleural effusion that is associated with bacterial pneumonia or lung abscess is termed a *parapneumonic effusion*. The term *pleural empyema* (or pyothorax) implies the presence of pus within the pleural space. Fluid in the pleural space that is anatomically confined and is not free flowing within the pleural space is termed a *loculated effusion*. Loculated effusions occur when there are adhesions between the visceral and parietal pleurae. Traumatic hemothorax is a distinct type of pleural effusion that is approached in Chapter 37.

Anatomy and Physiology

Under normal circumstances, a thin layer of fluid lies between the visceral and parietal pleura. Pleural fluid is produced from systemic capillaries at the parietal pleural surface and absorbed into the pulmonary capillaries at the visceral pleural surface. Although lymphatics play an

BOX 63.2 Causes of Pleural Effusion

Transudates
Congestive heart failure
Cirrhosis with ascites
Nephrotic syndrome
Hypoalbuminemia
Myxedema
Peritoneal dialysis
Glomerulonephritis
Superior vena cava obstruction
Pulmonary embolism

Exudates
Infections
Bacterial pneumonia
Bronchiectasis
Lung abscess
Tuberculosis
Viral illness

Neoplasms
Primary lung cancer
Mesothelioma
Pulmonary or pleural metastases
Lymphoma

Connective Tissue Disease
Rheumatoid arthritis
Systemic lupus erythematosus

Abdominal or Gastrointestinal Disorders
Pancreatitis
Subphrenic abscess
Esophageal rupture
Abdominal surgery

Miscellaneous Conditions
Pulmonary infarction
Uremia
Drug reactions
Postpartum
Chylothorax

essential role in removing pleural fluid, the direction of pleural fluid flow is generally governed by the difference in hydrostatic pressures between the systemic and pulmonary circulations (Fig. 63.5). Under normal circumstances, pleural fluid exists in a dynamic equilibrium with approximately 1 L of fluid traversing the pleural space every 24 hours. The net accumulation of fluid in the pleural space is small (approximately 0.1–0.2 mL/kg body weight) and clinically insignificant. Pleural effusions develop when the influx of fluid into the pleural space exceeds the efflux.

Pathophysiology

Pleural effusions are classically divided into two groups according to the composition of the pleural fluid: transudates and exudates. Transudative effusions are ultrafiltrates of the plasma and contain very little protein. A transudative effusion develops due to an increase in hydrostatic pressure or decrease in oncotic pressure within the pleural microvessels. The most common cause of transudative effusion is congestive heart failure with an associated increase in hydrostatic pressure. Patients with severe malnutrition also develop transudative effusions because of profound hypoalbuminemia and loss of plasma oncotic pressure. Other conditions such as cirrhosis and nephrotic syndrome are also associated with an increase in hydrostatic pressure and loss of plasma oncotic pressure.

In contrast, exudative effusions contain a relatively high amount of protein, reflecting an intrinsic abnormality of the pleura. Any pleural or pulmonary disease associated with inflammation can result in an exudative effusion. The most common cause of exudative effusion is a parapneumonic effusion. Malignant effusions are another common form of exudative effusion and often reflect alteration in pleural permeability and altered lymphatic drainage. Exudative effusions may also arise from inflammatory abdominal conditions, such as pancreatitis. As an exudative effusion is resorbed, the fibrinous tissue left behind can give rise to ongoing inflammation and pleural adhesions.

Some pleural effusions have characteristics of both transudative and exudative pleural effusions. For example, in the case of PE, the pathogenesis of pleural effusion is multifactorial and involves increased pulmonary vascular pressure (leading to a transudative effusion) and ischemia and inflammation of the pleural membrane (leading to an exudative effusion).

Massive pleural effusions (>1.5–2 L) are usually associated with malignancy but can also arise in the setting of heart failure and in other conditions of volume overload. Massive effusions can restrict respiratory movement, compress the lung parenchyma, and result in intrapulmonary shunting. In extremely rare cases, tension hydrothorax can develop with mediastinal shift and circulatory compromise.

Clinical Features

Pleural inflammation, with or without effusion, is associated with pleuritic pain (i.e., sharp and worse with deep breathing) or with pain referred to the ipsilateral shoulder. Symptoms generally depend on the size of the effusion and underlying cause. Small pleural effusions are typically asymptomatic, and generally dyspnea does not develop until the volume of pleural fluid in adults reaches at least 500 mL.

Physical findings also depend on the size of the effusion. A pleural friction rub may be the only finding in a patient with isolated pleurisy, whereas patients with massive pleural effusions can have hemodynamic compromise. Classical physical signs of pleural effusion include diminished or distant breath sounds, dullness to percussion, and decreased tactile fremitus. The technique of auscultatory percussion (i.e., percussing the chest while listening for dullness with the stethoscope) may be more sensitive and specific for the physical diagnosis of pleural effusion. Egophony and enhanced breath sounds are often appreciated at the superior border of the effusion because of the underlying atelectatic lung disease.

Differential Diagnosis

The differential diagnosis of pleural effusion includes a wide variety of diseases characterized by dyspnea or chest pain and ranges from congestive heart failure and volume overload, pneumonia, pulmonary embolism, and pericardial effusion. Of note, many of these conditions may coexist with pleural effusions. The presence of a pleural effusion requires thoughtful consideration of the underlying cause. Specifically, an unexplained pleural effusion should raise concern for malignancy and requires follow-up.

Diagnostic Testing

The diagnosis of pleural effusion should be confirmed by chest X-ray, CT, or bedside ultrasound. A volume of approximately 200 mL is required before a pleural effusion can be demonstrated on an upright,

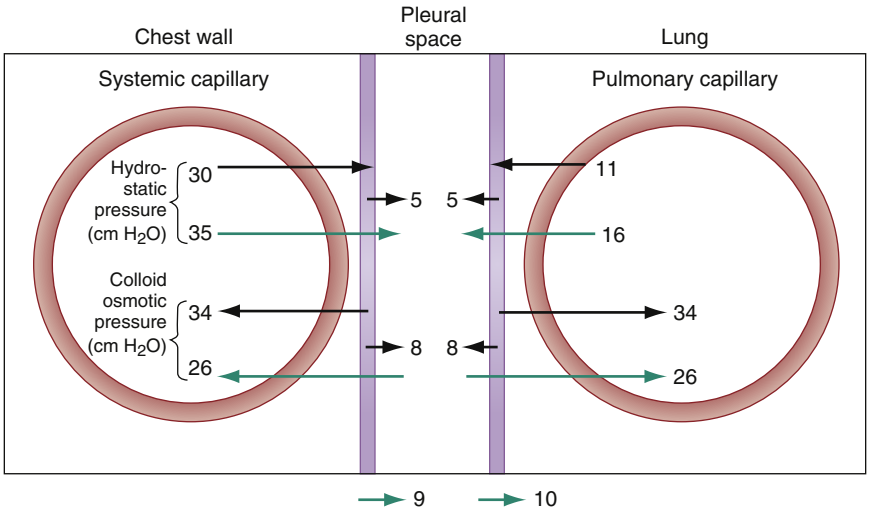

Fig. 63.5 Diagrammatic representation of the pressures involved in the formation and absorption of pleural fluid. (Adapted from Robert G, Fraser GA, Paré PD, et al. *Diagnosis of Diseases of the Chest*, ed 3, Philadelphia: WB Saunders; 1989.)

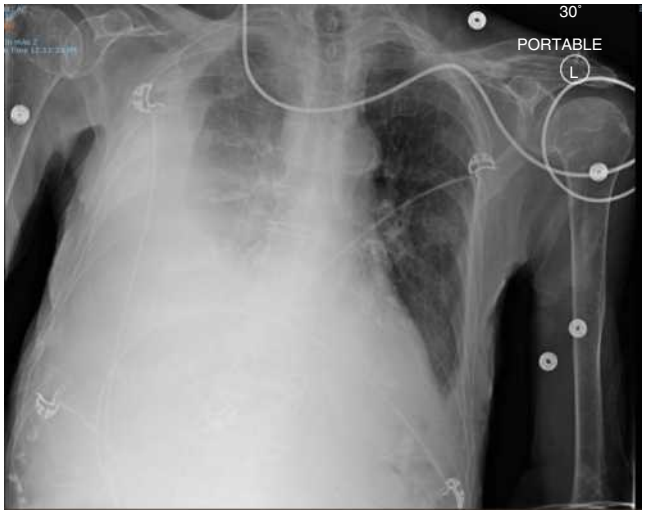

Fig. 63.6 Radiograph of a right-sided pleural effusion.

frontal chest x-ray. A smaller amount of fluid may be demonstrated in the posterior costophrenic gutter on the lateral projection. The classic radiographic appearance of a pleural effusion is blunting of the costophrenic angle. With larger pleural effusions, the hemidiaphragm may be obscured entirely, typically with an upward concave appearance because pleural fluid tends to layer higher laterally than centrally (Fig. 63.6). Pleural fluid can also extend up a major fissure and appear as a homogenous density in the lower portion of the lung field. Massive pleural effusions can completely opacify the hemithorax.

Pleural effusions are more difficult to diagnose on a supine radiograph. In the recumbent position, free pleural fluid gravitates superiorly, laterally, and posteriorly and thus, pleural effusions may not be clearly discernable. If the effusion is large enough, diffuse haziness or partial opacification of a hemithorax may be seen. Other findings on the supine radiograph may include apical capping, obscuring of the hemidiaphragm, or a widened minor fissure. Loculated fluid in a pleural fissure may assume a fusiform appearance and can simulate a mass. The lateral recumbent view historically has been useful for demonstrating small loculated effusions. It has been largely replaced by ultrasound or CT. Some pleural effusions can be challenging to diagnose on plain chest radiograph and further imaging may be required.

CT scan can detect as little as 3 to 5 mL of pleural fluid and is the gold standard for the diagnosis of small pleural effusions. CT is particularly useful in distinguishing between pleural based disease and parenchymal disease to identify an underlying cause (e.g., PE, malignancy, pneumonia). It can also help quantify the amount of fluid and may help guide thoracentesis.

Thoracic ultrasound is more sensitive than chest radiography in diagnosing and estimating the size of pleural effusion and is readily available at the bedside. Ultrasound can identify pleural effusions as small as 50 mL of fluid. On ultrasound, pleural effusions can be classified as simple or complex. Simple transudative pleural effusions often appear as hypoechoic fluid above the diaphragm and are best visualized with a curvilinear or phased array probe in the midaxillary line (Fig. 63.7). Often, compressed lung can be visualized within the effusion. Complex pleural effusions are subtyped as heterogenous or homogenous echogenicity. Hemothorax and pyothorax may appear heterogeneous, with echogenic material or septations extending through the effusion. Effusions with heterogenic echogenicity with swirling echoes suggest a high cellularity content often seen in malignant effusion. Fibrinous stranding, septations, and loculations also suggest an exudative effusion.

Identification of fluid above the diaphragm, compressed lung tissue, as well as localization of the diaphragm, liver, and spleen can help aid in the correct localization for thoracentesis or tube thoracostomy. If available, ultrasound should be used to identify pleural effusions and to guide interventions, such as thoracentesis. Iatrogenic pneumothorax is the most common complication after a thoracentesis, and it can be significantly reduced by using ultrasound guidance.[5]

Most patients with a pleural effusion should undergo diagnostic thoracentesis to determine the nature of the effusion (i.e., transudate, exudate) and identify an underlying cause. Occasionally, the clinical scenario provides an obvious apparent cause (e.g., congestive heart failure) and thoracentesis is unlikely to contribute to changes in therapy. Not all pleural effusions need to undergo thoracentesis in the ED. In the ED, thoracentesis may be performed to evaluate the etiology of life-threatening pathology (e.g., empyema, esophageal rupture) or to

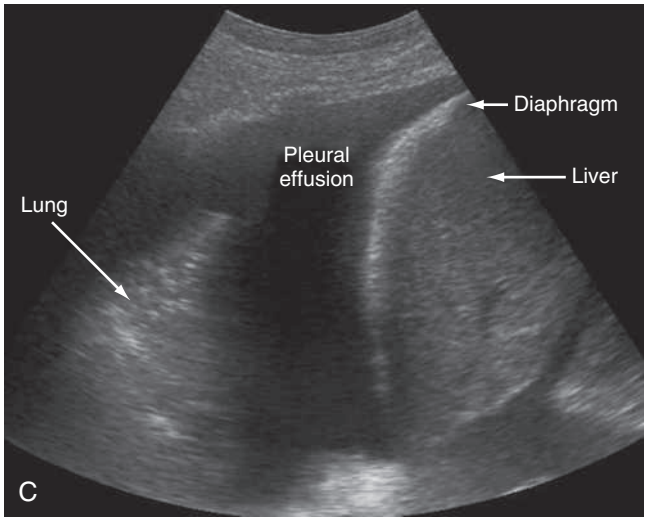

Fig. 63.7 Ultrasound image of the right upper quadrant demonstrating the typical hypoechoic appearance of a pleural effusion.

BOX 63.3 Light's Criteria for Differentiating Transudates from Exudates

Pleural fluid is considered an exudate if one or more of the following conditions are met:

1. Pleural fluid protein level/serum protein level exceeds 0.5.
2. Pleural fluid lactate dehydrogenase (LDH) level/serum LDH level exceeds 0.6.
3. Pleural fluid LDH level exceeds two-thirds of the upper limit of normal for the serum LDH level.

provide urgent symptomatic relief. In many other cases, diagnostic thoracentesis may be deferred.

Although numerous classifications have been proposed, Light's criteria remain the most widely accepted means of differentiating transudates and exudates (Box 63.3). Briefly, these criteria identify exudative effusions as being protein-rich and high in lactate dehydrogenase (LDH). A pleural fluid pH of less than 7.3 is associated with parapneumonic effusion, malignancies, rheumatoid effusions, tuberculosis, and systemic acidosis. A pH of less than 7.0 strongly suggests empyema or esophageal rupture and is an indication for tube thoracostomy. Pleural fluid should also be sent for Gram stain and culture to rule out empyema or parapneumonic effusion. If the diagnosis of malignant pleural effusion is being considered, and tumor is not already diagnosed, pleural fluid should be submitted for cytologic examination. The sensitivity for diagnosis of pleural malignancy does not depend on the volume of fluid collected during thoracentesis.

In the absence of a traumatic thoracentesis, bloody fluid suggests trauma, neoplasm, or pulmonary infarction. If the hematocrit of the pleural fluid is greater than 50% of the peripheral blood, the effusion is, by definition, a hemothorax. Atraumatic hemothorax is relatively rare but can occur with spontaneous rupture of a tumor or blood vessel.

Management

Most pleural effusions do not require emergent drainage, and there are few indications for urgent therapeutic thoracentesis in the emergency department. For the patients with massive effusions (>1.5–2 L), urgent thoracentesis may stabilize respiratory or circulatory status. Patients with empyema require timely chest tube drainage in the ED, operating room, or with interventional radiology in order to obtain source control and prevent complications. Traditionally, large-bore (28–40 Fr) chest tubes were placed in patients with empyema; however, small-bore tubes such as pigtail catheters (14 Fr) are now generally accepted as first-line therapy.[6] In most other cases, the timing of therapeutic thoracentesis can be individualized. For example, therapeutic thoracentesis would be reasonable to perform in the ED for a recurrent malignant pleural effusion if symptomatic relief would allow for discharge or would alter the diagnostic dyspnea workup.[7]

Relative contraindications to thoracentesis include coagulopathy and other bleeding disorders, history of pleurodesis, and chest wall infections. Pleural adhesions are also a relative contraindication to thoracentesis due to the potential for pneumothorax, but this risk can be minimized with ultrasound guidance.

Following a diagnostic or therapeutic thoracentesis, a chest radiograph or bedside ultrasound assessment should be obtained to evaluate for complications such as iatrogenic pneumothorax. Other potential complications include hemothorax, lung laceration, shearing of the catheter tip, infection, and transient hypoxia due to ventilation-perfusion mismatch. Hypotension can also occur after the removal of large volumes of fluid, particularly in patients that are already volume depleted.

Reexpansion pulmonary edema is a rare complication of thoracentesis and is traditionally correlated with large volume (>1500 mL) drainage. The symptoms of reexpansion pulmonary edema are generally mild and can be managed with supplemental oxygen and gentle diuresis. Safe aspiration of larger volumes of fluid has been described while using pleural manometry, however complications are rare when aspirating greater than 1500 mL during a single thoracentesis attempt. Therefore, the British Thoracic Society recommends removing no more than 1500 mL of pleural fluid in a single procedure to reduce the risk of reexpansion pulmonary edema (Grade C).

Disposition

The natural progression of pleural effusions is determined largely by the underlying diagnosis. The decision to admit a patient with a pleural effusion to the hospital must be individualized, considering the patient's underlying diagnosis, respiratory and hemodynamic status, and predicted clinical course. For example, small pleural effusions are common after abdominal surgery and in the postpartum state, but they almost always resolve spontaneously within a few days. Viral pleuritis, with or without effusion, is generally self-limited and resolves with only symptomatic support. In patients with congestive heart failure, pleural effusions generally respond well to diuresis, but patients may require admission for intravenous diuretics. Effusions may persist in patients with poorly compensated disease. In nearly 20% of pleural effusions, no definitive diagnosis can be established, even after investigation, and most of these effusions resolve spontaneously without sequelae.

Parapneumonic effusions contribute significantly to the morbidity and mortality associated with pleural disease. For this reason, the presence of a parapneumonic effusion is a reason to hospitalize a patient with community-acquired pneumonia. Empyema will develop in 5% to 10% of parapneumonic effusions and early surgical drainage results in better outcomes than conservative management.

Pleural effusions associated with malignancy are a marker of significant morbidity and mortality. Therapeutic thoracentesis can provide symptomatic relief in the short term, but malignant effusions tend to recur and often do so rapidly. Close management of recurrent malignant pleural effusions improves the patient's quality of life. Strategies for managing recurrent pleural effusions include chemical or mechanical

pleurodesis to obliterate the pleural space or placement of a permanent indwelling catheter or pleural peritoneal shunt to provide continued drainage.[7] Consistent use of definitive procedures in recurrent pleural effusions leads to fewer ED performed procedures and fewer complications when compared with repeat thoracentesis.[8] Patients with benign but recurrent pleural effusions refractory to other treatments may also benefit from chemical or mechanical pleurodesis or placement of an indwelling pleural catheter.[9]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 63: QUESTIONS AND ANSWERS

1. What is the most common condition associated with secondary spontaneous pneumothorax in adults in the United States?

a. Chronic obstructive pulmonary disease
b. Collagen vascular disease
c. *Pneumocystis* pneumonia
d. Pulmonary malignancy

Answer: A. Chronic obstructive pulmonary disease is the most common condition associated with secondary spontaneous pneumothorax, although all the conditions listed may also be causes.

2. Which of the following are indications of a pneumothorax on bedside ultrasound?

a. Identification of a lung point
b. Lack of lung sliding identified
c. When in M-mode, you see a "barcode" appearance
d. All of the above

Answer: D. Pneumothorax may be difficult to identify on bedside ultrasound and there are several ways to help identify a pneumothorax. Identifying an area of lung that lacks lung sliding and has a "barcode" appearance on M-mode indicates that the parietal and visceral pleura are not sliding over each other and is highly suggestive of a pneumothorax. Identifying a lung point, the point where a pneumothorax transitions to a normal pleural interface, can also help identify a pneumothorax.

3. A 32-year-old male with no significant past medical history presents with acute onset of right pleuritic chest pain, cough, and shortness of breath. The symptoms occurred at rest. Physical examination is remarkable for a tachycardia of 110 beats/min and respiratory rate of 32 and use of accessory muscles to breathe. Chest radiography reveals an estimated 5-cm right pneumothorax. Which of the following would be suitable management?

a. Admission for 100% face mask oxygen and repeat radiography in 1 day
b. One-time air aspiration and repeat radiography in 6 hours
c. Reassurance and observation
d. Tube thoracostomy

Answer: D. Large (2 cm) primary spontaneous cases and patients who are showing signs of respiratory distress should be treated with tube thoracostomy. If the primary spontaneous pneumothorax is small (<2 cm), then observation alone is appropriate. For a larger primary spontaneous pneumothorax (> 2cm) without significant symptoms, either observation alone or intervention with either simple aspiration or tube thoracostomy may be appropriate and a shared decision-making discussion with your patient is appropriate to determine best course of action.

4. Which of the following statements is true regarding the routine application of suction after tube thoracostomy?

a. It improves the rate of lung expansion.
b. It increases the risk of reexpansion pulmonary edema.
c. It is associated with increased rates of empyema.
d. It is not routinely indicated.

Answer: D. Suction neither accelerates lung reexpansion nor improves outcomes. It is indicated when reexpansion with a Heimlich or water seal device does not occur after 24 to 48 hours. A pressure of at least −20 cm H_2O should be used.

5. A 68-year-old man with a history of esophageal cancer presents with progressive fever, chest pain, and shortness of breath over 24 hours. Chest radiography demonstrates a possible left lower lobe pneumonia and large left pleural effusion. Pleural fluid analysis reveals pH of 6.95, glucose level of 47 mg/dL, 11,500 white blood cells (WBCs)/mm^3 (82% neutrophils), and protein level 75% of plasma levels. What are the indicated next steps in management?

a. Antibiotics and fluid resuscitation
b. Antibiotics and tube thoracostomy
c. Antibiotics, tube thoracostomy, and esophageal oral contrast study
d. One-time pleural aspiration for fluid analysis

Answer: C. This is an exudative pleural effusion as defined by Light's criteria (see Box 63.3). A pH less than 7.0 suggests emphysema or esophageal rupture. This patient is at risk for both; hence, the need to assess esophageal integrity. A pH less than 7.0 with glucose level less than 50 mg/dL are indications for tube thoracostomy. Normal pleural fluid has a WBC count of less than 1,000/mm^3.

64

Acute Coronary Syndromes

George F. Glass III and William J. Brady

KEY CONCEPTS

- Symptoms of acute coronary syndrome (ACS) are variable. Clinicians must consider ACS in a broad range of presentations, especially in patients prone to subtle or non-chest pain presentations (for example, women, older patients, or those with comorbidities such as diabetes).
- The ECG is crucial in the initial evaluation of ACS. Limitations of the 12-lead ECG in suspected ACS include initial nondiagnostic findings, evolving fluctuations with ongoing symptoms, anatomic myocardial blind spots, and confounding or obscuring patterns, such as left bundle branch block (LBBB).
- It is crucial to recognize ECG patterns that may indicate ischemia or impending infarction but do not meet traditional STEMI criteria (e.g., Wellens syndrome, significant aVR elevation, de Winter syndrome, Sgarbossa criteria). Patients with these findings may benefit from prompt catheterization.
- Patients with ECG findings of STEMI should undergo emergent reperfusion therapy. Percutaneous coronary intervention (PCI) is recommended with a goal door-to-balloon time of 90 minutes. If PCI is not feasible, patients should be administered fibrinolytic therapy within 30 minutes.
- Clinical decision tools, such as EDACS or the HEART score, may assist in the risk stratification of patients with suspected ACS.
- Serial troponin testing, combined with an accelerated diagnostic protocol, allows for identifying patients at low risk for ACS. High-sensitivity troponin (hs-T) testing may further reduce the time needed for evaluation. Validation of hs-T testing protocols is ongoing. Clinicians should be aware that testing characteristics vary by assay.
- Patients with suspected ACS who are low-risk by diagnostic protocols are unlikely to benefit from further diagnostic testing in the ED or admission and may be discharged with outpatient follow-up.

FOUNDATIONS

Acute coronary syndrome (ACS) refers to the constellation of clinical diseases occurring as a result of acute myocardial ischemia or infarction. ACS includes a spectrum of clinical presentations ranging from unstable angina (UA), involving ischemia, to acute myocardial infarction (AMI), characterized by myocardial cell death. Non–ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI) are the two AMI subtypes. Sudden cardiac death (SCD), involving pulseless ventricular tachycardia or ventricular fibrillation, is frequently included in the ACS spectrum of illnesses and represents the most extreme clinical manifestation of acute coronary syndrome. ACS, particularly AMI and its sequelae, remain among the leading causes of death in the developed world.

Several advances in the mid-20th century have drastically changed the approach to acute coronary care. The first developments of significance—external defibrillators, cardiac pacemakers, and new pharmacologic agents—have provided emergency clinicians with effective approaches for treating life-threatening dysrhythmias occurring due to ACS. The introduction of selective coronary arteriography revolutionized the management of patients with coronary artery disease (CAD), including chronic, stable presentations and acute coronary syndrome. In 1960, Kouwenhoven inaugurated the era of cardiopulmonary resuscitation (CPR), providing an important tool in the management of SCD.

These developments led to the recognition that the time between onset of symptoms and initiation of therapy is critical. Fibrinolytic therapy and interventional catheter-based techniques revolutionized the treatment of patients with STEMI, starting in the late 1980s. Combination therapies with antiplatelet, antithrombotic, and fibrinolytic agents continue to be studied for STEMI patients, further optimizing reperfusion and adjunctive therapies. Interventional success has improved with the use of newer stenting devices and various platelet and coagulation system inhibitors.

STEMI systems of care address the management of STEMI from a systems-based perspective, starting with EMS in the prehospital setting through the ED to the cardiac catheterization laboratory (CCL) and coronary care unit (CCU). This systems-based approach stresses several factors crucial in the management of STEMI, including the time-sensitivity of treatment, the multidisciplinary composition of the

management team, and multistep nature of the overall process. In addition to further development of the STEMI systems of care approach, current efforts focus on the establishment of regional cardiac centers and expansion of interventional capabilities to smaller hospitals.

Diagnostically, methods of evaluation of potential ACS patients without obvious STEMI or other diagnostic findings continue to mature. The rule-out (R/O) myocardial infarction (MI) strategy has been shortened in total time, rendered more efficient, and made safer with respect to detection of ACS events. The R/O MI process is appropriately performed in various clinical venues, including the ED, observation settings, and acute and critical care hospital units. The most recent development is the addition of high-sensitivity troponin testing, which can increase the detection of significant ACS events and reduce the total evaluation time, thus improving throughput.

Although the modern chest pain evaluation strategy is more efficient than previous approaches, further improvements in reducing the already low missed MI rate in the ED are under development. However, attempts to lower the missed MI rate may increase unnecessary testing with associated risk, health system costs, and less resource availability for higher-risk patients. Patients, physicians, and society must recognize that atypical, unusual, unanticipated ACS presentations will occur and not be diagnosed initially, at times with poor outcomes. These "missed" MIs do not represent inappropriate medical practice.

EPIDEMIOLOGY

The overall age-adjusted prevalence of heart disease is 10.6%; the age-adjusted prevalence of coronary heart disease is 7.2% for men and 4.2% for women. Heart disease, including CAD and related ischemic heart disease, continues to be the leading cause of death among adults in many industrialized countries, including the United States and Canada. Ischemic heart disease accounts for over 1 million deaths in the United States annually, of which approximately 160,000 occur in persons 65 years of age or younger. More than half of all deaths from cardiovascular disease occur in women, and CAD remains a major cause of morbidity and mortality in women beyond their middle to late 50s. The incidence of cardiovascular disease is expected to increase due to lifestyle changes that promote heart disease.[1]

A significant reduction in age-adjusted mortality from CAD has occurred in the United States and Canada over the past 5 decades; this decline continues while ACS incidence is increasing. In large part, the decline has been accompanied by diminished mortality from AMI. This decrease results from a significant reduction in the incidence of AMI and a sharp drop in the case-fatality rate. Reduction in cigarette smoking and improved management of hypertension, hyperlipidemia, and diabetes mellitus undoubtedly play a role, along with significant advances in medical treatment.

Chest pain is the second most common reason for patient attendance in the ED, accounting for approximately 7.49 million annual visits to EDs in the United States. Among men, chest pain is the primary cause for presenting to the ED whereas, in women, chest pain is the third most common reason. The admission rate for ACS has not significantly changed over the past 15 years.[2] In the United States, approximately 900,000 persons experience an AMI every year. Thirty percent of these patients die within 30 days of acute myocardial infarction; approximately half of these deaths occur soon after symptom onset and before arrival in the ED, usually from an ACS-related dysrhythmia within 2 hours of event initiation. Approximately half of all patients with an MI are rehospitalized within 1 year of their index event. Overall, the prognosis is highly variable and depends largely on the extent of the infarct, time to intervention, whether the patient underwent some form of revascularization, and residual left ventricular function. Approximately 2% of patients with ACS, including both UA and AMI, are discharged from the ED and represent the true rate of "missed ACS in the ED."

Spectrum of Illness: Coronary Artery Disease and Acute Coronary Syndrome

Coronary heart disease occurs across a wide spectrum of acuity and severity. Asymptomatic CAD and stable angina are less severe, and the more severe manifestations of coronary heart disease include acute coronary syndrome, ranging from UA to AMI. AMI is further subdivided into NSTEMI and STEMI. Some experts also include sudden cardiac death, resulting from pulseless ventricular tachycardia or ventricular fibrillation, as the most severe form of ACS.

Stable Angina

Stable angina pectoris, not considered a form of ACS, is transient, episodic chest discomfort resulting from myocardial ischemia. This discomfort is typically predictable and reproducible, with a constant frequency of attacks over time. Physical or psychological stress (e.g., physical exertion, emotional stress, anemia, dysrhythmias, environmental exposures) may provoke an attack of angina that resolves spontaneously with rest or with nitroglycerin (NTG).

The Canadian Cardiovascular Society (CCS) classification for angina is defined as follows:

- Class I—no angina with ordinary physical activity;
- Class II—minimal limitation of normal activity as angina occurs with exertion or emotional stress;
- Class III—severe limitation of ordinary physical activity as angina occurs with exertion under normal physical conditions; and
- Class IV—inability to perform any physical activity without discomfort as anginal symptoms occur at rest or with minimal physical exertion

Unstable Angina

Unstable angina, the least severe form of ACS, should be considered from both semantic and pathophysiologic perspectives; when considered together, unstable angina is best defined from its description as well as the results of the clinical evaluation. From the semantic perspective, unstable angina is broadly defined as angina that is new onset or occurring at rest or with minimal exertion. Furthermore, it is defined as angina that is worsening from a previously stable pain occurrence pattern in terms of frequency or duration of attacks, resistance to previously effective medications, or provocation with decreasing levels of exertion or stress.

Rest angina is defined as angina occurring at rest, lasting longer than 20 minutes, and occurring within 1 week of presentation. New-onset angina is angina of at least CCS classification class II severity, with onset within the previous 2 months. Increasing or progressive angina is diagnosed when a previously known anginal pattern becomes more frequent, longer in duration, or increased by one class within the previous 2 months of at least class III severity. Symptoms that last longer than 20 minutes, despite cessation of activity, are consistent with angina at rest; in the appropriate clinical setting, such a presentation could be considered UA.

Unstable angina is also referred to as preinfarction angina, accelerating or crescendo angina, intermediate coronary syndrome, and preocclusive syndrome, underscoring its difference from stable angina. In its more severe forms, UA should be considered a possible harbinger of AMI and should be treated aggressively in such instances. These various UA definitions are made with overall consideration of the specific patient's presentation.

UA can also be defined from a pathophysiologic perspective. Plaque rupture, accompanied by thrombus formation and vasospasm,

illustrates the intracoronary events of UA. These events are frequently characterized by chest pain and electrocardiographic abnormality, including T wave and ST segment changes.

Variant angina—also known as Prinzmetal angina—is caused by coronary artery vasospasm at rest with minimal fixed coronary artery lesions; it may be relieved by exercise or NTG. The ECG reveals ST segment elevation that is impossible to discern from plaque rupture–related STEMI clinically and electrocardiographically.

Acute Myocardial Infarction

On a cellular level, acute myocardial infarction is myocardial cell death with necrosis of the myocardium. The American College of Cardiology (ACC) and European Society for Cardiology (ESC) developed clinical criteria to define both myocardial injury and myocardial infarction, referred to as the Fourth Universal Definition of Myocardial Infarction.[3] In addition, the clinical situation is also considered in AMI, resulting in types 1 through 5.

The term *myocardial injury* should be used with elevated cardiac troponin values with at least one value above the 99th percentile upper reference limit, and the injury is considered acute if there is a rise or fall of the troponin values.[3] Specifically, the term myocardial infarction should be employed when there is acute myocardial injury occurring in the setting of an abnormal serum troponin value elevated above the 99th percentile of the upper reference limit and associated with at least one of the following[3]:

- Symptoms of myocardial ischemia;
- Electrocardiographic abnormalities:
  - New changes consistent with myocardial ischemia (i.e., ST segment and/or T wave changes); or
  - Development of pathologic Q waves;
- Imaging evidence of a loss of viable myocardium or a regional wall motion abnormality consistent with ischemic cause; or
- Angiographic or autopsy evidence of coronary thrombus.

The subtype classification of AMI considers the myriad clinical situations in which acute myocardial infarction is encountered. The five primary types of infarction are described by the following classification[3]:

Type 1—spontaneous MI related to ischemia resulting from a primary coronary event, such as plaque erosion rupture, erosion, fissuring, or dissection with accompanying thrombus formation and vasospasm. Type 1 infarctions represent the true ACS event.

Type 2—MI secondary to ischemia caused by increased oxygen demand or decreased supply, as seen in coronary artery spasm, coronary embolism, severe anemia, compromising arrhythmias, or significant systemic hypotension related to a range of causes.

Type 3—sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST segment elevation or new left bundle branch block (LBBB) pattern. Fresh coronary thrombus is noted via angiography or autopsy; death occurs before appropriate blood sampling to detect the abnormal cardiac biomarker.

Type 4—MI associated with coronary instrumentation, such as occurring after percutaneous coronary intervention (PCI). For PCIs in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than three times the 99th percentile URL are designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is similarly recognized.

- Type 5—MI associated with coronary artery bypass grafting (CABG). For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than five times the 99th percentile URL, plus any of the following, are designated as defining CABG-related MI:
  - New pathologic Q waves or new LBBB;
  - Angiographically documented new graft or native coronary artery occlusion; or
  - Imaging evidence of new loss of viable myocardium.

This categorization is more than a simple semantic description of AMI. Diagnostic and management issues are different depending on the subtype of MI encountered. For example, the type 1 event should be approached with attention to platelet and coagulation system inhibition and therapy aimed at correction of vasospasm, whereas the type 2 infarction should be managed by identifying and treating the inciting pathophysiologic situation causing imbalance in oxygen delivery and myocyte requirements.

Serum markers and ECG abnormalities further classify AMI at presentation as either NSTEMI or STEMI. NSTEMI is noted with the presence of chest pain or other anginal equivalent complaint, abnormal ECG (lacking ST segment elevation), and elevated serum troponin (in the typical rise and fall pattern); STEMI is noted with the presence of chest pain or other anginal equivalent complaint, abnormal ECG with ST segment elevation, and elevated serum troponin. Previous descriptors, such as transmural, non-transmural, Q wave, and non–Q wave MI, fail to describe the coronary event and its related pathophysiology, electrocardiographic presentation, and pathologic outcome adequately. The differentiation between STEMI and NSTEMI has important implications in management, outcome, and prognosis for patients with AMI. The ACC and American Heart Association (AHA) have separate clinical guidelines for the management of patients with non-ST segment elevation ACS (UA and NSTEMI) and with STEMI.

PATHOPHYSIOLOGY

The underlying pathophysiology of ACS is myocardial ischemia as a result of inadequate perfusion to meet myocardial oxygen demand. Myocardial oxygen consumption is determined by heart rate, afterload, contractility, and wall tension. Inadequate perfusion usually results from coronary arterial vessel stenosis as a result of atherosclerotic CAD. Usually, the reduction of coronary blood flow does not cause ischemic symptoms at rest until the vessel stenosis exceeds 95% obstruction to flow. Myocardial ischemia, however, may occur with increased physiologic stress and increased myocardial oxygen consumption with minimal to no vessel stenosis.

CAD is characterized by thickening and obstruction of the coronary vessel arterial lumen by atherosclerotic plaques. Although atherosclerosis is usually diffuse and multifocal, individual plaques vary greatly in composition. Fibrous plaques are considered stable but can produce anginal symptoms with exercise and increased myocardial oxygen consumption because of the reduction in coronary artery blood flow through the fixed stenotic lesions. Vulnerable, or unstable, fibro-lipid plaques consist of a lipid-rich core separated from the arterial lumen by a fibromuscular cap. These lesions are likely to rupture, resulting in a cascade of inflammatory events, thrombus formation, and platelet aggregation that can cause acute obstruction of the arterial lumen and myocardial necrosis; this rupture initiates the pathophysiologic process of ACS.

Thrombus formation is an integral factor in ACS, from UA to AMI. These syndromes are initiated by endothelial damage and atherosclerotic plaque disruption, which leads to platelet activation and thrombus formation. Platelets play a major role in the thrombotic response to rupture of coronary artery plaque and subsequent ACS. Platelet-rich thrombi

TABLE 64.1 Clinical Characteristics of Classic Anginal Chest Discomfort

Characteristic	More Likely To Be Angina	Less Likely To Be Angina
Type of pain	Dull, pressure	Sharp, stabbing
Duration	2–5 min, often 15–20 min	Seconds or hours
Onset	Gradual	Rapid
Location	Substernal	Lateral chest wall, back
Reproducible	With exertion	With inspiration
Associated symptoms	Present	Absent
Palpation of chest wall	Not painful	Painful, exactly reproduces pain complaint

Adapted from: Zink BJ. Angina and unstable angina. In: Gibler WB, Aufderheide TP, eds. *Emergency Cardiac Care*. St. Louis: Mosby; 1994.

are also more resistant to fibrinolysis than fibrin- and erythrocyte-rich thrombi. The resulting thrombus can occlude the vessel lumen, leading to myocardial ischemia, hypoxia, acidosis, and eventually infarction. The consequences of the occlusion depend on the extent of the thrombotic process, characteristics of the preexisting plaque, the extent of the vessel obstruction, and availability of collateral circulation.

In the setting of UA, acute stenosis of the vessel is usually noted; complete obstruction, however, is encountered in only 20% of cases. In these cases, extensive collateral vessel circulation likely prevents cessation of blood flow, averting frank infarction. With AMI, the occlusive, fibrin-rich thrombus is fixed and persistent, resulting in myonecrosis of the cardiac tissue supplied by the affected artery. Angiographic studies have demonstrated that the preceding coronary plaque lesion is often less than 50% stenotic, indicating that the most critical factors in the infarction are the acute events of plaque rupture, platelet activation, and thrombus formation rather than the severity of the underlying coronary artery stenosis.

Another important aspect of ACS is vasospasm. After significant coronary vessel occlusion, local mediators and vasoactive substances are released, inducing vasospasm, which further compromises blood flow. Central and sympathetic nervous system input increases within minutes of the occlusion, resulting in vasomotor hyperreactivity and coronary vasospasm. Sympathetic stimulation by endogenous hormones, such as epinephrine and serotonin, may also increase platelet aggregation and neutrophil-mediated vasoconstriction. Approximately 10% of MIs occur due to coronary artery spasm and subsequent thrombus formation without significant underlying CAD. This mechanism may be more prevalent during UA and other coronary syndromes that do not result in infarction.

Further myocardial injury occurs at the cellular level as inflammatory, thrombotic, and other debris from the occlusive plaque lesion is released and embolizes into the distal vessel. Such embolization can result in obstruction at the microvasculature, leading to hypoperfusion and ischemia of the distal myocardial tissue, even after reopening of the more proximal, initial obstructing lesion. In particular, the introduction of calcium, oxygen, and cellular elements into ischemic myocardium can lead to irreversible myocardial damage that causes reperfusion injury, prolonged ventricular dysfunction (known as myocardial stunning), or reperfusion dysrhythmias. Neutrophils probably play an essential role in reperfusion injury, occluding capillary lumens, decreasing blood flow, accelerating the inflammatory response, and producing chemoattractants, proteolytic enzymes, and reactive oxygen species.

CLINICAL FEATURES

Clinical features associated with ACS vary based on the patient type, including sex, comorbid conditions, and age considerations. Original studies of ACS focused on men, leading to a narrow description of "typical" chest pain symptoms. Women, patients with diabetes mellitus, and older adults, among other populations, can exhibit differing presentations of ACS. Women may demonstrate less remarkable ACS presentations. Diabetic patients frequently exhibit nontraditional symptoms of ACS, such as dyspnea. Older adults commonly note only extreme weakness, significant mental status abnormalities, or other nonclassic symptoms as the primary manifestation of ACS.

Prehospital Evaluation

Diagnosing ACS in the prehospital setting is difficult because chest pain is a poor predictor of the diagnosis of AMI, and adjunctive diagnostic tools are limited. A prehospital 12-lead ECG offers high specificity (99%) and positive predictive value (93%) for STEMI in patients with atraumatic chest pain while increasing the paramedic scene time by only 1 to 3 minutes; the prehospital ECG significantly reduces the time to hospital-based reperfusion therapy. The EMS diagnosis of STEMI via the prehospital ECG offers many advantages, including the following: (1) earlier detection of STEMI; (2) ability to select patient destination based on the availability of PCI; (3) hospital-based preparation prior to patient arrival; and (4) more rapid initiation of hospital-based reperfusion therapy, either fibrinolysis or PCI.

Emergency Department Evaluation

History

The character of the chest discomfort, as well as the onset, location, and duration should be considered in the evaluation. Associated symptoms, especially of a cardiac, pulmonary, gastrointestinal, or neurologic nature, should be elicited. Results from any prior cardiac testing should be obtained, if logistically and practically possible.

The term *angina* refers to a tightening sensation, not a pain. Angina pectoris may not be pain at all but rather described as a discomfort, with a squeezing, pressure, tightness, fullness, heaviness, or burning sensation. Classically, it is substernal or precordial in location and may radiate to the neck, jaw, shoulders, or either arm; importantly, either shoulder or arm can be involved in this radiation of discomfort. If the discomfort does extend down the arm, it typically involves the ulnar aspect. Discomfort in the left chest and radiation to left-sided structures is usual, but location and radiation to both sides or only to the right side can be consistent with angina. Refer to Table 64.1 for characteristics of angina chest pain.

Symptoms characteristically associated with angina pectoris include dyspnea, nausea, vomiting, diaphoresis, weakness, dizziness, excessive fatigue, or anxiety. If these symptoms arise without chest discomfort, alone or in combination, as a presenting pattern of known ischemic coronary disease, they are termed *anginal equivalent symptoms.* Recognition that coronary ischemia may arise with an anginal equivalent

TABLE 64.2 Key Entities in the Differential Diagnosis of Chest Pain

Acute myocardial infarction	Unstable angina
Stable angina	Prinzmetal angina
Pericarditis	Myocardial or pulmonary contusion
Pneumonia	Pulmonary embolism
Pneumothorax	Pulmonary hypertension
Pleurisy	Aortic dissection
Boerhaave syndrome	Gastroesophageal reflux
Peptic ulcer disease	Gastritis or esophagitis
Esophageal spasm	Mallory-Weiss syndrome
Cholecystitis or biliary colic	Pancreatitis
Herpes zoster	Musculoskeletal pain

rather than a classic symptom is the key to understanding the nontraditional presentation of ACS.

Dyspnea is the most common angina equivalent presentation. Isolated diaphoresis, nausea, emesis, anxiety, and fatigue are very uncommon sole presenting symptoms in ACS. Weakness, dizziness, excessive fatigue, and anxiety may occasionally occur as the single presenting complaint in the ACS patient, especially in the extreme older patient population (Table 64.1).

Complaints of gas, indigestion, or heartburn in the absence of a known history of gastroesophageal reflux disease should raise suspicion of ACS. Additionally, if the heartburn is different from the patient's usual gastroesophageal reflux, or there is a lack of reproducible pain on abdominal palpation, ACS should be considered. These presenting complaints, however, do not indicate ACS in the majority of cases. Nonetheless, gastroesophageal and upper gastrointestinal (GI) maladies are common misdiagnoses in cases of missed AMI.

Although certain features of the chest pain history serve to increase or decrease the likelihood of ACS, none of them is strong enough to establish a diagnosis or endorse discharge of the patient based on the single historical elements alone.

Nontraditional History. A description of typical symptoms may not be present in ACS. This nontraditional presentation may be a result of atypical features of the pain (e.g., character, location, duration, exacerbating and alleviating factors) or the presence of anginal equivalent symptoms (e.g., dyspnea). Patients with an ultimate diagnosis of ACS can have pain that is pleuritic, positional, or reproduced by palpation to a certain extent. Some patients describe their pain as burning or indigestion, sharp, or stabbing. Of course, a single historical point or combination of points does not establish a diagnosis or dictate management strategy. Rather, the emergency clinician evaluating the patient must consider the chief and related complaints as well as the other features of the presentation—in other words, the entire diagnostic picture.

Previous studies have shown that of the ED patients ultimately diagnosed with AMI, one-third did not have chest pain on presentation. Multiple studies have identified risk factors for presentations of ACS that did not feature classic anginal pain, including diabetes mellitus, older age, female sex, nonwhite ethnicity, dementia, no prior history of MI or hypercholesterolemia, no family history of coronary disease, and previous history of congestive heart failure (CHF) or stroke.

Below age 85, chest pain is found in most patients with AMI, although dyspnea, stroke, weakness, and altered mental status are notably present. In those older than 85 years, however, other symptoms are more common than chest pain, with 60% to 70% of patients older than 85 years having an anginal equivalent complaint, especially dyspnea. Coincident ACS is more likely to occur in older adults; patients with another acute condition (e.g., trauma, infection) can experience concurrent coronary ischemia due to the physiologic stress.

Patients with diabetes mellitus are at heightened risk for ACS and presenting with anginal equivalents. Medically unrecognized AMI can occur in 40% of patients with diabetes mellitus compared with 25% of a nondiabetic population, and a myocardial scar unaccompanied by an antemortem diagnosis of MI is three times more likely in people with diabetes. As with age and diabetes, female sex is a significant risk factor for AMI without a classic chest pain presentation. In some series, fewer than 60% of women reported typical chest discomfort at the time of their AMI, with others reporting dyspnea, indigestion, or vague symptoms, such as weakness, unusual fatigue, cold sweats, sleep disturbance, anxiety, and dizziness. Women are more likely to attribute their cardiac symptoms to anxiety, and clinicians are less likely to think their presentations are cardiac in nature, as compared to presentations of male patients.[4]

Finally, nonwhite populations may have underrecognized symptoms in ACS. Compelling data have demonstrated a disparity in treatment approaches related to race and ethnicity in patients with acute manifestations of coronary heart disease. ACS presentations without classic anginal chest pain are associated with worse outcomes due to delayed ACS diagnosis and treatment. If the diagnosis is not suspected, appropriate treatment cannot be started. Patients with an AMI without chest pain had two- to three-fold increased in-hospital mortality compared to patients with chest pain and were more likely to experience stroke, hypotension, or heart failure requiring intervention, possibly reflecting the older age and greater comorbidities. Patients without typical chest pain seek medical care later and are less likely to receive ACS-focused treatment. Patients 65 years of age or younger with NSTEMI have a 1% chance of dying during hospitalization, but this risk is increased to 10% for patients aged 85 years and older. Emergency clinicians should recognize the varied presentations of ACS and consider the diagnosis for all patients presenting with any chest discomfort, shortness of breath, weakness, dizziness, nausea, or vomiting. Although most patients with these symptoms will not have ACS, understanding the variation in presentation is essential to minimizing missed cases and improving outcomes.

Traditionally, a history of risk factors for CAD is sought; these include age, tobacco smoking, hypertension, diabetes mellitus, hyperlipidemia, and family history of AMI at an early age (usually <50 years). Additional risk factors to consider include markedly elevated body mass index, artificial or early menopause, and cocaine (or other sympathomimetic agent) use. In general, the cardiac risk factor burden has a limited impact on the ED evaluation and diagnosis of ACS; these data are important but, by themselves, do not dictate evaluation strategy. In older patients, ACS is significantly more likely if four of the five major risk factors—diabetes mellitus, smoking, hypertension, hyperlipidemia, and family history—are present (compared with none). Nevertheless, Bayesian analysis indicates that risk factors are a population phenomenon and do not increase or decrease the likelihood of any condition in any one individual patient. Thus, the presence of an individual risk factor or collection of risk factors is far less important in diagnosing ACS in the ED when compared to the history of presenting illness, prior diagnosis of ischemic cardiac disease in the patient, presence of ST segment or T wave changes, or cardiac marker abnormalities, or all these clinical features considered as a whole.

Several less-common risk factors for CAD should be considered in appropriate patients. Antiphospholipid syndrome, rheumatoid arthritis, human immunodeficiency virus (HIV), and particularly systemic lupus erythematosus (SLE) are associated with a higher risk of cardiovascular disease. In fact, women with SLE who are 35 to 44 years of

age are more than 50 times more likely to have an MI than a similar age- and sex-matched Framingham population.

Physical Examination of the ACS Patient

The physical examination focuses on the cardiac, pulmonary, abdominal, and neurologic examinations, looking for complications of ACS as well as alternative diagnoses for chest pain (Table 64.2). In general, the physical examination in the ill ACS patient will demonstrate few findings suggestive of ACS; pale appearance, anxiety, and diaphoresis are frequent findings in patients with severe forms of UA and AMI. Bradycardia, tachycardia, hypotension, and pulmonary edema, common in the AMI patient, are manifestations of ACS as complications; these findings also are ominous signs in patients with known or suspected ACS.

Historical studies, using untrained emergency staff (i.e., not emergency physicians), identified reproducible chest wall tenderness in up to 15% of patients ultimately diagnosed with AMI, but these data are of uncertain validity. The real incidence of truly reproducible chest wall tenderness (the patient reliably identifies that the pain on palpation is identical to the pain leading to presentation) in ACS is probably extremely rare. Patients with chest pain that is significantly pleuritic, positional, or reproducible by palpation are at low risk, but not no risk, for ACS.

Early Complications of Acute Myocardial Infarction

Bradydysrhythmia and atrioventricular (AV) conduction blocks occur in 25% to 30% of patients with AMI; sinus bradycardia is usually seen. Symptomatic bradydysrhythmias in the first few hours after inferior STEMI tend to be atropine-responsive; conduction abnormalities that appear beyond 24 hours of AMI tend not to respond to atropine. Patients with AV block in the setting of anterior STEMI tend to respond poorly to therapy and have a poor prognosis.

Tachydysrhythmias are common in the setting of AMI and may be atrial in origin (e.g., sinus tachycardia and atrial fibrillation) or ventricular (e.g., ventricular tachycardia and fibrillation). Not all require treatment, such as a compensatory sinus tachycardia in patients with AMI complicated by CHF (see Chapter 65). Primary ventricular fibrillation occurs in an estimated 4% to 5% of patients with AMI, with 60% of those cases occurring in the first 4 hours and 80% within 12 hours.

Cardiogenic shock is defined as end-organ hypoperfusion resulting from decreased cardiac output unresponsive to restoration of adequate preload. Patients at risk include those with large infarctions, prior MI, low ejection fraction on presentation (<35%), older age, and diabetes mellitus. Adjunctive diagnostic measures include bedside echocardiography and invasive hemodynamic monitoring, with the latter demonstrating systemic hypotension, low cardiac output, elevated filling pressures, and increased systemic vascular resistance. Therapeutic measures include vasopressor and inotropic support, mechanical circulatory support (see Chapter 66), and early revascularization; fibrinolytic therapy does not decrease mortality in cardiogenic shock.

Mechanical complications of AMI occur, including left ventricular free wall rupture, interventricular septum rupture, and papillary muscle rupture (with acute mitral value regurgitation). Over the past 30 years, the occurrence of these catastrophic complications has declined significantly, though when they occur, the outcome is frequently poor.[5]

Left ventricular free wall rupture is uncommon. Approximately one-third of cases occur in the first 24 hours, and the remainder occur 3 to 5 days after large MIs, typically anterior wall STEMIs. Clinically, free wall rupture presents with sudden death, pulseless electrical activity, or precipitous hemodynamic deterioration in the presence of acute or very recent STEMI. Signs of pericardial effusion on the ECG or echocardiogram are suggestive of the diagnosis in this setting. This diagnosis is difficult to establish. Free wall rupture is almost universally fatal, although prompt diagnosis followed by emergent surgical intervention may rarely be lifesaving.

Rupture of the interventricular septum or papillary muscle with acute mitral value regurgitation may also occur. These ruptures also most commonly occur 3 to 5 days after large MIs. Both are characterized by a new loud holosystolic murmur heard best at the left lower sternal border and flash pulmonary edema with hemodynamic collapse. The diagnoses can be confirmed by echocardiography with color flow Doppler imaging. The presentation of acute catastrophic deterioration with a new loud systolic murmur should prompt immediate cardiac surgery consultation for repair of a septal defect or ruptured papillary muscle of the mitral valve. Medical therapy, including vasopressor and inotropic support, as well as intraaortic balloon counterpulsation, are essential bridges to the definitive surgical treatment. As with free wall rupture, these diagnoses are difficult to establish.

Pericarditis, when associated with AMI, can occur early or in a delayed fashion; the former is termed *infarct-related pericarditis,* and the latter is known as post-MI or Dressler syndrome. Infarct-related, or infarct, pericarditis is associated with transmural insult and thus principally involves the pinnacle of the infarct zone near the epicardium. Although the characteristic ST segment changes may be obscured by ST segment abnormalities related to the infarction itself, they are localized if they are evident. Infarct pericarditis is a common cause of new chest pain in the first week after MI. This pain is characteristically pleuritic and worse in the supine position, likely quite different from the chest discomfort experienced resulting from the AMI. Embolic complications are more common in patients with infarct pericarditis, possibly because this population also has a higher rate of ventricular aneurysm development than other patients with AMI.

Dressler syndrome, unlike infarct pericarditis, does not require transmural involvement. It is a relatively uncommon late complication occurring from 1 week to several months after MI. Clinical features include fever, malaise, pleuro-pericardial pain, and, at times, the presence of a rub on cardiac auscultation. Laboratory findings are highly nonspecific and include an elevated erythrocyte sedimentation rate and leukocyte count. The ECG may show ST segment–T wave findings of pericarditis although, as with infarct pericarditis, these changes may be overshadowed by the evolving changes of the recent MI. PR segment depression is a telltale clue. Pericardial or pleural effusions may be evident and can be serous or bloody. Echocardiography assesses pericardial fluid and risk of tamponade. The pericardial reaction is believed to be immune-mediated; treatment includes antiinflammatory agents.

Stroke may also complicate AMI, usually ischemic or thromboembolic. The major predisposing mechanisms with a recent MI are embolization from a left ventricular mural thrombus with decreased ejection fraction, embolization from the left atrial appendage with atrial fibrillation, and hypercoagulability with concomitant carotid arterial disease. It is known that the rate of stroke is higher in the setting of MI (approximately 1.0%, declining to 0.1% at day 28 after MI) than in similar non-AMI patients (approximately 0.01%).

Hemorrhagic stroke is a risk for the patient undergoing fibrinolytic therapy. The rate of hemorrhagic stroke with varying fibrinolytic agents is less than 1%; the rate is marginally higher in older patients. PCI lowers the overall risk of stroke compared with fibrinolytic therapy. The overall difference in stroke rate was highly significant in one large study, at 1.6% in the fibrinolytic group vs. 0.7% in the PCI group, and was 1.0% in the fibrinolytic group versus 0.1% in the PCI group for hemorrhagic strokes.

Adverse events of ACS therapy should also be considered as potential complications. The various antiplatelet, anticoagulant, and fibrinolytic therapies (as noted earlier) are all associated with hemorrhage as

a major complicating issue. Within a single class of medications, many of these agents are so similar in efficacy that superiority is determined by the rate of adverse effects, largely hemorrhagic in nature. The rate of adverse events with anticoagulant-antiplatelet medications is the most important factor for agent selection.

Procedural complications include arterial injury with hemorrhage related to percutaneous interventions; the most typical is a pseudoaneurysm of the femoral artery with hemorrhage into the thigh compartment or retroperitoneal area. The diagnosis is made based on pain, swelling, or ecchymosis in a patient with recent femoral artery cannulization. Physical examination findings, including extensive bruising in the thigh and bruits over the femoral artery, are suggestive; ultrasonography or CT of the thigh and retroperitoneal area can confirm the diagnosis.

DIFFERENTIAL DIAGNOSES

The differential diagnosis of ACS is broad and includes both life-threatening diagnoses as well as relatively benign conditions. When evaluating a patient for nontraumatic chest pain, strong diagnostic consideration should be given to other potentially life-threatening conditions such as pulmonary embolism, aortic dissection, aortic aneurysm with perforation, pneumothorax, esophageal perforation, myopericarditis, myocarditis, and pneumonia. Non–life-threatening causes are numerous and include costochondritis, musculoskeletal chest pain, herpes zoster infection, and various gastrointestinal maladies; although these entities are usually non–life-threatening, significant morbidity can occur (see Table 64.2).

DIAGNOSTIC TESTING

Electrocardiography

In the patient with chest discomfort or other symptoms suggestive of ACS, the 12-lead ECG can assist in many critical applications, including establishing the diagnosis, determining candidacy for various therapies, and performing risk assessment. In the setting of STEMI, the ECG is diagnostic.

Per the Fourth Universal Definition of Myocardial Infarction, ECG findings consistent with STEMI include new ST elevation of greater than 1 mm in at least two contiguous leads except for leads V2 and V3, where diagnostic cut-offs are as follows: elevation 1.5 mm or greater in females of any age, 2.5 mm or greater in males less than 40 years of age, and 2 mm or greater in males greater than 40 years of age.[3] Furthermore, the ECG provides pivotal information regarding therapeutic intervention; ST segment elevation establishes candidacy for emergent reperfusion therapy, via PCI or fibrinolysis.

Regarding risk assessment, several electrocardiographic findings, such as total ST segment deviation, LBBB, left ventricular hypertrophy (LVH), and QT interval prolongation, may indicate an increased cardiovascular risk. Other 12-lead ECG determinations include cardiac rhythm, the evolution of the ACS event, response to therapy, and clinical information suggesting an alternative diagnosis. Rhythm determination is essential, particularly if a compromising dysrhythmia is present. Finally, an alternative diagnosis, such as pulmonary embolism (PE) or acute myopericarditis, can be suggested by the ECG.

In ACS, morphologic changes may occur in the T wave, ST segment, and QRS complex; the PR segment can also demonstrate abnormalities (e.g., PR segment depression in atrial infarction or infarct-related pericarditis), yet the current clinical use of this information remains uncertain. The diagnostic abilities of the ECG are further limited by individual variations in coronary anatomy and preexisting coronary disease (e.g., previous MI, LBBB, collateral circulation, coronary bypass surgery) and because it does not view the posterior, lateral, and apical left ventricular walls well. The ECG may be normal or nonspecifically abnormal in the presence of an early ACS event, including AMI. Importantly, a single ECG in isolation is neither 100% sensitive nor 100% specific for AMI and reflects a single point in time of cardiac electrical imaging.

A normal or nonspecifically abnormal ECG in a currently asymptomatic patient with history of intermittent anginal chest pain can be misleading and should not be overemphasized. Patients with an initial nondiagnostic ECG who later develop AMI during hospitalization are often pain-free or minimally uncomfortable on initial ED presentation. The elapsed time from symptom onset to the normal ECGs does not necessarily rule out an AMI. Although the negative predictive value is high, it is not 100%, even up to 12 hours after the onset of the patient's chest symptoms. The patient's reported history, and the emergency clinician's interpretation of that history, remains the most important diagnostic study, and the ECG should be interpreted in this context.

Electrocardiographic Abnormalities in Acute Coronary Syndromes

The earliest electrocardiographic finding in STEMI is the hyperacute T wave (Fig. 64.1), a tall and peaked structure that can appear within minutes of the interruption of blood flow and initiation of acute infarction. It is usually broad-based and asymmetrical in structure; the ST segment can be elevated at the J (or junction between the QRS complex and ST segment) point. The hyperacute T wave progresses to ST segment elevation in typical STEMI. This hyperacuity may not be appreciated on the initial ECG in that the finding occurs early in the course of acute infarction and is transient with rapid progression to obvious ST segment elevation. In addition to the hyperacute T waves of acute ischemia, the differential diagnosis of the tall T wave also includes hyperkalemia, benign early repolarization (BER), LVH, LBBB, and acute pericarditis.

As the STEMI progresses, ST segment elevation may become evident, allowing for the more definitive diagnosis. Morphologic variations of ST segment elevation (Fig. 64.2) can be seen from the J point at the end of the QRS complex to the apex of the T wave. This upsloping portion of the ST segment usually progresses as it elevates from flat to convex, domed, or "tombstoned"; if flat, it is characteristically horizontal or oblique. At times, the ST segment may be concave or scooped in its elevation with STEMI. This morphology may progress to a convex shape or may stay the same throughout the infarction. The concave morphology, if noted in all elevated ST segments, is atypical for STEMI and is more commonly seen with other ST segment elevation syndromes. ST segment elevation is measured in millimeters; one block on the electrocardiographic tracing is equivalent to 1 mm in height. The baseline is usually considered to be the TP segment, although some advocate use of the terminal point of the PR segment. In general, the most definable, constant baseline evident on the ECG should be used.

ST segment elevation, benign and pathologic, is a common finding on the ECG in adults with chest pain (Table 64.3). Some degree of ST segment elevation is common, especially in young males, where it is present upwards of 90% of the time. Commonly referred to as "benign early repolarization" (BER), this elevation is seen in the precordial leads and is usually 1 mm or more in men and 1 mm or less in women. The ST segment elevation of BER is concave and is more prominent as the corresponding S wave (or negative deflection of the QRS complex) becomes deeper. Because of prevalence of this finding, it is not a normal variant but rather a normal finding. A helpful point in differentiating normal ST segment elevation from the pathologic ST segment elevation of STEMI is that the latter is a dynamic phenomenon. ECGs recorded sequentially over time, with waxing and waning symptoms,

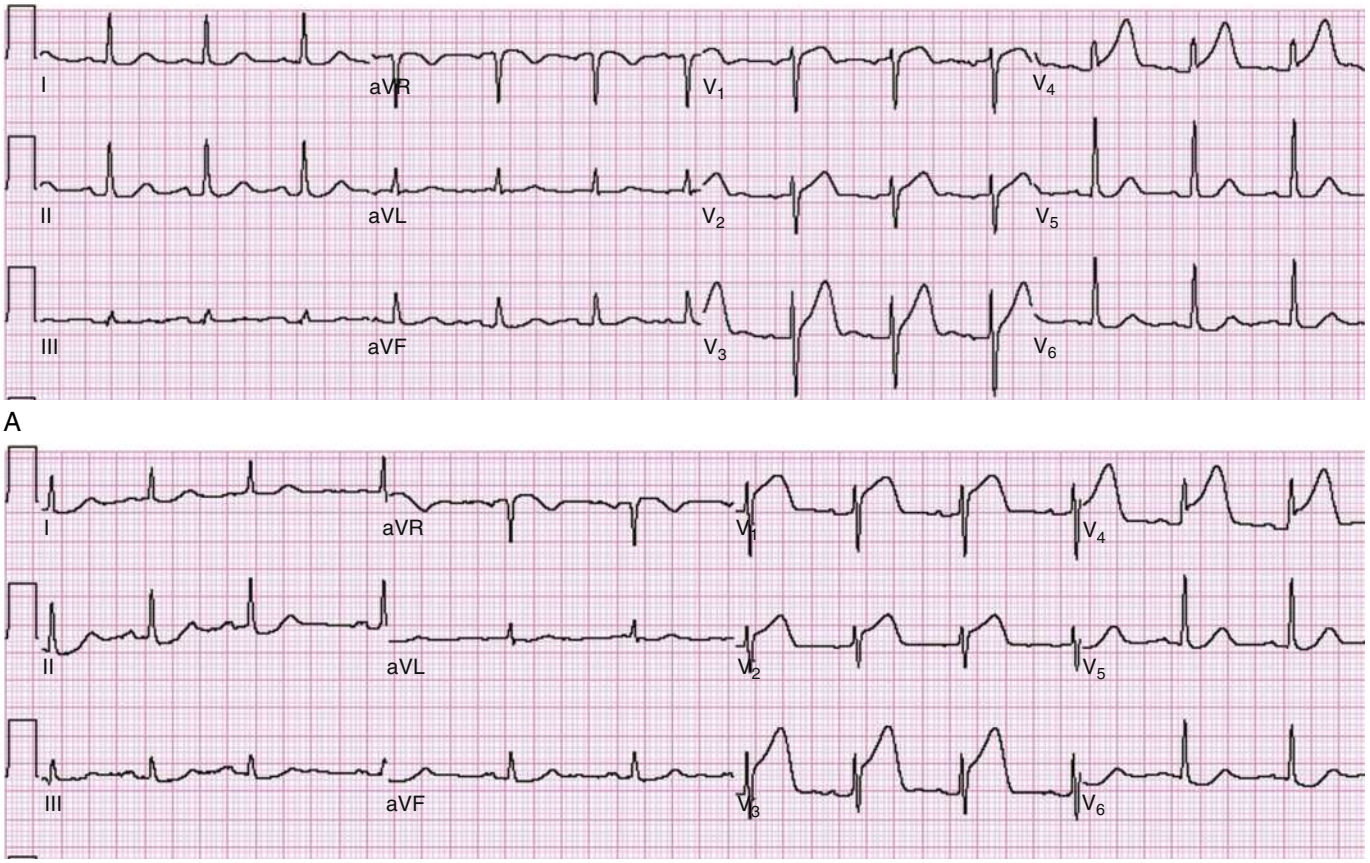


Fig. 64.1 Hyperacute T wave of acute myocardial infarction. (A) Note the broad, tall T waves in leads V_3 and V_4 in this patient with chest pain and diaphoresis. These are the hyperacute T waves of early ST segment elevation myocardial infarction. The ST segment is just beginning to rise in leads V_3 and V_4; leads V_1 and V_2 are also suspicious. (B) This tracing is from the same patient taken about 30 minutes after the electrocardiogram in A. Note the prominent ST segment elevation in leads V_1 to V_4.

should demonstrate some fluctuation in the degree of ST segment deviation in the presence of ACS.

ST segment depression generally represents subendocardial ischemia in ED patients presenting with chest pain or anginal equivalent. Ischemic ST segment depression is typically horizontal or downsloping; an upsloping contour may be seen but is less frequently associated with ischemia. Subendocardial ischemic ST segment depression may be diffuse, spanning anterior and inferior leads. This finding can be seen in unstable angina or NSTEMI; the distinction is made considering the clinical presentation and the results of serial serum markers. Additionally, the standard 12-lead ECG will demonstrate ST segment depression in the right to mid precordial leads when transmural posterior wall infarction occurs. The differential diagnosis of ST segment depression includes myocardial ischemia or infarction, repolarization abnormality of left ventricular hypertrophy (the so-called strain pattern), bundle branch block, ventricular paced rhythm (VPR), digoxin effect, hyperkalemia, hypokalemia, PE, intracranial hemorrhage, myocarditis, rate-related ST segment depression, postcardioversion of tachydysrhythmias, and pneumothorax (Fig. 64.3).

ST segment depression in ACS (1) may be seen in NSTEMI, (2) may precede ST segment elevation in STEMI, (3) may reflect a mirror image of ST segment elevation from posterior MI when found in the right- to mid-precordial leads (i.e., ST segment depression in V_1 to V_3 in posterior MI), and (4) may represent reciprocal ST segment depression seen with STEMI. With reciprocal ST segment depression, such changes are seen in leads on the opposite side of the heart from simultaneous ST segment elevation. For example, the ST segment depression seen in leads V_1 to V_3 seen in posterior MI actually represents reciprocal change resulting from the ST segment elevation that would be recorded in posterior leads V_8 and V_9. An inferior MI with ST segment elevation more frequently manifests reciprocal ST segment depression than does anterior STEMI. The reciprocal ST segment depression in inferior MI is best seen in lead aVL, which is 150 degrees removed from lead III when the positive poles of these leads in the frontal plane are considered. Anterior STEMI may feature reciprocal ST segment depression in one or more inferior leads (II, III, or aVF). Reciprocal changes in the setting of STEMI increase the specificity and positive predictive value of the ECG in AMI and coincide with larger infarction, greater chance of cardiovascular adverse events, and more frequent death. Fig. 64.3 depicts the various forms of ST segment depression.

T wave inversions, although nonspecific, may be suggestive of chronic ischemic change or ACS in the appropriate clinical context. Normally, the T wave is upright in the left-sided leads (I, II, and V_3 to V_6) and inverted in the right-sided lead, aVR. T wave vectors are variable in leads III, aVL, and aVF. They are normally inverted in V_1 and may also be normally inverted in lead V_2. The T wave inversions of ACS are classically narrow and symmetrical (Fig. 64.4). The preceding ST segment is typically isoelectric and may be bowed slightly upward or concave. Associated ST segment depression may occur. T wave

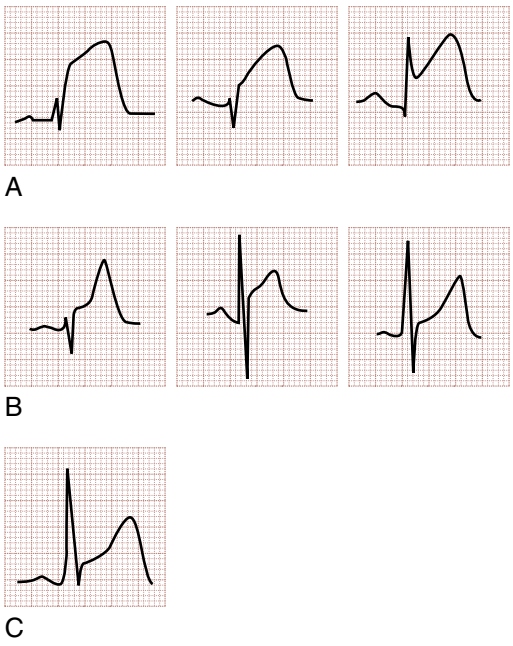


Fig. 64.2 Analysis of ST segment–T wave morphology in acute myocardial infarction (AMI), benign early repolarization (BER), and acute pericarditis. An analysis of the ST segment–T wave morphology (from the beginning at the J point to the end at the apex of the T wave) may be particularly helpful in distinguishing among the various causes of ST segment elevation (STE) and identifying the STE case. (A) The initial upsloping portion of the ST segment is usually flat (horizontally or obliquely) or convex in the patient with STEMI. This morphologic observation, however, should be used only as a guideline; it is not infallible. (B) Non-AMI causes of STE are seen here with concavity of the ST segment–T wave (*left,* BER; *middle,* pericarditis; *right,* BER). (C) Patients with STE related to STEMI may demonstrate concavity of this portion of the waveform. Serial ECGs may assist in discerning whether the presence of STE is pathologic.

TABLE 64.3 Differential Diagnosis of Electrocardiographic ST Segment Elevation in the Adult Chest Pain Patient

Acute myocardial infarction	Acute pericarditis
Left ventricular hypertrophy	Left ventricular aneurysm
Ventricular paced rhythm	Benign early repolarization
Normal variant	Osborn wave of hypothermia
Hyperkalemia	Brugada syndrome
Pulmonary embolism	Acute cerebral hemorrhage
Prinzmetal angina	Postelectrical cardioversion

inversions are best evaluated in comparison with the most recent prior ECG, given the multitude of normal variations.

A notable subgroup of ischemic T wave inversions is associated with Wellens syndrome: deep symmetrical T wave inversions (type I) or biphasic T wave changes (type II) in the anterior precordial suggestive of myocardial ischemia (Fig. 64.5). Other electrocardiographic features include isoelectric or minimally elevated (<1 mm) ST segments and lack of precordial Q waves. This finding may manifest in the anginal or pain-free state and may or may not be accompanied by cardiac marker elevations. Wellens syndrome is indicative of a lesion of the left anterior descending artery and the natural history of this presentation is progression to anterior wall STEMI.

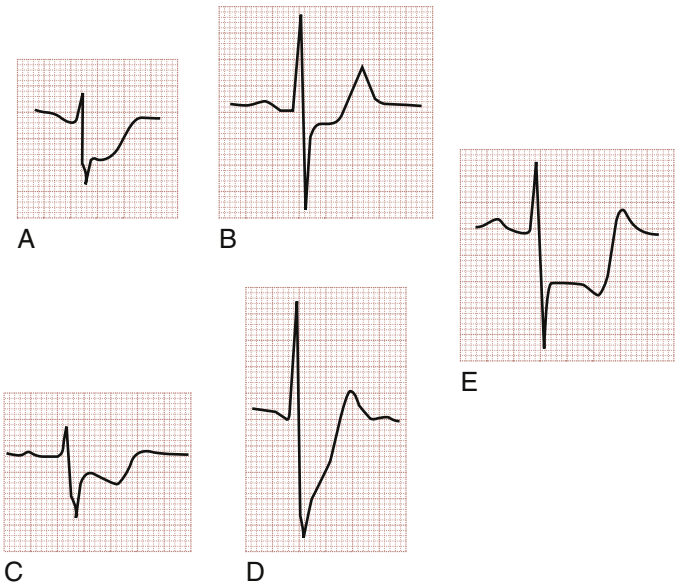


Fig. 64.3 ST segment depression (STD) in acute coronary syndrome. (A) Horizontal STD unstable angina pectoris (USAP). (B) Horizontal STD (non–ST segment elevation [STE] acute myocardial infarction). (C) Downsloping STD (USAP). (D) Upsloping STD (USAP). (E) Horizontal STD as seen in lead III in a patient with anterior wall acute myocardial infarction, an example of reciprocal STD, also known as reciprocal change.

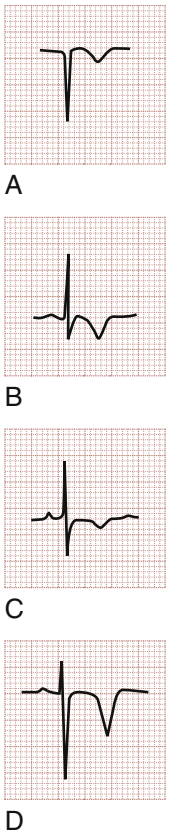


Fig. 64.4 T wave inversions of acute coronary syndrome (ACS). (A & B) T wave inversions in patients with ACS. (C) T wave inversion in a patient with non–ST segment elevation (STE) acute myocardial infarction. (D) Deeply inverted T waves in a patient with proximal left anterior descending artery stenosis—Wellens syndrome.

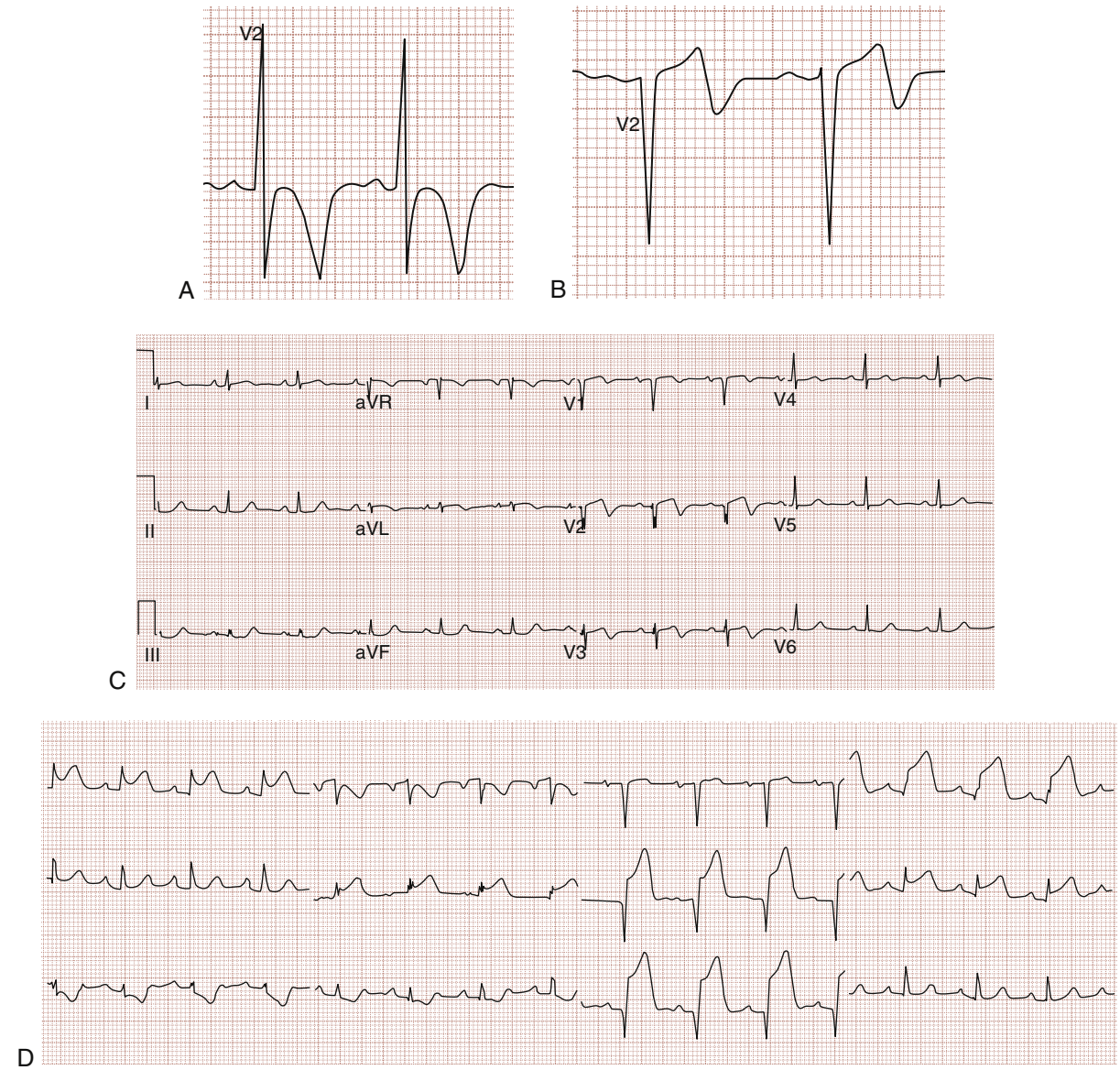


Fig. 64.5 Wellens syndrome. (A) Deeply inverted T waves seen in 75% of patients presenting with Wellens syndrome. (B) Biphasic T waves seen in 25% of patients presenting with Wellens syndrome. (C) Middle-aged male presenting with recent chest pain who is currently painfree; ECG demonstrates biphasic T waves in leads V_2 and V_3. (D) ECG in patient from "C" obtained 6 hours later with return of chest pain. Note the extensive anterolateral STEMI with STE in leads I, aVL, and V_2 to V_5. Emergency PCI was performed with stenting of a proximal LAD occlusion.

Although T wave inversion is sought as a harbinger of ACS, it can also occur as an evolutionary change after MI. In MI without culprit artery reperfusion, the T waves may invert as the ST segments return to baseline, although not particularly deeply. Following reperfusion, T wave inversion may follow ST segment elevation in a biphasic or deeply inverted morphology, an appearance much like the T wave changes of Wellens syndrome. The differential diagnosis of T wave inversion is broad and includes ACS, ventricular hypertrophy, bundle branch block, VPR, myocarditis, pericarditis, PE, pneumothorax, Wolff-Parkinson-White syndrome, cerebrovascular accident, hypokalemia, GI disorders, hyperventilation, persistent juvenile T wave pattern, and normal variants.

The emergency clinician must also consider pseudonormalization of the T wave as a potential electrocardiographic indicator of ACS. Pseudonormalization is the ECG finding of an apparently normal-appearing T wave on the ECG replacing a previously inverted T wave during an acute episode of chest discomfort or anginal equivalent. This "normal" appearing T wave may herald acute ischemia.

Q waves are generally representative of irreversible myocardial necrosis but are rarely the sole manifestation of AMI. Pathologic Q waves may emerge within the first hour of infarction but most commonly develop at 8 to 12 hours. It follows that ST segment elevation with concomitant Q waves does not preclude consideration of emergent reperfusion therapy; the patient's history is vital in considering the time of onset of continuous chest discomfort. Q waves may persist after MI as enduring markers of previous infarction on the ECG but may also disappear with time, regardless of whether the infarcted territory was reperfused.

Anatomic Location of Acute Myocardial Infarction

The regional distribution of an AMI can be derived from noting the pattern of the various morphologic changes that are described (Table 64.4).

Anterior infarctions are primarily evidenced by changes in the precordial leads V_1 to V_4 (Fig. 64.6). Septal involvement is reflected by changes in V_1 and V_2. Extension to the lateral wall (i.e., anterolateral MI) is evident if the pathologic changes extend beyond leads V_1 to V_4 to include leads V_5, V_6, I, and aVL (Fig. 64.7). In anterior STEMI, reciprocal ST segment depression may occur in leads III and aVF. The anterior wall is served by the left anterior descending artery. The first diagonal branch of the left anterior descending artery is likely to be involved when the ST segment elevation extends to leads I and aVL. Isolated occlusion of the diagonal branch of the left anterior descending artery displays similar findings, but of smaller amplitude, as those seen with left anterior descending artery occlusion (ST segment elevation in leads V_2 and V_3, and possibly leads V_1 and V_3, or both, along with ST segment depression in lead II and III, aVF, or both). Anterior or anterolateral STEMI resulting from left main coronary artery occlusion is a high-risk presentation; the ability to identify this high-risk

TABLE 64.4 Regional ST Segment Changes in Acute Myocardial Infarction (AMI)

Location	Leads	ST Segment
Anterior wall STEMI	V_1–V_4	Elevation
Lateral wall STEMI	I, aVL, V_5, V_6	Elevation
Inferior wall STEMI	II, III, aVF	Elevation
Right ventricular wall AMI	V_4R	Elevation
Posterior wall AMI	V_8, V_9 V_1–V_3	Elevation Depression

STEMI, ST segment elevation myocardial infarction.
Adapted from: Aufderheide TP, Brady WJ. Electrocardiography in the patient with myocardial ischemia or infarction. In: Gibler WB, Aufderheide TP, eds. *Emergency Cardiac Care*. St. Louis: Mosby; 1994.

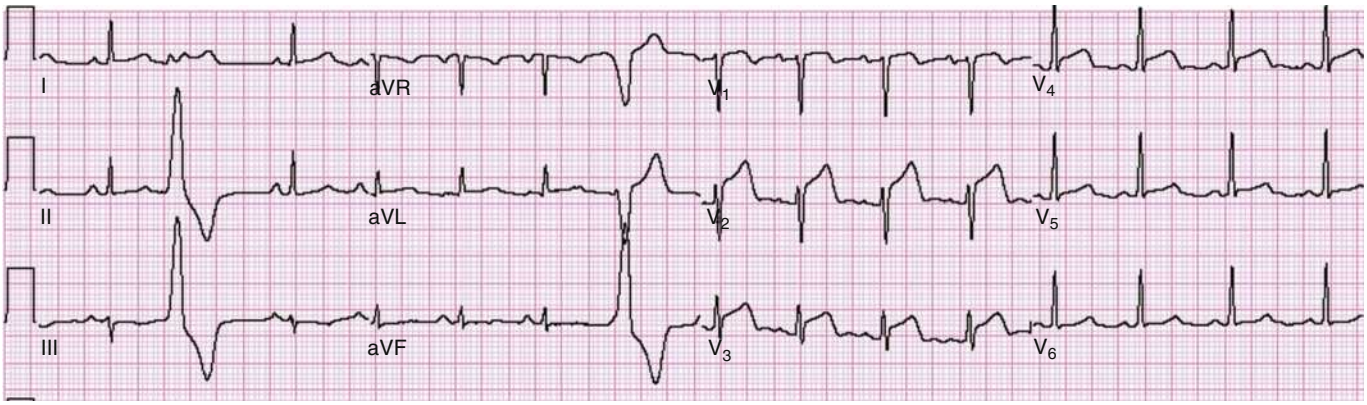


Fig. 64.6 Anterior wall acute ST segment elevation myocardial infarction (STEMI). ST segment elevation is evident in leads V_1 to V_4. The morphology seems obliquely straight. Emergency cardiac catheterization revealed a 90% stenotic lesion in the left anterior descending artery; the patient did well after placement of a coronary stent but showed serum marker evidence of acute myocardial infarction (AMI).

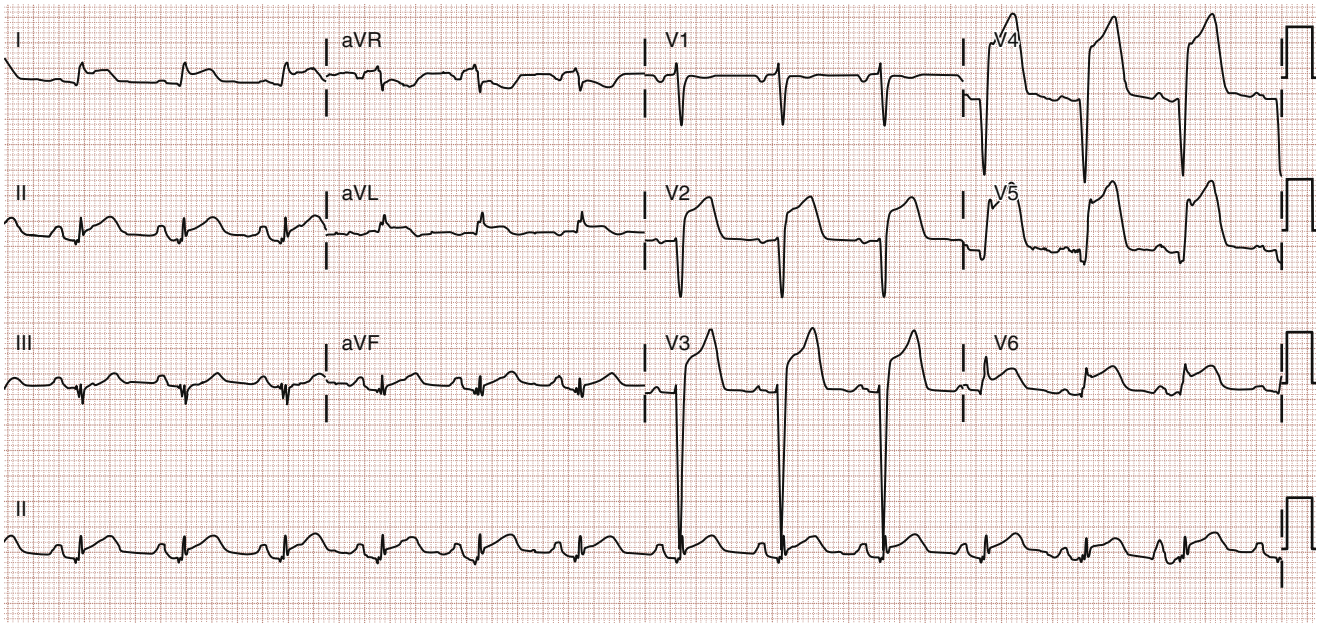


Fig. 64.7 Anterolateral ST segment elevation myocardial infarction (STEMI) with STE in leads V_2 to V_6, I, and aVL. The patient had previously undergone PCI with placement of an LAD stent 2 years prior. Emergency catheterization was undertaken and revealed a 100% in-stent thrombosis.

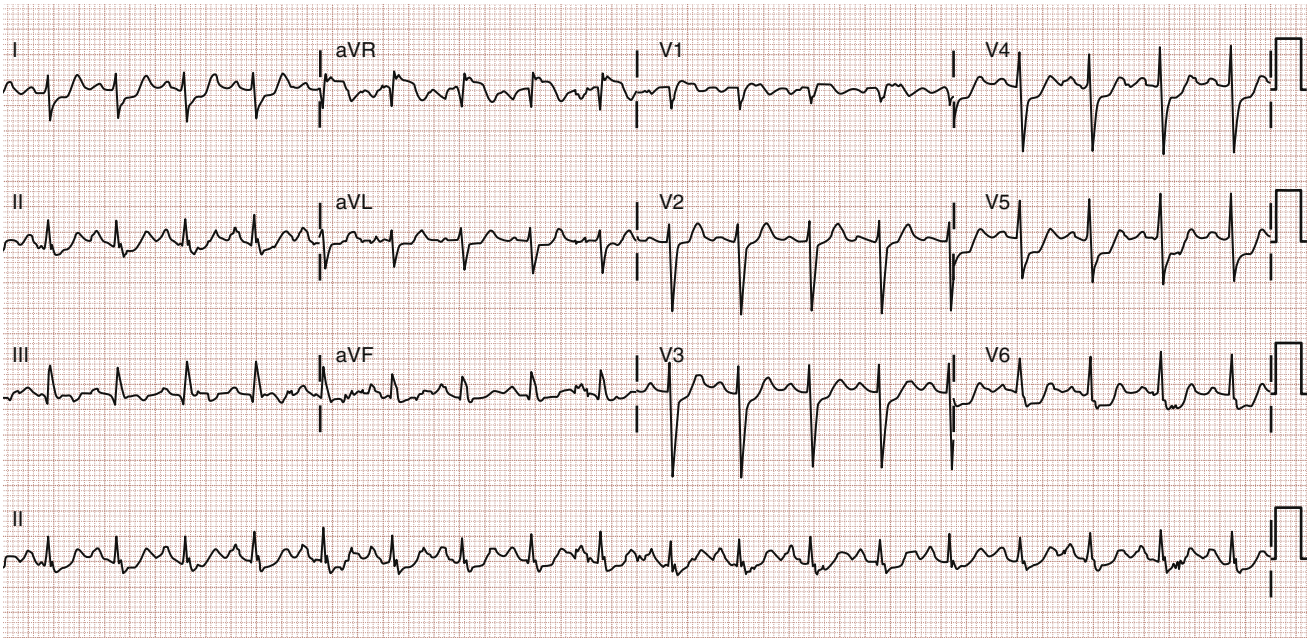


Fig. 64.8 ST segment elevation in lead aVR in a patient with history concerning for ACS. STE of greater than 1 mV is present in aVR. Widespread ST depression is also noted elsewhere on the ECG. The patient underwent catherization and was found to have an 80% stenotic lesion of the left main coronary artery.

STEMI subtype further enables the emergency clinician to adjust therapy appropriately.

In a patient with ACS symptoms, ST segment elevation in lead aVR should prompt consideration of occlusion of the left main coronary artery (Fig. 64.8). Data have demonstrated that ST segment elevation in lead aVR (>0.5 mV) is approximately 78% sensitive and 83% specific for left main coronary artery disease. Alternatively, this finding in lead aVR may represent multivessel disease, acute proximal left anterior descending occlusion, or, less commonly, left circumflex or right coronary occlusion. Similar findings may also be indicative of diffuse endocardial ischemia due to hypoperfusion. If ST segment elevation occurs in leads aVR and V_1, greater elevation in the former lead favors left main disease, whereas if it is greater in the latter lead, occlusion in the left anterior descending artery is more likely.

The so-called de Winter ECG pattern represents another presentation suggestive of ACS. The electrocardiographic findings associated with this presentation include prominent T waves with J point depression producing ST segment depression seen in the precordial leads, coupled with ST segment elevation in lead aVR (Fig. 64.9). Like Wellens syndrome, this presentation is associated with proximal left anterior descending artery lesions. These patients are usually ill-appearing with ongoing chest discomfort. ECG findings may progress to classic anterior STEMI, however lack of progression has also been associated with significant left anterior descending occlusion and subsequent large myocardial infarction. As such, some have advocated treatment of the de Winter syndrome as a so-called STEMI-equivalent.[6]

Lateral infarctions are frequently seen in concert with anterior infarction (anterolateral), inferior infarctions (inferolateral), or inferior infarctions with posterior extension (inferoposterolateral). This is because the lateral wall of the heart is variably served by the left anterior descending, right coronary, and left circumflex coronary arteries. Thus, lateral involvement is manifested by changes in some or all of the lateral leads I, aVL, V_5, and V_6 (Fig. 64.10). "High lateral" infarctions are manifest by ST elevation in leads I and aVL and suggest occlusion of the left circumflex coronary artery or first diagonal. The associated

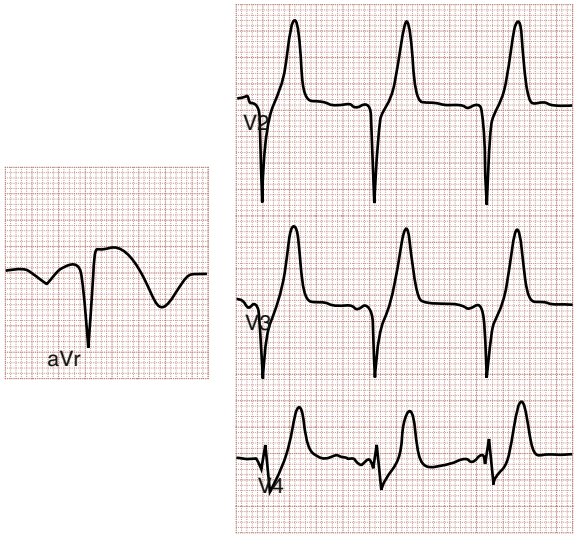


Fig. 64.9 The de Winter electrocardiographic finding, a pattern associated with proximal left anterior descending coronary artery obstruction. In the anterior leads, ST segment depression with depression of the J point is noted along with prominent, hyperacute T wave. In addition, ST segment elevation is also seen in lead aVR.

ECG findings may be subtle and potentially easy to overlook because leads I and aVL are not directly adjacent in the standard 12-lead format. ST segment elevation in these leads may also be accompanied by reciprocal ST segment depression in leads III, aVF, and V_1 (Fig. 64.11).

Inferior infarctions are characterized by morphologic changes in limb leads II, III, and aVF. The inferior wall of the heart and AV node are served by the right coronary artery in about 90% of cases (right dominant); in the remainder, the left circumflex artery serves that function (left dominant). An inferior STEMI is present if two or more contiguous inferior leads (II, III, aVF) are involved; reciprocal

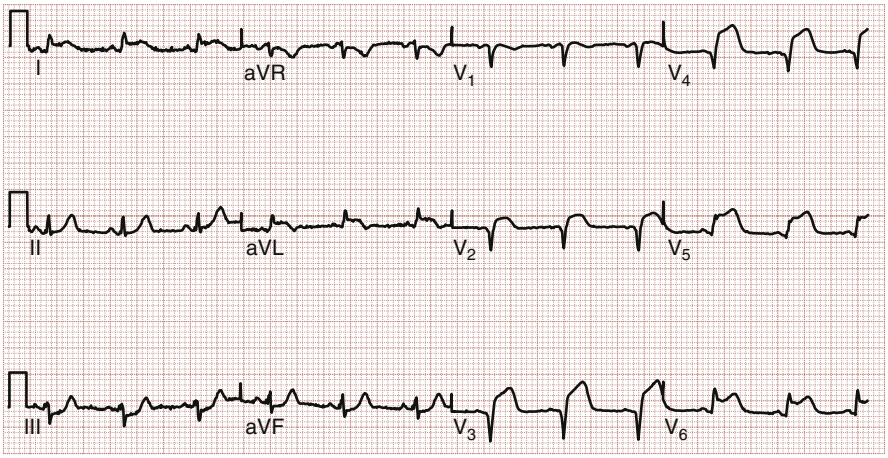


Fig. 64.10 Anterolateral ST segment elevation myocardial infarction. ST segment elevation is seen in leads V_1 to V_4 (anterior leads) and in leads I, aVL, V_5, and V_6 (lateral leads). A proximal left anterior descending artery lesion with thrombus was noted at emergent percutaneous coronary intervention.

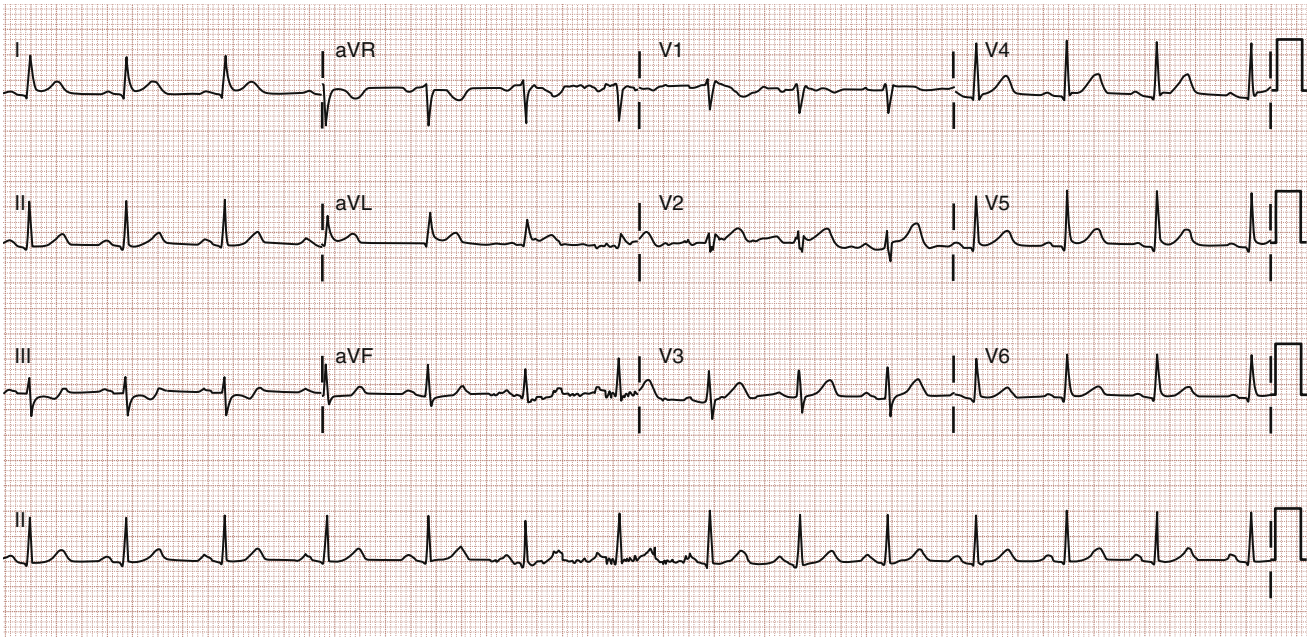


Fig. 64.11 High lateral acute myocardial infarction. ST elevation in leads I and aVL may be indicative of obstruction of the left circumflex, or first diagonal (D1). Findings may be accompanied by reciprocal ST depression in leads III, aVF and V_1. ST elevation in lead V_2 may also be appreciated, as seen here. This patient was taken for emergent catheterization and found to have a 90% stenotic lesion at the bifurcation of the LAD and D1 which was successfully treated with PCI.

ST segment depression is frequently seen in lead aVL, lead I, or both (Fig. 64.12), and perhaps in the anterior precordial leads, V_1 less than V_2 and V_3. ST segment depression in leads V_1 to V_3 in the presence of an inferior MI can be caused by reciprocal change, posterior extension, or simultaneous anterior ischemia during inferior infarction. ST segment elevation inferiorly that is greater in lead III than in lead II, accompanied by ST segment depression in lead aVL, I, or both, is 90% sensitive and 71% specific for right coronary artery occlusion. ST segment elevation in lead V_1 in the presence of an ST segment elevation inferior MI (with elevation greater in lead III than in lead II) suggests concomitant right ventricular infarction. Coexistent reciprocal change with inferior STEMI is associated with larger infarct size and increased mortality. Occlusion of the left circumflex artery may be occult on the 12-lead ECG. If it is responsible for inferior ST segment elevation, the ST segment elevation in lead III would not be expected to exceed that seen in lead II, and lead aVL may display an isoelectric or elevated ST segment.

Posterior infarctions are estimated to contribute to 15% to 20% of all AMIs and usually are seen with inferior or inferolateral infarctions. Posterior infarctions occur in isolation in approximately 5% of AMI cases (demonstrating elevated ST segments only in accessory leads, posterior leads V7 through V9). The culprit lesion may be in the right coronary artery, its posterior descending branch, or left circumflex artery. Because the 12-lead ECG features no electrodes placed directly over the heart's posterior wall, one has only the reciprocal ST segment changes in the right precordial leads (V_1 to V_3) with which to infer AMI of the posterior wall. Findings seen in leads V_1 to V_3 suggestive of acute posterior myocardial infarction include the following:

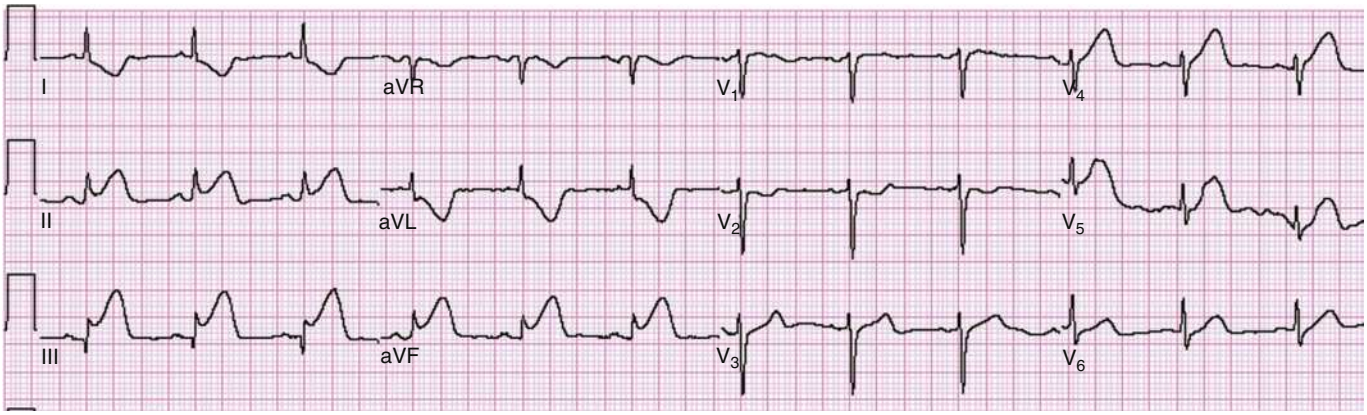


Fig. 64.12 Inferior acute myocardial infarction with reciprocal changes. Marked ST segment elevation is seen inferiorly (leads II, III, and aVF). Classic reciprocal ST segment depression is evident in leads I and aVL.

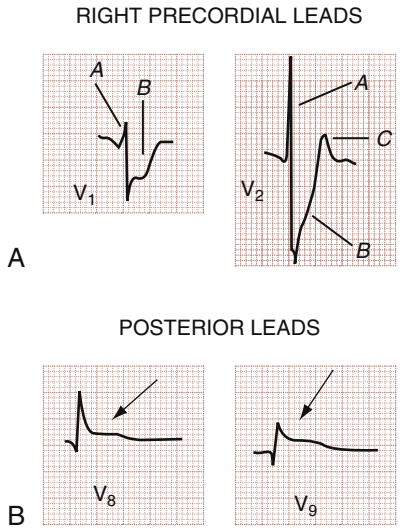


Fig. 64.13 ECG findings of acute posterior wall myocardial infarction. (A) Leads V_1 and V_2, which indirectly image the posterior wall of the left ventricle, demonstrate prominent R waves, ST segment depression (horizontal in lead V_1), and upright T wave (in lead V_2), findings consistent with acute posterior wall myocardial infarction. (B) Additional ECG leads (posterior leads) V_8 and V_9, which directly image the posterior wall, with subtle ST segment elevation, consistent with acute posterior wall myocardial infarction.

(1) horizontal ST segment depression; (2) an upright T wave; (3) tall, wide R wave; and (4) R wave amplitude–to–S wave amplitude ratio greater than 1 (Fig. 64.13). The combination of horizontal ST segment depression with an upright T wave increases the diagnostic accuracy of the 12-lead ECG for acute posterior MI. Furthermore, in that the tall R wave in the right precordial leads is actually the mirror image of a posterior Q wave, its emergence may be delayed in posterior infarction. Additional leads (posterior leads V_8 and V_9) may increase the sensitivity for detection of acute posterior MI. Patients with inferior MI who have ST segment depression in leads V_1 to V_3 or ST segment elevation in the posterior leads V_8 and V_9 generally have larger infarction zones, lower resultant ejection fractions, and higher rates of cardiovascular morbidity and mortality than patients with isolated inferior MI. Cardiac MRI suggests that these so-called posterior infarctions producing tall R waves in leads V_1 and V_2 are actually lateral left ventricular wall MIs. A consensus document has suggested reclassifying posterior infarctions as inferobasal MIs.[3]

Right ventricular infarctions rarely occur in isolation and are usually associated with inferior or inferoposterior MI, although only about one-third of inferior infarctions have associated infarction of the right ventricle. At times, an anterior MI involves some (but <50%) of the right ventricular wall. It follows that occlusion in any of the major coronary arteries may lead to right ventricular infarction, although the right coronary is most commonly involved. Clinically, right ventricular infarction features include elevated jugular venous pressure and hypotension in the setting of inferior wall MI. These findings, however, may also be suggestive of pericardial tamponade. Nitrate-induced hypotension may also be suggestive of right ventricular infarction or tamponade. Bedside cardiac ultrasound can distinguish between these two entities easily with the presence or absence of a pericardial effusion. Initial therapy for both would include volume loading and avoidance of vasodilators or other agents that may lower the blood pressure.

ST segment elevation in lead V_1 in the setting of inferior STEMI (i.e., ST segment elevation in leads II, III, and aVF rather than concomitant ST segment elevation in all anterior precordial leads) is suggestive of right ventricular infarction. This is not surprising because lead V_1 is the most rightward, or right ventricular–oriented, of the precordial leads. These changes occasionally extend into lead V_2 with right ventricular infarction. ST segment elevation is usually greater in lead III than in leads II and aVF when right ventricular infarction coexists with inferior STEMI. The positive vector of lead III (in the frontal plane) is also more rightward than that of leads II and aVF. Application of so-called right-sided precordial leads is the best means to diagnose right ventricular infarction with the ECG. These leads, as a mirror image of the left precordial leads, demonstrate ST segment elevation with right ventricular infarction in leads V_3R to V_6R, with V_4R having the highest sensitivity. Electrocardiographic changes in the right-sided precordial leads with right ventricular infarction may be subtle because of the smaller muscle mass of the right ventricle and resulting diminution in QRS complex size (Fig. 64.14). Patients with inferior STEMI with concomitant right ventricular infarction have larger infarcts, experience more in-hospital complications, and have higher mortality rates.

Electrocardiographic Differential Diagnosis of ST Segment Elevation

ST segment elevation on the ECG in the context of a presentation compatible with ACS is considered to represent STEMI until proven otherwise. Several other conditions, particularly LBBB and LVH, also feature ST segment elevation that mimics infarction (see Table 64.3). ST segment elevation resulting from STEMI is not the most common cause of ST segment deviation in adults with chest pain who are suspected of

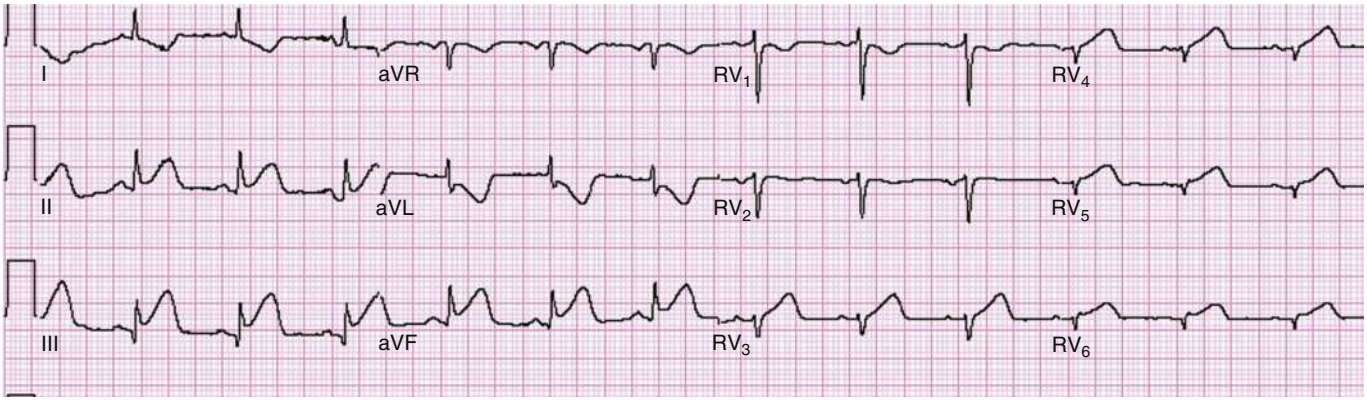


Fig. 64.14 Right ventricular infarction demonstrated with right-sided precordial leads (RV_1 to RV_6). This tracing is taken from the same patient as in Figure 64.12. The ST segment elevation of inferior acute myocardial infarction is still present, as is the reciprocal ST segment depression in leads I and aVL. The precordial leads are right-sided chest leads, as might be inferred from the relatively low voltage. ST segment elevation is noted in leads RV_3 to RV_6 (V_3R to V_6R), consistent with right ventricular infarction.

AMI. Caution is required when interpreting ST segment elevation in regard to the decision to initiate reperfusion treatment, whether it be PCI or fibrinolytic therapy.

Benign early repolarization (BER) is a normal electrocardiographic variant that does not imply or exclude ACS or CAD. BER includes the following electrocardiographic characteristics: (1) ST segment elevation; (2) upward concavity of the initial portion of the ST segment; (3) notching of the terminal portion of the QRS complex at the J point (i.e., junction of the QRS complex with the ST segment); (4) symmetric concordant T waves of large amplitude; (5) diffuse ST segment elevation on the ECG; and (6) relative temporal stability over the short term, although these changes may regress with advancing age. J point elevation is usually less than 3.5 mm, and the concave ST segment is usually elevated less than 2 mm in the precordial leads (although it may be elevated as much as 5 mm in some cases) and 0.5 mm in the limb leads. Maximal ST segment elevation in BER is typically seen in leads V_2 to V_5. Isolated BER in the limb leads is rare and should prompt reconsideration of STEMI (Fig. 64.15A and 64.16).

Pericarditis, in the acute phase, also features diffuse ST segment elevation. In pericarditis, the ST segments are concave, with an initial upsloping contour, and are usually less than 5 mm in height. Occasionally, the initial contour is obliquely flat, but convex or domed ST segment morphology strongly suggests STEMI. The ST segment elevation is usually seen in all leads except for aVR (where it is depressed); V_1 is variable. Focal pericardial inflammation manifests as a more accentuated change in the leads reflecting the affected region. PR segment depression is an insensitive yet specific associated electrocardiographic finding in pericarditis, which is typically best seen in the inferior leads and lead V_6; correspondingly, PR segment elevation may be evident in lead aVR (Fig. 64.17 and Fig. 64.15B). The pericardium is electrically silent; thus, ST segment changes result from epicardial irritation. Hence, the most appropriate term is *myopericarditis*, rather than pericarditis.

Left ventricular aneurysm (LVA), wherein a focal area of myocardium paradoxically bulges outward during systole, has characteristic electrocardiographic changes that can be difficult to differentiate from STEMI. Considerable overlap exists between populations of patients with potential for STEMI and LVA, and the electrocardiographic changes of LVA tend to be regional rather than diffuse. Anatomically, LVA is usually found anteriorly, and changes are most often seen in leads V_1 to V_6 and leads I and aVL. ST segment elevation may be of any morphology (e.g., convex or concave), and Q waves may be present

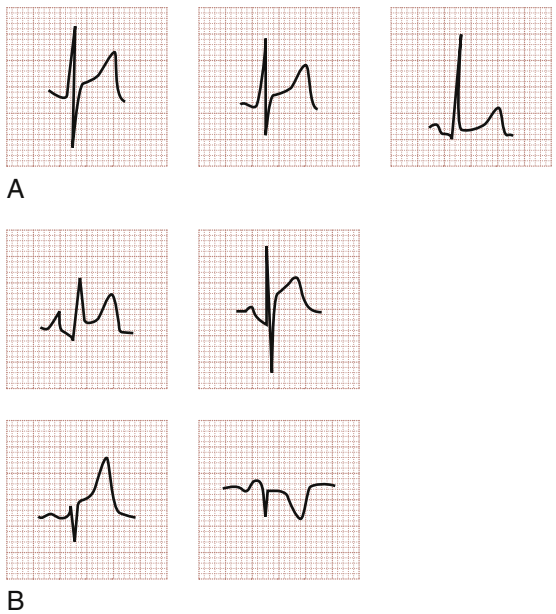


Fig. 64.15 Noninfarctional ST segment elevation (STE). (A) Benign early repolarization (BER) with concave STE. (B) Acute pericarditis with concave STE and PR segment depression (*upper two panels*); concave STE without PR segment abnormalities (*lower left panel*); and reciprocal STE and PR segment elevation in lead aVR (*lower right panel*).

(Fig. 64.18). The calculation of the ratio of the amplitude of the T wave to the QRS complex may help distinguish acute anterior MI from LVA. It has been shown that if the ratio of the amplitude of the T wave to the QRS complex exceeds 0.36 in any single lead, the ECG probably reflects STEMI. If the ratio is less than 0.36 in all leads, however, the findings are likely the result of a ventricular aneurysm.

LBBB is a confounding pattern that reduces the ECG's ability to indicate ACS. Furthermore, in a clinical situation strongly suggestive of ACS, a new LBBB may indicate ACS. Its sole presence, however, should not prompt AMI management. LBBB, whether new or preexisting, shares many similarities to various electrocardiographic findings of ACS. In the right precordial leads (leads V_1 to V_3), ST segment elevation and tall, vaulted, upright T waves mimic those seen in anterior STEMI. The QS pattern of LBBB in these leads resembles the Q waves seen in infarction. Depressed ST segments with T wave inversions are

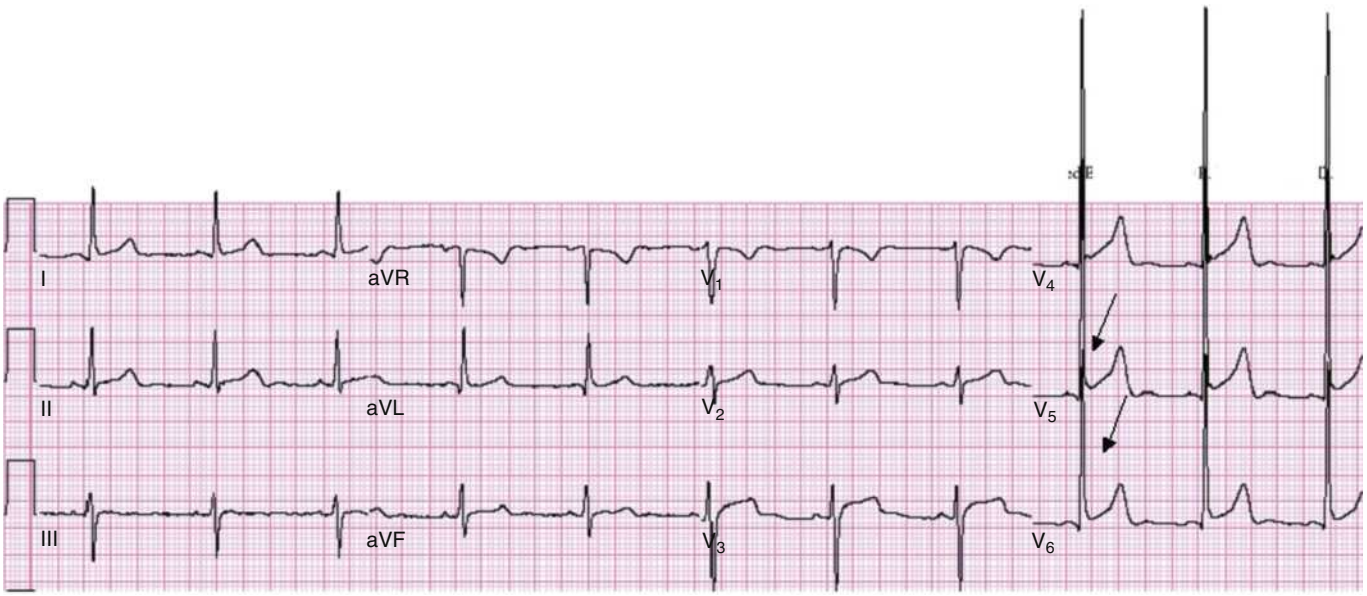


Fig. 64.16 Benign early repolarization. Note the upwardly concave ST segment elevation, best seen in leads V_4 to V_6. The T waves are relatively large in the same leads. Subtle irregularity of the J point is also seen in leads V_5 and V_6 (arrows). Prior electrocardiograms from this patient obtained approximately 18 months prior were unchanged.

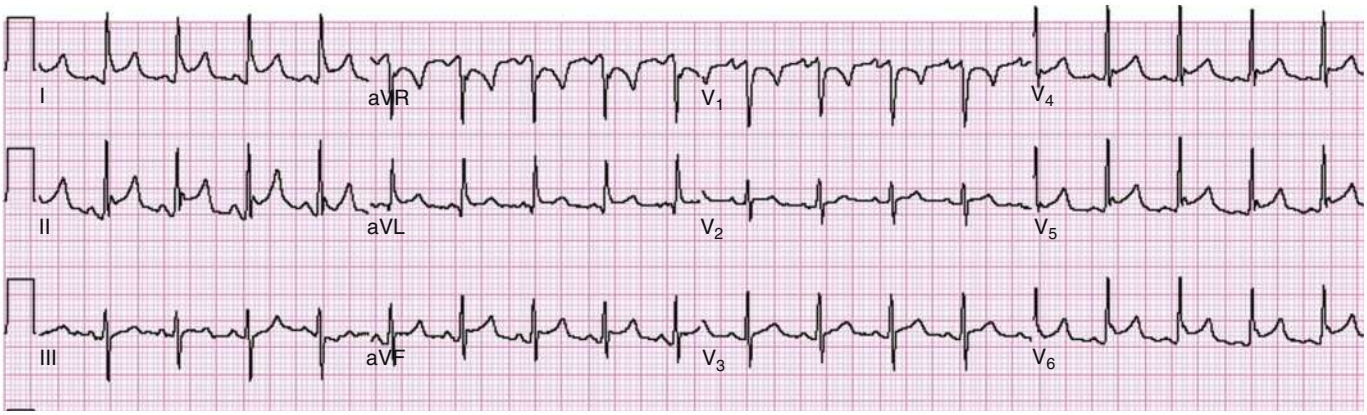


Fig. 64.17 Pericarditis. This tracing demonstrates several classic signs of pericarditis: (1) sinus tachycardia; (2) diffuse, concave upward ST segment elevation; (3) PR segment depression, best seen in lead II; and (4) PR segment elevation in lead aVR.

seen in some or all of the lateral leads (leads V_5, V_6, I, and aVL) in LBBB; both of these resemble ischemic changes seen in ACS. However, these findings in LBBB are merely expressions of the so-called "rule of appropriate discordance." The ST segment and T wave vectors are expectedly discordant, or opposite in direction, to the major vector of the QRS complex in those leads. Because LBBB is a frequent finding on the ECG of a patient at risk for CAD, the normal findings in LBBB (Fig. 64.19) and presentation of AMI in a patient with LBBB must be distinguished.

Sgarbossa and colleagues used a large AMI database to obtain a population of patients with LBBB and serum marker confirmation of AMI. Three independent electrocardiographic predictors of AMI in the presence of LBBB were identified: (1) ST segment elevation of at least 1 mm that is concordant with the QRS complex (Fig. 64.20 and 64.21A); (2) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3 (see Fig. 64.20A and 64.21B): and (3) ST segment elevation of at least 5 mm that is discordant with the QRS complex (see Fig. 64.20B and 64.21C). These findings were assigned weighted scores of 5, 3, and 2, respectively. For accuracy in diagnosis, a specificity of 90% requires a score of at least 3. Thus, if an ECG features only discordant ST segment elevation of 5 mm or more but neither of the other two criteria, further testing is recommended before concluding that the ECG indicates AMI.

A more recent variant of the Sgarbossa criteria omits the third component (discordant ST segment elevation ≥ 5 mm) and instead substitutes the ratio of discordant ST segment deviation to S wave amplitude. Excessive discordance, defined by an ST/S ratio of greater than 0.25 is considered diagnostic of AMI (see Fig. 64.21D). This "modified Sgarbossa criteria" reportedly yields increased sensitivity without significant loss of specificity.[7] Ultimately, the approach to the patient with LBBB and possible AMI remains complicated. If the clinical presentation is consistent with AMI, diagnostic adjuncts to the history and physical examination (e.g., serial ECGs, comparison with prior ECGs, echocardiography, serum cardiac marker measurement) should be applied when the ECG is not diagnostic for acute infarction as noted by the Sgarbossa criteria. A newly noted LBBB occurring in a patient

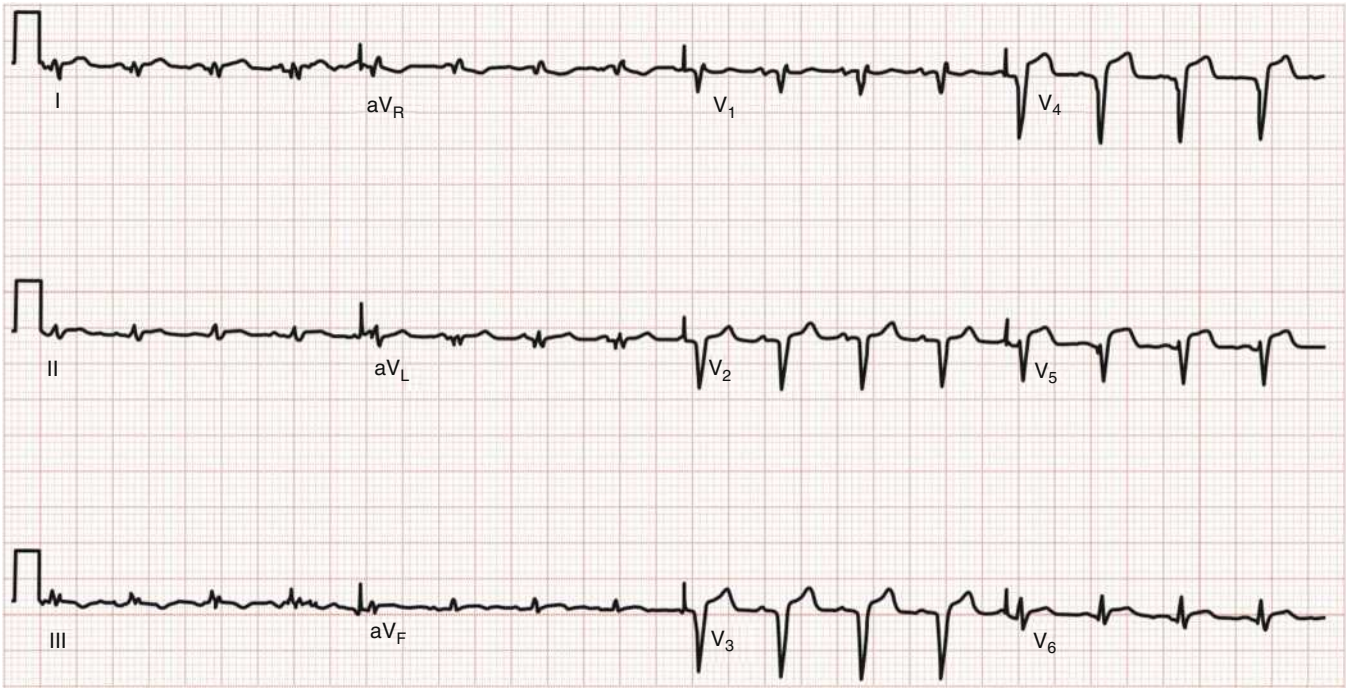


Fig. 64.18 Left ventricular aneurysm. This is a representative example of a 12-lead electrocardiogram from a patient with an anterior left ventricular aneurysm. Note the well-developed, completed Q waves in leads V_2 through V_5 and absence of reciprocal changes in contralateral leads. (Adapted from: Aufderheide TP, Brady WJ. Electrocardiography in the patient with myocardial ischemia or infarction. In: Gibler WB, Aufderheide TP, eds. *Emergency Cardiac Care*. St. Louis: Mosby; 1994: 196-216.)

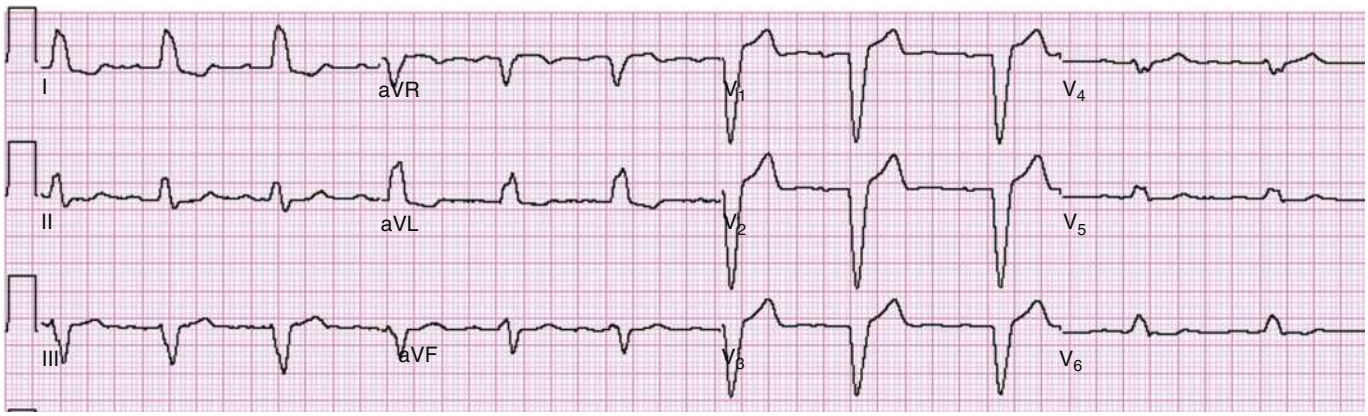
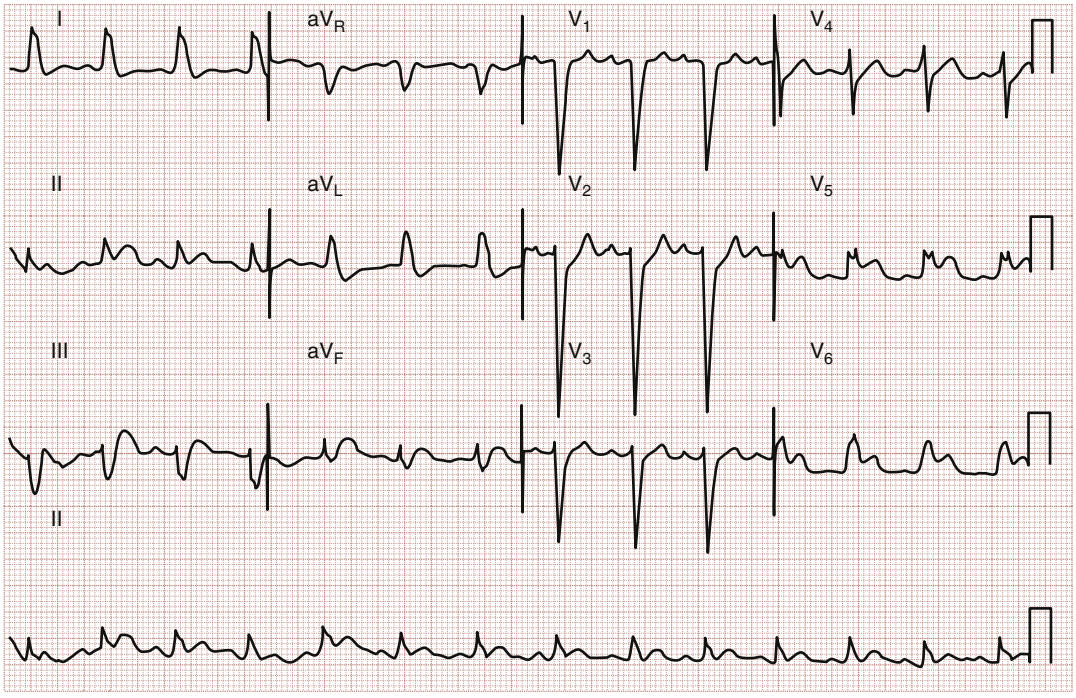


Fig. 64.19 Left bundle branch block (LBBB) with anticipated ST segment abnormalities and no ECG evidence of acute myocardial infarction. This tracing demonstrates the classic findings of LBBB: (1) QRS complex width > 0.12 sec; (2) absence of Q wave in lead V_6; (3) broad monophasic R wave in leads V_5, V_6, I, and aVL; (4) discordant ST segment–T wave changes in leads V_1 to V_3 (simulating acute myocardial infarction), I, and aVL. A first-degree atrioventricular block is also apparent.

with a compelling presentation for AMI should be considered a high-risk presentation. AMI in this situation is likely.

Ventricular paced rhythms (VPRs) can mimic and mask the manifestations of AMI. VPRs originating in the right ventricular apex create a wide QRS complex, with a pseudo-LBBB pattern. As with LBBB, the right precordial leads in VPR typically feature predominantly negative QRS complexes with discordant ST segments and T waves that are elevated and tall or vaulted, respectively. Unlike LBBB, however, VPR originating in the right ventricular apex often yields a predominantly negative QRS complex in leads V_5 and V_6 as well; this is oriented leftward and slightly downward, whereas the impulse generated from the pacemaker wire is oriented superiorly. Furthermore, small vertical pacemaker spikes immediately preceding the QRS complex should be a clue to VPR although, at times, these deflections are hard to detect on the 12-lead ECG.

Limited data exist to guide the emergency clinician in interpreting the 12-lead ECG in this setting. As with the LBBB scenario, the VPR pattern represents a significant confounding variable in the evaluation of the patient with chest pain suspected of having ACS. Sgarbossa and associates have advanced criteria for the detection of AMI in the presence of VPR that were derived from the same database of patients and are essentially the same as the LBBB criteria: (1) ST segment elevation of at least 5 mm discordant with the QRS complex; (2) ST segment elevation of at least 1 mm concordant with the QRS complex; and (3) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3 (Fig. 64.22).



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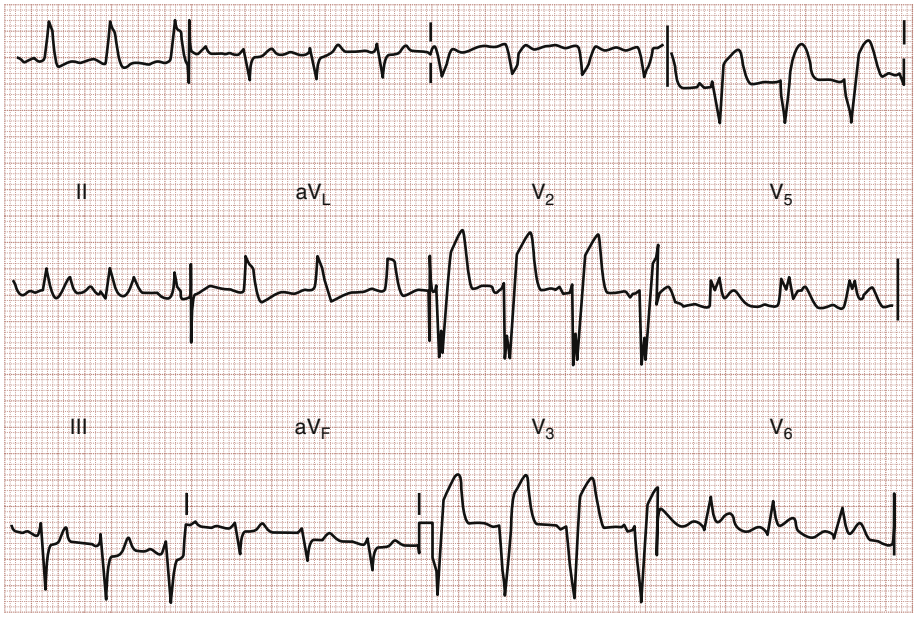


B

Fig. 64.20 Acute myocardial infarction (AMI) in left bundle branch block (LBBB). (A) Using the modified Sgarbossa criteria, there is strong evidence of AMI because of the concordant ST segment elevation greater than 1 mm in leads II, V_5, and V_6. Also suggestive of AMI is the concordant ST segment depression seen in lead V_2. (B) Again, using the modified Sgarbossa criteria, there is strong evidence of AMI due to the concordant ST segment elevation in leads V_5 and V_6 which is greater than 1 mm. Furthermore, there is excessive discordant ST segment elevation in leads V_2, V_3, and V_4; the magnitude of this discordant ST segment elevation is greater than 25% of the accompanying S wave. The degree of this discordant ST segment elevation is not proportionally correct for the size of the accompanying negative portion of the QRS complex.

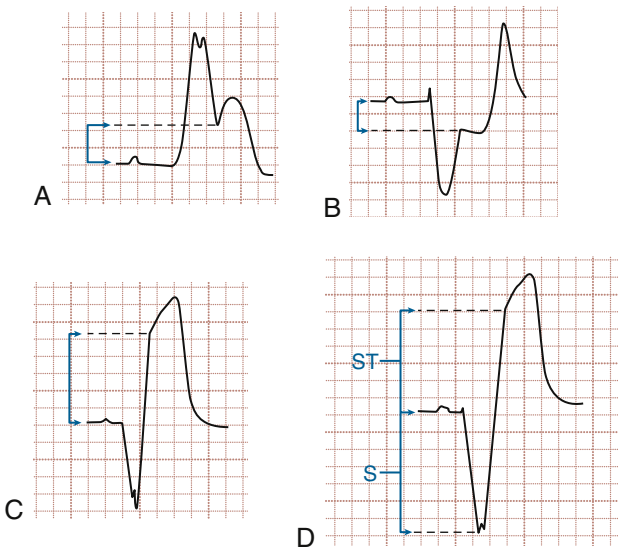


Fig. 64.21 In the presence of LBBB, the Sgarbossa Criteria, as follows, are suggestive of ACS. (A) ST segment elevation of at least 1 mm concordant with the QRS complex. (B) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3 concordant with the QRS complex, and (C), ST segment elevation of at least 5 mm that is discordant with the QRS complex. (D) The modified Sgarbossa criteria utilize the ratio of discordant ST segment deviation to the S-wave amplitude instead of an absolute 5 mm cut-off. An ST to S ratio greater than 0.25 is suggestive of ACS.

LVH may mimic or obscure ACS on the ECG. LVH may feature prominent left-sided forces, manifesting as large rS or QS complexes in the right precordial leads, yet these changes seldom extend beyond V_1 and V_2 in the case of LVH. Consistent with the rule of appropriate discordance, the leads demonstrating such a pattern feature discordant ST segment elevation and tall vaulted T waves, paralleling the changes of AMI. The initial portion of the elevated ST segment in LVH is generally concave, as opposed to the obliquely straight or convex pattern that usually (but not always) is seen with ST segment elevation in AMI. In LVH, the left precordial leads (and, at times, leads I and aVL) may show evidence of a repolarization abnormality (often referred to as a strain pattern), with ST segment depression and asymmetrically inverted T waves. The presence of this strain pattern in the left precordial leads is reassuring when ST segment elevation and tall T waves in the right precordial leads are being attributed to LVH rather than to AMI because one is essentially the mirror image of the other. The changes in LVH should be static over time (Fig. 64.23).

Takotsubo cardiomyopathy is referred to as left apical ballooning or so-called broken heart syndrome. It features ST segment elevation (or deep T wave inversions) without evidence of obstructive CAD. Positive serum markers for cardiac ischemia may be present, as well as hemodynamic compromise. It is characteristically associated with intense emotional stress. Ballooning of the left ventricular apex is seen on ventriculography or echocardiography. Prognosis is excellent, typically with recovery of normal wall motion within 1 month or less.

Non–ST Segment Elevation Myocardial Infarction

Non–ST segment elevation myocardial infarction, or NSTEMI, supplants "non–Q wave MI," previously termed "subendocardial infarction." Precise terminology is difficult because Q waves may disappear with time and the criteria for significant Q waves vary. Moreover, transient ST segment elevation may simply be missed on the ECG. Nonetheless, it is useful to describe the entity wherein there is serum marker evidence of MI in the appropriate clinical scenario but no documented ST segment elevation.

Pathophysiologically, the diseased artery may not have been totally occluded, or the infarct zone may have been partially spared by collateral circulation or therapeutic intervention. Electrocardiographic manifestations of NSTEMI include ST segment depression and T wave inversion, which may be deep and symmetrical; nonspecific ST segment or T wave abnormalities may also be seen in the NSTEMI presentation. Absence of STEMI, however, does not necessarily translate to better outcomes. Previous studies have demonstrated that patients with ST segment depression on the initial ECG have an in-hospital mortality rate similar to that of patients with ST segment elevation or LBBB (15%–16%). Furthermore, ST segment depression in leads V_1 to V_3 or V_4 may herald true posterior infarction on the 12-lead ECG. Acute posterior (inferobasal) MI is one entity wherein emergent revascularization is indicated in the absence of ST segment elevation on the 12-lead ECG.

Electrocardiographic Adjuncts in the Diagnosis of Acute Coronary Syndrome

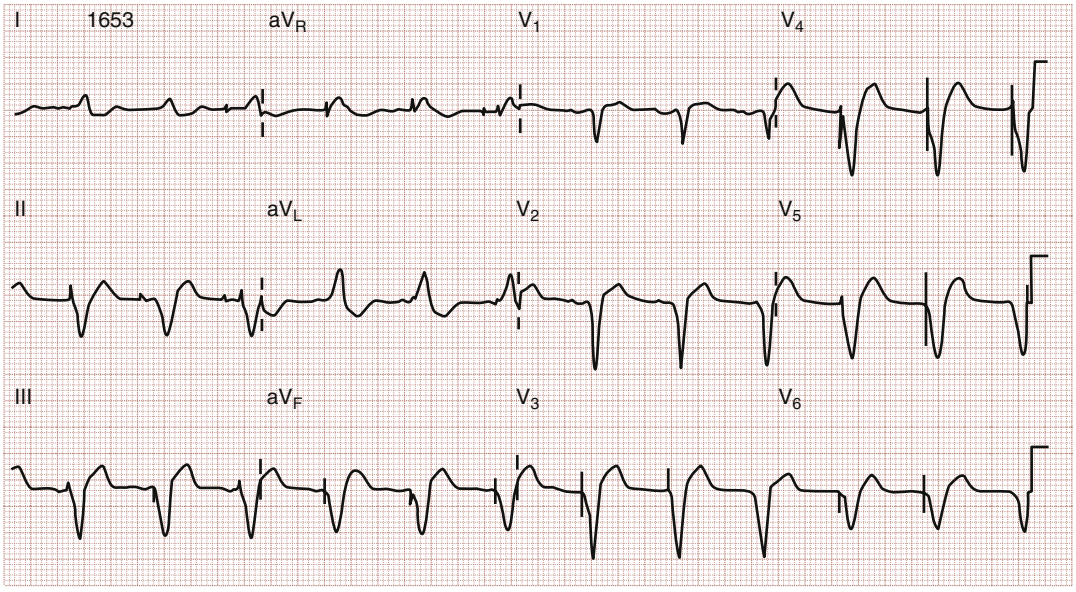
Additional lead ECGs can increase sensitivity for AMI by evaluating regions of the heart prone to electrical silence on the 12-lead tracing. Usually, additional lead ECGs use posterior (leads V_7 through V_9) and right ventricular (V_4R) electrodes, thus constituting the 15-lead ECG (Fig. 64.24). Posterior leads V_8 and V_9 are placed under the tip of the left scapula and at the left paraspinal area at the same level as leads V_4 to V_6. Morphologic changes in the posterior leads may be subtle, mainly because of the increased distance between these electrodes and posterior wall of the heart. Any elevation in these leads is considered ST elevation, even if it is not 1 mm.

Electrocardiographic imaging of the right ventricle is enhanced with the use of the right-sided chest leads V_1R to V_6R (also termed *RV_1 to RV_6*). These leads are placed in mirror image fashion across the right precordium. Of the right precordial leads, V_4R has the highest sensitivity for right ventricular infarction and is the lead of choice to include in the 15-lead tracing. Morphologically, less pronounced changes can be expected in the right-sided chest leads because of the relatively thinner wall of the right ventricle.

Use of the 15-lead ECG may improve diagnostic precision but does not appear to affect the rate of AMI diagnosis, use of reperfusion therapy, disposition, or outcome in all ED patients with chest pain evaluated for ACS. It has been shown that in the subset of ED ACS patients identified as candidates for admission to the cardiac care unit (i.e., high-risk patients), the 15-lead ECG increased the sensitivity of ACS detection by 12%.

Applications for additional lead ECGs include the following: (1) ST segment changes (depression or elevation) in leads V_1 to V_3, in an isolated lead or in more than one; (2) equivocal ST segment elevation in the inferior (II, III, aVF) or lateral (I, aVL) limb leads, or both; (3) all inferior STEMI; and (4) hypotension in the setting of ACS. Additional lead applications can be used, including the 18- and 24-lead ECG; electrocardiographic body mapping using multiple electrocardiographic leads, such as the 80-lead ECG, can also be used. Although it has been suggested that these additional lead ECGs can increase the rate of STEMI diagnosis, the data to indicate when additional ECG leads should be employed are limited and do not represent standard care. In general, opinion-based recommendations suggest that the patient with a classic ACS presentation who lacks significant 12-lead ECG abnormality may demonstrate findings consistent with AMI when additional electrocardiographic leads are applied.

Serial ECGs and ST segment trend monitoring overcome the limitations of the single snapshot of a 12-lead ECG. The use of increased



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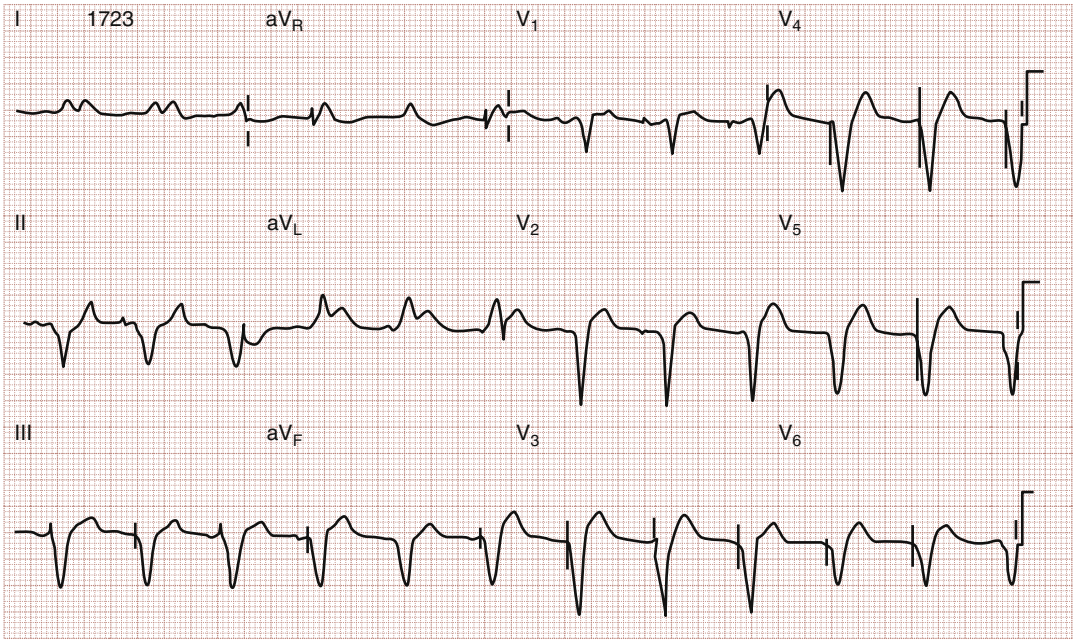


B

Fig. 64.22 Right ventricular paced pattern with evolution of electrocardiographic acute myocardial infarction in a patient with an implanted right ventricular pacemaker. (A) Appropriate ST segment–T wave findings in the patient with a paced rhythm. (B) Serial electrocardiogram from the patient in A, revealing evolution of changes worrisome for ST segment elevation myocardial infarction (STEMI), including concordant ST segment elevation in leads I and aVL consistent with lateral wall AMI.

electrocardiographic surveillance demonstrates diagnostic benefit in patients with recurrent or continuous chest pain, particularly patients with an initially normal nondiagnostic or possible ST segment mimicking syndrome ECG (e.g., ST segment elevation potentially resulting from BER) in whom there is a high clinical suspicion for ACS. The examination of ST segment trends (measured every 20 seconds for at least the first hour) and automated serial ECGs (at least every 20 minutes) in ED patients with chest pain can significantly increase the sensitivity and specificity for detection of STEMI (16%) and ACS compared with just the initial ECG (Fig. 64.25). In patients admitted with nondiagnostic initial ECGs and symptoms consistent with ACS, 12 hours of continuous 12-lead electrocardiographic monitoring in a coronary care unit setting revealed that only serum cardiac marker elevation and presence of ST segment episodes (defined as ST segment elevation or depression > 1 mm different from baseline that endured for at least 1 minute) predict cardiac death or MI.

Limitations of Electrocardiography in Acute Coronary Syndrome

The sensitivity and specificity of a single ECG for AMI are approximately 60% and 90%, respectively. Serial ECGs in the setting of continued or recurrent pain in a patient with a higher clinical suspicion

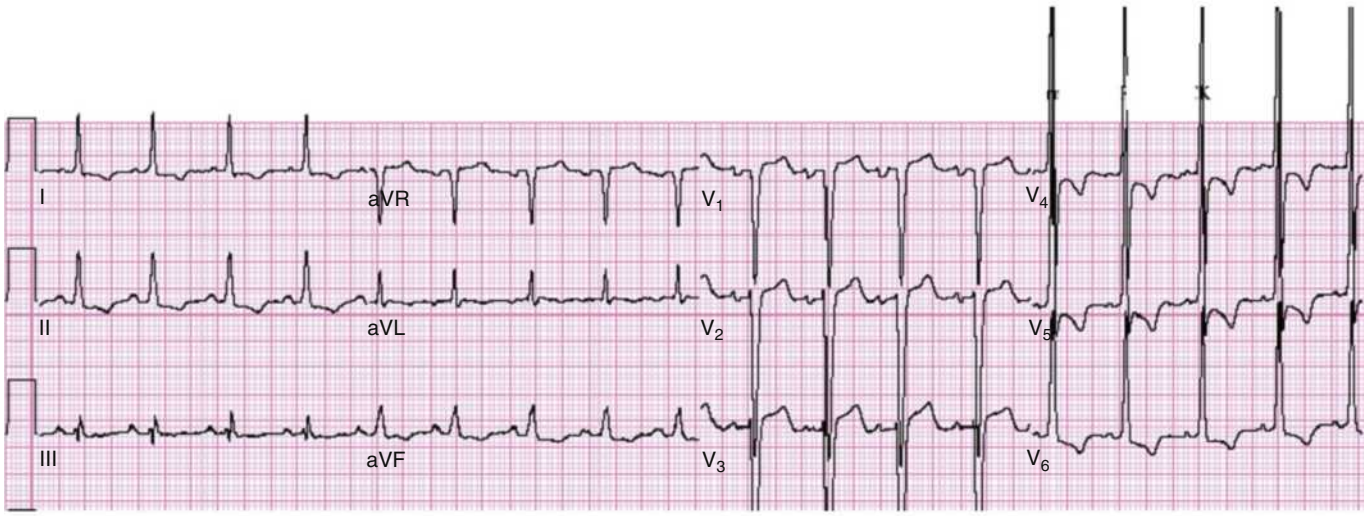


Fig. 64.23 Left ventricular hypertrophy (LVH) with repolarization abnormality. This tracing demonstrates classic repolarization abnormality with ST segment depression and inverted T waves in the left-sided (V_4 to V_6) precordial leads and large amplitude positive QRS complexes (prominent R waves); the T waves in these leads are asymmetrically inverted. The right precordial leads (V_1 to V_3), also demonstrating repolarization abnormality, demonstrate ST segment elevation with concave contour. These ST segment–T wave changes are the anticipated findings of the electrocardiographic LVH pattern with strain pattern; the strain pattern refers to the presence of these ST segment–T wave changes, seen in approximately 75% of patients with the LVH by voltage pattern.

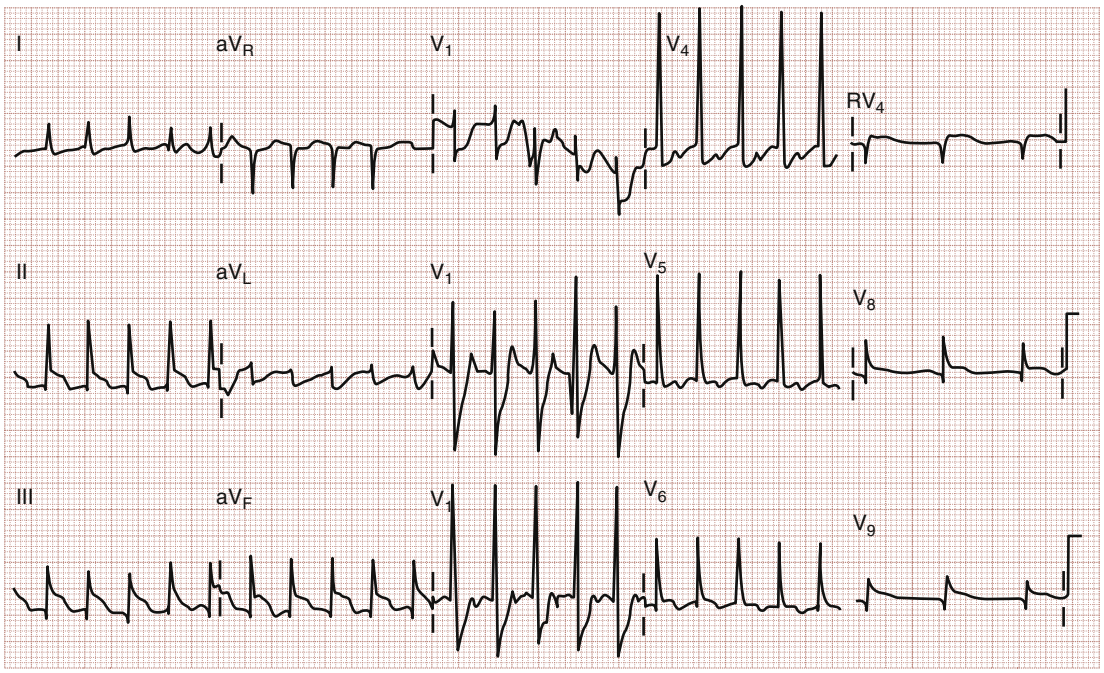


Fig. 64.24 Fifteen-lead electrocardiogram (ECG) with inferior, lateral, posterior, and right ventricular acute myocardial infarction (AMI). The standard 12-lead ECG reveals the typical ST segment elevation (STE) in the inferior and lateral leads, as well as ST segment depression (STD) with prominent R wave in the right precordial leads. Posterior AMI is indicated by the right precordial STD with a prominent R wave and the STE in posterior leads V_8 and V_9. Note that the degree of STE is less pronounced than that seen in the inferior leads because of a relatively longer distance from the posterior epicardium to surface leads. The right ventricular infarction is noted in this case, using the simplified approach with only RV_4, which demonstrates STE of relatively small magnitude.

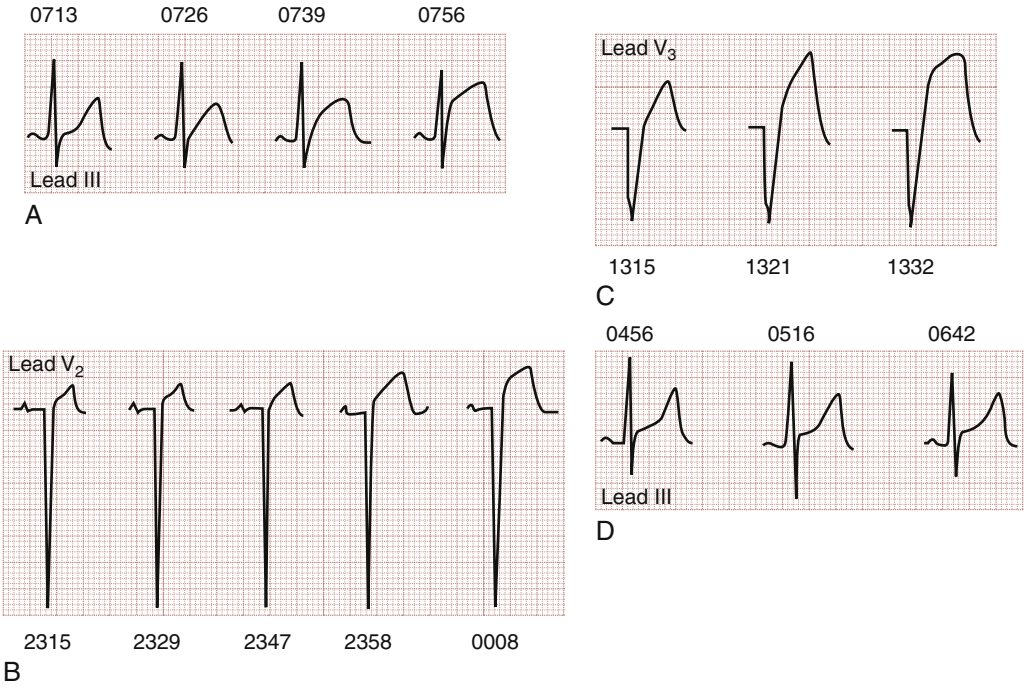


Fig. 64.25 Serial electrocardiography. (A) Representative example of lead III in a patient with chest pain and an initially nondiagnostic electrocardiogram depicting the evolution of ST segment elevation myocardial infarction (STEMI). (B) Representative example of lead V_2 in a patient with the left ventricular hypertrophy pattern. Serial sampling of this patient with ongoing chest pain and a confounding electrocardiographic pattern reveals the progression to STEMI. (C) Representative example of lead V_3 in a patient with left bundle branch block and evolving acute myocardial infarction (AMI). (D) Representative examples of lead III in a patient with chest pain and noninfarctional ST segment elevation (STE). Note the lack of change (degree of elevation as well as morphology of elevation) over time in this patient with benign early repolarization.

for ACS and an initially nondiagnostic ECG increase the diagnostic value. The initial ECG is nondiagnostic in approximately 50% of patients in the ED who are ultimately diagnosed with STEMI. Moreover, nondiagnostic and even normal ECGs do not exclude the diagnosis for AMI in that about 20% of patients ultimately diagnosed with AMI have nondiagnostic ECGs earlier in their course. As time elapses from symptom onset to electrocardiographic recording, the ability of the ECG to exclude AMI does not markedly increase. Thus, in a patient with a presentation concerning for ACS, a single normal or nondiagnostic ECG does not ensure the absence of ACS, even if the ECG was recorded well after the onset of symptoms. In patients being evaluated for ACS, only serial electrocardiography, combined with serial cardiac marker determinations, can exclude AMI and, even then, UA without actual myocardial necrosis may be present.

Chest Radiography

The chest radiograph does not have typical findings in ACS, but can provide ancillary information. For example, the mediastinal width can be considered an insensitive sign of aortic dissection (see Chapter 71) and pulmonary congestion can be seen in heart failure (see Chapter 67). AMI patients who develop CHF have increased mortality, and therefore, the presence of heart failure on the chest radiograph, present in one-third of AMI patients, indicates higher risk. These patients may benefit from an aggressive therapeutic approach.

The chronicity of the CHF syndrome may also be suggested by heart size. Patients with AMI complicated by pulmonary edema who have a normal heart size usually have no past history of CHF. AMI is the most frequent cause of pulmonary edema with a normal cardiac size. In other cases, patients with AMI and cardiomegaly, with or without pulmonary edema, frequently have a preexisting history of CHF, anterior wall infarct, and multiple-vessel CAD (Fig. 64.26).

Serum Markers

Biochemical markers play a pivotal role in the diagnosis, risk stratification, and guidance of treatment of ACS. The European Society of Cardiology and the ACC have defined AMI diagnosis criteria on biochemical grounds because specific markers, particularly troponins, indicate irreversible cell damage.[3] The advancement in diagnostic tests, as well as medical and interventional therapies for AMI, has made the diagnosis and intervention of AMI in the first minutes to hours of the ED visit not only possible, but essential.

For patients with a nondiagnostic ECG, early elevation of serum markers specific for myocardial necrosis (troponin I or T) confirms a presumptive diagnosis of NSTEMI. Caution is advised, however, when a single initial serum marker level is not elevated. This single test, in the first hours following symptom onset, is currently too insensitive to support a decision that the patient can be discharged or determine that no acute coronary event has occurred.[8] The patient's history remains the most vital portion of the diagnostic evaluation of potential ACS. Serial testing substantially improves the sensitivity of these tests for AMI (Table 64.5 and Fig. 64.27), but if the patient's presentation is consistent with unstable angina, no marker can be used to rule out that diagnosis. A sensitive and specific marker to identify myocardial ischemia without myocardial necrosis is not yet available.

Troponin Testing

The role of cardiac troponin (cTn) measurement in the evaluation of ACS has been well established. Elevation of cTN is demonstrably superior in both sensitivity and specificity to other available biomarkers and,

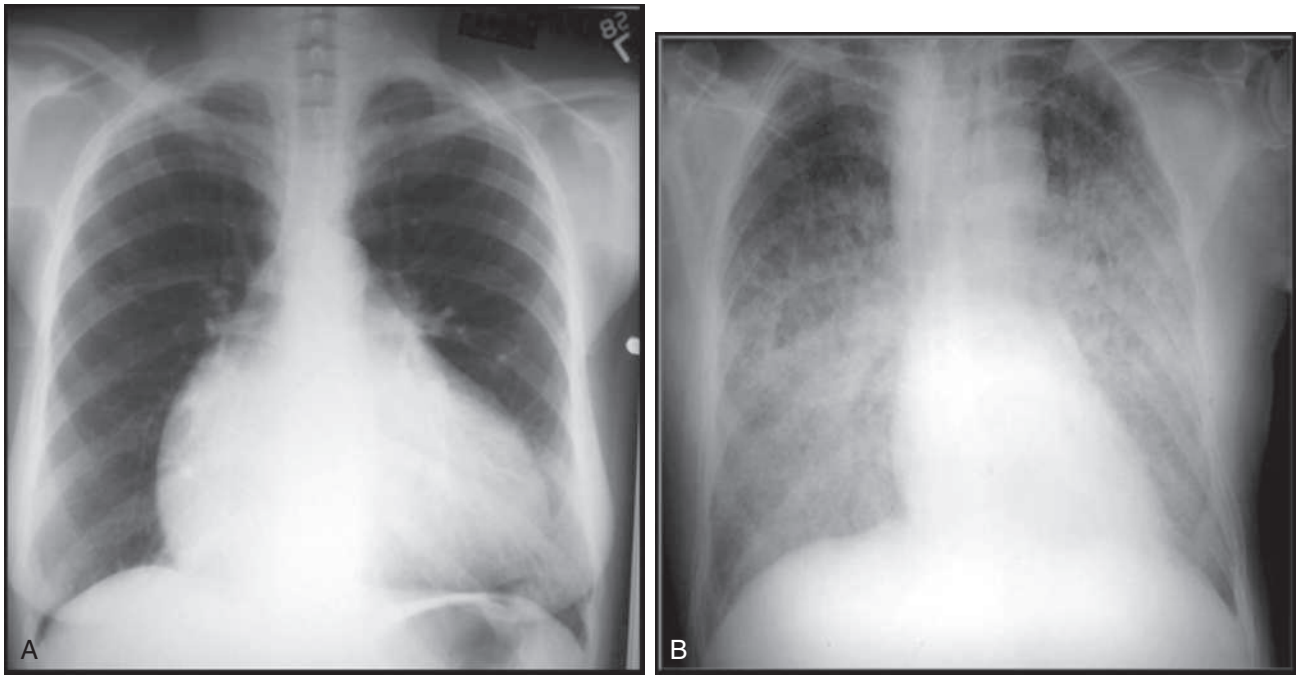


Fig. 64.26 Chest radiographs in patients with acute coronary syndrome. (A) Cardiomegaly. (B) Borderline cardiomegaly with pulmonary edema.

TABLE 64.5 Summary of Test Performance Studies of Diagnostic Technologies for Acute Coronary Syndrome in the Emergency Department

Test	Disease Studied	No. of Studies (Subjects)	Prevalence Range of Studies, %	Disease Sensitivity, % (95% CI)[a]	Disease Specificity, % (95% CI)[a]
Creatine kinase (single)	AMI	12 (3195)	7–41	37 (31–44)	87 (80–91)
Creatine kinase (serial)	AMI	2 (786)	26–43	69–99	68.84
CK-MB (presentation)	ACS	1 (1042)	20	23	96
	AMI	19 (6425)	6–42	42 (36–48)	97 (95–98)
CK-MB (serial)	ACS	1 (1042)	20	31	95
	AMI	14 (11,625)	1–43	79 (71–86)	96 (95–97)
Myoglobin (presentation)	AMI	18 (4172)	6–62	49 (43–55)	91 (87–94)
Myoglobin (serial)	AMI	10 (1277)	11–41	89 (80–94)	87 (80–92)
Troponin I (presentation)	AMI	4 (1149)	6–39	39 (10–78)	93 (88–97)
Troponin I (serial)	AMI	2 (1393)	6–9	90–100	83–96
Troponin T (presentation)	AMI	6 (1348)	6–78	39 (26–53)	93 (90–96)
Troponin T (serial)	AMI	3 (904)	5–78	93 (85–97)	85 (76–91)
CK-MB and myoglobin combination (presentation)	AMI	3 (2283)	9–28	83 (51–96)	82 (68–90)
CK-MB and myoglobin combination (serial)	AMI	2 (291)	11–20	100	75–91
Exercise stress ECG	ACS	2 (312)	6–10	70–100	82–93
Rest echocardiography	ACS	2 (228)	3–30	70 (43–88)	87 (72–94)
	AMI	3 (397)	3–30	93 (81–91)	66 (43–83)
Stress echocardiography	AMI	1 (139)	4	90	89
Sestamibi (rest)	ACS	3 (702)	9–17	81 (74–87)	73 (56–85)
	AMI	3 (702)	92 (78–98)	67 (52–79)	

[a]Point estimate from a single study or a range of reported values; meta-analysis not performed.
ACS, Acute coronary syndrome; *AMI,* acute myocardial infarction; *CI,* confidence interval; *CK-MB,* creatine phosphokinase MB fraction; *ECG,* electrocardiogram.
Adapted from: Pope JH, Selker HP. Diagnosis of acute cardiac ischemia. *Emerg Med Clin North Am.* 2003;21:27-59.

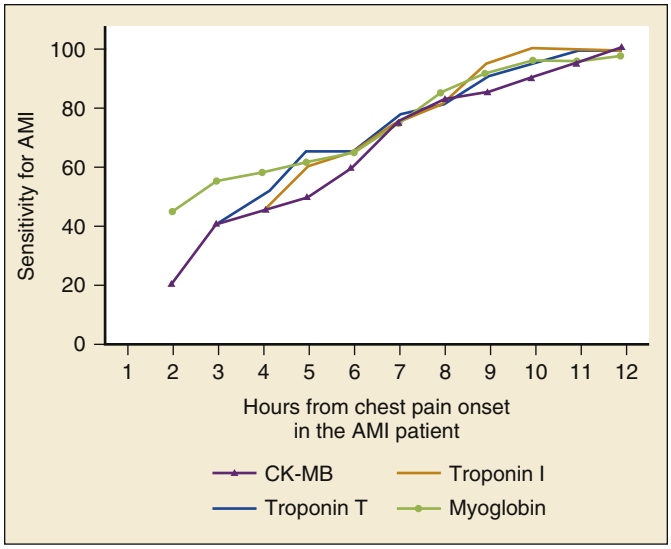


Fig. 64.27 Serum marker sensitivity relative to the time of onset of chest pain in the patient with acute myocardial infarction (AMI). *ACS,* Acute coronary syndrome; *CAD,* coronary artery disease; *CK-MB,* creatine phosphokinase MB fraction; *STEMI,* ST segment elevation myocardial infarction.

as such, is the only cardiac marker referenced in the consensus universal definition of MI.[3] Because of this, it is the only biomarker utilized by the HEART score, HEART Pathway, and EDACS-ADP pathway, as well as most other modern decision rules for evaluation of ACS. The term *cardiac troponin* represents two myocardium specific proteins, myocardial troponin I (TnI) and troponin T (TnT), which precede the release of creatine kinase-MB fraction (CK-MB) into the serum during myocardial ischemia. TnI and TnT are very similar in their diagnostic and prognostic value and their serum kinetics and rates of increase and decrease associated with myocardial ischemia, infarction, and ACS.

The biokinetics of troponin release relate to the location of the protein within the cell. Normally, small quantities of troponins are free in the cytosol while most is entwined in the muscle fiber. After injury, a biphasic rise in serum troponin levels corresponds to early release of the free cytoplasmic proteins, followed by a slower and greatly prolonged rise from breakdown of the actual muscle fiber. The slow destruction of the myocardial cell contractile proteins provides a sustained release of the troponins for 5 to 7 days. Serum troponin levels begin to rise measurably in the serum at about the same time as CK-MB level elevations become detectable, as early as 2 to 3 hours after onset, but troponin levels remain elevated for 7 days or more.

Troponin levels as measured by standard, or traditional, troponin assays are generally undetectable in the serum of healthy individuals. An elevated level is defined as that exceeding the 99th percentile in a healthy population. Sensitivity to detect abnormal low troponin levels, however, varies among the multiplicity of existing assays, particularly with respect to TnI. Emergency clinicians, therefore, must be familiar with the sensitivity and limitations of the particular assay used at their institutions and the cutoff concentrations for clinical decisions.

It should be noted that, given the biokinetics of troponin release, a single standard troponin on presentation has limited value in excluding AMI in the first hours of symptom onset and no ability to detect unstable angina without infarction, because cell injury is required to elicit biomarker elevation. As such, in evaluating patients presenting with recent onset of symptoms, serial measurements are recommended.[9,10]

The relatively recent introduction of high-sensitivity troponin (hs-T) into clinical practice has increased the ability to detect ischemia early in the presentation of non-ST elevation AMI. An assay is labeled "highly sensitive" when it results in reportable levels of troponin in greater than 50% of healthy subjects. These assays reduce the window during which troponin elevation remains undetectable in patients with ACS and may aid in more rapid risk stratification. Some clinicians, however, have expressed concerns that increased utilization of hs-T could increase the incidental finding of myocardial injury unrelated to ACS. It is important to note that data indicate that even very low hs-T level elevations are associated with adverse outcomes. This is true not only in patients with chest pain, but also in asymptomatic individuals. Detectable serum troponin levels with a high-sensitivity troponin assay are associated with the presence of structural heart disease and all-cause mortality.

Data increasingly support the use of serial hs-T assay testing with an interval as short as 1 to 2 hours when combined with other appropriate clinical data in the form of a validated accelerated diagnostic protocol (e.g., a nonischemic ECG and low HEART score). Such use can identify patients at risk of 30-day major adverse cardiac event (MACE) with greater than 99% sensitivity.[11] The European Society of Cardiology has recommended a 1-hour serial marker protocol in patients with chest pain with onset greater than 3 hours from presentation with subsequent discharge after two negative markers or only minimally detected troponin without significant rise—the delta—on repeat testing.[12] Other emerging data also suggest that a very low or undetectable hs-T level upon presentation may be sufficient in "ruling out" acute myocardial injury.[13,14] These data require further validation, however, and current expert opinion is that consideration of such a strategy should be reserved for lower-risk patients presenting greater than 3 hours from symptom onset and only with utilization of appropriate, assay-specific cutoffs.[8]

Additionally, it should be noted that troponin elevation in isolation is not diagnostic of ACS. Cardiac conditions that can result in significantly increased troponin levels in patients without evidence of ACS include myocarditis, pericarditis, CHF, LVH, and nonpenetrating cardiac trauma. Although the presence of elevated troponin levels in these conditions might be considered false-positive results, studies have supported the contention that the source of these levels is underlying noninfarction myocyte injury that occurs with these conditions. Troponin elevations can also be seen in noncardiac conditions, including extreme physical exertion, renal insufficiency, and multiple trauma. Troponin level elevation may result from right ventricular dysfunction and myocyte injury in the case of intermediate and high-risk pulmonary emboli (PE) and is a significant predictor of an adverse outcome. Elevated troponin levels have been reported in patients with sepsis and critically ill patients with multiple organ system failure. In each of these subsets of patients, troponin level elevations are associated with increased morbidity and mortality.

Elevated troponin levels are commonly seen in asymptomatic patients with end-stage renal disease. Earlier studies in asymptomatic hemodialysis patients using a high-sensitivity troponin assay have shown that as many as 100% of samples have troponin levels exceeding the 99th percentile value. This finding may relate to the high prevalence of cardiac disease in this population rather than any reduced renal clearance and may still represent subclinical myocardial damage. The TnT isoform is associated with elevated levels in renal failure more often than TnI, particularly in patients undergoing hemodialysis. Elevated troponin levels in the setting of renal failure are associated with increased risk of death and major cardiac and vascular morbidity and should not be ascribed to chronic renal failure unless old records are available to corroborate that the elevated troponin level is actually the patient's baseline level. In unclear circumstances, it is prudent to measure a repeat

troponin level to elucidate whether the elevated level may represent acute myocardial injury.

Other Serum Markers

Creatinine phosphokinase (CK) is found in large quantities, not only in cardiac muscle but also in skeletal muscle, brain, kidney, lung, and GI tract. Myocardial cells are the most abundant potential sources of CK-MB; thus, the appearance of CK-MB in the serum is highly suggestive of MI. The CK-MB fraction remains the best alternative to troponin levels as a cardiac marker. In the setting of AMI, CK-MB is released and is detectable in the serum as early as 3 hours after onset of the necrosis, peaks at 20 to 24 hours, and becomes normal within 2 to 3 days after injury. Unfortunately, skeletal muscle contains small amounts of CK-MB, particularly the pelvic musculature. Abnormal CK-MB level elevations may be seen in patients with trauma, muscular dystrophies, myositis, and rhabdomyolysis, and after vigorous exercise. Because of this lack of specificity, CK and CK-MB are used rarely in contemporary EDs. As troponin level assays have become more sensitive, with detectable levels in the serum preceding CK and CK-MB changes, CK-MB has been virtually eliminated from the modern clinical decision rules for ACS evaluation in the ED.

Myoglobin, a small protein (17 kDa) found in muscle tissue, is rapidly released into the circulation after cellular injury. In cases of myocardial injury, the myoglobin level rises in the initial 1 to 2 hours, peaks at 5 to 7 hours, and returns to baseline by 24 hours. Because of its rapid rise, myoglobin was previously used as an early indicator of myocardial injury. Myocardial myoglobin, however, is not currently distinguishable immunologically from skeletal muscle myoglobin. Thus, the myoglobin level is elevated in any clinical situation involving the skeletal muscle, such as trauma, exercise, and significant systemic illness. In addition, myoglobin level increases are seen in patients with renal failure because of reduced clearance. Despite its high sensitivity for AMI, particularly early in the course of ACS, myoglobin has largely fallen out of favor due to its lack of specificity for myocardial injury.

Biochemical assays for potential new cardiac markers for necrosis are being developed in the hope of finding those with improved sensitivity, risk determination capability, and prognostic power. One such cardiac-specific myonecrosis marker is heart-type, fatty acid–binding protein. Another, ischemia-modified albumin (so-called cardiac albumin), is a potentially useful ACS biomarker that reportedly detects early myocardial ischemia rather than the later myocyte necrosis. Its level may be elevated even earlier than myoglobin. Other potential ischemia markers include unbound free fatty acid and whole blood choline levels.

A variety of biochemical markers for inflammation and plaque instability may have value in evaluating the risk of a cardiac event. Chief among these are the inflammatory markers C-reactive protein (CRP) and high-sensitivity CRP (hsCRP), which have long-term prognostic value for cardiac events in healthy individuals and potential short-term prognostic value when combined with other markers for ACS. Elevated plasma levels of myeloperoxidase, an abundant leukocyte enzyme found in vulnerable coronary plaques that have ruptured, predict the short-term risk of adverse cardiac events, even with negative cardiac troponin levels and no evidence of myocardial necrosis. However, none of the biochemical markers of ischemia (without necrosis) or inflammation have yet shown significant diagnostic value for ACS in the ED setting.

Markers of hemodynamic status, including the natriuretic peptides, may also be useful in the evaluation of ACS patients. These markers have shown value in determining future prognosis, rather than in making the diagnosis of ACS in the ED. These markers, such as B-type natriuretic peptide (BNP) and NT-proBNP (N-terminal pro-BNP), are released from cardiac myocytes in response to increases in ventricular wall stress. BNP is generally used as a marker for heart failure but is a useful adjunct to the standard cardiac markers and has good predictive power for recurrent ACS events and cardiac-related deaths, as well as heart failure exacerbations, in patients with AMI. Moreover, the natriuretic peptides are excellent predictors of short- and long-term mortality in patients with UA, NSTEMI, and STEMI.

Historically, multimarker approaches to ACS evaluation were standard practice in the ED. With the advent of standard and high-sensitivity troponin assays, however, multiple studies have shown limited benefit to additional markers in the ED evaluation of ACS. In addition to simplifying the evaluation, it has been shown that there is significant potential cost savings to the hospital by limiting excess cardiac biomarker testing. The multimarker approach does not offer benefit over individual troponin level evaluations for ACS and is no longer recommended.

Exercise Stress Testing

Exercise stress testing for ED patients is feasible, but provocative testing should generally be reserved for patients who have had resolution of symptoms and when suspicion for ACS is low to moderate. Current guidelines suggest that it is reasonable for these patients to undergo provocative testing, myocardial perfusion imaging, or coronary CT angiography (CCTA) prior to discharge or within 72 hours of discharge.[9] It should be noted, however, that such testing in a low-risk population may lead to further downstream testing and intervention without significant reductions in future rates of infarction.[15] As such, it may be reasonable to discharge patients appropriately deemed low-risk with appropriate return precautions and short-term outpatient follow-up.

Previous studies in ED patients with low-risk chest pain (5% incidence of CAD), who underwent exercise testing after negative serial markers and 9 hours of electrocardiographic monitoring in the ED, showed that stress testing had a negative predictive value of 98.7% for the diagnosis of ACS or cardiac event within 30 days. An abbreviated ED-based, so-called rule-out MI protocol, followed by mandatory stress testing, appears to be one effective diagnostic method for detecting symptomatic CAD in low- to moderate-risk patients. Current guidelines on exercise testing state that such testing can be performed when patients are free of active ischemic or heart failure symptoms for a minimum of 8 to 12 hours.[9]

Patients with a high pretest probability of CAD have a significant rate of false-negative results, and patients with a low pretest probability have a significant rate of false-positive stress test results. The specificity of the test is decreased in the presence of underlying electrocardiographic abnormalities secondary to medications, electrolyte abnormalities, LVH, or artifact. A false-positive test outcome may result from aortic stenosis or insufficiency, hypertrophic cardiomyopathy, hypertension, arteriovenous fistula, anemia, hemoglobinopathies, low cardiac output states, chronic obstructive pulmonary disease, digitalis toxic states, LVH, hyperventilation, mitral valve prolapse, or BBBs. A higher rate of false-positive test results in women may decrease the usefulness of graded exercise testing in this population.

Echocardiography

Two-dimensional echocardiography detects regional wall motion abnormalities associated with ACS due to the close correlation between wall motion and myocardial blood flow. Impaired myocardial contractility can range from hypokinesis to akinesis, with associated impaired myocardial relaxation during diastole. After AMI, paradoxical wall motion and decreased ejection fraction observed during systole indicate the subsequent loss of muscle tone from necrosis.

TABLE 64.6 Emergency Department Bedside Echocardiography in Acute Coronary Syndrome—Pros and Cons

Pros	Cons
• Readily accessible, portable • Inexpensive • Safe, noninvasive • Detection of wall motion abnormalities, useful for early diagnosis and presentations involving diagnostic uncertainty • Identification of nonischemic causes of symptoms	• Skill level—operator- and interpreter-dependent • Limited sensitivity, particularly in small areas of myocardial injury • Limited visual windows in ≈10% of patients • Inability to distinguish acute wall motion abnormalities from chronic

Particularly in individuals with nondiagnostic ECGs, the presence of regional systolic wall motion abnormalities in a patient without known CAD is a moderately accurate indicator of AMI or infarction, with a positive predictive accuracy of about 50%. When echocardiography is performed shortly after ED arrival, during an episode of chest pain, wall motion abnormalities have been detected in up to 90% of patients with ACS. The age of wall motion abnormalities, however, often cannot be determined without prior echocardiograms for comparison.

The absence of segmental abnormalities (presence of normal wall motion or diffuse abnormalities) has a significant high negative predictive value, as high as 98% for cases of suspected MI. Moreover, segmental wall motion abnormalities can be seen in the zone of acute infarction and in regions of ischemic stunning. Resting echocardiography provides an assessment of global and regional function, an important predictor of complications and mortality in patients with ACS. Prior studies have indicated that patients with mild and localized, as opposed to extensive, wall motion abnormalities have a low risk of ACS complications. In addition, echocardiography can help evaluate other causes of clinical presentations mimicking ACS, including valvular heart disease, aortic dissection, pericarditis, mitral valve prolapse, and pulmonary embolus. Finally, echocardiography is a vital tool to assess for various complications of AMI, including acute mitral regurgitation, pericardial effusion, ventricular septal and free wall rupture, and intracardiac thrombus formation.

Technical limitations restrict the use of echocardiography in the ED. These include the expertise of the operator and of the reader interpreting the study. In addition, the inability of the two-dimensional echocardiogram to distinguish among ischemia, AMI, or old infarction and potential absence of wall motion abnormality in nontransmural infarctions can further limit the use of two-dimensional echocardiography (Table 64.6).

Stress echocardiography, as opposed to resting echocardiography, can detect CAD and assess cardiac function early after an AMI. This can be performed with graded increases in cardiac workload by standardized exercise or pharmacologic adrenergic-stimulating agents, such as dobutamine. Graded dobutamine stress echocardiography assesses myocardial viability and ventricular function within the first few days after an AMI. In addition, vasodilating agents, such as dipyridamole and adenosine, induce heterogeneous myocardial perfusion and reveal functional myocardial ischemia in susceptible patients. Stress echocardiography is superior to conventional treadmill testing for CAD in women. Clinical studies of patients with nondiagnostic ECGs, negative markers, and negative rest echocardiography have suggested a role for emergency pharmacologic stress echocardiography as a provocative test after a period of observation with at least two marker and ECG assessments in a chest pain or ED observation unit.

Myocardial contrast echocardiography (MCE) uses microbubble ultrasonic contrast agents to assess microvascular perfusion and regional function with echocardiography. MCE evaluation of perfusion and regional function allows accurate risk stratification of ED patients with chest pain and nondiagnostic ECGs, even before serum markers are available. Smaller studies have reported low rates of adverse cardiac events in chest pain patients with normal MCE findings after a nondiagnostic ECG and negative serum markers. The clinical value of MCE in the ED, like that of resting and stress echocardiography, remains uncertain.

Myocardial Scintigraphy (Nuclear Imaging)

Radionuclide tracer injection and scintigraphy, such as with single-photon emission computed tomography (SPECT), allows real-time assessment of myocardial perfusion and function. Technetium-99 sestamibi has a slow redistribution to ischemic myocardium. This property allows immediate injection and imaging, which detects altered distribution consistent with some form of ischemic heart disease, followed by subsequent scanning, which provides more definitive data regarding the particular subtype of ACS. In patients with a normal initial study, the likelihood of ACS is extremely low. In patients with an initial study revealing abnormal distribution (i.e., reduced uptake) of the tracer, some form of ischemic heart disease is likely. Subsequent imaging then reveals one of two patterns—normal redistribution (normal uptake) or continued reduced uptake. The redistribution pattern is consistent with active coronary ischemia, and continued reduced uptake is found in patients with MI, remote or recent. Myocardial scintigraphy has promising positive and negative predictive values for cardiac events, with high sensitivity and good specificity for CAD.

Immediate myocardial scintigraphy is useful for detecting ACS and the risk of cardiac events in patients in the ED with atypical chest pain, nondiagnostic ECGs, and low to moderate risk of AMI. Multiple studies have found a relatively high incidence of cardiac events, presence of AMI, and need for revascularization in patients with a positive nuclear scan. A cardiac event's probability is tenfold higher in patients with abnormal scans than in patients with a normal scan. The incidence of cardiac events with a normal scan is <1% for the 30-day period after the index study. Myocardial scintigraphy, if available, can reduce the number of patients admitted from the ED with chest pain who are ultimately determined not to have ACS, without reducing appropriate admissions for patients with ACS.

Coronary Computed Tomography Angiography

Coronary computed tomography angiography (CCTA) is an increasingly utilized noninvasive modality to assess for coronary artery disease in patients who have been ruled out for AMI and other active forms of ACS. In a noninvasive fashion, CCTA may provide information regarding coronary anatomy and stenosis similar to that obtained from cardiac catheterization.

When considering the presence or absence of CAD, CCTA is accurate in the detection of coronary artery obstructive lesions. For example, in a large meta-analysis, the accuracy for significant coronary artery obstructive lesions was very high, assuming that high-resolution, newer-generation CT is used. Figures 64.28A and B illustrate representative CCTA images demonstrating normal coronary anatomy; Figures 64.28C to E illustrates CCTA images with proximal left anterior descending (LAD) artery occlusion.

In symptomatic stable patients with low to intermediate pretest probability of CAD, CCTA may be an appropriate imaging study. CCTA is accurate, not only for the detection of significant coronary obstructive lesions, but is also predictive of outcome. Patients with low- to intermediate-risk chest pain with negative CCTA have a very low

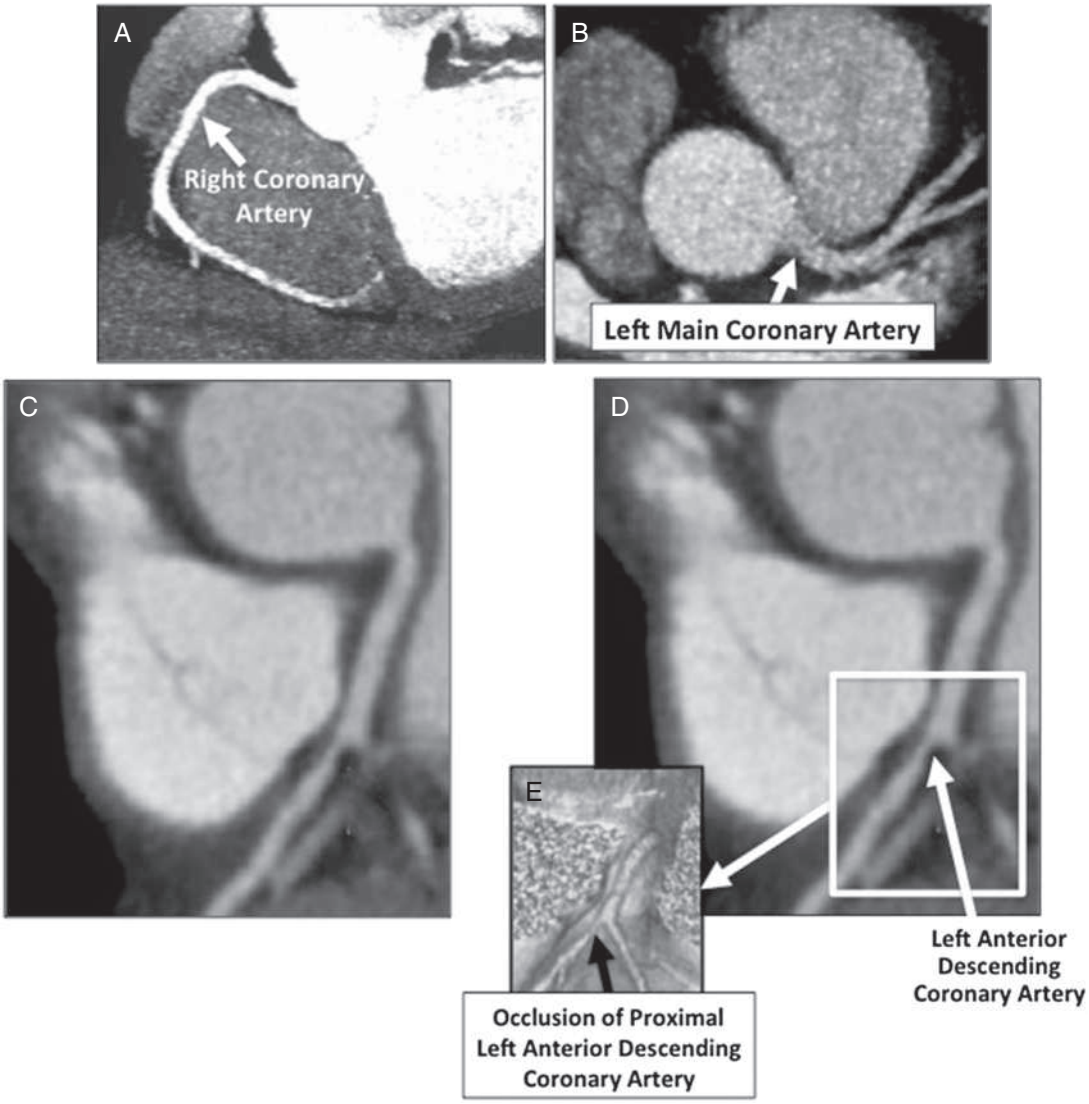


Fig. 64.28 Coronary CT angiography. (A) Normal right coronary artery. (B) Normal left main coronary artery. (C) Left anterior descending coronary artery (LAD) with proximal obstruction. (D) Labeling of LAD obstruction. (E) Three-dimensional image of LAD obstruction.

(<1%) incidence of MACE at 1 year.[16] In initial data of patients seen in the ED with symptoms suggestive of ACS, use of CCTA in the evaluation strategy improved ED throughput, with a reduction in length of stay and reduced rate of admission. An increase in outpatient testing was noted, ultimately resulting in no reduction in overall costs. Subsequent meta-analyses of CCTA studies have demonstrated no significant differences between CCTA and other functional stress testing on mortality or hospitalization for cardiac-related causes; however, they demonstrate a decrease in myocardial infarction patients with stable, but not acute, chest pain.[17,18]

The issue of radiation must also be considered in this study application. Newer CCTA testing modalities are associated with markedly lower doses of radiation. CCTA can be used with relatively smaller exposures to radiation, ranging from 2.0 to 5 mSv. For reference purposes, standard CT scanning and cardiac catheterization are associated with 9 mSv and 12 mSv, respectively.

Thus, in the ED population suspected of ACS, CCTA can be used in patients with low to intermediate suspicion for CAD after some form of ACS evaluation. This testing modality is accurate concerning the identification of significant CAD and prediction of adverse events related to ischemic heart disease. The test requires significant expertise for interpretation, whether by a radiologist or cardiologist. Utility may also be limited by the availability of appropriate equipment and the need for beta-blockade (or appropriately controlled heart rate) before imaging to optimize imaging quality. Although calcium scoring is not considered a useful testing modality in the ED population, calcium scoring may be considered when CCTA is performed. In general, a higher calcium presence in the coronary arteries is associated with less accuracy with the use of CCTA for the demonstration of significant CAD.

Risk Stratification Instruments

Risk stratification tools such as the GRACE risk model (Global Registry of Acute Coronary Events) and TIMI risk score (Thrombolysis in Myocardial Infarction) were derived for inpatients, examining the need for invasive therapy rather than the evaluation of individuals with undifferentiated chest pain. Neither tool was designed to identify patients who may safely be discharged from the ED. More recent developments, such as the Emergency Department Assessment of Chest Pain Score (EDACS), HEART Score, and HEART Pathway, have

TABLE 64.7 The HEART Score

Variable	Score of 0	Score of 1	Score of 2
History	Nonspecific history for ACS, a history that is not consistent with chest pain concerning for ACS	Mixed historic elements, a history that contains traditional & non-traditional elements of typical ACS presentation	Specific history for ACS, a history with traditional features of ACS
Electrocardiogram	Entirely normal ECG	Abnormal ECG, with repolarization abnormalities[a] yet lacking significant ST depression	Abnormal ECG, with significant ST deviation (depression ± elevation), either new or not known to be old (i.e., no prior ECG available for comparison)
Age (years)	Age less than 45 years	Age between 45 & 64 years	Age 65 years or older
Risk Factors[b]	No risk factors	1 to 2 risk factors	3 or more risk factors OR documented cardiac or systemic atherosclerotic vascular disease[c]
Troponin[d]	Troponin < discriminative level ± AccuTroponin I < 0.04 ng/ml	Troponin elevated 1–3 times discriminative level ± AccuTroponin I 0.04-0.12 ng/ml	Troponin elevated > 3 times discriminative level ± AccuTroponin I > 0.12 ng/ml

Total HEART Score: risk category & recommended management strategy
0–3: low risk, potential candidate for early discharge
4–6: moderate risk, potential candidate for observation & further evaluation
7–10: high risk, candidate for urgent or emergent intervention
[a]BBB, LVH, digoxin effect, implanted right-ventricular pacemaker, past MI, ± unchanged repolarization abnormalities.
[b]DM, tobacco smoker, HTN, hypercholesterolemia, obesity, ± family history of CAD.
[c]Peripheral arterial disease, MI, past coronary revascularization procedure, ± stroke.
[d]It is recommended to use the local hospital standards for troponin abnormality determination.

provided ED-appropriate, easily performed, accurate clinical decision tools for use in the ED by the emergency physician.

EDACS is a clinical aid for identifying low-risk individuals with a low short-term MACE rate eligible for discharge from the emergency department.[19,20] EDACS is calculated using demographic, historical, and patient complaint descriptors. After calculation of the EDACS score, serum troponin testing and ECG results are considered in the patient evaluation, illustrating the EDACS-Accelerated Diagnostic Pathway (EDACS-ADP).

Clinical data used in the EDACS-ADP risk calculation include the following: patient age, sex, history of CAD or three or more CAD risk factors, and several chest pain and related complaint descriptors (presence of diaphoresis [higher risk]; pain radiation to shoulder, jaw, neck or arm [higher risk]; pain worsened with inspiration [lower risk]; and pain reproduced with palpation [lower risk]).

In this rule, a history of CAD is defined as previous AMI, CABG, or PCI; CAD risk factors are defined as diagnosed medical conditions (dyslipidemia, diabetes mellitus, hypertension), current tobacco smoker, and family history of premature CAD. The risk score is calculated with patients divided into "low risk" and "not low risk" groups. Low-risk patients with two negative serum troponin values at 0 and 2 hours and an ECG without new ischemic changes can be safely discharged from the ED. Patients requiring additional evaluation include those identified as not low risk or having abnormal diagnostic results (serum troponins or ECG). EDACS-ADP performs reasonably well to identify low-risk patients, although not all studies are supportive.[19,20]

Similar to EDACS-ADP, the HEART Score is another beneficial prediction model for the ED to assist in the identification of low-risk patients, suitable for ED discharge after a limited evaluation.[21-23] This decision tool was developed in the Netherlands as a rapid risk stratification tool for patients with chest pain suspected of AMI in the emergency department. It is accurate in predicting short-term risk of MACE, defined as AMI, need for PCI or CABG, and death within 6 weeks of the index ED visit. Its value to the emergency physician and utility in the ED are based on the following characteristics: ease of use, separation of the patient population into three discrete risk subgroups, accuracy in identifying short-term cardiovascular risk, and readily available variables for calculation.

The HEART Score is easily calculated using information obtained from a standard ED evaluation. Based upon five different variables, the HEART Score is summed, using the patient history of the chest pain event (H), 12-lead ECG (E), patient age (A), risk factor burden (R), and single serum troponin determination (T). Scoring ranges from 0 to 2 for each of these five variables, with the lowest possible total score of 0 and the highest MACE rate possible total score of 10. Low-risk patients (a score 3 or less) were found to have a low rate of MACE (1.7%).These low-risk patients were categorized as appropriate and safe for ED discharge with short-term follow-up and without additional ED cardiac evaluation or inpatient admission; conversely, a higher score was associated with an increased MACE rate and warranted additional evaluation or intervention. In the higher score range, two additional subpopulations were noted, including intermediate- (or moderate) and high-risk groups. The intermediate-risk group, scored in the range of 4 to 6, is associated with a MACE rate of approximately 12% to 17%. The suggested ED evaluation strategy includes the consideration of ED observation and additional risk stratification testing, with or without cardiology consultation. The high-risk group, with a score of 7 to 10, is associated with a MACE rate of approximately 50% to 65%; in this score category, the patient is likely objectively ill and warrants the consideration of coronary intervention as well as admission to the hospital. The HEART score has been validated in many studies, both retrospective and prospective.[22-24]

The HEART Score was designed for use in ED patients suspected of AMI and should not be used in clinical settings outside of the ED population. In addition, an understanding of the five variable components of the HEART Score is mandatory; the application of incorrect variable definitions can result in inaccurate, and thus potentially compromised, scoring (Table 64.7 and Fig. 64.29)

When applying the HEART Score, clinicians can be hesitant to base clinical decision making on a single troponin. Consequently, the HEART Pathway was developed with additional improvement in diagnostic accuracy; it involves a combination of the HEART Score with

an additional troponin obtained at 3 hours.[25] To use this pathway, the clinician determines an initial HEART Score; patients are divided into two groups, including lower (HEART Score 0-3) and higher (HEART Score 4-10) risk groups. A repeat serum troponin is then obtained at 3 hours with further risk categorization into three evaluation-strategy groups: early ED discharge with short-term follow-up (HEART Score 0–3 and serial troponin negative); observation unit or short-term admission with consideration of additional testing (HEART Score 0–3 with serial troponin positive or HEART Score 4–10 with serial troponin negative); and inpatient admission with cardiology evaluation (HEART Score 4–10 with serial troponin positive). The HEART Pathway has been noted to have a higher sensitivity and greater negative predictive value for MACE as compared with the HEART score itself[25] (Fig. 64.30).

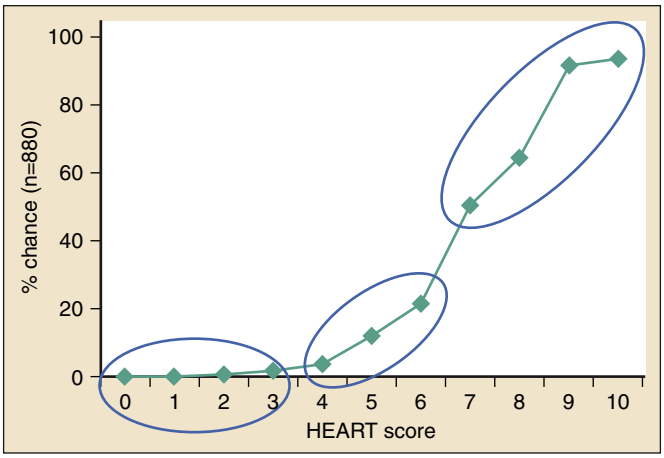


Fig. 64.29 Risk stratification via the HEART score can help identify patients at low, moderate, or high short-term risk of major adverse cardiac events.

Application of any of these decision tools can improve resource utilization in the ED. However, these decision tools applied in isolation of clinician judgment do not dictate evaluation or management strategies of the ED patient suspected of ACS. Treatment and intervention are guided by the patient's condition, local resource availability, and physician assessment.

ED Evaluation of the Chest Pain Patient with Suspected ACS

The ED evaluation of the patient with chest pain, or related complaint, suspected of ACS occurs during three distinct phases of care (Fig. 64.31),

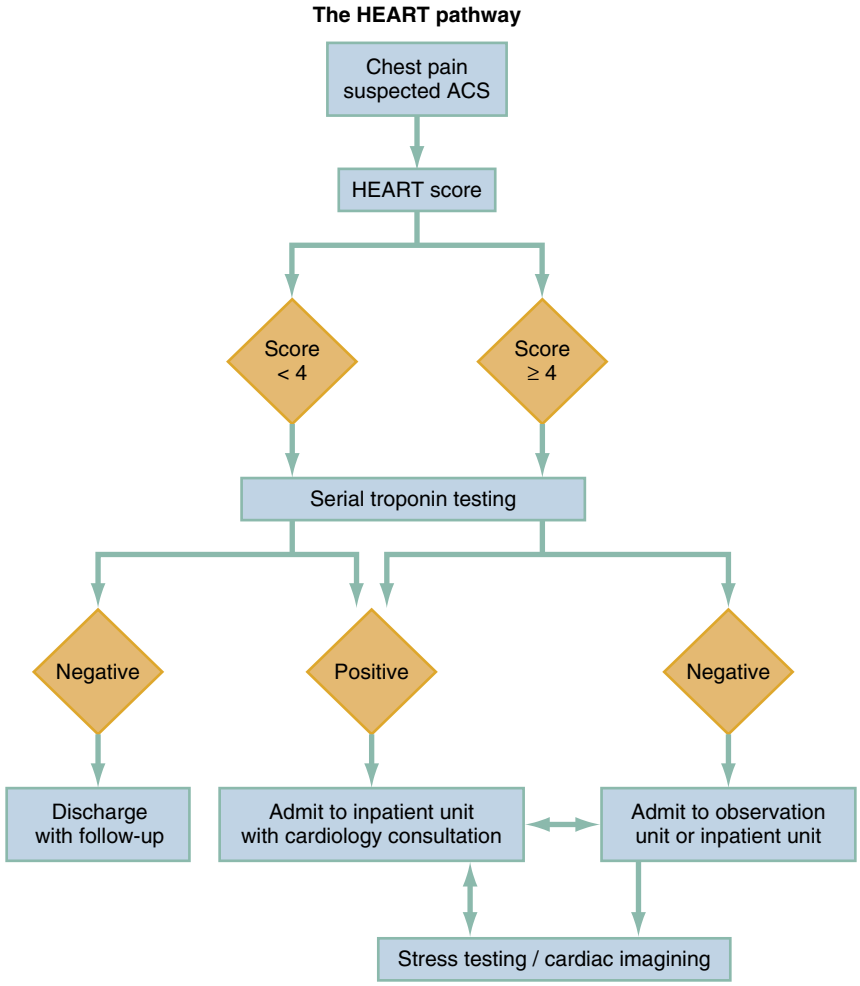
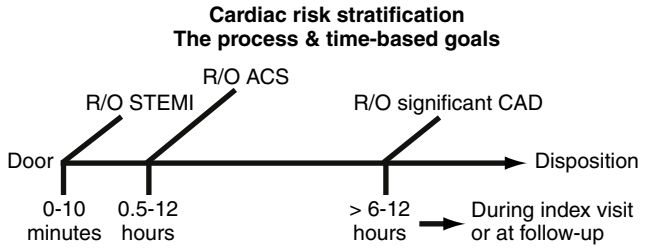


Fig. 64.30 The HEART Pathway utilized a combination of the HEART score and serial troponin testing at 0 and 3 hours. Patients deemed low-risk via the HEART Pathway may be eligible for early ED discharge with short-term follow-up. The HEART Pathway has a higher sensitivity and greater negative predictive value for MACE than the HEART score alone.



Time period	Goal	Tools
0 to 10 min	STEMI identification	Focused exam & ECG
0.5 to ~6-12 hrs	ACS identification	Serial exam, ECG, & biomarkers
>~6-12 hrs	CAD identification	Potential cardiac imaging

Fig. 64.31 The process of evaluation of the chest pain patient suspected of acute coronary syndrome (ACS) occurs through three distinct phases of care, including ST segment elevation myocardial infarction (STEMI) recognition, rule-out (R/O) acute coronary syndrome (ACS), and consideration of significant coronary artery disease (CAD) phases.

including STEMI recognition, rule-out of ACS, and consideration of significant CAD; this last phase may or may not occur in the ED. During this evaluation, risk assessment occurs. In the first phase, STEMI is the primary diagnostic consideration; rapid performance and competent interpretation of the 12-lead ECG are important goals during this stage so that STEMI is recognized with prompt activation of appropriate ED- and hospital-based resources. These patients are either admitted to the hospital for further care or transferred expeditiously to a more appropriately resourced facility. This phase of evaluation, the recognition of evolving STEMI, is usually quite short, likely less than 10 minutes.

If STEMI or other significant ACS presentation is not found, then the second phase focuses on a traditional rule-out MI approach, in which the patient is monitored clinically as serial ECGs and serum marker determinations are performed. The evolution of STEMI as well as the diagnosis of NSTEMI and significant ACS will be made during this phase of ED evaluation. Alternative diagnoses can be established during this period. If the patient "rules in" for NSTEMI or other significant ACS presentation, inpatient admission or transfer will follow. If the patient "rules out" for AMI and more significant ACS, then the final evaluation phase is considered.

Approximately 75% to 80% of patients with chest pain can be safely evaluated in the ED or observation unit with ultimate discharge to home. Expedited ED evaluations without hospital admissions result in significant cost savings, more appropriate resource utilization, and avoidance of complications related to hospital stays, with typical charges and actual costs ranging from 20% to 50% of the usual inpatient costs. This phase of care is quite variable in length and is largely based on the chosen serum marker determination strategy, ranging from an hour with one troponin sampling up to approximately 12 hours with serial serum biomarker assessments. This approach does require significant and appropriate resourcing of the ED in terms of space, personnel, and equipment.

In this final phase, the consideration of significant (i.e., obstructive) CAD is made. Multiple appropriate pathways, both during the ED stay and also after ED discharge, exist for this last goal and are highly dependent on many factors, including patient presentation features, patient stability, physician judgment, local medical resources, local resource availability, and patient desires; these different pathways include the following strategies:

- ED discharge with no further outpatient evaluation needed;
- Outpatient follow-up with primary care physician or cardiologist;
- Continued additional ED or observation unit evaluation with or without cardiology consultation; and
- Inpatient admission with continued diagnostic evaluation.

The first two dispositions end the ED stay most rapidly with discharge to home whereas the latter two dispositions extend the ED or hospital stay by hours or longer.

Patient risk stratification occurs during the first and second phases of the evaluation, using physician judgment, the results of the ED evaluation, and (potentially) clinical decision rules, such as EDACS-ADP, the HEART Score, and HEART Pathway. High-risk patients, those individuals with identified STEMI and other significant ACS presentations (i.e., obviously abnormal ECG, elevated serum troponin values, higher EDACS-ADP score, HEART score, or HEART Pathway result, or other significant clinical issues), are managed appropriately with inpatient admission or expeditious transfer to a resource-appropriate facility; furthermore, those patients with alternative non-ACS findings noted during evaluation are managed according to the specific diagnoses. Removing these ill patients from the consideration leaves the intermediate- and low-risk individuals.

These remaining patient groups, both in the intermediate- and low-risk categories, are identified using a range of qualitative and quantitative methods. The intermediate risk patient, identified by physician gestalt, diagnostic study results, ED course, or clinical decision rules, requires additional evaluation during that hospital visit. If used, intermediate HEART score or HEART Pathway results are found in this patient subgroup.

The intermediate-risk patient's continued evaluation can occur in the ED, an observation unit, or as an inpatient. The observation unit strategy can be employed in a specific unit designed for this type of evaluation; alternatively, the observation unit methodology can be employed in the ED, in essence using a virtual observation unit strategy. Regardless of the location within the hospital, a chest pain–accelerated diagnostic protocol is an appropriate approach to intermediate-risk patients. Many EDs, in partnership with cardiology, employ further ACS evaluation with stress testing, echocardiography, coronary CT angiography, or myocardial scintigraphy before disposition. Studies have compared the observation unit approach with the traditional hospital admission to rule out MI, showing a significant reduction in hospital admissions with no increase in adverse events.

The low-risk patient, identified using similar methodology as noted previously, likely can be managed as an outpatient with either primary care physician or cardiology follow-up. For instance, patients with either a low EDACS-ADP score, HEART score, or HEART Pathway result are safely discharged from the ED with subsequent follow-up. At follow-up, in some instances, no further evaluation for coronary heart disease is needed; in other cases, the outpatient physician can choose to pursue risk stratification via exercise stress testing, nuclear imaging, echocardiography, or coronary CT angiography. Alternatively, certain low-risk patients can be evaluated with further ED or hospital observation, as outlined for the intermediate-risk group.

MANAGEMENT

An understanding of the pathophysiology of ACS allows the emergency clinician to select the most appropriate therapies for the ACS patient. ACS pathophysiology includes the following: (1) endothelial damage through plaque disruption, irregular luminal lesions, and shear injury; (2) platelet aggregation; (3) thrombus formation causing partial or total lumen occlusion; (4) coronary artery vasospasm; and (5) reperfusion injury caused by oxygen free radicals, calcium, and neutrophils. In patients with noninfarction ACS, spontaneous fibrinolysis of the thrombus occurs rapidly, minimizing ischemic insult;

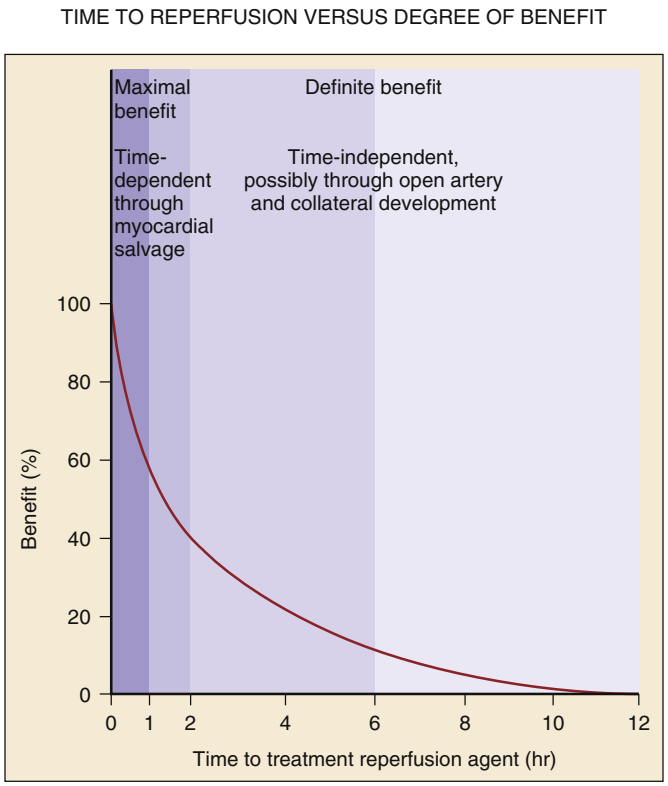


Fig. 64.32 Relationship between time to reperfusion and benefit in STEMI. This figure depicts combined human and animal data and represents the time-dependent benefit anticipated, depending on the length of the interval between coronary artery occlusion and reperfusion. (Adapted from: Tiefenbrunn AJ, Sobel BE: Timing of coronary recanalization. Paradigms, paradoxes, and pertinence. *Circulation.* 1992;85:2311; and from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute [NIH Publication No. 93-3278], September 1993, p 8. Copyright ©1992 American Heart Association.)

persistence of the occlusive thrombus often results in more severe ACS forms including NSTEMI, STEMI, and sudden cardiac death.

Time-Sensitive Nature of Acute Coronary Syndrome Therapy

Early patency resulting in myocardial salvage is the key benefit of emergent reperfusion therapy, using either fibrinolysis or PCI. Timely treatment within the first hours after symptom onset may result in substantial, if not complete, myocardial salvage. Delivered later, from 3 to 12 hours after STEMI onset, treatment may result in a more modest, but still significant, benefit. The opening of the occluded artery causes less adverse ventricular modeling, reduces the occurrence of ventricular aneurysm, increases blood flow to the myocardium, and improves electrophysiologic stability. Angiographic patency at 90 minutes is strongly associated with preserved left ventricular function and mortality at the 24-hour and 30-day endpoints. The relationship between rapid revascularization and mortality has been clearly demonstrated, and it has been shown that with each additional 30 minutes of delay to PCI, the relative 12-month mortality risk increases by 7.5%. Figure 64.32 depicts the relationship between time to reperfusion and benefit in STEMI.

Prehospital delay factors occur from the time the patient decides to seek medical attention until the patient arrives at the ED. For nearly half of patients with suspected AMI, the EMS system is the point of first medical contact. Wide variations in the availability of EMS systems and their varied levels of integration into their local ED and hospital ACS identification and evaluation processes can further complicate and delay care. EMS system resources are related to patient care ability; in systems with advanced and robust local resources, very comprehensive state of the art care is possible.

Further delays can occur between the time a patient arrives at the hospital and initiation of acute revascularization therapy. Although studies have shown that the average time to fibrinolysis ranges from 45 to 90 minutes, the AHA recommends that all patients with STEMI undergo primary PCI (i.e., device across the culprit artery) no later than 90 minutes after arrival or receive fibrinolytic therapy within 30 minutes of arrival.[26]

STEMI patients who receive hospital-based reperfusion therapies (e.g., PCI, fibrinolytic agent) progress through a sequence of steps that can define process time points. Within each interval, various impediments to timely care can occur. Reducing delay times is applicable to all time points in the ED by addressing the four Ds: ***d***oor (events before arrival at the ED), ***d***ata (obtaining the ECG), ***d***ecision (arriving at the STEMI diagnosis and deciding on therapy), and ***d***rug (administering the fibrinolytic agent or passing the angioplasty catheter across the culprit lesion for PCI candidates).[27]

Prehospital notification to the ED of the impending arrival of a patient with a suspected STEMI, particularly when ST segment elevation is suspected, has become standard practice in many established EMS systems. A field 12-lead ECG may assist in diagnosis and decrease the reperfusion time by initiating the hospital-based sequence of necessary events to occur in parallel, as opposed to serially. Some systems have been able to bypass the ED in selected prehospital notifications of STEMI, and these patients go directly from the ambulance to the CCL for PCI. These systems have shown significant decreases in door to reperfusion times. However, data demonstrating improvement in clinical outcomes, including mortality, are lacking.

Self-transported patients with possible ACS should be evaluated by the triage nurse immediately and an ECG acquired within 5 to 10 minutes of arrival. This ECG should be interpreted rapidly by a competent clinician capable of recognizing STEMI. This interpretation is primarily aimed at detecting STEMI and other life threats; formal interpretation of the ECG occurs later at the time of complete ED evaluation. The development of hospital-based protocols and system response plans to identify and rapidly treat patients reduces the amount of time to treatment.

When using fibrinolysis in uncomplicated cases where PCI is not available, the emergency clinician should activate the hospital-based system for reperfusion. Checklists of inclusion and exclusion criteria for fibrinolytic therapy should be available, and those fibrinolytic agents should be stored and administered in the ED. In a system in which fibrinolysis is the sole reperfusion therapy, the decision to administer that therapy rests with the emergency clinician. Nonconsultative communications with family physicians, internists, or cardiologists before administration of the agent may result in unnecessary delays. Consultative discussions before the administration of therapy should only be obtained in complicated situations.

If the hospital offers primary PCI, many hospitals activate so-called STEMI alert responses when a STEMI patient is identified prehospital or in the ED. Analogous to the trauma alert, the cardiologist and catheterization laboratory personnel are immediately mobilized. Prehospital or emergency clinician activation of the catheterization laboratory demonstrates very high rates of accurate STEMI diagnosis, with very low rates of false activation (i.e., the STEMI mimic) while markedly reducing the time to definitive therapy. Interhospital transfer of STEMI patients for PCI when they are also candidates for fibrinolysis should be discouraged if definitive therapy (i.e., catheter placement across the

TABLE 64.8 Medications Used in Emergency Department Management of Acute Coronary Syndrome (ACS)

Medication and Medication Class	Examples	Indications	Risk Issues
Nitroglycerin	Nitroglycerin (sublingual, topical, IV)	Chest pain, pulmonary edema medication, blood pressure medication	Hypotension
Opioids	Morphine, fentanyl	Chest pain	Hypotension, respiratory suppression
β-Adrenergic Blockers			
• IV	Metoprolol, labetalol, esmolol	Blood pressure agent, dysrhythmia agent	Hypotension, bradycardia, cardiogenic shock
• Oral	Metoprolol	None; inpatient use	
ACE inhibitors	Captopril, enalapril, lisinopril, ramipril	None; inpatient use	
Statins	Lovastatin, atorvastatin, simvastatin, pravastatin	None; inpatient use	
Calcium channel blockers	Diltiazem	None; inpatient use	
Aspirin	Aspirin	Chest pain	Hemorrhage, gastric irritation
Other antiplatelet agents	Clopidogrel, ticagrelor, prasugrel, ticlopidine	ACS (with objective confirmation)	Hemorrhage
Antithrombin agents	Heparin, enoxaparin, bivalirudin	ACS (with objective confirmation)	Hemorrhage, heparin-induced thrombocytopenia (for heparins)
Fibrinolytic agents	Streptokinase t-PA r-PA Tenecteplase	STEMI	Hemorrhage

culprit lesion) is likely to be delayed beyond 120 minutes, except in cases of hemodynamic shock (see later) or in patients for whom fibrinolysis is contraindicated.[26]

Pharmacologic Intervention

A range of medications can be used in the patient with ACS (Table 64.8). These agents range from the basic to the complex, including oxygen, IV fluids, antiplatelet and anticoagulant agents, nitroglycerin, opioid analgesics, β-adrenergic blocking agents, and fibrinolytic agents.

Oxygen

Oxygen is considered a medication, one with significant potential to benefit and harm the patient with ACS. A brief mention of the most appropriate strategy for oxygen treatment in the ACS patient is warranted. Respiratory compromise can occur during ACS, usually as a result of acute pulmonary edema or exacerbation of chronic pulmonary disease. Suspected ACS patients with respiratory compromise, demonstrated by physical examination or oxygen saturations, should receive supplemental oxygen as standard therapy. The historical rationale for this oxygen therapy was that maximization of oxygen saturation may improve oxygen delivery to the tissues and thus reduce the ischemic process and related negative outcomes.

Recent investigation suggests that routine supplemental oxygen therapy in ACS patients with normal oxygen saturations and the absence of respiratory compromise does not provide benefit from such intervention; infarction size, mortality rates, and the occurrence of adverse events are not reduced by such oxygen use.[28-30] Furthermore, oxygen therapy delivered to these normoxic ACS patients can increase both myocardial injury and infarct size.[31] The practice of administering oxygen to all patients, regardless of their oxygen saturation, is based on rational conjecture and research performed before the current reperfusion era in acute coronary care. More recent studies of this issue have suggested that supplemental oxygen therapy does not offer any benefit; specifically, mortality rates, recurrent MI, cardiogenic shock, heart failure, arrhythmias, or infarction size are not impacted by supplemental oxygen administration.[28-30]

Additional work suggests that supplemental oxygen therapy can increase the rate of adverse outcomes in the ACS patient, particularly involving STEMI. Hyperoxia, developing as a result of excessive supplemental oxygen therapy, can potentiate coronary vasoconstriction and increase oxidative stress, worsening outcomes in these patients. The AVOID trial demonstrated that oxygen therapy, delivered to patients suspected of STEMI who also had normal oxygen saturations and no other evidence of respiratory compromise, likely increased early myocardial injury and was associated with larger myocardial infarct size assessed at 6 months. Furthermore, reinfarction and cardiac dysrhythmia were also increased in the oxygen therapy group.[31]

Thus, in suspected or confirmed ACS patients, supplemental oxygen therapy is appropriate for patients demonstrating respiratory compromise, noted by physical examination or oxygen saturations less than 94%. Conversely, in patients without respiratory compromise, oxygen therapy can be withheld.

Nitroglycerin

Nitrates decrease myocardial preload and, to a lesser extent, afterload. Nitrates increase venous capacitance and induce venous pooling, which decreases preload and myocardial oxygen demand. Direct vasodilation of coronary arteries may increase collateral blood flow to the ischemic myocardium.

Nitroglycerin has been used for decades in patients with suspected or known ACS. Most studies of IV NTG in the setting of ACS, however, are from the prefibrinolytic era. Although data from multiple trials performed in the prefibrinolytic era noted a 35% mortality reduction with IV NTG in the setting of AMI, no contemporary evidence (i.e., in the reperfusion era of acute cardiac care) has shown improved outcomes with the routine use of any form of nitrate therapy in patients with

AMI. In patients with significant, symptomatic coronary vasospasm, NTG can be quite beneficial; unfortunately, the ability to identify the presence of significant vasospasm at the bedside is not possible.

In the ACS patient, it must be noted that the use of NTG in any formulation is a management option, yet its use is not mandatory. If hypotension is present or is anticipated to occur (i.e., inferior wall STEMI with identified or suspected right ventricular infarction), it is very appropriate to withhold NTG in all formulations.

Patients with possible ACS and a systolic blood pressure greater than 90 mm Hg can receive a sublingual NTG tablet (0.4 mg [400 μg]) on presentation. If symptoms and pain are not fully relieved with three sublingual tablets, topical or IV NTG can be considered. Topical nitroglycerin is administrated in the form of a paste with dosages delineated by the inch; initial topical applications range from 0.5 to 2 inches. For intravenous administration, an initial infusion rate of 10 μg/min is titrated to pain symptoms. The emergency clinician can increase the infusion at regular intervals of at least every 5 minutes, allowing a 10% reduction in the mean arterial pressure if the patient is normotensive and a 20% to 30% reduction if hypertensive. With bradycardia, hypotension, inferior wall STEMI, and right ventricular infarction, a sudden decrease in preload associated with NTG can result in profound hypotension. Caution is advised in these settings.

Morphine and Other Opioid Analgesic Agents

Morphine is a potent opioid analgesic with weak sympathetic blockade, systemic histamine release, and anxiolysis. If a patient with possible ACS is unresponsive to NTG or has recurrent symptoms despite maximal antiischemic therapy, administration of morphine sulfate is a reasonable analgesic intervention. The relief of pain and anxiety can decrease oxygen consumption and myocardial work. Some vasodilatory effects are also noted with preload reduction. Standard doses of morphine sulfate are 2 to 4 mg up to 0.1 mg/kg IV, repeated every 5 to 30 minutes as necessary. Caution is advised with morphine use in this setting.

Although appropriate, it must be remembered that morphine is a potent medication with significant vasodilatory effects and profound sedation, with resultant respiratory depression. In addition to allergic reactions, another significant adverse effect of morphine sulfate administration is hypotension, which is managed with IV crystalloid as a bolus.

Recent reviews of morphine use in various populations of chest pain patients, including those with suspected ACS as well as those already diagnosed with STEMI have demonstrated no increased rate of adverse outcomes.[32,33] Its use in small to modest amounts in most patients is reasonable. In addition to its analgesic properties, it is also an anxiolytic agent, a valuable feature in certain ACS patients. Withholding morphine and other analgesic agents is appropriate if the emergency physician is concerned about the potential for iatrogenic hypoperfusion, sedation, or respiratory depression.

Other opioid agents, such as fentanyl, are reasonable for use in the ACS patient. Fentanyl can be used in dosing range of 12.5 to 50 mcg IV, repeated every 5 to 30 minutes as needed. The same caveats and general recommendations as noted with morphine apply to fentanyl and other opioid agent administrations in the ACS patient.

Beta-Adrenergic Blockers

Historically, β-adrenergic blocking agents have been used to ameliorate catecholamine-induced tachycardia, including ventricular fibrillation, increased contractility, and heightened myocardial oxygen demand during the acute infarction period. Although beta blockade was shown to decrease mortality for patients with AMI, these observations occurred when adjunctive therapies were few and β-adrenergic blockade was essentially monotherapy in AMI.

Contemporary management strategies include highly effective reperfusion therapies coupled with potent anticoagulant and antiplatelet agents; thus, the widespread use of β-adrenergic blocking agents must be reconsidered. In fact, multiple studies have suggested that the widespread intravenous use of β-adrenergic blockade should be curtailed. The use of the early IV β-adrenergic blocking agents in these studies was associated with higher rates of death, heart failure, cardiogenic shock, recurrent ischemia, and pacemaker use as compared to patients who received early oral administration. These increases occurred despite the exclusion of patients with obvious contraindications, including preexisting hypotension, bradycardia, or heart failure. Several large studies evaluated patients with suspected STEMI and β-adrenergic blocking agent use, comparing early IV administration followed by continued oral therapy versus placebo; these studies found no significant difference between the two groups in terms of mortality; the group receiving β-adrenergic blockers, however, demonstrated a minimal reduction of reinfarction and the occurrence of ventricular fibrillation. These benefits were at the expense of a significantly higher rate of cardiogenic shock and increased rates of development of heart failure requiring treatment, persistent hypotension, and bradycardia.

The early IV use of β-adrenergic blocking agents, when coupled with contemporary therapy in the setting of ACS, does not appear to offer significant benefit and is associated with an increased rate of adverse events. Therefore, early IV administration in the ED ACS patient is discouraged. Conversely, oral administration of beta blockers to ACS patients without contraindications during the first 24 hours of management is a class I recommendation from the ACC/AHA and can be accomplished in the hospital after admission.[26] This strategy allows for stabilizing the patient while additional clinical data are obtained to determine appropriateness of this therapy.

Empirical therapy in the ED should be reserved for only those patients who have adverse effects from significantly elevated blood pressure or significant tachydysrhythmia, despite other appropriate medications. If IV therapy is needed in the ED, metoprolol 5 mg can be administered once. Additional doses of 5 mg can be given intravenously at 15- to 30-minute intervals for a maximum cumulative dose of 15 mg.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitor agents benefit patients with CHF. ACE inhibitors may also reduce morbidity and mortality after AMI. In particular, patients treated with ACE inhibitors experience a reduction in cardiovascular mortality, decreased rates of significant CHF, and fewer recurrent AMIs. These benefits increase when ACE inhibitors are used in conjunction with other agents, such as aspirin and fibrinolytic agents. The mechanism of action regarding a reduction in recurrent AMI is unknown but may involve a reduction in plaque rupture related to decreased intracoronary shear force or neurohumoral influences. Therapy should be initiated within the first 24 hours following an ACS event, although ED administration is not indicated.

HMG–Coenzyme A Reductase Inhibitors

HMG–Coenzyme A reductase inhibitors (statins) have demonstrated a reduction in inflammation and reinfarction, angina, and lethal arrhythmia in the first few days after an ACS event. Although there is no indication for statin therapy in the ED management of ACS, initiation of this therapy should occur within the first 24 hours or continue if patients are already undergoing statin therapy, because discontinuation during hospitalization is associated with an increase in near-term mortality and adverse events. The administration of statin therapy before elective or urgent PCI for ACS is reasonable to decrease periprocedural

AMI; however, there are no specific risk or safety data regarding its use in this setting.

Calcium Channel Blockers

Calcium channel blockers have a minimal role in the ED management of the ACS patient. As with beta blockade, the primary benefit of calcium channel blockers appears to be limited to symptom resolution. Unfortunately, these agents may be accompanied by significant vasodilation, resulting in hypotension and potentiation of the coronary ischemic process. Like beta blockers, calcium channel blockers have a substantial negative inotropic effect. AV nodal blockade is also a significant side effect that may be exacerbated in patients previously treated with beta blockers or with ischemia-related conduction disturbance. Unless used explicitly for rate control of supraventricular dysrhythmia (e.g., atrial fibrillation with rapid ventricular response) in a patient who cannot tolerate beta blockade, calcium channel blocker agents have no role in the ED management of ACS.

Antiplatelet Therapy

In non-AMI ACS patients (i.e., unstable angina), dramatic reductions in the progression to acute infarction are noted with appropriate antiplatelet therapy. The administration of antiplatelet therapy, particularly aspirin, is indicated in the ED for most ACS patients. For AMI, the administration of aspirin and other antiplatelet agents is associated with significant reductions in mortality, ranging from 25% to 50%; mortality reduction is most prominent in the AMI patient when aspirin is used in the setting of reperfusion therapy.

Aspirin. Aspirin, the prototypical antiplatelet agent, is the most cost-effective treatment in ACS care. It irreversibly acetylates platelet cyclooxygenase, thereby removing all activity for the life span of the platelet (8 to 10 days). Thus, aspirin stops the production of proaggregatory thromboxane A2 and is an indirect antithrombotic agent. Aspirin also has significant nonplatelet effects because it inactivates cyclooxygenase in the vascular endothelium, thereby diminishing the formation of antiaggregatory prostacyclin.

It is well established that aspirin independently reduces the mortality of patients with AMI without fibrinolytic therapy (overall 23% reduction) and is synergistic when used with fibrinolytic therapy (42% reduction in mortality). The usual dose is 324 mg of non–enteric-coated aspirin, chewed and swallowed. Enteric-coated aspirin should be avoided in the acute setting of ACS due to its delay in the onset of antiplatelet activity.

The administration of aspirin in the ED is strongly recommended as soon as possible for any patient with suspected ACS. It should be administered to all such patients unless significant allergy, hemorrhage, or other issues, such as suspected aortic dissection, contraindicates its use. It must be noted that a hemoccult positive stool result, without bright red blood or melena, is not a contraindication for aspirin administration. More recent studies have established that lower dose aspirin (<162 mg) appears to be as effective as higher dose aspirin (>162 mg) at preventing adverse cardiac events, with fewer bleeding risks, although most clinicians continue to administer 324 mg dose. These findings were consistent when given alone or with other antiplatelet agents (e.g., clopidogrel).

$P2Y_{12}$ Receptor Inhibitor Agents. The $P2Y_{12}$ inhibitors include the thienopyridines ticlopidine, clopidogrel, and prasugrel, as well as ticagrelor and cangrelor. They are more potent platelet inhibitors than aspirin. The thienopyridines inhibit the transformation of the $P2Y_{12}$ receptor into its high-affinity ligand-binding state, irreversibly inhibiting platelet aggregation for the duration of the life of the platelet. Ticlopidine has nonlinear kinetics and, with repeated administration, reaches a maximal effect after 8 to 11 days of use. Clopidogrel, a ticlopidine analogue, and prasugrel have the advantage of a rapid onset of action.

Clopidogrel has traditionally been the preferred ED agent of this class due to its relatively rapid onset of action, good safety profile, and efficacy when given in ACS and associated with thrombolytic therapy. Prasugrel incurs a higher bleeding risk than clopidogrel. Relative contraindications include use in patients older than 75 years and those who weigh less than 60 kg. Absolute contraindications include in those who have had a previous transient ischemic attack (TIA) or stroke, and those at high risk for bleeding. TRITON-TIMI 38 demonstrated that prasugrel was superior to clopidogrel using a composite outcome; however, this is tempered by an increased risk of bleeding. The ACCOAST trial showed no improvement in outcomes for patients treated with prasugrel in the ED versus dosing at the time of PCI. Because of this and other similar studies, prasugrel has traditionally not been recommended for upstream use in the ED in ACS patients.

Ticlopidine is associated with a risk of neutropenia, thrombotic thrombocytopenic purpura, and agranulocytosis; furthermore, it demonstrates a much slower onset of platelet inhibition. With clopidogrel, maximal platelet inhibition occurs after 3 to 5 days of clopidogrel therapy with 75 mg daily; an earlier onset of platelet inhibition is seen when a higher loading dose is used (300–600 mg). For example, there is clear benefit to clopidogrel administration (300 mg loading dose) at least 6 hours before PCI in patients with STEMI; higher doses (e.g., 600 mg) demonstrate a trend toward improvement at slightly earlier time periods (i.e., 3–4 hours).

Ticagrelor and cangrelor also act as $P2Y_{12}$ receptor inhibitors, although its activity is reversible and occurs via a different mechanism not requiring hepatic activation. Ticagrelor is rapidly absorbed, reaching peak serum concentration at 2.5 hours. Clinical data have demonstrated that ACS patients given ticagrelor were less likely to die from cardiovascular causes. However, these improved outcomes are tempered by higher rates of non-procedure-related bleeding, including more frequent fatal intracranial hemorrhage when compared with clopidogrel administration. Further analysis of the PLATO study has assessed the increased cost of ticagrelor versus clopidogrel when combined with aspirin and determined that, with the increased life expectancy, ticagrelor plus aspirin is cost-effective.

Cangrelor, an IV $P2Y_{12}$ receptor inhibitor, has potential for significant therapeutic advantages over the other drugs in this class due to its immediate onset of antiplatelet activity and very short half-life. It is administered IV in its active form (unlike clopidogrel), not as a prodrug requiring metabolism prior to its onset of action. Unlike the oral drugs in this class, which require 2 to 6 hours to reach active levels, cangrelor is active immediately on injection. This near-immediate onset of action has potential benefits in patients who are undergoing rapid PCI—specifically, the STEMI population with an invasive management plan. Some experts have also proposed its use in patients with STEMI who have been resuscitated from cardiac arrest and are unable to take oral medications.[34] Cangrelor also has a very short half-life (4–6 minutes), which makes the treatment of potential CABG patients with a $P2Y_{12}$ receptor inhibitor possible up until the time of surgery. Initial studies have demonstrated the ability to maintain low levels of platelet activity in the presurgical time period on cangrelor, compared to the recommended 5 days off of the other oral $P2Y_{12}$ receptor inhibitors, without an increase in major bleeding in CABG patients. Cangrelor also appears to have the potential for improved outcomes in patients undergoing PCI when compared to current antiplatelet therapy.

The 2013 AHA Guidelines for STEMI management recommend patients receive a loading dose of clopidogrel or ticagrelor in addition to standard ACS care (ASA, anticoagulants, and reperfusion therapy), assuming there are no contraindications to use, prior to PCI.[35] For patients with definite or likely NSTEMI, following the 2014 AHA

guidelines for NSTEMI management, the administration of a $P2Y_{12}$ receptor inhibitor should also be initiated in the ED prior to PCI.[9]

The current data to support one particular $P2Y_{12}$ inhibitor over another is mixed. Initial data from the PLATO trial favored the use of ticagrelor over clopidogrel, however more recent data have shown no significant differences in MACE rates at 1 year.[36] Additionally, the recent ISAR-REACT 5 trial demonstrated a decrease in 1-year MACE in ACS patients receiving prasugrel over ticagrelor.[37] Notably, in this trial, patients with NSTEMI randomized to ticagrelor received therapy as soon as possible after diagnosis and randomization, whereas prasugrel was held until after diagnostic angiography was completed, but given before percutaneous intervention. In STEMI patients, treatment was administered as soon as possible in both treatment groups.

Given the current state of the literature, therapy with clopidogrel, ticagrelor, or prasugrel is reasonable in patients likely to undergo PCI. Considerations should be given to each agent's potential risks and benefits (e.g., prasugrel should not be given in patients with a history of stroke or TIA and used with caution in patients ≥75 years of age or <60 kg). Clopidogrel administration is recommended (ACC/AHA class I indication) for patients with a high-risk ACS presentation and true aspirin allergy. This high-risk presentation would be characterized by objective clinical abnormality, including a significantly abnormal serum marker or 12-lead ECG.

In the patient with UA or NSTEMI, clinical benefit has been demonstrated with clopidogrel when a noninvasive treatment strategy is utilized, albeit with an increase in the incidence of major hemorrhage. Invasively managed patients receiving the drug with less time to procedure do not benefit from earlier treatment. Patients with NSTEMI demonstrate improved outcomes with clopidogrel therapy when a conservative treatment scenario is initially followed. Of note, a large portion of these patients will undergo PCI within the first 24 hours after admission; however, this so-called delayed PCI allows for benefit to occur from clopidogrel administered earlier in the course of management.

The medically managed STEMI patient (i.e., with a fibrinolytic agent) also benefits from clopidogrel use. Clopidogrel therapy in conjunction with fibrinolysis, followed by deferred cardiac catheterization occurring at least 2 days after AMI, decreases the rates of death, recurrent ACS, and urgent coronary revascularization. This improvement occurs without a significant increase in hemorrhage.

The potential need for urgent CABG should also be considered. The higher risk ACS patient will more likely benefit from $P2Y_{12}$ receptor inhibitor therapy, but that same patient is also more likely to need urgent CABG. It is difficult, however, to identify ACS patients requiring urgent CABG reliably, and reviews of ED ACS patients have been unable to demonstrate consistent clinical features apparent in the ED that reliably identify patients not requiring CABG. CABG patients undergoing dual antiplatelet therapy (DAPT) have a greater incidence of bleeding perioperatively. However, this increased hemorrhagic rate must be weighed against the benefit in reducing ischemic risk in these patients.[38]

The ACC and AHA have suggested, in the form of a class I recommendation, that clopidogrel or ticagrelor should be withheld for at least 24 hours before urgent on-pump CABG, if possible.[9] Nevertheless, the recommendation suggests that early $P2Y_{12}$ receptor inhibitor therapy be considered in patients who likely will not require CABG. Because it is not currently possible for the emergency clinician to predict which patients will require urgent CABG, collaborative multidisciplinary pathways should be developed, with emergency clinicians, cardiologists, and cardiovascular surgeons providing input.

Glycoprotein IIb/IIIa Receptor Inhibitors. Glycoprotein IIb/IIIa receptor inhibitors (GPIs) are potent antiplatelet agents; they include abciximab, eptifibatide, and tirofiban. GPIs, however, demonstrate clinical usefulness in only the subset of ACS patients undergoing PCI as a reperfusion strategy. Therefore, the primary indication regarding GPI administration is planned mechanical coronary intervention. Furthermore, the largest studies on GPI administration timing have not shown outcome benefit to upstream use in the ED when compared to catheterization laboratory administration. Currently, there is no clear indication for the ED administration of GPIs unless other antiplatelet agents are not tolerated or unavailable. This class of medications is not usually given in the ED setting, and other antiplatelet agents ($P2Y_{12}$ receptor inhibitors) are preferred for administration in the care of ACS. If administered, current guidelines suggest the use of eptifibatide or tirofiban as the preferred agents.[9]

Antithrombins

As with antiplatelet therapies in ACS patients, significant reductions in the progression to acute, recurrent, or extensive infarction and death are noted in individuals treated with aggressive antithrombin therapy. There are currently four options for antithrombin therapy in the setting of ACS, including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct thrombin inhibitors (bivalirudin), and factor Xa inhibitors (fondaparinux). Antithrombotic therapy is indicated for ACS patients with recurrent anginal pain, AMI (NSTEMI and STEMI), a significantly positive serum marker, or a dynamic 12-lead ECG.

Heparins. The term *heparin* refers not to a single structure but to a family of mucopolysaccharide chains of varying lengths and composition—hence, unfractionated—with pronounced antithrombotic properties. At standard doses, UFH binds to antithrombin III, forming a complex that is able to inactivate factor II (thrombin) and activate factor X. This prevents the conversion of fibrinogen to fibrin, thus preventing clot formation. Heparin by itself has no anticoagulant property. This indirect effect on thrombin inhibits clot propagation; it prevents heparin, however, from having any effect on bound thrombin in a thrombus. UFH also assists in the inactivation of factors XIa and IXa through antithrombin and interacts with platelets.

UFH has a profound synergistic effect with aspirin in preventing death, AMI, and refractory angina in ACS patients, particularly those with AMI and, to a lesser extent, high-risk UA. UFH should be administered early in patients with the following ACS features: recurrent or persistent chest pain, AMI, positive serum marker, or a dynamic ECG. In patients receiving thrombolytic therapy and UFH, it has been shown that bleeding and mortality were higher in patients receiving an 80-unit/kg bolus and 18-unit/kg infusion compared with patients with a lower bolus amount and infusion rate. Therefore, the weight-adjusted regimen recommended for UFH in the setting of a STEMI receiving thrombolytic therapy or non-ST elevation ACS patients is an initial bolus of 60 units/kg (maximum, 4000 units) and an initial infusion of 12 units/kg/hr with an activated partial thromboplastin time goal of 1.5 to 2.5 times the control value.[9,35] The weight-adjusted regimen UFH in STEMI patients receiving PCI is dependent on the planned use of a GPI during PCI. If GPI use is planned during PCI, the bolus dose should be 50 to 70 units/kg (no maximum dose) and, if no GPI use is planned, the bolus dose should be 70 to 100 units/kg (no maximum dose).

LMWHs constitute approximately one-third of the molecular weight of heparin and are less heterogeneous in size. LMWHs inhibit the coagulation system in a fashion similar to that of UFH. Approximately one-third of the heparin molecules bind to antithrombin III and thrombin. The remaining molecules bind only to factor Xa. The variable efficacy found among the LMWHs is attributed to different ratios of antifactor Xa to antifactor IIa. High-ratio preparations have a clear

advantage over standard heparin; enoxaparin has the highest ratio of available LMWHs. LMWH was designed based on the hypothesis that the inhibition of earlier steps in the blood coagulation system would be associated with a more potent antithrombotic effect than inhibition of subsequent steps. This results from the amplification process inherent in the coagulation cascade—that is, a single factor Xa molecule can lead to the generation of multiple thrombin molecules.

Potential advantages of LMWH over UFH include easier administration, greater bioavailability, more consistent therapeutic response among patients, and longer serum half-life, producing a more manageable administration schedule, albeit at a higher cost. The combination of aspirin, beta blocker, and LMWH significantly decreases the rate of nonfatal AMI or death in the first several weeks after treatment but has much less pronounced impact out to multiple months. Studies comparing outcomes between LMWH and UFH have shown mixed results; some show better outcomes with LMWH, but others do not. In summary, the LMWH enoxaparin demonstrates some degree of benefit compared with UFH in patients at higher risk for non–ST segment elevation ACS who are treated conservatively without immediate PCI (i.e., beyond 24 hours). For STEMI patients managed aggressively with rapid PCI, UFH is preferred over enoxaparin.

Enoxaparin is administered in a twice-daily regimen subcutaneously at a dose of 1 mg/kg for all ACS patients. If patients have renal dysfunction, with an estimated glomerular filtration rate of less than 30 mL/min, the dose should be reduced to 1 mg/kg in a single daily administration. Few safety data are available for enoxaparin in ACS patients with renal insufficiency, and UFH may be preferable.

Most patients with AMI require therapy with heparin, whether it is fractionated or unfractionated. Non-AMI ACS, however, is different because UA is a heterogeneous condition. Only high-risk UA patients with recurrent or continued pain, or new ischemic electrocardiographic changes, should be considered for heparin therapy. For example, the stable patient with a classic description of new-onset angina, who is pain-free with a negative serum marker and normal ECG, is still correctly diagnosed with UA. In contrast, an individual with ongoing pain, intermittent or constant, with a dynamic ECG clearly is experiencing an active, unstable coronary event. The latter patient, who is at higher risk, can benefit from heparin therapy more than the former.

Heparin therapy, however, can be a major contributor to morbidity and mortality among hospitalized patients. Major bleeding develops in 1 of every 90 patients treated, and heparin-induced thrombocytopenia in 1 of 34 patients. LMWH is as effective as UFH in patients with non–ST segment elevation ACS and does not greatly increase the bleeding risk while decreasing the risk of thrombocytopenia. Contraindications to any heparin therapy include known allergy, active ongoing hemorrhage, and predisposition to such hemorrhage. Furthermore, patients who have their heparin therapy changed (UFH to LMWH and vice versa) during the active treatment phase of their ACS care experience higher rates of bleeding.

Other Antithrombins: Bivalirudin and Fondaparinux. The direct thrombin inhibitor bivalirudin is a potent antithrombin anticoagulant providing significant theoretical advantages compared with heparin. Bivalirudin is a bifunctional 20–amino acid peptide designed on the basis of the structure of hirudin. It has properties similar to those of hirudin but also interacts with the catalytic site of thrombin.

Bivalirudin is at least as effective as heparin in reducing death or reinfarction in patients with ACS, particularly those patients undergoing very early PCI. Bivalirudin, compared with heparin, produces similar rates of ischemia and major bleeding at 1 month. Bivalirudin when used with clopidogrel is comparable to the combination of heparin and GPI before coronary angiography or PCI. When used alone, it is inferior to the combination of heparin and GPI. Bivalirudin should be considered an acceptable alternative anticoagulant agent in the STEMI patient undergoing PCI.[35] Its use is in the ED for ACS patients is primarily limited to those who cannot receive heparin (e.g., known heparin-induced thrombocytopenia).

Fondaparinux is a synthetic oligosaccharide with a structure similar to the heparins. It is the first widely used selective factor Xa inhibitor. In previous comparison studies, fondaparinux was found to be similar to enoxaparin in the short-term reduction of ischemic events, yet substantially reduced major bleeding and improved long-term outcome. When the use of fondaparinux was reviewed in STEMI patients managed medically with streptokinase, it was found that fondaparinux significantly reduced hemorrhage, MI, and death when compared to UFH and LMWH. As a result, fondaparinux has a class 1 AHA recommendation as an alternative to UFH and LMWH in NSTEMI and STEMI patients who are not undergoing PCI.[9,35] However, the increased risk of catheter-associated thrombi during PCI prevents its use without additional UFH administration when an invasive strategy is chosen.

Reperfusion Therapies

Rapidly reestablishing perfusion in the infarct-related coronary artery using fibrinolytic therapy or PCI increases the opportunity for myocardial salvage, with resultant reductions in mortality and improvements in quality of life post-MI. Pharmacologic and mechanical methods of reperfusion are both effective under specific clinical conditions. More than 3 decades ago, the importance of early coronary artery patency was recognized; furthermore, it was demonstrated that 90-minute patency predicts improved survival rates and preserves left ventricular function, thereby optimizing outcome.

Fibrinolytic therapy unequivocally improves survival in STEMI patients and remains an ACC/AHA class I recommendation.[26] Although fibrinolysis has widespread availability and proven ability to improve coronary flow, limit infarct size, and improve survival in STEMI patients, many individuals with acute infarction are not suitable candidates. Patients with absolute contraindications to fibrinolytic therapy, certain relative contraindications, cardiogenic shock, and non-ST segment elevation ACS (most NSTEMI and all UA patients) may not be eligible. PCI is the treatment of choice in the STEMI patient given the limitations of fibrinolytic therapy and the benefits of PCI. However, to provide the most significant benefit, PCI must be performed as soon as possible after the initial presentation. A substantially delayed PCI is inferior to fibrinolytic agents, assuming that the patient has no contraindications to this therapy.

Fibrinolytic Therapy

Fibrinolytic Agent Selection. Options for fibrinolytic therapy include streptokinase (the original fibrinolytic agent) and three types of plasminogen activator: tissue-type plasminogen activator (t-PA) and two recombinant tissue-type plasminogen activators, r-PA (reteplase) and tenecteplase (TNK). Due to more effective, contemporary options for fibrinolytic therapy, and easier to administer alternatives, streptokinase is no longer marketed in the United States. However, it is still used in many areas of the world due to its low cost compared to the other fibrinolytic options.

If t-PA is used, the most effective strategy is described as an accelerated or front-loaded regimen administered over 90 minutes, along with appropriate antiplatelet and anticoagulant therapies. In addition to mortality reduction in all subgroups (i.e., older patients, AMI location, and time since symptom onset), coronary artery patency and degree of normalization of flow were also improved with this protocol. In addition, the angiographic evaluation demonstrated a strong relationship between TIMI flow and outcome; patients with strong forward flow (i.e., TIMI grade 3 flow) at 90 minutes had significantly lower mortality rates than patients with little to no flow. This early t-PA patency

advantage over other agents was lost by 180 minutes after symptom onset. These observations were the first indications of the relationship between early coronary artery patency and improved clinical outcome.

Other large studies have compared accelerated t-PA with r-PA; r-PA can be administered in a fixed, double-bolus dose with no adjustment required for weight, which simplifies administration. r-PA has been found to be equivalent to accelerated t-PA, and results have been nearly identical for the two drugs. The one exception was the patient with presentation more than 4 hours after onset of symptoms, which is a significant number of patients at many institutions. In this group, accelerated t-PA is likely superior to r-PA because of its greater fibrin specificity.

The most recent fibrinolytic agent addition is tenecteplase, referred to in the clinical realm as TNK. TNK has several potential benefits over existing agents, including: (1) its longer half-life, allowing for a single bolus administration; (2) it is 14 times more fibrin-specific than t-PA and even more so than r-PA; and (3) it is 80 times more resistant to plasminogen activator inhibitor type 1 than t-PA. In comparisons of single-bolus TNK (30–50 mg on the basis of body weight) or accelerated t-PA (100 mg total infusion), there were no differences in mortality or intracranial hemorrhage. For the subgroup of patients presenting more than 4 hours after onset of symptoms, however, there may be a 30-day mortality benefit and fewer non-intracranial major bleeding episodes with TNK. Thus, it appears that TNK is marginally more effective, minimally safer, and easier to administer than t-PA, and thus is the recommended fibrinolytic agent. Furthermore, cost differences are minimal.

Eligibility Criteria for Fibrinolytic Agent Therapy. In the absence of contraindications, fibrinolytic therapy should be considered in patients with STEMI and the onset of ischemic symptoms within the previous 12 hours when it has been anticipated that primary PCI cannot be performed in a timely fashion.[26] The following section discusses the specific issues regarding fibrinolytic agent eligibility, with a focused discussion of contraindications.

12-Lead Electrocardiogram. Combined with the patient's history and physical examination, the 12-lead ECG is the key determinant of eligibility for fibrinolysis. The electrocardiographic findings should be consistent with STEMI based on the European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/AHA/World Heart Federation Task Force for the Fourth Universal Definition of Myocardial Infarction.[3] These findings include diagnostic ST elevation—in the absence of LVH, LBBB, and right ventricular paced pattern from an implanted pacemaker—including ST elevation at the J point in at least two contiguous leads with cutoffs as follows: (1) in leads V_2 and V_3, elevation of more than 2 mm in men greater than 40 years of age, 2.5 mm in men less than 40, or more than 1.5 mm in women of any age OR (2) more than 1 mm in other contiguous chest or limb leads. Evidence of acute posterior wall myocardial infarction, indicated by ST segment depression in two or more precordial leads (V_1–V_4), is also a potential indication for fibrinolysis.

Patients with new LBBB and AMI are at increased risk for a poor outcome and benefit significantly from the administration of rapid reperfusion therapy. The new development of LBBB in the setting of AMI suggests proximal occlusion of the LAD artery, placing a significant portion of the left ventricle in ischemic jeopardy. Contemporary data, however, note that a new or presumably new LBBB as a presentation of AMI occurs infrequently; thus, a new or presumably new LBBB at presentation should not be considered diagnostic of AMI in isolation. Stated more simply, a new or presumably new LBBB is no longer considered a STEMI equivalent pattern. Nonetheless, a new or presumably new LBBB, lacking any abnormality as described by the modified Sgarbossa criteria, is a marker of significant cardiovascular risk and can be the electrocardiographic presentation of AMI in a minority of patients. A new or presumably new LBBB, lacking electrocardiographic evidence of AMI, in an ill patient with a classic presentation for ACS should be expeditiously evaluated with a cardiology consultation, if possible, to expedite cardiac-focused care.

Patients with STEMI in anterior, inferior, or lateral anatomic locations benefit from fibrinolytic therapy. Acute, isolated posterior wall MI, diagnosed using either the standard 12-lead ECG or posterior electrocardiographic leads V_8 and V_9, may be another electrocardiographic indication for fibrinolysis. Although unproven in large fibrinolytic agent trials, patients with isolated posterior AMI may be considered for reperfusion therapy when ST segment depression is noted in the right to mid-precordial leads; the emergency physician at the bedside is in the most appropriate position to make these treatment decisions.

Fibrinolytic therapy should not be used routinely in patients with only ST segment depression on the 12-lead ECG. In fact, the mortality rate may be increased—with the noted exception of right to mid precordial lead ST segment depression, representing a posterior wall AMI. Multiple studies have demonstrated a significant increase in mortality in fibrinolytic-treated patients who presented with ST segment depression.

Patient Age. Past trials do not provide evidence to support withholding fibrinolytic therapy or choosing one particular agent over another on the basis of the patient's age. It is consensus at this point that age alone should no longer be considered a contraindication to fibrinolytic therapy. However, it must be noted that patients older than 75 years do have a higher incidence of hemorrhagic stroke than younger patients.

Time from Symptom Onset. The generally accepted therapeutic time window for administration of a fibrinolytic agent after the onset of STEMI is 12 hours. Patients treated within the first 6 hours of STEMI have the best outcome. Later administration, from 6 to 12 hours after STEMI onset, also confers benefit, although of a lesser magnitude. The Late Assessment of Fibrinolytic Efficiency (LATE) trial, which compared fibrinolytic therapy with placebo, found a significant 26% decrease in 35-day mortality in patients treated with t-PA, heparin, and aspirin 6 to 12 hours after the onset of symptoms. There was no significant decrease in mortality among patients treated 12 to 24 hours after symptom onset.

Blood Pressure Extremes. Patients with a history of chronic hypertension should not be excluded from fibrinolytic therapy if their blood pressure is adequately controlled or can be lowered to acceptable levels with standard therapy for ischemic chest pain. The admission blood pressure is also an important indicator of risk of intracerebral hemorrhage. It has been shown that the risk of cerebral hemorrhage increases with systolic blood pressure higher than 150 mm Hg on admission and further increases when systolic blood pressure is 175 mm Hg or higher. Despite an increased mortality rate during the acute setting, fibrinolytic therapy in the setting of hypertension has shown an overall long-term benefit for patients with systolic blood pressure higher than 150 to 175 mm Hg. The literature appears to indicate an acceptable risk-benefit ratio for patients with substantially increased systolic blood pressure. However, a persistently elevated blood pressure (higher than 200/120 mm Hg) despite administration of standard therapy for ischemic chest pain during the ED presentation is generally considered to be a contraindication to fibrinolytic therapy.

The benefit of fibrinolytic therapy in patients with hypotension is unclear. Multiple trials have shown no apparent reduction in mortality rate with fibrinolytic therapy among high-risk AMI patients. Reviews of data on STEMI patients, however, have demonstrated that patients with an initial systolic blood pressure below 100 mm Hg who were not treated with fibrinolytic therapy had a very high risk of death (35.1%), and those who were treated with fibrinolytic therapy had the largest

absolute benefit (60 lives saved/1000 patients). Although cardiogenic shock and CHF are not contraindications to fibrinolysis, PCI is the preferred method of reperfusion if it can be accomplished expeditiously. The physicians involved in the individual patient's care are in the best position to determine the most appropriate treatment strategy, considering the patient and current medical condition, local resources, and transport times if transfer is required.

Retinopathy. Active diabetic hemorrhagic retinopathy is a strong relative contraindication to fibrinolytic therapy because of the potential for permanent blindness caused by intraocular bleeding. There is no reason, however, to withhold the use of a fibrinolytic agent in a diabetic patient with evidence of simple background retinopathy. Patients with diabetes mellitus who sustain a STEMI have an almost doubled incidence of mortality. It is impossible to determine the presence or absence of active retinal hemorrhage in the ED during the care of STEMI; thus, the emergency clinician should consider the risk-benefit analysis with respect to the presentation and involve the patient in the decision making.

Cardiac Arrest Requiring Cardiopulmonary Resuscitation. CPR is not a contraindication to fibrinolytic therapy unless CPR is prolonged—more than about 10 minutes—or extensive chest trauma from manual compression is evident. Although the in-hospital mortality rate is higher in AMI patients who experience cardiac arrest and then receive fibrinolytic agents in the ED, no difference has been found in the rates of bleeding complications, specifically, hemothorax and cardiac tamponade. Even CPR prolonged beyond 10 minutes does not appear to be associated with higher rates of complication. Again, the emergency clinician should consider the risk-benefit analysis for the presentation in this high-acuity, complex situation. If available, PCI is the preferred method of reperfusion in these critically ill patients.

Previous Stroke or Transient Ischemic Attack. A history of a previous stroke or TIA is a major risk factor for hemorrhagic stroke after treatment with fibrinolytic therapy. A history of previous ischemic stroke should remain a strong relative contraindication to fibrinolytic therapy, and previous hemorrhagic stroke is an absolute contraindication.

Previous Myocardial Infarction or Coronary Artery Bypass Graft. In the setting of STEMI, a previous MI should not preclude consideration for treatment with fibrinolytic agents. Without treatment, there is a potential for greater loss of function in the newly infarcting region of the myocardium. In patients with a previous MI, studies of fibrinolysis have demonstrated a 26% relative mortality rate reduction, and patients with a history of past MI who received fibrinolytic therapy for recurrent acute infarction have a decreased mortality rate compared to control patients without fibrinolytic therapy.

Many studies have reported successful fibrinolysis in STEMI patients with a prior CABG, but these patients should be preferentially considered for PCI if available in timely fashion or fibrinolysis followed by "rescue" PCI if needed. Complete thrombotic occlusion of the bypass graft is the cause of AMI in approximately 75% of cases as opposed to native vessel occlusion. Because of the large mass of thrombus and absent flow in the graft, conventional fibrinolytic therapy may be inadequate to restore flow.

Recent Surgery or Trauma. Recent surgery or trauma is considered a relative contraindication to fibrinolytic therapy. The term *recent* has been subject to variable interpretation in fibrinolytic trials. The ACCF/AHA guidelines list significant head or facial trauma in the past 3 months and intracranial or intraspinal surgery within the past 2 months as absolute contraindications to fibrinolytic therapy in STEMI. Major surgery within the past 3 weeks and recent internal bleeding (2–4 weeks) are also listed as relative contraindications to fibrinolytic therapy in the setting of STEMI.

Menstruation. There is minimal clinical experience with fibrinolysis in premenopausal women. Any excessive vaginal bleeding that may occur after undergoing fibrinolytic therapy should be readily controllable by vaginal packing and therefore can be considered as a compressible site of bleeding.

Percutaneous Coronary Intervention. Although fibrinolysis has widespread availability and a proven ability to improve coronary flow, limit infarct size, and improve survival in STEMI patients, many individuals with acute infarction are not suitable candidates. PCI has many advantages over fibrinolysis, including an increased number of eligible patients, lower risk of intracranial bleeding, significantly higher initial reperfusion rate, earlier definition of overall coronary anatomy with rapid triage to surgical intervention if appropriate, and risk stratification allowing safe early hospital discharge. Potential disadvantages include lack of operator expertise and numerous catheterization laboratory logistic issues, including limited geographic availability and delays to therapy application.

Primary PCI has been compared with fibrinolysis in several trials. Compared with standard-dose t-PA, PCI reduces the combined occurrence of nonfatal reinfarction or death, is associated with a lower rate of intracranial hemorrhage, and results in similar left ventricular function. Other studies have indicated that PCI is associated with a higher rate of patency of the infarct-related artery, less severe residual stenotic lesion, better left ventricular function, and less recurrent myocardial ischemia and infarction than in patients receiving fibrinolysis. Longer term outcomes comparing PCI with fibrinolysis are less straightforward yet, with the widespread use of drug-eluding stents (DES), have shown sustained benefit to 6 months and 1 year, assuming continued dual-agent platelet therapy and continued management of comorbid illnesses and conditions. In sum, PCI is superior when applied early and rapidly in the STEMI patient but loses its treatment advantage over fibrinolysis if time to procedure is prolonged.

Rescue Percutaneous Coronary Intervention. Historically, rescue PCI was considered advantageous in patients whose infarct-related arteries failed to reperfuse after fibrinolytic therapy. These patients are profoundly ill, with markedly worse outcomes. Some centers routinely catheterize patients after fibrinolytic therapy to determine whether successful reperfusion has occurred and to perform PCI if feasible. Other centers catheterize patients after fibrinolytic therapy only if there is clinical evidence that the infarct-related artery fails to open, as suggested by continued chest pain or persistent ST segment elevation.

Large trials have compared outcomes after rescue PCI with a conservative management strategy in STEMI patients in whom fibrinolysis has failed. Rescue PCI has not been associated with improved short-term or long-term survival; furthermore, increased rates of stroke and transfusion were noted in this group. In a meta-analysis of STEMI patients who did not achieve satisfactory reperfusion after fibrinolysis, rescue PCI was not associated with a mortality reduction. In this very ill group, however, the incidence of heart failure and recurrent infarction was reduced. Repeat fibrinolysis was not associated with significant improvements in mortality or recurrent infarction. Although the decision to offer rescue PCI to the patient in whom fibrinolytic therapy has failed remains controversial, the evidence favors rescue PCI (class IIa recommendation) and does not support the use of repeat fibrinolysis.[26]

Facilitated Percutaneous Coronary Intervention. Facilitated percutaneous coronary intervention refers to combination therapy involving fibrinolysis coupled with emergent PCI. This concept was initially developed to maximize therapy in STEMI patients who would be transferred urgently for PCI. The patient would receive the additive benefit of medical therapy (a fibrinolytic agent) before transfer, optimizing perfusion in the culprit artery before arrival at the

PCI-capable institution. Unfortunately, outcomes from this facilitated approach are inferior to fibrinolysis or standard PCI alone. In fact, in the treatment of patients with suspected STEMI, the combined application of fibrinolytic therapy followed by immediate PCI is not recommended and has received a Class III indication from the American Heart Association.[26] A facilitated PCI approach should not be used at this time outside of a scientific investigation.

Choice of Reperfusion Therapy. As noted, the two primary choices for reperfusion therapy in the STEMI patient include fibrinolysis and PCI. Important issues to consider in this treatment choice include the selected form of reperfusion therapy, total elapsed time of infarction, patient's candidacy for fibrinolysis (i.e., presence or absence of contraindications), type of hospital facility (i.e., PCI-capable or not), and anticipated time to transfer to the PCI-capable facility. Regardless of the strategy selected, the system's reperfusion goal should be a first medical contact to therapy time that is within 30 minutes for the initiation of fibrinolysis and within 60 to 120 minutes for PCI performance, with the noted range based on the varying time interval defined as symptom onset to medical contact. These time periods include transfer for PCI.

Delays in reperfusion are associated with increased mortality for PCI and fibrinolysis treatment strategies and appear to be more pronounced in patients undergoing fibrinolysis. With respect to treatment benefit, there are critical time-based differences when one considers PCI and fibrinolysis. First, PCI is the preferred strategy for STEMI reperfusion therapy, assuming that it can be performed in timely fashion. Second, deterioration in efficacy as total infarction time increases is more pronounced with fibrinolysis than with PCI. The success of PCI in reestablishing perfusion in the early hours after STEMI does not change significantly with time. Conversely, the ability of fibrinolytic therapy to restore coronary perfusion decreases significantly with increasing time of infarction, reaching a significant reduction at approximately 6 hours of total STEMI time.

When a patient with a STEMI with onset of ischemic symptoms within the last 12 hours arrives at a non-PCI-capable facility, the preferred reperfusion strategy is immediate transfer without fibrinolysis to a PCI-capable facility within an appropriate time period (AHA class I recommendation).[9,26,35] If the patient is a candidate for fibrinolysis and cannot be transferred to a PCI-capable hospital within an appropriate time period, immediate fibrinolytic therapy should be administered, with consideration of subsequent transfer for cardiac catheterization within the next 24 hours; at this time, PCI can be performed, if indicated. If the patient is not a fibrinolytic candidate, transfer should be arranged as soon as possible.[9,26,35]

In this series of recommendations, "appropriate time period" is a key phrase and must be considered from the perspective of two important variables—the total time duration of acute infarction at the time of presentation and the anticipated time to performance of PCI. The summary recommendations for reperfusion management of the STEMI patient who arrives at a non–PCI-capable hospital are as follows. Note that time zero in these recommendations is based on symptom onset time, not time of first medical contact.

- If presentation is within 2 hours or less of symptom onset, consider immediate fibrinolysis unless transfer time for PCI is anticipated to be no more than 60 minutes (AHA class IIB recommendation).
- If presentation is within 2 to 3 hours of symptom onset, consider immediate fibrinolysis or PCI if time to transfer for PCI is anticipated to be no more than 60 to 120 minutes (AHA class IIB recommendation).
- If presentation is within 3 to 12 hours of symptom onset, consider PCI as opposed to initial fibrinolysis if time to transfer for PCI is anticipated to be no more than 120 minutes (AHA class IIB recommendation).

As the total STEMI time increases, the overall effectiveness of fibrinolysis decreases significantly; at 6 hours of STEMI time, a longer delay allowing for transfer for PCI is a reasonable management option.[26]

Conversely, for the STEMI patient who arrives at a PCI-capable hospital, PCI remains the reperfusion therapy of choice, with the same time recommendations as noted above. The STEMI patient should arrive in the catheterization laboratory with initiation of the procedure within 90 minutes of initial medical contact.[9,26,35] If PCI is not possible at the PCI-capable hospital, and the patient is a fibrinolytic candidate, fibrinolytic therapy should be administered if a delay beyond 120 minutes is anticipated.

Regardless of the initial hospital's PCI capability, other candidates for PCI include high-risk STEMI patients, so-called late presenters (i.e., >3 hours since the onset of STEMI symptoms), patients in cardiogenic shock, and individuals with contraindication to fibrinolysis. Furthermore, when the diagnosis of STEMI is in doubt, PCI is the most appropriate strategy, with both diagnostic and therapeutic value. Obviously, if the patient presents to a PCI-capable facility initially, these additional scenarios are most appropriately addressed in the cardiac catheterization laboratory; alternatively, if the patient initially presents to a non-PCI-capable facility, then expeditious transfer to a PCI-capable hospital is needed for appropriate management of these scenarios.

Hospitals should have a fibrinolytic therapy plan in place for the treatment of STEMI patients in the event of PCI delay or unavailability. If the time required to mobilize staff and arrange for PCI is prolonged, or if delays in transfer are anticipated, fibrinolysis is preferred within the first several hours of STEMI occurrence. Emergency physicians and cardiologists at institutions with invasive capability should collaborate on a transfer pathway so that PCI consideration does not introduce further delays in fibrinolytic drug administration.

A cooperative effort among all providers can markedly reduce the door to therapy time in STEMI patients.[27] A so-called STEMI alert system, analogous to the trauma alert approach, mobilizes hospital-based resources, optimizing the approach to the AMI patient. This system, whether activated by data gathered in the ED or in the field, has the potential to offer time-sensitive therapies in a rapid fashion. Emergency clinician activation of the catheterization laboratory has demonstrated very high rates of accurate STEMI diagnosis while markedly reducing the time to definitive therapy, with very low rates of inappropriate activation (i.e., the STEMI mimic). The ACC and AHA recognize the numerous challenges and potential difficulties in achieving these reperfusion therapy time goals.[35]

Reperfusion Therapy in Cardiogenic Shock. Patients with STEMI complicated by cardiogenic shock, occurring in up to 10% of cases, demand special consideration because of a mortality rate approaching 80%. Fibrinolysis is not effective in these patients, likely due to significantly lower coronary perfusion pressure resulting in the occlusive thrombus not being exposed to the fibrinolytic agent. Conversely, primary PCI is associated with a significantly lower mortality rate (40%) than placebo and historical controls.

In previous studies that compared the outcomes of STEMI patients in cardiogenic shock, patients were randomly assigned to emergency revascularization (PCI or emergent CABG) or initial medical stabilization, including fibrinolysis. Overall mortality at 30 days did not differ significantly between the revascularization and medical therapy groups, but the 6-month mortality was lower in the revascularization group. This finding of reduced mortality in PCI compared to fibrinolytic therapy for patients with cardiogenic shock in the setting of STEMI has been repeated in multiple studies. Thus, emergency revascularization

with PCI or CABG is preferred for patients with STEMI complicated by cardiogenic shock, irrespective of the delay to treatment.[35] Fibrinolytic therapy should be considered in eligible STEMI patients with cardiogenic shock who are not candidates for PCI or CABG, or for whom those interventions are not available.

Resuscitated Cardiac Arrest with Suspected ACS

In the patient who has been resuscitated from out-of-hospital cardiac arrest (OHCA), postresuscitation care in the ED includes many important areas of management. Beyond the essential critical care interventions, urgent coronary reperfusion should be considered in these patients, particularly in those who demonstrated pulseless ventricular tachycardia (pVT) or ventricular fibrillation (VF) during the arrest or who have been identified as experiencing a cardiogenic cardiac arrest. The OHCA population should be considered as the most severe form of ACS. These patients frequently have considerable coronary artery disease, including acute and acute-on-chronic presentations.[39,40] Regarding outcome, more than 50% of these resuscitated cardiogenic OHCA patients who have undergone urgent coronary reperfusion survive to hospital discharge, a survival rate markedly higher than the approximately 8% to 10% survival rate of all patients experiencing OHCA cardiac arrest in the United States. However, these findings likely reflect selection bias, as patients have to achieve return of spontaneous circulation to go to PCI. Most of these patients have satisfactory neurologic function at the time of hospital discharge.

Many OHCA patients have a cardiogenic cause responsible for the cardiac arrest; they frequently presented with either pVT or VF. In fact, ACS (both STEMI and NSTEMI) is considered to be the most frequent cause; not surprisingly, the ECG demonstrates ST segment deviation in many of these patients. For example, the alert patient with pVT or VF who has been resuscitated and demonstrates STEMI on the ECG likely will benefit significantly from emergent PCI.[39,40]

Current consensus statements and guidelines suggest that early cardiac catheterization with PCI, if needed, has both survival and neurologic outcome benefit for resuscitated OHCA patients demonstrating electrocardiographic ST segment elevation.[26,39,40] The evidence for resuscitated OHCA patients lacking ST segment elevation is heterogeneous and retrospective in nature. Thus, no consensus guidelines exist addressing the early application of cardiac catheterization with PCI, if needed, in patients presenting without ST segment elevation.

A recent investigation, the COACT trial, addressed the resuscitated OHCA patient without ST segment elevation. No survival or neurologic function benefit was found in individuals undergoing immediate coronary angiography with PCI, if indicated, compared to those who were medically managed initially and then taken to the cardiac catheterization laboratory once they had recovered neurologically.[41] Thus, the most appropriate candidate types for urgent coronary reperfusion have not been conclusively identified.

However, it must be noted that the AHA recommends urgent coronary angiography with PCI, if needed, in the resuscitated OHCA patient with a cardiogenic etiology of cardiac arrest.[26] The 2015 AHA guidelines suggested that urgent cardiac catheterization with PCI, if indicated, should be considered in the resuscitated OHCA patient, regardless of the presence or absence of ST segment elevation. These guidelines noted that "…coronary angiography with PCI, if indicated, should be performed emergently in those resuscitated patients with suspected cardiogenic cardiac arrest who demonstrate electrocardiographic ST segment elevation…" as a class I indication.

Importantly, a clinical presentation of coma after OHCA should not be considered a contraindication to reperfusion therapy because this finding is commonly present. Multiple investigations have followed patients with resuscitated cardiac arrest complicated by STEMI. Among those patients who were unconscious at the time of PCI, invasive therapy restored coronary perfusion not infrequently; these initially comatose patients demonstrated approximately a 50% survival rate and good neurologic outcome. The AHA guidelines state that emergent coronary angiography is a reasonable intervention in resuscitated comatose cardiac arrest patients who do not demonstrate ST segment elevation on the ECG, as a class IIA indication.[26]

A rational approach to the resuscitated OHCA patient suspected of experiencing ACS as a cause of the cardiac arrest is suggested by the Interventional Council of the American College of Cardiology[39] and supported by the AHA in a scientific statement addressing the evolving role of the cardiac catheterization laboratory in the management of OHCA patients.[40] In this approach, urgent consultation and evaluation by a multidisciplinary team, including the interventional cardiologist, is strongly encouraged.[39] A 12-lead ECG is recommended within the first 10 minutes of hospital arrival, with the presence or absence of ST segment elevation as the first major decision point.

At this time, unfavorable resuscitation features must be considered as the ECG is interpreted; these features include unwitnessed arrest, initial nonshockable rhythm, no bystander interventions, prolonged arrest time (>30 minutes), ongoing CPR at ED arrival, abnormal serum studies (pH < 7.20, lactate > 7 mmol/l), age over 85 years, end-stage renal disease, and noncardiogenic cause of arrest. The patient with ST segment elevation who lacks multiple unfavorable resuscitation features may be appropriate for emergency angiography with PCI if indicated. The patient without ST segment elevation and an absence of multiple unfavorable resuscitation features is also suitable for early coronary angiography with PCI if indicated. In either electrocardiographic presentation, the presence of multiple unfavorable resuscitation features likely describes the patient that is not an appropriate candidate for coronary angiography, either emergent or early.[39]

Management Summary: Potential Pharmacologic Management Approach

The patient with stable or resolved chest pain, with a normal to minimally abnormal ECG and a negative serum marker(s), is best managed initially with aspirin; NTG (sublingually, topically, or in combination) is also appropriate. Resolution of the discomfort with continued stability generally does not warrant further ED pharmacologic management. Continued or recurrent pain in the ED may be treated with NTG and parenteral opioids (morphine or fentanyl). Continued pain may ultimately require IV NTG, anticoagulation with UFH or LMWH, and additional antiplatelet therapy with a thienopyridine (e.g., clopidogrel, ticagrelor). The patient with stable UA (i.e., new-onset or altered pattern but now symptom-free and lacking abnormal serum markers and an abnormal ECG) does not require heparin or other more aggressive platelet inhibition therapy in most cases.

The ACS patient with an abnormal ECG, particularly ST segment and T wave abnormalities, or elevated serum marker levels may warrant numerous therapies, including ASA, heparin, and other antiplatelet agents (typically a thienopyridine). NTG may be administered by the topical or IV route. The patient with recurrent angina may also benefit from such an approach. Heparin therapy is generally indicated in this case.

The AMI patient without ST segment elevation—the NSTEMI patient—requires aspirin, NTG, heparin, and a thienopyridine or an alternative second antiplatelet agent; opioids can also be administered, using either morphine or fentanyl. The patient with STEMI is treated with the preceding medications noted and should be considered for urgent revascularization, achieved by PCI, fibrinolytic agents or, rarely, CABG after cardiac catheterization. If PCI is the selected reperfusion therapy, some of these medications can be administered in the

catheterization laboratory; the patient need not remain in the ED to receive all such agents if the catheterization laboratory is ready.

DISPOSITION

Just as coronary artery disease and ACS represent a spectrum of disease, there is a similar spectrum of disposition options for patients presenting to the ED with chest pain or other complaints concerning for ACS. These options include rapid transport to the cardiac catheterization laboratory (CCL) within minutes of arrival for emergent intervention, ICU admission, acute care admission with cardiac monitoring, observation unit placement (actual or virtual), and discharge to home after ED evaluation. Patients with evidence of an acute or ongoing ACS event will require admission to the hospital, at times with transfer if the initial facility is resource limited. The final location of these admissions will depend on the patient's clinical presentation, electrocardiographic findings, results of the troponin assay, and cardiorespiratory status.

If the patient's presentation and ECG are consistent with STEMI, the disposition is determined by the reperfusion options available at the facility. In a facility where interventional cardiology and PCI are available, the patient can be urgently transported to the CCL for reperfusion via PCI, as long as this can be accomplished without delay. If PCI is not available as a timely option, fibrinolytic therapy should be initiated rapidly, assuming the patient has no contraindications to such intervention. Regardless of the reperfusion strategy chosen, patients with STEMI will require ICU admission due to the significant risk of adverse events during the first 24 hours of hospitalization. All hospitals, regardless of their size or resources, should have a clear care pathway for STEMI patients that may include CCL activation or fibrinolysis, followed by admission to the ICU; an expedited transfer should also be considered for the appropriate patient, dependent on the initial facility's capabilities.

In patients who have evidence of ACS without STEMI, disposition is based on the emergency clinician's risk assessment of the patient and their clinical presentation. Patients with high-risk presentations, including dynamic electrocardiographic changes, uncontrolled ischemic pain, rising troponin levels (consistent with NSTEMI or unstable angina), or evidence of hemodynamic or rhythm instability will likely benefit from ICU-level care and monitoring due to their significant risk of adverse events.

If the patient has no evidence of active ischemia, most risk stratification tools recommend separating patients into categories based on the risk of ACS and adverse events. In this category of individuals, higher-risk patients without dynamic electrocardiographic changes or elevated troponin levels often benefit from hospitalization in a monitored bed, with further diagnostic testing and management. Intermediate risk patients often benefit from abbreviated stays in an observation unit (structural or virtual unit) for repeat troponin level tests and possible provocative testing or anatomic imaging, if indicated. Patients at low risk of ACS can often receive evaluation in the ED setting, followed by discharge with follow-up with either a primary care physician or cardiologist and possible outpatient testing, as indicated.

Transfer of a Patient with Acute Coronary Syndrome

There are several indications for the transfer of a patient with ACS to a facility with PCI capability. These include rapid access to PCI, persistent hemodynamic instability or ventricular dysrhythmias, and postinfarction or post-reperfusion ischemia (i.e., after receiving a full-dose fibrinolytic agent). Hospital transfer for PCI is also suggested for patients with fibrinolytic contraindications who may benefit from PCI or CABG.

The urgent transfer of a fibrinolytic-eligible STEMI patient to another institution for PCI is not recommended until fibrinolytic therapy has been initiated if a delay in PCI application is anticipated. The ACC/AHA guidelines have noted that in hospitals without PCI capability, immediate transfer for primary PCI is a treatment option when it can be accomplished within 60 to 120 minutes of first medical contact, depending on the duration of STEMI at the time of presentation.[26] If delays in PCI performance are anticipated, and the patient is an acceptable candidate for fibrinolysis, the fibrinolytic should be started before or during transport to the receiving hospital. This decision is made in conjunction with the receiving cardiologist.

Many institutions are not PCI-capable. Thus, the decision for the emergency clinician involves not only the relatively simple fibrinolysis versus PCI issue but also the potential need for urgent transfer to a larger center. Previous studies have revealed about a 25% reduction in the composite endpoints of death, recurrent infarction, stroke, or revascularization in patients treated with PCI compared to those treated with fibrinolysis. The conclusion was that the early benefit from a transfer-related invasive strategy was sustained over long-term follow-up, but the benefit was largely due to a lower event rate in the PCI patients in the first 30 days after presentation.

The potential need to transfer the STEMI patient over long distances can also affect reperfusion therapy decisions. This is usually seen in rural areas with long transport times to the nearest PCI facility. In this setting, organized processes for rapid transfer should be in place to address the expected delays, including a rapid initiation of transfer by the emergency clinician, an agreed-on expedited transfer process to the PCI center, and rapid access to a transport vehicle (ground or air) that will be needed for safe transport. Multiple investigations have suggested that rapid transfer for PCI in the STEMI patient can occur in the rural setting with acceptable time to therapy.

Missed Diagnosis of Acute Coronary Syndrome

Approximately 2% to 4% of patients with AMI in the ED are discharged without diagnosis. Missed ACS is the misdiagnosis that accounts for the most considerable payments by emergency clinicians in medical malpractice claims. Patients with undiagnosed ACS discharged from the ED are younger, more likely to be women or nonwhite, more likely to have non–chest pain presentations, and less likely to have electrocardiographic evidence of acute ischemia. Among all patients with cardiac ischemia, women younger than 55 years seem to be at the highest risk for inappropriate discharge. With respect to electrocardiographic findings, approximately 50% of patients with missed AMI and approximately 60% of patients with missed UA have normal or nondiagnostic (i.e., minimally abnormal) ECGs. Finally, the risk-adjusted mortality ratio for all patients with acute cardiac ischemia is 1.9 times higher among nonhospitalized patients. Factors associated with misdiagnosis of ACS in medical malpractice closed claims analysis include emergency clinicians with less experience who document histories less clearly, admit fewer patients, and misinterpret the ECG.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 64: QUESTIONS AND ANSWERS

1. A 44-year old male presents after an episode of left-sided chest pain without radiation that lasted for approximately 5 minutes. He described the pain as a "pressure" without radiation or other significant symptoms. Onset was at rest and the symptoms are now resolved. The patient is a non-smoker, and medical history is significant only for hypertension. There is no significant family history of CAD. ECG is significant for LVH without other findings. Initial troponin testing is negative (less than the normal limit). What is the most appropriate next step in management?

a. Admission for serial troponin testing
b. Coronary CT angiography
c. Discharge to outpatient follow-up
d. Stress echocardiography

Answer: C. Utilizing the HEART score can assist in the risk stratification of this patient. Ten minutes of chest "pressure" without other typical features of ACS may be considered "moderately suspicious." Given this, the patient's heart score is 3 (1 point each for history, nonspecific repolarization disturbance on ECG, and the presence of 1 to 2 risk factors). This patient is at low risk for ACS and may be appropriately discharged from the emergency department.

2. A 48-year-old man with history of hypertension and hypercholesteremia presents with chest pain and hyperacute T waves in an anterior distribution on the initial ECG. During your initial history and physical examination the patient experiences ventricular fibrillation that responds to cardiopulmonary resuscitation (CPR) and defibrillation after being pulseless for a period of 3 minutes. Following cardiac arrest, the patient is comatose, with the following vital signs: HR 110 beats/min, BP 160/98 mm Hg, RR 12 breaths/min (intubated), temperature 36.5°C, and O_2 saturation 96%. A repeat ECG demonstrates a large, evolving anterior STEMI. Which of the following treatment plans is most appropriate?

a. Administer aspirin, PSY_{12} inhibitor, IV UFH, IV fibrinolysis, and admission to intensive care unit (ICU)
b. Administer aspirin, PSY_{12} inhibitor, IV UFH, IV fibrinolysis, initiation of therapeutic hypothermia, and admission to ICU
c. Neurologic examination for brain death and admission to palliative care because outcome is almost universally fatal
d. Rapid revascularization with percutaneous coronary intervention (PCI), initiation of therapeutic hypothermia, and admission to ICU for comprehensive postresuscitation care
e. Supportive care, and admission to ICU

Answer: D. A neurologic examination immediately following cardiac arrest is poorly prognostic of a favorable neurologic outcome with modern postresuscitation care. In the absence of multiple "unfavorable resuscitation features" (prolonged arrest, unwitnessed arrest, nonshockable rhythm, advanced age, etc.), revascularization with percutaneous coronary intervention (PCI) and immediate application of therapeutic hypothermia is warranted. Although not contraindicated, fibrinolysis is inferior to PCI following cardiac arrest and should only be used when a patient is not a candidate for PCI.

3. Which of the following is an absolute contraindication to fibrinolytic therapy?

a. Age older than 75 years
b. Appendectomy performed 2 months ago
c. Previous coronary artery bypass grafting (CABG)
d. Previous hemorrhagic stroke
e. Systolic blood pressure of 175/90 mm Hg following administration of vasoactive agents

Answer: D. Although patients older than 75 years have a higher risk of intercerebral hemorrhage, age should not be considered a contraindication to fibrinolysis. Recent major surgery or trauma is a relative contraindication for fibrinolysis; however, the term *recent* is variably defined in the fibrinolytic literature and never as more than 6 weeks. Although prior CABG patients should be preferentially considered for PCI, there is no contraindication to fibrinolytic use in these patients if PCI is not available. Systolic blood pressure above 150 mm Hg is a risk factor for intracerebral hemorrhage. Only hypertension persistently above 200/120 mm Hg, despite reasonable efforts, should be considered an absolute contraindication.

4. Which of the following drugs provides mortality benefit in the setting of AMI?

a. Aspirin
b. Intravenous beta blocker
c. Intravenous morphine
d. Nitroglycerin
e. Oxygen

CHAPTER 64: QUESTIONS AND ANSWERS—Con't

Answer: A. The ISIS-2 trial has demonstrated that aspirin independently reduces mortality by 23% in the setting of AMI. Intravenous morphine has not been shown to improve mortality and has been associated with mortality. Although nitroglycerin does improve symptoms and cause vasodilation, it has never been proven to improve mortality. Oxygen beyond that needed to maintain an oxygen saturation of 94% has been associated with additional mortality. The use of intravenous beta blockers does not offer significant benefit and is associated with an increased rate of adverse events.

5. A 42-year-old male patient presents with 45 minutes of chest pain. The ECG is depicted below (Fig. Q64.5). You are working at a noninvasive (i.e., no PCI capability) hospital; transfer time to the closest major medical center with PCI capability is 4.5 hours considering weather and logistics. The patient has no contraindications for fibrinolysis. Which of the following statements is most appropriate?

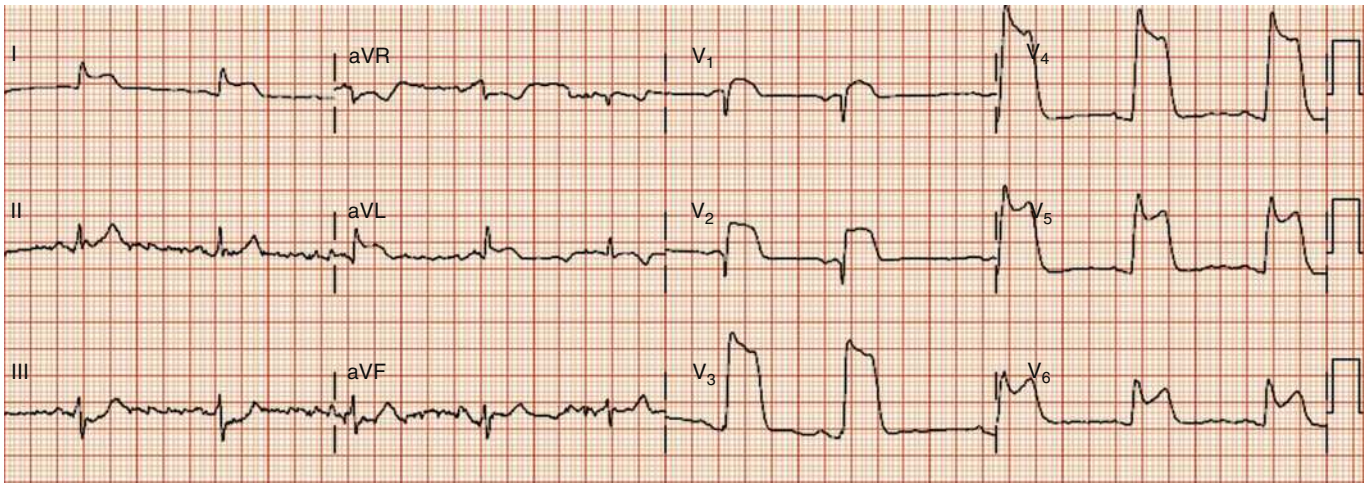
a. The patient must be transferred rapidly to the closest PCI center, with initiation of appropriate β-adrenergic blocking agents and antiplatelet and anticoagulant therapies before transfer.

b. The patient should receive a fibrinolytic agent followed by appropriate antiplatelet and anticoagulant therapies with admission to your hospital's ICU.

c. The patient should receive a fibrinolytic agent followed by appropriate antiplatelet and anticoagulant therapies, with transfer to the closest PCI center for immediate PCI.

d. The patient should receive a fibrinolytic agent followed by appropriate antiplatelet and anticoagulant therapies, with transfer to the closest PCI center within 24 hours for reevaluation and consideration of immediate PCI.

Answer: D. The ECG demonstrates an extensive anterolateral STEMI. The patient is young and has presented early in the STEMI evolution. This patient is at extreme risk due to the extensive nature of the STEMI and yet can benefit significantly from early reperfusion therapies. A delay of more than 60 to 120 minutes in this patient is not appropriate for the initiation of reperfusion therapies; furthermore, he is a candidate for a fibrinolytic agent. The early initiation of reperfusion therapy (fibrinolysis or PCI) is vital to reduce morbidity and mortality. Such a significant delay in this case for PCI is not justified, so a fibrinolytic agent is preferred. On arrival at the closest PCI center, the patient can be evaluated for PCI if he has not demonstrated successful reperfusion with resolution of chest discomfort and normalization of the ST segment elevation.



65

Dysrhythmias

Donald M. Yealy and Joshua M. Kosowsky

KEY CONCEPTS

- Electrical therapy is appropriate for unstable patients in whom a dysrhythmia is the cause of symptoms—pacing if the heart rate is slow, countershock with sedation if fast.
- Any regular new-onset, symptomatic, wide-complex tachycardia should be assumed to be ventricular tachycardia until proven otherwise.
- Type II second-degree AV block is never a normal variant and implies a conduction block below the AV node. When the conduction ratio is 2:1, a type II block should be assumed until proven otherwise. Pacing should be readily accessible.
- Any tachycardia exceeding a rate of 225 to 250 beats/min, regardless of the QRS complex morphology, should be considered an accessory pathway syndrome. Nodal blocking agents should be avoided.
- Irregularity can be difficult to appreciate in tachycardia over 200 beats/min. Atrial fibrillation can be missed if R-R intervals at fast rates are not carefully tracked.

FOUNDATIONS

Cardiac Cellular Electrophysiology

The term *dysrhythmia* denotes any abnormality in cardiac rhythm; it is often used interchangeably with the term *arrhythmia*. Understanding dysrhythmias begins with understanding the normal electrophysiologic function of cardiac cells. Electrophysiology depends on an intact resting membrane potential, largely the result of differential concentrations of Na^+ and K^+ on either side of the cell membrane, measuring approximately −90 mV in normal resting nonpacemaker cells. This gradient exists because of the Na^+ K^+ exchange pump and concentration-dependent flow of K^+ out of the cell. The influx of Ca^{2+} through passive exchange with Na^{2+} also allows for conduction and myofibril contraction (Fig. 65.1).

In normal nonpacemaker cells, an electrical stimulus causes the membrane potential to become less negative, termed *depolarization*. When the membrane potential reaches −70 mV, specialized Na^{2+} channels open, causing a rapid influx of positive charge into the cell. This so-called fast channel activity further decreases the membrane potential and is augmented at 30 to 40 mV by a second slow channel that allows Ca^{2+} influx. When these channels close, the resting potential is restored by the sodium-potassium pump, an event termed *repolarization* (Fig. 65.2).

In nonpacemaker cells, depolarization from a second electrical stimulus is not possible when the membrane potential remains more positive than −60 mV, called the effective refractory period (Fig. 65.3). When the membrane potential reaches −60 to −70 mV, some fast channels are capable of responding but impulse propagation is not normal; this is known as the relative refractory period. At a membrane potential of −70 mV or less, fast channels are ready for activity (see Fig. 65.3).

Pacemaker cells differ from non–impulse-generating cells in that they can spontaneously depolarize via slow Na^+ influx. Dominant pacemaker cells are present in the sinoatrial (SA) node, but other pacemaker cells exist in the atrioventricular (AV) node, within the His-Purkinje system, and elsewhere. With a failure of normal pacemaking cells, or in the setting of other pathologic conditions such as metabolic derangement or myocardial ischemia, nonpacemaker cells undergo spontaneous depolarization.

Anatomy and Conduction

The SA node is an area of specialized impulse-generating tissue at the junction of the right atrium and the superior vena cava. Its blood supply is from the right coronary artery (RCA) in 55% of patients and left circumflex artery (LCA) in 45%. The normal SA node produces spontaneous depolarization faster than other pacemakers and is usually the dominant pacemaker. In healthy adults, the SA node typically maintains a rate of 60 to 90 beats/min. Hypothermia and vagal stimulation slow the sinus rate, whereas hyperthermia and sympathetic stimulation increase the rate. Low or absent parasympathetic tone—for example, with certain drugs or after heart transplantation—results in a faster sinus rate.

In the absence of normal SA node impulses, other myocardial tissues may assume the role of a pacemaker. The AV node has an intrinsic impulse-generating rate of 45 to 60 beats/min. Infranodal pacemakers within the His bundle, Purkinje system, and bundle branches maintain intrinsic rates ranging from 30 to 45 beats/min. Under pathologic conditions, other atrial and ventricular tissues may pace the heart at varying rates.

Impulses from the SA node are propagated through the atrial tissue to the AV node. Atrial depolarization is characterized by the P wave on the surface electrocardiogram (ECG; Fig. 65.4).

The AV node is an area of conduction tissue separating the atria and the ventricles, located in the posterior-inferior region of the interatrial septum. Its blood supply is from a branch of the RCA in 90% of patients (right dominant) and from the LCA in the remaining 10% (left dominant). Transmission of impulses within the AV node is slower than in other parts of the conducting system (Table 65.1) because of a dependence on slow-channel ion influx for membrane depolarization. An accessory pathway refers to conduction tissue outside the AV node that forms an alternative, or bypass, tract between the atria and ventricles. The term *preexcitation* refers to early ventricular depolarization via an accessory pathway.

On the surface ECG, the time it takes to conduct an impulse through the atria to the ventricles is represented by the PR interval, normally ranging from 0.10 to 0.20 second (see Fig. 65.4). Impulses originating in lower atrial tissues or accessory pathways often have a shortened PR interval. PR prolongation is usually a result of nodal or supranodal conduction system disease.

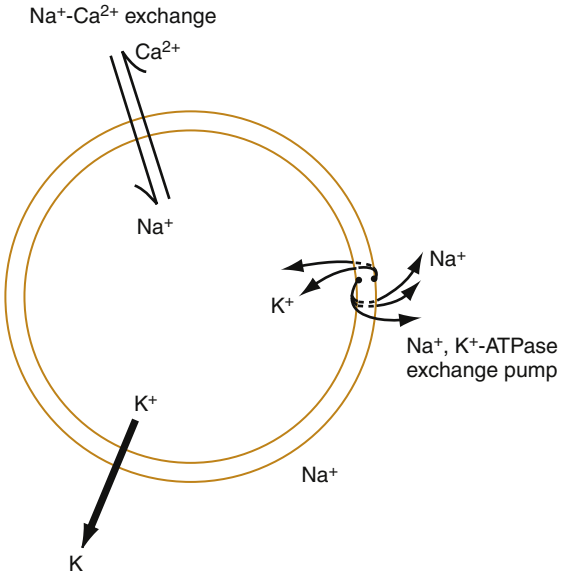


Fig. 65.1 Flow of various ions across the myocardial cell membrane. The Na^+-K^+ pump exchanges three Na^+ ions for each two K^{2+} ions, generating a net negative flow of 10 mV. The flow of K down the concentration gradient (*dark arrow*) generates another 80 mV of current. The Na^+–Ca^{2+} exchange adds little to the resting potential. *ATPase,* Adenosine triphosphatase. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby; 1989.)

After passing through the AV node, impulses propagate to the His bundle onto the three main bundle branch fascicles—the right bundle branch (RBB), left anterior-superior bundle (LASB), and left posterior-inferior bundle (LPIB). The RBB and LASB are typically supplied by the left anterior descending (LAD) artery, whereas the RCA or LCA may supply the LPIB. After conduction down the three main bundle branches, impulses are delivered to the Purkinje fibers, propagating impulses to myocardial tissues in a swift and orderly fashion, allowing for coordinated ventricular contraction. If an impulse arrives prematurely, it may be conducted abnormally (termed *aberrant*, associated with bundles that are relatively refractory) or blocked (if the bundles are entirely refractory).

On the ECG, the QRS complex represents ventricular depolarization (see Fig. 65.4), normally 0.09 second or less; 0.12 second or longer is abnormal. The T wave corresponds to ventricular repolarization and its duration depends, among other things, on the length of the cardiac cycle. The QT interval represents the total time of ventricular depolarization and repolarization and is altered by inherent physiologic abnormalities, metabolic changes, drugs, or structural changes. This interval is key to assess for QT prolongation in any patient with syncope or ventricular dysrhythmia, given the link to ventricular dysrhythmia recurrence.

Mechanisms of Dysrhythmia Formation

Enhanced automaticity refers to spontaneous depolarization in nonpacemaker cells or depolarization at an abnormally low threshold in pacemaker cells (Fig. 65.5). Classic examples of enhanced automaticity include the idioventricular rhythms of severe hyperkalemia or myocardial ischemia and the atrial or junctional tachycardias (JTs) associated with digoxin toxicity.

Triggered activity refers to abnormal impulse(s) resulting from afterdepolarizations. Afterdepolarizations are fluctuations in membrane potential that occur as the resting potential is restored. These fluctuations may precipitate another depolarization just before the full resting potential is reached (early afterdepolarizations) or after full resting potential is reached (delayed afterdepolarizations). The classic dysrhythmia associated with early afterdepolarization is acquired torsades de pointes, which typically arises in the setting of a prolonged QT interval and a new metabolic or drug trigger. Delayed afterdepolarizations classically arise in the setting of rapid heart rates and intracellular Ca^{2+} overload, as seen with digoxin toxicity or reperfusion therapy for acute myocardial infarction.

Reentry dysrhythmias arise from repetitive conduction of impulses through a self-sustaining circuit (Fig. 65.6). To maintain a reentry circuit, one conduction pathway must have a longer refractory period than the other so that when an impulse exits one limb of the circuit, it may then reenter the other in retrograde fashion. The cycle is then repeated, creating self-sustaining dysrhythmia. Reentry mechanisms are responsible for most regular narrow-complex tachycardias and many ventricular tachycardias (VTs). Treatment is predicated on altering conduction in one or both limbs of the circuit.

CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

The four classes of antidysrhythmic medications are categorized according to their electrophysiologic effects (Box 65.1). Class I agents exert their major effects on the fast Na^+ channels, resulting in membrane stabilization. The subclasses IA, IB, and IC have differing effects on depolarization, repolarization, and conduction. Class II agents are the β-adrenergic antagonists, which depress SA node automaticity, slow AV node conduction, and suppress conduction in ischemic myocardial tissue. Class III agents prolong repolarization and refractory period duration, predominantly via their effects on K^+ channels. Class IV agents are the Ca^{2+} channel blockers, which slow conduction through the AV node and suppress other calcium-dependent dysrhythmias. Other agents important in the emergency treatment of dysrhythmias include magnesium sulfate, digoxin, and adenosine.

Class IA Agents

Class IA agents slow conduction through the atria, AV node, and His-Purkinje system and suppress conduction in accessory pathways. As such, they slow both depolarization and repolarization. Class IA agents also exhibit anticholinergic and mild negative inotropic effects.

Procainamide

Procainamide is the only class IA agent commonly used in the emergency treatment of ventricular and supraventricular dysrhythmias, and it can alter normal and accessory pathway conduction. In stable patients, the recommended administration is a rate of 20 to 30 mg/min until the dysrhythmia is terminated, hypotension occurs, or the QRS complex widens (to 50% of the pretreatment width), up to a total dose of 18 to 20 mg/kg (12 mg/kg if congestive heart failure is present). Procainamide triggers hypotension from vasodilatory effects in 5% to 10% of patients and may be associated with or worsened by infusion rate. It is the preferred agent in treating Wolff-Parkinson-White syndrome.

Class IB Agents

Class IB agents slow conduction and depolarization less than other class I agents, and they shorten repolarization rather than prolonging it. Class IB agents have little effect on accessory pathway conduction.

Lidocaine

Lidocaine is the sole class IB agent used in emergency rhythm management. Lidocaine can suppress dysrhythmias from enhanced

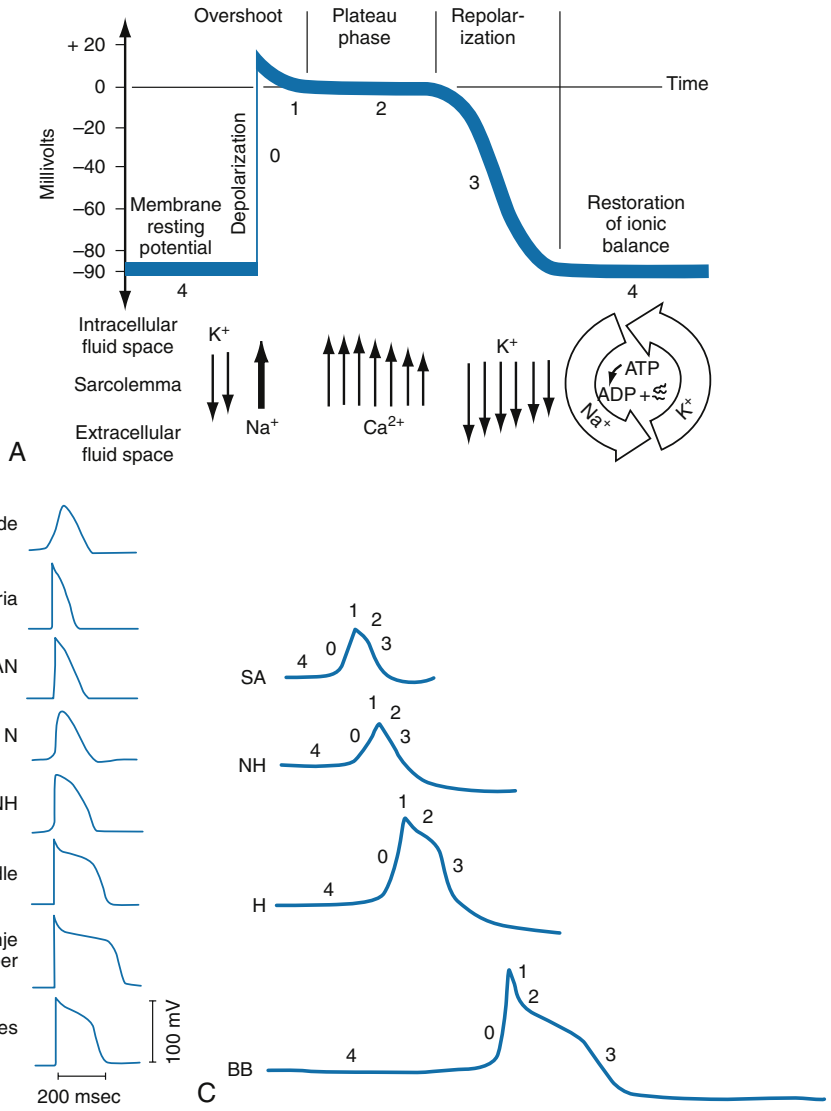


Fig. 65.2 (A) Action potential of a myocardial cell and its relation to ion flow. (B) Action potentials of various myocardial tissues. (C) Action potentials of various pacemaker cells. Note that phase 4 becomes flatter as its location becomes more distal. *AN,* Atrial-nodal; *AV,* atrioventricular; *BB,* bundle branch fascicles; *H,* His bundle; *N,* nodal; *NH,* nodal-His; *SA,* sinoatrial. ([A and B] From Calcium in cardiac metabolism, Whippany, NJ, 1980, Knoll Pharmaceutical; and [C] from Conover M. Understanding electrocardiography. ed 5. St Louis: Mosby; 1988.)

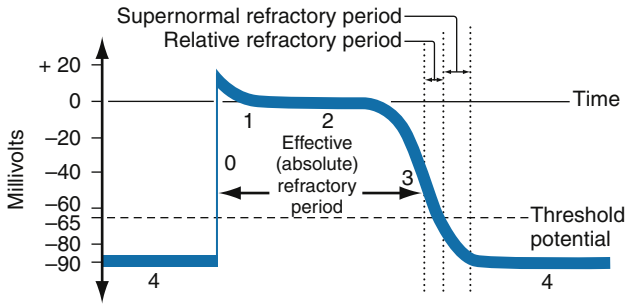


Fig. 65.3 Action potential showing various refractory periods. (From Calcium in cardiac metabolism, Whippany, NJ, 1980, Knoll Pharmaceutical.)

automaticity, such as VT. Lidocaine also suppresses SA and AV node function and is associated with asystole in the setting of acute myocardial ischemia. Lidocaine is an alternative to amiodarone but has no efficacy in SVT.

Class IC Agents

The class IC agents profoundly slow depolarization and conduction. More than any other class, these agents are associated with *prodysrhythmia*, the creation of a new dysrhythmia; this potential new dysrhythmic event also exists with class IA agents albeit much less than class IC. Class IC agents are approved for oral use in the United States.

Flecainide

Flecainide is a class 1C antidysrhythmic agent used for paroxysmal supraventricular tachycardia and certain forms of VT. Flecainide has high oral bioavailability, variable half-life, and narrow therapeutic index, all hampering its use. Flecainide is not recommended for patients with ischemic or structural heart disease.

Propafenone

Propafenone shares electrophysiologic properties with classes IA and IC agents and possesses some β-adrenergic and calcium channel-blocking

properties. Oral propafenone is used to prevent atrial fibrillation and ventricular dysrhythmias. Like flecainide, propafenone is used with caution in patients who have ischemic or structural heart disease.

Class II Agents

Class II agents—β-adrenergic blockers—suppress SA node automaticity and slow conduction through the AV node. Because of their effect on AV node conduction, class II agents are well suited to control the ventricular rate in patients with atrial tachydysrhythmias and can be useful to terminate AV nodal reentrant tachycardias (AVNRTs). In the setting of acute myocardial ischemia, beta blockers may lessen the frequency of ventricular dysrhythmias.

All beta blockers are active at β_1 and β_2 receptors (Table 65.2) to varying degrees; those with more prominent β_1 effects are called cardioselective. Relative contraindications to the use of beta blockers include advanced congestive heart failure and third-trimester pregnancy. Historically, beta blockers have been avoided in patients with asthma and chronic obstructive pulmonary disease. However, cardioselective beta blockers are not associated with an increased risk of asthma or chronic obstructive pulmonary disease (COPD) exacerbations.[1] Beta blockers should not be used in patients with preexisting bradycardia or heart block beyond first-degree. Acute side effects of beta blockers include heart failure, excessive bradycardia, and hypotension. In rare cases, they may cause bronchospasm, but most instances are not clinically apparent. Intravenous (IV) beta blockers can trigger additive side effects when used in conjunction with calcium channel blockers, notably hypotension or bradycardia. Only two beta blockers are commonly used in emergency care of dysrhythmias.

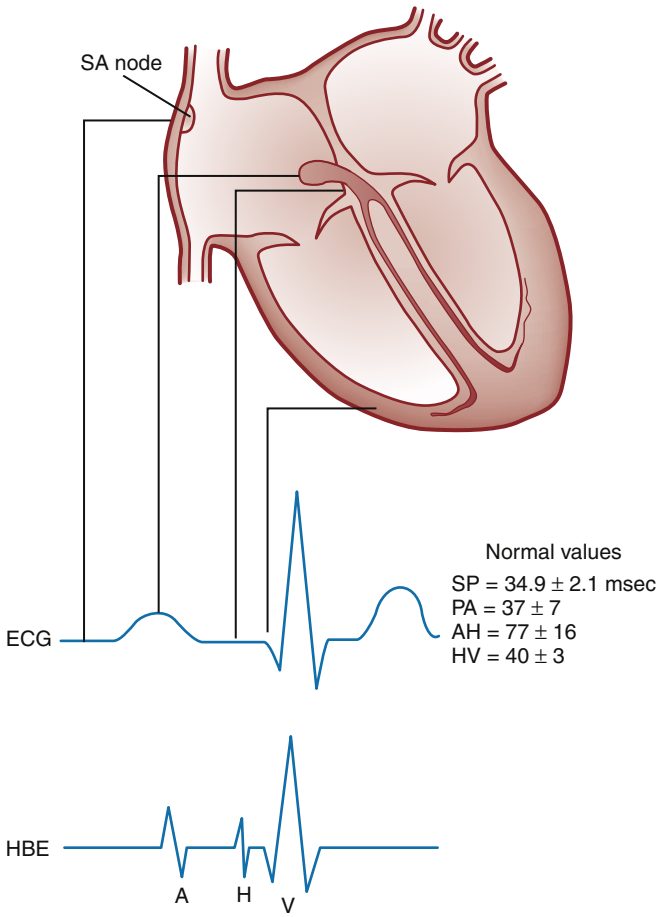


Fig. 65.4 Electrical events in the heart related to surface electrocardiogram (ECG) and His bundle electrogram (HBE). The approximate relationship of sinus node discharge is also related to the surface ECG. *AH,* Atrioventricular nodal conduction time; *HV,* His-Purkinje conduction; *PA,* intra-atrial conduction time; *SA,* sinoatrial; *SP,* SA conduction time. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby; 1989.)

Esmolol

Esmolol is an intravenous β_1-selective agent useful in the emergency setting because of its rapid onset of action and short elimination half-life (minutes). Common dosing of esmolol is an IV bolus of 500 μg/kg followed by a continuous infusion beginning at 50 μg/kg/min and titrating to need and effect.

Metoprolol

Metoprolol is available in oral and IV preparations. Although not approved for dysrhythmia treatment in the United States, metoprolol (5 to 10 mg IV every 10 to 15 minutes in an adult, titrated to response) will slow atrial and nodal tachycardias.

Class III Agents

All class III agents prolong the refractory period primarily by blocking K^+ channels, with variable effects on the QT interval. In general, class

TABLE 65.1 Conduction Velocities in Various Heart Tissues

Tissue	Velocity (m/s)
Atrium	1000
Atrioventricular node	200
His-Purkinje system	4000
Ventricles	400

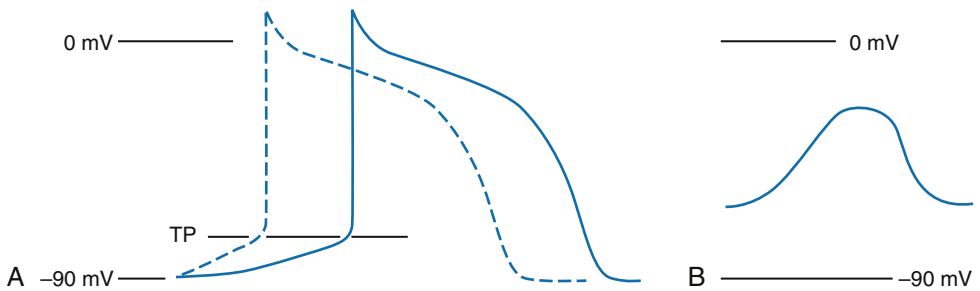


Fig. 65.5 (A) Enhanced normal automaticity (*dashed line*). (B) Abnormal automaticity. *TP,* Threshold point. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby; 1989.)

III agents are alternatives to class I agents for the treatment of many ventricular and atrial dysrhythmias.

Amiodarone

Amiodarone is approved for the treatment of ventricular and supraventricular dysrhythmias and is a first line drug treatment for acute ventricular tachycardia. In addition to features in common with all class III agents, amiodarone has other effects, including actions similar to those of class IA, II, and IV agents.

The serum half-life of amiodarone is 9 to 36 days after a single IV dose and up to 107 days during long-term oral use. Because of its unusual pharmacokinetics, oral regimens vary widely. The acute side effects of amiodarone include hypotension, bradycardia, and heart failure (Box 65.2). There is an additive risk of bradycardia and hypotension when amiodarone is used in conjunction with calcium channel or β-adrenergic blockers. Rates of prodysrhythmia are relatively low. Long-term amiodarone use may create extracardiac side effects, including both reversible and irreversible lung and thyroid disease. Amiodarone alters the pharmacokinetics of numerous other drugs, including digoxin and warfarin.

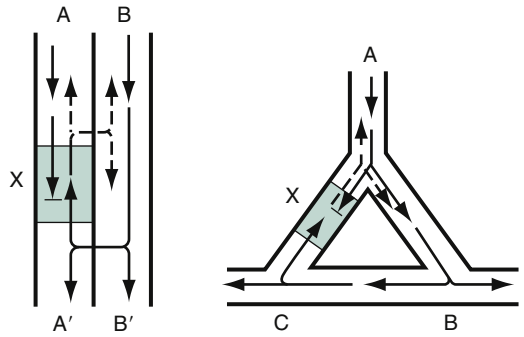


Fig. 65.6 Mechanism of reentry.

Ibutilide

Ibutilide is a parenteral agent that induces a slower inward Na^{2+} current, prolonging the refractory period. IV ibutilide approved indications include cardioversion of atrial fibrillation and atrial flutter. Because of QT prolongation and the risk of polymorphic VT, we recommend to start ibutilide with continuous cardiac rhythm monitoring.

Sotalol

Sotalol is an oral β-adrenergic receptor blocker with type III antidysrhythmic properties. Uses are for the suppression of supraventricular and ventricular dysrhythmias. Like ibutilide, sotalol initiation is best with cardiac monitoring setting, watching for QT prolongation; it has a very limited role in emergency care.

Dofetilide

Dofetilide is a powerful class III agent approved for chemical cardioversion and maintenance of sinus rhythm in patients with atrial fibrillation or flutter. However, because of its high risk for prodysrhythmia, it is used sparingly and prescribed by physicians with specialized training. It has no current role in emergency care.

Dronedarone

Structurally related to amiodarone, dronedarone displays class III properties in addition to those of other antidysrhythmic classes. Dronedarone is approved for oral use to maintain sinus rhythm in patients

BOX 65.1 Classification of Antidysrhythmic Drugs

Class I
Sodium (fast) channel blockers—slow depolarization with varying effects on repolarization. These drugs have membrane-stabilizing effects.

Class IA
Moderate slowing of depolarization and conduction; prolong repolarization and action potential duration.
Procainamide
Quinidine
Disopyramide

Class IB
Minimally slow depolarization and conduction; shorten repolarization and action potential duration.
Lidocaine
Phenytoin
Tocainide
Mexiletine

Class IC
Markedly slow depolarization and conduction; prolong repolarization and action potential duration.
Flecainide
Propafenone (shares properties with class IA agents)
Vernakalant (atrial-specific, investigational)

Class II
β-Adrenergic blockers
Propranolol
Esmolol
Metoprolol
Atenolol

Class III
Antifibrillatory agents—prolong action potential duration and refractory period duration with antifibrillatory properties.
Bretylium (historical significance)
Amiodarone
Dofetilide
Ibutilide[a]
Sotalol[b]
Dronedarone
Azimilide

Class IV
Calcium (slow) channel blockers
Verapamil
Diltiazem

Miscellaneous
Digoxin
Magnesium sulfate
Adenosine

[a] Shares activity with class I agents.
[b] Shares activity with class II agents.

TABLE 65.2 Cardiac and Respiratory β-Adrenergic Receptors and Responses to Pharmacologic Manipulation

Response to Receptors	Location	Stimulation	Antagonism
β_1-Adrenergic	Heart	Increased heart rate and ectopy	Decreased heart rate and ectopy
		Increased contractility	Decreased contractility
β_2-Adrenergic	Airway (smooth muscle)	Decreased tone (relaxation)	Increased tone (contraction)
	Peripheral vasculature	Decreased tone (relaxation)	Increased tone (contraction)

BOX 65.2 Adverse Effects of Amiodarone

Acute Effects
Hypotension
Slowing of heart rate
Decreased contractility

Long-Term Effects
Common Effects
Corneal deposits
Photosensitivity
Gastrointestinal intolerance

Less Common Effects
Hyperthyroidism
Heart failure
Pulmonary toxicity, fibrosis
Hypothyroidism
Bradycardia
Prodysrhythmic effect
Blue-green skin discoloration

Drug Interactions
Increased Levels
Phenytoin
Procainamide
Warfarin
Digoxin
Flecainide

with atrial fibrillation or flutter but is contraindicated in patients with severe or recent heart failure. It has no current role in emergency care.

Class IV Agents

Class IV agents block slow Ca^{2+} channels, slowing conduction within the AV node and suppressing the SA node to a lesser degree. Like beta blockers, these are used in patients with supraventricular tachycardia. All class IV agents are associated with peripheral vasodilation. Verapamil has the least effect on peripheral vascular tone, and diltiazem has an effect between that of verapamil and purely peripherally acting calcium channel blockers (e.g., nifedipine). Both agents can be given orally after IV use if needed. Class IV drugs are should be avoided in patients with second- or third-degree AV block unless the patient has an external pacemaker. Class IV drugs may cause excessive bradycardia in those with first-degree AV block.

Diltiazem

IV diltiazem dosing is a 0.25 to 0.35 mg/kg bolus over 2 minutes. For longer-term rate control, a continuous infusion (5 to 15 mg/hr IV initially, then titrated to need) or an oral dose (60 to 90 mg immediate-release formulation initially) will sustain the response.

Verapamil

Verapamil is rarely used in emergencies, although it is effective. A starting dose of 0.1 mg/kg IV over 1 to 2 minutes; for the average healthy adult, this translates to a dose of 5 to 10 mg, which can be repeated or increased by 50% if unsuccessful and there is no hypotension 10 minutes after administration. In older adults or those with borderline hypotension (systolic blood pressure of 90 to 110 mm Hg), use a smaller dose (0.05 mg/kg IV or 2.5 mg increments).

Miscellaneous Agents

Adenosine

Adenosine is a naturally occurring purine nucleoside used to terminate regular, nonatrial, narrow-complex tachydysrhythmias, notably junctional reentry. Administered as an IV bolus, adenosine causes an abrupt slowing of AV conduction in anterograde and retrograde pathways. Adenosine has an onset of action of 5 to 20 seconds and a duration of effect of 30 to 40 seconds. Except in rare cases, adenosine has little or no effect on infranodal conduction pathways. For this reason, adenosine is an option as a diagnostic (and sometimes therapeutic) agent in patients with wide-complex tachydysrhythmia when the specific rhythm is unclear. Patients with transplanted hearts are very sensitive to adenosine and may have profound nodal block.

Start adenosine by using a 6-mg rapid IV bolus (through a large, non–distal vein followed by a rapid flush) for adults (≥50 kg body mass); one key to success is the rapid bolus adherence. If no response is seen within 1 to 2 minutes, increase the dose to a 12-mg rapid IV bolus. If no effect is seen after a second 12-mg dose, then reassess the rhythm and use another therapy. There is no benefit to repeating adenosine when transient lowering of the heart rate occurs after a dose is given, followed by a return to the previous rhythm. Pediatric doses are 0.05 mg/kg initially, with doubling at similar intervals, up to a total dose of 0.25 mg/kg. Heart transplant patients should receive 0.025 mg/kg, for starting doses of 1.5 to 3 mg.[2]

Side effects occur in up to one-third of patients given adenosine but are usually minor and self-limited. These include flushing, dyspnea, chest pressure, nausea, headache, dizziness, transient bradycardia or heart block, sense of impending doom, and hypotension. Asystole is possible but generally transient.

Because of its short duration of action, adenosine is not an effective rate-control agent for atrial fibrillation or flutter, although it can help unmask these rhythms when not apparent on the initial surface ECG.

Digoxin

Digoxin compounds have a variety of effects on myocardial cells: They inhibit the adenosine triphosphate (ATP)–dependent Na^+-K^+ exchange pump, increasing intracellular Na^+ concentrations, and decrease intracellular K^+ concentrations. The resultant increase in intracellular Ca^{2+} concentration accounts for the positive inotropic effects of digoxin. The prodysrhythmic effects of digoxin are enhanced automaticity and triggered activity, particularly at high therapeutic or toxic doses. At the

BOX 65.3 Adverse Effects of Digoxin

Common Effects

Gastrointestinal intolerance (e.g., nausea, vomiting, abdominal pain, diarrhea, anorexia)
Fatigue
Drowsiness
Headache
Depression
Apathy

Less Common Effects

Psychosis
Cardiac symptoms
Heart block
Increased ectopy
Combined block and ectopy (multifocal atrial tachycardia with block or complete atrioventricular block with accelerated junctional rhythm, usually in the overdose setting)
Ventricular tachycardia
Visual color disturbances

same time, digoxin slows AV node conduction via lengthening of the refractory period. Classic (albeit not common) digoxin toxicity shows signs of both enhanced excitability and slowed conduction (rapid atrial activity with slow ventricular responses or AV block.)

Digoxin (0.25 to 0.5 mg IV) can control the ventricular rate in patients with supraventricular tachycardia, notably atrial fibrillation and atrial flutter. Because of its slower onset of action (often not therapeutic for 30 minutes or longer and peaking at 6 hours), digoxin is not a first-line agent for emergency therapy. However, digoxin can be beneficial in the acute treatment of dysrhythmias in patients with cardiogenic shock or heart failure.

Side effects of digoxin are listed in Box 65.3 and are aggravated by hypokalemia, hypercalcemia, hypomagnesemia, increased catecholamine levels, and acid-base disturbances. Digoxin toxicity is discussed in Chapter 147.

Magnesium

Magnesium can abort ventricular dysrhythmias via its membrane-stabilizing properties. Magnesium (1 to 2 g IV) may terminate torsades de pointes and is an adjunct in ventricular tachycardia therapy.

Isoproterenol

This non-selective beta-adrenergic agonist is used to treat some bradycardic patients—notably those with denervation like post-heart transplantation—or to prevent acquired torsades de pointes recurrence in some cases of beta-blocker overdose. It directly stimulates beta-1 and beta-2 receptions, speeding SA and AV activity and enhancing contractility while relaxing vascular and other smooth muscles. It may increase heart rate, but blood pressure effects vary by the relative impact on cardiac output (increase) and vasodilation (decrease). Administration is via IV bolus if needed (1 to 2 mcg), but more commonly by IV infusion (2 to 10 mcg/minute titrated to effect).

Clinical Features

Dysrhythmias are classified according to their electrophysiologic origin, appearance on the ECG, and underlying ventricular rate. Although overlap exists, the following categorization is useful:

- Bradycardias
- Extrasystoles
- Narrow-complex (QRS < 0.12 second) tachycardias (regular and irregular)
- Wide-complex (QRS ≥ 0.12 second) tachycardias (regular and irregular)

The clinical approach to a patient with suspected dysrhythmia starts with assessing clinical stability, which is driven by the effect on perfusion. Unstable patients have severe or multiple end-organ features of hypoperfusion, such as altered sensorium, respiratory distress, hypotension, syncope, or chest pain suggestive of myocardial ischemia. Stable patients may be asymptomatic or have mild symptoms, such as lightheadedness, dyspnea on exertion, palpitations, or mild anxiety. In practice, clinical stability is a continuum; in the absence of profound altered sensorium or hypotension, distinguishing stable and unstable patients with precision is often not possible. One simple axiom is important:

- Unstable patients with a dysrhythmia outside of a clear external trigger (e.g., bradycardia for hypothermia or tachycardia for hypovolemic or distributive shock) need prompt electrical therapy—a countershock if there is a fast rate with a pulse, or cutaneous pacing if there is a slow rate with a pulse. Care of patients with cardiac arrest (i.e., those with no pulse) is discussed in Chapter 8.

A key consideration is whether dysrhythmia is the cause or effect of a clinical presentation; for example, rapid atrial fibrillation may cause hypotension or may be a response to volume depletion. Failure to consider the clinical situation can harm a patient (e.g., giving a rate-slowing agent when the tachycardia is a response to hypovolemia). Thus, the most important decision is often whether dysrhythmia is likely the primary cause of instability. When there does not appear to be another cause, treating the dysrhythmia as primary is appropriate. In a stable patient, a more systematic approach allows identifying the cause and choosing the most appropriate therapy.

Initial Assessment of Stable Patients

The approach begins with gathering evidence from the history, physical examination, and 12-lead ECG with a rhythm strip. The symptom characteristics are important, including the timing, velocity of onset (gradual vs. abrupt), and duration. For patients with palpitations, clinicians should ask about the rate and regularity of the heartbeat or have the patient tap out the rhythm with a finger. Other important questions include precipitating events and associated symptoms, such as dizziness, chest pain, dyspnea, or syncope. A history of rhythm disturbances, ischemic or structural heart disease, and the medication history may raise a concern for specific rhythms. For example, a new and symptomatic wide-complex tachycardia in a patient with known ischemic heart disease is much more often VT than a supraventricular dysrhythmia. Occasionally, the family history helps, particularly if there are first-degree relatives with a history of dysrhythmia, unexplained syncope, or sudden death—all of which suggest an inherited disorder, such as an accessory pathway or Brugada syndrome.

Aside from palpating the pulse and listening to the heart sounds, the physical examination should be focused on detecting evidence of end-organ hypoperfusion or clues to an underlying cause of the dysrhythmia (e.g., left ventricular failure or thyromegaly). Observing the patient's rhythm on a continuous cardiac monitor while he or she reports symptoms can determine if symptoms link to electrocardiographic findings.

Differential Diagnosis

Loose leads, muscle contraction, shivering, tremors, and other movements can produce artifactual findings on a monitor, rhythm strip, or 12-lead ECG (Fig. 65.7). Such *pseudodysrhythmias* mimic serious dysrhythmias, including ventricular fibrillation. One should avoid

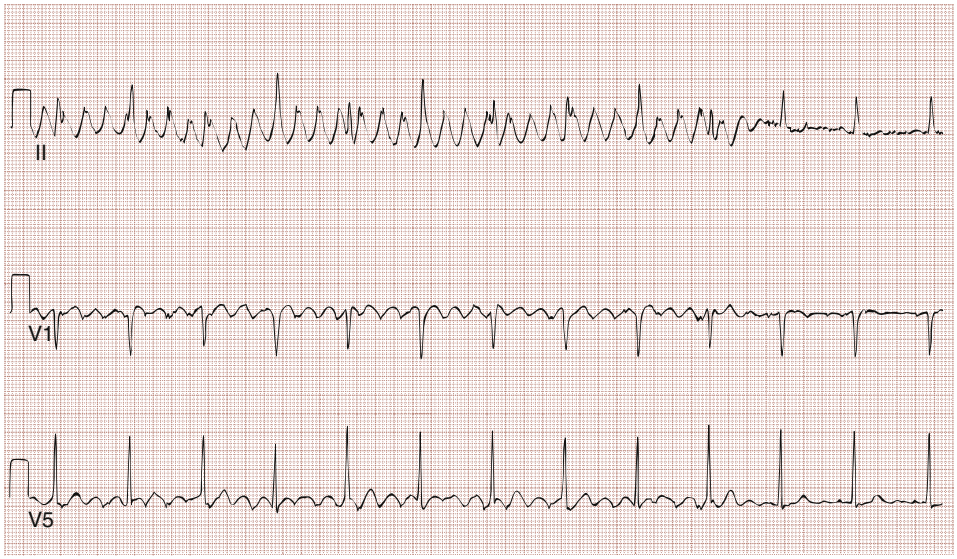


Fig. 65.7 Pseudodysrhythmia. In this case, atrial flutter waves appear to be present but are recognized as an artifact when the patient and right side of the electrocardiogram are examined.

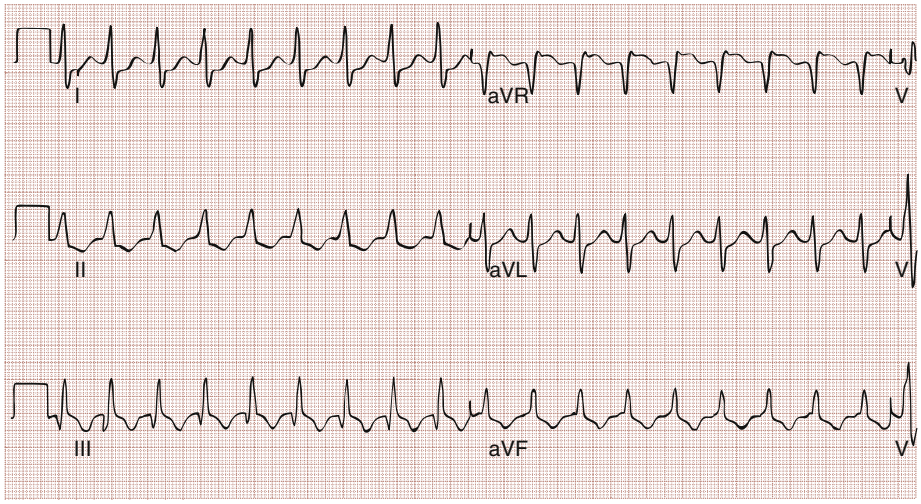


Fig. 65.8 Note the P waves before the QRS complexes in lead aVF.

decisions based solely on the ECG without incorporating the clinical context.

The 12-lead ECG is essential to evaluating any patient with a suspected dysrhythmia. The use of a single ECG lead is often adequate for diagnosis, especially in unstable patients; multiple leads are optimal in stable patients. The latter helps detect the presence or absence of P waves (often best seen in inferior leads or $V_{1\text{-}2}$; Fig. 65.8), the relationship between P waves and QRS complexes, prolongation of the QRS and QT interval, and evidence of ischemia or prior myocardial infarction (Box 65.4). For certain conditions, such as Brugada syndrome, the 12-lead ECG, together with a history of syncope, is diagnostic. Because useful information about paroxysmal dysrhythmias occurs at the onset or termination of the rhythm, inspect those areas carefully and save the strip(s) for future reference.

Vagal maneuvers, such as carotid sinus massage and the Valsalva maneuver, increase parasympathetic tone through the vagus nerve to transiently slow AV conduction, which may help uncover or terminate a supraventricular rhythm disturbance. In the ED, these maneuvers often fail, likely from a selection bias (easy responders terminate before arrival) or ineffective technique. The key to using physical methods of

BOX 65.4 Basic Electrocardiographic Observations During Dysrhythmia Analysis

1. Ventricular rate—fast (>100 complexes/min), slow (<60 complexes/min), or normal (60–100 complexes/min).
2. Rhythm—regular, completely irregular (irregularly irregular or chaotic), regular with occasional irregularity, or grouped impulses; calipers, long strips help detect subtle irregularities
3. QRS width—prolonged (>0.12 s), borderline (0.09–0.12 s), or normal. If determined without electrocardiogram being physically present (e.g., prehospital radio medical command), ask for QRS duration in "number of small boxes" from printed rhythm strip (each box = 0.04 s) to ensure accuracy.
4. P wave presence and relationship to QRS complexes—May require mapping of P waves with calipers to detect those falling within QRS complex or T wave.
5. Rhythm changes—examine these areas closely for clues.
6. Multiple leads, especially chest leads or esophageal lead if difficulties with P wave visualization are experienced.
7. Comparison with previous tracings (if available) is often valuable.

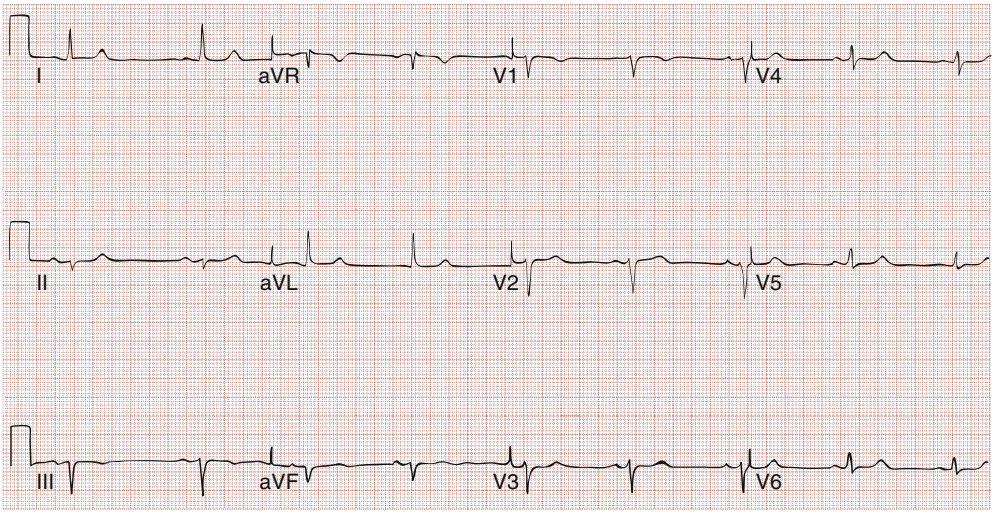


Fig. 65.9 Sinus bradycardia.

enhancing parasympathetic tone is to optimize technique—have the patient lie flat, lift the legs, and ask for a Valsalva effort, with or without massage, to enhance success. A nodal reentrant tachycardia may terminate abruptly with vagal maneuvers, whereas it often temporarily slows the ventricular rate in those with atrial fibrillation or atrial flutter; ventricular tachycardia patients rarely have any change after vagal maneuvers. Vagal maneuvers are frequently unsuccessful in the ED but rarely result in clinical deterioration. Auscultate the neck for bruits before carotid sinus massage, particularly in older patients, and avoid the maneuver if any are found or preexisting carotid disease is likely. Other vagotonic maneuvers, such as rectal or ocular massage and ice water head dunking, are impractical and less effective.

MANAGEMENT

Sinus Bradycardia and Sinoatrial and Atrioventricular Block

Bradycardia is defined as a ventricular rate of less than 60 beats/min, although in practice, rates above 50 beats/min are not usually a concern. Bradycardia occurs because of depression of the sinus node or because of a conduction system block; when the rate falls below a threshold, a subsidiary pacemaker elsewhere in the atrium, AV junction, or ventricle may assume the dominant role, resulting in an escape rhythm.

Sinus Bradycardia

Sinus bradycardia shows an ECG with a P wave assuming normal morphology, a fixed P-P interval equal to the R-R interval, and a ventricular rate below 60 beats/min (Fig. 65.9). This pattern may be found in healthy individuals, particularly well-conditioned athletes or young adults with a high resting vagal tone. Sinus bradycardia occurs in a variety of pathologic conditions associated with vagal stimulation, ranging from autonomic-mediated syncope to hemoperitoneum or acute inferior wall myocardial infarction. Other pathologic causes of sinus bradycardia include hypothermia, hypoxia, drug effects (especially β-adrenergic blockers and calcium channel blockers), and intrinsic sinus node disease (i.e., sick sinus syndrome). When sinus bradycardia drops below 40 beats/min, a junctional escape rhythm may emerge.

Sinus bradycardia is usually asymptomatic and requires no specific treatment. If needed, first-line treatment for symptomatic sinus bradycardia in adults is atropine, 1 mg IV every 3 to 5 minutes, to a total dose of 3 mg. Rarely, dopamine or epinephrine infusion may be administered. Emergency cutaneous pacing for sinus bradycardia is rarely indicated. In the post-heart transplant patient, use an isoproterenol infusion (2 to 10 mcg/min titrated to effect) as atropine is ineffective.

Sinus Dysrhythmia

Sinus dysrhythmia is a manifestation of the natural variation in heart rate that occurs during the respiratory cycle, manifested on the surface ECG as normally conducted P waves with a variable P-P interval (Fig. 65.10). It is a normal variant and frequent in children and young adults.

Sinus Arrest and Sinoatrial Exit Block

A lack of atrial depolarization occurs because of failure of the sinus node to generate an impulse (sinus arrest) or failure of impulse conduction out of the SA node (SA exit block; Fig. 65.11). With SA exit block, it is not uncommon to see dropped P waves in regularly occurring patterns, representing 2:1, 3:1, or 4:1 block. Sinus arrest and SA exit block may be from intrinsic SA node disease but can occur with increased vagal tone, whether benign or pathologic. When symptomatic, the approach to treatment is similar to that for sinus bradycardia.

Sick Sinus Syndrome

Sick sinus syndrome (SSS) is a group of dysrhythmias caused by disease of the sinus node and its surrounding tissues, creating sinus bradycardia, sinus arrest, or SA exit block. A variant of SSS known as bradycardia-tachycardia syndrome is characterized by one or more of these bradydysrhythmias alternating with a tachydysrhythmia, typically atrial fibrillation. SSS is most common in older adults, a result of fibrotic degeneration. It is associated with cardiomyopathies, connective tissue diseases, and certain drugs. In the acute setting, the specific rhythm should be treated, although subsequent bradycardia could require temporary pacing following the use of a nodal blocking agent (especially a calcium channel blocker) for the tachycardic presentation. Long-term management requires permanent pacemaker placement for symptomatic bradycardia to allow for pharmacologic therapy for atrial fibrillation.

Atrioventricular Block

AV block results from impaired conduction through the atria, AV node, or proximal His-Purkinje system. First- and second-degree AV blocks represent partial impairment of conduction, whereas third-degree block indicates complete interruption. Advanced or high-grade

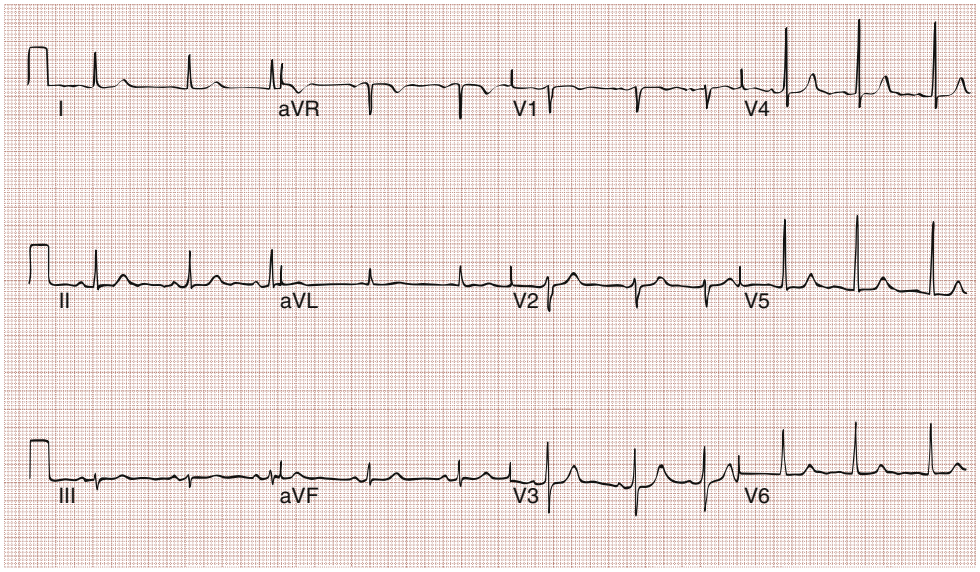


Fig. 65.10 Sinus dysrhythmia (note slight irregularity).

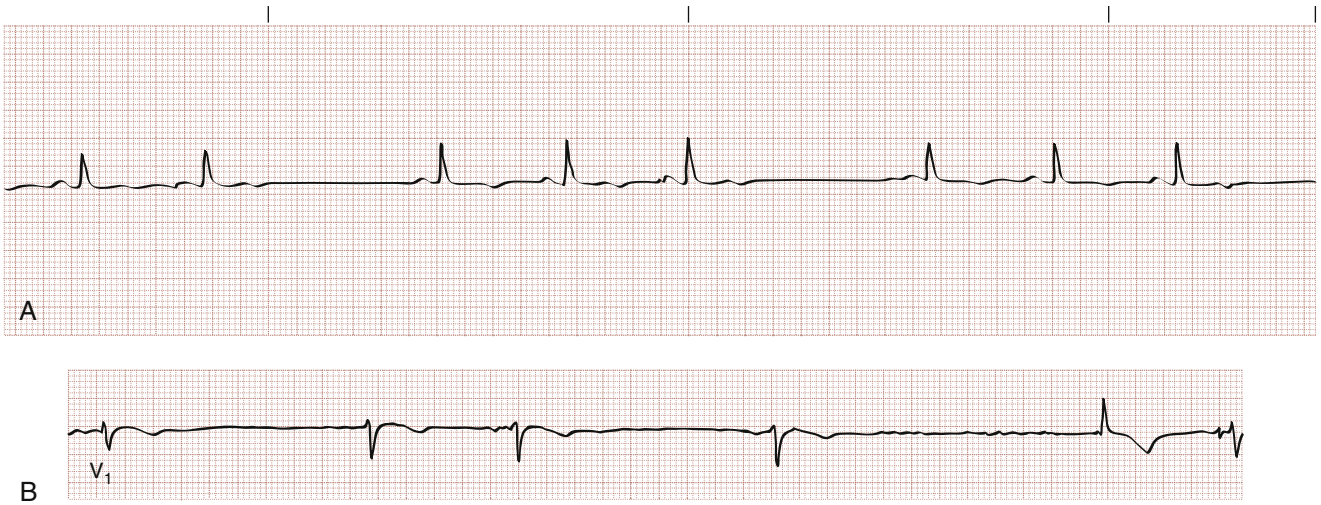


Fig. 65.11 (A) Incomplete sinus block. (B) Complete sinus block (sinus arrest) with ventricular escape rhythm.

AV block refers to AV block resulting in a ventricular rate that is pathologically slow.

First-Degree Atrioventricular Block

First-degree AV block is from prolonged conduction at the level of the atria, AV node (most common), or His-Purkinje system. On the ECG, first-degree AV block shows a prolonged PR interval (>0.20 second), typically with a narrow-QRS complex (Fig. 65.12). First-degree AV block is a normal variant in up to 2% of healthy young adults. First-degree AV block requires no specific treatment other than avoiding nodal blocking agents.

Second-Degree Atrioventricular Block

Second-degree AV block is when one or more (but not all) atrial impulses fail to reach the ventricles. The conduction ratio is the number of P waves to the number of QRS complexes over a period (e.g., 3:2, 2:1). When the atrial rate is unusually fast, such as with atrial flutter, a conduction ratio of 2:1 may be physiologic, reflecting the normal refractory period of the AV node. However, in most other cases, a conduction ratio greater than 1:1 is pathologic. Second-degree AV block is classified into two types based on the underlying pathophysiology and appearance of the ECG (Table 65.3).

Type I Second-Degree Atrioventricular Block. Type I second-degree AV block, also called Wenckebach or Mobitz I AV block, is associated with progressive impairment of conduction within the AV node. The surface ECG shows a lengthening of the PR interval from beat to beat until a P wave fails to conduct to the ventricle (so-called dropped beat). This pattern gives the appearance of successive P waves retreating into the preceding QRS complexes (Fig. 65.13). Grouped beating (e.g., pairs, trios) occurs but is not unique to type I second-degree AV block (Box 65.5).

Type I second-degree AV block occurs in a variety of conditions, benign and pathologic; often, these are associated with increased vagal tone and do not require specific treatment. In the setting of acute myocardial infarction, type I second-degree AV block is generally transient and associated with a good outcome.

Type II Second-Degree Atrioventricular Block. Type II second-degree AV block, or Mobitz II block, is a conduction block just below the level of the AV node. On the surface ECG, conduction of atrial impulses is sporadic and typically periodic, but the PR interval does

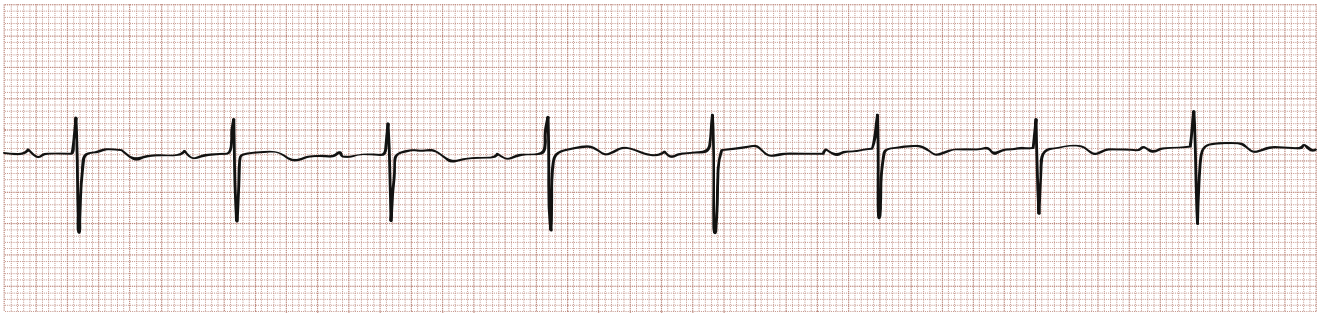


Fig. 65.12 First-degree atrioventricular block.

TABLE 65.3 Features of Types I and II Second-Degree Atrioventricular Block

Feature	Type I	Type II
Clinical	Usually acute	Often chronic
	Inferior myocardial infarction	Anteroseptal
	Rheumatic fever	Lenègre disease (Lev disease)
	Digoxin or beta blockers	Cardiomyopathy
Anatomic	Usually AV node	Infranodal
Electrophysiology	Increased relative refractory period	No relative refractory period
	Decremental conduction	All or none conduction
Electrocardiographic features	RP/PR reciprocity	PR interval stable
	Prolonged PR interval	PR interval usually normal
	QRS duration normal	QRS duration prolonged
Response to atropine and exercise	Improves	Worsens
Response to carotid massage	Worsens	Improves[a]

AV, Atrioventricular.
[a]Primarily refers to conduction ratio.

not widen from beat to beat (Fig. 65.14). The QRS complex is usually narrow, but concomitant infranodal conduction disturbances (i.e., bundle branch blocks) can be seen in those with type II second-degree AV block.

When the conduction ratio is exactly 2:1, it is hard to distinguish type I from type II second-degree AV block on the surface ECG. In general, a prolonged PR interval makes type I block more likely, whereas the presence of wide-QRS complexes makes type II block more likely.

Type II second-degree AV block arises from senescent degeneration, drug toxicity, ischemia, or other pathologic conditions; it generally carries a worse prognosis than type I second-degree AV block. In acute myocardial infarction, type II second-degree AV block is associated with anterior wall injury and is often a precursor to complete AV block. No specific therapy is needed aside from ensuring that pacemaking capability is immediately available.

Third-Degree Atrioventricular Block

Third-degree AV block, also known as complete heart block, is absent conduction of any atrial impulses (Fig. 65.15). Complete heart block is typically accompanied by a slow escape rhythm, with the width and frequency of QRS complexes depending on the site of the escape rhythm pacemaker. Pacemakers above the His bundle often have a narrow-QRS complex at a rate of 45 to 60 beats/min, whereas pacemakers at or below the His bundle produce a wide-QRS complex at a rate of 30 to 45 beats/min.

The hallmark of complete heart block is AV dissociation (i.e., no electrocardiographic relationship between P waves and QRS complexes), with an R-R interval longer than the P-P interval. Conversely, the presence of AV dissociation with an R-R interval shorter than the P-P interval (e.g., as occurs with accelerated junctional rhythms and VTs) does not imply third-degree heart block. When the atrial rate and the escape rates are similar (termed *isorhythmic*), detecting AV dissociation may require a long rhythm strip to track the P waves and QRS complexes. When a complete heart block occurs in the presence of atrial fibrillation, the fibrillatory atrial waves are accompanied by a slow and regular ventricular response (so-called regularized atrial fibrillation). This specific dysrhythmia is classically associated with digoxin toxicity.

Third-degree AV block can be congenital but is usually acquired because of senescent degeneration of the electrical conduction system or as a result of acute ischemia, drug therapy, or other pathologic conditions (e.g., Lyme or Chagas' disease).

In the ED setting, management of type II second-degree or third-degree block depends on the cause and presence of symptoms. Symptomatic patients with signs of hypoperfusion at rest should be treated with temporary transcutaneous or transvenous pacing, while reversible causes (e.g., ST-elevation myocardial infarction, beta-blocker overdose) are sought and treated. These patients require cardiology consultation for consideration of a permanent pacemaker. Atropine is usually ineffective; it should be avoided, particularly when the cause of the block is acute myocardial ischemia.

Extrasystoles

An extrasystole is an electrical impulse originating from an ectopic atrial or ventricular focus. Depending on the site of origin and timing of the impulse, there may not be an associated mechanical contraction. The terms *premature atrial contraction* and *premature ventricular contraction* are widely used but are misleading because contraction may not occur with the extra electrical activity seen on the ECG. The extrasystole and its preceding impulse are the couplet, and the coupling interval is the period between these two beats. Bigeminy (Fig. 65.16) occurs when there is an extrasystole after every native beat so that every other impulse is extrasystolic; trigeminy (every third beat) and quadrigeminy (every fourth beat) are similar. Most extrasystoles are the result of enhanced automaticity from the atria, AV node, His-Purkinje system, or ventricles.

Premature Atrial Contractions

Premature atrial contractions (PACs; Fig. 65.17) are common and usually have little clinical significance. PACs on the ECG are an abnormal

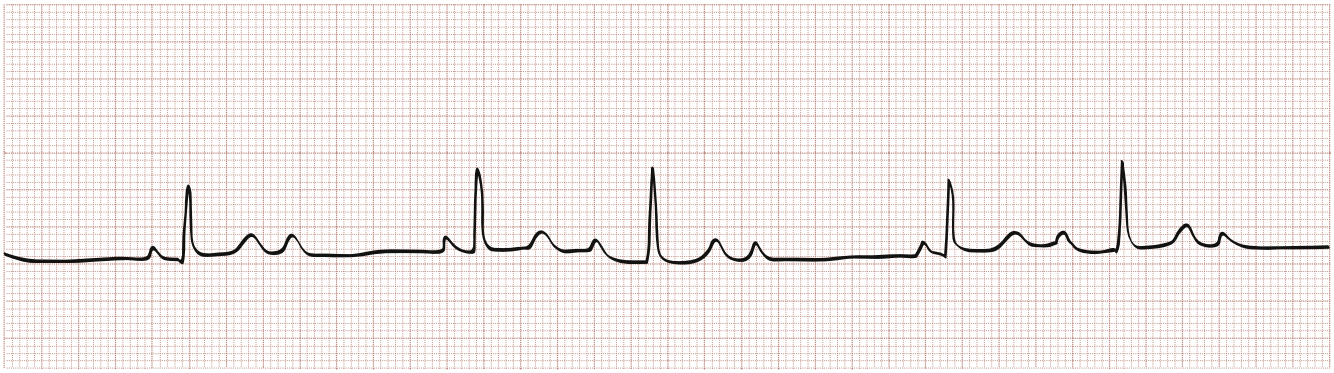


Fig. 65.13 Second-degree atrioventricular block, type I (Wenckebach). Note the prolongation of the PR interval between the second and third beats, followed by a nonconducted atrial impulse.

BOX 65.5 Causes of Grouped Impulses

- Wenckebach mechanism (usually at atrioventricular node, but can occur elsewhere)
- Sinoatrial exit block
- Atrial tachycardia or flutter with alternating conduction
- Frequent extrasystoles
- Nonconducted atrial trigemini
- Concealed or interpolated extrasystoles

P wave early within a cardiac cycle, although sometimes the P wave may be difficult to detect if it is buried within the preceding T wave.

Most PACs will depolarize the sinus node, resetting its refractory period. Because of this, the P-P interval between two sinus beats surrounding a PAC will be less than twice the intrinsic P-P cycle length (see Fig. 65.17). If a PAC reaches the AV node or infranodal conducting system during its absolute refractory period, there will be no ventricular depolarization. A nonconducted (or blocked) PAC typically results in a noncompensatory pause (i.e., R-R interval less than twice the intrinsic R-R cycle; Fig. 65.18) because the sinus node is reset. Blocked PACs are a common cause of electrocardiographic pauses and are easily overlooked. On occasion, a PAC can be the precipitant of a more important dysrhythmia, such as atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia (PSVT).

If a PAC reaches the infranodal conducting system during its relative refractory period, the QRS complex is widened (or aberrant), typically with a right bundle branch block (RBBB) pattern. Because the refractory period depends on the previous cycle length, an early-arriving PAC that follows a long cardiac cycle is more likely to be aberrantly conducted. This pattern can happen in atrial fibrillation, creating wide-QRS complex impulses that are not ventricular in origin.

PACs are benign and require no specific treatment, but they may accompany catecholamine excess, myocardial ischemia, heart failure, hyperthyroidism, or a metabolic abnormality.

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) occur in a wide variety of states. Occasional PVCs are common in healthy adults or conditions associated with catecholamine excess, such as pain, anxiety, and use of stimulants (e.g., caffeine, nicotine, cocaine, amphetamines). Pathologic conditions associated with frequent PVCs include myocardial infarction, potassium or magnesium disturbances, and medication toxicity (notably any with sodium channel-blocking or sympathetic enhancing activity). Although usually not requiring intervention, frequent PVCs may herald VT, especially in the setting of acute myocardial infarction or in patients with a prolonged QT interval.

A PVC appears as a wide-QRS complex extrasystole without a preceding P wave (Fig. 65.19). Because retrograde conduction of a PVC rarely extends far enough to capture and reset the SA node, atrial impulses continue to arrive at the AV node at the intrinsic sinus rate. As a result, the R-R interval surrounding a PVC ends up being equal to exactly twice the intrinsic R-R interval length (see Fig. 65.19), a phenomenon termed a *compensatory pause.* Rarely, a PVC will capture the SA node, resulting in a noncompensatory pause, or will fail to capture the AV node, leaving the underlying rhythm completely unaffected (a so-called interpolated PVC; Fig. 65.20).

The morphology of a PVC depends on the origin of the impulse, with a left bundle branch block (LBBB) appearance resulting from an extrasystolic focus in the right ventricle, and vice versa. Multiform (or multifocal) PVCs come from more than one source and have variable morphologies. When a PVC occurs at or around the time that a supraventricular impulse is set to depolarize the ventricle, the result is a fusion QRS complex (Fig. 65.21). Table 65.4 lists common features of PACs and PVCs.

Direct therapy for PVCs is focused on correcting any precipitating condition whether it is catecholamine excess, drug effect, electrolyte imbalance, or cardiac ischemia (Box 65.6). Often, PVCs do not require treatment in the ED. When occurring in isolation, symptomatic PVCs may be treated with a beta blocker (metoprolol, 5 to 10 mg IV or 25 to 50 mg PO), although this is rarely needed. Although IV lidocaine suppresses PVCs, it should not be used in the absence of VT because of the risk of asystole with limited clinical benefit.

Narrow-Complex Tachycardia

Narrow-complex tachycardias have a QRS complex duration of 0.12 seconds or less on the surface ECG and a ventricular rate of more than 100 beats//min. The term *supraventricular tachycardia* may be confusing; sometimes it is used specifically to note AV reentry tachycardia, but it can denote any tachycardia originating at or above the AV node.

ECG features that help distinguish between different narrow-complex tachycardias include the appearance of P waves and the regularity or irregularity of the R-R interval. For example, a narrow-QRS complex tachycardia with an irregular R-R interval and no clear P waves is almost certainly atrial fibrillation. With rapid tachycardias, evidence of atrial depolarization is often obscured by ventricular repolarization; for example, with a regular, narrow-complex

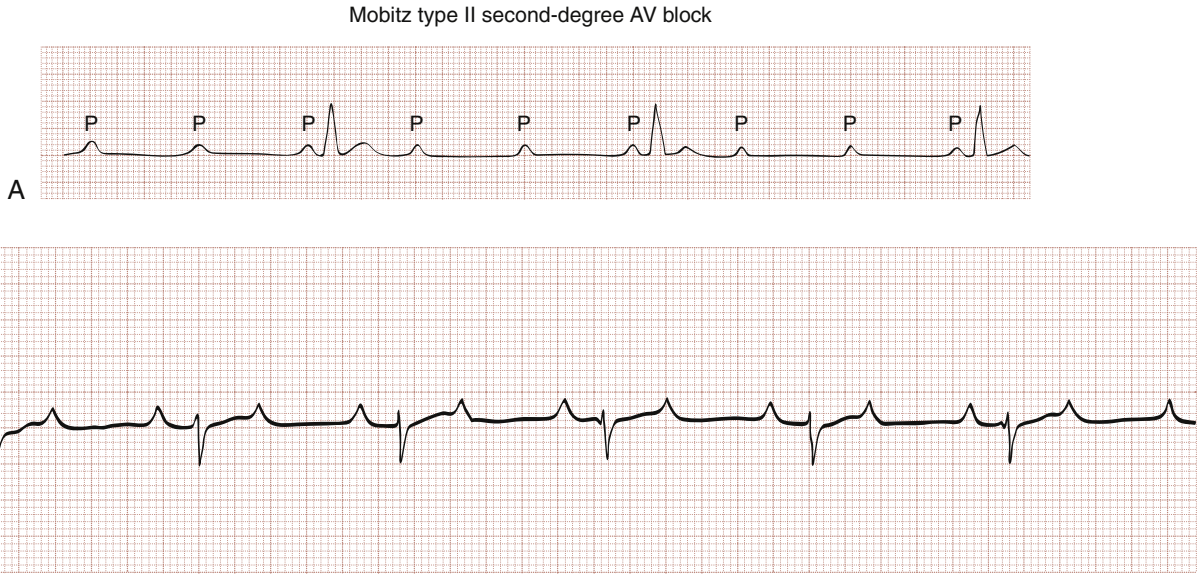


Fig. 65.14 (A) Second-degree atrioventricular (AV) block, type II. In this example, 3:1 conduction is shown. (B) Second-degree AV block with 2:1 conduction. From the rhythm strip alone, it is difficult to categorize this as a type I or II block. (**A** from Goldberger AL, Goldberger E. Clinical electrocardiography. ed 2. St Louis: Mosby; 1981.)

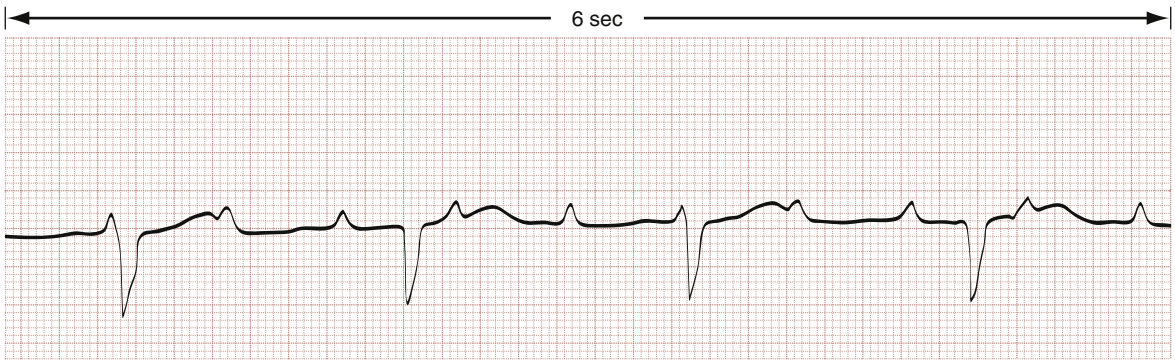


Fig. 65.15 Complete (third-degree) atrioventricular block. Note that there is no constant relationship of P waves to QRS complexes, even though some are noted in close proximity.

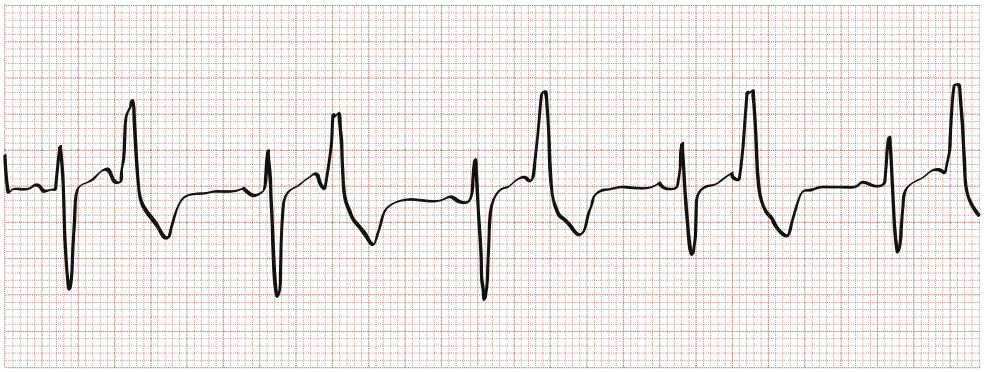


Fig. 65.16 Ventricular bigeminy.

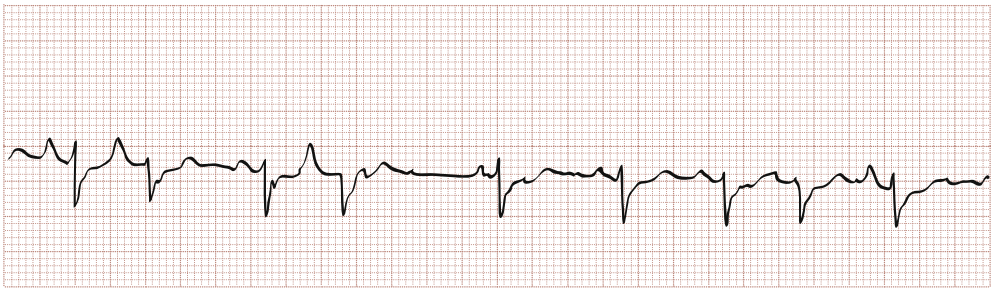


Fig. 65.17 Premature atrial contractions.

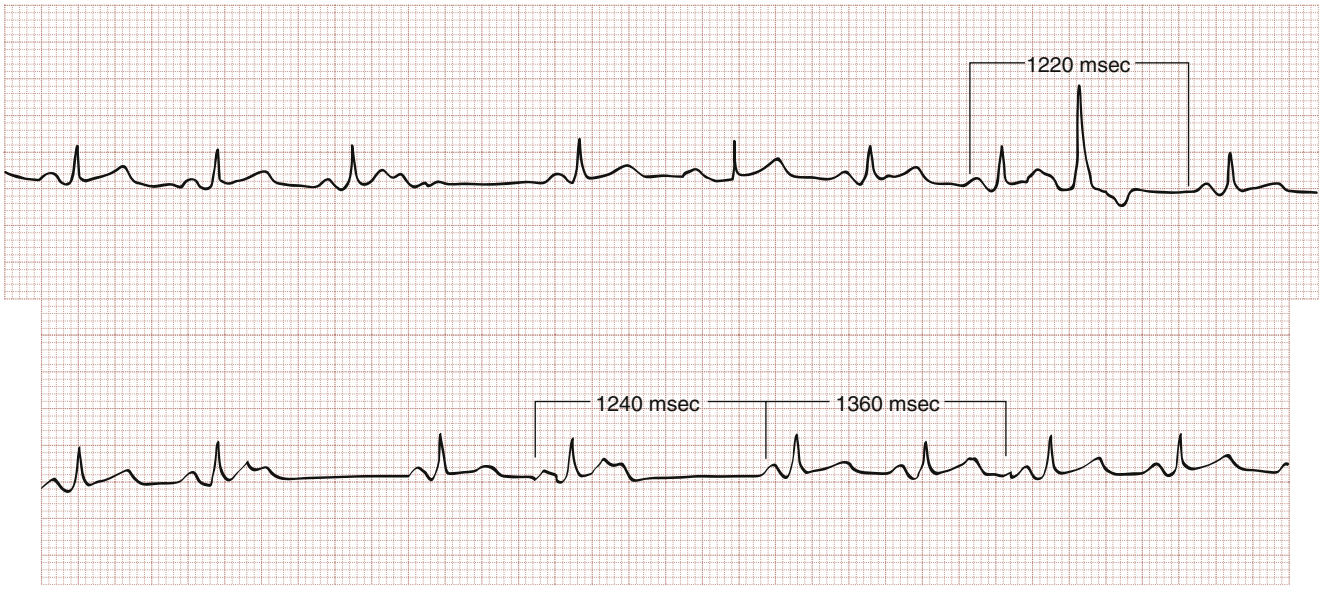


Fig. 65.18 Premature atrial contractions (PACs) with noncompensatory pauses and one aberrantly conducted impulse (*upper strip*). Note that conducted and nonconducted PACs reset the sinus node, with the latter creating a pause.

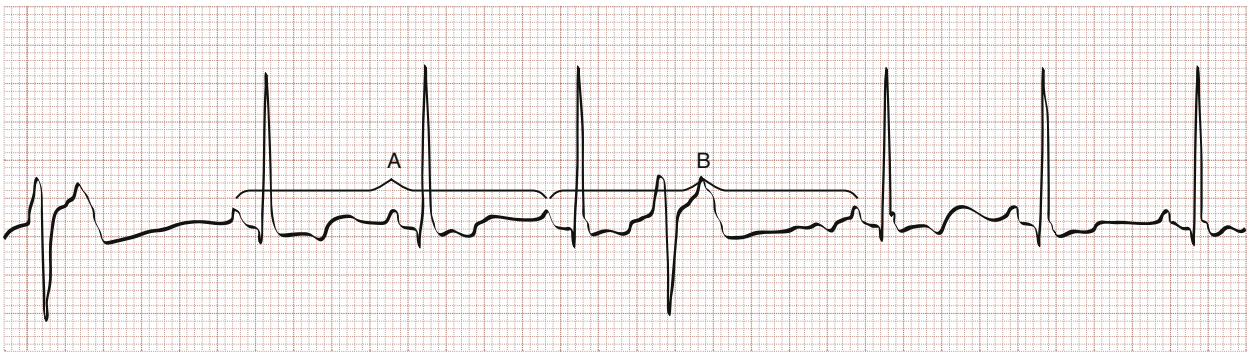


Fig. 65.19 Premature ventricular contractions with compensatory pause. Note that a sinus P wave can be seen in the T wave of the extrasystolic beat. Also, note the secondary T wave changes in beats 1 and 4 (the T wave is opposite the main deflection of the QRS complex).

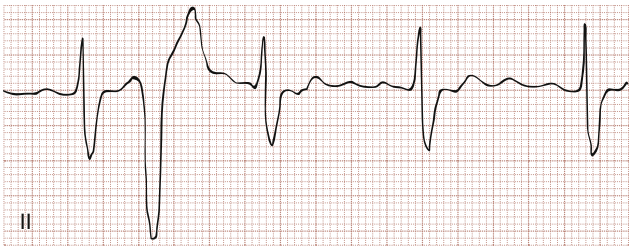


Fig. 65.20 Interpolated premature ventricular contraction.

tachycardia at a rate of 150 beats/min, it can be challenging to distinguish sinus tachycardia from atrial flutter or a junctional rhythm. Vagal maneuvers or adenosine may transiently slow AV nodal conduction and expose atrial depolarization to aid diagnosis. Alternatively, the patient may convert to sinus rhythm, in which case an AV nodal reentrant tachycardia exists. In the post-heart transplant patient or anyone with cardiac denervation, adenosine may cause an exaggerated response. It should be used carefully and doses of 1.5 to 3 mg for adults, if not avoided altogether.

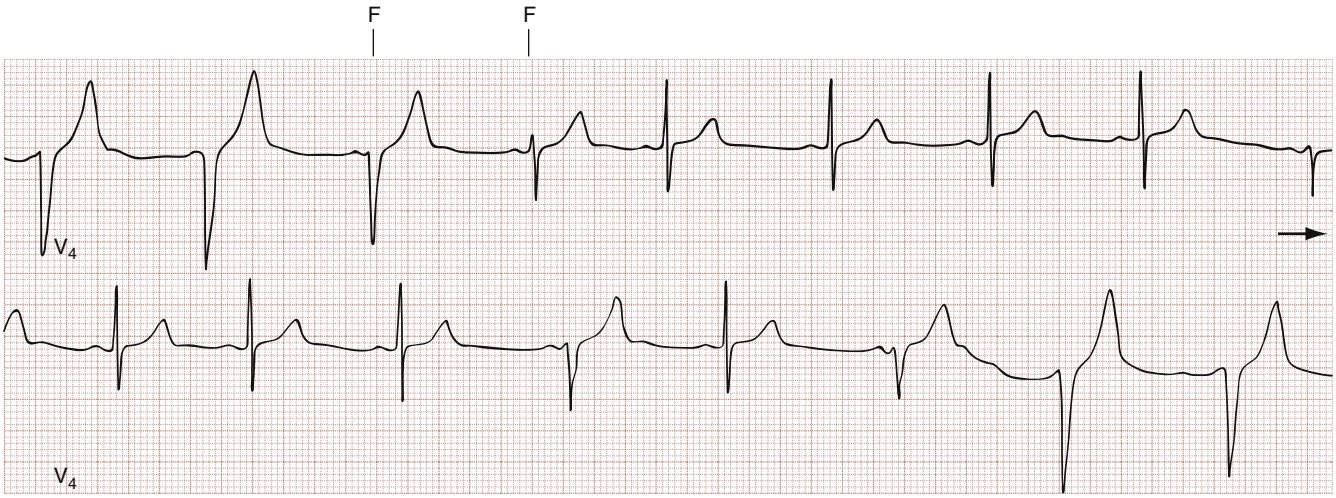


Fig. 65.21 Sinus rhythm with premature ventricular contraction and run of accelerated idioventricular rhythm. Note fusion beats (F) displaying a hybrid appearance of both morphologies.

TABLE 65.4 Features Distinguishing Premature Atrial Contractions With Abnormal Conduction From Premature Ventricular Contractions

Premature Atrial Contractions	Premature Ventricular Contractions
No compensatory pause	Fully compensatory pause (unless interpolated)
Preceding P wave (different from sinus P wave; occasionally buried in T wave)	No preceding P waves (although retrograde atrial conduction can cause inverted P wave after QRS)
Usually classic right bundle branch block pattern (especially if long-short cycle sequence appears) identical to sinus QRS	Left bundle branch block, right bundle branch block, or hybrid pattern
QRS axis normal or near-normal	Frequently bizarre QRS axis
QRS rarely > 0.14 s	QRS often > 0.14 s

BOX 65.6 Causes of Premature Ventricular Contractions and Ventricular Tachycardia

Acute or previous myocardial infarction or ischemia
Hypokalemia
Hypoxemia
Ischemic heart disease
Valvular disease
Catecholamine excess[a]
Other drug intoxications (especially cyclic antidepressants)
Idiopathic causes[b]
Digoxin toxicity
Hypomagnesemia
Hypercapnia
Class I antidysrhythmic agents
Ethanol
Myocardial contusion
Cardiomyopathy
Acidosis
Alkalosis
Methylxanthine toxicity

[a] Relative increase in sympathetic tone from drugs (direct or indirect) or conditions that augment catecholamine release or decrease parasympathetic tone.
[b] Isolated premature ventricular contractions (PVCs) can occur in up to 50% of young subjects without obvious cardiac or noncardiac disease; however, multiform and repetitive PVCs and ventricular tachycardia are rarely seen in this population.

Sinus Tachycardia

Sinus tachycardia displays a regular, usually narrow-complex tachycardia, with normal P waves preceding each QRS complex (Fig. 65.22) on the ECG. In adults, sinus tachycardia rarely exceeds a rate of 170 beats/min; in infants and young children, it is not unusual to see rates above 200 to 225 beats/min. Sinus tachycardia tends to speed up or slow down in a graded and continuous manner over time, relayed by history or observed under care.

Sinus tachycardia is often a response to physiologic stress or a compensation to increase cardiac output in the setting of a relative lack of perfusion or oxygen delivery. Usually, the effect is beneficial, as seen with hypovolemia, anemia, or hypoxemia; efforts to slow the heart rate compensation without addressing the underlying pathophysiology are likely to exacerbate the situation. Occasionally, sinus tachycardia is counterproductive, as in acute decompensated heart failure or aortic stenosis, in which a decrease in filling time further compromises cardiac output. Even in these settings, therapy is aimed first at the underlying problem rather than the tachycardia.

Sinus tachycardia can be seen with any sympathetic excess, whether endogenous (e.g., pain, anxiety, fever, hyperthyroidism) or exogenous (e.g., stimulants, other drugs). The approach to the patient with sinus tachycardia centers on identifying and addressing the cause(s). Beta blockers are rarely used to treat sinus tachycardia.

Atrial Tachycardia

Atrial tachycardia (AT) is an atrial rhythm with more than 100 QRS complexes/min arising from a nonsinus node atrial site(s). An ECG will be notable for abnormal P waves, all or mostly related to each QRS complex (Fig. 65.23). If the site of origin is close to the sinus node,

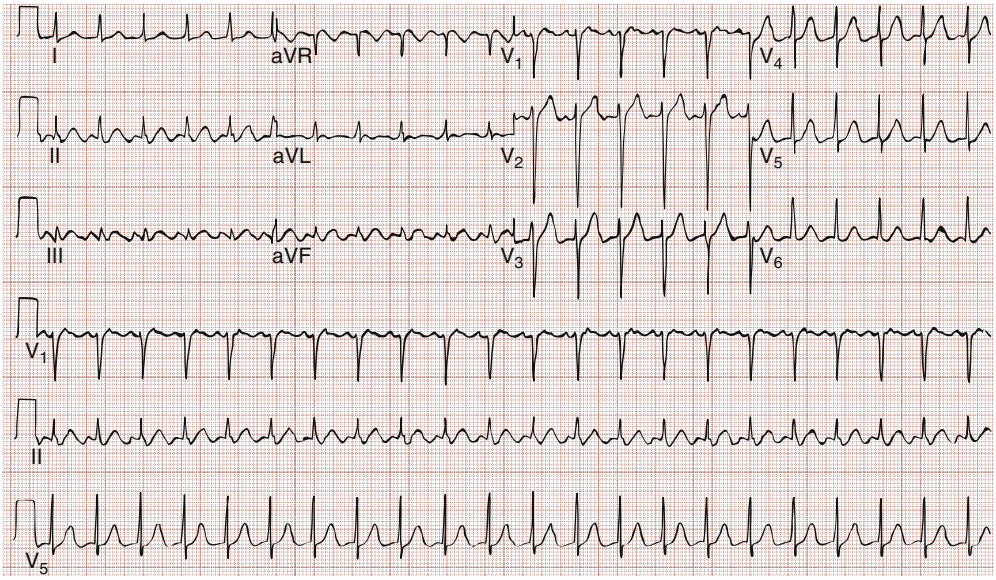


Fig. 65.22 Sinus tachycardia.

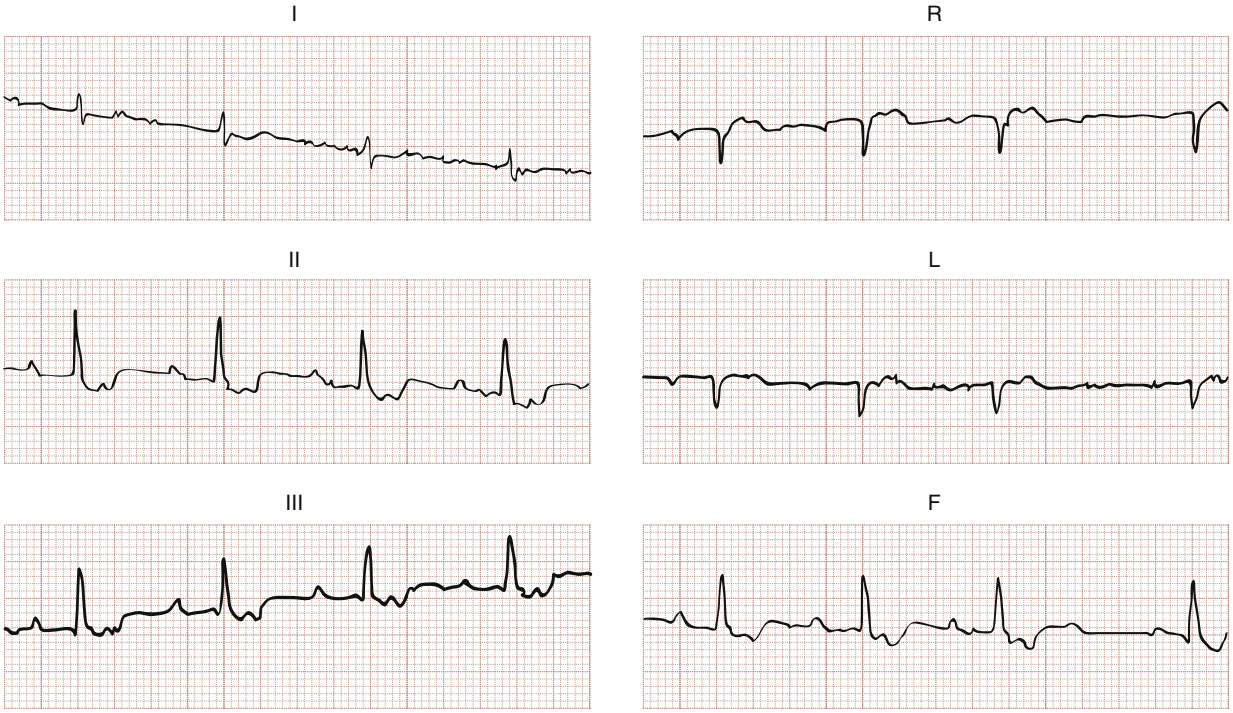


Fig. 65.23 Atrial tachycardia (with 2:1 conduction) in a patient with digoxin toxicity. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby; 1989.)

atrial depolarization waves may look like a normal P wave. Depending on the atrial rate, the AV conduction ratio may be 1:1, 2:1, or higher.

AT is common in children and young adults with structural heart disease, often precipitated by the occurrence of a PAC. The rhythm is usually transient and does not require specific therapy. AT can also occur in patients with hypoxemia, metabolic disturbances, or drug toxicity. In patients taking digoxin, suspect toxicity with AT, particularly in the presence of 2:1 or higher-grade AV block.

Multifocal AT (MAT) is a form of AT with three or more distinct P wave morphologies, and varying PR and P-P intervals from the multiple ectopic atrial foci (Fig. 65.24). MAT is associated with pulmonary disease (usually chronic obstructive pulmonary disease) in up to 60% of cases but can also be seen in the presence of primary cardiac pathology. On the surface ECG, MAT is often mistaken for atrial fibrillation because of the nonuniform atrial activity and irregular R-R intervals.

The approach to patients with AT is to identify and treat any precipitating factors, such as hypoxia or hypoxemia, electrolyte abnormalities, or drug toxicity. In patients with suspected hypomagnesemia, give supplemental magnesium (2 g IV over 5 minutes). Vagal maneuvers and adenosine are unlikely to be effective in AT or MAT, although these may help unmask the atrial activity. Pharmacologic therapy to slow AV conduction with a beta blocker or calcium channel blocker aids in the symptomatic but stable patient. Because AT and MAT are

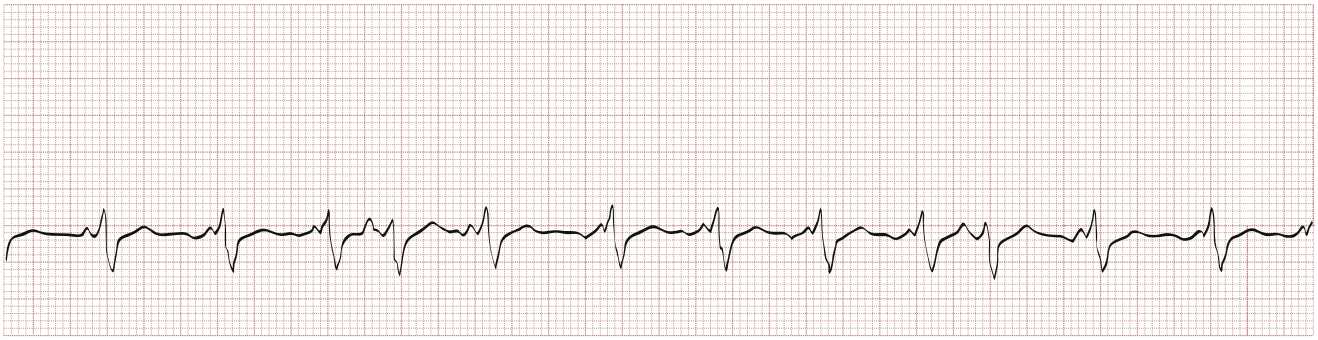


Fig. 65.24 Multifocal atrial tachycardia. Note that although the rhythm is irregular, at least three distinct P wave morphologies are present.

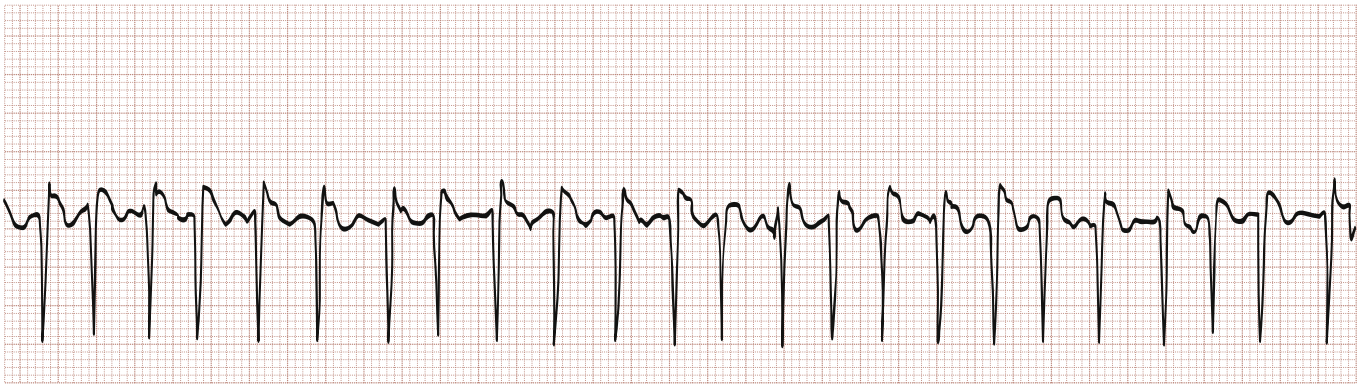


Fig. 65.25 Atrial fibrillation with rapid ventricular response. Note that the irregularity could be easily overlooked.

often precipitated by underlying illnesses, electrical cardioversion often fails or the rhythm recurs.

Atrial Fibrillation

Atrial fibrillation is electrical supranodal chaos; it starts from unpatterned depolarization of atrial tissues caused by multiple microreentry circuits, generating 300 to 600 atrial impulses/min. This chaotic activity reduces cardiac output due to both a loss of coordinated atrial contractions and a rapid ventricular rate, both of which may limit the diastolic filling and stroke volume of the ventricles.

Atrial fibrillation is the most common sustained dysrhythmia, increasing with age; it affects 1% of the population older than 60 years and 5% of those 69 years old or more. Patients with atrial fibrillation can develop left atrial thrombi, especially in the left atrial appendage, with consequent embolic events. The risk of stroke is three to five times greater than in those without atrial fibrillation. Appendageal occlusion through transcatheter approaches may alter the need for long-term, clot-directed therapy to mitigate embolic risks. Also, ablation therapies may restore sinus rhythm without the need for ongoing drug therapy.

Atrial fibrillation may be paroxysmal (spontaneously converts), persistent (requires cardioversion to convert), or permanent (when no further efforts to restore sinus rhythm are planned). Long-term approaches to management depend on many factors, including chronicity, symptomatology, underlying heart disease, and other comorbidities.

The electrocardiographic hallmark of atrial fibrillation is an irregularly irregular QRS pattern (Fig. 65.25). Although atrial fibrillation is not the sole cause of an irregular ventricular rhythm, it is the most common (Box 65.7). Atrial fibrillatory waves appear coarse or fine based on their amplitude and are often best appreciated in the inferior leads or lead V_1.

BOX 65.7 Causes of Completely Irregular (Chaotic) Rhythms

- Atrial fibrillation
- Atrial tachycardia or flutter with varying conduction
- Multifocal atrial tachycardia
- Multiple extrasystoles
- Wandering pacemaker (usually atrial)
- Parasystole

Typically, the ventricular rate in adults with atrial fibrillation does not exceed 150 to 170 beats/min and often is slower, particularly in the presence of nodal blocking agents. Atrial fibrillation in an adult with a ventricular rate exceeding 200 beats/min strongly suggests the presence of an accessory conduction pathway and has important implications for management (see later). Frequently, rapid atrial fibrillation with an accessory path will have a wide-QRS complex, but not always; if the irregularity of ventricular depolarization is not sought by the careful use of a caliper or similar measurement, it is easy to mistake this wide but chaotic rhythm for VT. When a wide-QRS complex is seen at rates below 200 beats/min but with ventricular chaos, an existing or acquired bundle branch block with atrial fibrillation is likely present.

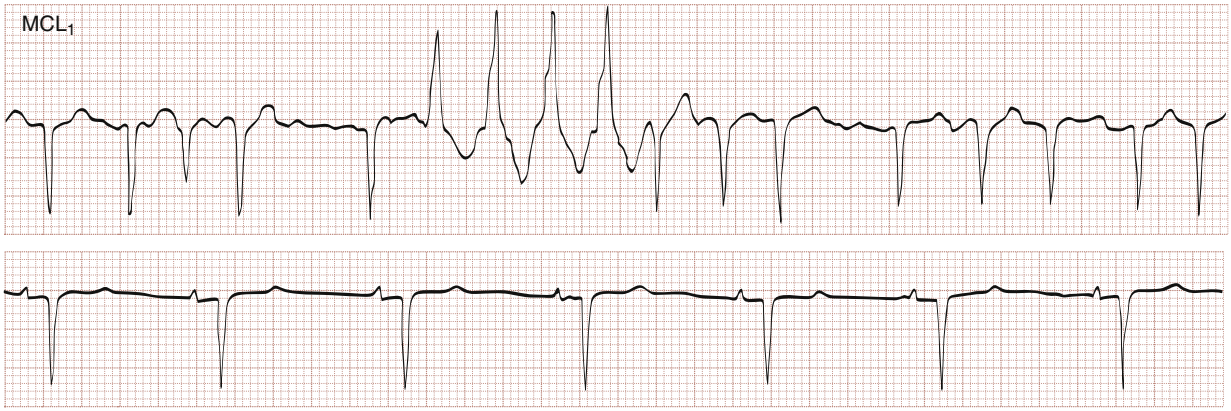


Fig. 65.26 Atrial fibrillation with classic Ashman phenomenon series of beats. Note the long-short cycle before aberrantly conducted impulses are sustained for four beats. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby; 1989.)

BOX 65.8 Causes of Atrial Fibrillation

Hypertensive heart disease
Cardiomyopathy
Ischemic heart disease
Valvular disease (especially mitral)
Congestive heart failure
Pericarditis
Hyperthyroidism
Sick sinus syndrome
Myocardial contusion
Acute ethanol intoxication (holiday heart syndrome)
Idiopathic
Cardiac surgery
Catecholamine excess
Pulmonary embolism
Accessory pathway (Wolff-Parkinson-White) syndrome

The Ashman phenomenon refers to aberrant ventricular conduction of an early-arriving atrial impulse following a relatively long R-R interval, the result of a partially refractory His bundle. Such aberrantly conducted impulses are commonly seen in atrial fibrillation but can occur in any irregular rhythm in which long-short cycle sequences occur; they typically assume an RBBB pattern (Fig. 65.26). Ashman beats can be mistaken for PVCs or runs of VT if sustained.

Atrial fibrillation is usually associated with underlying heart disease. The most common etiology is hypertension, but it can also occur with ischemic or valvular disease (Box 65.8). Atrial fibrillation may occur in isolation (lone atrial fibrillation) or as a manifestation of systemic conditions such as hyperthyroidism. As many as one-third of patients with congestive heart failure also have atrial fibrillation.

The presentation of patients with atrial fibrillation is variable.[3,4] For example, patients without underlying cardiopulmonary disease may tolerate atrial fibrillation with ventricular rates up to 150 beats/min, noting only palpitations or exercise intolerance. Conversely, a patient with left ventricular dysfunction and new atrial fibrillation may experience dyspnea at rest. In a patient with preexisting atrial fibrillation who presents with a rapid ventricular rate, the initial evaluation should determine if the tachycardia is a response to some other hemodynamic stress, such as decompensated heart failure, sepsis, hypovolemia, massive pulmonary embolism, or cardiac tamponade. Identifying acute underlying conditions may direct timely interventions.[5] Failure to recognize the underlying cause of tachycardia may result in counterproductive attempts at rate control or cardioversion.

For stable patients with rapid atrial fibrillation, administration of an AV nodal blocking agent to achieve a target ventricular rate of 120 beats/min or less is the first step.[3,4] IV calcium channel blockers (e.g., diltiazem, verapamil) or beta blockers (e.g., metoprolol) are easily titrated and can be followed by an oral agent. Nodal agents should not be used for rate control in the setting of anterograde (wider QRS) accessory pathway conduction because AV conduction may be preventing the ventricular rate from accelerating and degenerating into ventricular fibrillation.

The debate over rhythm or rate control for patients with established atrial fibrillation is ongoing without a definitive answer for all patient populations. Among patients with heart failure, a rhythm control strategy via catheter ablation (but *not* with antidysrhythmic drugs) is associated with improvement in clinical outcomes.

In choosing rate control for the long term, the ideal target is unclear, with some advocating for a resting rate of 80 beats/min or less (American Heart Association (AHA) class IIa recommendation) while acknowledging that for patients with preserved left ventricular function, a lenient rate-control strategy of <110 bpm may be reasonable as long as patients remain asymptomatic.[3]

If atrial fibrillation has been present longer than 2 days in the absence of therapeutic anticoagulation, cardioversion may increase the risk of systemic embolization from preexisting atrial thrombus. However, for patients with new-onset or newly recurrent atrial fibrillation (i.e, duration of 48 hours or less) or for those already on therapeutic anticoagulation, ED cardioversion is safe. Cardioversion can also be performed following transesophageal echocardiography demonstrating the absence of atrial thrombus.

The choice of electrical versus pharmacologic cardioversion depends on institutional factors and patient preference, but success rates are generally higher with electrical conversion.[3,4,6] A strategy of procainamide therapy first, followed by electrical cardioversion for patients not converted pharmacologically within 30 minutes, is another option that obviates the need for electrical cardioversion in about half of patients.[7] In patients with new or recurrent atrial fibrillation of less than 48 to 72 hours duration, up to 50% will convert spontaneously to sinus rhythm within 24 hours.

Various agents are available for the pharmacologic cardioversion of patients with stable atrial fibrillation in the ED, including the class

BOX 65.9 Pharmacologic Approach to Atrial Fibrillation and Flutter Conversion

IV procainamide, 30–50 mg/min, up to a total dose of 18–20 mg/kg (12 mg/kg in patients with congestive heart failure) or until conversion or side effects occur

or

Amiodarone, 150 mg IV over 10{en dash}15 minutes, followed by 1 mcg/min IV infusion for 6 hours then 0.5 mcg/min IV for 18 hours (or switch to oral)

or

Ibutilide, 0.015–0.02 mg/kg IV, over 10–15 min (conversion usually occurs within 20 min if successful)

or

Oral propafenone, 600 mg (contraindicated in the setting of structural heart disease or ischemia)

or

Oral flecainide, 300 mg (contraindicated in the setting of structural heart disease or ischemia)

NOTE: If needed, a calcium channel blocker can be given before the type IA agent (if no contraindications are present) to lower the ventricular response rate to below 120 beats/min and to attenuate further tachycardia from the vagolytic effects of these agents.

BOX 65.10 CHA_2DS_2VASC Scoring for Guiding Clot-Directed Therapy in Atrial Fibrillation

Clinical Feature	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 yr	2
Diabetes mellitus	1
Any previous stroke, transient ischemic attack, embolism	2
Gender—female	1
Age, 65–74 yr	1
Vascular disease (history of MI, PAD, or aortic atherosclerosis)	1

Vascular disease—myocardial infarction, peripheral vascular disease, aortic plaque

Actions:

- Score 0— no anticoagulant therapy
- Score 1—oral anticoagulation should be considered
- Score 2 or higher—oral anticoagulation is recommended

BOX 65.11 HAS-BLED Scoring System to Assess 1-Year Risk of Major Bleeding in Patients Taking Anticoagulants with Atrial Fibrillation

Condition		Points
H	*Hypertension*: (uncontrolled, >160 mmHg systolic)	1
A	*Abnormal renal function*: Dialysis, transplant, Cr >2.26 mg/dL or >200 μmol/L	1
	Abnormal liver function: *Cirrhosis* or Bilirubin >2× Normal or AST/ALT/AP >3× Normal	1
S	*Stroke*: Prior history of stroke	1
B	*Bleeding*: Prior Major Bleeding or Predisposition to Bleeding	1
L	Labile *INR*: (Unstable/high INR), Time in Therapeutic Range < 60%	1
E	Elderly: Age > 65 years	1
D	Prior Alcohol or Drug Usage History (≥8 drinks/week)	1
	Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)	1

A score of ≥3 indicates "high risk" and indicates the need for caution

IA, IC, and III antidysrhythmics (Box 65.9). In practice, ibutilide, amiodarone, and procainamide are most commonly used in the ED setting. Of these agents, ibutilide is associated with the highest rates of conversion to sinus rhythm, but, like all class IC antidysrhythmics, is best avoided in patients with structural or ischemic heart disease. Amiodarone is safe in this population and has the additional advantage of slowing the ventricular response. Procainamide is a first-line agent in patients with a suspected accessory pathway (very fast ventricular responses or known presence) because it does not impact AV conduction.

Rarely, rapid rates or irregularity make synchronized cardioversion efforts impossible; in this setting, it is appropriate to proceed with unsynchronized cardioversion while being prepared to re-shock if ventricular dysthymia ensues.[8,9] Following electrical cardioversion, there is an increased risk of thromboembolism in the initial 30 days.

Although long-term antiplatelet or anticoagulation therapy typically falls beyond the scope of the ED, starting early can enhance help avoid embolism and enhance patient compliance. The AHA and European Society of Cardiology recommend using the CHA_2DS_2-VASc score to guide anticoagulation therapy in those with atrial fibrillation (Box 65.10).[3,4] Anticoagulation reduces the overall risk of stroke by almost 70 percent, but with an increased risk of major bleeding; therefore, the risk-to-benefit ratio of any anticoagulation strategy must be assessed for patients at higher risk for bleeding (Box 65.11). The choice of coagulation therapy may be influenced by many institutional and patient-specific factors, but the direct oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, or rivaroxaban, have an overall safety profile that is superior to warfarin[10,11].

Atrial fibrillation alone is not an indication for hospital admission. Observation or admission are appropriate for atrial fibrillation complicated by other conditions, accompanied by acute or exacerbated cardiopulmonary disease, when duration is unknown and follow-up uncertain, and for symptomatic patients who fail cardioversion. Ablation therapy is another option after new-onset or recurrent episodes.[12]

Atrial Flutter

Atrial flutter has ECG features of atrial depolarization occurring at a regular rate of 250 to 350 beats/min (300 beats/min is classic) caused by an atrial reentry mechanism (Fig. 65.27). Flutter waves on the ECG are broad, sawtooth-appearing, regular depolarizations prior to QRS complexes, with the latter occurring at some fraction of the atrial rate. The ventricular rate in atrial flutter is often rapid, but in the absence of a bypass tract (in which 1:1 conduction is possible), the conduction ratio is limited by the refractory period of the AV node. With 2:1 conduction, the classic ventricular rate is 150 beats/min, often making flutter waves difficult to appreciate and allowing the rhythm to be mistaken for sinus tachycardia. Because the atrial rate can vary, the ventricular rate range widely varies also. When the conduction ratio changes from beat to beat, this is termed *atrial flutter with variable conduction*, with a resultant irregular ventricular rate. This can be distinguished from atrial fibrillation by looking for a pattern of atrial depolarization rather than chaotic atrial activity.

Atrial flutter often accompanies pulmonary disease, structural heart disease, particularly valvular heart disease, and cardiomyopathies. The acute management of atrial flutter parallels that of atrial fibrillation with a few special considerations. Because AV conduction occurs at fixed ratios in atrial flutter, the administration of beta blocker or calcium channel blocker therapy can result in an abrupt rate change, making it more challenging to titrate therapy to a desired target rate.

Atrial flutter is more sensitive to DC cardioversion (up to 90% conversion rate) than atrial fibrillation and usually requires lower energy (20 to 50 J) for conversion to sinus rhythm. Atrial flutter is more resistant to chemical cardioversion (<50% success) than new-onset, nonvalvular atrial fibrillation. In most other respects, ED patients with atrial flutter are managed similarly to those with atrial fibrillation; in particular, anticoagulation therapy at discharge should be considered similarly to atrial fibrillation.

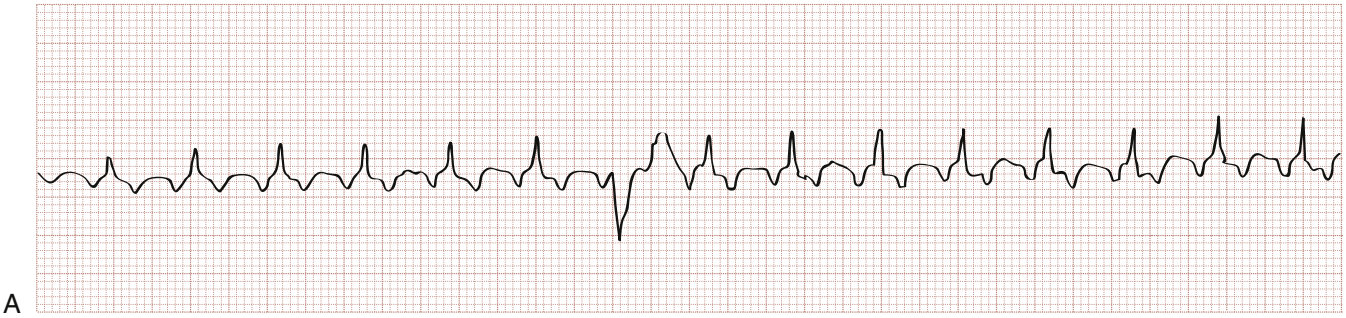
Atrioventricular Nodal Reentrant Tachycardia

Also known by the less precise term *PSVT*, or just SVT), AVNRT is a regular, narrow-complex rhythm with a ventricular rate of 130 beats/min or greater, commonly more than 160 beats/min (Fig. 65.28). It is the most common nonsinus tachydysrhythmia in young adults. AVNRT is the result of a reentry circuit within the AV node, with normal conduction (narrow QRS) down the bundles of His and with retrograde conduction (inverted P waves typically buried within the QRS) up into the atria (Fig. 65.29).

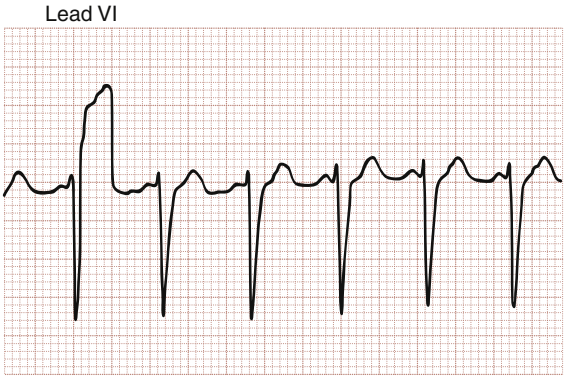
The onset and spontaneous end of AVNRT is typically abrupt, and it frequently arises in the context of strenuous exercise or emotional stress. Most patients with AVNRT are symptomatic, but hemodynamic instability is unusual in the absence of underlying cardiopulmonary disease.

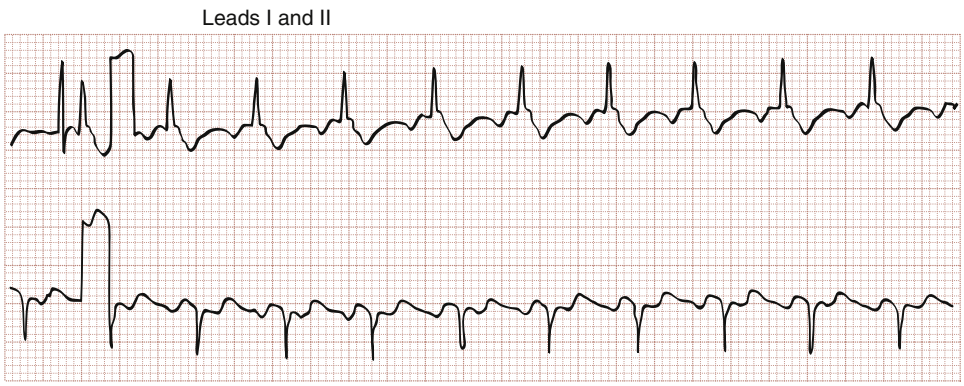
If vagal maneuvers fail to restore sinus rhythm, first-line therapy for AVNRT is adenosine (6 mg rapid, large-bore IV bolus followed by a flush; repeat with 12 mg if no effect on rate). This approach is successful in 85% to 90% of cases and is safe. In refractory cases, diltiazem, esmolol, or metoprolol are options. Rarely needed, synchronized cardioversion (at 100 to 200 J, biphasic preferred) can terminate AVNRT refractory to pharmacologic therapy or in a patient with hemodynamic instability.

No specific laboratory testing is needed, although mild troponin level elevations occur but are of uncertain significance aside from concerns for myocardial ischemia. Most patients can be discharged after



A





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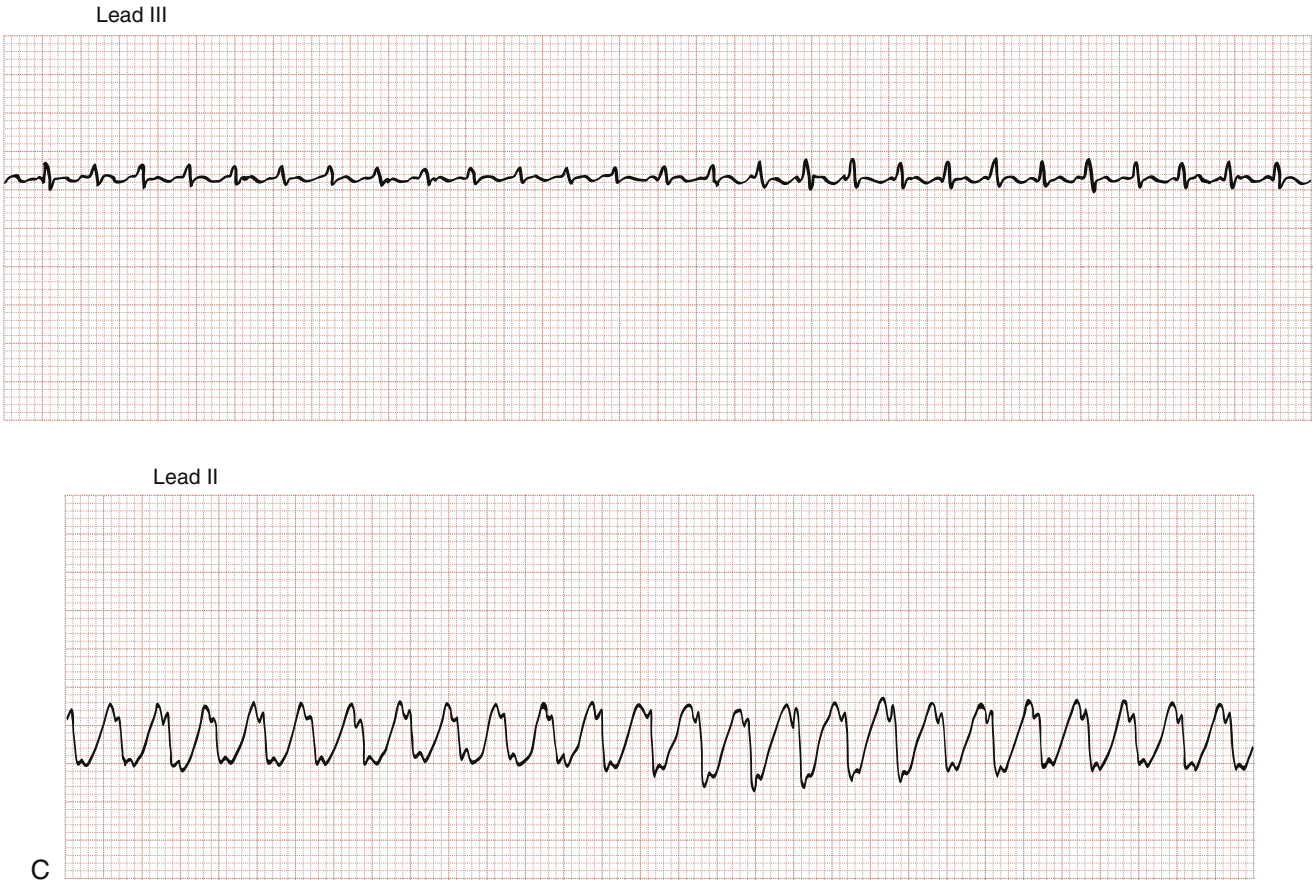


Fig. 65.27 (A) Atrial flutter with 2:1 conduction and isolated premature ventricular contraction. (B) Atrial flutter with 2:1 conduction. Lead II helps identify characteristic flutter waves. (C) Atrial flutter with 1:1 conduction. This is rare and can be mistaken for ventricular tachycardia (lead II).

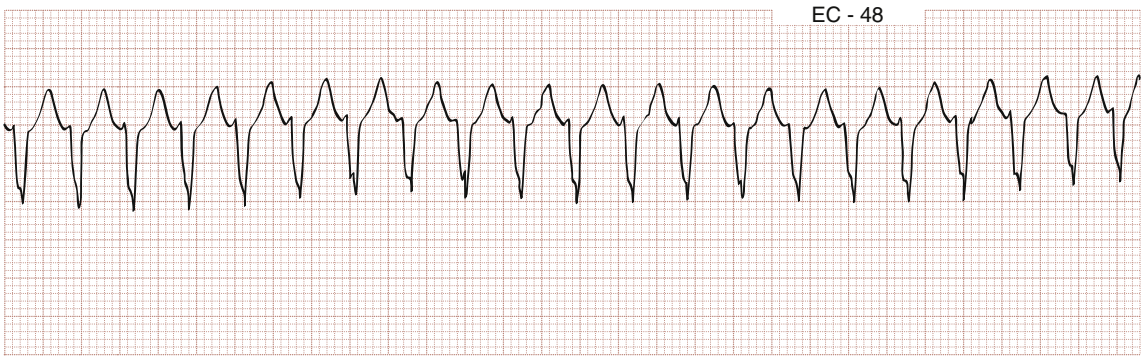


Fig. 65.28 Paroxysmal supraventricular tachycardia. Note the narrow, regular QRS complexes.

terminating AVNRT with adenosine or vagal maneuvers and typically require no testing beyond an ECG, including in the field setting. Patients with frequent recurrences are candidates for prophylaxis with a beta blocker or calcium channel blocker or ablation therapy. Starting prophylactic therapy from the ED is appropriate for those patients with an established plan for follow-up.

Junctional Tachycardia

In contrast to the bursts seen in AVNRT, JT show sustained ventricular rates but rarely exceeds 130 beats/min. JT is associated with structural heart disease, metabolic disturbances, or drug toxicity. Treatment should address underlying conditions, although a trial of nodal blockade with calcium channel blockers or beta blockers is an option if the rate seems to be deleterious.

Preexcitation and Accessory Pathway Syndromes

The term *preexcitation* is depolarization of the ventricular myocardium via an accessory pathway (or bypass tract) linking the atria to the ventricles, circumventing the normal AV node. Accessory pathways do not have the natural rate limits of the AV node, lending themselves

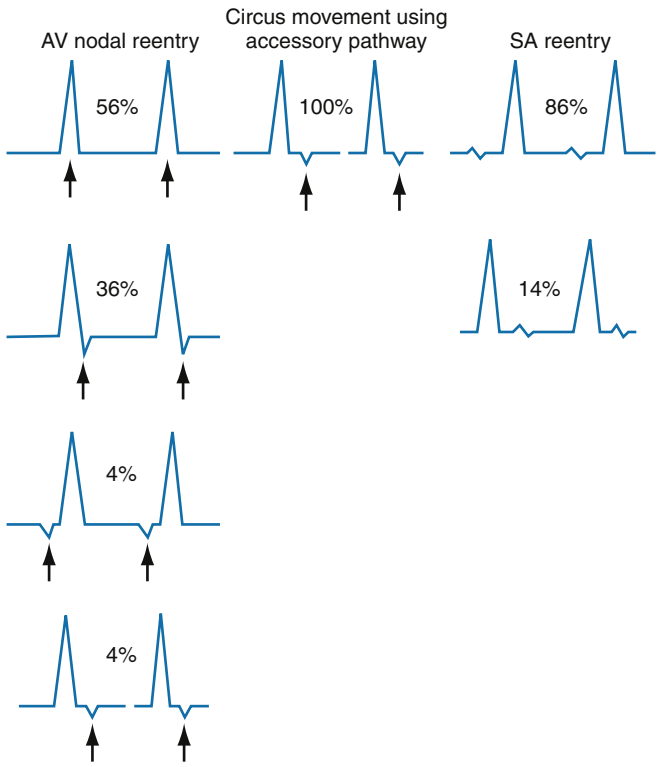


Fig. 65.29 Location of P waves in common causes of regular narrow-complex tachycardia. *AV,* Atrioventricular; *SA,* sinoatrial. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby, 1989.)

to reentry tachycardia and rapid ventricular rates. Wolff-Parkinson-White (WPW) syndrome is the classic accessory pathway syndrome, characterized by paroxysmal tachycardia and three resting electrocardiographic features (Fig. 65.30):

- Short PR interval (<0.12 second)
- QRS duration longer than 0.10 second
- Slurred upstroke to the QRS complex, referred to as a delta wave

Not all patients with WPW or other preexcitation syndromes have all the classic features on their surface ECG. Conversely, some patients with WPW-like patterns on their resting ECG never develop reentry tachycardia. Although some with WPW syndrome have structural disease, most patients have no other underlying cardiac abnormality (Box 65.12). Atrial fibrillation is seen in up to 30% of patients with WPW.

The presence of an accessory pathway can form a reentry circuit together with an AV nodal pathway to produce and sustain a rapid ventricular rate (Fig. 65.31). When the AV node is being used for anterograde conduction to the ventricles, and the accessory path is used for retrograde conduction, it is called an orthodromic AV reciprocating tachycardia. The QRS complex is typically narrow, and the ventricular rate is constrained by the refractory period of the AV node. Conversely, when the accessory pathway is the anterograde limb and the AV node is the retrograde limb of the reentry circuit, it is called an antidromic AV reciprocating tachycardia. In this scenario, the QRS complex is wide and ventricular rates can be extremely rapid.

Orthodromic AV reciprocating tachycardia is the most common presenting dysrhythmia in WPW syndrome and is indistinguishable clinically from AVNRT. Like AVNRT, orthodromic AV reciprocating tachycardia is treated with vagal maneuvers and adenosine as first-line therapies, followed by calcium channel blockers and beta blockers as second-line agents.

In contrast, antidromic AV reciprocating tachycardia has characteristic wide-QRS complexes and may have ventricular rates of 200 beats/min or more and clinical instability. When the typical QRS antidromic changes are coupled with tachycardia, AV nodal blocking agents may trigger degeneration into ventricular fibrillation. Similarly, in patients with a very rapid (>220/min) irregular tachycardia accompanied by a wide-complex QRS, nodal blockade may risk rapid deterioration to ventricular fibrillation from unbridled conduction down the accessory pathway. Procainamide is first-line therapy for tachycardia when wide-QRS complexes suggest conduction down an accessory pathway; amiodarone is an alternative. Use prompt synchronized electrical cardioversion (100 to 200 J) if there is any clinical deterioration, failure of pharmacologic therapy, or extreme tachycardia (>250 beats/min).

The Lown-Ganong-Levine syndrome is an uncommon accessory pathway syndrome associated with paroxysmal narrow-complex tachycardia, short PR interval, and normal QRS complex without a delta wave. The treatment parallels that for the WPW syndrome.

Refer all patients with a new or symptomatic accessory pathway for advanced electrophysiologic care, including pathway identification and ablation.

Wide-Complex Tachycardia

Wide-complex tachycardia refers to any tachydysrhythmia accompanied by a QRS duration of 0.12 seconds or more. Wide-complex tachycardia can start in the ventricles (i.e., VT) or can originate from above the AV node but be accompanied by aberrant AV conduction. The aberrant conduction is caused by an accessory pathway or a bundle branch block. The presence of AV dissociation or fusion beats on the 12-lead ECG clearly points to VT; older age and a prior history of myocardial infarction make VT more likely than a supraventricular tachycardia with aberrancy. On the other hand, an irregular tachycardia with a wide QRS approximating a bundle branch morphology is most likely atrial fibrillation with aberrant conduction. Although new-onset VT patients are usually unstable, the presence of hemodynamic stability does not exclude VT.

It can be difficult to make the distinction between VT and an SVT with abnormal conduction when confronted with a wide-complex tachycardia in a patient. Many of the decision rules rely on an ability to discern subtleties of the QRS morphology, and none has perfect discriminatory power. (Table 65.5; Fig. 65.32) As a general rule, consider any new wide-complex tachycardia to be VT until proven otherwise.

The classic Wellens criteria are time-honored but hard to use criteria because of their complexity and lack of order or weighting of findings. The Brugada ECG criteria describe four features of VT from among those described in the original Wellens criteria, any one of which makes the diagnosis of VT. The rhythm needs to be regular for these to be used because irregularity suggests atrial fibrillation with altered conduction. The sequential criteria are as follows (Fig. 65.33, see also Fig. 65.32):

1. Absence of any RS complexes in the precordial leads
2. RS duration (measured from beginning of R to deepest part of S wave) greater than 100 msec
3. AV dissociation (often present but overlooked; may be best appreciated in inferior limb leads and $V_{1\text{-}2}$; Fig. 65.34)
4. Specific VT morphologic criteria (see Fig. 65.33)

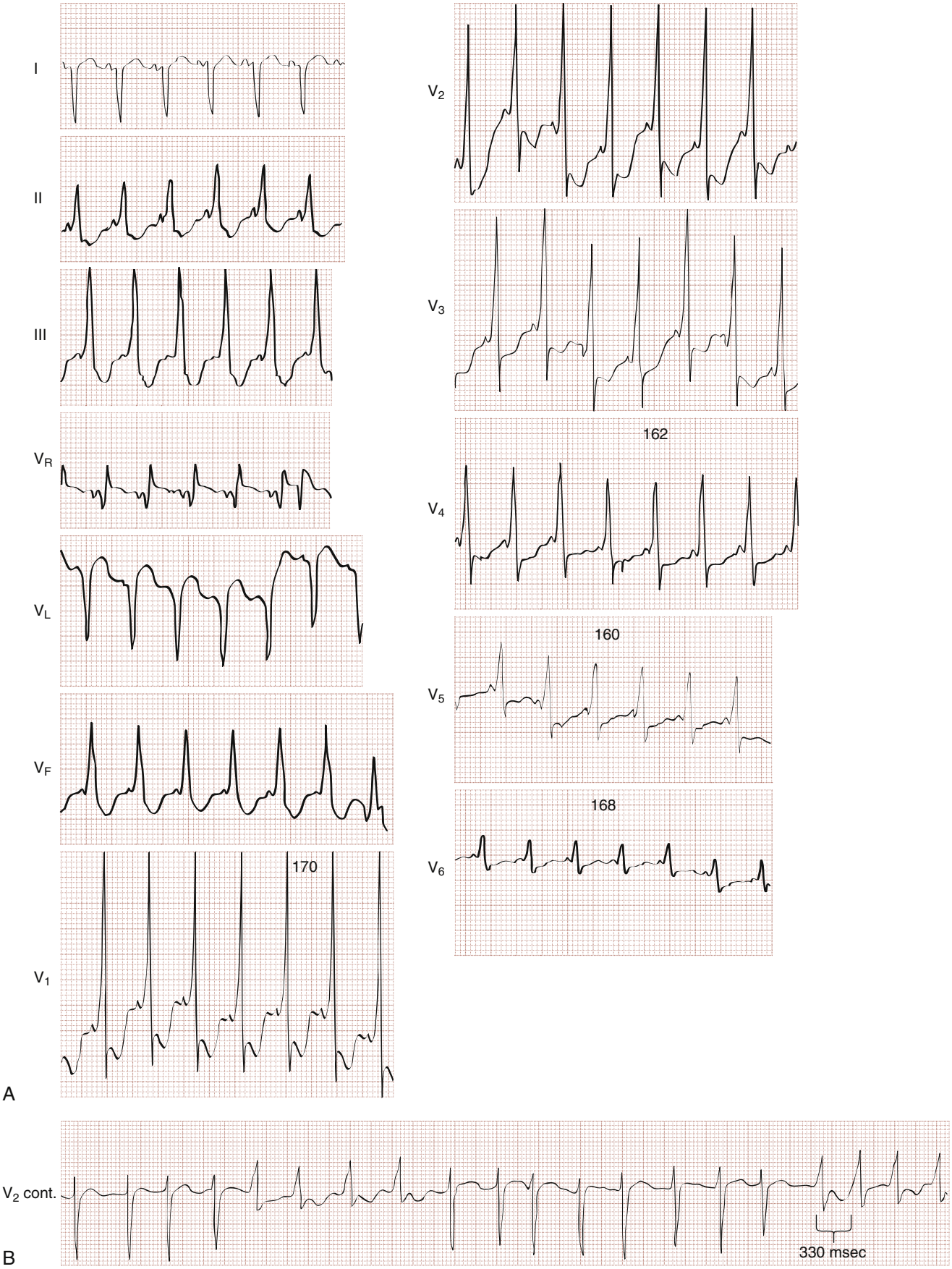


Fig. 65.30 (A) Wolff–Parkinson–White (WPW) syndrome. (B) WPW syndrome with atrial fibrillation. Note the short refractory period (330 ms). (**A** from Watanabe Y, Dreifus LS. Cardiac dysrhythmias. New York: Grune & Stratton; 1977.)

Only the absence of all the Brugada criteria allows the diagnosis of SVT. Although the original investigators found excellent sensitivity (98.7%) and specificity (96.5%) in detecting VT, follow-up investigations have shown a lower level of accuracy in ED patients (sensitivity of 92% to 94%). Often, emergency clinicians are not able to complete the assessment or agree on the findings. In patients receiving class I agents, the Brugada criteria are less reliable.

The Griffith criteria use a three-step approach to identify aberrancy, first through classic RBBB or LBBB morphologies in V_1 and V_6 to identify an SVT and then seeking AV dissociation in the remainder to identify VT (see Figs. 65.32 and 65.34). This approach has a sensitivity of 92% with a lower specificity than that seen with the Brugada approach. There are no direct, in-practice comparative data between these two approaches. Finally, the Vereckei criteria (Fig. 65.35) examine lead aVR to differentiate between VT and SVT; however, in practice, these have not been shown to be more effective or accurate, limiting their use.

Unstable patients with a wide-complex tachycardia should undergo electrical cardioversion (100 J, synchronized and biphasic, if possible). For borderline patients, electrical cardioversion with systemic sedation or analgesia or pharmacologic treatment with procainamide or amiodarone are options.

Adenosine is an option after a careful search of the ECG does not suggest VT. Adenosine is should be avoided in suspected VT

BOX 65.12 Diseases Associated With Wolff-Parkinson-White Syndrome

- Idiopathic[a]
- Cardiomyopathy (especially hypertrophic)
- Transposition of great vessels
- Endocardial fibroelastosis
- Mitral valve prolapse
- Tricuspid atresia
- Ebstein disease

[a] Most common.

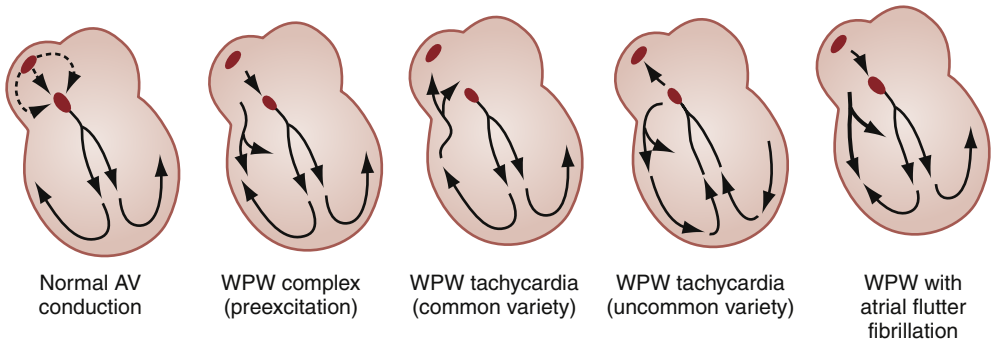
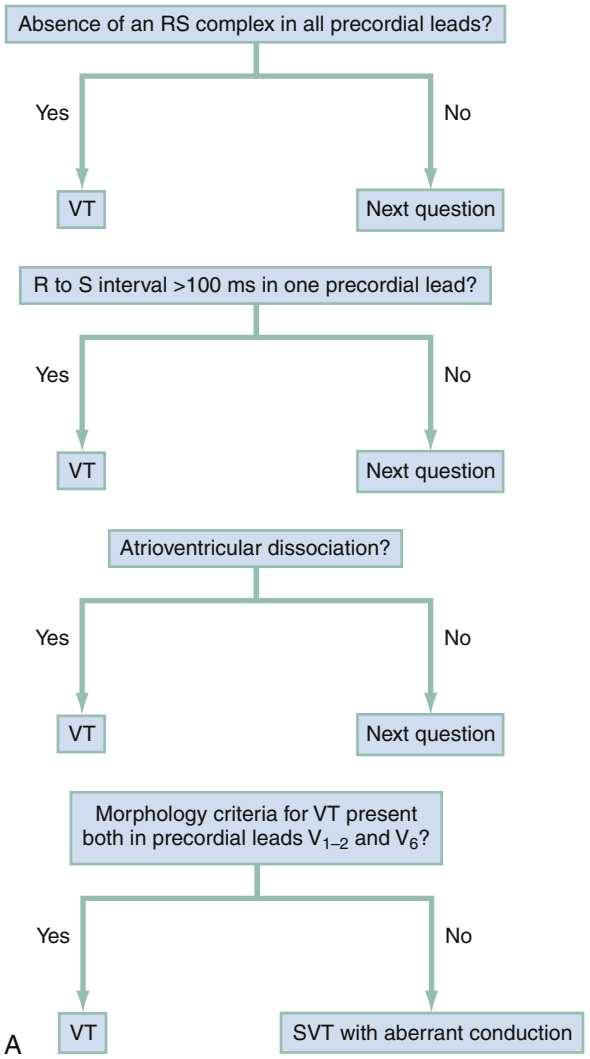


Fig. 65.31 Wolff–Parkinson–White (WPW) paths and associated rhythms. *AV,* Atrioventricular. (**A** from Watanabe Y, Dreifus LS. Cardiac dysrhythmias. New York: Grune & Stratton; 1977.)

TABLE 65.5 Features Distinguishing Ventricular Tachycardia From Supraventricular Tachycardia With Abnormal Conduction

Parameter	Ventricular Tachycardia	Supraventricular Tachycardia Plus Aberrancy
Clinical features	Age ≥ 50 yr	Age ≤ 35 yr
	History of myocardial infarction, congestive heart failure, CABG, or ASHD	None
	Previous history of ventricular tachycardia	Previous history of supraventricular tachycardia
Physical examination	Cannon A waves	Absent
	Variation in arterial pulse	Absence of variability
	Variable first heart sound	Absence of variability
Electrocardiogram	Fusion beats	None
	AV dissociation	Preceding P waves with QRS complexes
	QRS >0.14 s	QRS usually <0.14 s
	Extreme left axis deviation (30 degrees)	Axis normal or near-normal
	No response to vagal maneuvers	Slow or terminate with vagal maneuvers
Specific QRS patterns	V_1: R, qR, or RS	V_1: rSR′
	V_6: S, rS, or qR	V_6: qRs
	Identical to previous ventricular tachycardia tracing[a]	Identical to previous supraventricular tachycardia tracing[a]
	Concordance of positivity or negativity[b]	

ASHD, Arteriosclerotic heart disease; *AV,* atrioventricular; *CABG,* coronary artery bypass graft; *LAD,* left anterior descending.
[a] If proven by electrophysiologic studies or by a preponderance of evidence.
[b] Main deflection of QRS complex either positive or negative in every precordial lead.



A

	BBB pattern
Right	
V_1	rSR′ pattern with R′ > rRS (RS) pattern with R > S; Q wave
V_6	<40 msec and <2 mm (0.2 mV) were allowed
Left	
V_1	rS or QS pattern with time to 5 wave nadir <70 msec
V_6	R wave with no Q wave

BBB = bundle branch block.

If no classic BBB pattern as noted above that would define SVT with aberrancy, search for AV dissociation; if present, VT is diagnosed and if absent, SVT is diagnosed by default.

B

Fig. 65.32 (A) Brugada four-step approach for differentiating ventricular tachycardia (VT) and wide-QRS supraventricular tachycardia. Only when the response to all four questions is negative is a supraventricular rhythm with abnormal conduction diagnosed. As soon as a single "yes" answer is noted, VT is diagnosed. (B) Griffith approach, in which aberrant conduction is sought in leads V_1 and V_6 (right bundle branch block [RBBB] or left bundle branch block [LBBB], classic appearances), followed by a search for atrioventricular (AV) dissociation. If classic RBBB and LBBB patterns are absent, or if the remainder of the leads have AV dissociation, VT is diagnosed. ([A] From Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation.* 1991;83:1649–1659; [B] adapted from Griffith MJ, Garratt CJ, Mounsey P, Camm AJ. Ventricular tachycardia as default diagnosis in broad complex tachycardia. *Lancet.* 1994;343:386–388.)

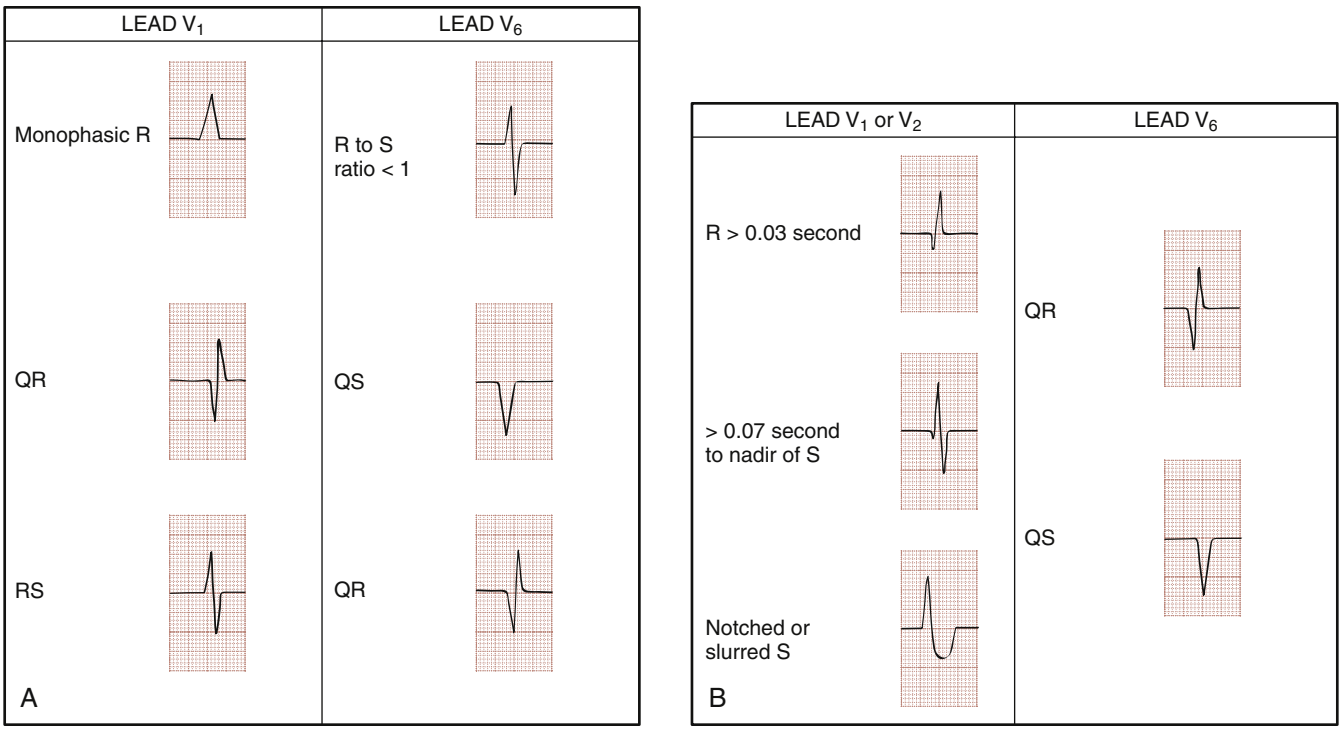


Fig. 65.33 Morphology associated with the fourth criterion in the Brugada system. (A) In patients with a right bundle branch-appearing complex. (B) In patients with a left bundle branch-appearing complex.

or if there is an irregular or very rapid ventricular rate (≥250 beats/min). It should be used with caution after heart transplantation. Most SVTs will slow or terminate with adenosine, and only rare VT forms respond; any ill effects of adenosine are usually fleeting. Other pharmacologic therapies for stable VT are discussed later. If pharmacologic treatment fails, synchronized cardioversion should be performed.

Ventricular Tachycardia

VT originates within or below the His bundle. Nonsustained VT refers to short episodes (<30 seconds) reverting spontaneously, whereas sustained VT is prolonged. Reentry mechanisms are the most common cause of VT, although automatic and triggered mechanisms occur. Most patients with VT have underlying heart disease, especially ischemic and nonischemic cardiomyopathy.

Monomorphic ventricular tachycardia is the most common form of VT and is characterized by morphologically consistent QRS complexes, usually in a regular pattern at a rate of 150 to 200 beats/min (Fig. 65.36). Polymorphic ventricular tachycardia is seen with varying QRS morphologies and suggests a more severe underlying disease (Figs. 65.37 and 65.38).

For stable patients with VT, amiodarone (3 to 5 mg/kg IV over 20 minutes, often 250 to 350 mg) is the first-line agent, with reported successful termination of up to 90%. Procainamide (30 to 50 mg/min IV, up to a total of 18 mg/kg or until VT is terminated) is a second-line agent. Lidocaine (1.0 to 1.5 mg/kg IV bolus, up to 3 mg/kg maximum, followed by an infusion) is an alternative to amiodarone with similar success rates in some studies. Unstable patients or those with VT refractory to pharmacotherapy should undergo synchronized cardioversion with 100 J (biphasic preferred); escalating doses of up to 200 J biphasic or 360 J monophasic are occasionally needed.

Cardiology should be consulted for patients with VT. Ablation therapy, along with medical optimization, may aid long-term management.

Torsades de Pointes

Torsades de pointes is translated as "twisting of the points" and is a paroxysmal form of polymorphic VT that meets the following clinical criteria (see Fig. 65.38):

1. Ventricular rate greater than 200 beats/min
2. Undulating QRS axis, with the polarity of the complexes appearing to shift about the baseline
3. Paroxysms of less than 90 seconds

Torsades de pointes occurs in the setting of a prolonged QT interval, a reflection of abnormal ventricular repolarization. A prolonged QT interval can be congenital or acquired. Women are at a greater risk for torsades de pointes. Acquired torsades de pointes is much more common than congenital and is pause-dependent, triggered by a slow heart rate.

Acquired QT prolongation is the most common form seen outside a specialized pediatric setting and usually has multifactorial causes (Box 65.13). Common triggers include electrolyte disturbances (e.g., hypokalemia, hypomagnesemia) or many different medications (notably class IA and IC agents but also many others; see Box 65.13), especially when used in combination.

Treatment of torsades de pointes in stable adult patients involves correcting any underlying metabolic or electrolyte abnormalities and increasing the heart rate to shorten ventricular repolarization. Class IA and IC antidysrhythmics should not be used in patients with torsades

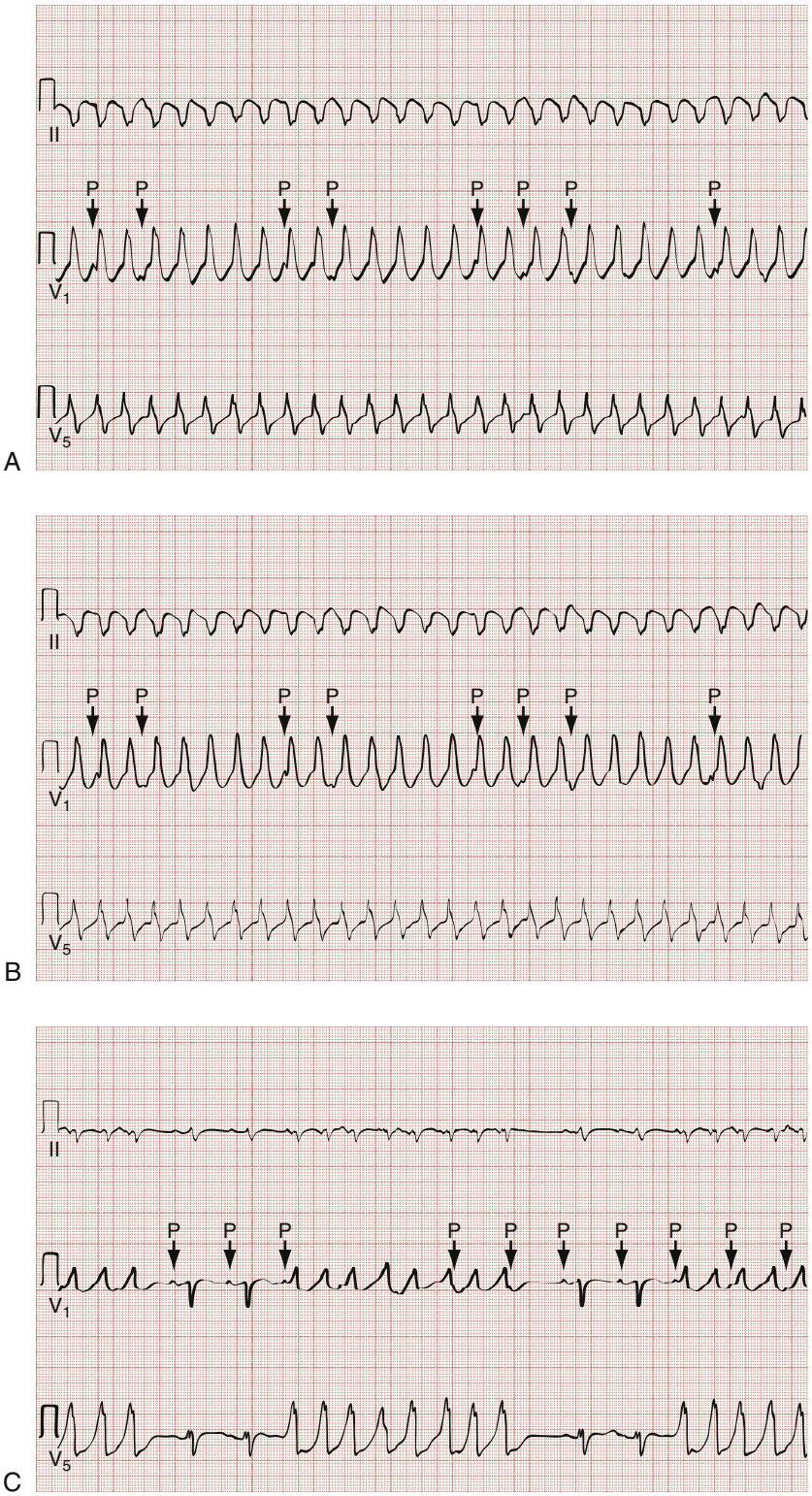


Fig. 65.34 (A, B) Ventricular tachycardia. Note atrioventricular dissociation. (C) Intermittent, nonsustained ventricular tachycardia. Atrioventricular dissociation is evident. (Courtesy Dr. Edward Curtis.)

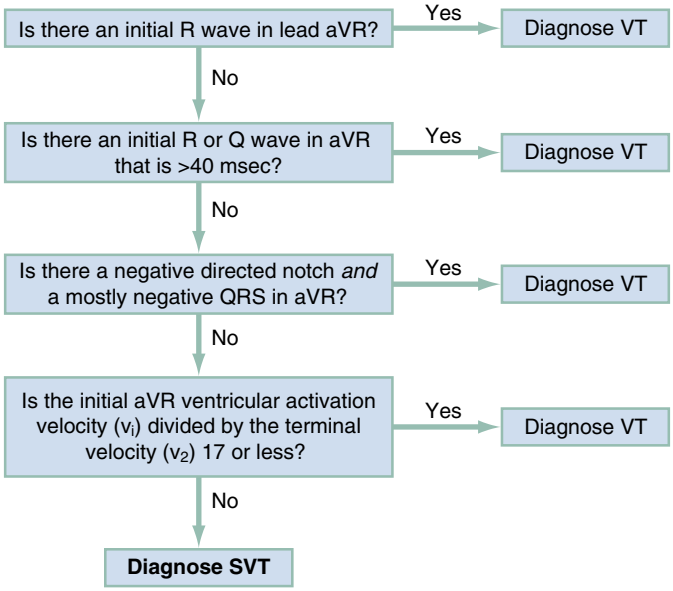


Fig. 65.35 Vereckei criteria for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT).

de pointes. Empirical IV magnesium sulfate (1 to 2 g quickly) effectively treats torsades de pointes, even in the absence of hypomagnesemia, and may prevent recurrence if electrical cardioversion succeeds.

A baseline ventricular rate of 100 to 120 beats/min is usually enough to prevent acquired torsades de pointes, achieved by overdrive pacing (i.e., external pacing at a rate greater than the patient's intrinsic rate) or via β-adrenergic (isoproterenol) infusion. Unstable patients or those with sustained torsades de pointes should undergo electrical cardioversion, recognizing that synchronization may not be possible.

Congenital torsades de pointes is rare and triggered by sympathetic excess or tachycardia; it is usually seen in children and young adults. Patients often have syncope during exertion and a prolonged QT interval on the ECG. In contrast to acquired forms, congenital torsades de pointes is treated with beta blockers.

Brugada Syndrome

Brugada syndrome is a ventricular dysrhythmia triggering syncope or sudden cardiac death in the absence of structural heart disease. This syndrome links to an inherited disorder of sodium channels and is commonly diagnosed in men during young adulthood. The Brugada electrocardiographic pattern shows a downward coved or humped (saddleback) ST segment elevation in leads V_1 to V_3 (Fig. 65.39), sometimes simulating an RBBB appearance. The ST segment findings may be transient or elicited only with pharmacologic stimulation or exertion.

Any patient with unexplained syncope and a Brugada pattern ECG requires admission for consideration of an implanted defibrillator. For patients in whom a Brugada pattern ECG is noted incidentally, there is no consensus on treatment, but we recommend referral to a cardiologist.

DISPOSITION

Patients with dysrhythmias that are symptomatic and nonresponsive to ED therapy require admission. Outpatient ambulatory monitoring and close contact with a cardiologist is an option for patients with no evidence of structural heart disease who are asymptomatic or only have palpitations and for patients whose dysrhythmias resolve.[4,6] When evaluating anyone with symptomatic rhythm changes, we recommend a cardiology consultation. Those with VT, torsades de pointes, type II second-degree block, or complete heart block require admission.

The references for this chapter can be found online at ExpertConsult.com.

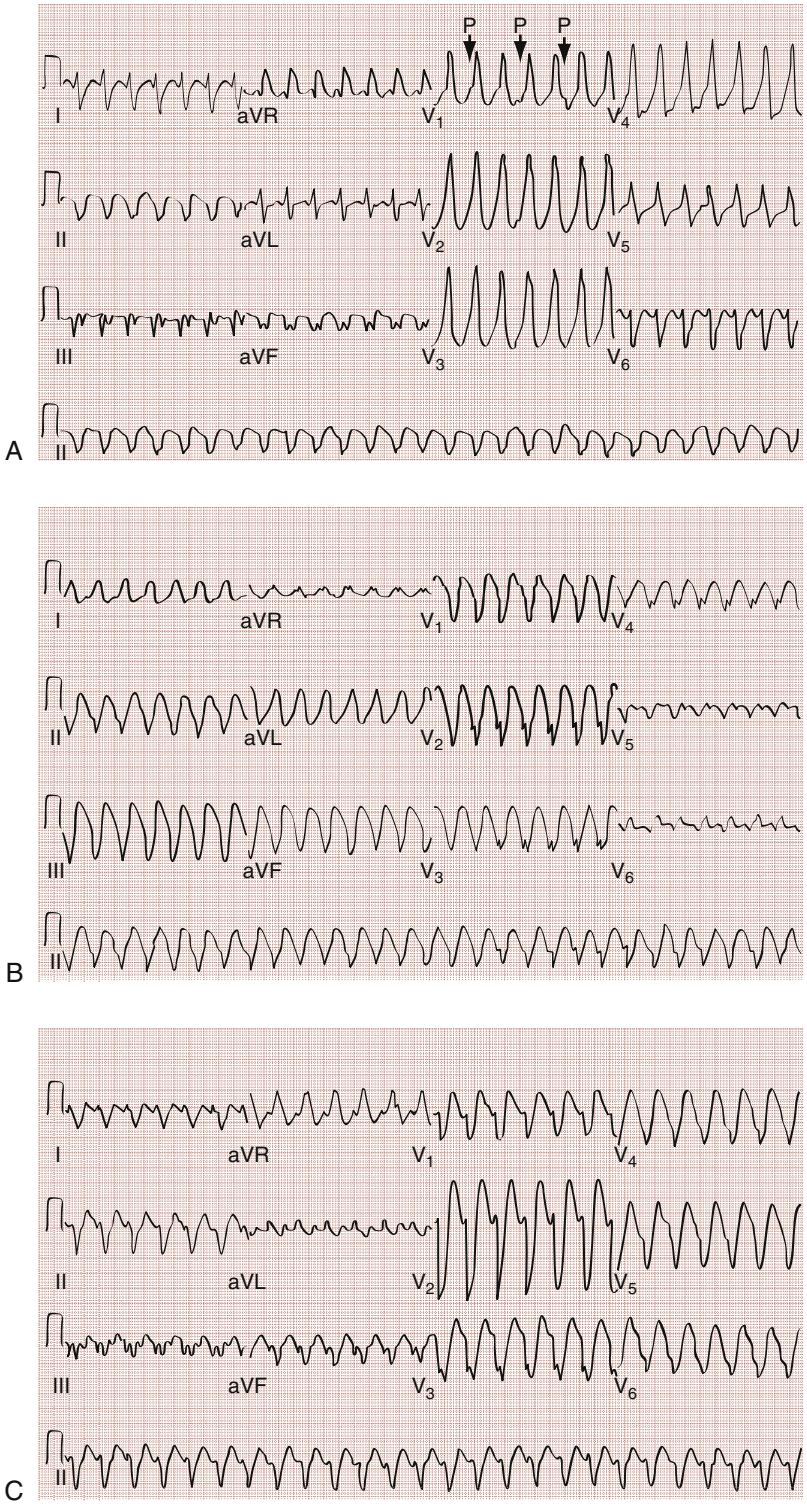


Fig. 65.36 Ventricular tachycardia. (A) RS complexes are present in chest leads, but RS duration is greater than 100 ms. Although the Brugada criteria indicate that no further analysis is necessary, atrioventricular dissociation is also evident, and QRS morphology in lead V_6 is consistent with ventricular tachycardia. (B) Some RS complexes are present, RS duration is no longer than 100 msec, and atrioventricular dissociation is difficult to appreciate. The morphologic criteria for ventricular tachycardia are fulfilled because S is notched in V_1 and QR is present in V_6. (C) Diagnosis is based on morphologic criteria because S is notched in V_1 and V_2 and QS are present in V_6. (Courtesy Dr. Edward Curtis.)

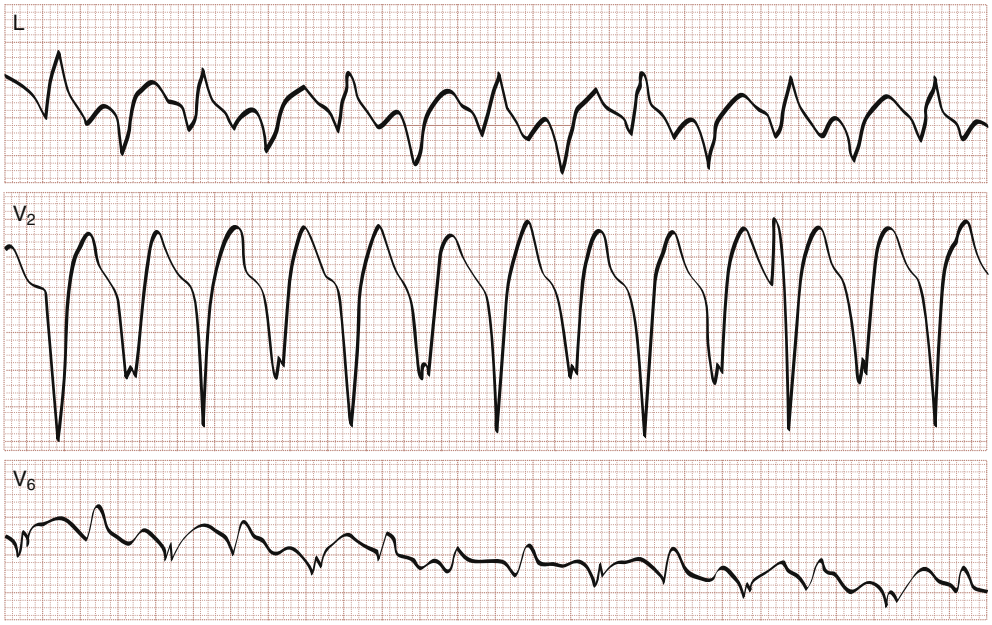


Fig. 65.37 Bidirectional ventricular tachycardia in a patient with digoxin toxicity. (From Marriott HJL, Conover MB. Advanced concepts in dysrhythmias. ed 2. St. Louis: Mosby; 1989.)

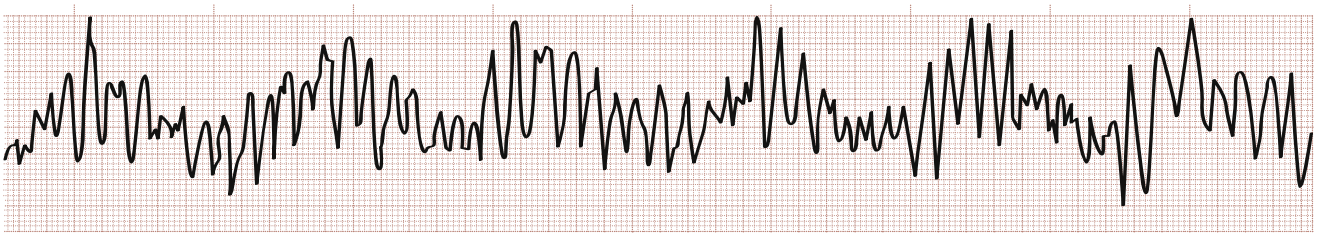


Fig. 65.38 Torsades de pointes with the classic spiraling of QRS complexes around the baseline.

BOX 65.13 Classification and Causes of Prolonged QT Syndromes That Produce Torsades de Pointes

Pause-Dependent (Acquired)

Drug-induced—class IA and IC antidysrhythmics; many phenothiazines and butyrophenones (notably haloperidol and droperidol), cyclic antidepressants, antibiotics (especially macrolides), organophosphates, antihistamines, antifungals, antiseizure and antiemetic agents

Electrolyte abnormalities—hypokalemia, hypomagnesemia, hypocalcemia (rarely)

Diet-related—starvation, low protein

Severe bradycardia or atrioventricular block

Hypothyroidism

Contrast injection

Cerebrovascular accident (especially intraparenchymal)

Myocardial ischemia

Adrenergic-Dependent (Tachycardia-Prompted)

Congenital

Jervell and Lange-Nielsen syndrome (deafness, autosomal recessive)

Romano–Ward syndrome (normal hearing, autosomal dominant)

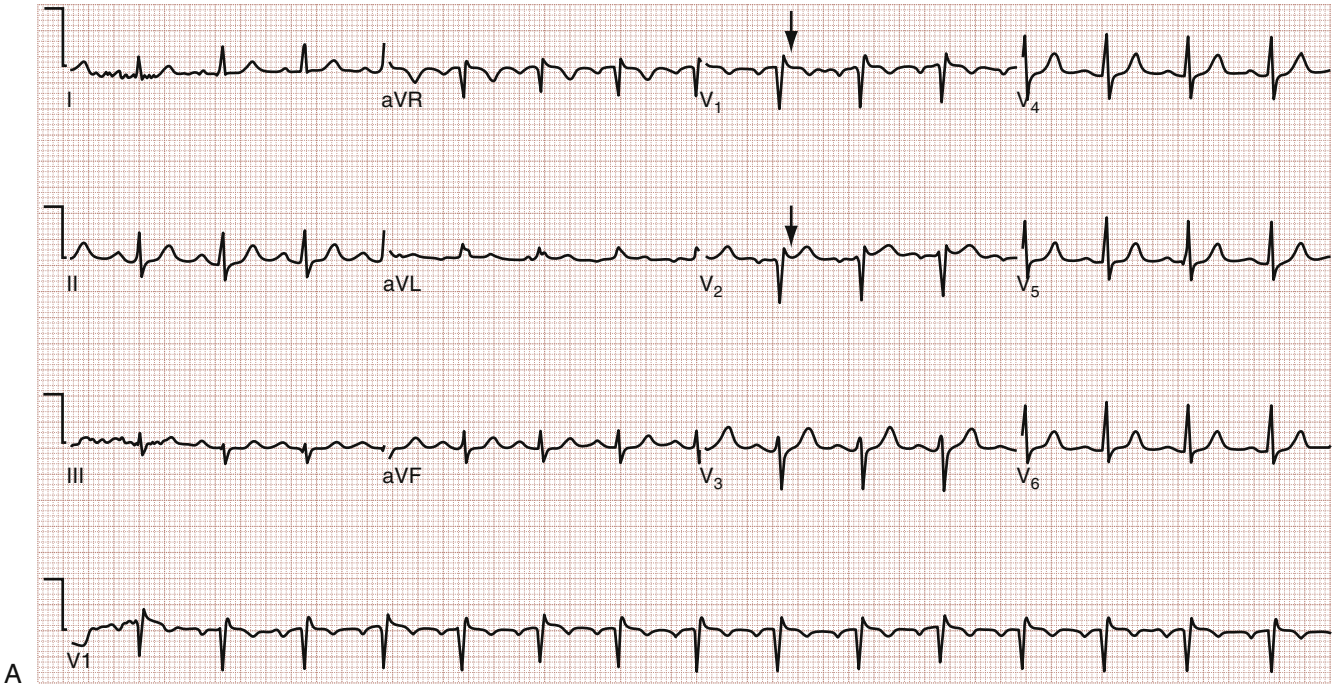
Sporadic (normal hearing, no familial tendency)

Mitral valve prolapse

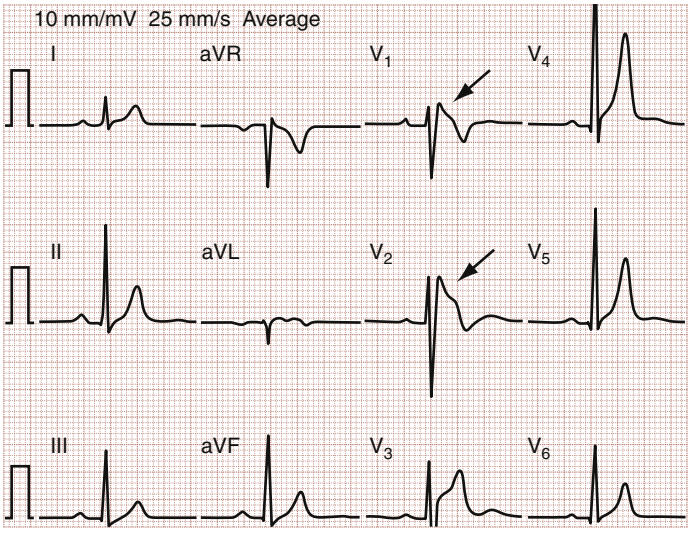
Acquired (Rare)

Cerebrovascular disease (especially subarachnoid hemorrhage)

Autonomic surgery: radical neck dissection, carotid endarterectomy, truncal vagotomy



A



B

Fig. 65.39 Brugada syndrome, with ST elevation in V_{1S}. The ST elevation is coved (*upper,* (A) or saddleback (*lower,* (B) and may be transient.

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CHAPTER 65: QUESTIONS AND ANSWERS

65.1. What is the primary electrochemical difference between pacemaker and nonpacemaker cells?

- **a.** Lack of a plateau phase 3 in nonpacemaker cells
- **b.** Rapid phase 0 upstroke in nonpacemaker cells after stimulus
- **c.** Slow calcium ion influx during phase 2 for pacemaker cells
- **d.** Slow phase 4 spontaneous depolarization in pacemaker cells
- **e.** Transient membrane repolarization by potassium channel closure during phase 1 for pacemaker cells

Answer: d. The spontaneous return to a depolarization threshold during phase 4 (diastole) characterizes pacemaker cells. Both cell types then exhibit a rapid phase 0 upstroke resulting from sodium ion (Na^+) influx, brief repolarization resulting from potassium ion (K^+) efflux (phase 1), plateau phase resulting from balanced calcium ion (Ca^{2+}) entry and K^+ efflux (phase 2), and then repolarization resulting from Ca^{2+} channel closure and K^+ efflux (phase 3).

65.2. For a reentrant tachydysrhythmia to occur, what three conditions exist?

- **a.** Electrolyte disturbance, ischemia, and altered conduction in an endogenous atrioventricular pathway
- **b.** Electrolyte disturbance, two conduction pathways, with one of the pathways being slower
- **c.** Ischemia, two conduction pathways, with one of the pathways being slower
- **d.** Two conduction pathways, one path being slower, and differing responsiveness
- **e.** Two conduction pathways with equal responsiveness

Answer: d. Remember that a conducting pathway is bidirectional. In a typical scenario, the alpha pathway of the atrioventricular (AV) node is the anterograde conducting limb, and the beta pathway is the retrograde conducting limb. Reentrant dysrhythmias are almost always AV nodal and narrow complexes that start and end abruptly.

65.3. Classic antifibrillatory effects are seen with which class of antidysrhythmic?

- **a.** IA
- **b.** IB
- **c.** IC
- **d.** II
- **e.** III

Answer: e. Class III agents, of which amiodarone is the prototype, prolong the action potential and refractory period duration. Class I agents have variable effects on depolarization rate and repolarization duration.

65.4. The most frequent proarrhythmic effects are seen with which class of antidysrhythmic?

- **a.** IA
- **b.** IB
- **c.** IC
- **d.** II
- **e.** III

Answer: c. Class IC agents, such as flecainide, encainide, and propafenone, markedly slow depolarization and conduction and prolong repolarization and action potential duration. Class IB agents generally have the least proarrhythmic effect.

65.5. A 49-year-old woman presents with a sudden onset of palpitations and shortness of breath. This has happened once before. She has no past history and takes no medications. Vital signs are temperature, 36.0°C (96.8°F) oral, blood pressure, 115/69 mm Hg, heart rate 156 beats/min, respiratory rate 24 breaths/min, and oxygen (O_2) saturation, 98%. Her electrocardiogram (ECG) is shown in Fig. 65.28. What is the most appropriate intervention?

- **a.** Adenosine, 6 mg IV
- **b.** Digoxin, 0.25 mg IV

CHAPTER 65: QUESTIONS AND ANSWERS—cont'd

c. Diltiazem, 0.4 mg/kg IV
d. Propranolol, 1 mg IV
e. Synchronized electrical cardioversion after IV sedation with midazolam

Answer: a. Adenosine causes slowing of conduction in the anterograde and retrograde pathways, with no effect on ventricular contractility. It converts a high percentage of narrow-complex tachycardias to sinus rhythm, but with a 25% recurrence rate. Diltiazem would not be unreasonable, but the quoted dose is too high. Calcium channel blockers also exert their effects only on the anterograde pathway, with little direct effect on accessory pathways. Contractility may be diminished. Digoxin use has been largely supplanted by adenosine and class IV agents. Its onset of action after IV use is 1.5 to 2 hours. Cardioversion would not be indicated unless the patient exhibited hemodynamic instability.

Implantable Cardiac Devices

Christopher R. Tainter and Gabriel Wardi

KEY CONCEPTS

- Pacemaker malfunction soon after implantation (within 6 to 8 weeks) is usually a result of a lead problem, such as a lead displacement, or a pacemaker programming issue, such as a pacing rate too slow for the patient's needs.
- Pacemaker malfunction is categorized as failure to pace, oversensing, undersensing, or pacing at an inappropriate rate (too fast or too slow).
- Pacemaker or implantable cardioverter-defibrillator (ICD) interrogation should be performed if a patient's presentation (e.g., shortness of breath, palpitations, syncope, shock, cardiac arrest, etc.) or ECG (electrocardiogram) is suggestive of device malfunction, abnormal intrinsic rhythm, or worsening cardiac function.
- Modern lithium-iodine batteries are highly reliable; battery-related issues are unlikely to be the cause of abrupt pacemaker failure.
- Consider pacemaker lead infection and endocarditis if a patient with a pacemaker has a fever of unclear cause.
- Right ventricular-paced complexes are normally conducted with a left bundle branch block pattern. A right bundle branch pattern is abnormal and suggests lead displacement.
- Magnet application turns off the sensing and inhibition function, causing the pacemaker or ICD to fire at a preprogrammed fixed rate (typically near 60 beats/minute) and inhibits antitachycardia pacing in ICDs. Magnet removal returns the pacemaker to its programmed pacing mode.
- Defibrillation is safe in patients with a pacemaker or ICD. Pads should be placed at least 10 cm from the subcutaneous implant site of the device.
- Most left ventricular assist device (LVADs) do not produce pulsatile flow; therefore, these patients will not have a palpable pulse.
- All modern VADs tolerate external defibrillation and cardioversion.
- Chest compressions can be performed in an unresponsive, nonperfusing patient with a VAD, supported by typical resuscitative measures.

PERMANENT PACEMAKERS

PRINCIPLES

Electrical cardiac pacing for the management of bradyarrhythmias was first described in 1952, and permanent transvenous pacing devices were introduced into clinical practice in the early 1960s. Implanted electrical devices for the management of cardiac dysrhythmias have changed significantly over the decades, with increasing complexity, miniaturization, and the development of leadless systems. Permanent pacemaker (PPM) placement is now almost exclusively performed via minimally invasive techniques and has a low complication rate. Over 250,000 new permanent pacemakers are placed each year in the United States. Indications for the use of permanent pacemakers have expanded beyond the treatment of dysrhythmias and now include cardiac resynchronization therapy (CRT), or biventricular pacing, for patients with depressed ventricular function and ventricular dyssynchrony. Patients may present to the ED after firing of an internal defibrillator or with symptoms related to malfunction of implanted devices.

CLINICAL FEATURES

Guidelines for the implantation of permanent pacemakers have been developed by a joint task force of the American Heart Association (AHA) and the American College of Cardiology (ACC), and are periodically updated.[1] Class I recommendations include conditions for which there is general agreement that a device should be implanted (listed in Box 66.1). A class II recommendation includes conditions for which these devices are frequently used, but for which there is disagreement about their need or benefit. Class III is reserved for conditions for which there is general agreement that a device is not needed. In general, pacing is recommended for patients with sinus node dysfunction, symptomatic heart block, symptomatic sinus bradycardia, and atrial fibrillation with symptomatic bradycardia in the absence of medications that affect atrioventricular (AV) conduction. International guidelines strongly recommend cardiac resynchronization therapy (CRT) for patients with systolic heart failure with left ventricular ejection fracture under 35% and left bundle branch block.[2,3]

Pacemaker Terminology

A descriptive letter code, initially established in 1974 and revised as technology advances, standardizes nomenclature for pacemakers. Table 66.1 includes a description of the five-letter code scheme and standard abbreviations. Most discussions regarding permanent pacemaker function truncate the abbreviation to just the first three or four letters.

Pacemaker Components

Traditional permanent pacemakers have two basic components: a pulse generator, which houses the battery, and a lead system, which connects the pulse generator to the endocardium. Nearly all pulse generators use lithium-iodine cells as an energy source. Contemporary pulse generators typically last 4 to 10 or more years, although this depends on many variables including size, current required for circuitry, and composition of the pacemaker. Power output of lithium-iodine cells decreases gradually (unlike the early mercury-zinc cells), which makes sudden pulse generator failure an unlikely cause of pacemaker malfunction. Leadless pacemakers have recently been introduced and are a self-contained generator and electrode system implanted directly in the right ventricle.[4]

Permanent pacemakers have endovascular leads that are positioned in contact with the endocardium of the right ventricle and, in the case

of a dual-chamber device, the right atrium. A subclavian or cephalic venous approach is used for insertion, whereas leadless pacemakers are inserted via the femoral vein. Biventricular pacemakers have conventionally placed right atrial and ventricular leads and an additional left ventricular lead positioned in a left ventricular epicardial location via the coronary sinus. An epicardial lead may be implanted during open-heart surgery performed for another indication, such as prosthetic valve insertion or correction of a congenital cardiac defect, although these are most commonly used only temporarily in the perioperative period.

Pacemaker leads may have either a bipolar or unipolar configuration. A bipolar endocardial lead has both the negative (distal) and the positive (proximal) electrodes, separated by approximately 1 cm, within the heart. A unipolar lead has the negative electrode in contact with the endocardial surface, and the positive pole is the metallic casing of the pulse generator. The unipolar configuration is not compatible with implantable cardioverter-defibrillator (ICD) systems and is prone to oversensing of myopotentials and electromagnetic interference, thus is less commonly encountered.

BOX 66.1 Class I Indications for Permanent Pacing in Adults

1. Patients with symptoms directly attributable to sinus node dysfunction
2. Patients with symptomatic sinus node dysfunction or AV block secondary to guideline-directed therapy for which no alternative therapy is available and continued treatment is necessary
3. Patients with permanent AF and symptomatic bradycardia
4. Patients with symptomatic AV block attributable to a known reversible cause (e.g., Lyme disease or drug toxicity) without resolution of the block despite appropriate therapy for the underlying cause
5. Patients with acquired second-degree Mobitz type II AV block, high-grade AV block, or third-degree block not attributable to reversible or physiologic causes, regardless of symptoms
6. Patients with neuromuscular diseases associated with conduction disorders (muscular dystrophy, Kearns-Sayre syndrome, etc.) with evidence of second- or third-degree AV block regardless of symptoms with meaningful survival greater than 1 year
7. Patients with syncope and bundle branch block with an HV interval > 70 ms or an infra-nodal block
8. Patients with an alternating bundle branch block
9. Patients with postoperative sinus node dysfunction or AV block with persistent symptoms or hemodynamic instability following coronary artery bypass, surgery for AF, valvular surgery or replacement
10. Patients with adult congenital heart disease and symptomatic sinus node dysfunction, chronotropic incompetence, symptomatic bradycardia from AV block, mean daytime heart rate below 50 bpm, complex ventricular ectopy, or ventricular dysfunction
11. Patients with Mobitz II AV block, high-grade AV block, third-degree block, alternating bundle-branch block after an MI following a waiting period

AV, Atrioventricular; *AF,* atrial fibrillation; *HV,* His bundle-ventricular interval (measured from the onset of the His potential to the onset of the earliest ventricular activation).

History

Patients with a pacemaker usually carry a pacemaker identification card that identifies the device, the indication for placement, and the pacing modality. If the card is not available, information may be obtained by calling the device manufacturer. All manufacturers provide support including representatives on call to respond to the hospital to interrogate a device. Over 90% of permanent pacemakers in the United States are produced by Medtronic, St. Jude, or Boston Scientific.

Most patients with pacemaker malfunctions have symptoms reminiscent of those that prompted pacemaker therapy (e.g., syncope, lightheadedness, palpitations). The majority of pacemaker complications occur within the first few weeks or months of pacemaker implantation. After wound healing, palpation of the pulse generator site should not elicit tenderness. A wound infection or pocket infection typically presents with localized pain and tenderness. Bacteremia secondary to infection of the pacemaker may present only with fever. Pacemaker placement can cause acute upper extremity venous thrombosis (see Chapter 74).

Patients who develop AV dyssynchrony with the loss of the atrial kick may have nonspecific complaints of easy fatigability, generalized weakness, dyspnea, or an uncomfortable fluttering or "pounding" sensation in the neck or abdomen. Syncope or near-syncope may also occur, but these complaints should prompt an evaluation for true pacemaker malfunction.

Physical Examination

Pacemaker infection should be suspected when there is evidence of erythema, tenderness, purulent drainage, or exposed device hardware. An unexplained fever should also prompt consideration of a pacemaker infection. Extremely low (<60 beats/min) or high (>100 beats/min in the resting patient) pulse rates are suggestive of altered pacing parameters. This may be caused by battery depletion if the battery is more than 5 to 7 years old, or may represent a pacemaker-mediated tachycardia. Cannon "A" waves on inspection of the jugular venous pulse wave indicate AV dyssynchrony. Left sided heart failure will present typically with bibasilar rales right sided failure may cause jugular venous pressure elevation.

During pacing, the first heart sound may vary in intensity as a result of AV dissociation (VVI mode), and the second heart sound may be paradoxically split when ventricular pacing occurs (the right ventricle is activated first). A pericardial friction rub or signs of tamponade (hypotension, muffled heart sounds, elevated jugular venous pressure) may

TABLE 66.1 Five-Letter Pacemaker Code

Letter 1: Chamber Paced	Letter 2: Chamber Sensed	Letter 3: Sensing Response	Letter 4: Programmability	Letter 5: Antitachycardia Functions
A = Atrium	A = Atrium	T = Triggered[a]	P = Simple	P = Pacing
V = Ventricle	V = Ventricle	I = Inhibited	M = Multiprogrammable	S = Shock
D = Dual	D = Dual	D = Dual (A and V inhibited)	R = Rate adaptive	D = Dual (shock pace)
O = None	O = None	O = None	C = Communicating	
			O = None	

[a]In the triggered response mode, the pacemaker discharges or fires when it recognizes an intrinsic depolarization. As a result, pacemaker spikes occur during initiation of the QRS complex, which results in high energy consumption and a shortened battery life and can be misinterpreted as pacemaker malfunction. This sensing mode is generally not used with modern pacemakers.

be present if the tip of the pacing catheter has perforated the wall of the right ventricle. Although the pacing catheter traverses the tricuspid valve, tricuspid regurgitation represents concomitant valvular disease.

12-Lead Electrocardiogram

The 12-lead ECG interpretation is facilitated by examination of the chest x-ray. A single lead in the apex of the right ventricle indicates a VVI pacemaker. The pacer spike (or stimulus artifact) is a narrow deflection that is usually less than 5 mm in amplitude with a bipolar lead configuration and usually 20 mm or more in amplitude with a unipolar lead. A wide QRS complex appears immediately after the pacer spike, usually with a morphology similar to a left bundle branch block, because depolarization begins in the right ventricular apex, and the spread of excitation does not follow normal conduction pathways. With VVI pacing, only one stimulus artifact is seen with each stimulated ventricular depolarization (Fig. 66.1). If sinus node activity is present, the paced QRS complex is dissociated from the intrinsic P waves. If separate leads are identified in the right atrium and right ventricle on chest x-ray, the pacing modality is most often DDD or DVI, and paced P waves and QRS complexes (two spikes for each QRS complex) are seen (Fig. 66.2). Although DDD and DVI units are capable of pacing both the right atrium and the right ventricle, only one spike may be seen if the other lead is inhibited during normal function (Fig. 66.3). In biventricular pacing, two stimulus artifacts or "spikes" may be seen preceding a paced QRS complex on the standard ECG (Fig. 66.4). A normal-appearing QRS complex may follow an intrinsic P wave as a result of normal sinoatrial node discharge if the intrinsic atrial depolarization is conducted to the ventricles. The intrinsic P wave and QRS complex are sensed, and inhibit stimulus discharge by the atrial and ventricular leads. A normal QRS complex follows a paced P wave if the paced atrial beat is conducted through the AV node and the programmed AV delay period is not exceeded. If the atrial impulse is not conducted to the ventricles (AV delay period exceeded), the pacemaker stimulates the ventricle, resulting in a paced P wave and a wide, paced QRS complex with left bundle branch block configuration.

DIFFERENTIAL DIAGNOSIS

Complications of Implantation

Infection

Pacemaker implantation carries a lifetime risk of infection below 2%, although this risk is up to threefold higher in patients with CRT or who

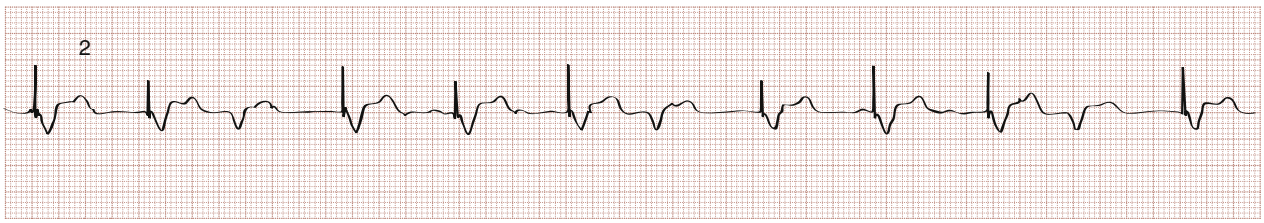

Fig. 66.1 Normal VVI pacemaker (rhythm strip). This rhythm strip was recorded in a patient with a VVI pacemaker implanted for the treatment of symptomatic complete heart block. Each pacemaker spike is followed by a paced QRS complex with a rate of 75 beats/min. The third QRS from the left has a slightly different morphology than the paced QRS complexes. It is an intrinsic QRS complex that is sensed by the pacemaker, and a paced beat does not occur again until the programmed rate of the pacemaker is exceeded.

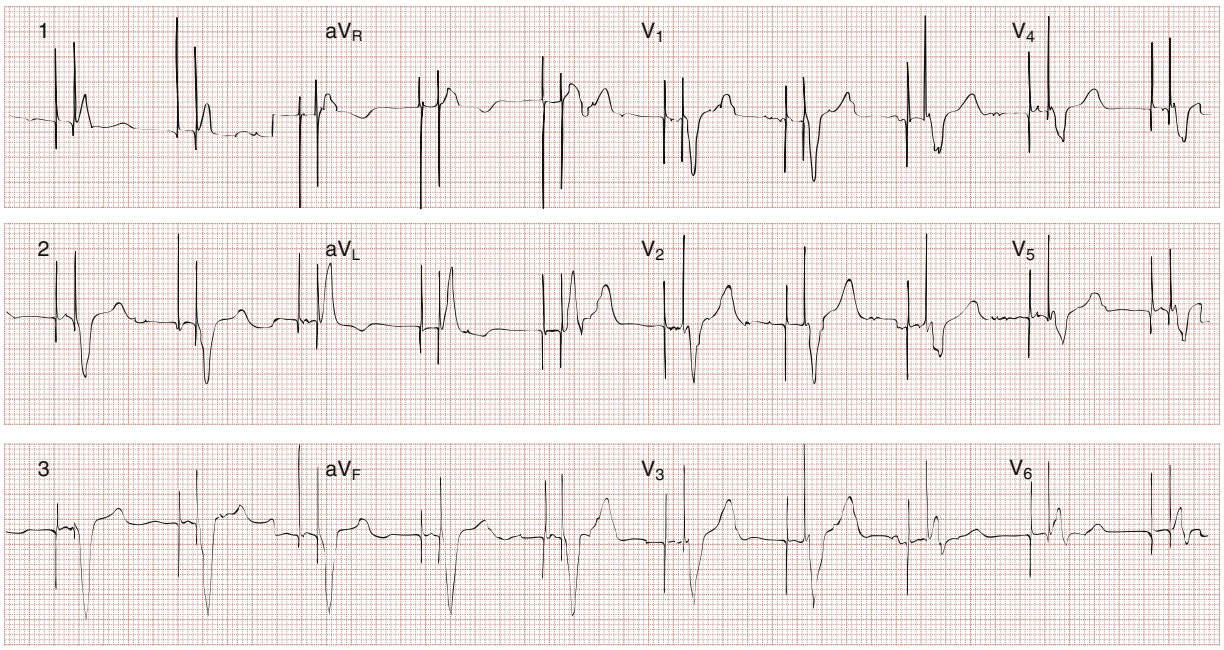

Fig. 66.2 Normal DDD pacemaker (12-lead electrocardiogram). Each QRS complex is preceded by two pacemaker spikes. The first spike results in atrial depolarization, and the second produces a wide QRS complex. The QRS complex is conducted with a left bundle branch morphology, which is expected with endocardial pacing at the right ventricular apex.

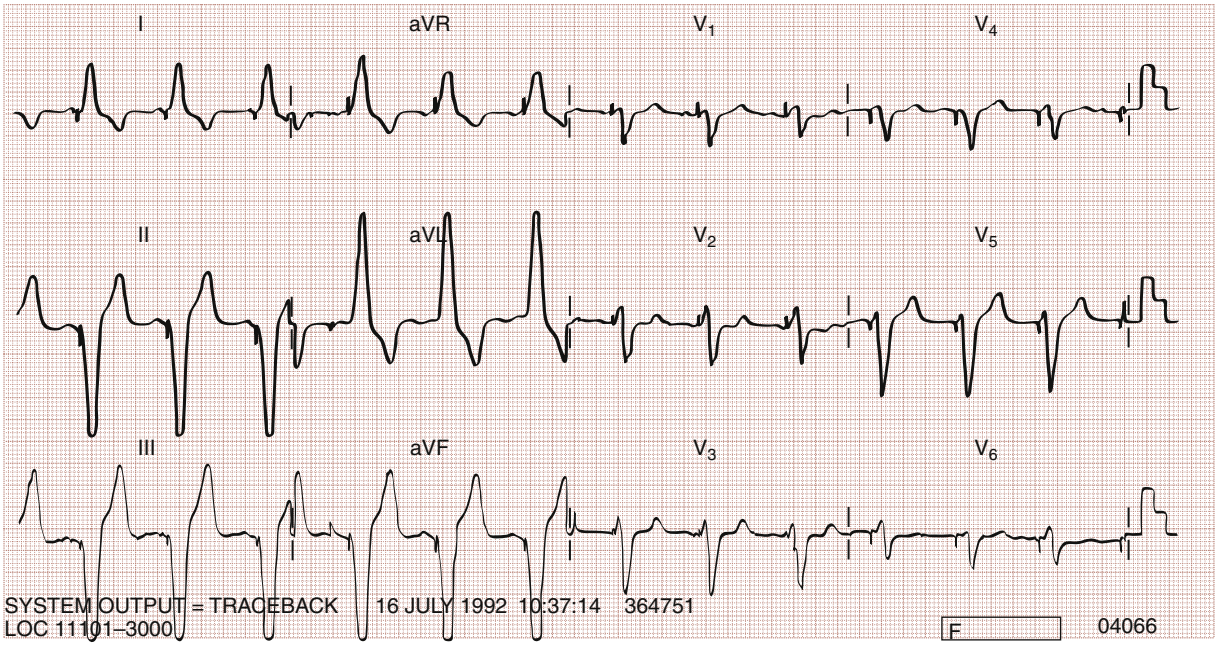

Fig. 66.3 Normal DDD pacemaker (half-standard 12-lead electrocardiogram). Three paced QRS complexes preceded by a stimulus artifact or spike are evident in leads I, II, and III. Paced QRS complexes occur after spontaneous or intrinsic P waves are sensed and atrioventricular (AV) conduction delay exceeds the pacemaker's programmed AV interval. The first QRS complex in the augmented leads, best seen in lead aVF, demonstrates both a paced P wave and a paced QRS complex. Although the pacemaker is a dual-chamber device, two spikes may not always be seen preceding every QRS complex, and the presence of only one spike, or no spikes, should not be interpreted as evidence of pacemaker malfunction.

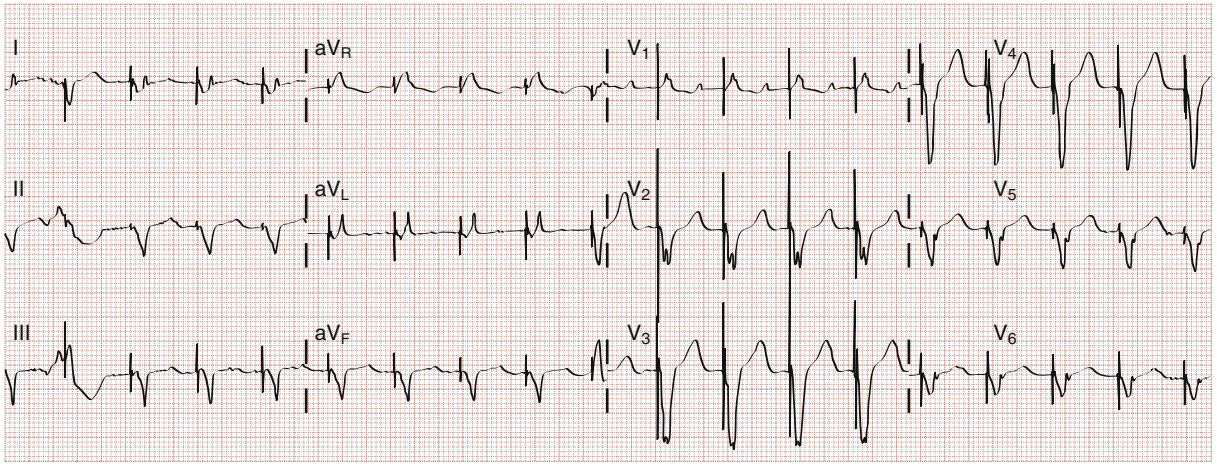

Fig. 66.4 Biventricular pacemaker (12-lead electrocardiogram) in an atrial sensed pacemaker in a patient with cardiac synchronization therapy (CRT) and implantable cardioverter-defibrillator system (CRT-D). The paced QRS complexes have an S wave in lead I and an R wave in lead V_1 that are distinctly different from the morphology and axes seen with right ventricular apical pacing. The second beat from the left is a premature ventricular contraction. There is a pacemaker "spike" superimposed on this complex, likely representing safety pacing in CRT-D.

undergo repeated manipulation of the device.[5,6] Risk factors for pacemaker infection are: chronic renal insufficiency, chronic obstructive pulmonary disease, chronic steroid use, diabetes mellitus, malignancy, and advanced age.[7] Pain and local inflammation at the site of the pacemaker are the first manifestations of a wound infection, cellulitis, or pocket infection. Approximately 20% to 25% of patients with a local infection have positive blood cultures. Bacteremia may occur in the absence of a focal infection and may arise with the typical manifestations of the systemic inflammatory response syndrome or sepsis. A hematoma of the pacemaker pocket may mimic a wound or pocket infection, but the patient will be afebrile and local inflammation will be minimal or absent. Diagnosis is confirmed by needle aspiration of the pocket under fluoroscopic guidance to ensure the needle does not damage the insulation surrounding the pulse generator or the portion of the pacemaker lead that lies within the pacemaker pocket.

When a local infection or bacteremia is suspected, blood cultures are obtained and intravenous antibiotic therapy should be initiated. Given the high prevalence of infection with *S. aureus* and *S. epidermidis*, first-line

therapy is vancomycin, with a loading dose of 20 to 35 mg/kg actual body weight (not to exceed 3000 mg) or 20 to 25 mg/kg actual body weight not to exceed 3000 mg in patients with obesity, followed by 15 to 20 mg/kg actual body weight every 8 to 12 hours. For patients who cannot tolerate this, we recommend daptomycin 6–10 mg/kg ideal body weight every 24 hours. For patients with hemodynamic instability, we recommend the addition of a second antimicrobial agent to broadly cover gram-negative pathogens, including *P. aeruginosa* (e.g., piperacillin-tazobactam 4.5 g every 6 to 8 hours IV or cefepime 2 g every 8 to 12 hours; see Chapter 127). In patients with a pocket infection, evidence of endocarditis, or blood cultures with pathogenic bacteria, the pulse generator and pacemaker leads are generally removed.[8]

Venous Thrombosis and Stenosis

Upper extremity deep vein thrombosis (UEDVT) associated with permanent pacemakers can involve the axillary, subclavian, and innominate veins or the superior vena cava (SVC). Patients with an acute UEDVT from their pacemaker typically complain of pain, swelling, and fatigue in the ipsilateral upper extremity. Chronic thrombosis of the veins of the upper arm is present in up to 23% of patients. These patients are usually asymptomatic owing to extensive venous collateral circulation. On examination, edema and warmth of the affected upper extremity are common in acute UEDVTs. Rarely, collateral vessels at the shoulder girdle or jugular venous distention may be present in chronic UEDVTs. If the proximal superior vena cava is obstructed, patients may present with facial plethora or chest wall edema. The initial imaging study of choice for patients with suspected UEDVT is venous duplex ultrasound. Indications for treatment and agent selection are as for non–pacemaker related UEDVT, as outlined in Chapter 74.

Venous stenosis is another recognized complication of PPM placement, occurring in over half of patients.[9] Complaints from stenosis are uncommon, however, unless complete occlusion occurs. Although rare, SVC syndrome can occur from pacemaker lead–induced thrombosis. The signs and symptoms of lead-induced SVC syndrome are identical to those described in patients with SVC syndrome and malignancy (see Chapter 112). Unlike patients with malignancy, however, these patients have excellent outcomes following endovascular repair.[10] Rare complications, such as septic thrombophlebitis and varices from vascular occlusion have also been reported.

Complications of Existing Pacemakers

The "Pacemaker Syndrome"

After single-chamber pacemaker implantation, a patient may develop symptoms of heart failure or report a worsening of the symptoms that prompted pacemaker placement. This constellation of symptoms is referred to as the *pacemaker syndrome* and is the result of AV and VV dyssynchrony with resultant increases in jugular and pulmonary venous pressures. Rarely, hypotension may occur due to loss of the atrial kick and impaired left ventricular filling. Approximately 20% of patients report symptoms suggesting pacemaker syndrome after PPM insertion. In most instances, symptoms are mild, and patients adapt to them. Treatment for severe symptoms usually requires replacing a VVI pacemaker with a dual-chamber pacemaker or lowering the pacing rate of the VVI unit to improve AV and VV synchrony. If symptoms occur in a patient paced in the DDD mode, optimizing the timing of atrial and ventricular pacing is usually required. Patients usually prefer dual-chamber pacing to the VVI modality for these reasons.

Complications Unique to Biventricular Pacing

Biventricular pacing carries risks related to placement of the left ventricular pacing lead through the coronary sinus. In large clinical trials, coronary sinus dissection occurred in 0.3% to 4.0% of patients and coronary vein or coronary sinus perforation in 0.8% to 2.0% of patients. Cardiac tamponade caused by perforation of the coronary venous system is seen in less than 1% of patients. Dislodgement of the left ventricular electrode with resultant loss of pacing occurs as an early complication in approximately 10% of patients.

Pacemaker Malfunction

The term *pacemaker malfunction* refers specifically to problems with the circuitry or power source of the pulse generator, the pacemaker lead (most commonly displacement or fracture), or the interface between the pacing electrode and the myocardium (pacing or sensing threshold). In addition, environmental factors, such as extracardiac or extracorporeal electrical signals, may interfere with normal pacemaker function. With use of the standard electrocardiogram (ECG), pacemaker malfunction can be separated into three broad categories: (1) failure to capture (2) inappropriate sensing or (3) inappropriate pacemaker rate. Symptomatic pacemaker malfunction after implantation occurs in less than 5% of patients and is rarely life-threatening. Malfunction is most commonly a result of inappropriate sensing, followed by failure to capture. Typical presentations and causes of pacemaker malfunction are listed in Box 66.2.

When a patient presents reporting symptoms consistent with intermittent pacemaker dysfunction (e.g., episodes of lightheadedness, palpitations, rapid pulse, weakness, or shortness of breath), and pacemaker sensing and capture cannot be assessed because the patient's native heart rate exceeds the pacemaker's set rate, the sensing function of the pacemaker may be temporarily disabled by placing a "pacemaker" magnet externally over the pulse generator. Magnet application causes closure of a reed switch, turning off sensing function, thus converting the pacemaker to fixed-rate pacing. Magnet application thus allows pacing to occur, despite the patient's native cardiac activity, and pacing rate and the presence of capture can be determined. Magnets are made by each manufacturer, but any cardiac pacemaker magnet will typically activate the reed switch in any device.

Failure to Capture

Failure to capture may range from the complete absence of pacemaker spikes to spikes not followed by a stimulus-induced complex (Fig. 66.5). A complete absence of pacemaker spikes may result from battery

BOX 66.2 Causes of Pacemaker Malfunction

Failure to Capture
- Lead disconnection, break, or displacement
- Exit block
- Battery depletion

Undersensing
- Lead displacement
- Inadequate endocardial lead contact
- Low-voltage intracardiac P waves and QRS complexes
- Lead fracture

Oversensing
- Sensing extracardiac signals: myopotentials
- T wave sensing

Inappropriate Rate
- Battery depletion
- Ventriculoatrial conduction with pacemaker-mediated tachycardia
- 1 : 1 response to atrial dysrhythmias

depletion, fracture of the pacemaker lead, or disconnection of the lead from the pulse generator unit. Current lithium-iodine batteries are not subject to sudden power failure, and they display typical end-of-life functional changes over a period of months to a year before complete depletion. Usually the first sign of voltage depletion is a gradual decrease in the programmed pacing rate. When voltage output falls to a critical level, stimulus strength falls below the required threshold, and failure to capture or intermittent failure to capture may be observed late in battery life. As a result, urgent or emergent battery replacement is rare.

Failure to capture, which may be complete or intermittent, is most commonly a problem with the pacing lead. Lead displacement is the most common cause and is most likely to occur within the first month of pacemaker insertion. Lead fracture, which is uncommon with the current polyurethane lead coating, produces an insulation break, resulting in failure to capture as a result of current leakage. It can be detected as a change in pacing threshold during pacemaker interrogation. Lead fractures occur at predictable locations, usually at the site of attachment to the pulse generator or at abrupt angulations, which serve as stress points. Inadequate contact of the lead with the pulse generator can mimic a lead fracture. Occasionally, when a lead fracture is complete or nearly complete, a break in the catheter or its insulation can be detected on an over-penetrated posteroanterior chest radiograph. Loss of lead-pulse generator contact can be detected on the chest radiograph with close inspection of the pulse generator.

Exit block (the failure of an adequate stimulus to depolarize the paced chamber) can also result in failure to pace. Exit block should be considered when the preprogrammed pacing stimulus output fails to result in capture in the presence of a normally functioning pulse generator and an intact lead system. Most commonly this problem is a result of changes in the endocardium in contact with the pacing system. Causes include ischemia or infarction of the endocardium in contact with the electrodes, systemic hyperkalemia, and the use of class III antiarrhythmic drugs (such as amiodarone), which affect ventricular depolarization. Although other drugs alter pacemaker threshold, the effect is small and is rarely clinically important.

Inappropriate Sensing

For a pacemaker to function in a noncompetitive mode, it must be capable of sensing the intrinsic or "native" electrical activity of the heart. The electrical activity that is sensed is determined by the pacing modality (see Box 66.1). Sensing parameters are determined at the time of pacemaker insertion on the basis of the signal size of the intracardiac ECG and can be changed or fine-tuned externally at a later time if needed.

Failure to sense may be complete or intermittent. It may result from a change in the sensing parameters selected at the time of insertion. This is most commonly encountered after acute right ventricular infarction or during the progressive fibrosis that accompanies many cardiomyopathies, causing intracardiac signals to decrease in amplitude. Lead displacement, fracture, and poor contact with the endocardium may also cause undersensing.

Undersensing is typically recognized electrocardiographically as the appearance of pacemaker spikes occurring earlier in the cycle than would be expected, based on the programmed rate. The spike may or may not be followed by a paced complex, depending on when it occurs during the cardiac refractory period (Fig. 66.6). Failure of a stimulus spike to produce a complex when it occurs during the atrial or ventricular refractory period does not represent failure to pace.

In rare instances, the pacemaker may detect electrical activity that is not associated with cardiac contraction, which is called *oversensing*. The result may be intermittent, irregular pacing or an apparent complete absence of pacemaker function. Myopotentials produced by the pectoralis muscle (Fig. 66.7) and extracorporeal electrical signals are frequently oversensed by unipolar lead systems. T waves that follow an intrinsic ventricular depolarization are the most common oversensed cardiac signals. Common medical sources of electrical interference include electrocautery, which can cause temporary pacemaker inhibition, and magnetic resonance imaging (MRI), which can alter pacemaker circuitry and result in fixed-rate or asynchronous pacing. Electromagnetic interference resulting from close proximity to a microwave oven should not cause problems with currently implanted

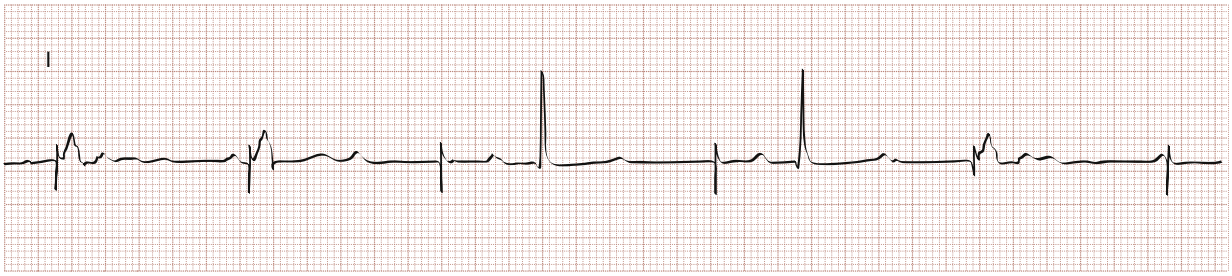

Fig. 66.5 Intermittent failure to capture and slow pacing rate (lead I) characteristic of a depleted battery in a VVI pacemaker. The first and second pacemaker spikes are followed by wide-paced QRS complexes; the third and fourth spikes are not. The pacemaker spikes occur at a rate of approximately 50 beats/min, although the device was programmed to pace at 75 beats/min.

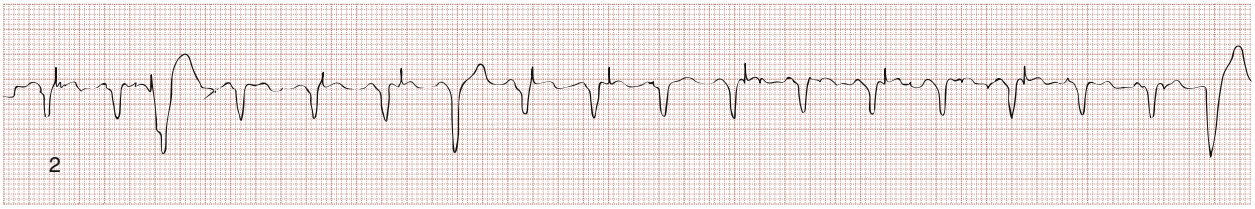

Fig. 66.6 Failure to sense or undersensing (lead II). Pacemaker spikes are evident during inscription of the ST segment on this rhythm strip. These spikes do not produce QRS complexes because they occur during the ventricular refractory period of the preceding spontaneous QRS complex. The third QRS complex on the strip is a paced QRS complex. The device is capable of capture but is undersensing the spontaneous rhythm.

pacemaker units. The current generation of cellular phones do not interfere with implanted pacemakers.

Inappropriate Pacemaker Rate

A pacing rate below the programmed rate is a typical finding in pulse generator depletion and does not occur abruptly with lithium-iodine batteries. An extreme increase in pacing rate, the so-called "runaway pacemaker," is rarely, if ever, encountered with current pacemaker technology and circuitry in which upper rate limits are set (typically 140 beats/min). An "endless loop" tachycardia may develop during dual-chamber pacing when ventriculoatrial conduction occurs, and the resulting retrograde atrial depolarization results in a stimulated or paced ventricular depolarization. If atrial flutter develops during dual-chamber pacing, flutter waves may be sensed and tracked, resulting in a rapid, paced ventricular rate. In both instances, the ventricular rate does not exceed its set upper limit. Patients with such rhythms may complain only of palpitations or symptoms of hemodynamic compromise. When such rhythms are detected, magnet application converts the pacemaker to a fixed rate and terminates the tachyarrhythmia.

DIAGNOSTIC TESTING

Chest Radiograph

A chest radiograph should be obtained to define pacing catheter tip position and to determine the number of pacing leads, unless this information is available from another source, usually the patient's pacemaker card or the medical record. A ventricular pacing catheter tip in the right ventricular outflow tract or an atrial catheter tip in the SVC or right ventricle is always abnormal.

12-Lead Electrocardiogram

A standard ECG and a long rhythm strip should be obtained in all patients. ECG interpretation was described previously.

Pacemaker Interrogation

Interrogation of a pacemaker allows for information regarding battery level, lead integrity, device settings, and identification of intrinsic dysthymias. Any patient complaint or presentation (e.g., shortness of breath, lightheadedness, syncope, cardiac arrest, etc.) or findings on ECG that suggest device malfunction, abnormal intrinsic rhythm, or worsening cardiac function should prompt interrogation.

Magnetic Resonance Imaging in Patients with a Pacemaker

Many modern pacemakers are approved for magnetic resonance (MR) by the Food and Drug Administration (FDA) for certain indications and are referred to as "MR-conditional" devices. Older devices that lack FDA approval for MRI use are referred to as "legacy" systems. No pacemakers are "MR-safe," a designation that requires there be no hazard in any MR environment. Recent studies have shown no long-term clinically significant adverse events or disruption of device components even for patients with "legacy" systems in place, but the devices did require reprogramming to an asynchronous mode prior to MRI.[11,12] Despite this, recent guidelines recommend institution-specific protocols and checklists to mitigate risk of adverse events even in MR-conditional devices.[13] Thus, the ability to obtain an MRI in a patient with a pacemaker is institution-dependent and specifically limited by the type of MRI system present, availability of necessary staff (including a cardiologist) to ensure proper patient safety, and potential need for temporary pacemaker reprogramming.

MANAGEMENT

Resuscitation

Electrical defibrillation at recommended shock strengths can be safely performed in a patient with a pacemaker. Place the sternal defibrillation pad adjacent to the sternum, at a safe distance (>10 cm) from the pulse generator. Alternatively, defibrillation electrodes can be placed in an anteroposterior configuration. All pacemakers should be interrogated after successful resuscitation. A chest radiograph should also be obtained to ensure that the pacing leads have not been displaced during chest compressions.

Immediate return of pacing (capture) may not occur after defibrillation; this is commonly the result of global myocardial ischemia and increased pacing threshold and is not an indication of pacemaker malfunction. Temporary transcutaneous or transvenous pacing may be needed if the pacemaker cannot be reprogrammed or normal pacing does not resume spontaneously. Transcutaneous pacing is preferred, using guidelines as for defibrillator pad placement, because temporary transvenous pacing can be challenging in the presence of a PPM, particularly if chronic venous thrombosis is present. Insertion through the femoral vein is also difficult because the permanently implanted catheter may prevent entry into the right ventricle.

DISPOSITION

As a result of the current design of modern pacemakers and the frequent follow-up evaluation of patients with pacemakers, life-threatening emergencies resulting from pacemaker malfunction requiring emergent intervention are rare. Most instances of malfunction are subtle and difficult to recognize without interrogation of the pacemaker with manufacturer-specific devices by an individual trained in pacer interrogation. In all instances of suspected pacemaker malfunction, the patient's cardiologist should be consulted. Patients with a pacemaker infection or symptoms due to significant pacemaker malfunction (e.g., lead fracture or displacement, battery depletion) require admission for device adjustment or replacement. If interrogation of the pacemaker does not show evidence of malfunction and a patient's presenting complaint can be attributed to another cause (e.g., electrolyte abnormality or inappropriate doses of cardiac medications), discharge.

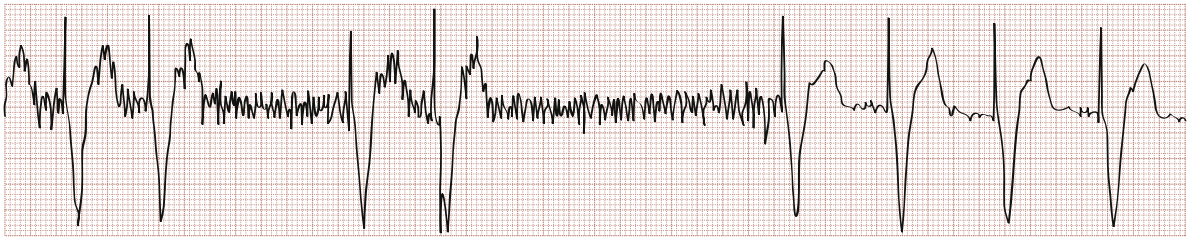

Fig. 66.7 Oversensing (lead II). This VVI unipolar lead pacemaker is oversensing myopotentials produced by contraction of the pectoralis major. Myopotentials result in the undulating and irregular baseline seen in the middle of the strip. After muscular contraction ceases, normal pacing resumes.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

PRINCIPLES

The implantable cardioverter-defibrillator (ICD) was first used clinically for treating ventricular dysrhythmias in 1980. Technical refinements to ICDs have progressed even more rapidly than refinements to the less complex standard pacemaker. A surge in the use of ICDs reflects improved survival with ICDs versus antiarrhythmic therapy in patients at risk for sudden cardiac death. Recent guidelines for ICD implantation are provided in Box 66.3. ICDs are placed for either primary prevention of sudden cardiac death or, in patients that have had cardiac arrest, secondary prevention.[14] Many patients still require drug therapy after ICD implantation to suppress ventricular dysrhythmias, minimize the frequency of ICD shocks, and decrease energy use, which prolongs ICD life and improves patients' tolerance.

CLINICAL FEATURES

Terminology and Components

The majority of ICDs are now placed in a percutaneous manner similar to that of the standard pacemaker. A transvenous electrode system has largely replaced epicardial lead placement, which required thoracotomy. The typical modern ICD consists of a power source, electronic circuitry, and lead system. In addition, the standard ICD has complex storage and monitoring abilities that allow for remote monitoring. The power source is lithium chemistry based with a battery life of 5 to 10 years. The longevity is largely determined by the frequency of shocks. All ICDs are also ventricular pacemakers. The right ventricular lead is used for sensing and pacing, and shocks are typically delivered between a coil in the right ventricular lead and the pulse generator. Patients with a depressed left ventricular ejection fraction and wide QRS may have a cardiac resynchronization therapy–defibrillator (CRT-D) that combines biventricular pacing with the ability to deliver a shock. If dual-chamber pacing is required, a second lead is placed in contact with the endocardium of the right atrium. A biphasic waveform is the preferred waveform for internal defibrillation because it is more effective at lower energies than monophasic waveforms.

The diagnostic and treatment functions of the ICD are determined at the time of implantation. The cardioversion and defibrillation thresholds are determined by inducing ventricular tachycardia (VT) and ventricular fibrillation (VF) and adjusting the shock strength at a level above the minimum required to terminate the induced rhythm. VT is typically managed with use of either low-energy shocks or antitachycardia pacing (ATP), a brief paced rhythm at a very high rate that interrupts the VT reentrant circuit and restores a normal sinus rhythm. In the setting of VF, ICDs are capable of delivering up to five additional shocks if the first shock fails.

BOX 66.3 Class I Indications for Implantable Cardioverter-Defibrillator Therapy

1. Patients with ischemic heart disease and sudden cardiac arrest resulting from VF or VT or stable sustained VT not caused by a transient or reversible event and meaningful survival is expected to be greater than 1 year
2. Patients with ischemic heart disease and unexplained syncope that have induced sustained monomorphic VT during electrophysiologic study and meaningful survival is expected to be greater than 1 year
3. Patients with depressed left ventricular function at least 40 days post myocardial infarction and at least 90 days post-revascularization and persistent heart failure symptoms if meaningful survival is expected to be greater than 1 year
4. Patients with nonsustained VT due to prior MI with depressed left-sided systolic function and inducible VT or VF during electrophysiologic study if meaningful survival is expected to be greater than 1 year
5. Patients with nonischemic cardiomyopathy, depressed left ventricular function if meaningful survival is expected to be greater than 1 year
6. Patients with sudden cardiac arrest or sustained ventricular arrhythmias from: nonischemic cardiomyopathy, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, cardiac sarcoidosis, neuromuscular disorders, cardiac channelopathies, high-risk patients with symptomatic long QT syndrome failing beta-blocker therapy, catecholaminergic polymorphic ventricular tachycardia failing beta-blocker therapy, Brugada syndrome, early repolarization, short QT syndrome, idiopathic polymorphic ventricular tachycardia, congenital heart disease

VF, Ventricular fibrillation; *VT,* ventricular tachycardia; *MI,* myocardial infarction.

DIFFERENTIAL DIAGNOSIS

Complications of Implantation

Complications of ICD implantation are similar in type and frequency to those of permanent pacemaker implantation, although the risk for infection is slightly higher. In patients with repeated instrumentation and repair of their ICDs, rates of infection may be as high as 11.7%.[6] Management is the same, whether from an ICD or permanent pacemaker.

Malfunction

Patients with ICD malfunction usually present with specific complaints (Box 66.4), the most common being the occurrence of a single or multiple shocks. An increasing shock rate may be appropriate if the patient is experiencing an increase in the frequency of VT or VF episodes, such as in the setting of hypokalemia, hypomagnesemia, myocardial ischemia, or the proarrhythmic effect of medications, and this may not be indicative of ICD malfunction. A "phantom shock" refers to the sensation of a shock without any evidence of this on device interrogation. This occurs in approximately 10% of patients with an ICD and is associated with significant psychosocial distress and posttraumatic stress disorder.

A single shock is a manifestation of ICD sensing malfunction if (1) a supraventricular tachyarrhythmia is inappropriately sensed as VT, (2) a shock is delivered for nonsustained VT, or (3) intracardiac T waves

BOX 66.4 Symptoms of Implantable Cardioverter-Defibrillator Malfunction

Increase or abrupt change in shock frequency
- Increased frequency of VF or VT (consider ischemia, electrolyte disorder, or drug effect)
- Displacement or break in ventricular lead
- Recurrent nonsustained VT
- Sensing and shock of supraventricular tachyarrhythmias
- Oversensing of T waves
- Sensing noncardiac signals

Syncope, near-syncope, dizziness
- Recurrent VT with low shock strength (lead problem, change in defibrillation threshold)
- Hemodynamically significant supraventricular tachyarrhythmias
- Inadequate backup pacing for bradyarrhythmias (spontaneous or drug induced)

Cardiac arrest
- Assume malfunction, but probably caused by VF that failed to respond to programmed shock parameters

VF, Ventricular fibrillation; *VT,* ventricular tachycardia.

detected by the ICD system are sensed as QRS complexes and the ICD interprets this as an increased heart rate. Temporary ICD deactivation with magnet application may be necessary if oversensing is the problem. Placement of a magnet will temporarily reprogram a PPM into an asynchronous mode (e.g., AOO, VOO, DOO) allowing for pacing at a preprogrammed rate without sensing, and it will disable interventions, including ATP and defibrillation. Syncope, near-syncope, dizziness, or lightheadedness in the patient with an ICD may indicate undersensing of sustained VT or inappropriately low shock strength to terminate the rhythm.

DIAGNOSTIC TESTING

As with pacemakers, chest radiograph can allow clinicians to identify lead placement, quickly detect lead fracture or displacement, and identify the type and make of ICD present. An ECG is indicated to evaluate for arrhythmias. ICD interrogation provides assessment of device function (battery life, lead integrity) and quantification of the burden of intrinsic dysrhythmias, shocks, and ATP. Any patient who presents with complaints of a shock, symptoms concerning for worsening cardiac function or device malfunction, or has an ECG with evidence of an intrinsic dysrhythmia requires ICD interrogation.

MANAGEMENT

ICD Defibrillation

It is helpful to differentiate between a single shock or multiple shocks, and whether they were appropriate. In cases in which the patient reports a single ICD shock, an assessment for acute cardiac ischemia, worsening of chronic congestive heart failure, symptoms of new-onset heart failure, and electrolyte abnormalities should be performed. When multiple defibrillator discharges are confirmed by interrogation, emergent consultation is required. Based on the findings of ICD interrogation, reprogramming may be necessary. If a lead problem is detected, reimplantation is required. Similar to a pacemaker, a magnet can be placed over the ICD to inactivate the defibrillator if the patient is receiving inappropriate shocks. This should be done only if the emergency clinician is confident that the ICD is delivering inappropriate shocks, such as in response to a supraventricular tachycardia. If frequent ventricular ectopy is noted, intravenous antidysrhythmic therapy is indicated (amiodarone IV/IO bolus 150 mg followed by an infusion of 1 mg/min for 6 hours followed by 0.5 mg/min for 18 hours, consider lidocaine 1 to 1.5 mg/kg IV/IO bolus followed by a maintenance infusion of 1 to 4 mg/min if amiodarone is unavailable or ineffective).

Resuscitation

An ICD does not prevent sudden death in all patients at risk. Cardiac arrest occurs in approximately 2% of patients with implanted devices annually. Resuscitation efforts in the patient with an ICD should be undertaken following current recommendations. Shockable rhythms should be treated with transthoracic defibrillation in the standard manner with a monophasic or biphasic defibrillator. The sternal electrode or paddle should be placed in a parasternal location at least 10 cm from the ICD subcutaneous pouch. ICD discharge during manual chest compressions poses no risk to providers, although the rescuer may feel a weak shock. Ventricular dysrhythmias may occur due to prolonged global myocardial ischemia during the arrest period, reperfusion, and the hyperadrenergic state, which is exacerbated by the use of intravenous epinephrine during resuscitation. ICD malfunction should be assumed, and these postresuscitation rhythms treated with standard pharmacologic agents (e.g., for VT/VF cardiac arrest: 300 mg amiodarone bolus via IV push followed by an additional bolus of 150 mg IV/IO if VT/VF persists, consider lidocaine 1 to 1.5 mg/kg IV/IO bolus if amiodarone is unavailable or ineffective; see "ICD Defibrillation" section above). Although class 1 antidysrhythmic agents may raise the defibrillation threshold of the ICD, their impact on the defibrillation threshold during transthoracic shocking is clinically inconsequential.

DISPOSITION

Patients who receive a single shock maybe discharged after ICD interrogation and discussion with the patient's cardiologist in the absence of a change in clinical status and if early follow-up can be arranged. If a single shock occurs due to a ventricular dysrhythmia secondary to myocardial ischemia or worsening heart failure, these patients benefit from admission. When multiple defibrillator discharges are confirmed by interrogation, admission to a telemetry monitored setting for extended observation is appropriate.

MECHANICAL CIRCULATORY SUPPORT DEVICES

PRINCIPLES

Mechanical circulatory support (MCS) devices are broadly classified as those providing temporary support (often percutaneously), and those providing more long-term support (surgically implanted). These devices may support the right side, left side, or both sides of the heart, each with their own advantages and complications. Although emergency clinicians may not be involved with the placement of the devices, they should be familiar with the available options and considerations.[15]

Temporary MCS is most commonly employed in the setting of cardiogenic shock (Table 66.2). The first commonly used device of this type was the intra-aortic balloon pump (IABP). It is placed percutaneously into the descending aorta and inflates in diastole to augment diastolic

TABLE 66.2 Temporary Mechanical Circulatory Support Devices

	IABP	Tandem Heart	Impella	VA ECMO
Flow (liters per minute)	≈0.5	up to 4	2.5–4.0[a]	≈2–6
Support type	Diastolic BP	LV[b]	LV[c]	Biventricular
Oxygenation	No	No[d]	No	Yes
Common Complications [a]	Thrombocytopenia	Hemolysis, bleeding, specialist insertion	Hemolysis, bleeding, displacement, specialist insertion	Hemolysis, bleeding
Advantages	Fast, available at most centers	Percutaneous LV bypass	Percutaneous LV support	Biventricular support

[a]Depends on device. There is also a surgically implanted version, which can provide up to 5 liters per minute of flow.
[b]This is the standard configuration (left atrium to aorta). There is also an RV catheter available to provide RV support.
[c]There is also a right ventricular version which can provide RV support.
[d]The TandemHeart Pump can be configured with an oxygenator to provide biventricular support and oxygenation.
IABP, Intra-aortic balloon pump; *VA ECMO*, venoarterial extra-corporeal membrane oxygenation; *LV*, left ventricle.

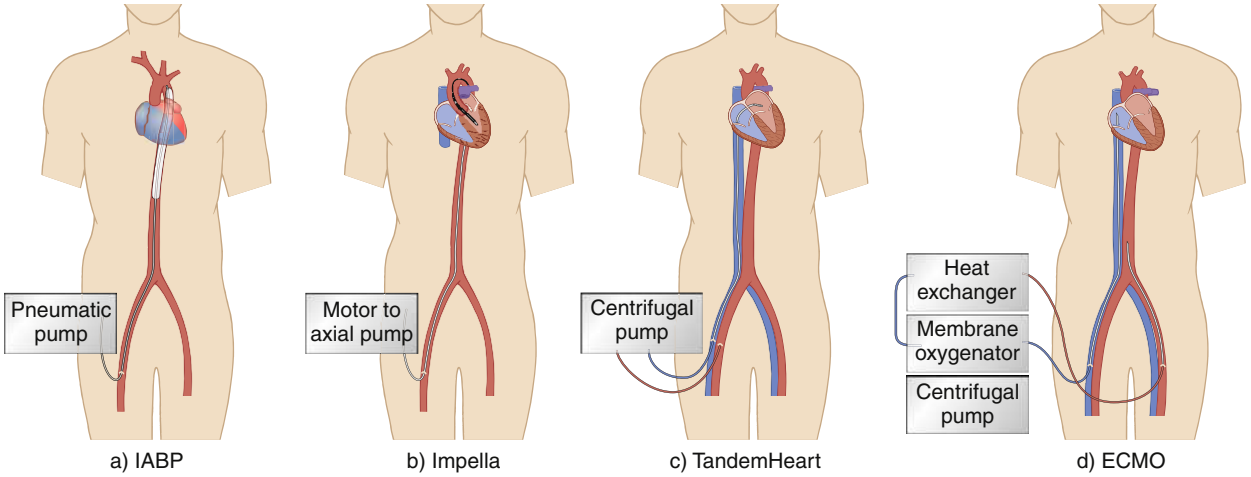

Fig. 66.8 Common configurations for temporary ventricular support. Schematic diagram to demonstrate the access sites and mechanisms of action of (A) IABP, (B) Impella, (C) TandemHeart and (D) ECMO (*ECMO*, Extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump). (Adapted from: Thiele H, Ohman EM, Desch S, et al. Management of cardiogenic shock. *Eur Heart J.* 2015;36(20):1223-1230, Fig 2.)

filling pressure. By deflating during systole, it may also decrease left ventricular afterload and augment cardiac output by approximately 0.5 to 1 liter per minute.[16]

More recently, other percutaneous devices have become more common. Although these devices are generally not placed in the ED, early specialist consideration may benefit ED patients presenting in refractory cardiogenic shock. The Impella devices are intravascular impeller pumps, placed either percutaneously or via a surgical technique. They can provide left- or right-sided support of 2.5 to 5.5 liters per minute, depending on the device. Extracorporeal pumps have also been configured to provide left- and right-sided support with a variety of configurations (TandemHeart, Rotaflow, CentriMag).

By attaching an oxygenator, it is possible to bypass the lungs and provide hemodynamic support by veno-arterial extracorporeal membranous oxygenation (VA ECMO), similar to cardiopulmonary bypass, but with more portability (Fig. 66.8). This may also be configured to provide oxygenation and ventilation in a venous-venous configuration (VV ECMO).

Recent data have suggested a benefit for temporary MCS, specifically VA ECMO, as a bridging therapy for definitive care or recovery after a cardiac arrest.[17-21] While this does represent a tremendous opportunity for improving outcomes in those with a definitive trajectory, caution must be taken to avoid nonbeneficial use in those without a suitable plan or decision pathway. In particular, patients with advanced age, multiple comorbidities, poor baseline function, or end-stage organ failure without possibility of transplant are unlikely to benefit from these invasive and resource-intensive interventions.

More long-term support is available in the form of intracorporeal (also called "implanted" or "durable") ventricular assist devices (VADs), most commonly supporting the left ventricle (LVAD). These devices may act as a bridge to recovery or a heart transplant, or as a destination therapy to improve quality and potentially duration of life. More than 2500 implantations of intracorporeal LVADs occur each year in the United States.[22] The most common devices in use are the HeartWare HVAD (Medtronic), the Heartmate II (Abbott), and the Heartmate III (Abbott) (Fig. 66.9).[23] Earlier devices providing pulsatile flow were limited by complications, especially hemolysis and thrombosis, and these newer, continuous-flow devices have become standard.[24]

CLINICAL FEATURES

Temporary MCS devices, including VA ECMO, provide augmented flow by partially bypassing one or both ventricles. They may be implanted percutaneously or surgically through the aorta or IVC, in a variety of configurations, depending on the device (see Fig. 66.8). Patients receive anticoagulation to prevent device thrombosis and embolic complications. Thrombotic complications and therapeutic anticoagulation strategies vary by device. Smaller devices like Impella, and exclusively right-sided devices like VV ECMO carry less risk for arterial embolization and require less anticoagulation. Devices that return blood to the arterial circulation have higher risk for devastating thromboembolic complications such as CVA, and receive higher levels of anticoagulation, with consequent increased bleeding risk.

Intracorporeal VADs support cardiac output via a mechanical pump that draws blood from an inflow cannula in the left ventricle and pumps it into the ascending aorta via an outflow cannula. The pump is connected to a percutaneous driveline connected to a controller and a power source. The controller and batteries are worn by the patient on a belt and shoulder harness, allowing them to be carried (Fig. 66.10). The controller displays battery life and alarms, and may provide additional information such as power level and estimated flow. Patients may be familiar with their baseline parameters, and may be able to report which changes have occurred. Listening to the epicardium should reveal a continuous "hum" if the pump is operating.

Modern VADs produce a relatively nonpulsatile flow, making traditional hemodynamic interpretation challenging. Adequate perfusion can be assessed by evaluating clinical signs, including mental status, urine output, and skin turgor, but these have obvious limitations. Automated oscillometric blood pressure cuffs may not work to measure blood pressure with LVADs because of the low pulse pressure. Blood pressure can be measured using a manual cuff and a stethoscope or Doppler probe. The cuff pressure is reduced until a continuous sound is heard, which represents the systolic pressure. This is essentially equal to the mean arterial pressure because of the low pulse pressure. Blood pressure can also be measured invasively using an arterial catheter.

Patients with intracorporeal VADs receive lifelong anticoagulation and antiplatelet therapy to prevent device thrombosis. Most patients also have a permanent pacemaker or automatic ICD placed. They

Device	HeartWare HVAD*	Heartmate II**	Heartmate III**
			
Pump type	Centrifugal	Axial	Centrifugal
Pulsatility	Continuous	Continuous	"Artificial" pulse
Flow (LPM)	Up to 10	Up to 10	Up to 10
Speed (RPM)	1800-4000	6000-15,000	4800-6500
Battery life (h)	4-6	14	17

Fig. 66.9 Modern intracorporeal ventricular assist devices. (*Reproduced with permission of Medtronic. **Thoratec, HeartMate II and HeartMate 3 are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved. Adapted from: Englert JAR, Davis JA, Krim SR. Mechanical circulatory support for the failing heart: continuous-flow left ventricular assist devices. *Ochsner J.* 2016;16:263-269.)

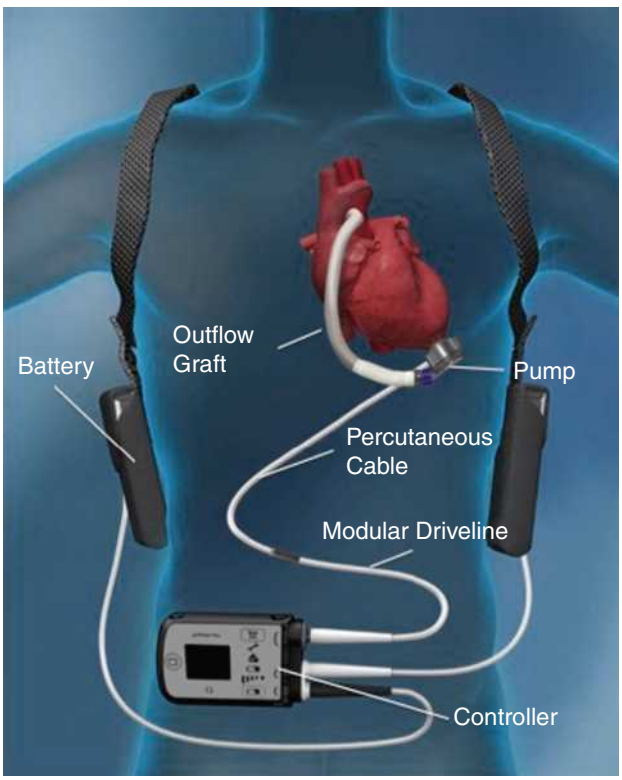

Fig. 66.10 Intracorporeal ventricular assist devices. (From: Netuka I, Sood P, Pya Y, et al. Fully magnetically levitated left ventricular assist system for treating advanced HF: a multicenter study. *J Am Coll Cardiol.* 66(23):2581;2015, Fig 1.)

commonly present with issues related to anticoagulation or their pacemaker/ICD, as well as issues related to the VAD itself (e.g., alarms, decreased flow).

DIFFERENTIAL DIAGNOSIS

Complications from both temporary and intracorporeal MCS may be related to the device itself, underlying physiology, or concomitant therapies such as anticoagulation. Thrombotic complications may include pump thrombosis (and subsequent hemolysis), ischemic CVA, or other thromboembolic phenomena such as limb or intestinal ischemia. Because the risk for thrombotic complications is so high, anticoagulation is nearly ubiquitous among these patients (who are usually treated with antiplatelet therapy as well). Consequently, bleeding is one of the most commonly encountered problems. This may range from life-threatening intracranial or gastrointestinal bleeding to epistaxis or musculoskeletal hematomas. Infectious complications are also common and can be devastating for patients with intracorporeal VADs.[25] In addition to typical infections (pneumonia, urinary tract infections, etc.) or endocarditis, they are at risk for cutaneous infections due to the transcutaneous nature of the driveline.

Mechanical complications limiting flow are a significant concern as well, because these devices support perfusion to all of the organs. These can broadly be classified as problems with preload (hypovolemia, hemorrhage, RV failure, dysrhythmia), problems with the pump itself (thrombosis, power source), or problems with afterload (sepsis). Device alarms may vary slightly between VAD models, but may help guide the provider toward appropriate therapy (Table 66.3).

DIAGNOSTIC TESTING

There is no single diagnostic strategy for patients with mechanical circulatory support, either temporary or intracorporeal. Testing should be directed at identifying and managing treatable complications. Generally, ECG and cardiac monitoring may help evaluate for dysrhythmias, which may impair flow. ECG recordings may demonstrate significant artifact from mechanical interference caused by intracorporeal VADs, but generally the rhythm is still discernable. Right ventricular failure or septal deviation (due to inappropriate pressure distribution between the ventricles) can be evaluated with point-of-care echocardiography. Coagulation studies (PT/INR, PTT, anti-Xa, etc.) should be sent to evaluate and manage thrombotic or bleeding complications. Haptoglobin or LDH levels evaluate for hemolysis, as can occur with a pump thrombosis. Additional testing (imaging, laboratory, etc.) should be directed by history and physical examination.

Problems with flow related to an intracorporeal VAD can also be generally classified into those related to preload, afterload, and pump function. The device controller may provide some guidance by paying attention to which alarms are present (see Table 66.3).

Inadequate preload will lead to decreased vascular volume and may cause "low flow" or "suction" alarms. Preload can be assessed with invasive pressure monitoring (central venous or pulmonary capillary wedge pressure), or noninvasively with point-of-care echocardiography, similar to patients without VADs. The most common causes for low preload are hypovolemia, hemorrhage, and vasodilation (e.g., sepsis), and should be treated accordingly. Additional causes for inadequate VAD preload include obstructive shock (e.g., pulmonary embolism, tamponade, tension pneumothorax), dysrhythmia, or other causes of contralateral heart dysfunction, particularly if a patient has a typical one-sided device (i.e., LVAD).

Low afterload (arterial hypotension) may result in increased VAD flow initially, as it becomes easier for the mechanical pump to eject blood into the aorta; however, it may lead to decreased LV volume and "suction" problems as the walls of the ventricle collapse on the VAD intake ports. This can lead to decreased flow, suction alarms, and ventricular dysrhythmias. The most common cause for excessive vasodilation in these patients is sepsis, and the percutaneous driveline places them at increased risk for significant infections. Vasopressors such as norepinephrine should be titrated to increase mean arterial pressure to a perfusing level (usually ≥ 65 mm Hg), as with other forms of sepsis. Antibiotics should be considered in line with local practice patterns, with broad coverage for potential sources, including skin flora and health care–associated organisms.

Failure of the mechanical device itself is exceedingly rare. However, if there is no power to the device, it will not function. If no alarms are heard, and there is no mechanical "hum" from the pump, it is likely that the power source has been interrupted and must be replaced immediately. Patients and EMS providers are advised to bring backup batteries and charging materials when they come to the hospital. It is important to ensure this as soon as the patient arrives, or request them from the heart failure specialists or VAD coordinator, because there is no available alternative.

TABLE 66.3 Common Intracorporeal VAD Alarms

Alarm Type	Problem	Cause	Action[a]
No display[b]	Power source	No power	Check connections
Low flow	High BP	High afterload	Antihypertensive
	Low BP	Hypovolemia, hemorrhage, RV failure, rhythm	IV fluids/Blood products, evaluate for sepsis
Suction	Low preload or afterload	Hypovolemia, hemorrhage, RV failure, rhythm, vasodilation	IV fluids, vasopressor, evaluate cause
High power[c]	Pump resistance	Thrombosis or high BP	Evaluate for hemolysis, anticoagulation
Low battery	Low battery	Low battery reserve	Replace battery or plug in to power source

[a]Call referral center and/or VAD coordinator.
[b]A loud alarm will sound for about 1 hour.
[c]May display "High Watts."
BP, Blood pressure; *RV*, right ventricle; *IV*, intravenous.

MANAGEMENT

Inadequate perfusion in the setting of a mechanical circulatory support device is most likely to benefit from efforts to increase flow through the device. These patients have severely abnormal heart function, so efforts toward restoring adequate native cardiac function are likely futile and efforts instead should be focused on optimizing device function.

Management of temporary MCS devices is generally performed in cooperation with expert consultation (e.g., critical care, cardiology, or cardiothoracic surgery). Issues focus on optimizing flow by adjusting vascular resistance (vasopressors), adjusting pump speed, or manipulating preload (IV fluids, blood products). In addition, anticoagulation must be optimized to mitigate thrombotic and bleeding complications.

An expert at a referral center should be contacted immediately for any patient presenting to an emergency department with an intracorporeal VAD, but initial management decisions may need to be directed by the emergency clinicians.[26]

Bleeding complications are common because of the need for anticoagulation, the development of arterio-venous malformations due to nonpulsatile flow, and acquired coagulopathies related to the device.[27] Hemorrhage should be managed by transfusion of blood products, which should be coordinated with the heart failure specialist or VAD coordinator, as they may have significant downstream effects such as antibody formation affecting transplant eligibility. Because the complications of device thrombosis are so severe, generally reversal of anticoagulation is reserved as a last-line measure, even for life-threatening bleeding.

Thrombotic complications may be managed initially with systemic anticoagulation if the patient is subtherapeutic on their home regimen. Ischemic thromboemboli (CVA, intestinal ischemia, etc.) are likely to benefit from expert consultation. Complete device thrombosis is often fatal. In addition to anticoagulation, thrombolysis may be considered, but is unlikely to succeed if there is no flow through the device and may lead to additional bleeding complications. Surgical replacement is the predominately viable option for device thrombosis, but often takes a significant amount of time to arrange.

Problems related to flow with a mechanical circulatory support device should be approached systematically (Fig. 66.11). If preload is inadequate, resuscitation with crystalloid, colloid, or blood products is appropriate. If hypotension persists after adequate volume resuscitation, systemic vascular resistance should be increased with vasopressor medications such as norepinephrine, which may be considered concurrently with volume resuscitation. Unstable dysrhythmias should be cardioverted or defibrillated immediately. Obstructive causes of shock should be relieved (tamponade, tension pneumothorax, pulmonary embolism, etc.). It is appropriate

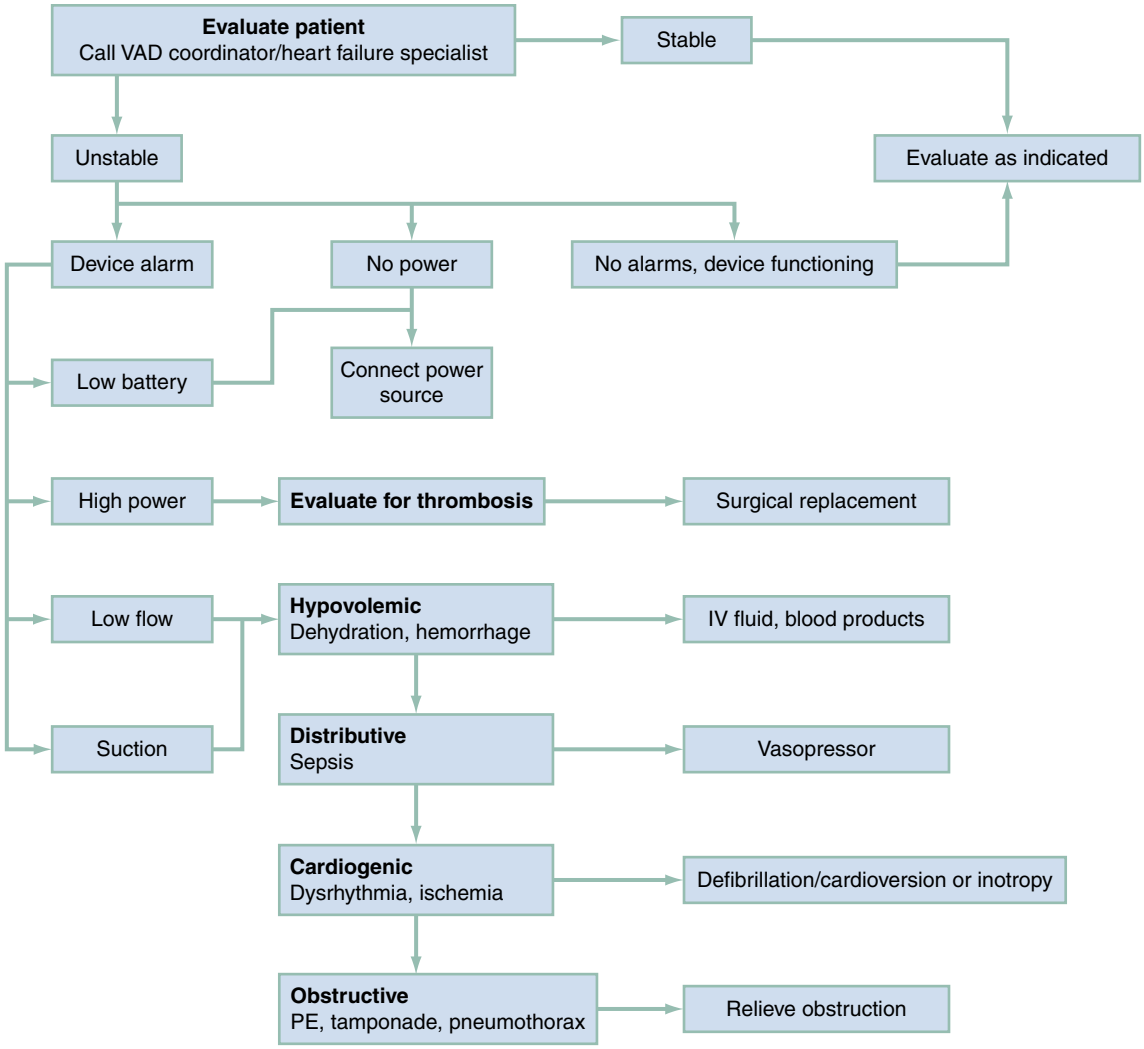

Fig. 66.11 Intracorporeal VAD emergency management.

to perform chest compressions if the VAD is not functioning and the patient is not perfused, while attempts are made to address the underlying physiology.

DISPOSITION

Patients with temporary MCS are admitted to an intensive care unit (ICU), usually with cardiology consultation. Although many complications related to intracorporeal VADs necessitate admission, a significant number of problems presenting to the emergency department may be managed in the outpatient setting, such as minor bleeding, dehydration, or medication adjustments.[28] These cases should be discussed with the advanced heart failure specialists following the patient, and close follow up should be arranged.

The references for this chapter can be found online at ExpertConsult.com.

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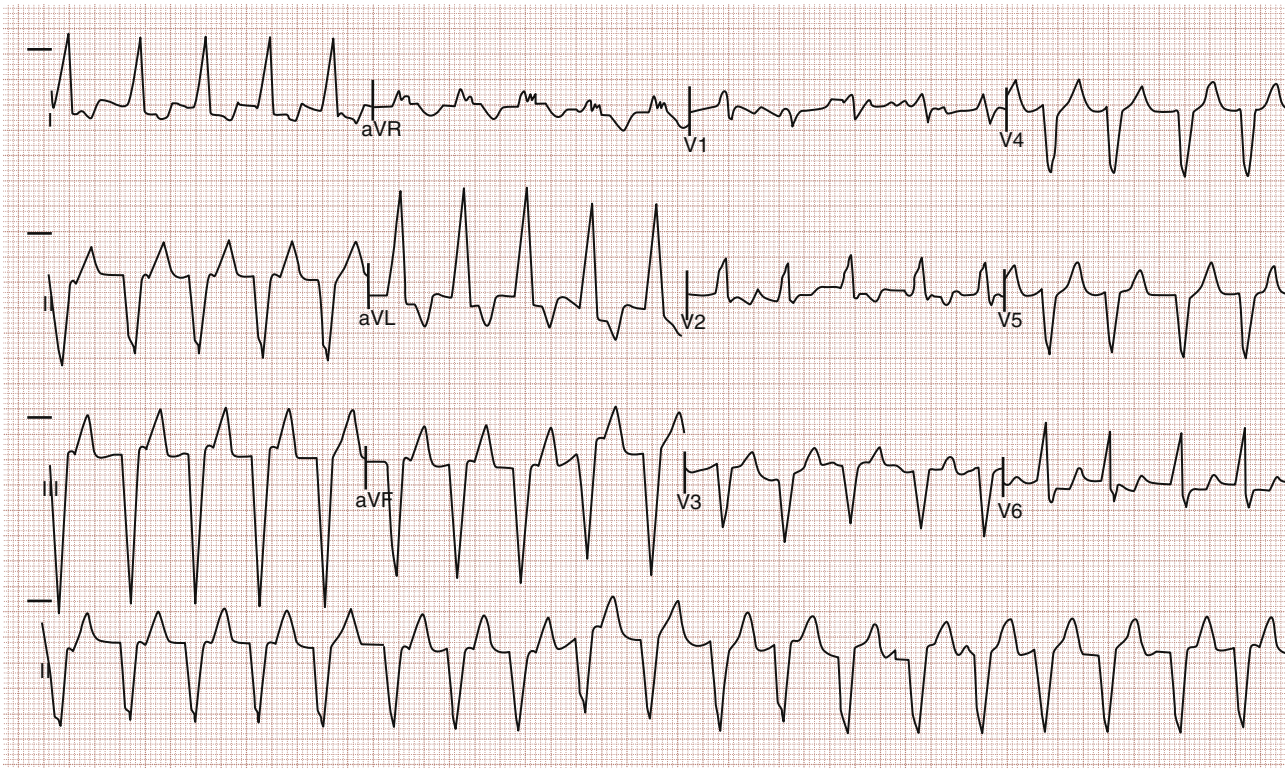
CHAPTER 66: QUESTIONS AND ANSWERS

1. Which of the following conditions is an indication for placement of a biventricular pacemaker?

a. Third-degree AV block
b. Brugada syndrome
c. Severely depressed systolic heart failure and a left bundle branch block
d. Slow atrial fibrillation

Answer: C. Cardiac resynchronization therapy, or biventricular pacing, is indicated for patients with systolic heart failure with an ejection fraction less than 35% and a left bundle branch block. By ensuring appropriate synchrony between the ventricles, cardiac output is improved, and multiple studies have shown a mortality benefit in these patients. Options A and C have an indication for a permanent pacemaker but would not benefit from biventricular pacing. Option B has an indication for implantable cardioverter-defibrillator.

2. A 67-year-old female presents with complaints of shortness of breath and a fluttering sensation in her chest. She had a dual-chamber pacemaker placed 10 years ago for sinus node dysfunction. Blood pressure is 124/96 mm Hg. On examination, she is anxious with clear lungs and no evidence of jugular venous distention or peripheral edema. There is no tenderness over her pacemaker insertion site. An ECG is provided as follows.



Which of the following is the next best step in the management of this patient?

a. Administration of IV amiodarone
b. Drawing blood cultures and starting antibiotics
c. Immediate cardioversion
d. Placement of a magnet over the pacemaker

Answer: D. This patient has a pacemaker with an inappropriately fast rate due to a pacemaker-mediated tachycardia. Management of this condition involves disruption of the circuit and can be accomplished by placing a magnet over the pacemaker, which sets the pacemaker into an asynchronous mode with no sensing (e.g., DOO). Cardioversion and amiodarone are less appropriate in this situation. Consultation with a cardiologist and interrogation of the pacemaker should be performed, although this can be done after placement of a magnet over the pacemaker. In the absence of potential for pacemaker infection, there is no role for blood cultures or antibiotics

3. A 67-year-old male with a history of an ischemic cardiomyopathy and an implantable cardiac defibrillator (ICD) presents with complaints of multiple shocks from his ICD in the past day. Interrogation of his ICD shows no evidence of any shocks in the past 2 months. What is the most appropriate management plan?

a. Administration of intravenous amiodarone
b. Cardiology consultation for reprogramming of ICD
c. Reassurance and follow-up with his cardiologist
d. Temporary ICD deactivation with magnet application

Answer: C. This patient has experienced 2 "phantom shocks." The perception of a shock in the absence of the actual ICD firing occurs in approximately 10% of patients with an ICD and is associated with significant anxiety and stress. Appropriate management includes reassurance and discharge with a patient's cardiologist. There is no role for IV amiodarone, reprogramming of the ICD or magnet application.

4. A 55-year-old man presents with chest pain and hypotension. ECG reveals ST-elevation MI in the inferior and lateral leads, and bedside echocardiogram shows poor systolic function of both ventricles. He has elevated jugular venous pressure, and a plethoric IVC on ultrasound. In addition to percutaneous coronary interventions, which of the following therapies would be most appropriate to consider?

a. Intra-aortic balloon pump
b. Temporary LVAD (e.g., Impella or Tandem Heart)
c. Veno-venous ECMO
d. Veno-arterial ECMO

Answer: D. This patient shows evidence of right heart failure, with poor RV systolic function and elevated jugular venous and IVC pressures. Intra-aortic balloon pumps and temporary left ventricular assist devices will support primarily the left ventricle. Veno-venous ECMO provides effective oxygenation and ventilation, but very little hemodynamic support. Veno-arterial ECMO may be considered as temporary biventricular support, if there is expected recovery of ventricular function, or if the patient is a candidate for another therapy (e.g., heart transplant or intracorporeal VAD).

5. A 65-year-old man with an intracorporeal left ventricular assist device (LVAD) presents to the emergency department and tells you he has felt lethargic for the past two days. A manual blood pressure cuff and Doppler ultrasound show a systolic blood pressure of 75 mm Hg, and a continuous "hum" is heard on auscultation. The cardiac monitor shows a wide complex tachycardia, and no pulse is palpable. Which is the most appropriate next step in management?

a. Administer amiodarone
b. Begin chest compressions

CHAPTER 66: QUESTIONS AND ANSWERS—cont'd

c. Call heart failure specialist and continue diagnostic evaluation
d. Immediate cardioversion/defibrillation

Answer: C. A low systolic pressure is expected with a continuous-flow LVAD, as there is generally a very low pulse pressure. The fact that the patient is awake suggests that he is adequately perfusing. His wide complex tachycardia may be a result of a ventricular dysrhythmia, or may be SVT or sinus tachycardia with aberrancy, and should be further investigated in a stable patient before starting interventions. He does not require chest compressions or immediate defibrillation/cardioversion with evidence of adequate perfusion, despite the lack of palpable pulse. While amiodarone may be an appropriate therapy, more information regarding his rhythm and current medications is required before giving this therapy.

67

Heart Failure

Nicholas Harrison and Phillip D. Levy

KEY CONCEPTS

- Heart failure (HF) is the clinical syndrome defined by signs and symptoms of elevated intracardiac pressures or depressed cardiac output, which in turn are due to either functional or structural cardiovascular (CV) abnormalities. By definition, HF presentations managed in the emergency department (ED) are acute heart failure (AHF) (ie, HF in which the signs and symptoms require unscheduled care).
- AHF is a multiorgan, multifactorial, and multiple phenotype disease state. Abnormalities in renal function, central venous volume and fluid shifts, arterial vascular tone, neuroendocrine overactivity, microvascular dysfunction, respiratory failure, or myocardial ischemia have bidirectional relationships with AHF as both potential causes and effects.
- Central congestion without hypervolemia is typically due to intercompartmental fluid shifts to the central circulation from venous reservoirs with reduced capacitance (increasing preload) or abrupt increases in central arterial tone (ie, increasing afterload).
- Emergency physician (EP) clinical gestalt based on history and physical exam is inaccurate for AHF diagnosis as often as a quarter of the time.
- The most useful diagnostic test for identifying lung congestion due to AHF is an 8-point lung ultrasound B-line scan, which is more sensitive than chest x-ray for pulmonary edema, and has a higher positive predictive value for AHF than natriuretic peptides.
- Focused cardiac ultrasound (FOCUS) for detecting reduced ejection fraction (EF) misses the 40% to 50% of AHF presentations with preserved EF. It adds little information to risk stratification because EF does not typically change with dynamic worsening of cardiac function or improvement after treatment.
- A useful clinical classification of AHF distinguishes between a vascular phenotype and a cardiac phenotype, though overlap can exist. Distinguishing between systolic and diastolic dysfunction is less helpful in the ED, because EF is preserved in about half of AHF cases, and most AHF patients have both systolic and diastolic dysfunction regardless of their EF.
- The "vascular phenotype" describes an AHF presentation where functional (ie, reversible) CV abnormalities such as increased vascular tone and fluid shifts predominate over structural (ie, irreversible) ones. These patients tend to be hypertensive, less likely to be hypervolemic, respond favorably to intravenous (IV) nitroglycerin, and have a better prognosis despite more abrupt symptom onset.
- The "cardiac phenotype" of AHF involves a predominance of structural (ie, irreversible) CV abnormalities such as more severe chronic myocardial disease, myocardial ischemia, and more complex multiorgan interactions (eg, cardiorenal syndrome). These patients are often hypervolemic and require high-dose IV diuresis. They typically present with a more indolent symptomatic progression, but paradoxically are at higher risk for worse outcomes.
- Noninvasive positive-pressure ventilation is the first-line approach for respiratory distress in AHF and may obviate a need for intubation in most cases.
- The initial dose of furosemide in the ED for AHF is 1 to 2.5 times the patient's total daily oral dose (or 40–80 mg if loop-diuretic naïve) and should be given IV. Although creatinine may rise after IV furosemide, it is rarely indicative of iatrogenic acute kidney injury, and patients with acute cardiorenal syndromes typically benefit from aggressive diuresis.
- Inotropes are only indicated in cases of cardiogenic shock (CS), because they may increase mortality as a pharmacologic class.
- Resuscitation and stabilization of CS should be followed by rapid evaluation from interjectional cardiology or cardiac surgery. While STEMI was traditionally the predominant cause of CS, it may only account for 30% of contemporary cases due to improvements in coronary intervention.
- Numerous high-moderate risk features in AHF define which patients likely require admission or observation, however, low-risk factors (ie, for discharge) are less well defined. When high or moderate risk factors are absent, the patient is adherent to the appropriate guideline-directed medical therapy, and can secure close outpatient follow-up (≤1 week), a shared decision-making discussion regarding discharge from the ED may be appropriate.

FOUNDATIONS

Background and Importance

Heart failure (HF) is a clinical syndrome defined by three components (Fig. 67.1)[1]:

- Structural or functional cardiovascular abnormalities
- Elevated intracardiac pressures or depressed cardiac output (CO) due to these abnormalities
- Clinically recognizable signs or symptoms (eg, dyspnea, edema, fatigue, exertional intolerance, or others) due to the elevated intracardiac pressures or depressed cardiac output

Management of clinical manifestations of HF with scheduled care is classified as chronic HF. Conversely, HF symptoms that require unscheduled care define the presentation of acute HF (AHF). Thus, when HF is managed and treated in the ED, it is, by definition nearly always AHF. Some exceptions exist (eg, a stable chronic HF patient presenting to the ED for a medication refill), however, these are relatively few, and AHF is therefore the primary focus of this chapter.

AHF may further be subdivided as decompensated chronic HF versus "de novo HF."[2,3] The former describes AHF occurring in a patient with known chronic HF history, while in the latter the AHF episode is the patient's first known clinical presentation of HF. De novo AHF accounted for over 50% of presentations in a large AHF registry study of Asia and Europe,[2] but is a less common ED presentation in North America. Epidemiologic registry data from 2005 to 2014 suggest that

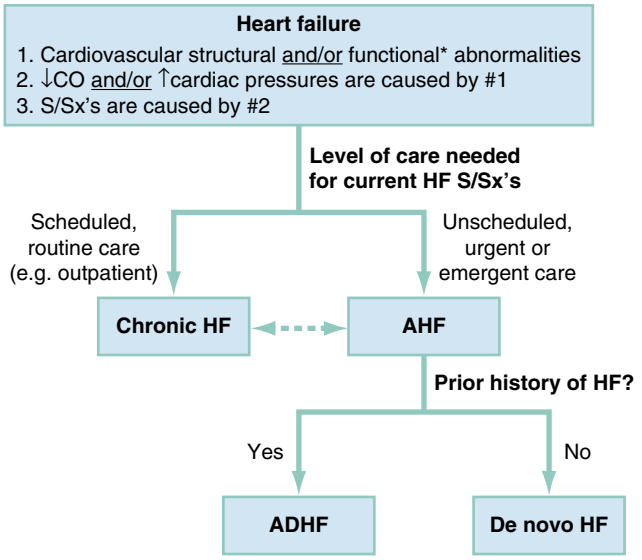


Fig. 67.1 Flowchart algorithm for clinical definition and classification of heart failure (HF). Three criteria define HF in general: cardiovascular structural or functional abnormalities, which cause decreased CO or increased intracardiac pressures, and clinical symptoms resulting from these physiologic derangements. Examples of cardiovascular structural (ie, fixed, anatomic) abnormalities include cardiomyopathies, valvular disease, myocardial scar and fibrosis, etc. Functional (ie, dynamic) abnormalities include arterial vasoconstriction, acute volume shifts and redistribution, transient ischemia without infarction, toxicologic or reversible metabolic myocardial dysfunction, and numerous others. In most cases, both structural and functional abnormalities coexist to cause depressed CO, increased intracardiac pressures, or both. HF is also by definition symptomatic, and does not include subclinical myocardial dysfunction (which nevertheless may progress to clinical HF with time or acute physiologic stressors). The three most common presenting signs/symptoms in the ED setting are (in order) dyspnea, edema/swelling, and fatigue. HF is further subdivided into chronic and acute (AHF), based on whether or not the symptoms lead a patient to seek urgent or emergent management in an acute setting such as the ED. When HF is treated in the ED, it is therefore (by definition) AHF. Many AHF patients will have a chronic HF history (ADHF), but a significant proportion will not (de novo AHF). For emergency medicine this distinction has mostly prognostic significance for disposition. *HF*, heart failure; *ED*, emergency medicine; *CO*, cardiac output; *S/Sx's*, signs and symptoms; *AHF*, acute heart failure; *ADHF*, acutely decompensated heart failure.

around 28% of ED AHF presentations in the United States (US) are de novo[3].

It is important to note that many HF terms commonly used in the past are now considered outdated, inaccurate, or clinically misleading. "Congestive heart failure," for instance, is no longer favored given that volume profiles in HF are heterogeneous and include many patients with normal or even hypovolemic total body water profiles.[4-7] Also, the terms "systolic HF" and "diastolic HF" are no longer used to describe patient phenotypes. The following, more accurate terms are preferred: "HF with reduced ejection fraction" when the ejection fraction (EF) is less than 40%; "HF with midrange EF" when the EF is 40% to 50%, and "HF with preserved EF" when EF is greater than 50% (HFrEF, HFmrEF, and HFpEF, respectively). The terms "systolic dysfunction" (ie, decreased inotropy) and "diastolic dysfunction" (ie, impaired relaxation) still apply as physiologic concepts but are often overlapping and do not describe clinical phenotypes that warrant particular approaches to management.[8] Combining terms to summarize a patient's presentation, such as "acutely decompensated chronic HF with reduced EF," is useful.

Epidemiology

Chronic HF is highly prevalent (≈2.5% of the US population) and is strongly associated with common cardiovascular risk factors.[9] Onset increases sharply with advancing age, such that, by age 65, the annual incidence of new chronic HF diagnosis approaches 2.1%.[3] Other risk factors observed in population-based samples include obesity, hypertension, diabetes mellitus (DM), tobacco smoking, hyperlipidemia, low socioeconomic status, and ischemic heart disease.[9]

Nearly 1 million admissions for AHF occur each year in the United States, and more than 80% of these originate from the ED with a nearly 50/50 split between HFpEF and HFrEF. Outcomes are poor with 30-day and 1-year mortality of 10% and 30%, respectively, after an AHF episode, and appear to be similar regardless of EF.[3] After hospital discharge, roughly 20% of AHF patients will be readmitted within 30 days.[10]

Myocardial Physiology and the Cardiac Cycle in Heart Failure

The cardiac cycle (Fig. 67.2A) and its relationship to CO is often described by three physiologic parameters: chronotropy, inotropy, and lusitropy. CO is the mathematical product of heart rate (HR; ie, chronotropy) and the stroke volume (SV). SV is itself the product of end diastolic volume (EDV; ie, lusitropy) and EF (ie, inotropy). Thus, mathematically

$$CO = HR \times EDV \times EF$$

and conceptually

$$CO = Chronotropy \times Lusitropy \times Inotropy.$$

Recall that the second criterion of the HF definition requires that CO be reduced or intracardiac cardiac pressures be increased; however, these two defining hemodynamic insults tend to coexist and are distinctly related.

Lusitropy and inotropy (Fig. 67.2C–E) may be chronically depressed due to underlying chronic structural or functional cardiac changes, as in the setting of ischemic heart disease or hypertensive heart disease, or acutely impaired by a new hemodynamic stressor such as hypertensive emergency, infection, volume redistribution or overload. As shown in Figure 67.3, AHF is also an inherently multiorgan process, with bidirectional feedback between cardiac dysfunction, vascular tone, and multiple organ involvement.

SV is classically modeled by the Frank-Starling mechanism, which describes a relationship between stroke volume and EDV (Fig. 67.4A). In the idealized scenario, increasing EDV leads to increasing SV because stretching myocardial sarcomeres further apart in diastole allows them a further distance to contract during systole, increasing inotropy. This model describes the preload-SV relationship well under conditions where EDV is far below the heart's maximum capacity. Eventually, an inflection point is reached where sarcomeric stretch is maximized and increases in inotropy level-off despite further increases in EDV, noted as the flat portion of a Starling curve. If EDV increases even further, sarcomeres are stretched into abnormal configurations that inhibit inotropy and produce systolic dysfunction. Even brief and transient exposure to excessive left ventricular (LV) EDV can trigger a cascade of stretch-related insults to myocardial function, including subendocardial ischemia with cardiomyocyte injury and necrosis with associated cardiac troponin [cTn] release. Further or sustained stretch results in myocardial stunning and sarcomere proteomic remodeling, culminating in clinical deterioration that manifests as AHF.[11,12,13,14]

Repeated exposures to increased LVEDV (and resultant LVEDP) cause fibrosis and myocardial hypertrophy that ultimately lead to a stiff, noncompliant ventricle.[15] The net effect is an impairment of lusitropy (ie, diastolic dysfunction) that serves to limit the degree

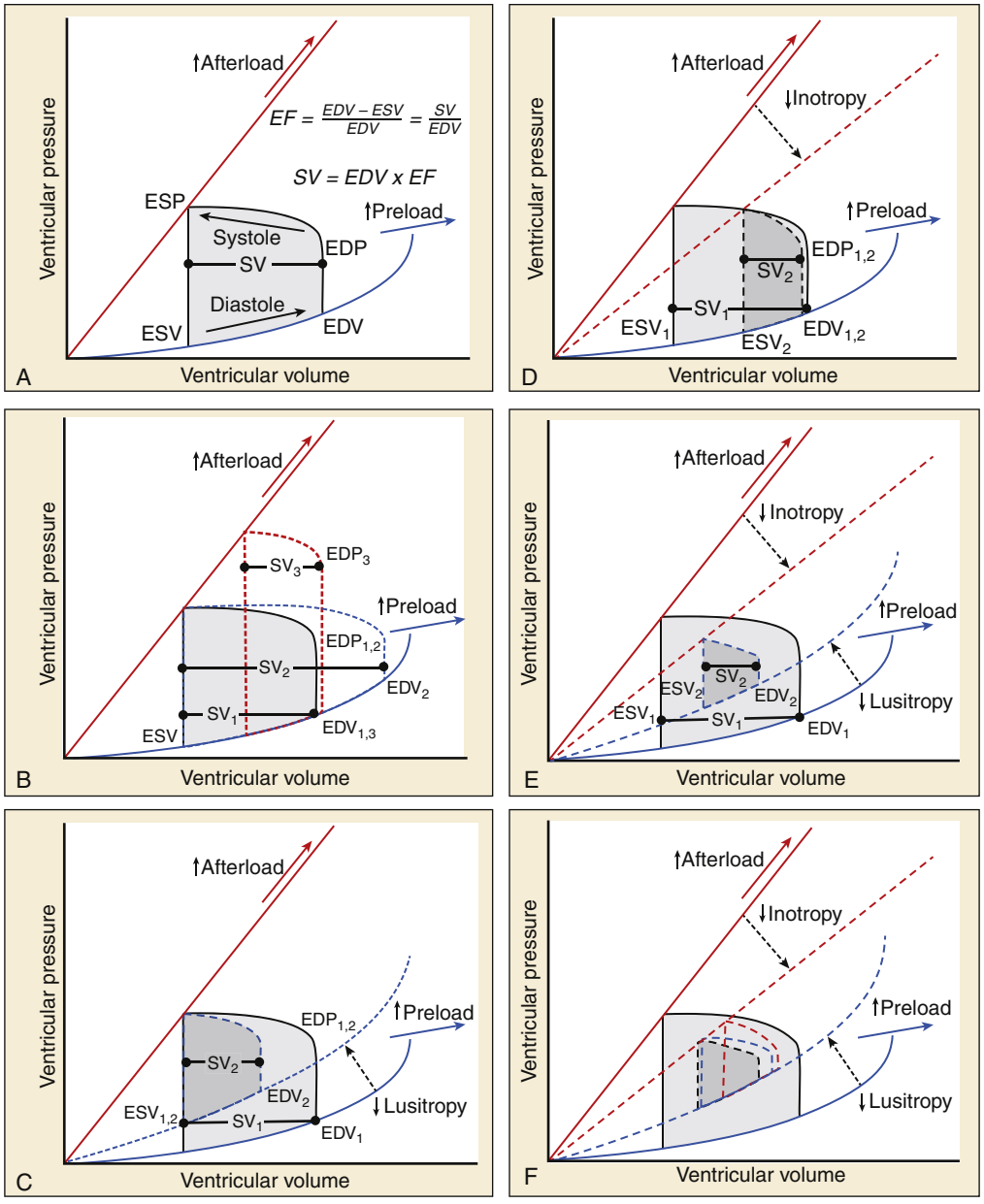


Fig. 67.2 Pressure-volume (PV) loop concept diagrams demonstrating the relationship between underlying cardiac function, SV, and changes in preload or afterload. Each loop is delimited by underlying limits to inotropy (top limit line) and lusitropy (bottom limit line). Stroke volume alterations (by changes in preload and afterload) are limited to these confines. (A) Baseline PV loop of a hypothetical healthy heart. (B) Isolated increases in afterload (*red dotted line*) or preload (*blue line*) under healthy conditions lead to decreased or increased SV, respectively. (C) Isolated impairment of lusitropy (ie, diastolic dysfunction) decreases SV by reducing EDV for a given EDP, ESP, and ESV (*dotted line*). This is representative of many, but not all, cases of HFpEF (since diastolic dysfunction may be isolated or may coexist with systolic dysfunction, even in HFpEF; see panel E). (D) Isolated impairment of inotropy (ie, systolic dysfunction) decreases SV by reducing ESV for a given EDP, ESP, and EDV (*dotted line*). EF is observed to decrease, though the reduction in SV is just as severe as isolated diastolic dysfunction in panel C. This curve is mostly hypothetical because in reality systolic dysfunction is nearly always accompanied by diastolic dysfunction in both HFrEF and HFpEF. (E) Combined inotropic and lusitropic impairment decreases SV by reducing ESV and EDV for a given EDP and ESP. This represents nearly all cases of HFrEF and many cases of HFpEF. (F) Compared to the healthy heart in panel B, preload (*blue dotted line*) has only marginal effects on SV in HF (ie, decreased preload tolerance). For afterload, the direction of effect is the same as the healthy heart: increased afterload reduces SV (*red dotted line*) when all other parameters are held constant. *SV*, stroke volume; *EF*, Ejection fraction; *EDP/ESP/EDV/ESV*, end-diastolic/systolic pressure/volume; *HF*, heart failure; *HFpEF*, HF with preserved EF; *HFrEF*, HF with reduced EF.

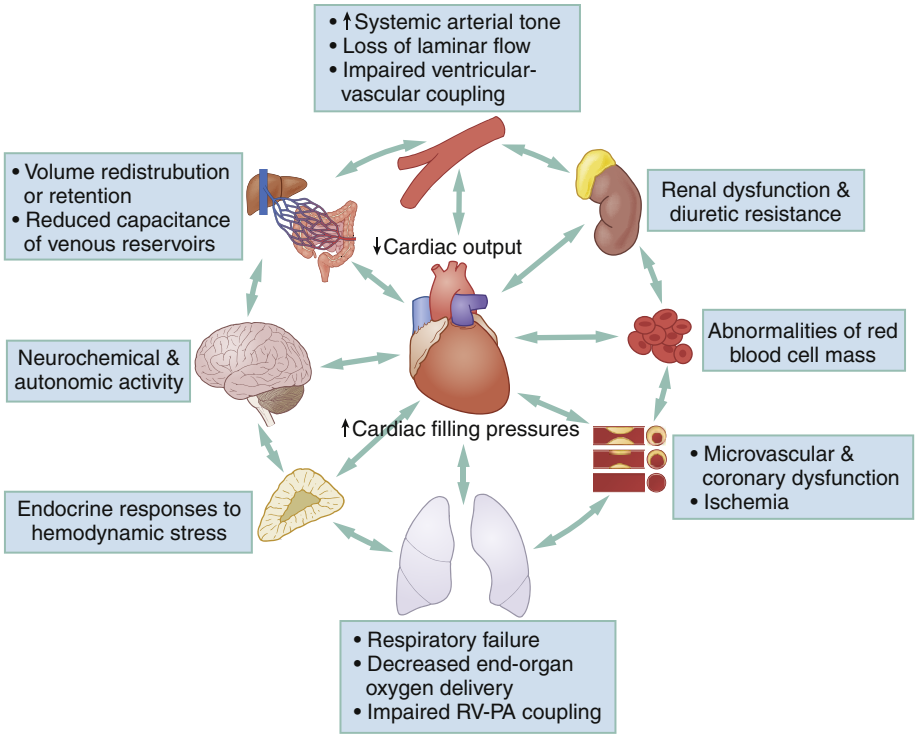


Fig. 67.3 A multiorgan, multidirectional concept chart of AHF. Increased intracardiac pressures or reduced CO (ie, a sine qua non of AHF) can be the result or the cause of other organ system dysfunction. Activation of the sympathetic and RAAS neurohomonal axes, for instance, can be a precipitant of AHF. However, depressed CO also will activate these neurohormonal mechanisms both directly and indirectly. Certain bidirectional relationships have been described as distinct and important syndromes, such as the cardiorenal syndrome. Not every cardiac to end-organ relationship pictured here is a key component of every AHF presentation, underlining the importance of AHF phenotypic heterogeneity and the fact that therapeutic approaches should be tailored to phenotype when possible. Also, many relationships not pictured are likely important in some cases since understanding of AHF physiology is continuously changing. *AHF*, acute heart failure; *CO*, cardiac output; *RAAS*, renin-angiotensin aldosterone system; *RV*, right ventricle; *PA*, pulmonary artery.

of myocardial stretch during future elevations protecting the myocardium from further stretch-induced myocyte death.[15] However, this comes with a tradeoff, because the ensuing diastolic dysfunction prevents accommodation of increased LVEDV, contributing to onset of symptomatic HF. In the early stages, a certain degree of diastolic dysfunction may be subclinical, or only induced upon stress with exercise, acute hypertension, or hypoxia.[16,17] As diastolic dysfunction progresses, demand from activities of daily living may be superimposed on diminishing cardiac reserve associated with other physiologic changes, including decreased myocardial oxygen reserve, abnormalities in nitric oxide signaling, decreased aortic and pulmonary artery compliance, decreased ventricular volume, right ventricular dysfunction, and worsening interventricular and ventricular-circulatory coupling, resulting in depressed tolerance of increased preload and afterload.[8,16-21]

Depressed SV resulting from acute diastolic or systolic dysfunction can be theoretically compensated for by increased chronotropy. However, the time between systolic cycling sets a "hard stop" on the upper limit of cardiac filling time and, at a certain point, further augmentation of CO through increased chronotropy becomes limited by diminished lusitropy (Fig. 67.5). Thus while increasing heart rate has early adaptive benefits, persistent sinus tachycardia in the setting of AHF is generally an ominous sign that CO has been stressed to its limit. This also explains why increased or decreased chronotropy (as in tachy- or brady-arrhythmias) is a relatively common precipitant of AHF.[2]

Abnormal Loading Conditions and Elevated Filling Pressures

Patients with chronic HF (eg, curves IV and V in Fig. 67.4) tend to stay near or beyond the inflection point of the Starling curve (red and yellow zones Fig. 67.4) because of their chronically impaired diastolic and systolic dysfunction. Even subtle increases in loading parameters (rightward shifts on the curves) can lead to fulminant AHF. Additionally, with relatively normal baseline cardiac function (curve III Fig. 67.4, curves I–II Fig. 67.6A), extremes that impede forward flow (eg, hypertensive emergency) can precipitate AHF through a large rightward shift on the curve. Multiple neurohormonal effects result from and contribute to loading conditions and filling pressures.[22,23] Natriuretic peptides (NPs) are especially important in this regard and are upregulated in HF where they result in natriuresis and diuresis, vasodilation, and antifibrotic effects that can reverse remodel the heart.[24-27] Produced directly by the heart, atrial-NP (ANP), B-type NP (BNP), and the N-terminal fragment of BNP's prohormone (NT-proBNP) are clinically useful for diagnosis and prognosis of HF.

Elevated intracardiac pressures are a defining characteristic in AHF (see Fig. 67.1), and even brief episodes can impair the normal cardiac cycle and lead to irreversible systolic or diastolic dysfunction.[12,15] Thus, episodes of AHF negatively impact the long-term prognosis of patients with chronic HF.[28] This is of particular relevance to ED management, with a physiologic justification for a "time-to-treatment" concept in AHF, similar to many other time-sensitive conditions seen in emergency medicine. Given the potential benefit of limiting myocardial

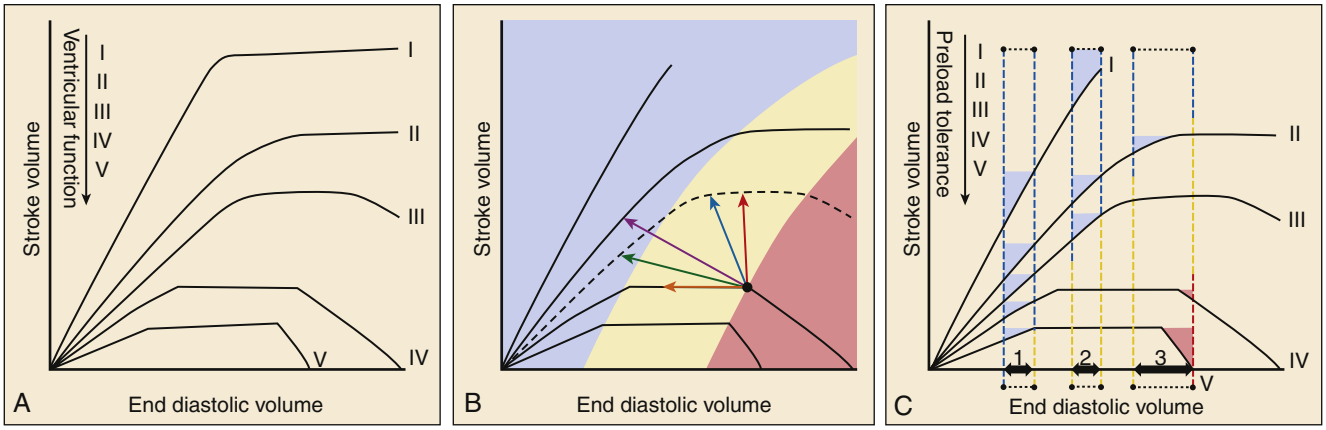


Fig. 67.4 SV versus preload curves describing the Starling mechanism in the context of AHF versus health. (A) Curves I through V represent progressive worsening of baseline cardiac function. Increased preload leads to increased SV early because of more favorable sarcomeric configurations in myocytes. Once all sarcomeres are at a maximal degree of stretch the ability to increase SV by preload is exhausted, and the curve levels off. At severe degrees of stretch, sarcomere configurations become disorganized and stretch-related myocyte injury mechanisms are activated, causing the curve to potentially invert with more preload ("falling off the Starling curve"). The inflection points of leveling off and then of curve inversion occur at less extreme levels of preload as cardiac pump function worsens. (B) For any given preload, patients with cardiac pump dysfunction (IV–V) are more likely to be in the flat or inverted part of the Starling curves (*yellow* and *red zones*, respectively) compared to those with normal or excellent pump function (I–III), and far less likely to be in the preload responsive part of the Starling curve (*blue zone*). Common ED treatment strategies for AHF either push the patient's preload "backwards" to a more favorable zone along the same Starling curve (IV diuretics only, *orange arrow*), move the patient "up" to a curve with improved cardiac performance (inotropes only, *red arrow*), or both (vasodilator only, *blue arrow*; vasodilator plus diuretic, *green arrow*; vasodilator, diuretic, and inotrope, *purple arrow*). (C) Preload tolerance is a conceptualization of whether a patient will benefit, have no change, or sustain harm from a fixed change in preload (intervals/arrows 1, 2, and 3). In AHF, relatively rapid increases in preload occur from intercompartmental fluid shifts, while slower increases occur from progressive volume overload. Interval 1 shows a severely hypovolemic state, in which all 5 patient curves benefit from an increase in preload (eg, a fluid bolus), though SV augmentation is only modest with cardiac dysfunction IV–V. Interval 2 represents a state in which increased central venous volume pushes patients IV–V closer to falling off the Starling curve (while achieving no change in SV), whereas SV is augmented in I–III. In interval 3, further increased central venous volume pushes the patients with myocardial dysfunction "off" the Starling curve, but given the same preload has neutral-to-positive effects for patients I– III. *AHF*, acute heart failure; *SV*, stroke volume.

damage through earlier normalization of intracardiac pressures, organizations such as the Heart Failure Society of America (HFSA), the Society for Academic Emergency Medicine (SAEM), the American Heart Association (AHA), and the American College of Cardiology (ACC) have all recommend that AHF treatment be started as quickly as possible after ED arrival.[28-31] Broadly speaking, the major classes of ED AHF therapies work by targeting the physiology underlying elevated intracardiac pressures either by moving the Starling curve leftward with diuretics or venodilators, moving the curve upward to a higher level of efficiency for a given EDV with inotropes or arterial vasodilators, or both. A simple but useful hemodynamic classification distinguishes between cardiac (ie, primary pump failure predominates) and vascular (ie, acutely increased preload or afterload predominates) phenotypes of AHF.[1] The ED management differs depending on which phenotype predominates.

Congestion and Preload

Congestion in AHF is very specifically the congestion of the central vasculature (ie, the vena cava, great arteries, and proximal organs such as the heart, lungs, and kidneys). Central congestion can occur from true volume overload associated with excessive fluid intake or retention, typical of the cardiac phenotype. Generally, this is an indolent process (Fig. 67.7A). When rapid decompensation occurs in AHF, fluid typically shifts from venous reservoirs to the central circulation in a process largely independent of total body water, more typical of the vascular phenotype. This, in part, explains why classic signs and symptoms of fluid overload may be absent in patients with AHF.[32]

One of the largest and most critical venous reservoirs in the body is the splanchnic circulation, containing 20% to 50% of total blood volume at any given time. The splanchnic vessels dilate or contract in response to central circulation baroreceptors and sympathetic tone, and the renin-angiotensin-aldosterone system (RAAS). Under normal physiologic conditions, regulation of fluid from the splanchnic to central circulation via the hepatic veins acts as a buffer to maintain central volume. In stress situations, volume can be rapidly mobilized from the splanchnic circulation to the central circulation by vasoconstriction. When HF is present, neurohormonal mediators are chronically activated, leading to basal splanchnic vasoconstriction and a reduction in the reservoir's buffering capacity. As a result, rapid fluid shifts can develop in response to any number of AHF precipitants (eg, infection, acute hypertension, ischemia, etc.), leading to central congestion even when total body water is normal (Fig. 67.7B, first curve). Experimentally, denervation of the splanchnic vasculature in AHF patients dramatically lowers intracardiac filling pressures while increasing cardiac output.[33]

In contrast, patients with the cardiac pathophysiology typically have gradual fluid accumulation superimposed on long-standing and intractable hemodynamic derangements. AHF patients with slow

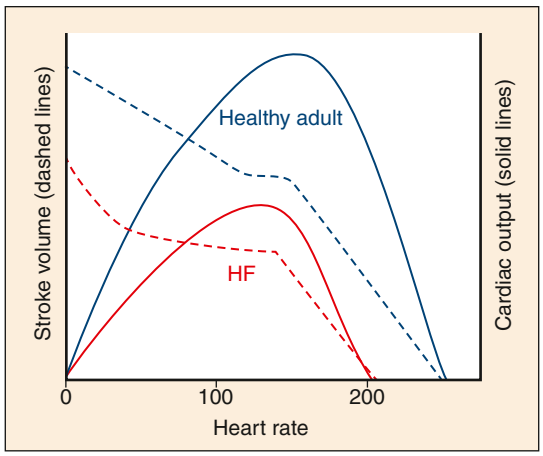


Fig. 67.5 Plot of SV (*dotted line*) or CO (*solid line*) versus HR for healthy and impaired myocardial function (*blue line* vs. *red line*, respectively). Myocardial stimulation in response to physiologic demands (eg, sympathetic drive in response to a physiologic stressor), can compensate by augmenting SV up to a ceiling dictated by the optimization of inotropy and lusitropy. Past this SV ceiling, the only way to augment CO to meet even higher physiologic demand is to increase HR (ie, tachycardia in AHF may signify severe mismatch between myocardial function and metabolic demand). After a certain point of tachycardia, SV will worsen due to insufficient time spent in diastole (ie, de-optimized filling time) and further increases in tachycardia will cause CO to decrease (ie, tachydysrhythmias precipitate hemodynamic instability at extremely high HRs in healthy patients, but at lower HRs in acute or chronic myocardial dysfunction). *SV*, stroke volume; *CO*, cardiac output; *HR*, heart rate; *AHF*, acute heart failure.

onset of symptoms tend to have less pronounced pulmonary edema on arrival and delayed dyspnea relief with worse in-hospital and post-discharge outcomes.[34] Thus, clinicians should not rely entirely on a patient's apparent clinical severity at presentation to determine how much decongestion they may need (Fig. 67.7B).

Afterload

Afterload is the pressure against which the ventricle must contract to eject blood. In practical terms, this means the aortic and pulmonary artery (PA) pressures for the LV and right ventricle (RV), respectively. The coupling of ventricular and vascular function is a dynamic relationship. As afterload rises, SV will gradually decline until extremes in ventricular pressure are reached and a precipitous worsening of ventricular function ensues (Fig. 67.6A). The RV is significantly more pressure-sensitive and volume-tolerant than the LV, though chronic elevated pressure can cause hypertrophic remodeling similar to the LV. The ratio of oxygen consumption to stroke work increases as afterload rises (a phenomenon referred to as ventricular-vascular decoupling), burdening a heart with already diminished oxygen capacity at baseline.[35] Whether intrinsic or exogenous, rises in afterload are often abrupt. Clinical deterioration rapidly follows, resulting in the onset of "flash" pulmonary edema. Though sometimes described as a distinct entity, flash pulmonary edema is the most severe form of afterload-mediated or hypertensive AHF.

Disorganized Contraction

In addition to perturbations in preload and afterload, the heart itself can contribute to AHF through disorganized contraction and relaxation.[20] Each ventricle can be divided into individual myocardial segments (eg, apex to base, anterior/posterior, septal/free wall), which under idealized circumstances all contract and relax simultaneously. In reality, some segments within a single ventricle may contract or relax slightly before others, and even slight asynchrony reduces the mechanical efficiency of contraction. The reasons for segmental asynchrony include relatively fixed myocardial lesions, such as a scar from past MI, and more acute, dynamic causes such as localized demand ischemia, stretch-related myocyte toxicity, coronary microvascular dysfunction, or acute MI. ED treatment of AHF, including noninvasive positive-pressure ventilation (NPPV), diuresis, and vasodilation, can significantly improve segmental contraction synchronization. Failure to improve mechanical synchrony on point-of-care echocardiography (POC echo) after ED AHF treatment is associated with adverse AHF outcomes.[36]

Right Ventricular Dysfunction and Pulmonary Hypertension

Right ventricular dysfunction (RVD) has been increasingly recognized as an important pathologic and prognostic marker in both chronic HF and AHF. RVD identifiable on ultrasound may be present in 28% to 46% of AHF cases and significantly declines in the first 24 hours after initial ED treatment.[36a,37,38] Missed antihypertensive medication within 7 days, ED PPV, COPD history, LVEF, lung ultrasound congestion severity, and right ventricular systolic pressure (RVSP) are significant predictors of RVD. RVD evident on POC echo is rarely recognized despite a high prevalence and potentially greater prognostic implications than LVEF.[36a] RVD in AHF is associated with higher all-cause mortality in AHF even after adjusting for LVEF and other measures of LV function.[39-42] More importantly, the association between RVD and AHF mortality strengthens when pulmonary hypertension is absent. The relationship between acute RV and LV dysfunction is bidirectional and inextricably interdependent (Fig. 67.8). Although the most common cause of right heart failure is left heart failure, RVD can precede, precipitate, or be concurrent with LV dysfunction in AHF. This is evident given that the path through the right heart, pulmonary circulation, left heart, and systemic circulation is a closed circuit and RV CO must equal LV CO. As a consequence, any hemodynamic derangement within the circuit will, on a beat-to-beat basis, adversely impact biventricular functionality. Additionally, the LV and RV share a common wall (the interventricular septum), meaning acute changes on one side do not occur in isolation.

RVD in AHF can result from factors intrinsic and extrinsic to the RV itself (see Fig. 67.8). Some AHF therapies affect the RV as much as or more than the LV, as suggested by the observation that improvement in RV stroke-work (but not LV stroke-work) during an episode of AHF is associated with decreased rates of death, transplantation, ventricular assist device implantation, or HF-related rehospitalization at 6 months.[42] Moreover, RVD independently predicts hyponatremia, worsening renal function after hospitalization, longer hospital length of stay, and higher rates of myocardial fibrosis.[43-47]

Myocardial Infarction Versus Injury

cTn is detectable in 10% to 30% of AHF patients using conventional sensitivity assays and in 80% to 90% of patients with high-sensitivity (hs-cTn) assays.[48-54] cTn is a marker of myocardial damage and can result from both acute and chronic processes.[55] Although acute myocardial infarction (AMI) is often a precipitant or accompanying factor in AHF presentations, an elevated troponin does not by itself indicate AMI. Two criteria must be met to satisfy the universal criterion definition of AMI: the cTn elevation is above the 99th percentile for a given assay, and there is clinical suspicion for ischemia.[56] A cTn value that is elevated but fails to meet one or both criteria for AMI is termed "myocardial injury" and is common in AHF.

Multiple ischemic (ie, infarction) and nonischemic (ie, myocardial injury) mechanisms are clinically relevant to AHF (Table 67.1). A clinical assessment for risk of myocardial injury and ischemia should be undertaken in all AHF patients presenting to the ED. Regardless of the assay or mechanism, an elevated troponin in the setting of AHF

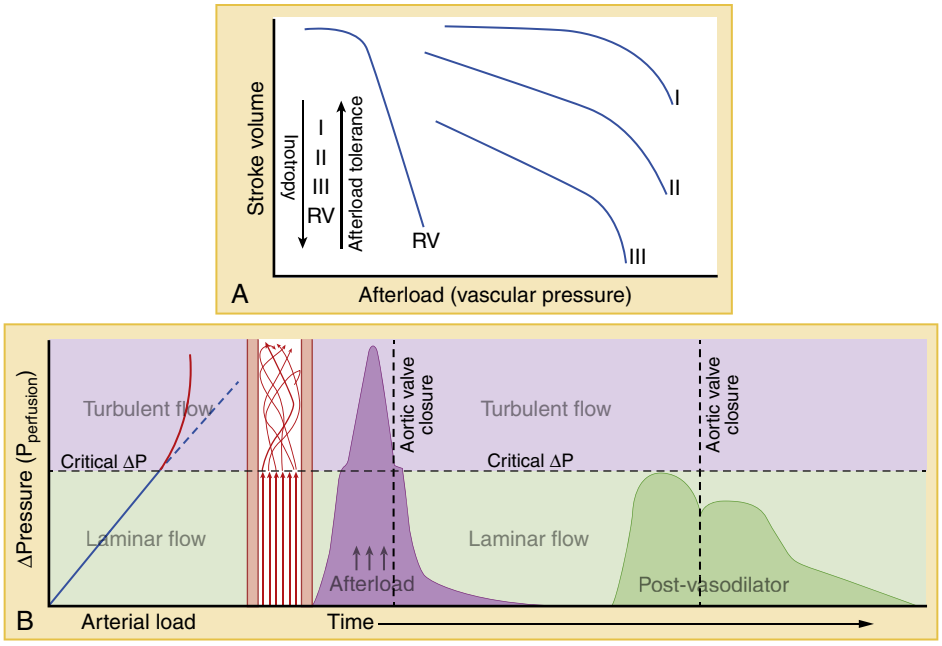


Fig. 67.6 (A) SV versus afterload relationship plotted for 3 levels of decreasing LV function (I–III) and the RV. Increasing afterload for a fixed degree of inotropic and lusitropic function causes a decline in stroke volume. However, resistance to this decline (a flatter slope) is higher with better baseline cardiac pump function. Eventually, regardless of ventricular resilience to afterload, vascular pressure can become high enough to induce a precipitous decline in stroke volume (ie, rapid ventricular-vascular decoupling). The RV is extremely pressure sensitive (but more volume tolerant) compared to the LV. (B) The relationship between the ventricular-vascular pressure difference ("driving pressure" or "delta pressure") and arterial flow rate (*right*) or time (*left*) for a set afterload. In order to overcome high afterload, cardiac driving pressure must increase to maintain arterial flow. This relationship is linear when flow is laminar, but flow becomes turbulent once the pressure difference reaches or exceeds a critical value. Under turbulent flow, further increases in the pressure difference yield decreasing rates of return in arterial flow despite steadily increasing cardiac MVO_2. Flow thus becomes highly inefficient as ventricular-vascular decoupling progresses (eg, in severe hypertension), as in the purple curve of the delta pressure versus time. When blood pressure is lowered (post-vasodilator *green curve*), a larger proportion of flow is laminar and the driving ventricular-vascular pressure difference is spread more evenly over time, leading to more efficient hemodynamics (ie, lower MVO_2 required to produce similar degree of flow). In AHF the "supply" of myocardial oxygen is lowered while the "demand" is increased, so decreasing MVO_2 for a given SV is physiologically beneficial. In the initial resuscitation of the hypertensive/vascular AHF phenotype this typically means IV bolus vasodilators such as nitroglycerin. *SV*, stroke volume; *LV*, left ventricle; *RV*, right ventricle; *MVO_2*, myocardial oxygen consumption rate.

portends a worse prognosis.[57] Even in the absence of critical coronary artery disease (CAD), coronary flow reserve may be decreased due to microvascular dysfunction and exacerbated when the ventricles are subjected to stress, resulting in myocardial ischemia.[14]

Cardiorenal Syndrome

The interaction between cardiac and renal dysfunction plays a critical role in both AHF and chronic HF. Worsening of renal function due to AHF, termed *acute cardiorenal syndrome* (acute CRS, also known as CRS type 1) occurs in approximately 40% of cases and is associated with increased risk for rehospitalization and postdischarge mortality.[58] While underlying chronic kidney disease (CKD) in patients with chronic HF (chronic CRS, also known as CRS type 2) is also a poor prognostic factor, superimposed acute CRS develops in 19% of AHF patients and is associated with a threefold greater risk of mortality.[59]

The kidneys receive approximately 25% of CO despite being relatively distal in the central arterial circulation, almost wholly by virtue of being a very low-resistance circuit.[58] Even a slight elevation in central venous pressure, therefore, causes renal venous hypertension (ie, "renal afterload") that leads to central congestion and acute kidney injury (AKI). Increases in intraabdominal pressure, typically secondary to decreased splanchnic capacitance, cause a similar effect. RVD may also play a role, and is independently associated with renal dysfunction and mortality.[60] AHF therapies that offload central venous congestion and right-sided cardiac pressures may improve renal perfusion and prevent or ameliorate CRS (Fig. 67.9). Requirement of a higher dose of diuretic per amount of urine output (ie, diuretic resistance) is a key clinical sign of CRS. When patients present to the ED in AHF despite a recent increase in their outpatient loop diuretic dose, acute CRS should be highly suspected. When acute CRS is suspected, a higher dose of IV diuretic or combination with a non-loop diuretic should be considered (Fig. 67.9B).

Though clinicians may be wary of giving high doses of IV diuretics when acute CRS is present, increased diuretic dosing in acute CRS is associated with greater fluid loss, better improvement in symptoms, and no significant increase in renal complications.[61,62] Moreover, when creatinine does rise after IV diuresis in AHF, it is not associated with true renal tubular damage and is not associated with short- or long-term adverse outcomes.[63,64] Likewise, vasodilators historically were thought to contribute to CRS by decreasing renal perfusion. However, in the absence of overt shock, renal autoregulation maintains a relatively constant renal blood flow across a wide range of mean arterial pressures (MAPs), making CRS unlikely to result from vasodilators. Moreover, preglomerular vasoconstriction does contribute to CRS

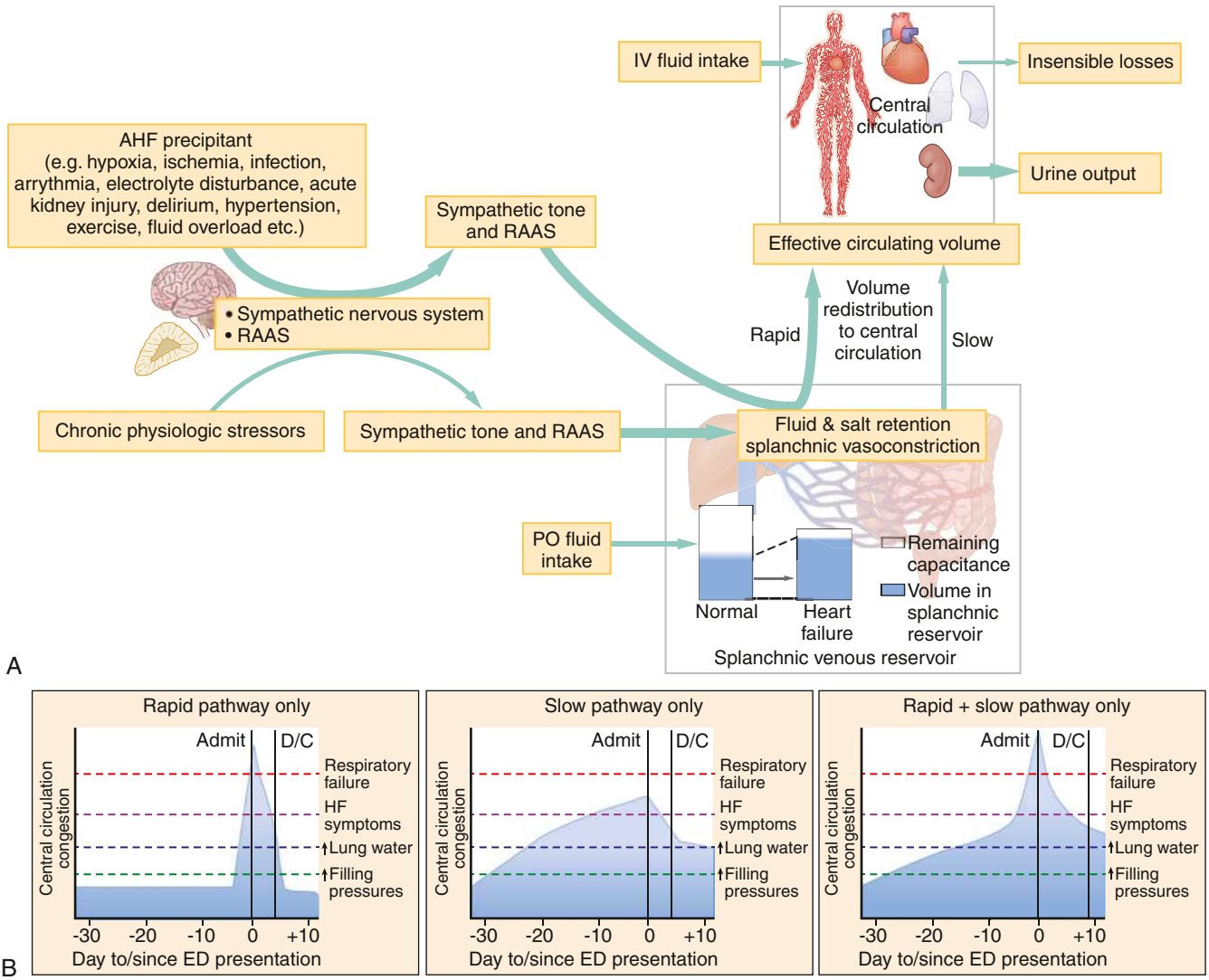


Fig. 67.7 (A) Concept flowchart of central circulation congestion in AHF. The splanchnic circulation under normal physiology holds up to half of total circulating volume, with a large residual capacity to buffer the central circulations against acute increases or decreases in total vascular volume. Neurohormonal activation (eg, alpha-adrenergic, RAAS, etc.) causes progressive splanchnic vasoconstriction that reduces the capacitance of the reservoir and decreases its residual capacity (ie, even without a change in total body water). This impairs the splanchnic buffering capacity, meaning that any increase in oral fluid intake more readily "spills over" to the central circulation while any decreases in central circulation fluid elimination (eg, renal impairment, insensible losses) are unable to be buffered against. The result is the "slow pathway" described in the figure, where progressive central congestion occurs over weeks to months. Left uncompensated, this can result in a slow but progressive descent into AHF. Additionally, if an acute stressor (eg, severe hypertension) rapidly and massively activates sympathetic drive and RAAS, fluid shifts from the splanchnic to central circulation will occur much more rapidly (the rapid pathway). (B) Plots of central congestion versus time, benchmarked by key clinical or physiologic events, to illustrate the ramifications of the rapid versus slow physiologies for AHF clinical presentations. In the rapid pathway only, the abrupt fluid shift produces dramatic and rapid symptoms over only a few days but may resolve quickly with appropriate AHF treatment. These patients, typical of the AHF "vascular phenotype," may present more dramatically by history but ironically have a better prognosis. In the slow pathway only, symptoms develop more indolently but also after significantly more intractable change because symptoms of HF can occur weeks after increases in cardiac pressures and increases in lung water under such conditions. This is typical of a slow decompensation in the "cardiac" AHF phenotype without any overt superimposed physiologic stressor/AHF precipitant to activate the rapid pathway as well. The presentation is less dramatic but prognosis is significantly worse, possibly because lung water and intracardiac pressures have been asymptomatically elevated for a longer period of time and are more intractable. The third curve describes a scenario in which the rapid pathway is superimposed on the slow pathway (in which cardiac and vascular AHF phenotypes are relatively intermixed) such as when a patient with the cardiac phenotype is afflicted by an acute AHF precipitant (infection, hypoxia from other disease, ischemia, etc) activating rapid fluid shifts superimposed on an already chronically reduced splanchnic buffering capacity.

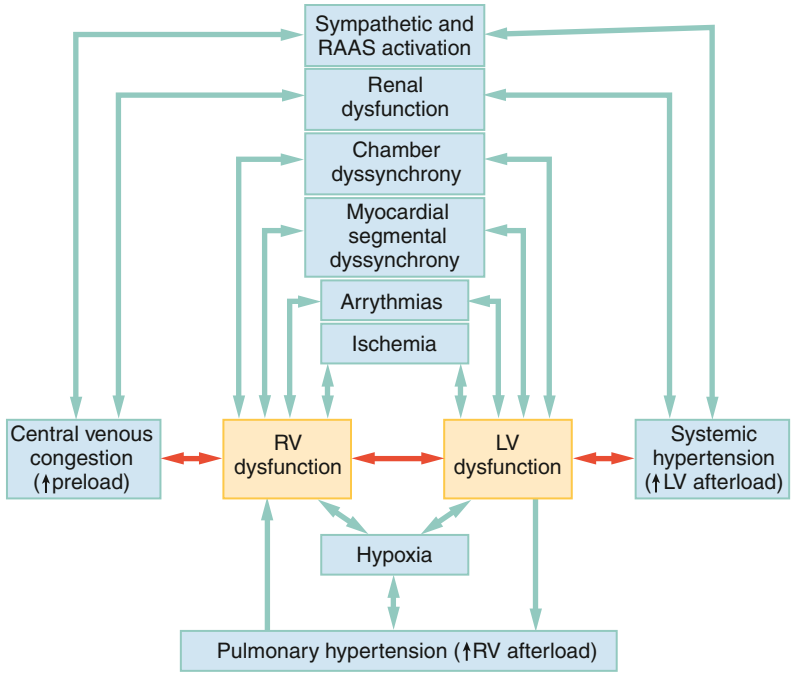


Fig. 67.8 A physiologic flow diagram of the biventricular nature of AHF. Although LVD has long been the focus of an understanding of AHF, it is now recognized that RVD is common, indicates severity of presentation, and predicts poor prognosis. Because both ventricles share (on average, beat to beat) a CO and a wall (ie, the intraventricular septum), forces affecting the RV affect the LV (and vice versa). RV and LV stroke work, however, is not inherently equal and it has been shown that improvement of the former in response to AHF treatment is associated with better outcomes than improvement in the latter. Disorganization of contraction, ischemia, volume overload, acute ventricular-vascular decoupling, or other insults in one ventricle are transmitted to the other ventricle through complex and somewhat unpredictable ways. LVD causing PHTN and subsequent RVD (the classic understanding of "right heart failure") is only one of many ways that RVD develops in AHF (ie, PHTN is neither necessary nor sufficient to produce acute RVD in AHF patients). *AHF*, acute heart failure; *LV*, left ventricle dysfunction; *RVD*, right ventricle; *LVD/RVD*, LV/RV dysfunction; *CO*, cardiac output; *RAAS*, renin-angiotensin-aldosterone-system; *PHTN*, pulmonary hypertension.

(Fig. 67.9A). Thus, vasodilators may even be beneficial in hypertensive/vascular AHF.[64]

Other Factors

Anemia is common in chronic HF and AHF, but represents a true decrease in red blood cell mass (RBCM) only 40% to 75% of the time.[4,5] Thus, outside of severe and life-threatening hemorrhage, transfusion of red blood cells in HF is rarely indicated.

Other factors that are germane to the ED assessment and management of AHF include valvular disease, specific cardiomyopathies, arrhythmias, pericardial disease, high-output heart failure states, and circulatory shunts. These topics are covered in greater depth elsewhere in this text.

CLINICAL FEATURES

History and Physical Exam

The most common symptom in AHF is dyspnea, present in approximately 93% of cases[3,34]; other "classic" HF symptoms are less reliably present (eg, orthopnea in 33%; paroxysmal nocturnal dyspnea in only 15%). A careful history should be obtained because patients may describe dyspnea differently, such as fatigue with exertion rather than shortness of breath. Inquiring about exertional tolerance, weight gain or swelling, syncope or presyncope, chest pain, and increases or decreases in urine output can provide important clues. The duration and rapidity of symptoms are also important, because rapid and severe onset may be indicative of the lower-risk vascular phenotype, as compared to the slow and progressive course of the cardiac phenotype.[34] The presence of a prior diagnosis of HF should be determined, as well as the patient's current medications, any recent changes, and current medication adherence. Inquiry regarding recent increases in diuretic dosing or decreased urine output may raise suspicion for acute CRS. Implanted devices, including a pacemaker, automatic implantable cardioverter-defibrillator (AICD), or implantable pulmonary artery monitor, should be identified in case they need to be interrogated. Comorbidities should be elicited, including an assessment of relative compensation, with particular attention to risk factors such as AMI, CAD, and hypertension.

The most common physical exam sign is peripheral edema (74%).[3] Other findings include jugular venous distention, rales on chest auscultation, the presence of an S3 gallop, or any murmurs. Close attention to vital signs is of particular importance, especially blood pressure and heart rate. Treatment differs significantly among hypertensive, normotensive, and hypotensive AHF presentations. The presence and degree of hypoxemia and any signs of increased work of breathing guide the need for respiratory support. Note any fevers, because infection is both

TABLE 67.1 Ischemic and Nonischemic Causes of cTn Elevation in AHF

Classification	Mechanism(s)	cTn >99th Percentile	Clinical Evidence of Ischemia[a]	Management
Type I MI	Acute thrombosis in epicardial coronary artery (eg, LAD, LCX, LM, RCA or major proximal branches)	Yes	Yes	PCI
Type II MI	Supply and demand mismatch of myocardial oxygenation May occur with obstructive (≥50%) CAD, nonobstructive CAD (<50%), or no CAD	Yes	Yes	1. Optimize myocardial oxygenation: • Address precipitants of O_2 supply/demand mismatch (eg, infection, tachydysrhythmia, hypoxia, vasoconstriction/HTN, etc.) • Directed therapy to ↓ intracardiac pressures (optimize preload, afterload, contractile synchrony with IV diuresis, NPPV, or vasodilators) 2. Consider PCI on urgent basis when optimized if CAD present
Acute Myocardial Injury	Stretch-related injury • Inflammatory or neurohormonal cell toxicity • Cytosolic cTn mobilization	+/-	Uncommon without concomitant MI (type I or type II)	1. Optimize AHF therapies, per clinical condition 2. Consider further investigation for MI if troponin rising despite optimal AHF therapy
Chronic Myocardial Injury	• Structural heart disease (myocardial scar, hibernating myocardium) • CKD	+/–	Uncommon without concomitant MI (type I or type II)	1. Obtain serial cTn to rule out acute injury or ischemia • By definition, troponin level must be stable (≤20% variation from known baseline or prior serial value) to be considered chronic injury 2. Consider acute injury/ischemia if no clinical history to suggest structural cardiac disease or CKD

[a]Defined as more than 1 of the following being present: (1) New ischemic ECG changes, (2) anginal S/Sx's other than dyspnea, (3) pathologic Q waves, (4) new regional wall motion abnormality on imaging (eg, cardiac US).

a common precipitant and poor prognostic factor.[2] Tachycardia may be chronotropic compensation for severe cardiac insufficiency (see Fig. 67.5). Rhythm is similarly important, and atrial fibrillation (AF) with a rapid ventricular response is the most common arrhythmia precipitating AHF.[2]

Unfortunately, virtually no sign or symptom is sufficiently sensitive or specific to make the diagnosis of AHF in isolation (Table 67.2).[32] Physician accuracy in predicting congestion based on physical exam features is also poor (area under receiver operating curve = 0.53).[65] Notably, many physical exam findings for HF, such as peripheral edema and weight gain, are proxies of chronic fluid overload and may not be present in up to half of patients with AHF. Although the combination of signs and symptoms may slightly improve diagnostic certainty, the diagnostic accuracy of emergency physician gestalt is approximately 74% overall.[29,66]

Precipitants

In addition to identifying signs and symptoms, consideration of precipitants for the current AHF episode is important for several reasons.[67] First, acute decompensation is often too quickly attributed to medication and dietary nonadherence, and premature closure on noncompliance as a precipitant can negatively affect patients.[28] Medication nonadherence as an isolated precipitant accounted for only 3.8% of AHF cases in a recent analysis of a large European and Asian registry, and contributed to only 14.1% of cases in a North American registry.[2] Second, the most common precipitants, including ischemia, infection, and arrhythmias, require etiology-specific therapies outside of general HF management. Third, certain precipitants in an AHF episode are associated with a low risk of in-hospital and short-term mortality (hypertension, nonadherence, arrhythmia) compared to others with a higher risk (ischemia, infection, cardiorenal dysfunction). Finally, AHF readmissions within 30 days are high at approximately 20%, yet in most cases, AHF is not the primary diagnosis.[10,29] Rather, common reasons for early readmission mirror some of the most commonly identified precipitants (infection, ACS, renal dysfunction, arrhythmia, etc.), some of which may have been present but unidentified at the index ED visit. However, in up to half of AHF cases, a clear precipitant may never be identified even after retrospective review.[2]

ACS is a particularly important example; it is among the most common precipitants of both AHF and 30-day readmissions and carries a significantly worse prognosis compared to other etiologies.[2] Nevertheless, ACS is significantly underdiagnosed and treated in AHF patients.[67] A thorough assessment of ischemic risk using cTn, electrocardiography (ECG), and clinical history should be undertaken in AHF presentations (see Table 67.1), particularly in those that have not had a prior evaluation for underlying CAD.

DIFFERENTIAL DIAGNOSIS

Common and important differential diagnoses are listed in Box 67.1. Some conditions may coexist with AHF or be a precipitant of AHF. This makes diagnosis more complicated, because ruling in AHF often does not rule out concurrent contributions from other conditions. The converse is also true: ruling in many differentials does not rule out AHF. Thus, rather than taking an "either/or" approach to the AHF differential, it is more useful clinically to determine if AHF is a component of a patient's presentation while also identifying other potentially coexisting diagnoses.

An illustrative example is the relationship between AHF, acute infections, and obstructive airway disease. Wheezing on exam in the ED does not significantly change the likelihood of AHF as a diagnosis compared to COPD, and the likely explanations are myriad.[32] First,

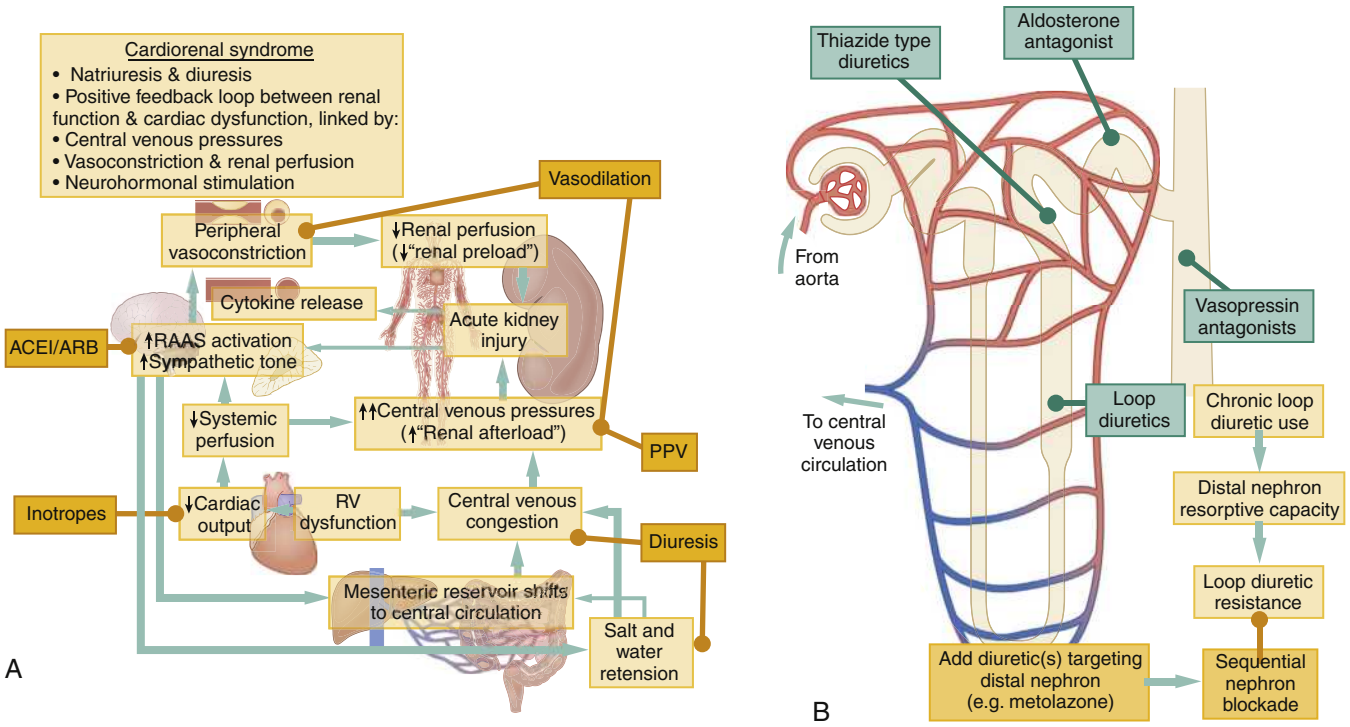


Fig. 67.9 (A) Flow diagram of mechanisms and therapeutic targets in the acute cardiorenal syndrome (CRS type 1) which complicates up to 40% of AHF presentations and predicts increased rehospitalization, mortality, and resistance to IV loop diuretics. Complex factors converge on two primary mechanisms causing CRS: venous hypertension from central circulation congestion and peripheral vasoconstriction limiting arterial flow to the kidneys. A decreased CO has generally been found to not independently correlate with CRS (possibly because autoregulation maintains renal blood flow in most circumstances short of overt cardiogenic shock). This is contrary to classic teaching and has important clinical relevance. Namely, administration of high-dose IV diuretics and IV vasodilators is generally safe in the CRS, potentially provides benefit, and any acute rise in creatinine that may be seen after administration of these drugs is unlikely to be representative of a true AKI. (B) Schematic of mechanisms and treatment targets in loop diuretic resistance, which can occur rapidly with the initiation of new loop diuretics, chronic loop diuretic use, or acute CRS. Diuretic resistance is a poor prognostic factor in AHF, and occurs at least partly due to the downregulation of molecular targets for diuretics in the loop of Henle. To bypass this, one clinical strategy is to simply give an IV loop diuretic dose in the higher range of recommended (see Fig. 67.13). Another, sometimes referred to as the "sequential nephron blockade," is to add a non-loop diuretic to be coadministered (eg, thiazide-type such as metolazone, or AVP antagonist such as tolvaptan) with the IV loop diuretic. *CRS*, cardiorenal syndrome; *CO*, cardiac output; *AKI*, acute kidney injury; *AVP*, arginine vasopressin; *RAAS*, renin-angiotensin-aldosterone system.

39% of AHF patients in the United States have comorbid COPD or asthma.[3] Second, self-report of COPD history is unreliable. One-third of HF patients who report COPD history have no evidence of it on pulmonary function testing (PFT), while as many as two-thirds of who report no COPD history do have PFT evidence of obstructive physiology.[68] Third, the most common precipitant of COPD exacerbation, infection, is also among the most common precipitants of AHF, and hypoxemia caused by either condition can further exacerbate both. Finally, up to a quarter of HF patients may develop obstructive airway physiology from the HF itself.[68] Empiric corticosteroids for presumed COPD exacerbation in which COPD is not present, but AHF is, does not increase 90-day mortality or AHF rehospitalization.[69] Data on the effects of adrenergic or anticholinergic nebulized therapy in AHF patients treated for COPD are lacking.

DIAGNOSTIC TESTING

Electrocardiogram

No ECG findings have a high sensitivity and specificity for AHF diagnosis (see Table 67.2).[32] Nevertheless, the ECG is a critical test because of the need to screen for signs of ischemia and arrhythmias, two of the most common precipitants of AHF.[2] Additional useful information may include signs of electrolyte disturbance or presence of a pacemaker.

Chest Radiography

Chest x-ray (CXR) has long been a mainstay of AHF diagnosis and management. The presence of pulmonary edema, cephalization, or Kerley B-lines strongly suggests a AHF diagnosis in the context of undifferentiated dyspnea (Table 67.2).[32] Unfortunately, the sensitivity of CXR to identify AHF is poor, with cardiomegaly serving as the most reliable finding (74.7% sensitive, negative likelihood ratio 0.43), followed by the presence of pulmonary edema (56.9% sensitive, negative likelihood ratio 0.48). Therefore, a normal CXR will not rule out the diagnosis of AHF unless the pretest probability is extremely low (Fig. 67.10A–C). CXR plus physician gestalt has an area under the receiver operating curve (AUROC) of only 0.62 compared to a reference standard of Doppler echocardiography in determining whether elevated cardiac filling pressures are present.[65] Nevertheless, CXR remains a useful and essential part of the AHF evaluation because it is accessible, inexpensive, relatively quick to perform, has high positive predictive value, and helps assess common differentials.

TABLE 67.2 Characteristics of History, Physical Examination, and Test Results for AHF Diagnosis in ED Patients with Dyspnea

Historical Feature	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Orthopnea	52.1%	70.5%	1.9	0.74
PND	46.2%	73.9%	1.6	0.79
Dyspnea at rest	54.6%	49.6%	1.1	0.88
Exertional dyspnea	82.4%	36.6%	1.3	0.48
No productive cough	82.0%	25.8%	1.1	0.6
Hx of HF	55.5%	80.2%	2.7	0.58
No Hx of COPD	78.9%	34.1%	1.2	0.7
Hx of CKD	32.0%	91.4%	3.4	0.75
Physical Exam				
Rales on auscultation	62.3%	68.1%	1.8	0.6
Wheeze on auscultation	22.3%	64.0%	0.6	1.8
S3	12.7%	97.7%	4	0.91
JVD	37.2%	87.0%	2.8	0.76
Hepatojugular reflux	14.1%	93.4%	2.2	0.91
Leg edema	51.9%	75.2%	1.9	0.68
ECG				
Ischemic changes	34.0%	84.2%	2.9	0.78
Atrial fibrillation	20.5%	89.9%	2.2	0.88
Normal sinus rhythm	55.4%	17.8%	0.7	2.88
CXR				
Interstitial edema	31.1%	95.1%	6.4	0.73
Alveolar edema	5.7%	98.9%	5.3	0.95
Any pulmonary edema	56.9%	89.2%	4.8	0.48
Cephalization	44.7%	94.6%	5.6	0.53
Cardiomegaly	74.7%	61.7%	2.3	0.43
Kerley B lines	9.2%	98.8%	6.5	0.88
Natriuretic Peptides				
BNP > 100	93.5%	52.9%	2.2	0.11
BNP > 500	67.7%	89.8%	9.1	0.34
NT-proBNP > 300	90.4%	38.2%	1.8	0.09
NT-proBNP > 1550	75.5%	72.9%	3.1	0.32
NT-proBNP > 450, Age < 50	85.7%	93.9%	14	0.15
NT-proBNP > 900, Age 50–75	79.3%	84.0%	5	0.25
NT-proBNP > 1800, Age > 75	75.9%	75.0%	3	0.32
Point of Care Ultrasound				
6-8 point B-line LUS Scan	85.3%	92.7%	7.4	0.16
Restrictive E/A Pattern	81.5%	90.6%	8.3	0.21
Reduced EF	80.6%	80.6%	4.1	0.24

BOX 67.1 Common and Important Differential Diagnoses for AHF

Pneumonia
Acute exacerbation of COPD or asthma
Acute coronary syndrome
Unstable tachy- or brady-arrhythmia
Acute respiratory distress syndrome (ARDS)
Aspiration pneumonitis
Severe anemia presenting with exertional dyspnea and fatigue
Acute renal failure with fluid overload ("acute renocardiac syndrome", ie, cardiorenal syndrome type 3)
Severe metabolic acidosis or toxicologic phenomena presenting as respiratory distress
Noncardiac causes of peripheral edema (eg, cirrhosis, amlodipine, peripheral venous insufficiency, nephrotic syndrome, venous thrombosis, etc.)
Pulmonary embolus
Pneumothorax
COVID-19

Laboratory Testing

Important laboratory tests to consider in the ED assessment of suspected AHF include a complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine, glucose, thyroid stimulating hormone (TSH), BNP or NT-proBNP, and cTn.[1,53,67]

A CBC helps to evaluate for evidence of infection and anemia, though anemia in HF is multifactorial and heterogeneous in terms of any actual reduction in RBCM.[4,5,70] Hemoglobin concentration may also provide clues to volume status, especially if changes are evaluated in the context of baseline information, as well as prognostic information. Electrolytes are helpful because disturbances are common and may portend a worse prognosis. Hyponatremia is a significant predictor of all-cause mortality in AHF, and hyponatremia may be related to the degree of sonographic RVD in AHF, with RVD having a strong independent association with mortality.[43] Setting a baseline is important as well, because a rise in serum sodium by day 3 of hospitalization compared to the ED value is suggestive of a 43% lower risk of death, rehospitalization, or transplant at 6 months.[46]

Although TSH is recommended if not previously known,[1,28] the yield of this test in the ED for AHF is relatively unknown. A recent study found that low levels of T3 (<2.3 pg/mL) predicted an 8.5% absolute risk increase in mechanical ventilation, 4 days longer length of hospital stay, and a 14.9% absolute increase in ICU admission.[71] If available promptly, T3 may be reasonable for risk stratification.

cTn should be obtained on ED arrival and trended if elevated or when clinical suspicion of ACS is present. The value, trend, and clinical picture, along with ECG findings, may help distinguish between myocardial ischemia and injury in AHF (see Table 67.1). In HFpEF with AHF, an elevated cTn is associated with a doubling of in-hospital mortality and an increase in 30-day mortality (4.8% vs. 0.6%).[50,57,72] Serial values are important, and increases or decreases correspond to worsened or improved prognosis, respectively.[51,73]

The potential for hs-cTn to identify low-risk AHF patients is still unclear. In one recent multicenter US study, patients with 0- and 3-hour hs-cTnT levels greater than the 99th percentile in the ED did not have a statistically significant lower odds ratio for the primary outcome of 90-day death, hospitalization, or ED revisit.[48] Nevertheless, no patient with serial hs-cTnT levels less than the 99th percentile died within 90 days. A low overall mortality in the cohort (2.7% at 30 days) may have contributed to neutral findings.

Natriuretic peptides have been given a class I recommendation for early AHF diagnosis by the AHA and ESC.[1,67] The two molecules, BNP and NT-proBNP, are related by a common pathway, though clinical assays pick up not only the primary molecule in each but also several precursors and metabolites.[26] As such, there is not a direct one-to-one comparison between the two clinical assays, though in general, both follow similar kinetics and clinical ramifications for their given cutoffs (see Table 67.2). In ED patients with dyspnea, a low level (BNP < 100 ng/L or NT-proBNP < 300 ng/L) is among the strongest tests to rule out the diagnosis of AHF. At high levels (BNP > 500 ng/L or NT-proBNP > 1550 ng/L), AHF is strongly supported though not necessarily confirmed. Intermediate levels (BNP 100–500 ng/L, NT-proBNP 300–1550 ng/L) do less to change pretest probability. Overall, when used by binary or tertile cutoffs, natriuretic peptides are most useful diagnostically when pretest probability is the indeterminate range (20% to 80%) (see Fig. 67.10). Additionally, common causes of elevated NPs in the absence of AHF include several differential diagnoses for AHF, including pulmonary embolus, COPD, and pneumonia, as well as many common HF comorbidities, such as CKD, hypertension, PHTN, AF, and advanced age. Given this, care must be taken in interpreting values. It may be useful to compare values to a known prior, though evidence-based cutoffs for "delta" BNP or NT-proBNP are lacking.

Caveats to NP measurement can impact clinical interpretation. Obesity and CKD both affect NP clearance, and their presence either decreases (obesity) or increases (CKD) NP concentrations. As a general rule, the NP concentration should be doubled when measured in an obese patient or halved when measured in a CKD patient. Although the effect of these comorbidities on BNP and NT-proBNP are relatively equal, the same cannot be said for patients on sacubitril-valsartan, which inhibits neprilysin resulting in diminished BNP degradation and increased concentrations. As a result, patients on this drug combination will have higher BNP levels; however, since sacubitril-valsartan is used exclusively in those with chronic HF, this should not affect the diagnostic utility of BNP in the ED. Because NPs are also used for tracking of treatment effectiveness and prognostic purposes, NT-proBNP, which is not altered by sacubitril-valsartan, has become the preferred biomarker in some institutions where the drug combination is commonly prescribed.

The use of NPs as a continuous variable or with interval likelihood ratios has much higher diagnostic utility than as a binary result (see Fig. 67.10D). The recently validated GASP4Ar mathematical model, which includes only age, EP pretest probability, and NT-proBNP concentration, has strong diagnostic utility for AHF in an undifferentiated ED population, with an AUROC of 0.93.[66] Age-adjusted cutoffs have also recently been derived for NT-proBNP, using simplified binary cutoffs while adjusting for a major confounder.[74] The age-adjusted cutoffs improve positive predictive value but reduce the negative predictive value (see Table 67.2). Additionally, the performance of test characteristics overall declines for each increasing age bracket, with age less than 50 years cutoff performing markedly better than the 50 to 75 or greater than 75 years cutoffs (both in terms of positive and negative predictive values).

Finally, as a prognostic factor in AHF, evidence for natriuretic peptides is mixed. Generally speaking, higher levels of BNP and NT-proBNP have been shown to portend worse outcomes,[53,54] though the utility for predicting short to intermediate (e.g., 30–90 day) outcomes from the ED is less clear. NPs have been included in some ED-based disposition decision instruments,[75] and serial measurement has been evaluated throughout a hospital stay to predict need for escalated treatment and readiness for discharge, albeit with no effect on outcomes.[76,77]

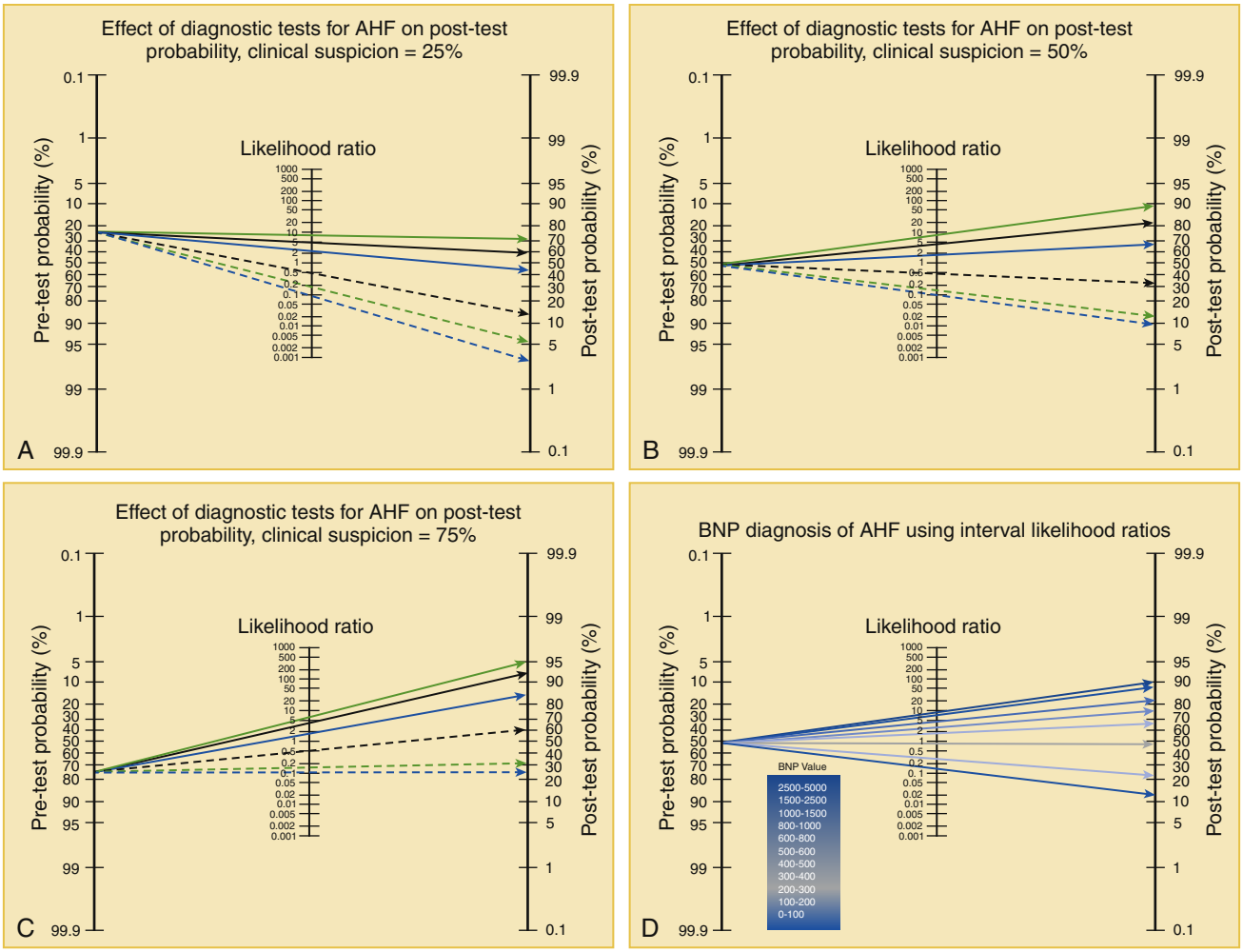


Fig. 67.10 (A–C) Comparative Fagan nomograms illustrating the diagnostic utility of CXR (*black line*), LUS (*green line*), and BNP when each of these tests is positive (*solid lines*) or negative (*dotted lines*) for a given level of clinical suspicion/pretest probability that a patient has AHF (pretest probability A = 25%, B = 50%, C = 75%). CXR, determined positive or negative by clinician or radiologist interpretation, is useful to rule in AHF when positive but ineffective at ruling it out across a wide range of pretest probabilities. BNP at the standard binary cutoff of 100 ng/dL is roughly the opposite: highly effective at ruling out AHF but poor-performing at ruling it in. LUS as an 8-point exam (two anterior and two lateral lung zones per hemithorax, positive if at least 1 lung zone on each side has ≥ 3 B-lines) provides a positive predictive value equal to or exceeding CXR as well as a negative predictive value similar to BNP and thus is the single most effective diagnostic test. LUS may also reduce time to AHF diagnosis (or alternative diagnosis) in the ED setting considerably. (D) Fagan nomogram of BNP distributed as a nonbinary test with interval likelihood ratios. BNP (and NT-proBNP) perform significantly better for "ruling-in" AHF when used as a nonbinary test where at the lowest levels AHF may still be ruled out, but at the highest levels AHF may now be effectively "ruled in" (and intermediate levels do little to change diagnostic suspicion either way). The arrows for each interval or BNP are shaded dark blue to light grey, where shades closer to the former are stronger evidence ruling in/out AHF and shades approaching the latter are more indeterminate results. *CXR*, chest x-ray; *LUS*, lung ultrasound; *BNP*, B-type natriuretic peptide; *NT-proBNP*, amino terminal pro-BNP; *AHF*, acute heart failure; *ED*, emergency department.

Lung Ultrasound

Perhaps the most useful ED-based diagnostic for AHF is lung ultrasound (LUS) (see Table 67.2, Fig. 67.10, and Fig. 67.11).[32,78,79] Lung US techniques and interpretation are well described in the literature.[80] An 8-point lung US exam is defined as viewing two anterior and two lateral intercostal spaces (ICS) in each hemithorax, with a scan considered positive if 3 or more B-lines are present in at least one ICS on each side (Fig. 67.11). This 8-point study maximizes sensitivity while providing a specificity equal to or greater than pulmonary edema on CXR.[32] Overall, the positive and negative likelihood ratios for LUS equal or outperform all other binary diagnostic tests.[32,78] Moreover, LUS speeds ED diagnosis without a loss of accuracy.[79,81] ED discharge change in B-lines, but not initial B-line count in the ED, are associated with higher 30-day death or AHF readmission.[36a,82] A randomized feasibility trial of LUS-guided decongestion showed that ED dosing of diuretics based on B-line count reduced pulmonary edema at 48 hours.[82a] Randomized studies designed to test patient-centered outcomes (i.e., use of LUS-guided therapy from ED arrival through discharge) are needed.

Echocardiography

POC echocardiography may also be used in clinical evaluation of AHF in the ED. The most familiar measure is a visual estimate of reduced versus

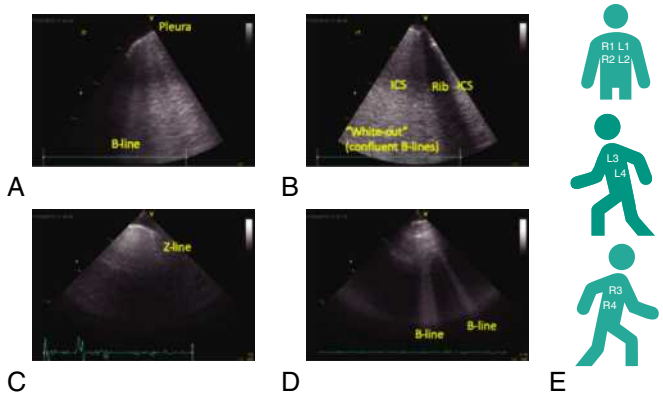


Fig. 67.11 LUS images in A and B are from the same patient prior to ED AHF treatment, and show single ICSs from the right and left hemithoraces, respectively. C and D are the same right and left ICSs on the same patient 72 hours later at hospital discharge. At least 3 B-lines (hyperechoic/bright stripes from pleura to >15 cm in depth) in at least one ICS space (eg, as in A) on each side are required for AHF diagnosis on an 8-point LUS exam. In cases where pulmonary edema is severe, B-lines may appear fused together so as to be indistinguishable (eg, US image B). In such cases of "white-out," counting B-lines is impossible but the number can be assumed to be greater than 3 for that ICS. In C, only a single "Z-line" (a hyperechoic line from the pleura that extends <15 cm and is nondiagnostic for increased lung water) remains as compared to A. In D, there remains at least 3 identifiable B-lines compared to image B, however given that ICS B had a full white-out appearance prior to ED treatment this still represents significant improvement. Panel E shows a diagram of positioning for the components of an 8-point LUS exam. Each hemithorax is divided into 4 quadrants (eg, R1–R4 on right, L1–L4 on left) from the posterior axial line to the sternum. Thus, two views on each side are on the anterior chest (R1–R2 or L1–L2) and two are lateral (R3–R4 or L3–L4). Images are typically obtained with the phased array or curvilinear US probe to achieve the depth required to differentiate B-lines from Z-lines (ie, >15 cm). This approach is the single best test to both rule in and rule out AHF in a dyspneic patient, and can significantly reduce time to diagnosis in the ED. *ICS*, intercostal space; *LUS*, lung ultrasound; *ED*, emergency department; *AHF*, acute heart failure.

preserved EF. However, except for patients with suspected de novo AHF, the utility of determining EF in the ED may be limited. Virtually all patients with chronic HF have a comprehensive echo at some point, and many will have recent echo data available.[28] There may be situations where a change in EF is suspected but, in isolation, this is unlikely to impact ED management. Further, looking at EF alone can be misleading given that nearly half of AHF presentations involve the HFpEF phenotype.[9] Adjusting for RVD and change in LUS congestion severity, LVEF adds virtually no risk-stratification value for 30-day death or AHF-rehospitalization (AUROC = 0.807 for RVD + LUS, 0.807 for RVD + LUS + LVEF).[36a]

As previously mentioned, the heart in HFrEF typically suffers from not only systolic but also diastolic dysfunction.[8,20] Systolic dysfunction in HFpEF may be less intuitive. The traditional definition of HFpEF versus HFrEF is based on two-dimensional echocardiographic (2D echo) EF, which does not accurately capture all forms of systolic dysfunction. Regional irregular or disorganized contraction can lead to the actual EF (ie, what would be measured by invasive volume measurement or 3D imaging) deviating from the EF on 2D echo. Thus, POC echo to determine the presence or absence of systolic dysfunction may not be accurate.

Strain imaging represents a potential adjunct to EF for assessing severity of dysfunction and response to ED treatment. Unlike EF,[3] 2D longitudinal strain on POC echo improves during a patient's AHF treatment in both HFrEF and HFpEF.[36] However, current availability and feasibility of POC echo strain values in the ED is limited to centers and physicians with advanced POC echo expertise.

The discovery that RVD is common in AHF and a strong predictor of numerous adverse AHF outcomes was made possible by improvements in US-based RV assessment over the past two decades. A tricuspid annulus systolic plane excursion (TAPSE) less than 17 mm is indicative of RVD, as are numerous other echo findings described elsewhere.[41,47,83-86] Thirty-day AHF rehospitalization or death is threefold higher for TAPSE <7mm on EP-performed US.[36a]

Although assessment of diastolic function is beyond the scope of most ED physicians, small studies suggest that it can be performed effectively by those with proper training.[32] A recent study tested a 3-minute POC echo protocol at ED arrival combining mitral flow velocity measures (E/e' >15) with lung US. The protocol had a reported 100% sensitivity (95% confidence interval [95% CI:] 91.4–100%) and 95.8% specificity (95% CI: 84.6–99.3%) with a 0.979 AUROC for the diagnosis of AHF.[87] Additionally, unlike EF, cardiac filling pressures, measured by the surrogate of mitral flow parameters, worsen on echo with the precipitation of AHF and improve with treatment. In another small study, a treatment strategy guided by E/e' greater than 15 from ED admission to hospital discharge led to greater decongestion despite a shorter hospital length of stay and lower 6-month mortality or rehospitalization.[88]

MANAGEMENT

Initial Evaluation

Figure 67.12 outlines a pathway for the initial and empiric management of AHF. The most critical initial consideration is whether the patient needs resuscitation for respiratory failure or shock. Signs and symptoms of respiratory failure or any significant increase in work of breathing should be treated with NPPV unless contraindicated. NPPV for the treatment of severe AHF reduces in-hospital mortality (number needed to treat [NNT] = 17), endotracheal intubation (NNT = 13), and does not appear to be associated with an increase in adverse events when compared to standard medical care.[89] If NPPV is contraindicated, but the patient requires immediate stabilization of respiratory failure, options include a trial of high-flow nasal cannula (HFNC) at 40 to 50 liters/minute or endotracheal intubation. The effectiveness of HFNC in AHF has not been sufficiently studied to make a strong recommendation regarding its use. Nevertheless, a randomized ED-based trial showed that HFNC may have benefits in a heterogeneous population with hypoxemic respiratory failure, and the adverse effects of HFNC are few.[90] Thus, it may be considered to prevent intubation, but only if NPPV is not an option. Intubation should be a last resort for the uncommon situation when NPPV has failed or is contraindicated.

Blood Pressure Considerations

Hypotension, with or without accompanying signs of shock, is uncommon in AHF (5–8%).[1] In patients with advanced chronic HF and severe functional impairment, a low BP may be optimal to minimize the resistance to forward flow. True cardiogenic shock (CS) is rare, but when present carries up to a 51% mortality.[91] The AHA and ESC have both proposed definitions of cardiogenic shock, with agreement that clinical and laboratory signs of hypoperfusion (eg, altered mental status, elevated serum lactate, oliguria, cold extremities) are needed for CS to be present. The ESC goes further by specifying an SBP < 90 mm Hg cutoff after adequate fluid resuscitation, while the AHA definition does not specify a blood pressure.[1,91]

For patients with low blood pressure absent true shock, routine use of inotropic agents or vasopressors is associated with worse outcomes and not recommended. When CS is present, ED management is aimed at two parallel goals: stabilizing measures and etiology-directed definitive treatment. Figure 67.13 outlines a strategy for both of these goals

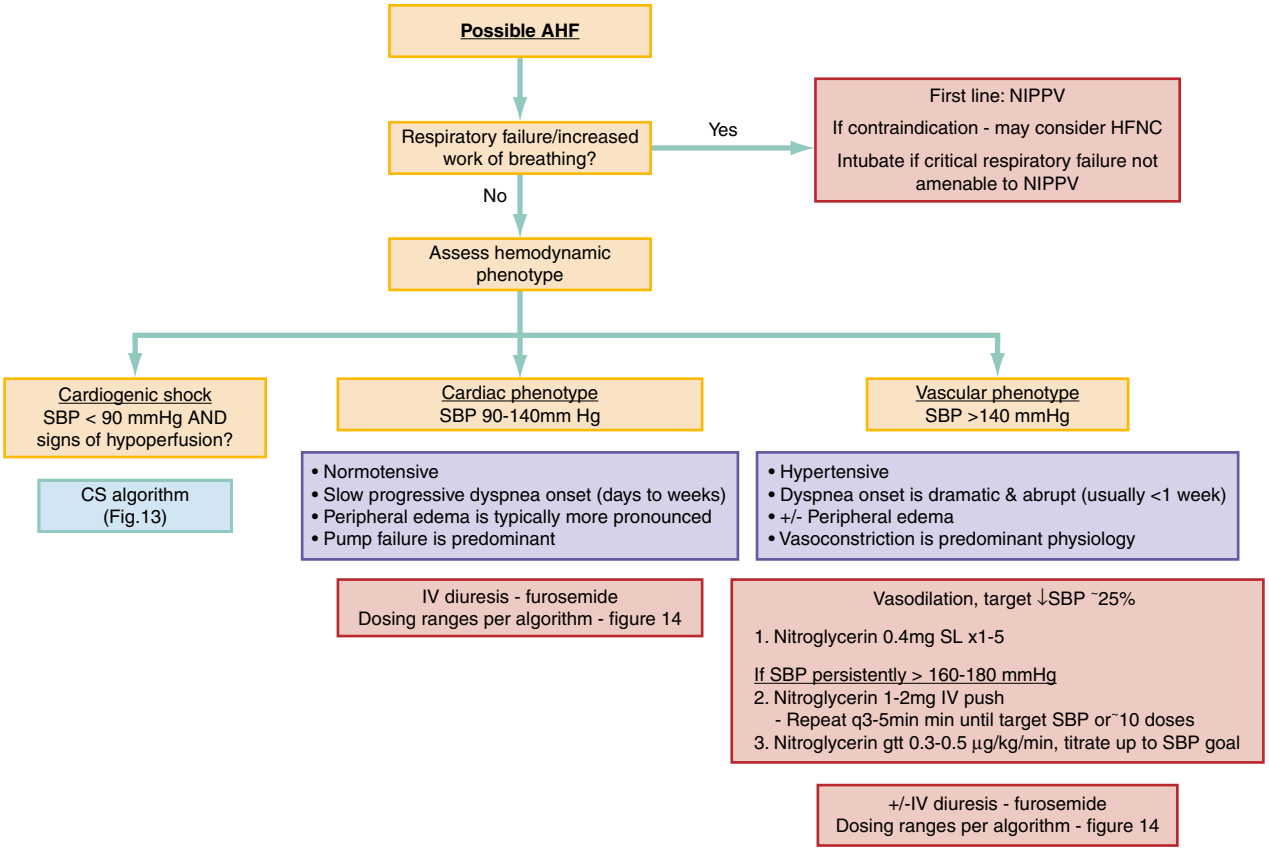


Fig. 67.12 Flowchart management algorithm for AHF in the ED. Respiratory failure is managed early with positive-pressure ventilation. Next, hemodynamic phenotype is assessed. Only a very small proportion of ED AHF patients will present in cardiogenic shock (see Fig. 67.13), and in general this diagnosis should rely on not only blood pressure but also careful assessment of physical signs and elimination of alternative (and more common) causes of shock (eg, septic, obstructive, hypovolemic). For the typical ED AHF patient (who does not show signs of shock), two alternative management strategies are considered, depending on whether the current presentation is predominantly the cardiac or the vascular AHF phenotype (ie, based on clinical history, vital signs, and judgement; see purple boxes). Although both phenotypes can coexist (eg, see Fig. 67.7B, third curve "rapid+slow pathway"), addressing the most highly suspected first and then reassessing the patient for clinical response may allow better discrimination and more targeted therapy because AHF presentations are extremely heterogenous. *AHF*, acute heart failure; *ED*, emergency department; *STEMI*, ST-elevation myocardial infarction; *NPPV*, noninvasive positive-pressure ventilation; *HFNC*, high-flow nasal cannula; *CS*, cardiogenic shock; *PCI*, percutaneous coronary intervention; *SBP*, systolic blood pressure; *MAP*, mean arterial pressure; *SL*, sublingual; *gtt*, continuous infusion.

in detail. Many CS patients need percutaneous coronary intervention, cardiac ICU care, cardiac surgery consultation, and/or mechanical circulatory support (please see Chapter 66). The AHA has proposed the concept of CS "Hub Hospitals" with these capabilities.[91] When such resources are not available at a receiving facility, CS patients should be transferred to an appropriate center as soon as possible. Traditionally, about 80% of CS has been due to STEMI, but in recent estimates, this proportion has been as low as 30%.[92,93] Improvements in PCI capabilities are hypothesized to have led to fewer CS cases due to STEMI, and more due to decompensation of end-stage advanced chronic heart failure (up to 60% of cases).[92] When STEMI is the cause, prompt PCI significantly improves mortality.[93]

In cases of CS not related to STEMI, 9% to 17% are due to mechanical cardiac complications, including papillary muscle rupture, ventricular septal rupture, or free wall rupture, in which prompt surgical intervention is key.[92] When decompensation of end-stage advanced chronic heart failure is the cause, chemical or mechanical circulatory support (eg, percutaneous VAD or intra-aortic balloon pump) may be needed to temporize until sustained hemodynamic recovery can be achieved.

While awaiting definitive treatment with PCI, if CS does not respond to small (250–500 mL) fluid boluses, norepinephrine is the first-line vasopressor therapy. A recent multicenter RCT of norepinephrine and epinephrine in CS showed that the former led to a lower incidence of refractory CS (NNT = 4) with fewer unfavorable effects on cardiac stroke work.[94]

Once the MAP is supported, pharmacologic support for CS involves pure inotropes, also known as inodilators for their effects on the systemic vascular resistance. These include dobutamine, milrinone, and levosimendan (not available in the United States). The degree of vasodilation varies among patients, because patients with extreme pump failure may already be maximally vasodilated in compensation for critically low CO.[93] We recommend titration of norepinephrine to mitigate hypotension from inotropes. All inotropes are associated with increased mortality in AHF, though causality is difficult to establish because only critically ill patients receive these drugs. Generally, inotropes should be initiated in CS for stabilization until definitive treatment or mechanical support can be arranged.[95-97] Many patients will require mechanical circulatory support, even temporarily, and thus urgent interventional cardiac surgery or

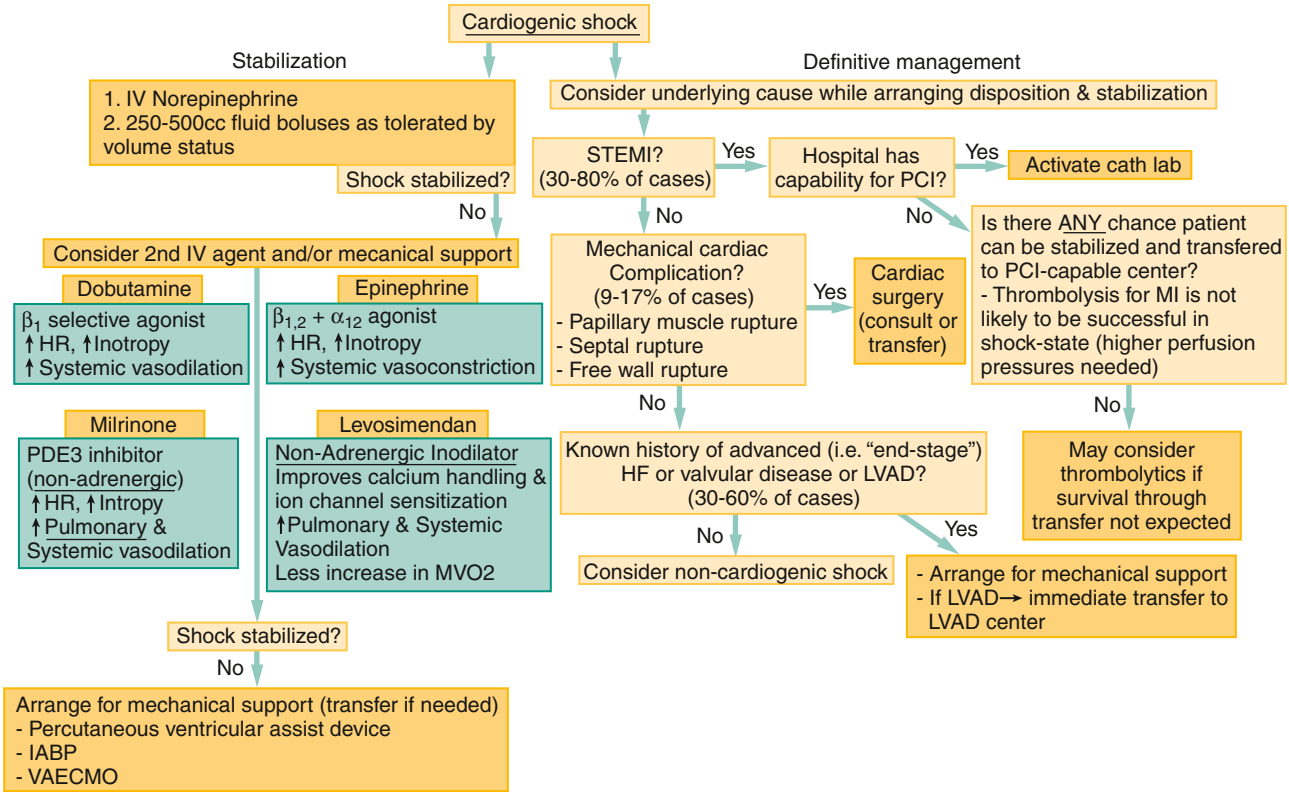


Fig. 67.13 Algorithm for management of CS. The algorithm focuses on two parallel goals: arranging for definitive management (right limb) and stabilization (left limb) until the patient can get there. In the absence of evidence for one of these three most common causes (STEMI, mechanical cardiac complication, or progression of end-stage/advanced pump failure), strong consideration should be given for the patient having an alternative type of shock (eg, distributive, hypovolemic, obstructive) since cardiogenic shock is very uncommon overall and is due to one of these three causes in as many as 99% of presentations. Because these three etiologies all potentially require advanced cardiac surgery or interventional cardiology techniques, definitive management will rarely be achieved in the ED. This means transfer to a center with the required resource for the given etiology (eg, PCI, CABG and valvular surgical capabilities, implantable temporary mechanical support, LVAD, cardiac transplant, IABP, ECMO) is required if not locally available and should be arranged as soon as possible while stabilizing the patient. Note also the wide estimates of prevalence among the three major causes of cardiogenic shock. This reflects apparent changes in etiologic trends over time. Specifically, STEMI as a cause of cardiogenic shock used to be by far the most common, but newer data suggest that PCI techniques and availability may have caused a decrease in STEMI-CS presentations. At the same time, advanced HF patients with near-end-stage disease may be becoming more common, as advanced HF cardiology has become a more robust discipline over time. *CS*, cardiogenic shock; *STEMI*, ST-elevation myocardial infarction; *ED*, emergency department; *HF*, heart failure; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *LVAD*, left ventricular assist device; *IABP*, intra-aortic balloon pump; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation; *PDE3 inhibitor*, phosphodiesterase-3 inhibitor.

interventional cardiology evaluation is indicated. Myosin activators (eg, omecamtiv mecarbil) are an investigational new class of agents that have shown promise in chronic HFrEF and may improve cardiac function in AHF, albeit with no effect on dyspnea or other outcomes.[98] The role of these medications in CS is to be determined.

The vast majority of patients in AHF presenting to the ED are normotensive (SBP 100–140 mm Hg) or hypertensive (SBP > 140 mm Hg). After addressing any further identified or suspected precipitants, the next decision point in AHF therapy is determining whether a vascular or cardiac phenotype predominates (see Fig. 67.12).[1] The vascular type tends to present with moderate to markedly elevated blood pressure (SBP > 160 mm Hg) and abrupt onset of symptoms, and often responds favorably to bolus IV vasodilator therapy even when presenting with severe respiratory distress (see Fig. 67.7B, first curve). In the cardiac type, blood pressure is often in the normal to moderately elevated range (SBP 100–160 mm Hg), onset tends to be subacute (often > 1 week), and symptoms are more likely to have a chronic component with fluid retention and peripheral edema (see Fig. 67.7B, second curve). An assessment to distinguish between the two early in the ED course can have significant impact for both treatment and risk stratification (see Fig. 67.12). Making this distinction can be difficult,[99] given that increases in cardiac filling pressure and lung water accumulation may begin weeks before AHF symptoms develop (see Fig. 67.7B). SBP has a roughly equal correlation with CO (r = 0.30) as it does vascular tone (r = 0.32) in ED AHF patients, while diastolic BP (DBP) has virtually no correlation to CO but a strong one with vascular tone (r = 0.587).[99a] As such, DBP elevation may help identify the vascular phenotype with even higher specificity than SBP.

Vascular Phenotype

In the vascular phenotype of AHF, IV vasodilators can provide rapid offloading of afterload, restore laminar arterial flow, and improve both myocardial oxygen supply and demand, while decreasing the work of

breathing.[96,97] Nitroglycerin provides both venous and arterial dilation at higher doses, providing preload and afterload reduction. In vascular phenotype patients with markedly elevated blood pressure, IV nitroglycerin delivered as a 1- to 2-mg bolus (repeated every 5 min as needed for symptom relief or until 25% SBP reduction) reduces ICU admission (48.4% versus 83% with usual care, NNT = 3), intubation (8.9% versus 16.9%, NNT=13), and hospital length of stay by 1.9 days.[100] The goal is rapid afterload reduction targeting a 25% decrease in SBP.[101,102] Continuous infusion of nitroglycerin may be started concomitantly to maintain blood pressure reduction after bolus therapy, but the continuous infusion in isolation is less efficacious than the bolus strategy.[100] Thus, if a continuous infusion is used as primary therapy, higher initial dosing (50–100 mcg/min) is recommended with up or down titration as needed. Sublingual (SL) nitroglycerin tablets or spray (400 mcg per dose) is rapidly absorbed and 100% bioavailable and may be considered an alternative, but multiple doses of SL nitroglycerin may be needed to achieve similar total dosing to the IV push/bolus strategy. Oral nitrate formulations have limited effectiveness in the ED setting[103] due to slow absorption, decreased bioavailability, and low peak serum concentration and are not recommended in the acute phase of care. Although IV sodium nitroprusside delivered by continuous infusion has historically been used for severe hypertensive AHF patients, it is cumbersome to administer, has the potential for unwanted side effects (eg, cyanide toxicity), and provides no benefit over aggressively dosed nitroglycerin therapy. As such, there is little reason to consider use of this agent.

In addition to IV nitroglycerin, IV enalaprilat (by bolus) may be used, though there is less ED-based evidence.[101] In one case series, enalaprilat given by IV bolus (0.625–1.25 mg repeated every 15 minutes up to 3.75 mg total) significantly reduced blood pressure in hypertensive AHF and was associated with improved respiratory status without adverse effects on renal function. However, data on other outcomes are lacking.[104] Large randomized trials involving other novel vasodilators such as serelaxin, ularitide, TRV027 (a biased ligand of angiotensin II receptor type 1), and nesiritide have shown them to be effective for symptom reduction but of no benefit for the in-hospital course of AHF or postdischarge outcomes including mortality and readmission.[96,105-107] Such data are consistent with systematic reviews of vasodilators in AHF, which show no mortality benefit with any agent including nitroglycerin.[101] Mortality in AHF has a strong inverse relationship with SBP, so reduction of mortality in this phenotype (with an already low risk) is less likely a feasible goal compared to reducing other adverse events like intubation.

To date, few vasodilator studies in AHF have enrolled patients upon ED arrival, making it difficult to know if the lack of benefit reflects specific drugs, timing of administration, or patient heterogeneity. Indeed, nearly all vasodilator studies have included mixed AHF patients rather than those with a hypertensive/vascular phenotype.[108] Importantly, adverse effects such as worsening or precipitation of acute cardiorenal syndrome, symptomatic hypotension, or precipitation of ischemia have not been demonstrated with IV vasodilator use even with large bolus doses of nitroglycerin as described.[100-102] Because vasodilators do result in rapid symptom improvement in respiratory status, a critical aspect of the vascular AHF phenotype,[109,110] they should be utilized early in the management of such patients. Of note, although morphine has historically been used in AHF for its theoretical vasodilatory properties, it increases the risk of respiratory depression and has been associated with higher mortality.[111,112] Given the existence of safer, more effective alternatives, morphine is no longer recommended for ED management of AHF.

Whether IV diuretics should be given in addition to vasodilator therapy depends on the presence or absence of concurrent fluid overload. In the vascular phenotype, central venous congestion occurs primarily due to fluid shifts alone (see Fig. 67.7B, first curve), and so diuresis can remove some of the acute preload and afterload by reducing central circulation congestion. Although there may be little harm in giving a single dose of IV diuretics, not all patients require diuresis.

Cardiac Phenotype

In the cardiac-predominant phenotype, intercompartmental fluid shifts remain important, but patients are more likely to have an increase in total body fluid volume, much of which may be retained in the splanchnic compartment and other reservoirs (see Fig. 67.7B, second and third curves). Thus, diuresis is a core component of ED management. Several days of diuresis may be needed to achieve adequate net fluid removal.[34]

Diuresis should generally involve an IV loop diuretic, with furosemide being the most commonly used. Furosemide by IV bolus is much more rapid-acting, and roughly twice as potent, as the oral formulation.[28,29] This provides rapid decongestion of the central circulation if the diuresis outpaces fluid redistribution from the splanchnic reservoir before the next dose of diuretic. Thus, both the initial dose and dosing interval are important (see Fig. 67.13). Unfortunately, diuresis and natriuresis decrease once an IV dose of loop diuretic has worn off. This process (the so-called "braking-phenomenon") starts within as little as 3 hours of bolus loop diuretic administration due in part to compensatory RAAS activation.[113] It is harder to overcome when diuretic use is chronic due to renal tubular remodeling that produces resistance to loop diuretics. With outpatient loop diuretic use or acute CRS, patients may have significant diuretic resistance on arrival to the ED. Diuretic efficiency (DE), or the amount of urine output per mg dose of diuretic per unit time, is highly associated with worsening heart failure after hospitalization, cardiorenal dysfunction, mortality, and other adverse AHF outcomes.[62,114-116]

Figure 67.13 describes a strategy for initial and possible repeat dosing of IV loop diuretics.[28,61,116] Loop diuretic–naïve patients should receive 40 to 80 mg based on current guidelines. When a patient takes PO loop diuretics at home, the IV dose should be at least 1x the home oral dose in furosemide equivalents (1 mg of bumetanide or 40 mg torsemide is considered equal to 40 mg of PO furosemide). Higher IV doses up to 2.5 times the home PO dose have been shown to be safe and may increase diuresis, though this approach yields no difference in mortality.[28] Continuous IV furosemide infusion, an alternative to bolus therapy, may increase total urine output over bolus therapy but does not improve mortality or hospital length of stay.[117]

No single definition of diuretic resistance has been validated in the ED. Nevertheless, in one ED-based study, a DE of less than 140 mL urine output per 40 mg of IV furosemide in the first 3 hours was associated with increased mortality.[116] While further ED-based studies are needed, these findings correlate with inpatient studies of diuretic resistance. Additionally, low natriuresis in the first hour (<35.4 mmol urine sodium) after ED administration of IV loop diuretic has been associated with worsening heart failure after hospitalization.[118,119] Close attention to urine output in the first 1 to 3 hours after an IV diuretic may allow identification of diuretic resistance and allow the ED clinician to more quickly implement an alternative strategy (Fig. 67.14). This strategy could include a repeated dose at a higher concentration, addition of a non-loop diuretic such as 5 to 10 mg of metolazone, or in the most refractory cases of oliguria, a consideration for ultrafiltration. None of these options has been shown to improve mortality when implemented in the ED, but may improve secondary outcomes such as rehospitalization or the rate of decongestion.[120-123]

Treatment initiation soon after arrival is important, and delays in administering IV diuresis from the ED have been associated with adverse outcomes. One large study found that giving IV furosemide in less than 60 minutes from ED arrival decreased in-hospital mortality for AHF (2.3% versus 6%, NNT = 28).[124] Another found that delays to ED diuresis were associated with an increased hospital length of

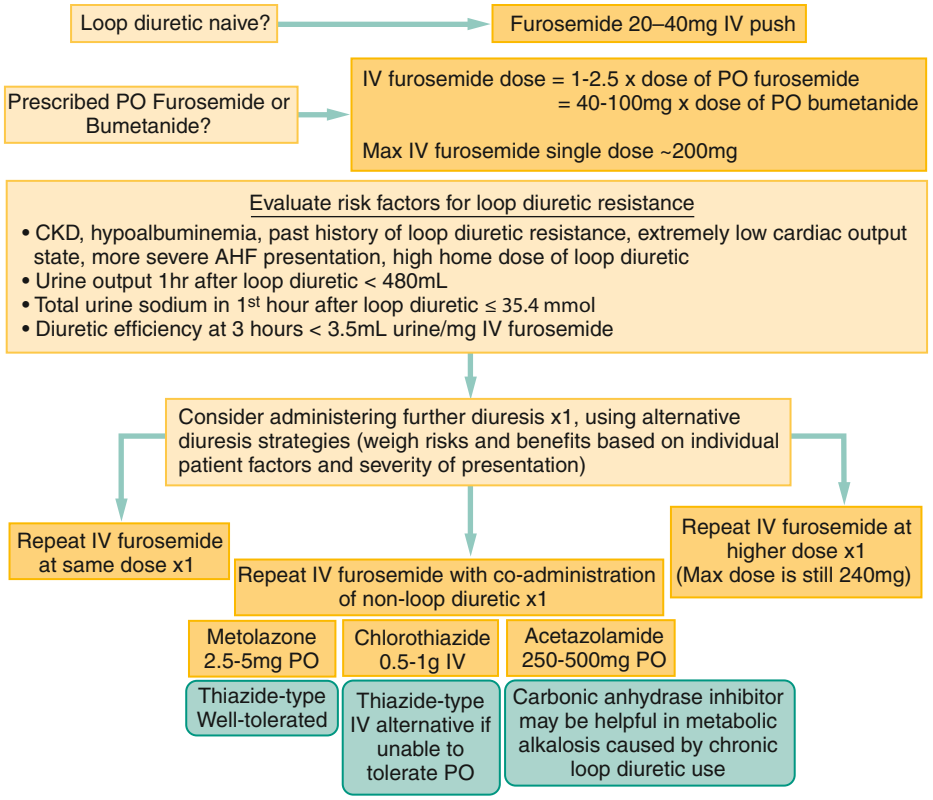


Fig. 67.14 Flowchart algorithm for determining initial IV diuretic dosing, including the management of diuretic resistance when observed or anticipated. IV furosemide, typically by bolus, is the mainstay of AHF treatment, and is preferred over PO treatment because of favorable pharmacokinetics/pharmacodynamics in the face of AHF physiology. IV bolus dosing more quickly offloads central circulation volume/pressure/congestion regardless of whether the patient is hypervolemic, euvolemic, or hypovolemic by clinical assessment of total body water (see Fig. 67.7), and is therefore recommended for both the cardiac and vascular AHF phenotypes (see Fig. 67.12). IV furosemide works over just 1 to 3 hours with a much higher peak concentration, which can help overcome diuretic resistance as well. However, a "braking phenomenon" exists where diuretic resistance can occur or worsen quickly after just a few high-dose IV administrations. Diuretic resistance may be anticipated or expected at time of ED presentation when the patient has a chronic high dose of PO loop diuretics, reports that they have worsening AHF symptoms despite increasing their home diuretic dose within the past few days to weeks, presents with signs of acute or chronic CRS, RVD or PHTN, or have severe baseline renal, cardiac, or hepatic disease. Reassessment after an initial IV furosemide dose in the ED may also suggest diuretic resistance, such as when observing a low diuretic efficiency (urine output/furosemide dose), low urine sodium in the first hour, or unexpectedly low urine output. When diuretic resistance is suspected or anticipated, consideration may be given to adjunct therapy (ie, concomitant non-loop diuretic for "sequential nephron blockade," see Fig. 67.10), using furosemide in doses on the higher end of recommended range (2–2.5 × PO dose), and/or repeat dosing. If concerned for fulminant renal failure (eg, total anuria, or failure of above strategies) arranging for ultrafiltration or renal replacement therapy may warrant consideration. *IV*, intravenous; *PO*, oral; *AHF*, acute heart failure; *ED*, emergency department; *CRS*, cardiorenal syndrome; *RVD*, right ventricular dysfunction; *PHTN*, pulmonary hypertension.

stay, especially among those of lower acuity on arrival.[125] There may be some hesitation to give IV diuresis early based on a fear of worsening a patient's renal function. However, numerous studies have found that increases in creatinine after IV diuresis for AHF are very rarely associated with renal tubular injury.[63,126] Instead, IV diuresis is shown to improve outcomes in acute CRS and AHF. Some trials have even shown paradoxically worsened outcomes when patients have small improvements in creatinine during hospitalization compared to those who have an initial (and transient) worsening in creatinine. This may be because central congestion and RVD play a leading role in the development of acute cardiorenal syndrome. Theoretically, the observed benefits with earlier diuresis could be mediated by an acute reduction of central venous congestion and offloading of the pressure-sensitive RV. Further studies are needed before recommending a specific time to diuretic target for all AHF patients, but current evidence suggests that patients may benefit from early diuresis even prior to lab results in the absence of clear contraindications.[64]

DISPOSITION

Hospital admission rates for AHF from the ED are high, exceeding 80% in the United States, yet as many as half of these may be unnecessary.[29,127] In Canada, ED discharge rates are markedly higher (~50%). The decision to admit a majority of AHF patients reflects both the difficulty in performing risk-stratification from the ED and the low tolerance for adverse outcomes. Emergency physicians tend to paradoxically predict high risk in the lowest-risk AHF patients.[128-130] The converse is also true, as EPs predict low mortality rates in the AHF patients who are actually at the highest risk. Numerous reasons may contribute: uncertainty in diagnosis, a lack of clinical practice

guidelines addressing ED disposition, misunderstanding of factors for low versus high risk in AHF, and others.[1,28,29]

Many studies have looked at ED risk factors for short-term outcomes that may inform disposition, several of which have been discussed throughout this chapter and are listed in Figure 67.15. There is stronger evidence for factors that predict high risk (eg, low blood pressure, elevated troponin, acute cardiorenal syndrome, diuretic resistance, RVD, advanced age, recent missed outpatient visits, number of comorbidities, etc.) than there is for low-risk factors that could predict appropriateness for discharge from the ED.[131-133] Figure 67.15 describes a potential pathway for ED risk-stratification based on assessing high to moderate risk factors that should prompt admission or observation. In the absence of any, consideration should be given to patient-level factors, including adherence to guideline-directed medical therapy, access to follow-up, and response to ED therapy, which could impact discharge appropriateness.

Multiple clinical decision rules (CDRs) have been developed for ED-based risk stratification of AHF. However, many lack external validation in a North American population,[75,134,135] were not derived in an ED population, or were found to perform suboptimally when applied to different populations.[136,137] The Emergency Heart Failure Mortality Risk Grade (EHMRG) is an exception in that it has both been externally validated and accurately predicts 7- and 30-day AHF mortality based on 10 routinely obtained ED clinical variables.[128,138] STRATIFY is another validated CDR, which predicts a ranked composite outcome of mortality and other serious adverse events (mechanical cardiac support, intubation, new or emergent dialysis, coronary intervention or MI) at 30 days. STRATIFY includes 13 clinical variables and demonstrated a negative predictive value of 98% at a risk threshold of 5% for the composite outcome. The use of any AHF CDR in a population other than the one in which it was validated is problematic because the regional heterogeneity of AHF is pronounced. For example, the Multiple Estimation of risk based on the Emergency department Spanish Score (MEESSI) CDR performs excellently for predicting AHF mortality in Spanish EDs where it was derived and validated initially. However, when applied in Switzerland, new cutoffs and calibrations were needed to produce similar results.[139]

Absent CS and a lack of availability of definitive care, few AHF patients need transfer. The exception is for LVAD or cardiac transplant patients, where early discussion with a patient's cardiologist regarding the need for transfer is indicated. If ACS is a possible precipitant and PCI is not available, transfer is appropriate. If ACS is considered (see Table 67.1) and PCI is locally available, cardiology consultation in the ED to discuss prompt PCI is warranted. Ischemic testing (eg, coronary catheterization, stress testing, myocardial perfusion imaging, etc.) is under-utilized in patients with AHF, particularly among de novo presentations and in HFpEF.[140,141] Early discussion with cardiology may facilitate ischemic testing, and AHF patients may have improved outcomes when cardiology is part of an inpatient multidisciplinary team. However, in the absence of these indications, routine consultation with cardiology is not needed during the ED course.[142-144]

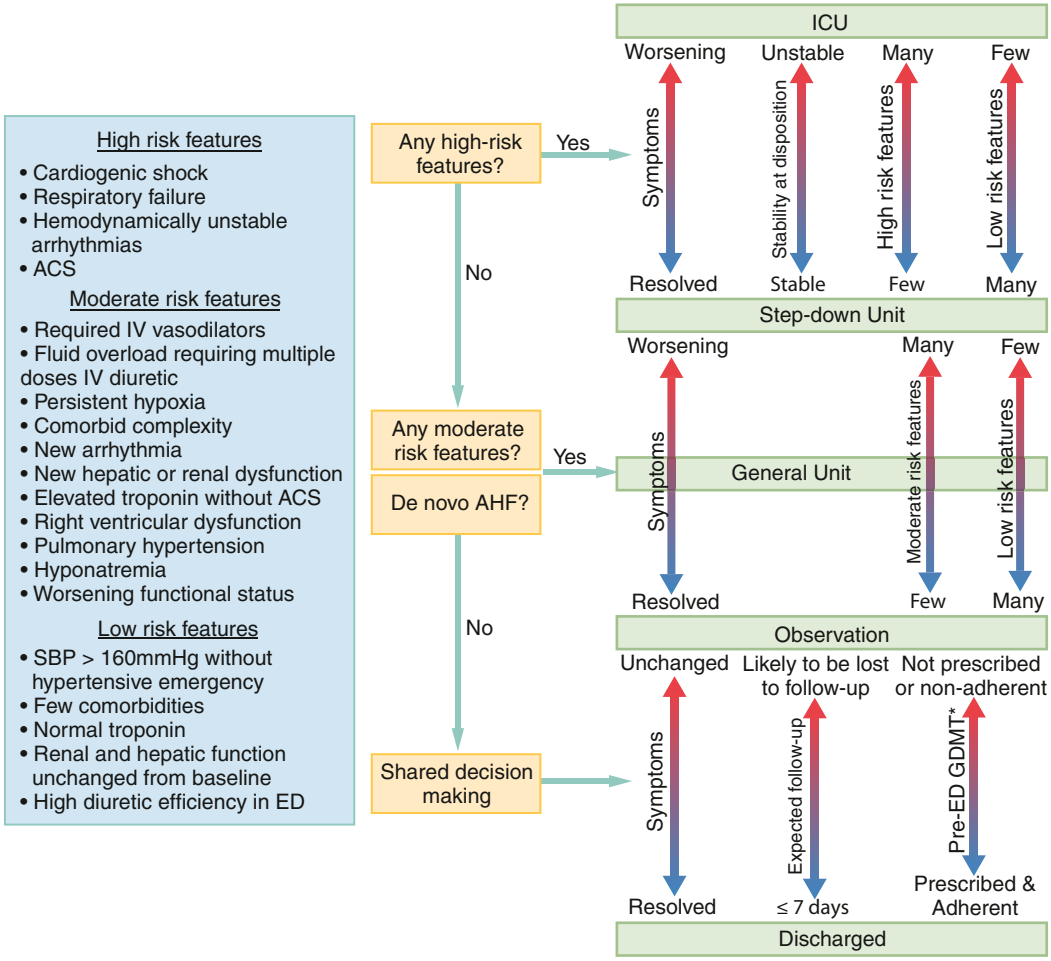
When a disposition decision for admission or observation is chosen, home medications should be reinitiated soon after stabilization. Altering or withholding guideline-directed medical therapies for HF during hospitalization is independently associated with increased mortality.[145] A failure to administer guideline-appropriate medical care occurs in over 10% of all AHF hospitalizations.[146]

The absence of high-risk features does not necessarily imply low risk. Thus, in patients without any high-risk features, 24-hour observation or "short-stay unit" disposition is a reasonable option.[127] Proposed criteria for observation appropriateness include SBP greater than 120 mm Hg, respiratory rate less than 32 breaths/min, BUN less than 40 mg/dL, creatinine less than 3.0 mg/dL, a lack of ischemic changes on ECG, and troponin less than the 99th percentile.[29] It should be noted that these criteria are based on an absence of high-risk factors, but validation is pending the results of a prospective multicenter North American trial currently underway.[127]

When a patient lacks any high or moderate risk criteria and discharge is considered, efforts should focus on improving symptoms with ED therapy, ensuring reliability of follow-up, and adherence to guideline-directed medical therapies (see Fig. 67.15).[28,29] Outpatient follow-up within a week of direct discharge from the ED is independently associated with a lower risk of 7-day mortality (relative risk of 0.17 for outpatient visits, 0.32 for email or phone follow-up).[147] Other risk factors for 7-day mortality among patients directly discharged from the ED include age 80 years or greater, baseline SBP less than 100 mm Hg, tachycardia, bradycardia, hypoxia on ED arrival, and hyperkalemia. Although mortality in the month following ED discharge is 3% to 4% overall, there does not appear to be significant differences in the daily rate of death across this timeframe.[147] This may suggest that once high-risk factors of a given ED AHF patient presentation have been ruled out, the remaining mortality risk is primarily based on intractable patient factors at baseline (eg, comorbidities, socioeconomic variables, severity of chronic HF, etc.). Conversely, rehospitalizations and repeat ED visits are far higher in the first 7 days, peaking at 2 days post-discharge, before leveling off during days 8 through 30 after discharge.

For patients with significant fluid overload, admission to the hospital rather than placement in observation status or a short-stay unit should be considered because prolonged diuresis may be needed. When AHF patients are admitted, not all require telemetry. Telemetry should be reserved for those with electrolyte abnormalities, evidence of myocardial injury, prior history or new onset of arrhythmia, or other conditions that predispose to altered electrical signaling in the heart. Likewise, intensive or cardiac care unit admissions should be reserved for those who require ventilatory support or use of IV vasoactive medication, recognizing that institution-specific guidelines may exist for the latter.

The references for this chapter can be found online at ExpertConsult.com.



*Guideline Directed Medical Therapy (GDMT)	
HFrEF	HFpEF
Beta blockers	Medical management of HTN and atrial fibrillation
ACE inhibitor or ARB or ARNI	
Aldosterone antagonist, if LVEF≤40% and eGFR>30	
Hydralazine-isosorbide dinitrate, if african american and NYHA Class III-IV	Loop diuretic, if signs/symptoms of congestion
Loop diuretic, if signs/symptoms of congestion	

Fig. 67.15 Disposition and risk stratification algorithm for ED AHF patients. The algorithm begins with ruling out the presence of moderate- to high-risk features, since the predictive value of these for ruling in a need for hospital admission is much better demonstrated than the value of low-risk features for determining who can be discharged from the ED. This difficulty in identifying low risk is a contributing factor to the fact that 80% of ED AHF patients are brought in to the hospital for admission or observation, but up to 50% of admissions are likely unnecessary. For the purposes of the algorithm, "high" versus "moderate" risk features both indicate a likely benefit to bringing the patient in to the hospital, with the difference being the relative level of care. High-risk features suggest consideration of ICU or step-down unit. Moderate-risk features support bringing the patient into the hospital, but potentially anywhere from observation to step-down depending on symptoms, the presence of low-risk features, and clinical response to ED therapy. De novo HF (ie, AHF without a previous diagnosis of chronic HF) should also prompt hospitalization in most cases, because such patients should undergo urgent evaluation for underlying causes of their HF, and initiation of GDMT. If a patient has no moderate- or high-risk features, history of HF is known, and there is no indication for transfer (eg, LVAD), they may be appropriate for direct ED discharge versus observation. Discharge is favored when the patient is prescribed appropriate GDMT, symptomatically improved with ED treatment (or had only mild/nonlimiting symptoms to begin with), and can obtain close outpatient follow-up (preferably within 1 week). Finally, this algorithm is meant to provide a suggested (and relatively conservative) framework rather than a definitive policy because no single risk-stratification approach is currently available to capture the heterogeneity of all AHF presentations seen in the ED. Thus, hospitalization versus discharge directly from ED may also be considered in the context of individual presentations, patient-specific goals/preferences, clinical judgment, and shared decision making when possible. *ED*, emergency department; *AHF*, acute heart failure; *ADHF*, acute decompensated heart failure; *ICU*, intensive care unit; *GDMT*, guideline-directed medical therapy; *PPV*, positive-pressure ventilation; *ACS*, acute coronary syndrome; *SBP*, systolic blood pressure; *AKI*, acute kidney injury; *CKD*, chronic kidney disease; *HFrEF*, HF with reduced ejection fraction; *HFpEF*, HF with preserved EF; *ACE inhibitor*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor-neprilysin inhibitor; *LVEF*, left ventricular ejection fraction; *eGFR*, estimated glomerular filtration rate; *HTN*, hypertension.

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CHAPTER 67: QUESTIONS AND ANSWERS

1. A 59-year-old female with a smoking history who has never been to the doctor before presents to the ED with 2 weeks of dyspnea and no known past medical history. Evaluation is notable for BNP 650, creatinine 1.5, wheezing on lung exam, CXR with cardiomegaly but no pulmonary edema, and LUS demonstrating more than 3 B-lines in 2 of 4 lung zones on each hemithorax. Which of the following is the most likely/appropriate diagnosis?
   a. Advanced chronic heart failure
   b. Acute decompensated heart failure
   c. Acute exacerbation of chronic obstructive pulmonary disease
   d. De novo acute heart failure

Answer: D. The patient presents with 3 or more B-lines in 2 of 4 lung zones on each hemithorax, which is highly specific for acute heart failure (AHF). Because the patient does not have a known past history of chronic heart failure, her more specific diagnosis is "de novo acute heart failure," and not "acute decompensated heart failure." "Advanced chronic heart failure" is a subset of chronic heart failure at the end stages of chronic pump dysfunction. Because the patient presented for unscheduled care due to heart failure (ie, true of essentially all patients presenting to the ED for HF symptoms, as opposed to a scheduled outpatient visit), this case is by definition acute heart failure and not chronic heart failure. Finally, although wheezes on exam may lead the clinician to think of COPD exacerbation, auscultated wheezing is common in AHF and neither sensitive nor specific (likelihood ratios positive and negative = 0.6, 1.8) enough to significantly inform a diagnosis of AHF versus COPD on its own.

2. A 68-year-old ED patient with a history of HFrEF presents with 3 weeks progressive edema and exertional dyspnea, pulmonary edema on portable CXR, respiratory rate 35, BP 128/67, and SpO_2 86% on room air. Last week his cardiologist increased his home dose of furosemide from 40 mg PO daily to 40 mg BID, with unchanged urine output and no improvement in symptoms. Which of the following is the best step in management?
   a. Nasal cannula oxygen, 160 mg IV push furosemide now
   b. Nasal cannula oxygen, 60 mg IV push furosemide only if creatinine is not elevated from baseline
   c. BiPAP, 160 mg IV push furosemide now
   d. BiPAP, 60 mg IV push furosemide only if creatinine is not elevated from baseline

Answer: C. This patient presents with hypoxia, tachypnea, and other signs of respiratory failure, and noninvasive positive-pressure ventilation (NPPV) such as CPAP or BiPAP should be the first-line resuscitative therapy. Although nasal cannula may sufficiently reverse the hypoxia, NPPV has beneficial effects on work of breathing and possibly on AHF hemodynamics. IV furosemide dosing should be 1 to 2.5 times the patient's daily home PO dose (or 40–80 mg IV if they do not take furosemide). Because this patient was recently increased to 80 mg, a dose of 80–200 mg IV would be possible. Additionally, since the change resulted in no change in symptoms at home, this would suggest the patient is experiencing some aspect of acute cardiorenal dysfunction, loop diuretic resistance, or both. Thus, a dose at the higher end of the acceptable range is likely advisable. Finally, elevations in creatinine due to acute cardiorenal syndrome are usually due to congestion, and if creatinine rises further after IV loop diuresis this typically represents a transient response not associated with long-term renal dysfunction. In other words, waiting for a creatinine level is not necessary in most cases, because worsening creatinine after furosemide rarely represents a true acute kidney injury. By contrast, delayed administration of furosemide in AHF is associated with adverse outcomes.

3. If the patient in the previous question instead had a BP of 200/125, and was diuretic naïve, which of the following would be the best management approach?
   a. BiPAP, nitroglycerin 1–2 mg IV push repeated until SBP 150 mm Hg, furosemide 40 mg IV push
   b. BiPAP, morphine 4 mg IV push, furosemide 40 mg IV push
   c. BiPAP, isosorbide mononitrate 60 mg PO, furosemide 40 mg PO
   d. BiPAP, nitroglycerin 1–2 mg IV push repeated until SBP <150, furosemide 40 mg PO

Answer: A. In this variation of question two, the patient is diuretic naïve and has features suspicious for the vascular phenotype of AHF. Furosemide should therefore be dosed at 40–80 mg IVP, and a 25% or less reduction in SBP should be targeted with repeated IV push nitroglycerin, 1–2 mg per dose. In patients with less distress or less severe hypertension who still show the vascular phenotype, sublingual nitroglycerin is a useful alternative because absorption and bioavailability are similar to IV. Transdermal and PO nitrates are not currently thought to be useful in AHF, by contrast, because of less favorable kinetics.

4. A 78-year-old patient presents to the ED with hypotension and acute respiratory failure. His daughter states he complained of severe crushing chest pain 7 days ago, but refused to go to the hospital. His ECG shows deep Q waves and T-wave inversions in the inferior leads without ST elevation, and harsh systolic murmur is heard on exam. What is the best next step in management?
   a. Dobutamine, consult cardiac surgery for mechanical hemodynamic support and repair of ruptured papillary muscle
   b. Dobutamine, consult interventional cardiology for PCI
   c. Norepinephrine, consult cardiac surgery for mechanical hemodynamic support and repair of ruptured papillary muscle
   d. Norepinephrine, consult interventional cardiology for PCI

Answer: C. This patient presents with cardiogenic shock, likely due to papillary muscle rupture given the murmur consistent with mitral regurgitation, and an ECG suggesting that a STEMI may have occurred several days ago. Surgical management is the definitive therapy. While arranging for surgical management, norepinephrine is the first-line vasoactive therapy for cardiogenic shock patients. Other inotropic and/or vasoactive medications such as epinephrine, dobutamine, milrinone, or levosimendan are reasonable second-line options.

5. In a patient with AHF and a history of HFrEF whose symptoms have resolved after a single dose of IV furosemide in the ED, which of the following profiles suggests the lowest risk to be discharged from the ED?
   a. No renal or hepatic dysfunction, takes no home medications
   b. SBP 165 mm Hg, compliant with home meds including carvedilol and sacubitril-valsartan
   c. Patient's PCP can see them for follow-up in 21 days from now
   d. No comorbidities, de novo presentation of AHF

CHAPTER 67: QUESTIONS AND ANSWERS—Cont'd

Answer: B. This patient who has resolution of or marked improvement in symptoms after initial ED treatment is a good candidate for discharge from the ED. In option A, a lack of acute renal or hepatic dysfunction would further increase the appropriateness for discharge, but having HFrEF the patient should be on a minimum of a beta-blocker and ACE/ARB/ARNI for guideline-directed medical therapy (GDMT). Discussion with the patient's physician to initiate these therapies and arrange close follow-up could be an appropriate strategy with answer A, but in answer B the patient is already on appropriate GDMT. Elevated BP in option B is also a sign of very low risk for morbidity and mortality. Patients who are able to follow up with their physician within 7 days of ED discharge after AHF therapy have significantly improved outcomes, so answer C is incorrect. Although option D would suggest a similarly low-risk presentation, with de novo AHF it is reasonable to keep a patient for further testing and evaluation for their cardiac dysfunction and its underlying etiology. Of final note, none of the answer options suggest a patient who necessarily requires a full hospital admission. A 24-hour-or-less observation stay would likely be appropriate for A,C, or D.

68

Pericardial and Myocardial Disease

Nicholas J. Jouriles

KEY CONCEPTS

- Pericarditis and myocarditis have chest pain, laboratory results, and ECG findings that can mimic acute myocardial infarction (AMI). When the diagnosis is not clear, early coronary angiography definitively identifies or excludes AMI.
- Acute pericarditis is treated with aspirin or nonsteroidal antiinflammatory drugs. Adding colchicine decreases the rate of recurrence.
- Cardiac tamponade presents many ways. Patients with dyspnea, distended neck veins, hypotension, and muffled heart sounds should have the diagnosis made by bedside ultrasound. Pericardiocentesis is therapeutic and may help establish the etiology.
- Myocarditis should be considered in any patient with viral illness symptoms and chest pain.
- Patients with newly diagnosed hypertrophic cardiomyopathy should avoid strenuous exertion until evaluated by a cardiologist. Beta-blockers are the mainstay of therapy; nitrates should be avoided.
- Dilated cardiomyopathy presents with symptoms of heart failure or rhythm disturbance.
- Many cardiomyopathies have genetic origins. Send patients for both cardiology and genetics follow-up.

MYOCARDIAL DISEASE

Cardiomyopathies are a heterogeneous group of diseases associated with myocyte injury, which leads to ventricular hypertrophy, fibrosis, or dilation. Clinical symptoms result from the underlying pathology.

Myocytes can be injured by genetic and nongenetic factors (Fig. 68.1). More than one thousand mutations in numerous genes have been identified as etiologies.[1] When injury occurs, pathophysiologic pathways are activated that include neurohumoral factors, immune factors, and cytokines. These cause myocyte dysfunction followed by remodeling, involving either hypertrophy or dilation. There is an increase in interstitial fibrosis, which impairs ventricular filling and leads to increased metabolic demand. At a cellular level, these may involve the troponin complex, intracellular concentration of calcium, myocardial subproteins, or the sarcomere. There is an alteration in the myocyte's ability to contract, and the electrophysiology is altered. The correlation between genotype, phenotype, nongenetic factors, and clinical presentation is not known.

Dilated Cardiomyopathy

Foundations

Dilated cardiomyopathy (DCM) is characterized by ventricular dilatation and decreased contractility.[2] Clinical DCM is the final common response to many genetic and non-genetic processes. The incidence of DCM is estimated to be 35 cases per 100,000 persons. The true incidence is probably underestimated because many asymptomatic cases are undiagnosed. DCM occurs in adults and children. Up to one-third of cases are caused by mutation of genes encoding the cytoskeleton, sarcomere, and nuclear envelope proteins. Secondary neurohumoral changes contribute to remodeling and ongoing myocyte damage.[3] Many of the genetic causes are mutations coding for the protein titan, which provides passive force and regulates sarcomere contraction and signaling.[4] The histology is irregular myocyte hypertrophy with fibrosis or necrosis, which leads to muscle changes. The result is impaired myocardial force generation, which initiates a vicious cycle that increases the burden on the remaining cells and leads to increased stress, more work, and more cell death. This results in the clinical symptoms of heart failure or dysrhythmias.

Clinical Features

Symptoms have an insidious onset. Heart failure occurs as the initial manifestation in 75% of adults, with dyspnea (usually with exertion or while supine) being the major symptom. Chest pain, peripheral edema, dysrhythmias, syncope, and sudden death also occur. Rhythm disturbances implicate conduction system involvement. Shortness of breath and fluid overload are the most common presentations in children.

Diagnostic Testing

Abnormal ventricular contractility defines DCM, and an ejection fraction less than 45% is required for diagnosis. Echocardiography shows left ventricular (LV) dilation, reduced systolic function, and variable wall motion abnormalities. End-diastolic and systolic volumes are increased by more than two standard deviations from normal.[3] Pulmonary arterial line placement is often performed, revealing elevated pulmonary capillary wedge pressure and central venous pressures.

Electrocardiogram (ECG) findings are nonspecific and may include poor R wave progression, intraventricular conduction delay, left bundle branch block or left ventricular hypertrophy (Fig. 68.2) with or without repolarization changes. Ectopy is common. Chest x-ray shows cardiomegaly and possible pulmonary congestion. Troponin and BNP may be elevated.

MRI showing delayed gadolinium enhancement can indicate necrosis or scarring.[3] Right-sided failure can develop from primary right-sided disease, persistent volume overload from left-sided disease, or may represent occult atrial septal defect. The echocardiogram or ventricular imaging during coronary angiography evaluate for right-sided pathology as well. For definitive diagnosis, endomyocardial biopsy may be necessary, although histologic abnormalities are nonspecific.

Differential Diagnosis

The most common nongenetic cause of DCM is ischemic cardiomyopathy caused by coronary artery disease. Other etiologies include toxins such as alcohol, cocaine, methamphetamine, chemotherapy with

anthracycline related agents, hemochromatosis, pseudoephedrine, ephedra, phenothiazines, lithium, anabolic steroids, clozapine, and hydroxychloroquine.[2]

Management and Disposition

Treatment is supportive to reduce heart failure, rhythm disturbances, and conduction system issues. Supportive measures include adequate rest, weight control, abstinence from tobacco, moderate salt and ethanol consumption, and structured physical activity.

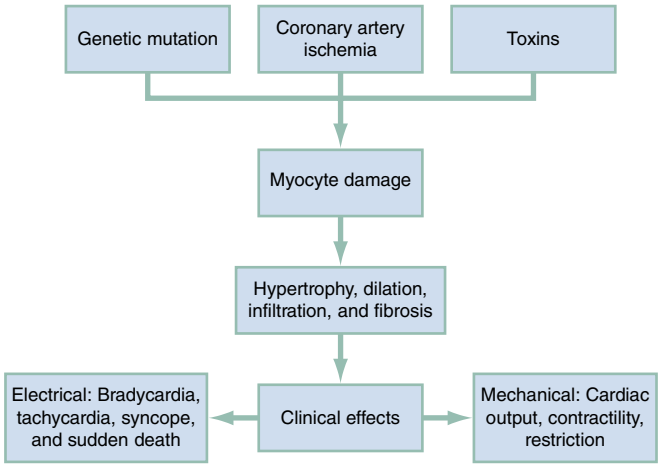

Fig. 68.1 Cardiomyopathy pathogenesis.

Medical treatment includes diuretics and vasodilators for patients who present with dyspnea or hypoxemia. We recommend starting with intravenous furosemide at one to two times the patient's baseline dose, or 10 mg if diuretic naïve. For vasodilators, nitroglycerine can be initiated at 5 mcg/minute and titrated upward, closely monitoring blood pressure and symptoms.

To improve long-term outcomes and reduce heart failure exacerbations, patients should be on a closely monitored heart failure regiment. For patients with mild exacerbations who may be discharged, the emergency clinician might initiate or titrate a medication in coordination with the patient's cardiologist. Angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and angiotensin receptor blockers (ARBs) have mortality benefit. Among beta-blockers, carvedilol (starting dose 3.125 mg BID, titrated up to target dose 25 mg BID) is well studied and has proven effective.[3,5] ARB treatment produces beneficial LV remodeling in nonischemic dilated cardiomyopathy. Maximal beneficial remodeling is achieved within 12 to 16 months.[6] Newer treatments include angiotensin receptor-neprilysin inhibitor valsartan/sacubitril, which has shown early promise in the management of dilated cardiomyopathy. Experimental treatments include sinoatrial modulator ivabradine[6] and autologous somatic tissue-derived stem cells transplanted into a DCM heart to stimulate native regeneration.[7] Both have shown limited clinical promise to date.

Biventricular pacing to coordinate both ventricles can help clinical function. ICD therapy reduces all-cause and cardiovascular mortality in patients with nonischemic cardiomyopathy.[8] Current guidelines call for implantable cardioverter-defibrillator (ICD) placement when ejection fraction (EF) is less than 35%. Patients with EF less than 35% who have not had electrophysiologic evaluation should be referred for

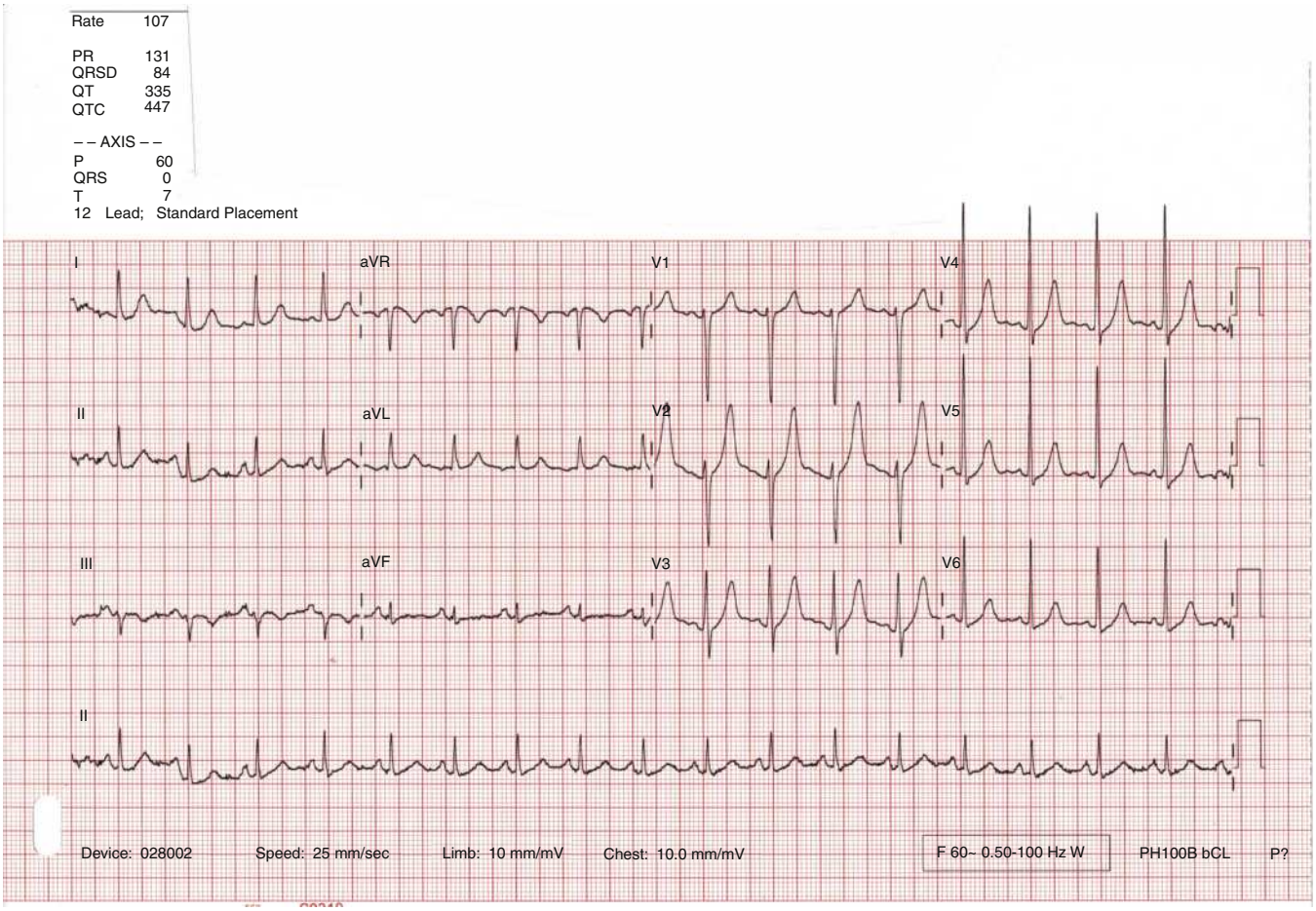

Fig. 68.2 EKG showing left ventricular hypertrophy.

consideration of ventricular synchronization pacing. A search for a more precise way to predict the need for an ICD is ongoing.[9]

Disposition

Patients with DCM show progressive deterioration. There is an increased risk of sudden death, especially with some genetic types. Because medical therapy usually fails, with a mortality of 20% by 3 years, DCM is the leading indication for cardiac transplantation.

Emergency department (ED) patients should be admitted if they have new rhythm disturbances that cannot be adequately controlled with oral medications, deterioration of cardiac function as determined by symptoms or diagnostic data, shock, or significant pulmonary fluid overload that cannot be reversed. Patients whose DCM is first diagnosed in the ED should be hospitalized unless the symptoms are mild and a cardiology consult is available in the ED. If the emergency clinician can control or convert atrial rhythm disturbances, obtain sequential testing for mildly elevated troponin levels, and control symptoms in patients with known DCM, discharge is possible. Medication adjustments, such as increased diuretic dose or adding a beta-blocker or ACEI, should be considered, but follow-up within 48 hours is indicated. Heart failure clinics have been shown to reduce morbidity and mortality, making them an excellent option if available locally. Otherwise, the patient should be referred to a cardiologist.

Hypertrophic Cardiomyopathy

Foundations

Hypertrophic cardiomyopathy (HCM) is one of the first diseases understood at the genetic, anatomic, pathophysiologic, and clinical levels. It is the most commonly inherited cardiac disease. HCM is caused by sarcomere gene mutations that result in left ventricular hypertrophy and scar formation, which then lead to dysrhythmias and heart failure.[10] It is inherited as autosomal dominant, but genotype-phenotype correlations have been inconsistent. More than 200 mutations have been identified.[11] Mutations for beta-myosin heavy chain and myosin binding protein C are the two most common genetic defects, but 40% of cases have no genetic abnormality identified to date. The mutations lead to abnormal cardiac proteins that affect actin-myosin bridging, stroke power, sensitivity to adenosine triphosphate (ATP), and sensitivity of the muscle to calcium. To compensate for abnormal protein, the muscle hypertrophies and fibroses. The combination of myocyte disarray, hypertrophy, and fibrosis leads to the clinical manifestation of dysrhythmias and heart failure. Nongenetic factors such as protein translation and the environment also affect phenotype and clinical outcomes.[12] Specific mutations correlate with sudden cardiac death. Only half of patients with Arg403Gln mutation survive past age 45 years.

The defining anatomic feature of HCM is a hypertrophied left ventricle in the absence of another cause. The ventricular cavities are small or normal, and atrial dilation is common. Hypertrophy is asymmetrical and generally most severe at the base of the intraventricular septum near the aortic valve. Left ventricle (LV) outflow is obstructed in one-third of cases and can be provoked, or dynamic, in one-third more. Histology is myocyte hypertrophy and disarray with interstitial fibrosis. The myocytes are enlarged with bizarre shapes and pleiotropic nuclei. The abnormal cells are widely distributed with a preference for the intraventricular septum.[12]

Clinical Features

Although HCM occurs at all ages, most patients are diagnosed between ages 30 and 40 years. Approximately 2% of cases are diagnosed in children younger than 5 years old, and 7% are diagnosed before 10 years old.

Presentation varies widely. Common symptoms are a result of diastolic dysfunction (exertional dyspnea, orthopnea, peripheral edema), LV outflow obstruction (exertional dyspnea or syncope), imbalance between myocardial oxygen supply and demand (chest pain caused by decreased blood flow into the coronary arteries), and dysrhythmias (palpitations, atrial fibrillation in 20%, ventricular tachycardias, and sudden death). Physical examination shows a displaced left precordial impulse, strong peripheral pulses, a harsh midsystolic grade 3 to 4 over 6 murmur loudest between the apex and the left lower sternal border. The Valsalva maneuver or changing from standing to squatting changes the murmur.[12] Often, the first presentation is sudden death, which most commonly occurs during periods of exertion.

In the ED, the diagnosis should be considered in anyone with a family history, characteristic murmur, and cardiopulmonary symptoms not explained by another condition.

Differential Diagnosis

In individuals with murmurs, HCM may be confused with valvular diseases or a ventricular septal defect. In the absence of a murmur, symptoms may suggest mitral valve prolapse, primary pulmonary hypertension or coronary artery disease.

Diagnostic Testing

The ECG is abnormal in approximately 90% of patients. The most common abnormalities are atrial fibrillation, left ventricular hypertrophy, ST segment alterations, T wave inversion, left atrial enlargement, abnormal Q waves, and diminished or absent R waves in the lateral leads. The chest radiograph may be normal or may show left ventricular or atrial enlargement.

Echocardiography findings include asymmetrical left ventricular hypertrophy, left ventricular outflow tract narrowing, a small left ventricular cavity, and reduced septal motion. Unlike fixed ventricular flow obstructions, the amount of obstruction imaged changes from beat to beat. This dynamic characteristic of HCM distinguishes it from the discrete forms of obstruction. Left ventricle obstruction at rest is an independent predictor of heart failure.

MRI can help with diagnosis and prognosis. It provides an accurate measure of wall thickness and identifies the location and extent of fibrosis. Extensive late gadolinium enhancement, which represents scarring, is associated with sudden death.[13] MRI for HCM is rarely available to the EP and should be used by the cardiologist to manage long-term care.

Management

Beta-blockers and calcium channel blockers are used to control exercise-related symptoms. A beta-blocker such as metoprolol 12.5 mg BID and titrate up to 100 mg BID is the first-line treatment. For those intolerant of beta-blockers, diltiazem 30 mg QID is indicated. Disopyramide (100 to 150 mg Q6H) is often added to reduce resting gradient across the aortic valve. These treatments do not alter the natural history of disease.[11] Spironolactone is not efficacious.[14] ARB agents are being studied.[10] A small model inhibitor of myosin MYK-461 has been effective in preventing HCM in mouse models.[15] Nitroglycerin should be avoided in HCM-associated chest pain because it decreases ventricular volume, exacerbating outflow tract obstruction.

Atrial fibrillation can cause marked hemodynamic compromise and severe CHF. Cardioversion and rate control should be attempted. If the patient is stable, start with diltiazem 0.25 mg/kg (based on weight) or esmolol 50 mcg/kg/min. These doses may be repeated or an infusion started. If not successful at rate control (HR < 100) or the patient is hypotensive (BP < 90 systolic), then electrical cardioversion is indicated. For HCM patients with atrial fibrillation, the risk of stroke is high, and anticoagulation (rivaroxaban 20 mg QD, apixaban 5 mg BID, or dabigatran etexilate 150 mg BID) should be started from the

ED.[12] Amiodarone (600 mg QD divided into 2 or 3 doses) is the drug of choice long term to treat atrial fibrillation as well as ventricular dysrhythmias. Phenylephrine is the vasopressor of choice for persistent hypotension when intravenous fluids have not improved blood pressure. Beta-agonists, such as dobutamine, increase the gradient across the outflow tract obstruction and should be avoided.

Invasive procedures, such as myomectomy or septal alcohol ablation, may be needed to treat severe cases. Dual-chamber pacing decreases outflow gradient and improves symptoms but does not improve mortality.[11]

Implantable cardioverter-defibrillators are indicated for patients who survive sudden cardiac death (SCD) or have certain risk profiles.[11] Risk calculation is based on patient age, family history of one or more first-degree relatives with SCD at age less than 40 years or with confirmed HCM, size of left ventricle and atrium, left ventricle outflow gradient, presence of ventricular tachycardia, and unexplained syncope. These factors all reflect the extent of interstitial fibrosis.[16]

Disposition

A patient with angina, syncope, near-syncope, dysrhythmias, and abrupt hemodynamic changes should be hospitalized. A patient suspected to have HCM should be seen by cardiology in the ED or hospitalized to expedite making the diagnosis.

The natural history of HCM is variable and probably reflects the many different genetic causes. The clinical course is either heart failure, atrial fibrillation, or sudden death. With modern therapy, most patients have low premature mortality.[11]

The evidence for the role of exercise is unclear. Newer evidence shows that the risk of SCD may be lower than previously reported, and moderate or recreational exercise may be beneficial.[17] HCM remains the most frequent cause of nontraumatic sudden death in the young, however, and some still recommend that patients not participate in competitive sports. Current evidence is unclear about which athletes benefit from SCD risk screening.[18] Given the current evidence, emergency physicians should advise their discharged patients to eliminate strenuous exercise until cardiology evaluation.

Restrictive Cardiomyopathy

Foundations

Restrictive cardiomyopathy (RCM) is a gradual and progressive limitation of ventricular filling secondary to myocardial infiltration. There is stiffness of the ventricles with normal diastolic volume and normal ventricular wall thickness.[19] RCM is the least common type of cardiomyopathy, accounting for less than 5% of all cases. The most common etiology in the United States is amyloidosis. Other causes include sarcoidosis, hemochromatosis, scleroderma, neoplastic cardiac infiltration, glycogen storage disorders, Fabry disease, Gaucher disease, and mutations related to myocardial muscle proteins.[20]

Restriction of ventricular filling and compliance results in low ventricular volumes, high end-diastolic ventricular pressures, and decreased cardiac output. Systolic function is maintained. Endomyocardial biopsy shows interstitial fibrosis and myocyte hypertrophy, neither of which is pathognomonic. There are no specific genetic mutations. Grossly, there is atrial enlargement and small ventricles. As the disease progresses, the ventricular cavities may become obliterated by fibrous tissue, scarring, or thrombus.

Clinical Features

Most patients are diagnosed in their 50s. The most common symptom is dyspnea. Signs and symptoms may include exercise intolerance (cardiac output cannot be increased because ventricular filling is compromised), pulmonary congestion, elevated central venous pressure, peripheral edema, pulmonary edema, and S_3 and S_4 gallops. Clues to making the diagnosis in children include trouble eating, lack of weight gain, and difficulty exercising.

Differential Diagnosis

Serum troponin and chemistry panel should be obtained to exclude myocardial infarction or renal and hepatic mimics. Because some causes of RCM can be treated or managed, it is important to search for etiologic causes, which requires extensive serologic testing and cardiac MRI. These can be performed as an inpatient or outpatient. Comprehensive echocardiography should be obtained to confirm the diagnosis.

Diagnostic Testing

ECG findings are not specific. Chest x-ray shows cardiomegaly and often pulmonary congestion.[21] BNP may be elevated. Point of care ultrasound (POCUS) shows thickened ventricles and no change in isovolemic relaxation time with respiration. Central venous pressure tracings show rapid filling causing a sudden dip in pressure and then a sudden plateau, yielding a curve similar to a square root sign. CT can also differentiate RCM from constrictive pericarditis. Pericardial calcification or history of radiation therapy favors constrictive pericarditis over RCM.

Management

Most of the underlying causes of RCM are untreatable, with the exception of hemochromatosis. Patients rely on high filling pressures, making volume management challenging. A trial of beta-blockers (metoprolol 25 mg BID or atenolol 25 mg QD) or calcium channel blockers (diltiazem 30 mg QID) may help increase filling time and thus cardiac output. ACEIs (lisinopril 10 mg QD) and ARBs (losartan 50 mg QD) may also help.[20] Patients with RCM should be maintained in sinus rhythm because they are dependent upon the atrial contribution to cardiac output. RCM is relentless, with 64% of patients dying within 5 years of diagnosis.

Disposition

Patients should be hospitalized for shortness of breath or hypotension that does not respond to ED treatment. Patients with either tricuspid regurgitation or small LV end-diastolic volume have a poor prognosis.[19]

Peripartum Cardiomyopathy

Foundations

Peripartum cardiomyopathy (PPCM) was first described in 1849. It is a rare, often dilated, cardiomyopathy with systolic dysfunction that presents in late pregnancy or the early postpartum period. Although the condition is prevalent worldwide, women with African ancestry seem to be at greatest risk even after confounders are eliminated. Other risk factors include preeclampsia, advanced maternal age, tocolytic use, twins, obesity, and cocaine use.[22] The incidence is thought to be between 1 in 1500 and 1 in 4350 live births and increasing, possibly because of improved detection or rising maternal age. The exact pathogenesis is unknown. Some women have an underlying sarcomere gene mutation.[22]

Clinical Features

PPCM is similar to DCM, with heart failure symptoms predominating on initial presentation. Patients have dyspnea and edema and may also have chest pain or palpitations. Unfortunately, these symptoms can be expected in normal pregnancy, making distinguishing pathology from expected physiologic changes challenging at times. Acute alterations in symptoms, sudden or worsening chest pain or dyspnea, or difficulty performing routine activities are diagnostic clues. Physical

examination often reveals tachycardia, tachypnea, pulmonary rales, and an S3 heart sound.

The ECG may show LV hypertrophy or nonspecific ST-T wave changes. On echocardiography, all four chambers are enlarged, with a reduction in left ventricular systolic function.

Differential Diagnosis

Other causes of symptoms should be evaluated. The differential diagnosis includes preeclampsia, myocardial ischemia including coronary dissection, pulmonary embolism, pneumonia, and primary rhythm disturbance.

Diagnostic Testing

As with any patient presenting with dyspnea, an ECG is a first-line diagnostic test to look for ischemia and rhythm disturbances. Laboratory values can assist in narrowing the differential. A chemistry panel evaluates for electrolyte disarray and renal impairment, while a troponin test assesses for ischemia or RV strain if pulmonary embolism is being considered. A D-dimer is of low utility, because it is elevated in most women from the third trimester until at least a month postpartum. Brain-natriuretic peptide will be elevated in PPCM. A chest radiograph may reveal pulmonary edema, and patients at high risk of PE by the Wells score should undergo CT angiography. Pulse oximetry should be used to monitor oxygenation and cardiac monitoring to assess for dysrhythmias. In cases of maternal instability, fetal monitoring is indicated to follow the pregnancy.

Management

Acutely, patients with PPCM can present with a range of mild symptoms to cardiogenic shock. The management will be titrated to the patient's presentation. Those with mild symptoms will benefit from reduction of preload, but furosemide is pregnancy category C. Afterload reduction with hydralazine (5–10 mg intravenous) is safe and effective. Patients in shock should be managed with vasopressors and inotropes, in consultation with cardiology and obstetrics (see Chapter 3). Delivery within 48 hours may be needed, especially if the patient is unstable. All patients should have obstetrics evaluation of the fetus either in the ED or by transfer to the OB floor.

Long-term treatment of PPCM includes judicious physical activity, beta-blockers, alteration of preload with nitrates and diuretics, increase ventricular contractility, and afterload reduction. Beta-blockers are likely safe but have not been studied. For those women who are still pregnant at presentation, ACE inhibitors and ARBs are contraindicated. The effect of breastfeeding on PPCM is unknown.[2]

Disposition

ED patients first diagnosed with PPCM require obstetrics consultation, often with cardiology consultation as well. Patients with pulmonary embolism or continued dyspnea should be hospitalized. Fetal monitoring for at least 6 hours is indicated if the patient is still pregnant. Recovery of LV function occurs in 45% to 78% of patients. Factors associated with favorable prognosis include small LV diastolic dimension, ejection fraction greater than 35% at the time of diagnosis, absence of troponin elevation, and absence of LV thrombus. Cardiomegaly that persists for more than 6 months has a 50% mortality at 6 years. There is a substantial risk of recurrence with subsequent pregnancies with high morbidity and mortality.[2] Mortality for PPCM in the United States is approximately 2%. Mechanical support or cardiac transplantation may be needed for those who do not fully recover.[22]

Takotsubo Syndrome

Foundations

Takotsubo syndrome (TS) is the preferred name for takotsubo cardiomyopathy because there is rarely significant long-term myocardial damage. Previous names also included stress cardiomyopathy, broken heart syndrome, or tako-tsubo cardiomyopathy.

TS was first reported in Japan in 1991, with hundreds of cases reported subsequently (Box 68.1). In Japanese, *tako-tsubo* means octopus trap, and the condition is so named because the observed shape of the left ventricle resembles the urn-like device used to catch octopi. Physical and emotional stressors can trigger TS. Elevated circulating catecholamines lead to cardiac myocyte dysfunction. The pathophysiology of the unique octopus trap shape is unknown.[23] One theory is that excessive stimulation of excitatory neurotransmitters produces regional cardiac stunning. Serum catecholamines are more than twice as high in TS patients than in those with myocardial infarction.[24]

Clinical Features

In the United States, TS presents most often in women, with 85% being over age 60, often after emotional stress. Risk factors include smoking, alcohol abuse, anxiety, and hyperlipidemia.[23] Symptoms include chest pain, palpations, and dyspnea on exertion. POCUS shows regional wall motion abnormalities that often extend beyond the distribution of a single coronary artery.

BOX 68.1 Published Causes of Takotsubo Syndrome

Achalasia
Addison disease
Anaphylaxis
Anesthesia
Asthma
Chemotherapy
Closed head injury
Depression
Diarrhea
Diving
Emotional stress
Foley catheter insertion
Hanging
Hypoglycemia
Inferior vena cava clot
Lightning strike
Multiple trauma
Myocardial infarction (MI)
Near drowning
Opioid withdrawal
Pancreatitis
Pheochromocytoma
Pneumopericardium
Pregnancy
Scorpion envenomation
Seizures
Sepsis
Sexual intercourse
Stress testing
Subarachnoid hemorrhage
Surgery or medical procedures
Thrombotic thrombocytopenic purpura
Thyrotoxicosis
Transient ischemic attack
Tricyclic overdose
Vomiting

Differential Diagnosis

Differential diagnosis includes acute myocardial ischemia or any syndrome with an adrenergic surge, be it toxic (cocaine, methamphetamine) or endogenous (stress).

Diagnostic Testing

ECG is often consistent with acute coronary syndrome and may include sinus tachycardia, ST elevations or depressions, and prolonged QT intervals. Chest x-ray is unremarkable. Serum troponin is mildly elevated. Serum natriuretic peptide levels are usually quite elevated, up to 6 times normal, and may be the laboratory test that correlates best with TS. Up to 80% of TS patients have elevated BNP. Though not usually available in the ED, MRI during the acute period shows myocardial edema as high signal intensity with a diffuse or transmural distribution which is not seen in myocarditis or ischemia.[23]

Management

In the ED, TS is usually not distinguishable from AMI, and patients should be treated accordingly, including cardiac catheterization for ST elevations on the ECG. There are no randomized trials for specific treatments. Beyond consulting cardiology for catheterization, the emergency clinician should provide supportive care. Phenylephrine is the vasopressor of choice for hypotensive patients, to reduce the risk of dynamic LV outflow tract obstruction.

After hospital discharge, beta-blockers (atenolol 25 mg QD or metoprolol 25 mg BID) may both help the heart and modulate catecholamine levels, and ACE inhibitors (lisinopril 10 mg QD) may improve one-year survival. There is no evidence for any treatment to prevent recurrence.[23]

Disposition

Patients that do not undergo catheterization should be hospitalized for rhythm monitoring and serial cardiac enzymes. Ninety-five percent of patients show complete resolution of symptoms and normalization of their LV apex ballooning and contractile function. Long-term prognosis matches controls at 4 years. The recurrence rate is 10%.

Arrhythmogenic Right Ventricular Cardiomyopathy

Foundations

This is primarily a genetic disease most commonly seen in Italy. Desmosome proteins provide electromechanical connections between myocytes and play a role in signaling cascades and ion channels. Mutations in genes encoding for cardiac desmosome proteins are found in 60% of cases. There is fibrofatty replacement of the myocardium that leads to diffuse myocardial atrophy, occurring most commonly in the RV. Myocardial replacement predisposes to ventricular dysrhythmias and slowly progresses to systolic dysfunction. Electrical changes occur before there is evidence of pathology on x-ray or echocardiography.[25] Endurance athletes develop AVRCM often. More exercise leads to earlier onset and worse symptoms than in non-endurance athletes. Whether this is causal or an association is under investigation.

Clinical Features

The age distribution is bimodal, with patients in either their teens or their forties. The most common symptom is ventricular dysrhythmia leading to syncope or sudden death.[25]

Differential Diagnosis

The differential diagnosis includes ingestion of toxins such as cocaine and methamphetamine, leading to rhythm disturbances, conduction system defects, and myocardial ischemia.

Diagnostic Testing

Clinical diagnosis is challenging. ED workup should include electrolytes, thyroid testing, family history, and ECG. ECG findings may include left bundle branch pattern, tachydysrhythmias, and T wave inversions in leads V1 to V3. Epsilon waves are the hallmark finding in ARVCM but are found in less than one-third of patients. Echocardiogram shows right ventricular dilation and segmental wall motion abnormalities.[18] The workup after the ED includes MRI, which shows similar findings as echocardiogram but with more diagnostic certainty.[26] Electrophysiologic studies and genetic testing may also be needed.

Management

Management includes anti-dysrhythmics, heart failure medication, catheter ablation, and ICD. Heart transplant may be indicated.[25] Amiodarone (200 mg TID) alone or with a beta-blocker (metoprolol 25 mg BID) is the best medical therapy for controlling symptoms as an adjunct to patients with frequent ICD firings.[27]

Disposition

Patients with LBBB or epsilon waves, ventricular tachycardia, newly diagnosed ventricular dilation, or unexplained syncope should be hospitalized. An ED cardiology consult or observation for consultation should be recommended for the rest. Patients should not participate in sports or exercise until cleared by cardiology.[18] Prognosis in ARVCM is related to ventricular dysrhythmias. Risk factors for SCD include dilated right or left ventricle, young age at diagnosis, amount of scar tissue, and genetic predisposition.[27] Patients and relatives should be sent for genetic testing.

Channelopathies

Several uncommon dysrhythmic diseases are caused by mutations of genes for ion channel proteins, which are cell membrane transport proteins for sodium, potassium, and calcium. Defects alter the action potential, predisposing to dysrhythmias. These include long QT syndrome, short QT syndrome, and Brugada syndrome. All can lead to sudden death.[28] Long QT is the most common channelopathy. There are currently 10 gene mutations identified. Short QT syndrome has an autosomal dominant transmission with three subtypes. Brugada syndrome has a high prevalence in Southeast Asia. The cause is either a decrease in sodium or calcium inflow or an increase in potassium outflow.

Clinical presentation is syncope, near syncope, palpitations or SCD.[29] A strong family history is helpful in making the diagnosis. Short QT syndrome usually presents in patients with a mean age of thirty years.

The ECG shows the characteristic interval changes in long and short QT syndromes. In Brugada syndrome, the ECG shows ST segment elevation in leads V1 to V3, and also often shows increased PR or QRS intervals (see Chapter 65). Electrolytes, chest x-ray, toxicology screen, and thyroid testing should be normal.

Patients should be admitted to monitored settings and undergo cardiology evaluation for ICD placement. After discharge, amiodarone (600 mg QD) may be efficacious for dysrhythmia treatment. Referral to genetics can follow thereafter.

Myocarditis

Foundations

Myocarditis is defined histologically by the presence of mononuclear cell infiltrates in myocardial cells. Up to 5% of patients with viral illness may exhibit a form of myocarditis. Some degree of myocarditis is detected in almost 10% of routine autopsies but is often not recognized clinically. The overall incidence is unknown and likely underdiagnosed.

BOX 68.2 Infectious Causes of Myocarditis

Adenovirus
Chagas disease
Chlamydia
Coxsackie B virus
Cytomegalovirus
Epstein-Barr virus
H1N1 virus
Hepatitis A
Hepatitis B
Hepatitis C
Human herpesvirus 6
Influenza A
Influenza B
Legionella
Lymphocytic choriomeningitis virus
Mononucleosis
Mumps
Mycoplasma
Parainfluenza
Parvovirus 19
Rabies
Rubeola
Rubella
SARS-COV-2
Streptococcus
Toxoplasma gondii
Varicella zoster

Any infectious agent can cause myocarditis (Box 68.2) In the 1980s and 1990s, enterovirus and adenovirus predominated as etiologic agents. Recently, H1N1 influenza virus, coronavirus (SARS-CoV-2), parvovirus 19, human herpes virus 6, Epstein-Barr virus, cytomegalovirus, hepatitis C virus, and HIV predominate.[30] Diphtheria, trichinosis, and Lyme disease all can have associated myocarditis, which is discussed with those diseases. The infectious agent can cause damage by direct injury of cellular integrity, RNA/protein dynamics, transcription, and translation. It also activates host antiviral immune response. Initial immune response limits the viral damage but when prolonged, the immune response leads to inflammation damage.[30] This turning of a normal immune response into one that causes cardiac damage has several predisposing factors and is not always induced by a virus. These include systemic/local primary autoimmunity, viral infection, HLA type, gender, and mimicry.[31] The exact pathogenesis varies by causative agent. Efficient clearing of the causative agent usually results in return to normal function. In some individuals, there is a breakdown of T-cell tolerance, which leads to chronic inflammation.[32]

Three stages of disease have been proposed: (1) acute with cytotoxicity and focal necrosis; (2) subacute, in which there is an increase in humoral factors leading to autoimmune injury; and (3) chronic, in which there is diffuse myocardial fibrosis and cardiac dysfunction that may lead to DCM.

There is a higher concentration of anti-beta-myosin antibodies in patients with myocarditis and DCM than in controls. Because myocarditis is linked to the development of DCM (up to 16% of cases in adults and 46% in children), idiopathic DCM after myocarditis may be predominantly autoimmune in origin, resulting from either shared antigens or molecular mimicry, in which the amino acid sequences of the virus and components of the myocardium are similar.

Clinical Features

The clinical presentation is varied. The first symptoms are usually flu-like, including fever, fatigue, myalgias, vomiting, and diarrhea. The most common presentation in children is dyspnea. In adults, it is dyspnea, chest pain, and dysrhythmias.[18] Toxic appearance or tachycardia disproportionate to the temperature may be the only findings. No symptom or sign is sensitive or specific. Cardiac examination is often unremarkable. Patients who present with severe dyspnea, heart failure, rhythm disturbances, or hemodynamic instability are at greatest risk for poor outcomes.[33]

In children, prominent physical findings include grunting respirations and intercostal retractions. Approximately 10% to 15% have rhonchi. Infants often have a fulminant syndrome characterized by fever, cyanosis, respiratory distress, tachycardia, and cardiac failure. When children have ventricular dysrhythmias, myocarditis and idiopathic DCM are commonly seen on endomyocardial biopsy despite a structurally normal heart by noninvasive studies. Long-term prognosis in children correlates with the severity of their initial presentation.

Differential Diagnosis

Diagnostic considerations include myocardial infarction and any other infectious process. Differentiating cardiac sequelae caused by an infection or inflammation elsewhere from primary myocarditis is often not possible. Patients with myocarditis are usually young and have few risk factors for coronary artery disease. In myocarditis, chest pain continues without evolving ischemic ECG changes. The diagnosis of myocarditis should also be considered in an otherwise healthy patient with symptoms and signs of new CHF or dysrhythmias.

Diagnostic Testing

Common ECG changes include sinus tachycardia, a widened QRS, and low voltages. There may be a prolonged QT interval, AV block, or an AMI pattern. ECG abnormalities may extend beyond the distribution of a single coronary artery. Troponin may be elevated. When the elevation occurs in the course of the disease is unknown. The prognostic significance of elevation is not known. A negative ED or serial troponin does not rule out the diagnosis because the damage could have occurred before ED evaluation. The WBC count, C-reactive protein, and ESR are of no diagnostic value. Echocardiographic features are nonspecific and include reduced left ventricular ejection fraction, global hypokinesis, and regional wall motion abnormalities that do not follow coronary artery anatomy. Coronary angiography usually shows normal arteries.

A formal diagnosis is made by biopsy with immunohistochemical data (Fig. 68.3). Biopsy has variable sensitivity and specificity because of sampling error. Biopsy sensitivity may be increased by MRI guidance to target abnormal regions.[34] Because biopsy is invasive, has variable sensitivity, and is unlikely to change clinical outcome, it is often not used, most often leaving the diagnosis to be made based on clinical findings.

Contrast-enhanced MRI may be diagnostic by showing areas of injury. The MRI pattern on initial diagnosis can predict outcome. Late gadolinium enhancement, especially septal, mid-wall, and patchy distribution, is associated with increased risk of sudden death or ischemia, with greater enhancement indicating greater risk.[34]

Management

Treatment is supportive and aimed at preserving LV function. This may include everything from a simple limitation of activity to rhythm and CHF treatment, extracorporeal membrane oxygenation, ventricular assist devices, and even cardiac transplantation.

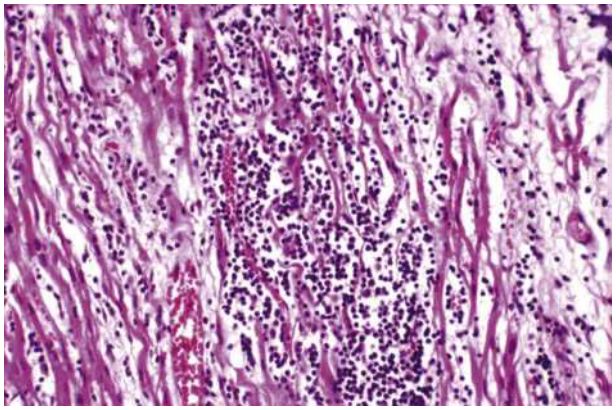

Fig. 68.3 Myocardial biopsy specimen showing myocarditis. Note the lymphocytic infiltrate.

Unfortunately, the majority of studied treatments have failed to improve outcomes.[33] Treatment attempts have been stage-specific. In the viral stage, antiviral agents, such as beta-interferon or ribavirin, are not supported by evidence. For the inflammatory stage, multicenter trials of immunosuppressive therapy with several months of prednisone and azathioprine have shown benefit in only the small subset of patients with heart failure of less than 6 months and no virus on biopsy.[27] Mouse models implicate aspirin and NSAIDs as causing harm.

Symptomatic treatment should be started in the emergency department. Because most patients will be diuretic naïve, start with furosemide 10 mg and add vasodilators, such as nitroglycerine starting at 5 mcg/min for CHF symptom management. In some cases, the deterioration of cardiac function is substantial enough to require inotropic agents, such as dobutamine 2 mcg/kg/min, or even mechanical circulatory support with ventricular assist devices (VADs) (see Chapter 66). Temporary or percutaneous VADs may provide short-term support while awaiting recovery. If the myocardium does not recover, a durable VAD or transplantation may be required.

Disposition

Patients with myocarditis should be hospitalized in a monitored bed. Those with persistent hemodynamic instability require intensive care. Those with mild viral symptoms and slightly elevated troponin may be observed for serial troponins and follow-up echocardiogram. Complications of myocarditis include ventricular dysrhythmias, left ventricular aneurysm, CHF, and DCM.

Given the wide variations in clinical presentations and etiologies, it is difficult to assign a long-term prognosis. The consensus is a 10% to 20% rate of major cardiac adverse events.[35] There is a significant difference in outcome for pediatric patients with fulminant and nonfulminant disease, with fulminant having a higher rate of in-hospital deaths, heart transplantation, and LVEF less than 55% at follow-up.[36] Patients who undergo transplantation because of myocarditis have decreased 1-year survival and higher rejection rates compared with patients who undergo transplantation for other reasons.

Patients with myocarditis, even when asymptomatic, are at higher risk for SCD. Exercise has been shown to worsen myocarditis in animal models. Athletes with myocarditis should not compete until signs of inflammation have resolved, and LV function has normalized.[18]

Chagas Disease

Chagas disease is one of the leading causes of myocardial disease in many countries, particularly in Central and South America. Chagas disease is caused by the protozoan *Trypanosoma cruzi* with transmission by insect vector. Elimination of the vector and improved blood donation screening has decreased the incidence.

Chagas disease should be considered in any patient with new cardiac symptoms and a travel history that includes Mexico, Central America, and South America. Acute infection presents as a nonspecific viral-like illness followed by a latent phase, then a cardiac phase with conduction abnormalities, and then DCM. Most seropositive patients never develop symptoms. Findings include fever, hepatic or splenic enlargement, and unilateral periorbital edema. Cardiac manifestations include angina-like chest pain, dysrhythmias, embolic episodes, heart failure, conduction abnormalities, and multifocal ventricular premature contractions. Syncopal or near-syncopal episodes occur in nearly two-thirds of patients.

The ECG shows ST segment elevation, T wave inversion or increased PR or QRS intervals. Ventricular tachycardia is common and considered a hallmark of the disease. Serum testing for parasites establishes the diagnosis, as does measuring anti-IgG for *T. cruzi*. Echocardiography may show a left ventricular apical aneurysm or scar, which is a reliable marker.

Treatment is with benznidazole for ages 2 to 12 years (5–8 mg/kg/day divided into 2 doses for 60 days) and nifurtimox for ages 12 to 17 years (15 mg/kg/day divided into 3 or 4 doses) and 18 years or over (8–10 mg/kg/day divided into 3 or 4 doses). Amiodarone (200 mg TID) may be useful to treat ventricular tachycardia. ACEIs (lisinopril 10 mg QD) provide a long-term benefit for patients with heart failure.

Up to 30% of patients develop CHF from 5 to 30 years after the initial infection. To whom and why this happens is not understood.

Cocaine Cardiotoxicity

Cocaine has a direct negative inotropic effect on cardiac muscle. Cocaine causes ischemia, myocarditis, and DCM. Myocarditis is a common autopsy finding in patients with cocaine abuse. The mechanism is largely unknown. Theories include increased sympathomimetic effect, severe oxidative stress, and metabolite interaction with ion channels. Patients who die with detectable cocaine levels have myocarditis and myocardial contraction bands more often than controls. The severity correlates with serum and urine concentrations of cocaine. This may supply the anatomic substrate for ventricular dysrhythmias. For further details on cocaine cardiotoxicity, please see Chapter 144.

Sudden Death

Approximately 25% of sudden deaths in patients younger than 21 years old can be attributed to disease of the myocardium. Cardiac causes include myocarditis, congenital abnormalities, HCM, channelopathies, and anomalous coronary artery circulation. Prodromal symptoms are reported in more than half of the patients with cardiac causes, most commonly chest pain in patients older than 20 years, and dizziness in patients younger than 20 years. SCD of coronary artery etiology is decreasing while that of cardiomyopathy etiology is increasing. The risk for SCD increases rapidly at age 25 to 40 and then gradually until age 75 when it decreases. Coronary artery disease is the leading cardiac cause (58%) of sudden death in people older than 30 years old. HCM and anomalous coronary arteries are seen more often in sports-related deaths.[37]

PERICARDIAL DISEASE

Pericarditis

Foundations

Pericarditis is inflammation of the pericardium caused by granulocytic and lymphocytic infiltration. Pericarditis is a relatively common cause of chest pain, accounting for 5% of all nonischemic chest pain.

BOX 68.3 Etiology of Pericarditis

- Infectious
  - Bacterial
  - Fungal
  - Parasite
  - Viral
- Postinjury
  - Blunt trauma
  - Medication
  - Myocardial infarction (MI)
  - Penetrating trauma
  - Radiation
  - Surgery
- Systemic diseases
  - Amyloidosis
  - Metastatic tumor
  - Rheumatoid arthritis
  - Sarcoidosis
  - Scleroderma
  - Systemic lupus erythematosus (SLE)
  - Uremia
- Primary tumors
- Aortic dissection

The pericardium envelops the heart and attaches to the great vessels. It consists of parietal and visceral layers, with a narrow potential space between. Each layer is 1 to 2 mm thick. An ultrafiltrate of plasma, 15 to 35 mL of fluid, is normally present in the pericardial space. The pericardium serves several functions: it maintains the heart's position, lubricates the heart's surface, prevents spread of infection, prevents cardiac overdilation, augments atrial filling, and maintains the normal pressure-volume relationships of the cardiac chambers. Patients with congenital absence (or surgical removal) of the pericardium, however, show few if any problems. Pericardial absence may be associated with other genetic-based issues, however.

In Western countries, 80% to 90% of pericarditis cases are labeled as idiopathic. The etiology may be infectious (viral or bacterial) or noninfectious (systemic inflammatory disease, cancer, post-cardiac injury) (Box 68.3). Tuberculosis is a common etiology in developing countries.[38] In one comprehensive study, pericarditis was diagnosed in 933 patients. No etiology was established in 516 patients (55%), 197 (21%) patients suffered from postinjury syndromes, and 156 (17%) had previously known diseases that were associated with pericarditis.[39]

There is an increase in the number of antibodies in the pericardial fluid of patients with pericarditis. Recent research has focused on the distinction between autoinflammatory and autoimmune pericarditis.[40]

Clinical Findings

The classic findings of pericarditis include chest pain, which can be severe, and pericardial friction rub. A history of fever and myalgias is common. The chest pain of pericarditis is sharp, pleuritic, waxes and wanes, and varies with position. It is relieved by sitting forward and worsened by lying down, deep inspiration, or swallowing. Pericarditis pain is retrosternal, can radiate to the trapezius muscles or back, or can present as isolated shoulder pain.

The classic physical examination finding is a pericardial friction rub. The rub may be caused by friction between inflamed or scarred visceral and parietal pericardium or from friction between the parietal pericardium and adjacent pleura. It may be audible anywhere over the anterior chest wall and is best heard using the stethoscope diaphragm positioned at the lower left sternal border with the patient leaning forward in full expiration. The rub also can be accentuated by a full inspiration, followed by a breath hold. The rub tends to be intermittent, migratory, and difficult to hear, but there can be a characteristic, obvious "scratchiness" and phasic nature of the rub.

Differential Diagnosis

The differential diagnosis includes myocardial infarction, inflammatory or infectious disease of the chest. Rarely pulmonary embolism can mimic pericarditis.

Diagnostic Testing

No single test is diagnostic for pericarditis. The diagnosis is based on chest pain, pericardial rub, ST elevation, and new pericardial effusion. The classic chest pain and ECG patterns are seen in only two-thirds of patients.

The ECG is the most reliable diagnostic tool (Fig. 68.4). It evolves through stages over time. The first stage occurs in the early hours to days of illness and includes diffuse ST segment elevation and reciprocal ST segment depression. Most patients with acute pericarditis have concurrent PR segment depression. In the next stages, the ST and PR segments normalize, but the T waves flatten followed by deep, symmetrical T wave inversion. At the last stage, the ECG reverts to normal, although the T wave inversions may become permanent. Ventricular dysrhythmias are rare in pericardial disease. Patients who have ventricular dysrhythmias should be presumed to have concomitant myocarditis, another cardiac disease, or to have been misdiagnosed.

ECG findings of acute pericarditis may be difficult to distinguish from acute myocardial infarction, coronary artery spasm, or benign early repolarization. In contrast to the ECG in AMI, the ST segment elevations in stage 1 acute pericarditis are concave rather than convex upward, simultaneous T wave inversions are not seen, and the findings are not bound to a single coronary artery distribution. Subsequent tracings do not evolve through a typical myocardial infarction pattern, and Q waves do not develop.

Up to 60% of patients have an effusion best seen with POCUS. A normal echocardiogram does not exclude pericarditis. The white blood cell (WBC) count and erythrocyte sedimentation rate are not sensitive or specific. Elevated C reactive protein has been proposed as a marker of inflammation, but the evidence is scant.[38] Other laboratory studies should be directed at determining nonidiopathic causes of pericarditis. Prominent pericardial delayed hyperenhancement on MRI suggests ongoing inflammation.[40]

Management

If a specific etiology of pericarditis is found, therapy should be directed accordingly. Otherwise, therapy for acute pericarditis is symptomatic. NSAID (ibuprofen 600 mg QID or indomethacin 25 mg TID) or aspirin (650 mg TID) for 10 days is the first choice. If the chosen NSAID is not effective within 1 week, a different class of NSAID (such as naproxen 250 mg BID) for 7 days may be tried. Adding colchicine improves treatment success and lowers the recurrence rate by 50%. Colchicine (0.5 mg QD if weight ≥ 70 kg; 0.6 mg BID if weight > 70 kg) should be used with caution in renal failure and pregnancy. It must be used for 3 to 6 months and has frequent side effects. Although the literature supports colchicine, this represents an opportunity for shared decision making with the patient because the side effect rate and recurrence risk are similar. The best choice is to start colchicine in the ED.[41] The second-line treatment is corticosteroids for those unable to take ASA or NSAIDs or those who take an anticoagulant. Low- to moderate-dose prednisone (0.2–0.5 mg/kg/day for 5 days has lower recurrence and complication rates than a higher dose (1.0 mg/kg/day).[38]

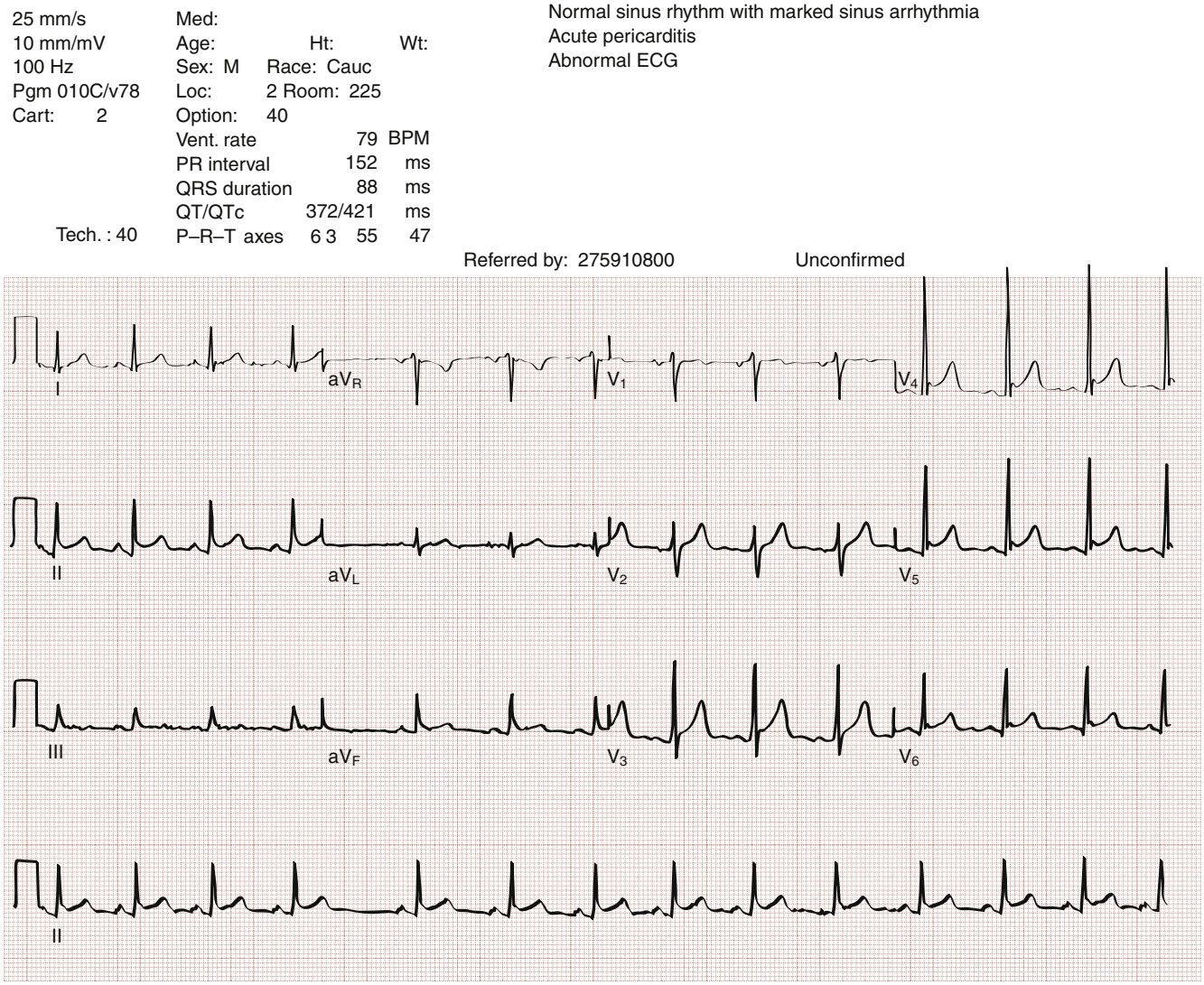

Fig. 68.4 Electrocardiogram (ECG) showing acute pericarditis. (Courtesy Ohio Chapter of the American College of Emergency Physicians.)

Treatment of recurrences that have failed NSAIDs, corticosteroids, and colchicine is difficult. Azathioprine and immunoglobulins have been trialed with little success. Preliminary results using the interleukin-1 beta recombinant receptor agonist anakinra have shown promise in patients whose pericarditis was refractory to colchicine or who could not be weaned from steroids.[42] Pericardiectomy may be needed if all other treatments fail.

Disposition

Most patients can be managed as outpatients unless there are hemodynamic abnormalities or diagnostic uncertainty with acute coronary syndrome. Temperature greater than 38°C/100.4°F, large effusion, and failure of first-round treatment are also indications for hospitalization. Athletes should not compete, though this recommendation is based on expert opinion without evidence to support it.[38]

The clinical course of pericarditis is variable: 60% of patients have complete recovery within 1 week, and almost 80% have complete recovery within 3 weeks. Up to 30% of patients suffer a recurrence, however. Patients with fever, pericardial effusion, a subacute course, or failure of initial NSAID treatment are more likely to have a recurrence. Patients with recurrent pericarditis should have repeat echocardiography to exclude tumor. Nonviral and nonidiopathic pericarditis have higher rates of conversion to constrictive pericarditis.

Uremic Pericardial Disease

Uremic pericarditis occurs secondary to renal failure or dialysis. The etiology is unknown. It occurs with both hemodialysis and peritoneal dialysis. For unclear reasons, it is more frequent with hemodialysis. The number of patients with end-stage renal disease (ESRD) is increasing, resulting in more cases of uremic pericarditis.[43]

Patients with uremic pericarditis have pleuritic chest pain and occasional fever. The ECG is often normal. Cardiac enlargement on chest radiograph in the absence of signs of volume overload or heart failure (HF) should prompt evaluation of pericardial effusion with POCUS. Uremic pericarditis is one of the most common causes of cardiac tamponade.

Patients with ESRD are immunocompromised, and occult infections may be present, including pericardial fluid infection. In considering the differential diagnosis, chest pain may be caused by coronary artery disease or pneumonia. Patients on dialysis frequently have hypotension, and cardiac tamponade must be evaluated in this differential.

Uremic pericarditis is initially treated with intensive dialysis, NSAIDs (indomethacin 25 mg TID), and may occasionally require drainage. Systemic steroids (prednisone 50 mg QD) or intra-pericardial injection of steroids (not an ED procedure) may be used in patients who do not respond to dialysis. If uremic pericarditis evolves into constrictive pericarditis, the patient may need a pericardial window or pericardiectomy.[43]

For patients with a large effusion or continued symptoms of dyspnea or chest pain, the best disposition is dialysis. If symptoms have improved, the vital signs are normal, and the effusion is small, the patient may be discharged home on NSAIDs with dialysis in the next 48 hours.

Post–Myocardial Infarction Pericarditis

Approximately 20% of patients with transmural MI experience chest pain of a different quality 2 to 4 days after infarction, characteristic of post-MI pericarditis. There is frequently low-grade fever and a transient pericardial friction rub. Early post-MI pericarditis is usually short-lived and treated with aspirin. The ECG changes of pericarditis may be masked by the AMI changes, making the diagnosis difficult. Patients with early post-MI pericarditis have more dysrhythmias and heart failure. Pericarditis in AMI may be an indicator of greater myocardial damage and a worse outcome.

Dressler reported a syndrome of delayed fever, pleuritis, leukocytosis, friction rub, and chest radiographic evidence of new pericardial or pleural effusions after MI. The cause of late post-MI pericarditis (Dressler syndrome) is unknown but is thought to be immunologic. This can occur any time, with most presenting 2 to 8 weeks postinfarct. The syndrome may also occur with pulmonary embolus and after pericardiotomy. Consider discontinuing anticoagulants to reduce the risk of hemorrhage. Delayed post-MI pericarditis is treated with NSAIDs (ibuprofen 600 mg QID or indomethacin 25 mg TID).

Postinjury Pericarditis

Postcardiac injury syndrome is defined as pericarditis after MI, cardiac surgery, or trauma. As such, it overlaps with Dressler syndrome. The incidence ranges from approximately 5% after MI to 30% after thoracic surgery or trauma. When it occurs after surgery, it is called postpericardiotomy syndrome. Infection, tamponade, and myocarditis may occur. An immune pathogenesis is suggested by the development of cardiac autoantibodies, although these autoantibodies are common after injury.

Symptoms and signs include pericardial rub, fever, and chest pain. Often there is a pericardial effusion. The interval between injury and the onset of pericarditis ranges from 4 to 12 days. During hospitalization, purulent pericarditis should be considered as a possible source of febrile illness in a patient with multisystem organ failure.

NSAIDs (ibuprofen 600 mg QID or indomethacin 25 mg TID) and colchicine (0.6 mg BID for weight > 70 kg) are the primary treatment choices. Steroids are reserved for refractory cases. Uncomplicated pericarditis secondary to blunt trauma usually resolves.

Since this is a complication of the original injury, these patients should be hospitalized. There is significant morbidity and mortality with the leading complications being constrictive pericarditis and cardiac tamponade.[44]

Neoplastic Pericardial Disease

Please see Chapter 112 for a discussion of neoplastic pericardial disease.

Radiation-Induced Pericarditis

Fewer than 5% of patients treated with radiation therapy develop pericarditis, an incidence that has decreased with improved techniques. The percentage of pericardial volume irradiated and the dosage determine which patients develop pericarditis. It is seen most commonly in patients with lymphoma or breast cancer. If this is the first episode of pericarditis after cure, tumor recurrence should be considered, and an oncologic workup either started or arranged from the ED.

Miscellaneous Causes of Pericarditis

Pericarditis occurs in approximately one-third of patients with rheumatoid arthritis, usually within 3 years of the initial diagnosis. It is rarely clinically significant. Prednisone is the initial treatment. Pericarditis, usually with effusion, is found at autopsy in more than 50% of patients with systemic lupus erythematosus (SLE). SLE pericarditis is treated with corticosteroids or NSAIDs. Patients with Sjögren syndrome, giant cell arteritis, ankylosing spondylitis, Behçet's disease, systemic sclerosis, and polyarteritis can all develop pericarditis. Pericarditis can rarely occur as an extraintestinal complication of inflammatory bowel disease and is independent of the clinical course of the gut disorder. Pericarditis can also occur as a complication of an implantable defibrillator or pacemaker, transbronchial needle aspiration or endoscopic variceal sclerotherapy. Pericarditis can be caused by erosion of a foreign body, such as a sewing needle or toothpick, through the esophagus into the pericardium.

Infectious causes of pericarditis include *Rickettsia conorii,* which causes Mediterranean spotted fever (treated with doxycycline), *Mycoplasma pneumoniae* (treated with a macrolide), *Nocardia asteroides* (treated with pericardiectomy and sulfisoxazole), *Chlamydia trachomatis* (treated with azithromycin or doxycycline), Epstein-Barr virus, cytomegalovirus infection, *Haemophilus actinomycetemcomitans* (treated with chloramphenicol), and coccidioidomycosis (endemic in the southwestern United States). Treatment is as for the systemic illness.

Tuberculous pericarditis is estimated to occur in 1% of patients with pulmonary tuberculosis and is associated with high mortality. In Africa, it is the most common cause of pericarditis. Coexisting HIV should be excluded.

Pericardial Effusion

The most common causes of pericardial effusion are viral or idiopathic pericarditis, malignancy, uremia, trauma, and radiation therapy. Drug reactions and autoimmune diseases are less common.

Pericardial effusion is often asymptomatic. Patients with known associated conditions, especially cancer or renal failure, who present with cough, fever, chest pain, or dyspnea should be considered to have an effusion until proven otherwise.

A minimum of 200 to 250 mL of pericardial fluid is necessary to produce cardiomegaly on chest radiograph. POCUS will confirm the diagnosis (Fig. 68.5) because it easily differentiates pericardial fluid from cardiac chamber enlargement and provides information about myocardial wall motion. CT or MRI may be useful when the echocardiogram is technically unsatisfactory. Nuclear scans may be useful to detect purulent pericardial effusions.

Small effusions may be treated with NSAIDs (ibuprofen 600 mg QID) and close follow-up to ensure no increase in size. Ultrasound-guided pericardiocentesis may be performed for either diagnostic or therapeutic purposes on large effusions.

Patients requiring pericardiocentesis should be hospitalized for serial examinations and determination of the underlying etiology of the pericardial effusion.

Purulent Pericarditis

Purulent pericarditis is a life-threatening process most commonly, but not exclusively, seen in hospitalized patients with systemic illness who

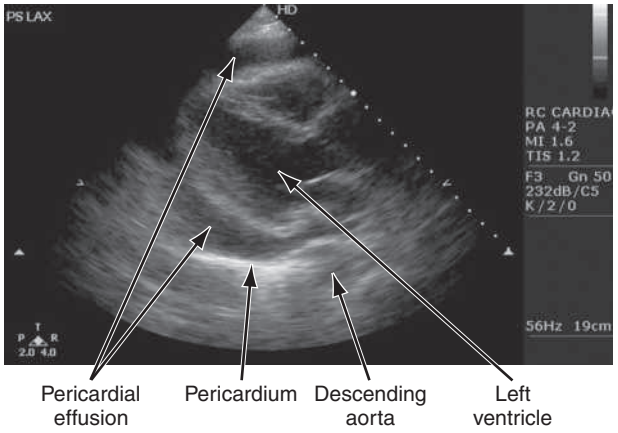

Fig. 68.5 POCUS showing a pericardial effusion. The effusion is best seen superior to the left ventricle at the top of the image. (Courtesy Jessica Resnick, MD.)

develop sepsis. It can occur in any age group and can be caused by any type of infectious agent. *Streptococcus* and *Staphylococcus* are the most common. *Candida* pericarditis is found after cardiac surgery and in patients with impaired host defenses. Purulent pericarditis occurs by several mechanisms: (1) spread from an adjacent infection, such as pneumonia or empyema; (2) hematogenous spread from a distant site; (3) direct inoculation of bacteria (trauma or procedure); and (4) spread from an intracardiac source. The most common mechanism is spread from a distant site.

Purulent pericarditis usually manifests as a febrile illness of several days' duration. Common presenting signs include tachycardia, dyspnea, hepatomegaly, elevated central venous pressure, chest pain, friction rub, and leukocytosis. It is most common in a hospitalized patient with a serious underlying disease who initially improves after treatment of the primary process but later develops fever, dyspnea, chest pain, and a pericardial effusion. Because many patients are discharged home before developing complications, purulent pericarditis is increasingly seen in the ED. A search for the common infection sources, including lungs, urine, and skin, is not successful and the patient gets worse until a pericardial source is considered.

Chest x-ray may show cardiomegaly, and POCUS will show fluid. Pericardiocentesis is necessary to establish the diagnosis, obtain fluid for microbiologic studies, and relieve cardiac tamponade if present.

Pericardiectomy is the traditional treatment of choice. Indwelling catheters, coupled with lavage, antibiotics, and fibrinolytics have been shown to be as effective. Intravenous antibiotics or antifungals and cardiorespiratory monitoring are needed. Fibrinolytic therapy may reduce the rate of constrictive pericarditis when surgery is not needed.

Because treatment requires interventions, ED patients will need hospitalization. The overall survival rate is approximately 30% with antibiotic therapy alone and 50% when combined with early surgical drainage. In addition to complications related to sepsis and tamponade, long-term sequelae include constrictive pericarditis.

Constrictive Pericarditis

Constrictive pericarditis (CP) can be a late consequence of any etiology of acute pericarditis. The incidence has increased as a result of improved survival in patients with chronic renal disease. The key pathophysiologic feature is a thickened pericardium that impairs diastolic filling by external cardiac restriction. Ventricular filling is rapid and completed within the first third of diastole.

Consider CP in any patient with right-sided heart failure symptoms. Dyspnea, fatigue, and weight gain are the most common symptoms. Hepatomegaly, marked pitting lower extremity edema and ascites also occur. The characteristic heart sound is a pericardial knock in early diastole. A friction rub may also be heard.

ECG findings include low voltage, nonspecific ST-T wave abnormalities, and atrial dysrhythmias. Heart size on the chest radiograph is usually normal. Pericardial calcification is suggestive. Liver function tests may be elevated due to passive hepatic congestion. Doppler echocardiography can differentiate constrictive pericarditis from RCM or cardiac tamponade. Cardiac catheterization to measure ventricular end-diastolic pressures or endomyocardial biopsy may be necessary. Pericardiectomy is the therapy of choice. CP is associated with mortality as high as 10%.

Cardiac Tamponade

Foundations

Cardiac tamponade is the result of compression of the myocardium by the contents of the pericardium. This compression is usually caused by fluid. It may also be caused by gas, pus, blood, or a combination of substances.

Cardiac tamponade occurs in a physiologic continuum reflecting the amount of fluid, the rate of accumulation, and the underlying condition of the heart. The most important factor in the development of tamponade is the rate of fluid accumulation. The three stages necessary for tamponade to develop are (1) fluid filling the recesses of the parietal pericardium, (2) fluid accumulating faster than the rate of the parietal pericardium's ability to stretch, and (3) fluid accumulation that exceeds the body's ability to increase blood volume to support the right ventricle filling pressure. The result is increased pericardial pressure, which causes decreased ventricle compliance and decreased flow of blood into the heart. The reduction of blood inflow into the right ventricle results in decreased stroke volume that leads to decreased cardiac output.

The heart initially responds to tamponade by increasing heart rate to maintain cardiac output. This compensatory mechanism is maintained until late in the clinical course, followed by rapid decompensation.

Cardiac tamponade should be suspected in patients with penetrating chest wounds. It is also common in patients with uremic pericarditis and cancer. Etiology includes malignancy (32%), infection (24%), idiopathic (16%), iatrogenic (15%), post-acute MI (7%), uremic (4%), and other causes (2%). The most common associated cancers are lung, breast, lymphoma, and gastrointestinal. Infections include staphylococcus, streptococcus, tuberculosis, and HIV. Iatrogenic causes include post–cardiac catheterization, post–cardiac surgery, and anticoagulant use. Post-MI tamponade is due to cardiac wall rupture 44% of the time.[46]

Clinical Features

Cardiac tamponade symptoms, though often nonspecific, include chest pain, cough, or dyspnea, any of which may be progressive and severe. Dyspnea is most common. The classic triad described by Beck is hypotension, distended neck veins, and muffled heart sounds. These signs may not be present, especially if tamponade develops quickly.

Differential Diagnosis

Cardiac tamponade can be confused with other causes of chest pain such as small pericardial effusion, myocardial ischemia, pericarditis, cardiomegaly, dilated cardiomyopathy, jugular venous distention, superior vena cava syndrome, and heart failure.

Diagnostic Testing

The chest radiograph may show cardiomegaly, but only if there is more than 250 mL of pericardial fluid. The ECG classically shows decreased voltage. Electrical alternans is helpful to make the diagnosis but rarely

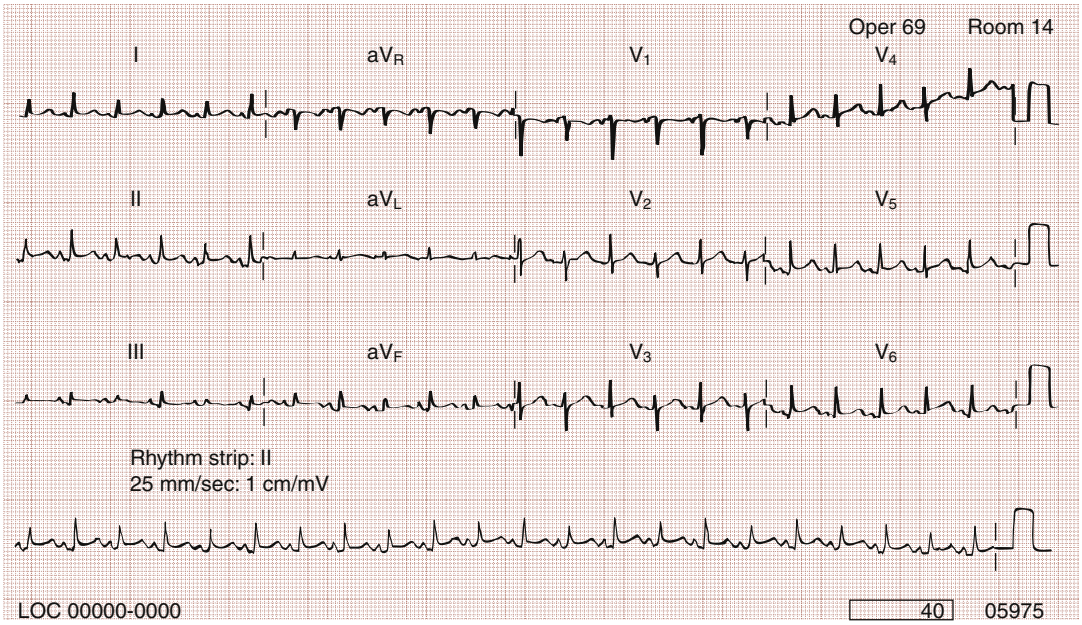

Fig. 68.6 Electrocardiogram (ECG) showing electrical alternans.

occurs (Fig. 68.6). POCUS confirms the diagnosis when effusion and chamber collapse are seen. Cardiac catheterization demonstrates equalization of right and left ventricle pressures (Video 68.1).

Management

Initial treatment is intravenous fluids to increase right-sided filling pressure and overcome pericardial fluid constriction. Pericardiocentesis or pericardial window is the treatment of choice. If tamponade recurs, pericardiocentesis may be repeated, or a drainage catheter may be left in the pericardial space. Pericardiectomy may be necessary.

Disposition

Patients with cardiac tamponade should be hospitalized, usually in a critical care setting. Cardiac tamponade has a high mortality rate, usually related to the underlying disease.

Pneumopericardium

Pneumopericardium is rare. Pneumopericardium is caused by the formation of fistulae between the pericardial and pleural space, bronchial tree, or upper gastrointestinal tract. It may result from bronchial carcinoma or infection with gas-producing microorganisms, or it can be idiopathic. Spontaneous pneumopericardium is caused by an increase in intra-alveolar pressure above atmospheric pressure, resulting in rupture of alveoli. It is associated with many causes including asthma, labor, barotrauma from positive-pressure ventilation, Valsalva maneuvers, weightlifting, and recreational drug inhalation from positive-pressure devices or when augmented by a Valsalva maneuver.

Physical findings depend on the quantity of fluid and gas in the pericardial space. Heart sounds may have a metallic quality accompanied by splashing sounds called the Hamman sign or mediastinal crunch. This is diagnostic. Clinical sequelae of tension pneumopericardium are similar to acute cardiac tamponade. The diagnosis of pneumopericardium is usually confirmed by chest radiograph, POCUS, or cardiac ultrasound, but if not, then CT scan is indicated. Tension pneumopericardium should be treated with emergency pericardiocentesis. Stable patients with uncomplicated spontaneous pneumopericardium may be discharged after all other life-threatening injuries and complications have been excluded. No long-term sequelae are expected.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 68: QUESTIONS AND ANSWERS

1. A 33-year-old man presents with a 4-hour history of left anterior chest pain associated with mild shortness of breath. He is otherwise healthy except for chronic tobacco use. Vital signs are: blood pressure, 142/92 mm Hg; heart rate, 120 beats per minute; respiratory rate, 24 breaths per minute; temperature, 100.4°F (38.0°C) oral; and oxygen saturation, 97%. Physical examination is remarkable for tachycardia and a friction rub. The patient's electrocardiogram (ECG) is shown below. Which of the following would be the most appropriate therapy?
   a. Cardiac catheterization
   b. Ibuprofen 600 mg QID and colchicine
   c. Nitroglycerin, aspirin 324 mg oral, cardiology consultation
   d. Oxygen, serial troponin levels

Answer: b. The ECG shows findings consistent with acute pericarditis. Clinically, diffuse ST elevation is seen in leads I, II, II, aV_L, aV_F, and V_2 to V_6. In contrast to finding an acute myocardial infarction (AMI), ST elevations are concave upward in acute pericarditis rather than convex upward as seen with a myocardial infarction (MI). PR depression is also a frequent finding. As the acute pericarditis resolves, ST changes revert to normal, followed by T wave flattening and later deep symmetrical inversion, which may persist. NSAIDs are the mainstay therapy for uncomplicated pericarditis. Colchicine helps decrease recurrence. Oxygen therapy is not helpful in patients with normal oxygen saturation. Because the ECG, examination, and history point to pericarditis, cardiac catheterization is not needed. There are case reports of thrombolytics use in pericarditis leading to pericardial hemorrhage and major complications.

2. Which of the following statements regarding post–myocardial infarction (MI) pericarditis is true?
   a. Classic pericarditis electrocardiogram (ECG) findings are reliably seen.
   b. It indicates a greater degree of myocardial damage than those without pericarditis.
   c. Large pericardial effusions are common.
   d. The incidence of congestive heart failure (CHF) is unchanged.

Answer: b. Both dysrhythmias and CHF are more common in patients who experience post-MI pericarditis. Large effusions are uncommon, and classic pericarditis ECG findings are often overshadowed by the changes of the recent or evolving MI.

3. A 15-year-old female presents during summer break with fever, cough, and chest pain. She has no history of illnesses or medication use. No street drug use. Her vital signs are BP 110/70, T 38.4, P 122, RR 16, SaO_2 96% on RA. ECG shows sinus tachycardia with normal intervals and low voltage. You order a troponin test and it is slightly above the normal range. Which other test result would you expect?
   a. Cardiomegaly on chest x-ray
   b. Elevated C-reactive protein
   c. Elevated sodium and creatinine
   d. Regional wall motion abnormalities on POCUS

Answer: d. Patients with myocarditis show regional wall motion abnormalities and global hypokinesis on POCUS. Even though there is inflammation, WBC and CRP are neither sensitive nor specific for myocarditis. Electrolyte and renal abnormalities should not occur. Cardiomegaly is a late finding if it occurs at all.

4. A 55-year-old woman presents with progressive dyspnea, chest pain, and cough over 5 days. She has a past history of renal failure and is on dialysis, last 2 days ago. She does not smoke. Vital signs are: temperature, 100.2°F (37.9°C) oral; heart rate, 120 beats per minute; respiratory rate, 26 breaths per minute; blood pressure, 100/60 mm Hg; and oxygen saturation, 96% on room air. Physical examination is remarkable for 3-cm jugular venous distention at 45 degrees, clear lung fields on auscultation, tachycardia without a friction rub, trace pretibial edema, and weak peripheral pulses that disappear during expiration. Chest radiograph shows an enlarged cardiac silhouette and clear lung fields. What would be the most appropriate initial intervention?
   a. Endotracheal intubation with rapid sequence induction
   b. Enoxaparin 1 mg/kg subcutaneous
   c. Computed tomography (CT) scan of the chest
   d. Isotonic fluid bolus and point of care cardiac ultrasound

Answer: d. This patient is presenting with cardiac tamponade, presumably secondary to an uremic pericardial effusion. Pulmonary embolus is a consideration but less likely, given the picture of normal oxygen saturation and an enlarged heart. The initial intervention should be fluid loading to maintain preload and cardiac output, followed by ultrasound confirmation and likely pericardiocentesis. Fluid loading in renal failure may easily result in pulmonary edema, so expeditious relief of tamponade is indicated. It is too early for intubation because the patient is oxygenating adequately.

5. A 44-year-old man complains of swollen legs. He just finished two courses of prednisone for wheezing related to asthma. The first course was prescribed 6 weeks ago in the emergency department (ED), where he was diagnosed with new onset asthma and normal chest radiograph. The second course was prescribed by his family physician 2 weeks ago. The patient denies fever and chest pain and is still mildly short of breath, which is worse at night or with exertion. Examination shows bibasilar rales in his lungs, normal heart sounds, and 1+ edema in both legs up to his knees. What is his diagnosis?
   a. Asthma exacerbation
   b. Idiopathic dilated cardiomyopathy (DCM)
   c. Prednisone-induced edema
   d. Prednisone-induced liver failure

Answer: b. The patient is unlikely to have a new diagnosis of asthma. He most likely had a viral process leading to reactive airway disease initially and viral myocarditis later. He unfortunately now has a DCM and symptoms of heart failure. Treatment is supportive. Prednisone-related end-organ damage usually does not occur this quickly.

69

Infective Endocarditis and Valvular Heart Disease

Bradley W. Frazee and Martha E. Montgomery

KEY CONCEPTS

- Infectious endocarditis (IE) is more often caused by Staphylococcus species than Streptococcus, and increasingly occurs in elderly, recently hospitalized patients, those with prosthetic valves and intra-cardiac devices, and in patients who inject opioids.
- IE should be considered in any patient with a predisposing condition plus fever; IE frequently presents with a complication, including heart failure, embolic stroke, or osteomyelitis.
- At least two sets of blood cultures (obtained before starting antibiotics) and transthoracic echocardiography are the key diagnostic tests to order for patients with suspected IE.
- Empiric antimicrobial treatment for IE should include vancomycin.
- Consultation with a cardiothoracic surgeon is recommended for left-sided vegetations.
- Acute rheumatic fever is a delayed nonsuppurative complication of streptococcal pharyngitis characterized by arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.
- In a patient with severe mitral stenosis, hypovolemia and tachycardia are poorly tolerated. "Slow and full" are appropriate goals.
- In patients with critical aortic stenosis, avoid excessive preload reduction with vasodilators and diuretics.
- In patients with acute aortic insufficiency, classic physical findings may be absent. Medical stabilization entails the cautious use of vasodilators and diuretics. Intraaortic balloon counterpulsation is contraindicated.
- Complications of prosthetic heart valves range from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis.

INFECTIVE ENDOCARDITIS

Foundations

Background and Importance

Infective endocarditis (IE) is defined as an infection of a native or prosthetic heart valve, the endocardium, or an indwelling cardiac device. While risk factors and common causative pathogens have shifted in developed countries in recent decades, IE incidence and mortality remain unchanged. IE is a disease with a highly variable and often nonspecific presentation, with the only consistent feature being fever. Early diagnosis and correct initial management remain very challenging, particularly in the emergency department (ED) setting.

Recent changes in the epidemiology of IE in industrialized countries have led to changes in disease presentation. While the overall annual incidence has changed little (9 to 15 cases/100,000), IE has increasingly become a disease of older adults, with the incidence rising dramatically in patients over age 60 and those with multiple comorbidities.[1,2] The incidence of prosthetic valve, intracardiac device (pacemakers and defibrillators), and healthcare-associated infections is increasing. Up to 36% of community onset IE is healthcare-associated, occurring in nursing home residents, patients undergoing dialysis or chemotherapy, or following a recent hospitalization.[1] As opioid addiction has increased in the United States, the proportion of IE cases linked to injection drug use (IDU) has risen nationwide, from 7% in 2000 to 12% in 2013, and exceeds 50% of cases in some communities.[3,4]

The 90-day mortality from IE averages nearly 25%. Predictors of poor outcomes include older age and presence of comorbidities, infection with *Staphylococcus aureus*, heart failure, and perivalvular extension.[1,5] Streptococcal and isolated right-sided infections are associated with better outcomes.

Pathophysiology and Microbiology

Development of IE requires either predisposing valve dysfunction, endothelial damage, or prosthetic material, conditions that all lead to formation of a platelet-fibrin thrombus, which is then seeded with bacteria (Box 69.1). Yet, at the time of presentation, up to 50% of IE patients have no known history of predisposing structural or valvular heart disease or prosthetic device.[6] Occult degenerative heart disease and bicuspid aortic valve are thought to account for many such cases. Rheumatic valvular disease, now uncommon in industrialized countries, remains a common predisposing condition in developing countries. Congenital heart disease predisposes to IE, with the highest infection risk being from cyanotic conditions and repaired lesions with residual prosthetic material, shunt, or valve regurgitation. A prior history of IE confers a high lifelong risk of recurrence, even when the source of endothelial damage remains occult.

IDU carries a high risk of IE, even in patients with normal heart valves. Injection of nonsterile illicit drugs leads to endothelial damage by a poorly understood mechanism, and the resulting thrombus can be seeded by frequent injection-related bacteremia. Though IDU-associated IE may involve any valve, it is much more likely to be right-sided than in non-IDU patients, occurring on the tricuspid valve in approximately 50% of cases.

Prosthetic heart valves and intra-cardiac device leads represent an increasingly common nidus for infection.[7] In community hospital populations, prosthetic valve and cardiac device-related infections now account for roughly 15% and 5% of IE cases, respectively, with even higher proportions in tertiary care centers.[1,8] Prosthetic valve endocarditis (PVE) complicates up to 6% of both bioprosthetic and mechanical valves, with an incidence of 0.3% to 1.2% per patient/year.[5] The highest risk for PVE occurs during the first 6 months after surgery, and these early infections have a worse prognosis. IE associated with pacemaker and defibrillator leads may occur via hematogenous seeding or device pocket infection. It begins as a right-sided infection, usually involving the tricuspid valve.

Bacteremia is also considered requisite for the development of IE, except when contamination occurs perioperatively during valve

BOX 69.1 High-Risk Populations and Predisposing Conditions for Infectious Endocarditis

Prior history of endocarditis
Congenital heart disease (see text for highest risk lesions)
Injection drug use
Prosthetic heart valve
Intracardiac device (pacemaker, defibrillator)
Hemodialysis
Recent hospitalization with central or long-term intravenous access

replacement or device implantation. Poor dentition, dental procedures, and cystoscopy are classically implicated sources of bacteremia. IDU, central and long-term intravenous lines in hospitalized patients and hemodialysis all lead to frequent staphylococcal bacteremia.

The microbiology of IE in industrialized countries has shifted in recent decades, along with the changes in its epidemiology and predisposing conditions. Gram-positive organisms continue to be the leading cause of IE, but Staphylococcus species now predominate, accounting for 30% to 40% of all infections.[1] *S. aureus* is a virulent pathogen, with a predilection for metastatic complications, particularly stroke, relatively acute infections, and high associated mortality. Methicillin-resistant *Staphylococcus aureus* (MRSA) now accounts for almost 15% of IE cases in the United States, and is more common in hemodialysis, IDU, and healthcare-associated infection. The skin commensal coagulase-negative Staphylococcus species, which are often methicillin-resistant and adhere well to prosthetic material, are more common in early PVE and hemodialysis-associated infection. Streptococcus species, including oral commensals belonging to the viridans group, remain the leading IE etiology in developing countries. *Streptococcus bovis* IE is associated with underlying gastrointestinal malignancies. *Enterococcus faecalis* causes both PVE and native valve infection, primarily in elderly and debilitated patients. Streptococcus and Enterococcus infections tend to cause classic, indolent, subacute endocarditis.

The remaining IE etiologies together account for about 15% of cases, and frequently produce initially negative blood cultures. The group of fastidious gram-negative bacteria, termed HACEK—*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*—can often be isolated within 5 days in modern blood culture systems.[9] Zoonotic etiologies include Coxiella burnetii (Q fever) and Brucella species from livestock, and Bartonella species from body lice and cats. Fungal endocarditis, mostly due to Candida and Aspergillus species, is primarily associated with prosthetic valves, IDU, and immunocompromised states.[10] The above organisms are considered typical of, or consistent with, IE, and blood cultures that grow any of these are a key component of the Duke diagnostic criteria (Box 69.2).

The concept of subacute versus acute infection is no longer used to classify IE. Rather, IE is now classified by the type of valve and by the setting in which it is acquired. Categories include native valve versus prosthetic valve; community-associated versus healthcare-associated (which is sub-classified as nosocomial or community onset); IDU-associated; and intra-cardiac device-associated. PVE is sub-classified as early (≤12 months) or late.

Cardiac and embolic complications develop over time as the infected vegetation grows. Valve leaflet distortion and destruction leads to regurgitant flow and impaired cardiac function. Aortic valve involvement carries the highest risk of clinical heart failure from acute aortic insufficiency. Bacterial invasion of the myocardium can lead to abscess formation and conduction blocks. Friable, infected material

BOX 69.2 Summary of Clinical Duke Criteria for Diagnosis of Infective Endocarditis

Definite Endocarditis
- Two major clinical criteria
- One major and any three minor clinical criteria
- Five minor clinical criteria

Possible Endocarditis
- One major and one or two minor clinical criteria
- Three minor clinical criteria

Major Criteria

Positive Blood Cultures

At least 2 sets positive with typical IE pathogen, including:
- *Staphylococcus aureus*
- Viridans streptococci species of *Streptococcus bovis*
- Enterococcus species
- HACEK group (see text)

Or persistent positive blood cultures with an organism consistent with IE
Or single blood culture or serology positive for *Coxielli burnetii*

Evidence of Endocardial Involvement by Echocardiography
- Pendulum-like vegetation on valve endocardium
- Paravalvular abscess
- Prosthetic valve dehiscence
- New valvular regurgitation

Minor Criteria

Predisposition—predisposing heart condition or intravenous drug use
Fever—temperature greater than 38°C (100.4°F)
Vascular phenomena—arterial emboli, septic pulmonary infarcts, mycotic aneurysm, conjunctival hemorrhages, or Janeway lesions
Immunologic phenomena—glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiologic evidence—positive blood culture not meeting major criteria
Echocardiographic findings—consistent with endocarditis but do not meet major criteria

can embolize from left-sided vegetations, causing downstream tissue infarction, metastatic abscess, mycotic aneurysm, or immune complex deposition. The cerebral circulation is the most frequent site of large vessel embolization, and hemorrhagic transformation of the infarct is common. Right-sided endocarditis produces septic pulmonary emboli.

Clinical Features and Differential Diagnosis

Symptoms of IE are nonspecific and diverse (Box 69.3). Patients often appear relatively well. However, depending on host factors, location of the vegetation, and microbial virulence, some present acutely ill with sepsis and multi-organ failure. The most common symptom is fever (90%). The list of additional possible symptoms includes chills, malaise, weight loss, cough, dyspnea, chest pain, headache, myalgias, arthritis, back or neck pain, altered mental status, or a focal neurologic complaint. A measured fever is present in the ED in about 80% of patients with IE. Since a new murmur, or worsening of a preexisting murmur, is present in only 68% of patients, often no murmur will be heard in the ED. In approximately 30% of cases, the primary presenting syndrome represents a complication of IE, including acute heart failure, stroke, septic pulmonary emboli, and vertebral osteomyelitis.[5]

With such a broad range of possible presentations, IE can easily be mistaken for another infection, such as a viral syndrome, meningitis, or pneumonia, particularly common with right-sided IE and septic

BOX 69.3 Presenting Clinical Syndromes and Findings in Infectious Endocarditis

Syndromes

- Mild and nonspecific febrile illness
- Acute heart failure
- Focal neurological deficit from septic cerebral embolus
- Altered mental status
- Axial spine pain from osteomyelitis
- Pneumonia from septic pulmonary emboli

Findings

- Heart murmur
- Splinter hemorrhages
- Cardiac device pocket inflammation
- Janeway lesions, Osler's nodes
- Roth spots
- Splenomegaly
- Anemia
- Glomerulonephritis

pulmonary emboli. It can also present similarly to a non-infectious problem, such as acute coronary syndrome, primary heart failure, or stroke. In these cases, fever may be the key sign prompting consideration of IE.

The most important clue to the diagnosis of IE is the presence of a predisposing condition (see Box 69.1). If IE is suspected, a core temperature should be correctly measured to assess for fever, multiple times if necessary, and a particularly careful cardiac auscultatory exam performed. Peripheral embolic and vasculitic stigmata should be sought (see Box 69.2), although each is found in only about 5% of cases, with splinter hemorrhages being the most commonly seen (Fig. 69.1).

Diagnostic Testing

Findings on standard laboratory tests in IE are nonspecific. Clinicians must consider IE when faced with a constellation of suggestive findings rather than looking for a single definitive test. Normocytic anemia and hematuria and proteinuria, suggesting glomerulonephritis, are classic findings in indolent infections. An elevated erythrocyte sedimentation rate and C-reactive protein are expected in roughly 60% of cases. A chest x-ray may show signs of heart failure or septic pulmonary emboli, and an electrocardiogram (ECG) may display conduction abnormalities related to a myocardial abscess.

When IE is suspected, it is the responsibility of the emergency clinician to ensure that blood cultures are obtained prior to administering antibiotics. Blood culture results are key to both definitive diagnosis and tailored antimicrobial therapy. At least two sets, each containing 10 cc of blood, should be drawn from separate sites and, if possible, separated in time by at least one hour. Three sets of blood cultures are required in suspected PVE or cardiac device-related infection because one of the most common pathogens in prosthetic device infections, coagulase-negative *S. aureus*, is also the most common blood culture contaminant.

Echocardiography is the other key diagnostic test in IE. Transthoracic echocardiography (TTE) should be performed as soon as possible whenever IE is suspected. While the diagnostic sensitivity of TTE for one of the definitive endocardial findings of IE (see Box 69.2) is no more than 70%, its specificity is very high. Hence, this noninvasive test stands to make the correct diagnosis very rapidly while the patient is still in the ED. More importantly, echocardiography can identify endocardial complications that may require urgent surgery, including acute

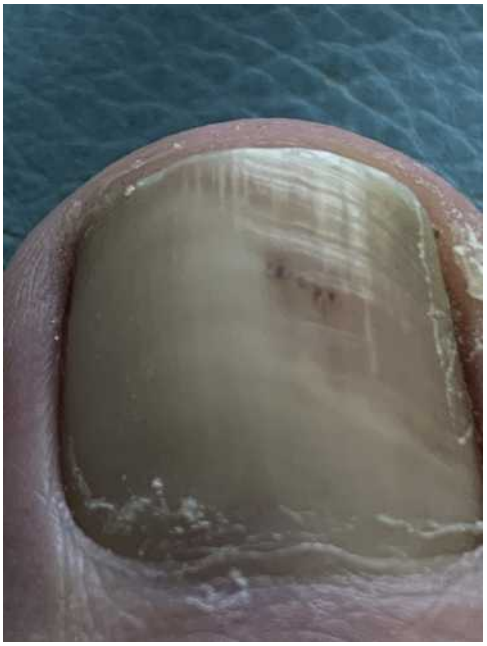

Fig. 69.1 Splinter hemorrhage on the great toe in a patient with aortic valve *Streptococcus bovis* infectious endocarditis. (Courtesy of Gene Hern, MD.)

BOX 69.4 Summary of Indications for Surgical Treatment for Infective Endocarditis

Aortic or mitral insufficiency with ventricular failure
Valve perforation or rupture
Perivalvular extension, abscess, fistula, associated heart block
Prosthetic valve dehiscence
Less than 10 mm vegetation on the anterior mitral leaflet
Recurrent embolization or persistent bacteremia on therapy

valvular insufficiency or perforation with heart failure, perivalvular extension, prosthetic valve dehiscence, and vegetation size greater than 10 mm, which presents an elevated embolic risk (Box 69.4).[5,11] The sensitivity of transesophageal echocardiography (TEE) is significantly higher than that of TTE, both for identifying vegetations and assessing for complications, particularly in PVE.

TEE is now recommended after TTE in all cases, though this invasive modality will usually be performed after hospital admission. The value of point of care TTE, performed immediately by experienced emergency clinicians in the setting of suspected IE, has been demonstrated in numerous case reports, although its role has yet to be evaluated in a large study (Fig. 69.2).[12]

Additional advanced imaging in patients with suspected IE should generally be driven by symptoms. Some advocate routine brain magnetic resonance imaging (MRI) in uncertain cases, even without neurological symptoms, because asymptomatic cerebral emboli are found in up to 60% of those with left-sided infection, and this finding constitutes a Duke minor criteria.

Management

In the sickest subset of IE patients, ED management begins with stabilization, including evidence-based therapy for sepsis, hemodynamic support, and positive pressure ventilation. Patients with suspected IE and acute heart failure require immediate consultation by a cardiothoracic surgeon, and emergency clinicians need to be

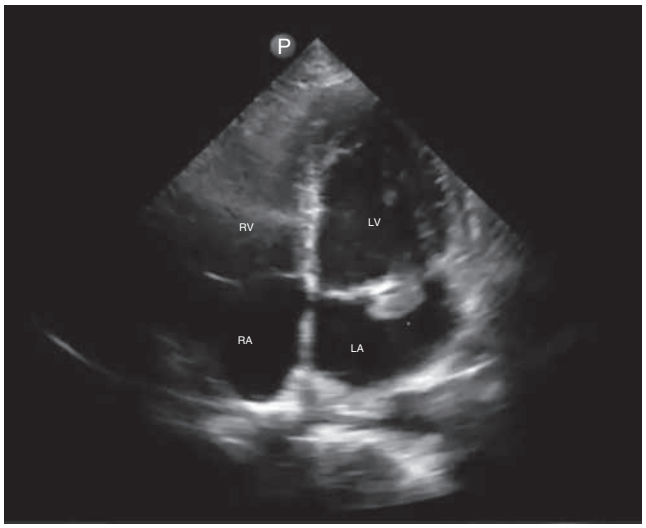

Fig. 69.2 Large mitral valve vegetation as seen on ED point of care ultrasound, apical 4 chamber view. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Courtesy of Highland Emergency Ultrasound Division.)

aware of additional echocardiographic findings that are indications for surgical therapy (see Box 69.4). In general, there has been a shift toward earlier surgical treatment in IE, with approximately one-half of patients with left-sided infection undergoing surgery during the index admission.[9] If possible, patients with left-sided IE should be managed by a multidisciplinary team at a center capable of cardiothoracic surgery.

In the ED, initial antimicrobial treatment of IE is almost always empiric. Occasionally, patients present because previously drawn blood cultures have returned positive; in such cases, isolate susceptibility-directed antibiotics should be selected in consultation with an infectious disease specialist. Consensus guidelines on IE treatment tend to focus on pathogen-specific therapy, with limited discussion or recommendations regarding empiric treatment.[5,13] Patient characteristics to consider in choosing the empiric regimen include whether there is a prosthetic valve, history of IDU, or recent health care exposure, as well as disease severity. If available, hospital-specific empiric treatment recommendations, which account for local susceptibility patterns and are updated regularly, supersede published guidelines, which are updated infrequently.

In most cases, empiric therapy in the ED should include vancomycin (20 to 35 mg/kg actual body weight loading dose, then 15 to 20 mg/kg every 8 to 12 hours not to exceed 3000 mg). Vancomycin alone for one or two doses is a reasonable approach for native valve and prosthetic valve infection and in IDUs. Addition of ceftriaxone (2 g/day) can be considered to cover HACEK and other gram-negative organisms, responsible for less than 6% of infections.[1,5] As soon as blood culture results return, pathogen and susceptibility-directed therapy is selected by an infectious disease specialist. Because of the complex pathology of bacterial growth within vegetations, 4 to 6 weeks of parenteral antibiotic therapy is generally required to eliminate infection. For selected stable patients who respond well to initial therapy in the hospital, IV treatment can be completed as an outpatient. Protocols that include partial oral therapy have recently proven effective and safe.[14]

Disposition

All patients with suspected IE, in whom blood culture results are pending, should be hospitalized. Increasingly, for selected stable patients who respond well to initial treatment in the hospital, IV antibiotic therapy can be completed at home.

Prophylaxis

The American Heart Association and European Society of Cardiology recommend antibiotic prophylaxis to prevent IE for individuals with very high-risk predisposing conditions before undergoing procedures that produce heavy bacteremia with potential IE pathogens. These primarily consist of dental procedures. High-risk predisposing conditions include a prior history of IE, certain forms of congenital heart disease (see previous) and the presence of a prosthetic valve. This issue is of limited relevance to emergency practice, since most commonly performed ED procedures do not produce the kind of bacteremia that requires prophylaxis—including local anesthesia injection into uninfected tissue, laceration repair, endotracheal intubation, and foley catheter placement in the absence of infection. Prophylaxis should be administered prior to cutaneous abscess drainage, however. A reasonable approach is to administer IV vancomycin (15 mg/kg) one hour before incision and drainage.

RHEUMATIC FEVER

Foundations

Background and Importance

From 1920 to 1950, acute rheumatic fever (ARF) was the leading cause of death in United States children and the most common cause of heart disease in individuals younger than age 40 years. During the 1960s and 1970s, the incidence of ARF in the United States and other developed countries declined dramatically because of widespread antibiotic treatment of streptococcal infections, the declining prevalence of the more virulent strains of group A streptococci, and improved hygiene and living conditions. In many developing nations, however, ARF continues to be a leading cause of childhood mortality. Children 4 to 9 years of age remain at greatest risk, with an annual incidence of ARF of 2 to 14 cases/100,000. Chronic rheumatic heart disease (RHD), a consequence of ARF, peaks in adults between the ages of 25 and 34 years. There are an estimated 34 million people worldwide living with RHD.[15]

Pathophysiology

ARF is a delayed nonsuppurative complication of streptococcal pharyngitis. ARF is thought to result from an exaggerated immunologic response to group A beta-hemolytic streptococci—antibodies cross-reacting with tissues in the heart, joints, skin, and central nervous system. Patients with a history of ARF are predisposed to recurrent Strep infections, and repeated infections lead to progressive heart damage.

Clinical Features and Differential Diagnosis

ARF occurs 1 to 5 weeks after the initial bout of pharyngitis. Up to one-third of patients with documented ARF do not remember having had pharyngitis in the preceding month. Fever is generally present during the acute phase of rheumatic fever, rarely lasting more than 2 weeks. Additional manifestations include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum (see Box 69.4).

A syndrome of mono- or poly-articular arthralgias and arthritis is the most common finding in ARF. Arthritis tends to occur early in the course of ARF and often coincides with a rising titer of streptococcal antibodies. It classically affects large joints, such as the knee, ankle, elbow, and wrist. The pain may be more severe than physical findings suggest (severe arthralgias). Synovial fluid analysis generally reveals a sterile inflammatory fluid.

Cardiac manifestations of ARF may be subtle and can include symptoms and signs of pericarditis, myocarditis, and endocarditis. The mitral valve is the most commonly affected, causing acute mitral regurgitation (MR). Inflammation of the valvular endocardium may result in permanent deformity and impairment of one or more valves over

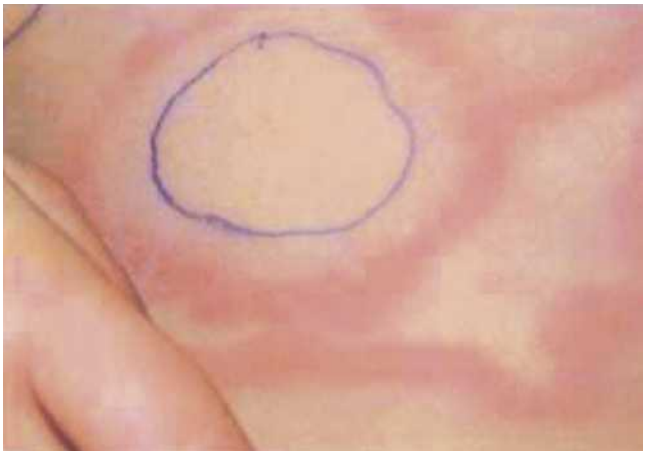

Fig. 69.3 Erythema Marginatum. This is one form of annular erythema seen in 10% of cases of children with acute rheumatic fever but is rare in adults with the disease. (From Cohen J, Powderly WG. *Infectious Diseases*. 2nd ed. New York: Mosby; 2004.)

the course of decades. Stenotic lesions of the mitral and/or aortic valve are common late manifestations of RHD (Fig. 69.3).

Chorea is a random, rapid, purposeless movement, usually of the upper extremities and face. Chorea is a relatively rare manifestation of ARF that tends to emerge after a long latency period. Subcutaneous nodules and erythema marginatum are found in fewer than 10% of cases of ARF. Their presence, however, should suggest the diagnosis. Subcutaneous nodules are pea-sized and nontender. They typically appear over the extensor surfaces of the wrists, elbows, knees and, occasionally, the spine. Erythema marginatum is a nonpruritic, painless, evanescent ring of erythema that commonly appears on the trunk and proximal extremities (see Fig. 69.3).

Diagnostic Testing

Diagnosis of ARF is clinical, based on the presence of the characteristic manifestations plus evidence of antecedent streptococcal infection. In 1944, Jones formulated major and minor criteria for the diagnosis of ARF, which, in revised form, remain the basis for making the diagnosis (Box 69.5).[16] Throat cultures are usually negative at the time of clinical onset of ARF, but antistreptolysin antibody titers remain positive for 4 to 6 weeks from the time of infection. The erythrocyte sedimentation rate and C-reactive protein levels are typically elevated, and a prolonged PR interval is common and suggestive in ARF.

Management and Disposition

All patients with ARF should receive antibiotic therapy, regardless of the clinical history of pharyngitis. Penicillin can be administered orally (250 mg for patients less than 28 kg, 500 mg for patients 28 kg and above, BID or TID for 10 days) or intramuscularly (600,000 units of penicillin B for patients less than 28 kg, 1.2 million units for patients 28 kg and above, as a one-time dose).

Treatment for arthritis consists of anti-inflammatory agents, usually aspirin, administered until symptoms resolve and the erythrocyte sedimentation rate and C-reactive protein concentration normalize. Patients with severe carditis are often treated with corticosteroids, but no evidence supports this treatment. Patients with congestive heart failure should be managed accordingly. Treatment is aimed at symptom relief and unfortunately does not decrease the likelihood of progression to RHD. Primary prevention involves treating those with group A streptococcal pharyngitis within nine days of the onset of symptoms, which decreases the risk of ARF. Following ARF, patients should receive prophylactic antibiotics (generally, penicillin) for up to 10 years, depending on the severity of carditis, to prevent recurrences.

BOX 69.5 Jones Criteria (Revised) for the Diagnosis of Acute Rheumatic Fever

Major Manifestations
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules

Minor Manifestations
Arthralgias
Fever
Increased erythrocyte sedimentation rate or C-reactive protein level
Prolonged PR interval

Evidence of Preceding Streptococcal Infection
Positive throat culture for group A beta-hemolytic streptococci or positive rapid streptococcal antigen test
Elevated or rising streptococcal antibody titer, usually antistreptolysin O

VALVULAR HEART DISEASE

Foundations

Anatomy and Physiology

There are four heart valves, three of which (tricuspid, pulmonic and aortic) are tricuspid, while the mitral valve is bicuspid. Each cusp is formed from a double layer of endocardium attached at its base to the fibrous skeleton of the heart. For the tricuspid and mitral valves, muscular projections from the ventricles (papillary muscles) merge with tendinous cords (chordae tendineae) which extend from the edges of the cusps. Contraction of the ventricle leads to contraction of the papillary muscles, resulting in the opening or closing of the valve.

Mitral Stenosis

The most common cause of mitral stenosis (MS) worldwide is RHD, a decades-delayed complication of ARF and carditis of the mitral valve. In the developed world, mitral annular calcification leading to degenerative valvular disease in the elderly is the most common etiology of MS.[17] Though uncommon, MS can also be a congenital condition.

Pathophysiology

The normal cross-sectional area of the mitral valve orifice is 4 to 6 cm^2. Stenosis becomes clinically significant when the area decreases to below 1.5 cm^2, or 1 cm^2/m^2 body surface area in larger patients. As the valve narrows, impeded inflow from the left atrium to the left ventricle results in decreased preload, decreased cardiac output, left atrial hypertension and, ultimately, pulmonary congestion. As the disease progresses, patients may develop pulmonary hypertension, right ventricular hypertrophy, and right ventricular failure.

The most common complication of MS is atrial fibrillation due to left atrial dilation. Atrial fibrillation leads to decreased atrial contraction and decreased diastolic filling with subsequently decreased cardiac output. Patients with underlying MS may also decompensate in the setting of pregnancy, anemia, infection, and hyperthyroidism, conditions that increase cardiac demand and decrease ventricular filling. Finally, right ventricular failure may cause left ventricular dysfunction due to chronic preload reduction and impaired contractility over time.

Clinical Features

Early symptoms of MS include decreased exercise tolerance and dyspnea on exertion. Patients with more advanced disease may have orthopnea and peripheral edema. Embolic events from atrial fibrillation may be the initial presenting feature. Hemoptysis from rupture of a bronchial vein, and hoarseness, caused by compression of the recurrent laryngeal nerve, are classic but uncommon presentations. Chest pain or discomfort is not a typical feature of MS.

Aside from the typical signs of heart failure, findings that suggest the presence of MS include a loud S1 and an opening snap in early diastole, accompanied by a low-pitched, rumbling, decrescendo diastolic murmur, best heard at the apex.

The chest x-ray may be normal, or cephalization of pulmonary vascular flow or pulmonary vascular congestion may be observed. Left atrial enlargement may be suggested by straightening of the left heart border in more advanced cases. ECG may demonstrate atrial fibrillation along with signs of left atrial enlargement or right ventricular hypertrophy. Echocardiography is the preferred method of diagnosis and assessment of disease severity[18,19] (Fig. 69.4). TTE is often sufficient for routine care,[20] however TEE typically provides more detailed information on valve morphology and evaluates for concomitant left atrial thrombus.

Management

Acute stabilization in the ED begins with identification and treatment of underlying precipitants, such as anemia or infection. Symptoms of vascular congestion (pulmonary and peripheral) are treated with diuresis. Rate control and anticoagulation are important if secondary atrial fibrillation is present. With long term medical management alone, 5-year survival rates with MS are 47%.[21]

Definitive surgical interventions include percutaneous and open approaches. Symptomatic severe MS is most commonly treated with percutaneous transvenous mitral commissurotomy, also known as percutaneous balloon valvulotomy, when valve anatomy is favorable, and when there is an absence of left atrial thrombus and moderate-severe regurgitation.[18,19] Surgical mitral valve replacement is considered based on surgical expertise, specific valve characteristics and patient comorbidities.

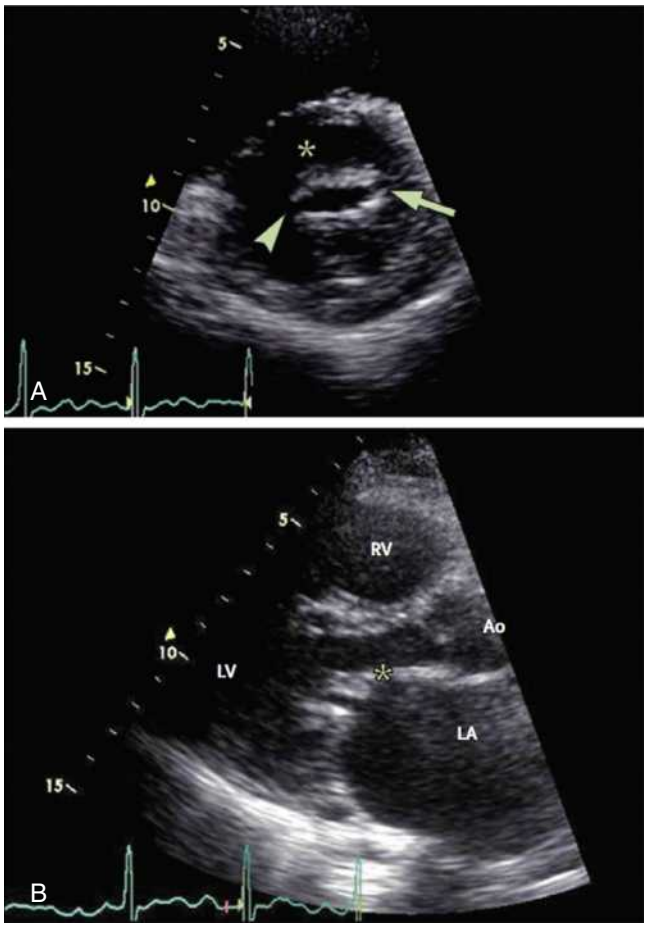

Fig. 69.4 Transthoracic echocardiography of symptomatic rheumatic mitral stenosis (*represents a thickened anterior mitral leaflet). *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle. (From Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet*. 2012;379:953–964.)

Mitral Regurgitation

MR is the most prevalent valvular disease worldwide.[22] Primary MR is caused by degenerative disease, RHD, IE, mitral valve prolapse (MVP) in connective tissue disease, and acute papillary muscle rupture, all leading to direct dysfunction of the valve leaflets or support structures (the annulus, chordae or papillary muscles) themselves. Secondary MR is caused by left ventricular enlargement and remodeling due to coronary artery disease or other cardiomyopathy, which over time distorts the architecture of the support structures and leads to secondary valve dysfunction.

Pathophysiology

MR causes retrograde flow of blood from the left ventricle to the left atrium during systole. Pathophysiology differs between acute and chronic presentations. Acute MR, as results from papillary muscle rupture secondary to myocardial infarction, is characterized by a sudden decrease in afterload, low left atrial compliance and sharply elevated left atrial pressure, resulting in acute pulmonary vascular congestion. Chronic MR, as results from cardiomyopathy, is characterized by stable afterload in the setting of cardiac remodeling, progressively increased left atrial compliance and near-normal left atrial pressures, resulting in preserved cardiac output—until the point at which decompensation ensues. Acute MR is a true cardiac emergency, whereas chronic MR may be occult and go undetected for many years.

Clinical Features

Acute Mitral Regurgitation

Acute MR presents as severe dyspnea, acute pulmonary edema, or cardiogenic shock, typically in a patient with no prior history of heart failure. Classically a harsh, high pitched midsystolic murmur can be heard, loudest at the apex. Radiation is usually to the axilla but depends on the direction of the regurgitant jet. In severe acute MR, there may be an S3 and a short diastolic rumble.

The chest x-ray usually demonstrates unilateral or bilateral pulmonary edema. The ECG may show signs of ischemia or infarction, including Q waves, ST-T changes and left bundle branch morphology. ED point of care TTE establishes a cardiogenic cause of acute dyspnea with high sensitivity/specificity,[23] and experienced ED sonographers can identify an MR jet (Fig. 69.5). Comprehensive echo will identify the incompetent valve, regurgitant flow, and papillary muscle rupture, if present, in addition to decompensated heart failure.

Chronic Mitral Regurgitation

The presentation of chronic MR is similar to that of chronic systolic heart failure, with clinical symptoms and signs of vascular congestion. The chronic MR murmur is classically described as holosystolic, heard best at the apex and radiating to the axilla. There may be a S3 present.

The chest radiograph may suggest left atrial enlargement. Atrial fibrillation is common, and the ECG often demonstrates left atrial and

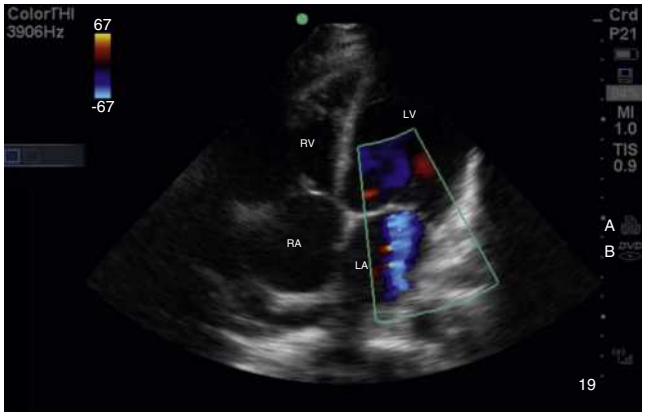

Fig. 69.5 Transthoracic echocardiography (apical four chamber view) of mitral regurgitation (*represents mitral regurgitant jet). *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Courtesy of Highland Emergency Ultrasound Division.)

ventricular hypertrophy. Echocardiography may show a normal or above-normal ejection fraction, but some portion of systolic flow is retrograde. TEE is the preferred diagnostic modality to evaluate valve anatomy and size and direction of the regurgitant jet. Increasingly, 3D TEE is being used to grade disease severity and guide valve replacement.[24]

Management

When the diagnosis of acute MR is suspected, emergency echocardiography and right heart cardiac catheterization should be pursued to assess the degree of regurgitation and urgency for surgery. Initial stabilization in the ED includes treatment of pulmonary edema with intravenous nitrates, diuretics and noninvasive positive pressure ventilation (CPAP or BiPAP). Norepinephrine is the first-line vasopressor for hypotensive patients, and once the blood pressure is supported with a mean arterial pressure of at least 65 mm Hg, inotropic support with dobutamine can be added for patients with persistent hypoperfusion. In a persistently hypotensive patient who does not respond to vasopressor and inotropic therapy, an intraaortic balloon pump (IABP) may stabilize the patient and provide a bridge to valve replacement surgery. A small subset of patients may improve and stabilize without surgical intervention, however rates of secondary pulmonary hypertension in this population are high. In cases of acute MR from inferolateral myocardial infarction, coronary artery revascularization can lead to complete resolution of MR.

Chronic symptomatic MR is managed with afterload reducing agents angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARB], and beta blocking agents are first-line therapy), and diuretics to prevent progression of left ventricular (LV) failure.[19] A long period of medical therapy and annual echocardiographic monitoring is the norm, with 15-year survival approaching 70% with medical therapy alone. Once the left ventricular ejection fraction (LVEF) falls below 60%, valve repair or replacement is recommended to avoid irreversible left ventricular dysfunction. Open valve repair or replacement remains the surgical treatment of choice in most cases. Recent studies support the use of transcutaneous mitral valve repair (MitraClip) for carefully selected patients with primary MR.[19]

Mitral Valve Prolapse

MVP is a form of abnormal mitral valve leaflet movement during systole. It may be inherited or sporadic. Epidemiological studies report a prevalence of approximately 2% to 3% worldwide.[25] While usually a benign condition, MVP can result in MR and rarely other complications.

Pathophysiology

MVP is characterized by myxomatous proliferation of the middle spongiosa layer of the valve leaflet, resulting in abnormal billowing of one or both leaflets into the left atrium during systole. MVP is usually an isolated primary disorder, but may be associated with connective tissue disorders, particularly Marfan and Ehlers-Danlos syndromes. Most patients with MVP have no or mild MR, however severe MR occurs in up to 10% of patients with MVP.[26] The most frequent complications of MVP are progressive MR (resulting in need for valve replacement), atrial fibrillation, heart failure and endocarditis.

Clinical Features

MVP is associated with a wide variety of clinical symptoms, from asymptomatic to palpitations, chest pain, dyspnea, lightheadedness, fatigue, and anxiety. A midsystolic click may be heard, caused by snapping of the chordae tendineae with prolapse of the valve. Occasionally a mid to late systolic murmur can be heard over the left lower sternal border. Echocardiography is the primary diagnostic modality.

Management

Patients with MVP should be reassured about the typically benign natural history of the disease. Beta-blockers may be used to control symptoms such as palpitations, chest pain, and anxiety. Lifestyle modifications, such as exercise, relaxation techniques, and avoidance of ethanol, caffeine, and other stimulants may also be helpful.

AORTIC STENOSIS

The most common cause of aortic stenosis is calcific degeneration, which is prevalent in older adults with atherosclerotic disease. Aortic stenosis also occurs in younger individuals with a bicuspid aortic valve and calcific changes. RHD can lead to atrial stenosis (AS), in which case it may coexist with MS.

Pathophysiology

The normal aortic valve area (AVA) is approximately 3 to 4 cm^2. Stenosis occurs through an active process of calcification, inflammation, oxidative stress and remodeling. Clinically significant obstruction of outflow from the left ventricle occurs when the AVA decreases by more than 50%.[27] As the valve narrows, increased left ventricular afterload leads to compensatory left ventricular hypertrophy (LVH) to maintain cardiac output. Left ventricular hypertrophy and increased wall tension predispose the patient to cardiac ischemia, even in the absence of significant coronary artery disease. Further progression of disease is associated with left ventricular dysfunction, left atrial enlargement, and atrial fibrillation. In advanced stages, cardiac output decreases while left atrial and pulmonary artery pressures increase, leading to pulmonary hypertension and right heart failure.

Severe aortic stenosis is defined by a peak velocity of ≥4 m/s, a mean pressure gradient (MPG) of ≥40 mm Hg, or a valve area of less than 1 cm^2.[18] Up to one-third of patients with severe AS have a preserved ejection fraction.[28] Individuals with severe AS are preload-dependent and have very little cardiovascular reserve. Any disruption of the delicate balance between myocardial oxygen supply and demand (e.g., rapid atrial fibrillation, dehydration, acute blood loss) can result in acute decompensation.

Clinical Features

AS is most commonly diagnosed incidentally on routine physical exam, or on echocardiography as part of a broader cardiology work-up. Symptomatic AS gradually progresses from fatigue, exertional dyspnea, and angina to lightheadedness and exertional syncope, to overt heart

failure. In an older patient with chest pain who appears preload dependent in the ED, the possibility of AS, with or without coronary artery disease, should be considered. In addition to the gradual progression of symptoms, patients may also experience acute decompensation due to triggers such as sepsis, anemia, or endocarditis.

The classic AS murmur is a crescendo-decrescendo systolic murmur, heard best at the right upper sternal border, radiating into the carotids. An S4 gallop may be present at the apex. As the severity of disease increases, the murmur peaks later and becomes less audible. Carotid pulses may be delayed (tardus) and diminished in intensity (parvus).

The chest radiograph is frequently normal except in cases of acute decompensation. In elderly patients with calcific degeneration, valve calcification may be visible and is often associated with a tortuous aorta. ECG typically reveals LVH. Evidence of left atrial enlargement, left axis deviation, left bundle branch block, and atrial fibrillation (in the late stage) may also be present. Echocardiography is the main modality used to diagnose AS and stage severity and can be reliably done in the ED setting.[23,29] AS severity is categorized using three echocardiographic parameters: aortic peak jet velocity (PVel), MPG, and calculated AVA.[18]

Management

The natural history of AS is one of slow asymptomatic progression over years to decades. If identified during this latent phase, AS can be managed medically or surgically based on patient preference. Antihypertensives are the only medical therapy recommended by the current American and European guidelines.[27] Statins may slow the rate of aortic calcification, but do not affect the rate of valve narrowing. Once symptoms develop, medical management has a limited role, and survival is markedly reduced unless the valve is replaced. The choice of surgical aortic valve replacement (SAVR) versus transcatheter aortic valve replacement (TAVR) is based on multiple factors, including surgical risk, patient frailty and comorbidity, and patient preference.[30] In high-risk patients, balloon valvuloplasty is feasible and safe as a bridge to valve replacement, but long-term survival is poor with valvuloplasty alone.[31]

In the ED setting, management of decompensated AS includes judicious fluid resuscitation, blood transfusion and restoration of sinus rhythm, if indicated. Vasodilators, diuretics and inotropic agents should be avoided, if possible. When required, first-line vasopressor support is with phenylephrine or norepinephrine. When there is no response to medical therapy and the patient is a candidate for valve replacement, an IABP may provide a bridge to surgery.

AORTIC REGURGITATION

Aortic regurgitation (AR) can be caused by disease of the aortic valve leaflets, or by distortion of the anatomy of the aortic root and ascending aorta. Aortic valve leaflet abnormalities are caused by calcific degeneration, a congenital bicuspid valve, infectious endocarditis, or RHD. Processes that affect the aortic root include idiopathic root dilation (ectasia), connective tissue disorders, syphilis, aortic aneurysm and aortic dissection. AR has an estimated prevalence of 4.9% in the Framingham data, with moderate or severe AR found in 0.5%.[32]

Pathophysiology

In acute AR, sudden development of AR leads to increased left ventricular end-diastolic pressure, reduced cardiac output, and subsequent acute pulmonary vascular congestion. In contrast, in chronic AR, progressive left ventricle remodeling and dilation allows the heart to maintain near-normal cardiac output despite significant regurgitation. The increased LV volume leads to increased stroke volume, allowing for the maintenance of cardiac output despite regurgitation.

Clinical Features

The clinical presentations of acute and chronic AR are clinically distinct.

Acute Aortic Regurgitation

Patients with acute AR can present with severe respiratory distress and cardiogenic shock, due to rapidly increased end-diastolic volume in the setting of low left ventricular compliance and acute pulmonary vascular congestion.

Patients are typically tachycardic, hypotensive, and hypoxic. The pulse pressure may be normal or only slightly widened. A short, soft, diastolic murmur may be present, but often is difficult to detect in the ED setting.

Chest x-ray may show pulmonary vascular congestion. The ECG is typically normal, but may show signs of demand ischemia. Emergent echocardiography is required to confirm the diagnosis. Point-of-care ultrasound in the ED using a parasternal long (PSL) axis view can rapidly identify valve failure using color doppler over the valve area to observe the regurgitant jet (Fig. 69.6).[23] The PSL axis view may also demonstrate a dilated aortic outflow tract suggesting a problem with the aortic root, and the apical four-chamber view may demonstrate a vegetation suggesting endocarditis as the primary etiology (see Fig. 69.2). Additionally, the suprasternal notch view is easily and rapidly obtainable view of the thoracic aorta which allows accurate visualization of a dissection flap if present.[33]

Chronic Aortic Regurgitation

Chronic AF tends to have a prolonged asymptomatic period, after which a patient develops dyspnea on exertion due to increased LV end-diastolic pressures and anginal symptoms due to decreased aortic diastolic pressure and increased oxygen demand.

Chronic AR is characterized by a wide pulse pressure. The point of maximal impulse is typically displaced and sustained. A high-pitched, blowing, diastolic murmur at the left lower sternal border is usually present. Classic physical findings of severe AR include a rapidly rising and falling carotid pulse (water hammer, or Corrigan's, pulse), head bobbing due to exaggerated carotid pulsations

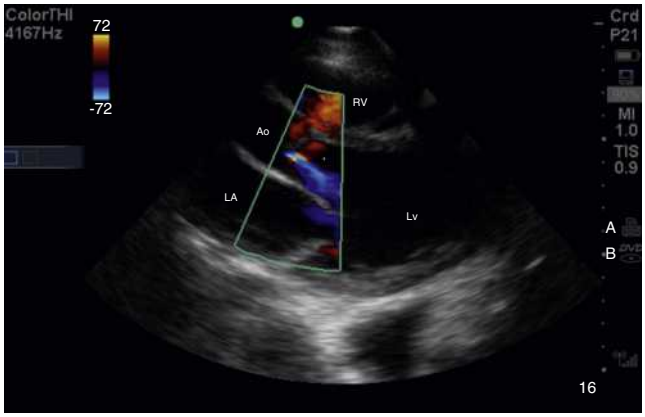

Fig. 69.6 Transthoracic echocardiography (parasternal long axis view) of aortic regurgitation (*represents aortic regurgitant jet). *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle. (Courtesy of Highland Emergency Ultrasound Division.)

(Musset's sign), spontaneous nail bed pulsations (Quincke's sign), or a bruit over the femoral artery (Duroziez's sign). An Austin-Flint murmur—a soft mid-diastolic rumble caused by a regurgitant stream against the anterior leaflet of the mitral valve—may also be present when auscultating the apex.

The chest radiograph may show cardiomegaly, and pulmonary vascular congestion in advanced or decompensated AR. The ECG usually demonstrates LVH. Echocardiography provides a definitive diagnosis, and is used to evaluate valve anatomy, and aortic root and ascending aortic dimensions, as well as LV size and function. Echocardiography can also determine the feasibility of valve or root repair.

Management

Acute AR is a surgical emergency necessitating urgent valve replacement, along with repair of any underlying aortic root pathology. Medical stabilization involves the cautious use of short-acting vasodilators (nitroprusside, nicardipine, or clevidipine) and diuretics. Use of an IABP is contraindicated in the setting of an incompetent aortic valve. Often, diagnosis and management of the underlying aortic dissection or IE must be undertaken simultaneously. For aortic dissection complicated by AR, beta-blocker therapy should be used with caution.

Chronic AR is managed like other types of decompensated heart failure, with emphasis on diuresis, as well as preload and afterload reduction, to prevent worsening left ventricular function and avoid aortic complications if an aneurysm is present. Ideally, valve repair or replacement should be performed before the development of left ventricular systolic dysfunction. Chronic severe AR has a yearly mortality of 10% to 20% without surgical treatment.

Complications of Prosthetic Valves

Prosthetic heart valves may be mechanical or biologic. Biologic valves include whole valve transplants (human or porcine) as well as bioprosthetic valves, typically manufactured from bovine pericardium. All prosthetic heart valves are associated with complications, ranging from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis (Box 69.6). In the acute setting, the diagnosis of a prosthetic valve complication can be challenging because symptoms and signs are often subtle.

Structural Failure

Primary structural failure is extremely uncommon with modern mechanical valves. When it does occur, the presentation is one of acute severe regurgitation and shock, and emergent valve replacement is required. With biologic valves, structural failure is more common but less dramatic. At 10 years, 20% to 30% of bioprosthetic valves exhibit some evidence of structural failure, and most are replaced electively. Symptoms are characteristically insidious in onset and are similar to those of native valvular disease.

BOX 69.6 Prosthetic Valve Complications

- Structural failure
- Valve thrombosis
- Systemic embolization
- Hemolysis
- Endocarditis

Valve Thrombosis

Prosthetic valve thrombosis occurs with both mechanical and biologic valves. When appropriately anticoagulated, mechanical valves have thrombotic complications at a similar rate (~2%/year) as biologic valves. Patient compliance with oral anticoagulation therapy therefore is an important consideration when evaluating for thrombotic and embolic complications. Symptoms of prosthetic valve thrombosis are generally subacute and may have characteristics of stenotic disease, regurgitant disease, or both. On physical examination, the diagnosis is suggested by a decreased or absent valve click, new regurgitant murmur, or louder than expected stenotic murmur. Echocardiography may demonstrate the thrombus or restricted leaflet motion. Treatment options include fibrinolytic therapy and surgery.

Systemic Embolization

The incidence of systemic embolization from a prosthetic valve is approximately 1%/year. Compared with aortic valve prostheses, mitral valve prostheses are associated with twice the risk of systemic embolization, with rates roughly equal for an appropriately anticoagulated mechanical mitral valve and a bioprosthetic valve. The vast majority of diagnosed embolic events (85%) involve the central nervous system and roughly 50% of these result in permanent impairment.

Hemolysis

Mild hemolytic anemia resulting from sheer forces across the prosthetic valve is common but usually subclinical. In more severe cases, presenting features include dyspnea, fatigue, and even jaundice. Iron replacement is effective therapy for most patients but transfusion may be required. Worsening hemolysis may be the result of a new periprosthetic leak or other structural failure, which should be evaluated by echocardiography.

Endocarditis

The incidence of PVE is highest during the initial months after surgery and is similar for mechanical and bioprosthetic valves. Early PVE, within 60 days of surgery, is presumed to be caused by a pathogen acquired perioperatively and is associated with relatively high morbidity and mortality, whereas late PVE is more likely due to transient bacteremia and generally has a better prognosis. As with other forms of IE, fever is the most common symptom and systemic embolization is a common presentation. A normal TTE does not rule out PVE, and a TEE is generally required for diagnosis and complete evaluation of the valve. Three sets of blood cultures are recommended to evaluate for PVE. The ED diagnosis of PVE is usually presumptive because definitive diagnosis requires positive blood cultures. Vancomycin is a reasonable initial empiric antibiotic choice, although gentamicin and rifampin are often added for definitive therapy in Staphylococcal PVE. Early consultation with both an infectious disease specialist and cardiothoracic surgeon should be obtained, and transfer to a center with cardiothoracic surgical capabilities should be considered.

Disposition

Patients with acute symptoms related to valvular heart disease should be admitted to the hospital until their condition has stabilized and the cause for their decompensation has been addressed. For patients with stable valvular disease, outpatient cardiology follow-up is recommended.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 69: QUESTIONS AND ANSWERS

1. What is the most common manifestation of acute rheumatic fever (ARF)?
   a. Carditis
   b. Chorea
   c. Erythema marginatum
   d. Polyarthritis

Answer: d. Arthritis occurs early in the course of ARF. The knees, ankles, elbows, and wrists are commonly affected, and pain can be out of proportion to physical findings. Cardiac manifestations are subtle and may reflect endocarditis, myocarditis, or pericarditis. Chorea and erythema marginatum are rare. Chorea is typically a late finding.

2. A 49-year-old woman presents with progressive dyspnea on exertion and orthopnea. Vital signs are temperature 36.7°C (98.1°F; oral), heart rate, 110 beats/min, blood pressure, 135/80 mm Hg, respiratory rate, 22 breaths/min, and oxygen (O_2) saturation, 97% on room air. The physical examination is remarkable for clear lung fields and an irregularly irregular rhythm with a 4/6 diastolic murmur in the left anterior axillary line. She has no peripheral edema. Which of the following would be appropriate hemodynamic management of her cardiac pathophysiology?
   a. Aggressive diuresis
   b. β_1-Agonist to increase chronotropy
   c. Beta blocker
   d. Selective arterial vasodilator

Answer: c. This patient has a picture consistent with atrial fibrillation and mitral stenosis. The apical diastolic murmur and left atrial enlargement, along with progressive dyspnea, all support the diagnosis. Tachycardia is poorly tolerated because of the need for higher left atrial pressures and a longer time during diastole to perfuse across the stenotic valve. Slow and full are appropriate goals. Diuresis might decrease venous return. Any agent producing tachycardia would decrease diastole time and left ventricular preload. An arterial vasodilator would have little effect, given the normal blood pressure and the fact that systemic vascular dilation would not be seen at the mitral valve level as long as the aortic valve was competent.

3. A 32-year-old woman with a history of injection drug use presents with persistent fevers, night sweats, and shortness of breath. Vital signs are temperature 38.2°C (100.8°F; oral), heart rate, 123 beats/min, blood pressure, 105/60 mm Hg, respiratory rate, 26 breaths/min, and oxygen (O_2) saturation, 93% on room air. The physical examination is remarkable for scattered rhonchi and a 2/6 systolic murmur in the left lower sternal border. Which of the following is the most appropriate antibiotic to start?
   a. Clindamycin
   b. Vancomycin
   c. Ceftriaxone
   d. Cefepime

Answer: b. In most cases, empiric therapy in the ED should include vancomycin, and vancomycin alone for one or two doses is a reasonable approach for native valve and prosthetic valve infection and in IDUs. Ceftriaxone can be added to vancomycin to cover HACEK and other gram-negative organisms, but these are responsible for less than 6% of infections. There is no role at this time for empiric use of clindamycin or cefepime.

4. A 62-year-old man with presents 3 days after being admitted for an inferior ST-segment elevation myocardial infarction (STEMI). He underwent a successful percutaneous coronary intervention (PCI) and was just discharged earlier in the day. He developed sudden onset shortness of breath at home, and he arrives in extremis. Vital signs are temperature 37.2°C (98.8°F; oral), heart rate, 112 beats/min, blood pressure, 85/68 mm Hg, respiratory rate, 24 breaths/min, and oxygen (O_2) saturation, 90% on room air. The physical examination is remarkable for severe respiratory distress, diffuse crackles, and a 2/6 systolic murmur in the left lower sternal border. Which of the following is the most appropriate intervention?
   a. Give 2L of crystalloid over an hour.
   b. Start dobutamine.
   c. Initiation of dialysis for volume overload.
   d. Initiate continuous positive airway pressure (CPAP) therapy.

Answer: d. This patient presents with likely acute mitral regurgitation (MR) from a papillary muscle rupture after an myocardial infarction (MI). Giving additional fluid will likely make his pulmonary edema worse. Starting dobutamine without a vasopressor while he is hypotensive could make the hypotension worse. When the diagnosis of acute MR is suspected, initial stabilization in the ED includes treatment of pulmonary edema with intravenous nitrates, diuretics, and noninvasive positive pressure ventilation.

5. A 38-year-old man with presents with progressive dyspnea over a day, starting 2 hours before arrival. Vital signs are temperature 38.9°C (102.0°F; oral), heart rate, 115 beats/min, blood pressure, 120/72 mm Hg, respiratory rate, 26 breaths/min, and oxygen (O_2) saturation, 92% on room air. The physical examination is remarkable for diffuse crackles and a 2/6 systolic murmur in the left lower sternal border. His echocardiogram demonstrates a large, mass on the mitral valve with severe mitral regurgitation (MR). In addition to managing his pulmonary edema, which of the following is the most appropriate intervention?
   a. Administer beta-blockade to reduce the risk of embolization.
   b. Consult Cardiac Surgery.
   c. Start a heparin infusion.
   d. Start digoxin for heart rate control.

Answer: b. Patients with suspected infectious endocarditis (IE) and acute heart failure require immediate consultation by a cardiothoracic surgeon. In general, there has been a shift toward earlier surgical treatment in IE, with approximately one-half of patients with left-sided infection undergoing surgery during the index admission. If possible, patients with left-sided IE should be managed by a multidisciplinary team at a center capable of cardiothoracic surgery. There is no role for addition of beta-blockade in this patient in heart failure. Heparin and digoxin are not indicated for IE.

70

Hypertension

Phillip D. Levy and Aaron Brody

KEY CONCEPTS

- Elevated blood pressure with or without associated symptoms is exceedingly common in the emergency department (ED).
- A true hypertensive emergency is defined by the presence of acute target organ damage (TOD) and is distinct from other clinical presentations.
- Commonly encountered hypertensive emergencies include ischemic and hemorrhagic stroke, myocardial infarction, acute heart failure, aortic dissection, and pre-eclampsia.
- Management strategies regarding target blood pressure reduction, rate of reduction, and agent choice vary widely among the discrete conditions defined as hypertensive emergencies. Thus, clinical decision making in this context requires knowledge of the physiology and an evidence-based approach to each condition.
- For patients without acute TOD, immediate antihypertensive therapy is not needed. However, emergency clinicians play an essential role in the care of this group, providing screening, ongoing surveillance, and linkage to care to prevent secondary complications of this disease.
- Initiation of long-term oral antihypertensive therapy in the ED for those with elevated blood pressure but no established history of hypertension is not recommended; however, emergency clinicians are encouraged to refill, reinitiate, or up-titrate antihypertensive medications in patients with elevated blood pressure who are known to have chronic hypertension.

FOUNDATIONS

Background and Importance

Hypertension (HTN) is an important but largely treatable risk factor for cardiovascular disease that affects almost half of Americans and approximately 1 billion people worldwide.[1,2] Recent society guidelines have lowered the diagnostic criteria and treatment threshold for HTN,[3] thus increasing the prevalence of HTN from 31% to 45%.[4] Under these definitions, the proportion of patients with controlled HTN has increased from 25% to 43% over the last two decades,[5] reflecting the partial success of awareness campaigns and new classes of antihypertensive medications. This has clear implications on the practice of emergency medicine. According to data from a nationwide emergency department (ED) sample between 2006 and 2012, one patient of every four in the ED was diagnosed with HTN,[6] and this number is steadily increasing. Hypertensive emergencies, while still rare (2 to 6 per 1000 visits), are also rising in prevalence.[7] Patients presenting to the ED for hypertensive events bear a four-fold increase in risk for long-term adverse cardiovascular outcomes, but this risk is attenuated by outpatient follow-up.[8]

Despite this understanding, there is a critical divide between what constitutes a true emergency condition and what does not when it comes to elevated BP in the ED. When associated with acute target organ damage (TOD), HTN represents a component of a truly critical condition that warrants emergent intervention. However, this is relatively rare, and, for the vast majority, acute TOD will not be present, even in the setting of markedly elevated BP. Although such patients have a low likelihood of near-term adverse events and are not classified as acute emergencies, interventions to control BP if chronically elevated can decrease their overall cardiovascular risk. Thus, this distinction is a key aspect of the approach to HTN in the ED and a core feature of emergency medicine practice.

Importance

HTN is a major modifiable risk factor for the development of cardiovascular, cerebrovascular, and renovascular disease. Uncontrolled BP is strongly associated with heart failure, myocardial infarction, stroke, vascular dementia, and chronic kidney disease. The risk of developing these conditions increases with the degree of BP elevation, and it has been estimated that the risk of cardiovascular disease doubles for each elevation of 20 mm Hg systolic and 10 mm Hg diastolic BP, starting at 115/75 mm Hg. Conversely, antihypertensive treatment can lower the risk for stroke by as much as 40%, myocardial infarction by 25%, and heart failure by 50%.

The distribution of HTN and the benefits of intervention are not uniform. According to data from the National Health and Nutrition Examination Survey (NHANES), African Americans have higher age adjusted rates of diagnosed HTN (males, 57.6%, females 53.2%) than whites (males, 46.7%, females 38.8%) or Hispanics (males, 44.4%, females 37.9%), and conversely, worse rates of BP control (22% for blacks, and 19.3% for Hispanics vs. 26.8% for whites), leading to an increased risk of adverse outcome.[2] This disparity, in combination with other economic, social, and lifestyle determinants, leads to a dramatically increased morbidity from cardiovascular disease in the African American population. HTN is by far the single most important contributor to racial differences in life-years lost from cardiovascular disease, accounting for 50% of the excess risk within the African American community.

Definition of Hypertension and Relevant Terminology

Although BP below 120/80 mm Hg is considered normal, an understanding of what constitutes HTN has been evolving. The most recent

TABLE 70.1 ACC/AHA 2017 Guidelines Definition of Hypertension Compared to Classic (JNC 7)

Systolic and Diastolic BP	JNC 7	ACC/AHA 2017 Guidelines
<120 SBP *and* <80 DBP	Normal	Normal
120–129 SBP *or* <80 DBP	Prehypertension	Elevated blood pressure
130–139 SBP *or* 80–89 DBP	Prehypertension	Stage I HTN
140–159 SBP *or* 90–99 DBP	Stage I HTN	Stage II HTN
>160 SBP *or* >100 SBP	Stage II HTN	Stage II HTN

ACC, American College of Cardiology; *AHA*, American Heart Association; JNC 7.

guideline from the American Heart Association (AHA)/American College of Cardiology (ACC) reduces the diagnostic cut-off for HTN from 140/90 to 130/80 mm Hg.[9] Additionally, these guidelines drastically change the classic categorical definitions as defined in the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation, and treatment of High Blood Pressure. Table 70.1 displays the change in diagnostic categories of HTN. These changes reflect an increasing awareness of the long-term cardiovascular risk associated with modest elevations in BP,[10] and de-emphasize the significance of severely elevated BP (i.e., stage II HTN) as a discrete clinical category.

Historically, the approach to BP measurement has been office-based, with a diagnosis of HTN considered to be present when BP of 140/90 mm Hg (now 130/80 mm Hg) or higher is detected on properly measured, seated readings on two or more occasions. Recent data have suggested that the 24-hour ambulatory BP measurement (ABPM) may be a better method to diagnose HTN.[11] ABPM enables the evaluation of BP over a range of conditions, minimizing the potential for so-called white coat effects while increasing the likelihood of detecting masked HTN. ABPM is recommended (class I, level of evidence A) in the AHA/ACC guideline to confirm a suspected HTN based on clinic measurement and to optimize antihypertensive therapy in those with uncontrolled BP. Importantly, ABPM provides a more accurate estimate of true BP compared with clinic-derived measurements. As a result, correction factors have been proposed with clinic BP values of 130/80, 140/90, and 160/100 mm Hg corresponding to ABPM measurements of 125/75, 130/80, and 145/90 mm Hg, respectively.[12]

How ED-measured BPs fit into this paradigm is not clear. Many ED patients with elevated BP will have an established history of HTN, but a sizeable proportion will not, presenting an opportunity to establish the diagnosis. Although this should be approached with caution based on a single ED measurement, a persistently elevated BP over several prior ED visits may be a reasonable indicator of true underlying HTN. Prior studies have shown that as many as 70% of patients with elevated BP in the ED will also have an abnormal BP at primary care follow-up, and this proportion increases with the ED BP value. Approximately half of a cohort of ED patients with elevated BP, but no diagnosis of HTN who were given devices for home BP measurements, were found to have persistent BP elevations.[13] Newer BP devices that perform automated, unattended serial measurements, discarding the first reading and averaging subsequent values, have been shown to improve the accuracy of clinic-based BP assessment and may be a useful adjunct in the ED for patients with suspected chronic HTN.[14]

More important in the ED setting than diagnosing chronic HTN is understanding the need for acute intervention among patients with marked BP elevations (i.e., ≥180/100 mm Hg). Although terms such as *hypertensive crisis*, *hypertensive urgency*, and *accelerated* or *malignant HTN*, are liberally applied to such patients, they are poorly defined and are often used interchangeably and incorrectly by emergency clinicians. A more contemporary term, "diffuse microvascular injury" denoting a group of vascular pathologies that may not produce clinical symptoms has been proposed to replace "malignant hypertension."[15] However, this clinical entity has not been well delineated or studied in large cohorts, and an association with short or long-term cardiovascular outcomes has not been demonstrated. A better approach focuses on the presence (or absence) of signs or symptoms attributable to acute TOD within the context of established or potentially new-onset HTN, thus distinguishing patients with active vasculopathy from those without.

Based on this conceptual model, there are three distinct subgroups of patients with elevated BP that are relevant to emergency medicine practice:

1. Hypertensive emergency—a disease state defined by acute TOD, manifest by newly developed clinical sequelae or diagnostic test abnormalities. A hypertensive emergency can exist in patients with or without underlying chronic HTN. Although it has been estimated that 1% to 2% of patients with chronic HTN will experience a hypertensive emergency in their lifetime, hospitalization for this condition is relatively rare, occurring in only 2 of every 1000 ED presentations and 6 per 1000 HTN-related ED visits in the United States.[7]
2. Poorly controlled chronic HTN—a presentation in which patients with established HTN are found to have elevated BP without specific attributable symptoms or evidence of acute TOD. Such presentations often result from inadequate medical management or nonadherence to treatment regimens, but may also reflect refractory disease. Concurrent use of seemingly innocuous medications, including nonsteroidal antiinflammatory drugs (NSAIDs), steroids, decongestants, appetite suppressants, over-the-counter stimulants, oral contraceptives, and tricyclic antidepressants or rebound from short-acting antihypertensives, such as clonidine, may be contributory.
3. Elevated BP without prior history of HTN—a relatively frequent occurrence in which routine ED vital signs identify an elevated BP. Such individuals also may visit the ED after an outpatient physical examination, community health screening event, or self-performed, automated BP measurement identifies elevated BP. Whether or not this truly represents HTN can be difficult to determine in the ED, and all such patients should have a repeat measurement of BP, ideally 1 hour or more after arrival and after analgesic treatment for those with acute pain. Depending on the circumstance, an evaluation for potential TOD may be warranted, along with referral for subsequent follow-up in an outpatient setting. As noted above, ABPM may be useful for confirming chronic HTN, but initiation of such testing is generally outside the purview of emergency clinicians.

An approach to elevated BP in the ED based on this understanding is presented in Fig. 70.1.

Physiology of Hypertension

Whereas BP is known to rise with increasing age, onset of HTN in non–older adults represent a complex interplay of multiple inciting factors including neurohormonal dysregulation, vascular modulation, sodium intake, psychosocial stress, and obesity. Alterations in cardiac and renal function are also important, serving as contributors to and consequences of ongoing BP elevation. Despite an advanced understanding of the pathophysiology of HTN, the definitive cause of elevated BP remains unknown in more than 90% of patients. These individuals are labeled as having primary or essential HTN, and the cause is considered idiopathic. In the subset of patients for whom an identifiable cause can be ascertained, the term *secondary HTN* applies (Table 70.2). Although it may not be possible to diagnose and treat

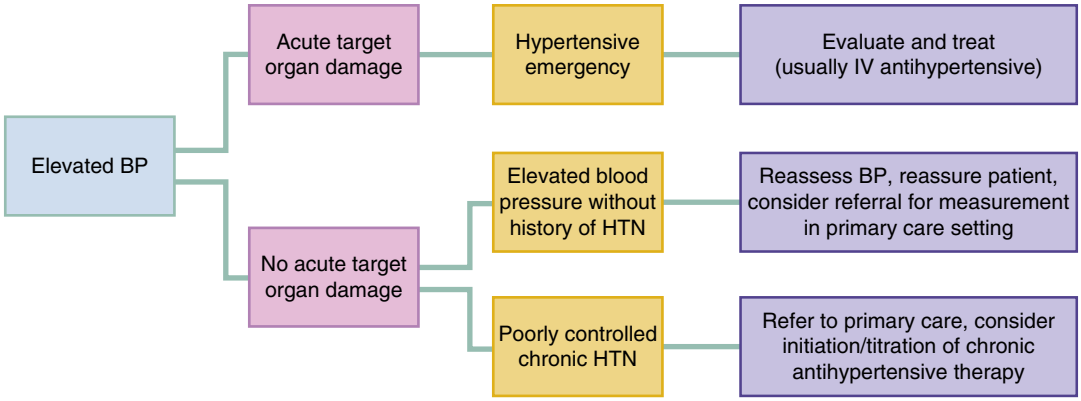

Fig. 70.1 Schematic for the approach to elevated blood pressure *(BP)* in the emergency department. *HTN,* Hypertension; *IV*, intravenous.

TABLE 70.2 Secondary Causes of Hypertension

Cause	Diagnostic Test	Clinical Clues
Endocrine		
Cushing's syndrome and other glucocorticoid excess states	History; dexamethasone suppression test	Glucose intolerance; purple striae
Hyperaldosteronism and other mineralocorticoid excess states	24-h urinary aldosterone level or other mineralocorticoids	Unexplained hypokalemia
Oral contraceptive use	History	
Pheochromocytoma	24-h urinary metanephrine and normetanephrine	Labile or paroxysmal HTN with palpitations, pallor, perspiration
Thyroid disease	Serum TSH	Temperature intolerance, weight loss, tachycardia; hypercalcemia
Parathyroid disease	Serum PTH	
Pulmonary		
Obstructive sleep apnea	Sleep study with O_2 saturation	Obesity; narcolepsy
Renal		
Chronic pyelonephritis	History; urinalysis, urine culture	
Diabetic nephropathy and other chronic kidney disease	Estimated GFR; urine albumin/creatinine ratio	
Nephritic and nephrotic syndromes	Urinalysis; renal biopsy	
Polycystic kidney disease	Renal ultrasound	
Renovascular conditions (e.g., renal artery stenosis)	Doppler flow study; magnetic resonance angiography	HTN onset before the age of 30 years or after 55 years; abdominal bruit; refractory HTN control; recurrent pulmonary edema; unexplained renal failure
Toxic or Metabolic		
Chronic alcohol abuse	History; ETOH level	
Sympathomimetic drug use	History; drug screen	
Tyramine-containing foods	History	Paroxysms of HTN, especially in those taking monoamine oxidase inhibitors
Vascular		
Atherosclerosis		
Coarctation of the aorta	CT angiography	Decreased lower extremity pulses

CT, Computed tomography; *ETOH,* ethyl alcohol; *GFR,* glomerular filtration rate; *HTN,* hypertension; O_2, oxygen; *PTH,* parathyroid hormone; *TSH,* thyroid-stimulating hormone.

such causes of secondary HTN in the ED, when suspected, early referral for outpatient evaluation or, in some cases, hospital admission to expedite evaluation, may be warranted.

Neurohormonal Dysregulation

The sympathetic nervous system (SNS) has a pivotal role in the development of HTN. Norepinephrine, the principal sympathetic neurotransmitter, is a potent stimulator of vasoconstriction. This effect is mediated through peripheral α_1-adrenergic receptor activation in vascular smooth muscle cells and occurs predominantly in small-diameter arterioles. Although individually, these vessels contribute a minuscule amount to BP, in aggregate, they serve as the primary driver of systemic vascular resistance (SVR) and constitute the main force that amplifies afterload in HTN. The SNS also stimulates β_1-adrenergic receptors in the heart, leading to an increase in CO through augmentation of stroke volume and heart rate, but these are considered lesser contributors to the pathologic process of high BP. Sympathoactivation exerts additional direct effects on the kidney that promote sodium reabsorption, leading to an increase in circulating blood volume, and trigger renin release, resulting in angiotensin II production and further vasoconstriction.

In addition to activation by the SNS, the renin-angiotensin-aldosterone system exerts critical, independent effects on BP. Renin is an enzyme produced by the juxtaglomerular cells in the kidney in response to several factors beyond adrenergic stimulation, including sodium load in the distal tubule and renal perfusion status. Renin cleaves angiotensin I from its plasma globulin precursor angiotensinogen. Angiotensin I is then converted to angiotensin II by circulating and tissue-bound (especially in the lung) angiotensin-converting enzyme (ACE). Angiotensin II exerts systemic and renal effects by binding to angiotensin II type I (AT_1) receptors, which results in arterial vasoconstriction, sodium reabsorption, and modulation of the glomerular filtration rate (GFR). Through AT_1 receptor binding in the adrenal gland, angiotensin II also serves as a potent stimulator of aldosterone release, promoting further sodium reabsorption and potassium excretion.

Vascular Modulation

Continued vascular stimulation by the SNS and renin-angiotensin-aldosterone system, coupled with an increase in wall tension caused by HTN itself, leads to ongoing remodeling throughout the arterial tree. In large vessels such as the aorta or carotid arteries, this results in increasing intima-media thickness, with minimal luminal narrowing—unless there is unrelated plaque buildup. In contrast, small-vessel and arteriolar remodeling reduce the lumen diameter. Although both forms of remodeling work to normalize wall stress associated with HTN, they reduce vasodilatory capacity and enhance the vasoconstrictor response when faced with a hypertensive stimulus.

Sodium Intake

The average American has a daily sodium intake of close to 3500 mg (150 mEq)—more than double the recommended level of 1500 mg (≈65 mEq) as recommended by the AHA/ACC in the 2017 HTN guidelines. Randomized trials have demonstrated a reduction in systolic BP with diminished daily sodium intake (up to 7 mm Hg/1200 mg, or a 52-mEq decrease in hypertensive individuals)[16]; however, the impact of this intervention on long-term cardiovascular outcomes is unclear.[15,17] Salt sensitivity is defined by an increase in BP with intake of a high-sodium diet. It is linked to obesity but may be more directly related to defects in renal ion transport mechanisms that lead to ongoing sodium retention and potassium depletion. Although not fully defined, the latter plays a critical role, because the entire effect of salt sensitivity on BP can be mitigated with high-dose (e.g., 100 mEq/day) potassium supplementation.[18]

Psychosocial Stress

Life stressors, especially socioeconomic status, are known to adversely affect health and wellness. Through its effects on the SNS function and the hypothalamic-pituitary axis, stress modulates BP and is a specific contributor to disparities in HTN. Although episodic stress reactions can lead to transient sympathetic surges, sustained stimulation related to ongoing concern over life circumstances (e.g., financial security, crime and safety, racism) triggers a chronic adaptive response and has emerged as an important consideration in patients with seemingly idiopathic HTN.

Obesity

Obesity is a known risk factor for the development of HTN. For every increase of body mass index by 5 kg/m^2, the relative risk of HTN increases by 1.5.[19] Elevated BP in obese individuals correlates with high circulating aldosterone and cortisol levels, which in turn may be related to salt sensitivity. Obesity, especially truncal, is also strongly associated with diabetes and obstructive sleep apnea, contributing to poor BP control. Conversely, weight loss is correlated with a modest reduction in BP, though long term mortality benefits are not clear.[20] Physical activity, which is closely linked to obesity, can mitigate the risk related and unrelated to weight loss.

Pathophysiology of Target-Organ Damage

Uninterrupted by treatment, continued vasoconstriction in chronic HTN leads to several deleterious consequences that culminate in TOD. On a macrocirculatory level, the central components of the cardiovascular system (e.g., heart, large blood vessels) are most affected. Sustained elevations in the SVR cause significant augmentation of the pressure wave reflected from the periphery back to the central circulation (termed the *augmentation index*), thus driving up left ventricular (LV) afterload; this increase manifests with a rise in the central aortic pressure and change in the morphology of its waveform. This results in increasing impedance to forward flow from the heart, which necessitates a greater contractile force to maintain the aortic valve opening and the duration of ventricular ejection. Active contraction against this resistance also increases intraventricular wall tension, which, together with ongoing stimulation from, among other things, the SNS and renin-angiotensin-aldosterone system, triggers cardiomyocyte hypertrophy and myocardial fibrosis. Initially, this leads to an increase in LV mass, enhancing the heart's pumping against excessive afterload. However, when progressive, the net result is LV stiffening and impaired diastolic function, with an increase in LV filling pressure and diminished flow from the left atrium to the left ventricle.

If the increase in afterload is sudden, an abrupt decrease in stroke volume occurs, precipitating backflow of fluid into the lungs and rapid onset of so-called flash pulmonary edema (see Chapter 67). If excess afterload is more gradual or even chronic, a subacute rise in LV end-diastolic pressure may cause increased wall tension, with compression of the subendocardial microvasculature and myocardial ischemia. Over time, this contributes to LV wall thinning, chamber dilation, and eventually systolic dysfunction.

On a microcirculatory level, the initial beneficial effect of vascular remodeling gradually gives way to critical luminal narrowing and the potential for regional ischemia from occlusion or loss of vessel wall integrity with leakage or rupture. Autoregulation, the intrinsic capacity of resistance vessels to dilate or constrict rapidly in response to dynamic perfusion pressure changes, works to maintain a relatively constant blood flow and is protective with moderate fluctuations.

Small-vessel ischemic episodes, many of which are silent, are the primary cause of chronic TOD, including progressive white matter (i.e., multi-infarct) disease in the brain and hypertensive nephropathy. Cerebral microbleeds identified on brain magnetic resonance imaging (MRI) scans as hemosiderin deposits, are a relatively new class of subclinical brain injury associated with chronic HTN and portend more rapid cognitive decline in older adults.[21]

Unlike the pattern of TOD that occurs with poorly controlled chronic HTN, a hypertensive emergency results from acute endothelial injury triggered by an abrupt rise in vascular pressure that overwhelms autoregulatory mechanisms. A subsequent drop in nitric oxide (NO)–mediated vascular smooth muscle relaxation and excess release of endothelin further increase SVR, which functionally maintains BP at severely elevated levels. Unchecked wall tension ensues, and terminal arterioles dilate and eventually rupture, leading to a proinflammatory hypercoagulable state, with fibrin deposition and diffuse ischemia. Rising pressure in the proximal capillary beds causes fluid leakage and tissue edema, which, combined with the process of fibrinoid necrosis, produces acute TOD along with microangiopathic hemolytic anemia and other signs of small vessel injury.

CLINICAL FEATURES

Although BP elevation alone does not define any particular clinical syndrome, acute TOD generally does not occur in the absence of moderate to severe HTN (≥180/110 mm Hg). Conversely, in the absence of symptoms, the mere presence of an excessively high BP in the ED (regardless of the level) does not herald imminent development of TOD.

Hypertensive Emergency

Most hypertensive emergencies occur in patients with chronic HTN; perhaps the most important exception is in pregnancy where abrupt rises in BP in previously normotensive women can lead to catastrophic acute consequences. Organ system involvement is relatively consistent and is dominated by vascular injury leading to impaired function of the heart, brain, or kidneys (Table 70.3). True hypertensive emergencies are defined by the target organ acutely involved. Focal neurologic deficit or altered mentation point to brain injury, whereas chest pain or shortness of breath may indicate cardiac or vascular involvement. Although frequently accompanied by an elevated BP, symptoms such as headache,[22] epistaxis,[23] and dizziness are not, in and of themselves, evidence of acute TOD and, in isolation, do not constitute a hypertensive emergency, nor do they indicate the need for acute BP reduction.

TABLE 70.3 Hypertensive Emergencies by Organ System

Injury Pattern by Target Organ	Approximate Incidence[a] (%)
Heart (cumulative)	27–49
• Acute heart failure	14–37
• Acute coronary syndrome	11–12
Brain (cumulative)	37–45
• Acute ischemic stroke	6–25
• Spontaneous intracranial hemorrhage	5–23
• Hypertensive encephalopathy	8–16
Kidney	
• Acute renal risk	15
• Acute kidney injury	8
Vascular	
• Aortic dissection	1–2
Other	
• Eclampsia	2
• Acute hypertensive retinopathy	1

[a]Adapted from Levy P. Hypertensive emergencies: on the cutting edge. Advancing the standard of care: cardiovascular and neurovascular emergencies. www.emcreg.org.

Hypertensive Encephalopathy

Hypertensive encephalopathy is the prime example of a hypertensive emergency. Resulting from diffuse, vasogenic cerebral edema, it is caused by a failure of autoregulation in the brain, with vasospasm, ischemia, increased vascular permeability, punctate hemorrhages, and interstitial edema. Severe headaches, vomiting, and altered mental status are common features that may progress to seizures or coma. Retinal involvement may cause blurred vision progressing to complete blindness. When present, focal neurologic deficits do not follow a singular anatomic pattern and may occur on opposite sides of the body, indicating diffuse cerebral dysfunction rather than an anatomically localized stroke syndrome or space-occupying lesions. Papilledema, which may be difficult to recognize with absent pupillary dilation, is often present, along with significant hypertensive retinopathy. Computed tomography (CT) may not show acute hemorrhage or other acute pathology. Diffuse or regional cerebral edema and small hemorrhages have been reported. The combination of altered mentation or diffuse neurological dysfunction on clinical examination, normal or nonspecific CT scan, and markedly elevated systemic BP, particularly if supported by objective findings such as papilledema or retinal hemorrhage, is sufficient to make a presumptive diagnosis of hypertensive encephalopathy and necessitates the initiation of acute antihypertensive therapy. Hypertensive encephalopathy is fully reversible with early, prompt BP reduction (30% to 40% decrease). Recently published data from the Nationwide Inpatient Sample have suggested that the overall in-hospital mortality rate is less than 1%.[24]

First defined in 1996, posterior reversible encephalopathy syndrome (PRES) has a neurologic presentation similar to that of hypertensive encephalopathy, albeit with less global and more region-specific features. Also caused by increased vascular permeability secondary to endothelial damage with vasogenic edema, PRES is characterized by a constellation of symptoms related to posterior cerebral impairment, including visual changes, headache, altered mental status, and seizures.[25] It is diagnosed by the visualization of white matter edema in the posterior parietal-temporal-occipital regions on MRI. As the name suggests, PRES is reversible by treating the underlying cause. HTN is the most common condition associated with PRES, although it may also be seen with kidney disease, malignancies, cytotoxic therapy, and autoimmune disease.

Other Hypertension-Related Emergencies

The clinical features of other HTN-related emergencies cross over with non-hypertensive manifestations, and they are described in greater detail elsewhere in this text. Moreover, these conditions are defined by more than just HTN and, in many cases, their onset is incidental to, not caused by, elevated BP. In specific conditions such as intracranial hemorrhage (ICH), the BP elevation may be compensatory to the associated pathology. However, long-standing HTN is often a contributor to the underlying problem and, when elevated BP is causal, effective treatment can have a dramatic impact on the clinical course. Elevated BP frequently accompanies acute ICH, and the rapid initiation of antihypertensive therapy is a routine component of ED care (see Chapter 87). HTN is the primary population-attributable risk factor for developing chronic cardiac dysfunction, and more than 50% of ED patients with acute heart failure have

elevated BP on presentation (see Chapter 67). Patients with acute heart failure and HTN respond well to vasodilatory agents and afterload reduction. Nitroglycerin has long been used in the setting of acute coronary syndrome (ACS) and demand ischemia (see Chapter 64), and antihypertensive therapy is a key component of ED management of acute aortic dissection (see Chapter 71). Acute kidney injury (AKI) in the setting of elevated BP may be a consequence of associated TOD, especially acute heart failure, particularly when these patients are on baseline diuretic or calcium channel blocker therapy. Recent or chronic NSAID or newly initiated ACE inhibitor therapy may also contribute, but the effect of these agents is usually transient (see Chapter 83). Preeclampsia and eclampsia are discussed in Chapter 173.

Acute Target Organ Damage in the Context of Systemic Illness

Any medical condition that leads to a hypermetabolic state can impair electrolyte homeostasis and trigger an intrinsic vasomotor response, causing the BP to rise acutely. Depending on the circumstance, this may also be associated with clinical or diagnostic evidence of acute TOD. Distinguishing this from a true hypertensive emergency necessitates demonstration that the elevated BP does not contribute directly to the pathologic condition. Treatment of the underlying disorder will often resolve the BP elevation, although BP reduction may play a role in supportive management.

Absence of Target Organ Dysfunction

Most patients who are found to have significantly elevated BP on intake vital signs measurement or who come to the ED because the BP was found to be elevated in an outpatient setting or by self-measurement do not have an acute hypertensive emergency. For such patients, acute reduction of BP is not indicated and offers no tangible outcome benefit. Although many patients who fall into this group have poorly controlled chronic HTN, some lack such a history. To connote an absence of acute TOD, these patients are often described by the term *asymptomatic*, but this is potentially misleading because nonspecific symptoms (e.g., low-grade or recurrent headache, chest pain, dyspnea, dizziness, generalized weakness, focal but anatomically uncorrelated weakness or numbness, vague visual disturbances) are frequently present. However, with the exception of dyspnea, the occurrence of these symptoms appears to be unrelated to the degree of BP elevation. In addition, despite widespread belief among the lay community and some members of the health care profession that acute severe HTN contributes to epistaxis, there is no evidence to support a causal relationship.

As a general rule, acute BP reduction is not indicated in patients with elevated BP who lack acute TOD, even when vague symptoms are present. BP will spontaneously improve with time or with treatment for concurrent pain or anxiety in many cases, and there is no need to hasten this with antihypertensive therapy. If chronic oral medications have been missed, these should be restarted; the first dose may be administered in the ED to reinforce the importance of future compliance, although this is in no way required and will not change any outcome. Regardless, no data support a threshold BP that warrants such treatment or a target BP to be achieved before discharge. Notably, the administration of a short-acting, potent antihypertensive agent such as clonidine or hydralazine simply to improve BP values lacks rationale or evidence of benefit and may be associated with an increased likelihood of subsequent ED visit for issues related to HTN. As previous experience with sublingual nifedipine has shown, BP reduction in the absence of acute TOD is also potentially dangerous, inducing relative hypoperfusion with increased related morbidity, especially in the cerebrovascular circulation. Therefore, we recommend not to administer medication in the ED solely to improve BP values.

DIFFERENTIAL DIAGNOSES

Differential considerations are based on patient subtype. For those with a suspected hypertensive emergency, the decision point centers on the potential causal relationship between patient presentation and acutely elevated BP. Clinical entities within this broader heading, such as stroke syndromes and acute heart failure, carry their own differentials, and a full discussion of each is beyond the scope of this chapter. Depending on the clinical scenario, ancillary testing may be needed to rule out alternatives to a hypertensive cause, particularly in patients with systemic illness.

For those with poorly controlled chronic HTN, a consideration of cause (primary vs. secondary) may be warranted. A related diagnostic evaluation (see Table 70.1) can usually be pursued on an outpatient basis. However, for some (e.g., individuals with multiple episodes of flash pulmonary edema, symptomatic paroxysmal episodes of labile BP, or suspected poor follow-up), initiation of treatment from the ED or admission to the hospital is needed.

The final factor to consider is whether a newly detected BP elevation is caused by true HTN. Although the diagnostic accuracy of BP can be enhanced by a second repeat measurement in the ED, the ideal approach may be to average several measurements taken over a brief period of observation. For those without a previous history of HTN, definitive diagnosis will typically require reassessment in an outpatient setting and may involve ABPM. This discussion is summarized in Box 70.1.

DIAGNOSTIC TESTING

The diagnostic evaluation of hypertensive emergency is guided by symptoms and signs identified on clinical examination but will often involve a number of tests. In selected cases, laboratory testing to look for acute or worsening renal dysfunction (e.g., basic metabolic panel, urinalysis) and microangiopathic hemolytic anemia (e.g., complete blood count with manual differential, peripheral smear) may be needed. Individuals with chest pain or shortness of breath generally require a chest radiograph, electrocardiogram, and cardiac biomarker (e.g., troponin, natriuretic peptide [NP]) measurement. Additional cardiovascular imaging by CT, transesophageal echocardiography, or MRI should be considered if there is clinical suspicion for aortic dissection. When focal neurologic deficits or altered mentation are present, brain imaging by CT and, in many cases, MRI, will be needed, along with laboratory tests to evaluate for potential toxic, metabolic, or infectious causes.

Hypertensive retinopathy identified on funduscopic examination signifies underlying TOD and, when present, is strongly associated with an enhanced risk of stroke in patients with HTN. Findings of acute hypertensive retinopathy include focal intraretinal periarteriolar transudates (whitish ovoid lesions deep in the retina), focal retinal

BOX 70.1 Differential Diagnoses for Elevated Blood Pressure in the Emergency Department

- True hypertensive emergencies (i.e., acute heart failure, ischemic stroke, pre-eclampsia)
- Elevated blood secondary to pain, anxiety, transient physiological conditions, and medications
- Inaccurate measurement

pigment epithelial lesions (evidence of choroidal injury), macular and optic disk edema, and cotton wool spots (fluffy white lesions that consist of swollen ischemic axons caused by small vessel occlusion). Hard exudates, which consist of lipid deposits located deep in the retina, are also a common but late occurrence. When identified, such fundoscopic abnormalities are considered diagnostic; however, they may be absent in more than 30% of patients with a clinically evident hypertensive emergency. Lesions of acute retinopathy are distinct from more chronic changes, including arterial narrowing, copper or silver wiring of the arterioles, arteriovenous nicking, and retinal hemorrhages. The spectrum of retinal findings in HTN can be graded on a five-point scale (Box 70.2). Despite such value, fundoscopy is infrequently performed adequately to evaluate severely elevated BP in ED patients. Technical challenges and a lack of experience likely contribute to this. Nonmydriatic digital fundus photography can help overcome these issues and has shown promise as an adjunct to detect chronic and acute changes associated with hypertensive retinopathy in the ED setting.[22]

Although fundoscopy provides useful information, whether this or any other form of diagnostic evaluation is needed in the ED as a routine screening tool for those without overt TOD is a matter of debate. Although recommendations on routine testing in the primary care setting exist, there is no similar guidance for the ED. In the only prospective multicenter study of recommended routine tests (e.g., basic metabolic panel, urinalysis, electrocardiography, chest x-ray) performed in the ED, clinically meaningful abnormalities were detected in only 6% of patients, none of which were definitively attributable to HTN. However, in settings where HTN-related kidney disease is prevalent (e.g., predominantly Black American communities), evaluation of renal function by a basic metabolic panel may be a reasonable consideration. Although such information is highly unlikely to affect emergent management, there is value in knowing baseline renal function and electrolyte levels, particularly if the initiation of chronic antihypertensive therapy is planned. Urine testing, especially spot measurement of the urine albumin-to-creatinine (Cr) ratio, is a reasonable alternative to detect subclinical kidney disease, although it does not provide information on electrolyte levels.

Unlike renal function, there is no simple, efficient test for detecting subclinical cardiac disease in the ED, and symptoms guide evaluation in this setting. Although chest x-ray and electrocardiography are often used, they have poor sensitivity for TOD (especially LV hypertrophy), and abnormalities, when identified, are unlikely to alter clinical management. Serum NP levels (e.g., B-type NP [BNP] and N-terminal pro-BNP [NT-proBNP]) have yielded conflicting results and are not optimal screening tests, nor are they indicated for the emergent evaluation of HTN unless there is suspected cardiac TOD. Based on findings from a study in which echocardiography was used as the criterion standard, the prevalence of subclinical hypertensive heart disease in select populations appears to be substantial (≈90%), suggesting the need to develop a more effective screening strategy. Bedside cardiac ultrasound in the ED focused on identifying LV hypertrophy and perhaps diastolic dysfunction has shown potential for this purpose[23–27]; however, validation of such an approach in large prospective trials will be needed before widespread adoption can be endorsed.

BOX 70.2 Funduscopic Grading of Suspected Hypertensive Retinopathy

Grade 0—normal
Grade 1—minimal arterial narrowing
Grade 2—obvious arterial narrowing with focal irregularities
Grade 3—arterial narrowing with retinal hemorrhages and/or exudate
Grade 4—grade 3 plus disk swelling

MANAGEMENT

Acute Blood Pressure Control

Antihypertensive Therapy

Immediate BP reduction using antihypertensive therapy is indicated when an acute hypertensive emergency is present. In such cases, the goal of acute antihypertensive therapy is to lower BP safely and effectively in a relatively rapid fashion while maintaining peripheral perfusion. Although some oral (e.g., clonidine) or sublingual (e.g., captopril, nitroglycerin) medications are capable of this, patients who truly require acute lowering of BP benefit from the predictable, controlled effects of a parenteral agent by titrated intravenous (IV) boluses or by adjustable infusion.

Mean arterial pressure (MAP), a summary measure representing the average arterial pressure during one cardiac cycle, is a composite of circulatory inputs. The relationship is defined by the following equation:

$$MAP = (CO \times SVR) + CVP$$

where SVR reflects vasogenic tone in the arterioles (afterload), CO reflects the pumping force of the heart, and central venous pressure (CVP) represents intravascular volume (preload) and the effective hydrostatic force in the circulatory system. The hemodynamic response to a specific medication or class of medications is a function of how they interact with this equation, and, as shown in Table 70.4, effects can differ substantially. Existing IV antihypertensive agents directly exert their effects through receptor-mediated actions (largely agonist or antagonist properties) or indirectly through a decrease in the production or release of endogenous vasoconstrictors. The magnitude of BP reduction reflects the mechanism of action as well as the pharmacokinetic and pharmacodynamic activity, with some variability in the latter based on aging.

Labetalol and nitroglycerin are the most common IV antihypertensive medications used in the ED setting, but outcome data related to different agents are lacking. Thus, although some studies have suggested more favorable effects on BP reduction with nicardipine, a dihydropyridine calcium channel blocker, as compared to labetalol, clear superiority of one drug over another has yet to be demonstrated. A general guide to IV antihypertensive therapy is provided in Table 70.5. However, certain agents may be more appropriate than others for a specific indication depending on the desired response profile.

Blood Pressure Goals

Optimal treatment of a true hypertensive emergency involves therapy that is directed toward the precipitant of specific TOD and the acute consequences of elevated BP rather than the BP itself. The longstanding approach to acute antihypertensive therapy has targeted a maximal reduction in MAP of 20% to 25% within the first hour and a goal BP of 160/100 mm Hg by 2 to 6 hours.[28] This arises from an understanding of the cerebral autoregulation curve, which maintains stable blood flow within a range of pressures (MAP of 60 to 160 mm Hg) under normal circumstances but resets in chronic HTN with a shift of the lower limit toward the right. This shift tends to settle approximately 25% below baseline MAP, resulting in concern for decreased cerebral blood flow with BP reduction beyond this.

Although this consideration is relevant for patients who have poorly controlled chronic HTN, BP is often well above baseline when a hypertensive emergency is present and far in excess of the lower limit of their individual autoregulation curve. Consequently, a margin of

TABLE 70.4 Hemodynamic Effect Profile of Common Intravenous Antihypertensive Medications

Classification	Agent(s)	HEMODYNAMIC EFFECT		
		Cardiac Output	Systemic Vascular Resistance	Central Venous Pressure
Adrenergic inhibitors				
• α 1-Blockers	Phentolamine, urapidil[a]	↑	↓	↑
• β1-Blockers	Esmolol, metoprolol	↓	↑↓	↑↓
• Mixed α1–β1 blockers	Labetalol	↓	↓	↑↓
Angiotensin-converting enzyme inhibitors	Enalaprilat	↑↓	↓	↑↓
Calcium channel blockers				
Dihydropyridine	Clevidipine, nicardipine	↑	↓	↑↓
Nondihydropyridine	Diltiazem, verapamil	↓	↓	↑↓
Direct-acting vasodilators	Hydralazine	↑	↓	↑↓
Dopamine-1 receptor agonists	Fenoldopam	↑↓	↓	↑↓
Loop diuretics	Furosemide, bumetanide, torsemide	↑↓	↓	↓
Natriuretic peptide receptor agonists	Nesiritide	↑	↓	↓
Nitric oxide donors	Sodium nitroprusside, nitroglycerin, isosorbide dinitrate	↑	↓	↓

[a]Also has serotonin-1A (5-HT1A) agonist properties.
Adapted from Levy P. Hypertensive emergencies: on the cutting edge. Advancing the standard of care: cardiovascular and neurovascular emergencies. www.emcreg.org.

TABLE 70.5 Guide to Intravenous Antihypertensive Therapy

Medication by Class	Bolus or Loading Dose	Infusion Rate	Time to Onset	Duration of Action	Comments
Adrenergic Inhibitors					
Phentolamine	5–15 mg q5min	0.2–0.5 mg/min	1–2 min	10–30 min	Avoid with coronary artery disease
Urapidil	12.5–50 mg q5min	9–30 mg/h	1–2 min	2.5 h	Not FDA approved
Esmolol	0.5–1 mg/kg × 1	50–300 μg/kg/min	1–2 min	20 min	
Metoprolol	5 mg q5min	None	10–30 min	5–8 h	
Labetalol	20–80 mg q10min	1–2 mg/min	2–5 min	3–6 h	Beta blocker effects predominate (1:7)
ACE Inhibitor					
Enalaprilat	0.625–1.25 mg q15min	1–2 mg/h	15–30 min	6–12 h	May produce prolonged hypotension; avoid in pregnancy
Calcium Channel Blockers					
Clevidipine	None	2–32 mg/h	1–2 min	1–5 min	
Nicardipine	None	5–15 mg/h	5–15 min	4–6 h	Avoid with aortic stenosis and liver failure (hepatic metabolism)
Diltiazem	0.25–0.35 mg/kg q15min	5–15 mg/h	5–15 min	6 h	Will decrease blood pressure but not often used for this indication
Verapamil	2.5–5 mg IV q15min	None	5–15 min	6 h	
Direct-Acting Vasodilator					
Hydralazine	5–20 mg q30min		10–20 min	2–4 h	Causes reflex activation of the sympathetic nervous system
Dopamine Antagonist					
Fenoldopam	None	0.1–0.3 μg/kg/min; titrate by 0.1 μg/kg	<5 min	30 min	Increases intraocular pressure; contains sodium metabisulfate—avoid in patient with sulfa allergy
Loop Diuretics					
Furosemide	40–240 mg q12h	10–40 mg/h	30–60 min	2–4 h	Limited antihypertensive effect compared with other agents listed
Bumetanide	0.5–4 mg q12h	None	30–60 min	2–4 h	
Torsemide	10–20 mg q12h	None	30–60 min	2–4 h	
Natriuretic Peptide					
Nesiritide	2 μg/kg × 1	0.01 μg/kg/min	15 min	18 min	Indicated only for use in acute heart failure
Nitric Oxide Donors					
Sodium nitroprusside	None	0.25–10 μg/kg/min	Immediate	1–2 min	May cause precipitous drop in blood pressure with right ventricular ischemia or renal artery stenosis; bolus administration controversial; risk of cyanide toxicity with nitroprusside; avoid entire class in patients taking phosphodiesterase–5 inhibitors (eg, sildenafil)
Nitroglycerin	1–2 mg q5min	5–200 μg/min	2–5 min	5–10 min	

ACE, Angiotensin-converting enzyme; *FDA,* US Food and Drug Administration; *IV,* intravenously.

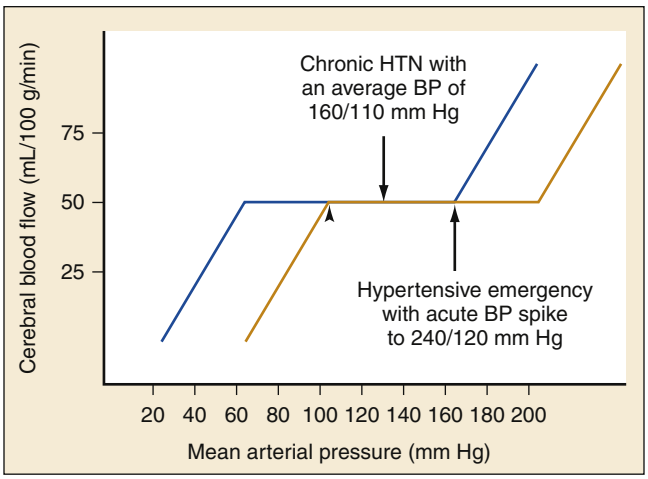

Fig. 70.2 Cerebral blood pressure *(BP)* autoregulation curve *(black line)* and its right shift response to chronic hypertension (HTN; *red line*). Data shown are for a hypothetical patient with chronic hypertension and poor blood pressure control at baseline *(blue arrow)* with a hypertensive emergency *(black arrow)*. As indicated by the *arrowhead*, the lower limit of the shifted autoregulation curve in this scenario sits well beyond a 25% reduction in mean arterial pressure.

safety exists in this case, with antihypertensive therapy serving to bring BP down to (rather than along) the perfusion plateau from the ascending portion of the autoregulation curve (Fig. 70.2). Use of a single BP goal for all hypertensive emergencies fails to account for this and may preclude the ability to interrupt the pathophysiology causing acute TOD effectively. Therefore, the best approach is to focus on condition-specific targets. An overview of respective treatment goals and relevant caveats for differing indications is found in Table 70.6.

Acute Coronary Syndrome and Acute Heart Failure

In ACS complicated by HTN, the primary goal (beyond expeditious reperfusion) is a decrease in cardiac work and improved coronary artery perfusion, each of which can be dramatically affected by changes in afterload (see Chapter 64). Similarly, in patients with acute hypertensive heart failure in which a rise in SVR—more specifically the augmentation index—impedes forward flow and exacerbates ventricular stiffness, intervention aimed at reducing afterload can offset resistive forces, enabling more effective contraction (see Chapter 67).

Medications that exert their effect by providing an exogenous nitric oxide (NO) source are known as NO donors, including nitroglycerin and sodium nitroprusside. Nitroglycerin can be highly beneficial in both ACS and heart failure because it produces small-vessel dilation, yielding a dose-dependent decrease in overall vascular resistance and

TABLE 70.6 Indication-Specific Approach to Management of Hypertensive Emergencies

Indication	Goals of Treatment	Optimal Agents	Alternative Therapy	Caveats
Acute coronary syndromes	Diminish cardiac workload and improve coronary artery perfusion	*Primary*—nitroglycerin *Secondary*—metoprolol, labetalol	Esmolol, nicardipine	Routine use of intravenous beta blocker therapy is controversial.
Acute heart failure syndromes	Reduce impedance to forward flow and diminish cardiac workload	*Primary*—nitroglycerin, furosemide *Secondary*—enalaprilat	Clevidipine, nicardipine, sodium nitroprusside	Intubation or noninvasive ventilatory support decreases preload and may drop BP. Enalaprilat may cause sustained hypotension. Although FDA-approved, use of nesiritide is controversial.
Aortic dissection	Reduce shear force and *dP/dt*	*Primary*—esmolol plus sodium nitroprusside *Secondary*—labetalol	Esmolol plus (clevidipine or nicardipine), diltiazem, verapamil	Avoid beta blockers if aortic regurgitation is present.
Acute ischemic stroke[a]	Reduce hemorrhagic conversion and edema while avoiding regional hypoperfusion	*Primary*—nicardipine or clevidipine *Secondary*—labetalol	Esmolol	Acute BP reduction is indicated only with planned fibrinolytic administration or when secondary target organ dysfunction is involved.
Acute intracerebral hemorrhage[a]	Reduce hematoma expansion and perihematomal edema	*Primary*—nicardipine *Secondary*—labetalol	Esmolol	BP may decrease with pain management alone. Clevidipine is currently under investigation.
Hypertensive encephalopathy[a]	Decrease brain edema, reduce intracranial pressure, improve autoregulatory control	*Primary*—nicardipine *Secondary*—labetalol	Esmolol, enalaprilat	Other causes of altered mental status should be considered in the evaluation.
Acute kidney injury	Decrease pressure in renal parenchyma and glomerular apparatus	*Primary*—*Secondary*—clevidipine, nicardipine	Labetalol, sodium nitroprusside	Angiotensin-converting enzyme inhibitors and diuretics should be avoided.
Preeclampsia and eclampsia	Decrease intracranial pressure while maintaining placental perfusion	*Primary*—hydralazine *Secondary*—labetalol	Nicardipine	Intravenous magnesium (4 g initially) is administered in all cases. Emergent cesarean section is definitive treatment.
Sympathetic crisis	Reduce alpha1-adrenergic receptor–mediated vasoconstriction	*Primary*—phentolamine *Secondary*—nitroglycerin	Fenoldopam, clevidipine, nicardipine, sodium nitroprusside	Benzodiazepines are first-line therapy when sympathetic crisis is caused by cocaine or amphetamines. Beta-blocker monotherapy (including labetalol) is relatively contraindicated.

[a]Nitric oxide donors and hydralazine should be avoided with these indications.
BP, Blood pressure; *dP/dt,* change in pressure/change in time; *FDA,* US Food and Drug Administration.
Adapted from Levy P. Hypertensive emergencies: on the cutting edge. Advancing the standard of care: cardiovascular and neurovascular emergencies. www.emcreg.org.

diminishing arterial waveform reflection intensity, thus improving systolic ejection time and diastolic coronary artery filling.

Rapid reduction in MAP, typically utilizing nitrates, has been associated with profound symptom resolution and improved short-term outcomes among patients with severe, acute hypertensive heart failure[29] and is recommended as first-line therapy.[30,31] As shown in Fig. 70.3, this may be due to improved coronary perfusion and decreased subendocardial ischemia. Achieving this may require high doses of nitroglycerin (e.g., 1 to 2 mg by IV bolus or infusion rates greater than 250 µg/min), but this approach is generally well tolerated, with no adverse effects, even at MAP reductions of 30% to 40%.

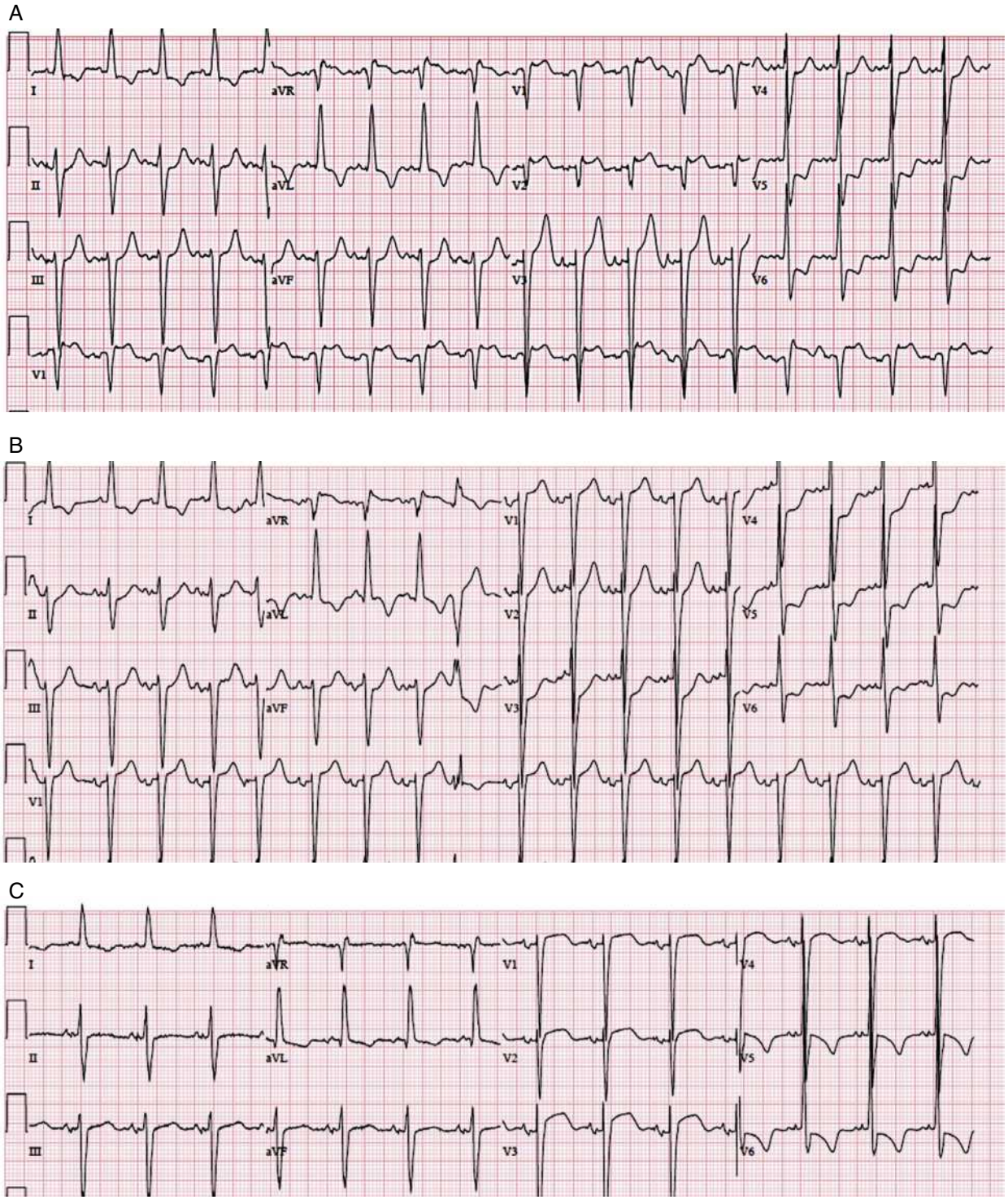

Fig. 70.3 Serial electrocardiograms demonstrating resolution of relative myocardial ischemia in a profoundly hypertensive patient with acute heart failure after treatment with high-dose intravenous nitroglycerin. (A) BP, 241/122 mm Hg. Anterior leads (V1–3) show ST segment elevation and lateral leads (V5–6) show ST depression. (B) BP, 192/103 mm Hg. Anterior lead ST elevation has resolved, but lateral lead ST depressions persist. (C) BP, 150/92 mm Hg. ST segment deviations have largely resolved.

Moreover, using nitroglycerin avoids the challenges associated with alternatives such as sodium nitroprusside, including the need for arterial line monitoring, risk of cyanide toxicity, and potential for compound photodegradation. The most important caveat is that NO donors should be avoided in patients who have taken a phosphodiesterase-5 (PDE5) inhibitor such as sildenafil or tadalafil within the preceding 24 to 48 hours because this can result in a more profound BP decrease and persistent hypotension.

ACE inhibitors are also well-tolerated and associated with rapid symptom improvement in patients with hypertensive heart failure. Enalaprilat can be administered by IV bolus or infusion and is the preferred ACE inhibitor in the setting of acute heart failure, but cautious dosages (0.625 to 1.25 mg/dose IV, up to a maximum of 2.5 mg over 30 minutes) are recommended because the drug is long-acting and can precipitate a sustained drop in BP.

Given their short half-life, third- and fourth-generation IV dihydropyridine calcium channel blockers (e.g., nicardipine [5 to 15 mg/hour IV], clevidipine [1 to 6 mg/hour]) are potential alternatives, with at least one prospective trial suggesting that this class can safely and effectively reduce BP while improving dyspnea more rapidly than standard therapy in those with acute hypertensive heart failure.

Labetalol and other IV agents with inhibitory β-adrenergic effects, such as metoprolol, should be avoided in the early stages of treatment because they produce a decrease in CO and, in ACS, may increase the risk of developing cardiogenic shock.

Although BP reduction drives symptom improvement in acute hypertensive heart failure, adverse events are more likely to occur when BP is rapidly normalized (i.e., decreased to ≤120/80 mm Hg), particularly in the setting of compromised cardiac function. Therefore, antihypertensive therapy for ACS or acute heart failure should be titrated to symptom resolution rather than a specific MAP, with short-term tolerance of persistently elevated BP in a clinically improving patient.

Aortic Dissection

With aortic dissection, unlike other hypertensive emergencies, BP control to a specific target (systolic BP <110 mm Hg) is essential because it decreases ongoing injury and reduces the likelihood of perioperative adverse events (see Chapter 71).[28] The immediate goal is to reduce intimal shear forces by driving down the pressure that results from LV ejection with each cardiac cycle (termed *dP/dt*). This is best accomplished by decreasing the heart rate and stroke volume through the administration of a rapid-acting IV beta-blocker, such as esmolol (bolus 500 mcg/kg IV, followed by maintenance 0.05 to 0.2 mcg/kg/min). Although a direct reduction in BP is also critical, beta-blocker therapy should be initiated before vasodilation because the latter can lead to reflex tachycardia and worsening of *dP/dt*. Once beta blockers have been initiated, and a heart rate of less than 60 beats/min has been achieved, agents such as sodium nitroprusside, nicardipine, or clevidipine can be rapidly titrated to reduce systolic BP as low as can be tolerated (and, ideally to <120 mm Hg) within 30 minutes. Because labetalol has both alpha and beta blocker properties, it may be an acceptable alternative. Note that labetalol has a long half-life, of about 4 to 6 hours, and is therefore not easily titratable as a continuous infusion. Diltiazem and verapamil, mixed calcium channel blockers (agents with cardiac and vascular effects), may also be used, although neither is ideal as monotherapy. For patients with persistently elevated BP, despite initial therapy, the use of multiple agents from different classes may be needed.

Acute Ischemic Stroke

Understanding the nuances of elevated BP in acute ischemic stroke is critical (see Chapter 87). A U-shaped relationship exists between mortality and BP, with worse outcomes at high and low extremes. Ischemic stroke is thought to impair cerebral autoregulation mechanisms, and thus cerebral perfusion is dependent on systemic BP. The elevated BP seen in the acute phase is likely a compensatory mechanism to achieve perfusion of the brain within low flow areas distal to occluded arteries. Disrupting this process is deleterious and can lead to worse outcomes. The 2018 AHA/American Stroke Association (ASA) guidelines call for a BP reduction to below 185/110 mm Hg only when thrombolysis is planned, with maintenance of BP at below 180/110 in such cases.[32] Otherwise, antihypertensive therapy is not indicated unless BP exceeds 220/120 mm Hg and, even in such cases, the goal is to decrease BP by approximately 15% gradually, over the first 24 hours after symptom onset. The AHA/ASA guidelines are supported by a meta-analysis that fails to show a mortality benefit associated with rapid BP reduction.

Based on these recommendations, and considering data from two large randomized studies[33] showing no benefit with BP reduction over the first 24 hours, there appears to be a limited role for ED management of elevated BP in patients with acute ischemic stroke who will not undergo thrombolysis. However, a subanalysis of one study showed a trend toward reduced vascular events (but not functional outcomes) among those treated within 6 hours of symptom onset, as well as those with large vessel occlusions,[34] suggesting a possible time-dependent component, with increased susceptibility to the adverse effects of sustained BP elevation earlier in the disease course.

For patients who need IV antihypertensive therapy, labetalol (bolus 20 mg IV q 10 minutes), and nicardipine (5 to 15 mg/hour IV) have emerged as the agents of choice because they maintain adequate cerebral perfusion while producing generalized reductions in vascular resistance. Nicardipine may offer some advantage over labetalol because it results in a more rapid and sustained achievement of BP goals with reduced BP variability, a potentially important determinant of patient outcome. As a fourth-generation calcium channel blocker, clevidipine offers similar benefits to nicardipine with the added advantage of being shorter-acting, making it easier to recover quickly if BP is lowered too much. Esmolol may also be used, although it reduces BP by reducing CO than SVR. While sodium nitroprusside is a highly effective antihypertensive option, it and other NO donors should be avoided because they can cause an increase in intracranial pressure.

Spontaneous Intracranial Hemorrhage

Spontaneous ICH is strongly associated with HTN, and persistently elevated BP contributes to hematoma expansion, vasogenic edema, and rebleeding (see Chapter 87). A large systematic review and several multicenter trials have shown improved outcomes with BP reductions to 140 to 150 mm Hg. In contrast to ischemic stroke, there is little evidence to suggest adverse outcomes from hypotension in ICH. The 2015 AHA/ASA guidelines recommend rapid reduction via continuous IV agents when the systolic BP exceeds 220 mm Hg and state that a target systolic BP of 140 mm Hg is safe for such patients. When more modest elevations are present (systolic BP >150 but <220 mm Hg), BP should be lowered, possibly more gradually, to 140 mm Hg—a strategy that has been shown to improve functional outcomes.[35]

Results from the Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) add to the AHA/ASA guidelines suggesting functional outcome but no mortality benefit with intensive antihypertensive therapy targeting a reduction of systolic BP to 140 mm Hg within 1 hour of diagnosis. However, in a post hoc analysis of INTERACT2, patients who achieved a reduction in systolic BP of 20 mm Hg or more within the first hour of treatment were 35% less likely to experience a poor outcome, suggesting that optimal recovery from acute ICH may be dependent on early, profound reductions in BP with antihypertensive therapy.

As with ischemic stroke, labetalol and nicardipine (or clevidipine) are the preferred agents for acute BP reduction. In INTERACT2, urapidil, an α-adrenergic antagonist not approved in the US, was the most commonly used agent (32.5%) in the intensive treatment arm, followed by nitroglycerin or nitroprusside (27.0%), nicardipine (16.2%), and labetalol (14.4%). However, in the ATACH-II study, in which nicardipine was used exclusively, no outcome benefit was associated with the lower BP target.[36] Nimodipine, an oral dihydropyridine calcium channel blocker, is specifically indicated for patients with subarachnoid hemorrhage, although its benefit appears to be related more to a reduction in intracranial arterial vasospasm than to an effect on SVR.

Hypertensive Encephalopathy

Unlike acute stroke syndromes, in which HTN may be reactive rather than causative, a direct association exists between the degree of BP elevation and neurologic symptoms in patients with hypertensive encephalopathy. Once alternative causes of altered mentation have been ruled out, therapy should be directed toward the initiation of rapid BP reduction. The goal is to return BP to a point at which autoregulation can regain control of cerebral blood flow, and the process leading to cerebral edema can be reversed, requiring the MAP to be brought back down to the pressure curve plateau. To achieve this, reductions in MAP of 30% to 40% may be needed. Whereas MAP targets should still be kept in mind, symptom resolution is the best gauge of therapeutic effectiveness, with treatment explicitly directed toward improvement of encephalopathy.

The agents of choice for BP reduction in hypertensive encephalopathy are labetalol (20 mg IV q 10 minutes), nicardipine (5 to 15 mg/hour IV), and clevidipine (1 to 6 mg/hour IV) because they produce an even decrease in resistance across vascular beds in different organ systems. In contrast, NO donors (nitroglycerin and nitroprusside), although widely used for this indication, have a differential effect on the cerebral and systemic circulations, resulting in a relative increase in cerebral BP and a shunt effect to the peripheral circulation. This decreases the cerebral blood flow and may produce a greater than anticipated reduction in cerebral perfusion, thereby increasing the risk of ischemia in watershed areas of the brain. This may be worsened by the relative increase in intracranial pressure known to occur with sodium nitroprusside therapy. Several case reports have described neurologic deterioration with administration of nitroglycerin in PRES, supporting this as an actual rather than theoretical concern. Similar differential circulatory effects may also occur with hydralazine (a direct-acting vasodilator that inhibits calcium release from the sarcoplasmic reticulum) and, unless BP is entirely refractory for other therapy, it is best to avoid use of these agents.

Acute Kidney Injury

Defined by an increase in serum creatinine level of 0.3 mg/dL or more in 48 hours, 1.5 or more times baseline in 7 days, or a urine volume of less than 0.5 mL/kg/hour over 6 hours, AKI represents an abrupt worsening of renal function (see Chapter 83). Although often a manifestation of ongoing glomerular injury from chronic poor BP control, deterioration of kidney function in the setting of severe HTN may be precipitated by prerenal causes, including volume depletion (often related to concurrent diuretic therapy), extrinsic alterations in the GFR (often triggered by drug-mediated, afferent arteriolar vasoconstriction and ACE inhibitor–induced autoregulatory modulation) or intrinsic nephron destruction caused by acute pressure overload. Consequently, some patients require fluid administration to augment volume, whereas others need antihypertensive therapy to mitigate pressure-mediated nephrogenic damage.

Laboratory testing is useful to differentiate which approach should be initiated. A blood urea nitrogen (BUN)/Cr ratio higher than 20 and a fractional excretion of sodium (FENa) calculated as

$$\frac{\text{Urine Na} \times \text{Serum Cr} \times 100}{\text{Serum Na} \times \text{Urine Cr}}$$

below 1% indicates a prerenal cause. Because diuretics alter sodium excretion, for those on chronic diuretic therapy, a fractional excretion of urea (FEurea), calculated as

$$\frac{\text{Serum Cr} \times \text{Urine Na} \times 100}{\text{Serum urea} \times \text{Urine Cr}}$$

below 35% indicates a prerenal state.

When antihypertensive therapy is indicated, fenoldopam, a potent dopamine 1A receptor agonist, is preferred because it leads to improved perfusion of the corticomedullary region and has been associated with a reduction in the need for subsequent dialysis and rate of in-hospital death. Enalaprilat should be avoided because it produces differential effects on the precapillary and postcapillary glomerular vascular bed (i.e., more significant vasodilation in efferent than afferent arterioles), which increases the risk of further deterioration in estimated GFR. Peripheral-acting calcium channel blockers such as nicardipine and clevidipine have no adverse effect on the glomerular autoregulation and are acceptable first-line alternatives to fenoldopam. Other agents, including labetalol and sodium nitroprusside, may also be used.

Preeclampsia and Eclampsia

Although delivery is the definitive treatment, BP control is a critical part of early management (see Chapter 173).[37] Similar to hypertensive encephalopathy, preeclampsia and, to a greater degree, eclampsia, represent an overwhelming of the cerebral autoregulation, and rapid BP reduction is essential. Because they are acute (rather than chronic) complications in a relatively healthy young population, there is generally no resetting of the autoregulation curve in preeclampsia or eclampsia, and adverse consequences can develop at seemingly "low" (but relatively high) pressures. Therefore, the threshold for intervention is set lower than with other hypertensive emergencies (e.g., systolic BP >160 mm Hg).

Magnesium sulfate (4 g IV loading dose, followed by 1 to 2 g/hour) is considered first-line therapy for all cases of preeclampsia and eclampsia. It relaxes the smooth muscle (partly through calcium antagonism), leading to some decrease in peripheral and cerebral vascular resistance, limiting cerebral edema formation by protecting the blood-brain barrier, and has central anticonvulsant activity. However, its antihypertensive effects are modest, and additional treatment is typically needed to control BP. Hydralazine (10 mg IV) and labetalol (20 mg IV) by IV bolus are equally useful for this purpose and have a limited impact on placental blood flow. Nicardipine (5 to 15 mg/hour) or clevidipine (1 to 6 mg/hour) are reasonable alternatives and may produce a more profound decrease in BP than labetalol.

Sympathetic Crises

Hyperadrenergic states can result from endogenous sources of catecholamine excess (e.g., pheochromocytoma) but, more commonly, they are triggered by the intake of exogenous substances that interfere with norepinephrine—and to a lesser degree, epinephrine—metabolism, such as cocaine, amphetamines, and tyramine-containing foods, especially in patients on monoamine oxidase inhibitors. The net result is a cardiostimulatory and vasopressor response that manifests clinically as tachycardia and marked HTN. In patients with cocaine or amphetamine intoxication, such peripheral effects are compounded by central sympathetic activation, and the hemodynamic derangements

can often be improved by the administration of benzodiazepines and other sedative medications.

When BP is persistently elevated, and target organ compromise is present, antihypertensive treatment is needed. Phentolamine (5 to 15 mg IV), a reversible pure alpha blocker, is considered first-line therapy, producing a reliable decrease in peripheral and coronary vasoconstriction, with few adverse effects. Nitroglycerin (1 to 2 mg IV bolus, or 50 to 200 mcg/min maintenance infusion) can also be used and is specifically indicated for patients with associated chest pain and suspected coronary artery vasospasm. Other agents, including fenoldopam, nicardipine, clevidipine, and sodium nitroprusside, are acceptable alternatives.

Heart rate control may also be needed, especially in patients with pheochromocytoma, in whom adrenal release of epinephrine may be exceptionally high, and a short-acting beta blocker such as esmolol is ideal for this purpose. However, to avoid precipitation of unopposed alpha receptor activity and a worsening of HTN, beta blocker therapy should be paired with a vasodilator. Although labetalol has combined alpha and beta blocker properties, beta receptor effects strongly predominate when the drug is administered in IV form (alpha/beta ratio of 1:7). Consequently, IV labetalol is susceptible to a similar differential response and should not be used in isolation in the setting of catecholamine excess.

Chronic Antihypertensive Therapy

Poorly controlled chronic HTN on a single visit or a clear trend toward persistently elevated BP over time requires a referral for timely follow-up, with reinforcement of goal BP recommendations and emphasis on the need for lifelong dietary and medication compliance. Initiation of oral antihypertensive therapy for those in whom a new diagnosis of HTN is suspected should be approached with caution. However, reinitiation or up-titration of medication for patients with chronic HTN is appropriate from the ED, especially when outpatient follow-up cannot be ensured. Although it is unclear whether this practice impacts long-term outcomes, it is associated with a substantial reduction in BP at follow-up and appears to be safe.

Although there are multiple medication options, a standardized approach to prescribing chronic antihypertensive therapy has been proposed by the AHA/ACC, starting with a thiazide diuretic for most patients. Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs) are included as acceptable first-line alternatives and recommended as add-ons for patients with persistent, poorly controlled BP. Because most patients with stage II HTN ultimately require multiple agents to control their BP, initiation of two-drug therapy when the systolic BP is higher than 160 mm Hg or diastolic BP higher than 100 mm Hg is recommended. There is increasing evidence that improved compliance with reduced side effects and outcome benefits can be achieved using low-dose combination tablets, especially combined ACE inhibitors and thiazide-like diuretics.

Preferential use of ACE inhibitors or ARBs in diabetic patients is no longer recommended, and lower BP targets (i.e., <130/80 mm Hg) for diabetics and those with chronic kidney disease are no longer endorsed. Moreover, the use of beta blockers as primary therapy has been greatly deemphasized, with inadequate BP control despite other maximum dosed agents or the presence of underlying coronary artery disease or heart failure serving as the main indications. A simplified algorithm to guide the initiation and escalation of antihypertensive therapy from the ED for patients without significant comorbidity is presented in Fig. 70.4.

As emphasized throughout this chapter, acute BP reduction in the ED provides absolutely no benefit to patients with chronic HTN without acute TOD and exposes them to unnecessary risk of potential hypoperfusion in regions in which blood flow has been governed by long-standing autoregulation. When these patients have symptoms such as headache or chest pain, and there is no suspicion of acute TOD, treatment should be directed toward the symptoms, not the BP. Anxiolytic or analgesic medication administration accompanied by resumption of chronic oral antihypertensive therapy is more rational and beneficial than the initiation of short-acting antihypertensive therapy. However, care should be taken to avoid prescribing NSAIDs and other medications that can have a negative impact on BP control and result in the development of cardiovascular complications.

Disposition

Individuals without evidence of acute TOD can be discharged home, but hypertensive emergency patients warrant admission, usually to an intensive care unit. Clinical features such as chest pain, dyspnea on exertion, or worsening renal function may confuse the picture, and short-term evaluation in an observation unit can be useful to determine whether the acute presentation represents a true emergency.

Outcomes associated with a given hypertensive emergency are largely a function of underlying TOD. However, data suggest that when severe HTN is present and IV antihypertensives are administered, risks are considerable with in-hospital and 30-day mortality rates of

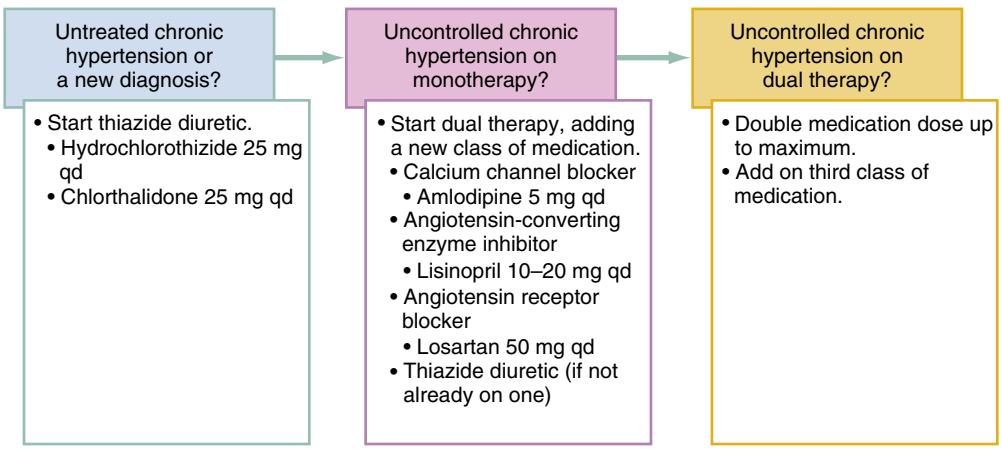

Fig. 70.4 Modified approach to the initiation and escalation of antihypertensive therapy for use in ED patients. Note that the proposed medications are representative of listed classes and may be substituted with equally dosed alternatives agents in the same class, as needed.

6.9% and 11%, respectively, and a 90-day readmission rate of nearly 40%. When associated with AKI, the relative mortality is even greater, with an odds ratio of 1.05 for each 10 mL/min estimated GFR decline. Although the risk for short-term deterioration is minimal in patients with elevated BP who lack evidence of acute TOD, the long-term risk of cardiovascular, cerebrovascular, and renovascular disease is relatively high, underscoring the need for the development of effective, patient-centric models of chronic HTN care at the system level.[38]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 70: QUESTIONS AND ANSWERS

1. An 85-year-old man presents with acute onset of right-sided weakness that began 1 hour before arrival. His family states that he was recently diagnosed with dementia and has refused to take any of his medications for more than 1 week but had otherwise been relatively healthy. Emergency medical services (EMS) report a prehospital blood pressure of 240/110 mm Hg. On examination, the patient has clear evidence of an acute stroke with severe deficit (National Institutes of Health [NIH] Stroke Scale = 24), but his gag reflex is intact. His initial blood pressure is 230/110 mm Hg. A head computed tomography (CT) scan shows diffuse white matter ischemic disease but no evidence of acute infarct or hemorrhage. The most appropriate next step is which of the following?

a. Repeat the blood pressure and, if 185/110 mm Hg or higher, start a nicardipine infusion at 5 mg/hour.
b. Contact neurosurgery for intracranial pressure monitoring.
c. Give a dose of tissue plasminogen activator (tPA) immediately.
d. Give sublingual nifedipine.

Answer: a. Despite his advanced age, this is a relatively high-functioning individual with acute onset of a severe stroke. He is within the time window for administration of tPA, but his blood pressure is excessively elevated. According to the American Heart Association/American Stroke Association guidelines, efforts should be made to reduce his blood pressure to less than 185/110 mm Hg before tPA administration. Other agents, such as labetalol, would also be appropriate to use.

2. A 27-year-old woman presents with lower back pain for 1 week. She recently moved into the community and has been busy unpacking and moving furniture. She denies any neurologic symptoms and has no medical history. Her triage blood pressure is 170/110 mm Hg, but vital signs are otherwise normal. With the exception of appreciable muscle spasm in her lower back, the physical examination is normal. You give her 10 mg of diazepam and observe her for 1 hour. She is feeling better but her blood pressure is still elevated, at 165/90 mm Hg. At this point you should do which of the following?

a. Give her 0.2 mg of clonidine.
b. Take a more extensive history to see if she is taking oral contraceptives
c. Ignore the blood pressure and discharge her without follow-up.
d. Order a 24-hour urine metanephrine and normetanephrine test.

Answer: b. This patient's blood pressure elevation is clearly not a reaction to her pain, and some further questioning is needed to identify a potential cause. In young women, oral contraceptive agents are a treatable cause of hypertension and should be considered when elevated blood pressure is encountered in these patients. Of note, the likelihood of contraceptive-related hypertension increases with the duration of use. It would not be unreasonable to discharge the patient without further exploring the potential cause of her elevated blood pressure, provided some provision of follow-up was sought. The clinical picture is inconsistent with renal artery stenosis or pheochromocytoma, and an evaluation for these conditions would be inappropriate at this point.

3. A 50-year-old man complains of dull chest pain that began 4 hours before arrival. The patient states he awoke this morning feeling well and that the pain began while shoveling his driveway. He has a 20-year history of hypertension and diabetes but has always been compliant with his medications, which include metformin, Norvasc, and Diovan. His initial blood pressure is 215/120 mm Hg, and his heart rate is 100 beats/min. On examination, his lungs are clear, heart sounds are normal, pulses are bounding and symmetric, and there are no neurologic deficits. An electrocardiogram shows nonspecific T wave inversions in the lateral leads, with no evidence of ST segment elevation or depression and normal intervals. The serum troponin level is elevated. Which of the following is the most likely explanation for his clinical presentation?

a. He has a ruptured dissecting aortic aneurysm that is leaking blood into the retroperitoneal space.
b. He is suffering from a massive pulmonary embolism.
c. He strained an intercostal muscle while shoveling.
d. He is suffering from subendocardial ischemia triggered by a cycle of increased afterload that began while he was shoveling.

Answer: d. Increased afterload can be triggered by exertional activation of the sympathetic nervous system. In the presence of long-standing hypertension, ventricular and aortic stiffness are likely to develop, increasing the potential for afterload-mediated effects on the heart. When suddenly faced with increased resistance, the left ventricular pressure may rise, leading to intrinsic compression of subendocardial myocytes and ischemia. Coupled with earlier transmission of the reflected arterial wave form, the diastolic coronary filling time may also be diminished, producing a clinical picture of acute coronary syndrome. He may also have a coronary artery lesion on which this is superimposed but, as described, the likelihood of his clinical presentation being caused by a complete right coronary occlusion is quite low.

4. Which of the following fundoscopic findings would be the earliest indicator of acute hypertensive retinopathy in a comatose patient whose blood pressure is 260/140 mm Hg?

a. Copper and silver wiring appearance to the retinal arterioles
b. Focal intraretinal periarteriolar transudates
c. Cotton wool spots
d. Diffuse atrioventricular (AV) nicking

Answer: b. Focal intraretinal periarteriolar transudates are the first abnormality to appear with acute hypertensive retinopathy, preceding all other findings, including cotton wool spots and disk edema. Other findings that are listed may also be seen, but they are indicative of chronic, not acute, retinal involvement. It is important to remember that acute retinal abnormalities may be absent in hypertensive emergency patients and, although fundoscopy is an important tool,

CHAPTER 70: QUESTIONS AND ANSWERS—cont'd

the diagnosis should be based primarily on the results of the clinical examination.

5. A 65-year-old woman presents to the emergency department (ED) with chief complaint of elevated blood pressure, which was discovered at her dentist's office prior to a routine dental procedure. Her blood pressure upon admission is 187/101 mm Hg. Otherwise, the patient has no acute complaints, however, she does note chronic low grade chronic headaches and intermittent blurry vision. She has had previous readings of mildly elevated blood pressure at church health fairs, although was never formally diagnosed, and does take medication. Which of the following steps would be appropriate in the context of and ED visit?
   - **a.** Obtain a CT of the head to rule out intracranial pathology.
   - **b.** Administer a short-acting antihypertensive to reduce her blood pressure prior to discharge.
   - **c.** Prescribe a diuretic such as chlothalidone or hydrochlorothiazide, and refer to outpatient follow up with a hospital affiliated primary care provider.
   - **d.** Discharge home with instructions to follow up with a primary care provider.

Answer: d. Most patients who are found to have significantly elevated BP on intake vital signs measurement or who come to the ED because BP was found to be elevated in an outpatient setting or by self-measurement do not have an acute hypertensive emergency. While many patients have vague symptoms, such as headache or mild blurry vision, these symptoms do not correlate with the degree of hypertension. For such patients, a head CT or acute reduction of BP is not indicated and offers no tangible outcome benefit. This patient has a physician and is already on medication. As such, there is no indication to start a new medication or make a new referral at this time.

71

Aortic Dissection

Keith A. Marill

KEY CONCEPTS

- Aortic dissection most commonly presents as abrupt, sharp, severe pain maximally intense at onset in the chest or back. There may be various seemingly unconnected associated symptoms due to altered blood pressure or insufficiency of disparate vascular beds.
- Definitive diagnosis is most commonly made with an imaging study such as computed tomography of the aorta with intravenous contrast. A combination of standardized clinical assessment, chest x-ray, and serum D-dimer testing can effectively rule out the condition in low-risk patients.
- The critical immediate therapeutic actions are medical therapy to decrease aortic sheer force and blood pressure control. Immediate surgical consultation is indicated.
- Surgical treatments, including endovascular stent placement, are advancing, leading to decreased mortality. This increases the importance and benefit of early diagnosis in the emergency department setting.

FOUNDATIONS

Background and Importance

Aortic dissection is a lethal disease that can be difficult to diagnose. The majority of patients present with abrupt, severe pain of the chest or back, but a significant minority of patients present with different symptoms that can mimic a variety of other more common conditions. The average age of presentation is about 64 years and 65% are male.[1] Approximately 5000 to 10,000 cases of aortic dissection are diagnosed annually in the United States. Consequently, an individual emergency physician can generally expect to see fewer than 1 case per year.

Anatomy, Physiology, and Pathophysiology

The aorta is composed of three layers: the inner endothelial intima, the smooth muscle media, and the connective tissue outer adventitia. In the media, elastic fibers composed of elastin and fibrillin intertwine with collagen and smooth muscle cells, providing the viscoelastic properties that enable the aorta to distend, storing a portion of the stroke volume and elastic potential energy during ventricular systole. The aorta then recoils during diastole so that blood continues to be propelled to peripheral end organs.

The aorta emanates from the left ventricular outflow tract of the heart, makes an approximate 180-degree curve, and travels posteriorly within the mediastinum of the chest until it crosses through the diaphragm. It assumes a retroperitoneal position within the abdomen and continues inferiorly until it bisects into the common iliac arteries at approximately the level of the umbilicus. Major arterial branches include the brachiocephalic, left common carotid, and left subclavian in the chest, and the celiac, superior mesenteric, bilateral renal and gonadal, and inferior mesenteric arteries in the abdomen. It provides the major supply to the anterior spinal artery and lumbar spinal cord via the artery of Adamkiewicz.

Aortic dissection is defined by separation of the media layer of the aortic wall, generally with formation of a hematoma or false lumen. This commonly occurs in the setting of degeneration of the medial layer with associated inflammation. Aortic dissection is classified as acute if it is diagnosed within 2 weeks of symptom onset, subacute if diagnosed with 2 weeks to 3 months of onset, or chronic if greater than 3 months from onset.

Aortic dissection is commonly described with the Stanford classification. Type A describes dissection involving the ascending aorta with or without descending involvement, and Type B dissection is limited to the descending aorta commencing distal to the left subclavian artery. The less commonly used DeBakey classification separates dissections into: type I, involving the ascending and descending aorta; type II, involving only the ascending aorta; and type III, limited to the descending aorta (Fig. 71.1). These classification systems were proposed in part to differentiate patients who required surgical or pharmacologic therapy, though these delineations have blurred with modern therapeutic advances including endovascular treatments.

Aortic dissection most commonly occurs due to a tear in the intimal layer subsequent to a process that has weakened the aortic media. Blood passes through the tear separating the intima from the media or adventitia, creating a false lumen that can propagate in an anterograde or retrograde fashion. Propagation of aortic dissection can cause complications such as visceral or neurologic malperfusion syndromes due to compromise of branch vessels, pericardial tamponade, or acute aortic insufficiency.

Intramural hematoma refers to hematoma formation within the wall of the aorta without evidence of intimal aortic tear. The hematoma may be localized or dissect along the plane of the aortic media. The risk factors, presentation, and natural course of this variant generally mirror those of typical aortic dissection due to intimal tear. However, over half of intramural hematomas occur in the descending aorta as a result of atherosclerotic disease or iatrogenic intravascular catheter manipulation trauma.[2] Intramural hematoma is most easily diagnosed with CT angiography and may be missed with conventional angiography.

Penetrating atherosclerotic ulcer results from erosion of an intimal atherosclerotic lesion. It is an alternative mechanism to intimal tear, allowing blood to dissect into the media of the aortic wall or beyond. This process develops gradually in elderly patients with extensive atherosclerosis and often is heralded by chest or back pain and hypertension. Ulceration may lead to hematoma formation in the dissected media, or it can extend into the adventitia with pseudoaneurysm formation and potential rupture. It is usually a localized process most commonly occurring in the descending aorta without retrograde aortic

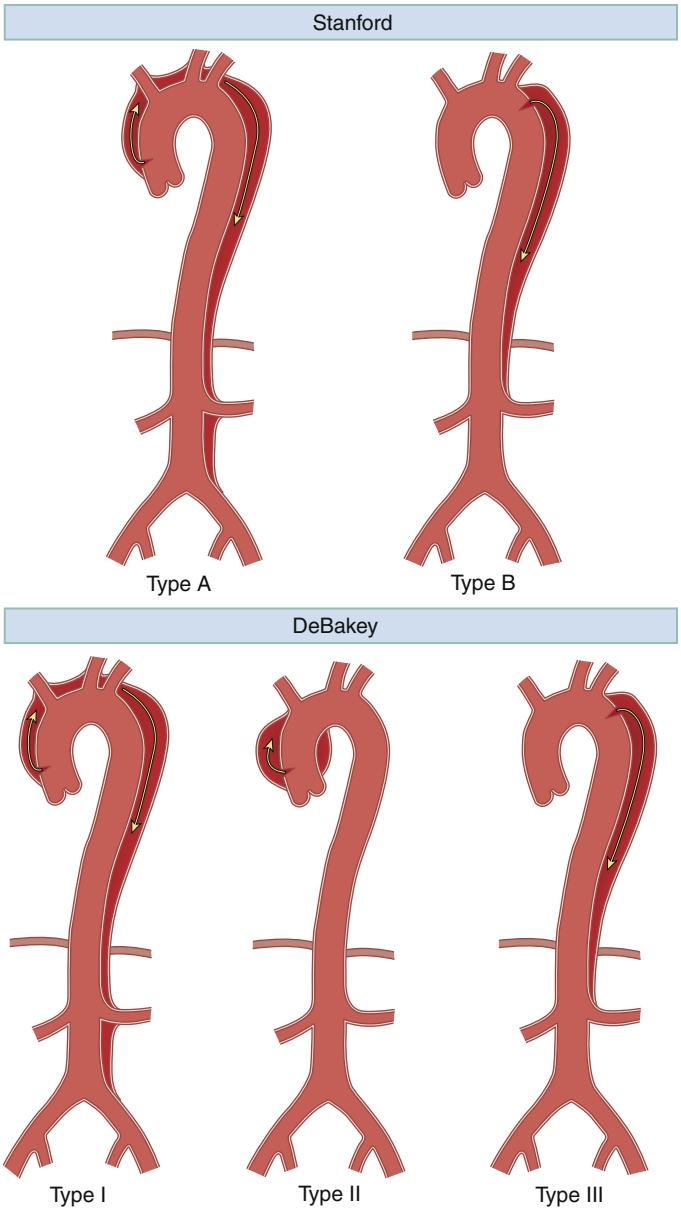

Fig. 71.1 Acute aortic dissection classifications. The Stanford classification divides dissections into those involving the ascending aorta from dissection originating there or proximal dissection of a more distal origin (Type A), or those limited to the descending aorta (Type B). The DeBakey classification divides dissections into those arising in the ascending aorta and extending distally beyond the innominate artery (Type I), arising in the ascending aorta with extension limited to the level of the innominate artery take-off (Type II), and arising at or distal to the left subclavian artery take-off with extension distally (Type III).

valve, pericardial, or branch vessel involvement and associated diffuse symptoms and signs (Fig. 71.2).

About two-thirds of aortic dissections are classified as type A, and the remainder as type B. Hypertension is the most common risk factor, present in a majority of patients.[1] Both type A and B patients may have a history of cardiac surgery, including aortic valve replacement. Patients may have a history of aortic aneurysm or a prior aortic dissection. Marfan syndrome is the connective tissue disease most commonly associated with acute aortic dissection. Other associated conditions include: atherosclerosis, a family history of thoracic aortic disease with or without a defined genetic syndrome, bicuspid aortic valve, coarctation of the aorta, a bovine-type aortic arch, when the brachiocephalic artery shares a common origin with the left common carotid artery, and infectious disease such as syphilis. Activities and events associated with increased aortic sheer force including crack cocaine use, weight lifting, the peripartum period,[3] and deceleration trauma can rarely cause aortic dissection. Traumatic aortic dissection most commonly occurs at the level of the left subclavian artery in the proximal descending aorta because the aorta is tethered at this point by the ligamentum arteriosum. Other causative genetic syndromes include Turner, type 4 Ehlers-Danlos, and Loeys-Dietz. Fluoroquinolones interfere with collagen synthesis and increase the risk of aortic dissection during treatment.[4]

CLINICAL FEATURES

Aortic dissection is classically characterized by an acute severe, sharp, ripping or tearing, painful sensation in the chest or central upper back

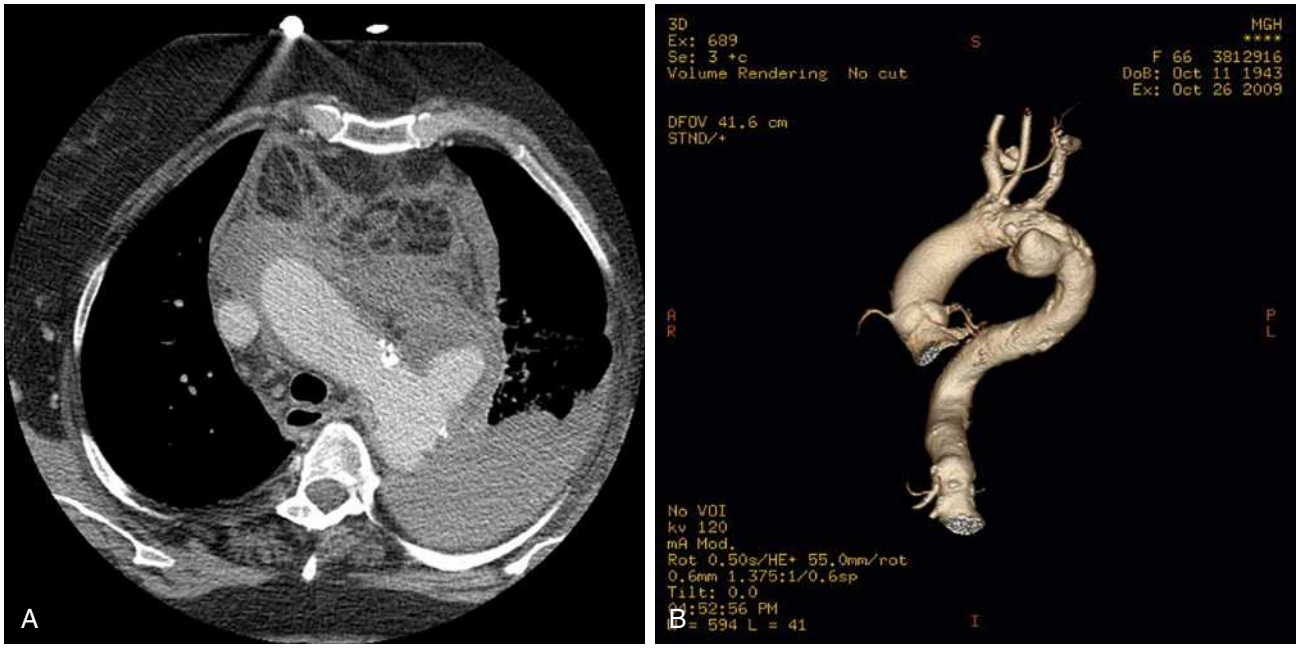

Fig. 71.2 Pseudoaneurysm due to penetrating ulcer. A 66-year-old female presented with sharp chest pain radiating to the interscapular area and was found to have a penetrating ulcer of her descending thoracic aorta just beyond the left subclavian artery with a contained hematoma and blood in the mediastinum and left chest. The patient was treated with emergent endovascular repair. (A) Cross-sectional computed tomography (CT) with contained hematoma (pseudoaneurysm) and left hemothorax, and (B) three-dimensional CT angiogram rendering of aorta with pseudoaneurysm.

with maximal intensity from onset, and associated apprehension.[5] When present, the pain generally radiates to the anterior chest or neck when the ascending aorta is involved, and to the back, abdomen, or down the legs when the pathology is in the descending thoracic aorta. Migratory pain is described in about one-third of cases. The radiation and migration of pain often reflect the anatomic extension of the dissection. Emergency physicians may have little difficulty diagnosing patients with a classic presentation. The challenge is that patients can present with a spectrum of pain, and some patients have no pain at all (Fig. 71.3). Additionally, many other symptoms may be present.

Other symptoms of type A dissection include lightheaded sensation or syncope, and less commonly, dyspnea related to congestive heart failure. Patients with either type A or B dissection may complain of neurologic deficits related to cerebral or spinal cord compromise. Type B dissection is considered complicated in the setting of refractory pain, rapid aortic expansion or rupture, uncontrollable hypertension, or insufficient perfusion of the renal, splanchnic, spinal, or lower extremity vasculature.

Signs of type A dissection include asymmetric pulse deficits,[6] and patients may present with hypertension, normotension, or hypotension. Pseudohypotension may occur when the blood pressure in one arm is lowered due to subclavian artery compromise. Syncope occurs in a minority of patients and is associated with increased mortality. It is classically due to pericardial tamponade from retrograde dissection into the pericardial sac, but other causes include cerebrovascular insufficiency, internal hemorrhage with hypovolemia, or dysrhythmia. Tamponade may be evidenced by dilated neck veins, diminished heart sounds, and decreased pulse or pulse pressure. A new diastolic murmur in the lower left sternal border suggestive of aortic regurgitation can occur when the dissection spans the aortic valve. All three components of the classic triad—abrupt tearing pain, pulse deficits, and aortic insufficiency—are seldom observed in a single patient.

Acute myocardial infarction due to coronary ostium compromise may occur in type A dissection, with the majority of these cases involving the right coronary artery ostium with infarction of the corresponding inferior coronary territory. Left main occlusion is the second most common site (Fig 71.4). Rarely, patients may present with isolated congestive heart failure when the dissection compromises aortic valve function.

The majority of patients with type B dissection have elevated blood pressure greater than 150 mm Hg. Syncope and pulse deficits can occur but are less common than with type A disease.

Neurologic symptoms and signs can occur in either type A or B dissection.[7] These include ischemic stroke, spinal ischemia leading to temporary or permanent paralysis in 1% to 3% of patients, and ischemic peripheral neuropathy. Up to one-third of patients who complain of neurologic symptoms at dissection onset have no complaint of pain.

Gastrointestinal complications can also occur in either type A or B disease. These can be due to fixed or dynamic arterial branch occlusion or global hypoperfusion. Mesenteric ischemia is the most common cause of death in type B disease. Gastrointestinal hemorrhage is less common and can be due to ischemic bowel or fistula formation. Nausea, vomiting, diaphoresis, and apprehension can be seen with all acute dissections.

Information from the history and physical exam can be combined systematically to estimate a combined risk of disease. The aortic dissection detection risk score (ADD) is a tool combining three domains of clinical information to assess for the risk of acute dissection: high risk conditions, pain features, and exam features (Table 71.1). Patients are classified on a score of one to three, scoring one point if any items in each of the three domains is positive. An ADD score of one or more is 95% sensitive for aortic dissection. Among patients with none of the identified clinical risk factors on the ADD, half had a widened mediastinum on chest x-ray. This suggests the ADD score and chest x-ray provide complementary information.

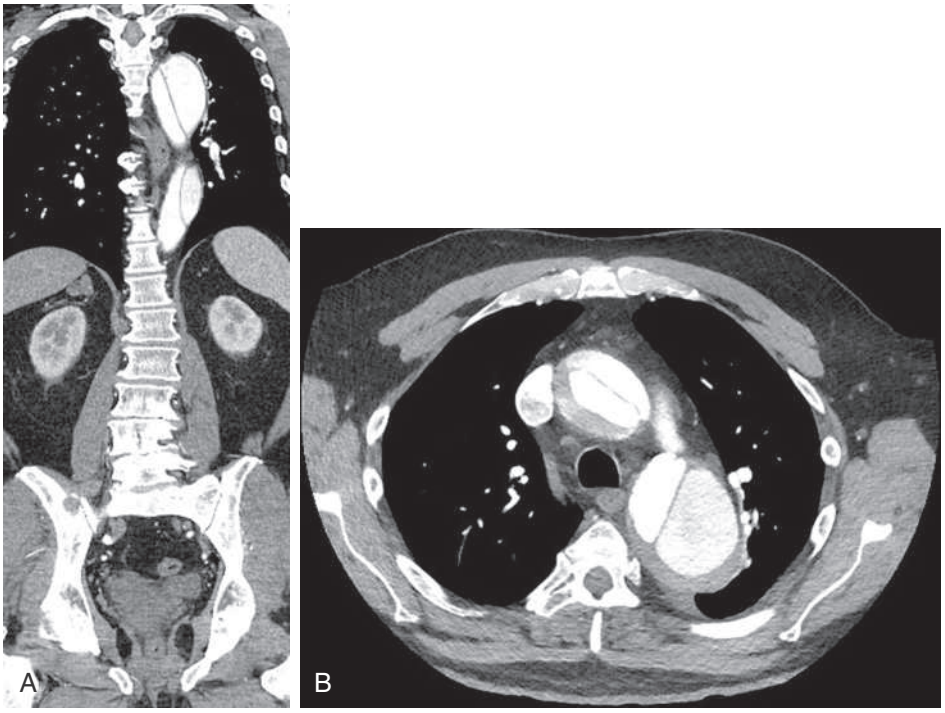

Fig. 71.3 Painless dissection presentation. A 64-year-old man with a history of atrial fibrillation on warfarin presented with transient blurred vision without pain or complaints in his chest or elsewhere. Magnetic resonance angiogram (MRA) imaging revealed dissection involving the carotid artery. Subsequent computed tomography angiogram (CTA) of the chest revealed a type B aortic dissection (A). Endovascular stenting was performed without event. The patient re-presented with chest pain 6 years later with an ascending dissection requiring operative repair. (B) Computed tomography angiogram (CTA) demonstrating original type B dissection and new type A dissection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for acute aortic dissection is broad and includes many conditions more common than dissection. It is perhaps most important to always consider the possibility of aortic dissection when diagnosing these other conditions. Dissection may coincide with or cause another condition on the differential. Some factors associated with a delay in diagnosis include fever, normal blood pressure, female sex, non-white race, and previous cardiac surgery.

Acute myocardial ischemia or infarction is an alternative, more common cause of chest pain or discomfort. In contrast to aortic dissection where pain is often at high intensity at onset, pain due to coronary ischemia may be provoked by exertion and crescendo with subsequent waxing and waning. It can sometimes be relieved by rest or nitroglycerin. Myocardial ischemia may be associated with suggestive ECG changes. Unfortunately, as noted, type A dissection can cause coronary ostial compromise and subsequent myocardial infarction, leading to misdiagnosis. Approximately one in every 1000 STEMIs is caused by a type A dissection. Acute pericarditis presents with chest pain, which is often positional, and evidence of pericardial effusion. Aortic dissection should be considered in any patient with pericardial effusion, with or without tamponade physiology, or new aortic regurgitation.

Pulmonary embolism can cause chest pain and syncope like aortic dissection, but commonly associated pulmonary symptoms such as shortness of breath or cough are absent in dissection. Patients with aortic dissection and neurologic symptoms may appear to be suffering from a primary central nervous system event such as ischemic or hemorrhagic stroke. Among patients with ischemic stroke, approximately 1% are suffering from acute aortic dissection.[8] Severe hypertension associated with dissection may further suggest intracranial hemorrhage.

Patients with mesenteric ischemia classically present with a soft abdomen and abdominal pain out of proportion to tenderness. This can also be observed with acute type A or B dissection. Mesenteric ischemia may present with bloody bowel movements, which is an uncommon finding in acute dissection. Other intestinal conditions can cause acute abdominal pain, but often with localized abdominal exam findings.

Other vascular emergencies such as renal artery aneurysm can present similarly to aortic dissection with severe pain and hypertension. These are important differentials, particularly in predisposed patients such as those with type 4 Ehlers-Danlos syndrome. Lumbar spinal disc disease can cause back pain radiating to one or both legs and associated neurologic compromise. These symptoms and signs are usually more geographically constrained to this portion of the body as compared to dissection.

DIAGNOSTIC TESTING

Diagnostic testing begins with bedside ultrasonography, which is indispensable to assess for reversible catastrophic conditions such as pericardial tamponade. Using a small footprint probe to allow access between the ribs, the exam should focus on the heart, and thoracic and abdominal aorta. The initial assessment should determine if there is a pericardial effusion, and if so, if there evidence of right ventricular free wall scalloping during diastole suggestive of tamponade physiology. The aortic root should be assessed for dilatation, dissection, and visible flap using the left parasternal long-axis view. The descending aorta is also inspected for dissection, flap, or dilatation.

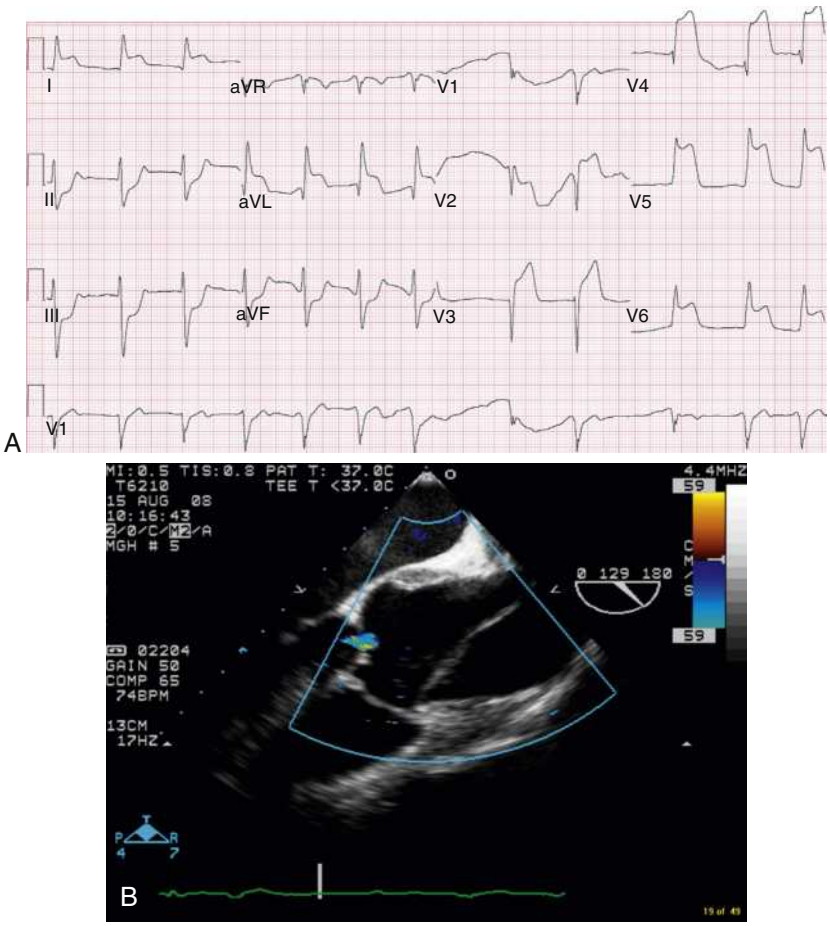

Fig. 71.4 Acute dissection complicated by left main STEMI. A 46-year-old man presented with acute, severe chest pain with vomiting and diaphoresis while lifting weights at the gym. Initial ECG (A) indicated acute antero-septal STEMI with reciprocal inferior ST depression. The patient was taken emergently to the cardiac catheterization lab. After temporizing stenting of his left main coronary as well as the left anterior descending and left circumflex arteries, he was taken to the operating room for aortic root graft replacement with CABG. Intraoperative transesophageal echocardiogram (TEE) (B) reveals type A dissection of the ascending aortic root extending to the aortic valve.

TABLE 71.1 Aortic Dissection Detection Risk Score

High-Risk Conditions	High-Risk Pain Features	High-Risk Examination Features
Marfan Syndrome	Chest, back, or abdominal pain described as any of the following:	Evidence of perfusion deficit:
Family history of aortic disease		Pulse deficit
Known aortic valve disease	Abrupt onset	Systolic BP differential
Recent aortic manipulation	Severe intensity	Focal neurologic deficit (in
Known thoracic aortic aneurysm	Ripping or tearing	conjunction with pain)
		Murmur of aortic insufficiency
		(new and with pain)
		Hypotension or shock state

Any positive attributes in each column yields a score of 1 for that column. Each column can have a score of 1 or 0. The total ADD score is the sum of the 3 columns (on a scale of 0 to 3).

Laboratory studies should be sent, including complete blood count, serum chemistry and renal function, coagulation profile, and blood typing. Additionally, clinicians should send serial troponin for patients with pain suggestive of coronary ischemia, B-type natriuretic peptide if there are signs of heart failure, and urinalysis if there is any concern for renal arterial involvement. None of these studies diagnose dissection, but they help to rule out other etiologies and define the extent of complications.

ECG may demonstrate STEMI due to coronary ostial compromise by the dissection or associated flap. Voltage may be decreased due to pericardial effusion. Left ventricular hypertrophy due to longstanding hypertension may be present in 20% of cases. Nonspecific ST-T

changes may be observed, and these can delay the correct diagnosis of dissection.[9] There is no ECG finding highly accurate for dissection.

Chest x-ray has a sensitivity of 67% for acute dissection. The most sensitive chest x-ray findings are a widened aortic silhouette or mediastinum where mediastinal widening was defined as a width of at least 8 cm at the level of the aortic knob or a mediastinal to chest width ratio exceeding 0.25.[7] Separation of aortic intimal calcification from the external aortic wall and pleural effusion have sensitivities of 9% to 16% and 16% to 37%, respectively. Two-view versus one-view chest x-ray technique does not improve sensitivity. Given the only fair sensitivity of this test, it is crucial that emergency physicians not let a normal chest x-ray defer or delay further evaluation when dissection is suspected.

A variety of serologic tests have been investigated to diagnose aortic dissection. Serum D-dimer is the most useful at present. It is rapidly performed and readily available due to its use to assess for pulmonary embolism. At a test threshold of 500 ng/ml, the test is approximately 96% sensitive and 70% specific with a negative likelihood ratio of 0.05 for acute dissection.[5] D-dimer alone is insufficient to rule out acute dissection confidently, but in concert with other information, it is useful to assess the need for CT imaging.[10,11] The combined strategy of ADD=0 and negative D-dimer was 99.7% sensitive for acute dissection.[10] Specificity was 18%. Applied in practice, this means CT imaging or equivalent could be avoided in 18% of the patients in whom dissection is considered, but not present. Conversely, in patients with an ADD score of 2 or above, 4% of patients had an acute aortic syndrome even if the d-dimer was negative. This suggests that D-dimer should not be used in patients with a high clinical probability of dissection; rather, these patients must receive an advanced imaging test.

Investigations of other candidate biomarkers for acute dissection continue. These include smooth muscle myosin components, soluble elastin fragments, microfibril fragments including fibrillin-1, fibrin degradation products, and an interleukin receptor, ST2.[12] None have demonstrated sufficient sensitivity to rule out acute dissection adequately.

The diagnosis of aortic dissection ultimately rests on diagnostic imaging. Techniques with acceptable test characteristics include multidetector CT angiogram of the aorta (MDCTA), conventional angiography, magnetic resonance angiography (MRA), and transesophageal echocardiography (TEE). The choice of test used is based on multiple factors, including accuracy, safety, contraindications, availability, speed, convenience, ability to identify alternative diagnoses, and cost. MDCTA is the initial imaging study in about three-quarters of patients today, followed by TEE.[1] Often multiple tests are used. Goals of imaging are to confirm the diagnosis, localize the tear, display the anatomy and extent of the dissection flap, and determine whether prompt lifesaving intervention is needed.

MDCTA is generally preferred throughout the United States because it is readily available, fast, both sensitive and specific, and usually meets the previously stated goals. In the event of serious contrast allergy requiring a prolonged pretreatment regimen, or inability to tolerate or fit on the CT scanner, then another modality must be used. TEE may generally be the preferred alternative choice if it can be performed expeditiously by a qualified specialist.

TEE offers some advantages over MDCTA. The TEE probe and procedure are portable. In addition to being highly sensitive for the identification of type A dissection, TEE is also useful when involvement of the aortic valve and the status of the left ventricle, pericardial space, and right and left coronary artery ostia are unknown. Transthoracic echocardiography (TTE) is useful if it demonstrates disease but is insufficiently sensitive to rule out dissection.

MRA is rarely used for diagnosis of dissection because it takes longer to perform than MDCTA or TEE. Additionally, clinical staff must maintain a distance from the potentially unstable patient during the study, leading to safety issues. When used, it demonstrates excellent spatial resolution and anatomic detail. Aortography is the historical gold standard, but it is seldom the initial test for aortic dissection today due to the ease and rapid acquisition of MDCTA in most instances. The reported false-negative rate for aortography ranges from 5% to 15%. Aortography is valuable for the patient with STEMI but some presentation characteristics suggestive of dissection. As time is essential for percutaneous transluminal coronary angioplasty (PTCA) or stenting for STEMI patients, the patient can be brought to the cardiac catheterization lab and aortography performed at the initiation of the procedure in lieu of other imaging. The emergency physician must share his or her concerns with the interventional cardiologist to plan this diagnostic approach.

"Triple rule out" imaging refers to MDCTA protocol to assess simultaneously for acute aortic dissection, myocardial infarction, and pulmonary embolism. ECG gating freezes cardiac motion allowing evaluation of the perivalvular area and coronary arteries. A broad spectrum of other chest and upper abdominal diseases also may be identified with this study. However, EPs seriously consider and test for all three diagnoses in only about 3% of chest pain evaluations. There are a host of limitations to this test including coronary calcifications or stents, renal insufficiency, atrial fibrillation, inadequate heart rate control, contrast allergy, obesity, cost, and concern for radiation exposure.

MANAGEMENT

The initial primary goal of care in the emergency department setting is to minimize dissection extension. This is accomplished by decreasing the force of cardiac contraction and resulting aortic sheer forces, and driving the heart rate down to 60 beats per minute or less. Acceleration of aortic blood flow, dP/dt, is minimized while maintaining blood pressure in the low normal range. Beta-1 adrenergic blockade therapy is the preferred treatment (Table 71.2). Favored agents include esmolol infusion due to its short 9-minute half-life and titratability, or metoprolol or labetalol if esmolol is not readily available. Labetalol also provides alpha-1 adrenergic blockade decreasing vascular tone and blood pressure. A selective beta-1 receptor blocker such as esmolol or metoprolol may be preferred for patients with chronic obstructive pulmonary disease (COPD) at risk for bronchospasm. Decreased cardiac contractility can also be achieved with infusion of the calcium channel blockers diltiazem or verapamil if beta blockers are contraindicated due to allergy or severe pulmonary disease, or unavailable.

Blood pressure control is critical in the setting of dissection. Hypotension should elicit an immediate search for potentially reversible causes such as pericardial tamponade or internal hemorrhage. In addition to any temporizing interventions such as pericardiocentesis, blood pressure may be supported with crystalloid infusion and vasopressors to provide adequate perfusion of vital organs, targeting a mean arterial pressure of 65 mm Hg. Norepinephrine or phenylephrine infusions are preferred to maximize peripheral vasoconstriction and minimize myocardial stimulation with resulting sheer stress. Antiadrenergic infusions should be stopped.

Hypertension is commonly encountered in type B dissections and must be treated with a target of 100 to 120 mm Hg systolic. Vasodilating agents such as nitroprusside can be infused, but only after initiation of antiadrenergic therapy to blunt the force of myocardial contraction. An ACE inhibitor such as enalaprilat may be beneficial, particularly if there is renal artery compromise. An arterial catheter should be placed in an uninvolved extremity to monitor and titrate therapy closely.

Analgesia is essential for patient comfort and to decrease pain-induced sympathetic discharge. Parenteral narcotics such as morphine,

TABLE 71.2 Acute Aortic Dissection Medications

Medications	Dosages (IV)
Contractile force and BP control	
Antiadrenergic	
Esmolol	0.5 mg/kg over 1 minute, then 50 μg/kg/min infusion
	Increase by 50 μg/kg/min every 4 min to max. 300 μg/kg/min
	Repeat 0.5 mg/kg boluses with each increase in dosing
Labetalol	10–20 mg up to every 10 minutes, or 0.5-2 mg/min infusion
Metoprolol	2.5–5 mg every few minutes
Vasodilation	
Nitroprusside	Begin 0.25–0.5 μg/kg/min and increase to max. 10 μg/kg/min
Enalaprilat	Begin 1.25 mg over 5 minutes, repeat up to 5 mg every 6 hours
Calcium channel blockade	
Diltiazem	Begin 10–20 mg, then 5 mg/hr infusion
	Infusion can be increased in 5 mg/hr increments up to 15 mg/hr
Verapamil	Begin 5 mg over 5 minutes, then repeat 5–10 mg up to every 15 minutes
	Or infuse 5 mg/hr with adjustment as needed
Analgesia (opioids)	
Fentanyl	0.5–1 mcg/kg every 30 min as needed
Morphine	0.1 mg/kg every 1 hr as needed
Vasopressor	
Norepinephrine	Begin 5 μg/min and titrate up to mean arterial blood pressure goal of 65 mm Hg
Phenylephrine	Begin 50 μg/min and titrate up to mean arterial blood pressure goal of 65 mm Hg

fentanyl, or hydromorphone are reasonable choices. Fentanyl benefits from a short half-life allowing titratability and relatively minimal secondary decrease in blood pressure. These characteristics are particularly valuable in the setting of hypotension.

Cardiac tamponade complicates up to approximately one-fifth of acute aortic dissections and carries a 50% mortality. Controlled catheter drainage with a pigtail catheter can be performed with ED ultrasound guidance to temporize and allow time to prepare for definitive operative care. We recommend insertion of an 8F pigtail catheter at the fourth or fifth intercostal space at or just medial to the left midclavicular line aiming for the pericardial effusion visualized beyond the apex of the heart. Once the catheter is inserted, 5 to 10 mL of hemopericardium can be aspirated with close observation of the resulting hemodynamics. Aspiration can be repeated as needed to attain a systolic blood pressure of 80 to 90 mm Hg.

Definitive therapy of acute aortic dissection has been defined by the type of dissection and continues to evolve, particularly due to advancing endovascular therapies. It is critical to consult surgical services as soon as dissection is identified to develop a coordinated plan. Type A dissection generally requires expeditious surgical repair due to progressive increasing risk of multiple complications, including rupture into the pericardial space, development of coronary or cerebral ischemia, aortic regurgitation, congestive heart failure, or free rupture of the aorta into the thorax.

For patients with type A dissection complicated by malperfusion, medical therapy, along with temporizing percutaneous reperfusion using aortic stenting or fenestration, and selective branch stenting may allow stabilization and reduce the risk of the operation. Repair of the patient's ascending aorta may proceed after a period of recovery.

Definitive aortic repair includes resection of the dissected aorta segment and insertion of an aortic graft. Restoration of aortic valve competence is paramount in patients who develop aortic insufficiency. This is usually achieved by resuspension of the native aortic valve or by aortic valve replacement, depending on the size of the aortic root and the condition of the aortic valve leaflets. Reimplantation of the coronary arteries to the new graft may also be necessary. Surgical mortality has slowly decreased but remains substantial at 18% overall in major centers.[1]

The cornerstone of type B dissection treatment is blood pressure control. Surgical intervention has been reserved for life-threatening complications such as ischemia of both kidneys leading to reversible renal failure, intestinal ischemia, limb ischemia, progressive aneurysm extension, impending or frank rupture, or intractable pain. However, modern endovascular therapy using stent grafts and fenestration is evolving this paradigm. The goals of this therapy include reconstruction of the thoracic aorta segment containing the entry tear, induction of thrombosis of the false lumen, and reestablishment of the true aortic lumen and side-branch flow. Aortic fenestration is indicated for carefully selected patients with malperfusion syndrome due to branch artery occlusion, and to provide a reentry tear for a dead-end false lumen. A less invasive strategy using stents may be preferable to surgery in higher-risk candidates. Endovascular aortic repair may even be employed for uncomplicated type B dissections to prevent subsequent aneurysm formation, which is otherwise common.[13]

Surgery and endovascular interventions require coordinated teams with expertise and experience to achieve success. Outcomes for type A dissection patients are generally better at high-volume centers. However, patient transfer incurs a delay in time-sensitive care. Recent data suggest regionalization of care with transfer a mean of 50 miles to high-volume centers is associated with lower operative mortality.[14]

DISPOSITION

Patients with acute aortic dissection generally require emergent surgical consultation and admission to the intensive care unit or operating room for further care. Consultation with surgical subspecialties could include cardiovascular surgery for type A dissections and vascular surgery for type B dissections but may vary based on local practice and resources.

The patient and family should be informed of the diagnosis and gravity of the situation. Type A acute aortic dissection carries a mortality of 1% to 2% per hour immediately after the onset of symptoms. The risk of death is increased in patients presenting with pericardial tamponade, coronary artery involvement leading to myocardial ischemia or infarction, or carotid artery involvement causing cerebral hypoperfusion. The most common causes of death are aortic rupture, stroke, visceral ischemia, cardiac tamponade, and circulatory failure. The long-term 1- and 3-year survival reported in the IRAD in the surgically treated patients surviving to hospital discharge are 96 ± 2.4% and 91 ± 3.9%, respectively, reflecting the timely surgical repair of the ascending aortic dissection. Patients with type B acute aortic dissection without

associated complications have a 30-day mortality of 10%. However, patients who develop ischemic complications with associated organ malperfusion syndrome, renal failure, visceral ischemia, or contained rupture often require urgent aortic repair, which carries a mortality of 20% by day 2 and 25% by day 30.

Survivors of aortic dissection require vigilant long-term surveillance with strict blood pressure control and monitoring. Patients who retain patency in the false channel of the aorta after either medical treatment or surgical repair have a significant risk of aneurysm formation and rupture of the false channel, especially in the first 6 months after initial therapy. Expansion, rupture, or both are more common in patients who are older and have poorly controlled hypertension and COPD. Other potential complications include redissection and progressive aortic insufficiency. The emergency physician should have a heightened level of concern and low threshold for definitive imaging for patients who return to the ED with relevant complaints after prior treatment for aortic dissection.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 71: QUESTIONS AND ANSWERS

1. The single most important agent to treat acute aortic dissection is:
- **a** Nitroprusside.
- **b** Aspirin.
- **c** Antiadrenergic.
- **d** Enalaprilat.

Answer: C. The initial primary goal of care for a patient with an aortic dissection in the emergency department setting is to minimize extension of the dissection. This is accomplished by decreasing the force of cardiac contraction and resulting aortic sheer forces, and driving the heart rate down to 60 beats per minute or less. Acceleration of aortic blood flow, dP/dt, is minimized while maintaining blood pressure in the low normal range. Beta-1 adrenergic blockade therapy is the preferred treatment.

2. A 70-year-old man with a history of poorly controlled hypertension presents with sharp central severe chest pain. ECG, chest x-ray, and serum D-dimer are normal. The next appropriate step is:
- **a** Transthoracic echocardiography in the radiology suite.
- **b** CT angiogram of the aorta.
- **c** Check serial troponin, and discharge with close follow up if negative.
- **d** Consult surgical service.

Answer: B. This patient had a presentation very concerning for an aortic dissection. In high-risk cases, chest x-ray and D-dimer cannot not be used to rule out a dissection. These patients must receive an advanced imaging test.

3. You are working in a small rural hospital when you diagnose a type A aortic dissection based on CT angiogram of the aorta. Vital signs are heart rate 85 beats per minute and blood pressure 130/85 mm Hg. The high-volume referral center is 25 minutes away by ambulance ride.
- **a** Arrange for immediate transfer to high-volume center.
- **b** Stabilize with arterial and central lines and intubation, then arrange transfer.
- **c** Call the intensivist to arrange medical ICU admission on labetalol infusion.
- **d** Call the general surgeon on duty to organize emergent surgery at your facility.

Answer: A. Surgery and endovascular interventions for aortic dissection require coordinated teams with expertise and experience to achieve success. Outcomes for type A dissection patients are generally better at high-volume centers. However, patient transfer incurs a delay in time-sensitive care. Recent data suggest regionalization of care with transfer a mean of 50 miles to high-volume centers is associated with lower operative mortality.

4. A 60-year-old woman presents with chest pain radiating to the back with onset while lifting a 50-lb pot in her garden, and her ECG demonstrates an inferior STEMI. The next appropriate step is:
- **a** MR angiogram of the chest.
- **b** Aspirin and TPA.
- **c** Diltiazem infusion.
- **d** Immediate cardiac catheterization with recommendation to interventional cardiologist for initial aortogram.

Answer: D. Aortography is valuable for the patient with STEMI but some presentation characteristics suggestive of dissection. As time is essential for percutaneous transluminal coronary angioplasty (PTCA) or stenting for STEMI patients, the patient can be brought to the cardiac catheterization lab and aortography performed at the initiation of the procedure in lieu of other imaging. The emergency physician must share his or her concerns with the interventional cardiologist to plan this diagnostic approach.

5. The connective tissue disorder responsible for the most cases of acute aortic dissection is:
- **a** Ehlers-Danlos, type I.
- **b** Ehlers-Danlos, type IV.
- **c** Marfan syndrome.
- **d** Loeys-Dietz syndrome.

Answer: C. Marfan syndrome is the connective tissue disease most commonly associated with acute aortic dissection.

6. There are about 150 million annual ED visits in the United States. An emergency physician who sees 3000 patients per year can expect to see an acute aortic dissection about every:
- **a** 6 months.
- **b** 1 year.
- **c** 5 years.
- **d** 15 years.

Answer: C. Aortic dissection is a rare condition, with only about 10,000 cases a year in the United States. If an emergency physician sees 3000 patients, and the rate of aortic dissection is 10,000 per 150,000,000 ED visits, this results in seeing 0.20 per year, or about 1 every 5 years.

Abdominal Aortic Aneurysm

Christopher B. Colwell

KEY CONCEPTS

- A ruptured abdominal aortic aneurysm (AAA) should be considered in any patient with otherwise unexplained abdominal or back pain. The complete triad of pain, hypotension, and a pulsatile mass may not be present.
- In a patient with an AAA and acute symptoms such as severe abdominal or back pain or hypotension, rupture is imminent or has already occurred.
- A patient with a ruptured AAA and initially normal vital signs can suddenly deteriorate at any time.
- The risk of rupture increases substantially with increased aneurysm size, and most ruptured AAAs have diameters greater than 5 cm.
- Bedside ultrasound may be used to document an AAA or free fluid and assist in the rapid diagnosis of a ruptured AAA.
- The abdominal CT scan is the diagnostic test of choice in the evaluation of the stable patient with suspected ruptured AAA; intravenous contrast is not essential in emergencies.
- The patient who has had endovascular repair of an AAA remains at risk for aneurysm rupture.

PRINCIPLES

An abdominal aortic aneurysm (AAA) is a true aneurysm, meaning a localized dilation of the aorta involving all three layers (intima, media, and adventitia) of the arterial wall (Fig. 72.1). A false aneurysm, or pseudoaneurysm, is a collection of flowing blood that communicates with the arterial lumen but is not enclosed by the normal vessel wall and is contained only by the adventitia or surrounding soft tissue. Pseudoaneurysms can arise from a defect in the arterial wall or a leaking anastomosis after AAA repair.

AAA is distinct from aortic dissection, which is sometimes incorrectly referred to as a *dissecting aortic aneurysm*. In aortic dissection, blood enters the media of the aorta and splits (dissects) the layers of the aortic wall. Aortic aneurysm and aortic dissection are different disease processes with different clinical presentations, complications, diagnostic methods, and treatments.

An aneurysm can develop in any segment of the aorta, but most are infrarenal. The diameter of the normal adult infrarenal aorta is approximately 2 cm, and a diameter of 3 cm or more defines an AAA.

Epidemiology

The prevalence of AAA increases with advancing age and is found in 2% to 5% of men older than 50 years. Men are affected more often than women, although recent research suggests AAA may be more common in women than previously suspected, particularly among women who smoke.[1] The patient often has concomitant atherosclerotic occlusive disease, including coronary, carotid, or peripheral vessels, which may influence the clinical presentations, complications, and management.

Several risk factors for the development of an AAA have been established, but risk factors are epidemiologic, not individual characteristics. Age is the most significant risk factor for the development of an AAA.[2] An AAA can be found in 5% to 10% of all older men who are screened with ultrasonography with increasing prevalence in those who have concomitant coronary artery disease or peripheral vascular disease. A family history of an AAA is a powerful risk factor; those with an affected first-degree relative have a markedly increased risk of developing an AAA. Although awareness of high-risk groups can speed the recognition of AAA, the consideration of AAA should not be restricted to patients in these groups. Some evidence suggests that women may experience delays in diagnosis and worse operative mortality after ruptured AAA. Up to half of AAAs in the United States occur in women, nonsmokers, or those younger than 65 (Table 72.1).

Pathophysiology

AAAs have traditionally been attributed to atherosclerosis, but patients with advanced atherosclerosis have occlusive disease, not aneurysms. Patients with AAA have biochemical abnormalities leading to the loss of elastin and collagen, which are the major structural components of the aortic wall. The propensity to form aneurysms may have a genetic basis, but the exact mode of inheritance is uncertain. The Society for Vascular Surgery has recommended labeling the typical degenerative AAA as "nonspecific," rather than "atherosclerotic," to reflect this uncertainty surrounding the etiology.

AAAs may also have specific etiologies, such as infection, trauma, connective tissue diseases, and arteritis. Such aneurysms are rare, however, compared with nonspecific degenerative aneurysms.

Natural History

AAAs progressively enlarge, ultimately resulting in rupture of the aneurysm and potentially fatal hemorrhage. Although other complications are possible, by far the most common and most clinically significant is rupture.

The most important factor determining the risk of rupture is the size of the aneurysm. The risk of rupture increases substantially with increased aneurysm size, and most ruptured AAAs have diameters greater than 5 cm. The growth rate of the AAA, in addition to other anatomic factors, may also be important in determining the risk of rupture. Although rupture of aneurysms smaller than 4 cm is rare, no aneurysm is completely "safe." Any aneurysm can rupture and cause significant consequences.

AAA most commonly ruptures into the retroperitoneum, where hemorrhage may be temporarily limited by clotting and tamponade at the rupture site, but 10% to 30% involve free intraperitoneal rupture, which is often rapidly fatal. Occasionally, rupture occurs into the gastrointestinal tract or the inferior vena cava.

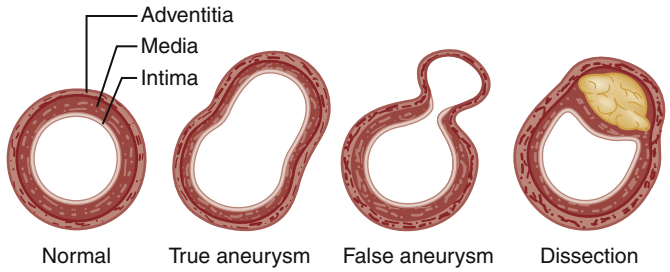

Fig. 72.1 Types of aortic aneurysms. (Adapted from LaRoy LL, et al. Imaging of abdominal aortic aneurysms. *Am J Roentgenol.* 1989;152:785.)

TABLE 72.1 Prevalence of Abdominal Aortic Aneurysms in Selected Risk Groups

Group	Incidence
Men aged 65 years or older	5% to 10%
Patients with coronary artery disease or occlusive peripheral vascular disease	10% to 15%
Brothers of patients with abdominal aortic aneurysms (AAAs)	20% to 30%

Complications can also arise from an intact AAA. The walls of an AAA are often lined with clot and atheromatous material, which can embolize and occlude distal vessels. Sequelae of occlusion and embolization may be the only diagnostic clues to AAA. Aortic thrombosis may occur rarely and patients can also have complications caused by impingement of the aneurysm on adjacent structures.

In approximately 5% of AAAs, a dense inflammatory and fibrotic reaction develops in the aneurysm wall and adjacent retroperitoneal tissue. In these "inflammatory" AAAs, periaortic fibrosis may incorporate and obstruct adjacent structures, such as the ureters or duodenum.

The principal concern in the patient with an AAA is the potential for rupture of the aneurysm, which can be prevented only by timely repair.

CLINICAL FEATURES

Unruptured Aneurysms

Because most AAAs do not cause symptoms until they expand or rupture, the prevalence of symptoms in patients with unruptured AAAs is difficult to determine. Patients may have symptoms that lead to the aneurysm's discovery before rupture. These symptoms can include pain in the abdomen, back, or flank; an awareness of an abdominal mass or fullness; or a sensation of abdominal pulsations. Clinical suspicion of AAA, which includes both the patient's history and physical examination findings, warrants further investigation with imaging.

The pain associated with stable, intact aneurysms often has a gradual onset and a vague, dull quality. It is usually constant but may be described as throbbing or colicky. Acute or severe pain is an ominous symptom that suggests imminent or actual aortic rupture.

In most cases, an AAA is asymptomatic and is discovered incidentally on physical examination, on a radiologic study done for unrelated issues, or by ultrasonography as part of an aneurysm screening program. Symptoms may not develop until the aneurysm ruptures, and the finding of an AAA may or may not be related to the patient's current visit. If determined not to be related, follow-up will be necessary even when found incidentally.

The most prominent physical finding is a pulsatile, expansile abdominal mass above the level of the aortic bifurcation. If the iliac arteries are also aneurysmal, the mass may extend below the umbilicus. The right border of an AAA may be palpable to the right of midline, whereas a normal or tortuous aorta is usually not. Most intact AAAs are nontender; tenderness suggests aneurysm expansion or rupture.

Symptomatic aneurysms are usually relatively large and are often palpable with a careful abdominal examination. However, an AAA may be challenging to palpate if the aneurysm is small or the patient is obese. Published reports indicate that 30% to 60% of unruptured aneurysms measuring 3.0 to 3.9 cm on ultrasonography can be detected by abdominal palpation; 50% to 70% of aneurysms measuring 4.0 to 4.9 cm and 75% to 85% of aneurysms 5 cm or larger can be palpated. These reports are based on the examination of patients with intact, asymptomatic aneurysms, with the examination specifically directed at sizing the aorta. The sensitivity is likely much lower when the abdomen is not palpated deeply, in hypotensive patients, or in those with significant abdominal guarding. There is virtually no risk of causing aneurysm rupture by abdominal palpation.

Physical examination may reveal findings consistent with an AAA even when the aorta is of normal size. A tortuous aorta may feel enlarged, and prominent aortic pulsations, especially in a thin patient, may simulate an aneurysm. Pulsations from a normal aorta may be transmitted to an adjacent abdominal mass.

An abdominal bruit is an uncommon finding in patients with AAAs. The presence of a bruit is also nonspecific, because bruits can originate from a stenotic renal, iliac, or mesenteric artery. A loud continuous bruit suggests the diagnosis of arteriovenous fistula, a rare complication of AAAs.

Perfusion distal to an AAA is usually well maintained, and most patients have normal femoral pulses. Diminished femoral pulses may result from iliofemoral occlusive disease or hypotension related to hemorrhagic shock in the patient bleeding from a ruptured aneurysm.

Thromboembolic complications can occur spontaneously or when atheromatous plaques are disrupted during invasive intravascular procedures. Large emboli can acutely occlude major vessels, such as the iliac, femoral, or popliteal artery, causing painful lower extremity ischemia with absent distal pulses. Rarely, the aneurysm itself can thrombose, rendering both lower extremities acutely ischemic. More commonly, microemboli consisting of cholesterol crystals or clot obstruct small distal vessels, such as the digital arteries of the toes and arterioles and capillaries of the skin. These patients can present with livedo reticularis; one or more cool, painful, cyanotic toes; and palpable pedal pulses. This constellation of findings, often called the *blue toe syndrome,* is highly suggestive of a proximal source of emboli. When an AAA is the source, the aneurysm is often too small to palpate and only recognized with radiologic investigation.

In rare instances, an intact AAA can cause symptoms by compressing adjacent structures, with symptoms arising from those structures involved. Large, long-standing aneurysms can cause vertebral body erosion and severe back pain. Compression of the duodenum between the superior mesenteric artery and an AAA can cause duodenal obstruction, vomiting, and weight loss. Obstruction of the ureters in the patient with an inflammatory aneurysm can cause symptoms suggestive of ureteral colic.

Ruptured Aneurysms

Pain-Hypotension-Mass Triad

Although the classic description of a ruptured AAA is the triad of pain, hypotension, and a pulsatile abdominal mass, many patients have only one or two components of this triad, and occasionally none of these classic features.

Acute rupture is often the first presentation of an AAA. Not infrequently, however, patients may have a previously diagnosed AAA that has not been repaired because the aneurysm was small or the patient was considered too high risk. Any new or acute symptoms in these patients should be considered acute aneurysmal rupture.

Most patients with a ruptured AAA experience pain in the abdomen, back, or flank. The pain is classically acute, severe, and constant. Although it may be difficult to localize, the pain can radiate to the chest, thigh, inguinal area, or scrotum. A history of pain may be more difficult to elicit if the patient's mental status is compromised by severe hypotension.

The source of the pain associated with aneurysm rupture is not clearly understood. It may be caused by the expansion of the aortic wall or by stimulation of visceral sensory nerves in the retroperitoneum. Identical pain can occur with intact but acutely expanding aneurysms, which may be impossible to differentiate clinically from ruptured aneurysms.

In patients with a ruptured aneurysm, the duration of symptoms before presentation can vary dramatically. Some patients present immediately after rupture because the pain is severe, sudden in onset, and may be accompanied by hypotension. In others, the rupture is initially contained in the retroperitoneum and blood loss is minimal. In these cases, the pain may be minor, waxing and waning, and the presentation delayed. Rare patients with a ruptured AAA may have symptoms for several days or even weeks before seeking medical attention; therefore, a long duration of symptoms does not exclude the diagnosis of ruptured AAA.

Rupture of an AAA may be accompanied by nausea and vomiting in addition to pain or, rarely, absent significant pain. Sudden hemorrhage may present as syncope or near-syncope. Compensatory hemodynamic mechanisms may restore blood pressure and cerebral perfusion to normal. Transient improvement in symptoms is common but will be followed by hemodynamic deterioration if the diagnosis and treatment are delayed. Ruptured AAAs are often large, and non-obese patients will have a palpable abdominal mass. The examination may be difficult if abdominal guarding is present or if an ileus causes significant distention. Aortic pulsations may not be prominent if the blood pressure is low.

Hypotension is the least consistent part of the triad, occurring in approximately half of patients, and is often a late finding. When the initial blood loss is minimal, vital signs may be normal. Patients with initially normal vital signs are more likely to be misdiagnosed and may quickly and unpredictably deteriorate and become hypotensive.

Occasionally, rupture into the retroperitoneum is contained for many weeks or months. When this occurs, patients develop abdominal or back pain, presumably at the time of aneurysm leakage, which subsequently diminishes or resolves completely. If the diagnosis is made, chronic rupture (organized hematoma) is found at surgery. These patients can have chronic pain and may progress to free rupture and massive hemorrhage at any time.

Aortoenteric Fistula

A primary aortoenteric fistula (AEF) is formed when an unrepaired AAA erodes into the gastrointestinal tract, most commonly in the third or fourth portion of the duodenum. A secondary AEF, a communication between the site of previous aortic surgery and the gastrointestinal tract, can occur as a late complication of AAA repair and should be considered in any patient with a severe gastrointestinal bleed and a history of aortic graft placement. An AAA can rupture into the gastrointestinal tract (AEF) or inferior vena cava (aortocaval fistula).

Early in the formation of a primary AEF, the adjacent AAA erodes through the bowel wall from the outside. This can lead to the leakage of intestinal contents, with local infection and abscess formation. Eventually, breakdown of the aortic wall leads to an AEF and may lead to gastrointestinal bleeding. A patient with an AEF may have abdominal or back pain, fever and other signs of intra-abdominal infection, or gastrointestinal bleeding. Because most of these fistulae are into the duodenum, hemorrhage usually manifests as hematemesis or melena. The initial bleeding results from erosion of vessels in the bowel wall and is often occult or minor. Massive bleeding from rupture into the intestinal lumen can occur days or even weeks after the initial bleeding. Primary AEF, although rare, should be considered in any patient older than 50 years with unexplained severe gastrointestinal bleeding. A patient with an AAA diagnosed by history, physical examination, or other modality, presenting with gastrointestinal bleeding should raise the concern for AEF.

Arteriovenous (Aortocaval) Fistula

An arteriovenous (usually aortocaval) fistula arises when periaortic inflammation causes adherence of the aorta to an adjacent vein, with pressure on the vessel walls causing the development of an arteriovenous communication. If concomitant extravasation of blood into the retroperitoneum occurs, the clinical presentation is similar to that of other patients with ruptured AAAs. More commonly, however, the aneurysm ruptures into the vena cava without leaking externally, and the signs and symptoms of a large arteriovenous fistula dominate the clinical picture.

As in other patients with AAAs, a patient with an arteriovenous fistula may have abdominal or back pain. An aneurysm that becomes fistulous with the vena cava is usually large, and 80% to 90% are palpable. A continuous abdominal bruit can be auscultated in approximately 75% of patients with arteriovenous fistulae, and 25% of patients have a palpable abdominal thrill.

Shunting of blood from the arterial to the venous system increases venous pressure, venous volume, and venous return to the heart. Signs and symptoms of high-output congestive heart failure (dyspnea, jugular venous distention, pulmonary edema) are often present. The increased venous volume and pressure can cause lower extremity edema or cyanosis, and dilated superficial veins can be seen on the legs or abdominal wall. Distention and rupture of veins in the bladder mucosa can cause gross or microscopic hematuria, and rectal bleeding can occur for similar reasons. Because of shunting of arterial blood into the venous system, the lower extremities may be cool with diminished pulses.

The patient with an arteriovenous fistula often has renal insufficiency caused by a decrease in renal perfusion as a result of high-output congestive heart failure and increased renal venous pressure. Such patients may exhibit hematuria, which is common when an arteriovenous fistula is present but not in other patients with AAAs. Computed tomography (CT), and preferably computed tomographic angiography (CTA), is essential for diagnosing or ruling out arteriovenous fistula formation.

DIFFERENTIAL DIAGNOSES

Symptoms consistent with ruptured AAA—abdominal, back, or flank pain, with or without hypotension—are seen in other conditions as well, which can lead to delayed or missed diagnoses (Box 72.1). The most common misdiagnosis is renal colic, followed by pancreatitis, intestinal ischemia, other nonspecific intra-abdominal disorders, and musculoskeletal back pain.

Presentation of epigastric pain and hypotension may lead to a presumptive diagnosis of acute myocardial infarction because patients with a ruptured AAA often have concomitant coronary artery disease,

and blood loss from a ruptured aneurysm may diminish coronary perfusion and cause chest pain or electrocardiographic changes consistent with cardiac ischemia. In the setting of abdominal or back pain, these findings do not exclude the presence of a ruptured AAA.

Ruptured AAA should be considered in patients with any part of the classic triad pain (abdomen, back, or flank), and hypotension. The diagnosis of ruptured AAA should also be considered in making the diagnoses listed in Box 72.1, especially when the diagnosis is not clear-cut or the patient is at risk for an AAA.

DIAGNOSTIC TESTING

Abdominal Radiography

Plain film radiography is not indicated in the evaluation of a patient for suspected AAA. A normal plain abdominal radiograph does not exclude the presence of an AAA and rarely identifies alternative pathology. Even if an aneurysm is identified on plain film because it is calcified, imaging with CT is necessary to determine whether the aneurysm is an incidental or culprit lesion in the patient's presentation (Fig. 72.2).

Ultrasonography

Ultrasonography is virtually 100% sensitive in detecting AAAs (Fig. 72.3) when a technically adequate study can be obtained. Measurements of aortic diameter are very accurate and reproducible. Because it is relatively inexpensive and requires no contrast agents or radiation exposure, ultrasonography is also used for aneurysm screening and to follow patients with known aneurysms after they have been characterized with CTA.

Point of care ultrasonography has distinct advantages in the emergency evaluation of a patient with a suspected ruptured AAA. It can be performed rapidly at the patient's bedside, obviating the need to take a potentially unstable patient to the radiology suite. If an aorta with a normal diameter throughout its abdominal course is visualized, the patient does not have an AAA. In addition, ultrasonography occasionally provides alternative explanations for the patient's pain by revealing other conditions, such as acute cholecystitis. Emergency clinicians can accurately identify the etiology of acute nontraumatic abdominal pain, including AAAs, using bedside ultrasound.[3]

Point of care ultrasonography does have limitations, including being more operator-dependent compared to other modalities, and therefore may be more prone to technical or interpretive error. In the emergency department (ED) the aorta may not be well visualized because of obesity or excess bowel gas. Although ultrasonography is extremely

BOX 72.1 Common Misdiagnoses in Patients with Ruptured Abdominal Aortic Aneurysms

- Renal colic
- Acute abdomen
- Pancreatitis
- Intestinal ischemia
- Diverticulitis
- Cholecystitis
- Appendicitis
- Perforated viscus
- Bowel obstruction
- Musculoskeletal back pain
- Acute myocardial infarction

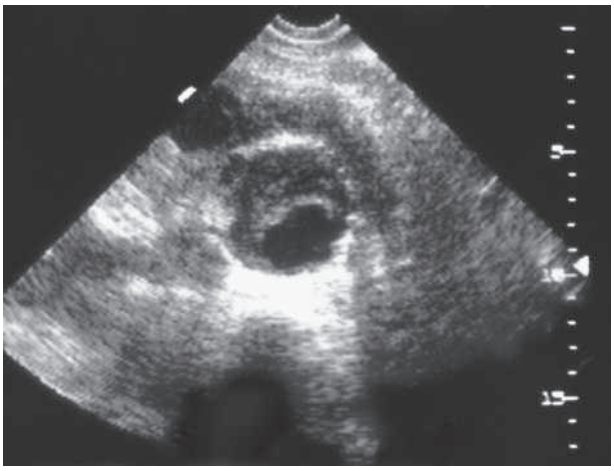

Fig. 72.3 Transverse sonogram of an abdominal aortic aneurysm (AAA). The central patent lumen is surrounded by an echogenic mural thrombus. (Courtesy Richard Rensio, MD.)

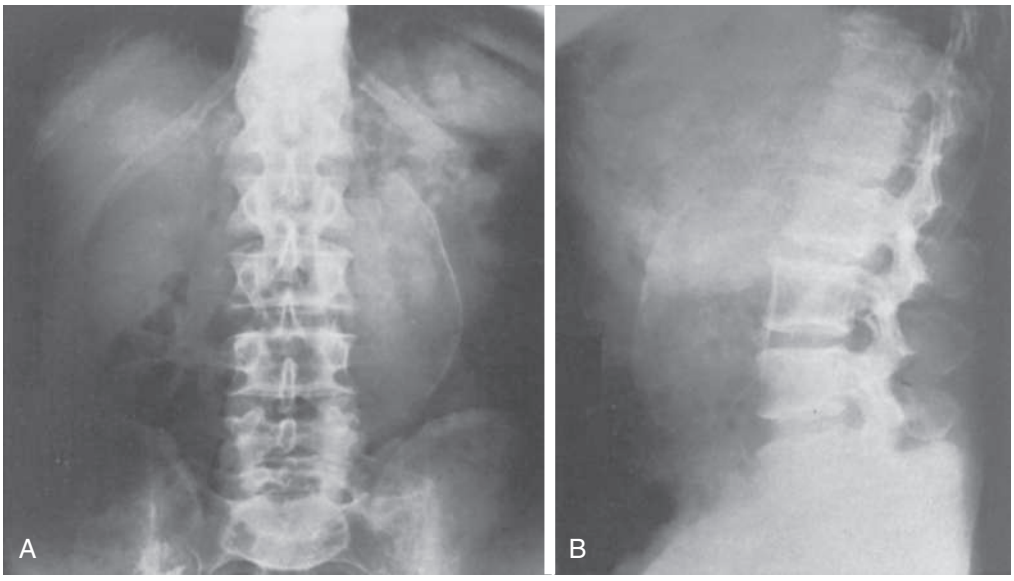

Fig. 72.2 Anteroposterior (A) and lateral (B) views of large abdominal aortic aneurysms (AAAs) with calcification of aortic wall. (From Juergens JL, et al. *Peripheral Vascular Diseases*, ed 5. Philadelphia: WB Saunders; 1980. By permission of the Mayo Foundation.)

sensitive in detecting an AAA, it cannot be relied on to reveal whether an AAA has ruptured.

Free intraperitoneal or retroperitoneal blood, seen in the presence of an AAA, confirms a rupture. However, the sensitivity of point of care ultrasonography in detecting extraluminal blood is very low. The purpose of the study is to confirm or exclude the presence of an aneurysm; clinical information (or a CT scan) must be used to determine the likelihood of rupture. Ultrasonography with the use of contrast agents may aid in the detection of leaking blood, but the clinical utility of this modality has not been determined. If ultrasonography reveals an AAA in an unstable patient, aneurysm rupture should be presumed, and prompt surgical evaluation for consideration of aneurysm repair should be initiated.

Computed Tomography

The abdominal CT scan is the diagnostic test of choice to evaluate the stable patient with suspected ruptured AAA. It is virtually 100% accurate in determining the presence or absence of an AAA and the presence of bleeding. CT also provides detailed anatomic information about the aneurysm.

An intravenous contrast agent is desirable, but not essential, in emergencies. Intravenous contrast will opacify the aortic lumen and distinguish the patent lumen from mural thrombus. It can also demonstrate peri-aortic fibrosis, because the soft tissue surrounding an inflammatory AAA will often enhance. Although intravenous contrast is not necessary to identify the aneurysm or acute hemorrhage, contrast will be helpful for accurate sizing and planning if an endovascular approach is being considered.

CT is more sensitive than ultrasonography in detecting retroperitoneal hemorrhage associated with aneurysm rupture. The reported sensitivity approaches 100% with current-generation scanning technology, with falsely negative studies sometimes occurring with very small ruptures. Blood is seen as a retroperitoneal fluid collection adjacent to the aneurysm, often tracking into the perinephric space or along the psoas muscle (Fig. 72.4).

Although a CT scan sometimes reveals signs of impending aneurysm rupture, such as hyperattenuation of the wall, peri-aortic hematoma, penetrating ulcer, or pseudoaneurysm cannot reliably determine whether an AAA is the cause of the patient's pain or whether rupture of the aneurysm is imminent. An alternative cause of pain can be diagnosed only if the CT scan shows no aneurysm or shows an intact aneurysm and clearly demonstrates an alternative explanation for the patient's symptoms.

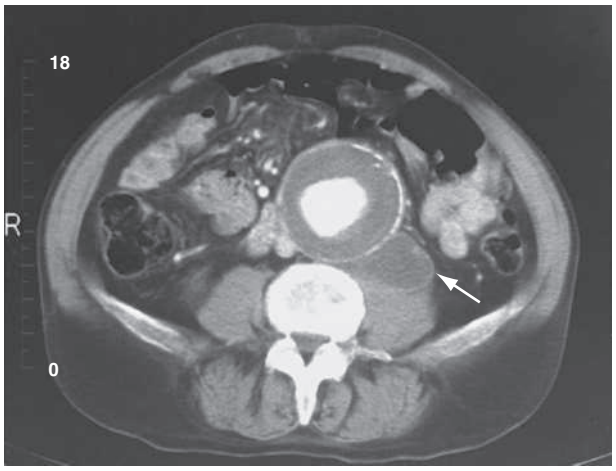

Fig. 72.4 Computed tomography (CT) scan of ruptured abdominal aortic aneurysm (AAA), with calcification of the aortic wall and intraluminal thrombus. The patent lumen enhances with the administration of contrast material, but the periaortic hematoma *(arrow)* does not. (Courtesy Richard Rensio, MD.)

Other Diagnostic Modalities

Conventional angiography has no place in the emergency evaluation of the suspected ruptured AAA. Because contrast opacifies only the patent lumen and not mural thrombus, angiography often underestimates aneurysm size and can miss an aneurysm entirely. In addition, angiography is time-consuming and performed away from the ED. If detailed information is needed about the anatomy of the aneurysm or its relationship to nearby vessels, a CT angiogram is the strongly preferred imaging choice.

Magnetic resonance imaging and magnetic resonance angiography can be very time-consuming, logistically challenging, and provide no benefit over CT scan. Magnetic resonance scanning is not indicated in the evaluation of a patient with suspected AAA in the ED.

MANAGEMENT

Ruptured Aneurysms

No patient with a known or suspected aortic rupture should be considered stable, regardless of the vital signs or initial hemoglobin level, until the aorta is cross-clamped in the operating room or stabilized with endovascular techniques. Ruptured AAA is a time-dependent disease, and patients taken to the operating room soon after ED arrival have a significantly higher survival rate than those in whom surgical care is delayed.

When the patient arrives in the ED, large-bore redundant intravenous access should be established and blood sent for type and crossmatch. At least 6 units of blood should be made available initially, with notification to the blood bank of the potential need for massive transfusion. The surgical and anesthesia teams should be notified emergently. If surgery is not available, transfer arrangements should be initiated as soon as possible. Further management will depend on the hemodynamic status and level of diagnostic certainty.

The hemodynamically unstable patient in whom a ruptured AAA has been diagnosed or is strongly suspected should be taken to the operating room as soon as possible (in this context, the term "operating room" includes other locations that may be used for endovascular aneurysm repair) and diagnostic testing should be kept to a minimum. The diagnosis can often be made on clinical grounds, and point of care ultrasonography can quickly confirm or exclude the presence of an aneurysm. A thin-sliced CT scan of the abdomen and pelvis with intravenous contrast is appropriate only if it can be obtained immediately. Time-consuming tests can lead to avoidable delay of definitive therapy and increase the risk of exsanguination. Hypotensive patients may have to be taken to the operating room based on a strong clinical presumption of the diagnosis, without definitive diagnostic imaging. Some of these patients will not have ruptured aneurysms, but they often have other acute abdominal conditions requiring laparotomy.

Attempts to resuscitate these patients to normalize vital signs in the ED can waste valuable time and should be avoided. Hypotensive patients need to be taken to the operating room so that the aorta can be clamped or occluded with a balloon and hemorrhage stopped.

Fluid Resuscitation

The right amount of preoperative volume resuscitation remains controversial. Preoperative hypotension is the strongest predictor of mortality in the patient with a ruptured AAA. Correction of hypotension before the aorta is clamped may not improve mortality and may even be harmful because hypotension slows bleeding in patients with AAA and allows local clot formation and tamponade of the rupture site.

Raising the intravascular volume and blood pressure before occluding the aorta may dislodge clots and cause further bleeding. Similar to trauma patients with uncontrolled hemorrhage, large volumes of crystalloid solution may contribute to bleeding by worsening acidosis and causing a dilutional coagulopathy.

However, delaying resuscitation of hypotensive patients until they reach the operating room may also have deleterious effects. The patient with a ruptured AAA often survives the surgery but dies in the early postoperative period. These deaths are caused by complications of prolonged hypotension, such as myocardial infarction, respiratory failure, and renal failure. The patient with a ruptured AAA is usually elderly, often has coexisting conditions, and tolerates hypovolemia and hypotension poorly.

No prospective studies have compared different preoperative fluid regimens in hypotensive patients with ruptured AAAs, and the optimal resuscitation strategy has not been determined. The priority in these patients is expeditious transportation to the operating room for definitive control of aortic hemorrhage. In the prehospital setting and the ED, the blood pressure should be raised with crystalloid, or preferably blood products, only to a level that maintains adequate cerebral and myocardial perfusion to prevent irreversible end-organ damage. An arbitrary blood pressure goal cannot be specified because the blood pressure necessary for vital organ perfusion varies among patients, but a reasonable target for this permissive hypotension is a systolic blood pressure of 70 to 90 mm Hg.[2]

If blood products are to be given in large amounts, fresh frozen plasma (FFP) and packed red blood cells (PRBCs) should be administered in patients with ruptured AAAs. As with trauma patients, a PRBC:FFP ratio of less than 2:1 may result in improved mortality.

Rarely, patients with a ruptured AAA may be hypertensive on presentation because of pain or underlying chronic hypertension. Unlike with aortic dissection, no evidence exists that lowering the blood pressure is beneficial in the patient with a ruptured AAA, and these patients are at risk of developing precipitous hypotension.

Diagnostic Confirmation

If an AAA can be diagnosed with bedside testing (abdominal examination or point of care ultrasonography), the surgeon will often proceed immediately to the operating room with a clinical diagnosis of aneurysm rupture, because a delay in surgery places the patient with a ruptured AAA at risk for sudden and unpredictable hemodynamic deterioration. If the patient remains hemodynamically stable and an AAA cannot be identified with bedside testing, or if anatomic detail is needed for endovascular repair, an abdominal CT scan should be obtained. This will confirm or exclude the presence of an aneurysm, define the aortic anatomy, and determine the patient's suitability for endovascular repair. The patient who is sent for a CT scan should be monitored closely and taken to the operating room emergently if hemodynamic deterioration occurs.

CT may provide confirmation of rupture or may show no evidence of rupture, potentially allowing the surgeon to avoid the complications of emergency surgery in a patient with an intact aneurysm. Emergency surgery may not allow detailed anatomic evaluation and careful preoperative evaluation and optimization of the patient's cardiopulmonary and renal function. Therefore, patients who are taken for emergency surgery and are found to have intact, symptomatic aneurysms have a higher mortality rate than patients undergoing elective aneurysm repair. Establishing a protocol for urgent or emergent management of a patient with a ruptured AAA based on available resources is essential for optimizing outcomes. A goal of door-to-intervention time of less than 90 minutes is recommended by the Society for Vascular Surgery, with time zero defined as the initial contact by an emergency physician and intervention defined as placement of an aortic occlusion balloon.[2]

Surgery and Mortality

Ruptured AAA is uniformly fatal unless treated surgically. Thus once this diagnosis has been made, repair should be attempted in almost all patients. Attempts have been made to identify patients with a very low likelihood of survival, and it has been suggested that surgery can be withheld in patients with prehospital or ED cardiac arrest. However, no variables assessed in the ED, including cardiac arrest, are universally predictive of a fatal outcome. Repair is indicated unless the patient has comorbidities such as severe renal, myocardial (in particular uncontrolled congestive heart failure or a recent myocardial infarction), or cerebrovascular disease, making surgery unreasonable, or if surgery is not within the patient's goals of care.

In part because patients with ruptured AAAs have a mortality of 30% to 40% with open repair, endovascular repair of ruptured aneurysms is becoming increasingly common, even in unstable patients. There is evidence that high-volume centers experienced with endovascular repair have a lower operative morbidity and mortality rate than open repair.

Not all patients with ruptured aneurysms will have an aorta that is anatomically suitable for endovascular repair. The method of repair will depend on the preference and skill set of the surgeon, as well as institutional capability and suitability for an endovascular approach. Planning for the care of such patients should include the development of a protocol or pathway that advises the ED staff about which services to mobilize and which diagnostic tests to perform in patients with suspected ruptured AAA.

Intact Asymptomatic Aneurysms

An incidental diagnosis of AAA may sometimes be made in the ED. The decision to repair an asymptomatic aneurysm depends on the risk of aneurysm rupture, comorbidities, and surgical risk. Surgical risk is determined by the patient's age and comorbidities, whereas the risk of rupture is largely a function of aneurysm size.

In two clinical trials, one of which has long-term follow-up, patients with small (<5.5 cm) aneurysms were randomized to early surgery or close follow-up. In the latter group, aneurysms were followed with serial ultrasounds or CT scans, and surgery was performed only if any symptoms developed, rapid expansion was documented, or a diameter of 5.5 cm was reached. Both studies showed equivalent survival rates in the two groups. As a result, fewer small aneurysms are now repaired electively, potentially leaving a larger group of patients who may come to the ED with complications of an AAA.

Traditional Repair

The conventional technique for repair of AAAs is an open approach with a laparotomy. The aneurysm is opened longitudinally and repaired from within (Fig. 72.5). A graft is inserted inside the aneurysm and anastomosed to uninvolved vessels above and below once lumbar vessels are ligated and the mural thrombus evacuated. When possible, a straight graft is used between the infrarenal and distal aorta, but if the aneurysm involves the aortic bifurcation or if iliac artery aneurysmal or occlusive disease is present, a bifurcation graft is used, with the distal anastomosis to the iliac or femoral arteries. Coagulopathy is addressed and the aneurysm wall is then closed around the graft to help separate it from adjacent structures in the retroperitoneum. The bowel is re-inspected, and the abdominal wall is frequently managed with temporary abdominal closure using negative pressure wound therapy when managing ruptured aneurysms.

Endovascular Repair

More than half of all AAA repairs are now performed without laparotomy, with use of endovascular techniques.[4] Perioperative mortality is lower than that with open repair, but it is unclear whether this mortality benefit is sustained in the long-term. More recent studies suggest the

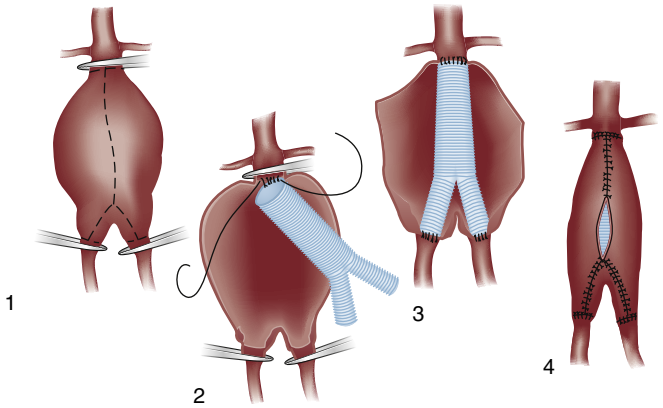

Fig. 72.5 Steps in repair of an abdominal aortic aneurysm (AAA). See text for details. (From Kent KC, et al. Surgical principles for operative treatment of aortic aneurysms. In Lindsay J Jr, ed. *Diseases of the Aorta*. Philadelphia: Lea & Febiger;1994: 287.)

survival advantage is maintained for 3 years.[5] Numerous studies have cited a clear reduction in early mortality associated with endovascular aneurysm repair (EVAR) but continue to emphasize the importance of an organized algorithmic approach with a specialized team.[6] Recent guidelines recommend EVAR when anatomically feasible and expertise is sufficient.[2] Although many hospitals have hybrid operating rooms, EVAR can be done with portable fluoroscopy in the operating room.

Stable patients can undergo bilateral femoral artery cut-downs to place sheaths and wires once in the operating room. Unstable patients, however, may require transfemoral access with a 12 French sheath followed by aortic balloon occlusion in the ED. Once an arteriogram is performed with a marking flush catheter, the endovascular plan is formulated unless a contrast-enhanced CT scan is available for stent graft sizing.

A stent graft (a fabric graft supported by a nitinol wire frame) is placed into the femoral artery percutaneously or through a groin incision and is advanced under fluoroscopic guidance to a position that spans the infrarenal aneurysm (Fig. 72.6A). The contralateral iliac limb is placed to form a bifurcated graft (see Fig. 72.6B). Once in position, the graft is deployed and expanded to fit tightly against the walls of the aorta. These self-expanding devices have radial forces but are also oversized 10% to 20% to ensure proper sealing. There are several devices approved by the US Food and Drug Administration (FDA) and all have unique features. Standard criteria for use include an aortic transverse diameter between 18 to 32 mm, angulation less than 60 degrees, and neck (lowest renal artery to start of aneurysm) length more than 10 mm, iliac landing zone diameter of 10 to 22 mm, and femoral access diameter more than 8 mm

Endovascular repair results in more frequent reinterventions for graft-related complications. Because not all aneurysms are anatomically suitable for endovascular repair, detailed preoperative imaging and planning are required to make this determination. In addition, patients who have had an endovascular aneurysm repair remain at risk for several complications—most importantly, rupture of the aneurysm. Some authors now suggest that endovascular repair has become the first choice of AAA treatment in almost all patients, with anatomic location remaining the most common indication for open repair.[7] Lack experience with endovascular operations remains the greatest barrier to the widespread application of evolving endovascular technologies for emergency use. Percutaneous endovascular repair is becoming more common and may represent a suitable alternative to open endovascular repair in some patients.[8]

Survival

The operative mortality rate for elective AAA repair is approximately 1% to 2% for endovascular repair and 3% to 5% for open repair, in contrast to the much higher operative mortality with ruptured aneurysms. Patients who survive the operation have an excellent prognosis, with a long-term survival close to that of the general population. After repair of the aneurysm, long-term survival is primarily limited by associated cardiac disease.

LATE COMPLICATIONS OF REPAIR

Graft infection, AEF formation, and anastomotic aneurysm (pseudoaneurysm) formation can occur at any time from weeks to years after the surgery. These complications can occur concurrently or sequentially and are diagnosed by similar mechanisms. In addition, endovascular aneurysm repair has several unique complications, the most important of which is endoleak.

Graft Infection

Graft infection can result from contamination of the graft at surgery, spread of a contiguous infection, or hematogenous seeding. Infection can disrupt the anastomosis between the native artery and graft, leading to leakage of blood from the anastomosis and pseudoaneurysm formation. The infection can be localized to a portion of the graft, most often the inguinal portion of an aortofemoral graft, or can involve the entire graft.

Infection of the distal limb of an aortofemoral graft may cause local signs of infection or a palpable false aneurysm. Intra-abdominal graft infection is often subtle, with low-grade fever and vague abdominal or back pain. Abdominal tenderness or a palpable mass may be present if there is a leaking anastomosis. Collections of fluid or gas around the graft on CT provide evidence of infection, although CT scans can be falsely negative.

Aortoenteric Fistula

As discussed earlier in this chapter, an AEF should be considered in any patient with gastrointestinal bleeding and a history of abdominal aortic surgery. Most of these patients, however, ultimately prove to have other, more common causes of gastrointestinal bleeding. The diagnostic approach depends on the patient's hemodynamic stability.

If the patient with a suspected AEF is unstable with massive bleeding, diagnostic testing may be dangerously time-consuming. In these patients, emergency laparotomy may be necessary to control hemorrhage and diagnose or exclude the presence of an AEF. Stable patients can be evaluated with endoscopy or a CT scan. Some patients with AEF may be treated endovascularly, which may result in improved perioperative morbidity and mortality.

Upper gastrointestinal endoscopy is recommended as the initial diagnostic test in the stable patient when available. Direct visualization of the fistula into the distal duodenum is sometimes possible. Endoscopy cannot be relied on to identify an AEF, however, and its main value is in establishing another diagnosis. Emergency surgery can be avoided if an active bleeding site that is not an AEF is clearly seen.

An abdominal CT scan can also be used to evaluate a suspected AEF. Although imaging of the fistula may not be possible, graft infection is almost invariably present in patients with secondary AEFs, and the CT scan will demonstrate the associated infection. Radiographically distinguishing an AEF from intra-abdominal graft infection alone may not be possible.

Pseudoaneurysm (Anastomotic Aneurysm)

Pseudoaneurysms can arise at the site of a leaking anastomosis. They may be associated with graft infection or AEF formation but more often result from degeneration of the native vessel.

The patient with an anastomotic aneurysm may have pain or a pulsatile mass in the abdomen or groin. The aneurysm may give rise to distal emboli or may rupture and cause life-threatening hemorrhage. Suspected pseudoaneurysms can be evaluated with angiography, CT scan, or ultrasonography.

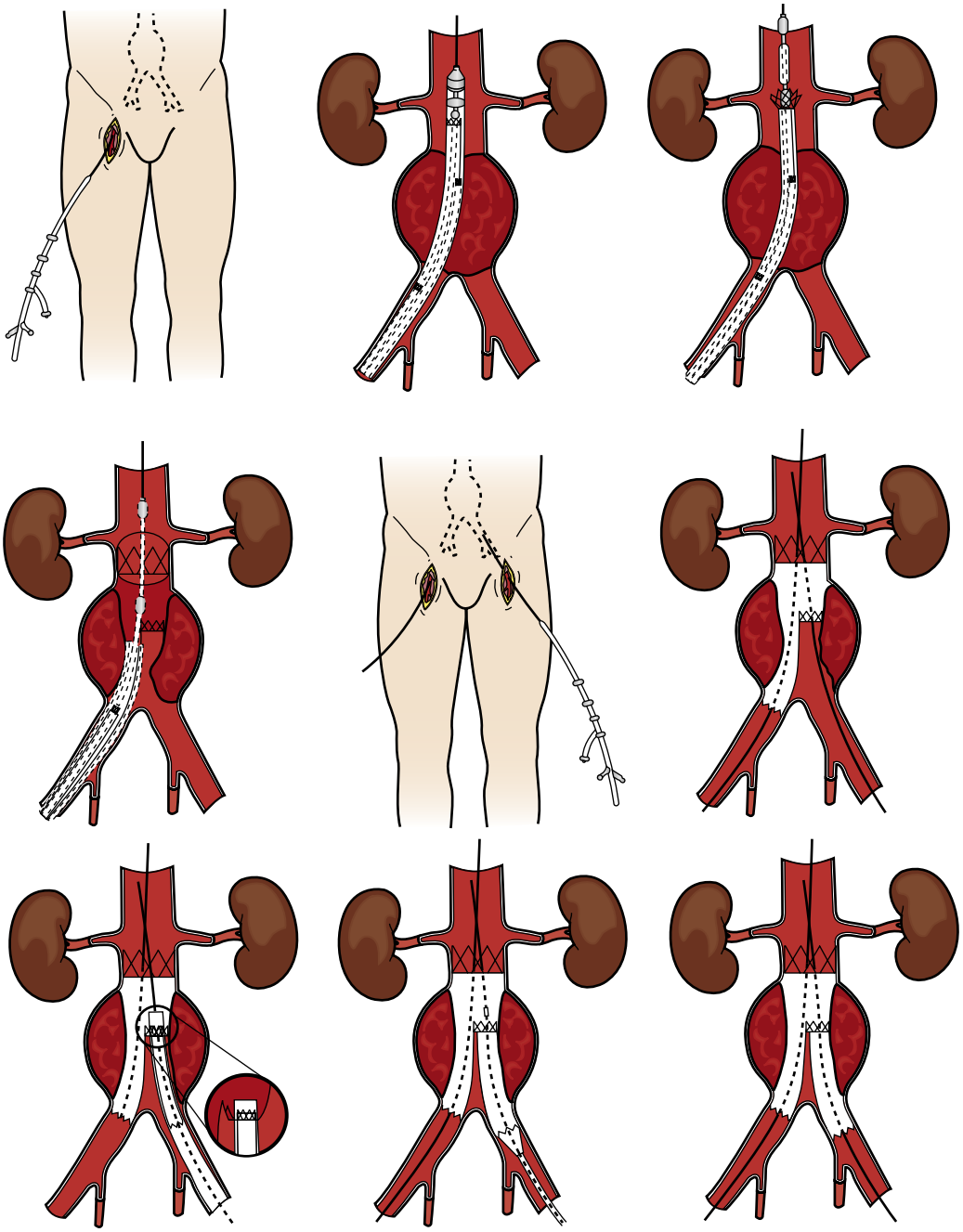

Fig. 72.6 Endovascular repair (ipsilateral and contralateral) of abdominal aortic aneurysm with a modular endograft. (From Hornacky A, Phillips N. Vascular surgery. In: Hornacky A, Phillips N, eds. *Berry & Kohn's Operating Room Technique*, 14th ed. Elsevier; 2021. Fig. 44.21.)

Complications of Endovascular Aneurysm Repair

An increasing percentage of elective AAA repairs are done with endovascular techniques, and these patients may come to the ED with postoperative complications. The most serious of these is endoleak—blood flow outside of the graft lumen but within the aneurysm sac, potentially allowing enlargement of the aneurysm. Endoleaks may be caused by separation of the proximal or distal end of the graft from the aortic wall (type I), back-bleeding into the aneurysm sac from branch vessels such as lumbar arteries (type II), leakage between the modular components of the graft (type III), leakage through the graft fabric itself (type IV), or in rarer cases when the sac enlarges without an identifiable leak, otherwise known as *endotension* (type V) (Fig. 72.7). Patients with persistent leakage of blood into the aneurysm sac are at risk for rupture of the aneurysm.

Endoleaks may develop soon after the procedure or much later. They have been reported in as many as 20% of patients who have had endovascular aneurysm repair. Because many type II endoleaks resolve spontaneously, patients are sometimes observed for months before repair of the leak with secondary endovascular procedures or surgical intervention.

Patients sometimes sustain other complications, such as graft migration, stenosis or thrombosis, and structural failure of various elements of the graft. These complications often lead to endoleak and the risk of rupture.

In the ED, CT with intravenous contrast should be used to evaluate for possible complications of endovascular repair. A specific CT imaging protocol may be desired; this should be discussed with the radiologist or vascular surgeon. Prompt surgical consultation should

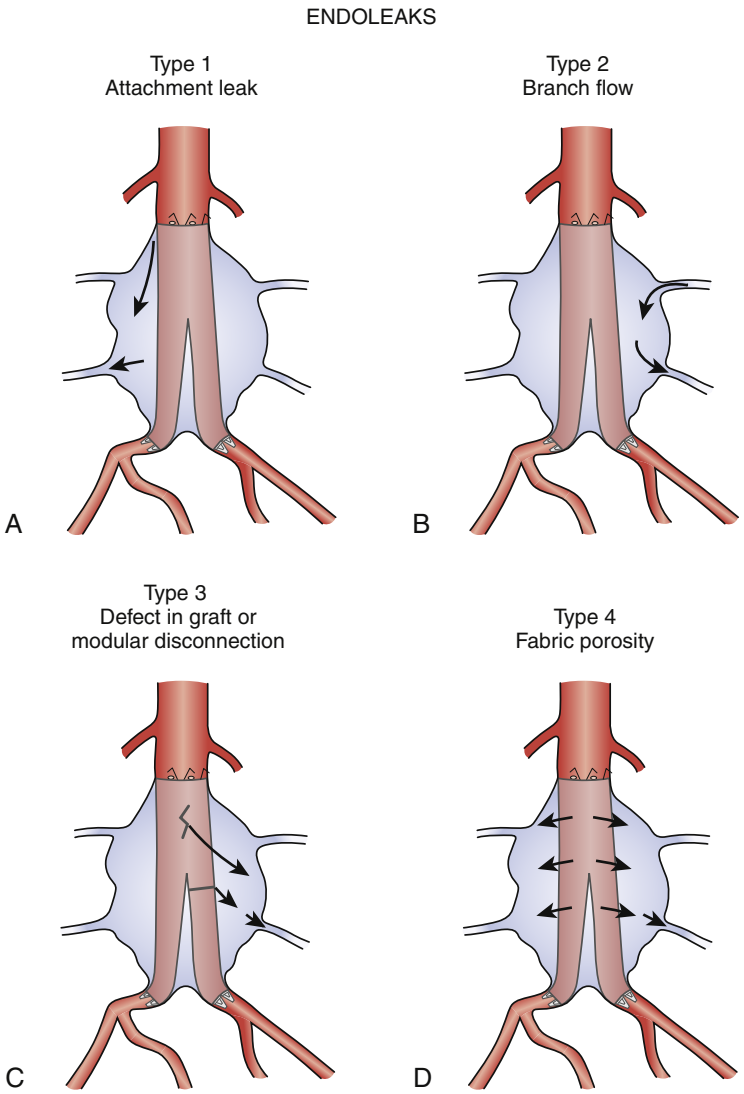

Fig. 72.7 Endoleaks of abdominal aortic aneurysm after endovascular aneurysm repair. (A) Type 1 leak (attachment leak). Blood continues to enter the aneurysm sac at one of the three ends of the bifurcated stent graft, the points where the stent graft should be tightly affixed to the arterial wall. Egress, as with all endoleaks, is through branches of the aorta that remain patent. Treament of type 1 leaks is indicated. (B) Type 2 leak (branch artery leak). Blood enters the aneurysm sace through a patent branch artery. This type of leak can be self-limited and may be just observed. Treatment is indicated if the aneurysm enlarges. (C) Type 3 leak (loss of integrity of stent graft). Either the modules of the stent graft have become separated or a rent has formed in the fabric of the stent graft. Blood enters the sac from the stent graft lumen through the site of loss of stent graft integrity. Treatment is indicated. (D) Type 4 leak (fabric porosity). Blood enters the sac from the stent graft lumen through intact cloth of the stent graft. This is self-limited and present only at surgery. The pore of the fabric quickly become occluded by blood products. (From Mustafaraj E, Bertino RE. The retroperitoneum. In: Rumack CM, Levine D, eds. *Diagnostic Ultrasound*, 5th ed. Elsevier; 2018. Fig. 12.9.)

be obtained for patients with any symptoms that could be related to device malfunction, and the potential for aneurysm rupture should always be considered.

DISPOSITION

A patient with an acutely symptomatic AAA requires emergency surgical evaluation and repair. A patient whose aneurysm is asymptomatic and discovered incidentally should be referred for consideration of elective repair. The patient with an AAA should be referred for an outpatient evaluation only if it is clear that the symptoms prompting the ED visit are unrelated to the aneurysm. Although the incidental detection of AAA is common, such patients may suffer from poor subsequent follow-up and monitoring. If the patient is discharged, appropriate referral for follow-up is crucial, and instructions should be given to seek immediate medical attention if abdominal, back, or flank pain develops.

In the patient who has a history of a repaired AAA, unexplained fever, abdominal pain, or gastrointestinal bleeding suggests the presence of a graft-related complication and the need for inpatient evaluation.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 72: QUESTIONS AND ANSWERS

1. What is the most common complication of abdominal aortic aneurysms (AAAs)?
- **a.** Renal artery infarction
- **b.** Rupture
- **c.** Development of an aortoenteric fistula
- **d.** Ureteral obstruction

Answer: B. Although all of the options are potential complications of AAAs, rupture is by far the most common. Rupture typically occurs into the retroperitoneum, allowing possible tamponade of the rupture site. Only between 10 and 30% of ruptures are freely into the peritoneum, which is often rapidly fatal.

2. An 82-year-old male presents after a syncopal episode, which occurred 1 hour prior to arrival and was without preceding symptoms. He has a past medical history significant for hypertension and a surgical repair of an abdominal aortic aneurysm (AAA) 15 years ago. Physical examination reveals a pale man with a heart rate of 112 beats per minute, a blood pressure of 86/54 mm Hg, and a respiratory rate of 24 beats per minute. There is melena on rectal examination and there is no palpable mass on abdominal palpation. Along with appropriate volume resuscitation, what is the most appropriate next step in the management of this patient?
- **a.** CT scan of the abdomen with contrast enhancement
- **b.** Abdominal x-rays
- **c.** Immediate vascular surgery consultation
- **d.** Addition of albumin to crystalloid infusion

Answer: C. The presence of gastrointestinal bleeding with evidence of an AAA or a history of aortic surgery is an aortoenteric fistula until proven otherwise. The most common site of vascular erosion is the third or fourth portion of the duodenum, causing hematemesis or melena. Initial bleeding may be minor, followed days to weeks later by massive bleeding. Surgical intervention is necessary. Unstable patients may need to be taken directly to the OR based on a strong clinical presumption.

3. Which of the following is true regarding the management of a patient with a suspected abdominal aortic aneurysm (AAA)?
- **a.** Aggressive crystalloid resuscitation to normalize the blood pressure is warranted.
- **b.** Permissive hypotension with a goal of a systolic blood pressure of 70 to 90 mm Hg is a reasonable target.
- **c.** Lowering the blood pressure in hypertensive patients has been shown to improve outcomes.
- **d.** Bedside ultrasound should always be followed by a CT scan to better define the aneurysm.

Answer: B. Permissive hypotension with a goal of a systolic blood pressure of greater than 70 mm Hg but not necessarily more than 90 mm Hg is a reasonable target. Aggressive crystalloid resuscitation may be harmful. Lowering the blood pressure in hypertensive patients has not been shown to improve outcomes in patients with abdominal aortic aneurysms as it has in patients with dissecting thoracic aortic aneurysms. Although a CT scan can be useful to better define the aneurysm prior to surgery in stable patients, bedside ultrasound may be the only imaging necessary in unstable patients.

4. What is the strongest predictor of mortality in patients with a ruptured abdominal aortic aneurysm (AAA)?
- **a.** Hypotension
- **b.** Presentation more than 12 hours after symptom onset
- **c.** Age older than 70
- **d.** Anemia on arrival

Answer: A. Although all of the options are predictors of higher mortality, preoperative hypotension is the strongest predictor. That said, there is little data guiding volume resuscitation, fluid choices, and target blood pressures in hypotensive patients with a ruptured AAA. Crystalloid resuscitation before surgical repair can cause dilutional coagulopathy and clot dislodgement by raising the intravascular volume. Judicious volume resuscitation with early use of blood products and a target systolic pressure of 70 to 90 mm Hg is reasonable.

5. Which of the following is most common in the patient with an intact (non-ruptured) 6-cm abdominal aortic aneurysm?
- **a.** Back pain
- **b.** Abdominal pain
- **c.** Sensation of abdominal distention
- **d.** Absence of any symptoms

Answer: D. Most intact AAAs are asymptomatic. They may be discovered incidentally on physical examination or a radiologic study done for other reasons or may be found in an ultrasonographic aneurysm screening program. Pain in the abdomen or back does not usually develop until the aneurysm ruptures.

Continued

CHAPTER 72: QUESTIONS AND ANSWERS—cont'd

6. A 67-year-old man presents with a several-day history of intermittent periumbilical abdominal pain. Physical examination and vital signs are unremarkable except for supraumbilical tenderness. Hemoglobin is 12 g/dL. Contrast-enhanced computed tomography (CT) scan of the abdomen details a 4.2-cm infrarenal abdominal aortic aneurysm (AAA) with an apparent old contained rupture with no obvious new or acute blood. All of his discomfort is relieved by a single dose of morphine sulfate. Which of the following would be the most appropriate course of action?

a. Vascular surgery clinic follow-up in 1 or 2 days
b. Emergency department (ED) observation for 6 to 8 hours with serial abdominal examinations
c. Gastrointestinal consultation for early follow-up and upper or lower endoscopy
d. Surgical consultation

Answer: D. Watchful waiting is indicated only for asymptomatic aneurysms, regardless of the size (up to 5.5 cm). The majority of "stable" AAAs are neither painful nor tender, and the presence of both in this patient suggests imminent rupture. Although the CT scan did not detect acute blood, the safest course of action would be surgical consultation, with early or imminent rupture as the presumed source of this patient's symptoms

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Peripheral Arteriovascular Disease

Tom P. Aufderheide

KEY CONCEPTS

- Acute arterial occlusion is a limb-threatening emergency requiring early anticoagulation and Fogarty catheter embolectomy. The clinical diagnosis is based on some variant of the five Ps: pain, pallor, pulselessness, paresthesias, and paralysis. Confirmatory tests are unnecessary and increase the limb's ischemic time.
- Atheroembolism (blue toe syndrome) is associated with cool, painful cyanotic toes in the presence of palpable distal pulses. A proximal source should be localized, most often an atherosclerotic aneurysm in the aorta or the iliac, femoral, or popliteal artery.
- Popliteal aneurysms are bilateral in 60% of patients and often coexist with an abdominal aortic aneurysm.
- The classic Raynaud attack is triphasic: the fingers become pale, blue, and then red. Raynaud disease has no detectable underlying cause and usually has a benign course. Conversely, Raynaud phenomenon has an underlying disorder, usually connective tissue disease.
- The only reliable clinical test for the detection of thoracic outlet syndrome is the elevated arm stress test (EAST).
- Partial arterial lacerations continue to bleed, resulting in an expanding hematoma. Complete arterial transections initially have only moderate bleeding but can result in delayed hemorrhage. Blunt arterial injury may produce intimal disruption resulting in dissection, thrombosis, or obstruction. Arterial vasospasm can accompany injuries adjacent to the blood vessel, but spontaneous resolution always occurs in the absence of arterial disruption or intimal injury.
- Aneurysms and arterial stenoses are characterized by a systolic murmur. Pseudoaneurysms, associated with prior surgical or trauma sites, are characterized by a loud systolic and possibly a separate, faint diastolic murmur. Arteriovenous fistulae are characterized by a harsh "to and fro" murmur associated with a palpable thrill.
- Intra-arterial injection of illicit drugs into the brachial or radial artery is associated with immediate onset of severe, burning pain, and emergency department presentation with patchy blue-purple skin discoloration. Identifying the injection site helps confirm this syndrome, which can be associated with persistent ischemia and tissue loss.

FOUNDATIONS

Arteries are classified into three categories based on their size and histologic features: (1) large or elastic arteries (the aorta and its immediate proximal, larger branches, including the innominate, subclavian, and common carotid, as well as the pulmonary arteries); (2) medium-sized or muscular arteries (located just distal to elastic arteries, including the common femoral, axillary, and internal carotid arteries); and (3) small arteries (usually <2 mm in diameter) that course in the substance of tissues and organs. This chapter considers diseases of medium and small arteries.

BACKGROUND

Arterial Anatomy

All arteries possess three layers: the tunica intima, tunica media, and tunica adventitia. As peripheral arteries diminish in caliber, these three layers become progressively indistinct and are no longer identifiable at the level of the arteriole, the precapillary vessel containing smooth muscle.

The tunica intima has an inner lining of endothelial cells surrounded by subendothelial connective tissue. The single layer of continuous endothelium is a unique thromboresistant layer between blood and the potentially thrombogenic subendothelial tissues. The integrity of the endothelium is fundamental for the normal structure and function of the vessel wall. Endothelial injury results in intraluminal thrombosis and contributes to atherosclerosis.

The tunica media is made up primarily of circular or spiral smooth muscle cells arranged in concentric layers. The outer limit of this layer is marked by a well-defined, external elastic membrane. The elastic content of the tunica media gives resilience to medium-sized arteries. With age, elastic fibers deteriorate, replaced by fibrous tissue. This loss of elasticity results in stretching and elongation and accounts for the progressive tortuosity and development of arterial aneurysms with aging. In addition, vascular smooth muscle cells may contribute to lipid accumulation in the vessel wall during atherosclerosis, which precipitates vasoconstriction and dilation.

The tunica adventitia is a layer of connective tissue in which nerve fibers and small, thin-walled nutrient vessels (vasa vasorum) are dispersed. Medium-sized arteries contain more nerve fibers than larger vessels, reflecting their role in the autonomic regulation of blood flow.

The peripheral arterial vascular system can be considered as a single end-organ subject to eight basic pathophysiologic processes: (1) atherosclerosis, (2) aneurysm, (3) embolism, (4) thrombosis, (5) inflammation, (6) trauma, (7) vasospasm, and (8) arteriovenous fistula. Two of these—atherosclerosis and thrombosis—are responsible for most cases of the disease.

Pathophysiology

Atherosclerosis

Atherosclerosis is a disease of large- and medium-sized muscular arteries. The basic lesion, the atheroma, or fibrofatty plaque, is a raised focal plaque within the intima; it has a lipid core covered by a fibrous cap. As the plaques increase in size and number, they progressively encroach on the lumen of the artery and the adjacent media. Atheromas compromise arterial blood flow and weaken the walls of the affected arteries.

The distribution of atherosclerotic plaques is relatively constant. The abdominal aorta typically is susceptible to more atherosclerotic disease than the thoracic aorta, and aortic lesions are much more common and prominent around the ostia of major branches. Other vessels

affected by atherosclerosis are the aortoiliac, femoral, and popliteal arteries; the descending thoracic aorta; the coronary arteries; the internal carotid arteries; and the circle of Willis. Upper extremity vessels are usually spared.

As atherosclerosis progresses, atheromas calcify, resulting in hard, brittle vessels. Rupture of the atheromatous plaques discharge debris, producing atheroemboli (cholesterol emboli). Ulcerated lesions produce in situ thrombosis, causing intraluminal occlusion. Hemorrhage into the plaque may further compromise the arterial lumen. Although atherosclerosis primarily affects the intima, in severe cases, the tunica media undergoes pressure atrophy and loss of elastic tissue, with sufficient weakening to create aneurysmal dilation.

Arterial Embolism

An embolus, by definition, is a foreign body, most commonly a blood clot, carried by the blood to a site distant from its point of origin. Most emboli are detached thrombus formations or thromboembolism. Less common emboli include debris from ruptured atherosclerotic plaques, tumor debris, or foreign bodies. Unless otherwise specified, the term *embolus* in this chapter is defined as thromboembolus.

***Thromboembolism.*.** Most arterial emboli (85%) originate from thrombus formation in the heart. Left ventricular thrombus formation resulting from myocardial infarction accounts for 60% to 70% of arterial emboli. Atrial thrombi associated with mitral stenosis and rheumatic heart disease account for only 5% to 10% of arterial emboli.[1] Coexisting atrial fibrillation is present in 60% to 75% of patients with peripheral arterial embolic events because atrial fibrillation predisposes patients to intracardiac clotting.[2]

Acute arterial emboli often cause distal tissue infarction. Clinical outcomes depend on the amount of collateral circulation, the size of the vessel, and the degree of obstruction. Patients with long-standing atherosclerosis have well-developed collateral circulation, whereas sudden occlusion of a normal artery without collateral pathways results in severe ischemia. After acute obstruction, the embolus can propagate proximally or distally, fragment and embolize further to distal vessels, or precipitate venous thrombosis by initiating a localized inflammatory reaction.

Because vessel diameters change abruptly at branch points, embolic occlusion most often occurs at major arterial bifurcations. The common femoral artery bifurcation is the most frequent site, accounting for 35% to 50% of all cases.[1] The smaller femoral and popliteal arteries are involved twice as often as the larger aortic and iliac vessels, reflecting the small size of most emboli.

Arterial emboli, causing arterial occlusion and subsequent ischemia, result in cell death and produce elevated concentrations of potassium, lactic acid, and myoglobin in the extremity distal to the occlusion. Revascularization may result in sudden release, which can produce life-threatening hyperkalemia, metabolic acidosis, and myoglobinuria. This myonephropathic-metabolic syndrome accounts for approximately one-third of the deaths from an arterial embolism after revascularization.[3]

***Atheroembolism.*.** *Atheroembolism* refers to microemboli consisting of cholesterol, calcium, and platelet aggregates dislodged from proximal complicated atherosclerotic plaques that lodge in distal end arteries. In the central nervous system, atheroemboli cause transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli characteristically cause cool, painful, and cyanotic toes, or the blue toe syndrome.[4]

Atheroemboli are caused by proximally located arterial lesions, usually atherosclerotic plaques or aneurysms. Bilateral distal extremity involvement implies an aortic source, whereas unilateral atheroemboli usually arise from sites distal to the aorta. Distal lesions are most common in the femoropopliteal arteries (60%) and the aortoiliac arteries (40%). Aortic lesions (e.g., aneurysms, polytetrafluoroethylene grafts) are a less common source of microemboli.[4]

Atheroemboli are small (100 to 200 μm in size). Single atheroembolic events seldom result in tissue loss, but atheroemboli tend to cluster. If unrecognized, repeated events ultimately result in the loss of collateral circulation, progressive symptoms, and extensive tissue infarction.[4]

Infectious emboli from bacterial endocarditis can produce septic infarcts that may convert to large abscesses. Rarely, cardiac and noncardiac tumors or foreign bodies may gain access to the arterial circulation and embolize. Primary or metastatic lung neoplasms, malignant melanoma, and bullet emboli have been reported. With cyanotic congenital heart disease (e.g., patent foramen ovale), venous emboli may pass directly to the arterial circulation (paradoxical emboli). Although rare, this possibility should be considered in any patient with simultaneous arterial and venous emboli, particularly if a source of the arterial embolus is not evident.

Arterial Thrombosis

Thrombosis is the in situ formation of a blood clot within the uninterrupted arterial vascular system. Complicated atherosclerotic plaques are usually responsible for the two major factors that cause in situ thrombosis: endothelial injury and alterations in normal blood flow. Less common causes include acute vasculitis and trauma. Thrombosis is rare in normal arteries.[5] Peripheral arterial thrombi are usually occlusive, firmly attached to the damaged arterial wall, and infrequently embolize. Clot propagation intensifies ischemia.

Aneurysms

A true aneurysm is an abnormal localized dilation of the intact vessel wall. With a pseudoaneurysm, the entire wall perforates or ruptures, and the extravasated blood is contained by the surrounding tissues, eventually forming a fibrous sac that communicates with the artery.

Mural and mechanical factors contribute to true aneurysm formation.[6] The major cause of aneurysms is a weakness or defect in the integrity of the arterial wall. The only aneurysms that develop in a normal arterial segment are poststenotic aneurysms, such as with coarctation. Acceleration of flow past a narrow point creates slower flow beyond the stenosis lateral to the jet stream, producing increased lateral pressure. Aneurysmal dilation accelerates, increasing the risk of rupture as diameter increases, as described by Laplace's law: tension (lateral pressure) in the wall of a hollow viscus varies directly with its radius (tension = pressure × radius).

The most common cause of aneurysms is severe atherosclerosis resulting from thinning and destruction of the tunica media. Atheromatous ulcers covered by mural thrombi are common. Mural thrombi form emboli that then lodge in distal vessels. When an entire aneurysm is filled with thrombus material, arterial occlusion results.

Aneurysms cause clinical symptoms through (1) rupture with subsequent hemorrhage, (2) impingement on adjacent structures, (3) occlusion of a vessel by either direct pressure or mural thrombus formation, (4) embolism from mural thrombus, and (5) a pulsatile mass.

Inflammation

Inflammatory arterial injury can be caused by drugs, irradiation, mechanical trauma, or bacterial invasion. The primary cause of arteritis is noninfectious systemic necrotizing vasculitis. Infectious arteritis is caused by direct invasion of the arterial wall. Septicemia, intravenous drug abuse, or infective endocarditis is most often responsible. Certain

fungal infections, particularly aspergillosis and mucormycosis, are frequently associated with vasculitis and thrombosis.

Trauma

Vascular trauma results in characteristic pathologic syndromes. Partial arterial lacerations continue to bleed because the intact portion of the vessel wall prevents retraction and closure of the arterial wound. This may form an expanding hematoma. Complete arterial transection usually has only moderate or insignificant bleeding because of arterial spasm of the transected ends and the formation of a temporary thrombus. Delayed hemorrhage results from relaxation of arterial spasm, liquefaction of the thrombus, or displacement of the thrombus by arterial pressure.

Blunt injury produces intimal disruption. Dissection then leads to progressive obstruction and thrombosis. Vasospasm can accompany injuries adjacent to traumatized blood vessels; spontaneous resolution always occurs in the absence of arterial disruption or intimal injury.

Vasospasm

Vasospastic disorders (Raynaud disease, Raynaud phenomenon, livedo reticularis, acrocyanosis, erythromelalgia) produce an abnormal vasomotor response in distal small arteries. The cause is unknown but may be related to the autonomic innervation of peripheral arterioles. Vasospastic disorders are characterized by the presence of ischemic symptoms and the absence of tissue loss. The arterial wall does not demonstrate any pathology. In contrast, patients with digital ulceration and gangrene always have fixed arterial occlusions in distal extremity arteries.

Arteriovenous Fistulae

Abnormal communication between arteries and veins may result from congenital defects, arterial aneurysm rupture into an adjacent vein, penetrating injuries, and inflammatory necrosis. The artery proximal and veins distal to the fistula become distended, tortuous, and aneurysmal. Proximal and distal veins respond to alterations in hemodynamics with intimal proliferation and fibrosis, followed by a decrease in the internal elastic lamina, resulting in distention, tortuosity, and aneurysm formation. Chronic venous hypertension causes dermatitis and ulceration of overlying skin. The size of the fistula generally increases with time.

Approximately 60% of arteriovenous fistulae are associated with a false aneurysm.[7] False aneurysm formation can occur as part of the fistulous tract or arterial or venous dilation.[7] Increase in cardiac output results in tachycardia, widened pulse pressure, or high-output failure.

CLINICAL FEATURES

History

Patients with peripheral arterial disease have pain and are at risk for tissue loss (ulceration or gangrene) or a change in sensation or appearance (swelling, discoloration, or temperature change). Related conditions suggest atherosclerosis, including cardiac disease, myocardial infarction, cardiac dysrhythmias (e.g., atrial fibrillation), stroke, transient ischemic attacks, and renal disease. Factors that increase the likelihood of atherosclerosis are cigarette smoking, diabetes, hypercholesterolemia, and hypertension. Intravenous drug use can lead to arterial injury. Risk factors unrelated to atherosclerosis include prior injuries or surgeries, a history of phlebitis or pulmonary embolism, autoimmune disease, arthritis, or coagulation abnormalities.

Physical Examination

A systematic assessment of the peripheral vascular system includes palpation of the pulse volume in the pairs of brachial, radial, femoral, posterior tibial, and dorsalis pedis arteries documented on a scale of 0 to 4+. It is important to note that approximately 10% of the population does not have one of the dorsalis pedis pulses.[8]

The lower extremities should be examined for signs of chronic and advanced ischemia. Muscular atrophy, particularly in the lower extremities, and loss of hair over the toes and feet with thickening of the toenails resulting from the slowness of nail growth are common signs of arterial insufficiency. As ischemia becomes more advanced, the skin becomes shiny, scaly, and "skeletonized" from atrophy of the skin, subcutaneous tissue, and muscle.

Test areas where ischemia is suspected by blanching with finger pressure; a delay in the return of normal color (compared with the unaffected extremity) implies reduced perfusion. Buerger sign provides reliable evidence of severe advanced ischemia. With the patient supine, the legs are elevated to 45 degrees to bring the feet more than 12 inches above the right atrium, and any pallor of the feet is noted. If the color does not change, the patient dorsiflexes the feet five or six times; pallor induced by exercise may also connote inadequate arterial flow. The patient is then moved to the sitting position with the feet hanging down. Within 10 to 15 seconds, color should return, and the veins should fill. Typically in the ischemic foot, the first return of color is cyanosis, transitioning to bright red as reactive hyperemia occurs. If the veins require more than 20 seconds to become distended, advanced ischemia is present. With severely restricted arterial inflow and chronic dilation of the peripheral vascular bed, the foot turns pale on elevation and intensely hyperemic after 1 minute of dependency. Localized pallor or cyanosis associated with poor capillary filling is usually a prelude to ischemic gangrene or ulceration.

Doppler ultrasonography should be used in patients with questionable or absent pulses. The ankle-brachial index (ABI) is made by comparing the systolic blood pressure at the level of the ankle with the brachial systolic pressure. Ankle systolic pressure can be accurately measured with a Doppler probe placed over the dorsalis pedis or posterior tibial artery. This pressure is normally 90% or more of the brachial systolic pressure; with mild arterial insufficiency, it is between 70% and 90%; with moderate insufficiency, between 50% and 70%; and with severe insufficiency, less than 50%.

The Allen test is helpful in assessing the patency of the radial or ulnar artery distal to the wrist. The patient initially opens and closes the hand and then clenches the fist to expel as much blood from the hand as possible; the examiner then compresses the radial and ulnar arteries. When the patient opens the fist, the hand is pale. The examiner then releases pressure from the radial artery but maintains it on the ulnar artery. If the radial artery is patent, the hand becomes pink rapidly; occluded, the hand remains pale. The maneuver is repeated maintaining pressure on the radial artery, releasing the ulnar artery. A comparison can be made with the opposite hand.

Inflammation

Inflammatory vascular disease manifests primarily as skin involvement. Skin lesions typically appear as palpable purpura; other cutaneous manifestations of vasculitis include macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. Skin lesions may be pruritic or painful, with a burning or stinging sensation. Lesions are common in dependent areas: lower extremities in ambulatory patients or sacral areas in bedridden patients. Edema and hyperpigmentation occur in areas of recurrent or chronic lesions.

Vasospasm

Vasospastic disorders cause a sharp border between ischemic and normal tissue. Raynaud disease is characterized by intermittent attacks of triphasic color changes: pallor, cyanosis, and then rubor.[9] The most

important element is pallor, and during which, the digits turn pale. Attacks last 15 to 60 minutes, and rewarming the hands restores normal color and sensation. Color changes do not occur above the metacarpophalangeal joints and rarely involve the thumb.

Livedo reticularis causes persistent cyanotic mottling of the skin with a typical "fishnet" appearance and may involve all parts of the extremities and trunk. Acrocyanosis, the least common vasospastic disorder, causes persistent, painless, diffuse cyanosis of the fingers, hands, toes, and feet. Cyanosis intensifies with exposure to cold and decreases with warming. The involved parts are cold, exhibit excessive perspiration, and have normal arterial pulses.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis related to peripheral arteriovascular diseases is extensive, requiring consideration of dermatologic, neurologic, neurosurgical, orthopedic, cardiac, malignant, diabetic, infectious, and other unrelated diagnoses. The differential diagnosis for specific arteriovascular diseases is reviewed in detail in the following sections.

DIAGNOSTIC TESTING

An accurate diagnosis of peripheral arterial occlusive disease can be achieved in most patients by careful history and physical examination supplemented by bedside and radiographic testing.

Noninvasive Assessment

Doppler ultrasonography measures blood flow velocity, detecting the frequency shift of sound waves reflected from red blood cells moving toward and away from the transducer. Doppler waveform analysis detects occlusive disease but is less accurate in determining the exact location.

Ultrasound is useful in detecting and evaluating atherosclerotic plaques, mural thrombi, and in sizing aneurysms of the abdominal aorta, iliac, femoral, and popliteal arteries.[10] B-mode ultrasonography is noninvasive, painless, less expensive than other modalities, and universally available. It is the diagnostic procedure of choice for the initial evaluation of the size of peripheral artery aneurysms. Bedside ultrasound can lead to rapid diagnosis of life-threatening conditions and reduce the number of delayed or invasive diagnostic procedures.[11] B-mode duplex ultrasonography combines B-mode ultrasonography images and sophisticated online computer analysis of Doppler waveforms to allow simultaneous acquisition of both the image of a vascular structure and the characteristics of blood flow velocity within it. Duplex scanning permits noninvasive diagnosis of peripheral vascular, cerebrovascular, and venous disease.

Color imaging of blood flow combined with duplex scanning is known as *color-coded Doppler, Doppler angiography*, or *angiodynography.* The procedure of choice for most conditions, it allows noninvasive and accurate detection of atherosclerotic plaques and stenoses, their effect on intraluminal blood flow, and the presence of venous thrombosis.

Contrast Arteriography

Angiography is the definitive test of abnormal peripheral artery anatomy. The risk/benefit ratio of this procedure should be considered. Contrast media have direct toxic effects on vascular endothelium and can cause severe idiosyncratic and allergic reactions. The risk of acute kidney injury with contrast media is debated, but it may worsen renal function in patients with a preexisting decrement in the glomerular filtration rate. Catheter-related complications, including embolization, catheter breakage, and vascular disruption, vary with operator skill and anatomic location but average 0.5%. Overall mortality rate from angiography is 0.03%.[12] Emergency angiography may be necessary in the following circumstances: (1) acute arterial embolus or thrombosis if the clinical diagnosis is uncertain, (2) consideration of emergency vascular bypass grafting, and (3) characterization of vascular abnormality before emergency surgical correction. Otherwise, traditional angiography has largely been replaced by computed tomography angiography.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography angiography (CTA) is the most useful test for evaluating the abdominal aorta.[13] In the peripheral arteriovascular system, CTA has replaced invasive arteriography as the diagnostic procedure of choice for assessing peripheral arterial occlusive disease and is also useful for atherosclerotic, infected, and false aneurysms and the cerebral circulation. Magnetic resonance imaging (MRI) with angiography (magnetic resonance angiography) and has been beneficial in delineating cerebrovascular problems (see Chapter 101); use has expanded in the evaluation of peripheral vascular disease. MRI detects changes in tissues' relaxation variables before obvious structural changes, uniquely differentiating blood, thrombus, fat, and fibrosis.

MANAGEMENT

Noninvasive Therapy

Acute Anticoagulation with Heparin

For acute arterial embolism, acute arterial thrombosis, and subclavian vein thrombosis, heparin is indicated at standard intravenous doses (80 units/kg bolus, followed by a maintenance infusion of 18 units/kg/hr). Heparin minimizes clot propagation, which can intensify limb ischemia and jeopardize tissues. Relative contraindications include recent neurosurgery (especially within 2 weeks), major surgery within 48 hours, childbirth within 24 hours, a known bleeding diathesis, thrombocytopenia, a potentially hemorrhagic lesion, and active bleeding.

Fibrinolytic Therapy

Low-dose intra-arterial fibrinolytic therapy is increasingly used for acute arterial occlusion. Patients with limb-threatening ischemia are usually not candidates because they cannot tolerate the time to achieve clot lysis with this approach (6 to 72 hours) without risk of tissue or limb loss. Fibrinolytic therapy is reserved for patients with in situ thrombosis and non-limb-threatening ischemia.

Intra-arterial fibrinolytic agents induce clot lysis in small, distal runoff vessels, decreasing outflow resistance and enabling the native artery to remain open longer. Fibrinolysis often uncovers a critical stenosis that, untreated, may lead to recurrent thrombosis. After successful fibrinolytic therapy, most patients require secondary bypass grafting or angioplasty. Streptokinase, urokinase, and tissue plasminogen activator have all been used successfully. Intravenous administration of a fibrinolytic agent is less effective than direct administration into the clot. Clots more than 30 days old are less likely to achieve successful lysis.

Invasive Therapy

Fogarty Catheter Thrombectomy

Patients with limb-threatening ischemia from embolism should undergo emergency Fogarty catheter embolectomy.[14] Patients with limb-threatening ischemia from in situ thrombosis require direct or Fogarty catheter thrombectomy and vascular bypass grafting.

Thrombectomy alone often fails because of recurrent thrombosis. Patients who cannot be bypassed, have irreversible ischemia, or are too ill to tolerate revascularization are treated with primary amputation. The Fogarty catheter is most frequently used for iliac, femoral, and popliteal embolectomy, often with only local anesthesia. Aortic saddle embolus is removed by sequentially passing the Fogarty catheter through bilateral common femoral arteriotomies. Newly formed in situ thrombosis may often be successfully removed with the Fogarty catheter. An older thrombus adheres more firmly to the damaged vessel wall, requiring direct surgical thrombectomy. The Fogarty catheter is not used in the venous system because of valves.

A patient with non-limb-threatening embolism is also treated with Fogarty catheter embolectomy. Non-limb-threatening in situ thrombosis is often aggravated by emergency surgical intervention and is best managed nonoperatively with emergent systemic anticoagulation and consideration of intra-arterial fibrinolytic therapy (Fig. 73.1).

Peripheral Percutaneous Transluminal Angioplasty

The initial success and long-term patency achieved with angioplasty depend on the location of the lesion and the extent of atheromatous disease. Proximal larger arteries (e.g., iliac, femoropopliteal) have the best initial and long-term results. Discrete stenotic lesions (<5 cm) have better long-term patency rates than vessels with diffuse involvement. Balloon angioplasty is the accepted treatment for isolated stenoses in the renal, iliac, and superficial femoral vessels.

Transluminal angioplasty with intravascular stent placement is used in more distal vessels, including the popliteal and tibial circulation, in cases of more diffuse lesions, and for patients who are prohibitive surgical risks, although its value continues to be assessed.[15] Recanalization devices include the percutaneous atherectomy catheter, percutaneous angioscope, hot-tip laser, excimer laser, and high-speed rotating wire and drill.

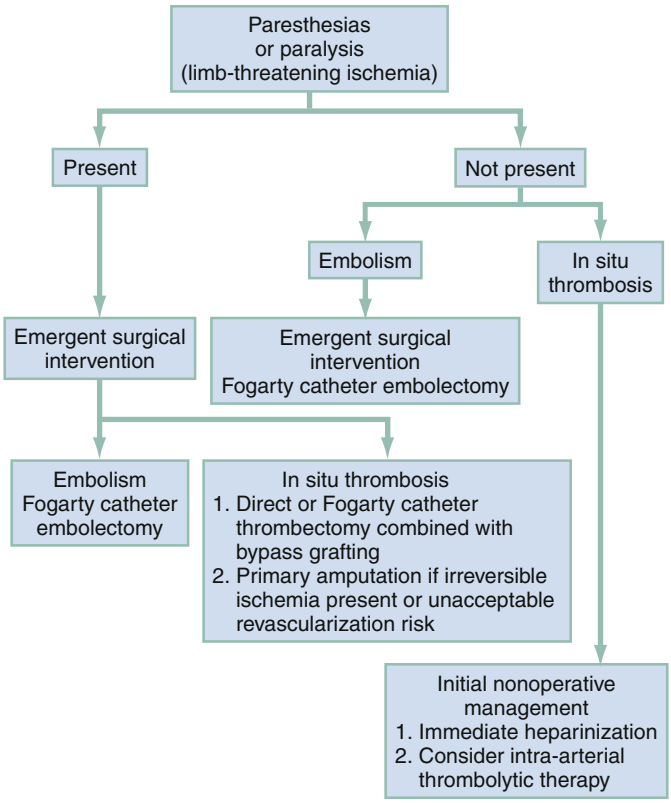

Fig. 73.1 Clinical presentation and management of acute arterial occlusion.

Grafting

Vascular grafting is associated with a variety of complications that can be diagnosed in the ED. Autogenous vein grafts (usually a reversed greater saphenous vein) provide excellent long-term patency for small arteries. They may develop atherosclerosis, which can lead to graft stenosis and thrombosis. False aneurysms can form along the suture line.

Polytetrafluoroethylene (Teflon) prosthetic grafts are used in medium and large arteries impossible to bridge with smaller vein grafts. Prosthetic grafts have higher rates of thrombosis than venous grafts. Distal emboli result from the poor fixation of luminal fibrin. Prosthetic grafts not adequately covered by viable tissue can erode into adjacent structures and hollow viscera. Prosthetic graft infection, a devastating complication, necessitates the removal of the entire graft.

Vascular grafts can be used to bypass arterial occlusions or reconstruct a diseased arterial bifurcation. They may also be interposed between sections of resected artery. The most common complications of both prosthetic and vein grafts are thrombosis or the development of a false aneurysm at one or more suture lines. Bypass grafting is most often used as palliative treatment for symptoms of atherosclerotic occlusive disease. Patients with localized unilateral stenosis may have comparable rates of success from angioplasty with or without stent placement.[16]

Patients with calf claudication from superficial femoral or popliteal occlusive disease can slow progression if they stop smoking and maintain an active exercise regimen. Patients who have progression of disease, significant rest pain, or tissue loss require surgical revascularization.

Hyperbaric Therapy

Scant objective evidence indicates that hyperbaric therapy alters the long-term course of chronic obliterative vascular disorders, presumably by accelerating the formation of fine vessels. More success has been achieved with healing chronic diabetic ischemic ulcers and salvaging ischemic skin grafts and flaps.[17] Referral to a hyperbaric unit for chronic therapy should be made by the patient's primary physician or vascular surgeon and not in the ED.

Disposition

Disposition of most patients with a suspected or confirmed peripheral arteriovascular diagnosis should be made in consultation with a vascular surgeon.

SPECIFIC ARTERIOVASCULAR DISEASES

Diseases of Chronic Arterial Insufficiency

Arteriosclerosis Obliterans

Arteriosclerosis obliterans (atherosclerotic occlusive disease, chronic occlusive arterial disease, obliterative arteriosclerosis) is the peripheral arterial presentation of atherosclerosis. Most often, arteriosclerosis obliterans affects the lower abdominal aorta, the iliac arteries, and the arteries supplying the lower extremities. Upper extremity manifestations are rare.

Arteriosclerosis obliterans is responsible for 95% of cases of chronic occlusive arterial disease. It is most common in persons older than 50 years, but as many as 19% of cases occur in patients 30 to 49 years old. Men are affected more often than women (5:1 to 10:1). Approximately one-third of patients with arteriosclerosis obliterans have coexistent coronary artery disease. The incidence of diabetes mellitus is 20% to 30%.[18]

Risk factors for arteriosclerosis obliterans include cigarette smoking, hyperlipidemia, and hypertension. Of patients with arteriosclerosis obliterans, 70% to 90% are smokers when first examined, 75% have hyperlipidemia, and 30% have hypertension.[18]

Clinical Features

History.. Acute arterial occlusion from embolism, thrombosis, or trauma is ruled out primarily by history. Chronic arterial insufficiency causes two characteristic types of pain: intermittent claudication and ischemic pain at rest. The location of arterial occlusion determines the location of claudication. Femoral and popliteal disease result in calf claudication, typically a cramping pain, reliably reproduced by the same degree of exercise and completely relieved by rest (usually 1 to 5 minutes). Aortoiliac occlusive disease causes claudication in the buttocks and hips, as well as the calves. The calf pain in aortoiliac disease is generally more severe than the buttock and thigh pain, which is more often described as an aching, discomfort, or weakness. Some patients do not have pain, noting only that the thigh or hip "gives out" with exercise. Bilateral hip or thigh pain indicate the possibility of aortoiliac occlusive disease. Aortoiliac occlusive disease severe enough to produce bilateral claudication is almost always associated with impotence in men (Leriche syndrome).

Chronic arterial insufficiency may progress to ischemic pain occurring at rest. Rest pain often begins in the feet and typically involves the foot distal to the metatarsals, awakening the patient from sleep. Ischemic rest pain is a severe, unrelenting pain aggravated by elevation and unrelieved by analgesics. Patients have prompt relief with any activity involving a standing position. Patients may sleep in a chair or with the leg dangling over the bed.

Physical Exam.. Atheromatous emboli from proximal ulcerated plaques or aneurysms cause small scattered ischemic lesions in the toes, feet, or legs, causing blue toe syndrome (Fig. 73.2). Peripheral pulses are present.

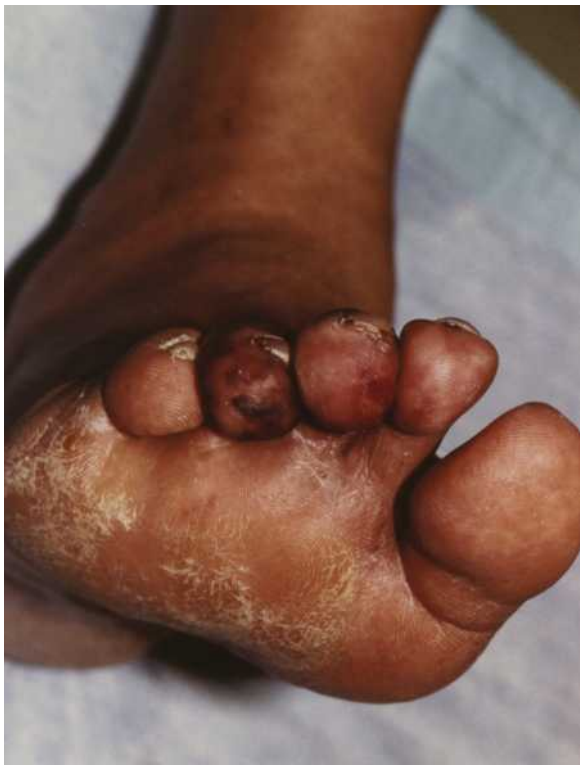

Fig. 73.2 Clinical presentation of atheromatous emboli, or blue toe syndrome. (Courtesy Gary R. Seabrook, MD.)

Approximately 5% of lower extremity ulcerations are caused by arterial insufficiency.[19] These are usually located distal to the ankle, typically at the terminal portion of the digits, around the nail beds, or between the toes, caused by friction of one toe on another. Less common locations include the metatarsal heads, heel, and malleoli. Arterial insufficiency ulcers are painful, but pain improves when the extremity is in a dependent position. They are associated with evidence of coexistent chronic arterial insufficiency (absence of hair growth on the dorsum of the feet, skin atrophy, absent pulses, and nail deformities). Ulcers are initially small, shallow, and dry. The base is gray, yellow, or black, with minimal or no granulation tissue. The rim of the ulcer is sharp and indolent, showing no signs of cellular proliferation or epithelialization.

Differential Diagnosis.. Exercise-induced claudication should be distinguished from nocturnal muscle cramps frequently seen in older patients. Aortoiliac occlusive disease can be differentiated from osteoarthritis of the hip, which tends to be more variable from day to day, is not relieved completely with rest, and is not reliably reproduced by the same amount of exercise. Pseudoclaudication from cauda equina syndrome is caused by narrowing of the lumbar canal from spondylosis, intervertebral disk disease, or spinal cord tumor. The symptoms mimic intermittent claudication but are less closely related to exercise and rest than true claudication.

The cause of lower extremity ulcers should be carefully determined. About 90% of lower extremity ulcers are caused by chronic venous insufficiency.[19] These occur proximal to or in the region of the ankle, especially near the medial malleolus. Venous stasis ulcers are mildly painful and improve with elevation of the extremity. Evidence of long-standing chronic venous insufficiency, including edema, prominent superficial veins, and stasis dermatitis, is present. Ulcers are moderate in size, with a weeping base and extensive granulation tissue. Rapidly developing ulcers are more suggestive of venous insufficiency.

Most of the remaining lower extremity ulcers are caused by diabetic neuropathy, alone or with arterial insufficiency.[19] The location reflects sites of repeated trauma, including the toes, heels, and plantar surface of the feet, especially the metatarsal heads. Neurotrophic ulcers are painless. Patients may have evidence of coexistent peripheral arterial insufficiency. The ulcers are deep and penetrating, often with suppurative drainage caused by an underlying infection or chronic osteomyelitis. Neurotrophic ulcers are usually surrounded by a rim of thick callus.

Hypertensive ulcers are rare and reflect long-standing, uncontrolled hypertension. These ulcers are typically near the lateral malleolus and start as painful, reddish-blue areas of infarcted skin. A hemorrhagic bleb develops and then breaks down into a superficial ulcer, which can reach a size of 5 to 10 cm. The ischemic ulcer has sharply demarcated borders, little granulation tissue, and minimal drainage. The pain is the most severe of all lower extremity ulcers.

Multiple ischemic ulcerations above and below the ankle suggest vasculitis or atheromatous embolization. Ulcers with regular edges in unusual locations may be factitial or may result from subcutaneous injection of illicit drugs. Thickened, rolled, and elevated edges with a central depression containing granulation tissue are characteristic of malignant ulcers.

Management.. The first step is to identify patients whose symptoms are the sole result of arteriosclerosis obliterans without coexistent thromboembolic disease. Treatment for symptomatic patients depends on whether patients have functional ischemia or limb-threatening ischemia.[20] Limb-threatening ischemia constitutes a surgical emergency. Computed tomography (CT) angiography should be arranged to identify sufficiently localized disease to permit emergency bypass grafting.[20] Patients with functional ischemia should have outpatient

arrangements for elective invasive or noninvasive vascular testing to determine treatment options.

Ischemic ulcers or skin lesions should be cultured in the emergency department (ED) and systemic antibiotics initiated to cover skin organisms if infection is present. Radiographs of underlying bones should be acquired when osteomyelitis is suspected. Patients with ischemic rest pain require hospitalization even if they are not surgical candidates. Bed rest, a warm environment, and maintenance of the limb in a dependent position usually relieve pain.

Buerger Disease (Thromboangiitis Obliterans)

Principles. First described by Buerger in 1908, thromboangiitis obliterans is an idiopathic inflammatory occlusive disease primarily involving the medium-sized and small arteries of the hands and feet.[21] Patients are usually men aged 20 to 40 years old who use tobacco, although recent reports indicate an increasing frequency of this disease in women. In the United States, the incidence is 20 per 100,000.[22] The exact pathogenesis is unknown, but virtually all patients are smokers.

Thromboangiitis obliterans is characterized by segmental acute and chronic inflammation in the smaller arteries of both upper and lower extremities. The initial arterial inflammatory process progresses to affect the adjacent veins and nerves, often leading to associated venous thrombosis and progressive fibrous encasement of these structures. These are painful, tender, or dark nodules over a peripheral artery with either a reduced or an absent pulse (phlebitis migrans).

Clinical Features. Clinical criteria for Buerger disease include (1) a history of smoking, (2) onset before the age of 50, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) absence of atherosclerotic risk factors other than smoking. A characteristic symptom of Buerger disease is foot or instep claudication caused by infrapopliteal arterial occlusion. Intense rubor of the affected extremity, particularly with dependency, is also characteristic. Foot pulses may be absent in the presence of normal femoral and popliteal pulses. Involvement of the hands is often bilateral and symmetrical, leading to the development of hand claudication or fingertip ulcers. Phlebitis migrans occurs early in the disease. Approximately 50% of patients experience Raynaud-type triphasic color response to cold. In the upper extremities, the digital arteries are usually more involved than the radial or ulnar arteries.[22]

Differential Diagnosis. Arteriosclerosis obliterans is most likely in patients older than 50 years old who have signs of peripheral ischemia. In young women, autoimmune diseases, such as scleroderma or systemic lupus erythematosus, should be considered.[22]

Diagnostic Testing. Adherence to diagnostic clinical criteria should suffice for ED diagnosis of Buerger disease. Noninvasive vascular laboratory testing confirms the diagnosis and extent of involvement. Rarely required, CTA demonstrates multiple segmental occlusions.

Management. Permanent complete abstinence from tobacco is the only effective treatment for Buerger disease. If a patient does not completely stop smoking, alternating periods of quiescence are followed by exacerbations of severe arterial insufficiency. Patients who quit smoking have a benign clinical course. Despite this, many individuals who have Buerger disease continue to smoke, incurring severe pain at rest, tissue loss, and eventually amputation.

With early symptoms without the threat of tissue loss, patient education and follow-up with a vascular surgeon are appropriate. Vascular surgery treatment options are varied for patients with severe symptoms or threatened tissue loss. Intractable pain can be controlled with epidural anesthesia. Intra-arterial or intravenous prostaglandin E_1 and antithrombotic agents, including aspirin and heparin, have been used successfully.[22] Patients with large-vessel arterial occlusion may benefit from arterial reconstruction. Sympathectomy is a potential treatment in advanced cases for cutaneous ulceration or relief of rest pain.[23] Because patients with Buerger disease have good healing, intensive conservative treatment is usually successful in avoiding amputation.

Diseases of Acute Arterial Occlusion

Arterial Embolism

Despite advances, acute arterial embolus continues to cause substantial morbidity and mortality. Approximately 50% of acute arterial occlusions are caused by arterial embolism, and the incidence is increasing. The other 50% are caused by in situ thrombosis.[1]

Clinical Features

History. Patients with acute arterial occlusion usually exhibit some variant of the five Ps: pain, pallor, pulselessness, paresthesias, and paralysis. Paresthesias and paralysis indicate limb-threatening ischemia requiring emergency surgical intervention regardless of the cause. A history of claudication is common with in situ thrombosis and rare with arterial embolism. Because acute arterial embolism usually occurs in patients without significant peripheral atherosclerosis or well-developed collateral circulation, it usually manifests as sudden limb-threatening ischemia. Patients describe a sensation of the leg's being "struck" by a severe shocking pain. Often, the patient has to sit or fall to the ground during the sudden event.

Physical Examination. The physical examination can help differentiate arterial embolism from in situ thrombosis. Sudden loss of a pulse is the hallmark of arterial embolism but may be difficult to recognize if prior pulse status is unknown or is abnormal because of atherosclerosis. A bounding pulse may be felt initially at the location of an embolus from transmitted pulsations through the fresh clot. Patients with arterial embolism have few physical findings suggestive of long-standing peripheral vascular disease. Tenderness to palpation may occur at the site of an embolic occlusion.

If arterial embolism is suspected, the physical examination should be directed toward identifying its source (a left ventricular mural thrombus [prior myocardial infarction] or a left atrial thrombus [mitral valve disease]). Coexistent atrial fibrillation is common. The limb distal to an embolic occlusion is initially pale. Because of the absence of blood in the sub-capillary venules, demarcation between ischemic and nonischemic tissue is sharp. With time, cyanosis appears from desaturation of blood with continued ongoing ischemia. Paresthesia or paralysis indicates limb-threatening ischemia. The presence of sensitivity to light touch is the best guide to the viability of the tissue. Complete anesthesia demands emergency surgical intervention. Paralysis represents severe muscle and neural ischemia, which may be irreversible. Involuntary muscle contracture with "woody" hardness represents irreversible ischemia.

Differential Diagnosis. Phlegmasia cerulea dolens is a massive iliofemoral deep venous thrombosis. The initial symptom is the acute onset of a swollen and painful leg. As swelling continues, secondary arterial insufficiency with associated pallor (phlegmasia cerulea albens) occurs. Early in acute arterial embolism, leg swelling is usually absent. Acute embolism produces a sharply demarcated pallor; phlegmasia cerulea dolens causes a cyanotic-appearing leg.

Aortic dissection may involve the arteries of the upper or lower extremity and may mimic acute embolus. Severe pain, the presence of aortic insufficiency, and involvement at multiple sites suggest dissection. Neurologic syndromes (e.g., transverse myelitis, spinal subarachnoid hemorrhage, ruptured intervertebral disk) may produce sudden onset of unilateral or bilateral lower extremity weakness or sensory loss that mimics an acute aortic saddle occlusion. Cold, blue extremities may result from low-output states, such as hypovolemia, decreased

cardiac output, and dehydration in patients with long-standing atherosclerotic disease.

Management. Acute arterial embolism is a surgical emergency. The likelihood of limb salvage decreases after 4 to 6 hours. On the basis of clinical diagnosis alone, full doses of intravenous heparin (80 units/kg bolus, followed by a maintenance infusion of 18 units/kg/hr) should be administered promptly to minimize clot propagation. Patients whose clinical findings clearly indicate an acute arterial embolism should undergo urgent Fogarty catheter embolectomy without prior angiography. In these patients, preoperative ultrasonography and angiography are rarely useful diagnostically and prolong the limb's ischemic time.

If the differentiation of acute embolism and in situ thrombosis is uncertain, CT angiography is usually diagnostic. Patients with acute emboli generally show minimal signs of atherosclerosis, occlusion at the site of an arterial bifurcation, sharply demarcated cutoffs, and lack of flow distal to the occlusion. In patients with in situ thrombosis, arteriography shows diffuse atherosclerosis, occlusion at sites other than arterial bifurcations, a tapered irregular cutoff, and well-developed collateral vessels (Table 73.1).

Intra-arterial thrombolytic therapy for acute embolism remains investigational. Present limb-threatening ischemia precludes consideration of treatment with thrombolytic therapy in most patients. Potential risks of thrombolytic therapy in arterial embolism patients with non-limb-threatening ischemia include partial clot lysis with distal embolization or recurrent embolic events from the primary source of the initial embolus.[24]

Atheroembolism (Blue Toe Syndrome)

Atheroemboli are microemboli consisting of cholesterol, calcium, and hemorrhagic debris that break off from proximal atherosclerotic plaques or aneurysms and lodge in distal end arteries. In the central nervous system, atheroembolism causes transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli are found in the lower extremities with cool, painful cyanotic toes in the presence of palpable distal pulses (Fig. 73.2).

Clinical Features. The typical presentation of atheroembolism is the sudden onset of a small, cyanotic, and tender area on the foot, typically the toe.[25] If bilateral, the distribution is not symmetrical. Posterior tibial and dorsalis pedis pulses are present. Physical examination should focus on a proximal source, such as an atherosclerotic aneurysm in the aorta or iliac, femoral, or popliteal artery.

TABLE 73.1 Differentiation of Embolus From Thrombosis

Clinical Findings	Embolus	Thrombosis
Identifiable source for embolus	Usual, particularly atrial fibrillation	Less common
History of claudication	Rare	Common
Physical findings suggestive of occlusive disease	Few; proximal and contralateral limb pulses normal	Often present; proximal or contralateral limb pulses diminished or absent
Demarcation of ischemia	Sharp	Diffuse
Arteriography	Minimal atherosclerosis; sharp cutoff; few collaterals	Diffuse atherosclerosis; tapered, irregular cutoff; well-developed collaterals

From Brewster DC, Chin AK, Fogarty TJ: Vascular surgery. Philadelphia, 1990, WB Saunders.

Differential Diagnosis. A variety of conditions can mimic blue toe syndrome. Acrocyanosis is painless, has a symmetrical distribution, and is located in the hands, nose, and lips. Poor peripheral perfusion from low cardiac output should be considered. Vasculitis typically causes palpable purpuric lesions and constitutional symptoms of low-grade fever and weight loss. Previous frostbite may leave the extremities sensitive to cold. Local injury to the diabetic foot is easily differentiated.

Management. Treatment is directed toward identifying and removing the proximal source of atheroembolism. CT angiography is the diagnostic procedure of choice for determining the source of emboli. If the source is an aortic aneurysm, vascular surgery should be consulted for consideration of an operative repair. Stenotic lesions in the iliac or femoral arteries can be treated with local endarterectomy, vascular bypass, or angioplasty.[15] Medical management with aspirin, dipyridamole, warfarin sodium (Coumadin), or steroids have variable results and are not routinely recommended.

Arterial Thrombosis

Approximately 50% of acute arterial occlusions are caused by in situ thrombosis.[1] Acute arterial thrombosis is almost always superimposed on a complicated atherosclerotic lesion but can be caused by vasculitis or trauma. With limb-threatening ischemia, CT angiography can be used to evaluate the feasibility of emergency bypass grafting. In non–limb-threatening ischemia, angiography may be required to distinguish acute embolism from thrombosis (see Table 73.1).

Physical Exam

Physical findings of in situ thrombosis are often accompanied by evidence of atherosclerotic occlusive disease. Proximal or contralateral limb pulses are usually diminished or absent. An embolic source, such as atrial fibrillation, is usually absent. Because of collateral circulation, demarcation of limb ischemia is less well defined in these patients (see Table 73.1).

Carotid, renal, and femoral arteries may have bruits, and there may be an abdominal aortic aneurysm. If occlusion of the upper extremity vessels is suggested, the subclavian artery should be palpitated for thrills and auscultated for bruits in the supraclavicular fossa.

A funduscopic examination may yield evidence of arteriosclerosis or hypertension. Hollenhorst plaques (atheromatous emboli containing cholesterol crystals in the retinal arterioles) may be detected. Roth's spots (round or oval white spots seen near the optic disk) may be present in patients with infective endocarditis.

Management. Heparinization (80 units/kg bolus, followed by a maintenance infusion of 18 units/kg/hr) should be started when the diagnosis is made. Patients with limb-threatening ischemia require emergency direct or Fogarty catheter thrombectomy combined with bypass grafting. Thrombectomy alone often fails due to rethrombosis. Patients who have atherosclerotic disease not amenable to vascular bypass, are too ill to tolerate revascularization, or have irreversible ischemia that require primary amputation.

Patients with non-limb-threatening ischemia are best treated nonoperatively. Endovascular options available to the vascular surgeon include catheter-directed thrombolysis, pharmacomechanical thrombolysis, catheter-directed thrombus aspiration, and percutaneous mechanical thrombectomy, involving a host of different catheters and devices, dependent on the medical condition and preference of the vascular surgeon.

Peripheral Arterial Aneurysms

A true aneurysm is an abnormal localized dilation of the intact vessel wall caused by mural weakness and hemodynamic forces. Aneurysms enlarge at a rate determined by the cause. Atherosclerosis etiologies

progress slowly over years; trauma or infectious causes enlarge over days, weeks, or months. The primary risk of central aneurysms (abdominal aorta, iliac arteries, and visceral arteries) is rupture (see Chapter 84). Peripheral arterial aneurysms rarely rupture; instead, they are complicated by thrombosis or embolism jeopardizing distal tissues.[26]

The etiology of an aneurysm is strongly associated with its anatomic location. Lower extremity aneurysms are most often atherosclerotic. Upper extremity aneurysms are usually caused by local trauma. Visceral aneurysms are from abnormal hemodynamics, atherosclerosis, or infectious causes.

Lower Extremity

Femoral and popliteal artery aneurysms almost always occur in older men with advanced atherosclerosis. Twenty-five percent of patients have distal atheroembolism or thromboembolism; an additional 15% have total aneurysmal occlusion from in situ thrombosis.[26] Popliteal aneurysms are the most common peripheral aneurysms, occurring bilaterally in 60% of patients.[26] Abdominal aortic aneurysm occurs in 80% of patients with bilateral popliteal aneurysms. Most patients have claudication, thromboembolic events, atheroembolic events, or gangrene. With aneurysmal dilation, venous compression and deep venous thrombosis occur. Femoral aneurysms are the second most common peripheral aneurysms and manifest similarly to popliteal aneurysms. Femoral aneurysm dilation can also compress the femoral nerve, producing anterior thigh pain or weakness.

Diagnosis of popliteal and femoral aneurysms is by palpation of a pulsatile mass. Plain radiographs may show unilateral or bilateral calcified aneurysms. Ultrasonography and CT are diagnostic. Arteriography yields definitive diagnosis and involvement of distal vessels. Patients with a lower extremity aneurysm should be evaluated for the presence of other aneurysms.

Asymptomatic patients can undergo elective surgical excision of the aneurysm and end-to-end anastomosis or graft interposition. Simultaneous repair of the coexisting abdominal aorta or contralateral extremity aneurysms combined with vascular bypass is typically done. Patients with limb-threatening thromboembolic events are first treated with Fogarty catheter embolectomy.[26]

Upper Extremity

Atherosclerosis generally spares the upper extremities, so peripheral arterial aneurysms in the upper extremities are rare and localized trauma is the most common cause. The causes of subclavian artery aneurysms are thoracic outlet obstruction, trauma, and, rarely, atherosclerosis. Subclavian aneurysms from atherosclerosis represent severe disease, and 30% to 50% of patients so afflicted also have aortoiliac or other peripheral aneurysms.[27] Symptoms depend on the aneurysm's anatomic location. Patients may have chest, neck, and shoulder pain from acute expansion. Compression of the right recurrent laryngeal nerve can lead to voice change. Compression of the trachea can lead to stridor or other respiratory complaints.

The chest radiograph may reveal a superior mediastinal mass and be confused with a neoplasm. The subclavian artery can be compressed by a complete cervical rib that articulates with the first rib, producing a poststenotic dilation from the proximal subclavian to axillary artery. This syndrome occurs more often in women and in the dominant upper extremity. Cervical ribs occur in 0.6% of the population.[28] Axillary artery aneurysms are caused by blunt trauma from inappropriate and prolonged use of crutches. Humerus fracture or anterior shoulder dislocation are uncommon causes.[27]

Subclavian, subclavian-axillary, and axillary artery aneurysms share complications of thromboembolism, limb-threatening ischemia, neuromuscular and sensory dysfunction from brachial plexus compression, and central nervous system ischemia from retrograde vertebral and right carotid thromboembolism. A systolic bruit and palpable thrill are common.

CT angiography to confirm the diagnosis and determine involvement of distal vessels is the diagnostic procedure of choice. Surgical treatment consists of aneurysm resection, vascular grafting, and reestablishment of arterial continuity.

The rare syndrome of ulnar artery aneurysm (hypothenar hammer syndrome) is associated with occupational trauma in which the heel of the palm is used to hammer, push, or twist objects.[29] Patients are often mechanics, carpenters, or machinists.

The ulnar artery fits snugly into the bony canal at the hypothenar eminence under the hook of the hamate bone. Long-term repetitive damage results in aneurysm formation.[29] The aneurysm may develop a mural thrombus that repeatedly embolizes to the superficial palmar arch or to a digital artery. Symptoms include paresthesias, pain, coolness, and cyanosis, most often in the little and ring fingers, occasionally in the middle and index fingers. The thumb is characteristically spared due to its radial artery blood supply.

Diagnosis is easily made by finding a pulsatile or non-pulsatile tender mass in the hypothenar eminence of the dominant hand. The Allen test may demonstrate occlusion of the ulnar artery. Angiography of the distal vessels is diagnostic. Proximal angiography may rule out the subclavian and axillary arteries as embolic sources. Surgical aneurysm resection is required to reestablish ulnar artery continuity. Adjunctive preoperative fibrinolytic therapy may be helpful.[29]

Viscera

Splenic Artery Aneurysms. Splenic artery aneurysms account for 60% of all visceral arterial aneurysms. They are the only aneurysms that are more common in women, with a female-to-male ratio of 4:1.[30] The cause of splenic artery aneurysms has been attributed to systemic arterial fibrodysplasia, portal hypertension, and increased splenic arteriovenous shunting that occurs in pregnancy.

Splenic artery aneurysms are most often asymptomatic. Symptomatic patients exhibit vague left upper quadrant or epigastric discomfort and occasional radiation of pain to the left shoulder or subscapular area. Because most splenic artery aneurysms are less than 2 cm in diameter, a pulsatile mass is not palpable. Occasionally, a systolic bruit can be heard.

Only 2% of splenic artery aneurysms result in life-threatening rupture.[30] More than 95% of ruptures occur in young women during pregnancy and can be confused with ectopic pregnancy or placental abruption. Splenic artery aneurysms are usually an incidental discovery on the abdominal radiograph as signet ring calcifications in the left upper quadrant. Ultrasonography, CT, and MRI can distinguish aneurysms from other cystic lesions in the left upper quadrant.[30] An angiogram is usually required to confirm the diagnosis. Symptomatic splenic artery aneurysms require urgent operative intervention, particularly in pregnant women or in women of childbearing age. The rate of maternal mortality from rupture during pregnancy is approximately 70%. In asymptomatic patients, transcatheter embolization is an alternative to surgery.[31]

Hepatic Artery Aneurysms. Hepatic artery aneurysms represent 20% of visceral artery aneurysms. The lesions are caused by atherosclerosis, infection (most often as a complication of intravenous drug abuse), major abdominal trauma, and polyarteritis nodosa. Hepatic artery aneurysms affect men twice as often as women and usually occur after 60 years of age.

Most aneurysms remain asymptomatic, but unruptured symptomatic aneurysms generally produce symptoms consistent with

cholecystitis: vague, persistent, right upper quadrant, or epigastric pain radiating to the back. Large aneurysms can cause severe upper abdominal discomfort, similar to pancreatitis. Hepatic artery aneurysms may rupture into the common bile duct, peritoneum, or adjacent hollow viscera, with a mortality rate of 35%.

An abdominal bruit or palpable pulsatile mass is usually not present on physical examination. Aneurysmal calcification may be seen on a plain abdominal radiograph, but the diagnosis can be made reliably by CT angiography. Ultrasonography and CT can detect asymptomatic hepatic artery aneurysms.[30]

Because of the high mortality rate with aneurysmal rupture, an aggressive approach to management is warranted. Surgical resection of the aneurysm is performed in operative candidates. Transarterial catheter occlusion can be used in patients who are high surgical risks.[32]

Superior Mesenteric Artery Aneurysms. Superior mesenteric artery aneurysms are the third most common visceral aneurysms. Nearly 60% are infected aneurysms caused by nonhemolytic streptococci from left-sided bacterial endocarditis. Atherosclerosis and trauma are much less common causes. Patients are usually younger than 50 years old; men and women are affected equally.

Patients generally have intermittent upper abdominal pain consistent with abdominal angina. Fifty percent have a pulsatile abdominal mass on physical examination. The stigmata of subacute bacterial endocarditis may be present. Plain abdominal radiographs may show a calcified aneurysm. Angiography is necessary to confirm the diagnosis. Management of superior mesenteric artery aneurysm should address any underlying infectious process. The surgical approach is difficult, varies with the condition of the patient, the shape of the aneurysm (saccular or fusiform), and the assessment of bowel viability.

Traumatic Aneurysms

Traumatic aneurysm refers to a pseudoaneurysm that follows perforation of the arterial wall with formation of a perivascular hematoma. Chronic traumatic aneurysms may or may not be associated with an arteriovenous fistula. *Pseudoaneurysm* is a synonym for *false aneurysm.* The usual presentation is a pulsatile mass found near the course of an extremity artery, with a history of trauma more than 1 month earlier.[33] The expanding aneurysm may compress associated peripheral nerves. Distal perfusion is usually well maintained, and thromboembolism is rare. A loud systolic and possibly a separate faint diastolic murmur are characteristic. Conventional angiography, digital subtraction arteriography, or CT confirms diagnosis. Surgical excision is indicated as soon as possible to decrease the risk of complications, including rupture, thrombosis, or neurologic dysfunction caused by continued expansion.

Infected Aneurysms

Mycotic Aneurysms. The term *mycotic aneurysm* is a source of confusion because there is no association with fungal disease. Although used to describe any infected aneurysm, it should be reserved for infected aneurysms resulting from bacterial endocarditis, as originally described in 1885 by Osler.[34,35]

Septic emboli from infective endocarditis implant in one of two ways. First, hematogenous seeding of bacteria can occur in non-aneurysmal arteries damaged by preexisting atherosclerosis. Second, septic emboli can become lodged in the vasa vasorum of larger vessels, causing vessel wall ischemia and infection. In smaller vessels, septic emboli tend to lodge at arterial bifurcations, arteriovenous fistulae, or sites of arterial stenosis. Mycotic aneurysms are most common in the aorta, superior mesenteric artery, intracranial, and femoral arteries.

The infecting organism in mycotic aneurysms reflects the bacteriology of infective endocarditis. Viridans streptococci are the most common organisms, although intravenous drug abusers are most often infected by *Staphylococcus aureus.* Patients who have mycotic aneurysms tend to be 30 to 50 years old. The mortality rate is 25% (Table 73.2).[34,35] Infective endocarditis is more completely discussed in Chapter 69.

Atherosclerotic Arteries. Currently, the most common cause of an infected aneurysm is sepsis with hematogenous spread of bacteria, such as *Salmonella, Staphylococcus,* and *Escherichia coli,* to atherosclerotic arteries. Large vessels (especially the aorta) rather than peripheral arteries are the most common site. Patients tend to be older than 50 and have well-established atherosclerosis. Perforation often occurs before diagnosis and carries a mortality rate of 75%.[34]

Preexisting Aneurysms. The incidence of infection in patients with preexisting atherosclerotic aneurysms is estimated at 3% to 4%, and patients with ruptured aneurysms have a higher incidence of positive bacterial culture results than those who have elective surgical treatment of an asymptomatic aneurysm. Gram-positive organisms, especially *Staphylococcus,* predominate (60%). The mortality rate is extremely high (90%) because of aneurysm rupture.[35,36]

Post-Traumatic Pseudoaneurysms. Post-traumatic infected pseudoaneurysms result from invasive hemodynamic monitoring, angiography, and intravenous drug use. The most common artery affected is the femoral because of its involvement in procedural cannulations.

TABLE 73.2 Clinical Characteristics of Infected Aneurysms

	Mycotic Aneurysm	Infection of Atherosclerotic Arteries	Infection of Existing Aneurysm	Post-traumatic Infected False Aneurysm
Cause	Endocarditis	Bacteremia	Bacteremia	Drug addiction Trauma
Age (years)	30–50	>50	>50	<30
Incidence	Rare	Most common	Unusual	Very common
Location	Aorta Visceral Intracranial Peripheral	Atherosclerotic Aortoiliac Intimal defects	Infrarenal Aorta	Femoral Carotid
Bacteriology	*Viridans streptococci*	*Salmonella*	*Staphylococcus*	*Staphylococcus aureus*
S. aureus	Others	Others	Polymicrobial	
Mortality	25%	75%	90%	5%

From Wilson SE, Van Wagenen P, Passaro E Jr: Arterial infection. Curr Probl Surg 15:1, 1978.

S. aureus is isolated in 30% to 70% of cases. Because of the more peripheral location and early identification, the mortality rate is low (5%).[36]

The clinical presentation of an infected aneurysm varies with anatomic location and underlying pathophysiologic process. Infected abdominal aneurysms are often misdiagnosed. Onset is usually insidious; low-grade fever may be present for several months. Common findings are fever (75%), back and abdominal pain (33%), and palpable aneurysm (53%). More peripheral aneurysms, especially infected femoral pseudoaneurysms, are characterized by a tender groin mass, some manifestation of sepsis, or bleeding.[37] Almost all are easily palpable. Although rare, fungal infections should be considered in patients who are chronically immunosuppressed, have been treated recently for disseminated fungal disease, or have diabetes mellitus.[37,38]

Positive blood cultures in a patient with a preexisting aneurysm should prompt treatment as an infected aneurysm until disproven. Bacteremia often is continuous, and blood cultures are positive in approximately 70% of cases, but negative blood cultures do not rule out this diagnosis. CT angiography should be performed when an infected aneurysm is suggested.[39] Indium-111-labeled white blood cells can confirm or rule out infected aneurysms.[36]

Treatment includes both antibiotics and surgical repair. Antibiotic therapy is usually continued for at least 6 to 8 weeks, although some physicians advocate lifelong treatment after successful surgical repair.[40] The most important intervention is timely repair.[37,38] Infected true and false peripheral aneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes is attempted; there is a high risk of prosthetic graft infection. Without surgery, aneurysm rupture with exsanguinating hemorrhage is inevitable.[36]

Vasospastic Disorders

Vasospastic disorders are characterized by an abnormal vasomotor response in the distal small arteries. Blood flow in the peripheral circulation is controlled by local, autonomic, and humoral mechanisms.[9] The cause of the increased vasospastic response is currently unknown.

Raynaud disease is the most common vasospastic disorder and occurs five times more often in women than in men. By definition, cases of Raynaud disease have no evidence of an underlying cause. The diagnosis is correct in 95% of cases that meet these criteria: (1) episodes are precipitated by cold or emotion; (2) symptoms are bilateral; (3) gangrene is absent or is minimal and confined to the skin; (4) no disease or condition that could cause a secondary Raynaud phenomenon is present; and (5) symptoms have been occurring for at least 2 years.[41]

The classic Raynaud attack is triphasic: the fingers become pale, then blue, and finally red. Initially, a complete closure of the palmar and digital arteries (and possibly arterioles) occurs, producing cessation of capillary perfusion. Slight relaxation of arterial spasm then occurs, with a slight return of rapidly deoxygenating blood into the dilated capillary bed, producing cyanosis. Arterial spasm then fully resolves, and reactive hyperemia produces a red extremity. Attacks are often precipitated by cold and emotional stress. Raynaud disease usually has a benign course. True histologic changes within the vessel wall are absent. Reassurance, education, and primary care follow-up are the only treatment necessary for true Raynaud's disease.

Raynaud phenomenon is the term given to Raynaud disease when there is an identifiable underlying causative disorder. Connective tissue disorders, including scleroderma, rheumatoid arthritis, and systemic lupus erythematosus, have the highest association with Raynaud phenomenon. Treatment should be directed toward identifying the underlying disorder and minimizing threatened tissue loss if present.[41]

Benign livedo reticularis is caused by spasms of the dermal arterioles. It is most common when skin is exposed to a cool environment, is never associated with histologic vascular abnormality, and quickly resolves when the exposed skin is covered or the environment is warmed. Other conditions, similar to the causes of Raynaud phenomenon, can have secondary livedo reticularis along with other peripheral vascular disease manifestations.[42]

Acrocyanosis is the least common of the vasospastic disorders and is characterized by persistent, painless, symmetrical cyanosis of the fingers, hands, lips, nose, and less often the feet. The disease is benign, unassociated with vascular abnormality or underlying disorder. Pain, trophic skin changes, and ulceration do not occur. It is more common in women, intensified by exposure to cold, and decreases with warming. The diagnosis is made by the bilateral and persistent nature of the findings, localized to the hands or feet in the presence of normal arterial pulses. The involved extremities are nearly always cold, and excessive perspiration is common. Except for reassurance and protection from cold, treatment is unnecessary.[42]

Primary erythromelalgia is a rare syndrome of paroxysmal vasodilation with burning pain, increased skin temperature, and redness of the feet and less often the hands. Secondary erythromelalgia can occur with underlying disease processes, most often systemic lupus erythematosus, myeloproliferative disorders, hypertension, venous insufficiency, or diabetes mellitus. Erythromelalgia is as common in children as adults, but in children, it is less likely to be associated with underlying systemic illness. Attacks are not triggered by cold and occur in modest ambient temperatures. Skin temperature of the involved digits is high compared with the patient's core temperature. Symptoms may remain mild for years or may become disabling. Tissue loss and trophic skin changes do not occur. Although elevation of the extremities, cold compresses, or immersion in ice can provide temporary relief, no consistently effective treatment has been found for the multiple, often daily episodes of pain that occur.[42]

Thoracic Outlet Syndrome

Thoracic outlet syndrome involves compression of the brachial plexus, subclavian vein, or subclavian artery at the superior aperture of the thorax. The subclavian artery courses over the first rib between the scalenus anticus muscle anteriorly and the scalenus medius muscle posteriorly, when passing under the clavicle to the axilla, where the brachial plexus lies posteriorly and laterally. Thoracic outlet syndromes were previously categorized by cause as scalenus anticus, costoclavicular, hyperabduction, cervical rib, and first thoracic rib syndromes. They are now most easily divided into three types—neurologic, venous, and arterial—depending on the predominant symptoms.

Compression of the brachial plexus causes the neurologic type of thoracic outlet syndrome and accounts for approximately 95% of all cases.[43] Symptoms begin between the ages of 20 and 50 years old, with women predominating at a ratio of about 3:1. Compression or thrombosis of the subclavian vein constitutes the venous type of thoracic outlet syndrome and is responsible for 4% of all cases. It occurs most often in men 20 to 35 years old. The arterial type of thoracic outlet syndrome is rare, occurring in approximately 1% of all cases, but is potentially the most serious of the three types. Fig. 73.3 demonstrates the relationship between anatomic abnormalities and neurovascular compression.

There are four basic concepts of thoracic outlet syndromes[44]: (1) patients who have a thoracic outlet syndrome develop an anatomic abnormality, predisposing them to symptoms under certain conditions; (2) brachial plexus compression or irritation constitutes approximately 95% of all thoracic outlet syndrome cases and is rarely caused by compression of the subclavian artery; (3) bedside testing for thoracic outlet syndrome based on positional compression of the

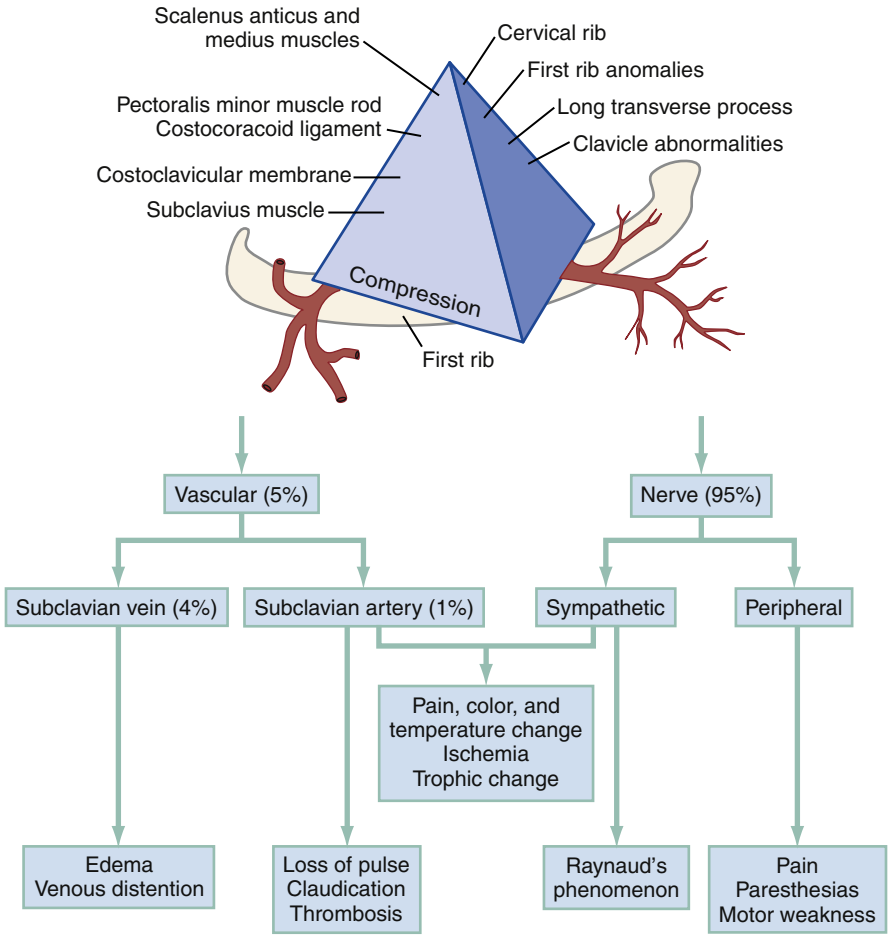

Fig. 73.3 Inter-relationships of muscle, ligament, and bone abnormalities in the thoracic outlet may compress neurovascular structures. (From Urschel HC Jr: Management of thoracic outlet syndrome. N Engl J Med 286:1140, 1972.)

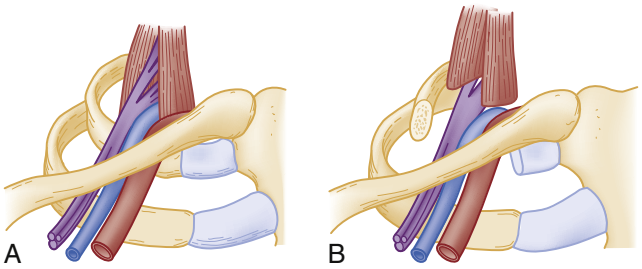

Fig. 73.4 (A) Thoracic outlet compression in costoclavicular space. (B) Decompression of thoracic outlet by resection of the first rib with disarticulation of the costochondral joint. (From Etheredge S, et al: Thoracic outlet syndrome. Am J Surg 138:175, 1979.)

subclavian artery is insensitive and unreliable; and (4) in advanced or refractory cases, the causative anatomic abnormalities are to be surgically corrected.

The neurologic and venous compression type of thoracic outlet syndrome can be associated with any underlying anatomic abnormality. Bony abnormalities (cervical rib, first thoracic rib, or clavicle) are the most common causes of the arterial type of thoracic outlet syndrome (Fig. 73.4A).

Clinical Features

Compression of the brachial plexus most often affects the lower two nerve roots, eighth cervical (C8) and first thoracic (T1), producing pain and paresthesias in the ulnar nerve distribution. The second most common pattern is the upper three nerve roots of the brachial plexus (C5, C6, and C7), with symptoms referable to the neck, ear, upper chest, upper back, and outer arm in the radial nerve distribution. Venous compression progresses to intimal damage and subclavian vein thrombosis, with venous engorgement and swelling of the affected extremity. Persistent subclavian artery compression results in poststenotic aneurysm formation and its sequelae.

Physical Examination. The most reliable test in screening for thoracic outlet syndrome is the elevated arm stress test (EAST).[44] With the patient sitting, the arms are abducted 90 degrees from the thorax and the elbows flexed 90 degrees, with the shoulders braced slightly behind the frontal plane. The patient is asked to open and close the fists slowly but steadily for a full 3 minutes and to describe any symptoms that develop. Normal patients perform this test without symptoms other than mild fatigue. The patient with thoracic outlet syndrome usually has early heaviness and fatigue of the involved limb, gradual onset of numbness of the hand, and progressive aching through the arm and top of the shoulder. Within the 3 minutes, the patient usually drops the hand to the lap for relief of the progressive, crescendo distress that becomes intolerable.

The EAST evaluates all three types of thoracic outlet syndrome: neurologic, venous, and arterial. Radial pulses can be palpated by the examiner during the test. The presence of a radial pulse and a positive EAST test result are strong indications that the basis of symptoms is neurologic involvement of the brachial plexus.

The hands should be observed for changes in skin color, warmth, moisture, or muscular atrophy. Triceps muscle strength (innervated by C7) should be tested bilaterally. Muscle strength of the interosseous muscles (innervated by C8 and T1) should be tested by asking the patient to spread the fingers apart against resistance. Gentle pressure with the thumb in the supraclavicular fossa over the brachial plexus may reproduce thoracic outlet symptoms. A blood pressure difference between the two arms is a reliable indication of arterial involvement.

Ancillary Evaluation. Cervical spine radiographs with oblique views and chest radiographs identify skeletal abnormalities (first rib, cervical rib, clavicle deformity), trauma, arthritis, scoliosis, Pancoast tumor, or other pulmonary disease. Electromyography, nerve conduction studies, and somatosensory evoked potentials are generally unreliable.[44] Patients thought to have cervical disk or spinal cord disease may require cervical CT or MRI.

CT angiography is recommended with (1) obliteration of radial pulse on the EAST, (2) blood pressure 20 mm Hg less than that of the opposite asymptomatic limb, (3) possible subclavian stenosis or aneurysm (bruit or abnormal supraclavicular pulsation), and (4) evidence of peripheral emboli in the upper extremity.[44] Duplex ultrasound is indicated for edema of the hand or arm, unilateral cyanosis, or a prominent venous pattern of the arm, shoulder, or chest.[45]

Differential Diagnosis

The differential diagnosis of thoracic outlet syndrome includes herniated cervical disk, cervical spondylitis, spinal cord tumor, ulnar nerve compression at the elbow, carpal tunnel syndrome, orthopedic shoulder problems, trauma, postural palsy, angina pectoris, and a variety of neuropathies, including those associated with multiple sclerosis, alcoholism, and diabetes.

Patients with a herniated cervical disk have more severe persistent pain radiating in a sharply demarcated dermatomal distribution (usually C4 to C5 or C5 to C6) and often have localized tenderness of the cervical spine at the affected level. Carpal tunnel syndrome is characterized by nocturnal symptoms of pain and paresthesias and an associated Tinel sign. Brachial plexus compression can be confused with other vascular conditions, such as Raynaud disease, vasospastic disorders, vasculitis, or arterial ischemia. Unilateral symptoms suggest thoracic outlet syndrome, whereas bilateral symptoms suggest a systemic process. Subclavian or axillary venous thrombosis from thoracic outlet syndrome should be differentiated from thrombophlebitis or mediastinal venous obstruction from a benign or malignant process (e.g., Pancoast tumor).

Management

Treatment depends on whether the involvement is neurologic, arterial, or venous. Brachial plexus involvement with minimal signs and symptoms often responds to conservative treatment with physiotherapy and shoulder girdle exercises. Patients with thoracic outlet syndrome who have cervical ribs, arterial involvement, or neurologic symptoms require surgical decompression, removal of anomalous fibromuscular bands, or resection of the cervical rib if present. First rib or anomalous muscle or fibrous tissue resection provides consistent relief of symptoms and minimal morbidity (see Fig. 73.4B).

Patients with arterial complications of thoracic outlet syndrome (thrombosis, thromboembolism, or acute ischemia) require immediate heparinization (80 units/kg bolus, followed by a maintenance infusion of 18 units/kg/hr) and CT angiography; Fogarty catheter embolectomy, if appropriate; and emergency or urgent surgical exploration. Patients with axillary and subclavian vein thromboses also require emergent heparinization and venography and are treated with surgical thrombectomy or systemic fibrinolytic therapy.[45] Subclavian and axillary aneurysms are treated with resection and end-to-end anastomosis or graft interposition.

Disposition. The correct diagnosis of thoracic outlet syndrome can be achieved in more than 90% of patients with a careful history, physical examination, and bedside testing alone.[44] Neurologic, orthopedic, or vascular surgery consultation is indicated according to the pathologic condition.

Peripheral Arteriovenous Fistulae

Arteriovenous malformations and fistulae, although rare, should be distinguished from vascular stenoses or aneurysms. Acquired peripheral arteriovenous fistulae are most often caused by trauma (gunshot wounds, stab wounds, or surgery), with malignancy, infection, and arterial aneurysms as less common causes. Patients seek care months after an invasive surgical procedure or penetrating injury.

Physical Exam

True aneurysms and arterial stenoses are associated with a systolic murmur. Pseudoaneurysms have a loud systolic and sometimes a separate faint diastolic murmur. Arteriovenous fistulae have a constant systolic and diastolic (to-and-fro) murmur associated with a palpable thrill, similar to a dialysis arteriovenous fistula. Arteriovenous fistulae can occur at prior operative or trauma sites. Skin overlying the lesion may be warm, but distally, the temperature is decreased. Peripheral veins are distended and varicose. Large arteriovenous fistulae produce high cardiac output and widened pulse pressure. Digital pressure on the artery leading to the fistula may decrease the tachycardia (Branham sign).

Differential Diagnosis

An arteriovenous fistula diagnosis can be made with clinical examination alone. A constant systolic and diastolic (to-and-fro) murmur with associated palpable thrill is characteristic. Sixty percent of arteriovenous fistulae have a coexisting false aneurysm. Patients with peripheral venous disease may have similar cutaneous manifestations (varicose veins and stasis pigmentation) but lack vascular bruits. Infection may complicate large fistulae.

Management

Acquired peripheral arteriovenous fistulae usually increase in size with time if surgery is delayed. Vessel dilation, peripheral ischemia, and cardiac output increase.[46] Surgical treatment of peripheral arteriovenous fistulae requires interrupting the fistula tract and restoring both arterial and venous continuity with end-to-end anastomosis or graft interposition. Transcatheter embolization with detachable balloons and liquid acrylic tissue adhesives (e.g., isobutyl 2-cyanoacrylate) is used for surgically inaccessible fistulae.[47]

Vascular Abnormality Caused by Drug Abuse

Principles

Parenteral drug use causes intravenous or intra-arterial injuries, including arterial ischemia, infected pseudoaneurysms, lymphatic obstruction, or neurologic injury. Acute arterial ischemia results from direct drug effects or endogenous catecholamine release after injection. Endothelial wall damage stimulates platelet aggregation and thrombus formation. Precipitated crystals, talc, or foreign body emboli cause arterial occlusion. Necrotizing arteritis produces ischemia, especially in patients who abuse methamphetamines.

Infected pseudoaneurysms associated with arteriovenous fistulae result from a through-and-through puncture of the artery with simultaneous bacterial contamination. These fistulae are the most common vascular lesions resulting from intravenous drug abuse. Secondary

infection of the vascular structure may be covered by a surrounding soft tissue infection (cellulitis or abscess). Infected aneurysms at sites distant from the injection can occur.

Patients who inject intravenous drugs can develop unilateral hand edema or "puffy hand syndrome" due to gradual obliteration of the superficial venous vessels and chronic lymphatic obstruction. Direct injury to adjacent nerves, polyneuritis, and ischemic neuritis can result. Coexisting infections include cellulitis, septicemia, and bacterial endocarditis.[48]

Clinical Features

Patients may not be comfortable discussing the use of intravenous drugs, but objective evidence such as track marks may be present. Distal ischemia after intra-arterial injection occurs in the upper extremity after injection of the brachial or radial artery. The immediate onset of severe, burning pain at the time of injection is a characteristic hallmark.[49] Patients have a painful, edematous upper extremity with patchy blue-purple skin discoloration. Distal pulses are generally present, but the skin temperature of the involved extremity is decreased. Because patients tend to seek attention early, the site of injection may be identifiable over the radial or brachial artery. Evidence of gangrene, pre-gangrenous changes, or neuromuscular deficits may accompany this syndrome.

Patients with infected pseudoaneurysms have a painful mass several days to weeks after injection, with resultant bleeding. The mass is pulsatile, and 50% have an associated bruit.[48] Infected pseudoaneurysm should be considered in the differential diagnosis of cutaneous abscess in a patient who injects intravenous drugs. Infected pseudoaneurysms are most often encountered in the lower extremities (80%). A peripheral vascular examination with auscultation for bruits should be performed. A radiograph can detect subcutaneous needle fragments. CT angiography is the diagnostic procedure of choice for suggested pseudoaneurysm or distal ischemia. Ultrasonography is often unable to distinguish an aneurysm from an abscess or cellulitis.

Management

Therapeutic considerations for acute ischemia from intra-arterial injection are primarily conservative. Intra-arterial vasodilators, heparin, low-molecular-weight dextran, fibrinolytic therapy, analgesics, systemic warming to stimulate vasodilation, antibiotics, elevation of the affected limb to promote venous drainage, and physical therapy have not significantly altered the outcome or amputation rate in this patient population. Surgical treatment is reserved for delayed amputation. Gradual resolution without surgical intervention is the most common outcome.

Patients with infected pseudoaneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes may require an extensive surgical approach.[48] Methicillin-resistant *S. aureus* and gram-negative rods are increasing in frequency as the causative agents. Broad spectrum coverage with vancomycin 5 to 20 mg/kg q8h to q12h and cefepime 1 to 2 g IV q8h should be initiated as soon as the diagnosis is considered and then tailored to the appropriate organisms as soon as possible.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 73: QUESTIONS AND ANSWERS

1. Where do most arterial emboli originate?
   - **a.** Abdominal aorta
   - **b.** Femoral artery
   - **c.** Left ventricle
   - **d.** Left atrium
   - **e.** Thoracic aorta

Answer: c. Eighty-five percent of arterial emboli originate in the heart. Of these, left ventricular thrombus formation after myocardial infarction (MI) accounts for 60% to 70%. Atrial thrombi account for only 5% to 10% of all peripheral arterial emboli.

2. What is the most frequent site of acute arterial embolic occlusion?
   - **a.** Carotid artery
   - **b.** Common femoral artery
   - **c.** Mesenteric artery
   - **d.** Popliteal artery
   - **e.** Renal artery

Answer: b. The bifurcation of the common femoral artery accounts for 35% to 50% of acute arterial occlusion due to arterial embolism. Embolic occlusion most often occurs at major arterial bifurcations because of the sudden change in vessel diameter at these locations.

3. A 63-year-old male presents with acute onset of left leg pain while walking. He describes it as a shock-like sensation that made his knee buckle. Past history is remarkable for hypertension, diabetes (diet controlled), tobacco use, and a recent lateral wall myocardial infarction. Current medications are aspirin, metoprolol, and lisinopril. Vital signs are temperature, 37.0°C oral; heart rate, 98 beats per minute; blood pressure, 160/105 mm Hg; respiratory rate, 20 breaths per minute; and oxygen (O2) saturation, 96%. Physical examination is remarkable for left lower extremity pallor with decreased light touch sensation, nonpalpable left foot pulses, and minimal capillary refill. What would be the most appropriate next step in the diagnosis and management of this patient?
   - **a.** Abdominal ultrasonography
   - **b.** Arteriogram
   - **c.** Serum lactate level
   - **d.** Thoracolumbar magnetic resonance imaging (MRI) scan
   - **e.** Vascular surgery consultation

Answer: e. This patient has acute limb ischemia from an acute arterial embolus, most likely originating from his left ventricle secondary to a recent myocardial infarction. Loss of light touch sensation on physical examination indicates jeopardized tissue viability, requiring immediate vascular surgery consultation for emergent Fogarty catheter embolectomy. Reliable diagnosis of an acute arterial embolism can almost always be made by history and physical examination alone. Any additional diagnostic evaluation constitutes an unnecessary delay. Serum lactate level, abdominal ultrasonography, and thoracolumbar magnetic resonance imaging (MRI) scan would not provide useful information. An arteriogram before going to the operating room is an unnecessary delay and may further exacerbate limb ischemia.

4. A supine patient is asked to raise his foot 12 inches above the estimated level of the right atrium and dorsiflex the foot five or six times. He is then brought to a sitting position with his feet hanging. In the absence of severe advanced ischemia, venous filling of the foot should return in less than how many seconds?
   - **a.** 1
   - **b.** 5
   - **c.** 10
   - **d.** 15
   - **e.** 20

Answer: e. This bedside test is Buerger sign and can provide reliable evidence of advanced ischemia. In the absence of severe advanced ischemia, the lower extremity veins should fill within 20 seconds after being placed in the dependent position.

5. A 73-year-old man presents with acute onset of right lower extremity pain. He has a long history of tobacco use, hypertension, and a several-year history of moderate calf claudication at 50 yards walking. Physical examination reveals signs of chronic atherosclerotic occlusive disease of the bilateral lower extremities, including muscular atrophy, loss of hair over the toes and feet, and thickening of the toenails. Examination of the distal right lower extremity reveals pallor, absent popliteal and foot pulses, and decreased sensation to light touch of the right foot. The cardiac examination is unremarkable, and the 12-lead electrocardiogram (ECG) reveals only normal sinus rhythm. Based on the most likely diagnosis, what is the most appropriate definitive therapy?
   - **a.** Acute hyperbaric oxygen therapy
   - **b.** Arteriogram to determine the presence of embolus versus in situ thrombosis
   - **c.** Intra-arterial thrombolysis
   - **d.** Surgical referral for Fogarty catheter embolectomy
   - **e.** Surgical referral for Fogarty catheter embolectomy with vascular bypass grafting

Answer: e. This patient has a history and physical examination consistent with long-standing peripheral atherosclerotic occlusive disease, no evidence of a proximal source for embolism, but acute onset of ischemic symptoms and loss of light touch in the affected extremity. The most likely diagnosis is a large, in situ thrombosis precipitating acute limb-threatening ischemia. When limb-threatening ischemia is present, emergent surgical referral for Fogarty catheter embolectomy is indicated, whether caused by acute in situ thrombosis or embolus. With limb-threatening ischemia caused by in situ thrombosis, simple Fogarty catheter embolectomy is insufficient and usually requires additional bypass grafting. Acute hyperbaric oxygen therapy has no role in the treatment of limb-threatening ischemia due to in situ thrombosis or embolism. An arteriogram to determine the presence of embolus versus in situ thrombosis is unwarranted, represents an unnecessary delay, and may further exacerbate ischemia. Intra-arterial thrombolysis takes 6 to 72 hours to work and is contraindicated in cases of limb-threatening ischemia.

6. What percentage of patients presenting with arteriosclerosis obliterans are younger than 50 years old?
   - **a.** 1%
   - **b.** 5%
   - **c.** 10%
   - **d.** 20%
   - **e.** 40%

Answer: d. Peripheral arteriovascular disease can occur in younger patients. Nineteen percent of patients presenting with atherosclerosis obliterans are between the ages of 30 and 50 years old. Of all arteriosclerosis patients, 33% have coexistent coronary artery disease, and 70% to 90% are smokers. The non-smokers have other risk factors including significant hypertension and hyperlipidemia.

CHAPTER 73: QUESTIONS AND ANSWERS—cont'd

7. A 49-year-old woman presents with severe left ankle pain. She describes a fairly sudden development of a left lateral malleolus hemorrhagic blister that transitioned to a painful superficial ulcer over 48 hours. She has no prior history of extremity ulcers, and her only significant past medical history is hypertension. She has a long-standing history of noncompliance with her hypertensive medications and smokes two packs of cigarettes per day. She has no history of myalgias, joint pain, fever, or systemic symptoms. Vital signs are: temperature, 36°C oral; heart rate, 90 beats per minute; blood pressure, 210/125 mm Hg; respiratory rate, 20 breaths per minute; and O2 saturation, 96%. Physical examination reveals a thin black female in distress because of pain. Cardiopulmonary examination is unremarkable. Abdominal, neurologic, and extremity examinations are likewise unremarkable except for a well-demarcated, shallow 4 × 3 cm ulcer over the left lateral malleolus. There is mild erythema but no evidence of active infection. Distal pulses and capillary refill are normal. What would be the most appropriate intervention?

a. Analgesics and admission for vasculitis evaluation
b. Surgical consultation for possible embolectomy
c. Wound care and blood pressure control
d. Wound care and tapering dose of prednisone
e. Venous Doppler scans and surgical consultation for possible skin grafting

Answer: c. This patient has a hypertensive ulcer, which is the most painful of lower extremity ulcers. They typically occur over the lateral malleolus, as opposed to venous stasis ulcers, which are more common anteriorly and medially. Ischemic arterial ulcers are more common distally over the digits. Although vasculitis or a collagen vascular disease are possible, the lack of any other systemic symptoms or prodrome argues against this.

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Pulmonary Embolism and Deep Vein Thrombosis

Christopher Kabrhel

KEY CONCEPTS

- Hallmarks of deep venous thrombosis (DVT) include unilateral limb pain and swelling, though these findings can be subtle and nonspecific.
- Patients with low pretest probability (PTP) can have DVT ruled out in the ED with a negative D-dimer or venous ultrasound (US), patients with high PTP can have DVT ruled out in the ED with a negative D-dimer and venous US.
- Three-point US evaluates the leg veins proximal to the knee and has a sensitivity of 95% and specificity of 95% for proximal DVT when performed by a certified sonographer. A negative three-point ultrasound in a patient with a moderate or high PTP for DVT should have a D-dimer test or repeat venous ultrasound within 7 days. A single, whole-leg ultrasound excludes DVT in all pretest probabilities.
- Anticoagulation for DVT and pulmonary embolism (PE) can be achieved with a direct-acting oral anticoagulant (DOAC), low-molecular-weight heparin (LMWH), unfractionated heparin or, in rare cases, an alternative anticoagulant. For DVT and most PE, DOACs are as effective as and safer than the combination of heparin and warfarin.
- The treatment of isolated calf vein DVT is controversial, and it is reasonable to withhold anticoagulation in favor of a repeat venous ultrasound within 7 days and close follow-up.
- Distal superficial vein thrombophlebitis can adequately be treated with nonsteroidal antiinflammatory drugs and warm compresses, but proximal superficial vein thrombophlebitis should be treated with anticoagulation.
- Most patients with DVT distal to the iliofemoral region can be safely treated as outpatients as long as close follow-up and access to anticoagulant medications is assured.
- PE can present asymptomatically, with dramatic clinical symptoms, or with sudden cardiac death. Even the most common symptom, dyspnea, is absent in a quarter of patients.
- The first step in the evaluation of possible PE is determining whether testing for PE is indicated.
- The patient's pretest probability for PE, as determined by clinical gestalt or a validated score (e.g., the Wells Score) dictates the approach to objective testing for PE.
- Patients with low gestalt pretest probability and a negative PERC rule may incur more harm than benefit if testing for PE (including D-dimer) is performed.
- Patients with non-high pretest probability (e.g., Wells Score ≤ 6) can have PE ruled out with a negative D-dimer.
- The D-dimer threshold can be adjusted according to the patient's age or the pretest probability of PE. The formula for age adjustment is Age × 10 ng/mL. Using an adjusted D-dimer threshold reduces the need for imaging by about 10% to 15%.
- Patients with high pretest probability or a positive D-dimer require imaging. For most patients, including pregnant women, computer tomography pulmonary angiography (CTPA) is the imaging test of choice.
- For pregnant women, the decision to undergo any testing for PE should be shared with the patient. To minimize fetal radiation exposure, diagnostic testing for PE should start with a combination of D-dimer and bilateral lower extremity venous ultrasound.
- For patients diagnosed with PE, typical resuscitative measures can be harmful. Endotracheal intubation and positive-pressure ventilation can decrease preload and precipitate cardiac arrest. Excessive intravenous fluid administration can lead to worsening right ventricular distention and left ventricular compression.
- Patients with PE should be risk stratified using a combination of vital signs, CTPA, echocardiography, and troponin. High-risk PE is defined by hemodynamic instability, intermediate-risk by right ventricular dysfunction, and low-risk by the absence of either.
- Patients with high-risk PE should be treated with thrombolysis or thromboembolectomy unless contraindicated.
- Patients with intermediate-risk PE are usually not candidates for thrombolysis but may be candidates for catheter-directed or low-dose systemic thrombolysis.
- About 25% of patients with low-risk PE can be treated as outpatients.

FOUNDATIONS

Background and Importance

Each year more than 500,000 people are diagnosed with venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). PE is the third most common cause of cardiovascular death in the United States. PE and DVT occur equally in women and men, and while PE and DVT can occur in any age group, older patients have a much higher incidence, at 1/10,000 in people 20 to 30 years old and 1/100 in people greater than 80 years old. However, even this high incidence grossly understates the importance of PE and DVT to the practice of emergency medicine. Because the clinical presentations of PE and DVT are highly variable, with symptoms and signs that overlap with many common ED diagnoses, PE and DVT are frequently on the differential diagnosis for patients who present with chest pain, dyspnea, syncope, tachycardia, hypoxemia, leg pain, edema,

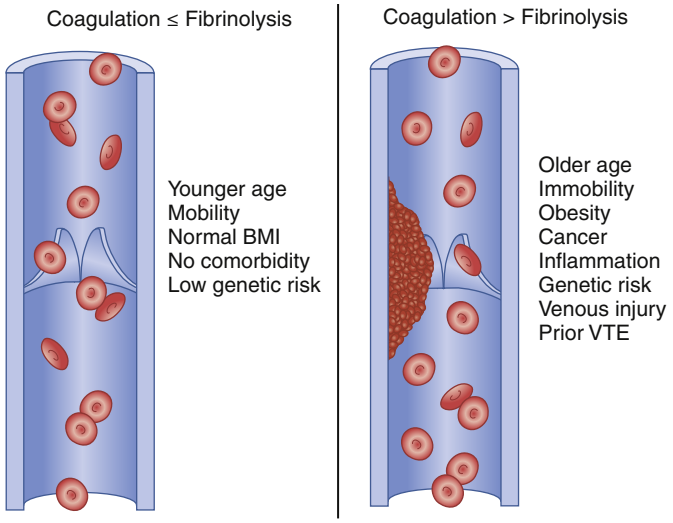

Fig. 74.1 Diagram of clotting in a lower extremity vein. Note how the clot forms in and around the cusps of the valve. (Illustration courtesy of Sadie A. Kabrhel.)

and other nonspecific complaints. The wide demographic range and nonspecific clinical presentation of PE and DVT is why as many as 1 in 10 emergency department (ED) patients are evaluated for possible DVT or PE. Emergency clinicians must, therefore, be knowledgeable and judicious in their approach to PE and DVT.

As illustrated in Figure 74.1, venous thrombosis occurs when the propensity of blood to coagulate overwhelms endogenous anticoagulant and fibrinolytic systems. Numerous factors associated with the classic triad of venous injury, venous stasis, and hypercoagulability have been associated with an increased risk of VTE in epidemiologic studies (Table 74.1). Emergency clinicians should be aware of factors that might increase a patient's propensity to clot and should consider these factors when determining whether a patient's clinical presentation warrants an evaluation for VTE. Important factors include older age, prior history of VTE, active cancer, recent surgery or trauma, recent hospitalization longer than three days, limb immobility, and estrogen use (especially if initiated in the past three months). Thus, the age and comorbid illness of the population served by an ED determine the frequency of VTE diagnoses.

However, not all epidemiologic risk factors are associated with an increased likelihood of an ED diagnosis of VTE (Table 74.1). For example, pregnant women are five times as likely to develop VTE as nonpregnant women of the same age, but only 4% of pregnant women tested for VTE in the ED have the diagnosis, compared to 12% of nonpregnant patients. This is because emergency clinicians have a low threshold to test pregnant patients for VTE. Similarly, travel is associated with a small increase in the absolute risk of VTE, but a history of travel often leads emergency clinicians to test for VTE, so travel does not seem to be associated with VTE in patients tested in the ED.[1] The decision to initiate an evaluation or treatment for VTE should be based on an analysis of the risk PE poses to the patient weighed against the risk imparted by testing and treatment.

As many as 50% of patients diagnosed with PE have no apparent clinical risk factors for PE or DVT at the time of diagnosis. However, the lack of a risk factor known at the time of the ED diagnosis does not mean that an occult risk factor does not exist. Between 4% and 11% of patients with PE or DVT will receive a new cancer diagnosis within 1 year of VTE diagnosis, depending on whether the VTE event is provoked or idiopathic. Genetic or acquired hypercoagulable states are often unknown until a patient has their first thrombotic event. Patients who develop PE or DVT after exposure to heparin may have heparin-induced thrombocytopenia, a hypercoagulable state leading to VTE. While the presence of an occult risk factor may only become known after a patient leaves the ED, a thorough history may suggest occult cancer (e.g., unintentional weight loss) or recent exposure to heparin that would enable the emergency clinician to adjust their assessment of a patient's risk of PE or DVT.

Anatomy, Pathology, and Pathophysiology of VTE

The venous anatomy of the lower extremity is divided into the deep and superficial systems (Fig. 74.2). The superficial venous system consists primarily of the greater and short saphenous veins and perforating veins. Distal greater saphenous vein thrombi are often referred to as superficial thrombosis, but greater saphenous clots near the connection with the femoral vein should be referred to as DVT. The deep venous system includes the anterior tibial, posterior tibial, and peroneal veins, collectively called the calf veins. Venous thrombi isolated to the calf veins are referred to as distal DVT. The calf veins join together at the knee to form the popliteal vein, which extends proximally and becomes the femoral vein at the adductor canal. Venous thrombi in the popliteal or more proximal veins are referred to as proximal DVT. The femoral vein (previously known as the superficial femoral vein), is joined by the deep femoral vein and then the greater saphenous vein to form the common femoral vein, which subsequently becomes the external iliac vein at the inguinal ligament. Venous thrombi in the proximal femoral and iliac veins are known as iliofemoral DVT.

Knowledge of the venous anatomy is also important for the performance and interpretation of ultrasound of the leg veins. Compression ultrasound, including point-of-care ultrasound, is typically limited to the common femoral, femoral, and sometimes popliteal veins. Duplex ultrasound includes compression ultrasound of the proximal veins as well as Doppler ultrasound of the calf veins. The anatomic location of a DVT also influences prognosis because proximal DVT are less likely to lyse spontaneously, more likely to embolize, and are associated with a greater risk of long-term complications such as post-thrombotic syndrome.

Although 90% of DVT form in leg veins, clots can also form in the arm, around venous catheters, pacemaker wires, or other foreign bodies such as inferior vena cava filters. Other sites of venous thrombosis rarely encountered in the ED include the jugular, ovarian, mesenteric, renal, portal, hepatic, cerebral, and retinal veins.

DVT formation typically begins when monocytes expose blood to tissue factor on their surfaces. This process overwhelms natural anticoagulant and fibrinolytic mechanisms and leads to the aggregation of red blood cells, platelets, and fibrin in the venous sinuses or cusps of the lower extremity deep veins. The formation of a DVT causes vascular congestion which, in turn, causes veins to dilate and valves to become incompetent. The lack of forward venous blood flow leads to venous stasis and further thrombus propagation.

When a DVT embolizes, it flows proximally through the venous system toward the vena cava and the heart. In 3% of cases, a portion of the clot will remain in the right atrium or ventricle, a condition known as clot-in-transit. Clots that pass through the heart and enter the pulmonary arterial circulation are called PE. A PE can be described as saddle if the clot is visualized across the bifurcation of the main right and left pulmonary arteries (Fig. 74.3A). More distal PE are typically described according to their anatomic location. Clots may lodge in a main pulmonary artery (Fig. 74.3B), or in a lobar (Fig. 74.3C), segmental (Fig. 74.3D) or subsegmental pulmonary artery branch. PE may extend from a proximal artery into distal branches, and PE frequently fragment, lodging in multiple arterial branches simultaneously.

TABLE 74.1 Epidemiologic Risk Factors and Physiologic Findings for Pulmonary Embolism in the Emergency Department Setting

Risk Factor from Epidemiologic Study	Mechanism	Strength of Association With PE or DVT in ED Patients
Surgery (within past 4 weeks, requiring general anesthesia)	Inflammation Venous Injury Stasis	++++
Trauma within past 4 weeks requiring hospitalization	Inflammation Venous Injury Stasis	+++
Older age	Hypercoagulability Stasis Association with other diseases of aging (e.g., cancer, surgery)	+++
Prior PE or DVT	Hypercoagulability Stasis (due to valvular damage)	++
Active cancer	Hypercoagulability	++
Inherited or acquired thrombophilia	Hypercoagulability	++
Limb or generalized immobility	Stasis	++
Estrogen	Hypercoagulability	++
Pregnancy or postpartum	Hypercoagulability	+
Recent travel	Stasis	Minimal
Connective tissue disease	Inflammation	Unknown
Inactive cancer (considered in remission)	Hypercoagulability	Not significant
Smoking	Inflammation and hypofibrinolysis	Not significant
Family history of VTE	Hypercoagulability (inherited predisposition)	Not significant
Symptoms	Mechanism	Strength of association with PE or DVT in ED Patients
Hemoptysis	Infarction	+++
Pleuritic chest pain	Lung infarction	+
Dyspnea	V/Q mismatch	+
Syncope	Obstruction of pulmonary outflow tract	+
Sudden onset of symptoms	Vascular obstruction	Not significant
Substernal chest pain	Presumed cardiac ischemia	Not significant
Signs		
Unilateral leg or arm swelling	Venous obstruction	++++
Unexplained hypoxemia (Sa_{O_2} < 95% [sea level])	$\dot{V}/\dot{Q}$ mismatch	+++
Pulse rate > 100 beats/min	Cardiac stress, baroreceptors	++

Note: Differences between epidemiologic risk factors and risk factors for a diagnosis of PE or DVT in the ED reflect the ability of these factors to differentiate patients who present with symptoms consistent with PE or DVT who are ultimately diagnosed with PE or DVT from those who have PE or DVT excluded after their ED workup.
PE, Pulmonary embolism; *DVT*, deep vein thrombosis; *ED*, emergency department; $\dot{V}/\dot{Q}$, ventilation/perfusion ratio; Sa_{O_2}, saturation of oxygen measured on pulse oximetry.

The physiologic effect of an obstruction in the pulmonary vasculature is variable. Small, subsegmental PE often lyse spontaneously and may be clinically inconsequential. Subsegmental thrombi that do not spontaneously lyse but obstruct blood flow to the lung's periphery can cause pulmonary infarction, necrosis, pleural inflammation, and severe pleuritic pain. The right ventricle normally pumps through a pulmonary vascular tree with a low resistance to flow, and young individuals without cardiopulmonary disease can tolerate at least 30% obstruction from a clot with minimal symptoms or signs. Larger PE can cause an acute increase in pulmonary artery pressure due to a combination of mechanical obstruction and chemically mediated vasoconstriction of unobstructed pulmonary arteries. Increased right ventricular (RV) afterload (i.e., when the pulmonary artery systolic pressure exceeds 40 mm Hg) can lead the thin-walled right ventricle to dilate and become hypokinetic. As illustrated in Figure 74.4, with normal PA pressures, the systolic RV is crescentic in cross-section and the left ventricle (LV) is circular. However, with increased PA pressures, the systolic RV dilates asymmetrically towards the intraventricular septum, compressing the LV into a "D" shape on cross-section. This can lead to underfilling of the left ventricle, decreased cardiac output, decreased coronary artery perfusion, myocardial ischemia, circulatory collapse, and death.

DEEP VEIN THROMBOSIS

Clinical Features

Hallmarks of DVT include unilateral limb pain and swelling, though these findings can be subtle and nonspecific. Patients may report only mild cramping or a sense of fullness in the calf. The clinical signs of DVT may include edema, erythema, and warmth of the affected extremity, tenderness to palpation along the distribution of the deep

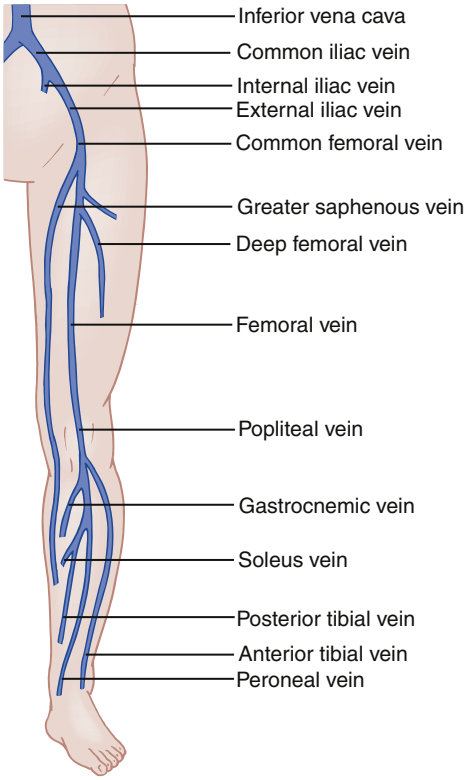

Fig. 74.2 Diagram of the leg vein anatomy relevant to the diagnosis of deep vein thrombosis. A three-point ultrasound includes the common femoral, femoral and popliteal veins. A whole-leg ultrasound adds the greater saphenous, posterior tibial, peroneal veins and the gastrocnemius vein. (Illustration courtesy of Sadie A. Kabrhel.)

venous system, dilation of superficial collateral veins, and rarely a palpable venous cord. Figure 74.5A shows a patient with a left leg DVT. To illustrate the difficulty of differentiating DVT from alternative diagnoses based on clinical examination, Figure 74.5B shows a patient with a ruptured Baker cyst in the left leg. Fever suggests an alternative diagnosis, such as cellulitis. Because the left iliac vein is vulnerable to compression by the left iliac artery (May-Thurner syndrome), leg DVT occurs with a slightly higher frequency on the left. Bilateral leg DVT is found in fewer than 10% of ED patients diagnosed with DVT.

More than 90% of upper extremity DVT occur in the presence of an indwelling catheter or similar device. Therefore, arm pain or swelling in the same arm as a catheter, infusion device, or pacemaker wire should raise suspicion for DVT. In the absence of a device, upper extremity DVT tends to occur in the dominant arm of young athletes, a condition known as Paget-Schroetter syndrome. Paget-Schroetter syndrome is an effort-induced form of thoracic outlet syndrome. Repetitive motion of the arm in the setting of hypertrophied scalene muscles or congenital cervical ribs causes compression of the subclavian vein and DVT.

Differential Diagnosis

Box 74.1 lists differential diagnoses for DVT. Venous insufficiency that causes congestion and inflammation is a common alternative diagnosis for DVT, especially since venous insufficiency increases the risk of DVT. Cellulitis is another common consideration. However, in a patient with clinical evidence of cellulitis, the frequency of concurrent DVT is only about 3%. Injuries to the gastrocnemius muscle or Achilles tendon can mimic the pain and swelling of DVT but are usually distinguished by history. Enlargement of the synovial membrane (Baker cyst) can cause popliteal pain and rupture of the cyst into the calf muscles causes inflammation that appears clinically similar to DVT. Spontaneous calf muscle hematomas can also cause pain and inflammatory changes. Many patients with systemic edema (e.g., from heart failure) will have asymmetrical swelling that raises concern for DVT.

Diagnostic Testing

Pretest Probability Estimation

Diagnosis of DVT (and PE) starts with an estimation of the pretest probability (PTP). PTP estimation helps guide the choice of diagnostic tests, the interpretation of results, and the need for follow-up testing. However, in the eyes of many clinicians the noninvasive, nonionizing nature of testing for DVT makes PTP estimation for DVT less critical than it is for PE. PTP estimation may be accomplished by the clinical gestalt of an experienced clinician or in conjunction with a clinical decision tool.

The most commonly used and well-validated clinical decision tool for DVT is the Wells DVT score (Table 74.2). Because the components of the Wells DVT score have been incorporated into clinical gestalt over the years since the score was developed, Wells DVT score and clinician gestalt have approximately equal diagnostic accuracy, and either method is acceptable. Although the Wells DVT score can categorize patients as low, intermediate or high PTP, the decision to test with a highly sensitive D-dimer or venous US is dichotomous. Therefore, it is easiest and appropriate to combine low and intermediate probability groups and consider the PTP of DVT to be low (−2 to 2 points) or high (≥3 points).

The Wells DVT score has not been validated in pregnant women, but the LEFt score has been validated in a study of 157 pregnant women. It consists of 1 point in case of left (*L*) leg suspicion, 1 point for edema (*E*), and 1 point if the suspicion occurred during the first trimester (*Ft*) of pregnancy. A LEFt score of 0 or 1 indicates low PTP. Although not validated, an approach that substitutes the LEFt score for the Wells score in pregnant women is reasonable.

Laboratory Evaluation

The D-dimer test measures the enzymatic breakdown of cross-linked fibrin from any intravascular thrombus. A normal quantitative D-dimer concentration in a patient with a low PTP (e.g., Wells score −2 to 0) excludes proximal DVT with a sensitivity of approximately 92% and a specificity of 45%.[2] This sensitivity is slightly lower than the sensitivity for PE, possibly because DVT tend to be subacute, and therefore less prone to release D-dimer, when diagnosed. Box 74.2 lists conditions other than PE and DVT that elevate the D-dimer. The specificity, and therefore the clinical usefulness, of the D-dimer may be low in patients with these conditions.

The US Food and Drug Administration (FDA) has cleared numerous D-dimer assays to aid in the diagnosis and exclusion of VTE, mostly using a cutoff of greater than 500 ng/mL to define abnormal. However, some D-dimer assays have cutoffs other than 500 ng/mL, so it is important for emergency clinicians to know the threshold considered positive in their practice setting.

Studies find that the need for venous US can be decreased by 5% by using a threshold for a positive D-dimer that is adjusted according to the patient's age using the following formula:[2-5]

$$\text{Age} \times 10\ \text{ng/mL}$$

Thus, an 80-year-old patient with a PE unlikely or non-high PTP can have DVT (or PE) excluded with a D-dimer concentration less than 800 ng/mL. This strategy maintains a diagnostic sensitivity near 95% but increases the percentage of patients who can have DVT excluded without venous ultrasonography. The safety of this strategy has not been tested with D-dimer assays with abnormal thresholds different than 500 ng/mL.

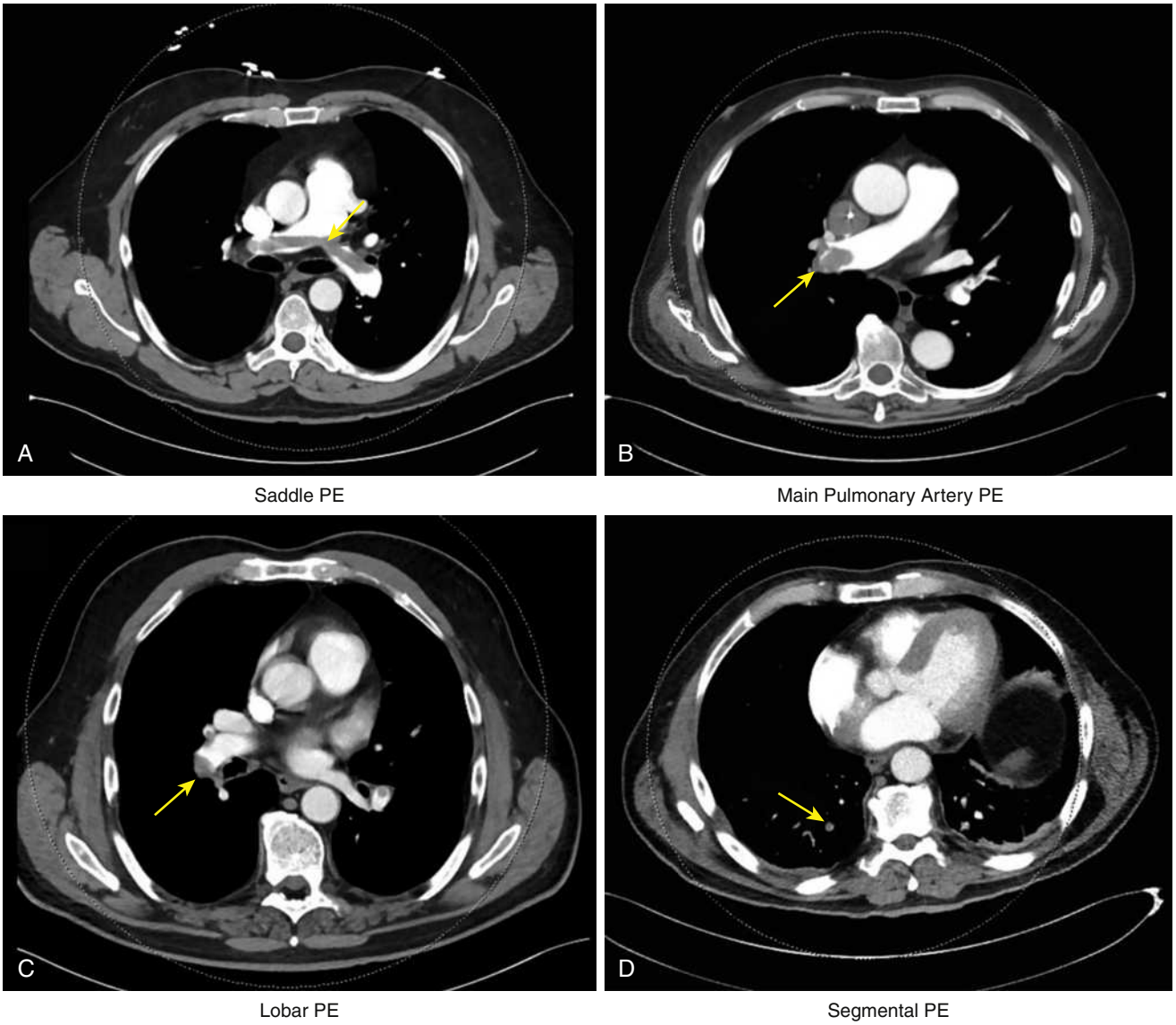

Fig. 74.3 Diagnostic computed tomography pulmonary angiography (CTPA) scans showing: (A) saddle PE, (B) right main pulmonary artery PE, (C) right lobar PE, (D) right segmental PE. The pulmonary arteries are enhanced by contrast, but PE appear as filling defects, as indicated by the yellow arrows.

An alternative to age adjustment is to apply a Bayesian approach, by which the threshold for a positive D-dimer is increased based on PTP. Using this strategy, patients with low PTP can have DVT ruled out using a threshold of 1000 ng/mL (for a test that normally uses 500 ng/mL). This approach has been shown to safely increase the proportion of patients with a negative D-dimer results from 50.9 % to 56.1%.[6]

Radiographic Evaluation

An expertly performed and interpreted positive venous ultrasound is sufficient to confirm the diagnosis of DVT. Several approaches to performing venous US are commonly used, and the emergency clinician should be aware of the US protocols used in their practice setting. Whole-leg US is the criterion standard and combines compression US of the proximal veins with ultrasound of the calf and saphenous veins. Whole-leg US is associated with a venous thromboembolism event rate at 3 months of 0.5%. A single normal whole-leg ultrasound excludes DVT regardless of PTP.

Three-point US, also called compression US, images the common femoral, femoral, and popliteal veins. Three-point US, when performed by a certified sonographer and interpreted by a board-certified radiologist, has a sensitivity of 95% and specificity of 95% for DVT. A negative three-point venous duplex ultrasound excludes the diagnosis of DVT in patients with low PTP. However, for patients at high risk, a negative three-point ultrasound is inadequate to exclude DVT as a single test. Patients with high PTP can have DVT ruled out in the ED with a combination of a negative three-point ultrasound and a negative D-dimer. A patient with high PTP, an elevated (or not performed) D-dimer, and a negative three-point ultrasound should be referred for a repeat venous US in 5 to 7 days to ensure their symptoms are not due to a distal (calf vein) DVT that later propagates proximally.

Bedside point-of-care ultrasound (POCUS) performed by a trained emergency clinician is 90% to 95% accurate compared to radiology-performed US.[7-9] Test characteristics are highest for femoral veins and lowest for saphenous and popliteal veins. POCUS of the upper extremity is not well studied and should be performed by radiology when necessary.

Ultrasound cannot be used to rule out iliac or pelvic vein thrombosis. For this, venography (typically CT) is needed. When duplex ultrasound is not available, the decision to empirically anticoagulate while awaiting the availability of ultrasound imaging should be based on the

PTP of DVT, and the risk anticoagulation poses to the patient. Generally, patients with low PTP do not need empirical anticoagulation while they wait for diagnostic imaging.

Magnetic resonance imaging (MRI) can evaluate the pelvic vasculature and inferior vena cava (IVC), which is not possible with ultrasound. Although CT venography can also visualize the pelvic veins and IVC, the accuracy varies across studies, and CT exposes patients to ionizing radiation. MRI does not produce ionizing radiation. Thus, MRI is a reasonable option to evaluate the pelvic veins of patients at high risk for pelvic vein thrombosis (e.g., a patient with gynecologic malignancy and bilateral leg swelling). Its use is limited by cost, availability, and patient tolerance. In only about 20% of patients with pelvic DVT is the clot isolated to the pelvic veins. Therefore, even when pelvic vein DVT is suspected, venous US is still the recommended first test.

Figure 74.6 provides a diagnostic flowchart for DVT that incorporates PTP. Patients with low PTP can have DVT ruled out in the ED with a negative D-dimer or venous US. Patients with high PTP can have DVT ruled out in the ED with a negative D-dimer and venous US. Patients with high PTP, a positive D-dimer, and a negative venous US of the proximal veins should have a follow-up ultrasound one week after ED discharge to look for the propagation of a distal DVT that might not have been detected during the initial ED visit.

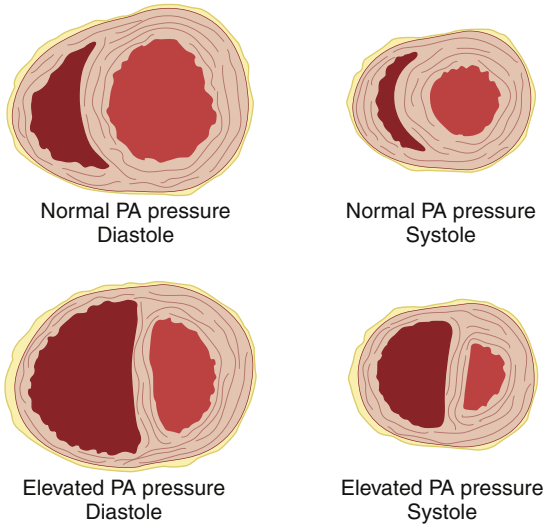

Fig. 74.4 Diagram showing the relationship of the right ventricle (RV) and left ventricle (LV) under conditions of normal pulmonary artery (PA) pressure and elevated PA pressure (i.e. in the setting of an acute PE). Note how, in the bottom right illustration, when PA pressure is elevated the RV dilates asymmetrically compressing the left ventricular septum. This can lead to decreased filling, decreased cardiac output, myocardial ischemia, hypotension and death. (Illustration courtesy of Sadie A. Kabrhel.)

Management

Patients with a positive ultrasound and patients with high PTP for whom imaging will be delayed (e.g., until the next day) should have anticoagulation initiated in the ED at the time of diagnosis, unless contraindicated.

Therapeutic anticoagulation for PE and DVT is the same. Options for initial anticoagulation are listed in Table 74.3. Direct-acting oral anticoagulants (DOACs) are as effective as warfarin at preventing recurrent VTE and are associated with fewer bleeding events, and in particular, intracranial bleeding events. They are well tolerated by patients and do not require injections or monitoring. The DOACs

BOX 74.1 Differential Diagnosis for DVT

- Venous insufficiency causing congestion and inflammation
- Cellulitis
- Muscle or tendon injury
- Baker cyst (including ruptured synovial membrane)
- Hematoma
- Arterial insufficiency and claudication
- Asymmetrical edema (e.g., due to congestive heart failure or liver disease)

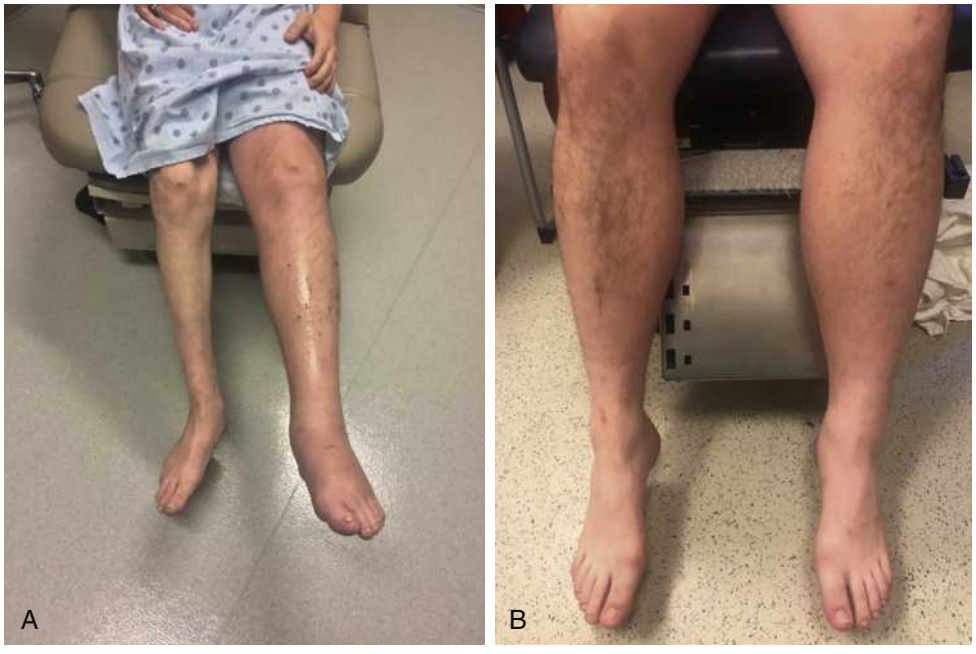

Fig. 74.5 Clinical photograph showing patients with (A) deep vein thrombosis of the left leg and (B) ruptured Baker cyst of the left leg. Note the similar clinical appearance with both patients presenting with leg pain and swelling.

rivaroxaban and apixaban do not require bridging with low-molecular-weight heparin (LMWH) and are the first-choice anticoagulants for most patients with DVT.[10-12]

TABLE 74.2 Wells Score for Deep Vein Thrombosis

Clinical Feature	Score
Active cancer (treated within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden (for ≥3 days or major surgery within 12 weeks requiring general or regional anesthesia)	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	–2

A score < 2 indicates that the probability of deep vein thrombosis is low. Adapted from: Wells PS, Anderson D, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1994;350:1795-1798.

For patients with active cancer, LMWH is associated with a lower risk of VTE recurrence than warfarin, but emerging evidence suggests that DOACs are also safe and effective in this population.[13,14] Concern about the ability to reverse anticoagulation should not dissuade an emergency clinician from starting DOAC therapy. Reversal agents are available for all DOACs (Box 74.3), and bleeding that does occur on DOAC therapy tends to be less severe than bleeding on warfarin.[15,16] However, DOACs are either contraindicated or not studied for the treatment of DVT associated with pregnancy, severe renal failure, liver failure, antiphospholipid antibody syndrome, and high-risk PE.

BOX 74.2 Factors Other Than VTE Associated With Positive D-Dimer Results

- Female sex
- Advanced age
- Black or African American race
- Cocaine use
- Immobility (general, limb, or neurologic)
- Hemoptysis
- Hemodialysis
- Malignancy (active)
- Rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus)
- Sickle cell disease
- Pregnancy and postpartum state
- Recent surgery (within 1 month)

Note: Warfarin use is associated with false-negative D-dimer results

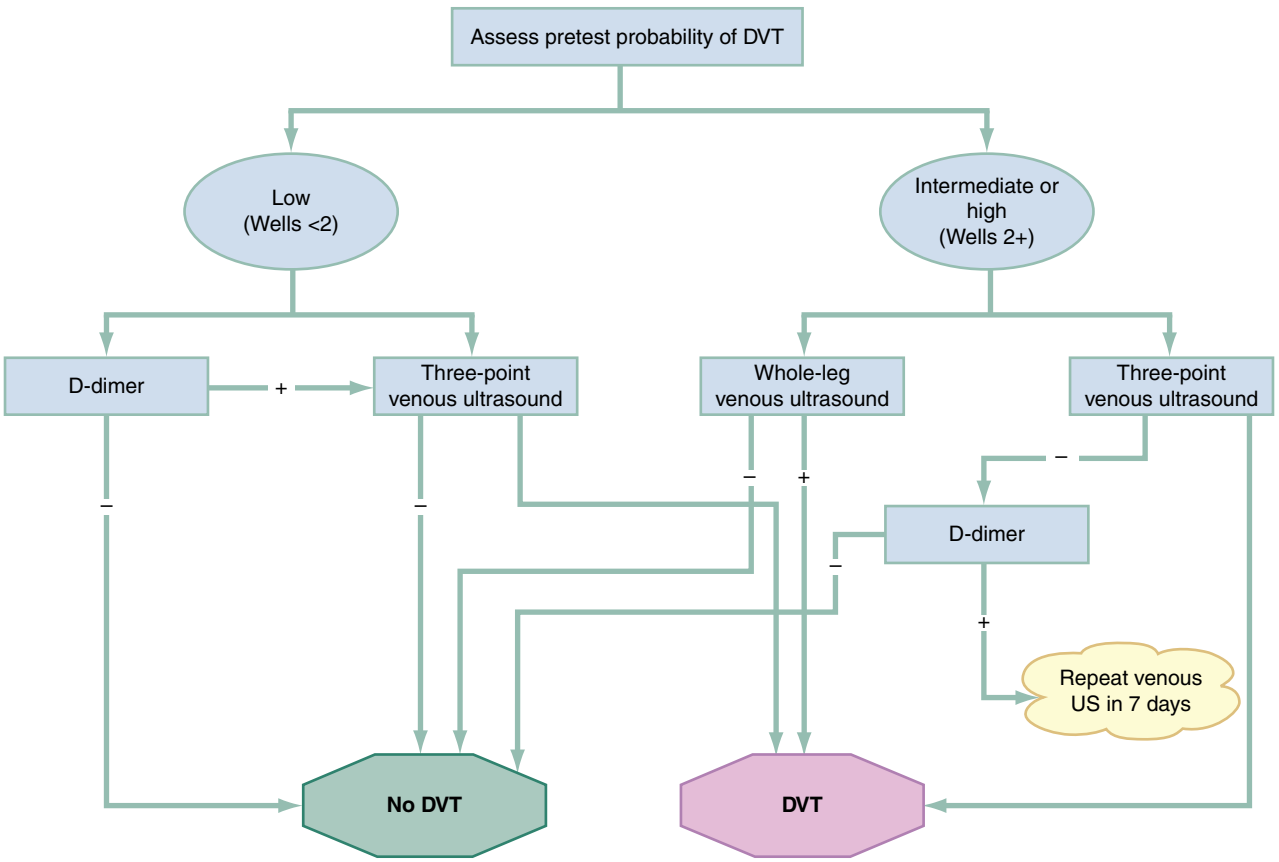

Fig. 74.6 Flowchart algorithm showing the diagnostic approach to a patient with possible acute deep vein thrombosis. *DVT*, Deep vein thrombosis; –, test negative; +, test positive; *US*, ultrasound.

TABLE 74.3 Anticoagulant Options for the Initial Treatment of DVT or PE

Anticoagulant	Initial Dose	Restriction	Time to Peak
Unfractionated heparin	70–80 U/kg, then 17–18 U/kg/h, IV	Heparin-induced thrombocytopenia	1 hour
Enoxaparin	1 mg/kg q12h or 1.5 mg/kg q24h subcutaneously	Creatinine clearance < 30 mL/min	3 hours
Dalteparin	200 unit/kg daily or 100 unit/kg q12h subcutaneously	Creatinine clearance < 30 mL/min	4 hours
Fondaparinux	5–10 mg subcutaneously	Creatinine clearance < 30 ml/min	3 hours
Rivaroxaban	5 mg by mouth q12h for 21 days with food	Creatinine clearance < 30 mL/min	2–4 hours
Apixaban	10 mg by mouth q12h × 7 days followed by 5 mg by mouth q12h with or without food	Creatinine clearance < 30 mL/min	3–4 hours

DVT, Deep vein thrombosis; *PE*, pulmonary embolism.

BOX 74.3 Reversal Agents for Anticoagulants

Anticoagulant	Reversal Agent
Heparin	Protamine sulfate
Warfarin	Fresh frozen plasma
	4-Factor prothrombin complex concentrate
	Vitamin K
Dabigatran	Idarucizumab
Rivaroxaban, Apixaban	Andexanet alfa

BOX 74.4 Contraindications to Anticoagulation

Absolute contraindications to anticoagulation include:

- Active bleeding into a critical organ or uncontrolled site
- Severe bleeding diathesis
- Recent, planned, or emergency high-bleeding-risk surgery or procedure
- Recent major trauma
- Recent intracranial, spinal or ocular hemorrhage

Relative contraindications to anticoagulation include:

- History of gastrointestinal major bleeding
- Intracranial or spinal tumors
- Previous bleeding into a tumor
- Large abdominal aortic aneurysm with concurrent severe hypertension
- Stable aortic dissection
- Recent, planned, or emergent low-bleeding-risk surgery/procedure

BOX 74.5 The VTE-BLEED Score

- Active cancer, 2 points
- Male patient with uncontrolled hypertension, 1 point
- Anemia, 1.5 points
- History of bleeding, 1.5 points
- Renal dysfunction (creatinine clearance 30–60 mL/min), 1.5 points
- Age ≥60 years, 1.5 points

Thrombolysis, whether systemic or catheter-directed, for DVT not associated with limb ischemia has not been shown to improve mortality or post-thrombotic syndrome (pain, paresthesia, induration, swelling, discoloration, and ulceration of the leg after DVT) but does increase the risk of bleeding.[17,18]

Compression stockings can no longer be advocated routinely for DVT, as the data do not support a reduction in post-thrombotic syndrome. However, the reduction in post-thrombotic syndrome may depend on how soon after DVT diagnosis the patient starts wearing the stockings, and some studies do show an improvement in quality of life, so some patients may find them beneficial.[19,20] Patients should be encouraged to ambulate after anticoagulation for DVT to reduce the incidence of post-thrombotic syndrome.

Assessing Bleeding Risk

Prior to initiation of anticoagulation for VTE, emergency clinicians should assess the patient's risk of bleeding. This is particularly important for patients with calf vein DVT without PE or isolated subsegmental PE without DVT, for whom withholding anticoagulation may be reasonable. Absolute and relative contraindications to anticoagulation are listed in Box 74.4. Bleeding risk can also be assessed using the validated VTE-BLEED score (Box 74.5). Patients with less than 2 points have a 0.5% risk of major bleeding, compared to 2.0% in patients with scores of 2 or more points.[21-23]

Superficial Vein Thrombophlebitis

Distal superficial vein thrombophlebitis can adequately be treated with nonsteroidal antiinflammatory drugs and warm compresses. The rate of DVT or PE within three months of superficial thrombophlebitis is about 3%, so patients with superficial vein thrombosis should be scheduled for a repeat ultrasound in 7 days to rule out progression. Based on the results of a large randomized controlled trial, patients with superficial thrombophlebitis involving the greater saphenous vein that extends above the knee are at risk for progression to DVT via the saphenous-femoral vein junction. In these patients, an abbreviated 45-day course of prophylactic-dose anticoagulation reduced clot extension, PE, and DVT, though the absolute rates of PE were less than 1% regardless of treatment allocation. If a greater saphenous vein clot is proximal (within 3 cm of the connection with the femoral vein; see Fig. 74.2), the risk of extension to the deep venous system is about 25% so therapeutic (full dose) anticoagulation is warranted for at least 30 days.

Isolated Calf Vein Thrombosis

The optimal management strategy for thromboses isolated to the calf veins remains controversial. About 15% of untreated isolated calf-vein DVT will extend into the popliteal vein or more proximally. Anticoagulation lowers the rate of proximal propagation and embolization.[19] However, it is not known whether the benefit of anticoagulation outweighs the risk, nor is it known whether anticoagulation is superior to a strategy

of serial venous ultrasound with anticoagulation reserved for DVT that propagate proximally. Several factors should lead the emergency clinician to favor anticoagulation, including: ongoing thrombotic risk (e.g., active cancer, immobility), severe symptoms, DVT longer than 5 cm, DVT close to proximal veins, or a history of prior VTE.[11] High bleeding risk favors surveillance without anticoagulation. When treatment with anticoagulation is used for isolated calf vein thrombosis, the dosing regimen is the same as for proximal DVT (see Table 74.3).

Phlegmasia Cerulean and Alba Dolens

Massive iliofemoral vein occlusion results in swelling of the entire leg, with extensive vascular congestion and associated venous ischemia, producing a painful cyanotic extremity. There may be associated arterial spasm resulting in phlegmasia alba dolens (painful pale leg), which may mimic an acute arterial occlusion. Elevated compartment pressures can also lead to limb ischemia. Phlegmasia is a limb-threatening emergency. Early diagnosis and prompt treatment with catheter-directed thrombolysis, percutaneous thrombectomy, or open surgical thrombectomy may be limb-salvaging. These procedures all require interventional-suite or operating-room capabilities. Therefore, emergency clinicians caring for patients with evidence of phlegmasia in hospitals without these resources immediately available should transfer to a capable center as soon as possible.

Upper Extremity Venous Thromboses

DVTs of the upper extremity have become more common in association with the increased use of indwelling venous catheters and wires for electronic cardiac devices. About half of all upper extremity DVTs are associated with an indwelling catheter, with peripherally inserted central catheters (PICCs) imposing the highest risk. Upper extremity DVT, especially axillary-subclavian vein thrombosis, occurring in the dominant arm of relatively young, physically active, patients is called Paget-Schroetter syndrome or "effort DVT." This is a form of thoracic outlet syndrome and may be secondary to compression of venous structures by hypertrophied scalene muscles or a cervical rib. While the data are not as robust as for lower extremity DVT, a similar diagnostic approach that combines pretest probability assessment, D-dimer testing, and ultrasound appears to exclude upper extremity DVT safely.[24]

Upper extremity DVT can cause PE, and all patients with DVT above the elbow require definitive treatment with anticoagulation prescribed at the same doses as lower extremity DVT (see Table 74.3). Acute PE from an upper extremity DVT occurs in 5% to 8% of patients, although the PE secondary to upper extremity DVT tend to be less severe. The recommended duration of anticoagulation for upper extremity DVT remains variable, but most published guidelines recommend at least 3 months.[11] In the absence of pain or infection, catheter-associated DVT does not automatically warrant catheter removal. The ability to anticoagulate the patient and the clinical necessity of the catheter should be considered. Optimal treatment of isolated brachial vein thrombosis, often the result of a recent intravenous infusion (infusion phlebitis), is uncertain. No study has demonstrated clear benefit for systemic anticoagulation of brachial vein thrombosis. It is reasonable to treat these clots similarly to superficial thrombophlebitis of the leg.

Complications

The most feared complication of DVT is fatal PE. However, DVT also damages venous valves, leading to venous insufficiency, varicose veins, and the post-thrombotic syndrome in 20% to 50% of patients.[25] The post-thrombotic syndrome includes persistent swelling, pain, burning sensation, varicose veins and skin changes, and nonhealing ulcers in 5% to 10% of cases.[25] Compression stockings may provide pain relief for patients with post-thrombotic syndrome, but for patients with a new diagnosis of DVT, compression stockings do not reduce the incidence of post-thrombotic syndrome.[20,26]

Disposition

Most patients with acute DVT can be discharged from the ED as long as reliable systemic anticoagulation can be established, including ensuring that the patient can obtain and pay for their anticoagulant, and follow-up with primary care, an anticoagulation clinic, or other appropriate specialty is available. Protocols that use monotherapy with a DOAC can facilitate outpatient management.[27,28] Patients without reliable follow-up or with challenges to complying with a treatment regimen should have care coordination and education in the ED, observation unit, or inpatient floor prior to discharge. Patients with severe pain may require admission. Patients with iliofemoral DVT are at higher risk for PE, especially when mobile thrombus is visualized on ultrasound, and admission is generally recommended for these patients as well. Patients with possible phlegmasia should be admitted.

PULMONARY EMBOLISM

Clinical Features

Symptoms

The clinical presentation of PE can vary from asymptomatic to sudden cardiovascular collapse. In fact, virtually any ED visit related to shortness of breath, chest pain, palpitations, dizziness, syncope, fatigue, weakness, nonspecific malaise, or functional deterioration could represent a potential PE. However, this does not mean that every patient with these symptoms should be evaluated for PE. Each patient's symptoms need to be considered in the context of the entire clinical picture, including the likelihood of alternative diagnoses.

The most common symptom of PE is dyspnea. If asked in a detailed way, 75% to 80% of patients with PE will report some sensation of dyspnea. Conversely, this means that the most common symptom of PE is absent in nearly one-fourth of patients, so clinicians should be wary of ruling out PE simply because the patient does not have dyspnea (or any particular symptom). A patient with PE typically presents with 2 to 3 days of constant or worsening shortness of breath, though symptoms can be sudden. The dyspnea may be constant or intermittent and perceived only with exertion. It may also be quite vague and described as fatigue or a feeling of not being able to take a complete breath.

Chest pain is the second most common symptom of PE. When chest pain is present, it may be described as pleuritic, achy, dull, or only as a vague discomfort. As many as one-third of patients with PE have no chest pain. Pleuritic pain is a severe, sharp pain that reproducibly halts respiration. When asked, many patients say that their pain is worse with deep breathing, but this is not necessarily pleuritic pain. While pleuritic pain is classically described, it is only present in 20% of patients with PE and is typically only associated with pleural inflammation from peripheral PE that causes pulmonary infarction and inflammation.

When PE causes pulmonary infarction, symptoms can be clinically similar to lobar pneumonia, including pleuritic chest pain, cough, hemoptysis, and fever. However, fever due to PE is typically low grade, and a temperature greater than 101.5°F (38.6°C) suggests infection rather than infarction. Moreover, the presence of several days of a cough productive of sputum suggests pneumonia rather than PE.

Unexplained, unilateral leg swelling is uncommon (<30%) in patients with PE, but when present along with dyspnea or chest pain, should raise suspicion for PE because this symptom is relatively specific.

Overall, fewer than 5% of patients who present with syncope have PE.[29-31] However, unexplained syncope, especially in a patient with PE risk factors, should be considered as a potential presentation of PE even in the absence of dyspnea or chest pain.[32]

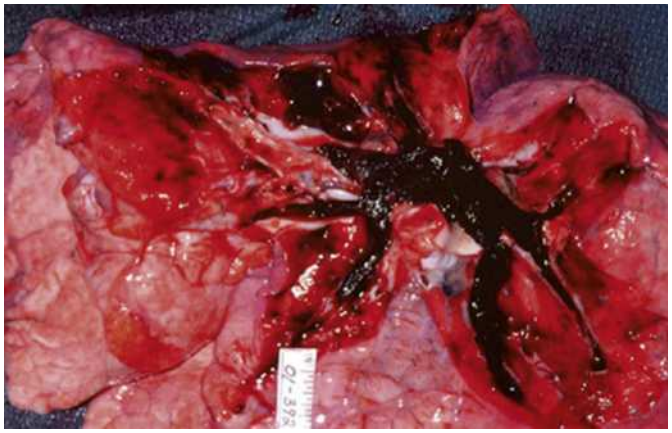

Fig. 74.7 Clinical autopsy photograph from showing a pulmonary embolism completely occluding the right ventricular outflow system.

In its most extreme form, PE can obstruct the entire right ventricular outflow system (Fig. 74.7), leading to sudden cardiovascular collapse and cardiac arrest. Approximately 25% of sudden cardiac deaths are thought to be due to PE. Prior to cardiac arrest, patients with PE typically have a heart rate higher than their systolic blood pressure (i.e., shock index >1),[33] overt respiratory distress, syncope or seizure-like activity, and significant anxiety. With impending cardiac arrest some patients manifest slow agonal rhythms, possibly due to septal wall tension leading to ischemia on the atrioventricular node and infranodal conducting pathways. Pulseless electrical activity ([PEA], >20 depolarizations/min, without palpable pulses) is the most common electrocardiographic (ECG) finding in patients with cardiac arrest due to PE. PEA manifests from right ventricular outflow obstruction and impaired right ventricular contractility. The survival rate from cardiac arrest from PE is about 20%, even if the arrest is witnessed and bolus fibrinolytic medication is given.

Vital Signs

The most common vital sign abnormality in PE is tachycardia, and about half of all patients with PE have a heart rate greater than 100 beats/min. Tachycardia may only be present or may be significantly worsened with ambulation. Tachycardia is associated with more severe PE and worse prognosis. About half of patients have an elevated respiratory rate (>20 breaths/min), though respiratory rate measurement is often variable in the ED. Hypotension (systolic blood pressure < 90 mm Hg) occurs in about 10% of patients but is the single most important predictor of PE mortality, associated with a four-fold increase in risk of death.[33] PE should be on the differential diagnosis for any patient with hypotension unexplained by an initial ED evaluation. Hypotension from PE is due to compression of the left ventricle by the deviated right ventricular septum. Left ventricular compression leads to decreased filling, decreased cardiac output, poor coronary perfusion, and a spiral of cardiac failure. Most studies evaluating the prognostic value of ED vital signs use the patient's worst vital signs (e.g., lowest blood pressure, highest heart rate). Significantly, normalization of a vital sign does not reduce the probability of PE.

Pulmonary embolism can produce hypoxemia (pulse oximetry reading <95% at sea level or <92% at higher elevations), but the degree of hypoxemia is unpredictable. Approximately half of all patients with PE have no evidence of hypoxemia, so a normal oxygen saturation, although reassuring, cannot rule out PE. However, hypoxemia that cannot be explained by a known disease process increases the likelihood of a PE diagnosis. When PE is diagnosed, the severity of hypoxemia represents a significant independent predictor of outcomes.

Physical Examination

Most patients with PE have no obvious abnormality on physical examination. The only finding that reliably increases the probability of a PE diagnosis is evidence of a DVT, such as unilateral leg asymmetry, unilateral edema, or tenderness along a deep vein.[1] On the other hand, the physical examination can provide clues to alternative diagnoses. Wheezing, or a prolonged expiratory phase on lung auscultation, suggests the alternative diagnosis of bronchospasm, which reduces the probability of PE. Bilateral rales suggest the diagnosis of left ventricular failure, although localized rales can also be heard over infarcted lung tissue.

Some clinical findings can also make the diagnosis of PE more difficult. A diagnosis of PE is more likely to be delayed in patients with baseline dementia, altered mental status, and multiple comorbidities. Additionally, symptoms, signs, and radiographic findings that support a diagnosis of pneumonia can lead to a missed or delayed PE diagnosis. Emergency clinicians may be prone to miss small, distal PE that produce pleuritic pain, rales, and peripheral densities on chest radiographs.

Differential Diagnosis

The differential diagnosis for PE includes any thoracic process associated with chest pain, dyspnea, or lightheadedness. Alternative diagnoses include pneumonia, acute coronary syndromes, aortic dissection, pericarditis, pleural or pericardial effusion, pulmonary hypertension, pneumothorax, acute decompensated congestive heart failure, asthma, chronic obstructive pulmonary disease, gastroesophageal reflux, dyspepsia, musculoskeletal pain, and nonspecific chest pain. Most alternative diagnoses can be ruled out with a thorough history, physical examination, chest radiographs, ECG, cardiac troponin testing, and echocardiography.[34,35] In ED patients evaluated for possible PE, pneumonia is the most common alternative diagnosis suspected by clinicians, and the most common alternative diagnosis found on computed tomography pulmonary angiography (CTPA), present on 5% to 10% of scans.

Diagnostic Testing

Figure 74.8 provides an algorithmic approach to PE diagnosis.

Bedside Assessment

The first step in the evaluation of possible PE is determining whether testing for PE is indicated at all. Each year, more than 16 million patients, or 12% of all patients who present to the ED, have chest pain or dyspnea. Not all of these require an evaluation for PE. Most ED patients have at least one risk factor for PE (e.g., advanced age, obesity, hormone use), so epidemiologic risk factors for PE do not necessarily mandate a workup for PE. Emergency clinicians currently evaluate 1% to 2% of all ED patients for PE with CTPA. Even more patients undergo D-dimer testing, the overuse of which has been shown to increase the use of CTPA. Because CTPA imposes risks to patients, including exposure to ionizing radiation, IV contrast, and the risk of a false-positive interpretation, it is essential to weigh the risk of a PE diagnosis against the potential risks of testing. The decision to pursue a diagnosis of PE should be based on each patient's presentation.

Determining whether objective testing is indicated requires the clinician to estimate the patient's probability of a PE diagnosis. The "test threshold" represents the point below which testing is more likely to harm than benefit the patient. For PE, the test threshold is from 1.5% to 2%. Patients with less than 1.5% to 2% probability of PE are more likely to be harmed by testing than to benefit, so testing is best avoided in these very low pretest probability patients. Conversely, patients with greater than 2% probability of PE are more likely to benefit from testing for PE than to be harmed. These patients should undergo objective

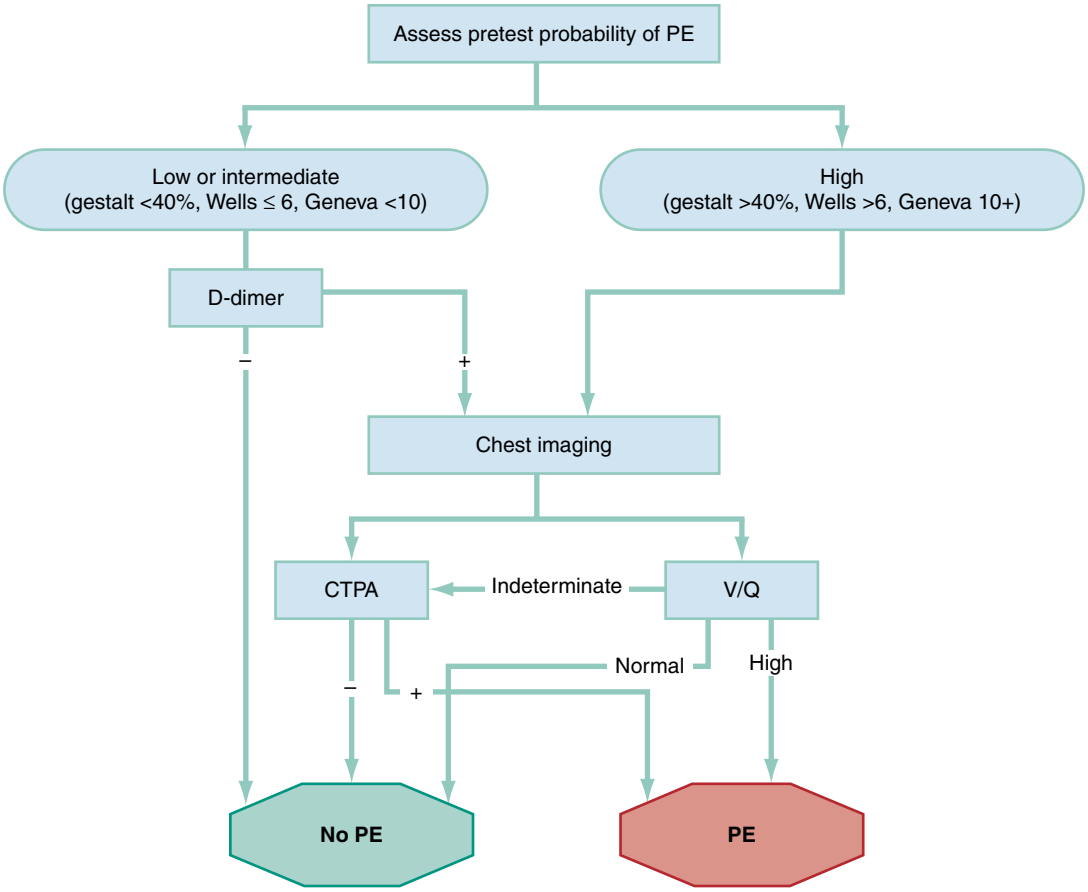

Fig. 74.8 Flowchart algorithm showing the diagnostic approach to a patient with possible pulmonary embolism. This algorithm starts with the assessment of pretest probability and includes a combination of D-dimer testing and pulmonary vascular imaging. In most cases, computed tomography pulmonary angiography (CTPA) will be the imaging test of choice, but ventilation/perfusion ($\dot{V}/\dot{Q}$) scanning is also appropriate for patients with normal chest radiographs and a contraindication to CTPA. *PE*, pulmonary embolism; *–*, test negative; *+*, test positive; *CTPA*, computed tomography pulmonary angiography; *$\dot{V}/\dot{Q}$*, ventilation/perfusion.

testing for PE unless there is a viable alternative diagnosis, as the presence of an alternative diagnosis significantly decreases the likelihood of PE in an ED patient.

It follows then that tests that demonstrate alternative diagnoses can affect the need for a PE workup, and most patients who present with symptoms suggestive of PE will have at least some testing that provides information on alternative diagnoses. Chest radiography, although nonspecific for PE, can provide evidence of pneumonia, congestive heart failure, or pneumothorax. However, chest radiographs must be interpreted carefully, as pulmonary infarction may be visible on chest x-ray as a pleural-based, wedge-shaped infiltrate, "Hampton's hump," which can be confused for peripheral pneumonia.

Like a chest x-ray, a 12-lead ECG provides more information about the presence of alternative diagnoses (e.g., pericarditis, cardiac ischemia) than the presence of PE. When PE does cause ECG changes, it is usually a result of acute or subacute pulmonary hypertension and associated right ventricular dysfunction. The most common finding of PE on the ECG is tachycardia. Symmetric T-wave inversion in the anterior leads (V_1–V_4), the McGinn-White S1Q3T3 pattern, and incomplete or complete right bundle branch block (Fig. 74.9) indicate acute cor pulmonale and are associated with more severe PE.[36] Although these findings are nonspecific, especially in the presence of preexisting lung disease, the presence of any one of them approximately doubles the probability of PE in a symptomatic patient.

Biomarkers including cardiac troponin, B-type natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), and lactate can all be elevated in PE. An elevated troponin indicates myocardial injury and is associated with higher mortality after PE.[37] The degree of troponin elevation predicts the degree of RV strain and mortality from PE. The appropriate use of high-sensitivity troponin assays is not well defined for PE.[38] BNP and NT-pro-BNP are released from cardiac myocytes in the setting of myocardial distention and increased pressure. Individuals with PE and high BNP or NT-pro-BNP levels are at increased risk of a complicated in-hospital course and 30-day mortality after PE. However, isolated elevated BNP is a nonspecific finding, and these results must be interpreted in the context of the complete clinical picture. PE can cause end-organ hypoperfusion, and normotensive PE patients with elevated plasma lactate (≥2 mmol/L) have significantly higher mortality, are more likely to develop of shock or hypotension, require intubation, or CPR.[39]

Bedside ultrasound can be useful when PE is suspected. The presence of acute DVT on bedside venous ultrasound in a patient with new symptoms of PE is equivalent to a PE diagnosis and sufficient to initiate treatment. Emergency clinician–performed venous ultrasound is 86% to 96% sensitive and 93% to 97% specific compared to radiology-performed ultrasound.[40] However, emergency clinicians must keep in mind that fewer than half of patients with PE have no ultrasound evidence of DVT, so a negative ultrasound is not sufficient to rule out PE.

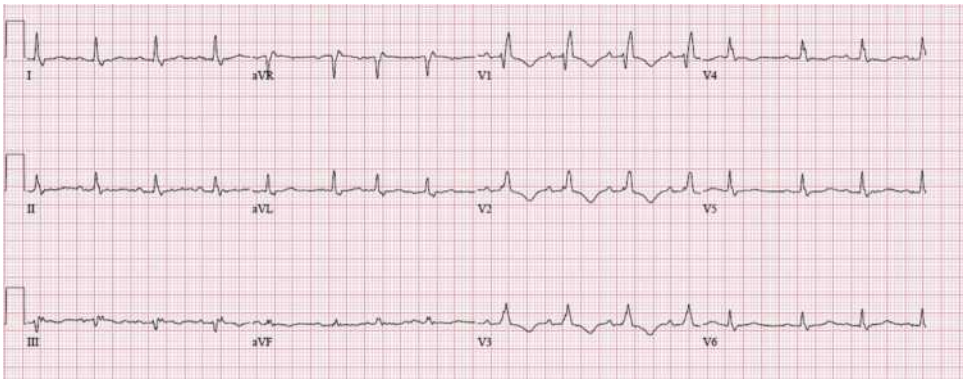

Fig. 74.9 Electrocardiogram from a patient who presented with PE in the right main pulmonary artery (see Fig. 74.3B). The presence of deep T-wave inversions in leads $V_{1–3}$, a new complete right bundle branch block, and the S1Q3T3 pattern all indicate right ventricular dysfunction (acute cor pulmonale) and are associated with poor prognosis.

TABLE 74.4 Wells Score for Pulmonary Embolism

Clinical Feature	Score
Previous PE or DVT	1.5
Heart rate > 100 beats per min	1.5
Recent surgery or immobilization (within 4 weeks of presentation)	1.5
Clinical signs of DVT (swelling or tenderness on palpation of the calf)	3
Hemoptysis	1
Active cancer (treated within the previous 6 months or currently receiving palliative treatment)	1
An alternative diagnosis is less likely than PE	3

A score <2 indicates that the probability of deep vein thrombosis is low, 2–6 intermediate, and >6 high.
PE, Pulmonary embolism; *DVT*, deep vein thrombosis.

TABLE 74.5 The Revised Geneva Score for Pulmonary Embolism

Clinical Feature	Score
Age >65 years old	1
Previous PE or DVT	3
Recent surgery or immobilization (within 4 weeks of presentation)	2
Active cancer (treated within the previous 12 months or currently receiving palliative treatment)	2
Unilateral leg pain	3
Hemoptysis	2
Heart rate	<75 = 0 75–94 = 3 >95 = 5
Pain on palpation and unilateral edema of the leg	4

A score <4 indicates that the probability of deep vein thrombosis is low, 4–10 intermediate, and >10 high.
PE, Pulmonary embolism; *DVT*, deep vein thrombosis.

Point-of-care echocardiography showing RV dilatation (a ratio of the RV to LV internal diameter in diastole [RV : LV ratio] >1 : 1) should also increase the clinical suspicion of PE, especially in a patient with no previous lung disease.

Pretest Probability Assessment

Once the decision to initiate a PE evaluation has been made, the next step is determining the patient's PTP of PE. The PTP guides what (if any) objective testing for PE should be performed and whether empirical therapy should be initiated. There are several acceptable methods for estimating PTP. An experienced emergency clinician can accurately assess PTP using their clinical experience, or "gestalt."[35] In fact, clinical gestalt has been shown to be the most accurate method of PTP assessment. Clinicians can also use one of several clinical scoring systems. The Wells Score (Table 74.4) and the Revised Geneva Score (Table 74.5) are both well-validated.

For the purposes of determining further testing, the Wells score can be divided into non-high (0–6 points) or high (>6 points) probability. A three-tiered interpretation of the Wells score is also accepted, but the intermediate-risk middle category is less easily adapted to binary ED decision making. The Wells score includes a subjective question that asks whether PE is the most likely diagnosis. This empowers the clinician to include elements that may be uncommon yet important to consider in the PTP assessment, such as inherited clotting disorders. However, the subjective component seems to power most of the predictive value of the Wells score and may introduce intrarater variability.

The Revised Geneva Score (and a simplified version of the score), includes only objective elements. Patients with 0 to 3 points are defined as low probability, 4 to 10 points as intermediate probability, and greater than 10 points as high probability. Several studies have found the Wells score and Geneva score perform similarly in clinical practice, and both of these systems can be built into clinical decision support systems to guide testing. Importantly though, when used alone, none of these methods reproducibly identify the very low-risk population whose PTP lies below the 2% test threshold.

Pulmonary Embolism Rule-Out Criteria

To identify the patients in whom PE can be safely excluded without objective testing, emergency clinicians should use the PE rule-out criteria, or "PERC rule" (Box 74.6).[41-43] When the clinician's unstructured PTP assessment (i.e., clinical gestalt) for PE is low, and each of the eight elements of the rule is satisfied, the PERC rule identifies patients whose probability of PE is below the 2% test threshold. For these patients, laboratory testing or imaging for PE is more likely to expose the patient to harm than to provide benefit, so testing should not be performed. The PERC rule has been validated in large studies in the United States and Europe.[41,43] When calculating the PERC, it is important that PTP be

BOX 74.6 Pulmonary Embolism Rule-Out Criteria (PERC Rule)

- Age < 50
- Pulse < 100
- Sao_2 > 94%
- No unilateral leg swelling
- No hemoptysis
- No recent trauma or surgery
- No prior PE/DVT
- No hormone use

determined using the clinician's gestalt, as the PERC rule contains similar elements to both the Wells and Geneva scores, so may not perform as well in combination with these methods of PTP assessment.

D-Dimer Testing

D-dimer assays are 95% to 98% sensitive and 40% to 55% specific for PE.[2,44] Therefore, patients with a non-high PTP (gestalt PTP < 40%, Wells score <6, or Revised Geneva score <5) can have PE excluded with a normal D-dimer concentration with negative predictive value of 99% to 100%. Large, real-world studies have shown that many ED patients still undergo CTPA despite a negative D-dimer. However, emergency clinicians should recognize that a false-positive CTPA is actually more likely than a false-negative D-dimer, so ordering imaging "to be safe" exposes the patient to unnecessary risk.

When false-negative D-dimer results do occur, it may be because the PE is subacute or chronic. The half-life of circulating D-dimer is less than 8 hours. However, the clinical relevance of the circulating half-life is unknown, because large PE continue to release D-dimer as they lyse over time. False-negative D-dimer measurements may also be seen with severe lipemia and ongoing warfarin therapy. Isolated subsegmental PE seen on CTPA may also be associated with negative D-dimer results, but in these cases the emergency clinician will need to determine whether the D-dimer is a false negative or the CTPA is a false positive.

Many conditions elevate the D-dimer other than PE and DVT (see Box 74.2). Because a positive result often necessitates diagnostic imaging, emergency clinicians should consider the likelihood of a positive D-dimer before ordering the test. This is especially true when CTPA carries additional risk to the patient (e.g., pregnant women, renal insufficiency) or is contraindicated (e.g., anaphylaxis with contrast dye).

The threshold for a negative D-dimer can vary by assay and local laboratory. In many laboratories, the threshold below which D-dimer is considered negative is 500 ng/mL. When the 500 ng/mL cutoff is used, the threshold for a positive D-dimer can safely be adjusted according to the patient's age using the following formula:[2-5]

$$\text{Age} \times 10\ \text{ng/mL}$$

This strategy maintains a sensitivity greater than 95% and negative predictive value greater than 98%, but increases the percentage of patients who can have PE excluded without pulmonary vascular imaging by 5% to 6% overall and 10% to 20% in patients greater than 70 years old.[5] The safety of this strategy has not been tested with D-dimer assays with abnormal thresholds different than 500 ng/mL.

As with DVT, emergency clinicians can also apply a Bayesian approach by which the threshold for a positive D-dimer is increased based on PTP. Using this strategy, patients with low PTP can have DVT ruled out using a threshold of 1000 ng/mL (for a test that normally uses 500 ng/mL).[45] A study of 2017 patients evaluated for PE found that this approach was associated with no missed PE diagnoses on follow-up and reduced the need for chest imaging by 17%.

The YEARS algorithm is another approach that uses three questions from the Wells score (clinical signs of DVT, hemoptysis, alternative diagnosis less likely than PE) to identify low PTP patients for whom the higher D-dimer threshold can be used.[46] YEARS has been validated in a large multicenter study and decreased the need for CTPA by 14%.[47] However, in the validation study, the same result was achieved using only the subjective question of the Wells score, "Are alternative diagnoses less likely than PE?," as the criteria for low PTP. The YEARS criteria have also been adapted for use in pregnant women.[48] In a study of 512 pregnant women suspected of having PE, CTPA was avoided in 195 (39%) patients, and 20 women were diagnosed with PE. However, the efficiency of the score varied significantly according to the trimester of pregnancy. Imaging was deemed not indicated for 65% of women in the first trimester of pregnancy, but for only 32% in the third trimester.

Computed Tomography Pulmonary Angiography

When the PTP is high or the screening D-dimer is positive, pulmonary vascular imaging is advised. Most centers use CTPA as the primary imaging method for evaluating possible PE. CTPA is readily available, minimally invasive, and can identify alternative processes that might explain the patient's symptoms.

Many PE, especially central PE, can be easily visualized by the emergency clinician. PEs appear as hypodensities in contrast-filled pulmonary arteries. Most PE will be in the central part of the lumen near the bifurcation of a vessel. Filling defects that appear peripheral or concentric may be chronic or may represent alternative processes or artifacts. A PE that extends across the bifurcation of both main pulmonary arteries is called a saddle PE. Although they tend to be large clots, many saddle PE are not occlusive, so patients may be minimally symptomatic. PE that extend into the pulmonary arteries may lodge in a main pulmonary artery, intralobar, lobar, segmental or subsegmental artery (see Fig. 74.3). PE are typically described according to their most proximal location, so a clot that extends from the lobar pulmonary artery into a segmental branch is described as lobar. While radiologists may describe a PE as "massive" based on the size of the clot, emergency clinicians should remember that "massive PE" is a physiologic diagnosis based on hemodynamic instability, and clot burden on CT has only a loose association with mortality. Due to this confusion, the term *high-risk PE* is a preferred term to describe the PEs resulting in hemodynamic instability.

A technically adequate CTPA scan, performed on a multidetector row scanner, has sensitivity and specificity of 90% to 95%. Technical adequacy requires more than 200 HU of contrast opacification in the main pulmonary artery and absence of motion artifact. Scans that are not technically adequate are less sensitive and specific for PE. Although the sensitivity of CT can be improved slightly by extending the scan to include the leg veins (CT venography), the technical reliability of this technique is limited and the additional radiation required is substantial, so most centers do not routinely perform "run-off" venography. As with any test, the probability of PE after CTPA should be based on a combination of the patient's pretest probability and the CTPA results. A negative CTPA in a patient with high pretest probability should be interpreted with caution because the negative predictive value in this population is only about 60%. Further testing such as leg ultrasound may be indicated to rule out PE. Similarly, an isolated subsegmental filling defect on CTPA in a patient with low pretest probability and no DVT on leg ultrasound is likely to be a false positive. In these cases, treatment should be based on shared decision making with the patient. The increased detection of isolated subsegmental filling defects on more thinly collimated CTPA images, combined with increased CTPA use, has led to the overdiagnosis of PE.

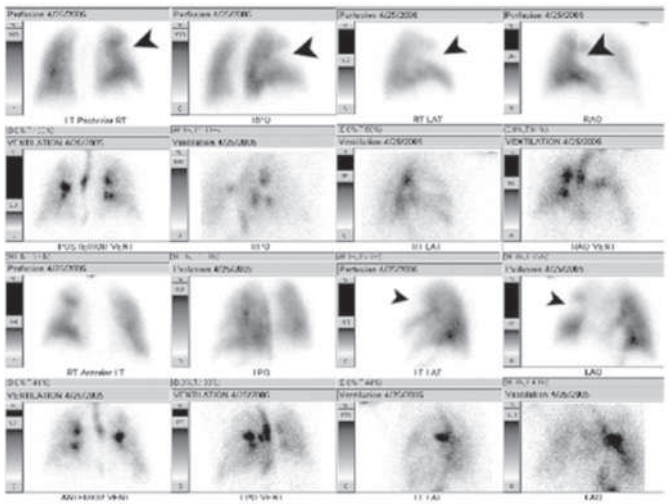

Fig. 74.10 Diagnostic ventilation/perfusion (V̇/Q̇) scan. These images are high probability for acute pulmonary embolism based on the criteria defined in the prospective investigation of pulmonary embolism diagnosis (PIOPED). The first and third rows project the perfusion phases of the examination, and the second and fourth rows show the ventilation phases. The black arrowheads point to wedge-shaped defects in the perfusion images. Comparison with the corresponding ventilation view immediately below shows relatively homogeneous scintillation activity in the anatomic segments that lack perfusion.

Ventilation/Perfusion Scan

The V̇/Q̇ scintillation scan remains a viable diagnostic option for patients with contraindications to iodinated intravenous contrast and vulnerable kidney function. The accuracy and precision of the V̇/Q̇ scan were shown in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, which compared the results of V̇/Q̇ scanning with the most accurate criterion standard test available at the time, catheter pulmonary angiography. Figure 74.10 shows the results of a high-probability V̇/Q̇ scan. A high-probability V̇/Q̇ scan confirms the diagnosis of PE, and a normal scan (i.e., no perfusion defect) excludes PE. However, only one-third of V̇/Q̇ scans fall into either the high-probability or normal categories. The remaining two-thirds of scans are read as either low probability or intermediate probability. These categories indicate indeterminate scans that are essentially nondiagnostic. Many patients, therefore, require additional diagnostic testing after an indeterminate V̇/Q̇ scan. When feasible, these patients should undergo CTPA, though negative bilateral venous ultrasonography of the legs can also be used to rule out PE in patients with a low PTP and a low-probability V̇/Q̇ scan.

V̇/Q̇ scanning is generally associated with lower fetal radiation exposure than CTPA. When the perfusion portion of the V̇/Q̇ scan is performed first, and the scan is normal, the ventilation portion of the scan may be avoided, further reducing the radiation exposure to the woman and the fetus. However, for technical reasons, most institutional protocols perform the ventilation portion of the scan first. In addition, because many women will require CTPA after an indeterminate V̇/Q̇ scan, and will be exposed to two doses of radiation, many institutions now recommend shielded, low-radiation CTPA rather than V̇/Q̇ scanning as the first test for pregnant women.

Pregnant Women

Pregnancy is a hypercoagulable state, and when combined with mechanical compression of the pelvic veins by the gravid uterus, increases the risk of PE, especially in the third trimester and postpartum period. However, when studied in ED patients undergoing diagnostic testing for PE, pregnancy does not appear to increase the risk of a VTE diagnosis.[1] This is because emergency clinicians tend to be conservative in their approach to the pregnant woman with signs or symptoms of PE and have a much lower threshold to order diagnostic testing. Most pregnant women whom emergency clinicians test for PE have a low clinical probability, though there is significant variation in the threshold to test because clinical decision rules, including the Wells score and PERC rule, have not been validated in pregnant women.

VTE in pregnancy is relatively rare, so even the largest studies are limited to a few dozen positive cases.[48] Because D-dimer levels are increased in pregnancy, the lower threshold to test employed by emergency clinicians results in many pregnant women being referred for imaging. However, pregnant women are justifiably cautious about fetal radiation exposure and may not choose to undergo CTPA when it is recommended. Emergency clinicians should have a predefined strategy for diagnostic testing of pregnant women with possible PE. Guidelines vary in their recommendations, and there is no single, data-driven approach to testing.

Before initiating any testing for PE, it is prudent to explain the diagnostic options to the patient, including the risks and benefits of different approaches, obtain her preferences, and document these stated preferences. Pregnant women should be given the opportunity to consider their testing preferences free from the bias associated with knowing D-dimer or other test results.

When the decision is made to pursue testing, it is best to begin with noninvasive, nonionizing testing. In a study of 395 pregnant women (28 [7.1%] with PE), bilateral lower extremity ultrasound and D-dimer testing were performed as first-line tests to either rule in or rule out VTE.[49] A positive lower extremity ultrasound for DVT in a pregnant woman suspected of having PE is sufficient to confirm the diagnosis of PE and to initiate treatment. When the conventional threshold for a positive D-dimer used for nonpregnant patients is applied (e.g., <500 ng/mL), a normal D-dimer excludes PE in pregnant women as reliably as in the nonpregnant population. However, most women will have a positive D-dimer and negative venous ultrasound results. In the previously mentioned study, 83% of women required CTPA or V̇/Q̇ scanning. Therefore, before pursuing this approach, pregnant women should be informed that imaging is likely to be needed. This will inform their shared decision to pursue a PE workup.

One reason a small proportion of women can be ruled out with noninvasive testing is that D-dimer levels fluctuate and steadily increase throughout pregnancy until they peak on the first day after delivery.[50] The proportion of women with normal D-dimer values is 50% to 85% in the first trimester, decreases to 23% to 33% in the second trimester, and to 0% to 4 % in the third trimester. Pregnancy-specific threshold values for each trimester have been suggested to help increase the proportion of women who can have PE ruled out without imaging. One model suggests using a threshold of 750 ng/mL in the first trimester, 100 ng/mL in the second trimester and 1250 ng/mL in the third trimester. However, outcome data supporting this approach are limited to studies with fewer than 20 pregnant women with VTE, so the safety of D-dimer adjustment based on pregnancy trimester has not been validated.

The YEARS approach has been modified for use in pregnancy, with a screening venous ultrasound performed first, followed by PTP-adjusted D-dimer based on the same three Wells score criteria used in the original study.[48] Among 498 women, 4 had DVT on screening ultrasound, and 16 were diagnosed with PE based on a combination of PTP adjusted D-dimer testing and chest imaging. Nearly one-third of women in the third trimester had PE ruled out without imaging, and only one subject was diagnosed with DVT after having PE ruled out in the ED. However, as with other studies of pregnant women, the small

TABLE 74.6 Fetal and Maternal Radiation Exposure Associated With Diagnostic Tests for PE

Imaging Method	Fetal Exposure (mSv)	Maternal Exposure (mSv)
Chest x-ray (two view)	<0.01	<0.01
Ventilation lung scan	0.1–0.3	<0.01
Perfusion lung scan	0.1–0.6	0.2–1.2
CTPA	0.01–0.66	7–70
Catheter pulmonary angiogram	3–6	15–20
CT venogram of the iliac veins	10–50	10–50

CTPA, Computed tomography pulmonary angiography; *CT*, computed tomography.
Adapted from: Linnemann B, Bauersachs R, Rott H, et al. Diagnosis of pregnancy-associated venous thromboembolism—position paper of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH). *Vasa*. 2016;45(2):87-101.

number of PE events makes it difficult to recommend this approach confidently.

For pregnant women for whom PE cannot be ruled in with ultrasound or ruled out with D-dimer, chest imaging is indicated. In this case, women often have questions about radiation exposure and the safety of the fetus. For comparison, the fetal radiation exposures of various tests for PE are presented in Table 74.6. The average dose of naturally occurring background radiation is 0.5 to 1.0 mSv over a normal gestation. Exposure to radiation doses lower than 50 mSv has not been shown to be associated with different pregnancy outcomes.[51] In the first two weeks after conception, a radiation dose of 50 to 100 mSv can cause the failure of blastocyst implantation and spontaneous miscarriage. Assuming the blastocyst implants, radiation effects are unlikely because blastocyst cells are omnipotent and damaged cells can be replaced (the "all-or-none period"). The embryo is most vulnerable to radiation between the eighth and fifteenth weeks of gestation. A definitive threshold has not been determined, but it is estimated that the risk of congenital malformations, intrauterine growth restriction, intellectual disability, and pregnancy loss increase at radiation doses beyond 100 to 200 mSv. The risk of cancer associated with fetal radiation exposure is difficult to predict, but even with higher radiation doses many times higher than those used for CTPA, the increase in lifetime cancer due to in-utero radiation exposure from diagnostic imaging seems to be negligible.[51]

Data comparing fetal radiation exposure do not clearly favor $\dot{V}/\dot{Q}$ or CTPA. Regardless of the approach, efforts should be made to minimize radiation exposure to the developing fetus. Because ^{99}Tc is excreted in the urine, prehydration with intravenous saline, frequent postscan urination, and insertion of a urinary catheter are unproven steps to reduce fetal exposure to radiation associated with $\dot{V}/\dot{Q}$ scanning. When CTPA is performed, shielding of the abdomen and tube voltage modulating technology may reduce fetal radiation exposure. Thus, while high-probability (i.e., diagnostic) or normal (i.e., exclusionary) $\dot{V}/\dot{Q}$ scanning may be associated with lower fetal radiation exposure than CTPA, the difference in radiation exposure of the two tests is minimal. However, many women have nondiagnostic $\dot{V}/\dot{Q}$ scans and need to undergo CTPA that will expose them to more radiation than if a CTPA had been performed first. Therefore, CTPA seems the best first test for most pregnant women.

Clinical Course

The clinical course of patients with obstructive PE can be unpredictable. The mortality of high-risk PE is greater than 25%,[52] but many patients with high-risk PE remain stable in the ED after initial resuscitation. In otherwise stable patients, clinical deterioration can occur rapidly due to embolization of clot material, release of mediators of pulmonary vasospasm, sudden dysrhythmias, or respiratory failure. Of ED patients without hypotension, 1% to 3% experience cardiac arrest while in the ED or die within 24 hours. Factors independently associated with clinical deterioration after PE diagnosis include ED hypotension, hypoxemia, prior coronary artery disease, residual deep vein thrombosis, and right heart strain on echocardiogram. Clues to oncoming cardiopulmonary decompensation include worsening respiratory distress and hypoxemia, increasing tachycardia and shock index, or a change in mental status. Deterioration in the ECG from a narrow-complex tachycardia to an incomplete right bundle branch block to a complete right bundle branch block also suggests life-threatening pulmonary hypertension.

Management

The treatment of acute PE depends on the risk that the PE poses to the patient (Table 74.7). PE are classified as high risk, or "massive," intermediate risk or "submassive," and low risk. These risk categories are defined by the hemodynamic status of the patient and the presence of right ventricular dysfunction, not by the size of the thromboembolism. Therefore, to avoid confusion sometimes associated with the term "massive" and "submassive" we use the terms high, intermediate, and low risk.

High-risk PE result in hemodynamic instability, defined as a systolic arterial pressure (SBP) less than 90 mm Hg that is sustained for 15 minutes and not caused by dysrhythmia or other etiology.[57] Patients who have a drop in their baseline SBP of greater than 40 mm Hg, who require vasopressors, or who have profound bradycardia (<40 bpm) can also be considered high-risk PE. It is also reasonable to require that the patient's PE be large enough to conceivably cause the patient's hemodynamic instability.

Intermediate-risk PE requires that the patient be hemodynamically stable and have evidence of RV dysfunction on echocardiogram or a positive troponin. Echocardiographic evidence of RV dysfunction includes RV dilatation, hypokinesis, or bowing of the intraventricular septum toward the left ventricle (LV). RV dilatation on CT (defined as an RV : LV ratio >1) is 88% sensitive for RV dysfunction on echocardiogram, but is only 39% specific.[58] CT evidence of RV dysfunction should, therefore, be confirmed with echocardiography. Some guidelines also use a clinical risk model (i.e., the pulmonary embolism severity index [PESI]) and troponin values to subcategorize patients as intermediate-low or intermediate-high risk.[59]

Low-risk PE are hemodynamically stable with no evidence of RV dysfunction. These risk categories are important because the mortality increases from less than 1% to 3% (low risk) to 3% to 15% (intermediate risk) to 15% to 50% (high risk). Accordingly, advanced therapies like thrombolysis or thromboembolectomy are not recommended

TABLE 74.7 Risk Stratification and Treatment Recommendations for Acute PE

Category	Criteria	Action
Low-Risk PE	Hemodynamically stable	Initiate anticoagulation (DOAC preferred)
	No right ventricular dysfunction	Safe for outpatient treatment based on Figure 74.12 or negative Hestia criteria
	Troponin negative	Optional admission to inpatient service or observation unit
Intermediate-Risk PE	Hemodynamically stable	Initiate anticoagulation (DOAC or heparin)
	Any of the following:	Thrombolysis or thromboembolectomy in a minority of cases
	• Right ventricular dysfunction on echocardiogram or CTPA	Activate PERT
	• Troponin positive	Admission to monitored bed or ICU
	• BNP/NT-pro-BNP positive	
High-Risk PE	Hemodynamically unstable	Initiate anticoagulation (heparin if thrombolysis or thromboembolectomy planned)
		Activate PERT
		Thrombolysis or thromboembolectomy unless contraindicated
		Admission to ICU

PE, Pulmonary embolism; *DOAC*, direct-acting oral anticoagulant; *CTPA*, computed tomography pulmonary angiography; *PERT*, pulmonary embolism response team; *BNP*, brain natriuretic peptide; *ICU*, intensive care unit.

for low-risk patients, sometimes recommended for intermediate-risk patients, and recommended for high-risk patients.

Figure 74.11 presents a comprehensive management plan for diagnosed PE. This algorithm includes the spectrum of treatment options, including some that may only be available in a large tertiary care service hospital. Emergency clinicians should be familiar with the treatment options where they practice. Pathways similar to this have been adopted by multidisciplinary PE response teams (PERT).[52,60-62] At the left-most side of the algorithm, patients can be discharged to home from the ED. At the right side, patients with a massive PE and no contraindications receive thrombolysis or are referred for emergent thromboembolectomy.

Airway, Oxygenation, and Ventilation

Hypoxemia is common in PE and hypoxemic vasoconstriction may worsen acute pulmonary hypertension, so supplemental oxygen should target pulse oximetry above 90%. However, intubation and positive-pressure ventilation increase intrathoracic pressure, lower preload, and can worsen RV compression of the LV. This may precipitate hemodynamic collapse and cardiac arrest in patients with severe PE. Intubation should, therefore, be avoided whenever possible. When intubation is necessary, the emergency clinician should optimize pre-intubation hemodynamics, including with vasopressors, prior to induction.[53]

Hemodynamic Resuscitation

For patients who present with actual or pending hemodynamic instability, the first priority is resuscitation. For hypotensive patients, small volume boluses (such as 250–500 mL) can improve cardiac output.[12] However, excessive administration of intravenous fluids can worsen RV distension and compression of the left ventricle by the intraventricular septum. Figure 74.5 shows that with increased pulmonary artery pressures, the dilated RV distends towards the intraventricular septum, which can decrease left ventricular volume. This, in turn, decreases cardiac output, increases myocardial ischemia, and can precipitate cardiac arrest.

If the administration of intravenous fluids is contraindicated or no longer beneficial, vasopressors should be administered, and norepinephrine should be the initial agent in blood pressure support.[12] Dobutamine is useful as an adjunct but may worsen hypotension unless coadministered with norepinephrine.

Extracorporeal membrane oxygenation (ECMO) can unload the right ventricle, increase cardiac output, and provide a bridge to thrombolysis or thromboembolectomy for patients with high-risk PE.[54] ECMO requires institutional infrastructure and expertise which is only available in specialized centers. Survival of patients with PE who require ECMO is about 70%.[54,55]

Pulmonary Vasodilators

Inhaled nitric oxide and epoprostenol have been shown to decrease pulmonary vascular resistance and pulmonary arterial pressure in case series. However, a clinical trial failed to show benefit of inhaled nitric oxide in hemodynamically stable patients with PE and right ventricular dysfunction.[56]

Standard Anticoagulation

Patients with imaging confirming DVT or PE should receive anticoagulation using one of the agents in Table 74.3, administered in the ED as soon as the diagnosis is confirmed. Patients with a high PTP, no contraindication to anticoagulation, and evidence of hemodynamic instability, including recent syncope, hypotension, hypoxemia, or right heart dysfunction, should receive empirical anticoagulation while awaiting pulmonary vascular imaging. Direct-acting oral anticoagulant medications apixaban or rivaroxaban are now considered first-line therapy for most PE.[11] These drugs specifically inhibit one enzyme in the clotting pathway, are orally available, and provide therapeutic anticoagulation effect as rapidly as subcutaneous LMWH. Clinical trials support the use of apixaban and rivaroxaban without prior or concomitant use of heparin. By obviating the need for twice-daily subcutaneous injections and blood monitoring, these drugs can also facilitate outpatient treatment of PE and DVT.[28] DOAC medications have not been extensively tested in patients with severe PE, pregnant women with PE, or in patients with hypercoagulable states like antiphospholipid antibody syndrome. For these patients, LMWH is preferred. Compared to unfractionated heparin, meta-analyses show that LMWH is associated with lower rates of major hemorrhage, heparin-induced thrombocytopenia, and recurrent VTE, and has similar cost. Most hematologists, internists, and obstetricians prefer that pregnant patients with VTE receive twice-daily LMWH. Both DOAC and LMWH effects can be unreliable in patients with severe renal impairment. For these patients, unfractionated heparin is usually preferred. Patients with a history of

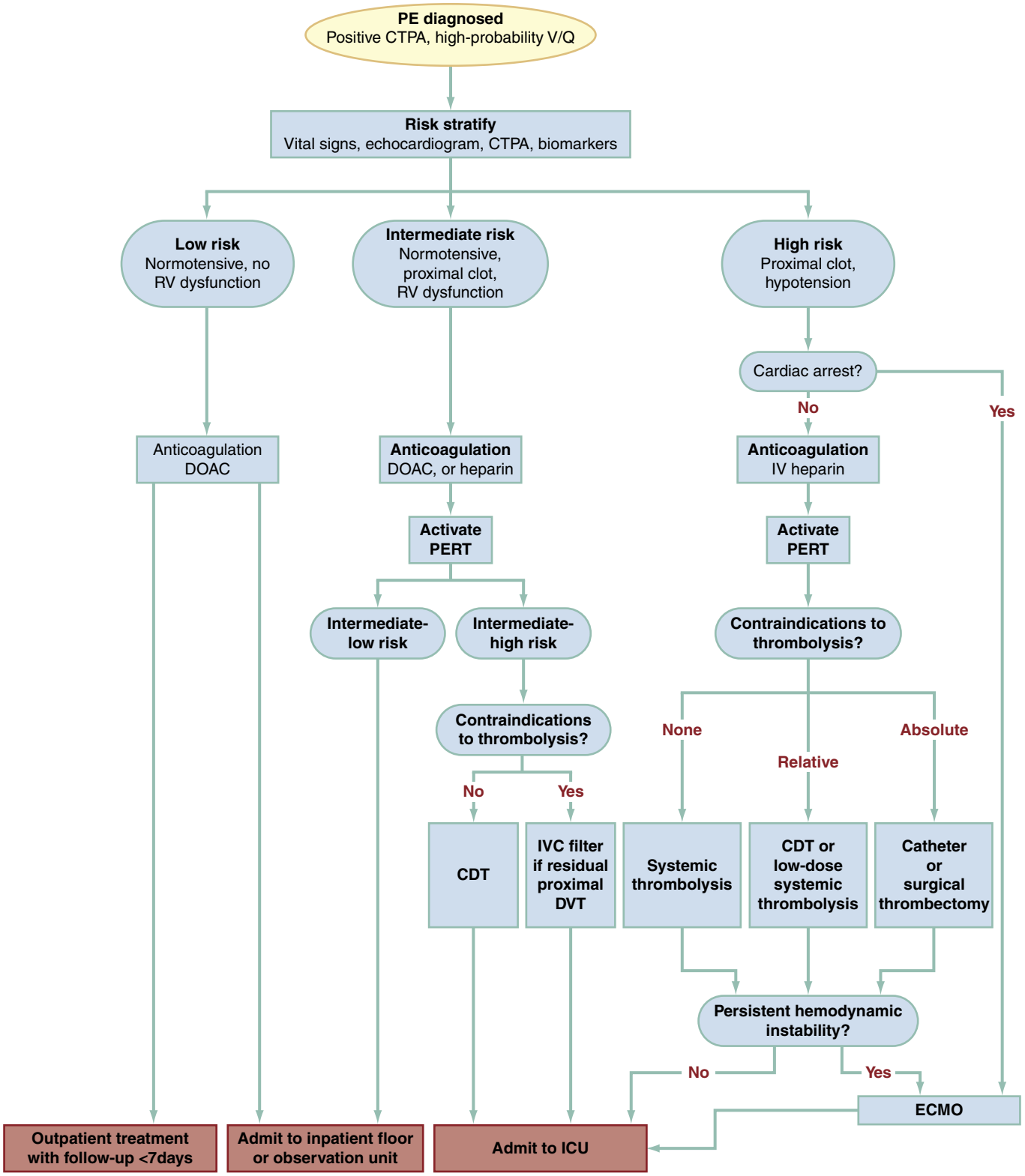

Fig. 74.11 Flowchart algorithm showing the treatment approach to patients diagnosed with acute pulmonary embolism (PE) in the emergency department of a full-service, tertiary-care hospital. This algorithm focuses on PE-specific treatment, rather than acute resuscitation. Low-risk PE are hemodynamically stable with no evidence of RV dysfunction. Intermediate-risk PE are hemodynamically stable but have evidence of RV dysfunction on echocardiogram or a positive troponin. Echocardiographic evidence of right ventricular (RV) dysfunction includes echocardiographic RV dilatation, hypokinesis or bowing of the intraventricular septum towards the left ventricle (LV) or RV : LV ratio >1 on CT. High-risk PE are hemodynamically unstable, defined as a systolic arterial pressure (SBP) < 90 mm Hg that is sustained for 15 minutes and not caused by a dysrhythmia or other etiology, a drop in baseline SBP of > 40 mm Hg, vasopressors, or profound bradycardia (<40 bpm). For dosing of anticoagulation, see Table 74.3. Pulmonary embolism response teams (PERT) can expedite the care and access to advanced therapies for patients with intermediate- and high-risk PE. Absolute contraindications to thrombolysis include: (1) gastrointestinal bleeding within previous 30 days; (2) active hemorrhage in any of the following sites at the time of enrollment—intraperitoneal, retroperitoneal, pulmonary, uterine, bladder, or nose; (3) head trauma causing loss of consciousness within previous 7 days; (4) any history of hemorrhagic stroke; (5) ischemic stroke within the past year; (6) history of intraocular hemorrhage; (7) known or suspected intracranial

metastasis; (8) liver failure with prothrombin time abnormal (international normalized ratio [INR] > 1.7); (9) surgery that required opening of the chest cavity, peritoneum, skull, or spinal canal within the previous 14 days; (10) subacute bacterial endocarditis under treatment; (11) pregnancy; (12) large pericardial effusion. Relative contraindications to thrombolysis include: age > 75 years; dementia; surgery more than 30 days but less than 60 days prior; any prior stroke; symptoms suggesting transient ischemic attack in the past 30 days; any prior gastrointestinal bleeding; concurrent use of a thienopyridine (e.g., clopidogrel); INR > 1.7 from warfarin use; any metastatic cancer, recent fracture, recent fall with head strike, history of hematuria, recent dental extraction, or orthopedic surgery. Systemic thrombolysis dosing regimens: alteplase (recombinant tissue plasminogen activator, rtPA) 100 mg IV over two hours, reteplase 10 units IV over two minutes and then repeated 30 minutes later or tenecteplase as a single weight-based bolus dose over 5 to 10 seconds. Low-dose thrombolysis dosing regimen: alteplase 25–50 mg IV over two hours. *PE*, Pulmonary embolism; *CTPA*, computed tomography pulmonary angiography; $\dot{V}/\dot{Q}$, ventilation perfusion; *RV*, right ventricle; *DOAC*, direct acting oral anticoagulant; IV, intravenous; *CDT*, catheter-directed thrombolysis; *DVT*, deep vein thrombosis; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit.

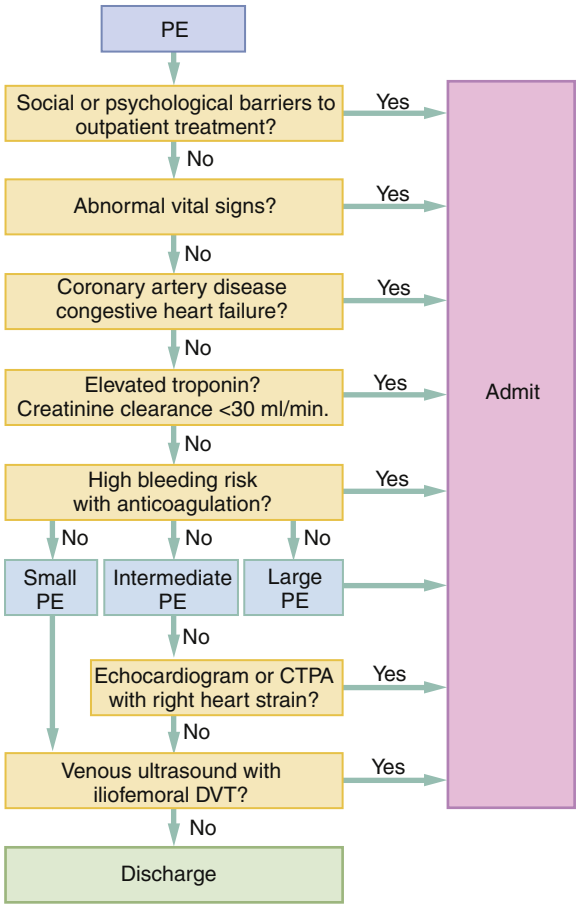

Fig. 74.12 Flowchart showing a validated algorithm for the identification of low-risk patients with acute PE who are candidates for outpatient treatment and discharge from the emergency department (or ED observation unit). Key to this approach is the availability of early follow-up and the ability of patients to obtain their prescribed anticoagulants after discharge. Abnormal vital signs include any hypotension or hypoxemia requiring oxygen therapy. Patients may be discharged with mild tachycardia, but patients with severe tachycardia should be observed in the hospital. Renal insufficiency (creatinine clearance < 30 mL/min) is not itself an indicator of higher risk PE, but severe renal impairment is a contraindication for both direct-acting anticoagulant (DOAC) and low-molecular-weight heparin (LMWH) anticoagulation. *PE*, pulmonary embolism; *CTPA*, computed tomography pulmonary angiography; *DVT*, deep vein thrombosis.

heparin-induced thrombocytopenia should receive fondaparinux, argatroban, apixaban, or rivaroxaban.

For patients in whom thrombolysis, surgery, or another advanced intervention is being considered, intravenous unfractionated heparin may be preferable because it has a short half-life, and anticoagulation should be discontinued prior to thrombolysis or a procedure. However, intravenous heparin provides unreliable anticoagulation, and many patients remain subtherapeutic throughout the first 24 to 48 hours of treatment.[63] As soon as it is decided that the patient will not receive thrombolysis or thrombectomy, it is best to convert to LMWH or a DOAC.

Anticoagulation therapy for patients with isolated subsegmental PE is controversial. If a patient has no evidence of DVT on bilateral lower extremity ultrasonography, no signs of right heart dysfunction, and no ongoing major risk for thrombosis (e.g., active malignancy, cast immobilization), it is reasonable to withhold anticoagulation. The decision to proceed with anticoagulation in this situation should be guided by individual patient risk profiles and preferences.[10,11]

Reversal of Anticoagulation. All anticoagulants commonly used in the ED, including the DOACs, now have effective reversal agents. The anticoagulant effect of unfractionated heparin can be almost completely and rapidly reversed with protamine sulfate, whereas LMWH can only be 50% neutralized with protamine. Protamine has no effect on fondaparinux, rivaroxaban, or apixaban. Andexanet alfa, a modified recombinant inactive form of human factor Xa, is now available to reverse anticoagulant effect (anti-factor Xa activity) in patients with life-threatening or uncontrolled bleeding on rivaroxaban and apixaban.[64,65] Although most patients treated in the single-arm trial achieved good hemostasis, the lack of a comparison (e.g., placebo) group makes it difficult to assess the effectiveness of andexanet alfa in reducing clinically important bleeding. The effectiveness of factor Xa inhibitor reversal using four-factor activated prothrombin complex, 50 U/kg IV, is limited and one meta-analysis concluded that these treatments may not result in more rapid reversal of anticoagulation than simply discontinuing the DOAC.[66-71]

Thrombolytic (Fibrinolytic) Therapy

Thrombolytic therapy in PE remains a controversial treatment. It is generally agreed that patients with arterial hypotension (systolic blood pressure < 90 mm Hg or > 40-mm Hg drop from baseline) should receive thrombolysis. Appropriate regimens for full-dose thrombolysis include alteplase (recombinant tissue plasminogen activator, rtPA) given as a 100-mg IV bolus over two hours, reteplase given as 10 units IV over two minutes and then repeated 30 minutes later, and tenecteplase given as a single weight-based bolus dose over 5 to 10 seconds. Practically speaking, two IV boluses of 50 mg separated by 15 minutes may be more realistic than a two-hour infusion of alteplase for an unstable patient. We recommend thrombolytic therapy for high-risk PE patients without contraindications, but specific regimens will vary by institution, availability, and pharmacy protocols.

For patients with intermediate-risk PE, data and clinical guidelines are conflicting. The PEITHO study randomized 1005 patients with intermediate-risk PE, defined as right ventricular dysfunction on echocardiogram and a positive troponin. Thrombolysis with tenecteplase was associated with significant reduction in the composite endpoint of clinical deterioration and 7-day mortality, but no decrease in mortality alone. There was, however, a significant increase in risk of intracranial hemorrhage, particularly in patients more than 65 years old. Subsequent meta-analyses of randomized trials that compared thrombolysis

plus heparin to heparin alone have reached different conclusions about mortality benefit, with one study finding significant improvement[72] and another no difference.[73] This difference seems to be mostly due to the definition of intermediate-risk PE used to characterize studies in the meta-analyses.

The benefit of thrombolysis for long-term outcomes in patients with intermediate-risk PE is also questionable. In the TOPCOAT trial of 88 patients with intermediate-risk PE, thrombolysis improved functional capacity and subjective perception of wellness. However, in PEITHO, thrombolysis had no effect on long-term mortality, residual dyspnea, or RV dysfunction.[74] Overall, we do not recommend full-dose intravenous thrombolysis for intermediate-risk PE except in carefully selected patients at high risk for clinical deterioration and low risk of bleeding. Intravenous thrombolysis for low-risk PE or DVT without PE is not indicated.

Thrombolytic regimens that use a lower dose (i.e., 50 mg of alteplase) thrombolysis have also been examined to determine whether lower thrombolytic doses reduce major bleeding associated with thrombolysis. While studies report low rates of intracranial hemorrhage, methodological issues and the outcome definitions used in the studies have tempered enthusiasm for this approach until further data are available.

Empirical thrombolysis has not shown benefit in undifferentiated cardiac arrest, but thrombolysis is recommended in cardiac arrest due to presumed PE, when there are no apparent contraindications. Both alteplase and tenecteplase may be given as a 50-mg bolus. To promote circulation of the thrombolytic medication, CPR should be continued for at least 60 minutes before terminating resuscitation.[75]

The primary risk of thrombolysis is bleeding. Studies suggest rates of major bleeding between 9% to 22%, and intracranial bleeding between 1.5% to 3%. The risk of intracranial hemorrhage appears to be highest in patients older than 65 years. One clinical prediction score for intracranial hemorrhage after thrombolysis for PE includes peripheral vascular disease, age greater than 65 years, prior cerebrovascular accident, and prior heart attack, though this study awaits external validation.[76]

Catheter-Directed Interventions

Catheter-directed interventions include catheter-directed thrombolysis and percutaneous thromboembolectomy. The advantages of catheter-directed thrombolysis include relatively low doses (4–24 mg of tPA over 12–24 hours) and delivery of thrombolytic medication near or directly into the PE.[77-79] Catheter-directed thrombolysis appears to be as effective as systemic thrombolysis in high-risk PE with a lower risk of bleeding[77-79] and may be superior to anticoagulation alone in intermediate-high risk PE, though, to date, only one small randomized clinical trial has compared catheter-directed thrombolysis to heparin alone. This study of 58 patients showed catheter-directed thrombolysis improved RV function at 24 hours, though there was no difference at 90 days. Single-arm studies have found similar results.[77-79]

Other catheter-directed interventions include clot maceration and suction thrombectomy. Clot maceration physically breaks up the clot, and may be used with thrombolysis, but can increase pulmonary hypertension through the release of vasoactive mediators. Suction thrombectomy devices mechanically withdraw clot from the pulmonary artery and have the benefit of not requiring thrombolysis or anticoagulation. While results are promising, there is no current evidence that catheter-directed interventions offer a survival advantage over systemic thrombolysis or anticoagulation alone.

Surgical Embolectomy

Surgical thromboembolectomy can be life-saving for patients with severe refractory hypotension or free-floating thrombi in the right heart ("clot-in-transit"), especially if the clot crosses a patent foramen ovale.[51] The perioperative mortality is highest for patients who require CPR before surgery, and lowest for stable patients who have an inferior vena cava (IVC) filter placed before surgery, so emergency physicians should involve an experienced cardiothoracic surgeon as early as possible in the care of a potential thromboembolectomy patient. Surgical embolectomy may be the best option for patients who have severe PE with a contraindication to fibrinolysis; however, extracorporeal perfusion requires intensive heparin anticoagulation, and the patient's mental status cannot be monitored during surgery—a key concern in patients with a high risk of intracranial hemorrhage. The administration of fibrinolytic therapy does not absolutely preclude surgical intervention. Patients treated with a fibrinolytic agent can undergo sternotomy or thoracotomy for thromboembolectomy and survive without fatal hemorrhage, but the decision to perform an open thromboembolectomy ultimately resides with the cardiothoracic surgeon.

Inferior Vena Cava Filters

For the vast majority of ED patients, placement of an inferior vena cava (IVC) filter is not indicated. However, for a patient diagnosed with PE in the presence of an absolute contraindication to anticoagulation, such as a recent cerebral hemorrhage, large cerebral infarction, or brain metastases, the appropriate consultant should be contacted for urgent placement of an inferior vena cava filter. Patients with a central PE who are unlikely to survive embolization of a proximal (e.g., iliofemoral), mobile DVT should also be referred for urgent IVC filter placement. The judgment that a patient is unlikely to survive an additional embolization is based on clinician experience and should be made alongside interventional radiology or cardiology consultants.

Pulmonary Embolism Response Teams (PERT)

PERTs are rapid response teams composed of multidisciplinary specialists, including emergency physicians, that can be mobilized to provide real-time expertise and expedite the care of patients with life-threatening PE. Approximately 60% of PERT activations originate in the ED.[58] PERTs have been shown to facilitate access to advanced therapies such as catheter-directed interventions, surgery, and extracorporeal membrane oxygenation, reduce disposition times, and improve overall care.[60,61] For patients with life-threatening PE, guidelines now recommend the involvement of a PERT.[12]

Mortality and Morbidity

For hemodynamically stable patients with PE, a multicenter registry of 1880 patients diagnosed with PE in the ED found 1.1% mortality directly attributable to PE and 5.4% all-cause mortality. In contrast, the mortality of hemodynamically unstable patients is 25% to 50%.[52] Approximately half of PE survivors will have exercise intolerance and dyspnea that degrades their quality of life,[80,72] and 40% to 50% of patients with DVT will have long-term symptoms consistent with post-thrombotic syndrome.[25,73] The etiology of exercise limitation after PE is not well understood but may have more to do with deconditioning than decreases in cardiac or pulmonary function.[80]

DISPOSITION

Approximately 20% to 30% of patients with PE can safely be discharged from the ED, usually with DOAC therapy and close outpatient follow-up.[27,28,81-84] Figure 74.12 shows a validated system for identification and risk stratification of patients with PE. This system has been shown to facilitate the outpatient treatment of up to 29% of ED patients with PE, with less than 1% all-cause 30-day mortality and 0.5% 30-day major bleeding.[28] The Hestia Criteria (Box 74.7) can also be used to identify patients who are safe for outpatient treatment.[82] The pulmonary

BOX 74.7 Hestia Criteria for the Outpatient Treatment of PE

Low-risk PE safe for outpatient treatment if:

- Systolic blood pressure > 100 mm Hg
- No thrombolysis needed
- No active bleeding
- Oxygen required to maintain oxygen saturation > 94%
- Not already anticoagulated
- Absence of severe pain requiring > two doses of intravenous narcotics
- Other medical or social reasons to admit
- Creatinine clearance > 30 mL/min
- Not pregnant, severe liver disease, or heparin-induced thrombocytopenia

embolism severity index (PESI) and its simplified version (sPESI) can be used to quantify patients' risk of all-cause mortality after PE, but these scores are less well suited to identify ED patients who require hospitalization.

Patients with PE who do not meet criteria for discharge should be admitted to an inpatient floor. Most patients should be admitted to a monitored (telemetry) bed, though low-risk patients can be admitted to an unmonitored bed or the ED observation unit. Patients with evidence of right ventricular dysfunction on echocardiogram, ECG, CTPA, or positive troponin assays should be admitted to a monitored bed. Patients who were hemodynamically unstable during any part of their ED stay should be admitted to a step-down or intensive care unit (ICU).

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 74: QUESTIONS AND ANSWERS

1. A deep vein thrombosis localized to which of the following veins can safely be treated without anticoagulation and early follow-up with a repeat venous ultrasound?
- **a.** Popliteal vein
- **b.** External iliac vein
- **c.** Anterior tibial vein
- **d.** Common femoral vein

Answer: C. See Figure 74.2. The popliteal, external iliac, common femoral, and deep femoral veins are all proximal veins. Proximal DVT should be treated with anticoagulation. DVT isolated to a calf vein like the anterior tibial vein can be observed, without anticoagulation, so long as a follow-up ultrasound can be performed within 7 days to look for propagation.

2. In which of the following patients would the D-dimer level likely be elevated (e.g., >500 ng/mL)?
- **a.** 52-year-old female with a history of breast cancer in remission
- **b.** 18-year-old male with an acute febrile illness
- **c.** 79-year-old male with a history of hypertension
- **d.** 24-year-old female with a history of obesity

Answer: C. See Box 74.2. Active cancer increases D-dimer levels, but inactive cancer (in remission) does not. Febrile illness, obesity, and long-haul travel do not increase D-dimer levels. While hypertension does not increase D-dimer levels, D-dimer levels do increase with advancing age. The specificity of the D-dimer test in a patient 79 years old is about 10% to 15%.

3. A 29-year-old woman, G2P1, 28 weeks pregnant presents with a brief episode of left-sided chest pain and vague cramping of her left leg. She agrees that she would like to pursue a workup for PE. Which combination of tests is the most appropriate first step?
- **a.** CTPA and bilateral venous ultrasound
- **b.** Ventilation/perfusion scan and echocardiogram
- **c.** D-dimer and CTPA
- **d.** D-dimer and bilateral venous ultrasound

Answer: D. While the radiation doses from both CTPA and ventilation perfusion scanning are lower than the minimum dose known to affect pregnancy outcomes, it is still best to minimize radiation exposure when possible. Therefore, a diagnostic testing strategy that starts with D-dimer, which can rule out PE if negative, and bilateral venous ultrasound, which can rule in VTE when positive, may obviate the need for imaging with ionizing radiation.

4. What is the preferred anticoagulant for a patient with low-risk PE?
- **a.** A direct acting oral anticoagulants (DOAC)
- **b.** A nonsteroidal anti-inflammatory drug (NSAIDs)
- **c.** Unfractionated heparin
- **d.** Warfarin

Answer: A. See Figure 74.11. For most patients, and especially for patients with low-risk PE, direct-acting oral anticoagulants (DOACs) are the treatment of choice. The DOACs apixaban and rivaroxaban are approved for the initial treatment of DVT and PE and are associated with lower rates of major hemorrhage than the combination of heparin and warfarin. Nonsteroidal antiinflammatory drug (NSAIDs) can be used to treat superficial thrombophlebitis, but not PE.

5. A 46-year-old woman presents to a tertiary-care hospital with syncope and hypotension. Her oxygen saturation is 88% on room air. Her systolic blood pressures are between 75 to 88 mm Hg during her 30 minutes in the ED. Her CTPA shows acute, bilateral main pulmonary artery PE and right ventricular dilatation. Three weeks ago, she had surgery to resect a glioma from the left cerebral hemisphere. The most appropriate next step is:
- **a.** 2 L normal saline bolus and endotracheal intubation.
- **b.** Consult cardiac surgery to consider surgical thromboembolectomy.
- **c.** Low-dose alteplase, 50 mg IV over two hours.
- **d.** Anticoagulation with rivaroxaban.

Answer: B. See Figure 74.11. This patient has high-risk, or "massive," PE. She has persistent hypotension and a large central clot with evidence of right ventricular dysfunction. She also has an absolute contraindication to thrombolysis having recently undergone resection of a brain tumor. Patients with right ventricular dilatation from PE may clinically decompensate with excessive IV fluid resuscitation and intubation. Fluid boluses, when given, should be small (250–500 mL). Intubation should be avoided if possible. DOACs like rivaroxaban have not been extensively studied in high-risk PE and, because of their long half-life, should not be used in patients who may undergo thrombolysis or invasive treatment for their PE. Because this patient is not a candidate for thrombolysis, the best first step is to consult a cardiac surgeon to consider open thromboembolectomy.

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Esophagus, Stomach, and Duodenum

Adam M. Nicholson and Jamie M. Hess

KEY CONCEPTS

Dysphagia

- Dysphagia can be caused by obstructive lesions (e.g., esophageal neoplasm), motility disorders (e.g., achalasia), or neuromuscular disorders that can be vascular (e.g., cerebral vascular accident), immunologic (e.g., myasthenia gravis, multiple sclerosis [MS]), infectious (e.g., botulism), or metabolic in nature.
- The incidence of achalasia increases with age, presenting insidiously with equal frequency for solids or liquids.
- Dysphasia can be the initial presentation of myasthenia gravis.
- Treatment of dysphagia is directed toward the underlying cause (e.g., myasthenia gravis, MS).
- An outpatient barium swallow or upper gastrointestinal endoscopy is indicated for most patients with dysphagia.

Upper Gastrointestinal Foreign Bodies

- Structural abnormalities of the esophagus are a major risk factor for foreign body obstruction; thus patients who obtain relief of foreign body sensation symptoms should be referred to a gastroenterologist for follow-up evaluation.
- Immediate intervention is indicated for button batteries, food boluses causing high-grade obstruction, or patients in significant distress (e.g., vomiting, gagging, choking, stridor, or inability to tolerate oral intake).
- Urgent (<24 h, and ideally <12 h) intervention is indicated for low-grade obstructions caused by sharp objects, coins lodged in the proximal esophagus, or food boluses.
- Urgent intervention is also recommended for gastric foreign bodies wider than 2.5 cm or longer than 5 cm.
- Flexible endoscopy with procedural sedation is the preferred therapeutic intervention to remove most proximal foreign bodies that can be reached by the scope.

Esophageal Perforation

- Iatrogenic causes, such as a complication of endoscopy, remain the most common cause of esophageal perforation.
- Water-soluble contrast should be used for initial diagnostic imaging studies when esophageal perforation is suspected.
- Admission with broad-spectrum antibiotics (e.g., intravenous vancomycin 15 mg/kg plus piperacillin 3.375 g) and early surgical consultation should occur in the majority of cases of esophageal perforation.
- Select stable patients with small, contained esophageal perforation may be managed conservatively by keeping the patient nothing per os (NPO), by administering broad-spectrum antibiotics and parenteral nutrition, and with a surgeon readily available.

Esophagitis

- Gastroesophageal reflux disease (GERD) is a diagnosis of exclusion in patients who present with chest pain. It is critical to first rule out other diagnoses, such as acute coronary syndrome (ACS).
- Empirical treatment of GERD with lifestyle modifications, H2 antihistamines, or proton pump inhibitors (PPIs) is appropriate, but if there is no improvement with these measures, patients should be referred for further evaluation.
- Sucralfate (1 g qid) can be safely used in pregnant patients with GERD.
- Eosinophilic esophagitis commonly presents as solid food dysphagia. Once food impaction is ruled out, a PPI should be initiated and the patient referred to a gastroenterologist.
- Infectious esophagitis primarily occurs in immunocompromised patients, and endoscopy may be helpful in differentiating among causal agents.
- Patients with pill esophagitis typically present with sudden onset retrosternal pain and odynophagia in the setting of taking medications without water; the diagnosis can often be made on the history alone.
- Medications associated with pill esophagitis include doxycycline, aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and potassium chloride.

Gastritis and Peptic Ulcer Disease

- Although gastritis cannot be definitively diagnosed based on clinical features alone, a clinical history such as recent NSAID use or alcohol ingestion in the setting of classic symptoms supports a presumptive clinical diagnosis of gastritis.
- The most common cause of gastritis is *Helicobacter pylori* infection.
- First-line treatment of *H. pylori* infection is a PPI (e.g., omeprazole 20 mg bid), amoxicillin (1 g bid), and clarithromycin (500 mg bid) for 14 days.
- The most serious complications of peptic ulcer disease (PUD) include hemorrhage, perforation, penetration, and gastric outlet obstruction.

Gastric Volvulus

- Acute gastric volvulus often presents with the combination of severe epigastric pain, distention, and vomiting, followed by violent nonproductive retching.
- Volvulus has a very high morbidity and mortality. Nasogastric tube reduction can be attempted in the emergency department, but ultimately these patients need emergent surgical intervention.

DYSPHAGIA

Foundations

Anatomy and Pathophysiology

Swallowing (also known as deglutition) is a complex phenomenon requiring voluntary and involuntary skeletal muscle activity coordinated by the swallowing center in the medulla. The cranial nerves provide afferent sensory inputs as well as efferent motor activity.

Swallowing is divided into oral, pharyngeal, and esophageal phases. Precise motor control of the act of swallowing is necessary to ensure that food is successfully transferred from the mouth through the

esophagus into the stomach. Failure at any one of these levels results in **dysphagia**, which literally means "difficulty swallowing."

Although dysphagia at any age is abnormal, it is particularly common in elders, with up to 60% of assisted living and nursing home patients having reported difficulty feeding.[1] Dysphagia is classified as two types, oropharyngeal and esophageal. Oropharyngeal dysphagia, also termed *transfer dysphagia*, involves difficulty transferring a food bolus from the oropharynx to proximal esophagus. Esophageal dysphagia involves difficulty in transporting material down the esophagus.

Oropharyngeal Dysphagia

Neuromuscular Disorders. Neuromuscular disease causes approximately 80% of cases of oropharyngeal dysphagia, with most remaining causes being localized structural lesions. Most neuromuscular causes of dysphagia result in misdirection of the bolus, sticking, and the need for repeated swallowing attempts. Liquids, especially at extreme temperatures, cause dysphagia more commonly than solids, and symptoms are often intermittent. Strokes resulting in pharyngeal weakness with failure of the cricopharyngeus muscle to relax are the most common cause of neuromuscular dysphagia. Weakness of the tongue may occur, resulting in poor transfer of the bolus, or weakness of the buccal muscles may produce drooling and difficulty prompting the swallowing process.

The second most common cause of neuromuscular dysphagia is inflammatory myopathy, such as polymyositis or dermatomyositis. These disorders are characterized by inflammatory and degenerative changes in striated muscle that can produce dysphagia from weakness of the palate, pharynx, and upper esophagus. Dysphagia may be a presenting symptom of patients with these disorders.

Myasthenia gravis is an important cause of oropharyngeal dysphagia. At least 40% of patients with myasthenia gravis have dysphagia, and it is the presenting symptom in up to 15% of patients. The dysphagia becomes progressively worse with repeated swallowing attempts and is temporarily reversible with edrophonium.

Structural Disorders. Congenital anomalies of the aortic arch may cause dysphagia in children and adults. In children, respiratory symptoms are usually present and commonly predominate. In adults, an anomalous right subclavian artery is the most common vascular cause for dysphagia, often termed *dysphagia lusoria.* Patients often do not become symptomatic until the fourth decade of life, and the most common symptoms are dyspnea on exertion and dysphagia. Vascular compression of the esophagus causing dysphagia may also occur with aneurysms of the aortic arch and great vessels. Bronchogenic carcinoma can cause dysphagia by direct involvement of the esophagus or by compression from enlarged lymph nodes.

Esophageal Dysphagia

Mechanical Disorders. Esophageal dysphagia is caused by mechanical lesions or a motility disorder. Mechanical lesions may be intrinsic or extrinsic to the esophagus. Intrinsic lesions include strictures, webs, rings, tumors, esophagitis, postsurgical changes, and esophageal foreign bodies. Pressure from extrinsic lesions such as osteophytes, mediastinal masses, or aortic aneurysms can also cause dysphagia.

An esophageal web is a thin structure composed of mucosa and submucosa usually found in the middle or proximal esophagus. Although webs can occur in isolation, they are also seen in Plummer-Vinson syndrome, which is characterized by anterior webs, dysphagia, iron deficiency anemia, cheilosis, spooning of the nails, glossitis, and thin friable mucosa in the mouth, pharynx, and upper esophagus. Most patients with Plummer-Vinson syndrome are women between 30 and 50 years of age. Patients usually report dysphagia that is initially intermittent and worse with solids. If untreated, it may progress and become constant. Rarely, motility disorders and surgical changes after a gastric bypass can also cause an esophageal obstruction.

Extrinsic compression of the esophagus can occur in a variety of conditions. In the neck, thyroid enlargement from goiter or carcinoma may cause dysphagia. Symptoms may also be seen with a pharyngoesophageal or Zenker diverticulum, a progressive outpouching of the pharyngeal mucosa as a result of increased pressure generated by failure of proper relaxation of the cricopharyngeus muscle. Noisy deglutition, dysphagia, halitosis, and a palpable compressible mass in the neck may be present. Laryngotracheal aspiration when the patient is supine results from the emptying of contents from the diverticulum.

Motor Disorders. Patients with esophageal dysphagia who have no readily identifiable mechanical cause may have a motor disorder. Intrinsic motor disorders of the esophagus include **achalasia**, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES). Systemic connective tissue diseases, such as scleroderma or CREST (***c***alcinosis, ***R***aynaud phenomenon, ***e***sophageal dysmotility, ***s***clerodactyly, and ***t***elangiectasia) syndrome, Chagas disease, or a paraneoplastic syndrome may cause secondary motor disorders.

Achalasia is a disorder of unknown etiology in which the resting pressure of the LES is markedly increased, and peristalsis is absent in the body of the esophagus. The incidence increases with age.

Diffuse esophageal spasm is another type of intrinsic motor disorder. When it is severe and prolonged, with associated high-intensity peristaltic waves, it is termed *nutcracker esophagus*.[2] Nonspecific motor disorders include repetitive esophageal contractions, nontransmitted esophageal contractions, and low-amplitude esophageal contractions.

Clinical Features

A careful history helps to differentiate oropharyngeal from esophageal dysphagia in up to 85% of patients (Box 75.1). The history focuses on determining the anatomic level involved (oropharyngeal vs. esophageal), types of food leading to symptoms (liquids, solids, or both), and whether the symptoms are intermittent or progressive. Associated pain, prior gastrointestinal (GI) history, and family history are also helpful in determining the cause.

The examination should include a thorough evaluation of the head and neck and a detailed neurologic examination. The patient should be observed while swallowing. It is helpful to note difficulty in initiating the swallow, misdirection of the bolus with regurgitation or aspiration, or unusual posturing of the patient when swallowing. Many patients with neuromuscular disorders depend on gravity to swallow, and having the patient swallow in the prone position may be helpful in rendering a diagnosis.

Oropharyngeal Dysphagia

Oropharyngeal dysphagia is characterized as an inability or excessive delay in initiation of swallowing, aspiration of the ingestate, nasopharyngeal regurgitation, or residual ingestate within the pharyngeal cavity following a swallowing event. This may be caused by misdirection of the food bolus, pain, or sticking and worsened with multiple swallowing attempts. Symptoms may include discomfort or pain in the cervical region, coughing, choking, drooling, or nasal regurgitation.

Tongue weakness can result in oral regurgitation. Inability to seal the nasopharynx because of obstruction or muscular weakness can cause nasal regurgitation. Inefficient laryngeal elevation from muscular weakness or a fixed larynx can result in laryngotracheal aspiration. Delayed aspiration can occur with pharyngeal weakness and with pooling of food in the piriform recesses or in a diverticulum. Inability

BOX 75.1 Causes of Dysphagia

Neuromuscular

Vascular
Cerebrovascular accident

Immunologic
Dermatomyositis
Multiple sclerosis
Myasthenia gravis
Polymyositis
Scleroderma

Infectious
Botulism
Diphtheria
Poliomyelitis
Rabies
Sydenham chorea
Tetanus

Metabolic
Lead poisoning
Magnesium deficiency

Other
Alzheimer disease
Amyotrophic lateral sclerosis
Brain tumor
Depression
Diabetic neuropathy
Familial dysautonomia
Metabolic myopathies (e.g., thyrotoxicosis)
Muscular dystrophies
Parkinson disease

Obstructive
Aortic aneurysm
Esophageal motility disorder (e.g., achalasia, diffuse esophageal spasm, nutcracker esophagus)
Esophageal rings
Esophageal stricture
Esophageal webs
Esophagitis
Foreign bodies
Hypertrophic cervical spurs
Inflammatory lesions
Left atrial enlargement
Mediastinal mass
Neoplasm
Thyroid enlargement
Vascular anomalies (e.g., enlarged aorta, aberrant subclavian artery)
Zenker diverticulum

Other
Alcoholism
Decreased saliva production (Sjögren syndrome, postirradiation)
Diabetes
Functional
Gastroesophageal reflux disease
Postoperative

to contract the pharyngeal muscles is often compounded by failure of the cricopharyngeus muscle to relax, which causes misdirection of the food bolus or necessitates repeated swallowing attempts. Inflammatory lesions of the tongue or oropharynx can result in odynophagia, which may impede swallowing.

Esophageal Dysphagia

Dysphagia from upper esophageal lesions is usually perceived 2 to 4 seconds after the initiation of swallowing. Dysphagia that the patient localizes to the substernal or retrosternal area may be anatomically accurate, but localization to the neck may be referred from anywhere in the esophagus.

Dysphagia is the most common presenting symptom of achalasia and usually begins insidiously, with equal frequency for solids and liquids. Patients may report that maneuvers that increase esophageal pressure (e.g., raising arms above the head, standing erect with back straight) help pass the food. Odynophagia from esophageal spasm may also be seen early in the course of achalasia. The symptoms are often worse with rapid eating and during periods of stress. The patient may also report chest pain as a symptom. As dilation occurs above the sphincter, retention of undigested food in the esophagus occurs, and the patient may be aware of gurgling while eating. Regurgitation of the undigested material can occur after a meal, prompting consideration of the diagnosis of an eating disorder, or with changes in position or vigorous exercise. The regurgitated food usually has no acid taste unless bacterial contamination causes fermentation of the undigested food. Laryngotracheal aspiration may occur, especially at night, and may cause nocturnal coughing. The physical examination is usually unremarkable, except for weight loss. Radiographically, a dilated esophagus is seen proximal to a narrowed gastroesophageal junction that has a "beaklike" appearance.

Esophageal spasm may be precipitated by swallowing very hot or cold liquids. Symptoms include chest pain, dysphagia, or both. Manometrically, simultaneous prolonged strong esophageal contractions are noted to be interspersed over normal peristaltic waves.

If a barium swallow is performed during a spasm, findings such as corkscrewing, or curling, of the esophagus may be noted.

Differential Diagnoses

The differential diagnosis of esophageal dysphagia includes acute coronary syndrome (ACS). Substernal chest pain is the main symptom in 80% to 90% of patients with esophageal motility disorders. The chest pain can be similar to angina, described as crushing or squeezing, with patterns of radiation similar to those of cardiac chest pain. Nitroglycerin may also relieve the pain of spasm, making the distinction between the two entities even more difficult.

Symptoms that suggest an esophageal cause of chest pain include pain that is prolonged and nonexertional, pain that interrupts sleep, pain related to meals, relief with antacids, and presence of other symptoms of esophageal disease, such as heartburn, dysphagia, or regurgitation. Given the considerable overlap in symptoms, a cardiac diagnosis should be excluded before attributing chest pain to an esophageal cause.

Diagnostic Testing

The history and physical examination direct the need for testing. Nasopharyngoscopy may be used to assess for upper structural

abnormalities. The decision and timing of swallowing studies (e.g., video esophagography), barium swallows, manometry, and impedance monitoring are best coordinated with consultants. These studies are rarely indicated in the emergency department (ED).

Management

Achalasia is the only motility disorder for which reasonably reliable studies support specific treatment. Previously, pharmacologic therapies such as nitrates and calcium channel blockers have been used with the goal of decreasing tone of the LES. More recently, surgical interventions such as peroral endoscopic myotomy (POEM) have been used as first-line therapy in patients with achalasia who are able to tolerate surgical intervention.[3] Pharmacologic therapy remains available as a bridge to more definitive intervention or in patients who are unable to tolerate an invasive procedure. Endoscopic botulinum toxin injection remains available as an acceptable treatment option in patients, although as with other medical therapies is commonly reserved for patients unable to tolerate more invasive procedures.

Medical therapy for esophageal motility disorders is limited, and clinical impacts are typically minimal. Anticholinergic drugs such as hyoscyamine sulfate or dicyclomine have been used because they decrease the amplitude of esophageal peristalsis and LES pressure. However, because these drugs delay gastric emptying and decrease esophageal peristalsis, they may exacerbate reflux symptoms. Other therapies include the use of calcium channel blockers, which decrease LES pressure and the amplitude of esophageal contractions.

Disposition

Patients at risk of aspiration or who are unable to maintain hydration may require hospitalization for expedited work-up and management. Otherwise, prompt outpatient evaluation by a gastroenterologist is indicated.

FOREIGN BODIES

Foundations

Background

Patients with esophageal foreign bodies are generally classified into four major groups: (1) pediatric patients; (2) psychiatric patients or prisoners (typically intentional ingestion); (3) patients with underlying esophageal disease; and (4) edentulous adults. Pediatric patients account for more than 75% of cases, with the peak incidence occurring in those between the ages of 18 and 48 months. Swallowing coins accounts for most cases of pediatric ingestion, whereas most adult impactions involve food, particularly meat or bones. Patients with underlying structural abnormalities of the esophagus are at greater risk for foreign body impaction. Edentulous adults are also at increased risk because of impaired oral sensation, which may contribute to their risk of accidental ingestion of a dental prosthesis.

Anatomy and Physiology

The esophagus begins in the hypopharynx, approximately at the level of the cricoid cartilage. On either side of this cephalad slit are the piriform recesses, which are blind pouches that may occasionally harbor a foreign body. There are four natural areas of narrowing where most foreign bodies become entrapped: The cricopharyngeus muscle (which is a component of the upper esophageal sphincter [UES]), aortic arch, left mainstem bronchus, and LES at the diaphragmatic hiatus. Pediatric entrapment occurs most commonly at the level of the cricopharyngeus muscle in the UES given the anatomic features present in young children, whereas adult entrapment occurs most commonly at the LES (Fig. 75.1).

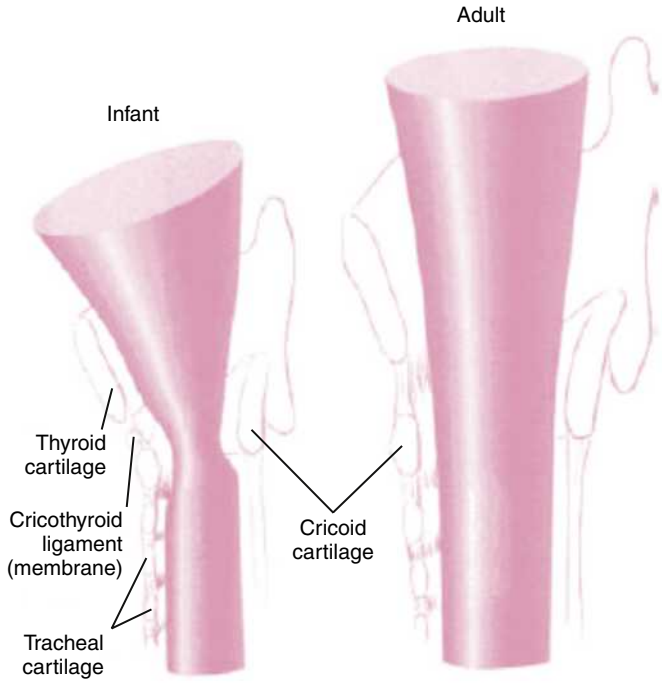

Fig. 75.1 Anatomic Differences Between Infant and Adult Airways.

The esophagus comprises two main bands of muscle, an inner circular layer and outer longitudinal layer. The resting tone of these muscles causes the inner epithelium to fold in on itself, effectively obliterating the lumen. Elastic fibers enable the esophageal lumen to expand and allow passage of a food bolus. The upper third of the esophagus, including the cricopharyngeus muscle, contains striated muscle to allow for the voluntary initiation of swallowing. The middle portion of the esophagus is a mixture of skeletal and smooth muscle, and the distal third is composed only of smooth muscle. Although it is relatively fixed at its origin, the esophagus becomes mobile as it traverses the mediastinum and can be easily displaced by adjacent structures. An enlarged left atrium or ventricle, goiter, or mediastinal tumor may cause enough displacement of the esophagus to impede the passage of a food bolus or foreign body.

Pathophysiology

Although obstruction may occur in a patient with a normal esophagus, preexisting structural abnormalities such as strictures (peptic or malignant), distal esophageal mucosal rings, or eosinophilic esophagitis are identified in nearly 90% of patients with an esophageal obstruction. Schatzki ring is a specific type of mucosal abnormality present in 15% of the population and characterized by a fibrous, diaphragm-like stricture near the gastroesophageal junction.

Clinical Features

Patients with an esophageal obstruction have a wide range of symptoms that typically begin minutes to hours following ingestion. Most adults are able to describe the precipitating event and commonly complain of dysphagia, odynophagia, and neck or chest pain. Patients are often able to localize retained foreign bodies due to somatic innervation of the upper esophagus. In contrast, entrapment in the lower esophagus causes more visceral-type generalized chest and epigastric discomfort. The obstruction may be partial or complete. The patient with complete obstruction is unable to swallow oral secretions. Large proximal impactions can impinge on the trachea, leading to airway compromise that manifests as cough, choking, or stridor.

Pediatric patients are often brought to the ED after a witnessed ingestion. However, up to 35% of children with proven esophageal foreign body impactions are asymptomatic at the time of presentation. Symptoms that should prompt consideration of unwitnessed foreign body ingestion include fever, wheezing, stridor, rhonchi, or poor feeding.

A so-called *café coronary*, which is a proximal esophageal obstruction caused by food (usually an incompletely chewed piece of meat), is characterized by sudden cyanosis and collapse as a result of airway obstruction. Similarly, *steakhouse syndrome* results when a large piece of food, usually improperly chewed, is swallowed and causes esophageal obstruction in the distal esophagus.

Patients may present to the ED with sharp throat pain and concern about swallowing a fish bone after eating fish. Despite the discomfort and concern of a retained fish bone foreign body, this rarely results in true esophageal obstruction.

Differential Diagnoses

Esophageal foreign bodies should be distinguished from those in the airway. This distinction can be especially difficult in small children because respiratory symptoms may be the only clue to the esophageal foreign body with associated tracheal compression. Patients with esophageal obstruction may have retrosternal pain that can appear similar to that of a patient presenting with ACS. The presence of odynophagia suggests an underlying mucosal lesion such as an abrasion, laceration, or perforation.

Diagnostic Testing

In most cases, the patient's history will be all that is necessary to confirm the diagnosis and initiate therapeutic intervention. Imaging studies may be necessary in unknown or equivocal cases, or in patients who are unable to provide a reliable history. Anteroposterior (AP) and lateral radiographs of the neck, chest, and abdomen are indicated when a radiopaque foreign body is suspected. Flat objects in the esophagus such as coins or button batteries typically orient in the coronal plane and appear as a circular object on an AP projection (Fig. 75.2). Button batteries can be differentiated from coins by a characteristic radiographic double-density appearance. Small bones or radiopaque objects may occasionally be visualized. Radiographs are typically unreliable in detecting a fish bone.

Nasopharyngoscopy can be useful in differentiating a retained foreign body from a mucosal abrasion. In the vast majority of patients with symptoms following ingestion of fish, no fish bone foreign body is identified. Air in the tissues may be present if perforation has occurred. However, failure to demonstrate a foreign body on radiographs does not rule it out. Persistent or concerning symptoms in a patient without evidence of a radiographic foreign body can be further evaluated by laryngoscopy and upper GI endoscopy.

Contrast studies with barium or gastrografin are rarely performed to evaluate for a foreign body because they present a risk for aspiration and can obscure visualization if subsequent endoscopy is necessary. Computed tomography (CT) may be used in equivocal cases to identify and localize foreign bodies before endoscopy. CT is more sensitive (90% to 100%) than radiography for identifying foreign bodies, including chicken or fish bones or other nonorganic objects. CT scans have the additional value of visualizing changes associated with perforation in the surrounding tissues.[4]

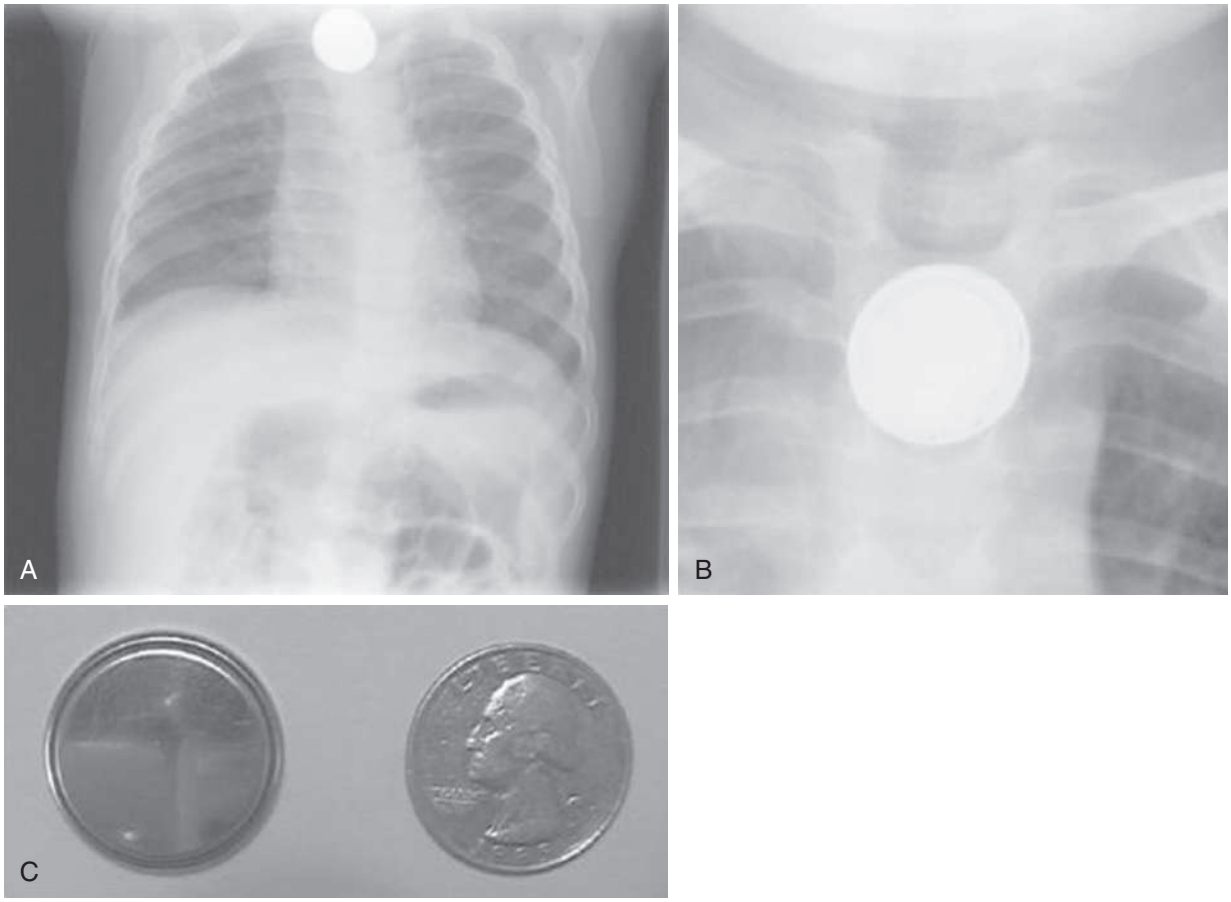

Fig. 75.2 Appearance of Coin and Button Battery Foreign Body on X-ray. (A) Coin in the upper esophagus. (B) Appearance of button battery on x-ray. (C) Frontal comparison of coin and button battery.

Management

Overview

Treatment for esophageal foreign bodies depends on the type and location of the object and clinical status of the patient. Flexible endoscopy using procedural sedation is recommended in most cases of complete esophageal obstruction, because rigid endoscopy requires general anesthesia and has a higher complication rate.

Urgent intervention (2 to 6 hours) is indicated for button batteries, magnets, large or sharp objects, coins lodged in the proximal esophagus, impactions that impair the handling of secretions, and food boluses causing signs of high-grade esophageal obstruction. Factors associated with a heightened risk of complications include a longer duration of impaction, bone, or other larger foreign bodies.

Although it is acceptable to delay endoscopy briefly in stable patients without symptoms of high-grade obstruction to allow a trial of spontaneous passage, the American Society for Gastrointestinal Endoscopy has recommended that food boluses causing incomplete obstruction be removed within 24 hours. Any object remaining in the esophagus for more than 24 hours carries a higher risk of complications, including perforation, aorto-enteric fistula, tracheoesophageal fistula, or abscess. These complications may occur in the near term or years after the ingestion. Follow-up endoscopic evaluation after an esophageal obstruction is necessary to assess for underlying pathologic conditions as up to 25% of patients will have an identifiable esophageal disorder.[4]

A recent retrospective review of patients who ingested sharp objects who had normal physical examination had a very low incidence of requiring surgical intervention. This suggests that perforation and obstruction rates may be less than traditionally thought, and careful observation may be appropriate in select cases.[5]

Upper Esophagus

Oropharyngeal foreign bodies can often be removed with a Kelly clamp or Magill forceps under direct visualization. Smooth upper esophageal foreign bodies such as coins can often be removed with a Foley catheter. This procedure requires an experienced clinician, cooperative patient, and fluoroscopic guidance. The patient is placed in a prone position, and the catheter is passed into the esophagus past the point of the foreign body impaction. The balloon is then inflated and the catheter withdrawn, pulling the foreign body with it. The literature reports that up to 80% of foreign bodies are successfully removed with this technique, and an additional 8% advance into the stomach. Failure rates are highest with infants younger than 1 year. Controversy exists regarding the safety of this technique because there is no direct control of the foreign body. However, large studies have shown complication rates to be less than 1% when patients are carefully selected for the procedure.

Foley catheter removal should not be used for a foreign body that has been impacted for more than 1 week, for objects that are not smooth, for patients with radiographic evidence of esophageal perforation, or for patients with any underlying structural esophageal abnormalities. This technique has a significant economic advantage when compared with the costs of general anesthesia in an operating room for the performance of rigid endoscopy.

Another technique is bougienage, which has been shown to be safe and effective in coin removal. In this technique, an esophageal dilator is passed through the mouth into the esophagus to advance the coin into the stomach; the dilator is then quickly removed. In a large study, this procedure had a significantly shorter duration to discharge when compared to endoscopy.[6]

Lower Esophagus

Lower esophageal obstruction is usually the result of an impacted food bolus. Anecdotally, intravenous (IV) administration of 1 mg of glucagon, up to a total of 2 mg, can cause enough relaxation of the esophageal smooth muscle to allow passage of a food bolus into the lower esophagus. However, a recent systematic review of the literature found no difference in efficacy of glucagon compared with placebo but did show an increased risk of adverse events with glucagon administration such as vomiting and potential aspiration.[7] Based on lack of evidence and the potential risks, we do not recommend using glucagon in the management of esophageal foreign bodies. IV benzodiazepines have anecdotally been used as a first-line approach for stable patients with a meat impaction, although the evidence supporting their benefit is sparse and suggests that effectiveness is not better than placebo.

Small studies have examined the role of effervescent agents in treating food bolus impaction. They have shown no clear evidence of benefit, and there is a theoretical risk of inducing perforation in the case of complete obstruction with associated distal esophageal ischemia. Similarly, the use of meat tenderizer (papain) to soften a food bolus is potentially dangerous and should not be used.

Endoscopy should be performed immediately for patients experiencing distress or for children with impaction of an alkaline button battery. Button batteries lodged in the esophagus can cause severe tissue damage in just 2 hours. Damage is primarily related to localized corrosive effects and occurs by three main mechanisms—leakage of an alkaline electrolyte, pressure necrosis, and generation of an external current that causes electrolysis of tissue fluids, thus generating hydroxide at the battery's negative pole and causing alkaline damage of the mucosa. Larger batteries carry a greater risk of impaction and leakage. Delayed complications include esophageal perforation, tracheoesophageal fistula, esophageal strictures, and exsanguination after the development of a fistula with a major blood vessel. In a review of more than 8000 battery ingestions that were reported to the National Battery Ingestion Hotline, outcomes have significantly worsened over the past decade. This is primarily attributable to the newer 20-mm-diameter lithium cell batteries that now account for 92% of fatal ingestions.

Batteries that pass into the stomach should be followed radiographically and clinically to ensure passage. Assistance with the management of a patient with button battery ingestion can be obtained through the National Button Battery Ingestion Hotline (1-202-625-3333) or at www.poison.org/prevent/battery.asp.

Stomach

Conservative outpatient management is appropriate for the vast majority of foreign bodies that have entered the stomach. However, certain foreign bodies that pass into the stomach still require endoscopic retrieval. Objects longer than 5 cm or wider than 2.5 cm in diameter (e.g., toothbrushes, spoons) rarely pass the duodenum. All sharp and pointed foreign bodies (e.g., toothpicks, bones) should be removed before they pass out of the stomach because there is a risk of intestinal perforation. Smaller objects that pass into the stomach can be followed with stool inspections and serial radiographs, if necessary, to confirm passage. Surgical removal should be considered for objects that remain in the stomach for more than 3 to 4 weeks or that remain in the same intestinal location for more than 1 week.

Disposition

The patient with an esophageal or stomach foreign body frequently requires a gastroenterology consult and consideration for upper endoscopy for foreign body removal. Discharge from the ED should follow foreign body removal, or consideration of the risks and benefits of a trial of spontaneous passage. Patients who undergo endoscopy should

be observed until awake from sedation and able to tolerate oral intake. These patients should be discharged with a proton pump inhibitor (PPI), and referral for further evaluation of structural abnormalities. If no foreign body is identified, and the patient is able to swallow liquids, they may be safely discharged with outpatient follow-up.

ESOPHAGEAL PERFORATION

Foundations

Background

Esophageal perforation can result from a rapid increase in intraesophageal pressure related to forceful vomiting or any Valsalva-like maneuver, including childbirth, coughing, or heavy lifting. Iatrogenic esophageal perforation can result during manipulation of the esophagus, such as during endoscopy, nasogastric tube placement, or endotracheal intubation. Other causes of perforation include foreign body ingestion, caustic substance ingestion, severe esophagitis, carcinoma, or direct injury related to blunt or penetrating trauma. Spontaneous rupture occurs because of a rapid increase in intraluminal esophageal pressure against a closed LES.

Anatomy and Physiology

More than 90% of spontaneous esophageal ruptures occur in the distal esophagus. In contrast, rupture resulting from blunt trauma to the neck or thorax usually occurs in the proximal or middle third of the esophagus. Most iatrogenic injuries occur at the pharyngoesophageal junction because the wall in this area is thin, there is no serosal layer to reinforce it, and force is frequently used to pass a tube or scope beyond the level of the cricopharyngeus muscle. Another site of frequent iatrogenic injury is the esophagogastric junction. In this area, the esophagus curves anteriorly and to the left as it enters the abdomen, and an endoscope has a greater likelihood of perforating the posterior wall. This usually occurs during therapeutic dilation for strictures or achalasia.

Clinical Features

Clinical presentations of esophageal perforation vary and depend on the cause, location, size, and degree of contamination. Symptoms related to iatrogenic perforation may not appear until several hours after the procedure. Patients with an upper esophageal perforation usually have neck or chest pain, dysphagia, respiratory distress, or fever. Odynophagia, nausea, vomiting, hoarseness, or aphonia may also result. Mackler triad of subcutaneous emphysema, chest pain, and vomiting is considered pathognomonic for spontaneous esophageal rupture. However, the complete triad is seen in less than 50% of cases.

Patients with perforation of the lower esophagus may have abdominal pain, pneumothorax, hydropneumothorax, and pneumomediastinum. The pain may radiate to the back, left side of the chest, and left or both shoulders. Physical findings include epigastric or generalized abdominal tenderness, often with involuntary guarding and rigidity. Up to 30% of patients develop mediastinal or cervical emphysema, which may be noted by crepitus on palpation or by the pathognomonic Hamman sign, with a crunching sound heard during auscultation. Patients with severe mediastinitis may present in fulminant shock.

Differential Diagnoses

Misdiagnosis occurs in more than 50% of patients with esophageal perforation or rupture because of the broad differential diagnosis of chest and abdominal pain. This includes pulmonary embolism, acute myocardial infarction, aortic dissection, perforated ulcer, pneumothorax, lung abscess, pericarditis, or pancreatitis, among others. The associated morbidity and mortality of patients with esophageal perforation increases significantly over time, so every effort should be made to quickly confirm the diagnosis.

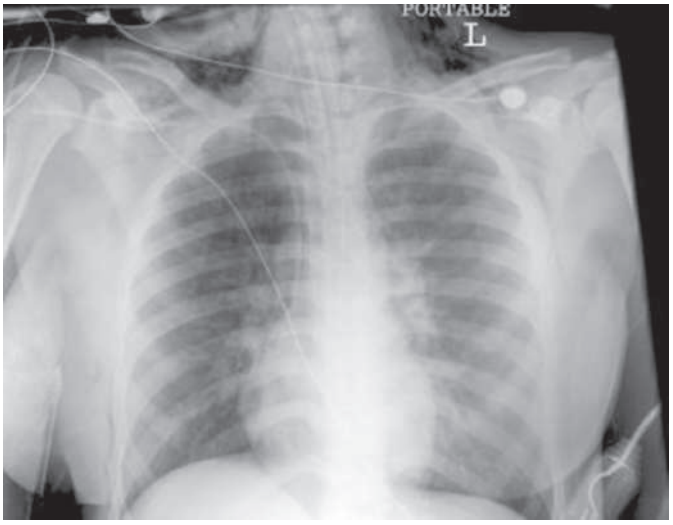

Fig. 75.3 Pneumomediastinum due to esophageal perforation following forceful vomiting.

Diagnostic Testing

Chest and upright abdominal radiography is generally the first diagnostic study performed in patients suspected of an esophageal perforation. Radiographic abnormalities may be detected in up to 90% of patients with esophageal perforation (Fig. 75.3). Patients with upper esophageal injuries commonly have chest radiographs that show pneumomediastinum alone with or without a right-sided pleural effusion, whereas radiographs in patients with distal esophageal perforations may demonstrate a left-sided effusion. Other radiographic abnormalities include subcutaneous emphysema, mediastinal widening, or pulmonary infiltrates. These radiographic changes are often not present in the first few hours after perforation; thus a normal early radiograph should not be used to exclude the possibility of esophageal perforation.

Patients with suspected perforation should undergo contrast enhanced radiographic studies. Barium sulfate is superior for identifying small perforations but may incite an inflammatory response in tissues. Water-soluble agents (e.g., Gastrografin) may be safer, but they are less dense and therefore may not demonstrate an abnormality. In addition, pneumonitis may result if these agents are aspirated because of their hypertonicity. We recommend an initial attempt with a water-soluble agent for patients who are not at risk for aspiration. If a perforation is not identified and suspicion remains high, a repeat study with barium is recommended.

CT of the chest may be considered if a contrast study does not demonstrate a clinically suspected perforation. It can also be used in patients who are intubated or cannot complete esophagography, or when alternative diagnoses are also being considered. Findings such as mediastinal air, extraluminal contrast material, or fluid collections or abscesses adjacent to the esophagus can confirm a perforation.

Flexible esophageal endoscopy is useful in directly visualizing the perforation, especially in cases of penetrating external trauma, with a sensitivity of 100% and specificity of 83%. This technique is not recommended for other situations because insufflation could potentially enlarge a small transmural opening.

Laboratory studies are not usually helpful soon after a perforation, although systemic leukocytosis may be noted.

Management

Clinically unstable patients with esophageal perforation require rapid resuscitation and treatment. There are no current randomized

controlled trials regarding antiinfective management of esophageal perforation, and as such, no definitive recommendation can be made regarding optimal antibiotic regimen to treat esophageal perforation. Common organisms found in the esophagus include gram-positive, gram-negative, anaerobic organisms, and at times fungal species as well.[4] Broad-spectrum IV antibiotics should be initiated early. We recommend IV vancomycin 15 mg/kg q8h to q12h plus IV piperacillin-tazobactam 3.375 g q6h, with consideration to add empiric antifungal coverage (fluconazole 400 mg IV daily) if patient has significant risk factors for fungal colonization. Patients should receive nothing by mouth (NPO), and early surgical consultation is warranted. Treatment within the first 24 hours has been found to improve survival when compared with delayed treatment.

There is evidence that some iatrogenic perforations in select patients at low risk can be managed conservatively. These patients must be clinically stable, have minimal symptoms, and have no signs of sepsis. In addition, they must have a perforation contained within the neck, and a surgeon must be available in the event of decompensation. Operative management in these patients has been reported to result in worse outcomes compared with nonoperative management including close monitoring, NPO status, broad-spectrum antibiotics, and parenteral nutrition. Other so-called palliative interventions, including endoscopic stent placement, drainage gastrostomy, feeding jejunostomy, and tube thoracostomy, have become more common.

Traumatic, noniatrogenic etiology of esophageal perforation is infrequent and associated with high morbidity and mortality. Factors associated with worse outcome include thoracic location of esophageal injury and more extensive esophageal damage. Early surgical treatment for these injuries improves survival rates.[8]

Disposition

Patients with esophageal perforation are at risk for rapid deterioration and require close monitoring in a hospital setting, often in an intensive care unit. Early surgical consultation is recommended.

ESOPHAGITIS

Foundations

Esophagitis is an inflammation of the esophagus. The most common cause is gastroesophageal reflux disease (GERD). Other important causes include eosinophilic infiltration, infection, foreign body, toxic ingestion, or radiation. Chapter 143 discusses esophagitis caused by caustic substance ingestion.

Gastroesophageal Reflux Disease

Asymptomatic reflux of gastric contents from the stomach into the esophagus often occurs several times a day as a normal physiologic phenomenon. GERD occurs when reflux becomes symptomatic or causes histopathologic alterations in the upper GI or respiratory tract. In the United States, symptomatic reflux in the form of heartburn occurs in 10% to 20% of the population.[9]

The primary mechanism that enables reflux of gastric contents into the esophagus is inappropriate relaxation of the LES. This can occur because of general hypotension of the LES, increased intra-abdominal pressure, or transient LES relaxation. Multiple risk factors can decrease LES pressure and lead to reflux, including medications (e.g., nitrates, calcium channel blockers, anticholinergics, albuterol), fatty meals, and chocolate. Other mechanisms that may contribute to GERD include esophageal motility abnormalities, increased intragastric pressure (e.g., obesity, pregnancy), acid hypersecretion, gastric outlet obstruction, and conditions that cause delayed gastric emptying (e.g., gastroparesis, neuromuscular disease).

Repetitive exposure to acid can lead to changes in the esophageal mucosa. Continued reflux can lead to thinning of the normal stratified squamous epithelial layer. With the development of esophagitis, an inflammatory response occurs in the mucosa and submucosa, with infiltration of polymorphonuclear leukocytes. The inflammatory response is the result of chemical irritation of the esophageal mucosa from reflux of gastric acid, pepsin, and bile acids. Both acid and alkaline refluxes produce the same pathologic changes. Continued exposure can lead to further endoscopically visible changes of erosion, ulceration, and scarring. Ultimately, stricture formation may result. The most severe histologic consequence of GERD is replacement of the normal stratified squamous epithelium with metaplastic columnar epithelium in a condition termed *Barrett metaplasia*. In patients with reflux undergoing endoscopy, approximately 10% to 15% are found to have Barrett esophagus. There is a strong correlation between the development of Barrett metaplasia and adenocarcinoma of the esophagus.

Eosinophilic Esophagitis

Eosinophilic esophagitis results from an eosinophilic infiltration within the esophageal mucosa or deeper tissues. Initially thought to be a disease of children, it is being diagnosed in adults with increasing frequency with a prevalence rate now approaching 3%.[10] The cause is unknown, although there is an association with food allergens, especially in the younger age group. More than 50% of patients have associated atopic disorders, such as asthma or eczema. The criteria necessary for diagnosis include clinical symptoms of esophageal dysfunction, more than 15 eosinophils in one high-power field on esophageal biopsy, and lack of responsiveness to high-dose PPI therapy.

Infectious Esophagitis

Esophageal infections primarily occur in immunocompromised hosts. When they occur in healthy patients, there is usually an underlying esophageal abnormality or local area of immune compromise, as might occur with the use of inhaled steroids. Iatrogenic alterations in host defenses through the use of immunosuppressive agents, potent chemotherapeutic agents, or broad-spectrum antibiotics can predispose an individual to the development of an esophageal infection. Other systemic diseases that weaken immunologic defenses in otherwise normal hosts can predispose the esophagus to infection, including diabetes mellitus, alcoholism, underlying malignancy, use of corticosteroids, or advanced age. The *Candida* species (primarily *Candida albicans*) are the most common esophageal pathogens.

Human immunodeficiency virus (HIV) is a risk factor for infectious esophagitis, but rates have decreased since the advent of highly active antiretroviral therapy (HAART). Patients with acute HIV seroconversion syndrome that occurs 2 to 3 weeks after primary exposure to HIV can develop esophageal ulcerations and severe odynophagia.

As empirical antifungal prophylaxis in immunosuppressive states has become more common, viral esophagitis has become more prominent. Herpes simplex virus 1 (HSV-1) and cytomegalovirus (CMV) are the most common viral pathogens. Human papillomavirus has been implicated as well. Bacteria, mycobacteria, other fungi, and parasitic organisms such as *Trypanosoma cruzi*, *Cryptosporidium,* and *Pneumocystis* are uncommon causes of infectious esophagitis and are usually diagnosed by culture or biopsy.

Pill Esophagitis

The incidence of pill esophagitis is unknown as most cases are unrecognized and therefore unreported. The condition results when a pill or capsule fails to pass into the stomach and remains in contact with the esophageal mucosa for a prolonged period. This results in inflammation and injury of the esophageal mucosa.

Pill esophagitis has been reported in all age groups. Predisposing factors include advanced age, decreased esophageal motility, or extrinsic compression. Large pills are more likely to be retained because these are coated with gelatin. Pills can stick to a normal esophagus, especially when taken without water or by a patient in the supine position. Any area of the esophagus can be affected, although sites of natural compression may be more susceptible. Sustained-release compounds may be more damaging than standard preparations. Injury can range from minor irritation to frank ulceration, hemorrhage and, ultimately, stricture formation. Some of the more common offending medications include antibiotics (especially the tetracycline family) and antivirals, aspirin and other NSAIDs, potassium chloride, quinidine, ferrous sulfate, alendronate, and pamidronate.

Radiation-Induced Esophagitis

Patients undergoing radiation treatment for underlying malignancy may develop esophagitis. The degree of injury is related to the total dose of radiation received. The mucosa becomes inflamed and friable. Agents used during sclerotherapy can also cause esophagitis.

Clinical Features

Esophagitis, regardless of cause, usually manifests with dysphagia or odynophagia. Chest pain is frequently present, and esophageal bleeding can occur, ranging from localized oozing as a result of inflammation to frank hemorrhage. Ulceration and perforation can result in mediastinitis.

Gastroesophageal Reflux Disease

The most common clinical manifestation of GERD is heartburn, defined as a burning sensation that begins in the subxiphoid area and radiates toward the neck. Reflux may also cause a dull discomfort, localized pressure, or severe squeezing pain across the middle of the chest. The patient may appear comfortable or may have associated diaphoresis, pallor, nausea, and vomiting, leading to the consideration of ACS. A detailed history is often helpful in differentiating cardiac chest pain from reflux, although the distinction may be difficult in the ED.

Other symptoms of GERD include regurgitation (spontaneous appearance of an acid or bitter material in the mouth or pharynx) and water brash (a vagally mediated hypersalivation response that may produce as much as 10 mL of saliva in 1 minute). Dysphagia and odynophagia may also be presenting complaints and may be associated with more serious complications.

Any condition or agent that decreases LES pressure, decreases esophageal motility, or prolongs gastric emptying predisposes patients to reflux (Box 75.2). Body positions that place the esophagus dependent to the stomach or increase intra-abdominal pressure tend to precipitate reflux. Stooping, bending, leaning forward, performing Valsalva-type maneuvers, or assuming a supine position are common precipitants.

GERD can manifest itself in extraesophageal locations. Reflux-induced asthma may result from microaspiration of gastric contents into the lung or activation of a vagal reflex arc from the gut to the lung. GERD has been identified in up to 80% of asthmatic patients based on pH probe monitoring, but up to 50% of these patients have no reflux symptoms. However, studies have shown no benefit in treating poorly controlled asthmatic patients with PPIs in the absence of GERD symptoms.

If the refluxate reaches the proximal esophagus, otolaryngologic manifestations may result, even in the absence of esophageal symptoms. Reflux can cause hoarseness, chronic laryngitis, refractory sore throat, and globus sensation. Refluxate that enters the oropharynx may lead to gingivitis, halitosis, or dental problems, such as erosion of the lingual sides of the teeth as a result of acid exposure. Otalgia and hiccups can also result from reflux.

BOX 75.2 Agents and Conditions Related to Gastroesophageal Reflux

Decreased Lower Esophageal Sphincter Pressure
Anticholinergic drugs
Benzodiazepines
Caffeine
Calcium channel blockers
Chocolate
Estrogen
Ethanol
Fatty foods
Nicotine
Nitrates
Peppermint
Pregnancy
Progesterone

Decreased Esophageal Motility
Achalasia
Diabetes mellitus
Scleroderma

Increased Gastric Emptying Time
Anticholinergic drugs
Diabetic gastroparesis
Gastric outlet obstruction

Eosinophilic Esophagitis

The most common symptom of eosinophilic esophagitis in adults is solid food dysphagia. In addition to dysphagia, patients may present with nausea and vomiting, food impaction, or heartburn. Children may present with more vague symptoms, such as vomiting, regurgitation, nausea, epigastric or abdominal pain, chest pain, water brash, or decreased appetite. Children with eosinophilic esophagitis have a higher rate of atopy, immunoglobulin E (IgE)-mediated food allergies, or family history of allergies. This diagnosis should be considered in patients who have severe GERD symptoms despite the use of acid suppression medications or in patients with chronic unexplained dysphagia or recurrent esophageal food impaction. The diagnosis is confirmed by biopsy during endoscopy.

Infectious Esophagitis

Infectious esophagitis usually causes severe odynophagia. Dysphagia of solids and liquids may be present. Pain may be so severe that the patient refuses to eat or drink. Heartburn and nausea may be presenting symptoms, although the pain is not improved by antacid therapy. Immunocompromised patients may have fever or bleeding, without dysphagia or odynophagia. Many patients with esophageal candidiasis also have oral candidiasis, but it is possible to have esophageal manifestations only, which makes it more difficult to diagnose.

Pill Esophagitis

Patients with pill esophagitis commonly present with chest pain (72%), odynophagia (39%), and dysphagia (30%). Most patients have no prior history of esophageal disease and experience sudden onset of pain worsened by swallowing. Dysphagia may be present. Although some patients complain that a pill has become stuck, the history of

pill ingestion can be difficult to obtain because symptoms may begin hours after the offending pill was taken. Atypical presentations include a burning type of pain, suggesting GERD as the cause.

Differential Diagnoses

Acute cardiac ischemia should be considered as a possible cause of chest pain in adults. It is difficult to differentiate between ischemic coronary disease and GERD based only on features of the pain, location, or radiation. Radiation of pain can be a feature in esophageal and cardiac chest pain. The occurrence of reflux after meals is another important feature in the history. A feeling of fullness after meals occurs commonly in reflux and is helpful in differentiating it from coronary artery disease.

Relief of chest pain from reflux by antacids may be a key point in the history, although it is not evidence against a cardiac cause. The relief is often short lived, and pain may recur in a short time. Esophageal pain may be provoked by swallowing. Other GI disorders such as gastritis, esophagitis, peptic ulcer disease (PUD), and biliary tract disease should be considered in the differential.

Diagnostic Testing

GERD is a common problem, and additional diagnostic testing in the ED is rarely necessary, assuming that other, more serious causes of the patient's symptoms have been excluded. Patients with dysphagia, odynophagia, or bleeding should be referred for further evaluation.

Endoscopy can be used to evaluate pathologic changes, but there is no direct correlation between symptoms and endoscopic features. With infectious esophagitis, direct visualization may reveal characteristic signs of infection, such as white plaques of *Candida* or herpetic vesicles. Definitive diagnosis can be made through brushings or biopsies. Radiographic studies are usually not helpful because the findings are nonspecific.

Management

Gastric Reflux

Lifestyle modification solely as an initial approach to GERD has little therapeutic benefit without concomitant medical management. Lifestyle modifications to reduce GERD symptoms include avoidance of foods that can precipitate reflux (e.g., caffeine, alcohol, chocolate, fatty foods) and avoidance of acidic foods that can cause heartburn (e.g., citrus products, spicy foods). In addition to these dietary changes, other behavioral modifications include weight loss, smoking cessation, elevation of the head of the bed, and avoidance of a recumbent position for several hours after eating. The only lifestyle recommendations that have evidence-based support include weight loss and head of bed elevation, although others can be useful adjuncts in select patients.

The pharmacologic therapy of GERD includes agents that neutralize acids, decrease acid production, act on the LES or affect motility, and protect the mucosa. The most effective treatment for GERD is reduction of acid production. Many patients self-medicate with antacids, over-the-counter (OTC) type 2 histamine receptor (H2)–receptor antagonists, or PPIs. A Cochrane systematic review concludes that PPIs are more effective than H2 blockers in eliminating symptoms and healing mucosal damage. However, H2 blockers are an acceptable alternative for patients with mild to moderate GERD. These agents do not stop the reflux but rather reduce the potency of the refluxate. Choices of H2 blockers and PPIs are listed in Tables 75.1 and 75.2. All these agents are generally regarded as safe and effective.

Another agent that may be of benefit in refractory cases of symptomatic esophageal reflux is sucralfate, which can be used with other agents such as PPIs and H2 blockers. The dose is 1 g every 6 hours. Sucralfate is a mucosal protectant that binds to inflamed tissue to create a protective barrier. It blocks the diffusion of gastric acid and pepsin across esophageal mucosa and can limit the erosive action of pepsin and bile. It has limited side effects and can be safely used in pregnant women.

Prokinetic agents treat GERD by increasing LES pressure. They may also be used for patients whose symptoms suggest a superimposed motility disturbance (e.g., regurgitation, choking, abdominal distention). In addition to improving the propulsive activity of the stomach and small and large intestines, the increase in esophageal peristalsis and LES tone is an effective therapy for reflux by improving the clearance of refluxate. Metoclopramide (10-mg dose) may be used, but its efficacy has not been conclusively demonstrated and prolonged use can cause significant irreversible extrapyramidal side effects such as tardive dyskinesia.

Patients with clinically suggested GERD who do not improve with empirical therapy and those who are at high risk for complications should be referred to a gastroenterologist for confirmation of the diagnosis and follow-up care. In these cases, further diagnostic evaluation may be necessary. Patients who are intolerant of acid-suppressive medications may be candidates for surgical therapy with laparoscopic fundoplication. Less invasive endoscopic therapies include thermal ablation to narrow the esophagus at the LES, suturing to create a plication at the LES, or injection or implantation techniques to fortify the LES.

Eosinophilic Esophagitis

These patients usually are seen after standard antireflux measures have failed or they have developed a food impaction. Once food

TABLE 75.1 Summary of Histamine Receptor Antagonists

Agent	GERD	PUD[a]
Cimetidine	800 mg bid or 400 mg qid	800 mg qhs or 400 mg bid
Famotidine	20 or 40 mg bid	40 mg qhs or 20 mg bid
Nizatidine	150 mg bid	300 mg qhs or 150 mg bid

[a]Maintenance dose for PUD is half the qhs dose.
GERD, Gastroesophageal reflux disease; *PUD*, peptic ulcer disease; *qhs*, at bedtime.

TABLE 75.2 Summary of Proton Pump Inhibitors[a]

Agent	GERD	PUD or NSAID-Induced Ulcers[b]
Esomeprazole	20 or 40 mg qd	40 mg PO qd
Lansoprazole	30 mg qd or 15 bid	30 mg PO qd
Omeprazole	20 mg qd or 20 bid	20 mg PO qd
Pantoprazole	40 mg qd or 20 bid	40 mg PO qd
Rabeprazole	20 mg qd or 20 bid	20 mg PO qd

[a]All doses should be administered before breakfast; second doses (when necessary) should be administered before the evening meal.
[b]Patients with duodenal ulcer should be treated for 4 weeks; patients with gastric ulcer should be treated for 8 weeks.
GERD, Gastroesophageal reflux disease; *NSAID*, nonsteroidal antiinflammatory drug; *PO*, orally; *PUD*, peptic ulcer disease.
Adapted from Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology*. 2000;118:S9–S31.

impaction is eliminated as the presenting problem, empirical treatment by initiation of a daily PPI and referral to a gastroenterologist for urgent endoscopy is recommended. Untreated eosinophilic esophagitis can lead to esophageal remodeling and stricture formation in up to 40% of adult patients. Although consensus has not yet been reached regarding an optimal treatment regimen, success has been reported with the use of topical (swallowed) corticosteroids. Additional therapies that are considered in patients with eosinophilic esophagitis include leukotriene receptor antagonists, mast cell stabilizers, azathioprine, 6-mercaptopurine, and biologic immunomodulators. These medications have been trialed with some success, although may be of limited utility due to side effects.[10] Pediatric studies have also shown efficacy of the use of oral viscous budesonide.

Infectious Esophagitis

For infectious esophagitis, therapy is directed at the causative organism. Patients with normal immune systems and mild cases of oropharyngeal candidiasis can be treated with clotrimazole troches (10 mg dissolved in the mouth, five times daily for 1 week) or nystatin (400,000 to 600,000 million units orally [PO] four to five times/day for 2 weeks). Patients with moderate to severe esophageal candidiasis should be treated with oral fluconazole (400 mg as a loading dose and then 100 to 400 mg daily for 14 to 21 days). In patients unable to tolerate oral medication, fluconazole can be given by the IV route.

Herpes esophagitis is generally a self-limited process that resolves within 1 to 2 weeks. Immunocompromised patients should be treated with antivirals, such as acyclovir (400 mg PO, five times/day for 7 to 14 days, or 5 to 10 mg/kg IV tid for 10 to 14 days), famciclovir (500 mg PO, tid for 10 to 14 days), or valacyclovir (1 g tid for 10 to 14 days). For CMV, initial treatment can begin with ganciclovir (5 mg/kg IV bid) or foscarnet (60 mg/kg IV tid or 90 mg/kg IV bid), although optimal duration of therapy is not currently clear.[11]

Pill Esophagitis

If a patient with suspected pill esophagitis has persistent symptoms, endoscopy may be necessary. It also helps determine alternative causes. No data support a specific treatment, although, intuitively, antacid medication may prevent further erosion of damaged mucosa. Symptoms may take up to 6 weeks to resolve.

The best treatment for pill esophagitis is prevention. Patients should be instructed to drink at least 4 ounces of liquid with any pill. All medications should be taken when the patient is in an upright position, and they should remain upright for several minutes after medication ingestion. Patients with underlying esophageal abnormalities or who are bedridden should avoid the use of pills whenever practical.

Disposition

Treatment of esophagitis is largely symptom based and supportive. Patients who cannot eat or drink because of injury to the esophagus should be considered for admission for IV fluid therapy. Treatment of GERD is directed at symptom management. GERD can be safely managed on an outpatient basis. ED disposition decisions are largely based on the ability to rule out other more serious causes of the patient's complaints, such as ischemic coronary disease. For infectious esophagitis, if the causative organism cannot be identified or the patient is severely debilitated, hospitalization may be required. In addition to therapy directed at the infecting organism, treatment with antacids, topical anesthetics, or sucralfate may provide symptomatic relief.

Patients discharged from the ED should receive appropriate follow-up with the relevant specialist (e.g., gastroenterology, infectious disease).

GASTRITIS AND PEPTIC ULCER DISEASE

Foundations

Background

Gastritis and PUD are often difficult to differentiate based on history alone. Strictly speaking, gastritis is a histologic diagnosis denoting inflammation of the gastric mucosa. Hence the diagnosis of gastritis can be made only by endoscopy and biopsy. However, it is common practice for clinicians to use the term *gastritis* to refer to symptoms of dyspepsia. To confuse the picture further, gastroenterologists frequently use the term to refer to the endoscopic finding of an edematous friable mucosa. However, without accompanying inflammation, this is more appropriately termed *gastropathy* rather than gastritis. This section considers gastritis and gastropathy together as one entity because the distinction has little importance to emergency care. Gastric and duodenal ulcers are often grouped together as PUD because of the similarity in their pathogenesis and treatment.

Pathophysiology

The most common cause of gastritis is infection with *Helicobacter pylori.* Although most patients are asymptomatic at the time of initial exposure, acute infection with *H. pylori* can cause severe gastritis and PUD. The identification of *H. pylori* has dramatically shifted our notion of PUD from an acid-related to an infectious disease–mediated process.

H. pylori is a spiral, flagellated, gram-negative rod whose natural habitat is the human stomach, between the epithelial cell surface and overlying mucus. It is estimated that up to 95% of patients with duodenal ulcer and up to 70% of patients with gastric ulcer are infected with *H. pylori.*[12] It is more prevalent in lower socioeconomic groups and in developing countries. It is most likely spread person to person by an oral-oral route, although the fecal-oral route and iatrogenic transmissions have also been hypothesized.

It is estimated that up to 40% of the US population is infected with *H. pylori.* It is found in people of all age groups, although infection is typically acquired during childhood. Its presence is believed to cause mucosal inflammation that disrupts the normal defense mechanisms and leads to ulceration. It also increases the risk of gastric carcinoma and, less often, lymphoma. Although there is a strong association between *H. pylori* and PUD, only 5% to 10% of infected patients develop ulcers. It is unclear what role environmental and host factors, such as diet, play. It is now broadly accepted that nearly all non–NSAID-related ulcers are caused by *H. pylori*. Eradication of infection with *H. pylori* results in more rapid healing of ulcers, fewer episodes of relapse, and a diminished rate of ulcer complications. It is also more cost-effective than chronic antisecretory therapy.

Suppurative gastritis, also known as acute phlegmonous gastritis, is a rare and often fatal disease that results from an acute bacterial infection of the stomach wall. *Streptococcus* bacteria species are involved in nearly 75% of cases. Patients usually have an underlying mucosal abnormality such as cancer, ulcer, or preexisting gastritis. Less common infectious causes of gastritis include mycobacterial, viral, parasitic, or fungal organisms.

Use of aspirin and other NSAIDs is the second most common cause of PUD. Up to 25% of chronic NSAID users develop ulcer disease, and 2% to 4% of these patients have serious complications, including perforation or bleeding. The cause of NSAID-related ulcers is suppression of

BOX 75.3 Risk of Gastrointestinal Complications From Nonsteroidal Antiinflammatory Drugs

Highest Risk
Indomethacin (relative risk [RR], 2.25)
Naproxen (RR, 1.83)
Diclofenac (RR, 1.73)
Piroxicam (RR, 1.66)
Tenoxicam (RR, 1.43)
Ibuprofen (RR, 1.43)

Lowest Risk
Meloxicam (RR, 1.24)

BOX 75.4 Substances and Conditions That Damage the Gastric Mucosal Barrier

Bile
Cigarette smoke
Ethanol
Glucocorticoids
Helicobacter pylori
Nonsteroidal antiinflammatory drugs
Pancreatic secretions
Shock conditions
Stress

gastric prostaglandin synthesis. Prostaglandins promote mucosal integrity by maintaining mucosal blood flow, promoting mucosal mucus and bicarbonate formation, and reducing mucosal acid secretion. It is believed that the inhibition of cyclooxygenase (COX) by NSAIDs leads to a diminished level of protective prostaglandins in the stomach. In addition, the antiplatelet aggregation effect of NSAIDs may increase the amount of bleeding associated with NSAID-induced ulcers.

NSAIDs differ in their ulcerogenic potential. Studies have shown a higher risk of upper GI bleeding with ketorolac and piroxicam, particularly if their use extends beyond 5 days. The COX-2–specific inhibitors (e.g., celecoxib, rofecoxib, valdecoxib) were initially thought to have a more favorable GI safety profile than traditional NSAIDs. However, further studies have refuted this belief and noted an increased risk of cardiovascular side effects, including myocardial infarction and stroke. As a result, rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the market. Celecoxib (Celebrex) is still available in the United States as a treatment for arthritis and familial polyposis but has a black box warning regarding an increased incidence of GI side effects as well as increased cardiovascular risk (Box 75.3).

Patients older than 60 years, those with a prior history of an ulcer or hemorrhage, those receiving higher doses of NSAIDS, and patients concurrently taking glucocorticoids or anticoagulants are at higher risk for NSAID-induced gastroduodenal toxicity. These patients should be considered for ulcer prophylaxis with a PPI or misoprostol.

Other drugs with ulcerogenic potential include 5-fluorouracil, mycophenolate mofetil, and the bisphosphonates. Other drugs implicated in causing gastritis are potassium preparations and iron supplements. Gastritis can result from short- and long-term exposure to ethanol.

Any condition that causes hypovolemia or hypotension can lead to gastritis. Ulcer formation may ultimately result. This may be a major causative factor in the development of gastritis and upper GI bleeding in intensive care unit patients. Other causes of gastritis include radiation, autoimmune reactions, Crohn disease, or sarcoidosis.

Many mechanisms can protect the gastric mucosa from the digestive effects of the hydrochloric acid, proteolytic enzymes, bile, and other deleterious substances to which it is exposed. Normally, a gastric mucosal barrier to intraluminal gastric acid is present and prevents the back-diffusion of hydrogen ions from the gastric lumen. Sodium ions are prevented from moving in the opposite direction. This ionic impermeability protects the gastric mucosa from gastric secretion-induced damage. Damage to the gastric mucosal barrier from any cause (Box 75.4) allows hydrogen ions and digestive enzymes to make contact with the gastric mucosa, leading to inflammation, bleeding, and potential ulceration.

H. pylori infection and use of NSAIDs account for the vast majority of PUD cases. Only 1% of PUD is caused by acid hypersecretion. Zollinger-Ellison syndrome is an acid hypersecretion syndrome caused by increased levels of circulating gastrin from gastrin-secreting tumors. Gastrin stimulates the parietal cells of the stomach to secrete more acid and causes parietal cell hyperplasia. Thus these patients have increased parietal cell mass and hypersecretion of acid, leading to ulcer formation.

PUD also occurs in infants and children. Infants with PUD usually demonstrate poor feeding, vomiting, or failure to thrive. Up to 25% of children have isolated hematemesis or melena as presenting signs. Toddlers and preschool children may have abdominal pain, vomiting, or bleeding. Of ulcers in this age group, 80% are stress ulcers associated with systemic illness such as sepsis, head trauma, burns, or sickle cell disease. Older children and adolescents usually have primary PUD, with presentations similar to those of adults.

Clinical Features

Acute gastritis and PUD may cause epigastric abdominal pain, nausea, and vomiting. By definition, gastritis or gastropathy cannot be diagnosed based on clinical features alone. However, a good clinical history such as recent NSAID use or alcohol ingestion in the setting of the epigastric burning pain supports a presumptive clinical diagnosis.

Patients with phlegmonous gastritis usually appear toxic. Patients with gastritis as a result of decreased mucosal blood flow may have symptoms of abdominal pain and upper GI bleeding in addition to those of their underlying disease. Complications of gastritis include perforation or gastric outlet obstruction.

The classic presenting symptom of PUD is epigastric pain described as burning or gnawing. However, up to 2% of patients with endoscopically proven PUD are asymptomatic. Patients may also present with atypical symptoms, including pain in other areas of the abdomen, chest, or back, and may describe the pain as vague or crampy. Associated symptoms include fullness, nausea, early satiety, and abdominal distension. Pain usually occurs 2 to 5 hours after a meal or at night. Having symptoms that awaken a patient from sleep between midnight and 3 AM is a classic indicator of ulcer disease, because in most people gastric acid output is highest at approximately 2 AM. Ulcer pain is usually not present on awakening in the morning because gastric acid output is at its lowest. Colicky pain is rarely gastric or duodenal in origin. Well-defined periods of exacerbation and remission are usually present with a duodenal ulcer and aid in the diagnosis. A constant pain lasting from weeks to months is uncommonly caused by ulcer disease. Relief of pain after eating is another feature of gastric or duodenal ulcer. The pain from a duodenal ulcer is usually worse immediately before a meal.

Although some patients with ulcers may vomit, alternative diagnoses such as gastric volvulus, gastric outlet obstruction, small bowel obstruction, pancreatitis, or biliary tract disease should be considered in patients

with epigastric pain and vomiting. Relief of abdominal pain with antacids is an important aspect of the history. Antacids usually afford relief of pain in PUD and gastritis. More than 90% of patients with PUD and 75% with gastritis experience pain relief with antacids. Patients with duodenal ulcer usually experience pain relief within 5 minutes.

Physical findings in patients with PUD are usually minimal. Mild epigastric tenderness may be elicited. A positive stool guaiac test may be evidence of a slowly bleeding ulcer, but other causes of occult bleeding should also be considered.

Complications

The most serious complications of PUD include hemorrhage, perforation, penetration, and gastric outlet obstruction. Hemorrhage is the most common complication, occurring in 15% to 20% of patients. Ulceration into an artery can lead to life-threatening hemorrhage. Patients older than 60 years are at greater risk. Approximately 2% to 10% of patients experience perforation, which occurs when an ulcer erodes through the wall and leaks air and digestive contents into the peritoneal cavity. Duodenal ulcers account for 60% of all perforations, followed by antral gastric ulcers (20%) and gastric body ulcers (20%). Penetration is pathologically similar to perforation, except that the ulcer erodes into another organ such as the liver (usually from a gastric ulcer) or pancreas (usually from a duodenal ulcer). Gastric outlet obstruction occurs in 2% of ulcer patients as a result of edema and scarring near the gastroduodenal junction. Symptoms may manifest as gastroesophageal reflux, early satiety, weight loss, abdominal pain, or vomiting.

Pain patterns may be helpful in diagnosing some of the complications of PUD. Pain from a perforated duodenal ulcer is usually appreciated first in the epigastrium but becomes generalized within a short time. Vomiting is present in 50% of patients, and peritoneal findings usually result. Pneumoperitoneum commonly occurs after duodenal ulcer perforation, and the accumulated air under the diaphragm may cause referred pain to the shoulder. One or both shoulders may be involved, depending on the location of the free air.

A history of ulcer-like anterior abdominal pain that begins to radiate into the back suggests penetration of a duodenal ulcer. The pain is usually described as steady and is perceived at the level of the lower thoracic and upper lumbar vertebrae. The pain becomes refractory to treatment with antacids and food. In addition, the pain may radiate to the chest, right upper quadrant, or left upper quadrant in up to 20% of patients. The sudden onset of pain, especially if unrelated to eating, suggests ulcer perforation or gastric volvulus.

Differential Diagnoses

Many other disorders can produce epigastric pain that mimics the pain of gastritis or PUD. Before either of these diagnoses can be made, other diseases that cause nausea, vomiting, and upper abdominal pain should be excluded, such as pancreatitis, biliary tract disease, or small bowel obstruction. Esophageal disorders such as GERD, esophagitis, or esophageal spasm include similar abdominal symptoms. Mesenteric ischemia should be considered, especially in elders and those with underlying vascular disease or atrial fibrillation. The possibility of ACS should also be considered.

It can be difficult to distinguish between gastritis and PUD. The discomfort associated with gastritis is often mild to moderate in severity and described as a hot burning pain or bloating. In particular, burning pain is twice as common in gastritis as in PUD.

Diagnostic Testing

Because the diagnosis of gastritis is made clinically, no specific diagnostic tests are necessary. Ancillary tests should be ordered as clinically indicated to rule out other possible diagnoses or to assess for complications of gastritis, such as bleeding, obstruction, or perforation.

Upper endoscopy is the procedure of choice for confirming the diagnosis. This is not typically performed in the ED unless it is necessary to treat complications of PUD, such as acute bleeding.

Abdominal and chest radiographs should be ordered if obstruction, perforation, or penetration is suggested or if a pulmonary cause is being considered, although negative radiographs do not definitively rule out these diagnoses. Newer studies show that careful multiplanar CT interpretation may visualize deep ulcers, secondary mural, and extraluminal signs of peptic gastroduodenitis. This can be helpful in facilitating expedited endoscopic evaluation to initiate appropriate treatment.[13]

Electrocardiography should be considered in any patient with the potential for a cardiac cause of pain. A pregnancy test should be considered in woman of childbearing age.

Patients can be tested for *H. pylori* by invasive or noninvasive methods. These include a urea breath test, serum antibody testing, stool antigen testing, and direct mucosal biopsy during endoscopy. None of these methods are practical in the ED; thus patients should be referred to primary care providers to facilitate additional testing.

Management

Therapy should be directed toward treating the suspected underlying cause. Acid suppression may improve symptoms of dyspepsia in patients taking NSAIDs. Patients with persistent symptoms should be referred to a primary care doctor or gastroenterologist for further diagnostic evaluation.

For NSAID-related ulcers, treatment should begin with discontinuation of the offending agent combined with initiation of PPI therapy. For ulcers not related to NSAIDs, treatment for *H. pylori* infection is recommended.

Recommended regimens combine antibiotics with acid-suppressing agents for treatment of *H. pylori* infection (Box 75.5). Commercially available combination products may also be prescribed that may assist in compliance (e.g., Prevpac, which contains lansoprazole, amoxicillin, and clarithromycin, and Helidac, which contains bismuth subsalicylate,

BOX 75.5 Suggested Treatment Regimens for *Helicobacter pylori*

Triple Therapy (10- to 14-day treatment regimen)
Clarithromycin, 500 mg bid
Plus
Amoxicillin, 1 g bid
Or
Metronidazole, 500 mg bid (if penicillin-allergic)
Plus
A PPI

Quadruple Therapy (10- to 14-day treatment regimen)
Bismuth subsalicylate (Pepto-Bismol), 525 mg PO qid
Plus
Metronidazole, 250 mg PO qid
Plus
Tetracycline, 500 mg PO qid
Plus
A PPI

PO, Orally; *PPI*, proton pump inhibitor.
Adapted from Chey WD, Wong BCI. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol.* 2007;102:1808–1825.

metronidazole, and tetracycline). Continued therapy with antisecretory agents following completion of an antibiotic-containing regimen is recommended.

Antacids

By the time most patients seek treatment for upper GI complaints, they have likely already tried some form of antacid therapy because many of these agents are readily available OTC. Antacids afford relief of pain symptoms for most patients with PUD and promote ulcer healing. Antacids also work by binding bile acids or inhibiting pepsin.

The choice of antacid should be individualized. The magnesium-containing antacids can produce diarrhea in up to 25% of patients. Magnesium-containing antacids can also lead to an increase in serum magnesium levels and should be used with caution or avoided altogether in patients with impaired renal function. Aluminum-containing antacids may cause constipation, and prolonged use may lead to phosphate depletion. Calcium-containing antacids have been marketed as acid neutralizers and as a means of calcium supplementation, particularly for postmenopausal women. Calcium-containing antacids have traditionally been believed to cause the highest incidence of acid rebound, a paradoxical increase in gastrin secretion and acid production. Calcium antacids can also lead to constipation, and their excess consumption can lead to hypercalcemia, alkalosis, and renal insufficiency—the milk-alkali syndrome.

Antacids can decrease the absorption of warfarin, digoxin, and some anticonvulsants and antibiotics. It is recommended that antacids be administered 1 to 3 hours after meals and at bedtime. Antacids are the least expensive drugs available to treat PUD, but their use is limited by efficacy, side effects, and inconvenient administration schedules.

Histamine Blockers

Histamine is the primary stimulus to gastric acid secretion. It binds to the histamine-2 (H2) receptor located on the basolateral portion of the parietal cell to stimulate the release of hydrochloric acid. The discovery of the ability of H2 blockers to inhibit gastric acid production was a major advance in antiulcer therapy because ulcers are not prone to develop in the absence of acid. These drugs are highly selective competitive inhibitors of histamine for the H2 receptor on parietal cells and reduce the volume of gastric juice and its hydrogen ion concentration. All of the currently available H2 blockers are rapidly absorbed after an oral dose, with peak levels reached within 1 to 2 hours. All have half-lives of approximately 2 to 3 hours, so their effects last for approximately 6 hours. Most are now available OTC in lower dosage strength than prescription forms.

H2 blockers are effective in treating duodenal ulcer and, to a lesser extent, gastric ulcer, although they are not as effective as the PPIs. They are widely prescribed for symptoms of dyspepsia and work well in patients with episodic heartburn. All H2 blockers are mainly metabolized hepatically and renally, with the exception of nizatidine, which is almost exclusively metabolized renally. Dosages of these agents should be reduced in patients with renal failure.

H2 blockers are safe and generally well tolerated. Side effects are rare but include central nervous system effects, such as somnolence, dizziness, and confusion. Transient increases in liver enzyme levels may be noted. Some patients may exhibit abnormalities in cardiac conduction as the heart contains H2 receptors. Cimetidine has been shown to cause gynecomastia. Dosages of the various agents are summarized in Table 75.1.

Proton Pump Inhibitors

The H^+,K^+-ATPase (proton pump) is located on the apical portion of the parietal cell and is responsible for the production of hydrogen ions in gastric acid. PPIs are the most potent inhibitors of gastric acid secretion. They work by irreversibly binding to stimulated proton pumps to block the secretion of hydrogen ions. Although they have no effect on the volume of gastric juice produced, production of acid can be reduced by up to 95%. Both basal and stimulated gastric acid secretions are reduced. The antisecretory effects last up to 72 hours.

PPIs should be administered before the first meal of the day because the number of proton pumps is maximized after a fasting state. At the cellular level, additional proton pumps are continually recruited to produce more acid in response to stimulation; therefore several doses of a PPI are necessary for the maximal antacid effect to be achieved. The use of these medications on an as-needed basis would not be expected to provide an adequate clinical response; H2 blockers are more suitable for this purpose.

PPIs are hepatically metabolized; thus dosage should be modified in patients with hepatic failure. Side effects are usually minimal, and the long-term safety of these drugs has been shown in multiple studies. PPIs may be used at significantly higher dosages in patients with Zollinger-Ellison syndrome. Dosages of the various agents are summarized in Table 75.2. Lansoprazole, pantoprazole, and esomeprazole are available as IV formulations.

PPIs have been linked to inhibition of the effects of thienopyridines used to treat cardiovascular disease. Retrospective observational studies have suggested a potential increase of reinfarction and hospitalization when clopidogrel was used in combination with PPIs; however, this has not been shown in prospective studies. Two prospective randomized control trials have been performed, and both failed to show an increased cardiovascular risk for patients using both clopidogrel and PPIs.[14] Overall, the data are mixed, and further research is needed to determine if there is an important clinical effect on patients taking both clopidogrel and PPIs.[15] We recommend using PPIs and clopidogrel together with caution, and only when the benefits of PPIs outweigh the potential risks. An additional risk of PPIs in elders is a significant association with hip fracture when compared with H2 blocker therapy. As such, we recommend caution when initiating PPIs in patients at high risk for hip fracture.[16]

Prostaglandins

Prostaglandins exert protective effects on the gastric mucosa by inhibiting acid secretion and decreasing the amount of cyclic adenosine monophosphate generated in response to histamine. Inhibition of gastric acid secretion, increased secretion of mucus and bicarbonate, and stimulation of mucosal blood flow have all been demonstrated. Misoprostol is an analogue of prostaglandin E_1, with a longer duration of action and greater potency than endogenous prostaglandins. It should be used only for the prevention of NSAID-induced gastric ulcers in patients at high risk. The dose is 200 μg qid PO with food, but crampy abdominal pain and diarrhea may necessitate the use of a somewhat less effective dose of 100 μg PO qid. Misoprostol is an abortifacient and therefore is contraindicated in any female patient of childbearing age who is not using contraception.

Other Agents

Sucralfate binds to epithelial cells, especially to ulcerated surfaces, providing a protective layer that inhibits further acid damage. Its mechanism of action is not completely understood, although it has been shown to enhance epithelial growth, suppress acid secretion, and inhibit the growth of *H. pylori*. The usual dose is 1 g PO qid given 30 to 60 minutes before meals. This can be an appropriate and safe choice to use during pregnancy, although there are currently preferred options with longer duration of action and higher efficacy that should be considered as first line for most patients.

Bismuth compounds such as bismuth subsalicylate decrease pepsin activity, increase mucus secretion, and form a barrier to further acid damage in ulcer craters. They also increase prostaglandin synthesis and retard hydrogen ion diffusion through the mucosal barrier. Bismuth may also help to heal ulcers through its bactericidal action on *H. pylori*. Bismuth compounds are not approved for the treatment of peptic ulcers.

Disposition

Referral to a gastroenterologist is suggested if any of the following signs or symptoms are present: Age 55 years or older with new-onset dyspepsia, dysphagia, progressive unintentional weight loss, persistent vomiting, iron deficiency anemia, or an epigastric mass. Most patients with PUD can be safely managed as outpatients, with referral to gastroenterology for confirmation of diagnosis with an esophagogastroduodenoscopy (EGD). Further evaluation is recommended for patients with high-risk clinical features (e.g., anemia, report of GI bleeding, intractable pain, signs of gastric obstruction) prior to discharge.

GASTRIC VOLVULUS

Foundations

Gastric volvulus is a rare cause of severe abdominal pain that occurs when the stomach rotates on itself more than 180 degrees, creating a closed loop obstruction. It is a rare condition with a true incidence that remains unknown as some types of volvulus are intermittent and resolve spontaneously. Gastric volvulus may be classified according to cause (primary vs. secondary), anatomy (axis of rotation), or onset (acute vs. chronic).[15]

The stomach is fixed at only two points, the esophagocardiac junction and pylorus. The remainder of the organ is relatively distensible and mobile and can occupy various positions within the abdomen. When a person is supine, the stomach lies entirely above the umbilicus, whereas it descends below the umbilicus when a person is in the erect position. Regardless of its position, the stomach maintains its familiar morphology because of ligamentous attachments to surrounding organs. A primary (or subdiaphragmatic) volvulus accounts for approximately one-third of cases and occurs when the stabilizing ligaments are too lax or are congenitally abnormal in such a way that the stomach is able to twist on itself.

Secondary (or supradiaphragmatic) volvulus occurs in patients with diaphragmatic defects such as a paraesophageal hiatal hernia, elevated diaphragm, gastric ulcer or carcinoma, diaphragmatic paralysis, extrinsic pressure on the stomach from other organs, or abdominal adhesions. The combination of one or more of these factors, as well as ligamentous laxity, makes a volvulus more likely.

Gastric volvulus can also be classified on the basis of its axis of rotation. The most common form is organoaxial volvulus, which occurs when the stomach twists on its long axis. Less commonly, in approximately one-third of cases, the stomach folds on its short axis from its lesser to greater curvature and is classified as a mesenteroaxial volvulus.

Clinical Features

Gastric volvulus typically occurs in persons 40 to 50 years of age and is often associated with the presence of a paraesophageal hernia. Approximately 20% of cases occur in infants younger than 1 year, frequently associated with a congenital diaphragmatic defect.[15]

The presenting features of a gastric volvulus vary, depending on the type. Primary volvulus may arise with the sudden onset of severe abdominal pain. The upper abdomen may demonstrate marked distention. Patients with secondary volvulus may experience predominant symptoms in the chest, with pain radiating to the back or shoulders, along with accompanying dyspnea. The abdominal examination may be unremarkable. Nonbilious vomiting is usually present and may be persistent and severe. The combination of severe epigastric pain and distention, vomiting followed by violent nonproductive retching, and inability to pass a nasogastric tube (Borchardt triad) increases the likelihood of a gastric volvulus and is present in up to 70% of patients. Up to 25% of children with acute gastric volvulus present with life-threatening events that necessitate resuscitation, including apnea, cyanosis, or acute respiratory distress.

A volvulus may be chronic if the rotation is minimal and there is no vascular compromise. Symptoms usually consist of mild intermittent upper abdominal pain. Early satiety, dyspnea, bloating, eructation, or upper abdominal distension may be present. It is unknown how often a chronic volvulus can lead to an acute volvulus.

Complications

If an acute volvulus is not identified and corrected early, it may lead to gastric ischemia, perforation, and death. The mortality rate from acute gastric volvulus has been reported to be as high as 50%. Fortunately, the frequency of gastric infarction is low (reportedly 5% to 28% for organoaxial volvulus) because of the redundant blood supply of the stomach. Other complications include ulceration, perforation, hemorrhage, pancreatic necrosis, or omental avulsion.

Differential Diagnoses

The differential diagnosis of gastric volvulus includes any disease that can arise with sudden upper abdominal pain and vomiting. Perforated peptic ulcer, gastric outlet obstruction, biliary tract disease, or acute pancreatitis should be considered. Symptoms of a volvulus may be similar to those of ACS.

Diagnostic Testing

A plain abdominal radiograph is often the initial diagnostic test, which can help quickly confirm the diagnosis if typical findings are seen. The classical x-ray will show a large, gas-filled loop of bowel in the abdomen or chest with an air-fluid level, often with an associated lack of air in the distal bowel (Fig. 75.4). A barium swallow may help

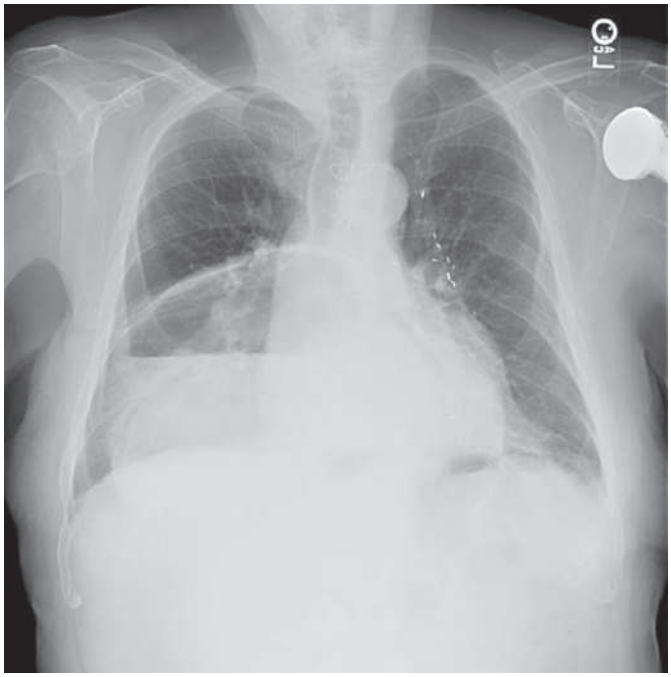

Fig. 75.4 Organoaxial Gastric Volvulus. (Courtesy Radiopaedia.org: Gastric volvulus. http://radiopaedia.org/cases/gastric-volvulus.)

visualize the abnormality, and CT can be used for confirmation in equivocal cases. There are no laboratory findings specific for volvulus, although elevations in amylase and alkaline phosphatase levels have been reported.

Management

The goal of treatment of an acute gastric volvulus is reduction. Mortality rates increase with delayed diagnosis because of ischemic complications. Acutely, clinicians should attempt immediate passage of a nasogastric tube, which may occasionally reduce the volvulus. Although somewhat controversial, patients without signs of gastric infarction may undergo an attempt at endoscopic reduction. Ultimately, treatment is a surgical emergency, with the goal of reducing the volvulus and preventing recurrence by fixating the stomach within the abdomen. Surgical repair of predisposing diaphragmatic defects is also recommended to prevent recurrence.

Disposition

Patients with an acute gastric volvulus require admission and surgical consultation due to the high morbidity and mortality associated with the condition.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 75: QUESTIONS AND ANSWERS

1. Which of the follow drug regimens is appropriate first-line treatment for *Helicobacter pylori* infection?

a. Bismuth subsalicylate, famotidine, and clarithromycin
b. Metronidazole and sucralfate
c. Omeprazole, amoxicillin, and clarithromycin
d. Omeprazole and bismuth subsalicylate
e. Famotidine, omeprazole, and amoxicillin

Answer: c. The recommended triple-treatment regimen for *H. pylori* infection is a proton pump inhibitor (PPI) (e.g., omeprazole, 20 mg bid), amoxicillin (1 g bid), and clarithromycin (500 mg bid) for 14 days. Quadruple therapy with Pepto Bismol, metronidazole, tetracycline, and a PPI is an alternative option. See Box 75.5.

2. What percentage of esophageal foreign bodies require a nonoperative intervention to facilitate removal?

a. <5%
b. 10% to 20%
c. 50%
d. 75%
e. >90%

Answer: b. Most foreign bodies pass spontaneously. Approximately 10% to 20% require intervention, but less than 1% require surgery for removal.

3. A 5-year-old child is brought to the emergency department (ED) by his mother after a possible ingestion of a plastic Lego piece. He has had no pulmonary symptoms but reports difficulty swallowing and declines to drink liquids that are offered. What would be the intervention of choice?

a. Contrast-enhanced CT scan of the chest
b. Endoscopy
c. Non–water-soluble barium swallow
d. Posteroanterior and lateral chest radiography
e. Water-soluble barium swallow

Answer: b. Because the patient is symptomatic, endoscopy is indicated. A CT scan of the chest is useful for organic and inorganic materials. A basic chest radiograph cannot reliably exclude a foreign body. Barium swallow is difficult in pediatric patients, particularly in a child who is refusing oral fluids. Water-soluble media administration risks development of pneumonitis if aspirated. Non–water-soluble materials risk increased inflammation if leakage occurs into the mediastinum. Barium may also obscure subsequent endoscopic visualization.

continued

CHAPTER 75: QUESTIONS AND ANSWERS—cont'd

4. Which of the following statements regarding the use of glucagon in esophageal obstruction from a food bolus is true?
   a. Glucagon should be administered by the oral route.
   b. Glucagon has antiemetic properties.
   c. Glucagon can facilitate passage of a food bolus localized anywhere in the esophagus.
   d. Glucagon is relatively contraindicated with sharp-edged foreign bodies.
   e. The success rate of glucagon approaches 90% when used with a few hours of food bolus impaction.

Answer: d. Glucagon is a smooth muscle relaxant, so it is theoretically useful only for distal esophageal foreign bodies. There are only anecdotal reports of success with glucagon, but a literature review shows no statistical benefit of glucagon in treating esophageal foreign bodies. There are many adverse effects, including flushing, nausea, and vomiting, that can potentially increase the risk of aspiration. It is contraindicated for use with sharp or damaging foreign bodies. There is only low-level evidence to support the use of effervescent agents, and they are relatively contraindicated after 24 hours because of perforation concerns.

5. Which of the following is an indication for urgent endoscopy?
   a. Button battery in the stomach
   b. Chest pain due to foreign body
   c. Coin in the proximal esophagus
   d. Nausea and vomiting
   e. Object failing to pass out of the esophagus after 12 hours

Answer: c. A coin that remains lodged in the proximal esophagus should be removed. Other indications are inability to handle secretions, sharp objects, esophageal button battery (alkaline), and impactions that fail to pass after 24 hours.

6. Ulcers in which portion of the upper GI tract are most likely to perforate?
   a. Hypopharyngeal
   b. Esophageal
   c. Gastric—antrum
   d. Gastric—body
   e. Duodenal

Answer: e. Duodenal ulcers account for 60% of all perforations, followed by antral gastric ulcers (20%) and gastric body ulcers (20%). Various upper gastrointestinal (GI) symptoms may lead to esophageal ulcerations and severe odynophagia, although perforation is infrequent.

7. A 32-year-old otherwise healthy man presents with acute onset of epigastric pain radiating to his chest that woke him from sleep at 2 AM. It was a burning pain associated with water brash. There were no associated pulmonary symptoms. His past medical history is unremarkable except for tobacco use and heartburn. His electrocardiogram and upright chest radiograph are normal. Vital signs and physical examination findings are unremarkable. He is currently pain free. His troponin level is normal. What is the most appropriate intervention?
   a. Cardiology consultation for catheterization
   b. Contrast-enhanced CT scan of the chest
   c. Discharge on aspirin, 325 mg once daily
   d. Serial troponins
   e. Trial of twice-daily proton pump inhibitor therapy

Answer: e. Peak gastric acid secretion occurs during the early morning hours between 1 AM and 3 AM, with a typical scenario of causing awakening from sleep. The shared afferent neural pathway makes the pain of gastroesophageal reflux disease (GERD) similar to that of pain of cardiac origin. Gastric acid secretion is lowest at approximately 6 AM; thus awakening in the morning with pain from GERD is unusual.

8. A 45-year-old woman presents several hours after an upper endoscopy with severe chest pain and neck discomfort. She is awake and alert, but rates pain as "10 of 10." What is the most appropriate test to confirm the diagnosis?
   a. Abdominal x-ray
   b. Barium contrast esophagography
   c. Gastrografin (water-soluble) contrast esophagography
   d. Ultrasound
   e. Upper endoscopy

Answer: c. We recommend an initial attempt with a water-soluble agent in patients who are awake and alert and are not at risk for aspiration. Barium sulfate is superior for identifying small perforations; however, it may incite an inflammatory response in tissue and should be used only if no initial perforation is identified with water-soluble contrast. Endoscopy is generally not recommended except in cases of penetrating trauma because insufflation could potentially enlarge a minimal transmural opening. CT imaging is a reasonable alternative.

76

Liver and Biliary Tract Disorders

Elizabeth J. Haines and Holly Thompson

KEY CONCEPTS

Viral Hepatitis

- The clinical presentation of viral hepatitis is highly variable, and many cases may be asymptomatic, particularly in children.
- Hepatitis A is transmitted through oral fecal spread, whereas hepatitis B and C are spread through parenteral or intimate contact.
- Highly effective immunizations exist against hepatitis A and B viruses.
- Postexposure, passive immunization exists for hepatitis A and B viruses, though its use is primarily in the setting of hepatitis B exposure in nonimmunized individuals.
- Direct-acting antiviral regimens using nucleoside inhibitors have revolutionized hepatitis treatment.
- Viral hepatitis may be a reportable disease dependent on jurisdiction.

Alcoholic Hepatitis

- Alcohol-induced liver disease may progress from steatosis to steatohepatitis to cirrhosis, and finally to hepatocellular carcinoma. It is estimated that 8% to 20% of patients with steatosis will eventually progress to cirrhosis. The risk for hepatocellular carcinoma (HCC) in decompensated alcohol-induced cirrhosis approaches 1% per year.
- With cessation of alcohol intake, steatosis may reverse within 2 weeks.
- Laboratory tests may help distinguish alcoholic hepatitis from viral hepatitis, with the former associated with milder transaminase level elevations and a relative predominance of AST to ALT.
- Hypoglycemia is common in patients with alcoholic hepatitis secondary to caloric insufficiency, chronically depleted glycogen stores, and suppressed gluconeogenesis.
- Management of alcoholic hepatitis is guided by severity scoring; Maddrey discriminant function (MDF) is the most commonly utilized and incorporates coagulopathy and bilirubin levels.
- Patients with alcoholic hepatitis and a MDF over 32 should be treated with prednisone, 40 mg PO daily, or methylprednisolone, 32 mg IV daily.

Cirrhosis

- Patients with cirrhosis most often present with complications resulting from loss of hepatocytes, including ascites, variceal bleeding, hepatorenal syndrome, or hepatic encephalopathy.
- The targeted platelet count should generally be greater than 50,000/mm^3 prior to the performance of invasive procedures in patients with cirrhosis. Management of coagulopathy may need to precede major diagnostic or therapeutic interventions.
- An elevated INR or thrombocytopenia is not a contraindication to paracentesis in patients with cirrhosis.
- Albumin, 8 g per L of ascitic fluid removed, should be administered when volumes over 5 L are removed by paracentesis.
- Upper GI bleeding in patients with cirrhosis, often from esophageal varices, carries a 10% to 15% mortality.
- When treating liver-associated coagulopathies in a patient with active bleeding, cryoprecipitate, 1 unit/10 kg body weight, is preferred over fresh-frozen plasma.
- Angiotensin-converting enzyme inhibiting drugs or angiotensin receptor blocking drugs should be avoided in patients with decompensated cirrhosis or ascites because plasma drug concentrations may increase, renal clearance may be markedly decreased, leading to impaired renal function.
- In patients with cirrhosis, mean arterial pressure (MAP) is an independent predictor of mortality.
- Hepatorenal syndrome is heralded by an increasing creatinine level in the setting of liver failure, and is associated with a high rate of mortality.

Hepatic Encephalopathy

- Hepatic encephalopathy is a state of cerebral and neuromuscular dysfunction secondary to an increased ammonia level and its effect on cerebral metabolism. However, the severity of hepatic encephalopathy does not directly correlate with the measured serum ammonia level.
- Underlying conditions that can precipitate encephalopathy in patients with cirrhosis include GI bleeding, hypokalemia, infection, and dehydration.
- Management of hepatic encephalopathy includes correction of underlying electrolyte abnormalities, dietary guidance, administration of lactulose (30–60 g/day), and rifaximin (400 mg PO every 8 hours).
- In addition to lactulose and rifaximin, infusion of branched chain amino acids has shown benefit without increased mortality in patients with hepatic encephalopathy.

Spontaneous Bacterial Peritonitis

- Spontaneous bacterial peritonitis (SBP) is an acute infection of ascitic fluid that should be considered in any patient with ascites and abdominal pain, fever, or unexplained clinical deterioration.
- SBP is most commonly caused by *E. coli* and *Klebsiella.*
- The diagnosis of SBP is dependent on obtaining ascitic fluid for analysis.
- An ascitic fluid granulocyte count greater than 250 cells/mm^3 (100 cells/mm^3 in peritoneal dialysis patients) is generally an indication for antibiotic treatment.
- Treatment of SBP includes cefotaxime 2 g IV every 8 hours for 5 days.

Hepatic Abscesses

- Abscesses may be amoebic or pyogenic in nature. Abdominal ultrasound or CT are the diagnostic imaging modalities of choice.
- Chest radiography may reveal a right lower lobe pleural effusion
- Imaging does not distinguish pyogenic from amebic abscesses.
- Treatment is initiated prior to abscess drainage.

- Treatment regimens for pyogenic abscess include:
  - Cefotaxime 2 g IV q8h + metronidazole 500 mg IV or PO every 8 hours
  - Ampicillin 2 g IV q4h + gentamycin 5– 7 mg/kg IV daily + metronidazole 500 mg IV or PO every 8 hours
  - Ciprofloxacin 400 mg IV q12h or 500 mg PO q12h or levofloxacin 750 mg IV or PO every 24 hours or moxifloxacin 400 mg IV or PO daily + metronidazole 500 mg IV or PO every 8 hours
  - Piperacillin-tazobactam 3.375 g or 4.5 g IV every 6 hours or imipenem-cilastatin 500 mg IV every 6 hours or meropenem 1 g IV every 8 hours + metronidazole 500 mg IV or PO every 8 hours
- Definitive treatment for abscesses larger than 3 to 5 cm includes image-guided percutaneous drainage.

Amebic Abscess

- Symptom onset with amebic abscess usually occurs approximately 12 weeks following exposure.
- Although similar in many ways to pyogenic abscess, the diagnosis of hepatic amebic abscess is made via stool analysis or ELISA testing.
- Most patients will have elevation in alkaline phosphatase and aminotransferase levels.
- Ultrasound may reveal specific findings unique to an amebic abscess, including a peripherally located, ovoid abscess with a well-circumscribed border and a homogeneous, hypoechoic center.
- Definitive treatment of amebic abscess is amebicidal therapy with IV or oral metronidazole (750 mg every 8 hours for 7–10 days).
- Percutaneous drainage is rarely needed.

Cholelithiasis

- Biliary colic should be considered in patients with nausea, vomiting, and right upper quadrant (RUQ) abdominal pain.
- Diagnosis with ultrasound of the biliary system or laboratory abnormalities including leukocytosis, elevated liver tests or pancreatic enzymes when present, suggests obstruction of the biliary tree.
- Initial management of cholelithiasis is supportive, with the goal of treating pain and correcting fluid or electrolyte abnormalities.
- Patients without findings of infection who are tolerating oral intake are typically managed in the outpatient setting.
- Definitive care requires outpatient surgical referral for cholecystectomy.

Cholecystitis

- Most patients with cholecystitis have gallstones, but approximately 8% have acalculous disease.
- Despite an unclear relationship between the pathophysiology and bacterial infection in cholelithiasis, antibiotic therapy is recommended. First-line treatment includes piperacillin-tazobactam 3.375 gm IV every 6 hours
- Patients with acalculous or emphysematous cholecystitis are at increased risk for gangrene or perforation and often require emergent cholecystectomy.

Cholangitis

- Cholangitis is an emergency condition resulting from extrahepatic bile duct obstruction and bacterial infection. Most commonly, the obstruction is secondary to gallstone impaction.
- The classic (Charcot) triad of cholangitis consists of RUQ pain, fever, and jaundice.
- Initial management of cholangitis requires prompt fluid resuscitation and administration of broad-spectrum antibiotics. First-line treatment choice of antibiotics should take into consideration individual risk factors and community versus health care–associated pathogens.
- Definitive management of cholangitis includes hospitalization and early biliary tract decompression, which can be achieved surgically, transhepatically, or by endoscopic retrograde cholangiopancreatography (ERCP).

HEPATIC DISORDERS

Hepatic disorders may be acute or chronic. Although acute disease is often self-limiting, it can progress to scarring, fibrosis, cirrhosis, or cancer. In the United States (US), acute hepatic disease prevalence has remained stable for the last three decades in contrast to chronic liver disorders which have increased, attributed primarily to a doubling of nonalcoholic fatty liver disease (NAFLD).[1] Etiologies of newly diagnosed chronic liver disease include: hepatitis B, hepatitis C, hepatitis C in combination with alcohol-related liver disease, alcohol-related liver disease, NAFLD, or alternative/undetermined etiologies. Hepatitis C is the most common etiology in the US. Overall mortality and anticipated cost burden is projected to increase with an aging patient cohort previously infected with hepatitis C.[2]

HEPATITIS

End organ inflammatory damage to the liver defines *hepatitis*. Although it commonly results from viral infection or toxic alcohol exposure, other etiologies include chemical or medication exposure; bacterial, fungal or parasitic infection; genetic disorders; or immune mediated pathology.

Viral Hepatitis

Foundations

Many viral infections are associated with some degree of measurable liver inflammation. However, the most significant and potentially severe cases of viral hepatitis are caused by type A, type B, type C, or delta viruses. The Epstein-Barr virus, the causative agent of mononucleosis, is also a common cause of hepatitis, although it is more important clinically for its nonhepatic effects.

Hepatitis A. Hepatitis A virus (HAV), is an RNA enteroviral picornavirus. It is spread by the fecal-oral route directly or through fecally contaminated water or food. Transmission by blood is possible though exceedingly rare. HAV can occur sporadically or more commonly in association with epidemics generally linked to common source outbreaks. HAV infection is common worldwide; serologic evidence of previous infection exists in nearly 100% of the adult population in some regions (Fig. 76.1). In the US, close to 50% of all urban-dwelling adults are seropositive for antibody for HAV.[3] High rates of seropositivity in association with the relatively small number of reported episodes support the notion that many cases may be subclinical or asymptomatic altogether. Occult disease appears to be more common in children with upwards of 70% of those infected

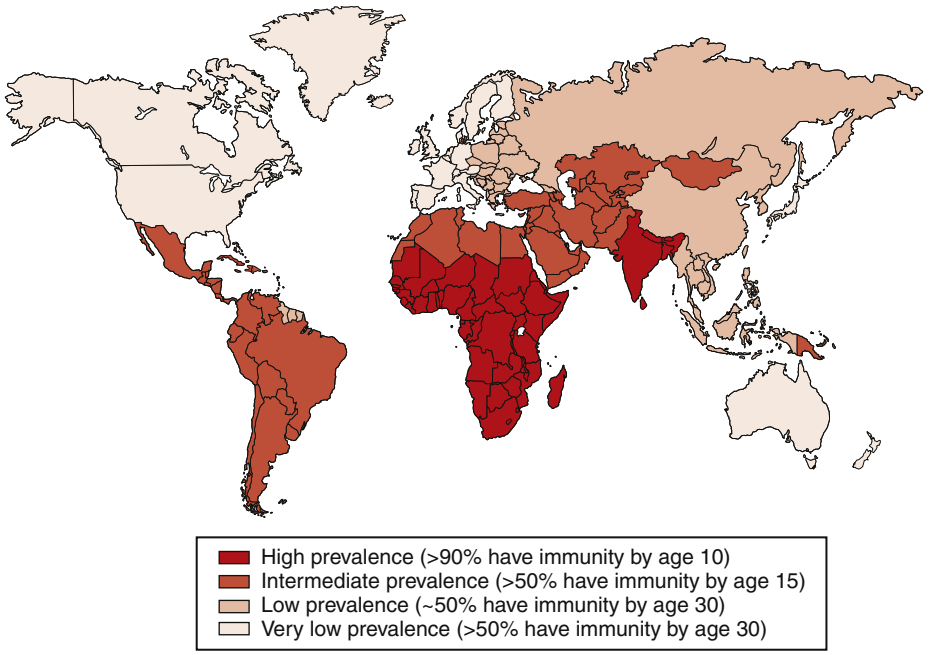

Fig. 76.1 Worldwide distribution of hepatitis A. (From Jefferies M, Rauff B, Rashid H, et al. Update on global epidemiology of viral hepatitis and preventive strategies. *World J Clin Cases*. 2018;6(13):589-599.)

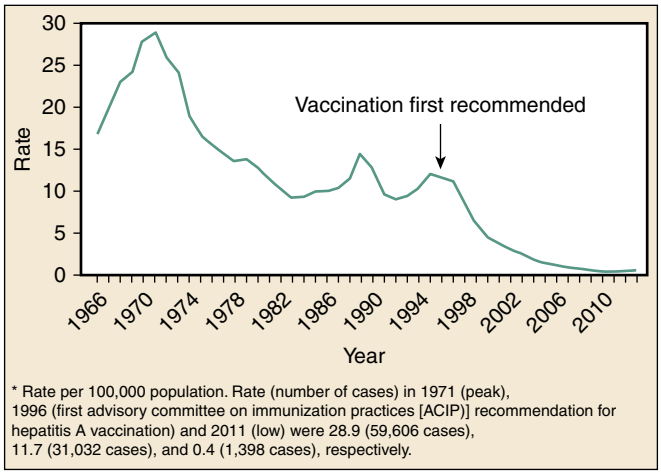

Fig. 76.2 Incidence of hepatitis A denoting 1995 approval of vaccination. (From Centers for Disease Control and Prevention (CDC). Progress toward eliminating hepatitis A disease in the United States. *MMWR Morb Mortal Wkly Rep*. 2016;65(1):29-41.)

asymptomatic.[3] The hepatitis A vaccine was approved in the US in 1995. Widespread vaccination has contributed to a profound shift in reported new cases to adults (Figs. 76.2 and 76.3). Travel to endemic areas is the most common risk factor for hepatitis A in persons more than 15 years of age.

The incubation period for hepatitis A ranges from 15 to 45 days (typically, 30 days), with a relatively short duration of viremia that is most prominent before the onset of symptoms. Most commonly, symptoms occur between 2 to 6 weeks after exposure.[4] Fecal shedding and maximum infectivity occur before the onset of symptomatic disease and generally have waned by the time jaundice appears (Fig. 76.4). HAV is not associated with a chronic carrier state.

Hepatitis B. Hepatitis B virus (HBV) is a virion that envelopes DNA polymerase, hepatitis B surface antigen (HBsAg), and hepatitis B core antigen (HBcAg). Hepatitis Be antigen (HBeAg) is not incorporated into the virion; rather, it is secreted from cells into the serum of infected patients. In contrast to HAV, for which there is only a single antigenic variety, several genotypes of HBV are recognized as defined by surface antigen. HBV is transmitted principally by parenteral exposure and also can be transmitted through intimate contact or body fluids. Transmission by blood transfusion, previously a common source of infection, has essentially been eliminated secondary to modern blood screening techniques. In contrast to HAV which has decreased, the incidence of hepatitis B has remained relatively stable despite increased rates of immunization. This is postulated in relation to increasing injection drug use and the ongoing opioid crisis in the United States, with 22,000 new HBV infections estimated annually[5] (Figs. 76.5 and 76.6). HBsAg has been detected in a variety of bodily fluids, including saliva, semen, stool, tears, urine, and vaginal secretions. The virus is highly stable and can survive outside of the body up to seven days with ongoing infective capacity.[6]

The mean interval between exposure and onset of clinical illness is 120 days; however, serologic markers of infection generally appear within 1 to 3 weeks (Fig. 76.7). Chronic hepatitis is typically defined as the presence of HBsAg in serum for longer than 6 months. Additional tests for HBV replication, HBeAg, serum HBV DNA, and ALT should be performed to determine if the patient is a candidate for antiviral therapy. Approximately 10% of adults, and 90% of infected neonates with immature immune systems, will become asymptomatic chronic carriers of HBsAg. Similar to HAV, children are more likely to have asymptomatic infections. The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. In other words, there exists an age-dependent protection against contracting chronic HBV.[7] HBV transmitted from HBsAg-positive mothers to their newborns results in HBV chronic carriage in up to 90% of infants, whereas only 6% to 10% of acutely infected adults become chronic carriers. This has led to strict prenatal screening and prophylaxis practices in the United States.

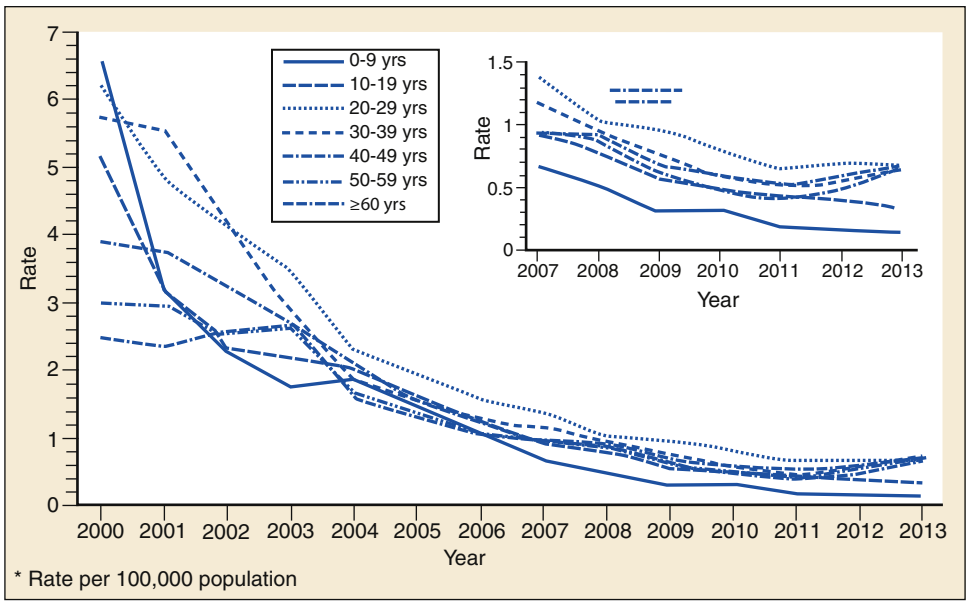

Fig 76.3 Incidence of hepatitis A by age group. (From Centers for Disease Control and Prevention (CDC). Progress toward eliminating hepatitis A disease in the United States. *MMWR Morb Mortal Wkly Rep.* 2016;65(1):29-41.)

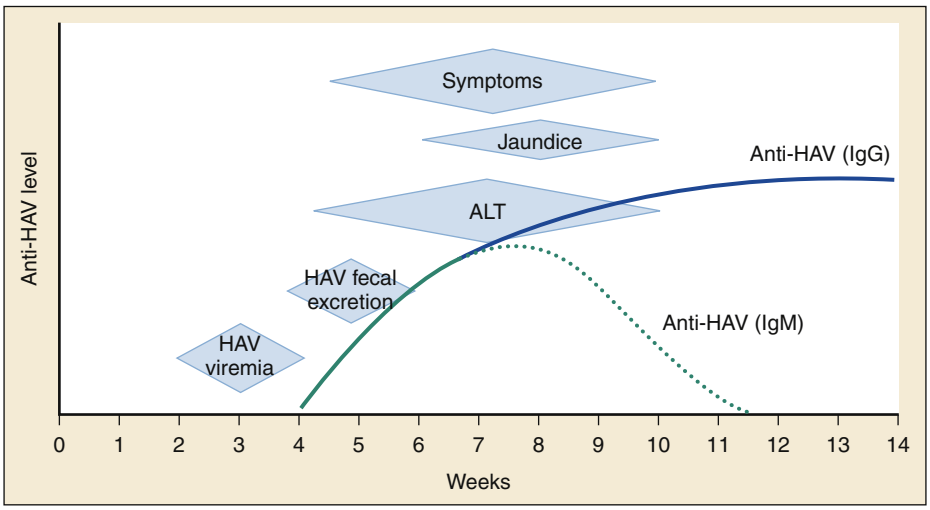

Fig. 76.4 Acute hepatitis A virus (HAV) infection. *ALT,* Alanine aminotransferase; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M. (From Oyama LC. Disorders of the liver and biliary tract. Anesthesia key: fastest anesthesia & intensive care & emergency medicine insight engine. Available at: https://aneskey.com/disorders-of-the-liver-and-biliary-tract/. Accessed May 10, 2021.)

Hepatitis C and E

Historically termed "non-A, non-B hepatitis," hepatitis C and E are caused by at least two distinct RNA viruses, hepatitis C virus (HCV) and hepatitis E virus. In the US, hepatitis C infection is currently the leading cause of cirrhosis, accounting for over 42% of cases of chronic liver disease.[2] Worldwide, HCV remains highly prevalent. The World Health Organization (WHO) in 2020 reported an estimated 71 million cases worldwide.[8] Hepatitis C is the most commonly reported bloodborne infection in the US. Data from the National Health and Nutrition Examination Survey (NHANES) estimates a prevalence of 1.2% to 2.0% among the US population.[9] Prior to 1992 and the advent of improved screening with antibody, PCR nucleic acid amplification, and aminotransferase (surrogate marker) testing, transmission by blood transfusion or solid organ transplant was common. Current risk of transfusion-acquired hepatitis C is less than 1 in 2 million units of blood transfused.[10,11]

Both in the United States and worldwide, the strongest risk factor for HCV infection is a history of intravenous drug use (IVDU). A 2017 study noted an HCV prevalence in the US of 53% among persons who inject drugs.[12] Another study estimates that the rate is closer to 75% among injection drug users coinfected with HIV.[13] Patients coinfected with HIV and HCV generally have a more aggressive course of both diseases. In upwards of 57% of patients with HCV, no source of infection is identified. The mean incubation period for hepatitis C is 50 days. Following the incubation period, a self-limited acute phase begins.[14] The acute phase persists for up to 12 weeks and is rarely associated with hepatic failure. Approximately 90% of HCV infections progress to chronic hepatitis. Over a 20- to 30-year period, clinical liver disease

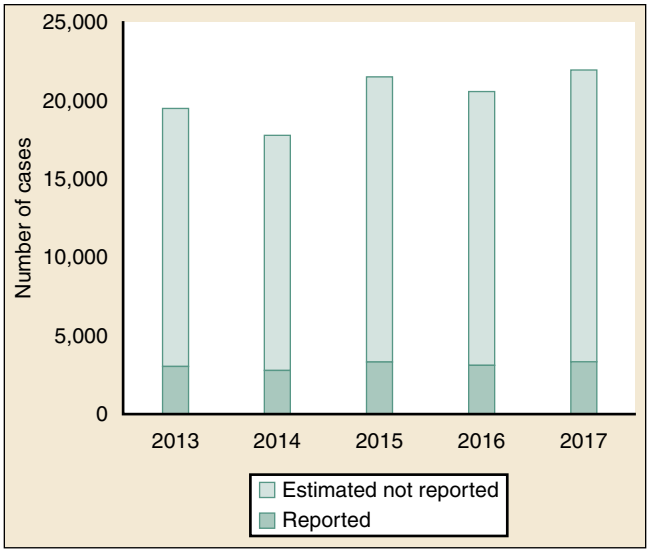

Fig. 76.5 Incidence of hepatitis B in the United States. (From Centers for Disease Control and Prevention. Viral hepatitis surveillance—United States, 2017. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm)

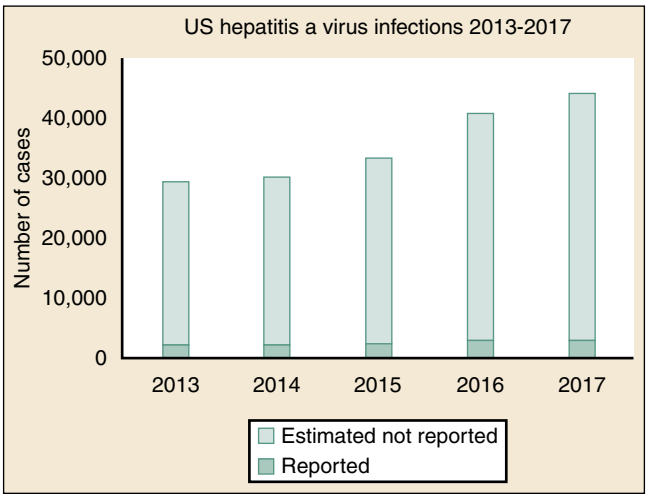

Fig. 76.6 Incidence of hepatitis A in the United States. (From Centers for Disease Control and Prevention. Viral hepatitis surveillance—United States, 2017. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm)

or cirrhosis develops in roughly 10% to 20% of those infected. Patients with cirrhosis are at elevated risk for development of hepatocellular carcinoma.[15] In the US, it has been estimated that 2.1 million persons are infected with HCV. Unlike HAV and HBV, HCV incidence has continued to increase. Antiviral treatments can reverse damage and effectively cure many patients with HCV.

Hepatitis D. Hepatitis delta virus (HDV) is a defective RNA virus that can infect only patients who are actively producing HBsAg (HBV disease), which is required for its viral coating. Worldwide, the prevalence of hepatitis D in those with hepatitis B is 5%.[16] As a result of HBV control in the US, the prevalence is lower. Given its association with chronic HBV infection, it is likely that many cases of HDV infection are misdiagnosed as acute or reactivated hepatitis B.

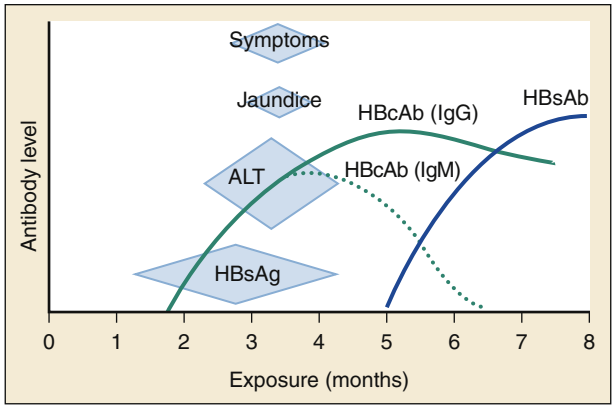

Fig. 76.7 Acute hepatitis B virus infection. *Ab,* Antibody; *Ag,* antigen; *ALT,* alanine aminotransferase; *HBc,* hepatitis B core; *HBs,* hepatitis B surface; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M. (From Oyama LC. Disorders of the liver and biliary tract. Anesthesia key: fastest anesthesia & intensive care & emergency medicine insight engine. Available at: https://aneskey.com/disorders-of-the-liver-and-biliary-tract/. Accessed May 10, 2021.)

HDV is spread in a manner similar to that of hepatitis B. Infection with HDV can occur concomitantly with HBV (coinfection) or subsequent to an existing HBV infection (superinfection), as HDV can only replicate in the presence of HBV. Cases of superinfection may present as acute self-limited disease to fulminant hepatitis or chronic infection. Fulminant hepatitis is more often observed with HBV-HDV coinfection than with HBV mono-infection. HDV further aggravates and worsens the disease course for patients with HBV.[17]

Hepatitis E and G. Hepatitis E, which is associated with fecal-oral transmission, is encountered most often in Asia, Africa, or Russia. Hepatitis E has an incubation period of 15 to 60 days. The most recently described hepatitis virus is hepatitis G (HGV). HGV is also referred to as hepatitis GB virus type C (GBV-C). It is an RNA virus that is transmitted through blood transfusion, parenteral exposure to blood products, or possibly during intimate contact. The virus has been identified in patients with acute and chronic hepatitis. Similar to HDV, it is believed to be a bystander virus, with disease manifestations attributable to coinfection with another hepatitis virus.

Clinical Features

The clinical presentation of viral hepatitis is highly variable, with a significant number of asymptomatic infections. The hepatitis viruses (A, B, C, D, E, G) are often clinically nondistinct. Common findings include malaise, fever, or anorexia, followed by nausea, vomiting, abdominal discomfort, or diarrhea. Stools may be described as pale or clay colored. The initial finding that may prompt further evaluation is jaundice. A small number of patients with hepatitis B may experience a prodromal illness characterized by arthralgia, arthritis, and dermatitis. The joint involvement typically is polyarticular; the small joints of the hands and wrists are usually affected. The characteristic dermatitis associated with HBV is urticarial though may be macular, papular, or petechial.

Fulminant hepatitis is characterized by an acute onset illness that progresses to hepatic failure and encephalopathy over a period of days characterized by altered mentation and spontaneous mucosal bleeding. Although most often encountered with HBV and HDV coinfection, fulminant hepatitis can occur in association with all the causative viruses (1% to 2% of all cases).

Physical findings may include fever, scleral or cutaneous icterus, and abdominal tenderness. There may be vomiting and dehydration

resulting in tachycardia or hypotension. Hepatomegaly may occur and is characterized by a smooth, homogeneous, tender liver surface. Even if liver enlargement is not appreciated, tenderness to percussion over the lower right ribs may be present. Scleral icterus is generally noticeable earlier than cutaneous discoloration. Muddy sclera, commonly found among African American patients, may obscure or confuse this finding; sublingual or subungual surfaces are alternative examination sites. Scleral icterus usually occurs once the serum bilirubin level is above 2.5 mg/dL. Spider angiomata and splenomegaly, although more often associated with chronic cirrhosis, may be features in acute presentations as well.

Differential Diagnosis

The generalized findings associated with hepatopathy, often heralded by an elevation in transaminases, renders the differential diagnosis broad in scope. In addition to nonhepatic viral illnesses (such as EBV or others) or biliary tract disease, various other infectious, chemical, or immunologic causes of hepatic inflammation should be considered. Many medications, herbal and dietary supplements, or other toxins are associated with hepatopathy. Common medications that can cause hepatopathy include acetaminophen (most common cause of acute liver failure in the US), antimicrobial drugs (such as amoxicillin-clavulanate, isoniazid, nitrofurantoin, and dapsone), anticonvulsive drugs (such as phenytoin and carbamazepine), and statins, among many other drugs. Herbal and dietary supplements that are associated with liver injury include weight-loss or fat-burning products (such as Hydroxycut), anabolic steroids, Indian and Chinese herbal medications (Ayurvedic compounds), green tea, and pyrrolizidine alkaloids. Chemical toxins that are associated with liver injury include organic solvents (toluene, dimethylformamide, carbon tetrachloride, and chloroform, among many others), vinyl chloride, aflatoxin, and polycyclic aromatic hydrocarbons.[18-21]

A viral cause may be suggested by the medical history and serologic tests provide confirmation. Alcoholic hepatitis is associated with a history of excessive or chronic alcohol consumption, less marked elevation of hepatic transaminase levels, and AST levels elevated above those of ALT. Extrahepatic obstruction, cholecystitis, and cholelithiasis are rarely associated with significant elevation of aminotransferase levels. Abdominal ultrasound or computed tomography (CT) imaging may be helpful in the evaluation of potential alternative diagnoses.

Diagnostic Testing

Laboratory findings are critically important in diagnosing hepatitis and determining the specific cause, including measurements of serum hepatic aminotransferase and bilirubin levels. Typically, hepatitis is associated with elevations (10- to 100-fold) of serum AST and ALT levels, with the ALT level generally elevated in excess of AST. The serum bilirubin level may be moderately increased (5–10 mg/dL), and occasionally is markedly elevated (15–25 mg/dL). Hyperbilirubinemia typically emerges several days to 1 week or more after the onset of clinical symptoms. Direct and indirect bilirubin levels are typically elevated in nearly equal proportions. Alkaline phosphatase and lactate dehydrogenase levels may be elevated, though rarely more than 2 to 3 times normal.

The prothrombin time (PT) or international normalized ratio (INR) is useful in assessing the degree of hepatic synthetic dysfunction. Elevation of the PT or INR may be the first clue to a complicated course. The white blood cell (WBC) count generally is not useful in the diagnosis because values range from leukopenia with a lymphocytic predominance to marked polymorphonuclear leukocytosis. Although determining the precise cause of hepatitis can rarely be achieved in the ED, serologic testing should be initiated as soon as feasible (Table 76.1) because results impact prognosis and may have public health importance.

TABLE 76.1 Serologic Markers in Hepatitis

Serologic Marker	Abbreviation	Interpretation
Antibody to HAV	Anti-HAV	Combination of IgG and IgM antibody defining infection with HAV, acute or past
IgM antibody to HAV	Anti-HAV IgM	Antibody to HAV, indicating acute infection
Hepatitis B surface antigen	HBsAg	Surface antigen associated with acute or chronic HBV infection
Hepatitis Be antigen	HBeAg	Antigen associated with active infection, acute or chronic, and indicative of high infectivity
Antibody to B surface antigen	HBsAb	Antibody indicative of acute or past infection or immunization
Antibody to B core antigen	HBcAb	Combination of IgG and IgM antibody defining infection with HBV, acute or past
IgM antibody to B core antigen	HBcAb-IgM	Antibody to B core antigen, indicating acute infection with HBV
Antibody to Be antigen	HBeAb	Antibody to e antigen, possibly representing resolving HBV infection and decreased infectivity
Antibody to HDV	Anti-HDV	Antibody defining infection with HDV; HBsAg is also likely to be present
Antibody to HCV	Anti-HCV	A new antibody that defines infection with HCV, acute or past

HAV, Hepatitis A virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis delta virus; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

From: Oyama LC. Disorders of the liver and biliary tract. Anesthesia key: fastest anesthesia & intensive care & emergency medicine insight engine. Available at: https://aneskey.com/disorders-of-the-liver-and-biliary-tract/. Accessed May 10, 2021.

Acute hepatitis A is diagnosed by the presence of immunoglobulin M (IgM) HAV antibody, whereas previous infection is determined by detection of an IgG antibody. Acute hepatitis B is characterized by the presence of HBsAg and IgM antibody to HBcAg. HBsAg alone does not establish the diagnosis of acute hepatitis B because it can be absent late in the course of acute disease or present chronically. Anti-HBcAg antibody generally is the best indicator of previous HBV infection, whereas anti-HBsAg antibody is the best marker for immunity to HBV. Figure 76.8 demonstrates the temporal relationships among infection, clinical symptoms, and serologic responses for the two most common causes of viral hepatitis, HAV and HBV.

Due to its prolonged incubation period, early diagnosis of hepatitis C is based on the exposure history and elimination of other causes. Screening is through serologic detection of hepatitis C antibodies. Due to delayed appearance of antibodies, confirmation by a polymerase chain reaction (PCR) assay that detects HCV RNA

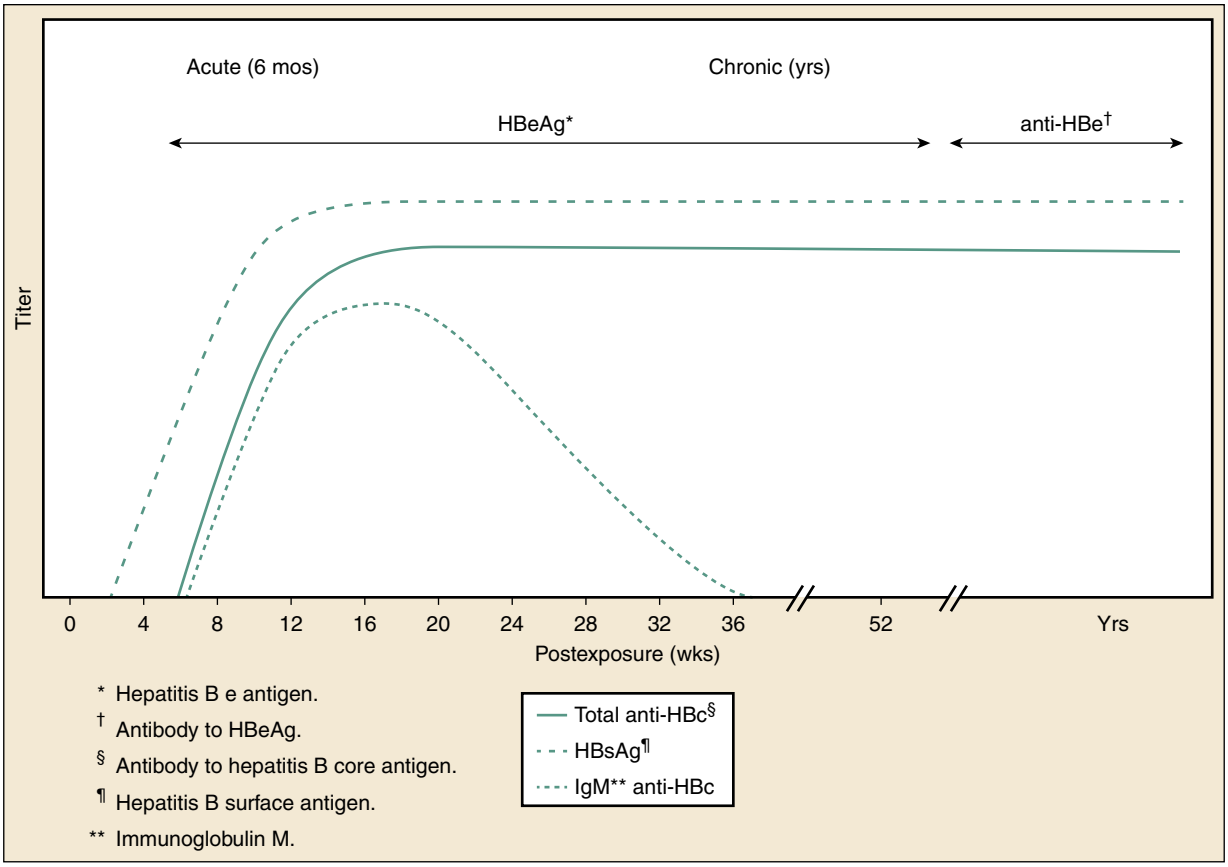

Fig 76.8 Serologic markers and symptom timing for hepatitis B. (From Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Morb Mortal Wkly Rep*. 2008;57:1-20.)

facilitates definitive diagnosis. HCV antibody testing does not distinguish acute from chronic infection. Repeat PCR testing at 6 weeks can be used to differentiate acute versus chronic hepatitis. Variable low levels of HCV RNA suggest acute infection, whereas nonvariable, higher HCV RNA levels are more consistent with chronic hepatitis C infection. Also, the presence of hepatic fibrosis assessed by histologic (biopsy) analysis or noninvasive serum and ultrasonographic testing can assist in evaluating for the presence of a chronic state. Among those in the US testing positive for hepatitis C, the majority are unaware of their infection.[22] Coupling this lack of awareness with the high prevalence of undiagnosed HCV has led many public health advocates to successfully implement HCV screening programs in the ED setting.[23]

Due to coinfectivity, diagnosis of HDV infection with a serologic test for the antibody to HDV (anti-HDV) requires a thorough testing approach because it may readily be mistaken for acute or chronic HBV infection. The presence of anti-HDV in conjunction with IgM antibody to HBcAg suggests coinfection with HDV and HBV. Anti-HDV in association with IgG antibody to HBcAg supports the diagnosis of superinfection.

Management

Most patients with viral hepatitis have self-limited disease, with symptomatic and histologic resolution in 2 to 4 weeks. ED management is primarily supportive with attention to fluid or electrolyte imbalances resulting from poor oral intake or excessive diarrhea or vomiting. Antiemetics may be helpful and fluid intake should be encouraged, with gradual advancement of diet. Medications with primarily hepatic metabolism should be dose adjusted or discontinued only in the setting of significant hepatic dysfunction, as indicated by elevated serum aminotransferase and bilirubin levels, encephalopathy, or rising PT or INR levels. Nonessential drugs with hepatotoxic potential should be avoided. Alcohol consumption should be completely discontinued until signs of liver injury have dissipated. Due to the lack of evidence, we do not recommend a role for corticosteroids in the treatment of acute viral hepatitis.

Complications include fluid or electrolyte imbalance or refractory emesis. Severe vomiting can result in upper gastrointestinal (GI) bleeding from an esophageal tear. The most severe complication of acute disease is the development of liver failure, usually heralded by hepatic encephalopathy.

Although hepatitis A is self-limited and does not progress to a chronic state, isolation precautions, hand hygiene, and attention to other hygienic practices is prudent, in both the inpatient and home setting. Patients are contagious during the incubation period and remain contagious until 1 week after the appearance of jaundice.

Prevention and Postexposure Management. Effective preexposure and postexposure prophylaxis for HAV and HBV are available. For HBV exposure in an unimmunized patient, passive immunization with immune globin may prevent disease. The window to effectively prevent HBV seroconversion is about 2 weeks from time of exposure. Owing to the self-limited nature of HAV disease, hepatitis A immune globulin is reserved for use as preexposure prophylaxis in nonimmune individuals who are at high risk of exposure to hepatitis A, immunocompromised patients, those who are less than 6 months of age, have chronic liver disease, or have demonstrated an allergy to hepatitis A vaccination.

Emergency health care workers are at increased risk for exposure to all types of hepatitis given frequent contact with bodily fluids, blood, or interaction with high-risk patients.

ED personnel involved in patient care or related activities should be vaccinated against HBV for occupational reasons. A safe and effective vaccine for HAV is available, though routine immunization for health care workers is not generally recommended, unless in the setting of an outbreak. The vaccines are highly effective and are associated with rare acute or delayed toxicity. A complete three-injection series of vaccine—to the deltoid muscle for optimal immunologic response—produces protective antibody approximately 95% of the time. Hepatitis B immune globulin (HBIG) is recommended for immediate passive immunization of those not previously immunized who have been exposed to potentially infective material. Immune globulin diminishes the risk of HBV infection by 75%. The exposed, nonvaccinated patient should receive HBIG, 0.06 mL/kg intramuscularly (IM), in addition to the HBV vaccine. Figure 76.9 outlines an approach for managing health care workers exposed to blood or other potentially infectious secretions.

The risk of seroconversion after percutaneous exposure from an HCV-positive source is approximately 1.8%. Despite the theoretic risk of blood-borne HCV exposure among health care workers (HCWs), the prevalence of HCV infection in this group is approximately the same as in the general population. No effective vaccine for HCV is currently available, one reason we continue to see rises in hepatitis C relative to hepatitis A and B. Figure 76.10 Previously, it was thought that the use of peginterferon alfa-2b may decrease seroconversion in HCWs exposed to blood from HCV-infected individuals. However, low transmission rates, coupled with no additional benefit to prophylactically treated HCWs, has resulted in no accepted preexposure or postexposure prophylaxis (PEP) regimen for HCV prevention following occupational exposure. Though some studies have considered employment of direct acting antiviral (DAA) agents in postexposure prophylaxis, there is insufficient evidence to support their use in a postexposure capacity.[24] Universal precautions—the use of gloves, masks, protective eyewear, and gowns—constitute the first and best means of defense for persons who work in proximity to potentially infective bodily fluids. Occupationally exposed individuals should be tested within 48 hours to establish baseline presence or preexistence of disease, as well as again at 6 months post exposure.[24]

Disposition

Hospitalization is rarely required for the management of viral hepatitis and generally is reserved for patients with a fluid or electrolyte imbalance, or complete oral intolerance. Patients with less severe illness may require hospitalization for concomitant medical problems or if suitable living arrangements are not available. Altered sensorium, a PT more than 5 seconds, or an INR more than 1.5 may suggest fulminant disease or an increased likelihood of a complicated course, necessitating consideration of hospitalization. Transfer to a facility that can offer liver transplantation should be considered in the setting of emergence of fulminant disease.

Treatment of chronic hepatitis C has improved greatly in recent years. Current therapy involves genotype-specific DAA regimens using nucleoside polymerase inhibitors (e.g., simeprevir, sofosbuvir, ledipasvir). The goal endpoint is a sustained virologic response (SVR), defined as absence of HCV RNA by PCR testing at 3 to 6 months following treatment. Treatment regimens take into account various patient factors, including naïveté to treatment, prior relapse, prior partial or null response (lack of quantified decline in viral load at 4 weeks), or history of protease inhibitor failure. DAA regimens demonstrate sustained virologic response rates that exceed 95%. Evidence supports reversal of hepatic fibrosis, scarring, and metabolic function with DAA use in patients with chronic HCV.[25,26] There are numerous effective combinations of orally administered DAA agents. Combinations are chosen in relation to disease genotype to optimize outcomes and avoid adverse drug events. Treatment regimens should be considered in conjunction with a hepatologist.[27]

Referral to a hepatic disease specialist for virus genotyping, treatment initiation, and ongoing surveillance is recommended. Communicability concerns may affect the ease of disposition. Patients with possible HAV infection should be advised to practice meticulous personal hygiene, not to share toiletries, and ensure thorough cleaning of utensils and kitchenware between uses. In children, caretakers should be counseled on hand washing around feeding and diapering. In patients with suspected HBV or HDV infection, the relatively low risk of transmission by intimate personal contact should be emphasized, in order to ease anxiety. In the US, the Centers for Disease Control and Prevention (CDC) aggregates data weekly for surveillance posting. Though underreported, the CDC provides adjusted predictions on the number of acute infections.[28]

Viral hepatitis is generally a reportable disease requiring notification of the local health department. Immuno-prophylaxis should be provided to the patient's family members and close personal contacts (if not previously immunized) pending serologic determination (see Fig 76.9; Tables 76.1 and 76.2). Patients with HAV infection who process or handle food must not return to work while potentially infectious. Although infectivity is greatly diminished by the time jaundice emerges, it is advisable to delay return to work until after the jaundice has cleared.

Alcoholic Hepatitis

Foundations

Alcoholic hepatitis is rising in incidence. It is the most extreme manifestation of ongoing alcoholic liver disease and requires specialized medical care. It results from long-term alcohol consumption and is defined by the syndromic appearance of hepatic decompensation or failure. Disease continuum exists from mild to life-threatening. In relation to estrogen effects, women are at higher risk.[29]

Alcohol and its metabolites are toxic to most organ systems and are largely eliminated by metabolic hepatic degradation; up to 15% of alcohol is excreted unchanged in the urine or expired air. Physiologically, alcohol stimulates fatty acid synthesis and inhibits fatty acid oxidation. This allows the accumulation of fat within the liver. Additionally, alcohol increases intestinal permeability. This, in turn, makes patients vulnerable to bacterial translocation and peritonitis.

Although susceptibility to liver damage varies based on genetic heterogeneity, a gross correlation is recognized between the amount of ethanol ingested and risk of developing liver disease. The risk of liver injury increases as daily consumption exceeds 80 g of ethanol daily in men or 20 g in women. For men, this is equivalent to a six-pack of beer, four to six glasses of wine, or three to four mixed drinks daily. Fatty infiltration appears to depend on the duration and amount of alcohol consumed and, in general, is reversible when the patient stops drinking.

The most common variety of alcohol-induced liver disease is steatosis. Fatty infiltration of the liver is most likely a consequence of altered fatty acid metabolism resulting from a diminished NAD^+/NADH ratio, which favors triglyceride production. Beyond enlargement of the liver, which usually is painless, this tends to be a benign process.

As alcohol-related liver disease progresses beyond steatosis to fibrosis, cirrhosis and, in some cases, hepatocellular carcinoma may ensue (Fig. 76.11). In more than 90% of those who regularly consume

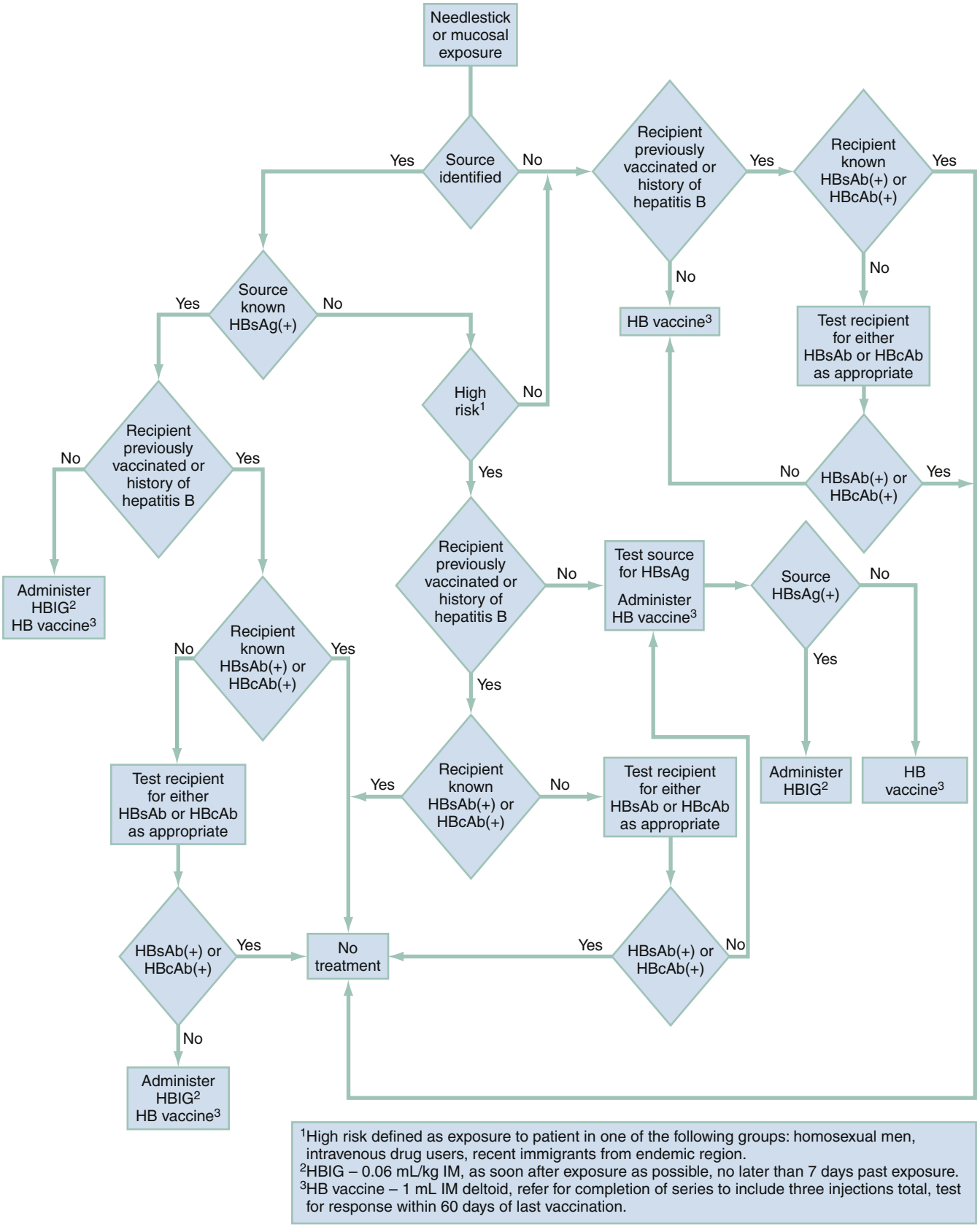

Fig. 76.9 Management of health care workers exposed to blood or other infectious secretions. *HB,* Hepatitis B; *HBIG,* HB immune globulin; *HBcAb,* hepatitis B core antibody; *HBsAb,* hepatitis B surface antibody; *HBsAg,* hepatitis B surface antigen; *IM,* intramuscularly. (From Oyama LC. Disorders of the liver and biliary tract. Anesthesia key: fastest anesthesia & intensive care & emergency medicine insight engine. Available at: https://aneskey.com/disorders-of-the-liver-and-biliary-tract/. Accessed May 10, 2021.)

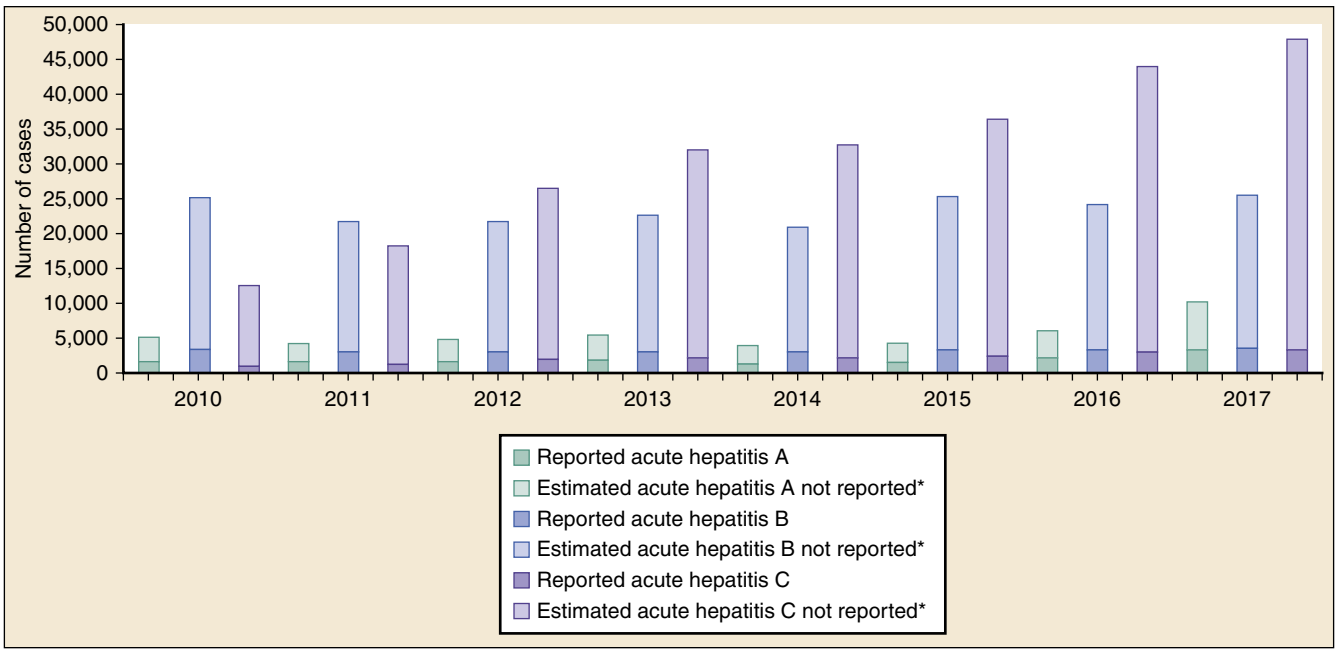

Fig 76.10 Reported cases of hepatitis 2010-2017 in the United States. (From Centers for Disease Control and Prevention (CDC). Surveillance for viral hepatitis—United States, 2017. Available at: https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm. Accessed May 10, 2021.)

alcohol, steatosis can be seen as early as 2 weeks. Within 5 years, 8% to 20% of those with steatosis of the liver progress to cirrhosis. Comorbidities that contribute to the progression of disease include viral hepatitis, HIV, or hemochromatosis. Approximately 3% to 10% of chronic alcoholics will develop hepatocellular carcinoma.

Clinical Features

Alcoholic hepatitis is a potentially severe form of alcohol-induced liver disease. Most cases are likely subclinical and the spectrum of presentation can range from nausea, vomiting, and abdominal pain to acute liver failure. Physical findings may include tachycardia, fever, and supine or orthostatic hypotension. Abdominal tenderness usually can be elicited, especially in the right upper quadrant. Coexistent fatty infiltration may produce palpable hepatomegaly; cirrhosis from chronic disease may result in a small nonpalpable liver. The characteristic physical signs of cirrhosis may be present—gynecomastia, spider angiomata, muscle wasting, ascites, or palmar erythema (Figs. 76.12 and 76.13). Jaundice can be noted in patients with a bilirubin level of at least 2.5 mg/dL. As disease advances, peripheral edema, abdominal distention, hematemesis, or melena may be present. Patients with clinical signs of alcoholic hepatitis should be assessed for symptoms of gastritis or GI bleeding.

Differential Diagnosis

The differential diagnosis of alcoholic hepatitis is broad in scope and includes many other alcohol-related GI maladies (e.g., gastritis, pancreatitis). The clinical history and aminotransferase profile typically facilitate an accurate diagnosis as other potential causative disorders are considered. Mild aminotransferase level elevation and marked bilirubin level elevation are consistent with alcoholic hepatitis; abdominal ultrasonography will aid in differentiating from common bile duct obstruction. Serum can be sent for testing for anti-HAV IgM and hepatitis B core antibody (HBcAb) IgM, though findings will likely result following ED disposition.

Diagnostic Testing

Laboratory tests reveal moderate elevations of AST and ALT levels. Values in excess of 10 times normal are unusual, even in severe cases associated with eventual liver failure. Compared with viral hepatitis, a relative predominance of AST to ALT is expected. AST can be 2 to 6 times the normal range. Leukocytosis, hyperbilirubinemia, and coagulopathy are common. The PT and INR level provide a rough assessment of hepatic dysfunction. An acutely prolonged PT or elevated INR level in a patient not suspected to have chronic cirrhotic disease suggests a complicated course. Electrolyte or acid-base disturbances may develop with excessive vomiting or alcoholic ketoacidosis. For alcoholic hepatitis, liver biopsy remains the diagnostic and prognostic gold standard, with a sensitivity ranging from 85% to 95% depending on the level of hyperbilirubinemia present. However, biopsy may be challenging secondary to hematologic abnormalities or ascites.

Management

The management of alcoholic hepatitis is principally supportive. Fluid and electrolyte imbalances should be corrected, usually requiring parenteral fluid replacement; antiemetics may mitigate the need for IV treatment. Alcohol may suppress gluconeogenesis, thereby causing hypoglycemia. The blood glucose level should be measured and supplemented, as necessary. Many alcoholics are malnourished and, if thiamine deficiency is suspected, thiamine should be given at a dose of 100 mg IV. Ethanol-induced magnesium wasting may not be apparent on serum magnesium measurement, and replacement should be given empirically unless the patient has a contraindication, such as renal failure or known hypermagnesemia. Magnesium can be given as the sulfate salt in a dose of 1 g IV or IM or as an oxide, chloride salt, or amino acid conjugate for oral replacement therapy at a daily dose of 200 to 1000 mg PO. Finally, short-term abstinence may result in increased risk for withdrawal, which requires management with short-acting benzodiazepines.

The overall nutritional status of the patient should be addressed with the administration of a high-calorie, vitamin-supplemented diet. Protein content may require restriction if evidence of cirrhosis and incipient encephalopathy exists. Coexisting gastritis should be treated with histamine H_2 antagonists, proton pump inhibitors, or antacids. Variceal bleeding is associated with a 5-year mortality rate of 65%;

TABLE 76.2 Postexposure Hepatitis Prophylaxis

Nature of Exposure	Recommended Treatment
Hepatitis A	
Close personal contact	ISG, 0.1 mL/kg IM
Daycare center	ISG, 0.1 mL/kg IM
• Employee	ISG, 0.1 mL/kg IM
• Attendee	
School contacts	None
Hospital contacts	None
Workplace contacts	None
Food-borne source	ISG, 0.2 mL/kg IM
• Within 2 wk of exposure	None
• After 2 wk of exposure	
After common source outbreaks have begun to occur	None

Nature of Exposure	Source	Exposed Individual Unvaccinated	Exposed Individual Vaccinated
Hepatitis B			
Percutaneous or mucosal	HBsAg (+)	1. HBIG ×1 2. Hepatitis B vaccination booster	Test exposed person for anti-HBs; if titer is adequate, no treatment. If anti-HBs titer inadequate: 1. HBIG ×1 2. Initiate hepatitis B vaccination series.
	HBsAg (–)	Initiate hepatitis B vaccination series	No treatment
	Unknown source (Treat as if HBsAg [+].)	1. HBIG ×1 2. Initiate hepatitis B vaccination series	Test exposed person for anti-HBs; if titer is adequate, no treatment. If anti-HBs titer is inadequate: 1. HBIG ×1 2. Hepatitis B vaccination booster
Intimate sexual	HBsAg (+)	1. HBIG ×1 2. Initiate hepatitis B vaccination series	Test exposed person for anti-HBs; if titer is adequate, no treatment. If anti-HBs titer inadequate: 1. HBIG ×1 2. Hepatitis B vaccination booster
Hepatitis C			
Unknown benefit from prophylaxis; ISG, 0.06 mL/kg IM can be considered for parenteral exposures in patients with evidence of viral hepatitis and negative results on serologic studies.			
Hepatitis Delta			
Same as for hepatitis B			

HBIG, Hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *IM,* intramuscularly; *ISG,* immune serum globulin.
The HB vaccine recombinant dose comes in three formulations: pediatric, adult, and those on hemodialysis. The adult formulation (without preservative) comes in a concentration of 10 µg/mL. The dose is 1 mL for adults. Each 1-mL dose contains 10 µg of hepatitis B surface antigen.
From: Oyama LC. Disorders of the liver and biliary tract. Anesthesia key: fastest anesthesia & intensive care & emergency medicine insight engine. Available at: https://aneskey.com/disorders-of-the-liver-and-biliary-tract/. Accessed May 10, 2021.

acute bleeds require pharmacologic intervention that decreases portal blood flow, such as octreotide (50-µg IV bolus followed by 25–50 µg/h IV), somatostatin (250-µg IV bolus and 250 µg/h IV infusion), or vasopressin (0.2 to 0.4 unit/min up to a maximum of 0.8 unit/min [off label] continuous IV infusion).[25] Treatment should not be delayed while identification of the source of bleeding is undertaken. If bleeding persists or recurs, treatment options include endoscopic variceal ligation, endoscopic variceal sclerotherapy, transjugular intrahepatic portosystemic shunt (TIPS), or surgical shunt placement.

The American Association for the Study of Liver Disease (AASLD) has recommended that treatment be based on the assessment of disease severity. There are several severity scales. The most widely used is the Maddrey discriminant function (MDF) score based on coagulation and bilirubin levels. The score is calculated by multiplying the increase in PT (seconds) by 4.6 and then adding the serum bilirubin (mg/dL) for a total discriminant factor (DF) score. A DF score of greater than 32 correlates with poor prognosis in alcoholic hepatitis and identifies which patients could benefit from steroid therapy. In the absence of GI bleeding, hepatorenal syndrome, or sepsis, the AASLD recommends the initiation of corticosteroids (oral prednisolone, 40 mg PO daily, or parenteral methylprednisolone, 32 mg IV daily) for those with alcoholic hepatitis and an DDF score more than 32.[25] Pentoxifylline, an inhibitor of cytokines such as anti–tumor necrosis factor alpha, has been shown to provide mild benefit over placebo and may be used in the setting of contraindications to corticosteroids.[30] Compared to corticosteroids, however, pentoxifylline is not associated with improved 28-day survival.

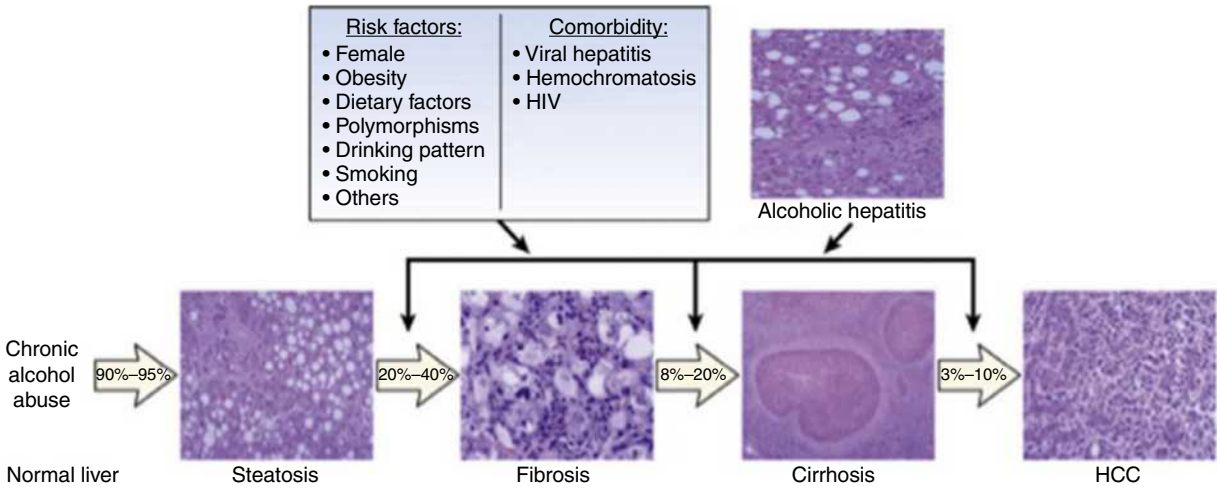

Fig. 76.11 Progression of alcoholic-related liver disease. *HCC,* Hepatocellular carcinoma.

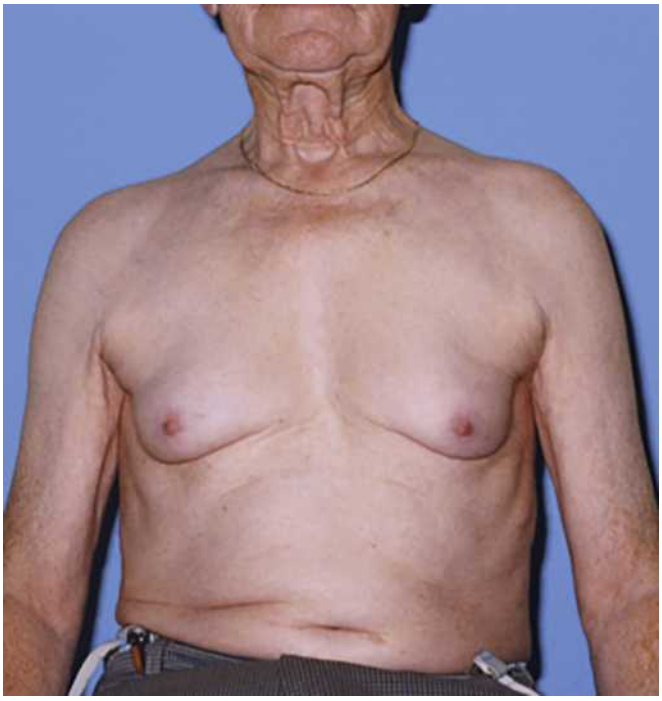

Fig. 76.12 Gynecomastia in a male patient with cirrhosis. (Biophoto Associates / Science Photo Library.)

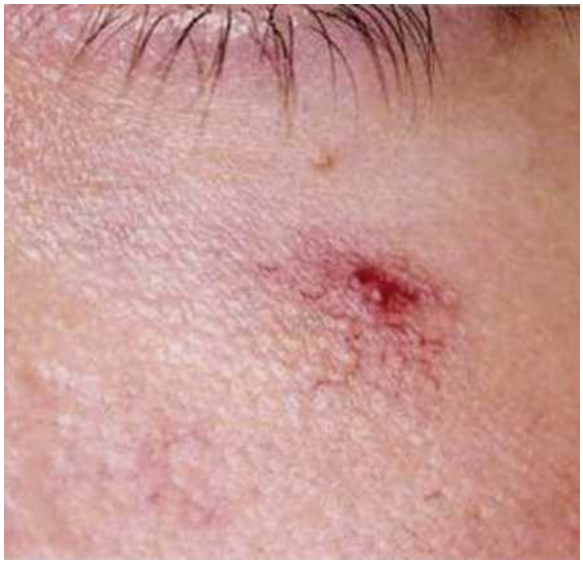

Fig 76.13 Close up view of the central arteriole (punctum) of a spider nevus. (From Benign neoplasms and hyperplasias. In: Wolff K, Johnson R, Saavedra AP, et al., eds. *Fitzpatrick's color atlas and synopsis of clinical dermatology*, 8e. McGraw Hill; 2017. Accessed September 07, 2021. https://accessmedicine.mhmedical.com/content.aspx?bookid=2043&sectionid=154898019. Chapter 9, figure 9-21.)

Disposition

The disposition is determined by the patient's clinical state—degree of fluid and electrolyte abnormality, ability to retain oral intake, and any coexistent illnesses or complications—and socioeconomic circumstances. Hospitalization generally is not required. Patients should be advised to abstain from further alcohol ingestion and, ideally, provided with information regarding detoxification or alcohol dependency treatment.

Autoimmune Hepatitis

Foundations

Autoimmune hepatitis (AIH) results from antibodies targeted to hepatospecific antigens. At onset, AIH can be difficult to differentiate from other forms of acute hepatitis, cirrhosis, or acute liver failure. Inflammation to the liver results from circulating autoantibodies. AIH remains rare, affects all ages—though is predominantly bimodal with peaks in the second, fifth, and sixth decades—and is more common among females. The disease physiologically stems from a complex interaction of genetic, immunologic, and environmental factors within the host.[31] There are two diagnostic types, based on the individual's expression of autoantibodies. There is some degree of overlap with primary sclerosing cholangitis or primary biliary cirrhosis.[32] Overlap with other autoimmune disorders is also observed, including with autoimmune thyroiditis, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease, or lupus. A United Kingdom study noted earlier age at presentation, higher circulating IgG levels, and broader overlap with lupus in patients of African descent.[33]

Diagnosis

AIH is a diagnosis of exclusion. For patients with suspected disease, the workup may include a combination of biomarker serologic testing demonstrating presence of at least one autoimmune or globulin marker, elevated aminotransferase levels, histologic evidence on biopsy, imaging studies such as MRCP to exclude primary sclerosing cholangitis, and the absence of an alternative pathologic etiology of hepatitis such as alcohol, drug-induced, or viral hepatitis (Fig. 76.14).[32]

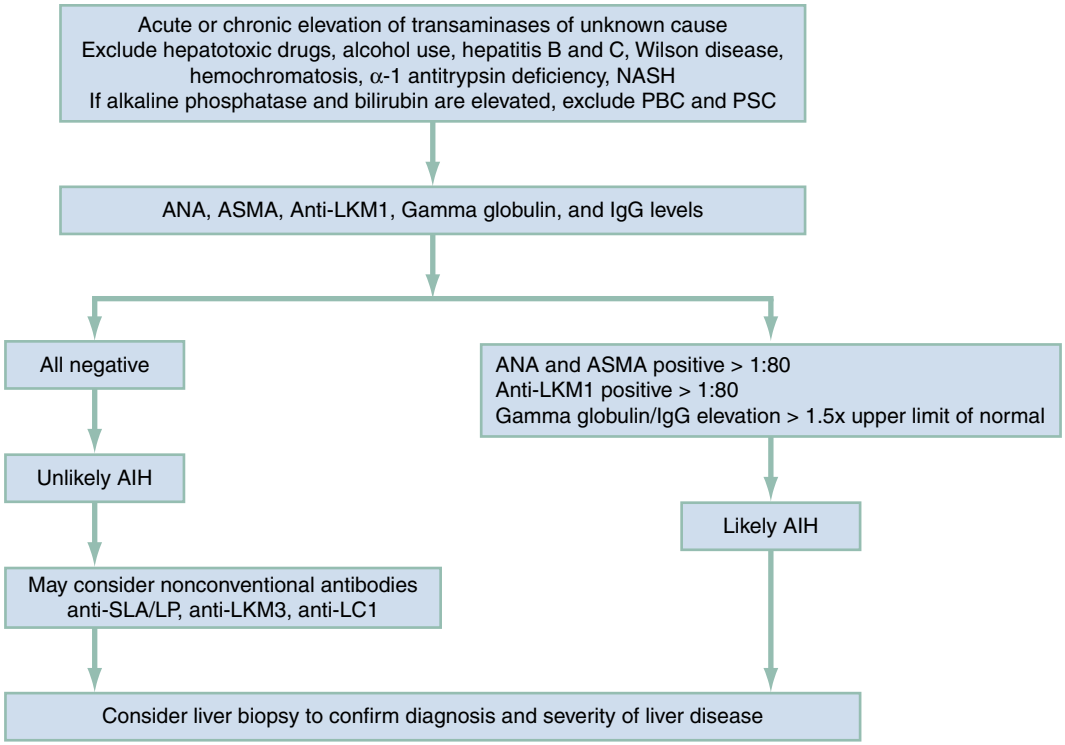

Fig 76.14 Diagnostic algorithm in autoimmune hepatitis. (From Cleveland Clinic Foundation Center for Continuing Education Disease Management Home. Fialho A. Autoimmune Hepatitis. Published July 2015. Accessed online at: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/chronic-autoimmune-hepatitis/)

Differentiation into type I versus type II AIH is based on autoimmune serologic testing. Though management does not differ between the two, prognosis differs with type II AIH being more severe.[34]

Management

Immunosuppression with corticosteroids is the primary treatment modality for AIH. Early randomized trials comparing corticosteroids with placebo demonstrated a poor prognosis for untreated AIH. The aim of treatment is remission, defined as normalization of aminotransferases, serum bilirubin, and IgG levels and absence of clinical symptoms. Azathioprine is occasionally used alongside or in lieu of steroids. Those without treatment demonstrated a 5-year survival of approximately 32%.[34] However, the ten-year survival rate with treatment is approximately 90%, which highlights the need for prompt diagnosis. Second-line therapy includes mycophenolate mofetil as the most widely supported of the alternative agents. Medication alone is often successful in achieving remission. Ultimately, transplantation is considered for life-threatening AIH. Post transplantation, patients are at risk for recurrent disease. Novel immunotherapies targeting the T cell–mediated hepatitis are currently under development.[35]

Disposition

Disposition depends on the presenting severity. Criteria exist for differentiating two different induction pathways. For asymptomatic patients with aminotransferase levels under 10 times the upper limits of normal, low-dose induction therapy with prednisone is standard. Those who are either symptomatic or have marked elevations begin either higher dose prednisone monotherapy or prednisone in combination with azathioprine if other diseases are present that increase an individual's side effect risk profile.[36] Management of patients with AIH should be in conjunction with a hepatologist or specialist with expertise in liver disease.

CIRRHOSIS

Foundations

Cirrhosis is a generic term for end-stage chronic liver disease characterized by the destruction of hepatocytes with resulting deposits of fibrotic tissue and regenerative nodules. Laënnec cirrhosis is a diffuse process that involves the entire lobule, with 10% to 20% of chronic alcoholics developing this disorder. Postnecrotic cirrhosis usually is nonhomogeneous, characterized by regions of fibrosis and hepatocyte loss alternating with normal areas. It most often is a consequence of chronic hepatitis of various causes—infectious (viral, bacterial, fungal), drug-induced, or metabolic. Biliary cirrhosis is much less common and is a consequence of chronic extrahepatic biliary obstruction or is a primary disorder of autoimmune-mediated intrahepatic duct inflammation and scarring. Nonalcoholic fatty liver disease has become an increasingly recognized cause of cryptogenic cirrhosis. This poorly understood disease, with features similar to those of Laënnec cirrhosis, is more common in the setting of obesity or type 2 diabetes mellitus.

Clinical Features

The clinical manifestations of cirrhosis are related to loss of hepatocytes, leading to metabolic and synthetic dysfunction, or to fibrosis and altered hepatic architecture, resulting in impaired portal vein blood flow and portal hypertension. Typically, the patient with cirrhosis complains of chronic fatigue and poor appetite. With the exception of those with biliary cirrhosis, many patients with cirrhosis can be asymptomatic until complications develop, such as GI bleeding, ascites, or hepatic encephalopathy. Patients with biliary cirrhosis generally complain of pruritus or exhibit obvious jaundice before end-stage cirrhosis or complications develop. Primary biliary cirrhosis may be associated with other immune-mediated disorders; these patients may have signs

and symptoms characteristic of scleroderma or the CREST syndrome (***c***alcinosis cutis, ***R***aynaud phenomenon, ***e***sophageal motility disorder, ***s***clerodactyly, and ***t***elangiectasia).

Physical examination may reveal muscle wasting, thinning of the skin with patchy ecchymosis, spider angiomata, palmar erythema, Dupuytren contracture and, in men, gynecomastia or testicular atrophy. Jaundice generally is absent in mild cases or in those with early disease. The liver may not be palpable if it is extensively scarred, but a large regenerative nodule, tumor, or fatty infiltration can result in hepatomegaly. Complications of cirrhosis include ascites, hepatic encephalopathy, and variceal hemorrhage. Ascites is the most common of these, particularly in those with advanced disease, and may be present with abdominal wall vein distention known as caput medusa.

Diagnostic Testing

Laboratory tests are not specific. Aminotransferase levels are rarely more than minimally elevated. The bilirubin level may be increased but usually not until cirrhosis is far advanced. Elevation of the alkaline phosphatase level out of proportion to other liver enzyme levels is suggestive of biliary cirrhosis. Coagulation studies commonly show abnormalities, and the serum albumin level is low as a result of impaired hepatic synthetic function. Mild to moderate anemia and thrombocytopenia often are present in Laënnec cirrhosis. An elevated blood urea nitrogen (BUN) or creatinine level suggests dehydration or hepatorenal syndrome. Ascites can be detected on a carefully performed physical examination or ultrasound. Bedside ultrasound demonstrating a diffuse nodular surface, with or without the presence of ascites, is consistent with cirrhosis (Fig. 76.15).

In patients with ascites and fever or abdominal pain, diagnostic paracentesis should be considered to rule out spontaneous bacterial peritonitis (SBP). Nuclear scintigraphy or computed tomography (CT) imaging may reveal a hepatic or splenic appearance characteristic of cirrhosis and portal hypertension but, in general, these tests should be deferred to an elective setting.

Management

Treatment of cirrhosis in the ED is limited in the absence of acute complications. Oral tolerance should be confirmed, fluid and electrolyte imbalances should be corrected, and nutritional supplements should be provided. Most patients can be discharged with referral to a general internist or gastroenterologist for further evaluation and treatment. The complications of cirrhosis include ascites with or without infection, GI bleeding, hepatorenal syndrome, or encephalopathy. The Model for End-Stage Liver Disease (MELD) score is used to predict 3-month mortality of patients with end-stage liver disease. The MELD score is calculated using serum creatinine, total bilirubin, INR, and sodium. It is mainly used as one of the factors in determining liver transplantation priority and in predicting survival rate after a TIPS procedure.[37]

Ascites

Ascites is the accumulation of fluid within the peritoneal cavity. It is most often caused by cirrhosis but may have other etiologies, such as malignancy. In cirrhosis, ascites occurs as a consequence of portal hypertension, impaired hepatic lymph flow, hypoalbuminemia, and renal salt retention. When severe, it can cause respiratory compromise or significant discomfort. The treatment is therapeutic paracentesis, generally with removal of 2 L of ascitic fluid or more. Paracentesis improves patient comfort, decreases respiratory effort, allows improved oral intake, and decreases the risk for bacterial peritonitis. Removal of large quantities of ascitic fluid can result in body fluid and electrolyte abnormalities, intravascular volume depletion, and hemodynamic instability, commonly known as paracentesis-induced circulatory dysfunction. When removing over 5 L of ascitic fluid via paracentesis, colloid infusion is typically necessary to avoid adverse cardiovascular, renal, and neurohumoral responses. Standard IV dosing of albumin after large-volume paracentesis is 8 g/L removed. The AASLD has established guidelines for the management of ascites secondary to cirrhosis.

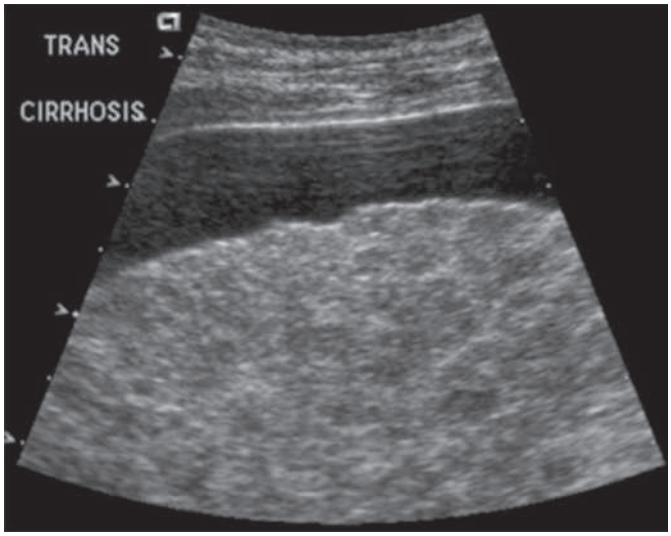

Fig. 76.15 Ultrasound of liver the demonstrating cirrhosis.

A low-sodium diet of less than 2000 mg of sodium, in conjunction with an aldosterone antagonist such as spironolactone 100 mg daily, may be of use in the chronic management of ascites. A low-dose regimen of a thiazide or loop diuretic (furosemide 40 mg PO daily) may accelerate resolution of ascites and is considered safe if the patient has coexistent peripheral edema and normal renal function. Furosemide should be given orally because IV dosing can result in a decline in renal function. The presence of peripheral edema allows the rate of diuretic-mediated fluid removal to be more precipitous than removal in those with ascites solely. To avoid brisk intravascular volume depletion and azotemia, those with ascites without accompanying peripheral edema should not exceed 500 mL of fluid removal/day. Finally, care should be taken to avoid medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II blockers (ARBs), or nonsteroidal antiinflammatory drugs (NSAIDs).

Gastrointestinal Bleeding

In patients with cirrhosis, acute upper GI bleeding carries a mortality of 10% to 15%.[38] GI bleeding is often related to esophageal or gastric varices, but over half of the cases result from another source (e.g., gastritis, duodenal ulcer). Coagulopathy and thrombocytopenia in conjunction with active bleeding should be considerations for platelet transfusion. The goal in this scenario is generally to correct the platelet count to greater than 50,000/mm^3. There is little support for the use of fresh-frozen plasma to correct asymptomatic abnormalities in PT and INR. Cryoprecipitate (1 unit/10 kg body weight) with a targeted fibrinogen level of more than 100 mg/dL may also be considered in active bleeding. Cryoprecipitate improves certain coagulopathies using a lower volume than fresh-frozen plasma. With uncomplicated prolongation of PT or INR in individuals with nutritional or gastrointestinal losses, treatment with oral vitamin K supplementation (10–20 mEq PO given every 6 hours to every 12 hours) may be used.

Mean arterial pressure (MAP) is an independent predictor of mortality in patients with cirrhosis. Lowering pressure may adversely affect survival. ACEIs, ARBs, and beta blockers, such as propranolol, should be used with caution.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as renal dysfunction occurring in the setting of cirrhosis without obvious renal pathology. An elevated creatinine or blood urea nitrogen (BUN) level may herald the onset of hepatorenal syndrome and typically necessitates hospitalization for optimal fluid and electrolyte management. There are two classifications, type I HRS and type II HRS. Type I is the more severe and is associated with serum creatinine levels exceeding 2.5 mg/dL. Despite the use of albumin and vasoactive medications such as norepinephrine to increase the MAP, hepatorenal syndrome carries a high mortality.

HEPATIC ENCEPHALOPATHY

Foundations

Hepatic encephalopathy, also termed portal-systemic encephalopathy, is a clinical state of altered cerebral function resulting from the diseased liver's failure to perform its normal metabolic functions adequately. Ammonia, formed primarily in the GI tract by bacteria, is normally absorbed and converted to urea in the liver. In severe hepatic disease, ammonia accumulates, crosses the blood-brain barrier, and combines sequentially with α-ketoglutarate and glutamate to form glutamine, which is thought to disrupt the gamma-aminobutyric acid (GABA) receptors. Serum ammonia levels correlate inconsistently with the severity of encephalopathy, though there is an association of ammonia levels with cerebrospinal fluid (CSF) glutamine levels. Whether glutamine is itself toxic or simply represents a marker for disordered central nervous system (CNS) metabolism is unknown. Severity can be graded, I to IV, with grade I classified as mild confusion and slurred speech, and grade IV marked by coma and unresponsiveness to painful stimuli.

Clinical Features

The clinical manifestations of hepatic encephalopathy range from mild cognitive dysfunction, irritability, and confusion to profound coma. Asterixis, a low-amplitude, alternating flexion and extension of the wrist that occurs when the wrist is held in extension, is characteristic of the neuromuscular dysfunction seen in mild to moderate degrees of encephalopathy. A similar finding may be elicited in the dorsiflexed foot or with extension of the neck. Fetor hepaticus, a musty breath odor presumably from mercaptans (products of methionine metabolism by gut bacteria and cleared by the liver), may be detected in severe cases. Physical examination commonly reveals signs of cirrhosis—spider angiomata, testicular atrophy, muscle wasting, superficial bruising, gynecomastia, or ascites.

Differential Diagnosis

The differential considerations in patients with suspected hepatic encephalopathy include all causes of altered sensorium. The scope of the differential diagnosis can be narrowed if the patient's history includes previous episodes of hepatic encephalopathy or if the patient has severe underlying liver disease and its supportive physical signs. In patients without a previous history of encephalopathy, a more in-depth evaluation for altered mental status, including testing of electrolyte levels, evaluation for toxins, and possibly neuroimaging should be considered.

Diagnostic Testing

Liver function tests, including albumin and coagulation studies, are recommended, although the results may be normal. Serum ammonia levels generally are elevated but do not necessarily correlate with the severity of encephalopathy. Results of tests reflective of hepatic synthetic function (i.e., serum albumin, PT, INR level) are generally abnormal. Evaluation for underlying treatable causes (Box 76.1) is imperative. Serum chemistry tests to evaluate electrolyte and metabolic derangements may reveal precipitating factors.

BOX 76.1 Common Underlying Causes of Hepatic Encephalopathy in Patients With Known Liver Disease

- Gastrointestinal bleeding
- Electrolyte abnormalities including hypokalemia and alkalosis
- Venous thrombosis
- Ileus and constipation
- Sedative medications
- Dehydration and hypovolemia
- Acute or chronic kidney injury
- Infection

The presence of hypoalbuminemia must be considered in patients who require medications with high protein-binding profiles. Decreased protein binding in the setting of hypoalbuminemia enhances the potential for drug toxicity. Drugs circulating in the extracellular compartment carry the largest risk. Some commonly prescribed drugs with high protein-binding profiles include phenytoin, morphine, and antimicrobial medications, including β-lactams, vancomycin, dalvance, and daptomycin. Additional dosing consideration should be given to agents that normally undergo hepatic metabolism with large first-pass extraction. With decreased hepatic flow and shunting, these agents are more apt to increase their bioavailability and serum concentrations. Finally, glutathione reduction and decreased renal elimination, which are commonly present in cirrhosis, may predispose individuals to further medication toxicity and liver injury, necessitating dosing adjustments by the treating emergency clinician.

Management

Aggressive management of the patient with hepatic encephalopathy may reverse the condition. As with any comatose patient, the airway is assessed first, not only to determine the need for respiratory support but also to prevent aspiration. Affected patients generally are hemodynamically stable but have an increased incidence of GI bleeding. Hypokalemia, alkalosis, and GI bleeding contribute to increased ammonia production or absorption, and the cause must be addressed when detected. Relatively mild degrees of hyponatremia, hypoglycemia, azotemia, or dehydration often will have a disproportionate effect on cerebral function and thus will require correction. CNS depressants or mild sedatives should be avoided to the extent feasible.

After identifying the precipitating cause, treatment aims to lower the blood ammonia concentration. The current approach in hepatic encephalopathy is treatment with nonabsorbable disaccharides (e.g., lactitol, lactulose). Lactulose decreases the absorption of ammonia through its osmotic cathartic effects and by altering the colonic pH to trap ammonia as ammonium in the stool. The usual dose of lactulose is 30 to 60 g (oral) or 200 g (rectal) daily or in a quantity sufficient to result in several loose bowel movements daily. The principal adverse effect is excessive diarrhea, with resultant fluid and electrolyte imbalances. A recent noninferiority trial compared lactulose alone to lactulose in combination with polyethylene glycol and found 24-hour improvement in severity scoring of hepatic encephalopathy in the combination group compared to lactulose alone. The dosing of PEG recommended for adults is 280 g (oral) daily.[39]

Oral antibiotics including rifaximin, neomycin, vancomycin, or metronidazole may be utilized in combination with lactulose.

The antibiotics aim to reduce ammonia-producing enteric bacteria in patients with hepatic encephalopathy. Rifaximin is a minimally absorbed, oral antimicrobial agent that concentrates in the GI tract. It offers minimal systemic bioavailability and fewer detrimental side effects than neomycin. It is therefore the preferred antimicrobial to utilize in patients with hepatic encephalopathy. Neomycin, which is reserved for those unable to tolerate or with contraindications to rifaximin, is administered orally (PO) at an initial dose of 250 mg every 6 hours to every 12 hours (maximum, 4000 mg/day). Neomycin carries additional risks for ototoxicity or nephrotoxicity. In obtunded patients, lactulose and neomycin can be administered by nasogastric tube or rectal enema. Multiple trials have assessed the use of infused branched chain amino acids in the treatment of hepatic encephalopathy. Because these showed benefit without increased mortality or negative impacts on nutrition or quality of life, their use should be strongly considered in patients with hepatic encephalopathy.[40]

Less commonly used in the US, L-ornithine–L-aspartate (LOLA) has demonstrated benefit in lowering postprandial serum ammonia levels alone and following TIPS procedures (known to increase or exacerbate hepatic encephalopathy). Complementary therapies include probiotics such as *Lactobacillus acidophilus* (to increase non–urease-producing bacteria), eradication of *Helicobacter pylori* (urease-producing), and zinc replacement (metabolism of ammonia is dependent on zinc that is deficient in liver disease).

Cirrhosis is commonly a comorbid condition associated with overall poor nutrition. Protein restrictions are associated with increased mortality and therefore protein should not be restricted in patients with active hepatic encephalopathy. Patients should be instructed to eat small frequent meals that include complex carbohydrates. Fasting results in the production of glucose from amino acids, with resultant ammonia production, obviously deleterious to patients with hepatic encephalopathy.

Disposition

Although many patients with hepatic encephalopathy will require hospitalization, those with grade I or II encephalopathy without complicating factors and a supportive home environment are candidates for outpatient management. In addition to a prescription for lactulose and rifaximin, nutritional guidance to ensure adequate caloric intake and a maximum of 1.5 g/kg/day of protein is essential.

SPONTANEOUS BACTERIAL PERITONITIS

Foundations

Spontaneous bacterial peritonitis is an acute bacterial infection of ascitic fluid in patients with liver disease, without an apparent external or intra-abdominal focus of infection. It can occur in any patient with ascites. Diagnosis is correlated with presence of elevated polymorphonuclear (PMN) leukocytes within the peritoneal fluid aspirate (>250 cells/mm^3) and established with positive identification of organisms upon peritoneal fluid culture. The pathophysiology of SBP is related to a combination of impaired phagocytic function in the liver and to portal systemic hypertension, which can cause bowel mucosal edema, alterations in gut flora, and transmural migration of enteric organisms. Bacterial seeding may also occur from other sites in the abdomen, such as the bladder, as well as the lungs or bloodstream. Gram-negative enteric organisms, primarily *Escherichia coli* or *Klebsiella,* predominate in SBP. Modern treatments of cirrhosis, including variceal ligation, TIPS placement, and long-term antibiotic prophylaxis, have changed the type and cause of acute bacterial infections in cirrhosis. With improved cirrhosis care, the cause in outpatients with cirrhotic neutrocytic ascites has been found to be predominantly gram-positive organisms. Polymicrobial and anaerobic infections are uncommon.

BOX 76.2 Runyon Criteria for Spontaneous Bacterial Peritonitis[a]

Total protein > 1g/dL
Glucose < 50 mg/dL
LDH > the upper limit of normal for serum

[a]Requires 2 or more be present in the peritoneal fluid analysis.
From: Akriviadis E, Runyon B. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. *Gastroenterol.* 1990;98(1):127-133.

Clinical Features

The clinical presentation of SBP is variable and may include acute onset of severe abdominal pain, insidious onset of abdominal discomfort, or encephalopathy. Objective or subjective fever may be present. Hemodynamic instability may be slow to develop. On physical examination, palpation of the abdomen may range from mild tenderness to abdominal rigidity and guarding with rebound tenderness. Although, by definition, ascites is essential for SBP to develop, free peritoneal fluid may not always be clinically apparent. One study has identified a positive peritoneal fluid culture rate of 3.5% among patients who were judged to have asymptomatic ascites. This observation underscores the exceptionally broad spectrum of manifestations and variability in physical findings, thus the diagnosis of SBP should be considered in any patient with severe liver disease who has abdominal pain or exhibits unexplained clinical deterioration.

Differential Diagnoses

The differential diagnosis for SBP is broad, and includes other causes of peritonitis or abdominal pain in patients with or without liver disease.

Diagnostic Testing

Diagnosis is made by culture of the ascitic fluid, with anticipatory treatment decisions in advance of culture results. An ascitic fluid granulocyte count greater than 500 cells/mm^3 correlates with positive cultures in more than 90% of cases; however, ED treatment for SBP should be initiated if the PMN count is greater than 250 cells/mm^3. Cultures of ascitic fluid guide the antibiotic choice. Also, fluid chemistry testing may aid in the diagnosis when the fluid neutrophil count is nondiagnostic or peritonitis secondary to another abdominal source (e.g., urinary tract infection, appendicitis) is suspected. Because cultures may be delayed, many advocate use of preliminary analysis of the peritoneal fluid to employ the Runyon criteria to assesses for SBP (Box 76.2). Determining peritoneal fluid total protein, lactate dehydrogenase (LDH), glucose, and alkaline phosphatase levels, as well as fluid Gram stain, assist in distinguishing SBP from other causes of peritonitis. An early indicator of SBP is a serum-ascites albumin fluid gradient (albumin in ascites subtracted from serum albumin level) greater than 1.1 g/dL. Serum laboratory parameters (e.g., aminotransferase and bilirubin levels, peripheral blood count) are not infrequently abnormal, although these findings are nonspecific and may be a consequence of underlying liver disease rather than SBP.

Testing of ascitic fluid prior to administering antibiotics is ideal, provided clinical stability and ability to rapidly obtain fluid. A single dose of antibiotic will produce negative cultures at 6 hours in 86% of patients with SBP.[41]

Management

Empiric antibiotics should be initiated in patients presenting with ascites and one or more of the following: temperature greater than 100°F, abdominal pain, abdominal tenderness, altered mental status, or peritoneal fluid containing greater than 250 cell/mm^3. Fever is the most

sensitive of these signs and symptoms.[37] The treatment of SBP requires IV antibiotics. The choice of agents is driven by the anticipated bacteriology. A third-generation cephalosporin, such as IV cefotaxime 2 g every 8 hours, is the agent of choice and is generally superior to two-drug regimens. In patients with contraindications to cephalosporins who are capable of oral therapy and who have not been on oral prophylaxis with cephalosporins, an alternative treatment is oral ofloxacin 400 mg PO every 12 hours. Unless an atypical response, risk profile, or resistant organism is identified, patients with SBP should be treated for a total of 5 days. Therapy may need to be tailored as guided by local antibiotic resistance patterns. Prevalence of multidrug resistance has been increasing among patients with decompensated cirrhosis.[42]

Peritonitis is a frequent complication in patients undergoing peritoneal dialysis (PD), and is associated with a high degree of morbidity and mortality. Similar to peritonitis in cirrhosis, peritonitis in patients undergoing peritoneal dialysis may be spontaneous or secondary to underlying urinary tract, GI, or lung disorders. The most common symptoms include abdominal pain and cloudy peritoneal effluent. The diagnosis is presumed with a dialysate WBC count of more than 100 cells/mm^3 with greater than 50% neutrophils, and is confirmed by culture. In patients with symptoms suggesting peritonitis, dialysate is collected for analysis and culture and treatment initiated. Consideration of catheter removal is also warranted. The most commonly isolated organisms are coagulase-negative staphylococcal species, with *S. aureus* and *S. epidermidis* accounting for over 50% of infections. Intraperitoneal antimicrobial administration is generally preferred over an IV regimen.[43] Current recommendations include empiric coverage with a third-generation cephalosporin (ceftazidime or cefepime) or an aminoglycoside (gentamycin, tobramycin or amikacin) along with vancomycin, covering gram-negative and gram-positive organisms, respectively.[44] Prophylaxis at the catheter exit site with topical application of mupirocin or aminoglycosides is associated with a reduced risk for infection.[45] PD patients or their caretakers will typically be facile in management of the PD catheter, including methods necessary for intraperitoneal antibiotic administration, once prescribed. Management decisions should occur in concert with input from the patient's nephrologist.

Disposition

Any patient with ascites is at risk for the development of SBP. This risk is markedly increased in patients with ascitic fluid protein levels less than 1 g/dL. Other important risk factors include serum bilirubin level greater than 3.2 mg/dL, platelet count less than 98,000/mm^3, or a previous history of SBP. Management with diuretics will help decrease the risk of developing SBP. Proton pump inhibitors (PPIs) may adversely alter acid secretion and gut flora thereby increasing SBP risk. However, some controversy remains regarding the use of PPIs; some studies have found an increased risk of SBP in patients using PPIs, though a recent prospective study demonstrated no increased SBP incidence.[46] We do not recommend the use of PPIs at this time. Beta blockers may increase risk secondary to resultant systemic hypotension.

Antibiotic prophylaxis for high-risk patients can reduce SBP incidence by 60% to 80% and can be cost-effective. Daily prophylaxis may consist of norfloxacin 400 mg PO daily, ciprofloxacin 500 mg PO daily or trimethoprim-sulfamethoxazole (TMP-SMX) 800/160 mg PO daily, however, these recommendations are not graded.

In patients with cirrhosis who are admitted for GI bleeding, prophylactic ceftriaxone (1 g IV daily) is recommended until the patient is taking food orally, at which time a switch to oral TMP-SMX is advised.

Long-term outpatient prophylaxis with either norfloxacin, ciprofloxacin, or TMP-SMX is recommended for patients who have cirrhosis, gastrointestinal bleeding, prior SBP or those with high-risk features including ascitic fluid protein less than 1.5 g/dL, serum BUN level greater than 25 mg/dL, serum creatinine greater than 1.2 mg/dL or serum sodium level less than 130 mmol/L.

Patients with diagnosed SBP typically require hospitalization. Many patients with SBP will not require repeat abdominal paracentesis. In those with inconsistent symptoms, abnormal treatment response, atypical organisms, or recent β-lactam exposure, repeat paracentesis may help differentiate secondary bacterial peritonitis potentially requiring surgical intervention.

HEPATIC ABSCESSES

Hepatic abscesses fall into two broad categories, pyogenic and amebic. Although there may be similarities in clinical presentation, the pathophysiology and treatment differ significantly. The multiple etiologies of hepatic abscess are summarized in Fig. 76.16.

Pyogenic Abscess

Foundations

Liver abscesses may be associated with biliary tract obstruction or cholangitis but can also be related to conditions that cause peritonitis and subsequent extension via the portal circulation, including: diverticulitis, pancreatic abscess, omphalitis, appendicitis, inflammatory bowel disease, or pneumonia. Pyogenic liver abscess as a consequence of liver trauma is possible, although rates have declined with the inception of nonoperative protocols for traumatic hepatic injuries.[47] Often no underlying cause for hepatic abscess is identified. Solitary and multiple abscesses occur with approximately equal frequency, usually in the right lobe of the liver. Patients with multiple lesions tend to be more severely ill, with less favorable outcomes. Causative organisms may be anaerobic and aerobic; *E. coli, Klebsiella, Pseudomonas,* and *Enterococcus* spp., anaerobic streptococci, or various *Bacteroides* spp. may be isolated.

Clinical Features

The clinical presentation is characterized by the onset of often high fever, chills, right upper quadrant (RUQ) pain, nausea, or vomiting. Patients generally have an acute presentation and appear generally ill, particularly if there is underlying cholangitis. Physical findings include elevated temperature, RUQ tenderness, hepatomegaly, and occasionally dullness to percussion or diminished breath sounds over the right lower chest. Jaundice may be apparent, especially if coexistent biliary tract obstruction is present.

Differential Diagnosis

The differential diagnosis of pyogenic hepatic abscess includes amebic liver abscess, hepatitis, cholangitis, and pancreatic or subphrenic abscesses, among others.

Diagnostic Testing

Laboratory findings include leukocytosis in 70% to 80% of cases, elevated alkaline phosphatase levels in up to 90%, and bilirubin level in excess of 2 mg/dL in 50% of patients. Although blood culture sensitivities are overall poor in patients with pyogenic abscesses, they should be obtained in advance of antimicrobial treatment if feasible and while awaiting definitive drainage from the abscess site. Serum aminotransferase levels commonly are elevated 2 to 4 times normal. Chest radiographs may reveal a right pleural effusion, basilar atelectasis, or an elevated right hemidiaphragm. The most useful, sensitive, and expeditious imaging modalities include ultrasonography and CT (Figs 76.17 and 76.18), with CT demonstrating higher sensitivity.

Management

The initial treatment of a pyogenic hepatic abscess is hemodynamic stabilization, IV antibiotics, and pain control. Pending definitive microbial identification, broad-spectrum antibiotic coverage should

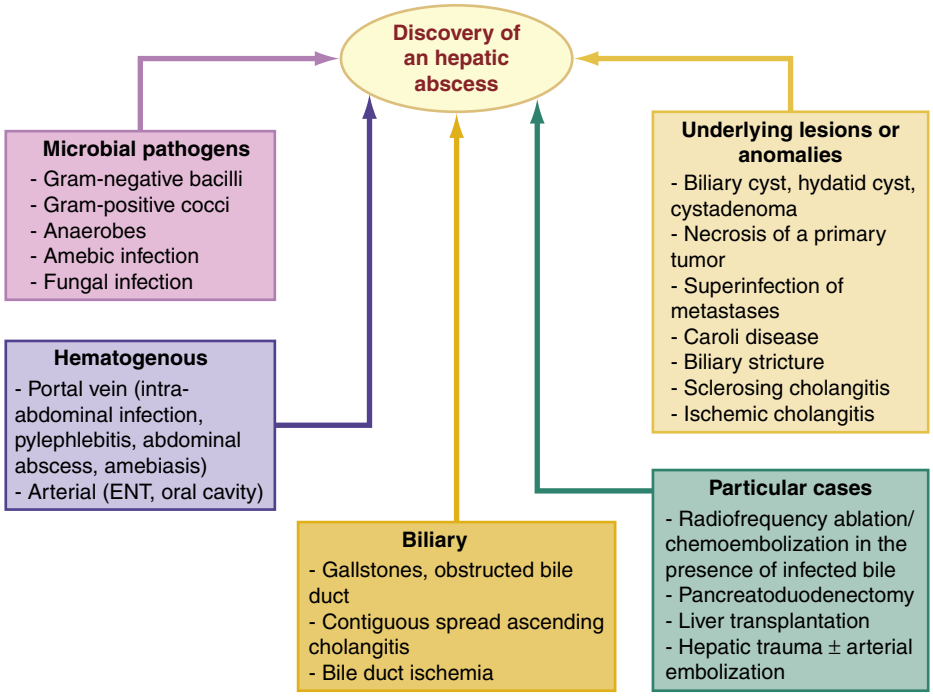

Fig. 76.16 Etiology of hepatic abscess. (From Lardiere-Deguelte S. Hepatic abscess: diagnosis and management. *J Visc Surg*. 2015;155(4):231-243.)

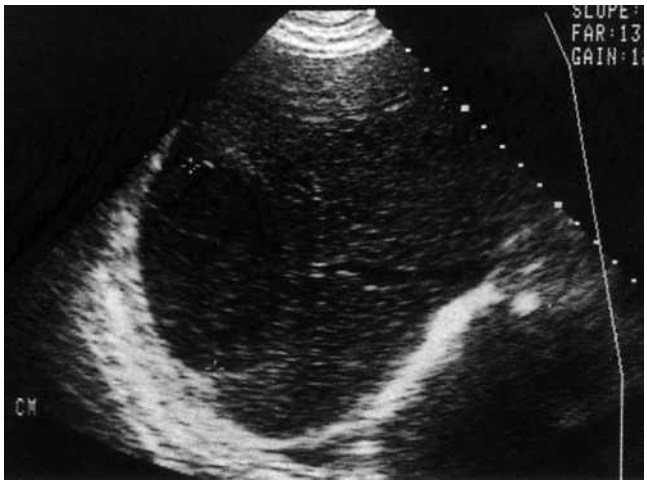

Fig 76.17 Typical ultrasound image of an amebic hepatic abscess. Note the peripheral location, rounded shape, with poor rim, and internal echoes. (From Thomas PG, Ravindra KV. Amebiasis and biliary infection. In: Blumgart LH, Fong Y, eds. *Surgery of the liver and biliary tract.* London: WB Saunders; 2000:1147-1166.)

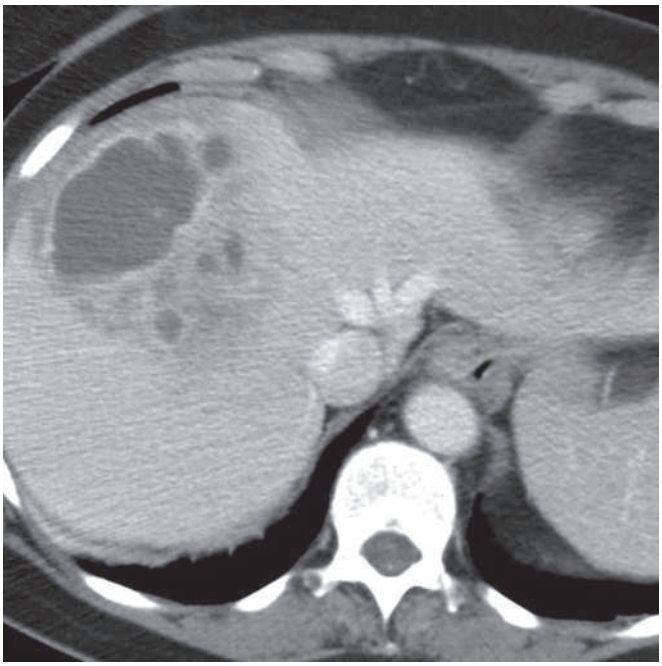

Fig. 76.18 Contrast-enhanced CT through the liver reveals the "cluster" appearance of a pyogenic hepatic abscess with several smaller peripheral abscesses that have coalesced. (From Vickers SM, Black SM, Prabhakaran S. Liver abscess. In: Yeo CJ, ed. *Shackelford's surgery of the alimentary tract*, 7th ed. Elsevier; 2013. Fig. 118-3.)

be promptly initiated, even in advance of a drainage procedure, and continued for up to 6 weeks, depending on the size of the abscess and patient response. Abscesses less than 5 cm are often treated with antibiotics alone, without drainage.[47] Although there has been no consensus on treatment regimens, IV antibiotic coverage targeting gram-negative bacilli, gram-positive cocci, and anaerobes is recommended. This may include cefotaxime 2 g IV every 8 hours; or ceftriaxone 2 g IV daily plus metronidazole 500 mg IV every 8 hours; or ampicillin 2 g IV every 6 hours in conjunction with gentamycin 1.7 mg/kg IV every 8 hours and metronidazole 500 mg IV or PO every 8 hours; or piperacillin-tazobactam 3.375 IV every 6 hours, imipenem 500 mg every 6 hours, or meropenem 1 gm every 8 hours in combination with metronidazole 500 mg IV or PO every 8 hours. The addition of vancomycin is indicated for an acutely ill or unstable patient, as well as any patient with gram-positive cocci on staining or when suspicion for enterococcal or staphylococcal organisms is high.

Definitive treatment for abscesses larger than 5 cm requires drainage. This usually is done percutaneously under imaging guidance, reserving open surgical drainage primarily for complex cases associated with intraperitoneal soiling, intestinal perforation, or biliary obstruction. Complications include rupture of the abscess into the peritoneal cavity or an adjacent anatomic structure (e.g., thoracic cavity, lung, pericardium). Aspirates containing bile should prompt further investigation of the biliary tract for sources of obstruction.[47]

Disposition

Patients with pyogenic hepatic abscess typically require hospitalization. Input from a general surgeon, gastroenterologist, or interventional radiologist may be helpful in determining optimal management.

Amebic Abscess

Foundations

Amebiasis related to the protozoan *Entamoeba histolytica* is one of the most common protozoal infections worldwide. Transmission generally occurs by the fecal-oral route, often as a consequence of ingesting contaminated water or food. Although intestinal disease is by far the most common manifestation of infection, extraintestinal disease can occur, with the liver most commonly affected. *Entamoeba histolytica* is the only ameba responsible for invasive disease, and only certain varieties of *E. histolytica* are pathogenic after invasion of the intestinal mucosa and transit through the portal venous circulation. As with a pyogenic abscess, involvement of the right hepatic lobe is more common.

Clinical Features

The clinical presentation generally is acute with fever, chills, nausea, vomiting, and abdominal pain. Median onset of symptoms is 12 weeks post exposure, although longer periods have been observed between exposure and occurrence.[48] Diarrhea is common in children though is present in less than one-third of adults. Careful questioning of patients without diarrhea often yields a history of intestinal illness several weeks prior to presentation. Many patients complain of cough, which may direct attention away from the liver. A chronic illness of several months' duration, although less common than the acute presentation, can occur. Physical findings include an elevated temperature, RUQ tenderness, hepatomegaly, and dullness, with decreased breath sounds over the right lower chest.

Differential Diagnoses

The differential diagnosis includes pyogenic abscess, biliary tract disease, hepatitis, pneumonia, appendicitis, or pancreatitis. Respiratory symptoms or abnormalities on the chest radiograph may cause confusion with pulmonary illnesses. Hepatic imaging is helpful in establishing the diagnosis; however, differentiation from pyogenic illness is difficult and requires additional laboratory testing. Amebiasis should remain high on the differential diagnosis in patients with supporting signs and symptoms and epidemiologically relevant history including travel to or residency in endemic areas including India, Africa, Mexico, Central or South America.

Diagnostic Testing

Laboratory findings are nonspecific. Neutrophilic leukocytosis is common. The alkaline phosphatase level is elevated in 75% of cases and aminotransferase levels in 50%. Hyperbilirubinemia is uncommon and, when present, is typically indicative of biliary obstruction. The chest radiograph may reveal a right pleural effusion, basilar atelectasis, or elevated right hemidiaphragm. Ultrasound examination of the liver may reveal specific findings unique to amebic abscess, specifically a peripherally based round or oval mass, with a well-circumscribed border and homogeneous hypoechoic center (Fig. 76.19). CT or magnetic resonance imaging (MRI) are alternative abdominal imaging modalities if ultrasonography is inconclusive. The diagnosis is supported by identification of a pathogenic protozoan in the stool, though even in cases of invasive intestinal disease, the yield may be low. Serologic antigen detection using enzyme-linked immunosorbent assay (ELISA) and counter-immune electrophoresis are the recommended diagnostic tests. The indirect hemagglutination test remains positive for an extended period and is therefore not helpful in establishing the presence of acute infection. At the time of presentation, nearly all patients with hepatic abscess will have antibodies present on serologic testing.

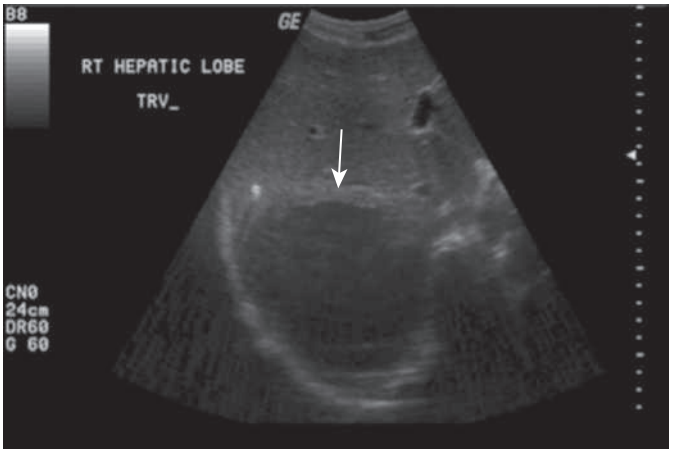

Fig. 76.19 Ultrasound of the liver demonstrating amebic abscess with a peripherally located abscess with a homogeneous, hypoechoic center (*arrow*).

Management

Management of an amebic abscess consists of supportive therapy and initiation of amebicidal therapy. Both tissue and luminal agents are required. Metronidazole, 500–750 mg PO every 8 hours for 7 to 10 days is the therapeutic tissue agent of choice. Following tissue therapy, clearance of luminal cysts is achieved with paromomycin 10 mg/kg PO every 8 hours for 7 days. Most patients will respond to this regimen with percutaneous catheter abscess drainage required only in refractory or complicated cases. The most serious complication of amebic liver disease is rupture into adjacent anatomic structures. Involvement of the lung occurs in 20% to 35% of cases of extrahepatic disease, often manifesting as a massive pleural effusion or consolidative pneumonia. With rupture into a bronchus, the patient can have cough productive of an anchovy paste–like substance, necrotic debris, or frank hemoptysis. Abdominal pain with peritonitis can result from rupture into the abdominal cavity. Involvement of the pericardium occasionally is seen with lesions in the left lobe of the liver and can be catastrophic, either acutely as a consequence of pericardial tamponade or chronically from constrictive pericarditis.

Disposition

Select patients with amebic liver abscess can be managed as outpatients. This approach is best suited for those with mild clinical disease, stable living circumstances, and adequate access to medications and follow-up care. In patients with more severe disease, evidence of complications, or questionable social circumstances, hospitalization is advised.

MISCELLANEOUS DISORDERS AND CONDITIONS OF THE LIVER

Liver Disease of Pregnancy

The incidence of liver disease in pregnancy (LDoP) is less than 1%, and can contribute to a range of maternal and perinatal morbidities, including maternal or fetal death.[49] The two primary hepatic disorders associated with pregnancy are benign cholestasis and acute fatty liver. Of note, LDoP often accompanies preeclampsia in the setting of the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and as such should prompt further assessment of blood pressure, mental status, and urine or serum studies when LDoP is detected during pregnancy or the postpartum period.

Benign Cholestasis

Benign cholestasis during pregnancy is common and has a familial linkage. Onset is in the late second or third trimester and is heralded by the development of progressive pruritus. Resolution is with delivery. Circulating estrogens are thought to be causative, because onset mirrors estrogen peaks and pregnancies with multiple gestations have a higher incidence. The bilirubin level may be elevated though not dramatically, thus jaundice is uncommon. Laboratory tests reveal elevated alkaline phosphatase, serum aminotransferases, and total and direct bilirubin levels. Although the primary concern to the mother is discomfort from pruritus, bile acids cross the placenta into the amniotic fluid and can adversely impact the fetus, with an associated increased incidence in prematurity, stillbirth, or fetal distress. In Patients with cholestasis of pregnancy, treatment with ursodeoxycholic acid (UDCA) 300 mg PO every 8 hours until delivery is recommended.[50]

Acute Fatty Liver

Acute fatty liver of pregnancy can progress rapidly to maternal or fetal demise. It is treated as an obstetric emergency and requires prompt identification. The illness occurs in the latter part of the third trimester (usually after 30 weeks) and is more common in primigravidas and twin gestations.[46] Differentiation of acute fatty liver disease of pregnancy from HELLP can be difficult. Additional organ involvement, including pulmonary or renal, is more suggestive of acute fatty liver disorder. Early clinical features include fatigue, anorexia, nausea, or vomiting. Physical findings include mild jaundice and abdominal tenderness, most prominently in the midepigastrium and right upper quadrant. Physical examination may not allow thorough palpation of the liver secondary to the enlarged, gravid uterus.

Abnormal laboratory findings include moderate elevation of aminotransferase levels (5 to 10 times normal), hyperbilirubinemia, hypoglycemia, or evidence of disseminated intravascular coagulation—prolonged PT and partial thromboplastin time, hypofibrinogenemia, elevated fibrin split products, and thrombocytopenia. Swansea criteria have high sensitivity and may aid in diagnosing acute fatty liver disease of pregnancy (Box 76.3). Positive screening requires presence of at least 6 of the 15 criteria.[51] Early detection remains critical to prevention of mortality. Treatment involves prompt delivery of the fetus and supportive maternal care. A combination of interventions including aggressive fluid and electrolyte support, glucose administration, management of coagulopathy, ventilatory support for ARDS, or dialysis necessitate monitoring in a critical care setting. N-acetylcysteine (NAC) has been utilized clinically though is not uniformly recommended because evidence is lacking.[51] Liver disease in pregnancy generally resolves without permanent sequelae after delivery.

Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) is caused by hepatic venous outflow obstruction located anywhere above the level of hepatic venules. There are two types based on etiologic entities. Primary BCS is caused by thrombosis (Fig 76.20) or phlebitis, whereas secondary BCS is due to external compression of the venous outflow tract (hepatic vein or IVC). The primary disorder is typically associated with hypercoagulable states, such as factor V Leiden, protein S or C deficiency, thrombophilia, antithrombin III deficiency, myeloproliferative disorder, Behçet disease, paroxysmal nocturnal hemoglobinuria, or oral contraceptive use.

Symptoms usually develop over weeks to months. Presentation ranges from fulminant hepatic failure in acute high-grade obstruction to the insidious onset of jaundice or ascites in more subacute forms. Clinical symptoms correlate with the degree of venous obstruction and rate of venous occlusion. Fulminant disease is clinically indistinguishable from acute hepatic necrosis secondary to viral infection or other hepatocellular disease. Because treatment options differ significantly, it is important to make the distinction between these two classes of hepatic failure. Prompt intervention in patients with BCS offers the possibility of effective relief with a potentially favorable outcome. Doppler ultrasound imaging of the hepatic vein has a sensitivity of 85% to

BOX 76.3 Swansea Criteria for the Diagnosis of Acute Fatty Liver Disorder of Pregnancy

Abdominal pain
Ascites
Vomiting
Polydipsia or polyuria
Encephalopathy
Bilirubin > 0.8 mg/dL
Hypoglycemia < 72 mg/dL
Elevated urea > 950 mg/dL
Leukocytosis > 11 × 10^9/L
ALT > 42 U/L
Ammonia > 66 μmol
Cr > 1.7 mg/dL
Coagulopathy or PT > 14s
Bright liver on ultrasonography
Microvesicular steatosis on liver biopsy

Adapted from: Liu J, Ghaziani T, Wolf J. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis and management. *Am J Gastroenterol.* 2017;112(6):838.

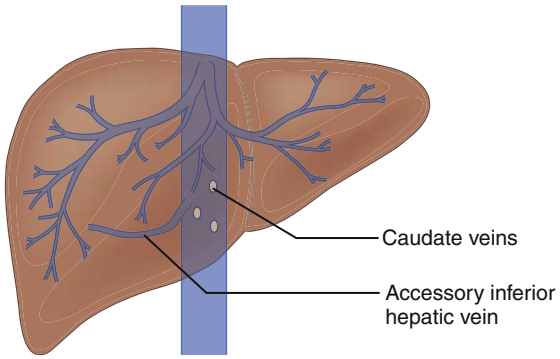

Fig. 76.20 Diagram of hepatic venous drainage depicts the small veins that drain from the caudate lobe and adjacent part of the right lobe directly into the inferior vena cava. The veins tend to be spared in hepatic venous occlusion in patients with Budd-Chiari syndrome, giving rise to hypertrophy of the caudate lobe and adjacent part of the right lobe. (Redrawn from: Khan AN, Chandramohan M, Amin Z. Budd-Chiari syndrome imaging. *Medscape.* 2020. https://emedicine.medscape.com/article/364420-overview)

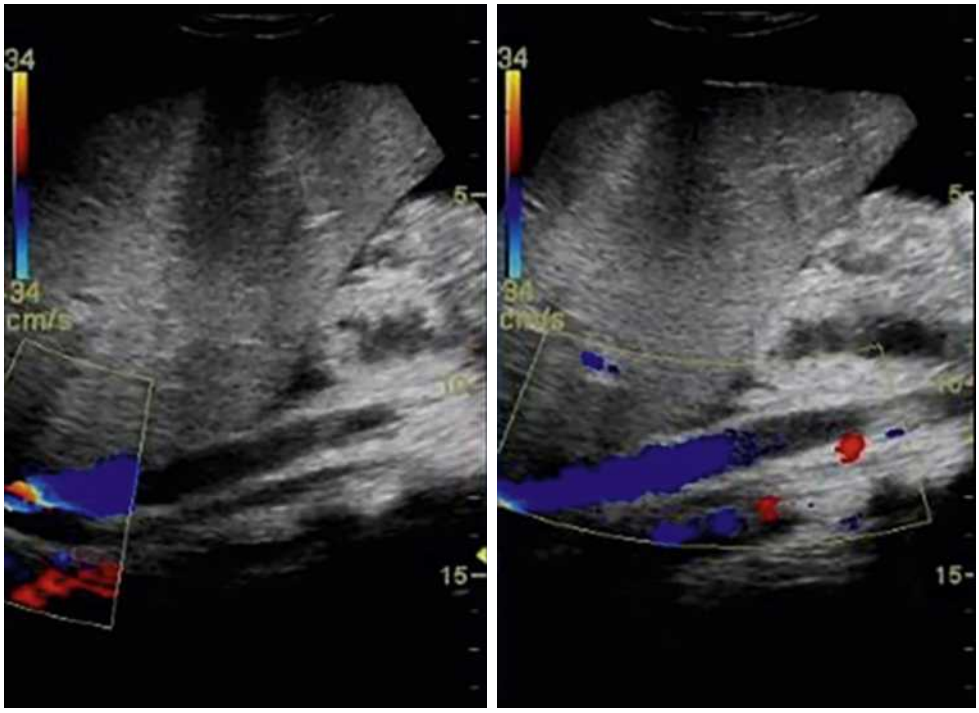

Fig. 76.21 Doppler ultrasound demonstrating patient IVC but no flow in the hepatic veins. (From: Khan AN, Chandramohan M, Amin Z. Budd-Chiari syndrome imaging. Medscape. 2020.)

95% for the diagnosis of BCS and emerges as the diagnostic modality of choice in the ED setting (Fig. 76.21). Venography with access through internal jugular, cephalic, or femoral veins is the most sensitive diagnostic modality. It is typically reserved for cases that remain highly suspicious despite nondiagnostic sonographic studies. Additionally, ascitic fluid analysis may help distinguish among etiologies of ascites, because the high portal pressure seen in BCS is associated with elevated serum-to-ascites protein gradients of greater than 1.1 g/dL.

The management of BCS relates to the severity and acuity of disease. Management focuses on relieving underlying disorders such as hypercoagulopathy as well as managing complications of portal hypertension. Newly diagnosed BCS with acute decompensation necessitates consideration of TIPS placement, percutaneous angioplasty, or thrombolytic therapy. Previously diagnosed disease with worsening ascites can be managed with modification of diuretics and therapeutic paracentesis, followed by referral to a primary care physician or gastroenterologist. In cases of primary BCS, anticoagulation is used to prevent clot propagation. Thrombolysis and stenting may be employed to restore flow. Portacaval surgical shunting or liver transplantation are options for disease refractory to medical or percutaneous interventions.

Liver Transplantation

Human orthotopic liver transplantation is an effective treatment option for patients with acute failure, end-stage disease or malignancy. Transplantation offers a 5-year survival rate of approximately 80%, though transplantation-related complications are common. Considerations for recipient selection include underlying disease, surgical risk, potential for recurrence, and risks of long-term immunosuppression. Early complications include bleeding, acute rejection, vascular or biliary tract issues, or infection. Delayed complications include recurrence of underlying disease, malignancy, infection, chronic rejection, medication toxicity, biliary complications, or renal failure. Many early complications will manifest during the immediate postoperative period. Delayed complications may occur 1 year or more after transplantation.

A combination of two to three immunosuppressive agents are utilized following liver transplantation to prevent rejection. Common regimens include a glucocorticoid such as prednisone along with a calcineurin inhibitor (e.g., cyclosporine or tacrolimus) plus either sirolimus, mycophenolate, or azathioprine. Corticosteroid toxicity includes potential for glucose intolerance, diabetes, osteoporosis, gastric ulceration, or muscle wasting. Cyclosporine and tacrolimus can cause renal impairment, which is the most common dose-limiting effect of these agents. Azathioprine can be hepatotoxic but is more often associated with bone marrow suppression, placing the patient at increased risk for infectious complications or bleeding diatheses.

As a result of their immunosuppression, liver transplant recipients are at increased risk for infections, which remain the leading cause of mortality in transplant recipients and occur frequently in the first three months following surgery, or may be delayed. Presenting signs and symptoms may be subtle secondary to immune suppression. Chronic rejection manifests with low-grade temperature elevation, fatigue, and jaundice. Expected laboratory abnormalities in rejection include elevated bilirubin and transaminase levels, prolonged PT or INR, and low serum albumin level. Evolving renal dysfunction may not be clinically apparent until the glomerular filtration rate has declined significantly. Routine serum creatinine level measurement is the best means of early identification.

Management of patients with complications related to their liver transplant is guided by the nature of the problem. Accordingly, assessment may include a CBC and determination of glucose, BUN, creatinine, serum electrolytes, transaminase, bilirubin and albumin levels, as well as coagulation studies. Hepatobiliary imaging is indicated if tumor, vascular occlusion, or biliary tract obstruction is suspected. Ultrasound studies with Doppler interrogation can be particularly useful in the ED setting. Serologic PCR testing for cytomegalovirus (CMV) is undertaken if patients are within the first three months of transplant or have a constellation of supportive symptoms including leukopenia, arthralgias, or fever. Engagement

of a transplantation specialist is recommended for any patient with a problem potentially related to the organ transplant or immune-modulating medications.

Management of the liver transplant patient is further discussed in Chapter 183.

BILIARY TRACT DISORDERS

CHOLELITHIASIS

Foundations

The principal cause of biliary tract disease is related to the development of gallstones, termed *cholelithiasis*. There are two categories of gallstones, cholesterol stones and pigmented stones. Stones are common in the US population, with a prevalence of 6% to 9%, with a female predominance. The majority of individuals with stones remain asymptomatic and may become aware of their cholelithiasis only incidentally upon imaging for other indications.

Cholesterol stones usually occur as a consequence of an elevated concentration of cholesterol in bile relative to the other principal constituents, bile acids and phospholipids. As cholesterol levels rise or bile acid and lecithin levels decline, cholesterol has an increasing tendency to form crystals. These crystals serve as a nidus for stone formation. Factors associated with an increased risk of cholesterol stone formation include increased age, female gender, obesity, rapid weight loss, cystic fibrosis, parity, drugs such as clofibrate or oral contraceptive agents, and familial tendency.

Pigmented stones are of two varieties, black and brown. Black stones occur exclusively in the gallbladder, contain a high concentration of calcium bilirubinate, and are usually encountered in older adults and those with intravascular hemolytic diseases such as sickle cell anemia or hereditary spherocytosis. Brown stones are associated with infection and can form in the gallbladder and intrahepatic or extrahepatic bile duct systems. All types of gallstones contain calcium bilirubinate and therefore may be visible on plain abdominal radiographs.

Clinical Features

The most common initial clinical manifestation of symptomatic cholelithiasis is biliary colic. The term *colic* can be misleading, because affected patients may report dull, steady pain, rather than intermittent or cramping discomfort. The pain most often is perceived in the RUQ but may be localized over a wide region of the upper abdomen. Radiation of pain, if it occurs, generally is to the base of the right scapula or shoulder. Associated signs and symptoms include nausea or vomiting, which may be severe enough to lead to fluid and electrolyte imbalances. Patients with biliary colic commonly report similar self-limited occurrences in the past and may offer an association between symptom onset and eating. Postprandial physiologic contraction of the gallbladder applying pressure to stones (or sludge, a mixture of particulate matter and bile, microlithiasis) against the cystic duct opening leads to elevated gallbladder pressure and transient wall inflammation. This cascade results in visceral pain. Physical findings include mild tenderness to palpation, without guarding or rebound in the RUQ or epigastric region. Patients with uncomplicated cholelithiasis usually appear well and without infectious or compensatory findings such as fever or tachycardia.

Differential Diagnosis

Differential considerations include cholecystitis, choledocholithiasis (with or without cholangitis), gallstone pancreatitis, peptic ulcer disease of the stomach or duodenum, or hepatitis. Cholelithiasis may occasionally lead to chest discomfort and as such it is prudent to consider cardiopulmonary syndromes as well. A compatible clinical history in conjunction with normal laboratory test values (ALT, AST, lipase, and alkaline phosphatase levels), gallstones on ultrasound, and minimal or no tenderness in the RUQ favor the diagnosis of uncomplicated cholelithiasis. If abnormalities are not visualized, a chest radiograph, electrocardiogram, or serum troponin levels in selected patients may help differentiate between cardiopulmonary and biliary pathology.

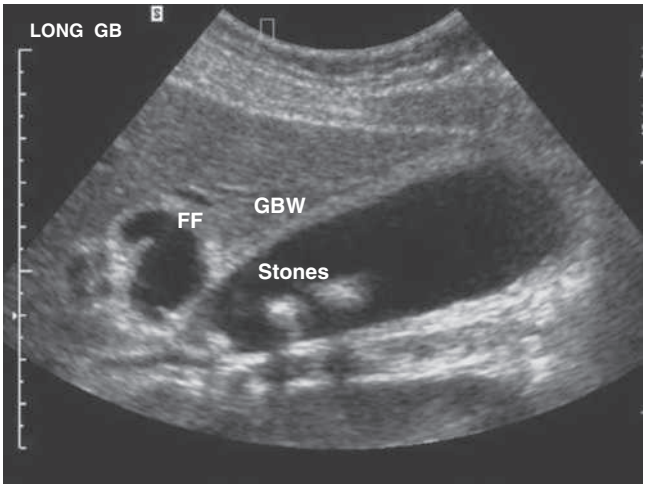

Fig 76.22 Gallbladder with gallstones (*Stones*), thickened gallbladder wall (*GBW*), and pericholecystic fluid (*FF*). Together with a sonographic Murphy sign, these findings constitute the sonographic findings in cholecystitis.

Diagnostic Testing

There is no pathognomonic test for cholecystitis. Results of commonly performed tests are often within normal limits. Important tests to perform include ALT and AST level measurements to evaluate for the presence of hepatitis, bilirubin and alkaline phosphatase level for common duct obstruction, and lipase level for pancreatitis.

The diagnosis of biliary colic is made clinically in conjunction with the demonstration of echogenic foci (stones) in the gallbladder. Transabdominal ultrasonography is the diagnostic modality of choice for investigating the gallbladder given that it can be performed rapidly, is highly sensitive, and also permits evaluation of local surrounding structures when necessary (Fig. 76.22). CT and MR imaging are alternative modalities when ultrasonography is not available or cannot be performed successfully. These alternative modalities have lower sensitivity than ultrasonography. Endoscopic ultrasonography, though invasive, has a higher sensitivity than transabdominal techniques and may detect smaller stones. Additionally, endoscopic ultrasound is performed in conjunction with endoscopic examination of the upper GI tract, which also serves to evaluate for alternative disorders.

Management

The initial management of biliary colic is correction of fluid and electrolyte disturbances and relief of symptoms. Vomiting is managed with antiemetics. Pain often can be controlled with nonsteroidal antiinflammatory drugs (NSAIDs) or opiate analgesic agents, as needed. The definitive management of symptomatic cholelithiasis usually involves surgical removal of the gallbladder. Alternative treatments include oral administration of bile acids (e.g., chenodeoxycholate, ursodeoxycholate) that can result in dissolution of small

to medium-sized stones over a period of months to years. Extracorporeal shock wave lithotripsy may be successful in a select, technically suitable set of patients who have functioning gallbladders and, ideally, have a small number of stones.

The most common complication of biliary colic is fluid and electrolyte imbalances secondary to vomiting. Other adverse consequences include Mallory-Weiss tears from uncontrolled emesis or cholangitis from unrecognized and persistent common bile duct obstruction.

Special Considerations

Biliary colic is an uncommon finding in children and is usually associated with an underlying hemolytic disorder such as sickle cell anemia or hereditary spherocytosis.

Cholelithiasis may be encountered in pregnant women, though the diagnosis is made more difficult by the common occurrence of nausea and vomiting, particularly in the first trimester, and the presence of an enlarged uterus in later pregnancy, which alters anatomic relationships and may interfere with abdominal examination. Ultrasound imaging is of considerable diagnostic use in this setting. ED management is the same for pregnant and nonpregnant patients; however, definitive therapy generally is delayed until after delivery.

Disposition

Hospitalization should be considered for unremitting pain, intolerance of oral intake, significant electrolyte abnormalities, or laboratory tests indicating obstruction or possible cholecystitis. In other patients, symptom control can often be achieved and electrolyte and volume depletion corrected such that the patient can be discharged home with antiemetics and agents for pain control after demonstrating tolerance for oral intake. Referral to a general surgeon as an outpatient for further evaluation and consideration of cholecystectomy should be considered in discharge planning.

CHOLECYSTITIS

Foundations

Acute cholecystitis is defined as sudden inflammation of the gallbladder. The risk factors for cholecystitis are similar to those for cholelithiasis—female gender, increasing age and parity, and obesity. Although gallstones play a prominent role in the pathogenesis of cholecystitis, a minority of cases occur without stones, termed *acalculous cholecystitis*.

Obstruction of the cystic duct appears to be the critical factor in the development of gallbladder inflammation. Gallstones are identified in 95% of patients with cholecystitis or may be located in the common bile duct. Causes of cystic duct obstruction unrelated to stone disease include tumor, lymphadenopathy, fibrosis, parasitic illness, or kinking of the duct, which leads to filling and distention of the gallbladder. The ensuing inflammatory reaction is related to mucosal ischemia from increased hydrostatic pressure as well as the action of cytotoxic products of bile metabolism (e.g., lysophosphatidylcholine). Although bacteria are isolated from the bile of inflamed gallbladders in most cases, the role of infection in the pathogenesis of cholecystitis is not completely understood. Coliforms such as *E. coli* represent the most common isolates, though anaerobes have been identified in as many as 40% of cases.

Clinical Features

The most common presenting symptom of cholecystitis is pain, usually in the right upper quadrant. Although the pain initially may be colicky, it near-uniformly becomes constant. A previous history of similar but less severe and self-limited symptoms is a valuable diagnostic clue, as is documentation of previous gallstones. Fever, nausea, and vomiting are typical features. Radiation of pain to the tip of the right scapula may be described.

Physical findings include tenderness in the RUQ or epigastric region, often with guarding or rebound. Murphy sign (tenderness and an inspiratory pause elicited by palpation of the RUQ during a deep breath) is compatible with, though not specific for, gallbladder inflammation.

Differential Diagnosis

Diagnostic considerations include hepatitis, hepatic abscess, pyelonephritis, right lower lobe pneumonia or pleurisy, pancreatitis, peptic ulcer disease with perforation or penetration, or appendicitis, among others. Accurate diagnosis often requires the use of sonographic or, less commonly, CT or hepatobiliary iminodiacetic acid (HIDA) scanning.

Diagnostic Testing

Leukocytosis or neutrophil predominance may be absent in nearly half of patients. Serum aminotransferase, bilirubin, and alkaline phosphatase levels may be mildly elevated but more often are within normal limits. An elevated lipase level should suggest the diagnosis of pancreatitis, instead of or in addition to cholecystitis. Plain abdominal radiographs rarely reveal calcified stones, gas in the gallbladder, or an upper quadrant sentinel loop, but are usually nondiagnostic.

Ultrasound imaging is the most useful test in the ED. Visualization of the gallbladder without identification of stones has an extremely high negative predictive value for cholecystitis, whereas the presence of stones, thickened gallbladder wall, pericholecystic fluid and a positive sonographic Murphy sign has a positive predictive value in excess of 90% (Fig. 76.23).

Hepatobiliary nuclear scintigraphy with technetium-99m–labeled HIDA generally is considered the most sensitive and specific imaging test for cholecystitis. The IV tracer is taken up by hepatocytes and secreted into the bile canaliculi. Failure to obtain an outline of the gallbladder within 1 hour of administration in the presence of hepatic and common duct visualization is consistent with cystic duct obstruction. In the appropriate clinical setting, this finding is diagnostic of cholecystitis. Conversely, visualization of the gallbladder and common duct within 1 hour of administration has a high negative predictive value. HIDA loses its sensitivity as the serum bilirubin level rises above 5 to 8 mg/dL; however, scintigraphy with diisopropyl iminodiacetic acid, or mebrofenin, allows visualization of the biliary tree in patients with total serum bilirubin as high as 20 to 30 mg/dL.

CT can identify cholecystitis with a sensitivity of 92% but much lower specificity.

Management

Definitive management of acute calculous cholecystitis includes cholecystectomy. Supportive measures include IV crystalloid administration to optimize volume status and antiemetics to manage emesis. Pain control can be addressed with NSAIDs or narcotic analgesics. Despite the questionable role of microbial infection in the pathogenesis of cholecystitis, initial antibiotics are recommended. Unless clinical evidence of sepsis exists, coverage with a single agent broad-spectrum antibiotic, such as IV piperacillin-tazobactam (3.375 g every 6 hours) is recommended.

Gangrene of the gallbladder is a significant complication, with necrosis and perforation. Localized perforation may lead to pericholecystic abscess or fistula formation, with the latter predisposing to gallstone ileus at a later date. Diabetics are at increased risk for bacterial invasion of the gallbladder wall and emphysematous cholecystitis (Fig. 76.24). In this case, complications related to delayed definitive surgical care include gangrene and perforation of the gallbladder, both of which are associated with significant mortality.

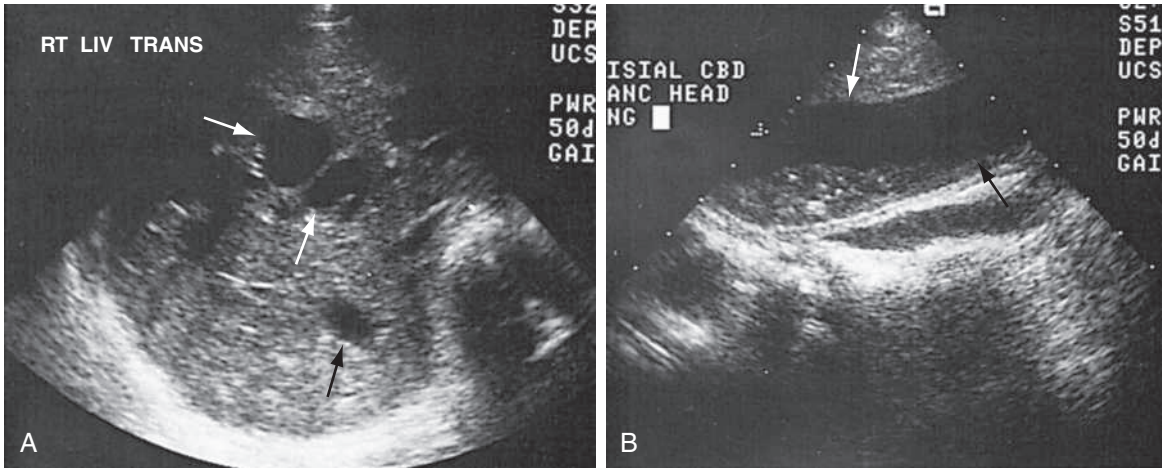

Fig. 76.23 Abdominal ultrasound images from a patient with common bile duct obstruction. (A) Multiple dilated intrahepatic ducts *(arrows)*. (B) Significant dilated common bile duct *(arrows)*. The duct measures 2 cm in diameter.

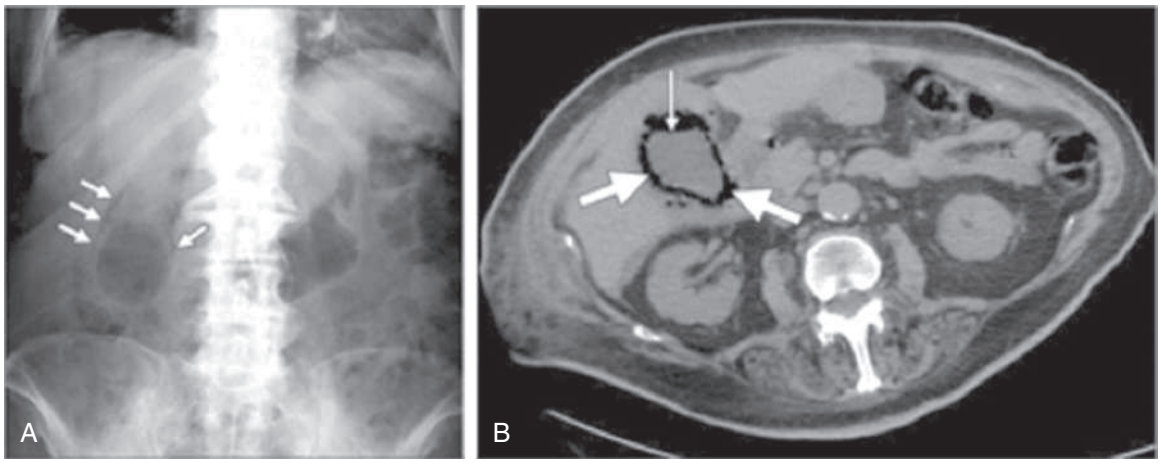

Fig. 76.24 (A) X-ray demonstrating air around the wall of the gallbladder and CT scan (B) demonstrating a luminal air-liquid level and air within the wall of the gallbladder.

Special Considerations

Cholecystitis is uncommon in children; however, when it occurs, it should be managed as for adult patients. Cholecystitis in the pregnant patient poses challenges in diagnosis and therapy. Initial therapy is identical to that for the nonpregnant patient, but the issue of surgical intervention necessitates discussion including surgery and obstetrics.

Acalculous Cholecystitis. Acute cholecystitis absent of stones is more common in older adults and is often found in patients who are recovering from non–biliary tract surgery. This disease should be considered in any critically ill patient presenting with either jaundice or sepsis of undifferentiated source. It is caused by inflammation in the gallbladder wall stemming from stasis and ischemia. Over the past decade, acalculous disease has been increasingly encountered as a complication of advanced AIDS, usually secondary to infection with cytomegalovirus (CMV) or *Cryptosporidium*. In comparison with calculous disease, acalculous cholecystitis tends to have a more acute and malignant course, with a high mortality rate. The same techniques are used to diagnose acalculous disease as for other forms of cholecystitis but are less sensitive and specific for this entity. Sonographic findings include thickening of the gallbladder wall, pericholecystic fluid, sonographic Murphy sign, intramural gas, sludge, and hydrops. HIDA findings are the same as for calculous disease.

Emphysematous Cholecystitis. This is an uncommon variant of cholecystitis, occurring in approximately 1% of cases. It is characterized by the presence of gas in the gallbladder wall, consequent to the invasion of the mucosa by gas-producing organisms such as *E. coli*, *Klebsiella* spp., or *Clostridium perfringens*. It is more common in diabetic patients, has a male predominance, and is acalculous in up to 50% of cases. Clinical presentation and physical findings are similar to those for cholecystitis. Plain radiographs or CT scans of the abdomen typically reveal gas in the gallbladder wall. Because of a high incidence of gangrene and perforation, emergency cholecystectomy is recommended. Antibiotic coverage should include ceftriaxone 1 to 2 g IV every 24 hours plus metronidazole 500 mg IV, every 8 hours, or monotherapy with a β-lactamase inhibitor such as carbapenem. The mortality rate for emphysematous cholecystitis is upwards of 15%.

Disposition

Patients are typically hospitalized for antibiotic therapy and pain management. Surgery is recommended for patients with cholecystitis, though the optimal timing for surgery is not well established. Surgery usually is performed after symptoms have subsided and while the patient is still hospitalized. Immediate cholecystectomy or cholecystostomy is typically reserved for the complicated case in which the patient has gangrene or perforation.

CHOLANGITIS

Foundations

Acute obstructive cholangitis is usually the consequence of common duct blockage by a gallstone but may be associated with structural compression by malignancy or a benign stricture. The key factors contributing to cholangitis include obstruction, elevated intraluminal pressure, and bacterial infection. Incomplete obstruction occurs more commonly than complete blockage. Bacteria may gain access to the obstructed common duct in a retrograde manner from the duodenum, by way of the lymphatics, or from portal vein blood. The most commonly encountered organisms are similar to those encountered in other varieties of biliary tract disease—*E. coli*, *Klebsiella, Enterococcus,* and *Bacteroides.*

Clinical Features

Patients most often experience fever, chills, nausea, vomiting, or abdominal pain. The classic triad of physical findings first described by Charcot consists of RUQ pain, fever, and jaundice. These findings are compatible not only with cholangitis, but also potentially with cholecystitis or hepatitis. Sepsis is a common complication and is evidenced by tachycardia, tachypnea, and frank hypotension. The presence of the Charcot triad along with the clinical signs of sepsis—hypotension and altered sensorium—is referred to as the Reynolds pentad.

Differential Diagnosis

Although patients with cholangitis generally have a higher fever and appear more ill than those with cholecystitis, considerable variability and overlap exist. The presence of jaundice is the clinical sign most helpful in differentiating between these two disorders. An elevated bilirubin level is characteristic of cholangitis and uncommon in cholecystitis. Ultrasonographic evidence of dilated common and intrahepatic ducts usually is required to distinguish cholangitis from cholecystitis.

Diagnostic Testing

Common laboratory abnormalities include leukocytosis, hyperbilirubinemia, elevated alkaline phosphatase level, and moderately increased aminotransferase levels. Blood gas measurements are useful to identify base deficit as an early sign of sepsis.

Sonography can be helpful if it demonstrates common and intrahepatic ductal dilation, whereas identification of stones in the gallbladder or common duct suggests the underlying cause of obstruction (see Fig. 76.22). Although nuclear scintigraphy (HIDA) scanning may not determine the cause, it is a more sensitive means to diagnose early obstruction. There is a high incidence of nonvisualization of the biliary tree with cholescintigraphy in patients with common duct obstruction when sonography fails to identify dilation.

Alternative imaging techniques include CT, percutaneous transhepatic cholangiography (THC), or endoscopic retrograde cholangiopancreatography (ERCP). Although these techniques may be more time-consuming, the latter two have the added benefit of offering potential therapeutic benefit. Endoscopic cholangioscopy can permit culture of bile, direct removal of obstructing stones, or decompression of the biliary tree through sphincterotomy or stent placement.

Management

Treatment of cholangitis includes hemodynamic stabilization with crystalloid fluid and, if necessary, vasopressors. Broad-spectrum antibiotic coverage should be initiated immediately after blood culture specimens have been obtained. The choice of antibiotics should be guided by local sensitivities and should provide coverage for enteric microbes. First-line single agents may include either ampicillin-sulbactam 3g IV every 6 hours or piperacillin-tazobactam 3.375 g IV every 6 hours. The key to successful treatment is early biliary tract decompression, which may be achieved with THC, ERCP, or surgery.

Disposition

Patients with cholangitis require hospitalization, preferably in a monitored setting. Prompt engagement of surgery, interventional radiology, or gastroenterology for biliary tract decompression is necessary.

SCLEROSING CHOLANGITIS

Sclerosing cholangitis is a chronic, idiopathic inflammatory disorder affecting the biliary tree characterized by progressive, diffuse fibrosis and narrowing of the intrahepatic and extrahepatic bile ducts as well as the extrahepatic biliary tree. It is commonly associated with inflammatory bowel disease, particularly ulcerative colitis; however, in 25% of cases, it appears as an isolated disorder. Patients usually report weight loss, lethargy, jaundice, or pruritus. Earliest symptoms include isolated fatigue and pruritis. Rarely, infective cholangitis may develop. Prompt diagnosis may be challenging because of the sclerotic nature of the bile ducts and absence of duct dilation on ultrasound imaging. Surgical exploration or ERCP often is required for diagnosis (Fig. 76.25). Sclerosing cholangitis is thought to be autoimmune in nature. Autoantibodies are often positive but are of unknown prognostic value. Of note, antimitochondrial antibodies may help distinguish sclerosing cholangitis from primary biliary cholangitis; they are often positive in primary biliary cholangitis but not present in sclerosing cholangitis.

The management of uninfected cases is primarily symptomatic. Cholestyramine, a bile acid sequestrant, may diminish pruritus. Elevations of bilirubin for more than 3 months from diagnosis correlates with poorer prognosis. Median survival after diagnosis is 9 to 10 years without liver transplantation.[52]

AIDS CHOLANGIOPATHY

Manifestations of advanced HIV disease, generally associated with CD4+ counts less than 200/mm^3, may include any one of a group of disorders collectively referred to as AIDS cholangiopathy. These disorders include bile duct stricture, papillary stenosis, or sclerosing cholangitis spurred by infectious etiologies. The pathophysiology is not completely understood but is related to infection with CMV, *Cryptosporidium,* microsporidia, or *Mycobacterium avium* complex. Cryptosporidium parvum is the most commonly isolated pathogen. The widespread use of highly active antiretroviral therapy has resulted in a declining incidence of AIDS-related cholangiopathy.

The clinical presentation is similar to that for other causes of cholangitis, with fever and RUQ pain, often with accompanying diarrhea related to the underlying pathogen. Laboratory tests include increased levels of alkaline phosphatase and minor elevation of transaminase levels. The bilirubin level is less commonly elevated than in other disorders that cause cholangitis. Ultrasonography generally is helpful in initially identifying bile duct stricture, thickening, or dilations. Secondarily, visualization using magnetic resonance cholangiopancreatography (MRCP) is helpful in identifying strictures and differentiating this entity from other causes of abdominal pain. Complications of longstanding AIDS-related cholangitis include sclerosis and liver failure. Management includes ursodiol (8–10 mg/kg/day by mouth every 8 or 12 hours) for patients with intrahepatic ductal disease. Isolated ductal stricture management involves endoscopic sphincterotomy or stent placement in conjunction with treatment of the underlying infection.

The references for this chapter can be found online at ExpertConsult.com.

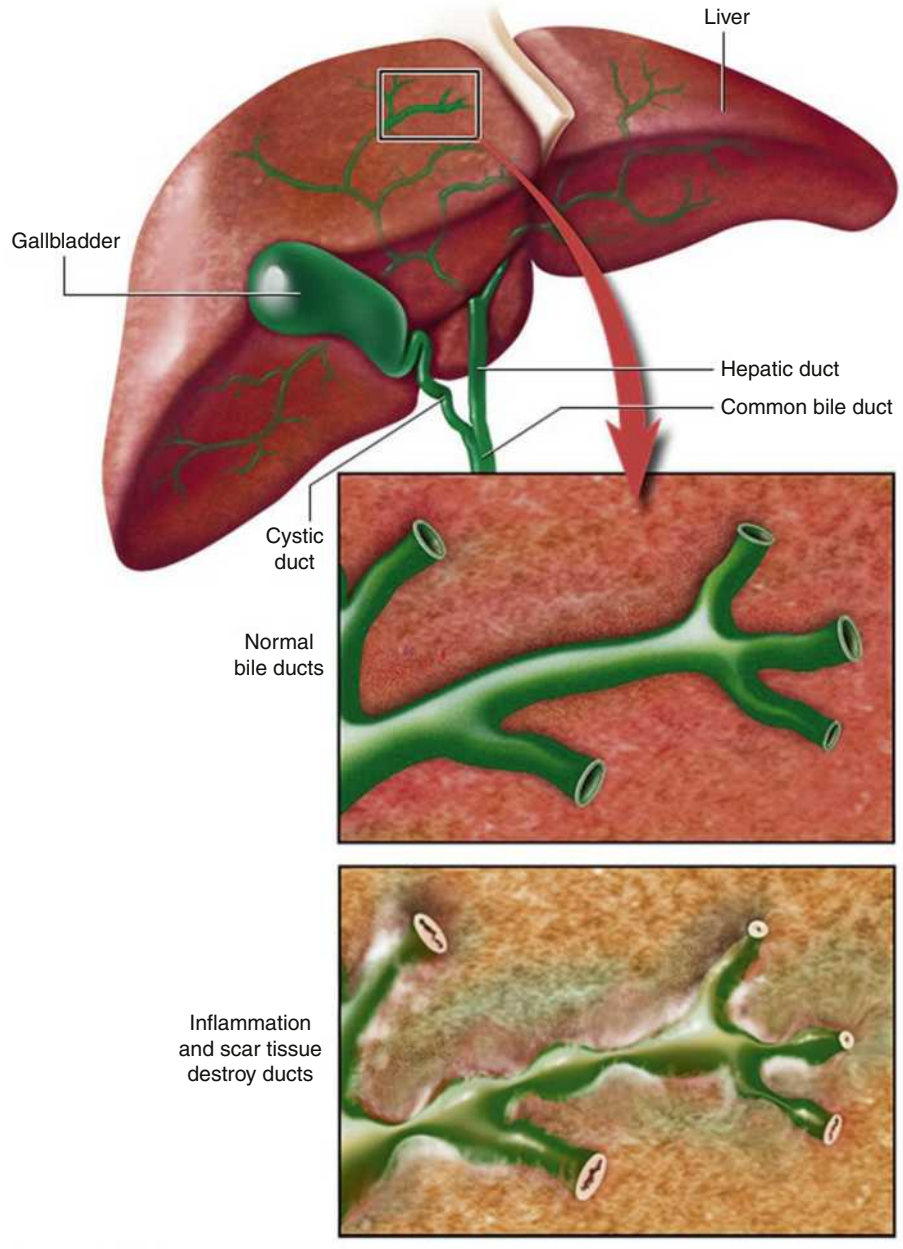

Fig. 76.25 Bile duct damage. The bile ducts carry bile from your liver to your small intestine. When bile ducts become damaged, bile can back up into the liver, causing damage to liver cells. This damage can lead to liver failure. (From: https://www.mayoclinic.org/diseases-conditions/primary-sclerosi-scholangitis/symptoms-causes/syc-20355797. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

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CHAPTER 76: QUESTIONS AND ANSWERS

1. Which of the following statements regarding hepatitis A is true?
- **a.** Fecal shedding and highest infectivity coincide with symptomatic disease.
- **b.** In the US, approximately 20% of urban-dwelling adults are seropositive.
- **c.** Occult disease is more common in children than in adults.
- **d.** The incidence is consistent across ethnic groups.
- **e.** The most common risk factor for children is travel.

Answer: c. Children are more likely to have occult disease (up to 70%). Adult seropositive rates approach 50% among urban-dwelling adults. The incidence varies widely across ethnic groups. In areas of pediatric vaccinations, increasing adult cases are seen among intravenous drug users (IVDUs) and males who have sex with males. The stage of highest infectivity precedes symptoms.

2. Which of the following statements concerning hepatitis D infection is true?
- **a.** Hepatitis D is spread primarily via the fecal-oral route.
- **b.** Infection with hepatitis D is an independent event with a course nearly identical to that of hepatitis A.
- **c.** It is common to see aspartate aminotransferase (AST) level elevations far in excess of alanine aminotransferase (ALT) level elevations.
- **d.** Many cases are misdiagnosed as acute or reactivated hepatitis B.
- **e.** Unconjugated bilirubin levels are 2 or 3 times higher than conjugated levels.

Answer: d. Hepatitis D virus infection can only occur with (coinfection) or after (superinfection) hepatitis B infection. It is spread via the parenteral route, such as by IV drug use. Many cases are misdiagnosed as acute or reactivated hepatitis B because HBV markers will be positive. There are no unique biochemical or laboratory patterns for any of the viral hepatitis infections. Hepatitis D appears to have a direct cytotoxic potential compared with other viral causes where the host immunologic response primarily leads to hepatopathy.

3. A 26-year-old man presents with complaints of pruritus and a raised rash for 7 days. The rash has been associated with nausea and painful symmetrical swelling of both wrists and metacarpophalangeal joints. He has no past medical history and takes no medications. He works in a retail store. Vital signs are normal, and the physical examination is remarkable for right upper quadrant tenderness, bilateral mild wrist effusion with minimal warmth and no erythema, and diffuse skin urticaria. The remainder of the examination is negative. Blood count, chemistries, and liver studies are remarkable for WBC of 11,800 cells/mm^3, AST of 212 IU/L, ALT of 395 IU/L, normal alkaline phosphatase level, and total bilirubin of 2.3 mg/dL. Which of the following diagnostic modalities would be most likely to yield the causative diagnosis?
- **a.** C-reactive protein level
- **b.** Hepatitis A antigen
- **c.** Hepatitis B surface antigen
- **d.** Joint aspiration
- **e.** Liver ultrasound

Answer: c. A small number of patients with hepatitis B develop a prodrome of arthralgias and arthritis (symmetric small joints) and dermatitis. The dermatitis is typically urticarial but may be macular, popular, or petechial.

4. Scleral icterus becomes clinically apparent at approximately which serum bilirubin level?
- **a.** 2 mg/dL
- **b.** 2.5 mg/dL
- **c.** 3 mg/dL
- **d.** 3.5 mg/dL
- **e.** 4 mg/dL

Answer: b. Icterus is often first noted in the sublingual or subungual areas when the serum bilirubin level is above approximately 2.5 mg/dL.

5. Which of the following statements regarding the typical laboratory profile for a patient with acute viral hepatitis is true?
- **a.** AST is generally elevated in excess of ALT.
- **b.** Direct and indirect bilirubin levels are elevated in almost equal proportions.
- **c.** Lactate dehydrogenase (LDH) levels are almost always normal.
- **d.** The alkaline phosphatase level is generally elevated 5 to 10 times normal.
- **e.** The WBC always shows a marked polymorphonuclear leukocytosis.

Answer: b. The alkaline phosphatase level is rarely elevated more than 2 or 3 times normal, and LDH levels are modestly elevated. The WBC count may range from low, with lymphocytic predominance, to a polymorphonuclear (PMN)-predominant leukocytosis. ALT is almost always elevated in excess of AST in the setting of acute viral hepatitis.

6. A 26-year-old woman returns for follow-up after initial evaluation for possible acute hepatitis. Her hepatitis panel has returned with the following results:

Hepatitis A IgM	Negative
Hepatitis A IgG	Negative
Hepatitis B surface antigen	Positive
Hepatitis B surface antigen IgG	Negative
Hepatitis B core antigen IgM	Positive
Hepatitis B core antigen IgG	Negative
Hepatitis C antigen	Negative

Which of the following is the most appropriate diagnosis?
- **a.** Acute hepatitis A
- **b.** Acute hepatitis B
- **c.** Immunity to hepatitis B
- **d.** Previous hepatitis A
- **e.** Previous hepatitis B

Answer: b. Acute hepatitis A is characterized by IgM to hepatitis A. Prior infection is determined by IgG antibody. Acute hepatitis B is characterized by the presence of surface antigen and IgM antibody to core antigen. Surface antigen alone may be absent late in the course of the disease or may present chronically unrelated to the current episode. IgG to the core antigen indicates previous infection. IgG to the surface antigen is the best marker for immunity.

CHAPTER 76: QUESTIONS AND ANSWERS—cont'd

7. A 39-year-old man presents with a 4-day history of abdominal pain and nausea. He has no significant past history and takes no medications. Vital signs include a temperature of 37.7°C (99.9°F) oral, pulse of 98 beats/min, respiratory rate of 20 breaths/min, and a blood pressure of 119/68 mm Hg. The physical examination reveals scleral icterus, a normal cardiopulmonary examination, moderate right upper quadrant tenderness without rebound, and guaiac-negative stool. Laboratory assessment reveals the following:

Total bilirubin	9.8 mg/dL
Conjugated bilirubin	4.6 mg/dL
Unconjugated bilirubin	5.2 mg/dL
AST	5300 IU/L
ALT	8400 IU/L
Alkaline phosphatase	750 IU/L
Albumin	3.9 mg/dL
INR	1.2
Hematocrit	42%
Platelet count	396,000/mm^3
WBC	9900/mm^3
Blood urea nitrogen (BUN)	53 mg/dL
Creatinine	0.9 mg/dL

Which of the following courses of action is most appropriate?

a. Admission for observation and GI consultation
b. CT scan of the abdomen with contrast
c. Gastrointestinal (GI) referral for interferon therapy
d. Reassurance
e. Tapering course of corticosteroids

Answer: a. Altered sensorium and prolongation of the PT beyond 5 seconds or INR beyond 1.5 suggests fulminant hepatic failure. Similarly, an unexplained elevation of the BUN or creatinine level may portend hepatorenal syndrome, which is associated with significant morbidity. The laboratory derangements warrant admission or transfer for hydration, close observation, and gastroenterology evaluation. Interferon has demonstrated some success in symptomatic hepatitis B patients but does not affect the early course. There is no role for corticosteroids.

8. The risk of liver injury in men increases as daily consumption of alcohol exceeds which of the following?

a. 10 g
b. 20 g
c. 40 g
d. 60 g
e. 80 g

Answer: e. 80 g of alcohol consumption is equivalent to a six-pack of beer, four to six glasses of wine, or three or four mixed drinks. For women, the risk increases with daily consumption of more than 20 g of alcohol.

9. A 63-year-old man with history of alcohol abuse presents with altered mental status. His family reports 3 days of decreasing ambulation and increasingly nonsensical conversation. He has no other known past medical history and takes no medications. Vital signs are unremarkable. Physical examination reveals a thin, unkempt man who is oriented to person only but is cooperative and follows commands. He falls asleep easily. There is no scleral icterus, and cardiopulmonary, abdominal, stool guaiac, and neurologic examinations are otherwise normal. A noncontrast CT scan of the head is negative for acute pathology. Pertinent laboratory findings are as follows:

Hematocrit (HCT)	34%
Hemoglobin	11.4 g/dL
Platelet count	108,000/mm^3
WBC	9300/mm^3
AST	148 IU/L
ALT	86 IU/L
Total bilirubin	2 mg/dL
Albumin	2.2 mg/dL
Alkaline phosphatase	158 IU/L
INR	1.8
BUN	38 mg/dL
Creatinine	2.1 mg/dL
Ethanol	0 mg/dL
Bicarbonate	30 mmol/L
Sodium	133 mEq/L
Potassium	3.6 mEq/L
Chloride	95 mEq/L

What is the most appropriate intervention?

a. Admission for lactulose, 30 to 60 g daily, titrated to modest diarrhea
b. Determination of further therapy, admission, and treatment based on serum ammonia levels
c. Discharge with the family; neomycin, 500 mg every 4 to 6 hours
d. Oral metronidazole, 250 mg PO every 6 hours
e. Oral vitamin K for 2 weeks

Answer: a. Ammonia accumulates in severe liver disease and crosses the blood-brain barrier to eventually form glutamine. Ammonia levels correlate poorly with encephalopathy. Lactulose is an osmotic cathartic that acidifies colonic contents, causing ammonia trapping. Neomycin is a poorly absorbed aminoglycoside that reduces colonic bacteria but is relatively contraindicated in cases of renal insufficiency. Therapies for hepatic encephalopathy that have been under clinical investigation include metronidazole, zinc, flumazenil, and eradication of *Helicobacter pylori*. Vitamin K would have modest benefit due to loss of hepatic synthetic abilities.

Continued

CHAPTER 76: QUESTIONS AND ANSWERS—cont'd

10. A 23-year-old G2P1 woman at 35 weeks of gestation presents with 3 days of fatigue, anorexia, nausea, and vomiting. She reports moderate epigastric and right upper quadrant pain. The physical examination is remarkable for icteric sclerae, slightly dry mucous membranes, and moderate tenderness in the right upper quadrant. She is afebrile and her uterus is not tender. Ultrasound shows a viable fetus at 34 weeks estimated gestation, with good cardiac activity, and liver and gallbladder ultrasound reveals no obvious gallstones or ductal dilations but moderate hepatomegaly. Laboratory analysis is remarkable for the following:

AST	1050 IU/L
ALT	1265 IU/L
Total bilirubin	9.9 mg/dL
Conjugated bilirubin	4.6 mg/dL
Unconjugated bilirubin	5.2 mg/dL
Alkaline phosphatase	328 mg/dL
Glucose	62 mg/dL
Hemoglobin	9.3 g/dL
Platelet count	105,000/mm^3
Serum electrolytes	Normal
Creatinine	0.6 mg/dL
Prothrombin time	14.8 sec
Albumin	3.1 g/dL

What is the most appropriate treatment?

- **a.** Clear liquids, antiemetics, and follow-up outpatient ultrasound in 48 hours
- **b.** Contrast CT scan of the abdomen
- **c.** Hydration, antiemetics, and discharge after symptom resolution
- **d.** Intensive care unit admission for monitoring for DIC
- **e.** Stabilization and urgent delivery

Answer: e. Acute liver failure of pregnancy typically presents in the later third trimester. Treatment involves aggressive fluid and electrolyte support, glucose administration, and immediate delivery. Liver disease generally resolves without sequelae. The illness is more common in primigravidas and twin gestations.

11. What is the most sensitive and specific imaging test for acute cholecystitis?

- **a.** Contrast CT scan
- **b.** Hepatobiliary nuclear scintigraphy with iminodiacetic acid (HIDA) scan
- **c.** Serum alkaline phosphatase level
- **d.** Serum bilirubin level
- **e.** Ultrasonography

Answer: b. Iminodiacetic acid administered IV is taken up by hepatocytes and secreted into bile canaliculi. Visualization of the gallbladder and common duct within 1 hour has a negative predictive value of 98%. Sensitivity of HIDA is diminished at bilirubin levels of 5 to 8 mg/dL.

77

Pancreas

Philippa Soskin

KEY CONCEPTS

- Acute pancreatitis represents a wide spectrum of disease, ranging from mild to severe life-threatening disease with a mortality rate as high as 30%.
- The most common causes of acute pancreatitis are gallstones and chronic alcohol consumption.
- Acute pancreatitis is diagnosed by the presence two of three criteria—characteristic abdominal pain, serum lipase or amylase levels greater than three times the upper limit of normal, and characteristic findings on abdominal imaging.
- Serum lipase level is preferred over the amylase level because of its greater sensitivity and specificity in diagnosing acute pancreatitis.
- Computed tomography (CT) scan is not routinely recommended in the diagnosis of acute pancreatitis. It should be used in cases of diagnostic uncertainty and assessing for complications.
- Abdominal ultrasound should be performed to evaluate for a biliary etiology of pancreatitis.
- Treatment of acute pancreatitis is mainly supportive with fluid resuscitation and pain management. Lactated Ringers is preferred over normal saline because it is more physiologic and may provide antiinflammatory effects. There is no evidence to support one analgesic agent over another.
- Prophylactic antibiotics are not indicated in the management of acute pancreatitis but should be used in cases of infected pancreatic necrosis or other clear evidence suggesting sepsis or infection.
- Endoscopic retrograde cholangiopancreatography (ERCP) is only indicated in cases of cholangitis or biliary obstruction.
- Most patients with pancreatitis require hospitalization for symptomatic control, monitoring of hydration and nutrition status, and management of complications.
- There are several scoring systems to aid in predicting severity and outcomes in pancreatitis, including Ranson criteria, Acute Physiology and Chronic Health Evaluation II (APACHE II), CT severity index (CTSI), and Bedside Index of Severity in Acute Pancreatitis (BISAP). They are similar in their predictive accuracy, and each has different strengths and weaknesses.
- Chronic pancreatitis is a progressive fibroinflammatory syndrome which impairs both exocrine and endocrine pancreatic function.
- Pancreatic cancer is the seventh most common cause of death from cancer globally with a 5-year survival rate of only 7%.
- Surgical treatment may improve survival in patients whose pancreatic cancer is diagnosed early without metastasis. Most patients have advanced disease at diagnosis.

PANCREATITIS

Anatomy, Physiology, and Pathophysiology

The pancreas is a retroperitoneal organ with endocrine and exocrine functions (Fig. 77.1). It contains three segments—head, body, and tail—that span across the upper abdomen. The pancreatic head sits within the concave C loop of the duodenum, located in the epigastrium. The body of the pancreas traverses posteriorly to the stomach, and the pancreatic tail abuts the hilum of the spleen in the left upper quadrant. A large main pancreatic duct (duct of Wirsung) courses within the pancreas from the tail to the head, where it meets the common bile duct to form the ampulla of Vater, which drains its contents into the duodenum via the sphincter of Oddi. The exocrine function of the pancreas is carried out by the excretion of various digestive enzymes, such as trypsinogen. The endocrine function of the pancreas includes secretion of the regulatory hormones insulin, glucagon, and somatostatin.

Injury to the pancreas begins with an inciting event, such as duct obstruction by a gallstone or exposure to a pharmacologic agent or a toxin such as alcohol. Cellular injury disrupts normal membrane trafficking and triggers the inappropriate activation of trypsinogen resulting in increased trypsin production which results in further cell injury and activation of other digestive enzymes. Autodigestion and the activation of the inflammatory cascade with the recruitment of macrophages and neutrophils lead to further destruction of pancreatic tissue. Cytokine release causes increased vascular permeability, which can result in complications such as edema, hemorrhage, and necrosis. The release of inflammatory mediators through a heightened autoimmune response may lead to systemic inflammatory response syndrome (SIRS), sepsis, and shock. Bacteremia can occur due to translocation of intestinal flora. Extrapancreatic organ dysfunction such as the development of pleural effusions, acute respiratory distress syndrome (ARDS), and renal failure may also occur.

Acute Pancreatitis

Foundations

Acute pancreatitis is an inflammatory condition leading to enzymatic autodigestion and the destruction of pancreatic tissue. Its presentation ranges widely from mild, self-limited disease to sepsis and multiorgan failure. Recurrent episodes of acute pancreatitis can result in the progressive fibrosis of chronic pancreatitis. Acute pancreatitis is the most common pancreatic disease worldwide and one of the top reasons for hospitalization due to gastrointestinal disease in the United States.[1,2] Mortality can run as high as 30% in severe cases; however, although

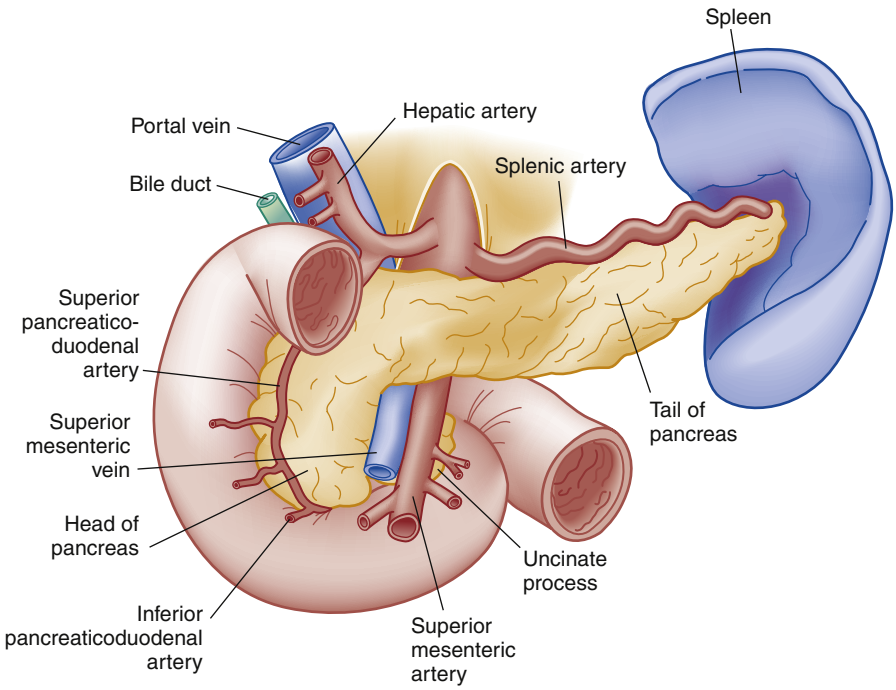

Fig. 77.1 Diagrammatic Representation of the Pancreas, Anterior View. (Redrawn from Feldman M, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management.* 7th ed. Philadelphia: Saunders; 2002.)

hospital admissions continue to increase, the overall mortality of acute pancreatitis has decreased.[3–5]

There are numerous causes of acute pancreatitis (Box 77.1), with gallstones (40% to 70%) and chronic alcohol consumption (25% to 35%) accounting for the majority of cases.[6–8] Other common causes include hypertriglyceridemia (serum triglyceride levels > 1000 mg/dL), complications from endoscopic retrograde cholangiopancreatography (ERCP), medications, trauma, and idiopathic. It is thought that many idiopathic cases may be due to occult to microlithiasis. Smoking and diabetes are independent risk factors for the development of pancreatitis.

Acute pancreatitis can be classified by type—interstitial edematous versus necrotizing pancreatitis—and by local complications. Most patients have the interstitial edematous type, which usually resolves within the first week of illness. Approximately 5% to 10% of patients develop necrotizing pancreatitis, which can involve the pancreatic parenchyma and surrounding tissue. Necrotic tissue may remain sterile, liquefy, or become infected. Infected lesions are associated with increased morbidity. Local complications usually occur after the first week and should be suspected in patients with prolonged or recurrent symptoms, secondary elevation of pancreatic serum markers, or signs of sepsis, such as fever and leukocytosis. The local complications of acute pancreatitis are summarized in Box 77.2.

Clinical Features

Patients with acute pancreatitis typically present with persistent epigastric or left upper quadrant pain that may radiate to the back, chest, or flanks. The pain is usually moderate to severe in intensity; however, the intensity of pain does not correlate with clinical severity. Associated symptoms include nausea, vomiting, and anorexia as oral intake may exacerbate pain. The pain may be alleviated by sitting up or bending forward.

Vital signs may be normal in cases of mild or early disease. Abnormalities commonly reflect patient discomfort or an existing inflammatory process, with rises in temperature, heart rate, or respiratory rate. Blood pressure may be slightly elevated secondary to pain, although in severe or complicated cases, hypotension and signs of shock may be present. Jaundice suggests an obstructive process such as a gallstone or tumor. Respirations may be shallow due to splinting from pain, and pulmonary auscultation may reveal decreased breath sounds or basilar crackles in the setting of pulmonary complications.

The abdomen can appear normal or distended. The classic clinical findings of Cullen sign (bluish periumbilical discoloration due to hemoperitoneum) and Grey Turner sign (reddish-brown discoloration around the flanks due to retroperitoneal bleeding) are rare and neither sensitive nor specific for acute pancreatitis but, when present, may confer a poor prognosis. Auscultation of the abdomen may reveal normal, diminished, or absent bowel sounds if the patient has concomitant ileus. Palpation of the abdomen often reveals epigastric tenderness with or without guarding and with rebound tenderness being a less common finding. Right upper quadrant tenderness and the presence of Murphy sign may be seen in cases of gallstone pancreatitis.

In addition to direct injury to the pancreas, patients may have local complications involving surrounding structures (e.g., bowel necrosis, splenic or portal vein thrombosis, gastrointestinal bleeding, or gastric outlet obstruction). Most of these tend to be late findings.

Systemic complications are related to the progression of local inflammation and may result in SIRS. Although in most cases these conditions resolve within days, if persistent there may be progression to fulminant sepsis, shock, and organ failure, especially if there is underlying chronic disease. The pulmonary, cardiovascular, and renal systems are the most important when assessing for organ failure. Increased microvascular permeability is the primary cause of pulmonary sequelae, although enzymatic degradation of surfactant may also play a role. Patients may develop ARDS, atelectasis, or pleural effusion, manifested as hypoxemia or respiratory distress. Pleural effusions are present in up to 50% of patients and tend to develop more frequently on the left side. Cardiovascular collapse, as evidenced by decreased mean arterial pressure or the need for inotropic support, may develop as shock results from fluid shifts and volume loss. Renal failure, demonstrated by an elevated creatinine level, may arise from a combination of hypoperfusion and the effects of inflammatory mediators.

In addition, coagulopathy occurs from cytokine-mediated activation of the coagulation cascade, potentially leading to thrombocytopenia or

BOX 77.1 Causes of Acute Pancreatitis

Toxic—Metabolic
Alcohol
Drugs
Hyperlipidemia
Hypercalcemia
Uremia
Scorpion venom

Mechanical—Obstructive
Biliary stones
Congenital—pancreas divisum, annular pancreas
Tumors—ampullary, neuroendocrine, pancreatic carcinoma
Post-ERCP
Ampullary dysfunction or stenosis
Duodenal diverticulum
Trauma

Infectious
Viral—mumps, coxsackie, HIV, CMV, EBV, varicella
Bacterial—TB, *Salmonella, Campylobacter, Legionella, Mycoplasma*
Parasitic—*Ascaris*

Vascular
Vasculitis
Embolism
Hypoperfusion, ischemia
Hypercoagulability

Other
Idiopathic
Hereditary
Diabetes mellitus, DKA
Autoimmune

CMV, Cytomegalovirus; *DKA,* diabetic ketoacidosis; *EBV,* Epstein-Barr virus; *ERCP,* endoscopic retrograde pancreatography; *HIV,* human immunodeficiency virus; *TB,* tuberculosis.

disseminated intravascular coagulation. Metabolic abnormalities are also common. Hyperglycemia results from decreased insulin production and hypocalcemia from low albumin and magnesium levels.

Differential Diagnoses

A number of disease processes have the ability to mimic the presentation of acute pancreatitis and should be considered in the differential diagnosis (Box 77.3). Inflammation of nearby intra-abdominal organs, such as the gallbladder, stomach, and duodenum, is often characterized by a similar pattern of epigastric or upper quadrant abdominal pain. Myocardial infarction, pneumonia, and aortic pathology may also present as lower thoracic or upper abdominal pain, with radiation to the back.

Diagnostic Testing

Acute pancreatitis is generally diagnosed by the presence of at least two of the following three criteria: (1) abdominal pain characteristic of acute pancreatitis, (2) serum lipase or amylase levels greater than three times the upper limit of normal, and (3) characteristic findings seen on abdominal imaging.

Laboratory Tests. Laboratory diagnosis of pancreatitis is made primarily by serum lipase and amylase levels. Lipase is an enzyme produced predominantly by the pancreas to aid in the breakdown of dietary triglycerides into free fatty acids. Amylase is an enzyme

BOX 77.2 Local Complications of Acute Pancreatitis

Interstitial Edematous Pancreatitis
- Acute peripancreatic fluid collection—homogeneous fluid collection adjacent to pancreas; seen within 4 weeks of symptom onset
- Pancreatic pseudocyst—homogeneous fluid collection with well-defined wall; seen >4 weeks from symptom onset

Necrotizing Pancreatitis
- Acute necrotic collection—heterogeneous collection of fluid and necrosis; intrapancreatic and/or extrapancreatic
- Walled-off necrosis—heterogeneous collection of fluid and necrosis with well-defined wall; intrapancreatic and/or extrapancreatic; seen >4 weeks from symptom onset

Adapted from Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013;62:102–111.

BOX 77.3 Differential Diagnosis for Acute Pancreatitis

Abdominal Disorders
Peptic ulcer disease
Gastritis
Gastroenteritis
Cholelithiasis
Cholecystitis
Choledocholithiasis
Cholangitis
Nephrolithiasis
Bowel obstruction
Perforated viscus
Mesenteric ischemia
Abdominal aortic aneurysm
Ectopic pregnancy

Cardiopulmonary Disorders
Myocardial infarction
Pneumonia
Pericarditis
Pleural effusion

Systemic Disorders
Sickle cell crisis
Diabetic ketoacidosis

produced by the pancreas and salivary glands, as well as multiple other organs to a smaller extent, to aid in the digestion of carbohydrates. Elevated lipase levels are both more specific and more sensitive than amylase levels in the diagnosis of acute pancreatitis. Although both enzymes begin to rise in the first few hours following symptom onset, amylase remains elevated for approximately 3 to 5 days compared with lipase which peaks more quickly and remains elevated for approximately 1 to 2 weeks.

Serum amylase levels may be high in a number of conditions, including macroamylasemia (a condition where amylase forms large molecular complexes with immunoglobulins resulting in decreased renal excretion), renal failure, salivary gland disease, liver disease, appendicitis, cholecystitis, intestinal obstruction, intestinal ischemia, peptic ulcer disease, and gynecologic diseases.[7] Elevated serum lipase

levels may also be seen in extrapancreatic conditions such as renal failure, appendicitis, and cholecystitis; however, it is generally recognized that elevated lipase levels have greater sensitivity and specificity for pancreatitis when compared with amylase levels. Amylase levels may be falsely negative in cases of alcohol and hypertriglyceridemia-induced acute pancreatitis, particularly early in the disease course. We recommend use of the lipase level in the diagnosis of acute pancreatitis. Testing for both enzymes does not improve diagnostic sensitivity or specificity. For both enzymes, three times the upper limit of normal is the most commonly used cutoff value because studies have demonstrated high sensitivity at this level. The degree of lipase or amylase level elevation does not correlate with disease severity or prognosis.

Alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin levels should be drawn to evaluate for gallstones or another obstructive process as a cause of pancreatitis. ALT has been shown to be particularly specific for biliary pancreatitis, with a positive predictive value of 95%. Calcium and serum triglyceride levels, particularly in the setting of an absence of gallstones or significant history of alcohol use, may also be useful in determining an etiology (triglyceride levels >1000 mg/dL). A complete blood count (CBC) and basic metabolic panel (BMP) should be drawn to evaluate for SIRS and signs of organ failure.

Radiologic Tests. Abdominal imaging by computed tomography (CT) or magnetic resonance imaging (MRI) is not routinely recommended in the diagnosis of acute pancreatitis. CT is recommended only in the following three circumstances: (1) in cases of diagnostic uncertainty (e.g., atypical abdominal pain) or normal pancreatic enzyme levels in the setting of high clinical suspicion; (2) to rule out other suspected intra-abdominal pathology (e.g., bowel obstruction or aortic aneurysm); and (3) to assess for complications in patients who fail to respond to appropriate therapy after at least 48 to 72 hours.[3,7] The evaluation of complications of pancreatitis by CT is of most utility when done at least 3 to 7 days after presentation because CT findings of pancreatic necrosis are often not identified early on and abscesses and pseudocysts do not generally develop until several weeks after symptom onset. Studies show that patients undergoing early CT have increased costs and exposure to radiation with no additional diagnostic benefit or change in medical management.[9–11]

If CT is performed, it should be done with intravenous (IV) contrast. The CT scan is normal in 15% to 30% of patients with mild cases of pancreatitis. Contrast-enhanced CT has a greater than 90% sensitivity and specificity in the diagnosis of acute pancreatitis.[7] Abnormal findings include pancreatic parenchymal enlargement with lack of enhancement, loss of its typical texture and borders, and surrounding retroperitoneal fat stranding (Fig. 77.2). Pancreatic necrosis is suggested by areas demonstrating no enhancement (Fig. 77.3). In cases for which contrast is contraindicated, CT without contrast may still be useful; alternatively, MRI can be performed.

The diagnostic utility and radiologic findings of pancreatitis with MRI are similar to those of CT. MRI provides superior imaging of the gallbladder and biliary tract but is more costly and often has limited availability and accessibility. Direct pancreatic ultrasonography may show an edematous swollen pancreas, but the study image is often obscured by bowel gas, and of limited diagnostic and prognostic value. Abdominal ultrasound (US) has limited value in the direct diagnosis of pancreatitis but is noninvasive and sensitive for imaging the gallbladder and biliary tract and should therefore be obtained to evaluate for a biliary or obstructive etiology. Abdominal ultrasound may also help to determine the need for further advanced imaging of the biliary tract with magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) as well as potential surgical or procedural management such as cholecystectomy or ERCP.[12] Abdominal

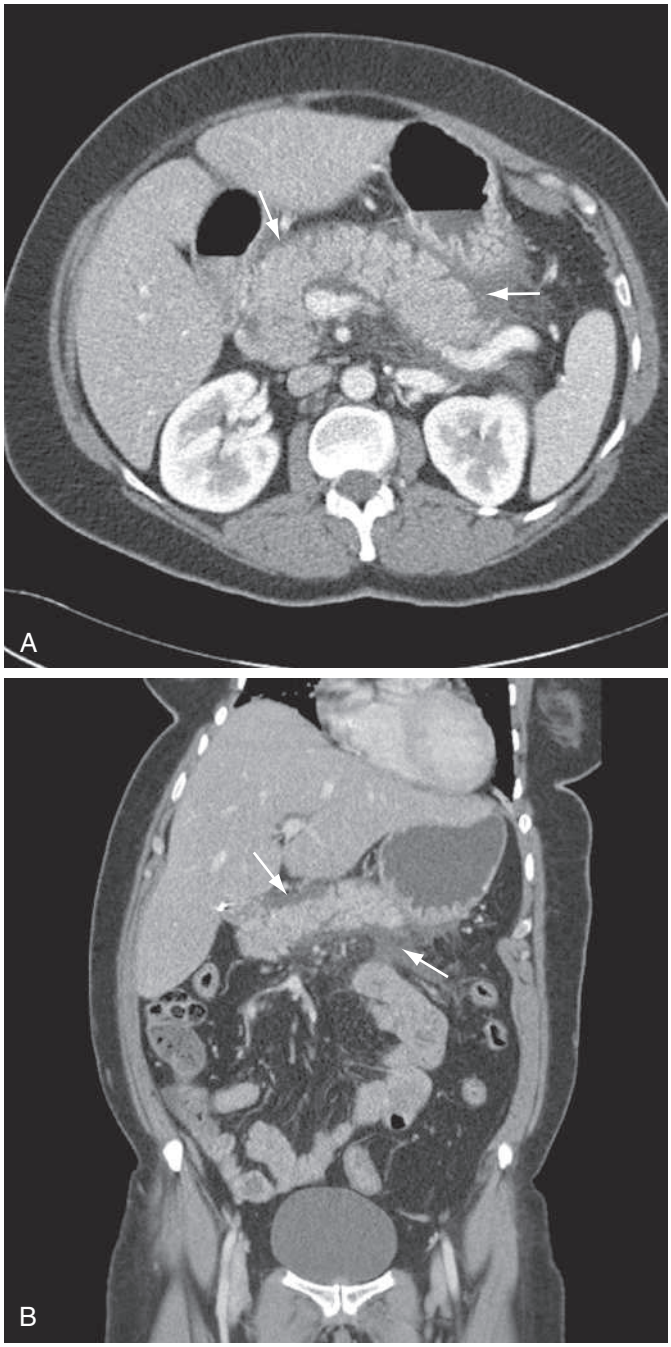

Fig. 77.2 Computed Tomography Scan Showing Acute Interstitial Pancreatitis With Mild Peripancreatic Fluid and Fat Stranding *(Arrows).* (A) Axial view. (B) Coronal view. (Courtesy Dr. David T. Schwartz.)

radiographs show primarily nonspecific findings and do not contribute to the diagnosis of pancreatitis. Chest radiography should be performed in the setting of an abnormal pulmonary exam or when pulmonary complications are suspected.

Predicting Disease Severity. Predicting the disease course in acute pancreatitis is challenging but important given the range in severity from mild cases to the critically ill. A number of classification schemes and severity scoring systems have been developed and these vary in their utility for use in emergency department (ED) management. The 2012 revision of the Atlanta Classification provides a framework to classify acute pancreatitis based on clinical and radiologic criteria

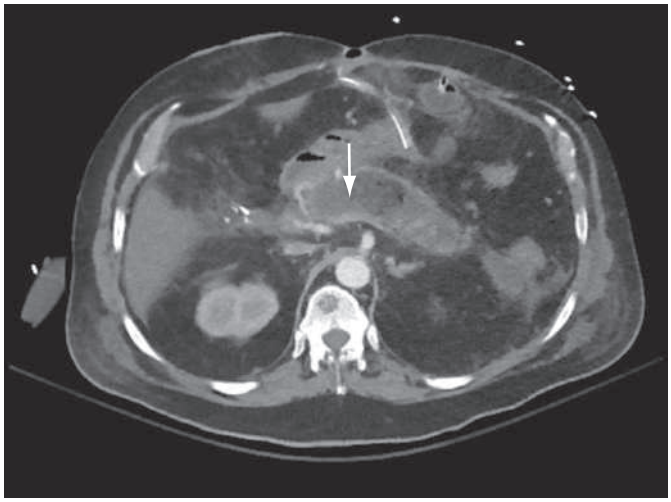

Fig. 77.3 Computed tomography Scan Showing Necrotizing Pancreatitis. There is decreased enhancement of the pancreas where the parenchyma has been replaced by necrotic fluid *(arrow)*. (Courtesy Dr. Cash Horn.)

BOX 77.4 Revised 2012 Atlanta Classification of Acute Pancreatitis

Mild
No organ failure
No local or systemic complications

Moderately Severe
Transient organ failure (<48 h)
Local or systemic complications

Severe
Persistent organ failure (>48 h)
Local complications—acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, walled-off necrosis
Systemic complications—exacerbation of a preexisting comorbidity
Organ failure—defined as a modified Marshall score of 2 or more for the respiratory, cardiovascular, or renal system.

Data from Banks PA, Bollen TL, Dervenis C, et al: Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.

(Box 77.4). This classification delineates three degrees of severity: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis. Under this system, patients cannot be diagnosed with severe pancreatitis until 48 hours following presentation which limits its use in the ED. The oldest and most well-known scoring system to assess the severity of pancreatitis is the Ranson criteria, which uses a combination of clinical features, vital signs, and serum markers at both presentation and 48 hours after admission to predict mortality. Another well-known score is the Acute Physiology and Chronic Health Evaluation II (APACHE II) system, which consists of 15 variables designed for use in the intensive care unit (ICU) to predict mortality. The modified CT severity index (CTSI) is a classification system based on CT imaging. The CTSI allots points for pancreatic enlargement, inflammation, necrosis, fluid collections, and extrapancreatic complications. A Ranson score ≥3, APACHE II score ≥8, and an MCTSI ≥4 are considered high risk for severe disease.

The practicality and usefulness of these tools in ED management are limited by their complexity and reliance on post-admission data. The Bedside Index of Severity in Acute Pancreatitis (BISAP) is a more recently developed scoring system that may improve on this given its simplicity and ability to be calculated during a patient's ED evaluation. The BISAP score evaluates five factors: ***b***lood urea nitrogen (BUN) level, ***i***mpaired mental status, ***S***IRS, ***a***ge, and ***p***leural effusions. These scoring systems (summarized in Table 77.1) show similar predictive accuracy for evaluating the severity of acute pancreatitis.[13–17] The Harmless Acute Pancreatitis Score (HAPS) aims to identify mild cases of acute pancreatitis using just three factors: presence or absence of peritonitis (rebound tenderness or guarding), creatinine, and hematocrit. HAPS has been shown to be 97% specific for mild disease, although it is not sensitive.

Several isolated serum markers have also been proposed as indicators of severity. Procalcitonin has been shown to be a predictor of severe acute pancreatitis, as well as C-reactive protein (CRP); however, CRP is more useful 24 to 48 hours after admission.[18,19] An elevated BUN is linked to poorer outcomes, and hemoconcentration represented by an elevated hematocrit is associated with necrosis; these are included in BISAP and HAPS, respectively.[20]

Management

The treatment of acute pancreatitis is mainly supportive. Fluid resuscitation is important because patients with pancreatitis are often volume depleted from decreased oral intake, emesis, and increased vascular permeability with third-spacing of fluid due to the release of inflammatory mediators. There is some debate regarding how rapidly fluid resuscitation should be undertaken. Inadequate fluid resuscitation in the first 24 hours is associated with increased need for invasive interventions and incidence of SIRS, organ failure, pancreatic necrosis, and ICU admission. There is also some concern that overly rapid fluid resuscitation may result in increased need for mechanical ventilation, abdominal compartment syndrome, and earlier and more frequent development of sepsis.[21]

Although there is a consensus that fluid resuscitation is important, particularly in the first 24 hours of the disease process, recommendations regarding the volume and rate of administration vary.[3,7,22–24] The International Association of Pancreatology (IAP) in collaboration with the American Pancreatic Association (APA) recommends goal-directed fluid resuscitation of 5 to 10 mL/kg/h based on clinical targets of heart rate less than 120/min, mean arterial pressure 65 to 85 mm Hg, and urine output greater than 0.5 to 1 mL/kg/h.[3] The American College of Gastroenterology (ACG) recommends 250 to 500 mL/h.[7] More rapid fluid administration may be necessary in cases of severe volume depletion with significant tachycardia and hypotension. Response to fluid administration and the need for additional therapy should be closely monitored. Hematocrit, BUN, and creatinine can be used as surrogate markers for these goals.[3,7,21,24] Lactated Ringers (LR) solution is thought to have some benefit over normal saline (NS) as the preferred isotonic crystalloid solution for fluid resuscitation in acute pancreatitis and is generally recommended but the evidence for this is not strong.[21,25] Large volumes of NS can result in a hyperchloremic metabolic acidosis. Acidosis can worsen the systemic inflammatory response and activate trypsinogen, thereby making pancreatic acinar cells more prone to injury and exacerbating the disease process. LR may also provide antiinflammatory benefits in patients with acute pancreatitis.[26] Colloids have not been shown to improve outcomes when compared with crystalloids and are not generally recommended; however, colloid administration may be beneficial in cases with a hematocrit of less than 24 or albumin less than 2 g/dL. We recommend moderate fluid resuscitation based on hemodynamic assessment with

TABLE 77.1 Summary of Severity Scoring Systems

Ranson Criteria	APACHE II Variables	Modified CTSI	BISAP
At admission	Age	**Pancreatic inflammation**	BUN > 25 mg/dL
Age > 55 years	Temperature	0: normal pancreas	Impaired mental status
WBC > 16,000/mm^3	Mean Arterial Pressure	2: intrinsic pancreatic abnormalities ± inflammatory changes in peripancreatic fat	• disorientation, lethargy, somnolence, coma
Glucose > 200 mg/dL	Heart Rate	4: pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis	≥ SIRS criteria
AST > 250 IU/L	Respiratory Rate	**Pancreatic necrosis**	Age > 60 years
LDH > 350 IU/L	PaO_2	0: none	Pleural effusion present
At admission (if biliary cause)	pH or HCO_3	2: 30% or less	
Age > 70 years	Serum sodium	4: more than 30%	
WBC > 18,000/mm^3	Serum potassium	**Extrapancreatic complications**	
Glucose > 220 mg/dL	Serum creatinine	2: one or more of pleural effusion, ascites, vascular complications, parenchymal complications and/or gastrointestinal involvement	
AST > 250 IU/L	Hematocrit		
LDH > 400 IU/L	WBC count		
At 48 h	Glasgow Coma Scale		
Hematocrit drop > 10%	Chronic health problems:		
BUN rise > 5 mg/dL	• Cirrhosis of the liver confirmed by biopsy		
Calcium < 8 mg/dL	• New York Heart Association Class IV		
PaO_2 < 60 mm Hg	• Severe COPD		
Base deficit > 4 mEq/L	• Hypercapnia, home O_2 use, or pulmonary hypertension		
Fluid needs > 6 L	• On regular dialysis		
At 48 h (if biliary cause)	• Immunocompromised		
Hematocrit drop > 10%			
BUN rise > 2 mg/dL			
Calcium < 8 mg/dL			
Base deficit > 5 mEq/L			
Fluid needs > 4 L			

APACHE, Acute Physiology and Chronic Health Evaluation; *AST,* aspartate transaminase; *BISAP,* Bedside Index of Severity in Acute Pancreatitis; *BUN,* blood urea nitrogen; *CTSI,* computed tomography severity index; *COPD,* chronic obstructive pulmonary disease; *LDH,* lactate dehydrogenase; *PaO2,* partial pressure of oxygen; *SIRS,* systemic inflammatory response syndrome; *WBC,* white blood cell.

LR at a rate of 5 to 10 mL/kg/h over the first 2 hours followed by 1.5 to 3 mL/kg/h for 12 to 24 hours with an overall goal of 2 to 4 L over the first 24 hours. If necessary, vasopressors (we recommend norepinephrine) should be initiated to maintain a map of 65 mm Hg.

As fluid status is being corrected, electrolyte levels may also need to be addressed. Hypocalcemia is frequently due to hypoalbuminemia, so calcium replacement is not necessary unless the ionized calcium level is low, in cases of QT prolongation or cardiac dysrhythmias, or when neuromuscular effects of hypocalcemia, such as Chvostek or Trousseau sign, are present. When concurrent hypomagnesemia is present, magnesium repletion should be done prior to correction of hypocalcemia. Hyperglycemia results from impaired insulin release, increased gluconeogenesis, and alterations in glucose uptake. Some patients will require exogenous insulin because untreated hyperglycemia may contribute to worsening pancreatitis and immune function.

Pain control is another important aspect of management. No specific analgesia strategy is found to be superior.[27] We recommend acetaminophen 1 g every 6 hours (650 mg PO every 8 hours in patients with liver disease or severe alcoholism) for initial pain control. Opioids should generally be avoided because they can promote ileus but may be required in some cases due to the severity of pain associated with pancreatitis. No particular opioid has been found to be more beneficial. Morphine is thought to possibly cause sphincter of Oddi spasm; however, there are no clinical studies showing that the administration of morphine causes or worsens pancreatitis or cholecystitis. Low-dose ketamine (0.1 to 0.3 mg/kg IV) is an opioid sparing alternative for parenteral pain management. Nonsteroidal antiinflammatory agents should be avoided in critically ill patients due to the increased risk of acute kidney injury. Antiemetics may also be needed for symptomatic relief.

Bowel rest by nothing per os (NPO) was once a standard part of the treatment of acute pancreatitis due to concern that oral or enteral nutrition would worsen disease by stimulating pancreatic secretions leading to autodigestion. It is now recognized that withholding enteral feeding may be detrimental because it can lead to gastrointestinal mucosal atrophy and bacterial overgrowth and translocation of gut bacteria. The alternative of total parenteral nutrition (TPN) is known to have many complications. Enteral nutrition provides nutritional support, can preserve gut function, and may help to regulate the systemic inflammatory response system.[28] In mild cases of acute pancreatitis, early oral feeding has found to be safe and may decrease length of hospitalization.[29]

Prophylactic antibiotics are not indicated in the treatment of acute pancreatitis because they have not been found to reduce the incidence of infected pancreatic necrosis.[3,7,30] Even in severe cases of pancreatitis, antibiotic prophylaxis has not been shown to improve mortality or the need for surgical intervention. Their use should be limited to toxic-appearing patients, those with infected necrotizing pancreatitis, and extrapancreatic infections such as cholangitis, pneumonia, and bacteremia. SIRS features such as tachycardia and tachypnea are common in acute pancreatitis but are nonspecific and do not necessarily portend sepsis or organ failure. Severe acute pancreatitis may be difficult to differentiate from sepsis during the ED presentation, and therefore antibiotics should be initiated if there is suspicion of an infectious source or sepsis. In cases of known infected pancreatic necrosis, the chosen antibiotic regimen should penetrate pancreatic tissue and cover gram-negative and gram-positive bacteria as well as anaerobes; carbapenems (meropenem 1 g, ertapenem 1 g, or imipenem-cilastin 500 mg) and quinolones with metronidazole (ciprofloxacin 400 mg with metronidazole 500 mg) are appropriate choices.[7]

ERCP in patients with gallstone pancreatitis without evidence of ongoing obstruction is not recommended because most gallstones will spontaneously pass into the duodenum. Early ERCP is indicated for patients with cholangitis or bile duct obstruction and is recommended within 24 to 48 hours of admission. Unstable patients who are unable to safely undergo ERCP may require biliary decompression with the placement of a percutaneous transhepatic gallbladder drainage tube. Suspicion of choledocholithiasis based on a dilated biliary tree on CT does not itself warrant ERCP. In the absence of cholangitis or clear evidence of biliary obstruction (e.g., jaundice, hyperbilirubinemia, and signs of sepsis), MRCP or EUS is preferred over ERCP because ERCP is a more invasive study and can itself trigger pancreatitis. No benefit of ERCP has been shown in patients with nonobstructive causes of pancreatitis regardless of severity.

Surgical intervention is rarely indicated at the time of presentation. It is recommended that patients with mild biliary pancreatitis undergo cholecystectomy during the index admission but not emergently. In cases of severe acute pancreatitis, surgical intervention is determined on a case-by-case basis, but cholecystectomy is generally delayed. Asymptomatic pancreatic necrosis and pseudocysts do not need treatment. Infected or symptomatic necrotizing pancreatitis often requires surgical, endoscopic, or radiologic intervention, but this is recommended after 3 to 4 weeks to allow better demarcation of the viable pancreatic tissue and area of necrosis.

Disposition

Discharge may be considered in well-appearing patients with mild presentations, adequately controlled symptoms, tolerance of oral intake, and no signs of complications. However, given the unpredictable course of pancreatitis and potential of decompensation and severity, inpatient management is typically warranted. Patients with severe symptoms, persistent pain, intolerance of oral intake, and gallstone disease and those who are older with comorbidities will likely require admission. ICU admission should be considered for patients with moderately severe and severe acute pancreatitis, persistent vital sign abnormalities, significant electrolyte abnormalities, older age and those deemed at high risk for deterioration. Patients who may require endoscopic, surgical, or interventional radiology procedures should be managed in or referred to a specialist center, defined as a high-volume center with daily access to these services.

Chronic Pancreatitis

Foundations

Chronic pancreatitis is a progressive fibroinflammatory syndrome of the exocrine pancreas. It is thought that pancreatitis is a continuum which is initiated with the inflammation of acute pancreatitis and progresses to chronic pancreatitis by repeated pancreatic injury due to recurrent episodes of acute pancreatitis. Recurrent inflammation of the pancreas leads to atrophy and fibrosis resulting in the destruction of acinar cells and the islets of Langerhans and thereby impairing both pancreatic exocrine and endocrine function. Approximately 36% of those with recurrent acute pancreatitis will go on to develop chronic pancreatitis.[31] Although both sexes have an equal risk of developing acute pancreatitis, men are twice as likely to progress to chronic pancreatitis compared with women.[31,32] Blacks are twice as likely to be diagnosed with chronic pancreatitis compared with White patients, in large part due to the prevalence of alcohol and tobacco use which are both significant risk factors.[31,33] Those with chronic pancreatitis are at higher risk of developing pancreatic cancer. Chronic pancreatitis can be classified as toxic-metabolic, idiopathic, genetic, autoimmune, related to recurrent and severe acute pancreatitis, and obstructive (Box 77.5).

BOX 77.5 TIGAR-O Causes of Chronic Pancreatitis

Toxic-Metabolic
Alcohol
Tobacco
Hypercalcemia
Hypertriglyceridemia
Chronic kidney disease
Medications

Idiopathic
Tropical chronic pancreatitis
Early onset
Late onset

Genetic
Autosomal dominant: hereditary pancreatitis
PRSS1 mutations

Autosomal Recessive/Modifier Genes
CFTR mutations
SPINK1 mutations
CTRC mutations
Other

Autoimmune
Type 1 (IgG4 related) and type 2

Recurrent and Severe Acute Pancreatitis
Postnecrotic (after severe necrotizing pancreatitis)
Vascular disease/ischemia

Obstructive
Pancreas divisum
Sphincter of Oddi disorders
Malignant pancreatic duct obstruction
Posttraumatic pancreatic duct scars and strictures

CFTR, Cystic fibrosis transmembrane conductance regulator; *CTRC,* chymotrypsin C; *IgG,* immunoglobulin G; *PRSS1,* cationic trypsinogen; *SPINK1,* serine protease inhibitor Kazal type 1.

Clinical Features

Patients with chronic pancreatitis often present similarly to those with acute pancreatitis: severe postprandial epigastric pain associated with nausea and vomiting that may radiate to the back and be helped by sitting forward. Exocrine pancreatic insufficiency may result in weight loss, steatorrhea, and signs of malnutrition and malabsorption. Endocrine pancreatic insufficiency may present in the form of diabetes and these patients are also at higher risk for hypoglycemia due to loss of counterregulatory glucagon and pancreatic polypeptide. Patients with alcoholic cirrhosis or biliary obstruction may be jaundiced. The abdomen is usually tender, and a palpable mass representing a pancreatic pseudocyst or tumor may be appreciated. Common complications of chronic pancreatitis include pseudocysts, pancreatic ascites, ductal strictures, duodenal stenosis, pleural effusions, pseudoaneurysms (splenic, hepatic, gastroduodenal, pancreaticoduodenal arteries), and portal and splenic vein thromboses.

Differential Diagnoses

The list of alternative diagnoses is similar to that for acute pancreatitis (see Box 77.3); however, chronic abdominal processes, such as peptic

ulcer disease, gastritis, biliary colic, pancreatic cancer, inflammatory bowel disease, and irritable bowel syndrome, should also be considered as alternative diagnoses for patients with recurrent episodes of upper abdominal pain. In addition, patients with chronic pancreatitis who are opioid dependent may have withdrawal symptoms that mimic an exacerbation of pancreatitis.

Diagnostic Testing

Clinical diagnosis of chronic pancreatitis may be challenging, particularly in its early stages. For acute exacerbations of chronic pancreatitis, the same diagnostic principles apply as for acute pancreatitis—clinical features, laboratory analysis, and imaging. However, laboratory tests are less helpful in chronic pancreatitis because serum lipase and amylase levels do not rise to the same degree and may be normal. Liver function test results (transaminase, alkaline phosphatase, bilirubin levels) may be elevated in patients with concurrent alcoholic liver disease or biliary duct obstruction. Hypocalcemia and hypoalbuminemia are common, and impaired pancreatic endocrine function may be reflected by hyperglycemia.

CT is the imaging modality of choice, and as with acute pancreatitis, it may be of limited utility in early or mild disease and is more helpful in evaluating later findings and complications. Intraductal pancreatic calcifications are the most specific finding on both CT and US. Other CT findings of chronic pancreatitis include pancreatic enlargement, dilated pancreatic ducts, pancreatic calcifications, atrophy, biliary duct dilatation, fluid collections, and changes in panpancreatic fat.[34] MRCP is superior at evaluating pancreatic duct abnormalities, and its ability to detect signal intensity changes in the pancreas may be useful in evaluating chronic pancreatitis at its early stages. Pancreatic stimulation with IV secretin may improve the diagnostic accuracy of MRCP.[35] CT, MRCP, EUS, and US have high diagnostic sensitivity for chronic pancreatitis and comparable diagnostic specificity.[36] US findings include pancreatic enlargement, calcification, and decreased echogenicity. EUS and ERCP have the highest diagnostic accuracy but are invasive tests, and ERCP is generally not recommended because it carries a 4% risk of precipitating pancreatitis. Although an abdominal radiograph is not necessary, up to 30% of patients have a characteristic finding of pancreatic calcification, which is pathognomonic for the disease. Abdominal imaging findings have not found to be predictive of pain pattern and severity.[33]

Management

The treatment of chronic pancreatitis is supportive and largely focused on pain management, correction of fluid and electrolyte imbalance, and lifestyle modification with the cessation of alcohol and tobacco use. Nonopioid pain medications such as acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are preferred as initial agents, although NSAIDs should be used judiciously due to their adverse effects on the gastrointestinal system and the predisposition of patients with chronic pancreatitis to peptic ulcer disease.[37,38] Given the severity of pain in chronic pancreatitis, it will likely be necessary to escalate to tramadol or more potent opioid analgesics; however, opioids should also be used with caution given the risk of misuse and dependence as well as adverse gastrointestinal effects such as opioid induced bowel dysfunction.[37,38] Adjunctive agents in the treatment of chronic pain such as tricyclic antidepressants, serotonin-reuptake inhibitors, and gabapentoids may also play a role in pain management.[38,39] In patients who fail traditional medical management, other pain control options with varying supportive evidence include oral enzyme replacement, octreotide, antioxidants, and celiac plexus block. Referral to a pain management specialist may be beneficial given the challenge of pain control, its chronicity, and risk of addiction.

Beyond ED care, endoscopy may be indicated for intraductal stone removal, stenting of ductal structures, and the drainage of symptomatic pseudocysts.[37,40] Surgical management is considered for duodenal or biliary obstruction, pancreatic drainage procedures, and in cases where cancer is suspected. Surgery is generally reserved for patients who have failed medical and endoscopic therapy, but some studies indicate that early surgery may be of benefit in the treatment of pain and improvement of pancreatic insufficiency.[40–43]

Disposition

Patients with chronic pancreatitis typically present to the ED with acute exacerbations of pain or complications of their disease. The prognostic indices used for acute pancreatitis can be applied to these patients. Most patients will require admission; chronic pancreatitis is emerging as the leading contributor of hospitalizations due to acute pancreatitis.[5]

PANCREATIC CANCER

Foundations

Pancreatic cancer is an aggressive and lethal disease which is the seventh most common cause of death from cancer globally.[44] Its incidence is greater in developed countries, and most patients are diagnosed older than 50 years of age, with peak incidence in the seventh and eight decades of life. Blacks have both a higher incidence and mortality when compared with Whites.[45–47] The median survival of patients with locally advanced disease is 6 to 9 months and only 3 months for those with metastatic progression. Pancreatic cancer carries an overall 5-year survival rate of just 7% owing to its often advanced stage at diagnosis, rapid progression of disease, and resistance to treatment options.[47] Risk factors for disease include tobacco use, alcohol abuse, obesity, type 2 diabetes mellitus, chronic pancreatitis, and a family history of pancreatic cancer.[48] The majority of pancreatic neoplasms are adenocarcinomas followed by neuroendocrine tumors such as gastrinomas (Zollinger-Ellison syndrome), insulinomas, and glucagonomas.

Clinical Features

Pancreatic cancer typically presents with epigastric pain often radiating to the back, unexplained weight loss, anorexia, nausea, and generalized weakness. Obstructing tumors may lead to cholestasis, jaundice, pancreatitis, and gastric outlet obstruction. Newly diagnosed diabetes is also a common presenting sign. Neuroendocrine tumors present with symptoms indicative of the hormone secreted by the tumor. For example, insulinomas are associated with hypoglycemia, glucagonomas with glucose intolerance, weight loss, and dermatitis, and gastrinomas with peptic ulcers, gastroesophageal reflux disease, and diarrhea. Most patients at the time of diagnosis have locally advanced disease, vascular involvement, and metastatic spread most commonly to the liver, peritoneum, and lungs.

Diagnostic Testing

Abdominal CT with IV contrast is the imaging modality of choice for diagnosis and guiding initial management. On CT, pancreatic carcinoma appears as an area of hypoattenuation. CT may also show secondary signs such as pancreatic duct cutoff, dilation of the pancreatic or common bile duct, atrophy, or border irregularities. Smaller tumors (<10 mm) are better detected on EUS than CT, and EUS guided fine-needle aspiration is often necessary to make a tissue diagnosis.[49]

Management

Treatment in the ED generally involves pain control and management of complications such as gastrointestinal bleeding, bowel obstruction, acute cholangitis, and venous thrombosis. In situations where the diagnosis of pancreatic cancer is made in the ED, the disease process may

be advanced, and patients may benefit from the emergency clinician expediting their evaluation and facilitating multidisciplinary involvement in the patient's case.

Surgical resection can be curative but is only possible in a very small subset of patients with no direct tumor extension. Ampullary masses, which make up a small percentage of cases, are associated with a better prognosis (up to 50% may be successfully resected) because they tend to cause biliary obstruction, leading to earlier presentation and diagnosis. The surgical management of pancreatic head tumors is usually a partial pancreaticoduodenectomy (also known as the Whipple procedure) with or without partial resection of the distal stomach. Tumors of the pancreatic tail generally require a distal pancreatectomy with splenectomy. Less than 20% of patients are diagnosed with resectable disease, and 80% of those who undergo surgical treatment and will relapse and ultimately die.[48] In patients with locally and systemically advanced disease, treatment is generally focused on slowing tumor progression and palliative care. Chemotherapy and radiation may prolong survival to a small extent. Identifying patients earlier in their disease course through risk determination and screening efforts may increase surgical treatment options and improve survival.[50,51]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 77: QUESTIONS AND ANSWERS

1. Which of the following statements regarding acute pancreatitis is true?
- **a.** Esophageal ultrasound is the diagnostic imaging of modality of choice for the diagnosis of acute pancreatitis.
- **b.** Hypertriglyceridemia is the likely etiology of acute pancreatitis in those with serum triglyceride levels greater than 1000 mg/dL.
- **c.** The most common cause of acute pancreatitis is alcohol abuse.
- **d.** Acute pancreatitis is the most lethal pancreatic disease globally.
- **e.** Pancreatic pseudocysts form within the first week of symptom onset.

Answer: b. Serum triglyceride levels greater than 1000 mg/dL with no other clear causes of acute pancreatitis points to hypertriglyceridemia as the etiology. Imaging is not routinely recommended in the diagnosis of acute pancreatitis. CT is the diagnostic modality of choice; endoscopic ultrasound (EUS) is invasive and not recommended as a first line imaging test. Although acute pancreatitis is the most common pancreatic disease globally, pancreatic cancer carries the highest mortality. Pancreatic pseudocysts generally form after 4 weeks from symptom onset.

2. Which of the following statements about serum lipase and amylase levels is true?
- **a.** Lipase is an enzyme which aids in the digestion of carbohydrates.
- **b.** In acute pancreatitis, amylase levels rise in 1 or 2 hours and normalize in 2 days.
- **c.** Higher lipase and amylase levels are correlated with more severe disease.
- **d.** Amylase is a less specific test than the serum lipase level for the diagnosis of pancreatitis.
- **e.** Testing for both lipase and amylase enzymes improves the diagnostic sensitivity and specificity for acute pancreatitis.

Answer: d. Lipase is more specific than amylase in the diagnosis of acute pancreatitis as amylase is produced by multiple organs other than the pancreas and lipase is produced predominantly by the pancreas. Lipase aids in the breakdown of dietary triglycerides into free fatty acids while amylase aids in the breakdown of carbohydrates. Levels rise within 6 to 24 hours and normalize in 3 to 7 days. Higher enzyme levels have not been found to correlate with disease severity. Testing for both enzymes has not been found to improve diagnostic sensitivity and specificity in the diagnosis of acute pancreatitis.

3. Which of the following statements regarding the use of radiographic studies for the evaluation of pancreatitis is true?
- **a.** Computed tomography (CT) is indicated in the evaluation of all cases of pancreatitis.
- **b.** Oral administration of a contrast agent for abdominal CT may aggravate pancreatitis.
- **c.** The initial study of choice in suspected gallstone pancreatitis is ultrasonography.
- **d.** CT and magnetic resonance imaging (MRI) of the abdomen are equally accurate for visualizing the biliary tract.
- **e.** Ultrasonography may help to differentiate pancreatitis from pancreatic pseudocyst.

Answer: c. Ultrasonography has a sensitivity of 94% for gallstones further imaging may be necessary to rule out biliary tract pathology. CT is not routinely recommended in the diagnosis of acute pancreatitis but is recommended in cases of diagnostic uncertainty, to rule out other diagnoses, and to assess for complications in patients who worsen or fail to improve. Oral contrast material does not aggravate pancreatitis. A non–contrast-enhanced helical scan may also be helpful if an oral contrast agent cannot be tolerated. MRI is superior to CT in visualizing the biliary tract although often more costly and less accessible. Ultrasonography is generally not helpful in assessing for pseudocysts.

4. A 28-year-old woman presents with recurrent pancreatitis. She is otherwise healthy and takes no medications. This episode of pain was preceded by several similar episodes of intermittent epigastric pain that lasted several hours at a time. A previous ultrasound examination of the liver, gallbladder, and pancreas was normal. She does not smoke, drink, or use over-the-counter medications. The physical examination is remarkable for moderate epigastric tenderness without rebound. Vital signs are normal. Laboratory evaluation reveals an elevated lipase level and moderate leukocytosis. Urinalysis and urine pregnancy test results are normal. What would be the most appropriate intervention?
- **a.** After stabilization, referral to a gastroenterologist for endoscopic retrograde cholangiopancreatography (ERCP)
- **b.** After stabilization, referral to a gastroenterologist for upper endoscopy
- **c.** CT scan of the abdomen to rule out pancreatic pseudocyst
- **d.** Repeated ultrasound examination of the liver, gallbladder, and pancreas
- **e.** Symptomatic treatment only unless her clinical picture worsens

Answer: a. Many cases of presumed idiopathic pancreatitis may be due to small stones or sludge that cannot be seen by ultrasound examination but may be seen by ERCP. Pancreatic pseudocyst is more likely in alcoholic pancreatitis and typically occurs gradually, several months after a severe episode.

CHAPTER 77: QUESTIONS AND ANSWERS—cont'd

5. A 68-year-old male presents with several months of epigastric pain, decreased appetite, weight loss, and weakness. Which of the following statements is true?

a. CT scan will rule out the diagnosis of pancreatic cancer.
b. His pancreatic adenocarcinoma is most likely to be confined to the pancreas.
c. Following the diagnosis of pancreatic adenocarcinoma, chemoradiation will be curative.
d. Chronic pancreatitis is a risk factor for developing pancreatic cancer.
e. Those residing in developing countries are at higher risk for pancreatic cancer.

Answer: d. Those with chronic pancreatitis are at higher risk of developing pancreatic cancer. Abdominal CT is the initial imaging modality of choice for the diagnosis of pancreatic cancer; however, smaller tumors (<10 mm) are better detected on EUS. Less than 20% of patients are diagnosed with localized and resectable disease. Chemoradiation is generally focused on slowing tumor progression and palliative therapy but is unlikely to be curative without resection. The incidence of pancreatic cancer is higher in developed countries.

78

Small Intestine

Chad E. Roline and Robert F. Reardon

SMALL BOWEL OBSTRUCTION

KEY CONCEPTS

- Small bowel obstruction (SBO) is a common clinical condition accounting for 2% of patients presenting to the emergency department with abdominal pain, leading to an estimated 300,000 hospitalizations annually in the United States.
- The most common cause of SBO is adhesions from prior abdominal surgery, which are found in approximately 60% of cases. Tumors and abdominal hernias account for another 20% and 10% of cases, respectively.
- The most common presenting symptoms of SBO include colicky abdominal pain, abdominal distention, nausea, or vomiting. However, no single component of the history or physical exam can reliably predict SBO.
- Initial evaluation should focus on identifying SBO patients in need of prompt surgical evaluation including findings concerning for peritonitis, bowel strangulation, or ischemia.
- For patients presenting with SBO likely due to adhesions, most can be successfully managed conservatively with bowel rest, pain control, intravenous fluid, and electrolyte replacement.

FOUNDATIONS

Background and Importance

Small bowel obstruction (SBO) is a common problem encountered in the emergency department (ED). Advances in imaging as well as operative techniques have greatly improved the prognosis for patients and have decreased the mortality rate from nearly 60% in 1900 to less than 8% today.

Anatomy, Physiology, and Pathophysiology

There are several different types of SBO. The term *mechanical obstruction* implies the presence of a physical barrier to the movement of the intestinal contents. Obstructions of this type can be further subclassified according to the cause of the obstruction relative to the intestinal wall (Box 78.1). Lesions external to the intestinal tract cause obstruction by compressing the gut. This is most commonly the result of post-operative adhesions, though hernias and intra-peritoneal neoplasms may also cause external obstruction. Lesions intrinsic to the intestinal wall itself can also cause mechanical obstruction, such as primary intestinal neoplasms, localized infection (e.g., intestinal wall tuberculosis), or trauma (e.g., a hematoma of the intestinal wall). Finally, lesions within the intestinal lumen can lead to obstruction, such as bezoars, ingested foreign bodies, or gallstone ileus.

Another important distinction of SBO is whether the obstruction is a *simple* or *closed loop* obstruction. A simple obstruction occurs at a single point. A closed loop–type obstruction involves obstruction at two locations, thus creating a segment of bowel with compromised blood flow proximally and distally. Closed loop obstructions are seen when a twist develops in the mesentery or, in the case of an internal hernia, when a loop of bowel becomes entrapped in a defect in the mesentery (Fig. 78.1). If not promptly recognized and relieved, a closed loop obstruction can quickly lead to intestinal infarction and necrosis, which has twice the mortality rate of simple small bowel obstruction.

In contrast to a mechanical obstruction, a *neurogenic* or *functional* obstruction occurs as a result of disruption of the normal coordinated peristaltic activity of the gastrointestinal (GI) tract in the absence of a physical blockage within the intestinal lumen, leading to dysfunction in the enteric propulsion. This is also commonly referred to as an adynamic ileus. The causes of adynamic ileus are listed in Box 78.2. It often occurs in patients who have undergone abdominal surgery and is usually transient in nature. Some degree of functional obstruction is considered normal after surgery and results from multiple factors, including an inflammatory response to intestinal manipulation, the release of several hormones and neurotransmitters triggered by surgery, and the effects of opioid analgesics. In addition to surgery, a number of medical conditions can lead to a functional SBO, including infection or metabolic abnormalities, particularly hypokalemia.

The term *pseudo-obstruction* refers to a poorly understood and complex syndrome in which the signs and symptoms of mechanical obstruction, including the appearance of dilated bowel on radiography, are present in the absence of a mechanical lesion. This is thought to involve disruption of intestinal pacemaker activity controlled by a specialized group of cells found in the GI tract called the interstitial cells of Cajal. These cells regulate the contractility of the intestinal smooth muscle and are under the influence of the enteric nervous and autonomic systems. Pathology at any one of these sites can lead to pseudo-obstruction. Causes include degenerative neuropathies, autoimmune or paraneoplastic disease including systemic lupus erythematosus, or scleroderma, as well as hereditary conditions. The symptoms of pseudo-obstruction are often chronic and respond poorly to treatment.

PATHOPHYSIOLOGY

Regardless of the etiology, with the development of an SBO the interruption of normal flow through the intestinal lumen triggers a cascade of physiologic changes that correlate with the progressive development of symptoms. In a mechanical obstruction, the bowel proximal to the blockage first becomes mildly dilated through the accumulation of partially digested food and normal intestinal secretions. These secretions are referred to as *succus entericus* and are secreted by cells lining the intestinal wall in response to mechanical stimulation. Increased intestinal dilation causes an increase in peristalsis throughout the intestines, which can trigger frequent and loose bowel movements early in the progression of the obstruction as well as episodes of nausea or vomiting.

BOX 78.1 Lesions Causing Small Bowel Obstruction Relative to the Intestinal Wall

External to Intestinal Wall
Postoperative adhesions
Hernias
Volvulus
Compressing masses (tumors, abscesses, hematomas)

Intrinsic to Intestinal Wall
Primary neoplasms
Inflammatory (e.g., Crohn disease, radiation enteritis)
Infectious causes (e.g., intestinal tuberculosis)
Intussusception
Traumatic (intestinal wall hematoma)
Intraluminal
Bezoars
Foreign bodies
Gallstones
Ascaris infestation

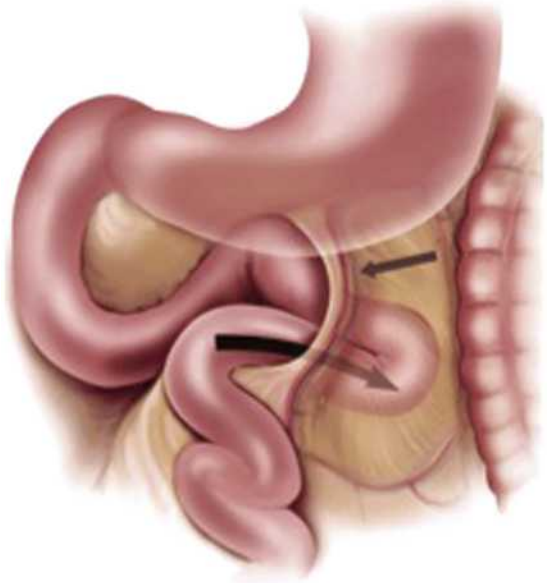

Fig. 78.1 Diagram of Internal Hernia. Note the formation of a closed loop, which creates a high risk for strangulation (*arrows*). (From Martin LC, Merkle EM, Thompson WM. Review of internal hernias: radiographic and clinical findings. *AJR Am J Roentgenol.* 2006;186:703–717. Reprinted with permission from the *American Journal of Roentgenology*.)

BOX 78.2 Causes of Adynamic Ileus

Metabolic disease (especially hypokalemia)
Medications (e.g., narcotics)
Infection (retroperitoneal, pelvic, intrathoracic)
Abdominal trauma
Laparotomy

As the process continues, the bowel wall becomes edematous and the normal absorptive function of the intestinal wall decreases, leading to further accumulation of contents in the intestinal lumen proximal to the obstruction. Owing to the loss of normal intestinal motility, bacterial overgrowth begins to occur in the proximal small bowel. It is this overgrowth in a location of the intestines that is normally relatively sterile that explains the feculent nature of the emesis observed in patients with SBO. As the obstruction continues, there is a transudative fluid loss into the peritoneal cavity, leading to worsening hypovolemia and dehydration. In addition, if the obstruction is proximal in location, continued bouts of emesis can lead to electrolyte abnormalities, metabolic alkalosis, severe hypovolemia, or shock.

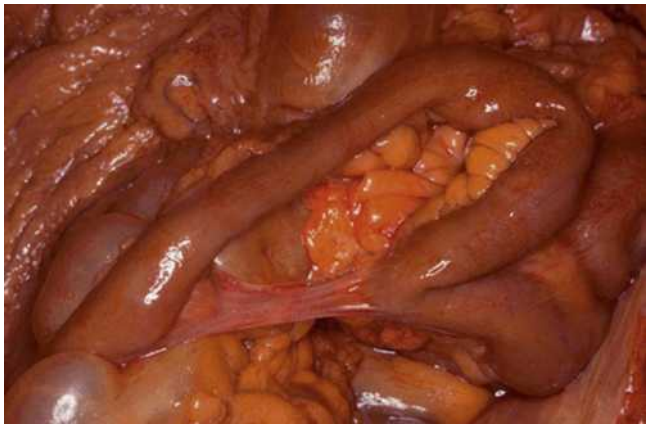

Fig. 78.2 Small Bowel Adhesion. (Courtesy Edward Klatt, MD.)

In a closed loop obstruction, the escalation in intraluminal pressure occurs much more rapidly as the intestinal contents cannot flow retrograde. Intestinal venous congestion and then arterial obstruction can also progress quickly to intestinal ischemia and infarction, referred to as a *strangulation* obstruction. If not promptly relieved, necrosis and intestinal perforation can occur. The resulting leakage of the intestinal contents into the peritoneum can lead to peritonitis and sepsis.

In the developed world, the most common cause of SBO is postoperative adhesions, which account for approximately 60% of cases (Fig. 78.2). A large meta-analysis estimated the overall incidence of adhesive SBO following abdominal surgery at 2%.[1] These adhesions develop as a result of a process involving the interaction among numerous types of cells, cytokines, and coagulation factors caused by damage to the peritoneal surfaces, with a subsequent increase in fibrin formation.[2] Operations on the small intestine, colon, appendix and uterus appear to have a higher risk of adhesion formation than procedures in the upper abdomen involving the gallbladder, stomach or pancreas. Emergency surgery also appears to be a risk factor compared to elective procedures.[3] Over the last several years, numerous physical bioabsorbable barriers and pharmacologic agents have been evaluated as potentially useful in decreasing the formation of post-operative adhesions with mixed results. Although they appear to minimize the formation of postoperative adhesions, they have not been shown to improve clinical outcomes.

The second most common cause of SBO is tumors, which are responsible for roughly 20% of cases. This includes malignancies, such as adenocarcinomas, carcinoid tumors, lymphomas, or sarcomas, as well as benign conditions, including adenomas, leiomyomas, or lipomas. In addition to these primary GI tumors, gynecologic cancers, especially ovarian cancer, are a common cause of SBO. Metastatic disease is yet another tumor-related cause of SBO, including metastatic breast, skin, or testicular cancer.

Hernias are the third most common cause of SBO, found in approximately 10% of cases. Similar to their relative frequency in general, ventral and inguinal hernias are usually encountered, but femoral, parastomal, lateral ventral (also called *spigelian hernia*), and internal hernias may also lead to SBO. Although rare in the general population, internal hernias are a recognized complication of bariatric surgery,

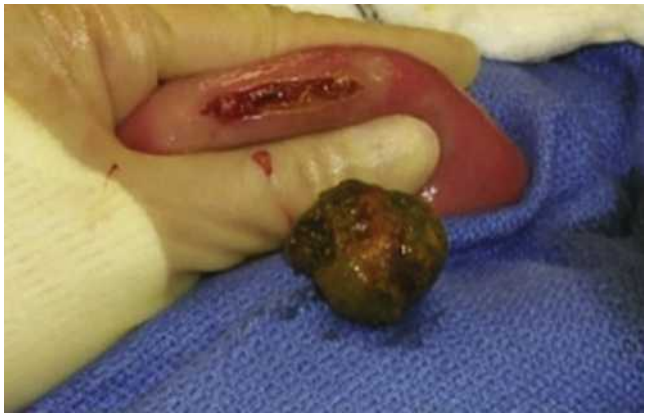

Fig. 78.3 Gallstone Ileus of the Small Intestine at Laparotomy. (Courtesy J.C. Campbell, Plymouth, England; www.surgical-tutor.org.uk.)

especially when a Roux-en-Y type procedure has been performed. In this group, internal hernias have been described in up to 5% of patients and usually develop at the mesocolic window. Another rare type of hernia is the obturator hernia. This hernia develops into the obturator foramen and is especially common in older women who have recently lost a significant amount of weight. The female pelvis is wider and the obturator canal is more oblique in women than in men. This, in combination with a loss of preperitoneal fat in older, often emaciated patients, predisposes to the development of an obturator hernia. Because an external mass is absent, the diagnosis can be especially challenging, which explains why it carries the highest mortality of any abdominal hernia, nearly 70%, when it is incarcerated.

Gallstone ileus is a rare but important cause of mechanical SBO (Fig. 78.3). It is responsible for 1% to 4% of all cases of mechanical obstruction and is most frequently seen in older adults with underlying medical problems. The pathogenesis involves the entry of a gallstone into the intestinal tract through a biliary-enteric fistula. This arises from the localized inflammation of cholecystitis and, in most cases, entry occurs via a cholecystoduodenal fistula. After entering the intestinal lumen, the gallstone migrates distally. As a stone moves through the intestinal lumen, it often increases in size as bowel content sedimentation becomes attached. Eventually, the gallstone becomes lodged, usually in the ileum, which is the narrowest segment of the small bowel, and the patient then develops symptoms of obstruction.

Small bowel volvulus occurs infrequently but is a potentially catastrophic cause of SBO. This condition results from the abnormal twisting of a loop of small bowel around the axis of its own mesentery. Although it accounts for only 3% to 6% of SBO cases in the West, it is much more common in Africa, India, and the Middle East, where it is responsible for up to 20% of cases. Primary small bowel volvulus occurs in an otherwise normal abdominal cavity; secondary small bowel volvulus occurs when a congenital or acquired abnormality leads to the development of the volvulus.

A reported increase in primary small bowel volvulus during Ramadan has been attributed to eating a large amount of food bulk after prolonged fasting, causing the proximal jejunum to descend into the pelvis, displacing empty small bowel loops upward and initiating malrotation. Alterations in gut motility and increased small bowel length have also been suggested as possible predisposing factors.

Causes of secondary small bowel volvulus include intestinal malrotation caused by the arrest of normal rotation of the embryonic gut, or post-operative adhesions. In the case of congenital malrotation, more than 50% of affected children present for evaluation before 1 month of age with small bowel volvulus. Because a small bowel volvulus is a classic closed loop obstruction, prompt recognition and surgical treatment are imperative because the risk of strangulation is high.

The term *intussusception* describes the invagination or "telescoping" of a part of the small intestine into itself. This results in the development of venous and lymphatic congestion, with consequent intestinal edema, which can lead to intestinal ischemia and perforation. Intussusception occurs in patients of all ages but is most frequently seen in children younger than 2 years. It is the most common cause of intestinal obstruction in infants 6 to 36 months of age. Unlike ileocolic intussusception, which can often be treated nonoperatively by enema reduction, surgery is more often required in cases of intussusception limited only to the small bowel. In children, the cause is usually idiopathic, but several studies have shown an association with adenovirus infection. It has been postulated that enteric adenovirus infection may trigger stimulation of the lymphatic tissue in the intestinal tract, which may create a lead point for the intestine to be dragged into itself by the normal peristaltic activity of the intestines. In contrast to the idiopathic nature of intussusception in children, a mechanical cause is found in more than 90% of adult cases. Tumors, benign or malignant, are discovered as the initiating cause in more than 65% of adult cases. Adult intussusception has been reported in association with acquired immunodeficiency syndrome (AIDS) as a result of lymphoma or unusual infections, such as atypical mycobacterial infections.

CLINICAL FEATURES

History

Patients with SBO commonly report colicky abdominal pain, abdominal distention, nausea, vomiting, constipation, or the inability to pass flatus, but no single historical feature can reliably predict SBO.[4] The pain is often described as periumbilical in location and typically has a crescendo-decrescendo pattern. The recurrent waves of discomfort can last from seconds to minutes. In more proximal obstruction, symptoms of nausea and vomiting can be much more severe, and the onset of symptoms is often more abrupt. Distal obstructions typically cause the gradual onset of symptoms over 1 to 2 days and are frequently accompanied by increased abdominal distention. The colon requires up to 24 hours to empty after the formation of an SBO, and the associated small bowel distention stimulates peristalsis; consequently, flatus and the passage of stool may continue, even in the presence of a complete obstruction. A history of previous abdominal surgery, small bowel obstructions, GI malignancy or inflammatory bowel disease should be elicited. The use of medications (especially opioids) that may affect bowel function should be reviewed.

Physical Examination

The physical examination includes evaluation of the patient's hemodynamic status, degree of distress, and general condition. Thus, appropriate interventions, including intravenous (IV) fluids, can be initiated early. Inspection of the patient includes a careful search for abdominal distention and hernias including umbilical, inguinal and femoral locations, as well as the presence of surgical scars. Although bowel sounds in SBO are frequently described as high-pitched and tinkling in nature, studies have shown that they may often be decreased or absent. One study of physicians listening to recordings of bowel sounds demonstrated the ability to identify SBO correctly in only 42% of affected patients.

The presence of peritoneal signs usually indicates late obstruction with complications, including strangulation or bowel ischemia. However, abdominal palpation in the setting of bowel dilation can give the false impression of peritonitis, as quick compression-decompression of dilated bowel may elicit a significant pain response. For this reason, it may be

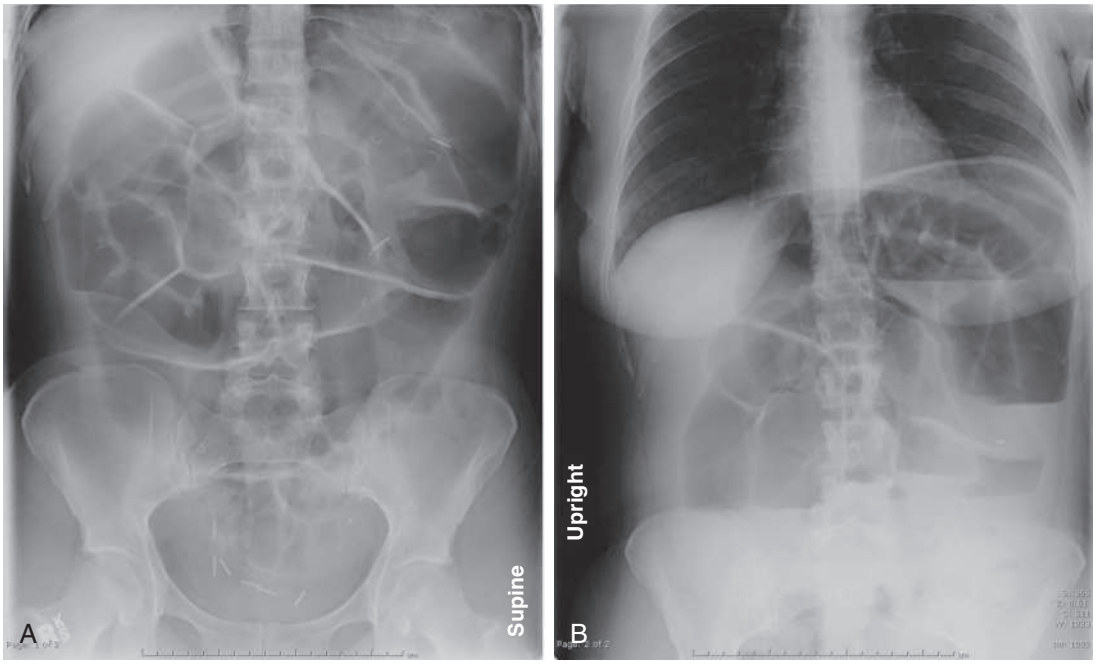

Fig. 78.4 (A) Supine plain film radiograph showing dilated loops of small bowel in a patient with small bowel obstruction. (B) Upright abdominal plain radiograph revealing multiple air-fluid levels and small bowel dilation, consistent with a diagnosis of small bowel obstruction.

helpful to determine the presence of pain with cough or gentle shaking of the patient's pelvis to more accurately investigate for true peritonitis.

DIFFERENTIAL DIAGNOSIS

The diagnosis of SBO should be considered in any patient with abdominal pain and vomiting, especially if there is a history of prior abdominal surgery. It may be difficult to differentiate SBO from nonobstructive intestinal motility disorders, such as adynamic ileus or intestinal pseudo-obstruction, by history and examination alone.

Other conditions to consider include gastroenteritis, mesenteric adenitis, constipation, cholelithiasis or nephrolithiasis, ectopic pregnancy, pancreatitis, peptic ulcer disease, atypical myocardial infarction, leaking abdominal aortic aneurysm (AAA), or mesenteric ischemia. These pathologies have typical signs, symptoms, and diagnostic findings that can help differentiate them from one another and from SBO, but this may be challenging, especially early in the course of illness.

DIAGNOSTIC TESTING

Laboratory

Although laboratory tests are of limited utility in diagnosing the presence of SBO, they can be useful in assessing the degree of dehydration and metabolic disruption resulting from the obstruction. Studies have evaluated the use of lactate and creatine phosphokinase (CPK) to identify strangulation complicating an SBO. Intestinal fatty acid-binding protein (I-FABP), which is released by necrotic enterocytes, has also been studied as a marker to identify strangulation. Unfortunately, all the biomarkers studied to date may be normal until very late in the process of intestinal strangulation. While recognizing this, an elevated lactate level should heighten clinical suspicion for strangulation.

Imaging

Traditionally, plain film radiographs have been the initial imaging test of choice in the diagnosis of SBO. Abdominal plain film radiographs should include supine and upright or decubitus views. An upright chest radiograph may also be obtained to evaluate for sub-diaphragmatic free air resulting from bowel perforation. Characteristic plain radiographic findings of SBO include distended loops of bowel, normally greater than 3 cm in diameter, often seen centrally in the radiograph (Fig. 78.4). In addition, unlike the haustra of the large intestine, which do not cross the full diameter of the bowel, the valvulae conniventes (or plicae circulares) of the small bowel cross the entire lumen of the small intestine, thus helping differentiate SBO from large bowel obstruction. In general, the greater the number of distended loops, the more distal the obstruction. No gas should be seen in the large bowel, unless the films are obtained early in the course of the obstruction or in the presence of a partial SBO. An adynamic ileus, on the other hand, tends to show extensive air-filled loops throughout the entirety of the GI tract without small bowel dilation. Unfortunately, plain radiographic studies have significant limitations in the evaluation of SBO. Plain radiographs are diagnostic in only 50% to 60% of cases, equivocal in 20% to 30%, and normal, nonspecific, or misleading in 10% to 20%. As a result, we do not recommend their use in the setting of suspected SBO.

Computed tomography (CT) has become an increasingly popular imaging modality for the evaluation of SBO, and is currently considered the gold standard for imaging in suspected SBO. CT detects SBO with a high degree of sensitivity and specificity. In addition, unlike plain radiographs, CT scans provide more information regarding the cause of obstruction by identifying the tumors. More important acutely, unlike plain radiographs, CT scans are highly sensitive for detecting strangulation, with a specificity of 96% and likelihood ratio of 9.3.[5] According to the American College of Radiology Appropriateness Criteria, the CT scan of choice for the evaluation of a suspected high-grade bowel obstruction is CT of the abdomen and pelvis with IV contrast and without oral contrast. This guideline states that "oral contrast will not reach the site of obstruction, wastes time, adds expense, can induce further patient discomfort, will not add to diagnostic accuracy, and can lead to complications, particularly vomiting and aspiration."[6]

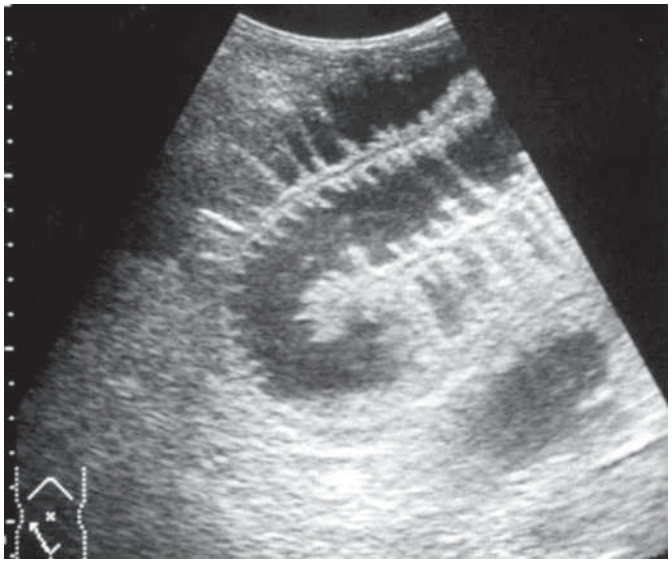

Fig. 78.5 Ultrasound Image of Fluid-Filled Dilated Small Bowel in Small Bowel Obstruction. (Courtesy Masaaki Ogata, Kobe, Japan.)

Historically, ultrasound had limited value in evaluating SBO due to significant artifact caused by gas within the GI tract. However, the improved resolution of newer scanning devices has made this modality much more attractive, with one recent meta-analysis finding that ultrasound performed with similar diagnostic characteristics to CT in identifying SBO, with the additional advantages of the potential for rapid performance at the bedside without exposure to ionizing radiation. Typical ultrasound findings in SBO include fluid-filled bowel with dilated loops greater than 2.5 cm in diameter with decreased or absent peristalsis with distally collapsed bowel (Fig. 78.5).[7] Abdominal free fluid between loops of dilated bowel (the Tanga sign) is suggestive of a high-grade obstruction.

In summary, CT scan with IV contrast is currently the preferred imaging test as it is the most sensitive and specific for detecting SBO, and is the most likely to identify both the cause and complications of the obstruction (specifically strangulation and bowel ischemia) with a high degree of sensitivity. Bedside ultrasound is quickly emerging as a useful tool in the diagnosis of SBO, though further research is needed with particular focus in the ED setting as well as the pediatric population.

MANAGEMENT

Hemodynamically unstable patients should be resuscitated with crystalloid solution via a large-bore catheter. Once SBO is diagnosed, if the cause is an abdominal hernia an attempt at bedside reduction is warranted. Clinical or imaging findings suggestive of bowel strangulation or ischemia should prompt rapid surgical consultation, as operative intervention is likely.[8] Although many emergency clinicians and surgeons consider the use of nasogastric decompression in all cases of SBO to be dogma, its effect in decreasing the duration of SBO has scant support in the medical literature, with some studies suggesting that nasogastric decompression may increase the risk of complications such as pneumonia.[9] We believe that it is reasonable to delay nasogastric tube insertion in the setting of a simple SBO suspected due to adhesions if nausea or vomiting can be adequately controlled with antiemetic medications (e.g., ondansetron 4 mg IV every 6 to 8 hours or metoclopramide 10 mg IV every 6 to 8 hours). However, in patients with persistent symptoms or large gastric volumes on imaging, a nasogastric tube attached to wall suction should be considered. There appears to be no benefit in using a long intestinal tube as an alternative to traditional nasogastric tube. Placement of a nasogastric tube is an uncomfortable procedure, and attempts should be made to anesthetize the patient's nasopharynx with topical anesthetic before insertion. In addition, the use of anxiolytics such as 2 mg of IV midazolam during insertion in appropriate patients, may reduce patient discomfort.[10]

Most simple SBOs related to adhesions will resolve with conservative treatment within 48 to 72 hours. Some surgical guidelines suggest administration of a water-soluble contrast medium at admission or after 48 hours of failed conservative treatment. Appearance of contrast in the colon within 24 hours of administration predicts nonoperative resolution of the obstruction.[11] The contrast media itself was once thought to have a therapeutic effect in resolving SBO, but recent studies have failed to show an effect.[12] A proposed approach to the management of SBO is shown in Fig. 78.6.

There is no convincing evidence to recommend the empiric use of antibiotics for the nonoperative management of a simple SBO. In patients in whom surgical exploration is planned or perforation is suspected, antibiotics are recommended and should provide coverage against the Gram-negative and anaerobic organisms that colonize the intestinal tract (e.g., a regimen with either a third-generation cephalosporin such as ceftriaxone 2 g IV daily or a fluoroquinolone such as ciprofloxacin 400 mg IV q12 hours, either combined with metronidazole 500 mg IV q8 hours. Single drug broad-spectrum options include piperacillin-tazobactam 3.375 g IV q6 hours or a carbapenem such as meropenem, 1000 mg IV tid).

SBO occurs in up to 30% of patients with colon cancer and in 50% of patients with ovarian cancer. Patients who may not qualify for surgical intervention because of intra-abdominal carcinomatosis, massive ascites, or poor overall health status may benefit from palliative relief with self-expanding metal bowel stents or the use of octreotide, 300 mcg/day IV given over three doses, or alternatively as a continuous infusion, to reduce GI secretions. A collaborative approach with the patent's oncologist and consulting surgeon can provide individualized treatment in this situation. In the setting of terminal metastatic disease, although surgery may provide temporary symptomatic improvement, it often comes at the cost of a significant proportion of the patient's remaining days being spent in the hospital.[13]

There are numerous potential serious complications associated with SBO. Persistent vomiting can lead to hypovolemia, metabolic alkalosis, and shock. If strangulation occurs, necrosis of the bowel can lead to perforation, and leakage of contaminated bowel contents into the peritoneal space can cause peritonitis, intra-abdominal abscess formation, and sepsis. Complications are more common in older adults and those with medical comorbidities. There are also several potential complications related to surgical intervention for SBO, including wound infection or short bowel syndrome. Unfortunately, the rate of recurrence of SBO is high; 40% for patients treated nonoperatively and 27% for those treated operatively. For patients with SBO secondary to adhesions, the relative risk of recurrence increases with the number of prior episodes of obstruction. For those with four or more episodes of adhesional SBO, the recurrence rate is more than 80%.

DISPOSITION

Patients with SBO routinely require inpatient admission to the hospital. One study has found that patients with SBO admitted to a surgical service for inpatient management had a shorter length of stay, lower hospital charges, and lower mortality compared to those admitted to a medical service. This was attributed largely to earlier identification of patients with failed conservative management and thus earlier surgical intervention. Regardless of the admitting service, patients with SBO need frequent reassessment to determine disease progression or resolution. Finally, although laparoscopic surgery was once considered inappropriate for the management of SBO, there has been a growing

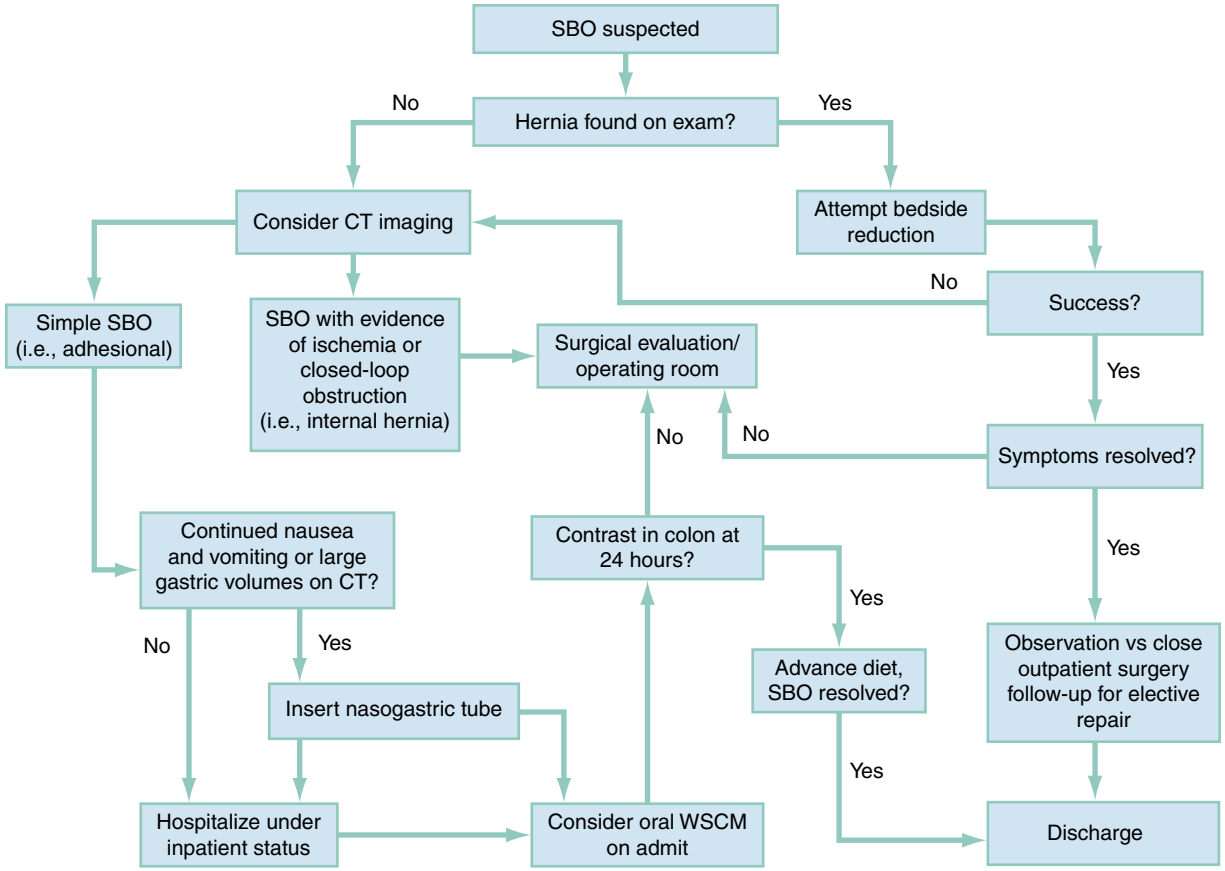

Fig. 78.6 Management Algorithm of Small Bowel Obstruction *(SBO). WSCM,* Water soluble contrast medium.

experience with its successful use, particularly those with obstructions caused by adhesions. Laparoscopy may decrease the incidence of subsequent obstructions, and several current guidelines suggest consideration of laparoscopy in stable patients in need of operative intervention for nonresolving SBO caused by adhesions.[14,15]

ACUTE MESENTERIC ISCHEMIA

KEY CONCEPTS

- Acute mesenteric ischemia (AMI) is a rare vascular catastrophe that involves the sudden reduction or loss of blood flow to the small bowel and possibly the right colon.
- Within the diagnosis of AMI are four distinct clinical entities with unique associated risk factors and treatments. These include:
  1. Mesenteric arterial embolism
  2. Mesenteric arterial thrombosis
  3. Nonocclusive mesenteric ischemia
  4. Mesenteric venous thrombosis
- CT angiography with IV contrast and thin axial images (1–3 mm) is currently the initial imaging study of choice in the evaluation of suspected AMI and has a very high level of accuracy.
- Successful management of acute mesenteric arterial embolism and thrombosis frequently requires multispecialty care including general or vascular surgery, interventional radiology, and critical care, with the goal of restoring mesenteric blood flow as quickly as possible.
- Unlike cases of arterial embolism or thrombosis, in the absence of peritonitis, mesenteric venous thrombosis is often successfully managed with anticoagulation alone.

FOUNDATIONS

Background and Importance

In his 1926 treatise on mesenteric vascular occlusion, A.J. Cokkinis wrote: "occlusion of the mesenteric vessels is apt to be regarded as one of those conditions of which…the diagnosis is impossible, the prognosis is hopeless, and the treatment almost useless." Since that time, significant advances in the understanding of this condition, as well as the development of endovascular approaches and surgical treatments have been made. Despite these advances, the mortality rate has remained as high as 60% to 80%, and the diagnosis and treatment of this vascular catastrophe has remained challenging.

Acute mesenteric ischemia (AMI) is the sudden reduction or loss of blood flow to the small bowel to a level that is insufficient to meet the metabolic demands of the small intestines.[16] This may at times involve the right colon. The left colon has a much higher degree of collateral blood flow and is less prone to mesenteric ischemia. When acute mesenteric ischemia occurs, rapid intestinal injury results. This condition should be clearly differentiated from chronic mesenteric ischemia (CMI), also referred to as *intestinal angina*, which often manifests as recurrent episodes of post-prandial abdominal pain resulting from insufficient intestinal blood flow during periods of increased metabolic demand, leading to food aversion and weight loss.[17] CMI does not usually require emergent therapy; however, it is also possible for acute mesenteric ischemia to develop in these patients.

Overall, AMI is a rare clinical problem. There are four specific clinical categories that make up the overwhelming majority of causes, each with distinct epidemiologic risk factors—mesenteric arterial embolus, mesenteric arterial thrombosis, nonocclusive mesenteric ischemia, and mesenteric venous thrombosis.

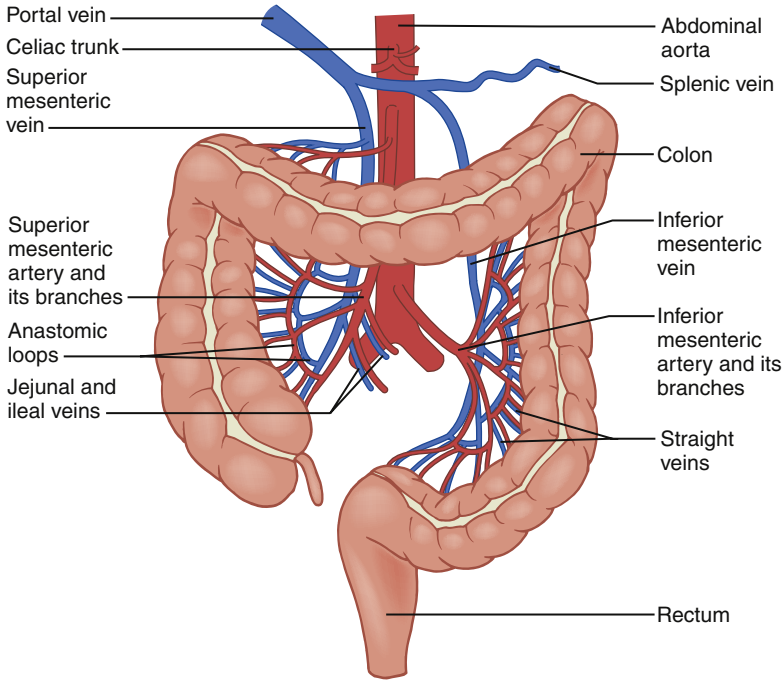

Fig. 78.7 Blood Supply of the Small and Large Intestine. (Reprinted with permission from Floch MH, Floch NR, Kowdley KV. *Netter's Gastroenterology*.)

Anatomy and Physiology

The mesenteric vessels arise from the primitive ventral segmental arteries. Although there is considerable individual variability, these vessels typically regress as embryologic development proceeds, with the exception of the 10th, 13th, and 21st segmental arteries. These become the celiac trunk, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA), respectively. The celiac trunk arises from the anterior aspect of the abdominal aorta and branches into the common hepatic, splenic, and left gastric arteries. These vessels supply the distal esophagus to the duodenum at the entrance of the bile duct. The SMA normally arises 1 cm below the celiac trunk and runs toward the cecum, terminating as the ileocolic artery. The SMA supplies the distal half of the duodenum to the proximal two-thirds of the transverse colon. The IMA originates approximately 6 to 7 cm below the SMA and gives rise to the left colic artery, sigmoid arteries, and hemorrhoidal arteries. Anatomically, this vessel provides blood flow to the distal third of the transverse colon to the rectum (Fig. 78.7). The gut receives 20% of cardiac output at rest and up to 35% after eating. Of this, up to 70% supplies the mucosa due to the high metabolic demands required for the absorptive function of this intestinal layer.

Intestinal blood flow is regulated by a complex combination of intrinsic and extrinsic mechanisms to match intestinal demands with blood supply. Intrinsic factors provide the moment-to-moment control of the intestinal circulation; they function independently from neural control. This intrinsic modulation has been proposed to involve the release of local metabolites produced as a result of mucosal ischemia. These metabolites then diffuse to the local arterioles, triggering relaxation in the smooth muscle and increased blood flow, thereby allowing for efficient adjustments to the intestinal blood supply. Smooth muscle relaxation can also be brought about directly by a decrease in the perfusion pressure in the arterioles themselves. These two mechanisms are referred to as the metabolic and myogenic pathways. Intestinal blood flow is also controlled extrinsically through neural and hormonal mechanisms. Increased sympathetic tone to the paired celiac ganglia located adjacent to the celiac trunk results in mesenteric and arteriolar vasoconstriction. Hormonal influences include the direct action of angiotensin II released as a result of decreased extracellular volume, as well as vasopressin, both of which cause mesenteric vasoconstriction.

Fig. 78.8 Gross Pathologic Image of Intestinal Ischemia and Infarction. Note mucosal hyperemia and hemorrhage. (From Gore RM, Yaghmai V, Thakrar KH, et al. Imaging in intestinal ischemic disorders. *Radiol Clin North Am.* 2008;46:845–875.)

PATHOPHYSIOLOGY

Although these mechanisms allow for the mesenteric circulation to adapt to wide variations in the metabolic needs of the gut and systemic perfusion, the bowel is quickly injured in the setting of acute compromise. Because of the high metabolic demands of the intestinal mucosa, structural damage to the intestinal villi can be observed histologically within 15 minutes of ischemia. If not corrected, mucosal sloughing occurs within 3 hours. After 6 hours, transmural necrosis is complete (Fig. 78.8). Complicating the situation, reestablishment of blood flow at this point results in the systemic release of several pro-inflammatory

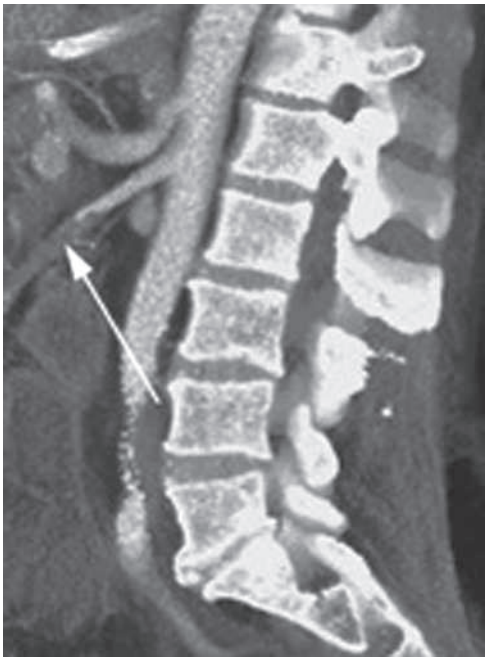

Fig. 78.9 Coronal Abdominal CT Angiogram With Large Superior Mesenteric Artery Embolism *(Arrow).* (From Gore RM, Yaghmai V, Thakrar KH, et al. Imaging in intestinal ischemic disorders. *Radiol Clin North Am.* 2008;46:845–875.)

cytokines and toxic oxygen radicals caused by reperfusion, which can lead to multi-organ failure and death.

Mesenteric Arterial Embolism

Arterial emboli, the most common cause of acute mesenteric ischemia, are responsible for approximately 50% of cases. The median age of patients with mesenteric arterial emboli is 70 years, and in contrast to other vascular disorders, two-thirds are women. Emboli are usually cardiac in origin and arise from left atrial or ventricular mural thrombi or valvular lesions. Risk factors for the development of thrombi include myocardial ischemia or infarction, cardiomyopathies, ventricular aneurysms, endocarditis, or atrial dysrhythmias, specifically atrial fibrillation. Compared with the estimated annual risk of stroke of 2.3%, the annual risk of AMI caused by thromboembolism secondary to atrial fibrillation is 0.14%. The SMA is most frequently affected because of the large caliber of the vessel and its narrow takeoff angle from the aorta. The embolus typically lodges 3 to 10 cm distal to the origin of the SMA (Fig. 78.9). The jejunum is most often involved, as it is distant from the watershed collateral flow provided from the celiac and inferior mesenteric arteries.

Mesenteric Arterial Thrombosis

Mesenteric arterial thrombosis results from the progression of atherosclerotic disease of the mesenteric vasculature. Risk factors for development include advanced age, hypertension, diabetes, and tobacco use. Affected patients frequently have a history suggestive of CMI of several months or years duration. Unlike embolic occlusions, thrombosis usually occurs in the proximal SMA at the origin of the vessel.

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia occurs as a result of mesenteric vasospasm in the absence of a physical obstruction. This vasospasm is triggered by mesenteric hypoperfusion or excessive sympathetic nervous system activity. Mesenteric hypoperfusion can result from a wide variety of conditions, including sepsis, severe dehydration, pancreatitis, or hemorrhagic shock. Excessive sympathetic activity can result from congestive heart failure, or the use of medications and drugs such as vasopressors, cocaine, or digoxin. Once initiated, this vasospasm often persists even after correction of the underlying condition, and repeated episodes of ischemia and reperfusion occur. Studies suggest that this recurrent pattern of ischemia and reperfusion may result in more severe histologic injury than a single episode of prolonged ischemia.

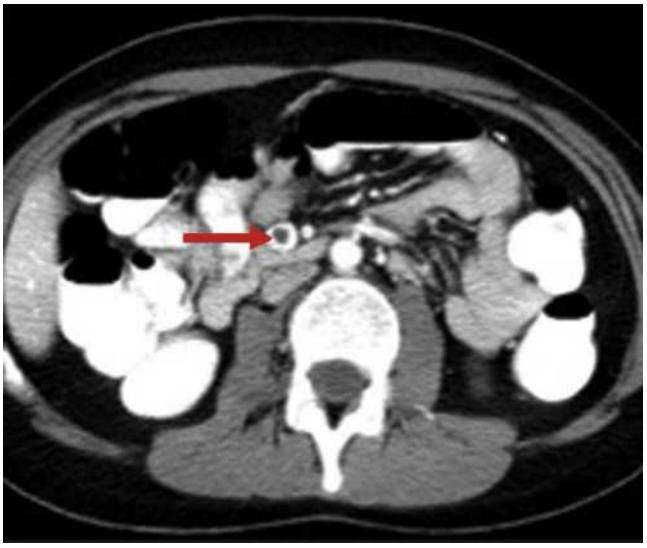

Fig. 78.10 Superior Mesenteric Venous Thrombus *(Red Arrow)* in a Patient With Nondescript Abdominal Pain. Hematologic evaluation revealed factor V Leiden thrombophilia. (From Gore RM, Yaghmai V, Thakrar KH, et al: Imaging in intestinal ischemic disorders. *Radiol Clin North Am.* 2008;46:845–875.)

Mesenteric Venous Thrombosis

Mesenteric venous thrombosis (MVT) is the least common cause of acute mesenteric ischemia, accounting for only 5% to 15% of all events. It usually involves the superior mesenteric vein and its branches (Fig. 78.10). In the vast majority of cases (>75%), an underlying inherited thrombotic disorder or inherited or acquired hypercoagulable state can be identified. The most common cause is factor V Leiden mutation, which is thought to account for 20% to 40% of cases. Other inherited prothrombotic states implicated in the development of mesenteric venous thrombosis include deficiency in antithrombin III, protein C, or protein S. Hematologic conditions predisposing to this condition include polycythemia vera and essential thrombocythemia. Oral contraceptive use accounts for 9% to 18% of the episodes of MVT in young women. Local intra-abdominal inflammation secondary to pancreatitis, malignancy, or inflammatory bowel disorders also increases the risk of mesenteric venous thrombosis. Finally, the venous stasis caused by portal hypertension is a recognized risk factor.

Box 78.3 summarizes causes of mesenteric venous thrombosis.

Unusual Causes of Mesenteric Ischemia

There are numerous case reports of unusual causes of mesenteric ischemia. These include SMA dissection leading to occlusion, tumor emboli, retroperitoneal fibrosis, and various types of vasculitis, including Buerger disease, polyarteritis nodosa, or Takayasu arteritis. Because these conditions involve a rare cause of an already rare condition, they frequently go unrecognized initially.

Clinical Features

History. The history at presentation of mesenteric ischemia is largely dependent on the nature of the underlying cause. The traditional historical triad of acute mesenteric ischemia is the sudden onset of poorly localized abdominal pain and gastric emptying (vomiting or

BOX 78.3 Factors Associated With Mesenteric Venous Thrombosis

Hypercoagulable States
Polycythemia vera
Sickle cell disease
Antithrombin III deficiency
Protein C or S deficiency
Malignancy
Myeloproliferative disorders
Estrogen therapy, oral contraceptive pills
Pregnancy

Inflammatory Conditions
Pancreatitis
Diverticulitis
Appendicitis
Cholangitis

Trauma
Operative venous injury
Postsplenectomy
Blunt or abdominal trauma

Miscellaneous
Congestive heart failure
Renal failure
Decompression sickness
Portal hypertension

diarrhea) in a patient with cardiac disease. This is especially true in cases of SMA embolism or thrombosis, in which symptoms and clinical deterioration can rapidly occur. In cases of MVT, the symptoms are often slower in onset and have been present for several days by the time the patient seeks medical attention. Approximately one-third of patients with acute embolic mesenteric ischemia and 50% of patients with acute MVT have a personal history of an embolic event, such as a pulmonary embolism, deep vein thrombosis, or ischemic stroke. Patients with nonocclusive mesenteric ischemia are often already critically ill, making it difficult or impossible for them to provide historical details to the treating physician.

Physical Examination. The pain in acute mesenteric ischemia is typically described as being out of proportion to the physical examination findings. The patient may be writhing in pain but have a soft abdomen without guarding, especially early in the course of the event, when only the visceral structures are ischemic. However, as the parietal peritoneum becomes ischemic, the abdominal physical findings progress. If the ischemia progresses to infarction, peritonitis may be present. Heme-positive stools may also be noted. Hypotension, tachycardia, and tachypnea are all signs of severe ischemia and suggest a poor prognosis.

DIFFERENTIAL DIAGNOSIS

Other potentially devastating conditions to consider in the differential diagnosis of acute-onset severe abdominal pain include leaking AAA, perforated viscus, bowel obstruction, biliary disease, or atypical myocardial infarction.

Diagnostic Testing

Laboratory Tests

Initial laboratory results in patients with acute mesenteric ischemia are often nonspecific and may include leukocytosis, an elevated hematocrit secondary to hemoconcentration, or metabolic acidosis. Several serum biomarkers have been investigated as early indicators including I-FABP, α-glutathione S-transferase (α-GST), serum lactic acid, ischemia modified albumin (IMA), and citrulline levels. A meta-analysis has shown a pooled sensitivity of 71% and pooled specificity of 74% for serum lactic acid.[18] To date, no biomarkers have been found that are sufficiently sensitive and specific to diagnose or eliminate mesenteric ischemia. Recognizing these limitations, the serum lactic acid level is currently the most useful laboratory test available. In addition to its wide availability and rapid turnaround time, the short half-life of serum lactic acid (≈20 minutes) may be useful to allow for serial measurements, especially early in the course of suspected acute mesenteric ischemia.

Imaging

CT angiography has become the initial imaging study of choice for the evaluation of suspected acute mesenteric ischemia. Several studies have shown that with the emergence of multi-detector CT scanners, the sensitivity and specificity for mesenteric ischemia are approximately 94% and 95%, respectively.[19] Duplex sonography has a specificity 92% to 100% for the detection of AMI but its sensitivity is only 70% to 89% due to limited evaluation beyond the proximal main vessels. It is also unable to provide information regarding complications of acute mesenteric ischemia, including bowel infarction or perforation. Plain abdominal radiographs are usually nonspecific and of little use. Later in the disease course, plain radiographic findings may show so-called thumbprinting, in which multiple, round, smooth soft tissue densities project into the intestinal lumen because of mucosal and submucosal edema and hemorrhage. More specific but very late plain radiographic findings indicating infarction include pneumatosis intestinalis and portal venous gas.

Management

Once AMI has been diagnosed, the goals of treatment are to restore mesenteric blood flow as rapidly as possible, manage underlying conditions, treat persistent mesenteric vasospasm if present, and mitigate the risk of further clot propagation. Initial interventions should focus on fluid resuscitation and hemodynamic stabilization. Unless contraindicated, patients should be anti-coagulated with intravenous unfractionated heparin (80 units/kg bolus followed by an 18 units/kg/h infusion).[20] Because these patients are often older adults with cardiac comorbidities, invasive monitoring may be indicated. If vasopressors are required, dobutamine, low-dose dopamine, or milrinone are recommended, because these have been shown to have less of a vasoconstrictive effect on the mesenteric vasculature than other agents (see Chapter 5). With evidence of infarction, perforation, or peritonitis, antibiotics suitable for enteric coverage, such as ceftriaxone 2 g IV qd, or ciprofloxacin 400 mg BID, in combination with metronidazole 500 mg IV TID, is recommended. Single drug options include piperacillin-tazobactam 3.375 g IV q6 hours, or a carbapenem such as meropenem 1000 mg IV TID).

The optimal care of this challenging condition often requires multispecialty coordination involving general surgery, vascular surgery, interventional radiology and critical care experts. Previously, the standard approach was emergent open surgery. If signs of intestinal infarction or perforation with peritonitis are present, prompt laparotomy is still recommended. The benefit to this approach is that it also allows the surgeon to assess the viability of the bowel at the time of the operation, which is not possible with endovascular treatment alone, and to resect necrotic bowel if needed. Open repair can also involve surgical embolectomy, or bypass grafting as well as an approach referred to as the hybrid technique, which includes intra-operative retrograde revascularization.[21] This approach involves open surgical evaluation of the bowel, as well as concurrent retrograde stenting of the occluded vessel,

thus combining the benefits of rapid revascularization with surgical evaluation of the bowel (Fig. 78.11). If bowel viability is questionable during the first laparotomy, a second-look procedure 24 to 48 hours later has been recommended.[22]

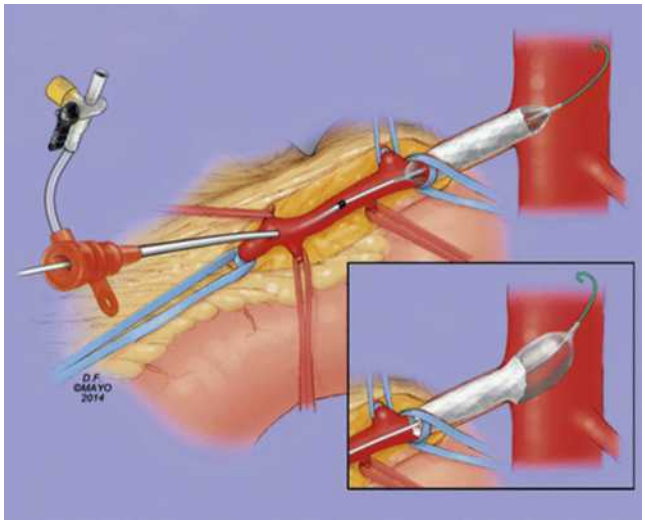

Fig. 78.11 Hybrid Technique With Retrograde Open Mesenteric Stenting. (From Moore JR, Achanchi SS, Panneton JM. Chapter 17: Techniques of open and hybrid mesenteric revascularization of acute mesenteric ischemia. In: Oderich GS, ed. *Mesenteric Vascular Disease*. New York: Springer Science & Business Media; 2015; used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

In addition to open surgery and the hybrid approach, similar to the developments in acute stroke care, the role and timing of endovascular treatments alone in the management of AMI also continues to evolve and appears to offer an additional treatment modality, especially in those patients deemed to be a poor surgical candidate due to underlying medical issues or patient goals of care. Numerous reports have detailed the use of thrombolytic agents, angioplasty, embolectomy, or vascular stenting to restore mesenteric blood flow. Although randomized control trials are needed, several retrospective studies have demonstrated favorable success and complication rates of endovascular revascularization of AMI. Patient vascular anatomy is a factor, as an angular or tortuous SMA can lower technical success of intervention.

The treatment of mesenteric venous thrombosis is unique in that in the absence of peritoneal findings, initial treatment with heparin infusion and then transition to long-term anticoagulation with warfarin. A targeted international normalized ration (INR) of 2.0 to 3.0 is adequate in 95% of cases. To date, non-vitamin K antagonist oral anticoagulants (NOACs) have not been studied for the treatment of MVT. A treatment duration of 6 months for patients diagnosed with a provoked and reversible cause is suggested, although life-long anticoagulation may be needed if a hypercoagulable condition is uncovered. If the case is refractory to anticoagulation or the condition of the patient worsens, catheter-directed fibrinolysis or thrombectomy may be considered.[23] If peritonitis is present or develops later in the patient's hospital course, bowel necrosis is likely, and prompt laparotomy is still indicated. Similar to mesenteric arterial occlusion, if bowel viability is unclear, a second-look laparotomy may also be needed. A suggestive outline of the management of occlusive mesenteric arterial and venous ischemia is presented in Fig. 78.12.

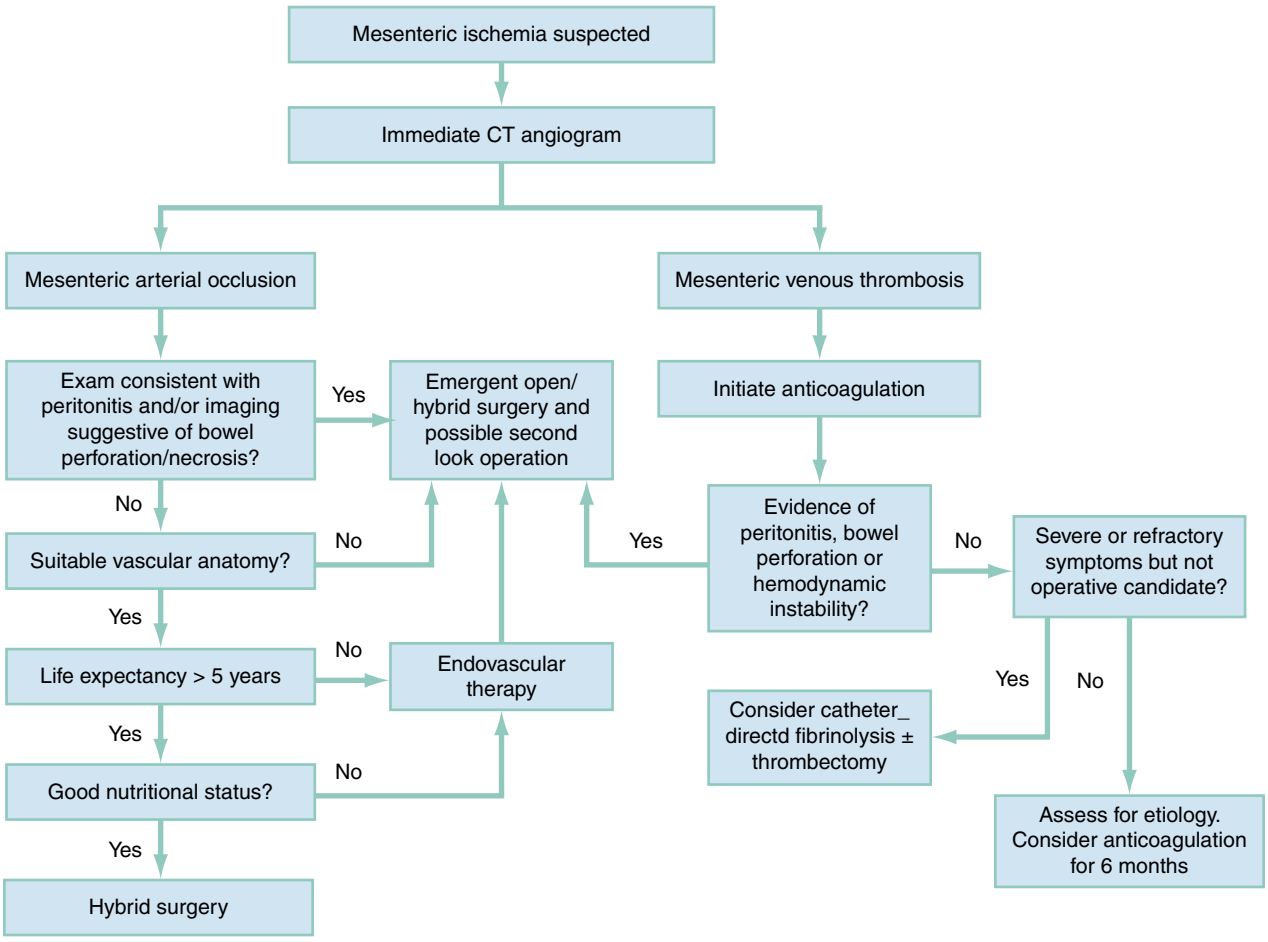

Fig. 78.12 Management Algorithm of Occlusive Arterial and Venous Mesenteric Ischemia.

Primary treatment of nonocclusive mesenteric ischemia involves interventions to reverse the underlying cause and consideration for papaverine infusion via angiographic catheter, as well as IV heparin to prevent thrombosis in the vasospastic vessel. Papaverine infusion is often maintained for 24 hours, at which time angiography may be repeated to evaluate for the resolution of vasospasm. If peritoneal signs develop, laparotomy is indicated. If the underlying medical condition persists, the mortality of nonocclusive mesenteric ischemia remains high.

Complications

Even with prompt recognition and treatment of acute mesenteric ischemia, a complicated course is expected. Secondary reperfusion injury is common, and bowel initially identified as viable may progress to necrosis requiring additional resection. Other complications include wound infections, sepsis, or pneumonia. Given the population in which AMI tends to occur, the physiologic stress of this disease process also places patients at high risk for myocardial infarction, renal failure, or pulmonary embolism while hospitalized.

Disposition

Patients with acute mesenteric ischemia routinely require hospital admission, with the majority requiring intensive care.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 78: QUESTIONS AND ANSWERS

1. What is the most common cause of small bowel obstruction in the developed world?

a. Gallstone ileus
b. Hernias
c. Intussusception
d. Postoperative adhesions
e. Tumors

Answer: d. In the developed world, postoperative adhesions account for approximately 60% of cases of small bowel obstruction. Patients with a history of intestinal or pelvic surgery are at the highest risk.

2. Which of the following patients is at the highest risk of developing an obturator hernia?

a. 2-year-old boy with no known medical problems
b. 45-year-old woman with a 1-year history of hysterectomy
c. 67-year-old man with a history of metastatic prostate cancer
d. 80-year-old woman with a 3-month history of rapid weight loss

Answer: d. This type of hernia is especially common in older women who have recently lost a significant amount of weight. The female pelvis is wider, and the obturator canal is more oblique in women. This, in combination with a loss of preperitoneal fat, predisposes to its development. Because an external mass is absent, diagnosis is especially challenging and explains why it carries the highest mortality of any abdominal hernia – nearly 70% when incarcerated.

3. A 55-year-old woman with a history of Roux-en-Y gastric bypass surgery presents with one day of worsening colicky abdominal pain and vomiting. A CT scan reveals an internal hernia. What is the most appropriate disposition?

a. Administer broad-spectrum antibiotics and admit to the medicine floor.
b. Arrange for barium swallow with small bowel follow-through.
c. Insert nasogastric tube and admit to the medicine floor.
d. Prompt surgical consultation and preparation for surgery.

Answer: d. Although rare in the general population, internal hernias are a recognized complication of bariatric surgery, especially when a Roux-en-Y type procedure has been performed. Because of the closed loop nature of an internal hernia, they are not suitable for conservative management and require surgical intervention.

4. What is the length of time from acute ischemia of the intestines to completion of transmural necrosis?

a. 15 minutes
b. 60 minutes
c. 2 hours
d. 6 hours
e. 24 hours

Answer: d. Although the mesenteric circulation is able to adapt to variations in circulation, the small bowel is quickly injured after acute ischemia. Within 15 minutes, structural damage to the intestinal villi can be seen histologically. If blood flow is not restored, mucosal sloughing can start to occur within 3 hours and, by 6 hours, transmural necrosis is complete.

CHAPTER 78: QUESTIONS AND ANSWERS—Cont'd

5. A 35-year-old woman taking oral contraceptive pills presents with 2 days of progressively worsening diffuse abdominal pain without peritoneal findings on examination. A CT scan reveals mesenteric venous thrombosis. What is the next most appropriate step?

a. Arrange for formal mesenteric venous angiography to confirm and treat.

b. Arrange for immediate exploratory laparotomy regardless of current clinical status, given the high risk of severe complications.

c. Discharge home because this will resolve without intervention.

d. Institute pain control and admit to the floor.

e. Start anticoagulation with therapeutic dosing of heparin.

Answer: e. The treatment of mesenteric venous thrombosis is unique in that in the absence of peritoneal findings, initial treatment with heparin alone may be adequate. In the vast majority of cases (>75%) an underlying inherited or acquired hypercoagulable state can be identified. Oral contraceptive use accounts for 9% to 18% of cases in young women.

79

Acute Appendicitis

David J. Carlberg and Nadine T. Himelfarb

KEY CONCEPT

- Appendicitis is a progressive illness caused by appendiceal luminal distention followed by appendiceal wall ischemia, transmural inflammation, and eventual perforation, with resulting peritonitis.
- Clinical history, physical examination, and laboratory findings need to be combined to formulate a comprehensive assessment. No one finding can definitively diagnose or exclude appendicitis.
- The most useful historical features in evaluating appendicitis are right lower quadrant (RLQ) pain, pain preceding vomiting, and migration of pain to the RLQ.
- The most useful physical findings in evaluating appendicitis are RLQ tenderness or rigidity.
- Cervical motion tenderness is not specific for pelvic pathology and is found in up to 28% of females with appendicitis.
- A rectal examination contributes little and should not be routinely performed in the evaluation of appendicitis.
- The white blood cell count alone is neither sensitive nor specific for appendicitis and offers little in the evaluation.
- When clinicians have a low pretest probability for appendicitis, the combination of a WBC count < 10,000/mm^3 and CRP < 8 mg/L support the exclusion of appendicitis as a likely diagnosis.
- A young, healthy adult patient with classic symptoms and signs of appendicitis should receive graded compression ultrasound as the initial imaging of choice, if available. If the ultrasound is negative or inconclusive and concern for appendicitis persists, the patient should receive a CT of the abdomen and pelvis with IV contrast, which is the most sensitive test for appendicitis. There is no need for oral or rectal contrast when ordering a CT for appendicitis.
- When there is a concern for acute appendicitis, pregnant women should first have graded compression ultrasound followed by MRI if the ultrasound is negative or nondiagnostic.
- Nonoperative management of acute appendicitis (IV antibiotics, admission) is gaining support. The patient should not have high-risk features on imaging (e.g., presence of a fecalith, abscess, tumor, fluid collection, or appendiceal diameter > 1.1 cm) and should be made aware of the risks of treatment failure and recurrent appendicitis, both of which generally require surgical removal of the appendix.
- Because of the risk of malignancy, guidelines recommend follow-up colonoscopy for patients > 40 years old treated with nonoperative management.
- Delays of 12 to 24 hours between appendicitis diagnosis and operative management are not associated with adverse outcomes. Many surgeons will perform an appendectomy the following morning if a patient presents in the evening or overnight hours. Early appendectomy should be considered in elderly patients, because up to 41% of patients 65 years or older develop perforation between diagnosis of appendicitis and surgery.

PRINCIPLES

Background

Appendicitis is the most common cause of acute abdominal pain requiring operative intervention in patients younger than 50 years, with a lifetime risk of 8.6% in males and 6.9% in females.[1] Approximately 69% of appendicitis cases occur in patients younger than 30 years, with the highest rates of presentation during the summer months. It is the most common nonobstetric abdominal emergency in pregnancy, with an incidence of 101 cases per 100,000 live births, occurring most often in the second trimester. Although appendicitis is less frequent in nonwhite individuals, these patients are at higher risk of perforation or experiencing complications of appendicitis, possibly due to health care access inequities.[2]

Formerly considered a vestigial organ, new research has revealed that the appendix likely performs an important immunologic function. It is postulated that a biofilm with bacteria-bacteriophage complexes contained within the appendix can reinnoculate the terminal ileum and proximal colon with intestinal flora when the intestinal microbiome becomes unbalanced in the setting of life stressors, dietary choices, or antibiotics.[3]

Anatomy and Physiology

The appendix is a blind-ended tube that originates from the cecum, approximately 3 cm from the ileocecal valve. It is considered part of the cecum and has the same histologic arrangement as the large intestine, although comparatively it has a larger amount of lymphoid tissue in the mucosa and submucosa. Although the appendix classically originates from the McBurney point (≈4 to 5 cm from the right anterior superior iliac spine on a straight line drawn to the umbilicus), anatomic variants may originate as distant as 10 cm from this site. Additionally, although it has an average length of 8 to 10 cm, the appendix may be more than 20 cm long. Therefore, an atypical origin and length may allow it to traverse into nearly any quadrant of the abdomen. The average appendix has a diameter ranging from 6 to 11 mm, and has an average wall thickness of 1.5 mm.

The appendix maintains afferent sensory fibers that follow the sympathetic innervation and enter the spinal cord at the 10th thoracic level (T10). This neurosensory pathway results in the periumbilical (visceral) pain of early appendicitis.

Pathophysiology

Appendicitis progresses in a stepwise fashion. First, the appendiceal lumen becomes obstructed, preventing egress of mucus and bacteria from the appendix. Continued mucus production and bacterial proliferation result in luminal distention, which stimulates the T10 visceral sensory nerves of the appendix. The resulting periumbilical pain classically lasts 4 to 6 hours. Intraluminal pressure eventually exceeds local capillary pressure in the appendiceal wall, preventing perfusion

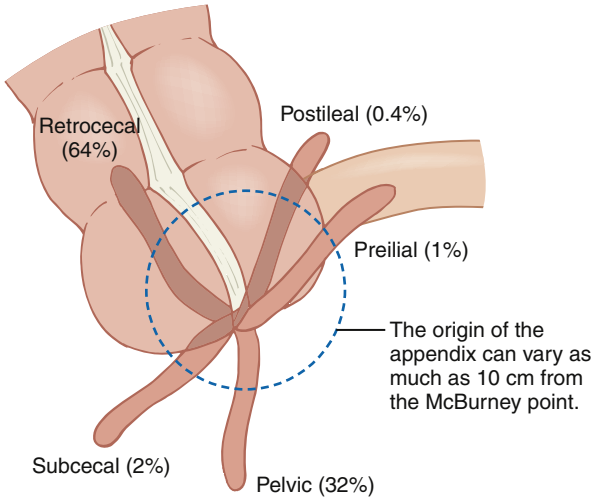


Fig. 79.1 This figure shows the variation in location of the base of the appendix and its course within the peritoneum. The McBurney point classically represents the point of maximal tenderness in appendicitis; however, depending on the path, length, and degree of inflammation of the appendix, the true point of maximal tenderness is highly variable.

and resulting in tissue ischemia and inflammation. The integrity of the appendiceal wall becomes compromised, allowing bacteria to invade the wall. This produces transmural inflammation, which extends into the surrounding tissues and causes localized somatic pain, typically focused in the right lower quadrant. If this process continues, the appendix becomes necrotic and perforates, releasing enteric contents into the peritoneum. The subsequent peritonitis typically causes diffuse abdominal pain. The length of time from the onset of symptoms to perforation is highly variable. Although rare, spontaneous resolution of appendicitis may occur.

Although the somatic pain from appendicitis classically occurs in the right lower quadrant, three important anatomic features determine the site of pain and tenderness: (1) the location of the origin of the appendix; (2) the course the appendix takes from its origin; and (3) the length of the appendix (Fig. 79.1). All these features are variable and result in a wide range of potential signs and symptoms: an appendix that courses into the left lower or right upper abdomen may cause pain in these areas; a retrocecal appendix may cause flank pain, psoas irritation, or obturator irritation; and an appendix that courses into the pelvis may cause pelvic pain, testicular or adnexal pain, diarrhea (as the inflamed appendix irritates the rectum), or even pyuria or dysuria (as the inflamed appendix irritates the urinary tract). Finally, when the inflamed appendix does not touch the parietal peritoneum, as sometimes occurs with pre-ileal and post-ileal appendicitis (see Fig. 79.1), patients may only exhibit vague abdominal discomfort or gastrointestinal symptoms until perforation occurs and inflammation becomes more diffuse.

Though it is commonly understood that obstruction of the appendiceal lumen triggers acute appendicitis, the causes of obstruction are variable and often go undetermined, even after imaging and pathologic evaluation. Fecaliths (hard stools) are the most common cause of obstruction in nonperforated appendicitis (65%), followed by appendicoliths (calcified deposits) and lymphoid hyperplasia (primary or secondary to an enteric infection). Other less common causes of obstruction are fecal stasis, foreign bodies (e.g., vegetable matter, inspissated barium), tumors, or intestinal parasites.

There are two additional pathologic processes associated with appendicitis: tip appendicitis and stump appendicitis. Tip appendicitis is inflammation localized to the distal end of the appendix, which carries a higher risk of missed diagnosis on imaging because of more subtle findings. Stump appendicitis results from inflammation of the appendiceal remnant that may persist after appendectomy. This phenomenon is rare, and its timing varies; it has been diagnosed between 4 days and 50 years after initial appendectomy.[4]

CLINICAL FEATURES

Selected patients presenting with classic historical and examination features of appendicitis may be rapidly diagnosed without the need for further testing. Unfortunately, however, periumbilical abdominal pain radiating to the right lower quadrant with associated right lower quadrant tenderness occurs in fewer than 50% of patients.

No one element of the history or physical examination can reliably diagnose or exclude appendicitis. Therefore, a comprehensive evaluation of the overall clinical picture is necessary to risk stratify a patient's likelihood of having appendicitis. Laboratory testing and advanced imaging (ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]) are frequently utilized to aid in risk stratification and diagnosis.

History

The history and review of systems frequently provide valuable insights, either demonstrating features of acute appendicitis or suggesting a compelling alternative diagnosis. A prior history of similar symptoms suggests alternative diagnoses, because appendicitis is rarely a waxing and waning or recurrent condition. Because appendicitis is usually a progressive process, the patient's symptoms typically worsen until perforation of the appendix occurs. Upon perforation, the patient may have temporary relief due to a decrease in appendiceal intraluminal pressure, but subsequent peritonitis generally leads to more severe diffuse abdominal pain and potentially clinical decompensation. Table 79.1 lists the value of common symptoms in predicting the likelihood of appendicitis.[5] Duration of symptoms is variable and may not aid in risk stratification.

Physical Examination

Patients with abdominal pain should be appropriately disrobed, and ideally placed in a room where a genitourinary examination can be performed if clinically indicated. Cervical motion tenderness (CMT) is not specific for pelvic pathology and is noted in 28% of female patients with appendicitis. A rectal examination contributes little to the assessment of appendicitis and is not routinely recommended unless it is indicated for evaluation of other potential etiologies.[6]

Classic, eponymous examination maneuvers for appendicitis have overall poor sensitivity but, if present, have a modest predictive value (Table 79.2). Although not sensitive due to the potentially variable location of the appendix in the abdominal cavity, tenderness at the McBurney point has been shown to have a modest predictive value for appendicitis.

DIFFERENTIAL DIAGNOSIS

There are many diagnoses that mimic appendicitis; alternatively, appendicitis may present atypically and should be considered in patients presenting with a wide variety of abdominal complaints. Table 79.3 lists common differential considerations when evaluating for appendicitis.

DIAGNOSTIC TESTING

General Principles

Acute appendicitis, though one of the most common surgical causes of abdominal pain in the emergency department (ED), remains a

TABLE 79.1 Value of Common Symptoms in Predicting the Likelihood of Appendicitis[6]

	ADULT		CHILD	
Sign/Symptom	**LR+**	**LR–**	**LR+**	**LR–**
Right lower quadrant pain	7.3–8.5	0–0.28	1.4	NA
Rigidity	3.8	0.82	NA	NA
Migration/periumbilical pain	3.2	0.50	1.8	0.70
Guarding	1.7–1.8	0–0.54	2.1	0.47
Rebound tenderness	1.1–6.3	0–0.86	2.2	NA
Fever	1.9	0.58	1.2	0.90
Anorexia	1.3	0.64	1.3	0.58
Nausea	0.69–1.2	0.70–0.84	NA	NA
Vomiting	0.92	1.1	1.3	0.65
Obturator sign	NA	NA	3.5	0.73
Psoas sign	2.4	0.90	3.2	0.70
Rovsing sign	NA	NA	1.6	0.72

NA, Not available.

TABLE 79.2 Common Maneuvers and Physical Findings Associated with Appendicitis and Their Predictive Values[a]

Maneuver	Description	Sensitivity and Specificity (%)
Iliopsoas (psoas) sign	Increased abdominal pain with patient lying on left side while provider passively extends the patient's right leg at the hip with both knees extended	Sensitivity: 13–42 Specificity: 79–95
Rovsing sign	Abdominal pain in the RLQ while palpating the left lower quadrant	Sensitivity: 7–68 Specificity: 58–96
Obturator sign	Increased abdominal pain in the supine patient as the provider internally and externally rotates the right leg as it is flexed at the hip	Sensitivity: 8 Specificity: 94

[a]Overall poor sensitivity decreases the value of these findings. However, if found, these signs moderately increase the likelihood of having appendicitis.
RLQ, Right lower quadrant.

TABLE 79.3 Selected Differential Considerations in Evaluation of Appendicitis

All Patients	Female Patients	Pediatric Patients
Nonspecific abdominal pain	Ectopic pregnancy	Henoch-Schönlein purpura
Gastroenteritis	Ovarian torsion	
Epiploic appendicitis	Pelvic inflammatory disease	Mesenteric lymphadenitis
Omental infarction	Ovarian cyst	Meckel diverticulum
Ureterolithiasis, nephrolithiasis		
Inflammatory bowel disease		
Ileus or bowel obstruction		
Intestinal perforation		
Testicular torsion (males)		

diagnostic challenge. Delayed diagnosis carries significant morbidity and mortality, and, as a result, missed appendicitis remains a common cause of litigation in emergency medicine.[7] As such, the diagnosis of acute appendicitis remains largely clinical.

Laboratory Testing

No single laboratory test has been proven an accurate predictor of acute appendicitis. Rather, laboratory testing may contribute valuable information to the overall clinical picture, and may aid in the risk stratification of patients with potential acute appendicitis. Laboratory testing is best interpreted in conjunction with the patient's history and physical examination.

White Blood Cell Count

Although often part of the evaluation for acute appendicitis, the white blood cell (WBC) count alone does not have enough sensitivity, specificity, or predictive value to be clinically useful for diagnosing or excluding appendicitis.[8] An elevated WBC count (>10,000–12,000/mm^3) has a sensitivity of 71% to 93%, a specificity of 49% to 66%, a positive likelihood ratio (LR) of 1.73 to 2.37, and a negative LR of 0.14 to 0.44.[9] In one study of 1024 patients with suspected acute appendicitis, the highest positive predictive value (PPV) of an elevated WBC count peaked at 74.2%, and only when the WBC count was greater than 20,000/mm^3 and patients had symptoms for more than 48 hours.[10]

C-Reactive Protein

The C-reactive protein (CRP) level is a nonspecific systemic inflammatory marker synthesized by the liver. It has a poor predictive value in diagnosing or excluding acute appendicitis.[8] An elevated CRP (>3 mg/dL) has a sensitivity of 38% to 70%, a specificity of 65% to 85%, a positive LR of 1.98 to 2.63, and a negative LR of 0.47 to 0.72.[9]

Urinalysis

Pyuria may be present in 7% to 25% of patients with acute appendicitis.[11] When the inflamed appendix abuts a ureter or bladder, urinary tract inflammation may result. Despite this common occurrence, alternative causes of abdominal pain should be equally considered when urinalysis shows greater than 30 red blood cells (RBCs) per high-power field (HPF) or greater than 20 WBCs/HPF.

Other Laboratory Tests

A serum or urine pregnancy test is recommended for any female of childbearing age or reproductive capacity with abdominal pain. A basic metabolic panel should be considered for patients with suspected appendicitis to assess for electrolyte derangements. Liver function tests and a lipase level may help evaluate for alternative causes of abdominal pain. Procalcitonin, proportion of polymorphonuclear cells (WBC count differential), D-dimer, and bilirubin do not individually play any role in the diagnosis of appendicitis due to their poor predictive value.[1,2]

Combined Laboratory Tests

Combined laboratory findings offer the greatest impact in excluding appendicitis among patients with a low pretest probability of the disease. In one study, while normal WBC and CRP levels offered NPVs of 64% and 55% respectively, normal values of WBC and CRP combined resulted in a NPV of 88%.[10] Commercially available panels have been developed combining WBC, CRP, and myeloid-related protein in a mathematical algorithm that holds promise for excluding appendicitis in low-risk children and adults. Trials of these panels have shown sensitivities of 97%, and NPVs of 95% in children and

98% in adults.[12,13] Additional research is required prior to standard adoption of these tests in the ED setting.

Clinical Decision Instruments

Multiple clinical decision instruments combine clinical signs and laboratory test results to assist providers in risk stratifying patients into low, moderate, or high-risk categories. They may help determine whether a patient warrants outpatient follow-up, diagnostic imaging, or surgical consultation.

The best studied and most well-recognized clinical decision instrument is the Alvarado score, validated in both children and adults. Similar, though specific to children, is the Pediatric Appendicitis Score. Finally, the Appendicitis Inflammatory Response Score, validated in both children and adults, has been shown to have comparable predictability to the Alvarado score.[5] Table 79.4 lists the components of each scoring system.[14,15]

Imaging

General Principles

The decision to pursue imaging is based on the provider's clinical assessment, which combines the patient's history, examination, and potentially laboratory data to determine the likelihood of appendicitis. When the likelihood is sufficiently low, a patient may be discharged from the ED without imaging after an informed discussion of the risks and an explanation of return precautions. If there is a moderate to high likelihood of appendicitis, imaging should be pursued.

Patients in industrialized countries rarely undergo surgical removal of the appendix without receiving imaging first. The negative appendectomy rate—the number of normal appendices that are surgically removed—is far lower when imaging is utilized: the rate decreased from 13.5% to 3.7% in children and from 12% to 6% in adults with imaging.[16] Nevertheless, the decision to perform an appendectomy without imaging on a patient with a classic presentation may be pursued at the surgeon's discretion. This most frequently occurs in young healthy males.

Plain Radiographs

Due to their poor sensitivity and specificity, routine radiographs are of no clinical value in the evaluation of appendicitis. In a patient with peritonitis, an upright chest radiograph may be helpful if it reveals free air under the diaphragm resulting from perforation. In this circumstance, surgical consultation is necessary for likely operative exploration.

Graded Compression Ultrasound

Graded compression ultrasound (US) is an imaging tool commonly used to evaluate for appendicitis. Steady pressure is applied with the US probe to reduce bowel gas and collapse normal bowel to promote visualization of the appendix. Studies involving graded compression US for the diagnosis of appendicitis show sensitivities of 74% to 94%, specificities of 85% to 93%, positive LRs of 4.68 to 11.66, and negative LRs of 0.07 to 0.31.[9] Table 79.5 lists the US criteria for the diagnosis of appendicitis, and Figures 79.2 and 79.3 show appendicitis seen on US.

The cost of US is less compared to other imaging modalities, and it lacks ionizing radiation and frequently decreases time to diagnosis. However, US has decreased sensitivity compared to other imaging modalities and may be associated with increased pain due to the transducer pressure needed for graded compression. The biggest limitation with US is that the appendix is frequently not seen (i.e., a nondiagnostic examination). Potential contributing factors include operator experience, patient body habitus, patient cooperation, superimposed bowel gas, or an atypically located appendix.[16] In cases with nondiagnostic US findings, the patient typically requires further imaging with CT (or MRI in pregnancy), or admission for observation and serial examinations. US is generally most useful in children, for whom the long-term risks of ionizing radiation are greatest and in whom rates of obesity are lower than

TABLE 79.4 Components of Appendicitis Clinical Decision Instruments[15,16]

ALVARADO SCORE		PEDIATRIC APPENDICITIS SCORE		APPENDICITIS INFLAMMATORY RESPONSE SCORE	
Signs/symptoms	**Points**	**Signs/Symptoms**	**Points**	**Signs/Symptoms**	**Points**
Migration of pain	1	Migration of pain	1	Vomiting	1
Anorexia	1	Anorexia	1	Right iliac fossa pain	1
Nausea/vomiting	1	Nausea/vomiting	1	Rebound pain, light	1
Right lower quadrant tenderness	2	Right lower quadrant tenderness	2	Rebound pain, medium	2
Rebound pain	1	Rebound pain	2	Rebound pain, strong	3
Temperature ≥ 37.7°C (99.1°F)	1	Right lower quadrant pain with coughing/hopping/percussion	2	Temperature ≥ 38.5°C (101.3°F)	1
Leukocytosis ≥ 10,000 per μL (10.0×10^9 per L)	2	Temperature ≥ 38°C (100.4°F)	1	Leukocytosis ≥ 10,000–14,900 per μL ($10.0–14.9 \times 10^9$ per L)	1
PMN ≥ 75%	1	Leukocytosis ≥ 10,000 per μL	1	Leukocytosis ≥ 15,000 per μL (15.0×10^9 per L)	2
Total possible score*	10	PMN ≥ 75%	1	PMN 70–84%	1
*High-risk score ≥ 7 gives adults 87% probability of appendicitis, and children 67% probability (Kollár, Pogorelić]		Total possible score*	12	PMN ≥ 85%	2
		*High-risk score ≥ 8 gives children an 80% risk of appendicitis (Pogorelić)		CRP 10–49 g/L	1
				CRP ≥ 50 g/L	2
				Total possible score*	12
				*High-risk score >9 gives adults 88% probability of appendicitis	

*High risk score.

TABLE 79.5 Diagnostic Criteria for Appendicitis on Imaging

Ultrasound	Computed Tomography	Magnetic Resonance Imaging
The first two criteria below must be fulfilled:	Not all criteria listed below need to be fulfilled, but the combination and severity of these findings contribute to a diagnosis:	Not all criteria listed need to be fulfilled but the combination and severity of these findings contribute to a diagnosis:
• Appendiceal diameter > 6–7 mm[a]	Appendiceal diameter (> 6 mm with surrounding inflammation or > 8 mm without such changes)	Appendiceal diameter > 7 mm
• Noncompressible appendix	Appendiceal circumferential wall thickening > 2 mm with mural enhancement (sign of inflammation)	Appendiceal circumferential wall thickening > 2 mm
Fat stranding (hyperechoic signals associated with periappendiceal inflammation) (secondary finding)	Calcified appendicolith	Signs of inflammation adjacent to the appendix, such as fat stranding or phlegmon formation
Peritoneal fluid surrounding the appendix (secondary finding)	Signs of periappendiceal inflammation (e.g., fat stranding, clouding of the adjacent mesentery)	Presence of an abscess or a fluid-filled appendix

[a]It is important to note that the diameter of a normal nondiseased appendix may be up to 11 mm, thus the other findings suggestive of appendicitis must also be factored in when evaluating for appendicitis on CT or MRI. Due to the graded compression technique employed during ultrasound examination for appendicitis, there is comparatively greater diagnostic certainty irrespective of appendiceal diameter because appendicitis is associated with noncompressibility regardless of size.

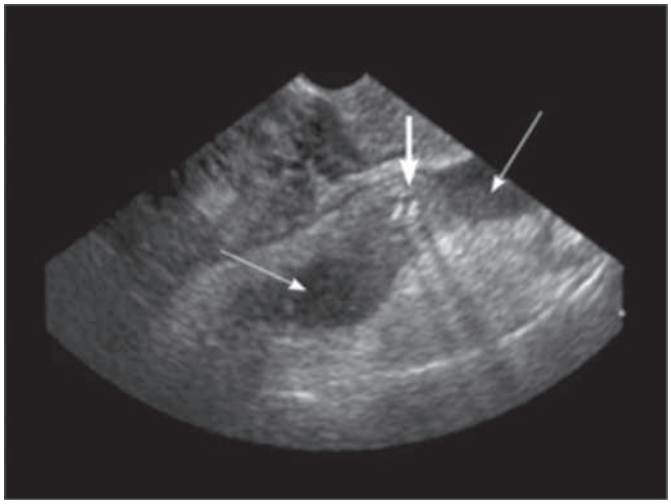


Fig. 79.2 Ultrasound image of appendicitis in an 8-year-old girl. Note the dilated noncompressible appendix *(thin arrows)* and the presence of a fecalith, with posterior acoustic shadowing *(thick arrow)*. (Courtesy Dr. Michael Cole, with permission.)

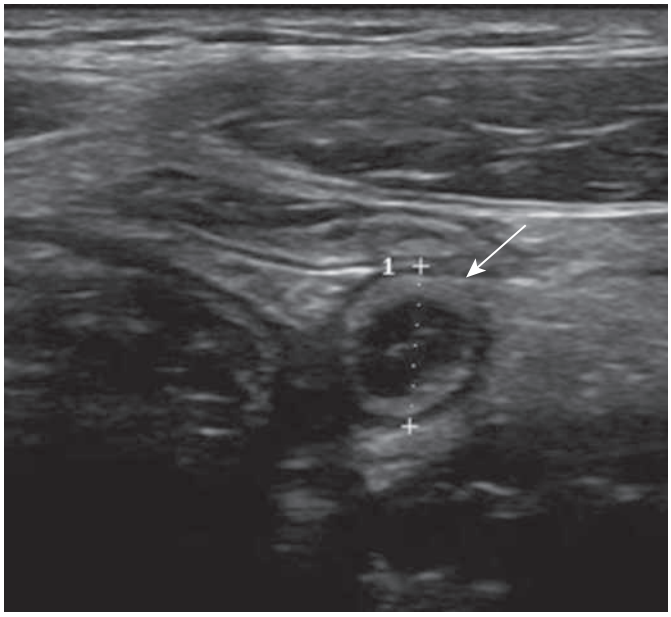


Fig. 79.3 Graded compression ultrasound scan demonstrating a dilated noncompressible appendix *(thin arrow)* representing appendicitis.

adults. US for appendicitis is also useful in pregnant females, but the rate of appendiceal visualization is lower in pregnancy.[5]

Previously, distinctions were made between radiology department US and nonradiologist physician point of care US (POCUS) examinations. A meta-analysis of POCUS studies on 6636 patients revealed a sensitivity of 91%, a specificity of 97%, a LR+ of 28.3, and a LR– of 0.09. Looking specifically at emergency physician performed POCUS, the sensitivity and specificity fell to 80% and 92%, respectively, with a LR+ of 10.2 and LR– of 0.22.[17] Ultimately, the diagnostic accuracy of US is dependent on the experience of the operator, and though helpful if it diagnoses appendicitis, given the variability of operator training and patient anatomy, US should not be utilized to exclude appendicitis in patients with high pretest probability.

Finally, in women with cervical motion tenderness, pelvic mass, or other suspected gynecologic pathology, pelvic US (which can be performed concurrently with US for appendicitis) evaluates for several alternative etiologies of pain. When a gynecologic source is suspected, performing pelvic US prior to CT may spare patients both cost and radiation, because pelvic US may provide a compelling alternative diagnosis and preclude further appendicitis workup.

Computed Tomography

CT of the abdomen and pelvis is considered the test of choice for definitive assessment for possible appendicitis in nonpregnant patients. It has a sensitivity of 95% to 100% and a specificity of 98% to 99.5%[1] CT is accurate and consistent in diagnosing appendicitis and decreases the negative appendectomy rate from 12% to 6%.[2] CT is readily available, can be performed rapidly, is not operator dependent, can be interpreted by most radiologists and surgeons, and has a greater likelihood of finding an alternative diagnosis than US. Figures 79.4 and 79.5 demonstrate appendicitis seen on CT.

The greatest disadvantage of CT is ionizing radiation. A CT of the abdomen exposes the patient to an average dose of 8 mSv of ionizing radiation. To place this in perspective, the average ionizing radiation dose associated with an abdominal x-ray is 0.7 mSv, and the average dose

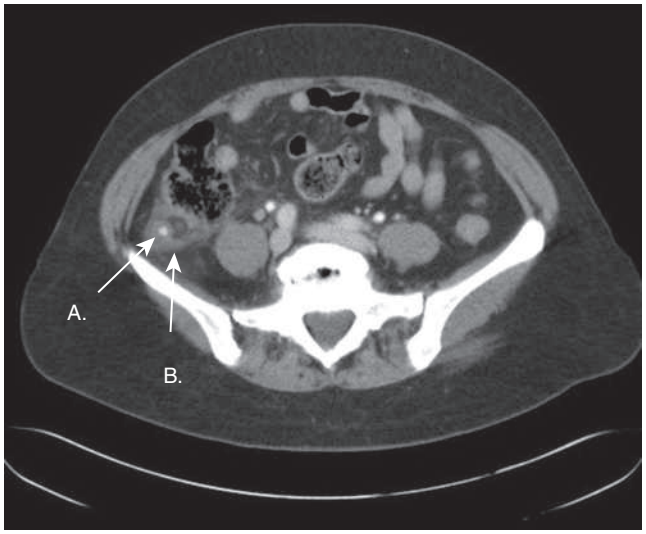


Fig. 79.4 CT scan of abdomen with typical findings of acute appendicitis (*Arrow A* = dilated appendix with wall thickening and central appendicolith, *Arrow B* = surrounding fat stranding indicating local inflammation).

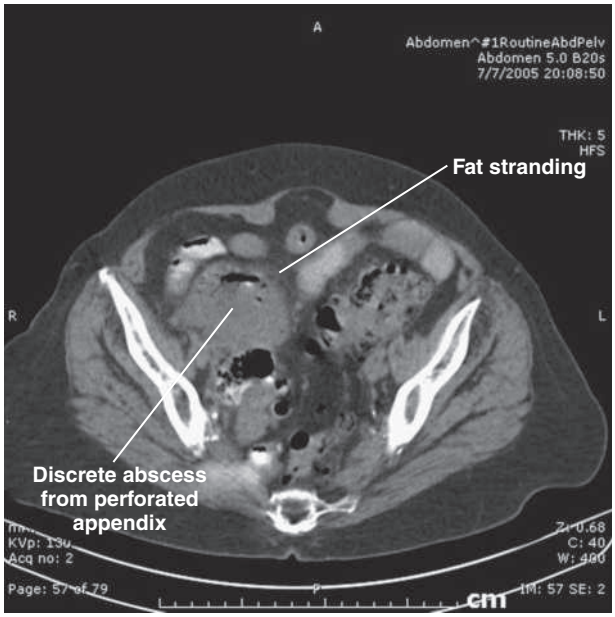


Fig. 79.5 CT scan showing discrete abscess from appendiceal perforation, with periappendiceal fat streaking. (Courtesy Jefferson Radiology, Avon, CT.)

associated with coronary angioplasty is 15 mSv. The risk of radiation-related cancers has led to the utilization of low-dose CT protocols for the diagnosis of appendicitis. Low-dose protocols decrease the average dose to approximately 2 mSv, with no detriment to the negative appendectomy rate. A diagnostic meta-analysis revealed no change in sensitivity and specificity between the standard and reduced-dose CT (96% and 94% respectively).[18]

CT findings of appendicitis include measurement of the highly variable appendiceal diameter (ranging 6–11 mm) and several others, as listed in Table 79.5. In some cases, the appendix cannot be visualized. In these cases, if CT demonstrates no findings of inflammation in the RLQ, appendicitis is unlikely. However, patients with a paucity of intra-abdominal fat may not display secondary signs of inflammation on CT, leading to false-negative results. The term *tip appendicitis* refers to obstruction and inflammation limited to the distal tip of the appendix and is a subtle finding on CT that frequently leads to a false-negative interpretation.

To assess for appendicitis, CT should be performed with IV contrast only. Enteric contrast of any type, oral or rectal, contributes little to the assessment of appendicitis. In addition, studies have demonstrated that non–contrast-enhanced CT has acceptable accuracy in diagnosing appendicitis. Furthermore, according to the American College of Radiology's appropriateness criteria for imaging suspected appendicitis, CT imaging with or without IV contrast are acceptable imaging modalities, with the use of enteric contrast deferred to institutional preference. Therefore, when IV contrast is contraindicated, non-contrast CT is generally sufficient to evaluate for appendicitis.[19]

Magnetic Resonance Imaging

Evidence supports the use of MRI to assess for appendicitis during pregnancy if US is nondiagnostic. MRI does not use ionizing radiation and is not operator dependent. However, its use is limited by cost, time required to acquire images, availability, and necessity for the radiologist or surgeon to be skilled in MRI interpretation.[20] A meta-analysis of MRI for acute appendicitis revealed a sensitivity of 94% and a specificity 97% for pregnant patients.[21] Table 79.5 lists the MRI criteria for the diagnosis of appendicitis.

In pregnant patients, IV gadolinium should not be used when evaluating for appendicitis due to potential harmful effects on the fetus. Enteric contrast may be used at the discretion of the interpreting radiologist or per institutional protocol.

Summary of Imaging Methods

Figure 79.6 illustrates a suggested imaging and management pathway for suspected acute appendicitis.

Nonpregnant Patients. Graded compression US may be considered first. In nonpregnant females, a pelvic US may also be considered to assess for pelvic pathology. The ability to visualize the appendix on US is operator dependent, and the provider's decision to use US may depend on the sonographer's level of experience with this examination.

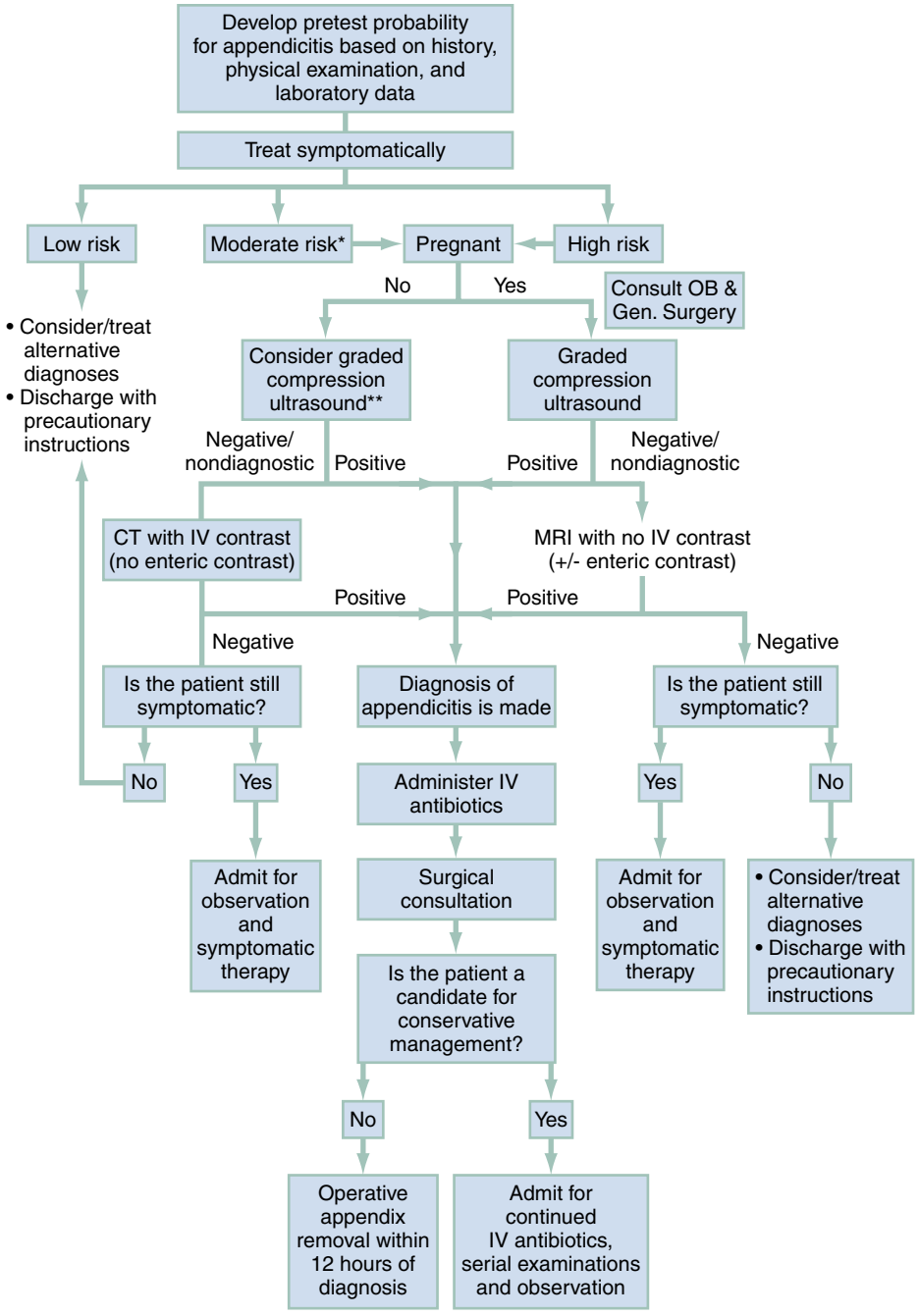
When US is negative or nondiagnostic (i.e., no appendix is visualized and no alternative pathology is noted) and clinical suspicion remains, the patient should undergo CT imaging of the abdomen and pelvis with IV contrast. An alternative to CT in low-risk cases with nondiagnostic US is admission for observation and serial examinations. Potential alternatives to CT in appropriately selected low-risk patients with a negative US include either continued ED observation or discharge with a planned reevaluation (e.g., in 6–12 hours).

Pregnant Patients. US should be the initial study of choice, followed by MRI of the abdomen without gadolinium in cases of nondiagnostic or negative US. If MRI is not available and transfer to a facility with MRI capabilities is not feasible, then, after consultation with appropriate specialists, including a radiologist, general surgeon, or obstetrician, abdominal CT with IV contrast may be indicated. However, in low-risk cases, admission for observation and serial examinations is an acceptable alternative with consultant support.

MANAGEMENT

Supportive Care

Once appendicitis is suspected, patients should be made NPO and supportive care should be initiated. Intravenous (IV) fluids, either normal saline or lactated Ringers, may be administered to maintain hydration. If necessary, pain should be treated with parenteral opiate analgesia (e.g., morphine sulfate 0.1 mg/kg IV), and nausea should be treated with parenteral antiemetics. Opiate analgesia does not limit abdominal examination for a potential surgical condition. Systemic signs of infection, which



*In moderate pretest probability patients, the provider may consider admission for serial examinations or discharge in select cases.

**In pediatric patients, graded compression ultrasound should always be the first imaging test performed.

Fig. 79.6 Suggested clinical management pathway for emergency department patients with possible appendicitis. *Gen.,* General; *OB,* obstetrician.

are more common in perforated appendicitis, should be treated with antipyretics and antibiotics as necessary. Acute uncomplicated appendicitis rarely causes severe sepsis or septic shock, however, such complications can arise with delayed presentation or diagnosis.

Antibiotic Therapy

Antibiotics should be administered upon diagnosis of appendicitis, or early in the management of septic patients with suspected appendicitis. Antibiotics should cover gram-negative aerobes, enteric gram-positive streptococci, and anaerobes. Pseudomonal coverage is not necessary for patients with mild to moderate disease severity and lack of health care–associated risk factors.

Acceptable antibiotic regimens for acute uncomplicated appendicitis include:

- Ertapenem 1g (adult) IV daily or 15 mg/kg (child, to max of 1g/day) IV twice daily,
- Piperacillin-tazobactam 3.375 g (adult) or 60–75 mg/kg of piperacillin (child, to max 3 g dose) IV every 6 hours, OR

- Ceftriaxone 1 g (adult) or 50–75 mg/kg (child, to max of 1 g) IV daily PLUS metronidazole 500 mg (adult) IV or 10 mg/kg (child, to max of 500 mg/dose) IV every 8 hours.

Patients with significant systemic illness, immunosuppression, or advanced age should receive imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, or metronidazole PLUS cefepime. Quinolone antibiotics were previously a mainstay in the management of acute appendicitis, but their side effects now make other comparatively lower-risk agents more appealing.

Definitive Treatment

Although management options for acute appendicitis have diversified significantly, surgical consultation remains vital. Although the final decision regarding operative management (OM) versus nonoperative management (NOM) is made between the patient and the surgeon, patients often ask emergency providers for insight and guidance; thus emergency providers should be educated on the indications for both treatment pathways.

Uncomplicated Appendicitis

Classically, the management of uncomplicated appendicitis (appendicitis without gangrene, phlegmon, abscess, or perforation) has involved either open or laparoscopic appendectomy. More recently, the possibility of in-hospital or outpatient antibiotic management has been explored.

Surgical appendectomy generally yields permanent resolution of appendicitis with little chance for recurrence. Multiple studies have demonstrated that delays of 12 to 24 hours between appendicitis diagnosis and OM are not associated with adverse outcomes.[22-25] Therefore, many surgeons will perform an appendectomy the following morning if a patient presents in the evening or overnight hours. Early appendectomy should be considered for elders, who are at high risk for developing appendiceal perforation after CT and before OM, with as many as 41% of patients 65 years or older developing perforation during this period.[22] Hospitalization for appendectomy is usually brief, with 87% of patients discharged on the day of, or day after, surgery.[26]

Despite its benefits, appendectomy puts patients at risk for intraoperative and postoperative complications. The overall complication rate of appendectomy ranges from 3% to 8%, with one study reporting serious complications (organ space infection, deep incisional infection, wound disruption, urinary tract infection, pneumonia, unplanned intubation, venous thromboembolism, acute renal insufficiency, septic shock, myocardial infarction, or cardiac arrest) in 2.2% of patients.[26-28] These complication rates markedly increase with age, reported as frequently as 13.7% in individuals 75 years or older.[28]

Although NOM spares patients the risks associated with surgery, there are other associated risks that need to be considered. Treatment failure and recurrent appendicitis, both of which are generally managed operatively, are realistic considerations for patients contemplating NOM. Treatment failure occurs in 2% to 6% of patients undergoing a trial of NOM.[29-32] The best known risk factor for treatment failure is the presence of a fecalith/appendicolith. Other risk factors for treatment failure and recurrence have been harder to elucidate. When NOM is successful, patients continue to remain at risk for recurrence. Approximately 25% of NOM patients require appendectomy during the first year after presentation, and approximately 40% receive appendectomy during the first five years.[29,30,33] Patients with recurrent appendicitis after initial NOM are not, however, at higher risk of developing complicated appendicitis.[30,34] Finally, when considering NOM, patients should be informed that 1% to 2% of appendicitis cases are associated with malignancy.[26,32,35-38] For this reason, guidelines recommend follow-up colonoscopy for patients over 40 years old treated with NOM.[39]

NOM may have both cost and quality-of-life benefits. Even when the costs of treatment failure and appendicitis recurrence after NOM are accounted for, the overall cost of OM is higher.[28,40,41] Additionally, NOM is associated with reduced pain and reduced disability when compared to OM.[40]

Once a patient is deemed appropriate for NOM and educated on the risks and benefits of this approach, many patients ultimately prefer a trial NOM over OM. In one study, 55 of 60 patients offered a choice between NOM and OM chose NOM.[34]

NOM has also been explored in children. As with adults, NOM in children has risks of treatment failure and recurrence, but the frequency of these events is not as well defined.[42-46] As in adult populations, presence of fecalith/appendicolith puts children at higher risk for failed NOM.[43] Children undergoing NOM have fewer days of disability but it is unclear whether overall costs are reduced with NOM, because these children are more likely to undergo advanced imaging, have more ED visits, and have more hospitalizations than children treated initially with OM.[45,47,48] One study showed that approximately 40% of caregivers would select NOM for their child after an explanation of the risks and benefits of OM and NOM.[49]

Previously, NOM required multiday hospitalization, however, recent research has demonstrated the potential for outpatient management. A small study determined that discharge from the ED was possible for patients meeting the following criteria:

- Age 14 years or older
- Systolic blood pressure > 90 mm Hg
- Heart rate < 100 beats per minute
- Temperature < 38.5°C
- Pain controlled by oral analgesics
- Tolerating oral fluids and medication
- Able to return for further evaluation
- Treating physician comfortable with discharge
- Patient comfortable with discharge

In this study, 14 out of 15 patients receiving NOM were eligible for outpatient management. Per protocol, enrolled patients were given 1 g of ertapenem IV in the ED and discharged with a planned next-day ED reevaluation. Patients who continued to do well at reevaluation were given an additional 1 g ertapenem IV and discharged with eight days of oral antibiotics (cefdinir 300 mg twice daily and metronidazole 500 mg every 8 hr). No NOM patients had treatment failure. Two of the 15 NOM patients later developed recurrent appendicitis, one having uncomplicated appendicitis and one having appendicitis with phlegmon.[40] Although these initial results are promising, outpatient treatment of appendicitis is not yet widely utilized and further data are needed. Studies have not evaluated outpatient NOM in children.

Finally, the evaluation and management of suspected appendicitis in pregnancy warrants special consideration. Because progression to complicated appendicitis is more common in pregnancy, diagnosis and management should be expedited as much as possible. Establishing a definitive diagnosis of appendicitis is crucial given that the risk of fetal loss with a negative appendectomy is 4% and the risk of premature labor is 11%.[50]

OM remains the generally preferred approach to appendicitis during pregnancy due to the risks associated with disease progression and the inability to predict which patients will fail NOM. When pregnant patients develop peritonitis from appendicitis, the risk of fetal loss increases from 2% to 6%, and the risk of premature labor increases from 4% to 11%.[50] One-third of pregnant appendicitis patients will develop perforation, with reported fetal loss rates of 24% to 36%.[50] Because of the increased risks associated with appendicitis

in pregnancy, emergency providers should strongly consider obstetrical consultation.

Complicated Appendicitis

Management of complicated appendicitis in both adults and children is rife with challenges. Surgical management may be high risk, but an antibiotics-only approach is often insufficient and is associated with longer hospitalization.[51,52] Interventional radiology may play an important role in the management of associated abscess. Complicated appendicitis generally requires hospitalization with surgical consultation and, when indicated, interventional radiology consultation.

DISPOSITION

There are three likely disposition pathways when a diagnosis of uncomplicated appendicitis is considered.

1. When a diagnosis of appendicitis is made based on imaging or, rarely, clinical assessment alone, IV antibiotics should be initiated, surgical consultation should be obtained, and the patient should be admitted for operative intervention or IV antibiotics and serial exams. In select cases, after surgical evaluation and a risk-benefit discussion, a reliable patient who (1) prefers outpatient management, (2) has a benign examination, (3) has no fecalith/appendicolith on imaging, and (4) has planned follow-up within 24 hours, can be discharged with oral antibiotics and strict return precautions.
2. When a diagnosis of appendicitis is considered, but the pretest probability is low based on clinical and laboratory assessment, a reliable patient may be discharged home if he or she has clinically improved, understands the concept of diagnostic uncertainty, and can follow strict return precautions. If these criteria are not met, advanced imaging or continued observation may be warranted. Alternative diagnoses should be considered as indicated.
3. When imaging results are inconclusive, or when imaging results are negative but posttest probability remains high (e.g., the patient is still symptomatic or has a concerning exam), the patient may be admitted for observation, symptomatic treatment, and serial examinations. If imaging is inconclusive but the overall suspicion for appendicitis is low and the patient is reliable, a reasonable approach includes discharge with close follow-up and strict return precautions after a shared decision-making discussion. Alternative diagnoses should also be considered.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 79: QUESTIONS AND ANSWERS

1. What percentage of women with acute appendicitis have accompanying cervical motion tenderness (CMT)?

a. <5%
b. 15%
c. 25%
d. 50%
e. 75%

Answer: c. Prior to the advent of routine imaging of the appendix, as many as 25% of women with acute appendicitis were initially misdiagnosed because of the presence of CMT.

2. Which of the following statements regarding ultrasonographic visualization of the appendix is true?

a. A compressible appendix is a positive finding.
b. An appendiceal diameter greater than 6 or 7 mm is a positive finding.
c. The sensitivity of ultrasound for appendicitis is 94% to 98%.
d. Ultrasonography has good reliability for detecting a retrocecal appendix.
e. Ultrasonography compares favorably with computed tomography (CT) scanning for the detection of appendicitis.

Answer: b. A noncompressible appendix with a diameter greater than 6 or 7 mm in a setting of clinical features of appendicitis is considered a positive finding. Ultrasound sensitivities are 75% to 90%. It is a less useful modality in the obese, those with peritoneal adhesions, or those with a retrocecal appendix. The sensitivity of CT is much higher than ultrasonography.

3. A 27-year-old G3P2 woman at 22 weeks of gestation presents with 2 days of right lower quadrant (RLQ) abdominal pain. It began midline and later became more pronounced in the RLQ. The physical examination is remarkable for RLQ tenderness without rebound. The gynecologic examination is negative except for a nontender gravid uterus, with good fetal movement by transabdominal ultrasound. Urinalysis shows 8 to 10 white blood cells (WBCs)/high-power field (HPF) and occasional bacteria. Complete blood count (CBC) shows a WBC count of 12,700/mm^3 with 77% neutrophils. Hemoglobin level is 11 g/dL. RLQ ultrasound examination is limited, without visualization of the appendix or secondary signs of appendicitis. Transvaginal ultrasound does not show a gynecologic or obstetric problem. Repeat examination shows continued RLQ tenderness. What is the most appropriate intervention at this point?

a. Administer cephalexin for urinary tract infection and schedule a 48-hour clinic recheck
b. Admit for observation and serial examination
c. Obtain surgical consultation for laparotomy
d. Order a CT scan of the abdomen.
e. Order a magnetic resonance imaging (MRI) scan

Answer: e. MRI for appendicitis is helpful in pregnant women, and radiation exposure should be minimized. Exploratory surgery carries significant risk of premature labor and fetal loss.

4. In young patients with classic symptoms and signs of appendicitis, what is the most appropriate initial intervention?

a. Antibiotics and serial abdominal examinations
b. CT scan of the abdomen
c. MRI scan of the abdomen
d. Surgery
e. Ultrasonography

Answer: e. Ultrasound is the most appropriate initial intervention because it uses no radiation and can often visualize and diagnose appendicitis without significant delay. It has become less common for a patient with a history and examination concerning for appendicitis to undergo surgery without imaging, and the use of advanced imaging has dramatically decreased the negative appendectomy rate. Graded compression ultrasound for appendicitis is specific but lacks the sensitivity of CT, so if clinical suspicion persists after a negative or nondiagnostic ultrasound, CT (or MRI in pregnant patients) is often the best next step.

Gastroenteritis

Thomas Nguyen and Saadia Akhtar

KEY CONCEPTS

- Gastroenteritis is usually self-limited and requires supportive care only. Routine laboratory testing or stool cultures are not indicated for most patients.
- Patients with gastroenteritis associated with fever, dysentery, bloody stools, severe dehydration, sepsis, a suspicion for *Clostridium difficile,* or an immunocompromised state should generally have a complete blood count, electrolytes, and stool cultures evaluated.
- Caution should be used in the care of the very young and elders with gastroenteritis, because these populations have the highest morbidity and mortality.
- Evaluate all individuals with gastroenteritis for dehydration. Use of oral rehydration therapy (ORT) with hypotonic oral rehydration solution (e.g., World Health Organization [WHO]-modified 245 mOsm ORT solution) is recommended.
- The use of antiemetic medications in patients with gastroenteritis may help with ORT. Ondansetron 0.15 mg/kg up to 8 mg given orally (PO) or intravenously is safe and cost effective.
- Early continuation of normal feeding is advised, and continuation of breastfeeding in mothers with gastroenteritis is suggested, if possible.
- *Campylobacter* and *Salmonella* are the top two causes of culture-proven bacterial enteritis in developed countries. Consult health authorities for local or regional outbreaks and pathogen prevalence.
- Norovirus, previously referred to as the Norwalk-like virus, is the most common cause of acute gastroenteritis in children and adults.
- Bacterial pathogens are responsible for approximately 80% of all cases of traveler's diarrhea, which is usually self-limited. Enterotoxigenic *Escherichia coli* (ETEC) is the most common etiology.
- Antibiotic treatments can prolong the shedding of *Salmonella* non-*typhi* organisms and therefore are not indicated in most gastrointestinal infections.
- Avoid antibiotic treatment in patients with gastroenteritis caused by *E. coli* O157:H7 or Shiga toxin 2–producing organisms as treatment increases the incidence of hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP).
- In patients with fever or bloody stools, if antimotility agents are to be given, they should be administered in combination with an antibiotic as these agents may increase the contact time of the toxin or invasive infectious organism within the intestinal mucosa.
- Classic food poisoning usually manifests 1–6 h post ingestion of preformed toxins from bacterial organisms such as *Staphylococcus, Bacillus cereus*, or *Clostridium perfringens*. Food poisoning is generally short-lived (24 h), and the treatment is typically supportive care only.
- Risk factors for *C. difficile* colitis include recent antibiotic use (1–4 weeks), recent hospitalization, living in a long-term care facility, solid organ transplant recipients, or the use of antacids.
- Evaluation with abdominal computerized tomography (CT) for toxic megacolon and pseudomembranous colitis is recommended for patients with *C. difficile* colitis who are older, appear septic, have a tender distended abdomen, or have a high leukocytosis. Consider empirical antibiotic treatment with vancomycin 125 mg PO every 8 h for 10 days for suspected *C. difficile.*
- Scombroid poisoning results from eating spoiled dark meat fish; scombroid poisoning is not an allergic reaction but results from ingestion of histamine.
- In addition to the regular enteropathic bacterial pathogens, human immunodeficiency virus (HIV)-positive patients, particularly those with a CD4+ count less than 200/mm^3, have increased susceptibility to certain viruses and parasites, such as *Cytomegalovirus, Cyclospora, Cryptosporidium, Isospora, Mycobacterium avium-intracellulare* complex, and *Giardia.*
- Consider *Giardia* for diarrhea lasting more than 2 weeks, with foul-smelling stools and symptoms of flatulence, abdominal bloating, cramping, and recent exposure to contaminated river water.
- Hand hygiene with soap and water or hand sanitizers will contain the spread of most infectious agents in gastroenteritis.

OVERVIEW

Foundations

Background and Importance

Gastroenteritis is an acute diarrheal infection of the gastrointestinal (GI) tract and is generally a self-limited illness. Most patients have nausea, vomiting, and diarrhea, often with diarrhea being the predominant symptom. Diarrhea is defined as the passage of three or more unformed liquid stools a day, stools of more than 250 g/day, or stool that takes the form of the container into which it is placed.[1] Dysentery refers to an inflammation of the intestine, particularly the colon, causing diarrhea associated with blood and mucus; it is generally associated with fever, abdominal pain, and rectal tenesmus (the sensation of incomplete defecation).

Gastroenteritis is one of the leading causes of morbidity and mortality worldwide, especially in children. Approximately 180 million cases of acute diarrhea occur each year in the United States, most of which are self-limited and without consequence. The incidence has been increasing due to heightened international travel, mass production of foods, and the increased consumption of raw produce, such as spinach or fresh fruits. Viruses account for most of the infectious causes.[2]

Diarrhea-related deaths in developed countries occur most often in elders or debilitated patients; *Clostridium difficile* and norovirus are most frequently implicated. Patients with *C. difficile*, human immunodeficiency virus (HIV) infection, immunocompromised-related enteritis, or fever and bloody stools require early diagnosis and treatment to maximize optimal outcomes. Diagnostic testing should be reserved for cases with a high suspicion for specific pathogens that cause more

severe clinical illness or cases occurring during an outbreak. Clinicians may play an important role in the surveillance and mitigate the spread of infection.

Diarrheal illnesses can be classified as being acute (<7 days), prolonged (7 to 13 days), persistent (14 to 29 days), or chronic (>30 days). Acute and prolonged gastroenteritis (13 or fewer days) are usually due to viral or bacterial causes. Persistent and chronic gastroenteritis (>13 days) is often caused by protozoans, parasites, or noninfectious conditions.[3,4]

Pathophysiology

The pathophysiology of an infection related to gastroenteritis involves one of four mechanisms—ingestion of preformed toxins, adherence of the infectious pathogens to the intestinal cell walls, invasion of mucosal cell walls, and production of enterotoxins and cytotoxins. Each mechanism leads to an increase in fluid secretion or a decrease in fluid absorption in the GI tract, resulting in diarrhea.

CLINICAL FEATURES

Patient History

The history of present illness should take into account epidemiologic factors that may help to identify the likely organism (Table 80.1). For example, travel outside of the United States to resource-poor countries raises suspicion for traveler's diarrhea, contact with persons on a cruise ship with a large GI outbreak is suspicious for norovirus, a recent camping trip with exposure to river water suggests giardiasis, and recent hospitalization or antibiotic use and patients in long-term care facilities are risk factors for *C. difficile* infection.

Associated factors are helpful in narrowing the list of possible causative organisms and in initiating treatments. For example, GI symptoms after a short exposure period (1 to 6 hours) may imply preformed toxins from Staphylococcal or *Bacillus* organisms. Diarrhea lasting more than 2 weeks may indicate the presence of *Giardia* or other protozoa, although noninfectious causes should be considered, such as inflammatory bowel disease (IBD). Norovirus classically causes a sudden onset of severe vomiting and only moderate diarrhea. Large-volume diarrhea usually indicates small bowel involvement, such as viral gastroenteritis or illness due to *Vibrio cholerae*. Colonic involvement causes smaller volume loss and more likely will be bloody or have fecal leukocytes from invasive organisms. A history of fever, abdominal pain, tenesmus, and bloody stools are signs of dysentery and may imply invasive organisms such as *Campylobacter* or *Shigella*. *Yersinia enterocolitica* GI infection may mimic acute appendicitis or regional enterocolitis due to its invasion of the local mesenteric lymph nodes. Vomiting without diarrhea generally should not be referred to as gastroenteritis. Alternative abdominal pathology such as appendicitis, cholecystitis, pancreatitis, or bowel obstruction should also be considered. Patients with lightheadedness or hypotension are likely to be dehydrated from diarrhea and vomiting. Muscle cramping may imply hypokalemia or hyponatremia from lack of oral intake or loss of electrolytes in diarrhea.

TABLE 80.1 Gastroenteritis: Epidemiologic Factors

Factor	Implications
Foreign travel	Traveler's diarrhea—enterotoxigenic *Escherichia coli* Southeast Asia—*Vibrio, Campylobacter* species South America, Asia, Africa—Rotavirus
Recent camping	*Giardia, Aeromonas, Cryptosporidium*
Recent antibiotics	Increase in *Clostridium difficile* infection
Daycare exposure	Rotavirus, Norovirus
Exposure to raw seafood	Noncholera *Vibrio*
Anal-receptive sex—men who have sex with men	*Shigella, Campylobacter, Salmonella, Entamoeba*
Human immunodeficiency virus (HIV)-positive status	*Mycobacterium avium-intracellulare* complex, microsporidia. cytomegalovirus, *Giardia, Salmonella, C. difficile, Shigella*
Outbreaks	Cruise ships—norovirus Contaminated local water, food, products, restaurants; organism usually identified by local health department (e.g., *Campylobacter, Salmonella, E. coli*)

Physical Examination

The physical examination focuses on the patient's general hydration status and assesses for life-threatening conditions. In the clinical setting of gastroenteritis, hypotension, and tachycardia likely indicate dehydration. Fever, altered mental status, or a toxic appearance may signify severe illness and possibly sepsis. Other disease states may mimic gastroenteritis, and a thorough examination is warranted.

Evaluation of the skin for the presence of petechiae or purpura, especially in the extremities, can suggest possible sepsis or disseminated intravascular coagulation (DIC). Dry mucous membranes, decreased skin turgor, or decreased urine output may also help to gauge hydration status. In children, weak pulses or sunken eyes are also good predictors of dehydration.[5] The abdominal examination focuses on conditions that may mimic gastroenteritis, such as small bowel obstruction (SBO), bowel ischemia, appendicitis, or colitis. In general, bowel sounds are hyperactive in acute gastroenteritis, although this may also be seen with intestinal obstruction. Abdominal findings such as focal tenderness, rebound, guarding, distention, or rigidity suggest a surgical process. A digital rectal examination can be performed to assess for gross blood, mucus, rectal lesions in the setting of blood or mucus in the stool, or complaints of rectal pain.

Differential Diagnoses

Other diagnoses to consider in patients with apparent gastroenteritis include SBO, diverticulitis, IBD, ischemic bowel disease, appendicitis, pancreatitis, hepatobiliary pathology, malabsorption, celiac disease, or irritable bowel syndrome.

An SBO is likely in the setting of recent abdominal surgery, crampy abdominal pain and vomiting, a distended and tender abdomen, and lack of passage of gas or stools. In diverticulitis, pain is generally localized to the left lower abdomen. IBD usually first presents in the young adult as recurrent diarrhea, with cramping. The stool may contain mucus or blood. Risk factors include obesity, smoking, and a family history of IBD, with the highest risk in females and Jewish persons of European ancestry. Patients with ischemic bowel may present with abdominal pain and tenderness, ranging from mild to severe with associated peritoneal signs. Risk factors include older age, low-flow states such as dehydration, recent congestive heart failure exacerbation, sepsis, smoking, atherosclerotic disease, or being at risk for thromboembolic events such as atrial fibrillation. Patients with gastroenteritis are generally not critically ill, and deterioration is not as rapid as seen in those with ischemic bowel disease.

Viruses account for up to 70% of cases of infectious gastroenteritis, bacteria 15% to 20%, and parasite approximately 10% to 15%. On initial presentation, it is often difficult to identify the exact organism causing the GI illness. The predominance of vomiting, along with upper respiratory symptoms, is more likely associated with a viral cause. Rapid onset of vomiting as the predominant symptom may suggest the presence of preformed bacterial toxins. The presence of high fever, fecal blood, abdominal pain, or colitis likely indicates an invasive bacterial organism.[3]

Diagnostic Testing

Diagnostic testing is guided by the clinical assessment. Routine laboratory tests are not needed in many cases. However, further evaluation may be required for patients presenting with severe illness or severe dehydration. A complete blood count (CBC) and serum metabolic profile should be considered for patients with high fevers, severe abdominal pain, bloody stools, or persistent diarrhea. Particular attention should be given to elders with abdominal pain as well as immunocompromised patients. For most cases of gastroenteritis, if the patient appears well and is likely to have a self-limited illness, stool cultures are not required. Stool cultures for *Salmonella, Shigella, Campylobacter, Yersinia,* Shiga toxin–producing *Escherichia coli* (STEC), and *C. difficile* may be considered for patients with severe illness, fever of 38.5°C (101°F) or higher, dysentery, immunocompromised state, recent hospitalization, or recent antibiotic use. With preliminary culture results, targeted antimicrobial treatment may be initiated to prevent the spread of infection (e.g., in an outbreak of daycare workers) and reduce the duration of symptoms. If diarrhea is persistent, stools for ova and parasite should be sent.[4] Stools sent for fecal leukocytes, lactoferrin, or hemoccult testing may help identify colonic inflammation with an invasive organism. Blood cultures should be considered in infants younger than 3 months of age, people of any age with signs of septicemia, those with suspicion for enteric fever, individuals with systemic manifestations of infection, immunocompromised states, high-risk conditions such as hemolytic anemia, or individuals who have traveled to or have had contact with travelers from enteric fever–endemic areas with a febrile illness of unknown etiology.[3] Tables 80.2, 80.3, and 80.4 summarize specific diagnostic testing and treatment for bacterial, viral, and parasitic infections, respectively.

Management

Patients who are severely dehydrated should receive an intravenous (IV) fluid bolus of an isotonic solution, such as lactated Ringers (LR). Electrolytes should be repleted, with particular attention to the sodium and potassium levels. Antiemetics can prevent ongoing loss of fluids and help with the initiation of oral rehydration therapy (ORT).

The exact cause of vomiting in gastroenteritis is not known, although it is thought to be due to peripheral stimuli arising from the GI tract primarily via the vagus nerve or by serotonin stimulation of the 5-hydroxytryptamine 3 (5-HT_3) receptors in the intestinal tract. These signals are transmitted to the emetic center in the brainstem that stimulates the muscles in the diaphragm, abdominal wall, and intestinal tract to produce vomiting.[6] Ondansetron 0.15 mg/kg up to 8 mg orally (PO) or IV is safe and potentially cost-effective due to its impact in decreasing IV fluid therapy needs and hospitalization rates in the pediatric population. Side effects of ondansetron include headache or diarrhea.[7]

The American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention (CDC), European Society for Pediatric Gastroenterology and Nutrition (ESPGHAN), and World Health Organization (WHO) all strongly support the use of ORT as first line treatment for

TABLE 80.2 Bacterial Gastroenteritis: Diagnosis and Treatment

Organism	Diagnosis	Treatment
Shigella	Stool culture (conventional)	Ciprofloxacin 500 mg PO bid for 3 days; or azithromycin 500 mg PO daily for 3 days
Salmonella enteritidis Nontyphoid	Stool culture (conventional); PCR	No treatment in nonsevere cases. For severe cases (fever, bloody diarrhea, bacteremia)—levofloxacin 500 mg IV or PO daily for 7–10 days
Salmonella typhi Typhoid	Stool culture (conventional)	Ciprofloxacin 500 mg PO bid for 7 days; or azithromycin 500 mg PO daily for 7 days; IV ceftriaxone, 1–2 g daily for 7 days
Campylobacter jejuni	Stool culture (conventional)	Azithromycin 500 mg PO daily for 3 days; or erythromycin 500 PO mg bid for 5 days
Vibrio cholerae	Stool culture with salt-containing media- TCBS	Doxycycline PO, 4 to 6 mg/kg, up to 300 mg, once daily for 3 days
Vibrio—noncholera *(Vibrio parahaemolyticus)*	Stool culture with TCBS	Ciprofloxacin 500 mg PO bid for 3 days; or azithromycin 500 mg PO daily for 3 days
Enterotoxigenic *Escherichia coli* (ETEC)	Stool culture; assay for toxin	Ciprofloxacin 750 mg PO once or 500 mg PO bid for 3 days, rifaximin 200 mg PO tid for 3 days; azithromycin 1 g PO once
Shiga toxin–producing *E. coli; E. coli* O157:H7	Sorbitol MacConkey and serotyping for O157:H7; PCR	No treatment, supportive care only; antibiotics increase risk for HUS
Yersinia enterocolitica	Cefsulodin-irgasan-novobiocin (CIN) agar	Supportive care; in severe cases, TMP-SMX (160 mg/800 mg) 1 Tab PO bid for 3 days, ciprofloxacin 500 mg PO bid for 3 days
Clostridium difficile	Stool for *C. difficile* toxin; PCR	Vancomycin 125 mg PO qid for 10 days or fidaxomicin 200 mg PO bid for 10 days. Alternative: metronidazole 500 mg PO tid for 10 days
Staphylococcus aureus	Food may be cultured for *Staphylococcus*, though not routine	Supportive care
Clostridium perfringens	Detection of spores in stool; PCR	Supportive care
Bacillus cereus	Food may be cultured, though not routine	Supportive care; for severe cases—vancomycin 125 mg PO qid; or clindamycin 500 mg PO tid for 7–10 days

HUS, Hemolytic uremic syndrome; *PCR,* polymerase chain reaction; *TCBS,* thiosulfate, citrate, bile salts, and sucrose; *TMP-SMX,* trimethoprim-sulfamethoxazole.

TABLE 80.3 Viral Gastroenteritis: Diagnosis and Treatment

Organism	Diagnosis	Treatment
Norovirus	Stool sample—real-time reverse transcription–polymerase chain reaction (RT-PCR) assay	Supportive care
Sapovirus	PCR, immunoassay	Supportive care
Rotavirus	Rotavirus antigen in stool sample	Supportive care; vaccine or natural infection do not uniformly provide immunity; vaccine alternatives include RotaTeq (RV5), given in three PO doses at ages 2, 4, and 6 months; *or* Rotarix (RV1), given in two PO doses at ages 2 and 4 months; *or* Rotavac, given in three PO doses 4 weeks apart, beginning at 6 weeks of age; *or* Rotasil, given in three PO doses 4 weeks apart, beginning at 6 weeks of age
Adenovirus	Antigen detection, PCR, virus isolation, serology	Supportive care
Astrovirus	PCR, electron microscopy, immunoassay	Supportive care

TABLE 80.4 Parasitic Intestinal Infections: Diagnosis and Treatment

Organism	Diagnosis	Treatment
Giardia lamblia	Stool microscopy for ova and parasite; immunoassay	Tinidazole 2 g PO single dose Metronidazole 500 mg PO bid or 250 mg tid for 5–7 days Nitazoxanide 500 mg PO bid for 3 days *Alternative agents* Albendazole 400 mg PO once daily for 5 days Mebendazole 200 mg PO tid for 5 days Quinacrine 100 mg PO tid for 5 days Paromomycin 10 mg/kg PO tid day for 5–10 days
Entamoeba histolytica	Stool microscopy, culture, immunoassay	Metronidazole 500–750 mg PO tid for 7–10 days; Tinidazole 2 g PO once a day for 3–5 days; Nitazoxanide 500 mg PO bid for 3 days *Intraluminal infection* Paromomycin 25–35 mg/kg PO divided tid for 7 days. Iodoquinol 650 mg PO tid for 20 days for adults Diloxanide furoate 500 mg PO tid for 10 days for adults
Cryptosporidium	Stool microscopy, culture, immunoassay	Nitazoxanide 500 mg PO bid for 3 days
Cyclospora cayetanensis	Stool microscopy, stool culture, acid-fast stain, fluorescence microscopy	Trimethoprim-sulfamethoxazole (TMP-SMX), one double-strength 160/800 mg tablet PO bid for 7–10 days

acute gastroenteritis, except in cases of severe dehydration. Although ORT has been extensively studied in children, the results can generally be applied to adults. It is known to be safe and effective as the treatment of choice for mild and moderate dehydration. Morbidity and mortality can be greatly reduced with the use of ORT. It is also associated with fewer major adverse events and results in shorter hospital stays.

Fluids containing glucose and electrolytes provide optimal rehydration due to the cotransport of the water across the intestinal lumen. Choices of oral rehydration solution (ORS) include the standard WHO ORS (331 mOsm/kg), reduced osmolarity WHO ORS (245 mOsm/kg), and Pedialyte (oral electrolyte solution for children; 250 mOsm/kg). Reduced osmolarity rehydration solution is associated with a reduced need for unscheduled IV infusions, lower stool volume, and less vomiting compared with a standard WHO rehydration solution. Simple home remedies, such as diluted fruit drinks and chicken broth, or commercial solutions such as Gatorade will also suffice.[1]

The official recommendation by ESPGHAN is to hydrate orally with reduced osmolarity or hypotonic fluids. Oral intake of food, if tolerated, should be continued during the illness, as fasting may worsen the capacity of the bowel to absorb fluid. The presence of food in the bowel lumen also promotes mucosal recovery and improves fluid absorption.[8]

Zinc 20 mg PO given to moderately to severely malnourished children older than 6 months has been shown to decrease the duration of diarrhea by approximately a day. The side effects of zinc are vomiting and a metallic taste.[3,9]

Antimotility drugs such as loperamide (Imodium) and diphenoxylate hydrochloride (Lomotil) can help to limit the number of watery stools and prevent dehydration. The initial dose of loperamide is 4 mg PO, followed by 2 mg after each unformed stool, up to a maximum of 16 mg/day for 48 hours. Loperamide is generally not recommended for patients younger than 18 years of age due to a high incidence of abdominal distension, ileus, lethargy, or death (in children younger than 3 years old). In patients with suspected bacterial dysentery, it is recommended that if antimotility agents are to be administered, it should be done in conjunction with antibiotics, as antimotility agents may serve to increase the contact time with the toxins or invasive organisms.[1,3]

In general, antibiotics are not indicated for the treatment of the vast majority of cases of acute gastroenteritis. However, empirical antibiotic therapy can be considered in patients who appear toxic, have a fever, or have dysentery (see discussion later); in patients with severe traveler's diarrhea; patients with suspected *C. difficile* colitis; in patients who are

immunocompromised; or when a known organism has been isolated from a community outbreak. The recommendation for empiric antibiotic treatment is azithromycin 500 mg daily PO for up to 3 days or ciprofloxacin 500 mg PO bid for up to 3–5 days, pending culture results. Tables 80.2 and 80.4 summarize recommended antibiotics for treating various bacterial and parasitic infections, respectively.

Disposition

Most patients with gastroenteritis can be managed on an outpatient basis. Written instructions should be given with recommendations for oral fluid intake, diet, and follow-up care. Hospitalization should be considered for patients with a toxic appearance, severe or persistent symptoms, inability to tolerate oral liquids, significant electrolyte abnormalities, or severe dehydration. Special consideration should be given to patients at the extremes of age or who are immunocompromised. These patients may require more extensive evaluation and further care.

BACTERIAL GASTROENTERITIS

In the United States, foodborne diarrheal illness caused by bacteria has increased over the past decades. The four most commonly reported bacterial pathogens are nontyphoid *Salmonella, Campylobacter*, STEC, and *Shigella*.[10] The cause of most diarrheal illness is rarely identified. Most laboratories are equipped to culture only the common pathogens, and routine stool cultures for diagnostic testing often miss organisms such as enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli,* and noncholera *Vibrio* spp.

There are several risk factors that influence the development of bacterial gastroenteritis. Very young patients have low immunity, and passive maternal immunity is lost after weaning from breastfeeding. Elders are at risk due to the age-related intestinal mucosal alteration of mucosa production, gut flora, and cell surface receptor affinity for toxins. The use of antacids, such as proton pump inhibitors, decreases the bactericidal effect of gastric acid. Antibiotic use reduces healthy intestinal flora and therefore increases the colonization of pathogens such as *C. difficile*. Immunosuppressed patients such as those with HIV disease or undergoing treatment with chemotherapeutic agents are predisposed to nontyphoid *Salmonella*. Poor sanitation and overcrowded conditions also enhance the spread of infectious organisms.

Bacterial organisms are broadly categorized as invasive or noninvasive. Invasive gastroenteritis is a clinical diagnosis made in the presence of signs or symptoms of intestinal mucosal invasion, such as fever, gross or occult blood in the stool, tenesmus (feeling of constantly needing to pass stool), or severe abdominal pain (Table 80.5). Patients with noninvasive gastroenteritis generally do not exhibit fever, produce bloody stools, or experience significant abdominal pain. Noninvasive gastroenteritis likely suggests the presence of a viral pathogen or toxin-producing bacteria. This illness typically is brief and self-limited, and diagnostic testing is unlikely to be of benefit (Table 80.6).

INVASIVE BACTERIA

Campylobacter Enteritis

Epidemiology

Campylobacter is the most commonly diagnosed cause of bacterial enteritis in developed countries. It is more common during the summer months. *Campylobacter* species are a common cause of so-called backpacker's diarrhea, along with *Giardia*, both of which are frequently acquired by drinking water from wilderness sources.

TABLE 80.5 Invasive Bacteria Gastroenteritis: Causes and Clinical Features

Organism	Clinical Features	Incubation Period (I), Duration (D), Source (S)
Campylobacter jejuni	Most common bacteria; organism identified in stool cultures; acute watery diarrhea, fevers, dysenteric characteristics	I, 2–5 days D, 5–14 days S, food, water, chickens
Salmonella Nontyphoid	Usually foodborne (e.g., poultry); acute watery diarrhea, often with fever; common in sickle cell and immunocompromised patients	I, 12–24 h D, 2–7 days S, eggs, poultry, unpasteurized milk, pets
Salmonella Typhoid	Fever, abdominal pain, ileus, systemic effects; most infections acquired during international travel	I, 12–24 h D, 2–7 days S, food, person to person
Shigella	Common worldwide; acute watery diarrhea, fever, dysenteric characteristics; toxigenic; high incidence in men who have sex with men	I, 1–2 days D,2–7 days S, water, person to person
Yersinia enterocolitica	Acute diarrhea, dehydration; rare in the United States but common with travel to Asia; can mimic appendicitis	I, 12–48 h D, 5–14 days S, food, water, milk, cats, dogs, pigs
Vibrio, noncholera *(V. parahaemolyticus)*	Associated with seafood, shellfish; watery diarrhea, dysentery	I, 8–24 h D, 5–14 days S, raw, undercooked seafood
Escherichia coli Shiga toxin-producing; *E. coli* O157:H7	Watery, bloody diarrhea; foodborne—contaminated beef or produce; toxigenic; associated with HUS and TTP	I, 3–8 days D, 5–10 days S, uncooked beef, water, person to person, raw milk

HUS, Hemolytic uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.

Pathophysiology

Campylobacter organisms are small, spiral-shaped, gram-negative bacteria. The most common species isolated is *Campylobacter jejuni. Campylobacter* species produce disease primarily by direct invasion of the colonic epithelium. Most infections are acquired by ingesting tainted drinking water, dairy products, meats, or produce. The primary reservoirs for *Campylobacter* organisms are chickens.[11]

Clinical Features

The incubation period for *Campylobacter* is approximately 2 to 5 days. Disease onset usually is rapid, with signs and symptoms of fever, cramping abdominal pain, and diarrhea 24 to 48 hours later. Constitutional symptoms of anorexia, malaise, myalgias, or headache are common.

TABLE 80.6 Noninvasive Toxigenic Bacterial Gastroenteritis: Causes and Clinical Features

Organism	Clinical Features	Incubation Period (I), Duration (D), Source (S)
Staphylococcus aureus	Short incubation period, 2–7 h; preformed toxin; vomiting; lasts <24 h	I, 1–6 h D, 6–12 h S, mayonnaise, potato salad, food handlers
Clostridium perfringens	Watery diarrhea, seen in large foodborne outbreaks	I, 6–24 h D, 1 day S, Steam table meat, poultry, gravy
Bacillus cereus	Vomiting or diarrhea, typically from contaminated rice	I, 1–12 h D, 1–2 days S, contaminated foods, rice
Vibrio cholerae	Enterotoxin; acute "rice water" diarrhea, dehydrating. Rare in the United States but common with travel to Asia	I, 1–2 days D, 6–8 days S, raw shellfish, oysters
Noncholera *Vibrio* (e.g., *V. vulnificus*)	Enterotoxin. Acute diarrhea, occasional dysentery. Seen in Gulf coast in the United States. Can cause septic shock, wound infection	I, 1–2 days D, 6–8 days S, raw shellfish, oysters
Marine bacteria flora (scombroid fish poisoning)	Histamine toxin; tachycardia, itching, flushing, cramping, dizziness, metallic taste	I, 5–60 min D, 6 h S, mahi mahi, tuna, other dark meat fish
Marine dinoflagellate *Gambierdiscus toxicus* (ciguatera fish poisoning)	Ciguatoxin-heat stable; pain, paresthesias, dysesthesias, vomiting, diarrhea	I, 2–6 h D, 7–14 days S, coral reef fish
Enterotoxigenic *Escherichia coli* (ETEC)	Acute watery diarrhea. Common cause of traveler's diarrhea, but in the United States increasing cause of foodborne disease	I, 1–3 days D, 1–7 days S, unsanitary water or food
Clostridioides difficile	Colitis, diarrhea, fever, toxic megacolon. Recent antibiotic or proton pump inhibitor use. High mortality in elderly and immunocompromised.	I, 5–14 days D, variable S, person to person, contaminated surfaces

Typically, the stools are loose and bile colored but then become watery and grossly bloody approximately 40% of the time. At the height of the illness, patients usually pass 8 to 10 stools or more per day.

Most patients recover within a week, although diarrhea can persist for an extended period. Relapses are common, although generally milder than the original episode, and fatalities are rare.

Diagnostic Testing

Because the clinical presentation is similar to that of other invasive bacterial pathogens, the identification of the *Campylobacter* pathogen requires stool culture or real-time polymerase chain reaction (PCR) assay. Specimens should be obtained from patients with acute enteritis associated with fever, abdominal pain, occult blood, or hematochezia. Blood culture results are rarely positive and therefore not routinely indicated.

Management

Empirical antibiotic therapy is not usually recommended for otherwise healthy patients without severe illness, except in the setting of travel-related diarrhea. Initial treatment of invasive diarrhea should focus on rehydration. The decision to initiate antibiotic therapy should be deferred pending identification of a specific organism via stool studies.

For patients who are not improving, antibiotic therapy shortens the duration of campylobacteriosis by approximately 1.3 days. Erythromycin, 500 mg bid PO for 5 days, or azithromycin, 500 mg daily PO for 3 days, is the recommended first line therapeutic regimens. Ciprofloxacin, 500 mg bid PO for 7 days, can be used as the second choice of treatment, but alarming resistance to the fluoroquinolones has emerged. Approximately 20% of *Campylobacter* strains in the United States are now resistant to fluoroquinolones, and resistance of more than 80% has been documented in Southeast Asia. Because *Campylobacter* infection causes an invasive enteritis, antimotility agents are not recommended unless treatment with antibiotics is also given.

Complications of *Campylobacter* infection are rare. Cholecystitis, pancreatitis, and massive GI bleeding all have been reported, as have meningitis, endocarditis, and osteomyelitis. There is an association between *Campylobacter* infection with reactive arthritis and Guillain-Barré syndrome, with an incidence of approximately 1/1000 cases.

Salmonellosis

Epidemiology

Salmonella is the most common cause of bacterial enteritis in the United States. Enteritis caused by this organism affects people of all age groups but particularly children, with those younger than 5 years accounting for 20% of cases. Almost all *Salmonella* infections are acquired from the ingestion of contaminated food or drink. Poultry products and beef are the most common sources; other sources include unpasteurized milk, eggs, fish, or domestic pets. Approximately 10% of household dogs and cats excrete salmonellae, and pet reptiles, such as turtles, snakes, and iguanas, have been responsible for outbreaks. In the United States, the most common isolates are the *S. enterica* serovars *typhimurium*, *enteritidis*, and *Newport*, which together account for approximately half of culture-confirmed serotypes. *S. enterica* serovar

typhi is associated with enteric fever (typhoid fever) and is most prevalent in the late fall.[12]

Pathophysiology

Relatively large numbers of salmonellae must be ingested for illness to be produced. However, a carrier state can be induced with ingestion of 10 to 100 times fewer bacteria that needed to cause illness. In infants or adults with certain underlying diseases, a much smaller inoculum may produce illness. Decreased gastric acidity or alteration of intestinal flora resulting from the administration of antibiotics can impressively reduce the size of the required inoculum. Rates of invasive infection and disease severity are increased in infants, elders, or those with hemoglobinopathies such as sickle cell anemia, malignant neoplasms, or acquired immunodeficiency syndrome (AIDS).

Clinical Features

Family outbreaks and sporadic cases are more common than large epidemics. Ingested salmonellae penetrate the intestinal mucosal cells and lodge in the lamina propria. After an incubation period of 8 to 48 hours, the typical patient with *Salmonella* gastroenteritis develops a fever, colicky abdominal pain, and loose, watery stools, occasionally containing mucus and blood. Nausea and vomiting are common but rarely are severe or protracted. Mild to moderate diffuse abdominal tenderness can be elicited in most patients, but severe tenderness and even rebound tenderness may occasionally be noted. Symptoms usually abate within 2 to 5 days, and recovery typically is uneventful. Sustained or intermittent bacteremia may occur, especially in those with sickle cell anemia, malignancy, or AIDS.

Diagnostic Testing

The diagnosis of salmonellosis is confirmed with stool cultures or a real-time PCR assay. Blood culture results occasionally are positive, and blood samples should be obtained from severely ill or immunocompromised patients. The possibility of an underlying disease or immunodeficiency state should be considered in patients with a severe *Salmonella* infection.

Management

Empirical antibiotic therapy is not recommended for otherwise healthy patients with suspected *Salmonella* enteritis. Antibiotic therapy does not shorten the duration of the disease and may prolong the duration of the carrier state. Although its effectiveness is unproven, antibiotic therapy is recommended for patients with severe colitis and infants younger than 3 months, adults older than 50 years, and those at risk for severe disease, including those who are immunocompromised, with sickle cell disease, or with prosthetic grafts. Persons who represent a public health risk also should be treated in an attempt to eradicate the carrier state and prevent the spread of the organism. Any of the following antibiotic regimens are generally useful for the outpatient management of *Salmonella* gastroenteritis: ciprofloxacin, 500 mg PO bid for 5 to 7 days or azithromycin 1 g PO followed by 500 mg/day for the next 6 days. Treatment with fluoroquinolones PO for 28 days is effective in the treatment of chronic *S. typhi* carriers; however, this can prolong shedding of non–*S. typhi* organisms. Patients requiring hospitalization are best treated with IV ceftriaxone until the results of sensitivity studies become available.[13]

Follow-up with the patient's primary care physician should be arranged. Food handlers and health care personnel should not return to work until their carrier state has been eradicated. Repeated stool studies help guide further decision-making regarding return to job or school. Personal hygiene should be emphasized as untreated patients may continue to shed infective organisms in the stool for weeks or even months. As with other invasive pathogens, the use of antimotility drugs alone should be avoided. These drugs prolong fever and diarrhea, increase the incidence of bacteremia, and promote the development of a carrier state in patients with *Salmonella* enteritis. However, the administration of loperamide is safe when given concomitantly with an antibiotic.

Prevention of salmonellosis depends on cooking meat to an internal temperature of greater than 160°F (71°C) and minimizing how long foods are allowed to remain at room temperature, to reduce the chance of bacterial growth to an infectious inoculum. Careful personal hygiene, including handwashing, also is essential.

Shigellosis

Epidemiology

Shigellosis, or bacillary dysentery, is worldwide in distribution and is particularly common in countries lacking adequate sanitation. *Shigella sonnei* is responsible for approximately 75% of the infections occurring in the United States. *Shigella flexneri* causes most of the remaining cases, with *Shigella boydii* and *Shigella dysenteriae* responsible for less than 4% of cases.

Shigella infections are common in confined populations, such as those in mental or penal institutions, nursing homes, or daycare centers. Children younger than 5 years of age account for 30% of cases. An increased incidence has been documented among men who have sex with men and in the setting of AIDS. It is spread by the fecal-oral route, and humans are the only natural hosts. Outbreaks have been associated with recreational water venues such as swimming pools, water parks, fountains, hot tubs, or spas.

Pathophysiology

Shigella requires a very small inoculum to produce disease; as few as 50 to 100 *Shigella* bacilli are capable of causing infection. No other enteric pathogen is so efficient at producing overt disease in humans. Infection generally is superficial, localized to the epithelial lining of the colonic mucosa; therefore bowel perforation or invasion into the bloodstream is extremely rare. Bleeding occurs from superficial ulcerations of the mucosa.

Clinical Features

Clinical presentation varies among *Shigella* species. *S. sonnei* typically causes high-volume, watery diarrhea, with relatively few systemic signs. Infection with *S. flexneri, S. dysenteriae,* or *S. boydii* typically causes low-volume bloody diarrhea and more severe systemic symptoms.

The usual incubation period is 24 to 48 hours, and clinical manifestations vary considerably. When true dysentery develops, it ordinarily is preceded by a recognizable period of watery diarrhea lasting a few hours to a few days. Patients with dysentery have grossly bloody diarrhea, tenesmus, and constitutional symptoms and signs, such as fever, nausea, vomiting, headache, or myalgias. If symptoms are severe enough, profound dehydration and even circulatory collapse can occur. Children younger than 2 years of age may have associated neurologic manifestations, usually seizures; lethargy or frank coma develops in a small percentage of patients. *S. dysenteriae* type 2 (Shiga toxin–producing strains) infections are associated with hemolytic uremic syndrome (HUS).[14]

Diagnostic Testing

A definitive diagnosis of shigellosis is made with stool culture or real-time PCR assay. Stool culture results are positive in more than 90% of cases when samples are obtained during the first 3 days of illness, or 75% of cases when received more than 1 week after the onset of diarrhea.

Management

Treatment primarily involves the correction of fluid and electrolyte abnormalities. If *S. sonnei* or *S. flexneri* is cultured from the stool, the decision to administer antibiotics is based on the patient's clinical condition and feasibility of sanitary control. Asymptomatic or recovering patients do not require antibiotics, unless treatment is necessary for public health considerations. Patients whose condition is not improving or those who are immunocompromised should be treated with antibiotics.

Antibiotics shorten the clinical course and eradicate the pathogen from the stool, often within 48 hours. Whenever *S. dysenteriae* is isolated, the patient should be treated to prevent outbreaks of dysentery, even if the patient is asymptomatic when the culture result returns from the laboratory.

In the United States, *Shigella* organisms are highly resistant to ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX). Therefore ciprofloxacin 500 mg PO bid or azithromycin 500 mg PO daily is the drug of choice. Treatment is required for only 3 days in immunocompetent patients but should be extended to 7 to 10 days in those who are immunocompromised.[14]

Yersinia enterocolitica Gastroenteritis

Epidemiology

Yersinia enterocolitica, a gram-negative facultative anaerobic bacterium, is a member of the family Enterobacteriaceae. *Y. enterocolitica* is a relatively infrequent cause of enteritis in the United States. Yersiniosis is more prevalent among the pediatric population where infections are evenly distributed throughout the calendar year. The consumption of contaminated milk or raw pork has accounted for sporadic cases and several large outbreaks. Fecal-oral transmission to humans from a variety of animals (particularly dogs, cats, or pigs) and direct person-to-person spread probably occur, but communicability appears to be low.

Pathophysiology

After oral ingestion, the bacterium invades the intestinal epithelium and localizes to lymphoid tissue of the intestinal mucosa, particularly Peyer patches. It then invades the regional mesenteric lymph nodes. Invasive enteritis is the clinical presentation in approximately two-thirds of patients. Pseudoappendicitis and mesenteric adenitis account for the remainder of presentations.

Clinical Features

The clinical picture with *Y. enterocolitica* often resembles that with infection by other invasive intestinal organisms, including fever and colicky abdominal pain. The diarrhea may be watery, greenish, and sometimes bloody. The constitutional symptoms include anorexia, vomiting, or malaise. In cases of *Y. enterocolitica* gastroenteritis, abdominal pain, and diarrhea can often persist for 10 to 14 days or longer.

In a substantial number of patients with yersiniosis, particularly adolescents or young adults, an ileocecitis may develop. In these cases, lower abdominal pain with little or no diarrhea is the predominant symptom, and the clinical presentation may mimic that of acute appendicitis. Postinfection manifestations may occur, such as erythema nodosum, persistent polyarthritis, sacroiliitis, ankylosing spondylitis, Reiter syndrome, exudative pharyngitis, pneumonia, empyema, or lung abscess.

Diagnostic Testing

The diagnosis of yersiniosis can be confirmed with stool cultures or real-time PCR assay; however, most laboratories do not routinely include *Y. enterocolitica* in standard stool testing. *Yersinia* identification can be performed if clinically indicated, such as a history of *Yersinia* exposure, prolonged invasive enteritis despite a negative result on standard stool culture, or right lower quadrant pain with signs of invasive diarrhea.

Management

In general, *Y. enterocolitica* infection is self-limited at the diarrheal stage and resolves without treatment. As with other invasive GI pathogens, antiperistaltic drugs are not recommended unless the patient is simultaneously treated with antibiotics.

Treatment with antibiotics is not essential or efficacious in the management of uncomplicated *Y. enterocolitis*. *Yersinia* organisms usually are susceptible to TMP-SMX DS, one tablet PO bid, which is the agent of choice when antibiotic therapy is indicated. Doxycycline, 100 mg PO bid, is an alternative regimen, as is single-agent treatment with a quinolone. In immunocompetent adults, a 3-day course is sufficient; the course is extended to 7 to 10 days if the patient is immunocompromised. Treatment should be considered for patients who are still significantly ill at the time stool results return, particularly if they are immunocompromised or have an underlying medical illness, or in cases in which the fecal shedding could represent a public health hazard. Patients with *Y. enterocolitica* often continue to shed organisms in the stool well into convalescence, long after diarrhea subsides. The mean duration of fecal shedding is approximately 6 weeks. In patients who interact with potentially susceptible persons, appropriate steps should be taken to ensure that they do not spread their infection.

Vibrio parahaemolyticus Gastroenteritis

Epidemiology

Vibrio parahaemolyticus is a halophilic (salt-requiring) gram-negative bacillus found naturally in warm marine environments such as the coastal seawaters of Japan, the United States, and other temperate zone regions. In Japan, *V. parahaemolyticus* is the most common cause of bacterial enteritis, being responsible for approximately 70% of cases. The typical source is raw fish. In the United States, *V. parahaemolyticus* disease is much less common, although its incidence has been increasing. US cases are typically related to the consumption of raw or undercooked shellfish, especially oysters. Many cases occur as outbreaks on cruise ships or in persons who have patronized a common restaurant or seafood market. *V. parahaemolyticus* enteritis is much more common in the summer months when warm seawater temperatures favor proliferation of the organism.

Pathophysiology

The mechanism whereby *V. parahaemolyticus* causes human enteritis is thought to be related to the production of two thermostable direct hemolysin (TDH) virulence factors. Serotypes that produce one or both virulence factors attach to the colonic epithelium and induce secretory diarrhea, as well as local cell lysis. An infectious dose of *V. parahaemolyticus* is considered to be 100,000 colony-forming units (CFUs) or more. Although enteritis is the most common clinical presentation, accounting for 60% to 80% of cases, *V. parahaemolyticus* infections also manifest as wound infections (34%) or septicemia (5%). Serious wound infections and septicemia occur primarily in persons with underlying liver disease, alcoholism, or diabetes mellitus.

Clinical Features

Signs and symptoms usually appear 8 to 12 hours after the ingestion of contaminated food, but the incubation period can range from 4 to 48 hours. The predominant manifestation is acute diarrhea, although the volume of fluid lost generally is not significant. Moderately severe abdominal cramping is common, and vomiting is typically not prominent. The illness is almost invariably self-limited

and seldom lasts longer than 24 to 48 hours. *V. parahaemolyticus* infection should be suspected when a common-source outbreak of acute diarrheal disease occurs in persons exposed to fresh or frozen seafood.

Diagnostic Testing

The diagnosis of *Vibrio* gastroenteritis is made by stool culture or real-time PCR assay. Although blood agar and other nonselective media support the growth of this species, isolation from the stool usually requires the use of a selective medium containing thiosulfate, citrate, bile salts, and sucrose (TCBS) agar.

Management

Because the disease is self-limited, most patients require no therapy. Although data on the efficacy of antibiotic therapy are lacking, patients who still have diarrhea when culture results become available may benefit from treatment with tetracycline, fluoroquinolones, ceftriaxone, or another antibiotic, as guided by susceptibility testing. Ciprofloxacin 500 mg PO bid for 3 days *or* azithromycin 500 mg PO daily for 3 days, if susceptible, is recommended. Antimotility agents are not indicated. Because *V. parahaemolyticus* is widely present in coastal waters, the only effective preventive measures are adequate cooking, refrigeration, and hygienic practices in the preparation of seafood for human consumption.

Shiga Toxin–Producing *Escherichia coli*

Epidemiology

STEC was first recognized as a human pathogen in 1982 after two outbreaks of hemorrhagic colitis were traced to undercooked ground beef contaminated with *E. coli* serotype O157:H7 and distributed at a fast-food restaurant chain. It is now recognized that *E. coli* O157:H7 is one of more than 30 serotypes of *E. coli* known to produce *Shigella*-like toxins that, as a group, constitute a major cause of hemorrhagic colitis, HUS, or thrombotic thrombocytopenic purpura (TTP) in humans. Children younger than 10 years are at the highest risk for severe STEC infection. Approximately 15% of children with STEC diarrhea develop HUS.[3,15]

Inadequately cooked ground beef has caused many large outbreaks. STEC, present in the intestines of healthy cattle, contaminates the meat during slaughter, and the grinding process then transfers the organisms from the surface of the meat to the interior. The infectious dose is low, approximately 100 bacteria. The US Department of Agriculture food safety regulations now require that cooking of ground beef to an internal temperature of 70°C (160°F) to kill *E. coli* organisms effectively. Outbreaks also have occurred from consumption of fruits or vegetables, contamination of municipal water supplies, animal contact in petting zoos, and person-to-person spread in daycare centers. Food handlers with STEC-related diarrhea may lead to contaminated meals, causing institutional outbreaks. STEC enteritis is more common in the summer months.

Pathophysiology

Ingested STEC multiplies in competition with healthy bacterial enteric flora, adheres to the intestinal epithelial cells, and produces Shiga toxin. Toxins bind to absorptive enterocytes on the luminal surface of the small and large intestines, enter the cell, and irreversibly inhibit protein synthesis, resulting in enterocyte death. Shiga toxins can then enter the bloodstream via damaged intestinal epithelium and cause the death of vascular endothelial cells by the same mechanism. Endothelial cell lysis is accompanied by platelet activation and aggregation, cytokine secretion, vascular constriction contributing to fibrin deposition, and clot formation within the capillary lumen. Microangiopathy propagates distally as the toxins are carried to the kidneys, causing the clinical syndrome of hemolysis and renal dysfunction (HUS). The development of HUS is associated primarily with serotypes that produce Shiga toxin 2. The CDC has estimated that 90% of US cases of HUS are caused by *E. coli* O157:H7.

Clinical Features

After an incubation period of 3 to 4 days, patients initially produce watery diarrhea that becomes bloody hours to days later. Approximately 90% of patients report bloody stools. The amount of blood varies, but stools passed may appear to consist wholly of blood, and the infection may masquerade as GI bleeding from noninfectious causes. Bloody diarrhea typically is accompanied by severe abdominal cramps, pain, and often vomiting. Fever is a feature in fewer than one-third of cases and, if present, usually is low grade. Uncomplicated infection resolves spontaneously over 7 to 10 days. A carrier state may last another 1 to 2 weeks and resolves spontaneously.

STEC colitis has been associated with two serious complications, HUS and TTP (discussed in Chapters 168 and 111, respectively). These clinically similar disorders share the features of microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic deficits, and renal dysfunction. In TTP, neurologic findings predominate, and renal dysfunction is unusual. Renal dysfunction predominates in HUS, which is more common in children, especially those younger than 4 years, occurring in up to 15% of cases. Of these, 5% are fatal. Older adults, such as occurs in nursing home outbreaks, can also acquire HUS, with a high mortality rate. TTP is rare but is most often seen in immunosuppressed patients. HUS and TTP typically appear 5 to 20 days after the onset of infection. Death from STEC colitis alone or resulting from complications occurs primarily among elders.

Diagnostic Testing

The CDC recommends that if stools are submitted for routine testing in the setting of acute community-acquired diarrhea, *E. coli* O157:H7 should be simultaneously cultured for—regardless of age, season, or presence or absence of blood in the stool. An assay that detects non–O157 Shiga toxin should also be performed. In addition to the routine battery of media, specimens should be plated on the sorbitol MacConkey (SMAC) medium.

Management

Treatment is symptomatic. Antibiotic treatment is of no clinical benefit and may serve to increase the risk of HUS by eliminating competing bowel flora; thus it is not recommended for patients with known infection with *E. coli* O157:H7. Empirical antibiotic treatment for bloody diarrhea should be approached with caution. It is not recommended in children because of the risk of HUS. In adults, if general empirical treatment is initiated in patients with diarrhea, it is generally recommended for patients with a temperature greater than 38.5°C (101°F), because the presence of significant fever suggests a pathogen other than *E. coli* O157:H7.

NONINVASIVE TOXIN-FORMING BACTERIA

Pathogens associated with toxin-induced bacterial enteritis are summarized in see Table 80.3. In general, gastroenteritis caused by toxin-forming bacteria (classically known as food poisoning) will manifest as acute noninvasive enteritis, with watery diarrhea, minimal fever, little or no abdominal cramping, and absence of fecal leukocytes and erythrocytes. Treatment is primarily supportive, and diagnostic testing generally is not indicated for otherwise healthy patients. A specific

diagnosis may be of help in attempting to identify a common source during large outbreaks.

Staphylococcus spp.

Epidemiology

Staphylococcus-related food poisoning occurs after the multiplication of an enterotoxin-forming strain of *Staphylococcus* that is present in the food before ingestion. Food contamination with *Staphylococcus* is extremely common because the organism is ubiquitous in the environment. Most protein-rich foods support the growth of staphylococci, especially ham, eggs (even hard-boiled), custard-filled pastries, mayonnaise, milk, or salads such as egg, tuna, chicken, potato, and macaroni. Foods that require considerable handling during preparation and are then kept slightly warm after preparation are frequent offenders. Temperatures of 45°F to 140°F (7°C to 60°C) for only a few hours will allow the proliferation of the organism and production of sufficient enterotoxin to cause disease. Foods containing sufficient enterotoxin to produce violent illness usually are normal in appearance, odor, and taste. Large outbreaks are common worldwide, particularly in institutions such as school or hospital cafeterias, military bases, airlines, or restaurants.

Pathophysiology

Although the bacterium itself is killed by cooking at temperatures greater than 140°F (60°C), *Staphylococcus* enterotoxin is heat-stable. Thus, once it is present in food, reheating or even boiling will not prevent illness. The toxin has no local effect on the digestive tract. It is a potent stimulator of T lymphocytes in the host, resulting in their proliferation and the release of cytokines. The GI effects are believed to be mediated by the release of interleukin-2, tumor necrosis factor beta, and interferon from mast cells. Stool, vomitus, or blood can be tested for the presence of the enterotoxin, but this is typically performed by local health departments or the CDC during large outbreaks and is rarely done in routine clinical laboratories.

Clinical Features

The illness has an explosive onset, beginning 1 to 6 hours after ingestion of contaminated food. Cramping and abdominal pain, with violent and often-repeated retching and vomiting, are the predominant symptoms. Diarrhea is a variable feature; it usually is mild, occasionally absent entirely, and infrequently profuse. Fever occasionally is present. Staphylococcal food poisoning is short lived, usually subsiding in 6 to 8 hours and rarely lasting as long as 24 hours. Patients often are recovering by the time they seek medical attention. The short incubation period and multiple cases among persons eating the same meal are highly suggestive of this disease. Examination of the stool is noncontributory, and no practical laboratory test is clinically available to confirm the diagnosis.

Management

Rapid, uncomplicated, spontaneous recovery is the rule. Parenteral antiemetic agents help to control vomiting. IV fluids should be given to patients who are dehydrated or who have ongoing vomiting, particularly the very young, elders, or debilitated patients. Antibiotics are of no value because staphylococcal food poisoning is caused by preformed enterotoxins. Adherence to strict personal hygiene practices by food handlers and prompt refrigeration of foods not intended for immediate consumption are the most important preventive measures. Ordinary refrigerator temperatures prevent the production of the enterotoxin. Food should not be allowed to stand at room temperature for long periods before being served.

Clostridium perfringens

Epidemiology

Clostridium perfringens food poisoning is one of the most commonly reported foodborne illnesses in the United States. Most cases occur in large groups, with dozens or even hundreds of persons affected. The illness is caused by the ingestion of meat or poultry heavily contaminated with *C. perfringens* type A heat-resistant spores. The organism also is ubiquitous in the environment and in human or animal feces. Typically, poisoning results from ingesting food that is cooked more than 24 hours before consumption, allowed to cool slowly at room temperature, and then served cool or rewarmed. During this period of incubation, spores that survived cooking germinate, and clostridia multiply to reach sufficient numbers to constitute an infectious inoculum.

Pathophysiology

Ingestion of live organisms is required to produce disease, but illness is not caused by infection; rather, it is caused by an enterotoxin produced by sporulation of the organism in the GI tract. The enterotoxin is responsible for the symptoms of *C. perfringens* food poisoning.

Clinical Features

Symptoms usually appear within 6 to 12 hours but can occur up to 24 hours after ingestion of the contaminated food. Frequent passage of watery diarrheal stools and moderately severe abdominal cramping are the major symptoms. Fever, nausea, and vomiting are rare. The illness is self-limited and rarely lasts for more than 24 hours. *C. perfringens* food poisoning should be considered in a patient who experiences an acute onset of abdominal cramps and watery diarrhea shortly after eating a suspect meat or poultry dish, and when others who have eaten the same meal are similarly ill. Leukocytes and erythrocytes are not present on stool examination.

Management

Occasionally, a patient will need IV fluid replacement. Antibiotics are of no value because of the toxigenic nature and brief duration of the disease. Food poisoning from *C. perfringens* can be prevented by avoiding long periods of warming or cooling of foods that have already been cooked.

Bacillus cereus

Epidemiology

Bacillus cereus is an aerobic, spore-forming, gram-positive rod that is a common cause of foodborne illness. The organism is one of the most frequently isolated soil bacteria. Because of its abundance and the hardiness of its spores, *B. cereus* contaminates nearly all agricultural products and plays a major role in the spoilage of food items, including pasteurized milk and milk products. It is commonly isolated from pasta, rice, dairy, and dried milk products, spices, dried foods, meat, chicken, vegetables, seafood, fruits, and grains. Because it is ubiquitous and tolerates extremes of temperature, control of this bacterium in the food-processing environment is challenging to achieve.

B. cereus causes two distinct clinical syndromes: An emetic form produced by a heat-stable, *Staphylococcus*-like enterotoxin known as cereulide, and a diarrheal form resulting from a heat-labile enterotoxin known as HBL (a hemolysin consisting of three proteins, B, L_1, and L_2), which is similar to that of *E. coli*. The emetic form usually is caused by the ingestion of contaminated rice, although beef, poultry, vanilla sauce, pasteurized cream, milk pudding, pasta, potato, cheese, and infant formula also have been implicated. The diarrheal syndrome usually is associated with the ingestion of HBL in meats or vegetables.

Pathophysiology

The heat-resistant spores of *B. cereus* survive boiling and then germinate when boiled foods such as rice are left unrefrigerated. The vegetative forms multiply and produce toxin. Flash frying or brief rewarming of the food before serving often is not sufficient to destroy the preformed, heat-stable, emetic toxin. Improper holding temperatures for cooked food are the most common feature of *B. cereus* foodborne illness.

Clinical Features

The emetic syndrome is clinically indistinguishable from that caused by staphylococcal enterotoxin. After an incubation period of 1 to 5 hours, profound vomiting and abdominal cramping occurs. Diarrhea is present in approximately 25% to 30% of persons affected. The duration is short, usually less than 10 hours, and patients recover uneventfully.

The diarrheal syndrome begins after an incubation period of 6 to 14 hours and is characterized by diarrhea and abdominal cramps. Vomiting is less common. The duration of illness ranges from 12 to 36 hours. Symptoms are essentially the same as for food poisoning produced by *C. perfringens*. *B. cereus* food poisoning should be suspected when an illness localized predominantly to the upper GI tract develops less than 6 hours after eating, or when a predominantly lower intestinal tract illness occurs 6 to 24 hours after a suspect meal, usually of meats or vegetables.

Diagnostic Testing

Because of the brief and noninvasive nature of the illness, diagnostic testing typically is not performed. In response to large outbreaks, public health authorities may elect to test common food sources. Isolation of 10^5 CFU/g from incriminated foods confirms the diagnosis. *B. cereus* enteric infection can also be confirmed via detection of the emetic or diarrheal toxin in stool, emesis, or food, but this is done only in reference laboratories typically during the investigation of large outbreaks.

Management

Both syndromes generally are mild and self-limited. Antibiotics are not indicated as symptoms are mediated by enterotoxins. Parenteral antiemetic agents provide effective relief in patients with violent vomiting. *B. cereus* food poisoning is preventable if boiled rice or cooked foods are promptly eaten or refrigerated and not left to sit at room temperature.

Cholera and Noncholera *Vibrio* Species

Epidemiology

In addition to *V. parahaemolyticus*, other halophilic marine *Vibrio* species (e.g., *V. cholera* and *V. vulnificus*) have increasingly been implicated in acute gastroenteritis associated with seafood. Their epidemiology is similar to that of *V. parahaemolyticus*—presence in coastal seawater, outbreaks associated with eating raw or inadequately cooked shellfish, and an incidence largely limited to the warmer months of the year. Outbreaks of true *V. cholera* continue to occur sporadically along the US Gulf Coast from inadequately cooked crabs or oysters. Other identified foods include imported seafood, cooked rice, frozen or fresh coconut milk, and commercially prepared cut cantaloupe. Cholera outbreaks in the developing world have led to an increasing number of cases of cholera imported into the United States.

Pathophysiology

Cholera and noncholera Vibrio strains produce an enterotoxin in vivo that stimulates enterocyte adenylate cyclase, disrupting mucosal fluid absorption and leading to secretory diarrhea. Therefore symptoms resemble those of other forms of enterotoxin-induced gastroenteritis. The enterotoxin of the noncholera *Vibrio* species is antigenically similar to *V. cholerae* enterotoxin and produces similar secretory diarrhea, although it is much less severe.

Clinical Features

Patients with classic epidemic cholera experience copious so-called rice water diarrhea, abdominal cramps, and often nausea and vomiting within 24 to 48 hours after ingesting contaminated seafood. A low-grade fever may be present. In severe cases (cholera gravis), rates of diarrheal fluid loss can reach 1 L/h; fatality rates can reach 25% to 50% in untreated populations. The median duration of illness is approximately 7 days. Despite the notoriety of the classic form of cholera, the CDC estimates that only 1 in 20 cases is associated with cholera gravis. Most affected patients experience a relatively mild diarrheal illness that may go undocumented.

The other species, *Vibrio vulnificus,* is also associated with eating raw seafood, especially oysters. *V. vulnificus* can cause self-limited gastroenteritis, with onset approximately 16 hours after ingestion of contaminated food by healthy persons. In the compromised host, this organism may cause serious wound infections when contaminated seawater comes into contact with open wounds. It may also result in a syndrome of primary septicemia characterized by hemorrhagic bullae of the skin and rapidly progressive septic shock.

V. vulnificus infection is the leading cause of death in the United States associated with the consumption of seafood. Septicemia carries a mortality rate of approximately 50% in patients with significant underlying disease, particularly chronic liver disease. All patients with chronic liver disease, alcoholism, AIDS, or other immunodeficiency states should be advised to avoid all raw shellfish.

Diagnostic Testing

Because these are noninvasive *Vibrio* species, unlike *V. parahaemolyticus*, stained fecal smears will not show leukocytes or erythrocytes. Stool cultures will quickly identify *V. cholerae* if plated on TCBS medium. *V. vulnificus* infection can be diagnosed with stool, blood, or wound cultures. The clinical laboratory should be notified when this infection is suspected so that specific culture media can be used.

Management

Patients with cholera often will lose enough fluids to require rehydration therapy. The WHO oral rehydration formula has been used successfully to treat cholera worldwide. The use of oral or IV fluid hydration is dictated by the clinical picture. The role of antibiotics in the treatment of intestinal infections caused by noncholera *Vibrio* spp. has not been clearly established. However, antibiotics will decrease the severity and duration of cholera and may have the same effect on the other diarrheal diseases caused by these marine *Vibrio* spp.

Antibiotics should be guided by strain-specific sensitivities, if available. Typical choices include a single oral dose of doxycycline 300 mg PO, or a 3-day regimen of ciprofloxacin 500 mg PO bid or azithromycin 500 mg PO daily, or double-strength TMP-SMX PO bid, tetracycline 500 mg PO qid, or erythromycin 500 mg PO qid. Preventive measures include the use of bottled water, meticulous attention to handwashing before eating and after using the bathroom, avoidance of fecal soiled water sources, thorough cooking of food, peeling of fruits and vegetables, and bathing and toileting at least 30 yards away from drinking water sources. Cholera is a nationally reportable infection.

An oral cholera vaccine is available and appears to provide better immunity, with fewer adverse effects than the previously available parenteral vaccine. The CDC strongly recommends the cvd 103-hgr oral cholera vaccine for travelers to cholera-endemic areas.[16]

If *V. vulnificus* infection is known or suspected, antibiotics should be initiated immediately because this has been shown to improve survival. Wounds should be débrided because they may progress rapidly, sometimes necessitating fasciotomy or amputation. Single-agent antibiotic regimens include levofloxacin or ciprofloxacin. The combination of doxycycline 100 mg PO bid or IV, plus a third-generation cephalosporin, such as ceftazidime 1 to 2 g IV or intramuscularly (IM) tid, is also recommended. Children can be treated with TMP-SMX plus an aminoglycoside.

Enterotoxigenic *Escherichia coli*

Epidemiology

Enterotoxin-producing *E. coli*, or ETEC, is recognized as a major cause of acute diarrheal disease throughout most of the world. It is a major cause of diarrhea in persons traveling to underdeveloped areas, especially South Asia, sub-Saharan Africa, or Latin America. ETEC is increasingly being recognized as a cause of foodborne illness in developed countries, including the United States. Infection is acquired from fecally contaminated food or drink. Unpeeled fruits, leafy vegetables, unsanitary drinking water, and ice are the most common sources. Most tourists are careful about their food and drink, but there seems to be a poor correlation between individual eating habits and the incidence of traveler's diarrhea. It is likely that the quality of hygiene at a particular food source is the major determinant of risk; travelers should choose locations that have a reputation for excellence in hygiene.

Pathophysiology

For an *E. coli* strain to cause diarrhea, it must possess a surface factor that allows colonization (although not invasion) of the small intestine and the ability to secrete an enterotoxin that causes the outpouring of fluids and electrolytes into the small bowel lumen. The enterotoxin-induced secretion occurs in the absence of any demonstrable histologic damage to intestinal epithelial cells or the capillary endothelial cells. *E. coli* produces heat-labile and heat-stable toxins. The intestinal fluid losses are qualitatively identical to those seen in cholera and other toxigenic diarrheas.

Clinical Features

After an incubation period of 24 to 72 hours, an abrupt onset of watery diarrhea occurs. Severity varies, with the illness ranging from a fulminant, cholera-like disease to the much more common and milder turista, in which the symptoms of mild, watery diarrhea and abdominal cramps are more troublesome than life threatening. Fever is unusual. Vomiting occurs in less than one-half of affected adults and is seldom responsible for significant fluid losses. Even in severe cases, diarrhea rarely lasts longer than 48 to 72 hours, and the response to oral or IV fluids is uniformly good. Milder disease generally subsides more gradually, occasionally persisting for 1 week or longer. Virtually all persons recover entirely, without long-term sequelae.

ETEC disease should be suspected when a child or adult has frequent watery diarrhea and few other symptoms. It often is mild, nonspecific gastroenteritis that resolves spontaneously. ETEC is the most common cause of traveler's diarrhea, so most people who acquire toxigenic diarrhea while visiting a developing nation probably have this disease.

Diagnostic Testing

There are no easy or rapid means for laboratory diagnosis of ETEC infection. Methods that rely on the identification of specific *E. coli* serotypes are unreliable because *E. coli* is part of the healthy colonic flora and its ability to produce enterotoxin is not restricted to any specific serotype. Methods based on detection of the heat-stable and heat-labile toxins through the use of the real-time PCR assay have been developed but are generally available only in reference laboratories. Stool preparations demonstrate no erythrocytes or leukocytes.

Management

Because ETEC infections are almost always a self-limited disease process, no treatment other than maintenance of hydration is required. However, if the organism is identified while symptoms are still active or if the patient is traveling in an endemic area, antibiotics can afford clinical relief. For milder symptoms, a single oral dose of ciprofloxacin 750 mg PO, in addition to loperamide, is usually effective. For more severe symptoms, TMP-SMX 160 mg/800 mg PO bid or ciprofloxacin 500 mg PO bid for 3 days should eradicate the organism.

Clostridium difficile Colitis

Epidemiology

C. difficile is an anaerobic, spore-forming, gram-positive bacillus that is one of the leading causes of healthcare-associated infectious diarrhea. It has been associated with a range of illnesses, from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death. It is the leading cause of morbidity and mortality among hospitalized elders and nursing home patients. The annual incidence of *C. difficile* infection has recently plateaued at historic highs, with approximately 450,000 cases annually in the United States.[17] The continued high incidence of *C. difficile* cases underscores the need for contact isolation procedures when there is a suspected case in the emergency department (ED).

Pathophysiology

C. difficile infections are usually related to antibiotic use that alters the gut flora and allows the *C. difficile* bacteria to colonize and proliferate. *C. difficile* colitis can manifest concomitantly with current antibiotic use or up to 4 weeks afterward, although most *C. difficile* infections will occur within 2 weeks of antibiotic use. Other risk factors include recent hospitalization, living in a long-term care facility, solid organ transplant recipients,[18] or use of antacids.[19] *C. difficile* spores are highly resistant to heat, acid, and antibiotics, making them highly contagious for person-to-person or surface-to-person infections. *C. difficile* bacteria secrete toxins A and B that cause inflammation, mucosal injury, and secretory diarrhea.

Clinical Features

Manifestations of *C. difficile* colitis include watery diarrhea up to 10 to 15 times daily, with lower abdominal pain, cramping, low-grade fever, or leukocytosis. Fever is associated with *C. difficile* colitis in approximately 15% of cases. Examination initially focuses on the patient's fluid status, including assessment for dry mucosa, tachycardia, hypotension, or lightheadedness. The abdomen is assessed for evidence of an acute surgical process. A rigid or distended abdomen may represent bowel perforation. A stool sample is taken for *C. difficile* toxins. The examiner should wear gloves and a protective gown. Vigorous handwashing with soap and warm water after each patient encounter is performed to decrease person-to-person infections because hand sanitizers do not kill *C. difficile* sufficiently.[20]

Diagnostic Testing

The stool of infected persons is assayed for *C. difficile* toxins A and B using enzyme immunoassays (EIAs). Nucleic acid amplification tests (NAATs) for *C. difficile* toxin genes (e.g., PCR assays) are superior to EIA for toxins A and B and are therefore recommended for definitive diagnostic testing. Glutamate dehydrogenase (GDH) screening with subsequent toxin A and B EIA testing has a lower sensitivity but is an

alternative diagnostic approach when NAAT testing is not available. In addition, a CBC, metabolic panel, and lactate level determination are considered based on the patient's fluid status and severity of symptoms. Leukocytosis in the setting of *C. difficile* colitis is common, with the white blood cell (WBC) count often greater than 15,000 cells/mm^3.

Persons at extremes of age tend to have more severe infections. The past decade has seen the emergence of a fulminant form of *C. difficile* in patients older than 65 years. Elders with a leukocyte count greater than 20,000 cells/mm^3, nosocomial infection, renal failure, or immunosuppression are at increased risk for complications such as toxic megacolon, shock, need for colectomy, and death. If a person has any of these risk factors, appears septic, or has a tender and distended abdomen, an emergent computed tomography (CT) scan abdomen with a surgical or GI consultation is recommended to evaluate for toxic megacolon.[20] A colonoscopy may provide direct visualization of the colon for the presence of pseudomembranous colitis and should be performed with caution in patients with toxic megacolon, because it may cause a bowel perforation.

Management

The management of *C. difficile* colitis includes discontinuation of any inciting antibiotic and rapid initiation of treatment. Vancomycin 125 mg PO qid for 10 days, is the first drug of choice or fidaxomicin 200 mg PO bid for 10 days. A third alternative is metronidazole 500 mg PO tid for 10 days.[20] Patients generally become afebrile and show clinical improvement within 36 to 72 hours of treatment. Diarrhea usually resolves over 5 to 7 days, even though the results of toxin assays and stool cultures may remain positive for weeks. Up to 30% of patients experience a relapse regardless of the antibiotic chosen, its dosage, or duration of treatment. Risk factors for recurrent disease include new exposure to antibiotics, age older than 65 years, severe underlying disease, low serum albumin level, need for admission to an intensive care unit, or extended hospital stay of 16 to 30 days. Most of these patients will respond to another course of antibiotic therapy.

Hospitalization is indicated for elders, nursing home patients, those with comorbid conditions such as renal failure, an immunocompromised state, or severe dehydration. Patients are placed in contact isolation, and hospital protocols should be followed for *C. difficile* infections. Outpatient therapy is appropriate for individuals without comorbid conditions who are non–toxic appearing, with mild disease, and who can tolerate oral hydration.

VIRAL GASTROENTERITIS

Most cases of gastroenteritis are caused by viruses, which include norovirus, rotavirus, *Sapovirus*, adenovirus, and astrovirus. Clinical features suggestive of a viral cause consist of an intermediate incubation period (24 to 60 hours) and short infectious duration (12 to 60 hours). The rate of rotavirus-associated gastroenteritis has significantly decreased with the increasing use of the rotavirus vaccine in children. Patients with viral gastroenteritis can present with nausea, vomiting, abdominal cramping, or diarrhea. Physical findings may include fever and abdominal tenderness. Symptoms and signs of dehydration can occur in severe cases. Norovirus and rotavirus are among the two most prevalent viral causes of gastroenteritis. Table 80.3 and Table 80.7 contain summaries of common causes, clinical features, diagnostic studies, and treatment of viral gastroenteritis.

Norovirus

Epidemiology

The norovirus, previously referred to as the Norwalk-like virus, is the most common cause of acute gastroenteritis in children and adults in the United States and usually occurs in the winter months. It is also the most common cause of foodborne disease and person to person outbreaks in the United States. Norovirus causes approximately 20 million illnesses/year, with approximately 400,000 ED visits. Patients who are immunocompromised or at extremes of age (adults >65 years and children <5 years) are at greatest risk of complications or death.[21]

Pathophysiology

Transmission of norovirus occurs via the fecal-oral route, including ingestion of contaminated food or water, or exposure to airborne droplets of vomitus-containing viral particles and fomites. It has an incubation period of 1 to 2 days, with symptoms typically lasting for 48 to 72 hours. Norovirus is highly infectious for all age groups, and only a small inoculum (≈100 virions) is needed for virus transmission. Shedding of the virus in the stool can occur up to 2 to 3 weeks after onset of symptoms.[22]

Clinical Features

The onset of symptoms is commonly abrupt and vomiting is a prominent feature. Patients develop diarrhea that is usually moderate in amount, defined as four to eight stools over a 24-hour period. The diarrhea is characterized as a non-bloody stool with a loose to watery consistency that lacks mucus. Associated symptoms include generalized malaise, myalgias, headache, or fever, which occur in approximately 50% of cases. Recovery is typically rapid, but the infection may be protracted, and symptoms may be present for a longer period due to prolonged viral shedding, especially in the immunocompromised. Advanced age is a risk factor for a fatal outcome from the disease. In rare circumstances, patients may present with central nervous system (CNS) complications, such as seizures or encephalopathy.

TABLE 80.7 Viral Gastroenteritis: Causes and Clinical Features

Organism	Mode of Transmission	Clinical Features
Norovirus	Ingestion of contaminated food and water; touching contaminated surfaces; highly contagious	Most common cause of gastroenteritis in the United States, and most common cause of US foodborne-disease outbreaks; fever, headache, myalgias, nausea, vomiting, abdominal pain, diarrhea; incubation period, 12–48 h
Sapovirus	Ingestion of contaminated food or water; fecal-oral route	Fever, nausea, vomiting, diarrhea; usually causes mild illness
Rotavirus	Ingestion of contaminated food or water; touching contaminated surfaces	Fever, nausea, vomiting, abdominal pain and watery diarrhea; incubation period ≅ 2 days
Adenovirus	Close personal contact; touching contaminated surfaces	Rare cause of serious illness; fever, diarrhea; can cause nongastrointestinal illness (e.g., bronchitis, pneumonia, conjunctivitis)
Astrovirus	Fecal-oral route	Malaise, headache, abdominal pain, diarrhea; vomiting less common

Diagnostic Testing

The diagnosis of viral gastroenteritis is commonly based on clinical features. A norovirus outbreak in the community is suspected when these criteria are met: A greater proportion of cases with vomiting than with fever, bloody diarrhea in less than 10% of cases, and vomiting in greater than 25% of cases.[23]

The identification of the exact causative viral agent is not usually necessary. However, in the setting of an outbreak, it is important to isolate the causative organism so that successful mechanisms that disrupt viral transmission can be recognized. The preferred specimen used to detect norovirus is a stool sample, which contains a higher quantity of virus as compared with vomitus or rectal swabs. The diagnosis of norovirus infection involves the detection of viral antigen or viral RNA. Quantitative reverse transcription-polymerase chain reaction (RT-qPCR) assays are used to detect norovirus in stool, vomitus, food, water, or in environmental specimens.[24] Norovirus antigen can also be detected in stool samples by the use of commercial EIAs. However, these kits have poor sensitivity (50% to 75%) and hence have limited use in the diagnosis of sporadic cases of gastroenteritis.[21]

Management

Viral gastroenteritis due to norovirus has no specific treatment. Management is based on the clinical condition of the patient. Supportive care, including oral hydration or IV fluid replacement, may be required. Implementation of proper hand hygiene is key to prevent the disease from occurring. During outbreaks, patients should be placed on contact precautions in a cohort setting. Routine disinfection and cleaning of environmental surfaces and equipment should also take place.[25]

Rotavirus

Epidemiology

Rotavirus predominantly infects infants and young children, with a milder disease occurring in adults. Prior to the development of the rotavirus vaccine, it was the leading cause of diarrhea in the US among infants and children. Rotavirus is a stable virus and primarily transmitted via the fecal-oral route or direct contact with contaminated surfaces. US epidemics occur typically in the winter and spring, from December to June.

Pathophysiology

Pathogenesis of the illness is associated with diarrhea, which occurs as a result of three main mechanisms: The direct effect of the rotavirus enterotoxin NSP4, loss of brush border enzymes, and activation of the enteric nervous system.

Clinical Features

Clinical features of rotavirus infection in children include fever, nausea, vomiting, and non-bloody watery diarrhea. Rotavirus causes severe acute gastroenteritis in a higher proportion of cases compared with norovirus.[26] Rotavirus has an incubation period of approximately 2 days, and symptoms can last from 3 to 8 days. Patients may also present with loss of appetite and signs of dehydration, including dry mucous membranes or decreased urinary output. Children with rotavirus can also have concurrent respiratory symptoms or CNS complications, including seizures, encephalopathy, and encephalitis. A milder form of rotavirus infection occurs in adults, especially in household members of infected children. Elders and immunocompromised patients are at increased risk for more severe disease with protracted illness, thus remain important factors in determining the duration of isolation and repeat testing to ensure eradication of the virus.

Diagnostic Testing

Rotavirus infection is best diagnosed with antigen-detection immunoassays or RT-PCR based nucleic amplification tests on stool specimens. Oral swabs have a lower sensitivity to detect enteric viruses.[27,28]

Management

Rotavirus is a self-limited illness that lasts for a few days in healthy individuals. Treatment involves supportive care and managing fluid status. Prevention of rotavirus infection occurs with the use of live, attenuated oral vaccines.[29] Neither natural infection nor vaccine ensures protection from future infections, so vaccinated and unvaccinated children may develop multiple episodes of rotavirus gastroenteritis. Hospitalizations from rotavirus and all-cause acute gastroenteritis have substantially decreased with the use of the rotavirus vaccines.[30]

PARASITES

Table 80.8 lists the clinical features of common parasites causing gastroenteritis, and Table 80.4 summarizes appropriate diagnostic tests and treatment.

Giardia

Epidemiology

Giardia lamblia enteritis is caused by the flagellated protozoan pathogen, *G. lamblia (G. duodenalis, G. intestinalis)*. The disease is one of the most common protozoan infections in the United States; it can also cause sporadic or epidemic gastroenteritis worldwide.[31] The disease is spread via the fecal-oral route or ingestion of contaminated food or water. It is easily transmittable between close contacts because the ingestion of as few as 10 cysts can result in illness. The illness occurs more commonly in developing countries that have poor sanitary conditions. Infants, young children, travelers, immunocompromised individuals, or patients with cystic fibrosis or hypochlorhydria (low stomach acid) are at most significant risk for developing the disease.

TABLE 80.8 Parasitic Gastrointestinal Infections: Causes and Clinical Features

Organism	Mode of Transmission	Clinical Features
Giardia lamblia	Ingestion of contaminated food or water; fecal-oral route	Nausea, vomiting, abdominal cramping, flatulence, greasy stool that may float
Entamoeba histolytica	Ingestion of contaminated food or water; touching contaminated surfaces; fecal-oral route	Fever, anorexia, abdominal cramping, watery or bloody diarrhea; illness ranges from asymptomatic infection to fulminant colitis, peritonitis to extraintestinal amebiasis
Cryptosporidium	One of the most frequent causes of waterborne disease in the US population	Abdominal cramping, diarrhea
Cyclospora cayetanensis	Ingestion of contaminated food or water; fecal-oral route	Nausea, vomiting, loss of appetite, weight loss, bloating, abdominal cramping, diarrhea

Pathophysiology

G. lamblia exists in two forms, trophozoite (active form) and cyst (inactive form). Trophozoites attach to the mucosal lining of the small intestine and cause symptoms. This active form of the parasite is unable to survive outside the body for an extended period of time and hence cannot spread infection to others. However, the cystic form is viable outside of the body for prolonged periods and, once ingested, changes into the trophozoite form. Trophozoites generate the cysts that exit the body via the feces. Giardiasis is a common cause of diarrhea in hikers exposed to contaminated water. Infection can also be transmitted via anal intercourse.

Clinical Features

Clinical features of acute giardiasis consist of sudden onset of diarrhea associated with malaise, weight loss, nausea, abdominal cramping, or bloating. Stools are characterized as being foul-smelling and greasy. Most cases of giardiasis are self-limiting. A small percentage can develop chronic symptoms, including abdominal pain, functional dyspepsia, intermittent chronic diarrhea, malnutrition, or weight loss.

Diagnostic Testing

Immunoassays have higher diagnostic sensitivities than stool microscopy and are the preferred diagnostic modality, when available. Several immunoassay tests are available, including direct immunofluorescent assays, immunochromatographic assays, and enzyme-linked immunosorbent assays (ELISAs).

Stool microscopy can identify ova and parasites, especially in the acute phase, when cysts and trophozoites appear in the stool. In subacute, chronic, or asymptomatic cases, trophozoites may be present in the stool in small numbers or on an intermittent basis. Collection of multiple stool samples (e.g., three stool samples collected on separate days) can increase the sensitivity of the test.

Biopsy of duodenal-jejunal tissue or aspiration of the duodenal-jejunal area by endoscopy may be required to make the diagnosis when repeated stool samples tested for ova and parasites do not yield any organisms.[3]

Management

Treatment of symptomatic cases consists of a single PO dose of tinidazole 2 g PO. Metronidazole 500 mg PO bid or 250 mg PO tid daily for 5 to 7 days, or nitazoxanide 500 mg PO bid for 3 days, may also be given. Alternative agents include albendazole, paromomycin, mebendazole, or quinacrine.[32,33] Treatment of asymptomatic giardiasis is controversial. Asymptomatic carriers, especially children or food handlers, may need to be treated to reduce the risk of spread and decrease the risk of developing chronic intermittent diarrhea. Prevention of the disease is promoted by the use of strict handwashing and the avoidance of ingesting contaminated water. Patients diagnosed with giardiasis and who are incontinent or wearing diapers should be placed on contact precautions.

Amebiasis

Epidemiology

Amebiasis is caused by the protozoan *Entamoeba histolytica*, which is found worldwide. The genus *Entamoeba* is composed of many species, but *E. histolytica* is the only one linked to disease.

Amebiasis is more common in developing countries with poor sanitary conditions. Most *E. histolytica* infections are asymptomatic, with only 10% of carriers presenting with symptoms. Specific groups of individuals are more predisposed to amebic colitis, such as those at the extremes of age, pregnant females, or malnourished individuals. Travelers to endemic areas are also at risk for infection.

Pathophysiology

E. histolytica exists in two forms, the trophozoite and cystic forms. The parasite is transmitted by the ingestion of the cystic form, which is the infective stage of the disease. Cysts can survive in the environment for weeks to months and can be found on the contaminated hands of food handlers or in fecally contaminated food and water. The infection can also spread through the ingestion of cysts via anal-oral sexual practices. Trophozoites are formed when excystation occurs in the terminal ileum or colon, resulting in the invasive stage of the disease. Trophozoites can cause tissue destruction by penetrating the colonic mucosal barrier, leading to secretory bloody diarrhea and colitis. Extraintestinal disease can also occur by the hematogenous spread of trophozoites via the portal circulation to the liver or other organs.

Clinical Features

Intestinal amebiasis includes asymptomatic colonization. However, the infection can progress to a symptomatic intestinal illness. Acute amebic dysentery has an incubation period that ranges from 1 week to 1 year. Patients present with acute onset of severe abdominal cramps associated with fever, profuse, bloody diarrhea, and tenesmus. Gradual onset of symptoms can result in chronic amebic colitis. Individuals present with intermittent diarrhea, with two to four foul-smelling stools daily, usually containing blood-streaked mucus. Associated symptoms of fever, weight loss, abdominal cramping, or flatulence can be present. The clinical condition may have alternating symptomatic and asymptomatic periods, which last over months to years. The most common serious complication of amebic colitis is amebic liver abscess.

Diagnostic Testing

The diagnosis of amebic colitis in the past was based on microscopic identification of cysts and trophozoites in stool samples. Trophozoites can also be identified in biopsy samples obtained during colonoscopy. The development of stool antigen assays has enhanced the diagnostic process for amebic colitis. EIA kits for *E. histolytica* antibody and antigen detection are available. However, they require fresh, not fixative-preserved stool for analysis. Molecular analysis by PCR-based assays is the gold standard with very high sensitivity and specificity.[34]

Management

For asymptomatic carriers, treatment consists of paromomycin 25 to 35 mg/kg/day PO divided tid for 7 days. Oral iodoquinol 650 mg tid for 20 days, or diloxanide furoate 500 mg PO tid for 10 days, can also be given. For mild to moderate intestinal amebiasis, metronidazole 500 mg to 750 mg PO tid for 7 to 10 days can be prescribed, followed by paromomycin treatment. Paromomycin can cause diarrhea as a side effect, thus making it difficult to assess the patient's response to metronidazole if both drugs are given together. Alternate therapies include tinidazole 2 g PO each day for 3 to 5 days or nitazoxanide 500 mg PO bid for 3 days. For amebic liver abscess, metronidazole 750 mg PO tid for 10 days or tinidazole 2 g PO each day for 5 days or nitazoxanide 500 mg PO bid for 3 days can be given.[34]

FOOD POISONING

Foundations

Foodborne gastroenteritis is an illness caused by the ingestion of food contaminated by viruses, bacteria, or bacteria toxins. *Food poisoning* is the term typically used for gastroenteritis caused by the ingestion of preformed toxins, such as staphylococcal toxins, *B. cereus* toxins, histamine-like substances from scombroid fish poisoning, ciguatoxins from ciguatera fish poisoning, or *Clostridium botulinum* toxins.

The enterotoxins can also be produced in vivo after the ingestion of the bacterium and subsequent production of the enterotoxin in the intestinal lumen. Examples include *C. perfringens, B. cereus, C. botulinum,* ETEC, *V. cholerae*, and noncholera *Vibrio* spp. such as *V. enterocolitica*.

Clinical Features

Food poisoning usually manifests 1 to 6 hours after the ingestion of preformed toxins from *Staphylococcus, B. cereus* (short incubation form), and scombroid fish or ciguatera fish poisoning. Moderate incubation periods of 8 to 16 hours are seen after the ingestion of toxin-forming bacteria such as *C. perfringens* or *B. cereus* (long incubation form). Longer incubation periods of more than 16 hours are associated with ETEC, STEC, and *Shigella* and *Vibrio* spp.

The clinical presentation usually involves an abrupt onset of nausea, vomiting, or abdominal cramping, followed by watery diarrhea. Fever is usually absent, and symptoms typically resolve within 24 hours. In some cases, *B. cereus* predominantly causes diarrhea and cramping. Often, there is a clear food exposure, such as at a picnic with many people who have the same illness at the same time.

Diagnostic Testing

Diagnostic testing is usually not indicated in cases of food poisoning, and most individuals will recover within 24 hours. A detailed history of the timing, types, and places of recent sources of food ingestion should be obtained. Similar patterns of GI illness involving others who may have ingested the same foods may assist in identifying the cause. If identification for outbreak surveillance is needed, stool samples can be sent to test for specific organisms.

Most state health departments encourage consumers to report food poisoning incidents to their local health department. Physicians and laboratories must report each singular diagnosed infection that is included in a notifiable disease list maintained by local, state, or federal agencies (www.cdc.gov/foodsafety). Foodborne illnesses are included in the notifiable disease lists. Examples include: Salmonellosis, shigellosis, cholera, STEC, norovirus, and hepatitis A. Physicians should suspect an outbreak when they detect a larger than normal number of people exhibiting the same symptoms.

Management

In general, oral hydration is the mainstay of treatment. Antiemetics such as ondansetron 0.15 mg/kg up to 8 mg PO, or metoclopramide 10 mg PO, may be used to enhance oral hydration. Antibiotic therapy is rarely required, and most patients will have a self-limited illness.

Scombroid Fish Poisoning

Epidemiology

Scombroid fish poisoning remains one of the most common forms of fish poisoning in the United States. The disease takes its name from the family Scombridae (e.g., tuna, mackerel, skipjack, bonito, and related species) but results from the ingestion of a wide variety of dark meat fish, including nonscombroid species such as herring, bluefish, anchovy, sardine, amberjack, black marlin, and mahi mahi. The fish species most commonly implicated include mahi mahi, tuna, and bluefish.

Most US cases occur in Hawaii and Florida, followed in frequency by California, New York, Washington, and Connecticut. However, scombroid poisoning can occur in any location where fresh fish is available.

Pathophysiology

The meat of implicated species naturally contains unusually high levels of histidine. Scombroid fish poisoning results from the ingestion of heat-stable toxins produced by bacterial action on the histidine present in the dark meat of the fish. The bacteria responsible are normal constituents of the surface marine flora, rather than contaminants. The histidine decarboxylase activity of these organisms produces histamine and histamine-like substances, which cause the symptoms of scombroid fish poisoning. High levels of histamine in the fish correlate directly with the occurrence of the illness.

Formation of the scombrotoxins is directly related to improper preservation and refrigeration of the fish from the time they are caught until when they are cooked. In general, the problem is caused by improper refrigeration by the supplier rather than being the fault of the restaurant serving the fish. Other foods, notably Swiss cheese, contain sufficient amounts of histidine and have also been implicated.

Clinical Features

The symptoms of scombroid fish poisoning resemble those of histamine intoxication. While eating the fish, the patient may note a metallic, bitter, or peppery taste, although many affected fish do not have an abnormal odor or taste. Symptoms usually develop abruptly within 20 to 30 minutes and consist of facial flushing, diarrhea, severe and throbbing headache, palpitations, or abdominal cramping. Other manifestations may include dizziness, dry mouth, nausea, and vomiting, or urticaria. The facial flushing resembles a sunburn and can extend over the entire skin surface. The conjunctivae usually are injected. The duration of the major symptom complex generally is less than 6 hours, and, although weakness and fatigue persist longer, the clinical course usually is benign. The attack rate is high; most persons sharing the same toxic fish will become ill.

Management

Parenteral antihistamine therapy, such as diphenhydramine 25–50 mg IM or IV, or cimetidine 300 mg IM or IV, usually relieve symptoms promptly. This is not an allergic reaction, so patients should not be told that they are allergic to these fish, nor should they be prohibited from eating them again in the future. Suspected cases of scombroid should be immediately reported to the health department.

Ciguatera Fish Poisoning

Epidemiology

Ciguatera fish poisoning is a common public health problem, with appreciable economic significance. It is endemic in tropical regions but is found worldwide. Fish caught around Hawaii and Florida cause most US cases but, because the responsible ocean fish are now commonly transported inland, cases can be seen virtually anywhere. More than 400 fish species that frequent coral reefs have been implicated as ciguatoxin carriers, but fewer than 50 are commercially important, including amberjack, barracuda, grouper, king mackerel, parrotfish, sea bass, snapper, sturgeon, surgeonfish, and ulua.

Pathophysiology

Ciguatera fish poisoning results from the ingestion of the ciguatoxin neurotoxin. Ciguatoxin is produced by the marine dinoflagellate *Gambierdiscus toxicus*, which attaches itself to marine algae and is passed up the food chain. The lipid-soluble toxin accumulates in the tissues of the larger predacious coral reef fish, with the highest concentrations in the liver, intestines, head, and roe. It does not affect the fish in any way. Only humans suffer its ill effects when the toxin is ingested.

Ciguatoxin is heat- and acid-stable, odorless, and tasteless. It is not deactivated by cooking or freezing, nor is the toxin eliminated by drying, salting, smoking, marinating, or pickling. It is not possible to predict whether a fish contains sufficient amounts of the toxin to produce illness.

Ciguatoxin has anticholinesterase and cholinergic properties, although its neurotoxicity is mediated by its effect on sodium channels. Ciguatoxins cause a hyperpolarizing shift of the voltage dependence of channel activation so that sodium channels are open at the resting membrane potential. Spontaneous firing of neurons occurs as tetrodotoxin-sensitive sodium channels are activated, giving rise to the typical neurologic signs and symptoms.

Clinical Features

Ciguatera fish poisoning is usually seen in the spring and summer months. The incubation period is approximately 2 to 6 hours, but a delay of 12 to 24 hours is not unusual. Attack rates are very high, with 80% to 90% of persons exposed becoming ill. Symptoms tend to be related to the amount of toxin ingested and vary considerably in their severity. If not fully recovered from an initial ingestion of ciguatoxin, affected persons are likely to have much more serious symptoms from a second ingestion.

Classically, patients exhibit GI and neurologic symptoms. The GI symptoms (e.g., nausea, vomiting, profuse watery diarrhea, crampy abdominal pain) tend to appear first and resolve over the first 24 hours. The constellation of neurologic symptoms consists largely of dysesthesias and paresthesias around the throat or perioral area. The sensation of burning feet, which may resemble alcoholic peripheral neuropathy, loose, painful teeth, and sometimes CNS changes, such as ataxia, weakness, vertigo, visual hallucinations, or even confusion and coma, may also occur.

Distortion of temperature perception is vividly described by patients with ciguatera poisoning. Cold allodynia, defined as dysesthesia experienced on contact with cold water or cold objects, is almost pathognomonic of ciguatera poisoning and often is incorrectly referred to as cold-hot temperature reversal. Another classic feature is a return or a worsening of associated symptoms after the ingestion of alcohol.

Ciguatera poisoning lasts an average of 1 to 2 weeks, but at least 50% of victims are still symptomatic at 9 weeks. The neurologic symptoms, particularly the paresthesias and dysesthesias, tend to persist longer than the GI symptoms and have been reported up to years later.

Management

Treatment is primarily supportive. IV fluids are given to replace volume losses from vomiting and diarrhea, and analgesics are used as needed. In severe cases, the toxin may exhibit some anticholinesterase activity, manifested as bradycardia and hypotension, which can be treated with atropine, 0.5 mg IV, or dopamine 5 to 20 μg/kg/min via IV infusion. Patients should be told to abstain from alcohol in any amount until symptoms have completely resolved. Pruritus may be managed with a histamine H1 receptor antagonist, such as diphenhydramine 25 mg PO qid, or cetirizine 10 mg PO once daily. Amitriptyline 25 mg PO bid can bring about a dramatic reduction in the pruritus and dysesthesias, two of the most disturbing and protracted symptoms.

SPECIFIC GROUPS WITH GASTROENTERITIS

Traveler's Diarrhea

Epidemiology

Traveler's diarrhea is the most common illness afflicting people traveling from resource-rich regions to the developing world. The traveler's destination is the most important factor in assessing the risk of developing disease. Ingestion of contaminated food and water is the primary mode of transmission of traveler's diarrhea.

Pathophysiology

The ingestion of fecally contaminated food or beverages causes traveler's diarrhea. Most cases are caused by bacterial pathogens. ETEC is the most common bacterial cause for traveler's diarrhea. A variety of viruses and parasites also causes the disease. Bacterial and viral pathogens have an incubation period ranging from 6 to 48 hours. Parasitic causes have a longer incubation period, up to 2 weeks in duration. Causative agents are listed in Table 80.9.

Clinical Features

Traveler's diarrhea is the sudden onset of abnormally loose or liquid, frequent stools resulting in an illness that is tolerable (mild), distressing (moderate), or incapacitating (severe) for the individual.

The classification is now based on functional impact on the traveler rather than the number of stools.[35] Patients commonly present with low-grade fever, abdominal cramping, or watery diarrhea. Traveler's diarrhea is typically a self-limited illness. Dysentery presents with fever, nausea, vomiting, abdominal pain, tenesmus, or blood in the stools.

Diagnostic Testing

Typically, traveler's diarrhea is self-diagnosed. Determination of the pathogen is generally unnecessary in the uncomplicated case. Diagnostic testing should be reserved for patients with severe or persistent symptoms. Routine stool cultures are rarely necessary, because EAEC and ETEC cannot be differentiated from nonpathogenic *E. coli* on stool culture. The cultures are mainly reserved to confirm outbreaks. If stool cultures are sent, testing should specifically look for ETEC, *Shigella*, *Campylobacter,* and norovirus. If the enteritis is chronic (>2 weeks in duration), associated with foul-smelling and excessive flatulence, the stool should be examined for *Giardia*.[35]

TABLE 80.9 Traveler's Diarrhea: Causative Organisms and Treatment

Severity	Definition
Mild	Diarrhea that is tolerable, not distressing, and does not interfere with planned activities. Antibiotics are not recommended.
Moderate	Diarrhea that is distressing or interferes with planned activities. Antibiotics may be indicated (e.g., immunosuppressed, solid organ transplant, elderly)
Severe	Diarrhea that is incapacitating or prevents planned activities; all dysentery (passage of grossly bloody stools) is considered severe. Antibiotics are indicated for severe traveler's diarrhea.[35]
Organism	**Treatment**
Enterotoxigenic *Escherichia coli* (ETEC)	Ciprofloxacin 500 mg PO bid or 750 mg PO once daily for 1–3 days
Enteroaggregate *E. coli* (EAEC)	Ciprofloxacin 500 mg PO bid or 750 mg PO once daily for 1–3 days
Campylobacter	Azithromycin 500 mg PO daily for 3 days
Salmonella	Levaquin 500 mg PO daily for 7 days
Shigella	Ciprofloxacin 750 mg PO daily for 3 days
Norovirus	Supportive care
Rotavirus	Supportive care
Giardia	Metronidazole 500 mg PO bid or 250 mg PO tid for 5–7 days

Management

The best strategy regarding traveler's diarrhea is prevention. Travelers should avoid eating dairy products, raw fruits, and vegetables, or undercooked meat and seafood. Individuals should use water that has been boiled, which is the most reliable method to make the water safe for consumption. Travelers should avoid ice or food served at room temperature. The risk of developing traveler's diarrhea is also reduced by the use of alcohol-based hand sanitizers (containing >60% alcohol) and meticulous hand hygiene. Table 80.10 lists preventive medications and treatment of traveler's diarrhea.

Management of traveler's diarrhea depends on the clinical scenario and the severity of illness. The mainstay of treatment is hydration. Commercially available oral rehydration packets can be used by travelers to maintain their fluid status. For mild or moderate diarrhea, symptomatic therapy, including antimotility agents such as loperamide or diphenoxylate can be used by travelers to reduce the rate of stooling. In severe cases, antimotility agents should be taken in conjunction with an antibiotic, as the antimotility agent may increase the contact time of the toxin or invasive infectious agents with the intestinal mucosa. Antimotility agents do not treat the cause of diarrhea and should be avoided in cases of dysentery.

The antacid bismuth subsalicylate decreases the incidence of traveler's diarrhea by 65% due to its antibacterial and antisecretory effects. The recommended dose is two tablets PO qid or one fluid ounce PO qid. Bismuth subsalicylate should be avoided in those who are allergic to aspirin because it contains salicylate. Potential side effects include blackening of the tongue or stool. It should not be taken for more than 3 weeks.

The risk of traveler's diarrhea can be reduced by more than 90% with the use of prophylactic antibiotics. However, due to the development of adverse side effects and resistance, prophylaxis is recommended only for individuals with comorbidities that place them at high risk for complications of diarrhea (e.g., transplant patients, patients with renal failure, or IBD, or patients who are immunosuppressed).[36] Prophylactic antibiotics should not be given for more than 2 to 3 weeks.

Antibiotics such as quinolones, azithromycin, and rifaximin can be prescribed when indicated (see Table 80.8). The decision to initiate treatment for traveler's diarrhea is based on the functional impact of the diarrhea, the associated signs and symptoms, and need for resolution of the diarrhea in regard to the patients' travel plans. In patients with moderate to severe traveler's diarrhea, antibiotics can shorten the duration of disease by 1.5 days. The choice of antibiotic is based on the location of the traveler. Single-dose azithromycin, levofloxacin, and rifaximin with loperamide have been shown to be comparable for the treatment of acute watery diarrhea.

Azithromycin 500 mg PO daily for 3 days is the drug of choice. Rifaximin 200 mg PO tid for 3 days is an alternate antibiotic that can be prescribed for patients with noninvasive illness. It is not effective against invasive pathogens such as *Campylobacter*, *Salmonella,* and *Shigella* spp.[35] Fluoroquinolones are no longer the first line antibiotic choice for treatment of traveler's diarrhea due to the widespread resistance and evidence for the increased risk of multidrug-resistant organisms. In November 2018, the US Food and Drug Administration approved rifamycin for the treatment of traveler's diarrhea. It is an enteric antibiotic that is similar to rifaximin and poorly absorbed with a low rate of adverse events. Rifamycin can also be used as an alternative for treatment of moderate to severe cases of traveler's diarrhea. The dose of rifamycin is 388 mg PO bid for 3 days.[37]

GASTROENTERITIS IN THE IMMUNOCOMPROMISED HOST WITH HIV/AIDS

Epidemiology and Pathophysiology

The evaluation of gastroenteritis in HIV-positive patients deserves special attention because these patients are at risk for opportunistic enteric infections and are more likely to develop chronic gastroenteritis. Rates of regular gram-negative bacterial enteric infections are at least 10-fold higher among HIV-infected adults than in the general population, but these rates decline when patients are treated with highly active antiretroviral therapy (HAART). The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) count. Those with a CD4+ count of less than 200/mm^3 are more susceptible to certain viruses and parasites, such cytomegalovirus (CMV), *Cyclospora, Cryptosporidium, Isospora, Mycobacterium avium-intracellulare* (MAI) complex, or *Giardia*. HIV itself may also cause diarrheal illness. Although not precisely clear, it is thought that HIV may cause direct infection of the enterocytes and invasion of the lymphoid tissues of the GI tract. Patients with an extremely low CD4+ count, less than 100/mm^3, tend to develop opportunistic infections that are chronic in nature.[38]

Clinical Features

The history should ascertain treatment with HAART, the CD4+ count, and viral load. A history of previous enteric pathogen-related diarrheal

TABLE 80.10 Traveler's Diarrhea in Adults: Preventive Medications and Treatment

Pharmacologic Agent	Recommended Dose	Adverse Effects/ Notes
Prevention		
Rifaximin	200 mg PO daily or bid for duration of trip, not to exceed 2 weeks	Considered safe as it is not absorbed
Bismuth subsalicylate	524 mg PO qid (1 oz liquid or two tablets) for duration of trip, not to exceed 2 weeks	Contains hydrogen sulfide, which turns stool or tongue black in color
Treatment		
Bismuth subsalicylate	524 mg PO qid (1 oz liquid or two tablets)	Contains hydrogen sulfide, which turns stool or tongue black in color
Loperamide	4 mg PO initially, then 2 mg PO after each unformed stool; not to exceed 16 mg/day.	Lowest effective dose should be taken to limit rebound constipation
Azithromycin	500 mg PO daily for 3 days or 1000 mg PO in single dose	First treatment of choice. Nausea is common adverse effect
Rifaximin	200 mg tid PO for 3 days	Considered safe because it is not absorbed. Alternative agent.
Rifamycin	388 mg PO bid for 3 days	Alternative for moderate to severe diarrhea.
Ciprofloxacin	500 mg PO bid for 3 days or 750 mg PO single dose	Achilles tendon damage; *C. difficile* infection. High resistance

illness is important as recurrence rates are common. Anal receptive intercourse may predispose to colonic pathogens, such as *Giardia, Entamoeba,* CMV, *Shigella,* and *Campylobacter*.

Antiviral therapy-induced diarrhea has also been known to cause watery diarrhea in HIV-infected patients. In HAART-naïve populations, *Cryptosporidium* and CMV infections are the two most common causes. Chronic high-volume watery diarrhea often is indicative of small bowel disease from one of the coccidia, *Cryptosporidium,* or *Cystoisospora belli*. Although self-limited in the healthy host, coccidial disease often is persistent in patients with CD4+ counts less than 200/mm^3. CMV and MAI also produce a chronic illness in those with CD4+ counts less than 100/mm^3.

Fever, weight loss, or abdominal pain are prominent; diarrhea is mild to moderate and sometimes bloody, typical of colonic disease. Microsporidia have emerged as a common cause of diarrhea in patients with AIDS in whom the CD4+ count is less than 100/mm^3. *Salmonella* infections, especially with *S. typhimurium,* are common in immunocompromised hosts. Patients with AIDS who acquire *Salmonella* enteritis are at increased risk for bacteremia and metastatic focal infection compared with normal hosts. *C. difficile* enteritis occurs more commonly in patients with AIDS owing to the common use of prophylactic antibiotic therapy and frequent hospitalizations. It is the most common bacterial enteritis in the AIDS population.

Diagnostic Testing

In patients with AIDS, the presenting signs and symptoms generally do not allow consistent classification of diarrheal illness, given the prevalence of multiple, concomitant enteric pathogens among this population. However, some clinical syndromes are typical. Patients with a fulminating clinical course usually have a disseminated infection, such as infection with CMV or MAI complex. Massive weight loss is also associated with diarrhea caused by infection with these two organisms, as well as the coccidia *Cryptosporidium* and *Cystoisospora*. Voluminous watery diarrhea usually is a result of one of the coccidial organisms, including *Cyclospora* or *Isospora*. Patients with a proctocolitis-like picture most often have herpes simplex virus or CMV infection.[39]

Laboratory testing should initially focus on testing stool samples for *C. difficile* toxins and other bacteria, specifically *Salmonella*. If the stool is bloody and the CD4+ count is less than 200/mm^3, stool should be sent for CMV and MAI testing. If the diarrhea is present for more than 14 days, three stool samples for stool ova and parasites should also be sent. An acid-fast smear should be requested to look for *Cryptosporidium, Cystoisospora, Isospora,* and *Cyclospora* if suspected as described.

If the patient has suspected infectious colitis but recent stool analyses have been negative for any organism, a flexible sigmoidoscopy may be performed by a specialist to enhance the yield of a pathogen. Small bowel biopsy and duodenal aspiration may be indicated when stool examination, cultures, and sigmoidoscopy fail to yield a definitive diagnosis. Small bowel studies are most helpful for detecting infection with *Cryptosporidium,* CMV, MAI, *Giardia*, or *C. belli.* Small bowel enterocolitis generally presents with watery diarrhea without fever or fecal leukocytes.[3]

Management

Treatment should be directed toward the presumptive causative organism. As for immunocompetent patients, a cautious approach to initiating any antibiotic is suggested. Empirical antibiotic treatment should be initiated if the patient has a fever, bloody stool, appears ill, or has a low CD4+ count. Ciprofloxacin 500 mg PO bid or IV ceftriaxone 1–2 g daily may be empirically initiated while the evaluation is in progress. If *Giardia* or *C. difficile* is suspected, metronidazole 500 mg PO tid or vancomycin 125 mg PO qid should be added, respectively. If CMV colitis is suspected, foscarnet 90 mg/kg IV bid should be given. See Tables 80.3, 80.4, and 80.5 for the treatment of specific organisms.[38]

Treatment failure is common and is often due to incorrect initial therapy. For example, CMV colitis can also mimic invasive bacterial pathogens because it can also cause severe colitis with bloody stool, fever, and abdominal cramps. Treatment failures are also due to the propensity for infections to recur or become chronic. Parasitic infections in immunocompromised patients may be difficult to eradicate, even with the correct treatment.

Gastroenteritis in the HIV-positive patient is often complex, prolonged in duration, and difficult to treat. It is recommended that an infectious disease specialist be involved in the care of these patients. Patients who have AIDS or are immunocompromised should generally be considered for admission for further management.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 80: QUESTIONS AND ANSWERS

1. After eating undercooked ground beef, a patient develops fever, abdominal pain, bloody diarrhea, and rectal tenesmus. Local health authorities are investigating a common source from a local diner, as 10 other patrons have presented with the same symptoms. Which of the following organism is likely to produce this dysentery outbreak?

a. Giardia
b. Norovirus
c. Shiga toxin–producing *Escherichia coli* (O157:H17)
d. *Staphylococcus aureus*

Answer: c. This patient is most likely infected with Shiga toxin–producing *E. coli* (ETEC) which often results from eating undercooked ground beef. Watery diarrhea that becomes bloody with significant abdominal pain is typical. The diarrhea may be grossly bloody and mimic inflammatory bowel disease or intestinal ischemia. Toxin assays are recommended. Endoscopic findings would be identical to those of any other severe colitis. Antibiotics are not effective and may increase the risk of hemolytic uremic syndrome (HUS) in children. Thrombotic thrombocytopenic purpura (TTP) is a risk in older children and adults. Norovirus

typically causes watery non-bloody diarrhea without severe abdominal pain. *S. aureus* causes the classic food poisoning with abdominal cramping and vomiting 1 to 6 hours after ingestion the preformed toxin.

2. A patient from a resource-rich country has traveled to a resource-poor developing country. He develops diarrhea, up to four times a day, with yellow watery stools. There is no fever or abdominal pain. Which of the following organism is most commonly the etiology of Traveler's Diarrhea?
   - **a.** Enterotoxigenic *Escherichia coli* (ETEC)
   - **b.** *Giardia*
   - **c.** *Shigella*
   - **d.** *Vibrio* noncholera

Answer: a. ETEC is the most common cause of traveler's diarrhea, especially with travel to resource poor countries. It is usually self-limited, requiring antibiotic treatment only in severe cases. *Giardia* causes persistent diarrhea for more than 14 days. Giardiasis is commonly acquired from the ingestion of contaminated water, classically a camper who has ingested river water. The symptoms include diarrhea, abdominal cramping, and bloating, with foul-smelling stools. Shigellosis usually causes a more severe illness with dysentery.

3. A 5-year-old patient with a likely viral gastroenteritis for 3 days is determined to be dehydrated. What is optimum mode of rehydration therapy in this patient?
   - **a.** High-glucose solution (e.g., apple juice)
   - **b.** IV normal saline (0.9%)
   - **c.** Oral hydration with clean water
   - **d.** Reduced osmolarity (245 mOsmol/kg) oral rehydration solution

Answer: d. Fluids containing glucose and electrolytes provide optimal rehydration due to the cotransport of water across the intestinal lumen. Reduced osmolarity rehydration solution (e.g., WHO ORS 245 mOsm/kg) is associated with a reduced need for unscheduled IV infusions, lower stool volume, and less vomiting. High-glucose solutions have high osmolarity, and pure water has a low osmolarity; thus neither are optimal for water resorption. IV hydration is generally not indicated or cost effective in patients with mild or moderate dehydration.

4. A patient comes to the emergency department (ED) with a complaint of abdominal cramping and vomiting twice; the first time was the food ingested from a buffet 8 hours ago and the second time yellowish vomitus. There is no diarrhea or fever. There is continued retching intermittently in the ED. What is the likely causative organism?
   - **a.** *Clostridium perfringens*
   - **b.** *Escherichia coli* O157:H7—Shiga-producing toxin
   - **c.** Norovirus
   - **d.** *Salmonella enteritidus*

Answer: a. *Clostridium perfringens* is a common source of foodborne illness. Food cooked in advance, cooled, and rewarmed is the typical culprit. This is a toxin-mediated, diarrhea-predominant syndrome that is almost always self-limited. Ingestion of live organisms or spores is required, and antibiotics are not indicated. Symptoms usually appear within 6 to 12 hours, slightly longer than for staphylococcal food poisoning.

5. A patient presents with non-bloody diarrhea for 5 days, crampy abdominal pain, and bloating. The white blood cell (WBC) is 16,000/mL. Which of the following types of patient and scenario is most likely to put the patient at high risk for *Clostridium difficile*?
   - **a.** A 3-year-old toddler in daycare
   - **b.** Elderly nursing home patient
   - **c.** Nurse who works in the emergency department
   - **d.** Traveler on vacation returning from Mexico

Answer: b. Elderly nursing home patients have the highest risk for acquiring *C. difficile*. These patients are in close quarters and have multiple daily contacts with staff members, making person to person transmission more likely. Antibiotics and antacids are frequently utilized in these patients, which are risk factors for *C. difficile*. The *C. difficile* spores are highly resistant to heat, acid, and antibiotics, making them highly contagious for person to person or surface to person infections. The WBC is generally greater than 15,000/mL.

81

Large Intestine

Natasha Thomas and Andrea W. Wu

KEY CONCEPTS

Irritable Bowel Syndrome

- Irritable bowel syndrome (IBS) is a chronic disorder that includes both abdominal pain and bloating and is either diarrhea-predominant, constipation-predominant, or a mixed picture.
- Treatment of IBS is challenging and commonly involves a combination of diet, pharmacological, and behavioral therapy, along with reassurance.

Diverticular Disease

- Diverticular disease can consist of diverticulosis, which can cause bleeding but is often asymptomatic, or inflammation of the involved diverticula, termed diverticulitis.
- Uncomplicated diverticulitis can typically be managed on an outpatient basis, with oral antibiotics if indicated. Complicated diverticulitis may require admission and intravenous antibiotics, often with surgery consultation.

Large Bowel Obstruction

- The most common cause of large bowel obstruction in the United States is colorectal malignancy. Treatment consists of endoscopic placement of an intraluminal stent with surgical resection at a later date.
- Acute colonic pseudo-obstruction commonly occurs in hospitalized elders. Treatment involves medical management, with endoscopic decompression if refractory.

Volvulus

- Sigmoid volvulus often affects elders or those that are in long-term care facilities and can usually be treated by endoscopic decompression.
- Cecal volvulus often affects younger patients and requires surgical management.

Intussusception

- Intussusception is the second most common cause of an acute abdomen in the pediatric population after appendicitis, is usually idiopathic, and may be successfully treated with hydrostatic or pneumatic reduction.
- In adults, intussusception is often associated with neoplasm or malignancy, typically requiring surgical management.

Inflammatory Bowel Disease

- Inflammatory bowel disease (IBD) is characterized by chronic, relapsing, and remitting inflammatory disease. Crohn disease's (CD) transmural inflammation can affect any area of the gastrointestinal (GI) tract, whereas ulcerative colitis (UC) inflammation is more superficial and is limited to the colon and rectum.
- Effective management of IBD requires prompt recognition and treatment of acute relapses, and appropriate choice and monitoring of medications for maintenance of remission. Most patients with CD respond to ileal-release budesonide or systemic steroids; aminosalicylates are less effective. In contrast, aminosalicylates are first-line therapies for UC, with steroids reserved for use only when necessary. Refractory exacerbations for both CD and UC may be treated with immunomodulators or biologic agents.
- Common complications of IBD include the formation of fistulae, strictures, or abscesses; less common yet more severe complications include fulminant colitis, toxic megacolon, or intestinal perforation.
- Chronic inflammation can have extraintestinal effects. Thromboembolic events affecting the venous and arterial systems in IBD patients may be underdiagnosed.

Colonic Ischemia

- Colonic ischemia (CI) typically presents in elders and is the most common ischemia disorder of the GI tract. Local hypoperfusion and reperfusion injury cause crampy abdominal pain over the segment of the colon involved, followed by a short course of bloody diarrhea.
- Although abdominal computed tomography (CT) is not diagnostic for CI, it is useful in supporting the clinical suspicion, assessing the extent of colon involvement, diagnosing complications, and excluding other disorders. Colonoscopy within 48 hours of symptom onset is the most accurate diagnostic study.
- CI is usually self-limited, and most patients experience resolution of symptoms with supportive medical management with bowel rest, hydration, and pain management. Those with more severe disease, especially those with right-sided colonic involvement, may develop peritoneal signs from transmural ischemia requiring antimicrobials and possible surgical intervention.

Stercoral Colitis

- Stercoral colitis is a rare complication of chronic constipation that is typically diagnosed on CT and is associated with high mortality. The condition primarily affects the elderly, individuals living in nursing homes, young patients with neurological impairment, and those with chronic opioid use.
- Fecal impaction leads to increased intraluminal and colonic wall pressure, which then causes inflammatory changes and pressure wall necrosis of the colon. It can be complicated by CI, stercoral ulcer formation, and subsequent perforation.

Radiation Proctocolitis

- Radiation proctocolitis occurs commonly in those that have received pelvic radiation. Acute radiation proctocolitis occurs during the course of treatment and is often self-limited. Chronic radiation proctocolitis can occur months after completion of treatment. Management typically varies based on severity and can range from stool softeners to hyperbaric therapy.

Neutropenic Enterocolitis

- Neutropenic enterocolitis, or typhlitis, occurs in those that have hematologic malignancies, are undergoing chemotherapeutic regimens, or are immunosuppressed for other reasons. It is characterized by neutropenia, fever, and abdominal pain. Treatment involves broad-spectrum antibiotics, bowel rest, and interventions to stimulate leukocyte count recovery.

IRRITABLE BOWEL SYNDROME

Foundations

Background

IBS is a chronic condition that affects approximately 7% to 21% of the general population. It is a disabling disease that can lead to a significant reduction in the quality of life. It is more commonly found in women and is characterized by abdominal pain, bloating, and altered bowel habits. IBS was previously considered a diagnosis of exclusion when no specific anatomical or biochemical abnormalities were found on workup, but new research shows that specific pathophysiological findings are associated with IBS.

There are numerous comorbidities associated with IBS, including functional pain syndromes, psychiatric disorders, as well as other intestinal disorders. This can result in frequent relapses and varying symptoms between relapses. These variable symptoms make both diagnosis and treatment of IBS challenging in the emergency department (ED). This is compounded by the fact that lab and imaging findings are often unrevealing. Patients tend to be discharged from the ED without a specific diagnosis.

Anatomy, Physiology, and Pathophysiology

The pathophysiology of IBS remains unclear, though there are many factors that are thought to contribute to its development. These include intestinal permeability, immune function, alterations in the gut microbiome, motility, and psychosocial status. For example, increased gas production by bacteria in an altered microbiome may result in intestinal reflex responses that create bowel distention. Other theories suggest the possibility of a brain-gut association in certain patients, especially in those with an underlying psychiatric disorder; there is also a potential converse gut-brain association, evidenced by the effect of probiotics in improving symptoms for some patients.

Clinical Features

The diagnosis of IBS is made with a detailed history as well as the exclusion of certain disorders. The Rome IV criteria are generally used to confirm the diagnosis of IBS (Box 81.1). These criteria account for the frequency of episodes, alterations in bowel habits, and the lack of any traditional "warning signs" such as the onset of symptoms over the age of 50 with the lack of age-appropriate colorectal cancer screening, gastrointestinal bleeding, or family history of colorectal cancer.

There are four distinct subtypes of IBS, and identification is important in determining treatment options. The subtypes include IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed symptoms of constipation and diarrhea (IBS-M), and unsubtyped-IBS. There is also a postinfectious IBS that can cause persistent symptoms in approximately 10% to 30% of patients with gastroenteritis.

Common symptoms include recurrent abdominal pain, abdominal bloating, and changes in bowel habits. The following symptoms would be concerning for more sinister pathology: age at onset greater than 50 years, no previous colon cancer screening, evidence of gastrointestinal bleeding, unintentional weight loss, or a positive fecal occult blood test, among others. Of note, it is unusual for IBS to be diagnosed for the first time in the ED, so attention should be paid to ensure more sinister diagnoses are considered, as they may warrant further evaluation.

Differential Diagnoses

The differential diagnosis for IBS depends on the particular subtype in question and can be rather broad (Box 81.2). Other gastrointestinal disorders such as colitis, gastroenteritis, pancreatitis, hepatitis, or biliary pathology should be considered, along with possible urological or gynecological disorders, based on the clinical history.

BOX 81.1 Rome IV Criteria for Irritable Bowel Syndrome

Patient has recurrent abdominal pain (>1 day/week in the previous 3 months), with an onset >6 months before diagnosis.

Abdominal pain is associated with at least two of the following three symptoms:

Pain related to defecation
Change in frequency of stool
Change in form (appearance) of stool

Patient has none of the following warning signs:

Age >50 years, no previous colon cancer screening, and presence of symptoms
Recent change in bowel habits
Evidence of overt gastrointestinal bleeding
Nocturnal pain or passage of stools
Unintentional weight loss
Family history of colorectal cancer or inflammatory bowel disease
Palpable abdominal mass or lymphadenopathy
Evidence of iron-deficiency anemia on blood testing
Positive test for fecal occult blood

From Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393–1407.

BOX 81.2 Differential Diagnosis in Irritable Bowel Syndrome

IBS With Constipation

Bowel obstruction
Malignancy
Adult-onset Hirschsprung disease
Rectocele
Paradoxical closure of the anus during defecation

IBS With Diarrhea

Bacterial or parasitic intestinal infection
Inflammatory bowel disease
Lactose intolerance
Malabsorption
Radiation proctocolitis
Celiac disease

IBS With Mixed Symptoms

Inflammatory bowel disease
Ureteral colic
Bowel obstruction
Diverticular disease
Gastroesophageal reflux of ulcer
Liver or pancreatic disease
Lead toxicity
Porphyria

IBS, Irritable bowel syndrome.

Diagnostic Testing

There are no specific tests to assess for IBS in the ED setting. A complete blood count (CBC) may be performed to assess for anemia in patients where malignancy is on the differential. Fecal calprotectin is a

test typically performed in an outpatient setting that may help differentiate IBS from IBD, as it may be increased in the latter.

Management

The management of IBS is largely based on the subtype. Typically, treatment involves a combination of diet, behavioral, and pharmacological therapies. Traditionally, small dietary changes such as increasing soluble fiber can improve IBS-C. Low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diets have been shown to improve abdominal pain and bloating associated with IBS. FODMAPs are a group of fermentable carbohydrates that can potentially aggravate symptoms. Fermentable oligosaccharides include wheat, rye, and certain legumes such as garlic and onions. Disaccharides are lactose-containing foods. Monosaccharides are found in some fruit such as mangoes and figs and also include honey and agave nectar. Certain fruits and vegetables such as blackberries and lychee contain polyols, as well as some low-calorie sweeteners that might be in sugar-free gum. Ondansetron (4 mg by mouth [PO] three times daily) and loperamide (4 mg PO as an initial dose, followed by 2 mg PO for subsequent doses, up to a maximum of 16 mg daily) may improve stool consistency for those with IBS-D. Probiotics have been associated with improvement in symptoms. Cognitive-behavioral therapy (CBT) and hypnotherapy may be useful. Evidence points toward using an individualized approach, with a focus on affirming the diagnosis of IBS, in order to help reduce symptoms. Unfortunately, management is typically not curative but may help improve quality of life.

Disposition

IBS is typically a non-emergent condition that can be managed on an outpatient basis. Emphasis should be placed on maintaining close follow-up in order to optimize therapy. Strict return precautions should be provided, and patients should be educated on monitoring for any of the warning symptoms that may point to a more concerning alternative diagnosis.

DIVERTICULAR DISEASE

Foundations

Background

Diverticular disease is one of the most common gastrointestinal diagnoses in the Western hemisphere, affecting 5% of patients younger than 40 years, and up to 60% of patients over the age of 80.[1] There are multiple theories regarding the increasing incidence of diverticular disease including diet, obesity, and bacterial colonization. There was once thought to be a link between fiber intake and the development of diverticular disease, but that theory is now questioned.

Risk factors for diverticular disease include smoking, use of NSAIDs, physical inactivity, obesity, red meat, and a diet high in refined carbohydrates.[2] Diverticular disease involves the development of false diverticula, which is the herniation of the inner mucosal and submucosal layers of the intestinal wall through the muscular layers. Diverticulosis refers to the presence of multiple diverticula. While the sigmoid colon is most often involved, interestingly, in the Japanese population, the right colon tends to be affected. The sigmoid colon is thought to be affected more commonly because of specific anatomic features including noncircumferential muscle layers, along with the location of insertion of the vasa recta (intestinal arteries) (Box 81.3).

Anatomy, Physiology, and Pathophysiology

Diverticulosis refers to the asymptomatic condition of having multiple diverticula. Diverticulitis results from inflammation of the diverticula. Diverticulitis can be uncomplicated, which can most often be managed in the outpatient setting. Complicated diverticulitis can include abscess formation, fistula formation, strictures, along with perforation or acute peritonitis. The pathophysiology of this inflammation is thought to involve changes in gut motility as well as increases in intraluminal pressure in the colon, which can lead to localized perforation. If the perforation occurs into the abdominal cavity, this may result in peritonitis, whereas if the diverticulum is covered by mesentery, perforation can create a phlegmon or abscess.[2]

Diverticulosis is also the cause of 40% of lower gastrointestinal hemorrhages. Severe hemorrhage occurs in 3% to 5% of all patients with diverticulosis. The bleeding is typically painless, as there is no associated inflammation.

BOX 81.3 Factors That Contribute to the Development of Colonic Diverticula

Weakness of the Bowel Wall
Noncircumferential muscular layers
Insertion of the vasa recta
Localized ischemia
Connective tissue disorders
Ehlers-Danlos syndrome

High Intraluminal Pressure
Increased collagen crosslinking with ageê more distensible, more contractile bowelê segmentation
Obstruction of diverticula
Colonic stasis, chronic constipation
Low fiber intake

Other Associated Factors
Seasonal variation (summer months)
Smoking
Age

Obesity
Alcohol use
Immunocompromised state
Composition of intestinal flora

From Meara MP, Alexander CM. Emergency presentations of diverticulitis. *Surg. Clin. North Am.* 2018;98:1025–1046.

Clinical Features

Diverticulosis

Most patients with diverticulosis are asymptomatic. It can result in bleeding, and it can also occasionally result in vague abdominal complaints, such as abdominal bloating. Diverticulosis progresses to acute diverticulitis in up to 25% of individuals and results in recurrent episodes of diverticulitis in up to 40%.

Diverticulitis

As the majority of patients develop diverticula in the sigmoid colon, diverticulitis tends to present with persistent left lower quadrant pain. Many patients will present with persistent pain over 24 hours, possibly with a low-grade fever. Other associated symptoms may include nausea, vomiting, or alterations in bowel movements. Physical examination may reveal tenderness in the left lower quadrant and possibly abdominal distention. Patients with more complicated cases may present with high fever or other vital sign abnormalities concerning sepsis.

Patients that are predisposed to developing diverticula in the right colon will present with right lower quadrant abdominal pain and tenderness on examination, which may be difficult to distinguish from

appendicitis. There may also be referred pain to the suprapubic region. Additional findings suggest various complications—diffuse tenderness with rebound or guarding may be associated with gross perforation or abscess rupture; dysuria can be present with a colovesical fistula; a palpable mass may be associated with localized abscess formation; vomiting with abdominal distention may suggest proximal obstruction; and feculent vaginal discharge may suggest a colovaginal fistula. Almost any organ adjacent to the colon can be involved in the inflammatory process. Elders and immunocompromised patients may present more subtly despite the potential for having an even more severe disease. Perforation is seen more frequently in this population and is associated with a high mortality rate.

Differential Diagnoses

Other diagnoses to consider include colitis (either inflammatory or ischemic), ureteral stones, inguinal hernia, or pelvic or ovarian pathology, including an ectopic pregnancy or pelvic inflammatory disease. Appendicitis should be considered when symptoms are predominantly right-sided. Diffuse abdominal pain and tenderness should prompt an evaluation for other causes of peritonitis. An underlying colonic malignancy should be considered, but it is typically safe to wait until the resolution of the acute presentation before further investigation.

Diagnostic Testing

Patients with prior history of diverticulitis that present with similar symptoms may not need further testing. As long as symptoms are relatively mild, without concerning findings on physical examination, the patient may be started on empirical treatment for diverticulitis without the need for bloodwork or imaging. When other diagnoses are being considered, or the clinical severity of diverticulitis is concerning, further testing is indicated. A CBC is not necessary to make the diagnosis, but many patients will have varying degrees of leukocytosis. A urinalysis is suggested when there is concern for a colovesical fistula.

Abdominal CT has become the standard of care for diagnosing diverticulitis. A CT without contrast can identify the presence of diverticular disease. CT with intravenous (IV) contrast is commonly used to assess for diverticulitis. However, CT with both IV and enteric (either oral or rectal) contrast is the ideal method to assess for diverticulitis and any associated complications, with 98% sensitivity and 99% specificity. CT findings may include colonic wall thickening, pericolonic fat stranding, localized perforation (also known as micro-perforation), abscesses, as well as free air or fluid (Figs. 81.1–81.3).[2] While generally outside the scope of ED practice, the Hinchey staging system can be used to stratify diverticulitis based on the level of abscess formation or perforation (Box 81.4).

There are other imaging methodologies that were once used or suggested for the evaluation of diverticulitis that are no longer recommended, such as barium enemas, water-soluble contrast enemas, ultrasonography, and plain radiography. Colonoscopy was previously indicated after resolution of the acute episode to assess for underlying malignancy; however, it is now recommended to follow age-appropriate screening guidelines for colonic malignancy.

Management

Diverticulosis

Patients with diverticulosis are recommended to initiate a high-fiber diet in order to reduce abdominal symptoms. Physical activity has been associated with a decreased risk for developing acute diverticulitis, although the mechanism behind this benefit is unclear. Patients were previously instructed to avoid foods that may obstruct diverticula, such as nuts, small seeds, and popcorn, but this has been largely discredited due to the lack of evidence.

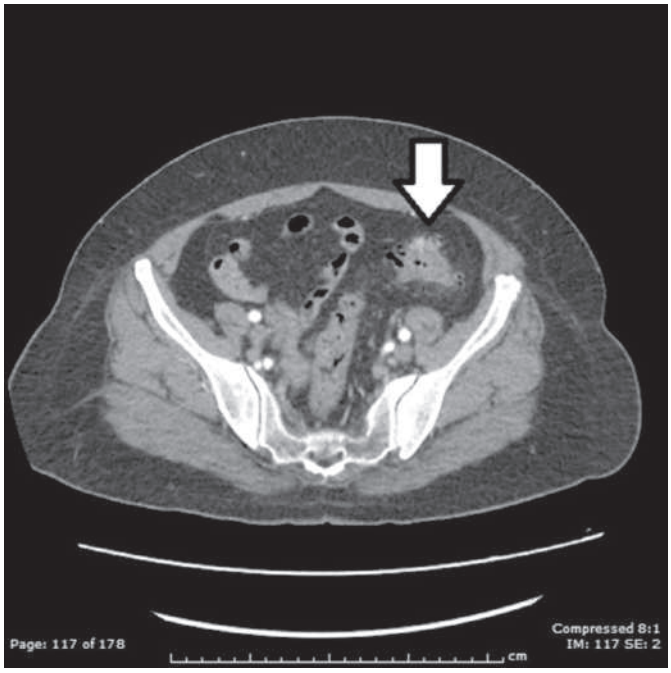

Fig. 81.1 Uncomplicated diverticulitis *(arrow)* showing multiple air-filled structures lining the edge of the left colon (diverticuli), and hazy outer border of bowel segment (fat stranding) indicative of inflammation.

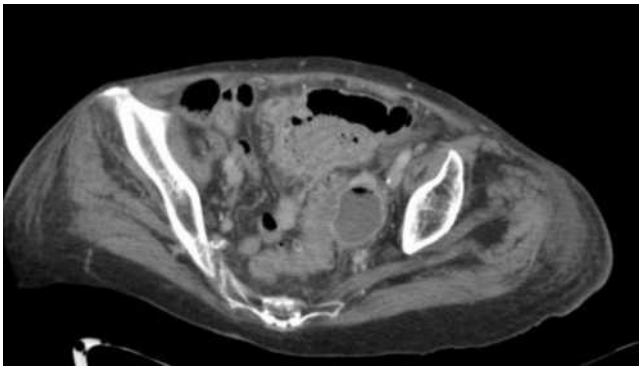

Fig. 81.2 Computed Tomography Imaging Demonstrating Diverticulitis With Abscess Formation. (From Sartelli M, Moore FA, et al. A proposal for a CT driven classification of left colon acute diverticulitis. *World J. Emerg. Surg.* 2015;10(3):1–11, Fig. 4.)

Uncomplicated Diverticulitis

There is more evidence to suggest that acute diverticulitis is an inflammatory process and not an infectious process. In fact, guidelines published by the American Gastrointestinal Association in 2015[1] advocate for the selective (as opposed to routine) use of antibiotics in treating uncomplicated diverticulitis. If antibiotics are utilized, oral antibiotics should cover both Gram-negative aerobic and anaerobic bacteria (Box 81.5). The vast majority of patients with uncomplicated diverticulitis can be managed on an outpatient basis. Studies have shown no benefit in the use of IV antibiotics when compared with oral antibiotics for uncomplicated diverticulitis. Liquid diets with instructions to advance as tolerated should be recommended for patients that are managed as outpatients.

Hospitalization for IV antibiotics and bowel rest is often required for elders, patients who are immunocompromised or have multiple

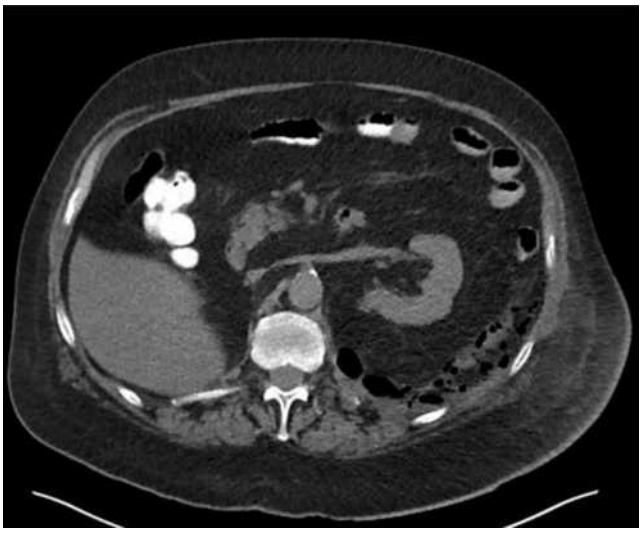

Fig. 81.3 Computed Tomography Imaging Illustrating Diverticulitis With Free Air Formation as a Result of Perforation. (From Sartelli M, Moore FA, et al. A proposal for a CT driven classification of left colon acute diverticulitis. *World J. Emerg Surg.* 2015;10(3):1–11, Fig. 5.)

BOX 81.4 Hinchey Classification of Diverticulitis

1a. Pericolonic phlegmon and inflammation without fluid collection
1b. Pericolonic abscess <4 cm
2. Pelvic abscess or abscess >4 cm
3. Purulent peritonitis
4. Feculent peritonitis

BOX 81.5 Oral Therapy for Uncomplicated Diverticulitis

- Ciprofloxacin, 500 mg PO bid *and* metronidazole, 500 mg PO q8h
  or
- Amoxicillin-clavulanate, 875 mg–125 mg PO BID

comorbidities, and individuals who cannot tolerate oral liquids or have poor social support in the outpatient setting.

Complicated Diverticulitis

Patients with complicated diverticulitis should generally be admitted for IV antibiotics (Box 81.6) and bowel rest. Surgical consultation is indicated when there is concern for peritonitis or perforation, continuing clinical decline, or sepsis resistant to medical management. Small abscesses (4 cm or less) may resolve with IV antibiotics alone, whereas larger abscesses are often treated with percutaneous drainage, with possible surgical management if unsuccessful. Fistulae are usually repaired surgically on an elective basis. Surgical resection may be considered in patients with recurrent episodes of diverticulitis.

Disposition

Younger patients and those who are immunocompetent with uncomplicated diverticulitis may be discharged from the ED. If antibiotics are prescribed, a 7- to 10-day course is recommended. Follow-up evaluation is advised within a few days to determine the efficacy of treatment. Approximately 95% of patients will have a resolution of symptoms with this approach. If not improving, further diagnostic imaging to look for possible complications,

BOX 81.6 Intravenous Antibiotic Coverage for Bowel Flora

Mild to Moderate Infection

- Pediatric:
  - Metronidazole 7.5 mg/kg IV q6h AND ceftriaxone 50 mg/kg IV once daily OR
  - Gentamicin 2.5 mg/kg IV q8h AND metronidazole 7.5 mg/kg IV q6h
- Adult:
  - Metronidazole 500 mg IV q8h *plus*
    - Ceftriaxone 1 g IV q24h *or*
    - Ciprofloxacin, 400 mg IV q12h *or*
    - Levofloxacin 750 mg IV q24h *or*
  - Ampicillin-sulbactam, 3g IV q6h

Severe/Complicated Infection

- Piperacillin/tazobactam 3.375 g IV q6h or 4.5 g (100 mg/kg) IV q8h OR
- Metronidazole 500 mg IV q8h (7.5 mg/kg IV q6h) PLUS Cefepime 2 g (50 mg/kg) IV q12h OR
- Ertapenem, 1g IV q24h (weight-based dose in pediatrics: 15 mg/kg/dose IV BID) *or* imipenem/cilastatin, 500 mg IV q6h (weight-based dose in pediatrics: 60 to 100 mg/kg/day divided q6h) *or* meropenem, 1 g IV q8h (weight-based dose in pediatrics: 20 mg/kg/dose IV q8h)

such as abscess formation, is prudent. Patients with complicated diverticulitis should be hospitalized for IV antibiotic therapy and bowel rest. Most patients (65% to 85%) recover with medical management alone, though some may require surgical intervention. Mortality rates range from 1% to 6% but increase to 12% to 18% for those requiring surgery.

LARGE BOWEL OBSTRUCTION

Foundations

Background

Large bowel obstruction (LBO) is not as common as small bowel obstruction but is a more ominous condition frequently associated with malignancy. Most cases of LBO are due to a progressive narrowing of the intestinal lumen from intrinsic lesions within the lumen. Approximately 50% of all cases of LBO are eventually found to be secondary to underlying colorectal malignancy. Diverticular disease and volvulus are the next most common causes of LBO. Other less common intrinsic causes of LBO include IBD, ischemia, adhesions, endometriosis, or radiation. Extrinsic lesions can also cause LBO from an impingement of the intestinal lumen. The most common causes of extrinsic lesions causing LBO include ovarian cancer, followed by hernias.[3]

Anatomy, Physiology, and Pathophysiology

The most common location for LBO is the sigmoid colon. Anatomically, it is important to note if the obstruction is proximal or distal to the splenic flexure for management purposes. Approximately 75% of colonic tumors are located distal to the splenic flexure.[4] LBO along the left side of the colon may manifest sooner than obstruction along the right side of the colon due to the smaller lumen of the sigmoid and descending colon.[5]

When mechanical obstruction is caused by an obstructing lesion, either intrinsic or extrinsic, the bowel proximal to the lesion becomes increasingly dilated. As the distention progresses, intraluminal pressure increases. When intraluminal pressure approaches systolic blood pressure, blood flow to the bowel wall is compromised, causing edema and subsequent transudation of fluid into the lumen. Transudation, along with decreased reabsorption of intraluminal fluid, further increases intraluminal pressure and decreases arterial flow to the bowel

wall, which can lead to ischemia and gangrene. The translocation of bacteria from compromised bowel can lead to sepsis. Perforation of the bowel wall follows if the process is left uninterrupted.

Acute colonic pseudo-obstruction (ACPO), also known as Ogilvie syndrome, may mimic LBO. It refers to acute colonic dilation without evidence of mechanical obstruction. ACPO tends to affect the cecum and right hemicolon, although dilation can extend all the way to the rectum.[6] It is thought to be a functional obstruction that results from either increased sympathetic tone or decreased parasympathetic tone. ACPO is often associated with other conditions that can affect autonomic intestinal innervation.[6] ACPO tends to affect elders, chronic opioid users, postoperative patients, and those with severe electrolyte disturbances or other significant acute comorbid conditions.

Clinical Features

The typical presenting complaints in LBO are abdominal pain, abdominal distention, obstipation, or vomiting. Vomiting tends to occur in patients with an incompetent ileocecal valve, as it causes backflow into the small intestine. Patients with a competent ileocecal valve less frequently present with emesis and instead will exhibit both significant distention and pain.[4] The time frame of symptom development varies in accordance with the etiology of the obstruction. LBO associated with a volvulus can develop rapidly, whereas obstruction from cancer tends to be gradual. The degree of stenosis is often associated with the acuity of presentation.[4]

Patients seen later in the course of obstruction may be significantly dehydrated. Fever or tachycardia should prompt an investigation for gangrene or perforation. A palpable abdominal mass may represent a tumor, abscess, or simply distended bowel. A rectal examination is helpful to look for an obstructing rectal mass or large volume of hard stool in the rectal vault consistent with fecal impaction.

Differential Diagnoses

The most common causes of LBO are colorectal cancer (53%), volvulus (17%), diverticulitis (12%), and compression from other malignancies or metastatic disease (6%). Other less common causes are strictures, incarcerated hernia, fecal impaction, adhesions, or pseudo-obstruction.

Diagnostic Testing

Laboratory Tests

A chemistry panel is important to identify electrolyte derangements, as fluid and electrolyte replacement therapy tend to be the mainstay of ED treatment for LBO. An elevated white blood cell (WBC) count should raise suspicion for gangrenous bowel. Anemia may suggest the possibility of colorectal cancer. An elevated serum lactate level may point toward ischemic bowel as a complication.

Imaging Studies

Plain Radiography. Both supine and upright plain films are advised for the workup of LBO and ACPO (Fig. 81.4). A distended colon (>6 cm diameter) is the hallmark of LBO, although the small bowel may be distended as well (>3 cm diameter) if the ileocecal valve is incompetent. A cecal diameter >6 cm is abnormal and when >12 cm is associated with a higher risk of perforation, although perforation has been known to occur at smaller diameters. The actual location and cause of the LBO are usually not evident on plain films.

Computed Tomography. CT is a valuable tool for determining the cause of the obstruction, especially if it is a diverticular abscess or intussusception. CT has the ability to locate the obstructing lesion in 96% of cases, especially if performed with both oral and rectal contrast.[4] CT can also help determine if the cause of obstruction is either intraluminal or extraluminal. Diagnosis of ACPO is suggested with increased colonic diameter without evidence of an obstructive lesion.

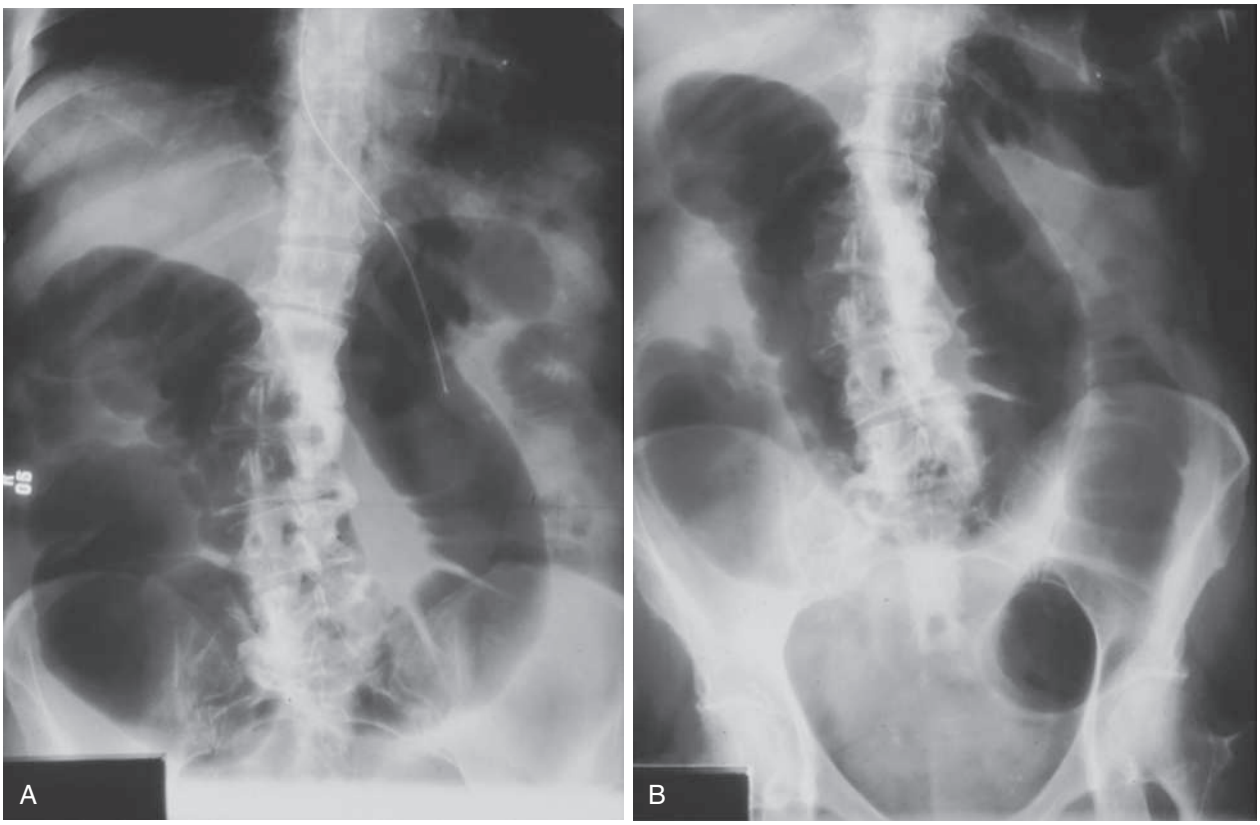

Fig. 81.4 Plain Radiographs Showing Large Bowel Obstruction at the Sigmoid Colon Caused by Carcinoma. (A) Upright view. (B) Supine view.

Colonoscopy and Water-Soluble Contrast Enema. Water-soluble contrast enemas are no longer advised, given that CTs are now more accurate in making the diagnosis of LBO. Colonoscopy can be used to identify the location of the lesion; however, it is more commonly used now in the management of LBO.

Management

Management of LBO and ACPO in the ED is directed at symptomatic relief and supportive care. Many of these patients will require large volume fluid resuscitation and electrolyte replacement. Intravenous (IV) pain control is often required. Gastric decompression with a nasogastric tube may be helpful in cases in which vomiting is prominent. The patient should be kept no food by mouth (NPO). Antibiotics are indicated if gangrene or perforation are suspected (see Box 81.6).

Definitive management depends on the cause of obstruction. Endoscopically placed self-expanding stents are now the mainstay of treatment for obstructing lesions.[4] These can either be placed as a bridge to surgery or can be used definitively for palliative management. Diverticular abscesses can be managed either with percutaneous or surgical drainage. Volvulus can be managed with endoscopic decompression or surgery (depending on whether it is sigmoid or cecal, respectively). Other less common causes of LBO, such as strictures, adhesions, or hernias, are typically managed surgically.

For ACPO, focus should be directed toward identifying and treating reversible factors such as electrolyte disturbances, or pharmacologic or metabolic factors. If conservative management is unsuccessful for up to 3 days, neostigmine (2 mg IV) or colonic decompression may be considered.[3] Neostigmine theoretically increases acetylcholine, which promotes colonic motility. Endoscopic decompression is used to treat ACPO refractory to medical management.[6]

Disposition

Most cases of LBO require procedural intervention to achieve resolution. Patients typically require hospitalization and consultation with a specialist capable of performing the appropriate procedure. Emergent surgical consultation is warranted for patients with evidence of gangrenous bowel or perforation. Oftentimes, ACPO develops in patients already hospitalized for other conditions associated with high morbidity,[5] but it can also develop in the long-term care facility setting, prompting ED evaluation. Patients should be admitted for both conservative medical management and for decompression if necessary.

VOLVULUS

Foundations

Background

Volvulus occurs in all age groups, but older adults (mean age 60 to 70 years) are affected most often. Mortality rates with sigmoid volvulus exceed 50% in patients when associated with gangrenous bowel. Cecal volvulus tends to occur in younger patients and is more commonly seen in women.

Anatomy, Physiology, and Pathophysiology

Volvulus is defined as a loop of bowel that twists around itself and its associated mesentery, resulting in obstructive pathology. If the mesentery is twisted enough such that blood supply to the intestine is affected, ischemia may arise. Colonic volvulus typically occurs in a redundant colonic segment with an elongated mesentery along a narrow base.[7] This most commonly occurs in the sigmoid and cecum, followed by transverse colon, or at the splenic flexure. Volvulus can result in ischemia, gangrene, perforation, and death. It is the third most common cause of colonic obstruction, following colorectal malignancy and diverticular disease.

Sigmoid Volvulus. Residents of long-term care facilities and patients with neurologic or psychiatric disease are predisposed to sigmoid volvulus, possibly as a result of alterations in colonic motility. There is an association of chronic constipation with the development of sigmoid volvulus, though this association is unclear. The mesentery of the sigmoid colon can withstand up to 180 degrees of twisting, and anything beyond this may result in colonic obstruction, ischemia, or necrosis. This occurs as a result of proximal colon forcing gas and liquid into the obstructed segment of the colon, causing a sometimes massive dilation of the distal colon. Electrolyte disturbances can occur secondary to third spacing, and respiratory compromise occasionally results from massive abdominal distention. Vascular supply can become compromised if left untreated.

Cecal Volvulus. The mobility of the colonic segment involving the cecum is likely a result of a congenital incomplete fusion of the cecal mesentery to the posterior abdominal wall.[8] Risk factors for cecal volvulus also include chronic constipation, as well as a high-fiber diet, frequent laxative use, and a history of laparotomy, pregnancy, pelvic surgery, or colonoscopy. Long-distance running is also considered a risk factor.[8]

Clinical Features

Sigmoid Volvulus

The hallmark of sigmoid volvulus is the triad of crampy lower abdominal pain, distention, and constipation. The extent to which the sigmoid colon can twist on itself varies, so the presentation can vary from subtle to dramatic. The clinical picture may range from one of minor discomfort that has been present for several days to an acute onset of severe abdominal pain associated with gross abdominal distention and unstable vital signs.

Physical examination may reveal a distended tympanic abdomen, often with most of the distention in the upper abdomen. Significant tenderness, fever, lack of bowel sounds, peritonitis, or cardiovascular instability suggests gangrenous or ischemic bowel and should prompt immediate surgical consultation. The absence of these findings does not exclude gangrene, and the duration of symptoms alone is not predictive of gangrene.

Cecal Volvulus

While up to 90% of patients with cecal volvulus present with acute abdominal pain, constipation, and abdominal distention are rarely seen. Vomiting is only seen in 50% of patients. Some patients with "mobile cecum syndrome" may have episodes that spontaneously resolve.

Differential Diagnoses

Any underlying pathology that may cause LBO can mimic volvulus, including neoplastic disease, paralytic ileus, toxic megacolon, or ACPO.

Diagnostic Testing

There are no specific laboratory tests that are essential for the diagnosis of volvulus. With this said, patients may have electrolyte derangements or coagulopathies that are important to identify.

Sigmoid Volvulus

The diagnosis of sigmoid volvulus is most often made with plain radiographs. Imaging findings include a large dilated loop of the colon (Fig. 81.5), absence of rectal gas, along with a "coffee bean sign" (where the bowel may have the appearance of a bent inner tube). Free air may be

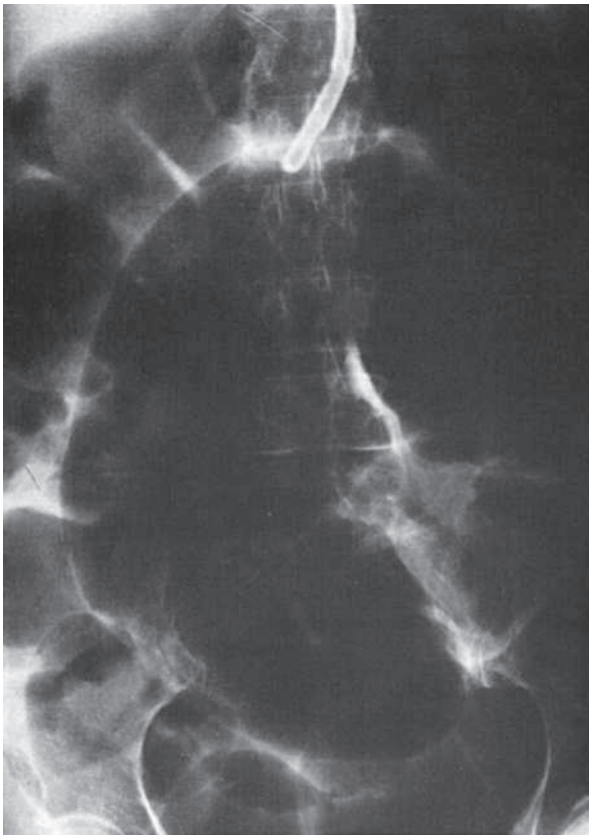

Fig. 81.5 Plain Film of the Abdomen Shows a Large Dilated Loop Characteristic of Sigmoid Volvulus.

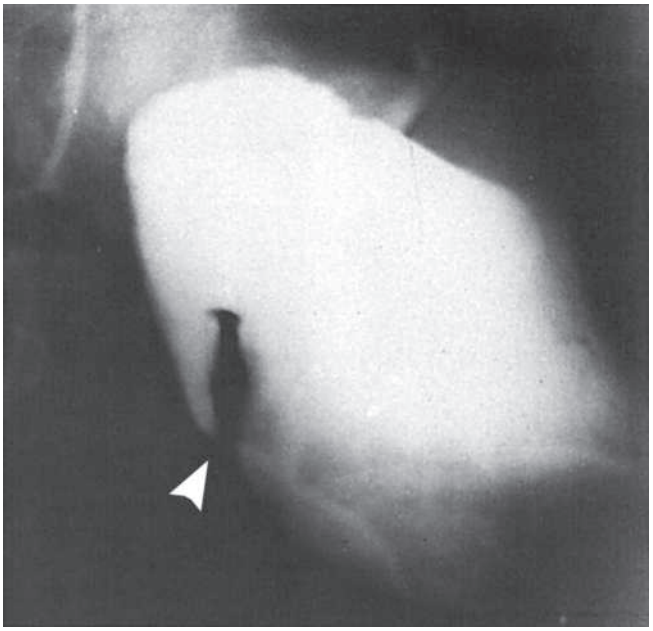

Fig. 81.6 Characteristic Bird's Beak Sign of Volvulus *(arrowhead)* Shown on This Image From a Barium Enema Study.

seen on an upright chest radiograph or lateral decubitus radiograph in patients with perforation. Gas backing up into the rest of the colon may obscure the typical appearance of sigmoid volvulus on plain radiographs, resulting in a number of nondiagnostic study results. When the diagnosis is in doubt, contrast enema may be helpful. Contrast material fills up the colon to the tapering point of torsion, causing a bird's beak appearance to the column of contrast material (Fig. 81.6). Sigmoidoscopy is diagnostic in many cases, as there is direct visualization of a spiral sphincter-like twist in the colonic mucosa. CT imaging is associated with a 100% sensitivity and over 90% specificity, but the diagnosis can often be made with plain radiographs alone. CT findings include a "whirl sign" (twisting of the mesentery and mesenteric vessels) along with a bird's beak sign.

Cecal Volvulus

Plain radiographs are often helpful in establishing a diagnosis of cecal volvulus. The cecum appears markedly dilated and may contain an air-fluid level. The small bowel is often distended as well. In contrast with sigmoid volvulus, the distal colon should have a paucity of gas. Free air suggests perforation and necessitates emergent surgical consultation (Fig. 81.7). If the differentiation of sigmoid from cecal volvulus is unclear, a contrast enema may be helpful in showing the site of torsion. On CT, the aforementioned "whirl sign" may be present (Fig. 81.8).

Management

Sigmoid Volvulus

Patients with any type of volvulus should undergo fluid resuscitation, especially if a shock state has developed. Electrolyte derangement should be corrected, and coagulopathy addressed. Antibiotics are indicated if gangrene or perforation are suspected (see Box 81.6). Endoscopic detorsion with flexible sigmoidoscopy can be attempted by an experienced operator, during which a lubricated flexible tube

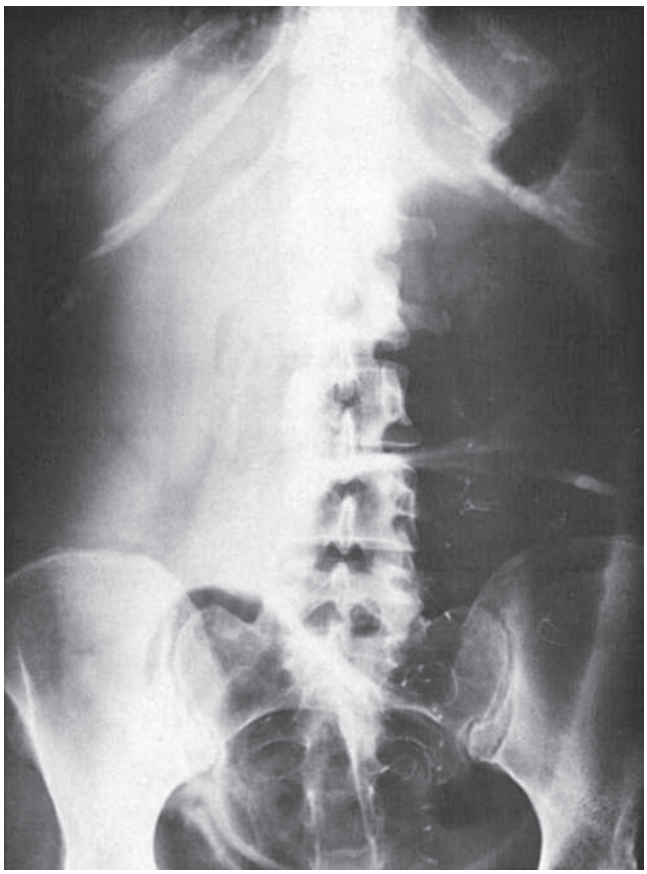

Fig. 81.7 Plain Radiograph Shows Distended Colon Characteristic of Cecal Volvulus. Note presentation in the left lower quadrant and absence of right-sided gas shadows.

is inserted through the obstruction. With decompression of gas and liquid stool, the bowel is able to undergo self-detorsion. Endoscopic decompression is successful in 70% to 95% of cases. If the patient has gangrenous bowel or if the volvulus does not respond to endoscopic decompression, surgical intervention is indicated.

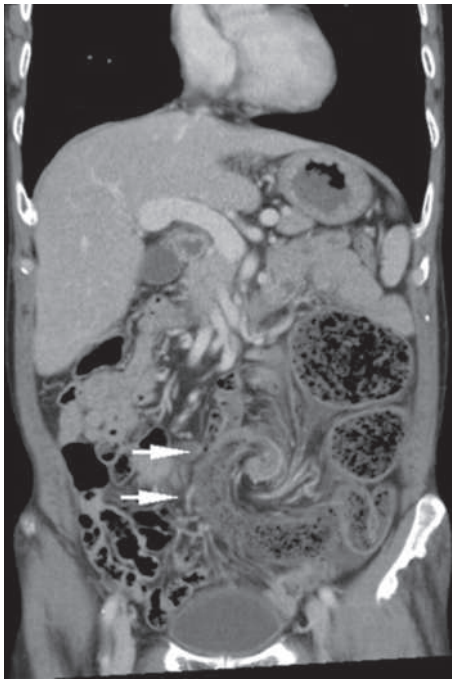

Fig. 81.8 CT scan of mesentery and intestine twisted into whirl pattern *(arrows)*, in this case from a sigmoid volvulus. (From Shaw W, Huang C, Hung T, Yeh Y. Typical whirl sign in sigmoid volvulus. *J Emerg Med.* 2014;46:383–384.)

Percutaneous endoscopic colopexy may be indicated for high-risk surgical patients.[9] Elective resection of the redundant sigmoid is recommended, given recurrence rates that are estimated at 60%. The mortality rate for sigmoid volvulus is 20% overall and exceeds 50% in those with gangrene.

Cecal Volvulus

Endoscopic evaluation and decompression are not options for cecal volvulus given its proximal location.[7] Cecal volvulus should be managed surgically, typically via resection of the cecum. Recurrence after resection is rare.

Disposition

Patients with volvulus require admission for procedural intervention.

INTUSSUSCEPTION

Foundation

Background

Intussusception is considered the primary cause of bowel obstruction in children and the second most common cause of an acute abdomen in children after appendicitis. The peak incidence is between 4 and 10 months of age, and the etiology is usually idiopathic. In contrast, adult intussusception is a rare cause of obstruction and is more often associated with a coexisting neoplasm or malignancy, particularly when occurring in the large bowel. In adults, the condition occurs over a wide range of ages, with a mean age at presentation of 50 years (Table 81.1).[10]

There is a small increased risk following rotavirus vaccination; however, the well-documented benefits of rotavirus vaccine have been found to outweigh the possible small risks of intussusception.[11]

Anatomy, Physiology, and Pathophysiology

The exact mechanism of intussusception is unknown, but it is believed that a lead point lesion changes the motility properties of the intestine, allowing a proximal segment to invaginate into a more distal segment. As peristaltic activity pushes the invaginated segment along with its mesentery and mesenteric blood vessels distally down the bowel, the blood supply to the segment can be compromised, and ischemia may occur. Edema associated with the intussusception can lead to a mechanical obstruction of the bowel. If not treated promptly, reduced blood supply can lead to bowel necrosis or perforation. The most common locations are at the junctions between freely moving segments, retroperitoneally, or adhesionally fixed segments.

In most infants, the intussusception involves the ileum invaginating through the ileocecal valve into the cecum and is typically idiopathic. In the pediatric population, there is an association with hyperplasia of lymphoid tissue in the small intestine (Peyer patches) secondary to viral infections. Adult intussusceptions that occur in the small bowel are caused by benign lesions 60% of the time; the remainder of small bowel intussusceptions are caused by malignancy (30%), which are generally metastatic tumors, or are idiopathic (10%). In contrast, most colonic intussusceptions (60% to 65%) are caused by malignancy.[10]

TABLE 81.1 Comparison of Pediatric Versus Adult Intussusception

	Pediatric Intussusception	Adult Intussusception
Typical age	Infants to toddlers	>50 years
Etiology	Idiopathic	Neoplasm, malignancy
Symptoms	Acute onset, intermittent, colicky abdominal pain with crying with pulling up knees, vomiting	Acute onset abdominal pain, vomiting, rectal bleeding
Diagnosis	Ultrasound	CT
Management	Reduction—either hydrostatic or pneumatic	Surgery

Clinical Features

Intussusception manifests in one of two patterns, acute or subacute. In pediatric intussusception, the classic presentation is acute, with abrupt onset of intermittent, colicky, abdominal pain, which can cause episodes of crying and pulling the knees up. The typical features of crying, abdominal pain, vomiting, pallor, abdominal mass, or lethargy are clinical indicators of pediatric intussusception. Individually, each variable is not helpful, but when multiple are present concurrently, there is a high probability of the disease.

In adults, the most common presentation is that of acute, partial intestinal obstruction, since only a small proportion of intussusceptions cause complete obstruction. The typical presenting complaints include abdominal pain, with vomiting and rectal bleeding. Constipation may also be present. The abdomen may be distended, and bowel sounds often are decreased. A mass is seldom palpated, especially if symptoms have been present for over 24 hours, as the overlying bowel distention will obscure it. The classic triad of abdominal pain, mass, and heme-positive stools noted in children is found in only 20% of pediatric intussusceptions and is rarely found in adults. Similarly, currant jelly stools or altered mental status are infrequent presentations and often occur late in the disease progression.

The subacute presentation is subtler, with intermittent abdominal pain for months. The diagnosis usually is made only when the pain becomes unrelenting or has been recurrent enough to prompt imaging.

Differential Diagnoses

The differential diagnosis includes other causes of bowel obstruction, including strangulated inguinal hernia; therefore, a genitourinary exam is an important component of the assessment. Gastroenteritis is a consideration, but the diarrhea in intussusception is of small volume and short duration. In pediatric patients, Hirschsprung disease is a differential consideration but typically involves a later age of onset with severe constipation history. Acute appendicitis is rare before the age of 2 years but can present similarly, and ultrasound may be helpful in distinguishing between the two conditions.

Diagnostic Testing

Ultrasound Examination

Ultrasonography is helpful in detecting intussusception, though is not as useful as CT in excluding other conditions. For facilities that have skilled ultrasound technicians available, ultrasound is the primary diagnostic test recommended in the pediatric population. A transverse view of the intussusception has a doughnut or target shape, with multiple concentric rings. A longitudinal view has an ultrasound appearance similar to that of a kidney (so-called pseudo–kidney sign), with a bright central area often surrounded by a darker outer layer (Fig. 81.9A and B).

Plain Radiography

Plain radiography is a reasonable screening test in a patient suspected of having bowel obstruction but usually shows only nonspecific large bowel dilation.

Computed Tomography

CT is the most useful test for adult patients with suspected intussusception but may not always detect the actual intussusception. The characteristic findings on CT include a target- or sausage-shaped soft tissue mass with a layering effect, with mesenteric vessels within the intestinal lumen (see Fig. 81.10A and B).

Colonoscopy

Colonoscopy is helpful in defining the lesion causing intussusception but does not usually detect the intussusception itself.

Management

The management of intussusception in the ED is supportive and aimed at optimizing fluid status, managing the patient's pain, decompressing the stomach with a nasogastric tube, recognizing perforation, administering antibiotics if compromised bowel is suspected, and securing appropriate surgical consultation when necessary. Occasionally, intussusception may resolve spontaneously, but an evaluation to exclude a pathologic lead point should still be pursued.

In pediatric intussusception, the treatment of choice for the stable child is a trial of pneumatic reduction with x-ray guidance, or hydrostatic reduction with ultrasound guidance when appropriate radiologic facilities are available.[12] The choice of hydrostatic or pneumatic reduction is largely dependent on institutional preference. Both have higher reduction rates when compared to barium. The reduction procedure is typically performed by a radiologist and may prevent the need for surgery. Reduction of pediatric intussusception is sufficient treatment in 80% of patients. One advantage of hydrostatic reduction with ultrasound guidance is the avoidance of radiation in children. A delayed repeat enema has been a recent advancement in the management of intussusception, as there is a 50% chance of successful reduction each time the enema is repeated. as the bowel edema subsides with each partial reduction. These advances have reduced operative rates, and surgical cases tend to occur when resection is required due to ischemic bowel necrosis or pathological lead point. Indications for surgery have been restricted to those with peritonitis, suggestive of bowel necrosis. Pediatric patients who improve rapidly after fluid resuscitation may still be candidates for reduction.

Surgery is required in most cases of adult intussusception. Because of the high incidence of malignancy and the concerns of spreading malignant cells from potentially malignant lead points, reduction often is not attempted in adults prior to surgical exploration. Surgical treatment is recommended for patients who are acutely ill, who have evidence of perforation, for whom non-operative reduction is unsuccessful, who need evaluation or resection of a pathologic lead point, or who are treated in a setting where radiologic facilities are unavailable.

Disposition

Recent literature suggests that discharge from the ED following reduction of intussusception is safe for carefully selected pediatric patients. Practice guidelines state that discharge can be considered if (1) there

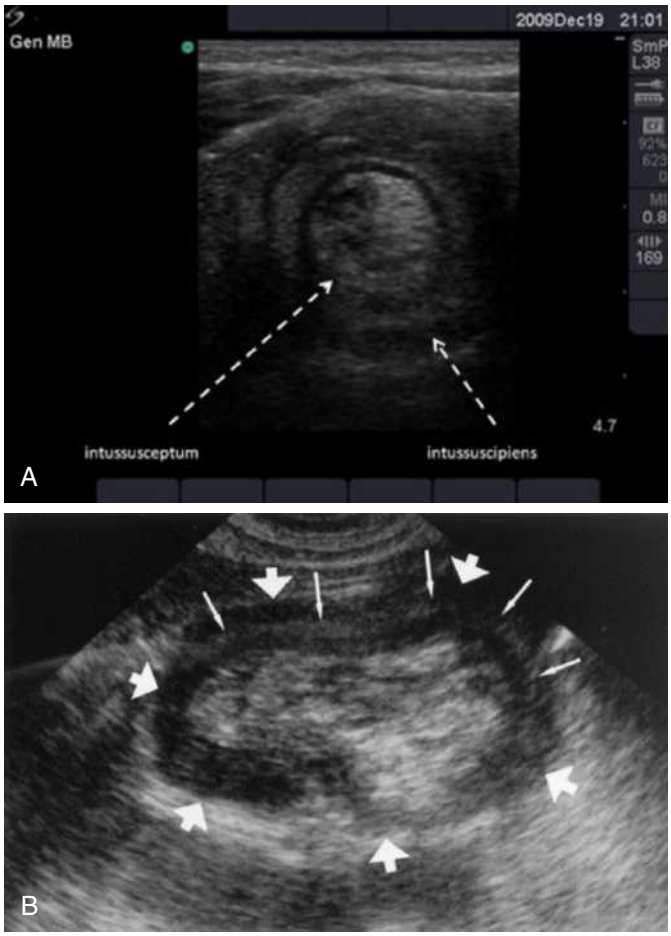

Fig. 81.9 Ultrasound of Intussusception. (A) Transverse view showing donut or target shape, with multiple concentric rings. (B) Oblique-transverse view on ultrasound showing a kidney-shaped mass (pseudo–kidney sign). *Large arrows* indicate the outer margin of the bowel; *small arrows* indicate the contiguous surfaces of the telescoping bowel. (A, From Riera A, Hsiao AL, Langhan ML, et al. Diagnosis of intussusception by physician novice sonographers in the emergency department. *Ann Emerg Med.* 2012;60:264–268. B, From Dean AJ, Lafferty K, Villanueva TC. Emergency medicine bedside ultrasound diagnosis of intussusception in a patient with chronic abdominal pain and unrecognized Peutz-Jeghers syndrome. *J Emerg Med.* 2003;24:203–210.)

are no signs of peritonitis on examination; (2) the patient is able to tolerate oral fluids 2 hours after reduction without nausea, vomiting, or abdominal pain; and (3) the patient remains symptom-free for 2 hours following the PO trial. Clinical studies evaluating this approach have not encountered adverse outcomes or significant recurrence rates.[13,14] Exclusions for discharge include failed reduction, sustained abdominal pain following reduction, history of prior abdominal surgery or neuromuscular disease, developmental delay, preterm birth <37 weeks, or revisit due to recurrence.

Adult patients diagnosed with intussusception typically require hospitalization. Operative mortality tends to be minimal.

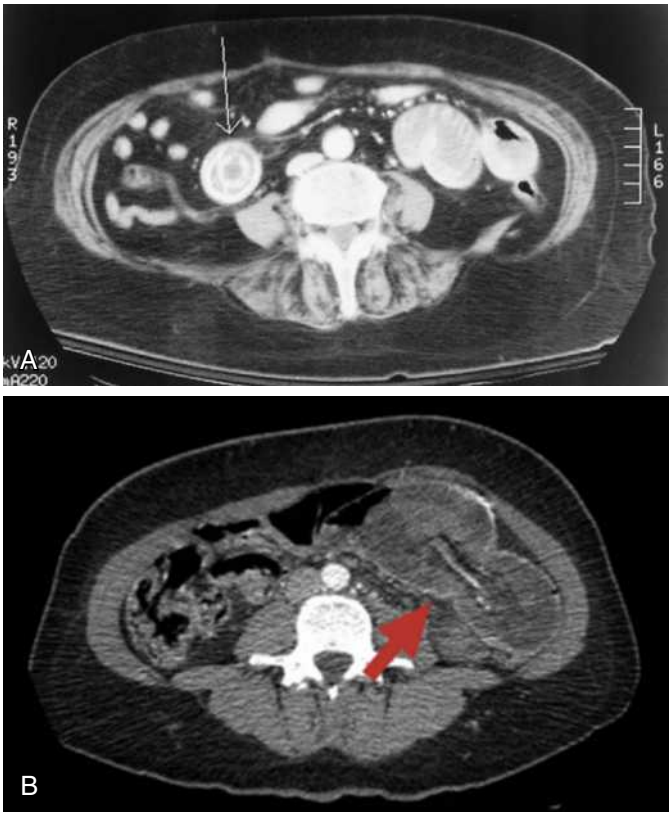

Fig. 81.10 CT With Intussusception. (A) Target- or sausage-shaped soft tissue mass with a layering effect, with mesenteric vessels within the intestinal lumen. (B) Pseudo–kidney sign *(arrow)*. (A, From Davis JM, Vilke GM. An elderly patient with intussusception. *J Emerg Med*. 2003;24:221–222. B, From Shyy W, Knight RS, Teismann NA. Ultrasound diagnosis of adult intussusception. *J Emerg Med*. 2015;49:498–499.)

INFLAMMATORY BOWEL DISEASE

Foundations

Background

IBD includes two clinically similar but distinct diseases, CD and UC. Table 81.2 summarizes important differences between CD and UC. Both diseases are characterized by chronic and unpredictable relapsing inflammation of the GI tract. The prevalence is more common in industrialized societies in North America and Europe, with increasing incidence in newly industrialized countries. The globalization appears to be associated with the Westernization of diets and environments, which affects the intestinal microbiome and increases the risk of IBD in genetically susceptible individuals.[15] IBD can occur at all ages, with a peak incidence in the second to fourth decade with no significant gender prevalence. Up to 25% of IBD cases develop during childhood or adolescence, whereas 10% to 15% of patients with IBD will receive their diagnosis when older than 60 years. Stable patients more often remain well controlled, whereas those with flares more frequently relapse. The long-term management of IBD is a complex stepwise process that involves multiple medications as well as surgical options.

The goals of ED evaluation are to (1) recognize potential new cases of IBD, (2) consider and exclude serious complications in patients with IBD, and (3) identify patients with IBD who require hospitalization. Treatment plans are best developed in collaboration with a physician experienced in the long-term management of IBD.

Anatomy, Physiology, and Pathophysiology

IBD is thought to develop as a result of dysregulation of the immune system driven by an immune response to normal intestinal flora in a genetically susceptible host. In essence, it is the loss of the normal tolerance to normal intestinal bacteria. In normal gut epithelium, the mucosal layer is relatively devoid of bacteria. In UC, a thinned mucosal layer is seen, and in CD, a defective mucosal layer is present. Both conditions lead to bacterial contamination and chronic inflammatory changes. The resulting defective mucosal barrier against bowel flora plays a major role in pathogenesis. The concentration of normal gut flora is highest in the terminal ileum and colon, where manifestations of both CD and UC are most commonly found. IBD is no longer thought of as an autoimmune disease, but rather a complex mucosal barrier disorder. Increased familial prevalence is found in patients diagnosed early in life, whereas environmental modifiers are thought to influence later onset. Chronic inflammation of the gut results, as well as extraintestinal manifestations.

TABLE 81.2 Comparison of Crohn Disease and Ulcerative Colitis

	Crohn Disease	Ulcerative Colitis
Inflammation type and location	Transmural inflammation, skip lesions, anywhere in gastrointestinal tract	Superficial, continuous involvement of colon or rectum
Most common extraintestinal symptoms	Arthritis, aphthous stomatitis, uveitis, erythema nodosum, and ankylosing spondyloarthropathy	Inflammatory arthropathies and primary sclerosing cholangitis
Diagnosis	Endoscopy, elevated fecal calprotectin, stool lacterferrin, ASCA	Endoscopy, elevated fecal calprotectin, stool lacterferrin, P-ANCA
Treatment	Ileal-release budesonide, systemic steroids, immunomodulators, biologics, may require multiple surgeries	Rectal or oral aminosalicylates, steroids, immunomodulators, biologics, surgery (colectomy) could be curative

ASCA, Anti-Saccharomyces cerevisiae antibodies; *P-ANCA*, perinuclear anti-neutrophil cytoplasmic antibodies.

Crohn Disease

CD may affect any part of the gastrointestinal tract, usually impacting the distal small intestine and proximal colon and, less commonly the esophagus, duodenum, or stomach. Because of the transmural inflammation, potential complications include the development of intestinal strictures, abscesses, or fistulae with adjacent organs. Although the onset of the disease can occur at any time of life, CD affects primarily younger patients, with an age of onset typically in the teens or 20s. Pediatric-onset disease is more often severe and extensive, with a higher likelihood of upper gastrointestinal tract disease when compared to adult-onset. Despite remission therapy, CD is often progressive, with half of the patients requiring surgery within 10 years of diagnosis and 80% within 20 years, due to stricture or fistula-related complications. Many patients will require multiple surgeries over their lifetime, as surgery is not curative.

Extraintestinal manifestations, such as arthritis, aphthous stomatitis, uveitis, erythema nodosum, or ankylosing spondyloarthropathy, occur more often in CD than UC.

Ulcerative Colitis

UC causes inflammation and ulceration throughout the colon and rectum but spares the small intestine. Inflammation is more superficial than in CD. Typically, the inflammation exists as one continuous lesion originating in the rectum and extending a variable distance into the colon, although cases of discontinuous disease (so-called skip lesions, similar to CD) have also been reported in UC.

Inflammatory arthropathies and primary sclerosing cholangitis are the most common extraintestinal manifestations of UC. Other extraintestinal manifestations include involvement of the skin, eyes, or bones.

Clinical Features

Typical presenting complaints in patients with IBD include abdominal pain or tenesmus, bloody diarrhea, and weight loss.[16] Patients with CD may have a history of nocturnal diarrhea and more non-gastrointestinal symptoms such as fatigue, fever, or weight loss, which helps differentiate CD from IBS. The physical examination may reveal significant abdominal tenderness, or an abdominal mass representing an abscess. Patients with CD may have fissures, ulcerated hemorrhoids, strictures, or cutaneous abscesses around the anus. Onset of symptoms usually occurs before the age of 30 years, although the diagnosis can be difficult to make in the early stages. The most useful clues of possible IBD in children or adolescents with abdominal pain include diarrhea, growth or pubertal delay, weight loss, rectal bleeding, anemia, pallor, fatigue, perianal skin tags, fistulae or abscesses, erythema nodusum or pyoderma gangrenosum, seronegative rheumatic joint pain, or family history of IBD.[16]

Patients often come to the ED with a known diagnosis of IBD and worsening abdominal symptoms. A common reason for relapse is the interruption of medications that have kept the disease in remission. Patients may become complacent during quiescent periods and stop taking IBD medications. Adherence to continuous, lifelong, maintenance therapy has been shown to reduce the risk of acute attacks and cancer. Common complications of IBD include the formation of fistulae, strictures, or abscesses; less common but life-threatening complications include fulminant colitis, toxic megacolon, or intestinal perforation.

Toxic Megacolon

Toxic megacolon is a pathologic dilation of the colon resulting from inflammation of the smooth muscle layers of the intestine, leading to muscle paralysis, dilation, and eventually perforation if left untreated. The hallmark of toxic megacolon is colonic dilation in a systemically toxic patient with a known inflammatory condition of the colon.

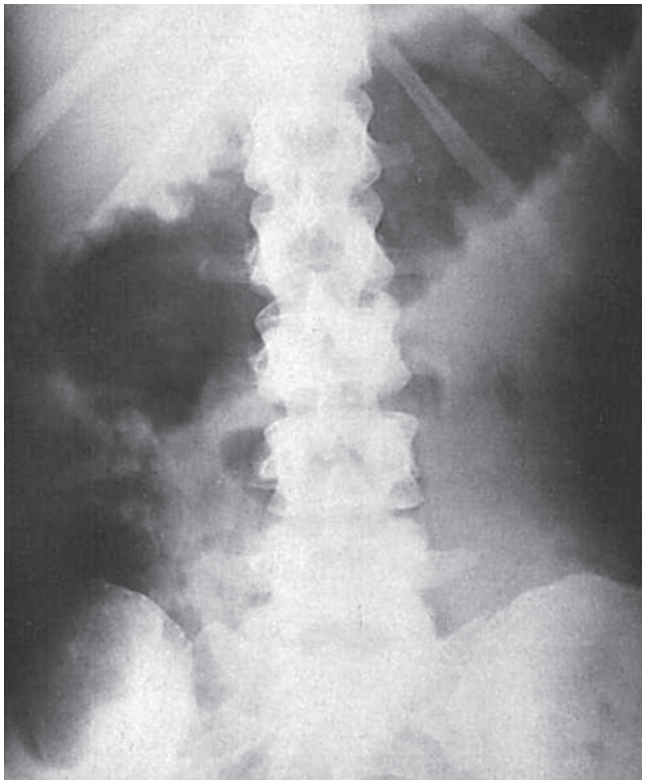

Fig. 81.11 Toxic Megacolon Secondary to Ulcerative Colitis. The smooth indentations seen along the margin of the colon represent pseudopolyps.

Systemic toxicity differentiates toxic megacolon from other disorders that cause colonic dilation, including mechanical obstruction, pseudo-obstruction, and congenital or acquired megacolon (Fig. 81.11).

The triggering event may be the recent ingestion of anticholinergics, antimotility agents, narcotics, or antidepressants. Patients usually have experienced severe symptoms of colitis for several days before the onset of toxic megacolon. Patients may have more than 10 stools daily, continuous bleeding, abdominal pain, distention, and acute, severe toxic symptoms, including fever or anorexia.

Extraintestinal Manifestations

About a third of IBD patients will have extraintestinal manifestations, where almost every organ system can be affected. Extraintestinal manifestations include inflammatory conditions of the skin (e.g., erythema nodosum, pyoderma gangrenosum), eyes (e.g., episcleritis, scleritis, uveitis), joints (e.g., arthritis, sacroiliitis), bone (e.g., osteoporosis), spine (e.g., ankylosing spondylitis), or liver (e.g., primary sclerosing cholangitis). Having one extraintestinal manifestation increases the risk of developing another, and the symptoms often parallel the underlying intestinal inflammation, and many will respond to treatment. Thromboembolic events in IBD patients are often overlooked and underdiagnosed, affecting the venous or arterial systems. The inflammatory process initiates clotting and decreases the activity of intrinsic anticoagulation mechanisms. There is a 60% increase in thromboembolic disease (including deep venous thrombosis [DVT] or pulmonary embolism [PE]) compared to the general population. Cerebrovascular complications, including cerebral sinus thrombosis, are more frequent during bouts of inflammation. There is also an increased risk of ischemic heart disease or mesenteric ischemia. Peripheral neuropathy is the most common neurologic complication of IBD, thought to be due to immune-mediated changes, metronidazole toxicity, or vitamin

deficiency. Chronic inflammation may be the most important driver of these complications in IBD.

Differential Diagnoses

History should include detailed questioning about the onset of symptoms, recent travel, food intolerances, medication (including antibiotics and non-steroidal anti-inflammatory drugs), and history of appendectomy. Particular attention should be paid to proven risk factors including smoking, family history, or recent infectious gastroenteritis. Careful questioning about nocturnal symptoms, features of extraintestinal manifestations involving the mouth, skin, eye, or joints, episodes of perianal abscess, or anal fissure is needed. General examination should include perineal and oral inspection, digital rectal examination, and measurement of body mass index.[16] Symptoms and signs overlap with those of many common abdominal conditions, including appendicitis, IBS, pancreatitis, infectious colitis, ischemic colitis, radiation colitis, diverticular disease, cancer, or bowel obstruction. In children, the differential diagnosis can also include Henoch-Schönlein purpura, celiac disease, or functional abdominal pain. Intestinal infections commonly mimic the symptoms of IBD, including those caused by *Escherichia coli* O157:H7, *Clostridium difficile,* or amebiasis.

Diagnosis

Endoscopic evaluation with biopsy confirms the diagnosis of IBD. Diffuse, continuous mucosal inflammation involving the rectum and extending to a point more proximal in the colon are suggestive of UC, whereas a complex or fistulizing lesion, involvement of the upper gastrointestinal tract, skip lesions, or granulomata are suggestive of CD.

Stool studies may be helpful in diagnosing IBD. Elevated fecal calprotectin is 89% to 98% sensitive and 81% to 91% specific for IBD and is now standard. Stool lacterferrin levels are 80% sensitive and 82% specific for IBD. Both fecal calprotectin and stool lacterferrin can predict clinical relapse are used to guide therapy as well as short-term follow-up.[16] As intestinal infections commonly mimic the symptoms of IBD, it is suggested that new patients should have microbiologic studies for bacterial or other infection.[16] Stool studies contain fecal leukocytes secondary to inflammation, but cultures and microbiologic studies should otherwise remain normal in IBD. Established patients who have recently been hospitalized or utilized antibiotics should be considered for *C. difficile* testing.

Biomarkers are commonly used to assess disease activity and predict relapse. Both an elevated C-reactive protein level or erythrocyte sedimentation rate can be useful for categorizing the severity of the disease and in differentiating it from IBS. Tests targeting antibodies to *Saccharomyces cerevisiae* (ASCA) or antineutrophil cytoplasm (P-ANCA) help differentiate between CD and UC. An elevated ASCA value is more suggestive of CD, whereas an elevated P-ANCA level is more suggestive of UC. Electrolyte abnormalities may result from severe diarrhea, and anemia may occur from gastrointestinal blood loss.

Plain radiographs should be limited to patients suspected of complications such as bowel obstruction, toxic megacolon, or perforation. For diagnosing toxic megacolon, plain radiographs are diagnostic and show a colon with a diameter of 6 cm or larger, although this feature may not be present in the early stages (see Fig. 81.11). CT of the abdomen and pelvis with at least IV contrast, and preferably with oral contrast if tolerated, is the preferred study to evaluate for extraluminal complications. Magnetic resonance imaging (MRI) enterography (with oral contrast) can locate affected bowel segments and identify fistulae, stenoses, or abscesses. It also has the advantage of limiting radiation exposure, which is preferable in children as well as individuals likely to undergo multiple imaging studies over time. Small bowel capsule endoscopy has a high negative predictive value for CD and is typically reserved for patients with a negative evaluation but high clinical suspicion for CD.[16,17]

Management

Since IBD is not curable, treatment goals are to minimize symptoms, improve quality of life, and minimize progression or complications of disease. Medical management is the mainstay of therapy for most patients. Treatment is typically driven by the severity of symptoms. The potential negative consequences of potentially toxic immunosuppressive or anti-inflammatory agents remain an important consideration. Newer treatment models have recommended symptom remission and endoscopic remission to prevent complications from disease progression due to chronic inflammation. Treatment regimens should be discussed with a gastroenterologist catered to consider the patient's preference, compliance, cost, safety, and response to selected agents.

Treatment of CD and UC differ significantly.[17] The choice of agents depends on the classification of the disease as mild, moderate, or severe (Box 81.7). Extraintestinal manifestations usually respond to therapy for intestinal disease. The dosages described are suggested induction doses. DVT and PE prophylaxis is important for admitted IBD

BOX 81.7 Disease Severity Criteria in Inflammatory Bowel Disease

Ulcerative Colitis

Mild Disease

- Fewer than four stools/day
- Stools may contain some blood
- No systemic signs of toxicity (e.g., fever, tachycardia, anemia, elevated erythrocyte sedimentation rate)

Moderate Disease

- More than four stools/day
- Minimal signs of toxicity

Severe Disease

- More than six bloody stools/day
- Signs of systemic toxicity

Crohn Disease

Mild to Moderate Disease

- Patient ambulatory and able to eat
- No dehydration
- No toxicity
- No significant abdominal pain or mass
- Weight loss of 10%

Moderate to Severe Disease—Any of the Following

- Mild disease that has failed to respond to treatment
- Patient may have some systemic toxicity, significant weight loss, anemia
- Fever, some abdominal pain or tenderness, intermittent nausea or vomiting

Severe Disease

- Persistence of symptoms during corticosteroid or biologic (e.g., infliximab) therapy
- High fever, persistent vomiting
- Intestinal obstruction
- Rebound tenderness
- Cachexia
- Abscess

Adapted from Hanauer SB, Present DH. The state of the art in the management of inflammatory bowel disease. *Rev Gastroenterol Disord.* 2003;3:81–92; and Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol.* 2009;104:465–483.

patients.[18] For patients in remission, ongoing endoscopic monitoring is required given the increased risk for the development of colorectal cancer.

Crohn Disease

Mild to Moderate Disease. Since CD can affect any area of the GI tract, location of disease and severity of symptoms are important factors in treatment decisions. In general, mild disease can be treated by budesonide or oral steroids, whereas more severe disease often requires systemic IV corticosteroids, immunomodulators, or an anti-tumor necrosis factor (TNF) biologic strategy.

For remission-induction treatment for mild to moderate ileocecal CD, the recommended therapy is ileal-release budesonide at 9 mg PO once daily for 8 weeks.[16,17] Budesonide has unique delivery to the ileum and proximal colon, is degraded on its first pass through the bloodstream, and thus has fewer systemic side effects. For disease more widespread than isolated ileocecal, including mild to moderate CD colitis or ileocolonic CD, an 8-week course of systemic corticosteroid is recommended.

For mild esophageal or gastroduodenal CD, only a proton pump inhibitor is recommended. Patients with extensive small bowel CD should be initially treated with systemic corticosteroids, and with a biologic agent, such as an anti-TNF strategy. Prednisone is often initiated and then tapered, with induction dosing of 0.5 to 0.75 mg/kg/day PO, with higher dosage for more severe disease, typically 40 to 60 PO mg daily. Methylprednisolone 1 mg/kg/day IV is also used.[16] IV steroids are often reserved for hospitalized patients with severe disease. Steroids are avoided for maintenance treatment, as prolonged use of steroids can lead to gastrointestinal mucosal injury, problems with wound healing, osteopenia with fractures, or frank osteonecrosis.

Moderate to Severe Disease. For moderate to severe CD that is responsive to systemic steroids, early introduction to an immunomodulator, such as thiopurines or methotrexate, can be considered to reduce the risk of flare when steroids are withdrawn. Immunomodulators have a relatively slow onset, so are used adjunctively, and have limited use as monotherapy. Azathioprine 1.5 to 2.5 mg/kg/day PO or mercaptopurine 0.75 to 1.5 mg/kg/day PO may be used as an adjunctive therapy or steroid sparing agent. Methotrexate 25 mg/week subcutaneously or intramuscularly is the standard induction dose, with measurement of CBC and liver function tests prior to the initiation of therapy. Patients taking these medications should be assessed for bone marrow suppression or pancreatitis.

Aminosalicylates, such as mesalazine and sulfasalazine, are no longer routinely recommended for induction or maintenance of CD. Earlier trials showed oral aminosalicylates to be an effective treatment for CD, and they gained popularity due to comparatively limited toxicity. However, systemic reviews and meta-analyses of clinical trial data have not shown any clinically relevant improvement in CD with aminosalicylates over placebo.[16]

Biologic therapy with a US Food and Drug Administration (FDA) approved anti-TNF agent, such as infliximab, adalimumab, or certolizumab pegol, is recommended in patients with disease refractory to immunomodulatory therapy. Infliximab is given intravenously, and adalimumab subcutaneously; they are of equivalent efficacy and result in remission in roughly half of all patients treated. Vedolizumab, an IV anti-integrin inhibitor, is a newer alternative to anti-TNF agents, or for patients who are refractory to other medications.[16] Vedolizumab inhibits T-lymphocyte migration into inflamed GI parenchyma. All biologic agents have an increased risk of certain cancers or infections, including reactivation of tuberculosis. A step-up approach of adding therapies is commonly employed; however, a top-down approach at an early stage may also be tried.[16]

Antibiotics should be limited to treating complications such as abscess or fistula formation. Ciprofloxacin 500 mg PO twice daily and metronidazole 500 mg PO three times daily for 7 to 10 days are most commonly used. See Box 81.6 for recommended intravenous antibiotics. Bowel rest is not beneficial, except as preparation for surgical intervention. There is insufficient evidence to support the use of enteral nutritional supplementation.[16]

Severe to Fulminant Disease. Severe to fulminant disease requires aggressive therapy, gastroenterology consultation, and often hospitalization. For patients with symptoms suggestive of obstruction, mass, or abscess, surgical consultation is prudent. Evaluation includes CBC, complete metabolic panel, blood cultures, stool culture, C difficile toxin antigen, urinalysis, and abdominal CT or MRI. Treatment begins with intravenous steroids, bowel rest, fluid resuscitation, intravenous antibiotics, and often parenteral nutrition. Biologic therapy is an alternative in patients' refractory to high-dose intravenous steroids. Surgery is often indicated for patients who fail to improve after 1 to 2 weeks of intensive medical therapy.

Surgery is typically reserved for patients with severe disease who do not respond to medical therapy, or for those with serious complications. Percutaneous or surgical drainage may be necessary in the treatment of an abdominal abscess. Strictureplasty is a safe alternative to resection for those with shorter strictures <10 cm.[19] Perianal fistulization is managed with surgical drainage and antibiotic therapy. Complex disease often first requires surgical drainage followed by an anti-TNF agent.

Ulcerative Colitis

Mild to Moderate Disease. For mild to moderate UC, aminosalicylates (5-ASA) including mesalazine and sulfasalazine are mainstays of treatment.[18] Combined topical (suppository or enema) and oral 5-ASA has been shown to be superior to oral therapy alone.[17] Mild to moderate proctitis can be treated with either topical 5-ASA, such as mesalazine suppositories (at least 500 mg/day per rectum [PR]). For ulcerative proctosigmoiditis, mesalazine enemas may be effective, as enema formulations are capable of reaching the splenic flexure. For disease of the transverse or ascending colon, oral formulations are necessary. 5-ASA therapy is associated with renal toxicity and complications; thus, it is important to obtain baseline renal function and trend.[17]

For patients who do not respond to 5-ASA, steroid treatment is initiated. Budesonide may be used in mild-moderate UC to limit use of systemic corticosteroids, as there are colonic release formulations, rectal enemas, and rectal foams.[17] Topical budesonide rectal formulations can be used to induce remission in mild-moderate ulcerative proctitis and proctosigmoiditis. If unsuccessful in controlling symptoms, then topical steroids, such as hydrocortisone, can be given, which is available in suppository, enema, or foam preparations. Tacrolimus suppositories are a possible option for refractory UC proctitis, though there is limited data.

Mild to moderate active left-sided colitis or pancolitis is treated with topical rectal mesalazine foam or enemas combined with oral mesalazine (at least 3 g/day PO). If symptoms fail to improve, then corticosteroids should be given systemically with 0.5 to 1 mg/kg PO prednisone, or alternative equivalent steroid. Once symptoms improve, a steroid taper can be initiated. However, if symptoms persist, an immunomodulator such as azathioprine 2 mg/kg/day PO can be given. Infliximab can be effective in refractory disease.

Moderate to Severe Disease. Vedolizumab was approved to treat moderate to severe UC resistant to immunomodulators, steroids, or anti-TNF therapy. While some centers still utilize cyclosporine 2 to 4 mg/kg IV daily, rescue therapy with infliximab is used more

commonly in hospitalized patients given its ease of use and fewer side effects. Although most patients tolerate it well, cyclosporine has significant potential toxicity, including myelosuppression, electrolyte disturbances, and hepatic toxicity or nephrotoxicity. Opportunistic infections, including *Pneumocystis* pneumonia, have also been known to occur.

Symptoms typically requiring inpatient treatment include severe pain, abdominal distention, bleeding, or severe systemic symptoms.[18] Severe flares generally necessitate hospitalization for IV steroid treatment. Antibiotics should be considered in severe disease or with immunosuppressive drug use. Avoidance of drugs (anticholinergics, antidiarrheals) or procedures (colonoscopy, barium enema) that increase the risk of toxic megacolon is recommended. Early surgical consultation is recommended for most hospitalized UC patients, or for those that do not respond to aggressive medical management.

Surgery is reserved for patients with severe disease refractory to medical management or for patients with complications such as intestinal obstruction, significant bleeding, abscess, or fistula. Up to 25% of patients with UC will eventually require colectomy for uncontrolled disease. A colectomy can be curative for UC and improves the quality of life.

For most patients, remission can be maintained with 5-ASA agents. Azathioprine can also be used for patients who do not stay in remission with 5-ASA. Similarly, infliximab can be used for maintenance therapy if a patient is unresponsive to other drugs.

Managing Special Populations With Irritable Bowel Syndrome

Pregnancy can exacerbate active disease and is associated with a high risk of spontaneous abortion, low birth weight, premature birth, ischemic placental disease, stillbirth, or cesarean delivery. Concern for fetal effects may lead to discontinuation of medications; however, many treatments are safe during pregnancy. Selected antibiotics or steroids are relatively low risk during pregnancy. Ciprofloxacin and metronidazole should generally be avoided in the first trimester. Steroid use may increase the risk of gestational diabetes or low birth weight. 5-ASA agents, immunomodulators, and anti-TNF mediations are generally safe to use in pregnancy. Less is known about the newer anti-integrin inhibitors, such as vedolizumab. It is important to employ a multidisciplinary approach with an obstetrician as well as a gastroenterologist when treating pregnant IBD patients.

Elders often have delayed or misdiagnosis due to the wide differential for IBD symptoms. A new diagnosis of IBD in an older adult should be made only after the exclusion of CI. Due to polypharmacy and complex medication interactions, elderly patients may be more difficult to manage. Decreased glomerular filtration in the elderly may necessitate renal dosing for medications, including methotrexate and azathioprine. Since elderly patients are more likely to be taking multiple medications, such as warfarin, care must be taken to check for medication interactions. Several medications used to treat IBD interact with warfarin, including azathioprine and metronidazole. This patient population is also more prone to the negative side effects of steroids, including altered mental status, or exacerbation of diabetes and hypertension, as well as osteoporotic-related fractures and osteonecrosis.

Toxic Megacolon

Treatment for toxic megacolon includes fluid hydration, IV corticosteroids, antibiotics covering bowel flora (see Box 81.6), and evaluation for potential intestinal infection, especially in immunocompromised patients. Hypokalemia or hypomagnesemia should be corrected if present because it can exacerbate colonic dilation. The mortality rate has decreased to less than 2% as a result of early recognition and treatment.

Disposition

Consultation with a gastroenterologist is recommended. Most patients with an uncomplicated mild to moderate exacerbation of IBD need only to restart their maintenance therapy if it was interrupted, or add oral steroids to their regimen. Patients with severe disease or those in whom oral steroids have failed to effect improvement may need hospitalization for administration of parenteral steroids. Some patients with steroid refractory disease may need immunomodulators or biologic medications to control symptoms. Emergent surgical consultation should be sought for life-threatening hemorrhage, perforation, or toxic megacolon. Urgent surgical intervention is indicated if the bowel is obstructed. Abscesses may be treated percutaneously with imaging guidance or surgically. Chronic fistulae initially are treated medically. After hospital discharge, close follow-up by the physician monitoring the patient's disease is important to ensure that remission is achieved in a timely fashion and that the patient complies with suppressive therapy after the acute event.

COLONIC ISCHEMIA

Foundations

Background

CI is the most common intestinal ischemic disorder and a common cause of lower GI bleed.[20] It is also commonly referred to as ischemic colitis. Its presentation overlaps with that of many other abdominal diseases and is difficult to diagnose without endoscopic visualization of the colonic mucosa. Although 90% of CI cases occur in patients older than 60 years, it can occur in all age groups. There is a female predominance. Mortality rates range from 4% to 12%,[20] and in isolated right-sided colonic ischemia (IRCI), mortality rates are higher, around 20%.[21]

Anatomy, Physiology, and Pathophysiology

Nonocclusive CI due to hypoperfusion and reperfusion injury is the predominant mechanism,[2] usually affecting watershed areas with limited collateralization, such as the splenic flexure and rectosigmoid junction.[20,21] CI represents a spectrum of disease whose manifestations vary with the extent of the ischemic insult. Reversible disease is characterized by bowel wall edema and subepithelial hemorrhage, leading to ulceration of mucosa visible as acute colitis. In most cases, the ischemic episode is self-limited, and the condition resolves completely with conservative therapy; however, in one-third of patients, a prolonged or severe insult results in transmural ischemia, gangrene, intestinal perforation, scarring, or stricture formation of the colon. Disruption of the colonic epithelial barrier function leads to bacterial translocation. Reperfusion injury results in inflammatory changes that can lead to cell death.[20,21] The greater frequency in elders suggests a relationship to degenerative vascular changes.

The primary insult is a low blood flow state associated with a variety of factors. These causes include cardiac (arrhythmias, heart failure, shock), vascular (atherosclerosis, embolic, thrombotic, vasculitis), infectious (*E. coli* 0157:H7, Hepatitis B, cytomegalovirus), iatrogenic (surgical interventions on the aorta), physiologic (long-distance running), or illicit drugs (cocaine or methamphetamine abuse). Chronic obstructive pulmonary disease (COPD) is associated with a 4-fold increased risk of CI and predicts a more severe disease course.[20] CI is diagnosed about 3.5-fold more frequently in patients with IBS. Chronic kidney disease also is associated with increased risk and mortality from CI.[21] Younger patients may develop CI in the setting of collagen vascular disease, hematologic disorders, or long-distance running. Medications associated with CI include vasoactive drugs (antihypertensives or vasoconstrictors), antipsychotics, oral contraceptives, antidiarrheal

agents, pseudoephedrine, and immunosuppressive agents. Although less common, it is important to consider that distally obstructing lesions of the colon can also theoretically raise intracolonic pressure and cause CI by reducing colonic blood flow.

CI can occur in any part of the colon, including the rectum. The colon is particularly susceptible to vascular hypoperfusion as it has the lowest flow state of all splanchnic organs, with limited collaterals. CI is usually left-sided correlating with the inferior mesenteric artery distribution. IRCI occurs in only 10% to 25% of cases and is associated with a worse outcome than CI, affecting any other region on the colon. As the superior mesenteric artery (SMA) supplies the right side of the colon as well as the small intestine, it is thought that IRCI could be the heralding presentation of an acute SMA occlusion.

Clinical Features

The presentation of CI typically involves the acute onset of mild crampy abdominal pain over the involved segment of the bowel. Most patients will have pain in the left lower quadrant, with abdominal distention and blood in the stool. IRCI presents with more right-sided pain and less frequently with bloody stools.[20] The typical patient has had recent surgery or significant medical illness. Nausea and vomiting can occur with obstruction secondary to a stricture or ileus. Tenderness over the affected colon may be present but often is not dramatic. Peritoneal findings, fever, and an elevated WBC count are suggestive of gangrenous bowel or perforation. Toxic megacolon is a recognized complication. Without surgical intervention, fulminant gangrenous CI can lead to perforation, multiorgan failure, and death.

Differential Diagnoses

The symptoms of CI are nonspecific and overlap with those of numerous alternative disorders, including IBD, diverticulitis, infectious colitis, and other causes of non-profuse, lower gastrointestinal bleeding. If strictures are present, the possibility of diverticulitis or colon cancer should also be considered.

Diagnostic Testing

Laboratory Tests

There are no sensitive or specific biochemical markers for CI. Decreases in hemoglobin and bicarbonate or increases in lactate, WBC, or LDH are the most frequently seen abnormalities in severe CI. Decreased albumin or the presence of metabolic acidosis can be used to predict severity.[21] Serum electrolyte levels should be checked if diarrhea or vomiting has been severe or prolonged. Stool studies such as *C. diff* toxin, ova and parasite, or culture can help to exclude infectious etiologies.[21] Blood and WBCs in the stool are common findings in several of the entities that present similarly to CI, including IBD and infectious colitis. Unfortunately, the definitive diagnosis of CI is rarely made in the ED setting.

Imaging Studies

Plain Radiography. Plain radiographs often show only nonspecific dilated bowel. Findings specific for CI occur in approximately 20% of patients. Classic findings include (1) intraluminal prominences, known as thumbprinting, which represent submucosal hemorrhage and swelling, and (2) wall thickening and ahaustral segments. Air in the portal venous system or bowel wall suggests significant ischemia and imminent intestinal infarction.

Computed Tomography. Although CT does not allow the definitive diagnosis of CI, it is useful to support the clinical suspicion, assess the extent of colonic involvement, diagnose potential complications, and exclude other disorders. CT features suggestive of CI include mesenteric fat stranding, abnormal colon wall enhancement, thumbprinting, wall thickening, or luminal narrowing and inner wall hypoperfusion, the so-called double halo sign (Fig. 81.12).[22] Pneumatosis linearis, bowel dilation, and peri-colonic free fluid are associated with severe ischemia.

Colonoscopy. Emergent colonoscopy should be performed after the colon is prepped with an enema. It is the most useful within 48 hours of symptom onset when it is more likely to reveal subepithelial hemorrhage and ulcerations typical of CI. Biopsy specimens help differentiate between cancer and other nonischemic causes of colitis. Colonoscopy can also detect necrotic bowel by its distinct cyanotic or black appearance. If colonoscopy is delayed, pathologic changes consistent with CI may have already resolved. The diagnosis may be missed on colonoscopy in up to one-third of cases.

Angiography. Angiography is usually not helpful in the diagnosis or management of CI. In most cases, the blood flow defect is at the microvascular level and has resolved by the time the patient seeks evaluation. The exception is IRCI, in which case only the ascending colon is affected, suggesting an SMA thrombosis.

Management

In the absence of surgical complications, the treatment of CI is supportive and includes bowel rest, hydration, and pain management. Broad-spectrum antibiotics covering bowel flora are indicated for patients with more significant symptoms (see Box 81.6).[21] If CI is precipitated by an episode of hypotension, the underlying cause must be sought and treated, and cardiac output should be optimized. A cardiac evaluation should be considered, and if congestive heart failure or cardiac arrhythmia is identified, medical treatment should be initiated. Vasopressors, steroids, nonsteroidal antiinflammatory drugs (NSAIDs), and oral cathartics should be avoided. Serial imaging or endoscopic evaluations of the colon and continued monitoring of the hemoglobin and electrolyte levels are indicated until the patient's condition stabilizes. Colonic distention should prompt surgical consultation and decompression with a rectal tube to lower the transmural pressure and improve colonic perfusion. Patients not recovering with medical management should

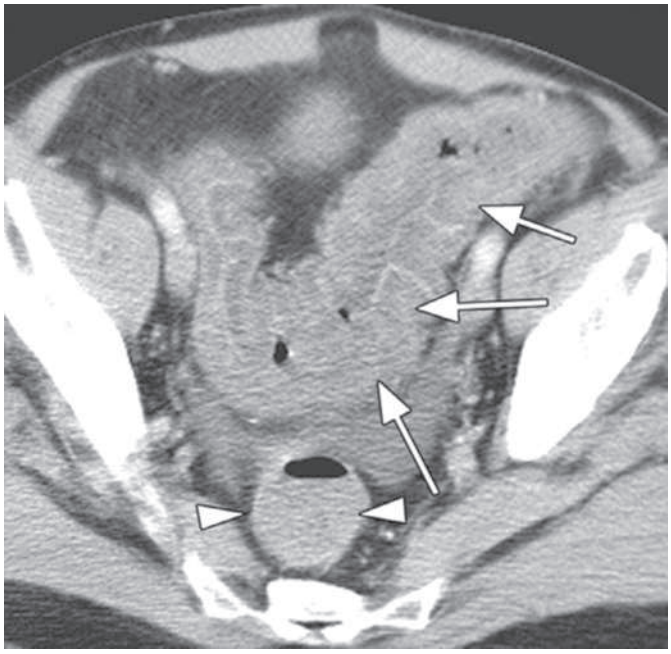

Fig. 81.12 CT scan of a patient with colonic ischemia showing thumbprinting *(arrows)* with thickening of the sigmoid colon associated with multiple nodular defects. Note that the rectal wall *(arrowheads)* is normal. (From Thoeni RF, Cello JP. CT Imaging of colitis. *Radiology*. 2006;240:623–638.)

receive surgical evaluation. Prompt surgical consultation should be considered in the setting of sepsis, peritoneal changes, free abdominal air, significant fever, massive bleeding, or a significant leukocytosis suggesting colon infarction or perforation.[21]

Disposition

Patients with mild symptoms and minimal abdominal tenderness or bleeding can be managed on an outpatient basis if they have reliable ability to obtain follow-up and are referred for urgent colonoscopy after discussion with gastroenterology. Patients with more significant findings, especially if the diagnosis of gangrenous bowel cannot be excluded, require hospitalization and surgical consultation. A high mortality rate (60%) is expected for patients undergoing emergent surgery, although deaths before the age of 50 years are rare. Most patients improve without surgical intervention, and only 5% have a recurrence of CI. In those with continuing significant symptoms, colectomy is usually curative.

STERCORAL COLITIS

Foundations

Background

Stercoral colitis (SC) most frequently occurs in the elderly, bedbound patients or young patients with neurologic disorders due to physical inactivity, comorbid chronic neurologic or psychiatric disorders, metabolic, or colonic function disorders, pharmacotherapy (especially narcotics), or inappropriate diet and fluid intake.[23–25] There have also been case reports of SC in the pediatric population.[26]

Anatomy, Physiology, and Pathophysiology

SC is a rare complication of chronic constipation and fecal impaction that can lead to increased intraluminal pressure wall necrosis, ischemic colitis, stercoral ulcer formation and ultimately perforation if left untreated.[25] Common locations for SC include the anterior rectum, rectosigmoid junction, and apex of the sigmoid colon. Overall mortality is around 30%.

Clinical Features

Patients typically present with lower abdominal pain in the setting of chronic constipation. Abdominal distention or vomiting may also be present. Some patients may have minimal to no abdominal pain in the initial stages.

Differential Diagnoses

The differential for constipation is wide but includes bowel obstruction, medication-related effects, diverticulitis, and behavior or diet-related causes.

Diagnosis

Given the neurologic and psychiatric comorbidities that are common in patients with SC, imaging with a CT scan is usually needed to make the diagnosis. CT findings include fecal impaction with a hard calcified fecal mass (fecaloma), colon dilation, colon wall thickening, mucosal discontinuity, pericolonic fat stranding, or extraluminal free air.[25]

Management

Treatment is focused on relieving constipation with bowel regimen, enemas, and manual fecal disimpaction, provided there is no evidence of peritonitis on examination or perforation on CT. Some cases may require endoscopic guided disimpaction. Antibiotic therapy or surgery may be indicated in the setting of perforation.

Disposition

Patients are typically admitted for serial abdominal examinations and surgical consultation given the high associated mortality. If the patient has no signs concerning for perforation, and symptoms have improved after relieving fecal impaction, then discharge for selected patients is reasonable. If the patient's symptoms persist or there is a concern for perforation, then IV antibiotics (see Box 81.6), admission, and surgical consultation are indicated.

RADIATION PROCTOCOLITIS

Foundations

Background

Radiation proctocolitis (RP) is a common and unfortunate side effect of radiation therapy that can occur in 50% to75% of patients receiving radiation to the pelvis. The dose of radiation determines the severity and duration of symptoms in RP. Presentations can be acute or chronic. Acute RP begins during or shortly after a course of radiation therapy, typically within 12 weeks, and is self-limited. Chronic RP occurs in 5% to 10% of patients who have undergone pelvic radiation therapy[27] and can begin any time following completion of radiation therapy, making the diagnosis challenging. Symptoms most often occur within 8 to 12 months. Recent advances in radiation techniques have resulted in a more targeted external radiation beam, which helps minimize the development of chronic RP.

Anatomy, Physiology, and Pathophysiology

Radiation is an important and effective treatment modality for neoplastic disease, but it also damages rapidly growing intestinal epithelium. The mucosal injury results in loss of normal barrier function, and luminal microbes trigger an acute inflammatory response leading to further mucosal damage. Impaired recognition of bacterial translocation worsens the inflammatory response and can lead to chronic inflammatory changes, such as strictures, fibrosis, or ischemia. The fixed portions of the colon, cecum, and rectum are at greater risk of receiving high doses of radiation.

Acute Radiation Proctocolitis. Intestinal epithelium normally sloughs off and is replaced at a rapid rate. After the initiation of radiation therapy, growth of replacement epithelium is slowed, but sloughing continues at the pre-exposure rate. This mismatch leads to gaps in the epithelium, which over time coalesce into ulcerations. In addition, edema and inflammatory changes of the submucosa cause excessive mucus secretion and bleeding. When radiation therapy has ended, the cycle of damage stops, and healing occurs over the next few weeks.

Chronic Radiation Proctocolitis. The pathologic mechanism in chronic RP is entirely different and results from a progressive endarteritis, with abnormal tissue collagen deposition. The affected intestine has a decreased microvascular density, with subsequent decreased perfusion. Over time, the affected bowel gradually becomes more ischemic, leading to ulceration, scarring, and ultimately narrowing of the bowel lumen.

Clinical Features

Acute RP presents with abdominal and rectal pain, along with diarrhea, hematochezia, and tenesmus.[27] Onset occurs during the course of radiation therapy. Symptoms can be severe and result in interruption of therapy or alterations in the treatment plan in 5% to 15% of cases.

Chronic RP has a more insidious onset with a number of possible presentations including ulcerative disease, stricture formation, obstruction, fistulae, or bowel perforation. Bleeding is common but is usually not significant. Decreased caliber of stool, along with increased

straining or constipation, suggests a stricture. Fistulae can develop between the affected bowel and any adjacent organ, but the most common site is rectovaginal.

Some patients with either acute or chronic RP may exhibit anal sphincter dysfunction. Fecal incontinence has been reported in up to 20% of patients, which can be devastating to quality of life.

As the most common indication for pelvic radiation therapy is malignancy, it is important to assess for any recurrence of the primary cancer in patients with chronic radiation proctitis. A digital rectal examination should be performed to evaluate sphincter tone, especially if the patient presents with fecal incontinence.

Differential Diagnosis

Recurrence of the primary malignancy should be considered in patients with chronic RP. Symptoms are generally indistinguishable from other causes of bowel inflammation, including IBD, infectious colitis, or ischemic colitis.

Diagnostic Testing

Acute RP is a clinical diagnosis based on history. Further evaluation in the ED is typically not necessary.

Chronic RP is a diagnosis of exclusion. Endoscopy may reveal pale, thickened, and friable mucosa with prominent telangiectasias. Biopsies may show chronic inflammation; however, biopsies are often contraindicated due to the friability of intestinal mucosa.

Management

Acute Radiation Proctocolitis

Management of acute RP largely involves supportive care. Treatment plans should be discussed with the patient's radiation oncologist. Measures to improve nutritional status should be considered. Possible interventions include steroid enemas (i.e., hydrocortisone enema, 100 mg bid) to reduce inflammation, sucralfate enemas (2 g of a 10% suspension in water bid) to stimulate epithelial healing, and water-absorbing stool softeners (e.g., docusate sodium) to reduce mucus-containing diarrhea. Reduction of the daily radiation dose may also help reduce symptoms. Butyrate enemas (short-chain fatty acids) may accelerate healing given that these short-chain fatty acids are an important nutrient for colonocytes.

Chronic Radiation Proctocolitis

Chronic RP treatment also involves supportive care. If rectal involvement is significant, stool softeners, analgesics, anti-inflammatory agents (i.e., sulfasalazine, mesalazine), and sucralfate enemas may be helpful. Metronidazole, 500 mg orally tid, for 4 weeks was previously suggested, but current guidelines advocate against its use due to a lack of adequate evaluation in the management of RP.[27] Continued rectal bleeding may be managed with topical formalin or laser photocoagulation. Other interventional treatments include hyperbaric therapy or radiofrequency ablation.[27] Hyperbaric therapy has shown significant improvement in patients with refractory colitis. Minimally symptomatic strictures can be managed with stool softeners or enemas in order to reduce the extent of luminal narrowing. Fistulae and significant stricture typically require surgical repair. Approximately 20% of all patients with chronic radiation injury to the intestinal tract require some form of surgical intervention.

Disposition

Unless symptoms are severe, patients with acute or chronic RP can usually be managed on an outpatient basis, under the care of their radiation oncologist. Suspected perforation necessitates surgical consultation; likewise, signs of bowel obstruction should prompt consideration of surgical consultation. Stricture or fistula formation can usually be managed on an outpatient basis, with surgical referral in the case of worsening symptoms.

NEUTROPENIC ENTEROCOLITIS

Foundations

Background

Neutropenic enterocolitis (NE), also known as typhlitis, is a rare but important condition to consider in all immunosuppressed individuals who present with acute abdominal pain. Initially, NE was only described in pediatric leukemia patients. It is now seen in children and adults with hematologic malignancies such as leukemia, lymphoma, multiple myeloma, aplastic anemia, and myelodysplastic syndrome. It can also be seen in individuals that are immunosuppressed from AIDS, therapy for solid tumors, or organ transplantation. The incidence in hospitalized adults is reported to be approximately 5.6%.[28] The associated mortality of NE can be as high as 50%.[28] Mortality has been shown to decrease with early recognition and management, making this an important diagnosis to consider in the ED.[29]

Anatomy, Pathology, and Pathophysiology

The pathogenesis of NE is not completely understood.[28] The main factors include intestinal mucosal injury, neutropenia, and an immunocompromised state. Anatomically, NE most commonly affects the cecum and terminal ileum. The cecum is thought to be most commonly implicated given its distensibility and limited vascular supply.[28] Pathogenesis tends to involve intestinal damage stemming from neutropenia and intensive chemotherapeutic regimens, followed by microbial and sometimes fungal invasion. This can cause bowel inflammation, ulceration, and eventually necrosis and perforation.[30] Neutropenia can result in intestinal edema, causing a disrupted mucosal surface, making it more vulnerable to bacterial intramural invasion. Chemotherapeutic agents can cause mucosal injury or can alter intestinal motility, thereby causing bowel distention and necrosis.[28] Some of the chemotherapeutic agents associated with the development of NE include cytarabine, gemcitabine, vincristine, doxorubicin, and cyclophosphamide.[28] Another consideration in the pathogenesis of NE is the infiltration by neoplastic cells. This infiltration can cause bowel ulceration and perforation, which is why some cases of NE are seen prior to the initiation of chemotherapy.[30]

Clinical Features

Patients with NE will often present with abdominal pain, diarrhea, and fever. Abdominal pain is typically localized in the right lower quadrant. Other symptoms include nausea, vomiting, abdominal distention, and rectal bleeding. Symptoms most commonly begin in the second week after chemotherapy.[28] Patients with bowel necrosis or perforation may present with peritoneal signs or hemodynamic instability.

Differential Diagnoses

Other diagnoses to consider when NE is clinically suspected include pseudomembranous colitis, appendicitis, ischemic colitis, and IBD.

Diagnostic Testing

Laboratory Tests

Neutropenia is the most important factor in establishing the diagnosis of NE. An absolute neutrophil count (ANC) less than 500 cells/μL is associated with the development of NE.[28] In addition to calculating an ANC, a CBC also screens for anemia or thrombocytopenia. Other helpful laboratory tests include a chemistry panel to assess for electrolyte abnormalities and coagulation studies. Blood cultures for aerobic

and anaerobic bacteria, as well as fungi, should be obtained. Blood cultures may show enteric organisms such as *E. coli*, *Clostridium septicum*, and enterococci.[28] Importantly, bacteremia from enteric organisms in febrile neutropenic patients with no other source should prompt evaluation for NE.[31] Fungal cultures are important given invasive fungal disease can occur in approximately 20% of NE cases.[32] Stool cultures and assays to assess for *C. difficile* toxin are important to rule out other potential causes of abdominal pain in neutropenic or immunosuppressed patients.

Radiologic Tests

Abdominal x-rays are generally unhelpful in the diagnosis of NE; however, if obtained may show pneumatosis intestinalis or pneumoperitoneum, which would respectively suggest necrosis and perforation. Abdominal ultrasound is an important diagnostic tool, especially in the pediatric population, that may help limit radiation exposure. Ultrasound imaging may show bowel wall thickening, and any thickness greater than 0.5 cm is considered to be diagnostic for NE.[30] CT is the most accurate imaging modality for NE.[28] Findings suggestive of NE on CT include bowel wall thickening, cecum dilation, pericolonic inflammation, pericecal fluid, and pneumatosis intestinalis or perforation in more severe cases. Barium enema should be avoided in neutropenic patients, as it can cause colonic perforation and bacteremia.[28] Colonoscopy is also contraindicated in these patients given the risk of perforation.[28]

Management

Patients that are thought to have NE should undergo fluid resuscitation (at 20 mg/kg IV), correction of any electrolyte imbalances, bowel rest, and expedient IV antibiotic administration. Antibiotic coverage includes gram positive, gram negative, and anaerobic pathogens. Common monotherapy options include piperacillin-tazobactam (3.375 g IV, every 6 hours for adult patients, or 100 mg piperacillin/12.5 mg tazobactam per kilogram every 8 hours in pediatric patients), imipenem-cilastatin (500 mg IV every 6 hours or 1 g IV every 6 to 8 hours for adults, or 15–25 mg/kg every 6 hours in pediatric patients). Dual therapy can be used with cefepime (1g IV every 8 hours in adults, or 50 mg/kg every 8 hours) with metronidazole (1 g IV every 6 hours in adults or 30 mg/kg/day divided every 6 hours in pediatric patients). Antifungal treatment targeting *candida albicans* should be used in severe cases or in patients not showing any improvement after 72 hours of antibiotic treatment.[28] Intravenous fluconazole can be used (800 mg on day 1, followed by 400 mg daily until 2 weeks after neutropenia resolves in adults, or 6 to 12 mg/kg daily until 2 weeks after neutropenia resolves).

Leukocyte count recovery has been shown to be associated with favorable outcomes in patients with NE. Granulocyte colony-stimulating factor can be considered in patients with severe neutropenia (ANC < 100 cells/μL), hemodynamic instability, or concern for invasive fungal infection.[28] Severe anemia and thrombocytopenia should be corrected if lower gastrointestinal bleeding occurs. Surgery is indicated when there is bowel perforation. Interventional radiology may be consulted along with surgery with severe rectal bleeding for embolization, if necessary.

Disposition

Patients with NE are often critically ill. Hospitalization is indicated, and most patients will require an intensive care unit. Surgical consultation is indicated in cases complicated by bowel necrosis, perforation, or severe bleeding, or when the diagnosis is uncertain.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 81: QUESTIONS AND ANSWERS

1. A 59-year-old man with a past history of diverticular disease presents with his second episode of left lower quadrant (LLQ) abdominal pain. He is afebrile, and laboratory examination is remarkable for a leukocytosis of 13,800/mm^3. Physical examination reveals moderate LLQ tenderness without masses or rebound. A computed tomography (CT) scan of the abdomen reveals a small (4 cm) abscess adjacent to the sigmoid colon, with moderate diverticulitis. Which of the following would be the most appropriate treatment?

a. Admission for intravenous antibiotics
b. Confirmation with double-contrast barium enema
c. Discharge on oral antibiotics with 2-day follow-up
d. Radiology consultation for percutaneous drainage
e. Surgical consultation for laparotomy

Answer: a. Abscesses smaller than 5 cm are typically treated with intravenous antibiotics followed by an outpatient oral regimen. Larger abscesses may be drained surgically or percutaneously.

2. What is the most common cause of large bowel obstruction in the US.?

a. Adhesions
b. Colon cancer
c. Diverticulitis
d. Intussusception
e. Volvulus

Answer: b. Colon cancer accounts for 53% of cases. Volvulus and diverticulitis account for 17% and 12% of cases, respectively. Extrinsic compression from malignancy accounts for 6% of cases. Adhesions, unlike for small bowel obstructions, are a rare cause of large bowel obstructions.

3. Which of the following statements regarding intussusception is true?
   - **a.** Bowel obstruction typically occurs.
   - **b.** CT scans have a high sensitivity for detection of intussusception.
   - **c.** Most adult cases involve the large bowel.
   - **d.** Most adult cases require surgery.
   - **e.** Most children have a causative lesion.

Answer: d. In contrast to children, most adult cases have a causative pathologic lesion, usually located within the small bowel. Complete obstruction occurs in less than 20% of cases. CT scans may miss as many as 50% of cases of intussusception. Surgery is usually required for adults with intussusception.

4. A 29-year-old woman presents with a 4-month history of intermittent abdominal pain with bloating and diarrhea. The diarrhea has been watery, nonbloody, and often nocturnal. Physical examination is remarkable for mild diffuse abdominal tenderness and brown, guaiac-positive stool. Rectal examination also demonstrates a small anal fissure at the 3-o'clock position. Laboratory evaluation is remarkable only for a normocytic anemia with a hemoglobin level of 11.5 g/dL. The diagnosis would most likely be confirmed by which of the following?
   - **a.** Colonoscopy
   - **b.** CT scan of the abdomen
   - **c.** Erythrocyte sedimentation rate
   - **d.** Mesenteric angiography
   - **e.** Response to a high-fiber diet

Answer: a. This presentation is typical for inflammatory bowel disease. Nocturnal diarrhea, blood in the stool, and presence of an eccentric (nonposterior midline) anal fissure argue against IBS or benign diarrhea. Ischemic colitis is unlikely in this age group. Endoscopy with biopsy is the diagnostic intervention of choice.

5. Which of the following statements regarding colonic ischemia is true?
   - **a.** CT scanning of the abdomen is diagnostic
   - **b.** It is rarely associated with bloody stool.
   - **c.** It is typically due to nonocclusive disease.
   - **d.** Isolated right-sided ischemic colitis is associated with comparatively lower mortality.
   - **e.** Specific serum biomarkers may be helpful.

Answer: c. Colonic ischemia is typically due to nonocclusive microvascular disease. It occurs due to low-flow conditions related to congestive heart failure (CHF), renal failure, hypovolemia, or recent illness or surgery. Bloody stools are predictable. It may also occur in younger patients with collagen vascular disease, hematologic abnormalities, or cocaine abuse. Isolated right-sided ischemic colitis is associated with comparatively higher mortality. There are no sensitive or specific laboratory tests, and although sometimes suggestive, CT scanning primarily rules out alternative processes.

82

Anorectum

Wendy C. Coates

KEY CONCEPTS

- Anorectal conditions can be approached using an algorithm that addresses the presence or absence of pain, bleeding, swelling, and pruritus, in combination with an assessment of the patient's overall health (see Fig. 82.2).
- Patients who seek treatment for nonspecific anorectal complaints should be evaluated for the presence of underlying systemic disease (e.g., cancer, diabetes mellitus, immunodeficiency) because disorders of the anorectum may be the initial presentation of associated conditions.
- Patients with a sexually transmitted disease (STD) should be evaluated for HIV infection, use of the anus for sexual purposes, and the possibility of domestic violence or abuse.
- Most anorectal conditions can be symptomatically improved by adherence to the WASH regimen (***w***arm water, ***a***nalgesics, ***s***tool softeners, ***h***igh-fiber diet).
- Thrombosed external hemorrhoids are covered by modified anoderm and may be excised and drained within 48 hours of formation. After 48 hours, the clot begins to dissolve, and conservative management with the WASH regimen is indicated.
- Internal hemorrhoids are covered with mucosa and should be referred to a colorectal surgeon for definitive management.
- Acutely thrombosed, gangrenous fourth-degree internal hemorrhoids require urgent surgical consultation.
- Fistulous tracts should not be probed.
- Pilonidal abscesses should be drained with needle aspiration or with a longitudinal incision off the midline.
- Pruritis ani is caused by a variety of conditions, including infection, hemorrhoids, topical irritants, cutaneous conditions, cancer, and hypersensitivity to foods and drugs (see Box 82.5).
- Sensitivity is required when managing patients with anorectal foreign bodies. Health care provider safety is imperative when evaluating foreign bodies with sharp edges.
- Distal anorectal foreign bodies often can often be removed in the ED, whereas proximal or sharp ones should be removed in the operating room.

FOUNDATIONS

Patients visit the emergency department (ED) with a variety of anorectal complaints. Particular focus on sensitivity and a professional demeanor is important in these interactions, because patients may find it challenging to discuss historical details openly and to describe physical complaints related to this area of the body and its function.

The anorectum begins at the rectosigmoid junction at the level of the third sacral vertebra (S3). The rectum follows the sacral curvature for 12 to 15 cm and then sharply turns posteriorly and inferiorly at the puborectalis muscle (Fig. 82.1). Here the anal canal begins its 4-cm course to the anus, which is supported by three muscle groups—levator ani and the internal and external anal sphincters. Anal valves and crypts with mucous glands for lubrication are located 2 cm proximal to the anal verge at the dentate line. Proximal to the crypts are the columns of Morgagni, where the epithelium of the anal canal changes from pink columnar (as in the rectum) to squamous.

The superior, middle, and inferior hemorrhoidal arteries provide blood supply to the anorectum. They arise from the inferior mesenteric, internal iliac, and internal pudendal arteries, respectively. The superior hemorrhoidal veins drain into the portal system, and the inferior hemorrhoidal veins drain into the caval system. Lymphatic drainage is to the inferior mesenteric nodes above the dentate line and to the inguinal nodes from all areas of the anorectum.

Sympathetic and parasympathetic nervous systems function together to retain the contents of the rectum until evacuation is desired. Sympathetic fibers from L1 to L3 (upper rectum) and presacral nerves (lower rectum) inhibit the contraction of rectal smooth muscle, and L5 fibers cause the internal sphincter to contract. Elimination occurs when parasympathetic fibers from the anterior roots of S2 to S4 cause the rectal wall to contract and the internal sphincter to relax. Voluntary external sphincter control is mediated by motor branches of the pudendal nerve (S2, S3) and the perineal branch of S4. The levator ani is supplied by the pudendal nerve and pelvic branches of S3 to S4 fibers. Sensory perception of rectal distention relies on parasympathetic fibers from S2 to S4. The abundant sensory nerve endings of the distal anal epithelium transmit via the pudendal nerve.

Defecation begins as the rectum becomes distended, the internal sphincter relaxes, and stool enters the anal canal. At an appropriate time and place, the external sphincter relaxes to complete the process of elimination. When voluntary straining is required, abdominal muscles contract, the rectal angle straightens, and the pelvic floor descends. To postpone defecation, the external sphincter contracts voluntarily, relaxing the rectal wall and quelling the urge to defecate unless there is an underlying sphincter disorder or an overwhelming volume of stool.

CLINICAL FEATURES

A history of anorectal and gastrointestinal (GI) symptoms, as well as underlying systemic conditions, elucidate the diagnosis of most anorectal disorders (Box 82.1; Fig. 82.2). Common complaints include bleeding, swelling, pain, itching, and discharge. History includes questions about onset, duration, and quality of symptoms, and details of bowel habits (changes in color, frequency, or consistency of the stool and the presence of straining, flatus, or incontinence of solid or liquid stool). Sexual practices or history of radiation exposure are also relevant in most cases. Underlying GI disorders (e.g., Crohn's disease, cancer, polyps) often produce atypical presentations and patients with an underlying systemic disease such as AIDS, cancer, diabetes mellitus,

or coagulopathy may develop more severe complications of standard anorectal conditions.

In patients presenting with rectal bleeding, the color, amount, and relationship to defecation are essential factors. Pain and bright red blood are consistent with anal fissures or hemorrhoids. Fissure pain is sharp, sudden in onset, and is not associated with swelling, whereas pain from a prolapsed or thrombosed hemorrhoid is gnawing, continuous, and more gradual in onset. Painless rectal bleeding may occur with internal hemorrhoids, cancer, or precancerous lesions. Red blood on the toilet paper usually is caused by anal fissures or external hemorrhoids, though minute quantities can result from any irritating condition.

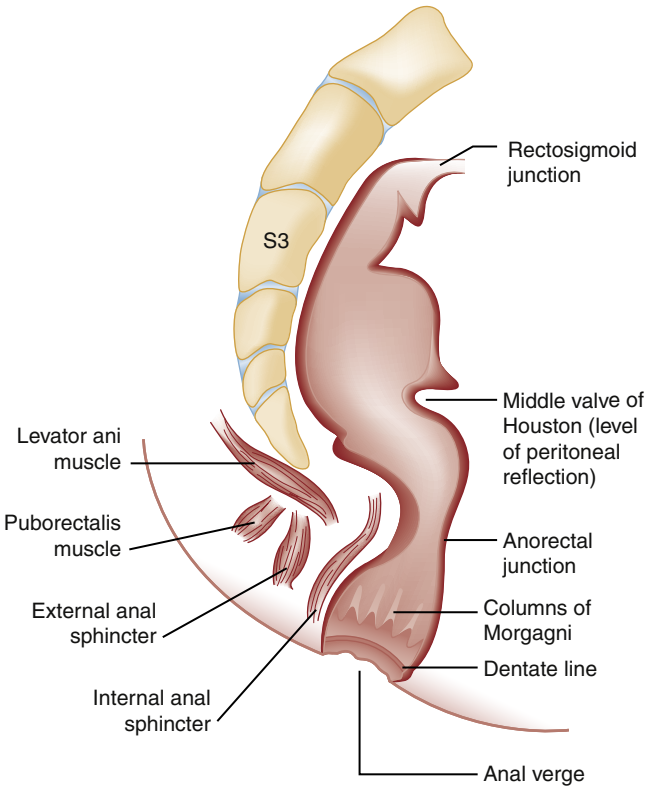

Fig. 82.1 Anorectal anatomy.

BOX 82.1 Medical History in Diagnosis of Anorectal Disorders

Anorectal History
Pain
Bleeding
Swelling
Itching
Discharge
Urgency

Gastrointestinal History
Change in bowel habits (straining, flatus, color, consistency, frequency)
Nausea or vomiting
Incontinence of stool
Underlying GI disease (Crohn's disease, cancer, polyps)

Systemic Disease History
Diabetes mellitus
Coagulopathy
Cancer
HIV infection

Sexual History of the Anus
Penetration
Known STDs
Assault

GI, Gastrointestinal; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease.

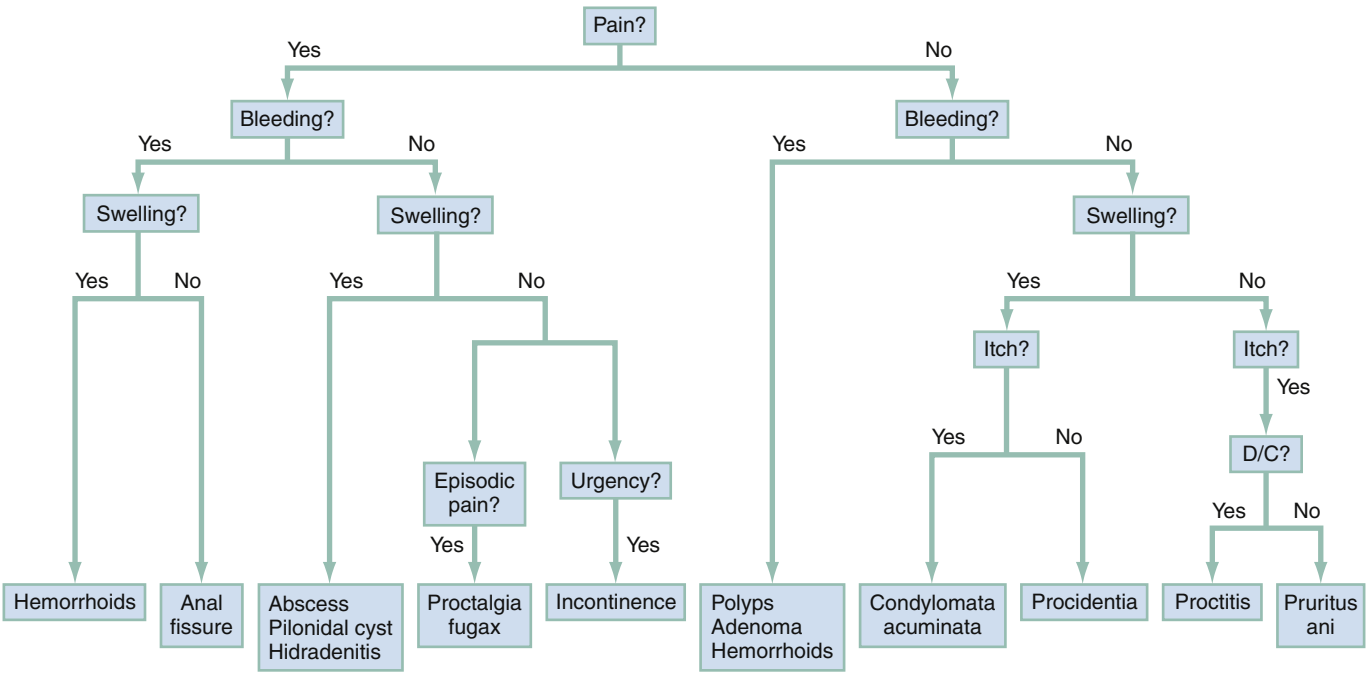

Fig. 82.2 Algorithm for anorectal complaints. *D/C,* Discharge.

Bright red blood that drips into the toilet bowl or streaks around the stool is frequently caused by internal hemorrhoids. Blood mixed with stool typically originates above the rectum, whereas melena indicates an upper GI source, proximal to the ligament of Treitz. Bloody mucus is associated with cancer, inflammatory bowel disease, and proctitis.[1]

Patients who experience perianal swelling or have the sensation of rectal fullness often list hemorrhoids as their chief complaint. Painful swelling that bleeds is usually a thrombosed hemorrhoid, but abscesses, pilonidal disease, and hidradenitis suppurativa should be considered. Painless, itchy swelling may be caused by condylomata acuminata or secondary syphilis. A mass protruding through the anal orifice may signal rectal prolapse or cancer (Fig. 82.3).

Severe, episodic anorectal pain that is not associated with bleeding or swelling may represent proctalgia fugax or levator ani syndrome. Perianal itching (pruritus ani) is caused by poor hygiene or any lesion that makes it difficult to clean the perineum, or may result from exposure to certain foods or medications.

The physical examination should ensure the patient's comfort and privacy. With the patient in the lateral decubitus position and partially covered with a sheet, inspect the buttocks and anal orifice. Note elements of personal hygiene and anatomic disruptions, such as fissures, skin tags, protruding hemorrhoids, abscesses, or other lesions. Ask the patient to strain and note the integrity of the pelvic floor, prolapse of hemorrhoids, or rectal mucosa. Placing the fingertips of both hands along either side of the anus, as close to the anal verge as possible, and applying gentle outward traction allows the anus to be slowly everted, which often reveals anal abnormalities. If the area is slippery, placing 4-by-4-inch gauze pads under the fingers will facilitate sufficient traction. A digital rectal examination begins by placing a well-lubricated gloved finger flat against the anal opening and exerting gentle pressure until the external sphincter relaxes, allowing the finger to enter the anus. Assess anal sphincter tone by asking the patient to squeeze the anal muscles against the examining finger. Accessible areas of the anorectum are examined for masses and areas of tenderness with a circumferential sweep. The cervix or prostate is palpated through the rectal wall. On withdrawal, the contents on the glove are assessed for frank or occult blood, mucus, or pus.

If desired, direct visualization of the anus may be accomplished by anoscopy. A lubricated anoscope is inserted into the anus, with the obturator in place. When the obturator is removed, the area can be viewed for sites of bleeding, hemorrhoids, masses, or abnormal tissue, as well as the dentate line and anal epithelium.

SPECIFIC ANORECTAL PROBLEMS

Hemorrhoids

Foundations

Hemorrhoids occur when the three anal vascular submucosal cushions become engorged. Blood supply arises from the arterial system, causing hemorrhoidal bleeding that is bright red. The muscularis submucosa cushions the anal canal during defecation and aids fecal continence. As the supportive tissue deteriorates, the veins draining the area become distended and prolapse through the anal orifice, which may result in bleeding and/or thrombosis. Some controversy exists about whether straining and constipation cause these changes by producing venous backflow when intra-abdominal pressure increases.[2] A familial predisposition is recognized, but whether this is a result of genetics or acquired factors such as diet is unknown. Direct pressure on a hemorrhoidal vein can produce symptomatic hemorrhoids in pregnant women, and thrombosed hemorrhoids are associated with prolonged labor or deliveries that result in traumatic tears.

Hemorrhoids are not varicose veins; rather, they are normal structures that manifest symptoms when the muscularis submucosa weakens and the anal cushions are displaced distally. Conditions that increase sphincter tone correlate with a higher prevalence of hemorrhoids. Portal hypertension does not typically cause hemorrhoids in adults, although it appears to be a cause in children.[3] Bleeding in patients with portal hypertension may be caused by rectal varices, which are vascular communications between the superior and middle hemorrhoidal veins.

Clinical Features

Patients often refer to any perianal condition as "hemorrhoids." Bleeding with defecation is the most common complaint and, unless the hemorrhoids are thrombosed, is typically painless. Patients report variable amounts of bright red blood on toilet paper when wiping or in the toilet bowl. Many complain of swelling, itching, mucoid discharge, or a moist perianal area. History should address recent stool patterns such as diarrhea or constipation, chronic medical problems such as portal hypertension or bleeding disorders, and a dietary and family history. Frequent bowel movements, prolonged sitting, heavy lifting, and straining while defecating exacerbate symptoms.

Physical examination should ascertain the type and degree of hemorrhoids by visual inspection at rest and during straining. Nonprolapsing hemorrhoids can be visualized on anoscopy as a focus of bleeding or as they bulge when the patient is asked to strain. Anoscopy is painful and not useful in cases of prolapsed or thrombosed hemorrhoids

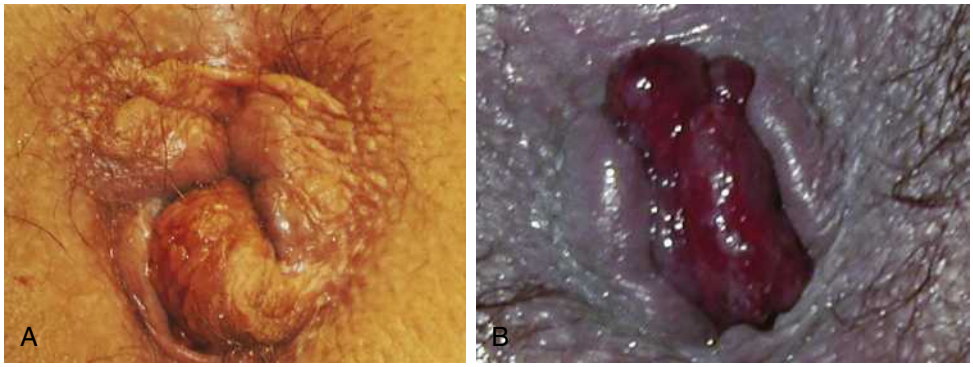

Fig. 82.3 Thrombosed hemorrhoids. (A) External. (B) Internal. Note the engorged external hemorrhoids surrounding the thrombosed internal hemorrhoids. (A, Courtesy Dr. Michelle Lin, Harbor-UCLA Medical Center; B, courtesy Dr. Gershon Effron, Sinai Hospital of Baltimore; from: Seidel HM, et al, eds. *Mosby's Guide to Physical Examination,* ed 4. St. Louis: Mosby; 1999.)

TABLE 82.1 Types of Hemorrhoids

Type	Origin	Epithelium
External	Inferior hemorrhoidal plexus Below the dentate line	Modified squamous epithelium (anoderm)
Internal	Superior hemorrhoidal plexus Above the dentate line	Transitional or columnar epithelium (mucosa)
Mixed	Superior and inferior hemorrhoidal plexus	Transitional, columnar, or modified squamous epithelium (mucosa and anoderm)

TABLE 82.2 Classification of Internal Hemorrhoids by Severity

Type	Prolapse	Mode of Reduction	Treatment
First degree	None	N/A	Medical
Second degree	During defecation	Spontaneous	Medical
Third degree	May be spontaneous or during defecation	Manual	Medical Optional surgical repair
Fourth degree	Permanent	Irreducible	Surgical repair

N/A, Not applicable.

BOX 82.2 WASH Regimen for Management of Hemorrhoids

Warm water
Analgesic agents
Stool softeners
High-fiber diet

(Table 82.1). Table 82.2 shows the classification of hemorrhoids based on history, physical findings, and reducibility.

Management

The symptoms of nonthrombosed external and nonprolapsing internal hemorrhoids can be ameliorated by a standard regimen, WASH (***w***arm water, ***a***nalgesics, ***s***tool softeners, and ***h***igh-fiber diet) aimed at combating the problems that led to their formation (Box 82.2). Anal canal pressures decrease in very warm water (40°C [104°F]—about the temperature of a well-heated "hot tub" or spa).[4] Patients can direct a shower stream at the area for several minutes or take sitz baths. This can facilitate spontaneous reduction of prolapsed hemorrhoids or other tissue and can ease the discomfort arising from tightly constricted musculature. Drinking water helps produce a softer stool. Mild oral analgesic agents such as acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) reduce pain. Passage of stool is more comfortable with stool softeners and fiber supplementation with psyllium (e.g., Metamucil©), one to two rounded teaspoons in eight ounces of water once a day, or a high-fiber diet (20–30 g of dietary fiber/day). Several over-the-counter preparations are available for the treatment of hemorrhoidal symptoms; their use improves hygiene and provides temporary symptom relief rather than correction of the condition. Topical anesthetics, corticosteroids, astringents (e.g., witch hazel), mineral oils, and cocoa butter are often applied as temporary soothing agents, although there is no evidence to support their use or the relative benefits of one over the other.[4] Astringents may promote better hygiene and reduce discomfort by preventing residual stool from further irritating the hemorrhoids. Lipophilic agents provide a smooth and greasy coating that can prevent the adherence of stool to the irritated areas and can promote a slippery pathway during defecation. We do not recommend use of topical corticosteroids beyond a few days because of risk of atrophic skin changes.

Patients with second- or third-degree internal hemorrhoids benefit from the WASH regimen and may be discharged from the ED. Permanent resolution of symptoms may require surgical banding, sclerotherapy, or elective hemorrhoidectomy (Table 82.3). Patients with acute, gangrenous, thrombosed fourth-degree internal hemorrhoids may require emergent hemorrhoidectomy.[5]

Acutely thrombosed external hemorrhoids can be excised (*not* incised and drained) to provide relief within the first 72 hours after the onset of symptoms (Fig. 82.4). Although incision may help to relieve pain in the short term, it results in incomplete evacuation of

TABLE 82.3 Surgical Management of Hemorrhoids

Classification	Management
Thrombosed external hemorrhoids	Excision in emergency department
Second- and third-degree internal hemorrhoids	Elective surgical repair Banding Sclerotherapy Hemorrhoidectomy
Fourth-degree hemorrhoids (nonthrombosed)	Nonemergent hemorrhoidectomy
Thrombosed or gangrenous fourth-degree internal hemorrhoids	Emergent hemorrhoidectomy

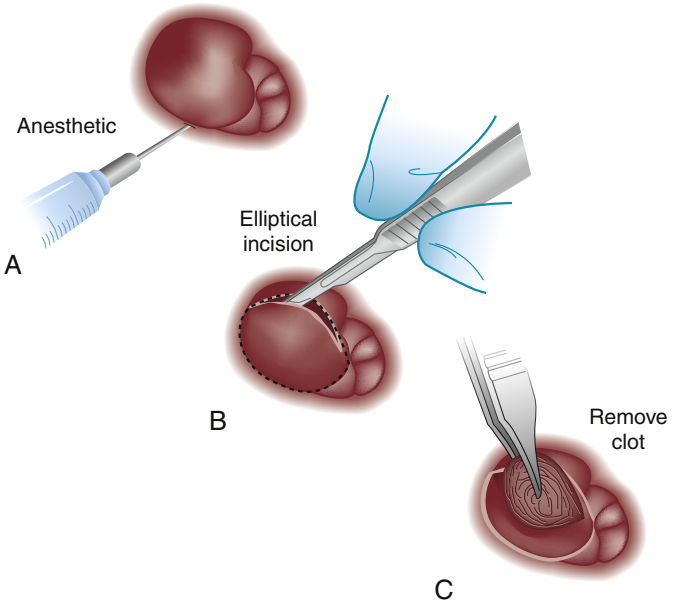

Fig. 82.4 Excision of thrombosed external hemorrhoid. (A) Field block with local anesthetic. (B) An elliptical incision is made around the hemorrhoid. (C) The thrombosed hemorrhoid is removed. (From Larson S, et al, eds. *Atlas of Emergency Procedures.* St. Louis: Mosby; 2001.)

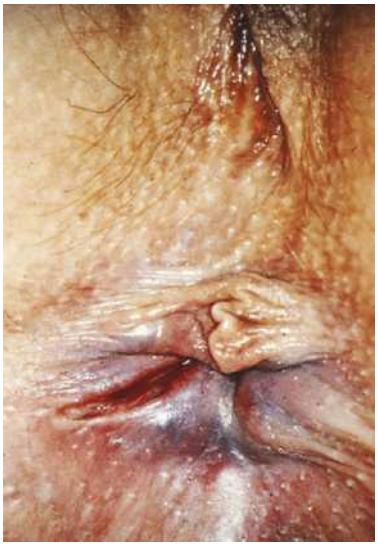

Fig. 82.5 Lateral anal fissure. (Courtesy Dr. Gershon Effron, Sinai Hospital of Baltimore; from: Seidel HM, et al, eds. *Mosby's Guide to Physical Examination,* ed 4. St. Louis: Mosby; 1999.)

the clot, subsequent rebleeding, swelling, and formation of a skin tag. If not excised, a thrombosed external hemorrhoid resolves spontaneously after several days when it ulcerates and leaks the dark accumulated blood. Residual skin tags may persist, making anal hygiene more challenging. In the ED setting, this procedure is not commonly performed in pediatric patients, pregnant women, or immunocompromised patients.

Nonsurgical therapy with topical nifedipine (0.2%) and lidocaine (1.5%) gel applied twice daily for a few days may alleviate symptoms in some patients. Although not widely used, the purported effectiveness of this regimen is related to the ability of nifedipine to modulate resting sphincter tone and thereby reduce the associated pain and inflammation.[6]

Anal Fissures

Foundations

The development of an anal fissure is the most common cause of intensely painful rectal bleeding of sudden onset. A superficial tear in the anoderm results when a hard piece of feces is forced through the anus, usually in patients who are constipated, or may occur during sexually related anal instrumentation. It is the most commonly encountered anorectal problem in pediatric patients, especially infants.[7] Most fissures occur along the posterior midline, where the skeletal muscle fibers that encircle the anus are weakest. Anterior midline fissures are more common in women than in men. Fissures that occur elsewhere may be associated with systemic diseases such as leukemia, Crohn's disease, human immunodeficiency virus (HIV) infection, tuberculosis (TB), or syphilis. If the fissure does not resolve promptly, the classical so-called fissure triad of deep ulcer, sentinel pile, and enlarged anal papillae may develop (Fig. 82.5). A sentinel pile forms when the skin at the base of the fissure becomes edematous and hypertrophic; it can form a permanent skin tag and underlying fistulous tract.

Clinical Features

The patient with an anal fissure reports sudden, searing pain during defecation that may be accompanied by a small amount of bright red blood on the stool or toilet paper. This is followed by a nagging, intermittent or constant burning sensation caused by internal sphincter spasm. Subsequent bowel movements are often quite painful and the external sphincter may exhibit a reflex spasm. A physical examination must be performed cautiously to avoid perpetuating the cycle of spasm and pain. If the patient can tolerate it, gentle anal eversion, as described above, often reveals the culprit fissure. The depth of the fissure, its orientation to the midline, and the presence of a coexisting sentinel pile should be noted. A digital rectal examination during an acute exacerbation often is challenging because of pain and sphincter spasm.

BOX 82.3 Treatment of Anal Fissures

- WASH regimen[a]
- Nitroglycerin ointment (0.4%) bid or tid
- Nifedipine gel (0.2%) bid with lidocaine (1.5%)
- Botulinum toxin (surgical consultation)
- Anal dilation performed with the patient under general anesthesia
- Surgical excision

[a] See Box 86.2

Management

We recommend a trial of conservative treatment with the WASH regimen (see Box 82.2), which focuses on eliminating constipation with a bulking agent, stool softener, and high-fiber diet. For severe discomfort, one to three days of topical anesthetic gel may be helpful. Specific measures for the treatment of anal fissures that do not resolve with conservative therapy are summarized in Box 82.3 and are often employed during follow-up visits with the patient's primary care provider or specialist. Parental encouragement of pediatric patients helps prevent encopresis, which can result from a fear of painful bowel movements. Most acute uncomplicated fissures resolve in 2 to 4 weeks.

For adult patients with recurring anal fissures, application of various topical agents aimed at reducing sphincter pressures and local pain may be effective. There is not uniform consensus for any of these treatments, however, some gastroenterologists and colorectal surgeons report that some individuals may benefit. It would be prudent to consult with the patient's ongoing provider to determine if one of these drug therapies is favored. Nitroglycerin ointment applied topically to the anoderm 2 or 3 times daily may relieve the pain but may cause a vasodilatory headache. Nifedipine gel (0.2%) in combination with lidocaine (1.5%) applied to the anal area twice daily is effective in promoting healing and reducing discomfort in the management of anal fissures by reducing anal canal pressures through local calcium channel blockade. Referral to a colorectal surgeon for definitive management may include injection of botulinum toxin, anal dilation, or sphincterotomy in patients who do not respond to conservative therapy.[8,9]

Abscesses and Fistulae

Foundations

Anorectal abscesses and subsequent fistulae occur in otherwise healthy adults when the mucus-producing glands at the base of the anal crypts occlude. In most cases, this is simply a functional collection of excess thick mucus, however, sometimes abscesses may result from intrarectal or penetrating trauma, or herald the presence of inflammatory bowel disease, cancer, radiation injury, or infection (TB, lymphogranuloma venereum, actinomycosis). Common causative bacteria are *Staphylococcus aureus, Escherichia coli, Streptococcus, Proteus,* and *Bacteroides.*

Anorectal abscess is an acute disease that naturally progresses to fistula formation in the body's attempt to drain the infection spontaneously. Symptoms vary depending on the site of infection, but incision and drainage constitute curative treatment (Table 82.4). Delays may allow extension of the infection and eventual compromise of the sphincter mechanism. Adjunctive antimicrobial therapy is indicated

TABLE 82.4 Types of Abscesses of the Anorectum

Feature	Perianal	Ischiorectal	Intersphincteric	Supralevator	Postanal
Incidence	40%–45%	20%–25%	20%–25%	<5%	5%–10%
Location	Outside and verge	Buttocks	Lower rectum	Above levator ani	Deep to external sphincter
Symptoms	Painful perianal mass	Buttock pain	Rectal fullness	Perianal and buttock pain	Rectal fullness, pain near coccyx
Fever, ↑ WBCs	–	±	±	+	+
Associated fistula	++	+	+++	+++	–
ED incision and drainage	+	±	–	–	–

ED, Emergency department; *WBCs,* white blood cells; –, does not occur; ±, occurs sometimes; ++, occurs often; +++, usually occurs.

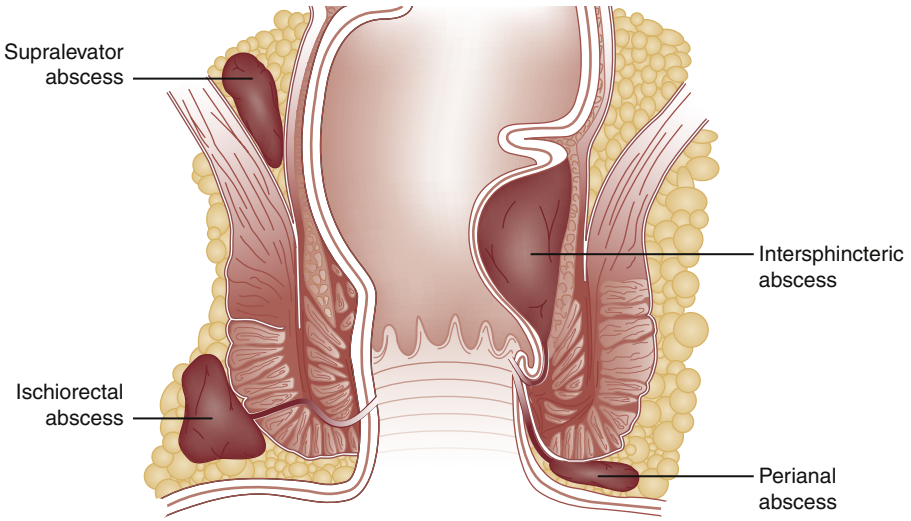

Fig. 82.6 Location of common anorectal abscesses. (Adapted from Gordon PH, Nivatvongs S. *Principles and Practice of Surgery for the Colon, Rectum, and Anus.* St. Louis: Quality Medical Publishing; 1992.)

in patients who are immunocompromised, diabetic, or have valvular heart disease. One-third of patients with AIDS develop anorectal abscesses and fistula. In these patients, antibiotic therapy choices should be guided by the patient's immune status in consultation with infectious disease specialists who are familiar with local antibiograms. HIV-infected patients are prone to having incomplete fistulous tracts, which impedes spontaneous drainage, highlighting the urgency of treating these patients promptly.[10]

Sites of anorectal abscess formation are depicted in Fig. 82.6. Early diagnosis may be difficult because pain often precedes physical findings of a mass or fluctuance.

Management

Perirectal and Perianal Abscesses. Perirectal and perianal abscesses account for about half of anorectal abscesses. They produce painful swelling at the anal verge that is worsened by defecating or sitting. Most patients are afebrile and have localized tenderness, erythema, swelling, and fluctuance that is particularly obvious on examination with palpation between the index finger (from within the rectum) and the thumb (through the outside skin). ED management by incision and drainage may be possible in patients without comorbidities (e.g., diabetes mellitus, extremes of age, compromised immune status), but the procedure can be very painful and often requires procedural sedation and/or field block with local anesthesia. The WASH regimen (see Box 82.2) may alleviate postprocedure discomfort. Antibiotics generally are unnecessary following incision and drainage of uncomplicated superficial abscesses in healthy adult patients, except in cases involving associated cellulitis. There is emerging evidence that adjuvant antibiotics may help reduce the likelihood of subsequent fistula formation, even in patients without cellulitis.[10-12] In consultation with infectious disease specialists at individual institutions to address local antibiograms and the prevalence of methicillin-resistant *Staphylococcus* aureus (MRSA), one could consider administering one or more of the following: cephalexin 500 mg PO bid-qid; sulfamethoxazole/trimethoprim (800 mg/160 mg PO Q12 hours; doxycycline 100 mg PO bid.

Ischiorectal Abscess. Ischiorectal abscesses account for one-fifth to one-quarter of anorectal abscesses. They form outside the sphincter muscles in the buttocks, and patients generally present complaining of severe pain. The diagnosis is evident if an indurated mass is seen on the buttocks but sometimes the abscess is deep in the tissue and not externally identifiable. Patients may have fever and/or leukocytosis. Ultrasound may be useful to localize fluid collections and guide aspiration, particularly if there is no significant induration. Although most of these abscesses will require drainage performed with the patient under general anesthesia, superficial abscesses can be treated in the ED. If the patient is febrile, we recommend a short course of antibiotics, such as cefazolin 1 g IM or IV administered before drainage, followed by cephalexin 500 mg orally qid for 5 to 7 days.[12]

Intersphincteric Abscess. One-fourth of abscesses form in the intersphincteric space, located deep to the external sphincter and inferior to the levator ani. The infection tracks cephalad and may appear to be a mass in the rectum and can be confused with a thrombosed internal hemorrhoid. Patients report continuous rectal pressure and

a throbbing pain exacerbated by defecation or sitting. These patients also may have fever and/or leukocytosis which are neither sensitive nor specific signs. External evidence of inflammation may be lacking, but a rectal examination reveals an indurated, and sometimes draining mass. Associated fistulae and inguinal lymphadenopathy are common. Surgical consultation and advanced imaging, such as CT scan or fistulogram, are necessary to evaluate and treat the entire abscess and fistula network.

Supralevator Abscess. Supralevator abscesses, which cause less than 5% of anorectal abscesses, present as perianal and buttock pain associated with fever and frequently, an associated leukocytosis. External evidence is usually absent, which often leads to a delay in accurate diagnosis. Patients are often obese or have diabetes, Crohn disease, pelvic inflammatory disease, or diverticulitis. A tender mass may be palpated on rectal or pelvic examination, but the abscess is often discovered on CT scan performed to evaluate the patient with significant symptoms but no identified cause. Emergent surgical treatment is indicated to drain the abscess and excise the fistulous network.

Postanal Abscess. Postanal abscesses are uncommon and occur posterior to the rectum, deep to the external sphincter and inferior to the levator ani. Patients experience severe rectal discomfort and coccygeal pain. They usually are febrile and have continuous pain that does not change with position. A rectal examination is painful, and anal drainage is rare. Many of these abscesses are missed on initial presentation, unless a CT scan is performed. These abscesses require surgical consultation and management.

Horseshoe Abscess. A large, communicating, horseshoe-shaped abscess may form in the ischiorectal, intersphincteric, or supralevator spaces. The extent of these abscesses is identified by CT scan and surgical management is necessary.

Necrotizing Infection. A delay in the management of an anorectal abscess may lead to the destruction of surrounding tissue, especially in diabetic or immunocompromised patients. Extensive cellulitis, necrotic tissue, or identification of gas on radiography suggest the possibility of necrotizing fasciitis, Fournier gangrene, or tetanus. Treatment is described in Chapter 126, and includes timely, wide surgical débridement, administration of intravenous antibiotics with anaerobic coverage such as a combination of piperacillin (4.5 gm IV q8h), vancomycin (15 to 20 mg/kg q8h to q12h), and clindamycin (900 mg IV q8h), and tetanus prophylaxis.

Fistulae. A fistula is a connection between two epithelium-lined surfaces and commonly develops in patients with abscesses. Other causes include Crohn's disease, trauma, foreign body reactions, TB, and cancer. The anorectal complaint may be the presenting symptom of the underlying disease. Patients notice a recurrent or persistent perianal discharge that becomes painful when one of the openings becomes occluded. A digital rectal examination may reveal a tract in the perineum or canal. Probing of fistulous tracts is not recommended because the danger of creating a new tract outweighs the benefit of identifying the path of the existing fistula. Spontaneous resolution of fistula-in-ano is rare.

Although symptoms may resolve when antibiotics are administered, they commonly return when therapy is discontinued. Definitive treatment of the fistulous network at the time of incision and drainage of the abscess prevents the ongoing progression of the disease. Fistulectomy or application of fibrin glue are commonly accepted practices of adult and pediatric colorectal surgeons.[13] New treatments that are underway include the use of biomaterials (e.g., platelet rich plasma) and laser closure techniques.[11]

Pilonidal Disease

Foundations

Abscesses containing hair and pus in the midline of the sacrococcygeal area afflict young adults with a 4:1 male predominance and are more common in obese and hirsute persons. Many of those who develop this disease have evidence of midline hair growth in other areas of the body, such as eyebrows that connect with each other. Pilonidal disease occurs more commonly in people who sit for long periods, and was first identified as "Jeep driver's disease" during World War II. The disease is rare after 40 years of age, even for those who were affected in their youth, and should not be confused with anal fistulae, perirectal abscesses, hidradenitis suppurativa, or granulomatous diseases (e.g., syphilis, TB). Pilonidal disease is believed to arise when bacteria enter the usually sterile hair follicle and produce inflammation and edema, thereby occluding the opening to the skin surface. The contents expand until the hair follicle ruptures, and the material spreads into the surrounding subcutaneous fatty tissue, where a foreign body reaction leads to abscess formation. The purulent material subsequently spreads to the presacral skin through an epithelialized tract. In those with chronic or recurrent disease, visible or palpable tracts containing hair and cellular debris may be identified.

Management

Treatment options vary, ranging from aspiration to extensive surgical excision. Supplementary antibiotics, such as cephalexin 500 mg qid for 7 days, are indicated in cases accompanied by cellulitis, but are not effective as the sole treatment for the long term. ED management of pilonidal disease involves aspiration or incision and drainage of the acute abscess for the immediate relief of symptoms. Aspiration of pus plus antibiotics and referral to a surgeon for follow-up may be effective for small pus collections.[14] If incision and drainage are performed, a longitudinal incision lateral to the midline prevents reaccumulation of debris and minimizes the inflammatory response in the midline. Fibrin glue application has shown promise in the early treatment of pilonidal disease and is usually applied by a specialist. Recalcitrant disease may require surgical unroofing, marsupialization, or wide excision.[15]

Hidradenitis Suppurativa

Foundations

Perianal hidradenitis suppurativa is an infection of the apocrine glands. It is most common in young adults and is associated with poor skin hygiene, hyperhidrosis, obesity, acne, diabetes mellitus, and smoking. Occluded apocrine ducts may be infected with strains of *Staphylococcus, Streptococcus, E. coli,* or *Proteus.* Extension through the dermis spreads the infection to neighboring ducts and forms a network of sinus tracts, leading to extensive scarring.[16]

Clinical Findings

Patients report one or more tender, draining pustules or abscesses in the perianal area, which may be associated with fever, malaise, or leukocytosis. Local lymphadenopathy and surrounding cellulitis are common.

Differential Diagnosis

This condition is often misdiagnosed as pilonidal disease or fistula-in-ano. Other considerations in the differential diagnosis include sebaceous cysts, furuncles, granulomas (from TB or syphilis), or Crohn disease.

Management

Treatment begins with careful attention to perianal hygiene, warm compresses, antibiotics (e.g., cephalexin, 500 mg PO qid for 7 days), and dietary modifications (avoidance of dairy products and foods with a high glycemic index). Drainage of isolated lesions by aspiration or incision and drainage may provide symptomatic relief, but the recurrence rate approaches 40%. Referral to a surgeon for wide excision of tissue involved in advanced chronic disease may be necessary.[17]

Proctalgia

Anorectal pain (proctalgia) that does not arise from an identified organic disorder can be severe and difficult to treat. Two common causes of this functional proctalgia are levator ani syndrome and proctalgia fugax. Their patterns of affliction can distinguish these disorders. Other causes of pelvic pain, such as tumors, cauda equina syndrome, or endometriosis, should also be considered.

Levator Ani Syndrome

Constant dull pressure in the sacrococcygeal region precipitated by defecation or prolonged periods of sitting suggests levator ani syndrome. The patient usually has tenderness of the levator muscles, which may be firmly contracted on examination. No standard treatment regimen has been studied, but anecdotal reports indicate that sitz baths, levator ani muscle massage, and benzodiazepines, such as diazepam (beginning with 2 mg PO bid to qid) can provide relief.[18]

Proctalgia Fugax

Proctalgia fugax is an intensely painful spasm in the rectal area that begins abruptly and lasts up to 30 minutes, resulting from a sudden spasm of the levator muscle complex or sigmoid colon. Professionals, managers, perfectionists, and people who frequent the toilet are more likely to be affected. Symptoms begin abruptly during sleep, defecation, urination, or intercourse. The pain has been compared to that of a charley horse (painful spasms in the leg muscles) and may radiate to the coccyx or perineum. Each patient has a unique but recurrent constellation of symptoms. Treatment includes a bowel-cleansing regimen, manual upward pressure on the anus, diazepam (beginning with 2 mg PO bid to qid).

Fecal Incontinence

Foundations

Fecal incontinence is a condition that affects parous women, elders, young children, and patients with a variety of neurologic or traumatic disorders in which the delicate balance among the pelvic floor muscles, sphincters, and anorectal sensation is disrupted. Complete incontinence is the inability to control the passage of solid feces. Partial incontinence is the loss of control of the passage of flatus or liquid feces.

Multiple causes of fecal incontinence have been described (Box 82.4). Liquid feces may seep around tumors or foreign bodies of the rectum or anal canal. Laxative abuse, inflammation, or infection can temporarily overwhelm a normal sphincter mechanism and cause explosive diarrhea. Encopresis may develop in young children experiencing emotional stress. In otherwise healthy children, sexual abuse involving the anus should be considered.

Clinical Features

The anorectum should be assessed for masses, hemorrhoids, evidence of previous surgery, and neuromuscular function. Careful neurologic examination, particularly if back or sacral pain is present, will identify sensory changes caused by neurologic disease, such as cauda equina syndrome, spinal epidural abscess, or mass. Neuromuscular causes of fecal incontinence are diagnosed by anorectal physiologic testing.

Management

Acute fecal incontinence caused by a neurologic condition requires urgent treatment, usually through consultation with a spine surgeon. If CT scan is obtained and confirms a colorectal mass, outpatient surgical referral is necessary for definitive treatment, unless bowel obstruction is present, requiring acute surgical consultation in the ED. The management of subacute or chronic fecal incontinence depends on the cause, and is best managed by an outpatient longitudinal care provider, such as a primary care physician. Depending on the cause, Kegel exercises, which contract the perineal muscles, biofeedback training, or surgical repair may be indicated. In cases of transient incontinence caused by diarrhea, a high-fiber diet and brief therapy with loperamide, 2 mg, after each bowel movement, up to a maximum of 16 mg a day, can solidify stool and enhance rectal compliance.

BOX 82.4 Causes of Fecal Incontinence

Traumatic Causes
Iatrogenic (surgical) nerve injury
Spinal cord injury
Obstetric trauma
Sphincter injury

Neurologic Causes
Spinal cord lesions
Dementia
Autonomic neuropathy (e.g., diabetes mellitus)
Obstetric—pudendal nerve damage from stretching during surgery, Hirschsprung disease

Mass Effect
Carcinoma of anal canal
Carcinoma of rectum
Foreign body
Fecal impaction
Hemorrhoids

Medical Causes
Procidentia
Inflammatory disease
Diarrhea
Laxative abuse

Pediatric Patients
Congenital
Meningocele
Myelomeningocele
Spina bifida

Other Causes
After corrective surgery for imperforate anus
Sexual abuse
Encopresis

Pruritis Ani

Foundations

Patients with pruritus ani complain of uncontrollable itching of the perianal area. The condition is more common in the summer and is more noticeable at night. The sensation of itching arises when the richly innervated perianal skin becomes irritated. Vigorous scratching may result in excoriation (which leads to more intense symptoms). The most common cause is the presence of feces on the perianal skin. Conditions ranging from poor personal hygiene to anatomic disorders allow feces to accumulate. Obesity, deep perianal clefts, hair, hemorrhoids, skin tags, rectal prolapse, anal fissures, and fistulae make the area difficult to clean effectively. Decreased air circulation from wearing tight pants or undergarments of synthetic, nonbreathable fabric may exacerbate symptoms. The causes of pruritus ani are summarized in Box 82.5. The acronym "ITCH" categorizes typical causes—***i***nfection, ***t***opical irritants; ***c***utaneous conditions and cancer; and ***h***ypersensitivity to foods and drugs.[19]

BOX 82.5 Causes of Pruritus Ani

Dermatitis

Fecal Irritation

Poor hygiene

Anorectal conditions—fissure, fistula, hemorrhoids, skin tags, perianal clefts

Systemic—caffeine, tea, beer, spicy foods, citrus fruits, quinidine, intravenous hydrocortisone, colchicine, tetracycline

Contact Dermatitis

Anesthetic agents, topical corticosteroids, perfumed soap

Systemic Diseases

Dermatologic

Psoriasis, seborrhea

Lichen simplex or lichen sclerosus

Nondermatologic

Chronic renal failure, myxedema, diabetes mellitus, thyrotoxicosis, polycythemia vera

Vitamin A or D deficiency, iron deficiency

Cancer—Bowen, Paget, Hodgkin disease

Infections

STDs

Syphilis

HSV infection

HPV infection

Other Infectious Processes

Scabies

Pinworm

Bacterial infection

Fungal infection

HPV, Human papillomavirus; *HSV,* herpes simplex virus; *STD,* sexually transmitted disease.

Diagnostic Testing

Pinworms are most commonly found in young children and their close contacts, as well as in institutionalized patients. The organisms can be identified by applying transparent tape to the perianal area and attaching it to a glass slide or simply inspecting the tape. The visualization of eggs under microscopy confirms the diagnosis, but is not necessary because the worms have a characteristic size and shape and are often identifiable.

Management

A careful history and physical examination will generally identify the cause of pruritus ani. Important considerations include hygienic care of the anus, coexisting anorectal or systemic conditions, diet, and sexual practices.

The first-line agent for pinworms is mebendazole (Vermox), 100 mg orally (over age 2) as a single dose. An alternative agent is pyrantel pamoate (Antiminth), 1 g orally (11 mg/kg, to a maximum of 1 g for pediatric patients over 7 months of age) as a single dose.[20] Repeat doses may be needed in 2 and 4 weeks, and one may consider treating family members. Scabies and pediculosis pubis should be treated with 5% permethrin cream application that can be repeated in 7 days. An alternative regimen for those over the age of 10 years is ivermectin 200 micrograms/kg orally as a single dose (repeated in 2 weeks).[21]

Fungal dermatitis causes a rash with sharply demarcated borders and is treated with clotrimazole 1% or nystatin cream, accompanied by meticulous hygiene and thorough drying of the area before application. Definitive treatment of concomitant anorectal conditions (e.g., fissures, fistulae, hemorrhoids, skin tags, rectal prolapse) can prevent recurrence of pruritus ani.

Underlying systemic diseases should be treated. Patients should be instructed to clean the area thoroughly with lukewarm water after each bowel movement and pat (rather than rub) dry with tissue that is free of chemical irritants. Loose-fitting underwear and exposure to fresh air may alleviate symptoms. The treatment of acute dermatitis includes a short course of topical corticosteroids, such as hydrocortisone 2.5%, calamine lotion, or systemic antihistamines. Some success with topical application of capsaicin cream has been reported, although there is insufficient evidence to support a recommendation.

Sexually Transmitted Disease and Proctitis

Foundations

Anorectal transmission of sexually transmitted disease (STD) is a concern in all sexually active patients with anorectal complaints, but especially in those with HIV. The history should ascertain whether sexual practices involve oral-anal contact or anal penetration and whether condoms are used. Education regarding the transmission of STDs and the efficacy of barrier methods is an essential means of public health prevention of disease.[21,22] Semen has a concentrated viral load, and the damaged epithelium of ulcerated anoderm provides a portal for entry. Syphilis, gonorrhea, and chlamydial infection have been documented in men who have sex with men.

Gonorrhea. The gram-negative diplococcus *Neisseria gonorrhoeae* causes gonorrhea. Proctitis (inflammation of the rectum) results from anal intercourse or autoinoculation from vaginal secretions and becomes symptomatic after a 5- to 7-day incubation period. Symptomatic patients report pruritus ani, tenesmus, and bloody or thick, purulent yellow drainage. Anoscopy reveals proctitis and mucus in the anal crypts. Recovery of the organism from the crypts increases the likelihood of identification. Water should be used to lubricate the anoscope because lubricants contain an antibacterial agent. Disseminated gonococcal infection may include arthritis, skin lesions, perihepatitis, endocarditis, and meningitis.

Chlamydial Infection and Lymphogranuloma Venereum. Infection with *Chlamydia trachomatis,* an intracellular organism that is endemic to the tropics, is a common STD in the United States. Signs and symptoms include mucoid or bloody rectal discharge and tenesmus. Some people are asymptomatic carriers of the organism. Lymphogranuloma venereum is a more serious manifestation caused by specific strains of *C. trachomatis.* It starts as a painful anal or perianal ulceration with an erythematous friable rectal mucosa, fever, and malaise. Prominent unilateral lymph nodes coalesce to form a bubo, which must be distinguished from the granuloma of secondary syphilis. Rectal cultures are unreliable because the organism is intracellular. In the final stage, rectal strictures and rectovaginal fistulae may form.

Herpes Simplex Virus Infection. Herpes proctitis is caused by herpes simplex virus type 1 (HSV-1) and HSV-2. Symptoms appear 1 to 3 weeks after exposure. Those with proctitis may have rectal pain, bloody mucoid discharge, tenesmus, constipation, sacral paresthesias, or urinary difficulties. An examination may be challenging without anesthesia. Single or coalesced vesicles and ulcerations occur in the perianal area and rectum, and the rectal mucosa is erythematous, friable, and ulcerated. Chronic mucocutaneous HSV infection is considered diagnostic for AIDS. Definitive diagnosis with viral or immunofluorescent staining relies on the collection of fluid and scrapings from the base of the vesicle.

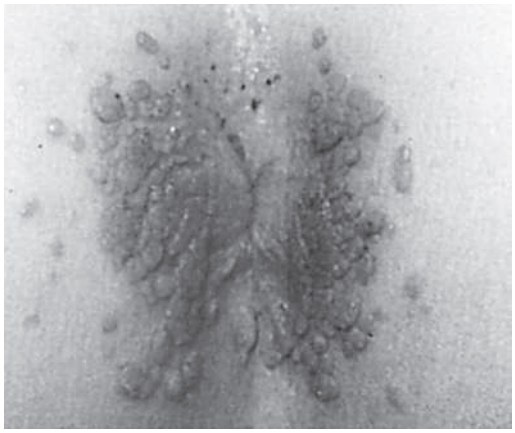

Fig. 82.7 Condylomata acuminata in a child.

Syphilis. Syphilis is caused by *Treponema pallidum,* a motile spirochete. During anal intercourse, the organism enters the rectal mucosa or anoderm and forms an ulcer (chancre) within 2 to 6 weeks. The chancre heralds the primary phase of syphilis and may resemble an anal fissure. Patients may experience discomfort during defecation, tenesmus, mucoid discharge, and inguinal adenopathy. Primary syphilis can be confused with lymphoma, but the diagnosis can be made by visualizing spirochetes on darkfield microscopy from scrapings taken from the base of the ulcer.

Serologic testing is useful several weeks after the appearance of the chancre. Treponemal tests such as the fluorescent treponemal antibody (FTA) yield a positive result earlier than the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests. If the chancre goes unnoticed, the patient may present with secondary syphilis, marked by a maculopapular rash that characteristically involves the palms and soles, and condyloma latum, a spirochete-laden, weeping, verrucous lesion in the perianal area that emits a foul odor. It is easily distinguishable from condyloma acuminatum, which has a drier, more keratinized appearance. Serologic testing results usually are positive. Tertiary syphilis is rare but may manifest as a rectal gumma with perianal pain and paralysis of the sphincters and may be mistaken for anal cancer.

Chancroid. Chancroid is caused by the gram-negative bacillus *Haemophilus ducreyi*, and begins as an inflammatory pustule or macule that ruptures to form an irregularly shaped ulcer. In several days, painful inguinal adenitis develops. Chancroid often is a diagnosis of exclusion.

Condyloma Acuminatum. Condyloma acuminatum (genital warts), the most commonly encountered anorectal STD, is caused by the human papillomavirus. The mode of transmission is primarily through sexual intercourse, but transmission can occur through close personal contact, as often happens in pediatric cases when an infected person changes a diaper and transmits the virus due to poor handwashing techniques. It is incumbent on the evaluating physician to consider sexual abuse in pediatric cases. Because half of HIV-positive patients have anal warts, HIV testing is recommended in patients with this diagnosis.

The pink to gray papilliform growths are a result of hyperplastic epithelial growth (Fig. 82.7). They may coalesce to form a massive patch that obscures the anal verge. Patients may be asymptomatic or report pruritus ani, hemorrhoids, or bleeding. Evaluation can include anoscopy because warts often grow within the anal canal. Failure to treat the internal lesions results in recurrence. The differential diagnosis includes condyloma latum (secondary syphilis) and squamous cell carcinoma. The preferred treatment is cryotherapy, but outpatient treatment with 0.5% podofilox solution or gel can be successful in limited cases.

BOX 82.6 Anorectal Lesions in the Patient With HIV Infection

Common Conditions

Anal fissure
- Abscess and fistula
- Hemorrhoids
- Pruritus ani
- Pilonidal disease

Common STDs

Gonorrhea
- Chlamydial infection
- Herpes
- Chancroid
- Syphilis
- Condyloma acuminatum

Atypical Conditions

Infectious

TB, CMV infection, actinomycosis, cryptococcosis

Neoplastic

Lymphoma, Kaposi sarcoma, squamous cell carcinoma

Other

Idiopathic anal ulcer

CMV, Cytomegalovirus; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease; *TB,* tuberculosis.

Ulcerative Lesions in HIV-Infected Patients. There is significant comorbidity between patients who are HIV seropositive and other STDs. Anorectal complaints in HIV-positive patients fall into three categories: (1) routine proctologic conditions, as seen in the general population, (2) STDs, and (3) opportunistic infections (Box 82.6). The treatment of routine conditions and common STDs is similar to that in other patients except that wound healing may be delayed.

Management

A summary of common infections and treatment guidelines is presented in Table 82.5. Empirical therapy is indicated for patients who have recently practiced anal-receptive intercourse and have a rectal discharge. The recommended regimen is a single dose of ceftriaxone, 250 mg intramuscularly, plus doxycycline, 100 mg bid orally for 7 days. Patients with anorectal infections and their partners should be referred for HIV testing. The possibility of sexual assault should be considered. The health care provider should report STDs and new diagnoses of HIV infection per state and local health department regulations.

In immunocompromised patients, the differential diagnosis of ulcerative anorectal lesions should include opportunistic infections, lymphoma, and Kaposi sarcoma. Patients with AIDS often exhibit idiopathic anal ulcerations with pain and bleeding. Before this diagnosis is made, other possible causes of the lesions must be considered (see Box 82.6). Symptomatic relief can often be achieved with the WASH regimen (see Box 82.2), but recalcitrant lesions may require surgical excision.

Radiation Proctitis

Radiation-induced injury of the rectum is often caused by the treatment of gynecologic, urologic, or GI malignancies. Immediate radiation proctitis usually is self-limited and responds to symptomatic treatment. Late radiation proctitis can manifest up to 2 years after exposure.

TABLE 82.5 Sexually Transmitted Diseases of the Anorectum[21]

Disease or Condition (With Specific Pathogen When Known)	Findings	Treatment
Ulcerative Conditions		
LGV	Unilateral inguinal adenopathy Fever, malaise Mucoid or bloody discharge	Doxycycline, 100 mg PO bid, for 21 days Azithromycin 1 g PO weekly × 3 weeks *For pregnant patients or those allergic to tetracyclines*—erythromycin, 500 mg PO qid, × 21 days
HSV infection	Rectal pain, tenesmus, constipation Bloody mucoid discharge Vesicles and ulcerations Fever, malaise, myalgias, paresthesias	*First episode*—Acyclovir, 400 mg PO tid, 7–10 days *or* Acyclovir, 200 mg PO, 5×/day, for 7–10 days *or* Famciclovir, 250 mg PO tid, for 7–10 days *or* Valacyclovir, 1 g PO bid, for 7–10 days
Early (primary) syphilis (*Treponema pallidum*)	Chancre Tenesmus, pain, mucoid drainage Inguinal lymphadenopathy	Benzathine penicillin G, 2.4 million units IM, once
Chancroid (*Haemophilus ducreyi*)	Inflammatory lesion progresses to ulcer Inguinal adenitis—bubo	Azithromycin, 1 g PO once, or Ceftriaxone, 250 mg IM once, or Ciprofloxacin, 500 mg PO bid, for 3 days or Erythromycin base, 500 mg PO tid, for 7 days
Idiopathic (usually HIV-positive)	Eccentric, deep, poor-healing, multiple lesions	Symptomatic relief or surgical referral
Nonulcerative Conditions		
Condylomata acuminata (HPV)	Keratinized vegetative growths in anus or skin Asymptomatic, pruritus ani, or bleeding	Podofilox, 0.5% topically, or Imiquimod 3.75 or 5% cream or provider-administered cryotherapy, excision, or trichloroacetic acid
Gonorrhea (*Neisseria gonorrhoeae*)	Pruritus ani Tenesmus Purulent yellow discharge	Ceftriaxone, 500 mg IM once, PLUS Doxycycline 100 mg PO BID × 7 d or Cefixime, 800 mg PO, once PLUS Doxycycline 100 mg PO BID × 7d
Chlamydial infection (*Chlamydia trachomatis*)	Mucoid or bloody discharge Tenesmus	Azithromycin, 1 g PO once, or Doxycycline 100 mg PO bid, for 7 days
Syphilis (secondary)	Maculopapular rash Condyloma latum	Benzathine penicillin G, 2.4 million units IM, once

HIV, Human immunodeficiency virus; *HPV,* human papillomavirus; *HSV,* herpes simplex virus; *IM,* intramuscularly; *LGV,* lymphogranuloma venereum; *PO,* orally.

Signs and symptoms of radiation proctitis include bleeding ranging in severity from spotting to hemorrhage, tenesmus, diarrhea, pain, fistula-in-ano, and rectal strictures. Diagnosis is often presumptive, based on the patient's history of radiation therapy, but can be confirmed by rectal mucosal biopsy.

Treatment regimens include supportive therapy and the use of antiinflammatory agents, formalin application, oral sucralfate therapy combined with sucralfate retention enemas, hyperbaric oxygen therapy, and sclerosing therapy.[23] When a patient with suspected radiation proctitis presents to the ED, the first measures should focus on pain management while coordinating a care plan with the primary physician, a gastroenterologist, or surgical specialist as needed.

Rectal Prolapse

Rectal prolapse, or procidentia, is a disease of persons at the extremes of age. Prolapse is complete if all bowel layers protrude and incomplete if only the mucosal layer is involved. In adults, complete procidentia is most common among older women and is caused by a laxity of attachment structures. It often is accompanied by uterine prolapse or cystocele. Patients report an anal mass that protrudes during defecation, coughing, or sneezing.

Findings may include fecal incontinence, bloody or mucoid discharge, or a foul odor. In some cases, the patient can reduce the prolapse manually, whereas in others, the tissue becomes edematous, and a red, ulcerated mass protrudes from the anus (Fig. 82.8). A reduction may be attempted by placing the patient prone and applying an osmotically active solution, such as sucrose-soaked gauze that can be applied to the mass. After several minutes, gentle diffusely applied pressure is used to guide the tissue back into the rectal vault. Care should be taken not to poke at the tissue, because this could cause penetrating trauma. When reduction is successful, the patient may be discharged with agents to relieve constipation. Surgical repair often is necessary.[24]

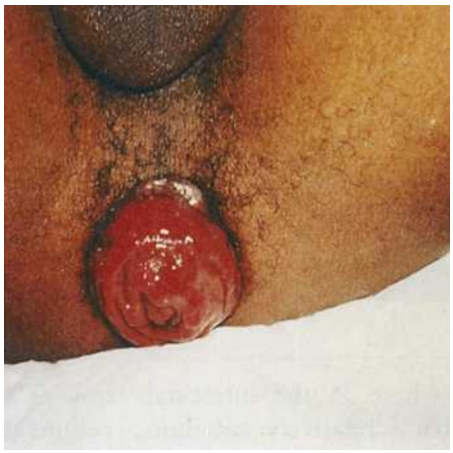

Fig. 82.8 Prolapse of the rectum. (Courtesy Dr. Gershon Effron, Sinai Hospital of Baltimore; from: Seidel HM, et al, eds. *Mosby's Guide to Physical Examination*, ed 4. St. Louis: Mosby; 1999.)

In children up to 4 years of age, procidentia often is associated with chronic constipation or diarrheal disease. However, it may herald the presence of malnutrition, parasitic infection, or cystic fibrosis. Children usually have mucosal prolapse. The parent reports protrusion during defecation, with small amounts of mucus or blood. This condition must be distinguished from a protruding juvenile polyp and intussusception. A gentle reduction may be attempted. Increasing the dietary fiber and fluid intake frequently is successful as first-line therapy.

Rectal Foreign Bodies

Foundations

Anorectal foreign bodies may result from the use of the anus for sexual gratification, although they also are found in children, psychiatric patients, and victims of assault or iatrogenic injury. Most objects are introduced directly into the anus, but some become lodged there after oral ingestion. Foreign bodies that are unlikely to pass on their own or that have dangerous features must be removed to prevent mucosal lacerations, intestinal perforation and obstruction, sepsis, and peritonitis.[25]

Some foreign bodies that are ingested pass through the GI tract and subsequently become lodged in the rectum or anal crypts. Patients at the highest risk for ingested foreign bodies are children, psychiatric patients, and body packers.

Clinical Features

Rarely, a foreign body such as an enema tip or broken rectal thermometer is introduced iatrogenically. In most cases, the foreign body is placed deliberately by the patient or a partner for medicinal or sexual purposes. Objects that are commonly retrieved include fruits and vegetables, household items, especially those whose morphology and dimensions resemble the penis. and items purchased specifically with an anal erotic intent. By the time patients arrive at the ED, sometimes days after the introduction of the foreign body, they have likely tried to remove it at home. The history often is reluctantly given or is vague and inconsistent. The initial ED evaluation, conducted in a nonjudgmental manner, should ascertain the type of foreign body involved, how long it has been there, what attempts have been made to remove it, and whether the patient has a fever, abdominal pain or rectal bleeding. The possibility of an assault should be considered.

Physical examination begins with an external examination for signs of trauma. If no sharp objects are suspected, a digital rectal examination and anoscopy may reveal the foreign body, lax sphincter, or mucosal injury. An abdominal examination may demonstrate signs of perforation or obstruction.

Diagnostic Testing

The foreign body may be visible on abdominal radiographs, or its presence may be inferred by a nonspecific gas pattern, free air, or signs of intestinal obstruction. If a perforation is suspected, water-soluble contrast material can be introduced to delineate the outline of radiolucent foreign bodies and may identify perforation with extravasation.

Management

Treatment depends on the location and type of object found. In general, objects that are soft and low-lying (<10 cm from the anal verge) can be removed safely in the ED. The awake patient can assist in expulsion by performing the Valsalva maneuver. Premedication with a benzodiazepine, such as lorazepam, 1 mg, is helpful to relax the sphincter and patient. With the patient in the lithotomy position, suprapubic pressure can assist in removal (Fig. 82.9).

Several methods are useful for removal. The easiest is to grasp an edge of the foreign body with forceps and apply traction while the patient bears down. If the foreign body does not have a convenient place to grasp, other methods are needed. A Foley catheter can be placed beside the foreign body and the balloon inflated proximally to it (Fig. 82.10). This maneuver breaks the suction of the rectal wall mucosa and provides a way to guide the object out of the rectal vault. Hollow objects may be filled with plaster of Paris, with an inset inflated Foley catheter to be used as a handle. If the foreign body is large, difficult to grip, or fragile (a light bulb meets all three criteria), patients often require removal under general anesthesia in an operating room.

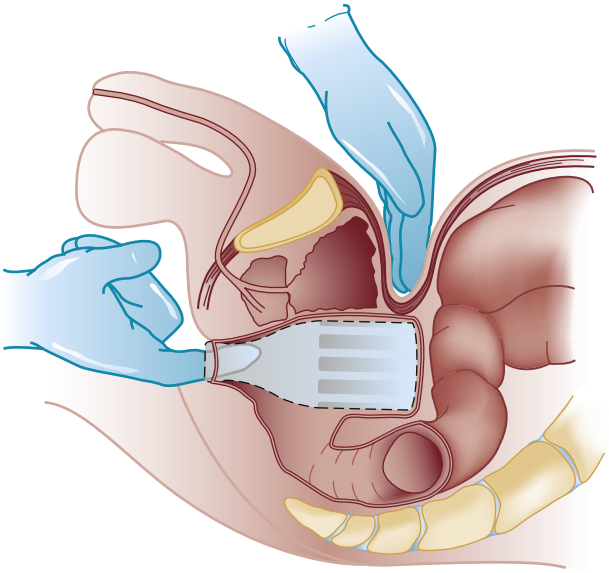

Fig. 82.9 Removal of a foreign body from the rectum.

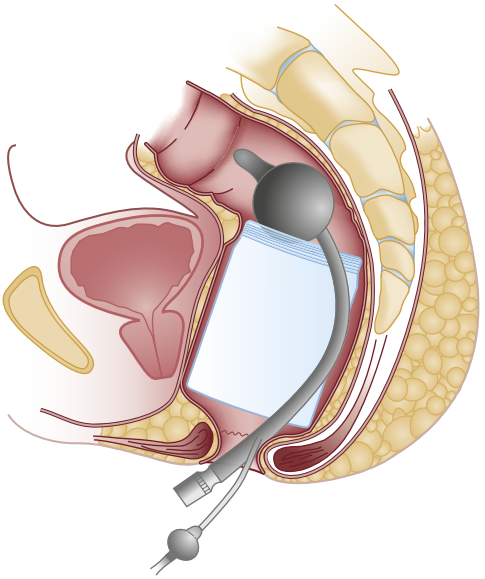

Fig. 82.10 Foley catheter–assisted removal of a rectal foreign body.

Large, hard, fragile objects and those that have migrated proximally are difficult to remove without anal dilation and instrumentation to assist in the passage through the sacral curve and sphincters. These are best performed with the patient under general anesthesia. After the removal of the foreign body, one should consider the possibility of mucosal tears or perforations. Discharge instructions should warn the patient about the signs and symptoms of perforation, peritonitis, and sepsis.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 82: QUESTIONS AND ANSWERS

1. Which of the following modifying factors is most likely to lead to the development of hemorrhoids as a result of portal hypertension?
- **a.** Alcoholism
- **b.** Obesity
- **c.** Pediatric age group
- **d.** Pregnancy
- **e.** HIV infection

Answer: c. Portal hypertension does not predispose to hemorrhoids, except in children. Bleeding in adults is likely from rectal varices. Most hemorrhoidal bleeding is from the superior rectal artery and thus is bright red. Approximately one-third of pregnant patients experience hemorrhoids in the third trimester or postpartum period. Traumatic deliveries can result in hemorrhoid development. Painless bleeding with defecation is the most common symptom (pain usually occurs if hemorrhoids are thrombosed).

2. What is the most common cause of sudden-onset rectal pain?
- **a.** Anal fissure
- **b.** Proctalgia fugax
- **c.** Sacral radiculopathy
- **d.** Thrombosed external hemorrhoid
- **e.** Thrombosed internal hemorrhoid

Answer: a. Anal fissures typically result from superficial tears in the anoderm, usually occurring in the posterior midline. The pain is heightened by secondary spasm of the anal sphincter.

3. Which of the following approaches to performing incision and drainage of a pilonidal cyst is most appropriate?
- **a.** Elliptic incision
- **b.** Horizontal incision at the center of the affected area
- **c.** Horizontal incision at the lower portion of the affected area
- **d.** Longitudinal incision along the midline
- **e.** Longitudinal incision lateral to the midline

Answer: e. Making a longitudinal incision lateral to the midline spares the area that is most vulnerable to reaccumulation of debris and the inflammatory response. Removal of pus, inflammatory tissue, and ingrown hairs relieves the pain of the abscess and promotes healing.

4. A 68-year-old woman presents with hemorrhoids. On examination, you note three protruding masses that are maroon in color and may be reduced manually into the anorectal opening. What is the most appropriate curative therapy?
- **a.** Application of a concentrated sucrose solution to the affected area
- **b.** Emergent surgical intervention (e.g., banding, sclerosing, hemorrhoidectomy)
- **c.** Prescription of a 7-day course of topical corticosteroid cream
- **d.** Referral to a surgeon for an outpatient procedure
- **e.** Removal of the hemorrhoid with an elliptic incision, including overlying tissue

Answer: d. Third-degree internal hemorrhoids may be manually reduced in the emergency department (ED) but are unlikely to heal spontaneously. Referral for operative therapy is curative. Excision of internal hemorrhoids is contraindicated. Acutely thrombosed external hemorrhoids may be excised in the ED. Temporizing measures include using the WASH regimen—using *w*arm water to encourage reduction of the protruded hemorrhoids, maintaining hygiene, *a*nalgesics, *s*tool softeners to ease passage of stool, and a *h*igh-fiber diet. Topical corticosteroids may be used for 1 or 2 days during an acute exacerbation, but their continued use promotes skin breakdown and itching. A sucrose solution may prove helpful in reducing procidentia (rectal prolapse). A thorough history should be obtained and a physical examination performed to learn if an underlying medical condition may be associated with the hemorrhoids.

83

Renal Failure

Allan B. Wolfson

KEY CONCEPTS

- The causes of acute kidney injury (AKI) can be classified as prerenal, postrenal, and intrinsic renal disorders. Abrupt cessation of glomerular filtration typically results in a rise of the serum creatinine level of 1 to 2 mg/dL per day.
- Management of AKI is directed first at potentially lethal complications such as hyperkalemia or volume overload and then at reversal of the underlying cause of renal dysfunction. It is important to avoid any further hemodynamic or toxic insults to the kidneys.
- Patients with acute or chronic kidney disease have a limited ability to handle fluid and solute loads and have altered metabolism of many drugs. Therefore, the patient's impaired renal function must be considered when fluid is administered or drugs are prescribed.
- The most rapidly lethal complication of acute and chronic kidney disease is hyperkalemia.
- The most common problems with vascular access devices used for hemodialysis are thrombosis, hemorrhage, and infection. Access infection often presents as fever without an obvious source and, if suspected, appropriate IV antibiotics should be administered presumptively while awaiting blood culture results.
- Peritoneal dialysis–associated peritonitis typically presents with cloudiness of the peritoneal dialysis effluent. The diagnosis is made by a positive Gram stain or finding of more than 100 WBC/mm^3 in the effluent, with at least 50% polys. It is generally treated on an outpatient basis with intraperitoneal antibiotics self-administered by the patient.
- Chest pain in the dialysis patient should be presumed initially to be due to acute coronary syndrome, although other potentially serious causes may also be responsible. Serum troponin levels tend to be elevated in patients with poor renal function, but patients with myocardial infarction show the typical temporal pattern of rise and fall of troponin levels.
- Hypotension in patients with chronic kidney disease (CKD) may be caused by infection but may also be the result of rapid fluid removal during dialysis. This often responds readily to fluid administration. Pericardial tamponade is another cause of hypotension that should be considered for these patients.
- Altered mental status is most commonly due to causes similar to those seen in patients without renal disease but is sometimes the result of overrapid shifts in intravascular fluid and solutes during dialysis, termed *disequilibrium syndrome.*

RENAL FAILURE

The evaluation of renal disease in the emergency department (ED) requires an approach that incorporates the urinalysis, serum and urine chemical determinations, and renal imaging studies. This approach assesses the degree of renal dysfunction and establishes the foundation for distinguishing acute kidney injury (AKI) from chronic kidney disease (CKD).

ACUTE KIDNEY INJURY

Foundations

The hallmark of AKI (formerly termed *acute renal failure* [ARF]) is progressive azotemia, which commonly is accompanied by a wide range of other disturbances, depending on the severity and duration of renal dysfunction. These include metabolic derangements (e.g., metabolic acidosis, hyperkalemia), disturbances of body fluid balance (particularly volume overload), and a variety of effects on almost every organ system (Box 83.1).

The causes of AKI are divided into those that decrease renal blood flow (prerenal), produce a renal parenchymal insult (intrarenal), or obstruct urine flow (obstructive, or postrenal). Identification of a prerenal or postrenal cause of AKI generally makes it possible to initiate specific corrective therapy; if these two broad categories of AKI can be excluded, an intrarenal cause is implicated. The renal parenchymal causes of AKI can be usefully subdivided into those primarily affecting the glomeruli, intrarenal vasculature, or renal interstitium. The term *acute tubular necrosis* denotes another broad category of intrinsic renal failure that cannot be attributed to a specific glomerular, vascular, or interstitial cause (Fig. 83.1).

Renal failure can lead to numerous other systemic and organ-specific effects. Uremia impairs host defenses, particularly leukocyte function, and infection is a significant cause of morbidity and mortality in AKI. Pericarditis, which has a prevalence of 10% to 20% in dialyzed patients with CKD, also may occur in patients with AKI. Urgent dialysis is indicated when there is associated pericardial effusion and tamponade. Neurologic abnormalities in AKI may be precipitated by electrolyte abnormalities, medications, or uremia. Anorexia, nausea, vomiting, gastritis, and pancreatitis also are associated with AKI and significant gastrointestinal (GI) hemorrhage is seen in about 10% of patients.

Impaired erythropoiesis, shortened red blood cell (RBC) survival, hemolysis, hemodilution, and GI blood loss all play a role in the normocytic normochromic anemia that usually accompanies AKI. Although mild thrombocytopenia may be present, it is the qualitative defect in platelet function thought to be caused by the effect of circulating uremic toxins that contributes to these patients' bleeding tendencies.

Clinical Features

When the presence of azotemia or renal failure has been discovered, the first consideration in the ED evaluation should be the possibility of potentially life-threatening complications (e.g., hyperkalemia, pulmonary edema). Assuming that these have been satisfactorily ruled out, the next step is to determine whether the condition represents AKI or is the result of preexisting renal disease. The clinical distinction between AKI and CKD often is difficult, especially if prior records and laboratory results are not available. The finding of small kidneys on abdominal imaging or bone changes of secondary hyperparathyroidism on hand films demonstrating abnormal calcifications suggests that the renal failure is chronic. Anemia, hypocalcemia, and hyperphosphatemia, however, should not be relied on to identify patients who have CKD because these abnormalities can develop rapidly in AKI.

In evaluating the patient with azotemia, the emergency clinician uses history, physical examination, and laboratory studies to seek clues to the cause and to identify signs and symptoms of uremia, volume overload, or other complications of renal failure. In attempting to identify the cause, the general strategy is to rule out prerenal and postrenal causes before considering the many intrinsic renal causes. First, potential sources of volume loss and causes of decreased cardiac output are sought in the history, and the patient should be questioned about lightheadedness, bleeding, GI fluid loss, abnormal polyuria, or symptoms of congestive heart failure (CHF). In men, a history of nocturia, frequency, hesitancy, or decreased urinary stream suggests prostatic obstruction. A history of lower tract symptoms or of abdominal or pelvic tumor in either gender is sought, as is a history of kidney stones or chronic urinary tract infection (UTI). A history of acute anuria, defined as the production of less than 100 mL of urine/day, is most often the result of high-grade urinary tract obstruction, although it also may accompany severe volume depletion, severe acute glomerulonephritis, cortical necrosis, or bilateral renal vascular occlusion. Intermittent anuria, on the other hand, is characteristic of obstructive disease. Medication use and possible exposure to radiographic contrast agents or other exogenous toxins are other key components of the history. A history of hypertension, dark-colored urine, rash, fever, or arthritis suggests intrinsic renal disease or a multisystem disorder.

The physical examination focuses on signs of volume depletion, such as tachycardia and decreased skin turgor. Documented short-term changes in body weight also offer a valuable clue in assessing volume status, particularly in patients who are chronically ill. Volume overload

BOX 83.1 Clinical Features of Acute Kidney Injury

Cardiovascular
Pulmonary edema
Arrhythmia
Hypertension
Pericarditis
Pericardial effusion
Myocardial infarction
Pulmonary embolism

Metabolic
Hyponatremia
Hyperkalemia
Acidosis
Hypocalcemia
Hyperphosphatemia
Hypermagnesemia
Hyperuricemia

Neurologic
Asterixis
Neuromuscular irritability
Mental status changes
Somnolence
Coma
Seizures

Gastrointestinal
Nausea
Vomiting
Gastritis
Gastroduodenal ulcer
Gastrointestinal bleeding
Pancreatitis
Malnutrition

Hematologic
Anemia
Hemorrhagic diathesis

Infectious
Pneumonia
Septicemia
Urinary tract infection
Wound infection

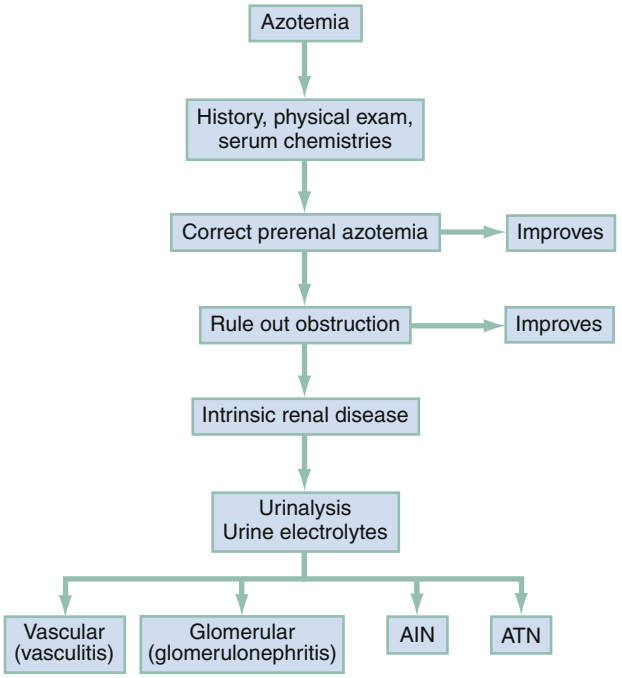

Fig. 83.1 Evaluation of azotemia. *AIN,* Acute interstitial nephritis; *ATN,* acute tubular necrosis.

is suggested by findings of jugular vein distention and the presence of rales or peripheral edema.

A distended bladder is percussible when it contains at least 150 mL of urine, and the dome is palpable abdominally when the bladder contains 500 mL. Ultrasonography can be used to detect bladder distention or postvoid residual volume if there is a question of urinary retention. A prostate examination in men and pelvic examination in women are also necessary components of the examination. The presence of rash, purpura, pallor, or petechiae on skin examination may be noted, as is arthritis, musculoskeletal tenderness, and findings suggestive of infection or malignancy.

Differential Diagnosis

The management of AKI requires a systematic approach to the potential underlying causes. Once prerenal and postrenal causes are considered, the diagnostic and management strategies focus on the intrarenal pathologies.

Prerenal Azotemia

Decreased renal perfusion that is sufficient to cause a decrease in the glomerular filtration rate (GFR) results in azotemia. The possible causes are grouped into entities causing intravascular volume depletion, volume redistribution, or decreased cardiac output (Box 83.2). Patients who have preexisting renal disease are particularly sensitive to the effects of diminished renal perfusion.

Prerenal azotemia is characterized by increased urine specific gravity, a blood urea nitrogen (BUN) to creatinine ratio generally between 10:1 and 20:1, urine sodium concentration less than 20 mEq/dL, and fractional excretion of sodium (FENa) less than 1%. The condition generally can be corrected readily by expanding extracellular fluid volume, augmenting cardiac output, or discontinuing vasodilating antihypertensive drugs. However, severe prolonged prerenal azotemia can result in acute tubular necrosis (ATN).

BOX 83.2 Causes of Prerenal Azotemia

Volume Loss
Gastrointestinal—vomiting, diarrhea, nasogastric drainage
Renal—diuresis
Blood loss
Insensible losses
Third-space sequestration
Pancreatitis
Peritonitis
Trauma
Burns

Cardiac Causes
Myocardial infarction
Valvular disease
Cardiomyopathy
Decreased effective arterial volume
Antihypertensive medication
Nitrates

Neurogenic Causes
Sepsis
Anaphylaxis
Hypoalbuminemia
Nephrotic syndrome
Liver disease

Patients who have CHF or cirrhosis form an important subset of those with prerenal azotemia. These patients often are sodium-overloaded and water-overloaded, yet the effective intra-arterial volume is decreased. Administration of diuretics has the potential to decrease intravascular volume further, resulting in decreased glomerular filtration and prerenal azotemia. For some patients with advanced CHF or hepatic disease, a state of chronic, stable, prerenal azotemia may be the best achievable compromise between symptomatic volume overload and severe renal hypoperfusion.

Glomerular perfusion also may be decreased in patients with normal intravascular volume and normal renal blood flow who take angiotensin-converting enzyme (ACE) inhibitors or, more commonly, prostaglandin inhibitors. All nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, inhibit prostaglandin synthesis. Renal vasodilator prostaglandins are critical in maintaining glomerular perfusion in patients with conditions such as CHF, chronic renal insufficiency, and cirrhosis, in which elevated circulating levels of renin and angiotensin II decrease renal blood flow and GFR. In this setting, a decrease in the production of vasodilator prostaglandins may result in acute intrarenal hemodynamic changes and a reversible decrease in renal function. This phenomenon also is seen with the selective cyclooxygenase-2 inhibitor class of NSAIDs. Other risk factors include advanced age, diuretic use, renovascular disease, and diabetes. This entity is distinct from other renal complications of NSAIDs such as interstitial nephritis and papillary necrosis.

Postrenal (Obstructive) Acute Kidney Injury

Obstruction is an eminently reversible cause of AKI and should be considered in every patient with newly discovered azotemia or worsening renal function. Obstruction may occur at any level of the urinary tract but usually is caused by prostatic hypertrophy or functional bladder neck obstruction (e.g., secondary to medication side effects or neurogenic bladder; Box 83.3). Intrarenal obstruction may result from the intratubular precipitation of uric acid crystals (e.g., with tumor lysis), oxalic acid (as in ethylene glycol ingestion), phosphates, myeloma proteins, methotrexate, sulfadiazine, acyclovir, or indinavir. Bilateral ureteral obstruction (or obstruction of the ureter of a solitary kidney) may be caused by retroperitoneal fibrosis, tumor, surgical complications (such as inadvertent ligation of the ureter), stones, or

BOX 83.3 Causes of Postrenal Renal Failure

Intrarenal and Ureteral Causes
Kidney stones
Sloughed papillas
Bilateral ureteral compression related to malignancy or benign gynecologic causes
Retroperitoneal fibrosis
Uric acid, oxalic acid, or phosphate crystal precipitation
Sulfonamide, methotrexate, acyclovir, or indinavir precipitation

Bladder
Kidney stone
Blood clot
Prostatic hypertrophy
Bladder carcinoma
Neurogenic bladder

Urethra
Phimosis
Stricture

blood clots. A sudden deterioration in renal function in the setting of diabetes mellitus, analgesic nephropathy, or sickle cell disease suggests papillary necrosis.

Intrinsic Acute Kidney Injury

Of the specific intrarenal disorders that cause AKI, glomerulonephritis, interstitial nephritis, and abnormalities of the intrarenal vasculature are amenable to specific therapy and are important to consider as possible causes. These entities are responsible for only 5% to 10% of cases of AKI in adult inpatients; most cases are caused by ATN. In adults in whom AKI develops outside the hospital, the incidence of glomerular, interstitial, and small vessel disease is much greater. In children, these entities account for approximately 50% of the cases of AKI (Box 83.4).

Acute Glomerulonephritis. This may represent a primary renal process or may be the manifestation of any of a wide range of other disease entities (see Box 83.4). Patients may have dark urine, hypertension, edema, or CHF (secondary to volume overload) or may be completely asymptomatic, in which case the diagnosis rests on an incidental finding on urinalysis. The hematuria associated with glomerular disease may be microscopic or gross and may be persistent or intermittent. Proteinuria, although often in the range of 500 mg/day to 3 g/day, is not uncommonly in the nephrotic range, defined as 3.5 g/day or more. The presence of hematuria, proteinuria, or red cell casts is highly suggestive of glomerulonephritis. Conversely, the absence of red cell casts, proteinuria, and hematuria essentially excludes glomerulonephritis as the cause of AKI.

The specific diagnosis of acute glomerulonephritis caused by primary renal disease often is ultimately made by renal biopsy. However, when glomerulonephritis is secondary to a systemic disease such as systemic lupus erythematosus, the clinical signs and symptoms and results of laboratory assessment aid considerably in narrowing the scope of the differential diagnosis. As a rule, extensive laboratory testing to identify the cause of acute glomerulonephritis is not indicated in the ED setting and is more appropriately performed as part of an inpatient evaluation.

Acute Interstitial Nephritis. Acute interstitial nephritis (AIN) is usually precipitated by drug exposure or by infection. Drug-induced AIN is poorly understood, but the absence of a clear relationship to the dose, and recurrence of the syndrome on rechallenge with the offending agent, suggests that an immunologic mechanism is responsible. The most commonly incriminated drugs are the penicillins, diuretics, and NSAIDs. AIN has been reported in association with bacterial, fungal, protozoan, and rickettsial infections.

Patients with AIN typically have rash, fever, eosinophilia, and eosinophiluria, but it is common for one or more of these cardinal signs to be absent. Pyuria, gross or microscopic hematuria, and mild proteinuria are observed in some cases. A definite diagnosis sometimes can be made only on renal biopsy. Treatment of AIN is directed at removing the presumed cause; infections should be treated and offending drugs discontinued. Renal function generally returns to baseline over several weeks, although chronic renal failure has been reported to occur.

Intrarenal Vascular Disease of the Kidney. This can be classified according to the size of the vessel that is affected. Disorders such as renal arterial thrombosis or embolism, which affect large blood vessels, must be bilateral—or affect a single functioning kidney—to produce AKI. Whether to attribute such cases of AKI to a prerenal or intrarenal vascular cause is a matter of semantics. The most common cause of thrombosis probably is trauma; thrombosis also may occur after angiography or may be secondary to aortic or renal arterial dissection. Renal atheroembolism is thought to occur commonly, at least on a microscopic level, after arteriography but it is an uncommon cause of AKI. Similarly, patients with chronic atrial fibrillation or infective endocarditis may experience embolization of the kidney but rarely develop AKI as a result. Renal arterial embolism can

BOX 83.4 Intrinsic Renal Diseases That Cause Acute Kidney Injury

Vascular Diseases

Large-Vessel Diseases

Renal artery thrombosis or stenosis
Renal vein thrombosis
Atheroembolic disease

Small- and Medium-Sized Vessel Diseases

Scleroderma
Malignant hypertension
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
HIV-associated microangiopathy

Glomerular Diseases

Systemic Diseases

Systemic lupus erythematosus
Infective endocarditis
Systemic vasculitis (e.g., periarteritis nodosa, Wegener granulomatosis)
Henoch-Schönlein purpura
HIV-associated nephropathy
Essential mixed cryoglobulinemia
Goodpasture syndrome

Primary Renal Diseases

Poststreptococcal glomerulonephritis
Other postinfectious glomerulonephritis
Rapidly progressive glomerulonephritis

Tubulointerstitial Diseases and Conditions

Drugs (many)
Toxins (e.g., heavy metals, ethylene glycol)
Infections
Multiple myeloma

Acute Tubular Necrosis

Ischemia

Shock
Sepsis
Severe prerenal azotemia

Nephrotoxins

Antibiotics
Radiographic contrast agents
Myoglobinuria
Hemoglobinuria

Other Diseases and Conditions

Severe liver disease
Allergic reactions
NSAIDs

HIV, Human immunodeficiency virus; *NSAIDs*, nonsteroidal antiinflammatory drugs.

cause acute renal infarction, generally manifested by sudden flank, back, chest, or upper abdominal pain. Urinary findings, including hematuria, are variable. The diagnosis usually is made by renal flow scanning or arteriography.

Several diseases that affect the smaller intrarenal vessels can cause AKI (see Box 83.4). Patients whose disease is severe enough to cause AKI also are generally found to have hypertension, microangiopathic hemolytic anemia, and other systemic and organ-specific manifestations. Infection with *Escherichia coli* O157:H7 has emerged as a major cause of hemolytic uremic syndrome, an important cause of AKI in children.

Patients with scleroderma (systemic sclerosis) may have so-called scleroderma renal crisis, characterized by malignant hypertension and rapidly progressive renal failure. Whereas vasculitis associated with glomerular capillary inflammation typically causes gross or microscopic hematuria and the formation of red cell casts, vascular involvement of the medium-sized vessels, such as that produced by scleroderma, often spares the preglomerular vessels and tends not to produce an active urine sediment. Extrarenal manifestations (e.g., rash, fever, arthritis, pulmonary symptoms) are usually evident.

For malignant hypertension, both as a separate entity and as a part of scleroderma renal crisis, appropriate treatment can produce remission of AKI. Patients with malignant hypertension have been reported to recover renal function after aggressive antihypertensive therapy, with temporary maintenance on dialysis if necessary. In patients with scleroderma renal crisis, specific therapy with ACE inhibitors has been shown to result in improvement in renal function in a significant proportion of cases.

Acute Tubular Necrosis. ATN refers to a generally reversible deterioration of kidney function associated with a variety of renal insults. Oliguria may or may not be a feature. The diagnosis is made after prerenal and postrenal causes of ARF and disorders of glomeruli, interstitium, and intrarenal vasculature have been excluded. In a few disorders, these discrete categories overlap. For example, AKI associated with multiple myeloma or ethylene glycol toxicity is associated with intrarenal obstruction and interstitial disease, as well as a probable direct toxic effect on the renal tubule itself.

The most common precipitant of ATN is renal ischemia occurring during surgery or after trauma and sepsis. The remainder of cases occur in the setting of medical illness, usually as a result of the administration of a nephrotoxic aminoglycoside antibiotic or in association with rhabdomyolysis. Multiple causes can be identified in some cases; in others, a definitive cause cannot be established.

Decreased renal perfusion results in a continuum of renal dysfunction that ranges from transient prerenal azotemia at one extreme to ATN at the other. Early during the period of renal ischemia, renal function can be restored completely by restoring renal blood flow but, at some point, continued hypoperfusion results in renal dysfunction unresponsive to volume repletion, and ATN supervenes. ATN may occur in the absence of frank hypotension; even modest renal ischemia may result in ATN in susceptible persons. Individual susceptibility to ATN may be related to the balance of prostaglandin-mediated vasopressor and vasodilatory influences on the renal vasculature.

Postischemic ATN can occur in the setting of volume loss from the GI tract (upper or lower), skin, or kidneys or can result from severe hemorrhage or major burns. Heat stroke commonly is associated with the development of ATN, which is thought to result from a combination of volume loss, hyperpyrexia, and rhabdomyolysis. Another cause of ATN is hyperglycemic hyperosmolar syndrome, which can be associated with loss of as much as 25% of total body water. ATN also is seen in the setting of cardiogenic shock, sepsis, and third spacing of fluids in pancreatitis and peritonitis.

ATN is common in postoperative patients, although not all cases can be attributed to intraoperative hypotension or hemorrhage. Concomitant sepsis, increased age, preexisting renal disease, and other comorbid conditions are associated with a worse outcome.

Recently, it has been noted that patients hospitalized for coronavirus disease 2019 (COVID-19) may develop AKI during the course of their illness, particularly when intensive care is required. The mechanism is likely to be multifactorial, including hypovolemia, cardiac dysfunction, exposure to nephrotoxins, and direct renal endothelial damage related to viremia, immune dysfunction, or hypercoagulability. Patients may initially present with proteinuria early in the course; AKI is felt to be a marker of the severity of disease. Treatment is supportive, with careful management of fluid balance and optimization of renal perfusion. More severe cases require hemodialysis or other forms of renal replacement therapy.[14]

Nephrotoxins constitute the other major cause of ATN. Among the most prominent of these are the endogenous pigments myoglobin and hemoglobin, associated with rhabdomyolysis (Box 83.5). Hypotension secondary to fluid loss into damaged muscle is thought to worsen the effects of myoglobinuria on the renal tubule, as does acidemia. Hemolysis, resulting in the release of hemoglobin into the circulation and hemoglobinuria, can cause ATN but usually only in the presence of coexisting dehydration, acidosis, or other causes of decreased renal perfusion. ATN may be associated with the hemolysis of as little as 100 mL of blood.

ATN associated with rhabdomyolysis is often oliguric; it is characterized by rapid increases in the serum creatinine, potassium, phosphorus, and uric acid levels. Creatine released from muscle is metabolized to creatinine, which may result in serum creatinine level increases of more than 2 mg/dL/day, in contrast to the increase of 0.5 to 1.0 mg/dL/day typically seen in other forms of AKI. The BUN/creatinine ratio often is *less* than 10 : 1. Intracellular potassium released from damaged muscle may raise the serum potassium level by 1 to 2 mEq/L in several hours. Likewise, phosphate released from muscle may cause dramatic increases in the serum phosphate level. Uric acid, produced by the metabolism of purines released from damaged muscle, may accumulate to levels high enough to cause acute uric acid nephropathy.

BOX 83.5 Causes of Pigment-Induced Acute Kidney Injury

- Rhabdomyolysis and myoglobinuria
  - Crush injury
  - Compartment syndrome
  - Electrical injury
  - Myonecrosis from coma or immobilization
  - Acute arterial occlusion
  - Vigorous exertion
  - Status epilepticus
  - Hyperthermia/heat stress
  - Metabolic myopathy
  - Drugs/toxins
  - Hypokalemia
  - Hypophosphatemia
- Hemoglobinuria
  - Acute hemolysis
  - Transfusion reaction
  - Drugs/toxins
  - Infections

G6PD, Glucose-6-phosphate dehydrogenase; *RBCs*, red blood cells.

Urine dipstick testing yields a positive result for heme in, at most, 50% of patients with rhabdomyolysis, because myoglobin is rapidly cleared from the serum and may therefore be undetectable in the urine at the time of presentation. Thus, a negative result on urine dipstick testing does not rule out the diagnosis. Serum creatine kinase (CK) is cleared much more slowly, so measurement of serum CK levels is a more sensitive test.

Antibiotics are commonly implicated in the development of ATN, with aminoglycosides being the most commonly associated. Higher doses and longer duration of therapy are associated with higher serum drug levels, leading to greater accumulation of drug in the renal parenchyma and a greater likelihood of nephrotoxicity. Increased age, impaired renal function, dehydration, and exposure to other nephrotoxins are additional risk factors. Once-daily administration of a somewhat higher dose is associated with less nephrotoxicity but has equal antimicrobial effectiveness.

Aminoglycoside-induced ATN typically has a gradual onset. Clinically significant renal dysfunction usually occurs only after several days and often after more than 1 week of therapy. However, renal failure can develop as late as 10 days after a drug has been discontinued, an observation that appears to be explained by the prolonged tissue half-life characteristic of these agents. Renal function returns to normal after an average of 6 weeks, but the condition occasionally progresses to permanent renal injury.

Radiographic contrast agents have long been considered a common cause of hospital-acquired renal insufficiency. AKI associated with these agents has been defined as an increase in serum creatinine level of 25% or an increase of 0.5 mg/dL over baseline, with a temporal relation to contrast medium administration and in the absence of other identifiable causes. Cases have been noted after any procedure involving intravascular administration of contrast material.

Radiocontrast-associated AKI presents on a spectrum ranging from asymptomatic nonoliguric renal insufficiency to severe renal failure requiring dialysis. Most cases are mild, however, likely due at least partially to the broad criteria by which the entity has been defined.[1-3] Typically, an increase in the serum creatinine level is noted within 3 days of exposure, with a return to normal levels within 10 to 14 days.

The most important risk factor for radiocontrast agent–induced AKI is preexisting renal insufficiency. Diabetes mellitus, multiple myeloma, age older than 60 years, and volume depletion are also associated with greater risk. Diabetic patients with a serum creatinine level less than 1.5 mg/dL appear to be at lower risk than those whose serum creatinine level is more than 1.5 mg/dL. Importantly, large doses and repeated doses of contrast material are associated with increased risk of ATN, particularly if a second study is performed within 72 hours of the first.

Volume depletion is an independent risk factor for contrast nephropathy, and aggressive volume expansion before contrast exposure appears to have a protective effect.[4] Modest volumes of intravenous normal saline (3 mL/kg over 1 hour, followed by 1.5 mL/kg/hr for 4 hours after contrast exposure) appear to be effective in decreasing the likelihood of nephrotoxicity. Sodium bicarbonate does not appear to offer an advantage over normal saline, and the weight of evidence does not favor a beneficial effect of administering oral *N*-acetylcysteine as part of the treatment regimen.[5]

Diagnostic Testing

Laboratory evaluation of renal dysfunction begins with a dipstick and microscopic urinalysis and measurement of urine output. BUN, serum creatinine, urine sodium, and FENa levels are determined to help evaluate renal function and provide clues about the cause of AKI. A complete blood count, serum electrolyte panel (expanded to include calcium, phosphorus, and magnesium determinations), electrocardiogram (ECG), and chest radiograph help establish the patient's baseline status and provide information about possible complications.

Urine Volume

Urine flow does not diminish until the GFR is sharply decreased; thus, urine volume is a poor indicator of renal dysfunction. Oliguria, defined as a urine volume of 100 to 400 mL/24 hr, may be seen with prerenal (blood flow–dependent), intrinsic (intrarenal), or postrenal (obstructive) causes of AKI. Although uncommon, alternating oliguria and anuria (the latter defined as less than 100 mL/24 hr), is a classic indicator of intermittent obstruction, which occurs as urine collects behind an obstructing stone or tumor and then is allowed to flow past as the obstructing material shifts position.

Urinalysis

The standard urinalysis consists of dipstick screening for heme pigment, protein, glucose, ketones, pH, leukocyte esterase, and nitrite and microscopic examination of a spun specimen of freshly voided urine and should be performed on all patients with AKI. Dipstick testing for heme and protein can provide important information related to renal function.

Heme. The dipstick detects free hemoglobin from lysed RBCs (or myoglobin) and the hemoglobin inside RBCs but is more sensitive to free hemoglobin. Although as few as three RBCs/high-power field (hpf) can be detected, on any given sample the dipstick may fail to identify 10% to 15% of patients who are otherwise found to have microscopic hematuria, typically defined as more than three RBCs/hpf. A positive result on dipstick testing should prompt microscopic examination of the urine. If red cells are seen, the diagnosis of hematuria is confirmed, though a level of two to three RBCs/hpf is commonly accepted as normal. If the dipstick result is positive but findings on microscopic examination are negative, pigmenturia (myoglobin or free hemoglobin) is suspected.

Protein. The dipstick test for protein, which uses the color change of tetrabromophenol blue, can detect protein at concentrations of 10 to 15 mg/dL but does not yield reliably positive results until the concentration is greater than 30 mg/dL. Moreover, the relation between color intensity and protein concentration is only approximate. The dipstick reagent is three to five times more sensitive to albumin than to globulins and immunoglobulin light chains (e.g., Bence Jones protein), an important limitation. False-positive results are caused by alkaline urine, hematuria, or prolonged immersion of the dipstick in the urine. False-negative results are seen with dilute urine. After dipstick testing has been completed, the sediment from a spun urine specimen is examined under the microscope.

Casts are formed from urinary Tamm-Horsfall protein—a product of the tubular epithelial cells that gels at low pH and high concentration and when mixed with albumin—or from red cells, tubular cells, or cellular debris in the urine. The composition of a cast reflects the contents of the tubule. Casts are classified according to their appearance or constituents (e.g., hyaline, red cell, white cell, granular, or fatty casts). Hyaline casts, those that are devoid of contents, are seen with dehydration, after exercise, or in association with glomerular proteinuria. Red cell casts indicate glomerular hematuria, as seen in glomerulonephritis; the presence of even a few red cell casts is significant. White cell casts imply the presence of renal parenchymal inflammation. Granular casts are composed of cellular remnants and debris. Fatty casts, like oval fat bodies, generally are associated with heavy proteinuria and nephrotic syndrome.

Microscopic examination of the urinary sediment can be helpful in establishing the cause of AKI. A sediment without formed elements

or with only hyaline casts is characteristic of prerenal azotemia or obstruction. Red cell casts suggest glomerulonephritis or vasculitis. Fatty casts also suggest glomerular disease. In ATN, the urinary sediment commonly shows granular casts and renal tubular epithelial cells. Large numbers of polymorphonuclear leukocytes are observed in interstitial nephritis, papillary necrosis, and pyelonephritis. Eosinophil-containing casts, appreciated only after staining of the sediment, are typical of allergic interstitial nephritis. Uric acid crystals suggest uric acid nephropathy but are extremely nonspecific; oxalic acid or hippuric acid crystals may be seen in cases of ethylene glycol ingestion.

Serum and Urine Chemical Analysis

Creatinine and Blood Urea Nitrogen. The normal range for the serum creatinine level extends from 0.5 mg/dL in thin people to 1.5 mg/dL in muscular persons. Spurious elevations (up to 2 mg/dL) can be caused by acetoacetate, which cross-reacts with creatinine in some commonly used assays, and by certain medications (such as trimethoprim and cimetidine) that reversibly inhibit tubular creatinine secretion, causing a modest elevation of the serum creatinine despite a normal GFR. Serum creatinine concentration is a function of the amount of creatinine entering the blood from muscle, its volume of distribution, and its rate of excretion. Because the first two are usually constant, changes in the serum creatinine concentration generally reflect changes in GFR. The creatinine clearance is commonly estimated by the Cockcroft-Gault equation:

$$\text{Creatinine clearance (mL/min)} = ([140 - \text{age}] \times \text{weight}) / (72 \times \text{serum creatinine}) \quad (\times 0.85 \text{ if female})$$

Under steady-state conditions, if the GFR is halved, the serum creatinine doubles. Abrupt cessation of glomerular filtration causes the serum creatinine level to rise by 1 to 2 mg/dL per day. Thus, a daily increment of less than 1 mg/dL suggests that at least some renal function has been preserved. Rhabdomyolysis releases creatine into the plasma and may cause the serum creatinine level to increase by more than 2 mg/dL per day. The BUN level also rises with renal dysfunction but is also influenced by many extrarenal factors. Increased protein intake, GI bleeding, and the catabolic effects of fever, trauma, infection, and drugs such as tetracycline and corticosteroids all increase protein turnover and result in increased hepatic urea production and increased BUN levels. Conversely, the BUN level tends to be decreased in patients with liver failure or protein malnutrition.

When glomerular filtrate has been formed, renal urea clearance is largely a function of flow rate. Urea clearance is thus decreased in patients with prerenal azotemia or acute obstruction, despite preservation of tubular function. In such cases, the BUN/creatinine ratio usually is greater than the normal value of 10:1, whereas this ratio usually is not markedly increased in cases of uncomplicated intrinsic AKI.

Urine Sodium and Fractional Excretion of Sodium. Normally, urine sodium concentration parallels sodium intake. A low urine sodium concentration thus indicates not only intact tubular reabsorptive function but also the presence of a stimulus to conserve sodium. The urine sodium concentration, as well as the FENa, an additional measure of tubular sodium handling, helps distinguish between the two most common causes of AKI, prerenal azotemia and ATN.

Measurement of urinary indices can be helpful in oliguric patients. An oliguric patient with a urine sodium concentration less than 20 mEq/L and FENa less than 1% is likely to have prerenal azotemia, whereas a urine sodium concentration more than 40 mEq/L and FENa more than 1% suggest ATN. Values in patients with prerenal azotemia overlap somewhat with those in patients with nonoliguric ATN, particularly if the renal injury is mild and some capability to retain sodium has been preserved. Thus, intermediate values for urine sodium concentration and FENa are of little help in differentiating between the two conditions. The administration of mannitol or a loop diuretic within the several hours preceding urine collection also may make interpretation of urine values difficult because the urinary sodium level will tend to be higher and the urine less concentrated, causing the results in prerenal azotemia to resemble those in intrinsic renal failure.

In glomerulonephritis, the urinary indices generally reflect intact tubular sodium handling, but the diagnosis is more accurately made by urine microscopy. In obstructive uropathy, the values of the urinary indices depend on the duration of obstruction and cannot be relied on to indicate the presence or absence of obstruction.

Renal Imaging

Renal imaging is often helpful in the evaluation of the patient with kidney dysfunction, particularly when obstruction is suspected. Computed tomography (CT) scanning provides an anatomic image of the urinary tract but does not provide an evaluation of renal function. The classic CT findings of obstruction are kidneys that are normal to large in size, and demonstration of hydronephrosis or hydroureter. Since contrast-enhanced CT subjects the kidneys of an already azotemic patient to the risk of an additional potential insult from the contrast agent, ultrasonography and noncontrast CT are much preferred for patients with preexisting renal insufficiency (Fig. 83.2).

Computed Tomography. Noncontrast CT may be useful in evaluating some azotemic patients. Hydronephrosis can be recognized without the use of contrast material. Often, dilated ureters can also be seen without contrast enhancement, and the level of obstruction can be determined. The cause of obstruction (e.g., bilateral stones, lymphoma, retroperitoneal hemorrhage, metastatic cancer, retroperitoneal fibrosis) often can also be delineated. Occasionally, bilateral ureteral obstruction produced by malignancy or retroperitoneal fibrosis may not cause detectable proximal dilation of the urinary tract. When noninvasive studies yield negative results, the diagnosis of obstruction can be made by retrograde pyelography or antegrade pyelography performed via a percutaneous nephrostomy.

Ultrasonography. Ultrasonography is a safe and reasonably reliable method for excluding obstruction as a cause of AKI. The normal kidney shows an echo-free renal parenchyma surrounding the echogenic central

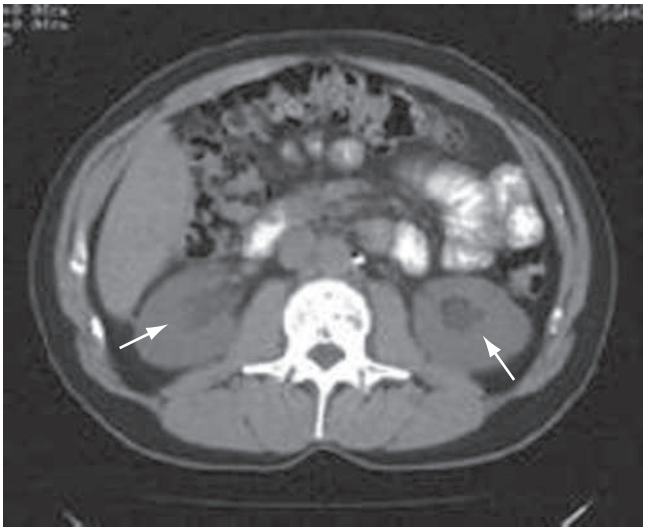

Fig. 83.2 CT scan of bilateral hydronephrotic kidneys without IV contrast medium.

urothelium of the renal pelvis and calices. The sonographic appearance of the kidney in obstruction is that of an enlarged, central, sonolucent area that spreads the normal central echo densities. A similar pattern may be produced by renal cysts, but without associated ureteral dilation. Dilation of the collecting system generally is apparent within 24 to 36 hours of the onset of obstruction, but obstruction may not be evident in patients who are evaluated early in the development of obstructive AKI.

Diagnosis

Prerenal azotemia is suspected in the setting of volume loss, volume redistribution, or decreased effective renal perfusion. It typically is associated with a normal urinalysis, high BUN/creatinine ratio, increased urine osmolality, urine sodium concentration less than 20 mEq/L, and FENa less than 1%. A rapid response to volume repletion also is characteristic.

Urethral or bladder neck obstruction is documented by the finding of significant amounts of residual urine in the bladder by catheterization or ultrasound examination after the patient has voided or attempted to void spontaneously. An important point is that the ability to void does not rule out obstruction. In fact, the urine volume in the presence of obstruction may range from zero to several liters per day. Flank pain is likewise an insensitive marker for obstruction. Urine indices and the BUN/creatinine ratio tend not to be helpful, although an increase in the latter is common in obstruction. A renal parenchymal disorder often can be diagnosed by its manifestations on microscopic urinalysis or by associated extrarenal manifestations (e.g., with multisystem disease) or clinical setting (e.g., recent exposure to a new medication). The absence of evidence of prerenal or postrenal causes in a patient with AKI may be taken as presumptive evidence of an intrarenal parenchymal process. Among these, the possibility of an acute or ongoing vascular insult should be kept in mind because timely intervention can be important in preserving ultimate renal function.

Management

ED management of AKI is directed at reversing decreases in GFR and urine output (if possible) while minimizing further hemodynamic and toxic insults, maintaining normal fluid and electrolyte balance, and managing other complications of AKI, as required. Because renal failure alters the metabolism and action of many drugs, often in ways that are not predictable, great care should be exercised in prescribing all medications. Easy access to online sources that provide guidelines for drug dosages in renal failure, and readily available consultation with a hospital pharmacist are of great help for this purpose.

After ensuring that the vital signs are adequate and the patient is in no immediate danger from volume or metabolic derangements, the next step is to correct prerenal and postrenal factors, if any are identified. Intravascular volume is repleted in hypovolemic patients and maintained in euvolemic patients by matching input to measured and insensible output. Inadequate cardiac output is augmented when possible. Postrenal or obstructive AKI is treated by restoration of normal urine outflow. Bladder outlet obstruction may be relieved by passage of a Foley catheter, whereas upper tract obstruction may require percutaneous nephrostomy.

Renal insufficiency secondary to NSAIDs generally is reversible after withdrawal of the causative agent. For patients who are at increased risk but require treatment with NSAIDs, a short-acting preparation (e.g., ibuprofen) should be prescribed and follow-up monitoring of renal function and the serum potassium level should begin within days rather than weeks. If renal function is unchanged after a short course of treatment, adverse effects from continuing therapy are unlikely, although other potential mechanisms for the development of renal dysfunction (e.g., interstitial nephritis) should be kept in mind.

Treatment of postrenal AKI consists of relief of the obstruction. In the absence of infection, full renal recovery is possible, even after 1 to 2 weeks of total obstruction, although the serum creatinine level may not return to baseline for several weeks. Because the onset of irreversible loss of renal function with obstruction appears to be gradual, a few days' delay in diagnosis generally is considered acceptable. Still, common sense dictates that obstructions should be detected and relieved promptly.

When prerenal and postrenal factors have been ruled out, the challenge is to identify the cause of intrinsic renal AKI, keeping in mind the multitude of known possible causes (see Box 83.4). The differential diagnosis can often be significantly narrowed by considering the clinical setting and physical and laboratory findings. The clinical picture is often most consistent with the broad category of ATN.

Patients who have oliguric AKI have a significantly higher mortality rate and much greater risk of complications than those who are not oliguric. The difference in prognosis may simply reflect a more severe renal insult in patients who are oliguric, however, and it is not clear that interventions aimed at converting oliguric to nonoliguric AKI have a beneficial effect on renal function or mortality. Nevertheless, because nonoliguric patients are easier to manage, an attempt to increase urine flow is warranted.

The use of loop diuretics or mannitol often is effective in increasing urine flow when intravascular volume deficits have been corrected. Furosemide has not been shown to shorten the clinical course or affect mortality. Mannitol appears to be most useful when given at the time of, or shortly after, the renal insult; the recommended adult dose is 12.5 to 25 g, intravenous (IV). If urine output does not increase, further doses may cause hyperosmolality and clinically significant intravascular volume overload in patients with impaired renal function. Dopamine also has been used in an effort to increase urine output, but it has not been proven effective.

Certain specific considerations apply to toxin-induced ATN. Pigment-induced ATN may be prevented by avoidance of hemolysis and muscle injury and correction of the factors (e.g., dehydration, acidemia) known to predispose patients with pigmenturia to the development of renal failure. When hemolysis or rhabdomyolysis has occurred, treatment is directed at eliminating the cause and preventing the development of renal failure.

Mannitol has been shown to prevent AKI in experimental models of myoglobinuria, presumably by inducing osmotic diuresis and decreasing intratubular deposition of pigment. Furosemide, on the other hand, has not consistently shown a beneficial effect. Other studies have suggested that myoglobin precipitates in an acidic urine but not in an alkaline urine. Thus, aggressive volume repletion, alkalinization, and mannitol infusion have traditionally been recommended after crush injuries to reduce the likelihood or severity of AKI. However, there is good evidence that aggressive volume resuscitation alone is equally effective. When AKI has occurred, management is similar to that for other forms of AKI, but early dialysis may be required to control rapidly developing hyperkalemia, hyperphosphatemia, and hyperuricemia.

Patients who have radiocontrast agent–induced ATN usually require only supportive therapy. A more significant aspect of ED management is identifying patients who are at risk when contrast studies are being considered. BUN and serum creatinine levels should be checked before contrast exposure in patient with risk factors, such as older age, diabetes, volume depletion, and underlying renal disease. Patients at risk should be volume-repleted (if not contraindicated) before undergoing the study, the administered dose of contrast agent should be kept as low as possible, and multiple exposures to contrast should be avoided, as should concomitant use of other nephrotoxins.[4]

In addition to general measures aimed at minimizing decreases in GFR and increasing urine output, an important component of the management of AKI is the prevention or control of systemic complications. Of particular significance in this regard are metabolic derangements (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia, metabolic acidosis) and complications of volume overload (e.g., hypertension, CHF).

Hyperkalemia and Other Metabolic Derangements

Hyperkalemia. The most common metabolic cause of death in patients with AKI results from an inability to excrete endogenous and exogenous potassium loads. In oliguric patients, the serum potassium level typically increases by 0.3 to 0.5 mEq/L per day, but greater increases occur in catabolic, septic, or traumatized patients and in the presence of acidosis or exogenous potassium loads from diet or medication. This is of particular concern in patients with rhabdomyolysis and associated AKI.

Hyperkalemia results in serious disturbances in cardiac electrophysiology that may culminate in cardiac arrest. Calcium chloride is considered the second choice agent given its irritating effect when administered parentally. Hyperkalemia is essentially asymptomatic until major manifestations of cardiotoxicity appear. Accordingly, detection of hyperkalemia is a primary consideration in these patients. Electrocardiographic changes correlate only roughly with the serum potassium level. Mild hyperkalemia (serum potassium < 6.0 mEq/L) may be cautiously observed without specific treatment while all exogenous sources of potassium are eliminated. If the serum potassium level is greater than 6.5 mEq/L, and particularly if electrocardiographic changes are present, urgent intervention is necessary.

When cardiotoxicity must be reversed immediately (e.g., when there is hemodynamic compromise), IV calcium (10 mL of 10% calcium gluconate infused over 2 minutes, repeated after 5 minutes if necessary) is the treatment of choice. Calcium directly antagonizes the membrane effects of hyperkalemia. IV insulin, given with glucose to prevent hypoglycemia, temporarily shifts potassium to the intracellular space. The safety and efficacy of β-agonists in hyperkalemic patients have been well documented; like insulin, inhaled albuterol (in a dose of 10–20 mg for adult patients; for pediatric patients, a fixed dose should be given based on patient weight [<25 kg: 2.5 mg, 25 to 50 kg: 5 mg, >50 kg: 10 mg]) causes potassium to move into cells, thereby controlling hyperkalemia for 2 hours or more. Bicarbonate appears to be less effective in shifting potassium into cells than once thought. It should be used with caution in patients with renal failure because of its potential to cause volume overload and provoke hypocalcemic tetany or seizures. Sodium polystyrene sulfonate (Kayexalate), a potassium-binding ion exchange resin, has long been administered with sorbitol to promote elimination of potassium from the body, but it is no longer considered to be effective or free of adverse effects.[6] More recently, other nonabsorbable cation exchangers such as patiromer and sodium zirconium cyclosilicate have been used to control hyperkalemia in patients with renal failure, but they have not been evaluated in patients who present with acute hyperkalemia.[7]

Hypocalcemia. Hypocalcemia is a common feature of AKI that can develop rapidly after its onset. Vitamin D–dependent intestinal absorption of calcium is decreased in AKI because of decreased renal synthesis of 1,25-dihydroxyvitamin D. Another factor promoting hypocalcemia is the complexing of calcium with retained phosphate. Rhabdomyolysis-associated AKI, in particular, is often associated with the deposition of complexed calcium in muscle and other tissues. Asymptomatic hypocalcemia requires no immediate treatment, but subtle or frank tetany should be treated with IV calcium (10–20 mL of 10% calcium gluconate infused over several minutes).

Hyperphosphatemia. Hyperphosphatemia resulting from decreased renal elimination of phosphate is another common feature. The serum phosphorus level usually ranges from 6 to 8 mg/dL but may be much higher with rhabdomyolysis or in catabolic states. A calcium-phosphate product greater than 70 mg^2/dL^2 may result in metastatic soft tissue calcification. Hyperphosphatemia often is treated with oral calcium-based antacids that bind ingested phosphate in the gut.

Acids produced in normal metabolic processes accumulate in AKI and are buffered in part by serum bicarbonate, resulting in a decrease in the serum bicarbonate level and a high anion gap metabolic acidosis. Compensatory hyperventilation may be mistakenly attributed to primary cardiac failure or volume overload. The metabolic acidosis associated with AKI usually is mild, and treatment generally is not necessary if the serum bicarbonate level is greater than 10 mEq/L. Overzealous correction may result in hypokalemia, hypocalcemia, or volume overload.

Hypermagnesemia. This may complicate AKI when patients are given magnesium-containing antacids or laxatives. Thus, these products, as well as magnesium itself (e.g., when given for preeclampsia or for treatment of arrhythmia or wheezing), should be avoided in the setting of AKI.

Disturbances of Volume Regulation. These can be expected to occur in most patients with AKI. Some nonoliguric patients excrete enough salt and water to produce intravascular volume depletion if adequate fluid replacement is not provided. Volume depletion prolongs recovery from AKI. Much more commonly, AKI is complicated by volume overload because sodium and water excretion may be inadequate to match even modest intakes. Volume overload is largely responsible for the hypertension often seen in those with AKI and commonly leads to CHF and pulmonary edema. Iatrogenic volume overload is particularly common and can be prevented only by careful attention to fluid intake and output, with prudent estimates of insensible loss. Volume overload can be treated with diuretics or intravenous nitroglycerin while preparations are being made to initiate dialysis.

Disposition

Patients with new-onset severe AKI should be hospitalized. If nephrology consultation and dialysis facilities are not available, transfer to another institution is advisable once volume and metabolic abnormalities have been controlled and the patient is hemodynamically stable.

Decisions regarding dialysis generally are made by the nephrology consultant and take into account many factors, including laboratory test abnormalities and the presence or absence of signs and symptoms of uremia (e.g., nausea, vomiting, change in mental status). Many nephrologists choose to initiate dialysis when the BUN level exceeds 100 mg/dL or the serum creatinine level exceeds 10 mg/dL. Intractable volume overload and life-threatening hyperkalemia are the two most common indications for emergency dialysis.

CHRONIC KIDNEY DISEASE

Foundations

CKD denotes kidney damage or decreased renal function for 3 months or longer and is characterized by irreversible nephron loss and scarring. Chronic renal insufficiency, which denotes a condition in which the GFR has been moderately reduced but not to a degree sufficient to cause clear-cut clinical symptoms, has been replaced by an indication of the degree to which the GFR is reduced. End-stage renal disease, now termed *kidney failure,* describes a condition in which renal function has diminished to a low level and in which serious, life-threatening manifestations can be expected to occur without dialysis or transplantation. At this stage, the kidneys often are shrunken and diffusely scarred to such a degree that it may be impossible to make an etiologic diagnosis, even on pathologic examination.

The causes of CKD are numerous; their relative frequency depends primarily on the population studied. As with AKI, they can be conveniently classified as prerenal (vascular), intrinsic renal (glomerular and tubulointerstitial), or postrenal (obstructive; Box 83.6). Glomerular disease accounts for approximately one-third to half of the cases of CKD; in the United States, diabetic nephropathy forms the largest group of these. Hypertensive nephrosclerosis is another important cause, particularly among blacks, in whom it may be the cause of 25% or more of cases of CKD. Among children and adolescents, reflux nephropathy is the most common cause of CKD. Renal failure related to IV drug use or human immunodeficiency virus disease is a major consideration in some populations. Clues to other specific causes may be gained from elements of the history, physical examination, and laboratory and imaging studies. Although determining the underlying cause of CKD can permit the underlying disease to be treated and can lead to some improvement in renal function in some cases, this is the exception rather than the rule.

BOX 83.6 Major Causes of Chronic Kidney Disease

Vascular Causes
- Renal arterial disease
- Hypertensive nephrosclerosis

Glomerular Causes

Primary Glomerulopathies
- Focal sclerosing glomerulonephritis (GN)
- Membranoproliferative GN
- Membranous GN
- Crescentic GN
- IgA nephropathy

Secondary Glomerulopathies
- Diabetic nephropathy
- Collagen vascular disease
- Amyloidosis
- Postinfectious
- HIV nephropathy

Tubulointerstitial Causes
- Nephrotoxins
- Analgesic nephropathy
- Hypercalcemia or nephrocalcinosis
- Multiple myeloma
- Reflux nephropathy
- Sickle nephropathy
- Chronic pyelonephritis
- Tuberculosis

Obstructive Causes
- Nephrolithiasis
- Ureteral tuberculosis
- Retroperitoneal fibrosis
- Retroperitoneal tumor
- Prostatic obstruction
- Congenital abnormalities

Hereditary Causes
- Polycystic kidney disease
- Alport syndrome
- Medullary cystic disease

HIV, Human immunodeficiency virus; *IgA*, immunoglobulin A.

Barring renal transplantation, CKD is an essentially irreversible condition generally characterized by a relentless decrease in renal function. The most common problems requiring emergent intervention are severe hyperkalemia and symptomatic volume overload. In the patient with CKD who has an acute problem, the focus should be on the identification and treatment of an intercurrent illness that has caused clinical decompensation, with the goal of returning the patient to a stable, chronically compensated status.

Pathophysiology

Progressive loss of renal function eventually results in a recognizable syndrome termed *uremia*. Clinical manifestations do not generally appear, however, until the GFR has been reduced to approximately 15% to 20% of normal. As the patient becomes unable to excrete an ingested salt or water load promptly, the external balance of sodium and water is affected; volume overload or hypernatremia or hyponatremia may result. Inability to concentrate the urine is an early manifestation of renal insufficiency and may be manifested as nocturia. Potassium homeostasis is likewise disrupted, and a relatively small potassium load may lead to dangerous hyperkalemia. The acid-base balance is affected because the kidney fails to clear the daily metabolic acid load owing to a decreased ability to excrete ammonium and phosphate; the result is a non–anion gap acidosis in the earlier stages of CKD and a superimposed anion gap acidosis as the GFR decreases further. Calcium and phosphate metabolism is affected as well; retention of phosphate and progressive loss of the kidney's capacity to synthesize 1,25-dihydroxycholecalciferol, the active form of vitamin D, lead to hypocalcemia, secondary hyperparathyroidism, and eventually the development of renal osteodystrophy.

Nitrogenous byproducts of protein catabolism retained in the blood are the presumed cause of many of the diverse abnormalities of organ function in renal failure. Most patients with CKD show decreased glucose tolerance, although it is rarely severe enough to require treatment unless the medical history includes established diabetes. In the latter case, insulin or other hypoglycemic therapy may need to be continued, but generally at a lower dosage than required before the onset of renal failure because the normal kidney has a major role in insulin degradation. Alterations in lipid metabolism result in elevated low-density lipoprotein levels and hypertriglyceridemia in many patients with CKD.

Clinical Features

Uremia has specific effects on a variety of organ systems. Many of these manifestations are relieved by dialysis, but others are not. A number have been attributed in some degree to the retention of nitrogenous wastes and to derangements in vitamin D and parathyroid hormone metabolism.

Cardiovascular System

The cardiovascular system is perhaps most dramatically affected in CKD. Many of the manifestations can be attributed to the effects of chronic volume overload, anemia, hyperlipidemia, alterations in calcium and phosphorus metabolism, and volume- and hormone-mediated hypertension. Pericarditis, with or without pericardial fluid accumulation, also is common in CKD, particularly among patients who have not undergone dialysis.[8]

Pulmonary Effects

Uremic pleuritis, with or without associated pleural fluid collections, may develop in some patients. So-called "uremic lung," often manifested radiographically by bat wing perihilar infiltrates, represents pulmonary edema and is almost always caused by volume overload

or myocardial dysfunction. Noninflammatory pleural effusion caused by volume overload also is fairly common. Of special importance in the ED evaluation is that the radiographic appearance in pulmonary edema may at times be misleading, simulating an infectious lobar infiltrate or even assuming a nodular appearance in some cases.

Neurologic Features

Neurologic dysfunction is common in those with advanced uremia and may manifest as lethargy, somnolence, difficulty concentrating, or frank alteration in mental status. Seizures may occur, although causes other than uremia alone must be ruled out. Uremic encephalopathy commonly manifests with hiccups, asterixis, or myoclonic twitching. The latter should not be confused with tetany caused by hypocalcemia, which also is common in untreated CKD patients. In the peripheral nervous system, uremia often causes cramps and a distal sensorimotor neuropathy.

Gastrointestinal System

Anorexia and nausea are nearly constant features of uremia. These GI manifestations are caused by the accumulation of nitrogenous wastes that correlate roughly with the BUN level and may be relieved even in the undialyzed patient by introduction of a low-protein diet.

Dermatologic Features

The skin of patients with CKD has a characteristic yellowish tinge. Uremic frost, the result of the deposition of urea from evaporated sweat on the skin, is a classic finding that, like so-called uremic fetor, is seen only rarely now with the widespread use of dialysis (Fig. 83.3). Diffuse pruritus is often a major source of discomfort for the patient with CKD; in some cases, it may be caused by calcium deposition in the skin secondary to derangements in calcium metabolism.

The use of gadolinium-based contrast agents for magnetic resonance imaging has been associated with the development of nephrogenic systemic fibrosis, a potentially fatal disorder that occurs in patients with moderate-to-severe chronic kidney failure.

Musculoskeletal System

The complex disturbances of calcium and phosphate metabolism in CKD result in renal osteodystrophy, a clinical entity encompassing several overlapping varieties of bone disease that can cause bone pain or frank fractures. Patients with CKD generally are treated with long-term oral calcium and vitamin D in an effort to prevent secondary hyperparathyroidism and uremic osteodystrophy. Occasional patients will have a poor response to therapy and require parathyroidectomy. A specific type of arthritis caused by the deposition of calcium hydroxyapatite or calcium oxalate crystals in joints is seen in some patients, as are periarticular calcium deposition, spontaneous tendon rupture, myopathy, and carpal tunnel syndrome.

Fig. 83.3 Uremic frost. Note the fine white powder on the skin of this patient with kidney failure.

Immunologic Considerations

Uremic patients have long been noted to have an increased susceptibility to infection due to alteration of both humoral and cellular immunity. The relative importance of each in the pathogenesis of infection in renal failure is not completely clear, but defects in cellular immunity appear to be more significant clinically. Although patients with renal failure should be considered to be immunocompromised, most infections in patients with CKD are caused by common pathogens rather than opportunistic organisms.

Hematologic Effects

A pronounced normochromic normocytic anemia, with a hematocrit value commonly in the range of 18% to 25%, is nearly universal in those with untreated CKD, except among patients with polycystic disease. It is caused primarily by the kidneys' decreased production of erythropoietin, a hormone that stimulates red cell production by the bone marrow. Other contributing factors are increased red cell hemolysis, nutritional deficiencies, and increased bleeding secondary to platelet dysfunction.

Although the platelet number generally is normal in uremia, the bleeding time is prolonged because of defective platelet adhesiveness and activation. Numerous ecchymoses, seen in many patients with CKD, are a common manifestation.

Differential Diagnosis

Patients with CKD commonly present with nonspecific complaints that are often of insidious onset, such as generalized weakness, poor appetite, or deterioration of mental functioning. However, because CKD can affect all organ systems, a number of life-threatening conditions, including hyperkalemia and myocardial infarction, are in the differential, and a comprehensive evaluation is generally indicated.

In patients without an established diagnosis of CKD, the first consideration is to determine that the renal failure is chronic rather than acute. An explicit history to that effect, obtained from previous medical records or from the patient or family, provides the most straightforward and reliable confirmation, as does the presence of a dialysis access device on physical examination. If such a history is unavailable, the finding of bilaterally small kidneys, readily detected by plain abdominal radiography or ultrasonography, constitutes equally good evidence. However, the converse is not necessarily true—a finding of normal-sized or large kidneys does not rule out CKD. In such cases, additional diagnostic steps are required to establish the diagnosis. A convincing history of the long-standing presence of the presenting symptoms or of symptoms, such as nocturia, may be helpful in suggesting chronicity, as may a history of familial kidney disease, such as polycystic kidney disease or Alport syndrome.

Laboratory abnormalities such as anemia, acidosis, hyperuricemia, hypocalcemia, and hyperphosphatemia can occur in patients with acute kidney failure as early as 10 days after onset. Although urinary findings likewise tend not to be helpful, the presence of broad waxy casts on microscopic examination is suggestive of chronic disease, whereas the finding of an active sediment (e.g., red cell casts) is good evidence for an acute process.

Although as a rule chronic kidney failure is irreversible and slowly progressive, an essential component of the ED evaluation is to exclude the possibility of potentially reversible factors (in effect, ruling out "acute on chronic" renal failure) and to ensure that treatable causes of CKD—disorders that if treated might allow for some return of renal function—have not been overlooked. These potentially reversible factors and treatable causes of CKD are important to keep in mind because they represent the only potential opportunity to reverse the patient's disease rather than simply to manage its results (Box 83.7).

Primary among superimposed reversible factors are those that lead to decreased renal perfusion. Of these, the most common is volume depletion. Regardless of the initiating cause, the process is exacerbated by the diseased kidney's impaired ability to conserve sodium and concentrate the urine appropriately. Decreased renal perfusion caused by cardiac dysfunction of any cause is another extremely common and potentially reversible factor. An uncommonly encountered but important vascular cause of reversible deterioration of renal function is scleroderma renal crisis, a syndrome of accelerated hypertension and severe vasoconstriction in patients with underlying scleroderma that can be reversed by timely treatment with ACE inhibitors. Increased catabolism caused by infection, trauma, surgery, corticosteroids, or GI bleeding is another reversible factor that often is responsible for worsening azotemia and the development of uremic symptoms.

Drugs and toxins constitute another important group of reversible factors. Not only may these agents exacerbate renal insufficiency by causing intravascular volume depletion (diuretics), decreased renal perfusion (antihypertensive agents), or increased catabolism (tetracycline), they also can cause ATN (aminoglycosides, rhabdomyolysis), AIN (many drugs), or inhibition of renal prostaglandin synthesis (NSAIDs). Particularly noteworthy is the dramatic decrease in renal function produced when an ACE inhibitor is administered to a patient with renal insufficiency caused by bilateral renal artery stenosis or renal artery stenosis in a solitary kidney.

Postrenal reversible factors also are important because of their frequency, particularly obstructive disease in the older male patient and reflux nephropathy in the child. Papillary necrosis should remain a consideration in the diabetic patient and the patient with sickle cell disease. Stone disease, retroperitoneal fibrosis, and even rarer entities such as ureteral tuberculosis also should not be overlooked.

Finally, treatment of the underlying disorder that has caused the CKD can occasionally result in the return of some renal function, most notably in cases of myeloma kidney, some forms of secondary glomerulonephritis, and severe hypertensive disease. Although this consideration relates to long-term care and follow-up, it is appropriate that ED management address this issue to ensure that appropriate evaluation and disposition are arranged.

BOX 83.7 Reversible Factors and Treatable Causes of Chronic Kidney Disease

Reversible Factors
Hypovolemia
Congestive heart failure
Pericardial tamponade
Severe hypertension
Catabolic state, protein loads
Nephrotoxic agents
Obstructive disease
Reflux disease

Treatable Causes
Renal artery stenosis
Malignant hypertension
Acute interstitial nephritis
Hypercalcemic nephropathy
Multiple myeloma
Vasculitis (e.g., systemic lupus erythematosus, Wegener granulomatosis, polyarteritis nodosa)
Obstructive nephropathy
Reflux nephropathy

Diagnostic Testing

Diagnostic testing for CKD generally follows the principles outlined for AKI (see earlier section "Acute Kidney Injury: Diagnostic Testing"), though prerenal causes are of concern mostly as exacerbating factors in patients with CKD.

Management

CKD patients are susceptible to infection, bleeding, and the numerous other complications associated with renal failure, as well as those that may be associated with the underlying causative disorder. Moreover, these patients are more vulnerable to the effects of any intercurrent illness or trauma. Those who are maintained with chronic hemodialysis or peritoneal dialysis are subject to potential complications from the dialysis therapy itself.

Patients with CKD also are uniquely susceptible to iatrogenic illness. First, they are less able to handle fluid and solute loads than normal persons. Just as important, the presence of renal failure significantly alters the metabolism and action of many drugs, often in ways that are not predictable (Box 83.8). Thus, the dose and schedule of every agent administered, even those that are apparently innocuous, such as antacids, laxatives, antiemetics, or multivitamin preparations, should be carefully considered, and the hospital pharmacist or other dependable resource consulted. In general, consultation with the patient's nephrologist is recommended on completion of the initial ED evaluation because management and follow-up monitoring after the patient has left the ED are often complex.

In the United States, most patients with advancing CKD eventually will require dialysis, but several true emergencies may develop in the patient with CKD before chronic dialysis has been instituted. Specific diagnostic and therapeutic considerations apply to the management of these conditions, regardless of whether they occur in dialyzed or undialyzed patients.

Hyperkalemia

Potentially the most rapidly lethal complication of CKD is severe hyperkalemia. As a rule, this condition is clinically silent until it causes

BOX 83.8 Mechanisms of Drug Toxicity in Renal Failure

Excessive drug level
Impaired renal excretion of drug
Impaired renal excretion of active metabolite
Impaired hepatic metabolism
Increased sensitivity to drug
Changes in protein binding
Changes in volume of distribution
Changes in target organ sensitivity
Metabolic loads administered with drug
Misinterpretation of measured serum drug level (i.e., change in therapeutic range)

potentially life-threatening manifestations. Accordingly, hyperkalemia must be looked for in every patient with CKD. These patients can become severely hyperkalemic when required to handle even modest exogenous and endogenous potassium loads; moreover, even drugs that have only minimal effects on the serum potassium level in normal persons, such as β-blockers and ACE inhibitors, can cause hyperkalemia in these patients. There is concern that the use of succinylcholine in patients with CKD has the potential to cause rapid deterioration in patients who are already hyperkalemic, although this appears to be rare.

An ECG should be obtained whenever hyperkalemia is a possibility and, if signs of hyperkalemia are noted, appropriate therapy should be started immediately, even before laboratory confirmation of a high serum potassium level. Electrocardiographic changes may be completely absent, even when hyperkalemia is severe; thus, a normal ECG does not preclude the need for laboratory confirmation of a normal serum potassium level. A potassium level of 6 mEq/L should be considered potentially dangerous, even though many patients with CKD chronically tolerate levels somewhat above this threshold, without electrocardiographic changes. A patient with CKD who is in cardiac arrest should be assumed to be hyperkalemic and treated accordingly while the usual resuscitative measures are taken. See earlier ("Acute Kidney Injury: Management") and Table 83.1.

In patients who still retain some renal function, the most effective way to treat hyperkalemia in patients with CKI may be to administer an IV diuretic such as furosemide (if the patient is not hypovolemic) and to provide volume, if necessary. Large doses of diuretic may be necessary for a satisfactory diuresis to be induced. In light of the potential for ototoxicity with the use of loop-active diuretics, these drugs should be administered by slow infusion rather than by bolus and may be contraindicated in patients who also are receiving other potentially ototoxic agents. During the course of any of these therapeutic interventions, the electrocardiographic and serum potassium levels must be monitored frequently.

Pulmonary Edema

Perhaps the most common ED problem in patients with CKD is pulmonary edema secondary to volume overload. Surprisingly, the diagnosis is not always straightforward. A history of increasing dyspnea on exertion or paroxysmal nocturnal dyspnea may be suggestive, but the physical examination may not reveal the expected signs of CHF, and even chest radiography may be deceptive. Recent weight gain or a body weight considerably over dry weight (typically >5 pounds) is the most reliable clue and, in the absence of convincing evidence of another cause for dyspnea, volume overload should be assumed to be the cause.

Treatment of pulmonary edema in the patient with CKD is of necessity somewhat different from that in other patients. Arrangements for initiation of dialysis should be made as soon as possible because it is the most rapidly effective means to decrease intravascular volume in the absence of renal function. Other immediate measures should be instituted in the meantime. Although such measures may occasionally prove to be effective enough to avoid dialysis temporarily in patients who possess some residual renal function, it should nevertheless be anticipated that the response to even extremely aggressive medical therapy, short of dialysis, will be inadequate.

The CKD patient with pulmonary edema is placed in the sitting position, and high-flow oxygen is administered by mask. The use of continuous or bilevel positive airway pressure (CPAP or BiPAP) is a useful adjunct for patients with CKD, as it is for patients without renal failure. Sublingual nitroglycerin can be administered immediately and functions rapidly to reduce preload and afterload; an IV infusion beginning at 10 to 20 μg/min can be initiated promptly and titrated to effect. Diuretics are not expected to be helpful unless the patient has retained a significant level of renal function.

Infection

Because infection is a major contributor to morbidity and mortality among patients with CKD, the possibility of serious infection should be entertained, even when the expected classic findings are not all present. For example, bacteremia may manifest with fever alone, just as in other patients with impaired immunity. Patients with pneumonia may have only vague dyspnea or malaise, symptoms that may be attributed to volume overload or uremia. Thus, all diagnostic possibilities should

TABLE 83.1 Treatment of Hyperkalemia

Agent or Modality	Dose and Regimen	Onset/Duration of Action	Mechanism of Action	Comments
Calcium gluconate (10%)	10 mL IV (may repeat × 2 prn every 5–10 min)	1–5 min/≈1 hr	Antagonizes membrane effects of K	Monitoring of ECG required; do not mix with HCO_3^- *Beware*—hypercalcemia
Albuterol	10–20 mg (nebulized) by inhalation	30 min/2 hr or more	Intracellular movement of K	Relatively free of significant side effects; tachycardia
Glucose and insulin	10–20 units regular insulin/100 g glucose	30 min/while infusion continued	Intracellular movement of K	*Beware*—hyperglycemia, hypoglycemia Infused volume may be decreased by giving $D_{10}W$, $D_{20}W$, or $D_{50}W$
Sodium bicarbonate	150 mEq/L IV infusion (rate variable)	Approximately 10–15 min/1–2 hr	Possible intracellular movement of K	Most effective with organic acidosis
Dialysis	HD, PD	Minutes/while continued	Removal of K from blood	HD may remove 50 mEq/hr *Beware*—K rebound PD may remove 15 mEq/hr
IV diuretics (IV fluid if patient is hypovolemic)	Furosemide 40–80 mg IV	15 minutes/while diuresis continued (depending on renal function)	Urinary K excretion	Only in patients with some residual renal function

$D_{10}W$, 10% dextrose in water; *$D_{20}W$*, 20% dextrose in water; *$D_{50}W$*, 50% dextrose in water; *ECG*, electrocardiogram; *HD*, hemodialysis; *IV*, intravenous; *PD*, peritoneal dialysis; *PO*, orally.

be pursued, and empirical broad-spectrum antibiotic coverage often is advisable until infection has been ruled out in the hospital. Bacteremia resulting from vascular access infection is common in patients undergoing hemodialysis, as is peritonitis in patients undergoing peritoneal dialysis.

A UTI can occur even in patients with minimal urine output or those with long-standing renal failure. Urinary stasis is undoubtedly a predisposing factor. However, asymptomatic pyuria is common in these patients and is not necessarily indicative of infection. For patients with symptoms, urine culture is helpful in guiding treatment decisions. An upper UTI associated with a clinical picture typical of pyelonephritis or renal colic is unusual, but when seen it is often in patients with polycystic kidney disease and requires parenteral treatment. A clinical diagnosis can be made presumptively in the ED, but invasive measures sometimes are necessary to document infection and guide therapy. For infected cysts, lipid-soluble antibiotics (e.g., ciprofloxacin, trimethoprim-sulfamethoxazole) offer the best antibiotic penetration, although surgical intervention for these infections sometimes becomes necessary.

Dialysis

Dialysis can normalize fluid balance, correct electrolyte and other solute abnormalities, and remove uremic toxins or drugs from the circulation when the patient's kidneys are unable to do so. Dialysis also can reverse some uremic symptoms, but generally to a lesser degree, and permit better long-term control of hypertension, anemia, and renal osteodystrophy.

The two major dialysis modalities are hemodialysis and peritoneal dialysis. Each is based on a technique whereby the patient's blood comes into contact with a semipermeable membrane, on the other side of which is a specially constituted balanced physiologic solution. Water and solutes diffuse across the membrane by moving along concentration and osmotic gradients, effectively normalizing the blood's composition.

Hemodialysis. This requires special access to the patient's circulation, generally through a surgically created arteriovenous fistula or an implanted artificial graft or through a surgically placed tunneled catheter. The vascular access site must be treated with care because hemodialysis cannot be performed without it. Careless manipulation or puncture can cause bleeding, infection, or thrombosis, which may result in loss of the access. The involved arm should not be used for blood pressure determinations and a tourniquet should not be applied.

In general, blood is drawn and IV lines are established in other locations. In exceptional circumstances, if no other site is available and it is essential to obtain blood samples quickly, the fistula or graft may be used, but with precautions. A tourniquet is not applied, the area is cleansed scrupulously before the puncture, and extreme care is taken not to puncture the back wall of the access. After the puncture, firm but nonocclusive pressure is applied for at least 10 minutes. The presence of a thrill before and after the procedure is documented. Similar precautions are taken in the exceptional cases in which the fistula or graft must be used for IV access. If this is done, an automated infusion pump is essential to control the infusion rate into these relatively high-pressure blood vessels.

Peritoneal Dialysis. In peritoneal dialysis, the patient's peritoneum functions as the dialysis membrane. Dialysate is infused through a surgically implanted Silastic catheter (Tenckhoff catheter) that penetrates the lower abdominal wall. Fluid exchanges are generally performed several times daily, typically by the patient at home. As compared with hemodialysis, peritoneal dialysis offers the theoretical advantages of greater patient independence, avoidance of anticoagulation, and smoother control of volume and hypertension, without the intermittent rapid shifts of solute typical of hemodialysis. Medications such as insulin and antibiotics can be administered via the intraperitoneal (IP) route, allowing smoother absorption and more stable blood levels. The main disadvantage of peritoneal dialysis is a significant incidence of bacterial peritonitis, which is usually readily treatable.

Indications for Dialysis. The decision to initiate chronic dialysis in the patient with CKD generally is made by the patient's nephrologist in the setting of a gradually decreasing GFR and progressive manifestations of renal failure. The absolute value of the BUN or serum creatinine level generally is used only as a rough guide to determine when chronic dialysis should be instituted. The provision of vascular or peritoneal access usually has been arranged weeks to months before the anticipated initiation of dialysis to allow the access site to mature and to minimize any mechanical complications of the procedure.

For patients who come to the ED with AKI, however, as well as for patients with CKD in whom acute problems have developed, the emergency clinician must be prepared to make the decision to arrange for emergent dialysis (Box 83.9). How urgently dialysis must be initiated depends not only on the severity and acuteness of the presenting problem, but also on the availability of technical facilities and trained dialysis personnel and the effectiveness of available temporizing measures for the problem at hand.

The most common problem requiring emergent dialysis, particularly in the patient with CKD, is pulmonary edema secondary to volume overload. In general, the inciting cause is over-ingestion of fluid and salt in excess of the patient's greatly diminished renal excretory capacity. Despite the effectiveness of temporizing measures, many of these patients require immediate dialysis—emergency hemodialysis or, in the case of the patient maintained on peritoneal dialysis, intensification of the usual dialysis regimen.

A related problem that may require emergent, or at least urgent, dialysis is malignant hypertension, particularly when associated with hypertensive encephalopathy or cardiovascular decompensation. Because hypertension in patients with renal failure is commonly volume-dependent, correction of volume overload, even if not apparent clinically, is a central component of therapy. Temporizing measures such as the administration of IV nitroglycerin often permit hypertension to be controlled sufficiently for dialysis to be delayed for several hours. However, in many cases, hypertension and associated symptoms are difficult to control until dialysis permits the volume overload to be corrected. Because blood pressure often is dramatically responsive to reduction of circulating volume, other antihypertensive agents with more prolonged effects should be withheld until after dialysis to avoid hypotension after circulating volume has been acutely reduced.

Severe hyperkalemia is another common indication for emergent or urgent dialysis, particularly in the patient with AKI who is hypercatabolic. In the patient with CKD, hyperkalemia usually is caused by excessive potassium intake, but endogenous causes such as hemolysis or rhabdomyolysis should also be kept in mind. The available temporizing measures can be used to control the serum potassium level, but dialysis remains the most effective means of removing potassium from

BOX 83.9 Indications for Emergency Dialysis

- Pulmonary edema
- Severe uncontrollable hypertension
- Hyperkalemia
- Other severe electrolyte or acid-base disturbances
- Some overdoses
- Pericarditis (possibly)

the body. For rapid control of the serum potassium level, hemodialysis leads to high clearance rates and is preferred to peritoneal dialysis.

Other severe electrolyte and acid-base disturbances, including diabetic ketoacidosis, may sometimes necessitate emergent dialysis. Occasional patients with renal failure and severe hypercalcemia uncontrollable by other modalities (e.g., patients with multiple myeloma causing both renal failure and hypercalcemia) may require dialysis. The occasional patient with renal failure in whom severe hypermagnesemia develops after inappropriate therapy or magnesium ingestion may require immediate dialysis to reverse life-threatening paralysis or cardiac dysrhythmia. Severe metabolic acidosis in the setting of renal failure is another indication for emergent dialysis, particularly if volume overload or hypocalcemia (with the risk of tetany and convulsions) precludes the administration of bicarbonate.

A related situation is one in which a patient with renal failure has taken an overdose or inadvertently been administered medication that is ordinarily cleared by the kidneys. If the agent is adequately dialyzable and its continued presence in the circulation poses a significant risk to the patient, immediate dialysis can be lifesaving. An example is the ingestion of methanol or ethylene glycol by a dialysis patient. Similarly, ill-advised use of magnesium-containing cathartics or phosphate-containing enemas by patients with CKD can lead to dangerous hypermagnesemia and hyperphosphatemia and may necessitate urgent dialysis.

The serum creatinine and BUN levels themselves are not considered definitive indications for dialysis. A creatinine level of 10 mg/dL or BUN level of 100 mg/dL often is used as a guideline for beginning chronic dialysis in the patient with progressive renal failure. In dialyzed patients, however, the serum creatinine level often is considerably greater than 10 mg/dL but is a reflection of total body muscle mass more than of the adequacy of dialysis. The BUN level is a somewhat better indicator; in well-dialyzed persons, it generally is in the range of 50 to 80 mg/dL and is more than 100 mg/dL in less well-dialyzed patients. Neither blood level, however, correlates more than roughly with uremic symptoms, even in undialyzed patients, or has any direct bearing on how urgently dialysis should be initiated.

The occurrence of uremic symptoms or signs such as nausea, vomiting, lethargy, or twitching indicates a need for dialysis but does not necessitate immediate initiation of dialysis unless symptoms are severe. Pericarditis, even in the absence of cardiac tamponade, often is considered an indication for urgent dialysis, but pericarditis can also occur in well-dialyzed CKD patients. In a previously undialyzed patient with progressive renal insufficiency, the appearance of pericarditis indicates that it is time to initiate dialysis, although not necessarily on an emergency basis.

COMPLICATIONS OF DIALYSIS

A number of complications can be manifested after dialysis has been initiated.

Hemodialysis

Vascular Access–Related Complications

The performance of hemodialysis depends on reliable vascular access, and it is the vascular access device that is responsible for the complications of dialysis that most often require evaluation in the ED setting. These problems must be attended to promptly to minimize the risk of losing the patient's dialysis lifeline.

Bleeding from the dialysis puncture site can occur hours after a hemodialysis treatment, either spontaneously or after inadvertent minor trauma to the site. Such bleeding can usually be stopped by applying firm pressure to the access site. Care should be taken not to occlude and possibly cause thrombosis of the vessel by compressing it too vigorously, and the presence of a thrill immediately after the procedure should be documented in the chart. It may be necessary to keep the patient in the ED for a time to ensure that bleeding does not recur. Recurrent bleeding, especially from an aneurysm or a pseudoaneurysm, is best evaluated by a vascular surgeon.

Similarly, if the patient reports that the thrill in the access has been lost, a vascular surgeon is consulted immediately. Although thrombolytic agents are generally used, definitive treatment is usually surgical revision. The access device should not be forcefully manipulated or irrigated because rupture of the vessel or venous embolization may result.

Infection of the vascular access can result in persistent or recurrent bacteremia, as well as loss of the access. Infection appears to be a consequence of contamination at the time of puncture for dialysis, and most infections are caused by staphylococci typical of skin flora. Infections are more likely to occur in grafts than in native fistulas. The signs and symptoms of an access infection—redness, warmth, and tenderness over the site—often are obvious, but in many cases localizing findings are absent and the patient has only a fever or a history of recurrent episodes of fever and documented bacteremia. For this reason, it is common practice to obtain blood cultures for all patients on hemodialysis who have a fever without an obvious source of infection and to treat them presumptively for an abscess infection. A careful search for other sources of infection should be performed before an abscess infection is assumed to be the cause. Infections such as odontogenic abscess, extremity cellulitis (particularly in diabetics), and perirectal abscess can easily be missed.

Although some nephrologists prefer to admit all dialysis patients with fever to the hospital, management of these patients on an outpatient basis often is possible, provided that they otherwise feel well and do not appear to be septic and provided that they can care for themselves at home and return promptly if their condition worsens. This course is made possible by the fact that they can be loaded with IV antibiotics that dependably maintain adequate blood levels until the next scheduled dialysis treatment, at which time the culture and sensitivity test results can be checked and therapy adjusted accordingly. IV vancomycin, 1 to 1.5 g, given as a single loading dose, is the drug of choice in this case because most abscess infections are staphylococcal and because this drug is only minimally hemodialyzable and needs to be given only every 4 to 7 days in the chronic dialysis patient. If a gram-negative infection also is thought to be likely, as in a patient who has had recent episodes of gram-negative bacteremia, a loading dose of a second drug (e.g., a third-generation cephalosporin or aminoglycoside) also can be administered. Patients can be reloaded with these drugs at the end of their next hemodialysis session if culture results prove to be positive.

Non–Vascular Access–Related Complications of Dialysis

The hemodialysis procedure itself, which entails invasion of the vasculature, anticoagulation, and significant shifts of fluid and solutes, often is associated with acute complications such as hypotension, shortness of breath, chest pain, and neurologic abnormalities.

Hypotension. Hypotension that occurs after dialysis is usually the result of an acute reduction in circulating intravascular volume and failure of the patient's homeostatic mechanisms to compensate for it. Because hemodialysis is episodic, each treatment must remove the excess fluid that has accumulated over the period since the last dialysis (generally, 2–3 days), and patients often are relatively volume-overloaded at the beginning of each treatment. With rapid removal of extracellular fluid, there is inadequate time for transcellular fluid shifts to replace intravascular volume. Antihypertensive medications that are

BOX 83.10 Differential Diagnosis of Hypotension in Hemodialysis Patients

Hypovolemia
Excessive fluid removal
Hemorrhage
Septicemia
Cardiogenic shock
Dysrhythmia
Pericardial tamponade
Myocardial infarction
Myocardial or valvular dysfunction
Electrolyte disorders
Hyperkalemia or hypokalemia
Hypercalcemia or hypocalcemia
Hypermagnesemia
Vascular instability
Drug-related
Dialysate-related
Autonomic neuropathy
Excessive access arteriovenous flow
Anaphylactoid reaction
Air embolism

required when the patient is in a volume-expanded state, particularly β-blockers, can contribute to the hypotension when intravascular volume is normalized.

Most episodes of hypotension that occur during hemodialysis resolve spontaneously or can be readily managed by a decrease in blood flow rate or by infusion of small volumes of saline (to cause transient volume expansion) or hypertonic solutions (to reverse transient acute hypo-osmolality). Patients with significant hypotension who do not respond to these maneuvers often are brought to the ED for further evaluation. Patients on dialysis with persistent hypotension should be considered to be at risk for acute myocardial infarction, acute dysrhythmias, and sepsis (Box 83.10).

Acute blood loss is another consideration when a hemodialysis patient presents with hypotension, symptomatic angina, or CHF. Dialysis patients are commonly treated with epoetin or darbepoetin to prevent severe anemia; untreated patients typically have low baseline hemoglobin levels. Serum levels of clotting factors are normal in CKD, but patients are routinely anticoagulated for each hemodialysis treatment and, although transient thrombocytopenia may occur during the dialysis procedure, the qualitative platelet defect characteristic of renal failure is an important factor in bleeding that continues beyond the peridialytic period. This abnormality is only partially reversed by dialysis but can be corrected by the administration of desmopressin (DDAVP), which increases the release of factor VIII–von Willebrand factor polymers from vascular endothelium. DDAVP has been used successfully to normalize the bleeding time in preparation for surgery in patients with CKD.[9] Cryoprecipitate and conjugated estrogen both have been shown to produce similar effects for a longer period.

Overt bleeding from the GI tract, often caused by angiodysplasia or peptic ulcer disease, is common and can be dramatic. Occult hemorrhage in other locations, however, can present a diagnostic challenge because symptoms and signs of volume loss tend to be overshadowed by local manifestations of bleeding into a closed space. Spontaneous retroperitoneal or pleural hemorrhage may manifest with flank pain or with chest pain and shortness of breath, respectively.

Acute pulmonary embolism and acute air embolism are two less likely possibilities. The former, although it does occur occasionally in dialysis patients, is unusual. The latter, although reported occasionally in the past, has been all but eliminated by improved dialysis monitoring equipment and safety mechanisms.

Two additional entities in the differential diagnosis for hypotension are of particular importance in the patient with CKD—acute pericardial tamponade and severe, life-threatening hyperkalemia. Acute pericardial tamponade may be the result of sudden pericardial hemorrhage or sudden worsening of a formerly compensated pericardial effusion after acute correction of elevated preload. The clinical features of tamponade in the dialysis patient are similar to those in other populations, but the common preexistence of cardiomegaly may make the chest film difficult to interpret unless it shows the typical water bottle shape and a definite increase in heart size from previous examinations.

Similarly, an elevated central venous pressure is of little use in differentiating tamponade from underlying right-sided heart failure. Even the finding of pericardial fluid on bedside ultrasonographic examination, although suggestive, is not proof that tamponade is present, because many dialysis patients chronically have pericardial effusions that do not cause hemodynamic compromise. The ultrasonographic demonstration of right ventricular diastolic collapse is more specific. A definitive diagnosis of tamponade depends on the direct demonstration of equal pressures in the right and left atria on cardiac catheterization.

Emergency pericardiocentesis must occasionally be performed in the ED to relieve acute tamponade, but there often is enough time for the patient to be transported to the catheterization suite or operating room for safer and more definitive therapy in a controlled setting. If immediate pericardiocentesis is believed to be necessary, the emergency clinician should not hesitate to perform this potentially lifesaving procedure, despite the many potential complications and increased risk of bleeding in patients with CKD. Similarly, in the case of a dialysis patient who is in cardiac arrest, pericardiocentesis generally should be attempted if initial resuscitative efforts have not been successful.

Severe life-threatening hyperkalemia, although unusual in a dialyzed patient, can occur in the presence of underlying catabolic illness or with a prolonged period of hypotension and low flow. Patients who are hyperkalemic can have profoundly slow heart rates, particularly if they have been treated with β-blockers or calcium channel blockers. If a dialysis patient is in cardiac arrest, it should be assumed that hyperkalemia is present, and IV calcium should be given immediately.

Shortness of Breath. Shortness of breath in dialysis patients generally is caused by volume overload. In the patient who becomes short of breath while being dialyzed, however, other causes must be sought—primarily sudden cardiac failure, pericardial tamponade, pleural effusion, or pleural hemorrhage. Air embolism and anaphylactoid reactions are unusual causes. Pneumonia or underlying reactive airway disease may be responsible.

Chest Pain. Cardiovascular disease is a leading cause of death in patients with CKD, and most episodes of chest pain occurring during dialysis are likely to be ischemic in origin. Most dialysis patients have risk factors for coronary artery disease, related to CKD itself or to the underlying condition that led to renal failure, and many have well-documented coronary artery disease. CKD is commonly associated with hypertension, hyperlipidemia, carbohydrate intolerance, and disturbances of calcium and phosphorus metabolism. In addition, dialysis patients may be anemic, and many are chronically volume-overloaded. During hemodialysis, these underlying factors may be added to acute physiologic stresses such as transient hypotension and hypoxemia, which often are associated with the dialysis procedure, thereby increasing myocardial oxygen demand while decreasing oxygen delivery.

In evaluating presumed ischemic chest pain in a patient with CKD, reversible precipitants should be considered. It should be determined whether increasing anemia, poorly controlled hypertension, or uncorrected volume overload are factors, particularly when a patient whose angina has been stable begins to experience more frequent or more severe anginal episodes. Patients who repeatedly experience chest pain during dialysis are candidates for a complete cardiac evaluation. Dialysis patients who have repeated ED visits for chest pain should have a coordinated strategy developed by their nephrologist and cardiologist to set guidelines regarding further admissions.

The presence of renal failure and its associated electrolyte and acid-base disturbances does not obscure the usual electrocardiographic changes of angina or acute myocardial infarction. The pattern of change of serum cardiac enzyme levels with acute infarction also is not altered by CKD, although the baseline level of these enzymes may be higher than in the general population.[10-12] Troponin appears to perform best as a marker of infarction in patients with CKD.[10-12] Treatment of ischemic chest pain is the same as for other populations.

Among nonischemic causes of chest pain, pericarditis should always be a consideration, even in the well-dialyzed patient. The presentation is essentially the same as in nonrenal patients; fever, a friction rub, or atrial dysrhythmias may be associated findings. Signs of pericardial effusion or early tamponade should be sought by bedside ultrasonography. Indomethacin often is effective in relieving pain, but some patients eventually require further measures, such as pericardiocentesis with corticosteroid instillation or pericardial stripping. Patients with pericarditis may require more frequent or intensified dialysis because pericarditis is thought to be a marker for inadequate dialysis.[8]

Neurologic Dysfunction. Neurologic symptoms during or immediately after hemodialysis may be caused by disequilibrium syndrome, a constellation of symptoms and signs thought to result from rapid changes in body fluid composition and osmolality during hemodialysis. It usually occurs only in patients with high BUN levels who are just starting hemodialysis and does not occur with peritoneal dialysis. Typically, patients have headache, dizziness, nausea, vomiting, and muscle cramps, but in more severe cases features may include altered mental status, seizures, or coma. Symptoms resolve over several hours as fluid and solutes are redistributed across cell membranes.

Altered mental status in the CKD patient should not be attributed to disequilibrium syndrome unless other causes have been ruled out (Box 83.11), particularly when symptoms persist, fluctuate, or worsen during a reasonable period of observation. Likewise, when seizures occur during dialysis, they should not be attributed to disequilibrium syndrome without considering other potentially serious causes, even in patients who have had seizures in the past. Any new focal neurologic abnormality requires an immediate head CT scan to detect intracranial hemorrhage. Similarly, if fever or other evidence of infection is present, meningitis should be a serious consideration. Other considerations include hyperglycemia and hypoglycemia, especially in the diabetic patient, as well as electrolyte abnormalities, hypoxic states, hypotension, and other toxic or metabolic causes. The acute treatment of seizures in patients with CKD is essentially the same as for other populations.

BOX 83.11 Differential Diagnosis of Altered Mental Status in Dialysis Patients

Structural Conditions
Cerebrovascular accident (particularly hemorrhage)
Subdural hematoma
Intracerebral abscess
Brain tumor

Metabolic Conditions
Disequilibrium syndrome
Uremia
Drug effects
Meningitis
Hypertensive encephalopathy
Hypotension
Postictal state
Hypernatremia or hyponatremia
Hypercalcemia
Hypermagnesemia
Hypoglycemia
Severe hyperglycemia
Hypoxemia
Dialysis dementia

Peritoneal Dialysis

As with hemodialysis, most of the complications of peritoneal dialysis are related to the dialysis access device, in this case the peritoneal catheter. In contrast to hemodialysis, however, the dialytic process in peritoneal dialysis occasions few immediate difficulties.

Peritonitis is the most common complication of peritoneal dialysis. Fortunately, it is generally much less severe than other types of peritonitis and can be treated readily on an outpatient basis, despite the continued presence of a foreign body—the Tenckhoff catheter—in the peritoneal cavity. Occasionally, when an episode of peritonitis responds poorly to antimicrobial therapy or when a patient has repeated episodes of peritonitis caused by the same organism, the catheter must be removed and the patient sustained with hemodialysis until the infection is completely cleared and a new catheter can be placed. Repeated infections carry the risk of permanently altering peritoneal permeability or effective surface area and necessitating a permanent switch to hemodialysis.

Peritonitis in patients who are on peritoneal dialysis is presumably caused by inadvertent bacterial contamination of the dialysate or tubing during an exchange or by extension of an infection of the exit site or subcutaneous tunnel into the peritoneal cavity. Most cases of peritonitis are caused by *Staphylococcus aureus* or *Staphylococcus epidermidis,* and most of the remainder (≈30%) by gram-negative enteric organisms.[13] Fungal infections are uncommon but generally are refractory to medical therapy and are often considered as an indication for catheter removal. Polymicrobial infection suggests direct contamination from the GI tract and mandates a search for the site of perforation or fistula, although such a source is identified in only a minority of cases. No organism is identified in approximately 10% to 20% of cases of peritoneal dialysis–associated peritonitis.

The diagnosis of peritonitis usually is made by the patient when a cloudy dialysis effluent is noted, corresponding with the appearance of white blood cells (WBCs) in the dialysate. Peritonitis is often accompanied by nonspecific abdominal pain, malaise, or fever. When a patient has fever or abdominal symptoms, even in the absence of cloudy fluid, it is advisable to consider peritonitis and check the fluid, because early peritonitis may manifest in an atypical manner. In more severe cases, peritonitis is accompanied by nausea, vomiting, severe pain, and hypotension, necessitating hospitalization and consideration of the possibility of acute surgical disease.

In the ED setting, the diagnosis of peritonitis is confirmed by the finding of more than 100 WBCs/mm^3 in the peritoneal fluid, with more than 50% neutrophils, or by a positive result on Gram stain. A sample of fluid is obtained for analysis. If a specialized dialysis nurse

is available to obtain the fluid, this may be preferable. If not, the fluid is obtained through the use of sterile technique. Fluid is sent for cell count and differential, Gram staining, and culture, with the use of blood culture bottles.

Peritoneal dialysis–associated peritonitis is treated with an initial intraperitoneal (IP) loading dose of antibiotic, followed by a 10- to 14-day course of IP antibiotics self-administered by the patient on an outpatient basis. After the diagnosis has been confirmed, consultation with the patient's nephrologist or dialysis nurse specialist is indicated to determine antibiotic therapy and to plan for outpatient management and follow-up evaluation or, occasionally, if peritonitis is severe or outpatient management is precluded by psychosocial considerations, for hospitalization. A common treatment regimen is a loading dose of vancomycin, 15 to 30 mg/kg IP, followed by further IP doses every 4 to 7 days, plus ceftazidime or cefepime, 1 g IP, or gentamicin, 0.6 mg/kg IP. The last two regimens are given as a loading dose followed by maintenance doses administered IP once daily at the time of an exchange.[13] Heparin, 500 to 1000 units, may also be added to each liter of dialysate for the first few days of treatment to help reduce the formation of fibrin strands that may obstruct the catheter. Patients should be seen by the dialysis nurse in 24 to 48 hours for assessment of the response to therapy and adjustment of antibiotic therapy as necessary after review of the results of culture and sensitivity testing.

Catheter contamination or leaks from the catheter, tubing, or dialysate bag should be managed in the same fashion as for frank peritonitis. The site and cause of leakage are identified, and damaged elements are promptly replaced. Occasionally, with leakage of peritoneal fluid from around the catheter, surgical correction of the underlying problem will be necessary.

Patients who have severe abdominal pain, vomiting, ileus, chills or high fever, or hypotension require hospital admission and management. Likewise, patients with severe underlying illness and those who cannot reliably perform exchanges or administer antibiotics at home also require inpatient management. Dialysis exchanges are continued on the same schedule. The inpatient antibiotic regimen is essentially the same as for outpatients.

Perhaps the most serious potential pitfall in caring for the patient maintained on peritoneal dialysis with abdominal pain or other signs of peritonitis is to overlook other serious intra-abdominal conditions whose presentation may mimic that of peritonitis. Patients on peritoneal dialysis are at increased risk for abdominal wall or inguinal hernia because of chronically increased intra-abdominal pressures; previous abdominal surgery also places them at risk for hernia, as well as for obstruction secondary to adhesions. The manifestations of serious disorders unrelated to dialysis (e.g., acute appendicitis, diverticulitis, cholecystitis, acute pancreatitis, ischemic bowel, perforated viscus, or spontaneous bacterial peritonitis in patients with chronic liver disease) also may be attributed to ordinary peritoneal dialysis–associated peritonitis, with the potential for disastrous consequences. The accessibility of the peritoneal fluid for examination may prove to be helpful in documenting the presence of an inflammatory process, but it also has the potential to mislead ED investigation of its cause. A finding of brownish or fecal material in the peritoneal drainage should suggest a ruptured viscus until proven otherwise and immediate surgical consultation should be sought. Detection of a localized tenderness, palpable mass, or incarcerated hernia on physical examination can be extremely helpful in making the diagnosis. Plain abdominal radiography or abdominal CT may be useful for demonstrating the presence of ileus, but pneumoperitoneum may reflect only the introduction of air during a recent fluid exchange rather than a perforated viscus.

Infection of the catheter exit site or tunnel is another relatively common problem for which the patient on chronic peritoneal dialysis may seek care in the ED. These infections tend to be caused by typical skin flora and manifest with local signs of infection. Although not serious in themselves, exit site infections may lead to infection of the subcutaneous tunnel, which can cause repeated episodes of peritonitis and may ultimately necessitate removal of the catheter. Any visible exudate is cultured and Gram-stained and therapy with an oral antibiotic such as cephalexin or dicloxacillin is started, pending the results of culture and sensitivity testing. The patient is instructed to cleanse the site meticulously several times a day using povidone-iodine or peroxide solution.

Tunnel infections can be difficult to detect on physical examination and may be suspected only after the patient has several bouts of peritonitis caused by the same organism. As with other closed space infections, tunnel infections tend to be difficult to eradicate unless the tunnel is partially unroofed and drained.

Patients maintained on peritoneal dialysis also may come to the ED with positional or mechanical problems with the site, of which the most common is failure of the dialysate to drain completely at the time of an exchange. Occasionally this problem is caused simply by kinking or inadvertent clamping of the external catheter or tubing. More often, however, it is the result of catheter obstruction by fibrinous debris or kinking or migration of the catheter within the peritoneal cavity, often associated with constipation. Catheter position is best assessed by a CT scan of the abdomen. Specific intervention may be guided by a contrast catheterogram. Fibrinolytic agents have been used successfully to open occluded catheters, but surgical intervention for catheter replacement often is required. Severe metabolic disturbances are much less common among patients on peritoneal dialysis than patients on hemodialysis, because in the former group dialysis is being performed essentially continuously and the blood remains in near-equilibrium with the dialysate. However, significant disturbances do occasionally occur, usually in association with hypercatabolic states, major dietary indiscretions, or significant GI fluid loss. One derangement that occurs occasionally in diabetic patients undergoing peritoneal dialysis is a syndrome of severe hyperglycemia—sometimes even despite continuation of the usual insulin dose—that results from absorption of glucose from the hyperosmolar dialysate, with associated nonspecific symptoms of malaise, weakness, and headache. Although glucose levels may be as high as 1500 mg/dL in these patients, they cannot undergo an osmotic diuresis and remain clinically euvolemic. Correction of hyperglycemia must be undertaken carefully to avoid causing rapid osmolar and volume shifts.

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CHAPTER 83: QUESTIONS AND ANSWERS

1. Of the following choices, which is the correct match between type of urine cast and pathologic condition?
- **a.** Fatty casts—glomerulonephritis
- **b.** Granular casts—renal parenchymal infection
- **c.** Hyaline casts—dehydration, exercise
- **d.** Red cell casts—nephrotic syndrome
- **e.** White cell casts—acute tubular necrosis (ATN)

Answer: c. Hyaline casts are associated with dehydration, exercise, and glomerular proteinuria. The following are the other correct associations:
- Fatty casts—nephrotic syndrome
- Red cell casts—glomerulonephritis
- White cell casts—renal parenchymal infection
- Granular casts—ATN

2. A 34-year-old man with chronic kidney disease has missed his last two hemodialysis treatments and presents with generalized fatigue and dyspnea on exertion. Vital signs include a blood pressure of 165/94 mm Hg but are otherwise normal. Room air Sao_2 is 94% at rest. A portable chest x-ray shows vascular congestion. Which of the following is an indication for immediate dialysis?
- **a.** Blood urea nitrogen (BUN) level of 87 mg/dL and serum creatinine level of 10.6 mg/dL
- **b.** Serum calcium level of 6.8 mg/dL and serum albumin level of 3.0 g/dL
- **c.** Serum potassium level of 7.6 mEq/L (not hemolyzed)
- **d.** Serum sodium level of 124 mEq/L
- **e.** Serum troponin level of 0.08 ng/mL

Answer: c. Severe hyperkalemia is an indication for immediate dialysis in this patient. An ECG should be obtained stat to determine the degree of cardiotoxicity, and immediate medical treatment for hyperkalemia should be given while awaiting initiation of dialysis. Abnormalities of the serum sodium or calcium level can generally be treated without hemodialysis. A minimal troponin level elevation may be seen in patients with chronic kidney disease, but does not generally require specific treatment without other signs of cardiac ischemia; dialysis is not required.

3. What is the most common cause of nontraumatic hematuria?
- **a.** Carcinoma of the kidney or bladder
- **b.** Cystitis
- **c.** Kidney stones
- **d.** Prostatic hyperplasia
- **e.** Transfusion reaction

Answer: c. In descending frequency, the most common causes are kidney stones, lower urinary tract infection (UTI), benign prostatic hypertrophy (BPH), carcinoma of the kidney or bladder, urethritis, and glomerulonephritis.

4. A 53-year-old man presents with painless gross hematuria. His only past medical history is an aortic valve replacement for which he takes warfarin. The physical examination is nonfocal. Laboratory evaluation is remarkable for a normal chemistry panel and blood count, too numerous to count (TNTC) red blood cells (RBCs) on urinalysis, and international normalized ratio (INR) of 1.8. What is the next indicated step?
- **a.** Admission and observation
- **b.** Parenteral vitamin K
- **c.** Reassurance
- **d.** Renal imaging
- **e.** Withholding warfarin (Coumadin) for 3 days

Answer: d. When hematuria is associated with anticoagulant use, underlying disease can be identified in a significant proportion of patients.

5. A 33-year-old woman presents with mild nonfocal abdominal pain and subjective fever. Her past medical history is significant for hypertension-induced renal failure, for which she is on peritoneal dialysis (PD). The physical examination is remarkable for a temperature of 38°C (100.4°F), blood pressure 190/110 mm Hg, and mild nonfocal abdominal pain. Slightly cloudy peritoneal fluid is aspirated from the PD catheter and sent for analysis. Which of the following statements regarding this patient's condition is correct?
- **a.** A peritoneal fluid white blood cell (WBC) count >50/mm^3 is diagnostic.
- **b.** Intravenous antibiotics should be started empirically.

CHAPTER 83: QUESTIONS AND ANSWERS—cont'd

c. Most cases are due to *Staphylococcus*.
d. No organism is identified in 50% of cases.
e. Polymicrobial infections suggest sample contamination.

Answer: c. Most PD-associated cases of peritonitis are due to *Staphylococcus aureus* or *Staphylococcus epidermidis*. No organism is identified in 20% of cases. A polymicrobial infection warrants GI evaluation for possible perforation or intra-abdominal abscess. A PD fluid count >100 cells/mm^3, with a neutrophil count >50% or positive Gram stain, is considered confirmatory. Treatment is typically with intraperitoneal antibiotics given for a 10- to 14-day course.

Sexually Transmitted Infections

Jeffry McKinzie

KEY CONCEPTS

- The emergency department (ED) diagnosis of sexually transmitted infections (STIs) is often based on clinical findings. Empirical antibiotic treatment is warranted to cover the most likely infecting organisms based upon history and physical examination findings. Rapidly available diagnostic tests (Gram stain, darkfield microscopy, wet mount microscopy, and other point-of-care tests) increase diagnostic sensitivity and specificity.
- Confirmatory diagnostic studies (PCR, culture, serology, and others) should be considered even when results are not immediately available. A mechanism for follow-up of test results should be established and appropriate patient contact information obtained.
- STIs frequently coexist. Diagnosis of one STI should prompt consideration and screening for others, including HIV.
- Genital herpes, the most common ulcerating STI, is often transmitted by persons who are unaware that they are infected or are asymptomatic at the time of transmission.
- In a patient with a genital ulcer, visualization of spirochetes on darkfield microscopy is highly specific for the diagnosis of syphilis and provides rapid confirmatory results.
- Single-dose antibiotic therapy should be used for treatment of STIs when possible. Directly observed therapy administered in the ED enhances treatment compliance. Single-dose antibiotic therapy is recommended for treatment of uncomplicated gonorrhea, primary and secondary syphilis, chancroid, and trichomoniasis in men.
- HIV, syphilis, gonorrhea, chlamydia, and chancroid are reportable diseases in all 50 of the United States (US).

FOUNDATIONS

Sexually transmitted infections ((STIs) are a diverse group of conditions caused by more than 30 viral, bacterial, and parasitic organisms that are transmitted through sexual contact. Four of the pathogens that contribute most to the global incidence of STIs (chlamydia, gonorrhea, syphilis, and trichomoniasis) are curable, often with a single dose of an antibiotic.[1,2] More than 1 million newly acquired cases of these curable STIs occur worldwide each year.[3] Viral pathogens responsible for common STIs (herpes simplex virus, human papillomavirus, and HIV) cause chronic infection in which symptoms and progression of disease can be modified with appropriate antiviral therapy.

STIs are seen across all demographic, cultural, and socioeconomic strata, and all sexually active persons are at risk for acquiring them. Factors associated with higher risk for STIs reflect the importance of individual sexual practices and risk-taking behaviors (i.e., multiple sex partners, substance abuse, commercial sex workers, men who have sex with men, and unsafe sex practices), as well as various demographic and social determinants that influence health status (i.e., adolescents and young adults, minorities, and low socioeconomic status).

STIs are among the most common urogenital conditions encountered in the ED. The management of patients with STIs is particularly challenging for multiple reasons: (1) the clinical presentation is highly variable; (2) available diagnostic tests have limited sensitivity and results are usually delayed; (3) compliance with treatment, follow-up, and partner notification is often poor; and (4) misdiagnosis and suboptimal treatment can result in serious sequelae. In addition to the morbidity associated with individual STIs, many of these infections also increase the risk of human immunodeficiency virus (HIV) transmission and acquisition in both the infected person and their sexual partners. Thus, STIs have a significant impact on both individual and public health.

Patients with STIs frequently present with complaints related to the genitalia but may also present with a variety of nonspecific dermatologic, gastrointestinal, musculoskeletal, and systemic complaints. Because the signs and symptoms of many common STIs are often nonspecific, one must maintain a high level of awareness for these conditions and their associated complications. A thorough history, including sexual history, and focused physical examination facilitate appropriate diagnosis and treatment. The sexual history should include number and gender of sexual partners, types of sexual practices, use of barrier contraception (condoms), and past history of STIs. Obtaining an accurate sexual history may be difficult due to the sensitive nature of the subject, lack of established physician-patient rapport, and other constraints of the ED setting. Evaluation is facilitated by the use of a nonjudgmental approach, maintenance of patient privacy, and assurance of confidentiality.

The differential diagnosis for STIs is extensive, including many other infectious and noninfectious conditions (Table 84.1). Most STIs can be broadly categorized as conditions characterized by one of the following manifestations: genital ulcers, genital discharge, epithelial cell infections, and infestation by ectoparasites. Some STIs, such as syphilis, frequently have associated systemic symptoms in addition to their genitourinary manifestations. Other STIs, such as HIV, may have systemic manifestations in the absence of genitourinary signs and symptoms.

STIs frequently coexist. Diagnosis of one STI should prompt consideration of other coexisting infections, which may not be clinically apparent. Screening for other STIs, including HIV, should be considered, because early diagnosis and treatment benefits both the individual patient and the public health. Despite current recommendations from the Centers for Disease Control and Prevention (CDC) for routine HIV screening among patients age 13 to 64 years in all health care settings, systematic HIV testing is not routinely performed in most EDs. When available, rapid HIV testing should be considered. Patients should be counseled regarding the need for HIV testing if it is not performed in the ED.

Empirical antibiotic treatment designed to cover the most likely infecting organisms is recommended for patients with suspected STIs

TABLE 84.1 Differential Diagnosis of Common Sexually Transmitted Infection Syndromes

Genital Ulcers	Genital Discharge	Epithelial Cell Lesions	Ectoparasites
Genital herpes	Gonorrhea	Genital warts	Pubic lice
Primary syphilis	Chlamydia	Secondary syphilis	Scabies
Chancroid	Nongonococcal urethritis (NGU)	Molluscum contagiosum	Other lice (body, head)
Lymphogranuloma venereum	Pelvic inflammatory disease	Neoplasm	Other mites (chiggers)
Granuloma inguinale	Trichomoniasis	Nevi	Ticks
Trauma	Bacterial vaginosis	Skin tags	
Neoplasm	*Candida* vaginitis		
Behçet disease	Foreign body		
Abscess (draining)	Irritants/allergens		

to maximize eradication of disease in the individual patient and reduce the spread of infection to other susceptible persons. Empirical therapy is particularly important when there are concerns about the patient's ability to obtain appropriate follow-up care. Confirmatory diagnostic studies should still be considered, even when empirical therapy is provided. Microbiologic diagnosis confirms the appropriate choice of empirical therapy, provides guidance for potential changes in treatment, and facilitates reporting of specific STIs to public health authorities. Point-of-care rapid diagnostic testing may minimize the need for empirical antibiotic treatment by providing confirmatory test results before treatment decisions are made and prior to patient discharge from the ED. This reduces the unnecessary use of antibiotics with associated costs, side effects, and development of antimicrobial resistance.

The diagnosis of an STIs provides the physician with a "teachable moment" to educate the patient regarding important factors, including (1) nature of the infection and how it is transmitted; (2) compliance with prescribed therapy and recommended follow-up; (3) importance of preventive measures, including condom use and other safe sex practices; and (4) partner notification and treatment. Patients diagnosed with STIs should be counseled to abstain from sexual intercourse for at least 7 days after the patient and partner(s) complete treatment. Proper counseling helps to ensure the success of initial treatment and reduce the incidence of reinfection. When the diagnosis of an STI is suspected but not confirmed, the patient should be informed of the uncertainty of the diagnosis and the rationale for empirical treatment. The physician should be sensitive to the stress and anxiety that may ensue when discussing the diagnosis of an STI, particularly with a patient who assumes he or she is in a monogamous relationship. A respectful, nonjudgmental, and compassionate approach should be maintained.

The CDC recommends the use of expedited partner therapy (EPT) to ensure treatment in sexual partners of selected patients diagnosed with gonorrhea or chlamydia. With EPT, the clinician provides patient-delivered medication or prescriptions for sexual partners without personally evaluating them. The use of EPT in the ED is potentially problematic due to lack of knowledge regarding the partner's medical history, allergies, pregnancy status, and other factors. In addition, some states prohibit the prescribing or dispensing of medications to patients who have not been seen and are unknown to the provider. Updated information regarding the use of EPT and applicable state regulations is available online from the CDC website.[4] All patients diagnosed with an STI in the ED should be advised to notify their sexual partners to seek prompt evaluation and treatment.

An organized mechanism for follow-up of positive diagnostic test results is recommended when these results are not available until after the patient and physician have left the ED. Obtaining accurate contact information at the time of the initial visit is important in ensuring timely patient notification. Reporting requirements vary by state, but the following STIs must be reported in all 50 states: gonorrhea, chlamydia, syphilis, chancroid, and HIV. Reporting may be laboratory-based or provider-based, or both. The clinician should be familiar with applicable state reporting requirements and the reporting mechanism used at their hospital.

This chapter reviews the clinical features, diagnosis, and treatment of selected common STIs encountered in the ED setting. Readers are referred to the "Sexually Transmitted Infections Treatment Guidelines" published by the CDC for additional information regarding the diagnosis and treatment of these conditions, as well as other less common STIs.[5] Updates regarding changes in treatment guidelines are provided by the CDC in the *Morbidity and Mortality Weekly Report,* available at www.cdc.gov/mmwr.

DISORDERS CHARACTERIZED BY GENITAL ULCERS

Genital ulcers may be caused by several different STIs, as well as various other infectious and noninfectious conditions. Genital herpes is the most common ulcerating STI seen in the United States, followed by syphilis. Chancroid is an uncommon cause of genital ulcers in the United States, and other STIs that may be manifested by genital ulcers (lymphogranuloma venereum, granuloma inguinale) are rare. Although the history, clinical appearance of the ulcers, and other associated findings provide helpful clues in differentiating the various causes of genital ulcers, these features are not specific enough to provide a definitive diagnosis. Diagnostic studies such as darkfield microscopy, serology for syphilis, polymerase chain reaction (PCR), and viral culture should be considered to discriminate between the various etiologies and facilitate a definitive diagnosis, even when empirical therapy is initiated. Diagnostic testing is particularly important in patients that are unresponsive to previous empirical antibiotic therapy. Ulcerating STIs play an important role in facilitating the transmission and acquisition of HIV.

Herpes

Background and Importance

Genital herpes is a lifelong viral infection caused by one of two types of herpes simplex virus (HSV): HSV-1 or HSV-2. Sexual transmission occurs more commonly with HSV-2, but both types of HSV can be transmitted through sexual or nonsexual contact. Many cases of HSV are undiagnosed. HSV is often transmitted by persons who are unaware that they are infected, or who are asymptomatic at the time of transmission. HSV transmission occurs through viral contact with a break in the skin or intact mucous membranes. The average incubation

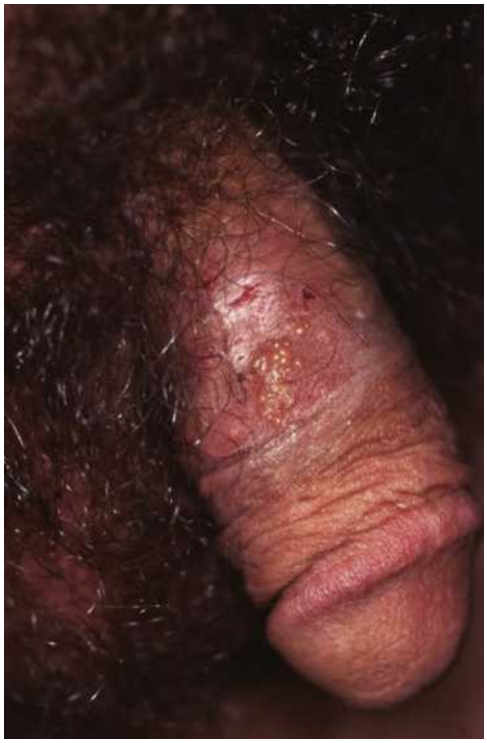

Fig. 84.1 Genital herpes lesions on the penile shaft.

period is 4 days but may range from 2 to 12 days. The virus ascends via sensory nerves to the dorsal root ganglia, where it becomes latent but may reactivate periodically. Herpes, like other ulcerating STIs, facilitates the transmission and acquisition of HIV. Herpes infection in pregnant women may result in transmission to the infant at the time of delivery, with devastating associated neonatal morbidity and mortality.

Clinical Features

Typical herpetic lesions begin as a cluster of small erythematous painful vesicles, which quickly ulcerate (Fig. 84.1). Lesions may occur anywhere the organism is inoculated, but they are typically seen on the skin of the external genitalia, perineum, and buttocks and on the mucous membranes of the vagina, rectum, and oropharynx. Primary infection occurs when a patient is infected with HSV-1 or HSV-2 with no preexisting antibodies to either type. The primary infection is usually more painful and symptomatic, with associated tender regional lymphadenopathy, fever, malaise, headache, and other systemic symptoms. Dysuria is common due to the proximity of the lesions to the urethra. The symptoms of untreated primary infection typically last from 2 to 4 weeks before resolving spontaneously.

Recurrent episodes of genital herpes tend to be less symptomatic and shorter in duration, with lesions occurring in the same distribution due to reactivation of latent HSV infection in the affected nerve roots. Recurrences are more frequent with infection caused by HSV-2 than with HSV-1. Recurrent outbreaks are often heralded by prodromal symptoms of itching, burning, and paresthesias prior to the development of skin or mucous membrane lesions. Reactivation of latent HSV may occur in response to a variety of stressors, including acute illness or injury, immunosuppression, psychological stress, and menses. Recurrences typically become less frequent and less severe over time. Extragenital complications of HSV infection include meningoencephalitis, transverse myelitis, hepatitis, pneumonitis, and disseminated infection. Asymptomatic viral shedding and transmission occurs even in the absence of visible lesions on the skin or mucous membranes.

Diagnostic Testing

The diagnosis of genital herpes is frequently made based upon clinical findings. Although the presence of typical skin or mucous membrane lesions is suggestive of herpes, the clinical diagnosis is both insensitive and nonspecific. A history of similar lesions in the same anatomic distribution supports the clinical diagnosis. HSV type-specific nucleic acid amplification tests (NAATs) are the diagnostic tests of choice, with the highest sensitivity and specificity in the presence of active lesions. Viral culture is also specific but less sensitive than NAATs. Darkfield microscopy and serologic testing for syphilis should be considered to help differentiate cases of syphilis. The utility of these diagnostic studies is limited in the ED because test results are delayed, but results may be helpful at the time of follow-up. Direct fluorescent antibody (DFA) and serology for HSV are available, but less commonly used in the ED setting. Cytologic testing (Tzanck preparation) is nonspecific and insensitive and should not be relied upon to make the diagnosis of HSV.

Management

Genital herpes is treated with the antiviral medications acyclovir, famciclovir, or valacyclovir. Antiviral therapy is not curative but has been shown to decrease the duration and severity of symptoms and the development of complicated HSV infection, particularly when started early during the primary infection. Prompt initiation of antiviral treatment is key to obtaining optimal clinical benefit. Although most studies have evaluated drug initiation within 72 hours of symptom onset, antiviral therapy may still be offered after this time frame in the presence of ongoing symptoms and the development of new lesions. Multiple regimens are available for treatment of primary and recurrent episodes of genital herpes with oral antiviral medications (Table 84.2). Oral antiviral therapy is generally well tolerated with few side effects. Suppressive therapy with daily antiviral use has been shown to decrease the frequency of recurrences while the medication is being taken, but it does not affect the frequency or severity of recurrences after the drug is discontinued. Topical antiviral therapy provides minimal clinical benefit and is not recommended.

Disposition

Most patients with genital herpes are managed as outpatients. Hospitalization for parenteral therapy with acyclovir is indicated for systemic complications of HSV infection, including meningoencephalitis, hepatitis, pneumonitis, and disseminated infection. Patients with genital herpes should be counseled that transmission may occur even in the absence of clinical symptoms. Condom use has been shown to reduce but not eliminate the incidence of HSV transmission. Discordant couples (i.e., those in which one partner is HSV+) should be advised to avoid sexual contact during active outbreaks, which is when viral transmission is highest. Condoms should be used during asymptomatic periods. Patients with genital herpes should also be counseled regarding the increased risk of acquisition and transmission of HIV in the presence of genital ulcers.

Syphilis

Background and Importance

Humans are the only known host for *Treponema pallidum,* the spirochete that causes syphilis. The incidence of syphilis has declined significantly since penicillin became widely available in 1945, but outbreaks still occur intermittently. After a progressive decline in the incidence of syphilis from 1990 to 2000, there has been an increase in recent years. More than 35,000 cases of primary and secondary syphilis were reported to the CDC in 2018.[6] The rates of primary and secondary syphilis are higher among those between 20 to 34 years old, minority groups, and men who have sex with men (MSM). It is more common in

TABLE 84.2 Treatment of Common Ulcerating Sexually Transmitted Infections[a]

Disease	Recommended Treatments
Herpes simplex	
Primary episode	Acyclovir 400 mg PO tid for 7 to 10 days *or* Valacyclovir 1000 mg PO bid for 7 to 10 days *or* Famciclovir 250 mg PO tid for 7 to 10 days
Recurrent episodes	Acyclovir 800 mg PO bid for 5 days *or* Acyclovir 800 mg PO tid for 2 days *or* Valacyclovir 500 mg PO bid for 3 days *or* Valacyclovir 1000 mg PO daily for 5 days *or* Famciclovir 125 mg PO bid for 5 days *or* Famciclovir 1000 mg PO bid for 1 day *or* Famciclovir 500 mg PO once, then 250 mg bid for 2 days
Syphilis[b]	
Primary, secondary, and early latent syphilis	Benzathine penicillin G 2.4 million units IM single dose
Neurosyphilis	Aqueous penicillin G 3 to 4 million units IV every 4 hours for 10 to 14 days
Chancroid	Ceftriaxone 250 mg IM single dose *or* Azithromycin 1000 mg PO single dose *or* Ciprofloxacin 500 mg PO bid for 3 days Erythromycin 500 mg by mouth TID × 7 days

[a]Alternative treatment regimens for selected patients (including pregnancy, drug allergies) can be found at www.cdc.gov/std/treatment.
[b]Pregnant women with syphilis who are allergic to penicillin should be admitted for desensitization and treatment with penicillin.
IM, Intramuscular; *PO,* per os (by mouth).

the western and southeastern United States compared to other regions of the country.

Clinical Features

Syphilis has been called "the great imitator," because its clinical manifestations are protean. The classification and staging of syphilis based upon clinical and serologic findings was updated in 2017.[7] The primary and secondary stages of syphilis are most commonly seen in the ED setting. Transmission occurs when the spirochetes gain access through disrupted epithelium of the skin or mucous membranes. The average incubation period is approximately 21 days but may range from 3 to 90 days.

Primary syphilis is initially manifested by the development of a painless papule at the site of inoculation. The lesion ulcerates, forming the chancre of primary syphilis (Fig. 84.2). The chancre is classically described as a relatively painless clean-based ulcer with well demarcated indurated edges, measuring approximately 1 to 2 cm in size. Nontender regional lymphadenopathy may be seen. Although the chancre often occurs in the genital or perianal area, it may occur at any site of inoculation, including the oropharynx, breasts, hands, and other sites. The chancre will heal spontaneously over the course of 3 to 6 weeks. Because the chancre is relatively painless, it may go unnoticed by the patient.

Secondary syphilis will develop in approximately 25% of patients with primary syphilis over a period of several weeks to months. Manifestations of secondary syphilis include rash, generalized lymphadenopathy, mucous membrane lesions, and systemic symptoms. The rash is diffuse, involving the face, trunk, and extremities, including the palms and soles.

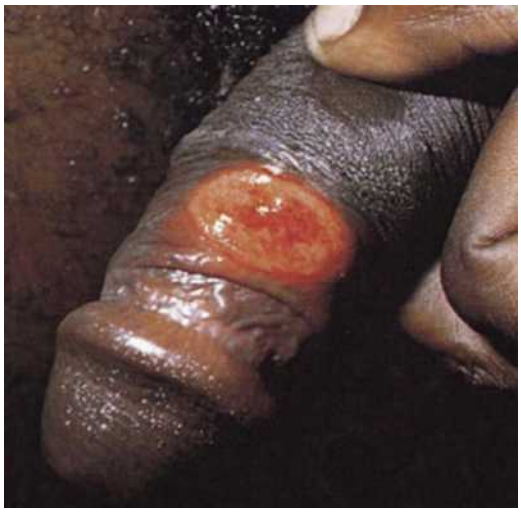

Fig. 84.2 Chancre of primary syphilis. (From: Morse S, Ballard RC, Holmes KK, et al, eds. *Atlas of Sexually Transmitted Diseases and AIDS*, ed 4. London: Saunders/Elsevier; 2010: Fig. 7.9, p 185.)

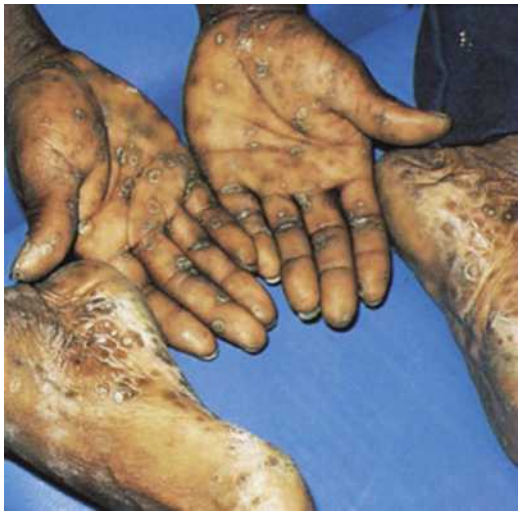

Fig. 84.3 Rash of secondary syphilis on palms and soles. (From: Morse S, Ballard RC, Holmes KK, et al, eds. *Atlas of Sexually Transmitted Diseases and AIDS*, ed 4. London: Saunders/Elsevier; 2010: Fig. 7.24, p 188.)

The appearance of the rash is highly variable. Lesions may be macular, papular, scaly, or pustular in appearance (Fig. 84.3). Mucous patches are multiple shallow erosions of the oropharyngeal mucosa that are usually accompanied by other dermatologic and systemic manifestations of secondary syphilis. Condyloma lata, which resemble genital warts, are broad-based papular lesions that occur on the genitalia and perineum and typically have a moist surface appearance (Fig. 84.4). Lymphadenopathy is typically diffuse, rubbery, and nontender. Epitrochlear adenopathy is particularly suggestive of secondary syphilis. A nonspecific "moth-eaten" alopecia may be seen. Systemic manifestations include low-grade fever, anorexia, headache, malaise, myalgias, and weight loss. Symptoms of secondary syphilis will resolve without treatment, with subsequent progression to latent syphilis.

Patients infected with syphilis who exhibit no clinical manifestations of primary or secondary syphilis are classified as *early nonprimary, nonsecondary syphilis* if infection occurred within the past 12 months. *Unknown duration or late syphilis* includes those patients infected more than 12 months previously and those in whom time

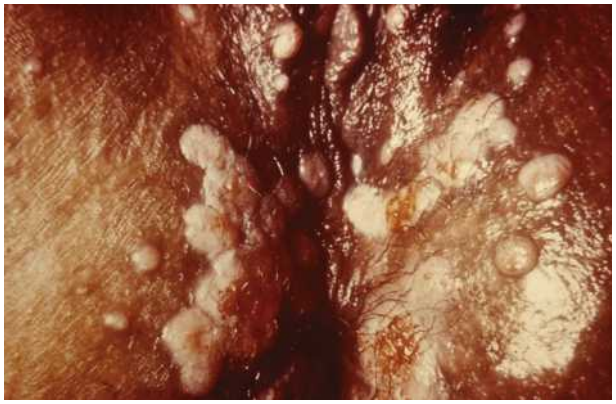

Fig. 84.4 Condyloma lata of secondary syphilis.

of infection is unknown.[8] Neurologic, ophthalmologic, and otologic manifestations can occur at any stage of syphilis. *Neurosyphilis* may be manifested by meningitis, dementia, tabes dorsalis, and general paresis. Patients with *ocular syphilis* may exhibit uveitis, optic neuropathy, and retinal vasculitis. Otic syphilis may cause sensorineural hearing loss, vertigo, and tinnitus.

Tertiary syphilis, which includes cardiovascular manifestations and gummatous disease, is uncommon in the United States. Aortitis, aortic aneurysm, and gummatous lesions of the skin, bones, and other organs may be seen. In patients with untreated syphilis, the estimated risk of eventual progression to tertiary syphilis ranges from 25% to 40%.

Congenital syphilis is transmitted perinatally to the fetus and has significant associated morbidity in infected children. Although relatively uncommon in the United States, congenital syphilis has increased in prevalence in recent years.

Diagnostic Testing

T. pallidum is fastidious and cannot be cultured in the laboratory. The diagnosis of syphilis can be confirmed with darkfield microscopy or by serologic testing. Visualization of the spirochete on darkfield examination of specimens obtained from a chancre or from the moist lesions of secondary syphilis provides an immediate diagnosis. Darkfield microscopy is particularly useful in primary syphilis when false-negative serology is common. The utility of darkfield microscopy is limited by the need for specialized laboratory equipment and appropriately trained personnel, which are lacking at many hospitals.

Serologic tests for syphilis include nonspecific nontreponemal tests and specific treponemal tests. Nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR). The VDRL and RPR provide quantitative measurements of nonspecific antibodies that are produced in response to *T. pallidum* infection. The titers correlate with disease activity, typically rising with active syphilis infection and declining after successful treatment. The sensitivity of nontreponemal tests is approximately 70% to 80% in primary syphilis but rises to nearly 100% in secondary syphilis. False-positive nontreponemal tests may be seen in a variety of conditions, including pregnancy, endocarditis, autoimmune disease, and other acute or chronic illnesses. A positive nontreponemal test should always be confirmed with a specific treponemal test. Specific treponemal tests include the *T. pallidum* enzyme immunoassay (TP-EIA), the fluorescent treponemal antibody absorption (FTA-ABS) and the microhemagglutination test for antibodies to *T. pallidum* (MHA-TP). These treponemal tests provide qualitative measurements of specific antitreponemal antibodies. Although these treponemal tests are highly specific for syphilis, they may remain positive for life even after successful treatment and cure.

The traditional testing algorithm begins with a nontreponemal test for screening purposes, because the quantitative titers serve as a better marker for acute infection. A specific treponemal test is used to confirm the diagnosis when the nontreponemal test is positive. An acceptable alternative testing algorithm begins with the specific treponemal test, which is then confirmed with the quantitative titers of the nontreponemal test. Both types of serologic testing are necessary for the proper diagnosis of syphilis.

Management

Penicillin is the cornerstone of treatment for syphilis, with *T. pallidum* remaining highly sensitive to penicillin. The dosage and preparation of penicillin and the length of treatment vary depending upon the stage of the disease and the associated clinical manifestations (see Table 84.2). A single dose of long-acting benzathine penicillin G (2.4 million units intramuscularly [IM]) is curative in the majority of cases of primary and secondary syphilis. Patients with significant penicillin allergy can be treated with doxycycline or tetracycline (preferred in late latent syphilis) for 2 weeks if no contraindication to these drugs exists. Ceftriaxone has antitreponemal activity, but the optimal dosage and duration of therapy have not been established. Azithromycin has some efficacy but is not recommended as a first-line therapy due to documented resistance and treatment failures. Penicillin remains the drug of choice for patients with neurosyphilis, congenital syphilis, and syphilis during pregnancy even in the presence of penicillin allergy, due to the known efficacy of penicillin and the absence of proven alternative therapies. Patients with these conditions should be admitted for desensitization and treatment with penicillin.

The Jarisch-Herxheimer reaction is an acute worsening of symptoms that may develop after antibiotic therapy is initiated for syphilis. The patient typically reports worsening malaise, myalgias, and fever within 24 hours of antibiotic treatment. The condition has traditionally been thought to be caused by the sudden lysis of spirochetes, but the mechanism is poorly understood. Treatment is supportive, including rest, hydration, and antipyretics. The symptoms resolve spontaneously. Anticipatory guidance regarding the appropriate management of this common self-limited reaction may prevent a return visit to the ED.

Disposition

Most cases of syphilis are treated on an outpatient basis. Hospitalization is recommended for patients with penicillin allergy who require desensitization prior to penicillin therapy, including pregnant women with syphilis and patients with neurosyphilis or congenital syphilis.

Chancroid

Background and Importance

Chancroid is an ulcerating STI caused by the gram-negative organism *Haemophilus ducreyi.* Chancroid is common in parts of the developing world but is rare in the United States, with only 3 cases reported in 2018. Like other ulcerating STIs, chancroid is a cofactor for the transmission and acquisition of HIV.

Clinical Features

After an incubation period of less than 1 week, a tender erythematous papule develops at the site of inoculation. The initial lesion rapidly ulcerates, and multiple painful ulcers subsequently develop (Fig. 84.5). The ulcers typically have an irregular, inflamed, and "dirty" appearance compared to the well circumscribed clean-based chancre of syphilis, and the smaller punched-out appearance of herpetic ulcers. Painful inguinal lymphadenopathy is common and may progress to bubo formation. A *bubo* is a large, painful, fluctuant unilateral inguinal lymph node, which may spontaneously rupture and drain purulent material.

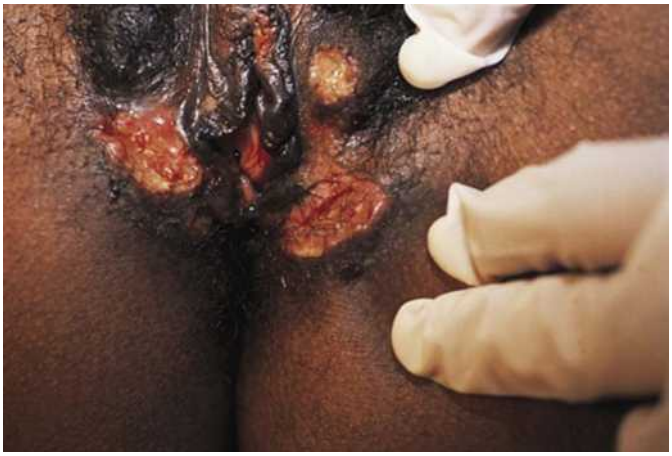

Fig. 84.5 Multiple vulvar ulcers due to chancroid. (From: Morse S, Ballard RC, Holmes KK, et al, eds. *Atlas of Sexually Transmitted Diseases and AIDS*, ed 4. London: Saunders/Elsevier; 2010: Fig. 8.14, p 219.)

Diagnostic Testing

Differential diagnosis of genital ulcers includes herpes and syphilis, both of which are more common than chancroid in the United States. Although the appearance of the ulcers may suggest the diagnosis of chancroid, the clinical diagnosis may be inaccurate. Darkfield microscopy and serologic testing are useful in identifying syphilis, whereas NAAT and viral culture can confirm HSV infection. Chancroid is usually a clinical diagnosis based upon the presence of typical painful genital ulcers and associated tender adenopathy. Culture provides definitive diagnosis but is difficult due to the fastidious nature of *H. ducreyi,* which requires special culture media. No FDA-approved NAAT is available in the U.S., but some clinical laboratories have developed their own NAAT and have performed the necessary Clinical Laboratory Improvement Amendment (CLIA) studies to allow for their use in the diagnosis of chancroid.

Management

Patients with chancroid are treated as outpatients. Single-dose therapy with azithromycin or ceftriaxone is recommended for suspected chancroid (see Table 84.2). Alternative treatment regimens include oral ciprofloxacin or erythromycin.

DISORDERS CHARACTERIZED BY GENITAL DISCHARGE

Foundations

Some STIs, including gonorrhea, chlamydia, trichomoniasis, and pelvic inflammatory disease (PID), are frequently characterized by the presence of genital discharge in absence of genital ulcers and lymphadenopathy. The differential diagnosis of genital discharge is broad, including infections that are not sexually transmitted and noninfectious conditions (see Table 84.1). For example, bacterial vaginosis and candidiasis are common conditions that are not considered to be sexually transmitted but are frequently found during the evaluation of a woman with vaginal discharge. Urethritis, cervicitis, and vaginitis caused by various organisms can present with associated genital discharge.

Infectious causes of urethritis are generally divided into two categories: gonococcal urethritis and nongonococcal urethritis (NGU). Urethritis occurs in men and women and may be asymptomatic, particularly in persons with NGU. When present, symptoms include dysuria, urethral pruritus, and urethral discharge. The absence of visible discharge does not exclude the diagnosis. A clinical diagnosis of urethritis can be made on the basis of any of the following findings in the setting of compatible symptoms: (1) mucoid, mucopurulent or purulent urethral discharge, (2) Gram stain of urethral discharge containing two or more white blood cells (WBCs) per oil immersion field, (3) first-void urine sediment containing 10 or more WBCs per high-power field, and (4) positive leukocyte esterase test on first-void urine. Diagnosis and management of specific causes of urethritis are discussed later.

Cervicitis is characterized by the presence of purulent or mucopurulent discharge from the endocervix and the presence of cervical friability. Many women with cervicitis are asymptomatic. The discharge may be visible in the endocervical canal or noted on an endocervical swab specimen. Cervical friability is demonstrated when endocervical bleeding is easily induced with gentle passage of a swab through the cervical os. Gonorrhea and chlamydia are common causes, but trichomonas and HSV may also cause cervicitis. Frequently, no organism is isolated despite the presence of clinical findings consistent with cervicitis. Women with cervicitis may complain of abnormal vaginal discharge, dyspareunia, and postcoital vaginal bleeding. Pelvic examination may demonstrate endocervical discharge and friability. These findings are insensitive, and the absence of these findings on history and examination do not exclude the diagnosis of cervicitis. Specific causes of cervicitis and their management are discussed later.

Gonorrhea

Background and Importance

Gonorrhea is the second most commonly reported STI in the United States, with more than 500,000 cases reported to the CDC annually. Humans are the only reservoir for the causative organism, *Neisseria gonorrhoeae,* a gram-negative intracellular diplococcus. The prevalence of gonorrhea varies widely, with higher rates of gonorrhea seen among adolescents and young adults, minorities, people with low socioeconomic status, those with a history of substance abuse, and those who engage in high-risk sexual behaviors.

Clinical Features

The signs and symptoms of gonorrhea vary depending upon the sex of the patient, the site of inoculation, and the local or systemic spread of the infection. The incubation period for gonorrhea typically ranges from 3 to 7 days. Most men with gonococcal urethritis become symptomatic within 1 to 2 weeks, prompting them to seek curative treatment. Patients complain of urethral discharge and dysuria. The discharge is usually copious and purulent, although the clinical appearance alone cannot differentiate gonococcal urethritis from NGU (see Fig. 84.6). Women with gonococcal cervicitis are often asymptomatic until ascending infection develops. Because many women remain asymptomatic for prolonged periods, a larger reservoir of untreated women exists. When present, symptoms of gonococcal cervicitis may include abnormal vaginal discharge, dyspareunia, and intermenstrual bleeding. Women with gonococcal cervicitis may also complain of dysuria due to associated urethritis.

Gonococcal proctitis may occur in men and women who engage in receptive anal intercourse and in women who are inoculated by infected vaginal secretions. Patients with gonococcal proctitis are often asymptomatic but may complain of rectal pain, tenesmus, rectal discharge, or bleeding. Anoscopy may reveal abnormal discharge and inflamed friable rectal mucosa.

Gonococcal pharyngitis is usually acquired from oral sexual exposure. Patients with pharyngitis are usually asymptomatic but may complain of sore throat. Tonsillar erythema and cervical lymphadenopathy may be present. Differentiating gonococcal pharyngitis from common

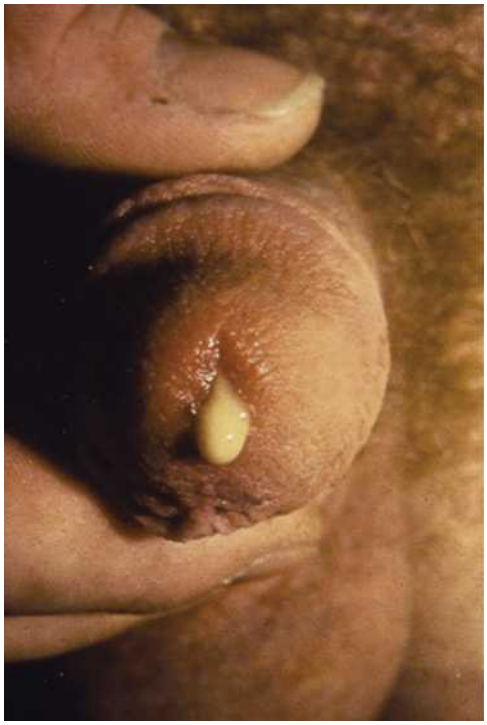

Fig. 84.6 Purulent urethral discharge due to gonococcal urethritis.

viral or bacterial forms of pharyngitis requires a careful history in patients presenting with symptoms of pharyngitis.

Gonococcal conjunctivitis was historically seen most often in infants born to infected mothers. Because infants are now routinely prophylaxed at birth, gonococcal conjunctivitis is now more common in adults who self-inoculate by rubbing the eye with contaminated fingers. Severe conjunctival injection with copious purulent discharge is typically seen. The infection can progress rapidly to corneal ulceration, perforation, and blindness if untreated.

Disseminated gonococcal infection (DGI) results from hematogenous spread of *N. gonorrhoeae.* DGI may occur in the absence of any signs or symptoms of the initial local infection. Characteristic clinical findings include rash, polyarthralgias, tenosynovitis, and septic arthritis. The rash usually consists of petechial or pustular lesions in an acral distribution on the distal extremities. The rash is sparse, with 2 to 10 skin lesions being typical and more than 40 lesions uncommon. Septic arthritis presents as a swollen, red, warm, and painful joint. One or more joints may be involved. The knees, wrists, and ankles are the most common sites. Rarer complications of DGI include hepatitis, meningitis, and myocarditis.

Diagnostic Testing

Nucleic acid amplification tests (NAATs) have replaced culture as the gold standard for the diagnosis of gonorrhea. These tests are widely available and have a higher sensitivity compared to culture. A wide variety of specimens can be used for NAATs, including first-void urine and swabs from the urethra, cervix, vagina, oropharynx, and rectum. Suitable specimens can be obtained by the examining clinician or provided by the patient.

Culture with selective Thayer Martin media is still useful in selected patients and has the advantage of allowing antimicrobial susceptibility testing. Isolation of *N. gonorrhoeae* from the blood, synovial fluid, or skin lesions establishes a definitive diagnosis of DGI, but sensitivity of these cultures is poor. The organism may be more readily identified from other sites (urethra, cervix, rectum, or pharynx) even in the absence of localized symptoms at these sites. When accompanied by the appropriate clinical presentation, identification of gonorrhea by NAATs or culture from any site is sufficient for a presumptive diagnosis of DGI. In symptomatic men, a Gram stain of urethral discharge that reveals gram-negative intracellular diplococci has a sensitivity and specificity approaching 100% for the diagnosis of gonorrhea. A positive Gram stain does not exclude coinfection with chlamydia or other organisms. Gram stain of genitourinary specimens in female patients is not recommended due to potential false-positive results caused by nonpathogenic *Neisseria* organisms that may be normal flora in the female reproductive tract.

Treatment

Recommended treatment options for gonorrhea have changed in recent years due to the increasing antimicrobial resistance of *N. gonorrhoeae.* Ceftriaxone remains the drug of choice for the treatment of gonorrhea. Single-dose therapy with an intramuscular injection of ceftriaxone 500 mg is recommended for gonococcal urethritis, cervicitis, proctitis, and pharyngitis in patients weighing <150 kg. The recommended single dose of ceftriaxone is increased to 1 g IM for patients weighing ≥150 kg (see Table 84.2). Concomitant single-dose therapy with azithromycin is no longer recommended for treatment of gonorrhea due to increasing antimicrobial resistance patterns. When chlamydial infection has not been excluded, antichlamydial therapy should also be administered (discussed later in this chapter). The use of oral cephalosporins or fluoroquinolones is also no longer recommended. DGI and gonococcal arthritis are treated with parenteral ceftriaxone 1 g daily. Several parenteral antibiotic regimens are available for treatment of severe or complicated PID (discussed later in this chapter).

Disposition

Uncomplicated gonococcal infections are treated on an outpatient basis. Hospitalization may be warranted for more severe cases of upper tract infection, such as PID or epididymo-orchitis. Admission and treatment with parenteral ceftriaxone is recommended for DGI, septic arthritis, and conjunctivitis.

Chlamydia

Background and Importance

Chlamydia is the most commonly reported STI in the United States, with more than 1.7 million cases reported to the CDC in 2018. *Chlamydia trachomatis,* an obligate intracellular organism, is the causative pathogen. Approximately 50% of men and 70% of women who are infected with chlamydia are asymptomatic. Adolescents and young adults 15 to 24 years old have the highest rate of chlamydia infection. The reported rate of chlamydia is twice as high among women compared to men, reflecting the higher number of women screened for this infection.

Clinical Features

Chlamydia infection is a common cause of NGU. When present, the urethral discharge associated with chlamydia is typically scant, mucoid, and less purulent than the discharge seen with gonorrhea. Dysuria is less pronounced and presentation is often delayed. Chlamydia cervicitis may present with mucopurulent cervical discharge or postcoital bleeding but is often asymptomatic. When untreated, chlamydia can progress to upper tract infection, including epididymitis and orchitis in men and PID in women. Patients with epididymitis and orchitis complain of unilateral scrotal pain and swelling, and they may also report symptoms of urethritis. Swelling and tenderness of the epididymis and testicle are usually present. Epididymitis is more common with chlamydia infection alone or combined gonorrhea and chlamydia infections, rather than with gonorrhea alone. Chlamydia frequently

TABLE 84.3 Treatment of Sexually Transmitted Infections Associated With Genital Discharge[a]

Disease	Recommended Treatments
Gonorrhea	
Urethritis, cervicitis, proctitis, pharyngitis	Ceftriaxone 500 mg[b] IM single dose
Chlamydia	
Urethritis, cervicitis, proctitis, pharyngitis	Doxycycline 100 mg PO bid for 7 days
Nongonococcal urethritis (NGU)	Doxycycline 100 mg PO bid for 7 days
Trichomoniasis	Men: Metronidazole 2 g PO single dose Women: Metronidazole 500 mg PO bid for 7 days

[a]Alternative treatment regimens for selected patients (including pregnancy, drug allergies) can be found at www.cdc.gov/std/treatment.
[b]For weight ≥150 kg, ceftriaxone 1 g IM single dose.
IM, Intramuscular; *PO,* per os (by mouth).

contributes to the development of PID, which may be indolent or clinically silent, but results in significant chronic sequelae.

Diagnostic Testing

Differentiation between chlamydial and gonococcal infection based solely upon history and physical examination is unreliable, and these infections frequently coexist. NAATs are the diagnostic test of choice, with sensitivity greater than 90% and specificity of 99% for the diagnosis of chlamydia. Concurrent testing for gonorrhea can be performed on the same NAATs specimen obtained from either genital or extragenital sites.

Management

The recommended treatment for chlamydia urethritis, cervicitis, pharyngitis or proctitis is doxycycline 100 mg PO bid for 7 days (Table 84.3). Single-dose azithromycin 1 g PO is no longer the preferred treatment for uncomplicated chlamydia infection, but remains an alternative treatment for use during pregnancy or when doxycycline is otherwise contraindicated. Levofloxacin may also be used in the nonpregant patient. Suspected upper genitourinary tract infection with chlamydia (i.e., epididymitis, PID) requires a longer course of antibiotic therapy ranging from 10 to 14 days (Table 84.4).

Empirical treatment for both gonorrhea and chlamydia is recommended when confirmatory test results are unavailable, because history and physical examination cannot reliably differentiate these conditions and coinfections often occur. Weight-based single-dose ceftriaxone IM plus doxycycline 100 mg PO bid for 7 days treats uncomplicated gonorrhea in addition to lower tract chlamydia infection.

Disposition

Most chlamydia infections are treated on an outpatient basis. Patients with severe upper tract infection and those with associated complications may require hospitalization for parenteral antibiotics. Indications for admission include suspected tubo-ovarian abscess, Fitz-Hugh-Curtis syndrome, patients with intractable vomiting, septic patients, those with peritonitis, prepubertal children, and women with an indwelling intrauterine device (IUD).

Nongonococcal Urethritis

NGU is most often caused by *Chlamydia trachomatis,* but may also be caused by *Trichomonas vaginalis, Mycoplasma genitalium,*

TABLE 84.4 Treatment of Complicated or Upper Genitourinary Tract Sexually Transmitted Infections[a]

Disease	Recommended Treatments
Disseminated gonorrhea	Ceftriaxone 1 g IV or IM every 24 hours *Hospitalization and infectious disease (ID) consult recommended*
Gonococcal conjunctivitis	Ceftriaxone 1 g IV or IM single dose[b] *Consider hospitalization & ID consult*
Epididymitis/orchitis	Ceftriaxone 500 mg[b] IM single dose *plus* Doxycycline 100 mg PO bid for 10 days[c] *Or* Ceftriaxone 500 mg[b] IM single dose *plus* Levofloxacin 500 mg PO every day for 10 days[d] *Or* Levofloxacin 500 mg PO every day for 10 days[e]
Pelvic inflammatory disease (PID)	
Inpatient	Cefotetan 2 g IV every 12 hours *plus* Doxycycline 100 mg PO or IV every 12 hours *Or* Cefoxitin 2 g IV every 6 hours *plus* Doxycycline 100 mg PO or IV every 12 hours *Or* Ceftriaxone 1 g IV every 24 hours *plus* Doxycycline 100 mg PO or IV every 12 hours *plus* Metronidazole 500 mg PO or IV every 12 hours
Outpatient	Ceftriaxone 500 mg[b] IM single dose *plus* Doxycycline 100 mg PO bid for 14 days ± Metronidazole 500 mg PO bid for 14 days

[a]Alternative treatment regimens for selected patients (including pregnancy, drug allergies) can be found at www.cdc.gov/std/treatment.
[b]For weight ≥150 kg, ceftriaxone 1 g IM single dose.
[c]For suspected gonorrhea and/or chlamydia.
[d]For suspected gonorrhea and/or chlamydia *and* enteric organisms (i.e., men who practice insertive anal intercourse).
[e]For suspected enteric organisms.
IM, Intramuscular; *IV,* intravenous; *PO,* per os (by mouth).

other *Mycoplasma* species, *Ureaplasma* species, and other organisms. Patients with NGU are often asymptomatic. Symptoms, when present, are usually less prominent than those seen with gonococcal urethritis. Clinical features are not sufficiently specific to distinguish between gonococcal urethritis and NGU, and coinfection is common. NAATs have high sensitivity and specificity for chlamydia, gonorrhea, trichomoniasis and *M. genitalium* infection. Wet mount microscopy can identify cases of trichomoniasis, but is less sensitive than NAATs, which are now the gold standard. Diagnostic testing is not routinely performed for other causes of NGU. Recommended treatment for NGU is doxycycline 100 mg PO bid for 7 days. Additional empirical treatment with weight-based single-dose ceftriaxone IM is recommended when gonorrhea has not been ruled out with negative NAATs. Treatment of trichomoniasis is discussed separately.

Persistent or recurrent NGU may be caused by treatment failure or reinfection following successful treatment. Management of these patients should be guided by results of diagnostic testing for causative organisms, when possible. *M. genitalium* is increasingly recognized

Fig. 84.7 Frothy vaginal discharge due to trichomoniasis. (From: Morse S, Ballard RC, Holmes KK, et al, eds. *Atlas of Sexually Transmitted Diseases and AIDS*, ed 4. London: Saunders/Elsevier; 2010: Fig. 5.23, p 140.)

as a cause of NGU that may be resistant to treatment with doxycycline alone. NAATs for *M. genitalium* should be obtained. The recommended two-stage treatment for confirmed *M. genitalium* infection is doxycycline 100 mg PO bid for 7 days, followed by moxifloxacin 400 mg PO once daily for 7 days. If antimicrobial resistance testing confirms sensitivity to macrolides, then azithromycin 1 g PO initial dose, followed by 500 mg PO once daily for 3 additional days may be considered as an alternative to moxifloxacin following the recommended 7 day course of doxycycline.

Trichomoniasis

Background and Importance

Trichomonas vaginalis is the flagellated protozoan organism responsible for trichomoniasis, the most common curable STI worldwide. Women are typically more symptomatic than men, but asymptomatic infection occurs in both sexes. Trichomoniasis usually causes mild disease, but significant morbidity can occur. Trichomoniasis has been associated with PID, preterm birth among pregnant women, prostatitis, epididymitis, and increased susceptibility to HIV acquisition.

Clinical Features

Trichomoniasis causes vaginitis in women. Common symptoms include vaginal discharge, pruritus, dysuria, urinary frequency, dyspareunia, and postcoital bleeding. The discharge is classically described as malodorous, frothy, and greenish yellow in color (Fig. 84.7). Pelvic examination may reveal erythema of the vaginal mucosa and vulva, in addition to the discharge. Punctate hemorrhages of the cervix ("strawberry cervix") are seen in up to 10% of cases. Trichomoniasis is often asymptomatic in men but may cause urethritis with associated dysuria and urethral discharge.

Diagnostic Testing

The diagnosis of trichomoniasis is often confirmed with microscopic examination of a saline wet mount slide, which reveals motile flagellated trichomonads and leukocytes (Fig. 84.8). The sensitivity of the wet mount slide is approximately 50% to 65%. Trichomonas may be seen incidentally on microscopic analysis of the urine sediment. NAATs are superior to microscopic examination, with reported sensitivity and specificity greater than 95% for some assays. Point-of-care antigen detection kits are now available. Culture is also confirmatory, but seldom used in the ED.

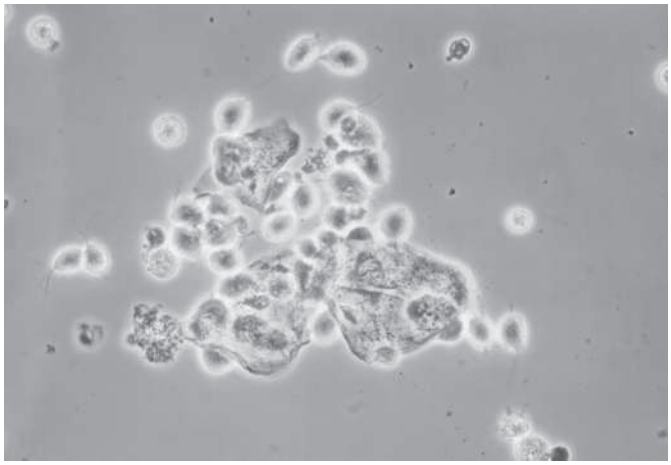

Fig. 84.8 *T. vaginalis* on a wet mount slide prep. (From Centers for Disease Control and Prevention [CDC]: Public Health Image Library [PHIL]. Image #14500. Available at phil.cdc.gov/phil/.)

Management

Treatment of trichomoniasis is indicated in both symptomatic and asymptomatic men and nonpregnant women. Although single-dose metronidazole 2 g PO was previously recommended for treatment of trichomoniasis in men and women, studies have demonstrated increased efficacy using a multi-dose regimen of metronidazole in women. The recommended treatment in women is metronidazole 500 mg PO bid for 7 days. Metronidazole 2 g PO single dose is still recommended for treatment in men. (see Table 84.3). Tinidazole 2 g PO single dose is an acceptable treatment alternative in men and nonpregnant women, but should be avoided during pregnancy. Metronidazole is the recommended treatment for symptomatic trichomoniasis during pregnancy. The treatment of asymptomatic pregnant women with trichomoniasis is controversial, because there is conflicting data regarding the possible increased incidence of preterm labor in pregnant women treated with metronidazole.

Disposition

Trichomoniasis is treated on an outpatient basis. Patients should be counseled to avoid alcohol use for at least 24 hours after completion of metronidazole therapy and 72 hours after completion of tinidazole therapy, due to the occurrence of a disulfiram-like reaction following alcohol use.

Pelvic Inflammatory Disease

Background and Importance

PID is an ascending infection that begins at the level of the endocervix but progresses to the upper reproductive tract, causing endometritis, salpingitis, and peritonitis. *N. gonorrhoeae* and *Chlamydia trachomatis* have traditionally been implicated in the development of PID, but many women diagnosed with PID do not test positive for either of these organisms. Negative testing for gonorrhea and chlamydia from endocervical specimens does not reliably exclude them as a cause for upper tract infection. Polymicrobial involvement is common, with anaerobes, enteric organisms, vaginal flora, and other STIs often implicated in PID. An estimated 10% to 20% of women with gonorrhea or chlamydia may develop PID if they do not receive proper treatment. Other recognized complications of PID include chronic pelvic pain, infertility, and ectopic pregnancy.

Clinical Features

PID causes a spectrum of illness ranging from asymptomatic infection to severe illness with associated peritonitis and systemic toxicity. Lower abdominal pain is the most common presenting complaint. Other

TABLE 84.5 Diagnosis of Pelvic Inflammatory Disease[a]

Minimum Criteria	Additional Criteria[b]
Cervical motion tenderness *or*	Mucopurulent cervical discharge
Adnexal tenderness *or*	Cervical friability
Uterine tenderness	Oral temperature >101°F
	Elevated erythrocyte sedimentation rate
	Elevated C-reactive protein
	White blood cells (WBCs) on microscopy of vaginal secretions
	Laboratory confirmation of endocervical gonorrhea or chlamydia

[a]In a sexually active woman at risk for sexually transmitted infections (STIs) who presents with abdominal pain and no alternative diagnosis is identified, a presumptive diagnosis of pelvic inflammatory disease (PID) may be based upon the criteria listed in this table.
[b]Additional criteria increase specificity but decrease sensitivity for the diagnosis of PID.

symptoms include dyspareunia, abnormal vaginal discharge or bleeding, dysuria, and fever. Nausea, vomiting, diarrhea, and anorexia may be present, mimicking gastrointestinal conditions. Physical findings may include lower abdominal tenderness, cervical friability, mucopurulent discharge, cervical motion tenderness, and adnexal tenderness. Vital sign abnormalities, such as fever and tachycardia, may be seen.

Diagnostic Testing

PID is a clinical diagnosis. No single historical, physical, or laboratory finding or combination of findings is sufficiently sensitive or specific to make a definitive diagnosis of PID. Because PID causes significant morbidity, the CDC recommends a low threshold for the diagnosis and empirical treatment of PID. The diagnosis of PID should be considered and presumptive treatment initiated in any sexually active woman at risk for STIs who presents with lower abdominal or pelvic pain if no alternative diagnosis is identified and if one or more of the following findings are present on pelvic examination: (1) cervical motion tenderness, or (2) uterine tenderness, or (3) adnexal tenderness. These criteria have high sensitivity but low specificity for the diagnosis of PID. Because the use of these criteria will result in the over-diagnosis of PID, one should consider other possible diagnoses. The use of the additional criteria improves the specificity of the diagnosis of PID but decreases the diagnostic sensitivity (see Table 84.5).

NAATs for gonorrhea and chlamydia are recommended. A pregnancy test should always be obtained, because ectopic pregnancy and other pregnancy-related conditions may mimic PID. Computed tomography (CT) and pelvic ultrasonography may reveal findings supporting the diagnosis of PID, including evidence of swelling and inflammation within the endometrial cavity and fallopian tubes. Imaging studies are also helpful in ruling out other diagnoses, such as appendicitis, and for identifying complications of PID, such as tubo-ovarian abscess. Laparoscopy can confirm the diagnosis but is of limited utility due to its invasive nature, limited availability, and expense. In addition, laparoscopy may not identify mild cases of PID.

Management

Treatment should be initiated as soon as possible after the diagnosis is made and should not await the results of microbiologic testing or other delayed diagnostic studies. Delays in the initiation of antibiotic therapy contribute to the development of complications of PID. Multiple inpatient and outpatient antibiotic regimens are available for the treatment of PID (see Table 84.4). The total duration of antibiotic therapy is 14 days. Antibiotic selection should include empirical coverage of gonorrhea and chlamydia. Anaerobic coverage with metronidazole was previously considered optional, but is now recommended in the routine outpatient treatment of PID. Recommended inpatient parenteral treatment regimens also include anaerobic coverage with metronidazole or cephalosporins. Supportive care measures include analgesics, antipyretics, and hydration. Sexual intercourse should be deferred until symptoms have resolved and antibiotic therapy has been completed by the patient and her partner.

Disposition

Most women with PID are treated as outpatients. Current recommendations no longer mandate hospitalization for adolescents or for HIV-positive patients with PID. Follow-up within 72 hours is recommended to ensure appropriate response to initial treatment. Women who meet any of the following criteria should be considered for inpatient treatment of PID:

- Surgical emergencies cannot be excluded (i.e., appendicitis)
- Pregnancy
- Tubo-ovarian abscess
- Severe illness, nausea and vomiting, or high fever
- Inability to follow or tolerate outpatient oral regimens
- Failure to respond to oral antibiotic therapy

In addition, to chronic pelvic pain, ectopic pregnancy, and infertility, other complications of PID are common. Tubo-ovarian abscess or pyosalpinx may be identified on pelvic ultrasound or CT. Perihepatitis, known as *Fitz-Hugh-Curtis syndrome,* is occasionally seen and may result in associated right upper quadrant abdominal pain.

Bacterial Vaginosis

Background and Importance

Bacterial vaginosis (BV) is the most common cause of abnormal vaginal discharge in the United States. Although BV is not considered to be an STI, it is often encountered during the evaluation of patients with an abnormal vaginal discharge. BV is due to an alteration in the vaginal flora with replacement of normal *Lactobacillus* species by a polymicrobial group of organisms, including *Gardnerella vaginalis,* anaerobes, and others.

Clinical Features and Diagnostic Testing

Many women with bacterial vaginosis are asymptomatic. Symptomatic women complain of a malodorous thin whitish vaginal discharge. A fishy odor is often reported and can be accentuated with the addition of 10% potassium hydroxide (KOH) solution to a wet mount slide at the time of pelvic examination (the "whiff test"). The pH of vaginal fluid is greater than 4.5. Microscopic examination of the wet mount slide reveals clue cells, which are vaginal epithelial cells with indistinct borders due to a coating of bacteria. Multiple available NAATs have high sensitivity and specificity for BV. Bacterial vaginosis is associated with an increased risk of PID and complications of pregnancy (premature rupture of membranes and preterm delivery). Bacterial vaginosis may also be a cofactor in the acquisition and transmission of other STIs, including HIV.

Management

Treatment is recommended for all symptomatic women with bacterial vaginosis, regardless of pregnancy status. The established benefit of therapy is the relief of vaginal symptoms. There is conflicting data regarding the efficacy of treatment in reducing the incidence of associated illnesses in pregnant and nonpregnant women. Treatment of bacterial vaginosis in asymptomatic women is not recommended.

Treatment of male sexual partners is of no benefit. Recommended treatment regimens for bacterial vaginosis include: (1) metronidazole 500 mg PO twice a day for 7 days, (2) metronidazole gel 0.75% 5 g intravaginally once a day for 5 days, and (3) clindamycin cream 2% 5 g intravaginally at bedtime for 7 days. Symptomatic pregnant women can be treated with the same oral or topical regimens recommended for nonpregnant women. The use of intravaginal *Lactobacillus* preparations and other probiotics are of no proven benefit in the restoration of normal vaginal flora or in the treatment of bacterial vaginosis.

Vulvovaginal Candidiasis

Background and Importance

Vulvovaginal candidiasis is usually caused by the yeast species *Candida albicans.* An estimated 75% of women will have at least one episode of candidiasis during their lifetime, and recurrent episodes are common. Like bacterial vaginosis, candidiasis is not considered to be an STI but is frequently encountered in the evaluation of patients with abnormal vaginal discharge.

Clinical Features and Diagnostic Testing

Common nonspecific symptoms include pruritus, abnormal discharge, dyspareunia, and external dysuria. Pelvic examination may reveal vulvar erythema and edema with satellite lesions, erythema of the vaginal mucosa, and a thick curdy whitish vaginal discharge. Microscopic examination of a wet mount slide may reveal the presence of budding yeast or pseudohyphae. Diagnosis is facilitated with the use of 10% KOH, which disrupts other cellular structures and facilitates visualization of fungal elements. Fungal culture is the diagnostic gold standard but is rarely performed.

Management

Multiple topical antifungal azole drugs are recommended for the treatment of vulvovaginal candidiasis, including clotrimazole, miconazole, butoconazole, terconazole, and tioconazole. Several topical agents are available over the counter. Fluconazole is the only oral antifungal agent approved by the FDA for treatment of candidiasis. A single dose of fluconazole 150 mg PO is highly effective in nonpregnant women but is contraindicated during pregnancy. A 7-day course of topical azoles is recommended during pregnancy. Single-dose and short-course therapy with azoles is associated with a cure rate of 80% to 90% in uncomplicated *Candida* vulvovaginitis. Male sexual partners may develop *Candida balanitis,* which typically responds to topical antifungal therapy. Treatment of asymptomatic sexual partners is of no proven benefit.

EPITHELIAL CELL INFECTIONS

Condyloma Acuminata (Genital Warts)

Background and Importance

Genital warts are caused by human papillomavirus (HPV). More than 40 types of HPV can infect humans, with the majority of HPV infections remaining asymptomatic or unrecognized. Clinically apparent warts occur in approximately 1% of cases. HPV types 6 and 11 cause most cases of visible genital warts and are considered non-oncogenic. HPV types 16 and 18 are responsible for most cases of cervical cancer and are also associated with vaginal, vulvar, anal, penile, and oropharyngeal cancers. The 9-valent vaccine currently available in the United States provides protection against the most common HPV types that cause cancer and visible genital warts. This vaccine is approved for use in women and men from 9 to 45 years of age, with the optimal timing of vaccine initiation prior to an individual's sexual debut.

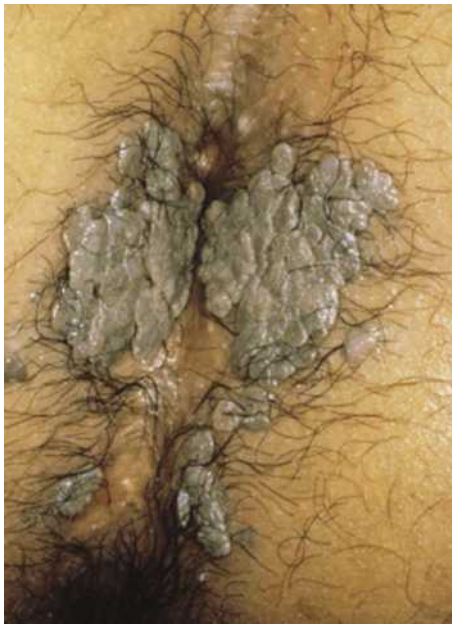

Fig. 84.9 Perianal condyloma acuminata. (From: Morse S, Ballard RC, Holmes KK, et al, eds. *Atlas of Sexually Transmitted Diseases and AIDS*, ed 4. London: Saunders/Elsevier; 2010: Fig. 11.10, p 294.)

Clinical Findings

Genital warts are typically manifested by small painless fleshy papular lesions on the skin or mucous membranes (Fig. 84.9). The slow-growing lesions gradually become more lobulated, pedunculated, or verrucous in appearance. Lesions may become friable and painful due to local irritation or secondary infection. Warts are typically found on the external genitalia, buttocks, and perineum, but they may occur anywhere the organism is inoculated.

Diagnostic Testing

A clinical diagnosis of genital warts is usually made by visual inspection. Differential diagnosis includes molluscum contagiosum, skin tags, nevi, neoplasm, and condyloma lata. Genital warts may have a moist appearance in intertriginous areas, but they do not usually have the denuded surface typically seen with condyloma lata in secondary syphilis. The duration of lesions and presence of associated symptoms are helpful features, because genital warts are often present for months or years but have no associated systemic symptoms. Darkfield microscopy and serology are useful in excluding a diagnosis of syphilis. Although not generally performed in the ED, biopsy can confirm the diagnosis and exclude neoplasm. The application of topical acetic acid to mucosal lesions to screen for HPV is nonspecific and is not recommended.

Management

All available treatments for HPV have significant failure rates. Treatment options include patient-applied regimens and provider-administered regimens. Patient-applied regimens include topical application of imiquimod cream, podofilox solution or gel, or sinecatechins ointment. The patient must be able to adequately visualize and reach the lesions to use these patient-applied agents. These modalities are preferable to some patients, because they can administer the treatment in the privacy of their own home. Provider-administered treatments include surgical excision, cryotherapy, or topical therapy with trichloroacetic acid (TCA) or bichloracetic acid (BCA). Podophyllin-based therapy is contraindicated during pregnancy due to possible teratogenic effects. The emergency clinician may

elect to defer initiation of treatment for genital warts and refer the patient to a primary care provider or STI clinic, because the condition is not emergent and a prolonged course of treatment is usually required.

Molluscum Contagiosum

Molluscum contagiosum is a localized skin infection caused by a member of the pox virus family. The condition is common in childhood when it is usually acquired via nonsexual contact. It may be sexually acquired in adolescents and adults. Clinical appearance consists of one or more small 2- to 5-mm papules. The lesions have a waxy appearance, and central umbilication is common. Spontaneous resolution typically occurs within 6 to 12 months. Differential diagnosis may include genital warts, skin cancers, nevi, skin tags, and other benign skin lesions. Clinical diagnosis is made based upon the typical appearance of the lesions. No specific diagnostic testing or treatment is necessary in the ED. The patient can be referred to a primary care provider or dermatologist for curettage, cryotherapy, or treatment with topical agents for lesions that persist.

ECTOPARASITES

Pediculosis Pubis

Pediculosis pubis is a parasitic infestation caused by *Phthirus pubis,* the pubic louse. Although pubic lice are usually sexually transmitted, they can be transmitted via nonsexual contact with infected individuals or contact with infested fomites, such as linen or clothing. Symptoms include pruritus and mild discomfort at the site of the bites. Small erythematous maculopapular lesions with associated punctate bleeding may be seen. The lice are visible in the pubic hair or attached to the skin while feeding. The eggs (nits) are attached to the shaft of the pubic hairs. Diagnosis is confirmed by visual inspection.

Treatment includes topical permethrin 1% creams and rinses which are available over the counter. Permethrin should be applied to the affected area and washed off after 10 minutes. Alternative topical agents include pyrethrin shampoo and malathion. The patient should attempt to remove any visible nits, because topical treatment is not always ovicidal. Potentially infested linen and clothing should be washed in hot water with detergent. Repeat topical treatment can be applied in 1 to 2 weeks to kill any newly hatched lice. Resistance to pediculicides has been widely reported. An alternative topical agent or oral ivermectin may be used for treatment failures.

Scabies

Sarcoptes scabiei is the mite responsible for scabies. The organism is transmitted via direct person-to-person contact or exposure to infested linens and clothing. Although sexual transmission is common, many cases occur from nonsexual contact. The mite creates superficial burrows in the skin where eggs and excrement are deposited. Intense pruritus is caused by a hypersensitivity reaction to the foreign material in the skin. Careful inspection often reveals characteristic burrows in the skin. Excoriations, papules, and nodules are frequently seen. Commonly affected areas include the groin, genitalia, axilla, and interdigital web spaces of the hands. Diagnosis can be confirmed by microscopic examination of scrapings from characteristic skin lesions, which reveals the mites. Recommended treatments for scabies includes topical permethrin 5% cream, topical ivermectin 1% lotion or oral ivermectin. Permethrin is nontoxic and can be used safely in pregnancy and in patients of all ages. Linen and clothing should be washed in hot water with detergent.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 84: QUESTIONS AND ANSWERS

1. A 30-year-old pregnant female presents for evaluation of a genital ulcer. Darkfield microscopy reveals spirochetes. She is allergic to penicillin. Which of the following statements is false?

- **a.** Azithromycin is an acceptable treatment alternative for primary syphilis during pregnancy in a patient with known penicillin allergy.
- **b.** Nontreponemal serologic tests for syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) may yield false-negative results in primary syphilis.
- **c.** Primary syphilis facilitates the transmission and acquisition of human immunodeficiency virus (HIV) infection.
- **d.** Syphilis is a reportable disease in all 50 states.
- **e.** The chancre of primary syphilis will heal spontaneously without antibiotic therapy.

Answer: A. Penicillin remains the drug of choice for treatment of syphilis during pregnancy. A pregnant patient with syphilis and known penicillin allergy should be admitted for desensitization and treatment with penicillin. Nontreponemal serologic tests may yield false-negative results in primary syphilis when antibody titers have not yet risen. False-positive serology may be seen with a variety of other medical conditions. Visualization of spirochetes on darkfield microscopy confirms the diagnosis of syphilis. All sexually transmitted infections (STIs) facilitate the transmission and acquisition of HIV. Reportable STIs in all 50 states include gonorrhea, chlamydia, syphilis, HIV, and chancroid.

2. A 17-year-old female presents with complaints of pelvic pain. She reports multiple sexual partners and inconsistent condom use. Pelvic examination reveals yellow cervical discharge, cervical motion tenderness, and bilateral adnexal tenderness. Pregnancy test is negative. Which of the following statements regarding this scenario is true?

- **a.** All adolescents with pelvic inflammatory disease require hospital admission for intravenous antibiotics.
- **b.** A negative nucleic acid amplification test for gonorrhea and chlamydia reliably excludes the diagnosis of pelvic inflammatory disease.
- **c.** In the absence of an identifiable alternative diagnosis, the clinical diagnosis and empirical treatment of pelvic inflammatory disease is warranted.
- **d.** The clinical diagnosis of pelvic inflammatory disease requires the presence of lower abdominal tenderness *and* cervical motion tenderness *and* adnexal tenderness on physical examination.
- **e.** Women treated as outpatients for pelvic inflammatory disease should have a follow-up evaluation in 2 weeks.

Answer: C. The clinical diagnosis of pelvic inflammatory disease is warranted in a sexually active woman at risk for sexually transmitted infections (STIs) if no alternative diagnosis is identified and any one of the following findings is present on examination: (1) cervical motion tenderness, (2) uterine tenderness, and/or (3) adnexal tenderness. Additional diagnostic criteria (mucopurulent cervical discharge, fever, elevated white blood cell count, positive testing for gonorrhea or chlamydia, and others) improve specificity but decrease sensitivity in the diagnosis of pelvic inflammatory disease (PID). Adolescents with PID may be treated as outpatients using the same criteria as adult women. Women receiving outpatient treatment for PID should be advised to seek a follow-up evaluation within 48 to 72 hours.

3. Which of the following antibiotic regimens is acceptable for outpatient treatment of pelvic inflammatory disease in a 70-kg woman?

- **a.** Azithromycin 1 g *per os* (by mouth) (PO) (single dose) *and* metronidazole 500 mg bid for 14 days
- **b.** Ceftriaxone 125 mg IM (single dose) *and* doxycycline 100 mg bid for 7 days
- **c.** Ceftriaxone 250 mg IM (single dose) *and* azithromycin 1 g PO (single dose)
- **d.** Ceftriaxone 500 mg IM (single dose) *and* doxycycline 100 mg PO bid for 14 days *and* metronidazole 500 mg PO bid for 14 days
- **e.** Metronidazole 2 g PO (single dose) *and* doxycycline 100 mg PO bid for 14 days

Answer: D. Pelvic inflammatory disease is typically a polymicrobial infection. *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* are frequently implicated organisms, but anaerobes, enteric organisms, and normal vaginal flora may also be present. Empirical treatment of PID should include adequate coverage for gonorrhea and chlamydia. A single dose of ceftriaxone 500 mg IM is adequate treatment for upper tract gonococcal infection in a patient weighing <150 kg. A 14-day course of antibiotics is recommended for adequate coverage of chlamydia and anaerobes in PID.

4. A 24-year-old sexually active male presents with painful genital ulcers. Physical examination reveals a cluster of 2- to 3-mm tender superficial ulcers on the penile shaft. He reports a history of similar lesions in the same location sporadically in the past. Which statement regarding this clinical scenario is false?

- **a.** Both herpes simplex virus (HSV)-1 and HSV-2 can be transmitted through sexual contact.
- **b.** Genital herpes is a lifelong viral infection.
- **c.** Prompt initiation of antiviral medication reduces the duration and severity of symptoms.
- **d.** Topical antiviral therapy is not recommended.
- **e.** Use of condoms is not necessary to prevent transmission in the absence of clinically apparent lesions.

Answer: E. Genital herpes is a lifelong infection caused by herpes simplex virus. Sexual transmission is more common with HSV-2 but

may also occur with HSV-1. Condom use is recommended during asymptomatic periods, because viral shedding and transmission may occur even in the absence of clinically apparent lesions. Antiviral therapy is not curative. Prompt initiation of systemic antiviral medication within 72 hours (acyclovir, famciclovir, or valacyclovir) reduces the duration and severity of symptoms, particularly at the time of primary infection. Topical antiviral therapy is not recommended.

5. A 24-year-old female presents to the emergency department (ED) complaining of vaginal discharge. A copious frothy whitish discharge is noted on speculum examination. Microscopic examination of a saline wet mount reveals motile flagellated organisms. Which of the following statements regarding this patient's treatment is true?
   - **a.** Metronidazole is the drug of choice for treatment of symptomatic trichomoniasis during all stages of pregnancy.
   - **b.** Punctate hemorrhagic lesions are seen on the cervix in most cases of trichomonas vaginitis.
   - **c.** Tinidazole is a safe alternative for treatment of trichomoniasis during pregnancy.
   - **d.** Trichomoniasis is always symptomatic in men and women.
   - **e.** Wet mount microscopy approaches 100% sensitivity in the diagnosis of trichomonas vaginitis.

   Answer: A. Metronidazole is the drug of choice for treatment of symptomatic trichomoniasis during all stages of pregnancy. Tinidazole should be avoided in pregnant women due to limited data regarding safety for use in pregnancy. Visualization of flagellated protozoans on wet mount microscopy of vaginal discharge is highly specific, but only 50% to 65% sensitive for the diagnosis of trichomoniasis. Punctate hemorrhagic lesions on the cervix (so called "strawberry cervix") is seen in up to 10% of cases. Nucleic acid amplification tests for trichomonas are highly sensitive and specific. Trichomoniasis may be asymptomatic in men and women.

6. Single-dose antibiotic therapy is recommended for treatment of which of the following STIs?
   - **a.** Nongonococcal urethritis (NGU)
   - **b.** Vaginal trichomoniasis
   - **c.** Primary and secondary syphilis
   - **d.** Pelvic inflammatory disease
   - **e.** Chlamydia proctitis

   Answer: C. Primary and secondary syphilis are treated with a single dose of benzathine penicillin. Gonococcal urethritis, cervicitis, pharyngitis, and proctitis are treated with a single dose of ceftriaxone. Single-dose metronidazole is no longer recommended for vaginal trichomoniasis, but is still recommended for trichomoniasis in men. A 7-day course of doxycycline is now recommended for chlamydia urethritis, cervicitis, pharyngitis, and proctitis in men and nonpregnant women. Treatment of NGU should include chlamydia coverage. Treatment of upper genitourinary tract STIs, including pelvic inflammatory disease and epididymoorchits, requires a longer course of antibiotic therapy.

Urologic Disorders

Carl A. Germann

KEY CONCEPTS

- Urinary obstruction should be considered in patients with a urinary tract infection (UTI) with risk factors for obstruction. Urinary obstruction should be ruled out in patients presenting in septic shock.
- Patients presenting with acute ureteral obstruction require a urinalysis to rule out the presence of a superimposed UTI.
- Acute, uncomplicated UTIs should be treated with fosfomycin, nitrofurantoin, or trimethoprim-sulfamethoxazole. Fluoroquinolones are not recommended as first-line therapy for uncomplicated UTI.
- Acute bacterial prostatitis (ABP) generally affects men between the ages of 20 and 40 years old with a second peak in men older than 60 years old. A very tender and swollen prostate gland is present in more than 90% of patients with acute prostatitis.
- The three primary predictors of stone passage without the need for surgical intervention are calculus size, location, and degree of patient pain. The most important factor that relates to passage of a calculus though the genitourinary tract is its size (stone <5 mm has a 90% chance of passing spontaneously in 4 weeks).
- Imaging is not needed in all patients with renal colic. It should be performed when symptoms and signs are atypical and the diagnosis is uncertain, when high-grade obstruction is suspected, or when the patient appears toxic or has a solitary or transplanted kidney.
- Testicular torsion should be suspected in all patients presenting with acute scrotal pain. There is no historical factor or physical finding that reliably differentiates torsion from other causes of testicular pain.
- Approximately 10% of patients with testicular trauma have associated torsion and require prompt identification and detorsion.
- Sexually active males should receive ceftriaxone and doxycycline to treat epididymitis. Patients in whom enteric organisms are likely the cause of epididymitis should receive fluoroquinolones. Most cases of pediatric epididymitis are idiopathic, and antibiotics are not routinely recommended.
- Acute urinary retention (AUR) is usually caused by an obstructive lesion but also can be the presenting manifestation of other pathologic processes. Patients with AUR and concomitant infection, pelvic mass, or neurologic deficits warrant imaging in the emergency department.
- Although generally associated with a benign process, the presence of gross or microscopic hematuria requires consideration of life-threatening causes such as aortic abdominal aneurysms and malignancy.

URINARY TRACT INFECTION IN ADULTS

Background

Urinary tract infections (UTI) occur when bacteria, often from the skin or rectum, ascend the urethra and infect the urinary tract. In the United States, the urinary tract is the most common source of infection of patients presenting in septic shock, with an associated mortality of 10% to 20%.

UTI describes an inflammatory response of the urothelium to microorganisms in the urinary tract, resulting in clinical symptoms that include dysuria, frequency, urgency, hematuria, and suprapubic or costovertebral angle discomfort. The diagnosis of a UTI requires the presence of urinary-specific symptoms or signs in a patient who has bacteriuria and no other identified source of infection. Bacteriuria is the presence of bacteria in the urine but is not considered to represent a UTI in the absence of clinical manifestations. Bacteriuria accompanied by symptoms should be treated, whereas bacteriuria in the absence of symptoms should be treated only in select patients (e.g., pregnant women, immunosuppressed patients).

UTIs are classified as lower (confined to the bladder) or upper (involving the ureters or kidneys) and as uncomplicated or complicated. An uncomplicated infection occurs in a nonpregnant individual with a structurally and functionally normal urinary tract. A complicated UTI is a heterogeneous term that may be associated with an underlying functional or structural abnormality, history of urinary instrumentation or organ transplantation, or systemic disease, such as renal insufficiency, diabetes, and immunodeficiency. UTIs in men are generally categorized as complicated given the higher incidence of associated urologic abnormalities. However, men can experience a UTI without an underlying structural or functional abnormality. Complicated UTIs often require a prolonged course of antibiotic therapy and a more in-depth approach to testing and anatomic evaluation.

The term *urethritis* refers to the inflammation of the urethra secondary to an infection or trauma. Frequently, urethritis may be a manifestation of a sexually transmitted infection (STI), such as gonococcal urethritis in *Neisseria gonorrhoeae* infection, but may occur in other clinical scenarios as well. *Cystitis* generally refers to inflammation of the bladder resulting in increased urinary frequency, urgency, dysuria, and suprapubic pain. The causes of cystitis can be separated into bacterial and nonbacterial (e.g., radiation) categories. *Acute pyelonephritis* is a UTI involving the renal parenchyma and collecting system, manifesting with the clinical syndrome of fever, chills, and flank pain. Management and disposition of patients with acute pyelonephritis depend on whether the infection is simple or complicated.

Anatomy and Physiology

In women, the urethra is short and opens close to the vulvar and perirectal areas. This contributes to the much higher incidence of UTI in women. The route of infection in men is also usually ascending, from the urethra to the prostate to the bladder and then to the kidney. Risk factors for cystitis and pyelonephritis include sexual intercourse, use of spermicides, previous UTI, new sex partner, and history of UTI in a first-degree female relative suggestive of possible inherited urethral anatomic pathology.

Pathophysiology

UTIs arise when urinary pathogens from the bowel or vagina colonize the periurethral mucosa and ascend through the urethra and into the collecting system. Infrequently, bacterial infection of the urinary tract arises from hematogenous or lymphatic sources. This is frequently the pathologic mechanism in debilitated and chronically ill patients who are immunosuppressed. Obstruction from any cause, with resultant stasis of urine, is a common contributor to infection. Urinary calculi may cause obstruction and increased susceptibility to the development of a UTI. Likewise, numerous abnormalities of the urinary tract may interfere with its innate ability to resist infection.

Subgroups of patients who are more susceptible than the normal population to UTIs include diabetics, pregnant women, elders, patients who are unable to empty their bladder completely, patients with indwelling urinary catheters, and those with immunodeficiency disorders. Lower UTIs are more common in aging men in the setting of prostatic enlargement or obstruction.

Escherichia coli is responsible for approximately three-quarters of cases of UTI in men and women.[1] Other less common bacteria that may be responsible for infection include *Staphylococcus saprophyticus* and other members of the Enterobacteriaceae family (*Klebsiella pneumonia* and *Proteus mirabilis*). Unusual microorganisms may be found in institutionalized or hospitalized populations. Such settings and conditions predispose the patient to alterations in the normal gastrointestinal (GI) flora, leading to complex UTIs. The uropathogens in these patients include more resistant strains of *Escherichia, Klebsiella, Proteus,* and *Enterobacter,* as well as *Pseudomonas, Enterococcus, Staphylococcus, Providencia, Serratia, Morganella, Citrobacter, Salmonella, Shigella,* and *Haemophilus* spp., *Mycobacterium tuberculosis,* and fungi.

Clinical Features

UTI is usually manifested as dysuria, with or without frequency, urgency, hematuria, or suprapubic discomfort. Symptoms of dysuria, frequency, hematuria, nocturia, and urgency all increase the probability of UTI, whereas vaginal discharge decreases the likelihood of UTI. The probability of cystitis is greater than 90% in women who have dysuria and frequency without vaginal discharge or irritation.

Symptoms of UTI in men may also represent storage or voiding disturbances that are common in aging men (e.g., prostatic enlargement). Commonly, men with lower UTIs have symptoms of urinary urgency, frequency, dysuria, hematuria, and suprapubic pain. If fever and chills are present in association with irritative symptoms and difficulty voiding, acute bacterial prostatitis should be strongly considered. A digital rectal examination of the prostate gland with attention to size, shape, and consistency can identify prostatic enlargement, inflammation, or cancer.

Clinical signs and symptoms suggestive of pyelonephritis include fever, chills, flank pain, costovertebral angle tenderness, and nausea or vomiting, with or without symptoms of cystitis. The presentation of UTI and pyelonephritis can be particularly challenging in those who are debilitated and elders because they may not be able to verbalize their symptoms and can present without fever; these patients may present with nonspecific complaints such as altered mental status, lethargy, abdominal pain, or generalized weakness.

Differential Diagnosis

Bacterial UTI is the most common cause of dysuria. Differential considerations include acute urethritis or acute vaginitis from STI, as well as mechanical trauma or irritation (Table 85.1). In the ED setting, UTI is often overdiagnosed and associated with missed STI diagnoses.[2] In general, if historical information includes contact with multiple sexual partners, recent change in sexual partners, or sexual partner with dysuria or discharge, *Chlamydia trachomatis* and *N. gonorrhoeae* infection should be strongly considered. Because the diagnosis of UTI is rarer in men, a high suspicion for an STI such as gonococcal or nongonococcal urethritis should be maintained. Trauma, calculi, chemical irritation, candidal infections, psychogenic disorders, neoplasm, and malformations or space-occupying lesions compressing the distal genitourinary tract can also cause dysuria.

TABLE 85.1 Clinical Differentiation of Major Causes of Dysuria

Cause	Clinical Features
Urinary tract infection	Internal dysuria
	Frequency, urgency, voiding small volumes
	Abrupt onset
	Suprapubic pain
	Often associated with diaphragm use
	Presence of pyuria
	Presence of hematuria (50% of patients)
Sexually transmitted disease	Internal dysuria
	Occasional history of frequency, urgency, voiding small volumes
	Gradual onset
	History of new or multiple sexual partners
	Vaginal discharge
Vaginitis	External dysuria
	Gradual onset
	Vaginal discharge
	Vaginal odor
	Pruritus

Diagnostic Testing

Urinalysis and Urine Culture

A clean-catch, midstream specimen is the preferred type of urine sample for analysis. This is particularly important in woman in whom contamination from the perineum may result in a false-positive test result. However, even when the procedure is performed correctly, a specimen may be contaminated because the surrounding areas can be difficult to clean. A predominance of epithelial cells suggests that the specimen is contaminated. Sterile catheterization is the most accurate method of obtaining a urine specimen in women and may be the best solution for achieving a reliable urinalysis if the patient is unable to provide a clean-catch specimen or is actively menstruating. In men, the specimen is usually not affected by lack of cleansing or by the timing of specimen collection. Therefore, it is not appropriate to catheterize an adolescent or adult man for the purpose of collecting a urine specimen unless he is experiencing urinary retention.

Urine screening tests provide a quick and inexpensive diagnostic tool, with a goal of reliably predicting specimens that will provide positive or negative cultures. The most commonly used screening tests measure urinary leukocyte esterase and nitrite. Both can be detected by a color change on dipstick testing. Leukocyte esterase is an enzyme found in neutrophils, and nitrite is produced from nitrate reductase, present in gram-negative bacteria. Nitrite positivity is highly sensitive at 95% or greater. However, not all uropathogens, such as *S. saprophyticus* and *Enterococcus*, convert nitrate into nitrite. A urine dipstick test indicating the presence of nitrite and leukocyte esterase has a specificity of almost 100% for UTI. However, dipstick tests should be used

with caution because they can be less sensitive than the microscopic examination of urine (urinalysis). Given the limited negative predictive value of urine dipstick testing, a UTI may be difficult to rule out, even when all features are negative.[3] However, when there is a low pretest probability of UTI, a negative dipstick result for leukocyte esterase and nitrites excludes infection.[4] When the history is strongly suggestive of a UTI and the dipstick is negative, we recommend that a urine culture be sent.

Urine microscopy is an adjunct to the dipstick and helps reduce the number of urine cultures performed. Although no accepted level of pyuria is diagnostic of UTI, careful quantitation with a hemocytometer chamber will find pyuria in nearly all cases of acute UTI caused by coliforms. Pyuria is defined as 10 or more WBCs/mm^3. Microscopic examination of urine to identify bacteria remains the most reliable test for a diagnosis of UTI, but availability varies by institution.

The diagnosis of a UTI can be made only with clinical symptoms and the determination of bacteriuria; however, the diagnosis is confirmed with urine culture. A generally accepted definition of a positive culture is 10^5 or more colony-forming units (CFU)/mL. There is no absolute number of CFUs that is definitive for a UTI; the culture results alone are not diagnostic of infection and must be combined with symptoms suggestive of a UTI. The presence of 10^5 CFUs/mL of bacteria in a urine culture is associated with a 95% likelihood of infection, whereas 10^4 CFUs/mL is associated with a 50% likelihood of infection. The presence of bacteria on culture in the absence of clinical manifestations does not always indicate infection but may be due to patient colonization or contamination of the specimen.

The decision to perform a urine culture should be assessed for its relevance to patient care. Patients with frequency, dysuria, urgency, and suprapubic pain should be treated on the basis of symptoms, and a urine culture is not required to guide therapy. Patients with relapse or recurrent infections, complicated infection, or those in whom multidrug-resistant organisms are suspected based on previous microbiology or exposure to antibiotics should have a culture performed (Box 85.1).

An STI may mimic a UTI and, in sexually active patients, cultures for *C. trachomatis* and *N. gonorrhoeae* should be considered. Other causes of acute dysuria include infections with *Trichomonas vaginalis* and herpes simplex virus.

BOX 85.1 Patient Groups for Whom Urine Culture Is Indicated

- Children
- Adult men
- Immunocompromised patients
- Patients with treatment failure (i.e., with persistent urinary symptoms despite recently completed course of antibiotics)
- Patients with duration of symptoms more than 4–6 days
- Older patients at risk for bacteremia
- Ill-appearing patients with signs and symptoms suggestive of pyelonephritis or bacteremia
- Pregnant women
- Patients with known chronic or recurrent renal infection
- Patients with known anatomic urologic abnormalities
- Patients in whom urinary tract obstruction is suspected (e.g., stones, benign prostatic hypertrophy)
- Patients with serious medical diseases, including diabetes mellitus, sickle cell anemia, cancer, and other debilitating diseases
- Patients with alcoholism or drug dependence
- Recently hospitalized patients
- Patients taking antibiotics
- Patients who recently have undergone urinary tract instrumentation (e.g., cystoscopy, catheterization)

Imaging

Most patients with acute cystitis or pyelonephritis do not need emergency imaging of the urinary tract. Imaging is reserved for patients with a clinical suspicion for underlying structural abnormalities or complicating factors such as abscess, urolithiasis, or emphysematous pyelonephritis. Patients with pyelonephritis who have severe or worsening illness or persistent fever 48 to 72 hours after the initiation of appropriate antimicrobial treatment should undergo imaging to exclude renal stones, abscesses, or obstruction.

Ultrasonography is indicated to assess for potential urinary obstruction. Ultrasound is a sensitive tool for detecting postvoid residual bladder volume, intrarenal and perinephric abscess, and presence of hydroureter and hydronephrosis (Figs. 85.1 and 85.2). Ultrasound can also detect the presence of pyelonephritis and congenital anomalies. Regardless of patient age, this procedure is relatively inexpensive and avoids the hazards of contrast and radiation exposure. A suggestion of obstruction based on clinical suspicion or lack of response to medical therapy necessitates performance of an abdominal ultrasound or noncontrast CT scan.

A contrast CT scan of the abdomen is the most comprehensive test for assessing the kidneys, ureters, and bladder.[5] It has a high sensitivity for detecting abscess, obstruction, and acute inflammation. Imaging with an abdominal CT scan is recommended for those with pyelonephritis and known functional or anatomic abnormalities, recent instrumentation, immunosuppression, or concern for obstruction. Its disadvantages include radiation exposure, cost, and potential to induce contrast reactions.

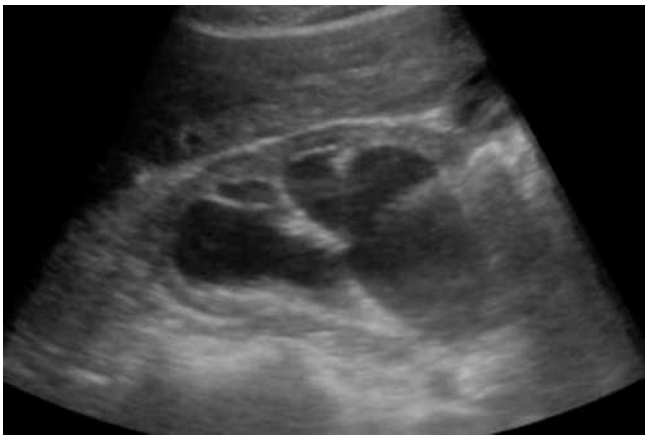


Fig. 85.1 Ultrasound Image Demonstrating Hydronephrosis With a Dilated Collecting System. (Courtesy Dr. Peter Croft.)

Management

Simple Urinary Tract Infection

The options for treating uncomplicated lower UTI include single-dose therapy with fosfomycin, 5 days of nitrofurantoin, or 3 days of trimethoprim-sulfamethoxazole (Table 85.2). Fluoroquinolones such as ciprofloxacin or levofloxacin should not be used as first-line agents for empirical treatment of uncomplicated UTIs. Instead, they should be reserved for patients who have failed or have contraindications to first-line antibiotics. Fluoroquinolones achieve therapeutic levels in renal and prostate parenchyma and are indicated for complicated or more severe infections. However, they are not routinely used for

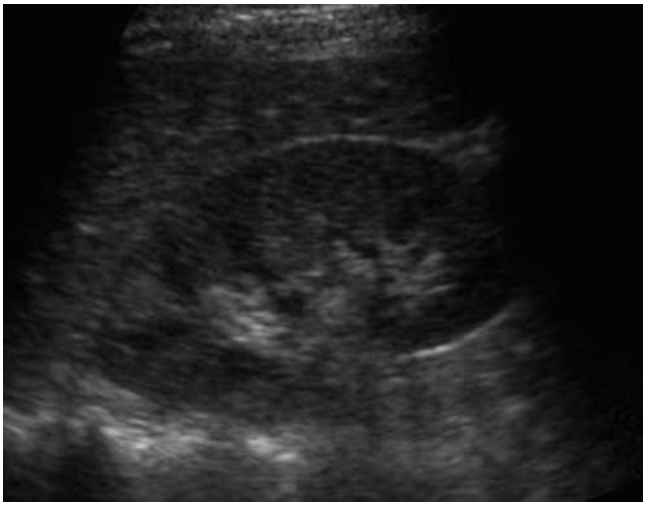


Fig. 85.2 Ultrasound Image Demonstrating a Normal Kidney. (Courtesy Dr. Peter Croft.)

TABLE 85.2 Antibiotic Options for Acute Uncomplicated Cystitis

Antimicrobial	Dose (Oral)	Duration	Common Side Effects
Trimethoprim-sulfamethoxazole	160/800 mg bid	3 days	Nausea, vomiting, anorexia, hypersensitivity reactions
Nitrofurantoin	100 mg bid	5 days	Gastrointestinal disturbance, headache, allergic reactions
Fosfomycin	3 g as a single dose		Diarrhea, nausea, headache, vaginitis, dizziness

uncomplicated cystitis due to adverse side-effect profiles and increasing resistance.

Antibiotics should be chosen with local resistance patterns in mind. The Infectious Disease Society of America (IDSA) recommends avoiding antimicrobial agents when local resistance exceeds 20%, emphasizing the need to be familiar with local outpatient resistance patterns. Although most hospitals monitor the resistance of organisms cultured in their microbiology laboratory, these data may reflect drug-exposed, hospital-acquired organisms more than community-acquired, outpatient-based illnesses. Thus, hospital antibiograms likely overestimate community resistance patterns.

Nitrofurantoin is a useful drug for the treatment of acute bacterial cystitis. It is inexpensive and maintains low serum and high urine levels. Nitrofurantoin is effective against *E. coli* but is inactive against other pathogens, such as *Proteus* and *Pseudomonas aeruginosa.* The rate of clearance is proportional to the creatinine clearance, and dose adjustments are necessary with renal impairment. The most common adverse effects of using nitrofurantoin are GI effects, including nausea, vomiting, and diarrhea.

Fosfomycin is an inhibitor of cell wall synthesis, structurally unrelated to any other antibiotic, and is active against most urinary tract pathogens, including multi-drug resistant gram-negative organisms. Fosfomycin is appealing for emergency department (ED) use because it can be given as a single dose for simple cystitis and does not require that a patient go to a pharmacy. However, we recommend the use of Fosfomycin only when other first-line therapies cannot be used because overuse might lead to an increased rate of resistance. Both nitrofurantoin and fosfomycin remain effective against extended-spectrum, β-lactamase–producing bacteria.[6]

A useful adjunctive therapy for UTIs in patients experiencing significant discomfort is phenazopyridine (Pyridium). It produces topical analgesia in the urinary tract and helps relieve dysuria. Patients should be cautioned that body secretions and excretions (e.g., tears, urine) will turn orange. This side effect can stain contact lenses and alarm unknowing patients.

The clinical presentations of UTIs and STIs can overlap. When coexisting vaginitis or pelvic inflammatory disease is suspected, empirical treatment should include the possibility of coinfection. In such cases, levofloxacin (500 mg/day for 7 days) has activity against common uropathogens as well as chlamydia and can be used with a single intramuscular dose of ceftriaxone (500 mg) for gonorrhea coverage.

Complex Urinary Tract Infection

Patients with mild to moderate pyelonephritis without complicating factors can be safely treated on an outpatient basis as long as the patient is able to eat and drink, has achieved adequate pain control, and has appropriate social support in the home. Given the risk for systemic illness, bacteremia, and progression to severe sepsis, medications must achieve therapeutic levels not only in the urine but also in the renal tissues and bloodstream. Therefore, fluoroquinolones are a first-line choice (Table 85.3). In areas in which the prevalence of resistance of fluoroquinolones is less than 10%, we recommend a 7-day course of ciprofloxacin for empirical outpatient treatment for uncomplicated pyelonephritis. In areas in which there is more than 10% fluoroquinolone resistance, the most recent IDSA guidelines recommend giving a long-acting parenteral antibiotic, such as 1 g ceftriaxone, followed by 10 to 14 days of an oral cephalosporin. Trimethoprim-sulfamethoxazole (TMP-SMX) for 10 to 14 days is an alternative treatment. Nitrofurantoin and fosfomycin do not achieve adequate blood and tissue levels and therefore are not effective for pyelonephritis.

A severe upper tract UTI necessitating hospitalization initially should be treated with parenteral antibiotics, such as cefepime, ceftriaxone, piperacillin-tazobactam, aztreonam, or a fluoroquinolone, with transition to oral therapy after the patient has been afebrile for 24 to 48 hours (Table 85.4). Oral therapy should be continued for 10 to 14 days. Follow-up urine cultures are recommended given the diverse flora and high rate of antimicrobial resistance.

In men, if there are no signs of toxicity, the patient can be treated on an outpatient basis with any of the urinary antibacterial agents (e.g., TMP-SMX, nitrofurantoin, fluoroquinolones) for 7 to 14 days. If concomitant prostatitis is suspected, TMP-SMX or a fluoroquinolone is recommended for 14 days. If evaluation demonstrates suspicion for prostate involvement, recurrent infection, or hematuria, the patient should be referred to a urologist for further evaluation. Patients with symptoms of prostatic enlargement can be treated with α-adrenergic receptor antagonists and/or 5-alpha-reductase inhibitor therapy (Table 85.5). Surgical treatment produces the most significant, long-term symptom improvement; it includes transurethral

TABLE 85.3 Antibiotic Options for Acute Uncomplicated Pyelonephritis

Antimicrobial	Dose (Oral)	Duration	Common Side Effects
Ciprofloxacin	500 mg bid	7 days	Gastrointestinal disturbance, headache, dizziness, tremors, restlessness, confusion, rash, *Candida* infections
Levofloxacin	750 mg once daily	5 days	Same as for ciprofloxacin
Trimethoprim-sulfamethoxazole	160/800 mg bid	10–14 days	Nausea, vomiting, anorexia, hypersensitivity reactions

TABLE 85.4 Antibiotic Options for Complicated Pyelonephritis

Antimicrobial	Dose (IV)	Common Side Effects
Cefepime	1–2 g every 8 h	Abdominal pain, muscle cramps, nausea, vomiting
Ceftriaxone	1 g every 24 h	Fever, cough, sore throat, fatigue
Piperacillin-tazobactam	3.375 g every 6 h	Diarrhea, nausea, vomiting, rash
Aztreonam	1 g every 8–12 h	Cough, abdominal pain, nausea, vomiting
Ciprofloxacin	400 mg every 12 h	GI disturbance, headache, dizziness, tremors, restlessness, confusion, rash, *Candida* infections
Levofloxacin	500 mg every 24 h	Same as for ciprofloxacin

TABLE 85.5 Medication Options for Prostatic Enlargement

Antimicrobial	Dose
Alpha-Adrenergic Receptor Antagonist	
Alfuzosin	10 mg once daily
Doxazosin	1 mg once daily
Tamsulosin	0.4 mg once daily
Terazosin	1 mg once daily or at bedtime
5-Alpha-Reductase Inhibitors	
Dutasteride	0.5 mg once daily
Finasteride	5 mg once daily

prostate resection, open prostatectomy, laser vaporization, transurethral microwave therapy, or needle ablation. Decisions regarding treatment options are based on the degree of obstruction and symptoms.

Disposition

Hospitalization is required in the presence of clinical toxicity (e.g., fever, tachycardia, hypotension, vomiting), inability to take oral medications, an immunocompromised state, third-trimester pregnancy, failure of oral outpatient therapy, urologic abnormalities, or patients with significant comorbid conditions, including heart failure and renal insufficiency. Patients who don't fall into these categories often benefit from short-term treatment in the ED or observation unit with IV hydration, pain and fever control, and the first dose of an IV fluoroquinolone. If these patients improve clinically, and can tolerate food and drink, they can be safely discharged home on a 10- to 14-day course of an oral fluoroquinolone, with close primary physician follow up. Urine culture with sensitivity testing and further diagnostic evaluation are not necessary in this patient population.

COMPLICATED URINARY TRACT INFECTION IN HIGH-RISK POPULATIONS

Pregnancy

UTI during pregnancy represents a special situation. Although the incidence of UTI in pregnancy is approximately the same as in nonpregnant women, pyelonephritis is more common during pregnancy. This is likely a result of the physiologic changes that occur within the urinary tract of pregnant women, which include ureteral and renal pelvis dilation. Factors associated with a higher risk of bacteriuria include a history of prior UTI, preexisting diabetes mellitus, increased parity, and low socioeconomic status.

Unlike bacteriuria in nonpregnant females, bacteriuria in pregnant women, even if they are asymptomatic, should be treated. Untreated bacteriuria in pregnancy is associated with premature labor, low birth weight, perinatal mortality, maternal anemia, and maternal pyelonephritis. Like nonpregnant women, *E. coli* is the most common uropathogen. The symptoms of UTI and pyelonephritis are also the same as in nonpregnant patients; however, urinary frequency and urgency may be symptoms of a normal pregnancy. Specimen collection and diagnostic strategies are also similar. A urine culture specimen should be obtained, along with a follow-up culture as a test of cure.

Options for empirical treatment for UTI include amoxicillin-clavulanate, cefpodoxime, nitrofurantoin, fosfomycin, and TMP-SMX (Table 85.6). The evidence regarding an association between the nitrofuran and sulfonamide classes of antibiotics and birth defects is mixed.[7] Previous American College of Obstetricians and Gynecologists (ACOG) recommendations were to avoid TMP-SMX and nitrofurantoin during the first trimester. Current recommendations state that it is appropriate to prescribing sulfonamides or nitrofurantoin in the first trimester when no other suitable alternative antibiotics are available.[7]

During the second and third trimesters, sulfonamides and nitrofurantoins may be used as first-line agents for the treatment of UTIs.[7] Fluoroquinolones should be avoided in pregnancy.

Hospital admission should be considered for patients in their last trimester, who appear ill, or who have evidence of pyelonephritis and would benefit from treatment with parenteral antibiotics and IV fluids. Parenteral regimens for the empirical treatment of pyelonephritis are similar to those for nonpregnant patients, except the use of fluoroquinolones, and include ceftriaxone, cefepime, aztreonam, and piperacillin-tazobactam (Table 85.7). Nitrofurantoin and fosfomycin do not achieve tissue levels adequate to treat pyelonephritis

TABLE 85.6 Antibiotic Options for Bacteriuria in Pregnancy

Antimicrobial	Dose (Oral)	Duration	Contraindications
Amoxicillin-clavulanate	500 mg tid	3–7 days	
Cefpodoxime	100 mg bid	5–7 days	
Nitrofurantoin	100 mg bid	5–7 days	First trimester and 38 weeks to delivery
Fosfomycin	3 g as a single dose		
Trimethoprim-sulfamethoxazole	160/800 mg bid	3 days	First trimester and term

TABLE 85.7 Parenteral Antibiotic Options for Pyelonephritis in Pregnancy

Antimicrobial	Dose (IV)
Ceftriaxone	1 g every 24 h
Cefepime	1 g every 8 h
Piperacillin-tazobactam	3.375 g every 6 h
Aztreonam	1 g every 8–12 hours

appropriately. Hospitalized pregnant patients who are afebrile for 48 hours can be discharged on oral antibiotics, directed by culture susceptibility results, to be completed in 10 to 14 days.

Indwelling and Temporary Urinary Catheters

Catheter-associated UTI (CAUTI) is defined as urine containing greater than 1000 CFU/ml of one or more bacterial species in a catheterized patient with suggestive symptoms, such as pelvic discomfort, flank pain, fever, rigors, malaise, altered mental status or lethargy with no other identified cause, costovertebral angle tenderness, or acute hematuria.

Screening for or treating asymptomatic bacteriuria in patients with indwelling catheters is not indicated. Antibiotic treatment results in the development of resistant microorganisms, whereas removal of the catheter leads to the spontaneous elimination of bacteria in many patients. Treatment of patients with a UTI in whom permanent removal of the catheter is contraindicated includes antibiotic therapy and urine culture and sensitivity. Replacement of the catheter and strong consideration for hospitalization is indicated in those who exhibit altered vital signs, systemic symptoms, or a toxic appearance.

Many patients with indwelling urinary catheters who present to the ED are older and not able to verbalize their symptoms or lack clinical signs of infection. Given that a catheter-associated UTI is a common cause of subsequent bacteremia and mortality, empirical antimicrobial therapy, in addition to replacement or removal of the catheter, is often appropriate in such patients. Urine culture with antibiotic sensitivity testing will help guide antibiotic therapy in this patient population. The most important risk factor for bacteriuria is the duration of catheterization. The most effective strategy for addressing CAUTIs is to prevent the infection from occurring by placing urinary catheters only when necessary and considering the use of intermittent catheterization and condom catheters, when appropriate.

PROSTATITIS

Background

Males with cystitis often have involvement of the prostate.[8] Prostatitis encompasses four distinct clinical processes—acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis–chronic pelvic pain syndrome, and asymptomatic inflammatory prostatitis.

Acute bacterial prostatitis generally affects men between the ages of 20 and 40 years, with a second peak in men older than 60 years. Acute prostatitis is caused by a bacterial infiltration that is usually precipitated by reflux of urine infected by *E. coli, Klebsiella, Enterobacter, Proteus,* or *Pseudomonas* spp.

Chronic bacterial prostatitis is a persistent bacterial infection of the prostate lasting more than 3 months. Approximately 10% of acute bacterial prostatitis cases develop into chronic bacterial prostatitis.[9] This can be caused by undertreated acute bacterial prostatitis or highly virulent strains. Like acute bacterial prostatitis, gram-negative bacteria are responsible for most cases of chronic prostatitis.

Whereas acute and chronic bacterial prostatitis have clear bacterial etiologies and are managed as infectious diseases, *chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)* is characterized by chronic pelvic pain and voiding symptoms in the absence of a clear bacterial etiology.[10] CPPS is defined as urologic pain in the pelvic region associated with urinary symptoms or sexual dysfunction lasting for at least 3 of the previous 6 months. Symptoms of chronic bacterial prostatitis may not differ from those of CP/CPPS. It is a heterogeneous condition with broad diagnostic criteria and uncertain cause, making it difficult to determine an effective treatment regimen reliably.

Asymptomatic inflammatory prostatitis is a painless inflammation of the prostate gland in the absence of infection. It is a common finding in men with benign prostatic hyperplasia and a diagnosis of exclusion in the ED.

Clinical Features

Patients with acute prostatitis often report UTI symptoms such as fever, chills, dysuria, urinary frequency or urgency, and/or perineal and low back pain. A rectal examination will reveal an exquisitely tender and swollen prostate gland in more than 90% of patients. There is no evidence that performing a rectal examination induces clinically significant bacteremia.

Clinical manifestations of chronic prostatitis vary widely, making recognition difficult. Most patients report some degree of voiding symptoms (e.g., frequency, urgency, dysuria), low back and perineal pain and, occasionally, myalgias. Fever and chills are uncommon except during an acute exacerbation of the chronic infection. Findings on the physical examination, including examination of the prostate, often are unremarkable. The diagnosis is based on history, physical examination, and positive urine culture.

Diagnostic Testing

Acute bacterial prostatitis is a clinical diagnosis. A urine Gram stain and culture are recommended to identify causative organisms and guide treatment. Blood cultures are recommended for patients with acute prostatitis and fever who have not yet received antibiotics.[8] Although acute bacterial prostatitis is usually caused by typical urinary pathogens, an STI such as chlamydia and gonorrhea should be

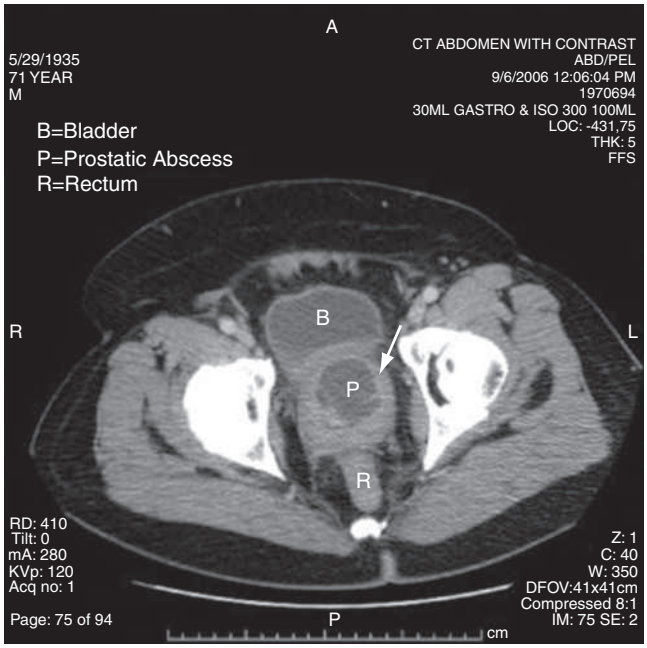


Fig. 85.3 Prostate Abscess. *B,* Bladder; *P,* prostate; *R,* rectum. (From Vandover JC, Patel N, Dalawari P. Prostatic abscess. *J Emerg Med.* 2011;40:e83–e85.)

considered, especially in sexually active patients. Urethral swabs or first-voided urine, with subsequent culture or DNA amplification, should be obtained if a STI is suspected.

The most common complications of acute prostatitis are acute urinary retention (AUR) and prostatic abscess. Approximately 10% of men with acute prostatitis will have some urinary retention, which can be diagnosed using bedside ultrasound. Transrectal ultrasound or CT can detect prostatic abscess and should be considered in patients who fail to improve with antibiotics (Fig. 85.3).

Management

Outpatient therapy can be used if the patient is not systemically ill, can tolerate oral medications, and does not have urinary retention. General support measures for outpatients should include bed rest, analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), hydration, and stool softeners. Alpha blocker therapy is also recommended for obstructive voiding symptoms related to prostatitis (see Table 85.5).

There is no consensus regarding an optimal treatment regimen, so regional patterns of antibiotic resistance should be considered. Few antimicrobial agents are able to penetrate the prostrate and achieve sufficient concentrations to eradicate infection. Fluoroquinolones, such as ciprofloxacin or levofloxacin, achieve the highest concentrations in the prostate and are the first-line agents in the treatment of bacterial prostatitis. Empirical parenteral antibiotics such as ciprofloxacin, levofloxacin, or ceftriaxone are recommended until fever and other symptoms have subsided. After improvement, oral antibiotics are recommended for at least 4 weeks (Table 85.8). Hospitalization for parenteral antibiotics is recommended for patients who appear systemically ill, cannot tolerate oral medications, or have urinary retention as determined by ultrasound or catheterization. Antibiotic options include ciprofloxacin 400 mg IV every 12 hours, levofloxacin 500 mg IV every 24 hours, or ceftriaxone 2 g IV every 24 hours. Following clinical improvement, the patient may be transitioned to an oral regimen, such as a fluoroquinolone. The duration of treatment should be a minimum of 2 weeks, although 4 to 6 weeks may be necessary.

TABLE 85.8 Oral and Parenteral Antibiotic Options for Prostatitis (4 to 6 Weeks' Duration)

Antimicrobial	Dose
Ciprofloxacin	400 mg every 12 h (IV)
Levofloxacin	500 mg every 24 h (IV)
Ceftriaxone	2 g every 24 h (IV)
Ciprofloxacin	500 mg every 12 h (PO)
Levofloxacin	500 mg once daily (PO)
Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)

The treatment of chronic bacterial prostatitis consists of antibiotics for 4 to 12 weeks. Of the researched treatments, α-adrenergic receptor blockers and antibiotics used alone or in combination result in the greatest improvement in symptoms (see Tables 85.5 and 85.8). Anti-inflammatories may also be beneficial. Patients thought to have chronic prostatitis or CPPS should be referred to a urologist.

Treatment of prostatic abscess consists of broad-spectrum intravenous antibiotics (e.g., ciprofloxacin, 400 mg IV every 12 hours) and urologic consultation for perineal drainage or surgical debridement.

RENAL CALCULI

Background

Urolithiasis affects about 12% of the world population and occurs approximately twice as much in men than women.[11] Multiple pathogenic factors interact to cause the formation of renal calculi. Risk factors include older age, male gender, obesity, and family history (Box 85.2). Its incidence depends on geographic, ethnic, dietary, and genetic factors. Approximately 50% of patients will have a recurrence within 5 years.

Pathophysiology

Most ureteral calculi originate in the kidney and then pass into the collecting system. The chemical composition of urinary tract stones is the key factor for determining optimal management. Stones are generally composed of calcium, struvite, or uric acid. Most stones (75%) are composed of calcium oxalate, alone or in combination with calcium phosphate. The hyperexcretion of calcium is a major contributor to stone formation; its most common identified cause is hyperparathyroidism. Other medical conditions that lead to increased calcium levels include hypercalcemia of malignancy, sarcoidosis, and excessive calcium ingestion or increased absorption from the gut. The other major component of calcium stones, oxalate, is influenced by diet. Hyperoxaluria occurs in the presence of small bowel disease, bariatric surgery, Crohn disease, ulcerative colitis, and radiation enteritis.

Magnesium ammonium phosphate (struvite) stones account for approximately 15% of all renal calculi. Struvite stones occur almost exclusively in patients with UTIs and are sometimes referred to as infection stones. They form as a result of the presence of urea-splitting organisms, such as *Proteus, Providencia, Klebsiella, Pseudomonas,* and *Staphylococcus.* Patients with anatomic abnormalities that predispose them to recurrent UTIs are at increased risk of developing struvite stones. Most staghorn calculi—stones that fill the greater part of the collecting system—are composed of struvite.

Uric acid stones account for 10% of all stones in the United States. Approximately 15% of patients with symptomatic gout have uric acid calculi, and the incidence of uric acid stones increases with the use of uricosuric agents. In addition to hyperuricosuria, aciduria is

BOX 85.2 Risk Factors for Urolithiasis

- Metabolic disease or disturbance
  - Crohn disease
  - Milk-alkali syndrome
  - Primary hyperparathyroidism
  - Hyperoxaluria
  - Hyperuricosuria
  - Sarcoidosis
  - Recurrent UTI
  - Renal tubular acidosis (type I)
  - Gout
  - Laxative abuse
- Positive family history
  - Hot arid climates (southeast United States)
  - Male gender (white men affected more commonly than black men)
  - Previous kidney stone
  - Dehydration

UTI, urinary tract infection.

considered necessary because the precipitation of uric acid is unlikely at a higher urine pH. A distinctive feature of uric acid stones is their radiolucency.

Impaction along the genitourinary tract is a serious complication of renal calculi and can cause several physiologic changes. Once obstruction occurs, a rapid redistribution of renal blood flow results in a decrease in the glomerular filtration rate (GFR). As glomerular and tubular function decrease, renal excretion shifts to the unaffected kidney. Obstruction also causes a rapid decrease in ureteral peristaltic activity. In the presence of infection, renal and ureteral function may be impaired. Complete obstruction of the ureters may lead to loss of renal function with an increased incidence of irreversible damage after 1 to 2 weeks. Partial obstruction is associated with a lower likelihood of renal injury but may still result in irreversible damage.

Although calculus size and location are important determinants of the degree of disease, the major cause of progressive renal damage is associated infection. The stone behaves as a foreign body and leads to stasis and obstruction, decreasing host resistance and increasing the incidence of infection. Subsequent infectious complications include pyelonephritis, perinephric abscess, and gram-negative bacterial sepsis.

The three primary predictors of stone passage without the need for surgical intervention are calculus size, location, and degree of patient pain. The most important factor that relates to passage of a calculus though the genitourinary tract is its size. Approximately 90% of stones smaller than 5 mm pass spontaneously within 4 weeks. This percentage decreases to 15% for stones 5 to 8 mm in size. Up to 95% of stones larger than 8 mm become impacted along the genitourinary tract, and lithotripsy or surgical removal is usually required. Surgical intervention can be performed on an outpatient basis, provided the patient is able to tolerate oral intake and has adequate pain control unless the stone is infected, renal damage is considerable, there are bilateral obstructing stones, or there is obstruction of a solitary or transplanted kidney. Spontaneous passage is more frequent with stones located below the midureter than those located above the midureter.

Renal calculi seldom cause complete obstruction. There are five sites along the ureter at which calculi are likely to become impacted (Fig. 85.4). First, a stone may lodge in the calyx of the kidney or pass into the renal pelvis and become lodged at the ureteropelvic junction. Second, the relatively large renal pelvis (1 cm) narrows abruptly at its distal portion, where it is equal in diameter to its adjoining ureter (2 to 3 mm). The third region is near the pelvic brim, where the ureter arches over the iliac vessels posteriorly into the true pelvis. The most constricted area along the ureter, and a common location for impaction, is the ureterovesicular junction. This is the site at which the ureter enters the muscular coat of the bladder (intramural ureter). At the time of diagnosis, up to 75% of stones are located in the distal third of the ureter. Finally, calculi may become lodged in the vesical orifice.

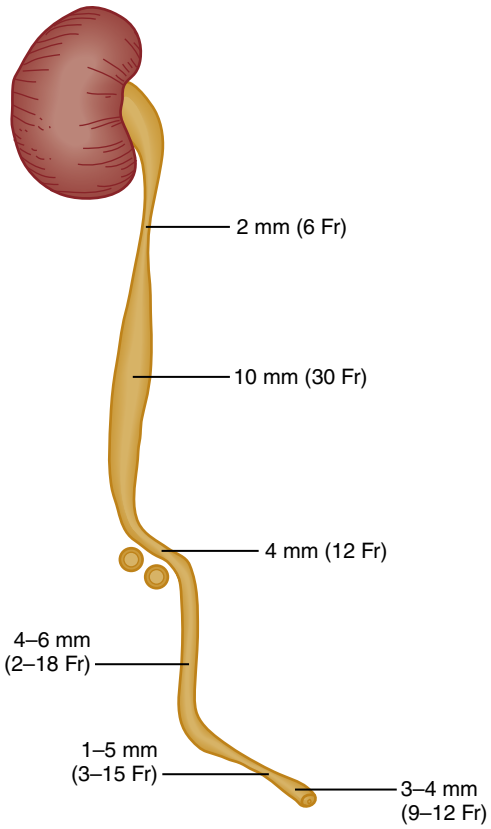


Fig. 85.4 Variations in Caliber of the Ureter. *Fr,* French catheter size. (Adapted from Eisendrath, Rolnick. Lich R Jr, et al. Childhood disorders and diseases. In: Harrison JH, Gittes RF., eds. *Campbell's Urology*. Vol. 1. 4th ed. Philadelphia: WB Saunders; 1978.)

Clinical Features

The onset of pain usually is abrupt, with a crescendo of extreme pain that begins in the flank, extends laterally around the abdomen, and radiates into the groin. Pain may radiate to the testicles in men and the labia majora in women. A constant, underlying dull ache in the flank is common between episodes of colic. The cause of colicky, severe flank pain is hyperperistalsis of the smooth muscle of the calyces, pelvis, and ureter, whereas the cause of a dull ache can be acute obstruction and renal capsular tension. GI symptoms of nausea and vomiting are common.

One-third of patients experience gross hematuria, with or without blood clots in the urine. Symptoms of urinary urgency and frequency often develop as the stone nears the bladder. A history of fever and chills strongly suggests superimposed infection; these cases should be regarded as true urologic emergencies.

BOX 85.3 Differential Diagnosis for Pain Associated With Urolithiasis

Urologic Disease

Upper Urinary Tract

Renal infarct
Renal parenchymal tumors
Urothelial tumors
Papillary necrosis
Pyelonephritis
Hemorrhage (blood clot)

Ureter

Urothelial tumors
Hemorrhage (blood clot)
Previous surgery (e.g., stricture)
Metastatic tumors

Lower Urinary Tract

Urothelial tumors
Urinary retention

Nonurologic Disease

Intra-abdominal

Peritonitis (especially appendicitis)
Biliary colic
Intestinal obstruction

Vascular

Abdominal aortic aneurysm
Superior mesenteric artery occlusion

Retroperitoneal

Retroperitoneal lymphadenopathy
Retroperitoneal fibrosis
Tumor

Gynecologic

Cervical cancer
Endometriosis
Ovarian vein syndrome

Musculoskeletal

Muscle strain or bony injury

A patient with renal colic often is in severe pain and paces or writhes in pain on the stretcher, unable to find a comfortable position. The abdomen should be auscultated and palpated in search of bruits and thrills over the abdominal aorta and iliac vessels because the clinical manifestations of aortic abdominal aneurysms (AAAs) may mimic those of renal colic. Patients commonly have intermittent pain that may nearly resolve between episodes of severe discomfort.

Differential Diagnosis

A number of clinical diseases can produce pain similar to that of renal colic (Box 85.3). Potentially serious or life-threatening alternate diagnoses include pulmonary embolism, ectopic pregnancy, biliary disease, bowel obstruction, incarcerated inguinal hernia, pancreatitis, appendicitis, AAA, renal vein thrombosis, and renal malignancies and infarction.

Diagnostic Testing

Urinalysis and Culture

Red blood cells (RBCs) generally are found in the urine of patients with urolithiasis. However, the absence of RBCs in the urine does not exclude the diagnosis. Up to 20% of patients with documented urolithiasis have no microscopic hematuria.[12] Furthermore, there is no correlation between the degree of obstruction and absence of hematuria.

Sterile pyuria can occur in the absence of infection as a result of ureteral inflammation, but the presence of a UTI should be investigated if other clinical signs of infection are present, such as fever and chills. A urinalysis with culture should be performed to look for pyuria and bacteriuria and to measure nitrite and leukocyte esterase levels when infection is suspected.

The kidney does not produce urine with a pH greater than 7.5 under normal conditions, so a urinary pH higher than 7.5 should raise suspicion for the presence of urea-splitting organisms such as *Proteus*. Renal tubular acidosis and ingestion of absorbable alkali also may increase the urinary pH and should be considered in the differential diagnosis. A pH less than 5 often is associated with the formation of uric acid calculi.

Other Laboratory Tests

Measurement of blood urea nitrogen (BUN) and serum creatinine levels is not routine but should be performed in patients who have a renal calculus with a solitary kidney, transplanted kidney, or history of renal insufficiency. On rare occasions, urolithiasis can present as acute renal failure resulting from obstruction of both ureters or the ureter of a solitary kidney. A slightly elevated white blood cell (WBC) count in patients with renal calculi may be the result of demargination from acute pain, but this is not a sensitive test and should be performed only in patients who are thought to be infected. A significantly elevated WBC count or left shift on the differential suggests active infection.

Imaging

Imaging is not needed in all patients with renal colic but should be performed when signs and symptoms are atypical and the diagnosis is in question, the patient has a solitary or transplanted kidney, or appears toxic, or high-grade obstruction is suspected.

Radiography of the Kidney, Ureter, and Bladder

As an initial imaging study, kidney, ureter, and bladder (KUB) radiography provides only presumptive evidence of calculi (<70% specificity), so it should be followed by a more definitive study or avoided altogether. It is of limited usefulness on its own except to monitor progression of a previously identified radiopaque stone in a stable patient.

Intravenous Pyelography

Intravenous pyelography is an accurate imaging modality to detect renal stones, but is seldom used now because CT scanning and ultrasonography have become first-line imaging modalities. It is very sensitive, capable of establishing the diagnosis of calculous disease in 96% of cases, and it can quantify the presence and severity of obstruction (Fig. 85.5A and B).

Computed Tomography

Non–contrast-enhanced helical (spiral) CT scanning is the standard imaging modality in the U.S. It is 95% sensitive and 98% specific for

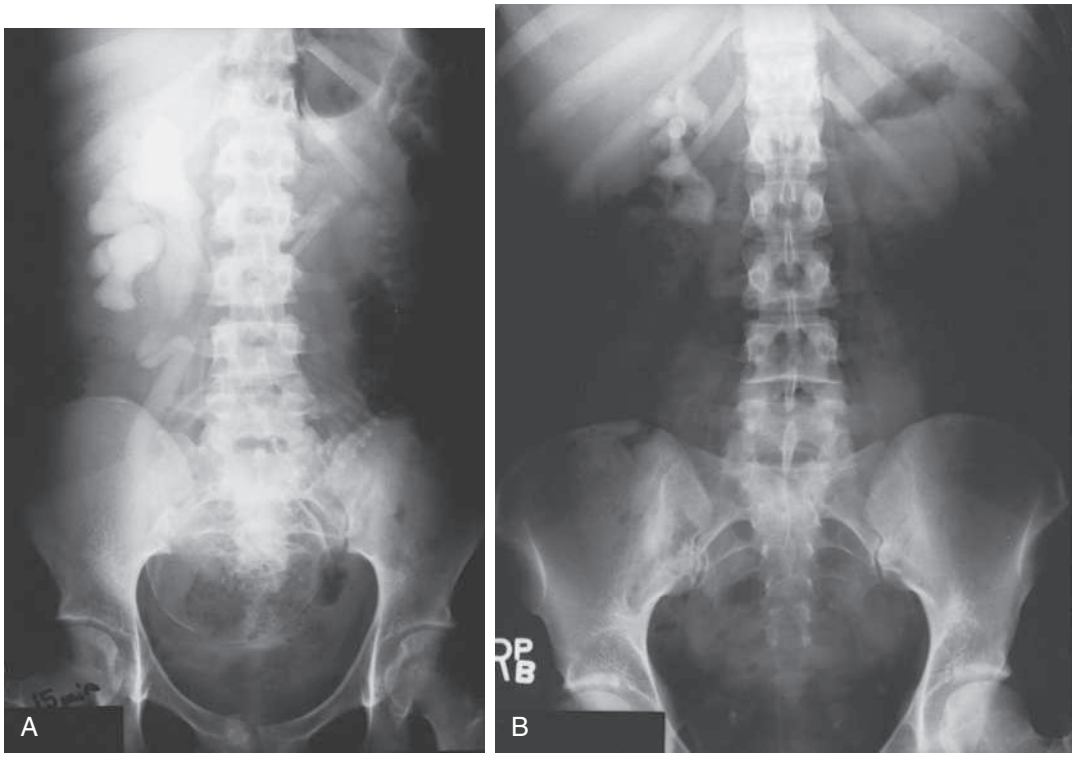


Fig. 85.5 (A) In a near-term pregnant woman with an obstructed left kidney, this intravenous pyelogram demonstrates a delayed nephrogram. (B) The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

detecting ureteral calculi.[13] CT may detect calculi as small as 1 mm in diameter and provide direct visualization of complicating conditions such as hydroureter, hydronephrosis (Fig. 85.6), and ureteral edema. Some kidney stones, such as uric acid stones, may be radiolucent. CT is also superior to alternate imaging modalities in its ability to recognize other pathologies, such as malignancy, renal abscess, and AAA. Other advantages include lack of contrast exposure, short duration of testing, and ease of interpretation. For patients with a body mass index less than 30 kg/m^2, low radiation dose protocols can be used, with sensitivities and specificities still reported as more than 90%.[14] However, many patients with a history of nephrolithiasis and clinical picture consistent with renal colic do not require imaging. Patients with a history of nephrolithiasis who lack fever, a urinalysis showing infection, a solitary or transplanted kidney, suspicion for complicated urolithiasis, or diagnosis other than renal colic may forego CT imaging.[15]

Ultrasonography

Ultrasound, whether performed by a radiology technician or point of care in the ED, may provide diagnostic information to guide further evaluation and treatment. Performing an ultrasound as the initial imaging test often eliminates the need to obtain an abdominal and pelvic CT scan and decreases radiation exposure to the patient. Ultrasound has been found to be up to 100% sensitive and 90% specific for the diagnosis of ureteral obstruction in patients presenting with acute flank pain.[5] This has resulted in some guidelines to recommend it as the initial imaging modality for suspected obstructing ureterolithiasis and identification of hydronephrosis (Fig. 85.7).[16] Ultrasound may also guide clinical suspicion and need for further imaging in patients with less typical signs and symptoms of calculi. It is also the study of choice for ruling out hydronephrosis for pregnant and pediatric patients if obstructive urolithiasis is a concern.[17]

Ultrasound is less sensitive and specific than CT imaging for detecting stone size and location and has been found to be 54% sensitive and 91% specific for the diagnosis of urolithiasis.[18] For potential urological intervention, CT is generally performed given the accuracy for identification of stones and identification of other potential etiologies of flank pain.

Management

The first priority for a patient with a presumed diagnosis of kidney stone is adequate pain control. NSAIDs are first-line agents, but parenteral administration often is necessary because of nausea and vomiting. Ketorolac, 30 mg IV, or diclofenac, 75 mg intramuscularly (IM), provide rapid effective analgesia and decrease both ureteral spasm and renal capsular pressure by diminishing the GFR in the obstructed kidney. Accordingly, caution is advised with use of these agents in patients with underlying renal insufficiency or peptic ulcer disease. An IV narcotic such as fentanyl (1 to 2 µg/kg) is also very effective in providing rapid analgesia. The combination of NSAIDS and opiates may reduce length of stay in the ED. In the patient who is unable to tolerate oral fluids, IV fluids and an antiemetic such as ondansetron, 4 mg IV, should be given. There have been no definitive studies proving that high-volume fluid therapy in those with acute renal colic facilitates stone passage or improves outcomes.[19]

Concomitant infection with an obstructive stone and hydronephrosis constitutes a true urologic emergency and may warrant immediate urologic intervention for placement of ureteral stents or decompression of the renal pelvis by percutaneous nephrostomy.

Disposition

Indications for Admission

Hospitalization is recommended for patients who are severely dehydrated, are experiencing unrelenting pain or vomiting, or have an

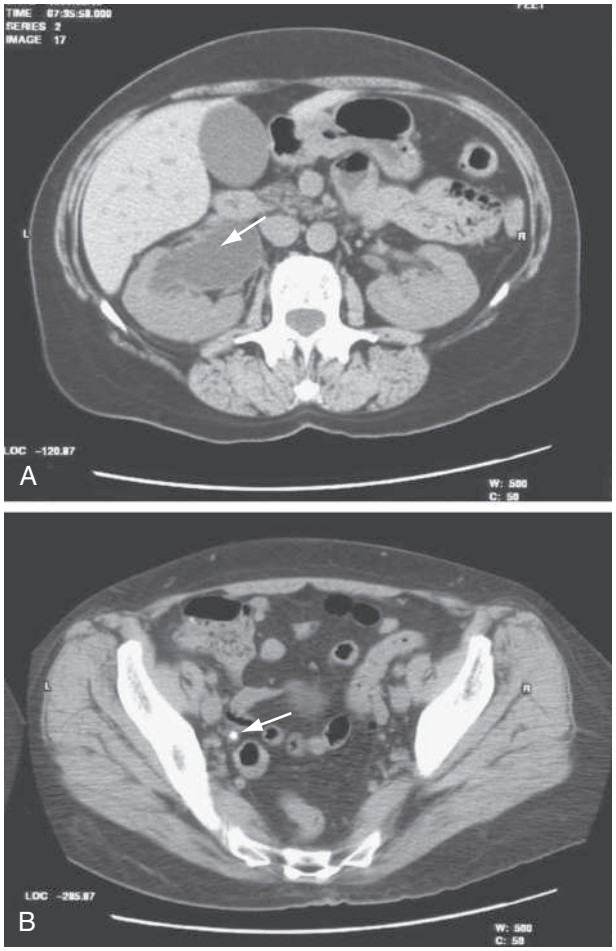


Fig. 85.6 CT Scans Obtained in a Patient With Renal Colic. (A) Right-sided hydronephrosis. (B) Right ureteral calculi.

underlying urinary infection (Box 85.4). Sepsis and renal damage are risks in the presence of obstruction and infection, so these patients require an emergent urologic consultation to evaluate the need for immediate operative intervention to provide drainage and relieve the obstruction. If signs of sepsis (e.g., tachycardia, fever, hypotension, shock) are present, parenteral antibiotics, such as ceftriaxone 1 g IV, should be given and fluid resuscitation carried out pending urologic evaluation.

Several interventional strategies are available to the urologist for the management of stones that do not pass spontaneously. Optimal therapy depends on the size, location, and composition of the stone. Ureteroscopy and extracorporeal shock wave lithotripsy (ESWL) are the two most commonly used techniques. Ureteroscopic removal of ureteral stones, compared to ESWL, achieves a greater stone-free state and lowers the need for retreatment.[20] Both treatment options have a low complication rate.[20] Percutaneous nephrolithotomy, which establishes a tract from the skin to the collecting system, is used for stones too large or hard for ECSWL or ureteroscopy by removing them directly from the renal pelvis.

Outpatient Management

Most patients with nephrolithiasis may be safely managed as outpatients. They should be instructed to return to the ED immediately for intractable or severe pain, persistent nausea and vomiting, fever or chills, or difficulty voiding. Spontaneous passage usually occurs within 4 weeks after the onset of symptoms. Patients with first-time stones or those who have not had chemical analysis of their stones should strain all urine or simply void into a glass jar; the calculus should be visible at the bottom. The stone can be submitted to the follow-up urologist for analysis. If a stone has not been passed within 4 weeks, intervention is indicated, because the risk of complications such as ureteral stricture and renal function deterioration increase. The patient should be instructed to drink a moderate amount of fluids, take analgesics as needed for pain, and engage in activity as tolerated.

Medical expulsive therapy is a potentially useful treatment modality for the management of ureteral stones. α_1-Antagonists (e.g., tamsulosin, 0.4 mg PO daily) may facilitate stone expulsion and decrease the time to spontaneous stone passage by blocking ureteral smooth muscle contraction and improving antegrade stone movement.[21–23] Some studies have questioned the effectiveness of tamulosin,[24–26] while others have suggested, and current guidelines acknowledge, a therapeutic benefit for patients with larger distal stones (5 to 10 mm).[22,25,27,28]

BLADDER (VESICAL) CALCULUS

Background

Approximately 5% of calculi originate in the bladder. Bladder stones occur almost exclusively in older men, often as a complication of an infection of residual bladder urine with urea-splitting organisms or an indwelling catheter. Other disorders predisposing to the formation of bladder stones include bladder neck obstruction (usually secondary to prostatic hyperplasia), neurogenic bladder, vesical diverticula, damage from irradiation, and schistosomiasis.

Clinical Features

Bladder stones cause pain on voiding and hematuria. The patient may report a sudden interruption of the urinary stream, which strongly suggests a vesical stone that intermittently obstructs the bladder outlet. Frequency, urgency, and dysuria are described by up to 50% of patients, and UTIs are common.

The physical examination is rarely helpful; the rectal examination may reveal an enlarged prostate or prostatic malignancy. Poor sphincter tone may suggest a neurogenic bladder.

Diagnostic Testing

Urinalysis generally reveals pyuria, bacteriuria, and hematuria. Plain radiographs of the pelvis reveal a bladder stone in 50% of cases. Contrast scans may demonstrate obstructive changes in the upper tracts or bladder diverticula. Ultrasonography also is useful in the diagnosis of bladder stones.

Management

Surgery is currently the gold standard of care. Depending on the size of the stone, an endoscopic or open approach is used.

ACUTE SCROTAL PAIN

Background

The most common causes of acute scrotal pain are epididymitis and torsions of the testicle and testicular appendage (Table 85.9). Some are emergent surgical conditions such as Fournier gangrene and incarcerated hernias. Others require less invasive and time-dependent therapies, such as antibiotics for epididymitis and observation for benign masses or torsion of the appendix of the testes. Box 85.5 lists a number of other disorders that can present as scrotal swelling.

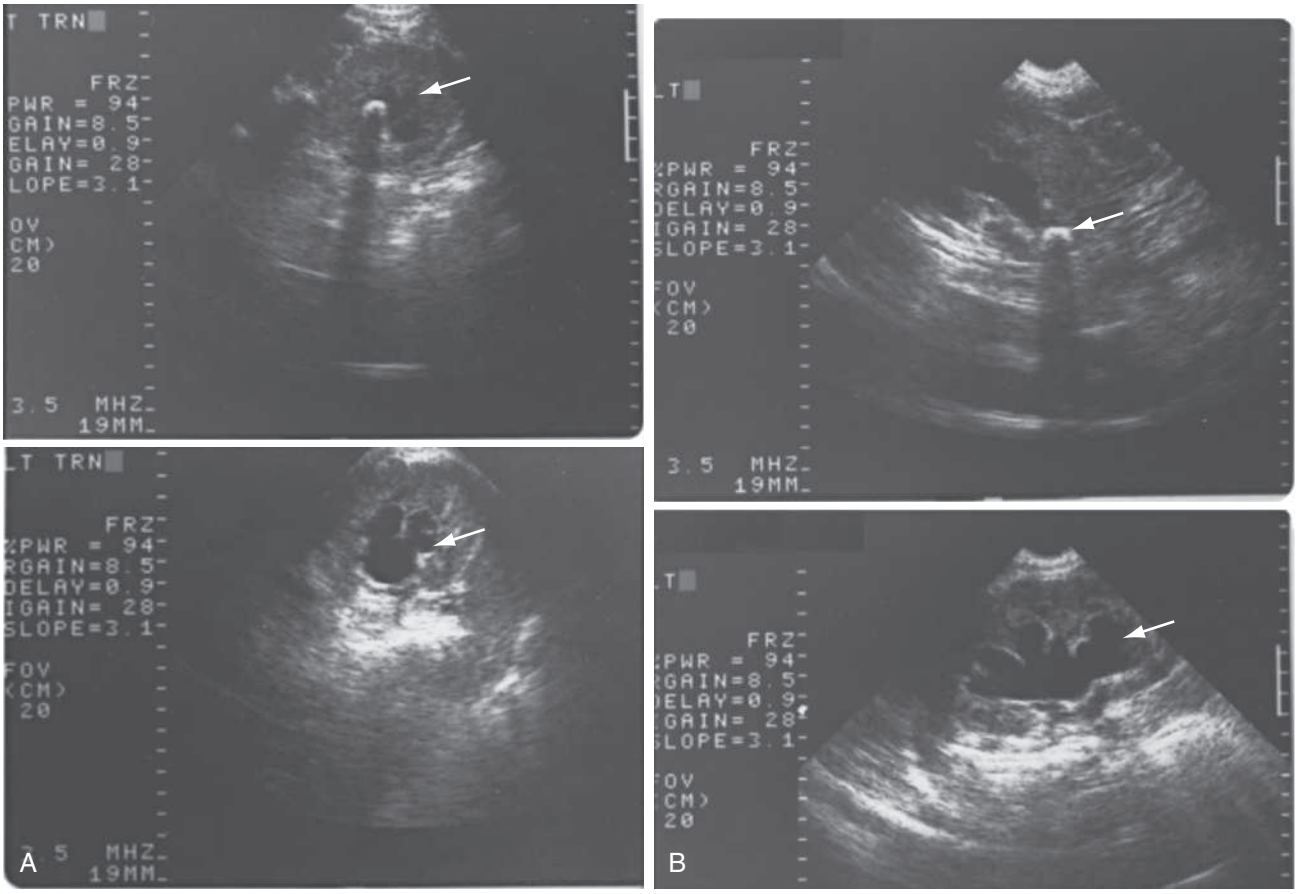


Fig. 85.7 (A) Ultrasound images of the kidney in a patient with renal colic. Hydronephrosis and a calcification with an acoustic shadow are visualized. (B) Ultrasound images of the kidney in a patient with renal colic. Short axis reveals a kidney stone and hydronephrosis.

BOX 85.4 Indications for Hospitalization of Patients With Urolithiasis

Absolute
Obstructing stone with signs of urinary infection
Intractable nausea or vomiting
Severe pain requiring parenteral analgesics
Urinary extravasation
Hypercalcemic crisis

Relative
Significant comorbid illness complicating outpatient management
High-grade obstruction
Leukocytosis
Solitary kidney or intrinsic renal disease
Psychosocial factors adversely affecting home management

Fig. 85.8 demonstrates the anatomy of the scrotum and testis. A normal scrotum is relatively symmetric, and both testicles are of equal mass and volume. The left testicle often is higher than the right because its blood flow empties into the large, low-pressure vena cava, whereas the right drains into the relatively smaller, high-pressure renal vein. A normal testis is found in the vertical axis with a slight forward tilt, and the epididymis is above the superior pole in the posterolateral position. The epididymis is located posterolateral to the testis and is normally nontender and soft. The cremasteric reflex is elicited by stroking or pinching the inner aspect of the thigh; more than 0.5 cm of elevation of the ipsilateral testicle is considered evidence of a normal reflex. This reflex normally is absent in 50% of male infants younger than 30 months.

SPECIFIC DISORDERS

Testicular Torsion

Background

The incidence of testicular torsion in males below 25 years old is approximately 1:4000.[29] Torsion can occur at any age, but has a bimodal age-incidence in the first year of life and at puberty during testicular growth (Fig 85.9). In neonatal torsion, extravaginal torsion usually occurs, with twisting of the entire cord including the tunica vaginalis. In older children and adults, intravaginal torsion (twisting of the cord within the tunica vaginalis) occurs and is commonly associated with a bell-clapper deformity.[30] A bell-clapper deformity is a congenitally abnormal fixation of the tunica vaginalis to the testicle that results in increased mobility of the testicle.

With torsion, abnormal testicular rotation of the spermatic cord results in obstruction of venous outflow, subsequent compromised arterial flow, and testicular ischemia. Testicular salvage hinges on the degree of torsion and duration of the ischemia. Testicular torsion in neonates has few known etiological factors, poor testicular viability, and rarely present to the ED.[31] Thus, the remainder of this discussion will focus on intravaginal torsion. Torsion that presents to the ED within 6 hours of the start of pain is associated with testicular salvage rates greater than 90%. After 6 hours of torsion, the rate of testicular

TABLE 85.9 Differentiation Among Common Causes of the Acute Scrotum

Parameter	Testicular Torsion	Appendix Torsion	Epididymitis
Age	<1 year, puberty	7–14 years	Adult
Onset	Hours	1–2 days	Days to weeks
Location of pain	Entire testicle	Upper pole	Epididymis
Testicle position	High-riding testicle Transverse alignment	Normal position Vertical alignment	Normal position Vertical alignment
Systemic symptoms	Nausea, vomiting	None	Possibly fever
Cremasteric reflex	No	Intact	Intact
Pyuria	Rare	No	Yes
Ultrasound findings	Diffusely hypoechoic Asymmetric testicles Normal or decreased flow Spermatic cord twist	Focally hypoechoic Symmetrical testicles Normal flow	Hypoechoic epididymis Symmetric testicles Increased flow
Treatment	Surgery	Supportive	Antibiotics; prepubescent—supportive only

Note: No single finding in patients with an acute scrotum can reliably differentiate torsion from other causative disorders. When torsion is a diagnostic possibility, prompt urology consultation and further testing are mandatory.

BOX 85.5 Causes of Acute Scrotal Swelling

Infant
Hernia
Hydrocele

Child
Hernia
Torsion
Epididymitis

Adolescent
Epididymitis
Torsion
Trauma

Adult
Epididymitis
Hernia
Trauma
Tumor
Torsion
Fournier gangrene

atrophy and orchiectomy increases rapidly. There is poor testicular viability if detorsion is delayed 24 hours or more.[29]

Clinical Features

Patients with testicular torsion typically report the sudden onset of rapidly escalating pain in the scrotum, lower abdomen, or inguinal area that awakens them from sleep or develops several hours after physical activity. While torsion can occur after trauma, it usually occurs without any specific preceding event. Patients with testicular torsion may describe similar pain in the past, caused by previous intermittent torsion in a predisposed testicle. Because torsion may present with abdominal pain and no scrotal pain, the scrotum should be examined in all patients presenting with abdominal pain.

The physical examination is more reliable than the history in determining the presence of testicular torsion. Patients with torsion frequently have a tender firm testicle that can be higher than the contralateral testicle owing to shortening of a twisted spermatic cord. Twisting also can leave the testicle in the transverse position and displace the epididymis from its usual location along the posterior aspect of the scrotum. Often, the patient's scrotum is so swollen and tender that a complete physical examination is impossible. The cremasteric reflex is usually absent in patients with torsion; however, its presence cannot be used to rule out torsion. The cremasteric reflex occurs when the ipsilateral testicle elevates after stroking the medial thigh. This reflex may be absent in normal patients as well as those with upper and lower motor neuron disorders or spinal cord trauma.[32]

Differential Diagnosis

There is no single historical or physical finding that reliably differentiates testicular torsion from other causes of acute scrotal pain (see Table 85.9).

Diagnostic Testing

Urinalysis

In patients in whom the history and physical findings strongly suggest torsion, emergent surgical consultation is warranted. If the diagnosis is equivocal, adjunctive tests should be performed to determine the cause of the pain. Although urinalysis results suggestive of infection are consistent with epididymitis, such findings also may be noted in patients with torsion and a concomitant UTI.

Imaging

Ultrasound is the diagnostic modality of choice for detecting torsion and has a sensitivity of 96% to 100% and specificity of 84% to 95%.[33] The torsed testicle is typically hypoechoic and enlarged (Fig. 85.10). False-negative findings occur when the testicle is examined early in the course of the disease, when blood flow is still present, and with intermittent torsion. Examination of the spermatic cord for twisting, instead of the testicle itself, has been shown to reduce the frequency of these false-negative results. Ultrasound is helpful when it demonstrates torsion in patients with equivocal findings on the history and physical examination, but it does not have sufficient sensitivity to rule out a diagnosis of torsion. A urologist should evaluate any patient in whom ultrasound findings are negative but history and physical

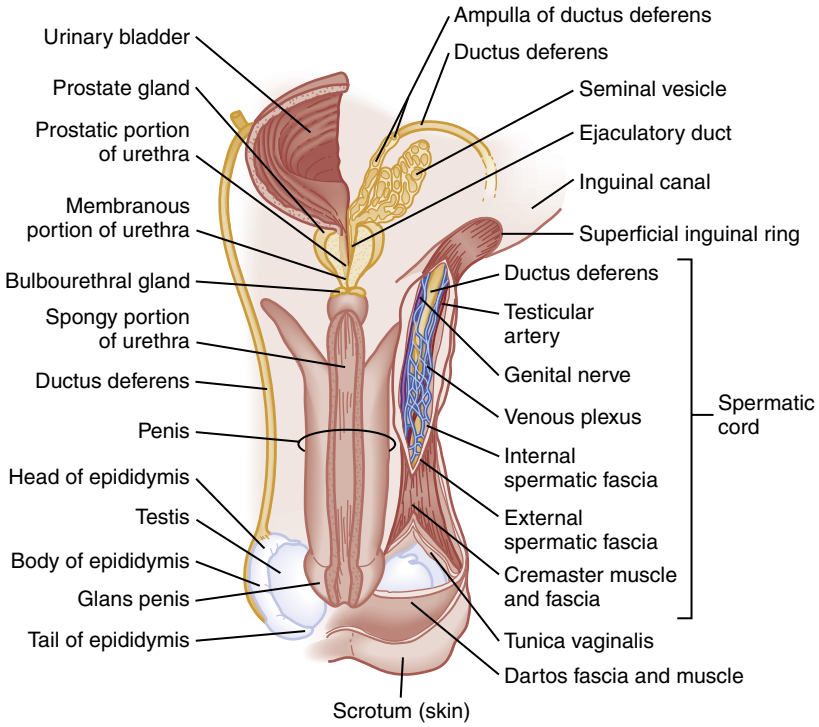


Fig. 85.8 Testes, Epididymis, Ductus Deferens, and Glands of the Male Reproductive System. (From Seeley RR, et al., eds. *Anatomy and Physiology*. New York: McGraw-Hill; 1985.)

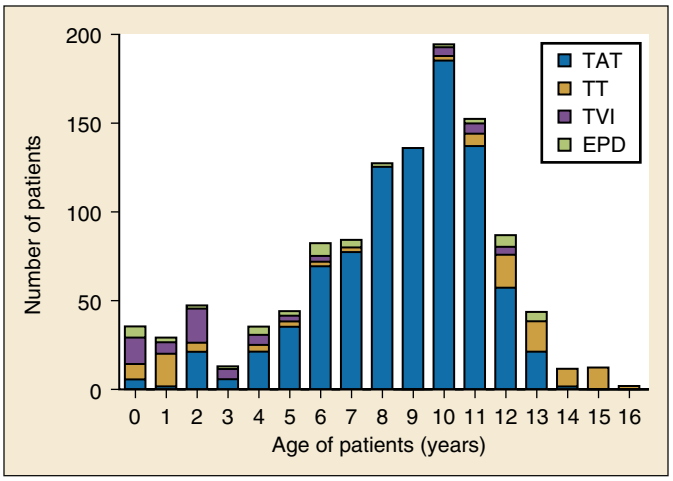


Fig. 85.9 Age distribution of boys with torsion of the appendix testis *(TAT)*, testicular torsion *(TT)*, tunica vaginalis inflammation *(TVI)*, and epididymitis *(EPD)*. (From Yang C, Song B, Liu X, et al. Acute scrotum in children: an 18-year retrospective study. *Pediatr Emerg Care*. 2011;27:270–274.)

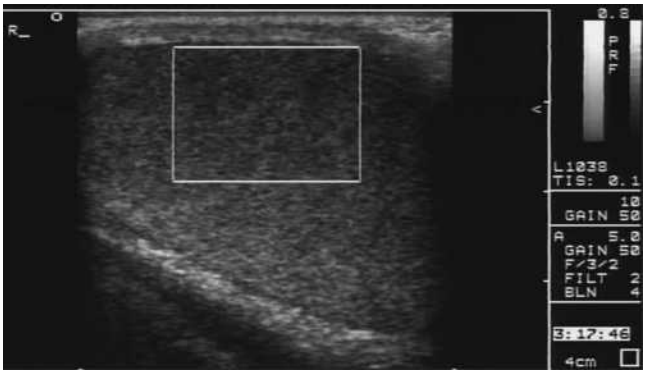


Fig. 85.10 Doppler ultrasound image showing a testicle with no flow as a result of torsion *(white box)*. (From Blaivas M, Brannam L. Testicular ultrasound. *Emerg Med Clin North Am*. 2004;22:723–748.)

findings are suggestive of torsion. Moreover, an ultrasound examination should never delay evaluation by a urologist in a patient with probable torsion.

Ultrasound imaging for testicular torsion includes both grayscale and Doppler examination. Grayscale imaging can identify a spermatic cord twist, called a "whirlpool sign," above the testis. The parenchymal echotexture on ultrasound may help predict the viability of the testicle. Homogeneous echotexture portends extremely well for testicular viability. However, varying degrees of heterogeneous parenchymal echotexture may be seen in testicular torsion and significant heterogeneity indicates late torsion and testicular nonviability.[34–36] Grayscale imaging can also identify other diagnoses such as inflammation due to epididymitis and scrotal masses.

The Doppler ultrasound appearance of the testicle depends on the degree of twisting of the spermatic cord. With 180 degrees or less of twisting of the cord, venous flow from the testicle ceases but arterial flow persists. This leads to edema of the testicle on ultrasound that can be misinterpreted as inconsistent with torsion. In contrast, with more than 180 degrees of twisting of the cord, arterial flow also ceases, leading to a lack of Doppler signal on ultrasound.

Doppler studies can be more difficult to interpret in younger boys because blood flow is physiologically low in the testicles of prepubertal boys. As many as 50% of boys younger than 8 years do not show intratesticular flow. This hypovascularity can result in false-positive diagnoses, which could potentially lead to unnecessary surgical exploration. Comparison with the contralateral testicle can help avoid this misdiagnosis; as in normal patients, blood flow to the two testicles will be similar.

Magnetic resonance imaging (MRI) and radionuclide scanning of the scrotum have also been used to diagnose testicular torsion but are time-consuming. They have largely been replaced by ultrasound.

Management

The first step in the management of suspected testicular torsion is immediate consultation with a urologist. The longer the spermatic cord remains twisted, the lower the likelihood of testicular salvage. In addition, early consultation allows the urologist to accompany the patient to ultrasound—if imaging is obtained—where images can be reviewed in real time with the radiologist. Analgesia is provided systemically or with a spermatic cord block.

If the urologist is not readily available, manual detorsion may improve testicular salvage and should be attempted (Fig. 85.11).[37] Relief should be felt when the operator rotates the affected testicle away from the midline, as if turning the pages of a book. If this maneuver is successful, patients should report immediate improvement of symptoms. If only partial relief of pain is noticed, an attempt should be made to untwist past 360 degrees because a higher degree of rotation may be present. If pain increases or there is no relief, consider reversing the direction of reduction because over one-third of patients may be torsed laterally.[36] Unfortunately, no independent predictors of the direction of torsion have been identified to guide decision-making on manual detorsion.[36] If manual detorsion is attempted, a spermatic cord block or systemic analgesics should be administered (see Fig. 85.11).

Evaluation by a urologist should never be delayed to perform manual detorsion or any other maneuver. Likewise, regardless of the outcome with manual detorsion, patients require prompt urological evaluation. A surgeon can confirm the reduction and stabilize the testes with orchiopexy. Even for symptoms lasting beyond 24 hours, testicular salvage is possible for incomplete torsion, and orchiopexy can help prevent recurrence. Removal of a necrotic testicle speeds recovery.

Disposition

Rapid diagnosis of testicular torsion is essential and should be followed by emergent surgical scrotal exploration and bilateral orchiopexy, if necessary. Loss of the testicle is usually a result of delay in seeking medical attention. However, many cases of failed testicular salvage have been attributed to misdiagnosis, which almost always leads to orchiectomy and represents a common source of litigation.

TORSION OF APPENDAGES OF THE TESTIS

Background

A normal scrotum has several vestigial appendages that can also twist and become ischemic, with resultant scrotal pain. This process is most common between 7 and 14 years of age, with a mean age of 10 years. In retrospective analyses, torsion of an appendage rivals epididymo-orchitis as the most common cause of the acute scrotum.

The appendix testis, a remnant of the paramesonephric duct, is present in 92% of patients. It is located on the superior aspect of the testicle, between the testis and epididymis (Fig. 85.12). This appendage is prone to torsion owing to its pedunculated shape. After several days of ischemia from torsion, it will undergo necrosis, with eventual reabsorption. Its loss does not permanently affect fertility or have any impact on surrounding structures.

Clinical Features

As with testicular torsion, patients with torsion of an appendage complain of scrotal pain but report milder symptoms, with a more gradual onset. They report nausea, vomiting, urinary symptoms, or previous episodes of similar pain less commonly than patients with testicular torsion. They usually seek medical attention later than patients with testicular torsion, generally after 48 hours of symptoms.

On physical examination, twisting of the appendix testis leads to formation of a hard, tender, 2- to 3-mm nodule at the upper pole of the testicle. Unlike in testicular torsion, the entire testicle is not tender. The testicle also does not change in overall size, and the scrotum typically does not swell until late in the disease process. The cremasteric reflex typically is intact. On transillumination, the ischemic appendage may rarely be seen as a blue dot.

Diagnostic Testing

Urinalysis should not show evidence of infection. On ultrasound imaging, the appendix under torsion will appear hypoechoic. Color Doppler ultrasound can show decreased flow in normal and torsed appendages. With torsion of the appendix, a hypoechoic spherical nodule with a diameter more than 5 mm is present over the superior aspect of the testicle (Fig. 85.13).

Management and Disposition

If testicular torsion is ruled out, surgical excision of the appendix is rarely necessary. Treatment consists of scrotal support, ice packs, and NSAIDs. Resolution of symptoms can be expected within 7 to 10 days. Surgical excision is reserved for uncontrollable pain.

EPIDIDYMITIS

Background

Epididymitis is the most common intrascrotal inflammatory disease. Most cases occur in men between 18 and 35 years of age, but the disease can affect males at any age. It is uncommon in prepubertal males. If untreated, it can lead to orchitis, testicular abscess and, rarely, sepsis.

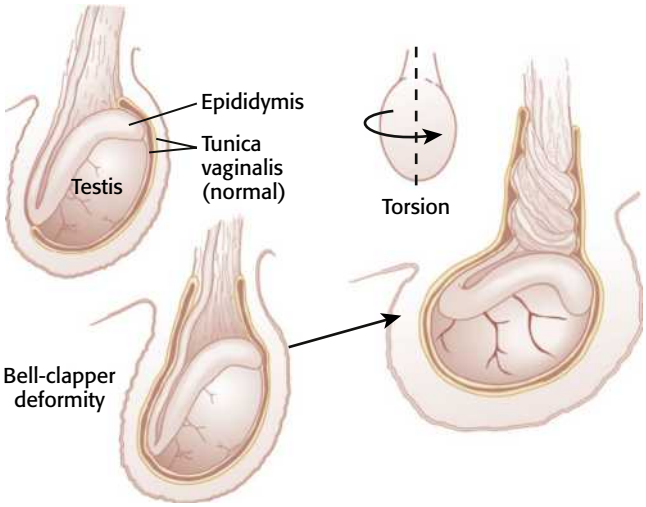
The epididymis is a tightly coiled tubular area along the posterior aspect of the testes, where sperm mature before their transit to the vas deferens. The epididymis becomes infected when organisms travel retrograde from the vas deferens. With infection, the ipsilateral testicle is also commonly involved, a condition referred to as epididymo-orchitis.

The common route of infection is local extension, mainly due to infections spreading from the urethra (sexually transmitted pathogens) or bladder (urinary pathogens). The particular organisms involved in the infection depend on the sexual activity of the patient. Although the literature classically describes men younger than 35 years who are prone to *C. trachomatis* and *N. gonorrhoeae* infections, all sexually active men, regardless of age, are at risk for epididymitis from these organisms. Acute epididymitis caused by sexually transmitted enteric organisms occurs in men who are the insertive partner during anal intercourse. Other rare causes of epididymitis include *M. tuberculosis, Treponema pallidum*, fungal infections, amiodarone use, and systemic inflammatory conditions such as Behçet syndrome.

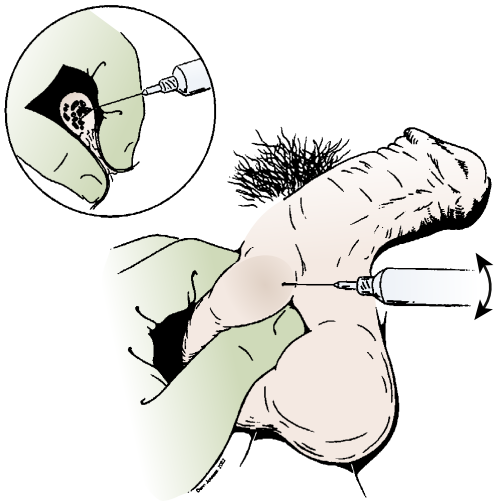
In men older than 35 years, urinary tract pathogens become the predominant cause of epididymitis. Unlike younger patients, older men with epididymitis tend to have urinary tract abnormalities that predispose them to these infections. Over 50% of men older than 60 years with epididymitis have lower urinary tract obstruction. Older men also are more likely to have concomitant prostatitis, benign prostatic hypertrophy (BPH), immunosuppression, or systemic disease or have undergone recent genitourinary instrumentation, surgery, or catheterization.

Epididymitis in children is usually idiopathic, although children can also have congenital genitourinary anomalies that predispose them to recurrent infection. The most commonly associated abnormality is neurogenic bladder, which produces increased pressure during urination and reflux into the ejaculatory ducts. In infants, bacterial causes are more common.

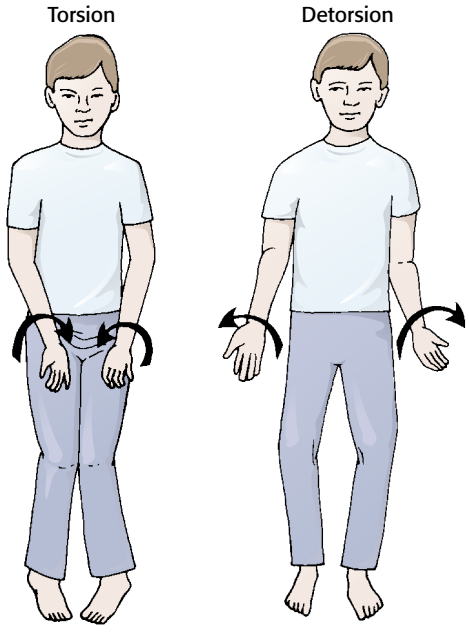
MANUAL TESTICULAR DETORSION



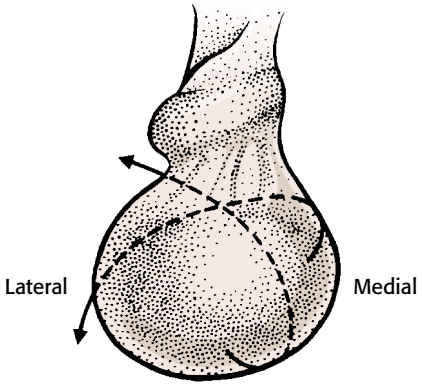
A. **Anatomy of testicular torsion**. Testicular torsion occurs when the testis twists within the tunica vaginalis. Patients with the bell clapper deformity (i.e. incomplete fusion of the tunica along the epididymis, which results in incomplete attachment of the testicle to the scrotum) are at higher risk.



B. **Spermatic cord block**. Grasp the spermatic cord between your thumb and index finger. Use a 30-gauge needle to infiltrate the entire cross section of the spermatic cord and its surrounding rim with anesthetic. This will cause visual ballooning of the grasped segment of the cord. Gently massage this bulge to disperse the anesthetic. Usually about 10 mL is required.



C. Testicular torsion more commonly occurs in a medial direction. Initially attempt detorsion by rotating the testis outward toward the thigh. This is most successful if attempted within the first few hours of torsion, before the onset of significant scrotal swelling. Intravenous narcotics (e.g. fentanyl) can be administered or a cord block performed before attempting detorsion.



D. **Detorsion maneuver**. Detorsion of the testicle may require testicular rotation through two planes. To release the cremasteric muscle, rotate the testis in a caudal-to-cranial direction simultaneously with medial-to-lateral rotation. The right testis is shown.

Fig. 85.11 Manual Testicular Detorsion. (Adapted from Roberts J, Custalow CB, Thomsen TW, eds. *Roberts and Hedges' clinical procedures in emergency medicine*. 6th ed. St. Louis: Elsevier Health Sciences; 2014.)

Clinical Features

Patients with epididymitis experience scrotal pain of gradual onset, prompting them to present later in the clinical course than patients with torsion. Initially, this pain may reside in the lower abdomen or flank, caused by inflammation of the vas deferens. Fever is uncommon. In the early stages of the disease, tenderness is localized to the epididymis but quickly spreads to the ipsilateral testicle. Later in the course, the scrotum can become edematous, erythematous, and extremely tender. The testis is located in the normal anatomic position, with an intact cremasteric reflex. Although Prehn sign—decrease in pain with

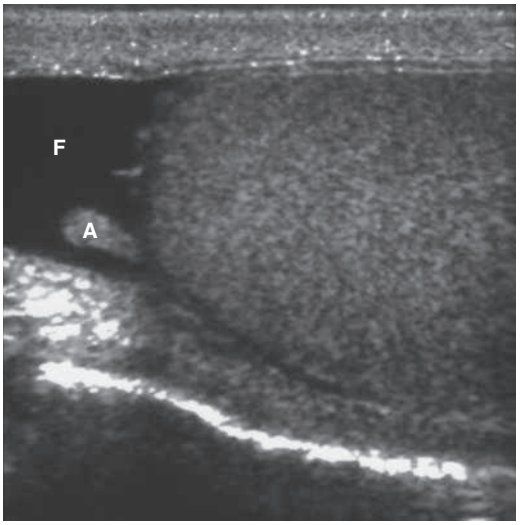


Fig. 85.12 Ultrasound image showing the testicular appendage *(A)* surrounded by a hydrocele *(F)*. (From Blaivas M, Brannam L. Testicular ultrasound. *Emerg Med Clin North Am.* 2004;22:723–748.)

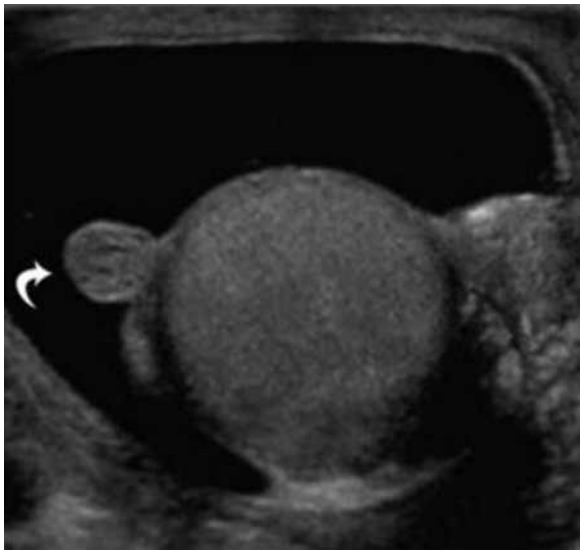


Fig. 85.13 Transverse ultrasound image shows a hyperechoic mass *(curved arrow)* with tiny central hypoechoic areas adjacent to the left testes and epididymis with a reactive hydrocele and mild scrotal wall thickening. (From Mirochnik B, Bhargava P, Dighe MK, Kanth N. Ultrasound evaluation of scrotal pathology. *Radiol Clin North Am.* 2012;50:317–332.)

elevation of the scrotum—has been touted as indicative of epididymitis, it has low sensitivity and specificity. Only 10% of patients with epididymitis from sexually transmitted organisms have symptoms of urethritis or a urethral discharge on examination. No single historical factor or physical finding has been shown to differentiate torsion from epididymitis reliably.

Diagnostic Testing

The diagnosis of epididymitis is typically made based on compatible physical examination findings and confirmed by laboratory testing. A urinalysis usually demonstrates evidence of pyuria. If patients are at risk for STI, a urethral swab or first-void urine sample should be tested for *C. trachomatis* and *N. gonorrhoeae;* a polymerase chain reaction (PCR) assay and other nucleic acid amplification tests have the greatest sensitivity and should be used, when available.

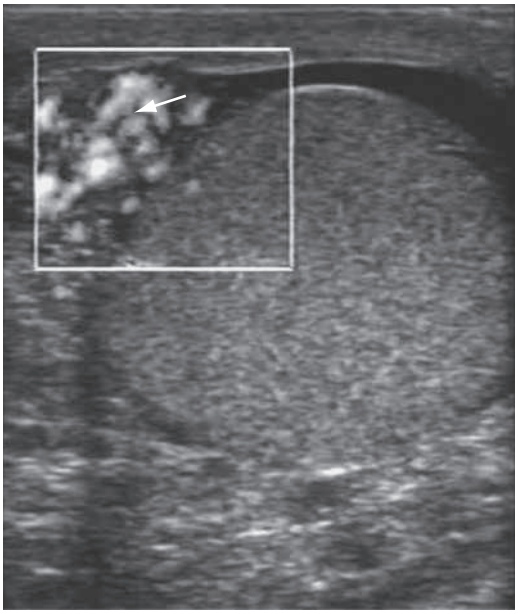


Fig. 85.14 Ultrasound of the testicle showing an enlarged epididymis and increased blood flow on Doppler ultrasound imaging *(white box).* (From Blaivas M, Brannam L. Testicular ultrasound. *Emerg Med Clin North Am.* 2004;22:723–748.)

Systemic leukocytosis may be present but is a nonspecific finding and does not differentiate epididymitis from torsion. In prepubertal children, urinalysis and urine culture rarely are positive. Nevertheless, in these patients, urine cultures should still be obtained to rule out bacterial infection because untreated bacterial infections may lead to long-term complications.

Because the history and physical examination features and laboratory results cannot reliably distinguish torsion from epididymitis or other diseases, equivocal presentation for epididymitis versus testicular torsion should be assessed using testicular ultrasound with Doppler. On ultrasound, an inflamed epididymis appears enlarged and hypoechoic (Fig. 85.14). However, a minority of patients with torsion have preserved flow that can appear similar to that of epididymitis; in these cases, the presence of a spermatic cord twist, indicative of torsion, should be sought.

Prepubertal children with recurrent epididymitis should undergo renal ultrasound and cystography to identify potential underlying urinary tract abnormalities. These are important to identify to reduce the risk of future inflammation.

Management

Empirical antibiotics are selected in accordance with the patient's risk for chlamydia and gonorrhea and/or enteric organisms (Table 85.10). Treatment goals include curing infection, preventing transmission, and reducing future complications such as infertility and chronic pain.

In patients with a suspected sexually acquired infection, ceftriaxone, 500 mg IM, should be given to treat possible *N. gonorrhoeae* infection. In conjunction, doxycycline, 100 mg PO twice a day for 10 to 14 days, should be started to treat *C. trachomatis* or *Ureaplasma urealyticum* infection.[38] Men with suspected or confirmed *N. gonorrhoeae* or *C. trachomatis* infection should be advised to abstain from sexual intercourse until they and their partners have been treated. Treatment of sexual partners should be arranged, even if the partner's culture demonstrates no growth.

In patients with infection by enteric organisms, levofloxacin, 500 mg PO once daily, or ofloxacin, 300 mg PO every 12 hours, is recommended. If the patient is high risk for STIs and enteric organisms,

TABLE 85.10 Treatment of Epididymitis

Drug of Choice	Dose and Route
Presumed Sexually Acquired Epididymitis	
Ceftriaxone *plus*	500 mg IM once
Doxycycline	100 mg PO twice a day for 10 days
Presumed Enteric Epididymitis[a]	
Levofloxacin	500 mg PO daily for 10 days
Potential Sexually Acquired or Enteric Epididymitis[a]	
Ceftriaxone *plus*	500 mg IM once
Levofloxacin	500 mg PO daily for 10 days

[a]Adjust antibacterial therapy according to results of urine culture.
IM, Intramuscularly; *PO,* orally.

treatment should include ceftriaxone and fluoroquinolones (see Table 85.10). Despite the absence of evidence to support benefit, we also recommend bed rest, scrotal elevation, ice packs, and NSAIDs. Discomfort may not completely resolve until weeks after completing an antibiotic regimen.

Most cases of pediatric epididymitis are idiopathic, and antibiotics are not routinely recommended. Urine culture specimens should be obtained and antibiotic therapy should be initiated only if cultures reveal bacteria. Despite the absence of evidence to support benefit, we recommend that boys limit activity, elevate the scrotum with ice packs, and reduce inflammation with NSAIDs. In contrast, infants often have bacterial epididymitis and should be treated empirically with antibiotics pending urine culture results.

Disposition

Patients with systemic signs of toxicity (fever, chills, nausea, vomiting) usually have extension of the infection to involve the testicle, termed epididymo-orchitis. These patients often require hospitalization and treatment with parenteral antibiotics. Most well-appearing patients with uncomplicated epididymitis can be managed as outpatients. Urology referral should be arranged for those likely infected with enteric organisms. Signs and symptoms of epididymitis that do not subside within 3 days require reevaluation of the diagnosis and therapy.

ORCHITIS

Background

Orchitis is a rare acute infection of the testis. With the exception of viral diseases, genitourinary tract infections seldom primarily involve the testis. Orchitis often presents as a progression of epididymitis and may be caused by bacterial or viral infection. Bacterial causes are usually associated with epididymo-orchitis. The most common viral cause of orchitis is mumps. Orchitis due to mumps tends to arise several days after the onset of parotitis. Although vaccination has significantly reduced the incidence of mumps infection, sporadic outbreaks have occurred. Infections in vaccinated individuals are increasingly common, presumably resulting from vaccine failure or antigenic differences between the infecting and vaccine strains.

Owing to the testes' relatively high threshold of resistance to infection, bacterial orchitis usually results from local bacterial spread from the epididymis, frequently referred to as epididymo-orchitis. The most frequent bacterial pathogens are *N. gonorrhoeae, C. trachomatis, E. coli, Klebsiella,* and *P. aeruginosa*. These organisms tend to infect postpubertal males and men older than 50 years with BPH.

Clinical Features

A patient with mumps orchitis has testicular pain and swelling that commonly begins 4 to 6 days after the onset of parotitis, although it can develop in the absence of parotitis. The clinical course varies, with adults having more severe symptoms. Clinical resolution generally occurs in 4 to 5 days.

Patients with bacterial orchitis typically have fever and scrotal pain. They often have constitutional signs and symptoms, including nausea, vomiting, myalgias, and malaise. The disease may be bilateral in up to 30% of patients. The affected testicle and scrotum are swollen, tender, and erythematous.

Diagnostic Testing

As with all causes of scrotal pain, the first priority is to exclude testicular torsion. If the patient clearly has mumps orchitis based on the clinical presentation and a history of preceding parotitis, no other tests are necessary. For all other patients, urinalysis, urine culture, and ultrasound should be performed. On ultrasound, orchitis shows hypervascularity, commonly described as a testicular inferno. Blood tests are typically not helpful, because false-negative results are common with serologic testing, particularly in vaccinated individuals.

Management

In sexually active patients, ceftriaxone and doxycycline should be used to cover *N. gonorrhoeae* and *C. trachomatis.* In older patients, fluoroquinolones provide the best coverage of gram-negative organisms (see Table 85.10). Treatment of viral orchitis is supportive only. Although steroids may improve symptoms, they can reduce testosterone levels. All patients should receive local scrotal care as described for epididymitis. Patients with marked pain, high fever, or constitutional symptoms merit hospitalization and parenteral antibiotics.

TESTICULAR TUMORS

Background

Tumor of the testis is the most common malignancy in young men but accounts for only 1% of all cancers in men. These tumors are more common in infertile patients and patients with cryptorchidism. Approximately 95% of testicular tumors are germ cell tumors, with 50% of these being seminomas and the other 50% being mixed types, including teratomas, choriocarcinomas, and yolk sac tumors. The other 5% of testicular tumors are sex cord stromal tumors. The disease course will depend on the type of tumor present, as well as the age of the patient.

Clinical Features

Testicular cancer usually presents as a painless, unilateral scrotal mass or as an incidental ultrasound finding. However, scrotal pain may be the first symptom in up to 20% of cases. Unlike other painless scrotal masses, such as hydroceles and varicoceles, tumors cannot be separated from the underlying testicle. Palpable tumors are more likely to be malignant compared with tumors identified only with imaging.

Diagnostic Testing

All patients with a scrotal enlargement or palpable scrotal lesions on physical examination should undergo a scrotal ultrasound examination. This study can reveal a concomitant hydrocele or homogeneous hypoechoic lesion. Intratesticular tumors are typically hypervascular, with irregular branching vessels. Leydig cell tumors are unique, because they show hypervascularity around the lesion but no internal color Doppler flow. Although helpful for staging purposes, CT scans of the chest and abdomen are necessary in the ED only if the patient has complaints related to these parts of the body. Most paratesticular masses are benign lesions such as epididymal cysts, epididymitis, spermatoceles, hydroceles, or hernias.

Management and Disposition

Urgent referral to a urologist is indicated for patients with intratesticular masses. The radiosensitive nature of seminomas renders the combined treatment of orchiectomy and radiation therapy highly successful for early-stage disease. Testicular cancer has become one of the most curable solid neoplasms, with an expected 5-year survival rate over 95%.[39]

TESTICULAR TRAUMA

The most concerning injury associated with trauma is rupture of the testicle. Testicular rupture is characterized by tear of the tunica albuginea and extrusion of the seminiferous tubules. The presentation can range from a tender, large, blood-filled scrotum to minimal swelling, with mild pain of the testicle. If there is any concern for rupture, scrotal ultrasound is indicated. Disruption in the echogenic tunica albuginea is 100% sensitive and 65% specific for rupture. Early surgical intervention is associated with higher rates of testicular salvage. Hematomas can be intratesticular or extratesticular, with or without testicular rupture. Similar to rupture, rapid evacuation of an intratesticular hematoma will reduce the risk of necrosis. Extratesticular hemorrhage into the tunica vaginalis is termed a *hematocele* and is the most common finding after blunt scrotal injury. Surgical exploration with hematoma extraction is recommended for patients with large hematoceles to prevent testicular atrophy. Approximately 10% of patients with testicular trauma have associated torsion and require prompt identification and detorsion.

INGUINAL HERNIA, ACUTE HYDROCELE, VARICOCELE, AND SPERMATOCELE

Inguinal hernias, hydroceles, varicoceles, and spermatoceles are considerations in the differential diagnosis of an acute scrotal mass. These clinical entities are typically painless and readily identifiable on physical examination.

Most children with inguinal hernias will not have a palpable mass on examination but will report a history of intermittent bulge in the groin that appears with straining or crying. Less commonly, an inguinal mass is palpable and may extend into the scrotum. If this mass becomes incarcerated, it will be tender, and often the overlying skin will be edematous and erythematous. Children typically will develop irritability, vomiting, or abdominal distention. Incarcerated hernias should be reduced promptly to prevent bowel infarction from strangulation. Reduction can be accomplished by placing the patient in a Trendelenburg position and applying gentle pressure to expel the gas and stool in the bowel from the hernia. Pressure is then applied over the distal aspect of the hernia to reduce the bowel. If this technique fails, surgery is consulted. After reduction of an incarcerated hernia, children typically require hospitalization and delayed surgical repair.

Acute hydroceles typically are benign. They are caused by the accumulation of fluid between the two layers of the tunica vaginalis. They are painless, localized to the scrotum, and will transilluminate.

Varicoceles are enlarged spermatic cord veins that typically are painless or cause only minimal discomfort. On examination, they are often described as feeling similar to a bag of worms, just superior to the testicle, and decrease in size when the patient is supine. In contrast, a spermatocele is a sperm-containing cyst that is palpated as a nontender mass posterior to the testicle. Ultrasound is diagnostic of these conditions. No emergent treatment is necessary, but patients require outpatient urologic evaluation.

Regardless of the cause of the scrotal swelling, concomitant pathology is always a consideration. A careful evaluation for torsion, epididymitis, and tumors should be performed.

ACUTE URINARY RETENTION

Background

AUR is the sudden inability to pass urine voluntarily from the bladder. The lifetime risk of AUR increases with age, occurring in 10% of men in their 70s and in 33% of men in their 80s. AUR is usually caused by an obstructive lesion but also can be the presenting manifestation of other pathologic processes. AUR in women is much less common than in men; common causes in women include an atonic bladder, inflammation occurring postpartum or secondary to herpes, Bartholin abscess, acute urethritis, or vulvovaginitis. Causes in younger patients include obstruction, cystitis, and neurologic disturbances.

Physiology and Pathophysiology

Holding urine requires relaxation of the bladder detrusor muscle, through parasympathetic inhibition and β-adrenergic stimulation, and contraction of the bladder neck and internal sphincter, through α-adrenergic stimulation. Conversely, micturition requires a coordinated contraction of detrusor muscle, with the simultaneous relaxation of the urethral sphincter muscle. AUR results from a disruption of this coordinated physiology caused by an increased resistance to flow via mechanical (e.g., urethral stricture, clot retention) or dynamic means (e.g., increased α-adrenergic activity, prostatic inflammation) or decreased neurogenic control of the detrusor muscle (e.g., drugs inhibiting bladder contractility, diabetes cystopathy).

The most common cause of AUR seen in the ED is obstruction of the urinary tract distal to the bladder. In men, BPH is the most common precipitant. Enlargement of the prostate coupled with constriction of the prostatic urethra from heightened α-adrenergic tone obstructs urinary output. Strictures of the urethra after prior procedural trauma, infection, or radiation therapy can also lead to AUR. Other less common obstructive causes of AUR include prostate cancer, phimosis (inability to retract the foreskin over the glans penis), and paraphimosis (inability to reduce the foreskin over an edematous glans). In women, the most frequent obstructive causes are pelvic masses and prolapse of pelvic organs such as the bladder, rectum, or uterus. These structures cause AUR by compressing the urethra and obstructing urine flow. Finally, congenital posterior urethral valves are the most common source of AUR in children.

Infectious and inflammatory conditions can also cause AUR from urethral edema and obstruction, particularly in the setting of underlying prostatic disease. The most common infectious causative disorder is acute prostatitis, followed by urethritis and vulvovaginitis. In pediatric patients. UTIs can induce sufficient dysuria that the child refuses to void, with consequent urinary retention.

Pharmacologic agents associated with AUR include the anticholinergic and sympathomimetic agents. Anticholinergic agents inhibit detrusor muscle contraction, whereas sympathomimetic agents increase α-adrenergic tone in the prostate. NSAIDs and calcium channel blockers have also been known to increase the rate of AUR by inhibiting prostaglandin and calcium-mediated detrusor muscle contraction.

Neurogenic causes of AUR result from a cortical, spinal cord, or peripheral nerve deficit in the sensory or motor nerve supply of the detrusor muscle. Most neurologic causes of AUR are chronic conditions such as multiple sclerosis, Parkinson disease, neoplasms, and diabetic peripheral neuropathy. Other more acute neurologic conditions that should be diagnosed emergently as causative factors in the ED include spinal trauma, stroke, epidural abscess, and intervertebral disk herniation.

Clinical Features

Although the potential causes of AUR are many, the history and physical examination can considerably narrow the scope of the differential diagnosis (Table 85.11). Most patients with AUR report sudden pain and have a distended tender bladder. Patients with dementia or limited verbal ability may only present with restlessness and agitation. With lesions proximal to the bladder, patients typically note pain in the flank, whereas lesions distal to the bladder can produce pain radiating to the scrotum or labia. With acute obstruction, pain is often quite severe. Patients with slowly developing or chronic obstructions are typically older and report overflow incontinence and little to no pain.

When obstruction is the cause of AUR, the patient often will recall multiple previous episodes of urinary retention. In addition to this history, patients with BPH report frequency, urgency, hesitancy, nocturia, difficulty initiating the urinary stream, decreased force of the stream, sensation of incomplete voiding, and terminal dribbling. The prostate is enlarged, firm, and nonnodular. Normal findings on the prostate examination do not exclude BPH. Patients with prostate cancer can have similar symptoms, but these are more often accompanied by weight loss, bone pain, and other constitutional signs and symptoms. These patients generally will have an enlarged nodular prostate. Examination of the penis is important to identify phimosis or paraphimosis. In women with obstruction, pelvic pain and pressure are symptoms commonly associated with AUR. A prolapsed bladder, rectum, or uterus and enlarged ovaries or uterus can be identified on pelvic examination.

Patients with an infectious cause for their symptoms may complain of dysuria, frequency, urgency, hematuria, fever, chills, and low back pain. In acute prostatitis, these symptoms can be associated with penile discharge and a tender boggy prostate. Despite the obstruction, the patient may nevertheless be able to void small amounts of urine. In vulvovaginitis and urethritis, presenting complaints also may include discharge, pruritus, and vulvar skin findings.

Patients with a neurogenic cause for AUR may already have a history of neurologic disease that contributes to AUR. The examination should focus on any findings suggestive of acute neurologic deficit. Strength, sensation, and reflexes in the lower extremities should be examined because they have similar innervation to that of the bladder. The status of the bulbocavernosus reflex, anal reflex, sphincter tone, and perineal sensation should also be assessed.

Differential Diagnosis

The differential diagnosis for AUR is very broad and dependent on the patient's symptoms (Box 85.6). AUR presenting as lower abdominal pain may present similarly to small bowel obstruction, UTI, or prostatitis. Flank and back pain secondary to hydronephrosis can be confused with nephrolithiasis, pyelonephritis, and spinal pathology. Urinary symptoms of overflow incontinence and urinary hesitancy can be confused with UTI or spinal cord compression. Genital pain may present similarly to trauma, testicular torsion, or inguinal hernia.

TABLE 85.11 Presentation and Diagnosis of Acute Urinary Retention

Cause	History	Physical Examination Findings	Diagnosis[a]
Benign prostatic hypertrophy	Frequency, urgency, hesitancy Prior retention	Enlarged, firm prostate	UA
Prostate cancer	Frequency, urgency, hesitancy Previous retention Constitutional symptoms	Enlarged, firm prostate Nodular prostate	UA
Phimosis, paraphimosis	Penile pain	Nonretractable foreskin Edematous penis	Clinical only
Prostatitis	Dysuria, frequency, urgency Fever, chills	Warm, tender, boggy prostate Penile discharge	UA Urine culture
Urethritis, vulvovaginitis	Dysuria, frequency, urgency Itching	Discharge	UA Urine culture Urethral or cervical culture
Pelvic mass	Pelvic pain pressure	Prolapse of rectum, bladder, uterus	UA Ultrasound imaging, CT
Neurogenic bladder	Other neurologic complaints	Neurologic deficits	UA CT, MRI

[a]In the emergency department setting, each of these diagnoses is made primarily by the history and findings on the physical examination. Additional tests are needed as described.

CT, Computed tomography; *MRI,* magnetic resonance imaging; *UA,* urinalysis.

Diagnostic Testing

A urinalysis is recommended for AUR as it can reveal infection or the presence of hematuria from infection, tumor, or calculi. A basic chemistry panel for the assessment of renal function should be performed only when renal damage or hydronephrosis is a concern. There is no history, physical examination, or ultrasound finding that can reliably correlate with an acutely elevated creatinine level. It should be considered for patients with prolonged obstruction or preexisting renal insufficiency.

Additional studies are selectively indicated based on the history and physical examination to identify potentially serious or reversible causes, or when the diagnosis of AUR is unclear. With an equivocal history or physical examination, bedside ultrasound can confirm AUR.

BOX 85.6 Causes of Acute Urinary Retention in Adults

Obstructive
Benign prostatic hypertrophy
Prostatitis
Phimosis
Paraphimosis
Meatal stenosis
Tumor
Foreign body
Calculus
Stricture
Hematoma
Carcinoma

Infectious, Inflammatory
Urethritis (severe)
Urinary tract infection
Prostatitis
Severe vulvovaginitis
Genital herpes

Neurologic Causes
Motor Paralytic
Spinal shock
Spinal cord syndromes

Sensory Paralytic
Tabes dorsalis
Diabetes
Multiple sclerosis
Syringomyelia
Spinal cord syndromes
Herpes zoster

Drugs
Antihistamines
Anticholinergic agents
Antispasmodic agents
Tricyclic antidepressants
α-Adrenergic stimulators
Cold tablets
Ephedrine derivatives
Amphetamines

Psychogenic Problems
Psychodynamic stressors (e.g., lazy bladder syndrome)

Renal and bladder ultrasound studies provide visualization of an elevated postvoid residual, obstruction, hydronephrosis, or other cause of upper urinary tract disease. Pelvic ultrasound examination and CT scan evaluate for masses or malignancy causing obstruction. MRI of the spine detects disk herniation, cord compression, and cauda equina syndrome. Cystoscopy and retrograde cystourethrography can identify problems in the lower urinary tract and usually are performed as outpatient procedures. A prostate-specific antigen assay is not helpful in diagnosing or differentiating prostate cancer from other causes of AUR and should not be routinely performed.

Management

Treatment focuses on bladder decompression and identification of the underlying cause. Immediate placement of a 14 to 18 Fr Foley catheter should provide decompression of the bladder. If this fails, placement of an elbowed catheter (coudé catheter) with a cephalad orientation should be attempted to assist bypassing by any obstruction. If both these techniques prove to be unsuccessful, urologic consultation is indicated. If obstruction is believed to be caused by retained blood clots, a three-way catheter should be placed to allow for bladder irrigation. When immediate bladder decompression is required and a urologist is not available, major urethral trauma is present, or the patient has recently undergone urethral surgery, suprapubic bladder drainage should be performed.

Placement of a catheter has been reported to cause post-obstructive diuresis, hypotension, and hematuria. Such problems are believed to be related to rapid bladder decompression so, historically, gradual decompression has been recommended to prevent these complications. Neither has been proven to have any clinical significance. We recommend that all patients with AUR undergo rapid and complete decompression of the bladder.

Although the catheter is an inconvenience for the patient, and chronic use has been associated with UTIs, trauma, stones, and urethral strictures, early removal of the catheter is also associated with heightened risk for recurrence of AUR, which has been reported in up to 70% of cases. Leaving the catheter in place for 3 to 7 days decreases the incidence of recurrent retention.

Studies have suggested that administration of an α-adrenergic blocker, such as tamsulosin, at the time of catheter insertion in patients with BPH improves the likelihood of spontaneous voiding after catheter removal and may also improve the likelihood that a patient will not require ongoing catheter placement (see Table 85.5). While we recommend this approach, these medications are associated with an increased risk of orthostatic hypotension, particularly in older adults, so initiation of treatment should be coordinated with the patient's primary care physician. 5-Alpha-reductase inhibitors, another agent typically used for BPH, have not been shown to reduce the recurrence of AUR.

Prophylactic antibiotic therapy is not recommended for patients with AUR. Although bacteriuria often develops in patients with indwelling catheters, it typically is not clinically significant, and the use of prophylactic antibiotics only promotes resistance.

Definitive therapy often requires surgical correction of any underlying obstruction. This should not be performed emergently because early surgery is associated with increased morbidity.

Disposition

After bladder drainage, healthy and reliable patients can be safely discharged from the ED with an indwelling catheter and urology follow-up. Patients with concomitant infection, significant comorbid illnesses, impaired renal function, neurologic deficits, or complications from catheterization require further diagnosis and treatment and probably admission.

HEMATURIA

Background

Blood in the urine can be microscopic or gross. Although generally associated with a benign process, microscopic hematuria can reflect serious underlying pathology, such as a urothelial malignancy. Therefore, following ED assessment, patients with any degree of hematuria require outpatient follow-up. Less commonly, patients come to the ED complaining of gross blood in their urine. Compared to microscopic hematuria, gross blood in the urine is more likely to be a presenting symptom of an underlying malignancy. Regardless of age or visibility of blood in the urine, patients with hematuria require evaluation in the ED to rule out life-threatening diagnoses, such as malignancy and AAA.

Gross and microscopic hematuria can arise from anywhere along or near the urinary tract. In the upper and lower portions of the urinary tract, infection, trauma, and renal calculi are the most common causative disorders. Patients also can have more serious causes of hematuria, such as malignancy or vascular lesions (e.g., AAA), and these diagnoses should be excluded. Up to 5% of patients with asymptomatic microscopic hematuria and 30% to 40% of patients with gross hematuria are found to have a urinary tract malignancy. The risk of urologic malignancy is increased in patients older than 35 years, male gender, and those with a history of smoking.

Occasionally, hematuria also has been attributed to warfarin use, BPH, and exercise. Supratherapeutic anticoagulant therapy can lead to blood in the urine, but therapeutic anticoagulation does not typically produce spontaneous hematuria. Similarly, BPH can lead to increased vascularity of the prostate but does not increase the risk of hematuria. High-intensity exercise also can produce hematuria. This bleeding typically is transient and clinically inconsequential. Because warfarin use, BPH, and exercise do not directly cause persistent hematuria, patients with ongoing bleeding require further urologic evaluation.

Clinical Features

A careful history will often identify a benign cause for hematuria, such as menstruation, recent heavy exercise or urologic procedure, sexual activity, or use of agents that can produce red urine without blood (Box 85.7). Repeated episodes of bleeding during and after menstruation in women suggest endometriosis of the urinary tract. Patients may report frequency, urgency, and dysuria in the setting of infection. They may note flank pain with urolithiasis or pyelonephritis. Microscopic hematuria in the setting of a UTI should resolve after appropriate antibiotic treatment.

The physical examination may point toward the underlying cause. For example, hypertension occurs with glomerulosclerosis and, in the setting of peripheral edema, suggests nephrotic syndrome. An abdominal bruit may be caused by an arteriovenous fistula, whereas a palpable abdominal mass may represent an AAA. Flank pain and tenderness can arise with pyelonephritis or nephrolithiasis. The external genital examination can show evidence of trauma or a tumor and may reveal a rectal or vaginal source for the bleeding. A pelvic examination should be performed in women to identify a vaginal or uterine source of bleeding.

Diagnostic Testing

Microscopic hematuria is defined as the presence of three or more RBCs/high-power field (hpf) of urinary sediment. A clean-catch or catheterized urine specimen should be obtained in all patients with hematuria. Catheterization itself induces hematuria in approximately 15% of patients, but the amount of bleeding is inconsequential, rarely exceeding three RBCs/hpf. If available, bedside urine dipstick testing should be performed. A negative urine dipstick rules out the presence of hematuria and obviates the need for urine microscopy. If positive for blood, urine microscopy should be performed.

BOX 85.7 Causes of Red-Colored Urine Without Hematuria

- Phenazopyridine
- Nitrofurantoin
- Rifampin
- Chloroquine
- Hydroxychloroquine
- Iodine
- Bromide
- Food coloring
- Beets
- Berries
- Rhubarb

As little as 1 mL of whole blood in 1 L of urine can produce gross hematuria, turning the urine red. A number of other substances and reactions can turn the urine red, and centrifugation of the urine and microscopic analysis differentiate these false-positive results from true hematuria. After centrifugation, the red color persists only in the urine sediment with hematuria. By contrast, a red supernatant that contains no RBCs on microscopic analysis typically represents a benign condition (see Box 85.7).

Microscopy will reveal WBCs in addition to RBCs in the presence of infection. Proteinuria, cellular casts, and dysmorphic RBCs are seen with glomerular disease. Patients with these findings may also have cola-colored urine and should be referred to a nephrologist.

Management and Disposition

The combination of a careful history, physical examination, and laboratory studies should identify benign causes of microhematuria such as infection, menstruation, vigorous exercise, and trauma. According to the American Urological Association (AUA) Guideline on Asymptomatic Microhematuria, once benign causes have been ruled out, a prompt outpatient urologic evaluation should occur.[40] This evaluation generally consists of an assessment of renal function (BUN and creatinine levels, calculated GFR) and multiphasic CT urography, including sufficient phases to evaluate the renal parenchyma and urothelium of the upper tracts.

CT urography identifies hydronephrosis, urinary calculi, and renal and ureteral lesions. For patients with contraindications to contrasted CT, MR urography is an acceptable alternative imaging approach. Finally, the AUA guidelines recommend that cystoscopy be performed on all patients aged 35 years or older or those with risk factors for urinary tract malignancy, such as tobacco use, exposure to carcinogenic chemicals (e.g., aniline dye, benzidine, petroleum products), or history of chronic UTIs.[40] Risk factors for urinary tract malignancy in patients with microscopic hematuria are listed in Box 85.8. For persistent microhematuria following a negative evaluation, yearly urinalyses are recommended, with consideration for a repeat urologic examination every 3 to 5 years.

By contrast, patients with gross hematuria require a thorough evaluation before discharge from the ED. Renal function should be assessed to rule out the development of renal insufficiency. The patient should also undergo appropriate imaging tests, although clear consensus is lacking on the appropriate radiographic study. If the initial assessment fails to identify a benign cause for the hematuria, a CT scan with contrast or renal ultrasound study should be performed. CT scanning is

BOX 85.8 Risk Factors for Urinary Tract Malignancy

- Age >35 years
- Past or current cigarette smoking
- Occupational exposure (chemicals or dyes)
- Analgesic abuse
- Chronic indwelling foreign body
- Chronic urinary tract infection
- Exposure to known carcinogenic or chemotherapeutic agent
- Gross hematuria
- Irritative voiding symptoms
- Pelvic irradiation
- Urologic disorder or disease

highly sensitive for stones, masses, and other diseases of the upper urinary tract. If contrast CT must be avoided owing to pregnancy, renal insufficiency, or history of anaphylaxis to contrast medium, ultrasound imaging is the modality of choice. Ultrasound is less sensitive than a CT scan for detecting stones, small masses, and traumatic causes of hematuria.

CT is the appropriate imaging modality for traumatic hematuria because its sensitivity and specificity exceed those of ultrasound. The exact level of hematuria that should trigger imaging is unclear, but it appears that patients without gross hematuria or evidence of coexisting abdominal or pelvic injuries are unlikely to have clinically significant injuries on CT.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 85: QUESTIONS AND ANSWERS

1. Which of the following medications is not an appropriate first-line choice for empirical treatment of uncomplicated urinary tract infections (UTIs)?

a. Fosfomycin
b. Nitrofurantoin
c. Trimethoprim-sulfamethoxazole
d. Ciprofloxacin

Answer: d. The options for treating uncomplicated lower UTI include single-dose therapy with fosfomycin, 5 days of nitrofurantoin, or 3 days of trimethoprim-sulfamethoxazole. Fluoroquinolones such as ciprofloxacin or levofloxacin should not be used as first-line agents for empirical treatment of uncomplicated UTIs. Instead, they should be reserved for patients who have failed or have contraindications to first-line antibiotics.

2. Which of the following drugs is not an appropriate first-line choice for treatment of an uncomplicated urinary tract infection (UTI) in women?
   a. Fosfomycin
   b. Ciprofloxacin
   c. Nitrofurantoin
   d. Trimethoprim-sulfamethoxazole
   e. All of the above

Answer: b. According to the Infectious Disease Society of America (IDSA) practice guidelines, fluoroquinolones should not be used as first-line agents for uncomplicated UTI because of increased resistance.

3. Computed tomography should be undertaken in the patient suspected of having renal colic if which of the following is present?
   a. The patient has a solitary or transplanted kidney.
   b. The patient has gross hematuria.
   c. The patient has had a prior history of nephrolithiasis.
   d. The patient presents in severe pain.

Answer: a. Imaging is appropriate for patients who have a history of nephrolithiasis who do not improve with treatment, have a urinalysis showing infection, have a solitary or transplanted kidney, or for whom a diagnosis other than renal colic is suspected.

4. What percentage of cases of acute bacterial prostatitis eventually develop into chronic bacterial prostatitis?
   a. 1%
   b. 5%
   c. 10%
   d. 20%

Answer: c. Chronic bacterial prostatitis will eventually develop in 10% of patients with acute bacterial prostatitis.

5. In testicular torsion, testicular salvage may be predicted by which of the following factors?
   a. Degree of torsion
   b. Duration of the ischemia
   c. Cremasteric reflex
   d. Age of the patient
   e. Both A and B

Answer: e. Testicular torsion results in obstruction of venous outflow, subsequent compromised arterial flow, and testicular ischemia. Testicular salvage hinges on the degree of torsion and duration of the ischemia.

6. To detorse a testicular torsion, you should first rotate the testis medially to laterally. If this does not produce immediate relief, you should do which of the following?
   a. Assume that the testicle is already necrotic and not amenable to further reduction attempts.
   b. Attempt untwisting past 360 degrees because a higher degree of rotation may be present.
   c. Both A and B.
   d. Reverse the direction of reduction.

Answer: d. Most testes torse laterally to medially, but some may torse medially to laterally. If no immediate relief is obtained by rotating medially to laterally, reverse the direction of the reduction attempt.

86

Gynecologic Disorders

Trevor R. Pour and Christina S. Hajicharalambous

KEY CONCEPTS

- Adnexal torsion is easily missed on initial presentation and should be considered in any patient with known risk factors, even if symptoms are subtle or atypical.
- Doppler ultrasound is the preferred initial imaging study for suspected adnexal torsion.
- An ultrasound examination may distinguish among the various types of ovarian cysts and identify associated complications, such as torsion, hemorrhage, and malignancy. Most ovarian cysts are simple follicular cysts that resolve without pharmacologic or surgical intervention.
- Abnormal uterine bleeding (AUB) has many structural, hormonal, and coagulopathic causes. Selected imaging and laboratory testing, based on a careful history and physical examination, can often lead to determination of the cause. Combined oral contraceptive pills can help to regulate the cycle and alleviate AUB.
- Emergency contraception is a safe, effective option to prevent an undesired pregnancy. Levonorgestrel and ulipristal are both effective oral medications and are associated with fewer side effects than the traditional combined contraceptive method. Intrauterine devices should also be considered for emergency contraception if a patient desires a long-term contraceptive option.

GYNECOLOGIC DISORDERS

Many women present to the emergency department (ED) with pelvic pain or vaginal bleeding. After the possibility of pregnancy-related diagnoses has been eliminated, the primary goal is to recognize the presence of conditions that warrant urgent intervention, such as adnexal torsion, versus those that can be managed as an outpatient, such as new postmenopausal uterine bleeding. Most patients also benefit from symptom relief and reassurance. This chapter specifically addresses the ED management of adnexal torsion, ovarian cysts, abnormal uterine bleeding (AUB), and emergency contraception. The general approach to vaginal bleeding is discussed in Chapter 30, complications of pregnancy are discussed in Chapter 173, and sexually transmitted disease is discussed in Chapter 84.

ADNEXAL TORSION

Foundations

The bilateral adnexal structures consist of the ovaries and fallopian tubes. Torsion accounts for approximately 3% of gynecologic emergencies and refers to the twisting of the ovary and/or fallopian tube on the axis between the utero-ovarian and infundibulopelvic ligaments. Although most commonly both structures are involved in this process, isolated ovarian torsion and, more rarely, isolated fallopian tube torsion may occur. In the early phases of torsion, venous and lymphatic obstruction initially occur, followed subsequent congestion and edema of the adnexal structures, which then progress to ischemia and necrosis.

In addition to loss of tubal or ovarian function, torsion left untreated can progress further to hemorrhage, peritonitis, and infection. Because of the dual blood supply of the ovary from the uterine and ovarian arteries, total arterial obstruction is rare but can develop (Fig. 86.1).

Ovarian torsion can occur at any age but is most common in the reproductive years due to the regular development of a corpus luteal cyst during the menstrual cycle. Torsion may be a complication of pregnancy, more likely to occur in the first and early second trimesters.[1] A history of tubal ligation is a risk factor for ovarian torsion.[2] A predominance of torsion on the right side has been noted in approximately a 2:1 ratio to cases on the left, likely related to the stabilizing effect of the fixed sigmoid colon.

In premenarchal patients, torsion frequently occurs despite normal ovarian size, thought to be secondary to the excessive mobility of the adnexa due to relatively longer supporting ligaments and the smaller size of the uterus.[3,4]

Most cases of torsion in the postmenarchal population are associated with an enlarged ovary with a diameter greater than 5.0 cm as the result of a benign neoplasm or cysts, which can be the result of ovulation induction, hyperstimulation syndrome, or polycystic ovarian syndrome. Masses prone to developing adhesions and therefore restricting mobility of adnexal structures, such as malignant tumors, endometriomas, or tubo-ovarian abscesses, are less likely to develop torsion than benign lesions.

Clinical Features

Despite advances in imaging modalities, the definitive preoperative diagnosis rate of ectopic pregnancy approaches only 40%, making clinical assessment the primary driver of management decisions. The classic symptoms of ovarian torsion are severe, sharp, unilateral lower abdominal pain accompanied by nausea and vomiting; however, these elements are not consistently present in all cases.[5] The presence of known risk factors, such as an ovarian mass or recent assisted reproductive treatments, may suggest the diagnosis in postmenarchal patients.

Patients typically report pain lasting from several hours to days, sometimes with intermittent resolution likely owing to spontaneous detorsion. Rarely, patients report pain for weeks to months in duration, most likely due to intermittent or chronic torsion.[6] Nausea and vomiting are present in approximately 60% to 70% of cases. Fever is a an uncommonly reported finding, typically seen late in the course of disease and likely secondary to ischemia and necrosis of adnexal tissue.

Most patients will have unilateral tenderness on abdominal palpation, but peritoneal signs are rare, especially in early presentations. Only 50% of patients will have a palpable adnexal mass on pelvic

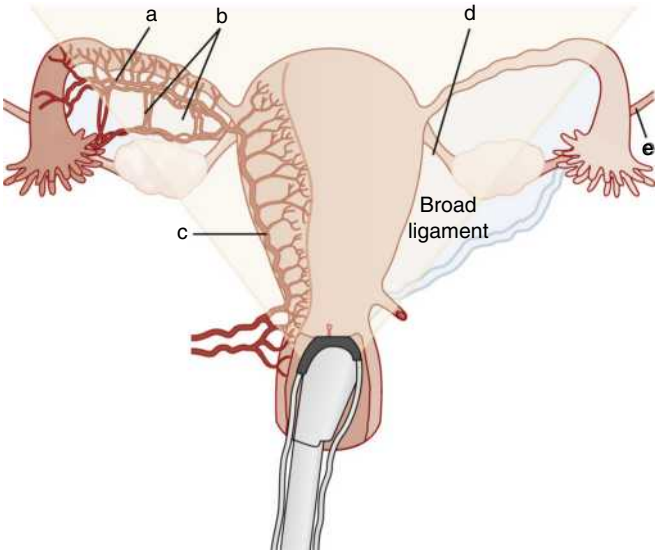

Fig. 86.1 Ovarian Blood Supply. *a,* Ovarian artery and vein. *b,* Branching arterioles supplying ovary. *c,* Uterine artery. *d,* Utero-ovarian ligament. *e,* Infundibulopelvic ligament. (From Andreotti RF, Shadinger L, Fleischer A. The sonographic diagnosis of ovarian torsion: pearls and pitfalls. *Ultrasound Clin.* 2007;2:155.)

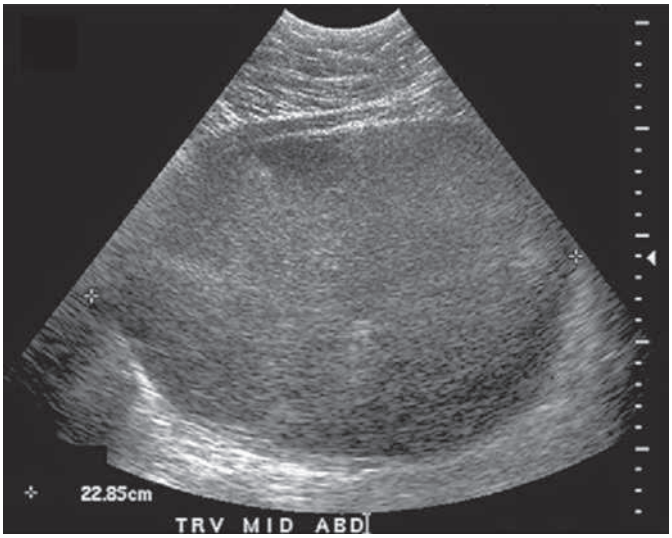

Fig. 86.2 Ovarian Torsion with a Large Pelvic Mass. This transabdominal image reveals a largely homogeneous 22.8-cm pelvic mass. (From Cicchiello LA, Hamper UM, Scoutt LM. Ultrasound evaluation of gynecologic causes of pelvic pain. *Obstet Gynecol Clin North Am.* 2011;38:85–114.)

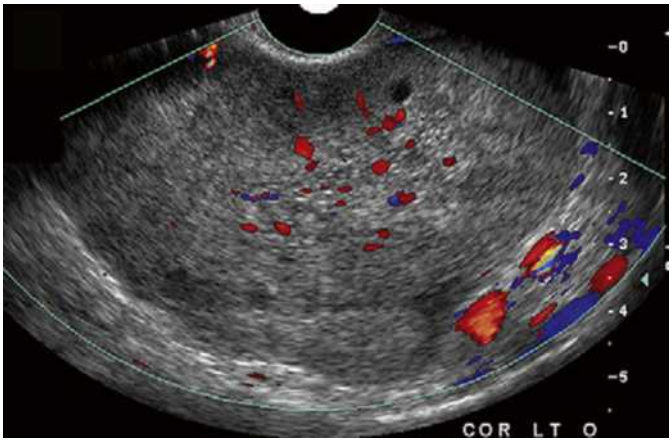

Fig. 86.3 Ovarian torsion with color Doppler image demonstrating venous and arterial flow. (From Cicchiello LA, Hamper UM, Scoutt LM. Ultrasound evaluation of gynecologic causes of pelvic pain. *Obstet Gynecol Clin North Am.* 2011;38:85–114.)

examination; a palpable mass is more common in adults than pediatric patients with torsion.[7] Predictive scoring systems for adnexal torsion—typically involving a combination of clinical elements and imaging or laboratory findings—have been developed but have not yet been shown to be generalizable to all populations and therefore cannot be recommended at this time.[8,9] Clinical signs of isolated tubal torsion are indistinguishable from those of ovarian or full adnexal torsion.[10]

Differential Diagnoses

The differential diagnosis of adnexal torsion includes appendicitis, ruptured ovarian cyst, cystitis or pyelonephritis, nephrolithiasis, pelvic inflammatory disease, uterine leiomyoma, diverticulitis, bowel obstruction, and ectopic pregnancy. A pregnancy test, physical examination, and imaging with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), if necessary, can typically distinguish among these possibilities.

Diagnostic Testing

Laboratory Tests

No specific laboratory tests are routinely used in the diagnosis of adnexal torsion, although preoperative labs should be drawn on all patients suspected of torsion. A negative pregnancy test may exclude ectopic pregnancy from the differential, but importantly a positive test does not rule out adnexal torsion. Leukocytosis and elevated C-reactive protein (CRP) are occasionally associated with torsion but both are nonspecific and cannot be used as reliable predictors.

Small studies on serum interleukin-6 (IL-6) and D-dimer levels have revealed moderate sensitivity and specificity for detection of ovarian torsion, especially when coupled with findings suggestive of torsion on ultrasonography.[11,12] These tests in combination may eventually prove to be useful if early findings are confirmed by larger trials, but neither is considered a routine test at this time.

Imaging Tests

Ultrasonography. Ultrasound examination is the optimal initial imaging test in the evaluation of patients with pelvic pain highly suggestive of torsion, but findings can vary depending on timing and duration of symptoms. Asymmetric enlargement of the ovary is the most common finding. Enlargement of an ovary with a heterogeneous stroma secondary to edema along with small, peripherally displaced follicles is the classic ultrasound appearance of torsion but is often absent, particularly in the setting of prolonged ischemia.[13] Ultrasound may also reveal a discrete ovarian mass, evidence of hemorrhage, or free pelvic fluid (Fig. 86.2). Hemorrhagic cysts and other nonneoplastic masses frequently are associated with torsion; these may appear fluid filled, exhibit a complex pattern with debris and septations, or be visualized as a solid mass. The characteristic appearance of torsion may be difficult to appreciate if the ovary is obscured by an associated mass. In isolated tubal torsion, tubal lesions such as hydrosalpinx or a tuboovarian abscess may be seen.

Doppler ultrasound findings are inconsistent in the definitive diagnosis of adnexal torsion. Up to 60% of surgically proven cases have ovarian blood flow on the preceding Doppler examination (Fig. 86.3).[14] These findings may vary depending on the time of the examination because torsion may occur intermittently, and

clinical symptoms commonly precede arterial compromise. If a large adnexal mass is present, the examination may also be technically difficult to perform. Despite these limitations, the Doppler examination is still useful, as recognition of ovarian enlargement or masses, as well as detection of abnormal venous flow is particularly important in early cases of torsion (Fig. 86.4). Absence of arterial flow is highly specific for torsion, with a positive predictive value nearing 100%. Visualization of the twisting of the pedicle and coiled vessels is referred to as a "whirlpool sign" and has a 90% positive predictive value for torsion.[15]

Computed tomography. When alternative abdominal pathologies are strong considerations in the differential diagnosis of a patient's acute pelvic pain, abdominopelvic CT may be the best initial study, particularly in patients who have a presentation less typical for torsion. In ovarian torsion, CT findings include asymmetric ovarian enlargement or asymmetric adnexal enhancement following intravenous (IV) contrast, fallopian tube thickening, twisted vascular pedicle, fat stranding surrounding the affected adnexa, and uterine deviation to the affected side.[16] Pelvic free fluid can also be seen, especially in cases of hemorrhagic infarction.

Multiple studies show that patients with ultrasonographic or surgically confirmed torsion have evidence of at least one abnormal finding on CT. This suggests that a completely normal contrast-enhanced CT scan of the abdomen and pelvis—including the absence of ovarian enlargement or masses in addition to the aforementioned findings—may be sufficient to rule out ovarian torsion.[17] Negative CT imaging findings should be interpreted with caution when clinical suspicion is high, but with lower suspicion, normal-appearing pelvic structures on a CT scan is reassuring and potentially sufficient imaging.

Magnetic resonance imaging. MRI may also demonstrate findings consistent with torsion. It is particularly helpful when the diagnosis is unclear, such as in patients who present with intermittent pain over days, or for pregnant patients when the history is suggestive of torsion but ultrasound findings are inconclusive or equivocal and CT scans are not preferred. Findings on MRI suggestive of torsion are similar to those on CT (Box 86.1).

Laparoscopy. Given the frequency of equivocal findings on imaging studies, the lack of reliable clinical decision tools, the absence of a proven biomarker, and the variable clinical presentation, adnexal torsion is commonly a surgical diagnosis. Diagnostic laparoscopy is therefore indicated for patients in whom clinical suspicion is high despite negative imaging results. Laparoscopy also allows for the diagnosis of other unsuspected conditions, including appendicitis or tubo-ovarian abscess.[18]

Management and Disposition

Once the diagnosis of suspected torsion has been made, the patient should be taken to the operating room as soon as possible. The adnexal

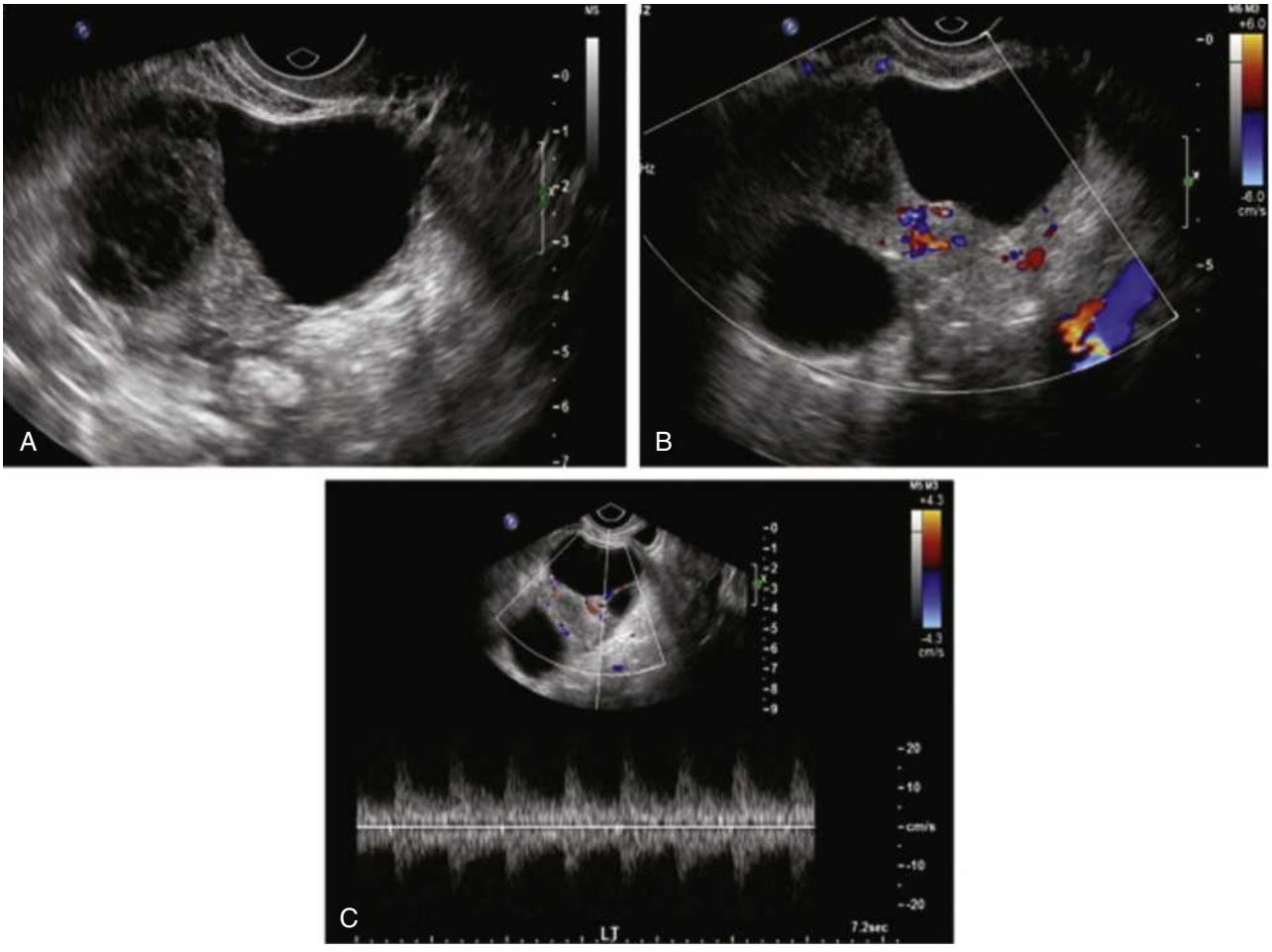

Fig. 86.4 (A) Ultrasound examination demonstrating a large associated hemorrhagic cyst. (B and C) Arterial Doppler signal without venous signal in a patient with surgically proven torsion. (From Andreotti RF, Shadinger L, Fleischer A. The sonographic diagnosis of ovarian torsion: pearls and pitfalls. *Ultrasound Clin.* 2007;2:155.)

structures often will recover, even if visibly ischemic or dusky in appearance at the time of surgery. Because of its dual blood supply and potential to recover function, attempts at ovarian salvage are warranted even if the diagnosis is delayed. This is particularly true in adolescent patients.

OVARIAN CYSTS AND MASSES

Foundations

Cysts are the most common cause of gynecologic masses. They occur at any stage of life but are most frequent in the reproductive years because of the cyclic changes of the ovary associated with menstruation (Fig. 86.5). Most ovarian cysts in premenopausal and postmenopausal women are benign and resolve without intervention, but on occasion they may be malignant or associated with complications such as hemorrhage or torsion.[19,20]

BOX 86.1 Imaging Characteristics of Adnexal Torsion

Ultrasonography
Enlargement of the ovary
Associated ovarian mass
Loss of enhancement
Edema
Free pelvic fluid
Loss of venous waveforms
Loss of arterial waveforms

Computed Tomography and Magnetic Resonance Imaging
Enlargement of the ovary
Associated ovarian mass
Thickening of the fallopian tube
Free pelvic fluid
Edema of the ovary
Deviation of the uterus to the affected side
Associated hemorrhage

The most common type of cyst is a simple follicular, or functional cyst, developing from a follicle that fails to rupture or regress, and is defined as pathologic when the diameter exceeds 3.0 cm. Follicular cysts are typically thin-walled and filled with clear fluid, whereas a corpus luteal cyst is often filled with hemorrhagic fluid. Several other types of cystic masses can occur in the ovary, including endometriomas (often called "chocolate cysts"), nonneoplastic lesions such as benign cystic teratoma or dermoid cyst, fibroma, cystadenoma, and various types of malignant neoplasms.[21]

Clinical Features

The most common presentation for patients with an ovarian cyst is pelvic pain. Rupture of a follicular cyst may produce transient pelvic pain, be associated with dyspareunia, or be asymptomatic. Because of the thin and fragile wall, a follicular cyst may rupture during sexual intercourse or during the pelvic examination. Follicular cysts are rarely associated with hemorrhage.

Presentation of a corpus luteal cyst may range from an asymptomatic mass to dull, chronic pelvic pain to severe pain associated with rupture. Rupture of a corpus luteal cyst is frequently associated with a significant degree of hemorrhage. As with a follicular cyst, rupture may follow a pelvic examination, sexual intercourse, exercise, or trauma. Rupture of a large or complex cyst may result in severe pain and peritoneal signs. Occasionally, a large cyst may be discovered on a routine pelvic examination as an asymptomatic mass, but this is uncommon.

Differential Diagnoses

Diagnostic considerations in the patient with symptomatic ovarian cysts and masses include other causes of pelvic pain that require urgent intervention, such as ectopic pregnancy, pelvic inflammatory disease, urinary tract infections, nephrolithiasis, appendicitis, and diverticulitis. Tumors or abscesses of the gastrointestinal tract may also mimic adnexal masses.

Diagnostic Testing

Laboratory Tests

The initial step in the evaluation of pelvic pain or a pelvic mass is to exclude pregnancy with a urine or serum β-human chorionic gonadotropin (β-hCG) test. A hematocrit may be valuable in the unstable

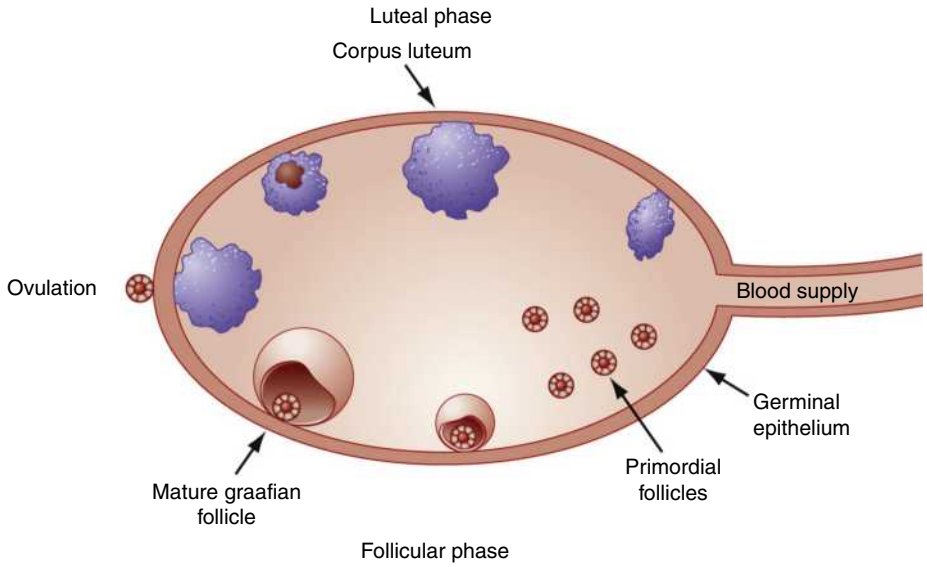

Fig. 86.5 Ovulatory cycle and maturation during the normal menstrual cycle. (From Lambert MJ, Villa M. Gynecologic ultrasound in emergency medicine. *Emerg Med Clin North Am.* 2004;22:683–696.)

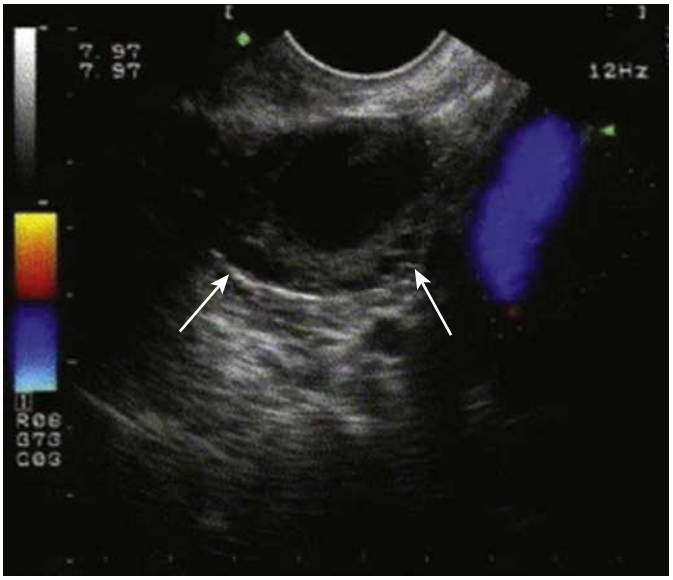

Fig. 86.6 Endovaginal ultrasound image of a normal ovary with a dominant follicle *(arrows)*. (From Lambert MJ, Villa M. Gynecologic ultrasound in emergency medicine. *Emerg Med Clin North Am*. 2004;22:683–696.)

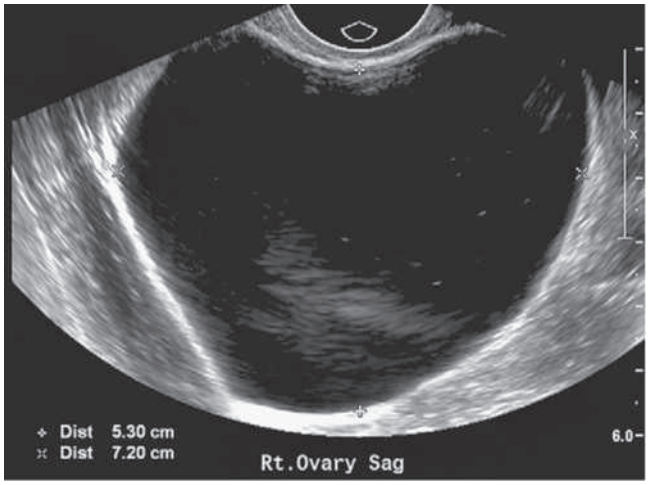

Fig. 86.7 Endovaginal ultrasound image of a follicular cyst, with smooth wall and posterior wall enhancement. (From Cicchiello LA, Hamper UM, Scoutt LM. Ultrasound evaluation of gynecologic causes of pelvic pain. *Obstet Gynecol Clin North Am*. 2011;38:85–114.)

patient as a marker of blood loss. The serum antigen CA-125 is elevated in 80% of women with epithelial ovarian cancer but can also be elevated by nonmalignant conditions such as endometriosis, pregnancy, and pelvic inflammatory disorder, limiting its usefulness in the emergency setting.

Imaging Tests

Ultrasonography. Ultrasonography is used to diagnose and characterize all ovarian pathologic processes and lesions, including cysts and masses. Approximately 90% of adnexal masses are adequately characterized by ultrasound imaging alone. Transabdominal and endovaginal examinations provide useful information. The transabdominal approach is performed with a full bladder as a sonographic window. It permits an overall view of the pelvis and will visualize large masses and pelvic free fluid. Use of the endovaginal probe, which should be performed with an empty bladder to reduce artifact, provides a detailed picture of the ovary. Follicles are part of the normal architecture of the ovary and are typically smaller than 1.0 cm in diameter, whereas the dominant follicle may measure up to 2.5 cm at the time of ovulation. Depending on the timing of the scan and degree of clot formation and lysis, hemorrhage may be seen; serial bedside abdominal ultrasound imaging can also serve as a rapid assessment tool to detect worsening hemoperitoneum in the setting of hemorrhagic cyst rupture. Fig. 86.6 demonstrates a normal ovary with a dominant follicle, Fig. 86.7 demonstrates a large cyst, and Fig. 86.8 demonstrates hemorrhage and free pelvic fluid. Ultrasound findings suggestive of malignancy include internal septations, solid elements within cystic structures, a thickened wall, and large amounts of ascites or free fluid.[22]

Computed tomography. When the differential diagnosis of unilateral pelvic pain is broad, particularly in the patient with symptoms or physical findings not solely confined to the pelvis, a CT scan may be a more appropriate initial imaging study. However, it is not recommended as the first line imaging study if an adnexal mass is of primary concern due to poor soft tissue discrimination.[23] However, once the diagnosis of potential malignancy has been made, ultrasound is insensitive for staging or follow-up imaging, and contrast-enhanced CT is indicated at that time. A CT scan can detect a cyst and associated complications, including torsion, as noted earlier in this chapter. CT findings suggestive of malignancy are a cystic solid mass, necrosis in a solid lesion, complex or cystic lesion with thick, irregular walls, and the presence of ascites, peritoneal metastases, and lymphadenopathy.

Magnetic resonance imaging. MRI provides better soft tissue contrast than CT and has been shown in multiple studies to differentiate benign from malignant adnexal masses better than ultrasound. Its use is often limited by availability, cost, and duration of examination. MRI should be considered for pregnant patients or those with equivocal findings on ultrasound or CT.

Management and Disposition

Patients with a simple cyst, no evidence of additional pathology, and improvement in symptoms may be safely discharged with referral for outpatient gynecologic follow-up to ensure resolution. Most uncomplicated simple cysts will resolve without further intervention. Pain should be controlled with nonsteroidal antiinflammatory drugs (NSAIDs) as a first line approach and with oral opioids reserved only for severe cases. Oral contraceptives are not recommended for the routine management of ovarian cysts; despite being theorized to accelerate the regression of ovarian cysts, multiple randomized controlled trials have shown no difference in cyst resolution when compared to expectant management.

A complex cyst concerning for malignancy requires more urgent gynecologic intervention. Such patients may benefit from gynecologic consultation in the ED, particularly if reliable follow-up is unlikely or if the patient is particularly symptomatic.

ABNORMAL UTERINE BLEEDING IN THE NONPREGNANT PATIENT

Foundations

An understanding of the normal menstrual cycle is necessary to understand the potential causes of AUB (Fig. 86.9). The menstrual cycle starts on the first day of menses. During the first part of the menstrual cycle, the endometrium thickens under the influence of estrogen, and a dominant follicle develops in the ovary, releasing an ovum at the midpoint of the cycle. After ovulation, the luteal phase begins and is characterized by the production of progesterone from the corpus luteum. Progesterone matures the lining of the uterus and, if implantation does

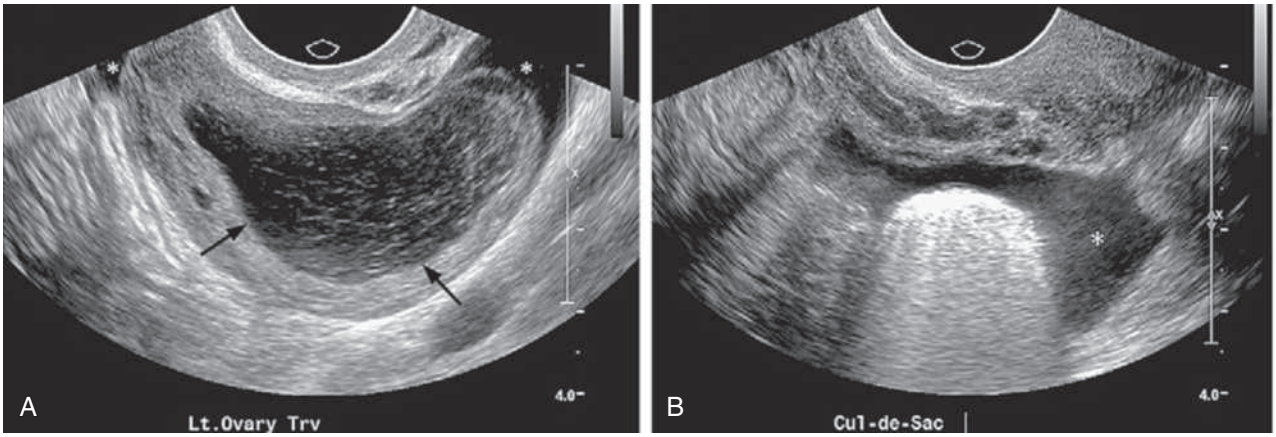

Fig. 86.8 Endovaginal ultrasound image of a hemorrhagic ovarian cyst with free fluid *(*)*. (From Cicchiello LA, Hamper UM, Scoutt LM. Ultrasound evaluation of gynecologic causes of pelvic pain. *Obstet Gynecol Clin North Am.* 2011;38:85–114.)

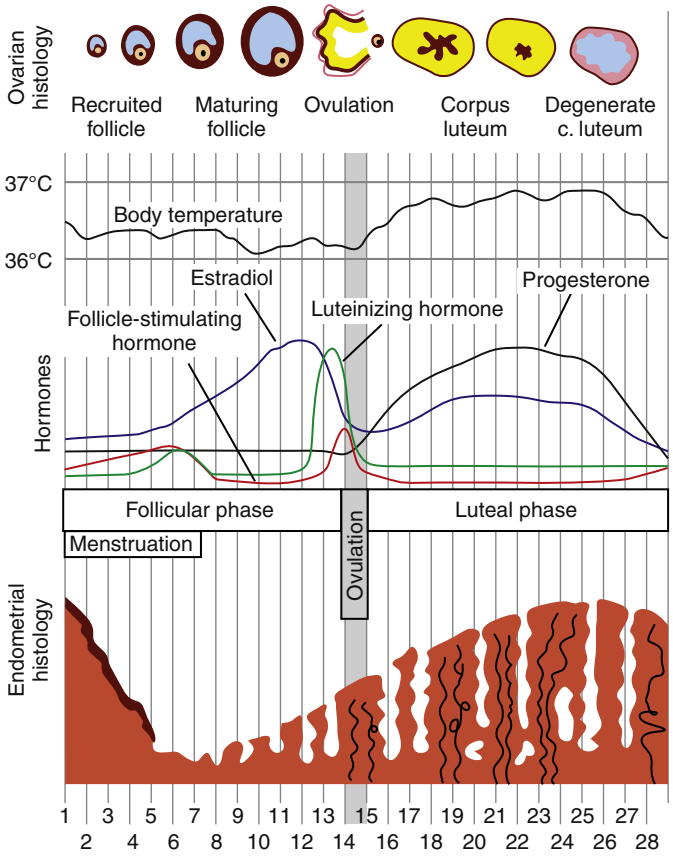

Fig. 86.9 Normal Menstrual Cycle.

not occur, the corpus luteum dies, accompanied by sharp drops in progesterone and estrogen levels. These changes typically are followed by menstruation. Menstrual bleeding is usually predictable, cyclic, and results from withdrawal of the effects of hormones on the endometrium, which occurs approximately 14 days after ovulation.

A revised system of terminology, PALM-COEIN, regarding AUB was created in 2011 by the International Federation of Gynecology and Obstetrics (FIGO) to standardize language and facilitate multiinstitutional investigation (Box 86.2).[24] The first four letters, PALM, represent structural causes for AUB—***p***olyp, ***a***denomyosis, ***l***eiomyoma, and ***m***alignancy or hyperplasia, whereas the latter, COEIN, represent nonstructural causes—***c***oagulopathy, ***o***vulatory dysfunction, ***e***ndometrial, ***i***atrogenic, and ***n***ot yet classified. The term *dysfunctional uterine bleeding* is obsolete and should not be used.

BOX 86.2 PALM-COEIN Classification for Abnormal Uterine Bleeding (AUB)

PALM—Structural Causes

Polyp (AUB-P)
Adenomyosis (AUB-A)
Leiomyoma (AUB-L)
- Submucosal leiomyoma (AUB-LSM)
- Other leiomyoma (AUB-LO)

Malignancy and hyperplasia (AUB-M)

COEIN—Nonstructural Causes

Coagulopathy (AUB-C)
Ovulatory Dysfunction (AUB-O)
Endometrial (AUB-E)
Iatrogenic (AUB-I)
Not yet classified (AUB-N)

Clinical Features

History

Many conditions cause AUB, defined as any change in the frequency, regularity, duration, or volume of bleeding. A systematic history and physical examination tailored to the patient's menstrual development will help narrow these possibilities. Vaginal bleeding in prepubertal patients can be concerning and may be the result of infection, trauma such as sexual abuse or a vaginal foreign body, or a structural lesion. Adolescents who develop heavy bleeding at the time of menarche may be presenting with their first sign of an inherited bleeding disorder. In the postmenopausal woman, any bleeding 12 months after the cessation of menses or unpredictable bleeding during hormone therapy is abnormal. The volume and frequency of bleeding, the duration of symptoms, and the relationship between bleeding and the patient's normal menstrual cycle should be established. A menstrual cycle shorter than 21 days in duration or more than 35 days apart, or flow for

less than 2 or more than 7 days, is classified as abnormal. A pattern of irregular bleeding between cycles or an abrupt change in the previous pattern of bleeding should also be determined.

Systemic conditions, such as liver or thyroid disease, may be associated with AUB. Endometrial cancer is associated with underlying diabetes mellitus, metabolic syndrome and obesity, anovulatory cycles, nulliparity, and age older than 55 years. Cervical dysplasia or other genital tract pathology may cause postcoital or irregular bleeding, and patients should routinely be questioned on risk factors for sexually transmitted infections. Prior history of cesarean section may contribute to iatrogenic AUB; studies have found that irregular scarring postoperatively leads to a higher prevalence of vaginal spotting.

Disruption along the hypothalamus-pituitary-ovarian pathway leading to anovulation is frequently the cause of AUB. Disruption of this pathway may be physiologic, such as during adolescence, perimenopause, or lactation. Pathologic causes include polycystic ovary syndrome (PCOS), hypothalamic dysfunction seen in anorexia nervosa, hyperprolactinemia, and primary pituitary disease.

Patients should be questioned about excessive bleeding or bruising or any family history of bleeding disorders because up to 20% of women presenting with heavy menstrual bleeding will have an underlying coagulopathy. Von Willebrand disease is the most common of these, seen in up to 13% of cases of AUB, and often first presents with heavy uterine bleeding since menarche.

Physical Examination

In the setting of acute, heavy bleeding, the initial physical examination should focus on signs of hypovolemia and anemia. PCOS is a common cause of AUB and suggested by the presence of obesity, acne, hirsutism, and acanthosis nigricans. The examination should include inspection of the thyroid, particularly for nodules, as well as a comprehensive skin examination for petechiae and ecchymosis. Other causes of bleeding include vaginal or cervical lesions, which may be visible on the vaginal speculum examination. A leiomyoma or fibroid uterus may be palpable on the bimanual examination.[25]

Differential Diagnoses

The differential diagnosis of AUB in the nonpregnant patient is extensive but may be narrowed by patient age. In adolescents, consider undiagnosed coagulopathy, pelvic infection, or hypothalamic-pituitary-ovarian axis dysregulation due to physiologic immaturity or PCOS. Young adults often have structural lesions such as polyps or leiomyomas, endometrial hyperplasia, or anovulation secondary to PCOS or the other conditions listed earlier. In patients older than 40 years but not yet postmenopausal, anovulatory bleeding due to perimenopause becomes more likely, as does endometrial carcinoma or hyperplasia and leiomyoma. Postmenopausal patients require an outpatient evaluation for malignancy.

Diagnostic Strategies

Laboratory Tests

A urine or serum pregnancy test is essential in evaluating a woman of reproductive age with vaginal bleeding. In a patient with excessive bleeding, hemodynamic instability, or clinical evidence of anemia (e.g., excessive fatigue, pale conjunctiva), a hemoglobin or hematocrit is indicated. If coagulopathy is suspected, platelet count, prothrombin and partial thromboplastin time should be measured. In the emergency setting, testing for von Willebrand disease and other specific coagulopathies can usually be deferred to outpatient follow-up. Sexually transmitted infections should be tested for in patients with risk factors or clinical signs of infection, particularly *Chlamydia trachomatis*. The presence of chlamydial antigens has been linked to AUB, likely due to endometrial inflammation. Thyroid dysfunction, particularly hypothyroidism, is associated with AUB, and therefore screening to determine the thyroid-stimulating hormone serum level is recommended.

Imaging Tests

The decision to perform ultrasound imaging to evaluate AUB in the ED depends on the urgency to determine the cause of bleeding and the reliability of outpatient follow-up. Transvaginal ultrasonography (TVUS) may reveal a fibroid uterus, endometrial thickening, or a focal mass (Fig. 86.10). In postmenopausal patients with AUB, an endometrium measuring less than 4 to 5 mm of thickness on TVUS reliably excludes endometrial cancer. A thickened endometrium may indicate an underlying lesion or excess estrogen. For most nonpregnant patients with AUB, ultrasound findings do not immediately affect ED decision making. In patients who have reliable access to outpatient gynecologic services, imaging may be deferred until follow-up evaluation.

Management

The likely causative disorder coupled with the volume of bleeding and overall stability of the patient will guide ED management. Patients with uncontrolled bleeding and hemodynamic instability on presentation should receive standard resuscitation IV fluids and blood products, and surgical options should be considered, including urgent dilation and curettage, uterine artery embolization, endometrial ablation, or hysterectomy. Alternatively, conjugated equine estrogen may be administered at a dose of 25 mg given IV every 4 to 6 hours for 24 hours or until the bleeding stops. In emergent situations, intrauterine tamponade with a 26-French foley catheter instilled with 30 mL of saline can also be attempted.

In less emergent situations, oral medications can be considered for the treatment of AUB. Disruption of the hypothalamic-pituitary-ovarian axis from a variety of causes can result in bleeding related to ovulatory dysfunction (AUB-O). Restoring the balance of estrogen and progesterone with oral contraceptives will help many patients regulate the cycle, with reduction in or cessation of AUB. Combination oral contraceptive pills can help regulate the cycle and counteract the long-term effects of unopposed estrogen on the endometrium. We recommend a combination oral contraceptive with 35 μg of ethinyl estradiol or 20 mg or medroxyprogesterone three times daily for 1 week. Contraindications must be reviewed with the patient prior to prescribing

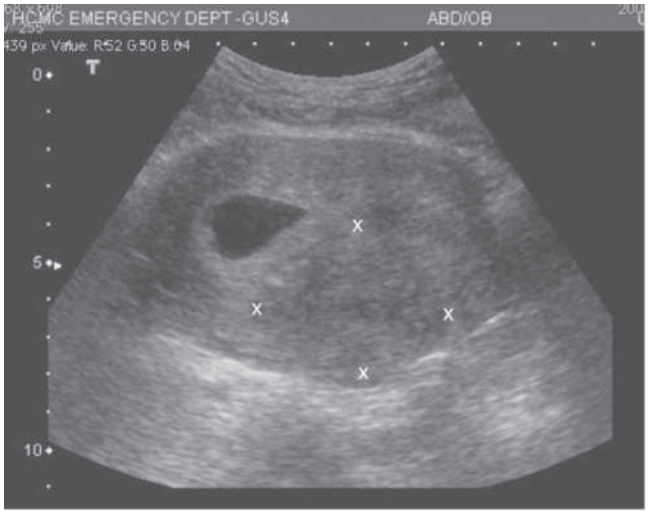

Fig. 86.10 Longitudinal view of the uterus with thickened endometrium. (Courtesy Dr. Robert Reardon, Hennepin County Medical Center, Minneapolis; with permission.)

these medications, specifically to determine a history of thromboembolic events, cigarette smoking, breast cancer, or liver disease. However, patients with contraindications to estrogen-progesterone combination treatment can also consider progestin-only treatment, given as 5 mg norethindrone orally three times daily for 1 week.[23] The levonorgestrel intrauterine device (IUD) is also a nonemergent option to treat AUB in patients who are interested in long-term contraception.[26]

Nonhormonal medications also have been shown to be effective in AUB. Tranexamic acid, an antifibrinolytic agent, may also be used for either emergent or outpatient management of bleeding. It can be administered IV at 10 mg/kg with a maximum dose of 600 mg, or orally at a dose of 1.3 g every 8 hours for 5 days. NSAIDs are generally safe and well tolerated and are effective for relief of associated cramping pelvic pain. They have also been shown to be more effective than placebo to reduce heavy menstrual bleeding, although less effective than either tranexamic acid or a hormonal IUD, with limited data to compare efficacy to oral contraceptives.[27,28] In patients with suspected bleeding disorders, specifically those with platelet dysfunction, NSAIDs should be used with caution.

Disposition

Most patients with pelvic pain from ovarian cysts or AUB without hemodynamic compromise may be managed with specific therapies to minimize symptoms and should be referred to a gynecologist for definitive management on an outpatient basis. Patients with severe, acute AUB and hemodynamic instability require urgent gynecologic consultation and hospitalization.

EMERGENCY CONTRACEPTION

Emergency contraception, more commonly known as the "morning after pill," consists of medical therapy to prevent pregnancy immediately following unprotected or inadequately protected sexual intercourse. At present, there are three oral formulations available: ulipristal acetate (a progesterone receptor modulator), levonorgestrel (a progestin), and combined oral contraceptives consisting of progestin and estrogen taken together and often referred to as the Yuzpe regimen. In addition to oral options, the copper IUD is extremely effective as emergency contraception and works through inhibition of sperm function, inhibition of fertilized egg transport, and likely inhibition of implantation.[29]

The most commonly used regimen, and the only formulation available without a prescription in the United States, consists of a single dose of 1.5 mg or two doses of 0.75 mg levonorgestrel spaced 12 hours apart. The one-time dose of 1.5 mg is simpler to use and is at least as effective as the two-dose regimen and is therefore recommended.[30] It is labeled for use for up to 72 hours following intercourse. Studies have indicated an association between higher patient body mass index (BMI) and decreased effectiveness of levonorgestrel, suggesting that perhaps an increased dose may be indicated in obese individuals. However, further study is necessary before this can be definitively recommended.[31]

Another regimen, a single tablet of 30 mg of ulipristal acetate, is available only with a prescription but has demonstrated effectiveness for up to 120 hours from intercourse, making it a preferred choice over levonorgestrel beyond the 72-hour window. Both forms of contraception—levonorgestrel and ulipristal—are maximally effective when used within 24 hours. Combined oral contraceptives, consisting of 100 μg of ethinyl estradiol and 0.5 to 1.0 mg of levonorgestrel, have largely fallen out of favor due to the simplicity and success of levonorgestrel alone.

Adverse effects of oral emergency contraception include nausea and headache, with the combined oral contraceptive regimen producing significantly higher rates of nausea than levonorgestrel or ulipristal alone. Irregular menstrual bleeding, which can occur within 1 week to 1 month after treatment, resolves without intervention.

The copper IUD is highly effective when placed within 5 days of intercourse and appears to be effective for as long as 10 days. It carries a 1/1000 risk of uterine perforation and is associated with uterine cramping but also provides ongoing contraceptive benefit. The major barrier to utilization for emergency contraception is the requirement to make a clinic appointment or visit with a qualified provider within the timeframe outlined earlier.[32]

Both levonorgestrel and ulipristal act to delay or inhibit ovulation, whereas the copper IUD prevents fertilization. As such, a common misconception is that emergency contraception is equivalent to medical abortion. None of the methods discussed involve the termination of a preexisting pregnancy, and emergency contraception has not been shown to have adverse effects on a developing fetus when taken during an established pregnancy. It is still possible for a patient who uses emergency contraception to get pregnant in the same menstrual cycle, so patients should be advised to use an alternative form of contraception and to undergo a pregnancy test if menstruation is delayed for more than 3 weeks. Patients who receive emergency contraception should be counseled regarding birth control and have a follow-up pregnancy test should they miss their next period.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 86: QUESTIONS AND ANSWERS

1. Which of the following statements regarding ovarian torsion is true?

a. Abdominal tenderness is predictable
b. Complete arterial obstruction is common
c. Computed tomography (CT) has a higher sensitivity than ultrasound
d. Most cases are associated with an ovarian mass
e. There is a left-sided predominance

Answer: d. Most cases are associated with a benign ovarian tumor or cyst. There is a modest right-sided predominance. Due to the collateral uterine and ovarian arterial supply, complete arterial obstruction is rare. In cases of intermittent or chronic torsion particularly, abdominal tenderness may be absent. CT has a lower sensitivity than ultrasound, which is still only approximately 71%. Interpret negative studies carefully.

2. Which of the following patterns of menses should be considered abnormal?

a. A 23-day menstrual cycle
b. A 40-day menstrual cycle
c. Bleeding 6 months after menopause
d. Seven days of menstrual flow
e. Three days of menstrual flow

Answer: b. A menstrual cycle shorter than 21 days or more than 35 days apart, or flow that is less than 2 days or more than 7 days, is considered abnormal. In the postmenopausal woman, any bleeding 12 months after cessation of menses is considered abnormal.

continued

CHAPTER 86: QUESTIONS AND ANSWERS—cont'd.

3. A 33-year-old gravida 3 para 3 woman presents with 7 days of heavy, painless vaginal bleeding. Her only other complaint is dizziness. Urine pregnancy test is negative. Vital signs are blood pressure, 85/40 mm Hg, and heart rate, 130 beats/min. The pelvic examination reveals copious vaginal bleeding through a partially open cervical os. The hemoglobin level is 6.8 g/dL. Which of the following interventions is most appropriate?

a. 20 μg of ethinyl estradiol daily until the bleeding subsides
b. 35 μg ethinyl estradiol bid until the bleeding subsides
c. Blood transfusion and urgent gynecologic consultation for dilation and curettage
d. Premarin, 25 mg intravenously every 6 hours
e. Saline hydration followed by a 2-day recheck

Answer: c. This patient is symptomatic, hypovolemic, anemic, and exhibiting ongoing bleeding. Oral estrogens are indicated in cases of modest bleeding. Parenteral estrogen may be used as an adjunct to other therapies for patients requiring admission. The degree of anemia in the face of ongoing bleeding in this case warrants gynecologic intervention.

4. To be most effective, the emergency contraceptive ulipristal should be given as soon as possible but is approved to be given within how many hours of intercourse?

a. 12
b. 24
c. 48
d. 72
e. 120

Answer: e. The efficacy of all emergency contraceptive pills in preventing pregnancy is greatest when a contraceptive is taken soon after intercourse. Ulipristal is labeled for 120 hours post coitus. Because it is not as effective as preplanned contraception, women should still be aware of the possibility of pregnancy after its use.

87

Stroke

Linda Papa and William J. Meurer

KEY CONCEPTS

- Anterior circulation strokes result in contralateral hemiparesis of the face and body.
- Vertebrobasilar strokes result in ipsilateral cranial nerve (CN) deficits and contralateral hemiparesis.
- Posterior cerebral artery stroke causes ipsilateral CN III palsy and contralateral homonymous hemianopsia.
- *Wallenberg syndrome* (lateral medullary syndrome) causes vertigo, Horner syndrome, ipsilateral facial numbness, loss of corneal reflex, along with contralateral loss of pain and temperature.
- Cervical artery dissection is a common cause of stroke in young patients; trans ischemic attacks (TIAs) preceding stroke in these patients are often misdiagnosed.
- The goal for eligible patients is to receive thrombolytics within 90 min of symptoms onset; the dose of the tissue plasminogen activator Alteplase (t-PA) is 0.9 mg/kg with 10% given as a bolus and the remaining 90% given over 1 h.
- Overly aggressive blood pressure (BP) management should be avoided in patients with acute ischemic stroke. If thrombolytic therapy is indicated, stringent control of BP is indicated to reduce the potential for intracranial hemorrhage.
- Accurate identification noting the last time a patient was known to be at his or her neurologic baseline should be documented in all patients with stroke.
- Acute ischemic stroke patients receiving Alteplase are at risk of developing a spontaneous intracranial hemorrhage; the risk is lowest in patients with a low National Institutes of Health Stroke Scale (NIHSS) score, no hypertension, no diabetes, and age younger than 70 years.
- In acute ischemic stroke, the patient and/or their families should be informed of the risk and benefit of treatment with thrombolytic therapy.
- The incidence of symptomatic intracerebral hemorrhage after intravenous (IV) thrombolysis is 2%–7%. The incidence of asymptomatic intracranial hemorrhage is higher with 30%–45% of patients experiencing >10 cerebral microbleeds.
- Beyond 4.5 h, the benefit of IV thrombolysis is not clear and should be determined after consulting with the neurologist or stroke specialist.
- In patients with mild nondisabling stroke symptoms, IV thrombolysis is not recommended. However, for otherwise eligible patients with mild but disabling stroke symptoms, IV thrombolysis is recommended for patients within 4.5 h of ischemic stroke symptom onset.
- Patients with a hemorrhagic stroke on coumadin should *be reversed* using vitamin K and prothrombin complex concentrate (PCC). Fresh frozen plasma (FFP) can be used if PCC is not available. However, PCC is preferred over FFP due to more rapid correction of international normalized ratio (INR), lower risk of infection, and lower administered volume.
- Prognosis is worse in acute stroke in the setting of fever, hypotension, hypoxia, and hypo/hyperglycemia. Measures should be taken to rapidly correct these.
- Carotid Doppler, magnetic resonance angiography (MRA), or computed tomography angiography (CTA) studies are recommended before discharge of a patient with TIA from the emergency department (ED).
- TIA has moved from time-based to tissue-based definition (defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction).
- MRI with diffusion-weighted imaging (DWI) has a greater sensitivity than computed tomography (CT) for detecting small infarcts in patients with TIA.
- Patients with TIA or nondisabling strokes are at increased risk of recurrent stroke and should be evaluated and treated immediately in order to reduce the risk of subsequent stroke.
- CTA with CT pulmonary angiogram (CTPA) or MRA with DW-MRI is useful for selecting candidates for mechanical thrombectomy between 6 and 24 h after patient was last known to be well.
- Mechanical thrombectomy can be used in addition to treatment with intravenous thrombolytics. However, pretreatment with intravenous thrombolytics (within 4.5 h of symptom onset) is not required prior to thrombectomy.

FOUNDATIONS

Background and Importance

Stroke is the fifth leading cause of death in the United States and a leading cause of long-term disability. It affects nearly 800,000 people per year. On average, someone has a stroke every 40 seconds, and someone dies of a stroke every 4 minutes.[1] Stroke patients have an in-hospital mortality rate of 5% to 10% for ischemic stroke and 40% to 60% for intracerebral hemorrhage (ICH).[2] Only 10% of stroke survivors will recover completely, 25% will recover with minor impairments, and 40% will have moderate to severe impairments, making stroke a leading cause of adult disability.

Stroke is any vascular injury that reduces cerebral blood flow (CBF) to a specific region of the brain, retina, or spinal cord, causing

neurologic impairment. The onset of symptoms may be sudden or stuttering, often with transient or permanent loss of neurologic function. Approximately 87% of all strokes are ischemic in origin, caused by the occlusion of a cerebral vessel, and 13% are hemorrhagic strokes caused by the rupture of a blood vessel into the parenchyma of the brain (ICH) or into the subarachnoid space (subarachnoid hemorrhage [SAH]). Only ischemic stroke involving the brain and ICH are discussed in this chapter. SAH is discussed in Chapters 16 and 33.

Current acute interventional treatment regimens are designed to reverse or minimize brain damage. Strategies include blood pressure (BP) management, anticoagulation, thrombolytic therapy, catheter-based interventions, and surgery.[3]

Ischemic Stroke

About 600,000 "first-ever" ischemic strokes occur each year in the United States. These may result from either in situ thrombosis or embolic obstruction from a more proximal source, usually the heart. In more than one-third of these first-ever strokes, no clear cause is identified. Strokes of all subtypes are more common in Blacks and Hispanics versus non-Hispanic whites.[1]

Approximately one-third of all ischemic strokes are thrombotic in nature, caused by either large- or small-vessel occlusions. Common areas for large-vessel occlusions are cerebral vessel branch points, especially in the distribution of the internal carotid artery (ICA). Thrombosis usually results from clot formation in the area of an ulcerated atherosclerotic plaque that forms in the area of turbulent blood flow, such as a vessel bifurcation. A marked reduction in flow results when the stenosis occludes more than 90% of the blood vessel diameter. With further ulceration and thrombosis, platelets adhere to the region. A clot then either embolizes or occludes the artery.

Lacunae, or small-vessel strokes, involve small terminal sections of the vasculature and more commonly occur in patients with diabetes and hypertension. About 80% to 90% of patients experiencing lacunar strokes have hypertension. The subcortical areas of the cerebrum and brainstem often are involved. Infarcts here range in size from a few millimeters to 2 cm and are seen most commonly in the basal ganglia, thalamus, pons, and internal capsule. They may be caused by small emboli or by a process termed *lipohyalinosis,* which occurs in patients with hypertensive cerebral vasculopathy.

One-fourth of all ischemic strokes are cardioembolic in nature. Embolization of a mural thrombus in patients with atrial fibrillation is the most common mechanism, and patients with atrial fibrillation have an approximate fivefold increased risk for development of a stroke. Noncardiac sources of emboli most commonly include diseased portions of extracranial arteries, resulting in an artery-to-artery embolus. One common example is amaurosis fugax, in which emboli from a proximal carotid artery plaque embolizes to the ophthalmic artery, causing transient monocular blindness. Aortic atheromas represent another non-cardiac source of emboli.

Although stroke risk increases with age, approximately 3% to 4% of all strokes occur in patients 15 to 45 years old, and there have been trends observed showing the average age of first stroke is becoming younger.[1,4] Atherosclerosis is the most common cause in elders while causative disorders and conditions in younger patients often are uncommon and may be reversible. Pregnancy, the use of oral contraceptives, antiphospholipid antibodies (such as lupus anticoagulant and anticardiolipin antibodies), protein S and C deficiencies, sickle cell anemia, and polycythemia all predispose patients to sludging or thrombosis, thereby increasing the risk of stroke. Fibromuscular dysplasia of the cerebral vasculature also may lead to stroke, and in rare instances prolonged vasoconstriction from a migraine syndrome causes stroke. Recreational drugs such as cocaine and amphetamines are potent vasoconstrictors that have been associated with both ischemic and hemorrhagic stroke. Infectious processes, particularly varicella and recently fungal meningitis, can induce vasculopathies that lead to stroke as well or can induce longer-term inflammatory processes that ultimately cause a clinical stroke.

Carotid and vertebral dissections often are associated with trauma but may follow mild events such as sneezing. Dissections are the leading determined cause of stroke in the young and are slightly less common than idiopathic strokes. Carotid and vertebral dissections also are seen more frequently in people with underlying pathology of the vessel wall, such as in fibromuscular dysplasia and connective tissue disorders. Alteration in the vessel intima can lead to vessel stenosis, occlusion, or embolism. The patient may report a minor preceding event, such as spinal manipulation, strenuous exercise, yoga, coughing, or vomiting. Presenting manifestations may include headache, facial pain, visual changes, cranial nerve (CN) palsies, pain over the affected vessel, Horner syndrome, amaurosis fugax, SAH, or an ischemic stroke. The headache frequently is unilateral and may occur days before onset of the other neurologic symptoms. Dissections are typically diagnosed by noninvasive modalities, such as ultrasonography, magnetic resonance angiography (MRA), and computed tomography angiography (CTA).

Transient Ischemic Attack

A transient ischemic attack (TIA) was previously defined as a neurologic deficit that completely resolves within 24 hours; however, a portion of TIA cases have evidence of permanent brain ischemia on neuroimaging. Therefore, the American Heart Association (AHA) has adopted a tissue-based definition: "A transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction."

About 240,000 TIAs per year occur in the United States, with an incidence rate of 8 per 1000 person years. TIAs constitute an important warning sign for the future development of cerebral infarction. Approximately 10% of the patients who experience a TIA will sustain a stroke within 3 months of the sentinel event, and one-half of these occur within the first 2 days. High-grade carotid stenosis in the neck and cardioemboli are two key causes that contribute to early stroke following TIA. In addition, recurrence data is primarily derived from an era where MRI was much less commonly used; patients with DWI negative TIAs generally have a much lower risk of recurrence.[5,6]

Hemorrhagic Stroke

Spontaneous ICH causes 10% to 15% of all acute strokes, affecting approximately 65,000 patients per year. It carries a 30-day mortality rate of up to 50% with one-half of patients dying in the first 2 days. Among survivors, only one in five are living independently at 6 months.

The two major underlying causes of ICH are hypertensive vasculopathy (caused by long-standing hypertension) and cerebral amyloid~angiopathy (usually found in elder patients, which is the result of amyloid deposition in cerebral vessel walls). Hypertensive hemorrhage results from degenerative changes in the small penetrating arteries and arterioles, leading to lipohyalinosis of small, deep penetrating arteries. Such hemorrhages generally occur in the deep regions, including basal ganglia and thalamus. The most common sites for hypertensive hemorrhage are summarized in Box 87.1. ICH caused by amyloid angiopathy tends to be lobar in nature and to occur more commonly in older adults.

Other factors leading to ICH include underlying vascular malformations (i.e., arteriovenous malformations [AVMs] and aneurysms, drug intoxication [particularly sympathomimetics, such as cocaine], malignant hypertension, saccular aneurysms, blood dyscrasias, venous sinus thrombosis, hemorrhagic transformation of an ischemic stroke,

BOX 87.1 Most Common Sites for Hypertensive Intracranial Hemorrhage

Affected Area (Frequency)
Putamen (44%)
Thalamus (13%)
Cerebellum (9%)
Pons (9%)
Other cortical areas (25%)

Common Clinical Presentation
Contralateral motor/sensory loss
Limb pain, speech difficulty
Uncoordinated movements of trunk and limbs
Numbness, weakness, ataxia, dizziness
Numbness, weakness, language disturbances

moyamoya disease, and tumors). High-risk features for such secondary forms of ICH include lobar location, presence of intraventricular blood, and younger age.

Anatomy, Physiology, and Pathophysiology

The cerebral vasculature supplies the brain with a rich flow of blood that contains the critical supply of oxygen and glucose necessary for normal brain function. When a stroke occurs, there are immediate alterations in CBF and extensive changes in cellular homeostasis. The normal CBF is approximately 40 to 60 mL/100 g of brain per minute. When CBF drops below 15 to 18 mL/100 g of brain per minute, several physiologic changes occur. The brain loses electrical activity, becoming electrically "silent," although neuronal membrane integrity and function remain intact. Clinically, the areas of the brain maintaining electrical silence manifest a neurologic deficit, even though the brain cells are viable. When CBF is below 10 mL/100 g of brain per minute, membrane failure occurs, with a subsequent increase in the extracellular potassium and intracellular calcium and eventual cell death.

The ischemic penumbra is the area of the brain surrounding the primary injury, which is preserved by a tenuous supply of blood from collateral vessels. This border zone of neuronal tissue is the area of greatest interest to investigators for possible salvage in both ischemic and hemorrhagic stroke. In ischemic stroke, the duration of occlusion plays a critical role in neuronal survival.

In ICH, acute vessel rupture is most often caused by underlying small vessel disease and causes injury by several mechanisms. First, there is mass effect from the hematoma itself, followed by activation of the coagulation cascade, release of inflammatory cytokines, and blood-brain barrier (BBB) disruption. This leads to perihematomal edema formation and secondary brain injury. Finally, continued bleeding, or hematoma expansion, occurs in many patients—either continued bleeding from the primary source, or secondary bleeding at the periphery of the hemorrhage.

Blood is supplied to the brain by the anterior and posterior circulations. The anterior circulation originates from the carotid system and perfuses 80% of the brain, including the optic nerve, retina, and frontoparietal and anterior-temporal lobes. The first branch off the ICA is the ophthalmic artery, which supplies the optic nerve and retina. As a result, the sudden onset of painless monocular blindness *(amaurosis fugax)* identifies the stroke as involving the anterior circulation (specifically the ipsilateral carotid artery) at or below the level of the ophthalmic artery. The ICAs terminate by branching into the anterior and middle cerebral arteries (MCAs) at the circle of Willis.

The anterior cerebral artery supplies the basal and medial aspects of the cerebral hemispheres and extends to the anterior two-thirds of the parietal lobe. The MCA feeds the lenticulostriate branches that supply the putamen, part of the anterior limb of the internal capsule, the lentiform nucleus, and the external capsule. Main cortical branches of the MCA supply the lateral surfaces of the cerebral cortex from the anterior portion of the frontal lobe to the posterolateral occipital lobe.

Although the posterior circulation is smaller and usually supplies only 20% of the brain, it supplies the brainstem (which is critical for normal consciousness, movement, and sensation), cerebellum, thalamus, auditory and vestibular centers of the ear, medial temporal lobe, and visual occipital cortex. The posterior circulation is derived from the two vertebral arteries that ascend through the transverse processes of the cervical vertebrae. The vertebral arteries enter the cranium through the foramen magnum and supply the cerebellum by the posterior inferior cerebellar arteries. They join to form the basilar artery, which branches to form the posterior cerebral arteries. Some variants exist, importantly, the fetal origin posterior cerebral artery, which is where the posterior cerebral artery is actually fed by the anterior circulation.

The extent of injury in either an anterior or a posterior stroke depends on both the vessel involved and the presence of collateral blood flow distal to the vessel occlusion. A patient with adequate collateral blood flow from the contralateral hemisphere may have minimal clinical deficits despite a complete carotid occlusion. By contrast, a patient with poor collateral flow may have hemiplegia with the same lesion.

CLINICAL FEATURES

Ischemic Stroke

The signs and symptoms of an ischemic stroke may appear suddenly and without warning or may have a stuttering, insidious onset. Disruption of the flow to one of the major vascular limbs of the cerebral circulation will result in physiologic disruption to the anatomic area of the brain supplied by that blood vessel. Ischemic strokes involve either the anterior or posterior circulation strokes and the neurologic deficits are highly dependent on amount of collateral blood flow. In addition to the vascular supply involved, ischemic strokes can be further described by the temporal presentation of their neurologic deficits.

A "stroke in evolution" is one in which focal neurologic deficits worsen over the course of minutes or hours. Approximately 20% of anterior circulation strokes and 40% of posterior circulation strokes will show evidence of progression. Since a single low score on the National Institutes of Health Stroke Scale (NIHSS) may not be sufficient to determine t-PA eligibility, repeating the NIHSS and reassessing these patients is recommended. Anterior circulation strokes may progress within the first 24 hours, whereas posterior strokes may progress for up to 3 days. Propagation of thrombus is postulated as a likely mechanism for progression. With anterior circulation strokes (involving primarily the carotid, anterior, and MCAs), the clinical presentation rarely includes complete loss of consciousness unless the lesion occurs in the previously unaffected hemisphere of a patient who has experienced a previous contralateral stroke.

Occlusions in the anterior cerebral artery mainly affect frontal lobe function. The patient has altered mentation coupled with impaired judgment and insight, as well as the presence of primitive grasp and suck reflexes on physical examination. Bowel and bladder incontinence may be features of anterior cerebral artery stroke. Paralysis and hypesthesia of the lower limb opposite the side of the lesion are characteristic. Leg weakness is more pronounced than arm weakness in anterior cerebral distribution stroke. Apraxia or clumsiness in the patient's gait is often observed.

Marked motor and sensory disturbances are the hallmarks of occlusion of the MCA. They occur on the side of the body contralateral to the side of the lesion and usually are more pronounced in the arm and face than the leg. Such disturbances may involve only part of an extremity or the face but almost always are accompanied by numbness in the same region as that of the motor loss. Hemianopsia, or blindness in one-half of the visual field, occurs contralateral to the lesion. Agnosia, or the inability to recognize previously known subjects, is common, and aphasia may be present if the lesion occurs in the dominant hemisphere. Patients often have a gaze preference toward the affected hemisphere because of disruption of the cortical lateral gaze centers.

Aphasia, a disorder of language in which the patient articulates clearly but uses language inappropriately or comprehends it poorly, also is common in dominant-hemisphere stroke. Aphasia may be expressive, receptive, or a combination of both. *Wernicke aphasia* occurs when the patient is unable to process sensory input, such as speech, and thus fails to understand verbal communication (receptive aphasia). *Broca aphasia* refers to the inability to communicate verbally in an effective way, even though understanding may be intact (expressive aphasia). Aphasia should be distinguished from dysarthria, which is a motor deficit of the mouth and speech muscles; the dysarthric patient articulates poorly but understands words and word choices. Aphasia is important to recognize because it usually localizes a lesion to the dominant cerebral cortex (typically the left side) in the MCA distribution. *Aphasia* and *dysphasia* are terms that are used interchangeably but must be distinguished from *dysphagia,* which is difficulty in swallowing.

Chemoreceptor Trigger Zone for Emesis

Pathology in the vertebrobasilar system (i.e., posterior circulation strokes) can cause the widest variety of symptoms and as a result may be the most challenging to diagnose. The symptoms reflect CN deficits, cerebellar involvement, and involvement of neurosensory tracts. The brainstem also contains the reticular activating system, which is responsible for mediating consciousness, and the chemoreceptor trigger zone (CTZ) for emesis (commonly referred to as the "vomiting center"). Unlike those with anterior circulation strokes, patients with posterior circulation stroke can have loss of consciousness and frequently have nausea and vomiting. The posterior cerebral artery supplies portions of the parietal and occipital lobes, so vision and thought processing are impaired. Visual agnosia, the inability to recognize seen objects, is a common feature, as is alexia, the inability to understand the written word. A third CN palsy may occur, and the patient may experience homonymous hemianopsia. One of the more unique facets of this syndrome is that the patient may be unaware of any visual problem (visual neglect). Vertigo, syncope, diplopia, visual field defects, weakness, paralysis, dysarthria, dysphagia, spasticity, ataxia, or nystagmus may be associated with vertebrobasilar artery insufficiency. Posterior circulation strokes also demonstrate crossed deficits, such as motor deficits on one side of the body and sensory loss on the other. In anterior circulation strokes, by contrast, abnormalities are limited to one side of the body.

A focused neurologic examination should assess level of consciousness, speech, CN function, motor and sensory function, and cerebellar function. Level of consciousness and fluency of speech can be rapidly assessed in a dialogue with the patient to determine the presence of dysarthria or aphasia. The head should be evaluated for signs of trauma. Pupillary size and reactivity and extraocular movements provide important information about brainstem function, particularly CN III through CN VI; an abnormal third nerve function may be the first sign of tentorial herniation. Gaze preference suggests brainstem or cortical involvement. Central facial nerve weakness from a stroke should be distinguished from the peripheral causes of CN VII weakness. With a peripheral lesion, the patient is unable to wrinkle the forehead. Assessment of facial sensation, eyebrow elevation and squinting, smiling symmetry, gross auditory acuity, gag reflex, shoulder elevation, sternocleidomastoid strength, and tongue protrusion complete the CN evaluation.

Motor and sensory testing is performed next. Muscle tone can be assessed by moving a relaxed limb. Proximal and distal muscle group strength is assessed against resistance. Pronator drift of the arm is a sensitive sign of motor weakness and can be tested simultaneously by having the patient sit with eyes closed and arms outstretched, with palms toward the ceiling for 10 seconds. Asymmetrical sensation to pain and light touch may be subtle and difficult to detect. Double simultaneous extinction evaluation tests for sensory neglect and can be performed by simultaneously touching the right and left limbs. The patient may feel both the right and left sides being touched individually but may not discern touch on one side when both are touched simultaneously. Similarly, the ability to discern a number gently scratched on a forearm, termed graphesthesia, is another readily performed test of cortical parietal lobe. These tests can help differentiate a pure motor deficit of a lacunar stroke from a sensorimotor MCA deficit.

Cerebellar testing and the assessment of reflexes and gait complete the neurological examination. Finger-to-nose and heel-to-shin evaluations are important tests of cerebellar functions. Asymmetry of the deep tendon reflexes or unilateral Babinski sign may be an early finding of corticospinal tract dysfunction. Gait testing is commonly omitted yet is a critical part of the neurologic examination when it can be safely performed. Observing routine ambulation and heel-to-toe walking can assess for subtle ataxia, weakness, or focal cerebellar lesions.

Several prehospital stroke scales have been created to assist emergency medical service (EMS) personnel with the rapid assessment of potential stroke patients. Many of these prehospital stroke scales have been prospectively validated for their accuracy in stroke detection. Two of the more commonly used scales include the Cincinnati Prehospital Stroke Scale (Fig. 87.1) and the Los Angeles Prehospital Stroke Screen (Fig. 87.2). Scales that can reliably identify patients with large vessel occlusion (LVO) who may benefit from preferential triage to a thrombectomy capable stroke center are being evaluated.[7] The Los Angeles Motor Score (LAMS) performed by paramedics in the field has potential for identifying individuals with LVOs.[8]

Cincinnati Prehospital Stroke Scale	
Facial Droop	
Normal:	Both sides of face move equally
Abnormal:	One side of face does not move at all
Arm Drift	
Normal:	Both arms move equally or not at all
Abnormal:	One arm drifts compared to the other
Speech	
Normal:	Patient uses correct words with no slurring
Abnormal:	Slurred or inappropriate words or mute

Fig. 87.1 Cincinnati Prehospital Stroke Scale. (Adapted from Kothari RU, Pancioli A, Liu T, et al. Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med.* 1999;33[4]:373–378.)

The NIHSS is a useful and rapid tool for quantifying neurologic deficit in patients with stroke and can be used in determining treatment options (Table 87.1). NIHSS scores have been shown to be reproducible, valid, and correlate well with the amount of infarcted tissue on computed tomography (CT) scan. The baseline NIHSS score can identify patients who are appropriate candidates for fibrinolytic therapy, as well as those at increased risk for hemorrhage. It is, however, possible for patients to have disabling strokes with an NIHSS of zero (severe truncal ataxia). In addition, it has been used as a prognostic tool to predict outcome and is currently being used by certain stroke centers to stratify patients for entry into treatment trials.

Hemorrhagic Stroke

The classic presentation of ICH is the sudden onset of headache, vomiting, severely elevated BP, and focal neurologic deficits that progress

Los Angeles Prehospital Stroke Scale (LAPSS)

Patient name: _____

Rater name: _____

Date: _____

Screening criteria	Yes	No
4. Age over 45 years	____	____
5. No prior history of seizure disorder	____	____
6. New onset of neurologic symptoms in last 24 hours	____	____
7. Patient was ambulatory at baseline (prior to event)	____	____
8. Blood glucose between 60 and 400	____	____

9. Exam: ***Look for obvious asymmetry***

	Normal	Right	Left
Facial smile / grimace:	☐	☐ Droop	☐ Droop
Grip:	☐	☐ Weak grip ☐ No grip	☐ Weak grip ☐ No grip
Arm weakness:	☐	☐ Drifts down ☐ Falls rapidly	☐ Drifts down ☐ Falls rapidly

Based on exam, patient has only unilateral (and not bilateral) weakness: Yes ☐ No ☐

10. If yes (or unknown) to all items above LAPSS screening criteria met: Yes ☐ No ☐

11. If LAPSS criteria for stroke met, call receiving hospital with "CODE STROKE," if not then return to the appropriate treatment protocol. (Note: The patient may still be experiencing a stroke if even if LAPSS criteria are not met.)

Provided by the internet stroke center — www.strokecenter.org

Fig. 87.2 Los Angeles Prehospital Stroke Screen. (Adapted from Kidwell CS, Starkman S, Eckstein M, et al. Identifying stroke in the field: prospective validation of the Los Angeles Prehospital Stroke Screen [LAPSS]. *Stroke*. 2000;31:71–76.)

TABLE 87.1 National Institutes of Health Stroke Scale Scoring Form

Item	Scoring Definitions	Score
1a. Level of consciousness (LOC)	0 = Alert and responsive 1 = Arousable to minor stimulation 2 = Arousable only to painful stimulation 3 = Reflex responses or unarousable	
1b. LOC-related questions: Ask patient's age and month. Must be exact.	0 = Both correct 1 = One correct (or dysarthria, intubated, foreign language) 2 = Neither correct	
1c. Commands: Open and close eyes, grip and release nonparetic hand. (Other one-step commands or mimic also acceptable.)	0 = Both correct (acceptable if impaired by weakness) 1 = One correct 2 = Neither correct	
2. Best gaze: Horizontal EOM by voluntary or doll's eye maneuver.	0 = Normal 1 = Partial gaze palsy; abnormal gaze in one or both eyes 2 = Forced eye deviation or total paresis that cannot be overcome by doll's eye maneuver	
3. Visual field: Use visual threat if necessary. If monocular, score field of good eye.	0 = No visual loss 1 = Partial hemianopsia, quadrantanopia, extinction 2 = Complete hemianopsia 3 = Bilateral hemianopsia or blindness	
4. Facial palsy: If patient is stuporous, check symmetry of grimace to pain.	0 = Normal 1 = Minor paralysis, flat NLF, asymmetrical smile 2 = Partial paralysis (lower face = UMN lesion) 3 = Complete paralysis (upper and lower face)	
5. Motor arm: Arms outstretched 90 degrees (sitting) or 45 degrees (supine) for 10 seconds. Encourage best effort. Indicate paretic limb in score box.	0 = No drift for 10 seconds 1 = Drift but does not hit bed 2 = Some antigravity effort, but cannot sustain 3 = No antigravity effort, but even minimal movement counts 4 = No movement at all X = Unable to assess owing to amputation, fusion, fracture, and so on	L or R
6. Motor leg: Raise leg to 30 degrees (from supine) for 5 seconds. Indicate paretic limb in score box.	0 = No drift for 5 seconds 1 = Drift but does not hit bed 2 = Some antigravity effort, but cannot sustain 3 = No antigravity effort, but even minimal movement counts 4 = No movement at all X = Unable to assess owing to amputation, fusion, fracture, and so on	L or R
7. Limb ataxia: Check finger-nose-finger, heel-shin position sense; and score only if out of proportion to paralysis.	0 = No ataxia (or aphasic, hemiplegic) 1 = Ataxia in upper or lower extremity 2 = Ataxia in upper *and* lower extremity X = Unable to assess owing to amputation, fusion, fracture, and so on	L or R
8. Sensory: Use safety pin. Check grimace or withdrawal if patient is stuporous. Score only stroke-related losses.	0 = Normal 1 = Mild-moderate unilateral loss but patient aware of touch (or aphasic, confused) 2 = Total loss, patient unaware of touch; coma, bilateral loss	
9. Best language: Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis.	0 = Normal 1 = Mild-moderate aphasia (speech difficult to understand but partly comprehensible) 2 = Severe aphasia (almost no information exchanged) 3 = Mute, global aphasia, coma; no one-step commands	
10. Dysarthria: Read list of words.	0 = Normal 1 = Mild-moderate; slurred but intelligible 2 = Severe; unintelligible or mute X = Intubation or mechanical barrier	
11. Extinction or neglect: Simultaneously check bilateral visual fields and auditory sensation, touch in both hands and recognition of body parts looking for extinction or neglect.	0 = Normal, none detected (visual loss alone) 1 = Neglects or extinguishes to double simultaneous stimulation in any modality (visual, auditory, sensation, spatial, body parts) 2 = Profound neglect in more than one modality	

Android Free App: https://play.google.com/store/apps/details?id=com.myprograms.nihss
Apple Free App: https://itunes.apple.com/us/app/nih-stroke-scale-from-statcoder/id408788598?mt=8
Online NIHSS Calculator: www.mdcalc.com/nih-stroke-scale-score-nihss/
EOM, Extraocular movement; *L,* left; *LOC,* level of consciousness; *NLF,* nasolabial fold; *R,* right; *UMN,* upper motor neuron.
Modified from Massachusetts General Hospital Stroke Service. NIH stroke scale materials. Scoring form. Available at www2.massgeneral.org/stopstroke/pdfs/scoring_form.pdf.

over minutes. Similar to ischemic stroke, ICH is often associated with a motor and sensory deficit contralateral to the brain lesion. Almost 40% of patients will demonstrate significant growth in hemorrhage volume within the first few hours.

Although headache, vomiting, and coma are common, many patients do not have these findings, and the clinical presentation can be identical to that of patients with ischemic stroke; the two cannot be reliably differentiated in the absence of neuroimaging.

Ongoing assessment of airway and mental status is part of a comprehensive care plan since patients with ICH can precipitously deteriorate. Emergency airway management requires careful judgment: On the one hand, airway control can prevent aspiration, hypoxia, and hypercarbia; on the other, sedation and paralysis can make it difficult to follow serial neurologic exams, which can help monitor for hemorrhage expansion, elevated intracranial pressure (ICP), seizure activity, and brainstem herniation.

As with ischemic stroke, the neurologic examination localizes the region and extent of injury. Baseline NIHSS and Glasgow Coma Scale scores can be used to assess stroke severity, although the Glasgow Coma Score (GCS) may be more practical to follow for neurologic or mental status deterioration (Table 87.2). In addition, serial examinations can detect early changes that may suggest ongoing bleeding during the acute phase. The ICH score can also predict mortality (Table 87.3).

Baseline characteristics associated with unfavorable outcome for patients with ICH include a decreased level of consciousness on arrival, intraventricular hemorrhage, and large ICH volume, all of which can be assessed in the emergency department (ED) (Fig. 87.3). Prognostic studies of ICH have been biased by early care limitation; newer research suggests a number of patients with early care limitations could have acceptable outcomes. Based on the uncertainty, emergency clinicians are best served in avoiding specific predictions regarding chances of recovery shortly after ICH.[9]

DIFFERENTIAL DIAGNOSES

Ischemic Stroke

Extra-axial collections of blood secondary to trauma can mimic stroke. An epidural or subdural hematoma can cause an altered mental status, focal neurologic signs, and rapid progression to coma. Elders, who represent the age group at highest risk for stroke, can be victims of recurrent falls that lead to chronic subdural hematomas (particularly those on anticoagulation therapy). Carotid dissection may occur after neck trauma or sudden hyperextension and may be associated with focal neurologic signs and symptoms, as with an aortic dissection that extends into the carotid arteries.

Other structural lesions that may cause focal neurological findings include brain tumors and abscesses. Air embolism should be suspected in the setting of marked atmospheric pressure changes, such as in scuba diving or during medical procedures or injuries that may allow air into the vascular system. Seizure activity, altered mental status, and focal neurologic findings also may be manifestations of air embolism.

Metabolic abnormalities also can mimic stroke syndromes. Hypoglycemia often is responsible for an altered mental status and is a common cause of sustained focal neurologic symptoms that can persist for several days. Wernicke encephalopathy from thiamine deficiency causes ophthalmoplegia, ataxia, and confusion that can be mistaken for signs of cerebellar infarction.

Complex migraines may present with focal neurologic findings, with or without headache. A seizure followed by Todd postictal paralysis may mimic stroke. Bell or peripheral facial nerve palsy, labyrinthitis, vestibular neuronitis, peripheral nerve palsy, and demyelinating diseases may all mimic stroke. Ménière disease may be difficult to distinguish from a posterior circulation stroke or TIA. Dizziness, vertigo, hearing loss, and tinnitus in Ménière disease are common, whereas difficulties with vision or speech or other focal symptoms are less common.

Similar to stroke, giant cell arteritis is a disease of elder adults. It may cause severe headache, visual disturbances, and, rarely, aphasia and hemiparesis. Other symptoms include intermittent fever, malaise,

TABLE 87.2 Glasgow Coma Scale Score[a]

Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4 = Spontaneous	5 = Normal conversation	6 = Normal
3 = To voice	4 = Disoriented conversation	5 = Localizes to pain
2 = To pain	3 = Words, but not coherent	4 = Withdraws to pain
1 = None	2 = No words; only sounds	3 = Decorticate posture
	1 = None	2 = Decerebrate posture
		1 = None

[a]Total score = E + V + M.

Shoestring Graphics: Glasgow coma score. Available at www.ssgfx.com/CP2020/medtech/glossary/glasgow.htm.

TABLE 87.3 Intracerebral Hemorrhage Score Predicting Mortality After Acute Intracerebral Hemorrhage

Feature	Points
Glasgow Coma Scale Score	
3–4	2
5–12	1
13–15	0
Intracerebral Hemorrhage Volume	
>30 mL	1
≤30 mL	0
Intraventricular Hemorrhage (Intraventricular Blood)	
Present	1
Absent	0
Intracerebral Hemorrhage Location	
Infratentorial	1
Supratentorial	0
Age	
≥80 years	1
<80 years	0
30-Day Mortalities for Total Intracerebral Hemorrhage Scores	
0 = 0%	
1 = 13%	
2 = 26%	
3 = 72%	
4 = 97%	
5 = 100%	
6 = Estimated to be 100%; no patients in the study fell into this category	

Adapted from Hemphill JC, Bonovich DC, Besmertis L, et al. The ICH Score. *Stroke*. 2001;32:891–897.

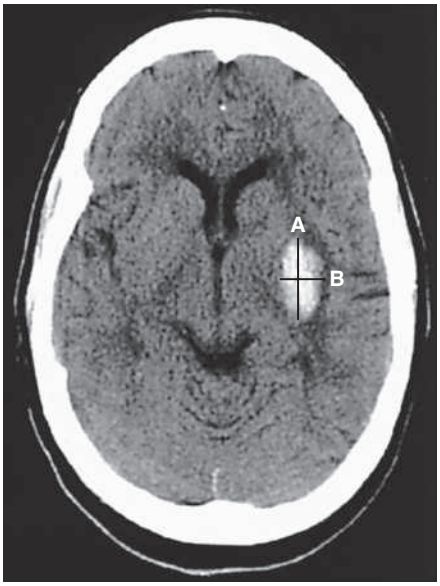

Fig. 87.3 The computed tomography (CT) slice with the largest area of hemorrhage is identified. The largest diameter of the hemorrhage on this slice is measured in centimeters *(line A)*. The largest diameter 90 degrees to A on the same slice is measured *(line B)*. C is the approximate number of 10-mm slices on which the intracerebral hemorrhage (ICH) was seen. (Many centers use 5-mm slices, in which case an adjustment can be made by dividing by 2.) The volume of the hemorrhage = A × B × C ÷ 2 (ABC/2).

jaw claudication, morning stiffness, and myalgias. The diagnosis should be suspected in patients with an elevated erythrocyte sedimentation rate (ESR) and is confirmed by temporal artery biopsy. Collagen vascular diseases such as polyarteritis nodosa, systemic lupus erythematous (SLE), and other types of vasculitis may cause stroke syndromes.

Cerebral venous sinus thrombosis (CVST) is another cause of focal neurologic symptoms that most commonly affects the superior sagittal sinus and lateral sinuses (see Chapter 89).[10] The diagnosis of CVST can be difficult because of the nonspecific nature of symptoms, as well as the variable time frame of symptom onset (from hours to weeks). Patients may have generalized headaches, nausea, vomiting, paresis, visual disturbances, depressed level of consciousness, seizures, or symptoms generally ascribed to psychiatric disorders (such as depression). Depending on the location of the thrombus, physical examination of the patient may reveal papilledema, proptosis, or palsies of CNs III, IV, and VI, as well as other focal neurologic signs. Risk factors for CVST include trauma, infectious processes, hypercoagulable states, low-flow states, compression of the venous sinus, dehydration, pregnancy, postpartum state, and certain drugs (such as androgens, designer amphetamines, and oral contraceptives).

Hemorrhagic Stroke

Differential diagnoses for ICH is similar to that for ischemic stroke; considerations include migraine, seizure, brain tumor, abscess, hypertensive encephalopathy, and head trauma. Hypertensive encephalopathy and migraine also can manifest with headache, nausea, and vomiting, although focal neurologic signs are less common in these entities. With hypertensive encephalopathy, patients usually exhibit marked elevation in BP and other evidence of end-organ injury, such as proteinuria, cardiomegaly, papilledema, and malignant hypertensive retinopathy. These patients usually improve with treatment of their hypertension. The posterior reversible encephalopathy syndrome (PRES) is a subset of hypertensive encephalopathy presentations and has characteristic CT or magnetic resonance imaging (MRI) changes.

Once ICH is diagnosed on neuroimaging, it can be difficult to determine the underlying cause. Primary ICH typically manifests as a parenchymal hematoma with new onset neurologic symptoms. Patients with hemorrhagic transformation of an ischemic stroke may have recurrence or worsening of previously established neurological deficits. Patients with known underlying cancer, or perihematomal edema out of proportion to the hemorrhage, should be considered for hemorrhage into a metastatic lesion or primary tumor. Finally, patients with known underlying venous thromboembolic risk factors may have underlying CVST.

DIAGNOSTIC TESTING

Ischemic Stroke

Although clinical data can help establish the diagnosis and location of the stroke, confirmatory diagnostic tests are often required to establish the final cause or to eliminate other processes. The immediate evaluation includes cranial imaging, an electrocardiogram (ECG), and laboratory testing, particularly blood glucose determination.

An emergent noncontrast cranial CT of the head is the standard initial imaging technique for evaluating a patient with a potential stroke. However, it has limited sensitivity to assess strokes involving the posterior circulation, especially in the posterior fossa structures. It can quickly differentiate an ischemic stroke from ICH and other mass lesions. This information is crucial to the subsequent therapeutic decisions that need to be rapidly made. A CT scan can identify the vast majority of parenchymal hemorrhages larger than 1 cm in diameter and it has a high sensitivity for the detection of SAH. With most ischemic strokes, gross signs of infarction will not appear on routine CT scans for at least 6 to 12 hours, depending on the size of the infarct. However, subtle, early ischemic changes have been noted in up to 67% of noncontrast CT head scans within the first 3 hours. These early ischemic changes include the hyperdense artery sign (acute thrombus in a vessel), sulcal effacement, loss of the insular ribbon, loss of gray-white interface, mass effect, and acute hypodensity (Fig. 87.4).

In addition, CTA or MRA can be used to identify the presence of intravascular thrombosis, vasculature dissection, or stenosis. CTA can be used for the triage of patients who may be candidates for endovascular therapy to determine if there is an LVO. CTA can be obtained concurrently with head CT. Imaging with CTA can also be helpful to identify patients who might benefit from thrombectomy following t-PA administration. Vigilance should be taken to avoid delaying administration of thrombolytics as the thrombectomy trials with the largest treatment effects were predominantly populated with patients who had received t-PA promptly prior to thrombectomy.

Automated CT perfusion (CTP) has emerged as an additional methodology to identify patients who may benefit from reperfusion in extended time windows.[11–13] CTP is generally not helpful in the first 6 hours following stroke onset in that most of these patients will either qualify for t-PA on clinical grounds and for thrombectomy based on CTA findings. MRI has also been investigated to identify candidates for systemic thrombolysis with "wake up" strokes.[14] Advanced imaging should not delay the administration of t-PA.

The clinical importance of early ischemic CT findings with regard to fibrinolytic therapy within 3 hours of symptom onset is controversial, because the ability of treating clinicians to reproducibly identify these findings is poor and their clinical significance is questionable. Only acute hypodensity and mass effect have been shown to be associated with an increased risk of ICH after fibrinolysis (over that in treated patients without these findings). However, these findings do

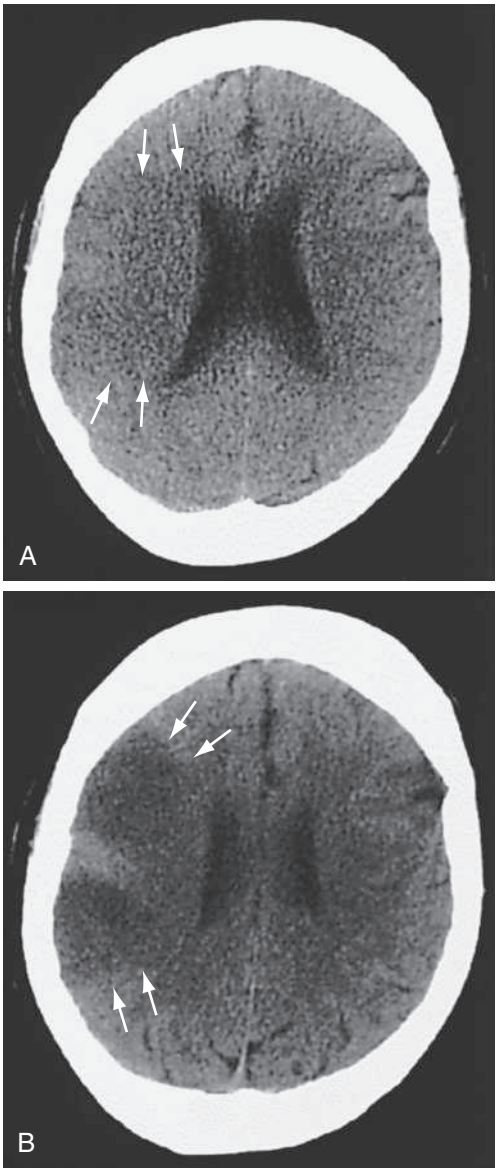

Fig. 87.4 (A) Computed tomography (CT) scan taken 2 hours and 50 minutes after a large right middle cerebral artery occlusion. There are subtle, ultra-early ischemic changes, including loss of the gray-white interface *(arrows)* and subtle evidence of sulcal effacement. (B) CT scan of same patient approximately 8 hours after symptom onset shows acute hypodensity *(arrows)* and more prominent sulcal effacement.

not exclude patients from fibrinolytic therapy, which is associated with an improved neurological outcome. Patients with a hyperdense artery sign and acute hypodensity of one-third of the MCA distribution tend to have a poorer prognosis. Their outcomes, however, are still better with t-PA treatment than without fibrinolytic therapy.

MRI can visualize ischemic brain infarcts earlier and identify acute posterior circulation strokes more accurately than CT, and it is as effective as CT in identifying ICH. However, availability, proximity to the ED, difficulty in accessing critically ill patients, and image time limit the use of MRI in acute stroke. Advances in MRA technology have allowed a noninvasive method of demonstrating large-vessel occlusions of the anterior and posterior circulation, although small intracranial vascular occlusions may not be readily apparent. With the improvements in MRI and MRA speed and resolution, some stroke centers are replacing CT protocols with limited "stroke protocol" MRI or MRA as the initial imaging modality of choice. The choice of initial cranial imaging modality is highly dependent on the speed with which these scans can be performed and interpreted at each individual center.

Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are MRI techniques that take minutes to perform and may allow differentiation between reversible and irreversible neuronal injury. Other potential imaging modalities include CTA and perfusion scans. In CTA, CT imaging is enhanced by an intravenous (IV) contrast agent to better define the vasculature of the brain. Areas of vascular stenosis and occlusion can be visualized with this technique. This information can then be used by interventionalists to determine whether a lesion is amenable to endovascular thrombectomy. Also requiring IV contrast, perfusion CT scans can reveal perfusion deficits within different regions of the brain. In addition, CTA and perfusion CT can differentiate reversible from irreversible ischemic insults.

An ECG is indicated in all patients with acute ischemic stroke; atrial fibrillation and acute myocardial infarction are associated with up to 60% of all cardioembolic strokes. The hematologic evaluation includes a complete blood and platelet count, prothrombin time (including international normalized ratio [INR]), partial thromboplastin time, troponin levels, and serum glucose measurement. Elevated blood viscosity, even when hematocrit levels are not polycythemic, can affect blood flow and prognosis. A platelet count can identify thrombocytosis or thrombocytopenia, which may precipitate a thrombosis or hemorrhage. Coagulation studies are especially helpful to guide management for patients in whom anticoagulation is being considered or for patients with an acute hemorrhagic stroke.

Other ancillary diagnostic tests to consider include an echocardiogram, carotid duplex scan, and angiogram. Some stroke centers are performing these studies as part of a TIA observation unit protocol to exclude a patent foramen ovale or valvular vegetation in those patients in whom a cardioembolic stroke is suspected. An echocardiogram should also be performed in patients with no obvious cause for their stroke.[3] Finally, conventional angiography can demonstrate stenosis or occlusion of both large and small blood vessels of the head and neck. It can detect subtle abnormalities, such as with dissection, that may not be demonstrated with noninvasive imaging techniques.

Transient Ischemic Attack

Patients with new-onset TIAs should receive an expedited evaluation and treatment owing to the substantial short-term risk of stroke and other adverse events. In 2016, a multi-national study reported a 2% stroke recurrence rate in the week following a presentation for TIA or minor stroke.[15] Emergency neuroimaging, vascular imaging (such as with a carotid Doppler study, MRA, or CTA), electrocardiography, and basic blood tests should be performed. A medically or surgically treatable cause for TIAs (e.g., high-grade carotid stenosis, mural thrombus) should be considered, which would require in-hospital treatment such as anticoagulation, stenting, or carotid endarterectomy.

Hemorrhagic Stroke

The hematologic evaluation for the patient with hemorrhagic stroke should be performed in the same manner as for the patient with ischemic stroke. Particular attention should be directed to uncovering the presence of a coagulopathy. A drug screen should be obtained to evaluate for use of sympathomimetics (such as cocaine) if substance abuse is suspected. Increased sympathetic outflow secondary to the hemorrhage may lead to an increase in dysrhythmias. Dysrhythmias also may signal impending brainstem compression from an expanding hemorrhage.

As in ischemic stroke, the cranial CT scan is the diagnostic test of choice to evaluate for an ICH. The noncontrast CT scan will reliably

diagnose patients with clinically relevant acute ICH. Hemorrhages that are several days old may not be as apparent as acute hemorrhages and appear as isodense regions on CT imaging.

Also, as with ischemic stroke, advanced neuroimaging modalities are gaining favor in ICH. CTA produces high-quality images of the larger arterial vessels and can help exclude secondary causes, such as aneurysm, AVM, or fistula. Some patients with primary ICH show contrast extravasation on CTA, and such patients are at particularly high risk of ongoing bleeding and hematoma expansion. A venous phase can be added to this study (computed tomography venography [CTV]) to evaluate for CVST. An MRI can help detect underlying lesions (such as a brain tumor) and may offer better resolution for evaluating perihematomal edema. When available, MRA and magnetic resonance venography (MRV) can be used in place of CTA and CTV.

MANAGEMENT

Ischemic Stroke

With a focus on rapid recognition, evaluation, and treatment of stroke, many medical centers have streamlined care to meet recommended time goals (Table 87.4). This has led to the development of stroke protocols, critical pathways, and acute interventional stroke teams that may even be deployed in the field by EMS personnel before the patient arrives at the ED.

Prehospital Considerations: In the prehospital setting, the focus should be on ensuring central nervous system (CNS) oxygenation and perfusion, rapid identification, early hospital notification, and rapid transport. Although it is unusual for patients with ischemic stroke to be unresponsive on presentation, their ability to communicate may be altered by dysphasia. After an ischemic stroke, patients usually can maintain their airway unless the brainstem is affected or significant cerebral edema is compressing the opposite hemisphere. Patients with intact protective airway reflexes should receive oxygen if they are hypoxic (oxygen saturation less than 95%). Routine oxygen supplementation of normoxic stroke patients should be avoided.

A monitor and IV line should be established. Overhydration should be avoided to prevent cerebral edema. By contrast, dehydration may lead to decreased cerebral perfusion, and saline infusion should be given if dehydration is suspected. Dextrose-containing solutions should be avoided in normoglycemic patients suspected of having had a stroke because elevated blood glucose levels may worsen an ischemic deficit.

Prehospital personnel should rapidly ascertain the patient's blood sugar. Both hypo- and hyperglycemia can mimic acute stroke presentations. Electrocardiographic monitoring is recommended to identify life-threatening arrhythmias and atrial fibrillation.[3]

Prehospital providers should document the exact time the patient was last seen to be neurologically normal and the level of neurologic functioning using one of the validated prehospital stroke scores. The level of consciousness, gross focal motor deficits, difficulty with speech, clumsiness, facial asymmetry, and any other focal deficits should be noted. Prehospital stroke scales assist in identifying patients who have had a stroke and who are potential candidates for fibrinolytic therapy. Early recognition, notification, and transport by EMS are associated with expedited delivery of fibrinolytic treatment and improved patient outcomes.

In the ED setting, the vital signs should be reassessed on an ongoing basis because patients may rapidly deteriorate even with subacute stroke. Some stroke patients are found at home 1 or 2 days after the event has occurred and may have concomitant illnesses, such as aspiration pneumonia, dehydration, hypothermia, rhabdomyolysis, or myocardial ischemia. Fever necessitates an evaluation to identify sources of infection, followed by prompt institution of treatment, including appropriate antibiotics. Even minor degrees of hyperthermia have been associated with increased neurologic injury. Oral medications, liquids, and food should be withheld until some form of swallowing assessment has been performed, given the risk of aspiration in patients with an acute stroke.

TABLE 87.4 National Institute of Neurological Disorders and Stroke Recommended Stroke Evaluation Targets for Potential Thrombolytic Candidates

Management Component	Target Time Frame
Door to doctor	10 min
Door to CT completion	25 min
Door to CT scan reading	45 min
Door to treatment	60 min
Access to neurologic expertise[a]	15 min
Access to neurosurgical expertise [a]	2 h

[a]By phone or in person.
CT, Computed tomography.

Blood Pressure Management

Current guidelines for the management of hypertension in patients with acute ischemic stroke recommend that antihypertensive treatment be reserved for those with markedly elevated BPs, unless fibrinolytic therapy is anticipated or specific medical indications are present. These medical indications include acute myocardial infarction, aortic dissection, hypertensive encephalopathy, and severe left ventricular heart failure. Oral or parenteral agents are withheld unless the patient's systolic pressure is greater than 220 mm Hg, diastolic pressure is greater than 120 mm Hg, or mean arterial pressure (MAP) is greater than 130 mm Hg (Box 87.2).

If thrombolytic therapy is indicated, stringent control of BP is indicated to reduce the potential for intracranial hemorrhage (see Box 87.2). Thrombolytic therapy is not recommended for patients whose systolic pressure is consistently higher than 185 mm Hg or whose diastolic pressure is 110 mm Hg at the time of treatment. Patients who have elevated BP and are otherwise eligible for treatment with IV thrombolytics should have their BP carefully lowered so that their systolic BP is less than 185 mm Hg and their diastolic BP is less than 110 mm Hg before IV fibrinolytic therapy is initiated. In patients for whom mechanical thrombectomy is planned and who have not received IV fibrinolytic therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure.[3] Simple measures can be used to lower the BP below this level: Recommended approaches include the use of IV labetalol 10 to 20 mg over 1 to 2 minutes; or continuous nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5 to 15 minutes (maximum 15 mg/h); or clevidipine 1 to 2 mg/h IV, titrate by doubling the dose every 2 to 5 minutes (maximum 21 mg/h). Other agents such as hydralazine and enalaprilat can be used.[3] Once thrombolytic therapy has been initiated, hypertension should be treated aggressively and monitored closely for the first 24 hours after treatment.

Just as problematic as an elevated BP can be, low BP can be equally detrimental to patients with ischemic stroke. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function. Normally normotensive stroke patients with low BP or normally hypertensive stroke patients with low or even

low-normal BP are given a fluid bolus to try to increase cerebral perfusion. This is especially important in patients in a dehydrated state. If initial fluid challenge is ineffective, the patient may require vasopressor therapy to gradually increase MAP and improve cerebral perfusion.

Temperature

Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke.[3] For patients with stroke peak temperature in the first 24 hours less than 37°C and greater than 39°C is associated with an increased risk of in-hospital death compared with normothermia.[16] The benefit of treatment with induced hypothermia remains unclear. To date, studies of hypothermia in acute ischemic stroke show no benefit in functional outcome and suggest that induction of hypothermia increases the risk of infection, including pneumonia.[3]

BOX 87.2 Emergency Antihypertensive Therapy for Acute Ischemic Stroke

Indication That Patient Is Eligible for Treatment With Intravenous Recombinant Tissue Plasminogen Activator or Other Acute Reperfusion Intervention

Blood Pressure Level

Systolic >185 mm Hg or diastolic >110 mm Hg

- Labetalol 10–20 mg IV over 1–2 min; may repeat 1 time
- *or*
- Nicardipine infusion, 5 mg/h; titrate up by 2.5 mg/h at 5- to 15-min intervals, maximum dose 15 mg/h; when desired BP attained, reduce to 3 mg/h
- *or*
- Clevidipine 1 to 2 mg/h IV, titrate by doubling dose every 2 to 5 minutes (maximum 21 mg/h)

Other agents (e.g., hydralazine, enalaprilat) may be considered when appropriate.

If BP does not decline and remains >185/110 mm Hg, do not administer rtPA.

Management of Blood Pressure During and After Treatment With Recombinant Tissue Plasminogen Activator or Other Acute Reperfusion Intervention

Monitor BP every 15 min during treatment and then for another 2 h, then every 30 min for 6 h, and then every hour for 16 h.

Blood Pressure Level

Systolic 180–230 mm Hg or diastolic 105–120 mm Hg

- Labetalol 10 mg IV over 1–2 min; may repeat every 10–20 min; maximum dose of 300 mg
- *or*
- Labetalol 10 mg IV followed by an infusion at 2–8 mg/min

Systolic >230 mm Hg or diastolic 121–140 mm Hg

- Labetalol 10 mg IV over 1–2 min; may repeat every 10–20 min; maximum dose of 300 mg
- *or*
- Labetalol 10 mg IV followed by an infusion at 2–8 mg/min
- *or*
- Nicardipine infusion, 5 mg/h; titrate up to desired effect by increasing 2.5 mg/h every 5 minutes to maximum of 15 mg/h

If BP not controlled, consider sodium nitroprusside.

BP, Blood pressure; *IV,* intravenous; *rtPA,* recombinant tissue plasminogen activator.

Adapted from Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of adults with ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(3):870–947.

Blood Glucose

Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia, and thus we recommend treating hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia. Hypoglycemia (blood glucose <60 mg/dL) should be treated with IV dextrose solution.

Reperfusion Therapy

The ultimate goal of reperfusion therapy for acute ischemic stroke is to improve outcome by reducing stroke-related disability and mortality. Restoring perfusion to ischemic areas of the brain that are not yet infarcted is critical to achieving this goal and is time dependent. There are two reperfusion strategies that have been extensively studied and proven effective: (1) IV thrombolytic therapy and (2) mechanical thrombectomy.

Thrombolytic Therapy

Agent and Dosage

Options for thrombolytic therapy that are proven effective include two types of recombinant tissue plasminogen activators (t-PA): IV alteplase and IV tenecteplase. Alteplase is the primary IV thrombolytic agent approved by the U.S. Food and Drug Administration (FDA) for treatment of patients with acute ischemic stroke within 3 hours of clearly defined symptom onset to restore blood flow to the regions of brain that are ischemic. Approval was initially based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trial. The dosage of alteplase is 0.9 mg/kg (maximum dose 90 mg) over 60 minutes with initial 10% of dose given as bolus over 1 minute. The ENCHANTED trial evaluated a low-dose alteplase (0.6 mg/kg IV) versus standard-dose alteplase (0.9 mg/kg IV) in 3300 patients (63% Asian) with acute ischemic stroke. Low-dose alteplase was noninferior to standard-dose alteplase with respect to death and disability at 90 days and there were significantly fewer symptomatic ICHs with low-dose alteplase.[17] Low-dose alteplase is the standard of care in Japan but current AHA/ASA guidelines still recommend 0.9 mg/Kg.

There is moderate- to high-quality evidence that IV tenecteplase 0.25 mg/kg (maximum 25 mg) given in a single bolus has similar rates of functional outcome, symptomatic ICH, and mortality at 90 days compared with alteplase.[18–20] The EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) randomized 202 patients with acute ischemic stroke within 4.5 hours of symptoms undergoing endovascular therapy to thrombolysis with tenecteplase versus alteplase.[21] Tenecteplase was associated with a higher incidence of reperfusion and better functional outcome compared with alteplase. Intracranial hemorrhage was similar between groups.[21] Tenecteplase can be used in place of alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.[3,21] From a practical standpoint, the bolus infusion of tenecteplase is easier to administer than a 1-hour infusion of alteplase.

The potential risks should be discussed with the patient when determining eligibility for thrombolysis and weighed against the anticipated benefits during decision making (Table 87.5).

Time Window

Within 3 hours of symptom onset: The safety and efficacy of alteplase treatment when administered within the first 3 hours after stroke onset are solidly supported by combined data from multiple RCTs[3,22] and confirmed by extensive community experience in many countries.[23] The eligibility criteria for IV thrombolytic therapy have evolved over time as its usefulness and true risks have become clearer (see eligibility criteria).

TABLE 87.5 2019 AHA/ASA Acute Stroke Management Guidelines for Alteplase Treatment in Acute Ischemic Stroke

A. Eligibility Recommendations for IV Alteplase in Patients With Acute Ischemic Stroke

Within 3 h	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state.
Within 3 h—Age	For otherwise medically eligible patients ≥18 years of age, IV alteplase administration within 3 h is equally recommended for patients ≤80 and >80 years of age.
Within 3 h—Severe stroke	For severe stroke, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms.
Within 3 h—Mild disabling stroke	For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.
3–4.5 h	IV alteplase is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well.
3–4.5 h—Age	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 years of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any oral anticoagulants, and without imaging evidence of ischemic injury involving more than one-third of the MCA territory.
Urgency	Treatment should be initiated as quickly as possible within the above-listed time frames because time to treatment is strongly associated with outcomes.
BP	IV alteplase is recommended in patients with BP <185/110 mm Hg and in those patients whose BP can be lowered safely to this level with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase.
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.
CT	IV alteplase administration is recommended in the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity).
Prior antiplatelet therapy	IV alteplase is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH. IV alteplase is recommended for patients taking antiplatelet drug combination therapy (e.g., aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH.
End-stage renal disease	In patients with end-stage renal disease on hemodialysis and normal aPTT, IV alteplase is recommended. However, those with elevated aPTT may have elevated risk for hemorrhagic complications.

B. Exclusions for IV Alteplase in Patients With Acute Ischemic Stroke

0- to 3-h window–Mild nondisabling stroke	For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state.
3- to 4.5-h window–Mild nondisabling stroke	For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well or at baseline state.
CT	There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering IV alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury.
ICH	IV alteplase should not be administered to a patient whose CT reveals an acute intracranial hemorrhage.
Ischemic stroke within 3 months	Use of IV alteplase in patients presenting with AIS who have had a prior ischemic stroke within 3 months may be harmful.
Severe head trauma within 3 months	In AIS patients with recent severe head trauma (within 3 months), IV alteplase is contraindicated.
Acute head trauma	Given the possibility of bleeding complications from the underlying severe head trauma, IV alteplase should not be administered in posttraumatic infarction that occurs during the acute in-hospital phase.
Intracranial/intraspinal surgery within 3 months	For patients with AIS and a history of intracranial/spinal surgery within the prior 3 months, IV alteplase is potentially harmful.
History of intracranial hemorrhage	IV alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful.
Subarachnoid hemorrhage	IV alteplase is contraindicated in patients presenting with symptoms and signs most consistent with an SAH.
GI malignancy or GI bleed within 21 days	Patients with a structural GI malignancy or recent bleeding event within 21 days of their stroke event should be considered high risk, and IV alteplase administration is potentially harmful.
Coagulopathy	The safety and efficacy of IV alteplase for acute stroke patients with platelets <100 000/mm3, INR >1.7, aPTT > 40 s, or PT >15 s are unknown, and IV alteplase should not be administered. (In patients without history of thrombocytopenia, treatment with IV alteplase can be initiated before availability of platelet count but should be discontinued if platelet count is <100,000/mm^3. In patients without recent use of OACs or heparin, treatment with IV alteplase can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.)

(continued)

TABLE 87.5 2019 AHA/ASA Acute Stroke Management Guidelines for Alteplase Treatment in Acute Ischemic Stroke—cont'd.

LMWH	IV alteplase should not be administered to patients who have received a full treatment dose of LMWH within the previous 24 h.
Thrombin inhibitors or factor Xa inhibitors	The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful. IV alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 h (assuming normal renal metabolizing function). (Alteplase could be considered when appropriate laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these ACs for >48 h and renal function is normal.)
Concomitant Abciximab	Abciximab should not be administered concurrently with IV alteplase.
Concomitant IV aspirin	IV aspirin should not be administered within 90 min after the start of IV alteplase.
Infective endocarditis	For patients with AIS and symptoms consistent with infective endocarditis, treatment with IV alteplase should not be administered because of the increased risk of intracranial hemorrhage.
Aortic arch dissection	IV alteplase in AIS known or suspected to be associated with aortic arch dissection is potentially harmful and should not be administered.
Intra-axial intracranial neoplasm	IV alteplase treatment for patients with AIS who harbor an intra-axial intracranial neoplasm is potentially harmful.

AIS, Acute ischemic stroke; *aPPT*, activated partial thromboplatin time; *CT*, computed tomography; *GI*, gastrointestinal; *ICH*, intracerebral hemorrhage; *INR*, international normalized ratio; *IV*, intravenous; *LMWH*, low molecular weight heparin; *MCA*, middle cerebral artery; *NCCT*, noncontrast computed tomography; *SAH*, subarachnoid hemorrhage; *sICH*, spontaneous intracerebral hemorrhage.

The benefit of IV alteplase is well established for adult patients with disabling stroke symptoms regardless of age and stroke severity.[24] Patients should receive IV thrombolytics without delay, if eligible, even if mechanical thrombectomy is being considered.

Three to 4.5 hours of symptom onset: Subsequent studies have demonstrated the usefulness of IV thrombolytics at 3 to 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Treatment with IV alteplase initiated within 4.5 hours of stroke onset improves functional outcome at 3 to 6 months for patients across the age spectrum and severities of stroke.[24,25] However, the earlier that treatment is initiated, the greater the benefit, as the benefit decreases continuously over time from symptom onset. Faster IV thrombolysis delivery is associated with less disability at 3 months especially for door-to-needle time less than 30 minutes.[26] IV tenecteplase has been compared with alteplase up to 6 hours after stroke and appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[3]

In patients with acute ischemic stroke known or suspected to be associated with extracranial cervical arterial dissection, who are otherwise eligible for thrombolysis, it is reasonably safe to administer thrombolytics within 4.5 hours of symptom onset.[3] However, the usefulness and hemorrhagic risk of thrombolytics in acute ischemic stroke known or suspected to be associated with intracranial arterial dissection remain unknown and thrombolysis is not recommended.[3]

4.5 to 9 hours of symptom onset or unwitnessed onset or "wake-up" stroke: In patients with acute ischemic stroke who awake with stroke symptoms or have unclear time of onset greater than 4.5 hours from last known well or at baseline state, MRI to identify DWI-positive (diffusion weighted imaging) and FLAIR-negative (fluid-attenuated inversion recovery) lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition (Fig. 87.5).[3] The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) randomized 503 patients who awoke with stroke (90%) or had unclear time of onset greater than 4.5 hours from last known well (10%) and were otherwise eligible for IV alteplase. Favorable outcome (mRS score of 0 to 1) at 90 days was achieved in significantly more patients in the IV alteplase group versus the placebo group (53% vs. 42%). Mortality rate was not significantly higher in the alteplase group (4% vs. 1%) as was the rate of symptomatic intracranial hemorrhage (2% vs. 0.4%).[14]

The EXTEND trial (EXtending the time for Thrombolysis in Emergency Neurological Deficits) enrolled 225 adults who had hypoperfused but salvageable brain tissue on automated perfusion imaging (CT or MRI) and could be treated between 4.5 and 9 hours after the onset of ischemic stroke or awoke with stroke symptoms (9 hours from the midpoint of sleep) and randomly assigned them to IV alteplase or placebo. Favorable outcome (mRS score of 0 to 1) at 90 days was more likely for the IV alteplase group compared with the placebo group (35% vs. 30%); when adjusted for age and severity, there was no significant difference between alteplase and placebo in the unadjusted analysis. Symptomatic intracranial hemorrhage within 36 hours of treatment was higher with alteplase (6% vs. 1%) ($P = .053$) though mortality was not significantly higher with alteplase (12% vs. 9%).[11] Similarly, in the ECASS-4 trial, IV alteplase administered between 4.5 and 9 hours after the onset of symptoms in patients with salvageable tissue did not result in a significant benefit over placebo.[27]

Therefore, beyond 4.5 hours, the benefit of IV alteplase is not clear. The application of DWI-positive (diffusion-weighted imaging) and FLAIR-negative (fluid-attenuated inversion recovery) lesions on MRI to identify patients with a stroke onset time greater than 4.5 hours or an unknown stroke onset time who would benefit from IV alteplase, is promising.

Thrombolysis for Mild Disabling Versus Nondisabling Acute Ischemic Stroke

For otherwise eligible patients with *mild nondisabling* stroke symptoms (NIHSS score 0 to 5), IV alteplase is not recommended for patients who could be treated within 3 or 4.5 hours of ischemic stroke symptom onset or patient last known to be well or at baseline state.[3] The PRISMS trial (A Study of the Safety and Efficacy of Alteplase in Patients With Mild Stroke) evaluated IV alteplase in 313 patients with mild acute ischemic stroke within three hours of symptom onset (NIHSS score 0 to 5) whose acute neurological deficits were judged to not interfere with activities of daily living or prevent return to work (nondisabling).

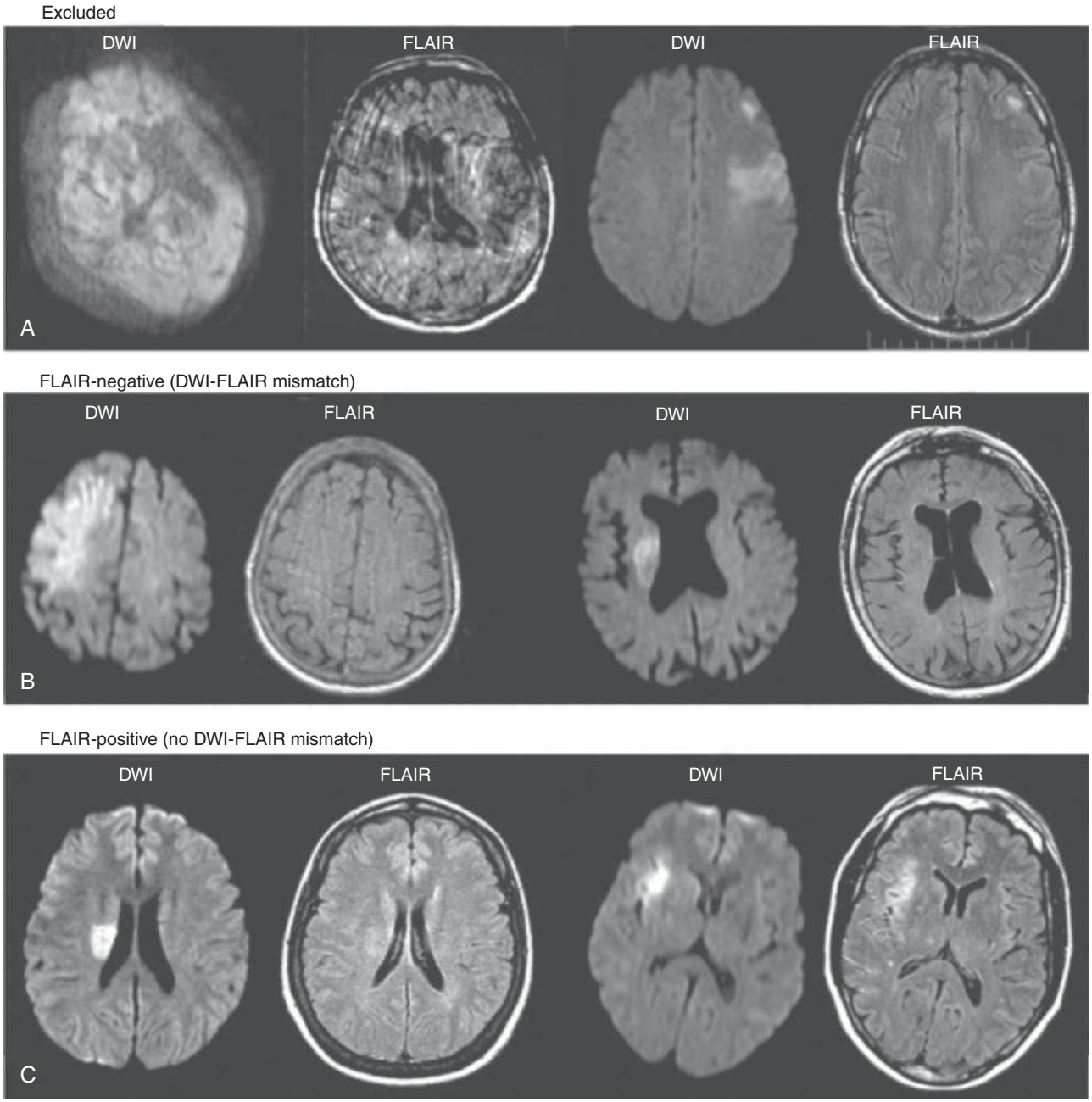

Fig. 87.5 Examples of DWI and FLAIR images. (A) Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) images excluded from the final analysis because of poor quality (left) or the presence of multiple acute and subacute ischemic lesions of different ages, precluding the attribution of symptom onset to one specific lesion (right). (B) Pairs of images showing acute ischemic lesions on DWI but not on FLAIR imaging (FLAIR-negative, DWI-FLAIR mismatch). (C) Pairs of images showing acute ischemic lesions on DWI together with a corresponding subtle (left) or obvious (right) parenchymal hyperintensity on FLAIR imaging (FLAIR-positive, no DWI-FLAIR mismatch). (Reprinted with permission from Elsevier. From Thomalla G, Cheng B, Ebinger M, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study. *Lancet Neurology*, 2011;10(11):981; Figure 2.)

There was no difference in the rate of a favorable functional outcome (mRS of 0 or 1) at 90 days for patients assigned to treatment with IV alteplase or to aspirin (78% vs. 82%).[28,29]

However, for otherwise eligible patients with *mild but disabling* stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours and within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known to be well or at baseline state (Powers et al., 2019).[30]

Thrombolysis in Patients on Anticoagulants Before the Stroke

Antiplatelet: IV alteplase is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of symptomatic ICH. Similarly, IV alteplase is recommended for patients taking antiplatelet drug combination therapy (e.g., aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of ICH.

LMWH: IV alteplase should not be administered to patients who have received a full treatment dose of low molecular weight heparin (LMWH) within the previous 24 hours.

Factor IIa and Factor Xa Inhibitors: The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful. Therefore, IV alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as activated partial thromboplastin time (aPTT), INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for greater than 48 hours (assuming normal renal metabolizing function).[3]

Symptomatic Intracerebral Hemorrhage Following Thrombolysis

IV thrombolysis with tissue plasminogen activator after acute ischemic stroke carries a risk of symptomatic ICH with an incidence from 2% to 7%[31] with greatest risk in patients with the most severe strokes.[25] Asymptomatic ICH occurs more frequently and usually occurs within 36 hours after t-PA infusion and half of the events are diagnosed within 5 to 10 hours. Intracranial hemorrhage occurring after 36 hours is unlikely to be caused by thrombolysis. Classification of symptomatic ICH after thrombolytic therapy is based on two main factors: (1) radiographic appearance of the hemorrhage and (2) the presence of associated neurological deterioration.[31] Unfortunately, variability in the definition of clinical neurological deterioration has a dramatic impact on the reported incidence of ICH in different studies.

Radiographically, hemorrhage is graded as: (1) *petechial* hemorrhage along the infarcted tissue margin (HI1), (2) *confluent petechial* hemorrhage within the infarcted tissue (HI2), (3) *parenchymal* hematoma involving 30% or less of the infarcted tissue with slight mass effect (PH1), (4) *parenchymal* hematoma involving greater than 30% of the infarcted tissue with significant mass effect (PH2). Subtype PH2 is the most clinically significant as it carries a poor prognosis, approaching 50% mortality and significant morbidity in survivors. Subtypes HI1, HI2, and PH1 occur more frequently than PH2.[32]

In a systematic review and meta-analysis of 55 studies, older age, greater stroke severity, higher baseline glucose, hypertension, congestive heart failure, renal impairment, diabetes mellitus, ischemic heart disease, atrial fibrillation, baseline antiplatelet use, leukoaraiosis, and visible acute infarction on brain imaging were all associated with increased risk of symptomatic ICH (Box 87.3).[31] Several risk scores have been developed to predict the risk of ICH or prognosis for patients treated with IV thrombolysis.[33] They include the HAT score, DRAGON score, SEDAN score, Stroke-Thrombolytic Predictive Instrument, SPAN-100 index, and the SITS SICH risk score. The predictive ability of the risk scores varies with absolute risk for symptomatic ICH for SITS at 0.2% for a score of zero to 14% for a score of 10 or more. For SEDAN the risk has ranged from 1% for a score of zero to 28% for a score of five points. For HAT the symptomatic ICH rate has ranged from 3% to 14%. Validation studies are needed to confirm their utility before they can be instituted in clinical practice.

Current protocols include ICU monitoring for 24 hours with repeat neuroimaging if there is any neurological deterioration. Treatment of post-thrombolytic hemorrhage includes cardiovascular and respiratory support, BP management, neurological monitoring, prevention of hematoma expansion, control of elevated ICP, and seizure control. Treatment options for ICH related to IV thrombolytics include the administration of agents to reverse the effects of thrombolytic therapy and antithrombotic therapy but no specific agent has been shown to be most effective.[31] These include antifibrinolytic agents (epsilon-aminocaproic acid and tranexamic acid), cryoprecipitate, fresh frozen plasma, platelets, prothrombin complex concentrate, and vitamin K. It's preferable to withhold the use of activated Factor VIIa (rFVIIa) until more studies establish its safety in this setting, given that it is associated with relatively high thrombosis rates.[31] Of these treatment options, we recommend cryoprecipitate. Once symptomatic ICH is diagnosed, consider immediately sending a fibrinogen level and empirically transfusing with 10 U cryoprecipitate intravenously over 10 to 30 minutes.[3] Additional cryoprecipitate may be needed to achieve a fibrinogen level of ≥150 mg/dL. Neurosurgical intervention may also be considered if clinically indicated.[31]

BOX 87.3 Factors Associated With Increased Risk for Symptomatic Intracerebral Hemorrhage After Thrombolysis

- Older age
- Greater stroke severity
- Higher baseline glucose
- Hypertension
- Congestive heart failure
- Renal impairment
- Diabetes mellitus
- Ischemic heart disease
- Atrial fibrillation
- Baseline antiplatelet use
- Leukoaraiosis (periventricular white matter disease)
- Visible acute infarction on brain imaging
- Cerebral microbleeds

Cerebral Microbleeds

Cerebral microbleeds (CMBs) are small accumulations of blood products in brain tissue that are associated with cerebrovascular disease, dementia, and aging. They occur in the setting of impaired small vessel integrity due to hypertension or cerebral amyloid angiopathy.[34] In the setting of acute ischemic stroke, CMBs are considered markers of bleeding-prone cerebral vessel microangiopathies that increase the risk of ICH[35–37] along with poor 3- to 6-month functional outcome after administration of IV thrombolysis.[37–39] The risk of symptomatic ICH in patients with greater than 10 CMBs is significantly greater (30% to 47%) than in those without CMBs (1% to 4%).[35,36,38] Thus, the presence of CMBs increases the risk of ICH and the chances of poor outcomes after thrombolytics, but it is unclear whether these negative effects fully negate the benefit of thrombolytics.[37] Therefore, in patients who have previously had a high burden of CMBs (>10) demonstrated on MRI, the benefits of thrombolytic treatment are uncertain.[3]

Mechanical Thrombectomy

The recent trials demonstrating clear benefit of endovascular thrombectomy come after a decade of negative studies. The difference in results is due to a combination of improved devices, emphasis on early intervention, advanced imaging techniques and careful patient selection. These studies have conclusively demonstrated that patients with severe strokes and evidence of proximal LVOs have significantly better functional outcomes when treated with the new-generation devices. Mechanical thrombectomy is now indicated for patients with acute ischemic stroke with large artery occlusion in the anterior circulation who meet selected criteria and who present within 24 hours of last known to be well regardless of whether they receive IV alteplase for the same ischemic stroke event.

Timing

Shorter time to endovascular-reperfusion therapy is significantly associated with better outcomes.[40,41] In pooled patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), shorter time from symptom onset to arterial puncture with mechanical thrombectomy was associated with lower degrees of disability at 3 months but the benefit became nonsignificant after 7 hours.[42] The majority of these patients also received thrombolytics. Among those who achieved substantial reperfusion each 1-hour delay to reperfusion was associated with a less favorable degree of disability and less functional independence, but no change in mortality.[42]

Zero to 6 hours of symptom onset: Guidelines from the AHA/American Stroke Association (ASA) recommend mechanical thrombectomy for adults with: (1) no significant prestroke disability (i.e., a mRS score of ≤1); (2) a causative occlusion of the ICA or the M1 segment of the MCA; (3) NIHSS score of ≥6; and (4) ASPECTS of ≥6 (associated with better functional outcome at 3 months). These guidelines are based on results from 6 recent randomized trials of mechanical thrombectomy using predominantly stent retriever devices (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE).[3]

The benefits of thrombectomy are uncertain for patients with occlusion of the ICA or proximal MCA (M1), who have a prestroke mRS score greater than 1, or an NIHSS score less than 6, or a larger infarct core (i.e., ASPECTS score <6). Using pooled patient data, the direction of treatment effect for mechanical thrombectomy over standard care appears favorable in M2 occlusions but does not reach statistical significance.[43–45] Therefore, the benefits of thrombectomy for distal MCA occlusion, MCA segment 2 (M2) or MCA segment 3 (M3), are uncertain. Additionally, the benefits are uncertain in those with occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.

Pooled patient-level data showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥70 years of age and ≥80 years of age.[43,44,46] However, the number of patients in these trials who were ≥90 years of age was very small. As with any treatment decision in an elderly patient, consideration of comorbidities and risks should factor into the decision-making for mechanical thrombectomy.

Six to 16 hours of symptom onset: In selected patients with acute ischemic stroke within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended (without thrombolysis).[3]

The DAWN trial used clinical-core mismatch (a combination of NIHSS score and imaging findings on CT perfusion or diffusion-weighted MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known to be at their normal neurological baseline. This trial demonstrated an overall significant benefit in function outcome at 90 days in the treatment group (mRS score 0 to 2) of 49% versus 13%.[13] Only 12% with witnessed onset of symptoms. The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients had large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy (Fig. 87.6). This trial showed a significant benefit in functional outcome at 90 days in the treated group (mRS score 0 to 2) of 45% versus 17%.[12] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy greater than 6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice.[3,12,13]

Sixteen to 24 hours of symptom onset: In selected patients with acute ischemia stroke within 16 to 24 hours of last known normal who have

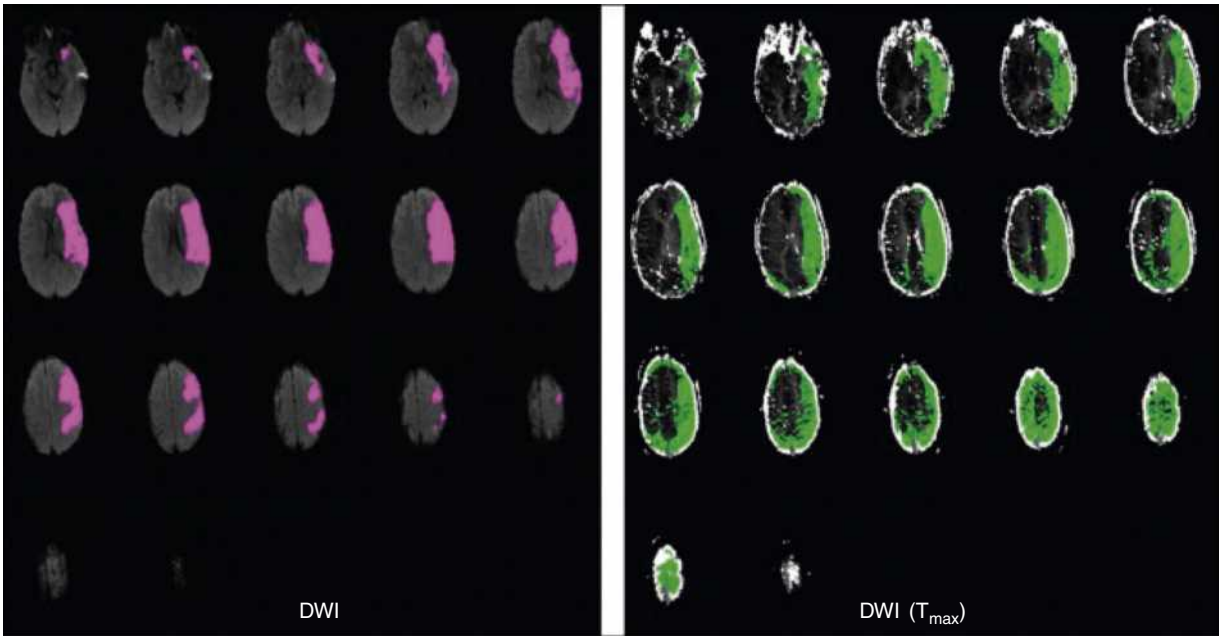

Fig. 87.6 Malignant penumbral profile unfavorable for treatment more than 3 h after stroke onset. MRI scan with DWI showing large established infarct core (*left*; 143 cm^3) and perfusion-weighted imaging showing extremely large region of tissue at risk (*right*; 255 cm^3). Although mismatch is present (ratio 1:8), and the patient presented within the treatment window, the large size of the already completed infarct in the dominant hemisphere shows reperfusion would probably be futile, because tissue loss sufficient to cause death or severe dependency has already occurred. DWI, diffusion-weighted imaging; Tmax, time-to-maximum of the residue function. (Images courtesy of Greg Albers, Stanford University, School of Medicine, CA, USA).

LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is a reasonable approach.[3]

Mechanical Thrombectomy and Thrombolysis

Mechanical thrombectomy can be used in addition to treatment with IV thrombolytics. However, pretreatment with IV thrombolytics (if initiated within 4.5 hours of symptom onset) is not required prior to thrombectomy.[26] Mechanical thrombectomy treatment should be initiated as quickly as possible and should not be delayed to assess the response to IV alteplase.[3] A post hoc analyses of pooled data compared thrombectomy alone versus dual therapy (IV thrombolysis and thrombectomy) for LVO and concluded that dual therapy was associated with a higher likelihood of 3-month functional independence and lower odds of 3-month mortality. The two groups did not differ in functional improvement or symptomatic intracranial hemorrhage.[47] There are no randomized controlled trials of mechanical thrombectomy for posterior circulation LVOs.[48]

Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of IV alteplase might be considered, but the consequences are unknown and therefore not recommended. In this scenario, mechanical thrombectomy with stent retrievers is recommended over intraarterial fibrinolysis as first-line therapy.[3]

Spontaneous Intracerebral Hemorrhage (Hemorrhagic Stroke)

Evidence from clinical trials to guide management for spontaneous ICH has lagged behind that of ischemic stroke and aneurysmal SAH. Initial goals of treatment include preventing hemorrhage expansion (which occurs in about 20% to 30% of patients) and prevention of secondary brain injury via stabilization of airway, breathing, and circulation. Patients may require intubation and mechanical ventilation, anticoagulation reversal, BP control, interventions for elevated ICP, treatment for seizures, or neurosurgical hematoma evacuation.

Monitoring

Patients with spontaneous ICH are frequently medically and neurologically unstable, particularly within the first few days after onset and they can deteriorate from hematoma expansion (which most often occurs within the first few hours), elevations in ICP, hydrocephalus, seizures, and herniation. Admission to an intensive care unit or dedicated stroke unit is recommended as it is associated with a lower mortality rate.[2]

Blood Pressure Management

Two large phase III, multicenter, prospective randomized controlled trials (RCTs) have shown that early lowering of SBP to less than 140 mm Hg is safe without significant adversary effects. The INTERACT2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2) trial evaluated the efficacy of intensive BP lowering within 6 hours of spontaneous ICH in 2839 patients with systolic BP between 150 and 220 mm Hg. Patients were randomized to intensive BP lowering (target systolic BP less than140 mm Hg within 1 hour) versus standard treatment (target systolic BP <180 mm Hg). Intensive lowering of BP did not result in a significant reduction in death or severe disability but did improve functional outcomes at 90 days. In the ATACH 2 trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage), IV nicardipine was administered within 3 hours of ICH in 1000 patients and the rate of death or disability was not different between subjects randomized to a target SBP of 110 to 139 mm Hg compared to a target of 140 to 179 mm Hg. The rate of renal adverse events within 7 days was significantly higher in the intensive-treatment group than in the standard-treatment group (9.0% vs. 4.0%).[49] A pooled analysis of individual patient-level data from INTERACT2 and ATACH2 showed early and steady reduction in SBP (potentially down to 120 to 130 mm Hg) seemed to be safe and associated with favorable outcomes in patients with ICH that were mild to moderate in severity. However, a rapid and large reduction (≥60 mm Hg) within 1 hour of the initiation of treatment was associated with some harm.[50] Further analysis on the INTERACT2 data revealed that intensive BP lowering was beneficial across a wide range of baseline BPs (<160, 160 to 169, 170 to 179, 180 to 189, and ≥190 mm Hg) and that lowering SBP to 130 to 139 mm Hg was likely to be maximally beneficial.[51]

Therefore, for ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome. For ICH patients presenting with SBP greater than 220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous IV infusion and frequent BP monitoring, but the target BP is less clear.[2] IV calcium channel blockers (e.g., nicardipine) and β-blockers (i.e., labetalol) are the treatments of choice for early BP reduction, given their short half-life and ease of titration. Nitrates should be avoided given their potential for cerebral vasodilation and elevated ICP.[52]

Reversal of Anticoagulation

All anticoagulants such as vitamin K antagonists (e.g., warfarin), antiplatelet medications (aspirin, clopidogrel, prasugrel, ticagrelor), and non–vitamin K antagonists known as direct oral anticoagulants (DOACs) such as Factor IIa (thrombin) inhibitors (e.g., dabigatran, argatroban and bivalirudin) or Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, darexaban) should be discontinued acutely and reversed immediately with appropriate agents.[53]

Patients taking vitamin K antagonists with INR ≥1.4 can be reversed with IV vitamin K and 3-factor or 4-factor prothrombin complex concentrate (PCC) or fresh frozen plasma administered intravenously.[53] Vitamin K 10 mg is administered slowly IV but its effects are delayed. 3-factor or 4-factor prothrombin complex concentrate is preferred over fresh-frozen plasma due to more rapid correction of INR, lower volume, and lower risk of infection and pulmonary edema.[53] PCC is an inactivated concentrate of factors II, IX, and X, with variable amounts of factor VII. Variation in factor VII concentrations in PCC has led to their classification as either 3- or 4-factor.[52]

Although direct thrombin inhibitors (Factor IIa inhibitors) have less risk of ICH than vitamin K antagonists, reversal is indicated if patients present within 3 to 5 half-lives of drug exposure.[52] Idarucizumab is a Fab fragment of a monoclonal antibody that binds to and inactivates dabigatran and 5 g is administered as two consecutive 2.5-g IV bolus injections.[54] If idarucizumab is not available or if other direct thrombin inhibitors have been ingested, clotting factor products such as prothrombin complex concentrates or fresh-frozen plasma can be used.[55] Dabigatran can also be reversed with hemodialysis. Idarucizumab should not be combined with other clotting factor products.

Patients requiring emergent reversal of Factor Xa inhibitors can be treated with Andexanet alfa or 4-factor prothrombin complex concentrates.[56] Andexanet alfa is a class-specific antidote targeted to competitively inhibit Factor Xa inhibitors.[57] The initial dose depends on the dose of the Factor Xa inhibitor and the interval since the last dose. Andexanet should not be combined with other clotting factor products.

There is inadequate evidence to support the routine use of platelet transfusion for ICH in patients taking preinjury antiplatelet medications.[58] Platelet transfusion should be considered for patients with aspirin- or adenosine diphosphate receptor (ADP) inhibitor-associated ICH who will undergo a neurosurgical procedure.[53] Desmopressin (ddAVP) (0.4 μg/kg IV single dose) can be considered in ICH associated with cyclooxygenase (COX) inhibitors or ADP receptor inhibitors.[53]

Hemostatic Agents

The TICH2 was an international double-blind randomized trial of 2325 patients with ICH comparing 2 g of tranexamic acid to placebo given within 8 hours of onset. Tranexamic acid did not affect functional status at 90 days compared to placebo, although potential benefits were seen with reductions in hematoma expansion, early death, and serious adverse events.[59]

Seizures

Patients with ICH have up to 16% risk of clinical seizures within 1 week, with the majority occurring at or near onset. There is no association between clinical seizures and neurological outcome or mortality.[52] Clinical seizures should be treated with anticonvulsants. Patients with a change in mental status who are found to have electrographic seizures on EEG should also be treated with anticonvulsants (e.g., levetiracetam 1000 to 1500 mg IV). Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status that is out of proportion to the degree of brain injury. However, prophylactic antiseizure medication is not recommended.[2]

Prognosis

Factors that may affect outcome after ICH include hematoma volume and location, hematoma expansion, age, GCS score on presentation, intraventricular extension, and anticoagulant use. However, none of the existing ICH prediction models has proven reliable.[52] When health care providers initiate early do not resuscitate (DNR) orders, patients with otherwise equivalent prognoses are more likely to die. Therefore, current AHA/ASA guidelines recommend early and aggressive care for ICH patients and postponement of any new DNR orders until at least the second full day of treatment. Patients with pre-existing DNR orders are excluded from this recommendation.[2] However, DNR status should not limit appropriate medical and surgical interventions, unless explicitly indicated.

Increased Intracranial Pressure

In patients with supratentorial ICH with radiographic hydrocephalus, especially in patients with decreased level of consciousness, an external ventricular drain is advised. Patients with a GCS score of ≤8, those with clinical evidence of transtentorial herniation, or those with intraventricular hemorrhage or hydrocephalus should be considered for ICP monitoring and treatment. A CPP of 50 to 70 mm Hg is recommended.[2]

Mannitol and hypertonic saline (HTS 3% or 23.4%) are the first-line medical therapies for patients with symptomatic cerebral edema and elevated ICP. In an analysis of the INTERACT2 patients, there was no significant difference in outcome in mannitol and non–mannitol-treated patients so mannitol was safe, but did not improve outcome.[60] In a small retrospective study, treatment with 23.4% of HTS was associated with rapid reversal of transtentorial herniation and reduced ICP. Early continuous infusion of 3% of HTS for sodium goal of 145 to 155 mmol/L was associated with less cerebral edema and ICP elevations. A meta-analysis showed that HTS is slightly more effective than mannitol for the treatment of elevated ICP.[52]

Both hyperglycemia and hypoglycemia should be avoided. Corticosteroids should not be administered for treatment of elevated ICP. The risk of central fever is increased in patients with larger ICH and in those with IVH and negatively impacts outcome.[61] Sources of hyperthermia (temperature > 38°C) should be identified and treated, and antipyretic medications should be administered.[3]

Neurosurgical Intervention

Urgent neurosurgical consultation is recommended for assessment for hydrocephalus and the possible need for surgical decompression or hematoma evacuation.[62] Cerebellar ICH is considered a neurosurgical emergency. Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible.[2]

For most patients with supratentorial ICH the benefits of surgical evacuation of the hematoma are still under investigation. Open craniotomy hematoma evacuation has not been found to have any benefit in large randomized trials.[63] Current guidelines suggest that evacuation may be considered in patients with supratentorial ICH who exhibit neurological deterioration, coma, midline shift, or elevated ICP refractory to medical treatment.[2]

As an alternative to open surgical approaches, minimally invasive approaches to evacuate clots are being investigated. These approaches use small incisions and burr holes and insert either a catheter into the clot for drainage or a small tube into the clot for direct evacuation. A meta-analysis of five randomized trials and nine prospective studies in patients with supratentorial ICH found that minimally invasive approaches conferred a mortality benefit, as well as a lower rate of rebleeding and higher rate of good recovery.[64] The MISTIE III (Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation III) trial was an open-label blinded endpoint trial that randomized 506 patients to minimally invasive surgery (catheter evacuation followed by thrombolytic irrigation of the clot with alteplase) versus standard medical treatment. Eligible patients had a supratentorial ICH measuring ≥30 mL, NIHSS ≥6, good baseline status, a CT angiogram negative for an underlying lesion, and a repeat CT demonstrating clot volume stability for at least 6 hours. At one year, the number of patients with good functional outcome (mRS score of 0 to 3) was similar for the minimally invasive surgery group compared with the standard care group (45% vs. 41%). Mortality was lower in the minimally invasive surgery group (19% vs. 26%).[63]

The ENRICH (Early MiNimally-invasive Removal of ICH) is a multicenter randomized clinical trial of ICH patients aged 18 to 80 years with a GCS score of 5 to 14 and an intraparenchymal hemorrhage volume of 30 to 80 mL comparing standard medical management to early surgical hematoma evacuation within 24 hours using minimally invasive parafascicular surgery (MIPS). An initial single-arm surgical evaluation of this endoport system in 39 patients with primary IPH reported functional independence in 52% of patients at follow-up and no mortality.[65]

Intraventricular extension of the ICH (intraventricular hemorrhage or IVH) occurs in up to 45% of patients with ICH[52] and puts patients at risk for hydrocephalus, especially if the third and fourth ventricles are involved because the normal circulation of cerebrospinal fluid (CSF) can become interrupted. Such patients should be closely monitored with frequent neurological assessments. When neurologic deterioration occurs, an emergent CT scan should be done to exclude the development of hydrocephalus. Patients with neurologic deterioration in the setting of ventricular enlargement may be candidates for ventriculostomy and external ventricular drainage.[2] The CLEAR III trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage III) was a double-blinded, placebo-controlled trial conducted in 500 ICH patients with intraventricular hemorrhage obstructing the third or fourth ventricles. Patients were randomized to irrigation of the extraventricular drain with alteplase versus saline. Alteplase did not substantially improve functional outcomes at the mRS 3 cutoff compared with irrigation with saline.[66]

Decompressive craniectomy is a procedure that removes a portion of the skull bone enabling the brain to expand to decrease ICP. In small non-randomized studies decompressive craniectomy treatment for spontaneous supratentorial ICH showed lower rates of in-hospital mortality and better functional status compared with medically managed patients

in certain populations.[67,68] The SWITCH trial (Swiss trial of decompressive craniectomy versus best medical treatment of spontaneous supratentorial ICH) is currently enrolling ICH patients between 18 and 75 years with hemorrhage into the basal ganglia or thalamus with a GCS 8 to 13, NIHSS ≥10 and ≤30, and volume of hematoma 30 to 100 mL.

TRANSIENT ISCHEMIC ATTACK

TIA is no longer defined by an arbitrary time of 24 hours. Patients with symptoms less than 24 hours can have representative ischemic lesions on diffusion-weighted or perfusion-weighted MRI, so TIA has moved from time-based to tissue-based definition. Patients with TIA or nondisabling strokes are at increased risk of recurrent stroke and should be evaluated and treated immediately in order to reduce the risk of subsequent stroke and to identify patients who may benefit from preventive therapy or from revascularization of large vessels.

Some centers have developed rapid outpatient TIA clinics to ensure an expedited evaluation within 24 hours of presentation. However, patients at higher risk for subsequent stroke should be hospitalized. Previous guidelines have used the ABCD2 score (i.e., ABCDD, for Age, BP, Clinical features, Duration of symptoms, and Diabetes) as a prognostic assessment tool designed to identify TIA patients at high risk of ischemic stroke and thus requiring admission (Table 87.6). More recent studies have found the score does not provide an accurate estimate of stroke risk.[69,70] Others have combined the ABCD2 score with imaging such as MRI and MRA (ABCD2-I and ABCD3-I)[6,71,72] to improve the short-term prediction of cerebral infarction but have yet to be validated.

Most patients without a contraindication will be started on antithrombotic therapy in the ED after consultation with a neurologist. Dual antiplatelet therapy with clopidogrel and aspirin is effective for secondary prevention after minor ischemic stroke or TIA.[73] Pooled analysis of two RCTs, POINT and CHANCE, showed that early and short-term clopidogrel-aspirin treatment was associated with a reduction in the risk of major ischemic events compared to aspirin alone. The benefit of dual antiplatelet therapy appeared to be confined to the first 21 days after minor ischemic stroke or high-risk TIA.[74] The risk for major hemorrhages in patients receiving either clopidogrel plus aspirin or aspirin alone after TIA was low. Nevertheless, treatment with clopidogrel plus aspirin increased the risk of major hemorrhages over aspirin alone from 0.2% to 0.9%.[75] In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.[3]

In patients with new onset atrial fibrillation, immediate anticoagulation should be considered, except those for whom the risks of bleeding exceed the benefits or those with a CHA2DS2-VASc score of 0 in men or 1 in women who have short paroxysms of AF that self-terminate (see Chapter 65 for suggested anticoagulants).

TABLE 87.6 ABCD2 Score for Assessing Stroke Risk in Patients With a Transient Ischemic Attack

Risk Factor	Points
Age >60 years old	1
Initial BP >140/90 mm Hg	1
Unilateral weakness	2
Speech Impairment	
Without weakness	1
Symptoms 10–59 min	1
Symptoms ≥60 min	2
History of diabetes	1
Result	
0–3 = Low risk (1% risk of stroke in 48 h)	
4–5 = Moderate risk (4.1% risk of stroke in 48 h)	
≥6 = High risk (8% risk of stroke in 48 h)	

BP, Blood pressure.

DISPOSITION

"Stroke center" definitions have been established, and there is a national certification process for primary stroke centers (PSCs) and comprehensive stroke centers (CSCs) in the United States. In broad terms, institutional certification as a PSC requires the establishment of a stroke infrastructure (i.e., a dedicated stroke team, stroke unit, patient care protocols, and support services, including CT/MRI scanning and laboratory testing availability), as well as institutional administrative support and specialty-qualified leadership. CSCs offer advanced imaging modalities, perform surgical and endovascular interventions, and maintain a core infrastructure, such as a stroke unit and stroke registry. The establishment of PSCs and CSCs is intended to improve outcomes for stroke patients by ensuring a high level of coordinated care. Early identification and transfer of patients with acute stroke to a PSCs or CSCs results in more favorable outcomes.

The most recent level of stroke classification for hospitals is the acute stroke-ready hospital (ASRH). These hospitals are typically smaller facilities with lower stroke patient volumes. An ASRH is capable of establishing the initial stroke diagnosis, as well as providing acute stabilization and treatment. The use of tele-technologies between the ASRH and PSC/CSC will likely serve a pivotal role in support of clinical care. After initial stabilization and treatment, stroke patients will frequently be transferred to PSC or CSC institutions. A systematic review of retrospective studies evaluating the safety and efficacy of IV alteplase delivered within 3 hours of symptom onset through telestroke networks concluded that there was no difference in mortality or functional independence at 3 months between telestroke-guided and stroke center–managed patients.[76]

Reducing the time interval from ED presentation to initial brain imaging can help to reduce the time to treatment initiation. Studies have shown that median or mean door-to-imaging times of ≤20 minutes can be achieved in a variety of different hospital settings.[77–79] The benefit of bypassing the closest hospital that offers thrombolytic therapy to transporting the patient directly to an institution that offers a higher level of stroke care (including mechanical thrombectomy) has not been established. However, it is reasonable to introduce prehospital procedures to identify patients who have a strong probability of LVO stroke and are eligible for thrombectomy and facilitate rapid transport of these patients to centers that perform mechanical thrombectomy.[3] Telestroke networks may also be reasonable for triaging patients with acute ischemic stroke who may be eligible for interfacility transfer in order to be considered for emergency mechanical thrombectomy.[76]

Patients with acute ischemic stroke may deteriorate over the first 24 hours and require close in-hospital monitoring. There is evidence suggesting a benefit from admission to a stroke-specific unit. Patients with large acute hemispheric strokes (associated with increased risk of herniation) or with significant posterior circulation-related changes and those treated with a fibrinolytic agent should be monitored in an ICU for at least 24 hours.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 87: QUESTIONS AND ANSWERS

1. Which of the following statements concerning ischemic stroke is true?
   a. Anterior circulation strokes are more likely than posterior strokes to show evidence of progression at the time of presentation.
   b. Anterior circulation strokes rarely present with complete loss of consciousness.
   c. Posterior cerebral artery strokes are associated with incontinence, leg weakness greater than arm weakness, and gait clumsiness.
   d. The presence of aphasia suggests an anterior cerebral artery (ACA) distribution stroke, typically left sided.
   e. The presence of diplopia suggests an anterior circulation stroke.

Answer: b. Forty percent of posterior and 20% of anterior circulation strokes present with progressive symptoms. It is rare for anterior circulation (carotid, ACA, and middle cerebral artery [MCA]) strokes to significantly alter consciousness, unless there has been a previous contralateral stroke. ACA strokes primarily affect frontal lobe functions and may also present with primitive grasp and such reflexes. In addition to contralateral motor and sensory defects, MCA strokes may present with expressive aphasia, agnosia, and ipsilateral hemianopsia.

2. Which of the following is not associated with posterior circulation strokes?
   a. Diplopia
   b. Homonymous cranial nerve (CN) and extremity motor deficits
   c. Loss of consciousness
   d. Loss of visual object recognition
   e. Nausea, vomiting, and ataxia

Answer: b. Posterior circulation (vertebrobasilar) strokes involve the vertebral, basilar, and posterior cerebral arteries. Because this system supplies the reticular activating system, cerebellum, brainstem, occipital lobe, and brainstem vomiting centers, loss of consciousness with vomiting, visual changes, and cerebral ataxia may be seen. Ipsilateral CN deficits (because these nuclei largely reside in the brainstem) occur with contralateral "body" deficits resulting from motor/sensory fiber decussation.

3. Headache, vomiting, and a decreased level of consciousness are most commonly seen with which of the following disorders?
   a. Ischemic stroke
   b. Intracranial hemorrhage
   c. Migraine headache
   d. Subarachnoid hemorrhage (SAH)
   e. Tic douloureux

Answer: d. The incidence of headache is highest by far in patients with SAH. Vomiting and depressed loss of consciousness are also generally more common in this group. Pure migraine headache rarely, if ever, causes a depressed loss of consciousness. Tic headaches do not cause loss of consciousness.

4. What percentage of patients with hemorrhagic stroke experience clinical deterioration because of growth in hemorrhage volume within the first hours?
   a. 10%
   b. 20%
   c. 30%
   d. 50%
   e. 75%

Answer: c. Thirty percent of patients with intracerebral hemorrhage (ICH) experience early hemorrhage expansion. Progression of neurologic deficits and decreasing mental status suggest the diagnosis.

5. A 69-year-old male presents with headache, vomiting, aphasia, a right lower facial palsy, and right upper greater than right lower extremity weakness. The symptoms began approximately 4 hours before arrival. Vital signs are temperature 99°C, blood pressure (BP) 180/90 mm Hg, respiratory rate 18 breaths/min, heart rate 92 beats/min, and oxygen saturation 96% on room air. Emergent computed tomography (CT) scan shows a left temporal intracerebral hemorrhage (ICH). Soon after presentation, the patient experiences increased vomiting and a diminishing level of consciousness. What is the most likely explanation for this deterioration?
   a. Accompanying subarachnoid hemorrhage (SAH)
   b. Acute brainstem herniation
   c. Hypoxia from neurogenic pulmonary edema
   d. Increase in volume of the ICH
   e. Myocardial infarction with cardiogenic shock

Answer: d. Approximately one-third of patients with ICH experience early hemorrhage volume expansion. Although brainstem herniation is a possibility, this is typically a delayed sequela with a more gradual presentation. Acute myocardial infarction may be associated with intracranial emergencies but would not likely cause an abrupt mental status change. Neurogenic pulmonary edema may accompany any condition with elevated intracranial pressure (ICP) and would not likely cause an abrupt mental status change.

6. After complete occlusion of cerebral vessels, irreversible neurologic deficits are expected to reliably occur within how many hours?
   a. 2
   b. 3
   c. 4
   d. 5
   e. 6

Answer: e. As a result, ischemic stroke trials, using fibrinolytic or antiplatelet agents, have attempted to recanalize occluded arteries and reperfuse ischemic areas of the brain within a 2- to 6-hour therapeutic window.

7. Which of the following areas of the brain is perfused by the posterior circulation?
   a. Internal capsule
   b. Posterior aspect of the temporal lobe
   c. Putamen
   d. Speech areas of the temporal lobe
   e. Thalamus

Answer: e. The thalamus is perfused by the posterior circulation. The other areas are perfused by the anterior circulation.

8. Which of the following statements regarding stroke etiology is true?
   a. Lacunar strokes reliably cause a pure motor deficit.
   b. Less than 1% of strokes occur in the 15- to 45-year-old age group.
   c. One-third of ischemic strokes are thrombotic.
   d. Strokes resulting from atrial fibrillation likely involve small vessels.
   e. Two-thirds of ischemic strokes are cardioembolic.

Answer: c. One-third of ischemic strokes are thrombotic. Lacunar strokes may cause a pure motor, pure sensory, or ataxic/hemiparesis stroke. Vessel occlusion resulting from atrial fibrillation–induced emboli more likely involves the large vessels. Three percent to 4% of ischemic strokes occur in the 15- to 45-year-old age group.

9. A 29-year-old female presents with a left-sided headache after a moderate-speed motor vehicle collision (MVC). She suffered no loss of consciousness and has no other complaints or obvious injuries. Physical examination is remarkable only for drooping of the left eyelid and slight miosis of the left pupil compared with the right. Which of the following would be the diagnostic test of choice?
- **a.** Brain magnetic resonance imaging (MRI) with gadolinium
- **b.** Contrasted computed tomography (CT) scan of the brain
- **c.** CT angiogram of the carotid arteries
- **d.** Uncontrasted CT scan of the brain
- **e.** Urine drug screen

Answer: c. Carotid or vertebral artery dissection can occur after trauma or mild events, such as yoga, twisting, or prolonged static positions looking upward. The hallmark is unilateral neck pain, face pain, or headache, often with accompanying Horner syndrome. Acutely, cerebral ischemic changes would not be seen on brain imaging. Carotid and vertebral dissection is not a contraindication for thrombolytic therapy in the eligible patient.

10. A 28-year-old G3P3 woman who is 2-week postpartum after an uncomplicated vaginal delivery presents with acute onset of mild headache, lethargy, and double vision. Physical examination is remarkable for normal vital signs and a left eye lateral gaze palsy. The most appropriate intervention is likely to be which of the following?
- **a.** Computed tomography (CT) scan of the brain with possible lumbar puncture
- **b.** CT scan of the brain and intravenous (IV) heparin
- **c.** Erythrocyte sedimentation rate (ESR) and IV corticosteroids
- **d.** IV magnesium
- **e.** Lumbar puncture and IV antibiotics

Answer: b. Cerebral venous thrombosis may present with headache, lethargy, cranial nerve (CN) deficits, seizures, or even psychiatric complaints. CT scan and/or magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) are likely to reveal the diagnosis. Treatment includes heparin. Neurosurgical consultation is not useful. Subarachnoid hemorrhage (SAH) would not be expected to cause a focal neurologic deficit. Eclampsia and meningitis would be expected to give characteristic findings on history and examination.

11. An 82-year-old male presents with an apparent stroke. He is rapidly evaluated and determined to be within the 3- to 4.5-hour window for fibrinolytic therapy. Which of the following exclusion criteria applies only to the 3- to 4.5-hour criteria and not the 0- to 3-hour criteria?
- **a.** Administration of heparin within the 48 hours preceding the stroke onset
- **b.** Age older than 80 years
- **c.** High clinical suspicion for subarachnoid hemorrhage (SAH)
- **d.** Seizure at the onset of the stroke
- **e.** Symptoms rapidly improving

Answer: b. In the 3- to 4.5-hour window, patients cannot exceed 80 years of age. Heparin administration within the 48 hours preceding stroke onset is a contraindication in both the 0- to 3-hour window as well as the 3- to 4.5-hour window. Similarly, high clinical suspicion for SAH, seizure at the onset of the stroke symptoms, and rapidly improving symptoms are contraindications to fibrinolysis in both time windows.

12. A 66-year-old female presents with a possible transient ischemic attack (TIA). Approximately 1 hour before her arrival, she had a 15-minute episode of strictly right arm and right leg weakness, and her symptoms have now resolved. Her blood pressure (BP) is 165/92 mm Hg. Her prior medical history is significant for hypertension, high cholesterol, and diabetes mellitus. What is her ABCD2 score?
- **a.** 4
- **b.** 5
- **c.** 6
- **d.** 7
- **e.** 8

Answer: c. The patient's ABCD2 score is 6 (age >60 years, BP >140/90 mm Hg, unilateral weakness, symptoms lasting 10 to 59 minutes, and history of diabetes). No speech impairment is reported.

13. A 72-year-old male presents with an apparent stroke. Computed tomography (CT) imaging of the brain demonstrates only a hyperdense middle cerebral artery (MCA) sign and no other ischemic changes. He was last seen neurologically normal 4 hours earlier. Which of the following is a contraindication to fibrinolytic therapy in this patient?
- **a.** His blood glucose is 372 mg/dL.
- **b.** His National Institutes of Health (NIH) Stroke Scale score is 24.
- **c.** His platelet count is 110,000/mm^3.
- **d.** His systolic blood pressure (BP) is 180 mm Hg.
- **e.** He takes warfarin daily.

Answer: e. Any oral anticoagulant treatment (regardless of the patient's international normalized ratio [INR]) is a contraindication to fibrinolysis in the 3- to 4.5-hour treatment window. Other contraindications include an NIH stroke scale score greater than 25, platelet count less than 100,000/mm^3, blood glucose greater than 400 mg/dL, and systolic BP greater than 185 mm Hg.

14. A 75-year-old man is brought to the emergency department (ED) for altered mental status. After computed tomography (CT) imaging of the brain is performed, he is found to have a large intracerebral hemorrhage (ICH). Which of the following options is *not* an appropriate strategy for lowering intracranial pressure (ICP)?
- **a.** Barbiturate-induced coma
- **b.** Hyperthermia induction
- **c.** Hypertonic saline administration
- **d.** Hyperventilation
- **e.** Mannitol administration

Answer: b. Hypothermia is an experimental modality for lowering ICP. Hyperventilation can serve as a temporizing measure for reducing ICP. Mannitol and/or hypertonic saline can also be administered. Inducing a barbiturate coma is also an experimental modality.

88

Seizure

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KEY CONCEPTS

- Epilepsy is a neurologic condition associated with an intrinsically lower seizure threshold and a higher risk of recurrent seizures without a clear trigger.
- The characterization of seizure semiology, duration, and etiology is important for accurate classification of seizures and status epilepticus; these impact definitive treatment choices.
- There is no single test to confirm that a patient seized, and several seizure mimics, including convulsive syncope, exist. A postictal alteration in mental status makes a seizure five times more likely than syncope.
- Key factors in the evaluation of epilepsy patients who present with breakthrough seizures include: changes in anti-seizure regimen, compliance, the addition of new medications that may lower the seizure threshold or levels of antiseizure drugs, presence of common infections or metabolic derangements, and recent sleep habits.
- Although most seizures are self-limited, the management of patients with seizures involves a targeted search for underlying pathology, treatment of complications associated with convulsions, and the prevention of future episodes.
- Serious systemic complications of seizures and status epilepticus include cardiac arrest, arrhythmias, apnea, hypoxia, acute kidney injury, rhabdomyolysis, acidosis, and death. The prognosis of status epilepticus is directly related to the etiology of seizures.
- Primary seizure prophylaxis should only be given for 7 days following traumatic brain injury. The period is shorter, although less well-defined, in unsecured aneurysmal subarachnoid hemorrhage. Prolonged primary prophylaxis is not recommended because it has not been demonstrated to reduce long-term seizure risk. The duration of secondary seizure prophylaxis and the antiseizure regimen in patients with acute brain injury who had a seizure during hospitalization should be individualized.
- Patients with a first-time seizure who have no known structural brain pathology, normal serum glucose and sodium levels, and normal neurologic examination can be discharged from the ED with appropriate outpatient follow-up.
- Emerging evidence supports the consideration of secondary seizure prophylaxis for first-time unprovoked seizures in selected patients. However, data are heterogeneous, and a thorough discussion with the patient and a specialist is advised before the initiation of anti-seizure drugs.
- Alcohol withdrawal syndrome can include seizures resulting from the cessation or reduction of alcohol consumption leading to an unopposed excitatory sympathomimetic response. Benzodiazepines are the drug of choice and should be supplemented by supportive measures, including electrolyte and thiamine supplementation. In pregnant patients, evaluations for new-onset seizures before 20 weeks should be the same as in nonpregnant patients. After 20 weeks, and up to 8 weeks postpartum, eclampsia is a major cause of seizures and should be included in the differential. IV magnesium remains first-line treatment for patients with eclamptic seizures and should not be delayed. Benzodiazepines and non-teratogenic antiseizure medications are reasonable alternatives in magnesium-refractory cases.
- Post-anoxic status epilepticus, including myoclonic status, frequently observed following cardiac arrest, was considered pathognomonic of poor neurologic outcome. However, in patients lacking factors with high predictive value for poor outcome post cardiac arrest, early antiseizure therapy can lead to improved outcomes.
- Therapeutic approaches to nonconvulsive status epilepticus are commonly extrapolated from convulsive generalized status epilepticus guidelines. However, the presumed etiology of seizures, extent of cortical area involved (focal versus diffuse or generalized), comorbidities, and response to therapy should be considered when selecting an antiseizure therapeutic algorithm.
- Immunomodulation remains the cornerstone of therapy for autoimmune epilepsies, in conjunction with antiseizure drugs. Transdisciplinary decision making is warranted before initiating immune-targeted therapy, which may include high-dose methylprednisolone, intravenous immunoglobulin, plasma exchange, rituximab, cyclophosphamide, and more recently, tocilizumab.

FOUNDATIONS

Background and Classification

Seizures are excessive excitatory neuronal activity associated with hypersynchrony of neighboring cells, resulting in sensory, motor, autonomic, or cognitive function alterations. *Convulsion* refers specifically to the motor manifestations of a seizure. The *ictal period* is the time during which a seizure or seizure-like activity occurs. A *postictal period* is an interval of transient neurologic dysfunction (commonly altered mental status or weakness) immediately following a seizure, generally lasting less than 1 hour. Longer ictal activity is associated with more prominent and prolonged postictal symptoms. When precipitating factors can be identified, provoked seizures are termed *acute symptomatic seizures.* Conversely, *primary seizures* are unprovoked and have no acute inciting pathology. Epilepsy refers to a condition of recurrent unprovoked seizures.

The International League Against Epilepsy defines epilepsy as a disease in which the threshold for seizures is lower than the normal population reflected by meeting at least one of the following: (A) diagnosis of epilepsy syndrome (e.g., juvenile myoclonic epilepsy, Lennox-Gastault syndrome, benign rolandic epilepsy, infantile spasms); (B) two or more seizures occurring more than 24 hours apart without an identified trigger; (C) one unprovoked seizure coupled with a higher likelihood of recurrent seizures over the subsequent decade

(similar to the recurrence risk for fulfilling criterion B, or ≥60% recurrence risk). For example, a patient who suffers head trauma might have a seizure in close proximity to the acute brain injury but would not be considered to have epilepsy unless unprovoked seizures recur remotely from the initial brain injury. Epilepsies are classified further according to seizure onset and semiology (focal with or without impairment of awareness, generalized or unknown onset; see Figure 14.1 in Chapter 14),[1] epilepsy syndrome (e.g., idiopathic generalized and self-limited focal epilepsies), and etiology (e.g., structural, genetic, infectious, metabolic, immune, or unknown).[2]

The majority of epilepsy syndromes have onset during childhood or adolescence. However, there have been reports of onset in early adulthood[2]; a thorough evaluation with a specialist is indicated in these cases. Breakthrough seizures in patients with epilepsy are commonly triggered by sleep deprivation, emotional or physical stress, and menses. Additionally, even slight adjustments in the antiseizure regimen or missing doses of medications may precipitate a recurrent seizure. A specific sensory stimulus, such as flashing lights or a specific smell, may also trigger seizures in epilepsies; these are still considered "unprovoked" when triggered by a process that would not cause a seizure in the patient that does not have epilepsy.

Medically refractory epilepsy (also known as "uncontrolled" or "drug-resistant") refers to patients who are unable to achieve or maintain seizure freedom despite 2 trials of adequately dosed antiseizure regimens. These patients continue to have seizures with a variable baseline frequency of occurrence. There are several definitions for seizure *clusters* reported in the literature: 3 or more seizures in 24 hours, 2 or more seizures in 24 hours, or 2 or more seizures in 6 hours.[3] The timely recognition of seizure clusters allows for prompt administration of seizure abortive measures (at home as instructed by the neurologist or epileptologist, in the pre-hospital, or in the hospital settings). Patients with medically refractory epilepsy presenting with seizure clusters are at a higher risk for status epilepticus.

Uncontrollable seizures, or status epilepticus, are seizures that have reached a prespecified duration according to specific seizure types (see Table 14.1 in Chapter 14) or recur with a frequency that does not allow a patient to return to the baseline neurologic status in between seizures.

Seizures may be provoked by a multitude of insults, such as acute brain injury (e.g., ischemic and hemorrhagic strokes, trauma, meningoencephalitis), toxins, and metabolic derangements. The main cause of status epilepticus and epilepsy in the elderly remains cerebrovascular disease. Patients with diabetes, higher stroke severity, cortical location of infarcts, and thromboembolic mechanisms are at the highest risk for experiencing seizures in the acute phase, with an incidence of up to 5% of all ischemic strokes in some series.[4,5] Nevertheless, the true incidence of seizures in the setting of stroke is difficult to ascertain because studies had variable methods of detection, use of primary seizure prophylaxis, and follow-up duration. Box 88.1 summarizes etiologies of seizures and status epilepticus according to the type of insult or neurologic process. Being familiar with common seizure triggers allows for identifying patients at higher risk for seizures and status epilepticus who may benefit from further diagnostic workup such as neuroimaging, EEG, or neurologic consultation.

When seizures are prolonged and the duration exceeds the respective threshold according to type (convulsive, nonconvulsive, or absence; see Table 14.1 in Chapter 14), they are termed *status epilepticus*. Overall, status epilepticus is associated with significant morbidity and mortality, particularly convulsive generalized status epilepticus. In the United States, reported status epilepticus incidence ranges from 10 to 40 persons per 100,000 annually. In a meta-analysis, the leading cause of status epilepticus globally was acute symptomatic (in close temporal relationship with a brain insult).[6] Overall case fatality rates were 15%; the highest case fatality rates were seen in low- and middle-income countries, refractory status epilepticus, and in the elderly population.

Several different scores exist to predict outcomes in status epilepticus. The Epidemiology based Mortality Score in Status Epilepticus (EMSE; Table 88.1) accounts for etiology of seizures, age, comorbidities, and EEG findings and performs well in predicting mortality and morbidity, but fails to predict responses to therapy satisfactorily.[7]

Anatomy, Physiology, and Pathophysiology

Neuronal cell membranes are stabilized by transmembrane electrochemical gradients and equilibrium among inhibitory neurotransmitters (e.g., GABA) and excitatory neurotransmitters (e.g., glutamate and acetylcholine). Seizures start when the equilibrium across the cell membrane is disrupted by an imbalance between these factors, leading to abnormal electrical discharge of cortical and subcortical neurons. The recruitment of neighboring neurons leads to spreading of this abnormal excitation. It may manifest clinically by propagating clonic activity in adjacent areas in the body following their corresponding topography in the brain (i.e., *Jacksonian March*, when focal motor seizure symptoms spread in a step-wise fashion). If there is involvement of large areas in both hemispheres, thalami, or deeper structures, and of the reticular activating system in the brainstem, impairment in consciousness ensues.

Physiologic mechanisms implicated in seizure termination involve reflex inhibition, hyperpolarization of neurons preventing their depolarization, and neuronal exhaustion, among others. Most drugs used to interrupt seizures act on $GABA_A$ subtype receptors, therefore enhancing inhibitory activity. However, with prolonged seizure activity, $GABA_A$ receptors are sequestered inside the cells and become unresponsive to GABA[8] (and GABA-ergic medications), whereas excitatory *N*-methyl-D-aspartate (NMDA) receptors may be upregulated. This perpetuates an excitatory state and leads to sustained seizure activity, explaining why timely treatment of seizures is of utmost importance.

CLINICAL FEATURES

In caring for patients who may have seized, the first step is to determine whether the event in question was truly a seizure. A common clinical scenario for the emergency clinician is the patient who presents with a history of having had a seizure-like episode, usually involving sudden loss of consciousness and some type of motor activity. Characterizing the episodes with particular attention to the predominant features at onset helps define the seizure type. In Chapter 14, Figure 14.1 depicts the revised expanded classification of seizure types according to their semiology at onset[1] and Table 14.1, the operational definition of status epilepticus according to time domains and seizure types.[9]

Once a seizure has met the criteria for status epilepticus, it can be further subdivided according to response to treatment: refractory status epilepticus when seizures persist despite 2 appropriately dosed antiseizure therapies, or super-refractory status epilepticus when seizures do not entirely resolve despite at least 24 hours of therapeutic coma with anesthetics (including propofol and benzodiazepines) or when seizures recur preventing tapering off anesthetics. Status epilepticus persisting for over 7 days despite appropriate management is termed prolonged and is associated with complications and longer hospital length-of-stay[10] (Table 88.2).

Recently revised definitions of clinical syndromes have been proposed for new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES).[10] NORSE includes patients without a known diagnosis of epilepsy or clear triggers (absent toxic exposure, metabolic derangements, or structural brain injury)

BOX 88.1 Etiologies of Seizures and Status Epilepticus According to Class of Insult/Pathology

Autoimmune
Acute disseminated encephalomyelitis
Antibody-mediated autoimmune and paraneuroplastic encephalitides
CREST, Goodpasture syndrome, and systemic lupus erythematosus
Multiple sclerosis
Rasmussen encephalitis
Thrombotic thrombocytopenic purpura

Cerebrovascular Disease
Acute ischemic stroke
Cavernous and arteriovenous malformations
Cerebral venous thrombosis
Intracerebral hemorrhage
Nontraumatic subarachnoid hemorrhage
Posterior reversible encephalopathy syndrome
Reversible cerebral vasoconstriction syndrome

Dementias
Alzheimer disease
Corticobasal degeneration
Frontotemporal dementia
Vascular dementia

Genetic Syndromes and Structural Anomalies
Focal cortical dysplasia
Hydrocephalus
Inherited metabolic diseases
Mitochondrial diseases
Polymicrogyria
Porphyria
Tuberous sclerosis complex
Wilson disease

Hypoxic-Ischemic Brain Injury
Cardiac arrest

Intracranial Tumor
Dysembryoplastic neuroepithelial tumor
Gangliogliomas
Gliomas
Lymphoma
Meningioma
Metastases
Primitive neuroectodermal tumor

Metabolic Derangements
Acidosis
Elevated blood urea nitrogen
Hyperammonemia
Hyperglycemia
Hypernatremia
Hypocalcemia
Hypoglycemia
Hypomagnesemia
Hyponatremia
Wernicke encephalopathy

Medications and Toxins
Alcohol intoxication and withdrawal
Alkylating agents
Baclofen intoxication and withdrawal
Benzodiazepine and barbiturate withdrawal
Beta-interferons
CAR-T (chimeric antigen receptor T cell therapy)
Carbapenems (imipenem in particular)
Cephalosporin (cefepime in particular)
Cyclosporine
Digoxin
Fentanyl
Heavy metals
Lidocaine
Metronidazole
Mexiletine
Theophylline
Tramadol
Tacrolimus
Subtherapeutic antiseizure drug levels

Systemic Disease
Acute and chronic renal failure
Cirrhosis

Trauma
Blunt or penetrating head injury (skull fracture)
Epidural hematoma
Subarachnoid hemorrhage
Subdural hematoma
Diffuse Axonal Injury

Although this list includes many recognized etiologies for epilepsy and acute symptomatic seizures, several entities were clustered into themes, and less common etiologies were omitted.

presenting with de novo refractory status epilepticus. FIRES is a subcategory of NORSE to specify the subset of patients with a clear prodrome of febrile illness for 24 hours up to 2 weeks prior to status epilepticus presentation; FIRES is common but not exclusive to the pediatric population. Box 88.2 summarizes other status epilepticus classifications according to their semiology, etiology, age, and EEG correlate.[9]

Classifications are important because they often dictate the aggressiveness of treatment. Not all types of status epilepticus warrant seizure suppression with third-tier therapy (therapeutic coma with anesthetics). An example is *epilepsia partialis continua* which, as the name implies, is characterized by continuous focal seizures that are notoriously refractory to antiseizure therapies. These patients learn how to live with ongoing focal clonic activity, and the therapeutic goal is shifted towards minimizing the side effects of medications. In this condition, seizures remain confined to a relatively small cortical region without spreading, which often leads to EEG recordings without epileptiform activity in most cases.

Seizures produce many secondary physiologic derangements that can result in poor outcomes. Epilepsy patients with poorly controlled generalized tonic-clonic seizures are at highest risk of sudden unexpected death in epilepsy (SUDEP), which exceeds the expected death rate in the general population by 24 times, primarily affecting young adults between 15 and 44 years of age.

The potential systemic complications of convulsive status are summarized in Table 88.3.[11,12] Sympathetic stimulation increases body temperature, heart rate, respiratory rate, serum glucose, and lactic acid.

The involvement of the insula, a highly epileptogenic area in which the cortical representation of the heart is also located, may be implicated in tachy- and bradyarrhythmias associated with ictal activity. Ictal asystole is a syndrome implicated in focal epilepsies, particularly of left temporal onset, female sex, and prior history of a heart condition. However, ictal asystole lasting longer than 30 seconds is associated with extra-temporal seizure focus and secondary generalized tonic-clonic seizures.[13]

Prominent autonomic dysregulation and apnea, possibly associated with spreading depolarization in the brainstem, and postictal diffuse suppression of cortical electrical activity have been implicated as potential mechanisms leading to SUDEP. With more prolonged convulsions, hypoglycemia, neurogenic pulmonary edema, skeletal muscle damage, and, rarely, frank rhabdomyolysis may ensue. A rise in the peripheral white blood cell count without an increase in bands is also often seen. Autonomic discharge and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting, tongue biting, and potential airway impairment. Rarely, the force generated by the muscle contractions in these seizures can be strong enough to cause posterior shoulder dislocations or fractures.

TABLE 88.1 Epidemiology-Based Mortality Score in Status Epilepticus (EMSE)[34]

Age	Points	Comorbidity (Score Each Disease)	Points
>80	10	AIDS, metastatic solid tumor	60
71–80	8	Moderate to severe liver disease	30
61–70	7	Moderate to severe renal disease, any tumor (includes lymphoma and leukemia), hemiplegia, diabetes with end-organ damage	20
51–60	5		
41–50	3		
31–40	2	Peripheral vascular disease, connective tissue disease, diabetes, myocardial infarction, cerebrovascular disease, congestive heart failure, dementia, mild liver disease, peptic ulcer disease, chronic pulmonary disease	10
21–30	1		
Score one	____	Score each disease	____
EEG	Points	Etiology	Points
Spontaneous burst suppression	60	Anoxia	65
		Acute central nervous system infection	33
		Acute cerebrovascular disease	26
After status epilepticus ictal discharges	40	Metabolic disorders	22
		Metabolic, sodium imbalance	17
		Brain tumor	16
Lateralized periodic discharges (LPDs)	40	Cryptogenic	12
		Head trauma	12
		Drug overdose	11
Generalized periodic discharges (GPDs)	40	Alcohol abuse	10
		Hydrocephalus	8
		Remote cerebrovascular event or brain injury	7
No LPDs, GPDs, or ictal discharges	0	Multiple sclerosis	5
		Drug withdrawal, reduction, or poor compliance	2
		Central nervous system anomalies	2
Score only worst	____	Score one	____
Total Score = Sum of above scores			

Leitinger M, Holler Y, Kalss G, et al. Epidemiology-based mortality score in status epilepticus (EMSE). *Neurocrit Care*. 2015;22(2):273-282.

TABLE 88.2 Status Epilepticus Nomenclature According to Refractoriness and Duration[10]

Subtype of Status Epilepticus	Refractoriness to Treatment
Refractory (RSE)	Ongoing seizures despite first-line (benzodiazepine) and at least one second-line (appropriately selected parenteral antiseizure drug) therapies. Both first- and second-line therapies must have been adequately dosed to meet this criterion; status epilepticus may have any duration.
Super-Refractory (SRSE)	Ongoing seizures lasting over 24 hours from initiation of third-line therapy (therapeutic coma with anesthetics, regardless of which drug); status epilepticus may have any duration. This includes those that had a partial response at any point, but not completely subsided (recurred after or during attempts to wean anesthetics).
± Prolonged (qualifier for either types: refractory or super-refractory)	Status epilepticus lasting over 7 days despite adequate step-wise escalation of therapy: it may be refractory (no anesthetic trial introduced) or super-refractory (therapeutic trial with anesthetics included).

Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. *Epilepsia*. 2018;59(4):739-744.

BOX 88.2 Status Epilepticus Subclassifications According to Semiology, Etiology, Age Group, and Electroencephalographic Correlate[35]

Semiology

Predominant motor features: convulsive status epilepticus (generalized, focal onset evolving to bilateral convulsive, unknown), myoclonic status epilepticus (with coma, without coma), focal motor status epilepticus (repeated focal motor, epilepsia partialis continua, adversive status, oculoclonic status, ictal paresis), tonic status epilepticus, hyperkinetic status epilepticus

Without prominent motor features (nonconvulsive status epilepticus): with coma, without coma (generalized: typical absence status, atypical absence status, myoclonic absence status; focal: without impairment of consciousness, aphasic status, with impaired consciousness; unknown focal versus generalized: autonomic status)

Etiology

Known or symptomatic: acute, remote, progressive, or status epilepticus in defined electroclinical syndromes

Unknown or cryptogenic

Age

Neonatal (0–30 days)
Infancy (1–24 months)
Childhood (>2–12 years)
Adolescence and adulthood (>12–59 years)
Elderly (+60 years)

Electroencephalographic Characteristics

Location: generalized, lateralized, bilateral independent, or multifocal

Pattern: periodic discharges, rhythmic delta activity, or spike-and-wave/sharp-and-wave

Morphology characterization of discharges according to sharpness, number of phases, amplitude and polarity

Time-related features of patterns according to prevalence, frequency, duration, onset, dynamics, daily burden

Modulation: spontaneous or stimulus-induced

Response to therapy

Leitinger M, Beniczky S, Rohracher A, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus: approach to clinical application. *Epilepsy & Behavior : E&B*. 2015;49:158-163.

Clinical History

Identifying the circumstances surrounding the event, such as possible inciting factors and progression and duration of symptoms, provides important clues regarding whether the episode was a seizure and the likely etiology (a framework of cardinal features of seizures is provided in Chapter 14). The clinician should obtain any history of trauma (either before or during the seizure), alcohol intoxication or abuse, and pregnancy. Although febrile seizures are common in children (see separate discussion of seizures in pediatric patients in Chapter 169), hyperthermia alone as seizure etiology of adults is uncommon, and seizures in the setting of fever are highly suggestive of meningoencephalitis. Immunocompromised patients and those with recent neurosurgical instrumentation with or without hardware (e.g., shunt, drug delivery devices, spinal cord stimulator) are at particularly high risk for infection. Other red flags suggesting acute brain injury is thunderclap and severe headache preceding seizures or sudden neurologic deficits. New or recent changes in medication regimen, and history of comorbidities are also important in both patients with new-onset seizures and epilepsy because they assist in unveiling potential triggers: medications lowering seizure threshold, interacting with antiseizure regimen, or even leading to severe metabolic derangements such as hypoglycemia or hypocalcemia (Table 88.4).

In epilepsy patients, characterizing typical seizure semiology, typical seizure frequency, last known seizure, common precipitating factors, and neurologic baseline provides a meaningful comparison with the current presentation. Noncompliance with the antiseizure regimen is the most common cause for the ED presentation of recurrent seizures. Certain recreational drugs (e.g., cocaine, phencyclidine, ecstasy, and synthetic marijuana) are known to decrease the seizure threshold. Common causes of adult-onset focal seizures in low- and middle-income countries include neurocysticercosis (especially Central and South America) and malaria, both of which should be considered in travelers and immigrants. Finally, investigating potential precipitants (such as sleep deprivation, infection, or new medications, especially those that can lower the seizure threshold or affect antiseizure drug metabolism) is key to managing the patient with a known seizure disorder who has a typical event while on medications. Further details on key historical features are provided in Chapter 14; a stepwise approach to evaluating a patient with suspected seizures in the emergency department is displayed in Figure 14.2.

TABLE 88.3 Potential Systemic Complications Related to Seizures and Status Epilepticus[11,12]

Cardiac and Others	Heme/Musculoskeletal and tegmentum/ Gastrointestinal	Pulmonary	Renal/Acid-Base/ Metabolic	Prolonged Course Complications
Arrhythmias and conduction abnormalities	Dislocation	Airway obstruction	Acute renal failure	Critical illness myopathy or neuropathy
Cardiac arrest	Fracture	Apnea/ hypoventilation	Acidosis: lactic, respiratory	Deep vein thrombosis or pulmonary embolism
Cardiomyopathy	Hepatotoxicity and pancreatitis	Aspiration	Hyperglycemia	Gastrostomy
Cardiac necrosis	Leukocytosis/leukopenia/ thrombocytopenia	Hypoxia	Hyperkalemia	Infection
Hypertension	Rhabdomyolysis	Mucous plugging	Myoglobinuria	Tracheostomy
Thermodysregulation	Life-threatening rash	Pulmonary edema		Skin breakdown and poor wound healing
	Ileus and bowel ischemia			

Sutter R, Dittrich T, Semmlack S, Ruegg S, Marsch S, Kaplan PW. Acute systemic complications of convulsive status epilepticus: a systematic review. *Crit Care Med*. 2018;46(1):138-145; Legriel S, Bresson E, Deye N, et al. Cardiac arrest in patients managed for convulsive status epilepticus: characteristics, predictors, and outcome. *Crit Care Med*. 2018;46(8):e751-e760.

TABLE 88.4 Management of "Special Situations" Seizures in the Emergency Department

Clinical Situation	Agent of Choice	Dosage/Comment
Hyponatremia	Hypertonic (3%) saline	Adults: 100 mL 3% NaCl over 10 min; children: 2 to 5 mL/kg, up to 150 mL/dose 3% NaCl over 20 min
Hypocalcemia	Calcium chloride or gluconate	Sequential ampules until seizures stop
Tricyclic antidepressant overdose	Sodium bicarbonate	Administer 1 to 2 mEq/kg IV bolus; repeat as needed to maintain ECG QRS complex ≤ 100 msec
Salicylate overdose	Sodium bicarbonate; hemodialysis for severe cases	Administer 1 to 2 mEq/kg IV bolus; repeat as needed to maintain a blood pH of 7.4 to 7.5
Isoniazid overdose	Pyridoxine	5 g IV (adult) or 70 mg/kg (pediatric)
Cocaine intoxication	Benzodiazepines	As per idiopathic seizures
Lithium toxicity	Hemodialysis	
Alcohol-associated seizure	Lorazepam	0.05 to 0.10 mg/kg, or fixed doses of 2 to 4 mg for adults
MDMA	Benzodiazepines	Be aware of possible hyperthermia or hyponatremia
Eclampsia	Magnesium sulfate	IV loading dose of 4 to 6 g over 15 to 20 minutes, then 1 to 2 g/h infusion; monitor patients for hyporeflexia; alternatively, lorazepam (Ativan) 4 mg IV over 2 to 5 minutes or diazepam (Valium) 5 to 10 mg IV slowly can be used to terminate the seizure, after which magnesium sulfate is administered

Physical Examination

An accurate set of vital signs is the foundation of any physical examination and may direct the clinician to potential etiologies (e.g., fever suggesting meningoencephalitis, tachycardia and hypertension suggesting sympathomimetic intoxication) and indicate the existence of an ominous intracranial diagnosis (e.g., hypertension and bradycardia suggest herniation syndromes).

If the patient presents actively seizing, observe the specifics of the motor activity and pay close attention to focal findings and asymmetries such as dystonic posturing, clonic or tonic activity, eye deviation, or nystagmus. Apply gentle manual pressure to the limb in an attempt to suppress clonic activity: if suppressible, this suggests nonepileptic spells or movement disorders. Anecdotally, pupils are often reported to be dilated during or after a seizure; persistent mydriasis may reflect anticholinergic or sympathomimetic toxicity. Subtle automatisms, facial myoclonus, and nystagmus following convulsive activity suggest nonconvulsive status epilepticus.

A systematic neurologic exam should be performed including mental status. Postictal patients may be hyperreflexic, have an extensor plantar response, or have a focal motor deficit (e.g., Todd paralysis), all of which generally resolve within one hour of a seizure. Todd paralysis is associated with a high likelihood of an underlying structural cause for the seizure. If it does not quickly resolve, a new structural lesion should be suspected.

Seizures are often associated with injury, and the patient must be evaluated for both soft tissue and skeletal trauma. Head trauma and tongue lacerations are common. Seizure activity can also produce dislocations and fractures. Posterior shoulder dislocations are extremely rare but, when present, should prompt suspicion that a seizure has occurred. Seizure-induced fractures are rare but frequently missed; the humerus, thoracic spine, and femur are most commonly involved. Extremities should be inspected for signs of intravenous drug use and signs of systemic embolism and endocarditis, which may raise suspicion for intoxication, septic strokes or cerebral abscesses. Dysmorphic features and stigmata of neurocutaneous diseases help diagnose epilepsy syndromes, particularly in the pediatric population.

DIFFERENTIAL DIAGNOSIS

Common differential diagnoses to consider when evaluating for seizure are summarized in Chapter 14 and listed in Box 14.2. The history surrounding the circumstances of the event and precipitating factors help distinguish seizures from their mimics. However, as a general rule, no single clinical feature or diagnostic modality is 100% confirmatory of the diagnosis of seizures.

Commonly regarded features suggestive of seizures include postictal disorientation and amnesia, lateral tongue biting, cyanosis during the event, auras (e.g., déjà vu or jamais vu, which are focal nonconvulsive seizures), non-suppressible rhythmic limb shaking, and dystonic posturing. Conversely, diaphoresis, palpitations, nausea, and dizziness preceding seizures may suggest arrhythmias and transient cerebral hypoperfusion.

Convulsive syncope is characterized by some component of motor activity, most commonly involving tonic extension of the trunk or myoclonic jerks of the extremities, at times associated with bradycardia. As cerebral perfusion is restored, abnormal muscle activity ceases, and there is no postictal period; these events are usually not associated with tongue biting, but urinary incontinence may occur.

Nonepileptic spells, or psychogenic seizures/attacks, are paroxysmal events that may be misdiagnosed as a seizure or as status epilepticus. Psychogenic seizures are rarely caused by malingering but are more commonly a psychiatric disorder (e.g., a conversion disorder). Avoidance of eye contact with the examiner, asynchronous, stop-and-go clonic activity, forward pelvic thrusting, horizontal head movements, maintaining eyes closed during the spell, and relative short postictal confusion are findings consistent with nonepileptic spells. Spells lasting 5 minutes or longer were 24 times more likely to be nonepileptic than ictal in a video EEG study.[14] Approximately 10% of subjects in clinical trials of convulsive status epilepticus are ultimately diagnosed with nonepileptic spells. Given the characteristically long duration and overt convulsions in nonepileptic spells, these patients are more likely to receive higher cumulative doses of benzodiazepines, and up to 15% result in intubation and mechanical ventilation in the emergency department.[15] Lack of leukocytosis and metabolic acidosis despite prolonged events may also help differentiate nonepileptic spells from seizures. Video EEG monitoring capturing the spell and documenting an absence of an associated electrographic ictal pattern is required to establish the diagnosis of nonepileptic spells.

DIAGNOSTIC TESTING

A thorough history and physical examination primarily directs the evaluation and management and may obviate the need for extensive

BOX 88.3 Proposed Seizure Triggering Thresholds for Metabolic Derangements

Serum Glucose: <36 mg/dl (2.0 mm); >450 mg/dl (25 mM) associated with ketoacidosis
Serum Sodium: <115 mg/dl (<5 mm)
Serum Calcium: <5.0 mg/dl (<1.2 mm)
Serum Magnesium: <0.8 mg/dl (<0.3 mm)
Blood Urea Nitrogen: >100 mg/dl (>35.7 mM)
Serum Creatinine: >10.0 mg/dl (>884 μM)

diagnostic testing. Due to the challenges of obtaining an accurate history in an actively seizing or postictal patient, vigilance in seeking collateral information is warranted from witnesses,[16] relatives, paramedics, medical alert bracelets, old medical records, and medication lists or containers. These data will often provide critical elements in the patient assessment.

Laboratory Studies

If a patient with a new-onset seizure has no significant comorbid disease and a normal examination (including mental status), the likelihood of an electrolyte disorder is extremely low; thus, extensive metabolic testing in patients who have returned to a normal baseline after a first-time seizure is not indicated.[17] Patients with persistent alteration of mental status, those in status epilepticus, and those who have fever or new neurologic deficit require extensive diagnostic testing, including serum glucose, electrolytes (i.e., sodium, magnesium, calcium), urea nitrogen, creatinine, complete blood count, pregnancy tests in women of childbearing age, antiseizure drug levels, AST, ALT, and drugs-of-abuse screening. Box 88.3 lists proposed cutoff values for metabolic derangements lowering the seizure threshold. Blood alcohol level and toxicology screening should be considered in patients with first-time seizures, although there is no evidence that such testing changes outcomes. A positive drug-of-abuse screen does not prove causation, and the patient may still require further evaluation with EEG and neuroimaging. Seizure due to alcohol intoxication or withdrawal is a diagnosis of exclusion because alcoholics are at increased risk for electrolyte abnormalities and traumatic injuries. Chapter 14 summarizes key laboratory diagnostics in patients presenting with seizures.

Radiology

Neuroimaging is recommended in patients with a first-time seizure, though in select patients who have a normal examination, have returned to baseline, do not have headaches, and have access to follow-up care, imaging can be obtained as an outpatient. Patients with a history of epilepsy and who have returned to baseline do not need neuroimaging in the emergency department. Urgent neuroimaging is indicated in cases with status epilepticus, focal neurologic deficits, prominent headache, known or suspected trauma, history of malignancy or immunocompromised state, and use of systemic anticoagulation. Additionally, elderly patients and those with neurocutaneous syndromes are at higher risk for structural brain abnormalities. Box 14.1 summarizes factors that should prompt consideration for neuroimaging.

Computed tomography (CT) has the advantages of being widely available and requiring shorter imaging acquisition times. However, other modalities such as magnetic resonance imaging (MRI) and CT perfusion may provide additional information (see Chapter 14). Figure 88.1 depicts the typical diffusion restriction corresponding to a seizure focus in an MRI of a patient with refractory focal status epilepticus.

Special Procedures and Tests

Lumbar puncture is indicated in patients with fever, severe headache, persistent altered mental status, or immunocompromise, unless a clear alternative diagnosis is present. Obtaining an EEG is often logistically challenging in the ED, but can be of high yield for patients whose diagnosis is unclear or who remain altered. EEG assists in the diagnosis of both epilepsy and nonepileptic spells, the detection of nonconvulsive seizures, and status epilepticus in those with altered mental status. Moreover, EEG guides management in monitoring the duration and depth of therapeutic coma management in refractory status epilepticus.

MANAGEMENT

Stabilization and Empirical Therapy

The initial approach to a patient with seizures centers on the characterization of the nature of events (seizures versus not seizures and underlying etiology), implementing supportive measures, and identifying critical and emergent diagnoses, listed in Box 14.3 in Chapter 14. The timely administration of adequate doses of first-line therapy (i.e., lorazepam 0.1 mg/kg [max 4 mg/dose] or midazolam 0.2 mg/kg [max 10 mg/dose]) remains the cornerstone of empirical abortive seizure therapy.[18,19] In status epilepticus, the use of benzodiazepines as the first line of treatment and a higher cumulative dose of antiseizure medications were associated with quicker cessation of status epilepticus.[20] Approximately 1 in 3 patients with status epilepticus require endotracheal intubation.[21] Proposed algorithms for the initial assessment, support, and implementation of empiric therapy of seizures and status epilepticus are displayed in Figure 14.2 and Figure 14.3, and most commonly used agents in first-, second- and third-line therapies are included in Table 14.2.

Definitive Management

While the empirical therapy centers on benzodiazepines as first-line therapy for most seizures that warrant abortive drugs, certain underlying pathologies warrant specific treatments; these are summarized in Table 88.3 which also provides specific dose considerations.

SPECIAL CASES

Alcohol-Related Seizures

Alcohol-withdrawal seizures account for a substantial portion of alcohol-related seizures. Alcohol suppresses glutamate-mediated excitatory tone while enhancing the inhibitory GABA-ergic receptors; in chronic use, there is upregulation of excitatory receptors. The interruption of alcohol use leads to excess excitation and a sympathomimetic response characterized by tachycardia, hypertension, disorientation, agitation, and seizures (See Chapter 137).

While seizures are witnessed in the setting of withdrawal, clinical findings cannot predict who is likely to have a recurrent seizure in the ED. Signs of alcohol withdrawal (tachycardia, confusion, or tremors) do not necessarily correlate with the likelihood of seizures. Although withdrawal seizures are an important etiology, patients with a history of alcohol abuse and dependence have several other potential risk factors for seizures, including increased incidence of traumatic brain injury, hypomagnesemia related to malnutrition, hyponatremia and hyperammonemia as a consequence of decompensated cirrhosis, hypoxic-anoxic events (i.e., aspiration) and co-ingestion of other toxins. In over half of the cases, alcohol-related seizures occur as a result of concomitant factors, such as epilepsy, structural brain abnormalities, and recreational drugs.

A first-time "withdrawal" seizure must be evaluated as any first-time seizure. Other conditions must be ruled out by history, physical examination, and diagnostic testing, including electrolytes, glucose,

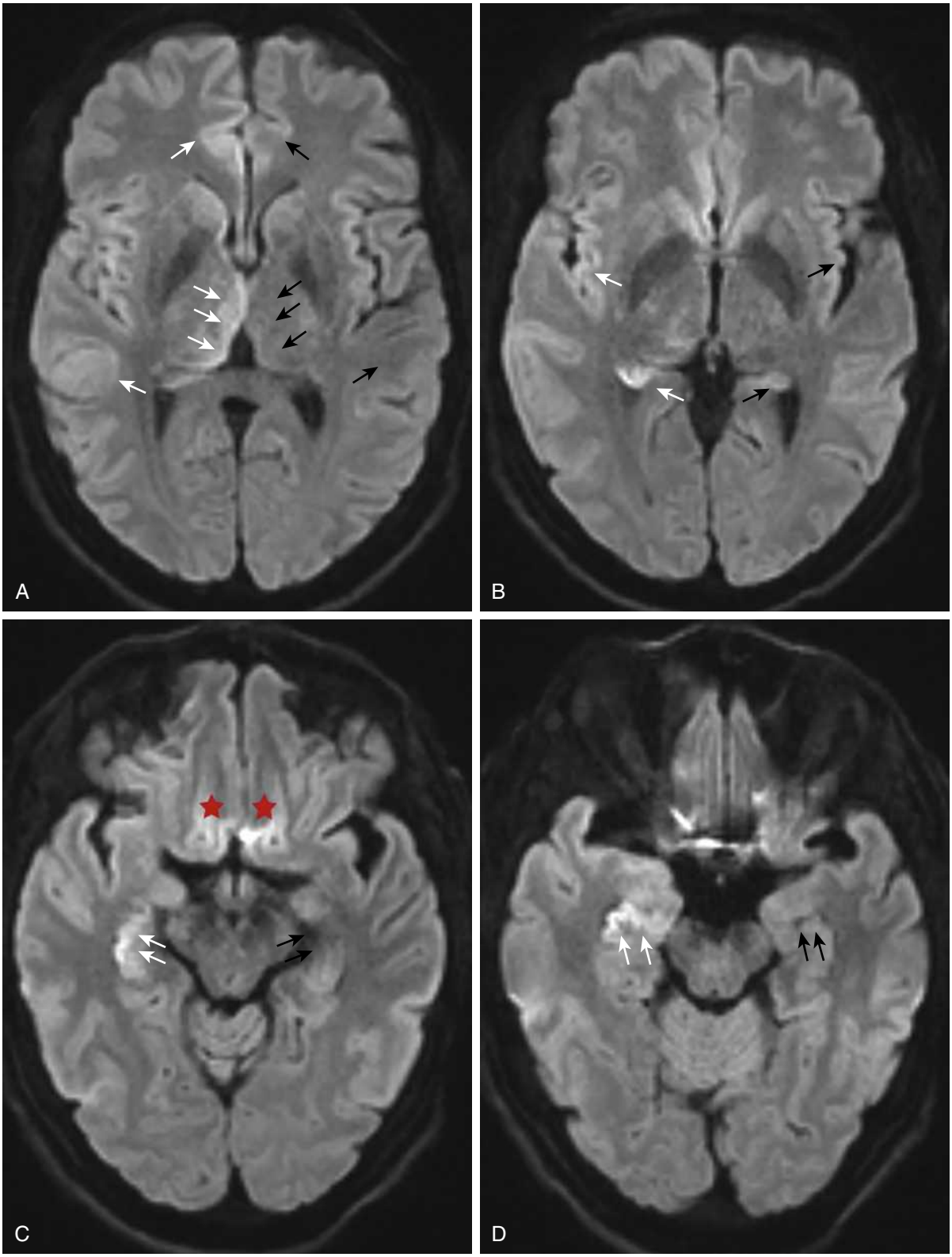

Fig. 88.1 Magnetic Resonance Imaging of Cortical Changes from Prolonged Seizures. Diffusion-weighted imaging (DWI) sequence of magnetic resonance imaging (MRI) of the brain of a 55-year-old woman with prolonged refractory status epilepticus from autoimmune etiology demonstrating restriction of diffusion (hyperintensities) in the areas of seizure involvement. From anterior to posterior, *white arrows* contrast the high signal in involved areas on the right hemisphere with the *black arrows* demarking spared areas in the contralateral left hemisphere. (A) Mesial frontal lobes, thalami, superior temporal cortex; (B) insular cortices and hippocampi; (C & D) hippocampi. *Red stars* depict artifactual symmetric hyperintensities in the inferior frontal lobes.

CT head, and lumbar puncture if indicated, particularly if fever is present. Testing results in an increased diagnostic yield in this population and is likely to affect management. After excluding other etiologies, the diagnosis of alcohol-withdrawal seizure is based on a history of recurrent events temporally related to ceasing or decreasing alcohol intake. Importantly, the presentation of alcohol withdrawal is frequently preceded by an illness or injury, leading to a decrease in alcohol consumption. A thorough history should include the precipitating reason for abstinence as well as a comprehensive assessment for concomitant illness if the cessation was not intentional. Alcohol-withdrawal seizures are usually generalized and occur between 6 and 48 hours after cessation of drinking. Judicious monitoring of these time intervals is warranted in scenarios where patients with a history of alcohol dependence are anticipated to have prolonged stays in the emergency department or are to be admitted.

Benzodiazepines are the treatment of choice in alcohol-withdrawal seizures, given the GABA-ergic pathway modulation, reducing the signs and symptoms of alcohol withdrawal and increasing the seizure threshold. All benzodiazepines appear to be equally efficacious in terminating an alcohol-withdrawal seizure; however, lorazepam is the only benzodiazepine that has been shown to decrease the incidence of seizure recurrence and decrease the need for hospitalization with a number needed to treat of 5 to prevent additional seizures in the subsequent 6 hours. Patients requiring 40 mg/h of diazepam equivalents are considered to have benzodiazepine-resistant alcohol withdrawal syndrome.[22] Adjunctive therapy such as phenobarbital[22] and ketamine (infusions ranging from 0.012 to 1.6 mg/kg/h) are potential alternatives in such cases.[23] The placement of a definitive airway may be considered in refractory withdrawal seizures where repeated intravenous bolus or infusion dosing is anticipated to control symptoms.

Seizures Related to Other Toxins

Other toxins may lower the seizure threshold by disrupting the balance between excitatory and inhibitory neuronal transmission. Treatment is supportive and relies on the use of benzodiazepines as first-line therapy in most cases. Cases of toxin-induced refractory status epilepticus pose a particular challenge because the mechanism of status epilepticus may be different from status epilepticus with other causes. Some toxins (e.g., isoniazid) cause depletion of GABA neurotransmitter. Some of the typical antiseizure medications act by sensitizing the GABA receptor, making them less effective when GABA is depleted. In these cases, early administration of pyridoxine may be advantageous because it replenishes GABA in the brain. As with alcohol-induced seizures, phenytoin is ineffective for most drug-induced seizures. In some cases, such as in theophylline or tricyclic overdose, it may be harmful due to the increased risk of cardiac toxicity given the sodium channel antagonism of phenytoin and other antiseizure drugs (Fig. 88.2).

Post-Traumatic Seizures

Post-traumatic seizures are the hallmark of acute symptomatic seizures related to acute brain injury. Early post-traumatic seizures occur within the first week, with over 50% occurring within the first 24 hours. For primary seizure prophylaxis, antiseizure drugs may be initiated in the absence of seizures on presentation following acute brain injury

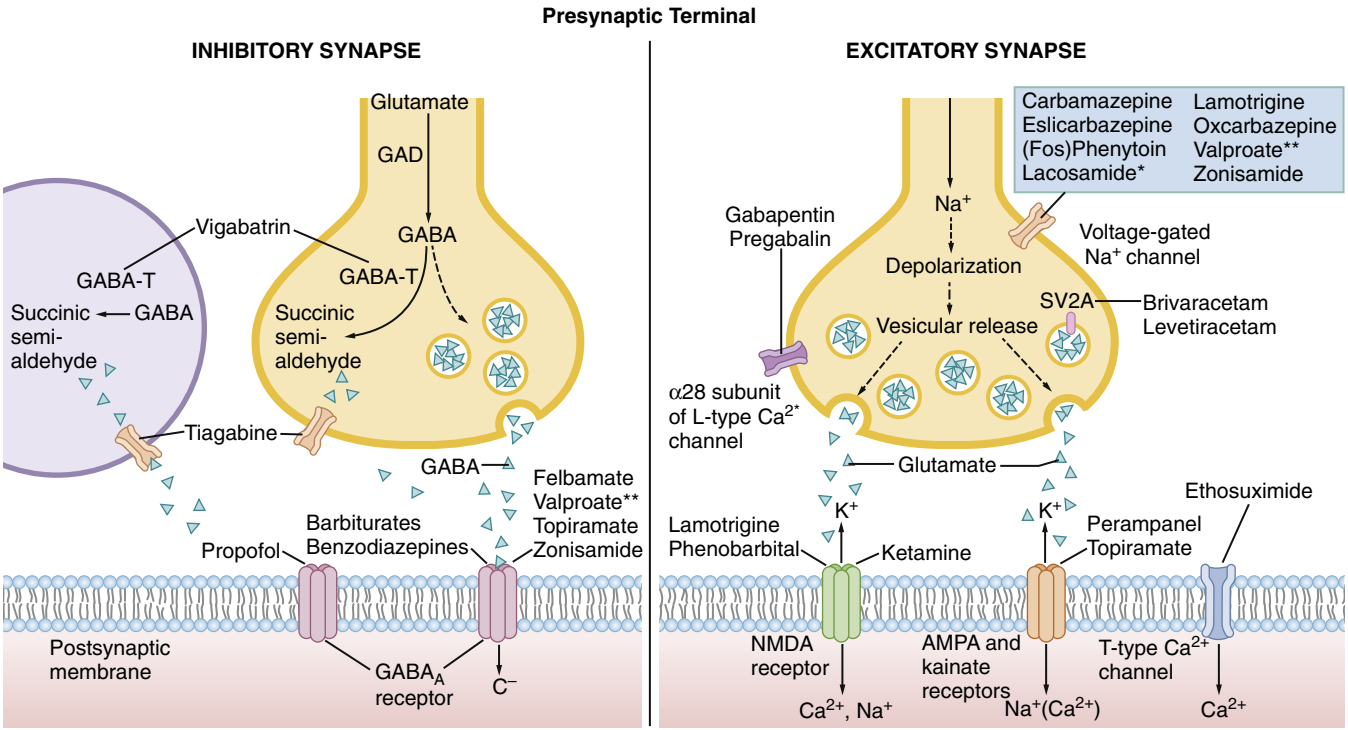

Fig. 88.2 Schematic Display Illustrating the Action Targets of Most Commonly Used Antiseizure Medications. *Lacosamide acts in Na^+ channels by enhancing the slow inactivation of voltage-gated Na^+ channels; other antiseizure drugs that target Na^+ channels act by enhancing their fast inactivation. **Valproic acid (valproate) is considered a broad-spectrum antiseizure drug because it acts in both inhibitory and excitatory pathways. The enzyme GAD is responsible for catalyzing the decarboxylation of glutamate into GABA. *AMPA*, Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; *GABA*, gamma-aminobutyric acid; *GABA-T*, GABA transaminase; *GAD*, glutamic acid decarboxylase; *GAT1*, GABA transporter; *NMDA*, *N*-methyl-D-aspartate; *SV2A*, synaptic vesicle glycoprotein 2A. (Adapted from Morris M, Owusu K, Maciel CB. Status Epilepticus. In: Rabinstein A, ed. *Neurological Emergencies: A Practical Approach*. Vol 1. 1 ed. Springer: Switzerland; 2020:15 47.)

(e.g., traumatic brain injury, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage). Guidelines recommend 7 days in traumatic brain injury[24] and short-term therapy in subarachnoid hemorrhage. Although secondary prophylaxis helps reduce the risk of seizures during the subacute phase following traumatic brain injury, it fails to impact the risk of late seizures (or localization-related epilepsy).

Seizures in Pregnancy

Seizures in pregnancy are classified as one of three types: (1) those that occur in epileptic patients who are also pregnant, (2) new-onset seizures in pregnant patients, and (3) seizures that occur in the setting of eclampsia. Among patients with a history of seizure disorders, factors that may lower the seizure threshold in women who are pregnant include noncompliance, sleep deprivation, nausea and vomiting, or an increase in drug clearance resulting in subtherapeutic levels of antiseizure drugs—in particular, lamotrigine, phenytoin, carbamazepine, levetiracetam, and topiramate.[25] Additionally, pregnant patients with epilepsy commonly undergo adjustments in antiseizure regimens because several drugs are known for their teratogenic potential; these adjustments may lead to breakthrough seizures in otherwise well-controlled epilepsies. Overall, there is not an increased risk of status epilepticus during pregnancy.

Although few data guide the use of antiepileptic drugs for status epilepticus during pregnancy, the risks to the fetus from status epilepticus–related hypoxia and acidosis are greater than the potential teratogenicity of anticonvulsant medications. Therefore, patients who are actively seizing should be managed as the nonpregnant patient. In patients who are more than 24 weeks pregnant, fetal monitoring during and after a seizure should be arranged.

Pregnant patients with noneclamptic new-onset seizures should be worked up as any new-onset seizure patient, with a metabolic profile, EEG, and head CT scan with appropriate abdominal shielding. Precipitating etiologies, such as infections and drug toxicities, should also be investigated. If no source is identified, anticonvulsants should be withheld, and the patient referred for close follow-up. Cortical vein thrombosis should be on the differential for pregnant patients who present with headaches and focal seizures, given the relative prothrombotic state of pregnancy. Eclampsia is a major consideration in pregnant patients of at least 20 weeks' gestation who present with new-onset seizures. The pathophysiology may be due to disruption of cerebral autoregulation and resulting hyperperfusion and edema, similar to posterior reversible encephalopathy syndrome (PRES). Generalized seizures in pregnant women are typically preceded by preeclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets), or hypertension.

Postpartum eclampsia represents 25% of eclamptic seizures, and importantly can occur up to 8 weeks after delivery without preceding preeclampsia or hypertension. Magnesium is the therapy of choice to treat acute eclamptic seizures and prevent a recurrence. It is more effective and has a better safety profile than phenytoin in preventing recurrence of convulsions and maternal death. Magnesium sulfate is also associated with benefits for the baby, including fewer admissions to the neonatal intensive care unit. Magnesium administration should not be delayed while awaiting definitive results when evaluating first-time seizures in a pregnant woman. An in-depth discussion of eclampsia can be found in Chapter 174.

First-Time Seizures

Adult patients with first-time unprovoked seizures may not have epilepsy, but should be informed that the risk of recurrence is highest in the subsequent 2 years, ranging from 21% to 45%,[26] especially in patients with prior brain insults such as trauma and stroke, those with epileptiform findings on EEG and abnormal neuroimaging, and nocturnal type of seizures. Starting secondary seizure prophylaxis reduces seizure recurrence in the initial 2 years; however, a careful risk-benefit assessment is warranted because there are conflicting data on the impact of antiseizure medicines on quality of life due to potential side effects.[26,27,28] Thus, starting an antiseizure regimen routinely in the emergency department is not recommended without input from a specialist and an individualized plan.

In children, the recurrence risk is much higher, particularly in those younger than 3 years.[29] One in three patients with newly diagnosed epilepsy remains untreated up to 3 years after diagnosis in the United States; this gap between diagnosis and adequate therapy may increase the risk of medical events and increase health care resource utilization.[30] Further, of those initiated in an antiseizure regimen, one-third discontinue treatment in the initial year.[31] The establishment of a reliable plan for follow-up care with a primary physician or neurologist is essential in patients with epilepsy.

Breakthrough Seizures

Patients with epilepsy presenting with breakthrough seizures should be evaluated for subtherapeutic levels whenever possible, as noncompliance and adjustments in regimens are common triggers. Table 88.5 includes reference levels for commonly used antiseizure drugs and suggested empiric reloading doses. A general formula for supplementing bolus of phenytoin is:

$$(\text{target total phenytoin level} - \text{current total corrected phenytoin level}) \times (\text{weight in Kg} \times 0.8).$$

A similar formula is available for valproic acid, and the volume of distribution is adjusted:

$$(\text{target total valproic acid level} - \text{current total valproic acid}) \times (\text{weight in Kg} \times 0.2).$$

Figure 88.2 includes a schematic display illustrating the action targets of most commonly used antiseizure medications.

Post-Anoxic Seizures

Post-anoxic seizures and status epilepticus are common after cardiac arrest, occurring in up to one-third of patients who remain unconscious after return of spontaneous circulation (ROSC). In the past, post-anoxic status epilepticus was associated with nearly 100% mortality, but immediate and aggressive seizure abortive measures may improve outcomes in select cases. Patients with a higher chance for recovery include those with the presence of brainstem reflexes, preserved median nerve somatosensory evoked potentials, and preserved EEG background reactivity to external stimuli.[32] In patients treated with targeted temperature management, seizures may occur at any time after ROSC, which should prompt early continuous EEG monitoring or repeated 30-minute EEG studies. No standardized antiseizure treatment has been proven beneficial in this population, and therapeutic algorithms are largely extrapolated from convulsive status epilepticus guidelines. Post-ROSC myoclonus may occur and requires EEG monitoring for an accurate diagnosis.

Nonconvulsive Status Epilepticus

The treatment of nonconvulsive status epilepticus should be individualized according to the risk of additional brain injury, extent of brain area involved by seizures, etiology of seizures, and comorbidities. No

TABLE 88.5 Loading Dose Route of Administration for Antiepileptic Drugs When Resuming Treatment in the Emergency Department

Drug	Loading Dose, Route, Therapeutic Range	Potential Adverse Effects
Carbamazepine	8 mg/kg oral suspension, single oral load Therapeutic level 4–12 μg/mL IV formulation recent; not widely available	Drowsiness, nausea, dizziness, nystagmus
Fosphenytoin	5–20 PE/kg depending on level IV at maximum rate of 150 PE/min; can also give IM Free level target ≈1.5 μg/mL; adjusted total level 15-20 μg/mL	Hypotension, bradycardia, nystagmus, dizziness, drowsiness
Gabapentin	900 mg/day oral at 300 mg tid for 3 days IV not available	Somnolence and fatigue, dizziness, myoclonus Uncommonly used as antiseizure regimen.
Lacosamide	200–400 mg IV or PO	Dizziness, somnolence, brady- or tachyarrhythmias
Levetiracetam	1000–2000 mg IV or PO	Somnolence or irritability. Usually well tolerated.
Oxcarbazepine	150–450 mg PO, single oral load IV formulation not available	Drowsiness, nausea, dizziness
Phenobarbital	15–20 mg/kg, IV or PO Therapeutic level 10–30 μg/mL	Drowsiness, sedation, hypotension
Phenytoin	5–20 mg/kg depending on level, IV or PO; if IV, infusion no faster than 50 mg/min Free level target ≈1.5 μg/mL; adjusted total level 15–20 μg/mL	Drowsiness, nausea, dizziness, nystagmus IV: Hypotension, bradyarrhythmias, extravasation injuries
Valproate	20–40 mg/kg depending on level, IV or PO Free level target 5–15 μg/mL; total level 50–100 μg/mL	Local irritation, thrombocytopenia, transaminitis, hyperammonemia

IM, Intramuscular; *IV*, intravenous; *PE*, phenytoin sodium equivalents; *PO*, by mouth
Medications were listed in alphabetic order; agent selection should be individualized.
Adapted from: Huff JS, Melnick ER, Tomaszewski CA, Thiessen ME, Jagoda AS, Fesmire FM. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures. *Ann Emerg Med.* 2014;63(4):437-447.e415; and Morris M, Owusu K, Maciel CB. Status epilepticus. In: Rabinstein A, ed. *Neurological Emergencies: A Practical Approach*. Vol 1. 1 ed: Springer: Switzerland; 2020:15-47.

specific guidelines address nonconvulsive status epilepticus, and treatment algorithms are extrapolated from convulsive status epilepticus literature. Nonconvulsive seizures and epileptiform patterns bordering nonconvulsive status epilepticus are associated with metabolic crisis in the acutely injured brain. The threshold for starting third-tier medications (anesthetic coma) should be ascertained based on the perceived risk-benefit assessment for each patient. For example, an older patient with focal refractory nonconvulsive status epilepticus and sepsis is not the ideal candidate for pentobarbital or high-dose midazolam, because the morbidity associated with this treatment may surpass the evidence justifying its benefits.

Inflammation-Related Seizures

Inflammation-related seizures and status epilepticus comprise a heterogeneous group of epilepsies that may be triggered by an infection, tumor (i.e., paraneoplastic syndrome), or idiopathic autoimmune response. In paraneoplastic and autoimmune cases, seizures tend to be refractory to conventional antiseizure therapies, and the role of immunotherapy has been increasingly recognized. High-dose methylprednisolone, intravenous immunoglobulin, rituximab, plasma exchange, cyclophosphamide, and more recently tocilizumab, are potential rescue therapies that have been reported with variable degrees of success. Immunotherapy for seizures and status epilepticus requires coordination of care with multiple specialties for most cases, such as hematology, neurology, and rheumatology.

DISPOSITION

Patients with status epilepticus and those with critical diagnoses require admission for continued monitoring for complications and response to therapy. Admission to the intensive or neurocritical care unit, when available, is preferred in patients who require therapeutic coma with anesthetic agents. Disposition plans are less straightforward in other scenarios, including those presenting after a first-time seizure. The best predictor of seizure recurrence is the causative etiology combined with EEG findings. This information often requires modalities that are not routinely available in the ED, and there are few ED-based studies to direct disposition. At present, there is insufficient evidence to guide the decision pertaining to admission. We recommend this decision be tailored to the patient and shared decision making be employed, taking into consideration the patient's access to follow-up care and social risk factors (e.g., alcohol use disorder or lack of health insurance). Patients with comorbidities (including those older than 60 years old), known cardiovascular disease, history of cancer, or history of immunocompromise, should be considered for admission to the hospital. Patients with medically refractory epilepsies who live in assisted care facilities are often best served by being discharged back to the facility if they have returned to their baseline following breakthrough seizures.

Patients and their families or caregivers should be counseled on basic safety measures to prevent complications during seizures. For example, patients should be advised to avoid swimming or cycling following a seizure, at least until they have been reassessed by their neurologist and their antiepileptic therapy optimized if needed. The need for a "medical alert" bracelet or other medical condition identifier should be considered, and state-specific regulations should be followed. A crucial point for seizure patients is education against driving. Although evidence remains controversial on this issue, there is general agreement that uncontrolled epileptic patients who drive are at risk for a motor vehicle collision, with potential injury to themselves and others. For this reason, most states do not allow these patients to drive unless they have been seizure-free on medications for at least 6 months to 1 year. Although physicians are required to report patients

with seizures to driving authorities in several states, mandatory reporting has not been proven to reduce the risk of motor vehicle crashes in patients with epilepsy.

Even a single seizure can induce an array of physical and psychosocial challenges that can affect the quality of life of the patient and caregivers. The psychological and social implications of the new diagnosis of a seizure disorder for the patient can be profound. Fear of seizures and stigmatization are common; employability and insurability may be adversely affected. Emergency clinicians may consider coordination with social work and the referral of patients with seizures to counseling and community-based local epilepsy support groups.

The references for this chapter can be found online by accessing ExpertConsult.com.

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CHAPTER 88: QUESTIONS AND ANSWERS

1. Which of the following statements regarding the pathophysiology of seizures is *true?*

a. During a seizure, prompt loss of consciousness implies a cortical focus.

b. Generalized seizures involve abnormal electrical activity in one hemisphere.

c. Regarding seizure activity, acetylcholine is inhibitory.

d. The clinical seizure activity typically reflects the brain focus of initiation.

Answer: D. Clinical seizure activity typically reflects the site of seizure origin. Generalized seizures involve both brain hemispheres. Acetylcholine is an excitatory neurotransmitter, and GABA is inhibitory. Prompt loss of consciousness with a seizure implies a subcortical focus involving the reticular activating system.

2. Which of the following statements regarding epilepsy is *true?*

a. Electrolyte disturbances are the most common cause of recurrent seizures in epileptic patients.

b. Epilepsy is a condition of recurrent provoked seizures.

CHAPTER 88: QUESTIONS AND ANSWERS—cont'd

c. Epileptic seizures are always generalized tonic-clonic.
d. Epileptic seizures can be triggered by smells or lack of sleep.

Answer: D. Epilepsy is a condition of recurrent, *unprovoked* seizures. Idiopathic epilepsy almost always starts in childhood. Medication noncompliance is the most common cause of recurrent seizures in epileptic patients. Epileptic seizures can be partial seizures. Some patients with epilepsy have seizures triggered by certain specific sensory stimuli, with flashing lights being the most well-known of these.

3. Which of the following factors does not put patients at risk for seizures?
   a. Acute stroke
   b. Chronic stroke-related lesions
   c. Hyperkalemia
   d. Hypomagnesemia

Answer: C. Indwelling intracranial shunts and other lesions, and hypomagnesemia (as seen in malnourished alcohol-dependent patients) are all risk factors for seizures. Stroke is one of the most common causes of seizures in the elderly. Seizures occurring acutely with a stroke are often partial and reflect the affected brain area, whereas those that occur chronically are often generalized. Hyperkalemia does not cause seizures unless it precipitates hypotension and consequent hypoperfusion of the brain.

4. Which of the following statements regarding patients presenting with first-time seizures is *true?*
   a. All patients should have basic serum electrolyte testing.
   b. All patients should receive a loading dose of an antiepileptic drug and a prescription for an oral regimen prior to discharge.
   c. Nondiabetic patients do not need to have serum glucose checked if their mental status returns to normal.
   d. Persistent altered mental status is an indication for a lumbar puncture.

Answer: D. Persistent altered mental status should trigger consideration of a lumbar puncture, serum glucose, and an electroencephalogram (EEG) among other testing. Non-contrast CT of the head is relatively high-yield in first-time seizure patients, and most guidelines recommend performing one. Patients with no comorbidities who return to baseline mental status do not need broad-based electrolyte testing, but hypoglycemia is a common cause of seizures even in nondiabetic patients and should be routinely tested for in first-time seizure patients. Initiation of antiepileptic drugs in the emergency department (ED) for first-time seizure patients without a known structural brain lesion may do more harm than good.

5. A 23-year-old woman is brought to the emergency department (ED) for a prolonged seizure. By emergency medical service (EMS) report, the patient has no past medical history and no history of seizures. Paramedics report tonic-clonic activity for approximately 15 minutes, refractory to diazepam 5 mg intravenously in the ambulance. Upon arrival to the ED, the patient's seizure activity abruptly ceases, and she lucidly responds to the history and physical examination. She is symptom free. What would be the most appropriate intervention?
   a. A trial of oral phenytoin after an intravenous (IV) loading dose in the ED
   b. Confrontation
   c. Neurology referral for electroencephalogram (EEG) and consultation
   d. Psychiatric consultation

Answer: D. No clinical criteria are 100% specific for the diagnosis of nonepileptic activity. Seizures and nonepileptic activity may coexist. For many patients, these episodes may not be deliberate. The most prudent course of action would be to treat them as possible ictus and refer to a neurologist. Initiation of antiepileptic drugs in the ED is not indicated in first-time seizures of healthy patients who return to normal.

89

Headache Disorders

Benjamin W. Friedman

KEY CONCEPTS

- The goals of headache evaluation in the ED are (1) to distinguish between benign primary headache disorders and potentially life-threatening secondary causes of headache and (2) to treat the headache pain effectively and rapidly without causing undue side effects.
- Patients with the following headache presentations are at risk for serious underlying disease: sudden explosive headache; new-onset headache after the age of 50 years; headache associated with papilledema, alteration in or loss of consciousness, or focal neurologic symptoms; subacute headache with increasing frequency or severity; headache associated with fever, cancer, or immunosuppression; and headache triggered by exertion, sexual activity, or Valsalva maneuver.
- The need for diagnostic studies is dictated by the suspected secondary cause of headache.
- Antidopaminergic agents, such as metoclopramide or prochlorperazine, are first-line therapy for migraine.
- Opioids are not first-line therapy for the primary headaches.
- Patients with migraine treated in the ED require a discharge "rescue plan" if the headache recurs.
- High-flow oxygen will terminate the majority of cluster headaches.
- The differential diagnosis of sudden severe headache includes subarachnoid hemorrhage, cerebral venous thrombosis, cervical artery dissection, and idiopathic intracranial hypertension.
- Cerebral venous thrombosis should be suspected in women who have a new type of headache and are pregnant or on birth control pills.
- Carotid artery dissection may cause headache, ptosis, and miosis.
- Patients with post-traumatic headache should only be imaged if they have high-risk features on the Canadian CT Head rule.

Headache is divided into primary and secondary disorders. *Primary headache disorders* include migraine, cluster, and tension-type headaches, and represent the majority of headaches seen in clinical emergency practice. *Secondary headache disorders* include a variety of organic illnesses in which head pain is a symptom of an identifiable, distinct pathologic process. To facilitate a standardized approach to headache management, the International Headache Society published a classification system and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain.[1] This comprehensive and widely accepted system includes 14 major categories of headache disorders and uses specific operational diagnostic criteria to define each headache type (Box 89.1). Most patients presenting to an ED with headache have a benign process requiring only symptomatic treatment and referral. The challenge for the emergency clinician is to identify the very small subset of patients who have headache as a symptom of a serious or potentially life-threatening disease.

PRIMARY HEADACHE DISORDERS

Migraine Headache

Principles

Migraine is a common, chronic, sometimes incapacitating neurovascular disease characterized by recurrent attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura causing visual, sensory, motor, or other neurologic symptoms. It is a primary headache disorder with a genetic basis.

Migraine is a common disorder; attacks typically begin in the second decade of life and peak in prevalence in the fourth decade, affecting about 1 of 4 women and 1 of 12 men. There is no gender difference in the prevalence of migraine in children. After menopause, the prevalence of migraine among women decreases.

Historically, migraine headaches were considered to be vascular in origin. However, this hypothesis is no longer tenable as alterations in cerebral blood flow do not correlate with the various phases of the headache attack or vascular territories and do not explain features of an acute migraine, such as premonitory mood disturbances, nausea, and osmophobia (aversion to odors). Rather, vascular changes are now thought to be an epiphenomenon to what is a primary neurologic event. Abnormal trigeminal nerve and thalamic activity, possibly triggered by a sterile neuropeptide-induced inflammatory process, leads to activity and sensitization of higher order neurons in the brainstem and thalamus. Descending modulation is likely to be compromised as well. It is not yet known what initiates the pathophysiologic process that leads to a migraine attack. Migraine is commonly thought of in two major categories: (1) migraine without aura, which accounts for approximately 75% of all cases (Box 89.2); and (2) migraine with aura, which has specific reversible neurologic symptoms that precede the actual headache (Box 89.3). Cortical spreading depression, a neuroelectrical event characterized by a slow wave of depolarization, is the mechanism behind the symptom of migraine aura.

Clinical Features

Migraine is by definition a chronic and recurrent disease. The headache, characteristically, is unilateral, pulsating in quality, moderate to severe in intensity, and exacerbated by routine activities. The side of the headache can vary with individual attacks, and the headache may be bilateral in 40% of patients. The onset usually is gradual, and the attacks typically last 4 to 72 hours. Headache frequency is variable;

BOX 89.1 International Headache Society Classification of Headaches

Primary Headaches

1. Migraine
2. Tension-type headache
3. Cluster headache and trigeminal autonomic cephalalgias
4. Other primary headaches

Secondary Headaches

5. Headache attributed to trauma or injury to the head or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to nonvascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Headache attributed to psychiatric disorder

Painful Cranial Neuropathies, Other Facial Pains, and Other Headaches

13. Cranial neuralgias and other facial pain
14. Other headache disorders

BOX 89.2 Migraine Without Aura Criteria

A. At least five attacks fulfilling criteria in B, C, D, and E
B. Attack lasts 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache, at least one of the following:
   1. Nausea or vomiting (or both)
   2. Photophobia and phonophobia
E. Not attributable to another disorder

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BOX 89.3 Migraine With Aura Criteria

A. At least two attacks that fulfill criterion B
B. Presence of at least three of the following four characteristics for a diagnosis of classic migraine:
   1. One or more fully reversible aura symptoms indicating focal cerebral cortical or brainstem dysfunction (or both)
   2. At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession
   3. No single aura symptom lasting longer than 60 minutes
   4. Headache beginning *during* aura or *afterward,* with a symptom-free interval of less than 60 minutes (also may begin *before* aura)
C. Exclusion of related organic diseases by means of an appropriate history, physical examination, and neurologic examination with appropriate diagnostic tests

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those patients with more than 15 headache days per month are considered to have chronic migraine. Associated symptoms and signs include nausea, vomiting, anorexia, photophobia, phonophobia, osmophobia, blurred vision, lightheadedness, vertigo, muscle tenderness, and nasal congestion. Many patients have dramatic light and sound sensitivity and seek a dark, and quiet room. Some patients experience premonitory cognitive impairment during the days leading up to the acute attack producing forgetfulness, irritability, and depression.

The migraine aura consists of focal neurologic symptoms that usually precede the headache, though patients may experience aura without headache. By definition, the aura is fully reversible and typically lasts 10 to 20 minutes, although it may continue for as long as 1 hour. The most common aura is visual; features may include scintillating scotoma (bright rim around an area of visual loss), teichopsia (subjective visual image perceived with eyes open or closed), fortification spectra (zigzagged lines that slowly drift across the visual field), photopsias (poorly formed brief flashes or sparks of light), and blurred vision. Less common auras include somatosensory phenomena, such as tingling or numbness, motor disturbances, and cognitive or language disorders.

Retinal migraine is a rare syndrome consisting of recurrent attacks of monocular visual dysfunction, including positive features (such as scintillations) or negative features (such as blindness). As with aura, these symptoms are completely reversible.

Hemiplegic migraine is characterized by a motor aura consisting of hemiparesis or hemiplegia. The progression of the motor deficit is gradual and, in most cases, is accompanied by a visual, sensory, or speech disturbance. The neurologic symptoms last up to 60 minutes, followed by headache. Rarely, the motor deficit is persistent, resulting from a true stroke. A familial version of hemiplegic migraine is associated with genetic channelopathies.

Migraine with brainstem aura presents with an aura referable to the brainstem. Common neurologic findings include dysarthria, tinnitus, vertigo, diplopia, and altered level of consciousness.

Status migrainosus is a severe unremitting migraine headache that persists unabated for more than 72 hours.

Many factors can trigger migraine headaches in predisposed persons. Common precipitants include sleep deprivation, stress, hunger, hormonal changes, including menstruation, and use of certain drugs, including oral contraceptives and nitroglycerin. In addition, some patients report specific food sensitivities to chocolate, caffeine, and foods rich in tyramine, monosodium glutamate, and nitrates. Alcohol, specifically red or port wine, has also been implicated. In others, certain sensory stimuli, such as a strong glare or strong odors, loud noises, and weather changes, can trigger an attack.

Differential Diagnoses

Among patients without stereotypical recurrent headaches, migraine may be difficult to distinguish from secondary causes of headache, see Chapter 16 and Table 16.1. Headaches with an acute onset may have a cerebrovascular etiology. Headaches that have lingered for longer than several weeks may be due to an intracranial mass lesion or other causes of high cerebrospinal fluid (CSF) pressure. Headaches that occur in the setting of upper respiratory infections may be due to sinus inflammation. Medication overuse headache, which is a disorder characterized by worsening headache frequency in the setting of increased use of analgesic or migraine abortive medication, may coexist with migraine.

Diagnostic Testing

Neuroimaging is not necessary for patients with typical recurrent migraine headaches. Neuroimaging should be considered for older or immunocompromised patients with new-onset headaches, headaches associated with unexplained neurologic abnormalities, and new headaches with an abrupt onset. (Please see Chapter 16 for the diagnostic

TABLE 89.1 Selected Medications for Acute Migraine Attacks

Medication	Dosage and Route Administered	Comments
Oral Medication		
Ibuprofen	400 mg PO	Gastrointestinal upset
Naproxen sodium	500 mg PO	Gastrointestinal upset
Acetaminophen + metoclopramide	650 mg + 10 mg PO	Combination therapy has better efficacy than acetaminophen alone
Sumatriptan	50–100 mg PO	Use cautiously in patients with cardiovascular risk factors
Eletriptan	40 mg PO	Use cautiously in patients with cardiovascular risk factors
Ubrogepant	50–100 mg	May cause transaminitis
First-Line Parenteral Medication		
Prochlorperazine	10 mg IV	Sedation and dystonic reaction
Metoclopramide	10 mg IV	Dystonic reaction
Droperidol	2.5 mg IV	QT prolongation; dystonic reaction
Ketorolac	15 mg IV or 15 mg IM	Gastrointestinal upset; avoid this medication in elderly patients and in patients with renal insufficiency
Sumatriptan	6 mg SC	Chest pain, throat tightness, flushing Contraindicated with hypertension, coronary artery disease, peripheral vascular disease, and pregnancy Cannot be used within 24 hours of ergot use
Second-Line Parenteral medication:		
Dihydroergotamine (DHE)	1 mg IV or IM; may be repeated in 1 hour	Nausea (pretreat with antiemetic) Often causes chest pain Caution in inhibitors of enzyme CYP450 3A4
Magnesium sulfate	2 g IV	More efficacious in migraine with aura
Procedures		
Greater occipital nerve block	6 mL of bupivacaine 0.5% injected bilaterally	Can also target lesser occipital nerve
To Prevent Headache Recurrence After Emergency Department Discharge		
Dexamethasone	10 mg IV	Use cautiously in diabetics

IM, Intramuscular; *IV,* intravenous; *PO,* per os (by mouth); *SC,* subcutaneous.

algorithm.) Such patients have a higher likelihood of having a secondary cause of headache, such as an intracranial bleed or space-occupying lesion. Among patients with an acute migraine headache, laboratory testing should be limited to a pregnancy test for those who are to be treated with medications that may be teratogenic and electrolytes for those patients with marked nausea, anorexia, or vomiting sufficient to require intravenous (IV) fluid hydration.

Management

The pharmacologic treatment of migraine is divided into abortive therapies, which attempt to limit the intensity and duration of a given episode, and preventive therapies, which are intended to decrease the frequency and intensity of attacks. The goals of abortive therapy include rapid pain relief, minimization of headache recurrence and medication side effects, and restoration of the patient's ability to function.

There are several approaches to treatment of the acute headache episode, depending on the severity of the attack (Table 89.1).[2] The choice of agents depends on the patient's previous response to specific therapies, the existence of comorbid conditions, and the presence or absence of nausea or vomiting. Gastric stasis is common during acute migraine attacks and may limit the effectiveness of oral agents.

For mild to moderate attacks, simple analgesics such as acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen or naproxen, are often effective. In the presence of nausea or vomiting, administration of intravenous metoclopramide 20 to 30 minutes before the oral analgesic enhances the absorption and effectiveness of these medications. Appropriate doses for these and other oral medications are listed in Table 89.1.

For moderate to severe attacks, three classes of medications are recommended as initial parenteral therapy: the antiemetic dopamine antagonists, such as metoclopramide and prochlorperazine; migraine-specific agents, such as the triptans and dihydroergotamine (DHE); and parenteral nonsteroidal medications, such as ketorolac.

Dopamine antagonists, such as the neuroleptic prochlorperazine, and the antiemetic metoclopramide, are highly effective as monotherapy for acute migraine attacks. Because of their efficacy, safety, tolerability, and few contraindications, we recommend either of these agents as first-line therapy for acute migraine. Metoclopramide is a less potent antinauseant, and is less likely to induce drowsiness and sleep, which can be factored into the choice of agents, depending on the patient's circumstances. For this class of medication, the mechanism of action is not known, but migraine pathogenesis likely involves dopaminergic pathways. The most common side effects after parenteral administration include sedation and extrapyramidal symptoms, most notably akathisia, which can be treated with diphenhydramine, 25 to 50 mg IV, or midazolam, 2 mg IV.

Sumatriptan, the first-approved medication of the triptan class, a class of selective 5-HT (1B/1D) receptor agonists, is the most frequently used triptan in the ED, and is available for oral (50 to 100 mg)

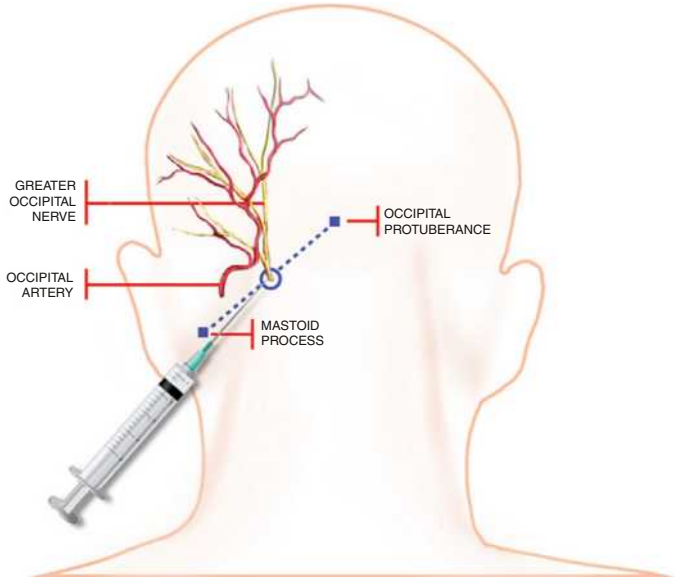

Fig. 89.1 Technique of Greater Occipital Nerve Block. The injector identified the appropriate location using landmarks on the patient's head. The medial landmark was the occipital protuberance. The lateral landmark was the mastoid process. Using these landmarks to form a line, the injector identified the correct location, which was one-third of the distance from the occipital protuberance along this line (two-thirds of the distance away from the mastoid process). The injector felt for pulsation of the occipital artery and attempted to elicit pain or paresthesia in the distribution of the GON by pressing slightly. The injector then used a fan technique, placing 1 mm of anesthetic at the correct spot, 1 mm slightly medial of the correct spot, and 1 mm slightly lateral to the correct spot.

and subcutaneous (6 mg) administration; the latter is more efficacious but also more likely to cause adverse effects. If the patient has experienced insufficient relief with sumatriptan previously, eletriptan 40 mg orally may be administered. Common side effects of triptans include tingling, flushing, warm or hot sensations, heaviness in the chest, and initial worsening of the underlying headache. Sumatriptan is contraindicated in patients with coronary artery disease and should not be used within hours of administration of an ergotamine-containing medication. Sumatriptan is classified as a category C drug for pregnancy, though there does not seem to be an increase in adverse pregnancy outcomes with its use. A smaller dose of subcutaneous sumatriptan may limit side effects.

DHE is often effective when prochlorperazine or metoclopramide have failed, and is administered intravenously in a dosage of 1 mg over 2 minutes; this can be repeated in 1 hour if pain control has not been achieved. Because DHE can cause nausea and vomiting, patients who have not already received an antiemetic, should be given metoclopramide 10 mg IV or prochlorperazine 10 mg IV at least 15 minutes before administration of DHE. Contraindications to use of DHE include pregnancy, breast-feeding, poorly controlled hypertension, coronary artery disease, and peripheral vascular disease. DHE should not be used if the patient has already taken any drug in the triptan class or if the patient is using macrolides or protease inhibitors.

Alternatively, greater occipital nerve block with bupivacaine 0.5% may be attempted among patients with symptoms refractory to first-line medications (Fig. 89.1).

Calcitonin gene related peptide (CGRP) receptor antagonists and monoclonal antibodies likely will play an increasing role in the management of migraine in the coming years as multiple placebo-controlled studies have demonstrated safety and efficacy. The relative efficacy and safety of these medications vis-à-vis the antidopaminergic antiemetics is still unknown. It is clear that CGRP is released during acute migraine attacks and contributes to migraine symptoms.

Opioid analgesics are nonspecific for migraine pain, and rarely, if ever, are indicated in the treatment of acute migraine. They have not been shown to be more effective than nonsteroidal antiinflammatory agents for treatment of migraine. Opioid requests by patients with "migraine" often represent misunderstanding of effective therapy based on past experience. We recommend that opioids not be used for treatment of migraine. Rare cases may exist where a neurologist who knows the particular patient's syndrome rationally validates the use of opioids. Opioids should not be administered on the basis of a "doctor's letter" or other document produced by the patient (see Chapter 151).

Status migrainosus can often be treated successfully using the various medications or combinations of the medications discussed in the previous paragraphs.

Recurrence of migraine within 24 hours of ED discharge occurs in two-thirds of patients who initially improve after treatment in the ED, regardless of medication administered or pain intensity at discharge. Patients should be discharged home with oral medication to treat the headache recurrence, such as naproxen 500 mg or sumatriptan 100 mg. Dexamethasone 10 mg IV decreases migraine recurrence after ED discharge and should be administered to all patients without contraindications.[2]

Preventive therapy is indicated for patients who have more than two or three functionally disabling headaches per month. Several classes of medications are used for migraine prevention, including beta-blockers, tricyclic antidepressants, antiepileptic drugs, and botulinum toxin. Patients who meet criteria for preventative therapy and are not on it, and those for whom preventative therapy has failed, should be referred to a primary care physician or neurologist for evaluation.

Disposition

Most patients who present to an ED for treatment of migraine can be treated and discharged after one or several doses of medication and IV fluids if required. Only rarely do patients with migraine require hospitalization. Patients requiring admission often have chronic migraine, with more than 15 days of migraine monthly, or concomitant *medication overuse headache*. Migraine patients admitted to the hospital receive IV fluids, frequent doses of parenteral migraine medication, and detoxification from medications contributing to the overuse headache.

Cluster Headache

Principles

Cluster headache is the only headache syndrome that is more common in men than in women. It typically occurs in young to middle-aged adults who smoke, almost always onsetting before the age of 50 years. The headaches tend to occur repeatedly during a defined time interval, hence the term *cluster.* Several attacks can occur in a single day, and a typical cluster period may last weeks to months. Several precipitating factors have been implicated, most notably the ingestion of alcohol. Stress and climate changes may also play a role in susceptible persons. As with migraine, abnormal activation of the trigeminal nerve contributes to headache nociception. Typically, secondary parasympathetic activation causes ipsilateral lacrimation and rhinorrhea, a characteristic of cluster headache syndrome.

Clinical Features

Cluster headaches occur suddenly with little warning, and multiple episodes can occur within a 24-hour period. Each headache lasts from 15 minutes up to 3 hours, with a mean duration of about two hours.

TABLE 89.2 Treatment of Cluster Headaches

Medication	Dosage and Route Administered	Comments
Acute Treatment		
First-Line		
Sumatriptan	6 mg SQ	
Oxygen	At least 6–12 L/ min	
Second-Line		
Octreotide	100 micrograms SQ	GI symptoms
Metoclopramide	10 mg IV	Dystonic reaction
Discharge Treatment		
Dexamethasone	10 mg IM or IV	Most efficacious dose unknown
Verapamil	240–480 mg/day PO in 2–4 divided doses	May cause constipation, use cautiously if BP or HR are low
Melatonin	10 mg qHS	Well tolerated

The headache typically begins with a unilateral sharp, stabbing pain in the eye, which may awaken the patient from sleep. The attacks occur exclusively in the territory of the trigeminal nerve. Unlike the patient with migraine, the patient with cluster headache presents agitated and anxious, rocking, rubbing the head, and pacing. The attack subsides rapidly, often leaving the patient exhausted.

Accompanying the headache are ipsilateral autonomic symptoms, such as ptosis, miosis, and forehead or facial sweating. The eye often is injected and tearing, and many patients have unilateral nasal congestion or rhinorrhea.

Differential Diagnoses

Other headache disorders that mimic cluster headache include carotid artery dissection, trigeminal neuralgia, and rare trigeminal autonomic cephalalgias, including paroxysmal hemicranias and short-lasting uniform neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Carotid artery dissection should be excluded as the diagnosis in patients who present with unilateral face or neck pain and Horner syndrome. With trigeminal neuralgia, the pain peaks within seconds, lasts only a few minutes, and can be provoked by specific trigger points on the face or oral mucosa. The less common trigeminal autonomic cephalalgias are manifested by brief unilateral headaches that recur dozens of times per day, often accompanied by the same unilateral eye and nasal symptoms as cluster.

Diagnostic Testing

Diagnostic testing is not indicated for patients with a well-established history of cluster headache. Cluster headache is a characteristic syndrome with specific onset, distribution, duration, and accompanying symptoms, so in patients younger than 50 years without a prior diagnosis, particularly if they have a previous pattern of similar attacks, the presumptive diagnosis can be made with confidence. Patients with a presentation more consistent with carotid artery dissection, particularly neck pain, Horner syndrome, or unilateral neurologic deficit, should undergo neurovascular imaging

Management

Treatment should focus both on relieving the acute headache and preventing the next headache in the cluster (Table 89.2). Because cluster headache is brief in duration, it may resolve before a patient presents to medical attention. For acute headache relief, high-flow oxygen is first-line therapy. It should be administered at rates of 15 liters/minute or greater through a non-rebreather mask until that headache has remitted completely. High-flow oxygen aborts the headache within 15 minutes in approximately 80% of patients. Subcutaneous sumatriptan, 6 mg, is also an effective therapy for acute cluster headache if the headache fails to resolve after 20 to 25 minutes of high-flow oxygen.[8] Larger doses do not confer additional benefit and may contribute to medication side effects. Antidopaminergic agents and NSAIDs can be used if the patient does not experience relief with oxygen and sumatriptan or if the patient has contraindications to the latter. As with migraine, opioid medications are not indicated for treatment of acute cluster headache, in part because of the evanescent nature of the headache symptoms.

Once the acute attack has been relieved, focus shifts to the ongoing "cluster" of headaches that likely will recur over hours to days. Corticosteroids have long been theorized to help break the cluster, although high-quality evidence is not available. Based on retrospective data, we recommend a 10-day prednisone taper, starting with 60 mg for at least two days. Verapamil, dosed at 120 mg three times a day, may decrease the frequency of attacks by the end of the first week of therapy and should be considered for patients without calcium channel blocker contraindications who are discharged from the ED.

Disposition

Patients with cluster headache usually do not require admission to the hospital. Because these headaches are likely to continue over the following days and weeks, the patient should be referred to a physician with expertise in headache management.

Tension-Type Headache

Principles

Tension-type headache is the most common recurrent headache disorder, with one year prevalence of 40% of the population in the United States, but it is an infrequent cause of ED visits. Women are affected slightly more frequently than men, and as with migraine, peak prevalence is in the fourth decade of life. These headaches typically do not cause substantial functional disability, and patients are able to continue with their normal daily activities. Autonomic symptoms, such as nasal congestion, nausea, or vomiting are absent. By definition, episodic tension-type headache lasts as little as 30 minutes and as long as 7 days.

The pathophysiology underlying tension-type headache is not yet clear. There is no consistent evidence that increased muscle activity is present. Physical examination will reveal tender areas of the scalp and neck with both tension and migraine headaches. Despite different epidemiologic profiles, a similar response to many therapeutics suggests

that tension and migraine headaches may share pathophysiologic mechanisms.

Clinical Features

Patients typically complain of a tight, bandlike discomfort or pressure around the head that is nonpulsating and dull. They also may experience tightening of the neck muscles. A majority of patients do not seek medical assistance, because the headache usually is mild in intensity and not functionally disabling. On occasion, the discomfort can build up slowly and fluctuate in severity for several days. Unlike in migraine, the headache does not worsen with physical activity, and accompanying symptoms (such as nausea, vomiting, phonophobia, and photophobia) are unusual. Anxiety and depression may coexist with chronic tension headache, which by definition, occurs more than 15 days a month and can be daily and unremitting.

Differential Diagnoses

Tension headache is the least distinct of all of the primary headache disorders, and its diagnosis is based mainly on the absence of features that would suggest another headache diagnosis. The most common disorders mimicking tension headache are migraine, IIH, cervical spondylosis, sinus or eye disease, and intracranial masses. Subtle indolent infections (such as cryptococcal meningitis) should be considered in the immunocompromised.

Diagnostic Testing

Patients who present with a headache similar in quality to previous headaches do not require diagnostic evaluation in the ED. New-onset headache with features of tension-type headache requires evaluation in patients 50 years and older, as well as immunocompromised patients. This evaluation can take place in the outpatient setting, where a scheduled MRI offers more sensitivity for a range of pathologies than a noncontrast CT.

Management

Because the pain of tension-type headache is rarely severe or disabling, the emergency physician should try to understand why the patient with tension-type headache presented to the ED. For a majority of patients with tension headaches, simple analgesics, such as acetaminophen or an NSAID, are adequate for pain control. Opioids are never indicated and consideration of a need for any parenteral treatment, such as metoclopramide, should prompt serious concern that the diagnosis of tension headache is not correct. For chronic outpatient management, acupuncture has shown benefit for some patients. Despite muscle pain and tenderness in many of these patients, spinal manipulation therapy is unlikely to provide a benefit for most patients.

Disposition

Absent comorbidities, patients with tension-type headache do not require admission to the hospital. Chronic tension-type headache is difficult to manage; these patients often have underlying mental health or personal stress issues, and should be referred to clinicians who can evaluate them for these underlying issues and work with them over time.

SECONDARY HEADACHE DISORDERS

Subarachnoid Hemorrhage

Principles

SAH refers to extravasated blood in the subarachnoid space. (For discussion of other intracranial hemorrhages, please see Chapter 87.) Presence of the blood activates meningeal nociceptors, leading to headache and, in about one-third of cases, signs of meningismus. SAH accounts for up to 10% of all strokes and is the most common cause of sudden death from a stroke.

Approximately 80% of patients with nontraumatic SAH have ruptured saccular (berry) aneurysms, which are small (usually <15 mm diameter) aneurysms that usually form at or near the junction of major cerebral vessels, particularly within the circle of Willis. The remainder are in the posterior circulation, particularly the basilar artery and its ramifications. Approximately 25% of people with a berry aneurysm have more than one aneurysm, and most aneurysms do not rupture, but are found incidentally by cerebral imaging or by autopsy. Other etiologies requiring emergent treatment include arteriovenous malformations, cavernous angiomas, mycotic aneurysms, neoplasms, and CNS vasculitis. Perimesencephalic hemorrhage is a benign form of SAH, in which a localized hemorrhage occurs anterior to the midbrain, without extension, and with no vascular abnormalities on cerebral vascular imaging. These hemorrhages resolve spontaneously and do not require intervention. SAH may also be caused secondarily by an intraparenchymal hematoma that dissects its way into the subarachnoid space.

The risk for aneurysmal SAH increases with age; most cases occur between 40 and 60 years old. In children and adolescents, aneurysms are uncommon, and SAH usually is secondary to an arteriovenous malformation. It is estimated that 2% of the general population harbor a berry aneurysm, with the vast majority never rupturing. Risk of rupture appears to be related to the rate of growth of the aneurysm and increases with aneurysmal size. Other risk factors associated with SAH include hypertension, smoking, excessive alcohol consumption, and use of sympathomimetic drugs. Both genetic and familial associations of cerebral aneurysms have been identified, and there is association with several diseases, including autosomal dominant polycystic kidney disease, coarctation of the aorta, Marfan syndrome, and Ehlers-Danlos syndrome type IV.

Less than 1% of patients presenting to the ED with a primary complaint of headache have SAH, but the diagnosis is of great importance because of the morbidity and mortality associated with aneurysmal rupture. One-quarter of patients with SAH die before reaching the hospital. Median mortality in the United States is about one-third with approximately one-third of survivors having functional and cognitive deficits.

Clinical Features

The clinical presentation of SAH is often distinctive. Most patients present with a sudden, cataclysmic thunderclap headache, which often is described as the worst headache of one's life. The onset of headache may be associated with exertion, the Valsalva maneuver, or sexual intercourse, but the majority occur in the absence of strenuous physical activity. The headache of SAH classically peaks in intensity within seconds to minutes. Headaches that take longer than 60 minutes to peak in intensity are unlikely to be SAH. Associated signs and symptoms include syncope, nausea and vomiting, neck stiffness, photophobia, and seizures. The patient may experience sudden syncope as the initial manifestation, with headache occurring as the patient regains consciousness and increasing thereafter.

Physical findings depend on the extent of the SAH. Up to 20% have focal neurologic abnormalities. Patients may have isolated third or sixth nerve palsy or meningismus. Oculomotor (third) nerve compression secondary to an expanding posterior communicating artery aneurysm causes pupillary dilation. Approximately 50% of patients with a ruptured aneurysm are restless or have a fluctuating or altered level of consciousness. Up to one-third of patients recall an earlier, less severe episode of headache (sentinel headache) days to weeks before the diagnosis of subarachnoid hemorrhage.[3]

TABLE 89.3 Hunt and Hess Clinical Grading Scale for Cerebral Aneurysms and Subarachnoid Hemorrhage

Grade	Condition
0	Unruptured aneurysm
1	Asymptomatic or minimal headache and slight nuchal rigidity
2	Moderate or severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis
5	Deep coma, decerebrate posturing, moribund appearance

BOX 89.4 Ottawa Subarachnoid Clinical Decision Rule

Age ≥ 40 years
Neck pain or stiffness
Loss of consciousness
Onset during exertion
Thunderclap (instantly peaking) headache
Limited neck flexion on examination

(Absence of all of these features obviates the need for further diagnostic workup.)

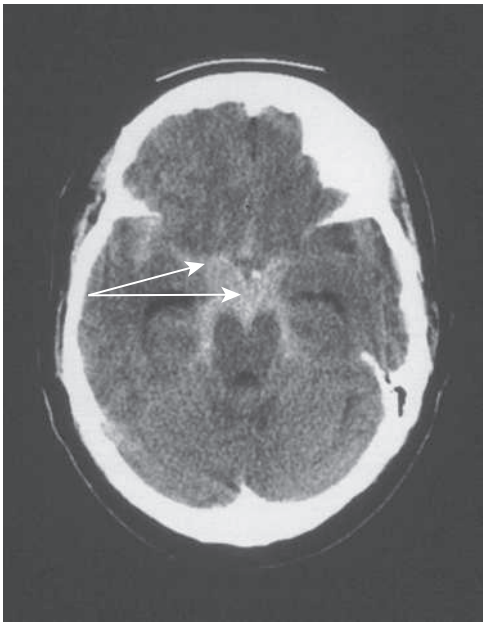

Fig. 89.2 Cerebral Aneurysm. Shown is a computed tomography (CT) scan of an aneurysmal subarachnoid hemorrhage (SAH) in a 55-year-old woman. Subarachnoid blood can be seen within the interpeduncular and ambient cisterns and the right sylvian fissure from a ruptured aneurysm at the junction of the right carotid artery and the posterior communicating artery. (From Brisman JL. Neurosurgery for cerebral aneurysm. Emedicine, updated Sep 23, 2010. Available at http://emedicine.medscape.com/article/252142-overview#a1.)

The patient's prognosis is related to neurologic status at hospital admission. The Hunt and Hess scale stratifies patients according to their clinical signs and symptoms at the time of presentation and is predictive of outcome (Table 89.3). Patients who present with a grade 1 or grade 2 hemorrhage tend to have a good prognosis. Patients with grade 4 or 5 hemorrhages tend to do poorly, presenting with an altered mental status, ranging from stupor to deep coma, together with focal neurologic signs and symptoms. Patients with grade 3 hemorrhage present with drowsiness or confusion and are at risk for rapid clinical deterioration.

Differential Diagnoses

Several clinical entities can mimic the abrupt onset headache associated with SAH. These include cervical artery dissection (CAD), cerebral venous thrombosis (CVT), reversible cerebral vasoconstriction syndrome, hemorrhagic or ischemic stroke, and primary headache disorders, including migraine and cluster headaches. CNS infections cause altered mental status and meningismus but can usually be distinguished by the presence of fever and much longer period of onset.

Diagnostic Testing

The Ottawa clinical decision rule can help risk stratify patients with possible SAH. In this rule, high (near 100%) sensitivity is achieved, but with low (less than 20%) specificity. Use of the rule may not improve accuracy compared to clinical gestalt, but a diagnosis of SAH is of sufficient gravity that high use of advanced imaging for diagnosing "positive" patients is justified (Box 89.4).

A non–contrast-enhanced head CT scan should be obtained emergently when SAH is suspected (Fig. 89.2). For acute hemorrhages less than 24 hours old, the sensitivity of third-generation multidetector row CT scanners in identifying hemorrhage is greater than 90%; however, sensitivity decreases to approximately 50% by the end of the first week, as blood is resorbed. The sensitivity of non–contrast-enhanced head CT performed within 6 hours of headache onset approaches 100%. For patients in whom CT has been performed more than 6 hours after headache onset, a normal non-contrast CT should be followed with subsequent diagnostic testing, which may include spinal fluid analysis or cerebrovascular imaging.[4] The choice of whether to perform LP or a subsequent imaging test depends upon patient preference, local availability, and what else is on the differential diagnosis. For example, if the physician is also concerned about meningitis or idiopathic intracranial hypertension, then an LP would be preferred; if the differential diagnosis includes other neurovascular etiologies such as cervical artery dissection or reversible cerebral vasoconstriction syndrome, then imaging is preferred. Options for cerebrovascular imaging include computed tomography angiography (CTA) or magnetic resonance angiography (MRA). The two-stage approach (non-contrast CT first followed by vascular imaging) is as sensitive as non-contrast CT followed by LP.

Interpretation of LP results can be challenging because up to one-third of spinal fluid analyses contain blood or blood degradation products. The presence of xanthochromia may help differentiate a traumatic LP from SAH. This yellowish pigmentation is secondary to the metabolism of hemoglobin to pigmented molecules of oxyhemoglobin and bilirubin, a process that can take up to 12 hours to occur. SAH cannot be ruled out if a substantial number of RBCs persist in tube 4; however, an RBC count of less than 100 in tube 4 indicates that aneurysmal SAH does not need to be pursued further. CSF xanthochromia in association with normal findings on the CT scan is suggestive of SAH. After the diagnosis is established, angiography should be performed to study the vascular anatomy and to identify the source of hemorrhage.

A normal non–contrast-enhanced head CT scan followed by a normal spinal fluid analysis definitively rules out SAH and does not need to be followed with angiography, even in patients at high risk of disease. However, this strategy does not rule out other causes of thunderclap headache that may be in the differential diagnosis, such as cervical

artery dissection, cerebral venous sinus thrombosis, and reversible cerebral vasoconstrictor syndrome.

Up to 90% of patients with SAH have cardiac arrhythmias or electrocardiographic abnormalities suggestive of acute cardiac ischemia, which may lead to an erroneous primary cardiac diagnosis, especially when syncope has occurred. Typical electrocardiographic findings include ST-T wave changes, U waves, and QT prolongation.

Management

The management of SAH is aimed at treating acute medical and neurologic complications, preventing recurrent hemorrhage, and forestalling the ischemic complications of vasospasm. Because of an altered level of consciousness, patients with SAH of grade 3 or higher are at risk for respiratory depression and hypercapnia, which can lead to further increases in intracranial pressure (ICP); therefore, early endotracheal intubation should be considered in these patients, using a technique consistent with that used for patients with elevated intracranial pressure (see Chapter 1). Blood pressure should be closely monitored because of the risk of continued bleeding or recurrent hemorrhage. The typical treatment goal is a systolic blood pressure below 160 mm Hg or a mean arterial pressure (MAP) below 130 mm Hg. To achieve this, the physician should use intravenous nicardipine or labetalol. Care is required to maintain MAP above 95 mm Hg, though, because iatrogenic hypotension may cause more harm than elevated blood pressure. Nimodipine, a calcium channel blocker, should be started soon after a diagnosis of aneurysmal SAH is made to lessen the likelihood of poor outcome due to vasospasm, even if the patient's blood pressure is normal. Because nimodipine may cause transient hypotension in some patients, hemodynamic monitoring is required during its administration. The recommended dosage is 60 mg by mouth or nasogastric tube every 4 hours.

Corticosteroids have not been demonstrated to be of benefit. Opioids should be used for persistent headache, though modest doses of short-acting agents should be used to avoid interference with evaluations of neurologic status. Intravenous fentanyl, titrated in 50 microgram aliquots is an appropriate first-line agent. In patients who are nauseated or at risk for vomiting, antiemetics such as metoclopramide 10 mg IV or ondansetron 4 mg IV should be administered. Agitated patients require sedation. Short-acting opioids such as fentanyl 50 micrograms IV may achieve this goal. If not, short-acting benzodiazepines such as midazolam 1 mg IV may be added. All patients should be placed on bed rest in a quiet and dark environment. Clinically evident seizures should be treated with levetiracetam or fosphenytoin. Prophylactic anticonvulsant therapy is of unknown benefit, and we recommend leaving this to the discretion of the admitting consultant or in consultation with the receiving consultant when transfer to another center is planned. For definitive management, endovascular coil embolization is preferable to neurosurgical clipping, but this decision is based on size, location, and morphologic features of the aneurysm, as well as local expertise.

Disposition

Patients with ruptured aneurysms require monitoring of hemodynamics and neurological status in an intensive care setting. Patients requiring transfer to a higher level center for care should be managed in collaboration with the receiving center, including contingency plans for complications (e.g. seizures, decreasing level of consciousness) that might arise in transport.

Intracranial Neoplasm

Principles

Headache may be a presenting complaint among patients with brain tumors, though is less common in older patients, presumably because of age-related atrophy. Headache can be caused by primary neoplasms of the CNS, as well as by metastatic lesions (Box 89.5). The most common causes of metastasis are lung and breast carcinoma, followed by malignant melanoma and carcinomas of the gastrointestinal tract.

BOX 89.5 Most Common Types of Intracranial Malignancy Causing Headache

- Metastatic
  - Breast
  - Lung
  - Gastrointestinal
  - Melanoma
- Meningioma
- Glioblastoma
- Primary CNS lymphoma
- Pituitary adenoma

The headache of intracranial neoplasms can be caused by several mechanisms, including traction on pain-sensitive structures (such as meninges or larger cerebral vessels), or it may be a symptom of increased ICP or hydrocephalus. The pain patterns produced are highly variable, depending on the location and size of the mass and the structures involved. Rapidly growing tumors are more likely to be associated with headache.

Clinical Features

The location of the headache may be ipsilateral, contralateral or bilateral and does not predict tumor location. The patient may present with complaints of a worsening headache that has been present for weeks to months. The headache may have been present initially only on awakening (most likely in patients with increased ICP), gradually becoming continuous. The classic triad of brain tumor headache—sleep disturbances, severe pain, and nausea and vomiting—is seen in a minority of patients. If increased ICP is present, the headache often is bilateral and worsened by coughing, sneezing, bending, defecation, and sexual intercourse. Other presentations of intracranial neoplasms include seizures, personality changes, and cognitive difficulties.

Differential Diagnoses

A number of disease processes can mimic brain tumor headache. These include other space-occupying lesions, such as an abscess or an intra-axial or extra-axial brain hemorrhage; diseases associated with increased ICP, such as idiopathic intracranial hypertension; and a vasculitis, such as giant cell arteritis (GCA). Once malignant causes of headache have been excluded, many of these patients will be diagnosed with a chronic headache disorder, such as chronic migraine, chronic tension-type headache, or *new daily persistent headache*, which is a primary headache disorder, characterized by abrupt onset and unremitting course.

Diagnostic Testing

The diagnosis of brain tumor headache may be suspected from the history and neurologic examination. Early in the course, patients may present with headache and an intact neurologic examination, although the majority of intracranial neoplasms will eventually cause focal neurologic deficits. Neuroimaging with CT or MRI is the most efficient way to confirm the diagnosis and is appropriate for all patients with a new persistent headache, particularly those patients older than 50 years. Contrast enhancement on CT often improves the identification of the underlying mass lesion and helps differentiate it from other causes, including abscess, hematoma, and vascular malformation.

Choice of imaging modality depends on local availability and should be tailored to the differential diagnosis.

Management

The treatment of headache associated with brain tumors depends on the type of tumor, patient functional status, and stage of the disease. Management consists of urgent referral to specialty care and treatment of any acute complications, including increased ICP and seizures. For patients who present with symptoms suggestive of increased ICP (e.g., headache, nausea, vomiting, confusion, weakness), treatment with corticosteroids to treat associated edema often provides dramatic temporary relief of headache and other symptoms of increased ICP. Dexamethasone is most commonly used. The exact dose of steroids necessary for each patient varies in accordance with histologic features, size, and location of the tumor and the amount of edema present. An appropriate starting dosage in the ED is 10 mg IV, followed by 4 mg every 6 hours. NSAIDs are appropriate initial therapy.

Patients with seizures should receive levetiracetam or fosphenytoin. Empirical or prophylactic treatment with antiepileptic medication should be avoided as this does not delay or prevent the onset of seizure activity and may expose the patient to unnecessary complications and toxicity.

Disposition

Patients with brain tumor headache should be managed in consultation with the patient's primary health care team. Hospitalization versus discharge will depend upon the severity of the patient's presentation.

Giant Cell Arteritis

Principles

GCA is an inflammatory vasculopathy that occurs in medium and large arteries with well-developed wall layers and adventitial vasa vasorum. It typically involves the major branches of the aorta and has a predilection for the extracranial branches of the carotid artery (e.g., temporal and occipital arteries). It can involve the ophthalmic, vertebral, and distal subclavian arteries, as well as the thoracic aorta. GCA is often named *temporal arteritis* because it commonly affects the superficial temporal arteries.

The mean age at onset of GCA is 71 years old, and it is rare before 50 years old. Women are affected more commonly than men. Pathologically, the arteritis causes an inflammatory infiltrate in the arterial wall resulting in intimal hyperplasia and subsequent stenosis and occlusion, leading to a variety of ischemic complications. In the vast majority of cases, loss of vision is due to anterior ischemic optic neuropathy.

Clinical Features

Temporal arteritis is the most typical presentation of GCA and presents with a broad spectrum of clinical features attributable to both ischemia and systemic inflammation (Box 89.6). Headache is the most common initial manifestation and occurs in more than 70% of patients. The headache often is of 2 to 3 months' duration and can be continuous or intermittent; it can worsen at night or on exposure to cold. The pain may be described as sharp, throbbing, boring, or aching and usually is localized to the temporal region but may occur anywhere in the head. The physical examination may reveal tenderness over the scalp in the area of the temporal artery, with exacerbation of the pain by wearing a hat or resting the head on a pillow. Patients also can experience jaw claudication secondary to vascular insufficiency of the masseter and temporalis muscles. Systemic signs and symptoms are often present, including fever, anorexia, and weight loss. Approximately 40% of patients develop symptoms of polymyalgia rheumatica, pain in their large proximal joints, with symptoms referable to the neck, torso, and lower back. The pain and stiffness are typically worse in the morning and lessen as the day goes on.

BOX 89.6 Diagnostic Criteria for Giant Cell Arteritis (Require 3 of 5)

- Age ≥ 50 years old
- New headache type, particularly in association with visual loss or jaw claudication
- Temporal artery tenderness or tenderness of other extracranial arteries
- ESR ≥ 50 mm/h or CRP ≥ 10 mg/L
- Positive imaging finding or temporal artery biopsy

The most serious complication of GCA is permanent visual loss, which occurs in approximately 15% of patients. Amaurosis fugax (transient monocular blindness) can occur before permanent visual loss. Other complications include peripheral neuropathies, transient ischemic attacks, and stroke. The physical examination may reveal abnormalities of the temporal arteries best detected by light palpation just anterior and slightly superior to the tragus of the ear. Findings include tenderness, reduced or absent pulsations, erythema, and nodularity or swelling. Visual acuity, visual field testing, and thorough funduscopic examination should be followed over time. The presence of a relative afferent pupillary defect (Marcus-Gunn pupil) should increase the suspicion for GCA, although these patients usually will also have a visual loss or a visual field defect.

Differential Diagnoses

The systemic symptoms of GCA are nonspecific. Therefore, the differential diagnosis is quite broad and includes infections, malignancies, and other vasculitides. Takayasu arteritis can affect the aorta and its primary branches as well, but it affects younger patients and visual loss is uncommon. Polyarteritis nodosa, microscopic polyangiitis, and granulomatosis with polyangiitis (formerly known as *Wegener granulomatosis*) can rarely affect the temporal artery but have different histopathology and vascular involvement. Ischemic stroke can cause headache with visual loss or amaurosis fugax. Pituitary apoplexy classically presents with thunderclap headache and bitemporal visual field loss.

Diagnostic Testing

The diagnosis of GCA is based on the history and physical examination, laboratory and imaging studies, and biopsy of the temporal artery. The majority of patients will have elevations of both the C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR), usually to more than 50 mm/hr and often more than 100 mm/hr, as well as the presence of thrombocytosis and anemia. The sensitivity of an elevated ESR or an elevated CRP has been reported in the range of 85%, but their specificity is only 30%. However, very few patients with GCA have both a normal ESR and CRP at the time of diagnosis. Ultrasonography of the temporal arteries may reveal a periluminal hypoechoic halo representing vessel wall edema. MRI of the temporal arteries has similar test characteristics as ultrasonography. The decision about which test to order should be made in consolation with the interpreting radiologist. If these imaging studies are performed in the ED, they may confirm the diagnosis and obviate the need for biopsy. Temporal artery biopsy is an imperfect test and is not required for diagnosis if the diagnosis is apparent based on clinical, laboratory, and imaging results (see Box 89.6).[4]

Management

Patients who present with visual symptoms (such as amaurosis fugax or diplopia) must be treated emergently with glucocorticoids, because

they are at risk for visual loss, which is typically permanent. Given the available evidence, we recommend methylprednisolone 1000 mg per day for 3 consecutive days to optimize immunosuppression and suppress tissue edema. For patients without visual symptoms, lower doses of steroids, in the range of 40 to 60 mg/day of prednisone should be used. Tocilizumab, a monoclonal antibody against the interleukin 6 receptor may be used in the outpatient setting to prevent relapse during corticosteroid tapering.[9]

Disposition

Patients with GCA should be managed in consultation with appropriate specialists, including neurology, ophthalmology, and rheumatology. They can be discharged if symptoms have resolved and rapid outpatient follow-up has been assured.

Carotid and Vertebral Artery Dissection

Principles

Approximately 2% of all ischemic strokes are caused by cervical artery dissection. In patients younger than 50 years old, cervical artery dissection is the most frequent cause of ischemic stroke and accounts for 10% to 25% of cases. These values likely underestimate the true incidence because patients with minimal symptoms are often not diagnosed. Although dissections may occur spontaneously, a careful history frequently identifies an association with sudden neck movement or trauma preceding the event. Reported mechanisms include neck torsion, chiropractic manipulation, coughing, minor falls, heavy lifting, various sports including basketball and volleyball, sexual intercourse, childbirth, and motor vehicle collisions. Early symptoms and signs may be subtle, and delays in diagnosis are common in the absence of neurologic findings. The median delay from symptom onset to diagnosis can be several days.

The pathologic lesion in cervical artery dissections is intramural hemorrhage within the media of the arterial wall. The hematoma can be localized or extend circumferentially along the length of the vessel, resulting in partial or complete occlusion. Damage to the intima results in platelet aggregation and thrombus formation further compromising vessel patency or causing distal embolization. The timing of these events is variable, and a patient may experience symptoms of cerebral ischemia days to years after dissection.

Clinical Features

The typical presentation of cervical artery dissection is the abrupt onset of pain in the head or neck, often in association with symptoms resulting from ischemic consequences of the dissection and emboli. Neurologic findings secondary to cerebral ischemia usually occur within the first few hours following the onset of the headache or neck pain. Although carotid dissection and vertebral artery dissection have many commonalities, their clinical presentations have some unique features.

Carotid Artery Dissection. The classic presentation of symptoms for carotid artery dissection includes (1) unilateral headache or neck pain, sometimes radiating to the ipsilateral eye; (2) ipsilateral ptosis and miosis (a partial Horner syndrome) ; and (3) either blindness, due to retinal ischemia, or contralateral motor deficits, caused by cerebral ischemia. However, this complete triad is only present in a minority of patients. The headache is often severe and throbbing but may be subacute and similar to previous headaches and may be associated with pulsatile tinnitus.

Acute severe retro-orbital pain in a previously healthy person with no history of cluster headaches is suggestive of carotid dissection. Patients with a carotid dissection are at risk of sustaining embolic cerebral ischemia. Warning symptoms include transient ischemic attacks, amaurosis fugax, episodic lightheadedness, and syncope. Spontaneous dissection of the carotid artery has a favorable prognosis and recurrence is uncommon. Factors associated with a worse prognosis include older age, occlusive disease on angiography, and stroke as the initial presenting symptom.

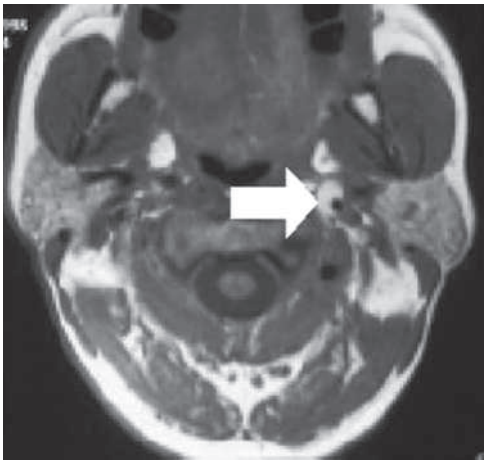

Fig. 89.3 Axial T1-weighted magnetic resonance image (MRI) demonstrating a crescent sign *(arrow)* in a patient with a left internal carotid artery dissection. (From Kidwell C. Dissection syndromes. Emedicine, updated Sep 19, 2011. Available at http://emedicine.medscape.com/article/1160482-overview.)

Vertebral Artery Dissection. Vertebral artery dissections are less common than carotid dissections. The classic presentation is that of a relatively young person with severe, unilateral posterior headache and a rapidly progressive neurologic deficit with symptoms of brainstem and cerebellar ischemia. Common findings include vertigo, severe vomiting, ataxia, diplopia, hemiparesis, unilateral facial weakness, and tinnitus. Stroke severity tends to be lower than that seen with carotid dissection. Spontaneous vertebral artery dissection appears to be relatively rare. Approximately 10% of patients who develop a vertebral dissection die during the acute phase, secondary to massive stroke. For patients who survive, the prognosis is usually good.

Differential Diagnoses

The differential diagnoses of unilateral headache and neck pain with or without Horner syndrome include migraine and cluster headache. Cluster headache in particular can present with ptosis. Cervical arterial dissection may present with an abrupt onset of severe headache, which may be confused with SAH or other vascular causes of headache. For patients who present with symptoms of cerebral ischemia, both ischemic and hemorrhagic stroke should be considered as possible etiologies. Conversely, cervical artery dissection should be considered in patients who present with acute stroke, particularly younger patients.

Diagnostic Testing

Identification of patients with dissection can be challenging, especially in the absence of cerebral ischemia. A non–contrast-enhanced head CT scan is often normal in uncomplicated dissection. Digital subtraction angiography remains the diagnostic gold standard, although several studies have found CTA and magnetic resonance angiography (MRA) to have sensitivities of approximately 95%, making them appropriate choices for initial screening. Cerebrovascular imaging of the head and neck should be considered in all patients in whom CAD is suspected and in young patients with stroke, because it is a more common cause of stroke in a younger population. Cerebrovascular imaging should be considered in unresponsive patients who may have basilar artery pathology. Figure 89.3 shows an example of carotid artery dissection on MRI.

Management

Cervical artery dissection patients with acute ischemic stroke are candidates for thrombolytic therapy or endovascular thrombectomy (see Chapter 87). Studies have shown these treatments to be safe with efficacy similar to stroke from other causes.

For patients with cervical artery dissection without acute ischemic stroke, the primary goal of treatment is the prevention of cerebral ischemic complications. Antiplatelet agents including aspirin, clopidogrel, or dipyridamole, and anticoagulation with unfractionated or low–molecular-weight heparin are comparably effective at preventing stroke, which is relatively uncommon.[5]

Disposition

Patients with cervical artery dissection should be admitted to the hospital for monitoring and further management.

Cerebral Venous Thrombosis

Principles

Thrombosis of the intracranial veins and sinuses is a rare disorder causing approximately 1% of all strokes. It typically presents with headache and disproportionately affects younger individuals without traditional cerebrovascular risk factors.

There are multiple causes for CVT, and risk factors are classically linked to the Virchow triad of blood stasis, blood vessel wall abnormalities, and a hypercoagulable state. Both genetic and acquired prothrombotic conditions have been associated with CVT. Inherited thrombophilias such as antithrombin III, protein C and protein S deficiencies, and factor V Leiden mutation are the most common genetic causes. Acquired causes for CVT include pregnancy and the puerperium, malignancy, head trauma, surgery, parameningeal infections, and exogenous hormones, such as oral contraceptives. Other causes include systemic inflammatory disorders, including vasculitis, inflammatory bowel disease and connective tissue disorders, and neurosurgical procedures.

Clinical Features

Clinical findings in CVT usually fall into two major categories, depending on the mechanism of neurologic dysfunction: (1) Those that are related to increased ICP due to impaired venous drainage, and (2) those related to focal brain injury from venous occlusion resulting in ischemia, infarction, or hemorrhage. Diffuse headache increasing in severity over days to weeks is the most common symptom experienced by patients with CVT and is often associated with increased ICP. Focal neurologic findings, when present, are related to the region of the brain that has been injured and bilateral brain involvement may occur. Seizures, both focal and generalized, frequently occur. Ocular findings associated with CVT include orbital pain, proptosis, chemosis, extraocular muscle paralysis, and papilledema.

Differential Diagnoses

The differential diagnoses of early CVT, when symptoms are limited to headache and papilledema, include brain tumor and idiopathic intracranial hypertension. Late presentations of CVT include altered sensorium, seizures, and focal neurologic deficits. At this point, the differential diagnosis includes ischemic and hemorrhagic stroke; intracranial infections, such as brain abscess, meningitis, and encephalitis; and systemic conditions, including sarcoidosis and systemic lupus erythematosus. With CVT, neurologic findings do not follow a typical arterial territory. CVT is a rare and often subtle diagnosis. To avoid missing the diagnosis, it should be considered for all patients with a new headache type who have thromboembolic risk factors or recent head or neck surgery.

Diagnostic Testing

Routine blood work including a complete blood count (CBC), chemistry panel, ESR, and clotting studies, including a prothrombin time (PT) and partial thromboplastin time (PTT), should be obtained in all patients with suspected CVT. These studies are helpful in determining the presence of an underlying hypercoagulable state, an infectious process, or an inflammatory disorder contributing to the development of CVT. A normal D-dimer can exclude this diagnosis among patients without thromboembolic risk factors or recent head or neck surgery who have a normal neurologic exam and the absence of papilledema.[6] The definitive diagnosis of CVT is based on neuroimaging of the area of thrombosis. This is best accomplished by a combination of MRI to visualize the thrombosed vessel and magnetic resonance venography (MRV) to detect nonvisualization of the same vessel. Non–contrast-enhanced CT by itself is an insensitive test, but it may reveal nonspecific late lesions, such as an infarct, hemorrhage, or edema. Occasionally, hyperdensity of a cortical vein or sinus may be seen. CTA and CTV may be used to visualize the cerebral venous system, especially in patients who have a contraindication to MRI.

Management

Patients with CVT should be anticoagulated to prevent propagation of the thrombosis and development of embolic complications. Treatment is adjusted dose unfractionated heparin or weight-based low–molecular-weight heparin in full anticoagulant doses, regardless of the presence of intracerebral hemorrhage. In patients whose clinical condition worsens despite anticoagulation, thrombolysis or thrombectomy may be considered in centers with expertise in interventional procedures. Seizures are treated with antiepileptic drugs such as phenytoin or levetiracetam.

The prognosis with CVT is based on the underlying etiology, the patient's condition at time of diagnosis, and the development of complications. The overall mortality is low compared with other types of strokes, but morbidity may be increased with delays in recognition and treatment.

Disposition

Patients with CVT require hospitalization, preferentially to a stroke unit, for systemic anticoagulation.

Idiopathic Intracranial Hypertension

Principles

Although this disease is sometimes called *pseudotumor cerebri,* the term *idiopathic intracranial hypertension (IIH)* best reflects current understanding of the pathophysiology and the fact that this disorder is not benign because permanent visual field loss can occur. Compared with other headache disorders, IIH is a relatively uncommon neurologic disease seen primarily in young, obese women of childbearing age. Several predisposing factors have been suggested, including antibiotics (most commonly tetracyclines), vitamin A and retinoids, and human growth hormone. The pathophysiologic mechanism of this disease is not understood, but it is often attributed to an imbalance between CSF production and reabsorption.

Clinical Features

Clinical and diagnostic criteria for IIH are listed in Box 89.7. The most prominent symptom is generalized headache, which may take the form of migraine or tension-type headache.[10] No specific localizing pattern has been documented, although in some patients the headache is worsened by eye movement. It may awaken the patient from sleep and is exacerbated by bending forward and the Valsalva maneuver, both of which impede cerebral venous return. Visual complaints are

BOX 89.7 Criteria for Diagnosis of Idiopathic Intracranial Hypertension

Headache that remits with normalization of CSF pressure
Papilledema (may not be appreciable in all patients)
May have CN VI palsy
Increased CSF opening pressure
  >250 mm in adults
  >280 mm in children
Normal CSF diagnostic studies
Normal neuroimaging studies
No other cause of increased ICP identified

CN, Cranial nerve; *CSF,* cerebrospinal fluid; *ICP,* intracranial pressure. It is essential to rule out space occupying lesions and inflammatory processes.

common, and patients may experience transient visual obscurations (TVOs), which are momentary blackouts of vision most likely due to temporary disruption of the microcirculation to the optic nerve head. They usually occur with postural changes and are not predictive of permanent visual loss. Patients may also complain of nausea, vomiting, dizziness, and pulsatile tinnitus. The physical examination will reveal papilledema, and visual field deficits or visual loss occurs in up to 50% of patients. Fortunately, in the majority of patients, visual defects are reversible with treatment. On occasion, a sixth nerve palsy is noted.[2]

Differential Diagnoses

The differential diagnoses of IIH include other causes of increased ICP in a patient presenting with headache. Important considerations include cerebral venous sinus thrombosis, mass lesions, obstructive hydrocephalus, and leptomeningeal infiltration by neoplastic or infectious processes.

Diagnostic Testing

Ultrasonographic measurement of the diameter of the optic nerve sheath, 3 mm behind the optic disc, is consistent with elevated intracranial pressure if greater than 5 mm. MRI with MRV or MRI with contrast is the preferred modality for diagnosing IIH. MRI should occur early in the workup of IIH because of its ability to detect not only mass lesions and hydrocephalus but also cerebral venous sinus thrombosis and other meningeal processes. If neuroimaging is normal, an LP should be performed in the lateral decubitus position to measure CSF opening pressure and to obtain CSF diagnostic studies. An opening pressure of 250 mm H_2O or more (normal is 70 to 180 mm H_2O) is necessary to make the diagnosis. Ophthalmology follow-up should be arranged for detailed visual field testing.

Management

Many patients present without visual field loss, and symptomatic therapy is all that is necessary. Historically, removal of a large enough amount of CSF (>20 mL) to decrease CSF pressure has been recommended to relieve headache. However, studies of patients with IIH reveal no association between CSF pressure and headache, and CSF is produced relatively quickly, which limits the duration of benefit.[10] Therefore, we believe treatment with NSAIDs such as ketorolac 15 mg IV or antidopaminergic medication such as metoclopramide 10 mg IV may allow the patient with an established diagnosis of IIH to avoid a therapeutic lumbar puncture. In patients with evidence of visual field loss, treatment with medications to lower ICP is indicated. Acetazolamide, starting at doses of 250 to 500 mg orally BID, can improve 6-month visual outcomes though it does not improve headache. If a patient is not responsive to medications or has progressive symptoms, an optic nerve sheath decompression or CSF diversion procedure (e.g., lumboperitoneal or ventriculoperitoneal shunt) may be indicated.

Disposition

Once the headache has been controlled, patients with IIH can be discharged, assuming visual loss is not marked and has not progressed rapidly. Because visual loss can occur early or late in the course of IIH, outpatient follow-up with ophthalmology and neurology should be recommended.

Post–Dural Puncture Headache and Other Low CSF Pressure Headaches

Principles

Post–dural puncture headache (PDPH) is the most frequent cause of low CSF pressure headache seen in the emergency department, though spontaneous intracranial hypotension can also cause orthostatic headaches. The former is a recognized complication of dural puncture, whether performed for diagnostic or therapeutic purposes or accidentally, as a complication of epidural anesthesia, whereas the latter is caused by spinal CSF leak without localized trauma.

The pathophysiology of low CSF pressure headaches is not entirely clear. The most likely explanation is a persistent CSF leak that exceeds CSF production, resulting in CSF hypotension. If sufficient CSF is lost, the brain descends in the cranial vault when the patient assumes the upright position, leading to increased traction on the pain fibers. Thus the headache is characteristically positional and increases with the upright position and decreases with recumbency. The amount of time a patient remains recumbent after lumbar puncture does not affect the incidence of PDPH.

Equipment-related factors have been implicated as causes of PDPH, including the size or diameter of the spinal needle, the orientation of the bevel during the procedure, and the amount of fluid withdrawn. Smaller-diameter needles (e.g., 20- or 22-gauge cutting needle) cause less leakage, and it is postulated that insertion of the needle with the bevel up (i.e., bevel pointing up when the patient is in the lateral position) minimizes damage to the dural fibers. Use of noncutting needles (e.g., Whitaker or Sprotte) also has been shown to reduce the incidence of PDPH.

Clinical Features

The cardinal feature of PDPH is orthostatic or positional headache that is precipitated by the upright position and relieved when the patient lies down. About 90% occur within the first 72 hours after the LP and typically resolve within 1 week, though headaches may persistent for months. Associated signs and symptoms include neck stiffness, nausea, vomiting, auditory disturbances including tinnitus and hypoacusis, and photophobia.

Differential Diagnoses

For most patients, PDPH is a benign disorder. However, in patients who do not respond to standard treatment modalities, other secondary headache disorders must be considered. This is especially true in the postpartum period when CVT and preeclampsia are important considerations.

Diagnostic Testing

The diagnosis of PDPH is based on clinical features, with a headache occurring after an LP or epidural catheter placement, and most patients have a benign course that requires no diagnostic testing. Spontaneous CSF leaks present with orthostatic headaches, which are sometimes severe and should be considered in the absence of a recent LP. The diagnosis is made when low CSF pressures are found on LP, which should be considered in patients with orthostatic headaches who have

not experienced recent dural puncture. In the postpartum period, CVT should be excluded with MRV.

Management

Most PDPHs resolve spontaneously within 5 to 7 days with bed rest, hydration, and analgesics. For persistent headaches not responding to over-the-counter analgesics, methylxanthine agents (such as caffeine 500 mg IV drip over 1 hour) and corticosteroids may be of benefit. For severe headaches that do not respond to these conservative measures, an epidural blood patch (EBP) should be used. This procedure involves the injection of 15 to 30 mL of autologous blood into the epidural space near the site of the original dural puncture resulting in a blood clot that seals off the dural hole.[7]

Disposition

The vast majority of patients with PDPH will have a benign course requiring only conservative treatment. These patients can be discharged home. For patients with persistent complaints, consultation with anesthesia or radiology for an EBP should be considered.

Post-Traumatic Headache

Principles

Headache is the most common symptom following a concussion or other traumatic brain injury (TBI). It is often part of a complex post-concussive syndrome that can include dizziness, fatigue, insomnia, irritability, memory loss, and difficulty with concentration. Persistent headache (>3 months) occurs in over 50% of patients who have suffered a TBI. Paradoxically, patients with milder injuries are more likely to report persistence of symptoms, as are patients with preexisting headache disorders. For the emergency clinician, management of post-traumatic headache (PTH) requires excluding life-threatening causes of headache and treating the headache, associated symptoms, and contributing factors (e.g., cervical strain, cranial neuropraxias). The pathophysiologic mechanism for the symptoms is unclear and may have both anatomic and functional components.

Clinical Features

By international criteria, PTH develops within 7 days of the injury or regaining consciousness. Acute PTH resolves within 3 months, whereas persistent PTH persists beyond 3 months. Patients in whom PTH develops after minor head injuries have normal findings on neurologic examination and routine neuroimaging studies. Many patients are more concerned about the cause of the headache than about the headache itself, underscoring the importance of patient education on the post-concussive syndrome.

PTH may assume a variety of characteristics, including the pulsating unilateral pain and associated features of migraine, the bland, squeezing pain of tension-type headache, or nonspecific headache often relating to the musculature of the neck.

Differential Diagnoses

In the acute setting, pathological causes of headache including intracranial hemorrhage, or skull or cervical fractures should be excluded. Cervical strain and subtle oculomotor nerve palsies are additional etiologies of PTH that should be considered. After the acute setting, it may be difficult to distinguish PTH from migraine or tension-type headache, a distinction that, as time passes, becomes less important.

Diagnostic Testing

In the acute setting following TBI, traumatic injuries to the brain, skull, and neck should be evaluated using available clinical decision rules (see Chapter 34). Patients who return to the ED with persistent symptoms after normal initial imaging should be reassured that follow-up imaging is not required, assuming the patient has a normal neurologic examination and is not using anticoagulants or antiplatelet medication. Neuroimaging is indicated in the setting of focal neurologic deficits or persistent altered mental status.

Management

We recommend that PTH be treated with the same armamentarium of medications used to treat acute primary headaches, specifically, antiemetic dopamine antagonists such as metoclopramide or prochlorperazine, and NSAIDs. Opioids should be avoided.

Disposition

Patients with PTH should be discharged home with appropriate outpatient follow-up. These patients should be informed that they may continue to suffer from headache and other symptoms over the subsequent weeks and should be provided with medication, advice about how to manage symptoms, and referrals to local physicians with relevant expertise.

Hypertensive Headache

Principles

There is uncertainty about whether elevated blood pressure can cause headache. Ambulatory blood pressure monitoring studies have not demonstrated an association, although these studies are limited by relatively modest blood pressure elevations during the study period. Nearly one-quarter of patients who present to an ED with headache have a systolic blood pressure above 150 mm Hg or diastolic blood pressure over 95 mm Hg. Patients who present with headache are more likely to have a markedly elevated blood pressure than patients with other chief complaints. However, the causal pathway, if one exists, is not apparent based on current evidence. In fact, both chronic hypertension and acute elevation in blood pressure have been linked to decreased pain sensitivity in animal and human models. International criteria attribute headache to elevated blood pressure when the pressure is greater than 180 mm Hg systolic or 120 mm Hg diastolic and when the headache resolves with resolution of the elevated blood pressure.

Clinical Features

The headache of severe hypertension is generally characterized as bilateral and throbbing. Early reports of a typical hypertensive headache come from patients with marked, untreated hypertension, who had early morning headaches that were of greatest intensity before the patient arose and typically resolved as the patient engaged in morning activities.

Differential Diagnoses

Based on population prevalence, the most likely diagnoses in patients with elevated blood pressure and headache are migraine or tension-type headache with concomitant hypertension.

Pre-eclampsia, a disorder characterized by elevated blood pressure and headache, should be considered in patients in the latter stages of pregnancy and the recent postpartum period. Posterior reversible encephalopathy syndrome (PRES) is characterized by white matter changes on diagnostic imaging. Malignant hypertension, including drug-induced hypertension, requires evidence of end-organ damage (Table 89.4).

Diagnostic Testing

In the absence of altered sensorium, focal neurologic deficits or visual deficits, a diagnostic evaluation is not indicated.

TABLE 89.4 Pathological Processes That May Present With Headache and Elevated Blood Pressure

Disease Process	Clinical Features	Diagnostic Criteria
Pre-eclampsia	Elevated blood pressure and proteinuria in the second half of pregnancy	Should be considered in all patients greater than 20 weeks pregnant with blood pressure > 140/90 mm Hg
Posterior reversible encephalopathy syndrome	Risk factors include immunosuppressant medication, chemotherapeutics, and underlying renal disease	Abnormal MRI imaging
Intracranial hemorrhage	Acute onset of focal neurologic deficits	Abnormal neuroimaging

Management

It is uncertain if strategies aimed at lowering the blood pressure acutely will alleviate the headache. We recommend use of antidopaminergic or nonsteroidal agents, with use of antihypertensive agents reserved for patients with evidence of end-organ damage. Blood pressure can be reassessed after the headache has improved. Oral antihypertensive therapy may be prescribed in the ED if timely outpatient follow-up cannot be assured (see Chapter 70).

Disposition

In the absence of objective neurologic symptoms, patients with hypertension and headache do not require admission to the hospital. Elevated blood pressure should be treated on an outpatient basis.

Reversible Cerebral Vasoconstriction Syndrome

Principles

Reversible cerebral vasoconstriction syndrome (RCVS) is a cerebral arteriopathy characterized by segmental areas of vasoconstriction within large- and medium-sized vessels. RCVS causes recurrent thunderclap headache in susceptible patients and may cause ischemic or hemorrhagic stroke. The prevalence of this presumably rare disorder is not known. RCVS is being reported with more frequency given the wide availability of noninvasive neurovascular imaging. Some data suggest that this disorder may cause the majority of thunderclap headaches.

Clinical Features

The headache of RCVS is characteristically a thunderclap headache, abrupt in onset, and severe. It is often throbbing and associated with nausea, vomiting, and photophobia. The headache may be provoked by use of vasoactive medications or substances such as recreational sympathomimetics or nasal decongestants.

Differential Diagnoses

The differential diagnoses for thunderclap headache include SAH and other hemorrhagic strokes, CVT, cervical artery dissection, and pituitary apoplexy. Unlike these other pathological diagnoses, RCVS is characterized by recurrent thunderclap headache within a discrete period of time. Thunderclap headache during sexual activity may occur pre- or post-orgasm and is classified as *primary headache associated with sexual activity* after other causes of thunderclap headaches have been excluded. Once that happens, a diagnosis of *primary thunderclap headache* is assigned.

Diagnostic Testing

Patients with the initial presentation of thunderclap headache should have a head CT and LP or neurovascular imaging performed to exclude SAH and other intracranial pathology. Repeat neurovascular imaging, or diagnostic angiography, should be pursued in patients with recurrent thunderclap headache if the diagnosis of RCVS was not confirmed by the initial imaging.

Management

There are no evidence-based treatment options available for RCVS. Goals of treatment include prevention of ischemic and hemorrhagic stroke and elimination of headache. To date, the natural history of this disorder is incompletely understood. Treatment with calcium channel blockers, such as nimodipine 30 to 60 mg PO q4h, has been described and we recommend that it be offered to patients with progressive or refractory symptoms.

Disposition

Patients with thunderclap headache who have received an appropriate diagnostic evaluation with neurovascular imaging in the ED may be discharged home with follow-up within a defined period. An inpatient workup is appropriate for patients with recurrent thunderclap headache, refractory pain, or for those with focal neurologic deficits.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 89: QUESTIONS AND ANSWERS

1. A 29-year-old female presents within 1 hour of the sudden onset of a severe, diffuse headache accompanied by meningismus and vomiting. Emergent computed tomography (CT) scan is negative. Lumbar puncture (LP) reveals 50,000 red blood cells (RBCs) in tube 1 and 30,000 RBCs in tube 4. Opening pressures are normal, and the sample is negative for xanthochromia. What would be the most appropriate next step?

a. Admission and observation
b. Cerebrovascular imaging study
c. Hydration, analgesics
d. Magnetic resonance imaging (MRI) scan with gadolinium

Answer: B. CT scan provides a sensitivity of approximately 90% for the detection of subarachnoid hemorrhage (SAH). A traumatic LP, even with diminishing RBC counts with sequential tubes, cannot differentiate between a SAH and traumatic tap. The lack of xanthochromia is predictable, given the acute onset of headache and the 12 hours required for cerebrospinal fluid (CSF) xanthochromia to develop. A cerebrovascular imaging study, such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), or standard angiography would be required next to exclude a source of bleeding, such as an aneurysm or arteriovenous malformation (AVM).

2. A 69-year-old male presents with several months of intermittent left-sided headaches that have been worse at night and occasionally on exposure to cold air. On several occasions, he has noted increased pain while eating. He has had no other symptoms other than modest fatigue. Physical examination is unremarkable with normal vital signs and ophthalmologic and neurologic survey. Laboratory evaluation shows only a mild anemia, with a hemoglobin of 11 mg/dL and normocytic indices. What would be the most appropriate next step?

a. Computed tomography (CT) scan of the brain
b. Electrocardiogram
c. Erythrocyte sedimentation rate (ESR)
d. Neurology consultation

Answer: C. Temporal arteritis may present with intermittent or continuous symptoms, sometimes associated with fatigue, myalgias, jaw claudication, and mild anemia. The ESR is usually, but not always, diagnostic and would confirm the diagnosis if elevated. Steroids and ophthalmology consultation would then follow. The presence of temporal artery tenderness may be variable because the vasculitis may affect any artery. The diagnosis must be suspected in any elderly patient with recurrent or continuous headaches.

3. With cavernous sinus thrombosis, the clinical picture is usually dominated by which of the following?

a. Facial pain
b. Lethargy
c. Nausea and vomiting
d. Ocular findings such as pain and proptosis

Answer: D. The symptoms may also include paralysis of extraocular movements. Ocular symptoms are most common with thrombosis of the cavernous sinus, rather than one of the other sinuses.

4. A 28-year-old man with a history of migraine and no other medical history presents with a pounding, bilateral 9/10 headache associated with nausea and vomiting that has lasted for 48 hours. The patient reports experiencing a similar headache about once every few months. Physical exam is noteworthy for a blood pressure of 180/110 mm HG in his right arm and 178/111 mm HG in his left arm. Physical exam, including a detailed neurologic exam, is otherwise completely normal. The most appropriate first step in the management of this patient is the following:

a. Non-contrast CT scan of the head
b. Metoclopramide 10 mg IV
c. Labetalol 20 mg IV
d. CT angiography of the head and neck

Answer: B. For patients who present with elevated blood pressure and an otherwise normal physical exam in the setting of a typical migraine headache, treatment should first focus on relieving the acute pain. Treatment of blood pressure should commence if the blood pressure remains persistently high after adequate control of pain. Head imaging is not indicated in a patient who reports a typical exacerbation of migraine. CT angiography of the head and neck is most appropriate to rule out cervical artery dissection. Sumatriptan is an appropriate treatment of acute migraine but is relatively contraindicated in a patient with markedly elevated blood pressure.

5. An obese 37-year-old female reports worsening headache × 3 months, which first responded to ibuprofen but now no longer does. The headache is bilateral, pulsating, associated with nausea, and improves when she assumes an upright position. She reports 5-second blackouts of her vision, which occur occasionally when she changes position. A neurologic exam is unremarkable. Retinal exam is deferred because of marked photophobia. Non-contrast

CHAPTER 89: QUESTIONS AND ANSWERS—cont'd

head CT scan is normal. The most appropriate next step in the diagnostic workup is:

a. MRV
b. D-dimer
c. CT angiography
d. Lumbar puncture

Answer: D. The provided history is most consistent with idiopathic intracranial hypertension, which can only be confirmed by lumbar puncture. Lumbar puncture will demonstrate elevated cerebrospinal fluid pressure >250 mm H_2O. MRV and D-dimer can be used to exclude the diagnosis of venous sinus thrombosis, which should be considered if the CSF pressure is indeed elevated. ESR is most useful to exclude giant cell arteritis, a diagnosis that does not occur in patients younger than 50 years. CT angiography can be used to diagnose cerebrovascular pathology.

Delirium and Dementia

Gallane Abraham and Patrick J. Maher

KEY CONCEPTS

- Delirium is an acute condition characterized by an altered level of attention and awareness. It develops during a short time, and symptoms tend to fluctuate throughout the day.
- Delirium is commonly caused by medications, drug intoxication or withdrawal, infections, metabolic disorders, CNS and cardiovascular events, and autonomic nervous system disturbances.
- Dementia is a chronic condition characterized by cognitive impairment. It is slow in onset and progressive in nature. This disorder has many causes, some of which are reversible with treatment. It is essential to search for reversible underlying etiologies that may be worsening a cognitive impairment.
- Patients with either dementia or psychiatric disorders may present with superimposed delirium, often making identification of the underlying cause of their abnormal behavior difficult.
- The clinician should be wary of attributing behavioral disturbances to psychiatric illness in the presence of abnormal vital signs or abnormal sensorium.
- Nonpharmacologic methods of controlling agitation including reassurance, verbal de-escalation, and avoidance of environmental triggers should be considered in the treatment of patients with dementia.
- Antipsychotics and benzodiazepines are used cautiously in the management of acute agitation in delirium and dementia. The choice of agent is determined by side effect profile and etiology of delirium or acute agitation.
- Antipsychotics may cause QTc prolongation and extrapyramidal side effects, especially when given intravenously.
- Lower doses of medications may be appropriate in older adults to decrease risk of adverse events while effectively treating acute agitation.

OVERVIEW

Delirium and dementia are syndromes defined through impairment of specific cognitive domains including attention, social cognition, memory, language, perceptual-motor ability, and executive function. Both delirium and dementia affect cognition but in different ways and over different time courses. However, delirium can occur concomitantly in a patient with dementia, making the diagnosis challenging. Other nonspecific terms including *acute confusional state, encephalopathy,* and *organic brain syndrome* have been used to describe a number of abnormal cognitive states with often overlapping symptoms. These terms are frequently used synonymously with *delirium* to reflect an alteration of consciousness from presumptive underlying medical etiology. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) classifies these pathologies as *neurocognitive disorders,* although prior editions have used the heading *delirium, dementia, amnestic,* and *other cognitive disorders.*

Delirium is characterized by a fluctuating neurobehavioral disturbance typically progressing over a short period. It is a direct consequence of an acute systemic or central nervous system (CNS) stressor. Dementia, on the other hand, tends to follow a more gradual course, with evolution occurring over months to years. Although patients with dementia may exhibit confusion, unlike delirium, a disturbance in attention is usually absent and other acute medical abnormalities cannot explain the changes in cognition.

The evaluation of patients who present to the emergency department (ED) with a neurobehavioral disturbance is best conducted in accordance with the following basic guidelines:

1. The first step is to establish a safe and supportive environment to facilitate further diagnostic and therapeutic efforts. Verbal de-escalation and nonpharmacological means of treating agitation are preferred, but sedative adjuncts may be employed if needed.
2. The second step is to determine whether this state represents delirium or dementia by obtaining a careful history from the patient, family members, and caregivers. Screening tools for delirium and cognitive assessments for dementia can assist in the diagnosis. Clinical findings may be subtle, and distinguishing between these syndromes can be challenging, especially as acute delirium may be superimposed on chronic dementia.
3. The third step is to rapidly treat the underlying disorder in patients with delirium and to evaluate for causes of reversible dementia.

DELIRIUM

Background

Delirium is an acute or subacute state of cognitive dysfunction caused by an underlying physiologic condition.[1] Several key features are necessary for a diagnosis of delirium (Box 90.1). The hallmark finding in delirium is the disturbance in attention and awareness, manifested as an inability to focus attention and reduced orientation to the environment. Patients with delirium may show changes in several other cognitive domains including memory, language, and perception. Arousal and awareness may be normal or impaired. These disturbances tend to develop during a short time (hours to days), but in certain cases they may last weeks to months despite treatment of the underlying cause. Symptoms often have a fluctuating course over time, in distinction to the progressive changes of dementia. Deficiencies in attention may be manifested by reduced maintenance of attention, increased distractibility, or reductions in task processing speed. Memory impairments can manifest as reduced recall of recent information or repeating oneself in conversation. Either expressive or receptive language may be affected. Perceptual disturbances include hallucinations and delusions. The extent of cognitive derangement may range from mildly disturbed to grossly disorganized. The patient's sleep-wake cycle may be altered or reversed; agitation often is present during the night. The level of psychomotor activity in delirium can be specified as hyperactive, hypoactive, or a mixed level of activity. Hyperactive individuals demonstrate

BOX 90.1 Diagnostic Criteria for Delirium

Four Key Characteristics

- Disturbance in attention and awareness.
- The disturbance develops over a short time period, represents a change from baseline attention and awareness, and tends to fluctuate in severity during the day.
- There are additional disturbances in cognition, such as memory, disorientation, language, visual-spatial ability, or perception.
- The disturbances are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in context of a coma.

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

TABLE 90.1 Risk Factors for Delirium

Advanced age
Male gender
Visual or hearing impairment
Alcohol and drug use
Dementia
Hypertension
Heart failure
Previous delirium
Chronic respiratory disease
Chronic kidney disease
Heart failure
Sedative medications (e.g., benzodiazepines and opioids)
Malnutrition
Depression

emotional lability, agitation, and may refuse care; hypoactive individuals demonstrate sluggishness and lethargy; the mixed type describes either a normal level of psychomotor activity but with disturbance of attention and awareness, or individuals having fluctuations in activity levels. Although hyperactive delirium is the most easily recognizable presentation, hypoactive delirium is the most common form and carries the highest risk of mortality.

Delirium occurs frequently, particularly in older ED patients, and it is associated with increased morbidity and mortality, particularly when unrecognized.[2] Predisposing factors for delirium include comorbid illness, dementia, older age, male gender, medications, neurologic deficits, and psychiatric illness (Table 90.1). Drug intoxication and withdrawal (including ethanol) are the most common cause of delirium in the younger adult population. Within the older population, medication side effects are another common cause of delirium; drugs with anticholinergic properties are often implicated but many drug classes can act as a precipitant. Environmental exposures (e.g., heavy metals, insecticides, cyanide, carbon monoxide), herbal medications, and ingestion of psychoactive botanicals (e.g., nutmeg, foxglove, jimsonweed, psilocybin-containing mushrooms) are yet other causes of delirium to consider.

Delirium can be a prominent feature of any CNS or systemic infection, particularly in the very young, older patients, and immunocompromised patients. Many metabolic disorders put patients at risk for delirium, with hypoglycemia and hypoxia being the most common. Delirium is common in patients with strokes, but isolated delirium without other neurologic abnormality is not a common stroke presentation. CNS vasculitis and paraneoplastic syndromes are additional considerations.

Pathophysiology

At a cellular level, delirium is the result of a widespread alteration in cerebral metabolic activity, with secondary deregulation of neurotransmitter synthesis and metabolism. Both the cerebral cortex and the subcortical structures are affected, producing changes in arousal, alertness, attention, information processing, and the normal sleep-wake cycle.

Although the exact pathophysiologic process is not well understood, multiple neurotransmitters have been implicated in causing delirium.[3,4] Given the phenotypic heterogeneity of delirium, it is likely that a number of various neurophysiologic mechanisms underlie the clinical presentation in different patients. Delirium has classically been associated with a derangement of central cholinergic transmission. Cholinergic deficiency is most pronounced in patients experiencing delirium secondary to anticholinergic drugs. Increased glutamatergic activity and neuroinflammation are seen in hepatic encephalopathy, uremic encephalopathy, sepsis, and alcohol withdrawal. Some of the disturbances that occur in delirium are deficiencies of substrates for oxidative metabolism (e.g., glucose, oxygen); GABA-ergic deficit; imbalance of normal noradrenergic, serotoninergic, dopaminergic, and cholinergic tone; and disturbance of the neuroendocrine axis.

Drugs and exogenous toxins can produce delirium through direct effects on the CNS. Although the limbic system appears to be particularly vulnerable to the effects of drugs, the cerebral hemispheres and the brainstem also can be profoundly affected. Tricyclic antidepressants can cause delirium by cholinergic inhibition; sedative-hypnotics depress activity in the CNS, especially in the limbic system, thalamus, and hypothalamus. Narcotics affect CNS activity primarily by interacting with various opioid receptor sites. Psychedelic drugs may act via agonism at serotonin receptor sites. Phencyclidine (PCP) antagonizes the NMDA receptor and inhibits dopamine reuptake.

Hyperthermia and hypothermia can cause delirium due to changes in the cerebral metabolic rate. Patients suffering from heatstroke may have cerebral edema and degenerative neuronal changes leading to the development of oxidative stress and neuroinflammation. Normalizing the core temperature can reverse these changes. Delirium occurring at temperatures below 40°C is not usually caused solely by increased core temperature, and infection should be considered in cases not meeting the criteria for heatstroke.

Delirium caused by metabolic abnormalities, such as hyponatremia, hypernatremia, hyperosmolarity, hypercapnia, and hyperglycemic disorders, is associated with a variety of metabolic disturbances at the cellular level. Such disturbances may include impairments in energy supplies, changes in resting membrane potentials, in cellular morphology, and in the brain water volume.

Most patients with delirium have reduced cerebral metabolic activity. This reduction in cerebral metabolism is reflected by a slowing of background electrical activity on the electroencephalogram (EEG). Exceptions are hyperthermia, sedative-hypnotic withdrawal, delirium tremens, and certain drug-induced states, in which the cerebral metabolism is either normal or increased. In addition, patients experiencing delirium due to a postictal state or to nonconvulsive status epilepticus can show abnormal epileptiform discharges.

Clinical Features

Delirium can present as the first manifestation of underlying disease. The natural history of a patient's delirium can progress from apathy to marked agitation over hours (see Box 90.1). Nonspecific prodromal symptoms such as anxiety, restlessness, and insomnia may emerge in the hours to days before diagnosis.

Key aspects of cognitive impairment should become evident during a careful history and physical examination. Disturbance in attention is central to the diagnosis of delirium. The patient can be easily distractible or have difficulty remaining focused on a particular topic or interacting with a single person. Disorientation often accompanies the inattention but is not an invariable feature. The patient usually is disoriented with respect to time and occasionally to place; in extreme cases, disorientation to person also may be noted. Delirium, however, may be present in a patient who is completely oriented to person, place, and time. A mental status examination that consists solely of questions that assess orientation will not detect delirium in these instances.

The patient with delirium frequently has some degree of memory impairment, with the greatest impact on short-term memory. Thought processes and speech may be disorganized in patients with previously normal cognition. Disturbance in the sleep-wake cycle often occurs early in the course of delirium. Perceptual disturbances, including poorly formed delusions and hallucinations, are common. Delusions may involve a perception of harmful intent of others. Hallucinations are classically visual, but can also be auditory, tactile, gustatory, or olfactory. In addition, the delirious patient has a reduced capacity to modulate fine emotional expression and may demonstrate extreme emotional lability.

The cognitively impaired patient may provide an unreliable history. Valuable information often can be obtained from family, friends, in-home medical care providers, and paramedics. The baseline premorbid mental condition of the patient in relation to the current presentation should be established early in the examination. Specific inquiry should be made about the patient's current medical problems and previous medical history, including diabetes, hypertension, kidney or liver disease, immune status, and any neurologic or psychiatric problems. A detailed medication history, including the use of prescribed and over-the-counter medications, dietary supplements, and alcohol or other substances, is essential. Information about the home environment, medication bottles belonging to the patient or found near the patient, and the possibility of trauma can help clarify the underlying condition leading to the delirium.

The physical examination should begin with a careful assessment of vital signs. The delirious patient often exhibits autonomic nervous system abnormalities, including elevated or decreased pulse rate, blood pressure, respiratory rate, and temperature. The examination also includes assessment of the head for signs of trauma and the pupils for size, symmetry, and light reflex; evaluation of the neck for nuchal rigidity, bruits, and thyroid enlargement; assessment of the heart and lungs; evaluation of the abdomen for organomegaly and ascites; and examination of the extremities for cyanosis. The skin should be carefully examined for rashes, petechiae, ecchymosis, splinter hemorrhages, and needle tracks.

The neurologic examination includes assessment of the cranial nerves, motor strength, sensation, reflexes, and presence of abnormal movements (e.g., ophthalmoplegia, tremor, asterixis, myoclonus). The reflexes are assessed for symmetry and presence of hyperreflexia or hyporeflexia. Signs that suggest either a metabolic or a structural neurologic problem are helpful but can be nonspecific. For example, asterixis is a hallmark of hepatic encephalopathy but can also be seen in uremia and hypercapnia. Likewise, focal neurologic signs typically associated with structural CNS lesions also can be present in metabolic abnormalities such as hypoglycemia, hyperglycemia, hepatic encephalopathy, uremia, and hypercalcemia. A specific constellation of physical and neurologic findings may suggest a diagnosis. One such example is the classic triad of Wernicke encephalopathy: ophthalmoplegia, ataxia, and confusion. Other examples would include the classic toxidromes found in the presence of sympathomimetic, anticholinergic, sedative/hypnotic, and opioid medications.

Standardized screening tools can facilitate recognizing delirium and avoid missing the diagnosis. Similar to the diagnostic algorithm in other conditions, a fast, sensitive screen may first be applied before proceeding with a longer, more specific test. The most recent guidelines for geriatric emergency care recommend the Delirium Triage Screen (DTS) followed by the brief Confusion Assessment Method (bCAM).[5] The DTS can be performed in less than one minute and is 98% sensitive for delirium. The bCAM, a modification of the full Confusion Assessment Method (CAM) often used during inpatient evaluations, is 84% sensitive and 96% specific for delirium in older emergency department patients. The bCAM uses four key features in screening for delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. For a definitive diagnosis of delirium, the first two features, and one of the last two, must be present (Table 90.2).

In addition to the above recommended tools, there are several other delirium assessments in clinical use, but these instruments lack similar acceptance and utility within the ED setting. The Richmond Agitation-Sedation Scale (RASS) can be performed rapidly but has reduced sensitivity and specificity when used alone.[6] The Mini-Mental State Examination (MMSE) evaluates cognition in multiple domains, but it takes longer to perform and is best used for baseline assessments of dementia, rather than delirium. Other screening tools include the 4A's Test (4AT), the Nursing Delirium Symptom Checklist (Nu-DESC), and 3-Minute Diagnostic Assessment (3D-CAM), among others.[7]

TABLE 90.2 Common Emergency Department Assessments for Delirium and Dementia

Tests for Delirium	Item(S)	Application	Administered By	Time (Minutes)
Delirium Triage Screen (DTS)	2	Clinical, screening	Interviewer	1–2
Brief Confusion Assessment Method (bCAM)	4	Clinical, screening	Interviewer	1–2
TESTS FOR DEMENTIA	ITEM(S)	APPLICATION	ADMINISTERED BY	TIME (MINUTES)
Short Blessed Test (SBT)	6	Screening	Interviewer	5–10
Abbreviated Mental Test (AMT-4)	4	Clinical, screening	Interviewer	1–2
Brief Alzheimer's Screen	5	Clinical, screening	Interviewer	2–5
Clock drawing test	1	Clinical, screening	Patient	3
Mini-Mental State Examination (MMSE)	30	Clinical, screening	Interviewer	5–10

Differential Diagnosis

Considerations in the differential diagnosis for delirium include dementia and psychiatric disorders. Dementia, depression, mania, paranoia, and schizophrenia all may resemble delirium but can be distinguished using historical and clinical features such as onset, time course, fluctuating mental status, and inattention (Table 90.3). Unlike delirium, dementia and psychiatric disorders tend to be insidious processes that develop over months to years. Typically, the patient's vital signs are normal. In addition, cognitive impairment of dementia exhibits little fluctuation during hours or days and occurs primarily in elders. However, patients with dementia are more likely to develop delirium, and as such, the two may often coexist.

Diagnostic Studies

Because delirium results from an underlying medical disorder, a comprehensive evaluation looking for structural, metabolic, and infectious etiologies is indicated (Table 90.4). Despite these diagnostic evaluations, no cause may ultimately be found for many patients. Basic laboratory tests, such as serum electrolytes, have variable diagnostic yield. An elevated anion gap (>15 mEq/L) may indicate the presence of unmeasured anions, such as ketoacids in diabetic or alcoholic ketoacidosis; lactate in postictal states or associated with hypotension; sulfate in renal failure; and exogenous toxins, such as ethylene glycol, methanol, and salicylates.

In addition to a pulse oximetry measurement to screen for hypoxemia, blood gas analysis from an arterial or venous sample is warranted in patients at risk for respiratory failure with hypercarbia. Urinalysis and chest radiography may be obtained to exclude an occult infection, which is the most common cause of delirium in older patients.

An electrocardiogram and troponin may be obtained to assess for an acute coronary syndrome in patients at risk for heart disease, including older patients. Thyroid hormone testing may reveal hypothyroid or hyperthyroid state. Furthermore, additional laboratory studies outside the usual scope of the ED evaluation may be appropriate when the cause of delirium remains unknown or when suggested by the clinical history and exam. These additional studies may include vitamin B_{12} and folic acid assays in cases of possible malnutrition, rapid plasma reagin test to exclude neurosyphilis, measurement of serum antinuclear antibodies if lupus encephalitis is suspected, urinary porphobilinogen assay in acute porphyria, and screens for heavy metals in intentional or accidental ingestions.

Adverse prescription medication effects, including drug-drug interactions, are another common cause of delirium and may occur at therapeutic doses and levels. A comprehensive review of all medications should be performed, with testing for levels when indicated and available. Standard toxicology screens may have limited usefulness in the evaluation of patients with delirium, since both false-positive and false-negative results may occur, and early diagnostic closure based on these tests may result in an incorrect diagnosis.

Neuroimaging with a head computed tomography (CT) scan should be performed on patients with a history or signs of trauma (especially those taking anticoagulant medications), recent neurosurgical procedures or with implanted devices (e.g., cerebrospinal fluid shunt), or focal neurologic signs to detect structural lesions causing delirium. Advanced imaging may be indicated if there is suspicion for

TABLE 90.3 Comparison of Delirium and Dementia

	DELIRIUM	DEMENTIA
Onset	Acute	Gradual
Attention	Impaired	Normal
Level of consciousness	Fluctuates	Normal
Orientation	Variable	Impaired
Memory	Often impaired	Impaired
Hallucinations	Present	Usually absent
Language	Slowed, aphasia	Word finding difficulty

TABLE 90.4 Delirium Diagnostic Studies and Clinical Findings

Diagnostic Studies	Examples of Delirium Precipitants
Vital signs	Hypoxemia, hypotension/hypertension, hypothermia/hyperthermia, pain, fever
Fingerstick glucose	Hypoglycemia/hyperglycemia
Blood gas	Hypoxemia, hypercarbia, respiratory alkalosis, metabolic acidosis
CBC: Hemoglobin, leukocyte count with differential, platelet count, mean corpuscle volume	Anemia, occult infection, thrombocytopenic purpura, megaloblastic anemia, hyperviscosity from myelogenous leukemia, polycythemia
Serum electrolytes: Glucose, sodium, calcium, chloride, bicarbonate, BUN, creatinine, magnesium, phosphate, osmolality	Hypoglycemia/hyperglycemia, hyponatremia/hypernatremia, uremia, hypo-osmolar/hyperosmolar, anion gap acidosis
Urinalysis: Nitrites, leukocytes, ketones	Occult infection, proteinuria
Chest x-ray	Occult infection, pneumothorax
Drug levels	Digoxin, lithium, quinidine, salicylate, antiepileptics
Additional tests: Troponin, liver and thyroid function studies, ammonia, PT, PTT, INR, vitamin B_{12} and folic acid assays, rapid plasma reagin test, measurement of serum antinuclear antibodies, urinary porphobilinogen assay, screens for heavy metals, toxic screens of blood and urine, methanol, ethylene glycol, carbon monoxide, cyanide	Myocardial infarction, liver failure, hypothyroid/hyperthyroid, bleeding disorder, excess anticoagulation, vitamin B_{12} or folate deficiency, occult infections, vasculitis, acute porphyria, toxins
CT Head/MRI	Cerebrovascular accident, structural lesions, traumatic head injury
LP/CSF analysis	Meningitis, encephalitis, subarachnoid hemorrhage
EEG	Nonconvulsive status epilepticus, delirium

BUN, Blood urea nitrogen; *CBC*, complete blood count; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *EEG*, electroencephalogram; *INR*, international normalized ratio; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *PT*, prothrombin time; *PTT*, partial thromboplastin time.

early infarctions, small brainstem lesions, closed head injuries, sagittal venous sinus thrombosis, or small isodense subdural hematomas that may be missed on a CT scan. In addition, a small percentage of acute subarachnoid hemorrhages are not detected by head CT scan and require LP for diagnosis.

The role of magnetic resonance imaging (MRI) in the evaluation of the delirious patient has not been clearly established. MRI is superior to CT for detection of small intracerebral and brainstem lesions, small brain contusions, certain infectious and inflammatory encephalitides, and abnormalities of white matter (e.g., leukoencephalopathy). The posterior reversible encephalopathy syndrome (PRES) can present with confusion, visual changes, and headache in the setting of malignant hypertension, with MRI abnormalities often, but not exclusively, in the posterior cerebrum.

Cerebrospinal fluid (CSF) analysis is an essential part of the evaluation in selected patients with delirium. In patients with fever and cognitive dysfunction, a LP should be considered to rule out infectious, inflammatory or neoplastic etiologies particularly in cases of new headache, meningismus, seizures, community-living adults, recent neurosurgery, or when other testing has failed to identify an infectious source. This test is particularly important in children under age 5, older adults over age 65, and immunocompromised patients, who are less likely to show classic signs of meningitis. Patients with focal neurologic deficits, immunocompromised states, or evidence of increased intracranial pressure should undergo head CT before LP. Antibiotic therapy should not be delayed for the results of LP testing.

Although it is rarely practical in the ED setting, the EEG can be a valuable tool for ruling out nonconvulsive status epilepticus (NCSE) in the presence of delirium. Typical EEG findings in delirium from metabolic causes include nonspecific generalized slowing without epileptiform discharges. In critically ill inpatients with no alternative explanation for decreased level of consciousness, observational studies have shown up to one-third of patients had NCSE on EEG. This condition, even when diagnosed promptly, may be associated with poor patient outcomes in acutely ill patients when mental status abnormalities fail to resolve.

Management

Delirium is a medical emergency. The outcome depends on the cause, the patient's overall health status, and the timeliness of treatment. The hypoactive form of delirium tends to be more common in older adults and carries a worse overall prognosis, perhaps because it often goes unrecognized. Acute recognition and management of delirium in older patients is essential because delirium in this population is associated with increased risk of long-term institutionalization, development of dementia, and increased overall mortality.[2,8]

After recognition of delirium, patients should be screened quickly for readily treatable causes, such as hypoglycemia, hyperglycemia, hypoxia, hypercarbia, and opioid overdose. Acute intoxication due to medications or illicit substances requires prompt attention, and antidotes provided when available.

Initial management of agitation in hyperactive delirium should be accomplished with nonpharmacologic interventions such as verbal reassurance, assistance from family caregivers when present, and calming environment. When nonpharmacologic measures fail, or in the setting of immediate threat to the patient or staff, sedative medications may be administered through an intravenous or intramuscular route to prevent unsafe behavior and facilitate rapid clinical assessment and management.

Supportive care for all patients with delirium ideally includes an environment with adequate lighting and minimization of sensory overload; the patient should be placed in an area that can be easily observed by staff, and use of stretcher side rails to prevent falls. Use of "sitters" may be necessary to provide continuous supervision on a 1:1 or 1:2 basis with the patient. The patient must be protected from self-harm or from injuring other patients or staff. In cases of hyperactive delirium, the patient may need to be initially physically restrained until pharmacologic control takes effect. Physical restraints should be viewed only as a temporizing action because they can increase agitation and the risk of injury to the patient. Death in restraint is a recognized phenomenon, occurring more frequently in patients restrained in nonsupine positions and with agitated delirium.

Following the initial evaluation, care should be directed towards conditions requiring immediate medical intervention. Patients with signs of acute meningitis or sepsis should rapidly receive antibiotics along with appropriate fluid resuscitation. Other conditions that may manifest as delirium and necessitate immediate intervention include severe hypothermia, hyperthermia, and CNS vascular conditions, including hypertensive encephalopathy, acute epidural or subdural hematoma, subarachnoid hemorrhage, and stroke. Patients with Wernicke encephalopathy require immediate treatment with 200 to 500 mg of intravenous (IV) thiamine, with titration of additional doses until the ophthalmoplegia resolves. Traditionally, glucose administration in patients with severe thiamine deficiency was deferred given concern for precipitating Wernicke encephalopathy, but evidence for this phenomenon occurring is poor.

The specific treatment of delirium tremens (and other alcohol withdrawal syndromes) involves the substitution of a long-acting drug that is cross-tolerant with the alcohol. Benzodiazepines are the agents of choice in treatment of delirium due to sedative withdrawal, but caution should be used with these medications in other conditions because they may worsen delirium severity. Treatment for delirium secondary to dehydration or electrolyte abnormality begins in the ED, but care is needed to prevent overcorrection in patients with sodium abnormalities because this can lead to permanent neurologic damage. In patients with hepatic or renal disease, inpatient treatment with medications for hepatic encephalopathy or dialysis for renal disease may be required before disturbances in cognition resolve.

Pharmacologic interventions are a cornerstone of behavioral management while the underlying medical condition that caused the delirium is being addressed. Antipsychotics and benzodiazepines have been used in the management of acute agitation in the undifferentiated patient with delirium (Table 90.5); opioids have no role.

Antipsychotic medications used to treat delirium include the typical antipsychotics, especially the butyrophenones including haloperidol and droperidol, and the newer atypical antipsychotic agents. Evidence for the superiority of any individual agent is limited, and no one drug is ideal for treatment of all cases. The typical antipsychotic, haloperidol, a potent dopamine-blocking medication with minimal anticholinergic and vasodilatory side effects, is recommended as monotherapy for controlling agitation in acute delirium on the basis of extensive clinical experience and best evidence base.[9] The main acute response to the drug is tranquilization. The incidence of extrapyramidal side effects in patients receiving IV haloperidol for management of delirium with agitation is relatively low, generally less than 10% of patients.

As with all the antipsychotics, haloperidol can prolong the QTc interval, more so when given intravenously, but this effect is clinically insignificant in most patients and does not require a pretreatment electrocardiogram. Caution is warranted with use of this agent in patients taking medications that prolong the QTc and in patients with acute coronary ischemia, uncompensated congestive heart failure, or hepatic dysfunction. Another agent in this class, droperidol, received a "black-box" warning from the US Food and Drug Administration (FDA) in 2001 for concerns of QTc prolongation. Although an effective therapy

TABLE 90.5 Medications for Agitation

Etiology	Agent	Dose	Notes
Acute undifferentiated agitation	Typical antipsychotics		
	• Haloperidol	0.5–1 mg IV or 1–2.5 mg IM	Maximum of 10–20 mg/day. Black-box warning of increased mortality in older patients with dementia-related psychosis.
	• Droperidol	2.5–5 mg IV or 5 mg IM Q30 minutes as needed	Maximum dose of 20 mg/day. Black-box warning for QT prolongation.
Parkinson dementia with agitation; acute undifferentiated agitation	Atypical antipsychotics		
	• Quetiapine	12.5–25 mg PO one to three times daily	Black-box warning of increased mortality in older patients with dementia-related psychosis.
	• Olanzapine	2.5–5 mg IM or IV every 2–4 hours	Maximum of 30 mg/day based on patient toleration. Black-box warning of increased mortality in older patients with dementia-related psychosis.
Agitation from acute intoxication or withdrawal syndromes; acute undifferentiated agitation	Benzodiazepines		
	• Lorazepam	0.5–1 mg IM or IV every 4–6 hours as needed	Maximum 4 mg per episode. Has additive CNS depressant effects with other medications.
	• Midazolam	2.5–5 mg IV or IM every 15 minutes as needed	Maximum 10 mg per episode. Has additive CNS depressant effects with other medications.

for agitation in many patients, this warning led to a reduction in the use of droperidol and research into its effects in comparison to other agents. Large observational studies of droperidol use in the emergency department have not supported this concern and we consider droperidol a viable option in the management of acute agitation.[10]

Dosing of haloperidol should be adjusted for the patient's level of agitation, age, weight, and response to treatment. In most patients, 2.5 to 5 mg intramuscularly or intravenously (adjusted according to weight and comorbidities) is well tolerated as an initial dose, and levels can be titrated as needed. For older patients, a lower initial dose of 0.5 to 1 mg is recommended. In highly agitated patients, combination therapy with haloperidol and lorazepam, 0.5 to 2 mg IV or IM, may be more effective than monotherapy with haloperidol. Combinations of sedatives with anticholinergics, such as diphenhydramine, is discouraged, given the likelihood of prolonging the delirium state.

The newer atypical antipsychotic agents (risperidone, olanzapine, ziprasidone, aripiprazole) may have similar efficacy but different side effect profiles, which may be desirable in some cases of acute agitation. The mechanism of action includes antagonism of alpha$_1$-adrenergic, serotonin, dopamine, and histamine receptors. These drugs can also block the reuptake of dopamine and serotonin. Olanzapine, since it has both IV and IM formulations, has received support in the literature as being a safe and effective treatment for acute agitation in the ED, with reduced need for additional sedation in comparison to haloperidol.[11-13] Because of the limited dopamine antagonism effect, atypical antipsychotics are preferred over haloperidol for patients with Parkinsonism and agitation, although benzodiazepines may be a better choice in this population given concerns about increased mortality with the use of atypical antipsychotics in Parkinson disease.[14]

Benzodiazepines are another means to effectively sedate patients with acute undifferentiated agitation, but they are especially useful in cases of substance intoxication or withdrawal syndromes. Lorazepam, with onset of sedation within 2 to 3 minutes, is the preferred agent for treatment of withdrawal symptoms. Midazolam has a similar onset of action to lorazepam, but shorter duration of effect, and may be preferable in some cases. Diazepam should be avoided as an agent for treatment of agitated behavior in most delirious patients because of its long half-life and risk of drug accumulation with repeated dosing. Both midazolam and diazepam have prolonged half-lives in hepatic and renal impairment.

The management of acute behavior change in elderly patients in the emergency department has been identified by national groups as an area requiring further research.[15] Based on the best available evidence, we recommend screening and treatment of readily reversible causes of delirium and initial nonpharmacologic management followed by a selection of pharmacologic agents based upon the etiology of delirium and patient comorbidities.[2] We recommend an antipsychotic (typical or atypical) be used as monotherapy for undifferentiated patients with agitated delirium, or benzodiazepines for patients suspected of having substance intoxication or withdrawal who require sedation. As an alternative, a combination of a low-dose antipsychotic plus benzodiazepine (e.g., haloperidol 5 mg plus lorazepam 2 mg IM) can be used in combative patients with immediate safety threats. The combination approach has been found to be superior to monotherapy in the control of undifferentiated acute agitation.[11,16]

Disposition

Patients with delirium secondary to acute drug intoxication may be discharged from the ED provided the process resolves during a short

period of observation and the drug has no potentially serious delayed toxicity. For most patients with delirium from metabolic, infectious, or CNS processes, hospitalization is necessary for further diagnostic evaluation and treatment. The only readily reversible metabolic problem associated with delirium that can be completely managed in the ED is hypoglycemia.

For most patients with treatable medical illness who have delirium, the outcome is full recovery. Time for return to baseline function can be prolonged, particularly in older patients. In some patients, a persistent decline in their baseline level of functioning may occur despite resolution of the acute cognitive dysfunction. Delirium in older adults hospitalized without baseline dementia is associated with higher 1-year mortality rates, higher rates of institutionalization, and a greater risk for development of dementia. These long-term consequences can occur despite optimal supportive multidisciplinary care.

DEMENTIA

Principles

Background

Dementia is a gradual progressive cognitive decline in complex attention, executive function, learning and memory, language, perceptual motor function or social cognition that interferes with daily function and independence. Dementia may be a primary progressive irreversible neurodegenerative disease, a secondary potentially reversible non-neurodegenerative disease or a mixed dementia arising from multiple etiologies. The predominant dementia is Alzheimer dementia representing 60% to 80% of all cases; vascular dementia represents 20% of all cases, and dementia from multiple etiologies represents 20%.

Dementia is not a single disease entity but rather a highly variable clinical syndrome characterized by the gradual progressive deterioration of cognitive function. Prognosis depends on the underlying cause (Box 90.2). Dementia onset may be categorized as "presenile" when arising before age 65, or "senile" dementia otherwise. Severity is classified according to the degree of cognitive impairment. Mild dementia implies some impairment of work and social activities; however, the capacity for independent living remains intact. With moderate dementia, independent living is hazardous, and some degree of supervision is necessary. With severe dementia, continual supervision and often custodial care are needed.

Primary neurodegenerative dementias include Alzheimer disease, dementia with Lewy bodies, subcortical dementias involving the basal ganglia and thalamus (e.g., progressive supranuclear palsy, Huntington chorea, Parkinson disease), and dementia of the frontal lobe type, which includes Pick disease. Dementia with Lewy bodies, clinically manifested by persistent, well-formed visual hallucinations and prominent extrapyramidal movements, has been found to be the third most common type of dementia. With advanced aging, dementia may have mixed causes, with Alzheimer disease and vascular dementia frequently coexisting. A smaller percentage of dementias are attributable to causes such as anoxic encephalopathy, hepatolenticular degeneration, tumors, alcohol abuse, and slow virus infections.

Potentially reversible secondary non-neurodegenerative dementias are caused by adverse drug reactions, endocrinopathies, metabolic abnormalities, intracranial processes, and depression. The disorder may manifest clinically as acute or gradual progressive cognitive impairment that reverses once the underlying etiology is addressed and resolved. Drug-induced dementia occurs primarily in older adults and can be caused by various psychotropic drugs, antihypertensive medications, anticonvulsants, anticholinergics, and miscellaneous medications, such as L-dopa.[17] Dementia also may be caused by heavy metals and other exogenous agents, such as carbon monoxide, carbon disulfide, and trichloroethylene.

Endocrinopathies and metabolic abnormalities that can cause secondary and potentially reversible dementia include hypothyroidism, hyperthyroidism, parathyroid disease, Addison disease, Cushing disease, and panhypopituitarism. Metabolic abnormalities such as nutritional deficiencies that cause dementia include thiamine deficiency (Wernicke syndrome), niacin deficiency (pellagra), vitamin B_{12} deficiency, and folate deficiency.

Intracranial processes, space-occupying lesions, and hydrocephalus may also cause dementia. Repetitive intracranial trauma resulting from contact sports can produce a chronic organic brain syndrome without evidence of hematoma or significant contusion (dementia pugilistica).

BOX 90.2 Causes of Dementia

Primary Degenerative Dementias
Alzheimer disease
Lewy bodies disease
Frontal lobe disease (Pick disease)

Subcortical Dementias
Parkinson disease
Huntington disease

Vascular Dementia
Multi-infarct dementia

Intracranial Processes
Space occupying lesions (tumor, subdural hematoma)
Hydrocephalus
CNS infections (i.e., HIV-1, neurosyphilis, chronic meningitis, encephalitis secondary to measles, John Cunningham (JC) virus, rubella, *Candida albicans*, Creutzfeldt-Jakob disease (CJD), and variant CJD subacute spongiform viral encephalopathies, or slow virus infections)
Repetitive head trauma

Endocrinopathies
Addison and Cushing diseases
Thyroid and parathyroid disease

Nutritional Deficiencies
Thiamine
Niacin
Folate
Vitamin B_{12}

Toxic Exposures
Heavy metals
Carbon monoxide
Carbon disulfide

Drugs
Psychotropics
Antihypertensives
Anticonvulsants
Anticholinergics

Depression
Pseudodementia

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

BOX 90.3 Diagnostic Criteria for Dementia

A. Cognitive decline from a previous level of performance in one or more cognitive domains: Complex attention, executive function, learning and memory, language, perceptual motor function, or social cognition.
B. The disorder has an insidious onset and gradual progression.
C. The deficits do not occur exclusively during the course of a delirium.
D. The cognitive deficits are not better explained by another mental disorder, such as major depression or schizophrenia.

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

Intracranial processes that may eventually lead to a chronic organic brain syndrome include infections with slow viruses, human immunodeficiency virus type 1 (HIV-1) infection, chronic meningitis (tubercular or fungal), brain abscess, and neurosyphilis. In addition to primary HIV-1 CNS infection, toxoplasmosis, cryptococcal meningitis, malignant disease, and infections due to herpesvirus, cytomegalovirus, varicella-zoster virus, and JC virus (progressive multifocal leukoencephalopathy) can cause progressive cognitive impairment in this compromised group of patients and must be excluded.

Worldwide, approximately 24.3 million persons suffer from dementia, and as the population ages, 4.6 million new cases are diagnosed yearly. The prevalence of dementia is approximately 10% in adults over 65 years old and 50% in adults over 85 years old. The incidence of dementia in the United States is expected to increase as life expectancy continues to increase, but rates may decline as risk factors are controlled in older adults.[18] ED-based studies of cognitive impairment report that up to 70% of older adults seen with cognitive impairment have undiagnosed dementia. Dementia is a strong predictor of mortality, which varies with age and subtype. Older adults with dementia have high rates of ED utilization, with greater numbers of comorbidities and higher rates of admission compared to those without dementia.[19]

DSM-5 criteria for the diagnosis of dementia are presented in Box 90.3. There must be cognitive impairment that interferes with independence in one of six domains: complex attention, executive function, learning and memory, language, perceptual-motor function, or social cognition. Several clinical features deserve emphasis. Impairment in memory must involve both short-term and long-term memory. The cognitive impairment commonly involves abstract thinking, judgment, and other higher cortical functions. The cognitive impairment must interfere with interpersonal relationships, work, and social activities. Although mild decline in intellectual functioning characterized as inability to learn and retain new information without impairment of daily functions can be part of the normal aging process, gross intellectual impairment of short- and long-term memory or confusion is not normal. Mild cognitive impairment is distinct from early dementia.

The goals of ED evaluation for suspected dementia are (1) to recognize the signs and symptoms of undiagnosed and potentially reversible forms of dementia, (2) to identify the manifestations of acute illness in the demented patient promptly, and (3) to assess the clinical findings in lieu of the patient's cognitive impairment and facilitate a safe disposition and expedited follow-up.

Pathophysiology

Alzheimer disease is the best-understood dementia and involves several characteristic anatomic, pathologic, and neurochemical changes. The predominant change is cortical atrophy most prominent in the temporal and hippocampal regions caused by progressive synaptic and neuronal loss in the cerebral gray matter. This atrophy generally is followed by loss of white matter (subcortical atrophy). The degree of neuronal loss correlates with symptomatic severity of Alzheimer dementia and is typically beyond the amount expected in normal aging. Not all patients with histopathologic features of Alzheimer disease will have extensive neuronal losses. There is no ischemic component to Alzheimer disease.

Histologic features characteristic of Alzheimer disease include extracellular deposition of β-amyloid protein and intracellular neurofibrillary tangles contributing to neuron loss. The abnormal processing of β-amyloid protein is likely central to the pathogenesis of Alzheimer disease. The neurofibrillary tangles are intraneuronal paired helical filaments composed of the abnormally phosphorylated protein tau, the structural protein involved in the regeneration of neurites. Senile plaques are extracellular lesions composed of the degenerating neuronal processes and abnormal β-amyloid protein. These plaques are extensively spread throughout the cerebral cortex and do not correlate with the severity of dementia. Other consistent neurohistopathologic changes in Alzheimer disease include granulovascular degeneration (membrane-bound bodies within vacuoles of hippocampal pyramidal cells containing small basophilic granules), Hirano bodies (eosinophilic rod-shaped bodies in hippocampal pyramidal cells composed of actin-associated protein aggregates), β-amyloid deposition in the small cortical blood vessels, and neuronal loss in the limbic area.

Many biochemical abnormalities have been described in patients with Alzheimer disease. A decrease in the neurotransmitter acetylcholine is characteristic. Levels of the enzyme choline acetyltransferase, which synthesizes acetylcholine in the brain, can be reduced to 20% of that in age-matched control subjects.

Risk factors for Alzheimer and vascular dementia range from potentially modifiable cardiometabolic and lifestyle factors to genetic factors. The Framingham Cardiovascular Risk Profile (FCRP) and Cardiovascular Risk Factors Aging and Dementia (CAIDE) risk score reflect the common risk factors of high cholesterol, high blood pressure, diabetes.[20] In addition, advancing age, gender, smoking, air pollution, depression, family history, low education level, and head trauma are associated risk factors for the development of cognitive impairment and dementia. The apolipoprotein E epsilon 4 allele on chromosome 19 has been associated with both familial and sporadic late-onset Alzheimer disease. Apolipoprotein E is responsible for transporting of the cholesterol and phospholipids necessary for dendritic and synaptic repair. There are several allelic variants, but those homozygous or heterozygous for the E4 variant have an increased risk for the development and expression of the disease. Abnormalities on chromosomes 1 and 14 also have been associated with Alzheimer disease.

The frontotemporal dementias are less prevalent than Alzheimer disease and are categorized by a frontal and temporal atrophy caused by cell death. The most common histologic finding in the frontotemporal dementias is the combination of prominent cell loss and gliosis in frontal and temporal regions of the cortex, termed *dementia lacking distinctive histology* (DLDH).

Approximately 15% to 20% of dementias are caused by multiple vascular insults to the CNS; the resulting deficit is termed *multi-infarct dementia.* The multiple infarcts typically involve the cerebral hemispheres and basal ganglia. Multi-infarct dementia often has an earlier age at onset than Alzheimer disease and occurs more often in adult men and patients with risk factors for atherosclerosis. Approximately 20% of dementias are mixed combinations of both ischemic cerebrovascular disease and Alzheimer dementia.

Inflammatory conditions of the CNS contribute to the development of dementia and can be caused by conventional viruses or fungal infections including subacute sclerosing panencephalitis from measles virus infection, progressive multifocal leukoencephalopathy from infection by the John Cunningham (JC) virus (a papovavirus), progressive

rubella encephalitis, HIV disease, and *Candida albicans*.[20] The unconventional viral infections include kuru, Creutzfeldt-Jakob disease (CJD), and variant CJD (which appears to be linked to bovine spongiform encephalopathy, the pathologic process in "mad cow disease"). The infectious agents in these diseases are virus-like particles known as *prions*. A prion is a proteinaceous infectious particle with the apparent ability to start a chain reaction that changes the shape of benign protein molecules into abnormal, slowly destructive forms. These diseases cause a fine vacuolation of the nervous tissue and hence are referred to as *subacute spongiform viral encephalopathies*. With these diseases, months to years pass between infection and the appearance of clinical illness.

One of the most prevalent slow virus infections causing progressive dementia is HIV-1 infection. HIV may produce a primary neurotrophic disorder in addition to causing the immunologic compromise that permits other viruses to replicate and damage nervous tissue. HIV dementia or acquired immunodeficiency syndrome (AIDS) dementia complex occurs in approximately one-fourth of patients with AIDS. It is believed to be caused by the HIV-1 virus targeting the microglial cells and the macrophages, which may produce cytotoxic substances, such as tumor necrosis factor and interleukins. Pathologic changes occur mostly in the hippocampus and basal ganglia and include atrophy, ventricular dilation, and fibrosis.

Several of the potentially reversible causes of dementia also are associated with neuropathologic or neurochemical abnormalities. Normal-pressure hydrocephalus generally affects younger people; 50% of patients are younger than 60 years. Most of the conditions that cause hydrocephalus involve a defect in uptake of CSF by arachnoid villi, which results in gradual ventricular dilation.

Chronic, heavy ethanol consumption is associated with dementia. The neurotoxicity of ethanol appears to be independent of thiamine deficiency. Heavy chronic alcohol consumption causes cerebral cortical atrophy, but no single alcohol-related dementia syndrome exists.

Clinical Features

Family or friends often bring the patient to the ED because of a sudden worsening in mental status, a change in the patient's activities (e.g., refusal to eat), or a change in the ability of the caregiver to manage the patient. Presentations vary by the cause of the dementia and the stage of progression. Many older adults with dementia have a superimposed delirium on presentation.

The symptoms, signs, and progression of chronic cognitive impairment rarely are so diagnostic as to permit identification of the specific cause of the dementia. Alzheimer disease begins insidiously. Signs and symptoms of cognitive dysfunction may be present for months to years before the diagnosis is made. The earliest symptoms and signs of Alzheimer disease often are vague and nonspecific; patients manifest anxiety, depression, insomnia, frustration, and somatic complaints that often are more prominent than the memory loss. Patients often deny any cognitive deficits and change the subject of the conversation frequently rather than admit their increasing forgetfulness. Physicians often overlook the subtle signs of dementia in this phase of the disease. Family and close informants are often the source of a reliable history of cognitive and functional changes for patients with chronic cognitive impairment. Various tests of cognitive function can be used to improve the detection rate of subtle cases, document a change in level of cognition or assist in determination of competency (see Table 90.2).

Depression often is the initial manifestation of Alzheimer disease and is present in up to 40% of cases. Early in the illness, short-term memory is affected with forgetfulness of recent events, such as appointments and names of new acquaintances. Patients often repeat questions. The memory impairment may cause them to withdraw from social situations and recreational pursuits. Attempts to perform complex tasks may produce anxiety and confusion. The patient often has difficulty with interpersonal relationships. Affect may be shallow and labile, and minor events may trigger inappropriate laughter or tears. Compensation for early deficits includes excessive orderliness and avoidance of situations in which the defects may be observed. Patients in this early phase who are treated with antidepressants with anticholinergic properties may experience worsening of their symptoms. Sedative-hypnotics prescribed for anxiety also may accelerate cognitive dysfunction.

As dementia progresses, cognitive deficits are more obvious and should be readily apparent on a mental status examination. Problems with recent memory, impairment of remote memory, language deficits, and difficulty with spontaneous speech may be noted. With moderate severity of the disease, patients have difficulty naming objects (dysnomia). As many as 50% of patients have delusions, usually of the paranoid type. Atypical presentations of Alzheimer disease include aphasia, visual agnosia, right parietal lobe syndrome, focal neurologic findings, extrapyramidal signs, gait disturbances, and pure memory loss. In the final stage of dementia, patients exhibit marked cognitive impairment, apraxia, and personality changes. They often are bedridden and unable to perform the routine activities of daily living.

Because Pick disease dementia affects the frontal and temporal lobes, patients often have frontal lobe release signs, including dramatic behavioral changes of disinhibition and social inappropriateness. Basal ganglia degenerative disorders that have dementia as a prominent feature are Huntington chorea, Parkinson disease, and Wilson disease. One of several features that distinguish cortical from subcortical dementias is a prominent movement disorder, including posturing, ataxia, tremor, and chorea, that tends to occur early in the illness. Other features of these dementias include slowness of speech, hypotonia, and dysarthria, which can progress to mutism.

Patients with vascular dementia have a stepwise deterioration in memory and cognitive function with each cerebrovascular insult. The clinical presentation may follow one of two scenarios. In the more common scenario, the patient suffers several strokes that involve large volumes of cortical and subcortical structures in both hemispheres. The patient then exhibits dementia along with other neurologic disabilities (e.g., focal weakness, hyper-reflexia, extensor plantar response). In a second group of patients, the presentation is subtle. These patients characteristically are hypertensive and suffer multiple tiny infarcts (lacunae) that involve deep subcortical structures. There may be no focal neurologic residua except progressive dementia with psychomotor retardation. Antihypertensive management in older adults moderately reduces the incidence of dementia and Alzheimer disease for patients with hypertension.[21]

The clinical manifestations of slow virus CNS infections are protean. After an insidious onset of mental deterioration in subacute sclerosing panencephalitis, a rapid progression ensues that is associated with myoclonic jerks, incoordination, and ataxia. In progressive multifocal leukoencephalopathy, neurologic signs and symptoms reflect diffuse asymmetrical involvement of both cerebral hemispheres. Sporadic CJD, of unknown etiology, tends to affect older people, with a rate of disease of one case per million people per year. Among these patients, rapidly evolving dementia with myoclonus is characteristic. The hallmarks of the disorder are mental deterioration, multisystem neurologic signs, myoclonus, and typical electroencephalographic changes that evolve during months. Variant CJD affects younger patients (median age of 24 years) with key features that include early affective symptoms progressing to cognitive impairment and gait disturbances and ultimately leading to progressive neurologic deterioration. The incubation period appears to be in the range of 10 to 15 years, and most patients die within 14 months after the clinical onset of symptoms.

The classic triad of progressive dementia, ataxia, and urinary incontinence occurs in patients with normal-pressure hydrocephalus. Hydrocephalus secondary to previous head trauma or infection carries a more favorable prognosis than that for primary hydrocephalus.

In approximately 20% of reversible cases, dementia is secondary to an intracranial mass. Patients may exhibit focal or nonfocal neurologic signs. Of the reversible dementias, 10% to 15% are caused by medications or chemical intoxications, frequently compounding a history of heavy alcohol use. Older adults have increased susceptibility to the toxicities owing to polypharmacy and age-related changes in metabolism. The clinical presentation of a patient with a drug-related or toxin-related dementia may be indistinguishable from that of a patient with a primary degenerative process.

In addition, chronic traumatic encephalopathy (CTE) is a controversial diagnosis that is proposed to be caused by repetitive mild traumatic brain injuries though well-designed studies have not eliminated confounders that could contribute to the process.[22] It is characterized by progressive neurodegeneration, deposition of hyperphosphorylated tau (p-tau) as neurofibrillary tangles in a distinct pattern and may present as dementia and cognitive impairment. This form of encephalopathy is proposed to develop many years after trauma and progresses to dementia, gait and speech abnormalities, and Parkinsonism. It is unclear if CTE is unique to trauma and its symptomatology overlaps with other types of dementias.

Differential Diagnosis

Senescent Forgetfulness

Subacute or chronic cognitive decline may be caused by a dementing illness or can be a manifestation of senescent forgetfulness, delirium, or depression. Senescent forgetfulness is an almost inevitable reality of aging. Mild impairment of both short-term and long-term memory is usual. Unlike dementia, the cognitive disturbance in senescent forgetfulness does not interfere with work or customary social activity.

Delirium

In most cases, the distinction between delirium and dementia is obvious (see Table 90.3). The onset of symptoms, progression of signs and symptoms, perceptual disturbances, abnormalities on assessment of vital signs, and fluctuations in the level of consciousness are key distinguishing features. However, dementia is a risk factor for delirium, and it is more difficult to differentiate delirium when superimposed on a patient with dementia.

Depression

Depression in older adults may closely mimic dementia. Diagnosis of pseudodementia or depression masquerading as dementia can be difficult and may require therapeutic interventions to confirm the clinical diagnosis. Confounding the issue, depression often coexists with dementia; one study found that 40% of patients with dementia were depressed. Depression, anxiety, and apathy are common in the prodrome and course of Alzheimer disease. Several distinguishing features suggest that the problem is depression rather than dementia. The onset of cognitive changes in pseudodementia often can be pinpointed, and symptoms usually are of short duration before medical help is sought. The progression of symptoms is rapid, and the family usually is aware of the severity of the dysfunction. A history of psychiatric illness is common. Patients with pseudodementia usually complain of cognitive dysfunction and emphasize their failures and disabilities. The affective change often is pervasive, and the patient makes little effort to perform simple tasks. Loss of social skills usually occurs early in the illness, and patients communicate a strong sense of distress and inability to function. Intellectual functioning in pseudodementia often is difficult to assess because of lack of patient cooperation or inconsistent findings on neuropsychometric testing. Attention and concentration often are intact, but patients commonly give answers such as "I don't know" on tests of orientation, concentration, and memory. Memory losses for recent and remote events usually are equally severe, and variability in the performance of tasks with similar degrees of difficulty may be marked. Tasks of high capacity (e.g., testing of delayed memory with distraction) may be helpful in identifying the depressed patient.

BOX 90.4 Elements of the Mental Status Examination in the Evaluation of Dementia

Routinely Observed
Appearance, behavior, and attitude
Mood and affect

Require Inquiry
Sensorium and intelligence: Cognitive impairment
Disorders of thought: Suicidal and homicidal ideation
Insight and judgment: Knowledge about illness
Disorder of perception: Hallucinations and delusions

Diagnostic Testing

The evaluation of the patient with suspected dementia includes a focused medical, psychiatric, and medication history plus a collateral history from family and friends. Physical examination should include a detailed neurologic examination with a mental status evaluation. Dementia often goes unrecognized in the patient who is alert, pleasant, and cooperative. A validated cognitive evaluation test can play a key role in the early identification of dementia in patients who have maintained social and conversational ability.

Cognitive Evaluation

A mental status examination should be performed in all patients suspected to have cognitive dysfunction. In the demented patient, mental status testing can uncover subtle forms of delirium. Assessment of orientation to person, place, and time are not sensitive enough to establish cognitive dysfunction. A cognitive assessment should include both psychiatric and neurologic components (Box 90.4).

Several standardized tools for rapid cognitive assessment have been successfully applied in the ED and can be performed in 7 to 10 minutes. Mini-mental status exam (MMSE) testing includes assessment of orientation, memory, attention, and concentration; several tests also incorporate assessments of constructional tasks, spatial discrimination, arithmetic ability, and writing. Memory assessment requires testing of the patient's ability to repeat short series of words or numbers (immediate recall), to learn new information (short-term memory), and to retrieve previously stored information (long-term memory). Constructional apraxia is assessed by having the patient perform tasks, such as drawing interlocking geometric figures or clock faces and connecting dots. Dysnomia (inability to name objects correctly) and dysgraphia (impaired writing ability) are two of the most sensitive indicators of delirium superimposed on dementia. Almost all acutely confused patients exhibit writing impairments, including spatial disorganization, misspelling, and tremor. Therefore, if patients screen positive for delirium the standardized tools cannot be used to assess for dementia.

No single bedside cognitive test that can be administered quickly is ideal. There are various tests of cognitive function, some of which have been tested in the ED (see Table 90.2). The MMSE developed by Folstein and colleagues has been validated more than any other test

and is regarded as the reference standard for dementia diagnosis in most studies in the ED as well. For hospitalized patients, this test has a sensitivity of 87% and a specificity of 82% for detection of organic brain syndrome. Limitations of the MMSE include copyright protection, meaning that official tests must be ordered individually through its distributor although multiple free versions are available online, concerns about false positives in certain lower socioeconomic groups and non-English speakers, and length of the test in comparison to brief screening tools.

The MMSE consists of a short series of questions that test orientation, registration (memory), attention, calculation, recall, and language scored on a 30-point scale. The time for the test to be administered can be reduced to 5 minutes by elimination of the writing and drawing components with only a modest reduction in sensitivity. The registration section tests both immediate and short-term memory; the recall section also assesses short-term memory. The ability to recall two of three objects has 81% sensitivity and 74% specificity for exclusion of organic brain syndrome. Asking the patient to subtract "serial sevens" backward from 100 assesses attention, concentration, and arithmetic ability. This test is specific but not sensitive for absence of an organic brain syndrome; up to 40% of nondelirious, nondemented people fail to perform the tasks of this test correctly, reflecting limitations due to language ability and education. A total score of 23 or less is considered markedly abnormal and indicates an organic brain syndrome. Generally, patients with mild cognitive impairment have a score of 18 to 26 out of 30, those with moderate impairment have a score of 10 to 18, and those with severe impairment have a score of less than 10.

The most recent Geriatric Emergency Department Guidelines, endorsed by the American College of Emergency Physicians and the American Geriatrics Society, suggest the Short Blessed Test (SBT) for ED Dementia Screening. The SBT is a 6-item screening tool evaluating a combination of orientation, registration, and attention. SBT scores correlate well with full MMSE testing, can be performed in 5 to 10 minutes, and has high diagnostic accuracy. Other tests include the clock drawing test, Montreal Cognitive Assessment (MoCA), Abbreviated Mental Test (AMT-4), and Brief Alzheimer's Screen.[23] The clock drawing test is scored on a 6-point scale from no errors to no reasonable representation of a clock. MoCA testing includes assessment of visuospatial, language (naming), memory, attention, recall, and orientation domains of cognition, for a total of thirty possible points. Both the AMT-4 and Brief Alzheimer's Screens are shorter mental status exams validated in the ED as screening tools to prompt more comprehensive testing. The AMT-4 focuses on memory and orientation, and the Brief Alzheimer's Screen includes a spelling item.

The screening tests provide limited detection of mild cognitive impairment (without dementia) or early dementia. In addition, bedside tests of cognition represent cognitive functioning at only one point in time and can be influenced by the patient's level of education and general intelligence; therefore, further history and testing is recommended to establish the diagnosis in symptomatic patients.

Alzheimer disease is a clinical diagnosis typically made on probability; no routine available laboratory tests have been found to confirm the presence of the disorder. MRI scans, functional scans looking at regional blood flow or glucose metabolism, assays for specific biomarkers, and CSF analysis can increase the probability of the presence of the disease. The physical examination is rarely helpful in detecting treatable dementias because of the considerable clinical overlap with irreversible dementias.

Laboratory Tests and Imaging Studies

Data clearly supporting or refuting the ordering of "routine" laboratory studies for evaluation of dementia are lacking; however, several studies are recommended to exclude treatable causes (see Box 90.2). For symptomatic ED patients with suspected undiagnosed dementia, a baseline laboratory evaluation, including CBC, comprehensive metabolic panel, and urinalysis, is recommended. If neurosyphilis is clinically suspected based on risk factors such as HIV co-infection or possible sexual exposure, a serum fluorescent treponemal antibody absorption test should be performed in addition to a Venereal Disease Research Laboratory (VDRL) test because the serum VDRL assay may yield negative results in patients with tertiary syphilis. Rapid Plasma Reagin (RPR) accuracy may be inferior compared to the VDRL for neurosyphilis. The radiologic evaluation may include a non–contrast-enhanced head CT scan. The CT scan is used to diagnose or to exclude the presence of hydrocephalus or space-occupying lesions, and CT findings may support a vascular etiology.

Patients may require additional laboratory tests on follow-up evaluation; such tests may include determination of serum vitamin B_{12} and folate levels, thyroid function studies, erythrocyte sedimentation rate, fluorescent antinuclear antibody assay, measurement of urine corticosteroid levels, and, if indicated by history, urine screens for drugs and heavy metals. Selected patients, particularly those younger than 60 years of age, those with rapidly progressive symptoms or patients in whom confirmatory biomarker testing is desirable, should undergo a LP with CSF analysis. Neuroimaging with head CT or MRI is controversial but indicated in patients with acute onset or rapid deterioration of cognitive impairment to identify rapidly progressive dementia and cerebrovascular accidents. An MRI finding of medial temporal atrophy suggests Alzheimer disease but is not specific or sensitive for diagnosis of this disorder. Confirmatory options in certain patients, most typically performed in outpatients being evaluated for Alzheimer disease, would include formal neuropsychological testing, testing of visual evoked potentials, brainstem auditory evoked potentials, and somatosensory evoked potentials. The EEG rarely is helpful in establishing the diagnosis of senile dementia, although in CJD characteristic slowing and periodic complexes may be electroencephalographic features.

Management

Initial management focus is on accurate diagnosis, symptomatic treatment of behavioral and sleep changes, nonpharmacologic environmental and safety interventions, management of chronic comorbid medical conditions, and specific pharmacologic therapies. Accurate and rapid identification of reversible dementias and conditions that cause worsening of baseline dementia require early diagnosis and disease-specific management. Determination of reversible causes of dementia during the ED evaluation occasionally is possible based on the history (including medication history), physical examination, and head CT scan. Patients with acute changes in mental status or a relatively rapid onset of symptoms will require hospitalization for comprehensive evaluation. Patients presenting with recent gradual decline in cognitive function without an underlying acute medical condition may undergo further evaluation and management on an outpatient basis.

Pharmacotherapy approved by the FDA for the treatment of mild to moderate Alzheimer disease includes the cholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). There are multiple randomized, placebo-controlled, large-scale clinical trials with these drugs establishing efficacy in improving cognitive functions and activities of daily living in patients with mild to moderate dementia. These drugs are not considered disease modifying, and there are limited data at present on the benefit of these drugs beyond 2 or 3 years (a significant number of patients discontinue medications because of side effects). The most common side effect of these agents is due to the cholinergic effects, including nausea, vomiting, and diarrhea.

Memantine (Namenda) is a disease-modifying agent that helps regulate the excitatory effects of glutamate by antagonizing the *N*-methyl-D-aspartate receptor. Whether this drug alters the underlying disease process is unclear, but short-term studies show improved cognition in patients with moderate and moderate to severe Alzheimer disease. There are conflicting studies on the effectiveness of other agents, such as gingko biloba, vitamin E, nonsteroidal agents, and statins. Estrogen replacement is not indicated for cognitive improvement or maintenance in women with Alzheimer disease and can be detrimental. Ultimately, the key to altering the course of the disease is halting neuron loss. In severe dementia, the goal of management is supportive care, and we recommend that initiation and maintenance of medical therapy be conducted by a patient's primary clinician or by a specialized clinic with a focus on dementia treatment.

Many therapies currently are under investigation for the modulation and early treatment of Alzheimer disease. These therapies include antibiotics (directed against *Chlamydophila pneumoniae*), secretase modulators to reduce serum β-amyloid levels, immunization to reduce amyloid plaque burden, chelators to promote dissolution of β-amyloid, nonsteroidal antiinflammatory medications, supplementation with omega-3 fatty acids, and testosterone. In addition, aerobic exercise, diet, cardiovascular and metabolic risk factor modification are recommended.

Increasing evidence suggests that certain nonpharmacologic measures, including behavioral methods and avoidance of environmental triggers, may be effective in reducing agitation and anxiety in patients with dementia. On occasion, medications are needed for behavioral symptoms of dementia. Affected patients typically do not improve with anxiolytics. Adverse effects offset the modest advantages in the efficacy of antipsychotic drugs for the treatment of psychosis, aggression, or agitation in many patients with Alzheimer disease, and these drugs should be avoided when possible. However, despite the lack of consensus in the indication for use and dosages in older demented patients, butyrophenones (such as, haloperidol, 1 to 2.5 mg IM) or atypical antipsychotic olanzapine (2.5 to 5 mg IM) have been found to be effective in the management of acute agitation.

Clozapine may be effective in treating psychosis associated with both Alzheimer- and Parkinson-type dementias. However, the FDA issued a black-box warning that the use of atypical antipsychotics to treat older patients with dementia-related psychosis was associated with an increased risk for death due to cardiovascular and infectious causes compared with placebo, thus the risks and benefits of using these drugs must be considered as part of a unified treatment strategy with the patient's outpatient clinicians, with the above shorter-acting agents used for acute agitation in the ED.

A clear treatment choice for agitation and psychosis in those with dementia has not been identified. The antipsychotics raise a concern for QT prolongation, extrapyramidal symptoms, sedation, and anticholinergic and drug-drug interaction; the benzodiazepines have a risk of falls, confusion, memory impairment, and oversedation. Regardless of intervention used, the lowest dose possible should be used and then titrated carefully to effect.

Agitation in patients with dementia may occasionally be due to unrecognized pain, depression or sleep disturbances. A trial of adequate pain management or selective serotonin reuptake inhibitors (SSRIs) (such as citalopram 20 mg PO) may be warranted. Selection of a SSRI should be based upon side effect profile and drug interactions, and the medication should be initiated only with a plan for follow-up assessments by a clinician capable of monitoring its effect. Sleep disturbances may be treated with temazepam (7.5 mg oral), though the half-life of temazepam is 8 to 10 hours, potentially placing patients at an increased risk for falls.

Disposition

Patients with dementia present to the ED because of an acute deterioration, behavioral change, or crisis due to family stress. A brief observation, acute inpatient medical or psychiatric hospitalization, nursing home stay, or other institutional stay (respite program) may stabilize the patient and give the family time to mobilize resources to resume the home care regimen. Social workers can play a vital role in attempting to facilitate continued management. A key to successful disposition planning is to use screening tools to assess the cognitive, functional, and psychosocial status of patients with delirium and dementia. Anticipating and addressing cognitive or functional barriers to compliance with discharge and transitional care planning is essential.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 90: QUESTIONS AND ANSWERS

1. Which of the following characteristics helps distinguish dementia from delirium?
   - **a.** Acute onset
   - **b.** Memory impairment
   - **c.** Disorientation
   - **d.** Delusions

Answer: A. Delirium is characterized by an acute onset of impaired cognition, in comparison to the slower onset of delirium. Memory impairment and disorientation can occur in either process. Delusions are more common in delirium, but can occur in the later stages of dementia as well.

2. A 78-year-old woman presents with 3 days of decreasing ability to concentrate, memory and cognition breakdown, sleep cycle disruption, and fluctuating levels of agitation. Her current medications include levofloxacin (Levaquin) 500 mg/day for a bladder infection, tramadol PRN for knee arthritis, and hydrochlorothiazide 25 mg/day for essential hypertension. Her examination is normal except for a baseline tachycardia, moderate agitation and restlessness, and orientation to person only. Laboratory analysis shows glucose 198 mg/dL, sodium 131 mEq/L, potassium 3.8 mEq/L, creatinine 1.4 mg/dL, white blood cell (WBC) count 11,300 cells/mm^3, hemoglobin 12 g/dL, bicarbonate 25 mEq/L, and a normal urinalysis. What is the most likely etiology for her delirium?
   - **a.** Early sepsis
   - **b.** Hyperglycemia
   - **c.** Hyponatremia
   - **d.** Medication effect

Answer: D. Medications are the most common cause of delirium in the older adult population. Common inciting medications include antibiotics (quinolones and macrolides), analgesics, sympathomimetics, antiinflammatories, sedatives, and cardiovascular agents. This level of hyponatremia would not be expected to cause delirium. Likewise, a modest hyperglycemia without associated acidosis would be an unlikely culprit.

3. An 82-year-old man presents with acute delirium. On examination, he is alert and mildly agitated. He is oriented to person and place but not time. He is easily distracted and exhibits a mild bilateral upper extremity resting tremor without asterixis. His neurologic examination is nonfocal. His short-term memory is impaired. What is the central component most key to the diagnosis of delirium in this case?
   - **a.** Agitation
   - **b.** Disorientation
   - **c.** Inattention
   - **d.** Memory dysfunction

Answer: C. Disturbance in attention is central to the diagnosis of delirium. Disorientation often accompanies this but is not invariably present. The patient is usually disoriented to time and, less often, place. The delirious patient may also experience visual, auditory, tactile, and olfactory hallucinations; may lose the ability to modulate emotional expression; and often exhibits fluctuating symptoms. Short-term memory is usually impaired, but this is also seen in dementia.

4. Which of the following associations is correct?
   - **a.** Droperidol: QT prolongation
   - **b.** Haloperidol: Dysphoria
   - **c.** Lorazepam: Excessive half-life
   - **d.** Meperidine: Cholinergic effects

Answer: A. This may also be seen with haloperidol and the phenothiazines. Meperidine causes dysphoria and possibly some anticholinergic effects. Diazepam results in the longest terminal *T*½ of the benzodiazepines.

5. A 63-year-old man presents with acute-onset delirium. He is a known alcoholic, and the family reports a cessation of alcohol intake 36 hours before presentation. He has no other known medical problems. Examination is remarkable for an acutely delirious patient who has active visual and auditory hallucinations and a tremor. Neurologic examination is otherwise negative. Finger-stick glucose is normal. Thiamine 100 mg intravenously fails to improve his symptoms. Which of the following is the intervention most likely to prevent further worsening?
   - **a.** Dextrose
   - **b.** Haloperidol
   - **c.** Lorazepam
   - **d.** Magnesium

Answer: C. This patient presents with symptoms of alcohol withdrawal. Wernicke encephalopathy should be considered and thiamine supplementation may be necessary, but lorazepam will prevent progression to withdrawal seizures. Magnesium acts as a cofactor for thiamine, and should also be repleted if levels are found to be low.

Brain and Cranial Nerve Disorders

Joshua Wallenstein

KEY CONCEPTS

Multiple Sclerosis

- The clinical picture of multiple sclerosis (MS); is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve over weeks.
- Magnetic resonance imaging (MRI) is a high-yield diagnostic test for MS. When the emergency department (ED) MRI is an option, it should be considered as it may expedite follow up and initiation of treatment.
- MS relapse is treated with high-dose methylprednisolone, typically 1000 mg IV over a course of 3 to 5 days. There is emerging evidence supporting oral therapy as efficacious in the treatment of relapse.

Cerebral Venous Thrombosis

- Cerebral venous thrombosis (CVT) should be suspected in patients (particularly female patients under age 50) presenting with stroke symptoms without risk factors, unexplained new seizures or refractory headaches, or signs of intracranial hypertension.
- The combination of MRI and magnetic resonance venography (MRV) is considered the gold-standard for diagnosis of CVT, though contrast-enhanced computed tomography (CT) with venous phase imaging is an alternative.
- Primary treatment of CVT in the ED is anticoagulation with a weak recommendation for low molecular-weight heparin over unfractionated heparin. Neuro-interventional treatment may have a role in severe cases, and hospital transfer may be needed for advanced neurological care.

Trigeminal Neuralgia

- Trigeminal neuralgia (TN) is characterized by intermittent, unilateral, severe and sharp facial pain precipitated by innocuous sensory stimuli and not explained by other local causes.
- Secondary TN can be associated with MS and other cranial nerve disorders and neurologic conditions. A careful history and physical examination can help identify these causes though imaging may be needed.
- Sodium-channel blockers are first line therapy, either carbamazepine (200 to 400 mg/day, titrated up to 1200 mg/day) or oxcarbazepine (300 to 600 mg/day in two divided doses, titrated up to 1800 mg/day); adverse side effects may lead to treatment failure. While secondary therapies are available, treatment failure with sodium-channel blockers is an indication for surgical referral.

Facial Nerve Paralysis

- The diagnostic dilemma related to facial nerve paralysis typically revolves around distinguishing Bell's palsy from other causes. While diagnostic imaging is not needed to make a diagnosis of Bell's palsy, it may be indicated in cases where the etiology of facial weakness is unclear.
- Patients at high risk for stroke and infection or with features atypical for Bell's palsy (particularly intact forehead movement or bilateral facial paralysis) should be considered for an alternate diagnosis and often require additional diagnostic testing.
- Corticosteroids improve the outcome in Bell's palsy and should be started as soon as possible to maximize their benefit. We recommend 5 days of prednisone, 60 mg, followed by a taper over 5 days.
- Adding antiviral therapy to corticosteroids confers little or no benefit and evidence supporting its use is very weak except in cases of Ramsay Hunt Syndrome.

Vestibular Schwannoma

- Vestibular schwannomas are a common cause of sensorineural hearing loss and may lead to other distressing neurological symptoms. The primary role of the emergency clinicians is referral for testing and treatment when the diagnosis is suspected or confirmed.

Diabetic Cranial Mononeuropathy

- The differential diagnosis for diabetic cranial mononeuropathy includes aneurysm and stroke; a careful history and physical examination can identify cases that require neuroimaging.
- Diabetic patients presenting with a CN III palsy with spared pupillary response and no other deficits in general do not require neuroimaging.

MULTIPLE SCLEROSIS

Foundations

MS is an inflammatory disease of the central nervous system (CNS) manifested by demyelination of discrete regions (plaques) with a relative sparing of axons. An environmental trigger superimposed on genetic susceptibility appears to be a likely etiology. One theory proposes that this trigger establishes autoreactive T cells in the CNS that after a long latency period become reactivated on subsequent exposure to a systemic trigger, such as a viral infection or superantigen. This sets off a complex immunologic cascade that leads to demyelination.

MS presents with highly variable symptoms, making the illness difficult to definitively diagnose on a patient's first presentation. Symptoms evolve over time with a broad range of severity. Women are more commonly affected than men, with a peak age of onset between 25 and 30 years. Management of MS continues to evolve, and early treatment with disease-modifying therapy results in improved outcomes.[1] The emergency clinician will encounter patients with established diagnoses presenting with acute exacerbations (relapse) and undiagnosed patients presenting with initial symptoms. While familiarity with treatment options for managing relapse is necessary, arguably the most important role for the clinician is to recognize symptoms of MS and expedite testing and referral.

TABLE 91.1 Clinical Features of Multiple Sclerosis

Function	Symptoms and Findings
Cranial nerves	Optic neuritis, diplopia, nystagmus, facial paresis, and pain
Motor	Weakness, spasticity, exaggerated deep-tendon reflexes
Sensory	Numbness, tingling, "pins and needles" paresthesia, coldness
Cerebellar	Gait imbalance, dysarthria, truncal ataxia.
Bladder, bowel and sexual dysfunction	Urinary incontinence, constipation, erectile dysfunction.
Cognition	Poor memory, distractibility, cognitive impairment

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve over weeks. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and degree and time course of progression. Four basic disease courses have been identified by the International Advisory Committee on Clinical Trials of MS. (2) The most common form is relapsing and remitting MS (RRMS, 85%), characterized by clearly defined attacks of new or increasing neurologic symptoms that are followed by periods of partial or complete recovery. The less common primary and secondary progressive MS syndromes are characterized by worsening neurologic function and accumulation of disability, either from symptom onset (primary), or after RRMS (secondary). The remaining course, radiologically isolated syndrome (RIS), has been used to classify those with radiographic abnormalities of MS who have no neurological symptoms or findings.

The clinical features of MS are divided into areas of specific CNS impairment and are described in Table 91.1: cranial nerves, motor pathways, sensory pathways, cerebellar pathways, bowel/bladder/sexual dysfunction, and cognition. While MS has no single pathognomonic finding, optic neuritis has a particularly strong association with the disease. Optic neuritis is a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss primarily affecting the central vision. It is the most common cranial nerve dysfunction related to MS, and not infrequently the first presenting symptom for which patients will seek care. It is the initial presentation in about 20% of MS patients. One study found that 65% of patients who presented to an ED with a first episode of optic neuritis were diagnosed with MS within one year.[2] Other common cranial nerve symptoms include diplopia and nystagmus. The nystagmus may be severe enough to cause oscillopsia (a subjective oscillation of objects in the visual field). Cranial nerve impairment may also include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways, specifically the corticospinal tract, are commonly involved. Paraparesis or paraplegia occurs with greater frequency than upper extremity lesions owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that is typically worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms may be bilateral, they are generally asymmetric. Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.

Impairment of the cerebellar pathway may result in gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), breakdown in the ability to perform complex movements, intention tremor in the limbs and head, truncal ataxia, and dysarthria. Impairment of bowel, bladder, and sexual function is also common with patients complaining of constipation, incontinence, and erectile dysfunction. Finally, cognitive impairments in MS are common, and may be underreported by patients, and underrecognized by care providers.

Differential Diagnoses

Given the marked heterogenicity of MS symptoms, the differential diagnosis is vast and includes central and peripheral nervous system disorders, ophthalmologic and neuropsychiatric disorders, and a large number of systemic and inflammatory/autoimmune disorders. Considerations will vary based on presenting symptoms, but may include ischemic and hemorrhagic stroke, CNS infection or malignancy, neuropathy, and rheumatologic conditions such as systemic lupus erythematosus. Several conditions can also present with radiographic features similar to MS. These include CNS tumors, spinal cord compression, vasculitides, Behçet disease, neuro-sarcoidosis, encephalomyelitis, HIV encephalopathy, Lyme disease, and vitamin B_{12} deficiency. The evolution of symptoms over time can be an important diagnostic finding in differentiating symptoms of MS from other conditions.

Diagnostic Testing

Patients previously diagnosed with MS presenting with acute exacerbations should be evaluated for an acute precipitating trigger, though most often one will not be found. The two most high-yield tests for diagnosing MS are a lumbar puncture (LP) and MRI of the brain and spinal cord. CT of the brain, with or without contrast, is not a useful test in evaluating MS but may be used to investigate other potential diagnoses. CSF analysis is abnormal in most cases of MS, but there is no definitive diagnostic biomarker and many of the more specialized CSF tests may not be done within the ED visit. Nevertheless, LP with CSF analysis can be useful in considering other causes of symptoms, and individual CSF proteins have been demonstrated to be biomarkers of disease activity and progression.[3]

The initial imaging test to aid in the diagnosis of MS is gadolinium-enhanced MRI of the brain and spinal cord. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity. Lesions usually are multiple and commonly are found in the periventricular white matter. Recent studies point to the important role of ED MRI in patients with suspected MS: In one study, concordance between signs of demyelination of ED-based MRI and later final diagnosis of demyelinating disorder was approximately 52%.[4] Given the importance of timely diagnosis and initiation of treatment, emergency clinicians should consider obtaining an MRI when feasible.

Management

Early treatment with disease-modifying therapies can lower relapse rates, reduce disability progression and improve survival. Management

of MS in the ED typically entails treating MS relapse. Ongoing therapies, including disease-modifying therapies and management of MS-related complications are best made by a patient's neurologist or primary care physician.

Treatment with high-dose IV corticosteroids diminishes the duration of symptoms and is an accepted best practice to manage MS relapse; however, there is no agreed upon best dosing regimens or durations of therapy. A common treatment regimen is IV methylprednisolone, 500 to 1000 mg daily for 3 to 5 days with or without a tapering dose of oral steroids (whether there is any benefit to divided doses versus a single daily dose is unclear).

There is an emerging body of evidence supporting the use of high-dose oral prednisone alone (typically 500 to 1250 mg daily) in the treatment of MS relapse. A recent meta-analysis failed to demonstrate clear-cut differences in efficacy and safety outcomes between oral and IV strategies.[5] Outpatient oral prednisolone therapy may reduce health system and patient-borne expenses related to IV infusions, hospital stay, and lost work productivity, as well as minimize patient discomfort and improve patient satisfaction. The decision of oral versus IV therapy should ideally be made through shared decision-making and in consultation with the patient's MS specialist. Other potential therapies of acute exacerbation include repository corticotrophin injection, plasmapheresis, and intravenous immunoglobulin.

Disposition

Patients with a history of MS who seek treatment for relapse must first be evaluated to rule out a worrisome acute trigger, and admission may be required for an identified systemic illness, infection, or other acute condition which is thought to have triggered the MS relapse. While patients initiated on IV steroids therapy will generally require admission for continued treatment, initiation and discharge home with high-dose oral prednisolone therapy is safe and effective. In these cases, the clinician should consider safety at home related to any neurologic disability brought on by the relapse, as well as management of pain and other symptoms.

When a new diagnosis of MS is suspected clinically or based on imaging results, further testing and treatment evaluation can often be performed as an outpatient, again assuming adequate mobility, home safety, and symptom control. Current consensus on quality standards for MS patients suggests that patients with new symptoms be referred to a neurologist within 4 weeks if not sooner.[6] While often an achievable goal after ED discharge, hospital admission for advanced diagnostic testing and neurology consultation may be considered, particularly when access-to-care is a concern.

CEREBRAL VENOUS THROMBOSIS

Foundations

Cerebral venous thrombosis (CVT) accounts for 0.5% to 1.0% of all strokes, often occurring in otherwise healthy young adults, though any age can be affected. The mean age at presentation is about 40 years, with the majority of cases (80%) presenting before the age of 50 years. Women are three times more commonly affected than men. Risk factors include thrombophilias (protein C and S deficiencies, factor V Leiden mutation), pregnancy and the post-partum period, oral contraceptives, infections of the head and neck, cancer, chronic inflammatory states, head trauma, and recent lumbar puncture or neurosurgical procedures. At least one risk factor is identified in 85% of patients, and multiple risk factors are found in 50% of patients.

CVT is caused by systemic or local imbalances in thrombotic and thrombolytic pathways, leading to thrombus formation in cerebral dural sinuses or veins. As the flow of venous blood from the brain is impeded, an increase in venous and capillary pressure occurs. Anastomoses of the cerebral venous system can initially compensate for increases in pressure, but when this capacity is overwhelmed a disruption of the blood-barrier occurs, leading to a decrease in cerebral perfusion pressure. This in turn, can lead to cerebral edema, infarction, and hemorrhage.

TABLE 91.2 Cavernous Venous Thrombosis Clinical Syndromes

Clinical Syndrome	Features
Intracranial hypertension	Persistent headache, decreased visual acuity, papilledema
Focal neurological deficits	Motor weakness, aphasia
Seizures	Focal, generalized, status epilepticus
Encephalopathy	Altered mental status, coma

Clinical Features

There are four major CVT syndromes, which overlap in presentation and are detailed in Table 91.2. The most common, isolated intracranial hypertension, typically presents with headache. Headache from CVT will often be described as localized, persistent or gradually worsening, though it may also be sudden, diffuse and severe, mimicking subarachnoid hemorrhage. Decreased visual acuity and papilledema may also result. Headache may worsen with transient increases in intracranial pressure (coughing, Valsalva). The second and third syndromes, focal neurologic deficits and seizures, are each found in approximately 30% to 40% of CVT cases. Motor weakness (which may be unilateral or bilateral) is the most common focal symptom, and aphasia may also be present. Sensory deficits are possible, though less common. Seizures may be focal or generalized and may present as status epilepticus. CVT should be considered in an at-risk patient presenting with both focal neurologic deficit and seizure. The final syndrome, encephalopathy, may present as altered mental status and confusion. This syndrome is less common and may be seen in more severe cases of thrombosis.

Differential Diagnoses

The differential diagnosis of CVT is vast owing to its highly variable clinical presentations. Depending on the clinical presentation, this may include the broad differential diagnoses of headache, papilledema, motor weakness, seizure, and altered mental status. It is vital to check for risk factors for CVT in considering this often easily overlooked diagnosis. Though only a subset of at-risk patients, women who are pregnant, postpartum, or on oral contraceptives should be considered for further testing when presenting with these symptoms in the absence of an identified cause.

Diagnostic Testing

Routine laboratory testing, including CSF analysis, may be helpful in considering alternative diagnoses of seizure, altered mental status, and other presenting symptoms, but generally have little value in the diagnosis of CVT. Studies evaluating the use of d-dimer in the evaluation of CVT have demonstrated its role; one recent study found that a normal d-dimer had a negative predictive value of 99% and concluded that the test may help guide further diagnostic testing.[7] The authors however noted a need for replication of this single-site study, and did not advocate relying solely on a negative d-dimer as exclusion in at-risk patients.

Imaging is the standard of care when CVT is suspected. The noncontrast head CT may demonstrate an elongated hyper-attenuating

clot ("cord sign") but is more likely to show indirect signs of CVT such as sulcal effacement and decreased grey/white matter differentiation, or it may not demonstrate any abnormality. Although this is an appropriate initial test, it is inadequate to rule out CVT. CT venography or MR venography (MRV) are far more sensitive in demonstrating signs of CVT, and MRI in combination with MRV is generally considered the gold standard. Given the young age of many patients with suspected CVT, radiation exposure further supports the choice of MRI/MRV when available. That said, CT venography has a sensitivity and specificity of 75% to 100% depending on anatomic location of the clot, and recent guidelines suggest that CT venography can be used as a reliable alternative to MRV.[8]

Management

Current therapeutic consensus strongly recommends systemic anticoagulation to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging. There is some evidence to support the use of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) based on improved outcomes with LMWH and lower hemorrhagic complications when compared to UFH. This recommendation does not apply to patients with contraindication to LMWH or in situations when rapid-reversal (such as surgical intervention) may be desired. The use of new oral anticoagulants such as rivaroxaban and dibigatran after initial heparin therapy has been evaluated, but there is insufficient evidence to support their use, particularly in the acute phase.

There is insufficient evidence to recommend the routine use of acetazolamide or steroids in the treatment of symptoms or signs thought to be related to increased intracranial pressure due to CVT. There is some evidence to recommend the short-term use of antiepileptic drugs in patient with supratentorial lesions who have had seizures as prophylaxis to prevent early recurrent seizures, but no evidence to support their long-term use. Finally, endovascular mechanical thrombectomy (EMT) may have a role in severe or refractory CVT and has been demonstrated to be an effective strategy with a reasonable safety profile.[9]

Disposition

All patients with confirmed or suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Considerations for hospital transfer include the need for and availability of neurocritical care with neurosurgical and/or interventional neuroradiology consultation.

CRANIAL NERVE DISORDERS

The cranial nerves are 12 paired nerves that emerge from the brainstem and primarily transmit information to and from structures in the head and neck, including sense organs and muscles controlling facial expression, eye movement, and mastication. Owing to these varied functions, cranial nerve disorders often lead to sense-organ dysfunction, as well as facial pain and motor weakness. Cranial nerve dysfunction can occur through multiple etiologies including compression, infection and inflammation, ischemia, and trauma (including injury resulting from surgery). Given the multiple diverse causes of cranial nerve dysfunction, there is no well-defined at-risk population, though cancer, immunocompromise, and microvascular disease certainly may be relevant risk factors for select patients.

Cranial nerve disorders can present either with sensory dysregulation, motor weakness, or as a mixed disorder. Many of these symptoms can also be related to inflammation of local facial structures as well as systemic infections, leading to a broad differential diagnosis. Table 91.3 describes the normal function and pathologic considerations for each cranial nerve.

Trigeminal Neuralgia (Cranial Nerve V)

Foundations

Trigeminal neuralgia (TN) is an often debilitating illness causing bouts of severe facial pain, often associated with chronic underlying pain. Triggers are usually innocuous sensory stimuli, and attacks can be unpredictable, leading to a marked disruption of normal daily activities. The term *tic douloureux,* often used synonymously with TN, describes the characteristic wince patients may exhibit with a pain paroxysm. TN is slightly more common in women than in men, and most frequently affects individuals over the age of 50 years.

Trigeminal neuralgia is an idiopathic disorder, though evidence points to vascular compression of the trigeminal nerve root in many cases. This compression may be caused by a tortuous arterial or venous loop in the posterior fossa, an arteriovenous malformation, or rarely a tumor.

Clinical Features

TN is defined by three or more attacks of unilateral facial pain occurring in one or more divisions of the TN that have at least three of the following four characteristics: recurring in paroxysmal attacks, severe intensity, electric shock-like or sharp/stabbing in quality, and precipitated by innocuous stimuli to the affected side of the face. The pain is commonly associated with physical triggers such as chewing and swallowing, facial hygiene (brushing, shaving, washing), and exposure to hot or cold temperature. Patients tend to experience the pain in clustered episodes that last a few seconds to several minutes. TN can be subclassified as TN with purely paroxysmal pain or with concomitant persistent pain, which can be seen in up to 50% of affected patients. TN most frequently affects the second and third trigeminal divisions with symptoms occurring slightly more commonly on the right side of the face. Bilateral TN is very rare and should raise suspicion for an alternate or underlying cause. Autonomic symptoms such as tearing and rhinorrhea may also occur during a pain episode.

TN can also be subclassified as idiopathic/classical, or as secondary TN caused by other neurological disease such as MS or cerebellopontine tumor. As such, patients may present with additional neurological symptoms or findings. Although there are no diagnostic physical examination findings of TN, special attention should be paid to alternate possible sources of facial pain, including the teeth, temporomandibular joints, sinuses, and ears. The skin of the face and scalp should be examined for the painful vesicular eruption of zoster. Though pain is not the dominant feature of other cranial nerve disorders, it can be an associated symptom and the cranial nerves should be carefully examined.

Differential Diagnoses

Other painful facial conditions that are considered in patients with facial pain include odontogenic infections, sinus disease, otitis media, acute glaucoma, temporomandibular joint disease, and herpes zoster. Although the temporal components of the pain in these conditions are not similar to the sudden onset, lancinating pain of TN, the distribution is similar and these diagnoses should be considered before anchoring on a diagnosis of trigeminal neuralgia. There is an association between TN and MS, and though not common, TN can be the first presenting symptom of MS, and this diagnosis should be considered in the presence of other unexplained neurologic findings.

TABLE 91.3 Cranial Nerve Function and Pathologies

Cranial Nerve	Clinical Function Relevant to Emergency Medicine	Pathologic Features	Possible Causes
CN I: Olfactory nerve	Sense of smell	Unilateral anosmia	Trauma: Skull fracture or shear injury interrupting olfactory fibers traversing the cribriform plate Tumor: Frontal lobe masses compressing the nerve
CN II: Optic nerve	Vision	Unilateral vision loss	Trauma: Traumatic optic neuropathy Tumor: Orbital compressive lesion Inflammatory: Optic neuritis (MS) Ischemic: Ischemic optic neuropathy
CN III: Oculomotor nerve	Extra oculomotor function via motor fibers to levator palpebrae, superior rectus, medial rectus, inferior rectus, inferior oblique muscles Pupillary constriction via parasympathetic fibers to constrictor pupillae and ciliary muscles	Ptosis caused by loss of levator palpebrae function Eye deviated laterally and down Diplopia Dilated, nonreactive pupil Loss of accommodation	Trauma: Herniation of the temporal lobe through the tentorial opening, causing compression and stretch injury to the nerve Ischemic: Especially in diabetes; microvascular ischemic injury to nerve causes extraocular muscle paralysis but usually is papillary sparing (often painful) Vascular: Intracranial aneurysms may press on the nerve, leading to dysfunction Myasthenia gravis can lead to atraumatic ocular muscle palsy
CN IV: Trochlear nerve	Motor supply to the superior oblique muscle	Inability to move eye downward and laterally Diplopia Patients tilt head toward unaffected eye to overcome inward rotation of affected eye	Trauma is the most common cause of nerve dysfunction
CN V: Trigeminal nerve	Motor supply to muscles of mastication and to tensor tympani Sensory to cornea, face, scalp, oral cavity (including tongue and teeth)	Partial facial anesthesia Episodic, lancinating facial pain associated with benign triggers, such as chewing, brushing teeth, light touch	Trauma: Facial bone fracture may injure one section, leading to area of facial anesthesia Tic douloureux
CN VI: Abducens nerve	Motor supply to the lateral rectus muscle	Inability to move affected eye laterally Diplopia on attempting lateral gaze	Tumor: Lesions in the cerebellopontine angle Any lesion, vascular or otherwise, in the cavernous sinus may compress nerve Elevated ICP: Because of its position and long intracranial length, increased ICP from any cause may lead to injury and dysfunction of the nerve
CN VII: Facial nerve	Motor supply to muscles of facial expression Parasympathetic stimulation of the lacrimal, submandibular, and sublingual glands Sensation to the ear canal and tympanic membrane	Hemifacial paresis: Lower motor neuron lesion leaves entire side of face paralyzed Upper motor neuron lesion leaves forehead musculature functioning Abnormal taste Sensory deficit around ear Intolerance to sudden loud noises	Lower motor neuron: Infection (viral): The likely cause of Bell's palsy Lyme disease: The most common cause of bilateral CN VII palsy in areas where Lyme disease is endemic Bacterial infection extending from otitis media Upper motor neuron: Stroke, tumor
CN VIII: Vestibulocochlear nerve	Hearing and balance	Unilateral hearing loss Tinnitus Vertigo, unsteadiness	Tumor: Acoustic neuroma Mimics Ménière disease, perilymphatic fistula

Continued

TABLE 91.3 Cranial Nerve Function and Pathologies—cont'd.

Cranial Nerve	Clinical Function Relevant to Emergency Medicine	Pathologic Features	Possible Causes
CN IX: Glossopharyngeal nerve	General sensation to posterior third of tongue Taste for posterior third of tongue Motor supply to the stylopharyngeus	Clinical pathology referable to the nerve in isolation is very rare Occasionally painful paroxysms beginning in the throat and radiating down the side of the neck in front of the ear but behind the mandible	Brainstem lesion Glossopharyngeal neuralgia
CN X: Vagus nerve	Motor to striated muscles and muscles of the pharynx, larynx, and tensor (veli) palatini Motor to smooth muscles and glands of the pharynx, larynx, thoracic and abdominal viscera Sensory from larynx, trachea, esophagus, thoracic and abdominal viscera	Unilateral loss of palatal elevation: Patients complain that on drinking liquids, the fluid refluxes through the nose Unilateral vocal cord paralysis: Hoarse voice	Brainstem lesion Injury to the recurrent laryngeal nerve during surgery
CN XI: Spinal accessory nerve	Motor supply to the sternocleidomastoid and trapezius muscles	Downward and lateral rotation of the scapula and shoulder drop	Trauma to the nerve
CN XII: Hypoglossal nerve	Motor supply to the intrinsic and extrinsic muscles of the tongue	Tongue deviations: Upper motor neuron lesion causes the tongue to deviate toward the opposite side Lower motor neuron lesion causes the tongue to deviate toward the side of the lesion, and the affected side atrophies over time	Stroke or tumor can cause upper motor neuron lesion Amyotrophic lateral sclerosis can cause bilateral lower motor neuron lesion with atrophy Metastatic disease to the skull base may involve the nerve

Diagnostic Testing

The diagnosis of TN is primarily based on history and physical as there are no definitive laboratory or imaging tests. Patients with normal findings on the head and neck examination and no neurologic deficits who have episodic, unilateral facial pain associated with nonpainful triggers are likely to have TN. The presence of a neurologic deficit should prompt suspicion of a structural lesion, such as aneurysm or tumor. Patients with a neurologic deficit require urgent imaging studies, typically MRI, to rule out a mass or vascular abnormality. As classical and secondary TN cannot be confidently separated based on history and exam, MRI of the brain and brainstem has been proposed as part of the early workup on TN,[10] though in the absence of a neurologic deficit there is no recommendation for imaging in the ED.

Management

The first-line treatment of TN is sodium channel blockers, either carbamazepine (200 to 400 mg/day, titrated up to 1200 mg/day) or oxcarbazepine (300 to 600 mg/day in two divided doses, titrated up to 1800 mg/day). Generally, sodium channel blockers are effective in most TN patients; however, high dosages are often necessary, leading to frequent adverse side effects including drowsiness, dizziness, tremor, and rash. Treatment failure is typically not due to drug inefficacy, but rather to side effects leading to treatment interruption or dosage reduction to ineffective levels. Oxcarbazepine may be preferred by patients due to its more favorable side effect profile, but its higher cost may put it out of reach for some. An ECG should be obtained prior to initiating therapy as both drugs are contraindicated in patients with atrioventricular block. A complete blood count and liver function studies are performed periodically to monitor for hematologic and hepatic side effects.

Combination treatment can be considered when carbamazepine or oxcarbazepine are not effective alone or not tolerated at higher dosages. Additional agents that have been used to treat TN include phenytoin, baclofen, lamotrigine, gabapentin, and levetiracetam. That said, guidelines recommend surgical consultation as a reasonable next step if sodium channel blockers prove ineffective. Microvascular decompression is the first-choice treatment for many patients, as it provides the longest duration of pain freedom compared to other surgical techniques. While major complications are rare, sensory loss and other mild or transient cranial dysfunction are more common. Stereotactic ("gamma knife") radiosurgery, is minimally invasive but less efficacious with more frequent minor complications.

Disposition

Patients with newly suspected trigeminal neuralgia should be referred for specialty evaluation and possible neuroimaging. In patients with established diagnoses presenting for management of symptoms, consultation with a neurologist can help in therapeutic decision making. Patients with an established diagnosis who present with uncontrolled pain refractory to maximum pharmacologic management may benefit from a neurosurgical referral.

Facial Nerve Paralysis (Cranial Nerve VII)

Foundations

The facial nerve (CN VII) has motor, sensory, and parasympathetic components. It controls facial musculature, sensation to portions of the external auditory meatus and taste to the anterior two-thirds of the tongue. It also controls salivary and lacrimal glands through its parasympathetic pathways. Facial nerve dysfunction can cause facial weakness and asymmetry, abnormalities of taste, as well as dry eyes and dry

TABLE 91.4 Clinical Features Associated With Causes of Facial Nerve Paralysis

Condition	Common Clinical Features
Bell's palsy	Abrupt onset of unilateral facial weakness involving forehead improving over weeks. May include mild to moderate pain, altered taste, hyperacusis, dry eye and mouth
Stroke	Forehead sparing facial weakness, other neurological deficits.
Neoplastic	Insidious onset, minimal improvement over time or recurrent episodes, other cranial neuropathies.
Ramsey-Hunt syndrome	Pronounced pain, vesicular eruptions, vestibulocochlear dysfunction
Lyme disease	Bilateral symptoms, rash, arthralgia, exposure to endemic area
Ear infection	Ear pain, fever, hearing loss

mouth. There are multiple etiologies of facial nerve dysfunction including stroke, compression or disruption from mass lesions and trauma, infection, and others. The most frequent cause of facial nerve paralysis, Bell's palsy, is incompletely understood, though the proposed mechanisms include viral infection and ischemia.

Facial weakness can be caused by lesions of the upper motor neurons in the contralateral motor cortex, or lower motor neurons in the ipsilateral facial nerve. The bilateral innervation of forehead musculature by upper motor neurons leads to a key distinguishing characteristic: upper motor neuron lesions spare the forehead while lower motor neuron lesions typically cause weakness affecting the entire ipsilateral face.

Facial nerve paralysis, while often transient, can be a devastating event for patients causing functional and esthetic issues, particularly when recovery is delayed or incomplete. The underlying etiology may impose additional morbidity and mortality, and there are a variety of etiologies with divergent treatment strategies that may be encountered. A careful history and physical exam (particularly of the face and neurologic system) are the primary diagnostic tools, with imaging indicated in select cases.

Clinical Features

The medical history in patients with facial paralysis focuses on the distribution, onset and timing of the paralysis, concentrating on forehead involvement (involved in peripheral disease and spared in central disease as the result of crossed innervation), rapidity of onset, and associated signs and symptoms. Common clinical features associated with causative conditions are described in Table 91.4.

Bell's palsy is characterized by an abrupt onset of a lower motor neuron paresis that typically develops over 72 hours and can progress over 1 to 7 days to complete paralysis. A prodromal viral-like illness is described by 60% of patients. Symptoms and signs frequently associated with the facial paresis include ear pain, perception of sensory change on the involved side of the face, decreased tearing, overflow of tears on the cheek, sound sensitivity (hyperacusis), and impaired taste.

To make the diagnosis of Bell's palsy, both the upper and lower facial muscles must be involved. If only lower face involvement can be appreciated, there should be a suspicion for a central lesion, such as a cerebral infarct or neoplasm. Other red flags that should prompt consideration of an alternative diagnosis include vestibular or hearing abnormalities (other than hyperacusis), severe pain, rash, an unwell appearing patient, and history of cancer or tick bite.

Ramsay-Hunt syndrome may present with paresis similar to Bell's palsy, but is also characterized by a herpetiform vesicular eruption, vestibulocochlear dysfunction, and marked pain. The vesicular eruption, which may follow the facial paralysis by a few days, may occur on the pinna, external auditory canal, tympanic membrane, soft palate, oral cavity, face, and neck as far down as the shoulder. The pain is considerably more severe than that associated with Bell's palsy, and it frequently is out of proportion to physical findings. In addition, outcomes are worse than with Bell's palsy, with a lower incidence of complete facial recovery and the possibility of sensorineural hearing loss.

Systemic symptoms or bilateral facial paresis should raise the possibility of Lyme disease or other systemic infection. Lyme disease is the most frequent vector-borne infection in the United States. It is caused by the spirochete *Borrelia burgdorferi* and is spread by the bite of *Ixodes* genus ticks. Neurologic manifestations can arise in any phase of the disease, and facial palsy accounts for up to 50% of the neurologic presentations. In regions in which Lyme disease is endemic, it is the leading cause of facial paralysis in children. Infectious mononucleosis can also cause bilateral facial paralysis.

Facial paralysis can be caused by acute bacterial infections of the middle ear, mastoid, or external auditory canal. While it is very rare for an uncomplicated ear infection to result in facial paralysis, this may be seen with malignant otitis externa. This disease entity is most commonly seen in immunocompromised patients and usually is caused by *Pseudomonas* infection.

Differential Diagnoses

In addition to the disorders previously discussed, paralysis of CN VII can be caused by disruption of the nerve as a result of trauma or surgical procedures. Neoplasia, either tumors of the facial nerve itself or tumors that compress the nerve, can also lead to facial nerve paralysis. The course is typically (though not always) of slower onset than Bell's palsy. Although very rare overall, a neoplastic cause should be suspected in patients who suffer from recurrent ipsilateral facial paralysis, significant pain, prolonged symptoms, or any other concomitant CN abnormality.

Diagnostic Testing

The diagnostic evaluation of acute facial nerve paresis is based on whether the clinical picture is suggestive of a disease process other than Bell's palsy, highlighting the importance of a focused history and physical examination. In the absence of atypical features or identifiable risk factors, routine laboratory testing and diagnostic imaging are not recommended.[11] The presence of a "central" seventh nerve paralysis (upper face sparing) should prompt imaging with CT or MRI, and consideration given to the possibility of an acute stroke or other hemispheric lesion. History or physical findings suggestive of a possible tumor require imaging to rule out a neoplasm. A history that poses potential exposure to Lyme warrants serologic evaluation for the disease.

Management

The primary medical therapy for Bell's palsy is corticosteroids. Multiple studies have demonstrated that corticosteroids reduce the incidence of post infection residual facial weakness. A recent meta-analysis calculated the number needed to treat (NNT) as 10 in order to prevent one person left with facial weakness.[12] Guidelines recommend a 10-day course of oral corticosteroids with at least 5 days of high dose (prednisolone 50 mg for 10 days or prednisone 60 mg for 5 days with a 5-day taper).[13] Early treatment improves outcomes and therapy should be started as soon as possible, ideally within 72 hours of symptom onset.

Reflecting on the theory that herpes simplex virus may be a cause of Bell's palsy, a number of studies have considered the use of antivirals, either alone or in combination with corticosteroids. One meta-analysis demonstrated that antivirals alone were less effective than corticosteroids alone, and that the addition of antiviral therapy to corticosteroid therapy added little to no benefit over steroids alone.[14]

The treatment of Ramsey-Hunt syndrome is similar to that of Bell's palsy; however, antiviral treatment (acyclovir 400 mg five times daily or valacyclovir 1000 mg TID) is recommended. Both prednisone and antiviral therapy should be continued for 7 to 10 days. Other infectious causes of facial nerve paralysis (Lyme disease, infectious mononucleosis, malignant otitis externa) should be treated with directed antimicrobial therapy; severe local infection (such as malignant otitis externa) may require surgical debridement.

Patient education regarding meticulous eye care is of key importance. Inability to close the eyelids combined with decreased lacrimation can lead to corneal abrasions, keratitis, and ulcers. Prophylactic eye care includes barrier precautions (protective glasses, eye patches) as well as artificial tears, ideally with a thicker protective ointment during sleep.

Disposition

Most patients who have a seventh CN paralysis will have a clinical diagnosis of Bell's palsy and may be discharged with referral for short-term follow-up. Patients with a possible hemispheric process, such as stroke or tumor, require further evaluation and often hospitalization. Patients thought to have Lyme disease require immediate initiation of antibiotic therapy. Patients should be counselled regarding their expected timeline for recovery. Although mild paresis typically recovers within 2 to 3 weeks, complete paralysis may take up to 6 to 12 months for recovery, and some patients may not fully recover all function.

Vestibular Schwannoma (Cranial Nerve VIII)

Foundations

Vestibular schwannomas (VS) are tumors of the vestibular nerve, that though histologically benign, can impact the quality of life through hearing loss, imbalance, and other symptoms. VS, also referred to as acoustic neuroma, account for 80% of all cerebellopontine angle tumors. The incidence has increased over recent decades, though this is likely related to increased frequency of neuroimaging for other causes and identification of VS as an incidental finding. The median age of onset is about 50 and hearing loss is almost always unilateral (bilateral disease occurs in approximately 5% of cases and generally associated with type 2 neurofibromatosis).

Vestibular schwannomas arise from the Schwann cells covering the vestibular branch of the CN VIII as it passes through the internal auditory canal. The tumor may compress the cochlear (acoustic) branch of the CN VIII, causing hearing loss, tinnitus, and disequilibrium. Continued growth of the tumor may result in compression of structures in the cerebellopontine angle, where CN V and CN VII may be compressed and damaged. Larger tumors may further encroach on the brainstem and, if large enough, may compress the fourth ventricle, ultimately resulting in signs of increased intracranial pressure (ICP).

Clinical Features

Asymmetrical sensorineural hearing loss is the hallmark of vestibular schwannoma. Up to 15% of patients with this tumor, however, will have normal results on audiometry. These patients typically have symptoms such as unilateral tinnitus, imbalance, headache, fullness in the ear, otalgia, and facial nerve weakness. Thus, patients with asymmetrical symptoms should be further evaluated for vestibular schwannoma even with normal findings on audiometry. Vestibular schwannomas are extremely slow-growing tumors, averaging a 1-mm increase per year, although some do not grow at all. The median time from symptom onset to diagnosis is 12 months.

Differential Diagnoses

While symmetrical sensorineural hearing loss has numerous causes, asymmetrical sensorineural hearing loss has few causes other than VS. Ménière disease may present with asymmetrical findings, but it can be differentiated from VS in that the tinnitus of Ménière disease is usually intermittent, whereas that of VS is continuous. In addition, patients with Ménière disease typically describe true vertigo, whereas those with a VS are more likely to describe imbalance or disequilibrium. Meningiomas, the second most common cerebellopontine angle tumor, more frequently cause symptoms of facial palsy or trigeminal nerve abnormality. However, there can be some clinical similarity between the two tumor types.

Diagnostic Testing

In general, diagnostic testing for VS can be performed as an outpatient. When suspected, testing includes MRI and audiometry. MRI is extremely sensitive and has led to earlier diagnosis and a decrease in mean size at detection of vestibular schwannoma. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of VS. The smaller the tumor at the time of diagnosis, the more options there are for therapy and the better the prognosis.

Management

There are currently three main approaches for managing newly diagnosed VS: observation with active surveillance, surgical resection, and stereotactic radiation therapy. Observation may be appropriate for elderly patients with comorbidities, small tumor size, and absence of symptoms. Due to the continued growth of most tumors however, observation is often associated with progressive hearing loss. In appropriately selected patients, there is little difference in long-term quality-of-life based on surgical resection versus radiotherapy. In general, tumors larger than 3 cm are recommended for microsurgery because radiation poses a risk of brain stem compressions due to posttreatment edema. Smaller tumors may be treated with surgery or radiation.

Disposition

Patients with suspected acoustic neuroma should be referred for audiometry or MRI and evaluation by a specialist in either otolaryngology or neurosurgery.

Diabetic Cranial Mononeuropathy

Foundations

Cranial mononeuropathies are uncommon and are usually a complication of diabetes. They most often affect the extraocular muscles causing ophthalmoplegia. The oculomotor nerve (CN III) is most commonly affected, followed by the trochlear (CN IV) and abducens (CN VI) nerves. CN palsies occur in 1% of diabetics versus 0.1% of nondiabetics. They are more likely to occur in patients over the age of 50 years. The pathologic basis of diabetic mononeuropathy appears to be ischemia caused by occlusion of an intraneural nutrient artery serving the nerve. This occlusion leads to injury located primarily in the core fibers, whereas the peripheral nerve fibers are less affected because they also are supplied by collateral vessels. In the oculomotor nerve, the preservation of the circumferentially located parasympathetic fibers explains the pupillary sparing that usually is found in this condition.

The anatomy of the third CN is particularly important to consider. Centrally located motor fibers controlling extraocular movement are likely to be affected by vascular ischemic disease. Parasympathetic

fibers associated with the pupillary light reflex run superficially within the nerve; while pupillary findings can result from microvascular ischemia, they should raise concern for compression of CN III from aneurysm in the posterior cerebral arteries.

Clinical Features

Diabetic cranial nerve palsy often results in diplopia, which may be worsened by the direction of gaze. Physical examination may demonstrate asymmetric positioning of the eyes at rest or with directional gaze. The physical manifestations of a CN III palsy include the inability to move the eye superiorly and medially (leading to the "down and out" position at rest), accompanied by ptosis. The pupillary light reflex usually is present. Although it is a less common finding, CN IV and CN VI may be affected. Patients with a CN IV palsy are unable to move the eye inferolaterally, and those with a CN VI palsy are unable to move the eye laterally. Because of the long intracranial course of CN VI, a patient with an isolated sixth nerve palsy should be evaluated for an intracranial lesion or increased ICP.

Differential Diagnoses

Diabetic mononeuropathy is generally a diagnosis of exclusion. Considerations in the differential diagnosis include trauma, tumor, vertebrobasilar ischemia, aneurysm, and brainstem hemorrhage. Unequal pupils or an abnormal pupillary light reflex should be considered a red flag for a more worrisome cause.

Diagnostic Testing

The key clinical dilemma in a diabetic patient presenting with new onset oculomotor neuropathy relates to the use of diagnostic imaging to rule out potentially life-threatening etiologies. There is no clear clinical consensus on neuroimaging, with a recent meta-analysis demonstrating discrepancies in practice between neurologists and ophthalmologists (with neurologists being more likely to use imaging).[15] It is generally accepted that pupillary involvement warrants evaluation for aneurysm with either MR or CT angiography. Similarly, if other CN are involved or there are other acute neurologic deficits, neuroimaging for stroke is warranted. While there is not a clear treatment recommendation for the ED provider, clinical history and physical examination are thought to be sufficient in the majority of cases, and there is no evidence that diagnostic imaging is required in the diabetic patient presenting an isolated CN III palsy with sparing of the pupillary light reflex and no other neurologic abnormalities.

Management

Treatment consists of patching the affected eye and administration of analgesics and antiplatelet therapy. The prognosis is good and the neuropathy generally resolves within 3 to 6 months.

Disposition

Assuming aneurysm and stroke have been excluded as causes of cranial mononeuropathy, patients may be discharged home. There is some evidence demonstrating that patients with diabetes diagnosed with a CN palsy have a higher risk of subsequent ischemic stroke.[16] While the evidence for this is limited, there is certainly no downside to using the clinical encounter to identify modifiable risk factors for stroke and encourage treatment compliance and outpatient follow up.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 91: QUESTIONS AND ANSWERS

1. A 30-year old woman with no past medical history presents complaining of weakness and spasms in both legs. She describes prior episodes of numbness in her feet that lasted for a few weeks at a time before resolving. She also notes right eye pain, and unilateral papilledema is noted on fundoscopic exam. What is the most appropriate next step in this patient's management?

a. Lumbar puncture
b. Ophthalmology consultation
c. Discharge home and referral to neurologist
d. MRI of the brain and spinal cord
e. IV corticosteroids

Answer: d. This patient is presenting with symptoms suggesting a new diagnosis of Multiple Sclerosis. Early diagnosis and initiation of therapy has been shown to improve outcomes. MRI is a sensitive test in identifying lesions consistent with MS. While MRI may not always be an option in the ED, it should be strongly considered and pursued when available. Lumbar puncture is also a useful test in the evaluation of possible MS, and while there are characteristic CSF findings, LP is of less initial utility than MRI. Non-contrast head CT may be useful in investigating other causes, but it will not identify MS lesions. Discharge home with neurology home is appropriate, but MRI in the ED would likely expedite diagnosis and initiation of therapy.

2. A 65-year-old woman with a history of MS presents with worsening pain, paresthesias, and weakness in her right leg over the last 3 days, which she describes as common symptoms during relapse. She has 4/5 motor strength and increased deep tendon reflexes in her right leg. These findings are noted on prior ED notes. She has a temperature of 102.6°F and otherwise normal vital signs: What is the most appropriate next step in this patient's management?

a. Obtain CBC, chest x-ray, and urinalysis
b. CT of brain
c. Rapid initiation of IV antibiotics followed by lumbar puncture
d. Discharge home with NSAIDs for fever and pain
e. Discharge home with oral corticosteroids

Answer: a. This patient is presenting with an exacerbation of MS. A relapsing and remitting pattern is characteristic. Infection is a common precipitating cause of MS relapse, and investigating the source of infection can help determine the need for and selection of antibiotic therapy. While there may be a need for lumbar puncture and imaging of the brain, these are not necessarily indicated in this scenario. In addition to a possible need for antibiotic therapy, IV or oral corticosteroids can be used to manage the symptoms of MS relapse.

3. A 38-year-old woman presents 8 weeks postpartum with a 1-week history of severe headache and progressively altered mental status, which culminated in a seizure several minutes before presentation. On examination, she is normotensive, appears postictal, but has no focal neurologic findings. Ophthalmoscopic examination reveals papilledema, and non–contrast-enhanced head computed tomography (CT) reveals a dense sagittal sinus and a small venous hemorrhage in the occipital region. What is the most appropriate next step in this patient's management?

a. 325 mg aspirin
b. Dexamethasone 10 mg IV push
c. Hypertonic saline 500-mL bolus
d. Mannitol 1 g/kg
e. Systemic anticoagulation with unfractionated heparin or low-molecular-weight heparin (LMWH)

Answer: e. The patient presents with a venous sinus thrombosis. Although large, randomized trial data do not exist, case series and expert consensus strongly suggest improved outcomes with systemic anticoagulation, even in the setting of venous hemorrhage on head CT. Osmotic agents and steroids have no proven benefit in the management of sinus thrombosis and may cause harm. Antiplatelet agents may be considered if absolute contraindications to anticoagulation exist but probably have lower therapeutic efficacy.

CHAPTER 91: QUESTIONS AND ANSWERS—cont'd.

4. A 26-year-old man presents with a left facial droop. The symptoms began painlessly 3 days ago without a prodrome. Examination reveals a left facial droop with an inability to wrinkle the forehead without other associated physical examination abnormalities. What is the most appropriate next step in this patient's management?
   a. Discharge home with reassurance that symptoms usually resolve in a few weeks
   b. Initiation of oral antiviral therapy
   c. Initiation of oral corticosteroids
   d. Serologic testing for Lyme disease
   e. Urgent non–contrast-enhanced computed tomography (CT) scan of the head

Answer: c. The patient has Bell's palsy, which is a painless left facial nerve palsy. The primary symptom is a left peripheral nerve paralysis often with unilateral dysgeusia, hyperacusis, and external canal and pharyngeal numbness. Facial sensation is intact. Corticosteroids have been shown to improve outcomes, and they should be initiated as soon as possible. Antiviral therapy in combination with corticosteroids may be considered (conflicting evidence exists) but they are less efficacious than corticosteroids when given alone. Given the classic picture and lack of other associated neurologic findings, CT scan of the head is not required and is not likely to provide benefit. Testing for Lyme disease should be considered in Lyme endemic areas or in patients with a history of a tick bite.

5. Which of the following clinical features would make a diagnosis of Bell's palsy less likely?
   a. Increased sensitivity to sound
   b. Decreased tearing on the affected side
   c. A prodromal viral-like illness
   d. Rash
   e. Altered sensation of taste

Answer: d. In addition to the unilateral facial weakness involving the forehead, Bell's palsy may present with increased sound sensitivity (hyperacusis), altered sense of taste (dysgeusia). Decreased tearing may also occur, and viral illness is known to be a precipitating cause. Rash is not characteristic of Bell's palsy, and the presence of a herpetiform vesicular eruption should raise suspicion for Ramsey-Hunt syndrome. Other features that raise suspicion for an alternative diagnosis include vestibular symptoms, bilateral or forehead-sparing distribution, involvement of other cranial nerves, and signs of systemic illness.

6. A 62-year-old woman presents with one day of episodic sharp unilateral facial pain brought on often by combing her hair. She has had several similar episodes over the last year. Examination of the head and neck, as well as cranial nerves, is unremarkable. Which of the following is the most appropriate next step in this patient's management?
   a. The patient should be started on carbamazepine and referred to a neurologist
   b. Neuroimaging
   c. Discharge with short course of oral prednisone.
   d. Timely referral to a neurosurgeon
   e. NSAIDs and reassurance that condition generally resolves without therapy

Answer: a. This patient has met diagnostic criteria for trigeminal neuralgia (TN). TN can be a debilitating condition and is marked by episodic severe episodic facial pain brought on by innocuous stimuli. TN is a clinical diagnosis, and while some suggest that MRI be part of the diagnostic process to evaluate secondary causes of TN, urgent neuroimaging is not indicated in the absence of neurologic deficit or other concerns. First line therapy are sodium-channel blockers such as carbamazepine. Patients who continue to have symptoms with pharmacologic therapy should be referred to a surgeon for consideration of microvascular decompression.

7. A 58-year-old woman presents with progressive right-sided hearing loss along with a sensation of fullness in the ear and otalgia. Her otic canal and tympanic membrane appear normal and she has no mastoid tenderness. Her cranial nerve exam demonstrates right sensorineural hearing less, and the remainder of her neurologic exam is normal. Which of the following is the most appropriate next step in this patient's management?
   a. Admission for IV steroid therapy
   b. Discharge home with instructions for outpatient workup
   c. Head CT
   d. Prompt otolaryngology consultation
   e. Discharge home with otic hydrocortisone/neomycin/polymyxin for pain control

Answer: b. This patient likely has a vestibular schwannoma (VS), a slow-growing tumor of the vestibular nerve that is the most common cause of asymmetric sensorineural hearing loss. Patients may also complain of headache, disequilibrium, and tinnitus. Workup of potential VS, which includes MRI and audiometry, can generally be performed as an outpatient, with subsequent referral to an otolaryngologist or neurosurgeon. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of vestibular schwannoma.

8. A 54-year-old man with a history of poorly controlled diabetes presents with diplopia. Physical exam reveals the inability to move the right eye superiorly and medially, accompanied by ptosis. The right pupil in larger than the left, and poorly responsive to light. Which of the following is the most appropriate next step in this patient's management?
   a. Oral corticosteroid therapy
   b. Discharge with patient education on importance of blood sugar control to minimize risk of stroke.
   c. Prompt referral to an ophthalmologist
   d. MRI brain
   e. Initiation of systemic anticoagulation therapy

Answer: d. Cranial neuropathies are uncommon and usually a complication of diabetes. They most often affect extraocular muscles, causing ophthalmoplegia. The oculomotor nerve (III) is most commonly involved, leading to the inability to move the affected eye superiorly and medially. The etiology of diabetic mononeuropathy is thought to be microvascular ischemia. Fibers controlling pupillary size and light reflex run superficially, and while they can be affected by microvascular ischemia, they are more suspectable to external compression. Ophthalmoplegia with pupillary involvement should raise concern of a posterior cerebral artery aneurysm causing compression of CN III. MRI or CT angiogram is indicated in this situation. In the absence of pupillary involvement or other cranial nerve abnormalities, there is not a clear requirement for imaging in the ED. Attention to modifiable risk factors is important as there may be an association of diabetic mononeuropathy with subsequent stroke risk.

92

Spinal Cord Disorders

Adam D. Hill and Micah J. Nite

KEY CONCEPTS

- Nontraumatic spinal cord disorders can be intrinsic or extrinsic, some of which require prompt diagnosis, advanced imaging, and specialist intervention to prevent or limit permanent neurologic dysfunction.
- The bulbocavernosus reflex is cord-mediated. Return of this reflex following a spinal injury marks the termination of spinal shock.
- Anterior cord syndrome is marked by symmetrical motor loss but intact proprioception and vibration sense.
- In patients with sudden severe back pain, consider spinal subarachnoid hemorrhage (SSAH) or spinal epidural hematoma (SEH), both of which are diagnosed using magnetic resonance imaging (MRI).
- Transverse myelitis is inflammation of the spinal cord often associated with a prior viral infection resulting in paraplegia and a defined sensory level impairment. MRI with contrast enhancement is the diagnostic modality of choice. Roughly one-third of patients have a good outcome.
- Cauda equina syndrome can be difficult to differentiate from conus medullaris lesions because both can result in bladder retention, fecal incontinence, leg weakness, and sensory loss in the perineum. Conus lesions are more typically bilateral, whereas cauda equina syndrome may be unilateral. Upper motor neuron findings are expected with conus lesions while cauda equina syndrome is associated with hypo- or areflexia.
- Central cord syndrome is often due to a hyperextension injury. Physical findings are represented with the mnemonic **MUD**: **M**otor deficits > sensory, **U**pper extremities > lower, **D**istal extremity findings > proximal.
- Brown-Séquard syndrome is due to a functional hemisection of the spine (frequently traumatic) resulting in ipsilateral loss of motor function, proprioception, and vibration with contralateral loss of pain and temperature sensation below the level of injury.
- The diagnostic imaging of choice in the majority of suspected spinal disorders is MRI with contrast.
- A syrinx is a cavitary lesion in the spinal cord that presents with a sensory disassociation predominately in the upper extremities. With progression, it can lead to upper extremity weakness and wasting. Symptom exacerbation with cough or Valsalva is typical.
- With compressive lesions of the spinal cord, neurologic status at the time of intervention and the duration of symptoms are directly related to outcome.
- Autonomic dysreflexia is a complication of spinal cord injury that can result in life-threatening hypertension. Hypertension may be the result of bladder distention, fecal impaction, pain, or infection. Treatment focuses on blood pressure management and the identification and treatment of inciting noxious stimuli.

FOUNDATIONS

This chapter focuses on nontraumatic processes affecting the spinal cord, both extrinsic and internal. The ultimate neurologic outcome of patients with many of these disorders depends on expeditious recognition and management in the emergency department (ED).

Anatomy

In adults, the spinal cord is approximately 40 cm long and extends from the foramen magnum, where it is continuous with the medulla oblongata, to the body of the first or second lumbar vertebra (L1 to L2). The spinal cord is covered in the same three meningeal layers as the brain: the pia mater (innermost), arachnoid mater (middle), and dura mater (outermost). Inferiorly, the cord tapers into the conus medullaris (L1), where several segmental levels are represented in a small area. The lumbar and sacral nerve roots form the cauda equina as they descend caudally in the thecal sac before exiting the spinal canal at the respective foramina. The filum terminale, a non-neural strand of fibrous tissue composed of pia whose function is to suspend the cord in the subarachnoid space, runs from the tip of the conus and inserts into the dura at the level of the second sacral vertebra (S2).

Two symmetrical enlargements of the spinal cord contain the segments that innervate the limbs. The first occurs at the junction of the cervical (C) and thoracic (T) vertebrae. The *cervical enlargement* (C5 to T1) gives rise to the brachial plexus and peripheral nerves of the upper extremity. The second area is located at the junction of the thoracic and lumbar (L) vertebrae. The *lumbar enlargement* (L2 to S3) gives rise to the lumbosacral plexus and peripheral nerves of the lower extremity. The space surrounding the cord at these particular levels is reduced leaving it more vulnerable to external compression. At each segmental level, anterior (ventral) and posterior (dorsal) roots arise from rootlets along the anterolateral and posterolateral cord surfaces. Anterior roots convey the outflow of the motor neurons in the anterior horn of the spinal cord while posterior roots contain neurons and fibers that convey sensory inflow.

The arterial supply of the spinal cord is derived primarily from two sources (Fig. 92.1). The single anterior spinal artery arises from the paired vertebral arteries at the base of the skull. It runs the entire length of the cord in the midline anterior median sulcus and supplies the anterior two-thirds of the spinal cord. Blood supply to the posterior third of the spinal cord is derived from the smaller paired posterior spinal arteries that arise from the vertebral arteries near the skull base and run bilaterally along the posterior cord. These three major spinal arteries receive segmental contributions from radicular arteries throughout their caudal projection, the largest being the artery of Adamkiewicz, which typically originates from the aorta between T8 and L4. The venous drainage of the cord largely parallels the arterial supply.

The internal anatomy of the spinal cord is divided into central gray matter, containing cell bodies and their processes, and surrounding white matter, where the ascending and descending myelinated fiber tracts are located. These white matter fiber tracts are organized into discrete bundles; the ascending tracts convey sensory information while the descending tracts convey the efferent motor impulses and visceral innervation.

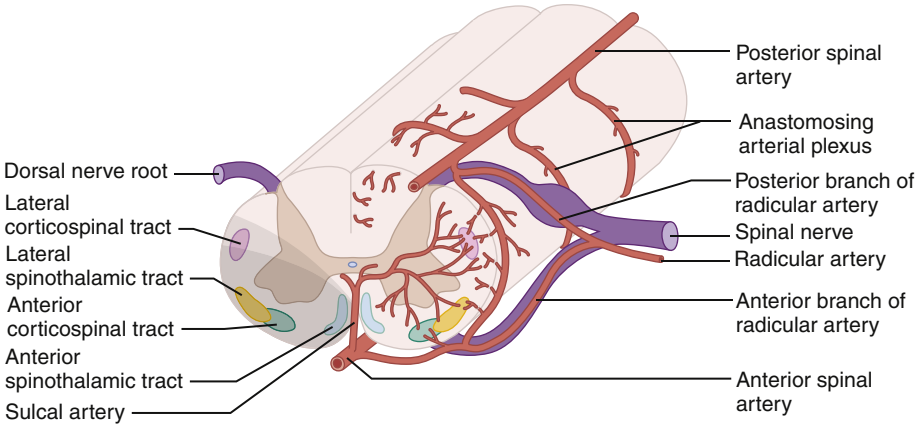


Fig. 92.1 Arterial blood supply to the spinal cord. The anterior spinal artery supplies blood to most of the anterior spinal cord, as well as the lateral column area of the cord (*darkly shaded area*). Some areas of the cord are supplied blood by both the anterior and posterior circulation (*light gray–shaded area*); there is variation among individuals. The anterior horn cells and lateral spinothalamic tracts rely on the anterior spinal artery for blood supply. (Modified from: Yang ML, Connolly AM. Other Motor Neuron Diseases of Childhood. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology*, ed 6. Philadelphia: Elsevier; 2017.)

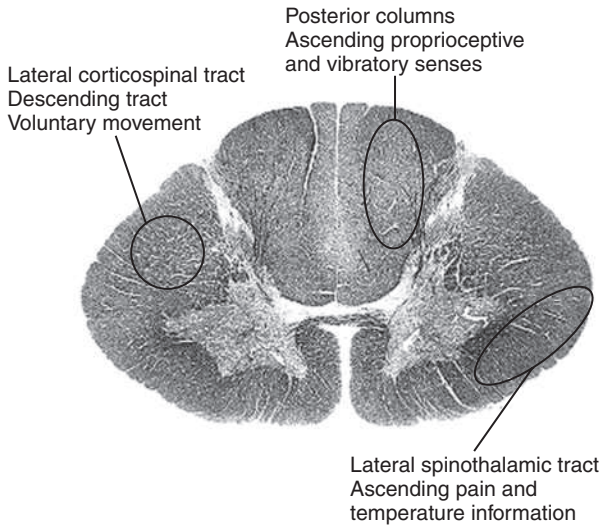


Fig. 92.2 Simplified spinal cord anatomy showing clinically essential motor and sensory tracts. (Photomicrograph courtesy John Sundsten, Digital Anatomist Project, University of Washington.)

For clinical purposes, neuroanatomy of the spinal cord may be greatly simplified, as depicted in Figure 92.2. Tracts are named starting with the point of origin followed by the destination; the spinothalamic tract, for example, arises in the spinal cord and travels to the thalamus. Major ascending sensory tracts are labeled on the right side of the figure, with descending motor tracts on the left. The posterior column (dorsal column) carries afferent ascending proprioceptive and vibratory information on the ipsilateral side of the cord from the area stimulated to the brain; crossing of these fibers occurs in the medulla resulting in contralateral cortical representation. Within the cord, the posterior column is arranged with the sacral fibers existing medially and the cervical fibers laterally. The lateral spinothalamic tract conveys afferent information about pain and temperature in a portion of the lateral column of white matter. The tract is arranged so that sacral fibers are located laterally and cervical fibers medially, a reversal from the posterior column arrangement. Crossing of fibers from this tract occurs near the level of entry of the spinal nerve resulting in contralateral representation in the cord. This is why an isolated cord lesion affecting a spinothalamic tract results in decreased or absent pain and temperature perception below the level of injury on the opposite side of the body.

The major descending motor tract is represented in the lateral corticospinal tract, originating in the cortex of the brain and traveling to the spinal cord. Crossing of this tract occurs in the medulla, similar to the ascending posterior column, meaning that motor signals from one side of the brain ultimately descend down the opposite cord side and result in motion of the contralateral body. This tract is organized similar to the lateral spinothalamic, with sacral fibers located laterally and the cervical fibers medially. The cell bodies of the lower motor neurons (anterior horn cells) are in the ventral portion of the gray matter of the spinal cord.

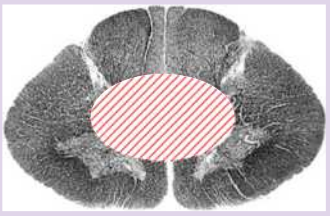
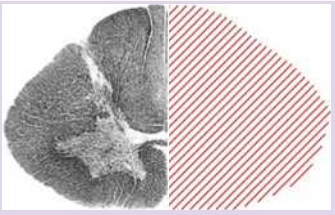
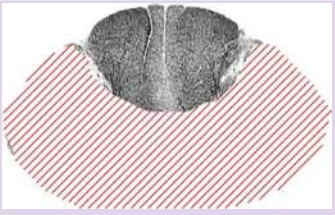
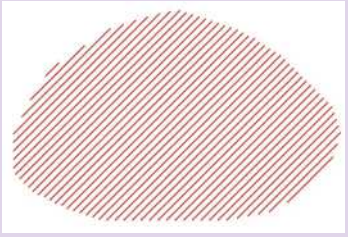
Classification of Spinal Cord Syndromes

The anatomic organization of the spinal cord lends itself to a corresponding anatomic-pathophysiologic classification of cord dysfunction (Table 92.1). Any of the different cord syndromes may be the final clinical picture of a variety of pathologic processes. These syndromes do frequently exist in partial or incomplete forms, adding to the diagnostic challenge.

Complete (Transverse) Spinal Cord Syndrome

Complete spinal cord lesions may be manifested as either acute or subacute processes. It is defined as a total loss of sensory, autonomic, and voluntary motor innervation distal to the spinal cord level of injury. Neural responses mediated at the spinal level, such as deep tendon reflexes, may persist but may also be absent (early stages) or hyperreflexic (later stages). Autonomic dysfunction may be manifested acutely with hypotension (neurogenic shock) or priapism. The most common cause of a complete cord syndrome is trauma, though other etiologies are possible including infarction, hemorrhage, and extrinsic compression. In patients with complete syndromes that persist for more than 24 hours, functional recovery almost never occurs. Any evidence of preserved cord function below the level of injury denotes a partial rather than complete lesion. Signs such as persistent perineal sensation (sacral sparing), reflex rectal sphincter tone or voluntary rectal sphincter contraction, and even slight voluntary toe movement suggest a partial cord lesion, which carries a better prognosis than a complete lesion.

TABLE 92.1 Spinal Cord Syndromes

Syndrome	Sensory	Motor	Sphincter Involvement
 Central cord syndrome	Variable	Upper extremity weakness, distal > proximal	Variable
 Brown-Séquard syndrome	Ipsilateral position and vibration sense loss Contralateral pain and temperature sensation loss	Motor loss ipsilateral to cord lesion	Variable
 Anterior cord syndrome	Loss of pain and touch sensation Vibration, position sense preserved	Motor loss or weakness below cord level	Variable
 Transverse (complete) cord syndrome	Loss of sensation below level of cord injury	Loss of voluntary motor function below cord level	Sphincter control lost
Conus medullaris syndrome	Saddle anesthesia may be present; Sensory loss may range from patchy to complete transverse pattern	Weakness may be of upper motor neuron type; Bilateral	Sphincter control impaired
Cauda equina syndrome	Saddle anesthesia may be present; Sensory loss may range from patchy to complete transverse pattern	Weakness may be of lower motor neuron type; Unilateral	Sphincter control impaired

Spinal shock refers to the loss of muscle tone and reflexes with a complete cord syndrome during the acute phase of injury. It typically lasts less than 24 hours but has been reported to occasionally last days or weeks. A marker of spinal shock is loss of the bulbocavernosus reflex, which is a normal cord-mediated reflex that may be preserved in complete cord lesions. The bulbocavernosus reflex involves involuntary contraction of the anal sphincter in response to a squeeze of the glans penis, clitoris, or outward tug on a Foley catheter. Termination of the spinal shock phase of injury is heralded by the return of the bulbocavernosus reflex, with increased muscle tone and hyperreflexia following later.

Incomplete (Partial) Spinal Cord Lesions

Incomplete lesions are characterized by functional preservation of various portions of the spinal cord. Of the many possible incomplete lesions, most can be classified as one of three clinical syndromes based on functionality: (1) central cord syndrome, (2) Brown-Séquard syndrome, or (3) anterior cord syndrome.

Central Cord Syndrome. Central cord syndrome is the most common of the partial cord syndromes. Because of the anatomic organization of the spinal cord, a central cord injury is characterized by bilateral motor paresis. The upper extremities and distal muscle groups are affected to a greater degree than the lower extremities and proximal muscle groups. Sensory impairment and bladder dysfunction are variable features. At times, burning dysesthesias in the upper extremities may be the dominant clinical feature. The mnemonic "MUD" can aid in recall of these features: **M**otor greater than sensory, **U**pper greater than lower, **D**istal greater than proximal.

Central cord syndrome affects the central gray matter and the central portions of the corticospinal and spinothalamic tracts. It is

most often caused by a hyperextension injury, frequently from falls or motor vehicle accidents. The postulated mechanism is squeezing of the cord anteriorly and posteriorly due to inward bulging of the dorsally located ligamentum flavum resulting in a contusion to the spinal cord which most affects the central cord. This injury often occurs in elders with degenerative arthritis and spinal stenosis in the cervical area but can affect patients with cervical canal narrowing of any etiology (i.e., disc protrusion, tumor, or congenital narrowing as in achondroplasia). The prognosis depends on the degree of injury at presentation as well as the patient's age, with advanced age predicting decreased functional outcome. In patients younger than 50 years old, more than 80% regain bladder continence and approximately 90% return to full ambulatory status; in patients older than 50 years, only 30% regain bladder function and approximately 50% regain the ability to ambulate.

Brown-Séquard Syndrome. Brown-Séquard syndrome is the result of an anatomic or functional hemisection of the spinal cord. Usually associated with penetrating injuries, Brown-Séquard syndrome also may be seen with compressive or intrinsic lesions. It has been reported in association with spinal cord tumors, spinal epidural hematomas, vascular malformations, cervical spondylosis, degenerative disc disease, herpes zoster myelitis, radiation injury, and as a complication of spinal instrumentation. In its pure form, it is characterized by ipsilateral loss of motor function, proprioception, and vibration sense with contralateral loss of pain and temperature sensation below the level of injury. Because fibers associated with the lateral spinothalamic tract ascend one or two spinal cord segments before crossing to the contralateral side, ipsilateral anesthesia (pain and temperature modalities) may be noted one or two segments above the lesion, although this observation is variable. Most patients with this syndrome incur only partial sensory and motor impairment, so the classic pattern is not always seen. Brown-Séquard syndrome carries the best prognosis of any of the incomplete spinal cord syndromes. Fully 80% to 90% of patients regain bowel and bladder function, 75% regain ambulatory status, and 70% become independent in their activities of daily living.

Anterior Cord Syndrome. Anterior cord syndrome is characterized by loss of motor function, pinprick, and light touch below the level of the lesion with preservation of the posterior column modalities, including position, vibration, and some touch. Although most reported cases of anterior spinal cord syndrome follow aortic surgery, it may also occur after severe hypotension, infection, myocardial infarction, vasospasm from drug reaction, and aortic angiography. Mechanically, the lesion may be caused by cervical hyperflexion resulting in a cord contusion or by protrusion of bone fragments or herniated cervical disc material into the canal. Rarely, it is produced by laceration or thrombosis of the anterior spinal artery or a major radicular vessel. Functional recovery varies, with most improvement occurring during the first 24 hours and little improvement thereafter. Although anterior cord lesions from ischemia usually are incomplete, patients without motor function at 30 days have little or no likelihood of regaining any motor function by 1 year. Only 10% to 20% of patients regain some muscle function, and even in this group there is little power or coordination.

Conus Medullaris and Cauda Equina Syndromes

The differentiation between conus medullaris and cauda equina lesions in clinical practice is difficult because the two disorders overlap in their clinical presentation. In addition, a combined lesion can mask clear clinical symptoms or signs of either an upper or a lower motor neuron type of injury.

Physical features of conus medullaris syndrome may involve disturbances of urination (usually from a denervated, spastic, autonomic bladder that manifests as overflow incontinence) and sphincter impairment (decreased rectal tone) or erectile dysfunction. Sensory involvement may affect the sacral and coccygeal segments, resulting in saddle anesthesia. Pure lesions of the conus medullaris are rare. Upper motor neuron signs, such as increased motor tone and hyperreflexia, may be present, but their absence does not exclude the syndrome.

Conus medullaris syndrome can be caused by central disc herniation, neoplasm, trauma, or vascular insufficiency. Because the conus is such a small structure, with lumbar and sacral segments represented in a minimal area, a lesion will usually cause bilateral symptoms. This finding may help distinguish conus medullaris lesions from those in the cauda equina, which often are unilateral.

Cauda equina (Latin for "horse's tail") is the name given to the lumbar and sacral nerve roots that continue on within the dural sac distal to the conus medullaris. Not a true "cord syndrome" as the cord itself is unaffected, cauda equina syndrome represents dysfunction at the level of nerve roots. The anatomic clustering of nerve roots within the lumbar dural sac allows insult to multiple nerve roots to occur simultaneously.

Cauda equina syndrome is usually caused by the midline rupture of an intervertebral disc most commonly at the L4 to L5 level, but any compressive mass can cause it. As in conus medullaris syndrome, patients generally present with progressive symptoms of fecal or urinary incontinence, impotence, decreased rectal tone, distal motor weakness, and saddle anesthesia. Deep tendon reflexes may be reduced. All of these findings have low sensitivity but moderately good specificity in the diagnosis, with saddle anesthesia and bowel/bladder changes having a specificity range of 70% to 89%.[1] Of note, a complaint of low back pain may or may not be present.

CLINICAL FEATURES

History

Weakness, sensory abnormalities, and autonomic dysfunction are the cardinal manifestations of spinal cord dysfunction. The tempo and degree of impairment often reflect the disease process. Past medical history is vital because an underlying coagulopathy or other systemic process may be elicited. A history of cancer suggests the possibility of metastatic disease. Recent trauma raises the possibility of vertebral fracture or disc protrusion. The acuity of pain can help narrow the differential diagnosis as well, with sudden pain or dysfunction more likely to be a vascular catastrophe, and slower onset, midline pain in the setting of fever points toward an infectious source.

Physical Examination

The physical examination pertinent to spinal cord dysfunction involves testing in three areas: (1) motor function, (2) sensory function, and (3) reflexes. Each component is best tested with the anatomic organization of the spinal cord in mind to help determine the level of dysfunction. A detailed description of neurologic deficits and their correlating spinal level can be found in Chapter 35.

Motor Function

Testing of motor function encompasses examination of muscle bulk, tone, and strength. Muscle bulk is easily examined in large motor groups, such as the thigh, the calf, or the upper arm. Inspection of intrinsic hand muscles may also be helpful in determination of bulk; wasting may be evident as hollowed or recessed regions of the hand. Any decreased mass, asymmetry, or fasciculations should be noted. Tone is tested with repeated passive knee, elbow, or wrist flexion, or by rapid passive forearm pronation-supination, with the examiner assessing for abnormally increased or decreased resistance. Increased

TABLE 92.2 Grading of Neuromuscular Weakness

Grade	Physical Findings
0	No firing of the muscle is present.
1	The muscle fires but is unable to move the intended part.
2	The muscle is able to move the intended part with gravity eliminated.
3	The muscle is able to move the intended part against gravity.
4	The muscle is able to move the intended part but not at full strength.
5	Full muscle strength is present.

tone may indicate spasticity or an upper motor neuron lesion whereas decreased tone corresponds with lower motor neuron, motor end-plate, or muscle problems. Motor strength is then graded in the upper and the lower extremities. Motor grading for the neurologic examination is relatively straightforward; scored on a scale of 0 to 5, as shown in Table 92.2.

A rectal examination and the bulbocavernosus reflex (involuntary anal sphincter contraction in response to a squeeze of the glans penis or clitoris or a tugging on a Foley catheter) are performed to assess voluntary sphincter contraction and resting tone. Although not commonly thought of as a physical examination maneuver, a post-void residual (PVR) urine volume is useful to evaluate bladder function. A PVR of more than 100 to 200 mL in a patient without prior voiding difficulty suggests bladder dysfunction of a neurologic cause.

Sensory Function

Sensory testing requires a cooperative patient and an attentive examiner. Assessment of the patient's response to pinprick and light touch (contralateral spinothalamic tract) and proprioception (ipsilateral posterior column) in all four extremities is necessary. Testing of sacral dermatomes is indicated, as sparing suggests that a lesion may be incomplete. The sensory fibers from these dermatomes are more peripherally located in the ascending fiber bundles, thus, central or partial cord lesions may ablate sensation in the extremities yet allow some perception in the sacral area.

Reflexes

Deep tendon (muscle stretch) reflexes are graded on a scale of 0 to 4+, with 2 being normal. Hyperactive reflexes suggest upper motor neuron disease (affecting the neurons or their outflow from the brain or spinal cord) as do sustained clonus and Babinski sign. If present, hyperactive or abnormally brisk reflexes may be a key finding suggesting a myelopathy. However, absence of hyperreflexia does not exclude one. Reflexes may be diminished or absent when sensation is lost, when spinal shock is present, or in diseases of muscles or the neuromuscular junction. In acute cord injury, reflexes can be diminished in the acute phase, therefore, the bulbocavernosus reflex may be helpful in this assessment.

DIFFERENTIAL DIAGNOSES

The prime principle in management of spinal cord dysfunction is to consider and diagnose potentially treatable and time-sensitive conditions. The clinician should rule out any nonstructural cause of neurologic dysfunction (e.g., hypoglycemia, hypokalemia) early in the evaluation process. Once a true neurologic entity is suspected, the next step is to differentiate the location of the lesion (i.e., brain, spinal cord, nerve or motor end-plate). When the pathologic process is suspected to be spinal in origin, liberal use of specialist consultation and imaging is generally warranted. Spinal cord disorders may mimic many other disease processes, and neither the history nor physical examination can reliably enable a true diagnosis until appreciable neurologic dysfunction has developed.

The picture of a complete (transverse) spinal cord syndrome with paraplegia, sensory loss at a clear anatomic level, and sphincter dysfunction cannot be fully mimicked by other anatomic lesions; incomplete or evolving spinal cord syndromes, however, can. Ataxia, for example, is often a finding in cerebellar disease but has been reported as a rare, isolated finding in spinal cord compression.

In general, pathologic processes involving the spinal cord may be divided into those affecting the cord or its blood supply (e.g., demyelination, infection, or infarction) and ones that compress the cord. Of note, *myelitis* is a comprehensive term for spinal cord inflammation with dysfunction. The clinical presentation is often similar across the many etiologies of cord compression, but the tempo of the process may yield a different clinical picture. In chronic compression, muscle wasting and abnormal reflexes may be present, whereas both of these findings are likely to be lacking in acute compression.

DIAGNOSTIC TESTING

The purpose of diagnostic testing in patients suspected of having spinal cord dysfunction is to detect or exclude extrinsic compressive lesions or other potentially treatable entities. Conventional radiographs and computed tomography (CT) scans are essential in patients with trauma or suspected bony involvement by tumor or degenerative process because they better define bone and can show some soft tissue abnormalities. However, due to its ability to clearly define the spinal cord and the soft tissue structures around it, magnetic resonance imaging (MRI) is the preferred modality in assessing spinal cord disorders. It may also detect tissue damage patterns within the cord, such as hemorrhage and edema, as well as bone pathology. When utilized, MRI assessment of the entire spine should be considered because lesions can frequently occur at multiple levels.

MRI with gadolinium contrast enhancement is indicated when looking for pathology that affects the blood–central nervous system (CNS) barrier. Specific indications include primary or metastatic tumor, multiple sclerosis (MS), and spinal infections (i.e., spinal epidural abscess, discitis, and osteomyelitis). An example of the utility of gadolinium enhancement is seen in Figure 92.3. CT myelography is an option when MRI is unavailable or contraindicated, although it does not yield the same level of detail.

After imaging studies exclude compressive lesions or other masses affecting the spinal cord, the possibility of inflammatory or demyelinating disorders remains. In these cases, lumbar puncture with cerebrospinal fluid (CSF) analysis may be diagnostic.

MANAGEMENT

The treatment of many of the disease processes causing spinal cord dysfunction is nonspecific and based on limited evidence. Steroids have been used with many nontraumatic causes of cord compression, particularly spinal cord tumors, despite the lack of rigorous clinical studies supporting this practice. Radiation treatment is recommended for cord compression by tumor; surgical consultation for decompression may be considered, although the indications and timing for surgery are controversial.

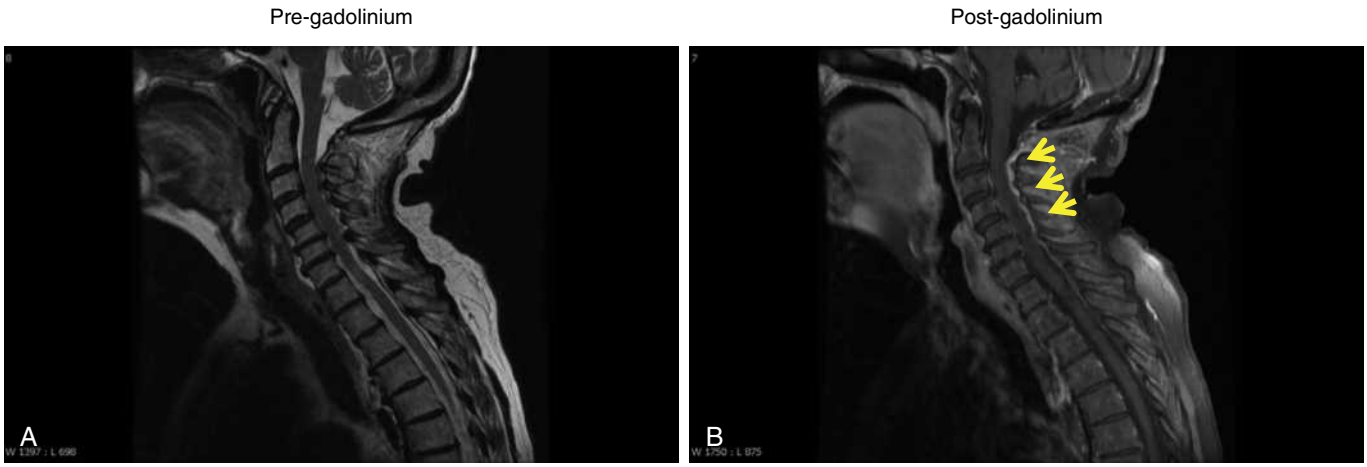


Fig. 92.3 90-year-old female with recent pyelonephritis presenting with severe neck pain. Pregadolinium sequence (A) compared with postgadolinium sequence (B) demonstrates posterior spinal epidural abscess (SEA) *(yellow arrowheads).*

TABLE 92.3 Causes and Characteristics of Nontraumatic Spinal Cord Dysfunction

Disease Process	Symptoms/Examination Findings	Testing	Treatment
Intrinsic Lesions			
Multiple Sclerosis	Symptoms include sensory, visual (optic neuritis), GI, fatigue, weakness, labile mood, hyperreflexia.	MRI, LP, consider biopsy	Steroids + disease-modifying medications
Transverse Myelitis	Paraplegia, transverse sensory impairment, and sphincter disturbance.	MRI	±Glucocorticoid therapy (etiology dependent)
Spinal Subarachnoid Hemorrhage	Usually have focal deficits on examination at level of bleed. May also complain of headache and/or demonstrate nuchal rigidity on exam.	MRI +/– LP	Anticoagulation reversal +/– clot evacuation
Syringomyelia	Headache with neck pain and sensory disturbances. Frequently demonstrate lower limb hyperreflexia with hand weakness and dissociative anesthesia.	MRI	Neurosurgical consultation vs. outpatient follow-up
HIV Myelopathy	Advanced HIV infection with weakness, gait disturbance, and sensory abnormalities.	Diagnosis of exclusion	Supportive therapy, HAART
Spinal Cord Infarction	Findings depend on location of infarction but anterior cord syndrome is most common.	Diagnosis of exclusion	Dependent on etiology
Surfer's Myelopathy	Back pain, paresis, and urinary retention.	MRI	Conservative therapy
Extrinsic Lesions			
Spinal Epidural Hematoma	Sudden severe radicular back pain usually presents prior to onset of deficits. Exam findings depend on location of hematoma.	MRI	Decompressive laminectomy
Spinal Epidural Abscess	Classically febrile with progressive neurological deficits. Back pain may be worse with percussion.	MRI	IV antibiotics ± surgery vs. needle decompression
Discitis	Children with back pain at level of lesion. Subacute presentation with fever but no neurologic deficits.	MRI	IV antibiotics
Neoplasm	Nighttime pain worse with lying flat. Deficits depend on location of lesion.	CT or MRI	Glucocorticoid therapy + radiation therapy or surgery

SPECIFIC DISEASE PROCESSES

Spinal cord disorders are grouped into lesions resulting from processes intrinsic to the cord or vasculature and lesions causing extrinsic compression (Table 92.3).

Intrinsic Cord Lesions

Multiple Sclerosis

Demyelination denotes a disease process with the prominent feature of partial or complete loss of the myelin surrounding the axons of the CNS. Multiple sclerosis (MS) is the most common example of such a process. The spinal cord is involved in as many as 90% of MS patients. In approximately 20% of patients, the spinal cord lesions will be the only area where plaques are identified. The pathophysiology, diagnosis, and management of MS is discussed in Chapter 94.

Transverse Myelitis

Foundations. *Acute transverse myelitis* (TM) refers to acute or subacute spinal cord dysfunction characterized by paraplegia, a transverse level of sensory impairment, and sphincter disturbance. It

is often considered part of a heterogeneous group of inflammatory processes known as neuromyelitis opticum spectrum disorders (NMOSD).[2] TM affects the spinal cord by interrupting the ascending or descending pathways. The presentation may be mimicked by compressive lesions, trauma, infection, or malignant infiltration.

The pathogenesis of transverse myelitis is unknown, although it is noted to follow a viral infection in approximately 30% of patients and therefore often termed *postinfectious myelitis*. Other postulated etiologies include infectious, autoimmune, and idiopathic disorders. It can be seen with a wide variety of connective tissue diseases, such as lupus, Sjögren syndrome, antiphospholipid syndrome, and other mixed connective tissue diseases. More recent research points to the presence of anti-AQP4 antibodies, particularly in cases thought to be part of NMOSD.[3] No cause is identified in 30% of patients. Progression of symptoms is usually rapid, with 66% of the cases reaching maximal deficit by 24 hours. However, symptoms may progress over days to weeks. The thoracic cord region is affected in 60% to 70% of cases, with the cervical cord being rarely involved. When TM lesions span 3 or more spinal cord levels, it is termed *longitudinally extensive transverse myelitis* (LETM) and is considered a hallmark of NMOSD.[4]

Clinical Features. In addition to motor, sensory, and urinary disturbances, patients with acute transverse myelitis may complain of back pain as well as a low-grade fever, raising concern for SEA. As with MS, the examination may reveal weakness progressing to paresis, hypertonia, hyperreflexia, clonus, Babinski response, and anal sphincter dysfunction. A distinct sensory level deficit is usually present. Autonomic dysfunction may also be noted as hyper- or hypotension and tachy- or bradycardia.

Differential Diagnoses. Considerations in the differential diagnosis for transverse myelitis include MS, SEA, spinal epidural hematoma (SEH), primary or metastatic spinal neoplasm, spinal cord infarct, surfer's myelopathy, and vitamin B_4 deficiency.[3]

Diagnostic Strategies. MRI with gadolinium enhancement is the diagnostic modality of choice for suspected transverse myelitis (Fig. 92.4). In cases of diagnostic uncertainty, a lumbar puncture may be performed; however, the results of CSF studies are normal in 40% of cases, with only mildly elevated protein levels or pleocytosis in the remaining 60%. The most essential aspect of the evaluation is to eliminate a potentially treatable cause. If testing is available, serum can be sent to detect the presence of specific antibodies (e.g., antiphospholipid, anti-AQP4, ANA).

Management. Treatment is tailored to the suspected underlying etiology. There are no good studies supporting a role for steroids. The exception for this would be in the setting of NMOSD-related TM, where steroids and immunosuppressant agents are the current recommended treatment. Methylprednisolone 1 gram IV is commonly administered. Neurologic consultation is suggested and hospitalization is usually required.

The clinical course of acute transverse myelitis varies widely, ranging from complete recovery to death from progressive neurologic compromise. Most patients with idiopathic disease have at least partial recovery, which usually begins within 1 to 3 months. Maximal improvement usually is obtained within 3 to 6 months with 30% of patients having "good" recovery, 25% "fair" recovery, and 30% having a "poor" outcome; there is 15% mortality at 5 years.

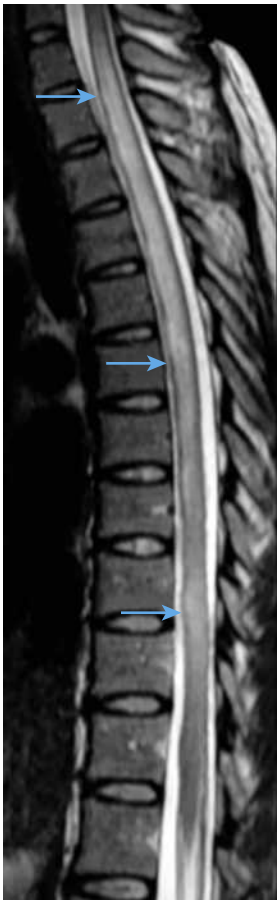


Fig. 92.4 Sagittal T2 MR shows a long segment of abnormal hyperintensity *(blue arrowheads)* and expansion of the visualized spinal cord, characteristic of transverse myelitis. (From: Merrow AC, Hariharan S. Transverse myelitis. In: Merrow AC, Hariharan S, eds. *Imaging in Pediatrics*, ed 1. Philadelphia: Elsevier; 2018.)

Spinal Subarachnoid Hemorrhage

Foundations. Intraspinal hemorrhage is rare and may occur in the same anatomic locations as intracranial hemorrhages; epidural, subdural, subarachnoid, and intramedullary hemorrhages are all possible. Spinal subarachnoid hemorrhage (SSAH) is usually caused by an arteriovenous malformation. Hemorrhage from tumors or cavernous angiomas and spontaneous hemorrhage secondary to anticoagulation therapy have also been reported. Diagnostic lumbar puncture is documented as a rare cause.[5] Bleeding may occur exclusively in the subarachnoid space or within the spinal cord tissue itself.

Clinical Features. Patients with SSAH present with excruciating back pain of a sudden and severe nature at the level of the hemorrhage. This pain may be in a radicular distribution or extend into the flank. Patients can complain of headache and exhibit cervical rigidity if the blood migrates into the intracranial subarachnoid space, simulating an intracranial subarachnoid hemorrhage. Variable neurologic deficits depend on the magnitude and anatomic location of the hemorrhage. These deficits typically include extremity numbness, weakness, and sphincter dysfunction. Nuchal rigidity or signs of meningeal irritation may also be present.

Differential Diagnoses. Considerations in the differential diagnosis include disc herniation, tumor, ischemia from aortic dissection, and anterior spinal artery thrombosis.

Diagnostic Testing. Because bone artifact may obscure the presence of blood in the spine, the diagnostic study of choice in patients with suspected SSAH is MRI without contrast. Lumbar puncture can help to confirm the presence of blood in the CSF. Angiography may be recommended if arteriovenous malformation is suspected. CT may be of benefit in detecting SSAH if MRI is not immediately available, but a negative CT does not definitively rule out the disease.[6]

Management. The treatment of spinal subarachnoid hemorrhage depends on the etiology of the hemorrhage. Neurosurgical referral is obtained for further evaluation and potential clot evacuation if compression is present. Reversal of anticoagulant medications should be considered in the proper clinical setting.

Syringomyelia

Foundations. Syringomyelia is the presence of a cavitary lesion within the tissue of the spinal cord. The word *syrinx* is derived from the Greek *surinx* for "pipe" or "channel." A syrinx is usually a chronic, progressive lesion with its specific location within the cord determining the constellation of neurologic findings. Ninety percent of patients with syringomyelia have a Chiari I malformation (projection of the cerebellar tonsils and medulla into the spinal canal) with nearly 5% of these patients requiring urgent surgical decompression due to acute neurologic deterioration.[7] This particular pathology, however, can be seen in almost all types of craniocervical junctional malformations.[8] Other etiologies of syringomyelia include spinal cord trauma (often months to years post-injury), compressive tumors, postinfectious (meningitis), and postinflammatory (transverse myelitis, MS).

Clinical Features. Headache and neck pain are the most common presenting complaints of patients with syringomyelia, followed by sensory disturbance, gait disorder, and lower cranial nerve dysfunction (CN IX–XII). Symptoms may be exacerbated by activities that increase intracranial pressure: sneeze, cough, or Valsalva maneuver. Patient-specific symptoms of syringomyelia develop and progress in accordance with the intracavitary pressure and anatomic location of the syrinx.

The most common features on physical examination are lower limb hyperreflexia, upper limb/hand weakness and muscle wasting, dissociated sensory loss, and gait abnormality. The classic pattern of sensory deficit involves a loss of pain and temperature sensation in the upper extremities with preservation of proprioception and light touch. This phenomenon is described as a "dissociative anesthesia" because of the discrepant loss of sensory modalities. This deficit often is described as being in a "capelike" distribution over the shoulders and arms. The anatomic basis for the neurologic features of a syrinx is the location near the central canal. Crossing fibers of the lateral spinothalamic tract carrying pain and temperature fibers are impaired while crude touch, position, and vibratory sensation from the posterior columns are unaffected. Sensory fibers from the lower limbs are similarly spared. Motor fibers from the corticospinal tract, when affected, will often result in upper extremity weakness due to the anatomic layout of the tract and the predominant cervical location of most syrinxes.

Differential Diagnoses. Considerations in the differential diagnosis for syrinx include intrinsic spinal tumor, demyelination, and trauma resulting in central cord syndrome.

Diagnostic Testing. Syringomyelia is best seen on MRI (Fig. 92.5). No other modality currently in widespread use is equivalent in diagnostic ability.

Management. When the diagnosis of syringomyelia is considered, emergent imaging in the ED may not be necessary if follow-up evaluation can be arranged; in approximately two-thirds of patients this condition is a slowly progressive process. If MRI studies are obtained and the diagnosis is made, referral to a neurosurgeon is indicated. Patients with acute neurologic deterioration, however, likely benefit from a more expedited evaluation, as urgent surgical decompression may be indicated in specific anatomic malformations (i.e., Chiari I malformations).

Human Immunodeficiency Virus Myelopathy

Human immunodeficiency virus (HIV) myelopathy typically occurs in patients with advanced HIV infection, often in conjunction with a very low CD4 count.[9] Weakness, gait disturbance, sphincter dysfunction, sensory abnormalities, and signs of spasticity are all features of this progressive process. Because diseases such as toxoplasmosis, lymphoma, varicella-zoster, and cytomegalovirus may produce a similar clinical picture in immunocompromised patients, HIV myelopathy is a diagnosis of exclusion. It more often affects the thoracic cord, so symptoms are frequently localized to the lower extremities. Treatment is primarily supportive, but improvement may be seen with utilization of highly active antiretroviral therapy (HAART).

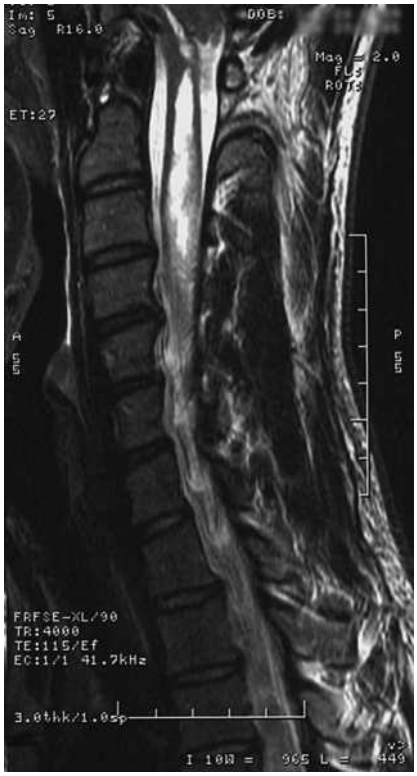


Fig. 92.5 T2-weighted magnetic resonance imaging of a patient with Chiari malformation and syringomyelia. (From: Batzdorf U. Syringomyelia. In: Shen FH, Samartzis D, Fessler RG, eds. *Textbook of the Cervical Spine*, ed 1. Maryland Heights: Saunders; 2015.)

Spinal Cord Infarction

Spinal cord infarction is extremely rare and considered a diagnosis of exclusion, but certain clinical clues may point to it. Aortic dissection, aortic surgery, and global ischemia are the most common causes. It can also occur as a complication of lupus or vasculitis or be cryptogenic. The clinical picture depends on the extent of infarct as well as the vascular territory affected (anterior versus posterior spinal artery). An anterior spinal cord syndrome is the most common clinical picture. Recovery is variable and etiology dependent.

Surfer's Myelopathy

Surfer's myelopathy is a recently described etiology of atraumatic cord dysfunction.[10] It is most often seen in novice or first-time surfers presenting with back pain, paresis, and urinary retention. Anesthesia or hyperesthesia may be present. The suggested mechanism is static hyperextension of the spine that occurs when lying prone on a surfboard with arms extended and head up for long periods of time, resulting in transient cord ischemia. Recovery is generally favorable but permanent paresis is possible. Awareness of this etiology is important, as it's symptoms mimic transverse myelitis.

Extrinsic Cord Lesions

Spinal Epidural Hematoma

Foundations. Spinal epidural hematoma (SEH) is a relatively rare condition where blood accumulates in the epidural space and can cause compression of the spinal cord. A hematoma may occur spontaneously but is more commonly traumatic or iatrogenic following lumbar puncture, epidural anesthesia, spinal surgery, and even acupuncture. SEH can occur at any level of the spine and can even extend to the cranium. It is more likely to occur in anticoagulated or thrombocytopenic patients such as those with liver disease or alcoholism. Spontaneous bleeding is rare but may arise from a spinal or dural arteriovenous malformation or a vertebral hemangioma. One-quarter of all cases are associated with anticoagulation therapy, including low-molecular-weight heparin and direct thrombin inhibitors.

Clinical Features. Patients usually present with sudden, severe, constant back pain. The pain is frequently radicular and may occur after a straining episode; it is often worsened by percussion over the spine and by maneuvers that increase intraspinal pressure (cough, sneeze, Valsalva).[11] Due to the severity of pain, patients are often in distress and seek care prior to the development of neurologic signs, which may actually lead to a delay in diagnosis. Neurologic deficits follow the onset of pain and may progress over a period of hours to days. Motor and sensory findings are variable because they depend on the level and size of the hematoma. Symptoms can include weakness, paralysis, loss of bowel or bladder function, and virtually any sensory deficit.

Differential Diagnoses. Considerations in the differential diagnosis include SEA, epidural neoplasm, acute disc herniation, and SSAH. SEH has even been known to mimic a stroke. This diagnosis should be considered in a patient presenting with a stroke syndrome who also has acute neck or back pain.

Diagnostic Testing. MRI with and without IV contrast is the diagnostic study of choice. CT myelography will frequently pick up the hematoma or show contrast medium in the subarachnoid space. The hematoma may initially be identified on CT due to its high density but is inferior to MRI in localizing and characterizing the lesion.

Management. In patients with SEH, recovery without surgery is rare. Neurosurgical consultation for emergent decompressive laminectomy is indicated as soon as the diagnosis is considered. Functional recovery is related both to the length of time the symptoms are present and to the initial neurologic status. Recovery after 72 hours of symptoms is rare but has been reported even without surgery, primarily in younger patients with rapidly improving symptoms. In the setting of anticoagulation therapy that is reversible, measures should be taken to do so.

Spinal Epidural Abscess

Foundations. Spinal epidural abscess (SEA) is an infectious process usually confined to the adipose tissue of the dorsal epidural space where there is a rich venous plexus. Abscesses that form in this space are limited by the bony confines of the spinal column. Damage to the spinal cord can be caused by direct compression on neural or vascular structures, but septic thrombophlebitis and vascular occlusion secondary to bacterial and inflammatory substances may also cause injury. Major risk factors for the development of SEA include underlying disease (immunosuppression, diabetes, chronic renal failure, alcoholism), spinal abnormality, recent spinal intervention (surgery, epidural analgesia), or local or systemic infection (skin and soft tissue infections, cystitis, sepsis, osteomyelitis, endocarditis, IV drug abuse), but the disease can be seen in individuals without any risk factors. The incidence of this disease is increasing, likely due to a higher rate of spinal instrumentation, an aging population, and higher prevalence of IV drug use. An acute or subacute presentation is most frequently seen in the ED, though some patients may develop a chronic form.

The thoracolumbar spine is the most frequent site of infection because the epidural space is larger and contains more adipose tissue. Infection typically extends over multiple vertebral segments but can also occur at noncontiguous locations. The dura mater limits the spread of an epidural infection, making subdural or intraspinal spread uncommon. Hematogenous spread to the epidural space from a discrete infection occurs in about half of the cases via the epidural space or the adjacent vertebra with subsequent extension into the epidural space. Local spread of bacteria occurs in another third of cases with the remainder having no clear source of infection identified.

Skin and soft tissue infections are the most frequently identified source of bacteria. *Staphylococcus aureus* is the most prevalent organism, cultured in nearly two-thirds of cases; the percentage of cases caused by MRSA has been increasing in recent years. Other frequently identified pathogens include gram-negative pathogens (*Escherichia coli*, *Pseudomonas aeruginosa)*, *Streptococcus*, and coagulase-negative *Staphylococcus*. Anaerobic or fungal causes are rarely identified. *Mycobacterium tuberculosis* should be considered as a potential cause in the developing world. Multiple organisms are identified in 10% of cases.

Clinical Features. The clinical presentation of SEA begins with back pain localized to the level of the affected spine, often associated with tenderness to percussion. Symptoms usually progress over a few days but may extend for weeks. Radicular symptoms develop as the disease progresses to involve the nerve root radiating from the involved vertebrae. Without treatment, myelopathic signs will result, usually beginning with bowel and bladder disturbance. Weakness and sensory deficits develop, followed by paraplegia or quadriplegia. Once paralysis develops it quickly becomes irreversible within 24 to 48 hours. Bacteremia, either as a cause or as a result of SEA, may be present in over 50% of patients. Patients should be questioned about fevers, chills, or rigors, as they are present in up to 75% of cases. The classic triad of back pain, fever, and progressive neurologic deficits is rarely present and thus a delay in clinical diagnosis is common. In rare cases, SEA may also present as acute delirium.

Differential Diagnoses. SEA is frequently misdiagnosed on initial presentation, especially in a patient who is neurologically intact. In someone with infectious symptoms, more common causes such as cystitis, pneumonia, bacteremia, or osteomyelitis may be incorrectly diagnosed. Any compressive spinal lesion can mimic the neurologic manifestations of SEA.

Diagnostic Testing. MRI with IV contrast is the imaging modality of choice and should be performed emergently if the diagnosis of SEA is considered (see Fig. 92.3). CT myelography is also highly sensitive (>90%) in diagnosing SEA but MRI is more useful for surgical planning and differentiating a mass from an abscess.[12] Plain radiographs or noncontrast CT may show bony vertebral lysis but should not replace MRI.

A white blood cell (WBC) count is usually elevated and may support the diagnosis but is neither sensitive nor specific. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests, although not highly specific for epidural abscess, are virtually always elevated with this condition and have been studied as screening tests for SEA in certain "at-risk" populations.[12] Blood cultures are not beneficial in diagnosis but should be obtained as they may help to identify the causative organism. Lumbar puncture is relatively contraindicated with known or suspected SEA, because the procedure may further seed the infection. If performed, CSF findings are consistent with a parameningeal infection, showing protein elevation and increased inflammatory

cells. The Gram stain is usually negative and CSF cultures are no more useful than blood cultures.

Management. Urgent surgical consultation for possible decompression is required for SEA. Antibiotics effective against the most common pathogens (particularly *S. aureus*) should be started empirically to cover gram-positive and gram-negative organisms: We recommend IV vancomycin (15 to 20 mg/kg IV every 8 to 12 hours) plus a third- or fourth-generation cephalosporin (e.g., ceftriaxone 2 g every 12 hours) or meropenem (2 g every 8 hours). If MSSA is a concern, nafcillin or oxacillin should be added. Cefepime (2 g every 8 hours) should be used in cases of known or suspected pseudomonas. CT-guided needle decompression is an option for drainage, particularly if the abscess is located posteriorly and the patient is a high-risk surgical candidate. Independent risk factors for failure of a nonoperative management plan include a motor deficit at the time of presentation, a pathologic or compression fracture, active malignancy, diabetes, and sensory changes.[13]

Outcome in SEA is related to the speed of diagnosis before the development of neurologic deficits. The primary indicator of final outcome is the patient's neurologic status just prior to the operating room. Even if treated, the disease can be fatal, and patients with neurologic changes rarely improve if surgical intervention is delayed more than 12 to 36 hours after onset of paralysis. Patients operated on before development of neurologic symptoms generally have good outcomes.

Discitis

Foundations. Discitis is an uncommon primary infection of the vertebral disc, specifically the nucleus pulposus, with secondary involvement of the cartilaginous end plate and vertebral body. Bacteria can spread to the disc by direct inoculation after surgical procedures, by local spread from infected tissue, or hematogenously. Children are more likely to develop primary infections of this space due to persistent vascular supply of the vertebral disc. Higher rates occur in immunocompromised patients and patients with systemic infections. The lumbar spine is the most common site of disease.

Clinical Features. Clinical presentation can be quite variable. In general, patients present with moderate to severe pain localized to the level of involvement and exacerbated by almost any movement of the spine. The hallmark of diagnosis, however, is a usual lack of neurologic deficits. In neonates or infants, cases are usually severe and present as sepsis with multiple infectious foci. In older children, symptom onset tends to be gradual; they may refuse to crawl, walk, or stand and demonstrate general irritability. Low-grade temperature elevations are noted in most patients. Radicular symptoms are present in 50% to 90% of cases. Because of the lack of neurologic deficits in the early stage, there is often a latent period (2 to 8 weeks) between the onset of back pain and the development of significant clinical findings on the physical examination. *S. aureus* is the most common pathogen, but gram-negative, fungal, and tuberculous infections have all been recognized. *Kingella kingae*, identified by PCR in a number of culture-negative cases of discitis, is an emerging pathogen in young children.[14]

Differential Diagnoses. Considerations in the differential diagnosis of discitis include vertebral osteomyelitis, spinal epidural abscess, neoplasm, and hematoma.

Diagnostic Testing. MRI with IV contrast is the radiographic study of choice for suspected discitis, because it not only enables diagnosis but also rules out paravertebral or epidural abscess. Plain radiographs usually are not helpful for early diagnosis of discitis, but destruction of the disc space is highly suggestive if present. Radiographic findings become abnormal after 2 to 4 weeks of disease. In addition to disc space narrowing, plain films may show irregular destruction of the vertebral body endplates. Aspiration of the affected disc for culture is generally not performed. Laboratory studies often show an elevated ESR, but the WBC count is often normal and blood cultures are frequently negative.

Management. With timely diagnosis and treatment, outcome is usually very good and medical treatment with IV antibiotics that cover *Staphylococcus* and *Streptococcus* in accordance with local resistance patterns is usually curative. An antibiotic regimen similar to that recommended for the treatment of SEA is appropriate. Of note, *K. kingae* is covered by this treatment regimen. In a patient with a severe penicillin allergy or contraindication to a cephalosporin, meropenem (2 g IV) or aztreonam (2 g IV) may replace the cephalosporin. Finally, in patients with a vancomycin allergy or high resistance, linezolid (600 mg IV) is recommended. Surgery is generally not necessary.

Neoplasm

Foundations. Spinal cord tumors are classified according to their relationship to the dura and spinal cord (extradural, intradural extramedullary, and intradural intramedullary). Primary spinal cord tumors are generally benign but produce neurologic symptoms by compression, invasion, or destruction of myelinated tracts. The resulting neurologic symptoms are directly related to the growth rate and the location of the tumor. Overall, primary spinal cord tumors account for less than 10% of CNS tumors and only 1% of all cancers.

Most tumors affecting the spinal cord are metastatic in origin. Approximately 10% of patients with known cancer are diagnosed with a spinal metastasis at some point in the course of their disease; 5% to 10% of patients ultimately diagnosed with cancer first present with spinal metastases. Lung, breast, and prostate cancer represent the majority of the primary malignant neoplasms that subsequently develop spinal metastases, spreading both hematogenously and via direct extension. Intramedullary spinal cord metastases are rare. Multiple myeloma and lymphoma are generally more widespread at diagnosis but may also cause symptoms of cord compression. Most spinal lesions occur in the thoracic spine, but nearly 20% of patients with metastases will have lesions at multiple levels.[15]

Clinical Features. In nearly all patients with spinal neoplasm, the initial complaint is pain, either in the back at the level of the tumor or in a radicular distribution. Pain often is characterized as dull, constant, and aching and may worsen with recumbency (whereas pain from a herniated disc is classically improved when lying flat). Nighttime pain that is severe is characteristic of spinal neoplasm. Any action that increases intraspinal pressure may be associated with increased pain. Neurologic deficits vary by the location of the lesion. Metastatic spinal cord compression may present as a Brown-Séquard syndrome. Motor deficits are estimated to be found in almost half of patients at the time of initial diagnosis while sensory changes are less often reported. Besides a thorough neurologic examination, a search for possible primary sites of malignancy should be performed during the patient assessment.

Differential Diagnoses. Considerations in the differential diagnosis of spinal neoplasm include any of the compressive lesions (e.g., hematoma, infection, disc herniation). Tumors can also mimic intrinsic spinal cord lesions, such as transverse myelitis and cord infarction.

Diagnostic Testing. Patients presenting with new back pain (<6 weeks) and no risk factors or neurologic deficits on examination generally do not require imaging. If imaging is performed, plain radiographs are usually the initial modality in patients with minimal risk factors for or no previous diagnosis of cancer. The sensitivity and specificity of plain radiographs in detecting abnormalities consistent with malignancy are 60% and 95%, respectively.[15] In the presence of normal radiographs, an ESR measurement is helpful in that a cancer diagnosis is very unlikely in a patient with a normal ESR, normal radiographs, no clinical findings, and no or low risk for neoplasm. Patients with neurologic abnormalities, a history of cancer, and

suspicious findings on plain films or elevated ESR are candidates for emergent MRI with IV contrast; in contrast-allergic patients, MRI without contrast is recommended.[13] CT myelography is an option if MRI is unavailable or the patient has contraindications.

Management. Acute compressive myelopathy from neoplasm constitutes an oncologic emergency. Immediate treatment is required to preserve function and prevent deterioration. With onset of paraplegia and incontinence, less than 5% of patients regain ambulatory status. Of patients who are ambulatory at the time of diagnosis, 60% will remain ambulatory. Spinal instability or neurologic deficits are indications for immediate surgical decompression. In patients with symptoms of cord compression, high-dose glucocorticoid therapy is recommended (i.e., 10 mg dexamethasone IV followed by 4 mg orally every 6 hours). Higher initial doses of dexamethasone have not been associated with better outcomes. Steroids are generally not initiated in patients with small lesions or in the presence of a normal neurologic examination.[16] Radiation therapy is frequently indicated in the treatment of spinal cord tumors and can be combined with surgical intervention, if indicated.

CHRONIC COMPLICATIONS OF SPINAL CORD INJURY

Autonomic Dysreflexia

Foundations

Autonomic dysreflexia (AD) is defined as the loss of coordination between heart rate and vascular tone in response to increased demand. It can be seen in spinal cord injury (SCI) due to a disruption of splanchnic innervation that occurs when the lesion is at or above the T6 level. Noxious stimuli below the injury level can result in an uninhibited sympathetic response causing vasoconstriction and resultant hypertension that is not overcome by compensatory parasympathetic activity (bradycardia and vasodilation) above the lesion. Over 50% of SCI patients suffer from AD with most developing symptoms within the first year post-injury. Common examples of noxious stimuli are bladder distention, bowel impaction, pain (even from sources as seemingly benign as in-grown toenails), pressure ulcers, tight clothing, and infection. AD will persist until the underlying cause is resolved.

Clinical Features

AD is defined as an elevation in systolic blood pressure 20 to 40 mm Hg or greater from baseline (15 to 20 mm Hg in pediatric population) or a systolic reading of 150 mm Hg or greater with symptoms in the absence of a known baseline; 88% of patients will present with severe headache and diaphoresis above the spinal level. Other possible symptoms include nasal congestion, blurred vision, anxiety, and nausea. There may be accompanying bradycardia due to the parasympathetic compensation but the absence of it does not rule out AD.

Management

Treatment centers on managing blood pressure while working to identify and treat the underlying cause. Assessing for bladder distention and, if present, relieving by catheterization or the flushing of an obstructed indwelling catheter may be necessary. Digital rectal exam will help assess for fecal impaction and a full skin examination will identify pressure ulcers, skin infections, or lesions. Removing tight clothing and sitting the patient upright if possible may help to engage hydrostatic redistribution.

Topical, oral, or IV anti-hypertensive medications may be indicated when an elevated blood pressure persists in order to prevent acute complications of severe hypertension. Application of 1 to 2 inches of 2% nitroglycerin paste to the skin above the spinal lesion is recommended to relax vascular smooth muscles and cause vasodilation. Likewise, IV nitroglycerin (5 mcg/minute increasing by 20 mcg/minute every 1 to 3 minutes to a maximum of 400 mcg/min) for severe cases is indicated. Beta blockers are avoided to prevent potential uninhibited alpha-adrenergic activity but not contraindicated. Oral anticholinergics and botulinum toxin injections into the bladder have been used to help manage neurogenic detrusor overactivity, the most common cause of bladder distention resulting in AD, but would be of little benefit in severe, acute cases in the ED.

Spasticity

More than 60% of SCI patients will develop spasticity to some degree, defined as a velocity-dependent increase in muscle tone (hyperexcitability). It is thought to be caused by disruption of descending inhibitory modulation of alpha-motor neurons. Care should be taken when evaluating spasticity because a sudden increase in patient or caregiver reported spasticity may be indicative of occult infection.

Treating spasticity is not only difficult but may not be beneficial as spasms and contractures can aid the patient or caregiver in transfer or other activities. Any suggested treatment should focus on functionality and often starts with physical therapy (stretching, braces) and progresses to include medications such as baclofen (5 mg PO 1 to 3 times daily, increasing by 5 mg per dose every 3 days up to 80 mg/day in divided doses), tizanidine (2 mg PO at bedtime, initially, increasing by 4 mg daily dose every 3 to 4 days up to 36 mg/day given in 3 to 4 doses), and benzodiazepines; unfortunately, these medications have little proven efficacy aside from tizanidine and are frequently limited by their sedative properties.

Infection

Pneumonia is a frequent complication of SCI with roughly 50% of SCI patients developing it during their acute hospital stay post-injury; it is often the ultimate cause of death in SCI patients. Pressure ulcers, frequently located over bony prominences, are an additional nidus of infection and a thorough skin exam should be performed on any SCI patient presenting with infectious signs or symptoms.

Urinary tract infections (UTIs) occur at an estimated rate of 2.5 episodes per patient per year and are the third leading cause of death among this population. This high rate is primarily due to patients with chronic indwelling catheters but also includes patients who void, have suprapubic catheters, or intermittently catheterize. In the latter group, it is thought that frequent catheterization not only introduces bacteria but the scheduled nature of the procedure allows for large volumes of urine to collect in the bladder prior to drainage, increasing the risk of infection. Symptomatic UTIs frequently present with fevers, foul-smelling urine, increased spasticity, or autonomic dysreflexia and should be treated with antibiotics. Asymptomatic bacteriuria, however, should not be treated as doing so has no effect on the frequency of symptomatic infections and risks increasing microbial resistance. An additional consideration in the management of symptomatic UTI is to consider a diagnosis of infected renal calculi in that up to 20% of SCI patients have hypercalciuria from altered bone metabolism which contributes to higher rates of nephrolithiasis.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 92: QUESTIONS AND ANSWERS

1. A 43-year-old man with a history of alcohol abuse and liver cirrhosis presents with a complaint of one week of progressive difficulty ambulating and low thoracic back pain. He is noted to be febrile on examination. Which of the following diagnostic modalities is most appropriate in this patient?

a. Blood cultures
b. CT myelography
c. Lumbar puncture
d. MRI with IV contrast
e. White blood cell (WBC) count

Answer: D. The patient has a presentation concerning for spinal epidural abscess (SEA). MRI is the imaging modality of choice and should be done emergently. Lab tests may be helpful in supporting the diagnosis but are neither sensitive nor specific. CT may show bony abnormalities concerning for SEA but should not replace MRI. Blood cultures are not useful as a diagnostic tool but may reveal the causative organism and help to guide antibiotic therapy. Lumbar puncture is relatively contraindicated in these patients because it may further seed the infection.

2. Which feature most often distinguishes a conus medullaris from a cauda equina lesion?

a. Back pain
b. Bilateral symptoms
c. Distal motor weakness
d. Sacral anesthesia
e. Urinary incontinence

Answer: B. Because the conus medullaris is a small structure with lumbar and sacral segments represented in a minimal area, a lesion will likely result in bilateral symptoms. As cauda equina is not a true cord lesion but rather reflects dysfunction at the level of nerve roots, the symptoms are frequently unilateral. Both can result in urinary retention, fecal incontinence, saddle anesthesia, and distal motor weakness. Conus medullaris may have upper motor neuron signs (hyperreflexia and increased tone), which will be absent in cauda equina.

3. A 27-year-old woman presents with complaints of back pain and difficulty walking. Her symptoms have been progressive for 2 days. She has no significant past medical history. On history it is discovered that she recently recovered from a bout of "the flu" approximately 3 weeks ago. Physical examination is remarkable for lower extremity hyperreflexia, moderate symmetrical lower extremity weakness, moderate increased tone, a T10 level of sensory loss, and a PVR urine volume of 350 mL. What should be the next intervention?

a. Antibiotics
b. Complete blood count, erythrocyte sedimentation rate (ESR), and antinuclear antibody levels
c. MRI scan with gadolinium enhancement
d. Emergent neurosurgical intervention
e. Steroids

Answer: C. Transverse myelitis is postinfectious in 30% of cases and also idiopathic in 30%. Other causes are autoimmune disorders and infections. Symptoms are typically rapid in onset and progress during 1 or 2 days. Symptoms are often sensory loss below the level of insult, extremity weakness, decreased sphincter tone, and urine retention (often exhibited with an elevated PVR). Back pain may accompany it. Emergent MRI is indicated to rule out other causes. There is no proven efficacious treatment, although steroids have been used. There is an association with multiple sclerosis (MS). Prognosis for recovery is only fair.

4. A 23-year-old male patient with no past medical history presents with longstanding, recurrent headache and neck pain that he reports has been gradually worsening over several months. He denies any fevers, weakness, numbness, vision changes, back pain, or bowel/bladder changes. He notes that he is often afraid to cough or sneeze because that makes the symptoms worse. What is another clinical feature of this patient's most likely diagnosis?

a. Normal gait
b. Loss of pain and temperature sensation in the upper extremities
c. Lower extremity weakness
d. Bladder dysfunction
e. Loss of proprioception and light touch

Answer: B. Syringomyelia typically presents with headache, neck pain, and variable upper extremity dissociative anesthesia: symmetrical loss of pain and temperature sensation with preserved posterior column function. With progression, upper extremity weakness or wasting and lower extremity upper motor neuron changes are expected. Exacerbation with cough and the Valsalva maneuver is typical. There is a 90% association with type I Arnold-Chiari malformation (cerebellar tonsils and medulla projecting into the spinal canal—often the cause of the typical occipital headaches). MRI is diagnostic.

5. In the majority of patients with an extrinsic compressive lesion, surgical outcome is most dependent on which of the following factors?
   - **a.** Age
   - **b.** Laterality of symptoms
   - **c.** Location of lesion
   - **d.** Neurologic status at the time of procedure
   - **e.** Primary source of neoplasm

Answer: D. In patients with SEH or SEA, prognosis is intimately linked with neurologic function at time of decompressive laminectomy or operative intervention. Patients who have had symptoms greater than 72 hours with SEH are unlikely to regain lost function. In SEA, neurologic status rarely improves if intervention is delayed longer than 12 to 36 hours from onset of paralysis.

6. A 37-year-old female with a prior history of transverse myelitis at the T4 level one year ago presents with several hours of sweating, nausea, and headache. At baseline, she is paraplegic to the lower extremities, performs intermittent bladder catheterization, and is insensate inferiorly to the T4 level. She has never had these symptoms before. Her vitals are: blood pressure 270/130, heart rate 54, respiratory rate 16, oral temperature of 97.2°F. ECG performed in triage shows no signs of ischemia or infarct. Which of the following actions should be taken next?
   - **a.** Manage blood pressure with nitrates and perform a thorough physical examination including bladder scan and rectal exam.
   - **b.** Administer aspirin and obtain cardiology consult.
   - **c.** Obtain an emergent CTA of chest to assess for aortic dissection.
   - **d.** Administer benzodiazepines.
   - **e.** Order an MRI with IV contrast.

Answer: A. The patient is experiencing autonomic dysreflexia, seen frequently in patients with spinal cord injuries above the T6 level. Her severe hypertension, diaphoresis, nausea, and headache can mimic other diagnoses, but her history of spinal cord lesion must be taken into consideration. Management focuses around aggressive blood pressure management with nitrates and investigation into the possible noxious stimuli that is causing the syndrome. Bladder-related etiologies (particularly distention or detrusor overactivity) cause most episodes of autonomic dysreflexia. Other causes are fecal impaction, pain, tight clothing, and infection.

7. A 34-year-old male presents after a motorcycle versus car collision. The patient was wearing a helmet but thrown from his bike. He reports burning discomfort and significant weakness to both arms. He also reports some mild numbness but no clear bladder symptoms. What additional findings would you expect to find on physical examination?
   - **a.** Decreased rectal tone
   - **b.** Loss of pain and temperature below the level of the injury
   - **c.** Distal muscle groups are affected more than proximal muscle groups
   - **d.** Loss of position, vibration, and light touch sensations
   - **e.** Lower extremity weakness

Answer: C. The patient has likely suffered a cervical hyperextension injury resulting in a central cord syndrome. Remember the pneumonic "MUD" for central cord syndrome: motor > sensory, upper > lower, distal > proximal. Patients with central cord syndrome have variable sensory impairment and bladder dysfunction and these symptoms are not hallmarks of this partial cord syndrome. Brown-Séquard syndrome is characterized by ipsilateral loss of motor function, proprioception, and vibration with contralateral loss of pain and temperature sensation below the level of injury. Anterior cord syndrome is characterized by loss of motor function, pinprick, and light touch below the level of the lesion with preservation of the posterior column modalities.

8. An 11-month-old female presents to your emergency department with low-grade fevers and progressive refusal to crawl or pull up. Mom reports she took the patient to her pediatrician last week but they didn't find any abnormalities. However, her symptoms have continued to worsen. On exam, you see an otherwise healthy infant who now appears somewhat irritable. Vital signs are as follows: HR 110, RR 18, T 100.2°F. The patient is being held by mom and resists movement. Most of her physical exam appears normal, including a nonfocal neurologic exam, but she cries as you palpate the lumbar spine. Which of the following is true of the likely diagnosis?
   - **a.** Blood cultures frequently reveal the causative organism.
   - **b.** WBC is a helpful finding if elevated.
   - **c.** Plain radiographs are sufficient for diagnosis.
   - **d.** IV antibiotics are usually curative.
   - **e.** The lack of associated neurologic deficits is unusual in this case.

Answer: D. The child has a presentation consistent with discitis. These children may present with sepsis and, as this is an unusual diagnosis, the provider should maintain a broad differential. Children are more likely to develop infections in the vertebral disc and usually have developed symptoms over several weeks. A hallmark of the diagnosis is that patients have normal neurologic exams. MRI is the imaging modality of choice as it is diagnostic and helps to rule out other conditions. The white blood cell (WBC) count is usually normal and blood cultures are usually negative. IV antibiotics are effective at treating discitis and surgery or aspiration are rarely needed.

Peripheral Nerve Disorders

Ethan E. Abbott and E. Bradshaw Bunney

KEY CONCEPTS

- The diagnosis of a specific peripheral neuropathy generally requires confirmatory ancillary testing; approach in the ED should focus on identifying one of seven categorical patterns.
- Diagnostic approach to peripheral neuropathies involves combining three clinical features: (1) right-left symmetry or asymmetry, (2) proximal-distal location, and (3) sensorimotor modalities affected.
- Any patient with symmetrical weakness, distributed both proximally and distally, with loss or diminution of deep tendon reflexes (DTRs) and variable sensory abnormalities should be treated as having Guillain-Barré syndrome (GBS).
- Respiratory compromise is the primary life-threatening event seen in some peripheral neuropathies; GBS is by far the most common peripheral neuropathic cause of respiratory arrest.
- The definitive treatments for GBS are plasma exchange or intravenous immune globulin (IVIG).
- Most polyneuropathies are characterized by a pattern of distal, symmetrical sensorimotor findings, worse in the lower than in the upper extremities, with a stocking-glove distribution of sensory abnormalities that gradually diminishes as one moves proximally.
- High-level evidence supports the use of pregabalin, gabapentin, and the serotonin and norepinephrine reuptake inhibitor duloxetine in the treatment of diabetic distal symmetrical polyneuropathy (DSPN).
- Radial nerve mononeuropathies are characterized by wrist and finger drop and mild numbness over the skin of the first dorsal interosseus muscle.
- Humeral shaft fractures are associated with radial nerve injury, with "wrist drop" being the hallmark clinical finding.
- The ulnar cutaneous innervation to the hand branches from the main trunk proximal to the nerve entering the Guyon canal. Thus, a lesion at the wrist should not produce sensory abnormalities, whereas one at the elbow would be expected to do so.
- The most specific finding for carpal tunnel syndrome (CTS) is splitting of the sensation on the fourth digit (i.e., normal sensation of the ring finger on the ulnar palmar side with abnormal sensation on the median [radial] palmar side of the same finger).
- Lateral femoral cutaneous mononeuropathy (meralgia paresthetica) is caused by injury to this pure sensory nerve as it passes through or over the inguinal ligament, where it may become entrapped or kinked.
- The most striking feature of a complete common peroneal mononeuropathy is footdrop caused by weakness of foot dorsiflexion.
- The most common neurologic abnormality in Lyme disease is unilateral or bilateral facial nerve palsy, usually occurring within a month of exposure.
- ALS is the most common form of motor neuron disease (MND), and diagnosis requires the presence of both upper and lower motor neuron findings.

OVERVIEW

Principles

The nervous system is divided into central nervous system (CNS) and peripheral nervous system (PNS) components. The PNS is subdivided into 12 cranial and 31 spinal nerves. Disorders of the cranial nerves are discussed in Chapter 91. Because diseases of the neuromuscular junction and the myopathies are located distal to the neuron itself, they are also considered separately in Chapter 95. Radiculopathies, which are disorders of the roots of the PNS, are so commonly associated with musculoskeletal neck and back pain that they are mentioned only briefly here and are discussed in detail in Chapter 36.

Current estimates suggest that about 2.4% of the population suffers from peripheral neuropathy, rising to 8% for those over 50 years of age. Diabetes mellitus is a leading contributor.

The simplest approach to categorizing diseases of the PNS is to distinguish focal from nonfocal disease. In the PNS, the first broad category is the focal group, which is divided into those with evidence of single versus multiple lesions of peripheral nerves, known respectively as *simple mononeuropathies* and *multiple mononeuropathies* (or *mononeuropathy multiplex*). The second broad category, which constitutes the nonfocal group of peripheral neuropathies, contains the polyneuropathies. These tend to produce bilaterally symmetrical symptoms and signs, reflecting the widespread nature of the underlying pathologic processes.

The evaluation of PNS disease involves a goal-directed history and physical examination targeted at answering the three questions, each of which corresponds to a stratum of the algorithm presented in Figure 93.1:

1. Are the sensorimotor signs and symptoms symmetrical or asymmetrical?
2. Are the sensorimotor signs and symptoms distal or both proximal and distal?
3. Is the modality involved exclusively motor, sensory, or mixed sensorimotor?

By systematically combining responses to these questions, seven discrete categories of peripheral neuropathy are identified, each of which contains a finite set of possible diagnoses. Because pure motor or pure sensory findings tend to occur mainly in an asymmetrical, distal distribution, this is the only category in Figure 93.1 subdivided into pure motor and pure sensory abnormalities.

The spinal component of the PNS is shown schematically in Figure 93.2. The anterior and posterior nerve roots exit the spinal cord at each segmental level. Just distal to the dorsal root ganglion they converge to form a mixed (motor and sensory) spinal nerve, of which there are 31

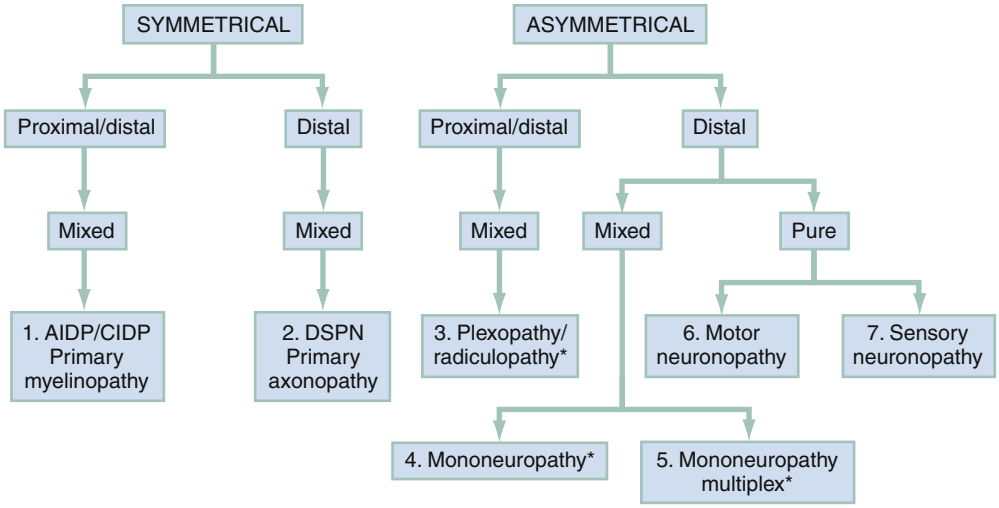

Fig. 93.1 An approach to peripheral neuropathy in the emergency department. *AIDP,* Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome); *CIDP,* chronic inflammatory demyelinating polyneuropathy; *DSPN,* distal symmetrical polyneuropathy. *A proximal distribution of sensorimotor findings may dominate the clinical picture in patterns 3, 4, and 5, depending on the location of the lesions.

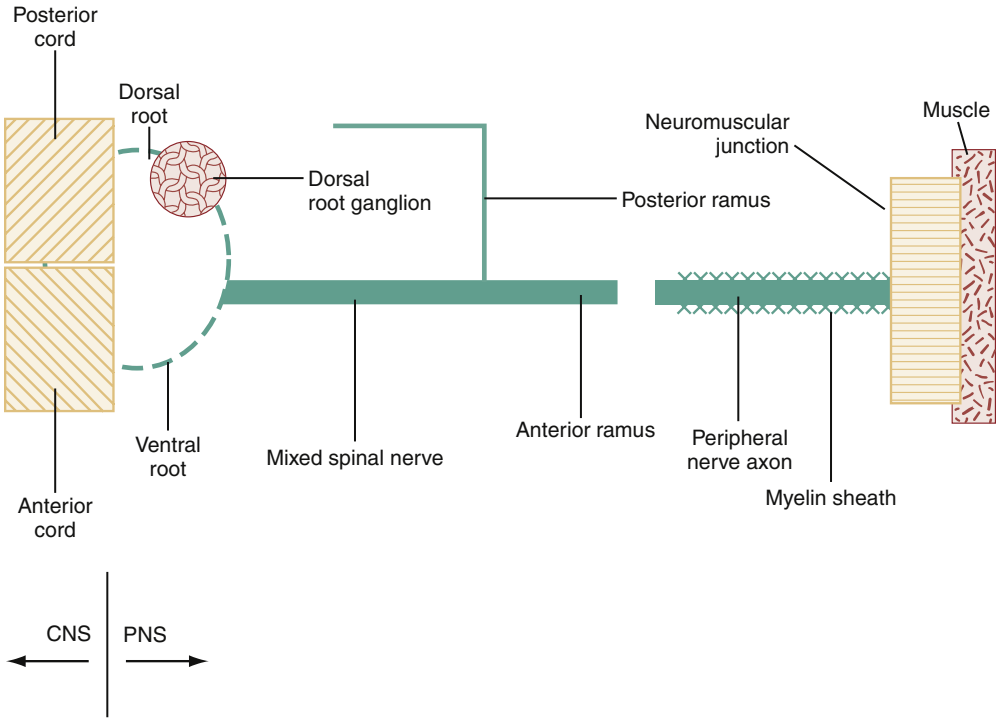

Fig. 93.2 Schematic representation of macroscopic and microscopic anatomy of the peripheral nervous system *(PNS)* and its interface with the central nervous system *(CNS).* See the text for an explanation.

pairs: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. The spinal nerves immediately bifurcate into anterior (ventral) and posterior (dorsal) rami. The posterior ramus travels to the back. The anterior ramus innervates the anterolateral portion of the body and supplies all peripheral nerves for the upper and lower extremities through the brachial and lumbosacral plexus, respectively. Interweaving of fibers occurs within a plexus, producing a mixed sensorimotor innervation of peripheral nerves exiting the plexus.

In addition to the motor and sensory modalities of the PNS, the autonomic nervous system has a peripheral component. Anatomically and functionally, the autonomic nervous system is divided into two parts: (1) a sympathetic (thoracolumbar) component and (2) a parasympathetic (craniosacral) component. Autonomic dysfunction may cause systemic abnormalities, such as orthostasis, or local problems, such as atrophic, dry skin.

The PNS has three basic categories of pathology (see Fig. 93.2): (1) the myelinopathies, in which the primary site of involvement is limited to the myelin sheath surrounding the axon; (2) the axonopathies, in which the primary site of involvement is the axon, with or without secondary demyelination; and (3) the neuronopathies, in which the cell body of the neuron itself is the primary site of involvement, ultimately affecting the entire peripheral nerve. Although overlap occurs, each of

BOX 93.1 Causes of Acute, Emergent Weakness and Possible Respiratory Compromise

- Autoimmune
  - Demyelinating
    - Guillain-Barré syndrome (GBS)
    - Chronic inflammatory demyelinating polyneuropathy
  - Myasthenia gravis
- Toxic
  - Botulism
  - Buckthorn
  - Seafood
    - Paralytic shellfish toxin
    - Tetrodotoxin (puffer fish, newts)
  - Tick paralysis
  - Metals
- Arsenic
- Thallium
- Metabolic
  - Dyskalemic syndromes
    - Acquired (especially with thyrotoxicosis)
    - Familial
  - Hypophosphatemia
  - Hypermagnesemia
  - Porphyria
- Infectious
  - Poliomyelitis
  - Diphtheria

Note: Although several of the disorders listed are myopathies (see Chapter 95) rather than peripheral neuropathies, they are combined here to emphasize the importance of identifying patients at risk for respiratory failure early in the course of their evaluation.

these prototypes has a distinctive clinical presentation, electrophysiologic profile, and microscopic appearance.

Differential Diagnosis

The differential diagnosis for any patient presenting with sensory, motor, or sensorimotor complaints, particularly if they are localized to the extremities, should include a peripheral neuropathy. Within this group, patients with focal weakness are most concerning, because they are at greatest risk for respiratory compromise. Box 93.1 lists the causes of acute weakness that may affect respiration.

As soon as the emergent causes of weakness have been excluded, the individuals with focal weakness are next assessed to exclude CNS disease (e.g., stroke; see Chapter 87). After a CNS cause has been exonerated, the systematic evaluation of peripheral neuropathy is performed. The distinguishing features of each of the seven peripheral neuropathic patterns are described by distribution and modality and represented by a disease prototype (see Fig. 93.1; Table 93.1).

Diagnostic Testing

Testing in the evaluation of the patient with a suspected peripheral neuropathy is presented in Box 93.2. Electrophysiologic testing (nerve conduction studies [NCSs] and needle electromyography [EMG]) detects underlying pathologic abnormalities. Because neither test is readily available in the acute care setting, they are discussed only briefly here. Information gathered from these tests can be used to obtain objective information regarding the anatomic distribution of involvement (symmetrical versus asymmetrical and distal versus proximal and distal) and the modalities involved (sensory, motor, or mixed).

TABLE 93.1 Patterns and Prototypes of Peripheral Neuropathies

Type	Pattern Distribution	Prototypical Disease Modalities
1	Proximal and distal, symmetrical, sensorimotor polyneuropathy	GBS
	Proximal and distal	Symmetrical
	Motor > sensory	
2	Distal, symmetrical, sensorimotor polyneuropathy	Diabetic DSPN
	Distal	Symmetrical
	Sensory > motor	
3	Proximal and distal, asymmetrical, sensorimotor neuropathy	Brachial plexopathy
	Proximal and distal	Asymmetrical
	Sensory and motor	
4	Distal, asymmetrical, sensorimotor mononeuropathy	CTS (median mononeuropathy)
	Distal	Asymmetrical
	Sensory and motor	
5	Distal, asymmetrical, sensorimotor mononeuropathy multiplex	Vasculitic mononeuropathy multiplex
	Distal	Asymmetrical
	Sensory and motor	
6	Distal, asymmetrical, pure motor neuronopathy	ALS
	Distal	Asymmetrical
	Motor	
7	Distal, asymmetrical, pure sensory neuronopathy	Pyridoxine toxicity
	Distal	Asymmetrical
	Sensory	

ALS, Amyotrophic lateral sclerosis; *CTS*, carpal tunnel syndrome; *DSPN*, distal symmetrical polyneuropathy; *GBS*, Guillain-Barré syndrome.

NCSs and EMG can also identify the level of the neuraxis affected by the disease process (i.e., root, plexus, or nerve). If the nerve is affected, electrophysiologic testing can help determine whether the lesion is mononeuropathic (either an isolated mononeuropathy or mononeuropathy multiplex) or polyneuropathic.

Finally, EMG and NCSs can distinguish axonal from myelin disease, further narrowing the differential diagnosis. Prognosis is determined by the nature of pathologic involvement of the PNS. Primary demyelination spares the axon and thus carries the best prognosis. The prognosis is worse in axonopathies because reestablishment of nerve function is dependent on the much slower process of axonal regeneration. Neuronopathies, which begin with primary destruction of the nerve cell body, produce pure motor or pure sensory syndromes. Eventually the entire nerve is affected, resulting in the worst prognosis of the three.

Antibody tests are commercially available that aim to aid in the diagnosis of peripheral neuropathies, especially those that are immune-mediated in etiology. However they are controversial, lack sensitivity and specificity, and may offer limited benefit beyond the focused neurologic examination and existing screening tests.

BOX 93.2 Ancillary Diagnostic Testing in Suspected Peripheral Neuropathy

Obtained in Most Patients

Complete blood count
Erythrocyte sedimentation rate
Glucose
Creatine kinase
Creatinine

Obtained in Some Patients Based on History

Human chorionic gonadotropin
Magnesium
Phosphate
Vitamin B_{12}
Hemoglobin A_{1c}
Serum protein electrophoresis with immune fixation electrophoresis
Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin screen with fluorescent treponemal antibody absorption test, as appropriate
Thyroid function
Human immunodeficiency virus (HIV) titer
Lyme enzyme-linked immunosorbent assay and Western blot
Rheumatoid factor and antinuclear antibody
Blood, urine, hair, or nails for metal, depending on suspected chronicity of exposure
Specific serum antibodies to components of peripheral nervous system (PNS)
Cerebrospinal fluid (CSF) for cells, protein, Lyme titer
Electrodiagnostic testing
- Nerve conduction studies (NCS)
- Electromyography (EMG)

Neurodiagnostic imaging
- Magnetic resonance imaging (MRI)
- Computed tomography (CT)
- Sonography

Quantitative sensory testing
Nerve biopsy
- Sural
- Intraepidermal nerve fiber density

SPECIFIC TYPES OF NEUROPATHIES

Type 1: Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

Principles

The pattern of symmetrical weakness, usually worse distally, accompanied by variable sensory findings is characteristic of acute Guillain-Barré syndrome (GBS). It is a heterogeneous and unpredictable disorder, characterized by areflexic paralysis with albuminocytologic dissociation, with marked variation in latency between antecedent infection and symptom onset.

Mortality rates in Europe and North America are estimated between 3% and 7% and up to 20% of patients remain disabled after six months, unable to ambulate without assistance.[1]

The most common form of GBS is an acute inflammatory demyelinating polyneuropathy, representing 90% of the cases seen in the United States. Less common variants are acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, and the Miller Fisher syndrome. Acute motor axonal neuropathy, which accounts for most of the remaining cases seen in the United States, afflicts those of Asian descent more often. Miller Fisher syndrome is a rare form of GBS characterized by the triad of ophthalmoplegia, ataxia, and areflexia (Box 93.3).

BOX 93.3 Demyelinating Polyneuropathies

Guillain-Barré syndrome (GBS)
- Acute inflammatory demyelinating polyradiculoneuropathy
- Acute motor axonal neuropathy
- Acute motor and sensory axonal neuropathy
- Miller Fisher syndrome

Chronic inflammatory demyelinating polyradiculoplexoneuropathy
Malignant disease
Human immunodeficiency virus (HIV) infection
Hepatitis B
Buckthorn
Diphtheria

Campylobacter jejuni infection is the most commonly associated etiology for GBS with a frequency reported in 25% to 50% of adult cases.[2] Cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumonia* have also been associated with the subsequent development of GBS.

Clinical Features

The majority of patients with GBS seek treatment days to weeks after resolution of an upper respiratory or gastrointestinal illness; patients present with progressive, symmetrical distal (and usually to a lesser extent proximal) weakness. Symptom progression ranges from rapidly progressive to a more insidious course over days to weeks. Signs and symptoms are usually worse in the lower extremities and are associated with diminution or loss of deep tendon reflexes (DTRs) in the affected limbs, variable sensory findings, and sparing of the anal sphincter. The presence of distal paresthesias increases the likelihood of GBS as the diagnosis.

About half of patients with GBS have autonomic dysfunction, experience a peak of disease severity within a week of onset, have some form of cranial nerve involvement (usually cranial nerve VII), and suffer long-term sequelae of their illness.

Patients with neck or bulbar weakness are more likely to require mechanical ventilation than those patients without. Predicting outcomes among GBS patients can be challenging and several scoring systems are available to aid with prognosis in the inpatient setting. The Erasmus GBS outcome score (EGOS) is a validated prognostic scoring tool, performed at 14 days of admission, that utilizes three measures: age of onset of disease, the presence or absence of diarrhea, and then folds in another scoring system, the GBS disability score, to predict inability to ambulate independently at 6 months. A modified EGOS (mEGOS) utilizes Medical Research Council score (MRC) instead of the GBS disability score and can be used earlier, at one week of admission. There is no score to predict outcomes from the ED, however.

Diagnostic Testing

GBS is typically diagnosed on clinical findings, but additional testing with EMG is indicated when the diagnosis is uncertain. The most frequent finding of demyelination includes nerve conduction slowing with prolonged distal motor latency.

In addition to electrophysiologic testing, cerebrospinal fluid (CSF) analysis and respiratory function testing may aid in the diagnosis of GBS. CSF analysis is useful when it demonstrates the characteristic picture of markedly elevated protein with only a mild pleocytosis (albuminocytologic dissociation). In the clinical setting of suspected GBS, this finding is highly specific. Early in the disease, however, patients may have normal CSF values. One study noted only 50% of patients had elevated protein and mild pleocytosis in the first week of symptoms, rising to 75% in the third week. Consequently, normal CSF

cannot be used to exclude GBS, though a lumbar puncture performed early in the disease process can help identify infectious or neoplastic causes that may present similarly to GBS. Because of the potential for a missed diagnosis, a lumbar puncture should be performed in the emergency department for patients in whom there is concern for GBS.

Individuals with suspected GBS should have their respiratory function tested, as they may present without overt signs of respiratory distress. A decrease in forced vital capacity (FVC) to less than 20 mL/kg is associated with pending respiratory failure and the need for intubation, whereas patients with an FVC of more than 40 mL/kg do not usually require intubation. Likewise, patients with a negative inspiratory force of less than 30 cm H_2O are more likely to require mechanical ventilation. Other tests, such as the forced expiratory volume in 1 second (FEV_1) and peak flow rate (PFR), can also be used to assess respiratory function, but there has been limited study of these modalities. A PFR of less than 250 L/min increased the likelihood of needing mechanical ventilation in a retrospective study of patients with GBS. Patients unable to perform these tests and those with less than 100% of predicted values should have a blood gas performed to assess for hypercapnia and an impending need for mechanical ventilation. However, hypercapnia may be a late sign of weakness, and therefore, the decision to intubate should be made considering the overall clinical picture.

Management

In practice, patients with symmetrical weakness of relatively acute onset, decreased or absent DTRs, and variable degrees of sensory loss are managed as if they have GBS or one of its variants. These patients are at risk for respiratory compromise, which develops in 20% of patients. Conversely, patients with predominantly sensory signs and symptoms are less likely to develop acute respiratory distress and have a more favorable prognosis.

The definitive treatments for GBS are plasma exchange or intravenous immune globulin (IVIG). Both of these treatments are supported by well-designed studies, although there are no studies comparing IVIG to placebo. Combination or sequential therapy confers no therapeutic advantage over either intervention alone. Plasma exchange is cumbersome and not available at many hospitals. IVIG is more readily available and is usually administered in a dose of 400 mg/kg per day for 5 days. However, IVIG is expensive, costing roughly double a standard course of plasma exchange.

Corticosteroids are not recommended; oral steroids have been shown to delay recovery, and intravenous steroids alone have no benefit. The combination of intravenous steroids and IVIG may hasten recovery but does not have an effect on long-term outcome and is not currently recommended.[3]

Disposition

Patients with suspected GBS should receive neurologic consultation and admission for respiratory monitoring and treatment with either plasma exchange or IVIG. Evidence of alveolar hypoventilation (elevated carbon dioxide [P_{CO_2}]) in a patient with an unsecured airway requires an intensive care level of monitoring, as these patients may require intubation.

Type 2: Distal Symmetrical Polyneuropathy

Principles

Distal symmetrical polyneuropathy (DSPN) is the most common type of peripheral neuropathy. Diabetes, alcoholism, human immunodeficiency virus (HIV) disease, and toxic metabolic causes are the most frequent etiologies (Box 93.4). DSPN in diabetics, termed *diabetic polyneuropathy,* is the most common chronic complication of diabetes mellitus.

BOX 93.4 Distal Sensorimotor Polyneuropathies

- Diabetes mellitus
- Alcoholism
- Neoplastic or paraneoplastic
- Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth)
- Cryptogenic sensorimotor polyneuropathies
- HIV infection
- Toxins
  - Organic or industrial agents
    - Acrylamide
    - Allyl chloride
    - Carbon disulfide
    - Ethylene oxide
    - Hexacarbons
    - Methyl bromide
    - Organophosphate-induced delayed polyneuropathy
    - Polychlorinated biphenyls
    - Trichloroethylene
    - Vacor
  - Metals
    - Arsenic
    - Gold
    - Mercury (inorganic)
    - Thallium
  - Therapeutic agents
    - Amiodarone
    - Antiretrovirals
    - Dapsone
    - Disulfiram
    - Isoniazid
    - Metronidazole
    - Nitrofurantoin
    - Paclitaxel (Taxol)
    - Phenytoin
    - Statins (HMG-CoA reductase inhibitors)
    - Thalidomide
    - Vinca alkaloids (vincristine, vinblastine)
  - Nutritional
    - Beriberi (thiamine or vitamin B_1)
    - Pellagra (niacin, B vitamins)
    - Pernicious anemia (vitamin B_{12})
    - Pyridoxine deficiency (vitamin B_6)
  - End-organ dysfunction
    - Acromegaly
    - Chronic pulmonary disease
    - Hypothyroidism
    - Renal failure (uremic neuropathy)
  - Paraproteinemias
    - Amyloidosis
    - Monoclonal gammopathy of unknown significance
    - Multiple myeloma
    - Waldenström macroglobulinemia
  - Porphyria

HIV, Human immunodeficiency virus; *HMG-CoA,* hydroxymethylglutaryl coenzyme A.

Although the association between alcoholism and peripheral neuropathy has been well established for centuries, demonstration of a direct neurotoxic effect of alcohol remains elusive. The preponderance of evidence from both observational studies in humans and

experimental data from animal models suggests that the association between alcohol and peripheral neuropathy may be confounded by nutritional status (i.e., deficiency states might be the true underlying cause of alcoholic peripheral neuropathy).

With the widespread use of highly active and effective antiretroviral treatment, peripheral neuropathies have become the most common neurologic complication of HIV infection. The typical HIV neuropathy is a DSPN, estimated to affect up to 35% of the HIV population; the pathogenesis is currently unknown.

Clinical Findings

Most polyneuropathies are characterized by a pattern of distal, symmetrical sensorimotor findings, worse in the lower than in the upper extremities, with a stocking-glove distribution of sensory abnormalities that gradually diminishes as one moves proximally. Motor weakness and loss of DTRs, which lag behind the sensory features, follow a similar pattern of progression from distal to proximal. The diffuse, distal, symmetrical nature of this pattern is most consistent with a toxic-metabolic disease process that causes a length-dependent axonopathy.

Initial symptoms usually consist of "positive" sensory complaints (e.g., dysesthesias, such as tingling and burning) beginning on the plantar surfaces of both feet. At the early stages of a typical DSPN, there may be some asymmetry. At this juncture, it may be impossible to distinguish a focal neuropathic process such as a mononeuropathy from a polyneuropathy, although this location strongly favors a polyneuropathy. As the process advances, the plantar surfaces of both feet become dysesthetic before the dorsum of either foot is involved.

Weakness of dorsiflexion of the big toe is usually the first motor sign, followed by weakness of foot dorsiflexion, footdrop, loss of the Achilles reflex, and later a "steppage gait," in which footdrop causes the toes to point downward and scrape the ground while walking, requiring the patient to lift the leg higher than normal when walking.

Sensory loss continues to move proximally, and before it reaches the knees, the fingertips are usually involved. DTRs are progressively lost, as is proprioception. If loss of proprioception becomes severe, patients may develop sensory ataxia. As the neuropathy continues to progress, sensory abnormalities ultimately involve all modalities and extend to a diamond-shaped periumbilical area. Far-advanced disease may affect sensation over the skull vertex and facial midline structures. Atrophy and areflexia occur as weakness worsens. Severely impaired patients may be unable to ambulate or to grasp objects. These symptoms have an impact on the patient's quality of life, affecting not only physical functioning but also sleep and emotional and social functioning. Many of these patients display signs of depression or anxiety. Polyneuropathies can be difficult to diagnose and are best approached by the performance of electrodiagnostic studies for patients with a constellation of symptoms and signs suggesting a particular neuropathy.

Diabetic foot ulcers are a common and often late complication of diabetes, ranging from 2% to 10% of the population. Repetitive stress or unperceived minor trauma is the leading cause, likely from the associated polyneuropathy.

The clinical picture of alcoholic neuropathy is similar to that of diabetic DSPN. However, in alcoholism, severe myopathy and cerebellar degeneration often complicate the clinical picture. Autonomic skin changes with atrophy and hair loss accompany the sensorimotor abnormalities. Often, other systemic effects of alcoholism are so severe that the patient may not notice the neuropathic symptoms.

Differential Diagnosis

Box 93.4 lists the differential diagnoses of DSPN. On the basis of results from a case-control study, the statins have been added to the list of drugs that are implicated.

Diagnostic Testing

Electrodiagnostic studies are commonly employed in the evaluation of DSPN. This includes both NCSs and needle electromyelography. Screening laboratory tests should be considered for all patients who present with DSPN. The high yield tests in evaluating a DSPN include blood glucose, serum B12, and serum protein immunofixation electrophoresis. A complete blood count (CBC), comprehensive metabolic panel, hemoglobin A1c or oral glucose tolerance test, and thyroid-stimulating hormone (TSH) are recommended as part of the initial workup.

Management

In diabetic DSPN, the initial steps in management focus on tight glucose control and lifestyle modifications. Tight glucose control in type 1 diabetes is associated with a more profound reduction in the incidence of DSPN than is found among those with type 2 diabetes. If discomfort is severe, the etiology of the neuropathy seems likely to be diabetic, and referral is delayed, it may be necessary to provide the patient with some symptomatic relief. Because the treatment of neuropathic pain has traditionally been linked to etiology, the choice of pharmacologic agents is empirical with substantial practice variation. Nonsteroidal antiinflammatory drugs (NSAIDs) have little proven efficacy and a high potential for renal impairment; therefore they are not a first-line therapy. Pregabalin, duloxetine, and tapentadol have all received regulatory approval by the US Food and Drug Administration for the treatment of DSPN, with duloxetine and pregabalin considered first-line treatments.[4] Pregabalin has a mechanism of action similar to that of gabapentin and is dosed at 50 to 150 mg/day in divided doses. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is effective at a dose of 60 mg per day. Tapentadol ER, dosed at 50 mg twice daily, also provides pain relief in patients with diabetic neuropathy, however, given the risk of addiction with opioids, it is not considered a first-line agent.[5] Other evidence supports the use of tricyclic antidepressants, anticonvulsants, and the serotonin and norepinephrine reuptake inhibitor duloxetine. Imipramine or amitriptyline are started at a daily dose of 25 mg at bedtime (10 mg in the elderly) and titrated slowly up to a dose of 100 mg. Gabapentin 900 to 3600 mg per day in divided doses are also effective treatments. Tramadol, a centrally acting analgesic and mixed opioid, has been effective in several trials for the treatment of DSPN, but safety concerns regarding its abuse potential make it a less desirable option. Topical capsaicin provides relief in some patients, but the burning associated with its application has limited its use. Topical lidocaine patches, 5%, are yet another option.

We recommend pregabalin, duloxetine, or gabapentin at a low dose to manage the pain from DSPN; this is best done in consultation with the patient's primary physician who can then titrate to therapeutic effect on follow-up. In patients who have localized symptoms, who cannot tolerate the side effects or have the potential for adverse drug interactions, topical agents such as lidocaine patches or capsaicin cream can be offered. In addition to pain management as discussed earlier, all patients with suspected alcoholic DSPN should receive dietary supplements and referral for outpatient management.

There are no first-line agents for the treatment of HIV-associated neuropathy, and limited randomized controlled trials have not demonstrated any specific analgesic that is more effective over placebo.

Type 3: Asymmetric Proximal and Distal Peripheral Neuropathies (Radiculopathies and Plexopathies)

Radiculopathies and plexopathies often result from trauma (Box 93.5). In general, a plexopathy, whether brachial or lumbosacral, is identified by process of elimination (i.e., a pattern of sensorimotor and reflex

BOX 93.5 Asymmetrical Proximal and Distal Peripheral Neuropathies

Brachial Plexopathy

Open
- Direct plexus injury (knife or gunshot wound)
- Neurovascular (plexus ischemia)
- Iatrogenic (central line insertion)

Closed
- Traction injuries
  - "Stingers" (neck or shoulder injury resulting in transient brachial plexus injury)
  - Traction neurapraxia
  - Partial or complete nerve root avulsion
- Radiation
- Neoplastic
- Idiopathic brachial plexitis
- Thoracic outlet

Lumbosacral Plexopathies

Open

Closed
- Traction injuries
  - Pelvic double vertical shearing fracture
  - Posterior hip dislocation
  - Retroperitoneal hemorrhage
- Vasospastic (deep buttock injection)
- Neoplastic
- Radiation
- Idiopathic lumbosacral plexitis
- Infectious
  - Herpesvirus (sacrococcygeal)
  - Herpes simplex 2
  - Herpes zoster
  - Cytomegalovirus polyradiculopathy (HIV infection)

HIV, Human immunodeficiency virus.

abnormalities that fit neither a radicular nor an individual peripheral nerve distribution). Although this approach does not exclude a mononeuropathy multiplex on physical examination alone, a careful history should determine whether the patient is at risk for development of a mononeuropathy or plexopathy based on underlying disease

Most plexopathies are seen in young men after motor vehicle accidents, many of whom present for evaluation of radicular pain several months after the initial injury. Therapeutic intervention is often delayed to maximize the potential for spontaneous recovery. Several surgical repairs exist, including neurotization.

Radiation (actinic) plexopathy occurs after a variable period of latency following treatment, which may extend to 20 years or more. Almost all series include women who received radiation treatment for breast cancer. Among neoplastic causes, most originate from the lung or breast. Patients with probable neoplastic brachial plexopathy need imaging studies and may require immediate radiation therapy. Pain control is the focus of management.

Thoracic outlet syndrome (TOS) describes a constellation of symptoms caused by compression of the neurovascular bundle at the thoracic outlet. As our understanding of this condition has improved, treatment has evolved but remains controversial. Manifestations include both neurogenic and vascular (arterial or venous) TOS. It is estimated that over 90% of cases are neurogenic in origin; 3% to 5% are venous, and less than 1% are arterial.

Neurogenic TOS is caused by compression of the brachial plexus, presenting with upper extremity weakness, numbness, paresthesias, and pain in a nonradicular distribution. Symptoms are usually present during normal daily activities and sleep. Treatment is typically nonsurgical, involving education, activity modification, and physical therapy.

Vascular TOS can be either arterial or venous and is characterized by swelling of the upper extremity, pain, and a feeling of heaviness after exertion. Discoloration can also be seen. If arterial TOS is occurring, caused by compression of the subclavian artery, the typical findings of arterial insufficiency can be seen—pain, numbness, coolness, pallor. Treatment is typically surgical, involving decompression of the thoracic outlet.

Because of the complexity of plexopathies, the goal in the ED is to localize the probable pathologic process to the brachial or lumbosacral plexus. Depending on severity and suspected etiology, the patient should either be admitted or referred to a neurologist with experience in PNS disease.

Type 4: Isolated Mononeuropathies

The pattern of asymmetrical, sensorimotor, usually distal, peripheral neuropathy is characteristic of a mononeuropathy. Mononeuropathies are of two main types: isolated and multiple. The isolated mononeuropathies are discussed in this section; the multiple mononeuropathies, also termed mononeuropathy multiplex, are discussed in the next section as a Type 5 peripheral neuropathy.

Isolated mononeuropathies are usually caused by trauma, either blunt or penetrating (Box 93.6). If the trauma is blunt, the injury may be secondary to compression from an internal or external source. Entrapment neuropathies are a subset of compression neuropathies occurring at anatomic locations where nerves traverse potentially constricting compartments or tunnels. Isolated mononeuropathies may be acute, intermittent, or chronic and continuous. Antecedent peripheral neuropathy may be a risk factor for the development of compression neuropathy (so-called double-crush syndrome), particularly in diabetics.

Radial Mononeuropathy

Principles. The radial nerve arises from the C5 to T1 roots. After exiting the brachial plexus, it passes behind the proximal humerus in the spiral groove and takes a lateral (radial) course down the upper arm (Fig. 93.3). At about the level of the antecubital fossa, it bifurcates into the posterior interosseous (pure motor) and superficial radial (pure sensory) nerves.

The radial nerve controls extension of the fingers, thumb, wrist, and elbow (triceps). In contrast to the median and ulnar nerves, the radial nerve provides only *extrinsic* motor innervation to the hand (i.e., it does not supply motor fibers to any muscles that both originate and insert within the hand). In further contrast to the median and ulnar nerves, which supply most of the sensation to the hand, the radial nerve makes a contribution only to a cutaneous dorsal area overlying the first dorsal interosseus muscle, sometimes extending part of the way up the dorsa of the thumb, index, and long fingers.

Radial mononeuropathy caused by involvement at the level of the axilla is uncommon. When it occurs, it is usually associated with other upper extremity mononeuropathies or a brachial plexopathy. Although improper use of crutches may cause this syndrome, it usually occurs after an extended period of unconsciousness during which the arm is positioned in such a way that prolonged, deep compression is applied to the axilla. The most common are due to the so-called "Saturday night palsies," which is derived from the association of radial mononeuropathy with improper positioning of the arm during deep, commonly inebriated sleep. Consequently, the radial nerve is trapped for a prolonged period between the humeral shaft and some firm surface, causing

BOX 93.6 Isolated Mononeuropathies

Upper Extremity

Radial nerve
- Axilla
- Humerus
- Elbow (posterior interosseous neuropathy)
- Wrist (superficial cutaneous radial neuropathy)

Ulnar nerve
- Axilla
- Humerus
- Elbow
- Condylar groove
- Cubital tunnel
- Wrist (Guyon's canal)
- Hand
  - Superficial terminal ulnar neuropathy
  - Deep terminal ulnar neuropathy: proximal hypothenar; distal hypothenar

Median nerve
- Axilla
- Humerus (musculocutaneous mononeuropathy)
- Forearm
  - Anterior interosseus
  - Pronator syndrome
- Wrist (carpal tunnel)
- Hand (recurrent motor branch)
- Suprascapular mononeuropathy
- Axillary mononeuropathy

Lower Extremity

Sciatic nerve

Femoral nerve
- Iliacus compartment (proximal)
- Saphenous mononeuropathy (distal)

Lateral femoral cutaneous (meralgia paresthetica)

Peroneal nerve
- Common peroneal mononeuropathy (fibular head, popliteal fossa)
- Deep peroneal mononeuropathy (anterior compartment)

Tibial nerve
- Popliteal fossa (proximal)
- Tarsal tunnel (distal)

Sural nerve
- Popliteal fossa, calf (proximal)
- Fifth metatarsal base (distal)

Plantar nerve
- Distal to tarsal tunnel
- Interdigital neuropathies (Morton neuroma)

Obturator mononeuropathy

an external compression mononeuropathy. "Bridegroom's palsy" is another eponym for radial mononeuropathy, so named because the radial nerve may be compressed by the bride's head resting on the bridegroom's arm during sleep. Axillary radial mononeuropathy is distinguished from the more common humeral form by the finding of triceps involvement in addition to typical wrist and finger drop. Triceps involvement occurs because the innervation to the triceps is proximal to the point where the nerve is most vulnerable as it winds around the humeral shaft (see Fig. 93.3).

Clinical Findings. Because innervation of the wrist and finger extensors occurs distal to this area of the humeral shaft, findings

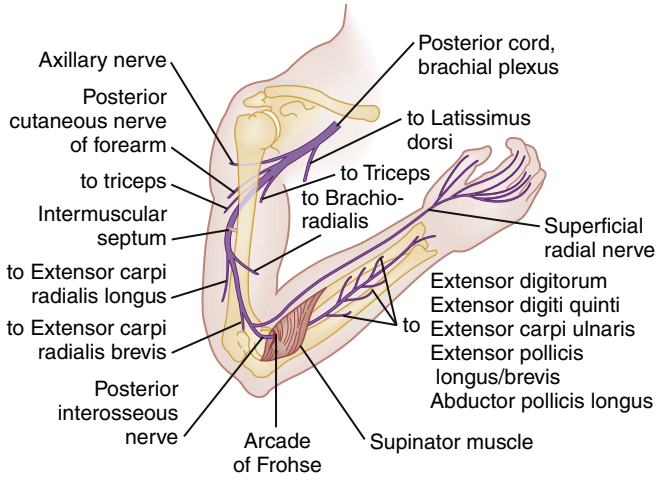

Fig. 93.3 Radial nerve, major branches, right arm, lateral view. (From Stewart JD. *Focal Peripheral Neuropathies*, ed 3. Philadelphia: Lippincott Williams & Wilkins; 2000.)

are characterized by wrist and finger drop and mild numbness over the skin of the first dorsal interosseus muscle. Depending on the level, degree, and duration of compression, some fascicles of the nerve may remain functional, resulting in a partial radial mononeuropathy. Thus the superficial radial nerve may remain intact, resulting in no loss of sensation, or loss of wrist and finger extension may be incomplete.

Because the finger drop of radial mononeuropathy places the hand at a mechanical disadvantage, examination of ulnar function by testing of the interossei may produce false-positive findings of weakness. To adjust for this, the examiner should ask the patient to place the palm on a horizontal supporting surface, such as a stretcher. With the fingers extended and no longer "dropped" at the metacarpophalangeal joints, interosseous strength can now be fairly tested. Failure to perform this maneuver may cause misdiagnosis of a simple radial mononeuropathy as a brachial plexopathy in an effort to explain what appears to be radial and partial ulnar nerve involvement.

About 90% of radial nerve palsies occurring during sleep, coma, or anesthesia recover fully, usually within 6 to 8 weeks. Evidence of denervation on EMG studies predicts a slower rate of recovery. Tourniquet injuries to the radial nerve usually recover spontaneously within 2 to 4 months. If axonal degeneration is seen on electrophysiologic testing, recovery may take longer, although virtually all radial mononeuropathies caused by tourniquets eventually resolve.

The radial nerve courses closely to the humerus, so it follows that about 22% of humeral shaft fractures are associated with radial nerve injury, with "wrist drop" the hallmark injury. Spontaneous resolution has been reported between 60% and 92%, so many authors suggest observation of these injuries is appropriate. In contrast, surgical intervention is needed to free the nerve from entrapment associated with complex fractures.

Diagnostic Testing. There exists no diagnostic test per se for this disease entity beyond the physical examination. EMG testing is employed to aid in predicting recovery times.

Management. While patients are waiting for spontaneous recovery to occur, the hand should be maintained in about 60 degrees of dorsiflexion. Although a simple dorsal plaster or fiberglass splint treats the wristdrop, atrophy and contractures can be minimized, and function of the hand can be improved if wide rubber bands anchored to the splint at a point proximal to the wrist are attached to individual fingers to provide passive dorsiflexion.

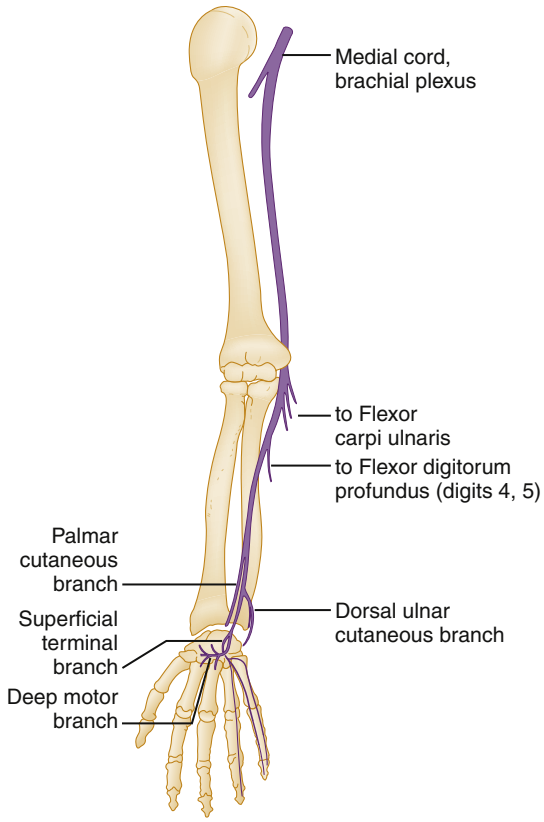

Fig. 93.4 Ulnar nerve, major branches, right arm, anterior view. (From Stewart JD. *Focal Peripheral Neuropathies*, ed 3. Philadelphia: Lippincott Williams & Wilkins; 2000.)

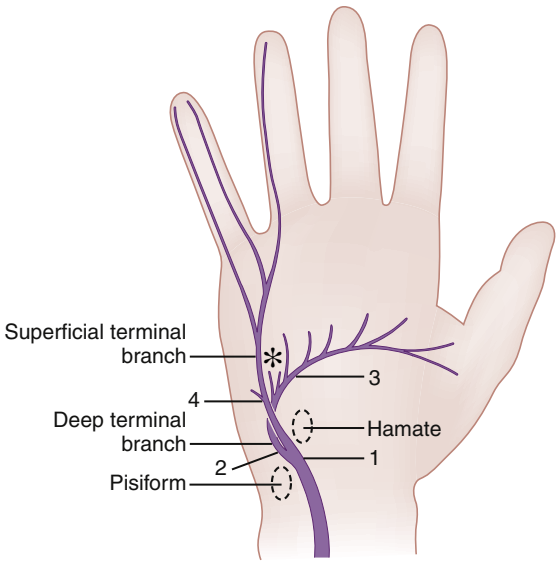

Fig. 93.5 Distal ulnar nerve and branches, right hand, palmar view. *Numbers* indicate four main sites of distal ulnar mononeuropathy in the wrist and hand. Asterisk *(*)* denotes hypothenar branches. (From Stewart JD. *Focal Peripheral Neuropathies*, ed 3. Philadelphia: Lippincott Williams & Wilkins; 2000.)

Ulnar Mononeuropathy

Principles and Clinical Findings. The ulnar nerve includes C7 to T1 roots and passes through the brachial plexus to descend medially, without branching, to the ulnar (medial) condylar groove at the elbow. It then enters the cubital canal, where it gives off branches to the ulnar wrist flexor and the deep flexors of the fourth and fifth digits.

Just proximal to the wrist, two important sensory branches leave the main trunk to supply cutaneous sensation to part of the hand (Fig. 93.4). These are the palmar and dorsal cutaneous branches, which do *not* pass through the Guyon canal. The palmar branch supplies sensation to the hypothenar eminence and the dorsal branch innervates the ulnar side of the dorsum of the hand, extending out nearly to the tip of the fifth and ulnar half of the fourth digit.

At the wrist, the nerve enters the Guyon canal (Fig. 93.5) between the pisiform and hook of the hamate, then bifurcates into the superficial terminal sensory branch and the deep motor branch.

The superficial sensory nerve supplies ulnar sensation to the palmar side of the fifth and half of the fourth digit (see Fig. 93.5). The deep motor nerve supplies the hypothenar muscles, then crosses to the radial side of the palm to innervate the ulnar intrinsics (all interossei and the ulnar lumbricals of the fourth and fifth digits), terminating in the first dorsal interosseus. The interossei abduct and adduct the fingers and are all innervated by the ulnar nerve. The lumbrical muscles flex the metacarpophalangeal joints and are evenly divided between the ulnar (fourth and fifth) and median (second and third) digits. The ulnar nerve can be thought of as the complement to the median nerve in the hand, because it supplies all of the muscles and all palmar sensation not innervated by the median nerve.

The ulnar nerve may be injured at two locations near the elbow: in the ulnar condylar groove and distally in the cubital canal. Because the condylar groove is shallow, the ulnar nerve runs superficially in this location and is vulnerable to injury, usually from external pressure or from a fracture or dislocation. The ulnar nerve has a propensity to develop a "tardy ulnar palsy," occurring years after a traumatic event. Many of these delayed ulnar mononeuropathies can be localized to the elbow on electrophysiologic testing.

Some ulnar mononeuropathies occur secondary to compression just proximal to entry into the cubital canal or are entrapped within the canal itself. Transient symptoms may occur during prolonged flexion or with repeated flexion and extension at the elbow.

Although it is difficult to distinguish a condylar from a cubital ulnar mononeuropathy, it is usually possible to localize the problem to the region of the elbow or the wrist. In addition to prior probability heavily favoring the elbow, the presence of sensory abnormalities in an ulnar distribution in the hand and fingers (i.e., usually including the fifth digit and "splitting" the fourth digit) strongly suggests that the lesion is at the level of the elbow rather than the wrist. The ulnar cutaneous innervation to the hand branches off from the main trunk proximal to the nerve entering the Guyon canal (see Figs. 93.4 and 93.5). Thus a lesion at the wrist should not produce sensory abnormalities, whereas one at the elbow would be expected to do so.

Compression of the ulnar nerve within the Guyon canal is rare. When it does occur, it affects all of the ulnar intrinsics (i.e., the two ulnar [fourth and fifth] lumbricals) and all the interossei. However, the ulnar extrinsics (i.e., the deep flexors of the fourth and fifth digits) are not affected, nor is the ulnar flexor of the wrist. The only sensory abnormalities are those in the distribution of the superficial terminal sensory branch, sparing other areas of ulnar innervation (see Fig. 93.5).

There are three ulnar mononeuropathies that occur distal to the Guyon canal in the hand. The two most common ones involve the deep terminal branch, either proximal or distal to the separation of the hypothenar branches (see Fig. 93.5). If the lesion is proximal, it produces weakness of all the ulnar-innervated muscles of the hand without sensory loss. If it is distal, the hypothenar ulnar intrinsics are spared, but the picture is otherwise similar. Usually, this occurs secondary to a laceration or repeated compression in the hand from use of certain tools, a cane, or the handle of a crutch.

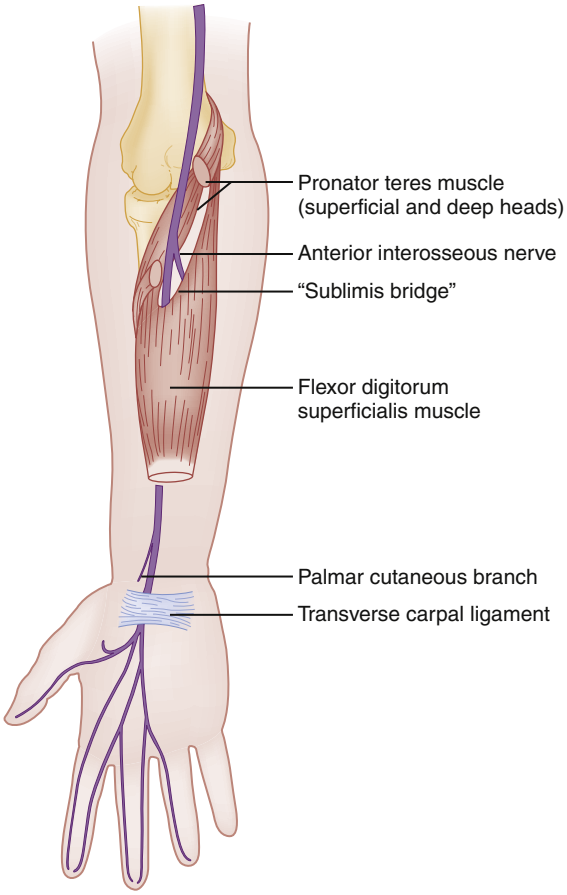

Fig. 93.6 Median nerve, major branches, right arm, anterior view. (From Stewart JD. *Focal Peripheral Neuropathies*, ed 3. Philadelphia: Lippincott Williams & Wilkins; 2000.)

Involvement of the superficial terminal branch (see Fig. 93.5) produces a pure sensory loss of the palmar surface of the fifth digit and ulnar half of the fourth digit caused by direct compression of this branch just distal to the Guyon canal. The dorsal surface of these two digits should have normal sensation except for the distal tips. This configuration of findings is due to the intact innervation provided by the dorsal and palmar cutaneous branches that enter the hand without passing through the Guyon canal (see Fig. 93.4).

Diagnostic Testing. There exists no true diagnostic entity for this disease process beyond the physical examination.

Management. Most ulnar mononeuropathies will spontaneously resolve. The evidence and options for nonoperative management are limited, but include splinting or padding, limiting flexion at the elbow, and activity modification. However, if muscle atrophy, particularly in the hypothenar area, is detected, surgery may be considered. There is no noted difference in outcomes between the two surgical options of simple decompression and decompression with transposition.

Median Mononeuropathy

Principles. The median nerve arises from the C5 to T1 spinal nerve roots and exits the brachial plexus through the lower trunk (Fig. 93.6). Median mononeuropathy is usually diagnosed as carpal tunnel syndrome (CTS), which is the most common of all entrapment neuropathies. The incidence of CTS is estimated at 1 in 1000 for the general population and a lifetime risk of 10%.[6] It is defined by the Academy of Orthopedic Surgeons as "a symptomatic compression neuropathy of the median nerve at the level of the wrist."

BOX 93.7 Conditions Associated With Carpal Tunnel Syndrome

Acromegaly
Amyloid
Diabetes mellitus
Hypothyroidism
Obesity
Pregnancy
Renal failure
Rheumatoid arthritis

Clinical Findings. Although the patient may complain of bilateral symptoms, a careful history usually reveals that symptoms in one hand preceded those in the other. A common symptom of CTS is awakening at night and shaking the hand. Symptoms are often worsened by activity. For unclear reasons, the pain may spread as high as the arm or shoulder, although the paresthesias are generally confined to the fingers. Many patients initially state that their entire hand is involved, although this is not elicited by careful sensory examination. Patients may note, progressively over time, that their hands are clumsy or weak, and also note associated loss of fine motor function. The skin of the fingers innervated by the median nerve may be drier and rougher to the touch than the corresponding ulnar skin, depending on the duration of entrapment.

When motor involvement occurs in CTS, it is confined to the median intrinsics, which innervate the *l*umbricals (flexion of the metacarpophalangeal joints) and subserve thumb *o*pposition, *a*bduction, and *f*lexion, known as the *LOAF* muscles. However, the hallmark of CTS is sensory involvement, with motor abnormalities occurring later. The typical pattern of sensory innervation of the hand by the median, ulnar, and radial nerves shows marked individual variation. The most specific finding for CTS is splitting of the fourth digit (i.e., normal sensation of the ring finger on the ulnar palmar side with abnormal sensation on the median [radial] palmar side of the same finger). The most sensitive finding is abnormal sensation of the distal palmar tip of the index finger. If sensory findings are absent in the presence of motor findings consistent with median nerve involvement, it is highly unlikely that the patient has CTS, and an alternative diagnosis should be sought.

CTS appears to be associated with the conditions listed in Box 93.7. Of these, the two most common are diabetes mellitus and pregnancy.[7] CTS associated with systemic illness is commonly bilateral. CTS in pregnancy appears to be common, but the prevalence varies widely in the literature from 30% to 60%; resolution occurs among the majority of patients postpartum, but several studies have demonstrated that symptoms can persist for months to years among a subset of patients even after delivery.

Diagnostic Testing. The Tinel sign (percussion of the median nerve at the wrist) and Phalen sign (maximal palmar flexion at the wrist) are provocative tests to reproduce the sensory symptoms of CTS if neither sensory nor motor symptoms are evident on initial examination. Unfortunately, neither sign has adequate sensitivity or specificity to determine which patients should be referred for electrodiagnostic studies. Dropping of objects is indicative of severe CTS. The best way to examine patients for sensory findings is to touch the distal palmar tips very lightly, asking the patient whether the sensation feels "abnormal."

A nerve conduction study is an objective test that provides information on the physiologic health of the median nerve across the carpal tunnel and is the diagnostic gold standard. Magnetic resonance

imaging (MRI) delineates the site of the nerve compression with a sensitivity of 96% but a specificity of 33% to 38%. Ultrasonography may be useful, particularly in patients with symptoms and a normal NCS. The most reliable ultrasonographic measurement is to obtain the cross-sectional area of the median nerve at the level of the pisiform. Thus, if all diagnostic studies in a symptomatic patient are normal, or if only the MRI result is abnormal, they should be repeated within three months if symptoms do not resolve. This recommendation is based on the theory that the CTS will progress over time to the point that an objective indicator, such as the NCS, will become positive.

Management. There are a variety of nonsurgical treatments, with splinting and steroid injections being the most common. A neutral wrist splint, typically worn at night during sleep, has commonly been used as the initial treatment. A Cochrane review found splinting more effective than no treatment in the short term, but the evidence that supported this conclusion was not robust.[8] A randomized trial comparing the effectiveness of night splinting versus a single corticosteroid injection found steroid injection benefit at six weeks, but at six months outcomes between the two treatment groups were the same.[9] We recommend providing patients with a splint to be worn during the night time hours and education regarding hand positioning or avoidance of repetitive activities that could lead to exacerbation of their symptoms. Oral NSAIDs can be offered, but there is no good quality supporting evidence.

Because of the possibility of a disabling "median hand" after inadvertent direct injection of the median nerve, we recommend that emergency clinicians defer the injection of the carpal tunnel with steroids to the consulting hand surgeon who can also obtain NCS and determine if splinting, injection, or surgical division of the transverse carpal ligament is indicated. Surgical treatment involves the division of the transverse carpal ligament, which reduces pressure on the median nerve by increasing the space in the carpal tunnel. This carpal tunnel "release" surgery can be performed open or endoscopically with no significant difference in outcomes noted.

Sciatic Mononeuropathy

Principles. The sciatic nerve includes L4 to S3 spinal nerve roots that pass through the lumbosacral plexus and divides into two terminal branches: the common peroneal and tibial nerves. The nerve exits the pelvis through the sciatic notch, passes behind the hip, and remains deep in the thigh until its terminal bifurcation in the proximal popliteal fossa (Fig. 93.7).

Lesions of the sciatic nerve occur with posterior hip dislocation or with virtually any form of penetrating or blunt trauma that causes formation of a buttock hematoma. Other causes include deep gluteal injection and prolonged supine immobilization on a firm surface. Because the sciatic nerve innervates the hamstrings and provides all sensorimotor function distal to the knee, a complete sciatic mononeuropathy is a devastating injury.

Clinical Findings. Ambulation is extremely difficult because of inability to flex the knee and a flail foot (i.e., neither flexion nor extension is possible at the ankle). Fortunately, many sciatic mononeuropathies are incomplete. For unknown reasons, a partial lesion typically involves only the trunk of the sciatic nerve, which subsequently becomes the common peroneal nerve, sometimes making the two difficult to distinguish from one another clinically.

Diagnostic Testing. This condition is mainly diagnosed by physical findings. If used, electrophysiologic studies show evidence of involvement of gluteal muscles or of any muscles innervated by the tibial nerve. This readily distinguishes a partial sciatic mononeuropathy from a lesion of the common peroneal nerve.

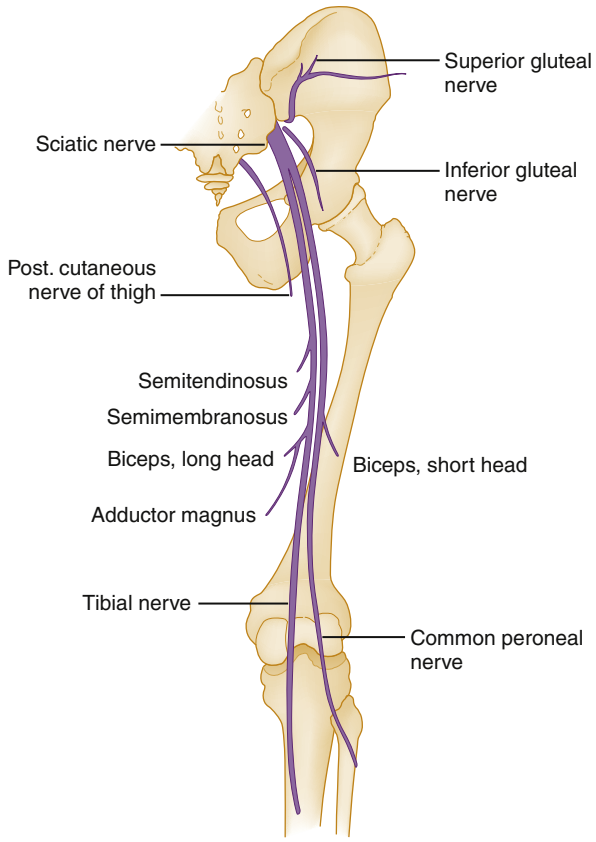

Fig. 93.7 Sciatic nerve, major branches, right leg, posterior view. (From Stewart JD. *Focal Peripheral Neuropathies*, ed 3. Philadelphia: Lippincott Williams & Wilkins; 2000.)

Management. Treatment of footdrop requires a posterior splint to maintain the ankle at 90 degrees until a brace can be obtained (see the Common Peroneal Mononeuropathy section).

Lateral Femoral Cutaneous Mononeuropathy

Principles. Lateral femoral cutaneous mononeuropathy (meralgia paresthetica) is a common syndrome believed to be caused by injury to this pure sensory nerve as it passes through or over the inguinal ligament, where it may become entrapped or kinked. Along with facial nerve neuropathy, meralgia paresthetica is one of the most commonly reported mononeuropathies associated with HIV infection. Risk factors include obesity, diabetes, pregnancy, and wearing tight-fitting clothing or belts. In addition, patients who have undergone surgical procedures of the hip and spine are also at risk for developing the syndrome.

Clinical Findings. Numbness and dysesthesia over the skin of the upper lateral thigh is typically found on physical examination.

Diagnostic Testing. There is no diagnostic test for this disease process beyond the physical examination.

Management. Resolution usually occurs spontaneously. In select patients, such as obese patients with BMI of 30 or greater, recommendations to avoid tight-fitting clothing or belts and/or to lose weight should be made. Ultrasound-guided nerve blocks utilizing corticosteroids and lidocaine are an option. Recurrence is possible and may require an inguinal ligament surgical release procedure.

Common Peroneal Mononeuropathy

Principles. The common peroneal nerve is a continuation of one trunk of the sciatic nerve. It is most vulnerable to injury where it winds around the fibular neck (Fig. 93.8). It then passes through the fibular

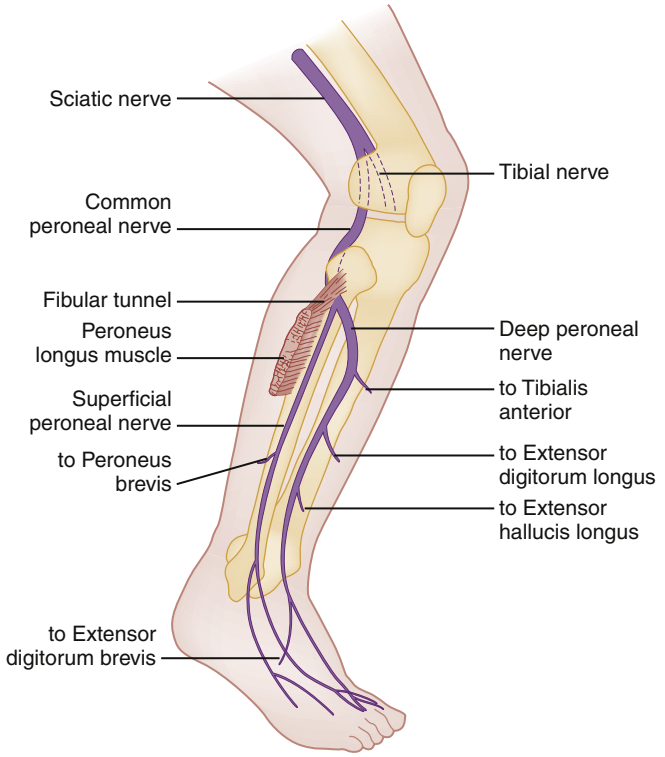

Fig. 93.8 Common peroneal nerve, major branches, right leg, anterolateral view. (From Stewart JD. *Focal Peripheral Neuropathies*, ed 3. Philadelphia: Lippincott Williams & Wilkins; 2000.)

canal and bifurcates into its terminal branches, the superficial and deep peroneal nerves. The superficial peroneal nerve innervates the peroneal muscles (foot evertors) and supplies sensation to the lateral, distal lower leg and dorsum of the foot. The deep peroneal nerve traverses the anterior compartment and supplies innervation to the dorsiflexors of the foot and toes plus cutaneous sensation between the first and second toes.

Most common peroneal mononeuropathies are idiopathic and thought to be related to compression where the nerve is superficially located lateral to the fibular neck. Because this common neuropathy is often noted on awakening, it may be secondary to position during sleep. Leg crossing may also be a risk factor for development of this mononeuropathy.

Clinical Findings. The most striking feature of a complete common peroneal mononeuropathy is footdrop caused by weakness of foot dorsiflexion. At testing, the evertors of the foot are also weak, but the inverters, which are innervated by the tibial nerve, remain strong. This is the single most reliable clinical feature distinguishing sciatic from common peroneal mononeuropathy. Analogous to radial mononeuropathy in the upper extremity, sensory abnormalities in the leg and foot are inconsistent and easily overlooked in peroneal mononeuropathy.

Diagnostic Testing. Most patients with peroneal palsy recover. Those who do not should be studied electrophysiologically to ensure that the point of compression is not proximal to the fibular neck (i.e., in the popliteal fossa). If the point of peroneal injury appears to be in the region of, or distal to, the fibular neck on EMG, patients whose footdrop does not resolve should be considered candidates for exploration to determine whether the nerve is compressed within the fibular canal.

Management. Treatment of common peroneal palsy requires a posterior splint to maintain the ankle at 90 degrees until the nerve regenerates. This splinting prevents the foot from falling into sustained equinus (plantar flexion), which in turn allows the intermalleolar distance to narrow, effectively locking the talus out of the ankle mortise.

The treatment of isolated mononeuropathies depends on their etiology, location, and natural history of spontaneous recovery. All penetrating neuropathies should have surgical exploration and repair performed. Blunt trauma may cause a mononeuropathy indirectly by entrapment of a nerve within a fracture, hematoma, or compartment, requiring surgical intervention. Alternatively, nerves may be injured at a point where they are superficial, either by a single direct blow or by sustained pressure caused by immobility (pressure palsies). Most of these resolve spontaneously over time, depending on the severity of injury and length of the nerve. If entrapment can be confirmed by imaging or electrophysiologic studies, a release procedure is indicated. The mononeuropathies that do not require timely surgical exploration should be referred for further evaluation to confirm the location of the neuropathic lesion.

BOX 93.8 Mononeuropathy Multiplex

- Vasculitis
  - Systemic vasculitis
    - Polyarteritis nodosa
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Sjögren syndrome (keratoconjunctivitis sicca)
  - Nonsystemic vasculitis
- Diabetes mellitus
- Neoplastic
  - Paraneoplastic
  - Direct infiltration
- Infectious
  - Lyme disease
  - HIV infection
- Sarcoid
- Toxic (lead)
- Transient (polycythemia vera)
- Cryoglobulinemia (hepatitis C)

HIV, Human immunodeficiency virus.

Type 5: Mononeuropathy Multiplex

Principles

Mononeuropathy multiplex is characterized by an asymmetrical, sensorimotor, usually distal pattern of peripheral neuropathy (Box 93.8). Common causes include vasculitis, diabetes, and Lyme disease.

Clinical Findings

As with isolated mononeuropathies, sensory abnormalities tend to be located in the same general anatomic region as the accompanying motor findings. Whether DTRs are affected depends on which nerves are involved. For example, if the process includes the femoral nerve, the patellar reflex is likely to be diminished or absent.

Lyme Disease. The PNS manifestations of Lyme disease are divided into early and late. The early PNS syndromes commonly include facial nerve involvement (rarely other cranial nerve palsies) and radiculoneuritis. Late PNS involvement occurs as a DSPN, mononeuropathy multiplex, or radiculoneuropathy. The most common neurologic abnormality in Lyme disease is unilateral or bilateral facial nerve palsy, usually occurring within a month of exposure. Patients may also complain of headache and constitutional symptoms. Early in the course of Lyme disease, severe neuritic pain may develop in a radicular distribution, often in or near the dermatome where the tick bite occurred. There may also be associated sensory changes,

motor weakness, and decreased reflexes consistent with nerve root involvement.

Patients with chronic Lyme disease present with sensory symptoms, particularly distal paresthesias in the lower extremities. Less commonly, they develop a picture consistent with mononeuropathy multiplex or a radiculopathy, which is much less severe than the early radiculoneuritis of Lyme disease.

Diagnostic Testing

Vasculitis-related multiple mononeuropathy is diagnosed with a sural nerve biopsy.

The most useful diagnostic tests for patients with suspected Lyme disease are a serum enzyme-linked immunosorbent assay, Western blot, and CSF examination. CSF abnormalities suggestive of Lyme disease are a lymphocytic pleocytosis, elevated protein level, and normal glucose concentration. The CSF is almost always abnormal in early radiculitis, sometimes abnormal with isolated facial palsy, and typically normal in chronic Lyme disease.

Management

Facial nerve palsy in Lyme disease without CSF abnormalities may be treated with oral doxycycline 100 mg twice a day for 2 weeks. Intravenous (IV) ceftriaxone is the drug of choice for all other neurologic syndromes associated with Lyme disease. The adult dosage is 2 g/day, and the pediatric dosage is 50 to 75 mg/kg per day. The standard course of treatment with IV ceftriaxone is at least 2 weeks.

Type 6: Amyotrophic Lateral Sclerosis

Principles

Although *amyotrophic lateral sclerosis (ALS)* and *motor neuron disease (MND)* are often used synonymously, the latter represents a spectrum of diseases ranging from primary lateral sclerosis, in which degeneration is confined to upper motor neurons, to progressive muscle atrophy, in which only lower motor neurons are involved. ALS, which requires the presence of both upper and lower motor neuron findings, resides in the middle of this spectrum, representing the most common form of MND. The incidence of ALS is 1.5 to 2.5 per 100,000. Most develop symptoms in middle-adult life, with motor weakness in the extremities, spasticity, paralysis, and eventually death, typically within 3 to 5 years of symptom onset.

In ALS, the primary pathologic process in the PNS component of the disease is a neuronopathy of the anterior horn cell. Because this structure is located proximal to the point where motor and sensory fibers merge to form mixed spinal nerve roots, the signs and symptoms of MND are purely motor (see Fig. 93.2). In the CNS, there is a loss of Betz cells from the motor cortex with secondary degeneration of the corticospinal tracts.

Clinical Findings

Box 93.9 lists some representative upper, lower, and mixed motor signs. Patients typically demonstrate asymmetrical distal weakness without sensory findings. Positive motor phenomena in the form of fasciculations are found in almost all patients at diagnosis but are rarely an initial complaint. Although there is electrophysiologic evidence of autonomic involvement in ALS, this is generally subclinical.

Diagnostic Testing

All patients in whom this diagnosis is suspected should be referred for electrophysiologic confirmation against standardized criteria, with denervation combined with the physical findings typically confirming the diagnosis. Confirmation is particularly important because multifocal motor neuropathy, a rare disease that masquerades as ALS, responds dramatically to cyclophosphamide and immune globulin administration.

BOX 93.9 Objective Clinical Findings Consistent With Amyotrophic Lateral Sclerosis

Upper Motor Neuron Signs
- Hyperreflexia
  - Sustained clonus, especially at ankle
  - Finger flexors and jaw jerk
- Spasticity, especially of gait
- Presence of Babinski sign

Lower Motor Neuron Signs
- Positive motor phenomena
  - Fasciculations
  - Cramps
- Negative motor phenomena
  - Asymmetrical distal weakness
  - Atrophy

Combined Upper and Lower Motor Neuron Signs
- Dysarthria
- Dysphagia
- Respiratory compromise

Management

Riluzole and edaravone are the only two drugs approved for treatment of ALS by the FDA. A systematic review found that riluzole increased median survival time by 2 to 3 months.[10] Edaravone, only recently approved for ALS in 2017, demonstrated a 33% decrease in ALS severity scores over six months and improved quality of life measures.[11] The development of a multidisciplinary team approach has had a much higher impact on overall quality of life for patients with ALS. This team includes ALS-focused neurologists, nurses, occupational therapy, and speech therapy amongst others. Patients presenting to the emergency department with undifferentiated or early signs of ALS can be challenging to diagnose and will benefit from prompt neurologic consultation to avoid a delay in diagnosis. Those with an established diagnosis of ALS and demonstrated disease progression are at high risk for aspiration pneumonia and respiratory compromise and may require admission to the hospital, which should be done with consideration for the patient's advanced directives and long-term goals of care.

Type 7: Sensory Neuronopathy (Ganglionopathy)

Principles

This category of peripheral neuropathy is characterized by a selective or predominant involvement of the dorsal root ganglion, producing a relatively pure sensory syndrome analogous to the pure motor syndrome of ALS.

Clinical Findings

Although all sensory modalities are affected, proprioception is profoundly altered, leading to sensory ataxia and loss of DTRs without weakness. The distribution is typically asymmetrical and distal at the outset, but depending on severity and extent of progression, it may become functionally symmetrical.

BOX 93.10 Sensory Neuronopathies (Ganglionopathies)

- Herpes
  - Herpes simplex 1 and 2
  - Varicella-zoster (shingles)
- Inflammatory sensory polyganglionopathy
- Paraneoplastic
- Primary biliary cirrhosis
- Sjögren syndrome (keratoconjunctivitis sicca)
- Toxin induced
  - Pyridoxine (vitamin B_6) overdose
  - Metals
    - Platinum (cisplatin)
    - Methyl mercury
- Vitamin E deficiency

Diagnostic Testing

Sensory ganglionopathies can be confirmed by MRI of the spinal cord and surrounding areas, showing degeneration of central sensory projections that localize the disease process to the dorsal root ganglion. Some of the more common causes of this type of peripheral neuropathy are listed in Box 93.10.

Management

The management of sensory neuropathies is symptomatic in nature and best left to the patient's primary physician.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 93: QUESTIONS AND ANSWERS

1. Which category of peripheral neuropathy tends to occur in an asymmetrical, distal distribution?
- **a.** Autonomic neuropathy
- **b.** Large-fiber neuropathy
- **c.** Mixed motor and sensory neuropathy
- **d.** Pure motor neuropathy

Answer: D. Pure motor and pure sensory peripheral neuropathies tend to occur in an asymmetrical distal pattern.

2. A 26-year-old woman presents with a chief complaint of weakness. She notes a 1- or 2-day onset of easy fatigability and diminished ability to navigate stairs. She has no past history and takes no medications. Vital signs are normal. Physical examination reveals absent lower extremity deep tendon reflexes (DTRs); symmetrical weakness of the quadriceps, calf muscles, and foot/toe dorsiflexion; and minimal sensory loss. Cranial nerve and upper extremity examination is normal. Which of the following is likely?
- **a.** An antecedent viral illness
- **b.** Lack of anal sphincter tone
- **c.** Onset of ocular muscle dysfunction
- **d.** Sparing of the autonomic nervous system

Answer: A. Guillain-Barré syndrome (GBS) is characterized by fairly acute onset of ascending weakness, loss of deep tendon reflexes (DTRs), and variable sensory loss. Antecedent infections often trigger, with common organisms being campylobacter, cytomegalovirus, Epstein-Barr virus, and mycoplasma. Rarely, symptoms begin in the upper extremities. Urinary retention is common, but anal tone is preserved. Ocular muscles are usually spared. Autonomic neuropathy is common, with marked variations in heart rate and blood pressure. Patients with predominantly sensory symptoms tend to have less risk of respiratory embarrassment and a more favorable prognosis. Lumbar puncture shows cerebrospinal fluid (CSF) pleocytosis or may be normal early on.

3. A 26-year-old woman presents with lower extremity weakness and difficulty walking. Examination is remarkable for lower extremity symmetrical weakness with mild symmetrical sensory loss and absent lower extremity deep tendon reflexes (DTRs). Symptom onset has been during 2 days. What should be the next step?
- **a.** Emergent magnetic resonance imaging (MRI)
- **b.** Intravenous immune globulin (IVIG)
- **c.** Lumbar puncture and antibiotics
- **d.** Pulmonary function studies

Answer: D. All patients with Guillain-Barré syndrome (GBS) are at risk of respiratory failure. A forced vital capacity (FVC) of less than 20 mL/kg and a negative inspiratory force of less than 30 cm H_2O are associated with impending ventilatory failure and the need for intubation.

4. Among patients with Guillain-Barré syndrome (GBS) who have normal pulmonary function, which of the following can be monitored to predict impending ventilatory failure?
- **a.** Deltoid strength
- **b.** Extensor neck strength
- **c.** Hand grip strength
- **d.** Masseter strength

Answer: B. Extensor muscle strength has been shown to correlate with ventilatory muscle strength.

5. A 53-year-old diabetic presents with a complaint of increasing difficulty walking in the last several months. He has no other past history but has been an insulin-dependent diabetic for 23 years. Current glucose level is 138 mg/dL, and chemistries and complete blood count are otherwise unremarkable. Examination is remarkable for bilateral lower extremity numbness extending symmetrically to above the knees, loss of the Achilles reflex bilaterally with footdrop, and steppage gait. Which of the following is true?
- **a.** Autonomic neuropathy is unlikely.
- **b.** Facial numbness would necessitate MRI.
- **c.** Hand numbness is expected.
- **d.** Erythrocyte sedimentation rate is likely to be elevated.

Answer: C. Diabetic neuropathy is a progressive, ascending mixed polyneuropathy. Hand numbness and upper extremity symptoms usually begin before the lower extremity symptoms ascend to the knees. Extensive motor loss can occur with gait and grip abnormalities. Skull and face numbness can occur. Autonomic dysfunction is expected.

Neuromuscular Disorders

Jeremy Rose, Trent She

KEY CONCEPTS

- In patients presenting with acute neuromuscular weakness, complaints of difficulty in breathing or swallowing are signs of bulbar nerve or respiratory muscle compromise with potential airway or ventilatory failure. In such patients, forced vital capacity (FVC) of less than 15 mL/kg or maximal negative inspiratory force of less than 15 mm H_2O is a potential indication for mechanical support, either by intubation or by noninvasive ventilation.
- Initiating new medications in patients with myasthenia gravis may precipitate a crisis. Commonly prescribed cardiovascular agents, including calcium channel blockers, beta-blockers and antidysrhythmics; commonly used antibiotics; and other agents, including corticosteroids, require particular vigilance.
- Myasthenic crisis is treated with either plasma exchange or intravenous immune globulin (IVIG).
- Botulism usually arises as a painless descending paralysis, often first affecting the cranial nerves (with diplopia) and bulbar innervated muscles, without sensory deficits or alteration of consciousness. The treatment is airway management with ventilatory support and administration of antitoxin.
- Injection drug use remains an important cause of wound botulism outbreaks.
- Botulism is an important consideration in evaluation a weak and floppy infant.
- Hypokalemic periodic paralysis is caused by intracellular shift of potassium and so requires frequent serum potassium measurement to avoid overcorrection during treatment with potassium infusion.
- Patients with newly diagnosed hypokalemic periodic paralysis should be evaluated for hyperthyroidism.

FOUNDATIONS

Disorders of the neuromuscular unit result in clinical presentations that range from subtle symptoms to acute respiratory failure. In most cases, the pathophysiologic mechanisms and characteristics of these disorders are well understood, which permits an organized approach to diagnosis and treatment based on the distribution and severity of the neuromuscular system affected.

The neuromuscular unit has four components: the anterior horn cells of the spinal cord, the spinal and peripheral nerves, the neuromuscular junctions, and the muscles. The level of the pathologic process determines associated signs and symptoms (Fig. 94.1 and Table 94.1). *Myelopathies* involve the spinal cord; *radiculopathies* involve the nerve roots as they leave the spinal cord; *neuropathies* involve the peripheral nerves; and *myopathies* involve the muscle. The use of physical signs to differentiate these disorders is discussed in Chapter 9.

Neuropathies involve the axon or the myelin sheath of the nerve. Nerve conduction studies can differentiate the locations of involvement. As the conduction along the axon is disrupted, the subsequent delay in transmission first causes symptoms in the muscles controlled by longer nerve axons, resulting in ascending weakness. Progression of the destruction or axonal degeneration causes a slowly progressive course of symptoms.

The neuromuscular junction comprises the presynaptic membrane, the postsynaptic membrane, the synaptic cleft, and the neurotransmitter acetylcholine (ACh), which carries the signal across the cleft between the two membranes. The neuromuscular junction features postsynaptic nicotinic ACh receptors, distinct from muscarinic ACh receptors that effect autonomic nervous system functions. Disorders of these postsynaptic nicotinic receptors produce weakness. Postsynaptic ACh receptors are continually turned over at a rate that is related to the amount of stimulation. A disorder of transmission often leads to an increase in the density of ACh receptors. Myasthenia gravis is the archetype of neuromuscular diseases.

CLINICAL FEATURES

History

Initial history of patients with complaints of weakness focuses on the acuity of the process and the potential for airway compromise. A complaint of difficulty in breathing or swallowing indicates possible bulbar or respiratory muscle compromise with the potential for life-threatening deterioration. As with other neurologic diseases, the anatomic distribution of symptoms can be the key to diagnosis. Neuromuscular diseases are often progressive or intermittent in nature, so a detailed history of the chronology of symptoms is important. Specific historical features, such as diarrhea (botulism), tick exposure (tick neurotoxin–mediated paralysis), or recurrent episodes of weakness over time (hereditary hypokalemic paralysis) may be helpful. Factors elicited during the history help to guide further history taking, targeted physical examination, and testing, as the differential diagnosis forms and is narrowed by the historical information the patient provides.

Physical Examination

The clinician should first assess adequacy of airway protection and ventilation before a more generalized examination evaluates for the degree of weakness and the location of the lesion. The presence of swallowing and a strong cough suggest that the patient has sufficient protective and ventilatory reserve. The muscles used to lift the head off the bed may weaken before those of respiration and should be assessed. A patient who is not yet intubated but is complaining of shortness of breath or difficulty in breathing should have frequent measurements of forced vital capacity (FVC). Normal FVC ranges from 60 to 70 mL/kg; when

the FVC reaches 15 mL/kg, ventilatory support is necessary. Maximal negative inspiratory force (NIF), also called a maximal inspiratory pressure (MIP), is an alternative to FVC. An NIF or MIP of less than 15 cm H_2O suggests the need for intubation. Neuromuscular disorders interfere with ventilation not oxygenation, so capnography is a better monitoring modality than pulse oximetry in these cases. Hypercarbia is a late finding and should be regarded as a sign of impending respiratory failure. A subnormal PCO_2 may also represent developing respiratory failure. As the patient's respiratory effort falls, tidal volume is reduced, and alveolar CO_2 is not exhaled sufficiently (hypopneic hypoventilation).

A systematic neurologic examination assesses the patient's mental status, cranial nerves, motor and sensory function, deep tendon reflexes, and coordination, including cerebellar function. The motor examination begins by determining whether the weakness is unilateral or bilateral and which muscle groups are involved. Key components of the examination include motor strength, muscle bulk, and presence of fasciculations. Box 94.1 provides the grading system used in motor strength assessment. Table 94.2 provides the findings used to distinguish upper motor neuron from lower motor neuron processes.

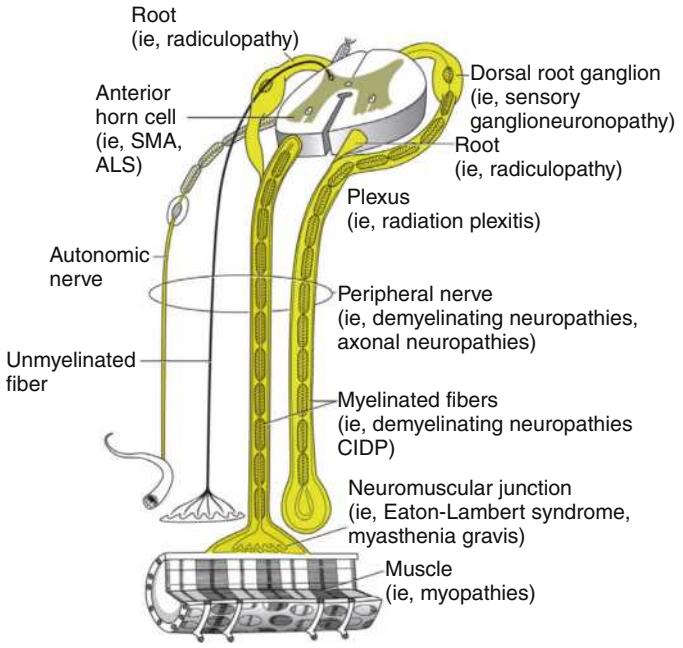

Fig. 94.1 The anatomic elements of the peripheral nervous system and related neurologic disorders. *ALS,* Amyotrophic lateral sclerosis; *CIDP,* chronic inflammatory demyelinating polyneuropathy; *SMA,* spinal muscular atrophy. (From Bertorini TE. Neuromuscular anatomy and function in neuromuscular case studies. In: *Neuromuscular Case Studies.* Philadelphia: Butterworth-Heinemann/Elsevier; 2008.)

DIFFERENTIAL DIAGNOSIS

Myelopathies

Myelopathies are spinal cord disorders that are manifested with signs of upper motor neuron dysfunction, such as muscle weakness with increased spinal reflexes, including an extensor plantar reflex (Babinski sign). There may be bladder and bowel involvement. When sensory findings are present, they often define the level of the lesion. The presence of back pain suggests a compressive lesion, such as a herniated intervertebral disk, tumor, or epidural hematoma. Concomitant systemic signs, such as a fever, or a history of intravenous (IV) drug use, can suggest an epidural abscess. Increasing postprocedural pain, for example following lumbar puncture, epidural anesthesia, or spine surgery, warrants consideration of an epidural hematoma. Acute, painless spinal cord lesions include transverse myelitis and spinal cord infarction.

Motor Neuron Disease

The characteristic findings of motor neuron disease combine signs of both upper and lower motor neuron dysfunction, including hyperreflexia, muscle wasting, and fasciculations. Pain is not a component of the clinical picture. Amyotrophic lateral sclerosis (ALS; Lou Gehrig disease) is the archetypal motor neuron disease.

BOX 94.1 Grading Score for Motor Strength

5 = Normal strength
4 = Weak but able to resist examiner
3 = Moves against gravity but unable to resist examiner
2 = Moves but unable to resist gravity
1 = Flicker but no movement
0 = No movement

TABLE 94.1 Clinical Characteristics of Neuromuscular Diseases

Disease	History	Strength	Deep Tendon Reflex	Sensation	Wasting
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No
Motor neuron disease (ALS)	Progressive difficulty swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, Amyotrophic lateral sclerosis.

TABLE 94.2 Distinguishing Upper Motor Neuron From Lower Motor Neuron Involvement

Motor Neuron	Deep Tendon Reflex	Muscle Tone	Atrophy	Fasciculations	Babinski Response
Upper motor neuron	Increased	Increased	No[a]	No	Present
Lower motor neuron	Decreased	Decreased	Yes	Yes	Absent

[a]Not significant but can occur.

Poliomyelitis affects the anterior horn cells and results in lower motor neuron disease without sensory involvement. The weakness is often asymmetric. Patients initially have a clinical picture similar to that of viral meningitis with fever and neck stiffness. The cerebrospinal fluid (CSF) analysis resembles that of viral meningitis. Polio has been eradicated in many parts of the world but remains prevalent in areas of conflict where public health systems have eroded.[1] The United States has seen an increase in acute flaccid myelitis (AFM), a paralyzing illness affecting pediatric patients that is described as "polio-like." AFM appears to have a temporal relationship with enteroviruses D68 and A71, but it is unclear if these viruses are the cause of the syndrome.[2]

Neuropathies

Weakness from a neuropathy is often noted first in distal muscles and then progresses centrally. Decreased grip strength and foot drop are common initial presentations. The differential diagnosis includes Guillain-Barré syndrome, toxic neuropathies, diabetic neuropathy, and tick paralysis (which is caused by inhibition of both nerve conduction and function of the neuromuscular junction). Neuropathies are discussed in Chapter 93.

Diseases of the Neuromuscular Junction

Disorders of the neuromuscular junction cause motor fatigability. The initial depolarization at the nerve end plate stimulates a maximum number of ACh receptors on the muscle cell, producing a normal or nearly normal strength response. Repeated stimulation leads to diminishing motor strength, which is caused by one of three mechanisms: blockage of the receptors, as in myasthenia gravis, decrease in the amount of ACh released, as in botulism, or inactivation of ACh by irreversible binding, as in organophosphate poisoning.

A decrease in the release of ACh can cause a combination of nicotinic and muscarinic effects. The clinical manifestations of this are anticholinergic findings, such as dilated pupils, confusion, urinary retention, tachycardia, low-grade fever, and dry, flushed skin. In the case of Lambert-Eaton myasthenic syndrome, weakness is more pronounced at the beginning of muscle use and improves with repeated use as more ACh builds up in the synaptic cleft with each stimulation. Muscle tone is generally diminished and sensation is preserved in diseases of the neuromuscular junction.

Myopathies

Myopathies produce generalized, symmetric weakness. Reflexes are diminished, muscle tone is usually diminished, but sensation is preserved. Myopathies due to inflammatory disorders (polymyositis, dermatomyositis, polymyalgia rheumatica, and viral myositis) cause muscle pain and tenderness. Metabolic disorders affecting muscle strength (e.g., electrolyte and endocrine disorders) cause diffuse weakness without pain. Electrolyte alterations affecting muscular and cardiac function are discussed in Chapter 114.

DIAGNOSTIC TESTING

Serum electrolyte determination, with emphasis on potassium, calcium, and phosphorus concentrations, should be assessed in patients with acute weakness. An electrocardiogram (ECG) may provide an earlier clue to potassium or calcium disturbance. Thyroid function tests are recommended in cases of suspected myopathies. A creatine kinase (CK) level assesses for muscle inflammation, and if CK is markedly elevated, serial renal function studies should be obtained to assess for developing acute kidney injury.

Magnetic resonance imaging (MRI) is the preferred imaging modality for suspected cases of acute myelopathy caused by a compressive lesion. CSF analysis is indicated when Guillain-Barré syndrome or transverse myelitis is suspected.

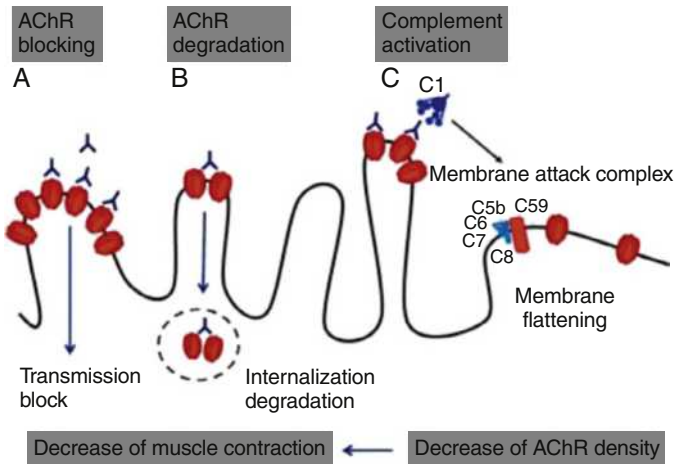

Fig. 94.2 Mechanisms of action of acetylcholine receptor *(AChR)* autoantibodies. Neuromuscular synapse in myasthenia gravis. AChR antibodies interfere with signal transduction by direct blocking of AChR (A), by cross-linking and increased degradation (B), or by immune-mediated destruction including complement activation (C). (From Sommer N, Tackenberg B, Hohlfeld R. The immunopathogenesis of myasthenia gravis. In Engel AG, ed. *Handbook of Clinical Neurology, volume 91, Neuromuscular Junction Disorders*. St Louis: Elsevier; 2008:169–212.)

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Principles

The age at onset of myasthenia gravis is influenced by gender; women are most commonly affected between 20 and 40 years old and men between 50 and 70 years old. Although new cases of myasthenia gravis are occasionally diagnosed in the emergency department (ED), it is much more common for patients with established disease to present with exacerbations of their disorder, often caused by precipitating factors.

In most patients with myasthenia gravis, weakness and fatigue result from circulating autoantibodies against the nicotinic ACh receptor on the junctional folds of the postsynaptic membrane. The effects are the result of several pathologic processes: direct blocking of the receptor, complement mediated destruction of the folds, and internalization and degradation of the receptors (Fig. 94.2). With

BOX 94.2 Drugs That May Exacerbate Myasthenia Gravis

- Cardiovascular
  - Beta-blockers
  - Calcium channel blockers
  - Quinidine
  - Lidocaine
  - Procainamide
- Antibiotics
  - Aminoglycosides
  - Tetracyclines
  - Clindamycin
  - Lincomycin
  - Polymyxin B
  - Tobramycin
  - Fluoroquinolones
  - Colistin
- Other
  - Phenytoin
  - Neuromuscular blockers
  - Corticosteroids
  - Thyroid replacement

repeated stimulation, fewer and fewer receptor sites are available for ACh binding, and fatigue develops. Fatigability and muscle weakness are the hallmarks of myasthenia gravis. Muscarinic receptors are also affected but to a much lesser extent, so muscular weakness is the dominant presentation of myasthenia gravis. Ocular muscle weakness is the first sign of myasthenia gravis in up to 40% of patients, although 85% of patients eventually have ocular involvement. When ptosis is present, it is often worse toward the end of the day. New-onset diplopia also may signal development of myasthenia gravis. Respiratory failure is rarely the initial symptom of myasthenia gravis. Bulbar muscles may be involved myasthenia gravis, producing dysarthria or dysphagia.[3] Facial and extremity muscles may also be involved, producing some classic symptoms of myasthenia gravis (i.e., difficulty in combing hair or brushing teeth, weakness of the muscles in the posterior neck causing a "dropped-head appearance," and a limited ability to form a full smile due to weakness of lateral facial muscles).

The prognosis for patients with myasthenia gravis has markedly improved in recent years due to the demonstrated benefit of thymectomy and the approval of the drug eculizumab for refractory cases.[4] Nevertheless, stable disease can be pushed to crisis by commonly used drugs that are known to exacerbate myasthenia gravis (Box 94.2). Even topical medications, such as tobramycin eye drops, can cause an exacerbation.[5] Assessing drug-disease interactions is a particularly important step when prescribing to patients with myasthenia gravis, even if the disease is well controlled.

Myasthenic crisis. *Myasthenic crisis* is defined as respiratory failure requiring mechanical ventilation. It occurs in 15% to 20% of patients with myasthenia gravis, usually within the first 2 years of disease onset. Although it is potentially life threatening, the mortality from this complication of myasthenia gravis has declined dramatically with appropriate care in the ED and intensive care unit (ICU) and the use of plasma exchange or immunomodulatory therapy with intravenous immune globulin (IVIG).

Crises are most often precipitated by underlying infection, aspiration, and medication changes, such as stopping anticholinergic medications or initiating a new medication that precipitates weakness. Other precipitants can be surgery and pregnancy (see Box 94.2).

Lambert-Eaton syndrome. Lambert-Eaton myasthenic syndrome is a rare disorder. Almost 50% of cases are associated with small cell carcinoma of the lung. Autoantibodies cause inadequate release of ACh from nerve terminals, affecting both nicotinic and muscarinic receptors. With repeated stimulation, the amount of ACh in the synaptic cleft increases, leading to a progressive increase in strength with muscle use, an effect opposite of that seen with myasthenia gravis. The classic syndrome includes weakness that improves with use of muscles, particularly proximal hip and shoulder muscles; hyporeflexia; and autonomic dysfunction, most commonly seen as dry mouth. Management focuses on treatment of the underlying cancer, although IVIG may be useful.

Diagnostic Testing

The diagnosis of new-onset myasthenia gravis is based on history, clinical findings, and a combination of serologic testing and electromyographic testing. In rare cases, the diagnosis is further clarified through bedside testing with the ice bag test (or, historically, the edrophonium test). Serum testing for ACh receptor antibodies is positive in 80% to 90% of patients with myasthenia gravis, but results are not available in the ED. Myasthenia gravis can be associated with a thymoma as a paraneoplastic syndrome. Initial evaluation of patients with newly diagnosed myasthenia gravis includes a contrast-enhanced computed tomography (CT) scan to evaluate for presence of a thymoma or other anterior mediastinal masses.

The edrophonium (Tensilon) test has an unacceptable number of false-positives and false-negatives and can cause serious adverse reactions through enhanced muscarinic effects of ACh. The test is rarely, if ever, indicated, and we do not recommend it.

The ice bag test can be performed at the bedside for patients with suspected myasthenia gravis and ptosis, whose diagnosis is otherwise uncertain. Cooling decreases symptoms in myasthenia gravis and heating exacerbates symptoms, so placing an ice bag to the eyelids can reduce ptosis. The degree of ptosis is measured before and after application of an ice bag. The distance from the upper to the lower eyelid in the most severely affected eye is measured first. An ice pack is applied to the affected eye for approximately 2 minutes. An improvement in the amount of ptosis of at least 2 mm is considered positive. The pooled sensitivity and specificity of the ice bag test for detecting ocular myasthenia are 0.94 and 0.97, respectively.

Management

The initial step in managing the myasthenic patient in crisis is stabilization of the airway and supporting ventilation. Respiratory failure ensues from muscle weakness, not inadequate oxygenation; therefore supplemental oxygenation does not address the problem, and mechanical ventilation is indicated. Endotracheal intubation may be necessary, but biphasic positive airway pressure (BiPAP) support may be sufficient if the patient is otherwise able to protect their airway. Capnometry monitoring can be useful in detecting respiratory fatigue well in advance of oxyhemoglobin desaturation and obvious clinical findings of respiratory distress.

Pyridostigmine, thymectomy, immunosuppressant drugs, steroids, rituximab, and eculizumab are all used for maintenance management of myasthenia gravis in the outpatient setting. The mainstays of ED myasthenic crisis management are plasma exchange or IVIG.

Plasma exchange, performed as multiple exchanges over 1 to 2 weeks, is effective in up to 95% of patients in acute myasthenic crisis and is generally considered the first line treatment for patients with severe myasthenic crisis.[5] IVIG is also effective for myasthenic crisis, usually given as 2 g/kg in divided doses over several days. Given the rarity of this condition, we recommend consultation with a neurologist with expertise in neuromuscular disease to aid in decision making between plasma exchange and IVIG and the initiation of either of these interventions. Patients treated by either IVIG and plasma exchange should also receive high-dose oral glucocorticoids, such as prednisone, 60 mg daily, beginning as soon as possible. High-dose steroids can worsen weakness, so they should be given only as a complement to plasma exchange or IVIG therapy, in consultation with a neurologist.

Ambulatory treatment of myasthenia gravis is often initiated using oral pyridostigmine, an acetylcholinesterase inhibitor. If the patient is newly diagnosed, or the patient's increased weakness is a result of discontinuation or dosage reduction of pyridostigmine, initiating or reestablishing treatment with pyridostigmine (60 to 120 mg by mouth every 4 to 6 hours) will prolong the presence and activity of ACh in the synaptic cleft and improve symptoms. Initiation or reestablishment of pyridostigmine therapy should be done in consultation with the outpatient physician from whom the patient will receive ongoing ambulatory management. The most common side effects of pyridostigmine are those of excessive cholinergic stimulation, such as increased airway secretions and increased bowel motility. These side effects can be treated with glycopyrrolate (1 mg with each dose of pyridostigmine), which preferentially blocks muscarinic cholinergic receptors that are responsible for these symptoms.

Cholinergic crisis, caused by excessive ACh activity related to acetylcholinesterase inhibitor therapy, is rarely seen, particularly with close management of pyridostigmine dosing. It may occur when patients deliberately or inadvertently take pyridostigmine in excess of the recommended dose. Cholinergic crisis is manifest by excessive cholinergic activity, which may include bradycardia, diarrhea and abdominal cramping, increased secretions, and muscle weakness, which might mimic a myasthenic crisis (Table 94.3).

Disposition

The decision to admit or to discharge a patient with myasthenia gravis from the ED is based on the potential for neuromuscular deterioration. Patients requiring plasma exchange or IVIG often require admission to ensure response to therapy and close monitoring for respiratory compromise. For some patients, a short stay in an observation unit under the care of a team comprising emergency medicine and neurology specialists will aid in evaluation of the patient's likelihood of successful outpatient treatment. Patients being admitted to the hospital should have an NIF or FVC measured to help determine the level of monitoring and care needed. These measurements need to be trended during the admission.

TABLE 94.3 Notable Differences Between Myasthenic Crisis and Cholinergic Crisis Pertaining to Myasthenia Gravis Patients

Myasthenic Crisis	Cholinergic Crisis
Generally minimal abdominal symptoms	Presence of abdominal pain, nausea and vomiting
Increased HR and BP	Decreased heart rate and blood pressure
Normal secretions	Increased secretions
Mydriasis	Miosis
Caused by undermedication of myasthenia gravis treatment	Caused by overmedication of myasthenia gravis treatment
Treat with cholinergic agent (edrophonoium)	Treat with anticholinergic agent (atropine)

Botulism

Principles

Botulism is a toxin-mediated illness that can cause weakness leading to respiratory insufficiency. In 2017, the Centers for Disease Control and Prevention (CDC) reported 182 cases of botulism in the United States: 10% food-borne, 77% infant botulism, 10% wound botulism, and 3% unknown etiology.[6] *Clostridium botulinum* is an anaerobic, spore-forming bacterium. Three of eight known toxins produced by *C. botulinum* (types A, B, and E) cause human disease. Recent outbreaks have been traced to home canned peas in New York[7] and whale flipper in Alaska.[8]

Clinical Features

The botulinum toxin blocks both voluntary motor and autonomic functions. There is no pain or sensory deficit. The onset of symptoms is 6 to 48 hours after the ingestion of toxin. Symptoms of gastroenteritis may or may not be present. The classic feature of botulism is a descending, symmetric, flaccid paralysis. Cranial nerves and bulbar muscles are affected first, causing diplopia, dysarthria, and dysphagia, followed later by generalized weakness. Because the toxin decreases cholinergic output, anticholinergic signs may be present: constipation, urinary retention, dry skin and eyes, and increased temperature and dilated, nonreactive pupils. This can help to differentiate botulism toxicity from myasthenia gravis. Deep tendon reflexes are normal or diminished.

Infantile botulism results from the ingestion of *C. botulinum* spores that are able to germinate and produce toxin in the high pH of the gastrointestinal tract of infants. Botulism spores can survive in honey, so it is recommended that honey not be fed to infants. The clinical presentation includes constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be included in the differential diagnosis of the floppy infant.

Wound botulism is a rare presentation of botulism stemming from the colonization of a wound or other skin lesion by *C. botulinum* spores, which are then able to produce toxin that can travel through the bloodstream to cause systemic effects. Wound botulism is generally seen in IV drug users, classically in users of "black tar" heroin. In addition to causing the classic symptoms of botulism as described earlier, wound botulism tends to present with fever and lesser gastrointestinal manifestations.

Diagnostic Testing

The diagnosis of botulism is made by both clinical findings and exclusion of other processes. The toxin can be identified in serum and stool, but the assay is not commonly available in most hospitals and requires a prolonged turnaround time. If the suspected food source is available, it should also be tested for the toxin. Wound cultures should be sent in anaerobic transport medium for patients with suspected wound botulism.

Management

Treatment is initially focused on stabilization of the airway and supportive measures. In 2010, the CDC announced a new equine heptavalent

botulinum antitoxin (HBAT) that is now the only antitoxin available in the United States for noninfant botulism.[9] For suspected cases and to obtain HBAT, clinicians should contact their state health departments. The CDC also maintains a 24-hour botulism duty officer at the CDC Emergency Operations Center (770-488-7100). An IV human-derived botulism immune globulin (BabyBIG) has been developed for treatment of infantile botulism and is available 24 hours/7 days through the California Department of Public Health Infant Botulism Treatment and Prevention Program on-call physician at 510-231-7600. Wound botulism patients should have emergent surgical consultation for débridement of the wound. Tetanus toxoid is administered unless previously received within the past 5 years. In addition, antibiotic coverage is recommended. Penicillin G 3 million units every 4 hours and metronidazole 500 mg every 8 hours intravenously provide effective coverage against *C. botulinum*. Aminoglycosides, tetracyclines, and polymixins are not recommended because they can potentially worsen neuromuscular blockade. The duration of treatment is generally 7 to 10 days but may need to be extended based on the severity of disease. We recommend infectious disease consultation for this rare disorder.

Disposition

All patients being treated for botulism need to be hospitalized, and most will be admitted to an ICU setting given the likelihood of progression of neuromuscular weakness. Infants and children will need to be transferred to the most appropriate neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU) setting.

Tick Paralysis

Principles

This extraordinarily rare cause of an acute, ascending, flaccid paralysis is most often found in North America (Rocky Mountain region, US Pacific Northwest, and Southwestern Canada) and the east coast of Australia. Although the pathogenesis of tick paralysis is not fully understood, it is thought that a salivary neurotoxin is injected while the female tick feeds. The toxin functions like botulinum toxin to decrease the release of ACh from the presynaptic membrane of the neuromuscular junction.[10]

Clinical Features

Tick paralysis causes an acute, ascending, flaccid motor paralysis that can be confused with Guillain-Barré syndrome, botulism, and myasthenia gravis. Symptoms usually begin 1 to 2 days after the female tick has attached and begun to feed, although delays of up to 6 days have been reported. There may be associated ocular signs, such as fixed and dilated pupils, that can help to distinguish it from Guillain-Barré syndrome.

Management

The management is supportive care and tick removal. A tick can be removed by use of forceps to grasp it as closely as possible to the point of attachment. Care should be taken not to leave mouth parts in the patient's tissue. Injecting a small amount of lidocaine with epinephrine just below the tick facilitates removal by starving the animal of blood supply and encouraging it to release. Although symptoms may resolve rapidly after removal of the tick, supportive measures such as intubation should not be withheld pending resolution of symptoms. Although there is little new research on the topic, there are many reports of cases misdiagnosed as other causes of weakness (e.g., Guillain-Barré syndrome, acute inflammatory demyelinating polyneuropathy) until the offending tick was found and removed.

Disposition

These patients may begin to show improvement upon removal of the tick and may be able to be discharged from the ED. If symptoms are slow to resolve, the patient is admitted to an observation unit.

DISORDERS OF THE MUSCLES

Newly acquired weakness originating at the muscle level can be divided into two types: inflammatory and toxic-metabolic. Inflammatory disorders usually produce pain and tenderness, whereas metabolic disorders do not.

Inflammatory Disorders

Principles

The most common inflammatory myopathies are polymyositis and dermatomyositis. Polymyositis may be idiopathic in nature, occur secondary to infections (viral or bacterial), or be seen in conjunction with other disorders, such as sarcoidosis and hypereosinophilic syndromes. Inflammatory myopathies cause weakness, pain, and tenderness of the muscles involved.

Clinical Features

Dermatomyositis and polymyositis can occur at any age, although adults are more often affected than children. They can be associated with various malignant neoplasms, such as of the breast, ovary, lung, and gastrointestinal tract, and lymphoproliferative disorders. Proximal muscle weakness predominates and leads to complaints of difficulty in rising from a seated position or climbing stairs and weakness in lifting the arms over the head. There is often pain and tenderness in these proximal muscles as well. There is a decrease in reflexes proportionate to the decrease in strength. Fasciculations are not seen, and atrophy is a very late finding. Inclusion body myositis, another type inflammatory myositis, has a similar presentation to polymyositis but presents more gradually and with predominantly distal muscle weakness that extends to proximal muscle weakness with progression of disease.

Dermatomyositis is similar to polymyositis, but it is also associated with classic skin findings. These are more prominent in childhood but are also found in adults. They include a periorbital heliotrope rash and erythema and swelling of the extensor surfaces of joints. The heliotrope rash is usually photosensitive and may also involve the exposed areas of the chest and neck.

Diagnostic Testing

The diagnosis of an inflammatory myopathy requires exclusion of electrolyte abnormalities. Serum CK level is interpreted in light of the entire clinical picture; an elevated CK level does not establish the cause of weakness as a myopathy because some neuropathies can also produce an elevated CK level. Similarly, a normal CK level does not rule out a myopathy as the cause of weakness. Electromyography and muscle biopsy are used to confirm the diagnosis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often normal or only mildly elevated, thus they have no role in diagnosis or prognosis. Aldolase and other specific myositis autoantibodies should be considered after consultation with a neurologist or rheumatologist.

Management

Inflammatory myositis syndromes are usually managed with oral prednisone in a dose of 1 to 2 mg/kg/day. When steroids prove ineffective and during acute exacerbations, cytotoxic drugs such as azathioprine (initial dose of 50 mg/day) and methotrexate (initial dose of 15 mg/week) are added. Fortunately, the degree of rhabdomyolysis seen with the inflammatory myopathies is not sufficient to cause renal impairment.

Disposition

The majority of these patients will likely be discharged, some following an observation period. Hospitalization should be considered for

patients with comorbidities, elders, and those who do not improve with treatment in the ED or observation unit.

Metabolic Disorders

Acute, generalized muscle weakness is seen with a number of severe electrolyte abnormalities of any cause: hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia. (See Chapter 114.) Acute painless myopathies are also seen with endocrine disorders involving the thyroid, parathyroid, or adrenal glands (see Chapter 117).

There are several disorders referred to collectively as the *periodic paralyses,* which include periodic paralysis of the hyperkalemic and hypokalemic forms and thyrotoxic periodic paralysis, which is similar to hypokalemic periodic paralysis except that it is associated with hyperthyroidism.

Periodic Paralysis

Principles. Periodic paralysis of the hypokalemic and hyperkalemic forms is a rare hereditary disorder of ion channels resulting in intermittent attacks of flaccid extremity weakness, which can be mild to moderate or sufficiently severe that the patient goes to the ground and cannot get up. The hypokalemic form is more common. Periodic paralysis is most often associated with an inherited genetic mutation. Patients usually report a personal and family history of similar episodes. Thyrotoxic periodic paralysis is an acquired rather than inherited form of hypokalemic periodic paralysis.

The clinical picture of thyrotoxic periodic paralysis is almost identical to that of periodic paralysis, and indeed a small number of patients with hypokalemic periodic paralysis have hyperthyroidism. In thyrotoxic periodic paralysis, symptoms related to hyperthyroidism are often present at the same time the patient has weakness. The relation of the hyperthyroidism to hypokalemia is probably due to increased sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) pump, which causes a rapid shift of potassium from the extracellular into the intracellular compartment. There is probably a genetic predisposition to this form of periodic paralysis, although it may be due to different genes in different patient populations.[11] Patients with a first episode of hypokalemic paralysis should undergo thyroid function testing.

Clinical features. Patients may suffer either isolated or recurrent episodes of flaccid paralysis. The lower limbs are involved more often than the upper, although both can be affected. Bulbar, ocular, and respiratory muscles are usually not involved. Onset is rapid often following a high oral carbohydrate intake (with subsequent insulin rise) and a period of rest. This reflects the intracellular shift of potassium rather than the total body depletion of potassium. A typical complaint is acute weakness noted on waking in the morning after a large meal.

Diagnostic testing. The ECG may demonstrate signs of hyperkalemia or hypokalemia. ECG findings of hyperkalemia include peaked T waves, prolongation of the PR interval and QRS complex, loss of P waves, and finally a sinusoidal pattern and asystole in severe cases. ECG findings of hypokalemia include flattening and inversion of T waves, prolongation of the QT interval, presence of a U wave and ectopic beats, and ventricular arrhythmias in severe cases. An immediate serum potassium level should be obtained; in the hypokalemic form, the potassium level during an attack falls to values well below 3.0 mEq/L. Magnesium and glucose levels should also be measured.

Management. Many cases resolve spontaneously with supportive care alone. The mainstay of management is the treatment of the underlying electrolyte imbalance, with awareness that the changes in potassium concentration in patients with periodic paralysis are not due to depletion or excess of potassium but rather intracellular and extracellular shifts (i.e., in the hypokalemic state, the total body potassium is not reduced but has shifted intracellularly). Thus, in the repletion of potassium, caution is necessary to prevent overtreatment. For this reason, we recommend that IV potassium be given sparingly at one or two 10-mEq IV doses of potassium chloride, each over 1 hour. This can be done in parallel with 40-mEq oral potassium repletion and retesting of serum potassium levels. IV hydration helps to redistribute the body's potassium stores; magnesium supplementation is not necessary. In the hyperkalemic state, glucose, insulin, and albuterol may be used to promote intracellular shifting of potassium. Treatment of the hyperthyroid symptoms in thyrotoxic periodic paralysis, such as tachycardia, may help the paralysis as well. Counseling should also be provided to the patient to avoid triggers. These include avoidance of sudden, high-intensity exercise followed by resting, excessive dietary potassium, and alcohol.

Disposition. In the past, most cases of periodic paralysis required an inpatient stay, but most patients can be managed in less than 24 hours in an observation unit. Admission may be necessary for patients with their first episode of periodic paralysis in the context of thyrotoxicosis.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 94: QUESTIONS AND ANSWERS

1. Which of the following is not found in a neuromuscular junction?
- **a.** Myelin sheaths
- **b.** Presynaptic receptors
- **c.** Postsynaptic receptors
- **d.** The synaptic cleft
- **e.** Acetylcholine

Answer: a. The neuromuscular junction is an important unit in regulating muscle function. It consists of both presynaptic and postsynaptic receptors that release and receive the neurotransmitter acetylcholine as it travels through the synaptic cleft. Myelin sheaths are important in quickening the transmission of signals along an axon but do not extend all the way to the neuromuscular junction.

2. Which of these features in a patient's history suggest a diagnosis of myasthenia gravis?
- **a.** History of small cell lung carcinoma
- **b.** Worsening of symptoms following a large meal
- **c.** Ascending paralysis
- **d.** An erythematous periorbital rash
- **e.** Improvement of symptoms following plasma exchange

Answer: e. Myasthenia gravis, along with several other neuromuscular disorders, can be treated with plasma exchange. History of small cell lung carcinoma is associated with Lambert-Eaton syndrome. Ascending paralysis is seen more commonly in Guillain-Barré syndrome and tick paralysis. An erythematous periorbital, or heliotrope, rash is seen in dermatomyositis.

3. A 40-year-old female patient with a history of myasthenia gravis presents to the emergency department with mild shortness of breath upon exertion. You are concerned for an impending myasthenic crisis. Which of the following patient factors would most suggest this diagnosis?
- **a.** Bilateral ptosis
- **b.** Inability to tolerate secretions
- **c.** A forced vital capacity (FVC) of 65 mL/kg
- **d.** A negative inspiratory force (NIF) of 40 cm H_2O
- **e.** Recent initiation of a new medication for hypertension

Answer: b. Myasthenic crisis is an emergent, life-threatening exacerbation of myasthenia gravis that involves acute weakness of the muscles of the respiratory system. Detecting signs of impending myasthenic crisis and differentiating this from a regular exacerbation of myasthenia gravis is crucial for emergency medicine providers. Pulmonary function tests, such as forced vital capacity (FVC) and negative inspiratory force (NIF) can suggest impending crisis, but these tests should not be the sole factors to consider. Physical exam findings of significant muscle weakness or respiratory distress are the most concerning signs for impending myasthenic crisis. Bilateral ptosis is a sign of acute myasthenia but, by itself, likely does not indicate a significant exacerbation. Inability of the patient to tolerate oral secretions, on the other hand, is a much more concerning exam finding and implies significant muscle weakness and impending crisis.

4. The previous patient continues to have worsening respiratory symptoms. Both neurology and critical care teams are consulted and are at bedside. The patient is started on pyridostigmine. Which of the following findings would indicate worsening myasthenic crises as opposed to overtreatment with pyridostigmine?
- **a.** An electrocardiogram showing a heart rate of 35
- **b.** Pupil size of 7 mm bilaterally
- **c.** Increasing respiratory fatigue
- **d.** Significant abdominal discomfort
- **e.** Excessive sweating

Answer: b. When treating myasthenia gravis, worsening of the patient's condition can be caused by worsening myasthenic crisis or by cholinergic crisis from overtreatment of the patient with anticholinergic agents. These two conditions can present similarly but have different causes and thus different treatments. Worsening myasthenic crisis occurs from undertreatment of the initial crisis by anticholinergic agents where cholinergic crisis occurs from overtreatment of the initial crisis. Patients in cholinergic crisis tend to present with bradycardia, abdominal pain, and increased secretions. In both cholinergic crises and myasthenic crises, increased weakness and respiratory distress can be present. However, mydriasis is much more likely to be seen in myasthenic crisis.

5. An 8-month-old infant presents to the emergency department with increasing weakness and poor feeding. Physical exam reveals an ill-appearing infant with decreased muscle tone. What is the most DEFINITIVE treatment?
- **a.** Administration of antibiotics against *Clostridium* species
- **b.** Administration of corticosteroids
- **c.** Contacting the Centers for Disease Control and Prevention (CDC) for antitoxin
- **d.** Contacting the California Department of Health for antitoxin
- **e.** Serum and stool testing for botulinum toxin

Answer: d. This patient likely has infantile botulism and the definitive treatment is obtaining IV human-derived botulism immunoglobulin, or BabyBIG, from the California Department of Health. The CDC has a heptavalent botulinum toxin for noninfantile cases. IV corticosteroids

CHAPTER 94: QUESTIONS AND ANSWERS—cont'd.

and antibiotics are not recommended for cases of infantile botulism. Serum and stool testing can diagnose botulism but often have a prolonged turnaround time and so are not useful in emergency department management.

6. Which of the following is TRUE about wound botulism?
- **a.** It is the most common form of botulism.
- **b.** Antibiotics do not have a role in wound botulism management.
- **c.** Compared with other forms of botulism, wound botulism patients more often have abdominal complaints.
- **d.** It is associated with enteroviruses.
- **e.** It is associated with topical tobramycin treatment.

Answer: c. Wound botulism is caused by infection of a wound with *Clostridium botulinum* which then causes systemic infection via hematogenous spread. It is an infrequent presentation of *C. botulinum* infection; infantile botulism is the most common form of botulism. Antibiotics as well as surgical consultation are first line in treatment. Patients with wound botulism often present with fever and less often present with abdominal symptoms compared with other forms of botulism. Enteroviruses are not associated with botulism but are associated with acute flaccid myelitis (AFM). Tobramycin treatment can be a trigger for acute myasthenia gravis but not for wound botulism.

7. A patient presents with an episode of flaccid lower extremity paralysis. He notes that he frequently gets these episodes and the condition runs in his family. His serum potassium concentration is 5.9 mEq/L. What is the next best treatment step?
- **a.** Intravenous (IV) immunoglobulin
- **b.** IV hydration
- **c.** Thyroid function testing
- **d.** Magnesium supplementation
- **e.** High-dose insulin and dextrose

Answer: b. This patient likely is having an episode of hyperkalemic periodic paralysis. Hyperkalemic periodic paralysis is due to an imbalance in the distribution of potassium at a cellular level. IV hydration helps to rebalance the body's potassium stores. Testing of thyroid function and high-dose insulin therapy may be indicated but are not the immediate next steps. IV immunoglobulin and magnesium supplementation are not indicated in this case.

8. An 8-year-old patient presents to the emergency department with diffuse weakness and myalgias. His parents note that he recently had a muscle biopsy which confirmed an unspecified illness. You also note a rash on the patient's chest. What would you likely find on the patient's physical exam?
- **a.** Difficulty in sitting upright from a supine position
- **b.** Difficulty in holding a pencil or pen
- **c.** Fasciculations of proximal muscle groups
- **d.** Atrophy of proximal muscle groups
- **e.** Increase responsiveness of the patellar reflex

Answer: a. This patient likely has dermatomyositis. Dermatomyositis is an inflammatory myopathy that most commonly affects the proximal muscle groups and spares the distal muscle groups. This patient likely would have trouble sitting up as it uses the proximal hip flexor muscles. Distal muscles, such as those in the hand, are less commonly affected. Fasciculations are not commonly seen. Atrophy is generally a much later finding in inflammatory myopathies. Patients also tend to present with decreased patellar reflexes.

9. Which of the following pairs is correct regarding a neuromuscular disease and its pathophysiology?
- **a.** Botulism—concomitant gastroenteritis is almost always present
- **b.** Myasthenia gravis—autoantibodies attack postsynaptic acetylcholine (ACh) receptors
- **c.** Periodic paralysis—hyperkalemic form is most common
- **d.** Polymyositis—distal muscle weakness precedes proximal muscle weakness
- **e.** Tick paralysis—symptoms resolve quickly after the tick is removed

Answer: b. Myasthenia gravis is caused by autoantibodies that attack postsynaptic ACh receptors at the neuromuscular junction. Botulism usually does not present with gastroenteritis. Periodic paralysis is most commonly associated with hypokalemia. Polymyositis usually presents first in proximal muscles. Tick paralysis may take days to weeks to resolve after removal of an offending tick.

95

Central Nervous System Infections

Benjamin H. Schnapp and Corlin Jewell

KEY CONCEPTS

- CNS infection should be considered in all patients with headache, nuchal rigidity, fever, altered sensorium, or diffuse or focal neurologic findings.
- Patients with suspected CNS infection should be asked about history focused on risk factors for CNS disease and infection and receive a full neurologic examination.
- CSF testing is the most reliable method of assessing the presence of meningitis and should be obtained in all patients in which there is a suspicion for CNS infection.
- Early initiation of empirical antimicrobial therapy is recommended in cases of suspected acute CNS infection. This should occur before imaging or lumbar puncture.
- Patients without focal neurologic symptoms, altered level of consciousness or signs of increased intracranial pressure do not require imaging prior to lumbar puncture.
- We recommend steroid treatment before or alongside treatment with antibiotics in all cases of suspected meningoencephalitis.
- First-line treatment for healthy adults with suspected bacterial meningitis is ceftriaxone or cefotaxime plus vancomycin in most countries given high antibiotic resistance.
- Acyclovir is recommended for patients with suspected encephalitis because HSV is a common pathogen.
- Clinical course and risk factors, such as immunosuppression, dictate the need to test and treat for fungal and tuberculous meningoencephalitis.
- In the absence of a clear clinical picture of viral meningitis, patients should generally be empirically covered for bacterial meningitis and admitted to the hospital.
- Antibiotic chemoprophylaxis should be given for close contacts of patients with meningitis resulting from *N. meningitidis* and contacts of patients with *H. influenzae* living with immunocompromised or unvaccinated individuals.
- CT or MRI can be used in patients with a suspected brain abscess.
- MRI with gadolinium contrast of the entire spine is the definitive imaging test for patients with suspected spinal epidural abscess.

FOUNDATIONS

Background and Pathophysiology

The etiology of CNS infections continues to change as a result of new therapeutic interventions, vaccines, and the growing number of immunosuppressed patients. Despite advances, however, the morbidity and mortality from a CNS infection remains high; good outcomes can be maximized with early recognition and treatment.

The two most common CNS infections, *meningitis* and *encephalitis,* are delineated by the tissue that is infected. Meningitis refers to an infection of the meningeal layers lying between the bony covering of the CNS and the brain tissue. If the infection is present in the brain parenchyma itself, then it is termed encephalitis. However, these disease states are not mutually exclusive and exist on a continuum of *meningoencephalitis*. Generally, greater degrees of encephalitis portend a worse prognosis, as more tissue is involved.

Bacterial Meningitis

Bacterial meningitis has a high mortality rate despite treatment, with rates variable depending on the organism, time to appropriate treatment, and patient factors. *Streptococcus pneumoniae* remains the predominant pathogen in adult patients, accounting for over half of cases despite a recent decline in incidence.[1] Other common causes in adults include *Neisseria meningitidis, Haemophilus influenzae*, and *Listeria monocytogenes. N. meningitidis* is the predominant organism in children. *Listeria* is more commonly seen in elderly adults and infants. In the first six weeks of life, Group B streptococcus species as well as *Escherichia coli* also represent common causes of bacterial meningitis. Bacterial meningitis caused by *H. influenzae* was previously responsible for a much larger proportion of cases, but the incidence has declined sharply since the introduction of the vaccine for type B (HiB).

Meningococcal disease refers to meningitis caused by *N. meningitidis,* and is most common in younger individuals, particularly those living in very close proximity to others such as in military barracks or college dormitories. A, B, and C represent the major groups. Group B is particularly prevalent in Europe, while group C is commonly isolated in the United States. A conjugate vaccine containing serogroups A, C, Y, and W-135 has been developed, as well as a separate vaccine for serogroup B. These vaccines are highly effective in children, but have yet to be broadly distributed to developing countries.

The infection process in bacterial meningitis generally begins with nasopharyngeal colonization and invasion of the mucosa. The varying capsular properties of each organism protect the bacteria. Once bacteria cross the blood-brain barrier to enter the CSF, host defense mechanisms within the CSF are often ineffective. Bacteria then proliferate, which causes the body to signal for leukocytes to enter the CSF. Meningeal and subarachnoid space inflammation is associated with the release of cytokines into the CSF, inciting an inflammatory cascade that promotes increased permeability of the blood-brain barrier, cerebral vasculitis, edema, and increased intracranial pressure (ICP). A subsequent decrease in cerebral blood flow can then lead to cerebral hypoxia.

Meningeal infection may also occur in association with a dural leak secondary to neurosurgery or trauma to the CNS. Skin flora, including coagulase-negative staphylococcus species, *Staphylococcus aureus,* and *Cutibacterium acnes* are seen most commonly in this population, though infections caused by *Pseudomonas aeruginosa* also occur.

Mortality from bacterial meningitis is highest in patients with advanced presentations, serious underlying disease or advanced age. The fatality rate is highest with *Listeria* meningitis with a mortality rate

up to 27%.[2] Overall, many survivors have some degree of residual neurologic deficit, with the highest rates found in those with pneumococcal meningitis.[3]

Meningitis from Lyme disease (*Borrelia burgdorferi*) presents similarly to other causes of bacterial meningitis, but can also cause other neurologic symptoms, including facial palsies and radiculopathies. Late Lyme infection, occurring in some cases years after initial infection, can cause encephalopathy which can manifest as migraines, psychosis, and somatoform disorders.

Viral Meningitis

Given the decrease in the incidence of bacterial meningitis, largely secondary to vaccination efforts, viral infections are now the most common cause of meningitis. Enteroviruses and herpesviruses are the most common causes,[4] often occurring in those with risk factors such as a suppressed immune system. The overall prognosis for the majority of cases of viral meningitis is excellent.

Viral Encephalitis

The same organisms responsible for viral meningitis may also be associated with encephalitis. A common mechanism of viral transmission is through the skin via insect vectors (e.g., Zika virus or West Nile virus), although clinical disease develops in only a small percentage of the people bitten. Tick-borne viral encephalitis is endemic to parts of Europe and Russia and is an important consideration for residents and recent travelers to those regions; a vaccine is available. Transmission of viral encephalitis often occurs by hematogenous spread from infections of the respiratory, gastrointestinal, or urogenital tracts. Other mechanisms include retrograde transmission along neuronal axons, as seen in the herpes virus, and direct invasion of the subarachnoid space after infection of the olfactory submucosa, as seen in rabies or herpes.

The outcomes in viral encephalitis, including permanent neurologic sequelae, are dependent on both the host and the infecting agent. Acyclovir treatment has reduced the mortality from HSV encephalitis from up to 70% down to 9%, but with 34% of surviving patients having moderate to severe neurologic disability.[5] Common complications include seizures, motor deficits, and impaired cognition. Encephalitis caused by Japanese encephalitis virus, Eastern equine virus, and St. Louis encephalitis virus is severe, with high mortality rates and high rates of neurologic sequelae among survivors. West Nile virus produces encephalitis in less than 1% of those infected but has resulted in 2000 deaths in the United States as of 2016.[6] Western equine virus and California encephalitis virus cause milder infections, and death is rare. Zika virus has been associated with the development of Guillain-Barré syndrome (GBS) as well as severe encephalitis in developing fetuses of infected mothers, resulting in devastating neurologic defects. It is not entirely clear if the virus also causes neuroinvasive disease in adults. Powassan virus, another tick-borne cause of CNS infection in North America, is known to cause severe encephalitis with a mortality of approximately 10% and a high rate of neurologic disability in survivors. CMV can also cause encephalitis, particularly in patients who are infected with HIV or are otherwise immunocompromised. Influenza virus, well-known for its respiratory effects, is another rare cause of high-mortality encephalitis in adults. Encephalitis secondary to measles and mumps has almost disappeared in the developed world due to widespread vaccination, but still can occur, particularly in those who are immunocompromised. Primary measles encephalitis is typically self-limited but carries a mortality of approximately 10% to 15%. Patients with this disease can go on to develop both subacute and chronic encephalitis (sometimes occurring years later) which is universally fatal.

Tuberculous Meningitis

Mycobacteria typically gain access to the CNS via hematogenous spread, and once present will begin to form granulomas. These can rupture, inciting an inflammatory response from the host. This can have the side effect of causing vasculitis and potentially a stroke. Tuberculous meningitis is also frequently complicated by hydrocephalus requiring neurosurgical intervention; in advanced disease, up to 25% of patients may require some neurosurgical procedure for obstruction (ventriculoperitoneal shunt or drainage). Tuberculous meningitis leads to severe disability or death in roughly half of the cases, and, as with bacterial meningitis, depends on the patient's age, comorbidities, time to diagnosis, and the progression of their disease.

Fungal Meningitis

CNS infections caused by fungal species are most commonly caused by *Cryptococcus* (typically *C. neoformans* and *C. gattii*) and have been increasing in recent years. Other common causes of fungal meningitis include *Aspergillus* species and *Coccidioides immitis.* Diabetic patients are at high risk of developing cerebral mucormycosis via direct invasion of the sinuses, and CNS invasion by *Histoplasma capsulatum* is also commonly seen in AIDS patients.

Over a million cases of fungal CNS infections are estimated to occur annually, likely via similar mechanisms as bacterial meningitis. Because these infections typically affect those with compromised immune systems, this increase is likely secondary to an increasing number of people living with iatrogenic chronic immunosuppression and HIV infection. Pulmonary exposure, followed by hematogenous spread, is the primary pathogenic mechanism in most cases of cryptococcal meningitis. Infection with *C. neoformans* is considered an acquired immunodeficiency syndrome (AIDS)-defining illness but can occur in those with immunocompromised states arising from other causes. Infection with *C. gatti* can occur even in immunocompetent patients. *Candida* species are also a major cause of fungal meningitis. These infections typically occur in those with candidemia or via the implantation of neurosurgical hardware (such as CNS shunts).

Common CNS complications of fungal meningitis include abscesses, increased ICP, neurologic deficits, seizures, bone invasion, fluid collections, and ocular abnormalities (seen in up to 40% of patients with cryptococcal meningitis). The mortality rate of fungal meningoencephalitis is usually around 20% to 30%, but may be up to 97% in untreated *Candida* meningitis, and varies with the severity of illness, timeliness of diagnosis, and administration of appropriate treatment.

Central Nervous System Abscess

CNS abscesses occur due to both local contiguous invasion as well as hematogenous spread from remote infections. They are also associated with intravenous (IV) drug use, neurologic surgery, and cranial trauma. In cases of contiguous spread, the location of the abscess within the brain is typically dictated by the source of invasive infection or the surgical procedure (Fig. 95.1). Brain abscesses secondary to otitis media are most often found within the temporal lobe or cerebellum, whereas cases arising from sinusitis usually result in abscesses in the frontal or temporal lobes. Hematogenous spread of microorganisms (most commonly from the pulmonary system) often results in multiple brain abscesses, although solitary lesions may also occur. Rarely, patients present without a clear source or the presence of risk factors. Antibiotic prophylaxis in the immunosuppressed, improved diagnostic imaging, and neurosurgical interventions have all contributed to more favorable outcomes.[7]

The spinal epidural space also represents a common site of CNS abscesses. Increasing numbers of spinal surgeries, immunosuppressed

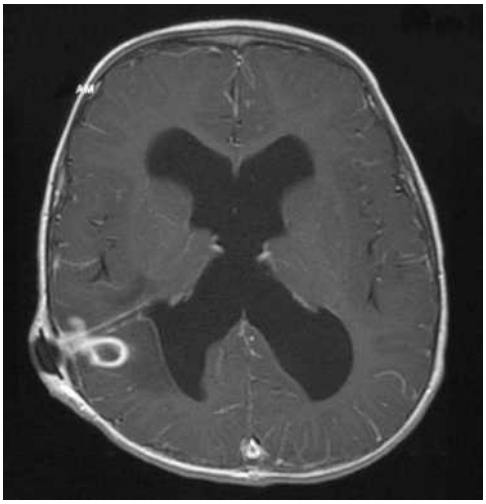

Fig. 95.1 A brain abscess which has developed adjacent to the site of a CSF shunt, as seen on MRI. CNS abscesses commonly develop adjacent to surgical sites, as this is one way bacteria can bypass the blood-brain barrier.

patients, and high rates of intravenous drug use are contributing factors to an increase in the incidence of these abscesses, which are associated with high rates of permanent neurologic morbidity. Infection typically enters the epidural space via the blood but can also arise from contiguous spread from nearby infections (e.g., psoas abscess, vertebral osteomyelitis).

CLINICAL FEATURES

Meningitis

The clinical picture of bacterial and viral meningitis is classically defined by fever, headache, photophobia, and nuchal rigidity. Unfortunately, subtle presentations lacking these classic features are common. In immunosuppressed or geriatric patients, alteration in mental status may be the only finding, and therefore requires a lower threshold for ruling out meningitis in these special populations. Clinical presentations in neonates may include a bulging fontanelle, but are often subtle, such as changes in behavior, decreased tone, or weakness as noticed by parents; consequently, guidelines universally recommend a lumbar puncture as part of the evaluation of a neonate with a suspected infection.

The physical findings in meningitis are variable depending on patient factors (e.g., age, comorbidities), pathogen, and time course of the disease (early vs. late). Two classic exam maneuvers, the Kernig sign (inability to straighten leg to a position of full knee extension when patient is lying supine with hip flexed to a right angle) and Brudzinski sign (attempts to flex the neck passively are accompanied by flexion of the hips), have a low sensitivity of less than 12%; however, they have a high specificity and strongly suggest meningitis if they are present (Table 95.1).[1]

Patients with suspected meningitis should first be examined for evidence of a structural lesion precipitating their symptoms, as these patients may require CT imaging to rule out other causes of their symptoms. Signs of mass lesions can include papilledema, decreased venous pulsations, new-onset seizures, abnormal level of consciousness, or focal neurologic deficits. An accurate fundoscopic exam can be challenging to obtain and bedside ultrasound offers an alternative tool for assessing intracranial pressure.[8] Patients without abnormal findings on neurologic examination may proceed to lumbar puncture without CT.[9]

Because meningitis can result from both contiguous and hematogenous spread, the physical examination should include a search for an inciting infection, such as a skin abscess, sinusitis, endocarditis, or osteomyelitis. Manifestations of endocarditis may be present, particularly in cases found to be due to *S. aureus*. Petechiae and cutaneous hemorrhages are widely reported with meningococcemia, typically on the extremities although they can occur anywhere on the body. Endotoxic shock with vascular collapse and DIC often develops in severe meningococcal disease, but shock may be present in the advanced stages of any bacterial meningitis. A finding of a systemic infection in a patient with signs of potential meningeal irritation should encourage rather than dissuade the clinician from considering the possibility of a concomitant CNS infection.

Cerebral venous thrombosis occurs in approximately 1% of patients with meningitis, likely due to coagulopathy induced by the robust CNS immune response; this rare complication can manifest as new-onset seizures, altered sensorium, and new focal neurologic deficits. Meningococcemia may cause Waterhouse-Friderichsen syndrome, or bilateral adrenal hemorrhage, often accompanied by other signs of severe systemic infection such as DIC and purpura.

The presentation of fungal meningitis can sometimes be subtle even in the healthy adult population. Headache, low-grade fever, malaise, and weight loss may be present but often to such a mild degree that CNS infection is not initially considered. Tuberculous meningitis, in contrast to other types of meningitis, can have a subacute or even chronic presentation, with symptoms developing months after onset of infection. Cases can be vague and nonspecific, including fever, weight loss, night sweats, and malaise, with or without headache and meningismus. In some cases, CNS involvement may be the only manifestation of tuberculosis, but CNS infection can also present alongside pulmonary tuberculosis or disseminated (miliary) infection.

Encephalitis

Encephalitis can occur from a viral, bacterial or fungal cause; it is not possible to definitively distinguish the etiology of the infection based on clinical features, although certain presentations can be suggestive. Viral encephalitis can occur secondary to primary viral invasion of the CNS, such as West Nile or rabies virus. Alternatively, it can be caused by reactivation of a previously dormant viral illness, such as varicella-zoster virus (VZV).

The diagnosis of encephalitis requires an alteration of consciousness or behavior without another known cause. Fever, headache, seizures, and disorientation can be present. The symptoms exhibited by the patient are representative of the affected area of the brain. For example, HSV has a predilection for the temporal lobes and therefore, patients with HSV encephalitis can present with psychosis, personality or behavior changes, or hallucinations, occasionally prompting an initial diagnosis of a psychiatric disorder. A thorough skin and mucosal examination may reveal the presence of herpetic lesions, as encephalitis can be associated with cutaneous outbreak in some cases. West Nile virus can result in neuroinvasive disease resulting in a wide range of symptoms, including muscle weakness, memory loss, behavioral changes, and difficulty concentrating. In cases of rabies encephalitis, patients also present with agitation, extreme hydrophobia, and muscular spasms.

Central Nervous System Abscess

The most common finding in patients with an intracranial abscess is headache. Findings seen consistently in other CNS infections, such as fever and altered mental status, may not be present. Most patients with intraparenchymal abscess have a subacute clinical course with symptoms progressing over 1 or more weeks. Just as with encephalitis, the

TABLE 95.1 Approximate Sensitivity, Specificity, Positive and Negative Likelihood Ratios of Clinical Findings and Examination Maneuvers for CSF Pleocytosis in Patients With Suspected Meningitis

	Sensitivity	Specificity	LR+	LR-
Headache	91%	16%	1.1	0.5
Fever	30%	58%	0.7	1.2
Jolt accentuation	21%	82%	1.2	1.0
Kernig sign	2%	97%	0.8	1.0
Brudzinski sign	2%	98%	1.0	1.0
Nuchal rigidity	13%	80%	0.6	1.1
Focal neurologic deficit	2%	96%	0.5	1.0
Vomiting	4%	85%	0.3	1.1
Rash	2%	96%	0.6	1.0
Physician suspicion	44%	40%	0.8	1.4

Adapted from Nakao JH, Jafri FN, Shah K, Newman DH. Jolt accentuation of headache and other clinical signs: poor predictors of meningitis in adults. *Am J Emerg Med.* 2014;32(1):24–28.

symptoms exhibited by patients depends on the site affected by the abscess. For example, those with abscesses near the frontal lobe may present with disinhibited behavior, and abscesses near the motor cortex may demonstrate focal weakness. Seizures occur in approximately 25% of patients. Abrupt neurologic deterioration and death can result from abscesses that rupture into the ventricular system.

Abscesses can also present in the epidural space in the spine, most commonly in the lumbar region.[10] However, multiple areas may be affected which can be discontiguous.[11] Like brain abscesses however, presentations can be nonspecific and mimic more benign causes of back pain. The most common presenting symptom of an abscess within the epidural space is midline pain, which is present in the majority of patients. Conversely, fever is only present in approximately half of cases, particularly early in the course. Complications of a spinal abscess primarily result from cord compression, including paralysis, motor and sensory deficits, and bowel and bladder dysfunction. These deficits may be permanent once they develop, even with prompt treatment, making prompt diagnosis critical to avoid serious morbidity.

CSF Shunt Infection

These infections typically manifest with signs of increased intracranial pressure and hydrocephalus such as headache, altered mental status, nausea, and vomiting. They most often occur within 6 months of shunt placement and are typically the result of skin flora being introduced into the CSF space.

DIFFERENTIAL DIAGNOSES

The diagnoses of acute, subacute, and chronic meningitis and the other potential pathologies that must be considered vary based on the time course of the presenting symptoms. *Acute meningitis* encompasses patients with clear signs and symptoms of meningitis who are evaluated within 24 hours of the onset of their symptoms. While other diagnoses can be considered during the initial evaluation, antibiotic therapy should be initiated as soon as possible in these patients to cover for the possibility of bacterial meningitis. In this group of patients with rapid onset of symptoms, the most important differential diagnostic considerations are viral meningitis, acute subarachnoid hemorrhage (SAH), acute arterial dissection, and the noninfectious causes of meningitis including drugs, malignancy, or autoimmune conditions.

Distinguishing between viral and bacterial meningitis is described in the Diagnostic Testing section. Because subarachnoid blood is irritating to the meninges, it will cause neck pain similar to meningitis, but can be distinguished using CT imaging and LP. Generally, patients with SAH and cervical artery dissection will lack associated infectious symptoms and signs, such as a prodrome or fever.

In *subacute meningitis,* symptoms develop over a period of 1 to 7 days. Although this time course makes viral meningitis most likely, bacterial and fungal etiologies remain possible. Brain tumor, spinal abscess, infections outside the CNS such as osteomyelitis, and drug effects are potential diagnoses. Other considerations that may mimic subacute meningitis include CNS malignancy, intracranial hemorrhage, brain abscess and nonconvulsive status epilepticus. CNS abscess should be considered especially if fever is minimal or absent or if there are focal neurologic findings. Nonconvulsive status epilepticus is a consideration in patients with altered mental status, especially if there is a seizure history or a known structural brain lesion.

The spectrum of *chronic meningitis* includes the viral meningitides, as well as meningitis caused by tuberculosis, syphilis, and fungi. Symptoms have generally been present in this group for at least 1 week and generally have a prolonged, indolent course. The potential causes of culture-negative meningitis symptoms are broad and varied, including rheumatologic, neoplastic, and medication-induced symptoms. Generally, these atypical causes will present during the timeframe for *chronic meningitis* but may occasionally be seen with a *subacute* course.

Spinal epidural abscess should be suspected in patients with back pain accompanied by fever, back pain with neurologic deficits on exam, or relatively rapid onset atraumatic back pain, though patients may not always present with classic signs and symptoms. Patients with spinal surgery and instrumentation, IV drug abuse, and immunosuppression are at higher risk, and benefit from a lower threshold for testing. Epidural hematoma, osteomyelitis, discitis, aortic aneurysm rupture, aortic dissection, and pulmonary embolism are other considerations.

DIAGNOSTIC TESTING

Blood Testing

Currently, no test can substitute for cerebrospinal fluid analysis. The complete blood count (CBC) with differential is a nonspecific adjunct in the diagnostic evaluation of a patient suspected to have a CNS infection. However, a normal leukocyte count and differential does not rule out the diagnosis of a CNS infection.

Procalcitonin has been shown in multiple studies to have some value in the discrimination between bacterial and viral etiologies of meningitis. With an estimated sensitivity of 90% and specificity of 98% for bacterial infection, it may be useful as an adjunct when the clinical picture is unclear, but it is currently not considered definitive to rule out bacterial meningitis.[12] In addition, elevation in serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are potentially useful but not diagnostic in the differentiation of bacterial and viral meningitis.[13]

A serum glucose level is needed to interpret the CSF glucose level. Although most patients do not require coagulation studies, patients who are taking warfarin should have their INR checked. Patients on direct oral anticoagulants can be checked for anti-Xa levels, if available, to assess for current anticoagulant activity. Coagulation status should be considered in patients on anticoagulants prior to attempting a lumbar puncture given the risk of bleeding complications.

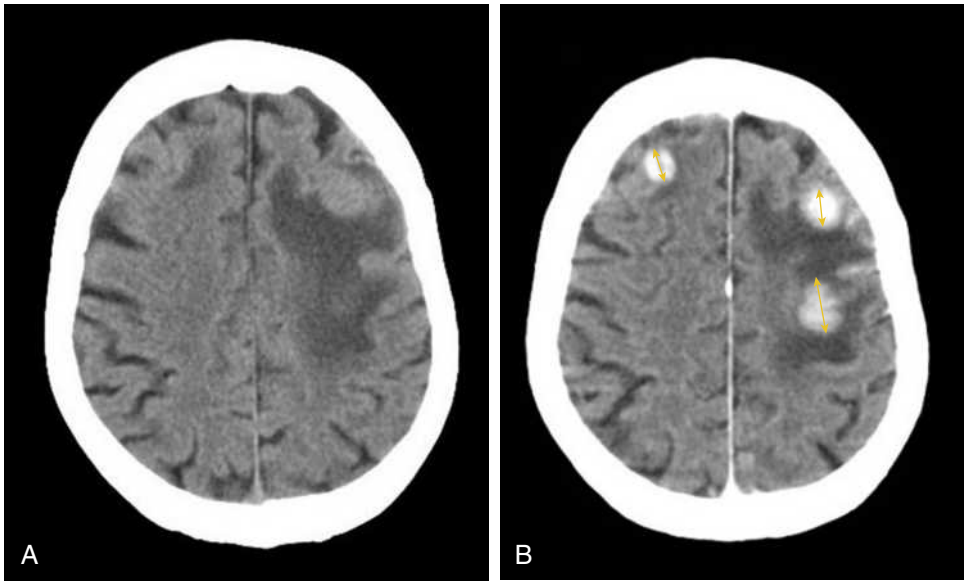

Fig. 95.2 CT image of multiple brain metastases with surrounding edema. When evaluating for CNS infection, findings such as this may suggest that LP is unnecessary or unwise.

Blood cultures should be obtained for all patients who are being evaluated for a CNS infection, ideally on arrival. However, they may still have benefit later in the patient's course even if antimicrobial therapy has already been administered, because pneumococcal and meningococcal infections may be identified in the blood of patients with these CNS infections.

Neuroimaging

A CT scan without contrast of the head or magnetic resonance imaging (MRI) scan of the brain is indicated in any patient with a suspected CNS infection in which an intracranial hemorrhage or mass lesion is suggested by history or examination. Contrast studies are more sensitive if a mass lesion is high on the differential (Fig. 95.2). A CT scan may show hypodense lesions in the temporal lobes in patients with HSV encephalitis, although an MRI scan reveals enhancement with greater sensitivity (Fig. 95.3). Neuroimaging should not delay antimicrobial therapy, which can be initiated prior to imaging, and LP should still be obtained expeditiously.

A contrast-enhanced cranial CT or MRI scan is diagnostic for a CNS abscess, though the MRI is more sensitive. Large lesions are generally visible on non–contrast-head CTs, although again, MRI is more sensitive and can show smaller lesions that may be mimicking meningitis or encephalitis. When evaluating for spinal abscess, CT imaging of the spine is insufficiently sensitive. MRI of the entire spine is the test of choice (Fig. 95.4), as lesions may be multiple and discontinuous, and can be difficult to localize by exam alone. In patients with contraindications to MRI, a CT myelogram of the spine is an alternative, although definitive testing is preferred if possible due to the high morbidity associated with missed spinal abscess. Transfer to an MRI-capable center may be appropriate if imaging is not available in a timely manner.

Bedside ultrasound of the optic nerve sheath diameter is a rapid and accurate way to evaluate for increased intracranial pressure. This is performed using a high-frequency probe placed over a closed eye. The optic nerve can be assessed in either longitudinal or transverse planes and measured 3 mm behind the globe of the eye;[14] the upper limit of normal for optic nerve sheath dilation is 5 mm (Fig. 95.5). A diameter greater than 5 mm suggests increased intracranial pressure but does not distinguish among potential causes.

Lumbar Puncture

A lumbar puncture (LP) for CSF analysis is indicated whenever meningitis or encephalitis is suspected unless the skin overlying the puncture site is infected or there is potential for brain herniation. In the majority of patients with suspected meningitis who have no focal neurologic findings (including no altered mental status), LP can be safely performed without delay and without preceding neuroimaging studies. Coagulation studies do not need to be routinely obtained prior to LP, but should be considered in those with personal or family history of coagulopathy, use of anticoagulation medications, organ failure, or evidence of DIC. A platelet count below 40,000 should also prompt consideration for delaying an LP. An INR greater than 1.4 in patients on warfarin is a relative contraindication to LP. The guidelines for DOACs depend on the agent being used; ideally these should be held at least 24 hours prior to an LP.[15] The need for a LP cannot be anticipated in most cases in the ED, however, and the emergent need for the procedure must be weighed against the increased risk of bleeding.

Herniation has been described in patients following LP, hence the recommendation to avoid a LP in patients with evidence of increased intracranial pressure. A recent study showed the risk of herniation to be only 0.1% in the first hour following LP, suggesting that some reported cases of herniation may be due to the infectious process itself.[9] Regardless, at the present time, we recommend that LP be avoided in those patients with the presence of papilledema, increased optic nerve sheath diameter on ultrasound, mass lesions on CT imaging or other signs of increased ICP. Early initiation of antimicrobial therapy should not be delayed pending LP for patients with high clinical suspicion for CNS infections. However, the CSF can be sterilized within as little as one hour post-antibiotics, so LPs should proceed as expeditiously as is feasible.

If the physician is unable to obtain CSF during the LP, consideration should be given to a prompt radiology-guided LP. If no LP can be performed, the blood cultures obtained on presentation may still be of assistance in identifying the causative microbe.

Opening Pressure

The normal upper limit of CSF pressure in an adult is 20 cm H_2O. The opening pressure is only valid for patients in the lateral recumbent position, because it may increase substantially when the patient is in

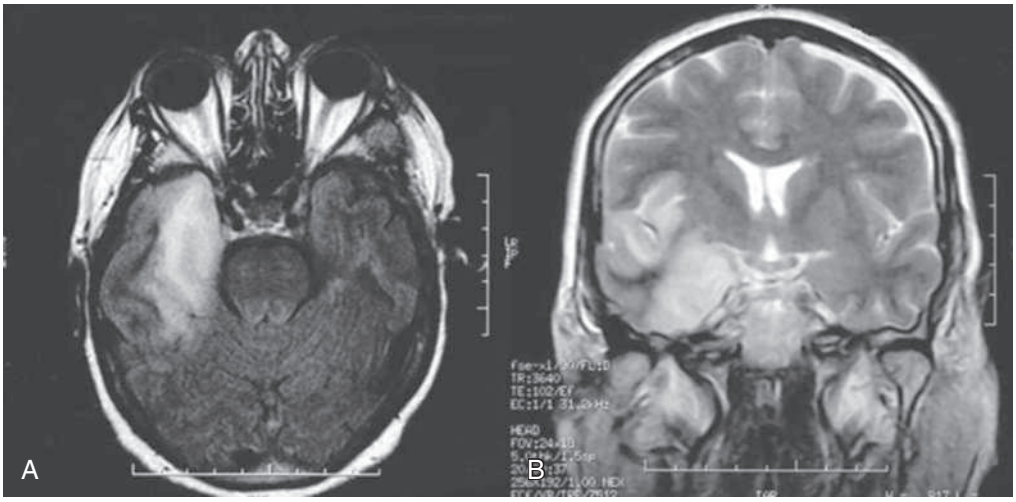

Fig. 95.3 Temporal lobe enhancement on brain MRI. This is a common imaging finding in patients with HSV encephalitis.

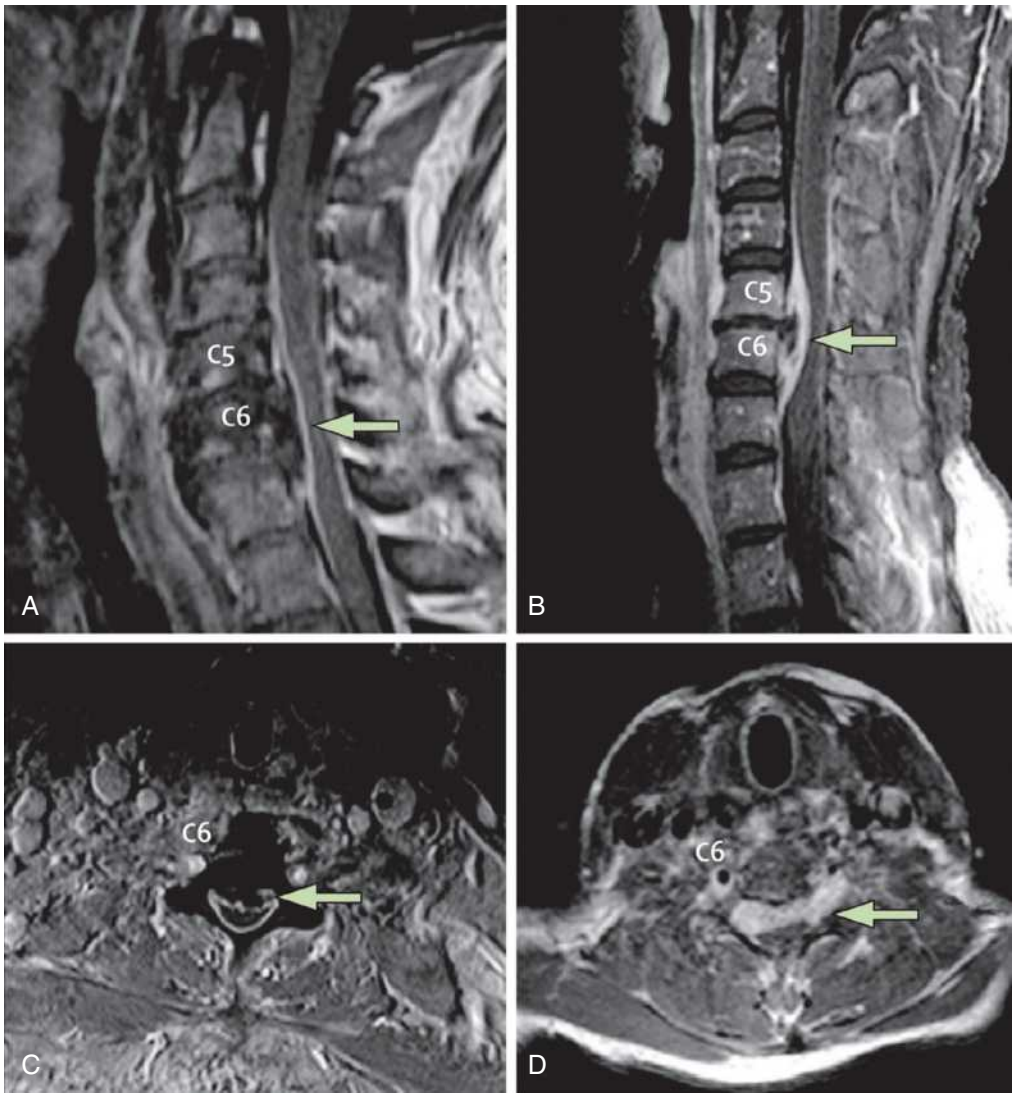

Fig. 95.4 Epidural abscess as seen on lumbar spine MRI. CT imaging may miss smaller spinal cord lesions such as these.

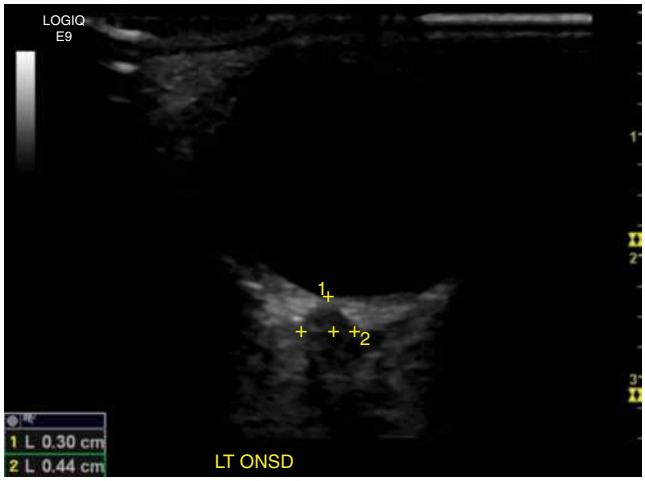

Fig. 95.5 The optic nerve sheath diameter using ultrasound is measured 3 mm behind the optic disc. This method can be used by the clinician at bedside to quickly assess patients for increased intracranial pressure.

Fig. 95.6 CSF specimens after collection. The clear appearance, indistinguishable from water, is a normal finding; any degree of cloudiness can suggest CNS infection.

the sitting position. It may also be falsely elevated when the patient is tense, has marked muscle contraction, or is obese. The pressure is often elevated in bacterial, tuberculous, and fungal meningitides and a variety of noninfectious processes, and often normal in viral meningitis. There is little data however on the sensitivity and specificity of this marker. As such, obtaining an opening pressure when possible prior to collecting CSF provides an additional data point to support a viral or bacterial clinical picture but cannot be used in isolation. If CSF collection requires the patient to sit up for mechanical reasons or patient comfort, opening pressure may be safely omitted.

Cerebrospinal Spinal Fluid Analysis

When possible, at least three sterile tubes each containing 1 to 1.5 mL of CSF should be obtained and numbered in sequence. A fourth tube is desirable in case additional studies are later necessary. The fluid should then be sent to the laboratory for immediate analysis of turbidity, xanthochromia, glucose, protein, cell count and differential, Gram stain, and bacterial culture. When only a small amount of fluid can be obtained, the most important studies are the cell count with differential, the Gram stain, and culture. Depending on the clinical scenario and patient risk factors, such as HIV, immunosuppression, travel history, or exposures, additional testing can be valuable as well. These studies can include cryptococcal antigens, acid-fast bacilli stain, or the Venereal Disease Research Laboratory (VDRL) test for neurosyphilis. Ideally, a cell count should be performed on both the first and last tubes collected to help differentiate true CSF pleocytosis from contamination of the specimen by peripheral blood from a traumatic LP.

The CSF should be assessed immediately for turbidity or cloudiness by the person performing the LP. Normal CSF is completely clear, colorless, and indistinguishable from water (Fig. 95.6); any degree of turbidity is pathologic. Changes in CSF clarity can generally be seen when leukocyte counts are greater than 200 to 500 cells/mm^3.

Cerebrospinal Spinal Fluid Cell Count

Normal adult CSF contains no more than 5 leukocytes/mm^3 with at most one granulocyte (polymorphonuclear [PMN] leukocyte); the presence of more than one PMN or a total cell count of more than 5 cells/mm^3 is evidence of CNS infection. The presence of any eosinophil in the CSF is abnormal; occasionally basophils may be seen in the absence of disease. The cell counts in bacterial meningitis often exceed 1000 cells/mm^3 with a neutrophil predominance (Table 95.2). However, the initial CSF analysis exhibits lymphocytosis (lymphocyte count greater than 50%) in approximately 10% of cases of bacterial meningitis. In some cases of *L. monocytogenes* meningitis, CSF analysis shows a cell count of less than 1000 cells/mm^3 with lymphocyte predominance but near-normal CSF glucose levels. In viral meningitis, encephalitis, tuberculous meningitis, or fungal meningitis, counts are typically less than 1000 cells/mm^3 with lymphocyte predominance. However, early (within 48 hours) viral presentations may reveal neutrophils and be indistinguishable from presentations of bacterial meningitis. Treatment with antibiotics before the LP will decrease the yield of Gram stain and cultures but likely does not affect the CSF cell counts or total CSF protein in meningitis.

A traumatic LP is suggested by the presence of 10,000 or more red blood cells (RBCs)/mm^3 or fewer RBCs in the final tube than in the initial tube. In the presence of a traumatic LP, the CSF white blood cell (WBC) pleocytosis can be estimated by subtracting one leukocyte for every 500 to 1000 RBCs.

Normal CSF cell counts, although reassuring, do not completely exclude bacterial meningitis, especially in immunocompromised patients. Lumbar puncture for brain abscess is unlikely to offer diagnostic yield except in cases of abscess rupture into the ventricular space. Although abnormalities can be seen, the CSF can also be entirely normal. Lumbar puncture is generally contraindicated in cases of spinal epidural abscess due to concern for seeding the infection.

Gram Stain

A Gram stain of a CSF specimen may identify the causative organism up to 75% of the time in cases of bacterial meningitis, however this is highly dependent on the concentration of the bacteria present. The yield is diminished to 40% to 60% when there has been prior treatment with antibiotics.[16] Gram-stain appearance of the CSF of a patient with *N. meningitidis* is shown in Figure 95.7.

Xanthochromia

Xanthochromia is the yellowish discoloration of the supernatant of centrifuged CSF specimens, detectable by visual inspection or spectrophotometry. Xanthochromia is an abnormal finding and is concerning

TABLE 95.2 Typical CSF Findings for Various Etiologies of Meningitis and Encephalitis

	Normal	Bacterial	Viral	Fungal/TB
Pressure (cm H_2O)	5–20	>30	Normal or increased	Increased
Protein (mg/dL)	18–45	Increased	Normal or increased	Normal or increased
Glucose	2/3 serum glucose	Decreased	Normal	Normal or decreased
Gram stain	Negative	60–90% positive	Negative	Negative
White blood cells	<5	Usually >1000	100–1000	50–500
WBC differential predominance	None	Neutrophils	Lymphocytes	Lymphocytes or monocytes

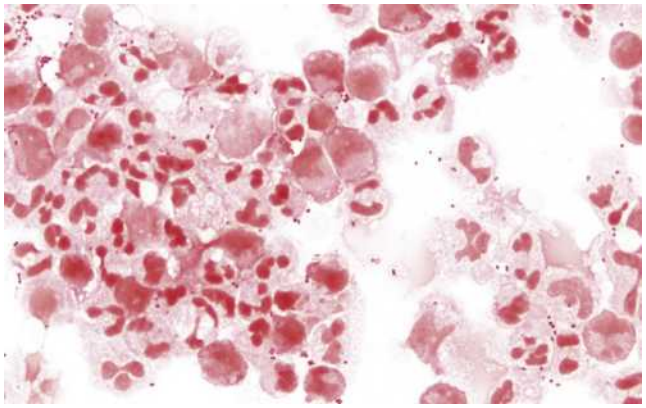

Fig. 95.7 The Gram stain appearance of a CSF sample infected with *N. meningitidis*, a gram-negative coccus. Magnification 1000x.

for SAH when detected. It results from the lysis of RBCs with the release of the breakdown pigments oxyhemoglobin, bilirubin, and methemoglobin into the CSF. This process takes hours to occur, though in patients presenting between 12 hours and 2 weeks of symptom onset, the sensitivity is close to 100% if analyzed using spectrophotometry. Visual inspection of the centrifuged specimen has been found to be much lower (47%). If a traumatic tap has introduced enough plasma to raise the CSF protein level to 150 mg/dL or more, blood pigments may cause xanthochromia. If the CSF protein level is less than 150 mg/dL, however, xanthochromia of a centrifuged CSF specimen almost always indicates that a SAH has occurred.

Glucose

The CSF glucose level is normally two-thirds of the serum glucose; when the serum glucose is within normal range, the CSF glucose is usually between 50 and 80 mg/dL. In the first 4 hours after food intake or parenteral glucose administration, however, the ratio is decreased, and the results are difficult to interpret with certainty. A CSF-to-serum glucose ratio of less than 0.5 in normoglycemic subjects is abnormal and may represent the impaired glucose transport mechanisms and increased CNS glucose use associated with bacterial meningitis. Mild decreases in the CSF glucose level may occur in viral, fungal, or tuberculous meningitis. However, bacterial meningitis should be presumed to be the cause of low CSF glucose until it is clearly excluded.

Protein

The normal CSF protein level in adults is typically below 45 mg/dL. An elevated CSF protein (higher than 100 mg/dL) commonly occurs with acute bacterial meningitis. When a traumatic LP has occurred, the CSF protein can be corrected for the presence of blood by subtracting 1 mg/dL of protein for each 1000 RBCs. Elevated CSF protein concentrations can result from any cause of meningitis, SAH, CNS vasculitis, syphilis, viral encephalitis, neoplasms, and demyelination syndromes. HSV and VZV can have higher CSF protein values than are typically seen in viral CNS infection (>100 mg/dL).

Other Stains

Historically, an India ink staining of the CSF was performed to diagnose cryptococcal meningitis. Though it is a rapid means of diagnosis, it has poor sensitivity (as low as 30% in non-AIDS patients). Cryptococcal antigen testing is now the gold standard for investigating cryptococcal infection, with baseline serum and CSF antigen titers providing a good estimate of fungal burden and prognosis but not response to therapy. Latex agglutination and enzyme immunoassay techniques have high sensitivity for cryptococcus as well but are inferior to antigen testing. Acid-fast bacilli (AFB) staining has been used for diagnosis of tuberculous meningitis but has poor sensitivity (typically <60%).

Lactic Acid

The normal reference range for CSF lactate is between 0.88 to 2.7 mmol/L. Although nonspecific, elevations in CSF lactic acid concentrations are suspicious for bacterial meningitis, while normal lactate levels (<2.7 mmol/L) are usually seen in patients with viral causes of meningitis. Recent studies have shown CSF lactate to have excellent predictive value in differentiating bacterial from viral meningitis,[17] and CSF lactate may be useful as an adjunct in the workup of suspected meningitis. We recommend its use, when available, to aid in determining the cause of CNS infection.

Antigen Detection

Nucleic acid amplification tests such as PCR have sensitivities of 67% to 100% for *H. influenza,* 79% to 100% for *S. pneumoniae,* and 91% to 100% for *N. meningitides;* specificities are nearly 100% for all three organisms.[1] The value of antigen testing has been demonstrated in multiple studies in which acute bacterial meningitis was confirmed only by PCR.[1] The sensitivity of bacterial culture is much lower and varies considerably based on the specific causative microorganism; under ideal conditions, cultures may miss a third of organisms, and sensitivity can be even lower if the patient has been treated with antibiotics. PCR testing has been demonstrated to have a sensitivity of 70% despite antibiotic therapy up to 1 week following initiation of treatment.[18]

Antigen and antibody testing have particular utility in HSV encephalitis. Although enzyme-linked immunosorbent assays (ELISAs) can detect HSV antibody production, the appearance of antibodies in CSF occurs too late to aid in any therapeutic decision analysis. PCR amplification and the identification of HSV DNA have a sensitivity of 96% and a specificity of 99% early in the disease, such that brain biopsy is no longer needed to make this diagnosis. PCR testing is sensitive for other viral infections as well, including VZV and enterovirus, though identification of the exact virus usually does not affect management. Diagnosis of VZV encephalitis is further improved by testing for IgG and IgM antibodies in the CSF.

TABLE 95.3 Common Bacterial Pathogens and Initial Antibiotic Regimens for Suspected Bacterial Meningoencephalitis,[a] Listed by Age Group and Risk Factors

Patient Subgroup	Most Common Bacterial Pathogen	Most Common Intravenous Therapy
Neonates (up to 4 weeks)	*S. agalactiae, E. coli, L. monocytogenes, S. agalactiae,* gram-negative bacilli	Ampicillin (100 mg/kg/dose q8h for 0-7 days and 75 mg/kg/dose for 8-28 days) AND Cefotaxime (50 mg/kg every 8 hrs; may increase to 50 mg/kg q6h for 8-28 days)
Infants and children	*S. pneumoniae, N. meningiditis*	Ceftriaxone (100 mg/kg every day) OR Cefotaxime (75 mg/kg every 6 hrs)
Adults	*S. pneumoniae, N. meningiditis*	Ceftriaxone (2 g every 12 hrs) OR Cefotaxime (2 g q4–6h) AND Vancomycin (loading dose: 20–35 mg/kg actual body weight [not to exceed 3000 mg] or 20–25 mg/kg actual body weight not to exceed 3000 mg in patients with obesity, then 15–20 mg/kg actual body weight every 8–12 hrs)
Elderly	*S. pneumoniae, N. meningiditis, L. monocytogenes*	Ceftriaxone (2 g every 12 hrs) OR Cefotaxime (3 g every 6 hrs) AND Vancomycin (loading dose: 20–35 mg/kg actual body weight [not to exceed 3000 mg] or 20–25 mg/kg actual body weight not to exceed 3000 mg in patients with obesity, then 15–20 mg/kg actual body weight every 8–12 hrs) AND Ampicillin (2 g every 4 hrs)
Immunocompromised	*S. pneumoniae, N. meningiditis, H. influenzae*	Ceftriaxone (2 g every 12 hrs) OR Cefotaxime (3 g every 6 hrs) AND Vancomycin (loading dose: 20–35 mg/kg actual body weight [not to exceed 3000 mg] or 20–25 mg/kg actual body weight not to exceed 3000 mg in patients with obesity, then 15–20 mg/kg actual body weight every 8–12 hrs) AND Ampicillin (2 g every 4 hrs)
Suspected hospital-acquired organism	*S. aureus, S. epidermidis,* aerobic gram-negative bacilli	Vancomycin (15–20 mg/kg every 8 hrs) AND Cefepime (2 g every 8 hrs) OR Meropenem (2 g every 8 hrs)

Adapted from Dorsett M, Liang SY. Diagnosis and treatment of central nervous system infections in the emergency department. *Emerg Med Clin North Am.* 2016;34(4):917-942.[25]

[a]In addition to dexamethasone (adults 0.4 mg/kg IV, up to 10 mg; infants and children 0.15 mg/kg, up to 10 mg

PCR has improved the diagnosis of tuberculous meningitis as well and newer assays continue to show improved performance characteristics. One of the latest assays, Xpert Ultra, was recently shown to have a sensitivity of 95% (compared to previous assays and culture with a 45% sensitivity) and has been endorsed as the initial diagnostic test of choice by the World Health Organization.[19]

Bacterial Cultures

Bacterial cultures of CSF should be performed despite some organisms, such as mycobacterium, being difficult to culture. Although results of cultures will not be available in the ED, they can be helpful to the subsequent treatment team for guiding antimicrobial therapy if positive. Bacterial culture yields can be decreased in patients pretreated with antibiotics, depending on the timing of the antibiotics and the cultures. Although antigen testing holds promise, it alone cannot replace bacterial cultures at this time.

Additional Investigations

Other ancillary investigations such as echocardiography, body fluid cultures, chest X-ray, CT of the maxillary region, and urinalysis may be undertaken as necessary to evaluate suspected coexistent disease, such as a distant infection that may be seeding the CNS.

Characteristic EEG abnormalities have been associated with HSV type 1 encephalitis, including diffuse high-amplitude slow waves, temporal lobe spike-and-wave activity, and periodic lateralized epileptiform discharges, although these changes are not specific enough to make them diagnostic. More than half of patients with viral encephalitis may have an abnormal EEG, most commonly in patients with HSV; it is not routine however to obtain an EEG emergently in the ED and EEG is unlikely to acutely change management unless nonconvulsive status epilepticus is diagnosed.

MANAGEMENT

Initial management of the patient with suspected CNS infection focuses on ensuring CNS oxygenation and perfusion. In cases of severely elevated ICP, management is with endotracheal intubation, mannitol, hypertonic saline, and maintenance of eucapnia on the ventilator.

Bacterial Meningitis

Treatment of bacterial meningitis requires bactericidal antibiotics that penetrate the blood-brain barrier and achieve therapeutic CSF concentrations. Until the causative organism is identified, broad-spectrum coverage of the most common pathogens is indicated (Table 95.3). Ceftriaxone (2 g every 12 hours) or cefotaxime (3 g every 6 hours) are the most commonly used agents, with vancomycin (15–20 mg/kg every 8 hours) added to cover potentially resistant organisms. In neonates, especially those with hyperbilirubinemia, ceftriaxone should be avoided, because it displaces bilirubin from albumin binding sites and can further increase bilirubin levels in the blood. Cefotaxime is instead recommended in this population. We recommend high-dose ampicillin (2 g every 4 hours) be added in adults over 50 years old and infants younger than 1 month old (100 mg/kg/dose q8h for 0–7 days and 75 mg/kg/dose for 8–28 days) because they are at risk for *Listeria*. If *Listeria* meningitis is suspected, gentamicin may also have a mortality benefit if added to ampicillin, though this should be used cautiously in patients with renal dysfunction.

Patients who have had a recent hospitalization, especially for surgery, may be at risk for hospital-acquired antibiotic-resistant organisms and may benefit from broader coverage with cefepime (2 g every 8 hours) instead of ceftriaxone. In patients allergic to cephalosporins, meropenem or chloramphenicol is recommended. Linezolid (600 mg

every 12 hours) or moxifloxacin (400 mg once daily) with vancomycin can be used in cephalosporin-resistant strains of pneumococcus.

Treatment with corticosteroids (0.15 mg/kg up to 10 mg IV dexamethasone every 6 hours for 4 days) decreases mortality in patients with pneumococcal meningitis and decreases the incidence of hearing loss in patients with *H. influenzae* meningitis. Interestingly, this benefit has only been shown in high-income countries and not in low-income countries, likely secondary to better access to medications and specialist care in the former.[20] Though some data suggest benefit persists if started within 12 hours of antibiotic initiation, the first dose of steroids should be given with or 20 minutes before initiation of antibiotics in suspected adult bacterial meningitis. However, a recent large, prospective study showed an increased incidence of adverse outcomes related to dexamethasone in cases of *Listeria* CNS infections and therefore steroids should be discontinued if this organism is identified.[21]

Tuberculous Meningitis

Early antimicrobial intervention in acute tuberculous meningitis improves the patient's prognosis and a strong clinical suggestion of this disease is an appropriate indication to begin antituberculous therapy. A standard treatment regimen consists of 4-drug therapy with isoniazid (5 mg/kg once daily; max dose 300 mg), rifampin (20 to 30 mg/kg once daily; max dose 600 mg), pyrazinamide (<40 kg: 35 mg/kg/dose; 40 to 55 kg: 1000 mg daily; 56 to 75 kg: 1500 mg daily; 76 to 90 kg: 2000 mg daily), and ethambutol (<40 kg: 25 mg/kg/dose; 40 to 55 kg: 800 mg daily; 56 to 75 kg: 1200 mg daily; 76 to 90 kg: 1600 mg daily). Alternative dosing strategies exist that involve less-frequent dosing and can be considered with infectious disease consultation. Neurosurgical consultation may be required in cases of hydrocephalus or mass lesions. Corticosteroids have also been shown to decrease secondary complications, and we recommend an initial dose of 0.15 mg/kg of IV dexamethasone.

Fungal Meningitis

Because fungal meningitis most often has a prolonged course and can be difficult to diagnose in the ED, the initiation of antifungal treatment is rarely required in the ED unless clinical suspicion is high. Four agents are commonly used to treat fungal meningitis: amphotericin B, flucytosine, miconazole, and fluconazole. Of these, amphotericin B, either alone or in combination with flucytosine, is the most common regimen. Fluconazole can be used if flucytosine is not available and can be used as monotherapy if amphotericin B is not available, though it is associated with higher rates of treatment failure.

Viral Meningitis

The majority of viral meningitis cases have a short, relatively benign and self-limited course followed by a complete recovery. Acyclovir (10 mg/kg IV every 8 hours) is recommended in immunocompromised patients with HSV meningitis and should be considered based on the theoretical benefit in immunocompromised patients with VZV meningitis. Benefit has not been shown in HSV or VZV meningitis in immunocompetent patients. In these cases, as with most types of viral meningitis, care is mainly supportive, because no treatments have been shown to be effective for relieving symptoms, shortening the course of disease, or preventing disease progression.

Early cases of viral meningitis may be indistinguishable from bacterial meningitis, and diagnostic certainty may not be provided by initial CSF analysis. When doubt exists about the veracity of the diagnosis, it is reasonable to initiate workup and empiric antibiotics and admit the patient to the hospital.

Viral Encephalitis

In cases of suspected viral encephalitis, empiric IV acyclovir (10 mg/kg IV every 8 hours) is recommended as it targets both HSV and VZV, two common causes of this disease. Patients with CMV encephalitis can be treated with ganciclovir (5 mg/kg every 12 hours), although this diagnosis is unlikely to be made in the ED. Otherwise, patients should largely be treated supportively.

Central Nervous System Abscess

The location, size, and number of abscesses influences the choice of medical management, surgical excision, or aspiration. Consideration of empiric antimicrobial therapy is ideally accomplished in consultation with neurosurgical providers, as it is reasonable to withhold antimicrobial therapy prior to aspiration or surgical excision if an urgent neurosurgical intervention is planned. If neurosurgery is delayed, however, we recommend initiating empiric treatment, as prolonged time without antibiotics has been associated with adverse outcomes.

Abscesses originating from sinus or ear infections are treated with cefotaxime (2 g IV every 4-6 hours) or ceftriaxone (2 g IV every 12 hours) plus metronidazole (500 mg IV every 6 to 8 hours). Abscesses related to trauma or neurosurgical procedures require vancomycin for *S. aureus* or methicillin-resistant *S. aureus* coverage. Patients at high risk for tuberculous, fungal, or parasitic abscess may also receive coverage for the suspected etiologic agent. Corticosteroids may mitigate superimposed cerebral edema and a recent meta-analysis did not show an increase in mortality with their use.[22] We therefore recommend 10 mg IV dexamethasone for CNS abscesses associated with cerebral edema.

Spinal epidural abscesses should also be managed with a combined medical and surgical approach. Neurosurgical consultation should be obtained as soon as possible to evaluate the need for emergent intervention, particularly if neurologic deficits are present. Additionally, we recommend empiric vancomycin (loading dose: 20 to 35 mg/kg actual body weight [not to exceed 3000 mg] or 20 to 25 mg/kg actual body weight not to exceed 3000 mg in patients with obesity, then 15 to 20 mg/kg actual body weight every 8 to 12 hrs) and ceftriaxone (2 g IV every 12 hours) for antimicrobial treatment. When atypical organisms such as *Pseudomonas* are present or suspected, broader coverage is recommended with a fourth-generation cephalosporin (e.g., cefepime 2 g IV every 8 hours).

CSF Shunt Infection

After obtaining neuroimaging (either CT or rapid MRI protocol), management generally includes neurosurgical consultation and empiric antibiotics directed at skin flora, including *S. aureus and Streptococcus* as well as MRSA and *Pseudomonas.* We recommend vancomycin (loading dose: 20 to 35 mg/kg actual body weight [not to exceed 3000 mg] or 20 to 25 mg/kg actual body weight not to exceed 3000 mg in patients with obesity, then 15 to 20 mg/kg actual body weight every 8 to 12 hrs) and an anti-pseudomonal beta-lactam, such as cefepime (2 g every 8 hours).

Chemoprophylaxis

The risk for developing meningococcal meningitis is increased 400 to 800 times in individuals with close contact with an infected person. Close contacts at risk include health care workers exposed to the patient's secretions (as might occur during endotracheal intubation or nasotracheal suctioning), those exposed for a prolonged period (e.g., spending more than 8 hours less than three feet away from the patient such as roommates, intimate partners, daycare attendants) or those exposed to an infected person's oral excretions. At risk contacts should be treated with four doses of oral rifampin (600 mg every 12 hours) or a single dose of oral ciprofloxacin (500 mg). Pregnant women can receive a single intramuscular (IM) dose of ceftriaxone (250 mg). In addition, close contacts should be advised to

TABLE 95.4 Recommended Population for Prophylaxis and Antibiotic Dosing Regimens, Listed by Exposure Type

	Population	Medication	Dose	Frequency
N. meningitidis	Close contacts (roommates, partners, daycare workers), health care workers exposed to secretions	Ciprofloxacin	500 mg	Once
		Rifampin	600 mg	Every 12 hours for 2 days
		Ceftriaxone	250 mg	Once (preferred in pregnancy)
H. influenzae	Immunocompromised children (including unvaccinated), contacts with unvaccinated children <4 years old	Rifampin	20 mg/kg	Daily for four days
All others (bacterial, viral, fungal)	All	None	None	None

watch for fever, sore throat, rash, or any symptoms of meningitis. If there are signs of active meningococcal disease, the close contact should be hospitalized for IV antibiotics as presented above, because rifampin is not recommended as therapy against invasive meningococcal disease.

Rifampin prophylaxis (20 mg/kg once daily; max dose 600 mg for four days) is currently recommended by the Centers for Disease Control (CDC) for contacts of patients with *H. influenzae* meningitis in households with members aged younger than 4 years who have not completed their vaccination schedule or immunocompromised children (<18 years old), regardless of their vaccination status. It is only recommended in childcare facilities caring for immunocompromised or unvaccinated children in instances where two confirmed cases have occurred. There is no current recommendation for chemoprophylaxis in pneumococcal meningitis. See Table 95.4 for a summary of the guidelines.

Immunoprophylaxis

Although vaccinations against pathogens implicated in CNS infection are not routinely administered in the ED, it is useful to be aware of currently available vaccinations so that patients and family members may be queried regarding their risk for vaccine-preventable diseases.

A quadrivalent meningococcal vaccine based on the polysaccharide capsule and conferring protection against group A, C, Y, and W-135 meningococci has been in routine use since it was approved in 1978. It is currently recommended for routine use in children and adolescents aged 11 to 21 years old. People living in close quarters with other individuals (e.g., college students, military recruits), travelers to endemic areas, as well as asplenic individuals are at increased risk of meningococcal disease and should receive the vaccine. Two vaccines targeting serogroup B also have been approved for use in the United States since 2014 but have yet to be routinely administered. The capsular polysaccharide vaccines used to immunize adults are not protective in children younger than 2 years old because of poor antibody response.

The development of a highly effective pneumococcal vaccine has been hampered by the large number of serotypes of the organism. Despite this, a single dose of the vaccine should be considered for elderly or debilitated patients, especially those with pulmonary disease, and for patients with impaired splenic function, splenectomy, or sickle cell anemia. Vaccination against pneumococcus is recommended in patients who have been treated for an episode of pneumococcal pneumonia to prevent recurrent infection. A heptavalent conjugated pneumococcal vaccine has also been developed and is recommended for universal childhood immunization by the ACIP.

A conjugate vaccine effective against Hib has been developed for use in the pediatric population and is recommended for all infants starting at 2 months.

DISPOSITION

With the exception of obvious presentations of viral meningitis, the majority of CNS infections require inpatient evaluation and treatment for IV antimicrobials, monitoring for acute decompensation, following of cultures, specialist input, and potential surgical intervention, depending on the infection. Because normal CSF cell counts do not completely exclude bacterial meningitis, patients with a high likelihood of meningitis require hospitalization with frequent reevaluation, antimicrobial therapy, and possible repeat LP.

Some patients with suspected viral meningitis should be considered for hospitalization. These include patients who are immunocompromised, patients with more severe disease or refractory symptoms, patients who are unable to tolerate oral intake, and those in whom the diagnosis is unclear.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 95: QUESTIONS AND ANSWERS

1. Which of the following presentations should receive a lumbar puncture to rule out CNS infection:
- **a.** 23-year-old healthy female with fever and stiff neck but minimal headache.
- **b.** 32-year-old male with diabetes and unexplained altered mental status.
- **c.** 67-year-old male with fever and new right arm weakness.
- **d.** All of the above

Answer: D. All patients with fever, headache, altered mental status or new neurologic deficits should be considered for possible meningitis or encephalitis. Lumbar puncture and CSF analysis is the most reliable method for assessing for CNS infection; imaging and blood tests are inadequate alone.

2. Patients with suspected bacterial meningitis should receive which of the following interventions FIRST?
- **a.** Non-contrast CT of the head
- **b.** MRI with contrast of the head
- **c.** Lumbar puncture to evaluate for bacterial cause
- **d.** Steroids and antibiotics for presumed bacterial infection

Answer: D. Patients with suspected bacterial meningitis should receive steroids and antibiotics first to cover for the possibility of bacterial infection. Treatment should not be delayed obtaining neuroimaging first (if necessary), or until the lumbar puncture is completed. However, lumbar puncture should still be obtained expeditiously, because culture yields begin to decrease after 1 hour.

3. Which of the following antimicrobial regimens would be appropriate coverage for suspected meningitis in a 40-year-old patient with no comorbidities in a country with high antibiotic use?
- **a.** Ceftriaxone
- **b.** Ceftriaxone and vancomycin
- **c.** Acyclovir and ceftriaxone
- **d.** Cefotaxime, vancomycin, and ampicillin

Answer: B. Ceftriaxone and vancomycin are the appropriate initial antibiotics for suspected meningitis or encephalitis in an adult patient. Ceftriaxone alone may be appropriate in lower income countries with less antibiotic use and resistance. Ampicillin is added for patients older than 50 years and neonates due to risk of Listeria. Acyclovir should be added for immunocompromised patients with suspected HSV or VZV infections. Cefepime should be used instead of ceftriaxone in patients at his risk for pseudomonas infections (e.g., recent surgical procedures).

CHAPTER 95: QUESTIONS AND ANSWERS—cont'd.

4. What is the most appropriate imaging test for a patient with low back pain, low-grade fever, and a history of IV drug use?
- **a.** CT lumbar spine without contrast
- **b.** CT myelogram of the lumbar spine
- **c.** MRI of the lumbar spine with contrast
- **d.** MRI of the cervical, thoracic and lumbar spine with contrast

Answer: D. Because exam findings can be inaccurate, patients with suspected epidural abscess should receive an MRI with contrast of their entire spine. Presentations can be subtle and may not include all of the classical features such as fever and back pain; patients must be queried for potential risk factors. CT myelogram of the entire spine is an acceptable alternative for patients unable to undergo an MRI.

5. Contacts with exposure to which of the following types of meningoencephalitis should receive prophylactic antibiotics?
- **a.** Pneumococcal
- **b.** Tuberculous
- **c.** Meningococcal
- **d.** West Nile

Answer: C. Close contacts with exposure to patients diagnosed with meningococcal meningitis or encephalitis should receive chemoprophylaxis, most commonly with oral rifampin. Chemoprophylaxis is also recommended for immunocompromised close contacts of patients with H. influenzae CNS meningitis.

96

Thought Disorders

Matthew P. Kelly and Dag Shapshak

KEY CONCEPTS

- Thought disorder symptoms can be precipitated by psychiatric, underlying medical, and toxicologic etiologies.
- Diagnostic testing should be patient specific and based on the particular medical processes that the clinician feels may be causing or exacerbating the thought disorder, rather than panels of routine tests.
- Consider nonphysical interventions first when appropriate, but chemical sedation or physical restraints may become immediately necessary for patients who demonstrate life-threatening aggressive and dangerous behaviors.
- Appropriate disposition depends on the etiology of the underlying psychosis and response to treatment while addressing patient and community safety considerations. Psychiatric consultation is often required.

FOUNDATIONS

Background and Importance

Patients with a history of mental disorders have a higher rate of emergency department (ED) visits than the general population. Patients with at least one primary psychiatric visit to an ED are four times more likely to become frequent ED users compared to patients with none, and the severity of mental illness correlates with the frequency of ED utilization.[1] The rate of ED visits for patients with mental disorders has increased substantially over the last several years for both adults[2] and children.[3] Schizophrenia is among the top 10 most disabling and economically catastrophic medical disorders as ranked by the World Health Organization, and the global burden of disease continues to increase,[4] affecting almost 1% of the world's population. Slightly more men than women are affected and at a younger age. The modal age of onset is between 18 and 25 years for men and between 25 and 35 years for women.

Groups at high risk for developing schizophrenia include migrants, urban dwellers, people born in late winter to early spring, and those with advanced paternal age at conception. The mortality rate for patients with schizophrenia is 2.5 times that of the general population and continues to grow, especially in populations with low socioeconomic status. Patients diagnosed with schizophrenia have a mean life expectancy almost 15 years shorter than the general population and a 5% to 10% life-time risk of death by suicide.[5] Financial costs associated with schizophrenia are disproportionally high relative to other chronic mental and physical health conditions, reflecting both direct costs of care, and indirect costs of lost productivity, criminal justice involvement, social needs, and homelessness.

Pathophysiology

Although the etiology of schizophrenia is multifactorial, it has a substantial genetic component with approximately 80% of disease expression attributed to genetic factors. In addition to genetic factors, environmental and neurodevelopmental influences increase risk of the disease.[6] Such influences include perinatal stress and hypoxia, poor nutrition, infections, and vitamin D and zinc deficiencies. Newer research is showing that schizophrenia may be detectable at earlier stages of development, prior to the first psychotic episode, which may open the window for earlier interventions.[7]

Alterations in the dopaminergic, serotonergic, cholinergic, glutamatergic, and GABA-ergic pathways have been implicated in the pathophysiology of schizophrenia. Symptoms may be caused by cortical excitatory-inhibitory imbalance and subcortical dopamine dysregulation in the frontal, temporal, and mesostriatal brain regions.[8] Imaging and postmortem studies have revealed disturbed oligodendroglia-related processes, altered gene expression, disturbed myelination, and altered numbers of oligodendrocytes in the brains of patients with schizophrenia.[9] Genetic predisposition, coupled with early neurodevelopmental disturbances during postnatal brain maturation, are thought to trigger the onset of overt schizophrenia.

Patients often present to the ED via family, police, or EMS exhibiting symptoms of disorganized thought and behavior. They may express language, ideas, and behavior found to be inappropriate and disruptive to accepted patterns of social interaction. Whether the issue involves thought content (delusions), hallucinations or thought form (structure of thinking), the clinical impression is that of psychosis (detachment from reality and societal norms). Acutely psychotic patients raise concerns for the safety of themselves, those around them, and those attempting to care for them.

The emergency clinician's role is to prevent and control violent and disruptive behavior while simultaneously determining if the underlying etiology of the psychosis is functional versus organic in nature. Functional causes include schizophrenia and schizophrenia-like illness, mania, and mood disorder–associated psychosis. Organic causes can mimic a functional psychosis. Medication effects, substance abuse,

and certain medical disorders must be excluded before symptoms of psychosis can be attributed to an underlying psychiatric illness.

CLINICAL FEATURES

Thought disorders broadly affect mental activity and can be associated with varying degrees of functional impairment. Schizophrenia is the most common thought disorder characterized by psychotic symptoms of hallucinations, delusions, and disorganized speech. The core psychopathology of schizophrenia and other thought disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) includes both negative and positive symptoms. Negative symptoms include decreased motivation, diminished expressiveness, cognitive deficits involving impaired executive functions, memory, and speed of mental processing.[10]

Positive symptoms of schizophrenia are the most easily identified and can be classified as delusions, hallucinations, and abnormal motor behavior in varying degrees of severity. Significant cognitive symptoms include disorganized speech, thought, and attention, which may impair the individual's ability to communicate. Hallucinations are the perception of a sensory process in the absence of an external source. They can be auditory, olfactory, visual, gustatory, or somatic in nature. The vast majority of patients with schizophrenia suffer with auditory hallucinations.

Patients with schizophrenia typically display disorganization of behavior and cognition. They use disjointed speech patterns that reflect poor organization of thought and lack of a coherent focus of ideas. Their speech patterns are tangential and circumstantial, causing the narrative to wander away from the initial topic of conversation. More severe thought disorders include derailment, neologisms (invented words), word salad (confused, incomprehensible language), and preservations (severely repetitious language). In debilitating cases, there may be no understandable content and speech is utterly incomprehensible.

A separate group of patients with a more extreme deficit in communication are those suffering from catatonia. Catatonia includes immobility, stupor, mutism, resistance to instructions, oppositionalism, echo phenomena, and withdrawal. Although classically associated with schizophrenia because of the profound communication and thought deficiencies, recent studies highlight a strong association of catatonia with mood and medical disorders with only a minority diagnosed with schizophrenia.[11] Treatment is with benzodiazepines.[12]

The development of schizophrenia involves three phases: premorbid, progressive, and residual phases. The premorbid phase is characterized by the development of negative symptoms with deterioration in personal, social, and intellectual functioning. The first indications of schizophrenia typically appear in the late teens and early twenties. Children who later develop schizophrenia may demonstrate social awkwardness, physical clumsiness, and lower IQs than peers and siblings. There may be years of subtle changes in behavior and declining function in school and interpersonal relationships. The progressive phase is often precipitated by a stressful life event precipitating the development of positive symptoms. The progressive phase is said to begin when the patient develops the classic characteristics of schizophrenia mentioned earlier. Patients can become agitated or exhibit a hypervigilant withdrawal state characterized by rocking, staring, violence, or bizarre behavior. It is during the progressive phase that the patient is most likely to be brought to the ED by family, friends, police, or concerned bystanders. The residual phase is characterized by persistence of progressive symptoms and disability. Impaired social and cognitive ability, poor hygiene, delusions, bizarre behavior, and social isolation, and homelessness can all occur. On average, functional outcome is poor and patients have varying levels of treatment resistance, especially in those with predominantly negative symptoms.[13]

BOX 96.1 Medical Disorders That May Cause Acute Psychosis

Metabolic Disorders
- Hypercalcemia
- Hypercarbia
- Hypoglycemia
- Hyponatremia
- Hypoxia

Inflammatory Disorders
- Sarcoidosis
- Anti-NMDAR encephalitis
- Systemic lupus erythematosus
- Temporal (giant cell) arteritis

Organ Failure
- Hepatic encephalopathy
- Uremia

Neurologic Disorders
- Alzheimer disease
- Cerebrovascular disease
- Encephalitis (including HIV infection)
- Encephalopathies
- Epilepsy
- Huntington disease
- Multiple sclerosis
- Neoplasms
- Normal-pressure hydrocephalus
- Parkinson disease
- Pick disease
- Wilson disease

Endocrine Disorders
- Addison disease
- Cushing disease
- Panhypopituitarism
- Parathyroid disease
- Postpartum psychosis
- Recurrent menstrual psychosis
- Sydenham chorea
- Thyroid disease

Deficiency States
- Niacin
- Thiamine
- Vitamin B_{12} and folate

HIV, Human immunodeficiency virus.

DIFFERENTIAL DIAGNOSES

Medical Disorders

Numerous acute and chronic medical conditions can precipitate thought disorders and mimic acute psychosis (Box 96.1). Patients with underlying psychiatric diseases may develop medical conditions that can exacerbate behavioral symptoms and cloud the distinction between psychiatric and organic brain disease.

BOX 96.2 Pharmacologic Agents That May Cause Acute Psychosis

Antianxiety Agents
- Alprazolam
- Chlordiazepoxide
- Clonazepam
- Clorazepate
- Diazepam
- Ethchlorvynol

Antibiotics
- Isoniazid
- Rifampin

Anticonvulsants
- Ethosuximide
- Phenobarbital
- Phenytoin
- Primidone

Antidepressants
- Amitriptyline
- Doxepin
- Imipramine
- Protriptyline
- Trimipramine

Cardiovascular Drugs
- Captopril
- Digitalis
- Disopyramide
- Methyldopa
- Procainamide
- Propranolol
- Reserpine

Drugs of Abuse
- Alcohol
- Amphetamines
- Cannabis
- Cocaine
- Hallucinogens
- Opioids
- Phencyclidine
- Sedative-hypnotics

Miscellaneous Drugs
- Antihistamines
- Antineoplastics
- Bromides
- Cimetidine
- Corticosteroids
- Disulfiram
- Heavy metals

Primary medical conditions are more commonly associated with the new onset of symptoms, acute changes in mental status, recent fluctuations in behavioral symptoms, onset in fifth decade of life or later, the presence of nonauditory hallucinations, lethargy, abnormal vital signs, and poor performance on cognitive testing, particularly orientation to time, place, and person. The onset of psychotic symptoms after a patient has been admitted to a medical care setting is often caused by a medical disorder.

Primary psychiatric conditions are more commonly associated with auditory hallucinations, family history of psychosis, and insidious onset in the late teens to mid-twenties, stable vital signs, and normal orientation. Medical delirium is common in elders and special attention should be paid to patients who develop psychosis later in life.[14]

Patients intoxicated with drugs of abuse are often brought to the ED with bizarre or dangerous behavior. Street drugs such as cocaine, cannabinoids, kratom, amphetamines, bath salts, hallucinogens, and synthetic cannabinoids affect the serotonergic and dopaminergic pathways and can provoke psychotic reactions resembling a primary psychiatric condition, or can unmask latent schizophrenia.[15] Certain pharmacologic agents may also cause acute psychosis mimicking a thought disorder (Box 96.2).

Psychiatric Disorders

Once medical causes have been reasonably ruled out, it can be helpful to classify the type of functional psychosis the patient is exhibiting. The DSM-5 uses four classes of information to distinguish among the various types of psychosis: type of psychotic symptom, course of illness, consequences of illness, and exclusions. Each category can help distinguish schizophrenia from other psychiatric disorders that include psychosis among their symptoms. The DSM-5 definition of schizophrenia is included in Box 96.3.

BOX 96.3 Diagnostic Criteria for Schizophrenia From *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (e.g., frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (i.e., diminished emotional expression or avolition)

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

A brief psychotic disorder involves the sudden onset of psychotic symptoms in response to major stress and lasts from several days up to one month. Peripartum psychosis is included under the diagnosis of brief psychotic disorder. Patients with schizophreniform disorder have similar symptoms to a brief psychotic disorder that lasts longer than one month but less than 6 months. Roughly one in three patients with schizophreniform disorder recover within 6 months; the others progress to develop clinical schizophrenia. Patients diagnosed with mood disorders may develop psychotic symptoms as part of their disease. If psychotic symptoms develop during periods of mood disturbances, the diagnosis of mood disorder with psychotic features applies. If symptoms consistent with schizophrenia persist for more than 2 weeks in the absence of prominent mood episode, the diagnosis of schizoaffective disorder is made. Patients with personality disorders may occasionally develop brief psychotic episodes, especially under duress. None of the aforementioned disturbances can be attributable to the effects of a substance or another medical condition.[16]

Delusional disorder is characterized by one or more delusions that are present for longer than one month, and the DSM-5 criteria for schizophrenia have not been met. Patients may believe famous people are in love with them (erotic type) or that they have extraordinary power or possess a special relationship with a deity or famous person (grandiose type). Other common delusions are sexual partners being unfaithful (jealous type), physical defect, or medical condition (somatic type). Function is not typically impaired, and behavior is often not bizarre separate from the impact of the delusions. Individuals may appear and behave normally when not actively discussing their delusions, but social, marital, work, and legal problems can result from the delusional beliefs.

DIAGNOSTIC TESTING

Diagnostic tests are indicated when a patient's clinical presentation cannot be explained by the history and physical examination alone. Often there is not enough information readily available to accurately ensure that the patient is suffering from a thought disorder alone. The potential medical causes of thought disorders are very broad; therefore, if a medical evaluation is indicated, testing should be patient specific and based on the particular medical processes that the clinician feels may be causing or exacerbating the thought disorder. The clinical judgment of the treating physician, rather than panels of routine tests, should be used to efficiently and appropriately guide diagnostic testing.

The evaluation of a "first-time" psychosis or thought disorder presentation in an emergency patient differs substantially from the evaluation of a patient with chronic disease who is experiencing recurrent symptoms. The evaluation for the first-time thought disorder patient may include a larger, more detailed laboratory and radiological evaluation. Complete blood counts, electrolyte panels, glucose levels, thyroid function, urine testing, vitamin B_{12}, and rapid plasma regain (RPR) testing are useful in certain clinical situations and should be ordered as appropriate for individual patients.

Neuroimaging for intracranial injury, vasculitis, demyelinating diseases, tumor, cerebrovascular disease, or abscess may be indicated based upon findings noted on the history and physical examination. A 2017 guideline from the American College of Emergency Physicians (ACEP) recommends the use of individual patient risk assessment to guide the ordering of brain imaging in the ED for patients presenting with new-onset psychosis without focal neurologic deficit.[17] The ACEP medical clearance guidelines are included in Box 96.4.

The new onset of primary thought disorders is rare in older adults. Medical illness often presents differently in elders, and a complete history and physical examination alone may not detect important medical presentations.[18] Geriatric medical assessment is more complex due to increased comorbidities, medication use, and variable baseline functional status with vague and nonspecific symptoms. Even for patients who have a previous psychiatric history or diagnoses, the presence of organic processes that may be exacerbating or contributing to the psychiatric decompensation should be considered. Most often, infections, electrolyte abnormalities, and medication side effects are the offending process. In one study, even after extensive ED testing was performed, a significant percentage of patients admitted to a geriatric psychiatric unit still required transfer out to a medical unit. The authors however concluded that further ED testing would not have prevented the transfers, which likely were related to the ongoing complex medical management issues rather than being related to missed opportunities for diagnosis in the ED.[18]

Ancillary testing beyond that required for medical clearance of psychiatric emergency patients rarely alters care, especially for patients with an established diagnosis of schizophrenia or other chronic thought disorders. Policies that require panels of testing prior to psychiatric admission are costly and unnecessary.[19] One of the largest unnecessary costs is incurred with the routine use of urine drug screens, which have been found to rarely alter disposition for psychiatric patients from the ED, especially when combined with a good substance abuse history. Greater emphasis should be placed on identifying a clinical toxidrome and history of use when attempting to determine if drugs and medications are contributing to the symptoms of psychosis.

BOX 96.4 Summary of ACEP Medical Clearance Guidelines

Level B Recommendation

1. In adult ED patients with primary psychiatric complaints, diagnostic evaluation should be directed by the history and physical examination.
2. Routine laboratory testing of all patients is of low yield and need not be performed as part of the ED assessment.

Level C Recommendations Regarding UDS

1. Routine urine toxicologic screens for drugs of abuse in alert, awake, cooperative patients do not affect ED management and need not be performed as part of the ED assessment.
2. Urine toxicologic screens for drugs of abuse obtained in the ED for the use of the receiving psychiatric facility or service should not delay patient evaluation or transfer.

Level C Recommendations Regarding EtOH

1. The patient's cognitive abilities, rather than a specific blood alcohol level, should be the basis on which clinicians begin the psychiatric assessment.
2. Consider using a period of observation to determine if psychiatric symptoms resolve as the episode of intoxication resolves.

Data from: Lukens TW, Wolf SJ, Edlow JA, et al. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emergency Med.* 2006;47:79–99.

American College of Emergency Physicians Clinical Policies Subcommittee on Critical Issues, et al. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med.* 2017;69(4):480-498.

MANAGEMENT

Maintaining patient and staff safety are important when a patient presents with aggressive and unpredictable psychotic behavior. Risk factors for violence in patients with schizophrenia include extreme excitement, prior violence, auditory hallucinations, systematization of delusions, incoherence of speech, and long duration of illness. In contrast, traits such as substance abuse and antisocial episodes are not recognized as significant violence-associated factors. Strategies to control disruptive and violent behavior in psychosis and thought disorders include de-escalation techniques, chemical sedation, and physical restraints.

Although chemical and physical intervention can be appropriate when patients are demonstrating dangerous behavior, verbal de-escalation should be considered first. The clinician should demonstrate a calm, nonjudgmental demeanor while showing appropriate concern and avoiding excessive stimulation, posturing, and prolonged eye contact. The patient should be given an opportunity to express their concerns, as well as identify unmet needs that can be easily corrected (e.g., inadequate pain control, communication failures, or social concerns). If available, consider recruiting trusted others (e.g., family, friends, case managers) to help prevent further agitation.

TABLE 96.1 Common Drugs for Sedation

Drug	Usual Adult Dose	Adverse Events
Midazolam	2.5 to 5 mg IM (rapid onset)	Respiratory depression Oversedation Hypotension Paradoxical excitation reaction in patients with organic brain disease
Lorazepam	1 to 2 mg PO or IM	
Diazepam	5 to 10 mg PO or IM (longer acting)	
Haloperidol	5 to 10 mg PO or IM	Increased mortality risk in elderly dementia-related psychosis
Ziprasidone	10 to 20 mg PO or IM	
Olanzapine	5–10 mg PO or IM	
Loxapine	10 mg PO or INH	Caution in prolonged QT or history of neutropenia

IM, Intramuscular; *INH*, Inhaled; *PO*, per os (by mouth).

When verbal de-escalation is ineffective or inappropriate, physical restraint or use of seclusion may be necessary. Risk factors predicting the need for restraint or seclusion include referrals initiated by a third party, patients arriving to the ED in restraints, and clinician perception of the patient as severely disruptive, already exhibiting psychosis, or experiencing a manic episode.

Chemical restraint for psychomotor agitation is a common and necessary intervention. Speed of onset and reliability of delivery are two important factors to consider when selecting a route of administration of sedation in the behaviorally disturbed patient. Oral sedation is indicated when the patient can be safely verbally de-escalated, is not at imminent risk of harm to self, and agrees to take oral medications. When more expedient sedation is required, parenteral and inhaled routes have the advantage of immediate effect and titration of dosing. Inhaled loxapine has also been found to be a safe and effective alternative medication to reduce agitation with rapid onset[20,21] and reduces risks of needle sticks in an un-cooperative patient. The goal of titration in this setting is the induction of rousable sleep, not unconsciousness.

Benzodiazepines and antipsychotics are the two medications most commonly used for chemical restraint with the trend of moving towards use of second-generation antipsychotics.[22,23] Using a single agent or, for more disturbed patients, a combination of the two classes, can be considered. Common agents and dosages are listed in Table 96.1.

Combined with concurrent physical restraint and the risk of previously ingested intoxicants, there is significant risk for over-sedation and respiratory compromise. The combination of haloperidol and lorazepam can cause respiratory depression in patients, with a significant number experiencing a hypoxic event. As a result, we recommend the use of pulse oximetry or CO_2 monitoring in chemically restrained patients to detect early signs of respiratory depression. In addition to monitoring of airway and level of consciousness, sedated and restrained patients should have frequent behavioral monitoring. The use of physical restraints may cause excess pressure on the patient's neck, chest or abdomen, and requires ongoing direct visualization. Potentially hazardous articles and possessions should be removed from the patient's area. Restrained patients are known to forcibly remove Foley catheters without deflation of the balloon if their limbs are released prior to removal of the catheter, resulting in urethral injury.

DISPOSITION

Making an appropriate disposition for patients with decompensated thought disorders is often difficult in today's emergency medicine practice environment. Although institutional and community psychiatric resources vary widely by region, there appears to be a nationwide trend of diminishing psychiatric referral resources in the presence of rising numbers of psychiatric-related ED visits. The number of inpatient psychiatric beds nationwide has decreased, and many EDs "board" psychiatric patients for extended periods of time.

Appropriate disposition is based on the etiology of the underlying psychosis, response to treatment, consideration of patient and community safety, and the availability of an appropriate outpatient follow-up plan. Patients who are actively suicidal, dangerous to others, possess severe mental debilitation precluding self-care, or are having their first psychotic episode should be hospitalized.[17] The evaluation and disposition of potentially suicidal patients is discussed in Chapter 101. Psychiatric consultation can help confirm safety for discharge, help facilitate inpatient admission or transfer, and aid in developing an outpatient follow-up plan. Telemedicine is emerging as a technology that may ease the growing lack of adequate psychiatric resources for ED patients by facilitating urgent psychiatric consultation. Telemedicine can often be used safely and is not associated with significant differences in care when compared with face-to-face psychiatric evaluations.

Medication noncompliance is a common reason for a known schizophrenic to present to the ED with a decompensated psychotic episode. A patient whose psychosis stabilizes in the ED with medication can sometimes be safely discharged back into the community. Safe discharge planning can be accomplished provided that the patient has adequate ability to care for self and does not pose a risk of harm to self or others. Insight by the patient and judgment to adhere to an agreed course of action, including taking medication, is typically required. Patients with severe underlying psychiatric illnesses may have some degree of persistent mental disability even when optimally treated. For these patients, recruiting family or friends familiar with the patient can help establish that the patient is back to his or her baseline to ensure safety.

A safe transition to the community setting requires adequate social support, including follow-up with a mental health service. However, even when appropriately discharged, patients with a history of alcohol or drug dependence, dementias, psychotic disorders, autism, impulse control disorders, and personality disorders are at high risk for ED recidivism with repeat visits within 12 months. Uninsured status was also highly associated with repeat psychiatric admission and ED visits.[24]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 96: QUESTIONS AND ANSWERS

1. Which of the following pharmacologic agents have been implicated in causing acute psychosis?
- **a.** Aripiprazole, hydralazine, nitroglycerin
- **b.** Diazepam, rifampin, captopril
- **c.** Hydrochlorothiazide, acetaminophen, albuterol
- **d.** Lorazepam, salsalate, rocuronium
- **e.** Penicillin, ceftriaxone, risperidone

Answer: B. Box 96.2 provides an extensive list of other agents that may cause psychosis.

2. Rapid tranquilization using a neuroleptic agent would be indicated in which of the following cases?
- **a.** An intoxicated schizophrenic
- **b.** Anticholinergic psychosis
- **c.** A lactating schizophrenic
- **d.** A phencyclidine overdose
- **e.** A pregnant schizophrenic

Answer: A. Neuroleptics are contraindicated in choices B to E. They should not be the sole agent for alcohol withdrawal but would be useful for acute psychotic agitation.

3. A 45-year-old woman presents to the ED complaining of severe anxiety and unrest. She has a history of moderate schizophrenia, for which she was placed on olanzapine 2 months prior. She has been compliant. Physical examination is remarkable for the presence of anxiety, clear sensorium and orientation, and normal speech. She is restlessly pacing the room and reports being compelled to keep moving. Urine drug screen is negative. What would be the most appropriate therapy?
- **a.** Benztropine orally
- **b.** Lorazepam orally
- **c.** Olanzapine intravenously
- **d.** Psychiatry consultation
- **e.** Ziprasidone intravenously

Answer: A. Akathisia is a state of motor restlessness characterized by a physical need to be constantly moving. The patient does not want to do so but feels compelled. It is most commonly seen in middle-aged patients within the first few months of starting treatment. It may be mistaken for an acute deterioration, but psychotic features are not increased. Treatment is with oral beta-blockers and anticholinergics (benztropine).

4. What is the most common adverse effect seen with neuroleptic agents?
- **a.** Akinesia
- **b.** Dystonia
- **c.** Orthostatic hypotension
- **d.** Pseudoparkinsonism
- **e.** Tardive dyskinesia

Answer: B. Dystonia occurs in 1% to 5% of this patient population. The reaction occurs because of a dopaminergic pathway disruption with a resulting cholinergic predominance. Anticholinergics should be administered parenterally (Benadryl 25 to 50 mg intravenous [IV] or Cogentin 1 or 2 mg IV), followed by 48 to 72 hours of oral follow-up treatment to prevent recurrence. Patients may experience tongue protrusion (buccolingual crisis), upward eye deviation (oculogyric crisis), back arching (opisthotonus), and, rarely, laryngospasm. Symptoms may lessen with voluntary muscle action and increase with stress.

CHAPTER 96: QUESTIONS AND ANSWERS—cont'd

5. A 27-year-old known schizophrenic is brought to the ED for altered mental status. His only known medication is clozapine, which he started 4 weeks ago with subsequent dose increases. He has no other past history. Physical examination reveals a muscular man who is somnolent and diaphoretic. He withdraws all extremities stiffly and grimaces in pain. Vital signs are temperature, 40.5°C; heart rate, 146 beats per minute; blood pressure, 205/125 mm Hg; and respiratory rate 28 breaths per minute. Rectal examination is guaiac positive. Foley placement shows brown urine. What should be the next diagnostic maneuver?

a. Creatine kinase level
b. Head computed tomography (CT) scan
c. Lumbar puncture
d. Thyroid hormone levels
e. Urine drug screen

Answer: A. Neuroleptic malignant syndrome is an idiopathic condition clinically similar to serotonin syndrome and malignant hyperthermia. Milder cases may be confused with serotonin syndrome. Severe cases, related to possible hypothalamic dysfunction, present with fever, rigidity, altered mental status, autonomic instability, elevated creatine phosphokinase (CPK), and possibly rhabdomyolysis. It is seen with both typical and atypical antipsychotics and generally occurs in the first few weeks of treatment. Complications may include hepatic/renal failure, gastrointestinal (GI) hemorrhage, and respiratory failure. Severe cases may require intravenous dantrolene or dopamine agonists (e.g., bromocriptine).

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Mood Disorders

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KEY CONCEPTS

- Patients with apparent mood disorders should be evaluated for medical disorders, medication effects, or substance abuse or withdrawal because these conditions can mimic both depression and mania.
- Mood disorders should be suspected in patients with multiple, vague, nonspecific complaints and in patients who are frequent, heavy users of medical care.
- Patients with mood disorders should be assessed for their suicide potential.
- Pharmacologic treatment and linkage to care after discharge are important parts of managing mood disorders in the emergency setting.

FOUNDATIONS

Background and Importance

Mood is a subjective emotional state. It is normal human experience to have fluctuations in mood in response to occurrences in everyday life. A change in mood becomes a "mood disorder" when it significantly impairs functioning. In the emergency department (ED), patients with mood disorders often present grossly debilitated, with thoughts of suicide, homicide, or profound self-neglect. These patients frequently present in moments of emotional crisis, but this may not be their presenting complaint. Approximately one-fourth to one-third of ED patients screen positive for mood disorders.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), divides mood disorders into two broad categories: depressive disorders and bipolar disorders.[1] Mood disorders may also be due to a general medical condition or substance-induced mood disorders. Because the specific pathophysiologic mechanisms of these disorders are not fully understood, they are categorized by groupings of symptoms that persist for defined lengths of time.

EPIDEMIOLOGY

The World Health Organization (WHO) ranks major depressive disorder as one of the most prevalent and disabling diseases in the world.[2] The 12-month prevalence for major depressive disorder is 5% and the lifetime prevalence is 13%. Patients with major depressive disorder frequently have other comorbid mental health issues, including anxiety disorders, personality disorders, and substance use disorders.

The lifetime prevalence of bipolar spectrum disorders is approximately 4%. Both severe depression and mania are serious and potentially life-threatening. Up to 80% of patients with bipolar disorder will exhibit suicidal behavior, and half will attempt suicide. Suicidal behavior can occur during all phases of bipolar disorder, but patients experiencing a depressed or a mixed episode are at higher risk, especially those with severe depressive symptoms and a sense of hopelessness.

Doctors, including residents and medical students, die by suicide at twice the rate of the general population, with 300 to 400 physicians dying by suicide every year. This also means doctors are in the highest risk profession for suicide. Unlike the general population, male and female physicians have equal rates of suicide attempts and suicide completion. While the high rate of suicide among physicians may seem counterintuitive, concerns about privacy, accessibility of services, and lack of time are commonly stated barriers to physicians seeking help. As a result, doctors fare worse with burnout, depression, and suicide than almost anyone else.[3]

Neuroanatomy

Neuroimaging studies of the brain suggest that abnormalities in certain areas and the interconnections between those areas may be involved mood disorders. A common magnetic resonance imaging (MRI) finding in patients with mood disorders, especially bipolar disorder, is an increased occurrence of subcortical hyperintensities in the periventricular areas, basal ganglia, and thalamus. High-resolution MRI demonstrates reduced volumes in the hippocampus, orbital cortex, and anterior cingulate. These findings are associated with more severe illness, bipolar disorder, and increased cortisol levels. Volume reduction in the hippocampus is associated with high illness chronicity.

The amygdala is a clustering of nuclei that process emotional stimuli, especially fear, anger, and sadness. Functional neuroimaging suggests that amygdala activity is increased when the subject is exposed to emotionally relevant stimuli. The amygdala has connections throughout the brain. A decreased amygdala volume has been associated with unipolar depression.

PATHOPHYSIOLOGY

The pathophysiology of the mood disorders is not well established, but much is known about the neurophysiology, genetics, and psychosocial aspects of the disorders.[4,5]

Neurophysiology

Antidepressants work by increasing the availability and activity of serotonin and norepinephrine at the synapse to stimulate the postsynaptic neuron. This is done by direct binding to the presynaptic and postsynaptic receptors, blocking reuptake of the neurotransmitter or inhibiting the enzymatic breakdown of the neurotransmitter. Because norepinephrine and serotonin systems traverse large portions of the brain, monoamine deficiency is hypothesized as a cause of depression. Depletion of oral tryptophan and tyrosine, amino acids essential for the production of serotonin and norepinephrine, respectively, can induce

a depressive episode in subjects with a history of depression but not in healthy controls. Monoamine metabolite levels in cerebrospinal fluid, plasma, urine, and postmortem brains of patients with depression have not been reliably found to be deficient, indicating that there could be downstream effects involving second-messenger systems, such as cyclic adenosine monophosphate and phosphatidylinositol.

Other neurotransmitter systems may play a role in the development of depression. Decreased levels of both glutamate and γ-aminobutyric acid (GABA) have been found in the prefrontal cortex of depressed subjects. Intravenous (IV) ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, induces a rapid antidepressant effect and suggests a role for glutamate in the pathophysiologic process of depression. The brain relies on the actions of protective and regenerative cytokines, such as brain-derived neurotrophic factor (BDNF). All known antidepressants raise levels of BDNF and subsequently result in neurogenesis of certain brain regions, such as the hippocampus. Other theories include the melatonergic system and related abnormalities in circadian rhythm, decreased neurosteroid synthesis, impaired endogenous opioid functioning, monoamine-acetylcholine imbalance, inflammatory effects of cytokines, and dysfunction of specific brain structures and circuits.

The neurophysiology of bipolar disorder is less well understood than unipolar depression, in part because of the fluctuating mood states and the heterogeneity of the disorder. Bipolar disorder may in part arise from abnormalities in the connections within and between structures in the brain.[5] Specifically implicated are circuits interconnecting the amygdala, hypothalamus, striatum, and subdivisions of the frontal cortex, all of which are involved in both the generation and regulation of emotion.[6]

Endocrine System

Physiologic changes such as increased alertness, decreased appetite, increased heart rate, and activation of the hypothalamic-pituitary-adrenal (HPA) axis occur when a person is stressed. The HPA axis may play a role in depression, especially in cases of early childhood and chronic stress. Activation of the HPA axis releases corticotropin-releasing hormone (CRH) from the hypothalamus. Although not specific, patients with depression may have increased levels of free cortisol in the plasma, cerebrospinal fluid, and urine. Increased CRH has been demonstrated in cerebrospinal fluid, and increased levels of CRH messenger RNA and protein have been demonstrated in limbic brain regions. Although none of these measures is reliable as a diagnostic tool, successful treatment to remission has been shown to reverse some of these abnormalities, and antiinflammatory agents have demonstrated benefit in the treatment of depression in small controlled trials.[5]

Genetics

Genetic vulnerability to mood disorders has not been traced to a single gene. It is likely to be due to the additive effects of many genes and environmental influences on how these genes are expressed. Family, twin, and adoption studies provide evidence that major depressive disorder is a familial disorder but is less heritable than bipolar disorder. Bipolar disorder is one of the most heritable medical illnesses with a heritability of 80% to 85% and a monozygotic twin concordance of about 40%.

Psychosocial Factors

The etiology of most psychiatric problems, including mood disorders, involves complex interactions between both biologic and psychosocial factors.[1] The complex neural mechanism that regulates mood responds to and is modified by each person's experience, including events in early childhood, such as childhood sexual abuse, reward and punishment during growth and development, other lifetime trauma, marital problems, low social support, and various kinds of loss. Psychosocial theories of mood disorder form the basis for psychotherapy.

CLINICAL FEATURES

Major Depressive Disorder

Major depressive disorder is characterized by one or more major depressive episodes, as defined by DSM-5 criteria (Boxes 97.1 and 97.2).[1] A major depressive episode is characterized by disturbances in four major areas: mood, psychomotor activity, cognition, and vegetative function. The patient must have at least five symptoms for a minimum of 2 weeks and one of the five must be depressed mood or anhedonia (decreased interest or pleasure).[1]

Mood Disturbances

Patients in a depressed state often feel profoundly hopeless and helpless. There are many words and phrases that can be used to describe feeling depressed; some patients will not recognize that they are "depressed" but rather they may describe the feeling in some other manner. Someone feeling no emotion (profoundly depressed) may answer "no" when asked about depressed mood.

On the other hand, a person may meet criteria for a major depressive episode and not be experiencing a depressed mood. Depression can also be manifested as a decreased capacity to experience pleasure or interest in otherwise pleasurable activities. This loss of interest is known as *anhedonia.*

As noted previously, the patient must exhibit a depressed mood or anhedonia to meet DSM-5 criteria for a diagnosis of a major depressive episode.[1]

Disturbances in Psychomotor Activity

Physical activity in depression can be either increased or decreased. Psychomotor retardation is a significant slowing of physical activity. When suffering from psychomotor retardation, thinking and speaking can be slow, causing delayed responses to answers. Depressed patients often describe feeling fatigued with a general lack of energy and motivation. Conversely, patients may display psychomotor agitation, which can be manifested as fidgeting, pacing, hand-wringing, or restlessness.

Vegetative Disturbances

Vegetative symptoms include disturbances in three major areas: sleep, appetite, and sexual function. Depressed patients may complain of insomnia or hypersomnia. Insomnia may be manifested as difficulty in falling asleep, frequent awakenings throughout the night, or early-morning wakening. Depressed patients with hypersomnia may report sleeping 12 to 14 hours or more a day. Alterations in appetite and eating patterns can also occur, resulting in significant weight gain or loss during a short time. Loss of interest in sexual activity and impaired sexual functioning may also accompany depression, although this is not listed as a DSM-5 criterion.

Thought Process and Content

Depressed patients often describe impaired concentration and forgetfulness. Executive functioning can also be impaired. In severe cases, this results in a decreased ability to perform basic activities of daily living.

Thought content tends to be negatively biased, such as recurrent thoughts of guilt, failure, worthlessness, and self-criticism. Patients in a depressed episode are at increased risk for suicide. Suicidal thoughts may range from vague notions that life is not worth living (passive) to fully envisioned suicide plans with definitive intent to kill themselves (active). All depressed patients must be questioned about suicidal

BOX 97.1 Summary of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* Criteria for a Major Depressive Episode

A. Five or more of the following symptoms have been present almost every day during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. *Note:* Do not include symptoms caused by a general medical condition.
   1. Depressed mood (can be irritable mood in children and adolescents)
   2. Loss of interest or pleasure in activities
   3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation
   6. Fatigue or loss of energy
   7. Feelings of worthlessness, or excessive or inappropriate guilt
   8. Diminished ability to think or concentrate, or indecisiveness
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, or a suicide plan or attempt

B. Symptoms cause clinically significant distress or impairment in social, occupational, or other functioning.

C. Symptoms are not caused by direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hypothyroidism).

D. Symptoms are not better explained by another mental health disorder.

E. There has never been a manic or hypomanic episode.

Modified from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

BOX 97.2 Mnemonics for the Symptoms of Depression and Mania

Mnemonic for the Symptoms of Depression
Sig E Caps
Sleep amount increased or decreased
Interest (anhedonia)
Guilt
Energy level decreased
Concentration decreased
Appetite increased or decreased
Psychomotor activity increased or decreased
Suicidal ideation

Mnemonic for the Symptoms of Mania
Dig Fast
Distractibility
Irritability
Grandiosity
Flight of ideas
Activity increased
Sleeplessness
Thoughtlessness (impulsivity, increased risk-taking)

thoughts. Because patients are not often forthcoming with their thoughts on suicide, a thorough review of risk factors and protective factors needs to form the basis of clinical decisions for providing the necessary level of care.

Patients with severe depression may have psychotic symptoms. The hallucinations and delusions that accompany depression are usually mood-congruent, meaning that the themes of the psychotic content are consistent with the depressed mood.

Masked Depression

Mood disorders may not be clear at presentation. The depressed patient may have only vague somatic symptoms. Common complaints include weakness, fatigue, headache, and abdominal pain with medical evaluations occurring in response. Patients may not be aware of their depression and are often heavy users of medical care. Over half of patients with major depressive disorder initially present with somatic symptoms only, which can mask a hidden depression. Clues that suggest a mood disturbance include the recent onset of a set of unusual behaviors, significant social disturbance, such as job loss, financial stress, and marital difficulties, and self-destructive behavior (e.g., substance abuse, sexual promiscuity).

Special Considerations

Children and Adolescents. Criteria for depression in children and adolescents are the same as for depression in adults. Depression in these age groups can, however, present differently. Prepubertal children are more likely to have somatic complaints, psychomotor agitation, and mood-congruent hallucinations and less likely to have disturbances in sleep and appetite. Some children are misdiagnosed as having attention deficit disorder, especially if symptoms involve poor concentration, listlessness, agitation, and withdrawal from daily activities.

Adolescents with depression may show increased irritability, oppositional behavior, and substance abuse. Other characteristics include social withdrawal, increased rejection sensitivity, and decline in school performance. Some adolescents may be first diagnosed with depression on receiving treatment for drug and alcohol problems.

Disruptive Mood Dysregulation Disorder. A newly described phenomenon for children who may have been previously diagnosed with depression or bipolar disorder is disruptive mood dysregulation disorder. Children and adolescents given this diagnosis display severe, recurrent outbursts that are out of proportion for the situation and are inconsistent with developmental level. The outbursts must occur three or more times a week, and the mood in between outbursts is irritable or angry most days. There are duration criteria of 12 months with no periods of three or more consecutive months not meeting criteria. Symptoms must occur prior to age 10.[1]

Geriatric Patients. Depression is more common in elders because of more frequent occurrences of loss, comorbid health issues, and loss of autonomy. The elderly have a tendency to report more somatic complaints when depressed. They are also more vulnerable to development of melancholic depression, which is characterized by early morning awakening, diurnal variation in mood, low self-esteem, and low mood reactivity. Older depressed patients can also present with symptoms involving memory loss, inattention, withdrawal from daily activities, and lapses in personal and social hygiene that suggest dementia rather than depression. When such symptoms are from depression, the condition is called *pseudodementia*. Serious depression in elders is a highly treatable, reversible condition.

Other Depressive Disorders

Peripartum Depression

Postpartum depression is a depressive disorder that occurs during pregnancy or within 4 weeks of delivery and would allow for the specifier "with peripartum onset." Symptoms of depression are common in the perinatal period. As noted in the DSM-5, between 3% and 6% of women will experience the onset of major depression during pregnancy

or within the following weeks to months.[1] Similarly, but less severe, up to 65% of mothers report some depressed mood after childbirth, often called *postpartum blues*. Symptoms are generally mild and transient; although in 10% of mothers, it may lead to a full-fledged episode of major depression.

Postpartum mood episodes with psychotic features can be particularly dangerous. Infanticide is most often associated with command hallucinations to kill the infant or associated delusions. The risk for this is most closely related to a past history of postpartum episodes with psychosis, a history of depression or bipolar disorder, or a family history of bipolar disorder.

Persistent Depressive Disorder

Persistent depressive disorder is a new diagnosis that combines two former diagnoses: chronic major depressive disorder and dysthymic disorder. Specific criteria include the following: depressed mood most of the day, most days for at least 2 years; two or more of the following: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness; never more than 2 months of the 2 years without symptoms; and must cause significant distress or impairment in functioning. Exclusion criteria include a history of hypomania or mania and a history of psychotic illness. Also, it cannot be due to a substance or medical condition.[1] There are multiple specifiers that can be applied to this diagnosis.

Premenstrual Dysphoric Disorder

Premenstrual dysphoric syndrome is a new diagnosis included in the DSM-5. At least five of the listed symptoms must be present in the final week before the onset of menses and start to improve within a few days after the onset of menses, and be absent or minimal in the week post menses. These symptoms must be present for most cycles over the preceding year. The onset can occur at any point after menarche. Risks for development include stress, history of interpersonal trauma, seasonal changes, and sociocultural aspects of female sexual behavior.

Seasonal Affective Disorder

Seasonal affective disorder is not a separate mood disorder, but rather, a specifier of major depressive disorder. An example of the use of a specifier is "major depressive disorder, recurrent, moderate, with seasonal pattern." This specifier can only be used with a recurrent major depressive disorder. The criteria for this include the following: a regular temporal relationship between the onset of a depressive episode and a particular time of year, full remissions at a specific time of year, two depressive episodes within 2 years that demonstrate a temporal relationship, no nonseasonal episodes within the same period, and substantially more seasonal depressive episodes than nonseasonal episodes over the person's lifetime.[1] Melatonin, a hormone secreted in the brain and produced at high levels in the dark, has been implicated in the etiology of this disorder. Phototherapy is an effective and safe treatment of seasonal depression. Light exposure to the eyes seems to be essential, but the exact mechanism of action is still unknown.

Bipolar Disorders

Bipolar disorder is a chronic, progressive illness with onset for men between their mid-teens and mid-twenties and for women between their mid-teens and mid-thirties. The illness involves extreme mood episodes associated with exacerbation of other symptoms and deterioration of function. Patients with bipolar disorder may require different forms and intensities of treatment at different stages of the illness. *Bipolar I disorder* includes at least one manic episode, and patients have typically had one or more major depressive episodes, although a depressive episode is not necessary for diagnosis. *Bipolar II disorder* involves a hypomanic episode and at least one major depressive episode. A hypomanic episode includes the features of a manic episode without psychosis, marked impairment of function, or the need for hospitalization.[1]

Manic Episode

During a manic episode (see Boxes 97.2 and 97.3), the disturbance in mood must be severe enough to include psychosis, the need for hospitalization, or marked impairment in functioning. Bipolar disorders are much less common than major depressive disorder. The overall prevalence of a manic episode is about 2% in both women and men.

In many cases, manic patients are brought to the ED by someone else (e.g., family, police, or emergency medical services). Patients who are experiencing a manic episode may present with extreme mood lability; at time gregarious, humorous, and engaging, alternating suddenly with belligerence and irritability. Patients may display pressured speech, in which they keep talking, often rapidly and loudly without pauses between thoughts or sentences and are difficult to interrupt. The thought process in mania is characterized by illogical associations and flight of ideas. An inflated self-esteem and grandiose delusions may lead them to also be argumentative, impatient, and condescending. Grandiosity often centers on very broad dramatic or universal themes, such as religion or politics. The patient may describe a massive undertaking, such as "uniting the world's churches" or "solving world poverty." These severe symptoms are usually accompanied by a profound lack of insight. Despite obvious altered behavior, impaired judgment, and poor impulse control, the patient may insist that there is nothing wrong or blame problems on others.

BOX 97.3 Summary of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, Criteria for a Manic Episode

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood, and abnormally and persistently increased goal-directed activity or energy lasting at least 1 week (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, three or more of the following symptoms have persisted (four, if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., buying sprees, sexual indiscretions, foolish investments)
C. Mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or social activities or to necessitate hospitalization to prevent harm to self or others, or psychotic features are present.
D. Symptoms are not caused by direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hyperthyroidism).

Modified from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

Manic patients have decreased or no need for sleep and typically report being awake for days. They may be involved in a massive project (e.g., writing a novel), may completely disregard consequences of actions, may have difficulty with spending (e.g., credit cards revoked), and may engage in risky behavior (e.g., sexual liaisons with strangers, risky driving). Because the patient's abnormal thought process can make the history of present illness unreliable, whenever possible, a corroborating history should also be obtained from family or others who know of the patient's behavior.

Manic patients may present as trauma patients, injured by an action reflecting the patient's grandiosity (e.g., attempting to fly), impulsivity, or belligerence (e.g., fighting, resisting arrest). A manic episode may be punctuated by abrupt periods of tearfulness and profound depression, including suicidal ideation. When depressive and manic features occur concurrently in such a manner, the episode is termed *mixed* or *bipolar, mixed phase.*

Cyclothymic Disorder

Cyclothymic disorder is characterized by chronic mood swings that do not meet criteria for a hypomanic or depressive episode. The mood episodes must occur over at least 2 years, present for at least half the time, and the individual cannot be symptom-free for more than 2 months at a time.[1]

Mood Disorders Caused by a General Medical Condition

This diagnosis requires a prominent and persistent period of depressed mood or anhedonia that predominates the clinical picture, with evidence that the disturbance is the direct pathophysiological consequence of a medical condition, and not better explained by another mental disorder or occurring during the course of delirium.[1] Bipolar disorder requires a prominent and persistent period of abnormally elevated, expansive, or irritable mood; and abnormally increased activity or energy that predominates the clinical picture, with evidence of direct pathophysiological consequence of another medical condition, and it is not better explained by another mental disorder or occurs during the course of delirium.[1]

Certain medical illnesses have a well-known association with mood disorder. In Parkinson disease, electrical stimulation to a certain area of the substantia nigra alleviates symptoms of depression. Stimulation of an area only 2 mm away can cause acute reversible symptoms of depression, such as crying, not wanting to live, and hopelessness. Parkinson disease has a well-known association with depression, with up to 40% of patients demonstrating major depression.

Certain malignant neoplasms have a well-known association with depression, including pancreatic carcinoma, brain neoplasm, and disseminated malignant disease (e.g., lymphoma). Coronary artery disease, myocardial infarction, stroke, end-stage renal disease, acquired immunodeficiency syndrome, several endocrine diseases, and connective tissue disease are also associated with major depressive disorder. After a myocardial infarction, patients with depression have a 3.5-fold increase in cardiovascular mortality compared with nondepressed patients. The development of stroke, diabetes, and osteoporosis is more likely in patients with depression than in those who are not depressed.

Depression related to medical conditions may be different in some respects from primary depression and responds less favorably than primary depression to antidepressant medication. Treatment-resistant depression, defined as depression that has not responded to at least two adequate trials of medication, should prompt clinical investigation for a general medical condition causing the depressive episode.

Mood Disorders Caused by Medications or Other Substances

These are very similar to mood disorders caused by medical conditions, with the exception that the symptoms must develop during or soon after substance intoxication or withdrawal, or after exposure to a medication capable of producing the symptoms.[1]

Many medications are associated with symptoms of mood disorders. Multiple antihypertensives, anticonvulsants, and hormones have been associated with depressive symptoms, and certain antibiotics and steroids are associated with manic symptoms. Intoxication with or chronic heavy use of alcohol, sedatives, hypnotics, anxiolytics, narcotics, and other depressants can cause symptoms of a major depressive episode. Stimulants such as cocaine, phencyclidine, hallucinogens, and amphetamines can cause symptoms of a manic episode. Mood disorder symptoms can also develop during withdrawal. To qualify for this diagnosis, the symptoms must not occur exclusively during a course of delirium, must cause significant distress or impairment of functioning, and must develop within a month of either substance intoxication or withdrawal. When the mood disorder predates the period of substance abuse or lasts longer than 1 month after the period of abuse, the diagnosis may be an underlying mood disorder, such as a major depressive disorder or bipolar disorder, with a comorbid substance use disorder.

DIFFERENTIAL DIAGNOSES

Medical Disorders, Medications, and Substance Abuse or Withdrawal

Medical disorders, medications, and substance abuse or withdrawal can either cause or mimic mood disorders. The patient with symptoms and signs of depression may have an unrecognized malignant neoplasm or sedative intoxication. Differential diagnostic considerations for manic symptoms include stimulant abuse (e.g., cocaine, amphetamines), hallucinogen abuse, alcohol or sedative withdrawal, delirium, hyperthyroidism, and other medical conditions causing agitation. See the previous section for further information. Patients may be treated with antidepressant medication for a variety of disorders other than depression, such as anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, pain syndromes, smoking cessation, and vasodepressor syncope.

Grief and Bereavement

Grief and bereavement are normal human reactions to the acute loss of another person, health, social position, or job. The period of mourning is characterized by sadness, diminished sense of well-being (somatic complaints), sleeplessness, and sadness triggered by thoughts of the loss. Normal grief, however, does not include loss of self-esteem, feelings of worthlessness, suicidal intent, psychomotor retardation, or occupational dysfunction. The duration of normal grief and bereavement differs among cultures and among individuals within cultures, but severe symptoms normally resolve within 6 to 12 months.

Adjustment Disorders

Adjustment disorders are behavioral or emotional disorders that occur in response to an identifiable stress or stressors, with marked distress that is out of proportion to the severity of the stressor. The emotional component can involve sadness, low self-esteem, suicidal behavior, hopelessness, helplessness, or other self-threatening behavior. Acute adjustment disorder occurs within 3 months of the stressor and does not last longer than 6 months.[1] The stressors are typically not as severe as those precipitating bereavement reactions, and the responses are often more maladaptive.

Borderline Personality Disorder

Borderline personality disorder is characterized by unstable personal relationships, unstable self-image, and self-destructive behaviors. The disorder may include chronic feelings of emptiness, which may

be misdiagnosed as depression, or reactivity of mood, which may be mistaken for mania or hypomania. These patients typically live lives of crisis and constant conflict.

Dementia

Dementia can be confused with depression but is characterized by abnormal mental status, including abnormalities in tests of memory, calculation, and judgment (see Chapter 90).

Diagnostic Testing

History and physical examination should focus on determining if the patient has a mood disorder or the possibility that drug abuse, medications, or a general medical condition may be responsible for the patient's condition instead. It is essential to identify medical conditions that may exacerbate a psychiatric presentation. The psychiatric history should ask about current symptoms, precipitating events (e.g., job loss or relationship), past psychiatric and substance use history, history of self-harm or suicide attempts, and identification of support systems. Even if not suggested by the patient, careful questioning of suicidal thoughts is necessary. If possible, history should be confirmed by speaking with the patient's regular health care providers and interviewing family, friends, or eyewitnesses to the events that precipitated the ED visit. A tentative diagnosis can be established by use of DSM-5 criteria.

Laboratory tests to investigate medical conditions may be necessary based on the specifics of the clinical presentation, but no tests can confirm or exclude mood disorders. Patients with new symptoms compatible with mood disorders need a more extensive medical and psychiatric investigation than those with a known disorder.

MANAGEMENT

Patients presenting with mood disorder symptomology are frequently in crisis, often overwhelmed, and frankly scared. The ED is a chaotic, stimulating environment that may cause or exacerbate the patients' level of agitation. Creation of a safe and stable environment for the patient is a high priority. Individuals experiencing an acute manic episode may be disruptive, refuse medical evaluation, and make repeated attempts to leave the ED. The initial step in treating such a disruptive patient is to offer assistance in reducing the agitation, which may begin with verbal de-escalation.[7] One key is offering anxiolytic medication early in the patient's presentation. If de-escalation techniques and medication do not resolve the agitation, the patient may need to be placed in seclusion or restraints for his or her safety and that of others. This is a last resort after other de-escalation measures have failed. Chapter 185 discusses the use of seclusion and restraints in the ED. If a medical cause for agitation is found, treatment is aimed at the underlying cause (e.g., oxygen for hypoxic delirium). Often in the ED, treatment may need to begin prior to the cause of the agitation being fully recognized.[8,9] Figure 97.1 shows a simple algorithm for approaching the agitated patient.

Treatment of depression in the ED is more controversial. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the main treatments for depression. For the patient who is awaiting inpatient psychiatric placement, these medications can be initiated in consultation with the admitting service. Patients with mild to moderate depression, not requiring hospitalization, may be started on an SSRI as long as they have close follow-up arranged. SSRIs are known to have a myriad of side effects that can lead to premature discontinuation.[10] For the patients who are already on psychotropic medications but have discontinued them for a reason unrelated to adverse effects, it is reasonable to restart these medications in the ED.

A non-agitated manic patient may be able to inform the treatment team about what has worked well in the past. There are two medication choices for acute mania: antipsychotics and mood stabilizers.[11] All of the atypical, or second-generation, antipsychotics have been approved to treat acute mania as monotherapy or as an adjunctive therapy, except paliperidone and iloperidone. Lithium, valproic acid/divalproate, and carbamazepine are the most well-studied mood stabilizers. Lithium and carbamazepine need to be titrated, but valproic acid can be loaded in the ED at 20 to 30 mg/kg a day in a healthy person with normal liver function.

The atypical antipsychotic medicines, including ziprasidone, risperidone, olanzapine, aripiprazole, quetiapine, asenapine, and lurasidone, have a lower risk of acute side effects (such as acute dystonia) than conventional antipsychotic agents. Oral doses should be offered first, and several agents, including risperidone, olanzapine, and aripiprazole, are available in rapidly dissolving tablet form. Two are available as a short-acting intramuscular injection: ziprasidone (Geodon) and olanzapine (Zyprexa). Ziprasidone 10 mg every two hours or 20 mg every four hours is effective; however, its use is limited to 40 mg per 24 hours. Olanzapine 2.5 mg to 10 mg is effective, but is limited to 30 mg per 24 hours. Also, olanzapine is associated with postural hypotension so should not be used in combination with parenteral benzodiazepines because of the risk of cardiopulmonary depression. It is valuable to obtain psychiatric consultation during the initiation of agitation treatment, because these patients will generally require significant ED treatment or psychiatric hospitalization.

DISPOSITION

To determine the appropriate disposition for patients presenting with a mood disorder, a suicide risk assessment is required. The Substance Abuse and Mental Health Services Administration developed a practical tool referred to as the Suicide Assessment Five-Step Evaluation and Triage (SAFE-T).[12] Current suicidal thoughts, risk factors, and protective factors should be identified, as well as past suicidal thoughts, plans, or acts. Chapter 101 provides an in-depth discussion of suicide assessment. It is only after considering this information that an appropriate intervention can be determined. With the help of social workers or a mental health worker, many patients can be safely discharged home with close follow-up. Patients receiving initial treatment in the ED, without a proper handoff to outpatient care, are at an increased risk for return. If available, it is preferred that a social worker or mental health worker connect discharged patients with outside agencies and services, rather than providing patients with a referral list.

The references for this chapter can be found online at ExpertConsult.com.

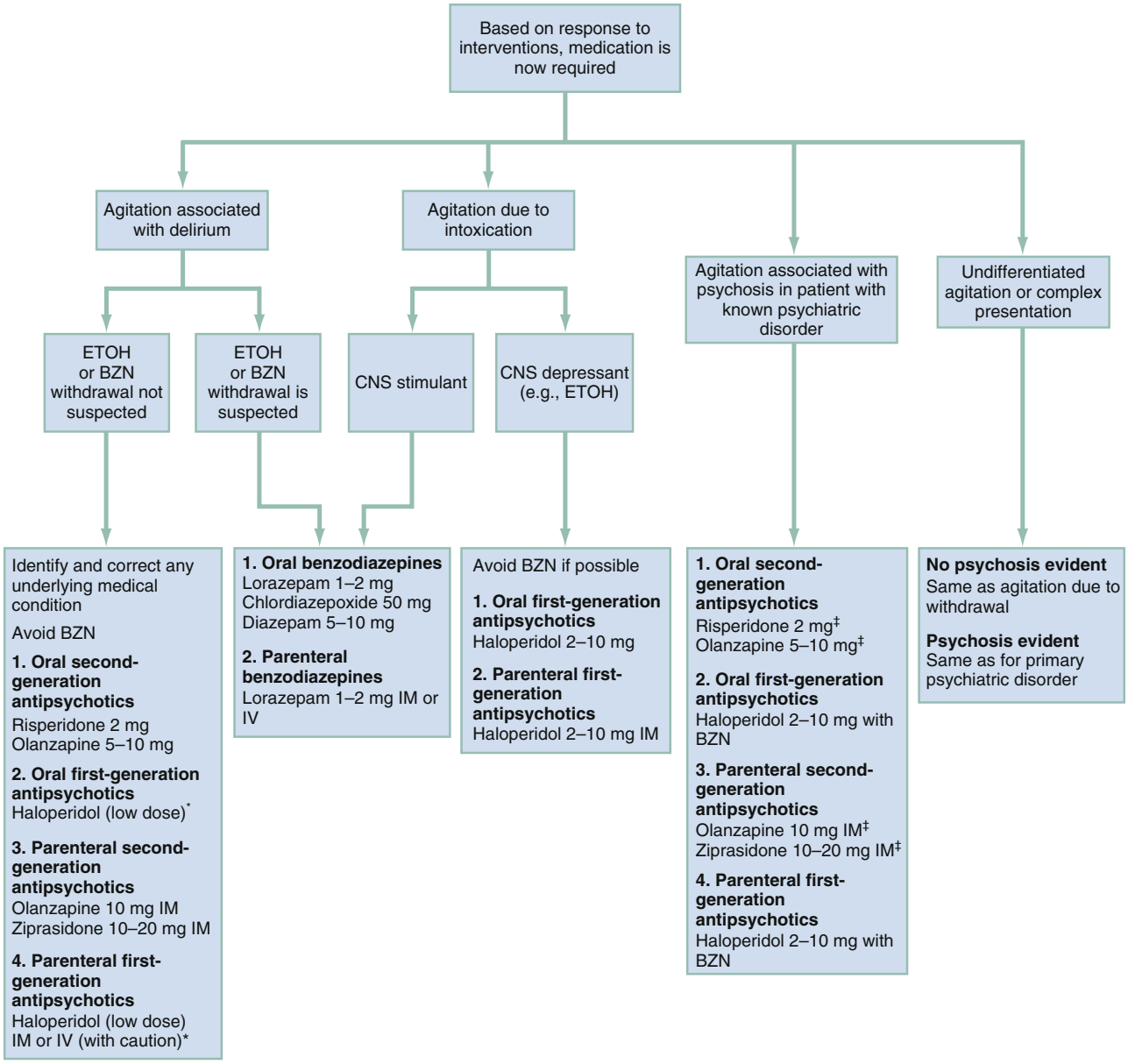

Fig. 97.1 Protocol for treatment of agitation. *BZN,* Benzodiazepine; *CNS,* central nervous system; *ETOH,* ethyl alcohol; *IM,* intramuscular; *IV,* intravenous. *See U.S. Food and Drug Administration (FDA) guidelines. ‡If an antipsychotic alone does not work sufficiently, add lorazepam 1 to 2 mg (oral or parenteral). (Redrawn from Wilson MP, Pepper D, Currier GW, et al. The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *WJEM.* 2012;13[1]:26-34.)

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CHAPTER 97: QUESTIONS AND ANSWERS

1. What is the lifetime suicide risk for people with major untreated depression?

a. 5%
b. 10%
c. 15%
d. 20%
e. 25%

Answer: c. Patients with major depression have a high lifetime suicide risk, and although episodes of acute decompensation with even higher risk can be identified and treated, a certain number of patients succeed in committing suicide.

2. Which of the following abnormalities of central nervous system neurotransmitters is associated with clinical depression?

a. Decreased hypothalamic-pituitary-adrenal (HPA) activity
b. Depressed serotonin levels
c. Elevated gamma-aminobutyric acid (GABA) levels
d. Elevated norepinephrine levels
e. Unchanged dopamine levels

Answer: b. The central biochemical features toward which pharmacologic management is directed are depressed levels of norepinephrine and serotonin. Data are also emerging that suggest decreased dopamine levels. The HPA axis may also be altered with elevated cortisol levels.

3. Which of the following statements regarding depression in children and elders is *true?*

a. Children with depression rarely present with somatic complaints.
b. Depression in children may be misdiagnosed as attention deficit disorder (ADD).
c. Depression presents differently from dementia in elders.
d. Diagnostic criteria for depression in children are different.
e. Serious depression in elders is generally refractory to treatment.

Answer: b. Depression in children and adolescents can be misdiagnosed as ADD. Somatic complaints are a common feature of children and adolescents presenting with depression, but the diagnostic criteria are not different. Geriatric depression may be manifested in a manner similar to dementia (pseudodementia), but unlike dementia, the depression is highly treatable and reversible once it is recognized.

4. A 31-year-old attorney is brought to the emergency department (ED) by his family for a chief complaint of agitation and a behavioral change. He has no past medical history and takes no medications. The family reports decreased sleep, increased talkativeness, marked increased time and involvement at work, and an uncharacteristic buying spree. Your examination is remarkable for distractibility, gregarious and pressured speech, flight of ideas, and mild psychomotor agitation. Laboratory examination and urine drug screen results are negative. The patient is adamant that he has important things to do and needs to leave. Which of the following statements regarding this patient's most likely diagnosis is true?

a. Antipsychotic agents are not effective.
b. Hallucinations would be atypical.
c. If treated, intravenous valproic acid is indicated.
d. Initiating treatment in the ED is not indicated.
e. Multiple antibiotics can cause this clinical picture.

Answer: e. This patient has a fairly classic presentation for acute mania with pressured speech, distractibility, grandiosity, increased involvement (in this case with work), and decreased need for sleep. Multiple drugs may precipitate this, including acyclovir, isoniazid, sulfonamides, the floxins, and chloroquine. An acute manic episode may be manifested with hallucinations and mimic an acute psychosis. ED treatment is usually indicated for this disorder. Acute stabilization is generally effective with major tranquilizers, such as haloperidol.

98

Anxiety Disorders

Leslie S. Zun and Joshua B. Nathan

KEY CONCEPTS

- Patients who present with predominant symptoms of anxiety may be suffering from medical disorders, medication effects, or substance abuse or withdrawal.
- Anxiety may accompany the onset of serious medical disease, cause significant metabolic demands, and stress a marginally compensated organ system.
- Anxiety caused by non-psychiatric illness is usually suggested by the patient's physical examination findings but may require testing to further delineate the cause.
- Oral, intravenous, or intramuscular medication may be necessary for patients who are a significant threat to themselves or others and for anxious patients with significant medical illness.
- Limited benzodiazepine therapy may be helpful for select patients.

FOUNDATIONS

Background and Importance

Anxiety is a specific unpleasurable state of tension that forewarns the presence of danger, real or imagined, known or unrecognized, and is often verbalized as an intense feeling of worry. Anxiety is often a normal adaptation to life events or stressors, and in many circumstances, could be considered appropriate given the context and would represent a reasonable emotional response to a perceived threat or circumstance. Even extreme levels of anxiety could be considered appropriate given the level of perceived threat. An anxiety disorder, however, describes a condition in which a response to a given circumstance or threat becomes significantly disproportionate or uncontrollable, leading to the deterioration of performance and an inability to cope. As the level of dysfunction increases, the patient is much more likely to have a true anxiety disorder. Anxiety disorders are considered to be among the most prevalent of mental health behavioral and emotional disorders worldwide.

Acute anxiety is common in emergency department (ED) patients who have primary anxiety disorders, concomitant anxiety disorders, and crisis situations. Emergency physicians are frequently called upon to diagnosis and treat anxiety disorders in the ED and therefore need to be familiar with both the diagnostic criteria as well as the differential diagnoses and treatment modalities. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for anxiety disorders include general anxiety disorder, panic disorder, agoraphobia, and specific phobia. Obsessive-compulsive disorders (OCD), post-traumatic stress disorder (PTSD), and acute stress disorder, which have now been moved to their own category in the DSM-5, will also be discussed in this chapter.[1]

Epidemiology

The most recent available national statistics on past-one-year and lifetime prevalence of anxiety disorders amongst adults (age 18 or older) is derived from the National Comorbidity Study Replication (NCS-R) originating from the Harvard Medical School National Comorbidity Survey (NCS). Data updated as of 2007 reveals 19.1% past-year prevalence with a female predominance (23.4% versus 14.3%) and an overall lifetime prevalence of 31.1% among all adults in the United States (US).[2]

Many patients seeking primary health care have significant mood and anxiety symptoms, such as panic disorder, generalized anxiety disorders (GAD), and depression, but almost half of these symptomatic patients never receive appropriate treatment. Patients with chronic illness and those who make frequent medical visits have higher rates of anxiety and depression. The prevalence of anxiety disorders surpasses that of any other mental health disorder, including substance abuse. There is a close relationship between alcohol abuse and anxiety disorders.

Anxiety disorders in children and adolescents lead to anxiety disorders in adulthood, but anxiety disorders often go unrecognized and untreated in the pediatric population.[3] The same is true of geriatric patients with a prevalence rate of 1.2% to 15%. Except for generalized anxiety disorder and agoraphobia, anxiety disorders typically start earlier in life.[4]

The incidence of specific anxiety disorders varies: specific phobia is 7% to 9%, social anxiety is 7%, panic disorder is 3%, and GAD is 3%. The lifetime risk for post-traumatic stress disorder (PTSD) is about 9%, but the 12-month prevalence is approximately 4%. Substance or medication-induced anxiety and anxiety due to a medical condition have an unknown prevalence but may be relatively high in those seeking emergency medical care.

A different form of anxiety related to fear of suffering from an illness, now known as *illness anxiety disorder* (formerly hypochondriasis), may be as high as 8% in ambulatory medical populations.[2] In these cases, patients may disguise their anxiety, presenting with a physical complaint rather than bear the perceived stigma associated with psychiatric complaints. This is distinct from patients with a somatoform disorder.

Pathophysiology

There are many forms of anxiety disorders and the precise mechanisms underlying the development of anxiety have not been fully established. However, the serotonin, noradrenergic gamma-aminobutyric acid (GABA) and dopaminergic systems are the most studied neurotransmitter systems implicated in anxiety disorders[5] (see Box 98.1). It is hypothesized that low serotonin system activity and elevated

BOX 98.1 Neurotransmitters Involved in Anxiety Disorders

Neurotransmitter	Neuroanatomical Association and Mechanism
Serotonin	Amygdala. Periaqueductal gray matter increased in AD
Dopamine	Mesolimbic mesocortical and nigrostriatal cortex; evidence of role in AD
Norepinephrine and epinephrine	Autonomic nervous system directly correlated in AD
GABA	Inhibitory neurotransmitter decreased in AD

Adapted from: Hingray C, McGonigal A, Kotwas I, Micoulaud-Franchi JA. The relationship between epilepsy and anxiety disorders. *Curr Psychiatry Rep*. 2019 Apr 29;21(6):40. https://doi.org/10.1007/s11920-019-1029-9. PMID: 31037466. Vismara M, Girone N, Cirnigliaro G, et al. Peripheral biomarkers in DSM-5 anxiety disorders: an updated overview. *Brain Sci*. 2020;10(8):564. Published 2020 Aug 17. https://doi.org/10.3390/brainsci10080564.

noradrenergic system activity may play a role, and thus selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are frequently used as treatment. There is also considerable comorbidity with depressive disorders, with evidence showing genetic and neurobiologic similarities, especially related to serotonin.

The well-established effectiveness of benzodiazepines in the treatment of anxiety has led to the study of the GABA system and its relationship to anxiety. GABA is the principal inhibitory neurotransmitter in the central nervous system, and benzodiazepines act on the $GABA_A$ receptors. Studies have also focused on the role that corticosteroids may play in fear and anxiety. Steroids are thought to induce chemical changes in select neurons that strengthen or weaken certain neural pathways to affect behavior under stress.

Family research suggests that genetic factors play a role in anxiety, but the precise nature of the inherited vulnerability is unknown. Five major anxiety disorders (panic disorder, GAD, phobias, OCD, and PTSD) share genetic and environmental risk factors. Psychological and environmental factors also contribute to the generation of anxiety in biologically predisposed individuals.

CLINICAL FEATURES

Anxiety may be a manifestation of another medical disorder or an expression of an underlying psychiatric disorder. It may be difficult to make the distinction between anxiety as a symptom and anxiety as a syndrome in the ED. The physical symptoms of autonomic arousal (e.g., tachypnea, tachycardia, diaphoresis, lightheadedness) may be the only manifestations of anxiety. Classic panic disorder symptoms of chest pain, shortness of breath, and the sense of impending doom will often lead the patient to the ED, especially if it is the very first episode. Box 98.2 lists clinical predictors of anxiety caused by an underlying medical disorder. Patients may also exhibit anxiety associated with experiencing uncertainty about their illness and the potential implications of the illness. In addition, many patients seeking care in the ED may experience anxiety related to encountering internal and external dangers, such as assaults on body integrity in the form of uncomfortable procedures and forced intimacy with strangers.

Clinical manifestations of specific anxiety disorders are considerably different, warranting a review of each of the major types.

BOX 98.2 Predictors of Anxiety Caused by an Underlying Medical Issue

Onset of anxiety symptoms after 35 years old
Lack of personal or family history of an anxiety disorder
Lack of childhood history of significant anxiety, phobias, or separation anxiety
Lack of avoidance behavior
Absence of significant life events generating or exacerbating the anxiety symptoms
Poor response to antianxiety agents

BOX 98.3 Characteristics of a Panic Attack

Abrupt surge of intense fear or discomfort that reaches a peak within minutes, in which four or more of the following occur:
Palpitations
Sweating
Trembling
Shortness of breath or feeling of being smothered
Feeling of choking
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy or lightheaded
Chills or heat sensations
Paresthesias
Derealization or depersonalization
Fear of losing control or going "crazy"
Fear of dying

Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

Panic Disorder

Panic disorder (PD) is a diagnosis of exclusion, even in patients with known psychiatric illness, because several mental illnesses cause panic attacks as a secondary manifestation. For a diagnosis of panic disorder, one must experience recurrent, unexpected panic attacks (Box 98.3), as well as either persistent concern of future attacks or a maladaptive behavioral change related to the attacks. As with other disorders, the disturbance should not be better explained by substance use, another medical condition, or another psychiatric illness.[2]

A panic attack, differentiated from panic disorder, is an abrupt fear or discomfort that reaches a peak within minutes and has associated physical and cognitive symptoms.[2] It may occur with any anxiety disorder or as part of another psychiatric or other medical disorder. A panic attack is not a diagnosis but rather an indication of an underlying disorder. The presence of panic attacks often influences the treatment and outcome of the primary illness. An attack can be replicated by intentional hyperventilation, which can be distinguished from medical hyperventilation by its irregularity and interruptions. When there is doubt, formal psychiatric evaluation is indicated, particularly before a potentially dangerous or addictive drug therapy is prescribed.

Generalized Anxiety Disorder

GAD is defined as excessive worry that occurs most days over a 6-month period involving several events or activities.[2] The anxiety must cause significant distress or impairment in functioning. GAD has been linked to overuse of medical services and often is not recognized, which leads to ineffective treatment.

BOX 98.4 Characteristics of Post-Traumatic Stress Disorder*

Exposure to actual or threatened death, serious injury, or sexual violence.
Presence of intrusion symptoms associated with the traumatic event.
Persistent avoidance of stimuli associated with the traumatic event.
Negative alterations in cognition and mood associated with the traumatic event.
Marked alterations in arousal and reactivity associated with the event.
Duration is greater than 1 month.
Disturbance causes clinically significant distress or impairment.
Disturbance is not attributable to the physiological effects of a substance or another medical condition.

* Specifiers include "with dissociative symptoms" and "with delayed expression."
Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

Post-Traumatic Stress Disorder

PTSD is caused by experiencing or witnessing a highly traumatic event. Those with PTSD manifest symptoms of re-experiencing the event, avoidance of triggers, changes in cognition and mood, and changes in arousal and reactivity (Box 98.4). Rates of PTSD are higher among military veterans and those whose occupation involves risk of traumatic exposure.[2] ED staff are also at risk for experiencing PTSD related to unusual traumatic events and unexpected deaths. Those suffering from PTSD may also be suffering from other disorders such as OCD, personality disorders, and substance use disorders, and may even exhibit suicidal ideations.

Specific Phobias

A phobia is an irrational fear that results in avoidance behavior. Phobia becomes a disorder when it interferes with day-to-day function in an individual's life. Social phobia, now termed *social anxiety disorder,* is characterized by clinically significant anxiety about one or more social situations in which the individual may be scrutinized.[2] This fear often leads to avoidance or other changes in behavior for such activities, such as public speaking, performing, visiting people, sitting in classrooms, attending social events using public showers or restrooms, or eating in public places.

Obsessive-Compulsive Disorder

OCD is characterized by recurrent, intrusive, unwanted thoughts (obsessions), such as fears of contamination, or compulsive behaviors or mental acts (compulsions) that a person feels compelled to perform, such as handwashing or counting. OCD is considered an anxiety disorder because (1) anxiety or tension is often associated with obsessions and resistance to compulsions, (2) anxiety or tension is often immediately relieved by yielding to compulsions, and (3) OCD often occurs in association with other anxiety disorders.[2] In summary, the obsessions and intrusive thoughts increase anxiety, and the compulsions and repetitive behaviors decrease anxiety but with significant disruption of one's life.

Hyperventilation Syndrome

Hyperventilation syndrome is a disorder characterized by intermittent episodes of increases in minute ventilation, together with feelings of doom and anxiety, associated with somatic symptoms such as dyspnea, chest pain, lightheadedness, perioral numbness and tingling, and muscle spasm of the hands and feet. Underlying conditions that may cause or contribute to this syndrome include primary psychological or neurologic dysfunction as well as cardiopulmonary etiologies. The diagnosis of hyperventilation syndrome may be challenging since there are no widely accepted diagnostic criteria. Patients presenting with new-onset hyperventilation require an extensive history, as well as physical examination and screening laboratories to rule out lethal etiologies. Patients with known hyperventilation syndrome from a psychological etiology can benefit from reassurance, breathing therapy, and low doses of benzodiazepines. A study of patients presenting to an ED with hyperventilation syndrome found 30% had previous episodes and more than 50% had a psychiatric comorbidity.[6]

Somatic Symptoms and Related Disorders

Although not necessarily categorized as anxiety disorders, this group of disorders has an undefined but established link to anxiety and depressive disorders and includes somatic symptom disorder, illness anxiety disorder (formerly hypochondriasis), conversion disorder (formerly functional neurological symptom disorder), and psychological factors affecting other medical conditions. With somatic disorders, the patient will complain about one or more physical symptoms, which cause impairment notwithstanding a negative evaluation. These symptoms are not intentionally feigned, as in the case of malingering or factitious disorder. A high utilization of medical services is correlated with these disorders, independent of comorbidity. Patients with somatoform disorders may seek as much psychiatric attention as do those with panic disorder.

DIFFERENTIAL DIAGNOSIS

It is important to differentiate the origin of anxiety to provide appropriate treatment. Many medical conditions mimic anxiety disorders, and up to 42% of patients initially thought to have anxiety disorders are later found to have a medical etiology.

Emergency clinicians should be able to distinguish between anxiety disorders and other medical illness (see Box 98.2) and, if necessary, treat both entities. Because anxiety states cause an increase in metabolic demands, they can cause a marginally compensated organ system to fail.

In patients who present with predominant symptoms of anxiety, even when the patients have known anxiety disorders, before considering which of the previously discussed DSM-5 anxiety-related diagnoses the patient might have, the clinician should first consider the possibility of medical and pharmacologic-related conditions associated with anxiety.

Patients with anxiety disorders may present with an apparently different medical disease, and many medical diseases are strongly associated with symptoms of anxiety. Several factors help distinguish an anxiety syndrome caused by an underlying medical issue from a primary anxiety disorder (see Box 98.2).

Anxiety may be the most obvious symptom of an underlying disease or condition, and therefore, the patient should be evaluated for exacerbation of known preexisting disease, as well as for the onset of new illness, because of the increased risk of acute medical exacerbation of chronic illness.

Anxiety disorder classifications in the DSM-5 include anxiety caused by another medical condition.[2] Post–myocardial infarction patients with anxiety have poorer outcomes than those without documented anxiety. Patients with respiratory diseases, such as asthma and chronic obstructive pulmonary disease, often have anxiety associated with long-standing illnesses. In addition, many of the medications used to treat these illnesses may induce anxiety. One of the most common medical causes of anxiety is alcohol and drug use from either intoxication or, more typically, withdrawal states.

Cardiac Diseases

Approximately 25% of patients with chest pain who present to the ED have panic disorder, which often goes undiagnosed, resulting in multiple visits and expensive cardiac evaluations. Symptoms of anxiety, like those of a myocardial infarction or angina pectoris, may include crushing chest pain, shortness of breath, nausea, palpitations, heavy perspiration, and a feeling of impending doom. The associated chest pain is usually described as atypical, and patients are generally female and younger. Because of the morbidity and mortality of cardiovascular disease, a patient warrants an appropriate cardiac evaluation when the differentiation between myocardial infarction and acute anxiety is unclear.

Cardiac dysrhythmias can also cause symptoms similar to a panic attack including palpitations, discomfort, dizziness, respiratory distress, and even syncope. Mitral valve prolapse syndrome can be associated with palpitations and panic attacks indistinguishable from a panic disorder. Benzodiazepines can be used to provide symptomatic relief to patients who experience chest pain due to anxiety.

Endocrine Diseases

The most common endocrinologic conditions associated with anxiety states are hypoparathyroidism, hyperthyroidism and hypothyroidism, hypoglycemia, pheochromocytoma, and hyperadrenocorticism. Anxiety is the predominant symptom in 20% of patients with hypoparathyroidism. Studies indicate a higher incidence of anxiety in the subset of patients with surgically removed parathyroid glands. Even though other symptoms may improve with supplementation, patients have been found to have significant depression, anxiety, somatization, and phobic anxiety, even after being given calcium and vitamin D.

Anxiety symptoms are seen in up to 40% of people with diabetes mellitus, and 14% of diabetic patients suffer from anxiety disorders.[7] There is evidence that people with diabetes mellitus and anxiety have worse glycemic control when anxiety is untreated.

Pheochromocytomas are rare tumors that produce elevated levels of catecholamine in the body. Pheochromocytoma attacks may manifest similar to panic attacks and can be precipitated by emotional stress. Elevated urinary catecholamine or plasma metanephrine levels confirm a pheochromocytoma.

Hyperthyroidism is one of the most frequently encountered endocrine diseases associated with anxiety. As with panic disorders, hyperthyroidism is associated with acute episodic anxiety. Thyrotoxicosis causes anxiety, palpitations, perspiration, hot skin, rapid pulse, active reflexes, diarrhea, weight loss, heat intolerance, proptosis, and lid lag. A substantial portion of patients continue to have psychiatric manifestations even after treatment.

Psychiatric presentations can be the first sign of hypothyroidism, occurring as the initial symptom in 2% to 12% of reported cases along with deficits of impaired recent memory and learning. The severity of anxiety disorders in hypothyroid states is related to the rapidity of thyroid hormone level changes and not to the absolute hormone levels. In general, checking serum thyroid-stimulating hormone and free thyroxine levels will suffice in the ED to establish the diagnosis of thyroid disease.

Respiratory Diseases

Most conditions causing airway compromise or impairment of gas exchange do not mimic psychiatric disorders. However, some conditions that cause hypoxemia or hypercarbia may lead to the development of significant anxiety. Up to a third of the patients with chronic obstructive pulmonary disease meet the criteria for anxiety disorder.

Patients who have severe asthma are twice as likely to have an anxiety disorder and almost five times as likely to have a phobia compared with nonasthmatics. Acute dyspnea from a pure panic attack with good air movement and normal lung sounds is easily differentiated from an asthma attack, but studies consistently show that anxiety disorders increase asthma morbidity and mortality.

Acute shortness of breath in any patient should not be immediately attributed to anxiety, especially because pulmonary embolism can present with only shortness of breath as the major symptom. Fortunately, pulmonary embolism can almost always be distinguished by history and physical examination, assessment of risk factors for thromboembolic disease, and laboratory testing (e.g., pulse oximetry, electrocardiography, chest radiography, and D-dimer assay) as indicated. The Multidimensional Dyspnea Profile tool uses the verbal subjective descriptors of feeling depressed, air hunger, and breathing concentration to help differentiate patients with pulmonary disease with and without panic disorder.[8]

Neurologic Disorders

Many neurologic conditions are associated with anxiety symptoms. For example, stress is one of the most common reported causes of seizures. Those who report stress as a trigger tend to have higher scores on anxiety tests, and the stress may be either acute or chronic.[12] Temporal lobe seizures, complex partial seizures, tumors, arteriovenous malformation, and cerebral ischemia or infarction have all been reported with panic attacks. Anxiety disorders also occur in the aftermath of traumatic brain injury (TBI). Approximately 23% of those who sustain a mild TBI are at risk for developing an anxiety disorder; this is frequently found in military personnel. In Huntington disease, anxiety is the most common prodromal symptom. Anxiety occurs in up to 40% of patients with Parkinson disease and up to 37% of patients with multiple sclerosis. Similarly, anxiety symptoms are common in moderate Alzheimer disease.

Drug Intoxication and Withdrawal States

Amphetamines, cocaine, and other sympathomimetic drugs are abused for their stimulant and mind-altering properties. Patients often present agitated and anxious, particularly when these drugs are taken in large doses and with prolonged use. Caffeine is a very commonly used stimulant, and studies suggest that about 400 mg/day is the threshold for toxicity in healthy adults (19 years or older), 100 mg/day in healthy adolescents (12-18 years old) and 2.5 mg/kg/day in healthy children (11 years old or younger). With the consumption of higher doses, caffeine intoxication may result, causing restlessness, nervousness, excitement, insomnia, diuresis, gastrointestinal disturbance, tachycardia, psychomotor agitation, as well as other unpleasant symptoms.[2] The acute symptoms of caffeine intoxication and GAD are almost identical.

Marijuana use may result in depersonalization that provokes severe anxiety, fearfulness, and symptoms of agoraphobia. Cannabis intoxication is associated with behavioral or psychological changes, such as anxiety, and physical signs, such as conjunctival injection, dry mouth, and tachycardia. Although marijuana use is sometimes associated with anxiety reduction, there is evidence to suggest that therapy for anxiety disorder using cannabis is limited with the potential harm out weighing the risk.[7]

Lysergic acid diethylamide (LSD), phencyclidine (PCP), and ecstasy (3,4-methylenedioxy-methamphetamine [MDMA]) are hallucinogens that can produce anxiety and paranoia from chronic use or "bad trips." Flashbacks affect some users of LSD; the person may experience the symptoms of anxiety and paranoia weeks or months after use.

Sedative, hypnotic, or anxiolytic drugs (e.g., benzodiazepines, barbiturates) are taken to relieve anxiety or sleeplessness, but their discontinuation can cause sedative withdrawal and rebound anxiety.[2] The severity of the withdrawal syndrome depends on the drug, dosage, duration of use, and speed of elimination. Symptoms include hyperalertness, motor tension, muscle aches, agitation, anxiety, insomnia, tremulousness, nausea, vomiting, convulsions, delirium, and even death.[2]

Although antidepressants are rarely abused, their abrupt cessation can cause a discontinuation syndrome, which may present as sensory and gastrointestinal-related symptoms, insomnia, lethargy, and extreme anxiety.[9]

Alcohol withdrawal can appear 6 to 12 hours after the last drink or significant reduction in consumption. Patients often have a detectable serum alcohol level at this time. Anxiety is one of the first and most prominent symptoms and is seen within 24 to 48 hours of the withdrawal state. Symptoms of anxiety, insomnia, and autonomic dysfunction can last up to 6 months following alcohol withdrawal.[2]

DIAGNOSTIC TESTING

The initial history and physical examination should focus on the presenting complaints to determine if the patient has an anxiety disorder or anxiety caused by drug abuse, medication use, or a general medical condition. The psychiatric history should, at minimum, include current symptoms, precipitating events and significant life stressors, past psychiatric and substance history, history of self-harm or suicide attempts, and identification of support systems. A thorough risk assessment for suicidality is key. Among ED patients, panic attacks have been found to be closely associated with suicidal ideation (43%) and intent (55%). Chapter 101 discusses suicide risk assessment.

A physical examination focused on any bodily area of complaint is necessary, even when there is no overt evidence of disease. Abnormal vital signs suggest an organic medical cause of the anxiety symptoms. Laboratory tests may be necessary based on the clinical presentation, but no tests can confirm or exclude anxiety disorders.[11] Patients with new symptoms require a more extensive medical and psychiatric investigation than those with a known disorder.

MANAGEMENT

The patient should be placed in a quiet area for evaluation. Some patients experience calm when they are removed from a chaotic ED environment. If that is not possible, reducing environmental stimulants, such as dimming lights, can be helpful. If the clinician encounters difficulty in calming the patient, supportive family members may help.

Pharmacologic Treatment

Use of oral, intravenous, or intramuscular medication may be necessary when an anxiety state results in the threat to safety for the patient or others. Medication may also be appropriate for the anxious patient experiencing a significant medical illness or undergoing a medical procedure. Low doses of benzodiazepines (e.g., lorazepam) in small increments can be helpful in alleviating the anxiety associated with substance withdrawal states. Midazolam reduces anxiety and increases amnesia for ED procedures.

SSRIs and SNRIs have become first-line treatment of most anxiety disorders because of their broad spectrum of efficacy and high tolerability by most patients. They have a low potential for dependence and are safer than older classes of antidepressants and anxiolytics. Improvement is usually seen in 4 to 6 weeks, but doses may have to be adjusted. Patients with known anxiety disorders may need a refill of their prescribed medication in the ED. Patients with new-onset anxiety may be started on an SSRI/SNRI in the ED in consultation with a psychiatrist or primary care physician who will see them in follow-up for a thorough evaluation of the type of anxiety and provide a long-term treatment plan. There is no difference in efficacy in drugs in the same class nor between SSRI and SNRI for all anxiety disorders except social anxiety disorders.[10]

Benzodiazepines can be prescribed for motivated patients with acute exogenous anxiety for time-limited stress. Benzodiazepines are an attractive alternative to the delayed response of an SSRI when an immediate reduction of symptoms is desired or a short-term treatment is needed. Benzodiazepines have a role in emergency medical treatment, but their use is questionable for long-term treatment. In most circumstances, benzodiazepines should be prescribed for a week or less. Patients may need to be prescribed several weeks of benzodiazepines until SSRIs/SNRIs take effect. Patients with a history of alcoholism or drug abuse, who are emotionally dependent, or who become anxious in response to normal stress are at greater risk of drug dependency and are not good candidates for this treatment. Hydroxyzine has also been used in select patients as an alternative to benzodiazepines for rapid anxiolytic effect, and are indicated for the treatment of anxiety.

Monoamine oxidase inhibitors and tricyclic antidepressants have been effective in treating anxiety but have been largely supplanted by SSRIs and SNRIs. Buspirone, a 5-hydroxytryptamine receptor 1A agonist, has been shown to work well for generalized anxiety disorders in some studies with few side effects but requires 1 to 3 weeks to become effective.[13]

Nonpharmacologic Therapy

Patients with associated agitation may need verbal de-escalation as first-line treatment prior to the use of medications. Supportive therapy can be used to calm patients and give them room to problem-solve. Emergency clinicians and staff can also use psychoeducation to normalize perception and to teach skills of coping such as breathing techniques. It is also particularly useful to educate the patient on the role that stimulants (e.g., caffeine) and depressants (e.g., alcohol) play in promoting anxiety.

There are multiple longer-term therapies that can be helpful for treating anxiety but are not applicable in the acute care setting. Psychotherapy may be helpful for individuals whose psychological makeup, coping style, interpersonal dynamics, and situational stressors contribute to their pathologic anxiety. The use of supportive, insight-oriented, or family therapy is helpful when these factors appear prominently in the patient's presentation. Cognitive-behavioral therapy helps the patient correct the cognitive misperceptions and overreactions that occur. Psychotherapy is as effective as medication in treating anxiety, but requires commitment from the patient. Meditation, biofeedback, and suggestive hypnosis may also have a role in long-term treatment.[13]

DISPOSITION

Patients receiving initial treatment in the ED without a proper referral to outpatient care are at an increased risk for return. If available, it is preferred that a social worker or mental health worker connect discharged patients with outside agencies and services, rather than providing patients with a referral list.

Most patients with an anxiety disorder can be safely discharged with close primary care physician or psychiatrist follow-up. Some who may have difficulty navigating the outpatient setting may benefit from a short stay in psychiatric observation or in a crisis stabilization unit even if suicide risk is low. Patients with an anxiety disorder associated with suicidal or homicidal ideation or with severe depression require urgent psychiatric attention and hospitalization.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 98: QUESTIONS AND ANSWERS

1. Which of the following is the most common mental health disorder?
- **a.** Anxiety
- **b.** Bipolar
- **c.** Depression
- **d.** Schizophrenia
- **e.** Substance abuse

Answer: A. Many of these patients never receive appropriate care, in part because they choose to present with a physical complaint and disguise their anxiety. Patients with chronic illnesses have higher rates of anxiety and depression than the rest of the population.

2. What is the most common cause of organic anxiety, anxiety that results from a physiologic origin?
- **a.** Adrenal disorders
- **b.** Alcohol and drug use
- **c.** Cardiac disease
- **d.** Hyperthyroidism
- **e.** Pulmonary embolus

Answer: B. This may be from intoxication or withdrawal states.

3. A 52-year-old woman presents with 2 months of recurrent episodes of anxiety, mild chest pain, subjective palpitations, hand paresthesias, and occasional muscle spasms. They have occurred weekly in the past but are now increasing in frequency. Her only past history is a thyroidectomy 4 months prior. She is taking levothyroxine (Synthroid) and had normal thyroid levels 2 weeks ago. Her vital signs, physical examination, and electrocardiogram are normal. Laboratory evaluation shows sodium 141 mEq/L, potassium 4.1 mEq/L, creatinine 1.0 mg/dL, bicarbonate 26 mEq/L, chloride 100 mEq/L, and calcium 7.1 mg/dL; a complete blood count is normal. Which of the following should be the next step in her management?
- **a.** Outpatient clonazepam
- **b.** Parathyroid hormone level
- **c.** Psychiatry consultation
- **d.** Thyroid hormone levels
- **e.** Urine drug screen

Answer: B. Anxiety is the predominant symptom in 20% of patients with hypoparathyroidism. Other symptoms include paresthesia, muscle cramps, and spasms. Most cases are idiopathic or due to inadvertent parathyroid gland harvest during thyroidectomy. The diagnosis is suggested by a low serum calcium and an elevated phosphate and is confirmed by a depressed parathyroid level.

4. Which of the following statements regarding anxiety and endocrine disorders is true?
- **a.** Anxiety can often be traced to reactive hypoglycemia.
- **b.** Anxiety is not a manifestation of hypothyroidism.
- **c.** Diabetics treated with antianxiety agents have improved hemoglobin A1c levels.
- **d.** Less than 5% of diabetics experience anxiety.
- **e.** Patterns of diaphoresis in pheochromocytoma mimic those of a panic attack.

Answer: C. Approximately 15% of diabetics have an anxiety disorder. Treatment improves hemoglobin A1c levels. Anxiety due to reactive hypoglycemia is rare despite the common perception among patients. Pheochromocytoma causes whole-body diaphoresis, whereas panic disorders primarily cause sweaty palms. Hyperthyroidism or hypothyroidism can cause significant anxiety manifestations. It is more related to the rate of change than the level of thyroid hormones.

5. A 23-year-old woman with a history of asthma presents with increasingly frequent episodes of panic attacks. Her medications are an inhaled beta-agonist and an intermittent steroid inhaler. She reports subjective increasing asthma severity as her panic episodes have worsened. When counseling the patient, which of the following statements is most correct?
- **a.** An anxiety disorder in an asthmatic patient does not increase morbidity.
- **b.** Anxiety does not precipitate asthma attacks.
- **c.** Anxiety does not worsen airflow.
- **d.** Asthmatics are more likely to have an anxiety disorder.
- **e.** It is difficult to differentiate dyspnea related to asthma from anxiety.

Answer: D. Anxiety can precipitate and prolong an asthma attack. Morbidity and mortality are increased in asthmatic patients who have a coexisting anxiety disorder. Patients who have asthma are twice as likely to have an anxiety disorder and five times as likely to have a phobia. Acute dyspnea from "panic" dyspnea can be differentiated from asthma by clear lungs on auscultation.

6. Which of the following syndromes is not associated with anxiety?
- **a.** Left hemispheric strokes
- **b.** Multiple sclerosis
- **c.** Right hemispheric strokes
- **d.** Transient ischemia attack
- **e.** All of the above can be associated with anxiety.

CHAPTER 98: QUESTIONS AND ANSWERS—cont'd

Answer: E. Anxiety may be a component of seizures, tumors, arteriovenous malformations, and ischemic events. It may be the only manifestation of some disorders (e.g., right hemispheric strokes and transient ischemic attacks [TIAs]). The coexistence of anxiety plays an important role in the prognosis and impairment of stroke patients.

7. A 38-year-old woman with a long history of anxiety and panic disorder presents with anhedonia, melancholy, sleep disruption, crying episodes, and some hostility feelings. She has no current anxiety symptoms. Her only medication is clonazepam. She has no known medical illness. Which of the following statements regarding this patient's symptoms is true?

a. Approximately 50% of patients with panic disorder develop major depression.
b. Depression with anxiety and hostility is usually refractory to treatment.
c. The first diagnostic step should be a thyroid panel.
d. The majority of patients with depression have panic attacks.
e. This is likely a drug-induced depression.

Answer: A. Approximately 50% of patients with a primary panic disorder will later develop major depression. Twenty percent of patients with depression have panic attacks. Depression with panic attacks is less responsive to treatment, but depression with anxiety and hostility responds well to antidepressants. Although benzodiazepines can exacerbate symptoms of depression, there is already a high spontaneous rate of depression with anxiety disorders.

8. Which of the following statements regarding benzodiazepine use and anxiety is true?

a. Benzodiazepines are first-line agents for anxiety disorders.
b. Several weeks of treatment are indicated after initial diagnosis.
c. Short-acting benzodiazepines produce a more severe abstinence syndrome.
d. They are particularly useful in patients with alcohol abuse.
e. Withdrawal rebound is less common than with selective serotonin reuptake inhibitors (SSRIs).

Answer: C. SSRIs are the first-line agents for anxiety and panic disorders, but the primary disadvantage is the several-week lag needed for maximal clinical benefit. Benzodiazepines work best for motivated, dependable patients when an immediate reduction of symptoms is indicated or a short-term treatment is necessary. Patients who do not benefit from benzodiazepines within a week are unlikely to do so. Patients with a history of alcoholism or drug abuse, who are excessively/emotionally dependent, or who become anxious from normal stress are at greater risk for dependency. Rebound withdrawal is more likely after short-acting agents.

9. A 29-year-old Caucasian female presents with excessive daytime somnolence. She states that she had been suffering from anxiety associated with her paralegal occupation, and 1 week ago her psychiatrist had started her on a 2-week course of once-daily benzodiazepine therapy, which she takes in the morning. Her anxiety symptoms are well controlled. She asks if you can change her to a new medication because the somnolence is significantly affecting her job performance. What would be the most appropriate course of action?

a. Counsel the patient that she should continue the medication as prescribed because she will soon adapt and the somnolence will likely subside.
b. Discontinue the benzodiazepine and refer her back to her psychiatrist.
c. Have her try dosing the benzodiazepine at bedtime, because this will likely continue to control her anxiety and limit daytime somnolence.
d. Switch the patient to a selective serotonin reuptake inhibitor (SSRI) and refer her back to her psychiatrist.
e. Switch the patient to a shorter-acting benzodiazepine.

Answer: C. Instituting an SSRI should be reserved for primary care physicians or psychiatrists who can monitor the patient more closely, because the response will be delayed. Some patients do adapt to the sedative effects of benzodiazepines but usually only after long-term use. Stopping the benzodiazepine may ultimately be necessary but at the risk of recurrent anxiety. Dosing benzodiazepines at bedtime may minimize daytime sedation and still provide an anxiolytic effect. Shorter-acting benzodiazepines produce a more severe abstinence syndrome when stopped abruptly, and thus most prescribers prefer longer-acting agents.

10. A 52-year-old male construction worker presents with chest pain. He states his symptoms began early this morning and have progressively worsened throughout the day. His symptoms include nervousness, tremors, chest pain, shortness of breath, and palpitations. He states that he has had anxiety for 30 years but has controlled it with the consumption of alcohol. He became unemployed 1 week ago, and his daily alcohol use has diminished significantly. His vital signs are blood pressure (BP) 185/95 mm Hg, heart rate 123 beats per minute, respiratory rate of 20 breaths per minute, and temperature of 98.9°F. His physical examination is remarkable for diaphoresis, tongue fasciculation, both resting and intention tremors, and mild psychomotor agitation while maintaining orientation with a congruent anxious mood and affect. What is the most likely etiology of this patient's symptoms?

a. Acute alcohol withdrawal syndrome
b. Exacerbation of endogenous anxiety secondary to diminished alcohol intake
c. Exacerbation of exogenous anxiety secondary to change in employment status
d. Hypertensive emergency with acute coronary syndrome
e. Reactive anxiety secondary to the onset of chest pain

Answer: A. Hypertensive emergency is unlikely given the level of this patient's BP. On the basis of the history alone, it may be difficult to differentiate organic versus functional anxiety or identify an exogenous trigger, but the abnormal vital signs and physical examination associated with a recent cessation of long-term alcohol consumption makes acute alcohol withdrawal the most likely cause. Given the significant morbidity associated with withdrawal states, this must be addressed acutely. Appropriate diagnosis and management of underlying psychiatric disease will be a secondary concern after the patient's withdrawal is managed.

99

Somatic Symptoms and Related Disorders

Karl Huesgen and J. Adrian Tyndall

KEY CONCEPTS

- Several conditions previously classified in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as somatoform disorders are now classified under DSM-V as *Somatic Symptom and Related Disorders* (SSRD). These include somatic symptom disorder (SSD), illness anxiety disorder (IAD), and conversion disorder. They share a common feature of patients' maladaptive and inappropriate psychological response to somatic (bodily) symptoms.
- SSRD patients have approximately twice the rate of medical disease seen in the general population. It is unclear whether this is the consequence of more frequent health care use or whether an increased disease burden prompts these patients to have a greater concern for bodily sensations.
- *SSD* is characterized by disproportionate or persistent health-related thoughts, anxiety, and time and energy devoted to somatic (bodily) symptoms, resulting in disruption of daily life.
- Patients with *IAD,* formerly known as hypochondriasis, have excessive anxiety regarding the possibly having or acquiring a serious medical illness in the presence of minimal or absent somatic symptoms.
- *Conversion disorder,* also known as *functional neurologic symptom disorder,* is characterized by abnormal sensory or voluntary motor function that is found to be incompatible with known neurologic or medical conditions, and that causes significant distress or life impairment.
- The differential diagnoses for SSRD may be broadly divided between (a) psychiatric disorders that manifest somatic symptoms and (b) medical conditions with signs or symptoms that might be attributed to psychiatric disorders.
- A "positive review of systems" in an emergency department (ED) evaluation is similar to a high score on SSRD symptoms severity scales and thus may serve as an inadvertent screen for SSRD. Further research is needed to ascertain whether this is clinically reliable.
- ED care goals for patients with SSRD include establishment of rapport, building a therapeutic alliance, legitimizing the patient's distress, and enhancing the patient's ability to function despite the symptoms.
- Multiple care modalities are available for SSRD treatment. These are typically managed by the patient's primary care physician or psychiatrist.

FOUNDATIONS

Somatic symptom and related disorders (SSRD), formerly known as somatoform disorders, are described as the borderland between psychiatry and medicine and are responsible for some of the most challenging and the least understood patient encounters in the emergency department (ED). Individuals who suffer from these disorders must be identified and treated appropriately to avoid patient suffering, inappropriate resource use, and iatrogenic injuries.

Box 99.1 lists the disorders classified in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as SSRD. They include somatic symptom disorder (SSD), illness anxiety disorder (IAD, formerly known as hypochondriasis), conversion disorder, psychological factors affecting medical illness, and factitious disorder (discussed separately in Chapter 100). Body dysmorphic disorder (excessive concern for a perceived defect in physical features) is no longer included in this group.

Although prior versions of the DSM emphasized medically unexplained symptoms and their putative psychological causes, current descriptions of these disorders focus on patients' maladaptive and inappropriate cognitive and affective responses to somatic symptoms rather than the lack of explanation for them.[1,2] These disorders are thought to be mediated by abnormal sensory perception, processing, interpretation, attribution to pathologic causes, and subsequent hypervigilance toward further sensations.[3–7]

SSRD are common, with a prevalence of approximately 5% to 7% of the adult population, and are present in many patients with medically unexplained symptoms.[1,8] The defining features of these disorders, a maladaptive response to bodily sensations, cause patients to seek help for their illness through medical routes rather than psychiatric avenues. However, the SSRD are typically formally diagnosed only via structured psychiatric interview, and these disorders may take many years to diagnose even in longitudinal primary care settings.[9] The disorders are even more challenging to diagnose during a brief ED encounter prioritizing life-threatening illness.

Difficulty identifying the root cause of patients' distress may cause frustration for both patients and physicians. For example, patients with SSD may have excessive anxiety regarding nonpathologic sensations, whereas patients with IAD may be certain they have a serious medical condition despite contradictory evidence. Thus, after a negative ED work-up, the very nature of the patients' psychiatric condition may leave them feeling that their concerns have not been adequately addressed, prompting pursuit of extensive, expensive, and invasive medical evaluations. SSRD patients have approximately twice the rate of medical disease seen in the general population. It is unclear whether this is the consequence of more frequent health care use or whether an increased disease burden prompts these patients to have a greater concern for bodily sensations.[10]

Clinicians may also feel frustrated by encounters with patients with SSRD. Frequent ED use by patients with unrealistic expectations and subsequent frustrations may cause physicians to feel these encounters were suboptimal. These patients frequently exhibit an extensive "positive review of symptoms," which clinicians may feel obligated to evaluate. Even when clinicians suspect SSRD, they are often unwilling to ascribe patient concerns to psychiatric illness at the exclusion of rare but consequential medical diagnoses with nonspecific presentations. However, if the patients' concerns are recognized and addressed within

BOX 99.1 Somatic Symptom and Related Disorders

Somatic symptom and related disorders share a common feature of patients' maladaptive and inappropriate psychological response to somatic (bodily) symptoms
Somatic symptom disorder
Illness anxiety disorder
Conversion disorder (functional neurologic symptom disorder)
Psychological factors affecting other medical conditions
Factitious disorder

BOX 99.2 Differential Diagnosis of Somatic Symptom Disorder

Psychiatric Conditions	Medical Conditions
Depression disorders	Transient ischemic attack
Anxiety disorders	Multiple sclerosis
Obsessive-compulsive disorder	Systemic lupus erythematosus
Schizophrenia	Thyroid and parathyroid disorders
Personality disorders	Electrolyte disorders
Substance abuse disorders	Human immunodeficiency virus (HIV)
Malingering	Anti-NMDA receptor encephalitis

a patient-centered framework, clinicians may recognize that the "difficult patient" with a "positive review of systems" may have a psychiatric illness requiring further evaluation in an outpatient medical or psychiatric setting.

CLINICAL FEATURES

Patients with SSRD experience physical symptoms associated with significant distress and impairment that cannot be adequately explained by demonstrable physical pathology despite appropriate medical investigation. These disorders are most common in women of lower socioeconomic status in their 20s and 30s but may be present in any demographic group. Depressive and anxiety disorders are common comorbid conditions, as are nonpsychiatric medical diagnoses.[1]

Somatic Symptom Disorder

Patients with SSD have disproportionate or persistent health-related thoughts, anxiety, and time and energy devoted to somatic (bodily) symptoms, resulting in disruption of daily life. Previous editions of the DSM described a causal relationship between a patient's emotions and subsequent symptoms (termed somatization). The disorder criteria now focus upon the abnormal psychological response to bodily sensations rather than to a lack of medical explanation for symptoms.[1] Research indicates these patients have abnormal autonomic activity and reactivity, as well as measurably altered emotional processing and bodily awareness.[7] A subset of SSD patients includes patients for whom pain is the primary concern. Previously called pain disorder, this diagnosis is now termed *SSD with predominant pain*. For these patients, pain may represent normal bodily function in conjunction with spinal or higher-CNS sensitization from prior experience and genetic factors.[1,11] Of note, because the diagnosis of SSD depends upon the maladaptive psychological response to bodily sensations rather than the lack of medical explanation alone, the symptoms alone from fibromyalgia, irritable bowel syndrome, or multiple chemical sensitivities do not meet criteria for SSD.[1]

Illness Anxiety Disorder

Patients with IAD have minimal or absent somatic symptoms but present with excessive anxiety regarding possibly having or acquiring a serious medical illness. Formerly known as hypochondriasis, IAD is now the preferred nomenclature to avoid pejorative connotations. IAD persists despite repeatedly negative medical evaluations, and the anxiety associated with this condition can produce either excessive health-related behaviors or maladaptive health care avoidance, resulting in care-seeking and care-avoidant subtypes, respectively. Care-seeking subtypes are at risk for iatrogenic complications of excessive testing.[1]

Conversion Disorder

Patients with conversion disorder, now commonly referred to as *functional neurologic symptom disorder*, have altered sensory or voluntary motor function that is found to be incompatible with known neurologic or medical conditions and that causes the patient significant distress or life impairment. This disorder may have a variety of presentations, including seizure-like activity, focal weakness, memory disturbances, dysphonia, blindness, or alterations of any sensory system. Upon medical examination, however, no pathologic correlates are identified, and serial neurologic examinations often demonstrate inconsistent disability. For example, in the Hoover test, a supine patient may demonstrate normal hip extension (pushing down) with a "paralyzed" leg when asked to flex (lift) the contralateral hip. Similarly, patients may demonstrate inability to turn their head toward a "paralyzed" side but use the "paralyzed" sternocleidomastoid to turn from it. Coincident life stress is associated with but not essential for the diagnosis. The presence of *la belle indifference* (i.e., an inappropriate lack of concern regarding a seemingly profound disability) is also associated with but not specific to this disorder. Proven intentionality is not necessary for the diagnosis.[1]

Factitious Disorder

In contrast to conversion disorder, factitious disorder is characterized by purposefully deceptive falsification of disease signs or symptoms for the sole purpose of causing others to see the person with the disorder as ill. In the case of Munchausen by proxy, the person induces symptoms in another patient, typically a child.[1,12] These disorders are discussed in greater detail in Chapter 100.

Psychological Factors Affecting Medical Illness

Psychological factors affecting medical illness is a separate category included in SSRD due to the predominance of somatic symptoms and propensity to present in medical settings. This includes psychological factors that exacerbate or delay recovery from medical conditions, reduce adherence to medical treatment, or pose additional risk harm. Examples include anxiety-exacerbated asthma, or stress-induced Takotsubo cardiomyopathy.[1]

DIFFERENTIAL DIAGNOSES

Other psychiatric disorders may initially present with somatic symptoms, including major depressive disorder and anxiety disorders. The differential diagnoses for the SSRD may be broadly separated into two groups: psychiatric disorders that manifest somatic symptoms and medical conditions with signs or symptoms that might be attributed to psychiatric disorders (Box 99.2).[1,13] For example, psychiatric patients with panic disorder may present with complaints of palpitations and dyspnea, and patients with major depressive disorder might present with sleep disturbances. Alternatively, many medical diagnoses can have subtle or variable presentations which might be attributed to psychiatric disorders (e.g., hypothyroidism-induced fatigue attributed to

depression, sensory loss due to multiple sclerosis, or behavioral disturbances secondary to anti-N-methyl-d-aspartate (NMDA) receptor encephalitis).[14]

DIAGNOSTIC TESTING

The very nature of SSRD often prompts repeated and extensive evaluations of patients' somatic complaints. Diagnostic testing for possible organic diagnoses should be based upon a physician's standard practice for evaluating a presenting medical complaint and not upon a patient's desire for additional testing to reassure them that an undiagnosed medical disorder is not present. Unnecessary testing may put patients at risk for diagnostic false-positives and iatrogenic injury. The exception to this rule is the patient with functional neurologic symptom disorder or conversion disorder. Neurologic disorders such as transient ischemic attacks, multiple sclerosis, and atypical migraine headaches may have subtle presentations. In these cases, it may require imaging studies and both neurologic and psychiatric consultations to avoid the misdiagnosis of a patient who requires intervention.

Specific SSRD diagnoses are suggested by the overall clinical picture rather than single discrete findings. For example, excessive anxiety despite a negative chest pain work-up would suggest SSD, or an inappropriate lack of concern regarding a hemiparesis would suggest conversion disorder. Diagnostic reliability for SSRD is improved with formal structured clinical interviews, typically in psychiatric or primary care settings.[15] Self-report questionnaires have shown promise in these settings.[16,17] Clinicians typically have neither the time nor the clinical training to perform structured clinical interviews for formal SSRD diagnosis; however, brief 2- to 3-minute self-report instruments (e.g., SSD-12) are available for outpatient screening of patients' symptom-related thoughts, feeling, and behaviors, although further research is needed regarding whether these are applicable to an emergency setting.[18,19] It is notable that tests of SSRD patients' symptoms severity (e.g., Patient Health Questionaire-15 [PHQ-15]) resemble a standard emergency medicine review of symptoms (e.g., has the patient had chest pain, shortness of breath, dizziness, nausea, headaches in the past month, and whether these symptoms bothered patient not at all, a little, or a lot). On this test, a score at greater than 10 indicates high risk for somatoform disorders.[20] Therefore a positive review of systems in a normal ED evaluation may serve as an inadvertent screen for SSRD. If organic causes of patients' symptoms are not identified, psychiatric consultation or referral could be considered for formal SSRD diagnosis.

MANAGEMENT

The management of patients with SSRD is challenging. Whereas most patients trust their doctors' conclusions, SSRD produce an inherent conflict between the patient beliefs and physician reassurance. Even patients with insight into their disorder may harbor unshakable beliefs of physical illness despite evidence to the contrary. On the other hand, one must be aware of the possibility of an unexplained medical illness that can confound diagnosis and management. It is thus incumbent upon the physician to build rapport by demonstrating attention, empathy, and the desire to alleviate the patient's suffering. One should recognize and communicate understanding of the life impact of the patient's somatic and psychiatric symptoms. After building a therapeutic alliance, it may be helpful to discuss the patient's illness with them in terms of a chronic disease that can be mitigated but not fully alleviated. In this way, patients may focus on maximizing life function in spite of their disorder rather than eliminating the symptoms.[13] Naming the disorder itself may improve the therapeutic alliance.[21] Long-term treatment of SSRD typically involves the use of medications (e.g., SSRIs) with or without therapy (e.g., cognitive behavioral therapy) that is best managed by primary care physicians or psychiatrists. These treatments are not initiated by an emergency clinician but may be started by a psychiatric consultant.[22]

DISPOSITION

In the absence other factors necessitating medical or psychiatric admission, patients with SSRD may be discharged with outpatient primary care or psychiatric follow-up. They should be told that acute life-threatening diagnoses have been ruled out and that further testing and additional medications are not indicated at this time. Emphasize to the patient that even in the absence of a satisfactory explanation for their symptoms, psychiatric intervention may be useful in mitigating life impacts of their symptomatology.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 99: QUESTION AND ANSWERS

1. Which of the following characterizes patients with somatic symptom disorder (SSD)?
- **a.** Patients have an inappropriate lack of concern for profound disability.
- **b.** Patients intentionally and deceptively falsify symptoms.
- **c.** Patients strongly believe they have a particular serious medical illness.
- **d.** Patients have a maladaptive psychological response to bodily symptoms.

Answer: d. The defining feature of SSD is the psychological response to somatic symptoms.

2. A patient presents with the inability to move the left side of his body, but he is easily able to turn his head to the right. He also appears relatively unworried about his symptom severity. This presentation suggests which somatic symptom and related disorder (SSRD)?
- **a.** Somatic symptom disorder.
- **b.** Illness anxiety disorder.
- **c.** Conversion disorder.
- **d.** Psychological factors affecting medical illness.

Answer: c. Normal sternocleidomastoid function ipsilateral to the otherwise-paralyzed side and presence of *la belle indifference* suggest conversion disorder.

3. A patient presents multiple, nonspecific symptoms and believes that she has cancer despite multiple previous evaluations in emergency, primary care, and specialist settings. She says she is certain of this diagnosis, that it causes a significant amount of anxiety and that she spends several hours each day researching the subject. Your standard work-up for her presenting symptoms is negative. What should you do?
- **a.** Perform a few more tests to reassure the patient.
- **b.** Tell the patient that this is "all in your head" and promptly discharge.
- **c.** Place the patient under an involuntary psychiatric hold for self-harm.
- **d.** Seek therapeutic alliance, provide reassurance, and refer the patient to primary care or psychiatry for management.

Answer: d. This patient's presentation is consistent with illness anxiety disorder, formerly known as hypochondriasis. Note that patients with this disorder may have few or no somatic symptoms.

4. A predominance of pain is a subtype of which of the somatic symptom and related disorders?
- **a.** Somatic symptom disorder.
- **b.** Illness anxiety disorder.
- **c.** Conversion disorder.
- **d.** Psychological factors affecting medical illness.

Answer: a. Predominant pain is a subtype of somatic symptom disorder in which pain is the defining symptom. This may be due to prior neural sensitization or genetic predisposition.

5. Which of the following is considered the gold standard for diagnosing somatic symptom and related disorders (SSRD)?
- **a.** Elimination of other possible medical conditions via extensive medical testing.
- **b.** Structured clinical interview.
- **c.** A positive review of symptoms.
- **d.** Emergency physician gestalt.

Answer: b. SSRD diagnoses are suggested by overall clinical picture and may be supported by self-report questionnaires. However, final diagnosis is typically based upon formal structured clinical interview in psychiatric or primary care settings. Note that a "positive ROS" is similar to high scores on SSRD symptom severity questionnaires.

Factitious Disorders and Malingering

Henry W. Young II and Joseph E. Thornton

KEY CONCEPTS

- Patients who have consciously synthesized symptoms and signs may be divided into two broad diagnostic categories: (1) those with obvious secondary gain (malingering), who control their actions, and (2) those with a motivation of achieving the sick role (factitious disorders), who cannot control their actions.
- The initial management of patients suspected of fabricating disease should include a caring, nonjudgmental attitude and a search for objective clinical evidence of treatable medical or psychiatric illness. Review of old medical records and interviews of family members are often helpful.
- Unnecessary tests, medications, and hospitalizations should be avoided in the absence of objective evidence of a medical or psychiatric disease, and patients should be referred for ongoing primary care.
- In cases of suspected factitious disorder imposed on another (FDIA) involving children or elders, protection of the victim takes first priority.

FOUNDATIONS

Patients may present to the emergency department (ED) with symptoms that are simulated or intentionally produced. The reasons that cause this behavior define two disorders: factitious disorders and malingering.

Factitious disorders are characterized by symptoms or signs that are intentionally produced or feigned by the patient in the absence of apparent external incentives.[1,2] These patients constitute up to 3% of general psychiatric referrals.[3] However, the prevalence of factitious disorders in emergency departments is thought to be higher because these patients rarely accept psychiatric treatment and are frequently undiagnosed.[2,4] These patients are often seen in other health care settings including infectious disease for fever of unknown origin, epilepsy clinics for psychogenic seizures, and nephrology clinics for renal stones.[3] Factitious disorders have been associated with costs up to $1 million per case.[3] Early diagnosis of factitious disorder can have a significant impact on the utilization of unnecessary investigations, treatments, and hospital admissions within a health care system.[3]

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) classifies factitious disorders into two types: factitious disorder imposed on self (FDIS) and factitious disorder imposed on another (FDIA).[1]

Munchausen syndrome, the most dramatic form of FDIS, was originally described in 1951.[8] This rare syndrome takes its name from Baron Karl F. von Munchausen (1720–1797), a revered German military officer and noted raconteur who had his embellished life stories stolen and parodied in a 1785 pamphlet.[4] While commonly discussed, the incidence of Munchausen syndrome is estimated to be approximately 0.5 to 2 per 100,000 children.[5] Other names used to describe FDIS include the "hospital hobo syndrome" (patients wander from hospital to hospital seeking admission), peregrinating (wandering) patients, hospital addict, polysurgical addiction, and hospital vagrant.[3,6]

Factitious disorder imposed on another (FDIA) involves the simulation or production of a factitious mental or physical disease in an individual by a caregiver. It was first described in 1977.[1] Due to the difficulty in identification, the prevalence of FDIA is not known.[5] This condition often involves a child and a mother. The condition excludes straightforward physical abuse or neglect and simple failure to thrive; mere lying to cover up physical abuse is not FDIA. The key discriminator is motive: the caregiver is making the child ill so that they can vicariously assume the sick role with all its benefits.[3] FDIA has a mortality rate of 6% to 30%.[6,7] Permanent disfigurement or permanent impairment of function can occur directly from induced disease or indirectly from invasive procedures, multiple medications, or major surgery. Other names applied to this condition include *Polle syndrome* (Polle was a child of Baron Munchausen who died mysteriously), *factitious disorder by proxy, pediatric condition falsification, Munchausen syndrome by proxy,* and *Meadow syndrome.*[3,7]

Malingering is the simulation of disease by the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives, such as avoidance of military responsibility, avoidance of work, obtaining financial compensation, evading criminal prosecution, obtaining medication, hospital admission (for the purpose of obtaining free room and board), or securing of better living conditions.[1] The most common goal among such "patients" presenting to the ED is to obtain medications, whereas in the office or clinic the gain is more commonly insurance payments or industrial injury settlements. The true incidence of malingering is difficult to gauge because of underreporting, but estimates include a 1% incidence among mental health patients in civilian clinical practice, and as high as 10% among inpatient psychiatric patients with suicidality.[8-10] In one review, 33% of patients assessed in a psychiatric emergency department were suspected of malingering.[8] Some clinicians are resistant to document malingering in a patients' chart due to concern for lack of reimbursement and legal liability.[8,9] The most likely conditions to be feigned are conditions that are difficult to exclude objectively, such as suicidal ideations, depression, mild head injury, fibromyalgia, chronic fatigue syndrome, and chronic pain.[3,7,11-13]

CLINICAL FEATURES

Factitious Disorders

Factitious Disorders Imposed on Self

The diagnosis of FDIS depends on specific criteria (Box 100.1).[1] With a factitious disorder, the production of symptoms and signs is compulsive; the patient is unable to refrain from the behavior even when its risks are known. The behavior is voluntary only in the sense that it is deliberate and purposeful (intentional) but not in the sense that the acts can be fully controlled. The underlying motivation for producing

BOX 100.1 DSM-5 Criteria for the Diagnosis of Factitious Disorder Imposed on Self

1. Falsification of psychological or physical signs or symptoms, or induction of disease or injury associated with identified deception.
2. The individual presents to others as injured, ill, or impaired.
3. The deceptive behavior is apparent even in the absence of external incentives.
4. The behavior is not better explained by another mental disorder.

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

these deceptions, securing the sick role, is primarily unconscious.[1,2] Individuals who readily admit that they have produced their own injuries (e.g., self-mutilation) are not included in the category of factitious disorders. Presentations may be acute, in response to an identifiable recent psychosocial stress (termination of romantic relationship, threats to self-esteem), or a chronic life pattern, reflective of the way in which the person deals with life in general. The symptoms involved may be either psychological or physical.[3,5,7]

Psychological Symptoms. Individuals may intentionally produce or feign psychological (often psychotic) symptoms suggestive of a mental disorder. Stimulants may be used to induce restlessness or insomnia; hallucinogens, to create altered levels of consciousness; and hypnotics, to produce lethargy. This psychological factitious condition is less common than factitious disorders with physical symptoms and is almost always superimposed on a severe personality disorder.[1,3,5]

Physical Symptoms. The intentional production of physical symptoms may take the form of fabricating symptoms without signs (e.g., feigning abdominal pain), simulation of signs suggesting illness (e.g., fraudulent pyuria, induced anemia), self-inflicted conditions (e.g., the production of abscesses by injection of contaminated material under the skin), or genuine complications from the intentional misuse of medications (e.g., hypoglycemic agents).[3] These patients are predominantly unmarried women younger than 40 years old.[1] They typically accept their illness with few complaints and are generally well-educated, responsible workers or students with moral attitudes and otherwise conscientious behavior. A majority of individuals with factitious disorder are employed in health care settings, including laboratory technicians, nurses, and physicians. There is an increased rate of personality disorders and depression among individuals with factitious disorder.[2-5,7]

These patients are willing to undergo incredible hardship, limb amputation, organ loss, and even death to perpetuate the masquerade.[4] Although multiple hospitalizations often lead to iatrogenic physical conditions, such as postoperative pain syndromes and drug addictions, patients continue to seek hospitalization for its own sake. They typically have a fragile and fragmented self-image and are susceptible to psychotic and suicidal episodes.[3] Interactions with the health care system and relationships with caregivers provide the needed structure that stabilizes the patient's sense of self.[4] Some patients are driven by the conviction that they have a real but as yet undiscovered illness. Consequently, artificial symptoms are contrived to convince the physician to continue a search for the elusive disease process. Factitious illness behavior has also emerged on the internet. "Virtual support groups" offering person-to-person communications through chat rooms or websites have been perpetrated by individuals, under the pretense of illness or personal crisis, for the purpose of extracting attention or sympathy, acting out anger, or exercising control over others.[4]

Munchausen Syndrome. The uncommon patient with true Munchausen syndrome has a prolonged pattern of "medical imposture," usually years in duration. The diagnosis may be delayed several years.[12] The average age at presentation is 34 years, and the syndrome is most commonly found in women. Patients' entire adult lives may consist of trying to gain admission to hospitals and then resisting discharge. The majority of patients work in the health care field.[2,3,14] The quest for repeated hospitalizations often takes these patients to numerous and widespread cities and states.[6]

These individuals see themselves as important people, or at least related to such persons, and their life events are depicted as exceptional. They possess extensive knowledge of medical terminology. There is frequently a history of genuine disease, and the individual may exhibit objective physical findings.[4]

The symptoms presented are "limited only by the person's medical knowledge, sophistication, and imagination."[1] Common presentations are those that most reliably result in admission to the hospital, such as abdominal pain, self-injection of a foreign substance, feculent urine, bleeding disorders, hemoptysis, paroxysmal headaches, seizures, shortness of breath, asthma with respiratory failure, chronic pain, acute cardiovascular symptoms (e.g., chest pain, induced hypertension, and syncope), renal colic and spurious urolithiasis, fever of unknown origin, and profound hypoglycemia.[3] Some self-induced conditions are highly injurious or even lethal.[15]

The patient usually presents during evenings or on weekends so as to minimize accessibility to psychiatric consultants, personal physicians, and past medical records. In teaching institutions, these patients often present in July, shortly after the change in resident house officers. They relate their history in a precise, dramatic, even intriguing fashion, embellished with flourishes of pathologic lying and self-aggrandizement. *Pseudologia fantastica,* or pathologic lying, is a distinctive peculiarity of such patients. In a chronic, often lifelong behavior pattern, the patient typically takes a central and heroic role in these tales, which may function as a way to act out fantasy.[16] The history quickly becomes vague and inconsistent, however, when the patient is questioned in detail about medical contacts. Attempts to manage the complaint on an outpatient basis are adamantly resisted. Once admitted, the patient initially appeals to the physician's qualities of nurturance and omnipotence, lavishing praise on the caregivers. Behavior rapidly evolves, however, as the patient creates havoc on the ward by insisting on excessive attention while ignoring both hospital rules and the prescribed therapeutic regimen. When the hoax is uncovered and the patient confronted, fear of rejection may abruptly change into rage against the treating physician, closely followed by departure from the hospital against medical advice.

Factitious Disorder Imposed on Another

The diagnosis of FDIA depends on specific criteria (Box 100.2).[2] FDIA is also referred to as Munchausen by proxy or medical child abuse, or a subset of battered child syndrome.[4,7,17] The diagnostic term is applied to the perpetrator of an abuse of a child, which is a criminal event and in most states requires referral once suspected.[4,18,19] The presenting complaints typically evade definitive diagnosis and are refractory to conventional therapy for no apparent reason. They usually present with more than five symptoms, presented in a confused picture; they are unusual or serious and, by design, unverifiable. Gold standard diagnostic methods include a separation test and covert video surveillance.[3,19]

Simulated illness, faked by the caregiver without producing direct harm to the patient (e.g., the addition of blood to a urine specimen), is present in 25% of cases. Produced illness, which the caregiver actually inflicts on the patient (e.g., the injection of feces into an intravenous line), is found in 50% of cases. Both simulated and produced illnesses are found in 25% of cases.[4]

BOX 100.2 DSM-5 Criteria for the Diagnosis of Factitious Disorder Imposed on Another

1. Falsification of psychological or physical signs or symptoms, or induction of disease or injury in another, associated with identified deception.
2. The individual presents another individual (victim) to others as injured, ill, or impaired.
3. The deceptive behavior is apparent even in the absence of external incentives.
4. The behavior is not better explained by another mental disorder.

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5. Arlington, VA: American Psychiatric Association; 2013.

FDIA most commonly arises with factitious bleeding, seizures, central nervous system (CNS) depression, apnea, diarrhea, vomiting, fever, and rash. Reported techniques of simulation or production of disease include fever manipulations and administration of drugs or toxins (e.g., chronic arsenic poisoning, mercury poisoning, ipecac, warfarin, salt, imipramine, laxatives, or CNS depressants), or caustics applied to the skin.[4,17] Techniques of asphyxiation include (1) covering the mouth or nose with one or both hands, a cloth, or plastic film, and (2) inserting the fingers into the back of the mouth. In such instances, even struggling infants may sustain no cutaneous markings. Cases involving seizures are common and may involve third-party witnesses. On personal questioning, however, these witnesses frequently deny the occurrence of seizure activity.[4]

Perpetrator Characteristics. Ninety-eight percent of perpetrators are biological mothers who come from all socioeconomic groups.[7,17,18] Many have a background in health professions or social work, or a past history of psychiatric treatment, marital problems, or suicide attempts. Depression, anxiety, and somatization are common, but overt psychotic behavior by the mother is atypical.[7] Perpetrators of FDIA are skilled in manipulating health care workers and child protection services. They are pleasant, socially adept, cooperative, and appreciative of good medical care. They often display a peculiar eagerness to have invasive procedures performed on their child. They often prefer to stay in the hospital with their child, cultivate unusually close relationships with hospital staff, and thrive on staff attention. This affable relationship with the medical team rapidly changes to excessive anger and denial when the perpetrator is confronted with suspicions.[7,18]

Most of these mothers have had an abusive experience early in life, and they use the health care system as a means to satisfy personal nurturing demands.[7] They often cannot distinguish their needs from the child's and satisfy their own needs first. They derive a sense of purpose from the medical and nursing attention gained when their children are in the hospital. Alternatively, the behavior may enable the mothers to escape from their own physical or psychological illnesses, marital difficulties, or social problems.[4]

Victim Characteristics. Victims of FDIA are equally male and female children. The proper diagnosis for the victims of FDIA is the coding for confirmed or suspected child physical abuse (995.4) and the appropriate injury code.[1,4] The child or vulnerable adult may also suffer physical or psychological consequences of unnecessary medical procedures. The mean age at diagnosis is 40 months, and the mean duration from the onset of signs and symptoms to diagnosis is 15 months.[17,18] A known physical illness that explains part of the symptoms is common among these children.[13] Most have a history of significant failure to thrive and have been hospitalized in more than one institution. Delays in many areas of performance and learning, difficulty with family relationships, attention deficit disorder, or clinical depression may coexist. Some of these victims may have factitious disorder later in life or even PTSD.[4] Elders may also be victims of FDIA, although this is uncommon.[4]

BOX 100.3 Characteristics of Malingering

1. Medicolegal context of the presentation (e.g., the patient was referred by his or her attorney)
2. Marked discrepancy between the person's claimed stress or disability and objective findings
3. Poor cooperation during the diagnostic evaluation or poor compliance with previously prescribed treatment regimens
4. The person exhibits or has a history of antisocial behavior

Malingering

Malingering is frequently found in association with antisocial personality disorder and substance abuse.[20] On questioning, malingerers are vague about prior hospitalizations or treatments. The physicians who previously treated them are usually unavailable. At times, malingerers may be careless about their symptoms and abandon them when they believe no one is watching. Common sources for secondary gain include opiate drug administration, shelter among the homeless, financial gains or avoidance of incarceration.[8,13] Since pain is a subjective experience, providers may have little objective evidence to quantify the degree of pain an individual is having. Malingerers who pursue drugs may report an unusually large number of drug allergies to persuade the physician to prescribe their drug of choice or simply insist on a specific drug (e.g., meperidine [Demerol] or hydromorphone [Dilaudid]). Unfortunately, the internet offers a wide availability of quality medical advice on how to convincingly feign pain and disability. In other persons, the external incentive may be obscure.

In contrast to the person with factitious disorders, the malingerer prefers counterfeit mental illness, because it is objectively difficult to verify or to disprove. Suicidal ideation is the most common psychological presentation, followed by psychosis, depression, and withdrawal syndromes.[8]

Malingering should be strongly suspected with any combination of certain factors (Box 100.3).[1] A definitive diagnosis of malingering is rare and can be established only with the patient's confession. Because malingering could constitute criminal behavior, documentation of this diagnosis must be made with care. In the absence of proof of wrongdoing, it is best to assume that the patient is not a malingerer but rather a somatizer. Due to the possible implications for diagnosing a patient as a malingerer, it is most appropriate to document the individual's behaviors.[27]

The clinical interview is especially important in identifying an individual that is malingering, with additional care to identify atypical presentations. The health care provider should be mindful in phrasing their questions to avoid providing insight on the typical presentation and begin the interview with open-ended questions, first allowing the individual to recount their symptoms in their own words and then asking more specific questions. Also be aware that patients who malinger often have true illnesses such as substance abuse or paranoia.[16,20,21]

DIFFERENTIAL DIAGNOSES

The most important diagnoses to be excluded are genuine medical and psychiatric conditions that might account for the presenting symptoms. Patients with conversion disorder, somatic disorder, delusional disorder of somatic type, and borderline personality disorder can present with symptoms similar to FDIS. The differences can be subtle and psychiatric consultation or referral is indicated.

Patients with factitious disorders are distinguished from malingerers because their desired hospitalization or surgery seems to offer no secondary gain other than to play the sick role.[1] The clinical presentation of the majority of patients with factitious disorders, unlike those with Munchausen syndrome, is relatively subtle and convincing. The complaints are generally chronic in nature rather than emergent and precipitous, and there are no obvious associated behavioral aberrations. The chronicity of malingering is usually less than that associated with factitious disorder, and malingerers are more reluctant to accept expensive, possibly painful, or dangerous tests or surgery.[4,21]

It can be useful to consider factitious disorders along a continuum of malingering, which are symptoms consciously produced for obvious secondary gain; factitious disorders, which are symptoms which are intentionally produced without obvious secondary gain; and somatization disorders, which are symptoms unconsciously produced for unconscious psychological gain. In fact, even within a patient, clinical presentations may present along this continuum at different times.[5,22] Additionally, it is important to know that there is significant morbidity and occasionally mortality associated with this spectrum of disorders. When a clinician suspects that there may be a factitious component to the clinical presentation due to an unexpected clinical course, it is useful to continue to think of a comprehensive and systematic differential diagnosis, but instead of aggressive pursuit of a rare diagnosis, to consider with the patient what problems the patient is facing and how their symptoms impact those problems.[4] The clinician can then formulate a treatment plan that addresses the root cause of these somatic symptoms.

DIAGNOSTIC TESTING

Unnecessary tests, medications, and hospitalizations should be avoided in the absence of objective evidence of a medical or psychiatric disease, and patients should be referred for ongoing primary care.

Factitious Disorder

The initial diagnosis of FDIS is often delayed because the possibility of factitious disease is not considered, physicians may be unfamiliar with this problem, or the physician is concerned about the consequences of making a mistaken diagnosis of FDIS.[9,23] Diagnosis may be confounded by genuine medical illnesses predating and coexisting with a factitious disorder. For example, patients with factitious hypoglycemia may have a history of insulin-dependent diabetes mellitus, or factitious skin disorders may be preceded by true dermatologic diseases.[4] Identification of a factitious disorder is usually made when (1) the patient's account of symptoms is patently inconsistent, (2) the patient's symptoms are too consistent with textbook descriptions, (3) laboratory findings are inconsistent (e.g., low C-peptide in context of high insulin confirms exogenous administration of insulin), (4) the patient is accidentally[4] discovered in the act, (5) incriminating items are found, (6) a combination of the preceding, or (7) the diagnosis is made by a historical pattern of medical documentation and exclusion.[4,21]

There has been increasing recognition of factitious illness produced by children. These children, ranging in age from 8 to 18 years old, are typically "bland, flat and indifferent during their extensive medical interventions, depressed, socially isolated, and often obese."[4] Among the most common presentations are fever without clear etiology, diabetic ketoacidosis, purpura, and recurrent infections. The prognosis is good if identification and psychotherapeutic intervention can be carried out at a young age.[4,12]

Suspected FDIA requires a detailed description of the event or illness and a search for caregiver witnesses, who should be interviewed personally. Although it is essential to see the child when the symptoms are present, the caretaker often makes this difficult.[7,11] Additional history of unusual illness in siblings and parents should be sought. Child victims who are verbal should be interviewed in private about foods, medicines, and their recollection of the symptoms or events. Prior medical records of the victim and, if possible, the siblings should be examined, although parents may impede such data-gathering.[5,11]

The major obstacle to early discovery of FDIA is its omission from the differential diagnosis. When it is considered, the diagnosis is generally made easily and quickly.[11] A suspected diagnosis may be confirmed through separation of the parent from the child or individual (with consequent cessation of symptoms), covert video surveillance during hospitalization, or toxicologic screens.[7] The caregiver may attempt to induce episodes surreptitiously while in the hospital.[7]

Malingering

There have been several tools designed to assist with the identification of malingerers. Two common tools are the Structured Interview of Reported Symptoms (SIRS) and the Miller Forensic Assessment of Symptoms Test (M-FAST). Although both tools have been assessed in a variety of populations, neither has been thoroughly assessed in the ED. The SIRS questionnaire has been well studied and validated, but its duration makes it less suitable for performance in an emergency setting. Although the M-FAST is considerably shorter, highly sensitive, and easy to interpret, there is inadequate data to recommend this tool for clinical use in the ED at this time.[10] Similarly, tests designed to assess malingered pain currently lack validity studies involving known populations with malingered pain and have not been found to reliably detect malingering pain.[24]

MANAGEMENT

The initial management of patients suspected of fabricating disease should include a caring, nonjudgmental attitude and a search for objective clinical evidence of treatable medical or psychiatric illness.

Factitious Disorders

Treatment options for factitious disorders depend on the patient's characteristics. Although it is challenging, management of common forms of factitious disorder can be more rewarding, especially with adolescents, than management of Munchausen syndrome.[5] The prognosis is more favorable for cases with an underlying depression than for those associated with borderline personalities.[5]

The best approach to patients with factitious disorder, other than Munchausen syndrome and FDIA, is controversial. Direct nonaccusatory confrontation has been advocated as "the foundation of effective management" when it is coupled with the assurance that an ongoing relationship with a physician will be provided. This may be the first step in the acceptance of outpatient therapy.[25]

Others point out that confrontation is ineffective in most patients and may even be counterproductive in that it threatens to undermine a needed psychological defense. Enforced recognition of external objective reality, while simultaneously disallowing the patient's subjective experience, may generate even more dysfunction directed at legitimizing and maintaining symptoms and may even place the patient at risk for escalation of symptoms.[9,25] Because emergency clinicians rarely, if ever, provide longitudinal care to patients with factitious disorders, we recommend referral for ongoing care, rather than direct confrontation in the ED.

Individuals with Munchausen syndrome typically demonstrate sociopathic traits or a borderline personality disorder and are demanding and manipulative, especially regarding analgesics. They can be difficult to treat. Early confrontation or limit-setting, especially regarding

drug use, is recommended. Although Munchausen patients typically do not want to be examined extensively, a thorough physical examination should be performed to rule out physical disease.[12,24,25]

FDIA constitutes a form of child (or elder) abuse, and appropriate action to protect the victim, including notification of state social service agencies, should take immediate priority. If available, a pediatrician who has expertise in child abuse should assess the case.[5,11] When the diagnosis has been established and the parents have been confronted, psychiatric care should be made immediately available to the parents because escalation of symptoms, including repeat abuse, abuse of siblings, and even fatalities, have been reported.[26]

Malingering

Malingerers do not want to be treated. Because they are "gaming the system" for personal gain, they do not want an accurate identification of their behavior and appropriate intervention. The emergency clinician should maintain clinical neutrality, offering the reassurance that the symptoms and examination are not consistent with any serious disease.[25] If there is no medical issue necessitating admission, admission is not recommended for malingerers. Among patients found to be malingering, admission was more likely in those feigning suicidality or seeking housing or social services.[8]

Some authors have characterized patients' use of medical resources under false pretenses as criminal behavior, and several states have enacted legislation against the fraudulent acquisition of medical services with successful prosecution of such behavior.[9,27] Conversely, patients with malingering disorders can and do sue.[27] In dealing with such patients, it is advisable to involve hospital administration and risk management. Clandestine searches are inadvisable, and respect for the patient's confidentiality should be maintained.[25]

DISPOSITION

Patients suspected of having a factitious disorder should be referred for primary care follow-up, and if it is acceptable to the patient, psychiatric referral should also be arranged. Referral to other medical specialists or hospitalization should be avoided when possible.[8,25]

The manner of presentation and the unavailability of past medical history often allow patients with Munchausen syndrome to achieve hospital admission. If the patient is discharged from the ED, outpatient primary care follow-up and psychiatric referral should be offered, although both are likely to be refused.

Because perpetrators of FDIA typically induce symptomatic episodes soon after hospitalization, admission of the victims (children or elders) without taking appropriate precautions may actually place them at increased risk. Visits by the suspected perpetrator should be closely supervised, and no food, drink, or medicines should be brought in by the family.[5] Protective services should be notified. Out-of-home placement of children in established cases of FDIA is recommended, and the best outcomes are seen among children taken into long-term care at an early age without access to their mother.[5] Children allowed to return home have a high rate of repeated abuse.[5] After the removal of the index child, the subsequent abuse rate of previous siblings is as high as 50%.[5]

After courteous but assertive reassurance, suspected malingerers should be offered primary care follow-up if the symptoms do not resolve. These individuals may become threatening when they are either denied treatment or overtly confronted.

There is a risk for escalation by the patient when they do not receive the therapy or outcome that they desire. This escalation can include threats of harm to the staff and/or the patient. While prior studies suggest that threats of suicide in these circumstances are usually not acted upon, the risk should be assessed. If necessary, consider involving psychiatry for a safety evaluation.[25]

Because prior encounters involving malingering and factitious disorder are important to recognizing similar presentations in the future, it is important to record visits for factitious disorder and malingering in the electronic medical record in a manner that is easily located such as in the problem list or past medical history. Included with the diagnosis should be a narrative including subjective and objective events during that encounter that were used to identify this disorder. In doing so, it is possible to limit unnecessary testing in the future. The goal of inclusion of this information is not to encourage cognitive bias for future providers, but to inform them of features of prior encounters that were concerning. It is important that every new complaint and encounter is evaluated, and that all identified medical needs are addressed.[25]

Once a decision for discharge is made, there should be a discussion with the treatment team including the concern that the patient may not receive the notice of discharge positively. A plan should be made with the treatment team to prepare for possible escalation by the patient. Consider having security presence nearby, if needed. All prescription orders and necessary forms should be prepared and readied to be provided to the patient at the conclusion of the conversation. During the discussion with the patient, direct language and a neutral tone should be used. After the patient is discharged, a debrief should be conducted among the treatment team to identify opportunities to improve the process in the future.[25]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 100: QUESTIONS AND ANSWERS

1. Which of the following statements regarding factitious disorder is true?

a. It involves voluntary and controllable symptom production.
b. Patients are generally well educated and otherwise responsible.
c. Presentations are not related to an identifiable event.
d. The symptoms produced are always physical ones.
e. The underlying motivation is a conscious one.

Answer: B. Many such patients are actually employed in the health care industry. The act of producing symptoms is voluntary but not controllable and derives from a subconscious motivation. Presentations are very often related to a "traumatic" event, such as a breakup. Produced symptoms may be physical (e.g., hematuria) or psychological. The typical patient is an unmarried female younger than 40 years. Despite undergoing invasive procedures and associated hardships, these patients seek more medical care and hospitalization.

2. Which of the following statements concerning Munchausen syndrome by proxy is true?

a. A known physical illness in the child is common.
b. Most perpetrators are demanding, uncooperative, and socially inept.
c. Most maternal perpetrators are not a biologic parent.
d. Psychosis is common in the maternal perpetrator.
e. The mean age of victim diagnosis is 7 to 9 years.

Answer: A. Victim children often have a legitimate illness. Mean age at diagnosis is 40 months. Most have a history of failure to thrive and multiple hospitalizations. The perpetrator receives some personal fulfillment from the care and attention of the hospital staff, which is often admiration for her persistence, willingness to sacrifice, and patience; and she is typically pleasant, medically savvy, and socially skilled. Invasive procedures on the child are often welcomed. Although psychosis is very unusual in the parent, depression, anxiety, and somatization are typical in the perpetrator.

CHAPTER 100: QUESTIONS AND ANSWERS—cont'd

3. A 2-year-old female presents with new-onset seizures. Her past medical history is unremarkable. Laboratory evaluation reveals blood glucose of 20 mg/dL. The patient's mother denies a family history of diabetes or having medications the child might have ingested at home. She works as a nurse at a local hospital and has been with the child all day. The child's symptoms improve with glucose administration and a meal. Your colleague remembers evaluating the child recently for hematuria with a negative evaluation. If you suspect Munchausen syndrome by proxy, which of the following tests would be most helpful in establishing the diagnosis?
   a. Basic metabolic panel
   b. Computed tomography (CT) scan of head
   c. C-peptide and insulin level
   d. Electroencephalography (EEG)

Answer: C. The diagnostic criteria for factitious hypoglycemia include high-serum insulin levels along with the absence of serum C-peptide. The C-peptide is removed during the purification of commercial insulin, and so its absence suggests the presence of endogenously administered insulin. In patients with insulinoma, both C-peptide and insulin levels are elevated and detectable.

4. A prison inmate presents after falling from the top bunk in his cell. He is complaining of lower lumbar pain and states he is unable to move or feel his lower extremities from his waist down. On physical examination, lower extremity reflexes are present but the patient denies feeling pain or light touch sensation below the waist. Lumbar spine CT and MRI are negative. Which of the following conditions is most likely?
   a. Cord contusion
   b. Factitious disorder
   c. Malingering
   d. Munchausen syndrome

Answer: C. Malingering is the intentional symptom production for secondary gain. There is a marked discrepancy between claimed disability and the actual objective findings. Confessions and proof are rare.

101

Suicidal Behavior

Henry W. Young II and Michael A. Shapiro

KEY CONCEPTS

- Many suicidal individuals see a physician shortly before their death. An ED visit for suicidal thoughts or behaviors represents an opportunity for a critical intervention that may prevent a subsequent suicide.
- Suicidal thoughts or behaviors are often triggered by short-term crisis, and most survivors are grateful to be alive.
- An empathetic, patient-centered, collaborative approach that incorporates information from collateral sources (e.g., family) can optimize care.
- Suicide precautions in the ED include appropriate use of staff to monitor the patient to prevent attempts of self-harm while in the ED.
- Routine laboratory tests provide little value for most ED patients with self-harm behaviors. Evaluation should be directed to specific concerning signs or symptoms.
- Suicide risk changes over time, and estimation of imminent risk is not currently evidence-based.
- Brief risk assessment by the clinician can identify patients in need of a comprehensive evaluation and consultation with a mental health specialist.
- Patients at low risk of suicide may be discharged to a safe and supportive environment where access to firearms or risk of overdose or poisoning is minimized.
- Discharged patients should receive education and safety planning in the ED and be referred for early mental health follow-up.

FOUNDATIONS

Background and Importance

Emergency clinicians care for many patients with suicidal ideation and self-harm behaviors. Two facts are especially important to remember in the care of suicidal patients. First, many suicide attempts occur during an acute crisis, such as a personal loss or the exacerbation of an underlying psychiatric disorder. This acute crisis is usually time-limited and is often resolvable or treatable. Second, suicidal patients are usually ambivalent about dying and grateful for help. An empathetic, patient-centered, and evidence-based approach by emergency care providers offers the opportunity to save lives.

Medical literature contains numerous terms to describe different types and degrees of suicidal thoughts and behaviors. *Suicidal behavior* refers to any observable mental state or outward behavior related to ending one's life. *Suicidal ideation* refers to thoughts of killing oneself. *Suicidal intent* refers to the desire to proceed with suicide. A *suicidal plan* refers to a conceived specific method in which a person would attempt suicide, such as by firearm, hanging, poisoning/overdose, or cutting oneself. *Lethal means* refers to someone having accessibility to a method in which to carry out a suicidal plan, for example, having physical possession of a firearm.

A suicide attempt is a self-directed act with the intent to die. *Non-suicidal self-injury* (NSSI) is an intentional act of self-harm without the intent to die as a result of the behavior. Terms to avoid because of implicit value judgement of a derogatory nature include *committed* or *successful* suicide, *suicidal gesture, manipulative act,* and *suicide threat.*[1]

Epidemiology

Suicide was the tenth leading cause of death in the United States in 2017.[2] It is the second leading cause of death for people 10 to 34 years of age, the fourth leading cause among people 35 to 54 years of age, and the eighth leading cause among people 55 to 64 years of age.[3] There were more than one million suicide attempts and 47,000 suicide deaths in the United States in 2017, and rates continue to rise.[3,4] It is estimated that in 2017 there were almost 500,000 visits to emergency departments (EDs) nationally for intentional nonfatal injuries.[5,6]

Contrary to popular belief, the majority of individuals (54%) in the United States who die by suicide do not have a known mental illness at the time of death; these individuals are much more likely to be male (84%) and to die by firearm (55%).[4] Of the individuals who die with known mental health conditions, the majority are still male (69%) and more likely to die by firearm (41%) or suffocation (31%).[4] Although women make up a higher proportion of suicide attempts, men are more likely to die by suicide due to use of more lethal methods.[4]

The ED plays a critical role in acute stabilization and initiation of appropriate preventative efforts to reduce subsequent suicide mortality.[7,8] It is estimated that 1 in 5 suicide fatalities are seen in an ED in the month prior to their death, which suggests 9,000 suicide deaths each year could be reduced through improved ED suicide prevention efforts.[9] An empathic, patient-centered, and evidence-based approach offers the opportunity to save lives.

Risk Factors

Precipitating Factors

Many precipitating factors are associated with suicide attempts among individuals with and without mental illnesses. The most common precipitants to suicide are "dynamic" factors such as interpersonal relationship stressors (42%), recent crises (29%), problematic substance use (28%), physical health problems (22%), financial circumstances, (16%), criminal or legal issues (9%), and homelessness (4%).[4] The most important risk factor for suicide is a previous suicide attempt.

At Risk Populations

In addition, there are also several "static" factors associated with increased risk of suicide, including age, ethnicity/race, geography, employment, and other population characteristics.

In a national survey of high school students in the United States, in the previous year 17% had serious thoughts of suicide, 13% made a suicide plan, and 8% made a suicide attempt.[10] Unfortunately, only half of the youths with suicide-related behavior sought mental health care or support.[10] Similar to adults, girls are more likely to attempt suicide, whereas boys are more likely to die by suicide; however, the rates for girls has been climbing.[4] History of suicide attempt and of non-suicidal self-injury are particularly strong risk factors in this population.[10]

Suicide rates are also particularly high in the geriatric population, especially older white men, who account for over 80% of suicide deaths among elders.[11] Older adults are more likely to die from suicide attempts because of the use of more lethal methods, more advanced planning, and a lower likelihood of asking for help or of having warnings recognized by others. Depression is the strongest risk factor for suicide among elders, with a prevalence of up to 80% among older suicide decedents.[11] Additional important risk factors in elders include cognitive dysfunction, decreased functional ability, bereavement or other stressful life events, social isolation, and loneliness.[11]

Suicide rates are highest across the life span among non-Hispanic American Indian/Alaska Native and non-Hispanic White populations. Other Americans disproportionately impacted by suicide include veterans and other military personnel. Among military personnel, suicide risk is increased in males and those with psychiatric history, alcohol abuse, or previous deployment.[12]

Certain occupations also convey higher suicide risk, including the health professions and physicians. Worldwide, physicians have a suicide rate almost twice that of the general population and the highest suicide rate of any profession, with the highest rates in the United States.[13] Female physicians have a suicide rate 250% to 400% higher than females in other professions and, unlike the general population, female physicians may be at higher risk for suicide than male physicians.[13] Physicians may also not seek help for their mental health for reasons that may include busy professional schedules, the de-emphasis of professional support or avoiding risk of disclosure.

Gender and sexual minorities, particularly youth, bear a large burden as well, and experience increased suicidal ideation and at-risk behaviors compared to their non–sexual minority peers.[14]

Suicide rates vary geographically, with higher rates in rural communities and in areas with higher levels of firearm ownership.[15] The rate of suicide with firearms is almost twice as high among rural compared to urban residents.[15] Important risk factors for suicide in rural areas include social isolation, lack of access to health care, socioeconomic factors such as unemployment and poverty, and sociocultural factors like increased mental illness stigma that prevent help-seeking.[15] In addition, the risk of death by suicide in rural settings is compounded by a decreased likelihood of rapid life-saving intervention as well as reduced timely access to emergency medical services and trauma centers.[15]

Mental Illness

The presence of a mood disorder, especially major depressive disorder, is a strong independent risk factor for suicide. The most common mental disorders presenting to the ED with suicidal ideation are adjustment disorders, mood disorders, and personality disorders.[16] However, many other psychiatric disorders are associated with increased rates of suicide. Overall, the risk of suicide in patients with mental illness increases with the presence of prior attempts, recent psychiatric hospitalization, male gender, more severe symptoms, comorbid psychiatric disorders, use of alcohol or drugs, and family history of suicide. In patients hospitalized for psychiatric disorders, the risk for suicide is greatest in the first month after discharge, and especially in the first week.[16]

Alcohol and Substance Abuse Disorders

Both chronic and acute alcohol abuse are associated with suicide.[17,18] Individuals with alcohol use disorder who die from suicide usually have multiple risk factors, including major depression, unemployment, medical illness, and interpersonal loss.[17] Acute alcohol use is associated with increased risk of suicide in both those with and without chronic alcohol abuse, and this risk persists for 24 to 48 hours, particularly after heavy drinking.[18] This effect is largest among younger adults and is more often associated with violent means of suicide (e.g., firearms or hanging).[18] Substance abuse is associated with increased frequency and lethality in suicide attempts, and illicit substances are often detected at the time of suicide.

Chronic Illness

Many chronic medical illnesses are associated with increased risk of suicide, particularly those that affect the central nervous system such as epilepsy,[19] or those with chronic pain or impairment in activities of daily living.[20] Infection with human immunodeficiency virus (HIV) or presence of the acquired immunodeficiency syndrome (AIDS) remains associated with increased risk of suicide, but specific risk factors may vary based on nationality, socioeconomic status, age, and comorbidity with mental illness.[21]

Pathophysiology

The etiology of a suicide attempt is a complex mix of social, genetic, and psychological factors, what psychiatrists would refer to as a "bio-psycho-social" model.[22] Several genetic and neurobiological factors have been proposed as contributors to suicide risk, including abnormalities in the serotonin transport system, the stress response systems (hypothalamic–pituitary–adrenal (HPA) axis and polyamine system), neuroinflammation, and lipid metabolism.[22] Psychological factors associated with the highest suicide risk are hopelessness and impulsivity.[23]

The social contributions to risk of suicide have perhaps the most immediate, temporal relationship with suicide attempts. Many of the most prevalent precipitating factors associated with suicide occur in the social domain, namely relationship problems, recent crises, financial problems, criminal or legal problems, and homelessness.[4] There is a growing body of evidence suggesting that adverse childhood experiences are strong risk factors for future suicide that affect individuals on biological, psychological, and social levels.[22,24,25]

Methods of Suicide

Firearms account for half of all deaths from suicide for patients with and without mental illness,[4] as this is the most lethal method with little to no opportunity for the individual to experience regret or ask for help. There is a well-established relationship between the presence of a firearm in the home and higher rates of suicide.[26,27]

The next most lethal method is hanging or suffocation (25%), followed by poisoning or overdose (16%).[4] Overdose and poisoning attempts are relatively common, and account for over two-thirds of ED visits for suicide attempt or self-harm.[28] Intentional overdose is particularly common among adolescents; 63% of all overdoses for patients ages 13 to 19 years were intentional.[28] These attempts are less frequently lethal due to delayed lethality from absorption, ability for the individual to express regret and ask for help, and opportunities for emergent treatment once help is obtained. Death by suicide from overdose is most commonly due to opioids, although it is often difficult in

public health records to distinguish death by suicide from deaths due to unintentional overdose, abuse, or misuse.[29] Children and adolescents use whatever is readily available, such as commonly used over-the-counter medications like acetaminophen and ibuprofen, which can be quite lethal or lead to severe complications.[30]

CLINICAL FEATURES

Initial Recognition and Screening

Due to stigma and fear of repercussions, patients who present to the ED following a traumatic event may not disclose the cause of their injury was a suicide attempt. The potential for suicide should be considered in patients who present with unintentional overdose or accidental gunshot wounds, lacerated wrists, automobile crashes, or falls from heights. Patients who are not overtly suicidal but who exhibit one or more of these high-risk presentations require assessment in an empathic but direct manner using a "graduated" approach. Rapport can first be established during a general medical and psychiatric history, with an evaluation of the patient's home, work, and social situation, followed by specific questions about recent psychosocial stressors, signs and symptoms of depression, and the presence of suicidal thoughts. Such questioning does not cause a person to consider suicide who has not already been considering it. This approach can be described as *indicated screening* of those with acute risk factors.[31]

A more systematic screening approach would be *selective screening* of all patients in high-risk groups, such as those with chronic risk factors for suicide including prior suicide attempts or mental illness.[32] *Universal screening* for suicidal risk involves questioning all patients about suicidal thoughts or behaviors.[32] Universal screening is supported by evidence suggesting that approximately 10% of all ED patients have recent suicidal ideation or behaviors, and 40% of suicide victims have visited an ED within the prior year.[33] For ideal functioning, any screening program can be integrated into available electronic medical records and work flow to optimize efficiency, increase provider uptake, and maximize impact.[34,35]

History and Physical Examination

The history includes details about the patient's suicidal thoughts (including onset and frequency), plans (including method, intent to act, and access to lethal means), and behaviors (including prior or recent attempts, as well as aborted or interrupted attempts). Other important points include prior medical and psychiatric conditions, prior outpatient or inpatient psychiatric care, current medications, and current drug or alcohol use (including recent use). The history also assesses for symptoms suggestive of concomitant medical illness. Intoxication does not preclude taking an initial history, but it is important to repeat interviews when patients are sober to ensure accuracy.

The physical examination assesses for evidence of drug ingestion, trauma, or associated medical illness, as well as evidence of self-harm behavior such as cutting. Roughly 10% of individuals presenting to the ED for suicidal ideation have an associated injury.[6] An evaluation of the patient's cognitive status, vital signs, pupils, skin, and nervous system are helpful in detecting organic conditions, particularly toxidromes associated with common ingestions (see Chapter 135).

The clinician should identify medical conditions requiring immediate treatment in the ED or acute or chronic conditions that may require less urgent but timely intervention, and note incidental findings requiring further outpatient management or conditions that may affect psychiatric care.

DIFFERENTIAL DIAGNOSES

Normal Colloquialisms and Expressions of Suffering

People in nonclinical settings may use colloquialisms such as "I could die!" to express exasperation or suffering that may be misinterpreted in clinical settings.[36] Individuals who have suffered with chronic illnesses or pain may vocalize statements akin to a "wish to hasten death," which could have many meanings aside from an intent to end one's life.[4] Such statements may serve to communicate feelings, thoughts, or wishes about suffering, relief, help, and concerns about the illness or dying process. These thoughts and statements typically have a theme of suffering and loss of control.[4] It is important to carefully ascertain the presence of true suicidal ideations in these circumstances.

Malingering

Malingering is not a psychiatric illness; it is the intentional fabrication of symptoms, such as that of a mental illness, or even a claim, exaggeration, or feigning of suicidality for the purpose of obtaining an external gain.[37] There are no indicated treatments for malingering and no role for hospitalization. Studies have suggested that up to 10% of patients admitted to psychiatric hospitals have fabricated or exaggerated suicidal ideation to gain hospital admission. Suicidal ideation is the most frequently malingered psychiatric symptom, likely because of its subjective nature and the implicit additional leverage associated with the risk of mortality if unaddressed.

Non-Suicidal Self-Injury

The term *non-suicidal self-injury* (NSSI) refers to "the direct, deliberate destruction of one's own body tissue in the absence of intent to die," such as cutting or burning oneself.[38] There is conflicting evidence regarding whether NSSI and suicidal behavior are diagnostically distinct or exist on a spectrum of self-harm behavior. There is, however, sufficient evidence to suggest that NSSI is a risk factor for future suicide attempts.[38] There are cases where NSSI may have potentially lethal consequences, even if the intent was not suicide, so it is critical to consider both lethality and intent when performing a safety assessment.

Unintentional Injury or Ingestion

Over three-quarters of all overdoses are classified as unintentional, including most cases in children ages 5 years and younger.[28] In almost a quarter of single-substance overdoses that involved pharmaceutical substances, the reason for exposure was intentional, compared to only 4% when the exposure involved a nonpharmaceutical substance. The ingestion of multiple drugs is more reflective of an intentional overdose, and generally leads to more serious and potentially lethal complications.[28]

Substance Intoxication, Abuse, or Misuse

Patients may make suicidal statements while intoxicated or when presenting with an injury that may be a result of a suicide attempt. Patients may also make suicidal statements or inflict self-harm while intoxicated, then deny suicidal ideation later. An electronic medical record study in the United Kingdom showed that patients who presented as an emergency due to any alcohol-related cause had a three-times higher risk of future suicide; and when they were admitted to the hospital, the risk was 22-fold higher in women and 5-fold higher in men. When the diagnosis was "toxic effects of alcohol or poisoning through alcohol," the risk was 30-fold higher for women and 18-fold higher for men, a risk even higher than for those with a previous mental health disorder.[39]

Suicide attempts using illicit drugs are relatively uncommon. Overdose with an illicit drug or a prescription pain medication may be lethal and intentional, but not with death as a desired outcome.

Opioids are the most frequent cause of fatal overdoses today, yet many of these are likely not suicides, but rather abuse, misuse, or the development of tolerance leading to high-dose use and fatal overdoses.[28]

Suicidal Obsessions or Preoccupations

Suicidal ideation must be differentiated from having "thoughts of suicide" or "thinking of hurting oneself," without the desire, intent, or plan to pursue an act of ending one's life. Such thoughts may represent obsessions, such as occur in obsessive-compulsive disorder (OCD), or the ruminations or preservative thinking that occurs in autism spectrum disorder (ASD).[40,41] It is important to note that individuals with OCD and ASD can experience frank suicidal ideation as well. To make the differentiation, it is helpful to clarify whether the patient prefers death over life, or harbors a desire, intent, or plan to end his or her life.

DIAGNOSTIC TESTING

Emergency clinicians are often asked to provide "medical clearance" for patients with psychiatric emergencies. However, this term substantially undervalues the importance of a focused medical assessment of patients who may have active acute or chronic conditions, to determine stability and appropriateness for treatment in a psychiatric setting.[42] Obtaining an adequate patient history and physical examination is essential in the focused medical assessment.

Mandatory nontargeted diagnostic testing of all suicidal patients is not necessary and has not demonstrated any clinical benefit, particularly in younger patients.[42,43] Less than 1% of suicidal patients have their disposition changed through use of testing believed to be unnecessary by the emergency clinician.[43] Targeted diagnostic testing should be based on clinical indications, including the new onset of psychiatric symptoms in those with no known past psychiatric history.[42,43] There is little evidence to show that screening urine drug testing alters management or disposition of the psychiatric patient in the ED.[42,43] However comorbid substance use is an important factor in subsequent treatment, and receiving psychiatric facilities may request this study, as it is a time-sensitive study and may affect the direction of further mental health treatment.[42,43] Local practices vary and some mental health facilities may require routine baseline testing. EDs and local receiving psychiatric facilities should create guidelines to clarify minimal testing required for medical clearance.

MANAGEMENT

Overview

Care of potentially suicidal patients requires an empathetic and patient-centered approach. Patients feel more comfortable discussing personal issues when health care personnel are friendly, nonjudgmental, and supportive.[44] Providers can improve the ED experience by explaining to patients what to expect from the evaluation, stating the estimated length of wait for evaluation and disposition, and focusing initially on basic comforts.[44] The use of a patient-centered approach can also enhance patient satisfaction and the likelihood of outpatient follow-up.[44] Attitudes towards suicide prevention are highly correlated with effective suicide prevention skills of emergency medical service providers.[44,45,46] Personal beliefs or inadequate training of clinical providers, or lack of time or personnel to provide appropriate psychiatric evaluation, can result in inadequate patient assessment and adversely impact outcomes.

The priority in management is immediate medical stabilization and treatment of injuries, poisonings, or overdose. Following stabilization, a focused medical assessment should be performed to identify and treat associated medical conditions that may underlie a patient's altered mental status or suicidal behavior. Hospitalization for significant injury, poisoning, or other acute medical problems is imperative so that medical problems can be treated as patients remain under constant observation for suicide risk and later receive appropriate psychiatric evaluation.

Suicide Precautions

Protocols for managing potentially suicidal individuals focus on patient safety and the prevention of self-harm. While the practice of constant physical observation by ED personnel of all patients exhibiting suicidal behavior may be considered essential, alternative means of monitoring through careful patient selection and use of technology may be similarly effective.[44,47,48] The effectiveness of electronic bracelets and other forms of virtual monitoring are currently being evaluated.[48]

As part of standard procedure, patients being evaluated for suicidal behavior are searched during the initial assessment for possible weapons, medications, and other possessions that might be used to inflict injury (e.g., belts, neckties, and long shoelaces),[44] and are evaluated in an area cleared of all potentially harmful objects, including medications, instruments, and glass objects.[44,47] Use of restraints is rarely necessary. Mechanical and chemical restraint use is most commonly employed for patients who are agitated or physically aggressive, but such measures are a last resort because they can be traumatic, impair rapport, exacerbate an underlying psychiatric condition, or impair early psychiatric evaluation.[44]

Pharmacologic Treatment

Prescription psychiatric medications are commonly used to treat depression and other underlying psychiatric disorders, but they are generally not effective for acute suicidality and may take weeks to become effective.[49]

Children, adolescents, and young adults may have increased suicidal thoughts or attempts soon after the initiation of antidepressant medications.[50] Although current studies do not support a direct causation between antidepressant medication and suicidality in youth, clinicians should recognize the time period around initiation of antidepressant therapy as one requiring heightened scrutiny for suicidal thoughts or behaviors.[51]

There are no generally accepted or evidence-based protocols for drug treatment of suicidal ideation in the ED. However, ketamine and its enantiomer, esketamine, have demonstrated promise as a potential acute treatment for suicidal ideations.[52-56] Ketamine at sub-anesthetic doses has been used in several studies for treatment-resistant depression, and such studies show that ketamine encompasses a specific and rapid suppression of suicidal ideation.[52,53,54] Meta-analyses have revealed single-dose intravenous (IV) infusion of ketamine to be associated with reduction of suicidality within as little as 40 minutes and lasting as long as 3 days to 2 weeks.[52-54] The intranasal form of esketamine was approved by the United States Food and Drug Administration for treatment-resistant depression in 2019, but patients must be monitored by a health care provider in a doctor's office, clinic, or hospital for at least 2 hours following administration due to risk of sedation and dissociation.[55]

Ketamine's application is not straightforward, as repetitive doses are required due to the short duration of action.[52-54] Additionally, use may be hindered by the drug's potential for abuse, dependence, and dissociative effects.[55] Despite increasing evidence showing the suicide-mitigating effect of ketamine, the underlying neurobiology is poorly understood, and a preliminary study suggests that the antidepressant effects of ketamine may actually be due to its action

at opioid receptors.[56] We do not recommend the routine use of ketamine for this purpose in the ED in the absence of psychiatric consultation.

Risk Assessment

Analogous to the evaluation of chest pain and other physical complaints, the emergency clinician's role in managing potentially suicidal patients lies in assessing suicide risk, providing brief interventions, and facilitating consultation with specialists as indicated.[57]

Suicide risk assessment should be performed when the patient is sober, although intoxicated patients who endorse suicidal thoughts may still be at risk, even if they disavow these feelings when sober.[58] Risk assessment includes collateral information from a family member or friend who can provide additional background information and discuss whether there are sufficient resources available to support a safe discharge if considered.[59] Such contacts are most appropriately made with the consent of the patient, if possible, but can occur without consent in cases when disclosure of protected health information is required to prevent or mitigate an imminent, serious safety threat to an individual or the public.[59]

Assessing hopelessness, desperation, and a wish or intent to die are also important predictors of future suicide.[60-62] Assessment of risk of the lethality of a plan for death by suicide is paramount even though patients with strong suicidal ideations without a plan may still remain at high risk.[60] Patients who initially hide or conceal their suicide attempt may also be at higher risk of death.[60-63]

A practical, stepwise approach to suicide risk assessment (see Fig. 101.1) consists of both brief and comprehensive steps. *Brief risk assessment* typically involves a short set of questions to assess suicide risk and help determine the most appropriate actionable steps.[64,65] An example is the short version of the Columbia-Suicide Severity Rating Scale (C-SSRS; see Fig 101.2), which is available for free in English and Spanish with suggested cut-points for referral and consultation.[66] The C-SSRS can be modified for use by clinicians in a variety of settings, including the ED. It is a quick 6-item questionnaire that helps triage patients as acutely low, medium, or high risk for suicide and allows for individual EDs, hospitals, or hospital systems to use the tool appropriately within their system depending on what resources are available.

A *comprehensive* or *formal risk assessment* involves more-detailed questions about a patient's various suicide risk and protective factors and is most often performed by a mental health consultant.[65] In cases where psychiatric consultation is not possible, the clinician can complete a comprehensive suicide risk assessment assisted by a validated tool such as the Suicide Assessment Five-step Evaluation and Triage (SAFE-T; see Fig. 101.3) tool. The SAFE-T is available as a pocket card or smartphone application. It guides one in assessing a patient's risk, the presence of protective factors and the specifics of suicidal thoughts or plans, and then combines these factors to estimate a level of suicide risk.[67]

The Ask Suicide-Screening Questions (ASQ) Toolkit is a free combined brief and comprehensive risk assessment developed by the National Institute for Mental Health (NIMH) and the Substance Abuse and Mental Health Services Association (SAMHSA) specifically for youth at risk for suicide.[32,68]

Ultimately, suicide risk assessment remains a matter of clinical judgment with tools such as the C-SSRS and SAFE-T to inform, reinforce, and justify the provider's decision making.[65]

Documentation

Documentation of the evaluation of potentially suicidal patients is important because of the variable nature of suicide risk, low compliance rates of follow-up with outpatient care, and the difficulty of predicting imminent risk. It is especially important when patients are either hospitalized involuntarily or discharged. If a patient requires involuntary hospitalization, providers should document why the patient is a danger to self or others. If the patient is discharged, appropriate documentation includes the decision making as to why the patient was considered to be at low risk of imminent self-harm, referencing access to potentially lethal methods of suicide, information from collateral sources, and the follow-up plan.[69] Use of standardized electronic health record templates may prove useful in ensuring sufficient system-wide documentation of suicide assessment and decision making.[70]

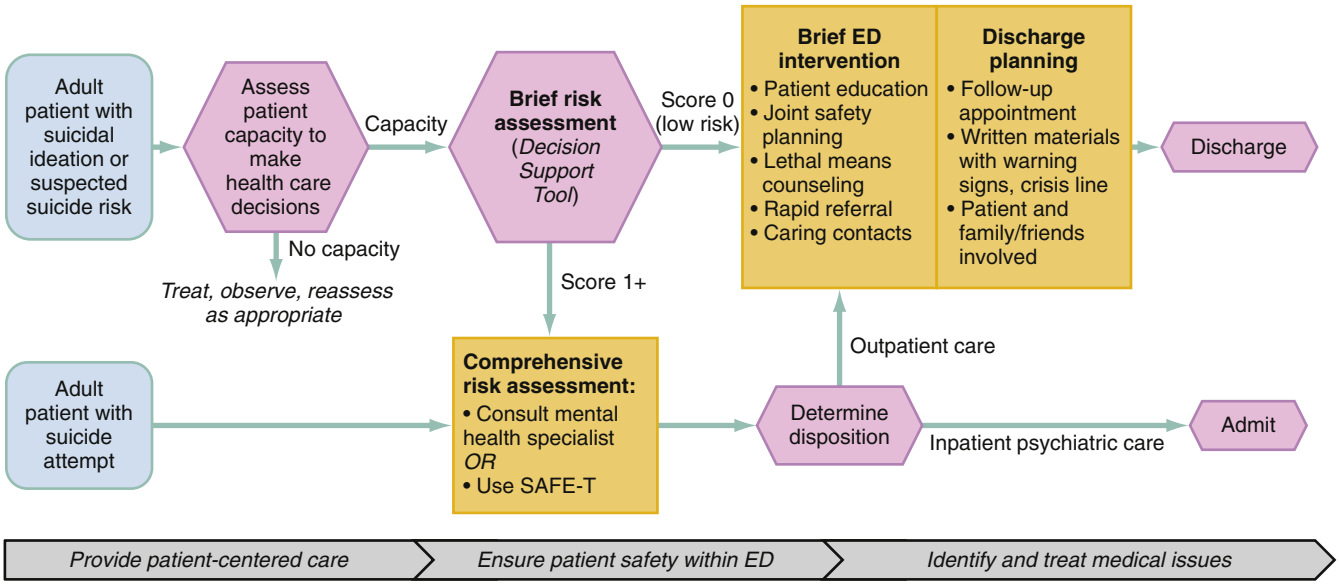

Fig. 101.1 Framework for using the decision support tool and emergency department (ED)-based suicide prevention interventions. (Adapted from: Capoccia L, Labre M. *Caring for Adult Patients With Suicide Risk: A Consensus-Based Guide for Emergency Departments*. Waltham, MA: Education Development Center, Inc., Suicide Resource Prevention Center; 2015.)

Columbia-suicide severity rating scale
screen with triage points for ***emergency department***

Ask questions that are bolded and underlined.	Past month	
Ask questions 1 and 2	**YES**	**NO**
1) ***Have you wished you were dead or wished you could go to sleep and not wake up?***		
2) ***Have you actually had any thoughts of killing yourself?***		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) ***Have you been thinking about how you might do this?*** E.g. *"I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it.…and I would never go through with it."*		
4) ***Have you had these thoughts and had some intention of acting on them?*** As opposed to *"I have the thoughts but I definitely will not do anything about them."*		
5) ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***		
6) ***Have you ever done anything, started to do anything, or prepared to do anything to end your life?*** Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.	**Lifetime**	
If YES, ask: *Was this within the past three months?*	**Past 3 months**	

Item 1 behavioral health referral at discharge
Item 2 behavioral health referral at discharge
Item 3 behavioral health consult (psychiatric nurse/social worker) and consider patient safety precautions
Item 4 immediate notification of physician and/or behavioral health and patient safety precautions
Item 5 immediate notification of physician and/or behavioral health and patient safety precautions
Item 6 over 3 months ago: Behavioral health consult (psychiatric nurse/social worker) and consider patient safety precautions
Item 6 3 months ago or less: Immediate notification of physician and/or behavioral health and patient safety precautions

Fig. 101.2 Columbia-Suicide Severity Rating Scale Triage and Risk Identification Tool from The Columbia Lighthouse Project. (From: Posner K, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011 Dec;168(12):1266-1277. PMID: 22193671. Available at https://cssrs.columbia.edu/the-columbia-scale-c-ssrs/risk-identification/.)

DISPOSITION

Determining the most appropriate disposition for the potentially suicidal patient involves integrating information about the precipitating crisis and event, the patient's current emotional state and prior mental health history, and the presence or absence of a safe and supportive environment. Addressing the crisis that precipitated a suicide attempt can substantially diminish the risk of suicide. Emergency psychiatric evaluation and psychiatric hospitalization are often strongly considered to ensure this crisis can be resolved.

Psychiatric Hospitalization

Voluntary hospitalization is preferable to involuntary hospitalization.[71] The efficacy of hospitalization as a long-term preventive measure is controversial and is not proved to prevent future suicide.[72-74] Still, hospitalization remains a primary intervention when patients are deemed acutely suicidal as a means to provide a safe environment for close monitoring where medical or somatic therapies can be started, positive coping skills can be taught and reinforced, and social supports can be mobilized.[75] Depending upon outpatient resource availability, other options may include partial hospitalization programs, intensive outpatient programs, and assertive community treatment.

Statutes regulating involuntary hospitalization, otherwise known as civil commitment, differ between states and regions. Most states have emergency involuntary commitment provisions that typically require that a patient both have a mental illness and pose a threat to self or others.[76] The length of emergency commitments varies by state, from 72 hours to 15 days.[76-79] In some states, patients who agree to hospitalization may still need involuntary commitment documentation completed for transport to a receiving psychiatric facility; this provides the legal basis for holding patients if they change their mind during transportation.

1. Identify risk factors

- **Suicidal behavior**: prior suicide attempts or self-injurious behavior
- **Current/past psychiatric disorders**: especially mood disorders, psychotic disorders, alcohol/substance abuse, ADHD, TBI, PTSD, Cluster B personality disorders, conduct disorders (antisocial behavior, aggression, impulsivity)
- **Key symptoms**: anhedonia, impulsivity, hopelessness, anxiety/panic, insomnia, command hallucinations
- **Family history**: of suicide, attempts, or Axis 1 psychiatric disorders requiring hospitalization
- **Precipitants/Stressors/Interpersonal**: triggering events leading to humiliation, shame or despair (e.g., loss of relationship, financial or health status—real or anticipated); ongoing medical illness (esp. CNS disorders, pain); intoxication; family turmoil/chaos; history of physical or sexual abuse; social isolation
- **Change in treatment**: discharge from psychiatric hospital, provider or treatment change
- **Access to firearms**

2. Identify protective factors

- **Internal**: ability to cope with stress, religious beliefs, frustration tolerance
- **External**: responsibility to children/pets, positive therapeutic relationships, social supports

3. Conduct suicide inquiry

- **Ideation**: frequency, intensity, duration–in last 48 hours, past month, and worst ever
- **Plan**: timing, location, lethality, availability, preparatory acts
- **Behaviors**: past attempts, aborted attempts, rehearsals (tying noose, loading gun), vs. non-suicidal self-injurious actions
- **Intent**: extent to which the patient (1) expects to carry out the plan and (2) believes the plan/act to be lethal vs. self-injurious
- **Explore** ambivalence: reasons to die vs. reasons to live

4. Determine risk level & intervention

- **Assessment** of risk level is based on clinical judgment, after completing steps 1–3

Low risk	Moderate risk	High risk
• Denial of suicidal thoughts, plan, intent • No or mild sadness or anger; no psychosis • No or 1 recent attempt with low lethality • No or limited substance use • Good support, accepting of help, hopeful for future	• Suicidal ideation, plan, intent, or attempt • Moderate depression, anger, hopelessness • Frequent ideation or threats; low lethality • Substance abuse • Moderate support, unwilling to accept help • Access to lethal means	• Frequent, intense, enduring ideation • Specific plans • High intent (e.g., attempt with high lethality) • Impaired self-control, severe dysphoria, hopelessness, worthlessness • Poor corroborative history • Many risk factors, refusing help

5. Document

- Risk level and rationale; treatment plan to address/reduce current risk (e.g., setting, medication, psychotherapy, ECT, contact with significant others, consultation); firearm instructions, if relevant; follow-up plan
- For youths, treatment plan should include roles for parent/guardian

Fig. 101.3 Suicide assessment five-step evaluation and triage. (Modified from: Davidson CL, Olson-Madden JH, Betz ME, et al. Emergency department identification, assessment, and management of the suicidal patient. In: Koslow SH, Ruiz P, Nemeroff CB, eds. *A Concise Guide to Understanding Suicide*. Cambridge, UK: Cambridge University Press; 2014: 244–255; Suicide Assessment Five-Step Evaluation and Triage [SAFE-T]. Substance Abuse and Mental Health Services Administration. Available at http://store.samhsa.gov/product/Suicide-Assessment-Five-Step-Evaluation-and-Triage-SAFE-T-/SMA09-4432; and Substance Abuse and Mental Health Services Administration [SAMHSA]. Suicide safe: the suicide prevention app for health care providers, free from SAMHSA. Available at http://store.samhsa.gov/apps/suicidesafe/.)

Patients may lack capacity to refuse hospitalization but maintain the capacity to accept or refuse other treatments, such as management of medical conditions and administration of medications for pain or agitation.[80]

Discharge

Some patients who report suicidal thoughts can be safely managed as outpatients if the risk of subsequent suicide is judged to be acceptably low. Although the emergency clinician can make this determination in many cases, evaluation by a mental health professional can be useful if the safety of outpatient management is in doubt. The patient can be discharged to a stable and supportive home environment with a willing friend or family member, and without access to guns or lethal medications. The discharge planning process ideally includes (1) brief patient education, (2) joint safety planning, (3) lethal means restriction counseling, (4) referral for outpatient care, and (5) provision of "caring contacts."[77,81-83]

Brief Patient Education

Brief patient education for suicide prevention includes the use of verbal and written information and "teach back" techniques whereby the patient explains the information back to the provider.[81] Information can include a personalized list of risk and protective factors, home care and follow-up instructions, and warning signs that would trigger a call for help. The educational process engages the patient in an empathetic and respectful manner and can, with patient consent, include family members or close friends.[81] Educational materials are available from a number of national organizations.

Joint Safety Planning

In joint safety planning, a provider works with a patient to develop a plan regarding what to do if symptoms worsen.[77,81] The plan should be in the patient's own words and easy to understand, and it includes warning signs, a list of coping strategies, and resources such as hotlines or contact information for trusted family or friends (specify "adults" in the case of suicidal children or adolescents). The National Suicide Prevention Hotline (1-800-273-TALK [8255]) and/or text line (741-741) is a helpful resource for all discharged patients; in late 2019 the Federal Communications Commission (FCC) approved using 988 as a three-digit suicide prevention hotline number.[84] Importantly, safety planning is not the same as a "contract for safety" or "no suicide contract." Such "contracts" not only lack evidence of effectiveness but may deter patients from being truthful in disclosing future episodes of suicidality.[83] These contracts may create a false sense of security regarding safety and should not be used.

Lethal Means Restriction Counseling

Counseling about lethal means restriction—one of only two suicide prevention approaches with a strong empirical foundation—is another valuable resource.[84-85] Many suicidal crises are acute and short-lived and are impulsive (sometimes with only minutes or seconds between the decision to act and the attempt). The method chosen may be the one most readily available, and the lethality of the chosen method affects the likelihood of mortality. Numerous studies have shown a consistent association between firearm access and death by suicide, even after controlling for other risk factors, with a strong correlation amongst males.[26,86-87] Safe gun-storage practices—namely keeping firearms locked, unloaded, and separate from ammunition—can mitigate the risk of suicide. At a population level, firearms regulations such as waiting periods and training requirements are associated with reduced rates of firearm-related suicide.[87,88]

ED counseling about lethal means safety can affect patient behavior, and lethal means counseling for suicidal patients is supported by multiple physician organizations and listed as a best practice for suicide prevention.[89] Clinicians should counsel potentially suicidal patients and their families to remove guns temporarily from the home for storage off-site in an appropriate location, or to use gun locks or cabinets to which the patient has no access.[90]

Referral for Outpatient Care

Suicide risk remains high shortly after discharge from the ED, so it is important to arrange short-term outpatient care, ideally within 72 hours of discharge.[89] Evidence-based outpatient treatment can reduce future suicide risk, and emergency clinicians play a key role in linking patients to care.[89] A significant number of discharged ED patients do not keep their follow-up appointments, but compliance with follow-up may be increased by making a specific appointment for patients. Employing the support of family or friends helps ensure that the patient keeps the follow-up appointment. In addition, it may be helpful to provide physician contact information or to provide a list of community mental health resources. With the patient's consent, the physician can send visit information to the patient's primary care provider or outpatient referral provider to enhance continuity of care.

Caring Contacts

Other promising interventions for discharged patients include caring contacts, or brief communications from the ED after discharge.[91,92] These empirically supported interventions take a variety of forms, including text messages, emails, phone calls, and postcards, and they may be unidirectional or bidirectional. An automated system, supported by the electronic health record, can facilitate the process, or the contacts can be made by a clinical or nonclinical ED staff member. Such continued contacts have been shown to improve follow-up to outpatient appointments and lower suicide risk.[92]

ADDITIONAL ETHICAL CONSIDERATIONS

Do-Not-Resuscitate Orders

The presence of a do-not-resuscitate (DNR) order in a patient with a suicide attempt raises ethical and legal dilemmas.[93] Policies vary among states, and there are unfortunately no definitive guidelines for emergency care providers.[81] When possible, consultation with an ethics consultant or committee or legal representation from the hospital can be helpful, but in emergent time-sensitive conditions it is preferred to err on the side of resuscitation.

The principle of beneficence dictates that treatment be pursued when a suicidal patient may not be capable of making decisions about his or her own welfare. Because DNR orders and palliative care generally apply to progressive terminal illnesses and do not exclude or limit all other care, it is necessary to treat self-inflicted conditions even in the presence of a DNR order.[89] Treatment does not have to be indefinite and can be discontinued later following appropriate consultation with ethics and legal experts. Institutions have a responsibility to examine these issues proactively and pursue policies that address how to respond to patients with a DNR order who attempt suicide.[93] Such policies need to address specific state laws regarding prehospital DNR orders.

Physician-Assisted Dying

As of 2018, five states and the District of Columbia have passed legislation legalizing assisted dying, with other jurisdictions considering such legislation.[94] Physician-assisted dying refers to patients who voluntarily and orally ingest medications that are prescribed to them only after they pass a series of safeguards. Such safeguards typically include (1) having a prognosis of fewer than 6 months, confirmed by two physicians: (2), retaining medical decision-making capacity: and (3) making multiple requests separated by time to allow adequate reflection and reconsideration. Although EMS and ED involvement may be rare (approximately 1% of cases in Oregon), when they do occur, they require rapid decision making, often with limited information and challenging emotions.[42] As more states allow physician-assisted dying, it is expected that more such cases will come to clinical attention in the ED. It is appropriate to involve palliative care and ethics consultations in such cases with supporting institutional protocols in place that achieve consensus on recommendations for action.[94] The legal authorization of physician-assisted dying intent draws a sharp distinction in these cases from an impulsive suicide attempt, and ED providers must be prepared to adapt to new state laws and their application in medicine.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 101: QUESTIONS AND ANSWERS

1. Which of the following statements regarding suicide is true?
- **a.** Many suicide attempts occur during an acute crisis.
- **b.** Suicide rates are highest in older men.
- **c.** Suicidal behavior may be chronic.
- **d.** Suicidal patients are usually ambivalent about dying.
- **e.** All of the above are true.

Answer: E. Many suicide attempts occur in response to a crisis that may be time-limited or resolvable. Suicide rates are particularly high in older white men. With the exception of psychotic patients, suicidal patients are usually ambivalent about dying. An example of chronic suicidal behavior is drinking in the face of liver disease.

2. Which of the following statements regarding suicide is true?
- **a.** Blacks attempt suicide more than whites.
- **b.** Men attempt suicide more than women.
- **c.** Marriage decreases the likelihood of suicide.
- **d.** Pregnancy increases the risk of suicide.
- **e.** Suicide rates are highest among female teens.

Answer: C. Marriage and pregnancy/motherhood decrease suicide risk. Whites attempt suicide more than blacks, with the highest rate among older white men. Women attempt suicide far more often than men but do not choose lethal means and therefore have a lower success rate.

3. Which of the following is a risk factor for suicide?
- **a.** Prior suicide attempt
- **b.** Access to firearms
- **c.** Alcohol abuse
- **d.** Veteran status
- **e.** All of the above

Answer: E. Additional suicide risk factors include, but are not limited to: adolescence and older age; male gender; certain races/ethnicities (White, American Indian, Alaskan Native); mental disorders; substance abuse; prior suicide attempt; psychosocial stressors (e.g., recent psychiatric hospital discharge, history of trauma or abuse, terminal illness, chronic pain, hopelessness, impulsiveness); environmental stressors (e.g., job loss, bereavement); and sociocultural factors (e.g., isolation, poor access to mental health care, stigma against seeking help, or media exposure to suicide).

4. Most completed suicides involve which of the following?
- **a.** Falls
- **b.** Firearms
- **c.** Piercing
- **d.** Poisonings
- **e.** Suffocation

Answer: B. Fifty percent of completed suicides involve firearms. Seventy percent of attempted suicides involve poisoning.

5. Discharge planning for suicidal patients should include which of these elements?
- **a.** Counseling about reducing access to guns and toxic medications.
- **b.** Involvement of family or friends.
- **c.** Rapid referral to outpatient mental health.
- **d.** Written materials with warning signs and hotline numbers.
- **e.** All of the above.

Answer: E. All of the listed elements are recommended components of ED care and discharge planning for patients evaluated for suicidal thoughts or behaviors but deemed safe for discharge home.

6. A 33-year-old Caucasian man presents with agitation and suicidal ideation. He has a long history of schizophrenia and is currently taking olanzapine and occasional clonazepam. He was hospitalized 3 weeks prior for an accelerated psychotic episode and released on an increased dose of olanzapine. His family brought him here today after visiting him in his apartment and finding him in a room with all the lights off. They note he has been unable to work for more than 2 years. He was formerly employed as an engineer. Your examination is remarkable for a blunted affect, moderate pressured speech, and a depressed mood. What is the most appropriate intervention?
- **a.** Addition of sertraline to olanzapine, 2-day follow-up
- **b.** Admission to psychiatry unit
- **c.** Increase olanzapine, release with family
- **d.** Overnight emergency department (ED) observation, 2-day psychiatry follow-up
- **e.** Parenteral ziprasidone, release with family

Answer: B. Approximately 10% of schizophrenic patients will kill themselves. Psychotic patients who kill themselves are often unmarried Caucasians of high intelligence. A recent psychiatric hospitalization is a suicide risk factor, particularly during the first month post discharge. This patient is high risk and needs admission.

7. Which of the following statements concerning risk assessment of suicidal patients is true?
- **a.** An empathetic approach will reinforce malingering behavior and subsequent ED visits.
- **b.** For patients at low risk of imminent suicide, providers can consider discharge without formal consultation with a mental health professional.
- **c.** Intoxicated patients who, once sober, disavow prior suicidal statements do not need a suicide risk assessment.

CHAPTER 101: QUESTIONS AND ANSWERS—cont'd

d. Routine screening labs should include serum chemistries and urine toxicologic panels.
e. Suicidal patients can be permitted to leave the ED prior to a risk assessment as long as they sign "Against Medical Advice" paperwork.

Answer: B. In a step-wise manner, the ED provider can complete a brief risk assessment to identify which patients do (or do not) require a comprehensive evaluation with a mental health professional. Diagnostic testing should be targeted to individual patients as clinically indicated. An empathetic approach can enhance patient evaluation and care and should be used with all suicidal patients. Acute and chronic alcohol use are both suicide risk factors; even if a patient denies suicidality once sober, a risk assessment may be prudent. No suicidal patient should be allowed to leave the ED before the risk assessment is complete.

8. Which of the following statements regarding involuntary commitment is true?
a. It is not associated with adverse psychiatric consequences.
b. It lowers the rate of future suicides.
c. Most states mandate attempts at involuntary commitment if there is imminent self-harm.
d. Patients who volunteer for admission may still need commitment papers.
e. Statutes are consistent among the states.

Answer: D. Statutes vary widely among the states. Some states require commitment papers even in cases of voluntary admission. Only two states mandate commitment in the face of suspected imminent self-harm. Involuntary commitment does not lower the rate of future suicides and is associated with adverse psychiatric consequences.

102

Arthritis

Korin Hudson, Miguel Agrait-Gonzalez

KEY CONCEPTS

1. Arthritis can be considered in three broad classes: degenerative, infectious, and inflammatory. The number of joints involved, time course, and presence of other systemic symptoms can help in classification.
2. Septic (acute infectious) arthritis should be considered in any patient presenting with acute monoarticular arthritis.
3. No singular physical examination finding, serum test, or synovial fluid test in isolation can diagnose or exclude the diagnosis of a septic joint.
4. Arthrocentesis can aid in diagnosis and should be considered if the diagnosis is unclear or any time infection is suspected.
5. Crystal arthritis and septic arthritis can and do frequently coexist. The presence of crystals in joint aspirate should not be used to exclude infection.
6. Gram stain of synovial fluid is positive only in 50% of patients with confirmed infection and should not be used in isolation to exclude infection.
7. Many common arthritis conditions, including gout, rheumatoid arthritis, and osteoarthritis, can be managed in the outpatient setting. Analgesics, specifically antiinflammatory medications, are the mainstay of initial therapy.
8. A systematic history and physical examination should be performed to evaluate for multiple joint involvement or signs of systemic disease.
9. Intra-articular corticosteroid injections can be considered in select patient populations where systemic therapy is either contraindicated or presents a significant risk to the patient.
10. Consider ultrasound evaluation of acutely painful joints to better evaluate for the presence of joint effusion requiring aspiration.

GENERAL APPROACH TO ARTHRITIS

Foundations

Background

Arthritis and its related conditions were among the earliest diseases described. Ancient cultures including the Romans, Greeks, and Egyptians all referenced conditions such as gout and rheumatoid arthritis (RA), while Hippocrates and others contributed to the further description and classification. In modern times, arthritis has become a common cause of disability in the United States and around the world. More than 20% of adults in the United States carry the diagnosis of arthritis, leading to millions of prescriptions, procedures, and profound activity limitations.[1] Patients with arthritis may present to the emergency department (ED) for a variety of reasons. First among these is pain related to their primary condition; however, complications related to systemic illness are also common in patients with autoimmune or inflammatory conditions. Furthermore, the medications and treatments used to manage these conditions may themselves have side effects which lead patients to seek emergency care.

Pathophysiology

Arthritis typically occurs in synovial or diarthrotic (moving) joints. These joints are made up of two ends of subchondral bone, each covered with articular cartilage and surrounded by a fibrous capsule (Fig. 102.1). This capsule is supported by ligaments, tendons, and muscle. The capsule is lined with a thin synovial membrane and contains synovial fluid, a viscous, lubricating substance which allows near frictionless movement of the joint. The bones of the joint are lined by a specific form of hyaline cartilage known as articular cartilage, which allows load bearing and contributes to the friction-free movement of the joint when combined with synovial fluid. Numerous conditions and specific processes will lead to degradation of these tissues and ultimately to degeneration and arthritis.

Clinical Features and Differential Diagnosis

When evaluating a patient with a complaint of joint pain, it is important to use a systematic approach and consider several key factors (Box 102.1).

It is also helpful to think of arthritis in three broad categories: degenerative/osteoarthritis (OA) including posttraumatic arthritis, infectious or septic arthritis, and inflammatory arthritis. Table 102.1 and Fig. 102.2 outline the differential diagnosis and decision pathways that may be used when evaluating patients with an acutely painful joint.

History

The acutely painful joint or joints is usually the primary complaint for the patient presenting with arthritis. The patient's age, as well as the timing of symptoms, specific location and description of pain, presence of associated symptoms, and factors that aggravate or alleviate symptoms, can provide clues to the etiology. Once the history and characteristics of the pain have been reviewed, further classifying the problem as monoarticular or polyarticular is of great importance. In cases of polyarticular arthritis, care should be taken to assess for the presence of symmetric versus asymmetric symptoms. These specific characteristics can be used when creating a differential diagnosis, as detailed in Table 102.1.

OA or degenerative joint disease is a clinical finding expected in the older population and is uncommon in younger patients except in the setting of previous traumatic injuries or prior surgeries or in patients

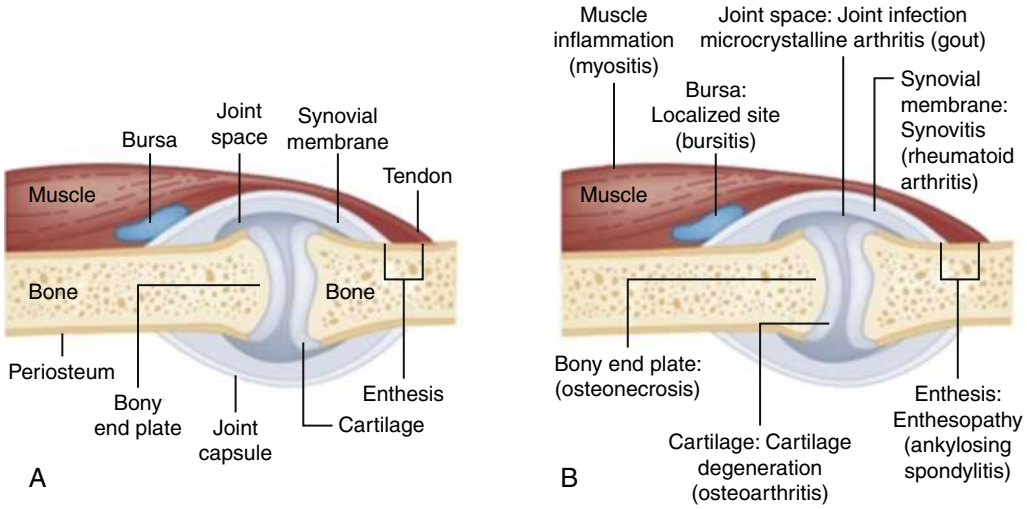

Fig. 102.1 Panel A: Example of a diarthrotic joint; Panel B: Sites of periarticular and articular disease and pain. (Redrawn from Goldman L, Ausiello DA, editors: *Cecil Medicine*, ed 23, Philadelphia, 2008, Saunders/Elsevier.)

BOX 102.1 Clinical Factors to Consider in the Evaluation of Joint Pain

Age
Single vs. multiple joint(s)
Time course:
- Acute (hours to <7 days)
- Subacute (7 days to 2–3 weeks)
- Chronic/progressive (>3 weeks to months)

History of acute or remote trauma to the joint
Associated systemic symptoms
Description and specific location of pain
Aggravating and alleviating factors

with certain comorbidities such as diabetes or obesity. OA will often present with pain in and around the joint, which worsens with activity. This pain is often accompanied by swelling, warmth, and discomfort to palpation diffusely around the joint. The most commonly affected joint in patients presenting to the ED will be the knee, but the shoulder, fingers, low back, or other joints may also be affected. In general, true arthritis pain will be more poorly localized in and around the joint. When the patient's pain is well localized and easily reproduced by palpation, common mimics such as bursitis or tendinitis should be considered.

Inflammatory or rheumatologic joint pain classically presents with symmetric and bilateral distribution with a predilection for the small joints of the hands. Inflammatory arthritides are more common in females and are usually diagnosed at an earlier age than degenerative arthritis. In general, the pain associated with inflammatory arthritis is worse in the morning and is associated with significant joint stiffness which improves with activity throughout the day. It is important to query the patient regarding the presence of systemic symptoms, because inflammatory conditions are often associated with symptoms distant from the affected joint. Many of the most common systemic symptoms are listed in Table 102.2. In addition, a careful medication history is important because many drugs can cause joint pain that mimics inflammatory arthritis. Certain viral conditions can also mimic inflammatory arthropathies and are discussed separately.

Acute monoarticular arthritis should always raise concern for the possibility of infectious arthritis, often referred to as septic arthritis, which is the most important condition to consider in the patient who presents to the ED with acute joint pain. There is significant morbidity and mortality associated with any delay in diagnosis of a septic joint. Therefore it is important to ask the patient about rapid progression of symptoms, associated skin changes, presence of fever, and any recent procedures or breaks in the skin that may have led to infection in the joint. Unfortunately, there are no adequately sensitive or specific findings either on history or physical examination that can safely rule out the possibility of a septic joint without a joint aspiration and analysis of joint fluid.

Physical Examination

General examination. The initial examination should focus on the affected joint or joints and should also assess for systemic or distant findings which may provide clues to the underlying problem. Vital signs, specifically presence of fever or tachycardia, should be noted because they may indicate infection, although most patients with confirmed septic arthritis will be afebrile on presentation.[2] The examination should begin with evaluation of general appearance, patient's position of comfort, and an assessment of ambulatory gait. A focused physical examination follows, directed by the patient's history and complaints.

Joint examination. The examination of the painful joint is performed in a systematic manner following the general principle of inspection, palpation, range of motion (ROM), neurovascular evaluation, special tests, and imaging when appropriate. Although the general examination is the same for all joints, each joint has different aspects to its exam and will be discussed independently. See Table 102.3.

Inspection. Begin the examination by watching the patient move in the exam room. Gait can provide important clues to discomfort and disability because pain, swelling, or weakness can all affect ambulation. The extent to which an affected joint is used and positions of comfort can also provide valuable information. Paired joints are compared, assessing each for deformity, skin integrity, erythema, swelling, ecchymosis, effusion, previous surgical scars, or rashes. Findings can suggest inflammation, infection, trauma, or prior surgery.

Palpation. When palpating, begin with an assessment of joint warmth. Large joints, such as the knee, should feel cool to the touch

TABLE 102.1 Differential Diagnosis of Arthritis

Monoarticular	Polyarticular: Symmetric	Polyarticular: Asymmetric
Septic arthritis	Rheumatoid arthritis	Gonococcal arthritis
Gout	Psoriatic arthritis	Lyme arthritis
Pseudogout	Polymyalgia rheumatica	Acute rheumatic fever
Osteoarthritis	Enteric arthritis	Reactive arthritis
Trauma, hemarthrosis	Ankylosing spondylitis	Viral arthritides

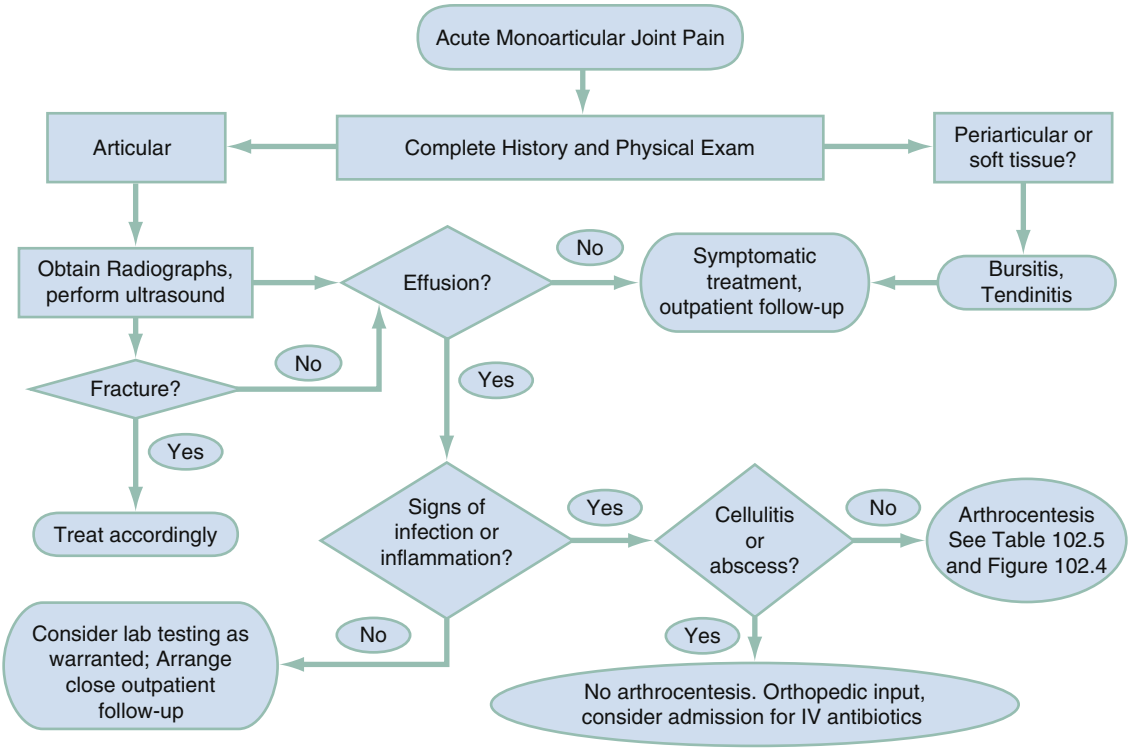

Fig. 102.2 Algorithm for Acute Monoarticular Joint Pain.

TABLE 102.2 Associated Systemic Findings for Common Arthritides

Condition	Findings
Rheumatoid arthritis	C-spine instability, pericarditis, pulmonary nodules, anemia
Psoriatic arthritis	Cutaneous plaques (most commonly on elbows, knees), inflammatory bowel disease
Ankylosing spondylitis	Uveitis/Iritis, cardiac abnormalities, aortic regurgitation, inflammatory bowel disease
Reactive arthritis	Conjunctivitis, genital/urethral discharge, oral ulcerations
Lyme disease	Erythema chronicum migrans, cardiac conduction abnormalities, Bell palsy
Gout	Tophi (usually nontender collections of uric acid crystals found most commonly in the subcutaneous tissue near affected joints)
Acute rheumatic fever	Erythema marginatum, chorea, carditis, subcutaneous nodules

or similar in temperature to the tissue proximal and distal to the joint. If a joint is found to be warm to the touch, this finding is suggestive of an inflammatory process or joint effusion. When a joint is hot to the touch, an infectious etiology should be considered.

Systematic palpation of the joint space and surrounding structures is performed with particular attention to areas of significant focal tenderness. Evaluate bony landmarks, ligamentous attachments, tendinous insertions, and nearby bursae. Identifying pain as articular (from the joint itself) or periarticular (due to proximate extra-articular structures) is important in determining diagnosis and management.

Range of motion. Both active and passive ROM should be assessed and compared with the unaffected extremity whenever possible. Active ROM refers to the patient moving the affected joint through its ROM, whereas passive ROM is performed by the physician without effort by the patient. Joints should be evaluated through their full ROM, which may be in multiple planes depending on the affected area. Pain with only active ROM or pain that is much worse with active ROM suggests a periarticular cause such as tendinopathy or bursitis, whereas pain with both active and passive ROM is more indicative of a true articular cause. Restricted or limited active and passive ROM due to severe pain suggests an inflammatory or infectious etiology.

TABLE 102.3 Components of a Comprehensive Joint Examination

Joint	Inspection	Palpation	Range of Motion (with normal ROM)	Neurovascular	Special Tests
Shoulder	Deformity Swelling Erythema Ecchymosis Muscle washing	Bony: SC joint, AC joint, scapular spine, grater tuberosity of humerus Soft tissue: subacromial space/bursa, biceps tendon	Forward flexion: 180° Extension: 35–45° Abduction: 180° IR and ER: 90° (both with arm adducted at side with elbow flexed and with arm adducted to 90°)	Neuro: Axillary nerve (deltoid sensation), radial, median, and ulnar nerves distally Vascular: radial and ulnar arteries at wrist	Numerous eponymic tests of variable clinical significance. No tests specifically for arthritis. Neer, Hawkins, O'Brien all evaluate RTC or labral pathology
Elbow	Deformity Specific location of pain (e.g., olecranon vs. radial head) Erythema Bruising Tophi (uric acid depositions)	Bony: olecranon, radial head, medial and lateral epicondyles of humerus Soft tissue: triceps tendon, distal biceps tendon	Supination and pronation Flexion: 150° Extension: 0°[a]	Neuro: Median, radial, ulnar nerves distally in forearm, wrist, and hand Vascular: radial and ulnar arteries at wrist	Valgus and varus stress at extension and slight flexion Resisted supination and resisted pronation
Wrist/Hand	Deformity Erythema Ulnar deviation Symmetric vs. asymmetric findings	Distal radius, scaphoid, anatomic snuffbox, ulnar styloid, CMC joint, TFCC, carpal tunnel, metacarpals	Wrist: Extension: 70° Flexion 80° Radial/ulnar deviation: 20° Supination 75°–90° Pronation: 90° Fingers/Thumb: Flexion, extension, abduction, adduction	Neuro: Radial, ulnar, median nerves, grip strength Vascular: radial and ulnar arteries at wrist, capillary refill in digits	Tinnel at carpal tunnel Finkelstein/Eichoff for De Quervain tenosynovitis
Hip	Observe gait Leg positioning at rest Shortening compared to contralateral leg	Bony: Greater trochanter, ischial tuberosity, pubic symphysis, iliac spine Soft tissue: proximal hamstring tendon, proximal quadriceps, inferior abdominal walls	Flexion: 90°–110° (Hyper)extension: 30° Abduction: 40° Adduction: 20° External rotation: 50° Internal rotation: 40° (performed with patient supine and hip flexed to 90° or by passive "log roll" with leg extended)[b]	Neuro: Evaluate strength and sensation in the foot to identify subtle muscle weakness or sensation deficits, patellar and Achilles ankle reflex Vascular: Dorsalis pedis in foot, posterior tibialis in ankle	FABER: Flexion, ABduction, External Rotation FADIR: Flexion, ADduction, Internal Rotation Log roll with internal and external rotation
Knee	Observe gait Swelling Erythema Fullness Calf or lower leg swelling	Bony: Patella, fibular head, distal femur, posterior patellar faces Soft tissue: peripatellar area, quad tendon, popliteal fossa, joint space, hamstring tendons, MCL, LCL Palpate for fluid in suprapatellar pouch	Flexion to 135° Extension to 0°	Neuro: Leg extension and flexion strength, patellar reflex Test strength more distally to find subtle weakness Vascular: Dorsalis pedis in foot, posterior tibialis in ankle	Lachman/anterior drawer Varus/valgus stress McMurray
Ankle/Foot	Swelling Erythema Bruising Arches	Bony: 5th metatarsal base, 1st MTP, medial and lateral malleoli, calcaneus, Lisfranc joint Soft tissue: Tibialis anterior tendon, Achilles insertion and tendon	Dorsiflexion: 20° Plantar flexion: 40° Inversion: 30° Eversion: 20° Toe flexion, extension	Neuro: Inversion (L4) Eversion (S1) Great toe extension strength (L5) Vascular: Dorsalis pedis in foot, posterior tibialis in ankle, capillary refill in toes	Anterior drawer Talar tilt Thompson test (Achilles)

[a]Limitation in terminal extension suggests joint effusion.
[b]Limited or painful IR suggestive of hip joint pathology
AC, Acromioclavicular; *CMC,* carpometacarpal; *ER,* external rotation; *IR,* internal rotation; *LCL,* lateral collateral ligament; *MCL,* medial collateral ligament; *MCP,* metacarpophalangeal; *MTP,* metatarsophalangeal; *SC,* sternoclavicular; *TFCC,* triangular fibrocartilage complex.

Neurovascular evaluation. Strength and sensation should be assessed in the affected joint, as well as the joints directly above and below the painful area. Strength is best assessed by testing small muscle groups whenever possible, because this allows the clinician to find subtle strength differences which may be missed when evaluating only large muscle groups (e.g., evaluate L4 with ankle inversion or L5 using great toe extension rather than testing leg extension). Distal pulses should be palpated and compared with the unaffected side. In the setting of severe peripheral vascular disease or difficult to palpate pulses, doppler or ultrasound may be useful in assessing peripheral arterial flow.

Diagnostic Testing

Radiographic Tests

Plain radiographs. Plain radiographs or X-rays (XR) are useful in determining possible etiologies of acute arthritis. Although they are more helpful in patients who have long-standing disease and therefore more obvious radiographic findings, even in the acute setting, radiographs may guide therapy by demonstrating soft tissue swelling, foreign bodies, or fractures. Whenever possible, weight-bearing images (Fig. 102.3) should be considered for lower extremity joints because they may provide information such as presence of joint space narrowing or significant degenerative changes (Table 102.4). XR has limited utility in the evaluation for joint effusion.

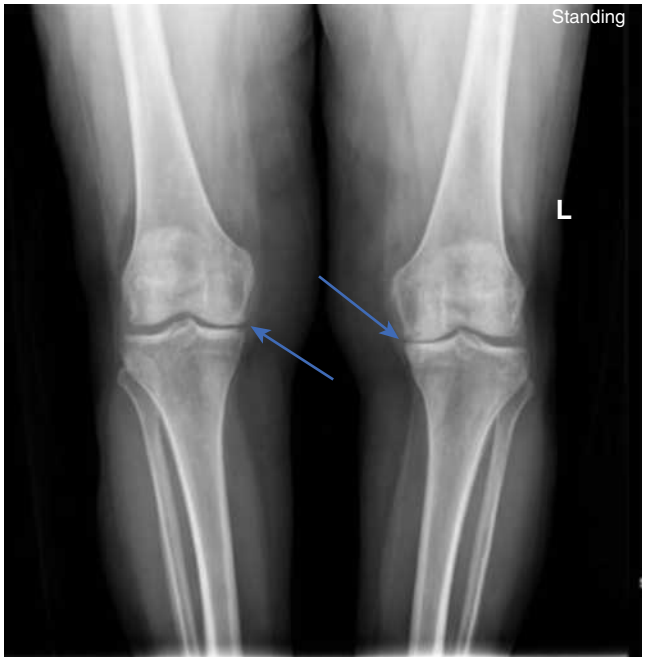

Fig. 102.3 Knee X-ray shows osteoarthritis with narrowing of the medial compartment bilaterally *(arrows)* on this weight-bearing radiograph.

Ultrasound. Bedside ultrasound may be used to complement the physical examination in cases of acute joint pain. The simple evaluation for joint effusion is safe, noninvasive, and easily learned by even novice ultrasound users. Evaluation of, and comparison with, the unaffected side allows direct, real-time visualization of the joint and surrounding areas, providing more expeditious diagnosis and disposition. Determining whether an effusion is present, as compared with a soft tissue abnormality such as an abscess or cellulitis without effusion, will inform the treatment course. Ultrasound may also be used to visualize the largest pocket of fluid in an effusion to help plan for and perform an arthrocentesis. Likewise, the use of bedside ultrasound has also been shown to decrease the incidence of nondiagnostic or "dry" joint taps. In rheumatologic illness, ultrasound has proved useful in determining active disease as well as the need for additional treatment modalities.

Computed Tomography and Magnetic Resonance Imaging. Advanced imaging modalities may add to the evaluation by showing the presence or absence of osteomyelitis, joint effusions, abscesses or other fluid collections, occult fractures, foreign bodies, and ligament or tendon injuries. Magnetic resonance imaging (MRI) is expensive, time-consuming, and generally not used in the ED for nonemergent indications. MRI should be considered when indicated to evaluate for specific conditions. For example, if the clinical suspicion for osteomyelitis is high, MRI is the diagnostic modality of choice. Computed tomography (CT) imaging can be useful if there are suspected fractures that were not visualized on XR, although the use of ionizing radiation should be minimized when feasible. In general, neither MRI nor CT should be used to guide the decision regarding performance of an arthrocentesis in the ED because the decision should be based on clinical findings and concern for infection. CT and MRI may show an effusion but will not be able to specify whether the effusion is infected or not.

Laboratory Testing

Aside from arthrocentesis and joint fluid analysis, specific laboratory tests lack adequate sensitivity or specificity to reliably exclude a septic joint. A serum white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) may be helpful, although it cannot be used to rule out an infectious cause and thus should not be used in isolation to guide ED decision making. An ESR level greater than 30 mm/h or CRP level of greater than 1.5 mg/mL has a sensitivity of greater than 90%, although it is poorly specific for septic arthritis, with specificities of approximately 20%.[2] Serum uric acid, although commonly ordered and elevated in patients with gouty arthropathies, provides little additional value in helping with diagnosis and patient

TABLE 102.4 Common Radiographic Findings in Arthritis

Arthritis	Findings
Acute arthritis (gout, pseudogout, septic)	Soft-tissue swelling
Late septic arthritis (>7–8 days)	Subchondral bone destructions, periosteal reaction, loss of joint space
Late pseudogout (knee, hip, radiocarpal, MCP)	Linear calcification in joint, asymmetric joint space narrowing
Degenerative arthritis (AC, CMC, MTP, DIP, knee, hip, c-spine, lumbosacral spine)	Asymmetric joint space narrowing (more pronounced on weight-bearing views), sclerosis of juxta-articular bone, bone spurs and cysts, minimal to no osteoporosis
Late rheumatoid arthritis (wrist MCP, PIP, MTP, 1st IP foot, atlantoaxial, glenohumeral)	Symmetric joint space narrowing, osteoporosis of periarticular bone marginal erosions

AC, Acromioclavicular; *CMC,* carpometacarpal; *DIP,* distal interphalangeal; *IP,* interphalangeal; *MCP,* metacarpophalangeal; *MTP,* metatarsophalangeal; *PIP,* proximal interphalangeal.

TABLE 102.5 Arthrocentesis Techniques by Joint

Joint	Patient Positioning	Landmarks	Needle trajectory	Ultrasound
Shoulder	Seated with arm flexed resting on thigh with hand supinated Or Lateral decubitus with affected arm internally rotated	Palpate posterolateral edge of acromion Coracoid process	Insert inferior to posterior acromial edge guided toward coracoid process	Performed in-plane: Probe on posterior aspect of acromion (parallel to floor if seated), needle from lateral to medial into joint
Elbow	Arm flexed and pronated Use supination and pronation to find radial head	Palpate lateral epicondyle of humerus and then anterior to it, palpate radial head. "Soft spot" between the two is joint space	Insert into soft spot just anterior to lateral epicondyle	Place probe on tip of lateral epicondyle and find radial head. Probe will be parallel to arm. Guide needled out of plane into joint space
Wrist	Wrist pronated resting on a towel in slight flexion	Lister's tubercle on dorsal radius and extensor pollicis longus tendon located radial to tubercle	Insert needled just ulnar to tendon and just distal to Lister's tubercle	Out of plane approach: Probe long to radius visualizing both radius and scaphoid. Joint space is between.
Hip	Supine in stretcher with leg neutral or slight external rotation if using US Internal rotation if performing without US	Greater trochanter (if not using US)	Insert needle superior to trochanter, horizontal and parallel to the stretcher. Aspirate throughout. Redirect slightly cephalad if bone encountered[a]	Low frequency curvilinear probe used for in-plane approach Find femoral head and neck, guide needled from distal to proximal (side to side on screen) to touch bone at femoral head-neck junction[b,c]
Knee	Supine with knee flexed ~20°	Lateral edge of superior half of patella	Lateral to medial guided to area just posterior to patella	Probe positioned transverse just superior to patella with quad tendon in short axis. Fluid will be inferior to tendon, superior to femur. Guide needle in plane from lateral to medial
Ankle	Supine with plantarflexed foot	Tibialis anterior tendon and anterior edge of medial malleolus	Insert between tibialis anterior and medial malleolus aiming directly posterior	Slight out of plane approach lateral to medial BELOW tibialis anterior tendon into joint space. Tibialis anterior tendon will be in long axis at top of screen
MTP	Supine or sitting with neutral foot, slight flexion of the affected toe	Distal metatarsal head, extensor tendon, and base of first phalanx	Insert dorsally medial to the extensor tendon	Out of plane. Probe is parallel to toe (short to joint), needle will be inserted from medial aspect of foot/toe into joint

[a]Not recommended.
[b]Preferred approach.
[c]Find and mark arteries to avoid in needle path.

disposition from the ED. Many patients with known gout and gouty arthritis have normal uric acid levels and many patients with elevated uric acid levels do not have gout. We therefore do not recommend the routine use of serum uric acid levels in the evaluation of acute arthritis in the ED setting.

Arthrocentesis and Synovial Fluid Analysis

Arthrocentesis. Joint fluid aspiration with synovial fluid analysis is the most important modality used to diagnose the cause of an acutely painful joint. Whenever possible, the procedure should be done with the aid of ultrasound which has demonstrated greater success rates in both aspiration and therapeutic injection when compared with palpation-guided techniques.[3] Arthrocentesis methods for various joints are discussed in Table 102.5.

Indications and contraindications. Indications for urgent arthrocentesis include (1) to obtain joint fluid for analysis for possible infection or crystals, (2) to drain a large hemarthrosis secondary to trauma or injury, (3) to inject medication into the joint, and, less frequently, (4) to evaluate a laceration for possible extension into the joint. Arthrocentesis should be considered for any patient with a newly swollen and painful joint in the absence of trauma.

Contraindications to the procedure are relative and should be discussed with the patient. It is generally accepted practice that arthrocentesis should not be performed if the needle must be inserted through an area of cellulitis or infected skin overlying a joint. Coagulopathy is a relative contraindication, although these procedures have been performed successfully with a less than 0.5% complication rate even in patients with therapeutic international normalized ratio (INR) levels. We recommend performing arthrocentesis in patients with suspected septic arthritis even if currently on therapeutic anticoagulation. A prosthetic joint should only be aspirated after discussion with the operating surgeon, and, in general, patients with prosthetic joints should have neither joint aspiration nor intra-articular injections until the case is discussed with an orthopedist. However, if orthopedic consultant is not available and suspicion for a septic joint remains high, arthrocentesis can be performed by the ED clinician.[4]

Complications. Patients should be counseled about the potential risks of the procedure, the most serious of which include inoculation of infection or bleeding, either into the joint or externally. Less serious complications include pain, allergic reaction to medication, or adverse outcomes when instilling corticosteroids or local anesthetics into the joint space. It is possible that the

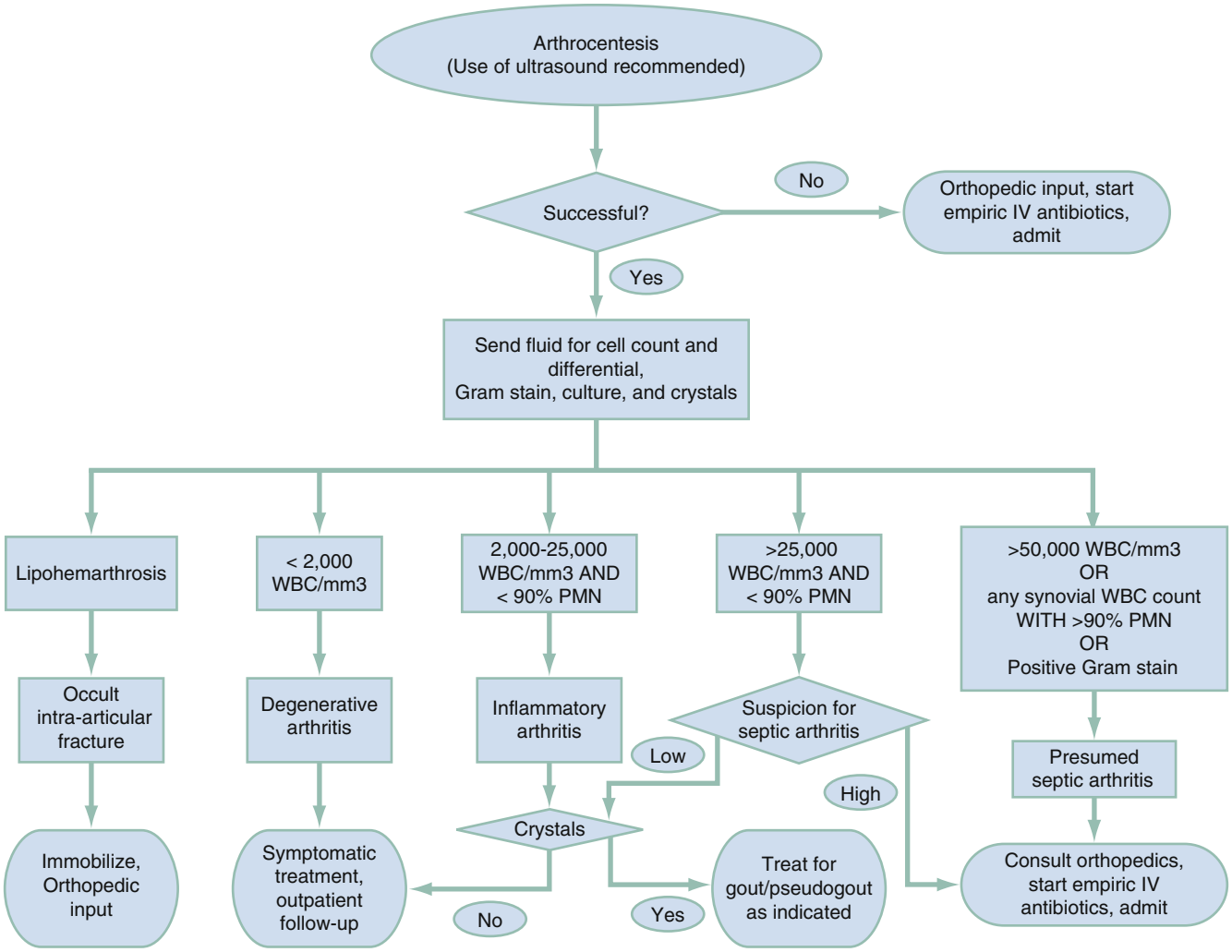

Fig. 102.4 Algorithm for Arthrocentesis for Suspected Septic Joint. *PMN*, Polymorphonuclear; *WBC*, white blood cell.

TABLE 102.6 Key Findings in Joint Fluid Analysis Among Various Causes of Arthritis

	Degenerative	Inflammatory	Septic/Infectious	Hemorrhagic
Color/appearance	Clear to yellow	Yellow	Cloudy/turbid, may be dark or purulent	Bloody, may contain fat droplets
Viscosity	Thick, stringy	Variable	Variable, usually thin	Variable
Synovial WBC count	<2,000/mm^3 <25,000/mm^3 (+LR 0.32)	2,000–50,000/mm^3	>25,000 (+LR 3.2) >50,000 (+LR 4.7) >100,000 (+LR 13.2)	<2,000/mm^3
Synovial PMN%	Variable	Variable, generally <90%	>90%	<25%
Gram stain	Negative	Negative	Positive in 50%–60% of confirmed cases	Negative

LR, Likelihood ratio; *PMN*, polymorphonuclear neutrophil; *WBC*, white blood cell.

aspiration attempt may be unsuccessful, although if ultrasound is used, the fluid can generally be visualized to maximize the chance for success.

Synovial fluid examination. Analysis of the joint fluid obtained via arthrocentesis is a critical step in determining the cause of acute arthritis. Examination should be based on the general appearance of the fluid, color, fluid WBC count, crystal analysis, Gram stain, and ultimately on bacterial fluid culture (Fig. 102.4 and Table 102.6).

General appearance. Visual inspection of the fluid upon aspiration can aid in diagnosis, although no findings are diagnostic without microscopic fluid analysis. Normal fluid is mostly clear and colorless but develops increased viscosity and a more intense yellow color with increased inflammation. Turbid, opaque, or grossly purulent fluid is more suggestive of acute infectious process. A hemarthrosis suggests internal derangement of the joint, including occult fracture or ligamentous injury. A lipohemarthrosis, identified by fat droplets in the aspirate, suggests a fracture, classically seen in a knee arthrocentesis with an occult tibial plateau fracture.

White blood cell count. The synovial WBC count is helpful in distinguishing different causes of arthritis. Although the number of WBCs is generally used to determine the cause of the effusion, there is significant overlap in accepted values among causes of arthritis and

the absolute numbers can be misleading. Classically, septic arthritis presents with greater than 50,000/mm^3 WBC in the synovial fluid, but it has been repeatedly shown that early, or partially treated, septic arthritis may present with significantly lower absolute numbers of WBCs. Nonetheless, the likelihood for septic arthritis increases along with the absolute number of WBCs. The relative number of neutrophils (polymorphonuclear [PMN] cells) is also used to diagnose septic arthritis with levels greater than 90% generally accepted to be associated with infection. No absolute number should be used to diagnose or exclude the presence of a septic joint when the clinical suspicion is high.

In inflammatory arthritis, WBC counts tend to be lower than in septic arthritis, in the range of 25K to 50K/mm^3. However, there may be significant overlap between inflammatory and septic arthritis, and there are instances where patients with RA or gout may have synovial fluid WBC counts well above 50,000/mm^3. We recommend that any synovial sample with a WBC count greater than 50,000/mm^3 be treated as presumptive septic arthritis until further information confirms another etiology.[5]

Prosthetic joints have significantly lower thresholds for diagnosis, and a WBC count greater than 1100/mm^3 should be considered diagnostic of infection.

Lactate and C-reactive protein. Much like synovial WBC count and pleocytosis, increasing lactate and CRP levels in the synovial fluid correlate with an increased likelihood of infection. However, these tests have not been shown to be significantly better than the synovial WBC count or PMN pleocytosis for predicting infection.[6] Due to the associated cost and unlikely additional benefit, we do not recommend the routine use of these tests in the evaluation of possible septic arthritis in the ED.

Crystal evaluation. Analysis under light microscopy to evaluate for monosodium urate or calcium pyrophosphate is used to diagnose gout or pseudogout, respectively. Monosodium urate crystals seen in gout are needle-shaped and negatively birefringent, whereas calcium pyrophosphate crystals seen in pseudogout are rhomboid-shaped and positively birefringent. Importantly, the presence of crystals does not rule out the possibility of infection and in fact, gout is a risk factor for septic arthritis due to chronic joint damage predisposing to hematogenous spread of bacteria into the joint.

Gram stain and culture. A positive Gram stain is diagnostic of septic arthritis though is only found in 30% to 50% of confirmed infections. A negative Gram stain does not exclude the possibility of a septic joint and thus should not be used in isolation to exclude infection. Gonococcal (GC) infections in particular are difficult to identify in synovial fluid and their diagnosis may depend on cultures of genital discharge or oral lesions taken at the same time. Whenever GC septic arthritis is suspected, we recommend obtaining samples from mucosal or skin lesions, as well as urine for nucleic acid amplification testing (NAAT) or Gram stain and culture.

A positive synovial fluid culture is the gold standard for the diagnosis of septic arthritis, but the results are not immediately available in the ED setting. For patients who are discharged, a mechanism should be in place for the follow-up of culture results with the patient. Blood cultures are recommended if septic arthritis is strongly suspected, because they may be positive in up to 50% of septic arthritis cases and may aid in identifying the causative organism if synovial cultures are negative.

Management

The mainstays of treatment of acute arthritis are antiinflammatory medications and, in the case of septic arthritis, antibiotics. The management of specific causes of acute arthritis are discussed in subsequent sections of the chapter.

Disposition

The ultimate disposition of the ED patient with acute arthropathy will depend on clinical findings. Although most patients with acute exacerbations of chronic conditions can be managed with oral medications in the outpatient setting, the challenge for the emergency clinician remains in identifying patients who are at risk for rapid deterioration, progressive disease, or permanent joint disability. When septic arthritis is suspected, hospital admission, parenteral antibiotic therapy, and orthopedic input remain prudent. Patients with known or suspected rheumatologic conditions can typically be followed on an outpatient basis. Patients with other noninfectious causes of joint pain can often be treated with analgesics or antiinflammatory medications until seen in follow-up by a primary care physician.

ACUTE MONOARTICULAR JOINT PAIN

Acute joint pain, when confined to a single joint and particularly if associated with erythema, warmth, or systemic infectious symptoms, should prompt urgent evaluation for a septic joint. However, acute trauma and inflammatory conditions of the periarticular tissues can also cause monoarticular joint pain. Therefore conditions such as bursitis, tendonitis, synovitis, and sprains or other trauma should also be considered.

Nongonococcal Bacterial Septic Arthritis

Foundations

The incidence of septic arthritis is approximately 6 per 100,000 population per year in industrialized countries. This number increases to 30 to 60 per 100,000 population per year in patients with underlying disease or prosthetic joints. Young children and elders are at greater risk, as are patients with immune compromise, diabetes, and history of hemodialysis or IV drug use. Patients with prosthetic joints or those who have had recent intra-articular steroid injections are at particular risk. The presence of chronic joint inflammation such as RA or gout is also a significant risk factor for joint infection, particularly as many of these patients are on chronic immunosuppression. Exacerbations of crystal arthropathies can coexist with infectious arthritis, and the presence of crystals should not be used to eliminate the possibility of septic arthritis. Box 102.2 lists factors that increase the risk of septic arthritis.

The most common method of joint space inoculation is by hematogenous spread although direct inoculation from local injury or infection in surrounding tissues may also occur. Once the joint space is inoculated, there is little defense against rapid bacterial proliferation. This unchecked bacterial growth and the associated inflammatory cascade typically leads to severe pain, synovial proliferation, neovascularization, and extensive

BOX 102.2 Factors Increasing Risk of Septic Arthritis

Age >80
Diabetes
Rheumatoid arthritis
Gout/pseudogout
Recent joint surgery
Hip or knee prosthesis
Skin infection
Prosthesis PLUS skin infection
Intravenous drug abuse
Endocarditis
Human immunodeficiency virus (HIV) disease

TABLE 102.7 Common Pathogens in Septic Arthritis

Group	Organisms
Neonates and infants	*Staphylococcus aureus,* group B *Streptococcus*
Children	*S. aureus,* group A *Streptococcus, Streptococcus pneumonia, Kingella Kingae,* Lyme
Adolescents and young adults	*Neisseria gonorrhea, S. aureus*
Older adults	*S. aureus, Streptococcus,* gram-negative rods
Sickle cell anemia	*S. pneumonia, Salmonella* (although more commonly causes osteomyelitis)
Intravenous drug use	Pseudomonas, *S. aureus,* gram-negative rods
Prosthetic joint	Coagulase-negative *Staphylococcus, S. aureus,* gram-negative rods, *Streptococcus* species

damage of the articular cartilage if not quickly identified and appropriately treated.

The most common bacterial causes of non-GC septic arthritis include gram-positive organisms such as methicillin-resistant or methicillin-sensitive *Staphylococcus aureus* and *Streptococcus* species, which are found in almost 80% of culture-confirmed infections. Anaerobes and mycobacteria are less common causes. Likewise, *Haemophilus* and pneumococcal species are less common in the postvaccine era. *Neisseria gonorrhoeae* accounts for less than 20% of monoarticular arthritis and more frequently presents as polyarticular arthritis. Certain patient populations are more likely to develop specific infections as discussed in Table 102.7.

Prosthetic joint infections deserve specific mention, with these infections classically being described as either early, defined as occurring within a month of surgery, or late. Late infections develop via hematogenous spread or by organisms introduced into the joint space during surgery, which may not become clinically evident for up to a year later. Arthrocentesis should be performed in discussion with, or optimally by, an orthopedic surgeon when feasible. In the prosthetic joint, a synovial WBC count of more than 1,100/mm^3 or PMNs greater than 60% are both sensitive and specific for joint infection. In the setting of a prosthetic joint, the host immune response and antibiotic delivery to the joint space are both impaired, and thus the management of infection can be complex.

Clinical Features and Differential Diagnosis

Patients with septic arthritis will often present with fever, joint pain, and effusion, most often in a large joint such as the knee. Fever response may be blunted in elders or those who have a suppressed immune system. At particular risk are patients with autoimmune arthritis, overwhelming sepsis, or meningococcal infections. Up to 20% of patients with septic arthritis may present with polyarticular involvement. Physical examination findings, such as decreased ROM, joint tenderness, or erythema, have inadequate sensitivity and specificity for determination of septic arthritis.

Diagnostic testing. Laboratory testing, including a serum WBC, ESR, and CRP, is commonly performed although often is of limited utility. Elevated values only slightly increase the likelihood of septic arthritis, and normal values do not exclude the condition. Likewise, radiographs are of limited utility in diagnosing a septic joint but may occasionally identify alternative diagnoses. Although plain radiographs may help to identify osteomyelitis, the bony changes associated with septic arthritis are a late finding. CT or MRI may be useful in identifying early changes associated with septic arthritis or may help to assess joints that are difficult to evaluate clinically, including joints that are challenging to aspirate.

TABLE 102.8 Empiric Antibiotics for Suspected Septic Arthritics Intravenous

Gram Stain Results	Antibiotic Regimen (IV Dosing)
Unavailable or negative Gram stain	Vancomycin loading dose: 20 to 35 mg/kg actual body weight (not to exceed 3000 mg) or 20 to 25 mg/kg actual body weight (not to exceed 3000 mg) in patients with obesity, then 15 to 20 mg/kg actual body weight every 8 to 12 hrs IV WITH IV cephalosporin (ceftriaxone 2 g, cefepime 2 g, ceftazidime 2 g) OR aztreonam 2 g IV OR daptomycin 6 mg/kg IV WITH IV cephalosporin OR linezolid 600 mg IV WITH IV cephalosporin
Gram-positive cocci	Vancomycin loading dose: 20 to 35 mg/kg actual body weight (not to exceed 3000 mg) or 20 to 25 mg/kg actual body weight (not to exceed 3000 mg) in patients with obesity, then 15 to 20 mg/kg actual body weight every 8 to 12 hrs IV OR daptomycin 6 mg/kg IV OR linezolid 600 mg IV
Gram-negative bacilli	Ceftriaxone 2 g IV OR aztreonam 2 g IV
Gram-negative diplococci	Ceftriaxone 2 g IV, can consider adding azithromycin 1000 mg orally (PO) for chlamydia coverage

The gold standard test for the patient with acute monoarticular arthritis remains joint aspiration and synovial fluid analysis. Elevated synovial fluid WBC count, increased proportion of PMNs, and elevated synovial fluid lactate all increase the likelihood of septic arthritis. A fluid Gram stain and aerobic and anaerobic cultures should be performed. Synovial fluid should also be evaluated for characteristic crystals of gout or pseudogout.

Management

Early identification and treatment of septic arthritis is crucial. Delays in definitive care can lead to increased morbidity and mortality. Hospitalization for intravenous (IV) antimicrobial therapy is appropriate. Empiric antibiotic therapy should be directed at organisms found on Gram stain, or alternatively, broad-spectrum therapy is appropriate and can be tailored once speciation and sensitivity results are available. Table 102.8 details recommended antibiotic therapy for suspected septic arthritis.

Depending upon the specific joints involved, either surgical drainage or repeated joint aspirations are often required. Early coordination with an orthopedic surgeon is critical in the management of infection in prosthetic joints. Antibiotics are often continued for several weeks and infectious disease input may be helpful in selecting the most appropriate antibiotic regimen.

CHRONIC MONOARTICULAR ARTHRITIS

Osteoarthritis

Foundations

OA or degenerative joint disease is the most common form of arthritis among adults and is more common in obese patients and elders. Changes in load on the joint, due to excess weight or trauma, combined with biochemical and genetic factors, lead to changes in cytokine signaling and thus alterations in composition of the extracellular matrix. This ultimately leads to overgrowth of subchondral bone, degradation of the articular cartilage, and inflammation of the synovium.

Clinical Features

Although OA most commonly involves multiple joints, patients often present complaining of severe pain in a single joint. Pain associated with OA is often described as worse with activity and improved at rest. Patients may have a joint effusion but rarely have signs of severe inflammation, such as warmth and erythema. There is often associated crepitus in the affected joint with both active and passive ROM. Associated systemic symptoms are not characteristic, which helps to differentiate OA from rheumatoid or inflammatory arthritis.

Diagnostic Testing

Plain radiographs often reveal asymmetric joint space narrowing, osteophyte formation, or subchondral cyst formation. However, there is no direct correlation between radiographic findings and the degree of symptoms. The role for laboratory testing in the evaluation of OA is limited, although laboratory evaluation may help in differentiating OA from infectious arthritis if the latter diagnosis is suspected. Synovial fluid may be more difficult to aspirate in patients with OA and fluid analysis classically reveals a mildly inflammatory pattern with few PMNs.

Management

The goal of ED management of OA pain is symptom relief. Many pharmacologic and nonpharmacologic treatment modalities have been used. Among nonpharmacologic options, weight loss, exercise, and ice may be effective for some patients. Bracing, splints or orthoses, and appropriate footwear may also be beneficial. Nutritional supplements such as glucosamine and chondroitin have demonstrated limited benefit.[7] Pharmacologic treatments include topical medications, oral analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), or corticosteroids. Fig. 102.5 details considerations regarding therapeutic modalities and medication coadministration.

Oral analgesics represent the mainstay of OA treatment. The use of acetaminophen is supported by multiple clinical trials and is recommended as first-line therapy for most patients with OA. Adverse effects associated with acetaminophen are less frequent and less severe than those associated with other oral medications.[8] More recent data suggest minimal impact on pain control with the use of oral acetaminophen as monotherapy in knee arthritis.[9,10]

NSAIDs should be considered when acetaminophen fails to provide adequate pain relief. They have been shown in several studies to be more effective than acetaminophen in terms of pain control, although the side effect profile of NSAIDs precludes long-term use in many patients, especially those with renal disease, cardiovascular risk factors, or history of gastrointestinal (GI) bleeding. The cyclooxygenase-2 (COX-2) inhibitors are associated with a lower risk of GI bleeding than other NSAIDs, but concerns about increased risk of cardiovascular events with long-term use remain. Fig. 102.5 details NSAID use and risk factors. Oral duloxetine, a centrally acting serotonin and norepinephrine reuptake inhibitor most frequently used in the treatment of mood disorders, has shown some

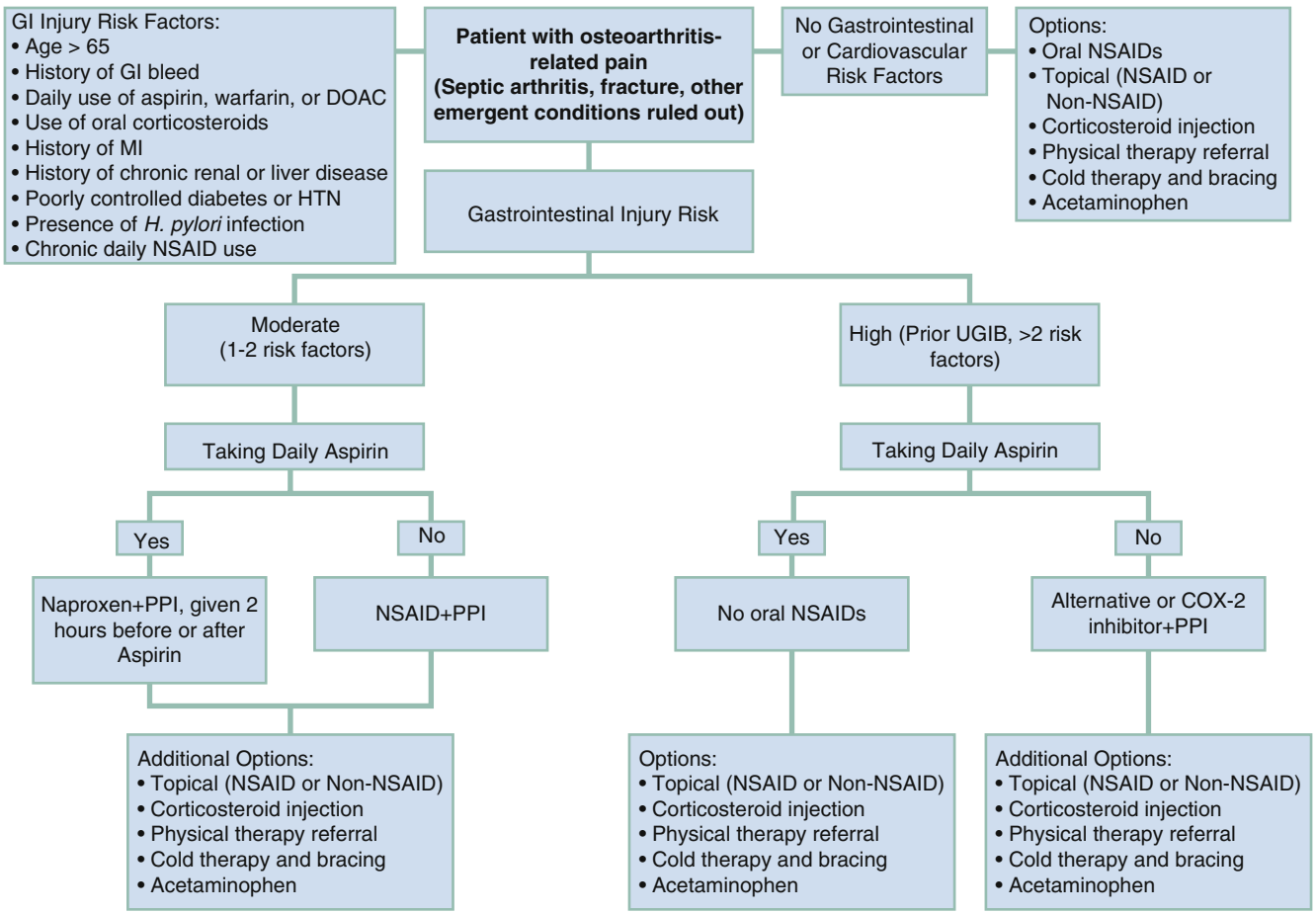

Fig. 102.5 Algorithm for weighing the risks associated with the use of nonsteroidal antiinflammatory drugs *(NSAIDs). COX-2*, Cyclooxygenase-2; *PPI*, proton pump inhibitor; *UGIB*, upper GI bleed. (From Young S, Bothwell J, Walsh R. Safely managing acute osteoarthritis in the emergency department: An evidence-based review. *Journal of Emergency Medicine* 51:6 648-657, 2016.)

efficacy in chronic musculoskeletal pain, including knee OA. It is not routinely used acutely in the ED setting and should generally be initiated in the outpatient setting, unless close follow-up has been arranged.[11]

Topical medications may be useful in treating patients with OA who are at risk of complications from oral NSAIDs. Several studies have shown that topical NSAIDs, such as diclofenac gel, have similar efficacy to oral NSAIDs, with lower risks of GI side effects. Topical capsaicin may help with OA pain either as a primary or adjunctive therapy, particularly in the small joints of the hands, with a low risk of systemic toxicity, although a moderate to high risk of local skin reaction limits its usefulness in many patients. Topical anesthetic (e.g., lidocaine) and topical salicylic acid preparations are also available, although there are no large studies confirming their long-term efficacy or safety. It is important to note that many topical and transdermal preparations may not penetrate deeply enough to be particularly effective for many patients with OA pain.

Corticosteroids can be considered for severe exacerbations of OA pain. Although systemic (oral or injectable) corticosteroids may be an option for some patients, most often, clinicians will consider intra-articular steroid injections. Intra-articular injections may provide acute pain relief and an improvement in symptoms for several weeks in some patients, although their effect can be unpredictable. Intra-articular steroids are unlikely to provide long-term benefit and may cause worsening of arthritis particularly with repeat injections. Intra-articular hyaluronic acid may provide improved function and decreased disability. It is best studied in the knee but may not provide long-term benefit and is generally unavailable in the ED setting. Intra-articular injections of amide anesthetics (e.g., lidocaine), either alone or in combination with corticosteroids, have been used for many years to provide pain relief in patients with acute discomfort. However, recent studies have suggested that intra-articular instillation of local anesthetics may be chondrotoxic.

There is little evidence to support the use of other oral analgesics. Tramadol has not been shown to have significant effect in patients with OA and is associated with significant risk of adverse outcomes with prolonged use.[12] Other opioid analgesics may be appropriate for short-term exacerbations of severe pain, particularly in patients with contraindications to other medications. However, risks of opioid use outweigh the benefit for long-term use in patients with OA.

ACUTE POLYARTICULAR JOINT PAIN

There are several conditions that may lead to polyarticular joint pain. These include gout, pseudogout, Lyme arthritis, GC arthritis, or various rheumatologic conditions. When classifying polyarticular arthritis, it is often helpful to consider whether the symptoms are acute or chronic, whether the involved joints are symmetric or asymmetric, and whether large or small joints are affected. It remains important to consider that a significant proportion of patients diagnosed with a septic joint may present with multijoint involvement; therefore considering septic arthritis in your differential is vital. GC arthritis in particular remains a key consideration in the setting of multijoint pain or effusions. Box 102.3 reviews the differential diagnosis of polyarticular arthritis. Viral causes of arthritis are reviewed in Table 102.9. An approach to polyarticular pain is outlined in Fig. 102.6.

Gonococcal Arthritis

Foundations

The US Centers for Disease Control and Prevention (CDC) estimates that there are approximately 820,000 new cases of gonorrhea in the United States each year,[13] and the World Health Organization (WHO) estimates 87 million cases annually worldwide.[14] Although GC arthritis represents only 1% of all septic arthritis cases, it remains the most

BOX 102.3 Differential Diagnosis of Polyarthritis

Polyarthritis:
Infectious: Lyme disease. Endocarditis. Gonococcal. Viral.
Rheumatic fever
Seronegative spondyloarthropathies:
Ankylosing spondylitis, psoriatic arthritis, reactive arthritis
Rheumatoid arthritis
Crystal arthropathies
Systemic rheumatologic illness

TABLE 102.9 Selected Viral Arthritides

Virus	Arthritis Presentation	Duration of Symptoms	Therapy
Hepatitis B	Symmetric, migratory joint symptoms	Subsides with onset of jaundice	Supportive
Hepatitis C	Symmetric rheumatoid arthritis-like mimic, or intermittent monoarticular arthritis	Variable, intermittent	Supportive; rheumatoid arthritis treatments are often helpful
Human immunodeficiency virus (HIV)	Often monoarticular arthritis involving feet and ankles, sometimes involving tendon, bursae, skin, or muscle inflammation	Variable	Generally treating underlying HIV is most important aspect of treatment. Otherwise, supportive treatment for joint symptoms
Parvovirus B19	Fifth disease in childhood, causes a connective tissue syndrome in adults	Self-limited but may recur	Supportive
Rubella virus, rubella vaccine virus	30% of females and 6% of males with rubella show symptoms of arthritis	Symptoms appear within 2 weeks of vaccination or a week of rubella infection; self-limited	Supportive
Alphaviruses (Ross River, Chikungunya, Mayaro)	Mosquito-borne, often seen in epidemics	May be abrupt or insidious onset; symptoms can last 3–6 months—some patients experience years of discomfort	Largely supportive; corticosteroids were once contraindicated but have more recently been demonstrated effective
Flaviviruses (Dengue, Zika, West Nile)	Mosquito-borne, often seen in epidemics	Usually acute joint and bone pain along with high fever	Supportive

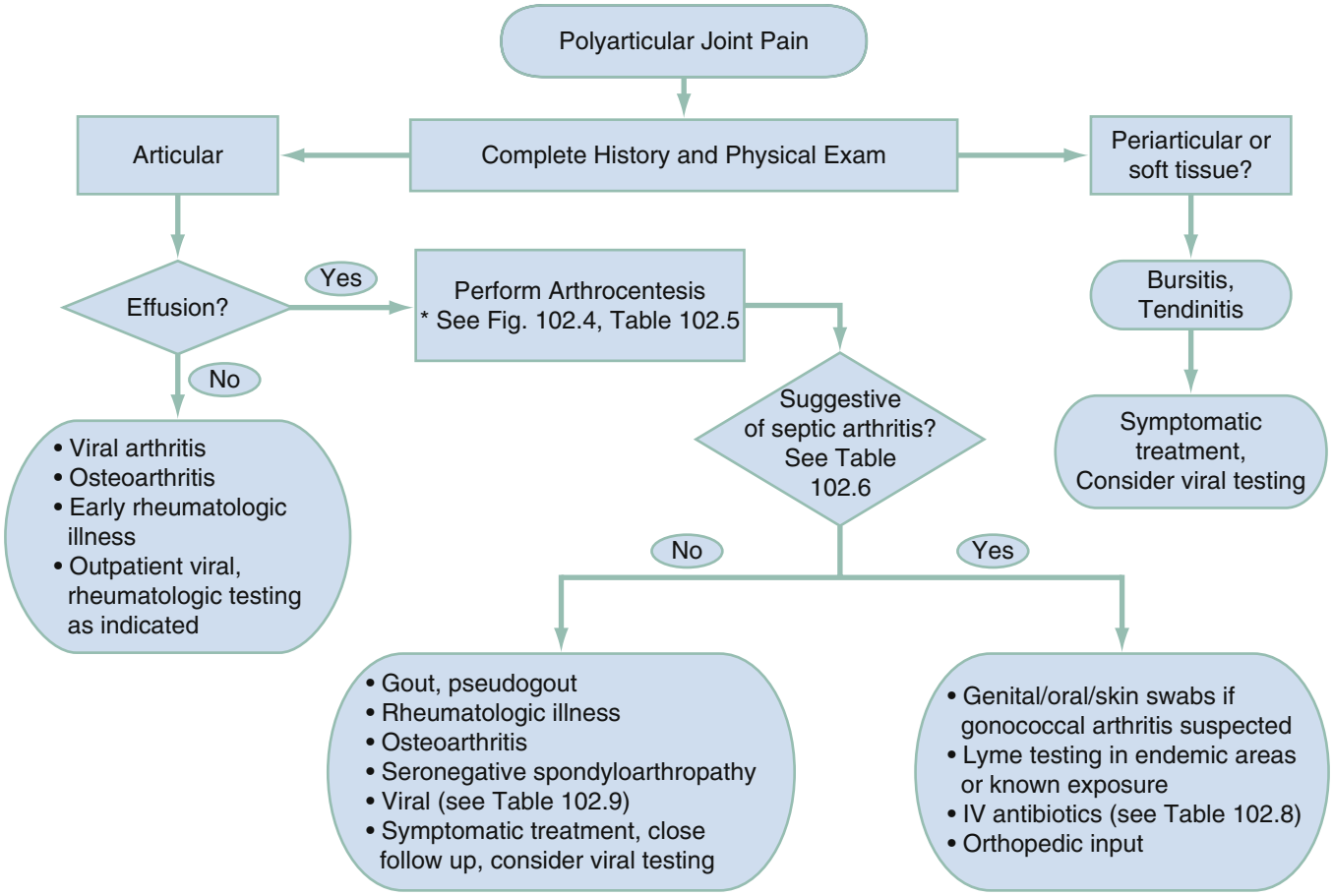

Fig. 102.6 Algorithm for Polyarticular Joint Pain.

common form of joint infection in the young, sexually active population. Hematogenous dissemination of the initial mucosal infection occurs in less than 3% of cases overall and is thought to play a major role in the pathogenesis of GC arthritis. The risk of dissemination is higher in immunocompromised patients, women (particularly during pregnancy), IV drug users, and patients with multiple sexual partners. The time from initial infection to presentation with arthritis symptoms may be 1 to 3 months.

Clinical Features

Although GC arthritis may present in a single joint, it often manifests as an oligoarthritis, affecting two to four joints simultaneously, often in the wrist, knee, or ankle. The effusions associated with this condition may be modest compared with other infections. Diffuse, migratory arthralgias and fever are also common. Simultaneous skin findings, also resulting from hematogenous spread, may also be present with small painless, nonpruritic lesions that may be papular, pustular, or vasculitic.

Management

The diagnosis of GC arthritis can be particularly challenging because cultures of blood and synovial fluid may be negative, although diagnostic yield is greatly improved when polymerase chain reaction (PCR) testing is performed. When GC infections are suspected, all possible sites should be tested, including blood, synovial fluid, oropharynx, genitalia, and any suspect skin lesions. When the diagnosis is made, hospitalization is advised, and treatment should be initiated with ceftriaxone 2 g IV or intramuscular (IM) every 24 hours. Antibiotic sensitivity results will assist the transition to appropriate oral antibiotics. Simultaneous treatment for chlamydia is advised with azithromycin 1 g PO, as is testing for other sexually transmitted infections. Repeated arthrocentesis is rarely required, and when diagnosed and treated promptly, residual joint damage is rare.

Gout

Foundations

Acute gout occurs in approximately 4% of adults in the United States, impacting approximately 5% of adult males and 3% of adult females. Gout is more prevalent among older adults.[15] Risk factors include obesity, hypertension, diabetes, and use of thiazide diuretics or cyclosporin. Acute gout attacks may be precipitated by a purine-rich diet including meats, beer, legumes, and seafood, especially shellfish or anchovies. Uric acid is a normal by-product of purine metabolism, and hyperuricemia results from its undersecretion by the kidney or, less commonly, from overproduction caused by inborn errors in metabolism. Acute attacks result from inflammation that occurs when uric acid crystals precipitate from supersaturated extracellular fluid. During an acute attack, these crystals are ingested by PMN cells, resulting in release of cytokines and an inflammatory reaction of the synovium. Asymptomatic hyperuricemia may exist for years, and the absolute serum uric acid level does not correlate well with the risk or frequency of acute attacks.

Clinical Features

Gouty attacks occur most commonly in the first metatarsophalangeal (MTP) joint, causing the condition termed podagra. The knee, ankle,

tarsal joints, and hand are also frequently affected. Usually patients experience an acute flair in a single joint, but up to 20% of patients have polyarticular involvement or associated bursitis, tenosynovitis, and skin changes that can resemble cellulitis (Fig. 102.7). Onset of pain is sudden, and the pain may be exquisite, both with movement and while at rest. Systemic symptoms, including fever, may be present and should raise concern for the possibility of septic arthritis. Acute episodes of gout are self-limited, usually with peak symptoms within 1 to 2 days and resolution within a week. If left untreated, attacks may become more frequent, involve more joints, and may have lasting sequelae including bony erosion and tophi, which are gritty, chalk-like nodules composed of deposits of monosodium urate crystals which are generally painless. These are most commonly found in the subcutaneous tissue, although they may also be found in bursae, joint space, or soft tissues.

Diagnostic Testing

Diagnostic evaluation for gout includes arthrocentesis and evaluation of joint fluid particularly in patients who are having their first episode of gout. Patients who have an established history of gout and are otherwise well appearing without other risk factors for septic arthritis may be treated without a joint aspiration. The acute gouty joint will have synovial fluid crystals visible that appear negatively birefringent when viewed with a polarizing microscope. Serum laboratory tests are largely unhelpful because gouty attacks can occur in patients with normal uric acid levels, and some patients may have elevated uric acid levels without signs or symptoms of clinical disease. Serum WBC count may be elevated, but this is also a nonspecific finding. It is reasonable to evaluate renal function because there is an association between gout and renal insufficiency and many of the treatments for gout are nephrotoxic.

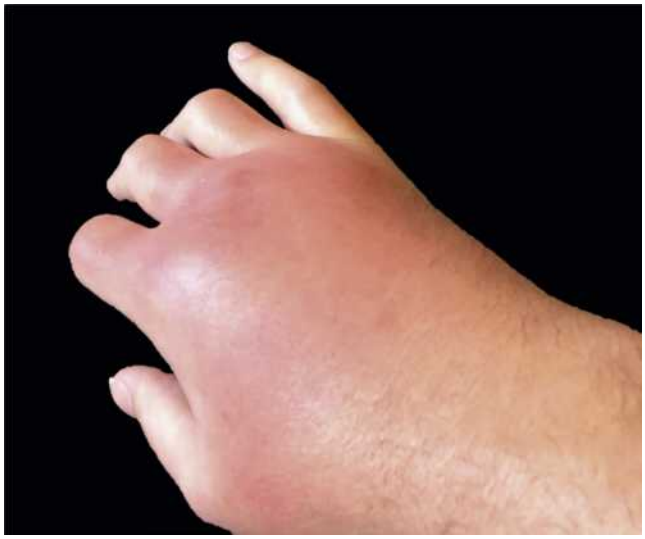

Fig. 102.7 Patient with confirmed gout in the second metacarpophalangeal joint mimicking hand cellulitis.

Plain radiographs of the acutely affected joint may show only the associated soft-tissue swelling. However, patients with long-standing disease may show signs of asymmetric, sclerotic-appearing bony erosions outside the joint capsule. Ultrasound may be useful in the evaluation of the acute gouty joint: The crystalline material reflects sound waves, revealing an irregular, hyperechoic signal along the surface of the articular cartilage, sometimes referred to as the "double contour sign"—one representing the crystals and the second the hyperechoic bony surface below. Chronic tophi may also be visible on ultrasound and are described as having the appearance of "wet clumps of sugar" with a heterogenous center and hypoechoic rim (Fig. 102.8).

Management

The management of gout is divided into therapies to treat acute attacks and those aimed at long-term treatment and prophylaxis against future attacks. Patients often present to the ED for symptoms related to an acute exacerbation. Contrary to previous guidelines, long-standing prophylactic medications, such as allopurinol, febuxostat, or probenecid, may be continued—although they should not be initiated—in the setting of an acute gout flare.[16] The mainstays for ED management of acute gout include NSAIDs, corticosteroids, or colchicine.

Although NSAIDs are often considered first line, there is little evidence to suggest superiority of one drug over another, or even to suggest that NSAIDs are better than other pharmacologic options. When started promptly after the onset of symptoms, relief typically occurs within 24 hours, and the NSAID should be continued for at least another 24 hours after symptom resolution. Indomethacin, naproxen, and ibuprofen are all reasonable choices. NSAIDs should be avoided in patients with a history of peptic ulcer disease, GI bleeding, renal insufficiency, or other known contraindications.

Colchicine acts by inhibiting the formation of microtubules, thereby inhibiting the inflammatory response to the presence of crystals in the synovium and has been shown to be effective for the treatment of gout. However, it is contraindicated in patients with renal or hepatic insufficiency, can cause GI distress in many patients, and has a narrow therapeutic window making it potentially lethal in overdose. Because it shares similar contraindications to NSAIDs as well as a similar efficacy, we recommend traditional NSAIDs over colchicine for acute symptom management.

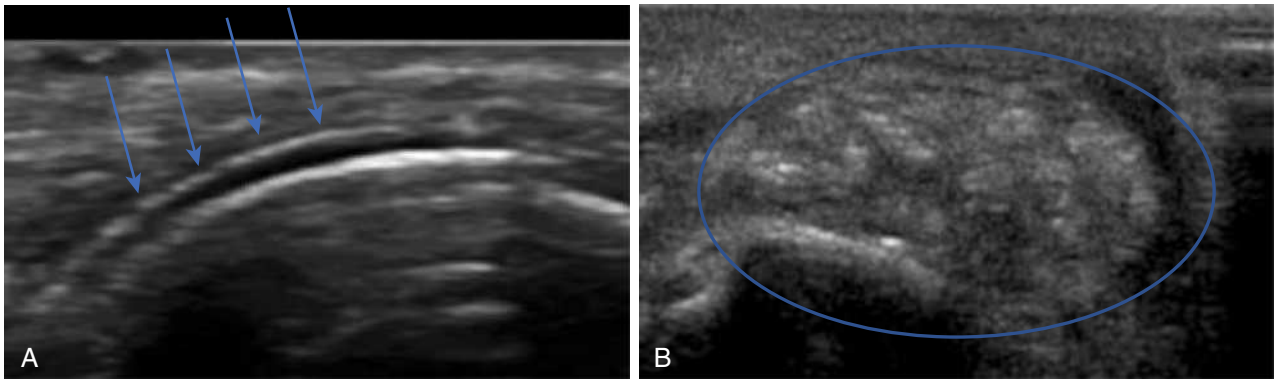

Fig. 102.8 Ultrasound Appearance of Gout. (A) Double contour sign showing gout in a metatarsal phalangeal joint. (B) Tophus seen on ultrasound showing "clump of sugar" appearance.

Steroids, whether oral or intra-articular, can also be beneficial in an acute gout attack. Intra-articular steroids may be most effective but should not be used in any patient with possible septic arthritis, and their use may be impractical in patients with small joint disease or when multiple joints are involved. Oral steroids, such as prednisone 40 mg daily for 5 to 7 days or a tapered pack of solumedrol, may also be effective.

Combination therapy, such as intra-articular steroid injection combined with colchicine or NSAIDs, is a reasonable option, particularly for patients with debilitating symptoms and those who have required such treatment previously. Oral corticosteroids with simultaneous NSAID use are not recommended due to the risk of GI side effects. Other treatment options include a short course of opioid analgesics, regional anesthetic blocks, or short-term cessation of diuretic therapy. Nonpharmacologic treatments such as ice, elevation, oral hydration, or avoidance of known triggers may also be helpful.

Pseudogout

Foundations

Calcium pyrophosphate deposition disease (CPPD), also known as pseudogout, is caused by deposits of calcium complex crystals on the articular surfaces. These deposits are evident on plain radiographs as chondrocalcinosis. The precipitation of these crystals leads to an inflammatory synovitis. Although the pathophysiology of the condition is not well understood, it is most commonly seen in elders and those with prior trauma or recent joint surgery. There is also an association with hemochromatosis, amyloidosis, hypothyroidism, and hyperparathyroidism. This condition is most often asymptomatic, but when acute inflammation occurs, the resulting condition is known as pseudogout.

Clinical Features

The acute presentation of pseudogout is similar to gout, although patients with pseudogout tend to be older and the knee is the most commonly affected joint. A warm and swollen joint that is acutely tender is typical, and it may be difficult to differentiate between the two conditions based on history and physical examination findings alone. However, compared with gout, acute pseudogout attacks may take longer to reach maximum symptom intensity and symptoms may persist for up to 2 to 3 months despite therapy.

Many patients with CPPD crystal deposition follow a chronic, progressive course of articular degeneration known as pseudo-OA. This may manifest in multiple joints, often involving the knees, wrists, metacarpophalangeal (MCP) joints, hips, shoulders, spine, elbows, or ankles. Approximately half of these patients will experience acute attacks of pseudogout superimposed on their chronic symptoms, whereas the remainder may present with signs and symptoms more consistent with classical OA.

Diagnostic Testing

Diagnostic testing for pseudogout is similar to that for gout. Plain radiographs may demonstrate chondrocalcinosis within the articular cartilage or in the joint capsule, although these radiographic findings may be present in less than half of cases. Given the association with systemic disease, laboratory testing may be warranted in select cases, including serum electrolytes, alkaline phosphatase, thyroid studies, or iron studies. Joint fluid analysis reveals weakly positive birefringent crystals that are rhomboid-shaped. As with gout, the symptoms may mimic septic arthritis, and it is important to note that crystals and acute infection may be present simultaneously.

Management

Asymptomatic CPPD does not require acute treatment unless it is directed at the underlying conditions (e.g., hypercalcemia due to hyperparathyroidism). When considering acute exacerbations of pseudogout, there are no specific pharmacologic agents that directly target the deposition of calcium crystals, and available anticrystal agents have not yet been proved to be effective in humans. In small studies, methotrexate, interleukin-1 (IL-1) inhibitors, and anti–tumor necrosis factor (TNF) alpha agents show promise in decreasing the frequency and severity of acute attacks, particularly in periarticular disease. Thus treatment is typically initiated using antiinflammatory medications. NSAIDs remain a mainstay of therapy, although they may be contraindicated in some older adults or those with comorbidities. Steroids, either systemic or intra-articular, can provide rapid symptomatic relief. Much like for gout, colchicine can be effective for acute exacerbations through its effect on PMNs; however, its narrow therapeutic window limits its utility.

Lyme Disease

Foundations

The spirochete *Borrelia burgdorferi* causes the infection responsible for Lyme disease, one of the most common vector-borne diseases in the Western Hemisphere. Transmitted by the *Ixodes* tick, the CDC estimates nearly 300,000 cases of Lyme disease per year in the United States.[17]

Clinical Features

Lyme disease presents as an unfolding pattern of symptoms which develop over weeks to months following infection. The early symptoms occur within weeks or months after a tick bite and may include rash as well as migratory myalgias or arthralgias without evidence of discrete arthritis. However, arthritis is the hallmark of the late stage of disease, and when untreated, approximately half of patients develop asymmetric arthritis within 6 months of initial infection. Lyme disease typically affects the large joints, in particular the knees, and if left untreated may cause intermittent episodes that persist for years. The arthritis associated with Lyme disease appears to be an autoimmune effect rather than a direct result of the spirochete infection. Early antibiotic therapy reduces the incidence of subsequent joint involvement.

Diagnostic Testing

The history of a tick bite, particularly in Lyme-endemic areas, or the classic erythema migrans rash may aid the clinician in making the diagnosis. However, many patients may not recall either the tick exposure or the resulting rash. The patient presenting with acute Lyme arthritis will typically have large joint effusions but may not have other systemic symptoms such as fever. Joint aspirate will reveal an inflammatory pattern with a predominance of PMNs. Although *B. burgdorferi* is difficult to culture from the synovial fluid, PCR testing may provide more accurate results when performed prior to the initiation of antibiotic therapy. Synovial fluid analysis and culture should be used to help exclude other etiologies, including septic arthritis. Lyme serologies (IgM and IgG) may be helpful in the outpatient setting but are of little utility in the ED. Routine lab testing is otherwise unhelpful.

Management

Prophylaxis against Lyme disease is not typically recommended unless an engorged *Ixodes* tick is found attached to a patient for greater than 24 to 36 hours in a Lyme-endemic area. In such cases, a single dose of doxycycline 200 mg PO (4.4 mg/kg in children) is recommended for prophylaxis. In the acute phase of disease, when patients present with

rash, myalgias, or arthralgias, the treatment is doxycycline 100 mg PO twice daily for 10 days. Lyme arthritis is treated with a 28-day course of doxycycline 100 mg PO twice daily. Amoxicillin 50 mg/kg/day divided every 8 hours (max 500 mg per dose) may be substituted for doxycycline in children, pregnant women, or the setting of tetracycline allergy. IV therapy, typically with a second- or third-generation cephalosporin (e.g., ceftriaxone 2 g IV daily), is reserved for patients with moderate or severe, persistent arthritis despite adequate oral antibiotic therapy. A small subset of patients may experience ongoing symptoms even after appropriate therapy, but a more prolonged course of antibiotics is unlikely to be beneficial.[18]

Acute Rheumatic Fever

Foundations

Acute rheumatic fever (ARF) is a complex systemic disease triggered by a hyperimmune response that follows pharyngitis due to group A streptococcal infection. The cellular and humoral response to the infection affects joints as well as cardiac tissue. The incidence of ARF has declined in recent years due to several factors including improved hygiene, increased antibiotic use, and mutations in prevalent group A *Streptococcus* strains. The worldwide incidence may be as high as 20 per 100,000, but in the United States and other developed nations the incidence is less than 2 per 100,000. In certain indigenous populations, including Australia and New Zealand, the incidence among children aged 5 to 14 years is significantly higher.

Clinical Features

The diagnosis of ARF is based on the Jones Criteria and the presence of two major criteria and one or more of the minor criteria (Table 102.10). Laboratory evidence of antecedent group A streptococcal infection is also required. Arthritis occurs in up to 75% of patients with ARF and presents as a migratory polyarthritis typically affecting the large joints and lasting 2 to 3 days per joint. Joints may appear inflamed and patients often display pain out of proportion to the apparent severity of the arthritis.

Diagnostic Testing

The value of laboratory testing for ARF is limited in the ED setting. Evaluation of synovial fluid reveals a sterile, inflammatory pattern. If suspected, obtain formal two-dimensional (2D) echo and Doppler imaging to evaluate for cardiac involvement.

Management

Recommended treatment of ARF includes IM benzathine penicillin 1.2 million units or a 10-day course of oral penicillin (penicillin V 500 mg PO 3 times daily for 10 days or amoxicillin 500 mg PO twice daily for 10 days). Oral clarithromycin 250 mg PO twice daily for 10 days may be used in penicillin-allergic patients. High-dose NSAIDs, such as oral aspirin 50 to 100 mg/kg/day divided into four daily doses may be used to treat arthritis and fever but do not have an effect on the cardiac sequelae. Small studies have suggested that oral or IM corticosteroids such as hydrocortisone 1 to 2 mg/kg/day PO slowly tapered over 2 to 4 weeks may be better than aspirin in patients with cardiac involvement. Recurrence may occur at a rate of 8% to 10% within 5 years; and monthly antibiotic prophylaxis with oral or IM penicillin for at least 5 years, or until adulthood, is recommended.

TABLE 102.10 Jones Criteria for Rheumatic Fever

Major Criteria	Minor Criteria
Joint pain (polyarthritis)	Arthralgia
Carditis (echo/Doppler used to diagnose)	Fever
Subcutaneous nodules	Elevated erythrocyte sedimentation rate (ESR) (>60 mm) or C-reactive protein (CRP) (>3.0 mg/dL)
Erythema marginatum	
Sydenham chorea	Prolonged PR interval

Two major criteria or one major with two minor criteria required for diagnosis. Also requires either elevated streptococcal antibody titer or positive throat culture/rapid streptococcus test.

CHRONIC POLYARTHRITIS

Rheumatoid Arthritis

Foundations

Although RA is typically a chronic condition with insidious onset and progression, approximately 20% of patients with RA present with acute exacerbations. With a worldwide prevalence of approximately 1%, incidence peaks between the ages of 35 and 50 years, and the condition is approximately 3 times more common in women. It is characterized by immune complexes that stimulate PMN cells to produce and release enzymes that lead to joint destruction. Over time, the number of synovial cells dramatically increases, leading to progressive release of inflammatory substances and progressive joint damage.

Clinical Features

At the time of initial diagnosis, patients may report weeks or months of fatigue, weakness, malaise, and joint pain, with or without associated fevers or weight loss. Over time, joint pain, swelling, and inflammation may progress often starting symmetrically in the proximal interphalangeal (PIP) and MCP joints of the hands, associated with stiffness that is worse in the morning. Over time, patients with RA may develop persistent symmetric polyarthritis of hands and feet, progressive articular deterioration with characteristic deformities including ulnar deviation, swan neck, and boutonniere deformities of the hands (Figs. 102.9 and 102.10). Patients may also have associated tenosynovitis and signs of extra-articular disease, including constitutional symptoms and difficulty performing activities of daily living. During an acute exacerbation, patients may present with only warm, swollen, or tender joints, which may be difficult to differentiate from other arthritides.

Diagnostic Testing

In the emergency setting, the evaluation of a patient with known or suspected RA should be directed at identifying other possible causes of acute arthritis, particularly septic arthritis. An elevated ESR and CRP may be seen in patients with either acute or chronic disease and remain nonspecific findings. Early radiographic findings are similarly nonspecific and include soft-tissue swelling or joint-space narrowing; subluxation or other bony deformities are late findings (see Fig 102.10). Synovial fluid analysis tends to reveal a nonspecific inflammatory pattern, although it may be useful in excluding crystal arthropathy or acute infection in selected patients.

Management

Care of patients with RA includes both pharmacologic and nonpharmacologic therapies. Pharmacologic options include NSAIDs, both biologic and nonbiologic disease-modifying antirheumatologic drugs (DMARDs), immunosuppressants, and corticosteroids. In acute exacerbations, relative rest and antiinflammatory medications are appropriate, including NSAIDs or low-dose systemic corticosteroids. Short-term use of additional analgesic medication may also be required.

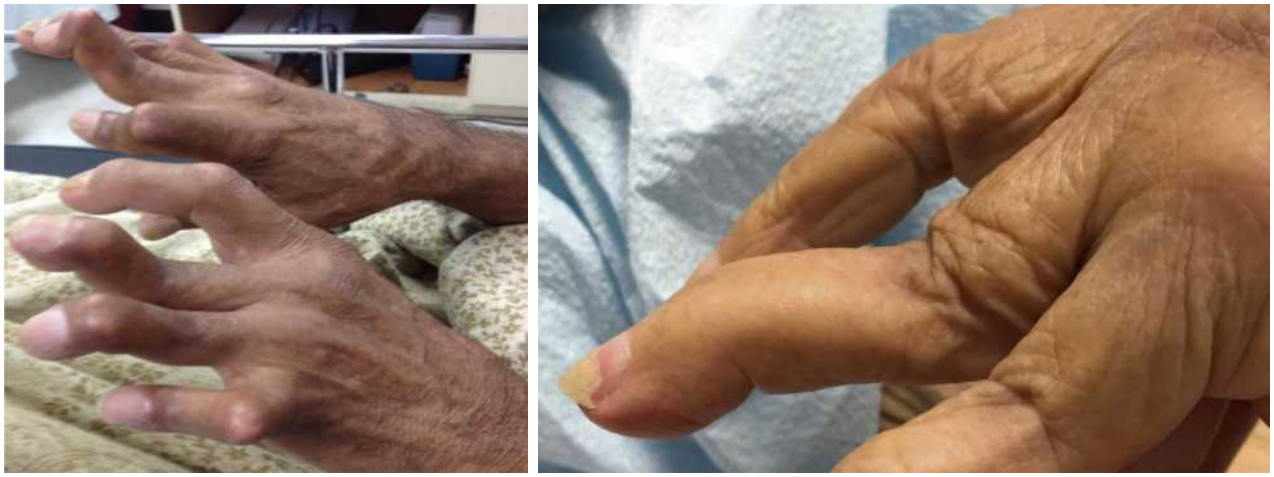

Fig. 102.9 Example of severe deformities including swan neck deformity of multiple digits in poorly controlled rheumatoid arthritis.

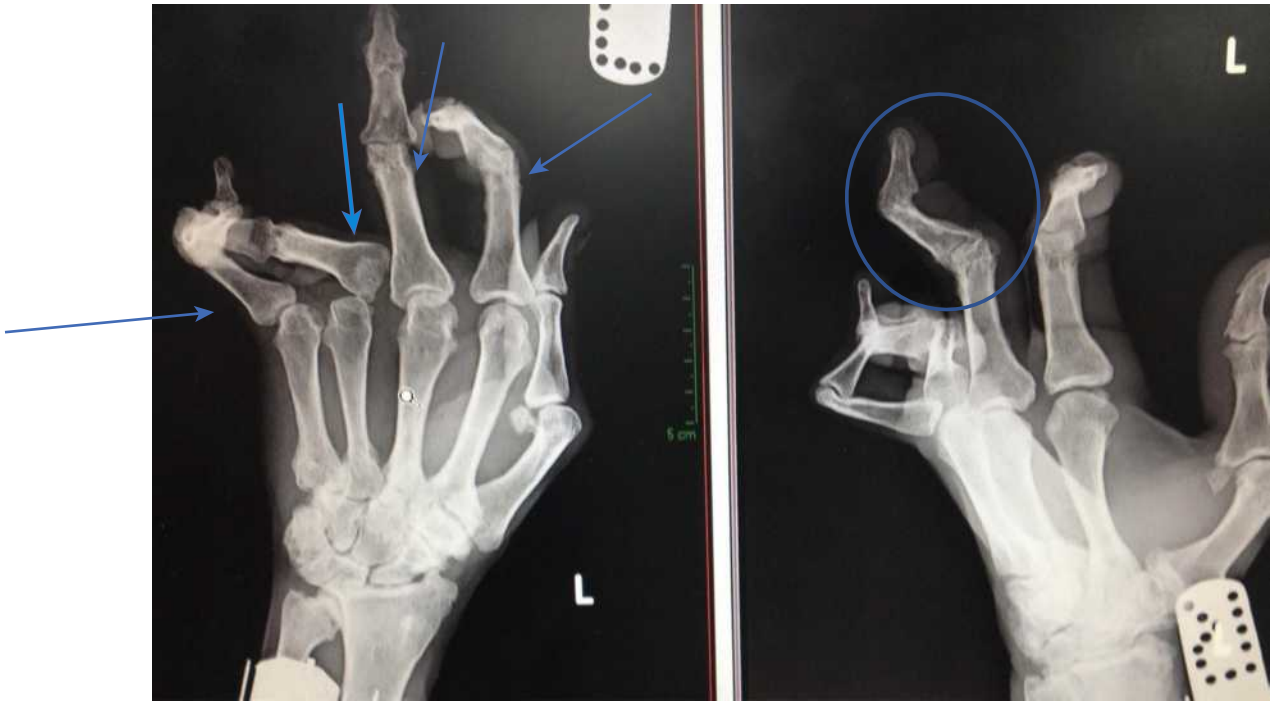

Fig. 102.10 X-ray demonstrating severe deformities associated with long-standing untreated rheumatoid arthritis. Note profound ulnar deviation *(small arrows)*, joint subluxations *(large arrow)*, and swan neck deformity *(circle)*.

Studies have shown that biologic agents may be the most effective option in patients who have failed other treatments as well as in patients who have not yet been started on any chronic maintenance therapy for their RA. Early initiation of biologic or nonbiologic DMARDs has become routine as they can lead to remission of symptoms as well as limit progression of disease. Nonpharmacologic interventions are generally directed at long-term mitigation of symptoms and include interventions such as exercise, diet, stress reduction, cryotherapy, physical therapy, massage, or surgery including synovectomy, arthroplasty, or arthrodesis.

Seronegative Spondyloarthropathies

Foundations

The seronegative spondyloarthropathies are a broad category of conditions that share the clinical features of sacroiliac joint involvement and inflammatory arthropathy affecting multiple distal/peripheral joints with pathologic changes seen at the entheses (ligament and tendon insertion sites, see Fig. 102.1). Rheumatoid factor is typically absent, and HLA-B27 may be positive. The most common of these conditions include ankylosing spondylitis (AS), reactive arthritis, psoriatic

arthritis, and arthropathy associated with inflammatory bowel disease, so-called enteropathic arthritis.

Ankylosing Spondylitis

Clinical features. Patients with AS are more likely to be male and younger (younger than 40 years of age) and often report chronic back pain with insidious onset. This may be associated with radiographic evidence of sacroiliitis or the characteristic "bamboo spine," as well as extra-articular disease, most commonly uveitis. Urethritis and vasculitis may also occur, including potentially life-threatening disease affecting the aortic root. Up to 30% of patients may have associated enthesopathies such as plantar fasciitis or Achilles tendinopathy.

Management. Acute therapies are directed at managing pain and reducing inflammation. Therefore analgesics and antiinflammatory medications are appropriate. Biologic or nonbiologic DMARD therapy will be appropriate for chronic management and to prevent disease progression.

Reactive Arthritis (Formerly Termed Reiter Syndrome)

Clinical features. Reactive arthritis, formerly termed Reiter syndrome, generally occurs in patients 20 to 40 years of age following infection with *Chlamydia*, *Salmonella*, *Shigella*, *Yersinia*, or *Campylobacter* species, with symptoms of arthritis presenting 2 to 6 weeks after an episode of dysentery, or cervicitis/urethritis in the case of *Chlamydia* species. The condition presents with asymmetric polyarticular pain, often affecting joints of the lower extremities. Associated conjunctivitis, uveitis, or oral ulcers may also be seen.

Diagnostic testing. In reactive arthritis, synovial fluid demonstrates an inflammatory pattern. The joint fluid is sterile, although antigen testing for *Chlamydia, Salmonella*, or *Yersinia* may be positive. Radiographs may reveal abnormalities at tendon insertion sites.

Management. Patients with reactive arthritis respond well to antiinflammatory treatment with NSAIDs. Antibiotics may be appropriate in patients with *Chlamydia* but have not been shown to improve the clinical course in patients with reactive arthritis following dysentery.

Psoriatic Arthritis

Psoriatic arthropathy may occur in 20% of patients with psoriasis, causing a range of clinical presentations such as asymmetric oligoarthropathy, symmetric polyarthropathy, spondylitis, distal interphalangeal (DIP) joint involvement—in distinction from other rheumatoid conditions that tend to affect the PIP or MCP joints—or arthritis mutilans, a particularly severe condition in which there is evidence of bone resorption with associated collapse of the soft tissue. First-line treatment is with NSAIDs, and local corticosteroid injections may also be considered. There is little evidence for systemic steroid use, and DMARDs are often initiated early.

Enteropathic Arthritis

Up to 40% of patients with inflammatory bowel disease will experience musculoskeletal manifestations. This may present as an acute, asymmetric, migratory, inflammatory polyarthritis, commonly affecting the knees. The acute exacerbations of joint pain often accompany acute flares of GI symptoms. Although NSAIDs are first-line treatment for joint pain, they may exacerbate GI symptoms. Sulfasalazine and intra-articular corticosteroid injections are alternatives for symptom management.

Other conditions such as fibromyalgia, polymyalgia rheumatica, and scleroderma may also have characteristic musculoskeletal pain and joint stiffness. These conditions tend to cause more widespread pain, rarely present with acute arthropathy or joint effusions, and do not represent a true arthritis.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 102: QUESTIONS AND ANSWERS

1. A 72-year-old male with history of gout presents to the emergency department (ED) with worsening knee pain and swelling. He states this pain is worse than previous gout episodes. A diagnostic arthrocentesis is performed. Which of the following synovial fluid results would be most consistent with a diagnosis of septic arthritis?

- **a.** Gram stain negative, positive crystals (needle-shaped), synovial white blood cell (WBC) count 25K, polymorphonuclear (PMN) 70%, turbid appearance
- **b.** Gram stain negative, negative crystals, synovial WBC count 12K, red blood cell (RBC) 1K, fat globules in aspirate
- **c.** Gram stain negative, positive crystals (needle-shaped), synovial WBC count 40K, PMN 92%, turbid appearance
- **d.** Gram stain negative, positive crystals (rhomboid-shaped), synovial WBC count 35K, PMN 60%

Answer: c. A synovial fluid sample with PMN greater than 90% is presumed to be consistent with septic arthritis regardless of total synovial WBC count. Answer choices **a** and **d** may represent septic arthritis in certain scenarios, but neither is diagnostic. These represent acute gout and pseudogout, respectively. Answer **b** is representative of a lipohemarthrosis consistent with intra-articular fracture. A positive Gram stain would also be diagnostic of septic arthritis, although approximately 50% of cases of septic arthritis are associated with a negative Gram stain.

2. A 38-year-old previously healthy female presents to the emergency department with a complaint of worsening elbow pain and swelling. She plays recreational soccer and fell on her elbow one week ago. There was a small laceration over the elbow, but she has been trying to keep it covered with gauze. Over the last two days, the elbow has become more swollen, red, and painful. Joint aspiration confirms septic arthritis with gram stain showing gram positive cocci. What is true about the treatment of this patient with septic arthritis?

- **a.** Intra-articular antibiotic treatment is the gold standard and should be given immediately.
- **b.** Septic arthritis can safely be treated with oral antibiotics as the first line of treatment as long as the patient does not have a fever.
- **c.** Synovial fluid aspiration is rarely helpful in the treatment of septic arthritis. Blood cultures are sufficient.
- **d.** Vancomycin is a good choice for initial antibiotic treatment in this patient with septic arthritis.

Answer: d. A is incorrect because intraarticular antibiotics do not play a role in the treatment of septic arthritis. IV antibiotics are the gold standard. B is incorrect because IV antibiotics are the first line of treatment. Fever is not always present with septic arthritis. C is incorrect because synovial fluid aspiration is extremely important in the treatment of septic arthritis. Drainage of the joint is important, but it can also guide your antibiotic choice. D is correct because vancomycin 15–20 mg/kg/dose every 8 to 12 hours is a good starting antibiotic, with a positive gram stain showing a gram positive organism. Ceftriaxone 2 g IV (or other cephalosporin, see Table 102.8) can be added if gram stain is inconclusive or if results are not readily available.

3. Which of the following statements regarding septic arthritis is true?

- **a.** *Streptococcus pneumonia* is the most common cause of bacterial arthritis
- **b.** Older patients are more likely to present with fever
- **c.** Synovial fluid C-reactive protein (CRP) is more accurate than serum CRP
- **d.** Blood cultures should be obtained when bacterial arthritis is suspected

CHAPTER 102: QUESTIONS AND ANSWERS—cont'd

Answer: d. Blood cultures are recommended in all suspected septic arthritis cases because bacteremia is a relatively common finding. The most common pathogen is *Staphylococcus aureus*. Older patients are less likely to present with a fever. Synovial and serum CRP levels are similar in diagnostic value.

4. A previously healthy 19-year-old female presents with an acutely swollen and painful left knee starting a few days ago. She denies trauma or any previous history of similar episodes. She denies fever or chills but has had minor pelvic discomfort and a vaginal discharge, as well as bilateral wrist pain that resolved spontaneously. In addition to performing diagnostic joint aspiration, what tests should be ordered on this patient?
   a. Oral and genital swabs for polymerase chain reaction (PCR)
   b. C-reactive protein (CRP) and sedimentation rate
   c. Serum uric acid levels
   d. Lyme titers

Answer: a. This patient has gonococcal arthritis. This bacterium is notoriously difficult to find in synovial samples, and it is recommended to obtain oral and genital samples, in addition to samples of any skin lesions that may be present, to maximize diagnostic possibilities. CRP or sedimentation rate may aid in diagnosis of a septic joint but are not helpful in distinguishing the actual causative agent. Uric acid level has limited utility in this setting. Lyme disease is less likely in this patient who also has complaints of vaginal discharge, but this may be considered in endemic areas with known or possible tick exposure.

5. A 54-year-old male with poorly controlled hypertension and coronary artery disease on daily aspirin presents with a swollen first metatarsophalangeal (MTP) joint on the right foot. You make the diagnosis of gout. Which of the following is the most appropriate initial treatment for this patient with a presumptive diagnosis of gout?
   a. Naproxen 550 mg twice daily
   b. Naproxen 550 mg twice daily coupled with daily proton pump inhibitor (PPI) therapy
   c. Colchicine
   d. Allopurinol and colchicine
   e. Febuxostat and naproxen

Answer: b. This patient is moderate risk for gastrointestinal (GI) injury due to history of poorly controlled hypertension and daily aspirin use; thus an oral nonsteroidal antiinflammatory drug (NSAID) coupled with daily PPI use is reasonable. If the patient had no cardiac or GI risk factors, use of NSAID alone would be appropriate. Colchicine is an alternative therapy, although given its side effect profile, another NSAID is generally preferred. Allopurinol and febuxostat are medications that may be used to prevent gout attacks but should generally not be started during an acute flair and are not typically initiated in the ED setting.

Tendinopathy and Bursitis

Christopher Hogrefe and Emily M. Jones

KEY CONCEPTS

Tendinopathy

- Mechanical overload and repetitive microtrauma are key underlying mechanisms in the development of tendinopathy. Patients most often present with a history of progressively worsening localized pain after repetitive work- or sports-related activities.
- Tendinopathy may also be associated with nonmechanical causes, including systemic manifestations of diseases, infectious etiologies, and the use of fluoroquinolones or statins.
- Most patients with tendinopathy can initially be treated with conservative measures, such as activity modification/protection, icing, medications (e.g., short-term use of nonsteroidal antiinflammatory drugs [NSAIDs] or nitroglycerin patches for certain tendinopathies), bracing/splinting, ergonomic modifications, and graduated exercises.
- Overuse syndromes can take at least 6 to 12 weeks to heal. Advise patients accordingly and provide appropriate referral for follow-up to a musculoskeletal specialist (e.g., a sports medicine, orthopedic, or physical medicine and rehabilitation specialist).
- Emergent imaging may be indicated in the ED when fracture or a condition such as calcific tendinopathy is suspected. The use of point-of-care ultrasound to evaluate tendinopathy can help to identify tendon disruption/rupture.
- Operative treatment may be indicated for selected cases of tendon injury that require primary repair (e.g., rupture of the Achilles tendon) or that have failed to respond to conservative treatment (e.g., rotator cuff tendinopathy).

Bursitis

- Consider the possibility of an infectious cause in all cases of acute bursitis.
- The definitive diagnosis of bursitis is made by aspiration of the bursa and evaluation of the fluid.
- Septic bursitis is most commonly caused by *Staphylococcus aureus*.
- Nonseptic bursitis may be traumatic, rheumatologic (e.g., gout and pseudogout), or idiopathic in nature. It is prudent to consider other conditions, such as septic arthritis, osteomyelitis, or an underlying fracture, in the differential diagnosis of bursitis.
- The management of bursitis includes treatment with appropriate medication (antibiotics for septic bursitis, NSAIDs for nonseptic bursitis), rest, application of ice, compression, elevation, and prompt referral for appropriate follow-up. Hospitalization should be considered for severe local infections, for patients who are immunosuppressed, and in the presence of systemic toxicity.

TENDINOPATHY

Foundations

Background and Importance

Tendons are collagenous, dynamic structures that connect muscle to bone. They transmit forces originating in muscles to bone by stiffening, thereby enabling joint motion. *Tendinopathy* is an umbrella term that also encompasses tendinitis and tendinosis. The diagnosis of *tendinitis,* a commonly used term implying "inflammation of the tendon," has long been associated with numerous overuse injuries. Many practitioners now advocate use of the term *tendinosis* as a more accurate reflection of the pathologic process, representing a degenerative process without evidence of inflammation. To date, reliable, well-conducted epidemiologic studies have not been performed for most tendinopathies; however, histopathologic analysis often reveals degenerative tendon pathology with few inflammatory cells. This chapter will utilize the term *tendinopathy*, referring to a painful, impaired tendon that encompasses the various pathologic processes.

Approximately 30% of all musculoskeletal evaluations performed in the emergency department (ED) or urgent care settings are attributed to tendinopathy, and the incidence is rising. A contributing factor is the increasing level of daily participation in athletics and fitness-related activities, up 3.6% across a recent 12-year period.[1] Nearly half of all sports participants will be injured at some point, with up to 50% of injuries involving tendinopathy. For instance, with approximately 1.5% of the population running on a daily basis the number of affected runners accumulates quickly.[1] One study found that over one year, 27% of novice runners, 32% of long distance runners, and 52% of marathon participants sustained injuries with the majority related to overuse.[2] In another investigation, 70% of professional and 25% of youth basketball injuries were due to tendinopathy.[3]

Exercise is not the only culprit precipitating tendinopathy, however. Occupational exposures are a prominent cause of tendinopathy, resulting from lower demand, highly repetitive tasks (contrasted with higher demand, explosive sporting activities). Professions that involve repetitive motion, localized contact stress, awkward positions, vibrations, or forceful exertion are more likely to result in overuse injury such as tendinopathy. Shoulder tendinopathies are particularly common in the workplace, representing up to 13.6% of all musculoskeletal complaints regardless of one's occupation.[4] The nature of such work is further

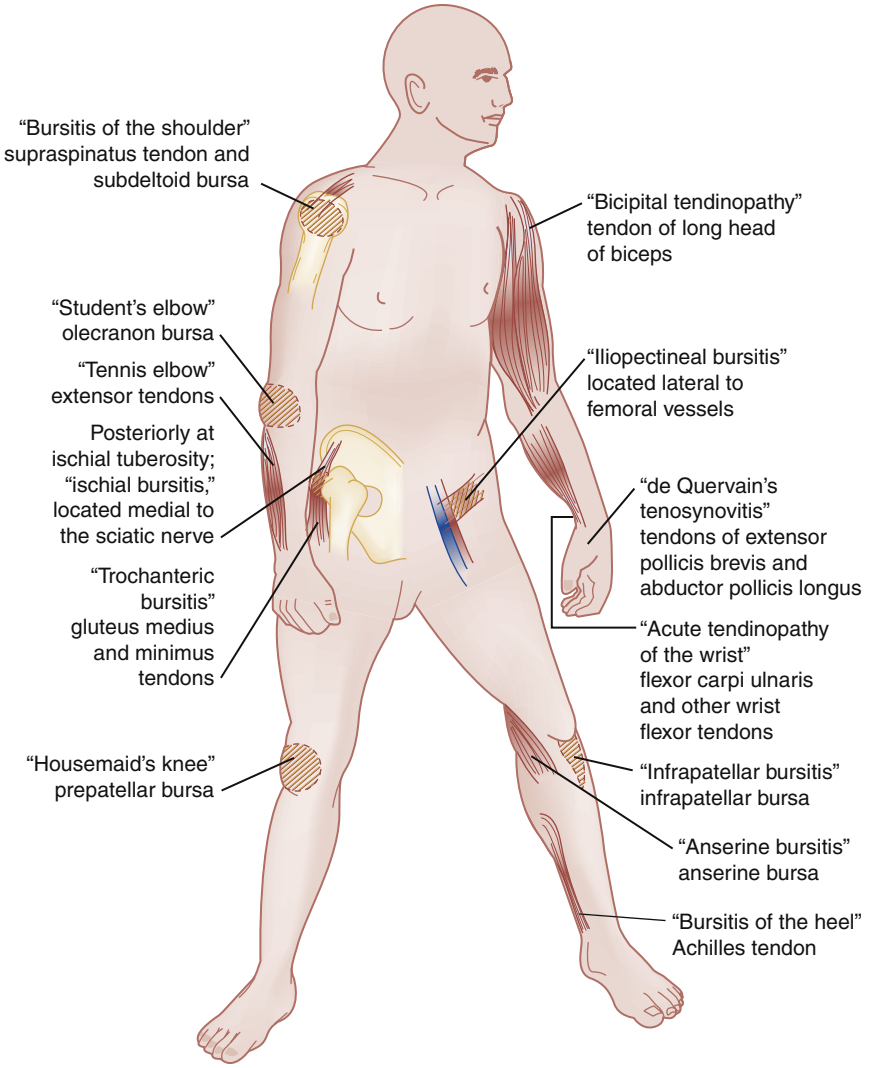

Fig. 103.1 Location of common sites for tendinopathy or bursitis. (Modified from Branch WT. *Office Practice of Medicine,* ed 2. Philadelphia: Saunders; 1987.)

compounded by longevity; those working 25 to 35 years are 7.1 times more likely to develop tendinopathy. The economic end result is staggering, with an estimate of nearly $800 billion in health care costs over a 3-year span attributed to these conditions.[5] Furthermore, for all nonfatal injuries in the United States (U.S.), tendinopathies account for the fifth most days away from work, totaling on average 14 days (with only fracture-related injuries accounting for more lost days of work).[6] Ergonomic and medical intervention programs may reduce the incidence of work-related injuries and decrease their socioeconomic impact.

Aside from the acute pain and functional limitations, tendinopathies often become chronic (i.e., greater than 3 months in duration) and can be disabling. Patients may experience symptoms for extended periods despite appropriate therapy and recurrence is common, affecting 49% of athletes with patellar tendinopathy.[7] Meanwhile, 40% to 50% of patients with rotator cuff tendinopathy exhibit symptoms at 6 to 12 months.[8]

Mechanical overload and repetitive microtrauma to the musculotendinous unit are thought to be the major precipitating causes of most tendinopathies. While the affected tendon is primarily under tensile overload, compression of the tendon occurs as well (e.g., fiber bundles contacting each other or friction/shearing against bone). Broadly, there are intrinsic and extrinsic factors that modify the pathophysiologic state of the tendon. Intrinsic factors such as age, gender, blood type O, adiposity, tobacco use, malalignment, joint laxity, muscle weakness, and imbalance can result in excessively high or frequent mechanical loads during normal activity. Extrinsic factors such as ergonomics, equipment changes, abnormal movements, excessive duration of activity, increased frequency or intensity of activity, and environmental conditions can also contribute to the development of tendinopathy.

Other potential contributing etiologies include excessive protein intake, systemic disease (e.g., coronary artery disease, diabetes mellitus, and gout), or medication use. An increased incidence of tendinopathy and tendon rupture, particularly of the Achilles tendon, has been attributed to fluoroquinolone antibiotics. This risk appears greatest within the first month of use, in those over age 60 years, in patients receiving corticosteroid treatment (4.68-fold increase for all tendons and 14.72-fold increase for Achilles tendon rupture), and in those with renal disease.[9] Statins have been implicated as contributing to tendinopathy as well (2% incidence), although simvastatin is thought to actually decrease this risk.[10] Overall, most tendinopathies are multifactorial in origin. Several of the common areas affected by tendinopathy are shown in Fig. 103.1.

Under optimal conditions, such as appropriately graduated athletic training, the musculotendinous units adapt to tension overload. This

results from the ability of bone to increase its load-bearing capacity combined with an increase in size and strength generated by the hypertrophy of existing muscle fibers. An enhancement of tendon and ligament strength occurs through an increase in collagen content, collagen cross-linking, and mucopolysaccharide content. Unfortunately, many athletes may not allow sufficient time for this adaptive process to occur. For example, a soccer player may increase the number of games played, the duration of time per game played, participation intensity, or any combination of these factors with haste, restricting the cellular changes required to adapt to the increased stress. Poor running technique, suboptimal playing surfaces, environmental conditions, or improper equipment (particularly footwear) may also contribute to the development of an overuse syndrome.

Pathophysiology

The pathophysiologic mechanism of tendon healing has mainly been described in the context of acute injury (e.g., rupture), and correlation to the healing process in tendinopathy remains under investigation. Acutely injured tendons go through several stages in the healing process, starting with the hemorrhagic phase as blood accumulates and clots at the site of injury. The inflammatory stage then follows as neutrophils and macrophages initiate phagocytosis, removing the existing necrotic material. Healing then progresses to the proliferative phase where extrinsic cells (e.g., tendon sheath, fascia, periosteum) and intrinsic cells migrate and proliferate at the injured tendon.[11] At this point, type III collagen is synthesized, which tends to be thinner and possesses less tensile strength than the tendon's original type I collagen. The process then advances to the formative stage, which can last upwards of 2 months. In this stage, collagen fibers mature and orient themselves to handle tension forces. Finally, the remodeling phase features a shift toward the normalization of the ratio between type I and type III collagen followed by the reintroduction of physiologic load into the tendon.[11] It may take up to 12 weeks for the tendon to regain its former strength. As the healing process ensues, unrestricted activity is generally avoided. However, atrophy associated with immobilization should also be avoided as the strength in healing tendons and ligaments increases more rapidly when controlled forces are applied. Consequently, optimal loading is now advocated as a means of advancing from rest to a balanced, incremental rehabilitation program. Such rehabilitation focuses on flexibility forces, core strengthening, eccentric strength training, and a measured return to resistive exercises so long as pain is minimal. Most patients with overuse tendinopathies fully recover within 3 to 6 months.

Clinical Features

General Tendinopathy

The history of the patient presenting with a tendinopathy can vary, although certain clinical features are characteristic. Recent repetitive stress may be reported due to work activities, changes in the workplace environment, or alterations in sport or recreational activities. It is important to ask patients to consider the weeks to months preceding the onset of symptoms to identify a potential inciting event or change (e.g., workplace ergonomics, protective footwear, new sports equipment). Occasionally, no cause is identified for a mechanical overload. A history of fluoroquinolone therapy, statin use, infectious disease, or other systemic illness (e.g., coronary artery disease, diabetes mellitus, gout) should also be obtained as initial presentations of rheumatologic disorders or infections, such as those from *Mycobacterium,* have been described.

Nonradiating, increasing pain at the site of the affected tendon is the most common presenting symptom of tendinopathy. The discomfort is frequently described as more severe following periods of rest. Unlike the discomfort of morning stiffness associated with arthritis, the pain of tendinopathy may resolve after initial movement only to be manifested as a throbbing pain after the cessation of exercise. Individuals may report similar prior episodes, whereas continued episodes may be accompanied by increased pain severity. Consequently, it may be helpful to inquire about a related previous diagnosis, how it was made, and which treatments (if any) were effective in resolving the prior episode.

BOX 103.1 Differential Diagnosis for Tendinopathy

- Tendon rupture
- Ligamentous injury
- Inflammatory arthritis (e.g., rheumatoid)
- Fractures (e.g., avulsion, stress)
- Tumors
- Tenosynovitis
- Osteochondrosis (e.g., Osgood-Schlatter disease)
- Bursitis
- Septic arthritis
- Osteoarthritis
- Foreign bodies
- Rhabdomyolysis
- Osteomyelitis
- Nerve entrapment syndromes
- Tendon sheath infections (e.g., pyogenic)

When evaluating a patient suspected to have tendinopathy, a thorough, directed musculoskeletal examination offers valuable diagnostic information. Edema, swelling, erythema, atrophy, deformity, asymmetry, or visible signs of trauma may be identified. Palpate the tendon, noting warmth or crepitus (particularly with movement), or tenderness over the tendon, especially when localized and reproducing the patient's pain. Although tendon palpation can be sensitive for reproducing tendinopathy-related symptoms, it is nonspecific in determining the affected structure. Check for underlying bone tenderness and consider the differential diagnoses listed in Box 103.1. Motor function (particularly passive and active range of motion), strength (and evidence of weakness or pain), and joint involvement/stability should be noted.

In narrowing the diagnosis, it is important to determine whether the source of pain is articular (within the joint capsule) or periarticular (around the joint capsule). Arthritis typically produces generalized joint pain, warmth, swelling, and diffuse tenderness. The discomfort of arthritis increases with both passive and active motion of the joint. Conversely, the pain of a tendinopathy tends to be more localized. Tenderness and swelling do not occur uniformly across the joint, and pain may be produced only with certain movements, particularly with resisted active contraction or passive stretching of the affected muscles or tendons. Mechanical hyperalgesia (i.e., increased pain with passive and active range of motion) may reduce the specificity of the commonly used clinical tests discussed later in this chapter.

Specific Tendinopathies

Shoulder. Tendinopathies of the shoulder joint include impingement syndrome (which includes subacromial bursitis or rotator cuff tendinopathy), bicipital tendinopathy, calcific tendinopathy, and adhesive capsulitis (frozen shoulder syndrome).

Impingement Syndrome and Rotator Cuff Tendinopathies. The shoulder joint is predisposed to soft tissue injury because of its extensive range of motion and unique anatomic structure (Fig. 103.2). Although inherently unstable, the muscles of the rotator cuff (supraspinatus,

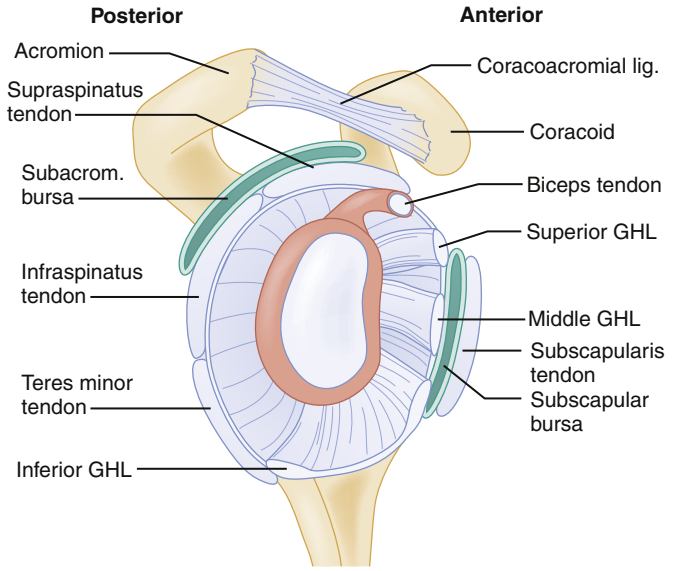

Fig. 103.2 Anatomy of the shoulder rotator cuff and supporting ligaments. *GHL*, Glenohumeral.

infraspinatus, teres minor, and subscapularis) and the glenohumeral ligaments (GHL) stabilize the joint. The muscles of the rotator cuff originate from the scapula and their tendinous insertions are found on the fibrous capsule of the glenohumeral joint after traversing through the subacromial space. The presence of the subacromial bursa serves to ensure fluidity of movement though may become inflamed as a part of an impingement syndrome.[12] Impingement of the tendons occurs because of their position interposed between the humeral head and the acromion. The functional arc of the elevated shoulder is forward and in the anterior plane. As a result of this position, the greater tuberosity of the humerus may compress (impinge) the tendons of the rotator cuff (usually the supraspinatus) against the undersurface of the anterior third of the acromion. Additionally, the long head of the biceps may be involved in impingement syndrome due to its location between the supraspinatus and subscapularis tendons in the rotator interval. This compressive component may combine with tensile loads on the rotator cuff to predispose patients to a chronic tendinopathy. Development of this tendinopathy may be the result of overuse of the extremity that leads to microtrauma of the tendinous fibers, individual anatomic differences (congenital or from the process of aging, such as osteophytic changes), or both. Other entities that may coexist and complicate an impingement syndrome include subacromial bursitis, bicipital tendinopathy, or calcific tendinopathy.

Ninety-five percent of rotator cuff tears are associated with impingement, exclusive of tears due to a one-time traumatic event. Three progressive stages of impingement syndrome as a result of overuse have been described. The first stage is frequently seen in athletes younger than 25 years of age who participate in sports that require repetitive overhead motions of the shoulder (e.g., swimming, volleyball, baseball). The pain is usually described as a dull ache over the anterolateral shoulder, extending from the shoulder to the middle upper arm, often occurring after an activity involving flexion and abduction of the arm. Point tenderness may be elicited over the greater tuberosity without the presence of weakness or loss of motion. This condition is generally believed to be reversible with appropriate treatment. In the second stage, as mechanical trauma continues, fibrosis and thickening of the tendon and subacromial bursa can occur. This generally affects patients between 25 and 40 years of age. The pain becomes constant and may worsen at night. Active motion may be limited by pain and any activity involving overhead movement can exacerbate the symptoms. Passive range of motion is generally preserved and on physical examination the pain is more diffuse and intense. The third stage resembles the second stage but may also involve a prolonged history of shoulder problems. At this point, the range of motion of the shoulder is usually decreased owing to either disuse or a partial rotator cuff tear. On pathologic examination, tendon degeneration may be present. Partial-thickness tears may occur or extend with stress or minor trauma. Complete tears of the rotator cuff, biceps tendon rupture, or osteophytic bone changes are sometimes seen.

Specific physical examination maneuvers can exacerbate the symptoms of shoulder impingement and suggest a diagnosis of rotator cuff tendinopathy. Because the supraspinatus tendon is most often involved, the *empty can test* (describing the position of the arm and hand as one empties an aluminum can, also referred to as the *Jobe sign*) is helpful in assessing the supraspinatus tendon via resistance testing. With the arm abducted at 90° in the scapular plane (30° anterior to the coronal plane), the arm is internally rotated with the thumb pointed downward. The examiner places a downward force on the distal upper extremity and the patient is instructed to resist the examiner and to keep the arm parallel to the floor (Fig. 103.3A). Weakness or pain is considered a positive finding. When assessing for supraspinatus tendinopathy, the empty can test has a sensitivity of 62% with a specificity of 54%. If the patient is unable to resist the force of the examiner, a supraspinatus tear should be suspected.

Another sign of rotator cuff tendinopathy is elicited by the *Neer test,* which suggests mechanical impingement due to a decrease of the subacromial space. The examiner forward flexes the arm to 180°, which causes impingement of the greater tuberosity of the humerus against the anterior and inferior edge of the acromion. A positive result elicits pain produced at the end range of the arc. Studies assessing the utility of this test report significant variability, with sensitivities ranging from 75% to 86% and specificities from 48% to 49%.

The *Hawkins-Kennedy test,* also indicative of mechanical shoulder impingement, is performed by forcibly internally rotating the proximal humerus while the shoulder is forward flexed to 90° and the elbow flexed to 90°. Pain with this maneuver constitutes a positive finding. Again, there is fluctuation in the literature regarding this test's sensitivity (75% to 82%) and specificity (44% to 48%).

A complete rotator cuff tear can be evaluated via the *drop arm test,* in which the arm is passively abducted at 90° and the patient is asked to slowly maintain control of the arm while adducting it (i.e., returning the arm to one's side) (Fig. 103.3B). If the arm drops to the side, a significant rotator cuff tear should be considered. Previous studies suggest that this test is 74% sensitive, although more recent literature reported a 10% sensitivity for full-thickness supraspinatus tears. The specificity is much better, cited as 98%. The *shrug sign* is exhibited when a patient with acute macrotrauma to the rotator cuff is asked to abduct the arm at 90° and appears to be giving a shrug with that side. This movement stems from the rotator cuff's inability to assist in abducting the arm. While such a finding may be secondary to other shoulder pathology (e.g., glenohumeral osteoarthritis or adhesive capsulitis), a positive result may suggest rotator cuff pathology.

Bicipital Tendinopathy. The tendon of the long head of the biceps, given its passage between the supraspinatus and subscapularis tendons in the anterior shoulder, can be associated with impingement syndrome. Patients with bicipital tendinopathy may describe pain in the anterior shoulder radiating to the elbow. Discomfort may occur when the individual rolls onto the shoulder at night, attempts to reach into a pocket, or turns a door handle. Focal tenderness may be provoked via direct palpation of the groove between the greater and lesser tuberosities of the anterior humerus. While the sensitivity (57%

Fig. 103.3 Illustrations of the proper positioning for (A) *empty can test* and (B) *drop arm test* when assessing for rotator cuff tendinopathy or a rotator cuff tear.

Fig. 103.4 A depiction of the *Yergason test* in the evaluation of biceps tendinopathy, which entails resisting a patient's supination.

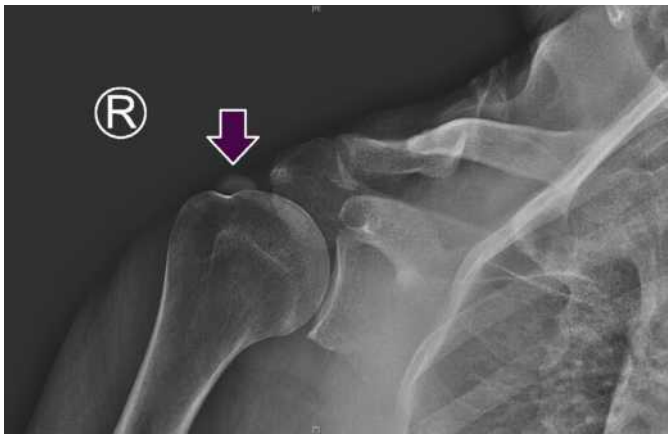

Fig. 103.5 Plain films of the right shoulder revealing a prominent calcium deposit in the supraspinatus tendon resulting in acute pain and decreased range of motion secondary to calcific tendinopathy.

to 85%) and specificity (49% to 72%) of this finding suggest that the test has utility, the accuracy of a clinician in directly palpating the long head of the biceps tendon has been questioned.[13] This accuracy can be further enhanced with the use of ultrasound.[14] The *Yergason sign* can also assist in the diagnosis of bicipital tendinopathy. This test is performed by having the patient flex the elbow to 90° with the arm against the body and the provider resisting the individual's forearm supination (Fig. 103.4). Pain in the area of the proximal tendon is considered a positive finding and indicative of biceps tendinopathy. Although the sensitivity is low (37%), the specificity (83%) and positive likelihood ratio (2.20) of this test are stronger.[15]

Another physical examination tool in the diagnosis of bicipital tendinopathy is *Speed's test*. With the elbow extended, the forearm supinated (i.e., palm facing upward), and the shoulder adducted at 60°, the patient is instructed to resist forward flexion of the shoulder. Pain in the area of the bicipital groove is indicative of a positive finding. Although Speed's test may be suggestive of glenohumeral labral pathology as well, meta-analyses suggest that it is more sensitive (61% to 83%) for bicipital tendinopathy with similar specificity (33% to 71%).[13,15]

Calcific Tendinopathy. Calcific tendinopathy is an acutely or chronically painful condition associated with the deposition of calcium crystals in or around tendons. Although it can impact any tendon, the condition appears to be more prevalent in the rotator cuff. The underlying cause is still debated though has been attributed to tissue hypoxia and degeneration due to overuse. More common in females, studies have shown an association with diabetes mellitus, thyroid disorders, and nephrolithiasis along with a potential genetic predisposition. While it can affect any of the rotator cuff tendons, it seems to have a predilection for the supraspinatus, up to 80% of the time. The symptoms are similar to those of an impingement syndrome and the condition generally affects individuals between the ages of 30 and 60 years. Calcium deposition occurs over time and then undergoes spontaneous resorption. This resorptive phase is thought to contribute to the observed pain, though the severity of the symptoms is not correlated with the size of the deposit. Pain is believed to be in response to the local chemical pathologic disorder or direct mechanical irritation. On physical examination, there may be specific tenderness over the greater tuberosity as well as symptoms consistent with impingement. Plain film radiographs may show calcification in or around the rotator cuff tendons (Fig. 103.5). The presence of calcium in the tendon does not necessarily confirm the origin of the pain because

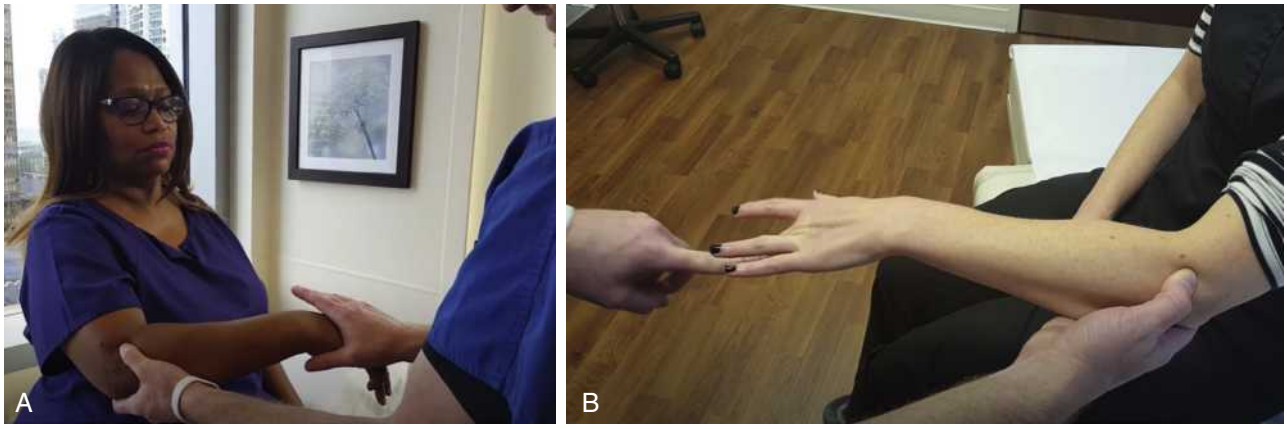

Fig. 103.6 When evaluating for lateral epicondylitis, (A) *Cozen's test* and (B) *Maudsley's test* may aid in confirming the diagnosis.

asymptomatic patients may demonstrate evidence of calcification on a routine radiograph. Ultrasound has proven useful in both the diagnosis and treatment (i.e., percutaneous needle lavage) of calcific tendinopathy.

Elbow. Increasingly, athletes of all ages and skill levels are participating in sports involving overhead arm motions. Consequently, the incidence of elbow injuries is rising. Such maladies also result from everyday life, including household chores and workplace exposures. From an anatomic and functional perspective, the extensors and supinators of the wrist attach to the lateral elbow, and the flexors and pronators attach medially.

Lateral Epicondylitis. Lateral epicondylitis ("tennis elbow") is a painful elbow condition that occurs at the insertion of the common extensor tendon (extensor carpi radialis brevis) onto the lateral epicondyle of the humerus. Although it occurs in many tennis players, epidemiologic studies suggest that less than 5% of patients with such a syndrome actually play tennis. Activities such as turning screws, using a wrench, and repetitive work on an assembly line have also been implicated. In fact, the prevalence of lateral epicondylitis in the workforce approaches 14.5%.[16] Symptoms often begin as a dull ache along the lateral aspect of the elbow. The discomfort can be exacerbated by activities that involve extension or supination of the wrist, such as grasping and twisting. *Cozen's test* is performed by grasping the patient's forearm with the one hand while resisting the patient's wrist extension (on the affected side) with the other hand. A positive finding includes the reproduction of pain at the lateral epicondyle and is associated with a sensitivity of 74%.[17] Studies have demonstrated poor specificity for this test.

Active extension of the middle finger (third digit) against resistance with the elbow in extension, or *Maudsley's test,* can also reproduce the pain over the lateral epicondyle at the insertion of the extensor carpi radialis brevis. Additionally, patients will typically note tenderness to palpation just distal to the lateral epicondyle, over the origin of the extensor carpi radialis brevis. With a sensitivity of 54%, its clinical utility in isolation is limited and it also offers poor specificity for this malady.[17] Illustrations of *Cozen's* and *Maudsley's tests* can be found in Figure 103.6.

Radiographs can be beneficial in cases of atypical or prolonged symptoms to rule out other pathologic conditions. Approximately 20% of patients demonstrate tendon calcification or a reactive exostosis at the tip of the epicondyle. The differential diagnosis of lateral epicondylitis includes fractures, posterior interosseus nerve entrapment (motor aspect of the radial nerve in the forearm), plica lesions, synovitis, chondromalacia, or adolescent osteochondral defects.

Medial Epicondylitis. Less common than its lateral counterpart, medial epicondylitis ("pitcher's elbow" or "golfer's elbow") can result from microtrauma at the site of the insertion of the flexor carpi radialis on the medial epicondyle. It is important to differentiate medial epicondylitis from other causes of medial elbow pain, including a medial ulnar collateral ligament injury. As a result of repetitive valgus stress placed on the joint, microtrauma and valgus instability at the ligament can also occur leading to disruption of the medial ulnar collateral ligament. Subsequently, abnormal stress is placed on the articular surfaces, which may lead to degenerative changes and osteophyte formation. Another diagnostic possibility worth considering is stress reactions/fractures. In the case of medial epicondylitis, patients will generally report tenderness over the flexor pronator origin slightly distal and anterior to the medial epicondyle. The pain of medial epicondylitis can be reproduced with resisted wrist flexion or resisted forearm pronation and may result in decreased grip strength. One should also evaluate for concomitant injuries elsewhere in the ipsilateral arm, which may be present in up to 84% of work-related injuries.

Wrist

de Quervain's Tenosynovitis. The wrist and hand include several tendons that pass through thick, fibrous retinacular tunnels. These help to prevent subluxation of the tendons and serve as a pulley system. Overuse syndromes are thought to result from changes of the synovial lining between these tendons and the retinaculum. de Quervain's tenosynovitis involves the synovial lining of the abductor pollicis longus and extensor pollicis brevis tendons. Although the term *tenosynovitis* suggests inflammation of the tendon sheath, it has been noted that there are many potential forms of tenosynovitis. Classic acute inflammatory changes that are characteristic of tenosynovitis may be related to systemic manifestations of disease (e.g., rheumatoid arthritis or gout). Tenosynovitis related to de Quervain's syndrome is referred to by some clinicians as *stenosing tenosynovitis.* The pathologic process of de Quervain's tenosynovitis does not generally involve inflammation but instead likely thickening of the extensor retinaculum covering the first dorsal compartment of the wrist combined with fibrous tissue depositions and increased vascularity in this region. It has been suggested that de Quervain's disease is a result of intrinsic degenerative mechanisms rather than extrinsic inflammatory ones.

The patient's history may consist of chronic, repetitive trauma or otherwise uncommon repetitive efforts, such as firmly grasping an object and moving the hand radially. However, studies have not found a causal relationship between this condition and specific occupational risk factors.[18] Direct trauma, such as a direct blow or fall,

Fig. 103.7 *Finkelstein's test* can be useful in identifying de Quervain's tenosynovitis. The provider should then deviate the wrist toward the ulna. Note the position of the thumb. The patient should not enclose the thumb in a fist, which constitutes *Eichhoff's test.*

has occasionally been implicated. Yet, in most cases of de Quervain's tenosynovitis the onset is gradual. The discomfort of de Quervain's tenosynovitis is typically localized over the radial styloid process. Radiation of pain proximally to the forearm or distally down the thumb has been described. The pain is generally constant but may be exacerbated by movements that include grasping, abduction of the thumb, or ulnar deviation of the wrist.

On physical examination, swelling (sometimes subtle) may be appreciated over the radial styloid. Crepitus may be palpated over the abductor pollicis longus and extensor pollicis brevis tendons with flexion and extension of the thumb. An increase in the tensile load (passive stretching or active contraction) of these tendons increases pain. The *Finkelstein's test* is the most pathognomonic physical sign of de Quervain's tenosynovitis. While the provider holds the thumb in a neutral position, the patient deviates the wrist toward the ulna (Fig. 103.7). Pain is elicited near the radial styloid, which is also the point of tenderness, reflecting a positive finding. This test is often confused with the *Eichhoff's test*, which entails the patient placing the affected thumb in the palm, making a fist, and then deviating the wrist toward the ulna. Finkelstein's test is preferred when assessing for de Quervain's tenosynovitis given its specificity of 100% (compared with 89% for Eichhoff's test).[19]

Radiographs are characteristically normal. The pertinent differential diagnosis includes scaphoid fracture (tenderness in the anatomic snuffbox or at the scaphoid tubercle) and osteoarthritis of the carpometacarpal joint (pain precipitated by longitudinal traction and compression involving that joint). It should be noted that Finkelstein's test can produce pain at the carpometacarpal joint, potentially reducing its specificity. Rarely, infections such as tuberculosis or disseminated gonococcal infections can manifest as tenosynovitis as well.

Knee

Patellar Tendinopathy. Patellar tendinopathy ("jumper's knee") commonly occurs in sports featuring a prominent jumping component, although it can also occur as the result of other sporting activities or occupations. Patients report pain at the inferior pole of the patella. The discomfort may abate with activity in the early stages of this tendinopathy but later progresses to the point of discomfort with both exercise and rest. When the quadriceps musculature is relaxed with the knee flexed at 30°, tenderness may be localized to the deep surface of the proximal attachment of the patellar tendon at the inferior pole of the patella. It should be noted that healthy active athletes sometimes have tenderness in this location on physical examination.

The differential diagnosis for patellar tendinopathy includes patellofemoral syndrome, which arises from imbalances in the forces that control patellar tracking during knee flexion and extension. Patients usually complain of anterior knee pain, described as "behind" or "around" the patella, which is classically worse with ascending or descending stairs or upon rising from a seated position. Occasionally, there is tenderness of the medial or lateral retinacula or facets.

Imaging with ultrasonography or magnetic resonance imaging (MRI) may reflect tendon degeneration, irregularity, or calcifications within the tendon. However, these findings should serve as an adjunct to the distinctive history and physical examination findings. It should be noted that some asymptomatic "jumping" athletes may have imaging findings similar to those of symptomatic individuals; thus, prognosis and outcomes are not predicted by imaging findings alone.

Ankle

Achilles Tendinopathy. Achilles tendinopathy is a common overuse syndrome that historically was thought to affect male athletes more frequently than their female counterparts, although that is currently subject to debate.[20] The Achilles tendon arises from the medial and lateral heads of the gastrocnemius muscle and the deep layers of the soleus muscle, inserting on the calcaneal tuberosity. Its major function is plantar flexion of the foot. The strongest and largest tendon in the body, it can withstand tensile loads more than 12 times the body's weight during running.

The Achilles tendon is vulnerable to injury from either trauma or overuse. A tendinopathy can also develop as a result of systemic disease (e.g., diabetes mellitus, renal disease, ankylosing spondylitis, reactive arthritis [previously known as Reiter's syndrome], gout, or pseudogout). The use of fluoroquinolones and statins have been associated with Achilles tendinopathy. Additionally, moderate alcohol use (7 to 13 units per week for men or 4 to 6 units per week for women) may predispose to this condition. The same association was not found for heavy alcohol use.[20]

The occurrence of Achilles tendinopathy is highest among individuals who participate in middle- and long-distance running, track and field, tennis, badminton, basketball, volleyball, or soccer. Some studies have noted a 5.2% incidence of Achilles tendinopathy in all runners and a 7.4% incidence in marathon runners.[21] Most cases of Achilles tendinopathy are thought to be multifactorial in origin. Anatomically, the vascular supply to the tendon creates a watershed area approximately 2 to 6 cm above the calcaneal insertion. This is responsible for the clinical symptoms and pathologic disruption commonly seen at this site. Otherwise, body mechanics and environmental factors (e.g., uneven terrain) may apply valgus or varus stress to the tendon. Activity technique (e.g., running form) and equipment (e.g., type of shoes) can also contribute to the development of tendinopathy.

The patient's history provides most of the information necessary to make the diagnosis. Pain, a cardinal symptom of Achilles tendinopathy, is often the impetus for an individual to seek medical evaluation. Some have argued that a patient's symptoms reflect the degree of tendon pathology, which has been validated in MRI studies assessing abnormal signal within the Achilles tendon. However, studies focusing on other changes associated with Achilles tendinopathy, such as neovascularization, have not shown a correlation with pain severity.[22] Regardless, as with many tendinopathies, pain after strenuous activity is reported in the early phase, whereas pain in the later phase occurs both during activity and at rest. Once an individual reaches this point, work and sporting activities are often limited by symptoms.

On physical examination, inspect the contour of the muscle-tendon unit while also assessing for swelling and erythema. In acute Achilles

tendinopathy, the tendon may be diffusely swollen and reveal tenderness to palpation, usually most prominent over the middle third. Typically, in such patients the area of swelling and tenderness does not move with dorsiflexion of the ankle joint. On palpation, warmth, crepitus, or palpable tendon nodules or defects may be noted. Examination for ankle instability and biomechanical faults (e.g., excessive ankle supination or pronation) should be entertained.

Achilles Tendon Rupture. Although rupture of the Achilles tendon most often occurs when it is preceded by tendon damage, it is possible for untrained athletes to apply excessive force and rupture the tendon in the absence of prior changes of tendinopathy. Partial and complete rupture may occur, most commonly in men between 30 to 40 years of age. Complete rupture is more common in the middle-aged recreational athlete. Historically, the patient may note a "pop" followed by acute weakness and an inability to continue with activity. Patients may report feeling as though they were "struck" in the posterior ankle.

On physical examination, a defect in the tendon can sometimes be palpated. If enough time has elapsed to allow hematoma formation, bogginess may be noted over the injured area. The ability to plantar flex the foot does not rule out a complete rupture of the Achilles tendon. There are multiple plantar flexors of the foot and toes. Muscles such as the tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus brevis, and peroneus longus can remain functional and therefore disguise a complete rupture given the persistent ability to plantar flex the foot.

Several observations can aid in the diagnosis of an Achilles tendon rupture by placing the patient in the prone position. Assess for decreased resting plantar flexion compared to the contralateral side, which is normally 20° to 30°. The *Thompson (Simmonds') test* can also be performed to evaluate for a complete rupture. With the patient prone and feet hanging over the edge of the bed, the examiner squeezes the calf muscles at their widest point and looks for passive plantar flexion. The absence of plantar flexion is considered a positive finding, indicative of a complete tear of the Achilles tendon. The presence of induced plantar flexion does not, however, eliminate the possibility of a partial tear of the Achilles tendon. Overall, the diagnosis of an Achilles tendon rupture can be made with 2 or more of the following findings on physical examination: palpable defect 2 cm to 6 cm proximal to its insertion, positive Thompson test, increased passive ankle dorsiflexion, and decreased plantar flexion strength. The absence of the first three of these findings has a negative predictive value of 100%, effectively ruling out the diagnosis of an Achilles tendon rupture.

Differential Diagnoses

The differential diagnoses of tendinopathy are listed in Box 103.1.

Diagnostic Testing

The diagnosis of tendinopathy is typically made on clinical grounds. While plain radiographs may be helpful in identifying calcific tendinopathy and in excluding bony abnormalities, ultrasonography has been recommended by some practitioners as the modality of choice for the evaluation of pathologic tendon conditions. Ultrasonography can be especially useful when other conditions, such as gouty arthritis, obscure the findings of concomitant tendinopathy. Emergency clinicians are proficient in identifying tendon injuries with point-of-care ultrasound, operating with 100% sensitivity and 95% specificity in such contexts. In cases of acute or chronic tendinopathy, one or more of the following features may be visualized: loss of the fibrillar echotexture, focal tendon thickening (Fig. 103.8), diffuse thickening, focal hypoechoic areas, extended hypoechogenicity, irregular and ill-defined borders, microruptures, intratendinous calcifications, or peritendinous inflammatory edema. Hypoechoic areas surrounding tendons are consistent with surrounding soft tissue inflammation. Tendon tears, both partial and complete, can also be delineated by ultrasonography.

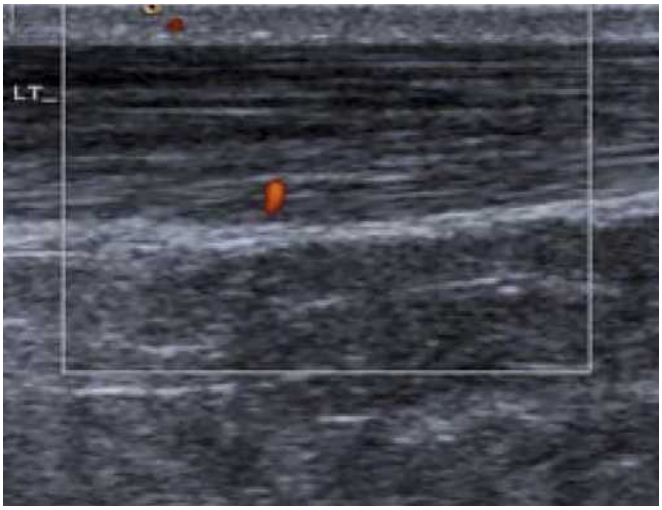

Fig. 103.8 A longitudinal view of the Achilles tendon showing focal thickening with peritendinous fluid.

MRI has been utilized to visualize pathologic conditions of the tendon. It provides high intrinsic tissue contrast, which permits the distinction between normal tendons and abnormal tendons as well as high spatial resolution that facilitates the identification of detailed anatomic structures. MRI has superb resolution of the soft tissue structures and can aid in the diagnosis of a variety of tendon disorders. Although the accuracy in identifying clinically relevant tendinopathy appears to be good (70%), perhaps counterintuitively, the sensitivity of MRI in these patients has been found to be as low as 50%. Additionally, cost, availability, the need to have the patient remain still during the examination, and the loss of the dynamic component compared with ultrasound examination remain relative disadvantages.

Management

General Tendinopathy

The management of tendinopathy is summarized in Box 103.2. Cryotherapy (cold treatments, 20 minutes at a time every several hours, for the first 24 to 48 hours) may be beneficial in reducing pain. However, there are no high-quality studies supporting its use to resolve the underlying tendinopathy or to increase load tolerance of the tendon. The role of NSAIDs in treating tendinopathy remains controversial. They can provide short-term analgesic benefits in some patients, although the efficacy is variable. The mechanism of their benefit remains unclear though likely relates to the progressive nature of the condition and associated inflammation of surrounding tissues. However, studies have shown that NSAIDs can impair long-term tendon healing. Thus, emergency clinicians should use their clinical judgement when considering NSAIDs for the treatment of tendinopathy, with a preference for a short course (e.g., one week) when prescribed.

Additional treatment modalities include graduated range-of-motion exercises. Aside from ruptures, complete rest is relatively contraindicated due to the subsequent loss of muscle power, decrease in mechanical properties of the tendon, and effect on the kinetic chain. Although pain may be immediately reduced with rest, it will increase again when the tendon is loaded due to the aforementioned physiologic sequelae. Unless the provider has in-depth

BOX 103.2 Components of Tendinopathy Management[8]

Identify the cause of discomfort
Eliminate the sources of the primary tendinopathy
Institute treatment modalities
- Analgesic medications (e.g., NSAIDs)
- Protection
- Relative rest
- Optimal loading (e.g., ergonomic alterations)
- Application of ice, compression, and elevation as necessary

Educate patients regarding the underlying mechanical causes
Modify patient behavior to minimize or eliminate sources of continuing irritation (e.g., biofeedback, coaching)
Enhance the patient's diet (e.g., add vitamin D sources)
Refer patients for appropriate follow-up care and early rehabilitation.

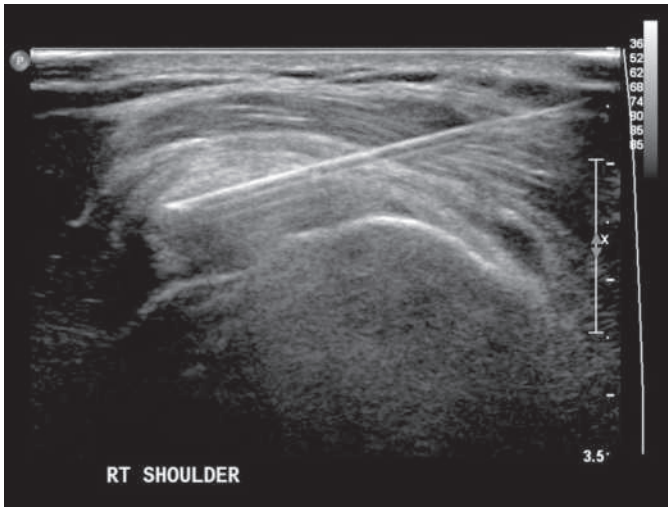

Fig. 103.9 Ultrasound-guided aspiration of a calcific deposit from the supraspinatus tendon causing calcific tendinopathy.

knowledge regarding the optimal rehabilitation regimen for a given tendinopathy (e.g., graduated eccentrics integrated with concentric exercises), it is prudent to avoid making specific recommendations. Instead, refer the patient to physical therapy, sports medicine, or an orthopedic specialist.

Corticosteroid injections have been utilized for short-term pain relief in the setting of tendinopathy. However, they likely have detrimental effects on both tendon pain and function for up to one year. Intratendinous corticosteroid injections should be avoided, particularly in the Achilles and patellar tendons, due to their potential for subsequent rupture. There are certain conditions that warrant consideration of peritendinous corticosteroid injections (i.e., de Quervain's tenosynovitis). Of interest, systemic corticosteroids may have a different impact on the healing process when administered after the early inflammatory stage of tendinopathy (e.g., post-injury day 5). A study in animal models assessing Achilles tendon injuries found that a five-day course of systemic dexamethasone starting at post-injury day 5 resulted in greater peak force, increased (beneficial) tendon stiffness, and decreased tendon thickness when compared to placebo.[23] While sufficient supporting evidence in humans has not yet been widely reported, this is an area of clinically relevant research to monitor moving forward.

The use of nitroglycerin patches has been shown to be effective in the treatment of certain tendinopathies. Questions remain as to whether their efficacy is due to an analgesic effect or promoting healing of the affected tendon. Medial and lateral epicondylitis, noninsertional Achilles tendinopathy, and rotator cuff tendinopathy typically respond well to this intervention.[24] However, no significant benefit in patellar tendinopathy has been reliably supported by the literature. Overall, chronic tendinopathies seem to respond better to nitroglycerin compared with acute injuries. Patients prescribed this treatment should be aware of the potential side effects, which include headaches and contact dermatitis. The use of nitroglycerin patches for tendinopathy remains off-label and is more likely to be prescribed by a musculoskeletal specialist.

Platelet-rich plasma (PRP) injections, a process by which a patient's platelets are concentrated in a centrifuge and then injected into the affected tendon, are utilized by some specialists in the management of tendinopathy. The literature on the efficacy of this intervention is widely variable. There is some support for this modality, although it is not definitively beneficial. It can be safely asserted that PRP should not be utilized as a first-line treatment and is most efficacious when administered under ultrasound guidance.[25,26] Accordingly, while some patients may reach this point in the treatment algorithm of tendinopathies, it is not advocated for use in the ED setting at this time.

Specific Tendinopathies

Impingement Syndrome and Rotator Cuff Tendinopathies. The treatment of rotator cuff tendinopathies and impingement syndrome follows the treatment of tendinopathy in general. Emphasis is placed on physical rehabilitation and graduated strengthening exercises. A significant proportion of patients will improve with conservative management; otherwise, surgical intervention (e.g., acromioplasty, debridement, or repair) may be considered.[27]

Calcific Tendinopathy. The initial treatment of calcific tendinopathy is mainly conservative and consists of analgesia and brief immobilization (e.g., a shoulder sling for rotator cuff calcific tendinopathy) because prolonged immobilization may result in decreased range of motion. Both extracorporeal shock wave therapy (akin to that which is used for nephrolithiasis) and ultrasound-guided needle lavage and aspiration (Fig. 103.9) are effective treatments for this condition. The latter option has been shown to result in improved pain and functional outcomes compared to extracorporeal shock wave therapy or corticosteroid injection.[28] A small percentage of patients who do not respond to these interventions may need surgery. Follow-up care from the ED is important because calcific tendinopathy has been described as the most well-known cause of reactive cuff failure.

Lateral and Medial Epicondylitis. In up to 95% of patients, epicondylitis will improve with time and conservative therapy. Initial efforts include making the patient more comfortable with the standard principles of protection, compression, medications (e.g., NSAIDs for significant pain), biomechanical or ergonomic adjustments, and physical therapy modalities. *Relative rest* is appropriate and implies the avoidance of overuse as opposed to the absence of activity. Activities that aggravate pain should be eliminated and an attempt to protect the tendon through strategies such as a reduction in playing time or intensity should be entertained. The use of a counterforce brace should be recommended in order to control force loads and improve performance technique. This intervention has been shown to significantly reduce the frequency and severity of epicondylitis-related pain in the short term (i.e., 2 to 12 weeks) as well as improve elbow function at 26 weeks.[29] Corticosteroid injections remain a commonly employed treatment despite ample evidence that they are ineffective. At 4 to 6 weeks, patients may note a reduction in pain. However, at

26 weeks, outcomes (e.g., pain and function) were worse in those who received a corticosteroid injection compared to those who received a saline injection or no treatment.[30] In fact, corticosteroid injections may serve to increase the risk of nonoperative treatment failure.[31] Consequently, corticosteroid injections should be avoided in the ED while follow-up with a musculoskeletal specialist is pursued.

de Quervain's Tenosynovitis. The initial treatment of de Quervain's tenosynovitis consists of immobilization with a thumb spica splint, antiinflammatory medications, and prompt referral. Corticosteroid injections have been shown to be a beneficial treatment of de Quervain's disease, and failure to respond may be due to anatomic variation or poor technique (Fig. 103.10). Studies have shown this intervention to be effective in resolving the associated pain 52% of the time.[32] A mixture of 20 mg of methylprednisolone acetate or triamcinolone combined with 1 mL to 2 mL of lidocaine or bupivacaine is appropriate for this injection. The associated benefit may be further enhanced when combined with a thumb spica splint or similar orthosis.[33] Surgical decompression of the first dorsal compartment may be indicated if these treatments fail.

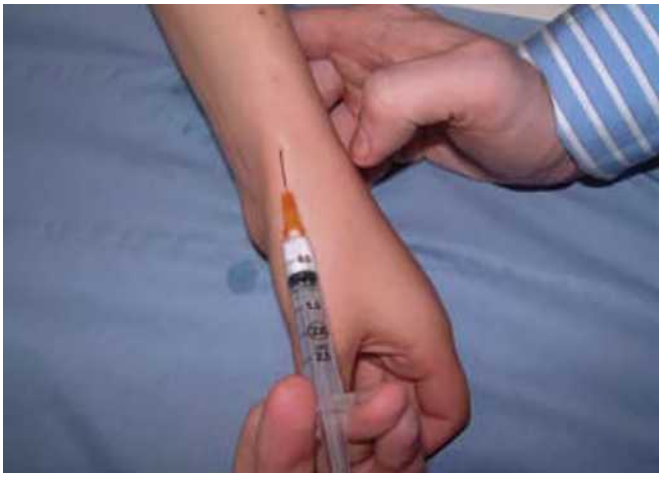

Fig. 103.10 The proper needle placement for a corticosteroid injection to address de Quervain's tenosynovitis.

Achilles Tendinopathy and Rupture. In addition to routine conservative treatment, patients with Achilles tendinopathy should be referred for orthopedic evaluation and correction of limb malalignment with the use of orthotics or heel lifts. Eccentric loading exercises (Fig. 103.11) and low-energy shock wave therapy are typically effective therapies for Achilles tendinopathy.

The management of Achilles tendon rupture may be either operative or nonoperative, depending on patient circumstances. In the ED, acute Achilles tendon ruptures should be treated with a posterior lower leg splint featuring the ankle placed in approximately 20° of equinus (i.e., plantar flexion). If this is not feasible for any reason, a walking boot with 2 inches of heel lift can suffice. This management brings the affected ends of the ruptured tendon closer to reapproximation, decreasing the amount of remodeling necessary to reconstitute the tendon. The individual should remain nonweightbearing until consultation by a musculoskeletal specialist is completed. Some authors contend that complete ruptures in active athletes should be treated surgically in most cases. And while scenarios differ, the outcomes for the nonoperative and operative management of Achilles tendon ruptures are similar, leaving both as viable options for many patients.[34]

Disposition

Most patients with tendinopathy are safely discharged home with proper instructions, relative rest of the tendon, analgesia, and appropriate follow-up care. Exceptions include elders and disabled patients

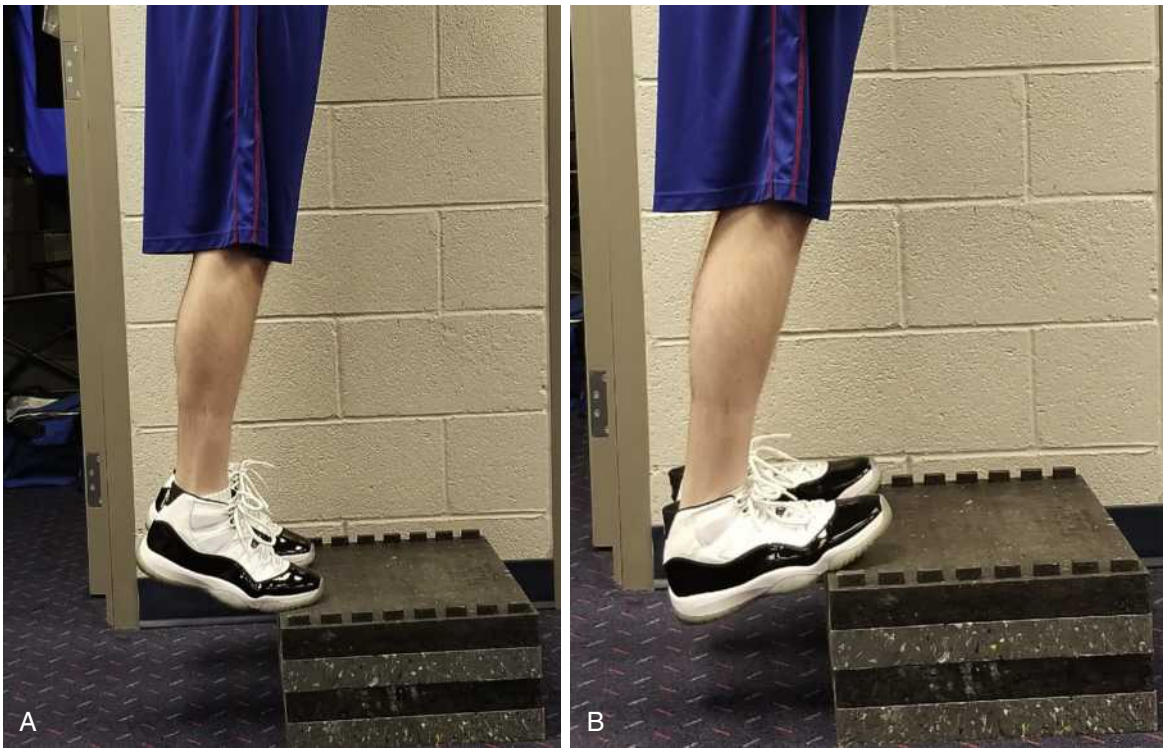

Fig. 103.11 Demonstration of eccentric Achilles tendon rehabilitation exercises, emphasizing bilateral toe raises (A). One should then lower the heel below neutral (B).

who may be unable to perform activities of daily living due to the tendinopathy. Although appropriate rest and analgesia provide symptomatic relief, underlying causes should be considered and addressed in follow-up.

BURSITIS

Foundations

A *bursa* is a closed sac lined by synovial membrane, which occurs in areas of friction between two layers of tissue. It permits fluid movement of soft tissue over areas of potential impingement (e.g., subacromial bursa) or friction (e.g., olecranon and prepatellar bursae). There are more than 150 bursae throughout the body. They develop after birth, most likely as a result of pressure or friction from movement. Superficial bursitis most commonly occurs in the olecranon and prepatellar bursae, which are located on the extensor surface of the elbow and knee, respectively.

Bursitis is most often due to trauma (acute direct trauma to or prolonged pressure on the bursa), systemic inflammation (from disorders such as gout, pseudogout, rheumatoid or psoriatic arthritis), or infection (most commonly due to *Staphylococcus aureus*). However, there are cases of idiopathic bursitis as well. Septic bursitis is most commonly due to spread from a nearby cellulitis, direct inoculation from trauma, or as a result of aspiration or injection.

Clinical Features

Olecranon and Prepatellar Bursitis

About one-third of patients with olecranon or prepatellar bursitis are found to have septic bursitis. Distinguishing septic from nonseptic bursitis can be difficult because clinical information and diagnostic data can be similar. Patients with septic bursitis generally present earlier in their clinical course and tend to have more pain, tenderness, erythema, and warmth compared to those with nonseptic bursitis. While septic and nonseptic bursitis are both frequently caused by trauma, septic bursitis is almost always preceded by some kind of trauma, including minor and repetitive microtrauma. Other predisposing factors include chronic illness (e.g., diabetes mellitus or alcohol abuse), chronic skin conditions (e.g., atopic dermatitis), and previous noninfectious inflammation of the bursae (e.g., rheumatoid arthritis or gout). It is also more common in people whose occupation results in repetitive knee or elbow trauma.

The olecranon bursa, found on the extensor surface of the elbow, is the only bursa of the elbow joint and is easily traumatized, which can result in inflammation, pain, and swelling. Infection can also occur from local trauma (e.g., puncture wounds or lacerations), but may also present without any preceding history of trauma. Hematogenous bacterial seeding is rare due to the limited vascular supply to the bursal tissue.

On physical examination, localized swelling and fluctuance are usually present over the bursa. There may or may not be evidence of trauma. Tenderness and warmth are typical in most patients with septic bursitis. Erythema with overlying cellulitis is also common in septic bursitis, and a fever can suggest infection, although this is inconsistent and reported to be present in 20% to 77% of patients. Tenderness, erythema, and warmth can also be seen in patients with purely inflammatory causes of bursitis, though the frequency and severity of these findings are less and patients with septic bursitis usually present earlier in their clinical course.

Passive range of motion should not produce noteworthy pain except for full flexion, at which point there may be discomfort as the inflamed bursa is compressed. Evidence of significantly diminished range of motion, generalized joint swelling, or other signs and symptoms of joint involvement (e.g., joint pain, warmth, effusion) should raise concern for septic arthritis. Although the olecranon and prepatellar bursae generally do not communicate with the joint space, septic arthritis should be considered in the differential diagnosis, especially if trauma is involved and the integrity of the underlying joint is disrupted. Arthrocentesis to assess for septic arthritis should be considered in these cases.

Subacromial Bursitis

The subacromial bursa lies between the rotator cuff tendons and the undersurface of the acromion, the acromioclavicular joint, and the deltoid muscle. Subacromial bursitis is thought to be nearly synonymous with supraspinatus tendinopathy and may be involved in the stages of rotator cuff impingement. Pain and tenderness to palpation, localized to the lateral aspect of the shoulder, in addition to signs of impingement may be noted on physical examination *(Neer test or Hawkins-Kennedy test)*. Septic subacromial bursitis is rare, but a few cases have been reported in the literature.[35]

Trochanteric Bursitis

The trochanteric bursa has both deep and superficial components. The deep bursa is located between the greater trochanter and the tensor fasciae latae; the superficial bursa is located between the greater trochanter and the skin. Trochanteric bursitis is more common in middle-aged women, who usually report acute or chronic pain over the bursal area as well as the lateral thigh. Lying on the hip and walking may exacerbate the pain. It can also occur as a complication of rheumatoid arthritis. On examination, the pain of superficial bursitis may be reproduced by direct palpation and hip adduction while the pain of deep trochanteric bursitis may be reproduced with hip abduction. The hip joint itself usually has normal examination findings. Septic trochanteric bursitis is rare but has been described.

Ischiogluteal Bursitis

The ischiogluteal bursa is located adjacent to the ischial tuberosity and overlies the sciatic and posterior femoral cutaneous nerves. Inflammation, known as *weaver's bottom,* is described as pain over the center of the buttocks with radiation down the back of the leg. It can be caused by prolonged sitting, running, repetitive jumping, or kicking. Sitting on a hard surface exacerbates the pain, and palpation over the ischial tuberosity causes discomfort.

Iliopsoas Bursitis

The iliopsoas bursa has been shown to be the largest bursa in the body. It lies between the iliopsoas tendon and the lesser trochanter. The pain of iliopsoas bursitis usually manifests as anterior hip pain that can radiate down the medial thigh to the knee and is exacerbated by hip extension.

Pes Anserine Bursitis

The anserine bursa lies deep to the three tendons (sartorius, gracilis, and semitendinosus) that form the pes anserinus ("foot of the goose") and superficial to the medial collateral ligament of the knee. Patients with anserine bursitis usually complain of medial knee pain approximately 2 or 3 cm distal to the joint line. There is usually tenderness to palpation in this area and occasionally swelling. Risk factors for pes anserine bursitis include osteoarthritis of the knee, diabetes mellitus, and possibly obesity.[36]

Differential Diagnoses

Conditions that mimic bursitis include underlying fracture, osteomyelitis, septic or inflammatory joint arthritis, and cellulitis. Radiography

BOX 103.3 Differential Diagnosis for Atraumatic, Nonseptic Bursitis

- Rheumatoid arthritis
- Pseudogout
- Ankylosing spondylitis
- Hypertrophic pulmonary osteoarthropathy
- Oxalosis
- Gout
- Scleroderma
- Systemic lupus erythematosus
- Whipple disease (an infectious bacterial disease that affects many different organ systems, including the musculoskeletal system with joint involvement)
- Idiopathic hypereosinophilic syndrome

and bone scan or MRI may be necessary to evaluate for these alternative conditions. Box 103.3 lists the differential diagnoses for atraumatic, nonseptic bursitis.

Diagnostic Testing

When there are signs of acute inflammation, aspiration of the bursa should be considered to exclude the presence of infection or crystal-induced disease. Bursal aspiration is performed with sterile technique utilizing an 18- to 20-gauge needle. A lateral approach to the aspiration of any bursa, when feasible, has been recommended to lower the risk of iatrogenic sinus tract formation, although the relation between the two is unclear. A distal approach can also be used when the olecranon bursa is aspirated. In cases of septic bursitis, the aspirate usually appears purulent though can occasionally appear serosanguinous or straw-colored. In the case of nonseptic bursitis, the aspirate varies from bloody to straw-colored. The bursal fluid is typically evaluated for white blood cell count with differential, crystal analysis, Gram stain, appropriate cultures and sensitivities, and glucose level. Peripheral blood is typically sent for complete blood cell count with differential, C-reactive protein, erythrocyte sedimentation rate, and glucose. A bursal fluid to serum glucose ratio of less than 50% was initially thought to be diagnostic of septic bursitis, though recent studies have shown this comparison to be unreliable.

The identification of organisms on either Gram stain or culture is diagnostic for septic bursitis. There are no definitive guidelines regarding the use of WBC count to distinguish between septic and nonseptic bursitis. A bursal fluid WBC count higher than 1000/μL^3 is almost always seen, and a value greater than 5000/μL^3 suggests bursal fluid infection, even in the presence of a negative Gram stain. However, counts can be much lower in septic bursitis or above this threshold in nonseptic cases. Culture is the definitive test though will not be available during the initial evaluation. *S. aureus* is by far the most common organism in bursal infection, followed by streptococcal and other staphylococcal species, remaining unchanged in the last several decades. Because most cases of septic bursitis occur in the olecranon or prepatellar bursae, the diagnosis is made clinically in conjunction with aspiration. MRI can be used to aid in the diagnosis of inflammation or infection of deep bursae. Ultrasonography has also been used as a modality for aspiration of deep bursae.

Management

Septic Bursitis

Large-scale clinical prospective trials are lacking, thus the optimal treatment of septic bursitis remains unclear. Debate persists regarding the use of outpatient (oral) or inpatient (intravenous [IV]) antibiotics, duration of therapy, role of needle aspiration or incision and drainage, and the need for operative intervention.

Patients who have bursal inflammation with suspicion (clinical or laboratory) of infection should be treated with appropriate antibiotics. Empirical therapy (including coverage for *S. aureus* and streptococcal species) is indicated until definitive culture results are available. A recent study on septic bursitis revealed the incidence of methicillin-resistant *S. aureus* (MRSA) as a causative pathogen to be around 17%.[37] It is more common in the United States compared to Europe, and MRSA was found to be the most common cause of community-onset adult septic bursitis in one case series from an ED population. Therefore, empirical coverage for this organism in septic bursitis should be considered. A trial of oral antibiotic therapy (up to 14 days) and treatment on an outpatient basis in the patient with uncomplicated septic bursitis and no underlying disease is reasonable. We recommend oral dicloxacillin (500 mg PO four times daily), trimethoprim/sulfamethoxazole (160 mg/800 mg strength, one to two tablets PO twice daily), or oral clindamycin (300 mg PO four times a day) for penicillin-allergic patients, as first-line therapy. However, failure in up to 50% of cases has been reported for outpatient treatment of septic bursitis. One of the largest observational studies on the successful outpatient treatment of septic bursitis showed an admission rate of only 1 of 118 patients, though all patients in this study received sequential IV antibiotics for approximately 4 days at an outpatient clinic followed by a course of oral antibiotic therapy. Consequently, treatment in an observation unit or inpatient setting with IV antibiotics is a consideration for patients with significant symptoms, overlying cellulitis, or those unlikely to receive close follow-up. For such patients, we recommend IV vancomycin (loading dose: 20 to 35 mg/kg actual body weight [not to exceed 3000 mg] or 20 to 25 mg/kg actual body weight [not to exceed 3000 mg] in patients with obesity, then 15 to 20 mg/kg actual body weight every 8 to 12 hours) as initial empirical treatment.

Needle aspiration is a technique commonly used for the diagnosis and management of septic bursae. Successful treatment of septic bursitis can typically be achieved in patients receiving oral antibiotics on an outpatient basis following initial needle aspiration. One study showed no difference between patients who received aspiration and those who did not, though patients who had more severe disease were also more likely to be selected for drainage. These patients were also initially treated with parenteral antibiotics. Furthermore, the diagnosis of septic bursitis was confirmed by culture in only 26% of patients, potentially underestimating the importance of bursal drainage in individuals with true septic bursitis. As needle aspiration is utilized in the diagnosis of septic bursitis, initial drainage at the same time seems reasonable. Those with a purulent aspirate may require repeated aspiration at 1- to 3-day intervals if the effusion persists. In all cases, appropriate follow-up to assess response to therapy should be arranged. Warm soaks and wound care are also indicated. Surgical incision and drainage or bursectomy may become necessary in severe, recurrent, or refractory cases.

Nonseptic Bursitis

Most cases of nonseptic bursitis improve with conservative therapy, although complete recovery can take many months. Initial treatment typically consists of NSAIDs, compression to prevent recurrent fluid accumulation, and occasionally aspiration of the bursa to relieve pain and increase range of motion. Systemic causes of bursitis (e.g., crystalline disease) should be treated as indicated. Avoidance of local trauma is important for treatment and successful prevention of bursitis. Recurrent olecranon bursitis may be caused by underlying anatomic disorders, such as bone spurs.

Bursal injection with a combination of local anesthetics and steroids at the time of diagnostic aspiration is often therapeutically

beneficial for inflammatory bursitis of deeper areas, such as the subacromial, pes anserine, medial collateral ligament, or trochanteric bursae. Injections into superficial bursae have been used as a treatment modality, but multiple complications have been described, including skin atrophy over the bursa, persistent pain, development of septic bursitis, bleeding, postinjection flare as a result of release of microcrystals, and tendon rupture. However, a systematic review of the treatment of olecranon bursitis found that patients who received a corticosteroid injection were no more likely to develop an infection or persistent pain than those who did not. A recent randomized trial comparing compression and NSAIDs versus aspiration alone versus aspiration and steroid injection showed no appreciable differences between groups in treatment success rates.[38] At this point in time, we recommend starting with noninjection treatment (e.g., compression, NSAIDs, and possible aspiration) for suspected inflammatory bursitis of superficial bursae.

Disposition

Patients without underlying medical problems who present with uncomplicated septic bursitis can usually be discharged with appropriate oral antibiotics. Those with underlying diseases (e.g., immunocompromise, leukopenia, diabetes mellitus) or those with systemic toxicity or signs of severe bursal infection (e.g., purulent drainage) are candidates for IV antibiotics and inpatient therapy. Patients with a purulent aspirate or persistent infection may require serial aspirations. Close follow-up is necessary to ensure an appropriate response to therapy. Patients with presumed nonseptic bursitis require close follow-up as well.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 103: QUESTIONS AND ANSWERS

1. What is the etiology of most tendinopathies?
   - **a.** Direct blow to the tendon
   - **b.** Recent or previous complete tendon rupture
   - **c.** High-grade inflammation of the tendon
   - **d.** Mechanical overload and repetitive microtrauma

Answer: D. Tendinopathies are thought to be precipitated by repetitive microtrauma and mechanical overload rather than true inflammation of the tendon

2. Which of the following interventions should routinely be used when treating patients with tendinopathies?
   - **a.** Activity modification
   - **b.** NSAIDs
   - **c.** Intratendinous corticosteroid injection
   - **d.** Immobilization of the affected tendon/joint

Answer: A. Patients with tendinopathy should be advised to modify their activities (including ergonomic workplace adjustments, when pertinent) to avoid exacerbating pain and further tendon injury. Some patients may benefit in the near term from a short course (e.g., one week) of NSAIDs, although this can result in impaired tendon healing in the long term. Thus, their use should be dependent on the circumstances of presentation, such as the severity of pain or comorbid conditions. Intratendinous corticosteroid injections and immobilization should not be routinely utilized as they may prove detrimental in the long term.

3. A 38-year-old male presents after feeling a "pop," followed by pain to the back of his leg while playing basketball. You note a defect to his Achilles tendon, decreased resting plantar flexion of the ankle, and a positive Thompson test on examination. What should be the next step in the patient's management?
   - **a.** Provide crutches and advise the patient to remain non-weightbearing until follow-up.
   - **b.** Splint the affected leg in an equinus position and refer for prompt follow-up.
   - **c.** Obtain emergent magnetic resonance imaging (MRI).
   - **d.** Perform a steroid injection to the affected tendon.

Answer: B. This patient meets the diagnostic criteria for an Achilles tendon rupture. Although MRI can be a useful adjunct when evaluating tendon injuries, obtaining such imaging in the acute care setting is not essential when the clinical diagnosis is obvious. The same can be stated for point-of-care ultrasound. Treatment consists of splinting the leg in 20° of equinus (plantar flexion) and close follow-up with a musculoskeletal specialist (e.g., sports medicine or orthopaedist) for either operative or nonoperative treatment. Implementing non-weightbearing status without proper splinting is insufficient in most cases.

4. What is the most important predisposing factor in septic bursitis?
   - **a.** Chronic obstructive pulmonary disease
   - **b.** Diabetes mellitus
   - **c.** Human immunodeficiency virus (HIV)
   - **d.** Trauma

Answer: D. Trauma is the most common predisposing factor in patients who develop septic bursitis.

5. What is the causative organism in the majority of cases of septic bursitis?
   - **a.** Beta-hemolytic streptococci
   - **b.** *Pseudomonas aeruginosa*
   - **c.** *Staphylococcus aureus*
   - **d.** *Prototheca wickerhamii*

Answer: C. *S. aureus* is the most common cause of infectious bursitis.

6. A 42-year-old female without significant past medical history presents with 4 days of edema, mild warmth, and mild erythema in the area of the right olecranon bursa. She is afebrile and has minimal tenderness to palpation of the bursa. Aspiration of the bursa reveals a white blood cell count of 1500/μL.[3] What is the most appropriate next step in the patient's management?
   - **a.** Admit for intravenous (IV) antibiotics.
   - **b.** Apply a compression dressing and give ibuprofen.
   - **c.** Discharge the patient to home with oral antibiotics.
   - **d.** Obtain magnetic resonance imaging (MRI) for further evaluation.

Answer: B. The clinical presentation and results of the fluid analysis highly suggest a nonseptic bursitis. Cases of nonseptic bursitis can be managed with a compressive dressing, nonsteroidal antiinflammatory drugs (NSAIDs), avoidance of local trauma, and close follow-up.

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Musculoskeletal Back Pain

Susan E. Farrell and Zheng Ben Ma

KEY CONCEPTS

- Most patients presenting to the emergency department (ED) with back pain have uncomplicated musculoskeletal pain that is self-resolving with conservative therapy and does not require imaging.
- Indications for emergent imaging include "red flags" such as an acute neurologic deficit, bowel or bladder dysfunction, or saddle anesthesia.
- Risk factors for compressive myelopathy include immunocompromised patients with a history of malignancy, injection drug use, fever, chronic steroid or anticoagulant use.
- Back pain due to metastatic disease is more common than primary tumors in the spine, and thoracic metastases are more common than lumbar metastases.
- Epidural abscess or hematoma, cauda equina syndrome (CES), spinal malignancy with compressive symptoms, and spinal osteomyelitis are all indications for emergent surgical consultation or transfer to a center where surgical spine consultation is available.
- Empirical parenteral antibiotics active against staphylococci, streptococci, and gram-negative bacilli should be administered for suspected epidural abscess. Specific antibiotics should be directed against the known pathogen if the culture or Gram stain of the aspirate is positive.
- Corticosteroids given as a single dose in the ED (10 mg dexamethasone) or as a 15-day tapering course after discharge (prednisone 60 mg, 40 mg, 20 mg daily for 5 days each) may improve functional ability but does not improve nerve root pain secondary to disc herniation.

FOUNDATIONS

Background

Back pain is one of the most common patient complaints encountered in emergency departments (EDs). Most cases of musculoskeletal back pain are related to physical motion of the vertebrae, intervertebral discs, or musculature of the back; however, a precise pathoanatomic etiology and diagnosis is identified in only 10% of cases.[1] As a result, the symptom of back pain can present the emergency clinician with a challenging diagnostic dilemma. Although most cases of acute or acute-on-chronic back pain are due to uncomplicated musculoskeletal causes, certain types of back pain are true emergencies requiring timely diagnosis and intervention. It is critical to distinguish between the large number of benign presentations of self-limited pain versus less common, high-morbidity causes of back pain that require immediate intervention.

Epidemiology

Back pain occurs in children and adults, females and males, with a lifetime prevalence in adults of 60% to 80%.[2] Total direct health care costs and indirect economic expenses associated with back pain are estimated to be in the tens of billions of dollars annually in the United States.[1-2] Risk factors associated with the development of back pain are numerous and include repetitive lifting and twisting movements, prolonged static (seated) postures, obesity, smoking, and psychosocial factors, such as anxiety and depression.[3]

Anatomy and Physiology

The spine consists of seven cervical, twelve thoracic, five lumbar, and five fused sacral and coccygeal vertebrae. The vertebrae articulate with each other superiorly and inferiorly at bilateral facet joints, creating four facet joints at each vertebral level. The thoracic vertebral bodies also have bilateral rib facets, which articulate with twelve pairs of ribs. Each vertebral body has bilateral transverse processes and a spinous process. Between the spinous process and the transverse processes are the lamina, and between the transverse processes and the posterior aspect of the vertebral body are the pedicles. Together, the pedicles and lamina form the neural arch, which, along with the posterior aspect of the vertebral body, forms the confines of the vertebral canal that contains the spinal cord and nerve roots. At each level, there are intervertebral (neural) foramina, where the spinal nerves exit.

Between the vertebral bodies are the intervertebral discs, which provide elasticity and stability to the spine. Each disc is comprised of the outer annulus fibrosis, a ring of fibrous tissue, and the collagenous inner nucleus pulposus. The spinal column is connected and stabilized by a network of spinal ligaments including anterior longitudinal ligament (ALL), the posterior longitudinal ligament (PLL), and the ligamentum flavum.

The spinal cord runs superiorly from the foramen magnum, inferiorly to the L1 to L2 interspace, but may extend as low as L3, where it then divides into the cauda equina. The cord is surrounded by three membranes: the tough dura mater, and the delicate arachnoid and pia mater (referred to as the leptomeninges). Cerebrospinal fluid bathes the spinal cord between the arachnoid and pia mater. The epidural space, between the bony vertebral canal and the dura, contains connective tissue padding and the spinal venous plexus. The dural sac ends between S1 and S3. The dura also protects the spinal nerve roots as the nerves exit the spine at each level, just below the correspondingly numbered vertebral body. The movements of the spine are governed by four groups of muscles: posterior extensor muscles of the back; forward flexors of the abdominal wall and the psoas and iliacus; lateral flexors, consisting of the quadratus lumborum, assisted by abdominal wall muscles; and rotators, which are a combination of the extensors and lateral flexors used with unilateral movements.

Pathophysiology

Nonspecific or Uncomplicated Back Pain

In as many as 90% of patients with back pain, no pathologic cause for the symptom can be identified.[1] Research indicates that in many instances

of nonspecific pain, factors that increase spinal loading pressure such as obesity and musculoskeletal dysfunction, also reduce spinal stability. Static postures that reduce lateral flexor flexibility and restrict hamstring range of motion contribute to reduced core muscle strength and inadequate support of the spinal column. Weakened core muscles, including those of the anterior abdominal wall, threaten the stability of the remaining muscular and ligamentous spinal support structures, placing patients at risk for activity-related strain.[3] Patients with nonspecific muscular back pain typically have localized pain without radicular symptoms.

Nerve Root Syndromes

Nerve root syndromes comprise a heterogenous group of disease processes that can present with similar clinical symptoms and signs. These syndromes result when there is compression or irritation of a nerve root, causing pain or paresthesias that often radiate into an extremity. Nerve root irritation may occur as the result of muscle tightness or intervertebral disc herniation; however, it can also be caused by pathologies that require urgent diagnosis and management. Therefore, nerve root syndromes should be carefully evaluated to avoid misdiagnoses of etiologies that require emergent intervention. There are multiple possible etiologies for nerve root syndromes. Three major etiologies are discussed in detail here.

With age, intervertebral discs desiccate and degenerate and the nucleus pulposus can herniate through the annulus fibrosis, compressing the nerve root at the neural foramen. Conversely, the annulus fibrosis itself can tear without a true herniation of the nucleus pulposus, also resulting in nerve root irritation. Herniations tend to occur at the L4 to L5 and L5 to S1 levels. This is because most flexion and extension of the spine occurs at the lumbosacral joint and to a lesser degree at L4 to L5, and the supporting PLL is relatively weak at this level of the spine. Although most disc herniations are posterolateral, causing unilateral symptoms, intervertebral discs sometimes herniate centrally, at the level of the cauda equina, causing severe compression of multiple nerve roots, resulting in cauda equina syndrome (CES), as discussed in the following.

Nerve root compression can also be caused by spinal stenosis. Aging causes intervertebral disc space narrowing and deterioration of spine joints. Osteophytes can form at the facet joints, and the ligamentum flavum calcifies over time. These degenerative changes can narrow both the neural foramina and the central canal, causing nerve root compression from osteophytes and increased intrathecal pressure in the narrowed canal. The subsequent pain is often bilateral, unlike that caused by disc herniation. Spinal stenosis also results in leg pain that is typically worse while walking and relieved with forward flexion (thus reducing pressure on the nerve root). This historical information is referred to as the *pseudoclaudication sign*.

Epidural space occupying lesions can also cause compression to nerve roots or to the cauda equina. Spinal epidural abscesses or hematomas causing nerve compression are true emergencies. Spinal epidural abscesses can result from hematogenous spread of bacteria (often staphylococcal species), in the setting of injection drug use, or from direct inoculation after epidural steroid injection or spinal surgery. Epidural hematomas can result from instrumentation of the epidural space or spinal surgery, although they can also develop spontaneously or following trauma in anticoagulated patients. Regardless of the cause, epidural space lesions causing nerve root compression requires emergent imaging and consultation.

Skeletal Causes of Back Pain

Common bony causes of back pain include fractures, infection, and malignancy.

Fractures may occur in any part of the spine secondary to trauma (see Chapter 35). Although a significant amount of force is required to fracture the bones of a normal spine, patients with osteopenia can incur bony fractures with minor trauma. Age-related osteopenia can result in vertebral compression fractures, causing sudden acute back pain with or without trauma. Spontaneous compression fractures occur most commonly within the thoracic or lumbar vertebral bodies. Vertebral fractures may cause radicular symptoms, depending on the location of the injury and impingement on the spinal canal or nerve roots.

Osteomyelitis of the spine is generally caused by hematogenous spread and seeding of the bone by bacteria, resulting in inflammation of the bone and periosteum, and subsequent pain. Injection drug use, spinal surgery, and tuberculosis of the spine (Pott disease), can all cause vertebral osteomyelitis.

Cancer of the vertebral bones is due to primary or metastatic lesions. Primary tumors, such as Ewing sarcoma, multiple myeloma, and osteosarcoma, are less common and usually occur in patients younger than 30 years old, often involving the posterior vertebral elements. Metastatic tumors typically involve the vertebral body and are most common in the thoracic spine, but multiple levels can be affected. Lung and breast cancers make up over 50% of metastatic spinal lesions. Lymphoma, melanoma, cancers of the gastrointestinal (GI) tract, prostate, and kidney, and multiple myeloma may also present as metastatic spinal lesions.

Skeletal back pain can also be caused by nontraumatic congenital or acquired abnormalities of the spine. Spondylolisthesis, or slippage of one vertebral body on another, results from degenerative changes but can also occur after trauma. Retrolisthesis occurs with the posterior slippage of one vertebral body on another. Facet arthropathy is an age-related degenerative cause of skeletal back pain. Inflammatory arthropathies, such as ankylosing spondylitis, rheumatoid and osteoarthritis, can cause similar spinal changes, including pathologic fractures.

CLINICAL FEATURES

History

A thorough history and a directed physical examination is essential in evaluating patients with back pain. Although nonspecific uncomplicated back pain is common, it is critical that emergency clinicians elicit historical information that indicates a higher risk of compressive myelopathy, including history of cancer, unexpected weight loss, trauma, chronic steroid use, anticoagulation, fever, an impaired immune system, injection drug use, or spinal surgery. It is important to assess for "red flag" findings that require emergent evaluation and intervention, such as bowel or bladder dysfunction, saddle anesthesia, and acute neurologic deficits such as bilateral extremity weakness. Important historical data concerning the pain includes: the onset, location, character, severity, duration and radiation of the pain (such as to the abdomen, chest or extremities).

Aggravating and alleviating factors are also important to elicit. Pain that is exacerbated by coughing, sneezing, or bearing down with bowel movements, all of which increase intrathecal pressure, may be associated with a radicular or spinal cause. Pain that is worse with walking or prolonged standing, particularly if relieved by bending forward, suggests spinal stenosis. Pain associated with stiffness that is worse in the mornings and improves through the day suggests a rheumatic etiology. In contrast, pain that is improved with rest is more likely to be muscular or skeletal in nature.

Prior history of back pain, medical or surgical history, and any traumatic events should be documented. Any history of malignancy, or systemic symptoms such as fever, chills, or malaise may indicate metastatic or infectious causes. A history of spinal procedures or surgery should be elicited. Medications such as anticoagulants (associated with epidural hematoma) or chronic corticosteroids (associated

with osteopenia) should be reviewed. A family history of autoimmune inflammatory diseases or malignancy may be contributory.

The patient should be asked about any neurologic findings that indicate serious pathology of the spine or nerve roots. These symptoms include sensations of numbness or paresthesias, pain in other locations of the spine, bowel or bladder dysfunction, or weakness in the extremities.

Physical Examination

A directed physical examination with the patient undressed is important in evaluating patients with back pain. The examination should include inspection, observation of the patient's normal movements, palpation, strength and sensory testing, specific maneuvers to assess for serious pathology, and an assessment of deep tendon reflexes. Inspect the overlying skin for erythema, warmth, or areas of swelling, noting any evidence of prior spine surgery or scoliosis. Observe the patient's general appearance including the presence of jaundice, rashes or contusions, and the patient's degree of discomfort. Observe the patient's gait and balance while ambulating. Because core and postural muscle dysfunction contributes to back pain through muscle inflexibility and tightness, range of motion should be tested in several planes.[3] Assess range of motion through flexion and extension at the waist, lateral flexion, and rotation. Palpate the spine to identify areas of maximal tenderness or the presence of muscle spasm.

Perform thorough neurologic testing for strength and sensation. Strength testing of the lower extremities is best done with the patient standing. Instruct the patient to flex both hips and knees, assuming a partial sitting or squatting position. Ask the patient to lift one leg briefly, then the other. Assess heel and toe walking (while holding the examiner's hands). Performing this activity requires full plantar and dorsiflexion strength, because the entire body weight is carried on a single extremity. If the patient is unable to comply with this approach to strength testing because of pain, this assessment can be performed with the patient reclining, although it is less reliable. Sensory testing is done with the patient reclining or sitting. Testing should include both upper and lower extremities, since some conditions, such as spinal stenosis, may occur at multiple spinal levels, including the cervical spine.

Straight leg and contralateral straight leg raise maneuvers are important in identifying radicular pain. The straight leg raise test is more sensitive but less specific than the contralateral straight leg raise test for the diagnosis of radiculopathy due to disc herniation.[4] The straight leg raise test is performed as follows:

- Position the patient supine with legs passively extended, without engaging the quadricep muscles. (This can be determined by noting that the patella can move freely side to side.)
- Raise each leg, flexing at the hip with the knee in extension.
- A positive test is elicited when pain is reproduced, radiating from the back to a point *below* the knee of the raised leg at 30 to 40 degrees of elevation. A positive result predicts lumbosacral radiculopathy with a high sensitivity though a relatively low specificity.[5]

Because L5 or S1 discs are implicated in the majority of disc herniations, a negative straight leg raise test is reassuring in ruling out disc pathology. Of note, radiation of pain from the back to the area of the posterior knee or above is a nonspecific finding and of less clinical value.

The contralateral straight leg raise test is performed in an identical manner. A positive test is elicited when pain is reproduced that radiates below the knee of the *contralateral* leg (the leg that is not being raised). Converse to the standard straight leg raise test, the sensitivity of the contralateral test for disc herniation is low, but the specificity is high. A positive contralateral straight leg raise test strongly suggests disc pathology at the L5 or S1 levels. In summary, if the straight leg raise test is positive, a positive contralateral straight leg raise test can be considered confirmatory of the presence of disc impingement. If the straight leg raise test is negative, but the contralateral straight leg raise is positive, disc herniation or impingement is still highly likely.

Further assessment can provide additional information. Assess the patellar and Achilles deep tendon reflexes, and the plantar reflex. Hyperreflexia, clonus, or a Babinski sign (positive plantar reflex) suggests upper motor neuron pathology, such as a cord impingement. Perineal sensation and anal sphincter tone should be assessed in patients with bilateral symptoms or findings, gait disturbance, severe pain, complaints consistent with saddle anesthesia, or bowel or bladder dysfunction. The cauda equina syndrome is a spinal cord compression below the termination at the conus medullaris (L1–L2) and loss of function of the lumbar plexus. The S3, S4, and S5 dermatomal nerves innervate the "saddle" region and compression causes numbness or tingling to the perineum, anus, and genitalia. Decreased rectal muscle tone may cause loss of bowel function. Bladder dysfunction due to an inability to urinate generally presents as overflow incontinence as a result of urinary retention.

Finally, because pain from abdominal or pelvic pathology often radiates to the back, a thorough abdominal examination, including an assessment of costovertebral angle tenderness and, when indicated, a prostate or gynecologic examination should be performed to exonerate non-musculoskeletal causes of low back pain.

DIFFERENTIAL DIAGNOSES

Table 104.1 lists various causes of low back pain and historical findings that are suggestive of specific etiologies. In constructing the differential

TABLE 104.1 Historical Clues to the Cause of Low Back Pain

Questions for Patient	Potential Diagnosis
Does the back pain radiate down past the knees?	Radiculopathy and possible herniated disk
Is the pain worse with walking and better with bending forward and sitting?	Spinal stenosis
Do you have morning back stiffness that improves with exercise?	Ankylosing spondylitis
Are you older than 50 years old?	Osteoporotic fracture, spinal malignancy
Has there been any recent history of blunt trauma?	Fracture
Do you take long-term corticosteroids?	Fracture, spinal infection
Do you have a history of cancer?	Spinal metastatic malignancy
Does your pain persist at rest?	Spinal malignancy, spinal infection
Has there been persistent pain for longer than 6 weeks?	Spinal malignancy
Has there been unexplained weight loss?	Spinal malignancy
Is the pain worse at night?	Spinal malignancy, spinal infection
Are you immunocompromised?	Spinal infection
Have you had fevers or chills?	Spinal infection
Do you have pain, weakness, or numbness in both legs?	CES
Do you have bladder or bowel control problems?	CES

CES, Cauda equina syndrome.

diagnoses of musculoskeletal back pain, the emergency clinician should incorporate key findings of the history and physical examination to assess the likelihood of common, nonspecific uncomplicated back pain, while determining the presence of serious findings that are associated with specific pathoanatomic etiologies that require urgent evaluation and intervention (Table 104.2).

Other nonmuscular life-threatening pathologies which cause back pain should be considered. As an example, patients with vascular disease can present with seemingly innocuous back pain, but this may be an early warning symptom of an abdominal aortic aneurysm or thoracic aortic dissection. Gastrointestinal, pelvic, and genitourinary causes of back pain should also be assessed and excluded.

DIAGNOSTIC TESTING

Most patients presenting with back pain have nonspecific uncomplicated musculoskeletal back pain that does not require diagnostic testing. When clinical suspicion exists for a concerning etiology, or red flags are noted on either history or physical examination, diagnostic testing is warranted to identify causes of back pain that require urgent or emergent intervention.

Laboratory Testing

Laboratory testing is generally not indicated for low back pain and when performed is often adjunctive to specific diagnostic imaging. An abnormal white blood cell count (WBC), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) may suggest an infectious or inflammatory etiology. For example, while the presence of an elevated ESR is not specific, it should increase the suspicion of spinal epidural abscess, osteomyelitis, or discitis. Marked elevations in the ESR and CRP are often due to infection, but noninfectious disorders such as malignancy, chronic or inflammatory disease, trauma, and tissue ischemia should also be considered. The presence of elevated inflammatory markers should prompt diagnostic imaging.

Coagulation testing is indicated for patients on long-term warfarin; however, the value of coagulation studies has diminished with the increasing prevalence of direct oral anticoagulant (DOAC) use. If coagulation studies are abnormal in the setting of low back pain, epidural or retroperitoneal bleeding should be explored. Urinalysis, and urine pregnancy testing in female patients, can be useful in establishing nonmusculoskeletal causes of back pain, such as nephrolithiasis, pyelonephritis or pelvic etiologies.

Imaging Studies

The vast majority of patients with self-limited, nonspecific back pain do not require emergent diagnostic imaging.[6] Routine imaging for low back pain is not associated with improved patient outcomes and abnormalities, if found, are often incidental and not necessarily the cause of the presenting symptoms.[7] Therefore, emergent imaging in the setting of acute back pain should be reserved for patients with suspected diagnoses that would necessitate emergent intervention. Signs, symptoms, and historical features that should lead the clinician to consider imaging studies are provided in Box 104.1.

Point-of-Care Ultrasound

Bladder dysfunction as a result of cauda equina syndrome can be evaluated by post-void ultrasonographic measurement of bladder volume. A completely normal bladder should have about 20 mL of residual urine after voiding. In adults, 100 mL of residual urine is considered to be an abnormal level; in children, a residual urine volume in excess of 10 per cent of bladder capacity is also considered abnormal.

Plain Radiographs

Clinicians may obtain plain radiographs when there is concern for spontaneous compression fractures in patients with osteopenia and nontraumatic back pain. The sensitivity of plain radiographs is inadequate to safely exclude traumatic injuries, whether in elderly patients with minor trauma, in patients with major trauma, or in presentations that are suggestive of pathoanatomic etiologies. In these scenarios, more accurate, advanced diagnostic imaging should be performed.

Computed Tomography

Computed tomography (CT) is superior to plain radiographs in delineating the nature and extent of acute fractures. As compared to MRI, CT also has superior sensitivity in detecting cortical bone abnormalities and is preferable to MRI for the evaluation of acute bony injuries. Therefore, when there is a high pretest probability of vertebral fracture, CT imaging is warranted. In a multitrauma patient undergoing CT scans of the head, neck, chest, abdomen, and pelvis (or whole-body CT "pan-scans"), CT images can be reconstructed to facilitate the evaluation of the spine.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the test of choice for evaluating the spinal cord and surrounding structures, including the canal, intervertebral discs, soft-tissue ligaments, and the epidural space. MRI defines the bony anatomy but is more sensitive and specific than CT in defining soft tissues and neural structures, such as the conus medullaris and spinal nerve roots within the canal and neural foramina. MRI can delineate epidural hematoma or abscess, herniated disc, ligamentous

TABLE 104.2 Physical Findings Corresponding to Herniated Disc Location

Level	Pain Location	Motor Loss	Sensory Loss	Reflex Loss
L3	Front of leg	Hip flexion and knee extension	Anterior thigh, medial calf	Loss of patellar
L4	Front of leg	Leg extension at knee	Around knee	Loss of patellar
L5	Side of leg	Foot dorsiflexion	Web of big toe	None
S1	Back of leg	Foot plantar flexion	Lateral foot	Loss of Achilles

BOX 104.1 Possible Indications for Advanced Imaging in the Setting of Back Pain

History
- History of malignancy or unexplained weight loss
- Fever with localized back pain
- Immunocompromised status
- History of injection drug use or bacteremia
- History of anticoagulant use
- Trauma of high force relative to patient
- History of recent spinal procedure or surgery

Physical Examination
- New weakness of extremities
- Sensory level or saddle anesthesia
- Abnormal reflexes, including positive Babinski sign
- Urinary retention or incontinence with post-void residual volume >100 mL
- Sphincter dysfunction: loss of sphincter tone or bowel incontinence

injury, and spinal stenosis, and it is the test of choice for diagnosing osteomyelitis. MRI is also the imaging study of choice in evaluating spinal infection and malignancy. Emergent MRI is indicated for suspected CES, epidural hemorrhage, or back pain accompanied by new neurologic findings in oncology patients. MRI is superior to plain radiographs or CT when determining the acuity or chronicity of a fracture. Contrast administration provides little additional information to MRI imaging except in the evaluation of possible intraspinal infection or metastasis.

When imaging to evaluate spinal cord lesions, it is important to clarify the possible level of the lesion. A thorough neurologic examination that includes the upper extremities may be used to exclude the need for cervical spine imaging. However, it is important to remember that spinal processes, such as malignancy or stenosis, can occur simultaneously in several levels, and the region of pain may not always correspond to the lesion causing a neurologic deficit, requiring imaging of the spine above or below the suspected affected area.

Computed Tomography Myelogram

Myelography is rarely performed in the emergency department setting and is generally indicated for patients who require advanced imaging but are unable to undergo MRI. Emergency clinicians should discuss the indications with their consulting radiologist and spine specialist before ordering this diagnostic study.

MANAGEMENT

Figure 104.1 presents a detailed algorithmic approach to ED management of patients with low back pain based on physical or ancillary test findings.

Nonspecific or Uncomplicated Back Pain

Emergency department management of acute or exacerbations of chronic back pain consists of supportive care, including patient reassurance and education and symptomatic relief. Current management guidelines for the treatment of patients with acute nonspecific back pain include attention to patient self-care and behavior modification, physical activity, and oral and topical analgesia.[8,9] Patients whose evaluations do not reveal red flags in history or physical examination should be given reassurance about the likely recovery from muscular back pain. Patients should be given advice and education about an early return to normal activities as tolerated, while avoiding heavy lifting or repetitive strenuous twisting movements. Physical activity, whether gentle exercise therapy or postural rehabilitation, has been shown to ease pain and facilitate recovery in both acute and chronic back pain. This approach also offers additional benefits of improving disability and mental health in those with nonspecific lower back pain.[8-11] Furthermore, those who use exercise to facilitate recovery are predicted to have better functional outcomes over time than those who do not exercise or use bedrest to help recovery.[11]

Topical therapies are a reasonable initial approach alone or in combination with pharmacologic treatment to offer symptomatic relief in uncomplicated back pain. Application of heat has been weakly recommended for short-term improvements in pain.[11,12] Topical capsicum or its derivative capsaicin has also demonstrated some relief in neuropathic pain, including neuropathic back pain due to lumbosacral radiculopathies.[13,14] Alternatively, transdermal application of lidocaine, whether in medicated gels, ointments, or more often in patches or plaster, has also gained increasingly widespread use. Despite the popularity of these topical agents, relatively little high-quality evidence exists for their definitive recommended use in low back pain.[11] Nonetheless, its

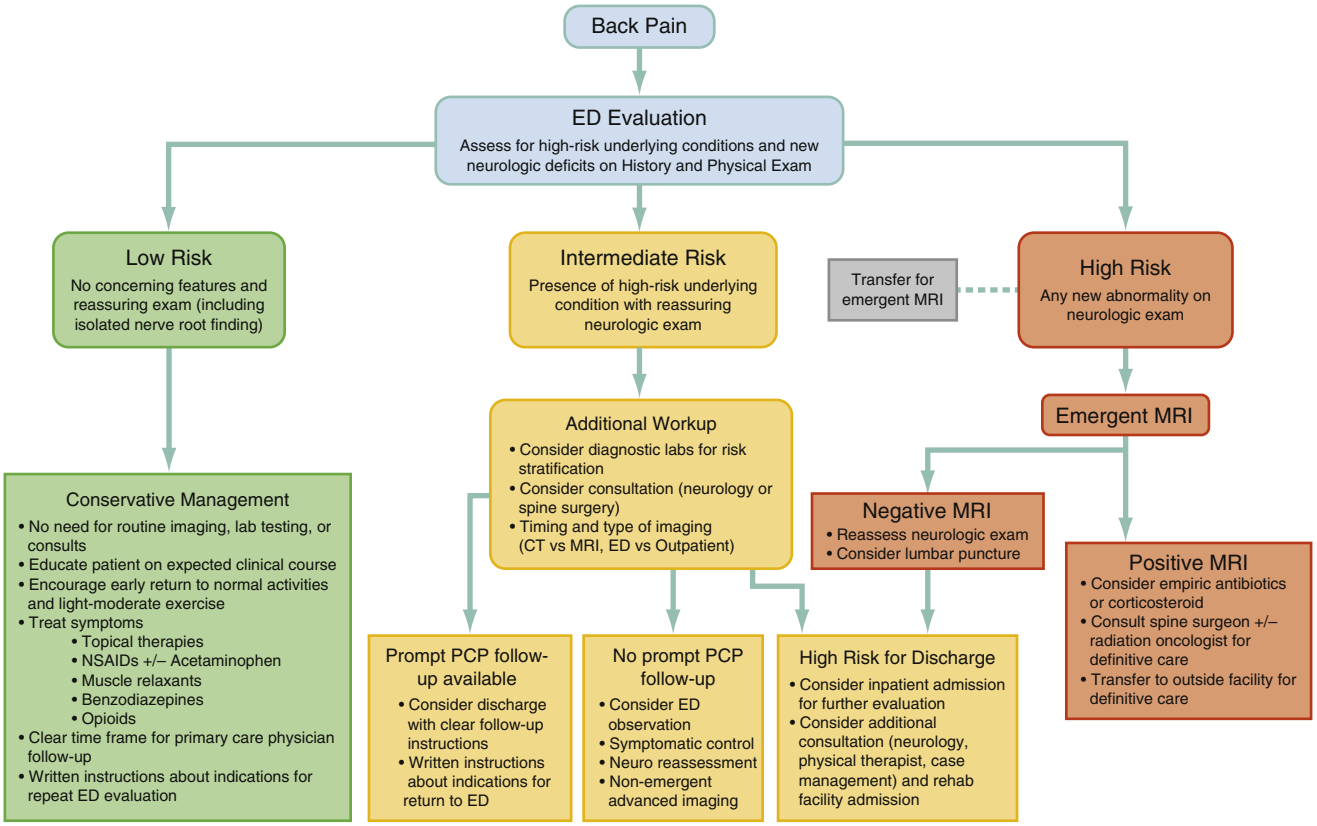

Fig. 104.1 Algorithmic approach to emergency department (ED) management of low back pain. *MRI,* Magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug; *PCP,* primary care physician.

low incidence of serious adverse effects confers a clinical benefit, particularly among the elderly and medically complex.[15]

We recommend oral analgesia consisting of nonsteroidal antiinflammatory drugs (NSAIDs) alternating with or without acetaminophen. A very short course of opioid therapy may be warranted for the treatment of severe acute back pain that limits the patient's normal activity.[16] However, the use of opioid pain medications in treatment of back pain should be cautiously limited.[11-12,16] Combination therapy with NSAIDs and opioids, as compared to NSAIDs alone, does not appear to improve functional outcomes or pain at one-week follow-up.[17] A benzodiazepine may be considered to supplement analgesia when the patient has failed an NSAID regimen or when the pain is causing substantial anxiety or sleep disturbance. However, the available evidence has not demonstrated substantial effects in pain, function, or long-term outcomes.[18,19]

Early return to work, with or without activity restrictions, is associated with better long-term outcomes. Physical therapy, spinal manipulation, and multimodal rehabilitation including acupuncture have not been consistently demonstrated to be superior therapies to the above recommendations.[11,18] Approximately 10% of patients develop long-term chronic pain, often because of contributing psychosocial factors, such as anxiety or depression. Chronic back pain is more likely to develop in patients with psychiatric disorders, obesity, poor overall health status, and nonorganic signs. Development is not associated with demographic variables, prior episodes of back pain, or chronic baseline pain.[20]

In summary, nonspecific uncomplicated etiologies will account for the vast majority of patients who present to the emergency department for back pain. For these patients, the emergency clinician should focus treatment on supportive care including moderate careful exercise, low-risk topical therapies, and educating the patient regarding the self-limited nature of the disease. In those who require pharmacologic therapy, nonsteroidal antiinflammatories and acetaminophen are considered first-line. Abbreviated courses of opioids and benzodiazepines are reserved for those who have failed initial therapy after consideration of the individual's benefits and risks. There is no role for invasive procedures, such as lumbar epidural injections, or certain classes of medications, such as anticonvulsants or antidepressants, for treatment of back pain in the emergency department.

Disc Herniation and Nerve Root Pain

Herniated disks and nerve root pain (often caused by intervertebral disc disease) without neurologic deficits on examination are initially managed similarly to nonspecific uncomplicated back pain. Signs and symptoms that indicate the need for advanced imaging and emergent spine service consultation include acute bowel or bladder dysfunction, new localized motor weakness or progressive leg weakness, and acute worsening of symptoms or findings in patients with known herniated discs and chronic back problems.

Although oral steroids do not have proven efficacy in general acute back pain, there is evidence that a subset of patients with nerve root pain and acute radiculopathy benefit from a single pulse dose of 6 to 10 mg of IV dexamethasone in the ED.[21] Alternatively, a 15-day course of a tapering dose of prednisone (60 mg, 40 mg, 20 mg daily for 5 days each) improves functional ability, but not pain.[20]

Epidural Abscess and Spinal Osteomyelitis

An epidural abscess is a surgical emergency. Emergent spine surgery consultation should be obtained at the treating hospital, or if unavailable, the patient should be transferred to a facility equipped for emergent spine surgery. Empiric antibiotics should be administered to cover suspected pathogens, usually *Staphylococcus, Streptococcus,* and gram-negative organisms. Vancomycin should be included to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection and pseudomonal coverage should be considered if hematogenous spread is suspected, particularly in immunocompromised patients with diabetes or sickle cell disease. As summarized in Box 104.2, appropriate empiric parenteral antibiotic regimens include:

BOX 104.2 Antibiotic Recommendations for Epidural Abscess and Spinal Osteomyelitis

Recommended Empiric Antibiotics Spinal and Epidural Infections	Regimen	Coverage
Epidural abscess	Vancomycin (loading dose: 20–35 mg/kg actual body weight [not to exceed 3000 mg] or 20–25 mg/kg actual body weight [not to exceed 3000 mg] in patients with obesity, then 15–20 mg/kg actual body weight every 8–12 hours)	Methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Streptococcus* species
	PLUS	Anaerobic species
	Metronidazole (500 mg IV every 6 hours)	Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus* species, and gram-negative species
	PLUS	Preferred for additional coverage of *Pseudomonas peruginosa*
	Cefotaxime (2 g IV every 4 hours)	
	OR	
	Ceftriaxone (2 g IV every 12 hours)	
	OR	
	Ceftazidime (2 g IV every 8 hours)	
Spinal osteomyelitis	Inpatient Treatment:	Methicillin-sensitive *Staphylococcus aureus* (MSSA)
	Nafcillin (2 g every 4 hours)	Methicillin-resistant *Staphylococcus aureus* (MRSA)
	OR	
	Vancomycin (30–60 mg/kg IV per day in two equally divided doses adjusted for renal function)	
	Outpatient Treatment:	Aerobic gram-negative organisms including *Pseudomonas aeruginosa* and *Salmonella* species
	Ciprofloxacin (750 mg PO two times a day)	Second-line for aerobic gram-negative organisms
	OR	
	Trimethoprim-sulfamethoxazole (1–2 DS twice a day)	

- Vancomycin (30 to 60 mg/kg IV per day in two equally divided doses adjusted for renal function) for empirical coverage of MRSA

plus

- Metronidazole (500 mg IV every 8 hours)

plus

- Either cefotaxime (2 g IV every 6 hours), ceftriaxone (2 g IV every 12 hours), or ceftazidime (2 g IV every 8 hours); ceftazidime is preferable when *Pseudomonas aeruginosa* is considered a possible or likely pathogen.

Spinal osteomyelitis is treated with antibiotics (with similar broad-spectrum coverage to that of epidural abscess) in conjunction with spine surgery consultation. Surgical intervention may be less emergent than in the case of epidural abscess as long as there is no compression on the spinal cord or a purulent fluid collection. Whenever possible, antibiotic therapy should be delayed in stable patients until tissue cultures can be obtained. If tissue culture is not obtainable and in advance of tissue culture results, broad-spectrum empiric therapy should be administered (see Box 104.2). These empiric antibiotics commonly include:

- Inpatient treatment:
  - Nafcillin (2 g every 4 hours) for methicillin-sensitive *Staphylococcus aureus* (MSSA) coverage *or*
  - Vancomycin (30 to 60 mg/kg IV per day in two equally divided doses adjusted for renal function) for empirical coverage of MRSA *or*
  - Cefepime (2 g IV every 8 hours) for gram-negative and *Pseudomonas* coverage
- Outpatient treatment:
  - Ciprofloxacin (750 mg by mouth BID) *or*
  - Trimethoprim-sulfamethoxazole (1 double-strength tablet twice daily)

Epidural Hematoma

An epidural hematoma is a surgical emergency. Emergent spine surgery consultation should be obtained at the treating hospital, or if unavailable, the patient should be transferred to a facility equipped for emergent spine surgery. Patients who are anticoagulated should have their anticoagulation reversed as described in Chapter 111.

Cauda Equina Syndrome

CES, when suspected, requires rapid confirmation by emergent MRI and emergent surgical decompression. Whenever possible, spine surgery consultation should be obtained in parallel with imaging to facilitate definitive treatment. Although prompt surgery provides the best opportunity for a good outcome, some patients may not recover function after decompressive surgery. In consultation with the spine specialist, surgical intervention may be deferred in patients with long-standing or chronic symptoms of CES. Emergent administration of intravenous corticosteroids should also be determined by the treating spine surgeon.

Malignancy

Patients who are diagnosed with a compressive malignant lesion of the spine or spinal cord may benefit from emergent corticosteroids to reduce the severity of any mass effect. Once this diagnosis is made, patients with neurologic deficits should receive a single dose of 10 mg intravenous dexamethasone in the ED.[22] The ameliorative effects of corticosteroids are transient, however, and prompt consultation with spine surgery and radiation oncology specialists is imperative to consider surgical decompression or directed radiation therapy.

Fracture

The management of acute traumatic spinal fractures is extensively discussed in Chapter 35.

DISPOSITION

Most patients presenting to the ED with acute back pain will be discharged with symptomatic treatment and an appropriate outpatient follow-up plan. As mentioned previously, patient reassurance and education about muscular back pain, in conjunction with oral and topical analgesics, are foundations of care. Patients with back pain thought to be secondary to a herniated disc with no neurologic findings should have prompt follow-up with a primary care physician or a spine surgeon.

Patients with suspected radiculopathy should be given clear return precautions, including the development of weakness, inability to stand or ambulate, saddle anesthesia, or bowel or bladder dysfunction. Patients who require emergent surgical intervention for spinal epidural abscess, compressive neoplasm, osteomyelitis, fracture, or other compressive spine lesions should be emergently transferred to the care of a spine surgeon, which may involve transfer to a tertiary or quaternary care center.

Patient transfer may be necessary if emergent spine surgery is not present at the treating facility or if emergent MRI is not available to image patients with suspected emergent infectious or compressive pathologies. Patients believed to have an epidural abscess or osteomyelitis should receive empiric parenteral antibiotics prior to transfer. Patients with findings consistent with CES or other compressive lesions due to malignancy should receive parenteral steroids prior to transfer if ordered by the receiving physician or the onsite consultant.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 104: QUESTIONS AND ANSWERS

1. A 55-year-old man presents with low back pain for one month. The pain is worse at night and is associated with a 10-pound weight loss. He denies any radicular symptoms. Which of the following is the most likely cause of the back pain?

a. Discitis
b. Muscle spasm
c. Osteosarcoma
d. Prostate cancer
e. Sciatica

Answer: D. The patient's subacute time course of back pain and worrisome finding of weight loss suggest a malignancy. Primary and metastatic bone neoplasms can cause back pain from tumor infiltration into the bone. Primary bone tumors, such as multiple myeloma, chordoma, Ewing sarcoma, and osteosarcoma, are 25 times less frequent than metastatic disease. Of the neoplasms, breast, lung, prostate, thyroid, lymphoma, and kidney are the most likely to metastasize to bone.

2. Which one of the following findings, in conjunction with low back pain, indicates a benign cause of pain?

a. Age of six years
b. Fever and night sweats
c. Negative sitting but positive supine straight leg raise test
d. Post-void residual of 500 mL
e. Saddle anesthesia

Answer: C. A positive supine SLR test but a negative sitting SLR test suggests a nonphysiologic cause for the pain. Low back pain and fever suggest an epidural abscess or osteomyelitis. Saddle anesthesia and post-void residual greater than 100 mL are indicative of cauda equina syndrome (CES). Children complaining of back pain must be investigated. They may have spondylolysis with varying degrees of spondylolisthesis, Scheuermann disease (kyphosis and osteochondritis of the vertebral end plates), infectious diseases, or neoplastic etiologies.

3. To avoid injuring the adult spinal cord, at what level should a lumbar puncture be performed?

a. L1 to L2
b. L3 to L4
c. L5 to S1
d. S2 to S3
e. Coccyx

Answer: B. The spinal cord ends at around L2 in adults, lower in children. When performing a lumbar puncture, to avoid injuring the spinal cord, insert the needle below the conus medullaris at level L3 to L4. Remember that between individuals, there may be significant anatomic variance.

4. A 55-year-old man complains of low back pain when walking downhill that is relieved with walking uphill. His neurovascular examination is unremarkable except for decreased bilateral Achilles reflexes. In addition to analgesia, what is the appropriate management of this patient?

a. Bedrest
b. Emergent spine surgery consultation
c. Lumbosacral plain radiographs
d. Magnetic resonance imaging
e. Surgical referral for pseudoclaudication

Answer: E. This patient presents with typical complaints of spinal stenosis. Patients with spinal stenosis should be managed conservatively with pain medications. In the absence of alarming red flag findings, these patients do not require emergent laboratory or radiographic studies. These patients may be candidates for surgery if they show any

CHAPTER 104: QUESTIONS AND ANSWERS—cont'd

of the following conditions: progressive neurologic deficit, progressive reduction in ability to walk secondary to pseudoclaudication, evidence of cauda equina syndrome (CES), or intractable pain.

5. Which of the following findings is most consistent with cauda equina syndrome (CES)?
   a. Absent patellar reflexes
   b. Bilateral buttock pain
   c. Decreased rectal tone
   d. Saddle anesthesia
   e. Urinary retention

Answer: E. The most consistent examination finding in CES is urinary retention. With a high sensitivity of 90%, the patient is unlikely to have this disease process if his or her post-void residual urine volume is less than 100 to 200 mL. Saddle anesthesia (sensory deficit over the buttocks, upper posterior thighs, and perineal area) is frequently an associated finding, with a sensitivity of 75%. In 60% to 80% of cases, the rectal examination reveals a decreased sphincter tone.

6. A 42-year-old man presents to the emergency department (ED) with a four-day history of low back pain after an episode of heavy lifting at work. He reports bilateral low back pain at the level of the iliac crests. He denies sensory or motor symptoms. He also denies bowel or bladder dysfunction. His neurologic examination is normal. What management is indicated?
   a. Erythrocyte sedimentation rate (ESR)
   b. Lumbar spine MRI
   c. NSAIDs and gentle stretching
   d. Oxycodone for three weeks
   e. Strict bedrest for two weeks

Answer: C. The patient most likely suffers from uncomplicated musculoskeletal low back pain. This is also commonly called *acute lumbosacral strain.* Most patients with this injury should not be placed on bed rest and should be allowed to return to normal activity, possibly with some restrictions. The patient has a relatively short history of low back pain with clear onset around an episode of lifting. Given a lack of concerning historical or examination findings, the patient does not require imaging at this time. Blood work would not be of help in evaluating the patient, because he lacks history or examination findings consistent with spinal infection.

7. A 35-year-old woman presents with a 3-day history of severe right lower extremity pain associated with mild low back pain. Her neurologic examination is normal except for a positive straight leg raise (SLR) test on the right and a negative contralateral straight leg raise (CSLR) test on the left. What therapy is indicated?
   a. Anxiolytic medication
   b. High-dose corticosteroids
   c. NSAIDs and gentle stretching
   d. Oxycodone for three weeks
   e. Strict bedrest for two weeks

Answer: C. Patients with herniated lumbar disks often present with radicular leg pain that overshadows the complaint of back pain. The treatment of radicular pain syndromes without neurologic deficit is similar to that of nonspecific uncomplicated back pain: NSAIDs and gentle stretching. It is very common for a patient with lumbar radiculopathy to have no clear motor or sensory deficit but have exacerbation of leg pain with SLR testing. The SLR has high sensitivity but low specificity. In contrast, the CSLR test has high specificity but low sensitivity. Given this, it is common for the patient with lumbar disk herniation to have a positive SLR but negative CSLR. The reverse is very uncommon. Diagnoses (such as spinal epidural abscess and spinal malignancy) usually present with prominent low back pain that is more significant than extremity pain.

8. A 68-year-old man presents with a 5-week history of worsening low back pain. He reports mostly midline spinal pain with occasional radiation into both lower extremities. Two weeks before the onset of his pain, he was discharged from the hospital after an inpatient admission for pneumonia. On examination, he has intact lower extremity motor and sensory function but tenderness to percussion over the lumbar spine. What diagnostic evaluation will confirm the diagnosis?
   a. Complete blood count
   b. Contralateral straight leg raise test
   c. Erythrocyte sedimentation rate (ESR)
   d. Lumbar computed tomography (CT)
   e. Lumbar magnetic resonance imaging (MRI)

Answer: E. The patient's history is suspicious for spinal epidural abscess. He is at higher risk because of his age and recent infection. In addition, the patient has tenderness with percussion of his spine. The optimal diagnostic evaluation to confirm this diagnosis is MRI. Patients with epidural abscess usually have an ESR elevated above 20 mm/hr. However, it is not uncommon for them to have a normal or only mildly elevated WBC count.

9. A 63-year-old man presents with a 9-month history of progressive low back pain with ambulation. He reports significant pain in his buttocks and posterior thighs when he walks distances greater than 25 meters. He says the pain is partially relieved when he flexes forward and completely relieved by recumbency. He reports the pain is not relieved if he stops walking but remains standing. On neurologic examination, he has intact lower extremity strength but diminished Achilles reflexes bilaterally. What is the expected finding on diagnostic imaging?
   a. Diminished Doppler flow in the tibial arteries
   b. Lumbar disc herniation at L5 to S1
   c. Normal lumbar MRI
   d. Post-void bladder volume of 500 mL
   e. Spinal stenosis at L4 through S1

Answer: E. The patient presents with classic findings of spinal stenosis and neurogenic claudication or "pseudoclaudication," including relief with flexing forward and recumbency. Persistence of pain with standing despite having stopped ambulating is also indicative of neurogenic claudication, as are diminished Achilles reflexes. Diminished pulses are indicative of vascular claudication. Pain from vascular claudication is generally relieved if a patient stops walking but remains standing. Unilateral disk herniation does not usually present with bilateral lower extremity symptoms.

Systemic Lupus Erythematosus and the Vasculitides

Eric Shappell and Eli M. Miloslavsky

SYSTEMIC LUPUS ERYTHEMATOSUS

KEY CONCEPTS

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can affect any organ system. A general approach to determine whether SLE is the cause of a nonspecific or single-organ symptom is to search for evidence of other organ involvement or systemic inflammation, which is expected in SLE-mediated presentations.
- Patients with SLE are at significantly higher risk of coronary artery or thromboembolic disease, which should prompt more thorough evaluation for these etiologies even in otherwise low-risk patients, such as young women.
- SLE itself, as well as its treatment, may lead to immunosuppression; thus, it is important to remain vigilant for the possibility of infection in patients with SLE.
- Glucocorticoids are the mainstay for the initial management of the majority of conditions that are associated with increased SLE disease activity, including musculoskeletal, cutaneous, renal, pleural, or pericardial disease.
- Antiphospholipid antibody syndrome (APS) is common in patients with SLE and carries with it an increased risk of venous and arterial thromboembolic disease.
- Rheumatology input may be helpful in diagnostic, management, or disposition decisions for select patients with SLE.

FOUNDATIONS

Background and Importance

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with complex pathophysiology that can affect nearly any organ system in the body. The prevalence of SLE varies by age, gender, geography, and race. Women are the most commonly affected group worldwide, representing approximately 90% of cases. The disease is more common in young people with more than two-thirds of cases diagnosed before the age of 50. In the United States, the prevalence of SLE is higher in African, Asian, and Hispanic Americans compared to Caucasians.

Patients with SLE have an increased risk of mortality (2.6-fold) as compared to the general population.[1] Morbidity and mortality for patients with SLE derive from four processes: (1) organ damage secondary to disease-mediated inflammation (e.g., nephritis, cerebritis, coronary artery disease), (2) hypercoagulability (e.g., stroke, pulmonary embolism), (3) complications of treatment (e.g., infection related to immunosuppression), and (4) increased risk of cardiovascular events. Care for the patient with SLE in the emergency department (ED) hinges on the recognition and treatment of these processes.

Etiology and Pathophysiology

The etiology of SLE is complex and incompletely understood. It appears to be related to multiple factors; genetics, hormones, and environmental factors such as smoking have all been implicated to varying degrees. With women representing 90% of SLE cases, a strong role for estrogen in disease development has been well supported in large cohort studies. The disease also has a strong genetic link, with high rates of monozygotic twin concordance.

The pathophysiology of SLE is mediated by the creation of autoantibodies with a multitude of downstream impacts. These effects include the formation and deposition of immune complexes leading to inflammation and tissue destruction (largely via complement activation) as well as autoantibodies directly targeting cell surface antigens and phospholipids, which may lead to tissue cell death, hemolysis, and hypercoagulability. The pathophysiologic mechanism of SLE may differ for each organ system. The organ systems involved in any given patient's disease may be different and relate to antigen expression in those tissues, among other factors.

CLINICAL FEATURES

Overview

SLE activity follows a relapsing and remitting pattern: acute episodes of increased disease activity ("flares") are separated by periods of stable disease or relative quiescence. The frequency and severity of flares can vary significantly between patients and over time, as can the baseline level of disease activity. While SLE is a chronic condition, it is not necessarily progressive. Whether additional organs become involved and the degree to which previously involved organs are affected is variable.

Recognition of SLE-mediated morbidity can be challenging, as SLE can affect nearly any organ system in the body, and many symptoms of the disease lack specificity. In general, ED presentations for SLE are related to one or more of the following: (1) flares of increased SLE disease activity (e.g., nephritis, arthritis), (2) SLE-mediated hypercoagulability (e.g., stroke, pulmonary embolism), and (3) complications of treatment for SLE (e.g., opportunistic infection due to immunosuppression).

Even with good medication adherence, patients with SLE are prone to flares. SLE flares are typified by worsening physical symptoms from increased organ inflammation and destruction. Flares commonly involve organ systems previously affected by SLE, though new organ systems may also become affected. As a systemic disease, worsening symptoms in one organ system are often associated with evidence of systemic inflammation and, commonly, evidence of disease activity in other organs.

As a general approach, when evaluating whether a symptom is due to SLE, providers should look for other SLE manifestations and biomarkers that can point to active disease, such as those in the Systemic Lupus International Collaborating Clinics (SLICC) Criteria for Systemic Lupus Erythematosus (Table 105.1). Single-organ symptoms without systemic inflammation should prompt consideration of

TABLE 105.1 Systemic Lupus International Collaborating Clinics Criteria for Systemic Lupus Erythematosus[a]

Criteria	Description
Clinical Criteria	
Acute cutaneous lupus	May include acute cutaneous lupus (lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash) or subacute cutaneous lupus
Chronic cutaneous lupus	Classic discoid rash, generalized hypertrophic (verrucous) lupus, lupus panniculitis, mucosal lupus, others
Oral ulcers	Palate (buccal, tongue) or nasal ulcers
Non-scarring alopecia	Diffuse thinning or hair fragility
Synovitis	Involving two or more joints (swelling, effusion, or tenderness and ≥30 minutes of morning stiffness)
Serositis	Pleural (pleuritis, effusion, rub) or pericardial (pericarditis, effusion, rub)
Renal disorder	500 mg protein/24 h or red blood cell casts
Neurologic disorder	Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathies, acute confusional state
Hemolytic anemia	
Leukopenia	<4000/mm^3 at least once
Thrombocytopenia	<100,000/mm^3 at least once
Immunological Criteria	
Anti-nuclear antibody	Any level above the laboratory reference range
Anti-dsDNA	Level above the laboratory reference range (or twofold the reference range if tested by ELISA)
Anti-Sm	Presence of antibody to Sm nuclear antigen
aPL antibody	As determined by a positive test for lupus anticoagulant or anti-2-glycoprotein, false-positive result for rapid plasma regain, medium- or high-titer anticardiolipin antibody level
Low complement	May include C3, C4, or CH50
Direct Coombs test	In the absence of hemolytic anemia

[a]Fulfillment of at least four criteria, with at least one clinical and one laboratory criterion, is required to establish the diagnosis of systemic lupus erythematosus.
aPL, Antiphospholipid; *ds,* double-stranded; *ELISA,* enzyme-linked immunosorbent assay; *SLE,* systemic lupus erythematosus; *Sm,* Smith.

pathology other than SLE. It is important to identify when overall disease activity is increased as this signals the need to initiate or escalate systemic therapy. In many cases, patients themselves are able to provide direction about the predictable course of their exacerbations and can be helpful in decision-making for therapy and disposition.

Specific Symptoms

Fever

Fever in a patient with SLE can be related to systemic disease activity, infection (including opportunistic infection related to immunosuppression), or pathology unrelated to SLE. Recurrent fevers without evidence of infection may be the presenting symptom that leads to an initial diagnosis of SLE. Similarly, patients with diagnosed SLE may present with fever as a symptom attributable to a disease flare. Before attributing fever to SLE disease activity, however, care should be taken to exclude acute infection. This is particularly important for patients taking immunosuppressive medications. Most infections in SLE are caused by typical organisms. However, largely because of the immunomodulating therapies that are the cornerstone of SLE management, opportunistic diseases are possible; *Pneumocystis (carinii) jiroveci* pneumonia, cryptococcal meningitis, *Listeria* infection, and herpes zoster have all been described.

Cardiopulmonary Presentations

There is a broad range of cardiac and pulmonary pathology associated with SLE that may present with chest pain or shortness of breath. Given the lengthy differential for this spectrum of presentations and the significant degree of overlapping symptoms for the varied underlying disease processes, an anatomic approach may be useful when working through the differential.

Coronary Artery Disease. As with other systemic inflammatory conditions, there is a significantly increased risk of coronary artery disease (CAD) in patients with SLE. While SLE is associated with higher incidences of traditional risk factors such as hypertension and hypercholesterolemia, the increased risk of CAD persists even after controlling for these factors.[4] Thus, whereas there are many considerations for the cause of chest pain in patients with SLE, acute coronary syndromes (ACS) should be considered highly in these cases, including in patients who would otherwise be deemed low risk (e.g., young women). Coronary disease should also be considered in patients with SLE presenting with atypical symptoms of ACS, such as shortness of breath, epigastric pain, or fatigue.

Pericardial and Myocardial Disease. Pericarditis and effusions of the pericardium occur commonly in patients with SLE and are among the classification criteria for the disease (see Table 105.1). An estimated 25% of patients with SLE will experience symptomatic pericarditis during the course of their lives, and pericardial effusion (often asymptomatic) occurs even more frequently. In patients with pericarditis, dyspnea and chest pain that is sharp, pleuritic, and positional (improved with leaning forward) are classic features of the disease. Auscultation may reveal a friction rub. Electrocardiography may reveal classic findings of diffuse ST elevation and PR depression (Fig. 105.1); however, patients with pericarditis may also have normal or nonspecific ECG findings. Given the increased risk of CAD in patients with SLE, obtaining cardiac biomarkers in patients with ST elevation that would otherwise be diagnosed as pericarditis is generally encouraged. If there is diagnostic uncertainty as to whether ST elevation is related to pericarditis or an ST elevation myocardial infarction (STEMI), urgent cardiology consultation for consideration of cardiac catheterization is warranted. There are no specific signs of pericarditis on echocardiography. Visualization of pericardial effusion is supportive of the diagnosis of pericarditis; however, this finding may also be present in patients with SLE that do not have symptomatic pericarditis. Echocardiography is also useful to assess for associated cardiac tamponade, which is a rare but life-threatening complication of SLE. The presentation and diagnosis of cardiac tamponade are the same for patients with SLE as the general population. SLE myocarditis may present with chest discomfort and symptoms of heart failure, though acute symptomatic presentations are rare.

Valvular Disease. SLE is associated with a type of noninfectious endocarditis known as *Libman-Sacks endocarditis* (Fig. 105.2). Mitral valve disease is most common, though other valves may also be affected. While the lesions formed on heart valves in this condition are more often associated with embolization than valvular dysfunction, some patients may develop valvular insufficiency that may present with shortness of breath, fatigue, or, in rare severe cases, pulmonary edema.

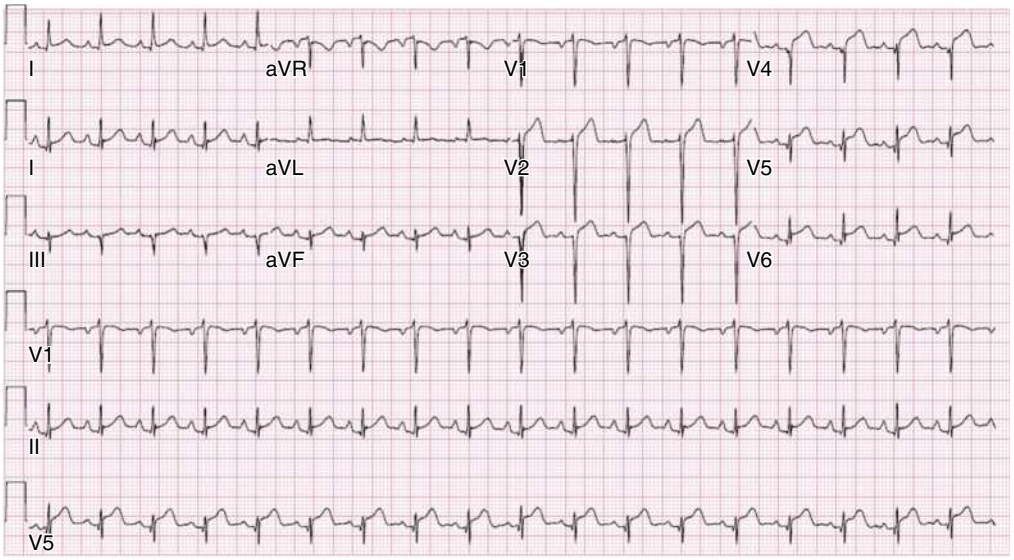

Fig. 105.1 Electrocardiogram of a 38-year-old woman with systemic lupus erythematosus (SLE) who presented to the emergency department (ED) with seizures and had chest pain while in the ED. Note diffuse ST elevation (with the absence of any reciprocal changes) and PR depression (particularly evident in lead II). Q waves anteriorly are related to prior myocardial infarct.

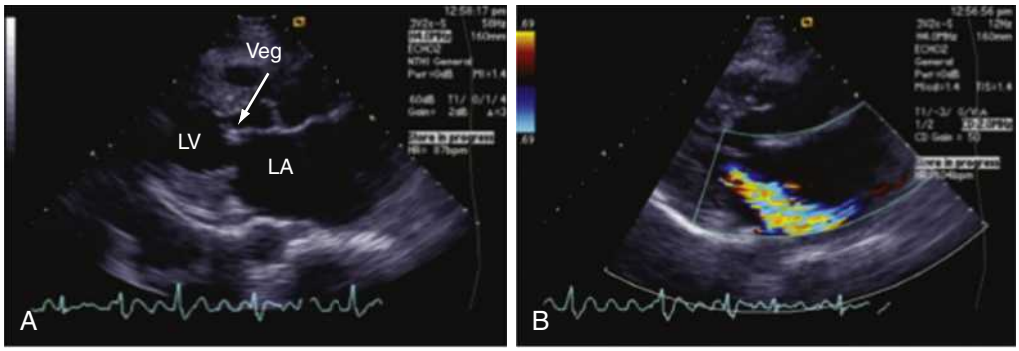

Fig. 105.2 Noninfectious endocarditis, known as a *Libman-Sacks lesion,* in a 56-year-old woman with systemic lupus erythematosus (SLE), a heart murmur, and dyspnea on exertion. (A) A parasternal long-axis view of the heart; a vegetation *(Veg)* is identified *(arrow)* on the mitral valve. (B) When color flow is superimposed on the valve, moderate to severe mitral regurgitation can be seen as a color jet entering the left atrium during systole. *LA,* Left atrium; *LV,* left ventricle. (Courtesy Martin Goldman, MD, Mount Sinai School of Medicine.)

Pulmonary Vascular Disease. Due to disease-associated hypercoagulability, deep venous thrombosis (DVT) and pulmonary embolism (PE) are more frequent in patients with SLE when compared to the general population. The degree of hypercoagulability in patients with concomitant **antiphospholipid syndrome** (APS) is even higher. Outside of the context of increased thromboembolic risk lowering the threshold for further testing, the evaluation for thrombosis and embolism in a patient with SLE does not differ from that of patients in the general population.

Though uncommon, patients with SLE may also develop pulmonary hypertension, which can present with shortness of breath, chest discomfort, and fatigue. Evaluation, in this case, may reveal a history of pathology known to lead to pulmonary hypertension (e.g., chronic thromboembolism, interstitial lung disease), physical exam findings of right heart failure, or evidence of right ventricular hypertrophy on electrocardiography or echocardiography. A definitive diagnosis is made via right heart catheterization.

Pleural Disease. Pleuritis is the most common respiratory condition occurring in SLE. Characterized by pleuritic chest pain with or without a pleural effusion or pleural rub, it has symptoms that overlap with those of other more serious conditions. A diagnosis of pleuritis should be arrived at only after other causes of pleuritic chest pain (e.g., PE) have been excluded.

Parenchymal Disease. Diseases of the lung parenchyma associated with SLE include infectious pneumonia, acute and chronic pneumonitis, interstitial lung disease, and, rarely, diffuse alveolar hemorrhage (DAH). The symptoms associated with infectious pneumonia, pneumonitis, and DAH have significant overlap; each of these entities may present with fever, cough, shortness of breath, and hemoptysis, and chest radiography may reveal nonspecific opacifications. Differentiating between these entities is difficult in the ED setting and may require further evaluation with bronchoscopy for bronchoalveolar lavage.

Mechanical Respiratory Disease. Shrinking lung syndrome is a rare condition associated with SLE that is characterized by symptoms of shortness of breath and pleurisy with low lung volumes and a restrictive pattern on pulmonary function testing. Patients may also have the elevation of one or both hemidiaphragms and pleural effusions. The

etiology of this syndrome is unclear but appears to involve some degree of restriction of chest wall expansion with or without diaphragmatic dysfunction.

Renal Disease

Renal disease is a common complication of SLE occurring in approximately one-half of patients.[5,6] Renal disease related to SLE may cause a nephrotic-type disease, primarily characterized by significant proteinuria or nephritic disease with hematuria and increased creatinine concentration. Diagnosis based on clinical criteria alone is not possible as many patients with renal impairment are asymptomatic. Patients that do have symptoms may report hematuria, foamy urine, generalized edema, or an elevated blood pressure from baseline. Given the high prevalence and morbidity of renal disease and its tendency to carry few if any symptoms, a screening urinalysis and basic metabolic panel are prudent in all but the most straightforward presentations concerning SLE-mediated disease. Renal biopsy is indicated for all patients with new-onset lupus nephritis and can be considered in those with relapsing or refractory disease.

Gastrointestinal Presentations

The most common gastrointestinal (GI) manifestation of SLE is oral ulceration. Esophageal dysmotility and reflux are also more common in patients with SLE and may present with dysphagia or pain in the epigastric region or chest. In patients with SLE, most causes of abdominal symptoms (e.g., pain, nausea, diarrhea, constipation) are the same as in the general population. Accordingly, the ED evaluation should be largely similar for each of the two groups. Special considerations for patients with SLE, however, include an increased risk of pancreatitis due to medications, mesenteric vasculitis (also known as lupus enteritis), peritonitis due to serositis, or the side effects of medications including chronic NSAIDs (e.g., peptic ulcer disease), glucocorticoids (e.g., peptic ulcer disease, perforation, infection), or immunosuppressive agents (infection).

Patients taking glucocorticoids or other immunosuppressive medications may also have masking of traditional symptoms, so a lower threshold for further testing (e.g., computed tomography [CT] imaging) should be used for this population.

Dermatologic Presentations

The most characteristic cutaneous manifestation of SLE is the malar rash. The rash has a "butterfly" distribution of raised erythema over the bridge of the nose and malar eminences while sparing the chin, forehead, and nasal-labial folds (Fig. 105.3). This sparing of the nasal-labial folds can help distinguish the classic malar rash from mimics such as rosacea or seborrheic dermatitis. Other common skin findings in patients with SLE include discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE). Each of these skin findings can present years before systemic manifestations of SLE occur, and while the characteristic malar rash is highly specific for SLE, DLE and SCLE more commonly present in isolation, without progression to SLE. DLE lesions are circular and raised, scaly lesions that may be commonly found on the face, scalp, and ears, often in association with pigment change, alopecia, and scarring (Fig. 105.4). SCLE lesions are annular with an erythematous border, scaling, and central clearing. At times, these areas may coalesce to form more complex linear patterns of erythema. These lesions can be triggered by sunlight and are most commonly found in sun-exposed areas of the upper extremities, torso, and neck. The face is not usually affected by SCLE.

Musculoskeletal Presentations

Arthritis commonly afflicts those with SLE, and increasing severity of joint pain may be a marker of increasing disease activity or an SLE flare. Arthritis or arthralgias are typically symmetrical and nonerosive (unlike rheumatoid arthritis, which is erosive) and always involve multiple joints. Arthritis most commonly presents in the hands (metacarpophalangeal and proximal interphalangeal joints), wrists, feet, and knees but may be manifested in any joint. While swelling may be present, often, the joint pain of lupus presents with arthralgia alone. Uncommonly, septic arthritis may complicate SLE. An isolated swollen joint is not typical of SLE and should prompt consideration for infectious arthritis. If septic arthritis is suspected, diagnostic arthrocentesis is recommended.

Myalgias are common in SLE and may be an early marker of increasing disease activity for some patients. It should be kept in mind that fibromyalgia may also coexist with SLE and chronic myalgia not associated with other disease activity or elevated inflammatory markers may point to this diagnosis. While generalized muscle pain is sometimes seen, muscle weakness is uncharacteristic. If muscle weakness is present, an underlying myositis or myopathy, potentially related to steroid or hydroxychloroquine use, should be considered. Musculoskeletal chest pain, related to underlying pectoral, intercostal muscle,

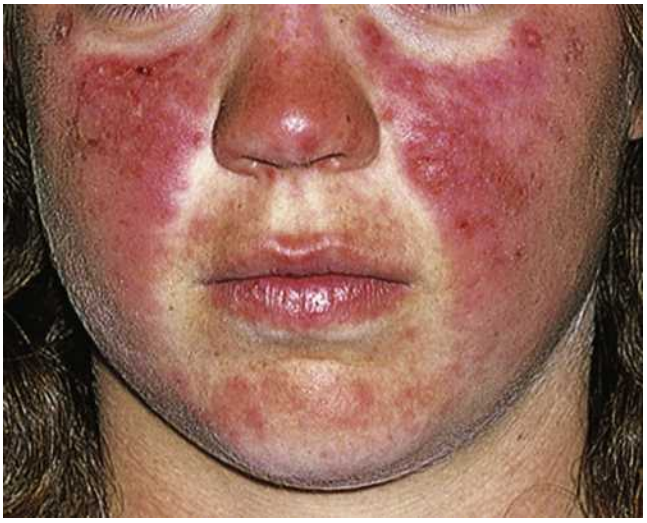

Fig. 105.3 The Malar or Butterfly Rash Is the Hallmark of Systemic Lupus Erythematosus (SLE). (From Habif TP. *Clinical Dermatology*. 5th ed. New York: Mosby; 2009:592–606.)

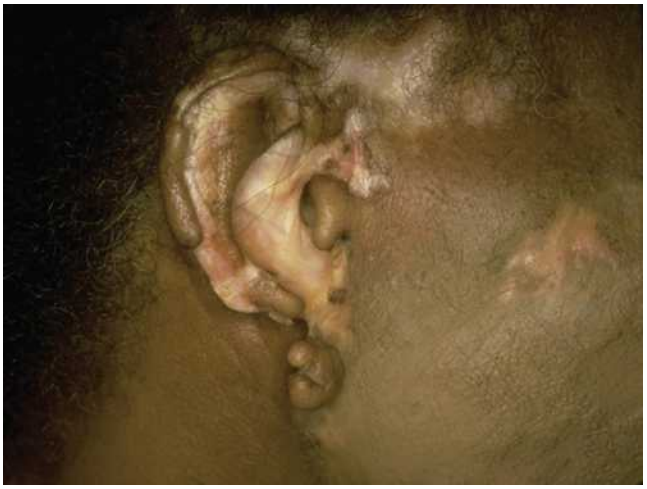

Fig. 105.4 Right Ear of a Patient Suffering From Chronic Discoid Lupus. Note pigment change and tissue destruction. (Courtesy Professor Gregory Raugi, University of Washington.)

or costochondral joint inflammation may also occur and should be treated the same as in patients without SLE. Similar to pleuritis, the threat of a more malicious underlying cause of the pain should prompt the clinician first to seek other causes before arriving at this more benign diagnosis.

Hematologic Disease

Anemia, present in up to 50% of patients with SLE, may present with a chief complaint of dyspnea or weakness. Iron deficiency anemia, anemia of chronic disease, autoimmune hemolytic anemia, or medication-induced bone marrow suppression can all contribute to anemia in a patient with SLE. SLE also shares a strong association with APS, which is associated with a significantly increased risk of thromboembolic disease.

Complications Due To Medications

Chronic NSAID use for the musculoskeletal consequences of SLE may contribute to peptic ulcer disease, especially if they are coadministered with glucocorticoids. Chronic glucocorticoids are associated with an increased risk of multiple conditions including CAD, osteoporosis, avascular necrosis, psychosis, hyperglycemia, hypertension, and weight gain, among many others. Therapy with antimalarials, such as hydroxychloroquine, is common and generally well tolerated; however, retinopathy has been associated with prolonged use. Medications that interfere with DNA synthesis such as cyclophosphamide, methotrexate, mycophenolate mofetil, and azathioprine suppress the immune response, leaving patients vulnerable to both conventional and opportunistic infections. These medications are also frequent causes of cytopenias and liver function test elevations. Cyclophosphamide is one of the most potent immunosuppressants and particular care should be given to assessing for infection in patients receiving this agent. Biologic agents such as rituximab and belimumab are also associated with an increased risk of infection or cytopenias.

DIFFERENTIAL DIAGNOSIS

In keeping with its highly varied presentations and permutations of disease activity, a number of other diseases may be confused with SLE before diagnosis. These include infection, thrombotic thrombocytopenic purpura (TTP), APS, vasculitis, rheumatoid arthritis, mixed connective tissue disease, undifferentiated connective tissue disease, Sjögren syndrome, fibromyalgia, and drug-induced lupus, among others. In the ED setting, the priority should be identifying severe illness with an acute threat to organ function or risk of death. Mild, subacute, and nonspecific disease processes generally do not require definitive diagnosis in the ED setting if not associated with evidence of near-term risk to organ function. Chief complaint-driven considerations for acute presentations of SLE are listed in Table 105.2.

DIAGNOSTIC TESTING

Patients carrying a diagnosis of SLE presenting with symptoms concerning SLE-related pathology will typically require evaluation for evidence of systemic disease activity in addition to symptom-specific testing. In general, patients will not undergo testing for an initial diagnosis of SLE in the ED.

The general approach to assessing whether a symptom is caused by overall SLE disease activity is to look for signs and symptoms of the disease in other organs or systemically. For example, a patient presenting with pleurisy, arthralgias, and fever that has laboratory testing consistent with increased disease activity and chest radiography that is negative for evidence of infection may be diagnosed with a lupus flare. A patient with isolated pleurisy in the absence of other symptoms, laboratory tests, or imaging studies consistent with active SLE, however, is less likely to be suffering from an SLE flare and therefore warrants further evaluation for non-SLE pathology.

Symptom-specific testing will be the same for patients with and without SLE, with the caveat that certain testing thresholds may be lowered for patients with SLE given the increased risks associated with this disease and its treatment (e.g., cardiovascular disease, thromboembolic disease, infection).

Laboratory Tests

While patients will not typically undergo laboratory testing for an initial diagnosis of SLE in the ED, special circumstances such as low resource settings, poor outpatient follow-up, or severe illness requiring expedited diagnosis may prompt emergency physicians to begin this evaluation.

TABLE 105.2 Common or Specific Differential Considerations for Patients With Systemic Lupus Erythematosus Based on Common Presentations, Comorbidities, or Complications

Chief Complaint	Condition
Altered Mental Status	Neuropsychiatric lupus Medication effect (e.g., steroid psychosis) Seizure Infection
Fever	Infection Increased disease activity (SLE flare)
Chest pain	Acute coronary syndrome Pulmonary embolism Pericarditis/pericardial effusion Pleuritis/pleural effusion Musculoskeletal chest wall pain (diagnosis of exclusion)
Shortness of breath	Acute coronary syndrome Pulmonary embolism Pulmonary hypertension/right heart failure Pneumonia Pericarditis/pericardial effusion Pleuritis/pleural effusion Interstitial lung disease Shrinking lung syndrome Anemia
Abdominal pain	Pancreatitis Peptic ulcer disease Pseudo-obstruction Lupus enteritis
Leg swelling	Deep venous thrombosis Nephrotic syndrome Renal failure Heart failure (left- or right-sided)
Pruritic or painful rash	Discoid SLE Drug reaction Sun exposure
Arthritis	Increased disease activity (SLE flare) Osteoarthritis Septic arthritis

SLE, Systemic lupus erythematosus.

For patients carrying a diagnosis of SLE with all but the most trivial presentations of potential SLE-mediated disease, laboratory studies are indicated to assess for increased disease activity as the etiology of the patient's symptoms.

Initial Diagnosis

The diagnosis of SLE can be difficult. The broad, heterogeneous, waxing and waning nature of the disease, lack of specificity of many presenting symptoms, multitude of diseases with overlapping symptoms, and lack of uniform diagnostic criteria all contribute to this difficulty. While classification criteria for SLE have been published by the European League Against Rheumatism/American College of Rheumatology and Systemic Lupus Collaborating Clinics, these are not set forth as diagnostic criteria.[7,8] However, clinicians may find these criteria helpful in remembering salient elements for the evaluation of a patient with possible SLE, including relevant laboratory studies. Laboratory testing relevant to SLE diagnosis includes a complete blood count to assess for leukopenia, lymphopenia, and thrombocytopenia; hemolysis testing if anemia is present; complement levels; urinalysis for hematuria, proteinuria, and casts; and immunologic assays including anti-nuclear antibody (ANA), anti-double-stranded DNA (dsDNA) antibody, anti-Smith (Sm) antibody, and aPL antibodies. The Ro, La, and ribonucleoprotein (RNP) antibodies may also be seen in lupus but are less specific for SLE and are also associated with Sjögren's and mixed connective tissue disease, respectively. A positive ANA is present in nearly all patients with SLE but is also present in more than 10% of the general population. The ANA titer is important to consider as the majority of patients with SLE have high-titer ANAs. In general, the temptation to pursue a new diagnosis of SLE in the ED should be avoided due to the lack of uniform diagnostic criteria, reliance on laboratory investigations that are uncommonly carried out in the ED, and rarity that a diagnosis made emergently will significantly change patient outcomes.

Disease Activity

Routine laboratory tests with correlation to increased SLE disease activity include a complete blood count (leukopenia, anemia, thrombocytopenia), basic metabolic panel (creatinine elevation), erythrocyte sedimentation rate (ESR, elevated), and urinalysis (hematuria, proteinuria). Patients found to have new or worsening anemia should be evaluated for hemolysis, which is associated with increased SLE disease activity. This evaluation may include a direct Coombs test, peripheral blood smear, LDH, and haptoglobin. It should be noted that the ESR is not always elevated in active disease; therefore, patients with compelling symptoms without an alternative explanation can be diagnosed with SLE flare despite normal inflammatory markers. C-reactive protein (CRP) is frequently normal in active lupus. Therefore, an elevated CRP should prompt strong consideration of infection. Other more specialized laboratory markers of SLE disease activity include low complement levels (C3, C4) and elevated anti-dsDNA.

Evaluation for Infection

Leukocytosis may suggest infection in some cases; however, it has poor specificity. This finding may be even less useful in SLE patients taking glucocorticoids, as these medications are associated with baseline leukocytosis. Leukopenia may also suggest infection in some cases; however, this is also a sign of active SLE and therefore cannot be relied upon as a marker specific for infection in patients with SLE. Immature cells (e.g., band cells) on a differential are relatively specific for infection and are not routinely associated with SLE disease activity. CRP may also be a useful marker as it can be normal despite increased disease activity in SLE but typically rises in the case of infection. ESR is nonspecific and will rise in both cases of infection and SLE flares.

Imaging Studies

While SLE is also associated with a wide variety of other pathology routinely diagnosed on imaging studies (e.g., stroke, pneumonia, PE), the imaging studies of choice for these entities do not differ between patients with and without SLE. Lupus cerebritis, a blanket term for organic SLE-related CNS pathology with neuropsychiatric manifestations and no alternate diagnosis, is typically evaluated with magnetic resonance imaging (MRI) of the brain in addition to lumbar puncture. MRI of the brain in patients with lupus cerebritis may be normal or reveal nonspecific findings such as hyperintense white matter lesions, and should assist in excluding alternate diagnoses (e.g., stroke).

MANAGEMENT

Emergent Stabilization

Emergent stabilization of patients with SLE does not differ from that of patients without the disease. Management of life-threatening presentations associated with SLE such as myocardial infarction, stroke, PE, seizure, and infection should all proceed as usual. For patients with SLE in refractory shock, stress dose glucocorticoids (hydrocortisone 100 mg IV q8h) should be considered given the high incidence of chronic steroid therapy and related adrenal suppression in this population. Advanced SLE therapies (e.g., immunosuppressive agents, plasma exchange) can be coordinated with the appropriate consulting services (e.g., rheumatology, nephrology) for patients with a critical illness.

General Systemic Disease Activity

Nearly all manifestations of active SLE are managed with the introduction or escalation of immunomodulatory therapy.

Patients Diagnosed With Systemic Lupus Erythematosus

For patients that carry a diagnosis of SLE and evidence of active disease, treatment and disposition will be guided by the severity of symptoms. Mild to moderate disease with manifestations such as joint pain, serositis, or cutaneous disease typically respond to prednisone 15 to 20 mg PO daily or NSAIDs in the case of joint pain and serositis. For pericardial and pleural effusions in the absence of hemodynamic compromise or respiratory distress, respectively, drainage in the ED setting is rarely required. For patients with severe disease and end-organ dysfunction (e.g., seizures, transverse myelitis, cardiac tamponade, nephritis), either pulse glucocorticoids (e.g., methylprednisolone 1 g/day IV) or prednisone 1 mg/kg/day PO and admission are generally appropriate. If worsening renal dysfunction is discovered, admission should be considered for hydration, escalation of therapy, and consideration of renal biopsy to help classify the disease and guide treatment. In each of the presented scenarios, management and disposition decisions can be made in consultation with a patient's rheumatologist, if available.

Patients Not Diagnosed With Systemic Lupus Erythematosus

For patients who do not carry a diagnosis of SLE and who have only mild evidence of disease (e.g., rash, arthralgias, uncomplicated pleurisy), symptomatic treatment and referral to a rheumatologist or primary care physician are appropriate provided that end-organ disease such as nephritis has been considered. In patients with evidence of severe systemic SLE-related disease (e.g., seizures, transverse myelitis, cardiac tamponade), empiric pulsed glucocorticoids should be considered while a formal diagnosis of SLE is pending.

Specific Presentations

Infection

Management of infection in patients with SLE includes appropriate antimicrobial coverage based on the suspected source, prior culture

data (as available), and the patient's degree of immunosuppression, as well as source control. Patients on chronic steroid therapy with refractory hypotension associated with infection should typically be treated with stress dose glucocorticoids (e.g., hydrocortisone 100 mg IV every 8 hours). Generally, nonglucocorticoid immunosuppression should be stopped while infection is treated, with the exception of hydroxychloroquine, which has not been associated with an increased risk of infection.

Musculoskeletal Pain

Much of the pain associated with SLE is related to inflammation that is amenable to treatment with NSAIDs or low-dose glucocorticoids. Ibuprofen 600–800 mg three times daily a day or naproxen 500 mg orally twice daily is useful for conditions such as pericarditis, pleuritis, arthralgias, myalgias, and fever. It is important to distinguish inflammatory joint pain from fibromyalgia, which does not typically respond to NSAIDs or glucocorticoids. Use of NSAIDs in patients with chronic kidney disease or a history of peptic ulcer disease is discouraged. In such patients, acetaminophen is used for mild to moderate pain. Adjunctive therapies such as lidocaine patches and heating or cooling packs may also be useful in controlling musculoskeletal pain related to SLE. The use of opioid medications is discouraged in the management of chronic rheumatologic diseases, including SLE.

Cutaneous Manifestations

In cases of isolated cutaneous findings, treatment with topical corticosteroids is preferable to systemic therapy. Topical therapy may be initiated with a medium potency steroid such as triamcinolone 1% cream to the affected area. In cases in which higher potency topical corticosteroids are necessary, preparation of 0.05% betamethasone dipropionate applied once daily to the affected area for 2 weeks is appropriate. Moderate to severe cases may be treated with topical calcineurin inhibitors or systemic therapy in consultation with the patient's internist, dermatologist, or rheumatologist. In nearly all cases of SLE, avoidance of sun exposure is advisable and will help minimize cutaneous disease.

SPECIAL CONSIDERATIONS

Antiphospholipid Syndrome

Foundations

Present in approximately 15% of patients with SLE, APS is considered when patients both have a clinical history of thrombosis and test positive for one or more antiphospholipid (aPL) antibodies. These antibodies include those corresponding to anticardiolipin, lupus anticoagulant, and β_2-glycoprotein I. The thrombotic risk profile varies based on which antibody or combination of antibodies are present. In addition to its role as a strong risk factor for both venous and arterial thrombosis, the presence of APS in SLE has been shown to be an independent predictor of more severe disease. Whether it is present in the context of SLE or independently, APS is an important cause of morbidity and mortality due to thrombosis.

Clinical Features

APS may present with a number of clinical features (Box 105.1), typically related to thrombosis or thromboembolism. A small subset of those with APS may present with multiple thrombotic sites or multiorgan failure due to microvascular thrombosis. Catastrophic APS (CAPS) is diagnosed when three or more sites or organs are affected.[9,10]

Diagnostic Testing

Similar to the workup for other hypercoagulable conditions, diagnostic testing for APS is unlikely to be indicated in the ED setting. Assays detecting the presence of aPL antibodies (anticardiolipin, lupus anticoagulant, and β_2-glycoprotein I), at two timepoints 12 weeks apart, are necessary for the laboratory component of the diagnosis of APS. Two additional laboratory findings that are supportive of APS (though not diagnostic) are a spuriously elevated PTT in the setting of a normal PT/INR, due to interference of the coagulation study by aPL antibodies, or a falsely positive Venereal Disease Research Laboratory (VDRL) assay to test for syphilis, as the antigen in the VDRL test contains cardiolipin.

Management

For acute thrombotic events, anticoagulation with heparin (unfractionated or low–molecular-weight) is generally indicated. After an initial thrombotic event, anticoagulation with a low–molecular-weight heparin or vitamin K antagonists such as warfarin is recommended indefinitely. Direct oral anticoagulants carry an increased risk of thrombosis compared to vitamin K antagonists and therefore are not recommended for first-line treatment. For patients with catastrophic APS, in addition to anticoagulation and glucocorticoids, intravenous immune globulin (IVIG), immunosuppressive agents, and plasma exchange may all be indicated. Arrangement of these therapies can be considered in discussion with the relevant consultants (e.g., rheumatology, hematology, nephrology). Despite treatment, mortality for catastrophic APS approaches 50%.

Drug-Induced Lupus

Drug-induced lupus is an SLE-like, self-resolving illness characterized by arthralgias, myalgias, rash, and serositis. It may be brought on by as many as 80 different medications, including hydralazine, isoniazid, and tumor-necrosis factor (TNF) alpha inhibitors. Notably, the malar rash and major organ involvement are rare in this condition. In drug-induced lupus, antibodies against the body's own histone proteins are common and purported to be a major mechanism of disease. Although the list of potentially implicated medications is long, those agents with the most evidence for causing drug-induced lupus are summarized in Box 105.2. The diagnosis is typically clinical and confirmed by resolution of symptoms with the withdrawal of the offending medication. In addition to cessation of the culprit drug, NSAIDs or glucocorticoids may be prescribed for control of symptoms in the interim.

DISPOSITION

Disposition for the patient with SLE will vary significantly by clinical presentation. For patients with mild presentations, such as increased musculoskeletal symptom burden, uncomplicated pleurisy, or cutaneous disease, discharge with symptomatic care, return precautions, and follow-up is usually appropriate. However, patients with more acute pathology, poor insight into their disease, significant comorbidities, or weak home support may require hospitalization.

Disorders characteristic of moderate SLE flares (e.g., nephritis, pneumonitis), thrombotic events, or infectious complications in the setting of immunosuppression usually require admission for initiation or escalation of systemic therapy (e.g., glucocorticoids, anticoagulation, antibiotics) and monitoring for response to treatment. Select

BOX 105.1 Common Clinical Features of the Antiphospholipid Syndrome

Venous thrombosis
Arterial thrombosis (including stroke or transient ischemic attack)
Recurrent miscarriage
Livedo reticularis (rash)
Thrombocytopenia

patients with milder forms of illness may still be appropriate for discharge, particularly if in collaboration with the patient's rheumatologist. Admission to the intensive care unit should be considered for those who, despite initial resuscitation, suffer persistent severe circulatory or respiratory derangement.

Finally, the complexity of SLE is challenging for physicians not specialized in its many nuances and intricate pathophysiologic changes. General reasons for rheumatologic consultation or referral of patients with SLE are presented in Box 105.3.

BOX 105.2 Selected Drugs Definitively Implicated in Causing Drug-Induced Lupus

TNF alpha inhibitors
Procainamide
Hydralazine
Methyldopa
Chlorpromazine
Isoniazid
Quinidine
Minocycline

BOX 105.3 Considerations for Rheumatologic Consultation or Referral for Patients With Systemic Lupus Erythematosus

To establish a new diagnosis
To assess disease activity and severity
To provide general disease management
To manage uncontrolled disease
To manage organ involvement or life-threatening disease
To manage or prevent treatment toxicities
Special circumstances: Antiphospholipid syndrome (APS), pregnancy, surgery

Modified from Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheumatol.* 1999;42:1785–1796.

VASCULITIS

KEY CONCEPTS

- Giant cell arteritis should be considered in patients with new onset headache, visual changes, or jaw claudication combined with elevated inflammatory markers. Large-vessel vasculitides also affect the aorta and the great vessels leading to stenosis, claudication, and aneurysm formation.
- Small- and medium-vessel vasculitis syndromes should be considered in the presence of constitutional symptoms, glomerulonephritis, diffuse alveolar hemorrhage, mononeuritis multiplex, or cutaneous vasculitis.
- Many patients with established vasculitis are receiving high-intensity immunosuppression, making them vulnerable to opportunistic infections and sepsis.

FOUNDATIONS

The vasculitides are a heterogeneous group of disorders characterized by inflammation of blood vessel walls. Arteries and veins of all sizes can be affected to varying degrees. Presentations can range from benign and self-limited to serious and life-threatening. Diagnosis can be challenging, as early vasculitis syndromes are nonspecific and can mimic infectious, inflammatory, or neoplastic conditions. Approximately 1 in 2000 adults are affected by some form of vasculitis, with a higher incidence in adults in their sixth to eight decades of life.

Most vasculitis syndromes are idiopathic, although infection, medications, or recreational drugs can be causative. The pathophysiology of vasculitic conditions is complex and heterogenous; however, two overarching mechanisms play a role. Inflammation in blood vessel walls results in wall damage and necrosis, leading to stenosis, occlusion, and subsequent end-organ ischemia. In addition, a number of symptoms such as fever, fatigue, and joint pain are caused by a generalized systemic inflammatory process. Serologic testing, imaging, and biopsy all have a role in the diagnostic workup that at times can begin in the ED setting. In addition, empiric treatment is sometimes necessary to avoid end-organ damage.

Early recognition of vasculitis is critical, as these conditions can lead to irreversible end-organ damage and, if untreated, have a high mortality rate. While vasculitis can affect almost any organ system, the recognition of cardinal features that are common across multiple vasculitic conditions is critical to diagnosis. Constitutional symptoms such as fever, night sweats, weight loss, joint pain, and fatigue are common to all vasculitic syndromes. However, other manifestations vary considerably by the size of the blood vessel involved; therefore, large-vessel vasculitides differ markedly in their presentation from medium- and small-vessel vasculitides, which have overlapping features.[11] Table 105.3 summarizes the common and unique features of different vasculitides.

LARGE-VESSEL VASCULITIS

Large-vessel vasculitis involves the aorta and its immediate branches and is generally caused by giant cell arteritis (GCA) and Takayasu arteritis (TAK). These two vasculitides have a similar distribution of large-vessel involvement but differ in two important respects. GCA typically presents with cranial symptoms caused by involvement of the branches of the external carotid artery and affects patients older than 50 years of age. TAK in contrast does not have the same cranial features and generally affects younger patients.

Giant Cell Arteritis

Background

GCA, also known as temporal arteritis, is a systemic vasculitis that affects the aorta and its branches as well as the branches of the external carotid artery, which are medium and small arteries.[12] The disease typically occurs in patients over 50 with the highest incidence in the eighth decade of life. It is the most common vasculitis in older patients. Women are affected more commonly than men. GCA is most common in patients of Scandinavian descent, and the disease is relatively rare in black patients. The most feared complication of GCA is irreversible vision loss, occurring in up to one-third of patients. Early treatment can help prevent this complication, and thus the diagnosis is an important consideration in patients older than 50 years old presenting with any combination of constitutional symptoms, headache, visual changes, jaw claudication, or symptoms of polymyalgia rheumatica,

TABLE 105.3 Common and Unique Features of Vasculitides

Vasculitis	Common Clinical Features	Unique Clinical Features
LARGE-VESSEL VASCULITIS		
Takayasu arteritis	Aortitis Vasculitis of great vessels Diminished pulses Claudication	Carotidynia
Giant cell arteritis		Headache, visual changes, jaw claudication, scalp tenderness, polymyalgia rheumatica
MEDIUM-VESSEL VASCULITIS		
Polyarteritis nodosa	Mononeuritis multiplex Mesenteric ischemia	Cutaneous ulcers, nodules, renal infarcts, testicular involvement Does not cause glomerulonephritis or lung involvement
SMALL-VESSEL VASCULITIS		
ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	Glomerulonephritis Diffuse alveolar hemorrhage	Granulomatous manifestations such as destructive sinusitis, nasal crusting, pulmonary nodules, retroorbital mass
Microscopic polyangiitis	Mononeuritis multiplex Mesenteric ischemia	Similar to GPA but without granulomatous manifestations
Eosinophilic granulomatosis with polyangiitis	Purpura	Eosinophilia, asthma, nasal polyps, cardiac involvement
Immune Complex Mediated Vasculitis		
Cryoglobulinemic vasculitis	Glomerulonephritis Palpable purpura Mononeuritis multiplex GI involvement	Associated with hepatitis B and C, lupus, Sjögren syndrome
IgA vasculitis		Rare in the absence of skin lesions Does not typically cause mononeuritis multiplex or pulmonary involvement Intussusception is unique

which is characterized by the subacute onset of symmetric shoulder and pelvic girdle pain and prominent morning stiffness.

Clinical Features

GCA symptoms typically develop over weeks. Headache, the most common presenting symptom, occurs in three-quarters of patients with GCA. Although it is classically described as temporal, the headache of GCA can occur in any location. The most salient historical feature is that the headache is new or markedly different from prior headaches. Temporal artery tenderness or other abnormalities on examination increase the probability of GCA but are not sensitive for the diagnosis. Constitutional symptoms are present in more than half the patients. Visual symptoms are also common and importantly can herald visual loss. GCA can present with a variety of visual symptoms; however, the presence of unexplained amaurosis fugax or double vision should raise particular concern in the appropriate clinical setting. Jaw claudication is a particularly important symptom because, when present, it is the most specific GCA feature. Importantly, jaw claudication should be distinguished from temporomandibular joint (TMJ) disorder, which is much more common. Jaw claudication only occurs with chewing, resolves completely with rest, and tends to be reproducible over time. In contrast to TMJ disorder, it does not occur with mouth opening or other specific motions of the jaw not associated with chewing. Scalp tenderness occurs in up to a third of patients and is typically described as superficial discomfort with pressure such as lying on a pillow. Finally, polymyalgia rheumatica (PMR), which manifests as the subacute onset of symmetric shoulder and pelvic girdle pain and prominent morning stiffness, is present in nearly half of GCA patients and represents another important clue to the diagnosis. It should be kept in mind that PMR is relatively common and, in up to 90% of cases, exists without GCA.

The large-vessel manifestations of GCA are similar to those of TAK. Involvement of the subclavian, axillary, or iliac arteries can lead to extremity claudication. Aortitis can lead to aneurysm formation and rupture. Thoracic aortic aneurysms are up to 17 times more likely to occur in patients with GCA compared with age-matched controls, and abdominal aortic aneurysm formation is twice as common. Involvement of vertebral-basilar arteries can lead to posterior circulation stroke. Other intracranial circulation is typically spared.

Diagnostic Testing

Inflammatory markers (ESR and CRP) should be evaluated when GCA is suspected. Normal inflammatory markers argue strongly against GCA, as more than 95% of patients have elevated markers at diagnosis. Temporal artery biopsy is the gold standard for diagnosis with sensitivity ranging from approximately 50% to 90%. Therefore, the diagnosis should be suspected even with a negative biopsy if suggestive clinical features are present in the setting of markedly elevated inflammatory markers without an alternative explanation. Increasingly, temporal artery ultrasound is being used in centers with experienced operators prior to biopsy. Demonstration of the halo sign around involved vessels is specific and can potentially eliminate the need for a biopsy. However, in patients with moderate to high suspicion of the disease and a negative ultrasound, biopsy should be pursued. Ophthalmologic evaluation is indicated for patients with acute visual symptoms. Fundoscopic examination can detect arteritic ischemic optic neuropathy, which is highly suggestive of GCA. The role of large-vessel imaging with CTA, MRA, or PET-CT is evolving.

Management

Patients with a moderate to high suspicion for GCA and no contraindication should be treated empirically with glucocorticoids, while simultaneously undergoing the diagnostic workup, to prevent visual loss. A typical initial regimen is oral prednisone 1 mg/kg. For patients with severe visual symptoms such as double vision or amaurosis fugax, admission for intravenous glucocorticoids (typically methylprednisolone 1 g daily for 3 days) can be considered. Tocilizumab (an IL-6 inhibitor) has recently been approved for the treatment of GCA in combination with glucocorticoids.[13] Initiation of tocilizumab should be made in consultation with rheumatology.

Takayasu Arteritis

Background

TAK is a systemic large-vessel vasculitis of unknown etiology.[14] It is eight times more common in women and is most prevalent in Asia, although it occurs worldwide. TAK typically affects a much younger population than GCA, with most patients diagnosed before the age of 40.

Clinical Features

TAK affects a similar distribution of arteries as GCA with the aorta and its branches being typically involved. However, in contrast to GCA, TAK typically presents with symptoms of more advanced vascular occlusion. This may be due to the absence of cranial symptoms as a heralding feature which leads to earlier diagnosis in GCA. The most common presenting symptoms include claudication (most commonly of the upper extremity, 35%), reduced or absent pulse (25%), hypertension (20%), or asymmetrical arm blood pressures (15%). Internal carotid artery involvement commonly causes carotidynia, lightheadedness, or headaches in approximately 20% of patients. In contrast to GCA, other cranial symptoms such as visual changes, scalp tenderness, and jaw claudication are absent. Aortitis can lead to aneurysm formation and aortic insufficiency. Constitutional symptoms are common in the early phase of the disease but are frequently absent in the stenotic phase when the disease is often diagnosed.

Diagnostic Testing

The diagnosis is made on the basis of clinical assessment and diagnostic imaging. Patients who present with symptoms of large-vessel occlusive disease (bruit, absent pulse, claudication) are candidates for imaging of the aorta and its major branches with CTA, MRA, or PET-CT.[15] Inflammatory markers are elevated in approximately 70% of patients with active disease. It should be noted that large-vessel vasculitis on imaging must be distinguished from atherosclerotic disease and noninflammatory vasculopathies, such as fibromuscular dysplasia or Ehlers Danlos syndrome, among others. Vasculitis typically causes long smooth stenoses and vessel wall thickening. In contrast, noncalcified atherosclerotic lesions cause focal stenoses. Noninflammatory vasculopathies generally cause beading, dissection, and aneurysm formation, rather than stenotic lesions and vessel wall thickening.

Management

TAK is managed with glucocorticoids in combination with steroid-sparing agents such as methotrexate, tumor-necrosis alpha inhibitors, or IL-6 inhibitors. Glucocorticoids are typically started at 60 mg and tapered over 6 to 12 months. Choice of steroid-sparing agent should be discussed with rheumatology. Surgical revascularization is reserved for patients with refractory stenotic lesions whose inflammatory disease is well controlled.

SMALL AND MEDIUM VESSEL VASCULITIS

Background

Small-vessel vasculitides as a group are the most common vasculitis syndromes. Polyarteritis nodosa, the only medium-vessel vasculitis affecting adults, is relatively rare but shares some common features with small-vessel diseases. Therefore, we will consider small- and medium-vessel vasculitis together.

Clinical Features

While each vasculitis causes multiple manifestations, it is important to recognize that there are common features shared by most small-vessel vasculitides which should alert the provider to consider this set of conditions. Specifically, the presence of DAH, glomerulonephritis, mononeuritis multiplex, mesenteric ischemia not due to atherosclerosis, or palpable purpura should prompt consideration of a small- or medium-vessel vasculitis. Joint pain and constitutional symptoms are also common to all forms of vasculitis.

DAH typically manifests with dyspnea and hemoptysis. Respiratory symptoms and signs of impaired gas exchange may develop before a drop in the hemoglobin level, which may be seen in cases of severe or persistent bleeding. It should be noted that hemoptysis is absent in approximately one-third of patients with DAH. CT imaging typically reveals diffuse ground-glass or consolidative opacities that must be differentiated from pulmonary edema or infection. The diagnosis is made on bronchoscopy with serial bronchoalveolar lavages returning increasingly bloody fluid. It should be noted that infection can also cause DAH.

Glomerulonephritis is typically asymptomatic although rarely patients will notice macroscopic hematuria. The key to diagnosis is an active urinary sediment with proteinuria and hematuria with red blood cell casts and dysmorphic RBCs. Pulmonary-renal syndrome, with both DAH and glomerulonephritis, is a classic presentation of small-vessel systemic vasculitis and anti-glomerular basement membrane (anti-GBM) disease.

While vasculitis can cause any type of peripheral neuropathy, the most common is mononeuritis multiplex, which is uncommon in other diseases. This condition generally affects large sensorimotor nerves in an asymmetric distribution. Patients may present with a combination of foot or wrist drop associated with sensory deficits, or less commonly cranial neuropathy occurring in an asymmetric manner over time.

Gastrointestinal manifestations are less common and can be nonspecific. However, symptoms of chronic mesenteric ischemia in the setting of elevated inflammatory markers or other systemic features without an alternative explanation, such as atherosclerotic disease, should prompt consideration of a small- or medium-vessel vasculitis.

The most common cutaneous manifestation of vasculitis is palpable purpura. Palpable purpura typically involves the lower extremities, is nonblanching, and is not painful or pruritic. A biopsy may be needed to distinguish the lesions of vasculitis from other causes of purpura.

Differential Diagnosis

A useful approach to vasculitis is to first recognize the common features of small- and medium-vessel vasculitis. Second, when evaluating patients with suspected vasculitis, it is important to confirm the scope of the disease by evaluating organs that may be asymptomatic such as the lung and kidneys. Finally, because these vasculitic features should prompt a workup for vasculitis but do not differentiate well between the various types of small- and medium-vessel vasculitis, it is important to focus on the differentiating features of each vasculitic condition to make a specific diagnosis. The differentiating

features include clinical symptoms, laboratory testing, and biopsy results.

Small-vessel vasculitides can be broadly divided into anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and vasculitis caused primarily by immune-complex deposition. There are three ANCA-associated vasculitides: granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome).[16] Immune complex vasculitides include cryoglobulinemic vasculitis, IgA vasculitis (IgAV, formerly Henoch–Schonlein purpura), drug-induced vasculitis, and connective tissue disease-associated vasculitis. Anti-GBM (Goodpasture disease) is not a true vasculitis but should be considered in the setting of either glomerulonephritis or pulmonary hemorrhage. Polyarteritis nodosa (PAN) is a medium-vessel vasculitis that shares some features with small-vessel diseases.

Specific Disorders

ANCA-Associated Vasculitis

Granulomatosis With Polyangiitis. GPA is a granulomatous vasculitis affecting small- and medium-sized vessels. It affects individuals in their fifth and sixth decade of life most commonly and has a slight male predominance. In addition to the vasculitic manifestations such as glomerulonephritis, DAH, mononeuritis multiplex, and palpable purpura, GPA is unique in that it causes "granulomatous" manifestations, mainly sinusitis and mass lesions. Sinusitis is one of the most common manifestations of GPA. The presence of significant nasal crusting may alert the physician to the presence of an inflammatory process because crusting is typically absent in allergic and bacterial sinusitis. Bony destruction and nasal septal perforation are other distinguishing features that may be present. In addition, GPA can cause pulmonary nodules (Fig. 105.5), bronchial lesions, retroorbital mass, or subglottic stenosis. Sensorineural hearing loss or otitis media can also be seen. Limited GPA is a well-recognized subset of disease and can present only with chronic sinusitis or other granulomatous features without vasculitic features.

The presence of ANCA in the appropriate clinical setting is highly suggestive of the diagnosis. It should be noted that when renal involvement is present, ANCA sensitivity is approximately 90% but drops to approximately 60% in nonsevere diseases without renal involvement. GPA is typically associated with proteinase 3 (PR3)-ANCA (c-ANCA immunofluorescence pattern). If the diagnosis is uncertain, biopsy of the affected organ should be performed. Pathology generally demonstrates vasculitis without significant immune complex deposition. Granulomatous inflammation may also be present.

Treatment of GPA requires the combination of glucocorticoids and another immunosuppressant (typically rituximab or cyclophosphamide).[17] In patients with glomerulonephritis or pulmonary hemorrhage, pulse dose glucocorticoids (methylprednisolone 1 g IV for 3 days) are often used. Plasma exchange has been used previously in severe cases, but recent studies have questioned the utility of this modality, except when ANCA-associated vasculitis occurs with anti-GBM disease.

Microscopic Polyangiitis. MPA is a non-granulomatous vasculitis affecting small- and medium-sized vessels. MPA most commonly affects patients in their sixth and seventh decades and has a relatively equal sex distribution. It shares the same vasculitic features as GPA but lacks the "granulomatous" manifestations. Therefore, sinusitis and mass lesions are not seen in MPA, and the most common presenting features include glomerulonephritis, pulmonary hemorrhage, mononeuritis multiplex, and palpable purpura. Diagnosis relies on the presence of myeloperoxidase (MPO)-ANCA (p-ANCA immunofluorescence pattern) that is present in approximately 70% of patients. If ANCA is negative or the diagnosis is uncertain, biopsy typically demonstrates findings of vasculitis lacking both immune complex deposition and granulomatous inflammation. Treatment is identical to that of GPA with a combination of glucocorticoids and rituximab or cyclophosphamide.

Eosinophilic Granulomatosis With Polyangiitis. EGPA is an eosinophilic vasculitis of small and medium vessels.[18] Mean age of the diagnosis is in the fourth and fifth decade with men and women equally affected. While it shares vasculitic features with GPA and MPA, it has a number of unique features related to the eosinophilic infiltration of organs. Over 90% of patients develop asthma as one of the first manifestations, typically preceding vasculitic features. The asthma is often severe, requiring treatment with agents such as prednisone. Migratory ground-glass opacities on CT chest imaging are common and may help differentiate EGPA from severe asthma. Allergic rhinitis and nasal polyps are also frequent. Eosinophilic myocarditis, which can present with arrhythmia or heart failure, is another unique feature, present in 10% to 20% of patients. Notably, cardiac involvement has been suggested to account for nearly half of the deaths due to EGPA.

All patients with EGPA have prominent peripheral eosinophilia, typically above 1000 cells/μL, which is not a feature of other vasculitides. It should be kept in mind that treatment with glucocorticoids markedly

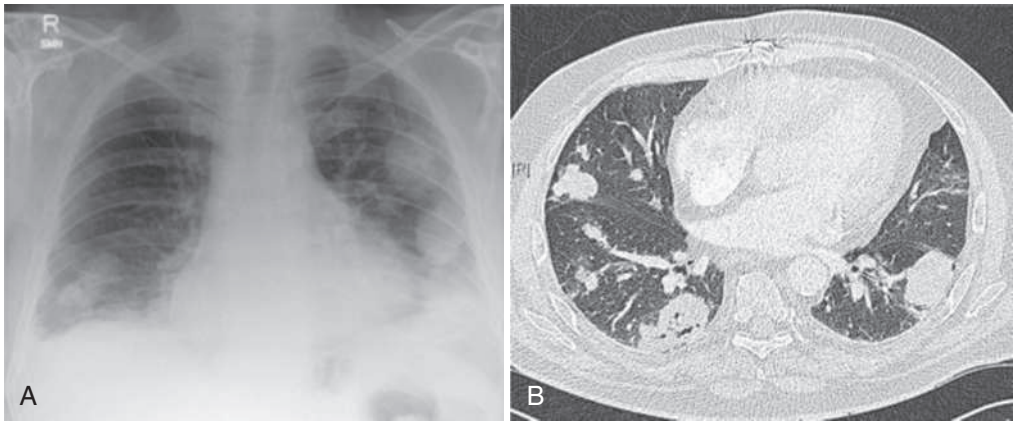

Fig. 105.5 (A) Multiple intrapulmonary nodules on a chest radiograph of a patient with granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis). (B) Pulmonary nodules seen on computed tomography (CT) imaging. (From Adam A, Dixon AK. *Grainger & Allison's Diagnostic Radiology*. 5th ed. Philadelphia: Churchill Livingstone; 2008.)

reduces peripheral eosinophilia; therefore, it may be absent in patients already receiving glucocorticoids. Differentiating EGPA from severe atopic disease or hypereosinophilic syndrome can be challenging. Generally, atopic disease lacks end-organ involvement outside of the lung, while hypereosinophilic syndromes lack asthma and vasculitic features. The diagnosis relies on the presence of MPO-ANCA, which is only seen in 50% of patients, or eosinophilic vasculitis on biopsy. Treatment of EGPA is dictated by disease severity. Severe vasculitic manifestations are generally treated similarly to GPA and MPA with a combination of pulse intravenous glucocorticoids and rituximab or cyclophosphamide. Patients without severe vasculitis may be treated with glucocorticoids alone or in combination with mepolizumab (anti-IL-5), methotrexate, azathioprine, or mycophenolate mofetil.

Anti-Glomerular Basement Membrane Disease (Goodpasture Disease)

Anti-GBM disease is caused by disruption of the basement membrane by circulating anti-GBM antibodies causing glomerulonephritis with or without alveolar hemorrhage.[19] The disease can affect individuals of all ages, with white patients more commonly affected. The incidence is bimodal; one peak occurs in 20- to 30-year-old men, and a second in 50- to 70-year-olds of both sexes. Because it is not a vasculitis per se, other vasculitic features are generally absent. The diagnosis is made by the presence of anti-GBM antibodies and demonstration of crescentic glomerulonephritis with linear staining along the basement membrane on immunofluorescence. Treatment requires the addition of plasma exchange to a combination of prednisone and cyclophosphamide. Of note, ANCA-associated vasculitis and anti-GBM disease can coexist; treatment of this syndrome is similar to that of anti-GBM disease alone.

Immune Complex Mediated Vasculitis

IgA Vasculitis. IgAV, formerly known as Henoch-Schonlein purpura, is a small- and medium-vessel vasculitis that is characterized by IgA deposition in vessel walls.[20] It is more common in children than adults at an approximately 3:1 ratio. IgAV has a strong association with infection, with 50% of cases occurring after an upper respiratory tract illness. It can also occur as a manifestation of a drug reaction. In contrast to other vasculitides, it does not typically involve the lung or the peripheral nervous system. The three organ systems typically affected are the skin, kidneys, and gastrointestinal tract. Joint pain and constitutional symptoms are also frequent. Skin manifestations, most commonly palpable purpura, are present in essentially all adults and the majority of children as the initial manifestation (Fig. 105.6). This is in contrast to other systemic vasculitides, where any of the manifestations can be the presenting feature. Gastrointestinal symptoms are nonspecific; intussusception is the most common finding, in contrast to other vasculitides where mesenteric ischemia tends to be the most common gastrointestinal presentation. Renal involvement manifests as hematuria most commonly but can be more severe with nephritic syndrome, particularly in adults, who have a worse renal prognosis. In children, the diagnosis is commonly made clinically, as it is much more common than other vasculitides. The diagnosis in adults typically requires a biopsy. Biopsy of an affected organ will demonstrate IgA deposition in vessel walls. IgAV is typically a self-limited illness. NSAIDs (e.g., naproxen 500 mg BID or ibuprofen 800 mg TID) can be helpful for fever and joint pain. Treatment with glucocorticoids should be considered in patients with severe renal or gastrointestinal manifestations. Similar to other vasculitides, prednisone should be started at 1 mg/kg or pulse intravenous dosing 1 g/day for 3 days in cases of severe end-organ involvement.

Cryoglobulinemic Vasculitis. Cryoglobulinemic vasculitis is characterized by a primarily small-vessel vasculitis in association with cryoglobulins in the peripheral blood, which are proteins that precipitate at temperatures below 37°C.[21] There are three types of cryoglobulins. Type I is typically associated with Waldenstrom macroglobulinemia and causes a hyperviscosity syndrome rather than a vasculitis. In contrast, types II and III cause vasculitis and are associated with chronic hepatitis C infection, malignancy, or autoimmune diseases (SLE, Sjögren's). Cryoglobulinemia can also be idiopathic. Cryoglobulinemic vasculitis generally causes vasculitic features such as glomerulonephritis, mononeuritis multiplex. palpable purpura, nonspecific myalgias, and arthralgias, or weakness are particularly common, while DAH is relatively uncommon. Diagnosis is made by demonstrating the presence of cryoglobulins in the bloodstream. Biopsy of an affected organ can be helpful if the diagnosis remains uncertain. Treatment includes immunosuppression if end-organ involvement is present, similarly to other vasculitides, and treating the precipitating illness (e.g., HCV).

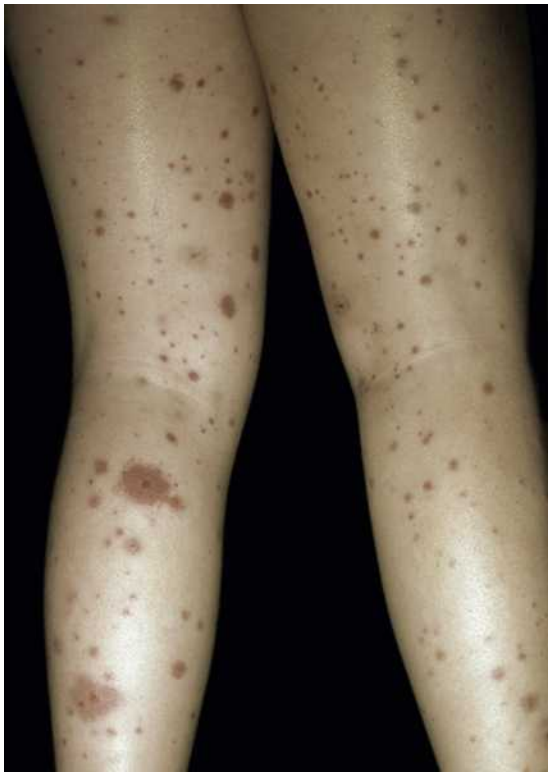

Fig. 105.6 Purpuric Lesions Associated with IgA Vasculitis, Some of Which Have Coalesced and Undergone Central Necrosis. (From Habif TP. *Clinical Dermatology*. 5th ed. New York: Mosby; 2009.)

Polyarteritis Nodosa

Polyarteritis nodosa is a necrotizing vasculitis primarily affecting medium-sized arteries.[22] It affects patients in their fifth and sixth decade of life and has a slight male predominance. A small percentage of cases are associated with hepatitis B infection. In contrast to the small-vessel vasculitides, it does not typically involve the lung and does not cause glomerulonephritis, as both of these manifestations are due to small-vessel involvement. The renal manifestations of PAN are typically reno-vascular hypertension or renal infarcts. Similarly, cutaneous features of PAN are typically ulcers or nodules rather than palpable purpura. However, similarly to the small-vessel vasculitides, PAN can cause mononeuritis multiplex, mesenteric ischemia, joint pain, or constitutional symptoms. A unique manifestation is testicular involvement. There are no antibodies associated

with PAN. Diagnosis is made by either biopsy of the involved organ demonstrating a medium-vessel vasculitis or abdominal imaging demonstrating characteristic microaneurysms in the splanchnic vasculature. Treatment includes glucocorticoids and another immunosuppressant, most commonly cyclophosphamide. Glucocorticoid dosing is similar to other vasculitides with pulse dosing for severe end-organ involvement and prednisone 1 mg/kg for less severe end-organ involvement.

Other Vasculitides

Behçet Disease. Behçet disease (BD) is a vasculitis that affects all blood vessel sizes and is characterized by the presence of recurrent oral aphthous ulcers.[23] It affects populations living along the Silk Road most commonly, such as Turkey, Saudi Arabia, Iraq, Iran, and China, but can occur in any part of the world. In contrast to other vasculitides, the typical manifestations of vasculitis such as glomerulonephritis, DAH, mesenteric ischemia, peripheral neuropathy, or palpable purpura are rare. The most common manifestations include inflammatory eye disease such as uveitis, genital ulcers, and various skin manifestations including erythema nodosum (Fig. 105.7), among others. Gastrointestinal manifestations mimic those of Crohn's disease. Importantly, because BD can involve large vessels, it can cause aneurysmal arterial lesions with resultant rupture as well as DVT, including Budd-Chiari syndrome or cavernous sinus thrombosis. Uniquely, BD can also cause central nervous system disease, with a predilection for the brainstem.

Diagnosis is made on clinical grounds. BD should be considered in patients with recurrent oral ulcers (Fig. 105.8) and the presence of genital ulcers, inflammatory eye disease, or other systemic features. In the evaluation for BD, it is important to exclude other causes of oral and genital ulceration, in particular, herpes simplex virus infection. Treatment is guided by disease severity. Mucocutaneous manifestations are generally treated with colchicine. Internal organ involvement requires glucocorticoids 1 mg/kg or pulse dosing in severe end-organ involvement. Another immunosuppressant such as azathioprine, cyclophosphamide, or TNF alpha inhibitors should be considered with end-organ involvement in consultation with rheumatology. Notably, DVT associated with BD generally requires treatment with immunosuppression, which has been shown to decrease the rate of recurrence. Anticoagulation should be considered on an individualized basis.

Cutaneous Vasculitis. Cutaneous small-vessel vasculitis (CSVV) is the most common single-organ vasculitis.[24] It has been previously known as hypersensitivity vasculitis or leukocytoclastic vasculitis, among others. CSVV can occur as a manifestation of a drug reaction or be idiopathic. It is only distinguished clinically from the systemic vasculitides such as ANCA-associated vasculitis, IgAV, and cryoglobulinemia due to the absence of other systemic symptoms, negative serology, and absence of IgA deposition on skin biopsy. Diagnosis is made on tissue biopsy with histology generally demonstrating leukocytoclastic vasculitis. It is critical to exclude systemic involvement; therefore, a urinalysis should be obtained in patients with CSVV to investigate for glomerulonephritis. Treatment may include topical corticosteroids, NSAIDs (e.g., naproxen 500 mg BID or ibuprofen 800 mg TID), colchicine (0.6 mg BID), dapsone (50 mg daily: dapsone requires lab monitoring and should be started in consultation with dermatology or rheumatology), or glucocorticoids (ranging from 20 to 60 mg daily depending on severity), among others.

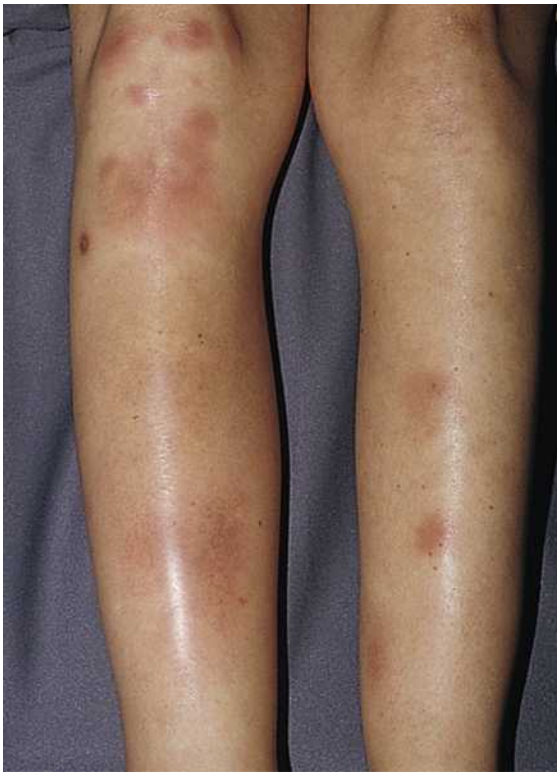

Fig. 105.7 Tender Subcutaneous Nodules Associated With Erythema Nodosum. (From Kliegman R. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia: WB Saunders; 2007.)

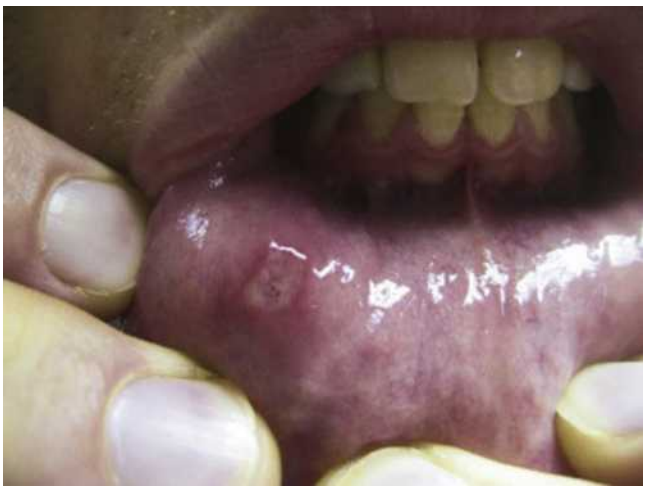

Fig. 105.8 Oral Aphthae Associated With Behçet Disease. (From Firestein GS. *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia: WB Saunders; 2008.)

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 105: QUESTIONS AND ANSWERS

1. Which of the following findings would decrease the likelihood that a patient's pleurisy is related to a lupus flare?
- **a.** Elevated erythrocyte sedimentation rate
- **b.** Low complement levels
- **c.** Negative review of systems
- **d.** Polyarthritis
- **e.** PR depression on electrocardiogram

Answer: c. The general approach to assessing whether a symptom is caused by SLE disease activity is to look for signs and symptoms of the disease in other organs or systemically. Patients experiencing an SLE flare are likely to have other signs or symptoms of disease (e.g., arthralgias, fever, malaise, elevated ESR, low complement levels) beyond an isolated chief complaint (in this case, pleurisy). PR depression can be suggestive of pericarditis, which may occur during flares of SLE.

2. A patient with a history of SLE presents actively seizing. In addition to respiratory support, what is the most appropriate initial step in management?
- **a.** Intravenous ceftriaxone and vancomycin
- **b.** Intravenous cyclophosphamide
- **c.** Intravenous lorazepam
- **d.** Intravenous methylprednisolone
- **e.** Intravenous tissue plasminogen activator

Answer: c. In nearly all cases (including seizure), the initial resuscitation and stabilization of the patient with SLE are the same as for patients without SLE. While this patient could have meningitis, lupus cerebritis, or a stroke, which could warrant some of the other treatments listed, the patient should be stabilized by treatment of the seizure first.

3. Which of the following symptoms is least likely to be seen in a patient presenting with giant cell arteritis?
- **a.** Amaurosis fugax
- **b.** Constitutional symptoms
- **c.** Dysphagia
- **d.** Jaw claudication
- **e.** Scalp tenderness

Answer: c. Patients presenting with giant cell arteritis (GCA) commonly have constitutional symptoms. Other presenting symptoms include headache and scalp tenderness. Jaw claudication is relatively specific for GCA, and visual symptoms (e.g., amaurosis fugax) may herald impending blindness from the disease if not treated. Dysphagia is not a presenting feature of GCA.

4. A patient with a history of SLE presents with acute bilateral arm weakness and decreased sensation below the clavicles starting 90 minutes prior to arrival. A CT of the head is normal, and an MRI of the brain and spine reveals T2 hyperintensity in the cervical spine. Which of the following is the most appropriate next step in management for this patient?
- **a.** Intravenous ceftriaxone and vancomycin
- **b.** Intravenous lorazepam
- **c.** Intravenous methotrexate
- **d.** Intravenous methylprednisolone
- **e.** Intravenous tissue plasminogen activator

Answer: d. This patient is presenting with transverse myelitis. The first line of treatment for this condition is high-dose glucocorticoids, such as methylprednisolone, and since this patient has a history of SLE, cyclophosphamide. Refractory cases may be treated with plasma exchange and additional immunosuppressive agents.

Continued

CHAPTER 105: QUESTIONS AND ANSWERS—cont'd

5. A patient with a history of SLE presents with shortness of breath. CT angiography reveals two segmental pulmonary emboli. Laboratory testing and bedside echocardiography are unremarkable. Chart review reveals positive anticardiolipin and β2-glycoprotein I titers. Which of the following is the most appropriate next step in therapy for this patient?

a. Aspirin
b. Enoxaparin
c. Rivaroxaban
d. Tissue plasminogen activator
e. Warfarin

Answer: b. This patient has SLE and antiphospholipid syndrome (APS) based on the history of thromboembolic disease and positive antiphospholipid (aPL) antibodies. The most appropriate anticoagulation for patients with APS is a vitamin K antagonist (e.g., warfarin) or a heparin analog (e.g., enoxaparin). In the acute setting, however, a heparin analog should be used due to the delayed therapeutic effect of vitamin K antagonists. Aspirin is insufficient to treat acute thromboembolic disease in APS, and direct oral anticoagulants have decreased efficacy when compared to vitamin K antagonists and heparin analogs. This patient does not have an indication for tissue plasminogen activator.

106

Allergy, Anaphylaxis, and Angioedema

Aaron N. Barksdale and Weston Ross

KEY CONCEPTS

- Anaphylaxis is a life-threatening systemic allergic (or nonallergic) reaction of acute onset and multiorgan involvement in which timely recognition and treatment remain essential.
- A history of sudden urticarial rash accompanied by respiratory difficulty, abdominal pain, or hypotension, strongly favors the diagnosis of anaphylaxis.
- The recommended treatment algorithm for anaphylaxis is shown in Box 106.7.
- Epinephrine is the first-line treatment in patients with anaphylaxis and should be given immediately. There are no absolute contraindications to the use of epinephrine in the setting of anaphylaxis.
- Antihistamines and corticosteroids are second- and third-line agents in the management of anaphylaxis and should not replace or precede epinephrine.
- Consider prolonged observation or admission for patients who (1) experience protracted anaphylaxis, hypotension, airway involvement, or unknown trigger; (2) receive IV epinephrine or more than one dose of IM epinephrine; or (3) have poor outpatient social support.
- Patients discharged after an anaphylactic event should be prescribed self-injectable epinephrine devices and instructed on use, encouraged to develop an emergency action plan, and referred to an allergist/immunologist.
- Patients with refractory hypotension may require a continuous IV epinephrine infusion or glucagon in patients with coexisting beta-adrenergic blockade).
- Non-histaminergic angioedema (nonallergic angioedema) does not typically respond to epinephrine and antihistamines, though they should be considered at initial presentation. Newer drugs, including icatibant, ecallantide, and human or recombinant C1 esterase inhibitor, have been approved for use in hereditary angioedema (HAE). Fresh frozen plasma (FFP) has been used with varying success in HAE, acquired C1 esterase inhibitor deficiency (ACID), and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema.

ALLERGY

FOUNDATIONS

Background and Terminology

The prevalence of allergic disease has significantly increased over the past several decades, particularly in developed societies. It is currently estimated that 30% of the worldwide population suffer from some component of allergy, including 5% to 8% with food allergies. This has contributed to increased financial burdens on our health care systems and morbidity in affected individuals.[1–4] This is largely attributed to changes in lifestyle, diet, antibiotic use, smaller families, and the "hygiene hypothesis," which centers around decreased microbial exposure in developed countries.[1,3]

The human immune system comprises cellular and humoral components working together in a highly complex and coordinated fashion to achieve the primary goal of protecting the human host from potentially harmful offenders. The immune system, however, can overreact to otherwise harmless agents, producing an inappropriate response that may be harmful to the host, thereby giving rise to allergy or allergic diseases. These hypersensitivity reactions are manifested in clinical symptoms ranging from nuisance-level to fatal. For practical purposes, the term *allergy* is used in this chapter to refer to mast cell–mediated hypersensitivity reactions. For most allergic diseases to occur, predisposed individuals require exposure to allergens through *sensitization.* Substances that elicit an allergic reaction are referred to as *allergens,* and those that elicit an antibody response are termed *antigens.*

On the allergic continuum, there are several important allergic syndromes (Fig. 106.1). *Urticaria* (wheels, hives) is a common allergic reaction to foods, drugs, temperature changes, or physical stimuli. It is clinically characterized by a raised central swelling of variable size with surrounding reflex erythema, combined with an itching or burning sensation, with the skin typically returning to its baseline appearance within 30 minutes to 24 hours.[5]

Angioedema is characterized by sudden swelling of the subcutaneous or mucous membranes and tends to be more painful than pruritic. In general, it is slower to resolve compared to urticaria, and if the tongue or larynx is involved, it can result in airway compromise.[5] Angioedema can occur through one of two different mechanisms. Allergic (histaminergic) angioedema occurs in response to exposure to foods, drugs, or physical stimuli. Nonallergic (non-histaminergic) angioedema may be hereditary (termed hereditary angioedema [HAE]) or medication-induced (e.g., angiotensin-converting enzyme [ACE] inhibitor angioedema).

At the other extreme of this allergic continuum is *anaphylaxis,* a life-threatening systemic reaction, characterized by acute onset and multiorgan involvement.[6–8] It is a type I hypersensitivity reaction (allergic), mediated by immunoglobulin E (IgE). In its most common form, anaphylaxis is precipitated by exposure to allergens in previously sensitized individuals (immunologic). Previously, the term *anaphylactoid reaction* referred to a syndrome clinically similar to anaphylaxis that is not mediated by IgE (non-immunologic). Its clinical presentation and treatment are identical to that of anaphylaxis. Non-IgE (non-immunologic) reactions appear to result from direct degranulation of mast cells (and basophils) and may follow a single, first-time exposure to certain inciting agents (e.g., NSAIDs, monoclonal antibodies, local anesthetics, chemotherapeutic drugs). The World Allergy Organization (WAO) guidelines use the term *anaphylaxis* to refer to both IgE- and

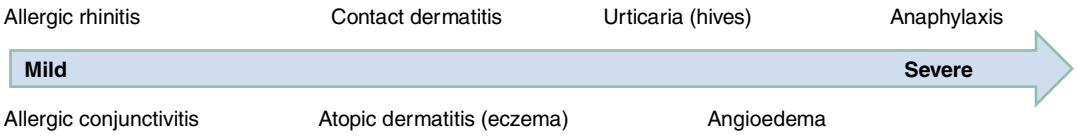


Fig. 106.1 Severity Spectrum of Allergic Disease.

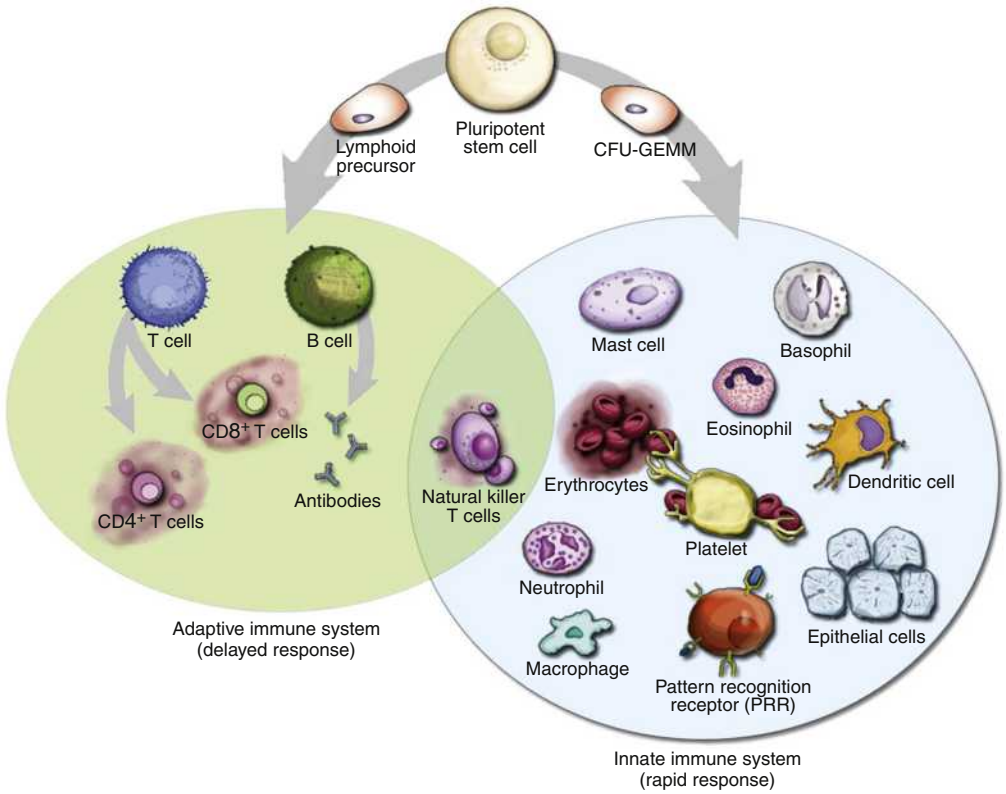


Fig. 106.2 Developmental Pathways of the Immune and Hematopoietic Systems. *CFU-GEMM,* Colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte.

non-IgE-mediated reactions, obviating the need for the term *anaphylactoid reaction,* although this term is still often used.[6,9]

Pathophysiology

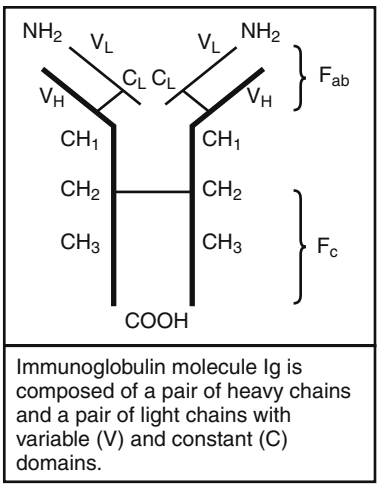
Immunologic responses to *antigens* are coordinated by two systems: the *innate* immune system, and the more recently evolved *adaptive* immune system (Fig. 106.2). The innate immune system is considered the first line of defense and is characterized by its nonspecific but rapid responses to offending agents or microbes. Its effector components include resident cells (epithelial cells, mast cells, macrophages, dendritic cells, antimicrobial proteins), infiltrative cells (natural killer cells, neutrophils, monocytes, dendritic cells), and various proteins (antimicrobial peptides, complements, cytokines, and the pathogenic pattern recognition receptor [PRR] system). The innate system responds to danger signals rapidly and nonspecifically, whereas the adaptive immune system takes time for antigen-specific cells (B and T cells) to amplify through a process known as *clonal expansion* to mount a specific immune response. The T and B lymphocytes are capable of recognizing a myriad of antigens through a vast library of antibodies and receptors (up to 10^{15}).[1,3,4]

The adaptive and innate immune systems originate from the common pluripotential hematopoietic stem cells. When the host encounters a foreign antigen, the cellular components of the adaptive immune system interact with the cellular and protein components of the innate immune system to mount a coordinated defense aimed at neutralization of the antigen.

Mast cells, basophils, and their mediators are the central effectors in allergy and anaphylaxis. Exposure of a genetically predisposed individual to an allergen leads to the synthesis and release of allergen-specific IgE by plasma cells into the circulation. Fixation of this allergen-specific IgE to surface receptors on mast cells completes the process known as *sensitization.* These IgE-bearing mast cells usually reside in the mucosal surfaces, submucosal tissue (around venules), and cutaneous surfaces, where they are capable of becoming activated on re-exposure to a specific allergen. Cross-linking of the mast cell receptors by a specific multivalent allergen sets off a cascade of conformational and biochemical events, causing the degranulation of preformed mediators, subsequent generation and release of arachidonic acid metabolites, elaboration of cytokines and chemokines, and activation of the cellular components by the innate and adaptive systems. This series of events ultimately leads to the clinical syndromes of allergy and anaphylaxis (Fig 106.3).[1,3,4]

Classification of Reactions

The term *allergy* is commonly used to describe clinical illnesses produced by excessive immune responses by a normal immune system to otherwise innocuous allergens. The classic Coombs and Gell



Immunoglobulin molecule Ig is composed of a pair of heavy chains and a pair of light chains with variable (V) and constant (C) domains.

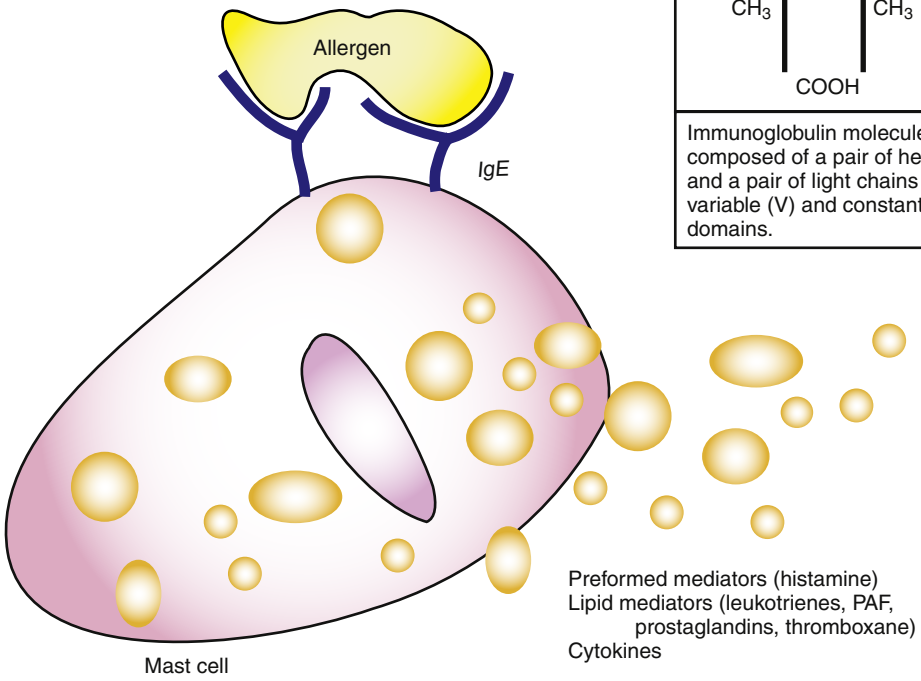


Fig. 106.3 Activation of mast cells with degranulation of mast cell mediators by antigen cross-linking of adjacent immunoglobulin E *(IgE)* on the cell surface. *PAF,* Platelet-activating factor.

BOX 106.1 Gell and Coombs Classification of Immune Reactions

Type I: Immediate Hypersensitivity
Binding of multivalent antigens to IgE on the surface of mast cells and basophils leads to degranulation of mediators. In previously sensitized individuals, the reaction develops quickly (minutes). This type of hypersensitivity reaction is seen in allergic diseases (e.g., hay fever, allergic asthma, urticaria, angioedema, and anaphylaxis). *Non-immunologic* (previously termed anaphylactoid) *reaction* refers to the direct release of preformed mediators of mast cells independent of IgE.

Type II: Cytotoxic Antibody Reaction
Antibody (IgM, IgG) binding of membrane-bound antigens leads to cytotoxicity and cell lysis of cells through the complement or mononuclear cell system (macrophages, neutrophils, and eosinophils). This type of reaction is seen in transfusion reaction and Rh incompatibility.

Type III: Immune Complex–Mediated Reaction
Binding of antibody (IgM, IgG) to antigens forms soluble immune complexes, which are deposited on vessel walls, causing a local inflammatory reaction (Arthus reaction) leading to inflammation and tissue injury. This type of reaction is seen in systemic lupus erythematosus and serum sickness (after antithymocyte globulin administration).

Type IV: Cell-Mediated Delayed Hypersensitivity
Sensitized lymphocytes (T_H1 cells) recognize the antigen, recruit additional lymphocytes and mononuclear cells to the site, and start the inflammatory reaction. No antibodies are involved. This type of reaction is seen in contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

IgE, Immunoglobulin E; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *T_H1,* type 1 helper.

classification can be adapted to categorize these hypersensitivity reactions (Box 106.1).

Type I reactions (immediate hypersensitivity) are IgE mediated and account for most allergic and anaphylactic reactions. Exposure to sensitizing allergens causes mediators from mast cells and basophils to be released through both IgE-dependent and IgE-independent (direct mast cell degranulation) mechanisms. Rhinitis caused by ragweed pollen and anaphylaxis caused by foods are examples of the IgE-dependent mechanism.

ANAPHYLAXIS

FOUNDATIONS

Epidemiology and Risk Factors

The prevalence of anaphylaxis and related hospital admissions has increased over the past two decades. The incidence is difficult to determine, but anaphylaxis is estimated to occur in roughly 2% of the

BOX 106.2 Risk Factors for Anaphylaxis and Increased Anaphylaxis Severity and Mortality

Risk Factors for Having Anaphylaxis
Age and sex
- Pregnant women, infants, teenagers, elderly

Route of administration
- Parenteral > oral

Higher social economic status
Time of the year
- Summer and fall (the outdoor seasons)

History of atopy
Emotional stress
Acute infection
Physical exertion
History of mastocytosis
Risk Factors for Increased Anaphylaxis Severity and Mortality
Extremes of age
- Very young (under-recognition)
- Elderly (decreased physiologic reserves)

Comorbid conditions
- Cardiovascular disease (heart failure, ischemic heart disease, hypertension)
- Pulmonary disease (asthma, obstructive airway disease)

Others
- Concurrent use of anti-hypertensive agents, specifically beta-blockers and angiotensin-converting enzyme (ACE) inhibitors
- Concurrent use of cognition-impairing drugs (e.g., alcohol, recreational drugs, sedatives, tranquilizers)
- Recent anaphylaxis episode
- Upright posture at the onset of symptoms

BOX 106.3 Etiologic Agents Causing Anaphylaxis by Immunologic Mechanisms

Immunologic Mechanisms (IgE-Dependent)
Foods: Peanut, tree nut, milk, egg, shellfish, soybean, cow milk, mammalian meats (after sensitization to alpha-gal protein following tick bite)
Medications: Antibiotics, NSAIDs, chemotherapeutic agents, immunomodulators
Insect stings: *Hymenoptera* venoms, fire ant stings
Natural rubber latex
Hormones: Insulin, methylprednisolone, parathormone, estradiol, progesterone, corticotropin
Local anesthetics: Mostly ester family (procaine, tetracaine, benzocaine)
RCM
Occupational allergens: Enzymes, animal protein, plant protein
Aeroallergens: Pollen, dust, spores, pet dander

Immunologic Mechanisms (Ige-Independent)
RCM
NSAIDs
Dextrans
Biologic agents: Monoclonal antibodies, immunomodulators

Non-Immunologic Mechanisms (Direct Mast Cell Activations)
Physical factors: Exercise, cold, heat, sunlight
Ethanol
Medications: Some opioids
Idiopathic (no apparent trigger)

IgE, Immunoglobulin E; *NSAID,* nonsteroidal antiinflammatory drug; *RCM,* radiocontrast media.

worldwide population and as high as 5% in the United States.[6–8,10] While fatal anaphylaxis is rare, representing less than 1% of cases, there is evidence that medication-induced fatalities are increasing in North America and that food-induced fatalities are increasing in Australia.[11]

The severity of anaphylaxis varies between different age groups depending on the specific trigger and cofactors, but in general, pregnant women, infants, teenagers, and elders have been shown to have an increased incidence of anaphylaxis.[6] Additional risk factors include atopy (genetic predisposition to develop allergic disease), peanut and tree nut allergy, emotional stress, seasonal occurrence in summer to fall months, higher socioeconomic status, premenstrual age, and the presence of acute infection. Severe anaphylaxis has been associated with poorly controlled asthma, history of mastocytosis, heavy physical exertion, exposure to a trigger during the concomitant use of certain medications (ACE inhibitors, beta-blockers, and nonsteroidal antiinflammatory drugs [NSAIDs]), history of a previous anaphylactic reaction, delayed epinephrine administration, and upright position at the onset of symptoms (Box 106.2).[6,8,10,12,13]

In general, the more rapid an anaphylaxis reaction occurs after an exposure, the more likely it is to be severe and potentially fatal. The dose, frequency, duration, and route of administration of a drug can also affect the tendency to develop an anaphylactic reaction (e.g., the parenteral route is more likely to lead to an anaphylactic reaction than the oral route).[6,7,10] One interesting aspect of drug-related anaphylaxis is the constancy of administration. An anaphylactic reaction may not occur in an otherwise susceptible patient as long as a drug is administered at regular intervals. The same patient, however, may experience an anaphylactic reaction if the drug is resumed after an interruption of therapy.

ACE-inhibitor use can cause an accumulation of kinins and bradykinin and thus can exacerbate the angioedema component of anaphylaxis. Beta-adrenergic blockers may oppose the actions of adrenergic agents used in anaphylaxis treatment. Recent evidence suggests that taking an ACE inhibitor or a beta-blocker increases the risk of severe anaphylaxis (and even more so when taken concurrently) but does not necessarily increase the incidence of initial anaphylactic reactions.[6,14]

Common Triggers for Anaphylaxis

Virtually any agent that is capable of activating mast cells or basophils can potentially precipitate an anaphylactic reaction. However, in up to 60% of adults and 10% of children, an inciting agent cannot be identified, which is classified as *idiopathic anaphylaxis*.[15] When a trigger can be determined, foods, insect stings, and medications are the most common causes. Box 106.3 lists many of the common agents by their proposed immunologic mechanism.[6,9,10,12]

Foods

Food allergens are the most common identifiable agents and represent up to a third of reported anaphylactic cases. The incidence has significantly increased over the past decade, especially among children. Symptoms typically occur within 5 to 30 minutes of ingestion with fatalities reported within 30 minutes of exposure, though in some cases onset can be significantly delayed. In particular, reactions to mammalian foods (e.g., beef and pork) can be delayed 3 to 6 hours following exposure; recent research strongly suggests sensitization to the alpha-gal protein following a tick bite in this circumstance.[16–19] The most commonly implicated foods include peanuts, shellfish, tree nuts, fish, soy, cow's milk, and eggs. Fatal outcomes have been more commonly

reported in adolescents and young adults, as well as those with a history of asthma, tree nut or peanut allergy, anaphylactic cases presenting without skin manifestations, or when epinephrine administration was delayed.[6,9–11] The majority of reactions occur after ingestion, but may also occur following inhalation of food particles or even after skin contact with vomit containing the instigating agent. In the setting of a known allergy, it may be difficult to avoid certain allergens, as their identity may be obscured during processing (e.g., consuming wine contaminated with *Hymenoptera* venom).

Drugs

Medications represent the second most frequent cause of anaphylactic reactions but are the most common trigger in adult subjects and result in the highest incidence of fatalities across all age groups. NSAIDs, antibiotics (specifically beta lactams), and neuromuscular blocking agents (NMBAs) are the most commonly reported triggers, but over the past decade, there has been a significant rise in chemotherapeutic or immunomodulator agent–related reactions.[6,10,20,21] Fatal drug-induced anaphylaxis has been associated with hypertension, obesity, male gender, beta-blocker use, and old age.[6,10,11]

Penicillin is the most common antibiotic cause of anaphylaxis. Although many report a history of penicillin allergy, studies have shown that less than 10% of individuals with a reported history of penicillin are truly allergic via skin testing. These individuals are often mislabeled as penicillin allergic at some point, or their allergy senesces after years of avoidance. Parenterally administered penicillin is responsible for the majority of anaphylactic reactions.[20,21]

Cephalosporins share the β-lactam ring structure and side chains of the penicillins, but allergic cross-reactivity appears to be low, in 1% to 8% of patients. Patients who have experienced urticaria or anaphylactic reactions after taking penicillin are more likely to have an adverse reaction to cephalosporins, but even in this setting, the risk of an anaphylactic reaction is low. There have been rare reports of cross-reactivity to aztreonam and carbapenems in penicillin-allergic patients, but these antibiotics should not be withheld when clinically indicated.[6,21]

NSAIDs are the most common trigger of drug-induced anaphylaxis and are believed to occur through interruption of the arachidonic acid metabolism, a non-IgE (non-immunologic) mediated process. The incidence of anaphylaxis to NSAIDs varies widely, and these reactions appear to be drug specific and without cross-reactivity to other NSAIDs. Aspirin exacerbated respiratory distress (AERD) and NSAID-induced respiratory distress syndromes are unique in individuals with a history of asthma or allergic rhinitis and are not considered anaphylactic reactions.[6,9,20,21]

Insect Stings

Anaphylactic reactions occur in up to 3% of adults and 1% of children who suffer an insect sting. The majority are associated with hymenoptera venoms (wasps, bees, ants, and sawflies) and fire ant stings. These reactions typically require a sensitizing exposure, but there have been numerous reports of anaphylactic reactions following first known stings or bites. Increased risk of fatal venom anaphylaxis has been associated with middle-aged white males, preexisting cardiovascular disease, and upright posture at the time of exposure.[9–11]

Natural Rubber Latex

Natural rubber latex (NRL) allergy is the result of sensitivity to the proteins or chemicals contained in the latex products. This sensitivity reaction can be delayed (type IV) contact dermatitis or an immediate hypersensitivity (type I) reaction (see Box 106.1). In addition to rubber gloves, NRL can be found in an array of other medical supplies, including endotracheal tubes, blood pressure cuffs, stethoscope tubing, airway masks, tourniquets, and catheters. In the United States, most health care settings have incorporated the use of non-NRL gloves and products, but in many countries, it is still a common anaphylactic trigger.[6] NRL can also found in balloons, condoms, pacifiers, sports equipment, and toys.

BOX 106.4 A Standard Treatment Protocol for Patients With a History of Radiocontrast-Induced Anaphylaxis

Prednisone 50 mg by mouth given 13, 7, and 1 h before the procedure
Diphenhydramine 50 mg PO given 1 hour before the procedure
Consider ephedrine 25 mg by mouth given 1 hour before the procedure
Consider an H_2 antagonist, such as famotidine 20 mg by mouth given 3 h before the procedure

Radiocontrast Media

Approximately 38 million computerized tomography (CT) scans, and 17 million magnetic resonance imaging (MRI) examinations using radiocontrast media (RCM) are performed in the United States annually.[22] CT scans use iodinated contrast media (ICM). ICM reactions can be divided into two types based on timing: immediate reactions occur within the first hour of administration, and delayed reactions occur from 1 hour to several days after administration. Anaphylactic reactions to ICM are largely idiosyncratic and occur within minutes of infusion. Delayed reactions are generally mild to moderate and typically limited to the integumentary system manifesting as maculopapular rash, urticaria, and angioedema. Delayed reactions rarely escalate to the levels of toxic epidermal necrolysis or Stevens-Johnson syndrome. The pathophysiologic mechanism of anaphylactic reactions to ICM is unknown, but it is believed to be non-immunologic (non-IgE). Risk factors for an anaphylactic reaction include a previous adverse reaction to ICM, a history of atopy or allergic disease, asthma, and certain medications including ACE inhibitors, β-blockers, or proton pump inhibitors.[23] A history of allergy to fish or shellfish is not a contraindication to the use of the currently available ICM, nor does it increase the risk of an adverse reaction to ICM. Clinically, the risk for severe adverse reaction to ICM is less than 1%. The death rate from ICM reactions is estimated at 1 per 170,000 administrations and accounts for 27% of drug-induced anaphylactic fatalities.[22,23] Protocols using pretest administration of antihistamines and/or glucocorticoids have been developed to minimize the risks of serious allergic reactions in patients who have had a previous adverse reaction to ICM (Box 106.4). However, there is currently little evidence to support the use of these agents to prevent anaphylaxis in patients receiving low or iso-osmolar RCM for emergently needed tests. We do not recommend delaying necessary tests for ED patients requiring emergent imaging with RCM to administer these medications as a prophylactic measure.[8]

Gadolinium-based contrast agents (GBCAs) are another type of RCM used in MRI. There is no cross-reactivity in allergies to ICM and GBCA, as they are unique structurally. Risk factors for reactions to GBCA include a history of asthma, food allergies, allergies to medications, and female gender. Reactions to GBCA are exceedingly rare, with an incidence of 0.004% to 0.01%, and typically occur within minutes of administration.[23] Like ICM, the pathophysiology of these reactions is poorly understood. Finally, adverse reactions to RCM are not related to iodine and these individuals should not be labeled as having an "iodine allergy."[8]

Exercise-Induced Anaphylaxis

Exercise-induced anaphylaxis (EIA) is a clinical syndrome in which anaphylactic-like reactions occur in relation to physical exertion.

TABLE 106.1 Mediators in Anaphylaxis and Their Physiologic Actions and Clinical Manifestations

Mediators	Physiologic Activity	Clinical Manifestation
Histamine, leukotrienes, thromboxane, prostaglandins, platelet-activating factor, nitric oxide	Vascular permeability, vasodilation, smooth muscle spasm, mucous gland secretion, nociceptor stimulation, myocardial depression	Generalized urticaria and angioedema, pruritus, wheezing, bronchoconstriction, rhinorrhea and bronchorrhea, coryza, conjunctivitis, syncope, tachycardia, hypotension, shock, abdominal pain, nausea, vomiting, diarrhea
Tryptase, carboxypeptidase, chymase, cathepsin G	Activation of the complement system, chemoattraction, activation, and degranulation of mast cells	Anaphylaxis response is amplified by recruitment and activation of the complement system and further degranulation of mast cell mediators
TNF-α, cytokines, chemokines, eosinophil chemotactic factors	Induction of anti-platelet-activating factor production, control migration of eosinophils and other inflammatory cells	May be responsible for the intensity, protracted symptoms, and multiphasic reaction of anaphylaxis

TNF-α, Tumor necrosis factor alpha.

There are two subtypes: Exercise-induced anaphylaxis (EIA), and food-dependent exercise-induced anaphylaxis (FDEIA). EIA can be dependent on other various cofactors including alcohol, environmental temperatures, pollen levels, medications such as NSAIDs (especially aspirin), or endogenous progesterone during female menstrual cycles. EIA can occur with varying levels of exertion or types of activity. While it is more commonly seen with moderate to intense physical activity, it has also been described during less strenuous activities like walking and raking leaves. Reactions can occur inconsistently with physical activities, thus increasing the difficulty of diagnosis. FDEIA only occurs if specific foods have been ingested prior to initiating exercise that would otherwise not cause symptoms without associated physical exertion. Wheat has been identified as the most common food to cause FDEIA. Avoidance of the offending food agent minimizes the risk of symptom development. Ingestion of triggering food 4 to 6 hours, or NSAIDs up to 24 hours, prior to physical activity may precipitate a reaction in susceptible individuals.[9,24–26]

Patients should be instructed to discontinue exercise at the first sign of symptoms, as continued activity can lead to clinical deterioration. Patients with suspected EIA should be prescribed epinephrine autoinjectors. They should be counseled to avoid exercising alone and preferably only exercise with a partner who is aware of their condition and able to administer an epinephrine autoinjector if necessary.[9,24]

Idiopathic Anaphylaxis

Thirty percent to 60% of adults, and up to 10% of children, have no identifiable trigger for an anaphylactic episode. The diagnosis of idiopathic anaphylaxis is often made after evaluation and testing by an allergist. In an attempt to prevent recurrent episodes, these patients may be treated with daily prophylactic medications, such as oral antihistamines with or without oral corticosteroids. A newer treatment option is omalizumab, which has been shown to reduce episodes of idiopathic anaphylactic reactions.[15] The prevalence of idiopathic anaphylaxis is unknown and difficult to estimate. Newly identifiable causes of anaphylaxis, such as alpha-gal, and other allergens have reframed prior idiopathic anaphylaxis diagnoses in some individuals.[27]

Pathophysiology

Anaphylaxis is the result of a variable intracellular signaling process, and severity depends on the specific allergen, route of exposure, and amount of effector cell activation. Mast cells and basophils appear to be the primary effector cells, but research has demonstrated other blood cell and platelet involvement as well.[28] Numerous mediators released by mast cells and basophils exert overlapping physiologic effects on target organs and tissues, making it difficult to ascribe specific clinical manifestations to any single mediator. Histamine and typtase are the two most abundant, with histamine serving as the predominant contributor to immediate hypersensitivity and inflammation.[28–30] Table 106.1 lists the primary mediators in anaphylaxis and their physiologic actions and associated clinical manifestations.

CLINICAL FEATURES

Anaphylactic reactions vary in duration and severity but typically are rapid in onset with most occurring within 2 hours of allergen exposure. Clinical presentations depend on the degree of hypersensitivity, the quantity, route, and rate of antigen exposure, as well as the target organ sensitivity and responsiveness. Presentations include a combination of clinical characteristics, affecting an array of organ systems including the skin (80% to 90%), respiratory tract (70% to 80%), gastrointestinal tract (25% to 30%), cardiovascular (30% to 50%), or the central nervous system (20% to 30%).[9,12,13,20] The National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) and WAO adopted specific diagnostic guidelines to help clinicians recognize and develop consistency in the diagnosis of anaphylaxis (Box 106.5). The criteria were initially validated with a sensitivity and specificity of 97% and 82%, respectively. A subsequent prospective validation study demonstrated a sensitivity and specificity of 95% and 71%, respectively.[31,32]

The majority of anaphylactic reactions (80% to 90%) involve the skin. This may present as isolated warmth and tingling, generalized flushing, pruritus, diffuse urticarial eruption, or any combination of these findings. Nasal congestion, sneezing, ocular itching, or tearing are also common. Patients presenting with angioedema complain of swelling and a burning sensation in the affected area. Respiratory symptoms (70% to 80%) are not always as severe as stridor or audible wheeze and may consist of cough, sense of chest tightness, subjective dyspnea, or throat tightness.[9,12,13] Hypotension or dysrhythmias may be manifested as lightheadedness or syncope. Seizure activity due to decreased cerebral perfusion is infrequently seen. Gastrointestinal symptoms are more common in elders or when triggered by a food allergen. This may include crampy abdominal pain, associated nausea and vomiting, diarrhea, or tenesmus.[9,12] Anaphylactic reactions vary a great deal from one individual to another and even among different episodes in the same individual. It should be noted that hypotension or shock are rarely presenting features in infants and children, and remain much more common in adults.[9,33] A summary of the clinical

BOX 106.5 Clinical Criteria for Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Sudden onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, itching or flushing, swollen lips-tongue-uvula) *and at least one of the following:*
   a. Respiratory compromise (e.g., shortness of breath, wheeze, cough stridor, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following occurring rapidly (minutes to several hours) after exposure to a likely allergen or other triggers for that patient:
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Sudden respiratory compromise (e.g., shortness of breath, wheeze, cough, stridor, hypoxemia)
   c. Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
   d. Sudden gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: Low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: Systolic BP of <90 mm Hg or greater than 30% decrease from that person's baseline

* Low systolic blood pressure for children is defined as <70 mm Hg from 1 month to 1 year old, <70 mm Hg + (2 × age) from 1 to 10 years old, and <90 mm Hg from 11 to 17 years old.
Modified from Simons ER, Ardusso LRF, Bilò MB, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol.* 2012:12:389–399.
BP, Blood pressure.

manifestations of anaphylaxis, along with related pathophysiologic changes, is presented in Table 106.2.

DIFFERENTIAL DIAGNOSES

The diagnosis of anaphylaxis is readily apparent in a patient presenting with acute rash, respiratory difficulty, and hypotension after allergen exposure. Common anaphylaxis mimics include syncope, panic attack, or acute asthma exacerbation. A history of asthma is commonly seen in patients experiencing anaphylaxis.[6,9] Flush syndromes may occur related to certain ingestions such as scrombroidosis, sulfites, or monosodium glutamate (MSG) but typically lack the hypotension, urticaria, or airway involvement that may be seen with anaphylaxis. Vasovagal syncope often presents with bradycardia, hypotension, and pallor, rather than the tachycardia, urticaria, and respiratory distress more commonly associated with anaphylaxis.[9,12] Differential diagnostic considerations for suspected anaphylaxis are found in Box 106.6.

DIAGNOSTIC TESTING

Anaphylaxis is primarily a clinical diagnosis. Box 106.5 lists the NIAID/FAAN and WAO diagnostic criteria for anaphylaxis. Elevated serum histamine levels acquired within 1 hour and tryptase levels (specifically in hymenoptera venom-induced anaphylaxis) within 3 hours of the onset of symptoms have been shown to correlate with anaphylaxis. In addition, there is now a commercially available serum-specific test for IgE anti-alpha-gal to help identify sensitivity to mammalian meats following tick exposure. These laboratory tests are rarely helpful in the acute setting as they take time to perform. In addition, tryptase levels may not be elevated in food-induced anaphylaxis.[6,9] Diagnostic studies should be aimed at excluding other emergency conditions that could potentially be confused with anaphylaxis (Box 106.6).

MANAGEMENT

Overview

Prompt recognition and initiation of the appropriate interventions remain key in avoiding adverse outcomes. Treatment delays, even by a few minutes, could potentially lead to hypoxia, circulatory collapse, and even death.[10]

Epinephrine should be immediately administered in the distal and lateral thigh once anaphylaxis is identified, followed by a quick effort to remove any triggering agent (e.g., insect stinger and infusing medication). Initial interventions should include continuous cardiac and pulse oximetry monitoring, intravenous (IV) access, and supplemental oxygen.[6,9,12] Most of the morbidity and mortality associated with anaphylaxis is caused by acute respiratory failure or cardiovascular collapse. Therefore, the next steps in management should focus on the triad of repeat epinephrine administration as necessary, maintenance of airway patency, and expansion of intravascular volume. Antihistamines (H_1 and H_2 blockers) and corticosteroids are commonly given for anaphylaxis, but there is no objective evidence that they improve the overall outcome and should not be considered first-line medications.[6,9,12] Box 106.7 summarizes the recommended treatment algorithm in anaphylaxis.

Positioning

Hypotensive patients should be placed in the supine position with their lower extremities elevated. If they are experiencing airway difficulties or vomiting, allow the patients to place themselves in a comfortable position and attempt to elevate their legs if possible. Pregnant women should be placed in the left lateral decubitus position to prevent vena cava compression and to promote the venous return of blood to the heart.[9,12]

Epinephrine

Epinephrine is the sole first-line medication and should be given immediately whenever anaphylaxis is suspected. Delay in administering epinephrine has been associated with increased ED length of stay, hospitalization, hypoxic encephalopathy, and death. Conversely, there is a strong correlation between early epinephrine administration and decreased hospitalization or fatality.[34,35] Despite NIAID/FAAN guidelines for diagnosis and treatment of anaphylaxis being established in 2006, studies have shown that only about 30% of patients receive epinephrine in the prehospital setting, and only 50% to 70% of those ultimately diagnosed with anaphylaxis receive epinephrine in the ED.[16,33–36]

The dose of aqueous epinephrine is 0.3 to 0.5 mg of 1 mg/mL intramuscularly (IM) for adults, and 0.01 mg/kg of 1:1000 concentration IM for pediatric patients. It can be repeated every 5 to 10 minutes, as up to 30% will require more than one dose and should optimally be administered IM in the lateral, distal thigh (vastus lateralis). This provides more rapid peak plasma concentrations (8 minutes) when compared to the previously suggested subcutaneous route (34 minutes). Subcutaneous or inhalation administration of epinephrine is no longer routinely recommended.[9,12,34,37]

TABLE 106.2 Clinical Manifestations of Anaphylaxis and Related Pathophysiologic Changes

Organ System	Reaction	Symptoms	Signs	Pathophysiologic Changes
Respiratory tract				
Upper	Rhinitis	Nasal congestion	Nasal mucosal edema	Increased vascular permeability
		Nasal itching	Rhinorrhea	Vasodilation
		Sneezing		Stimulation of nerve endings
	Laryngeal edema	Dyspnea Hoarseness Throat tightness Hypersalivation	Laryngeal stridor Supraglottic and glottic edema	As above, plus increased exocrine gland secretions
Lower	Bronchospasm	Cough Wheezing	Cough Wheeze, rhonchi	As above, plus bronchiole smooth muscle contraction
		Retrosternal tightness	Tachypnea	
		Dyspnea	Respiratory distress	
			Cyanosis	
Cardiovascular system	Circulatory collapse	Lightheadedness Generalized weakness Syncope Ischemic chest pain	Tachycardia Hypotension Shock	Increased vascular permeability Vasodilation Loss of vasomotor tone Increased venous capacitance
	Dysrhythmias	As above, plus palpitations	ECG changes: Tachycardia Nonspecific and ischemic ST-T wave changes Right ventricular strain Premature atrial and ventricular contractions Nodal rhythm Atrial fibrillation	Decreased cardiac output Decreased mediator-induced myocardial suppression Decreased effective plasma volume Decreased preload Decreased afterload Hypoxia and ischemia Dysrhythmias Iatrogenic effects of drugs used in treatment Preexisting heart disease
	Cardiac arrest		Pulseless	
			ECG changes:	
			Ventricular fibrillation	
			Asystole	
Skin	Urticaria	Pruritus	Urticaria	Increased vascular permeability
		Tingling and warmth	Diffuse erythema	Vasodilation
		Flushing		
		Hives		
	Angioedema	Nonpruritic extremity, periorbital, and perioral swelling	Nonpitting edema, frequently asymmetrical	Increased vascular permeability
Eye	Conjunctivitis	Ocular itching Increased lacrimation Red eye	Conjunctival inflammation	Stimulation of nerve endings
Gastrointestinal tract		Dysphagia Cramping, abdominal pain Nausea and vomiting Diarrhea (rarely bloody) Tenesmus	Nonspecific	Increased secretion of mucus Gastrointestinal smooth muscle contraction
Miscellaneous central nervous system		Apprehension Sense of impending doom Headache Confusion	Anxiety Seizures (rarely) Coma (late)	Secondary to cerebral hypoxia and hypoperfusion Vasodilation
Hematologic	Fibrinolysis and disseminated intravascular coagulation	Abnormal bleeding and bruising	Mucous membrane bleeding, disseminated intravascular coagulation Increased uterine tone Vaginal bleeding	Mediator recruitment and activation Uterine smooth muscle contraction Bladder smooth muscle contraction
Genitourinary		Pelvic pain	Urinary incontinence	
		Urinary incontinence		

ECG, Electrocardiographic.

BOX 106.6 Differential Diagnosis of Anaphylaxis

Acute generalized urticaria
Asthma exacerbation
Myocardial infarction
Pulmonary embolus
Syncope
Adverse cutaneous drug reaction
Anxiety/panic attacks

Flush Syndrome

Flushing associated with food
Alcohol
MSG
Sulfites
Scombroidosis
Carcinoid tumor
Peri-menopause
Thyrotoxicosis

Basophilic leukemia
Mastocytosis (systemic mastocytosis and urticaria pigmentosa)
Vasointestinal peptide tumors

Shock Syndromes

Septic shock
Hypovolemic shock
Cardiogenic shock
Distributive shock

Miscellaneous

Hypoglycemia
Acquired and HAE
ACE-inhibitor-associated angioedema
Red man syndrome (Vancomycin)
Neurologic disorders (seizure, stroke, autonomic epilepsy)
Vocal cord dysfunction syndrome
Pheochromocytoma

ACE, Angiotensin-converting enzyme; *HAE,* hereditary angioedema; *MSG,* monosodium glutamate.

BOX 106.7 Treatment Algorithm for Anaphylaxis

Emergency Measures (Taken Simultaneously)

Remove any triggering agent.
Place the patient in the supine position.
Begin cardiac monitoring, pulse oximetry, and blood pressure monitoring.
Begin supplemental oxygen if indicated.
Establish large-bore IV lines (e.g., 16 or 18 gauge preferred).
Ensure a patent airway.
Be prepared for endotracheal intubation with or without rapid sequence intubation.
Be prepared to use an adjunct airway technique (e.g., awake fiberoptic intubation, surgical airway).
Start a rapid infusion of isotonic crystalloid (normal saline):
- Adults: 1000 mL IV in the first 5 min in the adult (several liters of normal saline may be required), titrated to response
- Pediatrics: 20–30 mL/kg IV increments

Anaphylaxis Treatment Medications

First-Line Agent

Epinephrine is the first-line medication and should be given immediately at the first suspicion of an anaphylactic reaction.
- Adult: 0.3–0.5 mg IM (1 mg/mL concentration) in anterolateral thigh every 5–10 minutes as necessary
- Pediatric: 0.01 mg/kg IM (1:1000 concentration) in anterolateral thigh every 5–10 minutes as necessary

Alternatively, epinephrine (EpiPen, 0.3 mL; or EpiPen Jr, 0.15 mL) can be administered into the anterolateral thigh

Second-Line Agents (Should Not Precede the Administration of Epinephrine)

Antihistamines

Diphenhydramine:
- Adults: 50 mg IV or 50 mg oral
- Pediatric: 1 mg/kg IV or oral

Famotidine:
- Adult: 40 mg IV (40 mg oral)
- Pediatric: 0.5 mg/kg IV or oral

Aerosolized Beta-Agonists (if Bronchospasm Is Present)

Adult:
- Albuterol: 2.5 mg, diluted to 3 mL of normal saline; may be repeated as needed or continuous
- Ipratropium: 0.5 mg in 3 mL of normal saline; may be repeated as necessary

Pediatric:
- Albuterol: 2.5 mg, diluted to 3 mL of normal saline; may be repeated as needed or continuous
- Ipratropium: 0.25 mg in 3 mL of normal saline; may be repeated as necessary

Glucocorticoids (No Benefit in the Acute Management)

Methylprednisolone:
- Adult: 125–250 mg IV
- Pediatric: 1–2 mg/kg IV

Prednisone/prednisolone:
- Adult: 40–60 mg oral
- Pediatrics: 1–2 mg/kg oral

Refractory Hypotension

Consider continuous IV epinephrine drip (dilute 1 mg (1 mg/mL concentration) in 1000 mL of normal saline or D_5W to yield a concentration of 1 μg/mL)
Adults: 1–10 μg/min IV (titrated to desired effect)
Pediatrics: 0.1–1.5 μg/kg/min IV (titrated to desired effect)

Other Adjunctive Vasopressors to Consider

Dopamine: 5–20 μg/kg/min continuous IV infusion (titrated to the desired effect)
Norepinephrine: 0.05–0.5 μg/kg/min (titrated to desired effect)
Phenylephrine: 1–5 μg/kg/min (titrated to desired effect)
Vasopressin: 0.01–0.4 units/min (titrated between 0.01–0.04 units/min)

Patients Receiving Beta-Blockade

Glucagon: 1–5 mg IV over 5 min, followed by 5–15 μg/min continuous IV infusion

D_5W, 5% dextrose in water; *IM,* intramuscular; *IV,* intravenous.

For patients who remain hypotensive after multiple doses of IM epinephrine and adequate volume expansion aimed at increasing blood pressure, IV epinephrine should be considered. IV epinephrine increases the risks of cardiac dysrhythmias, thus requiring cautious cardiac and hemodynamic monitoring. Dilution and slow administration are recommended to reduce untoward effects.[12,38] In adults, we suggest preparing a concentration of 1.0 μg/mL and initially infusing at a rate of 1 μg/min. The rate should be increased until hemodynamic stability is achieved, or a maximum dose of 10 μg/min. This can be prepared by mixing 1 mg (1 mL) of 1:1000 concentration of epinephrine with 1000 mL of 5% dextrose in water or normal saline; this provides an infusion of 1 mL/min equaling 1 μg/minute. In children and infants, an infusion rate of 0.1 μg/kg/min is advised, increasing in increments of 0.1 μg/kg/min to a maximum of 1.5 μg/kg/min.[37] Central venous access is encouraged when administering IV epinephrine because of the risk of tissue necrosis from extravasation.

Epinephrine derives its therapeutic value from its combined alpha-adrenergic and beta-adrenergic actions that work directly to improve the most commonly observed clinical features.

Alpha$_1$-adrenergic stimulation increases vasoconstriction, increases peripheral vascular resistance, and decreases mucosal edema. Through beta$_1$-adrenergic stimulation, inotropic and chronotropic cardiac activity is enhanced. Beta$_2$-adrenergic stimulation also provides stabilization of mast cells and basophils, and it induces bronchodilation. These combined effects result in decreased mediator release from mast cells and basophils, which improves bronchospasm, decreases mucosal edema and swelling, and reverses systemic hypotension.[12,34]

Epinephrine can produce a number of undesirable side effects, though there is no absolute contraindication in the setting of anaphylaxis. Common side effects include palpitations, anxiety, tremor, pallor, dizziness, or headache. There is a common misconception that epinephrine should be avoided in patients with a history of cardiovascular disease due to the concern of inducing life-threatening arrhythmias and other adverse cardiovascular events. These events are rare, and the majority are associated with improper dosing or administration. The benefits of the early administration of epinephrine in anaphylaxis far outweigh the risks.[34,36,37]

Airway

Patients in respiratory distress and receiving multiple doses of epinephrine should be placed on supplemental oxygen and prepared for possible advanced airway management. Patients with bronchospasm may benefit from bronchodilators, but this should not preclude the administration of epinephrine. Upper airway obstruction from laryngeal angioedema can progress rapidly, so preparations for a difficult airway should be made early. This may include an awake intubation with assistance fiberoptic laryngoscopy or the equipment to convert to a surgical airway procedure if needed.[6,9,12]

Volume Expansion

Along with airway assessment, fluid resuscitation should be initiated. For adults, infuse 1 to 2 L of normal saline rapidly through large-bore (e.g., 16-gauge) IV lines. Pediatric patients should be given boluses in 20 to 30 mL/kg increments. When IV access cannot be established, intraosseous catheter placement is an alternative. The assistance of an infusion pump or pressure bag should be considered when administering fluids in this manner. Large volumes of normal saline (2 to 7 L) may be required to reverse the effects of fluid extravasation into the extravascular space and the circulatory collapse sometimes seen in anaphylaxis. Patients with heart or renal failure should be monitored closely for signs of volume overload.[6,9,12]

Antihistamines

H_1 and H_2-antihistamines should never be used as the sole or initial treatment in anaphylaxis. They may be considered as second- or third-line treatments and can be helpful in relieving cutaneous symptoms, such as urticaria, pruritus, flushing, eye, or nasal symptoms.[6,12,34] See Box 106.7 for suggested dosing.

Glucocorticoids

While glucocorticoids are frequently administered, they have no immediate effect on the management of anaphylaxis and thus should be considered a second- or third-line intervention. Their onset of action typically takes several hours. In theory, they may provide benefit by preventing protracted symptoms or a biphasic reaction, but there is no strong evidence to support their use for those purposes.[8,39–41] With these limitations in mind, glucocorticoids are an optional adjunct in the treatment of anaphylaxis but should never precede the administration of epinephrine. See Box 106.7 for suggested dosing.

Patients Receiving Beta-Blockade

Glucagon, with positive inotropic and chronotropic cardiac effects mediated independently of alpha and beta receptors, may be helpful in patients with anaphylactic reactions who are receiving beta-blockers and fail to respond to epinephrine or other standard treatments. The initial IV dose is 1 to 5 mg for adults or 20 to 30 μg/kg (maximum dose 1 mg) for children and may be followed by an infusion of 5 to 15 μg/min. Nausea and vomiting are common side effects, so the clinician should be prepared to administer an antiemetic when indicated.[9,12]

DISPOSITION

Up to 20% of patients with anaphylaxis may experience a biphasic reaction defined as a reoccurrence of anaphylactic symptoms without re-exposure to the triggering agent. Most of these reactions occur within 8 hours but have been reported as far out as 72 hours.[8] The majority respond to the appropriate treatment, and recent literature suggests that clinically important biphasic reactions and fatalities are actually much rarer than previously reported.[41,42] Many clinicians administer corticosteroids in hopes of preventing a biphasic reaction, but recent studies have failed to show significant effect.[8,39,40] Patients at increased risk for biphasic reactions include those presenting with hypotension, wide pulse pressure, unknown trigger, greater than 1 dose of epinephrine, cutaneous signs and symptoms, prior anaphylaxis, and delayed epinephrine administration.[8,43,44]

Consensus guidelines suggest that patients who respond to initial treatments and experience complete resolution of symptoms can generally be discharged home after an observation period of 4 to 6 hours. Recent literature suggested a 95% NPV of a biphasic reaction in those observed for 1 hour and 97.3% after 6 hours of observation. Therefore, we suggest a minimum of 1 hour of asymptomatic observation and 6 hours or longer in those with increased risk of biphasic reactions (as previously mentioned).[8,45] Hospitalization should be strongly considered for patients who present with protracted anaphylaxis, hypotension, or airway involvement; receive more than two doses of IM epinephrine; or have poor outpatient social support, or inability to acquire an auto-injectable epinephrine device.[8,9]

Prior to discharge, the clinician should take an active role in educating the patient or caretakers about their allergy and anaphylaxis. It is also important to explain and demonstrate how to use the auto-injectable epinephrine device. Patients should be encouraged to develop an individualized anaphylaxis emergency action plan and to consider acquiring a medical identification device (e.g., bracelet, wallet

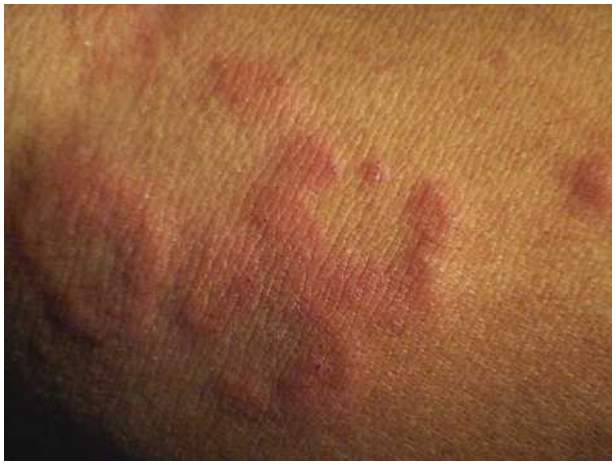


Fig. 106.4 Acute Urticaria. (©2001–2003, Johns Hopkins University School of Medicine. http://dermatlas.med.jhmi.edu/derm.)

card). Emphasis should be placed on timely follow-up, preferably with an allergist-immunologist.[9,34,46]

URTICARIA AND ANGIOEDEMA

PATHOPHYSIOLOGY AND CLINICAL FEATURES

Urticaria is commonly encountered in the ED. It is estimated that 25% of the population will experience an episode of urticaria in their lifetime. Urticaria is characterized by the presence of wheals (hives), angioedema, or both. It should be distinguished from other conditions, such as autoinflammatory syndromes or other causes of non-histaminergic angioedema. Urticaria appears as papules or wheals that consist of central swelling with surrounding reflex erythema and is associated with itching or a burning type sensation (Fig. 106.4).[5] These lesions are a result of mediators (predominately histamine) released from mast cells. They tend to occur on the extremities and are usually transient, with skin often returning to its normal appearance within 24 hours. Urticaria can be classified based on its duration, with acute urticaria lasting less than 6 weeks and chronic episodes lasting longer than 6 weeks. There are also several types of inducible urticaria including cold contact, delayed pressure, heat contact, solar, aquagenic, or cholinergic.[5]

Angioedema is characterized by edema of the subcutaneous or submucosal tissues, commonly involving the face, mouth, lips, tongue, extremities, or genitalia. It is a result of abrupt vasodilation and increased vascular permeability, allowing fluid to move from the vascular to the interstitial space. As the swelling is located in the deeper layers of the skin, the appearance is often normal in color and patients often complain of pain or a pressure sensation, rather than an itch. Of particular concern is when the tongue, posterior pharynx, or larynx is involved, which could progress to airway obstruction and compromise. Angioedema can be mediated by an allergic mechanism in response to exposure to foods, drugs, or physical stimuli or by a nonallergic mechanism such as HAE, acquired angioedema, or ACE-inhibitor-induced angioedema.[47]

Non-histaminergic (nonallergic) angioedema is typically a result of elevated bradykinin levels. This classification includes four subtypes: Hereditary angioedema (HAE) with or without C1 esterase inhibitor deficiency, acquired C1 esterase inhibitor deficiency (ACID), ACE-inhibitor-induced, and idiopathic angioedema. HAE is an autosomal dominant condition, with an estimated frequency of 1:50,000 globally.[48] The median age at which patients develop symptoms is 12 years.[47] ACID onset usually occurs later in life and may be associated with an underlying lymphoproliferative disorder such as lymphoma, or benign monoclonal gammopathy.[47,49] ACID is a rare condition with limited epidemiologic data. Other than familial history and age of onset, HAE and ACID are clinically indistinguishable. HAE with C1 inhibitor deficiency and ACID share the same mechanism: The lack of C1 inhibitor causes activation of the kallikrein-kinin system, increasing the consumption of kininogen, resulting in increased production of bradykinin. In the case of ACE-inhibitor-induced angioedema, bradykinin levels accumulate due to the inhibition of the angiotensin-converting enzyme, which is one of two main enzymes responsible for the breakdown of bradykinin. Bradykinin binds the bradykinin 2 receptor (β2), inducing vasodilation and vascular permeability, ultimately resulting in angioedema.[49–51]

Recent literature suggests that in the United States, non-histaminergic angioedema is responsible for approximately 110,000 ED visits annually, with 30% resulting from ACE-inhibitor-induced angioedema. ACE-inhibitor-induced angioedema has an overall incidence of 0.3% to 0.7% and is 3 to 4 times more likely in African Americans, and women are at a 50% higher risk than men. ACE-inhibitor-induced angioedema has a predilection for the face, often involving the lips, eyelids, tongue, larynx, or pharynx. The highest incidence occurs in the first month of therapy but has also been reported to occur years after initiation of therapy.[49–51]

DIAGNOSTIC TESTING

Similar to anaphylaxis, angioedema is a clinical diagnosis. Laboratory tests are not helpful in the acute setting. If a hypersensitivity reaction is suspected, a detailed history should focus on identifying any recent exposures to foods, drugs, physical stimuli, infection (especially viral hepatitis), occupational elements, or insect stings. Patients should also be questioned about prior history of similar symptoms as well as any family history of non-histaminergic angioedema.

MANAGEMENT

Angioedema With Urticaria

Angioedema that occurs in conjunction with urticaria is typically histaminergic (allergic) in nature. In cases that do not meet the criteria for anaphylaxis, antihistamines are considered the first-line treatment. Second-generation H_1-antihistamines, such as cetirizine, loratadine, and fexofenadine, are the preferred agents, and up to fourfold the conventional dose may be considered. Because 15% of dermal histamine receptors are H_2, the addition of an oral H_2-antihistamine may also be beneficial. A short course of oral corticosteroids (e.g., prednisone) may be considered as a second-line therapy.[5] In patients with severe symptoms and no cardiac risk factors, epinephrine should be given (anaphylactic dosing). In an effort to prevent reoccurrence, patients should be educated to avoid exposure to potential triggering agents.

Angioedema Without Urticaria

Acute attacks of non-histaminergic (bradykinin-related) angioedema do not typically respond to treatment with epinephrine, antihistamines, or steroids. In patients presenting with airway-threatening angioedema and no prior history, we suggest initially administering epinephrine and antihistamines at anaphylactic doses. In situations requiring intubation, awake fiberoptic intubation when available is the preferred method and paralytics should be utilized with caution. The clinician must be prepared to rapidly work through a difficult airway algorithm using alternative measures (e.g., fiberoptic laryngoscopy, surgical airway), as discussed in Chapter 1. When available, early

TABLE 106.3 Treatment Options for Hereditary Angioedema

Drug	Age Approved Use	Mechanism of Action	Dose/Route	Median Time to Symptom Relief
Berinert	Adult and pediatric patients	C1-INH protein replacement, human	20 units/kg IV	48 min
Ruconest	Adults and pediatric patients >11 years of age	C1-INH protein replacement, recombinant	50 units/kg IV (max 4200 units IV)	90 min
Ecallantide	Adults and pediatric patients >12 years of age	Plasma-Kallikrein inhibitor	30 mg SC	67 min
Icatibant	Adult patients >18 years of age	Bradykinin-2 receptor antagonist	30 mg SC	2 h

C1-INH, C1 esterase inhibitor; *IV,* intravenous; *SC,* subcutaneous.
Modified from Bernstein JA, Cremonesi P, Hoffmann TK, et al. Angioedema in the emergency department: a practical guide to differential diagnosis and management. *Int J Emerg Med.* 2017;10(15):1–11.

mobilization of ENT, anesthesiology, or another emergency physician colleague may be beneficial. In cases with suspected laryngeal or supraglottic angioedema, evaluation with nasopharyngoscopy may assist in formulating treatment plans, interventions, and disposition.

Fresh frozen plasma (FFP), which contains a C1 inhibitor, has been reported to be effective in acute attacks; however, there are rare reports of exacerbation of the angioedema by FFP. The FDA has approved four medications for use in the United States for patients with acute HAE (see Table 106.3).[49]

For ACE-inhibitor-induced angioedema, treatment is mainly supportive. Theoretically, the medications described for the treatment of HAE would be effective in ACE-inhibitor-induced angioedema, but none are FDA-approved for use at this time. There are multiple case reports of FFP being used with success in the treatment of ACE-inhibitor angioedema. Early treatment (within several hours of symptom onset) may be necessary to be successful.[52] Initial studies looking at ecallantide and icatibant have yielded mixed results, and there is no strong recommendation for their use at the time of this publication. We suggest administering one of these agents if available at your institution and the patient is showing signs of progressing airway involvement.[53–56]

Special Considerations

Thrombolytic induced angioedema is a well-recognized, yet rare complication following administration of recombinant tissue plasminogen activator (tPA). While usually transient in nature, it can be rapidly progressive and potentially life-threatening. The reported incidence is 1% to %5.[49] It is classically described as asymmetric orolingual angioedema. Increased risk is associated with ACE-inhibitor use. The mechanism of angioedema development is thought to be multifactorial. Also, tPA can increase bradykinin levels through its production of plasmin, which can also activate the complement cascade, triggering mast cell degranulation and histamine release. Recommended treatment includes antihistamines and corticosteroids. There are reports of successful treatment with epinephrine, although blood pressure control is a potential concern.[57,58]

DISPOSITION

There is a lack of data to provide concrete guidelines for disposition. Most will agree that patients who experience a complete resolution of angioedema or have only extra-oral facial involvement can be discharged home after a period of observation in the ED. Individuals suspected of HAE or ACID should be referred to an allergist, as further evaluation and potential preventative medications may be warranted. We suggest hospitalization for patients with persistent angioedema of the sublingual area, tongue, soft palate, pharynx, or larynx.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 106: QUESTIONS AND ANSWERS

1. Which of the following statements regarding the use of H_2-antihistamines in patients presenting with urticaria and pruritis is true?
- **a.** A portion of histamine receptors on the skin are H_2 receptors.
- **b.** Patients with skin manifestations often have concomitant reflux.
- **c.** H_2-antihistamines have synergistic properties when used with steroids.
- **d.** Use of H_2-antihistamines can effectively replace H_1-antihistamines and have fewer side effects.
- **e.** H_2-antihistamines are effective in preventing recurrence of pruritis and urticaria.

Answer: a. Because 15% of the histamine receptors in skin are H_2 receptors, the addition of an H_2-antihistamine (e.g., ranitidine) may be beneficial in the treatment of pruritis and urticaria. There is no proven synergistic effect when used with steroids. Second-generation H_1-antihistamines, such as cetirizine, loratadine, and fexofenadine, are the preferred agents in the treatment of urticaria and pruritis.

2. A 16-year-old female with a known history of hereditary angioedema (HAE) presents with facial swelling. Which HAE medication is not approved for patients in this age group?
- **a.** Ecallantide
- **b.** Icatibant
- **c.** Bertinert
- **d.** Reconest
- **e.** Cinryze

Answer: b. Icatibant is approved for treatment in adults aged 18 years or older. Berinert is approved for the treatment of HAE in adult and pediatric patients (no lower age limits). Ruconest approved for use in adults and pediatric patients ages 11 and older. Ecallantide is approved for adult patients and pediatric patients 12 years and older. Cinryze is a prophylactic HAE medication not approved for use in acute attacks.

3. Concomitant use of which of the following classes of medications is associated with increased risk of mortality in patients with drug-induced anaphylaxis?
- **a.** Penicillins
- **b.** ACE inhibitors
- **c.** NSAIDs
- **d.** Beta-blockers
- **e.** Fluoroquinolones

Answer: d. Fatal drug-induced anaphylaxis has been associated with hypertension, obesity, male gender, beta-blocker use, and advanced age. Beta-blockers may oppose the actions of adrenergic agents used in anaphylaxis treatment. These patients may require additional treatment with glucagon to counter the effects of beta-blockade.

4. What is the appropriate initial dose and route for a pediatric patient in the treatment of acute anaphylaxis?
- **a.** 0.3 to 0.5 mg of 1 mg/mL concentration epinephrine concentration, IM in anterolateral thigh
- **b.** 1 mL of 1:1000 epinephrine IV
- **c.** 0.01 mg/kg of 1:1000 epinephrine, IM in anterolateral thigh
- **d.** 2 mL of 1:10,000 epinephrine IV every 5 minutes
- **e.** 0.01 mg/kg of 1:10,000 epinephrine IV

Answer: c. 0.01 mg/kg (1:1000 concentration) given IM in the anterolateral thigh every 5 to 10 minutes as necessary is recommended for pediatric patients. Alternatively, an EpiPen Jr 0.15 mL can be considered in patients weighing 10 to 25 kg.

5. The majority of the clinical features of anaphylaxis syndrome are produced by which of the following mediators?
- **a.** Acetylcholine
- **b.** Histamine
- **c.** Leukotrienes
- **d.** Prostaglandins
- **e.** Tumor necrosis factor

Answer: b. All of the listed mediators contribute, but histamine is the predominant chemomediator.

107

Dermatologic Presentations

Catherine Anna Marco

KEY CONCEPTS

- Accurate descriptions of dermatologic lesions are essential for diagnosis and management. Primary and secondary lesions are described in Tables 107.1 and 107.2.
- Systemic illnesses with cutaneous findings include systemic infections, autoimmune or connective tissue disorders, malignancies, diabetes mellitus, endocrine disorders, and immunodeficiency states.
- Cutaneous signs of systemic disease include pruritus, urticaria, erythema multiforme, erythema nodosum, pyoderma gangrenosum, or others.
- Most skin and soft tissue infections should be treated with antibiotics to cover methicillin-resistant *Staphylococcus aureus*.
- Cutaneous abscesses are treated with incision and drainage plus antibiotics.
- Tinea capitis requires 4–8 weeks of systemic antifungal treatment.
- Onychomycosis requires long-term systemic treatment.
- Allergic reactions are treated with antihistamines and discontinuation of exposure to the allergen. Nonsedating antihistamines are the preferred agents to control pruritus and histamine-mediated rashes because they allow patients to remain active.
- Suspected infestations should be diagnosed clinically and treated expeditiously, even without definitive proof of the infestation.
- Medication reactions are common and may result from any agent, typically within 4–28 days after use.
- Rashes that are associated with mucosal lesions, blisters, or desquamating skin are often caused by significant soft tissue infections, drug eruptions, or immune disorders.
- Patients with Stevens-Johnson syndrome or toxic epidermal necrolysis require inpatient treatment, preferably in a burn unit.
- Clinicians should be familiar with one or two topical steroid preparations of low, medium, and high potency, and their appropriate therapeutic use.
- The majority of patients with dermatologic complaints are managed as outpatients. Indications for hospitalization include significant fluid and electrolyte abnormalities, disordered thermoregulation, systemic infection or other underlying disorder requiring inpatient management, and inability to care for self or maintain appropriate oral intake.

OVERVIEW

Foundations

Background and Importance

Diseases of the skin and subcutaneous tissue account for over 5 million emergency department (ED) visits annually, approximately 3.5% of all ED visits.[1] Dermatologic conditions often have a significant impact on quality of life.[2] Common diagnoses among ED patients include infections, inflammatory conditions, allergic reactions, or drug reactions.

Anatomy, Physiology, and Pathophysiology

The skin is composed of three layers: the epidermis, dermis, and subcutaneous layer (Fig. 107.1). The epidermis is a thin layer of stratified squamous epithelium, consisting mainly of keratinocytes, which progress through stages of differentiation as they migrate from the basal to the superficial layer. These layers are the stratum basale (base of the epithelium), stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (superficial layer). The epidermis also includes other cells, such as melanocytes and Langerhans cells. Melanocytes produce melanin, which functions to add pigment to the skin and also to absorb ultraviolet radiation. Langerhans cells are a component of the immune system and function to ingest and process foreign antigens. The epidermis lacks direct blood supply and is dependent on the dermis for nutrients by diffusion through the dermal-epidermal junction. This junction is the site of immunologic injury resulting in separation of these layers, which appears as bullae.

The dermis consists of connective tissue, blood vessels, lymphatic vessels, nerve endings, and immune cells. The main function of the dermis is to support the epidermis and contribute to the protective functions of the skin. Fibroblasts produce procollagen and elastic fibers used to form the connective tissues that give support and elasticity to the skin. Sweat glands and the network of blood vessels in the dermis assist with thermoregulation.

The subcutaneous layer is composed of connective tissue and adipose tissue, functions to cushion the overlying skin, and contains lymph and neurovascular structures.

The skin serves several important physiologic functions. It serves as a barrier between the internal and external environment. The skin protects from external toxic and infectious materials, and assures homeostatic balance of fluids and electrolytes. The skin serves an integral role in temperature homeostasis through its barrier function, sweating mechanism, and blood vessel dilation or constriction; it functions in the absorption of ultraviolet radiation and production of vitamin D; sensory nerve endings in skin serve important functions of sensation; and finally, certain cells within the skin serve important immunologic functions, including Langerhans cells, lymphocytes, mast cells, and keratinocytes.

Clinical Features and Differential Diagnoses

A step-by-step approach to evaluating an unknown rash is listed in Box 107.1.

Important historical factors include the time of onset, duration of symptoms, and exposure to potential allergens, such as foods, medications, soaps, pets, or jewelry. Information about changes over time should be sought, including whether the rash has progressed, improved, or waxed and waned. Associated pain, pruritus, fever, sexual history, occupation, and hobbies should be identified. Relevant past medical history includes medical conditions, skin conditions,

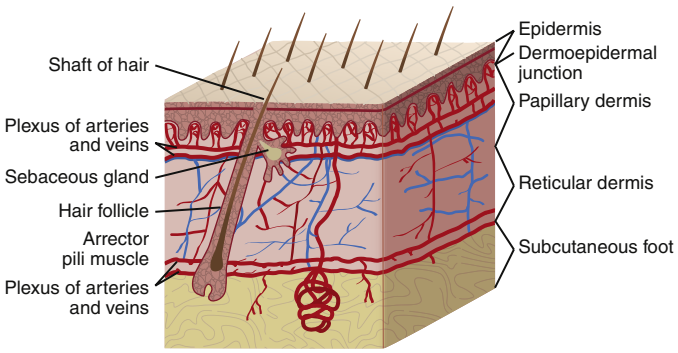

Fig. 107.1 Skin Anatomy.

BOX 107.1 Approach to Management of the Unknown Rash

1. Time of onset
2. Historical features
3. Medical history
4. Primary lesion
5. Secondary lesions
6. Distribution of the lesions
7. Systemic illness
8. Diagnostic tests
9. Category of rash
   a. Infectious
   b. Immune
   c. Vascular
   d. Allergic
   e. Malignancy
10. Treatment

medications, illicit drug use, allergies, recent travel, sunlight exposure, and family history.

The physical examination is essential to identifying the diagnosis. The examination should be performed with adequate lighting. Primary and secondary lesions, as well as characteristics and patterns of lesions, should be identified. Lesions may be palpated wearing gloves to identify texture, blanching, or sloughing characteristics. Nikolsky sign may be tested, and when positive, gentle rubbing of the skin results in sloughing of the top layer of the epidermis. For patients with systemic complaints, a thorough visual examination from head to soles of feet should be performed, including skin, mucosa, and genitalia.

Identification and description of lesions is essential. Lesions may be classified as primary or secondary lesions. Primary lesions arise directly from the disease process. Secondary lesions result from factors such as scratching, treatment, healing, or complicating infections. Primary and secondary lesions and descriptions are listed in Tables 107.1 and 107.2. The significance of distribution of lesions is outlined in Table 107.3.

Diagnostic Testing

Laboratory testing is unnecessary for most patients with a rash. Specific tests for clinically suspected diseases may be indicated, such as a blood test for secondary syphilis, heterophile antibody (Monospot) for mononucleosis, or throat swab for rapid testing and culture of group A streptococcus for scarlet fever. Adjunctive skin tests may be considered, including potassium hydroxide (KOH) prep, Tzanck smear, gram stain, erythrocyte sedimentation rate (ESR), or biopsy. For the patient with severe systemic illness, a complete blood count, blood cultures, lumbar puncture studies, electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and liver function tests may be considered. Ultrasound may be helpful in identifying features such as fluid collection, blood flow, septations, inflammation, and to determine the extent of soft tissue lesions.[3]

TABLE 107.1 Primary Lesions

Lesion	Description	Size
Macule	Flat circumscribed pigmented area	<0.5 cm in diameter
Patch	Flat circumscribed pigmented area	>0.5 cm in diameter
Papule	Elevated, solid, palpable lesion, variable color	<0.5 cm in diameter
Plaque	Elevated, solid, palpable lesion, variable color	>0.5 cm in diameter
Nodule	Solid, palpable, subcutaneous lesion	<0.5 cm in diameter
Abscess	Erythematous, fluctuant, tender, fluid-filled nodule	Any
Tumor	Solid, palpable, subcutaneous lesion	>0.5 cm in diameter
Vesicle	Elevated, thin walled, circumscribed, clear fluid-filled lesion	<0.5 cm in diameter
Bulla	Elevated, thin walled, circumscribed, clear fluid-filled lesion	>0.5 cm in diameter
Pustule	Elevated, circumscribed, purulent fluid-filled lesion	Any
Petechiae	Flat, erythematous or violaceous non-blanching lesions	<0.5 cm in diameter
Purpura	Erythematous or violaceous non-blanching lesions, may be palpable	>0.5 cm in diameter

TABLE 107.2 Secondary Lesions

Secondary Lesion	Description
Scale	Thickened area of keratinized epithelium
Crust	Dried area of plasma proteins, resulting from inflammation
Fissures	Deep cracks in skin surfaces, extending into dermis
Erosions	Disruption of surface epithelium, usually linear, traumatic
Ulcer	Deep erosion extending into dermis
Scar	Dense collection of collagen, a result of healing after trauma or procedures
Excoriation	Linear erosions typically secondary to scratching or rubbing
Infections	Bacterial, viral, fungal, or protozoal infection, caused by breaks in dermal-epidermal junction, often erythematous
Hyperpigmentation	Increase in melanin containing epidermal cells
Lichenification	Abnormally dense layer of keratinized epidermal cells

Management

The treatment of specific dermatologic conditions is addressed in the following sections of this chapter covering infectious, allergic, inflammatory, autoimmune, and malignant disorders. More detailed discussions of the systemic manifestations and overall management of many

TABLE 107.3 Distribution and Patterns of Selected Disease States

Dermatologic Diagnosis	Distribution and Patterns of Lesions
Atopic dermatitis, infantile	Face, scalp, flexor surfaces of extremities
Atopic eczema, adult	Face, neck, flexor surfaces of extremities
Dermatomyositis	Dorsal MCP joints, periorbital area
Disseminated gonorrhea	Distal extremities, near joints
Erythema nodosum	Anterior shins, ulnar surfaces
Herpes zoster infection	Dermatomal distribution, common on trunk
Lichen planus	Wrists, ankles, flexor surfaces
Nummular eczema	Distal extremities
Neurotic excoriations	Extremities, face, upper back, neck
Pityriasis rosea	Trunk, extremities, "Christmas tree" pattern
Porphyria cutanea tarda	Sun-exposed areas, hands, forearms, feet
Psoriasis	Extensor surfaces of extremities, sacral area
Rosacea	Face, neck
Sarcoidosis	Face, extremities, back
Seborrheic dermatitis	Chest, nasolabial folds
Secondary syphilis	Torso, palms, soles
Systemic lupus erythematosus	Nose and cheeks, head and neck, photosensitivity, alopecia
Tinea versicolor	Upper back and chest

MCP, Metacarpophalangeal.

of the conditions can be found elsewhere in this textbook. Soft tissue, bacterial, viral, tick-borne, and sexually transmitted infections are covered in Chapters 126, 118, 122, 123, and 84, respectively. Urticaria is discussed in Chapter 106.

Disposition

Most patients with dermatologic complaints are managed as outpatients. Indications for hospitalization include significant fluid and electrolyte abnormalities, disordered thermoregulation, systemic infection, underlying disorders requiring inpatient management, and inability to care for self or maintain appropriate oral intake. Dermatologic outpatient follow-up or inpatient consultation may be appropriate.

INFECTIOUS DISORDERS

Bacterial Infections

Impetigo

Impetigo is typically caused by *Staphylococcus aureus* or β-hemolytic *Streptococcus.* Pediatric patients are commonly affected. Streptococcal impetigo (ecthyma) is found most often on the face and other exposed areas. The eruption often begins as a single pustule and later progresses to multiple lesions, often with a golden yellow crust (Fig. 107.2). Lesions may be pruritic but usually are not painful. Regional lymphadenopathy is commonly present. Lesions are contagious among infants and young children and less so in older children and adults. Postpyodermal acute glomerulonephritis is a recognized complication of streptococcal impetigo.

Staphylococcal impetigo is differentiated from streptococcal impetigo in that it is more superficial, and there is little surrounding erythema. Other diagnostic considerations include herpes simplex virus (HSV) or inflammatory fungal infections. Methicillin-resistant

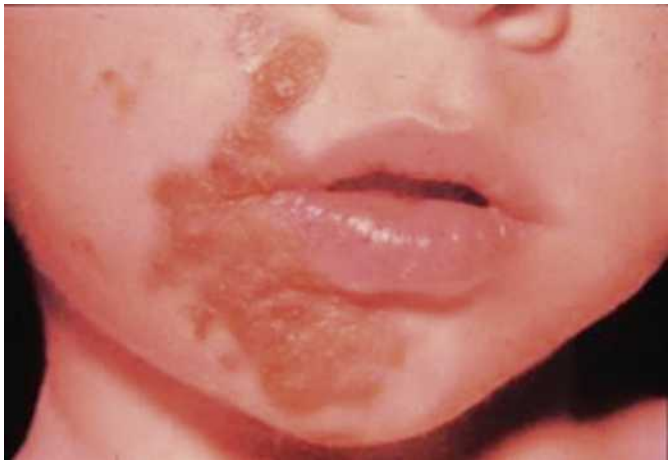

Fig. 107.2 Impetigo. (Courtesy Jonathan Singer, MD.)

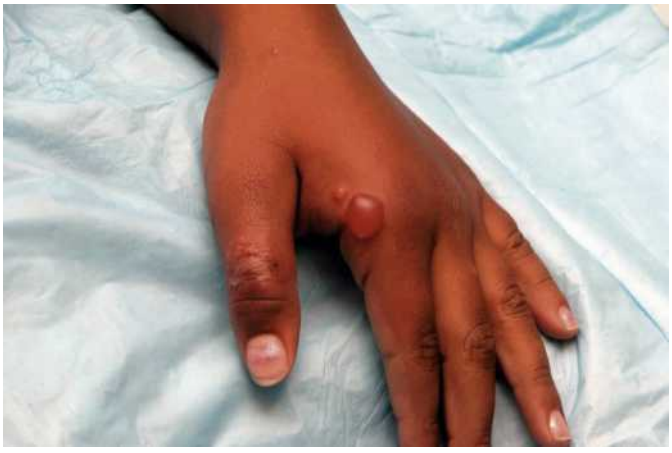

Fig. 107.3 Bullous Impetigo. (Courtesy David Effron, MD.)

Streptococcus aureus (MRSA) impetigo is increasingly common. Bullous impetigo is caused by the toxin released by staphylococcus. It is seen primarily in infants and young children. The initial skin lesions are thin-walled, 1- to 2-cm bullae (Fig. 107.3). When these rupture, they leave a thin serous crust and collarette-like remnant of the blister roof at the rim of the crust. The face, neck, and extremities are most often affected. The differential diagnosis includes contact dermatitis, HSV infection, superficial fungal infections, and pemphigus vulgaris.

Empirical therapy should be instituted with oral or topical antibiotics. Topical therapy is initiated with bacitracin, mupirocin, retapamulin, minocycline, or ozenoxacin.[4-7] Oral antibiotics are indicated for severe or multiple lesions. Oral therapies include an agent active against *S. aureus,* such as dicloxacillin or cephalexin. If MRSA is suspected, doxycycline, clindamycin, or trimethoprim-sulfamethoxazole (TMP-SMX) is recommended. Therapy for bullous impetigo consists of a systemic oral antibiotic, such as dicloxacillin, erythromycin, or azithromycin. Even without treatment, impetigo generally resolves within 3 to 6 weeks (see Chapter 126).

Folliculitis

Folliculitis is an inflammation in the hair follicle, usually caused by *S. aureus.* It appears as pustules with a central hair. The lesions are commonly on the buttocks and thighs, in the beard or scalp, and may cause mild discomfort. The differential diagnosis includes acne, keratosis pilaris, or fungal infection. Gram-negative folliculitis with

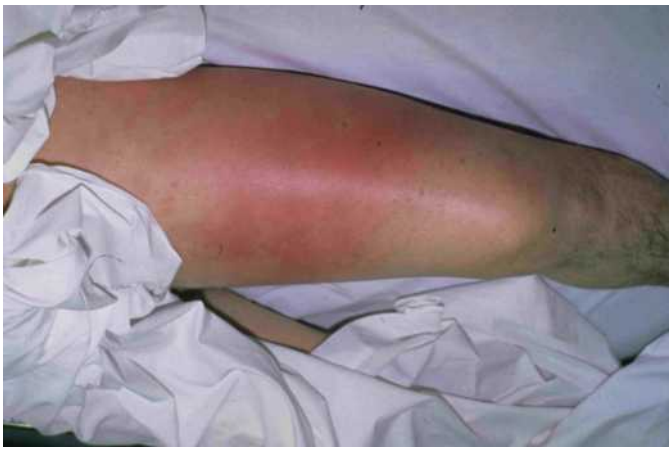

Fig. 107.4 Cellulitis. (Courtesy Jonathan Singer, MD.)

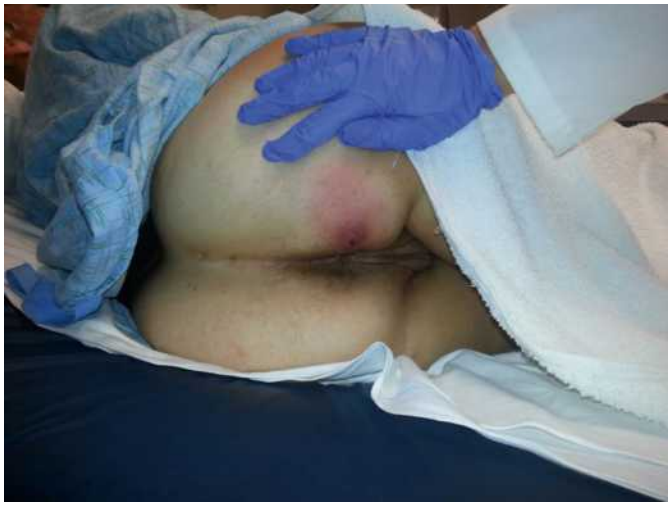

Fig. 107.5 Methicillin-Resistant *Staphylococcus aureus* (MRSA) Abscess With Cellulitis.

Pseudomonas aeruginosa can occur after exposure to infected hot tubs and swimming pools, or in individuals taking antibiotics for acne.

Local treatment with an antiseptic cleanser such as povidone-iodine or chlorhexidine every day or every other day for several weeks is usually adequate. For patients with extensive involvement, a course of systemic oral antibiotics may be added, such as doxycycline or dicloxacillin (see Chapter 126).

Cellulitis

Cellulitis presents with localized erythema, swelling, and pain of the soft tissues (Fig. 107.4). Erysipelas is a streptococcal infection of the skin and subcutaneous tissue and typically has an erythematous appearance with a well demarcated border, often with fever, malaise, or myalgias. Cellulitis may be a cause of sepsis. Ultrasound may be helpful in differentiating from abscess.

Mild cases of cellulitis may be treated with an oral antibiotic, such as a cephalosporin, dicloxacillin, or clindamycin. Moderate cases requiring IV therapy should be treated with a penicillin, ceftriaxone, cefazolin, or clindamycin. Severe cases should be treated with IV vancomycin plus piperacillin/tazobactam. Chapter 126 provides detailed management recommendations.

Abscess

Abscesses are accumulations of pus within body tissues. *Furuncles* are skin abscesses caused by staphylococcal infection involving hair follicles and surrounding tissue. They may present with localized soft tissue swelling, erythema, and fluctuance (Fig. 107.5). Ultrasound may be helpful in differentiating abscess, which appears as a fluid-filled cavity from cellulitis, which appears as cobblestoning, with fine reticular (net-like) areas of hypoechoic stranding.[8-10]

Carbuncles are large abscesses that develop in the thick, inelastic skin of the back of the neck, back, or thighs and usually involve multiple hair follicles. They may produce severe pain and fever. Septicemia may be a complication.

Abscesses should be treated with incision and drainage. Recent literature suggests higher cure rate for antibiotic treatment with TMP-SMX in addition to incision and drainage.[11-15] TMP-SMX and clindamycin have demonstrated efficacy in cure rates following incision and drainage.[16] Moderate or severe abscesses should ideally have culture and sensitivity performed. If IV antibiotics are indicated, agents may include vancomycin, daptomycin, linezolid, telavancin, or ceftaroline. Chapter 126 provides detailed management recommendations.

Hidradenitis suppurativa affects the apocrine sweat glands. Recurrent abscess formation in the axillae and groin resembles localized furunculosis. The condition tends to be recurrent and may be resistant to therapy. Ultrasound will help differentiate abscesses from vascular or lymphoid structures. Hidradenitis suppurativa may be treated with drainage of abscesses if they are fluctuant, painful, and large. Antistaphylococcal antibiotics are useful if they are administered early and for a prolonged period. Begin treatment for mild disease with topical clindamycin for 3 months. In patients with more severe or nonresponsive disease, oral clindamycin combined with rifampin for 3 to 6 months is indicated. Antiandrogen therapy may be considered if antibiotics fail to produce improvement. Recurrent cases should be referred for surgical management.

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

The incidence of community-associated MRSA has risen steadily since the first report in 1993. In many major cities in the United States, MRSA is now the most common pathogen cultured from ED patients presenting with skin and soft tissue infections. Hospital-acquired MRSA isolates can survive on a variety of inanimate surfaces, sometimes for weeks. Pets (including dogs and cats), livestock, and birds have been identified as MRSA carriers; their role in MRSA transmission to humans is unclear.

MRSA infections are most often manifested as skin and soft tissue suppuration, such as an abscess, furuncle, or cellulitis. Lesions frequently exhibit central necrosis and are often confused with spider bites by patients. Clinical features cannot distinguish with certainty skin and soft tissue infections caused by MRSA from those caused by methicillin-susceptible *S. aureus*. Although rare, MRSA infection can present as necrotizing fasciitis. Recurrences of MRSA cellulitis are common. Contagion among the close household contacts of patients as well as correctional facility, school, or sports team contacts is well recognized.

Local resistance patterns should guide therapy. Agents typically effective against MRSA include TMP-SMX, clindamycin, minocycline, or doxycycline. Cephalosporins and macrolides are typically ineffective against MRSA. Fluoroquinolones should be avoided as *S. aureus* resistance develops readily.

Patients with large abscesses, abscesses in high-risk locations, fever, signs of systemic infection, young age, or immunodeficiency should be considered for inpatient treatment. Vancomycin is considered the parenteral drug of choice for patients with invasive *S. aureus* infection, although clinical failures have been reported. It is reasonable to combine vancomycin with another effective

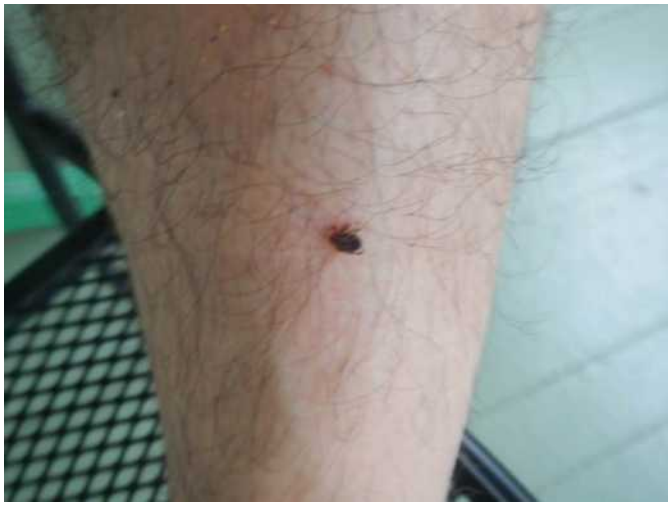

Fig. 107.6 Tick.

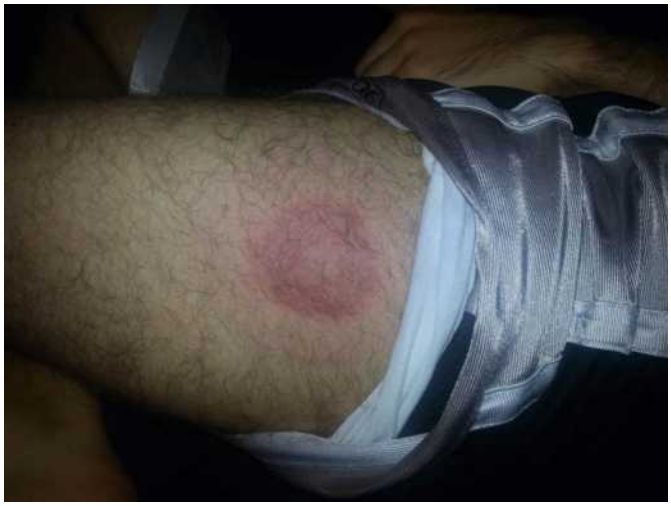

Fig. 107.7 Erythema Migrans.

anti-staphylococcal agent as many antibiotics have better bactericidal activity. In severely ill patients, carbapenems such as meropenem, panipenem, and ertapenem are recommended, because they are active against MRSA and synergistic with vancomycin. Other effective parenteral agents may include clindamycin, linezolid, daptomycin, tigecycline, or telavancin. Chapter 126 provides detailed management recommendations.

Although decolonization strategies have been recommended by some, neither the indications for their use nor their effectiveness in reducing the risk of recurrences has been established. Common antiseptics appear to retain reasonable activity against MRSA, although the results of studies are somewhat conflicting. Good personal hygiene, including appropriate handwashing techniques, separation of infected patients, and routine cleaning of shared equipment, remain essential to limiting MRSA spread.

Erythema Migrans

Lyme disease is caused by the organism *Borrelia burgdorferi* and is transmitted by the deer tick bite (Fig. 107.6). Most cases occur in the spring and early summer. Endemic areas in the U.S. include the Northeast, Midwest, West, and scattered other areas. Although 36 to 48 hours of tick attachment is necessary to transmit disease, less than 33% of patients recall a tick bite. The incubation period is 3 to 30 days.

Clinical presentations include three disease stages. Stage I occurs early and is manifested by malaise, headache, fever, lymphadenopathy, and arthralgias. Stage I typically resolves in 4 weeks. Erythema migrans occurs in 60% to 80% of cases and manifests as erythematous annular, non-scaling lesion with central clearing (Fig. 107.7). Stage II presents with secondary annular lesions, fever, lymphadenopathy, neurologic manifestations, or cardiac conduction abnormalities that may last weeks to months. Stage III manifests as chronic arthritis, dermatitis, or central nervous system (CNS) disease.

Diagnostic tests may include a nonspecific elevated ESR and serologic tests, which are helpful in establishing the definitive diagnosis but are not typically available acutely. Serologic testing includes a two-tiered serologic analysis consisting of an enzyme-linked immunoassay or immunofluorescence assay, followed by reflexive immunoblotting.[17]

Management should include appropriate antibiotic administration. The antibiotic regimen may include doxycycline or amoxicillin, for 10 to 21 days, or as alternates, cefuroxime, clarithromycin, erythromycin, or azithromycin.[18,19] Chapter 123 provides detailed management recommendations.

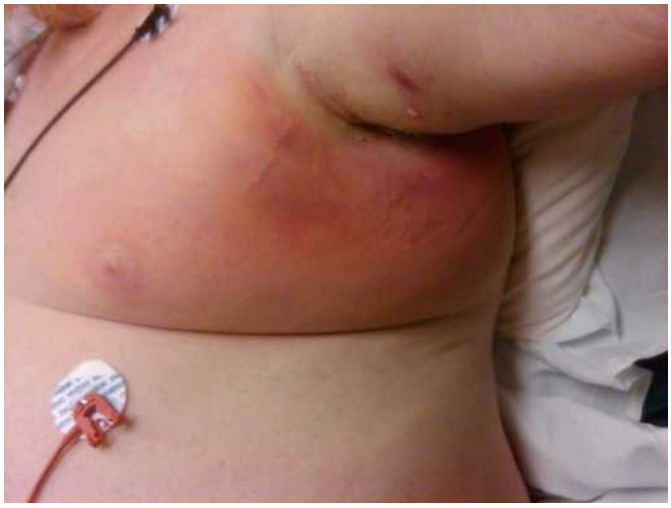

Fig. 107.8 Necrotizing Fasciitis.

Necrotizing Fasciitis

Necrotizing fasciitis should be considered with skin and soft tissue infection with signs of systemic toxicity, or severe infection (Figs. 107.8, 107.9, and 107.10). The etiology is often polymicrobial (mixed aerobic/anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). Radiographic tests may demonstrate soft tissue air. Prompt surgical consultation is indicated.

Empirical antibiotic treatment should be instituted with broad coverage, such as vancomycin or linezolid plus one of the following: piperacillin-tazobactam, carbapenem, or a combination of ceftriaxone and metronidazole. Chapter 126 provides detailed management recommendations.

Meningococcal Infection

Meningococcal infection is caused by the organism *Neisseria meningitides,* typically transmitted by respiratory secretions. Meningococcal disease may manifest as one of three syndromes: meningitis, bacteremia, or pneumonia. Meningococcal disease typically affects healthy children and adolescents, and it may result in significant morbidity and mortality. Infection is fatal in approximately 10% of cases.

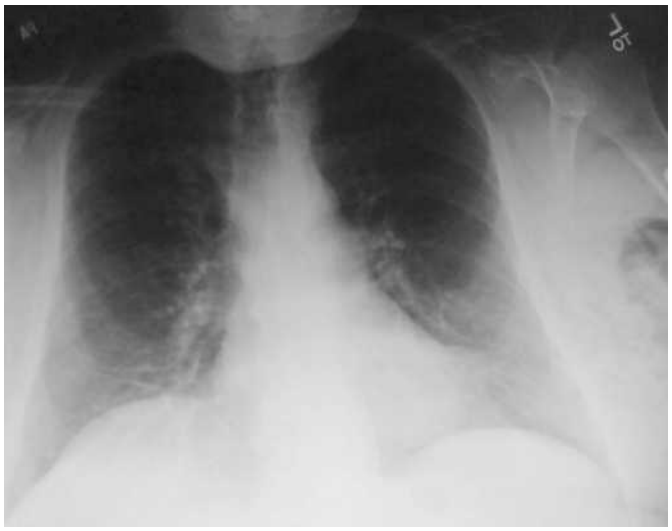

Fig. 107.9 Necrotizing Fasciitis. Note air in subcutaneous tissues.

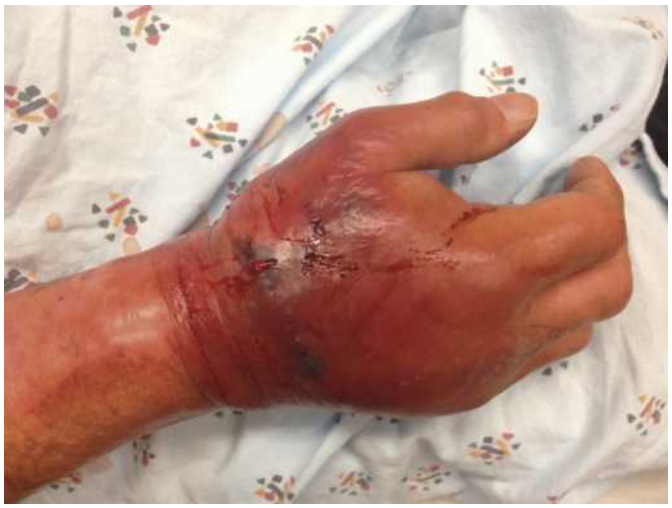

Fig. 107.10 Necrotizing Fasciitis.

Clinical presentation may include fever, malaise, arthralgias, nausea, and vomiting. Cutaneous findings of macules, papules, vesicles, or petechiae and purpura may be present.

Ten percent of cases may present with Waterhouse-Friderichsen syndrome characterized by shock with intracutaneous hemorrhage.

The diagnosis should be suspected clinically and treated promptly. Confirmatory tests may include blood cultures, cerebrospinal fluid (CSF) cultures, or skin scrapings.

Empirical therapy should be instituted with agents, such as a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) plus vancomycin. Alternative antibiotics may include penicillin G, chloramphenicol, a fluoroquinolone, or aztreonam. Dexamethasone should also be considered for suspected or proven meningitis.[20,21] Immunization against meningococcal infection is recommended for groups at increased risk for infection, including adolescents. Chapter 118 provides detailed management recommendations.

Scarlet Fever

Scarlet fever results from group A strep infection. The illness presents with fever, chills, malaise, and sore throat, followed within 12 to 48 hours by a distinctive rash that begins on the chest and spreads rapidly, usually within 24 hours. Circumoral pallor may be noted. The skin has a rough sandpaper-like texture due to a multitude of tiny papules. The pharynx is typically injected, and there may be erythematous lesions or petechiae on the palate. After the resolution of symptoms, desquamation of the involved areas may occur. Erythema marginatum may be seen in 10% of cases and presents with annular erythematous lesions that may be transient and reappear over days, weeks, or months (Fig. 107.11).

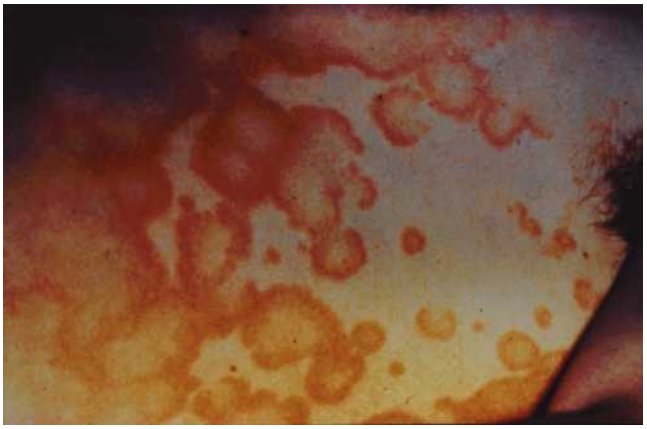

Fig. 107.11 Erythema Marginatum Associated With Rheumatic Fever. (Courtesy David Effron, MD.)

Complications include the development of a streptococcal infection of lymph nodes, tonsils, middle ear, or respiratory tract. Late complications include rheumatic fever or glomerulonephritis.

Treatment should be initiated with oral penicillin VK (children <27 kg: 250 mg twice daily or three times daily for 10 days; adolescents and adults: 250 mg four times daily or 500 mg twice daily for 10 days) or IM benzathine penicillin (given as Bicillin C-R (<27 kg: 600,000 units as a one-time dose; ≥27 kg: 1,200,000 units as a one time dose). In patients allergic to penicillin, treatment may be initiated with erythromycin, other macrolides, or a cephalosporin.

Syphilis

Syphilis is the third most common sexually transmitted infection in the United States (following chlamydia and gonorrhea) and is transmitted by direct contact with an infectious lesion. The incidence of reported cases has risen steadily since 2001. The causative organism is the spirochete *Treponema pallidum.* After an incubation period of 10 to 90 days, the primary lesion appears, which lasts 3 to 12 weeks and heals spontaneously. If untreated, in 6 weeks to 6 months after exposure, the secondary stage may be manifest. These lesions also heal spontaneously in 2 to 6 weeks as the disease enters the latent phase. Tertiary syphilis or latent syphilis may occur in months to years after untreated secondary syphilis.

The chancre is the dermatologic manifestation of primary syphilis. Chancres usually appear as single lesions but may be multiple. They appear at the site of spirochete inoculation, usually the mucous membranes of the mouth or genitalia. The chancre begins as a papule and characteristically develops into an ulcer approximately 1 cm in diameter with a central base and raised borders (Fig. 107.12). The chancre is typically painless unless it is secondarily infected, and it may be accompanied by painless lymphadenopathy. Many patients do not recall the primary chancre.

The secondary stage usually follows the primary stage by 6 weeks or more. There are a number of cutaneous manifestations of secondary syphilis. Lesions may be erythematous or pink macules or papules, usually with a generalized symmetric distribution. Secondary syphilis should be considered in the differential diagnosis of any maculopapular

Fig. 107.12 Primary Syphilis (Courtesy David Effron, MD.)

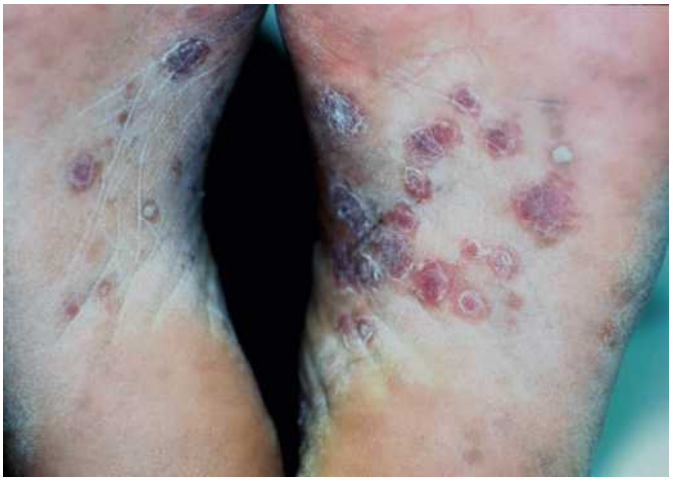

Fig. 107.13 Secondary Syphilis. (Courtesy David Effron, MD.)

rash. Pigmented macules and papules may appear on the palms and soles (Fig. 107.13). Generalized lymphadenopathy and malaise accompany the skin lesions. Moist, flat, verrucous condyloma latum may appear in the genital area. These lesions are highly contagious.

The diagnosis of primary or secondary syphilis should be made in the ED based on clinical presentation. Definitive diagnosis is made by the identification of spirochetes with darkfield microscopy and by serologic testing. The result of the Venereal Disease Research Laboratory (VDRL) test, the most commonly used diagnostic nontreponemal serologic test, is positive in approximately three-fourths of patients with primary syphilis but may be negative early in the course of the disease. The VDRL test result is positive in cases of secondary syphilis. Rapid plasma reagin (RPR) is an alternative nontreponemal test. The most specific and sensitive serologic test is the fluorescent treponemal antibody absorption (FTA-ABS) test.

Current guidelines for syphilis treatment, including in penicillin allergic individuals, are available at www.cdc.gov.[22] Treatment should be initiated in the ED based on clinical diagnosis. Primary and secondary syphilis is treated with benzathine penicillin G in a dose of 2.4 million units IM.[23] Pregnant women should be treated with the regimen appropriate for their disease state. Doxycycline or azithromycin are alternatives in patients with penicillin allergy. Patients with early latent syphilis are treated the same as patients with primary disease, whereas late latent syphilis and tertiary syphilis are treated with benzathine penicillin G, three doses of 2.4 million units IM at weekly intervals for a total of 7.2 million units. Treatment of neurosyphilis requires infusion of aqueous crystalline penicillin, 3 to 4 million units IV every 4 hours for 10 to 14 days. Following antibiotic therapy, patients may experience a *Jarisch-Herxheimer reaction,* with symptoms of fever, headache, and myalgia.

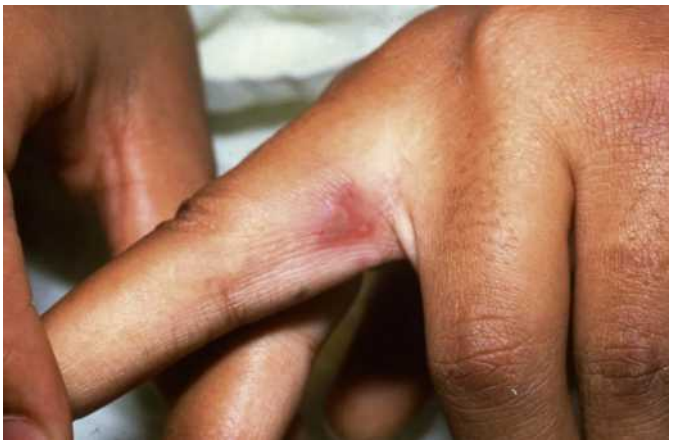

Fig. 107.14 Disseminated Gonococcal Infection. (Courtesy David Effron, MD.)

Disseminated Gonococcal Infection

Gonococcal infections are the second most common notifiable condition in the U.S., following *Chlamydia trachomatis* infections.[24] The incidence of reported gonococcal infection has risen consistently since 2009. Disseminated gonococcal infection (DGI) occurs in less than 2% of patients with gonorrhea, affecting women primarily. Symptoms typically include fever and migratory asymmetric polyarthralgias, tenosynovitis, or skin lesions. The lesions have a predilection for periarticular regions of the distal extremities. The lesions typically begin as erythematous or hemorrhagic papules that evolve into pustules and vesicles with an erythematous halo (Fig. 107.14). They may be tender and may have a gray necrotic or hemorrhagic center. Healing with crust formation usually occurs within 4 or 5 days, although recurrent crops of lesions may appear even after antibiotics have been started. Rare complications may include perihepatitis, endocarditis, or meningitis.

The organism may be cultured from the cutaneous lesions. A more reliable diagnostic technique is immunofluorescent antibody staining of direct smears from pustules.

Treatment should be initiated with ceftriaxone, 1 g IV q 24 hours, and treatment for chlamydia with doxycycline 100 mg bid for 7 days. Alternatives include cefotaxime or ceftizoxime, plus doxycycline. Patients allergic to β-lactam antibiotics or those with severe penicillin allergies may be treated with spectinomycin. Ciprofloxacin and ofloxacin are not recommended owing to increasing resistance patterns. Hospitalization is recommended for patients with DGI. Chapter 84 provides detailed management recommendations.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) typically occurs in children 6 years old or younger. It is caused by an infection with phage group 2 exotoxin-producing staphylococci. The illness begins with erythema and crusting around the mouth. The erythema then spreads

down the body, followed by bulla formation and desquamation. Mucous membranes are typically spared. After desquamation occurs, the lesions dry up quickly, with clinical resolution in 3 to 7 days.

Treatment should be initiated promptly with intravenous antibiotics, such as nafcillin, oxacillin, or vancomycin. For patients allergic to penicillin, alternatives may include clarithromycin or cefuroxime.[25] Chapter 126 provides detailed management recommendations.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is an acute febrile illness characterized by a diffuse desquamating erythroderma. Clinical presentation may include high fever, hypotension, constitutional symptoms, multiorgan involvement, and rash. The syndrome gained notoriety in the early 1980s because of association with tampon use. However, it is also well known in men and children. Its appearance has often been linked to exotoxin-producing *S. aureus*. Approximately 50% of cases are associated with menstruation. Other cases occur in the postoperative setting, or related to burns, postpartum infection, osteomyelitis, arthritis, empyema, fasciitis, septic abortion, pharyngitis, peritonsillar abscess, sinusitis, or subcutaneous abscess.[26]

TSS is typically caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. It has been reported in previously healthy patients, immunocompromised patients, and elders. Fatigue, localized pain, and nonspecific symptoms herald the onset of this disease, followed by septic shock and multisystem organ failure.

Diagnosis of TSS requires the presence of (1) temperature of at least 38.9°C; (2) hypotension, with a systolic blood pressure of 90 mm Hg or less; (3) rash; and (4) involvement of at least three organ systems. Systemic involvement may include the gastrointestinal tract, muscular system, or CNS and laboratory evidence of renal, hepatic, or hematologic dysfunction. Headache, myalgias, arthralgias, alteration of consciousness, nausea, vomiting, or diarrhea may be present.

The rash is typically a diffuse, blanching, macular erythroderma. Accompanying nonexudative mucous membrane inflammation is common. Pharyngitis, sometimes accompanied by a "strawberry tongue," conjunctivitis, or vaginitis, may be seen. As a general rule, the rash fades within 3 days of its appearance. This is followed by a full-thickness desquamation, most commonly involving the hands and feet.

Initial treatment of TSS consists of IV fluid replacement, ventilatory support, pressor agents, antibiotics covering *S. aureus* (including MRSA) and *S. pyogenes*. Initial empirical antibiotic regimens may include clindamycin, vancomycin, linezolid, imipenem, meropenem, ticarcillin-clavulanate, or piperacillin-tazobactam. Chapter 126 provides detailed management recommendations.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii,* an organism harbored by a variety of ticks. The organism is transmitted to humans through tick saliva at the time of a tick bite, or when the tick is crushed while in contact with the host. Many patients do not report tick exposure. Although originally described in the Rocky Mountain region, this disease occurs in other areas of North, South, and Central America. Most reported cases are from the southeastern United States.

The onset of the illness is usually abrupt, with headache, nausea and vomiting, myalgias, chills, and fever. On occasion, the onset is more gradual, with progressive anorexia, malaise, and fever. The disease may last 3 weeks and may be severe with prominent involvement of the CNS, cardiac, pulmonary, gastrointestinal, and renal systems, disseminated intravascular coagulation, or shock.

The rash develops on the second to sixth day. It begins with erythematous macules that blanch on pressure, appearing first on the wrists and ankles. These macules spread up the extremities and to the trunk and face. They may become petechial or hemorrhagic (Fig. 107.15). Lesions on the palms and soles are characteristic. Increased capillary fragility and splenomegaly may be present.

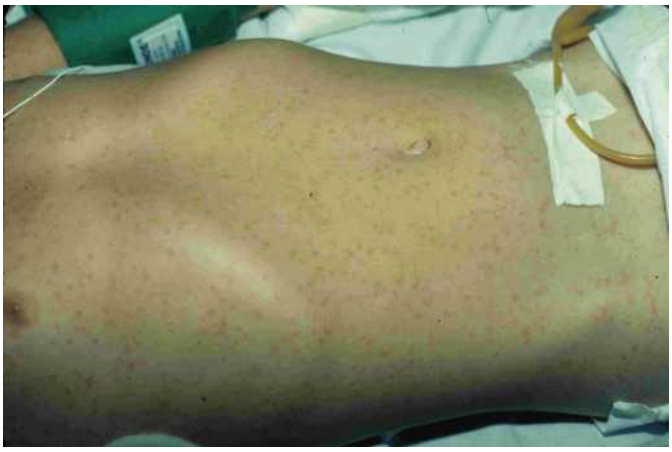

Fig. 107.15 Rocky Mountain Spotted Fever. (Courtesy Jonathan Singer, MD.)

The diagnosis of Rocky Mountain spotted fever should be made based on clinical presentation in the ED. Definitive testing is not available in the ED and may include the Weil-Felix reaction and more specific immunofluorescent procedures.

Treatment should be initiated promptly based on a clinical diagnosis (see Chapter 126). Failure to administer antibiotics in a timely fashion dramatically increases morbidity and mortality. Treatment should be initiated with doxycycline.[27] Chloramphenicol may be used for patients allergic to tetracyclines, or in children younger than 9 years old. Sulfa drugs should be avoided, as they may exacerbate the illness. Rickettsiae are routinely resistant to penicillins, cephalosporins, aminoglycosides, and erythromycin. Ehrlichiosis may be difficult to differentiate from Rocky Mountain spotted fever clinically, though it is also reliably treated with doxycycline.

Viral Infections

Herpes Simplex Virus

Two known variants of HSV routinely cause human infection: HSV-1 and HSV-2. HSV-1 primarily affects nongenital sites, whereas lesions caused by HSV-2 are found predominantly in the genital area and are transmitted primarily by sexual contact. There is significant variation in viral type and anatomic site of infection.

The characteristic presentation is painful, grouped vesicles on an erythematous base (Fig. 107.16). The lesions are usually localized in a clustered, nondermatomal distribution. The skin distribution may become more generalized in patients with atopic dermatitis or other dermatoses. Adults with HSV infection should avoid contact with children with atopic dermatitis, especially in the first 3 to 5 days of infection.

The mouth is the most common site of HSV-1 infections. Children are affected more commonly than adults. Small clusters of vesicles appear but are soon denuded, leaving irregularly shaped, crusted erosions. The severity of gingivostomatitis varies from the presence of small ulcers to extensive ulceration of the mouth, tongue, and gums accompanied by fever and cervical lymphadenopathy (Fig. 107.17). The infection may be so severe that oral fluid intake is difficult, and dehydration may result. Healing typically occurs in 7 to 14 days unless a secondary bacterial infection occurs.

Herpetic whitlow is a herpes infection of the hand, typically affecting the distal phalanx (Fig. 107.18). It may be caused by HSV-1 (60%) or HSV-2 (40%).

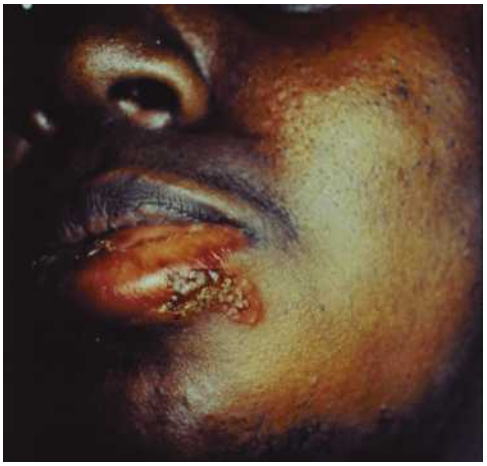

Fig. 107.16 Herpes Simplex Virus 1 (HSV-1) Infection. (Courtesy David Effron, MD.)

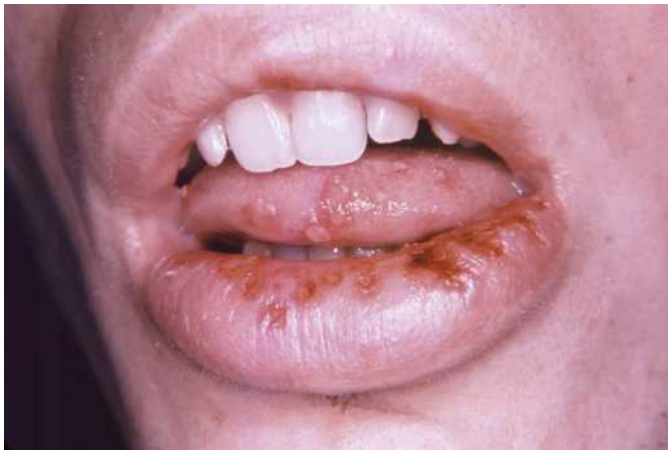

Fig. 107.17 Herpes Simplex. (Courtesy Centers for Disease Control and Prevention [CDC] Public Health Image Library, Robert E. Sumpter.)

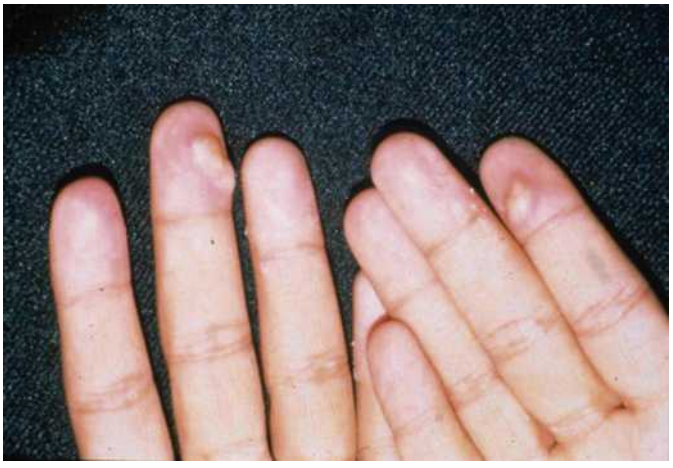

Fig. 107.18 Herpetic Whitlow. (Courtesy Jonathan Singer, MD.)

HSV-2 infections in men present with either single or multiple vesicles or erosions on the penile shaft or glans penis. Fever, malaise, and regional adenopathy may be present. A prodrome of local pain and hyperesthesia may precede the appearance of the cutaneous lesions. The vesicles erode after several days, become crusted, and heal in 10 to 14 days. Infections in women involve the introitus, cervix, or vagina.

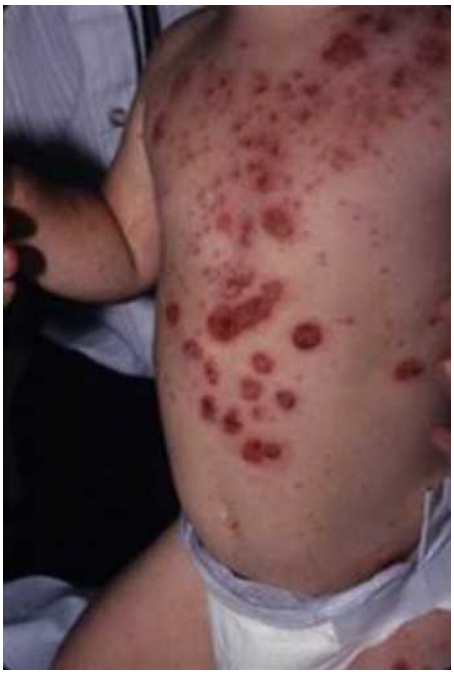

Fig. 107.19 Varicella Zoster. (Courtesy Jonathan Singer, MD.)

Vesicles may be grouped or confluent, and may be denuded, leaving erosions and ulcerations. Herpetic cervicitis or vaginitis may be the cause of pelvic pain, dysuria, or vaginal discharge. Recurrence is common, and recurrent episodes tend to be less severe.

Recommended treatment for a first clinical episode of genital herpes is with acyclovir, famciclovir, or valacyclovir. These agents reduce the duration of viral shedding, accelerate healing, and shorten the duration of symptoms, but they do not prevent recurrent episodes. Prophylactic administration of acyclovir may be effective in ameliorating the severity of recurrent genital herpes.

IV therapy should be considered for immunocompromised patients. A mucocutaneous herpes infection in such patients is potentially fatal, as it has a propensity for generalization and dissemination to the internal organs.

Any vesicular eruption on skin or mucous membranes in a neonate should prompt concern for HSV infection, as there is a high likelihood of dissemination in this group. Unless an alternative diagnosis is established, testing of the vesicle fluid for HSV and acyclovir therapy are indicated.

Supportive care and pain control are important components of treatment. Systemic analgesics or topical anesthetic agents may be useful. Education of the patient about the prevention or spread of the disease during sexual contact and the birth process is imperative. Chapter 119 provides detailed management recommendations.

Varicella-Zoster Virus

Varicella. Varicella, or chickenpox, is an infection caused by the varicella-zoster virus. After an incubation period of 14 to 21 days, the illness begins with a low-grade fever, headache, and malaise. The exanthem coincides with these symptoms in children and follows them by several days in adults.

The skin lesions rapidly progress from macules to papules to vesicles to crusting, sometimes within 6 to 8 hours. The vesicle of varicella is 2 or 3 mm in diameter and surrounded by an erythematous border (Fig. 107.19). An unusual form of varicella has larger bullae. The drying of the vesicle begins centrally, producing umbilication. The dried scabs typically disappear in 5 to 20 days.

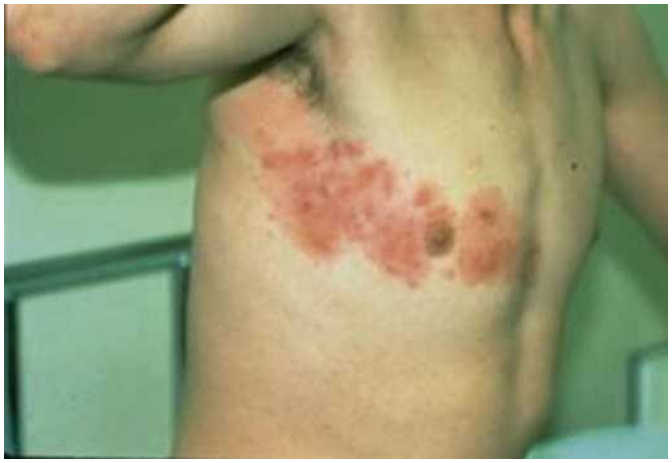

Fig. 107.20 Herpes Zoster. (Courtesy David Effron, MD.)

Lesions appear in crops on the trunk, where they are seen in the highest concentration, and on the scalp, face, or extremities. The hallmark of varicella is the appearance of lesions in all three stages of development in one region of the body. Extensive eruptions are often associated with a high and prolonged fever.

Complications include encephalitis or meningitis, pneumonia, secondary staphylococcal or streptococcal cellulitis, thrombocytopenia, arthritis, hepatitis, or glomerulonephritis. Varicella pneumonia occurs more commonly in adults than in children.

The illness is typically self-limited, and treatment is symptomatic. Salicylates should be avoided to minimize the risk of subsequent Reye syndrome. Oral acyclovir may be effective if it can be started within 24 hours of development of rash for patients with chronic respiratory or skin disease. Chapter 119 provides detailed management recommendations.

The disease has the potential to be contagious until all vesicles are crusted and dried, thus infected persons should be kept at home until this stage is reached. Isolation of infected patients is often futile as the disease may be transmitted before the diagnosis is clinically evident.

Varicella zoster immune globulin (VariZIG) is indicated for administration to high-risk individuals within 10 days (ideally within 4 days) of varicella zoster virus exposure.[28]

The varicella vaccine is a live attenuated virus; it is highly efficacious and very safe. A single dose is effective in children between the ages of 1 and 13 years. For older children, two doses separated by 4 to 8 weeks are recommended. In addition, the incidence of zoster occurring after vaccination appears to be lower than that of naturally acquired disease.

Herpes zoster. Herpes zoster, or "shingles," is an infection caused by the varicella-zoster virus. It occurs in individuals who have previously had chickenpox and is caused by reactivation of the latent virus from the dorsal root ganglion. At risk populations include female sex, Caucasian race, family history, or comorbidities including autoimmune diseases, asthma, diabetes mellitus, or chronic obstructive pulmonary disease.[29] Dermatomal pain may precede the eruption by 1 to 10 days and is variable in intensity; it may be described as sharp, dull, or burning in quality. The typical rash consists of grouped vesicles on an erythematous base involving one or several adjacent dermatomes. The thorax is involved in most cases, and the trigeminal distribution is the next most commonly involved region.

The vesicles initially appear clear and then become cloudy and progress to scab and crust formation. This process takes 10 to 12 days, and the crusts fall off in 2 or 3 weeks (Fig. 107.20). Herpes zoster has a peak incidence in patients 50 to 70 years old and is unusual in children. Complications may include CNS involvement, ocular infection, stroke, meningoencephalitis, myelitis, peripheral neuropathy, or myocardial infarction.[30] Ocular complications occur in 20% to 70% of cases involving the ophthalmic division of the trigeminal nerve. The severity varies from mild conjunctivitis to panophthalmitis, which threatens vision. Corneal dendritic lesions may be visible on fluorescein examination. Eye involvement may produce anterior uveitis, secondary glaucoma, optic neuritis, or corneal scarring. There is a close correlation between vesicles located at the tip of the nose and eye involvement (Hutchinson sign).

Herpes zoster generally tends to be more severe in immunosuppressed patients, especially those with acquired immunodeficiency syndrome (AIDS), Hodgkin disease, or other lymphomas. Individuals with immunosuppression or stress are at higher risk for disseminated herpes zoster infection.[31]

Herpes zoster infection is a clinical diagnosis, and treatment should be initiated based on clinical findings. If the diagnosis is in question, definitive diagnosis may be made by VZV DNA PCR or skin biopsy.

Antiviral medications are usually indicated, especially within 48 hours of onset of rash, to decrease the duration of symptoms and associated pain (see Chapter 119). Antiviral therapy may be initiated with first-line therapy with acyclovir, famciclovir, or valacyclovir. Intravenous acyclovir is indicated for treatment of disseminated HZV infection. Supportive care is important for pain and pruritus control. Burow's solution compresses (over-the-counter solution of aluminum triacetate) may be applied to hasten drying of lesions. Steroids have not been shown to reduce the incidence of postherpetic neuralgia.

IV administration of acyclovir may be of benefit in the treatment of severe ocular herpes zoster. Treatment includes mydriasis and the application of topical corticosteroids at the direction of an ophthalmologist. Eye involvement caused by herpes zoster does not appear to be exacerbated by corticosteroids, which differs from herpes simplex conjunctivitis.

Postherpetic neuralgia may occur in 15% of patients and is more common in the elderly. Treatments may include opioids, topical capsaicin, topical lidocaine, topical or oral gabapentin, or tricyclic antidepressants.[32-34] The varicella vaccine has been shown to reduce the incidence and severity of herpes zoster virus infection and is recommended for patients 60 years old and older.[35-37]

Viral Exanthems

An exanthem is defined as a skin eruption that occurs as a symptom of a general disease. In the pediatric population, an estimated 72% of cases of fever and rash are caused by viruses. Approximately 30 enteroviruses, predominantly the coxsackievirus and echovirus groups, and four types of adenoviruses are known to produce exanthems (Fig. 107.21). Most viral exanthems are maculopapular, although scarlatiniform, erythematous, vesicular, or petechial rashes are occasionally seen. The eruptions are variable in their extent, are typically nonpruritic, and do not desquamate. Oropharyngeal lesions may be present.

The classic viral exanthems are rubeola (measles), rubella (German measles), herpesvirus 6 (roseola), parvovirus B19 (erythema infectiosum or fifth disease), and the enteroviruses (echovirus and coxsackievirus).

Roseola infantum. Roseola infantum, otherwise known as *exanthem subitum* or *sixth disease,* is a benign illness caused by human herpesvirus 6 and human herpesvirus 7 and is typically spread by saliva. It is characterized by fever and a skin eruption. Ninety-five percent of cases are seen in children 6 months to 3 years old. The fever typically has an abrupt onset, with temperature rising rapidly to 39°C to 41°C, and is present consistently or intermittently for 3 or 4 days, at which time the temperature drops to normal. The rash typically appears with fever defervescence. The lesions are discrete pink or rose-colored macules

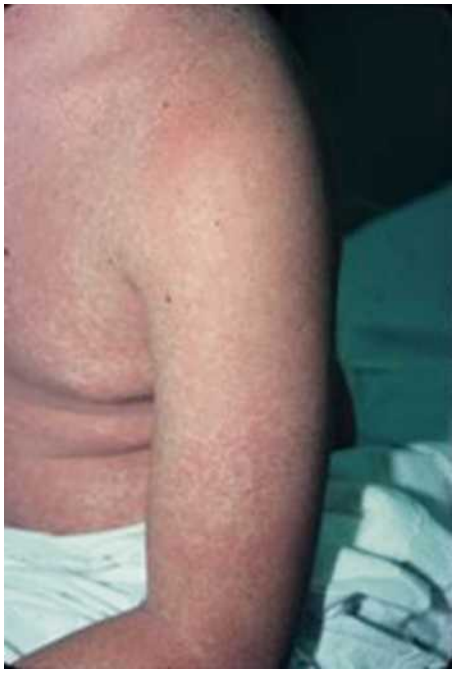

Fig. 107.21 Enterovirus. (Courtesy Jonathan Singer, MD.)

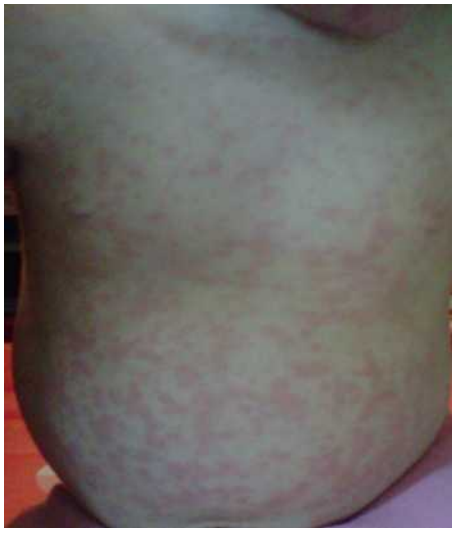

Fig. 107.22 Roseola.

or maculopapules, 2 or 3 mm in diameter, that blanch on pressure and rarely coalesce (Fig. 107.22). The trunk is involved initially, with the eruption typically spreading to the neck and extremities. The rash clears in 1 or 2 days.

Despite the presence of a high fever, the infant usually appears well. A febrile seizure may occur. Encephalitis is a very rare complication of the disease. The prognosis is excellent, and no treatment is necessary.

Measles. Measles, or rubeola, is a highly contagious viral illness spread by contact with infectious droplets, with an incubation period of 10 to 14 days. Although measles was declared eradicated in the US in 2000, the incidence has risen since that time.[38] Measles is most likely to infect unvaccinated individuals. Patients are considered to be contagious from 5 days prior to onset of symptoms until 5 to 6 days after the onset of dermatologic involvement.

Symptoms begin with fever and malaise. Symptoms include the "three C's": cough, coryza, and conjunctivitis. On the second day of the illness, Koplik spots, which are pathognomonic of the disease, may appear on the buccal mucosa as small, irregular, bright red spots with bluish white centers. Beginning opposite the molars, Koplik spots may spread to involve a variable extent of the oropharynx.

The cutaneous eruption of measles typically begins on the third to fifth day of the illness. Maculopapular erythematous lesions involve the forehead and upper neck and spread to involve the face, trunk, arms, and finally the legs and feet. Koplik spots begin to disappear coincident with the appearance of the rash. By the third day of its presence, the rash begins to fade, doing so in the order of its appearance, and the fever subsides.

Complications may include otitis media, encephalitis, or pneumonitis. Otitis media is the most common complication. Encephalitis or pneumonia may be life-threatening.

Treatment is primarily supportive and should include antipyretics, hydration, and treatment of pruritus (see Chapter 119). Vitamin A should be administered to hospitalized patients at the time of diagnosis and repeated the second day, to help prevent eye damage and blindness.[39] If bacterial invasion occurs with otitis media or pneumonia, antibiotics are indicated. Isolation of infected children is of limited value as exposure usually occurs before the appearance of the rash. Infection typically confers lifelong immunity. Postexposure prophylaxis may be administered with the measles virus vaccine or human immunoglobulin.

Rubella. Rubella, or German measles, is a viral illness characterized by fever, skin eruption, and generalized lymphadenopathy. It is spread by droplet contact, and peak incidence is in the winter and early spring. The incubation period is typically 14 to 21 days, and the rash heralds the onset of the illness in children. The maximum time of communicability is in the few days before and 5 to 7 days after the onset of the rash. Infants with congenital rubella may shed virus for more than 1 year. In adults, a 1- to 6-day prodrome of headache, malaise, sore throat, coryza, and low-grade fever precedes the rash. These symptoms generally disappear within 24 hours after the appearance of the skin eruption.

The rash of pink to red maculopapules appears first on the face and spreads rapidly to the neck, trunk, and extremities. Those on the trunk may coalesce, but lesions on the extremities typically do not. The rash remains for 1 to 5 days, and often disappears at the end of 3 days. Although clearing may be accompanied by fine desquamation, this sign is usually absent.

The major complications of rubella include encephalitis, arthritis, or thrombocytopenia. Rubella during pregnancy may result in congenital defects. No treatment is required in most cases of rubella. Antipyretics may be administered to treat headache, arthralgias, and painful lymphadenopathy.

Erythema infectiosum. Erythema infectiosum, or "fifth disease," is caused by parvovirus B19 infection and typically affects pediatric patients. It is characterized by mild systemic symptoms, fever in 10% to 15% of patients, and a characteristic rash. Arthralgia and arthritis occur commonly in adults but rarely in children. The rash is intensely red on the face and gives a "slapped-cheek" appearance with circumoral pallor. A reticular (netlike) maculopapular eruption, which may be noted on the arms, moves caudally to the trunk, buttocks, and thighs. The rash may recur with changes in temperature and exposure to sunlight. The incubation period is usually between 4 and 14 days. The infection is benign and management is supportive.

Fungal Infections

Fungal infections may affect the skin, scalp, or mucous membranes. The dermatophytoses are superficial fungal infections that are limited to the skin. Dermatophytes generally grow best in warm, moist environments,

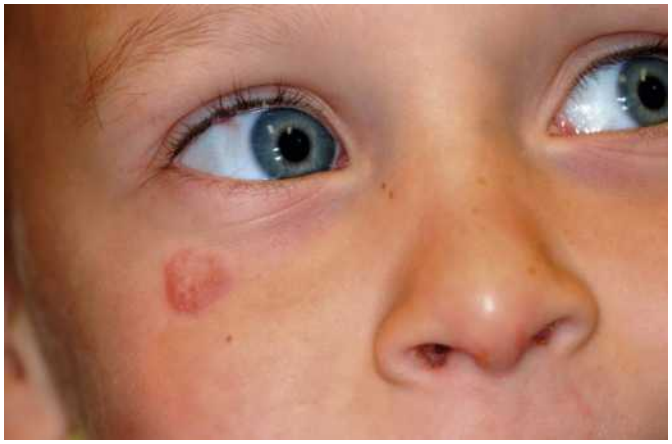

Fig. 107.23 Tinea Corporis. (Courtesy David Effron, MD.)

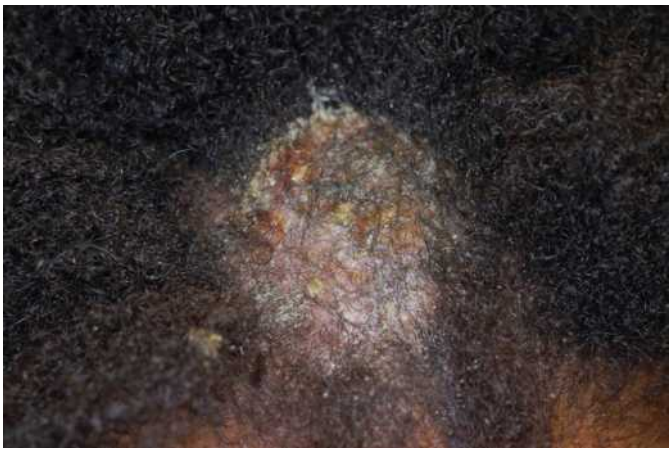

Fig. 107.24 Kerion of Tinea Capitis. (Courtesy David Effron, MD.)

and grow only in the keratin or outer layer of the skin, nails, or hair. Any potential dermatophyte infection can be examined under the microscope in a KOH preparation if available. The specimen is examined for the characteristic branching hyphae of the dermatophytes or the short, thick hyphae and clustered spores of tinea versicolor.

Tinea Corporis

Tinea refers to superficial dermatophytic infection of the skin, hair, or nails, usually by the *Trichophyton* organism. Tinea corporis, commonly referred to as "ringworm" infection, presents as a sharply marginated, annular lesion with raised or vesicular margins and central clearing (Fig. 107.23). Lesions may be single or multiple. Other related forms of tinea may be seen, including tinea cruris involving the groin, tinea manuum affecting the hands, and tinea pedis of the feet.

The differential diagnosis of tinea corporis includes erythema migrans (associated with Lyme disease, with annular lesions with central clearing without scale), granuloma annulare (idiopathic skin condition that causes raised annual lesions without scale), psoriasis (erythematous plaques with silvery scale), cellulitis (erythema without central clearing or scale), or erythrasma (superficial bacterial infection that presents with hyperpigmented patches).

Infections of the body, groin, or extremities usually respond to topical antifungal agents, such as clotrimazole, miconazole, tolnaftate, terbinafine, or naftifine. Two or three daily applications of the cream form of any of these preparations result in healing of most superficial lesions in 1 to 3 weeks.

Tinea Capitis

Tinea capitis is a fungal infection of the scalp, and it is the most common cutaneous fungal infection in children. Common organisms include *Microsporum* and *Trichophyton* species. Although it is often seen in pediatric patients 6 to 10 years old, tinea capitis may also occur in adults. Nosocomial transmission of dermatophyte infections, such as *Trichophyton tonsurans,* has also been reported. Alopecia may be seen, typically with thickened, scaly scalp. Broken hairs resembling black dots near the scalp may be seen. Hair loss is the result of hyphae growing within the hair shaft, rendering it fragile, so that the hair strands break off 1 to 2 mm from the scalp. The disease may be transmitted by close child-to-child contact, or contact with household pets, hats, combs, barber's shears, or similar items. Complications may include kerion formation, lymphadenitis, bacterial cellulitis or abscess, or scarring alopecia.

The differential diagnosis of tinea capitis includes alopecia areata (alopecia without scalp changes), atopic dermatitis (patches of thickened skin with scale), nummular eczema (eczema in small circular patterns), bacterial infection (such as cellulitis or abscess), psoriasis (erythematous patches with silvery scale), seborrheic dermatitis (pruritic yellow or white patches), or trichotillomania (hair pulling).

The diagnosis is made based on clinical presentation. If in question, a fungal culture specimen may be obtained.

Systemic therapy is required for tinea capitis, due to fungal invasion of the hair follicles. Treatment should be with a systemic antifungal agent, such as terbinafine (<25 kg: 125 mg/day PO for 6 weeks; 25 to 35 kg: 187.5 mg/day PO for 6 weeks; >35 kg: 250 mg/day PO for 6 weeks). Alternatives include itraconazole, fluconazole, or griseofulvin.[40] Therapy should be given for 4 to 8 weeks. Topical treatments such as selenium sulfide, ketoconazole, or ciclopirox shampoo in addition to systemic antifungal therapy may increase cure rates.[41] Patients should be referred for outpatient follow-up with primary care or dermatology within 4 weeks. Family members should be evaluated for possible infection.

Kerion

A kerion is a fungal infection affecting hair follicles that is characterized by intense inflammation, and a boggy, erythematous mass, typically affecting the scalp (Fig. 107.24). The lesion may contain frank pus. It usually affects the scalp and is more common in children and in African Americans. Local alopecia and scarring can result. Lymphadenopathy may be present. Accurate differentiation of a kerion with or without superinfection can be challenging. Wood's lamp examination can be helpful in confirming the diagnosis.

Kerions are treated the same as tinea capitis, with systemic antifungal agents for 6 to 8 weeks. If bacterial superinfection exists, an antibiotic is added. Antibiotic options include oral cephalexin, dicloxacillin, or clindamycin. Clindamycin is recommended when community-acquired MRSA is a concern. Surgical drainage of kerions is rarely helpful and should be avoided.

Tinea Pedis

Tinea pedis, commonly referred to as *athlete's foot,* presents with scaling, maceration, vesiculation, and fissuring between the toes and on the plantar surface of the foot. Common etiologies include *Trichophyton rubrum, Trichophyton interdigitale,* and *Epidermophyton floccosum.* Secondary bacterial infection may occur. The vesicular pustular form of tinea pedis should be considered when vesicles and pustules on the instep are noted. Interdigital lesions may cause minimal symptoms and serve as a portal of entry for bacterial cellulitis. The differential diagnosis includes contact dermatitis, and dyshidrotic eczema which usually presents as pruritic vesicles on the lateral aspects of fingers. A KOH preparation is helpful to differentiate among these processes.

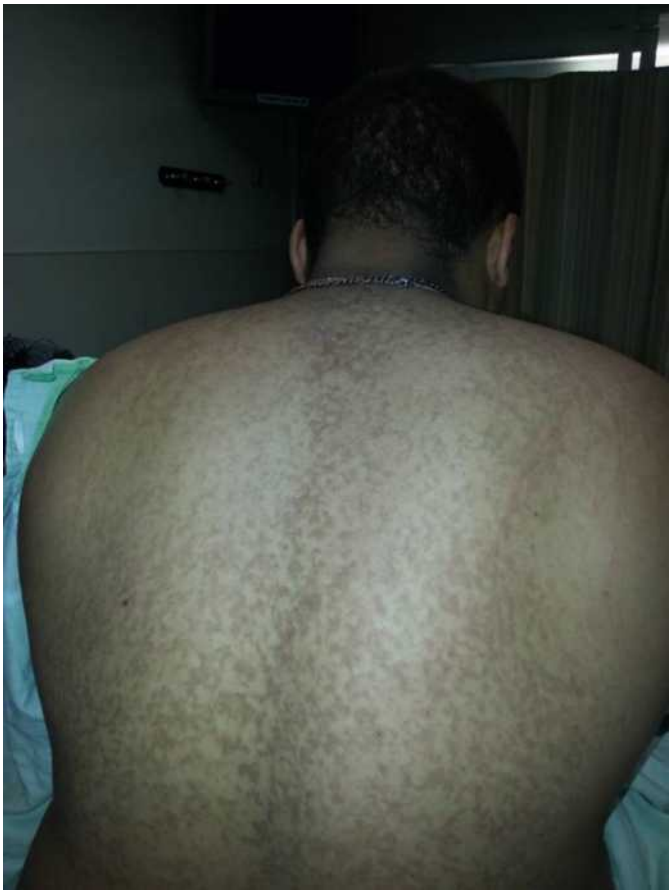

Fig. 107.25 Tinea Versicolor.

Treatment options include topical antifungal agents, such as terbinafine 1% cream, applied BID for 1 to 2 weeks. Alternatives include miconazole cream, powder, or spray, and clotrimazole cream, solution, or ointment. For severe disease or if topical treatment has failed, systemic therapy may be instituted with terbinafine, fluconazole, or griseofulvin.

Tinea Versicolor

Tinea versicolor, or pityriasis versicolor, is a superficial fungal infection caused by genus *Malassezia*. Superficial hypopigmented or hyperpigmented patches occur mainly on the chest and trunk, but may extend to the head and limbs. As the name implies, lesions can be a variety of colors, including pink, tan, or white. The disease may be associated with pruritus. On examination, a fine subtle scale is noted that may appear hypopigmented (Fig. 107.25). Pale yellow or orange fluorescence under Wood's light may be seen. The differential diagnosis includes vitiligo and seborrheic dermatitis. A KOH preparation reveals short hyphae mixed with spores ("chopped spaghetti and meatballs").

Tinea versicolor may be treated with topical antifungal agents, such as 2.5% selenium sulfide shampoo, applied daily for 1 weeks. Alternative therapies include imidazole creams, and ketoconazole cream or foam. For topical treatment failures, systemic therapy may be indicated, such as fluconazole, as a single 150- to 300-mg weekly dose for 2 to 4 weeks. Recurrence is common. Pigmentation may not return to normal for months.

Tinea Unguium (Onychomycosis)

Tinea unguium may be caused by dermatophytes, candida, or other fungal species. Paronychia or untreated tinea pedis may be predisposing factors. Onychomycosis presents with toenails or fingernails that are thickened, opaque, cracked, or destroyed. Subungual debris is present, and the nail may contain yellowish longitudinal streaks (Fig. 107.26). The nail of the great toe is most commonly involved. Differential diagnosis includes tinea pedis, psoriasis, or warts.

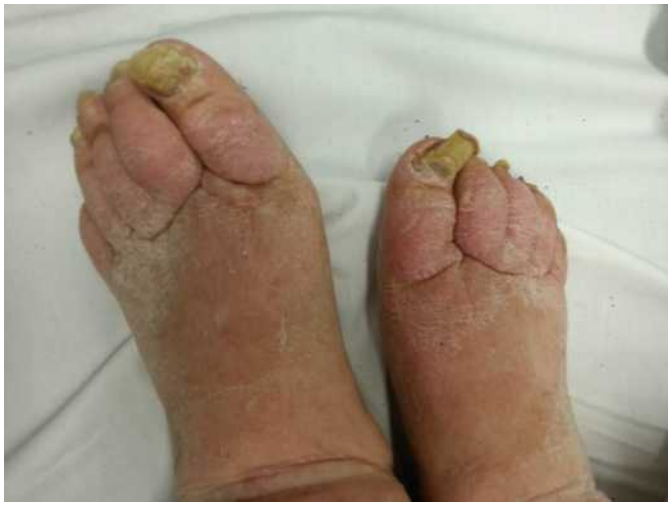

Fig. 107.26 Onychomycosis.

Topical therapy of the nails may be initiated if less than 25% of the nail bed is involved, but often may not result in cure due to poor penetration into the nail keratin.[42] Fingernails typically respond more rapidly to therapy than toenails. Involvement of one or two nails may be treated with topical antifungal agents. More extensive infection or risk factors (including advanced age, diabetes, immunosuppression, or widespread infection) requires systemic therapy with an antifungal agent, such as terbinafine (250 mg PO daily for 6 weeks [fingernail]) or 12 weeks [toenail]) or itraconazole (200 mg bid for 1 week, repeated q4wk for 2 mo [fingernail] or 200 mg/day PO for 12 weeks [toenail]).[43] Third-line agents may include griseofulvin or ketoconazole, which require prolonged courses, with high relapse rates and numerous side effects. Treatment failures or relapses are common, and they may be attributed to poor patient compliance, low bioavailability, lack of drug penetration into the nail, drug resistance, or drug interactions. Additional therapies may include surgical removal of the nail, photodynamic therapy, or laser therapy.

Candidiasis

Infection by *Candida albicans* may occur in patients of all ages. Many conditions predispose to infection, including diabetes mellitus, HIV infection, pregnancy, obesity, smoking, malnutrition, malignancy, or treatment with corticosteroids, antibiotics, or immunosuppressive agents.

Oral candidiasis. Oral candidiasis ("thrush") is the most common clinical expressions of *Candida* infection. It is common in newborns with one-third being affected by the first week of life, and also in elder persons, immunosuppressed individuals, or persons wearing dentures. It appears as patches of white or gray friable material covering an erythematous base on the buccal mucosa, gingiva, tongue, palate, or tonsils. Fissures or crust at the corners of the mouth may be present. The differential diagnosis of oral candidiasis includes lichen planus (which unlike *C. albicans* is not easily scraped off), or hairy leukoplakia (villous white patches on the lateral tongue). Oral mucous membrane infection with *C. albicans* is an AIDS-defining illness. If the patient does not use dentures and has not taken antibiotics recently, underlying immunosuppression should be considered.

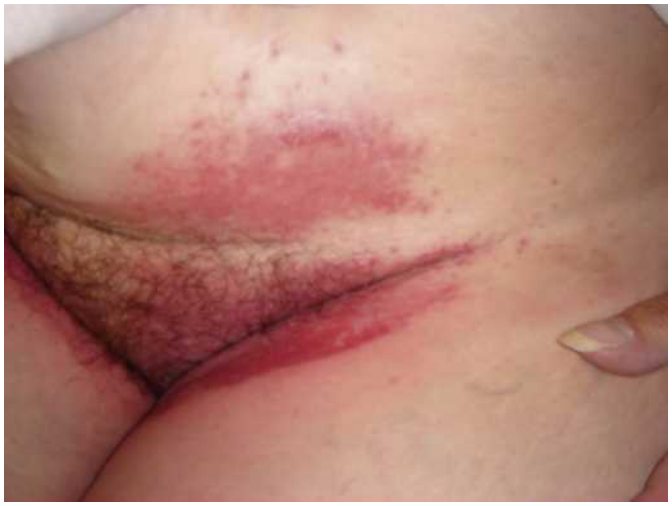

Fig. 107.27 Candida Intertrigo.

Treatment of oral candidiasis includes topical antifungal agents, such as clotrimazole troches five times daily, or oral nystatin suspension four times daily, or nystatin pastilles four times daily. Treatment is continued for 5 to 7 days after the lesions disappear. For esophageal candidiasis, systemic antifungal therapy is typically required, with oral fluconazole, IV fluconazole, or IV amphotericin B. Chapter 121 provides detailed management recommendations.

Cutaneous candidiasis. Cutaneous candidiasis affects intertriginous areas, including the interdigital web spaces, groin, axilla, and intergluteal or inframammary folds. Lesions appear as moist, bright red macules rimmed with a collarette of scale, with small satellite papules or pustules just peripheral to the main body of the rash (Fig. 107.27). These satellite lesions are typical indicators of a *Candida* infection. Intertriginous lesions are prone to bacterial superinfection.

The differential diagnosis of cutaneous candidiasis includes contact dermatitis, tinea cruris, intertrigo, herpes simplex such as herpetic whitlow, and folliculitis. Candidiasis, however, is less sharply demarcated than tinea cruris and brighter red than intertrigo. A KOH preparation of a specimen taken from a pustule and roof of the lesion will reveal hyphae and pseudohyphae.

Intertriginous lesions should be treated with topical imidazole creams, such as clotrimazole, 1% cream BID for 4 weeks. Alternative topical therapies include miconazole, ketoconazole, or sulconazole. Extensive infection may be treated with fluconazole (100 mg PO daily for 2 weeks) or itraconazole (100 mg PO daily for 2 weeks). The area should be kept dry.

Vulvovaginal candidiasis. Vaginal candidiasis accounts for 20% to 25% of vaginitis. It has been estimated that 75% of women will experience vaginal candidiasis at least once. Predisposing factors include diabetes, pregnancy, immunosuppression, or hormone replacement therapy. Pruritus is a common presenting complaint. Other symptoms may include dyspareunia, dysuria, or vaginal burning. Differential diagnosis includes sexually transmitted infection, bacterial vaginosis, or urinary tract infection. A KOH preparation will reveal hyphae and budding yeast forms.

Treatment should be initiated with over-the-counter intravaginal imidazoles, such as clotrimazole or miconazole, or a single 150-mg dose of oral fluconazole.

Sporotrichosis. Sporotrichosis, caused by a variety of *Sporothrix* species, is a fungal infection that may be transmitted by contact with soil, or by zoonotic transmission from animals such as snakes, birds, or cats. Most cases present with lymphocutaneous findings, such as papules, nodules, or ulcerations (Fig. 107.28). Rarely, systemic involvement may be seen with joint, pulmonary, or neurologic complications. Definitive diagnosis may be made with serologic testing. Treatment should be initiated with an oral antifungal agent such as itraconazole, 200 mg PO daily until 2 weeks after lesions have resolved, usually 3 to 6 months. Alternative oral agents include terbinafine, or intravenous amphotericin B in the setting of systemic sporotrichosis or treatment failure.[44] Dermatologic follow-up is essential to ensure adequate resolution.

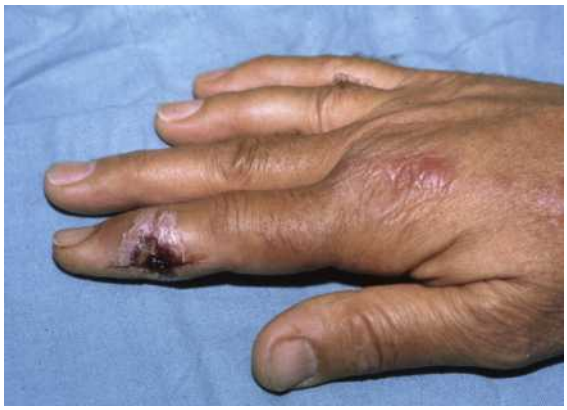

Fig. 107.28 Sporotrichosis. (Courtesy David Effron, MD)

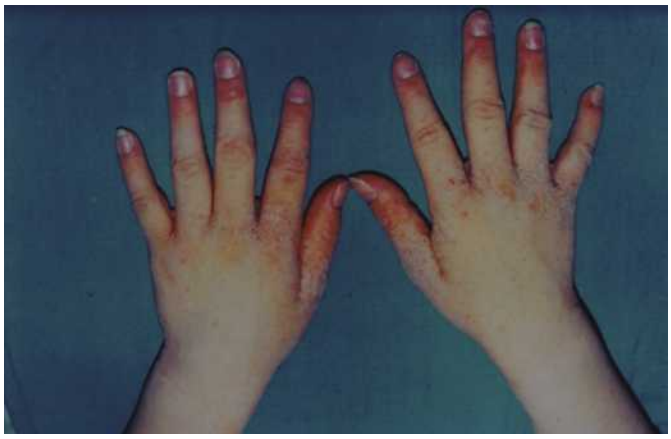

Fig. 107.29 Scabies. (Courtesy David Effron, MD.)

Infestations

Scabies

Scabies is a skin infestation caused by the penetration of the parasitic mite *Sarcoptes scabiei-var hominis* into the epidermis. It is an infestation of worldwide impact; over 100 million persons are affected annually. It occurs more commonly in winter months. It is transmitted mostly through close personal contacts. It may also be spread by exposure to fomites, as the scabies mite can live off the human skin for 3 days. The average number of mites harbored by a host is usually less than 20. Scabies presents with intense pruritus and rash, which usually develop after 1 to 8 weeks following exposure. The pruritus is typically worst at night. Clinical findings include small (<5 mm) papules or pustules, often with excoriations due to scratching. Burrows are uncommonly seen. Classically scabies affects several skin sites, including interdigital folds of the upper extremities and abdomen, genitalia, breasts, buttocks, or subungual skin of fingers (Figs. 107.29 and 107.30).[45] Scabies in infants and young children often

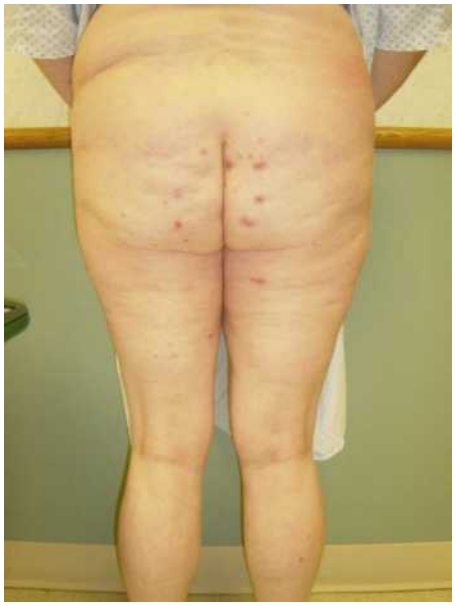

Fig. 107.30 Scabies.

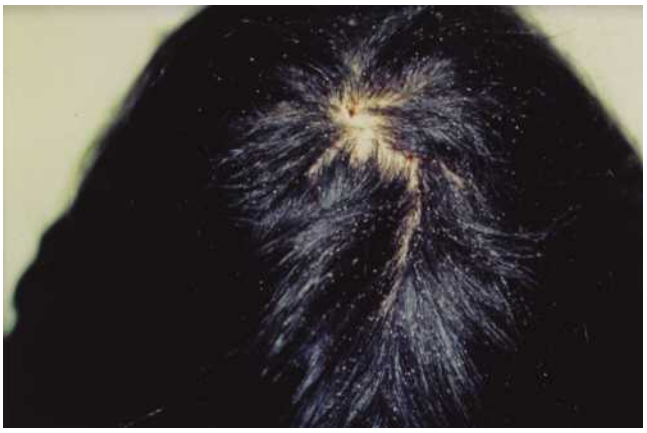

Fig. 107.31 Nits as Seen in Head Lice. (Courtesy David Effron, MD.)

may present with generalized involvement of the skin, including the face, scalp, palms, and soles. In infants, the most common presenting lesions are papules and vesicopustules.

In *crusted scabies* (previously known as *Norwegian scabies*), hyperkeratotic plaques develop diffusely, often on the palmar and plantar regions, with thickening and dystrophy of the toenails and fingernails. Crusted scabies is highly contagious, as a host may harbor thousands or millions of mites. Individuals with immunosuppression, including human immunodeficiency virus infection, elders, and patients with dementia or neuropathy are at risk of developing crusted scabies.[46,47]

Scabies is a clinical diagnosis that is based primarily on the history and examination. The definitive diagnosis is made by the microscopic identification of the scabies mites, eggs, or fecal pellets *(Scybala)*. As these techniques may be impractical in the ED, treatment should be instituted based on a clinical suspicion of the diagnosis.

The differential diagnosis of scabies includes pityriasis rosea (symmetric maculopapular rash), papular urticaria, secondary syphilis (symmetric maculopapular rash), folliculitis, contact dermatitis, atopic dermatitis, seborrhea, dermatitis herpetiformis (autoimmune blistering disorder associated with celiac disease), lichen planus (pruritic violaceous polygonal lesions on the extremities), and psoriasis (erythematous patches with silvery scale).

Scabies should be treated with topical permethrin 5% cream or oral ivermectin.[48,49] Permethrin cream should be applied from the neck down, covering all areas of the body including under the nails, in the umbilicus, around the nipples, and genitals. Face and scalp should be treated in affected infants and young children. Preferably, it should be applied prior to bedtime, left on overnight, and then washed off 8 to 12 hours later. It is vital to treat not only the patient but family members and close contacts as well. A second treatment should be administered in 1 to 2 weeks. Alternative therapy may be initiated with oral ivermectin, although the cure rate may be lower than permethrin.[50] For heavily infested or immunocompromised patients, it is recommended that ivermectin be given once a week for 2 to 3 weeks. Lindane, a previously utilized agent, is not recommended, due to potential neurotoxicity as well as resistance. Emollients and antihistamines may provide symptomatic relief of pruritus.[51]

Equally important in the treatment is the decontamination of clothing, bed linens, and towels by washing them in hot water and hot machine drying. Items that cannot be washed or dry-cleaned can be decontaminated by sealing the items in an airtight container for at least 72 hours.

Pediculosis

Pediculosis may affect the scalp hair (pediculosis capitis, caused by the mite *Pediculus humanus capitis*), body (pediculosis corporis, caused by *Pediculus humanus corporis*), or genitalia (pubic lice, caused by *Pthirus pubis*). Infestation is typically associated with significant pruritus. Lesions may be erythematous macules, papules, or wheals.

Pediculosis capitis is the most common form of lice infestation in the United States and is frequently seen in children 3 to 12 years old. An estimated 10% to 40% of school children in the United States have been infected with pediculosis capitis. It can be transmitted by sharing hairbrushes, combs, or hats, and through contact with infested furniture, clothing, or linens. Lice can live on fomites for up to 4 days. Hygiene and hair length are unrelated to infection. Incidence is greatest during autumn. Scalp, occipital, or postauricular pruritus are common in patients with pediculosis capitis. Neck and auricular erythema, papules, vesicles, or lymphadenopathy may be seen.

Pediculosis corporis can present with intense pruritus and erythematous macules or wheals. Pediculosis corporis typically occurs in patients with poor hygiene or living in crowded conditions.

Pediculosis pubic ("crabs") is a sexually transmitted disease and is most commonly seen among young adults. Other concurrent sexually transmitted diseases should also be considered.

The differential diagnosis includes conditions such as tinea capitis, seborrheic dermatitis, atopic dermatitis, eczema, scabies, folliculitis, or contact dermatitis.

The diagnosis of pediculosis is made by identification of lice or nits on the hair shaft (Fig. 107.31). Nits (eggs), which appear as white dots or grains, are more easily identified than the louse itself. Nits fluoresce with the Wood's lamp. Examination with a louse comb improves the diagnostic accuracy and is faster than direct visualization.

Therapy for pediculosis should be initiated with a pediculicide, such as pyrethrin shampoo or permethrin 1% lotion, with retreatment on day 9.[52,53] Spinosad 0.9% suspension (Natroba) is a newer agent with demonstrated pediculicidal efficacy. Spinosad 0.9% is approved for use in patients older than 4 years of age and is also effective against permethrin-resistant populations of lice. Spinosad is ovicidal, killing both nits and lice; thus extensive nit combing is not necessary. However, the cost may be prohibitive. Oral ivermectin has a high cure rate and may be used as alternate therapy (200 mcg/kg PO once).[54] Other treatments may be considered, including malathion, albendazole or

thiabendazole, benzyl alcohol lotion, or levamisole. Lindane, an older therapy, should be avoided, because of neurotoxicity and poor pediculicidal activity. Over-the-counter products have variable success rates, in part due to resistance. Nits should be removed with a special fine-toothed comb. The environment should also be treated. Hats, hairbrushes and combs, and linens as well as clothing should be treated. Items should be boiled or washed and dried at high temperatures. Floors and furniture should be vacuumed. Family members should be examined and treated if infested. Sexual partners of patients with pediculosis pubis should be treated. The American Academy of Pediatrics recommends that children do not miss school simply because of head lice.

Bed Bugs

Bed bugs *(Cimex lectularius)* appear brown and are approximately 5 to 6 mm in length. Bed bugs may be potential vectors for many fungi, viruses, and bacteria, including MRSA and vancomycin-resistant *Enterococcus faecium*, although disease transmission to humans has not been documented.[55] Bed bugs are found not only in linens, but on furniture, luggage, and in walls, baseboards, and buildings, including hotels, hospitals, or apartments.[56,57] They often feed on humans at night with a painless bite.

Clinical presentation may appear as erythematous welts, macules, papules, urticaria, purpura, vesicles, or bullae, with intense pruritus. The distribution is often over uncovered areas, such as arms, legs, or shoulders. Lesions resolve spontaneously in 1 to 2 weeks.

Symptomatic treatment should be undertaken with antihistamines and topical corticosteroids. If there is suspicion for scabies, empiric treatment should be initiated with permethrin 5% cream, ivermectin, or crotamiton. Eradication from the environment is challenging, due in part to increasing resistance to insecticides. Eradication methods may include insecticides, heat, steam, freezing, or vacuuming. The hazards of widespread insecticide use, including potential for malignancy or CNS adverse effects, have created a dilemma of eradication.

ALLERGIC REACTIONS

Contact Dermatitis

Contact dermatitis is an inflammatory reaction of the skin to a chemical, physical, or biologic agent, which acts as an irritant or allergic sensitizer. Allergic contact dermatitis is a form of delayed hypersensitivity mediated by lymphocytes sensitized by the contact of the allergen to the skin. It is less common than irritant contact dermatitis. Caustics, industrial solvents, or detergents are common causes of irritant dermatitis. Clothing, jewelry, soaps, cosmetics, latex, plants, and medications contain allergens that commonly cause allergic contact dermatitis. The most common allergens include rubber compounds; plants of the *Toxicodendron* species, including poison ivy, oak, and sumac; nickel, often used in jewelry alloys; paraphenylenediamine, an ingredient in hair dyes and industrial chemicals; and ethylenediamine, a stabilizer in topical medications.

The primary lesions of contact dermatitis are papules, vesicles, or bullae on an erythematous base. Streaky, linear, intensely pruritic lesions are characteristic. A pattern in the dermatologic region in contact with the allergen is typical (Fig. 107.32). Eruptions associated with contact dermatitis can appear as soon as several hours after the exposure or may be delayed for days.

Treatment of contact dermatitis includes avoidance of the irritant or allergen, and treatment of the resulting inflammation. Low-potency topical steroid creams may be applied to inflamed areas around orifices, and medium-potency creams can be used elsewhere, for example triamcinolone 1% cream bid for 1 week, or other options as listed in Table 107.4). Topical steroids are ineffectual on blistered areas. Oozing or vesiculated lesions should be treated with cool wet compresses of Domeboro or Burow's solutions (aluminum acetate). Topical baths, available over the counter, may also be comforting. Systemic antihistamines, such as hydroxyzine and diphenhydramine, may help control pruritus; nonsedating antihistamines are preferred for use during the day. If present, secondary bacterial infection should also be treated.

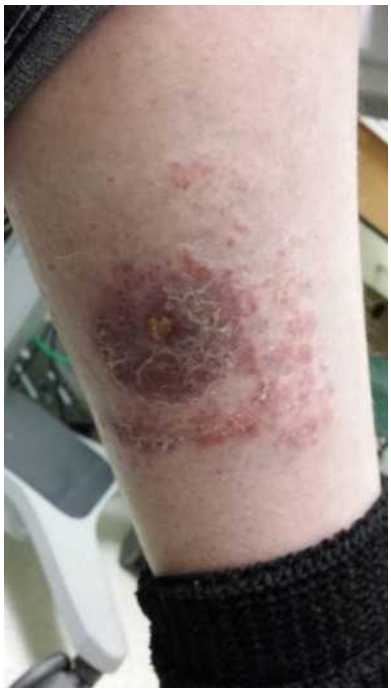

Fig. 107.32 Neomycin Allergy. (Courtesy Joanna Marco, MD.)

Urticaria

Urticaria may occur in isolation or as part of a systemic anaphylactic reaction. Approximately 15% to 20% of the population experiences urticaria during their lifetime. Acute urticaria is seen in both sexes. Chronic urticaria is more common in women in their 40s and 50s. Half of all patients with chronic urticaria have the disease for 5 years or more.

Various mediators, including histamine, bradykinin, kallikrein, and acetylcholine, are thought to play a role in urticaria production. Urticaria may be initiated by immunologic or nonimmunologic mechanisms. Nonimmunologic urticaria may be produced by degranulation of mast cells, which may be caused by foods and drugs, including aspirin and narcotics.

Almost any medication may produce urticaria, although penicillin and aspirin are the most common. Traces of penicillin may be present in dairy products, as well as in other medications. The mechanism of production of urticaria by aspirin is unclear, but is probably nonimmunologic, and the effects of aspirin may persist for weeks after ingestion. Substances that can cause urticaria by contact with the skin include foods, textiles, animal dander and saliva, plants, topical medications, chemicals, or cosmetics. Food allergies, such as seafood, tree nuts, peanuts, or eggs, may result in urticaria. In addition, foods such as lobster or strawberries can release histamine through a nonimmunologic mechanism.

Infection is a common cause of urticaria. Viral infections that produce urticaria include rhinovirus, rotavirus, hepatitis, mononucleosis, and coxsackievirus infections. Occult infections with *Candida,* the dermatophytes, bacteria, viruses, or parasites may also cause urticaria.

TABLE 107.4 Potency of Topical Steroids

Brand Name	Generic name
Class 1: Superpotent	
Clobex lotion, spray, or shampoo, 0.05%	Clobetasol propionate
Cormax solution, 0.05%	Clobetasol propionate
Diprolene ointment, 0.05%	Betamethasone dipropionate
Olux E foam, 0.05%	Clobetasol propionate
Olux foam, 0.05%	Clobetasol propionate
Temovate cream, 0.05%	Clobetasol propionate
Ultravate cream or ointment, 0.05%	Halobetasol propionate
Vanos cream, 0.1%	Fluocinonide
Class 2: Potent	
ApexiCon E ointment, 0.05%	Diflorasone diacetate
Diprolene cream AF, 0.05%	Betamethasone dipropionate
Halog ointment, solution, or cream, 0.1%	Halcinonide
Lidex cream, gel, or ointment, 0.05%	Fluocinonide
Psorcon ointment, 0.05%	Diflorasone diacetate
Topicort cream, spray, or ointment, 0.25%	Desoximetasone
Topicort gel, 0.05%	Desoximetasone
Class 3: Upper Midstrength	
Cutivate ointment, 0.005%	Fluticasone propionate
Elocon ointment, 0.1%	Mometasone furoate
Lidex-E cream, 0.05%	Fluocinonide
Luxiq foam, 0.12%	Betamethasone valerate
Class 4: Midstrength	
Cordran ointment, 0.05%	Flurandrenolide
Elocon cream, lotion, solution, 0.1%	Mometasone furoate
Kenalog cream, 0.1%, or spray, 0.2 mg/2 second spray	Triamcinolone acetonide
Synalar ointment, 0.025%	Fluocinolone acetonide
Westcort ointment, 0.2%	Hydrocortisone valerate
Class 5: Lower Midstrength	
Cordran cream, lotion, or tape, 0.05%	Flurandrenolide
Cutivate cream or lotion, 0.05%	Fluticasone propionate
Dermatop cream, ointment, 0.1%	Prednicarbate
Desonate gel, 0.05%	Desonide
Locoid cream, lotion, ointment, or solution, 0.1%	Hydrocortisone butyrate
Pandel cream, 0.1%	Hydrocortisone probutate
Synalar cream, 0.03%, 0.025%	Fluocinolone acetonide
Westcort cream, 0.2%	Hydrocortisone valerate
Class 6: Mild	
Aclovate cream or ointment, 0.05%	Alclometasone dipropionate
Capex shampoo, 0.01%	Fluocinolone acetonide
Derma-Smoothe/FS oil, 0.01%	Fluocinolone acetonide
DesOwen lotion, 0.05%	Desonide
Synalar cream or solution, 0.01%	Fluocinolone acetonide
Verdeso foam, 0.05%	Desonide
Class 7: Least Potent	
Aquanil HC, 1%	Hydrocortisone
Cortaid cream, spray, or ointment, 1%	Hydrocortisone
Hytone cream, 1%, 2.5%; lotion, 2%	Hydrocortisone
MiCort-HC cream, 2.5%	Hydrocortisone
Nutracort cream, 2.5%	Hydrocortisone
Synacort cream, 1%	

Modified with permission from National Psoriasis Foundation: Topical steroids potency chart. Available at www.psoriasis.org/page.aspx?pid=469.

Inhalation of pollens, mold, animal dander, dust, plant products, or aerosols may produce urticaria. Respiratory symptoms may accompany the dermatosis, and a seasonal pattern of occurrence may be present. Stings and bites of insects, arthropods, or various marine animals may also produce an urticarial eruption.

Systemic diseases such as systemic lupus erythematosus, lymphoma, carcinoma, hyperthyroidism, rheumatic fever, or juvenile rheumatoid arthritis may induce an urticarial eruption.

Physical agents may produce urticaria. Dermatographism is present when firm stroking of the skin produces an urticarial wheal within 30 minutes and is the most common form of physical urticaria. Pressure urticaria is distinct from dermatographism in that the onset of urticaria is delayed by 4 to 8 hours after the application of physical pressure.

Cold urticaria may be either familial or, more commonly, acquired. Cold urticaria may also be associated with underlying illness, such as cryoglobulinemia, cryofibrinogenemia, syphilis, or connective tissue disease. Antihistamines taken 30 to 60 minutes before cold exposure may be helpful. Cholinergic urticaria is induced by exercise, heat, or emotional stress. It may be associated with pruritus, nausea, abdominal pain, or headache. The lesions of cholinergic urticaria are wheals, 1 to 3 mm in diameter, surrounded by extensive erythematous flares and, occasionally, satellite wheals. Nonsedating antihistamines are generally used to treat cholinergic urticaria.

Heat is a rare cause of hives. Solar urticaria, also uncommon, is confined to sun-exposed areas of skin and clears rapidly when the light stimulus is removed. Extensive sun exposure may cause wheezing, dizziness, or syncope in a susceptible individual. Sunscreens have not been proven to be effective for the prevention of solar urticaria. Phototherapy may be used in an attempt to induce tolerance.

Urticaria appears as edematous plaques with pale centers and red borders and is easily recognizable (Fig. 107.33). Individual hives are typically transient, lasting less than 24 hours, although new lesions may continuously develop, which represents localized dermal edema produced by transvascular fluid extravasation.

The differential diagnosis of urticaria includes drug eruption, exanthems, erythema multiforme, erythema marginatum, and juvenile rheumatoid arthritis.

Treatment of urticaria involves the removal of the inciting factor, when applicable, and the administration of antihistamines or other antipruritics. Hydroxyzine can treat pruritus for symptomatic relief. For chronic urticaria, long-term therapy with antihistamines may be needed. Nonsedating antihistamines are preferred. Cetirizine, fexofenadine, or loratadine can be used. An H_2 blocker may be added.

Steroids may be a useful adjunctive therapy. Patients with moderate or severe urticaria may benefit from prednisone or dexamethasone. Patients with recurrent urticaria may benefit from longer courses of

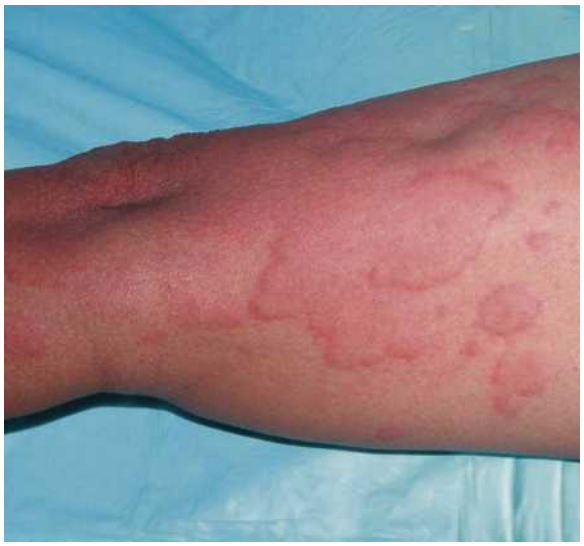

Fig. 107.33 Urticaria. (Courtesy David Effron, MD.)

oral steroids (14 to 21 days with a taper). Chronic administration of steroids is not recommended.

Patients with chronic urticaria may be treated with a prescription for a combination of an H_1 and H_2 antihistamine.

Poison Ivy

Exposure to *Toxicodendron* species may cause vesicular or bullous eruptions. Oozing, crusting, scaling, and fissuring may be found, with lichenification in chronic lesions. The distribution of the eruption depends on the specific contact and may be localized, asymmetric, linear, unilateral, or disseminated (Fig. 107.34). Mucous membranes are usually spared unless they are directly exposed to the inciting agent. Sensitization to poison ivy may result in sensitization to other plants in this family, including cashew, mango, lacquer, and ginkgo trees, thus patients may present with a dermatologic reaction to these exposures as well.

In addition to treatment regimens for contact dermatitis, a course of systemic corticosteroids may be indicated to treat *Toxicodendron*-associated dermatitis. Patients should be counseled to wash all clothes or items that might have contacted the plant as the irritant plant oil can remain on inanimate objects. Once the offending agent is reliably removed from the skin and clothes, ongoing outbreak is attributable to the initial contact, not spread from the serous fluid from the bullae. The patient is not contagious to others unless there is direct contact with the plant oil in those who are sensitized.

DRUG REACTIONS

Reactions to medications are common and are estimated to occur in 1% to 5% of patients. Cutaneous reactions are the most common type of reaction. Immediate reactions, occurring within 1 hour, may include urticaria, anaphylaxis, or angioedema.[58] Delayed hypersensitivity reactions often appear within 4 to 28 days after the drug is taken. Many medications have the potential to produce a drug reaction. Patients at higher risk of drug reactions include those with immunodeficiency, certain infections, or genetic predisposition. The most common eruptions are a morbilliform rash (Fig. 107.35), urticaria, or fixed drug eruption. More severe reactions may include vasculitis, erythema nodosum, angioedema, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, blistering dermatoses, drug-induced lupus, lichenoid drug eruptions, psoriasiform drug eruptions, drug-induced neutrophilic dermatoses (i.e., Sweet's

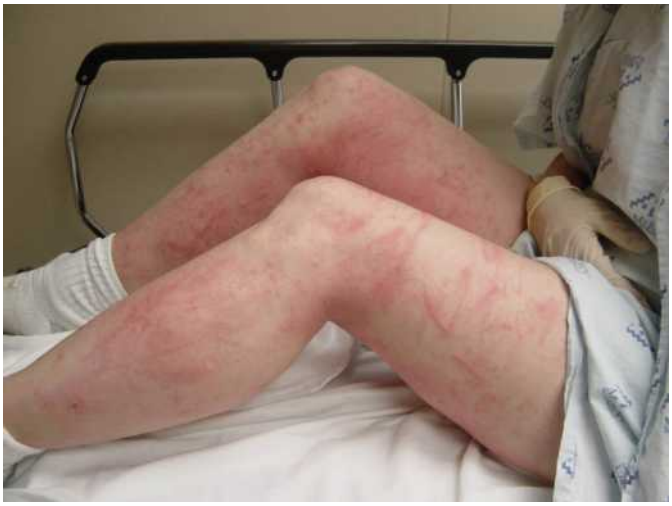

Fig. 107.34 Toxicodendron (Poison Ivy).

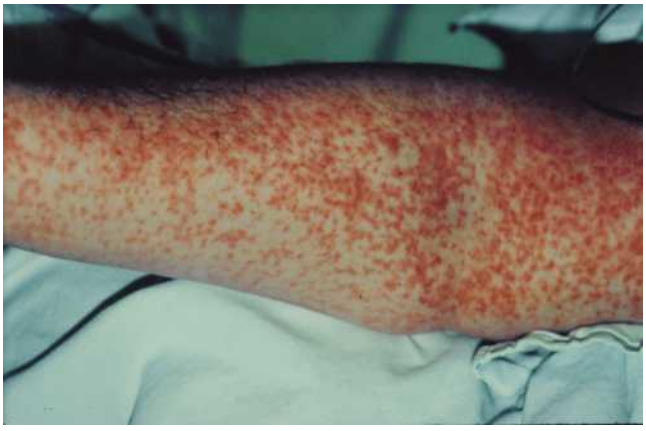

Fig. 107.35 Morbilliform Drug Eruption. (Courtesy David Effron, MD.)

syndrome, erythema nodosum, and pyoderma gangrenosum), and cutaneous lymphoma-like drug reactions.

Treatment of drug eruptions includes discontinuation of the inciting agent.[59] Most cutaneous drug reactions fade within 1 week of discontinuation. Antihistamines, H_2-antagonists, and topical or systemic steroids may be indicated for symptomatic treatment.

Toxic Epidermal Necrolysis

Stevens-Johnson syndrome and toxic epidermal necrolysis are considered a continuous spectrum of the same disease, an immune-complex–mediated hypersensitivity reaction. Stevens-Johnson syndrome is considered a minor form of toxic epidermal necrolysis with less than 10% body surface area (BSA) involved. Toxic epidermal necrolysis includes patients with more than 30% BSA involved. There is overlap with patients with 10% to 30% BSA involved.[60] The main feature of non–staphylococcal-induced toxic epidermal necrolysis, or Lyell's disease, is the separation of large sheets of epidermis from underlying dermis. Toxic epidermal necrolysis may be caused by medications, infection, malignancy, or idiopathic (30% to 50% of cases). Medications that can cause toxic epidermal necrolysis include sulfa drugs, nonsteroidal antiinflammatory drugs (NSAIDs), penicillin, aspirin, barbiturates, phenytoin, carbamazepine, or allopurinol.

Mortality may be up to 30% with toxic epidermal necrolysis. Risk factors for poor prognosis include age older than 40 years, underlying malignancy, heart rate greater than 120 beats/min, initial percentage

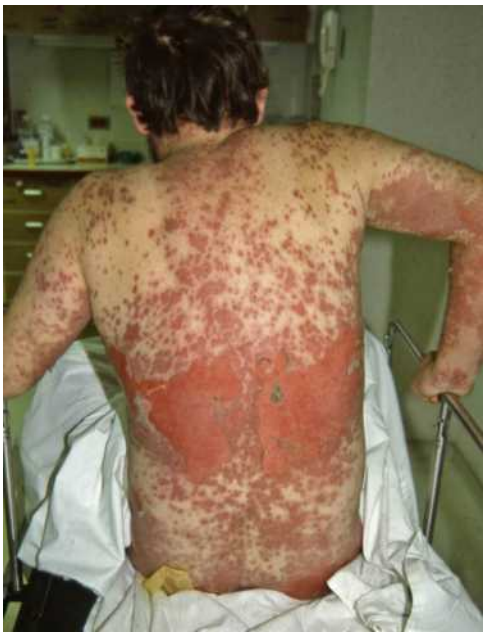

Fig. 107.36 Toxic Epidermal Necrolysis. (Courtesy David Effron, MD.)

of epidermal detachment more than 10%, BUN level more than 10 mmol/L, serum glucose level more than 252 mg/dL, and bicarbonate level less than 20 mmol/L.

Toxic epidermal necrolysis commonly begins with prodromal symptoms, such as fever, malaise, rhinitis, sore throat, or myalgias. These are followed by the abrupt development of a macular rash that may appear as target lesions. The extremities are commonly involved, although any area may be affected. The exanthem becomes confluent, and dermal-epidermal dissociation ensues; Nikolsky sign (denudation with shear stress) is present, and the skin is commonly painful to the touch (Fig. 107.36). Mucous membrane involvement may occur with erythema, blistering, sloughing, or necrosis (Fig. 107.37). Involvement of the conjunctivae and cornea may lead to permanent scarring and blindness. Systemic involvement may occur, with renal, gastrointestinal, or respiratory tract lesions, resulting in hematuria, diarrhea, bronchitis, or pneumonia. Morbidity and mortality are often related to infection and dehydration.

The treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis includes discontinuation of the offending agent and supportive care, including hydration, prevention of secondary infection, pain control, and wound management.[61,62] This is usually best accomplished in a center with burn care expertise. Treatment may also include systemic steroids, intravenous immune globulin (IVIG), or cyclosporin A.[61] Plasmapheresis may be considered in consultation with a specialist with experience in treating these serious skin disorders.[63]

DRESS syndrome. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a severe drug reaction characterized by a morbilliform skin eruption, fever, lymphadenopathy, hematologic abnormalities (eosinophilia, atypical lymphocytosis), and internal organ involvement (hepatic, renal, pulmonary, cardiac, gastrointestinal, neurologic, or endocrine abnormalities).[64,65] Mortality may be as high as 10%. Common inciting medications include anticonvulsants, antibiotics, or allopurinol. Onset may be 2 to 8 weeks after beginning the medication. Treatment includes withdrawal of the inciting agent and treatment with systemic steroids.

Fig. 107.37 Toxic Epidermal Necrolysis. (Courtesy David Effron, MD.)

INFLAMMATORY CONDITIONS

Atopic Dermatitis

Atopic dermatitis is a common dermatologic condition often referred to as *eczema* or *chronic dermatitis.* Atopic dermatitis is the cutaneous manifestation of an atopic state, and it is associated with allergic diseases, such as asthma and allergic rhinitis. Patients with atopic dermatitis are known to have abnormalities of both humeral and cell-mediated immunity. The exact mechanism is unclear, but eosinophil, mast cell, and lymphocyte activation triggered by increased production of interleukin-4 by specific T helper cells seems to be involved. The course of atopic dermatitis includes remissions and exacerbations. More than 90% of patients have the onset of atopic dermatitis before 5 years of age.

Atopic dermatitis is an inflammatory skin condition. Diagnostic criteria include itchy skin plus three or more of the following: generalized dry skin in the past year, history of asthma or hay fever, onset of rash before 2 years old, and flexural dermatitis.

Skin lesions generally appear as inflammatory thickened, papular, or papulovesicular lesions. The skin is typically dry and may be scaly, but in the acute phase, it may also be vesicular, weeping, or oozing. In the chronic stage, lesions are thickened and lichenified.

The distribution of lesions varies with the age. In infants, inflammatory exudative plaques are seen on the cheeks, on the extensor surfaces, or in the diaper area. Older children and adults have lesions in the antecubital and popliteal flexion areas, neck, face, or upper chest. Infantile atopic dermatitis usually begins in the fourth to sixth month of life and improves by the third to fifth year of life. The childhood form occurs between 3 and 6 years of age, and it resolves spontaneously or continues into the adult form.

Intense pruritus is a hallmark of atopic dermatitis. During flares, patients may present with complaints of intense itching and failure of routine treatments to control their symptoms. Patients may also present with secondary infections. The itching may be focal or generalized, is worse during the winter, and is triggered by increased body temperature or emotional stress. It may be particularly challenging at night. Excoriations may be prominent, and secondary bacterial infection of excoriated lesions is common. Repeated scratching and rubbing produce lichenification, a condition of hyperpigmentation, thickening of the skin, and accentuation of skin furrows. Lichenification is a common feature of chronic atopic dermatitis.

Treatment should be aimed at control of inflammation, dryness, and itching. Topical emollients and topical corticosteroids are the cornerstone of therapy.

Skin dryness is treated with topical emollients, such as oils, ointments, lotions, and creams. In some cases, emollients are as effective as topical steroids.[66] The choice of agent should be based on patient preference and may be applied several times daily. Pruritis may be treated with topical emollients and systemic antihistamines.

Approximately 80% of patients have improvement of symptoms with topical steroid treatment. When the dermatitis is severe, the application of a fluorinated corticosteroid ointment (such as betamethasone valerate) is recommended (Table 107.4). Fluorinated corticosteroids should not be used on the face, as they can produce cutaneous atrophy. Milder corticosteroid preparations, such as 0.025% triamcinolone ointment, may be used on the face or intertriginous areas. Patients with severe disease may require systemic steroids. Other treatment modalities include calcineurin inhibitors, topical phosphodiesterase inhibitors, or UV radiation.[67]

Patients with atopic dermatitis are susceptible to infection and colonization by a variety of organisms because of their defective skin barrier functions and local skin immunodeficiency. Widespread disseminated viral infections, such as eczema molluscum (molluscum contagiosum in the setting of eczema), eczema herpeticum (herpes virus infection in the setting of eczema), or recurrent staphylococcal pustulosis may complicate atopic dermatitis.

Inpatient admission is a consideration in rare cases, for those patients who have generalized erythema and exfoliation (erythroderma) or intractable itching with skin breakdown and heightened risk for severe secondary bacterial or viral skin infections.

Pityriasis Rosea

Pityriasis rosea is a mild skin eruption predominantly found in children and young adults. The etiology is unknown, although viral, bacterial, and fungal etiologies have been suggested. Patients aged 10 to 35 years are commonly affected. Clinical presentation includes multiple pink or pigmented oval papules or plaques 1 to 2 cm in diameter on the trunk and proximal extremities. A history may reveal an initial larger patch ("herald patch") that precedes the widespread eruption (Figs. 107.38 and 107.39). Mild scaling may be present. The lesions are parallel to the ribs, forming a Christmas tree–like distribution on the trunk and extremities. Oral lesions are rare. In children, papular or vesicular variants of the disease may occur. The eruption is usually asymptomatic, although pruritus may be present. The differential diagnosis includes tinea corporis (erythematous lesions with scale and central clearing), guttate psoriasis (small psoriatic lesions over trunk and proximal extremities), lichen planus (pruritic violaceous polygonal lesions), drug eruption, Lyme disease, or secondary syphilis (erythematous maculopapular lesions).

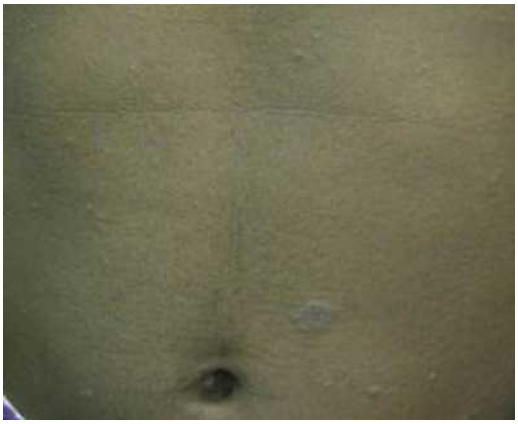

Fig. 107.38 Herald Patch of Pityriasis Rosea.

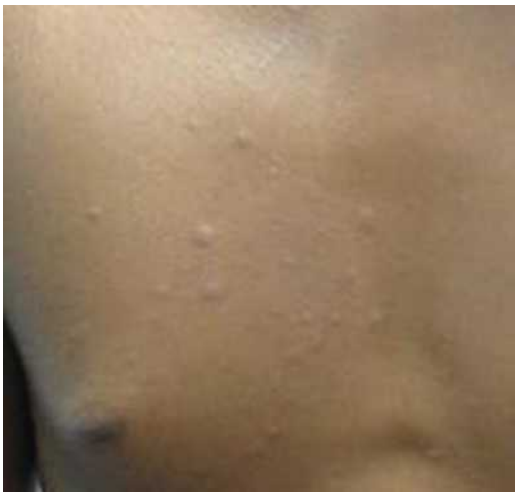

Fig. 107.39 Pityriasis Rosea.

Pityriasis rosea is self-limited, resolving in 8 to 12 weeks. Recurrences are rare. Treatment should include supportive care, including alleviation of pruritus. Topical zinc oxide or calamine lotion are useful for pruritus. Typically steroids are not indicated. If the disease is severe or widespread (e.g., vesicular pityriasis rosea), topical or oral steroids may be used (Table 107.4). No restriction of activity or isolation is indicated.

Kawasaki Disease

Kawasaki disease (mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood. The peak age is between 1 and 2 years old. The disease is very uncommon in children older than 14 years old or in adults. It is more common in boys. Although cases of Kawasaki disease have been reported in children of all ethnic origins, the highest incidence is among children of Asian descent. The disease typically occurs in winter and spring and is usually self-limiting, resolving spontaneously without treatment within 2 to 4 weeks. However, 15% to 20% of patients will develop complications, such as damage to coronary arteries, leading to myocardial infarction and heart failure. Kawasaki disease is the leading cause of pediatric acquired heart disease in the U.S.

Clinical features are characterized by three phases. The acute febrile period (phase I) is manifested by the abrupt onset of fever, lasting approximately 12 days. During phase I, cutaneous findings include erythematous lesions on the palms and soles. Within 2 days, the blotchy, erythematous, macular lesions spread to the extremities and trunk. Nonexudative injected conjunctivae, seen in approximately 90% of patients, may be present for 1 to 3 weeks. Diffuse oropharyngeal erythema with a "strawberry" tongue appearance is often present. Symptoms of diarrhea, arthritis, or photophobia may be present. In the subacute phase (phase II), desquamation, thrombocytosis, arthritis, arthralgias, or carditis may be present. This phase may last 30 days. There is a high risk for sudden death during this phase of the illness if it has gone untreated. During the convalescent phase (phase III), which occurs within 8 to 10 weeks after the onset of the illness, most signs of the illness have resolved. Coronary aneurysms present in 25% of cases and may be diagnosed by echocardiography or coronary angiography.

For epidemiologic surveillance, the Centers for Disease Control and Prevention (CDC) defines a case of Kawasaki disease as illness in

a patient with fever of 5 or more days duration, and the presence of at least four of the following five clinical signs[68]

- Rash
- Cervical lymphadenopathy (at least 1.5 cm in diameter)
- Bilateral conjunctival injection
- Oral mucosal changes
- Peripheral extremity changes.

The diagnosis is made based on clinical findings. Laboratory tests that support the diagnosis include elevated liver function tests, leukocytosis, thrombocytosis, and an elevated C-reactive protein (CRP). The ESR is elevated during phase II and returns to normal in phase III. Pyuria may be seen on urinalysis. Electrocardiography (ECG) may show PR and QT prolongation or acute ST/T wave changes.

Management of Kawasaki disease includes hospital admission, and treatment with high-dose IVIG and aspirin during hospitalization.[69] Treatment with IVIG within the first 10 days of illness reduces the incidence of coronary artery aneurysms fivefold, compared with children not treated with IVIG. Early cardiology evaluation is important to identify and treat possible coronary artery involvement.

Erythema Multiforme

Erythema multiforme is considered to be a hypersensitivity reaction. Potential etiologies include drug reaction; HSV infection or other viral infections; fungal diseases, such as dermatophytosis, histoplasmosis, or coccidioidomycosis; and bacterial infections, especially streptococcal infections or tuberculosis. Collagen vascular disorders have been known to precipitate erythema multiforme, including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, or periarteritis nodosa. Pregnancy and various malignant neoplasms have also been associated with erythema multiforme. The etiology is unknown in approximately 50% of cases. The differential diagnosis includes urticaria, scalded skin syndrome, pemphigus, and pemphigoid or viral exanthems.

Erythema multiforme is an acute, usually self-limited disease. It is characterized by skin lesions that are erythematous or violaceous macules, papules, vesicles, or bullae. Their distribution is often symmetric, most commonly involving the soles and palms, the backs of the hands or feet, and the extensor surfaces of the extremities. The presence of lesions of the palms and soles is particularly characteristic. The target lesion with three zones of color is the hallmark of erythema multiforme (Fig. 107.40).

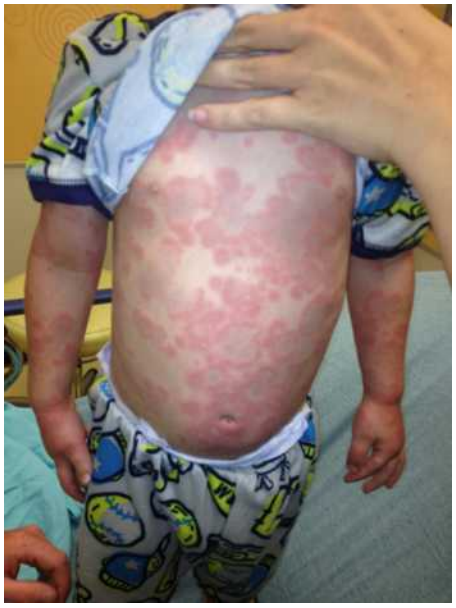

Fig. 107.40 Erythema Multiforme.

Treatment should include treatment of the underlying cause. Mild forms with no systemic symptoms, lesions limited to extremities, and no mucous membrane involvement typically resolve spontaneously in 2 or 3 weeks. Patients with lesions on the trunk or patients who are immunocompromised, especially those with multiple lesions, should receive a course of systemic steroids for 14 to 21 days with a taper and urgent dermatology referral.

Erythema Nodosum

Erythema nodosum is an inflammatory reaction of the dermis and adipose tissue that presents with painful, palpable erythematous or violaceous subcutaneous nodules. These painful nodules occur most commonly over the anterior tibia but may also be seen on the arms or body (Fig. 107.41). Fever and arthralgia of the ankles or knees may precede the rash. As the lesions evolve, they may turn yellow-purple and resemble bruises. Women are affected more often than men, with the highest incidence in the third to fifth decades of life.

A number of diseases are associated with erythema nodosum; these include drug reactions, sarcoidosis, coccidioidomycosis, histoplasmosis, tuberculosis, ulcerative colitis, regional enteritis, pregnancy, malignancy, or infections. Approximately 50% of erythema nodosum cases are idiopathic.[70]

Management includes treatment of the underlying etiology. Chest radiography may be considered to exclude findings characteristic of sarcoidosis, tuberculosis, or pulmonary fungal infection. Bed rest, elevation of the legs, and elastic stockings reduce pain and edema. Aspirin or other NSAIDs may provide pain relief. Erythema nodosum is a self-limited process that usually resolves in 3 to 8 weeks. Patients

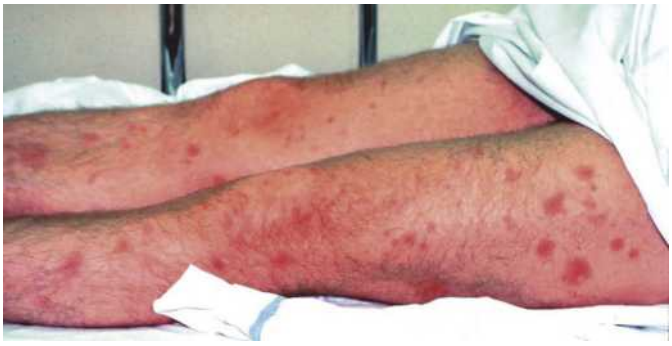

Fig. 107.41 Erythema Nodosum. (Courtesy David Effron, MD.)

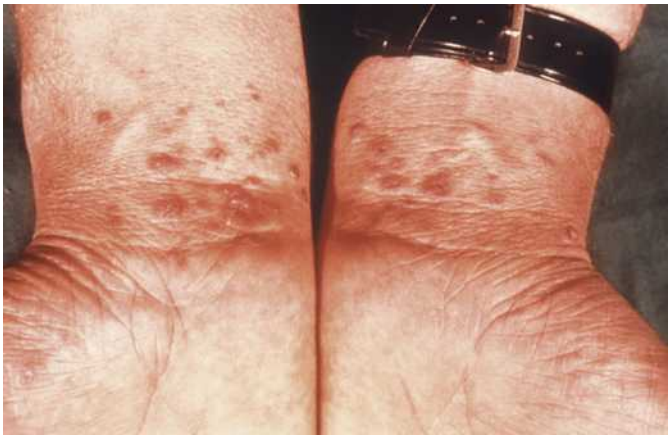

Fig. 107.42 Lichen Planus. (Courtesy Centers for Disease Control and Prevention [CDC] Public Health Image Library, Susan Lindsley.)

with severe pain may be treated with potassium iodide daily for 3 or 4 weeks.[71]

Lichen Planus

Lichen planus (LP) is an autoimmune condition that results in inflammation. LP typically presents with lesions that are flat-topped violaceous papules with pruritus (also known as the five "Ps": purple, planar, polygonal, pruritic, papules). Lesions typically appear on the wrists and ankles (Fig. 107.42). The lesions may occur in an area of trauma (Koebner phenomenon). Other areas may be affected, such as oral mucosa, anogenital region, scalp, or other areas.

Medium- to high-potency topical steroids are the treatment of choice (Table 107.4). Pruritus may be treated with systemic agents, such as diphenhydramine or hydroxyzine. Systemic steroids may be indicated if greater than 15% BSA is involved, or for topical treatment failures. Alternate therapies include topical calcineurin inhibitors, methotrexate, topical or systemic retinoids, or phototherapy.[72,73]

AUTOIMMUNE DISORDERS

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disorder that most commonly affects geriatric patients. Clinical manifestations are often pruritus and generalized blistering of the skin (Fig. 107.43). Nikolsky sign is negative. It often has a waxing and waning clinical course. It has been associated with numerous systemic conditions, including malignancy, diabetes, stroke, Parkinson disease, or cardiovascular disease.

Topical steroids may be prescribed as initial therapy.[74] For example, clobetasol propionate cream, 0.05% may be applied BID for 1 to 3 weeks. Systemic steroids or doxycycline may be necessary to treat widespread lesions. Patients with topical treatment failure may be treated with a systemic agent, such as doxycycline (100 mg BID for 1 to 3 weeks) or prednisone (40 mg daily for 1 to 3 weeks).

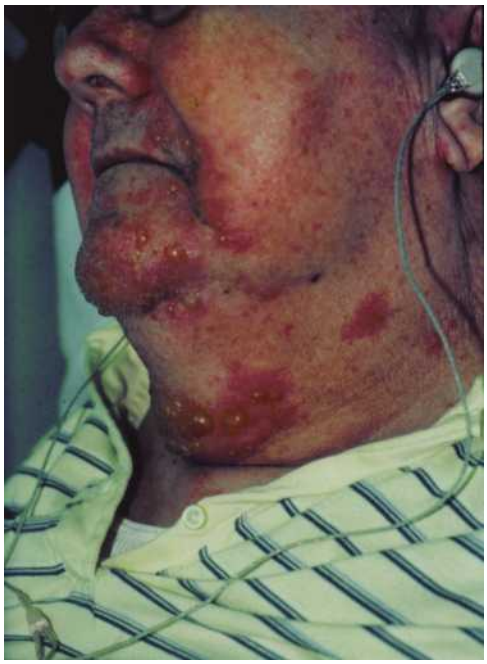

Fig. 107.43 Bullous Pemphigus. (Courtesy David Effron, MD.)

Pemphigus Vulgaris

Pemphigus vulgaris is an uncommon but important dermatologic disorder to identify. The mortality rate before the use of steroids was approximately 95%. The current mortality rate is 10% to 15%, with appropriate treatment. Pemphigus is a bullous disease, affecting both sexes equally, and is most common in patients 40 to 60 years old. The disease is mostly prevalent in people of Jewish, Mediterranean, or south Asian descent.

The typical skin lesions are small, flaccid bullae that break easily, forming superficial erosions and crusted ulcerations. Any area of the body may be involved. Nikolsky sign is positive and characteristic of the disease.

Many patients also have oral lesions (50% to 60%). The oral lesions typically antedate the cutaneous lesions by several months. The most common site is in the mouth, especially the gums and vermilion borders of the lips. Oral lesions are bullous but commonly break, leaving painful, denuded areas of superficial ulceration.

Pain control and local wound care are essential components of therapy. Treatment with oral glucocorticoids should be instituted. Other treatments may include immunosuppressive agents, intravenous immunoglobulins, immunoadsorption, or rituximab.[75] Morbidity and mortality may ensue, related to an uncontrolled spread of the disease, secondary infection, dehydration, side effects of steroid therapy, or thromboembolism.

CUTANEOUS MALIGNANCIES

The most common cutaneous malignancies are basal cell carcinoma, squamous cell carcinoma, and melanoma.[76]

Basal cell carcinoma is the most common skin cancer in the United States.[77] Basal cell carcinomas are commonly seen in patients with fair skin, sun exposure, outdoor occupation, and older age. Clinical presentation is typically on sun exposed areas, commonly on the head or neck. Clinical presentations include nodular, superficial, and morpheaform subtypes. The typical nodular appearance is a pearly papule with well-defined borders and telangiectasias. Suspicious lesions should be referred to a dermatologist for biopsy and management.

Squamous cell carcinoma is the second most common skin cancer in the United States. It is more common in men than in women. The risk of developing squamous cell carcinoma of the skin is increased with advancing age and sun exposure. Squamous cell carcinomas are typically found in sun-exposed areas, most commonly on the head or neck. The appearance is typically an irregular growth with erythema, induration, inflammation, crusting, or oozing. Suspicious lesions should be referred to a dermatologist for biopsy.

Melanoma is less common, and accounts for only 4% to 5% of skin cancers. However, it is responsible for most deaths from cutaneous malignancies. Risk factors include fair skin, dysplastic nevi, multiple (>50) nevi, prior history of melanoma, family history of melanoma, immunocompromised state, or xeroderma pigmentosum (an inherited condition resulting in UV light sensitivity). Melanoma may occur in any area of the skin, though tends to appear more often on lower extremities in women, and on the head, neck, or trunk in men. The typical appearance is an asymmetric lesion with irregular pigmentation, border, and texture, and diameter greater than 6 mm or increasing in size. Suspicious lesions should be referred to a dermatologist for biopsy.

Kaposi sarcoma appears more often in patients with underlying immunosuppression. Clinically, it presents with painless, raised, brown-black or purple papules and nodules that do not blanch. Common sites are the face, chest, genitals, and oral cavity, but widespread

TABLE 107.5 Cutaneous Signs of Systemic Disease

Anatomic Site	Sign	Systemic Disease
Generalized	Urticaria	Drug reaction SLE Infection
	Pruritus	Anemia Renal disease Cholestasis Polycythemia Lymphoma Malignancies Thyroid disease
Head and neck	Xanthelasma	Hyperlipidemia
	Spider nevi	Liver disease Hyperthyroidism
	Malar erythema	SLE
	Photosensitive rash	SLE Porphyria
	Alopecia	Thyroid disease Drugs Anemia Malnutrition SLE Fungal infection
	Heliotrope discoloration and eyelid edema	Dermatomyositis
Hands	Gottron papules	Dermatomyositis Internal malignancy
	Raynaud phenomenon	Normal Connective tissue diseases
	Clubbing	Normal Internal malignancy Cyanotic cardiac disease IBD Lung disease
	Erythema multiforme	Drugs Infections
	Palmar erythema	Normal Liver disease Pregnancy Rheumatoid arthritis SLE
Legs	Erythema nodosum	Strep infection Drugs Pregnancy Tuberculosis Sarcoidosis IBD
	Pyoderma gangrenosum	IBD Hepatitis Rheumatoid arthritis Malignancy
	Pretibial myxedema	Hypothyroidism Hyperthyroidism
	Necrobiosis lipoidica	Diabetes mellitus

IBD, Inflammatory bowel disease; *SLE,* systemic lupus erythematosus.

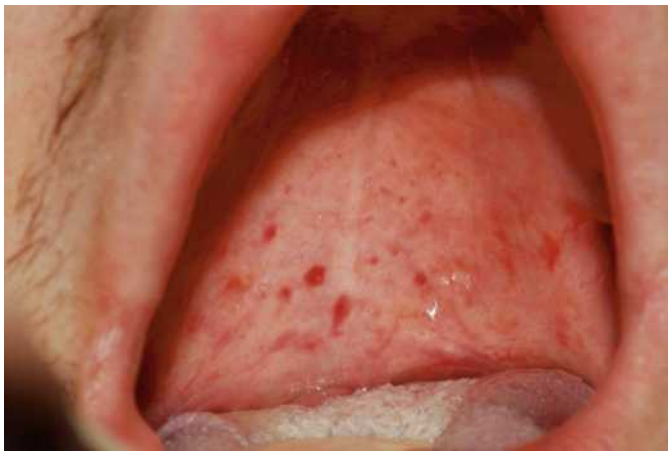

Fig. 107.44 Palatal petechiae secondary to thrombocytopenia in a patient with acute myelogenous leukemia (AML). (Courtesy Jason R. Pickett, MD.)

dissemination involving internal organs may occur. Because cutaneous Kaposi sarcoma is not generally associated with morbidity or mortality, therapy is indicated only for extensive, painful, or cosmetically disfiguring lesions.

Although the ED does not provide definitive management for cutaneous malignancies, recognition of possible malignant lesions may facilitate prompt and expeditious referral for definitive management. Any lesion with irregular pigmentation, irregular borders or texture, easy bleeding, or recent change in lesion should be referred to a dermatologist.

SKIN CONDITIONS ASSOCIATED WITH SYSTEMIC DISEASE

Systemic illness should be considered with generalized dermatologic presentations. Systemic illness should be suspected in patients with systemic symptoms, such as fever, fatigue, weight loss or gain, weakness, immunosuppression, or other generalized symptoms. Systemic illnesses with cutaneous findings may include systemic infections, autoimmune or connective tissue disorders, malignancies, diabetes mellitus, endocrine disorders, or immunodeficiency states (Table 107.5).

Cutaneous lesions most directly indicative of an internal malignant disease arise from the extension of the tumor to the skin, or by hematogenous or lymphatic metastasis. The neoplasms that most commonly produce cutaneous extension are lymphomas, leukemias, and carcinomas of the breast, gastrointestinal tract, lung, ovary, prostate, uterus, or bladder. Skin metastases generally signify a poor prognosis.

Pruritus may be a sign of systemic disease, such as liver disease, renal disease, endocrine disorder, rheumatologic disorder, malignancy, or neurodegenerative disease.[78] Malignancies associated with pruritus include Hodgkin disease, leukemia, adenocarcinoma or squamous cell carcinoma of various organs, carcinoid syndrome, multiple myeloma, or polycythemia vera. Pruritis may be present years before the underlying malignant disease is identified. It may be intractable and associated with urticaria, erythroderma, excoriation, or lichenification.

Purpura may be a manifestation of acute granulocytic and monocytic leukemia, myeloma, lymphoma, or polycythemia vera. Purpura is caused by vascular abnormalities, thrombocytopenia, or other coagulation defects. A variety of diseases and conditions may be the underlying cause, and the treatment should be directed toward this cause

whenever possible. Thrombocytopenic and nonthrombocytopenic forms are differentiated by the platelet count.

Petechiae are manifestations of intradermal hemorrhage. Petechiae may be associated with thrombocytopenia, allergic reactions, endocarditis, Rocky Mountain spotted fever, viral hepatitis, infections, trauma, or malignancy (Fig. 107.44).[79]

Generalized erythroderma may indicate systemic condition, such as drug reaction, SSSS, erythema multiforme, toxic epidermal necrolysis, malignancy, exacerbation of underlying skin condition, or collagen vascular disorder.[80]

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CHAPTER 107: QUESTIONS AND ANSWERS

1. Which of the following statements regarding tinea capitis is TRUE?
- **a.** It is contagious.
- **b.** It is not transmitted by household pets.
- **c.** Tinea capitis presents with alopecia with normal underlying scalp.
- **d.** Topical treatment is effective.
- **e.** Treatment should be instituted for 1 to 2 weeks.

Answer: a. Tinea capitis is the dermatophytosis that is contagious. Systemic treatment for 4 to 6 weeks is the minimum. It may be transmitted by pets. The underlying scalp is typically inflamed.

2. A 16-year-old boy presents with cellulitis of his left forearm. What is the appropriate initial antibiotic?
- **a.** Azithromycin
- **b.** Ceftriaxone
- **c.** Clindamycin
- **d.** Linezolid
- **e.** Penicillin VK

Answer: c. Clindamycin or trimethoprim-sulfamethoxazole are recommended first-line treatment choices for suspected methicillin-resistant *Streptococcus aureus* (MRSA) infection. Macrolides and penicillins are often ineffective against MRSA. Linezolid, although effective, is expensive and is generally not recommended as a first-line treatment.

3. What is the causative organism of erythema migrans?
- **a.** *Borrelia burgdorferi*
- **b.** Group A Streptococcus
- **c.** Methicillin-resistant *Staphylococcus aureus*
- **d.** *Neisseria meningitides*
- **e.** Parvovirus B-19

Answer: a. *Borrelia burgdorferi* is the causative agent of erythema migrans, or Lyme disease. Treatment should be instituted with doxycycline for 10 to 21 days, or as alternates, cefuroxime, ceftriaxone, or penicillin G. Group A *Streptococcus* is the causative organism of scarlet fever. *Neisseria meningitides* is the causative agent of Meningococcemia. *Parvovirus B-19* is the causative agent of erythema infectiosum.

CHAPTER 107: QUESTIONS AND ANSWERS—cont'd

4. A 26-year-old man presents with an erythematous maculopapular eruption of his torso, palms, and soles. He had a painless lesion on his penis 1 month earlier. What is the treatment of choice?
   a. Azithromycin
   b. Benzathine penicillin G
   c. Ceftriaxone
   d. Doxycycline
   e. Trimethoprim-sulfamethoxazole

Answer: b. Secondary syphilis is treated with benzathine penicillin G in a dose of 2.4 million units IM.

5. A 25-year-old female presents with fever, migratory polyarthralgias, and hemorrhagic papules on her fingers and wrists. What is the best treatment?
   a. Ceftriaxone
   b. Ciprofloxacin
   c. Doxycycline
   d. Ofloxacin
   e. Vancomycin

Answer: a. Treatment of disseminated gonococcal infection is with parenteral ceftriaxone, or ceftizoxime or cefotaxime. Patients allergic to β-lactam antibiotics or those with severe penicillin allergies may be treated with spectinomycin. Ciprofloxacin and ofloxacin are not recommended because of increasing resistance patterns. Hospitalization is recommended for patients with disseminated gonococcal infection.

6. Which of the following statements regarding gonococcal dermatitis is TRUE?
   a. Gonococci can usually be seen on gram stain from the lesions.
   b. It affects primarily men.
   c. It occurs in 1% or 2% of patients with gonorrhea.
   d. The lesions have a predilection for the knees and elbows.
   e. The skin lesions are not tender.

Answer: c. Women are affected primarily. The lesions have a predilection for distal joint skin. The lesions are often multiple and have a predilection for periarticular regions of the distal extremities. The lesions begin as erythematous or hemorrhagic papules that evolve into pustules and vesicles with an erythematous halo. They may be tender and may have a gray necrotic or hemorrhagic center. The organism may be cultured from the cutaneous lesions. Gram stain only occasionally reveals the organisms.

7. A 30-year-old man presents with headache, nausea and vomiting, myalgias, fever, and a petechial rash on his extremities and trunk. Lesions are clustered on the palms and soles. What is the best treatment?
   a. Cephalexin.
   b. Doxycycline.
   c. Erythromycin.
   d. Penicillin VK.
   e. Trimethoprim-sulfamethoxazole.

Answer: b. Patients with Rocky Mountain spotted fever present with headache, nausea and vomiting, myalgias, chills, and fever. The disease may last 3 weeks and may be severe with prominent involvement of the central nervous system, cardiac, pulmonary, gastrointestinal and renal systems, disseminated intravascular coagulation, or shock. The rash begins with erythematous macules that blanch on pressure, appearing first on the wrists and ankles. These macules spread up the extremities and to the trunk and face. They may become petechial or hemorrhagic. Lesions on the palms and soles are particularly characteristic. Doxycycline is the antibiotic of choice. Chloramphenicol may be used for patients allergic to tetracyclines and in children younger than 9 years of age. Sulfa drugs should be avoided because they may exacerbate the illness. Rickettsiae are routinely resistant to penicillins, cephalosporins, aminoglycosides, and erythromycin.

108

Blood and Blood Components

Christopher E. San Miguel and Colin G. Kaide

KEY CONCEPTS

- Red blood cell transfusion is indicated only to increase oxygen delivery at the tissue level.
- One unit of packed red blood cells (PRBCs) can be expected to raise an adult's hemoglobin level by 1 g/dL. A similar increase is expected in children following the transfusion of 10 mL/kg of PRBCs.
- Controlled trials have supported newer, restrictive, red cell transfusion strategies. Pending further trials, a transfusion trigger of a hemoglobin level below 7 to 8 g/dL is appropriate for most stable hospitalized patients.
- Platelet transfusions are typically used prophylactically for counts less than 10 K/μL in adults without bleeding. For patients undergoing central venous catheter placement, a level of 20 K/μL is recommended. Patients undergoing lumbar puncture and non-neuroaxial surgery should be prophylactically transfused to a level of 50 K/μL.
- Prospective and retrospective reports have suggested a benefit to massive transfusion protocols, with most advocating a 1 : 1 : 1 ratio of fresh frozen plasma (FFP) to platelets to PRBCs.
- When available, low-titer whole blood is safe and effective for transfusion and provides a physiologic mix of blood products.
- When available, prothrombin complex concentrate (PCC) should be given over FFP for reversal of vitamin K antagonism in the setting of a life-threatening bleeding. When PCC is not available, FFP can be used for this purpose, but is considered a second-line therapy.
- Transfusion reactions can vary from minor symptoms to fatal systemic reactions. If any transfusion reaction is suspected, the transfusion should be stopped while the cause and extent of the reaction is investigated.
- An intravascular hemolytic transfusion reaction is usually the result of ABO incompatibility and typically results in immediate symptoms that can include fever, chills, headache, nausea, vomiting, sensation of chest restriction, severe joint or low back pain, burning sensation at the site of the infusion, and feeling of impending doom. Treatment involves stopping the transfusion, fluid resuscitation, and monitoring for the development of renal failure and disseminated intravascular coagulation (DIC).
- Transfusion-related acute lung injury (TRALI) is now the leading cause of reported transfusion-related mortality. Treatment involves stopping the transfusion and providing supportive respiratory care, which may include noninvasive positive-pressure ventilation (NIPPV) or intubation and mechanical ventilation.
- Improved techniques for selecting and testing blood donors has dramatically reduced the risk of viral transmission of disease by transfusion.

FOUNDATIONS

Background and Importance

The modern blood transfusion era began with identification of the ABO red cell antigen system in the early 1900s. The subsequent discovery that adding citrate enabled the storage of anticoagulated blood led to the establishment of the first blood banks in the United States in the 1930s, and blood banking expanded rapidly after World War II. In subsequent decades, transfusion research focused primarily on critical issues such as developing component therapy, prolonging the storage life of blood products, and reducing the risk of transfusion reactions and transfusion-related infections. In 2015, approximately 11.4 million red blood cell units, 2.7 million plasma units, and 2 million platelet units were transfused in US acute care hospitals.[1]

Anatomy, Physiology, and Pathophysiology

Sound transfusion decision making is informed by a thorough working knowledge of the underlying physiology and pathophysiology, as well as familiarity with the key clinical trials that support up-to-date, evidence-based guidelines. This knowledge facilitates the effective ordering and interpretation of laboratory tests, delivery of blood products, and management of common or serious complications.

Blood Banking

Red blood cell (RBC) storage methods aim to ensure viability of at least 75% of the cells 24 hours after infusion. Blood collection bags contain an anticoagulant that ensures a shelf life of 35 days and a hematocrit of 70% to 80% for packed RBCs (PRBCs). Additive solutions provide additional nutrients and extend maximum storage to 42 days.

A number of biochemical and structural changes have been documented to occur during red cell storage, including loss of deformability, leakage of potassium, irreversible membrane changes, and biochemical alterations that have the potential to affect the ability of RBCs to unload oxygen in the microcirculation.[2] These changes worsen with increased storage duration and have been collectively referred to as the storage lesion. A number of observational studies and a few randomized prospective trials have reported conflicting results as to whether these changes are clinically relevant. The most recent four, large randomized trials have found no statistically significant difference in patient outcomes based on the age of the transfused blood product. Due to methodological limitations however, these results are not yet universally considered definitive.[3]

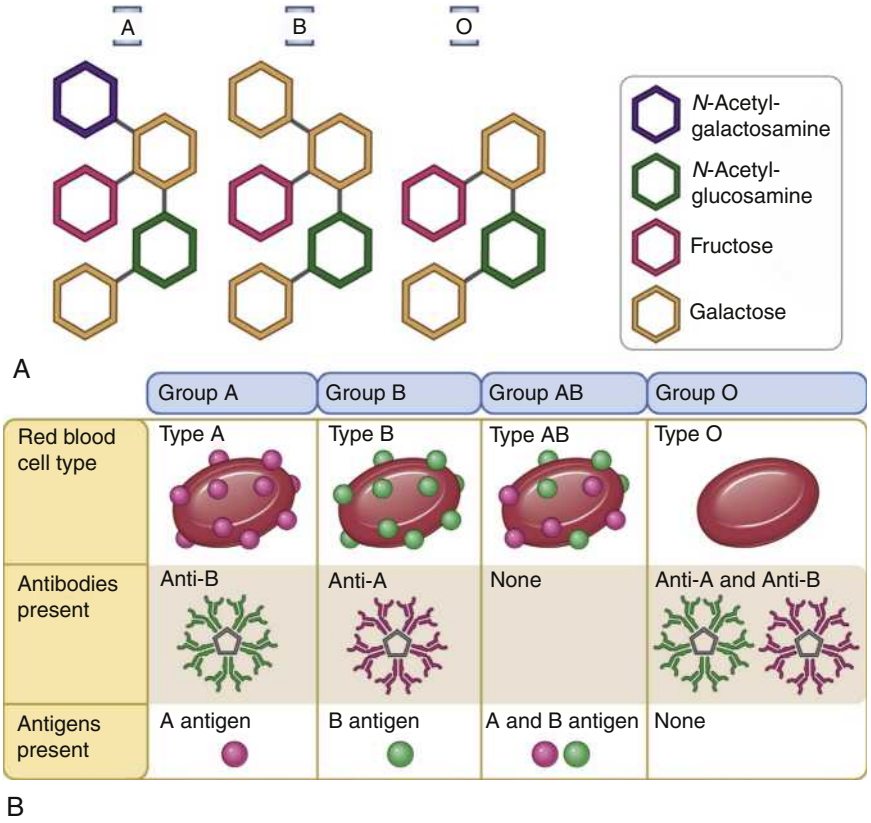

Fig. 108.1 Overview of red blood cell ABO grouping. (From: Abbas AK, Lichtman AH, Pillai S, eds. Transplantation immunology. In: *Cellular and Molecular Immunology*, 9th ed. Philadelphia: Elsevier; 2018.)

Blood Typing

Blood typing refers to the process by which blood is categorized by the antigens expressed on the red blood cells and the antibodies contained in the serum. There are currently over 30 known blood type systems, with the most important systems being the ABO and Rh systems. Kell, Duffy, and Kidd are examples of other blood type systems which generally have less of an impact on clinical practice.

Within the ABO system, there are type A and type B antigens. Red blood cells can express either, both, or neither of these antigens on their cell membranes. Throughout the first year of life, antibodies are formed against whichever antigens are not expressed on an individual's red blood cells. Type O blood, for instance, describes red blood cells that express neither type A nor type B antigens and thus is associated with anti-A and anti-B antibodies in the serum (Fig. 108.1). This seemingly spontaneous production of antibodies is theorized to be triggered by natural exposure to similar antigens in food, bacteria, or the environment and is unique to the ABO blood type system. Conversely, if type A, B, or both antigens are expressed on an individual's red blood cells (as is the case for type A, type B, and type AB blood respectively), the immune system recognizes these naturally occurring antigens as self-antigens and antibodies are not produced. Antibodies against antigens from other blood type systems can certainly be formed, but they generally require an exposure to red blood cells that express those antigens, for instance through blood transfusions or pregnancy. The "natural" production of ABO antibodies combined with the fact that ABO antigens and antibodies cause agglutination and hemolysis when mixed, means that patients can suffer from severe or even fatal transfusion reactions the first time they receive a PRBC transfusion from an ABO incompatible donor.

The second most clinically important blood type system is the Rh system. There are numerous known antigens in this system, but the D antigen is the most immunogenic. When a blood type is described as positive or negative (as in AB+), the report is referring to the presence or absence of the RhD antigen. Unlike in the ABO system, the mixing of Rh antigens and antibodies from a single transfusion is unlikely to result in a severe hemolytic reaction. This blood type system is most clinically relevant in the setting of pregnancy (or potential future pregnancies). If through a previous blood transfusion or pregnancy, an RhD negative mother has been exposed to RhD and subsequently developed anti-RhD antibodies, these antibodies can cross the placenta and into the fetal circulation. If the fetus is RhD positive, prolonged mixture of antigen and antibody can result in hemolytic disease of the newborn. Therefore, unstable hemorrhaging female patients who are not post-menopausal should receive O– blood, while male patients and postmenopausal female patients can receive O+ blood. Of note, hemolytic disease of the newborn is not seen with an ABO incompatible mother and fetus, as the vast majority of anti-ABO antibodies are IgM, which do not cross the placenta.

Type and Screen. An individual blood type and screen test includes ABO grouping, Rh typing, and antibody screen for unexpected, non-ABO/Rh antibodies. ABO grouping tests patient red cells with anti-A and anti-B serum and also with A and B red cells. Rh typing is accomplished by adding a commercial anti-D reagent to patient RBCs. To complete the antibody screen, the patient's serum is combined with commercially prepared mixtures of red cells expressing clinically significant antigens. The incidence of unexpected antibodies in the general population is low (<1%–2%), but a positive screen prompts further compatibility testing. In ideal circumstances, type-specific,

yet uncrossmatched, blood can generally be made available within 15 minutes of receiving a sample of the patient's blood.

Type and Crossmatch. When a unit of blood is ordered for transfusion, a crossmatch follows the initial type and screen. In an ideal situation, blood identical to the patient's own ABO and Rh group is utilized. Local blood supplies, however, might dictate that a nonidentical but compatible unit be used. Patients with blood group AB are known as universal recipients—they can receive packed red blood cells from any of the ABO groups, given their lack of anti-A and anti-B antibodies. Type O is commonly referred to as the universal donor of packed red blood cells, given the lack of A and B antigens.

A crossmatch procedure involves mixing the recipient's serum with donor RBCs and observing for agglutination as a final compatibility test before transfusion. If the antibody screen is negative, an abbreviated crossmatch at room temperature serves as a final check for ABO incompatibility. An antibody screen and abbreviated crossmatch requires at least 45 to 60 minutes to complete. If the antibody screen is positive, a complete crossmatch is generally required before transfusion. This requires the mixture of donor RBCs and recipient serum be incubated to 37°C (98.6°F) with the addition of antihuman globulin (Coombs reagent) to promote agglutination. Many blood banks also substitute a computer crossmatch for patients whose blood has been tested at least twice in their system. Complete crossmatch testing can take up to several hours, or even days, leading to delays in many urgent or emergent situations. If complete compatibility testing following a positive antibody screen would substantially delay transfusion of blood products to a critically ill patient, the emergency clinician may choose to bypass this step. Direct communication with the blood bank will facilitate determination of the best course of action.

Titer Testing for Whole Blood Donation. Although patients with type O blood are considered to be universal donors of packed red cells (PRBCs), whole blood from type O donors contains plasma and therefore may contain a concentration of anti-A and anti-B antibodies that can cause destruction of the recipient's type A or B RBCs. A strategy to mitigate this issue is either to transfuse only type-specific whole blood or to test donors or, more commonly, donor blood in advance to identify those with a "low titer" for anti-A and anti-B antibodies. Donors with a titer less than 256 saline dilution (immediate spin method) are designated low titer O universal whole blood (LTOWB) donors. A recent study showed LTOWB does not cause hemolysis when used in resuscitation of non–group O civilian trauma patients when up to 4 units are given.[4] LTOWB may be fresh (fresh whole blood, FWB) or stored (stored whole blood, SWB).

The use of LTOWB was standard practice in wartime settings for decades. In civilian practice in the United States, however, it has generally been unavailable and rarely used, comprising less than 1% of transfusions. More recently, interest in the use of whole blood has been growing, including the use of banked and fresh warm whole blood, despite the associated logistic hurdles.[5] In wartime settings, individuals designated as low-titer could be called upon to donate FWB acutely if needed. In the civilian setting, SWB is used on an as needed basis.

MANAGEMENT

Decision Making

Considerations in patient selection for blood product transfusion in the emergency care setting include the cause of the deficit, severity of symptoms, likelihood of ongoing hemorrhage, tissue oxygen requirements, and the patient's ability to compensate for decreased oxygen-carrying capacity. These considerations are influenced by the patient's age, underlying medical conditions, and hemodynamic stability. Clinical evaluation, including appearance (pallor, diaphoresis), mentation, heart rate, blood pressure, and nature of the bleeding (active, controlled, uncontrolled), as well as laboratory evaluation all inform transfusion decision making.

Pharmacology

PRBCs are administered through a filter and an intravenous (IV) line or intraosseous (IO) line, along with normal saline. No other in-line solutions should be utilized, unless approved for this purpose. For example, combining calcium containing fluids, such as lactated Ringers solution, with PRBCs can cause clotting in the line as the calcium binds with the citrate which is added to the PRBCs to act as an anticoagulant. Of note, this concern for clotting was mostly established in laboratory studies, and over the last 20 years there is anesthesiology literature that suggests that this clotting is not seen in clinical practice given the rapidity of administration and the PRBC to lactated Ringers ratios used. Nonetheless, no large study has demonstrated the safety of this practice, and therefore it is not routinely recommended. Dextrose containing fluids should also be avoided because the PRBCs may take up the dextrose, which causes osmotic shifts that can lead to cell lysis. Likewise, medications should not be added or pushed through the blood component transfusion line. There is growing literature demonstrating that some medications may be compatible with PRBC administration, and local guidelines or clinical pharmacist input is prudent if medication administration is necessary through the same line as a PRBC transfusion.

Devices and Techniques

Urgent or emergent transfusion requires flow rates faster than gravity can provide. An administration set with an in-line pump that is squeezed by hand is the simplest method to speed infusion. Pressure bags and rapid infusion devices are commercially available for clinical scenarios that require infusion of units of PRBCs within a matter a minutes. With high-pressure infusion, large-bore catheters are recommended so that hemolysis is prevented, however the literature supporting this recommendation is sparse.

Whole Blood

Reports on the successful use of FWB in military field hospitals have been published. In civilian practice in the United States, however, it has generally been unavailable and rarely used. The military experience with using whole blood dates back to World War I where type-specific, crossmatched blood was used in combat. This was almost 25 years before Rh typing was developed.[5] The use of citrate phosphate dextrose (CPD) or citrate phosphate double dextrose (CP2D) can allow for safe preservation of SWB for 21 days at 1°C to 6°C. The use of citrate phosphate dextrose adenine (CPDA-1) at 1°C to 6°C can increase storage time to 35 days. Owing to time dependent degradation of clotting factors and platelets, whole blood older than 2 weeks may require the addition of fresher whole blood or supplemental platelets to avoid contributing to coagulopathy.[5]

When PRBCs, plasma, and platelet transfusions in the 1 : 1 : 1 ratio are used, the mixture is significantly more diluted than when SWB is transfused. Average hematocrit and platelet count in 1 : 1 : 1 mixtures were 29% and 90 K/μl, respectively, when compared to 35% to 38% and 150 to 200 K/μl with SWB. Coagulation factors were also higher in SWB transfusions.

Current studies show that the use of SWB results in outcomes at least as good as component (RBC + plasma + platelet) therapy in hemorrhaging patients. We recommend the use of whole blood when available. Although the shelf-life of whole blood is shorter than component therapy, it can still be cost-effective owing to the higher cost of separating blood into components. The argument for using SWB early in the resuscitation process can be summarized as follows:[4,6-9]

- SWB provides a physiologic balance of blood components that are simultaneously transfused.
- A smaller volume of anticoagulant/preservative solution is transfused with SWB.
- Platelet function in SWB may be significantly enhanced compared to component therapy.
- Higher levels of hemostatic factors are delivered with SWB.
- Fibrinogen delivery is higher when utilizing SWB, as FFP does not deliver significant amounts of fibrinogen.
- Hemolytic transfusion reaction rate in SWB is low (about 1 : 120,000), therefore transfusions are generally safe and confer fewer donor exposures compared with component therapy, such as 1 : 1 : 1 protocols.
- Administration of all components together in one unit can improve the time to complete a transfusion.
- Errors associated with transfusion of type-specific blood can be minimized.

One potential complication from the lack of Rh typing in LTOWB, is the possibility of isoimmunization causing hemolytic disease of the newborn. Premenopausal women who receive LTOWB are potential candidates for anti-D immunoglobulin (Rhogam) and consultation with obstetrics.[9]

Autotransfusion may also be used in the emergency setting in the event of severe chest trauma. A large retrospective trial showed it to be both safe and effective. Autotransfusion is the process of giving a patient back his or her own blood that has been collected from an uncontaminated active bleeding site. This is most frequently done using blood from the thorax after trauma. This strategy has numerous advantages—immediate availability, blood compatibility, elimination of donor to patient disease transmission, lower risk of circulatory overload, and fewer direct complications related to the transfusion itself, such as hyperkalemia, hypothermia, hypocalcemia, or metabolic acidosis. It is also more acceptable to patients whose religious convictions prohibit non-autologous transfusions. It is impractical in some settings owing to a relatively limited number of appropriate trauma patients, specific training required to operate the equipment, and time required for equipment setup.

Packed Red Blood Cells

PRBCs are indicated only to improve oxygen delivery to tissues at the microvascular level and thus improve intracellular oxygen consumption, yet definitive demonstration of the efficacy of red cells for this purpose (or improved clinical outcomes) has proven elusive. A definitive randomized prospective study in which RBCs are withheld completely from one treatment group is unlikely to be conducted given ethical considerations.

In 2016, the AABB (formerly, the American Association of Blood Banks), published a clinical practice guideline regarding red blood cell transfusion after reviewing trials published between 1950 and May 2016. This review found strong support for using a restrictive transfusion strategy and a hemoglobin treatment threshold of 7 g/dL for most stable hospitalized patients. In those patients undergoing orthopedic surgery, cardiac surgery, or with preexisting cardiovascular disease, they recommend a hemoglobin treatment threshold of 8 g/dL. Of note, these recommendations are less universal to patients with a history of acute coronary syndrome, severe thrombocytopenia, or chronic transfusion–dependent anemia.[10]

For many patients, the decision to transfuse RBCs requires clinical judgment. The appropriate trigger for patients with active hemorrhage, for example, is not well-established, despite numerous trials.[11] With increasing support for permissive hypotension treatment strategies, clinicians must balance adequate tissue perfusion and hemostasis. We recommend transfusion with ongoing signs of inadequate perfusion, such as elevated serum lactate level, altered mental status, or decreased urinary output. Transfusions may be stopped once a patient has a stable blood pressure, even if hypotensive, combined with signs of adequate perfusion without overt ongoing hemorrhage. Of note, the hemoglobin level in acute hemorrhage can be misleading and should not exclusively be used to guide acute management. Because the hemoglobin level is a concentration, and individuals bleed whole blood and not just red cells, it takes time for fluid to shift into the intravascular space and cause the hemoglobin level to drop. Unfortunately, the amount of time required for this equilibration to occur has not been clearly established. A recent study of trauma patients demonstrated that a hemoglobin level of 11.8 g/dL or below on arrival to the hospital was only 88% sensitive for predicting significant hemorrhage.[12]

Special Preparations of PRBCs

Washed RBCs. PRBCs can be washed to remove residual plasma and any remaining leukocytes, platelets, microaggregates, plasma proteins, and free hemoglobin. Washing reduces the titer of anti-A and anti-B antibodies, thereby permitting safer transfusion of type O PRBCs into non–type O recipients. Washed cells are used in patients who have had recurrent allergic reactions to transfusion, as most of these reactions are a response to donor proteins in the plasma. Patients with IGA deficiency from circulating anti-IGA antibodies can react to IGA in the donor plasma and may also benefit from washed cells. Washing takes about an hour and reduces the viability of the unit to 24 hours.

Leukocyte-Reduced RBCs. A typical unit of whole blood or packed red cells can contain from 1 to 3 billion white blood cells (WBC), which can cause a variety of problems in the recipient including febrile (non-hemolytic) reactions, immune sensitization, or transmission of disease. Non-leukocyte-reduced products can be a major source of viral transmission, including human T-lymphotropic virus 1 and 2, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Additionally, increased rates of bacterial contamination and postoperative or vascular line infections have been associated with the use of non-leukocyte-reduced products.

By passing the blood through a leukocyte filter, the number of WBCs can be reduced by 99.99%. This can lead to a significant reduction in complications in vulnerable populations. Leukoreduction is not effective enough, however, to prevent transfusion-associated graft-versus-host disease (TA-GvHD), thus blood transfused to susceptible patients must be irradiated. Leukocyte-reduced red cell products are now used for more than 95% of patients in the United States.

Irradiated RBCs. Blood products can be irradiated to reduce the risk for TA-GvHD in susceptible patients, which occurs in about 1 per 1 million transfusions but is associated with 90% mortality.[13] Irradiation can be performed either directly before transfusion on an individual unit or batches of irradiated PRBCs may be maintained in locations for use in the care of immunosuppressed patients. Irradiation destroys donor lymphocytes. This prevents WBCs in donor blood from recognizing the host's cells as foreign and attacking them, potentially leading to severe illness or death. Susceptible patients are those who are unable to mount an immune response to the donor lymphocytes. Although there is some variation in the literature as to who should receive irradiated PRBCs, generally the categories center on those who are immunocompromised or who have a close human leukocyte antigen (HLA) match to the donor, as occurs in the case of a directed donation. The latter group may not be able to recognize the donor cells as foreign. As a result of irradiation, post-transfusion red cell recovery is decreased and the rate of intracellular potassium release increases. PRBCs irradiated within 14 days of collection expire 28 days after

TABLE 108.1 Indications for Special Preparations of PRBCs

Special Preparation	Process	Use
Irradiated PRBCs	Irradiation of the donor blood destroys WBCs thereby decreasing the risk of transfusion-associated graft-versus-host disease.	• Neonatal or intrauterine transfusion • Hematologic malignancy • Stem cell transplant patients or donors within a week prior to cell harvesting • Hodgkin lymphoma • Directed donations from family members (biological) • Congenital cellular immune deficiency • Transfusions from HLA-matched donors • Patients treated with antithymocyte globulin or chemotherapy with purine analogs (e.g., fludarabine, bendamustine, etc.)
Washed PRBCs[14]	PRBCs are washed with saline to remove residual plasma and protein. Reduces allergic reactions to foreign proteins.	• History of severe allergic transfusion reactions • IgA-deficiency • Paroxysmal nocturnal hemoglobinuria
Leukocyte Reduced PRBCs	PRBCs are filtered to remove 99.99% of the leukocytes	• Patients undergoing chemotherapy • Multiparous females • Patients receiving multiple transfusions
CMV Negative PRBCs[15]	CMV testing is performed on units of PRBCs	• Seronegative patients who are currently pregnant • Fetal or intrauterine transfusion • Solid organ, stem cell, or bone marrow transplant recipients who are CMV negative

collection, and PRBCs irradiated more than 14 days after collection expire either 5 days after irradiation or at the original expiration date, whichever comes first.

CMV Negative Blood. Because CMV is endemic worldwide and seropositivity rates in the United States are reported at 30% to 97%, most donated blood is CMV positive. Even after an acute infection with CMV is cleared, it remains present in leukocytes. CMV testing can identify units of PRBCs that are free of the virus and safe to transfuse in at-risk populations. Leukocyte-reduced PRBCs are typically an acceptable alternative if CMV negative products are not available. Indications for CMV negative PRBCs and other special preparations are summarized in Table 108.1.

Fresh Frozen Plasma

A unit of fresh frozen plasma (FFP) contains all the clotting factors and typically has a volume of 200 to 250 mL. It must be ABO compatible and is administered through blood tubing. Triggers for FFP are not clearly defined; indications for FFP are based primarily on observational trials and expert opinion. The following indications seem reasonable based on current evidence: massive hemorrhage, as a component of a plasma exchange procedure, emergency reversal of a vitamin K antagonist in the presence of clinically significant hemorrhage or in the treatment of ace inhibitor–induced angioedema. It is worth noting, however, that the therapeutic effect is difficult to predict, and the international normalized ratio (INR) level of FFP itself is around 1.5, thus FFP can't lower an INR level below 1.5. A large volume of FFP is needed to reverse coagulopathy caused by vitamin K antagonism (at least 10 mL/kg, and perhaps as much as 30 mL/kg), which can place patients at risk for volume overload. This, in part, justifies the recommendation for prothrombin complex concentrate (PCC) over FFP when available for reversal of vitamin K antagonism in the setting of life-threatening bleeding.

Evidence from retrospective trials has supported increased use of FFP in patients anticipated to require more than 10 units of PRBCs (massive transfusion). This should not be generalized to all patients receiving a transfusion, however, as limited benefit and increased complications have been observed in patients with mild or moderate active blood loss who receive FFP.

Likewise, limited available evidence has failed to support the use of FFP in patients with an elevated INR before invasive procedures such as central line placement or lumbar puncture. The INR level itself often proves to be a poor predictor of risk for clinical bleeding. If a specific factor deficiency is identified, as in hemophilia, targeted factor replacement, if available, is preferred over FFP.

The use of FFP has also recently been described in the treatment of ace inhibitor–induced angioedema, as FFP contains c1-inhibitor and kininase II enzymes. Case reports and series suggest that the administration of 2 units of FFP may lead to significant reduction of edema within 2 to 4 hours.[16]

Platelets

The decision to transfuse platelets is multifactorial. The underlying cause of the thrombocytopenia and the age of the patient are just two factors that greatly affect transfusion recommendations. In 2015, the AABB published a clinical practice guideline concerning the general transfusion of platelets. They recommended, in most cases, transfusing adults below 10 K/μL given the risk of spontaneous hemorrhage. For patients undergoing central venous catheter placement, consideration of transfusion is recommended below 20 K/μL. Patients undergoing lumbar puncture and non-neuroaxial surgery should be considered for transfusion below 50 K/μL.[17]

Other than in the setting of massive transfusion, pediatric platelet transfusion should be discussed with a hematologist. Children with immune thrombocytopenic purpura (ITP) and no signs of active bleeding can often be managed without transfusion, even at levels below 10 K/μL.[18] If thrombotic thrombocytopenic purpura (TTP) is suspected as the cause of thrombocytopenia, platelet transfusion should be avoided. Platelet transfusion in this case may serve to exacerbate the underlying problem by adding platelet substrate for unbalanced thrombotic reactions within the vasculature. Administration of platelets in TTP is associated with increased arterial thrombosis and mortality.[19] Similarly, platelet administration is not routinely

recommended in heparin-induced thrombocytopenia (HIT), though it may be beneficial in patients with significant active bleeding.[20]

Crossmatching is generally unnecessary for platelet transfusions, but Rh-negative, premenopausal women should be transfused with Rh-negative platelets because there may be enough red cells in the platelet concentrate to cause Rh sensitization. The use of leukocyte-reduced platelets has been shown to reduce the risk of HLA sensitization and is therefore beneficial in patients receiving frequent platelet transfusions. Once sensitization has occurred and patients have developed immune-mediated platelet refractoriness, various management strategies may be considered in consultation with a hematologist, including HLA-based donor selection or platelet crossmatching.

Cryoprecipitate

Cryoprecipitate is prepared from single-donor plasma by gradually thawing rapidly frozen plasma. The result of this process is the precipitation of fibrinogen, factor VIII, factor XIII, von Willebrand factor, and fibronectin. Per AABB standards, each unit (5–20 ml) of cryoprecipitate should contain at least 150 mg of fibrinogen and 80 IU of factor VIII. Because cryoprecipitate is a plasma product, ABO compatibility is necessary. Like FFP, cryoprecipitate has similar risks for both allergic and febrile reactions. It has also been associated with the development of TRALI.

Cryoprecipitate is indicated for patients with fibrinogen deficiency, congenital afibrinogenemia, or dysfibrinogenemia. Clinically, low fibrinogen levels are most often encountered in the setting of massive hemorrhage and DIC. Although not recommended as a primary treatment, cryoprecipitate can also be given to patients with hemophilia A or von Willebrand disease when recombinant factor VIII preparations are not readily available. As cryoprecipitate does not contain factor IX, it is of no value in the treatment of factor IX deficiency (hemophilia B).

Prothrombin Complex Concentrate

Both three- and four-factor PCC products are now FDA-approved in the United States, with four-factor products containing all the vitamin K–dependent clotting factors (factor II, VII, IX, and X), whereas three-factor products lack any significant amounts of factor VII. Guidelines published by the American College of Chest Physicians recommend that PCC be used for the reversal of an elevated INR level in patients with life-threatening bleeding or intracranial hemorrhage, and available evidence has shown that a more rapid normalization of the INR in these patients occurs with the administration of PCC rather than FFP. Studies comparing three- and four-factor PCCs in patients with serious warfarin-associated bleeding have found that the four-factor product is more reliable in reducing the INR to below 1.5 within 1 hour, and we recommend its use, when available.[21,22]

OUTCOMES

Safety and Effectiveness

In an average adult, 1 unit (≈450 mL) of PRBCs increases the hemoglobin level by about 1 g/dL or the hematocrit by about 3%. A similar increase in pediatric patients is observed with administration of 10 mL/kg of PRBCs. Most transfusions are given over 60 to 90 minutes. Owing to an increased risk of bacterial growth when PRBCs are exposed to room temperature, transfusion of a single unit should not last longer than 4 hours. Unused blood should be returned promptly to the blood bank. Any units unrefrigerated for more than 30 minutes should be discarded.

One unit of activity for any coagulation factor is equal to the clotting activity found in 1 mL of FFP. Appropriate dosing of FFP has not been well grounded in evidence from clinical trials. In massive transfusion, many centers now incorporate FFP in proportion with red cells and platelets. For other indications, it seems reasonable to start with an infusion of 10 to 30 mL/kg, recognizing that results will be variable and follow-up laboratory and clinical assessment is necessary to guide further management.

Platelets are often given to adults in a dose of 6 units of platelet concentrate ("six-pack" of platelets) and in children at a dose of 1 unit per 10 kg of body weight, an amount expected to raise the platelet count by about 40 to 60 K/μl in adults or children. Administering additional platelets does not generally improve hemorrhage outcomes.[17] The AABB recommends giving either a six-pack or three-pack of platelets. Alternatively, a single apheresis unit (derived from a single donor) provides roughly the same amount of platelets as a six-pack. The advantage of apheresis platelets is that they expose the recipient to the plasma proteins of only one donor as opposed to 6 donors in a pooled unit. This, in turn, decreases the risk of allergic reactions.

Cryoprecipitate is used to correct significant hypofibrinogenemia (<100 mg/dL). A typical adult dose of around 10 bags of cryoprecipitate raises the fibrinogen level by up to 1 g/L (100 mg/dL). Cryoprecipitate can also be used in cases of post-tPA (tissue plasminogen activator) bleeding. A consensus on dosing has not been reached, though many sources recommend between 10 and 12 bags.[23]

PCC dosing is based upon the concentration of factor IX, which varies between different specific formulations. Some products also have variable dosing based upon the pretreatment INR. Consequently, emergency clinicians should consult their local protocols and pharmacists to ensure proper dosing of PCC. We also recommend that all patients with life-threatening warfarin-associated hemorrhage also receive 10 mg of vitamin K by slow IV infusion, administered at 1 mg/min or slower.

Massive Transfusion Protocols

Massive transfusion was traditionally defined as the administration of more than 10 units of PRBCs over 24 hours, but a more practical and efficacious application of the concept is the transfusion of 3 units of PRBCs over an hour or the use of 4 components over 30 minutes. The concept of utilizing a massive transfusion protocol (MTP) that called for the use of plasma and platelets along with PRBCs was born from the understanding that acute blood loss involves more than just the loss of red cells. Physiologically it makes sense to replace all components of blood after more than a few units of PRBCs have been transfused. Although protocols for MTP are variable and often predicated on institutional protocol, most now use a ratio of 1 : 1 : 1 (PRBCs : FFP : platelets) when transfusion needs exceed 3 units of PRBCs. When large and ongoing blood loss is anticipated, the initiation of a MTP should be considered.

A systematic review concluded that the available evidence could not support any definite recommendations regarding specific ratios of blood components in massive transfusion.[24] A large, multicenter randomized clinical trial compared the use in massively transfused trauma patients of a 2 : 1 : 1 ratio (PRBCs : FFP : platelets) with a 1 : 1 : 1 ratio and found no difference in mortality at 24 hours or 30 days, although fewer patients in the 1 : 1 : 1 group died of exsanguination at 24 hours.[25] Until evidence supports otherwise, we recommend a 1 : 1 : 1 ratio of blood products when a MTP is initiated.

The use of thromboelastography (TEG) or rotational thromboelastometry (ROTEM) has been studied as a way to better predict which blood components may be helpful in normalizing coagulation. While TEG/ROTEM does alter transfusion patterns, a 2015 systematic review was unable to show that TEG/ROTEM was superior to standard coagulation studies, such as prothrombin time ratio and/or the INR.[26] A subsequent study in trauma patients compared goal-directed transfusion

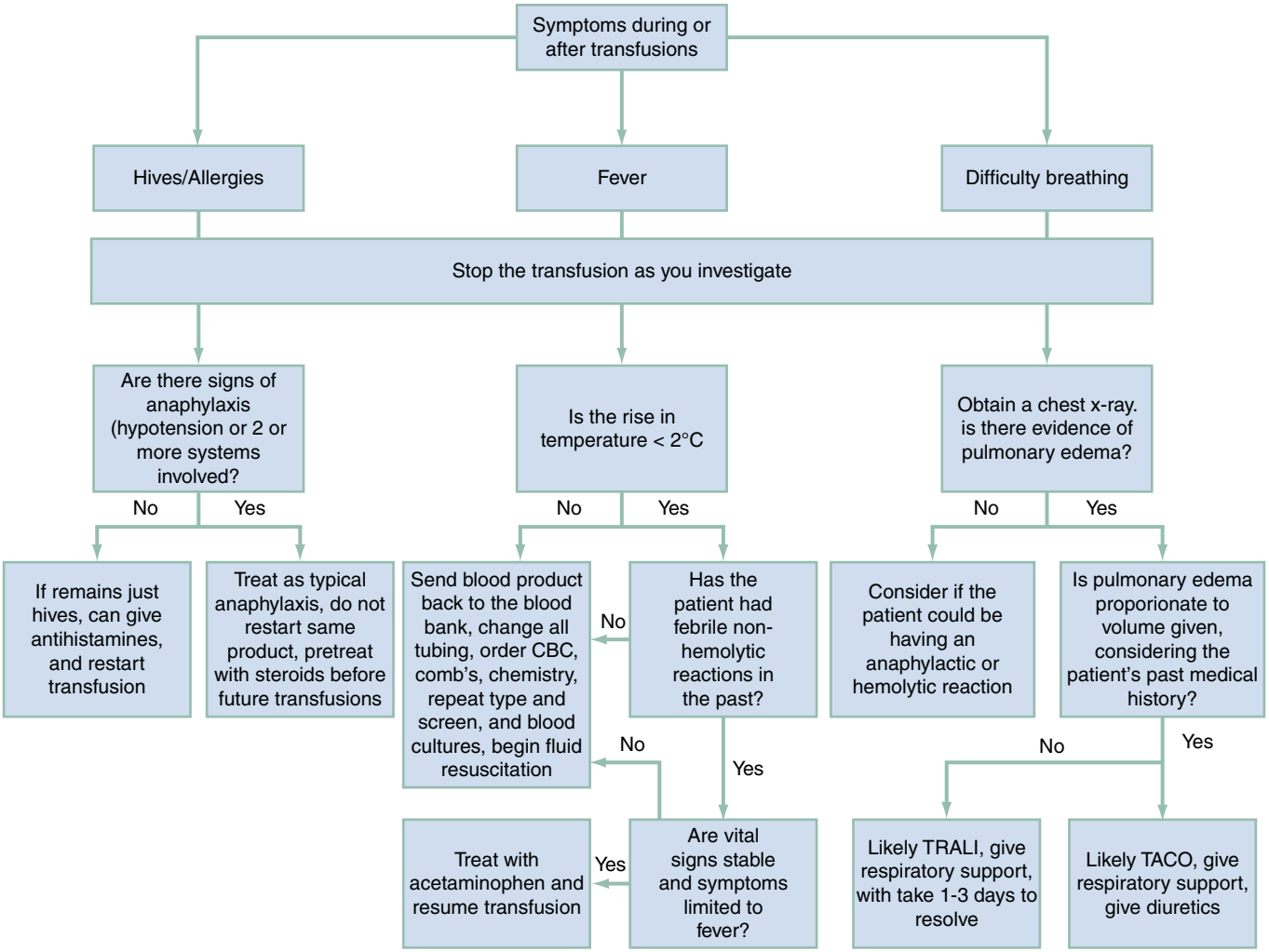

Fig. 108.2 Algorithm for treatment of transfusion reactions.

based on TEG to transfusion based on conventional coagulation parameters. In this study, the risk of death was higher in the conventional coagulation group.[27] While promising, further study is needed to clarify the role of routine TEG/ROTEM in trauma care.

Complications of massive transfusion are well-understood and many can be managed anticipatorily. Hypothermia is common and can reduce clotting factor activity. Warmed IV fluids, blood warmers, and warming lights or blankets are often needed. Frequent laboratory testing will identify electrolyte disturbances, including low magnesium and calcium levels and low or high potassium levels, which are generally treated in a standard fashion. Acidosis is a common finding with massive hemorrhage and can also be caused by hypoperfusion with or without contributions from transfused blood. Citrate from banked blood is metabolized in the liver to bicarbonate, which can result in metabolic alkalosis at times. With rapid infusion or reduced hepatic function, however, this pathway can be overwhelmed and the net effect of infusing large amounts of citrate can be worsening metabolic acidosis. A rational response to metabolic acidosis is to optimize oxygen delivery and ventilation. The benefit of administering sodium bicarbonate in this setting remains unproven and, as such, is not routinely recommended.

Complications and Adverse Effects of Nonmassive RBC Transfusion

Transfusion reactions are complications developing during or after transfusion of whole blood or individual blood components. Reactions can range from mild to life-threatening, with most acute reactions classified as mild and with upwards of 90% occurring rapidly after transfusion initiation. Delayed reactions tend to occur days to weeks after the transfusion is completed. See Figure 108.2 for a generalized and algorithmic approach to managing transfusion reactions.

Acute Transfusion Reactions

Minor Allergic. The most common manifestation of a minor allergic transfusion reaction is urticaria. In some cases, however, wheezing and angioedema can also be observed. Minor allergic reactions develop in 1% to 3% of transfusions and are generally attributed to an allergic, antibody-mediated response to donor plasma proteins. If a patient develops allergy symptoms, the transfusion should be stopped. The reaction can be treated like any other allergic reactions using antihistamines and steroids. If the reaction remains mild and is limited to the skin, the transfusion can be resumed after symptomatic treatment.

Anaphylactic. The reported incidence of transfusion-associated anaphylaxis is 1 in 20,000 to 50,000 transfusions, with most cases being idiopathic in nature. There are case reports of patients with IgA deficiency and anti-IgA antibodies developing anaphylactic reactions to IgA in donor blood, but this is not generalizable to most cases of transfusion-related anaphylaxis.

The presentation is similar to anaphylactic reactions from other causes and may include hypotension, angioedema, dyspnea,

bronchospasm, or laryngospasm. The symptoms are typically rapid in onset and begin within seconds to minutes of transfusion initiation. The transfusion should be stopped immediately, with symptoms treated in the same way as other forms of anaphylaxis. If a transfusion is still required, pretreatment with steroids and antihistamines 30 to 60 minutes before the transfusion is prudent, and the patient should be given a new transfusion product, rather than restarting the original product. In addition, transfusion of washed cellular products may further decrease risk.

Febrile (Nonhemolytic) Transfusion Reaction. A febrile, nonhemolytic transfusion reaction (FNHTR) is defined as a temperature elevation of 1°C (1.8°F) or higher that occurs with transfusion and for which no other medical explanation is identified. It is often associated with rigors and chills. Reactions are believed to result from both recipient anti-leukocyte antibodies that react with donor WBCs and from cytokines released during a storage lesion (damage to and loss of some RBCs over time during storage) of the transfused unit, the latter of which increases with the duration of blood storage.[28] The use of leuko-reduction has been shown to decrease the risk of FNHTR by around 50% for RBCs and up to 93% for platelets.

If a febrile reaction occurs in a first-time transfusion, it should be treated as an acute hemolytic reaction until proven otherwise. Similarly, any vital sign instability, rise in temperature greater than 2°C, or symptoms other than fever and chills should prompt the reaction to be treated as an acute hemolytic reaction, regardless of a history of FNHTR. The transfusion should be stopped, and testing should be done to prove the reaction is non-hemolytic (see the next section for details). When a hemolytic reaction is ruled out and the event is considered to be a simple FNHTR, treatment with acetaminophen is appropriate and the unit in question should be discarded with a fresh unit transfused in its place. Many institutions routinely utilize leukocyte-reduced blood, however if this is not the case, leukocyte-reduced blood may decrease the likelihood of a recurrent reaction. If the original unit was already leukocyte-reduced, switching to a different unit may also decrease the chance of another reaction.

Pretreatment, or treatment for symptoms, with antipyretics is appropriate for patients with recurrent reactions. If a patient has a history of FNHTR, no vital sign instability, no symptoms other than fever and chills, and the rise in temperature is less than 2°C, the transfusion may be continued as normal. Antihistamines are usually not helpful in either treatment or prophylaxis for FNHTR. Patients with severe chills and rigors may also benefit from other analgesics in addition to acetaminophen, such as ibuprofen or an opiate medication. The now infrequently used opiate pain medication meperidine has been recommended for the prevention and treatment of rigors at the dose of 0.5 to 0.75 mg/kg over 4 minutes. When meperidine is not available, other opiates such as hydromorphone (0.015 mg/kg IV) or fentanyl (0.5 to 0.75 mcg/kg IV) can be used.

Acute Hemolytic Transfusion Reaction. Intravascular hemolytic transfusion reaction is the most serious transfusion reaction. It generally results from ABO incompatibility, usually caused by a clerical or laboratory error. The incidence of acute hemolytic transfusion reactions ranges from 2 to 8 per 100,000 units transfused with a fatality rate of 1 per 100,000 units transfused. When incompatible blood is given, the impact may range widely from asymptomatic to death. While mortality from hemolytic reactions increases in proportion to the amount of blood transfused, as little as 30 ml can be fatal.

In an ABO incompatibility, the recipient's serum has preformed antibodies directed against the donor RBCs. The donor cells will begin to hemolyze within seconds or minutes. In most cases, donor blood is agglutinated (clumped and stuck together) and then hemolyzed. Vasoactive substances released by responding macrophages may cause fever, chills, hypotension, and shock.

BOX 108.1 Laboratory Abnormalities in Acute Hemolytic Transfusion Reactions

- Decrease in hemoglobin or hematocrit
- Hemoglobinemia
- Hemoglobinuria
- Increased serum lactate dehydrogenase (LDH)
- Increased serum indirect bilirubin
- Decreased serum haptoglobin
- Evidence of DIC, including: prolonged PT, PTT, decreased fibrinogen level, increased D-dimer
- Schistocytes or spherocytes on peripheral smear

BOX 108.2 The National Healthcare Safety Network Hemovigilance Surveillance Protocol Definition of TRALI

- No evidence of acute lung injury before transfusion, AND
- Acute lung injury onset during or within 6 hours of cessation of transfusion, AND
- Hypoxemia defined as either Pa_{O_2}/Fi_{O_2} less than or equal to 300 mm Hg or oxygen saturation less than 90% on room air, AND
- Radiographic evidence of bilateral infiltrates, AND
- No evidence of left atrial hypertension (i.e., circulatory overload).

(Adapted from Centers for Disease Control and Prevention (CDC). National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol. Available at: https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf. Accessed May 10 2021.)

The onset of symptoms is usually immediate but can take up to 24 hours to fully manifest. Fevers and rigors are an early indication of an AHTR. Patients may also complain of headache, nausea, vomiting, sensation of chest restriction, severe joint or low back pain, burning sensation at the site of the infusion, or a feeling of impending doom.

Treatment includes immediate cessation of the transfusion, replacement of all blood administration tubing, and initiation of vigorous crystalloid fluid therapy. The use of vasopressors or diuretics may also be considered in order to maintain a urine output of 1 to 2 mL/kg/hr. Blood and urine specimens, as well as the remainder of the transfusion and blood tubing, should be sent for laboratory testing. The diagnosis can be confirmed by detection of free hemoglobin in blood or urine and a positive result of Coombs test on posttransfusion, but not pretransfusion, specimens. See Box 108.1 for associated laboratory abnormalities in AHTR.

Recipient blood should be sent for a direct antiglobulin test (DAT), plasma-free hemoglobin level, CBC, chemistry, haptoglobin, LDH, bilirubin, PT/PTT, D-dimer, fibrinogen, and a repeat type and crossmatch. Urine should be tested for free hemoglobin. In cases of severe intravascular hemolysis, the urine and/or plasma can become pink or dark brown in color from the free hemoglobin. Dialysis is occasionally required for either severe hyperkalemia as a direct result of the hemolysis or renal failure as a result of DIC.

Transfusion-Related Acute Lung Injury. TRALI refers to noncardiogenic pulmonary edema occurring during or shortly after the transfusion of virtually any blood products. See Box 108.2 for the definition and diagnostic criteria of TRALI. Although TRALI has been traditionally associated more with platelet and plasma transfusion, the increased use of PRBCs relative to other components seems to have

TABLE 108.2 Acute Transfusion Reactions

Condition	Notes	Clinical Findings	Laboratory Findings
TACO	Proportional to volume transfused. Onset 6–12 hours after transfusion started.	Evidence of volume overload with dyspnea, edema, rales, tachycardia, hypertension	Elevated BNP level, pulmonary edema on chest x-ray
TRALI	Not associated with volume of transfusion	Hypotension, fever, hypoxia	pulmonary edema on chest x-ray
Anaphylaxis	Not associated with volume of transfusion	Hypotension, tachycardia, urticaria, wheezing	None specific
Hemolysis	Not necessarily associated with volume transfused though generally worse with increased amounts of incompatible blood	Fever, chills, hypotension, bleeding (DIC), back pain, discoloration of urine	Evidence of hemolysis (increased LDH, decreased haptoglobin, schistocytes) Evidence of DIC (prolonged PT/PTT, low platelets, decreased fibrinogen, elevated D-dimer, schistocytes)
FNHTR	Associated with fever	Fever	None specific, lack of evidence of hemolysis

TACO, Transfusion-associated circulatory overload; *TRALI*, transfusion-related acute lung injury; *FNHTR*, febrile non-hemolytic transfusion reaction; *DIC*, disseminated intravascular coagulation.

balanced the risk as similar across different blood products. Owing to strategies designed to mitigate TRALI, the incidence has decreased significantly in recent years. Nonfatal TRALI occurs in about 1 in 60,000 transfusions, but it still accounts for 29% of transfusion-related deaths.

A proposed mechanism for the development of TRALI includes a reaction between transfused antibodies and leukocytes in the recipient, as well as the effects of biologically active factors that accumulate in stored blood, including cytokines and lipids. Another proposed mechanism involves the alloimmunization of plasma from female donors. During a prior pregnancy the donor may have produced IgG antibodies against the paternally inherited antigens in the fetus. These antibodies can persist and be transfused into the recipient contributing to the TRALI reaction. This issue seems to become relevant when high-volume plasma transfusion is used. The ultimate effect is an increase in pulmonary capillary permeability leading to leakage of high protein fluid into the alveoli. Clinical effects can include noncardiogenic pulmonary edema, with dyspnea, hypoxemia, or bilateral infiltrates on the chest radiograph. Fever, hypotension, and transient leukopenia may also be seen.

If TRALI is suspected, the transfusion should be stopped, and the blood bank notified. Respiratory support should be provided, which may include noninvasive positive-pressure ventilation (NIPPV) or intubation and mechanical ventilation. It is safe to continue transfusion of blood products from a different donor. Complete resolution is usually seen within 48 to 96 hours. The overall prognosis is better than would be expected with many other causes of acute lung injury, with a reported mortality rate of 6% in one series. One strategy suggested for reducing TRALI has been to use only male donors for plasma to avoid allotypic leukocyte antibodies or to screen for these antibodies and exclude donors when the antibodies are found.

Transfusion Associated Circulatory Overload. Transfusion associated circulatory overload (TACO) is volume overload after transfusion that is proportional to the volume transfused. Smaller volume transfusions, such as cryoprecipitate, are less likely to produce an overload state than FFP or PRBCs. Risk factors for developing TACO include preexisting heart disease (e.g., CHF), significant renal insufficiency, and extremes of age. A recent animal model suggested a two-hit hypothesis for the development of TACO. The first hit is volume incompliance and the second hit is the composition of the fluid given (PRBCs versus crystalloid solutions). A preexisting volume incompliance (myocardial infarction [MI] or acute kidney injury) confers a significant and clinically relevant difference in left ventricular end-diastolic pressure (LVEDP), heart rate, and blood pressure in animals receiving PRBCs (the second hit) as opposed to equal volumes of lactated Ringers solution. This difference was not noted in animals without the first hit in whom equal volumes of PRBCs and lactated Ringers solution were given.[30] This appears to explain similar findings in humans with heart and kidney disease.

TACO appears to develop in about 1% of transfused patients, however this number may underestimate the true incidence since many cases spontaneously resolve with diuresis.[31] There is no specific test or single criteria to definitively diagnose TACO. It should be considered in patients who develop shortness of breath, hypertension, tachycardia, and other signs of volume overload. It is also important to distinguish TACO from immune-mediated conditions such as TRALI, allergic reactions or other conditions causing shortness of breath (e.g., pulmonary embolism, MI). Some clinical clues to help differentiate TACO from other causes can be seen in Table 108.2.

Management of TACO is similar to other causes of volume overload. The transfusion (if ongoing) should be stopped. Diuretics should be given. Theoretically, nitroglycerine would have similar effect in TACO as in any other volume overload situation and can be started at 50 to 100 mcg/min IV and titrated to effect. NIPPV can be initiated early to improve oxygenation and the work of breathing. If the patient develops intractable symptoms, intubation and mechanical ventilation may be required. In future transfusions, the rate of transfusion may be slowed, and prophylactic diuretics can be given to decrease the risk of another episode of TACO.

Infectious Complications of Transfusions

Though rare, transmission of infectious diseases is the transfusion-related complication most feared by the lay public. Transmission of a wide variety of infectious diseases has been reported, but modern screening methods, of both donors and the blood itself, have sharply reduced the frequency of transmission. The risks of transmission of viral infections such as HIV, hepatitis B, and hepatitis C are all well below 1 in a million. Concerns for bacterial infections prompted the practice of completing transfusions within 4 hours and returning unused blood products to the blood bank only if they have been unrefrigerated for less than 30 minutes.

In a recent study, bacterial culture positive transfusion reactions (BCPTRs) were defined as a positive bacterial culture result from the transfused blood product, from the recipient, or from both the blood product and the recipient. A septic transfusion reaction (STR) was further distinguished as a BCPTR that met definitive CDC hemovigilance criteria with absolute "imputability" and matching culture results from both the donor unit and the patient's blood culture.[32] Over an 8-year

period the study recorded 688,514 transfusions (52%, PRBCs, 23% apheresis platelets, 18% plasma, and 8% cryoprecipitate) and identified a total of 15 BCPTRs (0.002%). Further, only half of these met the more strict STR definition. A majority of the infectious cases resulted from platelet transfusions.[32]

Although a relatively rare occurrence, STR should be at least considered in any patient who develops a fever during a transfusion when it does not improve after cessation of the transfusion and the use of antipyretics.[33] The AABB developed criteria for consideration of STR which included a temperature of 38°C or higher and a 1°C rise above pretransfusion temperature in conjunction with associated symptoms such as rigors, nausea/vomiting, dyspnea, hypotension, or shock. They also used isolated hypotension or shock (and/or cardiovascular collapse) irrespective of fever as reasons to investigate for STR.

The Biomedical Excellence for Safer Transfusion (BEST) Collaborative found an increased sensitivity for detecting an STR with modification of the AABB criteria to include isolated high fever (>39°C) and a greater than 1°C rise above pretransfusion temperature irrespective of the presence of associated symptoms. In addition, they used predefined vital sign criteria to indicate hypotension (SBP < 90 mm Hg/DBP < 60 mm Hg or a 15% decrease from baseline) and tachycardia (HR > 100 or a 15% increase from pretransfusion baseline). Finally, they took into account the use of pretransfusion use of antipyretics which could blunt fever response.[34]

When an STR is suspected the transfusion should be paused and a culture of the transfusion unit and a blood culture from the patient are indicated.

Delayed Transfusion Reactions

Delayed Hemolytic Transfusion Reaction. A delayed hemolytic transfusion reaction (DHTR) typically occurs 3 to 10 days following transfusion with blood that initially appeared to be compatible. This can result from a non–ABO-mediated immune response, usually caused by an anamnestic response in a patient previously sensitized to red cell minor antigens through transfusion, pregnancy, or transplantation. Decreased survival of transfused red cells develops as a result of extravascular hemolysis. A related phenomenon termed delayed serologic transfusion reaction (DSTR) can develop when anamnestic antibodies are detected but there is no evidence of hemolysis. Together DSTR and DHTR occur in about 1 in 1500 transfusions, with the former occurring about four times more frequently than the latter.

Clinical effects can include fever, anemia, or jaundice. Symptoms are usually mild, though rarely significant complications such as oliguria or DIC can occur. Hemoglobinemia and hemoglobinuria are generally absent. Treatment is primarily supportive and the blood bank should be notified.

Transfusion-Associated Graft-versus-Host Disease. This rare but typically fatal complication results when transfused lymphocytes proliferate and attack a recipient who is incapable of mounting an immune response to the transfused cells.

Cell-mediated immunodeficiency places patients at risk, as does having an HLA type that is similar (sharing some but not all of the HLA antigens) between donor and recipient (most often seen among first-degree relatives).

Symptoms begin 3 to 30 days after transfusion and include fever, erythematous skin rash, diarrhea, elevated liver enzyme levels, and pancytopenia. Mortality is greater than 95%.

Efforts are directed at prevention through the use of gamma irradiation of cellular components, which renders the donor lymphocytes incapable of proliferating. The use of leukocyte-reduced components is not sufficient to prevent TA-GvHD. This condition should be kept in mind when transfusion is being considered for high-risk patients, including:

- Congenital immunodeficiency
- Hematologic malignancy (Hodgkin disease)
- Stem cell transplantation
- Treatment with purine analogues (e.g., fludarabine)
- Directed donor products from a close relative

Discussion with a hematologist is prudent when deciding whether to use irradiated cellular components in these high-risk groups.

Treatment is palliative and aims to restore the recipient's immune function. It is largely unsuccessful.[35]

Post-transfusion Purpura. Rarely, profound thrombocytopenia can develop 1 to 3 weeks after a transfusion associated with an antibody response to a platelet antigen. Eventually, this low-affinity antibody is eliminated, and the thrombocytopenia resolves spontaneously. Patients at risk for bleeding or with active hemorrhage are considered for treatment with high-dose immune globulin, plasmapheresis, or platelet transfusion.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 108: QUESTIONS AND ANSWERS

1. A 60-year-old man on warfarin presents to the emergency department after a fall. His non-contrast head CT shows a subdural hematoma, and his INR is 4. Which of the following is the recommended agent to reverse his coagulopathy?

a. Cryoprecipitate
b. Fresh frozen plasma
c. Prothrombin complex concentrate
d. Oral vitamin K

Answer: C. Prothrombin complex concentrate (PCC) is the recommended agent for reversal of elevated INR in life-threatening bleeding, including intracranial bleeding. 4 Factor PCC contains clotting factors II, VII, IX, and X making it the ideal agent for patients with elevated INR from warfarin as this medication inhibits synthesis of these vitamin K–dependent clotting factors. Cryoprecipitate contains fibrinogen, factor VIII, factor XII, von Willebrand factors, and fibronectin and is used most often clinically in cases of low fibrinogen

CHAPTER 108: QUESTIONS AND ANSWERS—cont'd

such as massive hemorrhage and DIC. Fresh frozen plasma can be used to reverse warfarin-induced coagulopathy; however, it often requires the administration of significantly more fluid volume and PCC more reliably lowers the INR in a shorter time frame. For these reasons PCC is the preferred treatment. Vitamin K will take hours to days to reverse the coagulopathy, as it relies on the bodies metabolic processes to synthesize clotting factors. It is, however, generally recommended to give IV vitamin K along with PCC, so that once the transfused factors have been consumed the body will have started to produce its own factors again.

2. A 36-year-old female patient is receiving a unit of packed red blood cells to treat her chronic anemia from end-stage renal disease when she develops a temperature of 38.2°C. The rest of her vital signs are normal. Which of the following is the best next step in management?
   - **a.** Administer acetaminophen
   - **b.** Given a bolus of 1 L of NS
   - **c.** Start broad spectrum antibiotics
   - **d.** Stop the blood transfusion

Answer: D. The first step in any suspected transfusion reaction is to stop the blood transfusion. If after investigation and brief observation this appears to be a non-hemolytic febrile transfusion reaction, you may administer acetaminophen and resume the transaction. Fluids resuscitation is the mainstay of treatment for hemolytic transfusion reactions, which can present as a fever. However, as is the case with any transfusion reaction, the first step is stopping the blood transfusion. Antibiotics are indicated in bacterial culture positive transfusion reactions. Typically patients will experience other vital signs abnormalities, such as tachycardia and hypotension, when having one of these reactions.

3. A 76-year-old female is receiving a unit of packed red blood cells, when she suddenly develops shortness of breath. On examination, she has crackles on auscultation of her lungs bilaterally. Which of the following is true regarding transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI)?
   - **a.** Chest x-ray can often distinguish between TACO and TRALI.
   - **b.** Only TACO should be treated with noninvasive positive-pressure ventilation.
   - **c.** TACO typically requires the presence of a significant comorbidity.
   - **d.** TRALI can be treated with aggressive diuresis.

Answer: C. While it is possible to receive enough blood products for a healthy person to become volume overloaded, TACO is much more commonly seen in patients with underlying heart or renal failure. Both TACO and TRALI result in pulmonary edema, meaning they can present with similar chest x-ray findings and physical exam findings. Both entities can be treated with noninvasive positive-pressure ventilation or intubation and mechanical ventilation, as both treatments are effective in treating pulmonary edema. TRALI, however, will not respond to diuretics, because the cause of the pulmonary edema is an inflammatory response within the lungs rather than systemic volume overload.

4. A 15-year-old male is receiving a transfusion of packed red blood cells after a traumatic injury when he complains of itching. On examination, hives are found, and soon the patient develops difficulty breathing, tachypnea, tachycardia, and hypotension. The transfusion is stopped. Which of the following medications should be administered first?
   - **a.** Diphenhydramine
   - **b.** Epinephrine
   - **c.** Furosemide
   - **d.** RhoGAM

Answer: B. Occasionally, anaphylaxis may be caused by an anti-immunoglobulin A (IgA) reaction to IgA found in the donor blood component. The patient is likely to have a congenital IgA deficiency. The presentation is similar to anaphylactic reactions from other causes. Washed red blood cells (RBCs) and plasma products from IgA-deficient individuals can be used to avoid recurrence with subsequent transfusions. As the patient is having an allergic reaction involving more than one organ system, this reaction should be treated as anaphylaxis with epinephrine; while the patient may also receive diphenhydramine, epinephrine is the critical life-saving treatment. Furosemide is indicated to treat transfusion-associated volume overload, which would not present with hives. RhoGAM is a purified anti-D antibody that can be given to Rh− individuals who have received Rh+ PRBC blood transfusions to prevent the patient from developing their own anti-D antibodies. Clinically this is most relevant for female patients to prevent hemolytic disease of the newborn in future pregnancies.

5. A 24-year-old female patient presents with cellulitis. A complete blood count demonstrates a hemoglobin level of 7.5 g/dL. On further questioning, it is discovered that her Ob/Gyn is treating her for menorrhagia, but she has no other comorbidities. She denies any lightheadedness, chest pain, dyspnea, or recent increase in bleeding. Her heart rate is 85 and her blood pressure is 136/84 mm Hg. Which of the following is the most appropriate next step in management of her anemia?
   - **a.** Discharge the patient to follow up with her outpatient provider.
   - **b.** Obtain a type and crossmatch and transfuse 1 unit of type specific packed red blood cells.
   - **c.** Order a STAT hematology consult.
   - **d.** Transfuse 1 unit of O− packed red blood cells.

Answer A. This patient is clinically stable, has a chronic source of blood loss, and her hemoglobin level is above the recommended treatment threshold of 7 g/dL, therefore it is safe to discharge her to follow up with her outpatient provider. Depending on the level of comfort, some physicians might offer a pelvic exam to characterize the degree of bleeding and/or obtain a second hemoglobin level after a brief period of observation. The patient does not warrant an emergent transfusion of either type specific or O− packed red blood cells. O− transfusions should be reserved for those patients with hemodynamic instability who are unlikely to tolerate the 60 to 90 minutes it takes to obtain a type and crossmatch. Similarly, while the patient may benefit from a hematology consult (in particular to be evaluated for von Willebrand disease) it is inappropriate to obtain this in the emergency department for a stable patient.

109

Anemia and Polycythemia

Meagan B. Verbillion and Alan A. Dupré

KEY CONCEPTS

- Anemia is caused by three basic mechanisms: loss of red blood cells (RBCs) through bleeding, destruction of RBCs, or decrease in production of RBCs.
- RBC indices along with a peripheral blood smear can help determine the mechanism of anemia.
- Anemia in the elderly often occurs as an exacerbation of pre-existing comorbid diseases.
- Anemia of uncertain etiology should be thoroughly evaluated. If the patient has no adverse hemodynamic consequences, the evaluation can proceed on an outpatient basis or management initiated in an observation setting until the patient is stable.
- Patients with sickle cell disease should be considered to have an acute pain crisis and treated appropriately until proven otherwise.
- Acute chest syndrome is one of the most common causes of death in sickle cell disease and presents with fever, dyspnea, cough, and a new infiltrate on chest radiograph.
- Transfusion therapy is most useful in sickle cell disease associated with acute stroke, acute chest syndrome, or splenic sequestration.
- Primary polycythemia vera is treated with serial phlebotomy to a goal hematocrit of less than 45%.

ANEMIA

Foundations

Background and Importance

Anemia affects a third of the global population and accounted for the primary hospital discharge diagnosis in approximately 188,000 emergency department (ED) visits in 2014 as reported by the Centers for Disease Control (CDC).[1] Anemia is an absolute decrease in the number of circulating red blood cells (RBCs). The diagnosis is made when laboratory measurements fall below accepted normal values (Table 109.1).

Anemia is divided into two broad categories: emergent, having immediate life-threatening complications, and typically secondary to acute blood loss; and non-emergent, with less imminent danger to the patient and many times can be further evaluated on an outpatient basis. Factors other than the absolute number of circulating RBCs may place the patient in one category or another (e.g., rate of onset and underlying hemodynamic reserve of the patient). Both groups necessitate a sound diagnostic approach, though emergent anemia may require immediate supportive therapy concomitant with or in advance of the definitive diagnosis. Although patients with non-emergent anemia are usually referred to a specialist, the urgency of consultation depends predominantly on the patient's hemodynamic tolerance of the anemia.

Anatomy, Physiology, and Pathophysiology

Understanding anemia starts with the structure and function of the RBC. RBCs are primarily composed of hemoglobin, which has a quaternary structure containing 4 heme polypeptide subunits bound to an iron molecule that is contained in the center of a porphyrin ring. The major function of the RBC is oxygen transport from the lung to the tissue, and carbon dioxide transport in the reverse direction. Oxygen transport is influenced by the amount of hemoglobin and its oxygen affinity, as well as blood flow. An alteration in any of these major components usually results in compensatory changes in the other two. For example, a decrease in hemoglobin is compensated for by both inotropic and chronotropic cardiac changes that result in increased blood flow and decreased hemoglobin affinity at the tissue level, thereby allowing more oxygen release. Due to disease severity or underlying pathologic conditions, these compensatory responses may fail, resulting in tissue hypoxia and cell death.

Anemia stimulates the compensatory mechanism of erythropoiesis controlled by the hormone erythropoietin, which is a glycoprotein produced in the kidney (90%) and liver (10%). It regulates the production of RBCs by controlling differentiation of committed erythroid stem cells and is stimulated by tissue hypoxia or products of RBC destruction during hemolysis. Elevated in many types of anemia, erythropoietin enhances the growth and differentiation of erythroid progenitors.

Bone marrow contains pluripotent stem cells that can differentiate into erythroid, myeloid, megakaryocytic, or lymphoid progenitors. When the late normoblast extrudes its nucleus, it still contains a ribosomal network, which identifies the reticulocyte. The reticulocyte retains its ribosomal network for approximately 4 days, 3 days of which are spent in bone marrow and 1 day in the peripheral circulation. The RBC matures as the reticulocyte loses its ribosomal network and becomes an erythrocyte which circulates for 110 to 120 days in the peripheral circulation. Erythrocytes are anucleate, flexible, biconcave discs. The erythrocyte is scavenged and removed by macrophages that detect senescent signals. Under steady-state conditions, RBC mass remains constant as an equal number of reticulocytes replace the destroyed, senescent erythrocytes.[2]

The most common cause of emergent anemia is acute blood loss. Common sites of blood loss in the trauma patient include pleural, peritoneal, pelvic, long bone (e.g., thigh), and retroperitoneal spaces. In non-traumatic circumstances, especially in patients receiving anticoagulants, the gastrointestinal tract, retroperitoneal space, uterus, or adnexa need to be considered. Certain hemolytic conditions, such as disseminated intravascular coagulopathy (DIC), can also cause rapid intravascular destruction of RBCs leading to emergent anemia (Box 109.1).

Non-emergent anemias can be subdivided into microcytic, normocytic, and macrocytic based on the mean corpuscular volume (MCV), which measures size and volume of the RBC. Microcytic anemias are caused by low iron production, gene mutations, toxins (e.g., lead poisoning), or defective heme synthesis. Normocytic anemias can be caused by primary or secondary bone marrow failure and can

TABLE 109.1 Hemogram Normal Values

Age	Hemoglobin (g/dL)	Hematocrit (%)	Red Blood Cell Count ($\times 10^6$)
3 Months	10.4–12.2	30–36	3.4–4.0
3–7 years	11.7–13.5	34–40	4.4–5.0
Adult man	14.0–18.0	40–52	4.4–5.9
Adult woman	12.0–16.0	35–47	3.8–5.2

BOX 109.1 Causes of Rapid Intravascular Red Blood Cell Destruction

Mechanical hemolysis associated with disseminated intravascular coagulation
Massive burns
Toxins (e.g., some poisonous venoms: brown recluse spider, cobra)
Infections such as malaria or *Clostridium* sepsis
Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency with exposure to oxidant stress
ABO incompatibility transfusion reaction
Cold agglutinin hemolysis (e.g., *Mycoplasma* organisms, infectious mononucleosis)
Paroxysmal nocturnal hemoglobinuria exacerbated by transfusion
Immune complex hemolysis (e.g., quinidine)

be further subdivided into hemolytic and non-hemolytic. Anemia of chronic disease is the most common non-hemolytic anemia, caused by an inflammatory response to underlying disease states. Hemolytic anemias are either intrinsic or extrinsic in nature. Intrinsic hemolytic anemias are typically caused by underlying genetic mutations or enzyme deficiencies (e.g., sickle cell disease) that lead to abnormal RBC production. Extrinsic hemolytic anemias result from defects outside of the RBC (e.g., DIC). Macrocytic anemias are caused primarily by nutritional deficiencies such as folate or vitamin B_{12}, as well as various disease states (e.g., alcoholism) that retard the maturation of the RBC.

Clinical Features

The clinical manifestation of anemia depends on how rapidly the hematocrit falls and on the patient's ability to compensate for the loss. Clinical signs and symptoms of acute blood loss include tachycardia, hypotension, orthostasis, lightheadedness, dyspnea, pallor, or tachypnea. Complaints of thirst, altered mental status, or decreased urine output may also be present. The patient's age, concomitant illness, and underlying comorbidities can tremendously influence the presenting clinical findings. Children and young adults may tolerate significant blood loss with largely unaltered vital signs, preceding a precipitant hypotensive episode. Elderly patients commonly have underlying disease states that compromise their ability to compensate for blood loss, which can lead to the earlier vital sign alterations and a higher potential for rapid clinical deterioration.[3] Pertinent elements of the history and physical examination of patients with acute anemia are listed in Box 109.2.

In contrast, nonemergent anemias are usually seen in ambulatory patients complaining of fatigue and weakness, irritability, headache, postural dizziness, angina, decreased exercise tolerance, shortness of breath, or decreased libido. The history and physical examination is typically paramount in helping to identify the cause of anemia (Box 109.3). The rate of loss of hemoglobin also dictates symptom onset. When anemia is slow in onset, the patient may compensate well until the hemoglobin is very low, at which point symptoms worsen or vital sign changes occur. Most of these patients do not need immediate stabilization and can be further evaluated in the outpatient setting.

BOX 109.2 History and Physical Examination for Clinically Severe Anemia

History
General
Out-of-hospital status, therapy, response to therapy
Bleeding diathesis
Previous blood transfusion
Underlying diseases, including allergies
Current medications, especially those causing platelet inhibition
Trauma: Nature and Time of Injury, Blood Loss at Scene
Nontrauma
Skin: Petechiae, ecchymoses
Gastrointestinal: Hematemesis, hematochezia, melena, peptic ulcer
Genitourinary: Last menstruation, menorrhagia, metrorrhagia, hematuria

Physical Examination
Vital Signs Measured Serially
Blood pressure, pulse, respiratory rate, oxygen saturation
Level and content of consciousness
Skin: pallor, diaphoresis, jaundice, cyanosis, purpura, ecchymoses, petechiae
Cardiovascular: Murmurs, S_3, S_4, quality of femoral and carotid pulses
Abdomen: Hepatosplenomegaly, pain, guarding, rebound on palpation, stool hemoglobin testing

BOX 109.3 History and Physical Examination for Nonemergent Anemia

History
Symptoms of Anemia
Chest pain, decreased exercise tolerance, dyspnea
Weakness, fatigue, dizziness, syncope

Bleeding Diathesis
Bleeding after trauma, injections, tooth extractions
Spontaneous bleeding, such as epistaxis, menorrhagia
Spontaneous purpura and petechiae

Sites of Blood Loss
Respiratory: Epistaxis, hemoptysis
Gastrointestinal: Hematemesis, hematochezia, melena
Genitourinary: Abnormal menses, pregnancies, hematuria
Skin: Petechiae, ecchymoses
Intermittent jaundice, dark urine
Dietary history: Vegetarianism, poor nutrition
Drug use and toxin exposure, including alcohol
Racial background, family history
Underlying disease
- Uremia, liver disease, hypothyroidism
- Chronic disease states, such as cancer, rheumatic or renal disease
- Previous surgery

Physical Examination
Skin: Pallor, Purpura, petechiae, angiomas, ulcerations
Eye: Conjunctival jaundice, pallor
Oral: tongue atrophy, papillary soreness
Cardiopulmonary: Heart size, murmurs, extra cardiac sounds, rales indicating pulmonary edema
Abdomen: Hepatomegaly, splenomegaly, ascites, masses
Lymph nodes
Neurologic: Altered positions or vibratory sense, ataxia, peripheral neuritis
Rectal and pelvic: masses

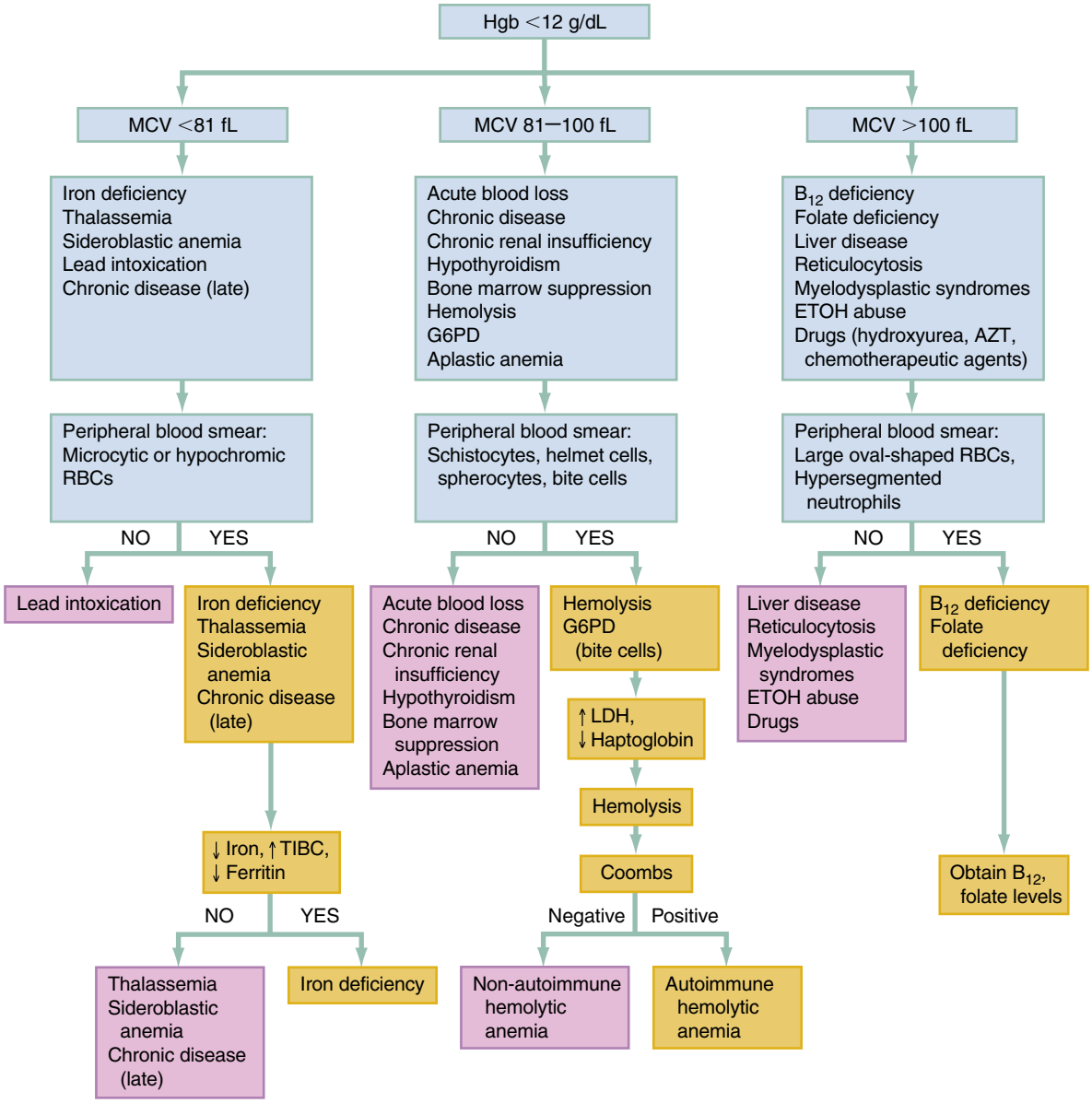

Fig. 109.1 Algorithm for the Evaluation of Anemia. *AZT,* Azathioprine; *ETOH,* ethanol; *fL,* femtoliter; *G6PD,* glucose-6-phosphate dehydrogenase; *Hgb,* hemoglobin; *LDH,* lactate dehydrogenase; *MCV,* mean corpuscular volume; *RBCs,* red blood cells; *TIBC,* total iron-binding capacity.

Differential Diagnoses

The differential diagnosis of anemia is facilitated by classification of the anemia into one of three groups: decreased RBC production, increased RBC destruction, and blood loss. A complementary approach uses RBC morphology and indices. Fig. 109.1 presents an algorithm for the evaluation of anemia.

Diagnostic Testing

In a patient suspected of acute blood loss, the following initial laboratory tests may be helpful, depending on clinical circumstances:

- Complete blood count and peripheral smear
- Blood sample for type and crossmatch
- Prothrombin time and international normalized ratio
- Partial thromboplastin time
- Serum electrolyte levels
- Glucose level (particularly if the patient has altered consciousness)
- Creatinine level
- Urinalysis for free hemoglobin

Obtaining a hemoglobin and hematocrit in the emergency department (ED) is useful for determining a baseline even though it may not be reflective of the true degree of blood loss for many hours. Depending on severity, a blood sample should be sent for type and crossmatch.

The initial laboratory evaluation for a patient with non-emergent anemia also includes a complete blood count with leukocyte differential, reticulocyte count, peripheral smear (Fig. 109.2), as well as RBC indices, including MCV, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). RBC indices are useful in classifying anemias caused by a production deficit (Table 109.2). MCV is a measure of RBC size and volume; decreases or increases reflect microcytosis and macrocytosis, respectively. MCH incorporates both RBC size and hemoglobin concentration. It is influenced by both and is rarely helpful in the ED setting. The MCHC index

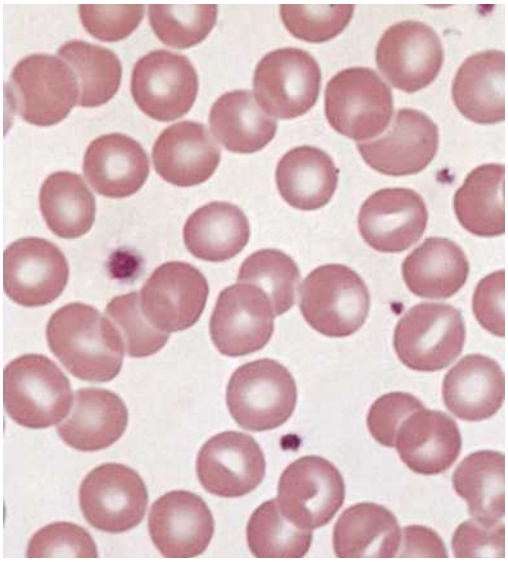

Fig. 109.2 Normal Smear. (From Hoffbrand AV, Pettite JE. *Color Atlas of Clinical Hematology*. 3rd ed. London: Mosby; 2000:22.)

TABLE 109.2 Calculation of Red Blood Cell Indices and Normal Values

Index	Formula for Calculation	Normal
Mean corpuscular volume	Hematocrit (%) divided by RBC count (10^6/μL)	81–100 fL
Mean corpuscular hemoglobin	Hemoglobin (g/dL) divided by RBC count (10^6/μL)	26–34 pg
Mean corpuscular hemoglobin concentration	Hemoglobin (g/dL) divided by hematocrit (%)	31%–36%

fL, Femtoliter; *RBC,* red blood cell; *pg,* picograms.

is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted in patients with decreased cell membrane relative to cell volume, such as in the case of spherocytosis. An additional index is the RBC distribution width (RDW), a measure of RBC homogenicity. RDW is automatically calculated as the standard deviation of MCV divided by MCV multiplied by 100. A normal RDW is 13.5 ± 1.5%. The RDW is elevated in anemias caused by nutritional deficiencies; however, it is not specific for any abnormality.

Measurements of coagulation status, serum electrolytes, glucose, blood urea nitrogen, and creatinine are useful in the diagnosis of underlying disease processes that may relate to the patient's anemia. When the cause of anemia is unknown and the patient requires transfusion, consider ordering folate, vitamin B_{12}, iron, total iron-binding capacity (TIBC), reticulocytes, and direct antiglobulin (Coombs test) pretreatment. Post-transfusion, these levels will be unreliable and could mask an underlying diagnosis.

Management

Stabilization of emergent anemia commonly runs in parallel with assessment. If the signs and symptoms suggest potential life-threatening conditions, multiple large bore intravenous lines are placed in preparation for resuscitation and transfusion.

Disposition

Criteria for the admission of patients with non-emergent anemia are shown in Box 109.4.

BOX 109.4 General Admission Criteria for Nonemergent Anemia

- Cardiac symptoms, such as dyspnea or chest pain, or neurologic symptoms, such as syncope.
- Initial unexplained hemoglobin value <8–10 g/dL or hematocrit <25%–30% in selected patients
- Difficulty in obtaining outpatient care for patients whose hemoglobin levels are significantly low or when comorbidity is present

BOX 109.5 Differential Diagnosis of Anemias Caused by Decreased Red Blood Cell Production Subclassification by Red Blood Cell Indices

Hypochromic Microcytic Anemias (Decreased MCV and Hemoglobin Concentration)
- Iron deficiency
- Thalassemia
- Sideroblastic anemia or lead poisoning
- Chronic disease (e.g., cancer, renal disease); can also be normochromic and normocytic

Macrocytic (Elevated MCV)
- Vitamin B_{12} deficiency
- Folate deficiency
- Liver disease
- Hypothyroidism

Normocytic (Normal MCV and Hemoglobin Concentration)
- Primary bone marrow involvement: Aplastic anemia, myeloid metaplasia with myelofibrosis, myelophthisic anemia
- Resulting from underlying disease: Hypoendocrine state (thyroid, adrenal, pituitary), uremia, chronic inflammation, liver disease

MCV, Mean corpuscular volume.

ANEMIAS DUE TO DECREASED RED BLOOD CELL PRODUCTION

Foundations

Anemias caused by decreased RBC production are insidious in onset and are associated with a decreased reticulocyte count. A subclassification by indices of anemias caused by decreased RBC production is listed in Box 109.5. RBC indices and a peripheral smear are useful in securing the diagnosis, although a definitive diagnosis may require more extensive outpatient work up including a bone marrow examination. Replacement of iron, vitamin B_{12}, or folate by the emergency clinician without proof of cause is generally unnecessary and not routinely recommended.

Hypochromic microcytic anemias are subdivided into deficiencies of the three building blocks of hemoglobin: iron (iron deficiency anemia; Fig. 109.3), globin (thalassemia), and porphyrin (sideroblastic anemia and lead poisoning). Anemia of chronic disease, a secondary iron abnormality, is also included on the differential and can be microcytic or normocytic.[2]

Iron Deficiency Anemia

Foundations

Iron deficiency is a frequent cause of chronic anemia seen in the ED. It is the most common cause of anemia globally.[4] It is defined by microcytic,

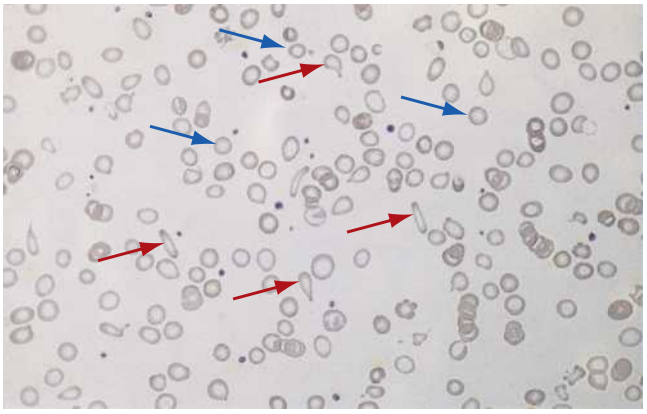

Fig. 109.3 Iron Deficiency Anemia With Hypochromic, Microcytic Cells and Poikilocytes (Abnormally Shaped Cells). (From Hoffbrand AV, Pettite JE. *Color Atlas of Clinical Hematology*. 3rd ed. London: Mosby; 2000:44.)

hypochromic RBC. Iron deficiency can either be absolute or functional. Absolute iron deficiency reflects low or exhausted total body iron stores, while functional iron deficiency is caused by inadequate iron supply to the bone marrow.[5] Iron is a critical component needed for effective erythropoiesis, and also essential for mitochondrial function, DNA synthesis, and cellular enzymatic reactions. Dietary iron is absorbed in the duodenum, thus nutritional deficiency or malabsorption syndromes can be a cause of iron deficiency anemia.[2] Occult blood loss should always be excluded in the setting of iron deficiency anemia. This is common in older patients, especially with gastrointestinal blood loss, as well as in menstruating women. Changes in RBC size, number, and hemoglobin content occur only after bone marrow and cytochrome iron stores are depleted; therefore, a patient may have early symptoms of iron deficiency (e.g., fatigue) without anemia. These non-hematologic symptoms are the result of impaired muscle-tissue oxidative capacity and decreased activity of iron-containing enzymes in the setting of iron deficiency.

Clinical Features

Most anemias secondary to iron deficiency are non-emergent in nature. The symptoms related to anemia are secondary to the body's ability to adapt to the low hemoglobin levels over time, and the eventual inability of the tissues to receive adequate oxygen for metabolic demands.

Diagnostic Testing

The diagnosis is made by laboratory evaluation of the fasting level of serum iron, serum ferritin, and TIBC. The laboratory interpretation and pitfalls are outlined in Table 109.3. A concentrated search for occult blood loss remains an important component of the evaluation.

Management

Therapy consists of oral iron replacement. A cost-effective form is ferrous sulfate. The dosage is 325 mg PO for adults (65 mg of elemental iron) three times daily, or 2 mg/kg/day of elemental iron orally for children.[5] This medication is generally well tolerated, although it may cause nausea, vomiting, or constipation. Ascorbic acid can improve the bioavailability of iron and is recommended in conjunction with iron replacement, although it can increase the frequency of side effects. Patients should be warned that iron frequently leads to black stools, and that bleeding from the digestive tract can also be manifested as black stool. In patients with poor oral tolerance or absorption, parenteral iron therapy may be necessary. Parenteral iron replenishes iron stores more effectively than oral replacement in CKD, inflammatory bowel disease, and in the post-partum period.[5,6]

The patient may experience a sense of improvement in as few as 24 hours after initiating replacement therapy. Reticulocytosis appears during a 3- to 4-day period in children, but may take more than 1 week in adults, with complete repletion of iron stores in approximately 3 to 6 months.[4] The hemoglobin concentration rises on a similar schedule. Failures of iron replacement therapy can occur due to a variety of causes, including patient noncompliance with iron supplementation, insufficient replacement, incorrect diagnosis, or presence of an additional process complicating the iron deficiency, such as anemia of chronic disease.

Thalassemia

Foundations

The hemoglobin molecule is present as two-paired globin chains. Each type of hemoglobin is made up of different globins. Normal adult hemoglobin (HbA) is made up of two alpha chains and two beta chains ($\alpha_2\beta_2$). HbA_2 is a variant of hemoglobin A that contains two alpha and two delta chains ($\alpha_2\delta_2$). Fetal hemoglobin (HbF) contains two alpha and two gamma chains ($\alpha_2\gamma_2$). A separate autosomal gene controls each globin chain.

Pathophysiology

Thalassemia is a genetic autosomal recessive disorder reflected by the decreased synthesis of and abnormal structure of globin chains. Deletions in these globin genes result in an absence or decreased function of the messenger RNA that codes for particular globins. The various globins (α, β, δ, and γ) may be affected by a number of genetic combinations. Decreased globin production in thalassemia precipitates the formation of reactive oxygen species leading to apoptosis of erythroblasts, decreased hemoglobin synthesis, and ineffective erythropoiesis, leading to hemolytic anemia.[7] Beta thalassemia is associated with reduced or absent beta-globin synthesis and an excess of alpha-globins, leading to the formation of alpha-globin tetramers. Alpha thalassemia results in an excess of β-globins and the formation of β-globin tetramers termed *hemoglobin H*. The abnormal formation of hemoglobin at various concentrations results in complications, including red cell membrane breakage and hemolysis. A common method of classification is by phenotype. Beta thalassemias are broken down into silent (carrier), minor, intermedia, and major variants. Alpha thalassemias include silent (carrier), alpha thalassemia trait, HbH, and Hb Barts. This historical classification method is now being replaced by a simpler system: transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT), with patients often shifting clinically between the two categories depending on their transfusion needs. NTDT includes thalassemia minor, mild HbE, HbH disease, and alpha-thalassemia trait. Despite its name, NTDT treatments can range from no transfusion requirement to intermittent transfusions required. Transfusion is also offered to some NTDT patients to prevent or manage disease complications. TDT includes thalassemia major, severe HbE/Beta-thalassemia, and Hb Barts hydrops. Hb Barts is almost always fatal at birth. TDT, as reflected in its name, typically requires regular, lifelong transfusions for survival, usually starting before the age of 2 years.[7]

CLINICAL FEATURES

Homozygous β-chain thalassemia (thalassemia major or Cooley anemia) occurs predominantly in Mediterranean populations. It is one of the most common single-gene disorders, resulting in no functional beta chains. The disease is characterized by severe anemia, hepatosplenomegaly, jaundice, abnormal development, and premature death. Symptoms are typically evident by the age of 2 years. Patients are transfusion dependent and die as a result of iron deposition in tissues, particularly in the myocardium, or infection.

TABLE 109.3 Diagnostic Tests for Iron Deficiency Anemia

Test	Normal	Iron Deficiency	Interpretation
Fasting serum iron	60–180 μg/dL	<60 μg/dL	Diurnal variation (draw in morning); increased by hepatitis, hemochromatosis, hemolytic anemia, or aplastic anemia; decreased in infection
Total iron-binding capacity	250–400 μg/dL	>400 μg/dL	Increased in late pregnancy or hepatitis; decreased in infection
Percentage of saturation (serum iron) of total iron-binding capacity	15%–45%	<15%	
Serum ferritin	10–10,000 mg/mL	<10 mg/mL	Reflects iron stores; may increase as an acute-phase reactant in infection
Bone marrow stainable iron	Hemosiderin granules in reticuloendothelial cells	Absent	Standard for assessment of iron stores

Heterozygous β-chain thalassemia (thalassemia minor or intermedia) results in some functional beta chains and is manifested as a mild to moderate anemia. Thalassemia minor patients are typically asymptomatic and rarely, if ever, require transfusion. Thalassemia intermedia patients usually have a moderate anemia and require occasional transfusions. Heterozygous beta thalassemia is most prevalent in Asia, the Middle East, and Mediterranean countries. This widespread distribution is attributed to a natural selection toward heterozygote carriers, as this offers protection against falciparum malaria.[7] This same protection is also offered in sickle cell trait carriers.

Alpha-thalassemia varies in spectrum from an asymptomatic carrier state to prenatal death. Four gene loci are responsible, and disease severity increases as the number of gene deletions increase. The tolerated forms are more commonly seen in Asians and African Americans. One missing gene results in a silent carrier state while two missing genes, commonly referred to as alpha thalassemia trait, results in a minor anemia. Three missing genes, also called hemoglobin H disease, can lead to a mild to moderate anemia, but most affected lead normal lives. Four defective genes result in Hb Barts, which causes hydrops fetalis and fetal death.[8]

Diagnostic Testing

Thalassemia is a microcytic, hypochromic anemia. Hypochromia, target cells, and basophilic stippling are noted on the peripheral smear. The MCV is commonly lower than seen with iron deficiency, and serum iron levels are typically normal. The diagnosis is made with hemoglobin electrophoresis and genetic testing. Screening for carriers is performed by measurement of RBC indices and estimation of the HbA_2 concentration. Prenatal diagnosis can be made by analysis of fetal blood or by fetal DNA obtained by chorionic villus sampling.[7]

Management

Usually, no treatment is necessary for silent carriers, beta thalassemia minor, and alpha thalassemia trait. Therapy for the remaining types of thalassemia consists of blood transfusions, where the goals of transfusion therapy include correction of anemia, suppression of ineffective erythropoiesis, and inhibition of increased gastrointestinal iron absorption. TDT requires transfusions every 2 to 5 weeks to maintain a pre-transfusion hemoglobin between 9 and 10.5g/dL. Transfusion is usually started when patients are young to ensure normal growth and physical activity capacity. Recurrent transfusion does increase risk of blood-borne infection, alloimmunization, and iron overload, the latter of which may lead to multi-organ dysfunction and is a common cause of death. Guidelines for transfusion are not well established in patients with NTDT, but transfusion should be considered during times of significant stress such as pregnancy, surgery, or infection, or when hemoglobin levels are low. More frequent transfusion may be used in children with NTDT if they develop signs of growth failure or reduced exercise tolerance.

Transfusion therapy improves long-term survival in patients with TDT when combined with iron chelation therapy. Iron chelation therapy can also reduce systemic and hepatic iron burden in NTDT, but it is not effective in all patients. Deferoxamine can be administered parenterally or subcutaneously. It was the first commercially available chelator. Its demanding treatment regimen, however, often leads to poor adherence. Dosages are weight based, with treatments required for 8 to 12 hours, 5 to 7 nights per week.[7] Two oral chelators are available, deferiprone and deferasirox. Deferiprone is administered two or three times daily, and deferasirox is a once-daily medication.[9,10]

Hydroxyurea, a cytotoxic anti-metabolite that induces fetal hemoglobin, is also used in some cases of NTDT. Hydroxyurea is hypothesized to improve chronic anemia and reduce the need for transfusion by reducing alpha and beta chain imbalance through the production of fetal hemoglobin. It is well tolerated by patients and has no major long-term adverse effects. Commonly reported side effects included mild transaminitis, nausea or vomiting, and transient bone marrow suppression. It is associated with a decrease in the need for recurrent transfusions. In patients with mild NTDT, it can raise baseline Hb by at least 1 g/dL and in some patients with severe NTDT (>3 transfusions per year) it can lead to a complete cessation of transfusion requirement.[11]

Splenectomy is considered in some patients and can improve hemoglobin concentration, decreasing the need for recurrent transfusions. Hematopoietic stem cell transplantation (HSCT) is another therapy in use and is potentially curative in patients with TDT with disease-free survival rates greater than 80% at 2 years. It is, however, only appropriate for a subset of patients due to age restrictions and the need for sibling donor compatibility. HSCT carries with it a 5% to 10% risk of mortality, as well as potential permanent fertility impairment.[7]

Gene therapy and gene editing are becoming more promising as possible future treatment modalities for thalassemia; data from clinical trials is in progress.

Sideroblastic Anemia

Foundations

Sideroblastic anemia involves a defect in porphyrin synthesis and can be congenital, idiopathic, or acquired. The resultant impaired hemoglobin production causes excess iron to be deposited in the mitochondria of the RBC precursor as well as increased serum iron, ferritin, and transferrin saturation levels. The defective heme synthesis results in ineffective erythropoiesis, mild to moderate anemia, and a dimorphic peripheral smear with hypochromic microcytes along with normal and macrocytic cells, as well as characteristic ringed sideroblasts.[12] A

ringed sideroblast is an erythroid precursor with a minimum of five siderotic granules covering the nucleus after Prussian blue staining.[13]

Clinical Features

Congenital sideroblastic anemia is a relatively rare disease resulting from iron metabolism related gene mutations.[14] The most common congenital cause is X-linked sideroblastic anemia (XLSA) which occurs secondary to missense substitutions in 5′-Aminolevulinste Synthase 2 (ALAS2) genes.[13] Idiopathic sideroblastic anemia is a common type of refractory anemia in elderly patients. Pallor and splenomegaly may be noted, and iron staining of the peripheral smear may demonstrate iron-containing inclusion bodies in RBCs. Idiopathic sideroblastic anemia is considered a pre-leukemic state, with acute myelogenous leukemia developing in approximately 5% of patients.

Differential Diagnoses

Acquired causes of sideroblastic anemia include drugs, alcoholism, copper deficiency, lead poisoning, zinc toxicity, myelodysplastic syndrome, or myeloproliferative disorders. Chloramphenicol, isoniazid, linezolid, and penicillamine are known causes of drug-induced sideroblastic anemia.[13] Lead poisoning, one reversible cause of sideroblastic anemia, may be suggested by basophilic stippling on the peripheral smear and the presence of metaphyseal lead lines on imaging. Elevated blood lead levels are diagnostic. Alcohol abuse may also result in disordered heme synthesis, which can be corrected by alcohol cessation or by parenteral pyridoxal phosphate (active form of vitamin B6) in cases of continued abuse. Oral pyridoxine (vitamin B6) may be ineffective because of impaired conversion to the active form in alcoholic patients.

Management

Management varies based on underlying cause. Most congenital or acquired sideroblastic anemia is treated with pyridoxine (vitamin B_6) and responds to treatment with 100 mg PO three times a day. Although a trial of treatment with pyridoxine is advised, most patients remain anemic and will require transfusion. If long-term transfusion therapy is necessary, iron overload will need to be managed and usually responds well to chelation therapy. Stem cell transplantation can be curative in some patients with congenital or myelodysplastic sideroblastic anemias.[13,14]

Anemia of Chronic Disease

Foundations. Anemia of chronic disease (ACD) is secondary to reduced erythropoiesis and reduced RBC survival time in the peripheral circulation in chronic inflammatory states, which result in decreased iron release from macrophages secondary to increased cytokines and hepcidin. It is a multifactorial, acquired disorder of iron homeostasis. Common causes include malignancy, arthritis, renal insufficiency, chronic heart failure, chronic obstructive lung disease, or chronic infections (e.g., tuberculosis or osteomyelitis).[2] ACD is commonly found in older adults and is associated with increased morbidity and mortality, largely due to the effects of anemia on comorbid disease processes and the underlying etiology of the ACD.[3]

Clinical Features

Symptoms are usually those related to the underlying disease and not from the anemia itself.

Diagnostic Testing

Anemia of chronic disease is common and typically normochromic, normocytic, though can be microcytic. It is characterized by low serum iron levels, low TIBC, and normal or elevated ferritin levels.[3] Bone marrow is typically normal, but staining reveals an abnormality in the mobilization of iron from reticuloendothelial cells. This anemia can be differentiated from iron deficiency by TIBC, ferritin, bone marrow examination, and non-responsiveness to a trial of iron therapy. A complete search for occult blood loss is prudent during evaluation. It should be recognized that true iron deficiency may also be superimposed on anemia of chronic disease.

TABLE 109.4 Clinicopathologic Correlation of Manifestations of Megaloblastic Anemia

Clinical Features	Pathologic Condition
Lemon yellow skin	Combination of pallor with low-grade icterus from ineffective erythropoiesis
Petechiae, mucosal bleeding	Thrombocytopenia
Infection	Leukopenia
Fatigue, dyspnea, orthostasis	Anemia
Sore mouth or tongue	Megaloblastosis of mucosal surfaces
Diarrhea and weight loss	Malabsorption from mucosal surface change
Paresthesias and ataxia	Related to myelin abnormality in vitamin B_{12} deficiency only

Management

Acute or emergent therapy is not usually required, as the hemoglobin and hematocrit is typically modest. Treatment should be directed at the underlying cause.

Macrocytic and Megaloblastic Anemias

Foundations

Macrocytic anemia is the hematologic manifestation of a total-body alteration in DNA synthesis caused primarily by vitamin B_{12} or folic acid deficiency, which appears clinically in tissues with rapid cell turnover, including hematopoietic cells or those of mucosal surfaces, particularly in the gastrointestinal tract. This deficiency is characterized by ineffective erythropoiesis and pancytopenia. Vitamin B_{12} and folate deficiencies have different developmental histories, but the clinical result is similar. Differentiation of folate and vitamin B_{12} deficiencies usually depends on laboratory measurements.

Clinical Features

Macrocytic anemias can be divided into megaloblastic and nonmegaloblastic categories. Megaloblastic macrocytic anemia is the most common cause of macrocytic anemia and pancytopenia. Table 109.4 lists a number of the problems associated with megaloblastic anemia and their underlying pathologic states. Nonmegaloblastic macrocytic anemia is caused by disease states such as alcoholism, liver dysfunction, hypothyroidism, myelodysplastic syndromes, and certain drugs (e.g., hydroxyurea, methotrexate, zidovudine, valproic acid).[15] Like other causes of anemia, easy fatigability is the most common symptom reported in patients with macrocytic anemia. Additional symptoms include anorexia, dyspnea on exertion, palpitations, oral ulcers, or weight loss.[16] A unique feature of vitamin B_{12} deficiency is its neurologic involvement. Patients may have paresthesias of their hands or feet, decreased proprioception, or decreased vibratory sense; weakness and spasticity of the lower extremities with altered reflexes; and variable mental changes, such as depression, paranoid ideation, irritability, or forgetfulness. The neurologic manifestations of folic acid deficiency overlap with those of vitamin B_{12} deficiency, but the neuropsychiatric manifestations (e.g., depression and forgetfulness) predominate in folic acid deficiency. A devastating consequence of vitamin B_{12} deficiency

BOX 109.6 Causes of Folate Deficiency

- Inadequate dietary intake
  - Poor diet or overcooked or processed food diet
  - Alcoholism
- Inadequate uptake
  - Malabsorption with sprue and other chronic upper intestinal tract disorders, drugs such as phenytoin and barbiturates, or blind loop syndrome
- Inadequate use
  - Metabolic block caused by drugs, such as methotrexate or trimethoprim
  - Enzymatic deficiency, congenital or acquired
- Increased requirement
  - Pregnancy
  - Increased red blood cell (RBC) turnover: Ineffective erythropoiesis, hemolytic anemia, chronic blood loss
  - Malignant disease: Lymphoproliferative disorders
- Increased excretion or destruction or dialysis

BOX 109.7 Causes of Vitamin B_{12} Deficiency

- Inadequate dietary intake
  - Total vegetarianism: No eggs, milk, or cheese
  - Chronic alcoholism (rare)
- Inadequate absorption
  - Absent, inadequate, or abnormal intrinsic factor, as seen in patients with pernicious anemia and gastrectomy; in pernicious, autoimmune antibodies act against gastric parietal cells and intrinsic factor
  - Abnormal ileum, as can occur in sprue and inflammatory bowel disease
- Inadequate use
  - Enzyme deficiency
  - Abnormal vitamin B_{12}–binding protein
- Increased requirement by increased body metabolism
- Increased excretion or destruction

is the development of subacute combined degeneration of the spinal cord resulting from loss of myelin in the dorsal and lateral columns. The syndrome has a gradual and uniform onset of progressive weakness, spastic paresis, ataxia, and loss of proprioception. Vitamin B_{12} deficiency can also cause elevated homocysteine levels which can lead to thrombosis.[15,16]

Differential Diagnoses

Folic acid, absorbed in the upper jejunum, is commonly found in green vegetables, cereals, and fruit. It may be destroyed completely by cooking. The recommended daily intake is approximately 240 µg/day in adults and 400 µg/day if pregnant or lactating. The body stores 6 to 20 mg.[15] Therefore, a 2- to 4-month body store is available for consumption before megaloblastic changes occur. Causes of folate deficiency are listed in Box 109.6. Most patients with folate deficiency have either an inadequate dietary intake, such as alcoholic patients, or increased use, as in pregnancy.

Vitamin B_{12} is found in foods of animal origin and is absorbed in the terminal ileum after binding to intrinsic factor, which is a glycoprotein secreted by gastric parietal cells. Once absorbed, B_{12} acts as a coenzyme to produce methionine from homocysteine which assists in folic acid conversion to its active form. Therefore, a deficiency in B_{12} can also contribute to folic acid deficiency. The adult requirement of vitamin B_{12} is 1 or 3 µg/day, with a body store of 5 mg. Therefore, megaloblastic changes and clinical problems may take 5 to 10 years to develop after cessation of vitamin B_{12} uptake. The various causes of vitamin B_{12} deficiency are listed in Box 109.7. The most common cause is chronic malabsorption resulting from pernicious anemia.[15]

Megaloblastic anemia that is not responsive to folate or vitamin B_{12} is commonly related to antimetabolites used in chemotherapy or rare inherited disorders of DNA synthesis.

Liver disease, often associated with alcoholism, is the most common cause of non-megaloblastic macrocytic anemia. However, alcoholism can also cause concomitant megaloblastic anemia secondary to poor dietary intake. Thyroid hormone stimulates erythropoietin; thus hypothyroidism is commonly associated with nonmegaloblastic macrocytic anemia as well as normocytic anemia. Drugs can also cause macrocytosis and anemia. Commonly implicated agents include antiretrovirals, phenytoin, chemotherapeutic agents, valproic acid, or azathioprine. Macrocytic target cells may be seen on the peripheral smear in conjunction with this disorder.[15]

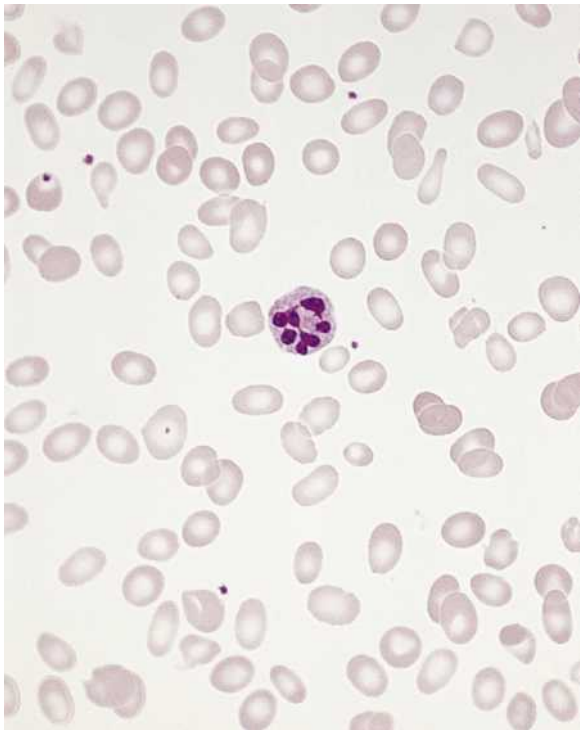

Fig. 109.4 Megaloblastic Anemia With Macrocytic Red Cells and Hypersegmented Polymorphonuclear Neutrophils. (From Hoffbrand AV, Pettite JE. *Color Atlas of Clinical Hematology*. 3rd ed. London: Mosby; 2000:61.)

Diagnostic Testing

Macrocytic anemia is suggested when the MCV is greater than 100 fL, but other criteria need to be met for megaloblastosis to be considered the cause of the macrocytic anemia. On the peripheral smear, large oval red cells (macro-ovalocytes), anisocytosis, hypersegmented polymorphonuclear neutrophils, as well as an elevated serum LDH level are diagnostic (Fig. 109.4). A bone marrow aspirate may reveal morphologic changes consistent with megaloblastic erythropoiesis. Other useful laboratory tests include vitamin B_{12}, folate level, and homocysteine levels. Laboratory techniques, values, and interpretations are listed in Table 109.5.

Management

As one form of deficiency may cause gastrointestinal absorption changes that beget other deficiencies, the clinician may need to initiate

TABLE 109.5 Serum Tests for Diagnosis and Differentiation of Megaloblastic Anemia

Test	Technique	Value	Interpretation
Vitamin B_{12}	Microbiologic or radioisotope	Normal: 300–900 μg/L Deficient: <200 μg/L	Vitamin B_{12} level is usually normal in folate deficiency.
Folate	Microbiologic or radioisotope	Deficient: <3 μg/L	Vitamin B_{12} deficiency may elevate folate levels by blocking transfer of serum folate to RBCs; hemolysis may elevate folate levels.
Lactate dehydrogenase	Spectrophotometric	Normal: 95–200 IU Megaloblastic anemia: 4–50 times normal	Normal in other macrocytic anemias; elevated two to four times normal in hemolytic anemias

RBC, Red blood cell.

therapy before the final diagnosis is made. However, it is important to obtain baseline laboratory specimens.

The usual dosage for patients with megaloblastic anemia secondary to folate deficiency is 1 mg of oral folic acid per day, and it is recommended to follow RBC folate levels to determine effectiveness as well as improvement in clinical symptoms. Parenteral administration is generally unnecessary as most cases are due to dietary deficiency.[15] In contrast, malabsorption is the most common cause of vitamin B_{12} deficiency, and parenteral therapy is initiated at 1000 mcg IM daily for 7 to 10 days, then monthly 1000 mcg IM injections. Weekly 1000 mcg IM doses for 4 weeks in between daily and monthly injections may be considered. If neurologic symptoms are present, therapy is initiated at 1 mg IM every other day for up to three weeks, followed by 1 mg IM weekly for up to twelve weeks. Thereafter, monthly 1 mg IM doses are necessary as needed to maintain B_{12} levels if the underlying cause of deficiency is not treatable. The response is often dramatic with levels of RBC, WBC, and platelets returning to normal within 4 weeks. During hematopoietic recovery, an iron deficiency may develop and should be treated in the usual manner.[15] We do not recommend vitamin B_{12} or folate supplements in patients with undiagnosed anemia. Unfortunately, the routine injection of vitamin B_{12} in the elderly is still a common practice.

Normochromic and Normocytic Anemias

Foundations

A hematologic parameter that can aid in the diagnosis of normocytic anemia associated with hypoproduction is the reticulocyte count, which reflects new RBC bone marrow production. Reticulocytes are released from bone marrow every 1 to 3 days and contain residual RNA that can be detected by supravital staining. With an average MCV of 160 fL, sufficient numbers of reticulocytes can increase the overall MCV of the total erythrocyte count. The reticulocyte count is expressed as a percentage of the total RBC population and needs to be related ("corrected") to the RBC count of the patient. The corrected reticulocyte count is equal to the measured percentage of reticulocytes multiplied by the patient's hematocrit (%), divided by the patient's normal hematocrit for age and gender.[17] The normal range is 1% to 3%.

Normocytic anemias may be classified as hemolytic or nonhemolytic. Nonhemolytic anemias are typically caused by chronic disease states or bone marrow failure, that is, decreased RBC production. Hemolytic anemia is defined by the premature destruction of RBCs.

Clinical Features

Non-hemolytic normocytic anemias include anemia of chronic disease, hypoendocrinism, aplastic anemia, and myelodysplastic or myeloproliferative syndromes.

Anemia of chronic disease may have microcytic or normocytic indices, and is associated with chronic inflammation (e.g., rheumatoid arthritis, chronic infections, or malignancy). The anemia of chronic renal failure is thought to be caused by a number of factors including decreased erythropoietin production, hemolysis, suppression by dialyzable factors, and increased blood loss caused by platelet abnormalities. Correction is with erythropoietin replacement therapy, as necessary.

BOX 109.8 Aplastic Anemia Caused by Drugs or Chemicals

- Chloramphenicol
- Phenylbutazone
- Anticonvulsants
- Insecticides
- Solvents
- Solvents
- Sulfonamides
- Gold
- Benzene

Hypoendocrinism caused by hypothyroidism, hypoadrenalism, or hypopituitarism results in a hypometabolic state in which the bone marrow responds poorly to erythropoietin, and erythropoietin levels may be low resulting in normocytic normochromic anemia.

Aplastic anemia results from destruction of myeloid stem cells leading to pancytopenia. It is suspected in anemic patients with normal indices, a low reticulocyte count, neutropenia, thrombocytopenia, or a history of exposure to certain drugs or chemicals (Box 109.8) which is the cause in 50% of cases. Autoimmune disease, viral hepatitis, radiation exposure, viral illness (Parvovirus B19, HIV, Epstein-Barr virus), and pregnancy have also been associated with aplastic anemia. Infection with Parvovirus B19 can precipitate an aplastic crisis in sickle cell patients and can lead to severe anemia requiring emergent transfusion. Patients can present with symptoms of anemia, however more commonly they present with infections secondary to neutropenia or mucosal bleeding from the accompanying thrombocytopenia. Diagnosis is suspected based on CBC findings, and can be confirmed with bone marrow evaluation. Treatment involves removal of any known causative factor as well as supportive care measures with avoidance of aspirin, effective oral hygiene, and pharmacologic suppression of menses if necessary. Transfusions of RBC or platelets are given in life-threatening circumstances. Bone marrow or peripheral blood stem cell transplantation from a histocompatible sibling can prove to be curative. In patients not amenable to transplantation, immunosuppression with antithymocyte globulin, antilymphocyte globulin, or other cytotoxic chemotherapy may be used. The disease has a wide range of severity, and the overall 5-year survival rate is 30% to 40%. Even with supportive therapy, severe aplastic anemia may prove fatal in up to 80% of patients.

Myelodysplastic syndromes are a class of hematopoietic stem cell disorders that are characterized by cytopenia, myelodysplasia, and ineffective hematopoiesis. It is caused by an accumulation of oncogenic mutations and is associated with an increased risk of progression to leukemic states. It is the cause of anemia in up to 5% of elderly patients. Laboratory evaluation can present with normocytic anemia, thrombocytopenia, and neutropenia. A definitive diagnosis is made by bone marrow examination with evidence of dysplastic cell lines and blast cells.

Treatment is selected based on MDS subtype and age and can range from supportive care to allogeneic hematopoietic stem cell transplantation.[15]

Myeloproliferative neoplasms, specifically primary myelofibrosis, results in primary bone marrow fibrosis and splenomegaly due to extramedullary hematopoiesis, that may ultimately transform to an acute leukemia. The diagnosis is made by bone marrow examination. Treatment is supportive, although a splenectomy or alkylating agents may help treat complications of extramedullary blood cell production, such as hepatosplenomegaly.[18]

Diagnostic Testing

Diagnostic testing in nonhemolytic normocytic anemias consists of a CBC with differential, and additional testing based on presumed underlying cause.

Management

Treatment is based on underlying cause, and in the ED is directed at resuscitation in the event of life-threatening anemia and appropriate admission or outpatient referrals.

Increased Red Blood Cell Destruction

Foundations

Hemolytic anemias are caused by premature RBC destruction. In the appropriate clinical context, this can be defined by evidence of anemia with elevated LDH and decreased Haptoglobin on laboratory evaluation. They can be acute or chronic, with acute hemolytic anemias requiring prompt intervention and management. There are multiple classification systems for describing hemolytic anemias based on Coombs test reactivity, intrinsic versus extrinsic defects, intravascular versus extravascular hemolysis, and congenital or acquired forms.

Pathophysiology

Defined by a shortened life span of the erythrocyte, acute hemolytic anemias can be devastating and require rapid diagnosis and intervention (see Box 109.1). Fortunately, they are relatively rare in comparison to the chronic hemolytic conditions. Chronic disorders may be related to primary blood disorders (e.g., sickle cell anemia) or may be a result of other disease states (e.g., chronic renal failure). These disorders may be manifested as acute hemolytic anemia if the tenuous balance between RBC production and destruction is upset. If the patient can be simultaneously demonstrated to have a normal hematocrit and reticulocyte count, differentiation between acquired and inherited hemolytic anemia is particularly challenging.

Clinical Features

The clinical signs and symptoms of hemolytic anemia are, in general, caused by either intravascular or extravascular processes, and this division assists in the differential diagnostic approach. Emergency physicians should consider hemolysis as a cause of anemia in patients presenting with the typical symptoms of anemia in addition to new-onset jaundice, hematuria, fever, hepatosplenomegaly, abdominal or back pain, or altered mental status.[17,19] A thorough past medical and family history is also critical in the evaluation of hemolytic anemias.

Intravascular hemolysis presents acutely and dramatically due to an acute decrease in oxygen-carrying capacity as the hemolytic process releases free hemoglobin into circulation. Free hemoglobin initially binds to haptoglobin and hemopexin. This complex is transported to the liver, conjugated to bilirubin, then excreted. Once the degree of hemolysis overwhelms the ability of the binding and transport system, free hemoglobin will start to appear in the bloodstream and urine leading to hemoglobinemia and hemoglobinuria, respectively.[17] Jaundice occurs due to excessive bilirubin production, and hemoglobin complexes can cause acute renal failure due to plugging of the microtubules.

The clinical appearance of intravascular hemolysis may vary from mild chronic anemia to severe acute anemia requiring emergent intervention. Mild anemia is commonly caused by mechanical hemolysis from prosthetic valves, or from chronic diseases such as paroxysmal nocturnal hemoglobinuria. Acute severe anemia can be seen with ABO incompatibility, autoimmune hemolytic anemias, infections, DIC, or toxins.

Extravascular hemolysis usually causes mild to moderate anemia, intermittent jaundice, and enlargement of the spleen. It occurs when RBCs are prematurely removed by macrophages in the liver, spleen, or bone marrow due to an abnormality in their shape or the binding of an antibody.[17] Hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency (G6PD), sickle cell disease, and some autoimmune hemolytic anemias represent the most common causes of extravascular hemolysis. The signs and symptoms vary with the severity and chronicity of the hemolysis. Splenic blood flow slows as RBCs travel in the sinusoids close to the reticuloendothelial system, which is uniquely designed for removal of older or damaged cells. Once disassembled in the reticuloendothelial cell, hemoglobin is recycled and ultimately converted to bilirubin and subsequently conjugated by the liver. Primary splenic overactivity, antibody-mediated changes, or RBC membrane abnormalities may cause this normal splenic function to increase to a pathologic degree.

Differential Diagnoses

Hemolytic anemias may be classified as (1) congenital or acquired, (2) Coombs positive or Coombs negative, or (3) caused by processes intrinsic or extrinsic to the cell membrane, and the latter classification provides a useful differential diagnosis of hemolysis (Box 109.9).

Intrinsic enzyme defects. Of the membrane-sustaining energy production of the erythrocyte, 85% to 90% is through the anaerobic glycolytic pathway. At least eight known enzyme deficiencies are associated with this pathway. The most common is pyruvate kinase deficiency, which is manifested with hemolytic jaundice that is usually diagnosed in infancy.

The remaining 10% to 15% of RBC glycolysis occurs by way of the hexose monophosphate shunt. This bypass mechanism occurs in the early stages of the glycolytic pathway and generates reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is important in maintaining reduced glutathione. Glutathione is essential in the protection of hemoglobin from oxidant injury. A deficiency of the first enzyme in this pathway, G6PD, is X linked and most common in African Americans or those of Mediterranean descent.[19] G6PD has a wide range of severity which is dependent on the degree of deficiency and the ability of the body to overcome oxidant stress. Clinical

BOX 109.9 Classification of Hemolytic Anemia

Intrinsic

Enzyme defect: Pyruvate kinase deficiency, G6PD deficiency
Membrane abnormality: Spherocytosis, Paroxysmal nocturnal hemoglobinuria
Hemoglobin abnormality: Hemoglobinopathies, Thalassemias (anemias)

Extrinsic

Immunologic: Alloantibodies, autoantibodies
Mechanical: Microangiopathic hemolytic anemia, prosthetic heart valve disease
Environmental: Drugs, toxins, infections, thermal
Abnormal sequestrations

BOX 109.10 Drugs Associated With Hemolysis in G6PD

Analgesics and antipyretics: acetanilid, aspirin, phenacetin
Antimalarials: Primaquine, quinacrine, quinine
Nitrofurantoin
Sulfa drugs: Sulfamethoxazole, sulfacetamide, sulfones
Miscellaneous: Naphthalene, fava beans, methylene blue, phenylhydrazine, nalidixic acid

symptoms present when oxidative hemolysis occurs typically as an acute hemolytic episode that may be both intravascular and extravascular. It occurs 24 to 48 hours after the ingestion of an oxidant drug (Box 109.10) or after acute infections, such as viral hepatitis. The anemia induced by oxidant drugs is dose related. The oxidant creates forms of activated oxygen, such as peroxide, that either denature the hemoglobin or destroy cell membranes. The former process produces Heinz bodies, which are clumps of denatured hemoglobin found in RBCs that are removed by the spleen. The diagnosis is made by enzymatic screening for G6PD, but this test cannot be performed immediately after the hemolytic episode. A 3-week delay avoids a false-negative result caused by a predominance of young cells. Treatment includes supportive care and discontinuation of oxidant drugs.[19]

Intrinsic Membrane Abnormality

These abnormalities are manifested in a number of ways. An altered shape is the main feature of autosomal dominant hereditary spherocytosis. It is caused by mutations in genes encoding the cytoskeleton of the RBC membrane resulting in spherically shaped, rigid RBCs that are susceptible to premature destruction by the spleen.[20] Clinical sequelae range from compensated asymptomatic anemia to severe life-threatening acquired aplastic crises. The diagnosis is made by reviewing the family history, RBC indices (increased MCHC and RDW), blood smear, and osmotic fragility testing. Treatment is supportive in mild cases. Splenectomy is the treatment of choice for patients with severe disease requiring therapeutic intervention, and usually results in disappearance of anemia with a median increase in hemoglobin by 3g/dL.[20] Due to the complications associated with splenectomy, if possible, it is delayed until the age of 6 years or older.

Paroxysmal nocturnal hemoglobinemia is a stem cell defect causing abnormal erythrocyte, neutrophil, and platelet sensitivity to complement. It is most often seen clinically as chronic hemolysis, hemosiderinuria, leukopenia, and thrombocytopenia. The peripheral smear is normal, and the direct Coombs test result is negative. Its major complication is thrombosis, with a predilection for the hepatic vein. Normal activation of complement with the use of sucrose or acid hemolysis (the Ham test) is diagnostic. Treatment is with supportive care and Eculizumab, a complement inhibitor that has been shown to improve RBC indices and clinical symptoms.[21] Transfusion can be life-threatening in patients with this disease as RBC lysis is caused by donor complement. Thus, only washed packed cells should be utilized. Treatment varies based on disease severity.

Intrinsic Hemoglobin Abnormality

More than 350 types of abnormal hemoglobin have been documented. Problems that may be seen include unstable hemoglobins that appear as Heinz body–positive anemia, M hemoglobins that fix iron in its ferric or methemoglobin state, or hemoglobins with increased oxygen affinity that result in tissue hypoxia and erythrocytosis.

BOX 109.11 Diseases Associated With Autoimmune Hemolytic Anemia

Neoplasms
Malignant: Chronic lymphocytic leukemia, lymphoma, myeloma, thymoma, chronic myeloid leukemia
Benign: Ovarian teratoma, dermoid cyst

Collagen Vascular Disease
Systemic lupus erythematosus
Periarteritis nodosa
Rheumatoid arthritis

Infections
Mycoplasma
Syphilis
Malaria
Bartonella
Virus: Mononucleosis, hepatitis, influenza, coxsackievirus, cytomegalovirus

Miscellaneous
Thyroid disorders, ulcerative colitis
Drug immune reactions

Extrinsic Alloantibodies

Alloantibodies are formed in response to foreign RBC antigens. In the case of the ABO system, these antibodies are preformed and ABO incompatibility resulting in donor cell destruction by the recipient's alloantibodies can be life-threatening. These immunoglobulin M (IgM) antibodies can act as a hemolysin, both agglutinating RBCs, fixing complement, and consequently causing intravascular hemolysis.

The Rh system is another set of antigens on the RBC. Individuals do not have antibodies that correspond to antigens in the Rh system unless they have been sensitized by previous exposure to antigens that they lack. The antibodies produced are IgG in nature, and they accelerate extravascular destruction of RBCs by the spleen and liver. Most autoimmune antibodies are directed toward antigens in the Rh system.

Extrinsic Autoantibodies

Evaluation of autoimmune hemolytic anemia (AIHA) is as complex as its origin, caused by autoantibody-mediated destruction against RBC surface antigens. Autoimmune hemolytic anemias are acquired disorders, with 40% to 50% remaining idiopathic. The remainder are associated with a number of diseases (Box 109.11). A sub-classification of autoimmune hemolytic anemias is based on the optimal temperature at which the antibody reacts with the RBC membrane. Therefore, there are warm-reacting (>37°C) and cold-reacting (<37°C) antibodies. The direct antiglobulin test (DAT) or Coombs test is useful in revealing cells coated with antibody or complement and can aid in diagnosis. A positive DAT alone, however, does not define AIHA and must be supported by clinical context and evidence of hemolysis on laboratory evaluation.[22] AIHA can have a varied presentation from compensated hemolysis with mild anemia and no symptoms to severe symptomatic anemia requiring immediate intervention. Splenomegaly, pallor, or jaundice are common exam findings.

Warm-reacting antibodies are characterized by a higher incidence in younger patients, predominance in women, variable complement fixation, and positive direct antiglobulin test result for IgG. IgG binds to either Rh proteins or glycophorins A-D. IgG-coated RBCs are then removed by reticuloendothelial macrophages and sequestered in the spleen for extravascular destruction. Warm agglutinins are common in

BOX 109.12 Drugs Associated With Immune Hemolytic Anemia

Hapten and drug absorption mechanisms: Penicillin, Cephalosporin, Tetracycline, Hydrocortisone, Oxaliplatin, Tolbutamide

Immune complex mechanism: Metformin, quinine, quinidine, amphotericin b, thiopental, diclofenac, doxepin, probenecid

Autoantibody mechanism: Cephalosporins, methyldopa, mefenamic acid, fludarabine, procainamide, diclofenac

Non-immunologic protein adsorption: Cephalosporins, carboplatin, cisplatin, oxaliplatin

Miscellaneous drug: insecticides, chlorpromazine, acetaminophen, ibuprofen, thiazides, omeprazole, erythromycin, streptomycin

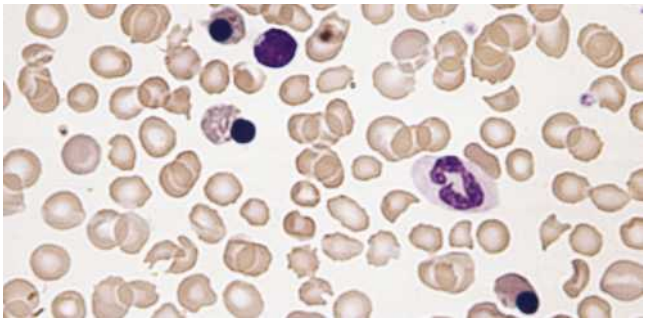

Fig. 109.5 Schizocytes (Fragmented Cell and Nucleated Red Cells). (From Hoffbrand AV, Pettite JE. *Color Atlas of Clinical Hematology*. 3rd ed. London: Mosby; 2000, p 115.)

systemic lupus erythematosus, common variable immunodeficiency, myasthenia gravis, autoimmune hepatitis, myelodysplastic syndromes, or lymphoma. First-line treatment is supportive with management of the underlying condition, in conjunction with glucocorticoids and rituximab. Second- or third-line treatments include intravenous immunoglobulin (IVIG), plasma exchange, hematopoietic stem cell transplantation, azathioprine, cyclosporine, or mycophenolate. Transfusion of blood products should be used in severe cases as needed. Splenectomy is an alternative treatment option for some patients, and up to 40% achieve complete remission post-operatively.[19,22] Disease course can be relapsing and remitting.

Cold-reacting antibodies, or cold agglutinins, are seen predominantly in men and older patients and with IgM complement fixation. IgM antibodies react with surface antigens at low temperatures and cause intravascular or extravascular hemolysis due to complement fixation and activation upon rewarming. Due to the high density of IgM-antigen complexes on RBC, RBC aggregates can be seen on peripheral blood smear. They may also be found in patients with infectious mononucleosis, *Mycoplasma* infection, or lymphoma. The DAT result is positive for complement. Treatment is largely supportive with folic acid and vitamin B_{12} supplementation if deficient, avoidance of triggers, and underlying disease control.[19,22] Blood transfusions should be utilized when anemia is severe. Thrombosis is a common complication of cold agglutinin disease due to agglutinating RBCs, thus thromboprophylaxis should be considered in patients with acute exacerbations or for chronic disease in high-risk situations (i.e., immobilization, long-flights, etc.).

Drug-induced hemolytic anemia may be difficult to diagnose. It is helpful to recognize the drugs most often associated with this Coombs-positive phenomenon, and realize that the result of this test is sometimes positive only in the drug's presence. Removal of the offending agent is the mainstay of treatment. Common drugs are listed in Box 109.12.[19,22]

Extrinsic Mechanical Causes

Hemolysis may be caused by trauma to RBCs. The peripheral smear may demonstrate schistocytes or fragmented cells (Fig. 109.5). Microangiopathic hemolytic anemia, cardiac trauma, and exercise-induced hemoglobinemia are the most commonly encountered forms of traumatic hemolysis.

Microangiopathic hemolytic anemia is a form of microcirculatory fragmentation by threads of fibrin deposited in the arterioles. An underlying disease may be found in renal lesions, such as malignant hypertension or preeclampsia, vasculitis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, or vascular anomalies. Signs and symptoms are those of intravascular hemolysis and thrombosis; treatment is supportive and directed at the underlying cause.[17]

Cardiac trauma to RBCs results from increased turbulence. This may be found in patients with prosthetic valves, arteriovenous fistula, aortic stenosis, or other left-sided heart lesions. Surgical correction may be necessary. Supportive therapy with iron is usually required.

March hemoglobinemia is a form of trauma caused by breaking of intravascular RBCs by repetitive pounding. Soldiers, marathon runners, or anyone with repetitive striking against a hard surface may incur this problem. Reassurance and a change in the patient's pattern of activity are the recommended therapies.

Environmental Causes

Hemolysis may be seen in cases of severe burns, freshwater drowning, or hyperthermia. Toxic causes of hemolysis have been documented to be of animal origin, such as brown recluse spider or some venomous snake bites; vegetable origin, such as castor beans or certain mushrooms; and of mineral origin, such as copper. Certain infections are associated with hemolytic states, including malaria, *Bartonella* infection, or *Clostridium* sepsis.

Abnormal Sequestration

Hypersplenism may be caused by any disease that enlarges the spleen or stimulates the reticuloendothelial system. An unfortunate cycle can be established in which the enlarged spleen traps more blood components and grows larger. It is usually apparent clinically as splenomegaly with pancytopenia and marrow hyperactivity. Therapy for symptomatic or severe disease is splenectomy. Adults usually tolerate splenectomy well, though children should be approached conservatively because the risk of postsplenectomy life-threatening sepsis is increased significantly.

Diagnostic Testing

Once hemolysis is suspected, the history and laboratory testing have diagnostic precedence over physical examination. Important historical and physical examination points are listed in Box 109.13. Important diagnostic tests for hemolysis are included in Box 109.14, and the interpretations of the laboratory evaluation of hemolytic anemias is included in Table 109.6. Reticulocyte count should be obtained to evaluate bone marrow response. An elevated reticulocyte count indicates the bone marrow's attempt to increase RBC production and is usually seen in hemolytic anemias due to premature destruction of RBCs.[17] Examination of spun whole blood demonstrates clear serum in myoglobinemia, pink serum with free hemoglobin in the setting of intravascular hemolysis, and yellow serum from increased bilirubin production in the case of extravascular hemolysis. The blood smear is often more diagnostic than bone marrow examination. The typical cell seen in intravascular hemolysis is the schistocyte (see Fig. 109.5). The classic cell of extravascular hemolysis is the spherocyte. It may be seen in congenital spherocytosis, but more commonly indicates splenic activity against an

BOX 109.13 History and Physical Examination for Hemolytic Anemia

History

Alteration of color in urine or feces
Association with drugs, cold, sleep
Early or recent-onset anemia history with symptoms
Ethnic background
Family history of anemia or jaundice
Drug or toxic exposure
Disease states associated with hemolysis, such as systemic lupus erythematosus, renal failure, lymphoma, infectious mononucleosis, prosthetic heart valve

Physical Examination

Jaundice
Hepatosplenomegaly
Ulcerations, particularly in the lower extremities
Enlarged lymph nodes

BOX 109.14 Diagnostic Tests for Hemolysis

Peripheral blood smear
Corrected reticulocyte index
Haptoglobin levels
Plasma free and urinary hemoglobin
Lactate dehydrogenase level
Fractionated bilirubin level
Direct and indirect Coombs test
Red blood cell (RBC) membrane stability (osmotic fragility)

antibody-coated RBC membrane. An increase in macrocytes reflects the presence of younger cells associated with reticulocytosis. The specific diagnosis may be made by a blood smear, as with sickled cells in sickle cell disease or Heinz bodies in G6PD deficiency.

Haptoglobin binds free hemoglobin on a molecule-for-molecule basis. Its absence implies saturation and degradation after binding with hemoglobin and is an early finding in hemolysis. A haptoglobin of less than 25mg/dL is 95% specific for hemolysis.[22] Haptoglobin is decreased in hepatic failure and increases as an acute-phase reactant. After haptoglobin is bound, hemoglobin binds with hemopexin, transferrin, and albumin before circulating in its free form. Plasma free hemoglobin levels are determined in suspected cases of intravascular hemolysis. The result is considered positive if the level is greater than 40 to 50 mg/dL. Hemoglobin is excreted by the kidney and may appear as a smoky red pigment that is orthotoluidine positive with no associated RBCs. Prussian blue–staining granules of hemosiderin may be found intracellularly in renal tubule cells excreted in urine during chronic hemolytic states.

LDH is released when the RBC is broken down peripherally or in the marrow. It is elevated in hemolytic, thalassemic, sideroblastic, or megaloblastic anemias but may also be seen in cases of uremia, heart failure, polycythemia vera, or erythroleukemia.

In extravascular hemolysis, bilirubin is often delivered to the liver faster than the conjugating mechanism can handle it, leading to an indirect or unconjugated hyperbilirubinemia. Normal total levels are less than 1.5 mg/dL, with an indirect component less than 0.5 mg/dL. Indirect bilirubin may rise as high as 4 or 5 mg/dL even with normal liver function. Higher levels connote some degree of underlying hepatic insufficiency.[17]

The DAT (Coombs) test detects antibody or complement on human RBC membranes by adding a polyspecific antihuman globulin reagent which will detect IgG, IgA, IgM, and complement. It is used in the evaluation of AIHA. The reaction causes an agglutination of RBCs that

TABLE 109.6 Laboratory Evaluation of Hemolytic Anemias

Extravascular Destruction	Lactate Dehydrogenase	Haptoglobin	Reticulocyte Count	Coombs Test	Peripheral Smear
Congenital Red Blood Cell Defects					
Enzyme defects (e.g., G6PD)	↑	↓	↑	Negative	"Bite" cells
Hemoglobinopathies (sickle cell disease)	↑	↓	↑	Negative	Sickle cells
Membrane defects (e.g., hereditary spherocytosis)	↑	↓	↑	Negative	Spherocytes
Acquired Red Blood Cell Defects					
Autoimmune hemolytic anemia	↑	↓	↑	Positive	Spherocytes
Liver disease	↑	↓	↑	Negative	Spur cells
Infections (e.g., malaria)	↑	↓	↑	Negative	RBCs with inclusions
Toxins (e.g., nitrates, dapsone, aniline dyes)	↑	↓	↑	Negative	Spherocytes
Hypersplenism	↑	↓	↑	Negative	Howell-Jolly bodies
Intravascular Destruction					
Microangiopathic hemolytic anemia (e.g., DIC, TTP, HUS)	↑	↓	↑	Negative	Schistocytes, helmet cells
Transfusion reactions	↑	↓	↑	Positive	Schistocytes, helmet cells
Sepsis	↑	↓	↑	Negative	RBC "ghost" cells, schistocytes, helmet cells
Paroxysmal nocturnal hemoglobinuria	↑	↓	↑	Negative	Schistocytes, helmet cells
Heat injury	↑	↓	↑	Negative	Schistocytes, helmet cells

DIC, Disseminated intravascular coagulation; *G6PD,* glucose-6-phosphate dehydrogenase; *HUS,* hemolytic uremia syndrome; *RBC,* red blood cell; *TTP,* thrombotic thrombocytopenic purpura.

is graded 0 to 4. Agglutinating properties depend on the size of the immunoglobulin. It can have false negative results if the RBC-bound antibodies are below the threshold of the test or in the presence of low affinity autoantibodies. A false positive DAT can occur after administration of intravenous immunoglobulins or Rh immunoglobulins. It is also important to recognize that a positive DAT can occur without AIHA and can be present in patients that have been recently transfused or have delayed hemolytic transfusion reactions.[22] The indirect test measures antibody titers in serum (cold agglutinin autoimmune hemolytic anemia). The indirect antiglobulin test (IAT) assumes that IgG or C3 is in the serum and tests for serum antibody activity against RBCs. Test RBCs are first mixed with patient serum, washed, and then incubated with polyspecific antihuman globulin reagent. Agglutination will occur if serum antibodies directed toward RBCs are present. Positive tests for immunologic markers do not correlate agglutination activity with the severity of hemolysis.[22]

Management. In patients with newly diagnosed reticulocytopenia or severe hemolytic anemia, the emergency clinician may need to institute rapid transfusion therapy. Compatible blood may be almost impossible to find as the antibody can react with almost all donors. The most compatible donor cells in terms of the ABO and Rh systems should be transfused with the knowledge that they will be no more compatible than the patient's own blood cells. If emergency blood transfusion is required, type-specific or type O blood (Rh-positive for men; Rh-negative for women of childbearing age) is indicated, as well as prednisone or its equivalent in a dose of 1 mg/kg to assist with slowing the rate of hemolysis. During transfusion, patients should be closely monitored for signs of hemolytic transfusion reactions. Death commonly results from uncontrolled hemolysis, infection, the underlying primary disorder, or pulmonary embolism.[17]

Sickle Cell Disease

Foundations

Sickle cell disease is an inherited autosomal recessive mutation that produces an abnormal hemoglobin known as HbS. It affects approximately 100,000 people in the United States, and an estimated 2 million Americans carry the sickle cell trait.[23,24] It is predominantly found in the African American population, however up to 10% of patients with various sickling disorders are not ethnically African American, includes people of Mediterranean, Indian, or Middle Eastern descent.[23,25]

The globin in hemoglobin is made up of two pairs of identical polypeptide globin chains. Each person has two non–sex-linked gene foci for β-globin chains, one from each parent. Six different types of hemoglobin from varying globin chain combinations are expressed: three embryonic hemoglobins, HbA (α2β2), HbA2 (α2δ2), and HbF (α2γ2, fetal hemoglobin). Embryonic hemoglobins are expressed only in utero, and after 6 months of age, HbA typically accounts for more than 95% of hemoglobin. The sickle syndromes result from mutations in the β-globin gene. Instead of HbA (α2β2), an abnormal hemoglobin, HbS, is produced. Embryonic and fetal hemoglobin do not contain β-globin; thus, there are no clinical manifestations in early infancy. As production declines, and normal HbA (α2β2) decreases, symptoms develop.

HbS is formed when an abnormal allele at the gene loci for the hemoglobin beta chain produces altered messenger RNA, which in turn results in replacement of glutamic acid by valine at the sixth position from the N-terminal end of the beta chain. When subjected to deoxygenation or various stressors, the RBC sickles and becomes a rigid, adhesive cell that is less deformable and prone to lysis. Sickled cells increase the viscosity and sludging tendency of blood, and ultimately undergo sequestration in the spleen and liver.[25,26] The clinical complex of vaso-occlusive events, chronic hemolysis, thrombosis, and organ injury is derived from this pathologic process.

In sickle cell trait (HbAS), the patient is heterozygous and only one parent contributes the abnormal S allele. In each cell, approximately 40% of the hemoglobin is HbS. Patients usually have a benign and asymptomatic clinical course. Sickle cell disease (HbSS) is homozygous, more than 85% of the hemoglobin is HbS, and it is associated with severe disease.[25] Because a parent may contribute alleles other than S, a wide number of variants can exist. Patients with HbSS are also subject to other causes of anemia such as iron deficiency, G6PD, or megaloblastic anemias. Two clinically important S variants are sickle cell–β-thalassemia and sickle cell–hemoglobin C disease.

The diagnosis is usually made after newborn sickle cell screening via hemoglobin electrophoresis. Most individuals with sickle cell trait are asymptomatic but can present with spontaneous hematuria, renal papillary necrosis, splenic infarction, pulmonary embolism, traumatic hyphema, exertional rhabdomyolysis, or exertional sudden death. In stark contrast to sickle cell disease, which is associated with increased maternal mortality and stillbirth, recent literature suggests that pregnancy in women with sickle cell trait is not associated with an increased risk of adverse events.[27]

Clinical Features

Sickle cell disease is characterized by two major clinical features, hemolysis and acute vaso-occlusive events. The hallmark manifestation of sickle cell disease and the most common reason for ED visits is painful vaso-occlusive crises.[25] Potential precipitating factors include antecedent infection, cold exposure, or stress such as trauma. A painful crisis is believed to have its origin in tissue ischemia which furthers irreversible sickling of cells, leading to increased viscosity, sludging, and microvascular obstruction. Sludging and vascular blockage cause stasis, deoxygenation, and local acidosis, which promotes continued sickling. Pain is caused by activation of nociceptors as inflammatory mediators are released in response to vascular damage. The pain is commonly deep and aching, and is most often found in the abdomen, chest, back, or extremities.[25,26,28] The disease may mimic an acute abdomen, pulmonary embolus, renal colic, or other painful condition. A directed history that relates this pain pattern to previous sickling episodes, a careful repeated physical examination, and specific organ-related laboratory tests can be used to differentiate "uncomplicated" crises from another serious pathologic condition. Children may be seen more often with skeletal crises, especially in the hips and lower extremities, leading to bone deformities. In these cases, osteomyelitis, avascular necrosis, and bone infarct needs to be differentiated. Acute pain crisis is treated with analgesia, including opioids and nonsteroidal anti-inflammatories, and intravenous hydration. Pain control adjuvants should be considered and include sedatives, anxiolytics, or antihistamines. If pain control is able to be achieved in the ED, patients can typically be discharged on an oral pain control regimen, otherwise, hospitalization may be required for further management.[23,28]

Neurologic complications include transient ischemic attack, cerebral infarction, intracranial hemorrhage, spinal cord infarction, or vestibular and hearing problems. Patients presenting with the sudden onset of acute neurologic abnormalities should be presumed to have a stroke until proven otherwise, typically necessitating prompt imaging. Risk factors for CVA in sickle cell patients include low hemoglobin level, history of acute chest syndrome, or history of hypertension.[23,25] Transcranial Doppler (TCD) is useful in children to identify those at highest risk of developing stroke by measuring the maximum time-averaged mean velocity of blood flow in the intracranial arteries.[25,28] TCD combined with brain MRI can be used in adults to assess stroke risk. The use of regular blood transfusions can reduce the risk of cerebrovascular events in selected patients. In the setting of an acute stroke, exchange transfusion is often recommended with the goal of

hemoglobin S of less than 30% and a total hemoglobin level of 10 g/dL.[23,25] Tissue plasminogen activator (tPA) should be considered in adult sickle cell disease patients with acute non-hemorrhagic strokes, although extreme caution is advised due to increased risk of intracranial hemorrhage.[23]

Acute chest syndrome is the most common pulmonary condition associated with sickle cell disease, and one of the most common causes of death.[23,25] Patients with acute chest syndrome often have fever, cough, hypoxia, chest pain, dyspnea, or new infiltrates on chest radiograph. The pathophysiologic mechanism of the syndrome is not well understood and is postulated to be related to pulmonary microvascular sludging, infarction of pulmonary parenchyma, and bone marrow fat embolization from infarcted bone. Macrovascular pulmonary embolism and infection may also have a pathogenic role. Acute chest syndrome is commonly associated with infection, including *Mycoplasma* or *Chlamydia* species. The differential includes pneumonia, pulmonary embolism, congestive heart failure, fat embolism, or adult respiratory distress syndrome. Management consists of hydration, analgesia, maintenance of adequate oxygenation and ventilation, and empiric antibiotics with a parenteral cephalosporin, such as ceftriaxone 1 to 2g (50 mg/kg) IV daily, and a macrolide, such as azithromycin 500 mg (10 mg/kg) IV daily.[23,25] Exchange blood transfusions should be considered in patients with multi-lobe involvement, persistent or worsening hypoxemia, neurologic abnormalities, or multi-organ failure.[28] However, there are no randomized controlled studies demonstrating an improvement in outcome with exchange transfusions. Acute chest syndrome can rapidly progress to acute respiratory distress syndrome due to pulmonary sequestration or infarct, and typically requires mechanical ventilation. Long-term complications include pulmonary fibrosis, pulmonary hypertension, and cor pulmonale.[23]

Sickle cell disease is a chronic hemolytic state, often with reasonably compensated hematocrit values in the 20% to 30% range and elevated reticulocyte counts. This compensated balance may be disrupted by iron deficiency or, more commonly, by folate deficiency. A potentially life-threatening aplastic crisis may be seen as a result of suppression of erythropoiesis by an acute post-infectious condition (e.g., Parvovirus B19) or folate deficiency. Aplastic crisis is suspected when the hemoglobin level falls 2 g/dL or more from previous stable levels and the reticulocyte count is low (<2%).

Children may have an acute splenic sequestration syndrome or can develop splenic auto-infarction. This commonly occurs between 10 and 27 months of age. Acute splenic sequestration syndrome involves acute splenic enlargement from increased intrasplenic sickling and obstruction. Rapid sequestration results in a rapidly falling RBC count and circulatory collapse.[28] A Hb drop by greater than 4 g/dL is associated with 35% mortality in the pediatric population.[23] Emergency management is aimed at restoring circulating blood volume with transfusion. Splenectomy is curative, although asplenia results in an increased risk of infection with encapsulated organisms such as *Streptococcus pneumoniae* or *Haemophilus influenzae*. Autosplenectomy occurs as a result of occlusion of the splenic artery, leading to infarction and functional asplenia.[23,25]

Bacterial infections are common due to functional asplenia, and may result in life threatening pneumonia, sepsis, or meningitis, especially in infancy or childhood. Pneumococcal vaccination has dramatically reduced the incidence of invasive pneumococcal disease in sickle cell patients and is a mainstay of preventative therapy, in addition to *H. influenza* type b and meningococcal vaccination series. Prophylactic daily antibiotics, with either amoxicillin or penicillin, are usually required for all children 2 months to 5 years old with functional asplenia.[23,25] A WBC count, blood cultures, urine cultures, and a chest radiograph should be considered in the evaluation of a febrile patient with sickle cell disease. Early institution of appropriate antibiotics, such as ceftriaxone 1 to 2 g IV or IM with consideration for vancomycin 15 mg/kg IV, is necessary in patients with a discernible source of infection or sepsis. An increased incidence of *Salmonella* osteomyelitis occurs in sickle cell patients and should be considered in the differential. The origin of immunologic deficiency in sickle cell disease is believed to be multifactorial, involving functional asplenia leading to increased infection risk with encapsulated organisms, poorly migrating neutrophils, and decreased opsonin production.

TABLE 109.7 Organ Damage Seen in Sickle Cell Disease

Organ or System	Injury
Skin	Stasis ulcer
Central nervous system	Cerebrovascular accident
Eye	Retinal hemorrhage, retinopathy
Cardiac	Congestive heart failure
Pulmonary	Intrapulmonary shunting, pulmonary hypertension, embolism, infarct, infection
Vascular	Occlusive phenomenon at any site
Liver	Hepatic infarct, hepatitis resulting from transfusion, hepatic sequestration, intrahepatic cholestasis
Gallbladder	Increased incidence of bilirubin gallstones caused by hemolysis
Spleen	Acute sequestration
Urinary	Hyposthenuria, hematuria, glomerulosclerosis, end-stage renal disease
Genital	Decreased fertility, impotence, priapism
Skeletal	Bone infarcts, osteomyelitis, aseptic necrosis
Placenta	Insufficiency with fetal wastage
Leukocytes	Relative immunodeficiency
Erythrocytes	Chronic hemolysis

Major, chronic organ damage in patients with sickle cell anemia is common (Table 109.7). Severe, life threatening multi-organ failure can also occur acutely due to sudden vaso-occlusion in the lungs, liver, or kidneys presenting as abrupt hemodynamic compromise.[23] Acute chest syndrome, sepsis, and multiorgan failure are the leading causes of death in HbSS.

Differential Diagnoses

Sickle cell–β-thalassemia disease is seen most commonly in those of Mediterranean descent. The severity of the disease is related to the concentration of HbS in RBCs, and the decrease in MCHC. It should be considered in a patient with a low MCV and a positive response on sickle preparation. The peripheral smear demonstrates a combination of sickled cells and normocytic target cells. It is generally a milder form than homozygous HbSS, though can also be severe.

HbSC accounts for 30% of the sickle cell disease in the United States and United Kingdom. HbSC results from co-inheritance of HbS and HbC beta globin gene mutations. HbC defect occurs due to a glutamic acid to lysine mutation at position six on the beta chain. Patients with HbSC disease have higher mean Hb and lower absolute reticulocyte counts. RBC lifespan is twice that of HbSS. Anemia in HbSC is mild, and both target cells and sickle cells are seen on peripheral smear. It is considered to be a milder variant, though may be associated with all of the typical HbSS complications as well as an increased incidence of retinopathy.[29]

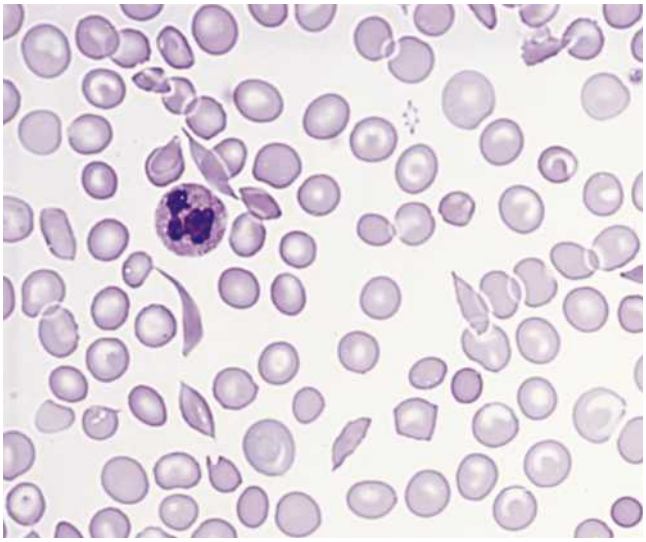

Fig. 109.6 Sickle Cells. (From Hoffbrand AV, Pettite JE. *Color Atlas of Clinical Hematology*. 3rd ed. London: Mosby; 2000:103.)

Diagnostic Testing

The initial diagnosis of sickle cell disease is usually performed via hemoglobin electrophoresis in the neonatal period as a screening test in at risk populations, or at the onset of symptoms. Patients with known or suspected sickle cell disease presenting to the ED should have a complete blood count with differential performed and compared with those of previous visits. A reticulocyte count is recommended whenever the patient's hemoglobin level has decreased by 2 g/dL from baseline. In sickle cell disease, the typical absolute reticulocyte count is three or four times the upper limit of normal. A reticulocyte count 3% or lower than the patient's usual value may suggest an aplastic crisis. A reticulocyte count greater than 12%, particularly if it is accompanied by numerous nucleated RBCs, may indicate rapid hemolysis. Unfortunately, no test is available that detects whether a patient is in a crisis, and the diagnosis is based largely on clinical presentation. In undiagnosed cases, the peripheral smear may show sickled cells (Fig. 109.6), but the definitive diagnosis of sickle cell disease is confirmed by hemoglobin electrophoresis.

Management

Current therapies, including rest, adequate nutrition, hydration, oxygenation, analgesia, transfusion, and therapy for infection, are directed toward symptomatic relief and attempts to interrupt the cycle of deoxygenated sickling and intravascular sludging. Although the use of supplemental oxygen may have some theoretical advantages, it has not been shown to reduce opioid use or hospitalization in patients that are not hypoxic.

Analgesia is a major benefit and essential early therapy for acute sickle cell vaso-occlusive crises. Many emergency clinicians caring for large populations of sickle cell patients have developed protocols to establish better physician-patient rapport, and to lessen the potential for narcotic addiction or manipulation. The following is a protocol for severe pain in adults and children weighing more than 50 kg: patients are evaluated, treated with oxygen and hydration, and given intravenous morphine sulfate, 5 to 10 mg every 2 to 4 hours, or intravenous hydromorphone, 1.5 mg every 3 to 4 hours. For children weighing less than 50 kg, intravenous bolus doses of morphine sulfate, 0.1 to 0.15 mg/kg, can be given every 2 to 4 hours, or intravenous hydromorphone, 0.015 to 0.020 mg/kg, can be given every 3 to 4 hours. At 4 to 6 hours, the patient is allowed to decide whether pain is appropriately controlled. Outpatient therapy includes 4 to 6 days of an effective oral analgesic. A 40-mg dose of oral morphine sulfate or equivalent is given 1 or 2 hours prior to discharge.[23] A major disadvantage of protocols has been a tendency to treat patients reflexively, rather than carefully considering the potential acute complications of sickle cell disease. A variety of analgesics (nonsteroidal anti-inflammatory drugs, mixed opioid agonist-antagonists, and opioids), dosages, and timing intervals may be selected. As many sickle cell disease patients can have varying degrees of hepatic or renal dysfunction, acetaminophen and nonsteroidal anti-inflammatory drugs should be used with caution. The most important aspect of pain management is a consistent, thorough, and attentive approach that offers true pain relief and helps mitigate potential under treatment.

The antisickling agent hydroxyurea reduces pain crises, the need for blood transfusions, and has reduced mortality.[28] The beneficial effects of hydroxyurea include the induction of fetal hemoglobin and mild myelosuppression. Hydroxyurea can reduce the incidence of acute painful crisis, with the potential to ameliorate chronic organ damage and prolonged survival.[26] However, the effects of hydroxyurea can take weeks to be appreciated, and it is not routinely recommended for acute episodes. Dosing of hydroxyurea should be titrated up to the maximum tolerated dose, usually ranging from 20 to 25 mg/kg/day PO.[26]

RBC transfusion is a mainstay in treatment, and more than 90% of adults with sickle cell disease have received at least one transfusion in their lifetime. Transfusion can be given acutely for severe acute exacerbation of chronic anemia with evidence of hypoxia or hypoperfusion, acute organ damage, or preoperatively as a prophylactic measure.[25] Acute chest syndrome, stroke, aplastic crisis, or acute splenic sequestration represent conditions that typically necessitate acute exchange transfusion, and the decision to initiate should be made in consultation with a hematologist. Chronic transfusions are indicated as stroke prevention in selected patients, or in those with progressive multisystem organ failure. The overall goal of transfusion therapy for symptomatic anemia is a hemoglobin level no higher than 10 g/dL, and a target HbS < 30%. Asymptomatic patients should not be transfused, regardless of hemoglobin value.

Alloimmunization, delayed hemolytic reactions, infection transmission, or iron overload are a few of the devastating complications that can result from long-term transfusion, thus transfusion needs should be carefully considered. Iron overload is treated in the usual manner with oral iron chelation therapy with deferiprone or deferasirox.[23,25]

Priapism is a painful complication of sickle cell disease that may lead to impotence. First-line therapy for priapism is aspiration of blood from the corpus cavernosum and irrigation with an α-adrenergic agent (e.g., phenylephrine). Urologic surgical management is typically reserved for patients who fail aspiration and irrigation.[23,28]

Stem cell transplantation offers the only current cure for sickle cell disease, and is associated with survival rates greater than 90% if the transplant comes from an HLA-matched, disease-free sibling. Due to the restrictive criteria for transplantation, as well as long-term conditioning regimen toxicities and transplant-related mortality, there is limited use of this modality and it remains unclear which patients will benefit most.[25]

Other agents and experimental therapies are showing promise and may have a future role in treatment, including steroids, statins, heme-oxygenase, Hb affinity modulators, antioxidants, and gene therapy.[24,28]

Disposition

If pain can be controlled, patients with painful crises can often be discharged with analgesics. Hospitalization may be warranted if pain cannot be adequately controlled. Hospitalization is also typically recommended in patients with acute chest syndrome, acute infections,

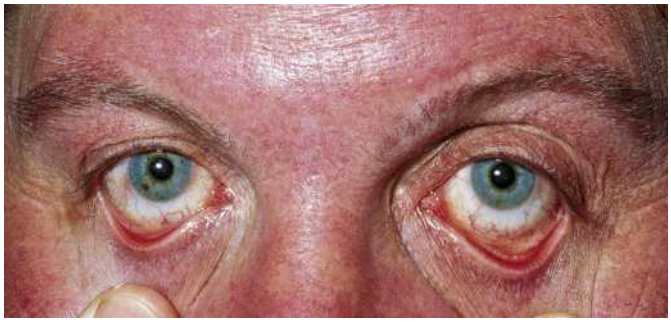

Fig. 109.7 Polycythemia Vera. Facial plethora and conjunctival suffusion in a 40-year-old woman (hemoglobin, 19.5 g/dL). (From Hoffbrand AV, Pettite JE. *Color Atlas of Clinical Hematology*. 3rd ed. London: Mosby; 2000:248.)

acute osteomyelitis, acute stroke, or other complications or disease states requiring further inpatient intervention.

POLYCYTHEMIA

Foundations

Polycythemia is a term commonly used for erythrocytosis (i.e., increased number of RBCs). This disorder is seen occasionally in EM, though rarely requires emergency intervention. An elevated RBC count, usually greater than the hematocrit, defines the disorder. It results in a low MCV, usually related to low serum iron and iron stores.

The major complications of polycythemia are related to the increase in blood viscosity associated with increased RBC numbers. As the hematocrit rises past 60%, viscosity increases in an almost exponential manner, resulting in reduced tissue flow, thrombosis, and hemorrhage.

Clinical Features

Symptoms may range from mild headaches to a fulminant syndrome of hypervolemia (vertigo, dizziness, blurred vision, or headache), hyperviscosity (arterial or venous thrombosis), and platelet dysfunction (epistaxis, spontaneous bruising, or gastrointestinal bleeding).[30]

On examination, the skin and mucous membranes may manifest plethora, engorgement, and venous congestion (Fig. 109.7). Other findings include venous congestion of the optic fundus, splenomegaly, or signs of congestive heart failure.[30] Investigation for uterine, central nervous system, renal, or hepatic tumors should be sought, as such tumors may result in secondary polycythemia.

Differential Diagnosis

Erythrocytosis can be absolute or relative (Box 109.15), and polycythemia is typically classified as primary, secondary, or apparent. Apparent polycythemia is a decrease in plasma volume, and RBC volume does not exceed the upper limit of normal. This is typically seen in the dehydrated patient and is consistent with volume contraction. Treatment is with hydration.

Primary polycythemia vera (PV) is a chronic myeloproliferative neoplasm caused by JAK2 mutations found predominantly in middle-aged or older patients. Initial symptoms are nonspecific and include headache, weakness, dizziness, excessive sweating, plethora, or pruritus after a hot water exposure.[31] The most serious complications include thrombotic episodes (cerebrovascular accident, myocardial infarction, or deep venous thrombosis), bleeding, and risk of leukemic or fibrotic transformation. Primary PV involves all cell lines—hematopoietic stem, erythroid, granulocytic, and megakaryocytic, and presents with elevated hemoglobin and RBC mass, thrombocytosis, and leukocytosis. The diagnostic criteria used by the World Health Organization and revised in 2016 are listed in Box 109.16.[31]

BOX 109.15 Causes of Absolute and Relative Polycythemia

Absolute Erythrocytosis

Right-to-left shunt
Pulmonary disease
Carboxyhemoglobinemia
High-altitude acclimatization
High affinity hemoglobins
Sleep apnea syndrome
Renal disease: focal sclerosing glomerulonephritis, renal transplantation
Tumors: hepatoma, adrenal tumors, meningioma, pheochromocytoma, hemangioblastoma
Drugs: Androgenic steroids, Recombinant erythropoietin
Polycythemia vera

Relative Erythrocytosis

Loss of fluid from vascular space: emesis, diarrhea, diuretics, burns, hypoalbuminemia
Chronic plasma volume contraction: hypoxia, hypertension, tobacco use, ethanol abuse

BOX 109.16 Diagnostic Criteria for Polycythemia Vera[a]

Major Criteria

1. Hemoglobin >16.5 g/dL in men or >16 g/dL in women or hematocrit >49% in men or >48% in women or increased red blood cell mass
2. Bone marrow tri-lineage proliferation with pleomorphic mature megakaryocytes
3. Presence of JAK2 mutation

Minor Criterion

Subnormal serum erythropoietin level

[a] Diagnosis of polycythemia vera requires all three major criteria or two major criteria and minor criterion.

The mainstay of therapy is phlebotomy to a hematocrit of less than 45% to assist in preventing thrombosis. The reduced hematocrit improves some symptoms, though neither leukocytes nor platelet counts are decreased.[30,31] In addition to phlebotomy, once-daily low-dose aspirin (40 to 100 mg PO) is recommended to prevent thrombosis. In patients with high-risk disease (history of thrombosis or >60 years of age), the addition of hydroxyurea is recommended at a dose of 500 mg PO twice daily. If there has been a prior history of arterial thrombosis, aspirin may be dosed twice daily. Venous thrombosis is typically treated with systemic anti-coagulation. In patients intolerant or resistant to hydroxyurea, interferon, busulfan, or ruxolitinib can be considered.[31] Complications necessitating additional therapy include hyperuricemia, refractory increased RBC mass, severe pruritus, excessive splenomegaly, or symptomatic thrombocytosis. Additional therapies may include paroxetine, transexamic acid, pipobroman, allopurinol, low-dose thalidomide, or prednisone. Splenectomy may be warranted in the setting of severe splenomegaly.[30] The natural history of the disease is protracted with survival less than but comparable to the general population. The most common causes of death include thrombosis, or worsening disease resulting from transformation to myelofibrosis or acute leukemia.[32]

Diagnostic Testing

Secondary polycythemia is classified according to appropriate erythropoietin response to abnormal tissue oxygen levels. This group of

disorders may be excluded by normal measured arterial oxygen saturation. Also, inappropriate autonomous erythropoietin production is considered, which can be assessed with an erythropoietin assay. Because of a strong association with renal pathologic conditions and malignancies, computed tomography should be considered to evaluate a patient with a suspected inappropriate erythropoietin response. Patients with secondary polycythemia infrequently have central nervous system symptoms or splenomegaly. As erythropoietin stimulates only the red cell pathway, WBC and platelet counts should be unchanged.

Management

The emergency treatment of symptomatic polycythemia is phlebotomy. A commonly employed approach is to remove approximately 500 mL of blood and replace it with a comparable amount of saline. Hemodynamic compromise should be averted if this procedure is performed slowly. In true emergencies, 1 to 1.5 L of blood may be removed during a 24-hour period. The initial goal is to lower the hematocrit toward 60%; the ultimate goal is a level less than 45%.

Disposition

Selected patients with known polycythemia may be managed by serial outpatient phlebotomies. Newly diagnosed or symptomatic patients should be considered for admission for further diagnostic evaluation.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 109: QUESTIONS AND ANSWERS

1. Anemia with an elevated mean corpuscular volume (MCV) is *not* typically seen with which of the following conditions?
- **a.** Folate deficiency
- **b.** Hypothyroidism
- **c.** Iron deficiency
- **d.** Vitamin B_{12} deficiency

Answer: c. Iron deficiency anemia typically presents as a microcytic anemia. Liver disease may present with either a macrocytic anemia or a normocytic anemia reflecting an anemia caused by multiple mechanisms.

2. An elevated mean corpuscular hemoglobin concentration (MCHC) is expected in which of the following conditions?
- **a.** Anemia of chronic disease
- **b.** Iron-deficiency anemia
- **c.** Sideroblastic anemia
- **d.** Spherocytosis

Answer: d. The MCHC index is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted only in patients with decreased cell membrane area relative to volume, such as spherocytosis.

CHAPTER 109: QUESTIONS AND ANSWERS—cont'd.

3. A 21-year-old man presents with easy fatigue and lack of energy. During a recent clinic visit, he was found to be anemic with a hemoglobin of 8 g/dL, mean corpuscular hemoglobin concentration (MCHC) of 25%, mean corpuscular volume (MCV) of 61 fL, and a peripheral smear remarkable for target cells and basophilic stippling. Serum iron levels were normal. What is the most likely explanation for his anemia?
   a. Iron deficiency
   b. Porphyria
   c. Sideroblastic anemia
   d. Thalassemia

Answer: d. Hypochromic, microcytic anemias with normal serum iron imply thalassemia (a defect in globin chain production). Both alpha- and beta-thalassemia manifest as a hypochromic microcytic anemia with target cells and basophilic stippling. The microcytosis is generally more severe than with iron-deficiency anemia. Sideroblastic anemia generally presents with elevated serum iron.

4. A 73-year-old woman presents with progressive fatigue. Her only past medical history is rheumatoid arthritis for which she takes methotrexate. She has no cardiopulmonary history and does not smoke. Physical examination is remarkable only for bilateral metacarpophalangeal, chronic swelling, and mild splenomegaly. Recent blood tests from the clinic are remarkable for a high normal serum iron, hemoglobin of 10 g/dL, and mean corpuscular volume (MCV) of 69 fL, with peripheral smear showing both microcytes and macrocytes. Which of the following is the most appropriate intervention?
   a. A trial of pyridoxine
   b. Hematology consultation for bone marrow biopsy
   c. Hematology consultation for iron chelation
   d. Send blood for vitamin B_{12} and folate levels

Answer: a. Sideroblastic anemia may be acquired or inherited. It is typically a refractory anemia in the elderly characterized by hypochromia and microcytosis but a dimorphic smear also showing normal cells and macrocytes. Some of these patients are pyridoxine deficient and may respond to a course of vitamin B_6. This anemia is a defect in porphyrin synthesis and is associated with rheumatoid arthritis, cancer, and infections. Lead poisoning is a subset. Elevated iron and ferritin levels are seen because the porphyrin defect does not allow iron incorporation and cells hemolyze in the bone marrow.

5. A 43-year-old woman presents with difficulty walking and complaints of depression that have progressively worsened over several weeks. She has no past medical history, takes no medications, and does not drink alcohol or smoke. Physical examination is remarkable for clinical depression, a spastic gait, decreased extremity proprioception, and lower extremity hyporeflexia. What test should be obtained next in this patient's evaluation?
   a. Complete blood count with differential diagnosis and RBC indices
   b. Lumbar puncture
   c. Magnetic resonance imaging (MRI) of the spine
   d. Serum potassium and calcium levels

Answer: a. Vitamin B_{12} deficiency presents classically with very low hemoglobin levels, a macrocytic picture, decreased proprioception or vibration, lower extremity spasticity/weakness with hyporeflexia, and often mental status changes, such as depression, forgetfulness, or even paranoia. Irritability and forgetfulness are also seen with folate deficiency.

110

White Blood Cell Disorders

Brian L. Springer and Alan A. Dupré

KEY CONCEPTS

- Chronic lymphocytic leukemia (CLL) is the most common leukemia in the elderly, and acute lymphocytic leukemia (ALL) is the most common leukemia in children.
- Splenomegaly is a common finding in leukemias.
- Leukostasis is usually not accompanied by clinical sequelae until the white blood cell (WBC) count is more than 500,000.
- Neutropenia plus a fever should be treated as a potentially life-threatening infection until proven otherwise.
- Infection is the most common cause of neutropenia in children.
- WBC count determination in the emergency department (ED) has poor sensitivity and specificity for any specific disease process.
- Inflammatory markers, absolute neutrophil count, bandemia, or immature granulocyte count may be more useful for identifying infection than the absolute WBC count.

FOUNDATIONS

Background and Importance

The white blood cell (WBC) and accompanying differential count are among the most common laboratory tests ordered in the emergency department (ED) setting. Unfortunately, the WBC count has not proved to be a highly sensitive or specific test, and the absence of leukocytosis does not exclude the presence of significant infection or disease. Acute infection remains the most common nonmalignant cause of leukocytosis. In evaluation of the bacterial infectious potential in febrile children and adults, the WBC and differential counts have demonstrated limited usefulness as stand-alone biomarkers. Other tests, such as procalcitonin and C-reactive protein (CRP), may have more predictive value.[1,2] Thus, the WBC count should be viewed as having limited screening value in the acute care setting. However, when combined with history and physical examination findings, the WBC and differential counts can be of utility in helping determine the presence of acute infection or other processes.[1,3]

Anatomy and Physiology

The WBC (leukocyte) series can be divided into three basic cell types: granulocytes (neutrophils, eosinophils, and basophils), monocytes (nongranulated cells that mature into macrophages), and lymphocytes. WBCs reach their site of action through the circulation. The rate at which new cells enter the circulation is usually in equilibrium with the rate of loss in tissues. The granulocytic series is primarily involved in phagocytic activity. Its origin is the pluripotential stem cells located in the bone marrow. A subset of these cells differentiates and matures into the phagocytic cell lines, which include neutrophils, basophils, and eosinophils. Nongranulated phagocytic monocytes also develop from this same lineage. Granulocytes originate, mature, and are stored in the bone marrow, with a lifespan of days once released into the peripheral circulation. The postmitotic storage pool for neutrophils, which represents 15 to 20 times the circulating population, contains metamyelocytes, band neutrophils, and mature neutrophils (polymorphonuclear neutrophils). The pool can be drawn on as a ready reserve during rapid consumption of granulocytes. Circulating neutrophils are subdivided equally into the circulating neutrophil pool and the marginal pool, consisting of mature cells adherent to the blood vessel walls. During times of physiological stress, the marginal pool can rapidly enter the circulating pool and cause a substantial increase, even doubling, of the WBC count with neutrophilic predominance. This typically resolves within 24 to 48 hours; persistent elevation may be an indicator of leukemia or other malignancy. These patients should be referred to a primary care physician or hematologist for further evaluation.

The lymphocytic series matures in lymphoid tissues located in the bone marrow, thymus, spleen, lymph nodes, or elsewhere. They are involved in the immune response against foreign substances. There are two morphologically indistinguishable lymphocyte cell types: B cells (humoral immunity) and T cells (cellular immunity). Because lymphocytes can freely leave and return to the circulation, the storage pools are less well defined. Only a relatively small number of total body lymphocytes are in circulation at any point in time.

One unique problem in WBC disorders is the wide variability in normal values and the multiple factors influencing them. WBC counts are generally performed automatically by electrical impedance or optical diffraction techniques. Although differential counts are commonly performed by direct examination of 100 to 500 cells with the oil immersion lens of the microscope, automated techniques are becoming more popular. Normal values for the WBC count are listed in Table 110.1. The "normal" count is age dependent and may be shifted upward by exercise, female gender, smoking, or pregnancy. Similarly, certain ethnic populations such as Blacks have a lower total WBC count and neutrophil, with a higher percentage of monocytes and lymphocytes.[4] Laboratory errors may be due to improper sample preparation, nucleated red blood cells (RBCs), or platelet clumping. The blood smear differential count may also be influenced by small sample size, improper cell identification, and age group (children). Differential ranges are listed in Table 110.2. One

common yet easily corrected error in laboratory analysis is reporting of results in terms of the percentage of cell types. Absolute counts for each cell type are more accurate and useful in assessing the risk for infection.

Pathophysiology

Alterations in cell counts are due to changes in production, the marginal pool, or the rate of tissue destruction. The differential diagnosis of increased or decreased WBC counts can be organized by processes impacting production, destruction, loss, or sequestration. Decreased production is caused by suppression of the bone marrow secondary to chemotherapy, radiation therapy, or viral infections. Beta-lactam antibiotics, rheumatoid arthritis, and other autoimmune diseases can destroy neutrophils and reduce the WBC count. Overwhelming bacterial infections can deplete the supply of WBCs faster than the bone marrow can increase production, resulting in net loss. Finally, sequestration may occur secondary to ischemic reperfusion injury, major trauma, or other tissue insults.

Given the spectrum of anticipated values, WBC count determinations should be interpreted in the context of the overall clinical picture. A careful history and physical examination, absolute cell counts, and review of the peripheral smear differential counts are valuable in determining the origins of quantitative WBC disorders.

Leukocytosis, or elevation in WBC count, is most frequently caused by increases in the neutrophil or lymphocyte cell lines. Neutrophilic leukocytosis (neutrophilia) is defined as an absolute neutrophil count greater than 7500 cells/mm^3 and is commonly associated with infection or inflammation (Box 110.1). This is manifested as a "left shift" in the differential count and represents movement of immature neutrophils from the postmitotic pool into the circulation. Because infection or inflammation is also associated with heightened peripheral neutrophil destruction, the proportion of immature (band) to mature neutrophils may increase beyond the baseline ratio of 1 band to 10 mature neutrophils.

WBC counts can also increase through demargination of neutrophils from the vessel walls, which often occurs in response to physiologic stress, endogenous or administered epinephrine, and exercise.[5,6]

Leukopenia is a broad definition that indicates any reduction in the circulating WBCs. The term *leukopenia* is often used interchangeably with *neutropenia*, which specifically refers to a reduction of the neutrophil cell line. Neutropenia is the most clinically significant leukopenia.

By definition, adult neutropenia is defined as an abnormally low absolute neutrophil count (ANC), calculated by multiplying the WBC count by the combined percentage of segmented and band neutrophils. An ANC below 1500 cells/mm^3 is considered mild neutropenia, less than 1000 cells/mm^3 is moderate, and less than 500

TABLE 110.1 Normal Ranges for the Blood Leukocyte Count (cells/mm^3)[a]

Age	Average	95% Range (Average Value ±2 Standard Deviation)
1 week	12,200	5000–21,000
6 months	11,900	6000–17,500
12 months	11,400	6000–17,500
4 years	9100	5500–15,500
8 years	8300	4500–13,500
Adults	7400	4500–11,000

[a]Normal leukocyte count varies with ethnicity, age, gender, smoking, pregnancy, and aerobic exercise.
Modified from: Lanzkowsky P, Lipton JM, Fish JD. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*. Sixth ed. London: Academic Press; 2016.

BOX 110.1 Common Causes of Leukocytosis

Leukocytosis

Primary

Myeloproliferative disorders: Chronic myeloid leukemia (CML), polycythemia vera
Hereditary neutrophilia
Familial myeloproliferative disease
Chronic idiopathic neutrophilia
Leukemoid reaction

Secondary

Infection
Tissue necrosis: Cancer, burns, infarctions
Metabolic disorders: Diabetic ketoacidosis, thyrotoxicosis, uremia
Non-hematologic malignant disease
Physiologic stress: Exercise, pain, surgery, hypoxia, seizures, trauma
Drugs: Epinephrine, corticosteroids, lithium, cocaine
Laboratory error: Automated counters, platelet clumping, precipitated cryoglobulin

Lymphocytosis

Viral infection: Mononucleosis, rubeola, rubella, varicella, toxoplasmosis
Lymphoproliferative: Acute or chronic lymphocytic leukemia (ALL, CLL)
Immunologic response: Immunization, autoimmune diseases, graft rejection

TABLE 110.2 Normal Percentages for the Leukocyte Differential Count in Blood[a]

Age	Segmented Neutrophils	Lymphocytes	Monocytes	Eosinophils
1 week	45% (5500)	41% (5000)	9% (1100)	4% (500)
6 months	32% (3800)	61% (7300)	5% (600)	3% (300)
12 months	31% (3500)	61% (7000)	5% (600)	3% (300)
4 years	42% (3800)	50% (4500)	5% (500)	3% (300)
8 years	53% (4400)	39% (3300)	4% (400)	2% (200)
Adult	59% (4400)	34% (2500)	4% (300)	3% (200)

[a]Numbers in parentheses indicate the average number of cells per cubic millimeter.
Modified from: Lanzkowsky P, Lipton JM, Fish JD. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*. Sixth ed. London: Academic Press; 2016.

cells/mm^3 is severe. Severe neutropenia is a well-known risk factor for increased susceptibility to bacterial infection.

Clinical Features

WBC disorders often present with clinical features characteristic of the underlying cause of the WBC disorder (e.g., characteristics of inciting infection in the setting of leukocytosis). The exception is hyperleukocytosis (WBC >100,000/mm^3) which can result in leukostasis, a syndrome characterized by metabolic abnormalities, coagulopathy, and multiorgan failure.[7] Although any organ system may be affected, symptoms most often arise from involvement of the cerebral, pulmonary, or renal microvasculature. Central nervous system (CNS) signs and symptoms may include headache, confusion, lethargy, dizziness, blurred vision, ataxia, papilledema, and retinal or intracranial hemorrhage. Pulmonary signs and symptoms may include dyspnea, tachypnea, hypoxia, pulmonary infiltrates, or respiratory failure. Mechanical obstruction of the capillaries also commonly results in peripheral vascular occlusion, acute renal failure, or myocardial infarction.

Differential Diagnoses

Leukocytosis can be caused by primary WBC disorders, including myeloproliferative disorders, hereditary leukocytosis, congenital anomalies, or a leukemoid reaction, which is a pronounced leukocytosis associated with acute inflammation or infection that may be mistaken for leukemia. Secondary forms of leukocytosis are more common. Box 110.1 lists common causes of primary or secondary leukocytosis, as well as lymphocytosis.

Diagnostic Testing

A complete blood count (CBC) often identifies the WBC disorder. Coexisting anemia, thrombocytopenia, or thrombocytosis may also have diagnostic significance. For example, the presence of pancytopenia may indicate aplastic anemia and bone marrow failure due to bone marrow neoplastic disease, toxins, chemotherapy or radiation therapy, or an autoimmune disorder. Additional laboratory tests that may aid in the evaluation of a WBC disorder include a peripheral blood smear, sedimentation rate, or CRP. Peripheral blood smears allow the clinician to examine the cells and identify abnormal cell morphology. Elevation of the ESR or CRP may indicate occult infection and guide the emergency physician to initiate antimicrobial treatment. In the setting of hyperleukocytosis, a chest radiograph or neurologic imaging are often indicated, particularly if pulmonary or CNS signs or symptoms are present, respectively.

Automated hematology counters are increasingly able to quantify the number of immature granulocytes (IG) in the peripheral blood stream. IG measurements include granulocyte precursors other than band neutrophils. Elevation of IG may have a role in identifying patients with severe sepsis and other diseases associated with systemic inflammatory response syndrome.[8]

Management

The management of most WBC disorders is related to the underlying disease process. Hyperleukocytosis, however, is a hematologic emergency and efforts should be made to lower the WBC as rapidly as possible. Reduction in the WBC can be achieved with chemotherapy, often hydroxyurea, or leukapheresis. Rapid reduction with chemotherapy may induce the tumor lysis syndrome. Decisions regarding chemotherapy and leukapheresis should be made with a hematologist. Because the presence of pulmonary or CNS clinical features resulting from hyperleukocytosis is associated with a high mortality rate, leukapheresis is often the therapeutic modality of choice.[9]

Disposition

As WBC disorders are most commonly associated with an underlying disease process, patient disposition is dependent on the type and severity of the underlying cause.

SPECIFIC DISORDERS

Chronic Myeloid Leukemia

Foundations

Chronic myeloid leukemia (CML) accounts for approximately 10% to 15% of newly diagnosed adult leukemia, making it the least common of the major leukemias. The vast majority of cases arise from a genetic translocation, resulting in an aberration known as the Philadelphia chromosome. The initiating factor that triggers this somatic mutation remains unknown, but the mutation is found only in affected cells and is not inherited. The resulting peripheral blood smear in the chronic phase is characterized by myeloid cells in all stages of differentiation demonstrating a leukocytosis with immature myelocytes, metamyelocytes, band cells, and mature polymorphonuclear leukocytes (Fig. 110.1). Risk increases with age, with the median age of diagnosis between 57 and 60 years, with a slight male predominance. Overall, rates of diagnosis have remained stable over the last several decades.[10]

Clinical Features

Clinical staging of CML reflects progression through three phases in the absence of effective treatment: chronic, accelerated, and blastic. Symptom onset during the chronic phase tends to be insidious, with up to 50% of patients remaining asymptomatic at the time of diagnosis. Eventually, the abundance of immature cells begins to crowd out and impair the function of normal white and red blood cells, as well as platelets and other elements of the circulatory system. The most common presenting features in those who are symptomatic include GI features such as abdominal pain, decreased appetite, nausea, or early satiety resulting from hepatomegaly and splenomegaly. Significant left upper quadrant pain may result from splenic infarction. Hypermetabolism associated with the disease can result in fatigue, weight loss, diaphoresis, or low-grade fevers. Patients in the accelerated or blastic phase often present with abnormal bleeding and bruising, petechiae, bone pain, or fever. Fever in the late stages often results from opportunistic infection. Hyperleukocytosis and hyperviscosity are uncommon, and the more mature granulocytes seen in CML are less likely to result in leukostasis.

Late problems in the natural history of CML involve progressive loss of cell differentiation or response to therapy. The term *blastic crisis* represents the sudden appearance of an acute form of leukemia, which is rare and associated with poor outcomes.[11] The condition may occur in lymphoid or myeloid forms. Presenting signs and symptoms of blastic crisis are related to leukostasis and bone marrow infiltration and include anemia, abnormal bleeding due to thrombocytopenia, dyspnea, or neurologic symptoms. Prognosis remains poor despite intensive supportive treatment with chemotherapeutic agents.

Differential Diagnoses

The differential diagnoses include a leukemoid reaction or lymphocytic leukocytosis, including CLL or ALL. The initial presentation may be similar to that of CLL or ALL, though patients tend to be older, with WBC counts greater than 50,000 cells/mm^3 in CML. A leukemoid reaction is a nonleukemic reactive leukocytosis that resembles CML. It may be triggered by infection, including *Clostridium difficile* disease, nonhematopoietic neoplasm, or bleeding.[12]

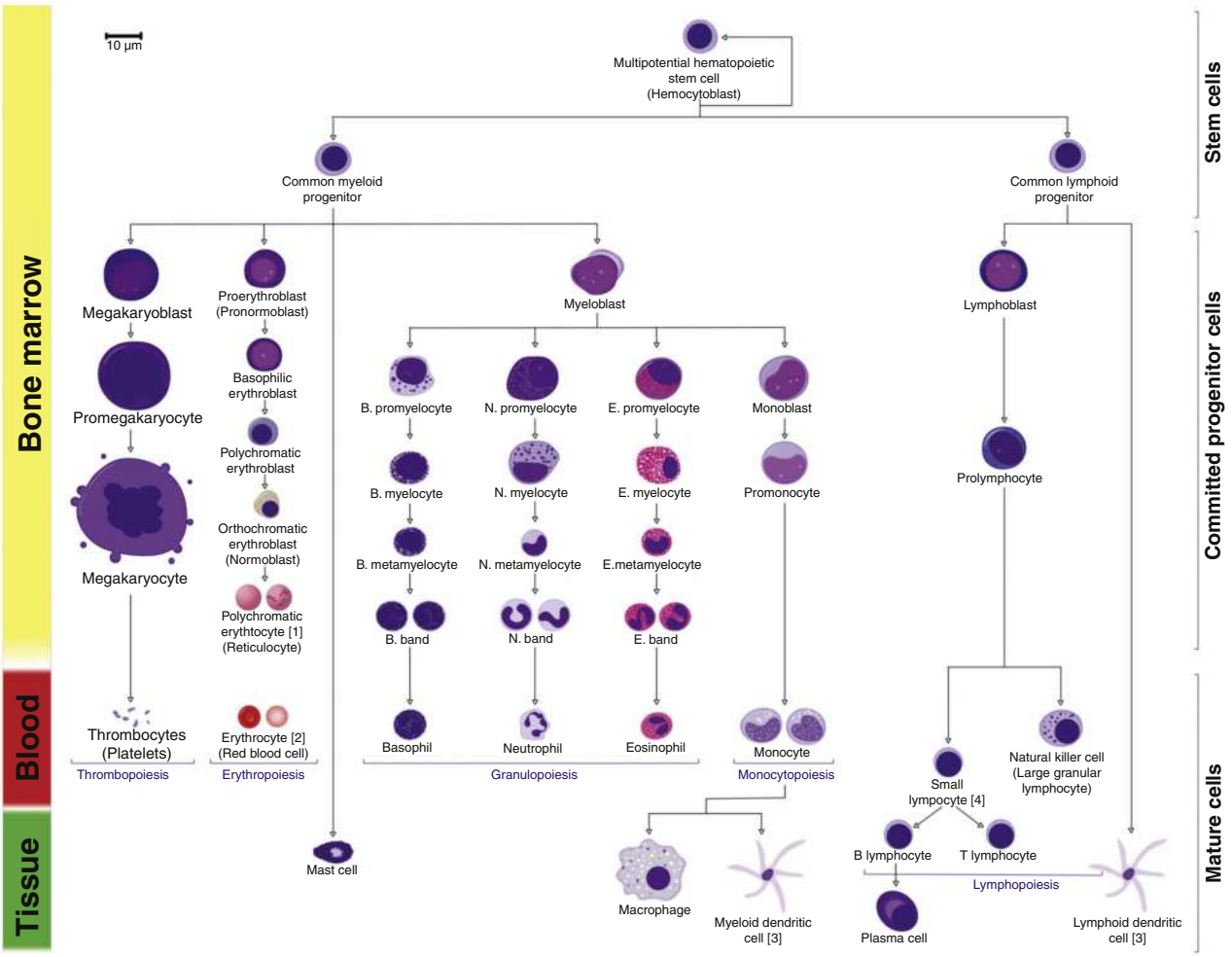

Fig. 110.1 Hematopoiesis, including myeloid and lymphoid cells in all stages of differentiation. Note immature myelocytes, metamyelocytes, band cells, as well as mature polymorphonuclear leukocytes present on the blood smear of patients with chronic myeloid leukemia. (From https://commons.wikimedia.org/wiki/Category:Mikael_Häggström/Medical_diagrams#/media/File:Hematopoiesis_(human)_diagram_en.svg.)

Diagnostic Testing

Associated laboratory abnormalities include a decreased leukocyte alkaline phosphatase and increased vitamin B_{12} levels, neither of which are associated with leukemoid reactions.

Management

Treatment for CML has evolved over the last several years to include the use of tyrosine kinase inhibitors (TKIs) that target the proteins that result from the Philadelphia chromosome genetic anomaly. Overall, survival has improved to the point where life expectancy nears that of the general population.[13] Patients in the accelerated phase may also respond to TKIs, although longer-term response to therapy tends to be limited. Patients in the blast phase may respond to chemotherapy agents targeted towards ALL, although long-term response is rare and palliative therapy may be indicated. Stem cell transplant, once a hallmark of treatment for CML, is rarely performed in the era of TKIs, though may be considered in young patients and in the setting of an accelerated or blast phase, or nonresponse to TKIs.

The need for urgent therapy in CML is usually related to hyperuricemia and renal injury, or severe anemia and subsequent angina or heart failure. Given the comparatively more mature, "less sticky" cells seen in CML, hyperleukocytosis rarely occurs unless WBC counts exceed 500,000 cells/mm^3. A higher cell count may cause leukostasis and result in deafness, visual impairment, pulmonary ventilation-perfusion abnormalities, or priapism. Treatment includes hydration, leukapheresis, allopurinol to prevent severe hyperuricemia, and specific chemotherapy. Given the risk of increased blood viscosity, red blood cell transfusion should be reserved for symptomatic anemia.[9]

Disposition

Asymptomatic patients should be promptly referred to an oncologist. Patients requiring urgent treatment for symptomatic anemia, leukostasis, or blast crisis will require hospitalization for emergent treatment, guided by oncology consultation.

Lymphocytic Leukocytosis

Foundations

The definition of lymphocytic leukocytosis (lymphocytosis) varies by age: greater than 9000 cells/mm^3 for ages 1 to 6 years, greater than 7000 cells/mm^3 for ages 7 to 16 years, and greater than 5000 cells/mm^3 for adults. It is seen in a variety of disorders, primarily infections or lymphoproliferative disease. The terms *acute* or *chronic* are currently utilized to describe the cell maturity, rapidity of onset, and aggressiveness of therapy. Chronic lymphocytic leukemia (CLL) is the most common

type of leukemia seen in individuals aged 50 years or older, and the most common leukemia seen in Western countries. The median age of diagnosis is 72 years. It is primarily a B-cell disorder, initiated by genomic alterations that impair apoptosis of clonal B cells. The disease is characterized by an accumulation of mature B lymphocytes in the peripheral circulation, bone marrow, lymph nodes, and spleen. The risk of developing CLL increases with age.[14]

Acute lymphocytic leukemia (ALL) is the most common cancer diagnosed in children. Like CLL, it is a clonal disease of the bone marrow, in this case characterized by proliferation of B-cell or T-cell precursors that ultimately crowd out and impair the development of other normal marrow elements. This results in anemia, neutropenia, and thrombocytopenia. Lymphoblasts outside the marrow result in lymphadenopathy, splenomegaly, or hepatomegaly. In pediatric ALL, an acquired or inborn genetic mutation creates susceptibility to the disease. It is theorized that a subsequent infection, toxin exposure, or other immune insult triggers further mutations that activates the disease process.[15] ALL is less common in older adults. The etiology of ALL in adults is less well understood and is related to genetic alterations that result in proliferation of lymphocyte precursors.[16]

Clinical Features

CLL is associated with a heterogenous presentation and clinical course. Patients are most often diagnosed after incidental findings such as an abnormal WBC count, enlarged lymph nodes, a palpable spleen, or an enlarged liver. Lymphadenopathy is common and seen in more than half of CLL patients at diagnosis, while splenomegaly is found in almost half. The most common symptoms are reflective of lymphocytic proliferation affecting other bone marrow cell lines and include fatigue and malaise, weight loss, decreased appetite, or decreased exercise tolerance. Signs include pallor, petechia, purpura, or other abnormal bleeding. Increased susceptibility to infection may be seen. The majority of patients follow an indolent clinical course, requiring either no treatment or delayed treatment once the disease becomes symptomatic. Rarely, patients experience aggressive early disease necessitating treatment and associated with recurrent relapses. The majority of patients have survival rates of 5 to 10 years, with increasing survival attributable to improvements in immunotherapy and chemotherapy.[17]

Although the symptoms commonly associated with ALL are nonspecific, persistence of symptoms may prompt further evaluation, particularly in the nonemergency setting. The potential for leukostasis increases in ALL when the blast count rises above 50,000 cells/mm^3.

Diagnostic Testing

The CBC may demonstrate a preponderance of B lymphocytes, with an absolute lymphocyte count greater than 5000 cells/mm^3 in adults. The diagnosis of CLL is confirmed when these B cells are determined to be monoclonal, either through flow cytometry or molecular assays.[18]

Abnormalities in ALL include anemia or thrombocytopenia. The WBC count may be normal, low or elevated, though the WBC differential will typically show diminished neutrophils at the expense of an increased percentage of lymphocytes. Definitive diagnosis is made through bone marrow aspiration and biopsy demonstrating proliferation of lymphoblasts. Immune and genetic testing help identify the disease subtype and specific cytogenetic-molecular abnormalities that may guide targeted therapy in order to improve survival.[19]

Management

Patients with CLL require treatment once they become significantly symptomatic. Progressive anemia or thrombocytopenia, symptomatic splenomegaly or lymphadenopathy, or rapid increase in lymphocytosis are indications for initiating treatment. Several treatment options exist, with multiple regimens of chemotherapy agents and monoclonal antibodies that may either be used as monotherapy or in various combinations. In patients aged 65 years or younger, combination chemoimmunotherapy is used and may have curative potential. Allogenic stem cell transplantation remains an option for high-risk patients, but is used less with the current availability of novel agents.[20] Hyperleukocytosis and leukostasis are rarely seen as complications of CLL, but when present warrant leuko-reduction via leukapheresis.

Multiagent chemotherapy regimens are effective in children, with complete remission seen in over 90% of patients. Adult ALL has a much poorer prognosis, with complete remission rates of only 20% to 40%. This is largely driven by intolerance to standard-dose chemotherapy regimens and high rates of myelosuppression-related complications and mortality.[16] The additions of tyrosine kinase inhibitors, monoclonal antibodies, and targeted immune therapies as treatment options appear to be improving remission and survival rates and are better tolerated by the elderly.[21] Adult patients who respond to initial chemotherapy were traditionally offered allogenic bone marrow transplant, though novel targeted and immune therapies lead to questions regarding the necessity of transplantation. Patient age, comorbidities, disease subtype, and genetics, as well as response to therapy all factor into decision making regarding transplant therapy.[22]

Leukopenia

Foundations

Leukopenia is a broad definition that indicates any reduction in the circulating WBCs. The term *leukopenia* is often used interchangeably with *neutropenia*, which specifically refers to a reduction of the neutrophil cell line. Neutropenia is the most clinically significant leukopenia.

By definition, adult neutropenia is defined as an abnormally low absolute neutrophil count (ANC), calculated by multiplying the WBC count by the combined percentage of segmented and band neutrophils. An ANC below 1500 cells/mm^3 is considered mild neutropenia, less than 1000 cells/mm^3 is moderate, and less than 500 cells/mm^3 is severe. Severe neutropenia is a well-known risk factor for increased susceptibility to bacterial infection.

Neutropenia may be caused by decreased production, impaired maturation, movement of circulating neutrophils into marginal or tissue pools, increased destruction, or artificially by laboratory error (Table 110.3). Neutropenia increases susceptibility to overwhelming infection. Infectious disease or drug-mediated reactions commonly cause neutropenia in adults. Common infectious etiologies include HIV, EBV, hepatitis, parasitic infections such as malaria, or bacterial sepsis.[23] Medications may cause an immune-mediated neutropenia by forming immune complexes or inducing antibody formation that destroys granulocytes, or by direct cytotoxic effects on the marrow stem cells or neutrophil precursors. Among cancer patients of all ages, treatment-associated neutropenia secondary to cytotoxic chemotherapy is the most common dose-limiting complication.[24] In children, the most common cause of acquired neutropenia is viral infection, followed by medications and autoimmune neutropenia. In healthy children, neutropenia typically resolves in step with resolution of viremia.

Clinical Features. Signs and symptoms of neutropenia are nonspecific and may include fatigue, sweats, or weight loss. Due to the body's inability to mount a substantial inflammatory or purulent response, symptoms of serious bacterial infection in neutropenic patients may be minimal or absent. The clinician should ask patients

TABLE 110.3 Linkage of Leukopenia to Phases of Neutrophil Maturation

Mechanism	Example
Proliferation in bone marrow	Aplastic anemia, leukemia, cancer chemotherapy (cyclophosphamide, azathioprine, methotrexate, chlorambucil) Drugs: Phenothiazines, phenylbutazone, indomethacin, propylthiouracil, phenytoin, cimetidine, semisynthetic penicillins, sulfonamides Infection: Viral, tuberculosis, sepsis
Maturation in bone marrow	Folate or vitamin B_{12} deficiency, chronic idiopathic neutropenia Starvation
Distribution	Hypersplenism: Sarcoidosis, portal hypertension, malaria
Increased use	Infection: Viral most common (mononucleosis, rubella, rubeola), *Rickettsia* organisms, overwhelming bacterial infection Autoimmune disease: Systemic lupus erythematosus, AIDS, Felty syndrome
Laboratory error	Leukocyte clumping, long delay in performing test

AIDS, Acquired immunodeficiency syndrome.

found to be neutropenic about their medication list, a personal or family history of neutropenia, as well as recent suspected infections or other illnesses. The physical examination is directed toward sites of infection, lymphadenopathy, hepatosplenomegaly, or underlying disease.

Diagnostic Testing and Management. Neutropenic fever, defined as a single oral temperature greater than or equal to 101°F (38.3°C) in a neutropenic patient, or greater than or equal to 100.4°F (38°C) for at least an hour, may herald a life-threatening infection and should prompt the initiation of a rapid workup and commonly the administration of broad-spectrum antibiotics. Neutropenic fever is common in those receiving chemotherapy, with up to 80% of patients developing it at least once during the course of treatment.[25] The evaluation should focus on identifying any infectious agents, with particular attention to common locations, such as the lungs, urine, or bloodstream. As such, consideration of chest radiography, urinalysis, and cultures of blood and urine remain prudent.

Disposition

The disposition for febrile neutropenic patients is evolving, and carefully selected patients may be eligible for discharge following ED evaluation. Although it remains the norm, inpatient treatment incurs significant costs and resource utilization, along with exposing the neutropenic patient to nosocomial pathogens. Select patients without significant comorbidities or signs of sepsis, and with reliable follow-up plans, may be considered for outpatient therapy. Disposition decisions should be made in conjunction with the patient's oncologist.[26] Septic patients will require hospitalization and neutropenic isolation precautions. Asymptomatic patients with incidental neutropenia can generally be referred for follow-up, which may include further investigation depending on repeat ANC or clinical course. Patients with a clear reversible source or without significant clinical findings and mild to moderate levels of neutropenia may have outpatient follow-up arranged, preferably after discussion with their physician.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 110: QUESTIONS AND ANSWERS

1. Which of the following statements best describes the use of the WBC count in emergency medicine decision making?
   - **a.** The absence of leukocytosis excludes the presence of significant disease.
   - **b.** The absolute neutrophil count, presence of bandemia, and immature granulocyte count may be more helpful than the total WBC count in identifying bacterial infection.
   - **c.** The total WBC count is both specific and sensitive for serious bacterial infection.
   - **d.** The WBC count is highly discerning in screening for illness in the acute care setting.

Answer: B. The WBC count and accompanying differential count are among the most common laboratory tests ordered in the ED. The WBC count has not proved to be a highly sensitive or specific test, and the absence of leukocytosis does not exclude the presence of significant disease. The WBC count has limited screening value in the acute care setting. The absolute neutrophil count or an elevated band count may be more helpful than the total WBC count in identifying bacterial infection. The immature granulocyte count can be used to help identify patients with or without sepsis.

2. Which of the following can affect the "normal" WBC count?
   - **a.** Age and ethnicity
   - **b.** Exercise
   - **c.** Gender
   - **d.** Tobacco use
   - **e.** All of the above

Answer: E. All of the statements are true. One unique problem in WBC disorders is the wide variability in normal values and the multiple factors influencing them. Normal values for the WBC count are listed in Table 110.1. The "normal" WBC count range is age-dependent and may be shifted upward by exercise, female gender, smoking, or pregnancy. Decreases in the total WBC count range by 1000 to 1200 cells/mm^3 have been noted in the Black population.

3. In evaluating a patient with severe neutropenia, which of the following is false?
   - **a.** If the patient is febrile, basic isolation techniques and specific therapies should be initiated after cultures are completed.
   - **b.** If the patient is febrile, urine and blood cultures should be obtained.
   - **c.** The clinician should ask about medications, history of neutropenia, family history, and also review information regarding recent infections.
   - **d.** The classic physical findings associated with infection will be obvious owing to the inflammatory response.
   - **e.** The review of systems focuses on bleeding problems, generalized symptoms such as fatigue, sweats, and weight loss, or autoimmune symptoms.

Answer: D. The classic physical signs of infection may be blunted in severe neutropenia, because the inflammatory or purulent response may be hampered by the limited numbers of neutrophils.

4. A patient with a known history of chronic myeloid leukemia (CML) presents with shortness of breath. The WBC count is 25,000 cells/mm^3. Which of the following conditions is LEAST likely to be the cause of the patient's dyspnea:
   - **a.** Angina
   - **b.** Heart failure
   - **c.** Hyperleukocytosis resulting in pulmonary ventilation-perfusion abnormalities
   - **d.** Renal failure and fluid overload
   - **e.** Severe anemia

Answer: C. Hyperleukocytosis can occur in CML, though the comparatively more mature, "less sticky" cells found in CML rarely cause problems unless the count exceeds 500,000 cells/mm^3. A higher cell count may cause leukostasis and result in deafness, visual impairment, pulmonary ventilation-perfusion abnormalities, or priapism. Treatment involves hydration, leukapheresis, transfusion as necessary, allopurinol to prevent severe hyperuricemia, and specific chemotherapy. The need for urgent therapy in CML is usually related to hyperuricemia and renal injury, or severe anemia and subsequent angina or heart failure.

5. When applied to lymphocytic neoplasms, the terms *acute* and *chronic* describe all of the following except:
   - **a.** Aggressiveness of therapy required in treatment
   - **b.** Cell maturity
   - **c.** Patient survival time
   - **d.** Rapidity of onset

Answer: C. Historically, *acute* and *chronic* were descriptive terms applied to lymphocytic neoplasms with respect to patient survival time. The terms *acute* and *chronic* are currently utilized to describe cell maturity, rapidity of onset, and aggressiveness of therapy required in treatment. Chronic lymphocytic leukemia (CLL) is primarily a B-cell disorder and is the most common form of leukemia in patients 50 years or older. Acute lymphocytic leukemia (ALL) is most commonly diagnosed in children younger than 10 years and is the most frequent malignant neoplasm in children younger than 15 years of age.

111

Disorders of Hemostasis

Jeremiah D. Gaddy and Alan A. Dupré

KEY CONCEPTS

- Although hemostatic disorders are confirmed through laboratory testing, a careful history and thorough physical examination may provide clues to the diagnosis.
- The use of antithrombotic agents remains widespread, whereas diseases such as hemophilia or disseminated intravascular coagulation (DIC) are encountered infrequently in the emergency department (ED) setting.
- Critical thrombocytopenia increases the risk of bleeding, particularly with trauma or invasive procedures. Platelet dysfunction may occur with platelet levels outside of or within the normal range. Aspirin therapy or renal disease, for instance, can cause platelet dysfunction in the setting of a normal platelet count.
- Patients with suspected new diagnosis of immune thrombocytopenic purpura (ITP) should typically be admitted for further management; glucocorticoid therapy is the mainstay of treatment.
- In patients with possible heparin-induced thrombocytopenia (HIT), clinical scoring systems are helpful in risk stratifying the possibility of HIT, prompting early cessation of heparin, alternative anticoagulation, and hematology consultation. Spontaneous HIT should be considered in patients following major surgery (typically an orthopedic procedure), or with recent serious infection.
- Thrombotic thrombocytopenic purpura (TTP) should be suspected if both thrombocytopenia and microangiopathic hemolytic anemia (MAHA) are identified. Early treatment includes plasma exchange therapy.
- Platelet transfusion is rarely indicated unless platelet counts are below 10,000/mm^3 or severe life-threatening bleeding occurs. Platelet transfusion should be avoided in the setting of thrombotic microangiopathies, such as TTP, hemolytic uremic syndrome (HUS), the "hemolysis, elevated liver function tests, and low platelets" (HELLP) syndrome complicating pregnancy, or HIT.
- Hemophiliacs are often highly informed about their disease. It is imperative that prompt intervention with replacement therapy occurs early when bleeding or the potential for bleeding is suspected. As a general rule, 1 U/kg of factor VIII will increase the circulating factor VIII level by 2%.
- Hemophilia with inhibitors creates a challenge for emergency resuscitation, and a treatment option is recombinant Factor VIIa.

FOUNDATIONS

Hemostasis is a dynamic process that is geared to preventing blood from escaping the boundaries of the vessel. This complex process occurs in phases: maintenance of vessel integrity, formation of a platelet plug, propagation of the coagulation cascade, subsequent clot development, followed by fibrinolysis and clot disintegration. Often the steps of platelet plug formation (primary hemostasis) and the coagulation process (secondary hemostasis) are utilized interchangeably, though the processes are distinctly unique yet collaborative. Common hemostatic abnormalities are acquired and result from iatrogenic causes such as medications (e.g., aspirin, warfarin, or direct thrombin inhibitor), from disease (e.g., hepatic insufficiency), and less frequently from congenital abnormalities. Disorders of hemostasis may result in hemorrhage. Identification and expeditious treatment of the underlying cause remains paramount.

Anatomy and Physiology

Vascular integrity is maintained by a lining of overlapping endothelial cells supported by a basement membrane, connective tissue, and smooth muscle. These cells are important in maintaining a barrier to macromolecules, secreting clot-preventing substances and, when injured, in contributing to the metabolic response and local vasoconstriction. The endothelium regulates clot formation by secreting substances such as tissue factor pathway inhibitor (TFPI) and heparin sulfate, preventing propagation of the coagulation pathway, as well as prostacyclin and nitric oxide, which prevent platelet aggregation and act as vasodilators. The endothelium also expresses CD39 (cluster of differentiation 39), which degrades adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP), a potent antiplatelet and antithrombotic, and adenosine, a potent locally acting platelet inhibitor that prevents platelet plug formation[1] (Fig. 111.1A). When the endothelium's physical barrier has been compromised, exposed von Willebrand factor (vWF) links to platelet glycoprotein Ib (gpIb) receptors allowing platelet adhesion to the intravascular surface. Normal inhibitory mechanisms are disrupted through damage to the endothelial cells, allowing ATP and ADP to interact with receptors to amplify platelet activation (Fig. 111.1B).

Platelets have multiple roles in hemostasis. They are complex cytoplasmic fragments released from bone marrow megakaryocytes largely regulated by thrombopoietin. After initial exposure to damaged endothelium, platelets display glycoproteins to aid in adhesion and aggregation, such as gpIb and gpIIa/IIIb. Platelets also contain lysosomes, microtubules, and granules, among other components. Granules contain over 300 metabolically active substances, including platelet factor 4, additional adhesive and aggregation glycoproteins, coagulation factors, and fibrinolytic inhibitors. Each participates in the process of coagulation and contributes to overall wound healing through the mediation of inflammation, immune response, and infection control. Platelet activity is summarized in Box 111.1. Any step in the platelet pathway may be absent, altered, or inhibited by inherited or acquired disorders. The coagulation cascade forms fibrin, and cross-linked fibrin serves to reinforce the initial platelet plug.

The coagulation pathway is a complex system of checks and balances that results in controlled formation of a fibrin clot. Coagulation factors are summarized in Box 111.2, and a simplified coagulation pathway is

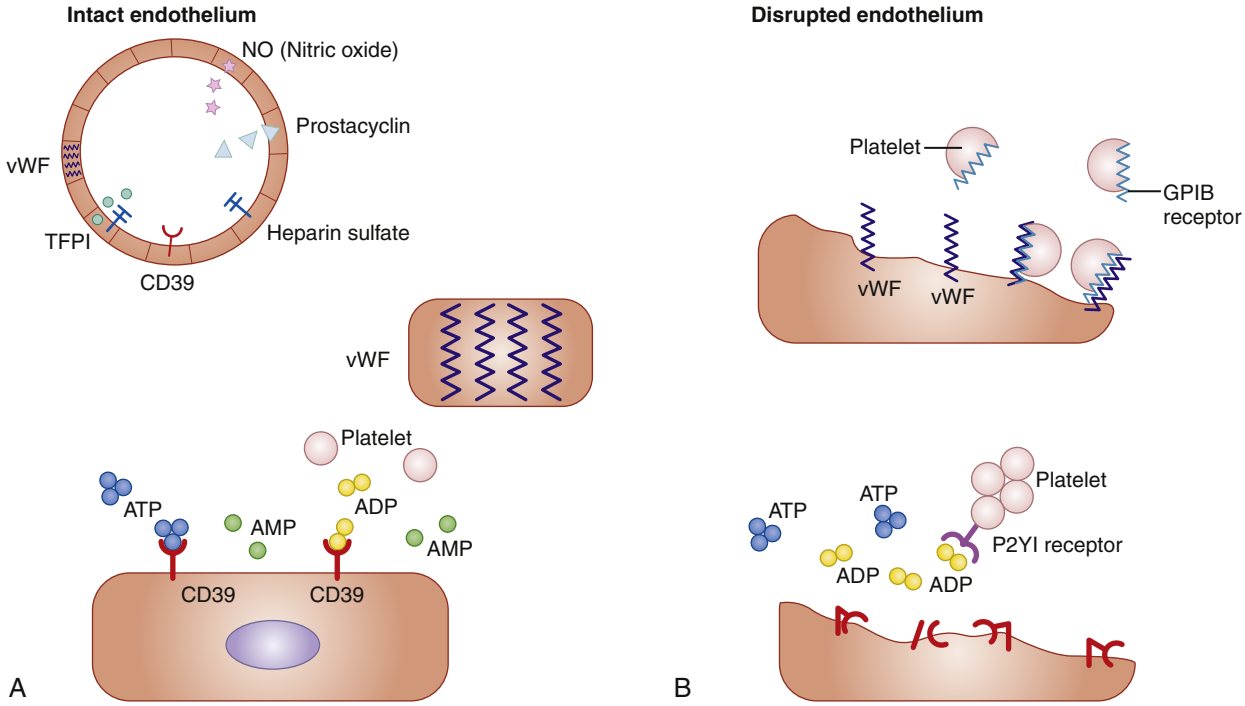

Fig. 111.1 (A) The endothelium regulates clot formation through expression of a number of substances including: CD39 (cluster of differentiation 39), which degrades adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP), a potent antiplatelet and antithrombotic, and adenosine, a potent locally acting platelet inhibitor that prevents platelet plug formation. (B) When the endothelium is injured the exposed von Willebrand factor (vWF) links to platelet glycoprotein Ib (gpIb) receptors allowing platelet adhesion to the intravascular surface and allowing ATP and ADP to interact with receptors to amplify platelet activation.

BOX 111.1 Role of Platelets in Hemostasis

1. Adhesion to subendothelial connective tissue: Collagen, basement membrane, and noncollagenous microfibrils; serum factor VIII and von Willebrand factor (vWF) permit this function; adhesion creates the initial bleeding arrest plug
2. Release of adenosine diphosphate, the primary mediator and amplifier of aggregation; release of thromboxane A, another aggregator and potent vasoconstrictor; release of calcium, serotonin, epinephrine, and trace thrombin
3. Platelet aggregation over the area of endothelial injury
4. Stabilization of the hemostatic plug by interaction with the coagulation system:
   - Platelet factor 3, a phospholipid that helps accelerate certain steps in the coagulation system
   - Platelet factor 4, a protein that neutralizes heparin
   - Pathway initiation and acceleration by thrombin production
   - Secretion of active forms of coagulation proteins
5. Stimulation of limiting reactions of platelet activity

BOX 111.2 Coagulation Factors

Factor I. Fibrinogen
Factor II. Prothrombin
Factor III. Tissue thromboplastin
Factor IV. Calcium
Factor V. Labile factor (proaccelerin)
Factor VI. Not assigned
Factor VII. Proconvertin
Factor VIII. Antihemophilic A factor
Factor IX. Antihemophilic B factor (plasma thromboplastin component, Christmas factor)
Factor X. Stuart-Prower factor
Factor XI. Plasma thromboplastin antecedent
Factor XII. Hageman factor (contact factor)
Factor XIII. Fibrin-stabilizing factor

presented in Figure 111.2. The clotting cascade is traditionally depicted as consisting of intrinsic and extrinsic pathways. A more modern approach is to view the extrinsic pathway as the initiation phase with exposed tissue factor at the site of vessel injury, and the intrinsic pathway as a parallel and amplification pathway. Both pathways converge to activate factor X, which then converts prothrombin to thrombin. Tissue factor is a critical cofactor that is required for activation of factor VII. Because of limited amounts of tissue factor and rapid inactivation by TFPI, the extrinsic pathway initiates the clot process, though sustained generation of thrombin and clot formation is dependent on the intrinsic pathway through activation of factor IX by activated factor VII. Once coagulation is initiated, controls are necessary to prevent overzealous local or generalized thrombosis (Box 111.3).

Pathophysiology

Hemostasis is dependent on normal functioning and integration of the vasculature, platelets, and coagulation pathway. The most commonly encountered disorder of hemostasis is antithrombotic drug administration, including use of antiplatelet or anticoagulant medications. Disorders of hemostasis may also be congenital, or secondary to disease states that affect the various steps of the hemostatic pathway

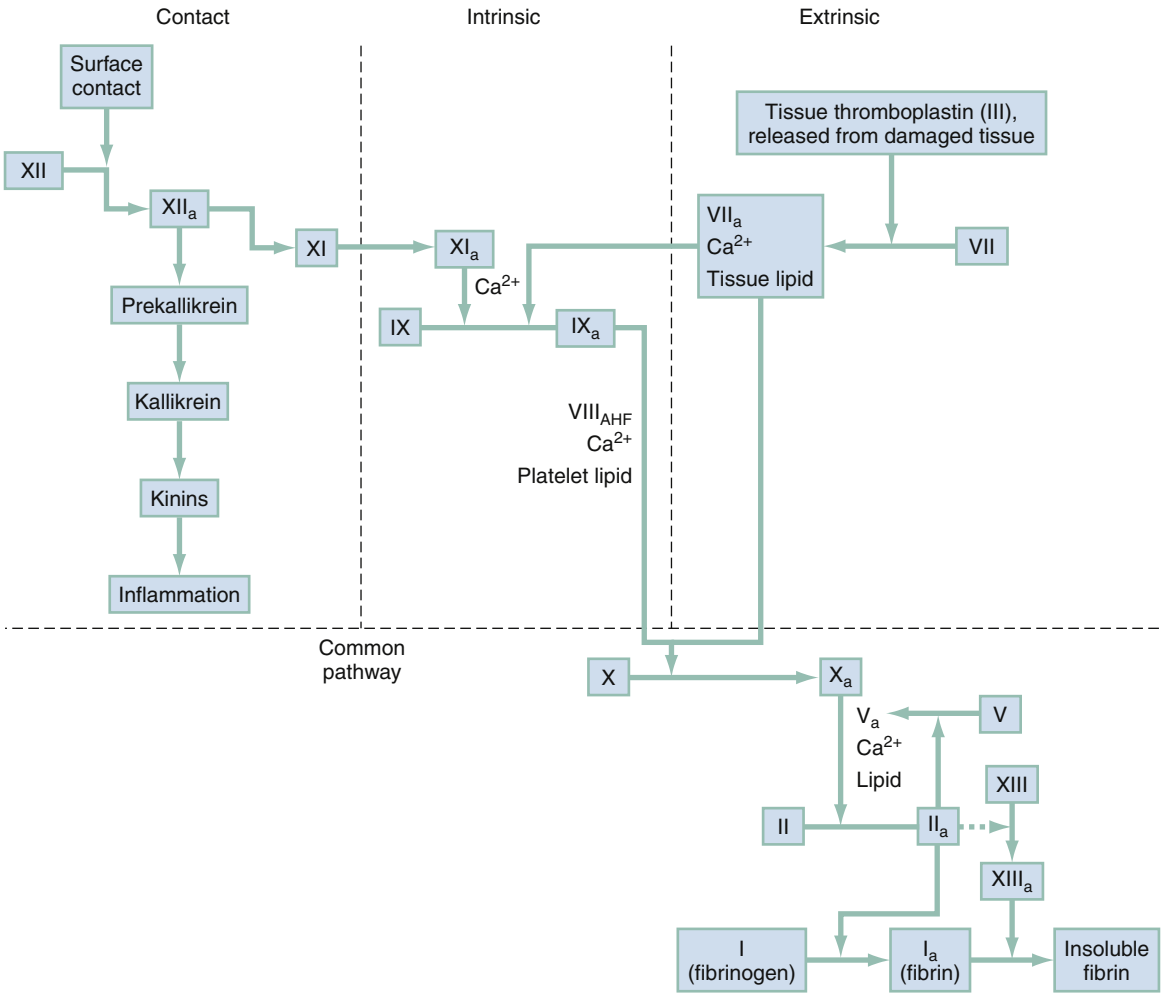

Fig. 111.2 Coagulation pathway.

BOX 111.3 Normal Controls of Coagulation

- Removal and dilution of activated clotting factors through blood flow, which also mechanically opposes growth of the hemostatic plug
- Alteration of platelet activity by endothelium-generated nitric oxide and prostacyclin
- Removal of activated coagulation components by the reticuloendothelial system
- Regulation of the clotting cascade by antithrombin III, protein C, protein S, and tissue factor pathway inhibitor (TFPI)
- Activation of the fibrinolytic system

such as malignancy or hepatic dysfunction. Due to the interconnectedness between the endothelium and platelets, vascular disorders may share similar historical or examination features with platelet disorders. Despite some overlap, disorders of hemostasis are frequently grouped into vascular disorders (often with a component of platelet dysfunction), platelet disorders, and coagulation disorders.

CLINICAL FEATURES

Disorders of hemostasis may become evident through hemorrhage that is out of proportion to what would otherwise be anticipated, excessive ecchymosis, or the presence of a petechial or purpuric rash. Hemostatic disorders may complicate any medical or traumatic problem, and platelet disorders or coagulopathy can rapidly develop in critically ill patients. Patients that fail to respond to usual hemostatic measures should be considered to have a potential bleeding disorder. When a bleeding disorder is diagnosed or suggested, the assessment initially includes stabilization, which may necessitate intravenous fluids, transfusion of red blood cells (RBC), or other blood component or factor replacement. In the setting of a known disorder, clinical complications associated with the underlying pathophysiologic condition must be considered. If the disorder is unknown, a rapid differential diagnosis should be pursued.

Key components of the history and physical examination are presented in Box 111.4. The history alone may in some cases be useful in differentiating between platelet and coagulation factor disorders.

Platelet disorders are usually manifested as acquired petechiae, purpura, or mucosal bleeding, and are more common in women. Platelet abnormalities can be caused by congenital disorders, though most are related to acquired conditions. The bleeding source is usually a capillary with resultant cutaneous and mucosal petechiae or ecchymosis. Epistaxis, menorrhagia, and gastrointestinal bleeding are common initial symptoms. The bleeding is generally mild and may occur immediately after surgery or dental extractions. The presence of petechiae or purpura may be noted on examination, and superficial ecchymoses may develop around venipuncture sites. The purpura associated with platelet disorders is typically asymptomatic and not palpable. This is

BOX 111.4 Clinical Evaluation of a Bleeding Patient

History

Nature of bleeding
- Petechiae
- Purpura
- Ecchymosis
- Significant bleeding episodes

Sites of bleeding
- Skin
- Mucosa: Oral or nasal
- Muscle
- Gastrointestinal
- Genitourinary
- Joints

Patterns of bleeding
- Recent onset or lifelong
- Frequency and severity
- Spontaneous or following injury

Challenges to hemostasis
- Dental extraction
- Operative or other invasive procedures
- Medications

Associated diseases
- Uremia: most commonly associated with platelet dysfunction
- Liver disease: most commonly associated with coagulation factor deficits
- Infection: could be associated with either platelet or coagulation deficits
- Malignant neoplasm: could be associated with either platelet or coagulation deficits

Previous transfusion history

Family history

Physical Examination

Vital signs

Skin: Nature of bleeding, signs of liver disease, petechial, purpura and distribution of skin abnormalities.

Mucosa: Oral or nasal, epistaxis

Lymphadenopathy

Abdomen: Liver size and shape, splenomegaly

Joints: Signs of previous bleeding (limited joint movement, pain mimicking osteoarthritis)

Other sites of blood loss: Pelvic, rectal, urinary tract, intramuscular or deep soft tissue

in contrast to purpura associated with vasculitis, which can burn or itch and is palpable. Vascular disorders such as vasculitis are associated with signs and symptoms similar to those of thrombocytopenic states. Inherited vascular disorders are rare, and acquired forms are usually associated with connective tissue changes or endothelial damage.

Coagulation issues may be congenital in nature, characterized by delayed deep muscle or joint bleeding, and occur more often in men. Clinically significant coagulation disorders have a number of characteristic features that help differentiate them from platelet disorders (Box 111.5).

DIFFERENTIAL DIAGNOSIS

The differential of platelet disorders is listed in Box 111.6. The differential of vascular disorders is listed in Box 111.7. The differential for coagulation disorders is listed in Box 111.8.

BOX 111.5 Features of Coagulation Disorders That Differentiate From Platelet Disorders

The bleeding source is often an intramuscular or deep soft tissue hematoma from small arterioles.

The congenital form of the disease occurs predominantly in men, often via sex-linked inheritance.

Bleeding may occur after surgery or trauma but may be delayed in onset up to 72 hours.

Epistaxis, menorrhagia, and gastrointestinal sources of bleeding are rare, whereas hematuria or hemarthrosis are common in severe cases.

The bleeding time is normal except in patients with von Willebrand disease (vWD).

BOX 111.6 Differential Diagnosis of Platelet Disorders

Decreased Platelet Count (Thrombocytopenia)

Decreased production
- Decreased megakaryocytes secondary to drugs, toxins, or infection
- Normal megakaryocytes with megaloblastic hematopoiesis or hereditary origin
- Platelet pooling and splenic sequestration

Increased destruction
- Immunologic
  - Related to collagen vascular disease, lymphoma, leukemia
  - Drug related
  - Infection
  - Post-transfusion
  - Immune thrombocytopenia
- Mechanical
  - Disseminated intravascular coagulation (DIC)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic-uremic syndrome (HUS)
  - Hemolysis elevated liver function tests & low platelets (HELLP) syndrome related to pregnancy
- Vasculitis

Dilutional secondary to massive blood transfusion

Platelet Dysfunction (Thrombocytopathy)

Adhesion defects such as von Willebrand disease (vWD)

Release defects: Acquired or drug related

Aggregation defects, such as in thrombasthenia

Elevated Platelet Count (Thrombocytosis)

Autonomous (primary thrombocythemia)

Reactive (secondary thrombocythemia)

Iron deficiency

Infection or inflammation

Trauma

Nonhematologic malignant disease

Post-splenectomy

Rebound from alcohol, cytotoxic drug therapy, folate or vitamin B_{12} deficiency

DIAGNOSTIC TESTING

A definitive diagnosis is dependent on laboratory evaluation. Tests pertinent to the ED setting are discussed in the following sections and are listed in Box 111.9.

BOX 111.7 Differential Diagnosis of Vascular Disorders

Inherited

Disorders of connective tissue
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome
- Osteogenesis imperfecta

Disorders of blood vessels
- Hemorrhagic telangiectasia

Acquired

Scurvy (vitamin C deficiency)
Simple or senile purpura
Purpura secondary to steroid use
Vascular damage
- Infection (meningococcemia)
- Hemolytic-uremic syndrome (HUS)
- Hypoxemia
- Thrombotic thrombocytopenic purpura (TTP)
- Dysproteinemic purpura

BOX 111.8 Differential Diagnosis of Coagulation Disorders

Inherited

Von Willebrand disease
Hemophilia A (factor VIII) or hemophilia B (factor IX)
Factor XIII, factor XI, factor X, factor VII, factor V or factor II deficiency
Afibrinogenemia/hypofibrinogenemia

Acquired

Medication
Snake bite (venom-induced consumptive coagulopathy)
Liver disease
Disseminated intravascular coagulation (DIC)
Autoimmune disorders (including autoantibodies towards factors such as fibrinogen)
Acquired factor inhibitors, from treatment of congenital disorder such as hemophilia, or malignancy

BOX 111.9 Diagnostic Hemostasis Tests

Complete blood count and smear (EDTA—purple top)
Platelet count (EDTA—purple top)
Bleeding time
Prothrombin time/International normalized ratio (PT/INR; citrate—blue top)
Partial thromboplastin time (PTT; citrate—blue top)
Other coagulation studies: Fibrinogen level, anti-factor Xa assay, thrombin time, clot solubility, factor levels, inhibitor screens
As necessary: Serum electrolyte levels; serum glucose, BUN, and creatinine concentrations; type and crossmatch

BUN, Blood urea nitrogen; *EDTA,* ethylenediaminetetraacetic acid.

Complete Blood Count and Blood Smear

The complete blood count can, in some cases, assess the degree of anemia associated with a bleeding episode. Reductions in hemoglobin and hematocrit often lag behind the actual loss of RBCs in acute hemorrhage owing to the time necessary for equilibration. The peripheral blood smear may demonstrate schistocytes or fragmented RBCs in microangiopathic hemolytic anemias, such as TTP or DIC. Teardrop-shaped or nucleated RBCs may reflect myelophthisic disease where hematopoietic bone marrow is infiltrated and replaced by fibrosis, tumors, or granulomas. Characteristic white blood cell morphologies are seen with thrombocytopenia associated with infectious mononucleosis (e.g., increased WBC cytoplasm and nucleoli in the nuclei), folate or vitamin B_{12} deficiency (e.g., hypersegmented neutrophils), or leukemia (e.g., immature WBCs, hairy cell lymphocytes, and myeloblasts with Auer rods).

Platelet Count

The platelet count may be estimated from the peripheral blood smear. Normally, one platelet is present per 10 to 20 RBCs. Often, the count is automated with a normal reference range of 150,000 to 400,000/mm^3. Thrombocytopenia is defined as a platelet count of less than 100,000/mm^3. With normal platelet function, the bleeding time with platelet counts below 100,000/mm^3 increases in direct relation to the level of thrombocytopenia. Levels below 20,000/mm^3 may be associated with serious spontaneous hemorrhage. However, the platelet count provides no information regarding platelet function.

Bleeding Time and Platelet Function Assay

Historically, bleeding time was considered the best test to determine both vascular integrity and platelet function. A normal bleeding time is 8 minutes. A bleeding time of 8 to 10 minutes is borderline, and a bleeding time longer than 10 minutes is considered abnormal. However, bleeding time is insensitive in identifying medication-related platelet dysfunction, Von Willebrand disease (vWD), or in predicting surgical bleeding. Many institutions have replaced the traditional bleeding time with a platelet function analyzer instrument, which is more convenient, with improved clinical value. The platelet function assay has been found to be highly sensitive in detecting moderate to severe vWD, medication-related platelet dysfunction, or severe platelet function disorders. Although less sensitive to mild disease, the platelet function assay is useful in detecting platelet pathology relevant to the emergency clinician. Given the pervasiveness of drug-induced platelet dysfunction, it is critical to inquire about the use of medications, particularly aspirin and other antiplatelet medications (e.g., clopidogrel). Platelet function testing is independent of the coagulation pathways.

Prothrombin Time

The PT tests the factors of the extrinsic and common coagulation pathways. The patient's anticoagulated plasma is combined with calcium and tissue factor protein. Sensitivity to factor deficiencies depends on the source of the tissue factor. The PT is capable of detecting deficiencies in fibrinogen, prothrombin (factor II), factor V, factor VII, and factor X. Results are reported in seconds or as the prothrombin ratio. To generate the prothrombin ratio, the time in seconds of the sample is given over the time of a normal control, for example, 12.5/11.5. Results are also usually reported as the international normalized ratio (INR), which compensates for differences in sensitivity of various thromboplastin reagents to the effects of warfarin by calculating the prothrombin ratio raised to the power of an international sensitivity index for specific thromboplastin reagents. The test is helpful in monitoring the use of coumarin anticoagulants, and the time may be prolonged in patients with liver disease or other abnormalities of vitamin K–sensitive factors.

If all other test results are normal with an abnormal prothrombin time, the elevated PT reflects an extrinsic pathway abnormality mediated through deficiency of factor VII. The hereditary form, congenital proconvertin deficiency, is caused by a rare autosomal recessive

gene on chromosome 13. The acquired form is commonly seen and may be a result of vitamin K deficiency, warfarin use, or liver disease. Given factor VII's short half-life (3 to 5 hours), it is typically the first to manifest a deficiency when its active form is underproduced. The PT is a sensitive gauge of hepatic function and the efficacy of warfarin administration. It is recommended with routine warfarin therapy that the INR level is maintained between 2.0 and 3.0, except in the setting of cardiac valvular disease, in which the target INR level is usually in the 2.5 to 3.5 range.

Partial Thromboplastin Time

The PTT tests the components of the intrinsic and common pathways, essentially all factors but factor VII and factor XIII. In this test, a phospholipid source and a contact-activating agent (kaolin) are added to anticoagulated citrate plasma. After an incubation period that allows factor XII to become activated, calcium is added and the clotting time is recorded. A normal control sample is run simultaneously. Normal ranges may vary by laboratory. The average time is 25 to 29 seconds. The sensitivity of the test varies from factor to factor, though factor levels less than 40% are typically required before the PTT is prolonged. The test may be altered by clotting factor inhibitors of external origin (e.g., heparin) or internal origin (e.g., anti–factor VIII antibody). Spurious high values may occur in the setting of heightened plasma turbidity. The activated PTT is most sensitive to abnormalities in the sequence of the coagulation cascade preceding activation of factor X.

Two groups of inherited disorders manifest as an isolated elevation in the PTT. The first group involves deficiencies of the contact factors, including factor XII (Hageman factor), prekallikrein (Fletcher factor), and high-molecular-weight kininogen. They may cause a relatively benign disorder in which the PTT is elevated but the patient has no bleeding diathesis. These deficiencies exist as isolated laboratory abnormalities, and thus they should not be invoked as a cause of the patient's bleeding problem. They may be specifically assayed when a precise diagnosis is necessary. The second group causes significant bleeding problems resulting from deficiencies of factors within the intrinsic coagulation system. They are the most common inherited abnormalities of the clotting system. Deficiencies of factors VIII, IX, and XI account for 99% of inherited bleeding disorders. Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be supported with fresh frozen plasma, 15 mL/kg, while additional information is being obtained and initial diagnostic studies are being performed.

In a patient with a prolonged PTT and a lifelong history of bleeding, the most important test is an assay of factor VIII and factor IX. This test measures the ability of the patient's plasma to correct the prolonged PTT of plasma deficient in a given factor. This ability is compared with that of normal plasma, and the result is given as a percentage of normal. These tests measure the procoagulant activity of the factor, although they do not discriminate between diminished activity resulting from abnormal factor VIII versus lower levels of normal factor VIII. Factor VIII deficiency is found in both hemophilia A and vWD, and factor IX deficiency is found in hemophilia B.

Anti-Xa Assay

The anti-Xa assay is a chromogenic assay that may be available to emergency clinicians for monitoring of unfractionated and low-molecular-weight heparin levels, or drug quantification of direct factor Xa inhibitors such as rivaroxaban and apixaban. When monitoring heparin levels, the test should ideally be performed 3 to 4 hours after medication administration for peak level monitoring. Because this test is not subject to the same variability as the PTT, it has become an attractive alternative as costs of the assay have declined in recent years. The test is considered the reference standard for measurement of in vivo heparin activity, and presently represents the only reliable means of quantifying rivaroxaban and apixaban drug levels.

Fibrinogen

Fibrinogen is the final coagulation substrate, and its level reflects the balance between production and consumption. It may be decreased by low production, as in severe liver disease, or by overconsumption, as in DIC. Low levels or altered function increase the PT, PTT, and thrombin clotting time. Because fibrinogen is an acute-phase reactant, certain conditions, including malignant disease, sepsis, inflammation, or pregnancy, may impact fibrinogen levels.

Thrombin Time

Measurement of the thrombin clotting time bypasses measurement of the intrinsic and extrinsic pathways by directly analyzing conversion of soluble fibrinogen to insoluble fibrin. It is a useful screening test for both qualitative and quantitative abnormalities of fibrinogen and inhibitors, such as heparin and fibrin split products. The test is also an available means to measure drug activity of direct thrombin inhibitors, such as dabigatran.

Clot Solubility

The result of clot solubility testing may be the only abnormality in disorders involving factor XIII deficiency, which has a role in cross-linking fibrin to stabilize the fibrin clot. A washed clot is incubated in acetic acid or urea. If the fibrin clot is not properly cross-linked by factor XIII, it dissolves.

Factor Level Assays

Factor levels are determined either by bioassay, in which the ability of the sample of plasma to normalize controlled substrate-deficient plasma is evaluated, or by immunologic assay. Inhibitor screening tests reveal antibodies in plasma that prolong the normal plasma clotting time when mixed. Inhibitors may play a disruptive role in disease states such as hemophilia or when associated with certain malignancies.

MANAGEMENT

Thrombocytopenia

Thrombocytopenia can be grouped into two main causes: decreased production or increased destruction. Most experts agree that thrombocytopenia is defined as a platelet count of less than 100,000 micro/mm^3. Thrombocytopenia from decreased bone marrow production is usually caused by the effects of chemotherapeutic drugs, myelophthisic disease, or direct bone marrow effects of agents, such as alcohol or thiazides. Splenic sequestration is a rare cause of thrombocytopenia seen primarily with hypersplenism resulting from malignant hematologic disease, portal hypertension, or disorders involving increased splenic red blood cell (RBC) destruction, such as hereditary spherocytosis, autoimmune hemolytic anemia, or sickle cell disease.

Most platelet disorders are not treated by platelet transfusion, as its efficacy is questionable and alloimmunization may occur. Platelet transfusions are commonly indicated for primary bone marrow disorders (e.g., aplastic anemia or acute leukemia). Assessment of the risk for spontaneous bleeding due to thrombocytopenia is an imprecise science. In contrast to disorders with primary bone marrow involvement, less mature platelets associated with peripheral consumption or sequestration generally have more robust functionality and thus patients are less prone to spontaneous hemorrhage. An estimate of platelet functionality is combined with the platelet count for a more accurate prediction of primary hemostasis potential. At counts higher than 50,000/

BOX 111.10 Immune Thrombocytopenia Chronicity

Newly diagnosed: Up to 3 months since diagnosis
Persistent: 3 to 12 months since diagnosis
Chronic: Over 12 months since diagnosis

mm^3, hemorrhage attributed to platelet deficiency is unlikely. At counts below 40,000/mm^3 to 50,000/mm^3, a variable degree of risk exists, particularly in the setting of trauma, gastric ulcers, or invasive procedures. Spontaneous bleeding in the absence of surgery, trauma, or other risk factors is more likely when platelet counts reach below 10,000/mm^3, thus prophylactic platelet infusions should typically be reserved for this degree of thrombocytopenia; however, this threshold may be lower in stable pediatric patients but should initiate hematology consultation.[2] Patients requiring urgent central venous access or lumbar puncture may require platelet transfusion if the count is less than 20,000/ mm^3 or 50,000/mm^3, respectively.[2] Although literature is sparse, platelet transfusion is generally recommended for patients requiring neurosurgical or invasive ophthalmologic intervention if counts are less than 80,000 to 100,000/mm^3.[2]

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is a broad acquired condition that results from autoantibodies against platelet antigens. ITP includes the diseases previously termed idiopathic thrombocytopenic purpura and autoimmune thrombocytopenic purpura. ITP is further broken down into separate categories: primary ITP; secondary ITP, typically resulting from pathogens, disease states, or malignancy; and drug-induced thrombocytopenia (DITP).

Primary ITP is an acquired autoimmune thrombocytopenia that has no apparent trigger or associated condition, and can result in both increased destruction as well as decreased platelet production. Severe ITP is characterized by a platelet count of less than 20,000 micro/mm^3. ITP is further characterized as newly diagnosed, persistent, or chronic (Box 111.10). The acute form of ITP is seen most often in children aged 2 to 6 years old. A viral prodrome commonly occurs within 3 weeks preceding its onset. The platelet count decreases, usually to less than 20,000/mm^3. The course is self-limited, with a greater than 90% rate of spontaneous remission. Morbidity and mortality rates are low, although full recovery may take several weeks. The chronic form of ITP is primarily an adult disease found three times more often in women. The onset of chronic ITP is insidious, generally without a prodrome, and is manifested as easy bruising, prolonged menses, and mucosal bleeding. Petechiae or purpura are common, with platelet counts typically between 30,000/mm^3 and 100,000/mm^3.

Secondary ITP results from various infectious or other chronic disease states. Autoimmune disease, particularly systemic lupus erythematosus and rheumatoid arthritis, may cause an antiplatelet antibody-related thrombocytopenia. Similar associations have been noted with leukemia and lymphoma, particularly lymphocytic lymphoma. Postinfectious immune thrombocytopenia is usually associated with viral diseases, such as HIV, hepatitis (HBV or HCV), Epstein-Barr virus (EBV), rubella, rubeola, or varicella.

DITP is caused by drug-dependent platelet antibodies, which is a distinct mechanism from drugs that cause direct bone marrow suppression. Numerous drugs have been associated with DITP, and the resulting thrombocytopenia is expected to resolve after discontinuation of the offending drug. Owing to its relatively high frequency of use, heparin is an important cause of drug-induced thrombocytopenia in hospitalized patients.

ITP treatment is often supportive, with treatment recommendations distinguished between adult and pediatric patients. Corticosteroids are recommended for newly diagnosed adult patients with platelet counts of less than 30,000/ mm^3 who are asymptomatic or have only minor mucocutaneous bleeding. Dexamethasone, 40 mg PO or IV daily for 4 days, is the preferred glucocorticoid. Admission for further diagnostic evaluation may be considered for newly diagnosed adult patients with platelet counts of less than 20,000 mm^3.[3] IVIG in addition to corticosteroids should be considered for patients with platelet counts of less than 10,000 mm^3, significant bleeding, or when a more rapid increase in platelet count is necessary, such as the need for surgery or invasive procedure. Use of glucocorticoids with IVIG can be associated with a more sustained response than with IVIG alone.[3] If IVIG is indicated, a one-time dose of 1 g/kg should be given. A thrombopoietin receptor agonist (TPO-RA), such as eltrombopag, should be considered for life threatening bleeding in the setting of inadequate response to corticosteroids, IVIG, and platelet transfusion. Because eltrombopag takes days to weeks to normalize platelets, this will rarely be given in the emergency department and discussion with a hematologist would be prudent. Plasmapheresis and recombinant factor VIIa are no longer recommended.[4] Splenectomy is often considered a last resort for ITP that is refractory to medical management.[3]

Pediatric patients with newly diagnosed ITP and only mild bleeding (skin manifestations) can typically be managed without medication, even when platelet counts are less than 20,000 mm^3.[3] Though the overall platelet count is low, a relatively high fraction of newly minted platelets with robust functionality is seen in the circulation, thus patients remain at relatively low risk for significant spontaneous hemorrhage. Admission should be considered when there is uncertainty regarding the diagnosis or lack of close follow-up. Prednisone, IVIG, or anti-D immunoglobulin are available options for pediatric patients with newly diagnosed ITP.[3] As with adult patients, IVIG can be considered if there is a need for a more rapid correction of the platelet count. Treatment options should be discussed with the child's pediatrician or a pediatric hematologist.

Drug-Induced Thrombocytopenia

A number of drugs have been associated with thrombocytopenia of immunologic origin. Quinine and quinidine are common offenders that affect platelets through an "innocent bystander" mechanism. The platelet is coated with a drug-antibody complex, complement is fixed, and intravascular platelet lysis occurs. Beta lactams, quinolones, digoxin, sulfonamides, phenytoin, and aspirin may also be associated with thrombocytopenia, usually within 24 hours of use. Clinical trials with platelet glycoprotein IIb/IIIa antagonists show an increased risk for associated thrombocytopenia, independent of heparin therapy.[5] The platelet count may fall below 10,000/mm^3 and be complicated by serious bleeding. Laboratory testing may confirm the presence of antibody, especially with the use of quinine and quinidine.

DITP is difficult to discern from ITP, especially during the initial evaluation by the emergency clinician. In DITP, the platelet count should improve within the first 1-2 days of cessation of the offending drug, and return to normal range within a week. In the setting of active bleeding with thrombocytopenia of unclear cause, corticosteroids, IVIG, and possibly platelet transfusion in selected patients are all considerations.

Heparin-Induced Thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated process associated with unfractionated heparin (UFH) and other forms of heparin such as low-molecular-weight heparin (LMWH). Heparin is thought to pair with platelet factor 4 (PF4), a procoagulant substance found in platelet granules. This paired complex results in rapid generation of

TABLE 111.1 4Ts Scoring System

4Ts	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥ 20	Platelet count fall 30–50% or platelet nadir 10–19	Platelet count fall < 30% or platelet nadir < 10
Timing of Platelet Count Fall	Clear onset between days 5–10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear; onset after day 10; or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count fall < 4 days without recent exposure
Thrombosis or Sequelae	New thrombosis (confirmed) or skin necrosis; acute systemic reaction post-intravenous unfractionated heparin (UFH) bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not proven)	None
Other Causes of Thrombocytopenia	None Apparent	Possible	Definite

TABLE 111.2 4Ts Point Risk Stratification

Total Points	Probability
<3 points	Low probability
4–5 points	Intermediate probability
6–8 points	High probability

antibodies, which coat platelets resulting in thrombocytopenia. The antibodies generated also activate platelets, thus creating a potential hypercoagulable state. Approximately 33% to 50% of patients with HIT will develop HIT with thrombosis (HITT).[6] A HIT-like reaction may also occur in the absence of exposure to heparin.

The overall risk for HIT ranges from 0.1% to 7.0% in patients receiving heparin.[6] The risk of HIT is related to drug and dosage factors, including duration of exposure (risk greatest following 5 days of heparin therapy), heparin type (UFH carries higher risk than LMWH), or dosage (greatest risk with higher doses). In addition, female patients are at twice the risk, and surgical or trauma patients have a higher risk for HIT than medical patients. Delayed HIT occurs a median of 14 days following the initiation of heparin, though may occur up to 40 days out.

The 4Ts Score for HIT is aimed at differentiating patients with HIT from those with alternative causes of thrombocytopenia (Tables 111.1 and 111.2).[6,7] Patients are stratified into low, intermediate or high risk based on degree of thrombocytopenia, timing of onset, presence of thrombosis, and other possible etiologies for the thrombocytopenia. For patients with intermediate or high risk for HIT based on 4Ts Score, heparin should be stopped and an immunoassay ordered. Most anti-PF4-heparin enzyme immunoassays have excellent negative predictive value, thus an unremarkable result effectively rules out HIT.[6] If the immunoassay is positive, a more specific functional test, such as a serotonin release assay, a heparin-induced platelet aggregation assay, or a solid-phase immunoassay, is indicated to confirm the diagnosis.

Current treatment recommendation for HIT is geared primarily toward management of thrombotic complications. If HIT is clinically suspected, immediate cessation of heparin is paramount. Vitamin K antagonists have been shown to increase thrombosis risk and potential for limb loss by decreasing the level of the endogenous anticoagulant protein C upon initiation.[6] Treatments for HIT include non-heparin anticoagulants, such as argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC).[6] Argatroban has US Food and Drug Administration (FDA) approval for HIT, has quick onset of action, and has the most evidence supporting its use and thus is the most widely utilized anticoagulant for the treatment of HIT. Danaparoid is an alternative available outside of the United States. Recently there has been evidence supporting the safety and efficacy of DOACs for HIT or HITT. Rivaroxaban is the most well studied though favorable results have been shown with apixaban and dabigatran as well.[8] Current recommendations suggest that argatroban or bivalirudin may be preferred in the setting of increased bleeding risk, critical illness, or the need for urgent procedures.[6] For patients with normal hepatic function and who are not critically ill, the initial dose of argatroban is 2 mcg/kg/min IV. An aPTT should be drawn after 2 hours with goal to be 1.5 to 3 times the baseline aPTT. For patients with compromised hepatic function (bilirubin >1.5 mg/dL), cardiac surgery, anasarca, or who are critically ill, the recommended dosage range is 0.5 to 1.2 mcg/kg/min IV with the same aPTT. In addition to anticoagulation, evidence is increasing regarding the utility of IVIG for severe HIT.[9,10]

Post-Transfusion Purpura

Post-transfusion purpura (PTP), also known as post-transfusion thrombocytopenia, is a rare disorder that causes a precipitous fall in platelets approximately one week following transfusion. It is frequently linked to human platelet antigen 1 (HPA1) on platelets, although other antigens have also been implicated. When an HPA1 antigen–negative patient receives a platelet transfusion, the platelets with attached HPA1 antibodies provoke an anamnestic response, though the actual mechanism of platelet destruction is uncertain. Patients are usually middle-aged women with a history of prior pregnancy, during which they may have been previously sensitized to the HPA1 antigen. The platelet count often falls precipitously below 10,000/mm^3, with a significant associated risk of major bleeding.

High-dose IVIG, 1g/kg IV, is considered the first-line treatment for patients with severe thrombocytopenia or major bleeding. Glucocorticoids may be given with IVIG. Plasma exchange therapy is no longer considered a preferred therapy. Transfused platelets are often rapidly destroyed, thus platelet transfusion is generally not recommended except in the setting of severe thrombocytopenia and life-threatening bleeding, preferably with HPA1-negative blood products.

Thrombotic Microangiopathy

Thrombotic microangiopathies (TMA) represent a group of disorders that are characterized by their clinical presentation of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, and confirmed by histopathology or other specific tests. Microvascular thrombosis leads to abnormalities in the vessel wall of arterioles or capillaries, leading to consumption of platelets and destruction of RBCs. Presence or severity of clinical symptoms guide treatment decisions. There are many systemic disease states that have characteristics similar to TMA, and

TABLE 111.3 Plasmic Score

Criteria	Response	
Platelet count < 30×10^9/L	No (0 point)	Yes (1 point)
Hemolysis (Reticulocyte count > 2.5%, haptoglobin undetectable, or indirect bilirubin > 2.0 mg/dL)	No (0 point)	Yes (1 point)
Active cancer or treated for cancer within the past year	No (1 point)	Yes (0 point)
History of solid organ or stem cell transplant	No (1 point)	Yes (0 point)
MCV < 9.0×10^{-14} L (<90 fL)	No (0 point)	Yes (1 point)
INR < 1.5	No (0 point)	Yes (1 point)
Creatinine < 2.0 mg/dL	No (0 point)	Yes (1 point)

TABLE 111.4 Plasmic Risk Stratification

Total Score	Risk
0–4 points	Low risk. Consider alternative diagnosis
5 points	Intermediate risk. Consult hematology and consider plasma exchange
6–7 points	High risk. Consult hematology and immediate plasma exchange

treatment is focused on the underlying disease. The most common primary TMA disorders include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS).

Thrombotic Thrombocytopenic Purpura. TTP is most often acquired and results from autoantibodies to ADAMTS13, an endothelial protein that cleaves large vWF multimers. Large vWF multimers increase adhesiveness to platelets, and large VWF-platelet aggregates can form microthrombi inducing tissue ischemia, platelet consumption, and MAHA.[11] TTP is rarely inherited, including disorders such as Upshaw-Schulman syndrome. HUS shares some similarities to TTP, and is generally associated with less central nervous system and more renal involvement than TTP. The first acute episode of TTP often occurs during adulthood (approximately 90%), and occurs twice as frequently in women.[12] HUS, on the other hand, frequently occurs in children, often after a gastrointestinal illness. TTP is classically, though not always, seen as a constellation of thrombocytopenia, MAHA (schistocytes seen on blood smear), and fluctuating neurologic symptoms such as mental clouding or confusion. It may be associated with cardiac (25% of the time) or mesenteric ischemia (35%), resulting in abdominal pain or diarrhea. Acute renal manifestations consist mainly of proteinuria or hematuria and rarely acute renal failure.[12] This is in contrast to HUS, where acute kidney injury is common. For patients with thrombocytopenia and MAHA, the PLASMIC score should be utilized in hospitalized patients to identify candidates for early initiation of treatment with plasma exchange (Tables 111.3 and 111.4).[13] The differential diagnosis for TTP includes HUS or other TMA syndromes associated with sepsis, malignancy, or pregnancy (HELLP).

Prior to the availability of plasma exchange, TTP followed a progressive and often fatal course, with a 90% mortality rate within a few months of diagnosis. Therapeutic plasma exchange is now the standard treatment, often with accompanying glucocorticoids.[11] Typical glucocorticoid dosage for patients without neurologic deficits or cardiac ischemia is prednisone 1 mg/kg PO daily. If patient is considered to be in severe condition, 1 g methylprednisolone intravenously for 3 days may be considered. If TTP is suspected, hematologist involvement is essential prior to initiation of therapies. Addition of rituximab may be considered in patients who are refractory to standard treatment, though its use in the acute phase of TTP is still debated. Additionally, caplacizumab (11 mg IV initial dose, followed by 11 mg subcutaneously daily for 10 days) may also be advantageous to add to the standard treatment of plasma exchange and immunosuppression.[11] With the exception of life-threatening bleeding, platelet transfusion is avoided, as platelets may cause additional thrombi in the microcirculation. Current trials are assessing the effectiveness of N-acetylcysteine, recombinant ADAMTS13, or an inhibitor of VWF-glycoprotein Ib binding.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia as a complication of massive transfusion, exchange transfusion, or fluid resuscitation. Current guidelines for 1 : 1 : 1 ratio of fresh frozen plasma (FFP), platelets, and RBCs may assist in alleviating dilutional thrombocytopenia in the setting of massive transfusion.

Hereditary Thrombocytopenia and Thrombocytopathy

Hereditary thrombocytopathy and thrombocytopenic syndromes are not as rare as once thought. It has been suggested that as many as 1 in 7 patients initially diagnosed with ITP have a hereditary thrombocytopenic syndrome.[14] This may in part explain the variable success rates in the treatment of ITP. A detailed history is important, as patients diagnosed with thrombocytopathy may have at least one family member who has been treated with splenectomy for presumed ITP. Inherited thrombocytopenias are often characterized by platelet size (large, normal, or small). A blood smear is helpful in evaluating platelet size and granules. Further evaluation with light transmission aggregometry or specific tests may also be necessary.

Thrombocytopathy. Knowledge of abnormal platelet function as a clinical disorder has grown rapidly in recent years, with identified disorders of platelet adhesion, aggregation, or granule secretion.

Adhesion Defects. Bernard-Soulier Syndrome (BSS) results from an abnormality in the platelet gpIb complex, which allows platelet adhesion to vWF and thus the subendothelium.

Aggregation Defects. Glanzmann thrombasthenia (GT) is a rare autosomal-recessive disorder that results from a defect in the integrin complex glycoprotein IIb/IIIa. This protein complex is important for platelet aggregation via fibrinogen. The glycoprotein IIb/IIIa complex is the site of action for particular antiplatelet agents utilized, often employed during percutaneous coronary intervention procedures.

Secretory Defects. Secretory defects comprise two pathologic groups: defective platelet granule formation or defective secretory machinery. These include "storage pool" syndromes with decreased amounts of adenosine diphosphate, calcium, and serotonin. Congenital disorders such as Hermansky-Pudlak syndrome will often be associated with other systemic features including immune or pigmentation defects. Other secretory defects may be acquired, such as in association with systemic lupus erythematosus, alcoholism, or lymphoma. Various medications may induce secretory issues. Aspirin blocks the enzyme cyclooxygenase, which participates in thromboxane A_2 formation. Decreased release of thromboxane A_2 results in diminished platelet aggregation and reduced local vasoconstriction.

Despite the advances in the diagnosis of inherited platelet disorders, little progress has been made in targeted therapies for specific platelet disorders. There has been an increase in use of tranexamic acid (TXA) for mucocutaneous bleeding, menorrhagia, or epistaxis. Patients with severe thrombocytopenia and bleeding may benefit from platelet transfusion, though this recommendation is limited to severe bleeding due to the risk of developing antibodies or platelet alloimmunization. Platelet transfusions should preferably include human leukocyte

antigen (HLA) matching and leukocyte depletion. Desmopressin has traditionally been utilized for the theoretical benefit of increasing factor VIII and VWF in patients with a diagnosed thrombocytopathy, but with only equivocal success in BSS, no evidence for benefit in GT, and variable response rates in secretory disorders.

Thrombocytosis

Thrombocytosis is defined as a platelet count of greater than 600,000/mm^3 (Box 111.6). It is frequently secondary to infection or iron deficiency, and in these circumstances, thrombocytosis is generally not associated with other platelet-related complications. Primary (or autonomous) thrombocytosis may lead to thrombosis or bleeding, resulting from high numbers of dysfunctional platelets. Primary thrombocytosis is associated with polycythemia vera, myelofibrosis, and chronic myelogenous leukemia, or Kawasaki disease in children. Primary thrombocytosis requires a thorough hematologic evaluation.

Coagulation Disorders

Hemophilia A

Hemophilia A is caused by a deficiency of factor VIII. Most cases are sex-linked recessive in nature, as the disease is carried on the X chromosome. The prevalence of hemophilia A is approximately 17 cases per 100,000 males, with approximately 1,125,000 affected worldwide.[15] Approximately 13,500 people in the United States have hemophilia A.[16] The severity of hemophilia is categorized by factor VIII activity level. Severe hemophilia is less than 1% of normal factor activity, moderate is 1% to 5%, and mild is 5% to 40%. Approximately 42% of cases are considered severe.[16] The more severe, the more likely the patient will need replacement factor VIII. Patients with severe hemophilia require more replacement therapy and have an increased risk to develop alloantibodies, termed inhibitors, that may serve to inactivate factor VIII and may therefore limit replacement therapy. Recombinant DNA technology currently supplies most factor utilized for replacement therapy, though there is evidence that plasma-derived factor VIII has reduced immunogenicity and is associated with a lower incidence of inhibitor development.[17] Emicizumab is a recombinant immunoglobulin that substitutes for part of the function of activated factor VIII and is utilized for prophylactic treatment. It works by bridging activated factor IX and factor X to restore the function of missing activated factor VIII that is necessary for effective hemostasis. Factor VIII typically circulates in low concentrations in plasma bound to vWF. Given this close relationship, a diagnosis of vWD may present with similar symptoms.

Hemophilia is seen as a disorder of secondary hemostasis with a characteristic pattern of bleeding. Bleeding can occur anywhere, though deep muscles, joints, the urinary tract, and intracranial sites are the most common. Recurrent hemarthrosis and progressive joint destruction are major causes of morbidity. Intracranial hemorrhage (ICH) is a major cause of death in all age groups, and studies indicate probabilities for ICH of 1 in 50,000 to 1 in 140,000 male patients.[18] Mortality from ICH remains around 20% in hemophiliacs.[19] Mucosal bleeding, such as epistaxis, oral bleeding, or menorrhagia, remain rare unless associated with comorbid vWD or platelet dysfunction, such as occurs with aspirin use. Gastrointestinal bleeding is rare unless peptic ulcer disease is present. Trauma is a common initiator of bleeding irrespective of perceived severity and the bleeding may be delayed for days or weeks following initial injury. As such, a careful history of distant or seemingly negligible trauma should be included.

Comprehensive management of hemophilia involves a team effort including physicians, specialized nursing, physical therapy, social work, as well as the patient and their caregivers. ED management of hemophilia is best accomplished with advanced planning, including protocols for the administration of factor VIII developed in collaboration with a hematologist. Emergency clinicians should have rapid access to relevant information, including primary care physician, hematologist, diagnosis, factor VIII activity level, blood type, antihemophilic factor antibodies (inhibitor) status, and date of last hospitalization.

BOX 111.11 Indications for Factor Replacement in Hemophilia

- Suspected bleeding into a joint or muscle
- Any significant injury to the head, neck, mouth or eyes
- Any new or unusual headache, particularly following trauma even if seemingly minor
- Severe pain or swelling at any location
- All wounds that require surgical closure (sutures, staples), wound adhesive, or Steri-Strip placement
- History of blunt trauma that might result in bleeding
- Prior to any invasive procedure or surgery
- Suspicion of uncontrolled GI bleeding leading to anemia or signs or symptoms of hypovolemia
- Acute fractures, dislocations or sprains
- Suspicion of uncontrolled heavy menstrual bleeding, leading to anemia or signs or symptoms of hypovolemia

The severity of hemophilia, with last known factor level, as well as inhibitor status, must be considered with any bleeding in a patient with hemophilia. Many patients are well versed in their disease and often come prepared with their own treatment. The emergency clinician should institute early therapy for patients in whom bleeding is suspected. It is advisable to engage the patient's hematologist, if able, prior to initiating therapy.

Treatment decisions should be based on the *suspicion* of a bleeding related complication (Box 111.11).[20] Factor replacement therapy may need to be administered prior to diagnostic studies, particularly if ICH is suspected.

Replacement typically includes recombinant-derived factor VIII, or alternatively the patient's usual product of choice. Plasma-derived concentrate is a suitable alternative in an emergency situation. Cryoprecipitate or fresh frozen plasma are no longer generally recommended unless faced with life-threatening bleeding without alternatives.

Desmopressin can be used for patients with documented mild hemophilia A without inhibitors who are experiencing bleeding that is not life or limb threatening. Desmopressin raises factor VIII by three to six times baseline levels. This therapy should be reserved for situations when there is history of a prior favorable hemostatic response.[20] With suspicion for more significant bleeding, treatment follows as for other forms of hemophilia A.

As a general rule, 1 U/kg of factor VIII will increase the circulating factor VIII level by 2%. If the patient has a known recent factor level, this may be utilized into the calculation. In emergent therapy, however, the present factor VIII level is presumed as zero. Factor VIII activity goals are typically 40% to 50% for minor bleeding or trauma, and 80% to 100% for serious or life-threatening bleeding or trauma. Table 111.5 provides guidelines for treatment in patients without inhibitors.[21] Because the half-life of factor VIII is 8 to 12 hours, the desired level is maintained by giving half of the initial dose every 8 to 12 hours.

The response to therapy can be monitored by clinical improvement, a decreasing PTT, and, optimally, serial factor VIII activity levels. Of note, aPTT-based assays including clot-based FVIII activity assays should not be performed if patients are on emicizumab as it will artifactually shorten aPTT and elevate FVIII activity.[22] The lack of a response to factor VIII administration should raise suspicion for the presence of

TABLE 111.5 Recommended Factor VIII Therapy and Dosing for Complications Associated With Hemophilia

Type of Bleeding	Initial Dosage	Comment
Skin		
Abrasion	None	Treat with local pressure and topical tranexamic acid
Superficial laceration	Usually none; if closure is needed then then 25 U/kg	Local pressure and tranexamic acid may benefit; watch 4 hours after suturing; reexamine in 24 hours
Deep laceration	25 U/kg	May need hospitalization for observation; repeated dose may be necessary for suture removal
Superficial muscle hematoma	25 U/kg	May be complicated by local pressure on nerves or vessels; monitor for compartment syndrome
Deep muscle hematoma (e.g., iliopsoas)	50 U/kg	May be complicated by local pressure on nerves or vessels; monitor for compartment syndrome if in an extremity
Epistaxis		
Spontaneous	Usually none; but if persistent, consider 25 U/kg	Uncommon; consider platelet inhibition; treat in usual manner and consider tranexamic acid application
Traumatic	25 U/kg to 50 U/kg	Trauma-related bleeding can be significant. Consider 50 U/kg given head trauma and possible development of ICH.
Oral		
Mucosa or tongue bites or other similar minor injuries	Usually none; treat with 25 U/kg if bleeding persists	Saliva is rich in fibrinolytic activity; oral ε-aminocaproic acid (Amicar) may be given as 5 g (or 100 mg/kg) during the first hour, then 1 g per hour for 8 hours or until bleeding is controlled to block fibrinolysis; oral tranexamic acid may also be used (25 mg/kg) PO every 6 to 8 hrs, check for contraindications (patients receiving PCC or high risk of thrombosis); hospitalize patients with severe bleeding
Traumatic oral lesion (laceration) or dental extraction	25 U/kg to 50 U/kg	Saliva is rich in fibrinolytic activity; oral ε-aminocaproic acid (Amicar) may be given as 5 g (100 mg/kg) during the first hour, then 1 g per hour for 8 hours or until bleeding is controlled to block fibrinolysis; oral tranexamic acid may also be used (25 mg/kg) PO every 6 to 8 hrs, check contraindications (patients receiving PCC or high risk of thrombosis); hospitalize patients with severe bleeding
Hemarthrosis		
Early or moderate	25 U/kg	Treat at earliest symptom (pain); knee, elbow, ankle more common
Late hemarthrosis or nonresponsive to earlier treatment	40 U/kg	Arthrocentesis rarely necessary, immobilization is a critical component of therapy
Hematuria	25 U/kg	Painless hematuria should be treated with bed rest and hydration. With persistent hematuria, an anatomic cause should be excluded. Antifibrinolytics are not recommended as they prevent lysis of clots in the ureter causing serious obstructive uropathy.
Major/Life-Threatening Bleeding	50 U/kg	Administer on the suspicion of a major or life threatening bleed.

inhibitors. Up to 20% of patients develop IgG inhibitor antibodies, and usually have a severe deficiency necessitating multiple factor VIII infusions. The treatment may be complex, thus discussion with a hematologist or hospitalization may be necessary. A variety of therapies have been considered, and current treatments of choice include bypassing agents or immune tolerance induction.[23] In the emergency care setting, generally the safest immediate action is to administer recombinant factor VIIa at a dose of 90 mcg/kg IV. For patients not currently on emicizumab, an additional consideration is activated prothrombin complex concentrate at a dose of 75 to 100 units/kg IV.[20]

Hemophilia B (Christmas Disease)

Hemophilia B is a deficiency of factor IX activity. Its genetic pattern and clinical findings are indistinguishable from those of hemophilia A, but its incidence is only a fifth that of hemophilia A. Factor IX is a vitamin K–dependent glycoprotein. Its deficiency is diagnosed by a factor IX assay, usually after the factor VIII assay is found to be normal.

Clinical presentations and treatment strategies associated with hemophilia A also generally apply to hemophilia B, including those for patients who have developed inhibitors. The replacement factor therapy is similar to that for hemophilia A, with use of a recombinant factor IX preparation. Plasma-derived concentrate is a suitable alternative in an emergency situation when recombinant factor IX is unavailable. Fresh frozen plasma is not routinely recommended for hemophilia B treatment, and cryoprecipitate does not contain factor IX. Given the comparatively longer half-life of factor IX, the maintenance factor dosing schedule is every 24 hours. When bleeding is severe, the appropriate dose of factor IX is 100 to 140 units/kg IV, which should result in a factor level of 80% to 100%. For hemophilia B with inhibitors, the safest immediate action is recombinant factor VIIa at a dose of 90 mcg/

kg IV. For those not currently on emicizumab, an additional consideration is activated prothrombin complex concentrate at a dose of at 75 to 100 units/kg IV.[20] As with hemophilia A, a hematologist should be included in the decision making as soon as is feasible.

von Willebrand Disease

Von Willebrand disease is the most common hereditary bleeding disorder, with an estimated prevalence of 1%. Quantitative or qualitative deficits in vWF are associated with clinical findings. Platelet adhering properties or factor VIII activity may be altered in vWD.

Manifestations of vWD are usually milder and less debilitating than those of hemophilia. The factor VIII activity level is in the 6% to 50% range. Bleeding sites are predominantly mucosal or cutaneous. Hemarthroses are rare, and menorrhagia and gastrointestinal bleeding are common.

Desmopressin, 0.3 mcg/kg IV, is of benefit in patients with mild to moderately severe vWD. Desmopressin is the preferred treatment for patients with mild to moderately severe disease, given its low risk profile and low cost. Adjunctive antifibrinolytic agents, such as tranexamic acid, have also shown benefit in vWD. In extreme circumstances, fresh frozen plasma or cryoprecipitate may be utilized. Severe vWD, with very low or absent vWF levels, is rare (1–5%) and presents early in life.

In patients with severe vWD, or in those with mild to moderately severe vWD who do not respond to desmopressin, replacement therapy with factor VIII in the form of lyophilized concentrate of factor VIII/vWF at a dose of 50 IU/kg is indicated. A unique response to the transfusion of plasma components in patients with vWD is the stimulation of a progressive increase in factor VIII activity that lasts 12 to 40 hours. After the initial dose, fewer units are necessary, and longer dosage schedules may be followed by clinical or laboratory response.

Miscellaneous Coagulation Disorders

A number of other disorders may be caused by deficiencies in the coagulation pathway. An altered level, or abnormal function, of fibrinogen may occur, leading to an abnormal thrombin time. The inherited forms are rare, and acquired forms are associated with fibrin-blocking substances or hypofibrinogenemia, which are found most often in the setting of DIC, or dysfibrinogenemia associated with macroglobulinemia, multiple myeloma, or hepatoma.

Rare inherited deficiencies may occur with other components of the common pathway (factors II, V, and X). Acquired forms are far more common and typically relate to vitamin K deficiency or warfarin use (decreased factor II, VII, IX, and X activity), hepatic insufficiency (potentially all factors except factor VIII), or massive transfusion of stored blood (low in factors V and VIII).

Medication-Induced Anticoagulation

The use of oral anticoagulants for conditions such as atrial fibrillation or venous thromboembolic disease continues to rise. Oral anticoagulation includes vitamin K antagonists such as warfarin, as well as the increasingly utilized direct-acting oral anticoagulants (DOACs). The first to gain FDA approval, dabigatran, is a direct thrombin inhibitor. Other common DOACs include rivaroxaban and apixaban, which are selective factor Xa inhibitors. Patients with impaired renal or liver function may experience excessive anticoagulation in the setting of DOAC use. Excessive anticoagulation related to warfarin occurs from a number of causes, including interactions between warfarin and other drugs or foods, or accompanying conditions that may interfere with its absorption or metabolism. Patients may present to the ED for concerns regarding supratherapeutic dosing of anticoagulants or for hemorrhage.

BOX 111.12 Critical Sites for Hemorrhage in Anticoagulated Patients

- Intracranial
- Intraocular
- Spinal
- Pericardial tamponade
- Airway (including posterior epistaxis)
- Thorax
- Intra-abdominal bleeding
- Retroperitoneal hematoma
- Intramuscular
- Intra-articular

Bleeding related to heparin therapy is less of an issue in the ED setting, though still can occur (e.g., patient coming from a dialysis center). In addition to discontinuation of heparin, protamine sulfate can urgently reverse the effects of heparin. The full neutralizing effect of UFH is achieved with 1 mg of protamine for every 100 units of heparin. Protamine can also be utilized in an attempt to reverse the effects of LMWH, though in a less predictable or complete fashion as occurs with UFH. This is an off-label use and should be considered in life-threatening bleeding and, if possible, discussed with a hematologist. In this setting, the dose of protamine is 0.5 to 1 mg for every 1 mg of LMWH depending on timing of last administration; if ≤8 hr, use 1 mg, if >8 hr, use 0.5 mg. Administration of protamine should not exceed more than 50 mg over 10 minutes, as more rapid injection may result in adverse effects including hypotension.

In the setting of over-anticoagulation or hemorrhage related to DOAC use, management has shifted with the more recent development of drug-specific reversal agents. Careful consideration of the risk of thromboembolic events weighed with the benefits of bleeding cessation must be taken into account. If bleeding occurs in critical sites (Box 111.12) or is associated with hemodynamic compromise, then reversal should be strongly considered.[24] For dabigatran, the FDA-approved reversal agent idarucizumab, 5 g IV, can be administered. If idarucizumab is unavailable, consider activated prothrombin complex concentrate (aPCC) at a dose of 50 units/kg IV. 4F-PCC has been studied in vitro, and healthy volunteer studies but not prospectively with dabigatran-associated bleeding at this time. If aPCC is unavailable, then 4F-PCC is a reasonable alternative.[24] 4F-PCC (K-centra) includes factors II, VII, IX and X along with protein C and S whereas aPCC such as Factor Eight Inhibitor Bypass Agent (FEIBA) has inactive factors II, IX, X, and activated VII. In addition, dialysis may be considered for dabigatran, as approximately 57% of the drug is removed with 4 hours of dialysis. Caution needs to be exercised in dialysis catheter placement, however. For apixaban or rivaroxaban, the FDA-approved reversal agent for use in life-threatening bleeds is andexanet alfa.[25] An alternative to andexanet alfa is 4F-PCC at a dose of 25 to 50 units/kg IV, or a fixed dose of 2000 units IV. aPCC has been studied in vitro, and healthy volunteer studies but not prospectively with oral factor Xa–associated bleeding at this time.[26] If no andexanet alfa or 4F-PCC is unavailable, then aPCC is a reasonable alternative for life-threatening bleeding. For other DOACs, such as edoxaban or betrixaban, off-label use of andexanet alfa is a possible intervention, or use of 4F-PCC at a dose 50 units/kg or fixed dose of 2000 units IV.

Management of excessive anticoagulation from warfarin depends on the degree of elevation of the INR and whether there is accompanying bleeding (Table 111.16). If the INR is below 4.5 and not accompanied with bleeding, treatment consists of withholding additional warfarin. If the INR level is between 4.5 and 10 without bleeding, we recommend holding additional warfarin doses for 1 to 2 doses. There

TABLE 111.6 Treatment for Supratherapeutic INR

INR Level/Bleeding	Recommendation
Major, life-threatening bleeding	Cessation of warfarin Vitamin K 10 mg (IV over 30 minutes)
Any INR	4F-PCC (KCENTRA) (See dosage in Table 111.7)
INR > 10, active bleeding	Cessation of warfarin Vitamin K 10 mg (IV over 30 minutes) 4F-PCC (KCENTRA) 50 U/KG, maximum dose 5000 units.
INR > 10, no bleeding	Cessation of warfarin Vitamin K 5 mg oral
INR 4.5 < 10, no bleeding	Cessation of warfarin If higher risk of bleeding or lower chance of thromboembolism, consider vitamin K 2.5 mg oral
INR < 4.5, no bleeding	Cessation of warfarin

TABLE 111.7 4F-PCC Dosage for Warfarin Reversal in Major Bleeding

Baseline INR Level	4F-PCC Dosage
INR 2 < 4	25 U/KG, maximum dose 2500 units
INR 4 < 6	35 U/KG, maximum dose 3500 units
INR > 6	50 U/KG, maximum dose 5000 units

are differing opinions on whether or not a small dose of 1.0 to 2.5 mg of oral vitamin K is indicated. It appears reasonable to give to those patients with a higher chance of bleeding or lower risk of thromboembolism vitamin K.[27,28] Treatment for patients presenting with an INR level above 10 but not bleeding includes holding warfarin and treating with 5 mg of oral vitamin K. Patients presenting with an elevated INR and active bleeding require cessation of warfarin, 10 mg of vitamin K IV, plus the administration of 4F-PCC or fresh frozen plasma (Table 111.17).[24,27] Vitamin K can be administered orally, intravenously, or subcutaneously. Oral dosing is superior to other routes of administration, and subcutaneous dosing is the least desirable method of administration owing to erratic serum level. Intravenous vitamin K given should be administered as a slow infusion over 20 to 30 minutes rather than a rapid bolus injection.

Disseminated Intravascular Coagulation

DIC is a relatively common acquired coagulopathy reflecting dysregulated coagulation and fibrinolytic pathways. Hemostasis is normally achieved by a fine balance between procoagulants and inhibitors, and thrombus formation and lysis. This balance may be disturbed by multiple pathologic processes, most often encountered in the critical care setting, resulting in DIC. The abnormal clotting sequence observed in DIC is shown in Box 111.13. Its ubiquitous nature, multiple origins, and potentially devastating sequelae, combined with potentially effective treatment modalities, make early diagnosis critical.

The clinical consequences include the potential for a life-threatening combination of bleeding from loss of platelets and clotting factors, fibrinolysis, and fibrin degradation product interference; small-vessel obstruction and tissue ischemia from fibrin deposition; and RBC injury and anemia from microvascular hemolysis. The condition should be considered in any patient in whom purpura, a bleeding tendency, and signs of organ injury, particularly of the central nervous system or kidney, develop. This is further confounded clinically by the variable acuteness and intensity of intravascular clotting, the effectiveness of fibrinolysis, and other systemic manifestations of the precipitating disease. The clinical diagnosis of DIC is confirmed by laboratory testing (Table 111.8).

BOX 111.13 Disseminated Intravascular Coagulation Abnormal Clotting Sequence

Platelets and coagulation factors are consumed, especially fibrinogen and factors V, VIII, and XIII.
Thrombin is formed, and it overwhelms its inhibitor system and acts to accelerate the coagulation process and directly activate fibrinogen.
Fibrin is deposited in small vessels in multiple organs.
The fibrinolytic system by means of plasmin may lyse fibrin and impair thrombin formation.
Fibrin degradation products are released and affect platelet function and inhibit fibrin polymerization.
Coagulation inhibition levels (e.g., antithrombin III, protein C, and tissue factor pathway inhibitor) are decreased.

Severe liver disease or primary fibrinolysis may be confused with DIC. Liver disease of this severity is usually manifested by clinical jaundice and splenomegaly. Primary fibrinolysis is a rare disorder that affects fibrinogen and fibrin, though generally preserves other coagulation components (platelets, factor V, and factor VIII) in the low-normal range. Additional laboratory tests can be used to confirm the diagnosis of primary fibrinolysis in conjunction with a hematologist.

When planning therapy, it is critical to factor that DIC is secondary to a serious underlying pathologic process. Once the underlying diagnosis is confirmed, the initial treatment is focused on reversal of the triggering mechanism. Many episodes of DIC are self-limited, such as in a transfusion reaction, or compensated, such as in association with a tumor mass, and do not require specific intervention other than general supportive care.

If the patient demonstrates active bleeding, a significant risk of bleeding and requires an invasive procedure, arterial or venous thromboembolism, skin necrosis, or acral ischemia, specific management of DIC is warranted. In these cases of severe hemorrhagic or thromboembolic complications, in addition to treatment of the precipitating condition, specific management is based on which of the two major pathologic components of DIC predominates the clinical picture. In the setting of active bleeding, replacement therapy with platelets, fresh frozen plasma, and cryoprecipitate is recommended. Replacement therapy is instituted simultaneously with attempts to manage the primary inciting condition. The goal is to avoid depletion of clotting factors. Selective replacement therapy can be based on both laboratory and clinical response. Slowing of bleeding, a decrease in fibrin degradation products, and a rise in platelet count and fibrinogen level are useful monitors. Normalization of clotting times occurs later in the course, thus is of less value in initial monitoring.

Heparin can be selectively utilized in the treatment of DIC when fibrin deposition and thrombosis predominate the pathologic picture. Certain disease states are associated more with fibrin deposition, in which case heparin therapy should be considered. Examples include purpura fulminans, retained nonviable fetus before delivery, giant hemangioma, or acute promyelocytic leukemia. Conversely, heparin is

TABLE 111.8 Laboratory Diagnosis of Disseminated Intravascular Coagulation

Test	Finding	Pathophysiology
Peripheral smear	Low platelets, schistocytes, RBC fragments	RBC fragmentation on fibrin strands; schistocytes not always seen
Platelet count	Low (usually < 100,000/mm^3)	Consumed in clotting
Prothrombin time (PT)	Prolonged	Factors II and IV (calcium) consumed
Partial thromboplastin time (PTT)	Prolonged	Factors II, V, and VIII consumed
Thrombin time	Prolonged	Factor II consumed, decreased fibrinogen levels from the consumptive process of DIC (actual fibrinogen levels are variable as discussed below), and in vivo fibrinolysis leads to prolonged thrombin time even when fibrinogen levels are normal
Fibrinogen level	Low	Factor II consumed; may be difficult to interpret because it is an acute-phase reactant
Fibrin degradation products (including D-dimer)	Negligible to elevated	Dependent on the amount of secondary fibrinolysis
Serum creatinine or urinalysis	May be abnormal	Functional assessment of the kidney, as it is commonly impacted by microvascular fibrin deposition

RBC, Red blood cell.

generally of little benefit in the setting of meningococcemia, abruptio placentae, severe liver disease, or trauma. LMWH may also be utilized as an alternative to UFH. Continuous monitoring of the clinical response, heparin activity levels, and bleeding status is essential.

Other therapeutic agents have been evaluated, including antithrombin III, PCC, recombinant factor VIIa, and activated protein C, though none has demonstrated an improved outcome in DIC.

The goals of emergency care for patients with DIC include early recognition and close monitoring, focus on mitigation of the precipitating condition when possible, identifying potential life-threatening complications, and only rarely initiation of blood product or anticoagulation therapy.

DISPOSITION

Patients with bleeding disorders of unknown cause or of a significant degree should be considered for admission for further evaluation. Transfer may be necessary, particularly if hematologic expertise is not readily available. Owing to the potential for delayed bleeding in hemophiliacs, long-distance transports may be especially hazardous. Early notification and appropriate primary care or hematologic follow-up is prudent for other patients.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 111: QUESTIONS AND ANSWERS

1. What platelet count is generally recommended prior to performance of a lumbar puncture?
   a. 100,000 mm^3
   b. 50,000 mm^3
   c. 40,000 mm^3
   d. 20,000 mm^3
   e. 10,000 mm^3

Answer: B. A platelet count above 50,000 mm^3 is recommended prior to performance of invasive spinal procedures such as lumbar procedure. A platelet count above 20,000 mm^3 is recommended for central line placement. A platelet count above 100,000 mm^3 is recommended prior to neurosurgical procedures or invasive ophthalmologic interventions

2. An isolated elevation in prothrombin time (PT) or INR indicates an abnormality or deficiency in which of the following?
   a. Calcium
   b. Factor VII
   c. Factor XI
   d. Fibrinogen
   e. Platelets

Answer: B. The PT or INR tests the components of the extrinsic pathway, and abnormalities or deficiency in factor VII will cause elevation in PT and INR. Calcium derangements do not typically cause aberrations in PT, INR, or PTT. Factor XI is a component of the intrinsic pathway reflected in the PTT. Fibrinogen function is reflected in both prothrombin time (PT) and PTT values. Platelet deficiencies do not prolong the PT or INR.

3. If initial treatment of ITP with glucocorticoids fails, which of the following is most reasonable additional treatment for severe thrombocytopenia?
   a. Splenectomy
   b. Four factor-PCC
   c. IVIG
   d. Tranexamic acid
   e. Thrombopoietin receptor agonist

Answer: C. IVIG has been shown to improve platelet counts in patients with severe thrombocytopenia secondary to ITP. Splenectomy is considered the last line of treatment. Tranexamic acid prevents fibrinolysis. Thrombopoietin receptor agonists are typically reserved for patients who are not responsive to glucocorticoids and IVIG.

4. A 52 year-old-female presents to the emergency department with confusion, shortness of breath, and fatigue. Laboratory evaluation reveals a platelet count of 14,000 mm^3 and hemoglobin of 7.2. mg/dL, a low MCV, indirect bilirubinemia, and a creatinine of 1.4 mg/dL. Electrocardiogram shows non-specific T wave abnormalities in the lateral leads. She denies chest pain and vitals are normal. What would be the most reasonable next step in management?
   a. Obtain a blood smear and utilize a validated risk score for possible TTP.
   b. Immediate platelet transfusion
   c. Administer tranexamic acid
   d. Start IVIG
   e. Administer heparin

Answer: A. Early identification of TTP is imperative. This patient presents with classic signs and symptoms (neurologic symptoms, fatigue, thrombocytopenia, and microangiopathic hemolytic anemia). A validated score such as the PLASMIC score should be used to rapidly assess the likelihood of TTP, as early plasma exchange is the treatment of choice. A platelet transfusion will more than likely exacerbate symptoms. Tranexamic acid prevents fibrinolysis, and therefore would likely cause harm in the setting of microthrombi in TTP. IVIG has not been shown to be the front-line treatment for TTP. Heparin will further increase this patient's bleeding risk. The nonspecific T wave changes are likely due to TTP.

5. A 22-year-old patient with hemophilia A presents to the ED with a headache. He has a history of migraines but this feels different from his previous headaches. He denies any recent significant closed head injury, though states he fell while skateboarding 1 week prior. He is concerned about the possibility of bleeding. Neurologic examination is unremarkable. Upon further review of available records, the patient has a history of severe hemophilia A with inhibitors. His headache is worsening. What would be the best next step in management?
   a. Obtain imaging of brain and cervical spine.
   b. Consult neurosurgery for possible intracranial bleed.
   c. Administer factor VII as expeditiously as possible.
   d. Administer factor VIII as expeditiously as possible.
   e. Administer a migraine "cocktail" for his headache and reevaluate in 30 minutes.

Answer: C. Patients with known hemophilia should be treated empirically with factor replacement when intracranial bleeding is first *suspected*. An atypical headache, particularly in the setting of trauma (even seemingly minor or incidental trauma), should be treated with factor replacement as expeditiously as possible. Neurosurgery may need to be contacted, though consultation should not delay factor administration. Although this patient has hemophilia A (factor VIII deficiency), the presence of inhibitors (antibodies toward factor VIII) limit the utility of factor VIII replacement. In the setting of hemophilia with known inhibitors and bleeding, recombinant factor VIIa is recommended. Medications for treatment of routine migrainous symptoms may be considered secondary to exclusion of life- or disability-threatening intracranial hemorrhage.

Oncologic Emergencies

David A. Wacker and Michael T. McCurdy

FOUNDATIONS

As improved therapies prolong the lives of cancer patients, the prevalence of oncologic emergencies continues to increase. However, nonspecific clinical features misattributed to the underlying cancer complicate their diagnosis. In this chapter, we review febrile neutropenia, metastatic spinal cord compression (MSCC), malignant pericardial disease, hypercalcemia of malignancy, tumor lysis syndrome (TLS), leukostasis, superior vena cava (SVC) syndrome, and complications of cancer immunotherapies including monoclonal antibodies, T-lymphocyte checkpoint inhibition, and adoptive cell transfer therapy.

KEY CONCEPTS

- Patients whose absolute neutrophil count is or is expected to soon be 500 cells/mm^3 or lower are considered severely neutropenic. A single temperature of 38.3°C or sustained temperature of 38.0°C for 1 to 2 hours or longer is considered fever.
- Any neutropenic patient with fever or with infectious signs or symptoms (even in the absence of fever) should be evaluated for an infectious source, including drawing of blood cultures, and started on empirical antibiotics. Those with high-risk features (e.g., prolonged or profound neutropenia, pneumonia, hypotension, abdominal pain, neurologic changes, Multinational Association for Supportive Care in Cancer (MASCC) score < 21) should be started on an antipseudomonal beta-lactam (e.g., cefepime, piperacillin-tazobactam, antipseudomonal carbapenem). Those with low-risk features may be appropriate for oral antibiotics. Empirical gram-positive bacterial, antifungal, and antiviral coverage is unnecessary unless the clinical situation dictates otherwise.
- Neutropenic patients with fever should generally be hospitalized, including all high-risk patients. Select low-risk patients may be managed as outpatients.

FEBRILE NEUTROPENIA

Foundations

Whether due to underlying malignancy or as a cytotoxic effect of chemotherapeutics, cancer patients regularly experience depleted levels of circulating neutrophils. Risk of infection rises when a patient's absolute neutrophil count (ANC) drops below 1000 cells/mm^3. However, the increase in risk is most marked in patients with ANC less than 500 cells/mm^3. Historically, ANC of 1000 to 1500 cells/mm^3 has been considered mild, 500 to 1000 cells/mm^3 moderate, and less than 500 cells/mm^3 severe. Current guidelines do not emphasize these gradations, and neutropenia is defined as an ANC less than 500 cells/mm^3 or an ANC expected to drop below this threshold within 48 hours.[1,2] The ANC is calculated from a complete blood count (CBC) with differential count by the following formula:

$$\frac{([\%\,\text{granulocytes}] + [\%\,\text{bands}]) \times [\text{total WBC count}]}{100}$$

Neutropenic patients are particularly susceptible to infection, even from their own existing microbial flora, and such infection carries significant mortality risk. Twenty to thirty percent of patients with neutropenic fever require hospitalization, and of those patients, about 10% will not survive to discharge.[1] Most commonly, neutropenic fever is caused by pneumonia, anorectal lesion, skin infection, pharyngitis, or urinary tract infection. However, because local inflammatory responses are dampened by the absence of granulocytes, the only sign of infection may be fever, defined as a single temperature 38.3°C or greater or a sustained temperature of 38.0°C or greater for 1 hour or more. However, fever is not a requisite for infection; any neutropenic patient with signs or symptoms of infection should be treated as having neutropenic fever, whether actually febrile or not. In fact, suppressed temperature on presentation (<36.5°C) may portend higher mortality than fever or normothermia.

Clinical Features

Due to underlying immunosuppression, neutropenic patients often do not manifest infectious signs or symptoms beyond fever, making a thorough history and physical examination crucial. The interview should include a standard infectious review of systems, questioning for presence of diarrhea, nausea or vomiting, headache, neck stiffness, rashes, dysuria, cough, dyspnea, and pain at any location, including the abdomen, chest, joints, throat, sinuses, and ears.[2] Specific note should be made of indwelling venous catheters, because these increase the risk of bacteremia and skin infection.[1] To evaluate for perianal infection, the perineal region should be examined and inquiry made about pain with defecation. Although there is no hard evidence, expert opinion suggests against digital rectal examination to avoid compromise of the barrier between blood and rectal flora. Due to the chemosensitivity of the rapidly dividing epithelial cells of the mouth, mucositis is a common adverse effect of chemotherapy and provides a portal for oral flora into the bloodstream. This can be evaluated by examination and inquiry about oral pain.

Differential Diagnoses

Causes of fever in cancer patients are diverse and include infection, venous thrombus or embolus, adverse effect of chemotherapy or other medication, and direct effect of tumor burden. A clear source of infection is identified in only about one-third of neutropenic fever cases. Nonetheless, because of the potentially life-threatening effects of an infection in this population, all febrile neutropenic patients should receive empirical antibiotics and a full evaluation for an infectious source.

Diagnostic Testing

Neutropenic patients with fever should have at least two sets of blood cultures drawn before administration of antibiotics. Both may be drawn peripherally in patients without preexisting central access. In patients with a preexisting central line, one of the two blood cultures should be obtained peripherally, whereas other cultures should be simultaneously drawn off each lumen of the central catheter. Bacterial growth in the catheter-drawn samples greater than 2 hours prior to the peripheral samples may suggest a catheter-associated infection. Patients with neutropenic fever should also have a CBC with differential count performed to assess severity of neutropenia, as well as urinalysis, urine culture, chemistries, and renal and hepatic function tests. Serum lactate should be measured if sepsis is suspected. Additional cultures may be sent according to the clinical presentation (e.g., sputum culture if productive cough, stool culture, and testing for *Clostridium difficile* if diarrhea or abdominal pain).[1,2]

Initial imaging usually consists of chest x-ray, although this is often low-yield in the absence of specific respiratory symptoms.[3] If fever persists for 72 hours without identified source, empirical computed tomography (CT) scan of the chest and sinuses, and bronchoalveolar lavage may be considered to evaluate for occult fungal infection. Patients with a history of invasive aspergillosis, and those with profound or prolonged neutropenia are at higher risk of fungal pneumonia, and consideration should be given to pulmonary imaging if there is little clinical response within the first day of therapy.[1] Similarly, directed CT scans may be performed sooner in the setting of appropriate clinical signs (e.g., chest CT for a patient with coughing and bronchial breath sounds, but a clear chest x-ray, abdominal CT for a patient with unexplained abdominal tenderness).

As nucleotide sequencing becomes more reliable, assays employing this technique for pathogen identification[4-7] are being aggressively developed. Although these assays provide a useful adjunct, and may direct antibiotic therapy prior to culture growth, they are not yet sufficiently developed to stand in lieu of conventional diagnostics, and a full set of cultures should always be obtained.

Management

Febrile neutropenic patients should receive antibiotics prior to confirmation of an infectious source. Recommendations for specific regimens are based on risk of clinical decompensation. According to the Infectious Disease Society of America (IDSA), high-risk features include an expected duration of neutropenia greater than 7 days, expected nadir ANC less than 100 cells/mm^3, hypotension, pneumonia, new-onset abdominal pain, neurologic changes, or existence of other significant medical comorbidities. A current or prior infection with a resistant organism and treatment at a center with a high prevalence of resistant organisms should also be viewed as high risk. Alternatively, several scoring systems exist to assess risk of deterioration in neutropenic fever. The Multinational Association for Supportive Care in Cancer (MASCC) risk index identifies low-risk patients based on clinical features (Table 112.1). Patients scoring at least 21 points are considered low-risk, because nearly 90% of cases have uncomplicated resolution of their fever within 5 days. Similarly, the Clinical Index of Stable Febrile Neutropenia (CISNE) index (Table 112.2) has been validated to indicate patients with low (score 0), intermediate (score 1–2), and high (score ≥ 3) risk of clinical deterioration.[8-11]

High-risk patients should receive a parenteral broad-spectrum antibiotic regimen. Local antibiograms should be considered when choosing specific agents, but guidelines recommend monotherapy using a broad-spectrum beta-lactam with antipseudomonal coverage, such as ceftazidime, cefepime, piperacillin-tazobactam, or antipseudomonal carbapenem.[1,2] Among head-to-head studies of these agents in neutropenic patients, all have shown good effectiveness and none has consistently out-performed the others.[12-14] For patients with signs of sepsis or septic shock, double coverage for gram-negative bacteria with a fluoroquinolone or aminoglycoside in addition to beta-lactam therapy should be considered;[15] however, a meta-analysis of studies comparing beta-lactam monotherapy with combination beta-lactam/aminoglycoside therapy showed that patients receiving aminoglycoside had no survival benefit and were more likely to suffer adverse events, including nephrotoxicity and fungal superinfection. We therefore recommend antipseudomonal beta-lactam monotherapy for patients with neutropenia and fever but without signs of sepsis and septic shock. Regimens meeting these criteria for patients with normal renal function include piperacillin-tazobactam 4.5 g IV q6 hours or cefepime 2 g IV q8 hours; dosing adjustments must be made for patients with renal impairment. Further empirical antibiotics administered will depend on clinical presentation and consultation with oncology or infectious disease consultants.

Despite increasing rates of bacteremia with gram-positive organisms in cancer patients,[16,17] randomized controlled studies and meta-analyses have failed to demonstrate a survival benefit to immediate empirical gram-positive–specific coverage[18] and have previously suggested increased rates of adverse effects. Empirical gram-positive–specific therapy, such as with intravenous vancomycin or other glycopeptides, is not recommended except in cases of suspected cellulitis, catheter-associated infection, or pneumonia, or in the case of

TABLE 112.1 Clinical Features and Corresponding Point Values for the Multinational Association of Supportive Care in Cancer (MASCC) Risk Index[a]

Clinical Feature	Point Value
Age < 60 years	2
Onset of fever while outpatient	3
Overall moderate symptom burden	3
Absence of dehydration	3
No prior fungal infections or solid tumor type	4
No history of chronic obstructive pulmonary disease	4
Absence of hypotension	5
Asymptomatic or overall mild symptom burden	5

[a]A score of ≥ 21 suggests low risk of complication and likely resolution of fever within 5 days.

TABLE 112.2 Clinical Features and Corresponding Point Values for the Clinical Index of Stable Febrile Neutropenia (CISNE)[a]

Clinical Feature	Point Value
Eastern Cooperative Oncology Group Performance status ≥ 2	2
Stress-induced hyperglycemia	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
Mucositis of grade ≥ 2	1
Monocyte count < 200 per μL	1

[a]A score of zero indicates low risk of clinical deterioration prior to resolution of the episode of neutropenic fever.

clinical instability. Similarly, randomized controlled trials have not shown a benefit in immediate, empirical antifungal therapy, and guidelines suggest against empirical antifungal agents, unless there is specific concern for a fungal source. Recent guidelines do suggest, however, that evaluation for fungal pneumonia with high-resolution chest CT scan, serum beta-galactomannan assay, and consideration of bronchoscopy with lavage is beneficial in patients with prolonged or profound neutropenia.[1] In cases requiring empirical antifungal coverage, echinocandins (e.g., micafungin 100 mg IV q24 hrs) compare well with other agents both in terms of effectiveness and safety profile.[19,20]

Neutropenic patients with community-acquired pneumonia should be covered for atypical pathogens and possibly pneumocystis pneumonia (PCP). For atypical pathogens we recommend either levofloxacin 750 mg IV q24 hrs or azithromycin 500 mg IV q24 hrs and doxycycline 100 mg q12 hrs (levofloxacin dose must be adjusted for impaired renal function). For PCP coverage, the preferred regimen is trimethoprim-sulfamethoxazole (TMP-SMX) at 15 to 20 mg of TMP per kilogram of patient's total body weight per day IV, divided into 3 or 4 doses per day (e.g., 5 mg/kg IV q6 hrs will result in a 20 mg/kg/day dose). TMP-SMX dosing must be adjusted for impaired renal function. For patients with gastrointestinal symptoms, one randomized controlled trial suggests improved 28-day survival with cefepime/metronidazole combination therapy when compared to piperacillin-tazobactam monotherapy. We recommend cefepime 2 g IV q8 hrs and metronidazole 500 mg PO q8 hrs (cefepime dose must be adjusted to renal function). Patients with a vesicular rash or other evidence of herpes infections should receive empirical acyclovir; an initial regimen of 5-10 mg/kg IV every 8 hrs is appropriate for severe cases. In the case of renal impairment, acyclovir dosing must be adjusted.

Although no specific timing of antibiotic administration is recommended in the current IDSA guidelines, evidence is mounting that delays in initiation of antibiotic therapy are correlated with worsened outcomes.[21,22] We therefore recommend that high-risk patients receive antibiotic therapy as soon as possible after obtaining blood cultures. Many process improvement efforts have been shown to reduce time to antibiotics in the ED setting, including implementation of neutropenic fever order sets and a dedicated neutropenic fever response team,[23] elevation of patients with neutropenic fever in the triage queue,[24] and establishment of a protocol for initiation of antibiotics by the bedside nurse in appropriate patients.[25]

Observational studies and a meta-analysis have demonstrated that low-risk patients may be treated with an enteral regimen, usually amoxicillin/clavulanate (875 mg PO q12 hrs) and a fluoroquinolone (e.g., ciprofloxacin 500 mg PO q12 hrs). Both amoxicillin/clavulanate and levofloxacin doses must be adjusted in the case of impaired renal clearance. Alternatively, low-risk patients may be started empirically on parenteral broad-spectrum therapy as outlined previously with transition to an enteral regimen after 24 to 48 hours if no complications arise.[26,27]

Disposition

Regardless of risk category, the majority of febrile neutropenic patients will be hospitalized for observation and initial treatment,[28,29] ideally to a unit specialized for oncology patients. Hemodynamically unstable patients and those with a deteriorating course should be admitted to an intensive care unit (ICU). A small fraction of patients may be safely treated with enteral antibiotics in the outpatient setting.[30,31] These patients should (1) meet the low-risk criteria of a MASCC score of 21 or less; (2) have no evidence of pneumonia, line infection, cellulitis, or organ failure; (3) have reliable daily follow-up with their oncologist; (4) demonstrate clinical stability during observation in the ED for 4 hours or longer; (5) carry low suspicion of infection with a drug-resistant organism.[26,27] Prior to discharge, an initial dose of parenteral antibiotics should be given in the ED, reliable follow-up and access to the outpatient antibiotic regimen must be ensured, and discharge should be coordinated with the patient's oncologist.[26,27]

METASTATIC SPINAL CORD COMPRESSION

KEY CONCEPTS

- Vertebral metastasis and spinal cord compression should be considered in any cancer patient, particularly those who have back pain, peripheral strength or sensory loss, or bowel or bladder dysfunction.
- MRI of the spine is the preferred diagnostic test when evaluating spinal cord compression. CT of the spine with myelography may be performed if MRI is contraindicated or unavailable. Plain films are not sufficiently sensitive to rule out spinal cord compression.
- Intravenous corticosteroids (dexamethasone 10 mg bolus) should be given to any patient with neurologic deficits from known or suspected MSCC. Consideration should be given to emergent surgical and radiotherapeutic intervention if compatible with goals of care.

Foundations

Malignancy-related compromise of the spinal cord most commonly occurs from an extradural neoplasm that has metastasized to the vertebral column. The lesion then typically expands locally from the marrow space through a vertebral vein foramen to invade the spinal canal. Although the resulting cord injury is termed *metastatic spinal cord compression (MSCC),* direct nerve compression by tumor is uncommon. Cord injury is more commonly caused by occlusion of the epidural venous plexus, leading to breakdown of the blood-cord barrier and vasogenic edema. If untreated, tumor expansion eventually leads to arterial obstruction, causing cord ischemia and infarct. Less commonly, direct compression of the cord over time may lead to demyelination and axonal injury.

The most common tumors causing MSCC are prostate, breast, and lung cancer, each accounting for about 15% to 20% of total cases. Renal cell cancer, non-Hodgkin lymphoma, and multiple myeloma each account for an additional 5% to 10% of all cases. Most cases of MSCC affect the thoracic spine (60%), with the lumbosacral and cervical spine each making up 25% and 15% of cases, respectively. Twenty to forty percent of patients with MSCC have multiple loci of spinal metastasis.

Clinical Features

Back pain, weakness, sensory loss, and autonomic function loss are the most frequent presenting symptoms of MSCC. Back pain occurs in more than 95% of patients with MSCC and is the most common initial symptom.[32] Extremity weakness occurs in up to 75% and generally (but not always) precedes sensory loss. Patients with MSCC may also present with autonomic nerve dysfunction, including loss of bowel or bladder function, but it is a late finding and rarely presents in isolation.

Differential Diagnoses

In addition to MSCC, patients with back pain with or without neurologic symptoms should be considered for nonmalignant musculoskeletal etiologies (e.g., muscle strain, ligamentous sprain, pathologic fracture, disc displacement, radicular stenosis, vertebral osteoarthritis) and paraspinal or vertebral infections (e.g., paraspinal abscess, vertebral osteomyelitis, discitis). In patients with known malignancy, new back pain and neurologic deficits (motor, sensory, or autonomic) carry high specificity for MSCC,[32] and this diagnosis should be presumed

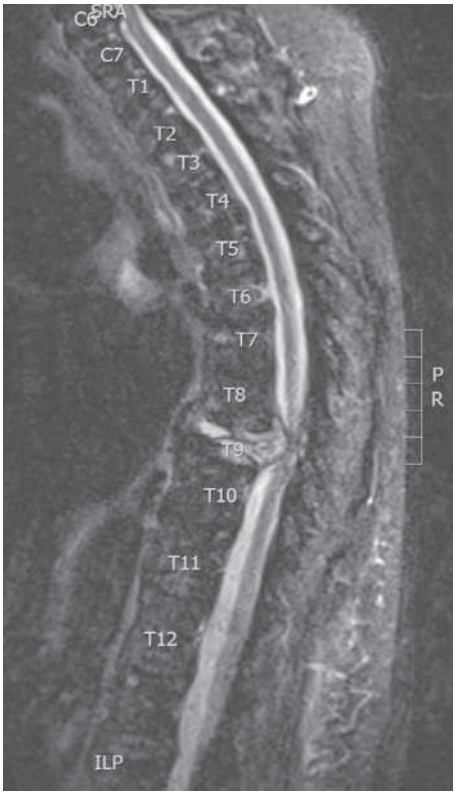

Fig. 112.1 Magnetic resonance imaging (MRI) short tau inversion recovery (STIR) image of T9 vertebral malignancy with pathologic fracture causing spinal cord compression in a patient with multiple myeloma. Vertebral numbering as marked. (Photo courtesy of the Department of Radiology, University of Maryland School of Medicine and Department of Internal Medicine, University of Maryland School of Medicine.)

and investigated. In patients without known cancer, however, new back pain is the heralding symptom of cancer in 20% of cases of MSCC, which commonly takes up to two months from original presentation to diagnose.

Diagnostic Testing

A thorough physical examination should be performed, including palpation of the entire spine, as well as testing of strength, sensation, deep tendon reflexes, and rectal tone. The diagnosis is confirmed by imaging, for which magnetic resonance imaging (MRI) has become the gold standard[32] with sensitivity of 93% and specificity of 97% (Fig. 112.1). Even in patients in whom MSCC has been established by another modality, MRI should still be performed when possible, because its added resolution changes treatment strategy in approximately 50% of cases. Because multiple separate lesions can occur simultaneously, both the thoracic and lumbar spine should be imaged in any patient with MSCC. Although the incidence of a second lesion in the cervical spine is much lower, this segment should also be included when possible.

If MRI is unavailable or contraindicated (e.g., patients with incompatible pacemakers), CT scan of the spine is the next most informative study. If vertebral metastasis is seen on initial scans, presence of cord compression can be assessed by CT myelography, in which contrast is introduced into the subarachnoid space.[32] Sensitivity of this technique rivals that of MRI, but MRI offers similar information noninvasively. Thus, CT myelography is reserved for those rare patients in whom MRI is contraindicated yet radiographic confirmation of cord compression as the cause of symptoms is required prior to intervention. Plain radiographs, positron emission tomography (PET) scans, and radionuclide scans may demonstrate vertebral metastasis, but sensitivity is limited. Furthermore, these techniques provide no information about the state of the spinal cord itself or the precise location of suspected compression. These studies are therefore insufficient to rule out MSCC.[32]

Management

Treatment of MSCC in the ED entails administration of corticosteroids and initiation of definitive treatment with surgery, radiation therapy, or both.[33,34] Corticosteroids provide the most immediately available therapy for cord compression; unlike surgery or radiation, their administration does not require significant logistical planning or knowledge of the exact anatomic location of tumor. Early steroid administration has been shown to improve ambulation rates at 3- and 6-month intervals, and patients receiving corticosteroids have improved long-term pain scores. Current guidelines suggest a 10 mg intravenous bolus of dexamethasone followed by 16 mg orally per day in divided doses for any patient with neurologic deficits believed secondary to MSCC.[34] Patients with severe deficiencies, such as paraplegia, may receive a higher dose of 100 mg intravenous dexamethasone, followed by 96 mg orally per day in divided doses. Steroids are generally unnecessary in patients with vertebral metastases on imaging but without neurologic deficits.

Corticosteroids temporize vasogenic cord edema, but cord damage will ensue without definitive correction with radiation therapy, surgery, or both. For patients who can tolerate surgery and have goals of care in line with surgery, a combination of surgical decompression followed by radiation therapy provides better long-term rates of continence, ambulation, and survival than radiation therapy alone, and combined management is recommended in the most recent guidelines.[34,35] Surgical intervention is especially important in patients with spinal instability or cord compression by bony fragments.[35] Although surgery carries a high complication rate,[36] development of mini-open approaches[37,38] and use of postoperative stereotactic body radiation therapy to limit the degree of necessary resection[35] show promise to reduce complication rates and shorten recovery times. For patients unable to tolerate surgery or with incompatible goals of care, radiation alone may be pursued. Conventional fractionated radiotherapy has previously been the standard of care and continues to be an important modality for radiation therapy. Stereotactic body radiation therapy (SBRT), which employs advanced tumor mapping and beam-focusing techniques to allow safe delivery of significantly higher bolus doses of radiation to tumor cells without collateral injury to nearby tissues, is rapidly developing a central role in the management of MSCC. This is particularly true for patients with tumor histology known to be insensitive to fractionated radiotherapy, and for those with tumor in an area that has already received a maximum allowable radiation dose.[39] Neurointerventional radiology technologies such as injection of cement into spinal column fractures, or intra-arterial tumor embolization and other ablative techniques also show promise for patients whose goals of care are incompatible with major surgery.[35]

Although some recovery of lost neurologic function is possible after decompression, often the greater impact of treatment is prevention of further damage. In fact, neurologic status at initiation of treatment is the strongest indicator of functional outcome, and every effort should be made to expedite appropriate therapy to prevent further neurologic decline. No direct evidence exists to guide the exact timing of treatment, but most experts recommend definitive treatment within 24 hours whenever possible.[32]

Disposition

Following corticosteroid administration, patients with neurologic deficits (i.e., motor, sensory, or autonomic) should be hospitalized

for definitive therapy. Asymptomatic patients with incidentally noted vertebral metastasis may be managed as outpatients, provided they have reliable follow-up. Given the complexity intrinsic to management of MSCC, a multidisciplinary approach involving oncology, radiation oncology, and neurosurgery should be employed regardless of disposition.[40]

MALIGNANT PERICARDIAL DISEASE

KEY CONCEPTS

- No clinical sign or symptom is entirely sensitive for cardiac tamponade, but echocardiographic findings of a large pericardial effusion (anechoic circumferential stripe around the heart) and right atrial or ventricular collapse during diastole, combined with clinical findings of shock are highly suggestive.
- If compatible with goals of care, pericardial effusion causing tamponade should be emergently drained. Intravenous fluid or inotrope administration may be trialed as a temporizing measure, but these therapies are unreliable and should not delay definitive management.

Foundations

Pericardial manifestations of malignant disease, including pericarditis, pericardial neoplasm (usually metastatic), and pericardial effusion affect greater than 10% of cancer patients and cause about 25% of all effusive pericardial disease in the developed world.[41] Approximately two-thirds of malignancy-associated pericardial disease is clinically insignificant. However, in the remaining one-third of cases, hemodynamic compromise, organ failure, or death occurs.

Neoplastic disease is believed to cause pericardial effusion when lymphatic flow, which normally drains fluid from the pericardium, becomes obstructed or reversed by congestion in proximal malignant lymph nodes. An effusion develops both by obstruction of fluid outflow, and by metastatic spread to the pericardial lining, leading to a nonphysiologic increase in pericardial fluid production. The most common culprits in this process are lung, breast, and hematologic tumors, as well as melanoma.[41] Effusions not directly caused by malignancy may also develop in cancer patients secondary to hypoalbuminemia or as an adverse effect of radiation or chemotherapy.

Although the pericardial sac has the elastic potential for gradual expansion to greater than 1 L, it is poorly distensible in short (i.e., hours to days) time frames, and rapid accumulation of even a few hundred milliliters of fluid may precipitate cardiac tamponade. This life-threatening condition occurs when intrapericardial pressures rise to match or surpass those of the atria and then ventricles, reducing or eliminating cardiac output and leading to shock.

Clinical Features

The classic presenting symptoms of pericardial disease are dyspnea and chest pain. Weakness and fatigue are often associated, and large, slowly accumulating effusions may result in mass effect on nearby structures, causing nausea, early satiety, cough, hiccups, hoarseness, or dysphagia. Cardiac tamponade presents with shock, but other classic stigmata of the disease are unreliable. Pulsus paradoxus, defined as a 10 mm Hg systolic blood pressure gradient between inspiration and expiration in the respiratory cycle, is the most sensitive sign, present in about 80% of cases. Kussmaul sign (paradoxically increased jugular venous pressure [JVP] with inspiration) and Beck triad (hypotension, elevated JVP, and muffled heart sounds) are seen in less than half of cases. Hypotension may not even be a presenting symptom, particularly in patients with underlying hypertension.

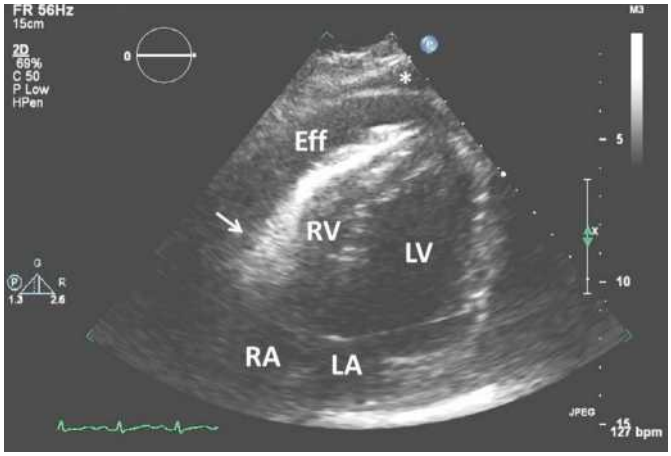

Fig. 112.2 Four-chamber apical view demonstrating pericardial effusion *(Eff)* with tamponade physiology in a patient with breast cancer. Buckling of the right ventricle wall is marked by a *white arrow*. Left ventricle *(LV)*, left atrium *(LA)*, right ventricle *(RV)*, and right atrium *(RA)* are all as marked. Incidentally noted pleural effusion is marked with an asterisk *(*)*. (Photo courtesy of the Division of Cardiology, Department of Internal Medicine, University of Maryland School of Medicine.)

Differential Diagnosis

Because of its nonspecific presentation, the differential diagnosis for malignant pericardial effusion is broad. Considerations should include acute coronary syndrome, acute heart failure or valve failure, pulmonary embolism, pleural effusion, pneumonia, and pneumothorax.

Diagnostic Testing

Evaluation for a patient with suspected malignant pericardial effusion should include chest radiography, electrocardiogram (ECG), and transthoracic echo (TTE). Electrocardiographic manifestations may include nonspecific ST or T changes, or low amplitude QRS voltage. Electrical alternans (alternating high and low QRS amplitudes) is only seen in 10% of cases. An enlarged cardiac silhouette on chest x-ray may suggest a large effusion. Echocardiography, which approaches 100% sensitivity and specificity for pericardial effusion, can also identify characteristics of tamponade physiology, such as cardiac chamber collapse and abnormal tissue imaging markers (e.g., tricuspid valve annular plane systolic excursion).[42] Emergency clinicians, who are trained in basic bedside cardiac ultrasound, can reliably identify pericardial effusion and should perform the initial examination to hasten diagnosis (Fig. 112.2).

Management

Malignant pericardial effusion generally serves as evidence of advanced cancer, and therapies should be tailored to match each patient's goals of care. If aggressive therapy is desired, cardiac tamponade is a medical emergency and warrants immediate drainage, ideally under real-time ultrasonographic guidance (Fig. 112.3). Ultrasound-guided drainage by the intercostal approach results in fewer complications and higher success rates than blind drainage by the subxiphoid approach. If ultrasound is unavailable, a subxiphoid approach should be employed by inserting the needle at a 15-degree angle to horizontal between the xyphoid process and left costal margin. After clearing the rib cage, the needle should be leveled and advanced toward the left shoulder until return of fluid is achieved. Temporizing measures such as inotropes (e.g., epinephrine in hypotensive patients, dobutamine in normotensive patients) or intravenous fluids may be attempted, but, despite

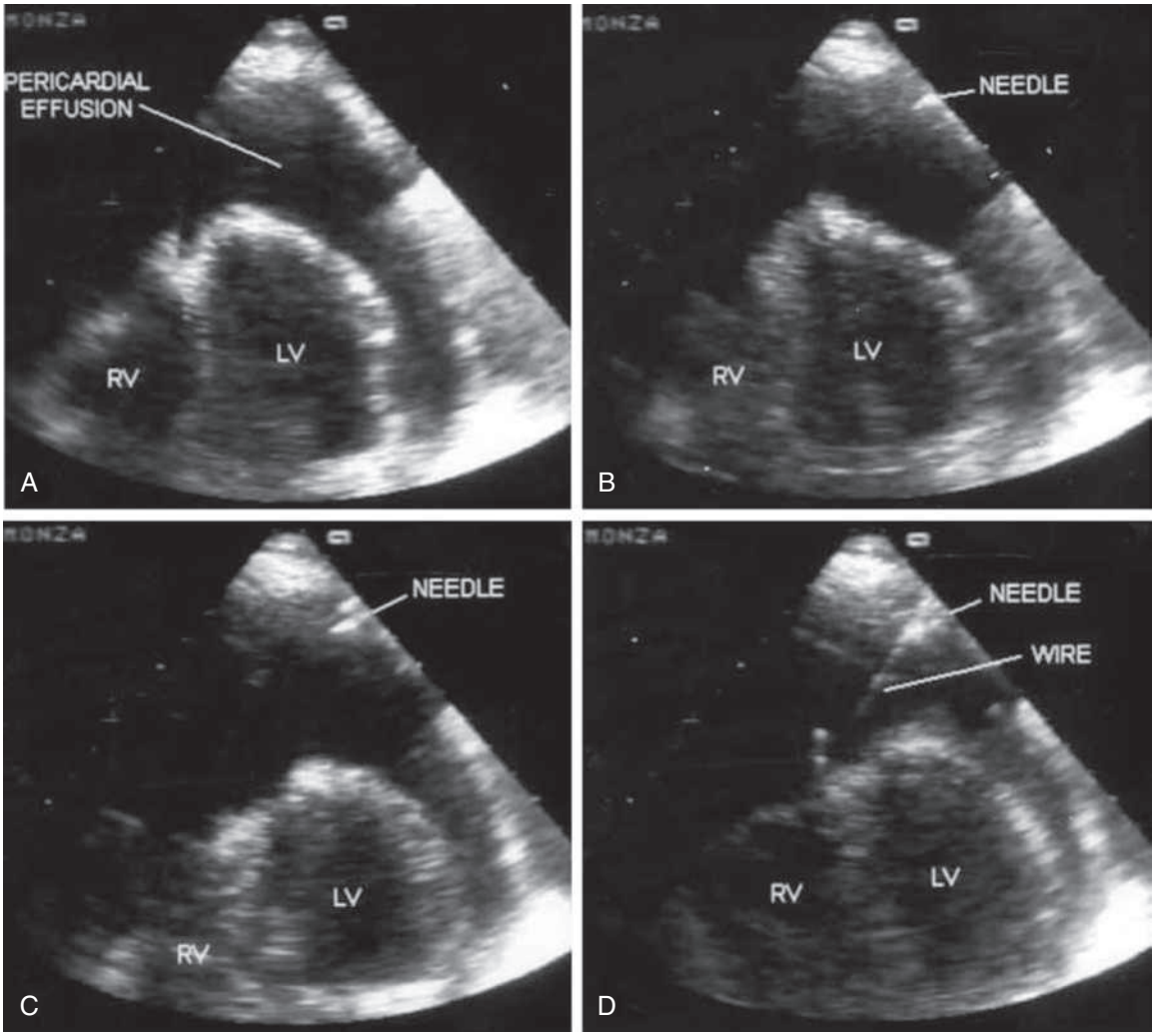

Fig. 112.3 Ultrasound-guided drainage of pericardial effusion. (A) A four-chamber apical view reveals a large pericardial effusion. (B and C) Under ultrasound guidance, a needle is advanced through an intercostal space and to the pericardial sack. (D) Upon reaching the pericardial sack fluid can be drained directly, or a wire advanced for drain placement by Seldinger technique. *LV,* Left ventricle; *RV,* right ventricle. (Reproduced from: Maggiolini S, et al. Echocardiography-guided pericardiocentesis with probe-mounted needle: report of 53 cases. *J Am Soc Echocardiogr.* 2001;14:821-824, with permission.)

early successes in trials on anesthetized animal models, these measures have not demonstrated reproducible benefit in humans and should not be viewed as a substitute for timely drainage.

Effusion without tamponade can be managed nonemergently. Fluid sampling for cytology and tumor marker analysis can help confirm etiology of effusion. This also allows intrapericardial chemotherapy or injection of sclerosing agents in a more controlled fashion. Malignant effusions tend to recur, so a long-term evacuation strategy by way of percutaneous drain,[43] surgical window,[44] or percutaneous balloon pericardiotomy[45] should be considered.

Disposition

Disposition depends on the hemodynamic effect of the pericardial effusion. Patients without tamponade or with a low likelihood of tamponade in the near future (i.e., slow evolution of symptoms) can be managed nonemergently as an outpatient. Those with tamponade or rapid development of effusion should undergo pericardiocentesis and be hospitalized to monitor for fluid reaccumulation.

HYPERCALCEMIA

KEY CONCEPTS

- Calcium levels in hypercalcemic patients should be assessed by measuring ionized calcium concentration, rather than total calcium concentration.
- First-line management of hypercalcemia includes intravenous fluids (1–2 L crystalloid bolus followed by 200–250 mL/hr), and loop diuretics only for volume management, as well as bisphosphonate therapy (pamidronate 90 mg or zoledronate 4 mg, intravenously). Calcitonin is faster acting than bisphosphonates, but tachyphylaxis may develop; consider calcitonin in hypercalcemic patients with active cardiac or neurologic symptoms (e.g., dysrhythmias, seizures).

FOUNDATIONS

Serum calcium regulation is achieved by parathyroid hormone (PTH) and calcitriol (the activated form of vitamin D), which both increase serum calcium level, and to a lesser extent by calcitonin, which

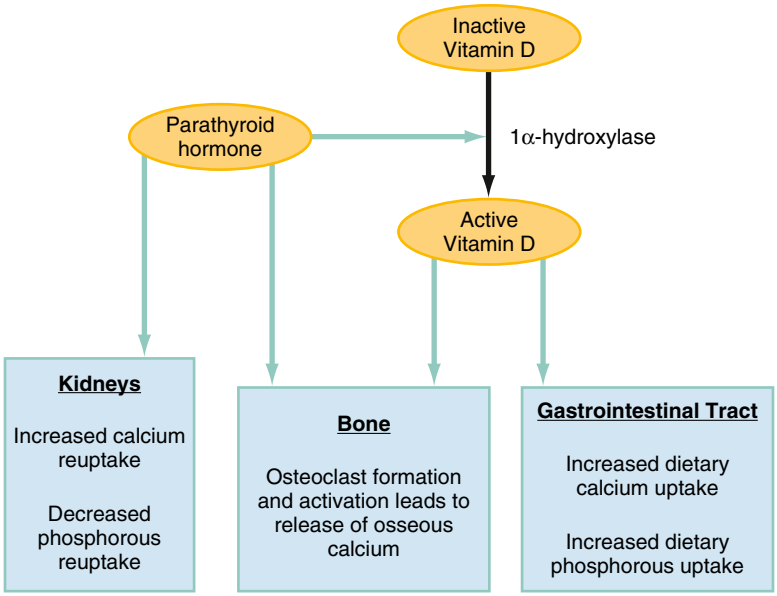

Fig. 112.4 Schematic representation of normal calcium homeostasis. Signaling molecules are represented by *circles,* targets of each signaling molecule and effects on the target are represented by *green arrows* and *boxes.* Activation of vitamin D by 1α-hydroxylase is represented by a *black arrow.*

decreases it (Fig. 112.4). Approximately a third of cancer patients will experience dysregulation of calcium homeostasis, usually caused by one or more of the following: (1) synthesis of the PTH analog PTH-related protein (PTHrP), (2) overproduction of calcitriol, (3) bone osteolysis due to direct spread of tumor, or, (4) less commonly, ectopic production of PTH.[46] In most cases, malignancy-associated hypercalcemia signifies advanced disease, with median survival of less than two months.[47-49]

Synthesis of PTHrP, classically called *humoral hypercalcemia*, causes about 80% of cases of malignancy-associated hypercalcemia, and is usually associated with squamous cancers, such as head and neck, lung, esophageal, cervical, ovarian, and endometrial carcinomas. Calcitriol overproduction is usually seen in Hodgkin and non-Hodgkin lymphomas, in which secreted cytokines inappropriately activate the vitamin D–activating enzyme 1α-hydroxylase in macrophages. Bony metastasis can cause local cytokine-induced osteolysis and, if extensive, can lead to hypercalcemia. Ectopic PTH production is a rare feature of malignancies, mainly limited to case reports. Primary hyperparathyroidism occurring coincidentally with cancer is much more common.[46]

Clinical Features

Presenting symptoms often include weakness, lethargy, confusion, abdominal pain, nausea, vomiting, constipation, polyuria, polydipsia, and kidney injury. Signs of dehydration may also be present. Manifestations depend not only on the absolute value of serum calcium but also on the patient's age and comorbidities and the rate of increase of serum calcium.[46] Acute hypercalcemia most commonly presents with neurologic abnormalities and acute kidney injury, as well as cardiac dysrhythmias if severe. Nephrolithiasis and nephrocalcinosis occur more commonly with chronic hypercalcemia, and they are infrequent manifestations of malignancy-associated hypercalcemia. Physical examination findings are often nonspecific. Electrocardiogram findings may initially exhibit QT interval shortening, progressing to dysrhythmias and heart block as hypercalcemia worsens.[50]

Differential Diagnoses

Because of its nonspecific presentation, the differential diagnosis for malignancy-associated hypercalcemia is quite broad. Consideration should be given to infection with systemic manifestations, direct neurologic injury (e.g., cerebrovascular accident or central nervous system [CNS] infection), or other metabolic derangements (e.g., hyper- or hyponatremia, acidemia, or TLS).

Diagnostic Testing

Accurate measurement of the free serum calcium level is the most important step in the evaluation of malignancy-associated hypercalcemia. Measurements of total serum calcium, which are often included in basic metabolic panels, include a large fraction of physiologically inert calcium, which is bound to albumin and other serum proteins. Approximations of the bound fraction of serum calcium can be made using serum albumin measurements, but factors affecting the avidity of calcium for serum proteins, such as pH and the presence of medications that compete for binding sites, as well as abnormal concentrations of non-albumin proteins, may lead to inaccuracies in this calculation. It is therefore recommended that free or ionized levels of calcium be obtained for any patient with suspected malignancy-associated hypercalcemia.

Testing for additional metabolic abnormalities including serum levels of sodium, potassium, bicarbonate, chloride, magnesium, and phosphorous should be performed, as should an assessment of kidney function with blood urea nitrogen and creatinine.[46] A brief review of reversible factors exacerbating hypercalcemia such as thiazide diuretic use or exogenous calcium supplementation may be helpful. Further testing to determine the etiology of malignancy-associated hypercalcemia (PTH, PTHrP, and calcitriol levels, as well as skeletal survey for bone metastasis) may eventually be undertaken but is generally unnecessary in the ED, because initial therapy is not etiology-specific.

Management

Severe hypercalcemia, especially if rapidly developing, will lead to death if untreated. First-line treatment for malignancy-associated hypercalcemia is intravenous fluid. Hypercalcemia impairs renal resorption of water and sodium, leading to hypovolemia. Hypovolemia further limits the kidneys' ability to eliminate calcium, creating a feedback loop that propagates hypercalcemia and hypovolemia. To break this loop, euvolemia must be restored, generally by

administration of intravenous fluid. An initial bolus of 1 to 2 liters of crystalloid followed by 200 to 250 mL/hr has been recommended.[46] We recommend that patients with acute oliguria or anuria be vigorously volume challenged, because poor urine output may simply be a product of hypovolemia. However, if urine output does not improve, as may be the case with heart or kidney failure, resulting hypervolemia should be treated with a combination of diuresis, dialysis, and positive-pressure ventilation. Historically, loop diuretics have been used even for euvolemic patients in an attempt to force calciuresis; however, this has led to high complication rates and the calciuretic effect is minimal.[46] We therefore recommend the use of loop diuretics only for volume overload. Thiazide diuretics enhance distal tubule calcium resorption and should be avoided in hypercalcemic patients. Hypercalcemic patients with baseline oliguria or anuria may require dialysis.

Bisphosphonates are the primary pharmacologic treatment for hypercalcemia. Analogs of pyrophosphate, which is produced in bone catabolism, bisphosphonates inhibit bone turnover by reducing osteoclast function and directly stabilizing hydroxyapatite crystals. Typical regimens consist of single doses of either 90 mg of pamidronate given over 2 to 4 hours, or 4 mg of zoledronate given over 15 to 30 minutes.[46] Both should be given intravenously, because oral availability may be limited. An average reduction of serum calcium concentration of 3 to 4 mg/dL can be expected with either regimen, but maximum effect may not be seen for 7 to 10 days. Bisphosphonates can cause an acute phase reaction in up to one-third of cases, consisting of fever, myalgia, arthralgia, and headache, usually within 36 hours. Such side effects can be managed with antipyretics and antihistamines. Bisphosphonates have also been associated with renal dysfunction and jaw osteonecrosis.

Although effective, bisphosphonates require days to lower serum calcium levels. Calcitonin has a quicker onset (12 to 24 hours) and may be useful for manifestations of hypercalcemia requiring immediate reduction of serum calcium level, such as dysrhythmias.[46] The effects of calcitonin are short-lived due to tachyphylaxis, so definitive therapy with bisphosphonates should be simultaneously given. Calcitonin should be given subcutaneously or intramuscularly 4 to 8 units/kg every 6 hours, which typically reduces the serum calcium level by 1 to 2 mg/dL.

Other pharmacologic therapies include denosumab, a human monoclonal antibody inhibiting the RANK ligand that has been used in patients with bisphosphonate-resistant hypercalcemia, as well as plicamycin (mithramycin) and gallium nitrate. Denosumab is not significantly more effective nor faster-acting than bisphosphonates but is more expensive, thus it is generally used second-line in cases of bisphosphonate failure. It may be the preferred agent in patients with renal dysfunction and CrCl <30 mL/min. Plicamycin and gallium nitrate have both fallen out of favor due to long administration times and unfavorable adverse effect profiles; we generally recommend against their use. Hemodialysis can quickly reduce serum calcium levels and should be considered in patients who are dialysis-dependent, recalcitrant to other therapies, or have life-threatening manifestations of hypercalcemia.[51,52] Regardless of other therapies, treatment of the underlying malignancy should be immediately pursued if this is compatible with goals of care, because this is the only way to reverse the underlying cause of hypercalcemia and generally does not increase serum calcium levels.

Disposition

Patients with severe hypercalcemia (>14.0 mg/dL) or an acutely increasing calcium level should be admitted to a monitored bed. Patients with a stable serum calcium concentration less than 14 mg/dL, and close, reliable follow-up may be managed on an outpatient basis in consultation with the their oncologist or primary care doctor.

TUMOR LYSIS SYNDROME

KEY CONCEPTS

- TLS is manifested by the combination of hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia, often accompanied by acute renal failure.
- Patients with TLS should have their potassium, phosphate, calcium, and uric acid levels, as well as renal indices monitored closely. Intravenous fluids should be administered, as well as therapies to reverse hyperkalemia. Hyperuricemia may be prevented with allopurinol or treated with rasburicase. Calcium should only be repleted in patients with cardiac or neurologic manifestations of hypocalcemia.

Foundations

TLS occurs when destruction of malignant cells occurs so rapidly that the body's mechanisms for regulating the unwanted products of this destruction are overwhelmed. Such cell lysis releases intracellular contents, causing hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Acute kidney injury, caused by crystal deposits of uric acid or calcium-phosphate in the renal tubules or by crystal-independent mechanisms of damage by uric acid, often accompanies TLS, further compounding the patient's ability to regulate serum electrolyte levels and eliminate products of cellular destruction. Not infrequently, kidney injury can occur to the point that renal dialysis is required.[53] TLS is most likely to occur in patients with tumors that are high-burden, rapidly growing, and highly chemosensitive, such as Burkitt lymphoma or acute lymphoblastic leukemia (ALL). TLS occurs less commonly in rapidly growing solid tumors, such as breast, testicular, and small cell lung cancers; overall the types of malignancies with potential for TLS is growing as more effective and fast-acting chemotherapeutics are developed.[54,55] Patient factors predisposing to TLS include preexisting renal failure, hypovolemia, and hyperuricemia.

Clinical Features

Although spontaneous TLS is possible, patients undergoing cytotoxic therapy are particularly at risk for TLS. Symptoms result from metabolic derangements or kidney failure and include nausea, vomiting, lethargy, confusion, edema, seizure, myalgias, and tetany; dysrhythmias may result in cardiac arrest. Release of immunoactive proteins such as cytokines from lysed cells may cause sepsis-like symptoms. Due to the immunocompromised state of these individuals, an infectious source should be presumed in patients with septic symptoms and empiric antibiotics should be administered. Electrocardiographic changes may include QT interval prolongation due to hypocalcemia and P-wave flattening, PR and QRS interval prolongation, and T-wave peaking due to hyperkalemia.

Differential Diagnoses

Differential diagnosis for patients with TLS varies with presenting symptoms. For those with nonspecific symptoms such as fatigue or myalgia, consideration should be given to other metabolic derangements such as malignancy-associated hypercalcemia, or systemic manifestations of an infectious source. Patients presenting with cardiac dysrhythmia should be considered for acute coronary syndrome, pulmonary embolism, other sources of metabolic derangements, and other causes of myocardial irritation. Seizure and other neurologic symptoms may suggest cerebrovascular accident, CNS infection or metastasis, or other metabolic abnormalities.

Diagnostic Testing

Evaluation begins with measurement of serum potassium, phosphate, ionized calcium, urea nitrogen, creatinine, uric acid, and lactate dehydrogenase (LDH). For patients who have received rasburicase, uric acid specimens should be sent on ice to prevent artificially low results.[56] If the patient is presenting with sepsis-like symptoms, investigation for a source including cultures and appropriate imaging should be undertaken. Renal imaging (e.g., ultrasound) to rule out obstructive pathology as well as urinalysis and measurement of fractional excretion of sodium (FE_{Na}) should be performed for patients presenting with acute kidney injury. Further evaluation may be indicated by specific presenting symptoms, such as head imaging for patients presenting with seizure, or abdominal imaging for patients with nausea and vomiting.

Management

Intravenous fluids to promote renal clearance of unwanted metabolites should be the initial therapy for TLS; volumes of 3 L/m^2/day are suggested, or as high as 5 to 6 L daily.[56] Acutely oliguric or anuric patients should be similarly fluid challenged because these may be the result of hypovolemia, but plans should be made for diuresis or renal replacement therapy if urine output does not improve or hypervolemia ensues. Patients with oliguria or anuria at baseline may require initial management with renal replacement therapy. Although previously recommended, treatment guidelines no longer support alkalinization of the urine, because this may instigate worse metabolic derangements, including phosphate nephropathy and xanthine crystal nephropathy.[56]

Hydration provides the primary therapy for hyperphosphatemia but limiting dietary phosphate intake and eliminating phosphate-containing supplements are also indicated. Hypocalcemia is a direct result of free calcium precipitating with excess phosphate to form the insoluble, nephrotoxic compound calcium phosphate. The extent of calcium phosphate formation is directly related to the product of serum calcium and phosphate concentrations. Products greater than 55 suggest a worsened long-term risk of calcium phosphate deposition in the viscera, although short-term outcomes are not well studied. To minimize the risk of calcium phosphate nephropathy, asymptomatic patients should go without calcium repletion. Patients with cardiac (e.g., dysrhythmia, heart blocks) or neurologic (e.g., seizure, coma) manifestations of hypocalcemia should receive intravenous calcium repletion.

Management of hyperkalemia is the same as that from any other etiology. Intravenous calcium given as a bolus can transiently (less than 1 hour) stabilize the myocardium of patients with existing or an imminent dysrhythmia (e.g., QRS widening). Efforts can then be made to shift potassium intracellularly via administration of insulin, bicarbonate, and beta-agonists. Ultimately, potassium must be removed from the body by the gastrointestinal tract with administration of potassium binders, by the kidneys with hydration and possibly loop diuretics, or by dialysis.

Uric acid is a metabolite in the degradation pathway of nucleic acids. Hyperuricemia from massive release of free nucleic acids can cause nephropathy both directly and by crystal formation in the renal tubules. In addition to hydration, hyperuricemia can be managed pharmacologically by administration of allopurinol, febuxostat or rasburicase.[56] Allopurinol, an analog of the uric acid precursor hypoxanthine, competitively inhibits enzymatic conversion of xanthine to uric acid. Although this decreases uric acid production, it does not eliminate uric acid already present in the body, and it leads to buildup of xanthine, which itself has limited solubility and potential to cause nephropathy. Febuxostat functions similarly to allopurinol, though its inhibition of the xanthine oxidase enzyme is noncompetitive. Febuxostat has been shown to be noninferior to allopurinol for prevention of tumor lysis syndrome,[57,58] however due to its high cost relative to allopurinol[59] it should only be used in patients who can't tolerate allopurinol (e.g., allopurinol allergy). Rasburicase, a recombinant form of the enzyme urate oxidase, eliminates uric acid directly by converting it into the more soluble metabolite allantoin. It is usually given as a single, intravenous dose. Significant reduction in uric acid levels within 1 day have been observed with weight-based doses of 0.05 to 0.15 mg/kg, and with fixed doses of 3 to 6 mg, with a single 6 mg dose for adults or 0.15 mg/kg dose for children reliably demonstrating effective reduction of uric acid levels.[60-62] Those with glucose-6-phosphate dehydrogenase (G6PD) deficiency should not receive rasburicase, because hydrogen peroxide is a byproduct of its activity and this may trigger hemolytic crisis. Methemoglobinemia may also result from rasburicase administration.[56]

Disposition

The Cairo-Bishop definition of TLS, a systematic classification of lab abnormalities and clinical manifestations of TLS, divides patients with only laboratory manifestations of TLS (laboratory TLS, or LTLS) from those with clinical manifestations of TLS (clinical TLS, or CTLS), such as kidney injury, dysrhythmia, or seizure. Patients with clinical TLS consisting of dysrhythmia or seizure should be admitted to an ICU; those with kidney injury may be admitted to a standard telemetry bed, but ICU care should be considered because mortality in patients with kidney injury and TLS increases relative to that with TLS alone. Patients with laboratory TLS only may be admitted to a monitored bed for observation and treatment.

LEUKOSTASIS

KEY CONCEPTS

- Leukostasis arises due to congestion of blood vessels by excessive numbers of leukocytes. This most often occurs in the lungs and CNS, and the resulting clinical picture may be difficult to differentiate from other diseases that afflict cancer patients (e.g., pneumonia, pulmonary embolism, CNS hemorrhage).
- Intravenous fluids should be administered in the ED to reduce blood viscosity, and red blood cell transfusions should generally be avoided. Therapies to lower the WBC count should be performed in consultation with an oncologist, and may include leukapheresis, administration of hydroxyurea, or initiation of chemotherapy.

Foundations

Leukostasis arises when the white blood cell (WBC) count is sufficiently high to cause vascular congestion, leading to organ dysfunction, typically in the lungs[63] or CNS. No single threshold exists for leukostasis to occur, and different types of leukemia cells cause leukostasis at widely variable cell counts. Patients with chronic lymphocytic leukemia (CLL) may tolerate WBC counts greater than 500,000 cells/μL, whereas patients with acute myeloid leukemia (AML) may develop leukostasis with WBC counts less than 100,000 cells/μL.

Two mechanisms are believed to drive leukostasis. First, blast cells are larger and less deformable than normal WBCs. As the number of blast cells in the blood increases, blood viscosity increases. Second, because certain cell types are more prone to causing leukostasis than others with similar size and physical characteristics, intrinsic features of leukemic cells, such as cytokine-induced activation of endothelial adhesion mechanisms, may also contribute.[64]

Clinical Features

Pulmonary leukostasis presents as dyspnea, tachypnea, and hypoxemia. Auscultation of pulmonary leukostasis may mimic lung infection with crackles or rhonchi, and bilateral opacities are often seen on imaging.[63] CNS leukostasis may present with confusion, audio or visual abnormalities, headache, ataxia, or coma. Intracranial hemorrhage may be seen on head imaging. Other clinical manifestations may include retinal hemorrhage, myocardial infarction, acute limb ischemia, priapism, renal vein thrombosis, and renal infarction.

Differential Diagnoses

Diagnosis of leukostasis is challenging because symptoms of leukostasis are similar to those of other problems common to leukemia patients. Pulmonary leukostasis presents with similar history, physical examination findings, and imaging as pneumonia or pulmonary edema. Patients with CNS leukostasis may present with nonspecific alteration of mental status, similar to that seen in metabolic derangement, medication side effect, or systemic manifestation of infection. Intracranial hemorrhage seen on head imaging may be related to leukostasis itself or may result from thrombocytopenia or disseminated intravascular coagulopathy (DIC), both of which often accompany hyperleukocytosis.

Diagnostic Testing

The gold standard diagnostic test for leukostasis is the presence of leukocyte-clogged blood vessels on tissue pathology. Because this is rarely available, the diagnosis must often be inferred and empirically treated based on knowledge of leukocyte count, cancer type, and clinical picture. A CBC with peripheral smear should be sent from the ED. Further evaluation is indicated to determine cancer type (if not known), including cytology and immunostaining, although results are not actionable in the ED. Symptom-specific imaging should be performed, such as chest plain films or CT for respiratory problems, and head CT or MRI for neurologic symptoms. Normal imaging findings do not exclude leukostasis, however.[63] If sent, blood gases should be processed immediately, because metabolically active leukocytes will continue to consume oxygen in the phlebotomized sample, resulting in falsely low oxygen levels.

Management

ED management of leukostasis centers on reduction of blood viscosity. Intravenous fluids should be administered to dilute the blood as much as possible. Although patients with hyperleukocytosis are often anemic, transfusion of red blood cells should be avoided in asymptomatic patients, because erythrocytes exacerbate blood viscosity. Platelets and plasma may be given as needed because these components make little or no contribution to blood viscosity.

The definitive treatment for hyperleukocytosis is reduction of leukocyte count, either by physically removing excess cells using leukapheresis or by destroying excess cells pharmacologically. Leukapheresis involves continuous removal of fractions of the patient's blood, selective extraction of leukocytes from the fractions, and return of the remaining product to the patient. Leukapheresis can reduce leukocyte count by 20% to 50% in only a few hours, but insertion of a central large-bore catheter is necessary, and leukapheresis requires specialized equipment not available at all institutions. Studies of outcomes with and without leukapheresis are small and nonrandomized, and none have shown a long-term survival benefit (>90-day survival) from the therapy. Results are conflicting as to short-term survival benefits of leukapheresis (7 to 30 days),[65,66] and expert opinion regarding use of leukapheresis for this application remains mixed overall.[67] Hydroxyurea, an inhibitor of deoxyribonucleotide synthesis, can pharmacologically reduce leukocyte burden by similar margins over 24 to 48 hours, and in studies has inconsistently shown a reduction in in-hospital mortality when used prior to induction chemotherapy.[68] Chemotherapy induction, which should only be initiated in consultation with an oncologist, can also quickly reduce leukocyte counts, but the patient should be monitored for signs of TLS.[67] Given the paucity of evidence supporting a single approach to leukoreduction, treatment varies significantly between hospitals, and should be guided by local experts. Due to the difficulty of clinically distinguishing leukostasis from other serious pathologies, treatments for other diagnoses may be simultaneously initiated. Such concomitant therapy (e.g., antibiotics) is particularly important for suspected pneumonia, because patients with hyperleukocytosis may be functionally neutropenic.

Disposition

Patents with leukostasis require hospitalization for monitoring, hydration, and leukocyte-reducing therapy. Asymptomatic patients with leukocytosis also warrant hospitalization if they have a blast count greater than 20,000 cells/μL, have a tumor type of AML, or have a new leukemia of unknown type. Patients with asymptomatic hyperleukocytosis who do not meet these criteria may be discharged with close, reliable follow-up, but this decision should be made in conjunction with the patient's oncologist.

SUPERIOR VENA CAVA SYNDROME

KEY CONCEPTS

- SVC syndrome occurs due to either external (e.g., tumor) or internal (e.g., thrombus) obstruction of the SVC.
- ED management of SVC syndrome is largely supportive. The head of the bed should be elevated, and supplemental oxygen provided if needed. If the cause of SVC syndrome is determined to be thrombus, anticoagulation may be initiated if not contraindicated.
- SVC syndrome is life-threatening only in the rare case of cerebral edema, hemodynamic collapse, or tracheal compromise. With the exception of these situations, definitive anti-cancer treatment should be postponed in order to allow for tissue diagnosis of the underlying mass if not already known.

Foundations

The superior vena cava (SVC) spans the final stretch of venous return from the upper body, spanning from the juncture of the brachiocephalic veins to the heart. The SVC is thin-walled, and blood pressures in the SVC are relatively low (≈2 to 8 mm Hg), making it particularly susceptible to external compression. When SVC flow is compromised, its internal pressure can reach 20 to 40 mm Hg, potentially resulting in symptoms or cardiac decompensation. Such clinical deterioration constitutes SVC syndrome.[69] Malignancy is the cause for more than 60% of total cases. Lung cancer and lymphoma cause over 90% of cases of malignancy-induced SVC syndrome. SVC syndrome due to an intraluminal mass, such as thrombosis, is increasing in prevalence. Cancer patients are at high risk for thrombosis due to their hypercoagulable state and indwelling venous catheters in the SVC.[69]

Clinical Features

Patients with SVC syndrome most commonly present with upper extremity, chest, or face edema or erythema, but dyspnea, dysphagia, chest pain, or cough may also be present. Physical examination

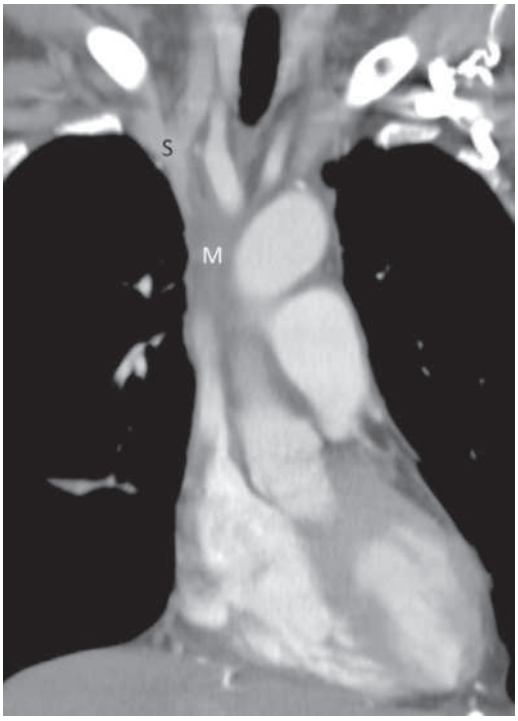

Fig. 112.5 Computed tomography (CT) scan of the chest with intravenous contrast demonstrating superior vena cava (SVC) compromise due to external mass in a patient with primary lung malignancy. *S,* SVC; *M,* intrathoracic mass. (Photo courtesy of the Department of Radiology, University of Maryland School of Medicine.)

findings often reflect elevated venous return pressures, including jugular venous distention (JVD) and edema, flushing, or cyanosis of the face, arms, and upper trunk. Distention of the SVC and compression of other nearby structures may cause vocal cord paralysis, blurred vision, and Horner syndrome.[69] Pleural effusion may be apparent on chest films or bedside sonography.[70] Overall, the type and severity of symptoms greatly depend on the acuity of SVC compression; patients with a slowly developing obstruction develop collaterals, which enable asymptomatic high-grade compression.

Differential Diagnoses

Edema and flushing isolated to the upper body is highly suspicious for SVC syndrome, particularly in a patient with known lung cancer or lymphoma. Other considerations include cellulitis or deep tissue infection (e.g., Ludwig angina), thoracic inlet syndrome, or obstruction of other deep veins (e.g., occlusive deep venous thrombosis in an internal jugular vein or subclavian vein). Other symptoms such as JVD, dyspnea, or cough are less specific and may suggest congestive heart failure, pneumonia, pericardial tamponade, or pulmonary embolism.

Diagnostic Testing

Thoracic imaging, and contrast-enhanced CT in particular, is the most important and commonly employed diagnostic modality for SVC syndrome (Fig. 112.5), but MRI is a viable alternative. In confirmed cases of SVC syndrome, a tissue diagnosis of the offending mass should be made prior to initiation of treatment.[69] This may be obtainable by sputum cytology, or by invasive means, such as bronchoscopy, lymph node biopsy, mediastinoscopy, or thoracotomy. Radiographically guided minimally invasive biopsy techniques performed by interventional radiologists have increasingly been employed for patients with SVC syndrome.[70] Moderate sedation or general anesthesia may be used safely to enable these procedures, however, in cases involving tracheal compromise, an airway should be emergently and carefully (e.g., awake fiberoptic intubation) established prior to anesthesia induction.

Management

In the ED, management of SVC syndrome is largely conservative. Elevating the head of bed to promote gravitational drainage of the upper body and administration of supplemental oxygen, when appropriate, may provide significant symptomatic relief. For patients with SVC syndrome due to obstructing thrombus, anticoagulation with or without thrombolytics should be initiated. Diuretics or steroids have historically been administered and in some practices continue to be used[70]; however, they have no proven benefit, may simply provoke complications, and we do not recommend them.

Although the symptoms of SVC syndrome are unpleasant, risk to life occurs only with the rare and extreme complications of airway obstruction, cerebral edema or hemodynamic compromise. Definitive treatment of malignant SVC syndrome can often be safely delayed until biopsy specimens are obtained because of the rare need for emergent therapy and the increasing ability to tailor anti-cancer therapy based on exact tissue diagnosis. Once a histologic diagnosis is made, the ideal combination of chemotherapy, radiation, and surgery, if indicated, is guided by specialty consultation.

In cases requiring emergent resolution of SVC syndrome, the initial steps in the ED are aimed at achieving basic medical stabilization (e.g., intubation and mechanical ventilation, hemodynamic optimization). Thereafter, endovascular stenting of SVC may be employed for rapid and effective reduction of SVC pressures.[69] Although no large randomized controlled trials have been performed, in smaller observational studies endovascular stenting for SVC syndrome has been safe and effective[71] and resulted in rapid symptomatic relief.[72] Stenting carries the additional advantages that a tissue diagnosis isn't required prior to implementation, and that stent placement doesn't interfere with later plans for radiation or chemotherapy.[69] Endovascular stenting may also be considered nonemergently in cases of failure of or contraindication to conventional therapies (e.g., radiation or chemotherapy).[69] Open surgical bypass or replacement of the SVC can be performed but is reserved for the most extreme cases, because less invasive measures are often successful.

Disposition

Although SVC syndrome is seldom life-threatening, symptomatic relief first requires diagnosis and treatment tailored to the underlying etiology. Hospitalization generally expedites this evaluation. Patients with hemodynamic compromise, cerebral edema, or tracheal compromise should be admitted to an ICU following initial stabilization.[70]

MONOCLONAL ANTIBODY THERAPIES AND COMPLICATIONS

KEY CONCEPTS

- Monoclonal antibody therapies function through various mechanisms using a range of targets. This leads to a diverse collection of known complications including infection and organ dysfunction.
- Identifying and treating infections, including opportunistic infections, is the most important element of management for the emergency physician in treating a patient with suspected complications of monoclonal antibody therapy.

Foundations

As the molecular foundations of cancer are further explored, it has become increasingly feasible to target therapeutics against

TABLE 112.3 Properties and Complications of Anti-neoplastic Monoclonal Antibody Therapies

	Target/Mechanism	Indication	Notable complications
Alemtuzumab	CD52/ADCC and CDC	CLL	Cytopenias, infusion reactions, opportunistic infections including PCP (black box warnings)
Bevacizumab	VEGF-A/direct inhibition	Glioblastoma, cancers of colon, lung, and renal cell	Bowel perforation, wound healing complications, bleeding complications (black box warnings)
Blinatumomab	CD19/BiTE	ALL	CRS, neurotoxicity (black box warnings)
Brentuximab	CD30/cytotoxic agent delivery	HL, ALCL	PML (black box warning)
Cetuximab	EGFR/direct inhibition	Cancers of colon, lung, head/neck	Anaphylactic reaction in those with alpha-gal antibodies
Ibritumomab tiuxetan	CD20/radioisotope delivery	B-cell NHL	Infusion reactions, cutaneous reactions, persistent cytopenias (black box warnings)
Inotuzumab ozogamicin	CD22/cytotoxic agent delivery	B-cell ALL	Hepatotoxicity, hepatic veno-occlusive disease (black box warnings)
Ofatumumab	CD20/ADCC and CDC	CLL, NHL	PML, hepatitis B reactivation
Panitumumab	EGFR/direct inhibition	Colon cancer	Dermatologic toxicities (black box warning), ocular keratitis
Pertuzumab	HER2/direct inhibition	Breast cancer	Embryo-fetal toxicity (black box warning), cytopenias
Rituximab	CD20/ADCC and CDC	NHL, HL, CLL	Severe infusion reactions, TLS, severe mucocutaneous reactions, PML (black box warnings)
Trastuzumab	HER2/direct inhibition, ADCC and CDC	Breast cancer	Cardiomyopathies, infusion reactions, pulmonary toxicity (black box warnings)

ADCC, antibody-dependent cell-mediated cytotoxicity; *ALCL*, anaplastic large cell lymphoma; *ALL*, acute lymphoblastic leukemia; *Alpha gal*, galactose-α-1,3-galactose; *BiTE*, bispecific T-cell engager; *CLL*, chronic lymphocytic leukemia; *CRS*, cytokine release syndrome; EGFR, epidermal growth factor receptor; *HER2*, receptor tyrosine-protein kinase erbB-2; *HL*, Hodgkin lymphoma; *NHL*, non-Hodgkin lymphoma; *PCP*, *Pneumocystis jirovecii* pneumonia; *PML*, progressive multifocal leukoencephalopathy; *TLS*, tumor lysis syndrome; *VEGF-A*, vascular endothelial growth factor A.

tumor-specific molecules. While this specificity can be achieved by small molecules such as tyrosine kinase inhibitors, the natural targeting abilities of antibodies lend themselves well to efficient development of new therapies, and this has led to steady expansion of the repertoire of anti-neoplastic monoclonal antibodies.

Monoclonal antibody therapies have been engineered to work by various mechanisms. In their simplest form, non-conjugated antibodies bind to tumor-associated targets, marking tumor cells for killing by antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Monoclonal antibodies tethered to cytotoxic payloads such as radioisotopes (e.g., ibritumomab) or cytotoxic medications (e.g., brentuximab) have increased the killing power of these therapeutics. Monoclonal antibodies tethered to the cytotoxic T cell–specific protein CD3, called bispecific T-cell engagers (BiTEs), are designed to amplify the efficiency of ADCC (e.g., blinatumomab). Monoclonal antibodies may also be designed to target and inhibit growth receptors on the tumor cell surface (e.g., trastuzumab) in addition to promoting cell destruction by ADCC and CDC. A list of common monoclonal antibodies along with their mechanisms of action and complications is given in Table 112.3.

Clinical Features

Because of the wide range of targets and mechanisms of action they employ, the complications of monoclonal antibody therapies are diverse, vary between therapies, and are too numerous to list here. A broad outline of the clinical features of common complications is provided in the following sections; additionally, Table 112.3 lists therapy-specific complications including black box warnings. Due to their immunomodulatory nature, patients receiving monoclonal antibody therapies are particularly susceptible to infectious complications. Clinical features will vary depending on the nature of infection, but may include fever, rigors, fatigue, malaise, and leukocytosis. Opportunistic infections have been noted (especially with use of alemtuzumab), so the emergency physician should be wary of features such as a vesicular rash which may represent reactivation of a herpetic virus, respiratory symptoms which may represent *Pneumocystis jirovecii* pneumonia (PCP) or activation of tuberculosis, or jaundice and liver function abnormalities which may represent reactivation of viral hepatitis. Monoclonal antibody therapies can also cause cytokine release syndrome (blinatumomab especially[73]) which may have presenting features very similar to infection and sepsis.

Infusion reactions can occur with all monoclonal antibody therapies but are especially common to rituximab, cetuximab, alemtuzumab, ibritumomab tiuxetan, and trastuzumab. These reactions typically occur during or shortly after infusion. Clinical features may be similar to a type I hypersensitivity reaction (anaphylaxis) or may be nonspecific. These can include rash, tachycardia, dyspnea, and hypotension.

Dysfunction of particular organ systems may also occur with monoclonal antibody therapies. Several adverse pulmonary events have been known to occur over a broad time frame, ranging from acute respiratory distress syndrome (ARDS) occurring within hours after an infusion, to organizing pneumonia developing weeks to months after completion of therapy. Various cardiac complications have been reported, including sudden cardiac death (cetuximab especially), and cardiomyopathy (trastuzumab especially). A broad range of neurologic symptoms may also occur, including progressive multifocal leukoencephalopathy (PML). Hepatotoxicity believed due to veno-occlusive disease has also been noted with inotuzumab.[74] As with all cancer therapeutics, rapid killing of cancer cells may lead to tumor lysis syndrome.

Differential Diagnoses

The differential diagnosis for patients with complications of monoclonal antibody therapies varies widely depending on presentation. Patients presenting with fever and symptoms of sepsis should be considered to have an infection until proven otherwise, though cytokine release syndrome and some infusion reactions can have a similar presentation. Opportunistic infection must also be considered. Patients with symptoms of heart or respiratory failure (e.g., dyspnea, chest pain, edema) may have primary toxicity from their therapy, but may also have pneumonia, pericardial disease, or acute coronary syndrome. For patients with neurotoxicity, other central nervous system insults such as cerebrovascular accident and meningitis should be considered.

Diagnostic Testing

Diagnostic testing must be guided by the patient's clinical picture. Patients with symptoms consistent with infection or sepsis should undergo blood and urine culturing, chest x-ray, and other workup as guided by presentation (e.g., sputum culture for productive cough). Those with symptoms of cardiac or pulmonary dysfunction should have cardiac biomarkers, electrocardiogram, chest x-ray, and echocardiogram performed. Patients with neurologic symptoms should undergo brain imaging.

Management

Aside from prompt recognition and treatment of infections, treatments for complications of monoclonal antibody therapies are largely supportive. Mild cases of cytokine release syndrome may be treated with antipyretics, and mild infusion reactions may respond to histamine blockers. However, both of these conditions may require hemodynamic support (e.g., IV fluids, vasopressors) in more severe cases. For patients experiencing infusion reactions, management with epinephrine IM and close airway monitoring should commence if there is any question of anaphylaxis. Cardiomyopathies may be managed with inotropic agents and diuresis. Pulmonary complications should be managed with appropriate respiratory support (including mechanical ventilation if needed), and corticosteroids may be considered once infectious etiology has been ruled out.

Disposition

Disposition of patients with complications of monoclonal antibody therapy depends largely on the clinical picture and severity of symptoms and should be determined in conjunction with the patient's oncologist.

T-LYMPHOCYTE CHECKPOINT INHIBITOR THERAPIES AND COMPLICATIONS

KEY CONCEPTS

- Because it involves reduction of immune self-tolerance, T-lymphocyte checkpoint inhibition therapy is marked by a wide variety of complications
- For symptoms severe enough to affect quality of life, systemic corticosteroids may be initiated. This should be done in consultation with an oncologist.

Foundations

Many cancer cells carry surface markers which are unique to tumor cells and not found on normal cells (e.g., due to mutations or fusion proteins).[75] Although these tumor-specific antigens (TSAs) can be recognized and attacked by host T cells, many are sufficiently similar to host antigens that they are protected by the same mechanisms that protect host cells from autoimmune attack, known collectively as self-tolerance.[76] The goal of T-lymphocyte checkpoint inhibitor therapy is to reduce T-cell self-tolerance, thereby allowing a T-cell immune response against TSA-bearing cancer cells.

Self-tolerance is achieved by several mechanisms, including a series of protein interactions known as checkpoints which are designed to prevent mature T cells in the peripheral tissues from attacking self-antigen bearing cells. By inhibiting these checkpoints, T-lymphocyte checkpoint inhibitor therapy enables a more vigorous antitumor immune response. Current therapies achieve this through antibody-driven inhibition of two such checkpoint pathways: the CTLA-4 pathway and the PD-1 pathway. Therapeutic antibodies targeting the PD-1 pathway exist both for PD-1 itself and its ligand PD-L1. The CTLA-4 pathway is targeted via the CTLA-4 protein (Table 112.4).[76]

Clinical Features

Inhibiting the mechanisms of the immune system that maintain self-tolerance imparts a steep price in the form of diverse complications across all organ systems. Clinical features of these complications as well as approximate rates of incidence are summarized in Table 112.5. Perhaps the most feared of these are hypophysitis, an immune-mediated pituitary disease which can cause shock due to glucocorticoid deficiency, and colitis, which can be life-threatening.[77] Additionally, patients undergoing checkpoint inhibitor therapy are susceptible to all of the other complications listed in this chapter, such as tumor lysis syndrome.[78]

TABLE 112.4 Molecular Targets for T-lymphocyte Checkpoint Inhibition Therapy, FDA-Approved Inhibitors, and Overall Complication Rates by Target

Molecular Target	Approved Inhibitors	Overall Complication Incidence
CTLA-4	Ipilimumab	60–85%[85]
PD-1	Nivolumab, Pembrolizumab	16–37%[85]
PD-L1	Atezolizumab, Avelumab, Durvalumab	12–24%[85]

TABLE 112.5 Immune-Related Adverse Events, Presenting Symptoms, Differential Diagnoses, and Initial Workup, Listed by Organ System

Organ System	Immune-Related Adverse Event and Approximate Incidence Rate (CR = case reports only)	Clinical Features	Differential Diagnosis	Diagnostic Testing
Cardiac	Pericardial effusion (CR[86-88])	See above section on Malignant Pericardial Disease.		
	Myocarditis (CR[89])	Dyspnea, fatigue, pulmonary edema[89]	ACS, pneumonia	CXR, ECG, echocardiogram
Endocrine	Hypophysitis (≈5% for all therapies; greater with anti-CTLA-4 therapy [up to 17%] than anti-PD-1 or anti-PD-L1[90])	Anorexia, fatigue, headache, nausea, diplopia, confusion, temperature intolerance, subjective fever and chills. Average onset 6–12 weeks after starting therapy.	Infection/sepsis, adrenal crisis, cerebral metastases[90]	Visual field testing; brain MRI (evaluate for pituitary stalk enlargement); pituitary function testing (e.g., thyrotrophin, gonadotrophin, and corticotrophin levels)[90]
	Thyroid dysfunction (≈10% for anti-PD-1 and anti-PD-L1 therapy; >50% for anti-CTLA-4 therapy[90])	Thyroiditis (thyroid gland pain/induration), fatigue, temperature intolerance	Hypophysitis, infection/sepsis	Thyroid function testing, antithyroglobulin and anti-thyroperoxidase antibody testing, corticotropin testing (rule out hypophysitis)
Gastrointestinal	Colitis (0–2% with anti-PD-1 therapy; 5–10% with anti-CTLA-4 therapy[90])	Abdominal pain, fever, diarrhea, hematochezia, constitutional symptoms. Average onset 6–7 weeks after therapy initiation.[90]	Infection/sepsis, bowel ischemia, cytomegalovirus colitis, *Clostridium difficile* infection, IBD, other intra-abdominal pathology[90]	CT imaging of abdomen/pelvis, testing for stool pathogens (e.g., *C. difficile* toxin), endoscopic examination of colon (e.g., colonoscopy, flexible sigmoidoscopy)[90]
	Diarrhea (12–14% with anti-PD-1 therapy; 30–35% with anti-CTLA-4 therapy[90])	Diarrhea only	Colitis, GI infection, bowel ischemia, cytomegalovirus colitis, *Clostridium difficile* infection, IBD, other intra-abdominal pathology	CT imaging of abdomen/pelvis, testing for stool pathogens (e.g., *C. difficile* toxin)
	Hepatotoxicity (5–10% for all therapies)[90]	Elevated transaminases; in severe cases abdominal pain, jaundice, coagulopathy, liver synthetic function loss	Infectious hepatitis, hepatic metastases	Liver function testing, testing of liver synthetic functions (e.g., albumin, coagulation studies), hepatic imaging (e.g., ultrasound)
Hematologic	Neutropenia (1% for anti-PD-L1 therapy[91])	Largely asymptomatic; may present with fever/infection	Neutropenia due to alternative cause (e.g., chemotherapy, primary malignancy)	Complete blood count with manual differential; workup for neutropenic fever (see separate section above) if symptoms dictate
	Anemia (10% for anti-PD-L1 therapy[91])	Largely asymptomatic; severe cases may present with fatigue or dyspnea	Anemia due to alternative cause (e.g., chemotherapy, primary malignancy, blood loss), autoimmune hemolytic anemia (incidence of 0.5% with anti-PD-1/PD-L1 therapy[92])	Complete blood count with manual differential, evaluation for hemolysis (e.g., lactate dehydrogenase, serum haptoglobin, bilirubin levels), iron studies, evaluation for sources of blood loss (e.g., inquire about history of melanotic or bloody stools)
	Immune thrombocytopenia (<0.5% for anti-PD-1/PD-L1 therapy[92])	Often asymptomatic; may present with bleeding-related complications (e.g., excessive bruising)	Immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation	Complete blood count with manual differential, evaluation for hemolysis (e.g., lactate dehydrogenase, serum haptoglobin, bilirubin levels), coagulation testing

Continued

TABLE 112.5 Immune-Related Adverse Events, Presenting Symptoms, Differential Diagnoses, and Initial Workup, Listed by Organ System—cont'd.

Organ System	Immune-Related Adverse Event and Approximate Incidence Rate (CR = case reports only)	Clinical Features	Differential Diagnosis	Diagnostic Testing
Integumentary	Skin toxicity (up to 25% with anti-CTLA-4 therapy[89])	Rash, pruritis, vitiligo. Onset usually within a few weeks of starting treatment, but can be delayed.[89]	Contact dermatitis, viral rashes, vasculitis[89]	Skin biopsy is usually feasible and yields definitive diagnosis.[89]
	Intraoral lesions (<10% for all therapies[93])	Mucositis, xerostomia, lichenoid tongue lesions[93]	Intraoral infection (e.g., herpes simplex, hand foot and mouth disease), mucositis from an alternative cause (e.g., chemotherapy)	Testing for intraoral infection (e.g., herpes serologies), consider biopsy of lesion if diagnosis is unclear
Neurologic	Myasthenia gravis (CR[89])	Weakness, ptosis, diplopia, dysarthria	Cerebrovascular accident, brain metastases, paraneoplastic syndrome, metastatic spinal cord compression	Brain imaging (CT or MRI), consideration of LP, electromyography can be helpful but often not needed in ED[89]
	Guillain-Barré syndrome (CR[89])	Weakness usually developing centrally from the extremities. Loss or attenuation of peripheral reflexes.	Cerebrovascular accident, brain metastases, paraneoplastic syndrome, metastatic spinal cord compression	Brain imaging (CT or MRI), consideration of LP, electromyography can be helpful but often not needed in ED[89]
Pulmonary	Pneumonitis (2–5% for anti-PD-1 therapy[90])	Dyspnea, hypoxemia, cough. Usual onset ≈3 months after initiation of therapy, but can occur as long as years later.[90]	Disease progression or pseudoprogression, infection, pulmonary embolus, exacerbation of coexisting lung disease[90]	Chest imaging (CXR or ideally high-resolution CT scan). Testing for underlying lung infection (sputum culture, urine legionella antigen, consideration of testing for PCP if immunocompromised, flu test if seasonally appropriate)
Renal	Acute kidney injury (≈2% for all therapies[94])	May be asymptomatic. In severe cases volume overload, uremia, acidosis, electrolyte disturbances.	AKI due to alternative cause such as sepsis, dehydration, or malignant obstruction of genitourinary tract	Measurement of serum creatinine, blood urea nitrogen, pH, and electrolytes. Renal imaging (e.g., ultrasound) to exclude obstruction. Fraction of excreted sodium testing (FENa).
Rheumatologic	Vasculitis (CR, most frequently large vessel and nervous system vasculitides[95])	Fever, fatigue, rash, numbness, weakness	Infection, paraneoplastic polyarteritis nodosa, leukocytoclastic vasculitis due to melanoma or other cancers, worsening metastatic disease, new onset of primary vasculitis[95]	Difficult to definitively diagnose from the ED; often requires biopsy of blood vessel or affected tissue[95]
	Myalgias and Arthralgias (2–12% for all therapies[89])	Morning stiffness, synovitis, proximal weakness[89]	New onset of primary rheumatologic disease (e.g., rheumatoid arthritis), drug-induced lupus or myositis	Testing for rheumatologic markers (e.g., rheumatoid factor, anti-nuclear antibody) to rule out new onset rheumatologic disease

ACS, Acute coronary syndrome; *CR*, incidence limited to case reports; *CXR*, chest x-ray; *ECG*, electrocardiogram; *LP*, lumbar puncture; *PCP*, *Pneumocystis jirovecii* pneumonia.

Differential Diagnoses

Differential diagnoses vary based on the presenting symptoms. Differentials for each complication are listed in Table 112.5.

Diagnostic Testing

Diagnostic testing varies based on the presenting symptoms. Diagnostic strategies for each complication are listed in Table 112.5.

Management

Management strategies for complications of checkpoint inhibitor therapy are laid out based on the severity of the complication. Scales to judge the grade of each type of complication have been developed[79] but are beyond the scope of this text. In general, symptoms that negatively impact daily life and are recalcitrant to targeted management (e.g., oral analgesics for myalgia, or topical prednisone for rash) are considered grade 3, and warrant initiation of prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d.[79] This is particularly true of suspected hypophysitis with hemodynamic instability, for which methylprednisolone 1 to 2 mg/kg/d intravenous should immediately be initiated. Whenever possible, steroids should be initiated in consultation with an oncologist. For severe colitis, initial reports suggest that infliximab may be helpful in steroid-recalcitrant cases.[77]

Disposition

Disposition will vary based on specific complication and severity and may range from discharge with close oncology follow-up to ICU admission. Whenever possible, disposition decisions should be made in consultation with the patient's oncologist.

ADOPTIVE CELL TRANSFER THERAPIES AND COMPLICATIONS

KEY CONCEPTS

- Adoptive cell transfer therapy (CAR T-cell therapy) involves using the patient's own T-cells to attack tumor cells. Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are the most common and serious complications of this treatment.
- Expressive aphasia is a very specific and early sign of ICANS. Presence of this finding should increase clinical suspicion for ICANS, though its absence should not be used to exclude the diagnosis.
- Tocilizumab (anti-IL-6 receptor antibody) and corticosteroids may be used to treat severe CRS. ICANS is typically only responsive to corticosteroids. Because of the effects these treatments may have on the underlying antineoplastic therapy, they should only be administered in collaboration with oncology.

Foundations

Adoptive cell transfer therapies, often referred to as chimeric antigen receptor (CAR) T-cell therapies, employ the patient's own T cells, reprogrammed to attack cancer cells. Following harvest of the patient's T cells via leukapheresis or other methods, the cells are genetically modified by insertion (e.g., by lentivirus) of a chimeric antigen receptor (CAR) protein expression cassette. The CAR protein subsequently expressed by the cells is a combination of a recognition domain for a tumor-specific antigen, and an effector domain that activates the T cells to armed effector status and triggers clonal expansion when the tumor antigen is bound. Following genetic modification, the altered T cells are expanded in vitro and then transfused back to the patient.[80]

As of August 1, 2020, two FDA-approved CAR-T therapies exist: tisagenlecleucel and axicabtagene ciloleucel. Both are designed to recognize CD-19, a B cell–specific surface marker which is often overexpressed on B cell lymphoma and leukemia cells.[80]

Clinical Features

As with other immunotherapies, reprogramming the immune system comes at the cost of severe adverse effects. In the case of CAR T-cell therapy, cytokine release syndrome (CRS), and immune effector cell–associated neurotoxicity syndrome (ICANS) are particularly prevalent.[81] CRS, in which uncontrolled cytokine release leads to a potentially life-threatening inflammatory syndrome, occurs in nearly 60% of patients receiving CAR T-cell therapy.[82] Severe CRS, causing end-organ dysfunction or requiring multiple pressors to achieve hemodynamic stability, occurs in up to 25% of patients.[82,83] CRS may appear clinically similar to infection or sepsis, as symptoms include fever, malaise, myalgias, fatigue, and rash. In severe cases, hypotension, respiratory failure, and end-organ dysfunction will develop.[81] Median time from CAR T-cell therapy to onset of CRS is 3 days.[82] ICANS, in which the central nervous system undergoes immune cell–mediated damage, occurs in up to 50% of patients receiving CAR T-cell therapy.[84] Clinical features range from confusion, headache, aphasia, tremor, behavioral changes, peripheral numbness, and weakness to grand mal seizures and cerebral edema.[84] Expressive aphasia is a very specific and early sign of ICANS in at least one study, and may help differentiate ICANS from other etiologies of neurologic insult, though the absence of this finding should not be used to exclude the diagnosis.[81] Median onset of ICANS is four to seven days after CAR T-cell therapy.[84] Interestingly, while ICANS is considered a distinct entity from CRS, severe cases of ICANS are rarely seen in the absence of accompanying or preceding CRS.[84]

Differential Diagnoses

Patients presenting with symptoms of CRS should be considered to have an infection and sepsis until proven otherwise. This is especially important because lympho-depleting chemotherapy is often given prior to CAR T-cell infusion, thus imparting some degree of immunocompromise.[80] The symptoms of ICANS overlap with other CNS injuries such as cerebrovascular accident, infectious meningoencephalitis, or CNS metastasis.

Diagnostic Testing

Patients suspected to have cytokine release syndrome should undergo thorough testing for an underlying infectious source of symptoms (see earlier section on neutropenic fever). Patients with symptoms of ICANS should undergo CNS imaging by CT or MRI and consideration should be given to lumbar puncture and electroencephalography as symptoms dictate. Although brain imaging studies may be normal in ICANS, MRI imaging may show T2 hyperintensities in the white matter and thalami,[84] and appropriate imaging may be used to exclude other diagnoses. Cerebrospinal fluid of patients with ICANS may have elevated levels of protein and leukocytes,[84] so infection-specific cultures and diagnostics may be needed to rule out infectious meningitis.

Management

Due to their propensities for CRS and ICANS, FDA approval of CAR T-cell therapies to date has been contingent on provision of specific risk evaluation and mitigation strategies (REMS) for grading and management of these conditions. Due to the complexities involved, CAR T-cell therapy patients should be treated at a facility approved to administer these therapies, and the patient's oncologists should be involved in all management decisions.

Low-grade CRS (fever, malaise, and constitutional symptoms, but otherwise normal vital signs and organ function) may be treated symptomatically. For patients with more severe CRS, REMS protocols vary somewhat but generally involve escalating to therapy with the anti-IL-6 receptor antibody tocilizumab, followed by corticosteroids in the most severe cases or if there is no response to tocilizumab. Supportive therapies such as intravenous fluids, vasopressors, and respiratory support should be provided. Similarly, patients with low-grade ICANS (symptoms not affecting activities of daily life) may be treated symptomatically. Those with more severe manifestations generally receive corticosteroids, as tocilizumab generally has minimal effect on ICANS.[81] In all cases, decisions to give corticosteroids should be made in conjunction with the patient's treating oncologist because this may have a detrimental effect on the antitumor effects of CAR T-cell therapy.[80]

Disposition

Disposition decisions should be made in consultation with the patient's oncologist, but most if not all patients with suspected complications of CAR T-cell therapy should be admitted to the hospital. Because of the specialized nature of these relatively new therapies, whenever possible the patient should be transferred to the center where they received CAR T-cell therapy, or another center experienced in these treatments.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 112: QUESTIONS AND ANSWERS

1. Which of the following statements regarding infections in cancer patients with febrile neutropenia is *true*?
- **a.** Blood cultures should be obtained from an indwelling catheter if present.
- **b.** Empirical antifungal coverage should always be immediately initiated.
- **c.** Head computed tomography (CT) is always indicated.
- **d.** Lumbar puncture (LP) should be routinely undertaken.
- **e.** Sinus imaging should be routinely undertaken.

Answer: A. In patients with a preexisting central line, one blood culture should be obtained peripherally while other cultures should be simultaneously drawn off each lumen of the central catheter. Bacterial growth in the catheter-drawn samples more than 2 hours prior to the peripheral samples is suggestive of a catheter-associated infection. Head CT is not routinely indicated. It may be performed if the patient demonstrates focal neurologic deficits, alteration in mental status, or a lumbar puncture is planned. LP and CT scans of the sinuses are not routinely done initially unless signs or symptoms suggest these are involved.

2. A 33-year-old woman with breast cancer presents with fever and neutropenia. She is status post mastectomy and undergoing chemotherapy. She denies respiratory symptoms and chest x-ray is unremarkable. Vital signs are T 38.8°C; HR, 110 beats/min; and BP, 110/60 mm Hg. Examination is otherwise normal. She has no indwelling catheters. Which of the following is the most appropriate empirical antibiotic regimen?
- **a.** Antibiotics should be withheld pending radiographs and cultures
- **b.** Cefepime as monotherapy
- **c.** Ceftazidime and gentamicin
- **d.** Meropenem and vancomycin
- **e.** Ticarcillin and amikacin

Answer: B. Monotherapy with imipenem, meropenem, ceftazidime, or cefepime is as effective as traditional dual therapy with an antipseudomonal penicillin and aminoglycoside. However, vancomycin should be included as well if any of the following exist:
- Hypotension or evidence of cardiovascular impairment
- Clinically suspected catheter infection
- Positive blood cultures for gram-positive organisms
- Known colonization with methicillin-resistant *Staphylococcus aureus* or cephalosporin-resistant *Pneumococcus*

3. Which of the following is not a risk factor for acute tumor lysis syndrome (TLS)?
- **a.** High-burden, rapidly growing and highly chemosensitive leukemias
- **b.** Hypovolemia
- **c.** Age older than 60 years
- **d.** Preexisting renal dysfunction
- **e.** Rapidly growing solid tumors

Answer: C. TLS is most likely to occur in patients with tumors that are high burden, rapidly growing, and highly chemosensitive, such as Burkitt lymphoma or acute lymphoblastic leukemia (ALL). TLS can also occur in rapidly growing solid tumors, such as breast, testicular, and small cell lung cancers; overall, the diversity of malignancies with potential for TLS is growing as we develop more effective and fast-acting chemotherapeutics. Patient factors predisposing to TLS include preexisting renal failure, hypovolemia, and hyperuricemia. Older age is not a known risk factor for TLS.

4. A 65-year-old male with a history of a large head and neck tumor presents with symptoms of fatigue, weakness, confusion, depression and malaise, nausea, vomiting, constipation, polyuria, and palpitations. His electrocardiogram (ECG) demonstrates a shortened QT

CHAPTER 112: QUESTIONS AND ANSWERS—cont'd

interval. Which of the following electrolyte abnormalities is likely to underlie his presentation?

a. Hypercalcemia
b. Hyperkalemia
c. Hyperuricemia
d. Hypocalcemia
e. Hypokalemia

Answer: A. This patient's presentation is most consistent with malignancy-associated hypercalcemia. Malignancy-associated hypercalcemia (MAH) signifies advanced disease, with median survival of less than 2 months. Synthesis of PTHrP, classically called *humoral hypercalcemia*, causes about 80% of cases of MAH, and is usually associated with squamous cancers, such as head and neck, lung, esophageal, cervical, ovarian, and endometrial carcinomas. Presenting symptoms often include weakness, lethargy, confusion, abdominal pain, nausea, vomiting, constipation, polyuria, polydipsia, and kidney injury. Electrocardiogram findings may initially exhibit QT interval shortening, progressing to dysrhythmias and heart block as hypercalcemia worsens.

5. Which of the following monoclonal antibodies is involved in the management of severe cytokine release syndrome due to adoptive cell transfer therapy (CAR T-cell therapy)?

a. Alemtuzumab
b. Cetuximab
c. Ofatumumab
d. Tocilizumab

Answer: D. Tocilizumab (anti-IL-6 receptor antibody) has been shown to effectively mediate the pro-inflammatory effects of cytokine release syndrome. The other options listed are antitumor agents.

113

Acid-Base Disorders

Nicole S. McCoin and Wesley H. Self

KEY CONCEPTS

- Metabolic acidoses are classified into wide anion gap and normal anion gap acidoses, based on basic metabolic panel (BMP) values. A wide anion gap metabolic acidosis is present when the gap exceeds 15 mmol/L.
- Common causes of a wide anion gap metabolic acidosis are summarized with the mnemonic MUDPILES (Methanol, Uremia, DKA, Paraldehyde, Polyethylene glycol, or Paracetamol (Acetaminophen), Iron, Lactate, Ethylene Glycol, Salicylates).
- When a wide anion gap metabolic acidosis is identified on the BMP, the potential underlying causes can be determined through analysis of the delta gap and the osmolar gap.
- Common causes of a normal anion gap acidosis are summarized with the mnemonic HARDUP (Hyperalimentation/Hospital-acquired administration of saline, Acid infusion, Addison's disease, Carbonic Anhydrase Inhibitors, Renal Tubular Acidosis, Diarrhea, Ureterosigmoidostomy, and Pancreatic drainage/fistula.)
- The optimal use of sodium bicarbonate therapy for metabolic acidosis is not clear and is the subject of ongoing research. A common strategy is to use sodium bicarbonate to increase pH above 7.10 in severe metabolic acidosis or above 7.20 for patients with severe metabolic acidosis and acute kidney injury.
- Metabolic alkalosis is associated with decreased circulating volume. GI-based chloride losses can be corrected with the administration of sodium chloride–containing intravenous fluids.
- Metabolic alkalosis caused by impaired renal excretion of sodium chloride that does not respond to intravenous fluids.
- Respiratory acidosis or alkalosis relates to carbon dioxide (CO_2) clearance, and thus is dependent on minute ventilation. Respiratory acidoses are caused by etiologies that decrease the ability of the body to rid itself of CO_2, such as primary lung disease, chest wall disorders, and entities that decrease respiratory drive.
- Respiratory alkalosis results from disorders that increase CO_2 clearance such as hyperventilation and salicylate toxicity. Values from the blood gas are used primarily to identify the presence of respiratory acid-base disorders.

FOUNDATIONS

The body's homeostatic mechanisms must keep acid-base balance under tight control. Acid-base disturbances can be life-threatening, with severe acid-base disorders leading to cellular compromise and death within hours due to alterations in hydrogen bonds, protein structures, and enzyme function.

The pH of the blood summarizes the systemic acid-base balance. pH is the negative logarithm of hydrogen-ion concentration (H^+) and has a normal range of 7.35 to 7.45. This normal pH is maintained by the kidneys' regulation of plasma bicarbonate (HCO_3^-) and the lungs' regulation of the partial pressure of arterial carbon dioxide ($Paco_2$). The relationship of $[HCO_3^-]$ and $Paco_2$ to pH is described by the Henderson-Hasselbach equation: $pH = pK + \log_{10} ([HCO_3^-]/[0.03 \times Paco_2])$, where pK denotes the acid dissociation constant, $[HCO_3^-]$ is measured in millimoles per liter (mmol/L), and $Paco_2$ is measured in millimeters of mercury (mm Hg).

The terms *acidemia* and *alkalemia* describe the summary acid-base state, or the pH of the blood, while the terms *acidosis* and *alkalosis* describe discrete conditions. Blood pH less than 7.35 defines acidemia, while a pH greater than 7.45 defines alkalemia. An acidosis is an acid-base disturbance that increases $[H^+]$ and lowers the pH. An alkalosis is an acid-base disturbance that decreases $[H^+]$ and increases the pH. Multiple acidoses and alkaloses may be present at the same time; in these situations, pH describes the balance among all the acid-base disturbances.

The "metabolic system" includes cellular production and renal excretion of acids and bases. The respiratory system ventilates acid, in the form of carbon dioxide, out of the body through the lungs. The metabolic system and respiratory system are tightly coordinated to maintain acid-base hemostasis. Metabolic acid-base disorders are caused by abnormalities of cellular function, altered renal excretion of acids and bases, and exogenous gain or loss of acids and bases through the gastrointestinal tract. In clinical medicine, the principal test to evaluate for metabolic acid-base disturbances is plasma bicarbonate concentration ($[HCO_3^-]$). When a primary metabolic acid-base disturbance develops, the respiratory system compensates through increased or

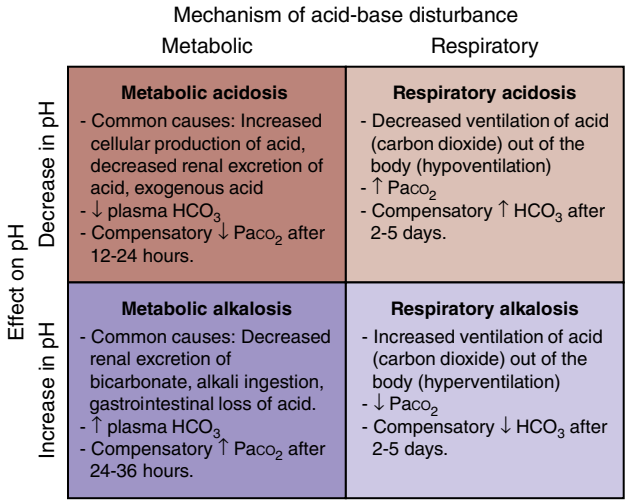

Fig. 113.1 Classification of the four major categories of acid-base disorders.

decreased ventilation of carbon dioxide to maintain acid-base hemostasis. Respiratory compensation typically takes 12 to 24 hours for a metabolic acidosis and 24 to 36 hours for a metabolic alkalosis.[1]

Respiratory acid-base disorders are caused by abnormalities in ventilating carbon dioxide out of the body through the lungs. In clinical medicine, a common method of evaluating ventilation is by measuring the partial pressure of carbon dioxide in arterial blood ($Paco_2$). After a primary respiratory acid-base disturbance develops, the metabolic system compensates by altering the excretion of acid in the kidneys to maintain acid-base hemostasis. Metabolic compensation typically takes between 2 and 5 days after a respiratory acidosis or alkalosis develops.[1]

Acid-base disorders are categorized by their pathophysiologic mechanism (metabolic or respiratory) and effect on pH (acidosis or alkalosis). Hence, the four broad categories of acid-base disorders are metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis (Fig. 113.1). A simple acid-base disturbance describes a physiologic state with a single acid-base disorder with or without compensation. A mixed-acid base disturbance describes a state with more than one primary acid-disorder, each with or without compensation.

This chapter provides an overview of the identification and classification of acid-base disorders in emergency medicine. Specific acid-base disorders are discussed in detail in other disease-focused chapters.

CLINICAL FEATURES

A variety of patient presentations may prompt a clinician to search for acid-base disorders. This typically occurs in one of the three following scenarios in the emergency department:

1. The patient presents with undifferentiated signs and symptoms and is ill-appearing with vital sign abnormalities, respiratory distress, or altered mental status.
2. The patient presents with signs, symptoms or chronic medical conditions known to potentially cause acid-base abnormalities, such as toxic ingestions, vomiting, diarrhea, pregnancy, diabetes mellitus, chronic kidney disease, chronic liver disease, chronic lung disease, or neuromuscular disease.
3. The patient is well-appearing and does not have an overt clinical presentation consistent with an acid-base disorder, but laboratory studies demonstrate an acid-base abnormality.

Once an acid-base abnormality is suspected, the clinician should initiate targeted diagnostic testing to identify the type of acid-base disorder present and its underlying cause.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TESTING

The initial phase of evaluating most patients with acid-base disorders is interpretation of laboratory data. These data can assist the clinician in classifying the type of acid-base disorder(s) present: metabolic acidosis, metabolic alkalosis, respiratory acidosis, or respiratory alkalosis. Once the class of acid-base disorder is identified, the clinician can develop a differential diagnosis for the cause of the disorder.

Diagnostic Testing

Acid-base disorders can be characterized by the pH, $Paco_2$, and HCO_3 concentration. Hence, interpretation of the basic metabolic panel (BMP) and blood gas is essential. Blood gas measurements can be obtained from either an arterial sample (arterial blood gas, ABG) or a venous sample (venous blood gas, VBG). Respiratory and acid-base physiology were classically described using ABG values, and ABG measurements provide a direct evaluation of oxygenation status as opposed to VBGs. However, obtaining an ABG requires arterial puncture, which is painful for patients, time-consuming for clinicians, and higher risk than venous blood sampling.

A VBG can be obtained from a routine venous blood draw with other laboratory studies and is a reasonable screening test in many settings. In the following sections, we provide a detailed discussion using ABG values; many of these concepts also apply to VBG values with the following considerations. On average, pH on a VBG is about 0.03 less than a concurrent ABG pH. The relationship between venous Pco_2 ($Pvco_2$) and $Paco_2$ is more variable, with $Pvco_2$ about 5 to 9 mm Hg higher than concurrent $Paco_2$ for many patients. $Pvco_2$ less than 45 mm Hg has nearly 100% negative predictive value for ruling out hypercapnia (defined as $Paco_2 > 50$ mm Hg). Pvo_2 does not correlate with Pao_2 and cannot be used to guide management decisions about oxygen supplementation. However, oxygenation can be adequately measured noninvasively in most patients with pulse oximetry providing saturation of peripheral oxygen (Spo_2) values. Hence, the combination of a VBG and Spo_2 is a useful screen for acid-base disturbances and hypoxemia in most patients. Patients with a complex acid-base disorder or severe respiratory illness often benefit from an ABG in addition to the initial screen with a VBG and Spo_2.

Goals for the clinician include identifying whether an acid-base disorder is present, and if so, determining the primary disturbance. Once the primary disturbance has been identified, simple formulas can be used to understand if an appropriate compensatory response has occurred and if another primary acid-base order is also present. Compensatory processes adjust the pH toward normal, but usually not completely to normal and never beyond normal.

Several methods for identifying, classifying, and understanding acid-base disorders have been described, including the physiologic, physiochemical (also known as the Stewart method), and base-excess approaches. A simplified method for acid-base classification that incorporates concepts from each approach can be rapidly applied by clinicians at the bedside and is described in detail below. This method involves a five-step approach that primarily focuses on the interpretation of the BMP to evaluate for metabolic acid-base disturbances and a three-step approach that primarily focuses on the interpretation of the ABG to evaluate for respiratory acid-base disturbances.

Basic Metabolic Panel Interpretation

The BMP is the primary test to evaluate for metabolic acid-base disturbances and includes plasma concentrations for the following: sodium (Na), chloride (Cl), potassium (K), bicarbonate (HCO_3), blood urea nitrogen (BUN), creatinine (Cr), and glucose. Normal ranges for

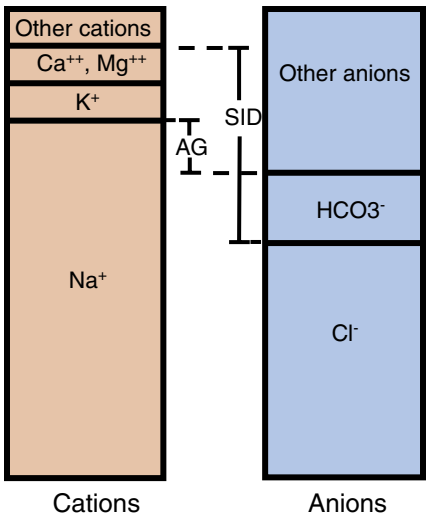

Fig. 113.2 Schematic representation of the anion gap (AG) and strong ion difference (SID). Human plasma is maintained at electroneutrality (no net charge). Thus, the sum of cations in plasma is equivalent to the sum of the anions. Calculation of the anion gap and strong ion difference can help identify the relative contribution of different cations and anions to plasma composition. An increase in anion gap indicates an increase in the contribution of "other anions," such as lactate in lactic acidosis or ketone bodies in diabetic ketoacidosis. A relative increase in chloride concentration compared to the strong cations (Na^+, K^+, Ca^{++}, Mg^{++}), such as occurs during saline infusion, leads to an increase in "other cations," including H^+, and a decrease in the SID.

laboratory tests vary, and clinicians should be familiar with the normal ranges in their institutions. Specific thresholds are shown below for illustrative purposes.

Five-Step Acid-Base Approach to the BMP

BMP Step 1. Check for Abnormal Values. Evaluate the BMP for any abnormalities. A low HCO_3 concentration (for example, <22 mmol/L) identifies a metabolic acidosis, whereas a high HCO_3 concentration (for example, >29 mmol/L) identifies a metabolic alkalosis.

BMP Step 2. Check the Anion Gap. The anion gap (AG) is calculated with the formula: $AG = [Na^+] - ([Cl^-] + [HCO_3^-])$. The anion gap is used to evaluate for the presence of a wide anion gap metabolic acidosis. A wide anion gap metabolic acidosis is present if the anion gap is elevated, regardless of values for HCO_3 and pH. The anion gap is normally between 9.0 and 15.0 mmol/L, and thresholds to signify a wide anion gap vary between 10 and 15 mmol/L due to differences in laboratory technique.[1] For illustrative purposes, a threshold of 15 mmol/L is used to define a wide anion gap in this chapter.

Plasma is electrically neutral. Hence, the sum of positive ion charges is equal to the sum of negative ion charges, as detailed in the equation: $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] + [H^+]$ + unmeasured cations = $[Cl^-] + [HCO_3^-] + [CO_3^{2-}] + [OH^-]$ + albumin + phosphate + sulfate + lactate + unmeasured anions. Clinical laboratories only routinely measure plasma concentrations of the major ions, resulting in some cations and anions being "unmeasured." A greater proportion of cation charge is typically measured than the anion charge, resulting in the concept of an "anion gap"—that is, the difference between measured cations and anions (Fig. 113.2). The calculation for the anion gap accounts for the most plentiful measured cation (Na^+) and the two most plentiful measured anions (Cl^- and $HCO3^-$).

Accumulation of "unmeasured anions"—that is, any anion other than chloride and bicarbonate—results in a wide anion gap metabolic acidosis. An acidosis in which the decrease in $[HCO3^-]$ is accompanied by an increase in $[Cl^-]$ of approximately the same magnitude results in a normal anion gap acidosis, also known as hyperchloremic metabolic acidosis.

BMP Step 3. If a Metabolic Acidosis is Present, Apply the Rule of 15. The rule of 15 is used to evaluate for concomitant respiratory acid-base disturbances in addition to a metabolic acidosis. According to the rule of 15, in an isolated metabolic acidosis, HCO_3 + 15 should equal the $Paco_2$ (±2 mm Hg) and the two digits of the pH following the decimal (±0.02). If measured $Paco_2$ equals the predicted value, simple respiratory compensation for a primary metabolic acidosis exists. If measured $Paco_2$ is less than the predicted value, there is a superimposed primary respiratory alkalosis on top of metabolic acidosis. If the $Paco_2$ is higher than the predicted value, a superimposed primary respiratory acidosis is present.

The rule of 15 has an important caveat. When HCO_3 falls below 10 mmol/L, the rule of 15 loses validity because HCO_3 and $Paco_2$ have a nonlinear relationship. In cases with HCO_3 between 5 mmol/L and 10 mmol/L, the expected $Paco_2$ is about 15 mm Hg and the expected pH is about 7.15 (this is known as the corollary to the rule of 15). Alternatively, in these cases with HCO_3^- less than 10 mmol/L, Winters equation can be used to calculate a more precise expected $Paco_2$: expected $Paco_2 = [HCO_3^-] * 1.5 + 8 \pm 2$. There are examples of the interpretation of the BMP using anion gap calculations and the rule of 15 available at the end of this chapter on ExpertConsult.com

BMP Step 4. If a Wide Anion Gap Metabolic Acidosis Is Present (Anion Gap ≥15), Check the Delta Gap. Calculation of the delta gap is used to identify additional metabolic acid-base disturbances superimposed on a wide anion gap metabolic acidosis. The delta gap explores the difference between the calculated anion gap and 15 mmol/L, which is the upper limit of normal for the anion gap, as well as the change in measured bicarbonate level from 24 mmol/L, which is the upper limit of normal for the bicarbonate level. In an isolated wide anion gap metabolic acidosis, each incremental increase in the anion gap is matched by an incremental decrease in HCO_3 of approximately the same magnitude. For example, each 1 mmol/L increase in the anion gap above 15 mmol/L is expected to be accompanied by a 1 mmol/L drop in HCO_3 below 24 mmol/L. A measured bicarbonate concentration higher than predicted by the delta gap calculation indicates a concomitant metabolic alkalosis. A measured bicarbonate concentration lower than predicted by the delta gap calculation indicates a concomitant normal anion gap metabolic acidosis. There are examples of delta gap calculations available at the end of this chapter on ExpertConsult.com

BMP Step 5. If a Wide Anion Gap Metabolic Acidosis Is Present (Anion Gap ≥15), But the Cause Is Not Evident, Check the Osmolar Gap. The osmolar gap is used to screen for the presence of abnormal particles dissolved in the blood. In the evaluation of acid-base disorders, calculation of the osmolar gap is commonly used to screen for the possibility of toxic alcohol ingestion as a cause for an unexplained wide anion gap metabolic acidosis.

Osmolality is a direct measure of the number of separate particles (solute) dissolved in a unit of water (solvent) within the blood. Calculated osmolarity is a calculated value of the expected number of osmotically active solutes in blood based on measured concentrations of the most common solutes. In normal physiologic states, the major solutes are sodium, the counter anions to sodium (e.g., chloride, bicarbonate, others), glucose, and urea. In patients who have been drinking ethanol, ethanol concentration (ETOH) is easily measured and is also a major contributor. Thus, the calculated osmolarity is calculated with the equation:

$$\text{calculated osmolarity} = (2 * \text{Na}) + (\text{glucose}/18) + (\text{BUN}/2.8) + (\text{ETOH}/3.7)$$

In this equation, Na is measured in mmol/L, and glucose, BUN, and ETOH are measured in mg/dL. Units for osmolarity are mOsm/kg of

water; the equation above has built-in constants that convert mg/dL to mmol/L.

Osmolality can be measured in clinical laboratories. The measured osmolality includes the solutes in the calculated osmolarity equation and other solutes in the blood not included in the equation. The difference between measured osmolality and calculated osmolarity is the osmolar gap:

$$\text{Osmolar gap} = (\text{measured osmolality}) - (\text{calculated osmolarity})$$

$$= (\text{Measured osmolality}) - [(2 * \text{Na}) + (\text{glucose}/18) + (\text{BUN}/2.8) + (\text{ETOH}/3.7)]$$

A normal osmolar gap is 10 mOsm/kg or less. A wide osmolar gap (>10 mOsm/kg) indicates accumulation of a significant volume of solute not included in the osmolarity equation (that is, a significant volume of "unanticipated" osmotically active solutes). In the setting of a wide anion gap metabolic acidosis, a wide osmolar gap may indicate the presence of toxic alcohols, such as methanol or ethylene glycol. However, it is important to note that a normal osmolar gap does not eliminate the possibility of a toxic alcohol poisoning, because the osmolar gap decreases as toxic alcohols are metabolized. Additionally, the calculation assumes a normal baseline osmolality, which is not always true. When an elevated osmolar gap is caused exclusively by a toxic alcohol, the plasma concentration of methanol or ethylene glycol can be estimated from the osmolar gap. To estimate the concentration of methanol in mg/dL, multiply the osmolar gap by 3. To estimate the concentration of ethylene glycol in mg/dL, multiply the osmolar gap by 6. There is an example of the osmolar gap calculation in Box 113.1.

Blood Gas Interpretation

Blood gases are the primary tests to evaluate for respiratory acid-base disturbances and include measurements for pH, the partial pressure of carbon dioxide (Pco_2) and the partial pressure of oxygen (PO_2).

Three-Step Acid-Base Approach to the ABG

ABG Step 1. Determine if the Patient Is Acidemic or Alkalemic. Evaluate the pH. A pH less than 7.35 indicates acidemia; pH greater than 7.45 indicates alkalemia. pH is a summary measure that describes the overall balance of acid-base status. A pH in the normal range (7.35 to 7.45) may indicate no acid-base disturbance is present, a disturbance is present with compensation resulting in pH within the normal range, or multiple disturbances are present that, when combined, result in a pH in the normal range.

ABG Step 2. Determine if a Predominant Respiratory or Metabolic Acid-Base Disturbance Is Present. Evaluate $Paco_2$ and place it into context with the pH. In predominant respiratory acid-base disturbances, the change in $Paco_2$ is in the opposite direction of the change in pH. Using $Paco_2$ of 40 mm Hg and pH of 7.40 as idealized normal values, a $Paco_2$ greater than 40 with a pH less than 7.40 indicates a predominant respiratory acidosis. In predominant metabolic acid-base disturbances, the change in $Paco_2$ and pH are in the same direction. For example, a $Paco_2$ less than 40 mm Hg with a pH less than 7.40 indicates a predominant metabolic acidosis. There are two examples illustrating the use of ABG to determine the predominant respiratory or metabolic acid-base disturbance available at the end of this chapter on ExpertConsult.com.

ABG Step 3. If a Predominant Respiratory Acid-Base Disturbance Is Present, Determine If There Is a Concurrent Metabolic Disturbance. Compare the magnitude of changes in $Paco_2$ and pH. In a pure respiratory disturbance, a 10 mm Hg change in $Paco_2$ results in approximately a 0.08 change in pH in the opposite direction. If this delta-$Paco_2$: delta-pH ratio of 10:0.08 is not present, a concurrent metabolic disturbance is present along with the primary respiratory disturbance. The predicted pH assuming an isolated respiratory disturbance can be calculated with the equation:

$$\text{predicted pH} = \text{normal pH} + [(\text{normal } Paco_2 - \text{measured } Paco_2)/10 * 0.08]$$

$$= 7.40 + [(40 - \text{measured } Paco_2)/10 * 0.08]$$

If the measured pH is higher than predicted for the magnitude of $Paco_2$ change, a metabolic alkalosis is also present. If the pH is lower than expected for the magnitude of $Paco_2$ change, a metabolic acidosis is also present. An example highlighting the three steps in the use of the ABG to determine which acid-base disorders exist both as primary and concomitant/compensatory processes is noted in Box 113.2. Another example of this three-step approach can be found at the end of this chapter on ExpertConsult.com.

BOX 113.1 Identifying Acid-Base Disturbances With the Five-Step Focused Algorithm for Interpreting a Basic Metabolic Panel (BMP)

Clinical Concern: Acute Antifreeze (Ethylene Glycol) Ingestion

Laboratory Data

Na = 140 mmol/L
Cl = 100 mmol/L
HCO_3 = 8 mmol/L
BUN = 30 mg/dL
Cr = 2.5 mg/dL
Glucose = 80 mg/dL
ETOH = 240 mg/dL
$Paco_2$ = 17 mmHg
pH = 7.13
Measured Osmolality: 425 mOsm/kg

1. *Check the numbers*: Na = 140 mmol/L; Cl = 100 mmol/L; HCO_3 = 8 mmol/L; BUN = 30 mg/dL; Cr = 2.5 mg/dL; Glucose = 80 mg/dL. A low bicarbonate indicates a metabolic acidosis.
2. *Calculate the anion gap*: AG = 140 – (100 + 8) = 32. A high anion gap indicates wide anion gap metabolic acidosis.
3. *Apply the rule of 15*: HCO_3 is below 10 mmol/L. According to the corollary to the rule of 15, simple respiratory compensation would lead to a $Paco_2$ of approximately 15 mm Hg (±2), which is consistent with the patient's measured $Paco_2$ of 17 mm Hg. The patient's acid-base status is consistent with a primary metabolic acidosis with respiratory compensation without an additional primary respiratory acid-base disturbance.
4. *Calculate the delta gap*: Change in AG = measured AG – 15 = 32 – 15 = 17. Change in HCO_3 = 24 – measured HCO_3 = 24 – 8 = 16. The predicted change in bicarbonate concentration is 17 mmol/L, and the measured change is very similar at 16 mmol/L; this indicates the metabolic acid-base state is fully accounted for by a wide anion gap metabolic acidosis.
5. *Calculate the osmolar gap*: Calculated osmolarity = (2*Na) + (Glucose/18) + (BUN/2.8) + (ETOH/ 3.7) = (2*140) + (80/18) + (30/2.8) + (240/3.7) = 360 mOsm/kg. Osmol gap = (measured osmolality) – (calculated osmolarity) = 425 mOsm/kg – 360 mOsm/kg = 65 mOsm/kg. An osmolar gap >10 mOsm/kg indicates accumulation of a significant volume of abnormal solute in the blood. In the setting of suspected ethylene glycol ingestion, the wide osmolar gap is presumed to be due to ethylene glycol until plasma ethylene glycol concentration results are available. The estimated ethylene glycol concentration = (osmolar gap) * 6 = 65 * 6 = 390 mg/dL.

BOX 113.2 Identifying Acid-Base Disturbances With the Three-Step Focused Algorithm for Interpreting an Arterial Blood Gas (ABG)

Clinical Concern: Salicylate Toxicity

Laboratory Data

ABG: pH = 7.47/$Paco_2$ = 25 mm Hg/Pao_2 = 180 mm Hg

Determine if the patient is acidemic or alkalemic. The patient's pH is 7.47, indicating alkalemia.

Determine if a predominant respiratory or metabolic acid-base disturbance is present. The patient's $Paco_2$ is low at 25 mm Hg and pH is high at 7.47. This is consistent with a respiratory alkalosis.

Determine if there is concurrent metabolic disturbance. Change in $Paco_2$ = 40 – measured $Paco_2$ = 40 – 25 = 15. Assuming a pure respiratory alkalosis with no metabolic acid-base disturbance, predicted pH = 7.40 + [(40 – 25) / 10 * 0.08] = 7.40 + 0.12 = 7.52. The measured pH of 7.47 is lower than the predicted pH of 7.52, indicating a concurrent metabolic acidosis.

Differential Diagnosis of Acid-Base Disorders

Each of the four acid-base disorders—metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis—have multiple potential causes.

Metabolic Acidosis

As previously described, the metabolic acidoses are classified based on anion gap. Accumulation of "unmeasured" anions results in a wide anion gap metabolic acidosis. A decline in bicarbonate with a concomitant increase in chloride results in a normal anion gap metabolic acidosis.

Wide Anion Gap Metabolic Acidosis. An elevated anion gap using the threshold of 15 mmol/L, regardless of the value of the pH or [$HCO3^-$], indicates that a wide anion gap metabolic acidosis is present. The mnemonic MUDPILES can be used to recall common causes of a wide anion gap metabolic acidosis (Box 113.3). Lactic acidosis is the most common cause of a wide anion gap metabolic acidosis, accounting for approximately half of the cases. Other important causes include ketoacidosis (e.g., diabetic ketoacidosis) and toxic alcohol poisoning (e.g., methanol and ethylene glycol). A normal anion gap does not eliminate the possibility of lactic acidosis, ketoacidosis, or toxic alcohol poisoning, and these acids should be directly measured when clinical concern is high despite a normal anion gap.

Normal Anion Gap Metabolic Acidosis. The mnemonic HARDUP (see Box 113.3) can be used to recall the causes of a normal anion gap metabolic acidosis, which is also called hyperchloremic metabolic acidosis. Common causes of normal anion gap metabolic acidosis include renal tubular acidosis (failure of the kidney to properly excrete acid), diarrhea (gastrointestinal loss of bicarbonate), and saline infusion (hyperchloremia leading to the retention of acid to maintain electroneutrality).

Metabolic Alkalosis

Metabolic alkalosis can be caused by an increase in alkali or impaired renal excretion of bicarbonate. The differential for metabolic alkalosis can be divided into chloride-responsive and chloride-unresponsive conditions.

Chloride-Responsive Metabolic Alkalosis. When the circulating volume is decreased, the renin-angiotensin-aldosterone system is activated, and the kidneys reabsorb filtered sodium, bicarbonate, and chloride. This leads to metabolic alkalosis through retention of bicarbonate and decreased concentration of urine chloride (spot urine chloride concentration < 25 mmol/L). When sodium chloride–containing fluids are administered, circulating volume increases, and the metabolic alkalosis is corrected. Causes of chloride-responsive metabolic alkalosis are listed in Box 113.4.

Chloride-Unresponsive Metabolic Alkalosis. Causes of metabolic alkalosis that cannot be corrected with infusion of sodium chloride containing fluids are called chloride-unresponsive metabolic alkaloses (see Box 113.2). A common mechanism is hyperaldosteronism, which causes inappropriate renal excretion of H^+ and Cl^- and a spot urine chloride concentration greater than 40 mmol/L.

BOX 113.3 Causes of Metabolic Acidosis, Divided into Wide Anion Gap and Normal Anion Gap Metabolic Acidosis

Wide Anion Gap Metabolic Acidosis—Mnemonic: MUDPILES

Methanol
Uremia
Diabetic ketoacidosis/alcoholic ketoacidosis
Paraldehyde/**P**olyethylene glycol/**P**aracetamol (acetaminophen)
Iron
Lactic acidosis
Ethylene glycol
Salicylates

Normal Anion Gap Metabolic Acidosis—Mnemonic: HARDUP

Hyperalimentation/**H**ospital-acquired administration of saline
Acid infusion/**A**ddison disease / Carbonic **A**nhydrase Inhibitors
Renal tubular acidosis (RTA)
Diarrhea
Ureterosigmoidostomy (and ileal diversion)
Pancreatic drainage/fistula

BOX 113.4 Causes of Metabolic Alkalosis, Divided into Chloride-Responsive and Chloride-Unresponsive Metabolic Alkalosis

Chloride-Responsive Metabolic Alkalosis

Nasogastric suction
Vomiting
Chloride-wasting diarrhea
Villous adenoma
Persistent diuretic use

Chloride-Unresponsive Metabolic Alkalosis

Primary hyperaldosteronism
Secondary hyperaldosteronism (Bartter syndrome, Gitelman syndrome, congestive heart failure, liver failure, chronic renal failure)
Steroids
Cushing disease
Severe hypercalcemia
Severe hypomagnesemia
Bicarbonate ingestion
Licorice overdose (glycyrrhizic acid)

BOX 113.5 Causes of Respiratory Acidosis Based on Pathophysiologic Mechanism

Respiratory Disease (Lungs and Airways)
Airway obstruction
Obstructive pulmonary diseases (e.g., chronic obstructive pulmonary disease)
Pneumothorax
Pulmonary effusion
Pulmonary edema
Pneumonia
Mechanical ventilation (iatrogenic hypoventilation)

Chest Wall Disease
Chest wall trauma (e.g., flail chest)
Obesity hypoventilation syndrome

Respiratory Muscle Weakness
Myopathies (e.g., muscular dystrophy)
Neuropathies (e.g., Guillain-Barré)
Electrolyte abnormalities (e.g., hypokalemia, hypophosphatemia)

Decreased Respiratory Drive
Brain space-occupying lesion (e.g., intracranial mass, intracranial hemorrhage)
Drugs/toxins (e.g., sedative-hypnotics, narcotics)

BOX 113.6 Causes of Respiratory Alkalosis Based on Pathophysiologic Mechanism

Respiratory
Conditions that cause hypoxemia (e.g., pulmonary embolus)
Mechanical ventilation (iatrogenic hyperventilation)

Gastrointestinal
Hepatic encephalopathy
Neurologic
Brain lesion

Genitourinary
Pregnancy

Psychiatric
Anxiety

Toxic-Metabolic
Drugs (e.g., salicylates, catecholamines, progesterone)
Hyperthyroidism

Infectious
Fever
Sepsis

Miscellaneous
Pain

Respiratory Acidosis

Failure to adequately ventilate carbon dioxide out of the body results in increased $Paco_2$ and respiratory acidosis. Mechanisms of respiratory acidosis include hypoventilation leading to hypercapnic respiratory failure and increased production of carbon dioxide overwhelming mild to moderately impaired pulmonary function. Common causes of hypercapnic respiratory failure and respiratory acidosis include primary lung disease, chest wall disease, respiratory muscle weakness, and decreased respiratory drive from central nervous system disease or toxins. Specific causes of respiratory acidosis within these categories are listed in Box 113.5.

Respiratory Alkalosis

Respiratory alkalosis occurs when increased minute ventilation (hyperventilation) leads to decreased $Paco_2$. In the emergency department, anxiety-related hyperventilation is a common cause of respiratory alkalosis, but other medical illnesses, including salicylate toxicity, can also present with respiratory alkalosis (Box 113.6). Of note, respiratory alkalosis results in increased binding of calcium to albumin, thereby decreasing free serum calcium. Many of the classic symptoms of acute respiratory alkalosis are caused by hypocalcemia—lip and extremity paresthesia, carpal pedal spasm, muscle cramps, syncope. These symptoms quickly resolve as pH declines and free calcium concentrations return to normal.

MANAGEMENT

The management of acid-base disorders focuses on treating the specific cause of an acid-base derangement (e.g., treating diabetic ketoacidosis, managing an overdose, providing ventilatory support). Detailed discussions on the management of specific causes of acid-base disorders are included in other disease-focused chapters. Here, we discuss general principles of managing acid-base disorders.

Intravenous Fluids

Intravenous fluid administration is a common method of both causing and treating acid-base disorders. Thus, understanding the typical clinical effects of common intravenous fluid formulations is key to acid-base management. Although many intravenous fluid formulations are available, intravenous fluid use in the ED is dominated by crystalloid solutions. Three of the commonly used crystalloids are saline (0.9% sodium chloride, "normal saline"), lactated Ringers (also known as Hartmann solution), and Plasma-Lyte (Table 113.1).

One liter of saline is composed of 9 g of sodium chloride diluted in water to a total volume of 1000 ml; therefore, the mass concentration of saline is 9 g/1000 ml = 0.009 or 0.9%. The misnomer "normal saline" likely stems from in vitro red blood cell studies in the 1880s that were incorrectly interpreted as showing human blood is 0.9% salt; the actual concentration is approximately 0.6%. Saline contains 154 mmol/L of both sodium and chloride, which is supraphysiologic compared with human plasma (see Table 113.1). Thus, saline is not "normal" or physiologic. In the early 20th century, saline was adopted as a preferred intravenous fluid for patient care. The rationale behind the adoption of saline over other fluids more similar in composition to human plasma is unclear but may have been related to the ease and low cost of producing saline at the time.

The effect of intravenous crystalloid composition on acid-base status is described by the physiochemical (Stewart) model of acid-base. A key determinant of acid-base status, or the concentration of H^+ in plasma, is the relative concentrations of strong cations (Na^+, K^+, Ca^{++}, and Mg^{++}) and strong anions (Cl^-). As the concentration of strong anions increases relative to strong cations, the concentration of H^+, a weak unmeasured cation, increases to maintain electroneutrality. Thus, a relative increase in Cl^- compared with the strong cations results in acidosis.

The "strong ion difference" is a summary measure of the relative concentration of strong cations and strong anions (see Fig. 113.2). In human plasma and crystalloid solutions, the strong ion difference is approximated by the equation:

TABLE 113.1 Composition of Human Plasma and Commonly Used Intravenous Crystalloid Solutions

			BALANCED CRYSTALLOIDS	
	Human Plasma	Saline	Lactated Ringer	Plasma-Lyte
Sodium (mmol/L)	135–145	154	130	140
Potassium (mmol/L)	4.5–5.0	0	4	5
Chloride (mmol/L)	94–111	154	109	98
Calcium (mmol/L)	2.2–2.6	0	2.7	0
Magnesium (mmol/L)	0.8–1.0	0	0	1.5
Bicarbonate (mmol/L)	23–27	0	0	0
Lactate (mmol/L)	1–2	0	28	0
Acetate (mmol/L)	0	0	0	27
Gluconate (mmol/L)	0	0	0	23
pH	7.35–7.45	5.0	6.5	7.4
Osmolarity (mOsm/L)	291	308	273	294
Strong ion difference (mmol/L)	≈42	0	28	50

$$\text{Strong ion difference} = [Na^+] + [K^+] + [Ca^{++}] + [Mg^{++}] - [Cl^-]$$

Decreases in the strong ion difference indicate that unmeasured weak cations contribute more of the cation charge. At a physiologic pH of 7.40, infusion of intravenous fluids that have a strong ion difference of about 24 mmol/L has no effect on pH. Infusion of intravenous fluids with a strong ion difference of less than 24 mmol/L results in an increase in $[H^+]$ and acidosis, while fluids with a strong ion difference of greater than 24 mmol/L lead to a reduction in $[H^+]$ and alkalosis.

With a composition of 154 mmol/L of sodium and chloride, saline has a strong ion difference of 0. Therefore, infusing saline into human plasma results in a relative increase in chloride concentration compared with the strong cations, a decrease in the strong ion difference, and acidosis. Through these mechanisms, saline administration leads to a normal anion gap hyperchloremic metabolic acidosis.

"Balanced crystalloids" are crystalloids that more closely match the composition of human plasma than saline in terms of electrolyte concentrations. An idealized balanced crystalloid would contain the same electrolytes and concentrations as human plasma. However, bicarbonate-containing solutions are difficult to store in plastic containers for prolonged periods. Hence, balanced crystalloids are developed with alternative anions that serve as substitutes for bicarbonate. Historically, the primary balanced crystalloid was lactated Ringers (chloride concentration = 109 mmol/L; strong ion difference = 28 mmol/L), which is modeled after a fluid Dr. Sydney Ringer developed in the late 19th century. The primary anion in lactated Ringers is lactate, which is metabolized to bicarbonate after infusion. In terms of effects on acid-base, lactated Ringers is considered a neutral fluid that does not induce either acidosis or alkalosis.

The balanced crystalloid Plasma-Lyte (chloride concentration = 98 mmol/L) was developed with the anions acetate and gluconate and concentrations of sodium, potassium, and chloride that closely match human plasma (see Table 113.1). The calculated strong ion difference of Plasma-Lyte is 50 mmol/L, but the effective strong ion difference is likely lower because gluconate does not fully metabolize into bicarbonate. The expected effect of Plasma-Lyte on acid-base status is a mild alkalinizing effect.

Saline infusion has been known to cause hyperchloremic metabolic acidosis since the early 20th century. While physiology studies have consistently suggested that saline-associated hyperchloremic metabolic acidosis may have negative effects on renal and immune function, the clinical consequences of saline infusion in human studies have only recently begun to emerge. The administration of balanced crystalloids instead of saline in volumes typically used in clinical medicine, including in the emergency department, reduces the number of patients who experience hyperchloremia and metabolic acidosis.[2,3] Additionally, recent data suggest balanced crystalloids lead to better patient outcomes than saline, including a survival benefit in sepsis.[2-4]

Although current data do not provide definitive evidence for scenarios in which clinicians should use balanced crystalloids instead of saline, it is reasonable to preferentially use a balanced crystalloid, such as lactated Ringers or Plasma-Lyte, in patients with hyperchloremia, metabolic acidosis, renal dysfunction, sepsis, and those receiving a large volume of fluid. Potential adverse effects of balanced crystalloids include the induction of metabolic alkalosis (especially with Plasma-Lyte), low tonicity potentially increasing intracranial pressure (especially with lactated Ringers), and hyponatremia (especially with lactated Ringers).

Sodium Bicarbonate Therapy

Although bicarbonate-containing solutions cannot be conveniently stored for prolonged periods, they can be mixed for immediate use. An isotonic sodium bicarbonate solution can be prepared by adding 150 mmol sodium bicarbonate, or three 50-ml ampules of 8.4% sodium bicarbonate, to one liter of D5W. This fluid can then be infused intravenously and has a strong alkalinizing effect. The addition of sodium bicarbonate to 0.9% sodium chloride (saline) should be avoided due to the hypertonicity and high sodium concentration of this mixture.

Intravenous sodium bicarbonate therapy is recommended for the treatment of some specific poisonings, such as sodium channel blocking toxicants and salicylates, but its role in the routine treatment of severe metabolic acidosis is controversial. Identifying and reversing the underlying cause of metabolic acidosis is the primary therapy. It remains unclear whether using sodium bicarbonate to increase pH while addressing the primary cause of acidosis provides benefit. Proponents of bicarbonate therapy in this setting note that acidosis can result in decreased myocardial contractility, systemic vasodilation, and decreased responsiveness to catecholamines. Opponents note potential harms of intravenous sodium bicarbonate therapy, including a paradoxical increase in CNS acidosis (bicarbonate does not readily cross the blood-brain barrier, and decreased drive for hyperventilation leads to increased CO_2 both systemically and in the CNS), hypernatremia, hypocalcemia, hypokalemia, increased lactate production, and fluid overload.

Historically, many clinicians have argued against bicarbonate therapy for metabolic acidosis due to its potential harms and no demonstrated clinical benefit. In a recent clinical trial of adults with metabolic acidosis (pH 7.20 or less), plasma bicarbonate concentration 20 mmol/L or less, and arterial lactate concentration 2.0 mmol/L or greater, sodium bicarbonate therapy demonstrated no effect on survival among all patients but was associated with a survival benefit among patients who presented with acute kidney injury.[5] Trial exclusions included diabetic ketoacidosis, respiratory acidosis, and severe chronic kidney disease.

While no evidence-based algorithms exist, a common and reasonable practice is to use intravenous sodium bicarbonate therapy for

metabolic acidosis with a pH less than 7.10 with the goals of increasing pH above 7.10 and plasma bicarbonate concentration above 10 mmol/L. For patients with concomitant acute kidney injury, we recommend use of sodium bicarbonate therapy for a pH less than 7.20.[5] Based on current understanding, bicarbonate therapy is thought to be more beneficial for acidoses caused by loss of bicarbonate (e.g., diarrhea) or impairment of acid excretion (e.g., renal failure) than those caused by endogenous acid production (e.g., lactic acidosis, ketoacidosis).

DISPOSITION

Disposition of patients with acid-base disorders is based on treatment needs for the underlying etiology as well as the severity of the acid-base disorder. Most of the causes of acute acid-base disorders benefit from hospital admission because hours to days of monitoring and therapy are often needed to reverse the disorder. In some instances, a patient may be fully treated in the emergency department for a mild acid-base disorder or etiology that can be rapidly remedied. In these cases, repeat laboratory testing before discharge is often useful to assure that the acid-base disorder has been appropriately addressed.

ACKNOWLEDGEMENTS

We would like to recognize Corey M. Slovis, MD for helping develop many of the concepts presented in this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 113: QUESTIONS AND ANSWERS

1. A patient presents to the emergency department with severe metabolic acidosis. In addition to initial stabilization, what should be a priority for the clinician?

- **a.** Infuse sodium bicarbonate to normalize pH to approximately 7.40.
- **b.** Induce a respiratory alkalosis to normalize pH to approximately 7.40.
- **c.** Identify the cause of metabolic acidosis and target therapy at that cause.
- **d.** Infuse saline with the goal of decreasing the strong ion difference.

Answer: C. The key steps to managing acid-base disorders are: (1) identifying the type of acid-base disorder(s) present; (2) identifying the underlying cause of the acid-base disorder; and (3) initiating therapy to reverse the underlying cause. Optimal therapy varies based on the underlying cause. For example, in the case of metabolic acidosis, primary treatment for diabetic ketoacidosis is insulin, for lactic acidosis from sepsis is increasing tissue perfusion with vasopressors and intravenous fluids, and for severe toxic alcohol exposure is a specific reversal agent. In some scenarios with severe metabolic acidosis, sodium bicarbonate infusion is a reasonable adjunctive therapy, especially those caused by loss of bicarbonate or renal failure, while the underlying cause is being addressed.

2. What causes an increase in the anion gap?

- **a.** A decrease in plasma bicarbonate concentration accompanied by an increase in plasma chloride concentration of the same magnitude
- **b.** An increase in the concentration of unmeasured anions in the plasma
- **c.** Saline infusion
- **d.** Hypoventilation

Answer: B. Plasma is maintained as electrically neutral, meaning equal charges from plasma cations and anions. Sodium [Na^+] is the major cation routinely measured in clinical laboratories. Chloride [Cl^-] and bicarbonate [HCO_3^-] are the major anions routinely measured in clinical laboratories. The anion gap is calculated as: [Na^+] − ([Cl^-] + [HCO_3^-]). In normal physiological states, "unmeasured" anions are more plentiful than "unmeasured" cations, and hence the anion gap is positive (typically between about 9 mmol/L and 15 mmol/L). Metabolic acidosis is defined by low [HCO_3^-]. A normal anion gap metabolic acidosis occurs when a decrease in [HCO_3^-] is accompanied by an increase of [Cl^-] by the same amount to maintain electroneutrality. A wide anion gap metabolic acidosis occurs when a decrease is bicarbonate is accompanied by an increase in anions other than chloride (so called "unmeasured anions").

3. A patient in the emergency department has the following laboratory values. Select the term that best characterizes this patient's acid-base status. pH = 7.36; $Paco_2$ = 36 mm Hg; Pao_2 = 135 mm Hg; Na = 142 mmol/L; Cl = 100 mmol/L; HCO3 = 21 mmol/L.

- **a.** Acidemia
- **b.** Alkalemia
- **c.** Respiratory alkalosis with metabolic compensation
- **d.** Metabolic acidosis with respiratory compensation

Answer: D. The patient's pH is in the normal range of 7.35 to 7.45. Therefore, neither acidemia nor alkalemia is present. However, the patient may have an acid-base disorder with compensation into a normal pH range, or multiple primary acid-base disorders that when combined result in a pH in the normal range. To classify an acid-base disorder, initially interpret the basic metabolic panel findings and then the arterial blood gas findings. This patient's bicarbonate is low at 21 mmol/L, indicating a metabolic acidosis. The anion gap is 21 mmol/L, indicating a wide anion gap metabolic acidosis. According to the rule of 15, respiratory compensation for this metabolic acidosis is expected to result in a $Paco_2$ of 36 mm Hg and a pH of 7.36, consistent with the patient's measured values. Looking at the ABG results, the pH is less than 7.40, indicating a primary acidosis, and $Paco_2$ is less than 40 mm Hg, indicating the respiratory findings are a compensatory effect rather than a primary disorder.

4. How can calculation of an osmolar gap be used clinically?

- **a.** To rule out toxic alcohol ingestion
- **b.** To assist with understanding potential causes of a wide anion gap metabolic acidosis
- **c.** To differentiate primary lung pathology from respiratory muscle weakness in a patient with respiratory acidosis
- **d.** To understand if metabolic compensation has occurred after respiratory alkalosis

Answer: B. Calculation of the osmolar gap is a method to help understand the cause of a wide anion gap metabolic acidosis. It can help identify the presence of a large amount of osmotically active solutes in the blood other than the primary osmotically active solutes that are commonly measured (Na, counter anions to Na, glucose, urea, and ethanol). An elevated osmolar gap occurs when measured osmolality is higher than predicated based on a calculation accounting for the commonly measured osmotically active solutes. An important cause of wide anion gap metabolic acidosis and elevated osmolar gap is toxic alcohol poisoning (e.g., methanol or ethylene glycol). Although an elevated anion gap with an elevated osmolar gap can suggest toxic alcohol poisoning in the right clinical setting, a normal osmolar gap does not rule out toxic alcohol poisoning because the osmolar gap decreases as alcohols are metabolized and calculation of the osmolar gap assumes normal osmolality before the poisoning, which may not be true, especially in chronically ill patients.

5. A patient presents to the emergency department with shortness of breath. Plasma bicarbonate concentration is 44 mmol/L. What is a potential explanation for this laboratory value?

- **a.** Administration of a large volume of saline
- **b.** Acute respiratory failure from a spontaneous pneumothorax sustained 2 hours prior to presentation
- **c.** Chronic respiratory failure from chronic obstructive pulmonary disease
- **d.** Diabetic ketoacidosis

Answer: C. A plasma bicarbonate concentration of 44 mmol/L indicates either a primary metabolic alkalosis or metabolic compensation for a respiratory acidosis. Metabolic compensation requires alteration of renal excretion of acid, which usually takes at least 2 days to develop. Therefore, metabolic compensation is typically not present with acute respiratory failure but is present with chronic respiratory failure. Administration of a large volume of saline increases plasma chloride concentration and decreases plasma bicarbonate concentration to maintain electroneutrality. Respiratory acidosis from a pneumothorax sustained 2 hours previously would not be associated with metabolic compensation because not enough time would have elapsed for the metabolic compensatory mechanisms to have an effect. Respiratory acidosis from chronic respiratory failure is associated with metabolic compensation and thus an elevated bicarbonate concentration. Diabetic ketoacidosis results in accumulation of "unmeasured" anions (acetoacetic acid and beta-hydroxybutyric acid) and a decrease in plasma bicarbonate to maintain electroneutrality.

ACID-BASE DISORDER SAMPLE CALCULATIONS

Rule of 15 Example 1

Na = 140 mmol/L; Cl = 110 mmol/L; HCO_3 = 10 mmol/L; $PaCo_2$ = 20; pH = 7.32.

- *Check the numbers:* The HCO_3 is low, indicating a metabolic acidosis.
- *Calculate anion gap*: AG = 140 − (110 + 10) = 20
  A calculated value of 20 indicates the presence of wide anion gap metabolic acidosis.
- *Apply the rule of 15*: HCO_3^- + 15 = 10 + 15 = 25.
  Simple respiratory compensation would lead to a $Paco_2$ of 25 mm Hg (±2) and a pH of 7.25 (±0.02). The patient's measured value for $Paco_2$ (20 mm Hg) is lower and the measured value for pH (7.32) is higher than predicted by the rule of 15. These "more alkalotic" values indicate the patient is hyperventilating more than expected to compensate for metabolic acidosis. This patient has a primary respiratory alkalosis in addition to a primary wide anion gap metabolic acidosis.

Rule of 15 Example 2

- *Check the numbers*: Na = 140 mmol/L; Cl = 100 mmol/L; HCO_3 = 20 mmol/L; $Paco_2$ = 35 mm Hg; pH = 7.35.
  A low bicarbonate value indicates metabolic acidosis.
- *Calculate anion gap*: AG = 140 − (100 + 20) = 20.
  A high anion gap indicates a wide anion gap metabolic acidosis.
- *Apply the rule of 15*: HCO_3 + 15 = 20 + 15 = 35.
  Simple respiratory compensation would lead to a $Paco_2$ of 35 mm Hg (±2) and a pH of 7.35 (±0.02). The patient's measured values match these expected values; hence, this patient has a simple wide anion gap primary metabolic acidosis with appropriate respiratory compensation.

Rule of 15 Example 3

- *Check the numbers*: Na = 140 mmol/L; Cl 105 mmol/L; HCO_3 = 10 mmol/L; $Paco_2$ = 32 mm Hg; pH = 7.14.
  A low bicarbonate indicates a metabolic acidosis.
- *Calculate the anion gap*: AG = 140 − (105 + 10) = 25.
  A high anion gap indicates wide anion gap metabolic acidosis.
- *Apply the rule of 15*: HCO_3^- + 15 = 10 + 15 = 25.
  Simple respiratory compensation would lead to a $Paco_2$ of 25 mm Hg (±2) and a pH of 7.25 (±0.02). The patient's measured value for $Paco_2$ (32 mm Hg) is higher and the measured value for pH (7.14) is lower than predicted by the rule of 15. These "more acidotic" values indicate the patient is hypoventilating in the context of a metabolic acidosis. This patient has a primary respiratory acidosis in addition to a primary wide anion gap metabolic acidosis.

Rule of 15 Example 4

- *Check the numbers*: Na = 140 mmol/L; Cl 105 mmol/L; HCO_3 = 10 mmol/L; $Paco_2$ = 32 mm Hg; pH = 7.14.
  A low bicarbonate indicates a metabolic acidosis.
- *Calculate the anion gap*: AG = 140 − (105 + 10) = 25.
  A high anion gap indicates wide anion gap metabolic acidosis.
- *Apply the rule of 15*: HCO_3^- + 15 = 10 + 15 = 25.
  Simple respiratory compensation would lead to a $Paco_2$ of 25 mm Hg (±2) and a pH of 7.25 (±0.02). The patient's measured value for $Paco_2$ (32 mm Hg) is higher and the measured value for pH (7.14) is lower than predicted by the rule of 15. These "more acidotic" values indicate the patient is hypoventilating in the context of a metabolic acidosis. This patient has a primary respiratory acidosis in addition to a primary wide anion gap metabolic acidosis.

Delta Gap Example 1

- *Check the numbers*: Na = 140 mmol/L; Cl 92 mmol/L; HCO_3 = 20 mmol/L; $Paco_2$ = 37 mm Hg; pH = 7.37.
  A low bicarbonate indicates a metabolic acidosis.
- *Calculate the anion gap*: AG = 140 − (92 + 20) = 28.
  A high anion gap indicates wide anion gap metabolic acidosis.
- *Apply the rule of 15*: HCO_3 + 15 = 20 + 15 = 35.
  Simple respiratory compensation would lead to a $Paco_2$ of 35 mm Hg (±2) and a pH of 7.35 (±0.02). The patient's measured value for $Paco_2$ (37 mm Hg) is consistent with the rule of 15, indicating no primary respiratory acid-base disturbance.
- *Calculate the delta gap*: Change in AG = measured AG − 15 = 28 − 15 = 13. Change in HCO_3 = 24 − measured HCO_3 = 24 − 20 = 4.
  The predicted change in bicarbonate concentration is 13 mmol/L, but the measured change is only 4 mmol/L. The measured bicarbonate is higher than predicted by the delta gap calculation, indicating the presence of a primary metabolic alkalosis in addition to the wide anion gap metabolic acidosis.

Delta Gap Example 2

- *Check the numbers*: Na = 140 mmol/L; Cl = 105 mmol/L; HCO_3 = 12 mmol/L; $Paco_2$ = 27 mm Hg; pH = 7.27.
  A low bicarbonate indicates a metabolic acidosis.
- *Calculate the anion gap*: AG = 140 − (105 + 12) = 23.
  A high anion gap indicates wide anion gap metabolic acidosis.
- *Apply the rule of 15*: HCO_3 + 15 = 12 + 15 = 27.
  Simple respiratory compensation would lead to a $Paco_2$ of 27 mm Hg (±2) and a pH of 7.27 (±0.02). The patient's measured value for $Paco_2$ CO_2 (27 mm Hg) is consistent with the rule of 15, indicating no primary respiratory acid-base disturbance.
- *Calculate the delta gap*: Change in AG = AG − 15 = 23 − 15 = 8. Change in HCO_3 = 24 − measured HCO_3 = 24 −12 = 12.
  The predicted change in bicarbonate concentration is 8 mmol/L, but the measured change is 12 mmol/L. The measured bicarbonate is lower than predicted by the delta gap calculation, indicating the presence of a primary normal anion gap metabolic acidosis in addition to a wide anion gap metabolic acidosis.

ABG Determination of Predominant Respiratory or Metabolic Acid-Base Disorder Example 1

ABG: pH = 7.31 / $PaCO_2$ = 53mm Hg / PaO_2 = 98mm Hg

- Determine if the patient is acidemic or alkalemic. The patient's pH is 7.31, indicating acidemia.
- Determine if a predominant respiratory or metabolic acid-base disturbance is present. The patient's $Paco_2$ is high at 53 mm Hg and pH is low at 7.31. This is consistent with a predominant respiratory acidosis.

ABG Determination of Predominant Respiratory or Metabolic Acid-Base Disorder Example 2

ABG: pH = 7.52 / $PaCO_2$ = 60mm Hg / PaO_2 = 84mm Hg

- Determine if the patient is acidemic or alkalemic.
  The patient's pH is 7.52, indicating alkalemia.
- Determine if a predominant respiratory metabolic acid-base disturbance is present. The patient's $Paco_2$ is high at 60 mm Hg and pH is high at 7.52.
  This is consistent with a predominant metabolic alkalosis. The high $Paco_2$ represents respiratory compensation via hypoventilation.

ABG Determination of Predominant and Concomitant/Compensatory Acid-Base Disorders Example 1

ABG: pH = 7.00 / $PaCO_2$ = 70mm Hg / PaO_2 = 105mm Hg

- Determine if the patient is acidemic or alkalemic.
  The patient's pH is 7.00, indicating acidemia.
- *Determine if a predominant respiratory or metabolic acid-base disturbance is present.* The patient's $PaCO_2$ is high at 70 mm Hg and pH is low at 7.00. This is consistent with a respiratory acidosis.
- Determine if there is concurrent metabolic disturbance.

Change in $PaCO_2$ = 40 − measured $PaCO_2$ = 40 − 70 = −30. Assuming a pure respiratory acidosis with no metabolic acid-base disturbance, predicted pH = 7.40 + [(40 − 70)/10 * 0.08] = 7.40 − 0.24 = 7.16. The measured pH of 7.00 is lower than the predicted pH of 7.16, indicating a concurrent metabolic acidosis.

Electrolyte Disorders

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KEY CONCEPTS

- Electrolyte abnormalities are common in emergency medicine and can vary greatly in importance, severity, and symptoms. Asymptomatic electrolyte abnormalities can be gradually corrected, whereas those causing alterations in consciousness or life-threatening dysrhythmias require immediate therapy to avoid permanent sequelae or death. In some cases, therapy for life-threatening electrolyte disorders may precede laboratory confirmation.
- Asymptomatic electrolyte abnormalities can usually be corrected slowly, but those that cause profound mental status changes or life-threatening arrhythmias require immediate correction to avoid cardiac arrest or seizures.
- IV calcium should be used only for hyperkalemic emergencies, defined as the following: widening QRS; sine wave; bradycardias and cardiac arrest believed to be due to hyperkalemia; or rapidly evolving electrocardiographic changes, from normal to development of tall peaked T waves and loss of the P wave. Acute, rapid rises in serum potassium concentration are rare but may be seen in tumor lysis syndrome, rhabdomyolysis, or massive hemolysis.
- After the critical decision about administration of calcium has been made, a beta$_2$-agonist, insulin and glucose, normal saline, and bicarbonate (if the patient is acidotic) can be given to shift potassium intracellularly.
- When treating hypokalemia, the physician should also replace magnesium sulfate, in addition to potassium, or the patient will excrete most of the infused potassium in the urine.
- Low serum potassium levels reflect a substantial total potassium deficit; correction of large deficits can require several days.
- Hypertonic saline should be reserved for severely hyponatremic patients (typically in the 100 to 110 mEq/L range) who present with coma, seizures, or focal neurologic deficits. Central pontine myelinolysis can occur if serum sodium concentration is raised rapidly by more than 8 mEq/day.

HYPERKALEMIA

Foundations

Hyperkalemia, defined as a serum potassium level greater than 5.0 mEq/L, is the most dangerous acute electrolyte abnormality, potentially leading to life-threatening arrhythmias and death. Although hyperkalemia may have vague and varied symptoms, it is usually totally asymptomatic and can present with cardiac arrest as its first "symptom." Serum potassium concentration is normally between 3.5 and 5.0 mEq/L and is tightly regulated by the kidneys. Hyperkalemia usually develops from impaired renal excretion or intracellular release; however, in advanced chronic kidney disease or end-stage renal disease, dietary intake of potassium may be a significant factor in its development. Risk factors for hyperkalemia include impaired potassium excretion, such as dehydration and renal failure, as well as medications that cause potassium retention. Evaluation of the 12-lead electrocardiogram (ECG) of patients at risk for this electrolyte disturbance guides management decisions. Hyperkalemia can be rapidly progressive, requiring lifesaving interventions at the earliest suspicion of toxicity.

Hyperkalemia causes cardiotoxicity by increasing the resting membrane potential of the cardiac myocyte, causing "membrane excitability," and conversely, sluggish depolarization, as well as decreased duration of repolarization. At very high levels, potassium causes the depolarization threshold to rise, leading to overall depressed cardiac function. Nearly any cardiac arrhythmia can be seen with hyperkalemia, including heart blocks, bradydysrhythmias, pseudoinfarction, ST-segment elevation, Brugada pattern, and the classic "sine wave" pattern.[1] As hyperkalemia advances, the end result is cardiac arrest, usually from deterioration into ventricular fibrillation, pulseless electrical activity, or asystole. A serum potassium level of 10.0 mEq/L is usually fatal, but decompensation and death can occur at any level above 7 to 8 mEq/L.

Clinical Features

Hyperkalemia is a difficult diagnosis to make on clinical grounds alone. Hyperkalemia is classified as mild (K 5.5 to 6.0), moderate (K 6.1 to 6.9) or severe (K >7.0). Patients with mild to moderate hyperkalemia are often identified during routine blood sampling for an unrelated condition. Patients with moderate to severe hyperkalemia may have gastrointestinal effects, such as nausea, vomiting, and diarrhea, which are often associated with their underlying disease. Patients with severe hyperkalemia may present with neuromuscular findings, including muscle cramps, generalized weakness, paresthesias, tetany, and focal or global paralysis. The signs and symptoms of progressive muscle weakness, paresthesias, dyspnea, and depressed deep tendon reflexes are neither sensitive nor specific, nor do they appear reliably with a particular serum potassium level. Patients with severe hyperkalemia may present with hemodynamic instability and cardiac arrhythmias requiring immediate intervention.

Differential Diagnosis

The most common cause of hyperkalemia is spurious elevation due to hemolysis during or after the blood draw. Thus, an ECG should be used to assess for true hyperkalemia while another sample is analyzed. Box 114.1 organizes the most common causes of hyperkalemia. The presence of one of these conditions may be the lone historical clue in hyperkalemia. Physicians should not rely solely on an ECG to determine the presence or absence of hyperkalemia in an otherwise stable patient.[2]

Diagnostic Testing

The ECG is helpful in making the diagnosis of hyperkalemia and can be used in unstable patients to initiate treatment (Figs. 114.1 to 114.3). Classic electrocardiographic changes—the peaked T wave, flattened p wave with prolonged PR interval or a totally absent P wave, wide QRS, and sine wave pattern, portending imminent cardiac arrest—have been well described as appearing sequentially with rising serum potassium

BOX 114.1 Five Most Common Causes of Hyperkalemia

- Spurious elevation: Hemolysis due to drawing or storing of the laboratory sample or post–blood sampling leak from markedly elevated white blood cells, red blood cells, or platelets
- Renal failure: Acute or chronic
- Acidosis: Diabetic ketoacidosis (DKA), Addison disease, adrenal insufficiency, type 4 renal tubular acidosis
- Cell death: Rhabdomyolysis, tumor lysis syndrome, massive hemolysis or transfusion, crush injury, burn
- Drugs: Acute digitalis overdose, succinylcholine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal antiinflammatory drugs (NSAIDs), spironolactone, amiloride, potassium supplementation

levels. Peaked T waves usually appear as serum potassium levels exceed 5.5 to 6.5 mEq/L; P wave disappearance and PR prolongation are common with levels above 6.5 to 7.5 mEq/L; and levels above 7.0 to 8.0 mEq/L can result in QRS prolongation. Although these changes may occur in only half the patients, recognition of these patterns is vital to rapid diagnosis and initiation of lifesaving treatment. A serum potassium level above 5.0 mEq/L is diagnostic of hyperkalemia, but the value itself does not always predict electrocardiographic changes or the degree of cardiotoxicity. Furthermore, stable patients who are otherwise unlikely to have elevated potassium should not be presumptively treated for hyperkalemia based on subtle electrocardiographic changes alone. In addition, hyperkalemia may present as an atropine-resistant bradycardia, with or without apparent heart block.[1]

Management

Patients with suspected or known hyperkalemia should have intravenous (IV) access and continuous cardiac monitoring. Treatment of hyperkalemia should be directed by the clinical scenario combined with the ECG and laboratory potassium value, and consists of three main steps: (1) stabilization of the cardiac membrane, (2) shifting of potassium into the cells, and (3) removal of potassium from the body. A variety of treatment options are considered for the acute management of hyperkalemia, including calcium, insulin, beta$_2$-adrenergic agonists, sodium bicarbonate, resins, and dialysis (Table 114.1).

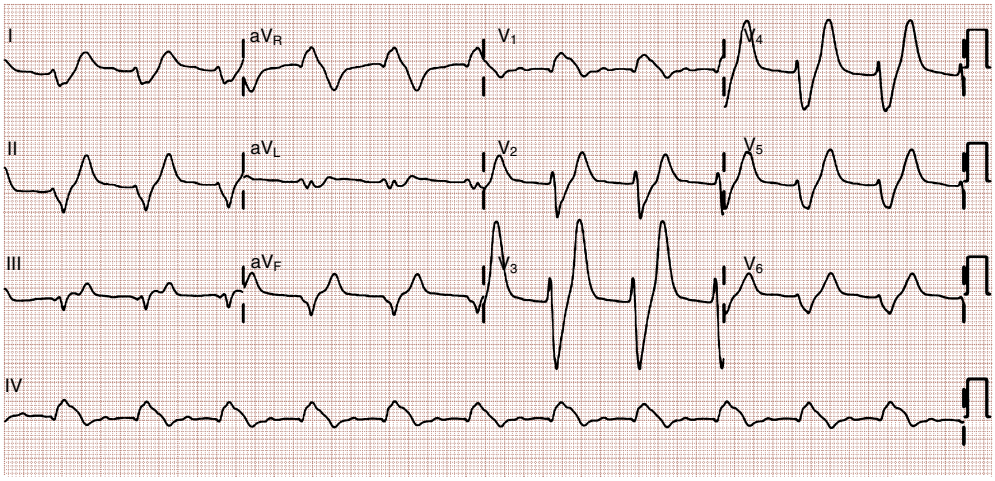


Fig. 114.1 Hyperkalemia with QRS widening merging into T wave, absent P wave.

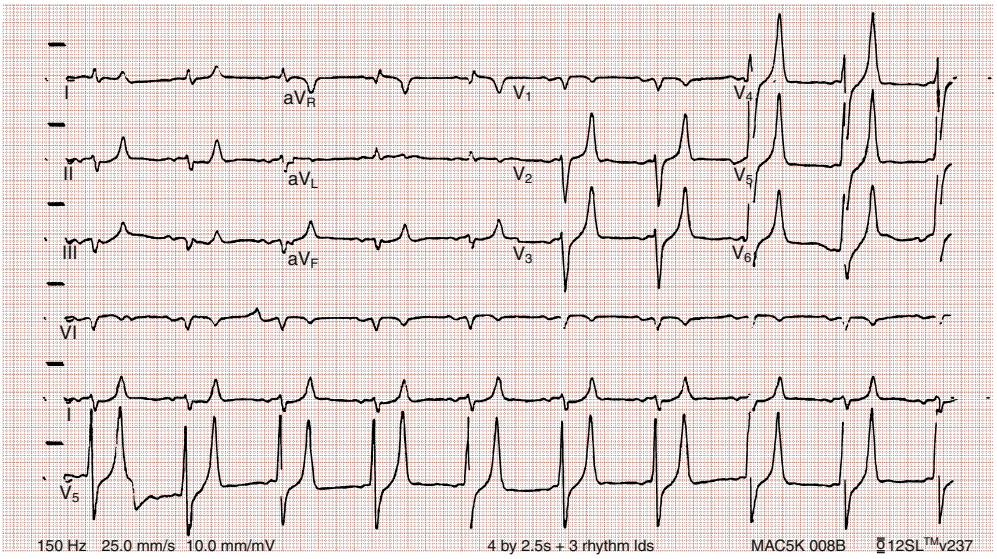


Fig. 114.2 Hyperkalemia in the same patient as in Figure 114.1 after potassium-lowering therapy has begun. Tall peaked T waves, decreased P wave.

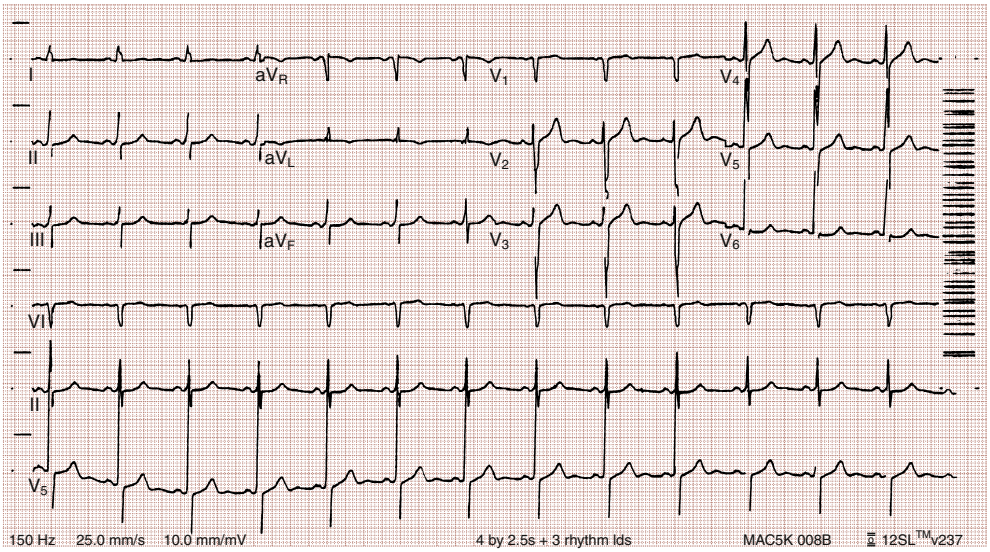


Fig. 114.3 The same patient as in Figures 114.1 and 114.2 after dialysis. The electrocardiogram (ECG) is now normal.

TABLE 114.1 Treatment of Hyperkalemia

Treatment	Medication	Features
Stabilize cardiac membrane	Calcium chloride 1 g or calcium gluconate IV 2 g	For wide QRS, restores the electrical gradient; does not decrease serum potassium Onset within minutes; lasts 30 to 60 minutes
Shift potassium into cells	Regular insulin, 10 units, IV push, combined with 100 mL of 50% dextrose, IV push; 5 units IV insulin if renal dysfunction to avoid hypolgycemia High-dose nebulized albuterol by face mask (10 to 15 mg by continuous inhalation) Bicarbonate 50 to 100 mL Normal saline 100 to 250 mL	Insulin: Onset <15 minutes; maximum effect 30 to 60 minutes (≈0.6 mEq/L decrease) Nebulized albuterol: Onset <15 minutes (0.5 to 1 mEq/L decrease) If severely acidotic In conjunction with nephrologist if dialysis dependent
Remove potassium from the body	Hemodialysis Normal saline and furosemide Ion exchange resin	Emergently in cardiac arrest, urgently in renal failure; may delay if renal function is normal In patients with rhabdomyolysis or tumor lysis syndrome with intact urine output, not effective acutely

IV, Intravenous.

IV calcium stabilizes the cardiac membrane by restoring the electrical gradient. Calcium increases the depolarization threshold and the calcium gradient across the cardiac membrane, quieting myocyte excitability and increasing cardiac conduction speed, thus narrowing the QRS. Calcium does not decrease serum potassium levels, and its effect is rapid (within 1 to 3 minutes), but transient (30 to 60 minutes or less). The dose is one ampule, or 10 mL of 10% calcium chloride solution. Calcium chloride is preferably administered through a central venous line due to the risk of tissue necrosis should it extravasate at the injection site. More than 10 mL of calcium gluconate will often be required, because it contains only one-third the calcium contained in calcium chloride. Calcium gluconate is preferred in pediatric cases, as well as in patients with less emergent (i.e., more chronic) hyperkalemic patients, when a slow infusion is desired or when only a smaller peripheral vein is available for administration.

Beta$_2$-agonists, insulin, saline, and potentially sodium bicarbonate shift potassium intracellularly. Insulin is the most reliable agent to move potassium into cells, but beta$_2$-adrenergic receptor agonists also provide benefit in some patients. Insulin, given IV in combination with glucose to prevent hypoglycemia, also shifts potassium into cells by stimulation of the sodium-potassium adenosine triphosphatase (Na^+, K^+-ATPase) pump. The onset of action is less than 15 minutes, and the effect is maximal between 30 and 60 minutes, with a maximal drop of 0.6 mEq/L on average. Clinicians should follow glucose levels closely for hours post-therapy with glucose and insulin.

Nebulized albuterol is effective in shifting potassium into cells by stimulation of the Na^+, K^+-ATPase pump. Nebulized albuterol begins to take measurable effect after 15 minutes and lowers the serum potassium level by 0.5 to 1 mEq/L, depending on the dose. The effective dose is at least four times higher than that typically used for bronchodilation. The combination of nebulized albuterol and insulin with glucose appears to be additive, lowering serum potassium, on average, by 1.2 mEq/L.

Saline infusions also stimulate the Na^+, K^+-ATPase pump; only a few hundred milliliters are required for beneficial effects. Saline infusions should be given judiciously in anuric patients and in consultation

with a nephrologist. Sodium bicarbonate is effective in hyperkalemic patients who are acidotic and has no benefit when used for hyperkalemia in non-acidotic patients. Sodium bicarbonate buffers hydrogen ions extracellularly while shifting potassium intracellularly, but it should be used in combination with other treatment options and reserved for patients with confirmed acidosis.[3]

Hemodialysis effectively and reliably decreases serum potassium levels by at least 1 mEq/L in the first hour and another 1 mEq/L during the next 2 hours. It is the only reliable method of potassium removal that has been experimentally studied and should be instituted early to treat life-threatening hyperkalemia in patients with renal failure. In patients with intact renal function, medical management alone is usually sufficient, even in extreme cases, and hemodialysis may not be necessary unless multiple medical modalities fail. There are no randomized trials addressing the use of diuretics (e.g., furosemide) in the emergent management of hyperkalemia. In cases such as rhabdomyolysis or tumor lysis syndrome, it may be appropriate to use a normal saline infusion supplemented by furosemide to enhance diuresis and urinary potassium excretion. Sodium polystyrene sulfonate (Kayexalate), does not decrease the serum potassium level within the first 4 hours of treatment, is not effective in the acute management of hyperkalemia, and may cause serious adverse gastrointestinal effects.[4]

Control of hyperkalemia in patients with chronic kidney disease and in those with heart failure continues to be difficult. However, two oral medications, patiromer and sodium zirconium cyclosilicate, have shown clinical promise in ongoing trials to lower serum potassium levels.[5,6] Zirconium is a highly selective cation exchanger that entraps potassium in theintestinal tract in exchange for sodium and hydrogen. Hypokalemia is often seen in association with hypomagnesemia, and patients with low serum potassium levels should be assumed to be hypomagnesemic also.

HYPOKALEMIA

Foundations

Hypokalemia is the most common electrolyte abnormality encountered in clinical practice. More than 20% of hospitalized patients and up to 40% of outpatients on thiazide diuretics have potassium values less than 3.5 mEq/L.[7] Moderate hypokalemia is a serum level of 2.5 to 3 mEq/L; severe hypokalemia is defined as a level less than 2.5 mEq/L. Although hypokalemia is usually asymptomatic, due to potassium's effect on the heart and muscle, very low levels can result in severe cardiac dysrhythmias or rhabdomyolysis, respectively.[8,9] Hypokalemia is often seen in association with hypomagnesemia, and patients with low serum potassium levels should be assumed to be hypomagnesemic as well.[10]

Clinical Features

Hypokalemia is usually asymptomatic but can present with nonspecific complaints, primarily weakness and muscle pain.[7] Although short periods of mild potassium depletion are typically well-tolerated in healthy individuals, severe potassium depletion can result in serious cardiovascular instability, neurologic dysfunction, glucose intolerance, gastrointestinal symptoms, and renal failure, as well as affect the acid-base balance in the body. The likelihood of symptoms appears to correlate with the rapidity of the decrease in serum potassium.

In patients without underlying heart disease, abnormalities in cardiac conduction are extremely unusual, even when the serum potassium concentration is below 3.0 mEq/L. Paresthesias, depressed deep tendon reflexes, fasciculations, muscle weakness, and confusion can occur when the serum potassium level is less than 2.5 mEq/L. However, in patients with cardiac ischemia or heart failure, even mild to moderate hypokalemia increases the likelihood of cardiac arrhythmias secondary to potassium's effect on the action potential. Hypokalemia is an independent risk factor contributing to reduced survival of cardiac patients and increased incidence of arrhythmic death. Based on available evidence, serum potassium concentrations should be maintained above 4.5 mEq/L in patients having an acute myocardial infarction. Hypokalemic patients can demonstrate first- and second-degree heart block, atrial fibrillation, ventricular fibrillation, and asystole. Life-threatening cardiac arrhythmias are managed by restoration of serum potassium levels into the normal range. Thyrotoxic periodic paralysis is a rare disorder characterized by acute hypokalemia and muscle weakness. It is usually seen in patients of Asian descent and is potentially fatal when involvement includes respiratory muscles.[8]

BOX 114.2 Five Most Common Causes of Hypokalemia

- Renal losses: Diuretic use, drugs, steroid use, metabolic acidosis, hyperaldosteronism, renal tubular acidosis, diabetic ketoacidosis (DKA), alcohol consumption
- Increased nonrenal losses: Sweating, diarrhea, vomiting, laxative use
- Decreased intake: Ethanol, malnutrition
- Intracellular shift: Hyperventilation, metabolic alkalosis, drugs
- Endocrine: Cushing disease, Bartter syndrome, insulin therapy

Differential Diagnosis

The five most common causes of hypokalemia are renal losses, increased nonrenal losses, decreased potassium intake, intracellular shift, and endocrine etiologies (Box 114.2). Increased excretion of potassium, especially coupled with poor intake, is the most common cause of hypokalemia, and patients receiving diuretics represent the single most common patient group encountered in clinical practice. Thiazide diuretics are more likely than loop or osmotic diuretics to cause hypokalemia, but both the thiazide and loop diuretics block chloride-associated sodium and increase delivery of sodium to the collecting tubules. Hypokalemia is a common adverse effect of treatment with diuretics and may cause fatal arrhythmias and increase the risk of digitalis toxicity.[9] In addition to diuretics, other drugs and disorders can cause significant renal potassium losses, including hyperaldosteronism, steroid excess, metabolic acidosis, DKA, renal tubular acidosis, and alcohol consumption. When given in large doses, penicillin and its synthetic derivatives promote renal potassium excretion by increasing sodium delivery to the distal nephron. Individuals with secondary hyperaldosteronism, whether due to congestive heart failure (CHF), hepatic insufficiency, or nephrotic syndrome, may also exhibit hypokalemia. Patients with renal tubular acidosis can become hypokalemic, because a defect in the distal tubule leads to increased potassium excretion.

Administration of insulin may reduce serum potassium because of insulin's ability to stimulate the Na^+, K^+-ATPase pump and move potassium intracellularly; hypokalemia can be a dangerous complication with intentional overdoses of insulin or during treatment of DKA. Although most patients with DKA present with high-normal or mildly elevated serum potassium levels, patients are usually 2 to 3 mEq/kg deficient in total body potassium. To avoid hypokalemic arrhythmias or cardiac arrest from hypokalemia, a potassium infusion should be started once significant hyperkalemia has been ruled out and intact renal function confirmed.

Hypokalemia can also occur from gastrointestinal and dermal losses. In diarrheal states, large quantities of potassium can be lost in the stool, with consequent secondary hyperaldosteronism. Large doses of laxatives and repeated enemas also cause excessive potassium loss in the stool. Although hypokalemia is often seen after protracted vomiting or nasogastric suctions, only 5 to 10 mEq/L of potassium is lost in gastric fluid. Hypokalemia in this setting is secondary to metabolic alkalosis, chloride losses, and hyperaldosteronism. On occasion, excessive

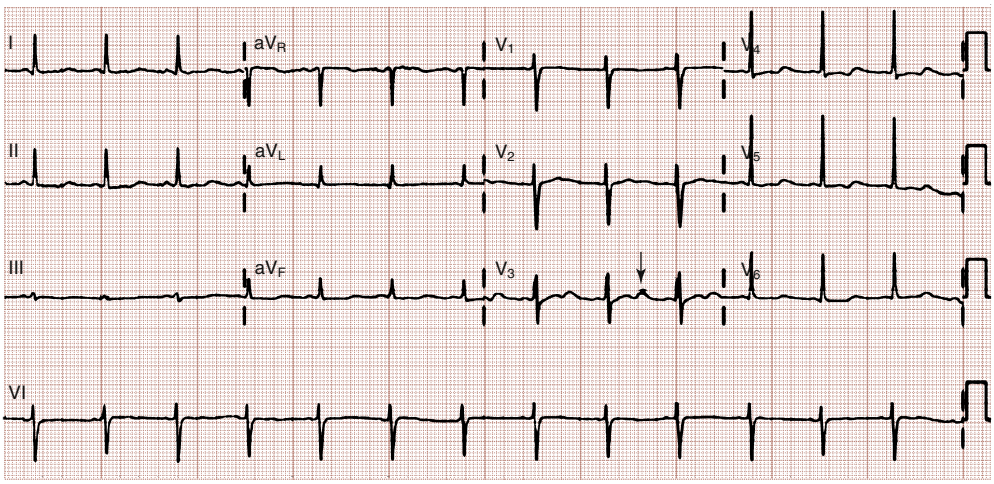
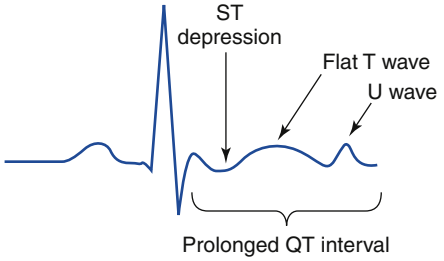


Fig. 114.4 Hypokalemic electrocardiographic changes, including flattened T wave, prolonged QT interval, nonspecific ST changes, and prominent U wave *(arrow)*.



Hypokalemia

Fig. 114.5 Electrocardiographic changes in hypokalemia.

sweating can lead to hypokalemia from potassium losses through the skin. Patients with extensive burns can also suffer from hypokalemia because of significant skin losses. Dietary potassium deficiency should be considered in the severely malnourished patient or chronic alcoholic. Poor potassium intake combined with increased nonrenal losses can result in severe hypokalemia.

Hypokalemia can also result from an acute shift of potassium from the extracellular compartment into cells, most commonly in patients with metabolic alkalosis or hyperventilation, and in patients taking medications such as beta-agonists or decongestants. Stimulation of beta-receptors can lead to hypokalemia, especially in patients using repetitive and high doses of beta-agonists for chronic obstructive pulmonary disease or asthma. A standard dose of nebulized albuterol reduces serum potassium by 0.2 to 0.4 mEq/L, and a second dose taken within 1 hour can reduce it by almost 1 mEq/L. Patients with starvation or near-starvation may develop hypokalemia when fed, because insulin secretion and increased cellular uptake can cause an acute exaggerated intracellular migration of potassium.

Diagnostic Testing

Hypokalemia is rarely diagnosed on clinical presentation alone and is typically made by measurement of the serum potassium concentration during routine laboratory studies. If there is any suspicion for hypokalemia or a patient presents with generalized weakness, palpitations, or arrhythmias, an ECG should be obtained. Just as tall-peaked T waves are characteristic of hyperkalemia, flattened T waves can be seen in hypokalemia. Hypokalemia may produce U waves, which are small deflections after the T wave (Figs. 114.4 and 114.5). Hypokalemia may also cause a dangerously prolonged QT interval. Although there is no threshold of QT prolongation at which torsades de pointes is certain to occur, once the QT interval becomes longer than 500 milliseconds, the risk of torsades de pointes increases twofold to threefold.[9] Hypokalemia is also notorious for causing nonspecific ST and T wave changes. In addition, prolonged potassium depletion of even a modest proportion can provoke or exacerbate kidney injury or hypertension. A severe degree of hypokalemia with paralysis is a potentially life-threatening medical emergency and may be seen as levels drop below 2.0 mEq/L.

Management

Because potassium is an intracellular cation; a low serum potassium level almost always reflects a significant total body potassium deficit; each 0.3 mEq potassium drop below normal correlates with an approximately 100 mEq total body deficit. In the absence of nausea or vomiting as the cause of hypokalemia, patients with mild or moderate hypokalemia may only need oral potassium replacement therapy. Oral replacement is available in liquid, powder, and tablet form. Potassium chloride is the most commonly used supplementation, and 40 to 60 mEq orally every 2 to 4 hours is typically well tolerated. If the cause of hypokalemia is not clear, or the hypokalemia is severe and associated with profound weakness, obtain a spot urine potassium level before starting therapy to assess whether the patient's kidneys are inappropriately wasting potassium from a renal or endocrine cause. Although a 24-hour serum is more accurate, a urinary potassium above 13 mEq/L per gram of creatinine is indicative of inappropriate renal potassium loses.[7] Treatment of hypokalemia is essential in multiple populations of patients. Hypokalemia is arrhythmogenic, especially in the settings of acute myocardial infarction, high catecholamine states, and hypertrophied or dilated ventricles. Hypokalemia is an important independent risk factor for morbidity and mortality in patients with heart failure, requiring serum potassium levels to between 4.0 and 5.0 mEq/L in this population.

If IV infusion is necessary, potassium chloride can be safely given at a rate of 10 to 20 mEq/hr. In the rare instance when IV repletion is planned at more than 20 mEq/hr, such as for levels below 2.0 mEq/L or QT interval greater than 500 milliseconds, the patient should have continuous cardiac monitoring and central line access established.

Hypokalemia is associated with hypomagnesemia, and the severity of the hypokalemia correlates with a similar degree of hypomagnesemia. Magnesium replacement should usually accompany potassium repletion.[10] Unless the patient receives at least 0.5 g/hr of magnesium sulfate along with potassium replacement, potassium will not move intracellularly and the patient will lose potassium through excretion. Correction of large potassium deficits may require several days, with simultaneous oral and IV replacement.

Disposition

Patients with mild hypokalemia, above 3.5 mEq/dl without any ECG changes can usually be discharged home with very close outpatient follow-up for a potassium recheck in a week. Hypokalemia due to diuretic therapy requires either increased potassium intake, the addition of a potassium sparing agent or switching the patient to a combined thiazide and potassium sparing diuretic.

Once the patient is discharged, if increased potassium intake is desired, then oral potassium repletion is best accomplished by encouraging the ingestion of potassium and magnesium-rich foods such as potatoes, avocado, black beans, tomatoes, and bananas.

Patients in whom the underlying cause of their hypokalemia cannot be successfully treated such as refractory nausea and vomiting require admission. Patients cannot be discharged until their potassium level is above 3.0 mEq/dl, they can tolerate food and liquids, and they have a QT interval of less than 500 msec.

HYPERNATREMIA

Foundations

Hypernatremia is defined as a serum sodium concentration above 145 mEq/L. It is rarely seen in previously healthy patients and usually portends a poor prognosis. Most hypernatremic patients have either an impaired sense of thirst or no access to water: elders, infants, patients with mental impairment, and those who are intubated and paralyzed are at highest risk for this disorder. Hypernatremia can be divided into three physiologic pairings: (1) hypernatremia with dehydration and low total body sodium, (2) hypernatremia with low total body water and normal total body sodium, and (3) hypernatremia with increased total body sodium (Box 114.3). Diabetes insipidus, an insufficient production of (or lack of response to) antidiuretic hormone, can lead to life-threatening hypernatremia (Box 114.4).

Clinical Features

Patients often have multiple causes of severe hypernatremia. Hypernatremia in adults is almost exclusively due to a free water deficit and should be considered in any patient presenting with altered mental status, as well as in bed-ridden patients with no access to water. Patients with impaired antidiuretic hormone function may complain of polyuria or polydipsia. Others may have obvious causes of extrarenal fluid losses, while some may have no complaints at all.

Diagnostic Testing

In addition to routine serum chemistries, serum osmolarity and urine sodium concentration and osmolality should be obtained. The degree of hypernatremia almost always equals the total body water (TBW) deficit in adults. The patient's TBW deficit can be estimated by the formula

$$\text{TBW deficit} = \text{TBW} \times (\text{serum } Na^{+} - 140)/140$$

A patient's TBW is calculated by multiplying the patient's body weight in kilograms times 0.6. However, because of differences in the percentages of body fat, based on the age and sex of the patient, it is more accurate to use the correction factors listed in Table 114.2.

Management

The treatment of hypernatremia has three interdependent goals: first, to quickly correct underlying shock, hypoperfusion, or significant hypovolemia with normal saline; second, to treat the underlying cause of hypernatremia, such as fever, vomiting, or diabetes insipidus; and third, to carefully lower the serum sodium level, usually by replacement of the body's total water deficit.[11,12] Until hypoperfusion and hypovolemia are corrected, homeostatic mechanisms for sodium balance promote sodium resorption to maintain intravascular volume, even at the expense of the serum sodium concentration.

The rate of correction in hypernatremia is extremely important to minimize morbidity and mortality. Both too quick and too slow

BOX 114.3 Three Types of Hypernatremia

Hypernatremia With Dehydration and Low Total Body Sodium
Heatstroke
Increased insensible losses: Burns, sweating
Gastrointestinal loss: Diarrhea, protracted vomiting, continuous gastrointestinal suction
Osmotic diuresis: Glucose, mannitol, enteral feeding

Hypernatremia With Low Total Body Water and Normal Total Body Sodium
Diabetes insipidus
Neurogenic
Elderly with "reset" osmostat
Hypothalamic dysfunction
Suprasellar or infrasellar tumors
Renal disease
Drugs (amphotericin, phenytoin, lithium, aminoglycosides, methoxyflurane)
Sickle cell disease

Hypernatremia With Increased Total Body Sodium
Salt tablet ingestion
Salt water ingestion
Saline infusions
Saline enemas
IV sodium bicarbonate
Poorly diluted interval feedings
Primary hyperaldosteronism
Hemodialysis
Cushing syndrome
Conn syndrome

IV, Intravenous.

BOX 114.4 More Common Causes of Diabetes Insipidus

Central
Idiopathic
Familial disease
Cancer
Hypoxic encephalopathy
Infiltrative disorders
Post supraventricular tachycardia
Anorexia nervosa

Nephrogenic
Chronic renal insufficiency
Polycystic kidney disease
Lithium toxicity
Hypercalcemia
Hypokalemia
Tubulointerstitial disease
Hereditary
Sickle cell disease

TABLE 114.2 Calculation of Body Water

Population	Total Body Water
Children and adult men	Body weight (kg) × 0.6
Adult women	Body weight (kg) × 0.5
Elderly men	Body weight (kg) × 0.5
Elderly women	Body weight (kg) × 0.45

correction speeds are associated with an increased risk of death, regardless of the initial sodium level.[11,12] In adult patients who develop hypernatremia over a short time due to sodium loading, "rapid correction" at a rate of at least 1 mEq/hr decrease in serum sodium appears relatively safe.[11,12] However, most adult patients develop hypernatremia over days to weeks. In this group of patients, serum sodium concentration should be corrected slowly, at no more than 0.5 mEq/hr or 10 to 12 mEq/day.

Normal saline should be started for volume replacement until the patient is hemodynamically stable, and then changed to half-normal saline at 100 mL/hr once vital signs have normalized. The treatment of central diabetes insipidus with desmopressin (DDAVP) is an effective means of improving polyuria and hypernatremia; initial doses in the acute setting range from 1 to 2 μg.

Disposition

The disposition is based on the patient's underlying etiology and severity of the hypernatremia. Almost all hypernatremic patients require hospitalization due to their dehydrated status and underlying comorbidities. Most of the time these patients have a free water deficit with a low chance of dangerous overcorrection. In mild cases, increasing water intake at home can restore the proper sodium balance.

HYPONATREMIA

Foundations

Hyponatremia, defined as serum sodium concentration of less than 135 mEq/L, is the second most common electrolyte abnormality encountered in clinical practice and can be a marker of underlying disease. The most common causes of severe hyponatremia in adults are therapy with thiazides, the postoperative state, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), psychogenic polydipsia, exercise-associated hyponatremia, and unintentional water intoxication. Gastrointestinal fluid loss, ingestion of overly dilute formula, accidental ingestion of excessive water, and receipt of multiple tap water enemas are the main causes of severe hyponatremia in infants and children. Most patients presenting to the emergency department (ED) with hyponatremia are asymptomatic and do not require emergent therapy. If symptoms are present, they are typically based on the degree of hyponatremia and how acutely the hyponatremia developed. Symptoms range from headache, nausea, and vomiting to confusion, seizures, and coma. There are two groups of hyponatremic patients that require treatment with either normal saline or hypertonic saline: (1) severe but asymptomatic hyponatremia with a sodium level of 110 mEq/L or less and (2) acute symptomatic hyponatremia with a sodium level below 120 mEq/L.

Central nervous system (CNS) damage due to hyponatremia may be caused by cerebral edema and increased intracranial pressure, by osmotic fluid shifts during overly aggressive treatment, or by both. When neurons are subjected to a hyponatremic environment, they become depleted of sodium and potassium in an attempt to limit their own osmolarity to prevent intracellular fluid shifts that would lead to cerebral edema. If fluid therapy raises extracellular sodium levels too quickly, fluids shift out of neurons and can cause diffuse demyelination.

BOX 114.5 Causes of Hyponatremia

Pseudohyponatremia
Hyperlipidemia
Hyperproteinemia (multiple myeloma, macroglobulinemia)

Dilutional
Hyperglycemia

Hypovolemic Hyponatremia: Decreased Total Body Water and Sodium, With a Relatively Greater Decrease in Sodium
Body fluid losses: Sweating, vomiting, diarrhea, gastrointestinal suction
Third spacing: Bowel obstruction, burns, pancreatitis, rhabdomyolysis
Renal causes: Diuretics, mineralocorticoid deficiency, osmotic diuresis, renal tubular acidosis, salt-wasting nephropathies

Hypervolemic Hyponatremia: Increased Total Body Sodium With a Relatively Greater Increase in Total Body Water
Heart failure
Chronic renal failure
Hepatic failure or cirrhosis

Euvolemic Hyponatremia: Increased Total Body Water With Nearly Normal Total Body Sodium
SIADH
Drugs causing SIADH (diuretics, barbiturates, carbamazepine, chlorpropamide, clofibrate, opioids, tolbutamide, vincristine)
Psychogenic polydipsia
Beer potomania
Hypothyroidism
Adrenal insufficiency
MDMA (ecstasy)
Accidental or intentional water intoxication

MDMA, N-methyl-3,4-methylenedioxyamphetamine; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.

This can result in a flaccid paralysis and death due to central pontine myelinolysis, a syndrome more accurately labeled as the osmotic demyelinating syndrome (ODS).[13,14]

Causes of hyponatremia fall into four general categories: pseudohyponatremia, hyponatremia with dehydration and decreased extracellular volume, hyponatremia with increased extracellular volume, and euvolemic hyponatremia with increased TBW (Box 114.5).

Pseudohyponatremia

Pseudohyponatremia is a falsely low sodium reading caused by the presence of other osmolar particles in the serum. The phenomenon of pseudohyponatremia is explained by the increased percentage of large molecular particles that do not contribute to plasma osmolality relative to sodium. Severe hypertriglyceridemia and hyperproteinemia are two common causes of this condition. Blood draw or laboratory error should also be considered as a possible cause of hyponatremia, especially if the blood sample was drawn near an infusion site using 5% dextrose in water (D_5W) when a very abnormal sodium level is reported in an otherwise healthy patient.

Hyperglycemia is sometimes considered a cause of pseudohyponatremia; however, it causes a dilutional hyponatremia by pulling water into the vascular space through osmosis. In true pseudohyponatremia, serum osmolality is normal and no shifts of water occur. Two different formulas based on the degree of a patient's hyperglycemia are currently

used to correct serum sodium levels. The most recommended formula advocates for the addition of 1.6 mEq/L to the measured sodium for every 100 mg/dL of glucose above 100. However, another acceptable formula recommends using this 1.6 mEq/dl only for the first 400 mg rise in glucose and then using 2.4 mEqs for each additional 100 mg/dl rise in glucose. Either formula is acceptable to use, the key concept being that as glucose levels rise significantly, a "normal" and not as lowered serum sodium is distinctly abnormal.

Hypovolemic Hyponatremia

Hypovolemic hyponatremia, or hyponatremia with dehydration, occurs when there is decreased extracellular volume combined with an even greater loss of sodium. Hyponatremia secondary to body fluid losses should be differentiated from that due to renal losses. Hyponatremia with dehydration due to body fluid losses includes sweating, vomiting, diarrhea, and gastrointestinal suction. Hypovolemic hyponatremia is also seen with "third spacing" in bowel obstruction, burns, and intra-abdominal sepsis. Hypovolemic hyponatremia due to renal causes includes diuretic use, mineralocorticoid deficiency, renal tubular acidosis, and salt-wasting nephropathy. Hypovolemic hyponatremia can be further exacerbated when fluid losses are replaced with hypotonic saline.

Hypervolemic Hyponatremia

Hypervolemic hyponatremia, or hyponatremia with increased extracellular volume, occurs when sodium and water are retained, but water retention exceeds sodium retention. Most of these patients present with edema. Hyponatremia with increased total body sodium occurs in patients with heart failure, chronic renal failure, and hepatic failure.[14,15] The fluid retention in these states is secondary to renal hypoperfusion, resulting in increased aldosterone secretion and a decrease in free water excretion.

Euvolemic Hyponatremia

The final category of hyponatremia is one in which patients are euvolemic but have increased TBW. Causes of this type of hyponatremia include SIADH, psychogenic polydipsia, beer potomania, hypothyroidism, diuretic use in patients with mild CHF, and accidental or intentional water intoxication. Euvolemic hyponatremia has also been described in patients after the use of the recreational drug *N*-methyl-3,4-methylenedioxyamphetamine (MDMA; or ecstasy). MDMA-induced hyponatremia is multifactorial and related to increased free water intake to avoid dehydration and rhabdomyolysis, along with the tendency to be very active while using the drug, leading to sweating and antidiuretic hormone secretion.[14] For similar reasons, there are extensive case reports of significant exercise-associated hyponatremia in endurance athletes.

SIADH is an important cause of hyponatremia that occurs when antidiuretic hormone is secreted independent of the body's need to conserve water. The process results from excess antidiuretic hormone production that increases TBW, causing the serum sodium to decrease. Patients with SIADH inappropriately concentrate their urine, despite a low serum osmolality and normal circulating blood volume. Despite excess TBW, they have no signs of edema, ascites, or heart failure, because most of the increased water is intracellular rather than intravascular. The three most common causes of SIADH are (1) pulmonary lung masses and infections, (2) CNS disorders, and (3) drugs (Box 114.6). Lung cancers (especially small cell cancer), pneumonia, and tuberculosis can lead to SIADH. CNS infections, masses, and psychosis can also cause SIADH. A large number of medications are associated with SIADH, the most common of which are thiazide diuretics, narcotics, lithium, oral hypoglycemics, barbiturates, and antineoplastics. The mainstay of treatment of most patients with SIADH and other causes of euvolemic hyponatremia is free water restriction.

BOX 114.6 Three Most Common Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Lung Masses
Cancer (especially small cell)
Pneumonia
Tuberculosis
Abscess

Central Nervous System Disorders
Infection (meningitis, brain abscess)
Mass (subdural, postoperative, cerebrovascular accident)
Psychosis (with psychogenic polydipsia)

Drugs
Thiazide diuretics
Narcotics
Oral hypoglycemic agents
Barbiturates
Antineoplastics

Clinical Features

The signs and symptoms of hyponatremia worsen as sodium levels decline and also correlate with how rapid hyponatremia develops. Nonspecific signs of hyponatremia include anorexia, nausea, vomiting, and generalized weakness. Acutely hyponatremic patients whose sodium level drops below 120 mEq/L over 24 to 48 hours may present with severe neurologic findings, including confusion, seizures, coma, and brainstem herniation. Determination of the hydration status of the patient may help establish the etiology of the hyponatremia and direct subsequent treatment. *Hypovolemic* hyponatremia is more likely in the patient with diminished skin turgor, increased capillary refill, dry mucous membranes, and orthostasis, whereas the patient with jugular venous distention, peripheral edema, or pulmonary congestion is much more likely to have *hypervolemic* hyponatremia. Patients with SIADH have no edema and normal skin turgor. Of note, in geriatric patients, the risk of hyponatremia doubles for those presenting with large-bone fractures.

Diagnostic Testing

A spot urinary sodium or urinary chloride level can help determine if hyponatremia is renal in origin (Table 114.3). Patients with hypovolemic hyponatremia due to nonrenal causes typically have a low urinary sodium or chloride level (<20 mEq/L), because they try to retain solute. Patients with hypovolemic hyponatremia due to renal causes have elevated urine sodium and chloride levels (>20 mEq/L) because their kidneys cannot retain sodium or chloride. Patients with euvolemic hyponatremia typically have a urinary sodium concentration more than 20 mEq/L secondary to volume expansion caused by water retention. Patients with psychogenic polydipsia who are ingesting large quantities of water have dilute urine with low quantities of urinary sodium. Patients with hypervolemic hyponatremia secondary to CHF or cirrhosis have urine sodium levels of less than 20 mEq/L because of renal hypoperfusion, whereas those with renal causes of hypervolemic hyponatremia or with SIADH have sodium levels more than 20 mEq/L, because their kidneys do not retain sodium. In interpreting serum sodium levels, consider the possibility of sampling error if the

TABLE 114.3 Spot Urine Interpretation

	Hypovolemic Hyponatremia	Hypovolemic Hyponatremia	Euvolemic Hyponatremia	Euvolemic Hyponatremia	Hypervolemic Hyponatremia	Hypervolemic Hyponatremia
Underlying etiologies	Nonrenal causes	Renal causes	SIADH, endocrinopathies	Psychogenic polydipsia	Edematous disorders: e.g., CHF, cirrhosis	Renal failure
Urinary sodium	<20 mEq/L	>20 mEq/L	>20 mEq/L	<20 mEq/L	<20 mEq/L	>20 mEq/L
Mechanism	Extrarenal solute loss	Renal solute loss	Volume expansion	Normal renal response to excess volume and sodium retention	Renal hypoperfusion	Renal solute loss

CHF, Congestive heart failure; *SIADH,* syndrome of inappropriate antidiuretic hormone secretion.

TABLE 114.4 Characteristics of Infusates

Infusate	Infusate Sodium (Mmol/L)	Extracellular Fluid Distribution (%)
3% Hypertonic saline	513	100
0.9% Normal saline solution	154	100
Lactated Ringers solution	130	97
Half-normal saline solution	77	73
0.2% Sodium chloride + D_5W	34	55
D_5W	0	45

D_5W, 5% dextrose in water.

reported value does not seem consistent with the patient's presentation and confirm that a diuretic such as furosemide, which will increase urinary sodium losses, has not been recently administered. Consider adrenal insufficiency when a dehydrated patient has both hyponatremia and hyperkalemia.

Of note, in geriatric patients, the risk of hyponatremia doubles for those presenting with large-bone fractures.

Management

Treatment of hyponatremia is guided by the patient's clinical presentation, severity of symptoms, estimated duration of illness, fluid status, and underlying cause of the sodium disturbance. Typically, sodium should be corrected during a time course of 48 to 72 hours. The neurologic changes, including flaccid paralysis, dysarthria, dysphagia, and hypotension, associated with overly rapid sodium correction are referred to as *osmotic demyelinating syndrome (ODS),* previously termed *central pontine myelinolysis.* Most ODS cases occur in the alcoholic, malnourished, and geriatric population, although this devastating side effect can occur in young, healthy patients as well. If a patient develops symptoms of ODS during therapy, all sodium-containing fluids should be stopped and D_5W administered immediately to temporarily lower sodium values. Most patients presenting to the ED with hyponatremia are stable and require no emergent therapy. However, patients who have serum sodium levels of significantly less than 120 mEq/L and those who have acute alterations in mental status, seizures, or new focal findings due to hyponatremia need immediate intervention. Table 114.4 presents the sodium concentration of various infusates, and the following equation is helpful to estimate the effect of 1 liter of any infusate on serum sodium:

$$\text{Change in serum } Na^+ - \text{serum } Na^+/TBW + 1$$

There is no consensus regarding the optimal treatment of symptomatic hyponatremia. However, there is agreement that correction should occur at a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid as to pose a risk for development of ODS.[13,14] For relatively asymptomatic patients with sodium values of 115 to 135 mEq/L, free water restriction is typically the most important treatment.

In more severe cases when the sodium value is 120 mEq/L or less and the patient has alterations in mental status, has focal findings, or is seizing, 3% hypertonic saline (513 mEq/L of sodium) is indicated.[15,16] Correction of hyponatremia by 4 to 6 mEq/L within 6 hours, with bolus infusions of 3% saline if necessary, is sufficient to manage the most severe manifestations of hyponatremia. Initially, 100 mL of 3% hypertonic saline should be infused over 10 minutes. If a second bolus is required, an additional 100 mL of the 3% solution may be administered during the next 50 minutes. To minimize the likelihood of ODS, it is essential that symptomatic patients with severe hyponatremia have serum sodium levels raised slowly. Previous guidelines endorsed the safety of raising the serum sodium by up to 10 to 12 mEq within the first 24 hours. However, in patients believed to have been hyponatremic for more than 48 hours, severe hyponatremia should be corrected by no more than 8 mEq in the first 24 hours.[13]

Potassium deficits should be replaced aggressively in the treatment of hyponatremic patients with a sodium disorder. If patients are retaining volume and diuresis is not adequate, furosemide can be used; D_5W is infused if the sodium level is rising too quickly.[16] Patients may be able to make full neurologic recoveries from ODS with the reinduction of hyponatremia in these extreme cases. Demeclocycline in a dosage of 600 to 1200 mg daily is effective in patients with refractory hyponatremia.

Hypovolemic Hyponatremia

Treatment of hypovolemic hyponatremia begins with rehydration. Hypotensive, dehydrated patients should be volume resuscitated with normal saline. Once the patient is hemodynamically stable, the infusion rate should be slowed. Typically, normal saline is started at 500 to 1000

mL/hr until the blood pressure is stable and then slowed to 200 mL/hr with frequent sodium checks. If the sodium value is below 120 mEq/L, the sodium concentration should be allowed to rise by less than an average of 0.5 mEq/hr or about 8 mEq/day until about 120 mEq.[13,15,16] The underlying cause of hyponatremia should be identified and treated.

Hypervolemic Hyponatremia

Normal saline and hypertonic saline can cause pulmonary edema in the hypervolemic hyponatremic patient. Restriction of fluid and sodium is the preferred treatment, although loop diuretics can be used in severe cases. Hemodialysis is an alternative in patients with renal impairment and should be considered for significantly hyponatremic renal failure patients with volume overload. Patients with CHF benefit from diuretics that increase water excretion and cause vasodilation to improve cardiac output.[17] In patients with liver failure, albumin is a consideration, along with diuretics and possibly paracentesis to improve the underlying pathologic process. Water restriction may make the largest impact on the long-term care of these patients.

Euvolemic Hyponatremia

The mainstay of treatment of euvolemic hyponatremia is free water restriction, as hypo-osmolality in SIADH results from a relative abundance of water in the intracellular and extracellular spaces, maintained by a reduced ability to excrete water. However, water restriction is insufficient to treat acute severe hyponatremia and is not recommended as a sole intervention for patients requiring more rapid correction based on clinical presentation. The only definitive treatment of SIADH is elimination of its underlying cause. Most cases of SIADH caused by malignant disease resolve with effective antineoplastic therapy; most due to medication resolve promptly when the offending agent is discontinued.

In patients with SIADH, normal saline may cause the serum sodium concentration to fall even more as free water is retained and hypertonic urine is excreted. If a patient is symptomatic because of a rapid decrease in serum sodium concentration, treatment with hypertonic saline is recommended. Rapid correction of hyponatremia may occur during hemodialysis. To minimize the risks of ODS, hemodialysis is reserved for patients with documented renal failure under close monitoring. Vaptans, which are oral agents that inhibit the effects of vasopressin, have been studied for treatment of patients with hyponatremia due to SIADH but need further evaluation before becoming standard of care.[15,16]

Disposition

Patients that are altered or lethargic with hyponatremia should be admitted to the ICU. Other hyponatremic patients that should be admitted to the ICU include patients on a hypertonic saline infusion and those who received a hypertonic saline bolus. In addition, nephrology should be consulted for patients with symptomatic hyponatremia or rapidly rising sodium to discuss the use of desmopressin or vaptans. Patients who have returned to neurologic baseline with stable sodium trended over 4 to 6 hours may be admitted to a monitored floor bed. Patients may be discharged once their sodium is approaching 130 mEq/L, their underlying cause has been identified and either corrected or more aggressively treated. Patients who have developed hyponatremia acutely (such as the endurance athlete) who present asymptomatically or with mild symptoms may be considered for discharge from the ED with close outpatient follow-up and a lab recheck.

HYPERCALCEMIA

Foundations

Hypercalcemia is usually defined as a serum calcium level above 10.5 mg/dL; normal levels are usually defined as between 9 and 10.5 mg/dL. Hypercalcemia is considered mild if the total serum calcium level is between 10.5 and 12 mg/dL; levels higher than 14 mg/dL can be life-threatening. Hypercalcemic crisis typically evolves from preexisting mild hypercalcemia, which develops into an acute severe hypercalcemic emergency.

Clinical Features

The clinical presentation of hypercalcemia is often vague and nonspecific. Symptoms include nonfocal abdominal pain, constipation, fatigue, body aches, anorexia, polydipsia, polyuria, nausea, and vomiting. Symptom severity depends on the degree of hypercalcemia, the rapidity of onset, and the patient's baseline neurologic and renal function. Neuropsychiatric disturbances include anxiety, depression, and hallucinations. The CNS manifestations that often predominate in more severe cases include lethargy, altered mental status, seizures, and coma. Death due to hypercalcemia is usually related to complications caused by coma, dehydration, or electrolyte disturbances. Cardiac conduction abnormalities may occur; bradydysrhythmias are the most common. Severe hypercalcemia (>14 mg/dL) has also been associated with sinus arrest, atrioventricular block, atrial fibrillation, and ventricular tachycardia.

Differential Diagnosis

There are five major causes of hypercalcemia (Box 114.7). Hyperparathyroidism is the most common cause of hypercalcemia in outpatients, whereas malignancy is the most common cause in hospitalized patients; together, these two etiologies account for the majority of hypercalcemia cases.[18] Mild hypercalcemia, in an otherwise normal person, may be due to thiazide diuretics in the setting of minimal dehydration. Other less common causes of elevated calcium concentration should be considered after malignant disease and parathyroid disease are ruled out. Malignancy-associated hypercalcemia occurs in up to 40% of all patients with advanced cancer and generally conveys a poor prognosis.[19] Other causes of hypercalcemia include granulomatous disease, such as sarcoidosis and tuberculosis; medications and pharmacologic agents; and a number of diverse conditions, such as rhabdomyolysis and prolonged immobilization.

BOX 114.7 Five Most Common Causes of Hypercalcemia

Malignant Disease
Ectopic secretions of parathyroid hormone, multiple myeloma, cancer metastatic to bone
Most common: Breast, lung, hematologic, kidney, prostate

Endocrine
Hyperparathyroidism, multiple endocrine neoplasias, hyperthyroidism, pheochromocytoma, adrenal insufficiency

Granulomatous Disease
Sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidioidomycosis

Pharmacologic Agents
Vitamins A and D, thiazide diuretics, estrogens, milk-alkali syndrome

Miscellaneous
Dehydration, prolonged immobilization, iatrogenic, rhabdomyolysis, familial, laboratory error

Diagnostic Testing

The diagnostic evaluation of a patient with suspected hypercalcemia begins with obtaining electrolyte and renal function tests and an ECG. Calcium is measured by determination of either a total serum calcium level or an ionized calcium level. Ionized calcium is the active form of the total calcium level. Ionized calcium is more accurate in the diagnosis and treatment of hypocalcemia but does need to be routinely evaluated in hypercalcemia. The serum total calcium level represents both bound and unbound calcium and, thus, should be corrected based on the albumin concentration. A correction of the total serum calcium is made by adjusting for deviations in the serum albumin level. The adjustment is accomplished by adding or subtracting 0.08 mg/dL to the measured total serum calcium for every 1.0 g/L of albumin below or above 4 g/L albumin, respectively.

A short QT interval can be seen in hypercalcemia and is considered a classic finding. However, although the incidence and duration of QT shortening appear to be correlated with the degree of hypercalcemia, it is not a reliable finding and is not routinely seen in most patients (Fig. 114.6). ST segment elevation may be the least well documented but most consistent electrocardiographic finding, making hypercalcemia a potential cause of ST segment elevation caused by conditions other than myocardial infarction.[20,21] Some hypercalcemic patients may have U waves in the precordial leads despite normokalemia, while others may have an Osborn wave despite normothermia.[22] In severe cases of hypercalcemia, sinus bradycardia, high-degree atrioventricular block, and ventricular fibrillation may also be seen.

Management

Patients in hypercalcemic crisis are usually dehydrated, often obtunded, and also predisposed to arrhythmias as a result of concomitant electrolyte disturbances; thus, they require IV access with a normal saline infusion and close monitoring. Normal saline inhibits proximal tubule reabsorption of calcium and corrects the patient's volume depletion. Normal saline should be infused "wide open" until blood pressure and perfusion are normalized. After the initial bolus, the saline infusion should be adjusted to a rate of approximately 200 to 300 mL/hr, depending on the patient's age, renal function, cardiac and other comorbid diseases, to establish adequate urine output (2 L/day). Although the administration of higher volumes of saline may further augment calcium excretion, it is much more likely to increase morbidity and mortality from volume overload, pulmonary edema, and myocardial ischemia. The routine use of furosemide in the management of hypercalcemia is no longer recommended.[18] Furosemide was once thought to block the distal reabsorption of calcium, thus complementing saline's proximal tubule effects. However, furosemide has not been shown to have significant calcium reabsorption blocking effects. The use of furosemide should be reserved for augmenting saline diuresis to avoid volume overload during the treatment of hypercalcemia. If a loop diuretic is given to patients who are not yet volume replete, not only can the patient's hemodynamics and renal status deteriorate, but hypercalcemia may worsen. Once calcium excretion by saline infusion has begun, other electrolyte values should be carefully monitored, with particular attention to serum potassium levels.

Osteoclast-inhibiting therapies for severe hypercalcemia are generally considered in consultation with the patient's primary physician or oncologist. Drugs that inhibit osteoclast-mediated bone resorption include the bisphosphonates, mithramycin, calcitonin, and glucocorticoids. IV bisphosphonates are the most extensively studied and most efficacious agents for the treatment of malignancy-associated hypercalcemia. Their calcium-lowering effect is achieved predominantly by inhibition of osteoclast function and survival. Zoledronic acid is the bisphosphonate of choice in hypercalcemia of malignancy. The infusion takes 15 minutes; zoledronic acid may be more effective than other bisphosphonates at keeping the calcium level down over time. The use of IV bisphosphonates is restricted to the treatment of acute hypercalcemia associated with serum calcium concentrations above 15 mg/dL and rapid deterioration of CNS, cardiac, gastrointestinal, and renal function. Denosumab for the management of hypercalcemia of malignancy provides a new option for the management of patients with persistent hypercalcemia despite bisphosphonates.[23] In the rare case in which a patient has a life-threatening hypercalcemic arrhythmia or heart block, hemodialysis should be considered. In cases of hypercalcemic crisis resulting from primary hyperparathyroidism, urgent parathyroidectomy is potentially curative. Hematology, oncology, and palliative care specialists should be involved early in the care of the patient with hypercalcemia associated with malignancy to assure the appropriate targeted therapies. Isolated mild hypercalcemia rarely requires urgent treatment; however, an outpatient hypercalcemia

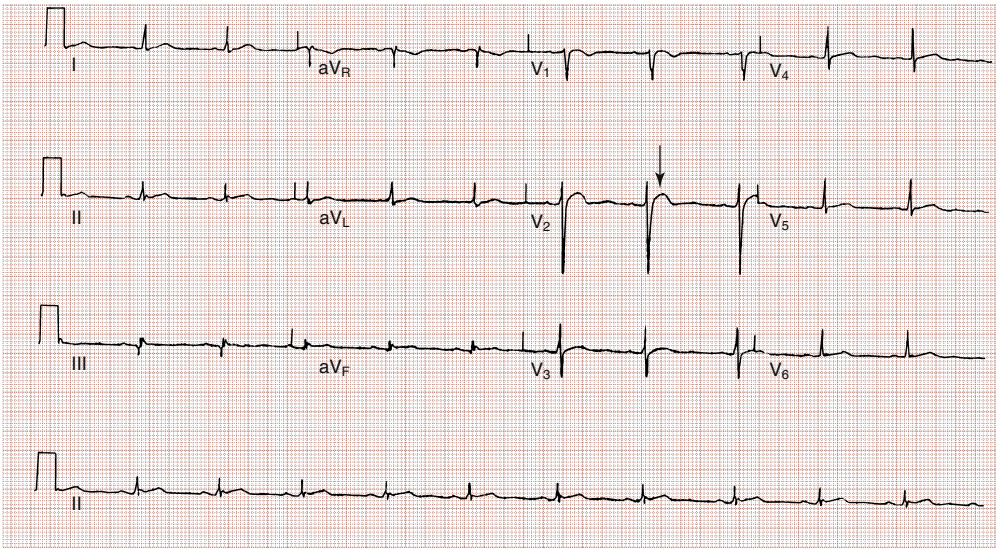


Fig. 114.6 Short QT interval *(arrow)* in a patient with multiple myeloma and a calcium level of 14.2 mg/dL. (Courtesy Dr. Barton Campbell.)

evaluation should be discussed at discharge, because many will ultimately be diagnosed with hyperparathyroidism.

Disposition

Patients with altered mental status or arrhythmias from hypercalcemia should be admitted to the intensive care unit for close monitoring, management of electrolytes, and frequent laboratory testing. In patients with symptomatic hypercalcemia, medical floor admission may be necessary for continuous fluid resuscitation and electrolyte monitoring. Patients with mild to moderate hypercalcemia may be discharged home with instructions to avoid dehydration and high calcium diets. In patients with known malignancy or suspicion for malignancy, disposition planning should be coordinated with the oncology team.

HYPOCALCEMIA

Foundations

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling. Total body calcium is controlled by a feedback system in which parathyroid hormone induces the bone and the kidneys to increase serum calcium levels. Vitamin D facilitates intestinal calcium absorption. Conversely, elevated calcium levels normally inhibit parathyroid hormone release.

Clinical Features

Although there are many clinical manifestations of hypocalcemia, neuromuscular and cardiovascular findings predominate. Severity of symptoms is related to not only the absolute calcium level, but also the rate calcium rise. The patient may complain of muscle cramping, perioral or finger paresthesias, shortness of breath secondary to bronchospasm, and tetanic contractions. Symptomatic hypocalcemia may result in cardiovascular collapse, hypotension, and dysrhythmias. More severe hypocalcemia can lead to cardiovascular collapse, hypotension, syncope, dysrhythmias, CHF, angina, hypotension, and QT prolongation. Patients with a calcium level lower than 8.95 mg/dL have a 2.3-fold higher risk of sudden cardiac activity than those with calcium levels higher than 9.55 mg/dL.[24]

Chronic hypocalcemia may manifest with cataracts, poor dentition, dry skin, coarse hair, and pruritus. Chvostek sign may be present: when the examiner taps the facial nerve, facial or eye muscle twitching will be elicited. Trousseau sign may also be present; when the examiner inflates the blood pressure cuff to 20 mm Hg above the systolic blood pressure for 3 minutes, carpal spasms will be induced because of the increased excitability caused by local ulnar and median nerve ischemia. Trousseau sign is relatively specific for hypocalcemia, whereas Chvostek test is less diagnostic.

Differential Diagnosis

There are multiple causes of hypocalcemia, of which hypoalbuminemia is the most common (Box 114.8). Because calcium is bound to albumin and other serum proteins, hypoalbuminemia will cause a fall in the measured serum calcium by about 0.8 mg/dL for every 1 g/dL reduction in serum albumin. The active form of calcium is ionized calcium, which is not affected by changes in albumin.

Hypoparathyroidism is a common cause of hypocalcemia and often develops after surgery for head and neck cancers; it occurs in 1% to 2% of patients after total thyroidectomy. Patients with vitamin D deficiency, including those with malabsorption syndromes, liver disease, malnutrition, and very little sunlight exposure, are at high risk for development of hypocalcemia. Derangements in magnesium and phosphate can also lead to hypocalcemia. Hyperphosphatemic patients often have hypocalcemia because of phosphate's affinity to bind calcium, whereas hypomagnesemia causes end-organ resistance to parathyroid hormone and inhibits the hypocalcemic feedback loop. Patients with sepsis demonstrate hypocalcemia usually associated with hypoalbuminemia.

BOX 114.8 Most Common Causes of Hypocalcemia

Hypoalbuminemia
Hypoparathyroidism: inherited, postsurgical, autoimmune, infiltrative
Vitamin D deficiency and vitamin D resistance: Malabsorption syndrome, liver disease, malnutrition, sepsis, anticonvulsants, lack of sunlight exposure
Chronic renal failure
Hyperphosphatemia
Hypomagnesemia
Respiratory alkalosis
Severe pancreatitis
Drugs: Bisphosphonates, phenytoin, phosphate, calcitonin
Tumor lysis syndrome
Rhabdomyolysis

BOX 114.9 Five Most Common Symptomatic Causes of Hypocalcemia Seen in the Emergency Department

- Hyperventilation: Anxiety, sympathomimetics
- Ethanol abuse, chronic malnutrition: Hypoalbuminemia
- Massive blood transfusion
- Toxins: Hydrofluoric acid, ethylene glycol
- Severe pancreatitis

The most common causes of symptomatic hypocalcemia are massive blood transfusions, toxins, pancreatitis, tumor lysis syndrome, and chronic malnutrition (Box 114.9). Patients receiving massive blood transfusions are at risk for development of hypocalcemia because of citrate toxicity.[25] Rapid blood transfusions and radiocontrast dyes containing citrate infusions should be monitored closely in patients with hepatic failure, CHF, or other low-output states to avoid hypocalcemia. Trauma patients that have sustained blood loss are at risk of hypocalcemia and those that require blood transfusions are at even higher risk of profound hypocalcemia.[26]

Hypocalcemia in acute pancreatitis is caused primarily by precipitation of calcium soaps in the abdominal cavity, but glucagon-stimulated calcitonin release and decreased parathyroid hormone secretion may play a role. Toxic exposures to hydrofluoric acid and ethylene glycol can cause profound hypocalcemia secondary to their abilities to complex and chelate with calcium. Patients being treated for malignant neoplasms are at risk for development of tumor lysis syndrome and multiple secondary electrolyte abnormalities. Hypocalcemia has been attributed to the precipitation of calcium phosphate salts. Finally, one should expect to encounter hypocalcemia in malnourished patients and chronic alcoholics who present to the ED, especially alcoholics with hyperventilation due to alcohol withdrawal.

Diagnostic Testing

Most cases of hypocalcemia are discovered by clinical suspicion followed by appropriate laboratory testing. A serum calcium level less than 8.5 mg/dL or an ionized calcium level less than 2.0 mEq/L is considered diagnostic. Total serum calcium is approximately 50% free

(ionized) and 50% bound, primarily to albumin; thus the serum level should be "corrected" when hypoalbuminemia exists. The ionized calcium level, which is not affected by the albumin level, is more accurate. It is best to perform the whole blood ionized calcium determination rapidly to avoid changes in chelation and pH. In select cases, a parathyroid hormone level may be sent to assist the admitting or consulting physician. Electrocardiography and cardiac monitoring are recommended in suspected hypocalcemia patients to evaluate the QT interval and to provide continuous monitoring for potential dysrhythmias. The most common ECG finding in hypocalcemia is QT prolongation as a result of ST segment lengthening and can mimic acute myocardial infarct with J point elevation, absence of ST segment, and shortening of the QTc interval.[27,28]

Management

Most asymptomatic patients and those with mild symptoms can be treated with oral calcium supplementation, such as calcium carbonate. IV calcium is administered, either as calcium chloride or calcium gluconate, to patients with moderate to severe symptoms; 100 to 300 mg of elemental calcium given over 5 to 30 minutes will raise the ionized calcium level 0.5 to 1.5 mEq. Calcium chloride contains 272 mg of elemental calcium but can be caustic to veins, so it should be given via central venous access unless patients are critically ill without central access. Calcium gluconate contains 92 mg of elemental calcium. Although this is one-third the amount contained in calcium chloride, it is safer to administer and can be given peripherally. Most patients requiring IV calcium should be admitted to the hospital for monitoring and treatment of nausea, vomiting, hypertension, and bradycardia. Patients taking digoxin have increased cardiac sensitivity to fluctuations in serum calcium, so IV calcium administration should be accompanied by continuous electrocardiographic monitoring. Hypocalcemia is an independent predictor of all-cause mortality in heart failure and chronic kidney disease patients and these patients should be monitored very carefully.[29]

Disposition

Hypocalcemic patients need to be admitted to a monitored bed if ongoing calcium repletion is necessary due to the risk of bradycardia and hypertension. Other patients may be discharged home with internal medicine follow-up and the consideration of outpatient evaluation by an endocrinologist.

HYPERMAGNESEMIA

Foundations

Hypermagnesemia is a relatively rare electrolyte abnormality defined as a serum magnesium concentration above 2.2 mg/dL. Hypermagnesemia is usually iatrogenic and seen in patients who cannot optimally regulate magnesium excretion (e.g., renal insufficiency), especially as their magnesium load increases.

In patients with normal renal function, large amounts of magnesium can be excreted daily in the stool and urine. However, in patients with impaired renal function, hypermagnesemia can be seen even with therapeutic doses of magnesium-containing products. An adult dose of 10 ounces of laxative syrup results in consumption of approximately 2.0 g of elemental magnesium per single dose. A healthy adult can excrete more than 6.0 g of magnesium daily, but renally impaired patients may not be able to tolerate small doses of laxative syrup. In patients with constipation, retention of magnesium-based laxatives can serve as a reservoir for continuous magnesium absorption.[30] Thus, a patient with renal insufficiency should be cautious and minimize the use of magnesium citrate for treatment of constipation.

TABLE 114.5 Clinical Effects of Hypermagnesemia

Effect	Level (Mg/Dl)
Decreased deep tendon reflexes	4 to 5
Hypotension	5 to 7
Respiratory insufficiency	10
Heart block	10 to 15
Cardiac arrest	10 to 24

Decreased gastrointestinal elimination and increased gastrointestinal absorption of magnesium due to intestinal hypomotility can also result in toxicity. Hypermagnesemia can be seen with bowel obstruction, colitis, gastric dilation, and use of medications that decrease motility, including narcotics and anticholinergics. Other less common causes of hypermagnesemia include adrenal insufficiency, hyperparathyroidism, hypothyroidism, lithium therapy, rhabdomyolysis, and tumor lysis syndrome.

Clinical Features

Clinical manifestations of hypermagnesemia are concentration dependent, and typically symptoms begin to develop around magnesium levels of 4 mg/dL (Table 114.5). Hypermagnesemia is easily overlooked because of its nonspecific symptoms. Patients with mild hypermagnesemia (less than 7 mg/ dL) may present with headache flushing, nausea, vomiting, and weakness. As the magnesium level rises (7 mg/dL to 12 mg/dL), the patient may also be confused, constipated, and found to have diminished deep tendon reflexes. When serum magnesium levels rise above 7 mg/dL, patients can have signs and symptoms of hypotension, respiratory insufficiency, and heart block. Severe hypermagnesemia (greater than 12 mg/dL) presents as progressive loss of neuromuscular, respiratory, and cardiovascular functions and can lead to coma and cardiorespiratory arrest. Magnesium acts as a calcium channel blocker and also blocks potassium channels needed for repolarization. As magnesium levels rise, hypotension and electrocardiographic changes, including QRS widening and QT and PR prolongation, begin to occur. In addition, hypermagnesemia can interfere with blood clotting by interfering with clotting time and platelet adhesiveness. Finally, hypermagnesemia causes suppression of parathyroid hormone secretion and can be associated with hypocalcemia. If a patient taking oral magnesium, especially an elderly patient, presents with clinical symptoms including altered mental status, hypotension, bradycardia, and respiratory failure, hypermagnesemia must be included in the differential.

Differential Diagnosis

Hypermagnesemia is most commonly seen in patients receiving parenteral treatment for pre-eclampsia or eclampsia, cardiac arrhythmias, or asthma exacerbations. In addition, hypermagnesemia is also seen in people utilizing laxatives and antacids, patients receiving cathartics for drug overdoses, and patients undergoing bowel preparations prior to colonoscopies. Even though most patients at risk for hypermagnesemia have underlying renal impairment, hypermagnesemia has been reported in patients with normal renal function, especially in elders.[31] Box 114.10 lists the most common causes of increased serum magnesium levels.

Diagnostic Testing

Measured plasma magnesium levels often do not reflect total magnesium content, making it difficult to correlate symptoms to specific

BOX 114.10 Five Most Common Causes of Hypermagnesemia

- Iatrogenic: IV administration, dialysate
- Oral administration: Laxatives, antacids, vitamins, cathartics, dialysate, parental
- Impaired elimination—hypomotility: Bowel obstruction, chronic constipation
- Impaired elimination—medications: Anticholinergics, narcotics, lithium therapy
- Miscellaneous: Hypothyroidism, tumor lysis syndrome, adrenal insufficiency, milk-alkali syndrome

BOX 114.11 Most Common Causes of Hypomagnesemia

Dietary
Gastrointestinal
Renal
Endocrine or metabolic
Drug induced

magnesium levels consistently. Although there is some question of the role of measuring ionized magnesium in patients with hypomagnesemia, only total body magnesium needs to be followed in hypermagnesemic patients.

Management

Management of hypermagnesemia is dictated by the neuromuscular, cardiovascular, and CNS changes that occur. Most stable or asymptomatic hypermagnesemic patients can be treated with cessation of their magnesium therapy. As symptoms become more pronounced, IV isotonic fluids are administered to dilute the extracellular magnesium. Diuretics (furosemide 1 mg/kg) can be used to promote excretion of magnesium in patients with normal kidney function and reverse mild symptoms.

In patients with higher levels of serum magnesium or more severe symptoms, renal consultation should be initiated immediately to arrange for dialysis with magnesium-free dialysate. A dialysis session of 3 to 4 hours can reduce the magnesium level up to 50%. IV calcium therapy to reverse magnesium toxicity should be reserved for patients with life-threatening symptoms while dialysis is being arranged. Calcium directly antagonizes the neuromuscular and cardiovascular effects of magnesium and is recommended in hypotensive patients with respiratory depression and cardiac instability. In treating life-threatening hypermagnesemia, initially administer 1 g calcium chloride or 2 g calcium gluconate and repeat as needed. When needed, a continuous infusion at 2 to 4 mg/kg/hr can be administered while dialysis is being arranged. Most stable or asymptomatic hypermagnesemia patients can be treated with cessation of their magnesium therapy and discharged home with close outpatient follow-up. However, patients with higher levels of serum magnesium or more severe symptoms, should be admitted to a telemetry bed with ICU level of care discussed with the inpatient team. Unfortunately, severe hypermagnesemia often ends in death despite robust attempts to lower serum magnesium levels.

Disposition

Most stable or asymptomatic hypermagnesemia patients can be treated with cessation of their magnesium therapy and discharged home with close outpatient follow-up. However, patients with higher levels of serum magnesium or severe symptoms should be admitted to a telemetry bed with ICU level of care discussed with the inpatient team. Unfortunately, severe hypermagnesemia often ends in death despite robust attempts to lower serum magnesium levels.

HYPOMAGNESEMIA

Foundations

Hypomagnesemia is a common electrolyte abnormality that often goes undetected. Normal serum magnesium levels range from 1.5 to 3.0 mEq/L. Symptoms of hypomagnesemia typically begin to be manifested at serum levels below 1.2 mEq/L, although symptoms are often not well correlated with the patient's serum level. This is because most of the body's magnesium is intracellular, and thus a single blood sample with a low serum magnesium level may not accurately reflect total body magnesium or the extent of true hypomagnesemia. The incidence of hypomagnesemia is estimated to be 2% in the general population. In hospitalized patients, the risk is highest for patient requiring ICU level care.[32]

Magnesium exists in three states: (1) ionized magnesium, (2) protein bound, and (3) complexed to serum anions. Even though studies show the importance of measuring ionized calcium, most research shows that ionized magnesium can be inferred from total magnesium. Currently, the clinical role of measurement of ionized magnesium is unclear, and measurement of ionized magnesium is not standard practice in the ED; there may be a role for measurement of ionized magnesium in the intensive care setting.[33,34]

Clinical Features

Determination of the clinical consequences of isolated hypomagnesemia is often confounded by coexisting hypokalemia, hypocalcemia, or hyponatremia. However, many signs and symptoms are reported to correlate with hypomagnesemia, including muscle cramping, diffuse weakness, palpitations, vertigo, ataxia, depression, and seizures. Women with an adequate intake of magnesium are less likely to be affected by preeclampsia. The clinical manifestations most likely seen in the ED involve the neuromuscular and cardiovascular systems. Patients may present with hyperactive deep tendon reflexes, muscle cramps, Trousseau and Chvostek signs, and dysarthria and dysphagia from esophageal dysmotility. Cardiac conduction abnormalities secondary to magnesium depletion, and often coexisting hypokalemia, can result in PR and QT interval prolongation. Dysrhythmias including atrial fibrillation, multifocal atrial tachycardia, premature ventricular complexes, ventricular tachycardia, torsades de pointes, and ventricular fibrillation are the most common cardiovascular manifestations of hypomagnesemia.

Differential Diagnosis

There are many causes of hypomagnesemia (Box 114.11). The following sections describe the five most common ED presentations of hypomagnesemia.

Patients Maintained on Diuretics

Patients using either loop or thiazide diuretics are at increased risk for hypomagnesemia. Both types of diuretics can inhibit magnesium reabsorption. Conversely, potassium-sparing diuretics are also magnesium sparing, because they enhance magnesium reabsorption and decrease magnesium excretion. The degree of hypomagnesemia induced by the loop and thiazide diuretics is generally mild, in part because the associated volume contraction will tend to increase proximal sodium, water, and magnesium reabsorption.

Malnourished and Alcoholic Patients

Healthy patients consume enough magnesium in green vegetables, legumes, fruits, shellfish, fresh meat, and cocoa on a regular basis to maintain normal total body magnesium stores. However, hypomagnesemia is common in patients with chronic protein-calorie malnutrition because of an associated lack of essential minerals and vitamins including magnesium. This is especially true in chronic alcoholics who may not eat foods rich in magnesium. Magnesium losses are further increased in chronic alcoholics because of alcohol's diuretic effects may combine with episodes of pancreatitis and diarrhea.

Hypomagnesemia may also be seen in patients with malabsorption disorders (celiac sprue and short bowel syndrome), patients with increased magnesium excretion (chronic diarrhea or inflammatory bowel conditions), and patients with severe body dysmorphic disorders.

Patients With Hypokalemia

Both potassium and magnesium are critical to help stabilize the membrane potential, to decrease cell excitability, and for function of the Na^+, K^+-ATPase pump. Approximately 50% of patients with hypokalemia also have concomitant magnesium deficiency. Increasing degrees of hypokalemia are correlated with an increasing likelihood of a magnesium deficit. Hypokalemic patients who are refractory to potassium replacement are likely to also be hypomagnesemic.

Patients With Acute Coronary Artery Disease and Ventricular Arrhythmias

There appears to be a relationship between low serum magnesium levels and the subsequent development of coronary heart disease likely because low magnesium intake is associated with higher incidence of diabetes, hypertension, and metabolic syndrome.[35] Patients who have had a myocardial infarction are more likely than controls to be hypomagnesemic.[36] Patients with acute myocardial infarction who have mild hypomagnesemia appear to have a twofold to threefold increase in the frequency of ventricular arrhythmias in the first 24 hours compared with those with normal magnesium levels

There is controversy about whether magnesium should be administered empirically after acute myocardial infarction. At present, magnesium supplementation is recommended only for those acute coronary syndrome patients who have evidence of hypokalemia, prolonged QT, or known hypomagnesemia. However, Yuksel et al. found that the serum magnesium level is an independent predictor for electrocardiographic no-reflow in patients with STEMI who underwent PCI. In addition, it was demonstrated that initial Mg level is an independent predictor for long-term mortality in patients with STEMI who underwent PCI.[37]

Dysrhythmia is the most common cardiovascular manifestation of hypomagnesemia. Magnesium affects the duration of phase 2 of the action potential, and hypomagnesemia can prolong the QT interval. Magnesium also has effects on phase 4, the resting membrane potential, where it keeps the cell more negative by stimulating the sodium-potassium pump. The exact mechanism underlying a possible association between hypomagnesemia and arrhythmias is unknown. Arrhythmias are likely to be due to concurrent hypokalemia, hypomagnesemia, or both, resulting in a prolonged QT interval and increases in spontaneous depolarization.

Patients Receiving Specific Medications

In addition to diuretics, many nephrotoxic drugs, including aminoglycosides, amphotericin B, cisplatin, digoxin, and pentamidine, can produce magnesium wasting. Solid organ transplant patients maintained on calcineurin inhibitors including tacrolimus and cyclosporine are at risk for hypomagnesemia.[38] Long-term use of proton pump inhibitors, especially when combined with diuretics, may be associated with decreased intestinal absorption of magnesium.[39,40]

Diagnostic Testing

Clinical manifestations of hypomagnesemia begin at serum levels below 1.2 mEq/L, but symptoms do not always correlate with the total serum magnesium level. Because most of the total body magnesium is intracellular, the magnesium level alone does not guide therapy. The possibility of hypomagnesemia is considered in patients with depression, malnourishment, significant or refractory hypokalemia, and ventricular arrhythmias. Electrocardiographic findings in hypomagnesemia are nonspecific and may be caused by both the hypomagnesemia and concomitant hypokalemia. Hypomagnesemia should be suspected whenever electrocardiographic findings of hypokalemia are noted, including PR and QT interval prolongation, ST segment depression, flattening and widening of the T waves, loss of voltage, and U waves.

Management

The route of magnesium repletion varies with the severity of the clinical manifestations. Patients at risk of magnesium deficiency or with symptoms consistent with hypomagnesemia should be considered for treatment even with serum magnesium levels within normal range.[41] Parenteral magnesium is recommended for life-threatening conditions. In patients with normal renal function, 1 to 2 g of IV magnesium sulfate is an appropriate loading dose. A stable patient with hypomagnesemia can be treated with a loading dose of 1 to 2 g IV of magnesium sulfate during 10 to 60 minutes, followed by a maintenance dose of 0.5 to 1 g/hr until symptoms have resolved. The administration of 1 g of IV magnesium increases the serum magnesium concentration by 0.15 mEq/L within 18 to 30 hours.[42] Patients in cardiac arrest should receive a bolus of 1 to 2 g magnesium sulfate by IV push.

Magnesium administration is strongly encouraged for patients receiving IV potassium repletion. A dose of 0.5 g/hr is safe in patients who are well hydrated and have normal renal function. There are potential adverse effects to rapid magnesium replacement at more than 1 to 2 g/hr, including decreased deep tendon reflexes, respiratory depression, and heart block. Magnesium gluconate oral supplementation can be given if the patient is only mildly hypomagnesemic and asymptomatic. Oral absorption is variable, but most commonly magnesium oxide 400 mg twice daily can be administered to patients with adequate renal function.

Disposition

Patients with cardiac arrhythmias from hypomagnesemia should be admitted to a telemetry bed or critical unit in collaboration with cardiology. Other symptomatic patients may also need to be admitted to a monitored bed for parenteral magnesium. Asymptomatic patients can often be managed with supplements and strict follow-up instructions. When preparing any patient with hypomagnesemia for discharge, physicians can encourage lifestyle changes, including adequate magnesium intake that may benefit blood pressure control, promote weight loss, and improve chronic disease risk.

HYPERPHOSPHATEMIA

Foundations

Hyperphosphatemia is defined as a serum level above 2.5 mg/dL, but it is usually clinically significant only when levels are greater than 5 mg/dL. Although rare in the general population, hyperphosphatemia is extremely common in patients with renal insufficiency or renal failure. Almost all patients with renal failure experience hyperphosphatemia at

some time during the course of their disease. Phosphate is a potential biomarker to predict mortality and disease severity in patients receiving dialysis.[43] Even in patients without renal failure, patients in the ICU with altered phosphate levels have increased morbidity and mortality.[44]

Clinical Features

Patients with hyperphosphatemia may present with multiple complaints related to electrolyte abnormalities, particularly hypocalcemia. Hyperphosphatemia causes hypocalcemia by precipitating calcium out of the blood and decreasing vitamin D production. It is this secondary hypocalcemia that can cause muscle cramping, tetany, and seizures. Chronic hyperphosphatemia can also lead to metastatic calcifications in joints, tissues, and arteries.

Differential Diagnosis

Hyperphosphatemia can occur via four major pathways: (1) decreased phosphate excretion, (2) excessive phosphate intake, (3) increased renal tubular reabsorption, and (4) shift of phosphate from intracellular to extracellular space. In addition, physicians should be aware of spurious elevations in phosphate (Box 114.12).[45]

Decreased excretion of phosphate combined with excessive intake is the most common mechanism for the development of hyperphosphatemia. Excessive phosphate intake alone is an uncommon cause of hyperphosphatemia in patients with normal renal function. When patients have glomerular filtration rates below 30 mL/min, the kidneys do not excrete the full amount of ingested phosphate to maintain homeostasis.[46] Exogenous phosphate, including IV or oral phosphate administration and phosphate enemas and laxatives can cause a large burden on the kidneys if they do not have normal baseline function. In 2014, the U.S. Food and Drug Administration (FDA) made a drug safety announcement after identifying over 50 cases of adverse events warning against utilizing a single dose of sodium phosphate larger than recommended or taking more than one dose in a day, especially in patients also taking medications that act on renal function.[47]

BOX 114.12 Five Most Common Causes of Hyperphosphatemia

Decreased Phosphate Excretion
Acute and chronic renal failure

Increased Renal Tubular Reabsorption
Hypoparathyroidism
Thyrotoxicosis
Excess vitamin D administration

Excessive Phosphate Intake
Phosphate enemas or laxatives
IV or oral phosphate administration

Shift of Phosphate From Intracellular to Extracellular Space
DKA
Tumor lysis
Rhabdomyolysis

Spurious Hyperphosphatemia
Paraproteinemia
Hyperbilirubinemia
Hemolysis
Hyperlipidemia

DKA, Diabetic ketoacidosis; *IV,* intravenous.

Hypoparathyroidism, vitamin D intoxication, and thyrotoxicosis increase renal phosphate reabsorption and may cause elevated phosphate levels. Hyperphosphatemia may also occur when there is a large shift of phosphate from the intracellular to the extracellular space and the kidneys' ability to excrete phosphate is overwhelmed. This cause of hyperphosphatemia is seen in rhabdomyolysis, tumor lysis syndrome, and DKA. Hyperphosphatemia can be a spurious finding in cases of hyperproteinemia, such as multiple myeloma, hyperlipidemia, hemolysis, or hyperbilirubinemia.

Diagnostic Testing

The diagnostic evaluation of a patient with suspected hyperphosphatemia begins with obtaining electrolyte and renal function tests with hyperphosphatemia defined as a serum level above 2.5 mg/dL. A low serum calcium level along with a high phosphate level is seen in patients with hypoparathyroidism, pseudohypoparathyroidism, and renal failure. The addition of the BUN and creatinine assist with narrowing down the differential to renal failure. Patients with hyperphosphatemia from renal failure are more likely to have elevated PTH levels when compared to those with hyperphosphatemia from hypoparathyroidism where low levels of PTH are expected.

Imaging studies are not typically indicated in the initial evaluation of hyperphosphatemia in the ED setting. However, some patients may need renal imaging studies and long-bone studies when admitted to differentiate the etiology of the hyperphosphatemia further.

Management

One of the most critical steps in management of hyperphosphatemia is the treatment of underlying causes while reducing the phosphate load in the body either by promoting urinary excretion or hemodialysis. Dietary restriction alone may suffice for control of hyperphosphatemia in persons with mild renal insufficiency, but it is inadequate for control in those with overt renal failure. Because most patients presenting with severe hyperphosphatemia also have hypocalcemia, treatment focuses on the correction of both.

In patients with normal renal function, phosphate excretion can be increased by saline infusion coupled with loop diuretics. Hyperphosphatemia usually resolves in 6 to 12 hours in patients with normal renal function. In patients with hyperphosphatemia with renal failure, hemodialysis or peritoneal dialysis should be considered early in the management. Currently, phosphate control is initiated only when hyperphosphatemia occurs, but it may be beneficial to intervene earlier in patients with chronic kidney disease. The optimal method for controlling serum phosphate in patients undergoing dialysis is unknown and may involve combinations of dietary modification, phosphate binders, and enhancement of phosphate clearance through longer dialysis sessions.[48]

Disposition

Often, hyperphosphatemic patients need to be admitted to reverse the underlying etiology of their electrolyte abnormality. All patients that require hemodialysis need to be admitted to a monitored bed on a phosphate-restricted diet. Patients should also be admitted to a monitored be if they require ongoing volume resuscitation with diuresis.

HYPOPHOSPHATEMIA

Foundations

Hypophosphatemia is defined as mild (2 to 2.5 mg/dL), moderate (1 to 2 mg/dL), or severe (<1 mg/dL). Mild to moderately severe hypophosphatemia is usually asymptomatic and, like hypomagnesemia, often goes unrecognized. Although most patients remain asymptomatic,

BOX 114.13 Clinical Manifestations of Hypophosphatemia

Central Nervous System
Irritability
Confusion
Paresthesias
Depression
Dysarthria
Seizure
Coma

Cardiovascular
Cardiomyopathy
Depressed myocardial contractility
Arrhythmias

Respiratory
Acute respiratory failure
Depressed myocardial contractility

Gastrointestinal
Ileus, dysphagia

Hematologic
Depressed levels of 2,3-diphosphoglycerate and adenosine triphosphate
Leukocyte dysfunction
Hemolysis
Platelet dysfunction

Renal
Acute tubular necrosis
Metabolic acidosis
Hypercalcemia

Endocrine
Insulin resistance
Hyperparathyroidism

BOX 114.14 Five Most Common Causes of Hypophosphatemia in the Emergency Department

Decreased Intake or Increased Absorptive States
Chronic alcoholism
Home parenteral nutrition
AIDS
Chemotherapy
Vomiting
Malabsorption syndromes
Secretory diarrhea
Vitamin D deficiency

Hyperventilatory States
Sepsis
Alcohol withdrawal
Salicylate poisoning
Neuroleptic malignant syndrome
Panic attacks
DKA
Hepatic coma

Hormonal and Endocrine Effects
Insulin loading
Glucose loading
Exogenous epinephrine
Hyperparathyroidism

Medications
Diuretics
Chronic antacid ingestion
Steroids
Phosphate binders
Xanthine derivatives
Beta2-agonists
Iron[49]

Disease States
Trauma
Severe thermal burns
Acute renal failure
Gout
Cannabinoid hyperemesis syndrome[50]

AIDS, Acquired immunodeficiency syndrome; *DKA,* diabetic ketoacidosis.

severe hypophosphatemia may result in potentially life-threatening complications. Major clinical sequelae usually occur only in severe hypophosphatemia. Symptoms of hypophosphatemia typically begin to be manifested at serum levels below 1.0 mg/dL.

Clinical Features

Mild to moderate hypophosphatemia is usually asymptomatic, but major clinical manifestations can occur with severe hypophosphatemia. Because phosphate is an essential component to adenosine triphosphate, hypophosphatemia can affect a variety of organ systems and a wide variety of symptoms (Box 114.13). Patients with hypophosphatemia may present with nonspecific complaints including joint pain, myalgias, irritability, and depression. Severe hypophosphatemia can be manifested as seizures, arrhythmias, cardiomyopathy, insulin resistance, acute tubular necrosis, rhabdomyolysis, and acute respiratory failure.

Differential Diagnosis

Hypophosphatemia is must commonly induced by one of the three causes: (1) Increased phosphate excretion, (2) inadequate phosphate intake, or (3) a shift in phosphate stores. Acute hypophosphatemia is most commonly due to a rapid intracellular shift. Hyperventilation, glucose, insulin, volume expansion, and resolving acidosis can lead to hypophosphatemia by rapid intracellular shift. The many causes of hypophosphatemia include decreased phosphate intake or increased absorptive states, hyperventilatory states, hormonal and endocrine effects, medications, and disease states (Box 114.14). The ED patients most likely to have hypophosphatemia are those who are malnourished with alcohol withdrawal, acute hyperventilation, or sepsis and patients with DKA or alcohol ketoacidosis in whom reintroduction of insulin and glucose causes phosphate uptake into cells.

Diagnostic Testing

The diagnostic evaluation of a patient with suspected hypophosphatemia begins with obtaining electrolyte and renal function tests with hypophosphatemia defined as a serum level below 2.5 mg/dL. Often, the etiology of hypophosphatemia can be determined by the history. However, if the etiology is unclear, the patient may need to have a renal

phosphate excretion measured or calculated upon admission. Imaging in hyperphosphatemia is rarely indicated unless there are confounding cardiac, neurologic, or respiratory factors.

Management

We recommend patients with phosphate levels below 2.0 mg/dL be given phosphate repletion; patients with levels below 1.0 mg/dL necessitate treatment. Because hypophosphatemia is often coupled with hypokalemia, patients with hypophosphatemia often require potassium repletion as well. Oral phosphorous, 250 to 500 mg twice daily, can be given to stable or asymptomatic patients. IV preparations are available as sodium phosphate (Na_2PO_4 and $NaPO_4$) or potassium phosphate (K_2PO_4 and KPO_4), and rate of infusion and choice of initial dosage should be based on severity of hypophosphatemia and presence of symptoms.

If the serum phosphorus concentration is less than 1.5 mg/dL (0.48 mmol/L), 1.3 mmol/kg of elemental phosphorous (up to a maximum of 100 mmol) can be given in three or four divided doses in a 24-hour period. For routine replacement, give 0.5 mL/hr K_2PO_4; this may be increased to 1 mL/hr in severely symptomatic patients. Each milliliter of K_2PO_4 contains 3 mmol of phosphorus and 4.4 mEq of potassium.

Typical replacement therapy provides approximately 1 g of phosphorus per day. Patients should be monitored for the development of hypocalcemia, hyperkalemia, and hyperphosphatemia while IV phosphate is administered, especially in patients with renal insufficiency. Patients with DKA are initially hypophosphatemic. However, no studies have shown significant benefit to routine phosphate therapy in DKA. Risks of routine treatment with phosphate include hyperphosphatemia, renal failure, hypocalcemia, and hypomagnesemia. In patients with severe malnutrition or significant hypophosphatemia, replacement can be considered, but more than 60 mmol/day should not be administered without reason.

Disposition

Mild asymptomatic hypophosphatemia can be treated with oral phosphate while patients with severe or symptomatic hypophosphatemia should be treated with IV phosphate therapy and admitted for monitoring and subsequent serum electrolyte testing. In general, all symptomatic patients need treatment with phosphate. The outlook for patients depends on the primary condition causing the hypophosphatemia.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 114: QUESTIONS AND ANSWERS

1. A patient with end-stage renal disease misses dialysis and presents feeling weak. His 12-lead electrocardiogram (ECG) shows peaked T waves, absent P waves, and a QRS duration of 240 milliseconds. Which of the following is the next step in emergency department (ED) management?
   - **a.** Calcium
   - **b.** Furosemide
   - **c.** Hemodialysis
   - **d.** Insulin with glucose
   - **e.** Nebulized albuterol

Answer: A. Calcium is the first medication that should be administered in this patient with a widened QRS. The treatment of hyperkalemia is based on the clinical scenario combined with the 12-lead ECG and the laboratory potassium value. Evaluating the ECG of patients at risk for this electrolyte disturbance is critical because results of the serum potassium level can be delayed. Hyperkalemia can be rapidly progressive, and lifesaving interventions should be instituted at the earliest suspicion of toxicity. Intravenous (IV) calcium is used to stabilize the cardiac membrane by restoring the electrical gradient. Calcium increases the depolarization threshold and the calcium gradient across the cardiac membrane, quieting myocyte excitability and increasing cardiac conduction speed, thus narrowing the QRS.

2. For which of the following patients would it be most appropriate to supplement potassium to keep serum levels above 4 mEq/L?
   - **a.** A 23-year-old woman with palpitations and no past medical history
   - **b.** A 42-year-old woman with poorly controlled diabetes mellitus
   - **c.** A 51-year-old man with hypertension, recently started on lisinopril
   - **d.** A 55-year-old man with history of coronary artery disease, chest pain, and premature ventricular complexes
   - **e.** A 68-year-old-man with chronic bronchitis and fever

Answer: D. The 55-year-old patient is at highest risk for life-threatening complications from hypokalemia secondary to his underlying comorbidities. In patients with cardiac ischemia or heart failure, even mild to moderate hypokalemia increases the likelihood of cardiac arrhythmias secondary to potassium's effect on the action potential.

3. A malnourished man with a long history of chronic obstructive pulmonary disease is brought to the emergency department (ED) in respiratory distress. He receives bronchodilators, intravenous (IV) dextrose, and thiamine. He improves significantly, but then begins to complain of severe muscle aches, diffuse weakness, and the feeling that he cannot breathe deeply. Supplementation with which of the following might have prevented his new symptoms?
   - **a.** Calcium gluconate
   - **b.** Diazepam
   - **c.** Normal saline
   - **d.** Potassium phosphate
   - **e.** Sodium bicarbonate

Answer: D. Patients with hypophosphatemia may present with nonspecific complaints, including joint pain, myalgias, irritability, and depression. Severe hypophosphatemia can be manifested as seizures, arrhythmias, cardiomyopathy, insulin resistance, acute tubular necrosis, rhabdomyolysis, and acute respiratory failure. Because hypophosphatemia often presents with hypokalemia, phosphate repletion should be considered in conjunction with potassium administration.

4. A 58-year-old man with history of small cell lung cancer is brought in for weakness and pleuritic chest pain. He is alert, with normal vital signs, nonfocal neurologic examination, and serum sodium concentration of 129 mEq/L. What is the most appropriate management of the hyponatremia?
   - **a.** Free water restriction
   - **b.** Hypertonic saline bolus
   - **c.** Intravenous (IV) furosemide
   - **d.** Normal saline bolus
   - **e.** Sodium chloride tablets

Answer: A. The patient with small cell lung cancer is demonstrating signs and symptoms of hyponatremia. Lung cancers, especially small cell cancer, can lead to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The mainstay for treatment of euvolemic hyponatremia is free water restriction. Because the hypoosmolality in SIADH results from a relative abundance of water in the intracellular and extracellular volumes and is maintained by a reduced ability to excrete water, the restriction of free oral water intake is usually the most effective therapy. For relatively asymptomatic patients with sodium values of 115 to 135 mEq/L, a trial of free water restriction to less than 0.8 mL/day to 1.25 L/day should be attempted.

5. A runner is brought in after collapsing during a race. He has been careful to drink at each mile marker. He has altered mental status and is combative even after 10 mg of diazepam. What is the most appropriate treatment after his witnessed tonic-clonic seizure?
   - **a.** 5% Dextrose solution
   - **b.** Fosphenytoin
   - **c.** 3% Hypertonic saline
   - **d.** Lorazepam
   - **e.** Pentobarbital

Answer: C. This runner is demonstrating symptoms concerning for exercise-associated hyponatremia, the occurrence of hyponatremia during or up to 24 hours after prolonged physical activity. Hypertonic saline is indicated in severe cases of hyponatremia when a patient has alterations in mental status, focal neurologic findings, or seizures.

Diabetes Mellitus and Disorders of Glucose Homeostasis

Gerald E. Maloney Jr. and Jonathan M. Glauser

KEY CONCEPTS

- The diagnosis of diabetes can be determined by one or more of four methods—random plasma glucose level above 200 mg/dL, fasting plasma glucose concentration above 126 mg/dL, 2-hour, 75-g post-load oral glucose tolerance test (OGTT) > 200 mg/dL, or HbA_{1c} value above 6.5%.
- Diabetic ketoacidosis (DKA) is diagnosed by the presence of hyperglycemia, anion gap metabolic acidosis, and elevated ketoacid levels.
- The essential treatment of DKA includes administration of insulin, correction of dehydration, correction of potassium level, correction of acidosis, and treatment of the underlying cause.
- The use of sodium bicarbonate to correct acidosis in DKA has not demonstrated any benefit and may be associated with worse outcomes.
- A hyperglycemic hyperosmolar state is usually seen in older adults with multiple comorbid conditions and is distinguished from DKA by the absence of ketoacidosis. In addition to fluid resuscitation and correction of hyperglycemia, treatment should address the underlying cause of the state, which includes infection, myocardial infarction, and cerebrovascular accident.
- Diabetic peripheral neuropathy is common and has multiple treatment options, including gabapentin, pregabalin, and duloxetine.
- Diabetic foot ulcers and other diabetic soft-tissue infections (e.g., gas gangrene, Fournier's gangrene) are frequently polymicrobial and require broad-spectrum antibiotic therapy covering gram-positives, gram-negatives, and anaerobes.
- Hypoglycemia may be associated with significant morbidity and mortality. When the diagnosis is suggested and, if possible, confirmed by laboratory evaluation, therapy should be initiated immediately.
- Hypoglycemia caused by sulfonylurea oral hypoglycemic agents may be prolonged. Patients should be observed for an extended period or hospitalized.

DIABETES MELLITUS

Diabetes Mellitus Foundations

Background and Importance

Diabetes mellitus is the most common endocrine disease. It comprises a heterogeneous group of hyperglycemic disorders characterized by a high serum glucose concentration and disturbances of carbohydrate and lipid metabolism. Acute complications include hypoglycemia and hyperglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). Long-term complications affect multiple organ systems through involvement of the microvasculature and include retinopathy, nephropathy, neuropathy, and angiopathy. As a result, complications such as coronary and cerebral vascular disease, blindness, chronic kidney disease, complicated infections, and amputations occur with a much higher incidence in patients with diabetes than in patients without. Diabetes is ranked as one of the five major chronic diseases that account for a significant proportion of our health care spending. Several trials have shown to varying degrees that tight glucose control can reduce the risk of death and severe microvascular complications. Patients with diabetes mellitus incur emergency department (ED) costs three times higher than those of nondiabetic patients and are admitted to the hospital four times more often.[1,2]

Epidemiology

The most recent data (2015) estimate that some 30 million people, or 9.4% of all Americans and 13% of adults older than 20 years have diabetes.[1] The incidence of diabetes in those younger than 20 approaches as high as 45/100,000 by the teenage years. The type of diabetes depends on age; most of those younger than 10 years have type 1, whereas type 2 predominates among the 10- to 19-year-olds.[2] Additionally, 33% of the total US population is thought to have prediabetes.

Type 1 is less common than type 2. The peak age at onset of type 1 diabetes is 10 to 14 years, and approximately 1 of every 600 schoolchildren has this disease. In the United States, the prevalence of type 1 is approximately 0.26% by the age of 20 years, and the lifetime prevalence approaches 0.4%. The annual incidence among persons from birth to 16 years of age in the United States is 12 to 14 per 1 million population. The incidence is age-dependent, increasing from near-absence during infancy to a peak occurrence at puberty and another small peak at midlife.[1,2]

The morbidity of diabetes is related primarily to its vascular complications. A mortality rate of 36.8% has been attributed to cardiovascular causes, 17.5% to cerebrovascular causes, 15.5% to diabetic comas, and 12.5% to renal failure.

Anatomy, Physiology, and Pathophysiology

Normal Physiology. Because plasma glucose is the predominant metabolic fuel used by the central nervous system (CNS), maintenance of the plasma glucose concentration is critical to survival. The CNS cannot synthesize glucose, store more than a few minutes' supply, or concentrate glucose from the circulation. Brief hypoglycemia can cause profound CNS dysfunction, and prolonged severe hypoglycemia may cause cellular death. Glucose regulatory systems have evolved to prevent and correct hypoglycemia.

The plasma glucose concentration is normally maintained within a relatively narrow range, between 60 and 150 mg/dL, despite wide variations in glucose levels after meals and exercise. Glucose is derived from three sources—intestinal absorption from the diet, the breakdown of glycogen (glycogenolysis), and the formation of glucose from precursors (gluconeogenesis), including lactate, pyruvate, amino acids, and glycerol. After glucose ingestion, the plasma glucose concentration increases as a result of glucose absorption. Endogenous glucose production is suppressed, and the plasma glucose level rapidly declines in response to insulin to a level below the baseline.

Insulin. Insulin receptors on the beta cells of the pancreas sense elevations in the blood glucose concentration and trigger insulin release. For incompletely understood reasons, glucose taken orally results in more insulin release than parenteral glucose. Certain amino acids induce insulin release and even cause hypoglycemia in some patients. Sulfonylurea oral hypoglycemic agents work, in part, by stimulating the release of insulin from the pancreas.

The number of receptors determines the sensitivity of the specific tissue to circulating insulin. The number and sensitivity of receptors are also the primary factors affecting the long-term efficacy of the sulfonylurea oral hypoglycemic agents. Receptor sites are increased in glucocorticoid deficiency and may be relatively decreased in obese patients.

Under normal circumstances, insulin is rapidly degraded through the liver and kidneys. The half-life of insulin is 3 to 10 minutes. Whereas insulin is the major anabolic hormone implicated in diabetes, glucagon is the major catabolic hormone in disorders of glucose homeostasis.

Although most tissues have the enzyme systems required to synthesize and hydrolyze glycogen, only the liver and kidneys have glucose-6-phosphatase, the enzyme necessary to release glucose into the circulation. The liver is essentially the sole source of endogenous glucose production. Renal gluconeogenesis and glucose release contribute substantially to the systemic glucose pool only during prolonged starvation.

Glucose Regulatory Mechanisms. Maintenance of the normal plasma glucose concentration requires precise matching of glucose use with endogenous glucose production and dietary glucose intake. The regulatory mechanisms that maintain systemic glucose balance involve hormonal, neurohumoral, and autoregulatory factors. Glucose regulatory hormones include insulin, glucagon, epinephrine, cortisol, and growth hormone. Insulin is the main glucose-lowering hormone. Insulin suppresses endogenous glucose production and stimulates glucose use. Insulin is secreted from the beta cells of the pancreatic islets into the hepatic portal circulation and has important actions on the liver and peripheral tissues. Insulin stimulates glucose uptake and storage, and it is used by other insulin-sensitive tissues, such as fat and muscle.

Counterregulatory hormones include glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. When glucose is not transported intracellularly because of a lack of food intake or lack of insulin, the body perceives a fasting state and releases glucagon, attempting to provide the glucose necessary for brain function. Glucagon is released in response to hypoglycemia as well as to stress, trauma, infection, exercise, and starvation. It increases hepatic glucose production within minutes, although transiently.

Epinephrine both stimulates hepatic glucose production and limits glucose use through direct and indirect actions mediated by α-adrenergic and β-adrenergic mechanisms. Epinephrine also acts directly to increase hepatic glycogenolysis and gluconeogenesis. It acts within minutes and produces a transient increase in glucose production but continues to support glucose production at approximately basal levels thereafter. Norepinephrine exerts hyperglycemic actions by mechanisms similar to those of epinephrine, except that norepinephrine is released from axon terminals of sympathetic postganglionic neurons.

Cortisol is released in response to stress, and it increases blood glucose by both increasing hepatic gluconeogenesis and inhibiting skeletal muscle uptake of glucose. These mechanisms contribute to the hyperglycemia seen during physiologic stress or illness.

Pathophysiology. Type 1 diabetes results from a chronic autoimmune process that usually exists in a preclinical state for years. The classic manifestations of type 1 diabetes—hyperglycemia and ketoacidosis—occur late in the disease, an overt sign of beta-cell destruction. The most striking feature of long-standing type 1 diabetes is the nearly total lack of insulin-secreting beta cells and insulin, with the preservation of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide–secreting cells.[3]

Although the exact cause of diabetes remains unclear, research has provided some clues. Studies of the pathogenesis of diabetes mellitus have demonstrated that the cause of the disordered glucose homeostasis varies from individual to individual. This cause may determine the presentation in each patient. Individual patients are currently not studied for the source of their disease, except on an experimental basis. The goals of ongoing research are to identify who is susceptible to the development of diabetes, prevent diabetic emergencies and sequelae, and prevent expression of the disease.

Types of Diabetes

The American Diabetes Association (ADA) defines four major types of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, and diabetes due to secondary disease processes or drugs.[1,4] Additionally, the diagnostic criteria of prediabetes was established for patients with glucose levels above the normal fasting range of 110 mg/dL but less than 126 mg/dL; this category has received much attention for the targeting of focused interventions to reduce progression to diabetes mellitus.[1] The 1997 National Diabetes Data Group discontinued the use of the terms *insulin-dependent diabetes mellitus* and *non-insulin-dependent diabetes mellitus* because they were confusing and clinically inaccurate. The most recent update to the standards of care for diabetes was published in January 2021.[1] The diagnostic criteria for the diagnosis of diabetes were changed in 2010 from the previous standards of elevated fasting glucose concentration and an abnormal result on the 2-hour oral glucose tolerance test (OGTT) to use of the hemoglobin A_{1c} (HbA_{1c}) value as the preferred confirmatory test.[4] A HbA_{1c} value above 6.5% is diagnostic of diabetes. However, the fasting plasma glucose concentration and 2-hour OGTT are still considered valid screening tests for diabetes, as is the presence of a random glucose measurement of more than 200 mg/dL in a non-fasting patient with symptoms of diabetes. Use of the fasting plasma glucose concentration may help identify patients at risk for diabetes when the glucose concentration is elevated but does not meet the threshold for the diagnosis of diabetes.

Type 1 Diabetes Mellitus. Type 1 diabetes is characterized by an abrupt failure of insulin production with a tendency to ketosis, even in the basal state. Parenteral insulin is required to sustain life. From 85% to 90% of patients with type 1 diabetes demonstrate evidence of one or more autoantibodies implicated in the cell-mediated autoimmune destruction of the beta cells of the pancreas. The autoimmune destruction has multiple genetic predispositions and may be related to undefined environmental insults.

Type 2 Diabetes Mellitus. Patients with type 2 diabetes may remain asymptomatic for long periods and show low, normal, or elevated levels of insulin. Ketosis is rare in type 2 disease. Patients frequently have hypertriglyceridemia and a high incidence of obesity. No association exists with viral infections, islet cell autoantibodies, or human leukocyte antigen (HLA) expression. Hyperinsulinemia may be related to peripheral tissue resistance to insulin because of defects in the insulin receptor. Defects in muscle glycogen synthesis have an important role in insulin resistance.

Gestational Diabetes. Gestational diabetes mellitus is characterized by an abnormal OGTT result that occurs during pregnancy and reverts to normal during the postpartum period or remains abnormal. The clinical pathogenesis is thought to be similar to that of type 2. The clinical presentation is usually nonketotic

hyperglycemia during pregnancy. Screening is performed around the 24th to 28th week with a 75-g oral glucose load in a woman with no prior history of diabetes.[4]

Diabetes of Other Causes. Myriad causes of diabetes have been identified, including chronic pancreatitis, cystic fibrosis, genetic defects in the beta cell or in insulin receptors, and chemical-induced (e.g., Vacor; statins; chemotherapeutic, antipsychotic, or antiretroviral medications). The management of diabetes due to these conditions is cause-specific and depends on whether the underlying pathophysiologic process more closely resembles type 1 or 2 diabetes.[3]

Prediabetes. Impaired glucose tolerance (IGT) has been replaced by the term *prediabetes* to identify individuals at high risk for the development of diabetes.[4] The pathogenesis of prediabetes is thought to be related to insulin resistance. This group is composed of persons whose plasma glucose levels are between normal and diabetic; they are at increased risk for diabetes and cardiovascular disease. Prediabetes encompasses patients with both impaired fasting glucose (110 to 125 mg/dL) or IGT (level of 140 to 199 mg/dL after a 75 g oral glucose load). Presentations of prediabetes include nonketotic hyperglycemia, insulin resistance, hyperinsulinism, and often obesity. Prediabetes is not associated with the same degree of complications of diabetes mellitus, and many of these patients have normal glucose tolerance. However, each year, about 1% to 5% of patients with prediabetes will develop diabetes mellitus.[4]

Diabetes Mellitus Clinical Features

Type 1

The patient with type 1 diabetes is usually lean, younger than 40 years at diagnosis, and prone to ketosis. Plasma insulin levels are absent to low; plasma glucagon levels are high but suppressible with insulin, and patients require insulin therapy to treat their symptoms. The onset of symptoms may be abrupt, with polydipsia, polyuria, polyphagia, and weight loss developing rapidly. In some cases, the disease is heralded by ketoacidosis. Myriad problems related to type 1 diabetes may prompt an ED visit, including acute metabolic complications, such as DKA, and late complications, such as cardiovascular or circulatory abnormalities, retinopathy, nephropathy, neuropathy, foot ulcers, severe infections, and various skin lesions.

Type 2

The patient with type 2 diabetes is usually middle-aged or older and overweight, with normal to high insulin levels. Insulin levels are lower than would be predicted for glucose levels, however, leading to a relative insulin deficiency. Type 2 patients demonstrate impaired insulin function related to poor insulin production, failure of insulin to reach the site of action, or failure of an end-organ response to insulin. Although most adult patients with type 2 are obese, 20% are not.

Symptoms in type 2 diabetes tend to begin more gradually than in type 1. The diagnosis of type 2 is often made by the discovery of an elevated blood glucose level on routine laboratory examination. Hyperglycemia may be controlled by dietary therapy, oral hypoglycemic agents, or insulin administration. Decompensation of the disease usually leads to HHS rather than to ketoacidosis.

Diabetes Mellitus Differential Diagnosis

The differential diagnosis for diabetes includes hyperglycemia due to physiologic stress, catecholamine release, or certain toxins. Calcium channel blocker overdose has been known to cause insulin resistance and thus present with both significant hyperglycemia and metabolic acidosis. The rodenticide PNU (vacor), which destroys the pancreatic islet cells, can induce a diabetes-like state. Patients with prediabetes may exhibit frank hyperglycemia with a large carbohydrate load or physiologic stress.

Diabetes Mellitus Diagnostic Testing

Serum Glucose Level

The diagnosis of diabetes can be established in one or more of four ways—random plasma glucose level above 200 mg/dL, fasting plasma glucose concentration above 126 mg/dL, 2-hour, 75-g post-load OGTT higher than 200 mg/dL, or HbA_{1c} value above 6.5%.[4] In the absence of hyperglycemia with metabolic decompensation, these criteria should be confirmed by repeated testing on a different day. Confirmation can be made by the same test or two different tests (e.g., fasting plasma glucose and HbA_{1c}). A fasting value above 150 mg/dL is likely to distinguish diabetic from nondiabetic patients more accurately. Formal OGTTs are unnecessary except during pregnancy or in patients who are thought to have diabetes, but who do not meet the criteria for a particular classification. The World Health Organization and ADA have provided protocols for performing the OGTT.[4]

Glycosylated Hemoglobin

Measurement of glycosylated hemoglobin (HbA_{1c}) is one of the most important ways to assess the level of glucose control. An elevated serum glucose level binds progressively and irreversibly to the amino-terminal valine of the hemoglobin β chain. The HbA_{1c} measurement provides insight into the quality of glycemic control over time. Given the long half-life of red blood cells, the percentage of HbA_{1c} is an index of glucose concentration of the preceding 6 to 8 weeks, with normal values approximately 4% to 6% of total hemoglobin, depending on the assay used. Levels in patients with poorly controlled disease may reach 10% to 12%. The ADA has recommended at least biannual measurements of HbA_{1c} for the follow-up of all types of diabetes. The ADA currently sets an HbA_{1c} value of less than 7% as a treatment goal. Different medical societies have advocated for patient-specific A_{1c} goals, particularly in the elderly, who are more prone to adverse effects from hypoglycemia resulting from attempts at tight glucose control.[5,6] For functionally independent older adults, the HbA_{1c} goal is 7% to 7.5%, and 7% to 8% is recommended for functionally dependent, frail patients, or patients with dementia.[5]

Urine Glucose Level

Urine glucose measurement methods are of two types, reagent tests and dipstick tests. The reagent tests (e.g., Clinitest) are copper reduction tests. The reagent tests are rarely used because they are difficult to perform, and the test material is toxic for ingestion or dermal exposure. Dipstick tests generally use glucose oxidase, which may also be affected by different substances. Dipsticks are inexpensive and convenient but may vary in their sensitivity and strength of reaction to a given concentration of glucose. Dipstick interpretation can vary significantly, depending on the observer and type of lighting. Both falsely high and falsely low urine glucose readings can also occur. With the plus system, 1+, 2+, 3+, and 4+ have different implications about urine glucose concentrations, depending on the brand of the dipstick. The use of reflectance colorimeters to read dipsticks increases accuracy.

Urine Ketone Level

Urine ketone dipsticks use the nitroprusside reaction, which test for acetoacetate but does not measure β-hydroxybutyrate. Although the usual ratio of acetoacetate to β-hydroxybutyrate in DKA is 1:2.8, it may be as high as 1:30, and in which case, the urine dipstick does not reflect the true level of ketosis. When ketones are in the form of β-hydroxybutyrate, the urine ketone dipstick may infrequently yield a negative reaction in patients with significant ketosis.

Dipstick Blood Glucose Level

Dipsticks for testing the blood glucose level are clearly more accurate than urine dipsticks as a means of monitoring blood glucose concentration, but they also may be inaccurate. Hematocrits below 30% or above 55% cause inaccurately high or low readings, respectively, and a number of the strips specifically disclaim accuracy when used for neonates. The sensitivity of dipsticks to a variety of factors varies with the particular brand. The largest errors are in the hyperglycemic range. Dipstick readings rarely err more than 30 mg/dL when the actual concentration is below 90 mg/dL. Although specific glucose concentrations may not be accurately represented, blood glucose dipsticks are useful for estimating the general range of the glucose value. Reflectance meters increase the accuracy of the dipstick blood glucose level determination. The use of glucometers has supplanted the use of dipsticks in most clinical settings and tends to be fairly accurate, except, again, at the extremes of glucose levels (<30 or >600 mg/dL). If maximum accuracy is desired, a laboratory blood glucose level should be determined.

Diabetes Mellitus Management

Management of Hyperglycemia

Patients often present to the ED with typical diabetic symptoms, such as polyuria, polydipsia, and polyphagia. Many have serum glucose concentrations above 200 mg/dL but are not ketotic. Patients with newly diagnosed hyperglycemia with normal electrolyte values may be treated with intravenous (IV) hydration alone or with insulin, often reducing the glucose concentration to 150 mg/dL. In reliable patients whose initial glucose concentration is greater than 400 mg/dL, initiation of oral hypoglycemic therapy may be appropriate, with lifestyle modification and coordination with a clinician who will provide longitudinal care. An HbA_{1c} value should be obtained before initiation of therapy to confirm a diagnosis of diabetes and to establish a baseline.

Detailed descriptions of oral hypoglycemics are provided below, but considerations for ED initiation in acute hyperglycemia are listed here. Initial therapy for type 2 diabetes generally includes metformin at a dose of 500 mg daily or twice daily depending on immediate or extended-release formulation. The extended-release formulation may be better tolerated in terms of GI side effects. Sulfonylurea therapy may be considered as well, with glyburide (2.5 to 5 mg once daily) or glipizide (5 mg once daily).[5–7] Patients with kidney disease may have complications from the use of a sulfonylurea or metformin and will likely need insulin therapy with or without a glucagon-like peptide-1 receptor agonist. Patients with heart failure or less severe renal disease might benefit from a sodium/glucose cotransporter-2 inhibitor (SGLT-2).[8–10] Recent studies have shown a mortality benefit to canagliflozin and empagliflozin. If possible, diabetic testing supplies should be given and patients should be taught how to test blood glucose prior to discharge. No target blood glucose level needs to be achieved for safe discharge; observational studies showed no difference in short-term outcomes whether a specific glucose target was achieved or not. Follow-up should be stressed and warning signs of hypoglycemia discussed.

Management of Diabetes Mellitus

Although emergency clinicians do not routinely provide longitudinal care for diabetic patients, these patients frequently present to the ED, and it is helpful to understand fundamental management principles of this important disease. The basic concepts of the diabetic diet remain unchanged, although many studies emphasize foods and medications that alter glucose absorption. Various high-fiber diets have improved glycemic control. The number of supplements or low–glycemic index snacks has risen in the last decade. Exercise continues to be a cornerstone of diabetes management, although care must be taken to balance it with appropriate calorie intake and medication use.

Oral Hypoglycemic Agents. Goals of diabetic management include lowering the hemoglobin A_{1c} to less than 7% and maintenance of the fasting blood sugar level to within 90 to 130 mg/dL. When started on monotherapy, after 3 years, approximately 50% of patients need a second drug. There have been an increasing number of oral agents for hyperglycemia available in recent years. (Table 115.1) Some of these have serious side effects, requiring the emergency clinician to be familiar with these drugs. If these effects are expected to be prolonged, the patient may require observation. Categories of oral agents may be divided into those that increase the insulin supply, including sulfonylureas, secretagogues, and insulin itself. Medications that decrease insulin resistance include the biguanides and thiazolidinediones; drugs that reduce the rate of glucose absorption include α-glucosidase inhibitors. Metformin is generally used as the first-line agent for oral therapy. If the goal of lower HbA_{1c} levels is not achieved, the addition of a sulfonylurea or pioglitazone should be considered.[8]

Biguanides. The ADA and European Association for the Study of Diabetes have recommended lifestyle changes, including weight control, at the time of diabetes diagnosis. Metformin (a biguanide) is the initial drug of choice because it does not induce weight gain, has low cost and good tolerability, and does not induce hypoglycemia. However, it lowers blood glucose by only about 100 mg/dL and lowers HbA_{1c} by approximately 1.5%. Newly diagnosed diabetics frequently require additional agents to control their serum glucose and to lower their HbA1c levels.[8]

Metformin is renally excreted and should not be used with a glomerular filtration rate (GFR) < 30. The Food and Drug Administration (FDA) also recommends not starting metformin in patients with a GFR of 30 to 45, though increased rates of adverse events were not noted in this group.[8] Metabolic and lactic acidosis are a concern with biguanides. Historically, holding metformin after IV contrast and rechecking renal function before restarting has been advocated. However, evidence has failed to show the necessity of this approach for most patients. Patients with existing kidney disease, or those with dehydration or hypoperfusion, should probably have metformin held after IV contrast. There is no clear evidence to support holding metformin

TABLE 115.1 Common Oral Diabetic Medications

Medication	Function	Details
Biguanides (metformin)	Decrease hepatic glycogenolysis	500–1000 mg daily or bid
Sulfonylureas (glipizide, glimepiride)	Stimulate pancreatic insulin release	2.5–5 mg daily or bid
Thiazolidinediones (pioglitazone, rosiglitazone)	Insulin sensitizers, decrease hepatic gluconeogenesis	Increased risk of adverse cardiac events
Meglitinides (repaglinide, nateglinide)	Stimulate postprandial insulin release	Take with meals only
Dipeptidyl peptidase 4 inhibitors (sitagliptin)	Decrease insulin degradation and gluconeogenesis	Once daily; can be found in multiple combination medications
α-Glucosidase inhibitors (acarbose, miglitol)	Delay breakdown of carbohydrates in the intestines	Major side effect is diarrhea

routinely for all patients. Metformin must be used with caution in patients with hypoxemia, pregnancy, heart failure, liver compromise, and alcohol abuse. These patients may be at increased risk for developing lactic acidosis, associated with a 50% mortality rate.[11]

Sulfonylureas. Developed in the 1940s, sulfonylureas have historically been a mainstay of oral diabetes treatment. These drugs increase insulin secretion by interacting with potassium channels in the beta cell membrane. This class of drugs is especially useful for patients with early-onset, type 2 diabetes mellitus, and fasting blood glucose levels less than 300 mg/dL. This class of drugs is contraindicated in patients with a known allergy to sulfa agents. Examples of sulfonylureas include glipizide (Glucotrol, Glucotrol XL), glimepiride (Amaryl), gliclazide (Diamicron), chlorpropamide (Diabinese), and glyburide (DiaBeta, Glynase PresTab, Micronase). The risk of hypoglycemia is greater in older adults and in those with impaired renal and hepatic function. This class of medication is also associated with weight gain. They generally lower the glucose level by 20%, and HbA_{1c} levels by 1% to 2%. Glipizide is shorter acting and therefore less likely than the other sulfonylureas to induce prolonged hypoglycemia. However, for all sulfonylureas, there have been several case reports of delayed onset of hypoglycemia from 12 to 21 hours after ingestion, leading to general recommendations to observe the patient for a 24-hour period. In addition to providing glucose, hypoglycemia due to sulfonylureas may be treated with octreotide, although the data supporting this recommendation is limited.

Thiazolidinediones. Thiazolidinediones reduce insulin resistance and are especially useful in patients who require large amounts of insulin and still lack adequate glucose control. They have been associated with hepatotoxicity and require liver function monitoring for at least 1 year after initiation. Due to its hepatotoxic effects, troglitazone has been removed from the market; pioglitazone (Actos) and rosiglitazone (Avandia) remain approved for monotherapy. Cardiovascular risks, including myocardial infarction, may be higher with rosiglitazone. These agents may also be associated with weight gain, fluid retention, and heart failure. They increase insulin sensitivity and may be expected to reduce the HbA_{1c} value by 0.5 to 1.4 points. They are contraindicated for patients with New York Heart Association class III or IV heart failure.[12]

α-Glucosidase Inhibitors. The *α-glucosidase inhibitors* delay intestinal monosaccharide absorption and prevent complex carbohydrate breakdown; these agents include acarbose (Precose and generic) and miglitol (Glyset). They must be titrated to minimize gastrointestinal (GI) side effects and should not be used in patients with certain GI disorders. Liver function must be monitored because of dose-dependent hepatotoxicity. The *α-glucosidase inhibitor* should be taken with meals because they delay the absorption of glucose. Side effects include abdominal pain, diarrhea, and flatulence from unabsorbed carbohydrates. They lower the $HgbA_{1c}$ by 0.5 to 0.8 points.

Meglitinides. The nonsulfonylurea secretagogues, the meglitinides, are similar to the sulfonylureas in action and mechanism. They bind to adenosine triphosphate (ATP)–sensitive potassium channels of beta cells to increase insulin secretion. They have a rapid onset of action and should be taken before a meal, involve less risk of hypoglycemia, and are suitable for patients allergic to sulfa medications. The specific agents available are nateglinide (Starlix) and repaglinide (Prandin). These may be better for patients with impaired renal function due to their hepatic metabolism. Similar to the management of refractory hypoglycemia with sulfonylureas, hypoglycemia due to meglitinides may be treated with octreotide by bolus or infusion.

Glucagon-Like Peptide Analogs and Agonists. Glucagon-like peptide (GLP-1) analogs and agonists stimulate the release of insulin from pancreatic cells. Exenatide (Byetta) is US FDA–approved for twice-daily subcutaneous injection in patients with type 2 diabetes who have not achieved satisfactory control with metformin, a sulfonylurea, pioglitazone, or lifestyle modifications. It lowers serum glucagon concentrations and slows gastric emptying. These agents should be used with caution if gastroparesis is a concern. Exenatide lowers HbA_{1c} by 1 to 1.5 points, even when administered once weekly.

GLP itself has a half-life of only a few minutes. The GLP agonists bind to the GLP receptor on the pancreas and have a much longer half-life. This class also includes the subcutaneously administered medications Liraglutide (Victoza), semaglutide (Ozempic), and lixisenatide. Recently, an oral version of semaglutide (Rybelsus) was approved by the FDA for once daily use. GLP-1 receptor antagonists have the following potential adverse effects: nausea, vomiting, diarrhea, renal impairment, pancreatitis, and thyroid carcinoma, with a warning against use if there is a personal or family history of medullary thyroid cancer. They have been associated with weight loss and may decrease hospitalization for heart failure.[9,10,13] Clinical experience with their toxicology is limited, but there have been episodes of hypoglycemia reported. Observation recommendations for hypoglycemia are not established, but, given the long half-life of the medications, we recommend a period of at least 24 hours.

Dipeptidyl Peptidase-4 Inhibitors. Dipeptidyl peptidase-4 (DPP-4) inhibitors include sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). DPP-4 degrades endogenous GLP; by preventing this degradation, the DPP-4 inhibitors prolong the half-life of GLP and increase insulin secretion. These are generally used as second- or third-line agents. Sitagliptin is FDA approved as monotherapy, but it is also available in combination with other oral hypoglycemic medications. Patients with chronic kidney disease may be at risk for hypoglycemia and should be treated symptomatically. DPP-4 inhibitors inhibit glucagon release and delay gastric emptying, and they are associated with a possible risk of pancreatitis.[10] Agents in the DPP-4 inhibitor class have not been associated with weight gain. They may be expected to produce a decrease in the HbA_{1c} of 0.4 to 0.8 points.

Amylin Analog. Pramlintide, administered three times daily before meals, is an amylinomimetic agent, or amylin analog, and decreases gastric emptying and glucagon secretion. It has been approved for use in patients with types 1 and 2 diabetes and may promote weight loss.

Sodium-Glucose Cotransporter 2 Inhibitors. Dapagliflozin (Farxiga), canagliflozin (Invokana), and empagliflozin (Jardiance) are sodium-glucose cotransporter 2 (SGLT2) inhibitors. Canagliflozin and empagliflozin have been FDA approved for cardiovascular risk reduction in patients with type 2 diabetes and established cardiovascular disease.[14] SGLT2 is a protein that transports filtered glucose from the proximal renal tubule into tubular epithelial cells, enhancing urinary excretion levels of glucose.[9] The typical threshold for urinary glucose excretion is typically a plasma glucose level of ~180 mg/dL the SGLT2 inhibitors decrease this threshold to ~40 mg/dL, markedly increasing urinary glucose excretion. They may also lower blood pressure and induce some degree of weight loss, possibly due to the loss of calories from glycosuria.[9]

SGLT2 inhibitors have been shown to reduce hospitalization for heart failure in people with diabetes, may reduce cardiovascular events, reduce albuminuria, and slow the progression of nephropathy.[9,10] Adverse events include hypotension, volume depletion, urinary and genital mycotic infections, and diabetic ketoacidosis, including normoglycemic DKA.

Insulin. Certain principles apply to all insulins, such as their ability to enhance gluconeogenesis and lipogenesis and suppress glycogenolysis. Human insulins are available today as regular insulin and neutral protamine hagedorn (NPH). Regular insulin, used in the treatment of DKA, has an onset of action within 30 to 60 minutes and is typically dosed 30 to 45 minutes before a meal. Its duration of action is approximately 4 to 12 hours. The longer-acting NPH insulin (e.g., Humulin, Novolin) is typically dosed 4 to 6 hours before a meal. It has

a 12- to 24-hour duration of action and is administered two or three times daily. Regular and NPH insulin may be combined to reduce the number of daily injections.

The development of insulin analogs, with modification of the terminal end of the A or B chain of the insulin molecule, has resulted in rapid-acting and long-acting formulations. The rapid-acting insulins currently on the market are glulisine, insulin lispro (Humalog), and insulin aspart (NovoLog). Their onset of action is approximately 10 to 30 minutes, and their duration is 3 to 5 hours. They are typically administered 5 to 20 minutes before a meal. Ultrafast-acting insulin analogs reduce postprandial glucose fluctuations and abnormalities.[12] The intent is to match insulin absorption and action to food-related rises in the plasma glucose level.[5] These basal insulin analogs may enable the time of administration of the insulin to vary widely.[12]

Long-acting insulin analogs are detemir (Levemir), deglutec, and glargine (Lantus); their onset of action is 3 to 4 hours, and their duration of action approaches 24 hours, similar to that of NPH. Insulin deglutec has a half-life of 25 hours, with a duration of action of 42 hours. Insulin glargine and detemir, being long-acting but without a peak response, more closely mimic continuous pump infusion. Advances in basal insulin formulations have resulted in products with longer durations of activity, less inter-patient variability in plasma concentration, and "flatter," more predictable pharmacokinetic properties, including a lower frequency of severe hypoglycemia.[15]

Although treatment for type 2 diabetes has traditionally started with oral agents, analog insulin therapy has been recently advocated as initial therapy for type 2 diabetes. Type 2 diabetes is associated with a decline of beta-cell function over time, and early intensive insulin therapy has been suggested to rest the beta cells and possibly preserve their function. Emergency clinicians may, therefore, see patients who were started on insulin therapy early after their diagnosis. Starting patients on 10 units/day of glargine, or detemir, 0.1 to 0.2 units/kg once daily in the evening or 10 units once or twice daily,[13,15] with 6 units of insulin aspart at mealtime, has been used as primary treatment for type 2 diabetes.[12] Basal insulin titration algorithms from numerous societies and colleges have recommended initial starting dosages of 10 units/day, titrating upward by 1 to 3 units every 1 to 3 days, with a target HbA_{1c} level below 6.5% to 7%.[16]

While many emergency clinicians are more comfortable starting patients on oral hypoglycemic agents to manage type 2 diabetes, on occasion, patients may be started on insulin from the ED. This approach involves the development of an outpatient protocol and follow-up with a specialty consultant, such as an endocrinologist. Glargine, detemir, or NPH insulin may be initiated at 0.1 to 0.2 units/kg, or roughly 10 units/day, with follow-up within 3 to 4 days for dose adjustment.

Pancreas Transplantation. Solid organ pancreas transplantation has become more common; several centers have performed combined pancreas and kidney transplants in those with end-stage kidney disease due to diabetic nephropathy. Transplantation ameliorates many secondary complications of diabetes, such as nephropathy, neuropathy, gastroparesis, retinopathy, and microvascular changes. The percentage of grafts functioning after 1 year and 1-year survival rate of patients is greater than 75% in selected medical centers. However, rejection, post-transplantation pancreatitis, and graft thrombosis, as well as other vascular and immunosuppression problems, continue to plague transplant recipients.

New Trends in Diabetes Management. Changes in the therapy of diabetes have recently included greater use of human insulin, which has prevented some of the adverse reactions to beef and pork products.[12] Unfortunately, some patients demonstrate sensitivity reactions, even to human insulin.

The initiation of immunosuppressive therapy at the initial diagnosis of type 1 diabetes can prolong the patient's ability to secrete insulin. This beneficial effect, whether achieved by azathioprine or cyclosporine, is not usually sustainable.[16] The potential side effects of immunosuppressive agents have precluded large trials in patients early in their disease.

Glycemic control now involves improved technology and more widespread individual monitoring of daily insulin dosage adjustments. Tight glycemic control limits the progression of microvascular disease, including neuropathy, renal disease, and certain types of retinopathy. However, those achieving tight control are more likely than other diabetic patients to experience hypoglycemic episodes.

Emergency clinicians and out-of-hospital care providers often encounter patients with insulin pumps.[17] Many types of insulin pumps are available, each with a pump mechanism, reservoir for insulin, tubing, and indwelling subcutaneous needles. They are attached, usually with tape, to the patient's body and administer insulin at a regular adjustable rate. Most pumps also allow the patient to administer additional boluses of insulin, as necessary. These pumps support tight glycemic control and are preferred by some patients. However, insulin pumps are associated with a variety of problems, including hypoglycemia. More recently, a wearable, automated bionic bihormonal pancreas has been noted to improve mean glycemic levels with less frequent hypoglycemic episodes among adults with type 1 diabetes mellitus. A consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology supported the use of continuous glucose monitoring (CGM) for use in type I diabetes in reducing hypoglycemia, improving glucose control, and possibly reducing health care costs.[18] Real-time CGM provides users with updated glucose readings every 5 minutes.[19] The bionic pancreas receives data from a continuous glucose monitor to control subcutaneous delivery of insulin and glucagon.[19]

Because glucose rotates the polarization of light waves, new fiberoptic technology has been developed to determine the blood glucose level noninvasively.[19] This technique may be applied to the insulin pumps of the future. Ultrafast-acting insulins and biosimilar insulins may also be available in the near future. An inhaled insulin (Afrezza) has recently been released but has been associated with coughing and may exacerbate symptoms of reactive airway disease.

The pharmacologic treatment of diabetes continues to improve, with newer agents offering the promise of improving glycemic control for longer periods, with fewer glycemic fluctuations, less weight gain, and less hypoglycemia. New insulin analogs, such as deglutec and U-500, improve glycemic control without contributing to hypoglycemia.[18] The U500 insulin is much more concentrated, and errors in dosing are more frequent when using this product, however. Other new areas of research have included agents that increase the urinary excretion of glucose or increase hepatic gluconeogenesis.

LATE COMPLICATIONS OF DIABETES

Late complications of diabetes develop approximately 15 to 20 years after the onset of overt hyperglycemia, resulting in significant morbidity and mortality. The Diabetes Control and Complications Trial (DCCT) has shown that tight glycemic control significantly reduces the risk of microvascular disease, such as microalbuminuria (the earliest sign of nephropathy), neuropathy, and retinopathy, but at the expense of greatly increasing the risk of recurrent hypoglycemia.[2]

Vascular Complications

Diabetes is associated with an increased risk for atherosclerosis and thromboembolic complications, a major cause of morbidity and premature death. The cause of accelerated atherosclerosis is unknown, although it is probably related to oxidated low-density lipoprotein, and

increased platelet activity. Atherosclerotic lesions are widespread, causing symptoms in many organ systems. Coronary artery disease and stroke are common. Diabetic patients have an increased incidence of so-called silent myocardial infarction, complicated myocardial infarctions, and congestive heart failure. Peripheral vascular disease is noted clinically by claudication, nonhealing ulcers, gangrene, and impotence. In addition, standard treadmill stress tests have a decreased sensitivity in the detection of coronary artery disease in diabetics. For this reason, exercise or pharmacologic stress echocardiography or a nuclear medicine imaging study should be considered when a provocative test is needed to evaluate the diabetic patient for acute coronary syndrome.[1]

Diabetic Nephropathy

Renal disease is a leading cause of death and disability in diabetic patients. Approximately 50% of cases of end-stage renal disease in the United States are caused by diabetic nephropathy. The appearance of microalbuminuria correlates with the presence of coronary artery disease and retinopathy. Azotemia generally does not begin until 10 to 15 years after the diagnosis of diabetes. The progression of renal disease is accelerated by hypertension. Meticulous control of diabetes can reverse microalbuminuria and may slow the progression of nephropathy. Blood pressure should be aggressively managed; angiotensin-converting enzyme inhibitors are effective in controlling hypertension and lowering microalbuminuria. Chronic hemodialysis and renal transplantation are unfortunate endpoints for many diabetic patients with renal disease.

Retinopathy

Diabetes is a leading cause of adult blindness in the United States. Approximately 11% to 18% of all diabetic patients have treatable diabetic retinopathy, ranging from mild to severe, and manifested in many forms. The severity of diabetic retinopathy is clearly related to the quality of glycemic control. Background retinopathy is found in most patients with prolonged diabetes and is characterized by microaneurysms, small vessel obstruction, cotton wool spots, soft or hard exudates, and macular ischemia. Proliferative retinopathy defines an entity of new vessel formation and scarring, as well as associated vitreal hemorrhage and retinal detachment. The diabetic patient may present with complaints ranging from the acute blurring of vision to sudden unilateral or even bilateral blindness. Less often, diabetic patients have more gradual vision loss caused by the common senile cataract (or snowflake cataract), which may disappear as the hyperglycemia is corrected. Diabetic patients with retinopathy should be referred to an ophthalmologist. Even in those with normal vision, ophthalmologic procedures may limit visual loss or prevent crises such as neovascular glaucoma.

Neuropathy

Autonomic and peripheral neuropathies are well-known complications of diabetes. The prevalence of peripheral neuropathy ranges from 15% to 60%. The cause of the neuropathy is not clearly understood, but studies have suggested several factors in its development, including the effects of diabetic vascular disease on the vasa nervorum. Neurologic manifestations of diabetes may regress with improved glycemic control.

Several distinct types of neuropathy have been recognized in diabetes.[20] Peripheral symmetric neuropathy is a slowly progressive, primary sensory disorder manifested bilaterally with anesthesia, hyperesthesia, or pain. The pain is often severe and worse at night. It affects the upper and lower extremities, although the lower extremities and distal most sections of the involved nerves are most often affected. There may be a motor deficit as well. The pain may be very difficult to control; opioid analgesics have been used, but nonopioid medications such as gabapentin, pregabalin, and amitriptyline are preferred. Nortriptyline has been used, but the effects seem to dissipate after about 3 months of use. Pregabalin seems to hold the most promise when used at higher dosages (up to 600 mg/day). Duloxetine at a dosage of 60 mg/day is also effective. Both pregabalin and duloxetine achieve significant pain control in at least 50% of patients. Gabapentin, 300 mg tid, has some efficacy, achieving significant pain relief in about one-third of patients; amitriptyline 25 mg daily demonstrates similar results, though if there is no improvement after 5 to 7 days, any further efficacy is unlikely. N-methyl-D-aspartate receptor (NMDAR) antagonists such as memantine and dextromethorphan have shown promise in reducing pain and hyperalgesia in diabetic neuropathy.[21] A reasonable approach for the emergency clinician is the initiation of duloxetine or pregabalin, with the understanding that it may take several days for a peak effect to be reached.[20]

Mononeuropathy, or mononeuropathy multiplex, affects motor and sensory nerves, generally one nerve at a time. The onset is rapid, with wasting and tenderness of the involved muscles. There may be a sudden onset of wrist drop, foot drop, or paralysis of cranial nerves III, IV, and VI. Diabetic mononeuropathies may be most bothersome at night and generally resolve in a few months. Diabetic truncal mononeuropathy occurs rapidly in a radicular distribution. In contrast to other mononeuropathies, it is primarily, if not exclusively sensory. If it causes pain, it may mimic that of a myocardial infarction or acute abdominal inflammation. Whereas diabetic mononeuropathy is often the first indication of diabetes, truncal mononeuropathy is more often found in known diabetic patients. Management is similar to other diabetic neuropathies, with the exception of CN III palsy, which is usually expectant management.

Autonomic neuropathy occurs in many forms. Neuropathy of the GI tract, with resultant gastroparesis, is manifested by difficulty in swallowing, delayed gastric emptying, constipation, or nocturnal diarrhea. Impotence and bladder dysfunction or paralysis may occur. Orthostatic hypotension, syncope, and even cardiac arrest have resulted from autonomic neuropathy. Diabetic diarrhea responds to diphenoxylate and atropine, loperamide, or clonidine. There are small case series that also describe success using 5HT3 receptor antagonists successfully as well. Orthostatic hypotension is treated by sleeping with the head of the bed elevated, avoidance of sudden standing or sitting, and use of full-length elastic stockings. For gastroparesis, metoclopramide is recommended for its prokinetic and antiemetic properties, though caution must be taken with prolonged use due to the risk of tardive dyskinesia. Many patients with gastroparesis present with abdominal pain; opioids are not recommended for this group due to the risk of worsening dysmotility of the GI tract. In patients with acute presentations of pain and vomiting due to gastroparesis, intravenous haloperidol has shown effectiveness in a few small trials.

The Diabetic Foot

Approximately 20% of hospitalizations in diabetic patients are related to foot problems.[17] Sensory neuropathy, ischemia, and infection are the principal contributors to diabetic foot disease. Loss of sensation leads to pressure necrosis from poorly fitting footwear and small wounds going unnoticed. The most common cause of injury is pressure on plantar bone prominences. All neuropathic foot ulcers should be assessed for infection, devitalized tissue débrided, and radiographs obtained to evaluate for the presence of foreign bodies, soft tissue gas, or bone abnormalities (see Chapter 126).[19]

Not all ulcers are infected. Infection is suggested by local inflammation or crepitation. Conversely, some uninflamed ulcers are associated with underlying osteomyelitis. Most mild infections are caused by gram-positive cocci, such as *Staphylococcus aureus* or streptococci, and may be treated with oral antibiotics with activity against gram-positive

TABLE 115.2 Common Serious Infections in Diabetics and Their Antimicrobial Therapy

Infectious Condition	Antimicrobial Therapy
Diabetic foot infection	Mild—consider trimethoprim-sulfamethoxazole, 800/160 bid or clindamycin 300 mg q6h Moderate to severe—piperacillin-tazobactam (Zosyn), 3.375 g IV q6h and vancomycin, 15 mg/kg IV q12h
Malignant otitis externa	Oral—ciprofloxacin, 500 mg PO bid for 10–14 days IV—ceftazidime, 2 g IV q8h ± gentamicin, 2 mg/kg IV q8h
Mucormycosis	Amphotericin B, 1–1.5 mg/kg/day Posaconazole, 400 mg bid
Mucocutaneous candidiasis	Ketoconazole, 200 mg PO daily; may need several weeks of therapy
Nonclostridial gas gangrene (including Fournier's)	Clindamycin, 600 mg q6h + third-generation cephalosporin + vancomycin, 15 mg/kg q12h

organisms, such as trimethoprim-sulfamethoxazole, 800/160 mg bid, a first-generation cephalosporin such as cephalexin, 500 mg qid, or clindamycin, 300 mg qid. A strict non-weight-bearing regimen, meticulous wound care, and daily follow-up are also vitally important to wound healing. This approach may not be possible when patients do not have adequate home support or do not have ready access to follow-up care.

Deeper, limb-threatening infections—as evidenced by full-thickness ulceration, cellulitis more than 2 cm in diameter, with or without lymphangitis, bone or joint involvement, or systemic toxicity—are usually polymicrobial in origin and caused by aerobic gram-positive cocci, gram-negative bacilli, and anaerobes (see Chapter 125, Bone and Joint Infections). These patients require hospitalization and, after culture, broad-spectrum IV empirical antimicrobial therapy (Table 115.2). Additional measures include strict non-weight-bearing status, tight glycemic control, early surgical intervention for débridement, and meticulous wound care. Occult osteomyelitis should be considered in all cases of neuropathic ulceration.[19] Hyperbaric oxygen has been shown to have some efficacy in treating complicated infections, especially with anaerobic organisms. Up to one-third of patients eventually undergo amputation.

Infections

Diabetic patients are more susceptible to complications of infections because of their inability to limit microbial invasion with effective polymorphonuclear leukocytes and lymphocytes. They have an increased incidence of extremity infections and pyelonephritis compared with the general population. In addition, they are particularly susceptible to certain other infections, such as tuberculosis, mucocutaneous candidiasis, intertrigo, mucormycosis, soft tissue infections, nonclostridial gas gangrene, Fournier's gangrene, osteomyelitis, and malignant *Pseudomonas* otitis externa (see Table 115.2). Glycemic control, and hospitalization are usually required.

Cutaneous Manifestations

Dermal hypersensitivity is manifested by pruritic erythematous indurations that occur at insulin injection sites. The declining prevalence of this condition has paralleled the improved purification of insulin. Similarly, insulin lipoatrophy is subcutaneous depressions at injection sites and seems to be a result of insulin impurities. Although lipoatrophy is more common than dermal hypersensitivity, its prevalence has also declined sharply because of improved insulin preparations. Insulin lipohypertrophy is manifested by raised areas of subcutaneous fat deposits at insulin injection sites. These lesions generally reflect the failure of the patient to rotate injection sites adequately. They resolve spontaneously over months if insulin injection is avoided in the affected areas and sites are properly rotated.

Insulin pumps are often associated with localized skin problems, usually a reaction to the tape securing the tubing and needles. On occasion, sensitivity to the catheters is seen. Skin infections at the site of injection are the most common complication of insulin pumps. A few patients have been noted to have hard nodules at the injection site. The cause of these nodules is uncertain.

Diabetic patients who use oral hypoglycemic agents may have rashes associated with these medications. After consumption of ethanol, approximately 38% of type 2 patients taking chlorpropamide exhibit a flush consisting of redness of the face and neck and a sense of warmness or burning. Patients may demonstrate urticaria in response to insulin and oral hypoglycemics.

Skin Conditions

Diabetic skin conditions include fungal infections, acanthosis nigricans, necrobiosis lipoidica diabeticorum, xanthoma diabeticorum, bullosis diabeticorum, and diabetic dermopathy.

Acanthosis Nigricans. This is characterized by a velvety, brown-black thickening of the keratin layer, most often in the flexor surfaces. It is the cutaneous marker for a group of endocrine disorders with insulin resistance.

Necrobiosis Lipoidica Diabeticorum. This begins as erythematous papular or nodular lesions, usually in the pretibial area but in other areas as well. The early lesions may contain telangiectasias. These lesions spread and frequently form a single pigmented area of atrophic skin, often with a yellow and sometimes ulcerated center and an erythematous margin. A history of previous trauma is sometimes found.

Xanthoma Diabeticorum. These lesions are evidence of the hyperlipidemia associated with diabetes, similar to the xanthoma found in nondiabetic hyperlipidemic patients. Xanthomas have an erythematous base and a yellowish hue.

Bullosis Diabeticorum. This is a rare occurrence. Bullae are usually filled with a clear fluid and are most often found on the extremities, especially the feet. The fluid is occasionally slightly hemorrhagic. The bullae usually heal spontaneously without scarring.

Diabetic Dermopathy. Also known as skin spots, this is the most common skin finding in diabetes. It arises as discrete, depressed, and brownish lesions generally less than 15 mm in diameter and found in the pretibial area.

Impetigo or Intertrigo. Resistant, aggressive impetigo or intertrigo may suggest diabetes.

Diabetes Disposition

The decision to admit or discharge a diabetic patient depends on multiple factors. Primary considerations include the severity of illness,

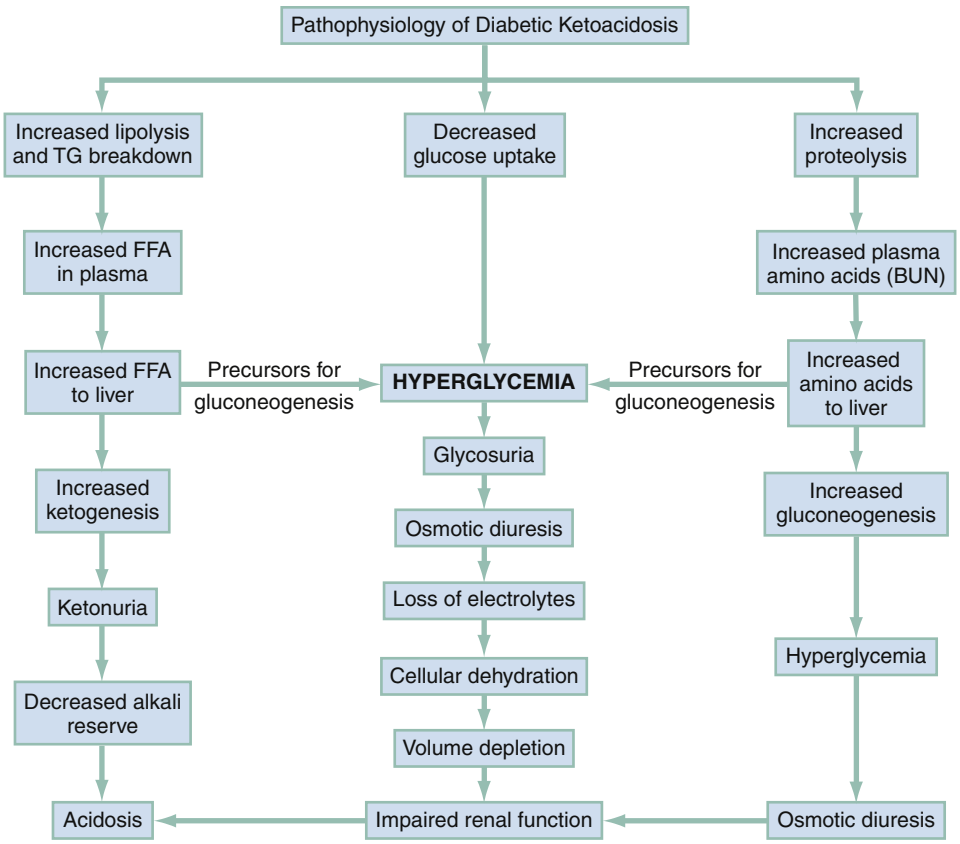

Fig. 115.1 Syndrome of Diabetic Ketoacidosis. *BUN,* Blood urea nitrogen; *FFA,* free fatty acids; *TG,* total glucose concentration.

whether this is a new diagnosis (where teaching, obtaining supplies, diabetic lifestyle education, and possibly insulin titration are needed) or an established diagnosis. Issues such as the ability to obtain medications and diabetic supplies and the ability to manage diabetes at home (particularly as relates to the measurement of blood glucose and insulin administration, which may be difficult in the elderly or those with low vision) are additional factors. Even in the absence of other complicating factors, such as DKA or infection, admission may be necessary for both achieving glycemic control and developing an appropriate outpatient plan for diabetes management. The elderly, socioeconomically disadvantaged populations, uninsured persons, and those with mental illness are at particular risk. Recent significant price increases for insulin have compelled many people with diabetes to forgo this part of their therapy. The mortality and morbidity rate from diabetes is also substantially higher in chronically underserved populations, such as African Americans; the rates of death, kidney disease, and amputations are all much higher in African-Americans as compared to Caucasians. African Americans have more than twice the incidence of diabetes compared to Caucasians (11.8 vs. 5.7) and are 2.3 times more likely to die from the disease as Caucasians.

DIABETIC KETOACIDOSIS

Foundations

Pathophysiology

DKA is a syndrome in which insulin deficiency and glucagon excess combine to produce a hyperglycemic, dehydrated, acidotic patient with profound electrolyte imbalances. All derangements producing DKA are interrelated and based on insulin deficiency (Fig. 115.1). DKA may be caused by the cessation of insulin intake or by physical or emotional stress, despite continued insulin therapy. The effects of insulin deficiency may be mimicked in peripheral tissues by a lack of insulin receptors or insulin sensitivity at receptor or post-receptor sites. When the hyperglycemia becomes sufficiently marked, the renal threshold is surpassed, and glucose is excreted in the urine. The hyperosmolarity produced by hyperglycemia and the dehydration are the most important determinants of the patient's mental status.[16]

Glucose in the renal tubules draws water, sodium, potassium, magnesium, calcium, phosphorus, and other ions from the circulation into the urine. This osmotic diuresis, combined with poor intake and vomiting, produces the profound dehydration and electrolyte imbalance associated with DKA (Table 115.3). Exocrine pancreatic dysfunction closely parallels endocrine beta-cell dysfunction, producing malabsorption that further limits the body's intake of fluid and exacerbates electrolyte loss.

In 95% of patients with DKA, the total sodium level is normal or low. Potassium, magnesium, and phosphorus deficits are also usually marked. As a result of acidosis and dehydration, however, the initially reported serum values for these electrolytes are often higher than actual body stores.

The cells, unable to receive fuel substances from the circulation, act as they do in starvation from other causes. They decrease amino acid uptake and accelerate proteolysis so that large amounts of amino acids are released to the liver and converted to two-carbon fragments.

Adipose tissue in the patient with DKA fails to clear the circulation of lipids. Insulin deficiency results in the activation of a hormone-sensitive lipase that increases circulating free fatty acid (FFA) levels. Long-chain FFAs, now circulating in abundance as a result of insulin deficiency, are partially oxidized and converted in the liver to acetoacetate and β-hydroxybutyrate. Despite the increased pathologic

TABLE 115.3 Average Fluid and Electrolyte Deficits in Severe Diabetic Ketoacidosis[a]

Weight	Water (mL/kg)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Phosphorus (mEq/L)
≤10 kg	100–120	8–10	5–7	6–8	3
10–20 kg	80–100	8–10	5–7	6–8	3
≥20 kg	70–80	8–10	5–7	6–8	3

[a]Per kilogram of body weight.

production of ketones, the body acts as it does in any form of starvation to decrease the peripheral tissue's use of ketones as fuel. The combination of increased ketone production with decreased ketone use leads to ketoacidosis.

Acidosis plays a prominent role in the clinical presentation of DKA. The acidotic patient attempts to increase lung ventilation to rid the body of excess acid with Kussmaul breathing. Bicarbonate is consumed in the process. Acidosis compounds the effects of ketosis and hyperosmolality to depress mental status directly.

Acidemia is not invariably present, even with significant ketoacidosis. Ketoalkalosis has been reported in diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation. The finding of alkalemia, however, should prompt consideration of alcoholic ketoacidosis, in which alkalemia is much more common.

DKA most commonly occurs in patients with type 1 diabetes and is associated with inadequate administration of insulin, infection, or myocardial infarction. DKA can also occur in type 2 diabetics and may be associated with any type of stress, such as sepsis or GI bleeding. Approximately 25% of all episodes of DKA occur in patients whose diabetes was previously undiagnosed.

Clinical Features

Clinically, most patients with DKA complain of a recent history of polydipsia, polyuria, polyphagia, visual blurring, weakness, weight loss, nausea, vomiting, and abdominal pain. Approximately 50% of these patients, especially children, report abdominal pain. In children, this pain is usually idiopathic and probably caused by gastric distention or stretching of the liver capsule; it resolves as the metabolic abnormalities are corrected. In adults, however, abdominal pain more often signifies actual abdominal disease that may be triggering the DKA.

Physical examination may or may not demonstrate a depressed sensorium. Typical findings include tachypnea with Kussmaul breathing, tachycardia, frank hypotension or orthostatic blood pressure changes, odor of acetone on the breath, and signs of dehydration. An elevated temperature is rarely caused by DKA itself and suggests an inciting infection.

Differential Diagnosis

Alcoholics, especially those who have recently abstained from drinking, with Kussmaul's breathing, fruity odor to the breath, and acidemic blood gas values may have alcoholic ketoacidosis. These patients may be euglycemic or hypoglycemic, and a large part of their acidosis is often caused by the unmeasured β-hydroxybutyric acid. Alcoholic ketoacidosis accounts for approximately 20% of all cases of ketoacidosis. Ketoacidosis can also develop with fasting, commonly in the third trimester of pregnancy and in nursing mothers who do not eat.

The differential diagnosis for DKA is broad and includes any entity that may cause elevated anion gap acidosis, ketosis, or both. The presence of DKA should not exclude investigation for other causes of anion gap metabolic acidosis, such as sepsis, poisoning, or lactic acidosis, because physiologic stress from one of these other causes can precipitate DKA.

TABLE 115.4 Typical Laboratory Values in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

	DKA	HHS
Glucose (mg/dL)	>350	>700
Sodium (mEq/L)	Low 130s	140s
Potassium (mEq/L)	≈4.5–6.0	≈5
Bicarbonate (mEq/L)	<10	>15
Blood urea nitrogen (mg/dL)	25–50	>50
Serum ketones	Present	Absent

DKA, Diabetic ketoacidosis; *HHS,* hyperglycemic hyperosmolar state.

Diagnostic Testing

Initial tests allow preliminary confirmation of the diagnosis and initiation of therapy (Table 115.4).[22] Subsequent tests are carried out to determine more precisely the degree of dehydration, acidosis, and electrolyte imbalance and reveal the precipitant of DKA.

Laboratory studies should include serum glucose, electrolyte, and venous blood pH. Although serum ketoacid levels are frequently measured, they are not necessary to diagnose DKA and may be elevated in non-DKA states (e.g., starvation ketosis from inadequate utilization of glucose stores) or dehydration. If determination of the pH is the sole concern, venous blood gas samples correlate well with arterial pH and are preferable as they are less invasive and have a lower complication rate than arterial sampling. If there is concern about the degree of respiratory compensation and better assessment of ventilation is required, then arterial samples should be obtained.

Blood gas measurement usually reveals a low pH, with the aforementioned rare exception of a concomitant alkalemia, resulting in a pseudo-normalization of the pH. Metabolic acidosis with an anion gap is primarily the result of elevated plasma levels of acetoacetate and β-hydroxybutyrate, although lactate, FFAs, phosphates, volume depletion, and several medications may also contribute. Rarely, a well-hydrated patient with DKA may have a pure hyperchloremic acidosis with no anion gap if they have been aggressively rehydrated with normal saline. Again, although rare, there have been case reports of a normal anion gap in a patient with DKA. This can occur with vomiting sufficient to cause a concomitant metabolic alkalosis, resulting in pH and bicarbonate levels in the normal range.[22]

Knowledge of the relationship between the rise in anion gap (delta AG) and the fall in bicarbonate (delta HCO_3), or delta gap (delta AG-delta HCO_3), can delineate the existence of a mixed acid-base disorder. A delta gap greater than + 6 indicates a concomitant metabolic alkalosis, and a delta gap less than -6 indicates a concomitant hyperchloremic metabolic acidosis. Winter's formula (expected $Paco_2$ = [1.5 × serum HCO_3^-] + [8 ± 2]) can be applied to determine if there is appropriate respiratory compensation or the presence of multiple acid-base disorders.

The glucose level is usually elevated above 350 mg/dL; however, euglycemic DKA (blood glucose level ≤ 300 mg/dL) has been reported in up to 18% of patients. The incidence of euglycemic DKA may be higher in patients treated with SGLT2 inhibitors.

If an immediate potassium level is not available through point-of-care testing or blood gas analysis, an electrocardiogram can reveal signs of hyperkalemia or hypokalemia. Initial serum potassium levels are typically normal or high in DKA due to intracellular potassium shifting out of cells in exchange for elevated serum hydrogen ions. However, as potassium is lost in the urine, the total body potassium usually declines by several hundred milliequivalents. This, in combination with the insulin doses administered in DKA, can result in life-threatening hypokalemia. A basic metabolic panel should be obtained to evaluate for an anion gap, potassium and glucose levels, and renal function. Because magnesium deficits are common in DKA, we recommend determining these levels as well. Urinalysis, in addition to the presence of ketones, may also help confirm a urinary tract infection as a precipitant of DKA. Whether to obtain blood or urine cultures should be determined by the clinical picture.

The serum sodium level is often misleading in DKA. It is often low in the presence of significant dehydration because it is strongly affected by hyperglycemia, hypertriglyceridemia, salt-poor fluid intake, increased GI and renal losses, and insensible loss. When hyperglycemia is marked, water flows from the cells into the vessels to decrease the osmolar gradient, thereby creating dilutional hyponatremia. Elevated lipid levels cause pseudohyponatremia by decreasing the fraction of serum that is water. Newer autoanalyzers remove triglycerides before the assay is performed, thus eliminating this artifact. The true value of the sodium level may be approximated by adding 1.6 mEq/L to the sodium value on the laboratory report for every 100-mg/dL glucose above the norm. Thus, if the laboratory reports a serum sodium level of 130 mEq/L and blood glucose level of 700 mEq/L, the corrected total serum sodium level is 139.6 mEq/L.

Acidosis and the hyperosmolarity induced by hyperglycemia shift potassium, magnesium, and phosphorus from the intracellular to extracellular space. Dehydration results in hemoconcentration, which contributes to normal or high initial serum potassium, magnesium, and phosphorus readings in DKA, even with profound total body deficits. The effect of acidosis on the serum potassium level determination can be corrected by subtracting 0.6 mEq/L from the laboratory potassium level for every 0.1-decrease in pH noted in the blood gas analysis. Thus, if the potassium level is reported as 5 mEq/L and the pH is 6.94, the corrected potassium value is 2 mEq/L, representing severe hypokalemia. As insulin is administered and the hydrogen ion concentration decreases, the patient needs considerable potassium replacement. The ADA algorithm for potassium repletion is helpful in guiding the management of potassium derangements. No conversion factor has been developed for the estimation of true magnesium levels, although initial values may be high.

All laboratory determinations must be interpreted with caution. Serum creatinine level determinations made by the autoanalyzer may be falsely elevated. Leukocytosis more closely reflects the degree of ketosis than the presence of infection. Only the elevation of band neutrophils has been demonstrated to indicate the presence of infection, with a sensitivity of 100% and specificity of 80% from a single retrospective study. Historically, the diagnosis of pancreatitis in a patient with DKA could be confounded by the elevation of amylase levels in DKA. Given the strength of the current literature demonstrating greater specificity of lipase for the diagnosis of pancreatitis, lipase (which must be three times the upper limit of normal to meet diagnostic criteria for pancreatitis) should be the blood test of choice if pancreatitis is a concern.

BOX 115.1 Summary of Treatment of Diabetic Ketoacidosis

Identify diabetic ketoacidosis—serum glucose, electrolyte, and ketone levels and arterial blood gas analysis; also obtain complete blood count with differential, urinalysis, chest radiograph, and electrocardiogram, if indicated.

Rehydrate.

- 1–2 L NS IV during 1–3 h
- Children—20 mL/kg NS during the first hour
- Correct electrolyte abnormalities.
- Sodium—correct with the administration of NS or 0.45% NS.
- Potassium—ensure adequate renal function. Add 20–40 mEq KCl to each liter (when serum potassium <5.5 mEq/L) of fluid until ketoacidosis is corrected and potassium is normalized. (Do not give insulin until potassium 3.3 mEq/L or greater.)
- Phosphorus—usually unnecessary to replenish.
- Magnesium—correct with 1–2 g $MgSO_4$. Serum magnesium levels may not correlate with body stores.

Supplement insulin.

- Insulin replacement—0.1 unit/kg/h regular insulin IV
- Change IV solution to D_5W/0.45% NS when glucose concentration is ≤300 mg/dL.

Correct acidosis.

- Administer IV fluids and insulin.

Search for and correct underlying precipitant.

Monitor progress and keep meticulous flow sheets.

- Vital signs
- Fluid intake and urine output
- Serum glucose, K^+, Cl^-, HCO_3^-, CO_2, pH
- Amount of insulin administered

Admit to hospital or intensive care unit.

Consider outpatient therapy in children with a reliable caregiver

and

- Initial pH ≥ 7.35
- Initial HCO_3^- ≥ 20 mEq/L
- Can tolerate oral fluids
- Resolution of symptoms after treatment in the emergency department
- No underlying precipitant requiring hospitalization

NS, Normal saline.

Management

When possible, intubation should be avoided in the patient with DKA. Patients often have tremendous respiratory drive, and matching this minute ventilation with the ventilator can be challenging. The comatose DKA patient, especially if vomiting, requires intubation however. Once the patient is intubated, maintenance of hyperventilation prevents worsening acidosis. The patient in hypovolemic shock requires aggressive fluid resuscitation with isotonic crystalloids before vasopressors are used, and clinicians should consider other possible causes of shock (e.g., sepsis or myocardial dysfunction secondary to myocardial infarction). Bedside ultrasonography may be of benefit in excluding other causes of hypotension and evaluating the volume status of an individual patient. Although it is not routinely used in the ED setting, in cases in which the volume status is difficult to ascertain because of complex underlying physiologic derangements (e.g., congestive heart failure, renal failure), the rapid ultrasound for shock and hypotension examination (see Chapter e5) or invasive hemodynamic monitoring may guide fluid therapy.

When hyperglycemia, ketosis, and acidosis have been established, fluid, electrolyte, and insulin therapy should be initiated (Box 115.1).

Intravenous Fluids

The severely dehydrated adult patient is likely to have a fluid deficit of 3 to 5 L. No uniformly accepted formula exists for the administration of fluid in this disorder. If the patient is in hypovolemic shock, the isotonic crystalloid solution should be given as rapidly as possible in the adult or in boluses of 20 mL/kg in the child until a systolic pressure of 80 mm Hg is obtained. There is no consensus regarding the ideal fluid to use; concerns have been raised using large amounts of normal saline exacerbating metabolic acidosis. At least one small trial has studied the use of a balanced crystalloid solution (Plasmalyte) in DKA, with reports of more rapid restoration of normal physiologic parameters.[18]

In the adult who has marked dehydration in the absence of clinical shock or heart failure, 1 L of fluid may be administered in the first hour. In general, 2 L of fluid resuscitation during the first 1 to 3 hours is followed by a slower infusion of a hypotonic solution, such as 0.45% normal saline solution. DKA patients without extreme volume depletion may be successfully treated with a lower volume of IV fluid replacement. An initial bolus of 20 mL/kg during the first hour is the usual fluid resuscitation therapy for a child. The fluid rate should be adjusted according to age, cardiac status, and degree of dehydration to achieve a urine output of 1 to 2 mL/kg/h.

Fluid resuscitation alone may help lower hyperglycemia. Because a low level of circulating insulin may be present, increased perfusion may transport insulin to previously unreached receptor sites. In addition, a large volume of glucose may be cleared by the kidneys in response to improved renal perfusion. The mean plasma glucose concentration has been noted to drop by 18% after the administration of saline solution without insulin.[18]

Acidosis also decreases after fluid infusion because increased perfusion improves tissue oxygenation and diminishes lactate formation while increasing lactate clearance. Increased renal perfusion promotes renal hydrogen ion loss, and the improved action of insulin in the better-hydrated patient inhibits ketogenesis. Although fluid administration decreases the serum glucose concentration and improves acidosis, the underlying deficiency in DKA requires administration of insulin for the correction of ketoacidosis.

Potassium

Potassium replacement is invariably needed in DKA. The initial potassium level is often normal or high, despite a large deficit because of severe acidosis. Potassium levels often plummet with correction of acidosis and administration of insulin. Once potassium levels reach 5.0 to 5.5 mEq/L and the patient is making urine, potassium should be administered while monitoring renal function (Table 115.5).[18] In patients with relatively lower serum potassium concentration at presentation (3.3 to 5.0 mEq/L), hypokalemia may become life-threatening when insulin therapy is administered; therefore, IV administration of potassium in concentrations of 20 to 40 mEq/L should be given with insulin administration. In patients with hypokalemia (<3.3 mEq/L), insulin should only be initiated once potassium has been replaced to achieve levels of 3.3 mEq/L or higher. The primary rationale for such conservative recommendations regarding potassium administration is that serum levels do not correlate with total body stores in the DKA patient, and the potassium level can drop more rapidly than anticipated with insulin administration.

TABLE 115.5 American Diabetes Association Recommendations for Potassium and Phosphorus Repletion

Potassium <3.3 mEQ/L	Replete to >3.3 mEQ/L before starting insulin
Potassium 3.3–5.5 mEQ/L	Supplement potassium to maintain these levels while starting insulin
Potassium >5.5 mEQ/L	Do not start potassium supplementation until <5.5 mEQ/L
Phosphorous <1.0 mEQ/L	Initiate supplementation with potassium phosphate

It was once believed that there was always a phosphorus deficit in DKA. However, there is no significant evidence to support this practice, and only isolated case reports have supported concerns about clinically significant hypophosphatemia in DKA. If the measured serum phosphorus level is low, it should be replaced with potassium phosphate.

Insulin

DKA cannot be reversed without insulin, and insulin therapy should be initiated as soon as the potassium level is determined to be adequate or potassium has been repleted. No randomized trials have compared insulin with placebo or other therapies for DKA. However, the mortality from DKA was 90% in historical controls before the development of exogenous insulin and 50% after insulin was introduced. With appropriate supportive therapy, mortality has reached the current levels of less than 10%.[11]

Although the dosing of insulin infusions has been established, an IV bolus before the infusion is no longer recommended. More recently, in selected patients with mild DKA, the subcutaneous or intramuscular administration of insulin has been proven safe and effective as IV administration of insulin. In selected cases with good outpatient follow-up, treatment of DKA with intermittent bolus dosing of regular insulin by the subcutaneous or intramuscular route without admission has also been shown to be safe. Such a strategy requires a well-hydrated, mildly acidemic patient, well versed in disease management, who has excellent outpatient follow-up. Poor perfusion may hamper the absorption of intramuscular or subcutaneous insulin, resulting in erratic absorption, making IV infusion the route of choice in sicker DKA patients.[5] The current initial therapy of choice, as recommended by the ADA, is regular insulin infused at 0.1 units/kg/h up to 5 to 10 units/h, mixed with IV fluids.

Children with DKA pose additional management challenges. Whereas the general principles of fluid and electrolyte repletion in concert with insulin therapy remain the same, controversy exists about the dosing and administration of fluids and insulin because of concerns related to the risk of inducing cerebral edema in children with DKA. Despite concerns about this complication, it remains rare, with an overall incidence of 1% in pediatric DKA patients. Virtually all current evidence supporting the contention that higher doses of insulin and aggressive fluid resuscitation contribute to the development of cerebral edema has come from retrospective reviews and small case studies. A recently completed large prospective study of 1255 pediatric DKA patients showed a similar risk of cerebral edema irrespective of restrictive or permissive fluid resuscitation.[15] Similarly, retrospective reviews of a large number of children with DKA did not show any significant difference in the development of cerebral edema based on insulin infusion rates. The degree of acidosis or uremia seem to be the best individual predictors of cerebral edema, as opposed to any specific fluid or insulin regimen, and earlier concerns about fluid resuscitation causing cerebral edema may have been the result of sicker patients getting more fluids (e.g., confounding by indication, since sicker patients are more likely to develop cerebral edema). Cerebral edema has a significant mortality rate, and patients should be carefully monitored and receive mannitol at the earliest suspicion of cerebral edema.

Because the half-life of IV regular insulin is 3 to 10 minutes, insulin should be administered IV by infusion rather than repeated bolus. When the blood glucose concentration has dropped to 250 to 300 mg/dL,

adding dextrose to the IV fluids reduces the risk of iatrogenic hypoglycemia and rapid shifts in osmolarity. In patients with euglycemic DKA, dextrose should be added to the IV fluids at the start of insulin therapy.

Insulin resistance rarely occurs in diabetic patients and requires an increase in dosage for a satisfactory response. Resistance may be caused by obesity or accelerated insulin degradation.

Magnesium

Magnesium deficiency is a common problem in patients with DKA without renal disease. Both the initial pathophysiologic process and therapy for DKA induce profound magnesium diuresis. Magnesium deficiency may exacerbate vomiting and mental changes, promote recalcitrant hypokalemia and hypocalcemia, or induce fatal cardiac dysrhythmia. If there is a concern for hypomagnesemia, we recommend adding magnesium to the IV fluids, with the typical adult patient requiring 1 to 3 g for repletion.

Sodium Bicarbonate

In the past, sodium bicarbonate was recommended for severely acidemic patients (pH < 7.0). However, research has demonstrated worse outcomes for patients receiving bicarbonate, including exacerbation of electrolyte deficits such as hypokalemia, delaying clearing of ketosis, paradoxical worsening of cerebrospinal fluid (CSF) acidosis due to suppression of respiratory compensations, and preferential permeability of the blood-brain barrier to CO_2. Unless needed to stave off impending cardiac arrest in a severely acidemic patient, we do not recommend routine bicarbonate administration. If a severely acidemic patient requires endotracheal intubation, the use of a bolus of bicarbonate in the immediate pre-intubation period may reduce the risk of cardiovascular collapse from a precipitous decline in pH after induction during rapid-sequence intubation; this recommendation is based on expert opinion as opposed to any specific clinical trials.[18]

Complications

The precipitating causes of DKA may have associated morbidity and mortality rates equal to or worse than those of DKA itself. These include iatrogenic causes, infection, and myocardial infarction. Morbidity in DKA is largely iatrogenic—hypokalemia from inadequate potassium replacement, hypoglycemia from inadequate glucose monitoring, failure to replenish glucose in IV solutions when the serum glucose concentration drops below 250 to 300 mg/dL, alkalosis from overaggressive bicarbonate replacement, and pulmonary edema from overaggressive hydration.

The mortality in treated DKA is approximately 5% to 7%. The primary causes of death remain infection, especially pneumonia, arterial thromboses, and shock. The decrease in the mortality rate over the last several decades has demonstrated the importance of appropriate therapy. Cerebral edema remains a rare but important cause of morbidity and mortality in children with DKA.

Cerebral edema should be considered when the patient in DKA becomes altered or lapses into a coma after the reversal of acidosis. Cerebral edema generally occurs 6 to 10 hours after the initiation of therapy, often without warning signs, and the associated mortality rate is 90%.[15] Cerebral edema is less common in adults or children older than 5 years and appears to be most strongly associated with severity of illness (acidemia and azotemia), although subclinical cerebral edema in children is probably common. Furthermore, subclinical cerebral edema may precede or follow the onset of therapy, raising the question of whether it is caused by therapy or is simply a manifestation of the basic pathophysiologic mechanisms of DKA. The treatment of cerebral edema is largely supportive. No large clinical trials have identified effective treatment, although some authors recommend mannitol. Steroids have not been shown to be effective.

Diabetic Ketoacidosis Disposition

Most patients with DKA require hospital admission, often to the intensive care unit. The use of observation units to manage uncomplicated DKA in selected patients has been shown to be effective (see Chapter e6). All pregnant diabetic patients in DKA require admission and consultation with an endocrinologist and obstetrician specializing in the care of high-risk pregnancies. Some children (initial pH ≥ 7.35; bicarbonate ≥ 20 mEq/L) who can tolerate oral fluids after 3 or 4 hours of treatment may be discharged home with a reliable caregiver. Patients who have mild DKA may be treated as an outpatient if the patient or parent can understand discharge instructions and are able to return, underlying causes do not require inpatient therapy, and close follow-up is confirmed.

HYPERGLYCEMIC HYPEROSMOLAR STATE

Foundations

HHS represents a syndrome of acute diabetic decompensation characterized by marked hyperglycemia, hyperosmolarity, dehydration, and decreased mental function that may progress to frank coma. The terminology has changed recently from the former term *hyperglycemic hyperosmolar nonketotic coma* because some patients have mild degrees of ketosis, and coma is not universally present.[4,18] Ketoacidosis is generally minimal or absent, although metabolic acidosis from another source, such as lactic acidosis from sepsis or uremia from acute renal failure, may be present. Focal neurologic signs may be present, or there may be a global encephalopathy. DKA and HHS may occur together.

Pathophysiology

As with DKA, the pathophysiologic mechanisms of HHS vary with the particular patient. Because most patients with HHS are older adults, decreased renal clearance of glucose produced by the decline of renal function with age often contributes to the illness. Decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose. The hyperglycemia pulls fluid from the intracellular into the extracellular space, transiently maintaining adequate perfusion. Soon, however, this fluid is lost in a profound osmotic diuresis, limited finally by hypotension, decreased renal perfusion, and a subsequent drop in the GFR. The urine is extremely hypotonic, with a urine sodium concentration between 50 and 70 mEq/L, compared with 140 mEq/L in extracellular fluid. This hypotonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity. Often, the patient is unable to take in adequate fluids because of stroke, Alzheimer disease, or other diseases, greatly exacerbating the dehydration.

The reason for the absence of ketoacidosis in HHS is unknown. FFA levels are lower than in DKA, thus limiting the substrates needed to form ketones. The most likely reason for the blunted counterregulatory hormone release and lack of ketosis seems to be the continued secretion of tiny amounts of insulin that block ketogenesis.

HHS is a syndrome of severe dehydration that results from a sustained hyperglycemic diuresis in which the patient is unable to drink sufficient fluids to offset the urinary losses. The full-blown syndrome does not usually occur until volume depletion has progressed to the point of decreased urine output.

HHS is most common in geriatric patients with type 2 diabetes but has been reported in children with type 1 diabetes. HHS may occur in

patients who do not have diabetes, especially after burns, parenteral hyperalimentation, peritoneal dialysis, or hemodialysis.

Clinical Features

The prodrome of HHS is significantly longer than that of DKA. Clinically, extreme dehydration, hyperosmolarity, volume depletion, and CNS findings predominate. If they are awake, patients may complain of fever, thirst, polyuria, or oliguria. Approximately 20% of patients have no known history of type 2 diabetes. The most common associated diseases are chronic renal insufficiency, GI bleeding, gram-negative pneumonia, and gram-negative sepsis. Approximately 85% of patients have underlying renal or cardiac impairment as a predisposing factor. Arterial and venous thromboses are common and often complicate the picture.

The patient often exhibits orthostatic hypotension or frank hypotension, tachycardia, and fever, with signs of marked dehydration. The depression of the sensorium correlates directly with the degree and rate of development of hyperosmolarity. Some patients have a normal mental status. Neurologic issues are common in HHS. Although a decreased level of consciousness is the most common neurologic finding, seizures, stroke syndromes, and movement disorders have been reported in various case series. Whether HHS is the cause or result of these disorders is unclear, and there is no current evidence to recommend the prophylactic use of antiepileptics or antithrombotic agents in HHS patients.

Differential Diagnoses

The differential diagnosis of HHS is identical to that of DKA (Table 115.6). In addition, diabetic patients receiving chlorpropamide are subject to water intoxication with dilutional hyponatremia, which may be manifested as coma without acidosis that is clinically indistinguishable from HHS. The patient with HHS who has a sharply depressed sensorium may not be initially distinguishable from the patient with profound hypoglycemia. When the blood glucose concentration cannot be rapidly checked, the immediate administration of one ampule of $D_{50}W$ minimally worsens HHS and may be lifesaving for patients with hypoglycemia.

Diagnostic Testing

Laboratory findings usually reveal a blood glucose level above 600 mg/dL and serum osmolarity above 350 mOsm/L. The blood urea nitrogen concentration is invariably elevated. Although patients with HHS do not have ketoacidosis caused by diabetes, they may have a metabolic acidosis secondary to some combination of lactic acidosis, starvation ketosis, and retention of inorganic acids attributable to renal hypoperfusion.

The patient with HHS typically has a more profound electrolyte imbalance than the patient with DKA. Levels of potassium, magnesium, and phosphorus may seem initially high, even in the presence of a marked total deficit. In the absence of acidemia, however, the discrepancy between the initial electrolyte reading and body stores is less than that of DKA. Initial serum sodium readings are inaccurate because of hyperglycemia.

Management

The fluid, electrolyte, and insulin regimens for the initial resuscitation in HHS are subject to the same controversies as the therapies for DKA (see Box 115.1). There have been varying recommendations about which IV fluids to administer, generally based on calculations of water deficits. There have been no well-done randomized trials comparing isotonic versus hypotonic fluid resuscitation; isotonic crystalloid is recommended in the volume-depleted patient. Cerebral edema has been noted in isolated case reports in adults, especially with glucose levels above 700 mg/dL. An association between IV fluid resuscitation and cerebral edema has not been shown in the literature; previous reports of this association may be due to the confounder that sicker patients often receive more aggressive fluid resuscitation.

Intravenous Fluids

For patients in hypovolemic shock, an initial IV fluid infusion is given as rapidly as possible. Glucose should be added to resuscitation fluids when the blood glucose level drops below 300 mg/dL. Because many HHS patients are older adults with coexisting diseases, such as congestive heart failure and renal failure, noninvasive or invasive forms of hemodynamic monitoring may be required to guide fluid administration when there is clinical suspicion of pulmonary edema or volume overload.

Electrolytes

Measurement of serum electrolyte levels should be used to guide replacement in the HHS patient. In particular, because acidosis is generally less, potassium levels more accurately reflect total body stores than they do in DKA.

Insulin

The pathophysiologic mechanisms of HHS are different from those of DKA, and there is usually enough basal insulin function to prevent frank ketoacidosis. Therefore, a continuous IV insulin infusion is not required in these patients, as with DKA. However, there are times when

TABLE 115.6 Features Distinguishing Diabetic Ketoacidosis Versus Hyperglycemic Hyperosmolar State

DKA	HHS
• Typically type 1 diabetic patients • Metabolic acidosis present • Blood sugars typically >250 mg/dL, though occasionally can be lower (euglycemic DKA) • May have infection, trauma, myocardial ischemia as underlying triggers, or may be due to inadequate insulin administration • Associated with significant fluid deficits • Insulin and fluids required to correct • Occurs across the age spectrum (toddler to geriatric)	• Typically type 2 diabetic patients • Usually do not have metabolic acidosis as a result of glucose abnormality • Sugars typically markedly high (>500 mg/dL) • Infection most common underlying cause, but may have other etiologies (dehydration, ischemic event, etc.) • Associated with significant fluid deficits • While insulin and fluids may be given, treatment is directed at an underlying cause • Typically seen in geriatric population

DKA, Diabetic ketoacidosis; *HHS,* hyperglycemic hyperosmolar state.

the use of an IV insulin infusion may help lower the glucose concentration in a more controlled fashion, particularly in patients with very high glucose levels (>700 mg/dL) or those who are severely hypoperfused, in whom intramuscular or subcutaneous insulin absorption may be erratic. If an IV insulin infusion is used, it should be a rate similar to that for DKA (0.1 unit/kg/h).

Other Considerations

A search for the underlying precipitant of HHS should be pursued. Response to therapy should be followed in the manner described for patients in DKA. Phenytoin (Dilantin) is contraindicated for the seizures of HHS because it is often ineffective and may impair endogenous insulin release.[5] Admitted patients should be given low-dose subcutaneous heparin to lessen the risk of thrombosis, which is increased by the volume depletion, hyperviscosity, hypotension, and inactivity associated with HHS.

Acute Complications

Reasons for high morbidity and mortality rates are not always clear, but many patients with HHS are older adults who have underlying cardiac and renal disease. Pediatric HHS differs from adult HHS in that children have a much higher incidence of fatal cerebral edema. Other causes of morbidity and mortality are similar to those described for DKA. The mortality rate of treated HHS patients has been 40% to 70% in the past but now ranges from 8% to 25%.[1,22]

Hyperglycemic Hyperosmolar State Disposition

In general, patients with HHS require hospitalization for IV hydration, glucose control, and evaluation of precipitating and complicating conditions.

DIABETES IN PREGNANCY

Before the discovery of insulin in 1922, diabetes in pregnancy was associated with a fetal death rate of 60% to 72% and maternal morbidity of approximately 30%.[7] In 1977, a linear relationship between glycemic control and perinatal mortality was discovered. Strict metabolic control is now a goal in all diabetic pregnancies.[6]

Pregnant patients are at particular risk from DKA due to the impact on both maternal and fetal health. For a variety of reasons, pregnant women are predisposed to glucose intolerance and excess ketone production. Although uncommon, DKA may reduce fetal oxygen delivery and cause perinatal asphyxia. Severe ketoacidosis is associated with a 50% to 90% fetal mortality rate due to hypoperfusion of the placenta.[18] Cognitive deficits in the offspring have been associated with maternal ketonuria from any cause. Hypoglycemia is common in pregnancy, in part because of intensive insulin treatment to maintain euglycemia. The effects of hypoglycemia on the fetus are unclear.

HYPOGLYCEMIA

Foundations

Hypoglycemia is a common problem in patients with type 1 diabetes, especially if tight glycemic control is practiced; it is the most dangerous, acute complication of diabetes. The estimated incidence of hypoglycemia in diabetic patients is 9 to 120 episodes/100 patient-years. As significant efforts continue to keep fasting and postprandial glucose concentrations within the normal range, the incidence of hypoglycemia may increase. The most common cause of coma associated with diabetes is an excess of administered insulin with respect to glucose intake.[22] Severe hypoglycemia is usually associated with blood glucose levels below 40 to 50 mg/dL and impaired cognitive function.

Protection against hypoglycemia is normally provided by the cessation of insulin release and mobilization of counterregulatory hormones, which increase hepatic glucose production and decrease glucose use. Diabetic patients using insulin are vulnerable to hypoglycemia because of insulin excess and failure of the counterregulatory system.

Hypoglycemia has many causes, such as missing a meal (decreased intake), increased energy output (exercise), and increased insulin dosage. It can also occur in the absence of any precipitant. Oral hypoglycemic agents have also been implicated in causing hypoglycemia, both when taken therapeutically and as an agent of overdose.

Hypoglycemia without warning symptoms, or hypoglycemia unawareness, is a dangerous complication of type 1 diabetes and is probably caused by previous exposure to low blood glucose concentrations because even a single hypoglycemic episode can reduce neurohumoral counterregulatory responses to subsequent episodes. Other factors associated with recurrent hypoglycemic attacks include overaggressive or intensified insulin therapy, longer history of diabetes, autonomic neuropathy, and decreased epinephrine secretion or sensitivity.

The Somogyi phenomenon is a common problem associated with iatrogenic hypoglycemia in type 1 diabetic patients. Excessive insulin dosing results in an unrecognized hypoglycemic episode that usually occurs in the early morning while the patient is sleeping. The counterregulatory hormone response produces rebound hyperglycemia, evident when the patient awakens. Often, the patient and physician interpret this hyperglycemia as an indication to increase the insulin dosage, which exacerbates the problem. Instead, the insulin dosage should be lowered or the timing changed.

Clinical Features

Symptomatic hypoglycemia occurs in most adults below a blood glucose level of 40 to 50 mg/dL. The rate at which the glucose level decreases, however, and the patient's age, gender, size, overall health, and previous hypoglycemic reactions contribute to symptom development. Signs and symptoms of hypoglycemia are caused by excessive secretion of epinephrine and CNS dysfunction; these include sweating, nervousness, tremor, tachycardia, hunger, and neurologic symptoms, ranging from bizarre behavior and confusion to seizures and coma. In patients with hypoglycemia unawareness, the prodrome to marked hypoglycemia may be minimal or absent, and these individuals may rapidly become unarousable. They may have a seizure or show focal neurologic signs, which resolve with glucose administration.

Differential Diagnoses

Hypoglycemia in the nondiabetic patient may be classified as postprandial or fasting. The most common cause of postprandial hypoglycemia is alimentary hyperinsulinism, such as that seen in patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy. Fasting hypoglycemia is caused when there is an imbalance between glucose production and use. The causes of inadequate glucose production include hormone deficiencies, enzyme defects, substrate deficiencies, severe liver disease, and drugs. Causes of overuse of glucose include the presence of an insulinoma, exogenous insulin, sulfonylureas, drugs, endotoxic shock, extrapancreatic tumors, and a variety of enzyme deficiencies.

Diagnostic Testing

The cardinal laboratory test for hypoglycemia determines the blood glucose concentration. It should be performed, if possible, before therapy is begun. As noted, POC fingerstick testing helpful in permitting rapid, reasonably accurate blood glucose level estimates before therapy.

Laboratory testing should address any suggested cause of the hypoglycemia, such as ethanol, other drug ingestion, sepsis, or acute kidney

injury causing decreased clearance of medications. If factitious hypoglycemia is suggested, testing for insulin antibodies or low levels of C peptide may be helpful. A patient who is surreptitiously administering exogenous insulin will have normal to low levels of C peptide and markedly elevated insulin levels.

Management

In alert patients with mild symptoms, oral consumption of sugar-containing foods or beverages is often adequate. In other patients, after blood is drawn for glucose determination, one to three ampules of $D_{50}W$ is administered IV while the patient's airway, breathing, and circulation are assessed and maintained. Augmentation of the blood glucose level by administration of an ampule of $D_{50}W$ may range from less than 40 mg/dL to more than 350 mg/dL. If alcohol use disorder is suggested, we recommend that thiamine be administered as well. In children younger than 8 years, providers should use $D_{25}W$ or $D_{10}W$. $D_{25}W$ may be prepared by diluting $D_{50}W$ 1:1 with sterile water. The dose is 0.5 to 1 g/kg body weight or 2 to 4 mL/kg when using $D_{25}W$. With recent shortages of $D_{50}W$, many emergency medical services (EMS) agencies and some hospitals have moved to the use of $D_{10}W$, giving boluses of up to 250 mL to achieve a similar glucose load to an ampule of $D_{50}W$.

If IV access cannot be rapidly obtained, 1 to 2 mg of glucagon may be given intramuscularly or subcutaneously. The onset of action is 10 to 20 minutes, and a peak response occurs in 30 to 60 minutes. It may be repeated as needed. Glucagon may also be administered IV; 1 mg has an effect similar to that of one ampule of $D_{50}W$. Glucagon is ineffective in causes of hypoglycemia resulting from absent glycogen, notably alcohol-induced hypoglycemia.

Families of type 1 diabetic patients are often taught to administer glucagon intramuscularly at home. Of the families so instructed, only 9% to 42% inject the glucagon when indicated. Intranasal glucagon has not been widely used. All patients with severe hypoglycemic reactions require aspiration and seizure precautions. Although the response to IV administration of glucose is generally rapid, older patients may require several days for complete recovery.

Treatment of hypoglycemia secondary to oral hypoglycemic agents depends on the agent. Metformin and the thiazolidinediones rarely cause significant hypoglycemia, whereas sulfonylureas, which are insulin secretagogues, can cause hypoglycemia. Sulfonylurea oral hypoglycemic agents pose particular problems because the hypoglycemia they induce tends to be prolonged and severe. Patients with an overdose of sulfonylurea hypoglycemic agents should be observed for a period of 24 hours if hypoglycemia recurs in the ED after management of the initial episode. Patients at risk for hypoglycemia from oral sulfonylureas include patients with impaired renal function, pediatric patients, and patients who are naïve to hypoglycemic agents. Although symptoms may occur after an overdose, several case reports in patients (e.g., with renal failure and pediatric patients) have described refractory hypoglycemia after ingestion of a single pill. One case series of pediatric patients presenting with sulfonylurea ingestion who were initially euglycemic demonstrated an average time to hypoglycemia of 8 hours.[22] However, in some patients, the onset of symptoms was delayed for up to 18 hours. As a result, we recommend 24 hours of observation for patients with known or suspected ingestion of hypoglycemic agents.

A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide, a somatostatin analog. Several case series have described the use of octreotide in adult and pediatric patients suffering from sulfonylurea-induced hypoglycemia, frequently reporting successful results, with a significant decrease in the number of episodes of recurrent hypoglycemia. A randomized clinical trial has concluded that patients receiving octreotide had a decreased glucose supplementation requirement.[22] No single set protocol for use has been described; however, typical adult doses have ranged from 50 to 100 μg IV or subcutaneously every 12 hours, with pediatric dosages of 0.1 μg/kg IV or subcutaneously. Although experience thus far with octreotide has been positive, it does not obviate the need for prolonged observation and serial glucose level measurements.

Disposition

Type 1 diabetic patients with brief episodes of hypoglycemia uncomplicated by other conditions may be discharged from the ED if a cause of the hypoglycemia can be identified and corrected by instruction or medication. All patients should be given a meal before discharge to ensure their ability to tolerate oral feedings and to begin to replenish glycogen stores in glycogen-deficient patients. Patients who are discharged should receive short-term follow-up for ongoing evaluation. Patients with hypoglycemia caused by long-acting sulfonylurea medications should be observed in the hospital if they have recurrent hypoglycemia after a period of observation in the ED. Other agents, such as metformin, do not typically produce hypoglycemia, although they may have other issues, such as lactic acidosis, that may require admission.

The determination of inpatient (and if inpatient, type of bed, and monitoring required) versus outpatient evaluation of hypoglycemia in a nondiabetic patient should be based on the suggested cause and nature of the episode (i.e., factors such as severity, persistence, and recurrence).

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 115: QUESTIONS AND ANSWERS

1. Which of the following statements regarding patients with impaired glucose tolerance is true?
- **a.** Spontaneous reversion to normal glucose tolerance is rare.
- **b.** The condition is associated with fewer complications than diabetes mellitus.
- **c.** The rate of decompensation to diabetes mellitus is greater than 10%/year.
- **d.** There is a predisposition to ketosis.

Answer: b. Patients with impaired glucose tolerance have a glucose level between normal and diabetic. They are at increased risk of cardiovascular disease and development of diabetes (1% to 5%/year), but it is not associated with the same degree of complications as with true diabetes. Many patients spontaneously develop normal glucose levels.

2. What percentage of adults with type 2 diabetes are obese?
- **a.** 40%
- **b.** 60%
- **c.** 80%
- **d.** 100%

Answer: d. Nonobese patients form a subgroup with a different disease, more similar to type 1 diabetes. Young people with maturity-onset diabetes often have an autosomal dominant inheritance, are nonobese, and have a relatively mild disease course.

3. A 56-year-old man with a 10-year history of type 2 diabetes and poor glucose control (HbA_{1c} = 10.7%) complains of constant burning pain in both feet. Which agent would be most appropriate to start in this patient for the initial management of his symptoms?
- **a.** Aspirin, 325 mg PO daily
- **b.** Naproxen, 500 mg bid
- **c.** Oxycodone/acetaminophen, 5/325 mg qid
- **d.** Pregabalin, 600 mg daily

Answer: d. Pregabalin in a dose of 600 mg daily gives pain relief in approximately 50% of patients with diabetic neuropathy. Duloxetine, 60 mg daily, achieves similar results. Gabapentin, 300 mg once a day up to tid, and amitriptyline, 25 mg daily, provide pain relief in approximately 33% of patients.

4. A 27-year-old juvenile-onset diabetic is brought by emergency medical services (EMS) for a hypoglycemic coma. Fingerstick glucose level is 30 mg/dL. The paramedics were not able to obtain intravenous (IV) access, and two immediate attempts at IV cannulation failed in the emergency department (ED). What should be the next step in the patient's management?
- **a.** Albuterol, 2.5 mg nebulized
- **b.** Central venous catheter placement, then $D_{50}W$ IV
- **c.** Epinephrine, 1 mg IV
- **d.** Glucagon, 2 mg intramuscularly

Answer: d. Intravenous dextrose (25 to 75 g for adults, 0.5to 1 g/kg for children) is preferable but, if unable to obtain IV access, administer glucagon, 1 or 2 mg intramuscularly (IM) or subcutaneously (SC; 0.025 to 0.1 mg/kg IM or SC in children). The onset of action is 10 to 20 minutes. It is ineffective in cases of glycogen absence, such as alcohol-induced hypoglycemia.

5. A 33-year-old juvenile-onset, insulin-dependent diabetic suddenly faints without prodrome or warning while walking through the ED. Relatives report that diabetes is his only past history. Which of the following findings is most likely?
- **a.** Autonomic neuropathy on later orthostatic testing
- **b.** Fingerstick glucose 27 mg/dL
- **c.** Hemoccult-positive stool
- **d.** Positive enzyme-linked immunosorbent assay (ELISA) D-dimer

Answer: b. Hypoglycemia without warning, or hypoglycemia unawareness, is a complication of type 1 diabetes caused by previous hypoglycemic episodes. A single hypoglycemic episode may blunt neurohormonal counterregulatory responses to later hypoglycemic episodes. Risk factors are overaggressive insulin therapy, longer history of diabetes, and autonomic neuropathy, which usually causes orthostasis on first standing or after being upright in a static position. These patients may become abruptly unarousable without warning.

CHAPTER 115: QUESTIONS AND ANSWERS—cont'd.

6. A 47-year-old man presents with hypoglycemia. He is a known type 2 diabetic on glyburide. Fingerstick glucose is 27 mg/dL. Twenty minutes after two ampules (50 g) of dextrose, his glucose level is 29 mg/dL. Which of the following agents is indicated?

a. Adenosine
b. Epinephrine
c. Hydrocortisone
d. Octreotide

Answer: d. A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide (a somatostatin analog). Sulfonylureas are insulin secretagogues.

7. What is the most important determinant of mental status in a patient with diabetic ketoacidosis (DKA)?

a. Acidemia
b. Calcium level
c. Glucose level
d. Osmolarity

Answer: d. The hyperosmolarity produced by dehydration and hyperglycemia is the most important determinant of mental status during an episode of DKA.

Rhabdomyolysis

Brit Long and Alex Koyfman

KEY CONCEPTS

- Rhabdomyolysis is a process wherein striated muscle cells break down, resulting in the release of creatine kinase, potassium, calcium, phosphate, and uric acid.
- Rhabdomyolysis is associated with a variety of causes including overexertion, extreme body temperature changes, ischemia, infection, immobility, drugs, toxins, endocrine disease, autoimmune reactions, trauma, and genetic conditions.
- The classic presentation of rhabdomyolysis is myalgia, weakness, and dark-colored urine. However, the absence of this triad does not exclude the condition. Clinicians should suspect the disease in patients with risk factors, dark urine, and elevated creatine kinase.
- Diagnosis of rhabdomyolysis is based on elevated creatine kinase more than five times the upper limit of normal (CK > 1000 U/L).
- Although most patients recover without complications, severe rhabdomyolysis is associated with renal failure, electrolyte disorders such as hyperkalemia, compartment syndrome, and disseminated intravascular coagulation.
- Rhabdomyolysis management includes treating the underlying etiology and administering intravenous (IV) hydration with a goal urine output of 2 to 3 mL/kg/hour and euvolemia. Mannitol, sodium bicarbonate, and loop diuretics should not be used routinely in management.
- Although most patients require admission for further evaluation and management, patients with normal vital signs, normal laboratory assessment, normal oral intake, clear etiology, and follow-up may be appropriate for discharge.

FOUNDATIONS

Background and Importance

Rhabdomyolysis is the result of damage to striated muscle, leading to release of creatine kinase, aspartate transaminase, lactate dehydrogenase, aldolase, the heme pigment myoglobin, and electrolytes. Patients most commonly present with diffuse muscle pain, weakness, and dark urine, which is caused by renal excretion of myoglobin pigment. Although most cases follow a benign course, patients with severe disease may experience renal failure, electrolyte derangements, compartment syndrome, or disseminated intravascular coagulation.

Anatomy, Physiology, and Pathophysiology

Skeletal muscle is 80% water and 20% protein, accounting for about half of the total body protein stores. Muscle cells require a significant amount of ATP and oxygen for appropriate cellular function, both at rest and with activity. Myoglobin delivers and releases oxygen to active skeletal muscle. Potassium, sodium, and calcium are strictly regulated by ATP-dependent cellular pumps, including sodium-potassium–adenosine triphosphatase (Na^+,K^+-ATPase) and an active calcium exchanger (Ca^{2+}-ATPase pump) (Fig. 116.1). Under normal physiologic conditions, the concentration of free ionized calcium in the extracellular space is approximately 10,000 times greater than that in the intracellular space. Because extracellular calcium functions as an intracellular regulator and results in a sizeable electrochemical force on Ca^{2+}, even minor changes in the permeability of the plasma membrane to calcium will produce significant fluctuations in the cytosolic concentration, with potentially unfavorable consequences for the integrity of the cell.

Rhabdomyolysis involves four pathophysiologic processes (Fig. 116.2):

1. Impairment of the muscle's production or use of ATP at the cellular level. ATP concentrations within the cell fall; energy-dependent mechanisms falter, including Na^+,K^+-ATPase pumps, leading to disruption of chemical gradients, sarcolemma and cell membrane compromise, and cell destruction.
2. Disruption in the delivery of oxygen, glucose, and other nutrients to skeletal muscle.
3. Increased metabolic demands beyond the ability of the organism to deliver oxygen and nutrients.
4. Direct myocyte damage.

The pathogenesis of rhabdomyolysis follows a final common pathway—increased cytoplasmic calcium concentration from cell membrane damage and ATP depletion. Calcium activates proteases, phospholipases, and other proteolytic enzymes, which result in further ATP depletion, direct intracellular toxicity, and increased cellular membrane permeability. Increased intracellular calcium causes skeletal myocyte destruction and the release of toxic components into the extracellular and vascular spaces. Damage to adjacent capillaries causes local edema, increased local pressures, and tissue ischemia, resulting in further damage and energy depletion. Leukocytes adhere to damaged tissue and release radical oxygen species and enzymes that result in further cell damage. Ischemic etiologies of rhabdomyolysis may include reperfusion injury to myocytes.

Table 116.1 lists the various risk factors and causes of rhabdomyolysis.[1-4]

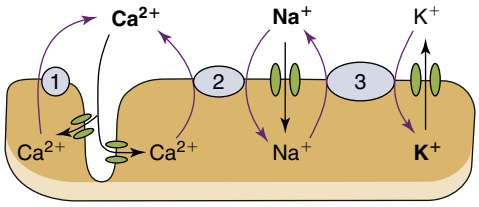
CLINICAL FEATURES

Rhabdomyolysis presents with a wide range of signs and symptoms. Patients may be asymptomatic or seriously ill with evidence of life-threatening complications, such as acute renal failure, disseminated intravascular coagulation, and dysrhythmias. In most patients, rhabdomyolysis presents in a mild form. Diagnosis in patients with a traumatic etiology is typically straightforward, but the diagnosis is often more challenging when rhabdomyolysis results from nontraumatic etiologies, or the patient is not able to provide a reliable history or cooperate with physical examination.

The classic presentation is localized muscle pain, stiffness, swelling, and tenderness, combined with dark-colored urine. However, this

combination of factors is found together in less than 10% of patients. Localized muscle pain is the most common symptom (80%), followed by localized muscle weakness and swelling. The thighs are most commonly involved, followed by the calves and back. Other symptoms may include fever, palpitations, tachycardia, nausea and vomiting, agitation, focal sensory deficits, pain with passive range of motion, skin changes, and decreased urine output. The finding of dark urine depends on the severity of the injury and the patient's muscle mass, urine concentration, and baseline renal function. The absence of visibly dark urine does not exclude the diagnosis of rhabdomyolysis.

Children are more diagnostically challenging. Most pediatric patients with rhabdomyolysis experience muscle pain, but fewer than 5% present with dark urine. Children also more commonly present with symptoms suggestive of a viral syndrome.



1 = ATP-dependent Ca^{2+} pump
2 = Na^{+}-Ca^{2+} exchanger (3:1)
3 = Na^{+}, K^{+}-ATPase pump (3:2)

Fig. 116.1 Normal Membrane Ionic Pump Function of Skeletal Muscle Cell. When the ATP supply is impaired, the intracellular sodium concentration increases, reversing the function of the Na^{+}-Ca^{2+} exchanger, with a subsequent increase in the intracellular calcium level.

A focused history provides important information regarding the symptoms of rhabdomyolysis, risk factors for the disease (see Table 116.1), prior history of the condition, or a family history consistent with rhabdomyolysis (due to inherited myopathies), which is associated with recurrent episodes of rhabdomyolysis. Other important historical points include changes in urine output and color, oral intake, and medication or illicit substance use. In patients with severe trauma or altered mental status, history from first responders, witnesses, or family members can assist.

Complications

Early Complications

Compartment Syndrome. Most skeletal muscles are encased in compartments formed by bones, fascia, and other structures. The massive influx of calcium and sodium in rhabdomyolysis leads to the accumulation of large amounts of extracellular fluid in myocytes, causing local edema and raised pressure within the compartments. Note that rhabdomyolysis can therefore be the cause and result of compartment syndrome.[5]

Electrolyte Disorders and Acidosis. Potassium released from damaged muscle may lead to hyperkalemia. Over 98% of the body's potassium is found in the intracellular space, and 60% to 70% of the total cellular mass of the human body consists of skeletal muscle. Therefore, damage to as little as 100 g of muscle may increase the serum

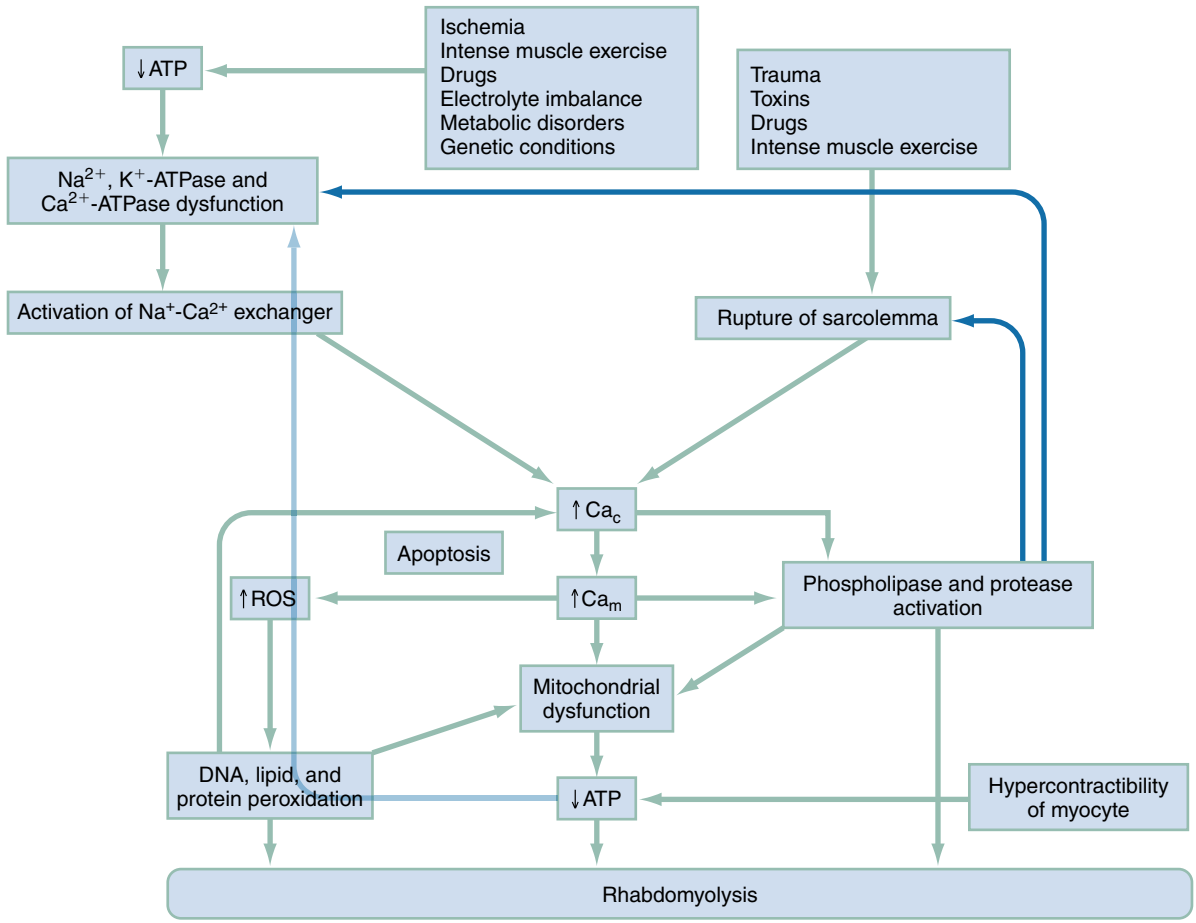


Fig. 116.2 Pathophysiology of rhabdomyolysis. Ca_c, cytosolic [Ca]; Ca_m, mitochondrial [Ca].

TABLE 116.1 Risk Factors and Etiologies of Rhabdomyolysis[1-4]

Exertion	Intense exercise, seizure, status asthmaticus, sickle cell crisis, alcohol withdrawal
Trauma or compression	Motor vehicle accidents, prolonged immobilization, crush syndrome, electrical injury, burns
Extreme changes in body temperature	Hyperthermia, hypothermia, serotonin syndrome, malignant hyperthermia, neuroleptic malignant syndrome
Electrolyte alterations	Hypokalemia, hypophosphatemia, hypocalcemia, hyponatremia, hypernatremia, hyperglycemia
Muscle ischemia/hypoxia	Arterial occlusion due to embolus, thrombus, or during vascular surgery
Infections	Sepsis, *Salmonella, Streptococcus pyogenes, Staphylococcus aureus, Clostridium* species, *Legionella*, influenza, coxsackie, Epstein-Barr virus, herpes virus, HIV
Drugs/toxins	Statins, anti-lipid agents (ezetimibe, clofibrate, gemfibrozil), proton pump inhibitors, psychiatric medications (SSRIs, SNRIs, TCAs, benzodiazepines, barbiturates, phenothiazines, lithium), alcohol, cocaine, opiates, amphetamines, LSD, phencyclidine, synthetic cannabinoids, bath salts, antihistamines, propofol, arsenic, carbon monoxide, azathioprine, quinidine, salicylates, succinylcholine, thiazides, vasopressin, pentamidine, terbutaline, theophylline
Endocrine	Thyroid abnormalities, hyperaldosteronism
Autoimmune	Dermatomyositis, polymyositis
Genetic	Krebs cycle disorders, G6PD deficiency, lipid metabolism disorders, mitochondrial chain disorders, muscular dystrophies
Foodborne	Ingestion of burbot, eel, pike, crayfish, buffalo fish, and other fish/crustacean species

HIV, Human immunodeficiency virus; *SSRI*, selective serotonin reuptake inhibitors; *SNRI*, serotonin norepinephrine reuptake inhibitors; *TCA*, tricyclic antidepressants; *LSD*, lysergic acid diethylamide; *G6PD*, glucose-6-phosphate dehydrogenase.
Data from Nguyen KA, Li L, Lu D, et al. A comprehensive review and meta-analysis of risk factors for statin-induced myopathy. *Eur J Clin Pharmacol*. 2018;74(9):1099-1109; Mousavi SR, Vahabzadeh M, Mahdizadeh A, et al. Rhabdomyolysis in 114 patients with acute poisonings. *J Res Med Sci*. 2015;20:239-243; Durand D, Delgado LL, de la Parra-Pellot DM, et al. Psychosis and severe rhabdomyolysis associated with synthetic cannabinoid use. *Clin Schizophr Relat Psychoses*. 2015;8:205-208; Fadila MF, Wool KJ. Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. *N Am J Med Sci*. 2015;7:122-124.

potassium by 1.0 mEq/L. Acidemia contributes to hyperkalemia and can be exacerbated by oliguria.

Rhabdomyolysis-related fluid sequestration or myoglobin-induced kidney injury reduces the kidney's ability to excrete acid. Metabolic acidosis is also caused by the release of organic acids (e.g., lactic acid, uric acid, and sulfur-containing proteins).

The disruption of muscle cells releases phosphoric components into circulation, and when massive, this can lead to hyperphosphatemia and ectopic calcification, typically depositing in necrotic tissue. In case of rhabdomyolysis with severe, extensive muscle damage, calcium phosphate crystal deposition in damaged muscle can lead to early-phase hypocalcemia, with potentially fatal dysrhythmias. This is rare and reported only in case reports. Hyperkalemia coupled with hypocalcemia predisposes patients to malignant dysrhythmias. Furthermore, excessively high phosphate levels shut down the 1α-hydroxylase enzyme of the kidneys, decreasing production of the active form of vitamin D, further contributing to early hypocalcemia. Late in the course of rhabdomyolysis, calcium initially deposited in the cytoplasm of necrotic muscle cells can reenter the plasma, resulting in late hypercalcemia.

Hypovolemia. In rhabdomyolysis, fluid moves from intravascular compartments into damaged muscle. In cases of massive muscle crush or electrical injury, this fluid shift may exceed 15 liters, causing profound intravascular volume depletion.

Hepatic laboratory abnormalities. Reversible elevations in aspartate transaminase (AST) levels may occur with rhabdomyolysis, possibly caused by myocyte release of proteases. The level of AST elevation is correlated with the severity of CK elevation in patients with rhabdomyolysis.[6] However, AST elevations may also be of skeletal muscle origin. Preexisting hepatic dysfunction may potentiate statin-induced rhabdomyolysis.[2] Rhabdomyolysis is not typically associated with abnormalities of other liver function tests or synthetic function such as alanine aminotransferase, prothrombin time, and albumin.

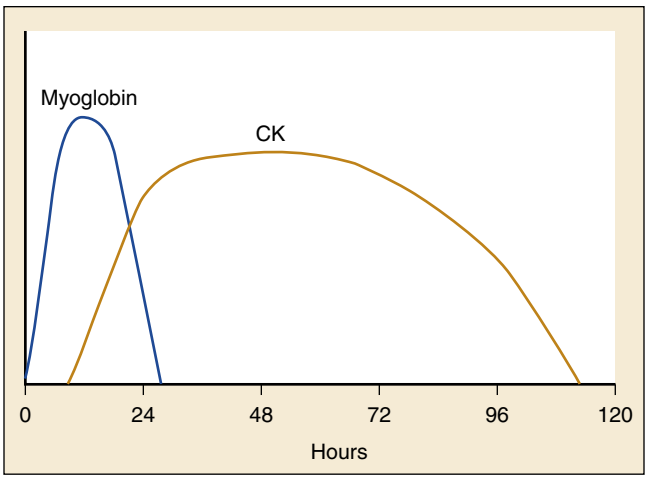


Fig. 116.3 Variations of Myoglobin and Creatine Kinase (CK) Levels During the Course of Rhabdomyolysis. Myoglobin is the first enzyme that increases but, because of its rapid clearance from the plasma, it returns to normal levels within the first 24 hours after the onset of symptoms. The CK level increases a few hours later than myoglobin, reaches its peak value within the first 24 hours, and remains at these levels for 3 days. CK is considered to be a more useful marker for the diagnosis and assessment of the severity of muscle injury because of its delayed clearance from the plasma.

Late Complications

Myoglobin-Induced Acute Kidney Injury. Experimental evidence suggests that myoglobinuric acute renal failure is caused by myoglobin cast formation in the distal convoluted tubules, the direct cytotoxic action of myoglobin on the epithelial cells of the proximal convoluted tubules, and ischemia from intrarenal vasoconstriction (Fig. 116.3).

Myoglobin concentrates along the renal tubules and precipitates in acidic urine with uric acid to form obstructive casts. This

is enhanced by volume depletion and renal vasoconstriction, which reduce blood flow and the glomerular filtration rate (GFR), promoting the accumulation of necrotic epithelial cells into tubular casts. Tubule obstruction occurs at the level of the distal tubule, whereas direct cytotoxicity occurs mainly in the proximal tubules. There remains some controversy about the exact mechanism of renal dysfunction in rhabdomyolysis; some experts believe that casts and tubular obstruction are not the cause, but rather the consequence, of poor tubular clearance.

When the concentration of myoglobin filtered at the glomerulus exceeds normal levels, tubular cells at the proximal convoluted tubule increase their resorptive capacity to limit the excretion of myoglobin into the urine, protecting the kidney from its nephrotoxic effects. At a urine pH of 5.6 or lower, myoglobin, an iron-containing heme protein, dissociates into free iron (Fe), ferrihemate (Fe-heme complex), and globin inside the proximal tubular epithelial cell. Oxidation of ferrous oxide in the Fe-heme complex in combination with free iron reaction with H_2O_2 produces free radicals which may result in nephrotoxicity. Free iron may also act as a free radical, although its role in rhabdomyolysis-induced renal injury is unclear. Myoglobin itself has been shown to exhibit peroxidase-like enzyme activity. Ferrihemate causes direct nephrotoxic effects along with the resultant increased oxidative stress within the tubular epithelial cell. More recent evidence has argued against free iron's role in oxidative stress–induced renal injury, instead emphasizing the role of ferrihemate-induced lipid peroxidation in cell injury.

Fluid shifts and renal dysfunction lead to activation of the renin-angiotensin-aldosterone system and production of vasoconstricting molecules such as endothelin 1 and vasopressin. There is also decreased production of vasodilatory prostaglandins. Nitric oxide (NO), a potent vasodilator agent, assists with the maintenance of renal blood flow. Myoglobin released from damaged muscle may act as a NO scavenger in the renal microcirculation, itself reduced by NO buffering against oxidant injury. When increased myoglobin concentrations overcome NO, the kidney is deprived of the ability to autoregulate blood flow and maintain adequate perfusion. Thus, myoglobin is free to cause damage in proximal tubular epithelial cells, specifically under acidotic conditions. Other locally stimulated vascular mediators, including thromboxane A_2, tumor necrosis factor alpha, and F_2-isoprostanes, also reduce renal blood flow and cause oxidant injury.

Disseminated Intravascular Coagulation. Extensive muscle damage may result in the release of prothrombotic substances, mainly thromboplastin, which activate the coagulation cascade. Although rare, this can lead to the formation of thrombi in the capillary tufts of the glomeruli and disseminated intravascular coagulation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rhabdomyolysis includes conditions that may present with influenza-like symptoms, myalgias, extremity pain, or urinary changes. Such conditions include heatstroke, sepsis, infective endocarditis, myocarditis, spinal epidural abscess, pyomyositis, toxic ingestion or carbon monoxide exposure, thyroid abnormalities, compartment syndrome, vascular injury, and orthopedic injuries.

Red or dark urine can be seen with hemoglobinuria, urolithiasis, porphyria, ingestion of specific foods (blackberries, beets, rhubarb, food coloring) and numerous medications, including laxatives, rifampin, doxorubicin, chloroquine, hydroxocobalamin, and deferoxamine.

Notably, many of the conditions that mimic rhabdomyolysis can also cause rhabdomyolysis (e.g., heatstroke, bacterial or viral infection, and toxic ingestions).

DIAGNOSTIC TESTING

Serum Creatine Kinase

The definitive diagnosis of rhabdomyolysis is made by serologic testing for creatine kinase (CK). CK functions as an energy reservoir for ATP: creatine + ATP = creatine kinase + ADP (adenosine diphosphate). CK has a half-life of 1.5 days; it increases in the first 12 hours after injury, peaks during the first three days, and normalizes at approximately five days. A CK level five times the upper limit of normal (≈1000 U/L), without an alternative cause, confirms the diagnosis.

Serum and Urine Myoglobin

Myoglobin is a dark-red protein composed of globin and a molecule of heme. It supplies oxygen to skeletal and cardiac muscle in times of need and is renally excreted. It is initially filtered at the glomerulus and reabsorbed in the tubules, where it is broken down into its component parts, globin and heme. As with all other low-molecular-weight proteins, a small amount is excreted in the urine. The normal concentration of myoglobin in the urine is less than 10 μg/L. A normal serum concentration of myoglobin is less than 100 μg/L.

During rhabdomyolysis, myoglobin released by damaged muscle is increasingly filtered at the glomerulus. This leads to an initial increased resorptive capacity by glomerular and tubular epithelial cells, developed presumably as a protective response to increased filtered myoglobin. When serum myoglobin concentrations exceed 0.3 mg/L and the renal threshold of 1.0 mg/dL is met, this resorptive capacity is overwhelmed, and excess myoglobin appears in the urine. This myoglobin is detected by urine dipstick as positive for blood with microscopic urine analysis showing few, or no RBCs (Table 116.2).

In the past, the diagnosis of rhabdomyolysis was made by measuring serum myoglobin; however, myoglobin has a serum half-life of 1 to 3 hours, is completely absent after 24 hours, and normal levels depend upon the patient's muscle mass. These factors make serum myoglobin an unreliable diagnostic test. This is also true of urine myoglobin levels, which depend on the degree of muscle injury, volume status of the patient, and urinary flow rate. A well-hydrated patient with normal renal function can rapidly clear myoglobin from the body. The absence of plasma or urine myoglobin does not rule out rhabdomyolysis (Fig. 116.4).

Urine Dipstick and Urinalysis

Myoglobinuria causes a false-positive result for blood in urine dipstick testing. The drawback of this test is its inability to distinguish among heme compounds. In myoglobinuria, microscopic analysis will show few if any red blood cells, thereby distinguishing between hemoglobin and hemoglobin-rich red blood cells (from hemolysis or hematuria). Myoglobinuria, in combination with an elevated plasma CK level, confirms rhabdomyolysis. At plasma concentrations above 100 to 300 mg/L, macroscopic myoglobinuria manifests as tea-colored urine.

The urine dipstick test or urinalysis result is generally acidic in rhabdomyolysis, which plays a role in cast and uric acid crystal formation and pathologic myoglobin metabolism in tubular epithelial cells. Proteinuria may be noted because of the detection of the globin component of myoglobin. Urine sediment will show myoglobin casts and dead epithelial cells (see Table 116.2).

Other Laboratory Findings

Common electrolyte disturbances in patients with rhabdomyolysis include hyperkalemia, hyperphosphatemia, and early hypocalcemia followed by late hypercalcemia. Late hypercalcemia is postulated to be due to the mobilization of calcium that was initially sequestered in damaged muscle.

TABLE 116.2 Causes and Microscopic Features of Red and Brown Urine

Cause	Results for Blood in Urine[a]	Sediment[b]	Supernatant
Hematuria	+++	Red	Yellow
Myoglobinuria	+++	Normal	Red to brown
Hemoglobinuria	+++	Normal	Red to brown
Porphyria	–	Normal	Red
Bile pigments	–	Normal	Brown
Food and drugs[c]	–	Normal	Red to brown

[a]Urine tested with dipstick test.
[b]Normal refers to white or yellow color.
[c]Food and drugs that can cause red urine include beets, blackberries, rhubarb, food coloring, fava beans, phenolphthalein, rifampin, doxorubicin, deferoxamine, chloroquine, ibuprofen, and methyldopa. Those that cause brown urine include levodopa, metronidazole, nitrofurantoin, iron sorbitol, chloroquine, and methyldopa.
Adapted from Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med*. 2009;361:62-79.

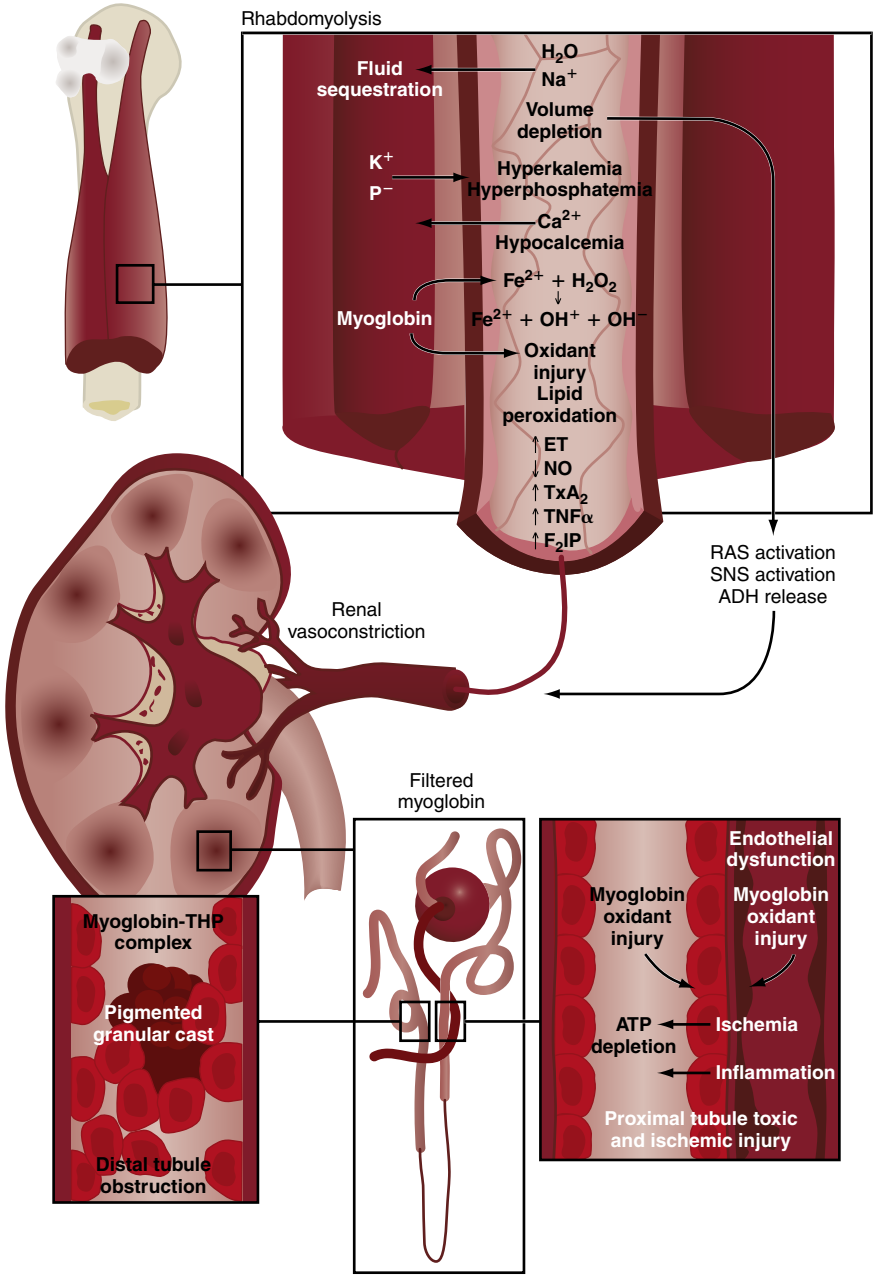


Fig. 116.4 Pathophysiologic Mechanisms in Rhabdomyolysis-Induced Acute Kidney Injury. *ADH,* Antidiuretic hormone; *ATP,* adenosine triphosphate; *ET,* endothelin; *F_2IP,* F_2-isoprostanes; *NO,* nitric oxide; *RAS,* renin-angiotensin system; *SNS,* sympathetic nervous system; *THP,* Tamm-Horsfall protein; *TNFα,* tumor necrosis factor alpha; *TxA_2,* thromboxane A_2. (Adapted from: Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med.* 2009;361:62-72.)

Hyperuricemia from the release of muscle nucleic acids is especially common in patients with large muscle mass, as is elevation in serum lactate dehydrogenase (LDH). Metabolic acidosis typically occurs from the generation of organic acids from damaged muscle—namely, lactate and uric acid. Hypoalbuminemia and anemia result from capillary damage and release into the extracellular space.

Both blood urea nitrogen (BUN) and creatinine (Cr) concentrations increase, but with a characteristic decrease in the BUN/Cr ratio due to large amounts of creatinine released into the serum from damaged muscle. A normal BUN/Cr ratio is 10:1; in rhabdomyolysis, it can be 5:1 or even less. In severe cases with significant muscle necrosis and electrolyte abnormalities, disseminated intravascular coagulation (DIC) can ensue with bleeding or thrombosis and abnormal coagulation panel, thrombocytopenia, low fibrinogen, elevated D-dimer, and fragmented RBCs, triggered by the released thromboplastin from damaged tissue.

Prognostic Tests in Rhabdomyolysis

Although CK levels may correlate with the risk of developing acute kidney injury in patients with rhabdomyolysis due to traumatic injury, such as crush injury, the degree of CK level elevation is not a reliable predictor of acute kidney injury, need for dialysis, or death.[7,8]

However, patients with an estimated glomerular filtration rate (eGFR) of more than 60 mL/min/1.73 m^2 appear to have low risk for acute kidney injury or death. Based on the cumulative evidence, CK should be used as a diagnostic marker for rhabdomyolysis, but not as a prognostic indicator of acute renal injury.[9] Once the diagnosis of rhabdomyolysis is made, the eGFR can be used to predict renal injury and help determine the need for admission. The eGFR is typically reported routinely on basic metabolic panels that include creatinine.

MANAGEMENT

Management of rhabdomyolysis focuses on treatment of the cause, prevention of renal failure, and management of life- or limb-threatening complications.

Fluid Replacement

Volume expansion is critical to avoiding myoglobin-induced acute renal failure in those who are hypovolemic.[10] Fluid expansion increases renal blood flow, glomerular filtration, and urine production, while reducing the risk of renal injury. Patients with rhabdomyolysis can present with severe dehydration due to fluid sequestration in the affected skeletal muscles. Several case series, mostly from victims of natural disasters with crush injury, have shown that some degree of intravascular volume contraction is a prerequisite for developing acute renal failure. Because acute renal failure appears to develop in hypovolemic patients with a longer delay to supportive therapy, fluid resuscitation should be instituted as early as possible.[11] Victims of mass casualty events often have prolonged extrication times, so fluid resuscitation should begin before complete extrication, when possible.

Fluid resuscitation should generally be initiated at CK levels more than five times the upper limit of normal (typically, 1000 IU/L) and should be continued until levels trend down and drop below this level. Fluid boluses are recommended in patients with hypovolemia or crush injury. In euvolemic or hypervolemic patients, over-resuscitation may be harmful. In general, titration to a urinary output of 2 to 3 mL/kg/hr or more and patient euvolemia are reasonable targets for adults.[3]

Balanced crystalloids such as plasmalyte or lactated Ringers solution are recommended for initial resuscitation, though there are no studies demonstrating improved outcomes with balanced fluids in rhabdomyolysis compared to normal saline. Normal saline contains supraphysiologic concentrations of chloride ions. Massive infusion of normal saline leads to a disproportionate increase in serum chloride concentrations, inducing an iatrogenic metabolic (hyperchloremic) acidosis that may exacerbate myoglobin precipitation, tubular obstruction, and risk of hyperkalemia-related complications.

Urine alkalinization, achieved through addition of sodium bicarbonate to IV fluids, is no longer recommended. Animal data suggested potential value for alkalinization, based on: (1) decreased renal myoglobin precipitation; (2) decreased reduction-oxidation (redox) cycling of myoglobin and lipid peroxidation, and thus tubule injury; and (3) decreased myoglobin-induced renal vasoconstriction.

However, the clinical benefits of alkalinization over IV hydration were never established, and sodium bicarbonate therapy has not been proven superior to normal saline diuresis at increasing urine pH, or more importantly, improving patient outcomes such as mortality and renal failure.

We do not recommend the use of sodium bicarbonate to induce urinary alkalinization in rhabdomyolysis because there is no evidence of improved outcomes with its use. However, isotonic bicarbonate infusion may be considered for those with non-anion gap metabolic acidosis or uremic acidosis.

Mannitol and Other Diuretics

In human studies, the addition of mannitol has not demonstrated benefit over fluid expansion alone, and no randomized controlled trials have shown any beneficial effect. Accordingly, we do not recommend the use of mannitol in the treatment of rhabdomyolysis. Animal studies demonstrated that the bulk of mannitol's effect is attributable simply to its osmotic diuretic action, but large accumulated doses of mannitol may be detrimental by causing renal vasoconstriction and tubular toxicity, a condition known as osmotic nephrosis, as well as exacerbating hypovolemia.

There also is no evidence to support the use of loop diuretics or carbonic anhydrase inhibitor diuretics in the treatment of rhabdomyolysis.

Experimental Therapies

Antioxidants such as glutathione and vitamin E analogues have shown promise in experimental animal models of myoglobin-induced oxidant injury and may have a future role in management. Grape seed proanthocyanidin extract has been shown to have renoprotective effects in animal models. The xanthine oxidase inhibitor, allopurinol, is being studied as a prophylactic agent in those at risk for exertional rhabdomyolysis.[12]

Renal Replacement Therapy

Renal replacement therapy (RRT) is needed in up to 20% of patients with acute kidney injury from rhabdomyolysis. As with other causes of acute renal failure, the indications for emergent RRT remain (1) uncorrectable metabolic acidosis, (2) life-threatening hyperkalemia and other electrolyte disturbances despite medical management, and (3) manifestations of uremia, and anuria or oliguria, despite volume expansion in patients with complications related to fluid overload. The current literature does not demonstrate a mortality benefit with RRT in the setting of rhabdomyolysis, but in those with a previously mentioned indication for RRT, RRT is associated with more rapid removal of myoglobin and improvement in electrolyte, BUN, and creatinine levels. RRT should be continued until the indication for it is corrected and the patient has improved.

DISPOSITION

The majority of patients with rhabdomyolysis require hospitalization for fluid resuscitation and close monitoring of renal function. Discharge with close outpatient follow-up or observation stays can be

considered in select, milder cases. Patients with a known etiology, mild symptoms, normal vital signs, normal renal function and electrolytes, and reliable follow-up may be discharged. Hemodynamically unstable patients or those requiring RRT should be considered for ICU admission, whereas those who do not meet these criteria or are not appropriate for outpatient management should be admitted to the hospital floor.

Prognosis

Rhabdomyolysis has an excellent prognosis when recognized and treated early. The majority of cases follow a benign course and resolve without complications. With the exception of hyperkalemia-related death or the rare complication of DIC, which typically occurs in patients with extensive muscle damage or crush injury, acute kidney injury is the most serious complication of rhabdomyolysis. Most patients who have acute renal failure will recover full renal function with fluid rehydration to euvolemia. Mortality data for patients with renal failure vary widely according to the study population, underlying etiology, presence of multiple causative agents, and comorbidities with no clear data; however, long-term survival among patients with rhabdomyolysis and acute renal injury tends to be very good when timely management is provided.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 116: QUESTIONS AND ANSWERS

1. Which of the following statements regarding muscle cell physiology and rhabdomyolysis is true?
- **a.** Acute renal failure from rhabdomyolysis is very rare.
- **b.** Hemoglobin has a higher oxygen affinity than myoglobin.
- **c.** The final common pathway of injury in rhabdomyolysis is cell membrane damage.
- **d.** The normal intracellular Na^+ concentration is high.
- **e.** The normal intracellular Ca^{2+} concentration is low.

Answer: E. Normal intracellular concentrations of Na^+ are low, creating a negative intracellular environment. This allows more facilitated transfer of Ca^{2+} from the intracellular to extracellular space, maintaining low intracellular Ca^{2+} concentrations. The final common pathway of injury is sarcolemma damage with intracellular Ca^{2+} accumulation, proteolytic enzyme inhibition, actin-myosin coupling dysfunction, and cell damage with release of intracellular contents (e.g., myoglobin, PO_4^-, uric acid, lactate dehydrogenase). Myoglobin, which has four times the O_2 affinity of hemoglobin, overwhelms the haptoglobin-binding capacity, is filtered at the glomerulus, and precipitates in renal tubules. Approximately 5% to 15% of cases of acute renal failure in the United States are related to rhabdomyolysis. This myoglobin precipitation is markedly facilitated by acidosis.

2. Which of the following statements regarding exertion (exercise)-related rhabdomyolysis is true?
- **a.** Eccentric (lengthening) muscle work is more damaging than concentric.
- **b.** Hypocalcemia increases the risk for this syndrome.
- **c.** It is the result of voluntary muscle exertion.
- **d.** It is seen exclusively in untrained athletes.
- **e.** The mechanism is different than after a crush injury.

Answer: A. Exertional rhabdomyolysis is seen in trained and untrained individuals as well as after exercise or situations of involuntary muscle activity (e.g., psychoses, seizures, tetany, myoclonus). The mechanism (e.g., failure of energy supplies, sarcolemma breakdown, intracellular calcium accumulation, enzyme dysfunction, cellular swelling) is the same. Hypokalemia is a risk factor because a low potassium level limits microvascular dilation and muscle perfusion.

3. Which of the following statements regarding drug-induced rhabdomyolysis is true?
- **a.** Cocaine myotoxicity is not related to the degree of intoxication.
- **b.** Colchicine and cyclosporine are myotoxins.
- **c.** Ethanol myotoxicity is potentiated by high carbohydrate intake.
- **d.** Statin myotoxicity is unrelated to state of hydration.
- **e.** The use of the drug ecstasy is not associated with rhabdomyolysis.

Answer: B. Statins, ethanol, cocaine, colchicine, cyclosporine, and many other drugs are myotoxic. Illicit drugs include amphetamine, ecstasy, LSD, and other sympathomimetics. Ethanol is a direct muscle membrane toxin, and this effect is potentiated by starvation, binge drinking, and coexisting electrolyte abnormalities (low K^+, PO_4^-, and Mg^{2+}). Intravenous cocaine use is more myotoxic than inhaled cocaine, and the severity seems to parallel the degree of intoxication.

4. What is the most common viral cause for rhabdomyolysis?
- **a.** Cytomegalovirus
- **b.** Epstein-Barr virus
- **c.** Herpesvirus
- **d.** Human immunodeficiency virus
- **e.** Influenza virus

Answer: E. Influenza is the most common viral etiology followed by HIV infection and enteroviral infection.

5. What is the most common bacterial cause for rhabdomyolysis?
- **a.** *Legionella*
- **b.** *Pseudomonas*
- **c.** *Salmonella*
- **d.** *Staphylococcus*
- **e.** *Streptococcus*

Answer: A. *Legionella* is the bacterium classically associated with rhabdomyolysis in adult patients. The pathogenesis is believed to be due to direct invasion and toxic degeneration of muscle fibers.

6. Which of the following electrolyte abnormalities has not been associated with rhabdomyolysis?
- **a.** Hypermagnesemia
- **b.** Hypernatremia
- **c.** Hypocalcemia
- **d.** Hyponatremia
- **e.** Hypophosphatemia

Answer: A. There are no reported cases of hypermagnesemia-induced rhabdomyolysis to date.

7. A 53-year-old intoxicated alcoholic is brought to the ED by EMS after being found unconscious for an unknown reason. He is now awake but mildly lethargic. He has no complaints of pain or

CHAPTER 116: QUESTIONS AND ANSWERS—cont'd.

disability. The physical examination is nonfocal. Which of the following statements is true?

a. A CK-MB fraction of 5% would indicate myocardial damage.
b. A negative urine myoglobin level would exclude rhabdomyolysis.
c. His lack of pain complaints would exclude rhabdomyolysis.
d. Hypocalcemia would be expected in the presence of rhabdomyolysis.
e. If rhabdomyolysis were found, normal phosphate level would be reassuring.

Answer: D. Hypocalcemia is the most common electrolyte abnormality after rhabdomyolysis. Hypercalcemia may follow later. Only 50% of patients with serum evidence of rhabdomyolysis have complaints of muscle pain. Likewise, the presence of urine myoglobin reflects the glomerular filtration rate, plasma myoglobin concentrations, urine flow, and plasma myoglobin binding. This test result may be negative, especially late in the course of the process. Hyperphosphatemia is expected, and a normal level raises the suspicion that hypophosphatemia was the cause of the rhabdomyolysis. CK-MB levels of 3% to 5% are often seen and reflect skeletal rather than cardiac muscle damage.

8. Which of the following is a proven cornerstone of management for rhabdomyolysis, along with hydration?

a. Alkalinization
b. Chelation therapy
c. Furosemide
d. Mannitol
e. None of the above

Answer: E. Furosemide is somewhat contraindicated because of its tendency to acidify the urine. Mannitol and alkalinization are not proven, although they are often used. Chelation therapy is under investigation.

117

Thyroid and Adrenal Disorders

Molly E.W. Thiessen

KEY CONCEPTS

Hyperthyroidism

- Hyperthyroidism induces a hypermetabolic state and increases β-adrenergic activity. The resulting clinical manifestations range from vague constitutional symptoms to more organ-specific symptoms (see Box 117.1).
- Hyperthyroidism in elders may be asymptomatic or may manifest with subtle nonspecific symptoms such as weight loss, shortness of breath, and/or dementia.
- The laboratory test of choice for suspected hyperthyroidism is the thyroid stimulating hormone (TSH) concentration with free T_4 and T_3 levels.
- Thyroid storm is a life-threatening thyrotoxic crisis that often presents with fever, extreme tachycardia, and/or altered sensorium. It requires prompt recognition and therapy, as well as identification and treatment of any precipitating cause, such as infection.
- The order of medication administration in thyroid storm is critical. Iodine can precipitate thyroid storm and must be given a minimum of 1 hour after thionamide therapy (PTU or methimazole). As such, the typical order is beta blocker (propranolol), PTU or methimazole, and then iodine (SSKI, Lugol solution).

Hypothyroidism

- Hypothyroidism results from lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism).
- Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure, which can lead to death (see Box 117.5).
- Determination of an elevated TSH level is the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism.
- Replacement with levothyroxine (T_4) remains the treatment of choice and resolves physical and psychological signs and symptoms in most patients.
- Myxedema coma is a life-threatening event that presents with altered mental status and hypothermia, along with a concomitant precipitating event (see Box 117.6). It usually occurs in patients with untreated or undertreated hypothyroidism. Treatment with thyroid hormone replacement must be initiated, often based solely on clinical findings.

Adrenal Excess States

- Adrenal excess states run the spectrum from Cushing syndrome, to primary and secondary hyperadrenalism, to pheochromocytoma.
- Symptoms of adrenal excess will vary, depending on the etiology, with chronic, nonspecific symptoms that arise from Cushing syndrome (generalized weakness, fatigue, menstrual irregularities, and weight gain), to simple refractory hypertension with hyperaldosteronism, to acute, refractory hypertension and hyperadrenergic symptoms with pheochromocytoma.
- Diagnosis of hyperaldosteronism is typically clinical, and confirmed by laboratory testing and imaging studies, depending on the etiology. In most cases, acute stabilization of the presenting complaint is paramount, and definitive diagnosis will occur outside the ED. Any adrenal incidentaloma discovered on imaging obtained in the ED, especially in the setting of hypertension, should prompt further evaluation for adrenal excess.

Adrenal Insufficiency

- Clinical manifestations of secondary adrenal insufficiency are often vague and nonspecific, including fatigue, weakness, dizziness, nausea, vomiting, and other nonspecific GI symptoms. Patients with primary adrenal insufficiency characteristically have more pronounced clinical manifestations and skin hyperpigmentation.
- The ACTH stimulation test and measurements of cortisol levels is the most convenient method and is considered the criterion standard to make the diagnosis.
- Refractory hypotension in the acutely ill patient may be the only clue to adrenal insufficiency and is readily treated with IV administration of glucocorticoids (hydrocortisone, 100 mg).

HYPERTHYROIDISM

Foundations

Background and Importance

Hyperthyroidism is a condition caused by overproduction and increased circulation of thyroid hormone. The disorder runs the spectrum from subclinical hyperthyroidism to thyrotoxicosis and thyroid storm, a life-threatening disorder. Thyrotoxicosis is a hypermetabolic condition that results from elevated levels of thyroid hormones—triiodothyronine (T_3) and thyroxine (T_4). This can occur from hormone overproduction, increased thyroid hormone release from an injured gland, or exogenous thyroid hormone. For the purpose of this discussion, the terms *hyperthyroidism* and *thyrotoxicosis* are used interchangeably.

Anatomy, Physiology, and Pathophysiology

The normal adult thyroid gland is a highly vascular bilobar organ overlying the anterior trachea (Fig. 117.1). The thyroid's function is to secrete two iodinated hormones, T_3 and T_4. Only about 20% of circulating T_3 is directly secreted by the thyroid; the remainder is produced by peripheral conversion of T_4 to the more biologically active T_3. The thyroid is the only endocrine gland that stores large quantities of hormone.

Hormone production is regulated by a negative feedback loop involving the hypothalamic-pituitary-thyroid axis (Fig. 117.2). As the serum levels of T_4 and T_3 fall, the hypothalamus releases the tripeptide thyrotropin-releasing hormone (TRH), which in turn stimulates the anterior pituitary gland's release of the polypeptide thyroid-stimulating hormone (TSH) from its thyrotroph cells. TSH then binds to epithelial

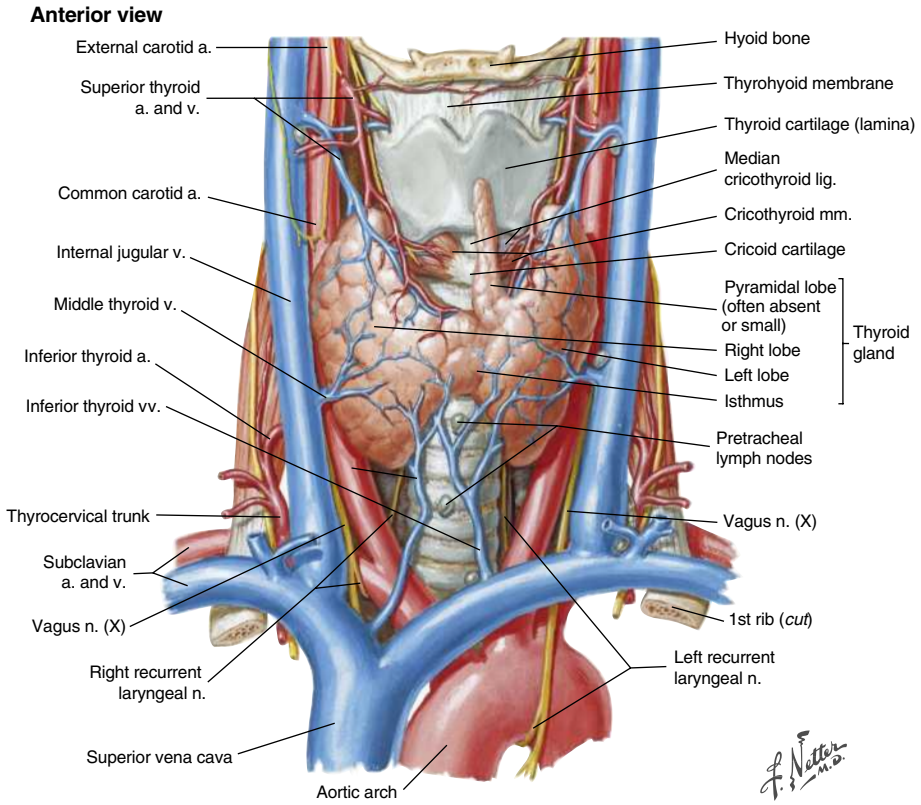

Fig. 117.1 Anatomy of the thyroid gland and related structures. (Netter illustration from www.netterimages.com. Copyright Elsevier. All rights reserved.)

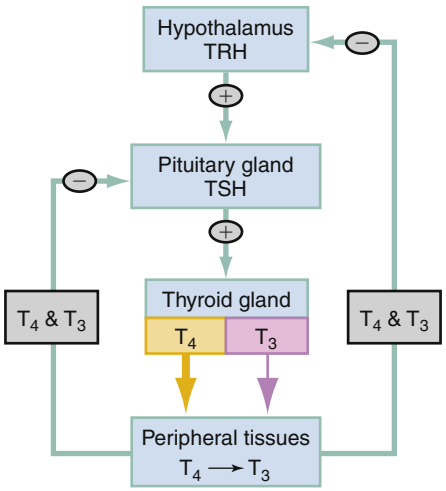

Fig. 117.2 Negative feedback loop of thyroid hormone regulation—hypothalamic-pituitary-thyroid axis. Thyroid hormone production is regulated by the hypothalamus and pituitary gland. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary thyrotropin (TSH) synthesis and secretion. In turn, TSH stimulates the production and release of thyroxine (T_4) triiodothyronine (T_3) from the thyroid gland. Once released, T_4 and T_3 exert a negative feedback mechanism on the production of TRH and TSH. T_4 is converted to T_3 in the peripheral tissues.

cells on the thyroid gland, stimulating follicular cells to synthesize and secrete the thyroid hormones T_4 and T_3. TRH release may also result from exercise, stress, malnutrition, hypoglycemia, and sleep.

The function of thyroid hormone is to influence the metabolism of cells by increasing their basal metabolic rate. It has a role in protein synthesis and functions together with other hormones necessary for normal growth and development. T_3 and T_4 increase the expression and sensitivity of β-adrenergic receptors, increasing the response to endogenous catecholamines.

T_4 is a prohormone with only mild intrinsic activity; its deiodination produces T_3, the biologically active hormone. More than 99.5% of thyroid hormones are protein-bound in the serum to thyroxine-binding globulin (TBG) and other proteins, rendering them metabolically inactive. As a result, only free T_4 and free T_3 are clinically relevant.

Although iodide is a necessary substrate for thyroid hormone production, excess iodide can have two opposing effects. In the Wolff-Chaikoff effect, excess iodine inhibits the release of thyroid hormone from the gland by blocking iodide trapping and thyroglobulin iodination. This inhibition is transient, typically lasting only a matter of days. An iodine load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and occult Graves disease.

Clinical Features

History and Physical Examination

Hyperthyroidism induces a hypermetabolic state and increases β-adrenergic activity. The resulting clinical manifestations range from vague constitutional symptoms to more organ-specific symptoms (Box 117.1). Altered mental status and coma typify thyroid storm, the most severe manifestation of disease.

Hyperthyroidism in older adults often manifests in more subtle ways, often asymptomatic or with nonspecific symptoms of weight loss, shortness of breath, and/or dementia. Elders are more prone to cardiac manifestations of hyperthyroidism and may present with atrial fibrillation.[1] Elders who smoke or have higher circulating thyroid hormone levels appear to have more severe symptoms. Thyrotoxic periodic paralysis is a rare manifestation that presents as a sudden and

BOX 117.1 Symptoms of Thyrotoxicosis

Constitutional: Weight loss despite hyperphagia, fatigue, generalized weakness
Hypermetabolic: Heat intolerance, cold preference, excessive perspiration
Cardiorespiratory: Palpitations, dyspnea, dyspnea on exertion, chest pains, poor exercise tolerance
Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia
Neuropsychiatric: Anxiety, restlessness, hyperkinesis, emotional lability, confusion, insomnia, poor attention
Neuromuscular: Myopathy, myalgias, tremor, proximal muscle weakness (difficulty getting out of a chair or combing hair)
Ophthalmologic: Tearing, irritation, wind sensitivity, diplopia, foreign body sensation
Thyroid gland: Neck fullness, dysphagia, dysphonia
Dermatologic: Flushed feeling, hair loss, pretibial swelling
Reproductive: Oligomenorrhea, amenorrhea, menometrorrhagia, decreased libido, gynecomastia, erectile dysfunction, infertility

BOX 117.2 Physical Findings in Thyrotoxicosis

Vital signs: Tachycardia, widened pulse pressure, bounding pulses, fever
Cardiac: Hyperdynamic precordium, systolic flow murmur, prominent heart sounds, systolic rub (Means-Lerman scratch), tricuspid regurgitation, atrial fibrillation, evidence of heart failure
Ophthalmologic: Widened palpebral fissures (stare), lid lag, globe lag, conjunctival injection, periorbital edema, proptosis, limitation of superior gaze
Neurologic: Fine tremor, hyperreflexia, proximal muscle weakness
Psychiatric: Fidgety, emotionally labile, poor concentration
Dermatologic: Warm, moist, smooth skin; rosy cheeks, blushing face; fine brittle hair; alopecia, flushed facies; palmar erythema; hyperpigmented pretibial plaques, nodules, or induration that is nonpitting; onycholysis (Plummer nails, separation of the distal portion of the fingernail from the nail bed)
Neck: Diffuse symmetric thyroid enlargement, sometimes with a bruit and palpable thrill; thyroid with multiple irregular nodules or a prominent single nodule; tracheal deviation, venous prominence with arm elevation (Pemberton sign)

profound muscle weakness progressing to flaccid paralysis, similar to familial hypokalemic periodic paralysis.

Ophthalmopathy is a classic finding in Graves disease. Patients subsequently present with eyelid edema, hyperemia, conjunctival hyperemia, and chemosis. Graves ophthalmopathy is also associated with restrictive extraocular myopathy, and exophthalmos. As the disease progresses, patients may experience restriction of their upward gaze from infiltration of the inferior rectus muscle and visual loss from optic nerve involvement (compression by inflamed, enlarged orbital contents). Increased activity at the sympathetic innervation of the eyelids leads to widening of the palpebral fissures, resulting in the characteristic stare and lid lag of thyrotoxicosis.

Physical examination findings of hyperthyroidism depend largely on age (Box 117.2). Younger patients typically present with signs of sympathetic stimulation, whereas older adults often lack the same adrenergic response and present with weight loss and fatigue, more consistent with apathetic hyperthyroidism.[1] In Graves disease, patients uncommonly have classic pretibial myxedema, which are confluent, painless, reddish raised nodules and plaques over the pretibial area and dorsum of the feet, often described as orange skin. Hyperpigmentation and induration are present, but pitting is absent. Pretibial myxedema is often associated with Graves ophthalmopathy.

Tachycardia is the most common cardiac finding. Other findings include a widened pulse pressure, bounding peripheral pulses and, rarely, a friction rub heard along the left sternal border (Means-Lerman scratch). Atrial fibrillation is more common in elders, especially those over 65 years of age. Dilated cardiomyopathy may develop as a complication of a high cardiac output state. Patients can also develop primary pulmonary hypertension, as well as increased chamber size and poor right ventricular function.[2]

Most hyperthyroid patients have an enlarged thyroid gland, especially in toxic multinodular goiter or Graves disease, although many elders with Graves disease have nonpalpable thyroids. Retrosternal enlargement can occur, making detection difficult while causing the obstructive symptoms discussed earlier. Facial and neck vein engorgement can be elicited when arms are elevated above the head (known as the Pemberton sign). The absence of thyroid enlargement should suggest exogenous (factitious) thyroiditis as well as ectopic thyroid hormone production, such as a hydatidiform mole or struma ovarii, an ovarian tumor composed of some thyroid tissue.

Thyroid Storm

Thyroid storm is a rare, life-threatening form of severe thyrotoxicosis, with multiorgan dysfunction and significantly higher mortality rates than thyrotoxicosis without storm.[3] Although it can occur as the result of unrecognized or undertreated thyrotoxicosis, more often, it is an acute reaction to surgery, trauma, infection, iodine load or parturition in patients with preexisting hyperthyroidism. Other precipitants include acute myocardial infarction, pulmonary embolism, hyperemesis gravidarum, preeclampsia, and diabetic ketoacidosis. Untreated, mortality approaches 100%, but prompt recognition and therapy have lowered mortality to 10% to 30%.[3,4] Death in thyroid storm is caused by multiorgan dysfunction, congestive heart failure, respiratory failure, arrhythmias, disseminated intravascular coagulation, hypoxic brain insult, or sepsis.

The typical clinical manifestations of thyroid storm include marked pyrexia (104°–106°F [40°–41°C]), extreme tachycardia (often out of proportion to level of fever), and altered mental status. These findings, coupled with the clinical picture of a patient with hyperthyroidism, lid lag, stare, goiter, ophthalmopathy, and tremor, should alert the emergency clinician to the diagnosis. Cardiovascular collapse can result in congestive heart failure, hypotension, and cardiac arrhythmias. Hypotension can also result from volume depletion secondary to nausea, vomiting, and diarrhea. Abdominal pain is common; hepatic failure with cholestatic jaundice is less common but carries a poor prognosis. Thyroid storm is a clinical diagnosis, and no validated diagnostic criteria yet exist. However, a scoring system developed by Burch and Wartofsky in 1993 is repeatedly cited and utilized by practicing endocrinologists. Although the test characteristics (e.g., sensitivity and specificity) have not been published, it may help distinguish among thyrotoxicosis, impending thyroid storm, and frank thyroid storm (Table 117.1).[5]

Differential Diagnoses

The differential diagnosis for the thyrotoxic patient is broad. An anxious patient may be interpreted to be manic or experiencing a panic attack. The hyperadrenergic state may be confused with that seen in patients with sympathomimetic intoxication, suffering from anticholinergic crisis, or experiencing withdrawal from alcohol or sedative-hypnotics. The hyperpyrexia and altered mental status seen in thyroid storm may mimic other hyperthermic disorders such as heatstroke, neuroleptic malignant syndrome, serotonin syndrome, bacterial

TABLE 117.1 Diagnostic Criteria for Thyroid Storm

Criteria	Score[a]
Fever (°F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104	30
Tachycardia (beats/min)	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Mental Status	
Normal	0
Mild agitation	10
Delirium, psychosis	
Extreme lethargy	20
Coma, seizures	30
Congestive Heart Failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Pulmonary edema	15
Atrial fibrillation	10
Gastrointestinal and Hepatic Symptoms	
None	0
Nausea, vomiting	10
Diarrhea, abdominal pain	
Unexplained jaundice	20
Precipitating Event	
None	0
Present	10

[a]Tally the maximum score from each category. A score of 45 or higher suggests thyroid storm, or impending storm, and a score below 25 is unlikely to represent thyroid storm.

meningitis, and sepsis. Elders with apathetic hyperthyroidism may be mistakenly diagnosed with psychiatric illness.

Diagnostic Testing

The initial diagnosis of thyrotoxicosis is based on the clinical picture and confirmed with laboratory values. Measurement of the serum TSH level is the most sensitive test for hyperthyroidism. In thyrotoxicosis, the serum TSH concentration is depressed or undetectable (<0.01 μU/mL in third-generation assays), and a normal TSH level excludes hyperthyroidism. Accuracy of the TSH determination is improved when the free T_4 test is added. Assessment of thyroid function during acute nonthyroidal illness is difficult, especially in critically ill patients.

TABLE 117.2 Thyroid Function Test Interpretation

Tsh	Free T_4	Free T_3	Disease
Normal	Normal	Normal	None
Low	High	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	Normal	High	T_3 toxicosis
Low	High	Normal	Thyroiditis, T_4 ingestion, hyperthyroidism in older adults or those with comorbid illness
Low	Low	Low	Euthyroid sick syndrome; central hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism; recovery from euthyroid sick syndrome

T_3, Triiodothyronine; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone.

Severe systemic illness depresses TSH production, leading to low levels of TSH, free T_3, and free T_4.

Elevation of free T_4 and free T_3 levels in conjunction with TSH suppression is diagnostic of thyrotoxicosis. Because nearly all T_3 and T_4 is bound to TBG, assays measuring total T_3 or T_4 are influenced by changes in TBG; they are therefore unreliable and should not be used. Subclinical hyperthyroidism is likely if TSH is suppressed and the free T_4 level is normal. T_3 toxicosis occurs in about 5% of patients with thyrotoxicosis. These patients have an elevated free T_3 level and a normal free T_4 level. When the reverse pattern is present—normal free T_3 level and elevated free T_4 level—the differential includes thyroiditis, exogenous levothyroxine ingestion, and hyperthyroidism in elders, often with suppressed T_4 to T_3 conversion due to comorbid illness (Table 117.2). Since Graves is caused by autoantibodies to the TSH receptor, the presence of thyroid receptor antibodies in the serum can help distinguish it from other causes. Additionally, a radioiodine scan can help discern Graves from exogenous intake or hyperthyroidism due to struma ovarii. A magnetic resonance imaging (MRI) test of the brain and an ultrasound of the thyroid may help differentiate whether excess levels of thyroid hormone are emanating from either the pituitary or the thyroid gland.

Many thyrotoxic patients have hyperglycemia. This is likely to be the result of increased glycogenolysis and catecholamine-mediated antagonism of insulin. Mild hypercalcemia can be seen, is related to hormone-mediated bone resorption, and is associated with osteoporosis and increased fracture risk. Other frequent laboratory abnormalities include abnormal liver function tests, leukocytosis, mild anemia, and low serum cholesterol levels.

In thyroiditis, the diagnostic evaluation is more difficult. An exquisitely tender gland and elevated erythrocyte sedimentation rate (ESR) or C-reactive protein make the diagnosis of subacute thyroiditis likely. The other forms of thyroiditis lack these findings.

Factitious thyrotoxicosis can often be diagnosed by history. Laboratory testing will demonstrate low thyroglobulin levels and a low T_3/T_4 ratio (<20 ng/microgram).[5] Furthermore, radioactive iodine uptake is depressed in thyroiditis and factitious thyrotoxicosis but increased in hyperthyroidism.

Management

Management of thyrotoxicosis is based on etiology and symptom severity. For those with mild symptoms, outpatient referral and management are appropriate. Patients with moderate to severe symptoms are best managed in the emergency department (ED) setting. Treatment is divided into supportive, symptomatic, and thyroid-directed therapy.

BOX 117.3 Management of Thyrotoxicosis

β-Adrenergic Blockade

Propranolol 60–80 mg PO every 4 hours
or
Metoprolol, 25–50 mg PO every 6 hrs
If IV route is required, propranolol, 0.5–1.0 mg IV slow push test dose, then repeat 1–2 mg every 15 min as tolerated to desired effect, then 1–2 mg every 3 hr
or
Esmolol, 50–100 μg/kg/min infusion
Strict contraindication to beta blocker—reserpine 2.5–5 mg IM every 4 hr

Inhibition of Thyroid Hormone Synthesis

Propylthiouracil, 500–1000 mg loading dose, then 250 mg every 4 hr
or
Methimazole, 60–80 mg/day in divided doses
Preferred route, PO or nasogastric (NG); alternative route: PR (in rectum), enema prepared by pharmacy; same dose for all routes

Inhibition of Thyroid Hormone Release

Saturated solution of potassium iodide (SSKI, 50 mg iodide/drop), 1–2 drops PO or PR tid
or
Lugol solution (8 mg iodide/drop), 5–7 drops PO or PR tid
or
Sodium iodide, dosing as per Endocrinology recommendations
or
If allergic to iodine, lithium carbonate, 300 mg PO or NG qid

Administration of Corticosteroids

Inhibit T_4 to T_3 conversion; treat relative adrenal insufficiency.
Hydrocortisone, 300 mg IV, followed by 100 mg tid
or
Dexamethasone, 2–4 mg IV qid

Diagnosis and Treatment of Underlying Precipitant

Consider empirical antibiotics if critical.

Supportive Measures

Volume resuscitation and replacement of glycogen stores with D_5/0.9 NS (dose varies, depending on volume status and CHF)
Acetaminophen
Cooling blanket, fans, ice packs, ice lavage

Miscellaneous

Lorazepam or diazepam as anxiolytic and to decrease central sympathetic outflow
Cholestyramine (blocks enterohepatic recirculation of thyroid hormone), 1–4 g PO twice daily for severe or refractory thyrotoxicosis

CHF, Congestive heart failure; *D_5W/0.9 NS,* 5% dextrose in 0.9% normal saline; *IV,* intravenously; *NG,* by nasogastric tube; *PO,* by mouth; *PR,* by rectum; *T_3,* triiodothyronine; *T_4,* thyroxine.

Specific dosages of the drugs discussed in the following sections can be found in Box 117.3. The order of medication administration in thyroid storm is critical. Iodine can precipitate thyroid storm and must be given a minimum of 1 hour after thionamide therapy (PTU or methimazole). As such, the typical order is beta blocker (propranolol), propylthiouracil (PTU), or methimazole, and then iodine (saturated solution of potassium iodide [SSKI], Lugol solution). In addition, it is important to identify and treat the precipitating cause of thyroid storm.

Supportive Treatment

Supportive therapy for thyroid storm patients should include management of hyperthermia with cooling and acetaminophen. Aspirin should be avoided in thyrotoxic patients because it decreases the protein binding of T_4 and T_3. Agitation is controlled with benzodiazepines. Fluid resuscitation is needed to compensate for insensible and gastrointestinal (GI) losses; dextrose-containing solutions are helpful because glycogen stores are often depleted. Electrolyte replacement is guided by laboratory values.

Symptomatic Treatment

Symptomatic treatment consists primarily of beta blockade to diminish the adrenergic response. Propranolol is the beta blocker of choice because it has the added benefit of blocking conversion of T_4 to T_3; its nonselective effects also improve tremor, weakness, hyperpyrexia, restlessness, irritability, and emotional lability. The onset of action after oral dosing is about 1 hour.

For more rapid beta blockade, propranolol can be administered intravenously (IV). A short-acting agent such as esmolol may be used when concerns about beta blockade exist, due to underlying asthma or COPD, or pulmonary edema from heart failure. In asthmatics, a β_1-selective drug such as esmolol or metoprolol may be considered.

If beta blockers are contraindicated, reserpine, 2.5 to 5 mg intramuscularly (IM) every 4 hours, is also an option. Patients should be closely monitored for hypotension, regardless of the agent used, because thyrotoxicosis can lower systemic vascular resistance and cause congestive heart failure. Patients who develop clinically significant heart failure should be treated with the usual medications for heart failure, including diuretics and angiotensin-converting enzyme inhibitors. Atrial fibrillation is often refractory to rate control until antithyroid therapy is instituted.

Thyroid-Directed Treatment

Thyroid-directed therapy has three goals: reduce thyroid hormone production, prevent thyroid hormone release, and block peripheral conversion of T_4 to T_3. In conjunction with this treatment, an additional goal is the avoidance of therapeutic interventions that may worsen thyrotoxicosis. As such, certain drugs should be avoided in the thyrotoxic patient. Amiodarone and iodinated contrast material both contain iodine and can increase thyroid hormone production. Aspirin can increase free thyroid hormone concentrations through its effect on protein binding. Pseudoephedrine, ketamine, and albuterol increase sympathetic tone and can exacerbate the adrenergic effects of thyrotoxicosis; when indicated, they should be used cautiously.

Reducing Thyroid Hormone Production. Thionamides inhibit oxidation and organic binding of iodine to thyroglobulin, thereby blocking the synthesis of thyroid hormone. PTU or methimazole can be used. PTU has the additional effect of impairing the conversion of T_4 to T_3; methimazole has a longer duration of action. Both PTU and methimazole may be given by nasogastric tube or rectum as needed. PTU is preferred in the first trimester of pregnancy, and methimazole is preferred in the second and third trimesters. Methimazole is available in IV form outside the United States, but its use is not recommended by the most recent American Thyroid Association guidelines.[6]

Side effects of thionamide therapy vary from mild to life-threatening. These can range from urticarial, rash, arthralgia, GI upset, to agranulocytosis, hepatotoxicity and vasculitis.

Inhibiting Thyroid Hormone Release. Inorganic iodine blocks the release of stored thyroid hormone. Because an iodine load can increase the synthesis of thyroid hormone, these agents should not be administered until 1 hour after the initiation of PTU or methimazole therapy. Traditionally, oral iodine in the form of potassium iodide (SSKI), or Lugol solution, is administered. Like the thionamides,

these agents may be given via nasogastric tube or retention enema, as needed. Lithium may be considered an alternative therapy for iodine-allergic patients. Lithium is also the agent of choice for iodine-induced hyperthyroidism, which is usually the result of the administration of amiodarone or iodinated contrast material.

Inhibiting Conversion of T_4 to T_3. Corticosteroids are capable of inhibiting the peripheral conversion of T_4 to T_3 and blocking the release of hormone from the thyroid gland. When steroids are used in conjunction with PTU and iodide, the concentration of T_3 can return to normal within 48 hours. Hydrocortisone may be administered, and dexamethasone is an alternative.

Miscellaneous Therapies

Cholestyramine, an anion exchange resin, interrupts the enterohepatic recirculation of thyroid hormone by binding it in the bowel lumen. Because it may help to decrease the level of circulating hormone more rapidly, its use is recommended for severe or refractory thyroid storm. Although it has been shown to result in a more rapid decline in hormone levels compared with thionamides alone, it requires weeks of therapy and, as such, is reserved for outpatient management.[7] Plasmapheresis has been used in thyroid storm as an attempt to remove circulating thyroid hormone.[5,8] Extracorporeal membrane oxygenation (ECMO) has been recently described as successful in supporting patients with severe thyroid storm and "rapid clinical deterioration."[9] Neither radioactive iodine nor surgery plays a role in the management of thyroid storm or thyrotoxicosis until a sustained euthyroid state has been established because these interventions can precipitate thyroid storm.

First-line treatment of subacute thyroiditis is the use of nonsteroidal antiinflammatory drugs (NSAIDs). Corticosteroids are used in refractory cases. Symptomatic patients are treated with beta blockers. Management of drug-induced hyperthyroidism depends on the inciting agent. In the case of AIT-1, treatment typically consists of stopping amiodarone and initiating antithyroid therapy. AIT-2 is managed with corticosteroids, and the decision to stop amiodarone is made on a case-by-case basis.[10] Management of drug-induced hyperthyroidism related to lithium involves stopping lithium. When related to immunomodulator therapy, discontinuation of the offending drug is not always mandatory.[11] Treatment is based on the determination of the type of reaction present; Box 117.4).

Identification and Treatment of the Precipitating Event

Thyroid storm is often precipitated by a physiologic stressor, such as infection, myocardial ischemia, pulmonary embolism, and stroke. Management of thyroid storm with PTU, followed by iodine, beta blockers, corticosteroids, fluid resuscitation, rapid cooling, and treatment of the precipitating illness, can resolve acute thyroid storm within 24 hours.

Disposition

The disposition of patients with hyperthyroidism is guided by symptom severity, with intensive care unit (ICU) admission for patients in thyroid storm. Patients with mild thyrotoxicosis controlled with a first-line medication who are otherwise stable can be managed as outpatients. Admission to the hospital may be appropriate for patients who require more than beta blockers for symptom control or whose symptoms persist despite therapy. Patients with rapid atrial fibrillation should be admitted to a monitored setting. Patients managed as outpatients can be sent to a primary care physician or referred to an endocrinologist. Lack of insurance and other socioeconomic factors have been linked to higher admission rates in patients with thyrotoxicosis.[12]

Note: Many subtypes and varying etiologies of hyperthyroidism have been identified. Table 117.3 provides descriptions of cases distinguished from the above general description.

BOX 117.4 Thyrotoxicosis and Thyroid Storm Special Situations

Congestive Heart Failure

If rate-related, high-output failure:
- Beta blockade is first-line therapy (dose as in Box 117.3)
- ACEI, digoxin, diuretics as needed

If depressed ejection fraction:
- Avoid beta blocker or one-quarter dose
- ACEI if blood pressure adequate
- Digoxin and furosemide as needed

If pulmonary hypertension:
- Oxygen
- Sildenafil

Atrial Fibrillation

Beta blocker preferred for rate control (dose as in Box 117.3)
Calcium channel blockers prone to hypotension; diltiazem, 10-mg test dose.
- Avoid verapamil.

Digoxin less effective but may be tried
Amiodarone should be avoided because of iodine load
Refractory to conversion to sinus rhythm unless euthyroid first

Thyroiditis (Subacute)

NSAIDs for inflammation and pain control
Prednisone, 40 mg/day, if refractory to NSAIDs
Beta blockade to control thyrotoxic symptoms
No role for PTU, methimazole, or iodides

Factitious Thyrotoxicosis

Beta blockade for thyrotoxic symptoms
Cholestyramine to block absorption of ingested thyroid hormone
No role for PTU, methimazole, or iodides

ACEI, Angiotensin-converting enzyme inhibitor; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PTU,* propylthiouracil.

HYPOTHYROIDISM

Foundations

Background and Importance

Hypothyroidism is a condition in which the thyroid gland fails to produce or secrete sufficient circulating thyroid hormone to meet the needs of the peripheral tissues. The condition results from lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism). Hypothyroidism is the most common functional disorder of the thyroid gland.

Thyroid disorders are the second most common endocrine condition after diabetes mellitus. Higher incidence rates are found in women than in men, which is attributed to the higher prevalence of autoimmune disease found in women in general. In the United States (US), 1% to 2% of women are affected by hypothyroidism. Subclinical hypothyroidism affects 4% to 10% of the population. The incidence of subclinical hypothyroidism in pregnancy is 5% to 8%.[13] There is no specific race or ethnic predilection, but older age groups are at a higher risk for the development of hypothyroidism.

Pathophysiology

Intrinsic gland failure accounts for up to 99% of all cases of hypothyroidism. Factors that may result in primary hypothyroidism include autoimmune disorders, infiltrative disorders, congenital thyroid dysfunction, pregnancy, radiotherapy, medications, infection, surgery,

TABLE 117.3 Hyperthyroidism Summary

	Background and Importance	Pathophysiology	Clinical Features	Diagnostic Testing	Management
Graves Disease	Most common form of hyperthyroidism in the United States Strong genetic association, with frequent occurrence in the setting of other autoimmune disorders[1] Some environmental causes, such as smoking	Autoantibodies bind to the TSH receptor and stimulate thyroid hormone production and release. Infiltration of the inferior rectus muscles Increased activity at the sympathetic innervation of the eyelids	Enlarged thyroid gland • May be absent in the elderly Ophthalmopathy • eyelid edema • hyperemia • conjunctival hyperemia • chemosis • restrictive extraocular myopathy • exophthalmos • restriction of upward gaze • visual loss secondary to optic nerve compression • widening palpebral fissure • lid lag Pretibial Myxedema • confluent, painless, reddish raised nodules and plaques over the pretibial area and dorsum of the feet, often described as "orange skin" • hyperpigmented • indurated • nonpitting	Thyroid receptor antibody positive Radioiodide uptake increased	Patients should first be treated to stabilize their acute thyrotoxic symptoms. Patients can then be referred for: • radioactive iodine therapy • OR long-term antithyroid drug administration • OR thyroidectomy
Toxic Multinodular Goiter	Second leading cause of hyperthyroidism in the United States More common in women >50 years old	Multiple autonomously functioning nodules	Enlarged, palpable thyroid gland Milder, more gradual in onset than Graves disease May present acutely when iodine replacement is given to iodine-deficient patients.	A ^{123}I or ^{99m}Tc pertechnetate scan	Patients should first be treated to stabilize their acute thyrotoxic symptoms. Patients can then be referred for: • radioactive iodine therapy • OR thyroidectomy Treatment with antithyroid drugs may be appropriate on occasion, when specific contraindications to the above exist
Toxic Adenoma	Typically affects the same population as toxic multinodular goiter, but is less common	Single hyperfunctioning nodule within the thyroid	Typical hyperthyroid signs and symptoms	A ^{123}I or ^{99m}Tc pertechnetate scan	Patients should first be treated to stabilize their acute thyrotoxic symptoms. Patients can then be referred for: • radioactive iodine therapy • OR thyroidectomy Treatment with antithyroid drugs may be appropriate on occasion, when specific contraindications to the above exist

Thyroiditis	Hashimoto thyroiditis is most common form in the United States	Any inflammatory process that results in thyroid gland inflammation can lead to thyroiditis: • autoimmune • drug-induced • infectious • traumatic Inflammation leads to follicular cell breakdown, with resultant release of preformed thyroid hormone, resulting in thyrotoxicosis Hashimoto is the result of thyroid antibodies and lymphocytic infiltration of the thyroid gland.	Exquisitely tender thyroid gland Hashimoto patients may have transient thyrotoxicosis, followed by painless goiter and hypothyroidism secondary to the destruction of thyroid tissue.	Elevated ESR and CRP Radioiodide uptake depressed	NSAIDS Corticosteroids for refractory cases
Postpartum Thyroiditis	5% of pregnant women will develop this. 70% recurrence rate in subsequent pregnancies Some women will have permanent hypothyroidism.	Autoimmune etiology, presents as the immune system returns to its normal function following pregnancy. Triphasic course: (1) thyrotoxicosis, 2 to 6 months postpartum, although this phase may be asymptomatic; (2) a hypothyroid state lasting 2 to 3 months; and (3) a euthyroid state by the end of the first postpartum year.	20% to 30% may have only thyrotoxicosis 40% may have only hypothyroidism	Diagnostic Triad: • Lack of previous history of thyroid disorder • Abnormal TSH concentration during the first postpartum year • Absence of TSH receptor antibodies or a toxic nodule	Supportive treatment Beta blockers are recommended to control pulse and other symptoms Atenolol is contraindicated in breastfeeding because of excretion in breast milk; propranolol and metoprolol are preferred.
Subacute Thyroiditis	de Quervain thyroiditis Most common in women, ages 40–60	Thought to be caused by a viral infection of the thyroid	Viral prodrome • fever • fatigue • myalgias • pharyngitis Anterior neck pain, may radiate to ears/jaw/throat Exquisitely tender thyroid, may be enlarged About 50% of patients have mild, typical symptoms lasting 3 to 6 weeks. About one-third of patients will then have hypothyroidism for up to 6 months, followed by a return to a euthyroid state 5–15% of patients will have persistent hypothyroidism.	Clinical suspicion based on history and physical exam TSH low Free T4 *may* be elevated relative to T3 Elevation of ESR, CRP May also see mild leukocytosis and anemia Radioactive iodine uptake is low	Initial treatment with beta-adrenergic blocking agents and NSAIDs. • May substitute corticosteroids for NSAIDs if moderate to severe thyrotoxic symptoms at presentation or failure to respond to initial interventions

Continued

TABLE 117.3 Hyperthyroidism Summary—cont'd.

	Background and Importance	Pathophysiology	Clinical Features	Diagnostic Testing	Management
Painless Thyroiditis	"Silent thyroiditis" Common cause of post-partum thyroiditis Also seen in nonpregnant women and men	Likely autoimmune Medication related • lithium • cytokine therapy	Similar to subacute thyroiditis, but typically without viral prodrome, neck pain or inflammatory response Small, nontender goiter Mild symptoms Triphasic course	ESR, CRP normal No leukocytosis Anti-thyroid peroxidase antibodies present in 50% of patients Low radioactive iodine uptake in thyrotoxic phase Typical lab findings for thyrotoxicosis in this phase (low TSH and high free T4)	Beta-adrenergic blocking agents Corticosteroids for severe cases
Acute Suppurative Thyroiditis	Rare Life-threatening	Infection of the thyroid gland • bacterial • parasitic (rare) • mycobacterial (rare) • fungal (rare)In adults, most often secondary to hematogenous spread or iatrogenic In children and adolescents, can be secondary to pyriform sinus fistula	Fever Anterior neck pain Neck swelling and induration Neck erythema Dysphonia Dysphagia Patients may be euthyroid.	Ultrasound or CT may demonstrate inflammation, destruction of the thyroid, and/or abscess formation; these findings may be absent early in the course of the disease.	Beta-adrenergic blocking agents for tachycardia Antibiotics and/or surgical drainage Definitive treatment of pyriform sinus fistula, when present.

Drug Induced Thyroiditis	Amiodarone
	Lithium
	Immunomodulators
	• immune checkpoint inhibitors
	• tyrosine kinase inhibitors
		Drug induced, related to specific drugs
		Amiodarone
		• Contains a large amount of iodine, and has a significant effect on thyroid function.
		• type-1 amiodarone induced thyroiditis (AIT)
		• iodine content of amiodarone unmasks subclinical Graves disease or goiters
		• type-2 AIT
		• direct destructive effect on thyroid cells, resulting in the release of preformed hormone[2]
		Immunomodulators
		• direct destructive effect on thyroid cells
		Lithium
		• more commonly causes hypothyroidism
		• exact mechanism unknown, theories include:
		  • Increased iodide retention and stores in the thyroid resulting in increased thyroid hormone production
		  • Autoimmune mechanism
		  • Direct toxic effect.[3]
			Exacerbation of the tachyarrhythmia for which the patient is being treated or heart failure.
			Immunomodulators
			• initial hyperthyroid phase (typically within a few weeks, but can present years later), followed by hypothyroidism[4]
				Typical lab findings for thyrotoxicosis (low TSH and high free T4)	Treatment depends on the inciting agent and type of reaction
					Amiodarone
					AIT-1
					• stop amiodarone
					• Antithyroid therapy
					AIT-2
					• corticosteroids
					• may or may not stop amiodarone
					Lithium
					• stop lithium
					Immunomodulators
					• inciting agent may or may not be stopped, depending on the type of reaction

Factitious Thyroiditis		Exogenous thyroid ingestion • intentional • nutritional supplements, particularly those marketed for weight loss.[5] • accidental	Thyroid enlargement not present on physical exam	Low thyroglobulin levels Low T3/T4 ratio (<20 ng/microgram) Radioactive iodine uptake is depressed	Cessation of offending agent
Subclinical Hyperthyroidism	Risk factor for cardiovascular morbidity and mortality, as evidenced by coronary artery disease, acute coronary events and atrial fibrillation Patients older than 65 years at higher risk	Subclinical hyperthyroidism with suppressed TSH and variable levels of functional thyroid hormone in the body Over time, some patients may remit and some will progress to full hyperthyroidism.	Patients are clinically euthyroid, but there is association with cardiovascular disease, osteoporosis, and changes in mood and cognition	Low TSH • lower TSH imparts higher riskNormal free T4 and T3	Treatment is recommended in patients over 65 with TSH <0.1 mU/L over time, IF They are asymptomatic but have risk factors for cardiovascular disease, osteoporosis, or are postmenopausal women not on estrogens or bisphosphonates OR They are symptomatic

Unless otherwise specifically noted, information in this table summarizes that presented in: Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016;26(10):1343-1421.

6 Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016;26(10):1343-1421.

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[2]Bartalena L, Bogazzi F, Chiovato L, Hubalewska-Dydejczyk A, Links TP, Vanderpump M. 2018 European Thyroid Association (ETA) Guidelines for the Management of Amiodarone-Associated Thyroid Dysfunction. *Eur Thyroid J*. 2018;7(2):55-66.

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[4]Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Factors associated with mortality of thyroid storm: analysis using a national inpatient database in Japan. *Medicine (Baltimore)*. 2016;95(7):e2848.

[5]Satoh T, Isozaki O, Suzuki A, et al. 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition). *Endocr J*. 2016;63(12):1025-1064.

inadequate dietary iodine intake, thyroid medication noncompliance, and previous treatment of thyrotoxicosis. Worldwide, iodine deficiency is the most common cause of hypothyroidism; however, in iodine-replete regions, the primary cause is autoimmune. Hypothyroidism may also be associated with other autoimmune diseases, most commonly diabetes mellitus.

Central causes of hypothyroidism are rare and result from hypothalamic dysfunction in the secretion of TRH or pituitary dysfunction in the secretion of TSH. Pituitary adenoma is the most common cause of central hypothyroidism. Other causes include pituitary hemorrhage (Sheehan syndrome), pituitary infiltrative processes, brain injury, and space-occupying mass. Sheehan syndrome is a result of postpartum pituitary hemorrhage that leads to pituitary ischemia and necrosis. Patients often have lactation failure, amenorrhea, adrenal insufficiency, and central hypothyroidism.

Clinical Features

History and Physical Examination

Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure, which may lead to death. Patients with early hypothyroidism often present with vague complaints. As a result, thyroid dysfunction should be considered in patients with generalized arthralgias, infertility or menstrual changes, depression, and hypercholesterolemia. Typical symptoms develop insidiously and progress with the disease (Box 117.5). Patients with subclinical hypothyroidism may present with varying nonspecific signs and symptoms similar to those of patients with overt hypothyroidism, but less pronounced. Patients with Hashimoto thyroiditis present typically with an insidiously developed goiter and hypothyroidism.

The thyroid plays a fundamental role in maintaining cardiovascular homeostasis in physiologic and pathologic states; it influences cardiac contractility, heart rate, diastolic function, and systemic vascular resistance. Increased peripheral vascular resistance and low cardiac output have been suggested to be additional links between hypothyroidism and impaired blood pressure regulation and resultant hypertension. Antihypertensive medications are usually ineffective in noneuthyroid individuals. The accelerated atherosclerosis in hypothyroidism is ascribed to dyslipidemia, diastolic hypertension, and impaired endothelial function. These cardiovascular findings are linked to overt and subclinical hypothyroidism.

Overt hypothyroidism leads to significant neuropsychiatric impairments of mood and cognition. Subclinical hypothyroidism may cause subtle deficits in memory and cognition.

Pulmonary abnormalities in hypothyroidism are primarily related to hypoventilation and hypercapnia; up to 65% of patients with pulmonary hypertension have concomitant thyroid dysfunction. Although the exact relationship is unknown, pulmonary artery pressures normalize after treatment of thyroid disease.

In pregnancy, hypothyroidism may be manifested typically, but it is often subtle and difficult to distinguish from normal changes in pregnancy.

In children, hypothyroidism may affect growth, development, and cognitive ability. Declining growth velocity noticed during several years might be the first clue to evaluate for thyroid disorders. T_4 replacement will induce a rapid growth spurt, although predicted bone maturation size might not be achieved. In adults, thyroid hormone functions to regulate and maintain bone mass; patients with hypothyroidism are at increased risk for fracture, although the underlying mechanism resulting in this association is unclear.

Myxedema Coma

Myxedema coma is a life-threatening event, presenting with altered mental status, hypothermia, and a concomitant precipitating event.[14] Precipitating events are listed in Box 117.6. Diagnosis must often be made on the basis of clinical findings (Box 117.7), and can be difficult because not all patients will present with all 3 elements described mentioned previously. Treatment of myxedema coma requires potentially toxic doses of thyroid hormone and can precipitate thyroid storm. Mortality rates are high, up to nearly 30%, even with optimum therapy. Higher mortality is seen in hospitalized patients who require steroids, mechanical ventilation, or exogenous catecholamines.[4] Without treatment, the mortality approaches 100%.

BOX 117.5 Symptoms and Signs of Hypothyroidism

Vital Signs
- Systolic blood pressure, normal or low
- Diastolic blood pressure, normal or elevated
- Slow pulse to sinus bradycardia
- Respirations, normal or slow, shallow
- Temperature, normal, but prone to hypothermia with stress

Hypometabolic Complaints
- Cold intolerance
- Fatigue
- Weight gain, but decreased appetite

Cutaneous
- Coarse, brittle hair
- Alopecia
- Dry skin, decreased perspiration
- Pallor, cool hands and feet
- Coarse, rough skin
- Yellow tinge from carotenemia
- Thin, brittle nails
- Lateral thinning of the eyebrows

Neurologic
- Slow mentation and speech
- Impaired concentrating ability and attention span
- Lethargy
- Decreased short-term memory
- Agitation, psychosis
- Seizures
- Ataxia, dysmetria
- Mononeuropathy
  - Carpal tunnel syndrome
  - Sensorineural hearing loss
- Peripheral neuropathy, paresthesias

Muscular
- Proximal myopathy
- Pseudohypertrophy
- Delayed relaxation of reflexes (hung up or pseudomyotonic)

Cardiac
- Decreased exercise capacity
- Dyspnea on exertion
- Sinus bradycardia
- Long QT with increased ventricular arrhythmia
- Chest pain, accelerated coronary disease
- Diastolic heart failure (delayed ventricular relaxation)
- Pericardial effusion (asymptomatic)
- Peripheral edema

Respiratory
- Dyspnea on exertion
- Obstructive sleep apnea
- Primary pulmonary hypertension

Gastrointestinal
- Constipation
- Ileus
- Gastric atrophy

Reproductive
- Oligomenorrhea and amenorrhea
- Menorrhagia
- Decreased fertility
- Early abortions
- Decreased libido
- Erectile dysfunction

Rheumatic
- Polyarthralgias
- Joint effusions
- Acute gout or pseudogout

Head, Ear, Eyes, Nose, and Throat
- Hoarseness
- Deep husky voice
- Macroglossia
- Hearing loss
- Periorbital swelling
- Broad nose
- Swollen lips
- Goiter

Differential Diagnoses

Differential considerations include other causes of the common clinical presentations of hypothyroidism, such as congestive heart failure,

BOX 117.6 Myxedema Coma: Aggravating or Precipitating Factors

Infection, sepsis (especially pneumonia)
Exposure to cold
Cerebrovascular accident
Drug effect
- Altered sensorium: sedative-hypnotics, narcotics, anesthesia, neuroleptics
- Decreased T_4 and T_3 release: amiodarone, lithium, iodides
- Enhanced elimination of T_4 and T_3: phenytoin, rifampin
- Inadequate thyroid hormone replacement: noncompliance; interference with absorption (iron, calcium, cholestyramine)

Myocardial infarction
Gastrointestinal bleeding
Trauma, burns
Congestive heart failure
Hypoxia
Hypercapnia
Hyponatremia
Hypoglycemia
Hypercalcemia
Diabetic ketoacidosis

T_3, Triiodothyronine; *T_4*, thyroxine.

BOX 117.7 Recognition of Myxedema Coma

Patient profile—older woman in the winter
Known hypothyroidism; thyroidectomy scar
Hypothermia—temperature usually <95.9°F (36°C); <90°F (32°C) is poor prognostic sign; as low as 75°F (24°C) reported; nearly normal in presence of infection
Altered mental status—lethargy and confusion to stupor and coma, agitation, psychosis, and seizures (myxedema madness)
Hypotension—refractory to volume resuscitation and pressors unless thyroid hormone administered
Slow, shallow respirations with hypercapnia and hypoxia; high risk of respiratory failure
Bradycardia (sinus), long QT and ventricular arrhythmias
Myxedema facies—puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism—skin, hair, reflexes, bradykinesis, voice
Acute precipitating illness (e.g., pneumonia)
Drug toxicity (e.g., sedative, narcotic, neuroleptic)
Hyponatremia

pulmonary edema, depression, encephalopathy, hypothermia, systemic infection, and shock.

Diagnostic Testing

Determination of an elevated TSH level is the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism. An elevated TSH level with a low T_4 level is indicative of primary hypothyroidism. Central hypothyroidism is associated with a low or normal TSH level, with a low T_4 level. An increased TSH concentration with a normal T_4 level represents subclinical hypothyroidism.

If the TSH level is normal but the T_4 level is low, hypothyroxinemia exists; patients are often asymptomatic but can experience pathologic effects. A useful confirmatory test is the presence of thyroid antibodies (antithyroglobulin, antimicrosomal). They may help determine the cause of hypothyroidism or may serve to predict a future occurrence. Other laboratory findings may include mild anemia, hypercholesterolemia, elevated hepatic enzyme levels, elevated prolactin level, and hyponatremia. Blood glucose levels may be normal to low.

The electrocardiogram is nonspecific in hypothyroidism. It might reveal sinus bradycardia with low-voltage complexes and nonspecific ST-T wave changes.

The presence of myxedema coma carries a high mortality, and inappropriate treatment can cause thyroid storm, so appropriate identification is essential. A recent scoring system was proposed that indicates the risk of myxedema coma and recommended treatments (Table 117.4). While this scoring system requires wider validation, the elements listed are helpful in guiding the clinician to the diagnosis.[14]

TABLE 117.4 Myxedema Coma Scoring Tool

Criterion	Score
GCS 0-10	4
GCS 11-13	3
GCS 14	2
GCS 15	0
TSH > 30 mU/L	2
TSH 15–30 mU/L	1
Low FT4 (<0.6 ng/dL)	1
Hypothermia (<95 degrees F)	1
Bradycardia (<60 beats/minute)	1
Precipitating Event	1

For total scores 8–10, myxedema coma is most likely and proceeding with treatment is recommended; for total scores 5–7, myxedema coma is likely, and treatment is recommended if there are no other likely diagnoses; for total scores <5, myxedema coma is unlikely and clinicians should consider other diagnoses.
Adapted from: Chiong YV, Bammerlin E, Mariash CN. Development of an objective tool for the diagnosis of myxedema coma. *Transl Res.* 2015;166(3):233-243.

Management

Hypothyroidism

Replacement with levothyroxine (T_4) remains the treatment of choice and resolves most physical and psychological signs and symptoms of hypothyroidism in most patients. Synthetic levothyroxine is a levo isomer of thyroxine and has activity identical to that of the endogenous hormone. Approximately 70% to 80% is absorbed from the GI tract, predominantly in the small intestine. T_4 levels peak approximately 4 hours after ingestion. The T_3 concentration rises more slowly because it depends on conversion from T_4. Dose optimization is guided by monitoring of serum TSH levels and symptoms.

Levothyroxine is the drug of choice for patients with subclinical hypothyroidism and a serum TSH concentration above 10 mIU/L and for symptomatic patients with a serum TSH concentration between 5.1 and 10.0 mIU/L. The usual daily dosage is between 50 and 75 μg. The TSH concentration guides thyroid hormone dosing, and should be checked every 6 to 8 weeks after initiation of treatment until TSH levels normalize. It is recommended that levothyroxine be taken at bedtime or 60 minutes before breakfast to improve absorption.[15]

Studies comparing combination therapy of levothyroxine (T_4) and T_3 (liothyronine) with levothyroxine monotherapy included variable combinations and dosages, and have not established a significant benefit for the vast majority of patients. The most recent American Thyroid

BOX 117.8 Treatment of Myxedema Coma

- Protect airway, ventilatory support; monitor for alkalosis
- Fluid resuscitation
  - 0.9 NS or D_5/0.9 NS if hypoglycemia
  - Watch for unmasking of CHF
- Thyroid hormone replacement
  - T4 200–400 μg IV (give lower doses to patients who are smaller, have coronary artery disease or a history of arrhythmia) loading dose
  - Subsequent daily replacement of 1.6 μg/kg body weight PO, give 75% of this dose if given IV
- Hydrocortisone—100 mg IV every 8 hrs
- Hyponatremia
  - Consider fluid restriction.
  - Avoid hypotonic fluids; use only 0.9 NS or D_5/0.9 NS.
  - If <120 mEq/L, consider 3% saline, 50- to 100-mL boluses.
- Passive rewarming
  - Regular blankets; prevent heat loss
  - If heating blankets are considered, pretreat with IV fluids and monitor blood pressure closely.
  - Avoid mechanical stimulation.
- Treatment of any precipitating illness, with special attention to infectious causes

CHF, Congestive heart failure; *D_5/0.9 NS,* 5% dextrose in 0.9% normal saline; *IV,* intravenous; *PO,* by mouth; *T_3,* triiodothyronine; *T_4,* thyroxine.

Association guidelines do not recommend combination therapy for routine treatment.[15]

Myxedema Coma

The cornerstone for the treatment of myxedema coma is rapid replacement of IV thyroid hormone (Box 117.8). An initial loading dose of 200 to 400 μg IV should be given, using lower doses in patients who are smaller, older, or have a history of coronary artery disease or arrhythmia. Subsequent daily replacement dose is 1.6 μg/kg body weight, decreasing the dose to 75% of the IV dose. In very ill patients, liothyronine administration can be considered in addition to levothyroxine therapy, with extreme caution because elevated levels of T3 in the serum are associated with increased mortality. Stress doses of an IV glucocorticoid are recommended due to possible concomitant adrenal insufficiency. Hydrocortisone, 100 mg IV, is the drug of choice because it has mineralocorticoid and glucocorticoid effects.

Hypotension may respond to crystalloid infusion, but vasopressors are occasionally required. In patients with initially refractory hypotension, the mere replacement of thyroid hormone may have a beneficial effect on improvement of blood pressure. Passive rewarming with blankets and removal from the cold are generally sufficient until the administered thyroid hormone takes effect.

Hyponatremia may occur and is associated with increased mortality. As with other causes of hyponatremia, hypertonic saline should be administered for severe cases of altered mental status or seizures and then corrected more slowly to avoid osmotic demyelination syndrome. The metabolism of sedatives, narcotics, and anesthetics may be slowed, prolonging their effects; lower dosages should be considered.

Disposition

Most patients with hypothyroidism may be treated on an outpatient basis. Patients with severe hypothyroidism or patients with myxedema coma require inpatient care, often in an ICU setting.

Note: There are varying etiologies of hypothyroidism, each with unique aspects of their pathophysiology, diagnosis, and management. These are summarized in Table 117.5.

ADRENAL EXCESS STATES

Foundations

Background and Importance

Adrenal excess states can arise from a variety of causes, including Cushing syndrome, primary and secondary hyperaldosteronism, and pheochromocytoma. Regardless of the etiology, these all result in an excess of adrenal function, which can result in various symptoms that will prompt a patient to present to the ED. In particular, adrenal excess states are to be considered in any patient with resistant hypertension.[16] Left untreated, the long-term metabolic and cardiovascular effects of these diseases can be devastating.

Cushing Syndrome

Pathophysiology

Cushing syndrome results from excessive exposure to cortisol. The most common cause of this syndrome is long-term exogenous steroid administration. Endogenous Cushing syndrome is caused by excessive release of cortisol internally, usually from a corticotropin (ACTH) released from the pituitary (Cushing disease), or cortisol secretion from primary adrenal lesions (adrenal adenoma or carcinoma or adrenal hyperplasia of the adrenal cortex), or ectopic production of a corticotropin-releasing hormone (CRH) by a nonpituitary or other neuroendocrine tumor.[17,18]

Clinical Features

Because of systemic excess in cortisol, patients with Cushing syndrome will present with a variety of nonspecific symptoms given the broad downstream effects of the glucocorticoid exposure. Patients may experience multiple nonspecific symptoms, including psychiatric symptoms, generalized weakness, fatigue, menstrual irregularities and weight gain. Physical examination may reveal obesity, hirsutism, abdominal striae, an increase in adipose distribution on the back and above the clavicles (the classic "buffalo hump") and thin skin.[16,18] According to Nieman and colleagues, easy bruising, facial plethora, proximal muscle weakness and abdominal striae are the physical findings most associated with Cushing syndrome.[18] Cushing syndrome has also been linked to hypertension, diabetes, central obesity, and osteoporosis.[17]

Differential Diagnoses

Because of symptoms that are similar across the spectrum of etiologies of adrenal excess states, the differential diagnosis spans the same gamut. Resistant hypertension and glucose disorders can also be seen in hyperaldosteronism and pheochromocytoma. It can be difficult to distinguish simple obesity and metabolic syndrome from Cushing syndrome.[19] There is also significant overlap in the presenting symptoms of simple depression. Menstrual irregularities can also be associated with a variety of other etiologies, in addition to Cushing syndrome.[18]

Diagnostic Testing

The diagnostic workup of patients with suspected endogenous Cushing syndrome is complex and usually performed in the outpatient setting. Patients who should be referred for evaluation include individuals with an incidentaloma consistent with adrenal adenoma on imaging; patients who have presentations that would not be typical for their age, such as hypertension or osteoporosis at a young age; and patients with multiple clinical findings that would suggest Cushing syndrome.[18]

TABLE 117.5 Hypothyroidism Etiologies

	Background and Importance	Pathophysiology	Clinical Features	Diagnostic Testing	Management
Primary	Most common etiology of hypothyroidism[1]	Results from thyroid hormone deficiency	Typical symptoms span the spectrum from hypothyroidism to myxedema coma	An elevated TSH level with a low T_4 level indicates primary hypothyroidism.	Levothyroxine replacement
Autoimmune	Hashimoto thyroiditis, also known as chronic autoimmune lymphocytic thyroiditis One of the most common organ-specific autoimmune diseases Most common cause of primary hypothyroidism in iodine-replete areas of the world	Infiltration of the thyroid gland by lymphocytic inflammatory cells results in destruction and eventual fibrous replacement of the gland's follicular tissue and subsequent functional hypothyroidism.	Patients typically present with an insidiously developed goiter and hypothyroidism.	Elevated TSH Low T_4	Levothyroxine replacement
Infiltrative disorders[1]	Rare cause of primary hypothyroidism	Infectious Malignant Autoimmune Inflammatory	Patients will present with typical hypothyroid symptoms	Elevated TSH Low T_4	Levothyroxine replacement
Congenital thyroid dysfunction	Most preventable cause of intellectual disability	Most commonly caused by thyroid dysgenesis, resulting in decreased production of T_4. Some infants have minimal thyroid tissue but it is insufficient to sustain normal thyroid hormone production. Cognitive deficit is directly related to the amount of delay in diagnosis and treatment	Typically discovered on newborn screening tests	Elevated TSH Low T_4	Levothyroxine replacement
Pregnancy-related hypothyroidism		Thyroxine binding globulin (RBG) and Total T_4 increase and peak by 16 weeks and stay elevated throughout pregnancy.[2] Human chorionic gonadotropin (hCG) and TSH have identical subunits, which then both stimulate the release of T_4 and T_3, resulting in a decreased level of TSH throughout pregnancy. Increased peripheral metabolism of thyroid hormone occurs primarily in the second and third trimesters	In pregnancy, hypothyroidism may be manifested typically, but it is often subtle and difficult to distinguish from normal changes in pregnancy. Other obstetric complications of hypothyroidism include miscarriage, anemia, abruptio placentae, postpartum hemorrhage, low birth weight, and neonatal respiratory distress[2]	TSH will be altered, interpret based on local trimester- specific TSH ranges[3]	Women with preexisting hypothyroidism will generally require increased doses of replacement hormone in pregnancy. At this time, the evidence is not sufficient to recommend universal screening for thyroid function and subsequent treatment in pregnant women without overt symptoms or risk factors for hypothyroidism.[2]
Medication related	Lithium Lithium causes overt hypothyroidism in 14–17% of patients, and subclinical hypothyroidism in 19–35% of patients.	Lithium inhibits release of T_4 and T_3. Lithium may increase autoimmunity to the thyroid if it was preexisting.	Typical hypothyroid signs and symptoms	Elevated TSH Low T_4	Lithium: Treatment with exogenous thyroid hormone is effective, and lithium therapy need not be discontinued.

Continued

TABLE 117.5 Hypothyroidism Etiologies—cont'd

	Background and Importance	Pathophysiology	Clinical Features	Diagnostic Testing	Management
	Amiodarone[4] • Anti-thyroid peroxidase autoantibodies and female gender are linked with an increased risk of amiodarone induced hypothyroidism (AIH) • Increased incidence in iodine replete areas	Amiodarone is a class III antiarrhythmic medication Chemical structure similar to that of T_4 Contains large amounts of iodine. Inhibits the peripheral conversion of T_4 to T_3 Directly cytotoxic to the thyroid Blocks thyroid hormone entry into cells Decreases T_3 receptor binding	Typical hypothyroid signs and symptoms	Elevated TSH Low T_4	If amiodarone therapy must be continued for arrhythmia control, patients with AIH may be successfully treated with exogenous thyroid hormone replacement and amiodarone use may continue.[4] Patients should be screened with a TSH prior to starting amiodarone.[5]
Inadequate dietary intake	Uncommon in developed nations, but still a major concern in areas where the iodine content in the water is low.	Insufficient dietary iodine intake leads to reduced T4 and T3 production, with compensatory increase in TSH concentration and gland cell proliferation, goiter.	Goiter	Elevated TSH Low T_4	Dietary iodine supplementation
Prior hyperthyroid treatment		Thyroid known to be functionally absent based on prior anti-thyroid treatment	Typical hypothyroid signs and symptoms	Elevated TSH Low T_4	Levothyroxine replacement
Surgically removed		Thyroid known to be surgically absent based on prior anti-thyroid treatment	Typical hypothyroid signs and symptoms	Elevated TSH Low T_4	Levothyroxine replacement
Nonthyroidal Illness Syndrome (NTSI)[6–8]	Previously known as euthyroid sick syndrome Transient form of central hypothyroidism that occurs in critically ill patients	Its molecular basis remains unclear, but its presence in critically ill patients predicts adverse outcomes and mortality.[6–8] In acute phases, this is likely related to changes in binding and uptake of thyroid hormone by cells, as well as decreased conversion of T_4 to T_3. In chronic phases, likely results from dysregulation of the hypothalamic-pituitary-thyroid axis in the setting of critical illness	Typical hypothyroid signs and symptoms in the setting of critical illness	Initially low T_3, followed by decrease in T_4 and TSH as illness progresses.	At this time, there is no evidence that treatment of patients with NTIS improves outcomes.

[1]Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet*. 2017;390(10101):1550-1562.
[2]Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017;27(3):315-389.
[3]Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;24(12):1670-1751.
[4]Bartalena L, Bogazzi F, Chiovato L, Hubalewska-Dydejczyk A, Links TP, Vanderpump M. 2018 European Thyroid Association (ETA) Guidelines for the management of amiodarone-associated thyroid dysfunction. *Eur Thyroid J*. 2018;7(2):55-66.
[5]Kinoshita S, Hosomi K, Yokoyama S, Takada M. Time-to-onset analysis of amiodarone-associated thyroid dysfunction. *J Clin Pharm Ther*. 2020 Feb;45(1):65-71.
[6]Gutch M, Kumar S, Gupta KK. Prognostic value of thyroid profile in critical care condition. *Indian J Endocrinol Meta*b. 2018;22(3):387-391.
[7]Kothiwale VA, Patil P, Gaur S. Correlation of thyroid hormone profile with the Acute Physiology and Chronic Health Evaluation II Score as a prognostic marker in patients with sepsis in the intensive care unit. *J Assoc Physicians India*. 2018;66(7):59-62.
[8]Padhi R, Kabi S, Panda BN, Jagati S. Prognostic significance of nonthyroidal illness syndrome in critically ill adult patients with sepsis. *Int J Crit Illn Inj Sci*. 2018;8(3):165-172.

Diagnosis begins with urine free cortisol, late night salivary cortisol and/or a dexamethasone suppression test, and additional imaging studies as indicated.[18] Given that these tests typically occur outside of the ED, these patients should be referred to a primary physician for definitive testing, or have workup by an inpatient team when admission is indicated.

Management

Management in the ED is directed towards treating the manifestation of Cushing syndrome that prompted the current presentation. Acute control of hypertension and glucose disorders is as per routine clinical practice. Definitive management of the underlying causes follows appropriate diagnosis via the methods described above and requires surgical resection of responsible lesions.[18]

Disposition

The need for hospitalization of patients who present with extremes of the disorders associated with Cushing syndrome (uncontrolled hypertension, glucose disorders, fractures) is determined by usual practices for these presentations. Most patients with chronic Cushing syndrome and milder symptoms can be discharged and referred for further workup as outpatients.

Hyperaldosteronism

Pathophysiology

Hyperaldosteronism is the result of excessive aldosterone production. Aldosterone acts on the kidneys, regulating sodium absorption, potassium excretion, and subsequently, hydrogen excretion. In primary hyperaldosteronism, excessive aldosterone is produced by the adrenal glands, independent of the signals from the renin-angiotensin system and sodium administration.[20,21] It is the most common cause of secondary hypertension and is significantly linked to cases of refractory hypertension.[21] Because aldosterone has toxic effects on vascular structures, it can result in cardiovascular disease and stroke, in addition to hypertension.[16] Primary hyperaldosteronism is caused by an intrinsic abnormality of the adrenal glands, such as hyperplasia or malignancy. Secondary hyperaldosteronism is caused by increased action of renin on the adrenal glands, as seen in states of renal hypoperfusion, but has the same downstream effects.

Clinical Features

Patients with hyperaldosteronism most commonly present with hypertension and its associated symptoms, as it is significantly linked with refractory hypertension. Patients may also present with a variety of other cardiovascular events, such as atrial arrhythmias, heart failure, and strokes. Primary aldosteronism is associated with the metabolic syndrome of obesity, high-density lipoprotein cholesterol and hypertriglyceridemia, and hyperglycemia. Laboratory workup may also demonstrate hypokalemia.[22]

Differential Diagnoses

Hyperaldosteronism can mimic any disease that presents with hypertension and/or disorders of potassium regulation. Its differential diagnosis includes essential hypertension, other adrenal disorders, thyroid dysfunction, and diabetes.

Diagnostic Testing

The most recent Endocrine Society clinical practice guideline recommends referral for testing for any patient with hypertension that is not controlled with three or more medications, or any patient requiring four or more medications, any patients with hypertension and hypokalemia, sleep apnea, family history of early onset hypertension or stroke, or a family history of primary aldosteronism. In the ED, significant hypertension and any incidentaloma on the adrenal should also be referred for further evaluation.[23] Workup (inpatient or outpatient) entails measurements of the plasma renin activity or plasma renin concentration and plasma aldosterone concentration, as well the plasma aldosterone/renin ratio. If the renin concentration or renin activity are suppressed, and the aldosterone level is inappropriately high, then further confirmatory testing with laboratory studies and imaging are indicated.[23]

Management

Presentations of acute cardiovascular events, refractory hypertension or severe electrolyte derangements are managed acutely in the ED according to usual practice. Further workup and treatment for underlying primary aldosteronism is initiated once the patient has been stabilized.

Disposition

Patients with severe, acute cardiovascular events or electrolyte derangements should be admitted to the hospital according to usual practice. Patients who are stable or improving and are otherwise appropriate for discharge based on their presenting symptoms and diagnosis can be discharged home with referral for further workup as described previously.

Pheochromocytoma and Paraganglioma

Pathophysiology

Emanating from adrenal medullary chromaffin cells, pheochromocytomas are rare catecholamine–secreting neuroendocrine tumors, whereas paragangliomas are catecholamine–secreting tumors arising from the thoracic and abdominal parasympathetic ganglia.[24] The excess catecholamine states result in significant downstream systemic effects, both based on the action of norepinephrine and epinephrine as vasopressors. There is also evidence that patients with pheochromocytomas and paragangliomas have increased circulating steroids, due to the interaction between the adrenal cortex and the medulla.[25] The tumors can be benign or associated with malignancy, especially in patients who are younger and have larger tumors.[26] Certain medications can potentiate the effects of catecholamines and result in an acute exacerbation of underlying pheochromocytoma. These include dopamine receptor antagonists, beta-blockers, sympathomimetics, opioid analgesics, norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, monoamine oxidase inhibitors, corticosteroids, peptides, and neuromuscular blocking agents.[24]

Clinical Features

Clinical features of pheochromocytoma and paraganglioma are characteristic of catecholamine excess. Classic symptoms include paroxysms of hypertension, diaphoresis, palpitations, headache, abdominal pain, nausea, vomiting, and weight loss. In extreme cases, patients may present with hypertensive crisis.[27] With increasing use of CT and MRI imaging, a larger proportion of patients are diagnosed after a tumor is discovered incidentally (e.g., "incidentaloma").

Differential Diagnoses

Because catecholamine excess mimics any hyperadrenergic state, the differential diagnosis includes sympathomimetic toxicity, withdrawal syndromes, hyperthyroidism, serotonin syndrome, neuroleptic malignant syndrome, and presentations of typical untreated or refractory hypertension and underlying arrhythmias.

Diagnostic Testing

Definitive testing for pheochromocytoma and paraganglioma entails establishing a biochemical diagnosis via plasma free metanephrines

or urinary fractionated metanephrines. Once the diagnosis is apparent via these tests, CT imaging of the thorax, abdomen, and pelvis with contrast is recommended. MRI is reserved for patients with metastatic disease, neck and skull base lesions, or other contraindications to CT.[24] Given the significant overlap in presentation and symptomatology with multiple diseases as listed previously, providers must maintain a high index of suspicion in certain patient populations. Testing for pheochromocytoma and paraganglioma is indicated for any patient with the signs and symptoms listed previously, especially if they are paroxysmal, symptoms like this that are precipitated by the medications listed previously, or a personal or family history of pheochromocytoma, paraganglioma, multiple endocrine neoplasia type 2 (MEN2), or Von Hippel-Lindau (VHL) disease. Any patient with an adrenal incidentaloma should also be referred, regardless of symptoms.[24]

Management

Acute management of pheochromocytoma and paraganglioma focus on controlling the catecholamine surge effects. The first-line treatment is typically alpha-adrenergic blockade, such as phenoxybenzamine (final dose typically between 20–100 mg daily) or doxazosin. If resultant tachycardia ensues, providers may add calcium channel blockers or beta-adrenergic blockers. Of note, in patients with pheochromocytoma and catecholamine excess, beta-adrenergic receptor blockade in isolation can result in hypertensive crisis because of unopposed alpha-adrenergic receptor stimulation. Beta-adrenergic blockade should only be performed following alpha-adrenergic blockade in these patients. Use of calcium channel blockers alone is not recommended as initial treatment, but can be used in patients with very mild hypertension or undesirable alpha-adrenergic receptor blocker side effects.[24] Surgical removal of the offending pheochromocytoma or paraganglioma is the definitive treatment, and is typically delayed until the hyperadrenergic state is adequately controlled.

Disposition

Patients who present in hypertensive crisis or other extreme presentation who are not controlled with initial doses of the medications listed above should be admitted for continued treatment and monitoring. Patients who are stable can be discharged for continued workup and referral as outpatients.

ADRENAL INSUFFICIENCY

Foundations

Background and Importance

Adrenal insufficiency is the failure of the adrenal glands to function appropriately, and is a potentially life-threatening disease. Acute manifestations of disease may result in severe, refractory hypotension. Secondary adrenal insufficiency is more common than primary adrenal insufficiency. Its most common cause is exogenous corticosteroid administration.

Anatomy and Physiology

The adrenal glands are responsible for the release of the hormone aldosterone, corticosteroids, and catecholamines. They are paired structures that sit in the retroperitoneum, one atop each kidney. The adrenal gland has two distinct structures—the outer adrenal cortex, comprised anatomically of the zona glomerulosa, and the medulla, comprised anatomically of the zona fasciculata and reticularis. The medulla acts in concert with the central nervous system to produce and secrete epinephrine and norepinephrine in response to sympathetic stimulation. It also secretes the mineralocorticoid cortisol from the zona fasciculata and androgens from the zona reticularis. The outer cortex, which includes the zona glomerulosa, secretes the mineralocorticoid aldosterone.

ACTH, produced and secreted by the anterior pituitary, stimulates the adrenal cortex to synthesize and produce cortisol, which regulates carbohydrate, protein, and lipid metabolism, and aldosterone, which regulates fluid and electrolyte balance through sodium and potassium homeostasis. Cortisol is the primary glucocorticoid in humans, accounting for approximately 95% of all glucocorticoid activity.

Pathophysiology

Primary adrenal insufficiency, or Addison disease, is the failure of the adrenal gland to produce cortisol, aldosterone, or both, with an intact hypothalamic-pituitary-adrenal (HPA) axis (Fig. 117.3). Its most common cause in adults is autoimmune destruction of the adrenal gland. It can also be caused by infectious diseases and certain medications.[16] Adrenal insufficiency may occur alone, with other autoimmune diseases.

In primary disease, the HPA axis remains intact. Primary adrenal insufficiency is characterized by absent or low cortisol with high levels of circulating ACTH because of reduced negative feedback effects on the anterior pituitary. The increased ACTH concentration results in secretion of other hormones with similar chemical structure. One classic feature exemplifying this relationship is ACTH stimulation of melanocyte-stimulating hormone, which causes melanocytes to form a black pigment and the characteristic skin hyperpigmentation seen in those with primary adrenal insufficiency.

Secondary adrenal insufficiency is a result of impaired stimulation of the adrenals from the disruption of normal secretion of ACTH by the pituitary (see Fig. 117.3). It is characterized by a low plasma cortisol level, with low circulating ACTH levels.

Tertiary adrenal insufficiency is caused by hypothalamic disease. There is a decrease in release of corticotropin-releasing hormone, resulting in minimal ACTH and cortisol production. Aldosterone, sex hormone, and catecholamine synthesis are normal; the most common cause is long-term exogenous steroid administration.

Adrenal insufficiency may be further characterized as acute or chronic (Box 117.9). The most common cause of acute adrenal insufficiency is the exogenous administration of glucocorticoids, which results in suppression of the HPA axis. Although the time for HPA axis recovery after exogenous suppression is highly variable, adrenal insufficiency should be anticipated to occur in patients who receive corticosteroid therapy for prolonged periods, typically more than several weeks.

Adrenal crisis is usually seen in patients with Addison disease because of mineralocorticoid deficiency but can also present in patients with secondary or tertiary adrenal insufficiency who undergo severe physiologic stress, or exogenous steroid withdrawal (after suppression of the HPA axis). These stressors deplete cortisol stores and impair the ability to mount a normal stress response.

Clinical Features

The clinical manifestations of chronic adrenal insufficiency are nonspecific, as seen in Box 117.10. Primary and secondary adrenal insufficiency result in hyponatremia from different mechanisms—aldosterone deficiency and sodium wasting in primary adrenal insufficiency and a low cortisol level and free water retention in secondary adrenal insufficiency.

Primary adrenal insufficiency characteristically has more pronounced clinical manifestations than secondary adrenal insufficiency. Patients have symptoms related to a deficiency of glucocorticoids,

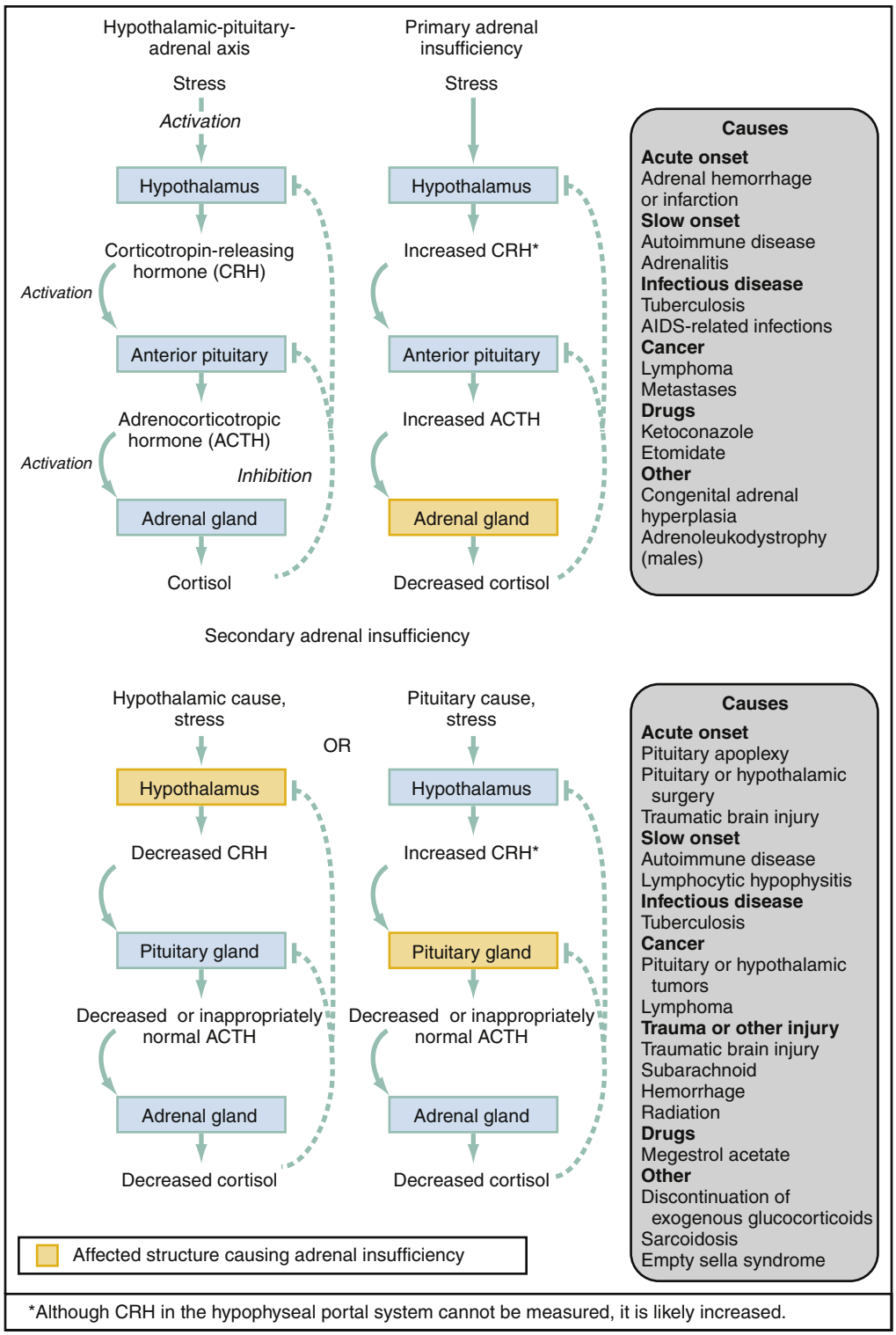

Fig. 117.3 Hypothalamic-pituitary-adrenal axis and causes of primary and secondary adrenal insufficiency. (Adapted from: Wallace I, Cunningham S, Lindsay J. The diagnosis and investigation of adrenal insufficiency in adults. *Ann Clin Biochem*. 2009;46[Pt 5]:351-367.)

mineralocorticoids, and androgens. Primary adrenal insufficiency more commonly presents with skin hyperpigmentation, particularly in areas exposed to the sun or subject to friction or pressure, salt craving, hyperkalemia, and acidosis. These patients may show signs of sodium and volume depletion (e.g., orthostatic hypotension and tachycardia). In secondary adrenal insufficiency, patients more often present with pale skin, loss of axillary and pubic hair, decreased libido, and impotence. Glucocorticoid deficiency and low ACTH concentrations may result in hypotension and hyponatremia with normal potassium levels.

BOX 117.9 Causes of Adrenal Insufficiency

Primary Adrenal Insufficiency

Chronic

Autoimmune adrenalitis (Addison disease): isolated or polyglandular deficiency, human immunodeficiency virus (HIV) infection (direct involvement or disseminated cytomegalovirus, *Mycobacterium avium-intracellulare,* tuberculosis, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, *Pneumocystis* pneumonia)
Tuberculosis and disseminated infections as seen with HIV
Metastatic cancer (breast, lung)
Infiltrative (sarcoid, hemochromatosis, amyloid)
Congenital (adrenal hypoplasia, adrenoleukodystrophy, ACTH resistance)
Bilateral adrenalectomy
Drug toxicity (e.g., etomidate, ketoconazole, rifampicin)

Acute

Adrenal hemorrhage
Meningococcemia and other sepsis
Anticoagulation (heparins and warfarin)
Anticardiolipin antibody syndrome
Trauma

Secondary Adrenal Failure

Chronic

Pituitary tumor (primary or metastatic)
Pituitary surgery or irradiation
Chronic steroid use with functional deficiency
Infiltrative (sarcoid, eosinophilic granuloma, tuberculosis)
Traumatic brain injury
Postpartum pituitary necrosis (Sheehan syndrome)
Empty sella syndrome

Acute

Pituitary apoplexy (hemorrhage into a pituitary tumor)
Postpartum pituitary necrosis (Sheehan syndrome)
Traumatic brain injury
Relative adrenal insufficiency (sepsis, hepatic failure, severe acute pancreatitis, trauma)

ACTH, Adrenocorticotropic hormone.

BOX 117.10 Clinical Features of Adrenal Insufficiency

General

Weakness, fatigue
Anorexia
Gastrointestinal symptoms
Weight loss
Hyponatremia
Blood pressure ≤ 110/70 mm Hg
Fevers (mild)
Depression, apathy
Myalgia, arthralgias
Auricular calcifications

Primary

Hyperpigmentation
Salt craving
Orthostasis, syncope
Vitiligo
Hyperkalemia
Hyperchloremia and acidosis
Hypoglycemia

Secondary

Hyperkalemia
Hyperpigmentation
Hypoglycemia
Orthostasis, hypotension
Amenorrhea
Axillary and pubic hair loss
Decreased libido

Crisis

Refractory hypotension

Adrenal crisis presents with hypotension and shock that does not respond to fluid resuscitation and pressors. Patients may have many other nonspecific symptoms, as listed above, but shock is the hallmark.

Differential Diagnoses

Because of the vague and nonspecific symptoms, the differential diagnosis of hypoadrenalism is extensive. The wasting associated with chronic adrenal insufficiency resembles that of anorexia nervosa or an occult carcinoma. The generalized weakness, fatigue, and myalgias can be confused with chronic fatigue syndrome, polymyalgia rheumatica, myopathy, hypothyroidism, or influenza syndromes.

Lack of recognition of acute adrenal crisis with refractory hypotension can result in evaluations for sepsis, GI bleeding, myocardial ischemia, or anaphylaxis. Abdominal pain in crisis may be clinically indistinguishable from an acute abdomen, especially if precipitated by adrenal hemorrhage. The headache and visual field cuts in pituitary apoplexy may resemble those of a hemorrhagic stroke. Finally, the constellation of symptoms seen in acute adrenal insufficiency—weakness, malaise, fatigue, nausea, dizziness, and arthralgias—is also present in steroid withdrawal syndrome. Because both can occur with the cessation of chronic glucocorticoid administration, history is critical to distinguish between the two disease processes.

Diagnostic Testing

Although there are many tests available to confirm the diagnosis of adrenal insufficiency, they require a significant amount of time or serial testing. For this reason, if there is suspicion of adrenal crisis, treatment should be initiated immediately, prior to confirmatory tests.

Mild to moderate hyponatremia, with levels typically above 120 mEq/L, are seen in primary adrenal insufficiency. Aldosterone deficiency leads to sodium wasting, and decreased cortisol levels lead to increased antidiuretic hormone, resulting in increased water absorption. Hyperkalemia may be seen in primary adrenal insufficiency secondary to a low circulating aldosterone concentration, but is not seen in secondary causes when aldosterone is not affected.

In stable patients, cortisol measurement is the mainstay for an accurate diagnosis. Measurement of the cortisol level in the ACTH stimulation test is the standard method. Random basal serum cortisol concentrations are of limited value for assessment of HPA axis reserve. In most emergent presentations, these tests are reserved for inpatient workup after initial ED stabilization.

Management

Patients with adrenal insufficiency require hormone replacement to correct a lack of circulating glucocorticoid and mineralocorticoid. Treatment of adrenal crisis should begin as soon as possible and prior

to diagnostic testing when crisis is suspected. The first-line treatment is hydrocortisone, 100 mg IV, with IV fluids, pressor support and glucose administration, as indicated (Box 117.11). An alternative is dexamethasone (4-mg IV bolus); in contrast to hydrocortisone, it does not interfere with serum cortisol assays.

Chronic management of adrenal insufficiency includes hydrocortisone (30 mg total daily in split doses; two-thirds of the daily dose is usually given in the morning and one-third in the late afternoon) and fludrocortisone, (50 to 200 μg/day) for mineralocorticoid replacement. In the setting of fever, infection, or other illness, these doses should be increased.

Whereas definitive treatment of secondary adrenal insufficiency is directed at replacement of missing hormone (ACTH or CRH) at the level of the hypothalamus or pituitary, in the ED setting, simple steroid hormone replacement is administered. Steroid tapering is necessary when gradual downregulation of the HPA axis has been provoked by exogenous glucocorticoids. There is no universally recommended method for steroid tapering.

Disposition

Severely ill patients should have the underlying disease process identified and treated; an ICU setting is indicated due to the high mortality rate. Most patients with mild symptoms of hypoadrenalism may be discharged for outpatient evaluation and treatment.

The references for this chapter can be found online at ExpertConsult.com.

BOX 117.11 Treatment of Hypoadrenalism

Maintenance

Hydrocortisone, 15–25 mg, divided into 2 or 3 doses daily
Fludrocortisone, 50–100 μg/day

Maintenance During Minor Illness

Hydrocortisone, double typical daily dosages
Fludrocortisone, 50–200 μg daily

Coverage During Procedural Stress

Hydrocortisone, 100 mg IV

Adrenal Crisis or Relative Adrenal Insufficiency of Critical Illness

Dexamethasone, 4 mg IV bolus
or
Hydrocortisone, 100 mg IV bolus, followed by additional dosing of 200 mg/24 hrs as bolus divided every 6 hrs or infusion if critically ill or major stress
0.9 NS, 2–3 L in the first few hours
Switch to D_5/NS if hypoglycemia
Treat precipitating illness

D_5/NS, 5% dextrose in normal saline; *0.9 NS,* 0.9% normal saline.

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CHAPTER 117: QUESTIONS AND ANSWERS

1 What is the most common presenting sign of thyrotoxicosis?

a. Atrial fibrillation
b. Means-Lerman scratch
c. Tachycardia
d. Wide pulse pressure

Answer: C. The most common cardiac sign of thyrotoxicosis is tachycardia. Widened pulse pressure, a Means-Lerman scratch (a systolic friction rub), dilated cardiomyopathy, and pulmonary hypertension are all cardiac findings in patients with thyrotoxicosis, with atrial fibrillation being more common in patients over the age of 65.

2. In thyroid storm, which of the following is the proper sequence of drug administration?

a. All three together (antithyroid drugs, sodium or potassium iodide, steroid) at the same time
b. Antithyroid drugs, sodium or potassium iodide, steroid
c. Sodium or potassium iodide, steroid, antithyroid drugs
d. Steroid, sodium or potassium iodide, antithyroid drugs

Answer: B. Iodine can precipitate thyroid storm and must be given a minimum of 1 hour after thionamide therapy (PTU or methimazole). As such, the typical order is beta blocker (propranolol), PTU, or methimazole, and then iodine (SSKI, Lugol solution). In addition, it is important to identify and treat the precipitating cause of thyroid storm.

3. A 32-year-old female with a history of bipolar mood disorder on lithium presents with asthenia, fatigue, cold intolerance, and dry skin. A TSH test confirms your suspected diagnosis. How should you counsel the patient regarding her lithium use?

a. Instruct the patient to continue the lithium, no other intervention is necessary.
b. Instruct the patient to continue the lithium, while initiating therapy with levothyroxine.
c. Instruct the patient to stop her lithium, while initiating therapy with levothyroxine.
d. Instruct the patient to stop her lithium immediately and follow up with her primary care physician for an alternative medication.

CHAPTER 117: QUESTIONS AND ANSWERS—cont'd

Answer: B This patient presents with symptoms of overt hypothyroidism, confirmed by a high TSH on laboratory testing. Instruct the patient that she may continue her lithium for her chronic bipolar mood disorder, while initiating levothyroxine therapy. A well-known cause of hypothyroidism, lithium causes overt hypothyroidism in 14% to 17% of patients, and subclinical hypothyroidism in 19% to 35% of patients. Most of lithium's effects on the thyroid is due to the inhibition of T_4 and T_3 release. Lithium also increases thyroid autoimmunity if it is present before the initiation of lithium treatment. Treatment with exogenous thyroid hormone is effective, and lithium therapy need not be discontinued.

4. A 52-year-old man is brought in by ambulance from his home with altered mental status and hypotension. EMS reports that he became ill with an influenza-like illness 4 days ago and stopped taking all of his medications secondary to vomiting. Despite multiple fluid boluses, he remains hypotensive. Laboratory results demonstrate severe acidosis, hyponatremia and hyperkalemia. What is the most appropriate treatment for this patient?
   a. Adrenocorticotropic hormone (ACTH)
   b. Continued normal saline (0.9%) fluid boluses
   c. Hydrocortisone
   d. Norepinephrine

Answer: C. This patient presents with adrenal crisis, as evidenced by refractory hypotension and electrolyte abnormalities typical for hypoadrenalism. While refractory hypotension in the acutely ill patient may be the only clue to adrenal insufficiency, the paramedics also report that the patient has been unable to take his usual medications, presumably for primary adrenal insufficiency, and in the setting of acute illness has resulted in adrenal crisis. Additional fluids and pressors will be ineffective until appropriate glucocorticoid treatment is initiated, hydrocortisone, 100 mg IV. ACTH administration is used for evaluation of adrenal insufficiency and is not appropriate for therapeutic administration during the acute crisis.

5. A 37-year-old male presents to the ED with complaints of palpitations, abdominal pain, nausea, vomiting, and diaphoresis. He reports episodes similar to this that have been increasing in frequency and severity over several months. His vital signs are P 127, BP 174/90, RR 28, T 37.1°C, and Sao_2 96%. Once stabilized, what is the most appropriate oral treatment for this patient?
   a. Amlodipine 5 mg PO daily
   b. Metoprolol, 100 mg PO BID
   c. Phenoxybenzamine 10 mg PO BID
   d. Propranolol ER 80 mg PO daily

Answer: C. This patient presents with episodic, or paroxysmal symptoms that are consistent with pheochromocytoma. Following initial stabilization and appropriate workup, the patient will require control of his vital sign abnormalities and symptoms leading up to surgery. The first-line treatment for pheochromocytoma is alpha-blockade, so in this question, phenoxybenzamine is correct. In patients with catecholamine excess, beta blockade alone can result in hypertensive crisis because of unopposed alpha-adrenergic receptor stimulation. Beta blockers can be used, but this should only be done following alpha-blockade; as such, propranolol and metoprolol are incorrect. Calcium channel blockers may be used in mild cases or in patients with undesirable alpha-blockade side effects, but are not considered first line; as such, amlodipine is also incorrect.

118

Bacteria

Manpreet Singh and Madonna Fernández-Frackelton

KEY CONCEPTS

- All septic patients should be treated with antibiotics as soon as possible, even before a definitive diagnosis is made. Patients with pneumococcemia, meningococcemia, and aggressive soft tissue infections can decompensate rapidly.
- The source of sepsis should be identified as soon as possible, and surgical causes should be addressed. A surgeon should be consulted as soon as possible for patients with sepsis and a débridable source of infection.
- Immunity to diphtheria, tetanus, and pertussis wanes significantly in adults. Pertussis should be considered a cause of persistent cough in adults. A tetanus vaccination history should always be obtained from patients with trauma or infection. When there is doubt about the history, the age-appropriate vaccine according to CDC guidelines should be administered.
- Consider botulism in the differential diagnosis for the infant with failure to thrive, constipation, or decreased muscle tone and for the patient who injects drugs with neurologic symptoms.

DIPHTHERIA

Foundations

Background and Importance

In the fifth century BCE, Hippocrates first described what was likely diphtheria, characterized by sore throat, membrane formation, and death from suffocation. In 1821, Pierre Bretonneau named the condition *diphtherite* (Greek for leather), describing the characteristic pharyngeal membrane. In 1890, von Behring and Kitasato created the first diphtheria antitoxin (DAT) and 1 year later administered the first dose of antitoxin to a human with diphtheria. Immunization dramatically decreased the incidence of diphtheria in the United States from 206,000 cases in 1921 with 15,520 deaths to only 2 cases between 2004 and 2017.[1,2]

Humans are the only known reservoir for *Cornybacterium diphtheriae*. Spread is person-to-person through respiratory droplets or by direct contact with secretions, skin lesion exudates, or rarely fomites or food. Transmission is associated with crowded living conditions. Individuals may spread the disease when they are actively ill, in the convalescent stage, or as asymptomatic carriers.[1,3,4]

Immunization against diphtheria is highly effective (Fig. 118.1). Before widespread immunization in the United States, the incidence of diphtheria exceeded 100 cases per 100,000 population, and the disease predominantly affected children. Most people acquired natural immunity to diphtheria by age 15, and recurrent exposure to toxigenic strains of the bacteria acted as a booster. Because childhood immunization nearly eliminates toxigenic strains in a population, adult immunity wanes, so more adults in industrialized nations are susceptible to diphtheria. By the 1980s the Centers for Disease Control and Prevention (CDC) reported 0 to 5 cases per year nationwide. Currently, sporadic cases occur primarily in inadequately immunized adolescents and adults.[2] Even in industrialized nations with high childhood vaccination rates, more than 50% of adults older than 40 years old lack protective antibodies. Recent reemergence due to disruption of national vaccination programs has led to outbreaks in Yemen and Venezuela, with a recent death in Spain from a traveling passenger from that region.

Anatomy, Physiology, and Pathophysiology

Diphtheria is caused by *C. diphtheriae,* an unencapsulated, nonmotile, gram-positive bacillus named for its shape (*korynee,* for "club") and its characteristic clinical presentation (*diphtheria,* for "leather," describing the leathery pharyngeal membrane).[1]

Infection with *C. diphtheriae* can occur at various sites of the respiratory tract or the skin. Respiratory diphtheria includes faucial (pharyngeal or tonsillar), nasal, and laryngeal (tracheobronchial) types, named for the primary location of infection. Cutaneous diphtheria can occur as a primary skin infection or as a secondary infection of a preexisting wound.[1,3]

Toxigenic strains of *C. diphtheriae* bacterium are lysogenized with the bacteriophage and produce an exotoxin that inhibits cellular protein synthesis. The diphtheritic membrane, composed of leukocytes, erythrocytes, fibrin, epithelial cells, and bacteria, results from necrosis caused by local effects of the exotoxin. Initially, the pharynx appears erythematous, but as necrosis occurs, grayish white patches appear and eventually coalesce. The membrane causes surrounding edema and cervical adenitis. The initial grayish white, filmy appearance changes to a thick, grayish black membrane with sharply defined borders. This membrane adheres to the underlying tissue, and bleeding occurs if removal is attempted.[1]

Circulating exotoxin causes the systemic symptoms of diphtheria, most profoundly affecting the nervous system, heart, and kidneys.[1,3] The degree of local and systemic toxicity depends on the location and extent of membrane formation. Pharyngeal diphtheria has the greatest toxicity and cutaneous diphtheria the least. As the exotoxin disrupts cellular protein synthesis, it causes peripheral neuropathy manifested

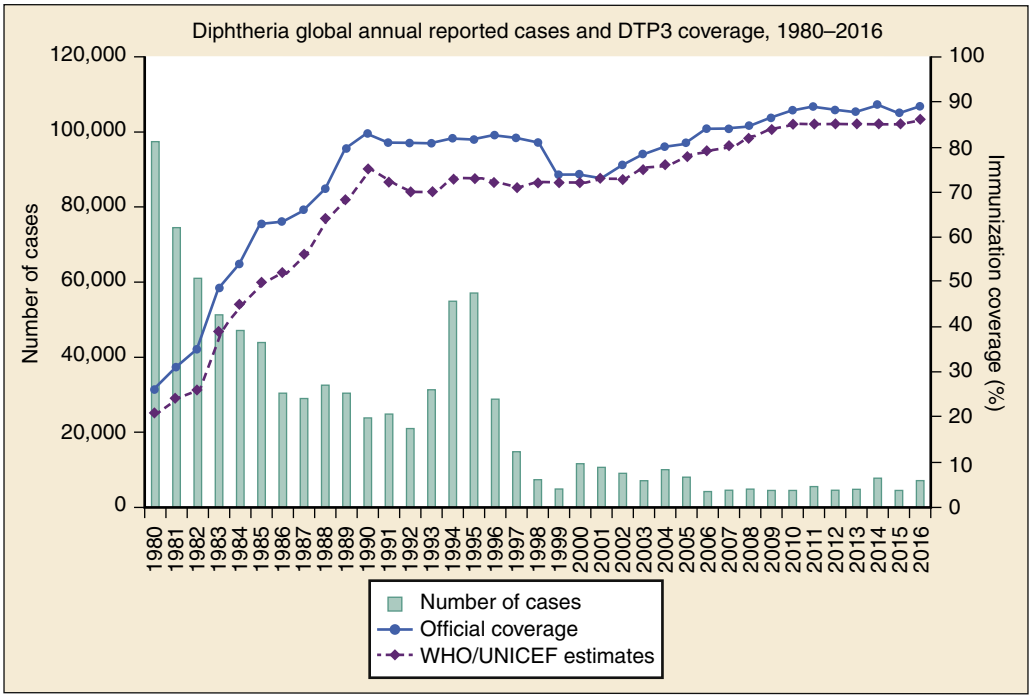

Fig. 118.1 Global annual reported cases of diphtheria compared with percentage of immunization coverage from 1980 to 2016. *DTP3,* Third dose of diphtheria-tetanus-pertussis vaccine; *UNICEF,* United Nations Children's Fund; *WHO,* World Health Organization. (From: World Health Organization, 2016 Global Summary. Geneva: WHO; 2016. World Health Organization: Immunization, vaccines and biologicals: diphtheria. Available at: www.who.int/immunization/monitoring_surveillance/burden/diphtheria/en/.)

by muscle weakness. About 5% of patients with respiratory infection develop polyneuritis; 75% of patients with severe disease have some form of neuropathy.[5] The muscles of the palate are usually affected first. Other cranial nerves, peripheral nerves, and the spinal cord may be affected. Degenerative lesions develop in dorsal root and ventral horn ganglia of the spinal cord and in cranial nerve nuclei. Cortical cells are spared. Proximal muscle groups are affected first. In severe cases, paralysis may develop in the first few days of illness. Paralysis typically does not last more than 10 days, but may last up to 3 months. Complete recovery over a longer time is the rule.[1]

The exotoxin directly damages myocardial cells. Cardiac dysfunction may appear 1 to 2 weeks after the onset of illness, but may arise earlier in severe cases. Electrocardiographic (ECG) changes suggestive of myocarditis occur in up to two-thirds of patients, but clinical manifestations of myocarditis occur in only 10% to 25% of cases.

Clinical Features

The average incubation period of respiratory tract diphtheria is 2 to 4 days (range 1–8 days). Signs and symptoms are indistinguishable from other upper respiratory tract infections, with low-grade fever and sore throat as the most frequent presenting complaints. Weakness, dysphagia, headache, voice changes, and loss of appetite are also common. Cough, shortness of breath, nasal discharge, and neck edema occur in less than 10% of patients. Cervical adenopathy occurs in approximately one-third of patients, and a membrane is observed in more than half of patients.

In patients with faucial diphtheria, the extent of the membrane parallels clinical toxicity. If the membrane is limited to the tonsils, disease may be mild; if it covers the entire pharynx, the onset of illness is usually abrupt and severe. Cervical lymphadenopathy and infiltration of neck tissues may be so extensive that the patient has a "bull-neck" appearance. Patients with this form of malignant diphtheria usually have high fever, severe muscle weakness, vomiting, diarrhea, restlessness, and delirium. Respiratory tract obstruction or cardiac failure from myocarditis can result in death.

Nasal diphtheria presents with serous or serosanguineous nasal discharge, and these patients do not usually have constitutional symptoms. A membrane may be visible. Treatment is important to prevent a persistent carrier state. Laryngeal diphtheria may begin in the larynx or spread downward. Respiratory tract edema with subsequent upper airway obstruction may develop. In cutaneous diphtheria, patients typically do not develop systemic toxicity. The skin characteristically has an ulcer with a grayish membrane; however, wounds from which *C. diphtheriae* is cultured are clinically indistinguishable from other chronic skin conditions.[1]

The most serious complications of diphtheria are airway obstruction, congestive heart failure, cardiac conduction disturbances, and muscle paralysis. Overall mortality is less than 3% but rises to 7% in patients with myocarditis and 26% in patients with the malignant form of the disease with neck swelling.[5] Although invasive disease is rare, endocarditis, mycotic aneurysms, osteomyelitis, and septic arthritis have all been described in immunocompromised hosts.[1]

Differential Diagnosis

It may be difficult to differentiate respiratory diphtheria from many other respiratory conditions, especially in the early phase of infection (Box 118.1). In general, the diphtheritic membrane is darker, grayer, more fibrous, and more firmly attached to the underlying tissues than in other conditions that have a membrane-like appearance. Acute necrotizing ulcerative gingivitis (ANUG) frequently involves the gingivae, which are unaffected in diphtheria. Acute bacterial epiglottitis has a more rapid onset than diphtheria, and laryngoscopy reveals an erythematous, edematous epiglottis without membrane formation.[1] Cutaneous diphtheria is difficult to differentiate from other acute and

BOX 118.1 Differential Diagnosis of Respiratory Diphtheria

Streptococcal pharyngitis
Viral pharyngitis (Epstein-Barr virus, adenovirus, herpes simplex)
Tonsillitis
Gonococcal pharyngitis
Acute necrotizing ulcerative gingivitis (ANUG)
Acute epiglottitis
Mononucleosis
Laryngitis
Bronchitis
Tracheitis
Candida albicans (thrush)
Rhinitis

chronic ulcerative skin lesions. *C. diphtheriae* can secondarily infect these lesions, especially in high-risk patients such as those with alcohol use disorder and unimmunized or underimmunized people.

Diagnostic Testing

The laboratory should be notified when *C. diphtheriae* is suspected, because routine cultures do not identify the organism. Throat or nasopharyngeal swabs should be obtained for respiratory diphtheria, and if present, membranous material should be examined. Samples should be obtained from skin lesions in cutaneous infections. Specimens should be collected before antibiotic therapy is initiated and transported to the laboratory for rapid inoculation onto tellurite selective culture medium.[1,3] Definitive identification is made using a combination of colony morphology, microscopic appearance, and fermentation reactions.[1] *C. diphtheriae* isolates should be tested for toxin production. The Elek test for toxin A is available at the CDC. Polymerase chain reaction (PCR), which is more reliable but not as readily available commercially, can detect the toxin structural gene. Newer methods that rapidly detect the toxin by mass spectrometry are not readily available but may be used in the future.[6] A positive culture for group A beta-hemolytic streptococcus does not exclude diphtheria, as up to 30% of patients with diphtheria test positive for streptococcal coinfection or carrier state.

Leukocytosis, mild thrombocytopenia, and proteinuria are common but neither sensitive nor specific for diphtheria. Changes on ECG are nonspecific and include ST-T wave changes, varying degrees of atrioventricular block, and dysrhythmias.[1] The ECG may be normal in the presence of myocarditis (see Chapter 68). An echocardiogram may show dilated or hypertrophic cardiomyopathy. Cardiac enzymes may be elevated; serum troponin levels correlate with the severity of myocarditis.

Management

Patients with evidence of diphtheria should be placed in respiratory isolation and treated presumptively for *C. diphtheriae*. The goals of therapy are to protect the airway, limit toxin effects, and stop future toxin production by terminating bacterial growth. Although airway obstruction from diphtheria is rare in the United States, the management is identical to that of other forms of airway obstruction. Early intubation should be considered for patients with laryngeal involvement. Patients may be dehydrated from fever and decreased oral intake related to dysphagia or neurologic impairment. In the course of resuscitation, the patient should be assessed for fluid responsiveness, as the toxin's effect on the myocardium may result in heart failure[1](see Chapter 3).

BOX 118.2 Check List for Assessing a Patient With Suspected Diphtheria

Suspect Case

- Pharyngitis, nasopharyngitis, tonsillitis, laryngitis, tracheitis (or any combination of these), absent or low-grade fever
- Grayish adherent pseudo-membrane present
- Membrane bleeds, if manipulated or dislodged

Probable Case

Suspect case above, plus one or more of the following:

- Stridor
- Bull-neck (cervical edema)
- Toxic circulatory collapse
- Acute renal insufficiency
- Submucosal or subcutaneous petechiae
- Myocarditis
- Death
- Recent return (<2 weeks) from travel to area with endemic diphtheria
- Recent contact (<2 weeks) with confirmed diphtheria case or carrier
- Recent contact (<2 weeks) with visitor from area with endemic diphtheria
- Recent contact with dairy or farm animals or domestic pets
- Immunization status: Up-to-date- any DTaP/DT/Tdap/Td shot within past 10 years?

Laboratory Confirmed Case

- Positive culture of *Corynebacterium diphtheriae* (or *Corynebacterium ulcerans*) and
  - Positive Elek test *or*
  - PCR for tox gene (positive for subunit A and B)

DT, Diphtheria-tetanus; *DTaP,* diphtheria, tetanus, and acellular pertussis; *PCR,* polymerase chain reaction; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.
Available at: www.cdc.gov/diphtheria/downloads/dip-cklist-diag.pdf.

Equine serum diphtheria anti-toxin (DAT) should be administered if the diagnosis of respiratory diphtheria is deemed probable (Box 118.2) and before laboratory confirmation.[1,7] DAT is currently not licensed by the U.S. Food and Drug Administration (FDA) for use in the United States, and several countries do not currently hold DAT stockpiles.[8] The CDC can be contacted at 770-488-7100 to distribute DAT to physicians as an investigational new drug. The size and location of the membrane, duration of illness, and patient's overall degree of toxicity determine the DAT dose. Patients with probable or confirmed respiratory diphtheria are eligible to receive DAT (20,000 to 40,000 units for pharyngeal or laryngeal involvement of 2 days' duration; 40,000 to 60,000 units for nasopharyngeal lesions; 80,000 to 100,000 units for systemic disease of 3 days' duration or more or for diffuse neck swelling).[7] After conjunctival or intradermal sensitivity skin testing, the antitoxin is administered intravenously (IV). If the patient exhibits sensitivity to the antitoxin, desensitization should be performed. Active immunization against diphtheria should also be initiated because clinical infection may not confer immunity.

After DAT, antibiotics are initiated to prevent growth and spread of the organism but are no substitute for the antitoxin. Erythromycin 40 mg/kg/day (maximum of 2 g) intravenously or orally in divided doses is the preferred treatment. Procaine penicillin G 300,000 units/day q12h intramuscularly (IM) for those weighing 10 kg or less, and 600,000 units/day in q12h for those weighing more than 10 kg is an acceptable alternative.[1,3] Treatment failures are more common with penicillin than with erythromycin. Azithromycin

and clarithromycin have activity similar to erythromycin in vitro and may result in better compliance. These agents have not been adequately tested in clinical disease. Daily oral therapy may be substituted when the patient can swallow. Negative cultures should be documented after treatment.

Myocarditis and neuritis are treated with supportive care and monitoring. Patients with ECG changes consistent with myocarditis have three to four times the mortality rate of those with normal ECGs. The mortality rate for patients with left bundle branch block and atrioventricular block is 60% to 90%. Serial ECGs are recommended, and survivors may have permanent conduction abnormalities. No data support the use of steroids.

Cutaneous lesions should be débrided of necrotic tissue and cleansed vigorously. A course of antibiotics is recommended, but DAT for cutaneous lesions is of questionable value. We recommend 20,000 to 40,000 units of antitoxin, but few data support its use in this setting.[1,7]

Carriers of *C. diphtheriae* should receive oral penicillin G or erythromycin for 7 days or IM benzathine penicillin (600,000 units for those weighing less than 30 kg and 1,200,000 units for those weighing more than 30 kg). Active immunization should also be provided to unimmunized and partially immunized carriers. After 2 weeks of therapy, cultures should be obtained; if positive, erythromycin therapy should be given for 10 additional days.[1]

Individuals who have been in close contact with infected patients should have cultures taken and be kept under surveillance for 7 days. Previously immunized close contacts should receive a booster of diphtheria toxoid if the last booster was more than 5 years earlier. The vaccine should be diphtheria, tetanus, and acellular pertussis (DTaP) or diphtheria-tetanus (DT or Td) as appropriate for age. Close unimmunized contacts or those whose immunization status is unknown should receive the same antimicrobial therapy as carriers (previously described), have culture specimens taken before and after therapy, and have active immunization initiated. Close contacts who cannot be kept under surveillance should receive IM benzathine penicillin to ensure compliance and a Td booster (appropriate for age and immunization history). DAT is not recommended for this group because of the risk of horse serum allergy.[7]

A universal primary immunization program with regular boosters every 10 years is the most effective method for controlling diphtheria. Emergency clinicians should routinely administer age-appropriate tetanus and diphtheria toxoids as part of wound management.

Disposition

All patients with possible pharyngeal diphtheria should be isolated, admitted, and monitored for arrhythmias. A cardiologist should be consulted for patients with evidence of myocarditis. The CDC should be contacted for all suspected or proven cases of diphtheria.

PERTUSSIS

Foundations

Background and Importance

Pertussis is an acute respiratory disease first described in 1578 when an epidemic swept through Paris. *Pertussis* means "violent cough." It is also called *whooping cough* because the severe episodes of coughing are followed by forceful inspiration, which creates a characteristic "whoop" sound. Bordet and Gengou identified the causative organism in 1900. Pertussis was a major cause of mortality among infants and children in the United States in the prevaccination era. A vaccine was developed in the 1940s, but pertussis remains a significant cause of morbidity and mortality worldwide.[9]

Pertussis is a highly contagious respiratory illness transmitted by aerosolized droplets. It can occur at any age but is predominantly a pediatric and adolescent illness. Infection rates are greater than 80% in adults exposed more than 12 years after completing a vaccination series and up to 90% in susceptible individuals with household exposure. Half of the cases in the United States occur from June through September. The average incubation period is 7 to 10 days (range less than 1 week to 3 weeks). Neither vaccination nor prior infection confers lifelong immunity.

Pertussis is prevalent worldwide. The World Health Organization (WHO) estimated over 24.1 million cases in 2017 with 160,700 annual deaths.[10] In the United States, annual pertussis rates declined sharply after the introduction of the vaccine, reaching a nadir of 1010 cases in 1976. There has been a steady increase since, with 11,647 cases reported in 2003 and more than 28,000 cases in 2014 (Fig. 118.2A and B).[11] The incidence is highest in infants who have not received the entire vaccine series (see Fig. 118.2C). Waning immunity in the adult population and increased reporting may be contributing factors, but the emergence of the antivaccination movement is a leading factor.

A 1991 report found a possible relationship between the vaccine and acute encephalopathy. Although there appears to be no relationship between the vaccine and long-term neurologic complications, the report resulted in a decline in the use of the whole-cell pertussis vaccine. The acellular pertussis vaccine has been approved in the United States since 1991 for persons 15 months to 64 years and since 1997 for infants.

Anatomy, Physiology, and Pathophysiology

Pertussis is caused by organisms of the *Bordetella* genus, which are small, aerobic, gram-negative coccobacilli. *Bordetella pertussis* and *Bordetella parapertussis* are responsible for human disease. The organisms are fastidious and require a medium containing charcoal, blood, or starch, and an optimal temperature of 95° to 98.6°F (35° to 37°C) to grow. *Bordetella bronchiseptica,* a flagellated, motile organism, causes illness in animals, including kennel cough, and may rarely cause respiratory infection in immunocompromised humans.[12] *Bordetella* adheres preferentially to ciliated respiratory epithelial cells, but does not invade beyond the submucosa and is seldom recovered in the bloodstream. It elaborates several toxins that act locally and systemically, including pertussis toxin, dermonecrotic toxin, adenylate cyclase toxin, and tracheal cytotoxin. Local tissue damage consists of inflammatory changes in the respiratory mucosa. Secondary pneumonia and otitis media may occur. Systemic effects of pertussis toxin include sensitization to the lethal effects of histamine and increased excretion of insulin. This hyperinsulinemia can cause hypoglycemia, particularly in young infants potentially leading to seizures.[9]

Clinical Features

Pertussis has three clinical stages: the catarrhal phase, paroxysmal phase, and convalescent phase. The *catarrhal* or *prodromal phase* begins after an incubation period of approximately 7 to 10 days and lasts approximately 1 to 2 weeks. Infectivity is greatest during the catarrhal phase, when the disease is clinically indistinguishable from other upper respiratory tract infections. Signs and symptoms include rhinorrhea, low-grade fever, malaise, and conjunctival injection. A dry cough usually begins at the end of the catarrhal phase.[9,12]

The *paroxysmal phase* begins as fever subsides. Cough increases and lasts 1 to 6 weeks, but may persist for up to 10 weeks. Paroxysms of staccato coughing occur an average of 15 times per day and are followed by a sudden, forceful inhalation that produces the characteristic "whoop." One-third of adults with pertussis develop this whoop, and it is rare in young infants, who may present with apneic episodes and

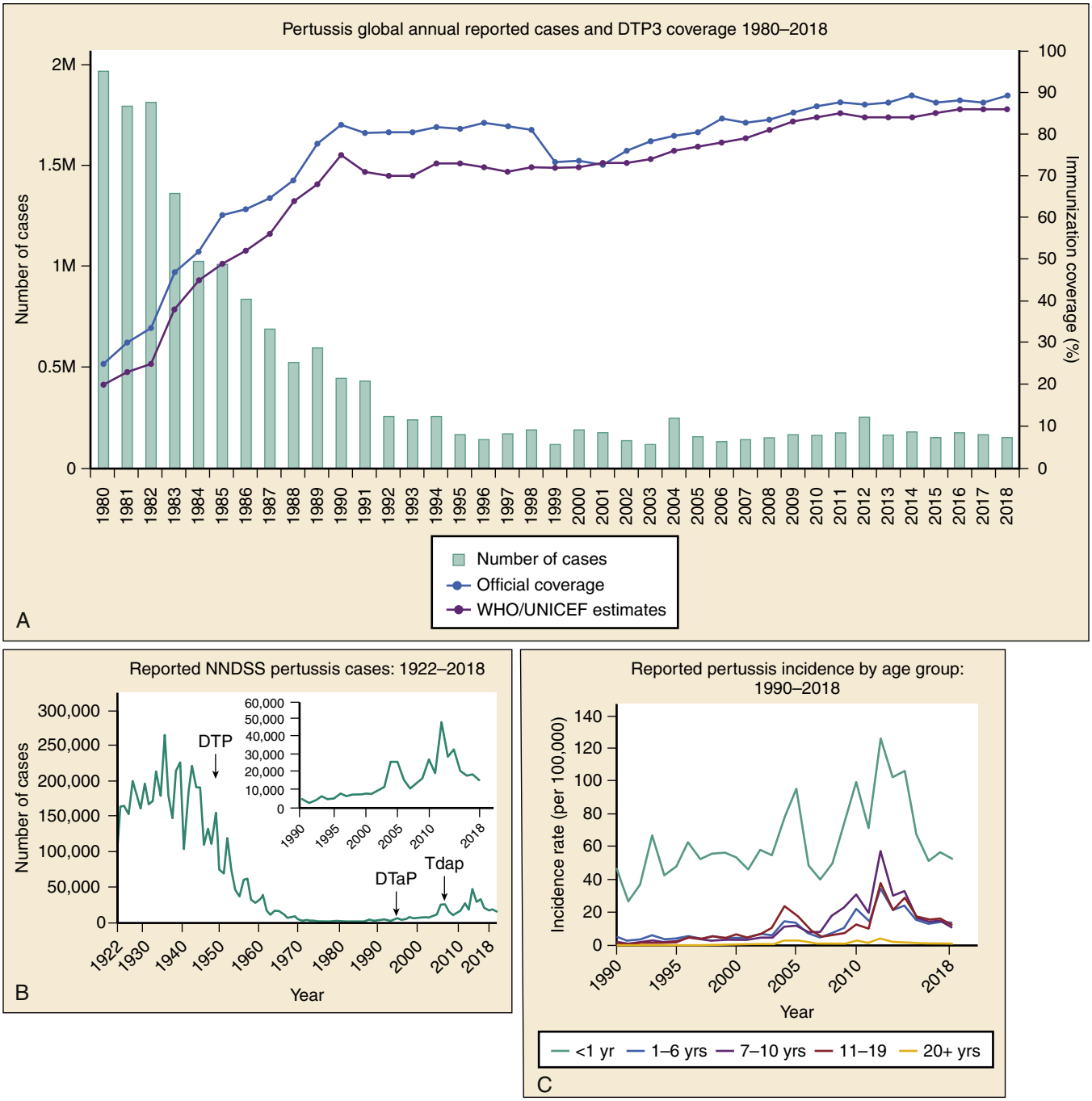

Fig. 118.2 (A) Global annual reported cases of pertussis compared with percentage of immunization coverage. (B) Incidence of reported pertussis cases in the United States by year. (C) Pertussis incidence in the United States by age, Centers of Disease Control and Prevention 2018. *DTaP,* Diphtheria, tetanus, and acellular pertussis; *DTP3,* Third dose of diphtheria-tetanus-pertussis vaccine; *NNDSS,* National Notifiable Diseases Surveillance System; *Tdap,* tetanus, diphtheria, activated pertussis; *UNICEF,* United Nations Children's Fund; *WHO,* World Health Organization. (A, From: World Health Organization. WHO/IVB database 2018; 194 WHO states. Available at www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/. B and C, From: Centers for Disease Control and Prevention: National Notifiable Diseases Surveillance System: Pertussis (whooping cough). Available at: www.cdc.gov/pertussis/surv-reporting.html.)

no other symptoms. Paroxysms may be spontaneous, occur more frequently at night, or be precipitated by noise or cold. During the paroxysm, the patient may exhibit cyanosis, diaphoresis, tongue protrusion, salivation, and lacrimation. Post-tussive vomiting, syncope, and apnea may occur. Infants may be exhausted after a typical paroxysm. Between episodes of coughing, patients do not appear acutely ill.[9,12]

In the *convalescent phase* a residual cough may last weeks to months. Paroxysms of coughing may be triggered by unrelated respiratory infection or by exposure to a respiratory irritant. This recurrence of coughing does not represent recurrence of pertussis infection.

Atypical presentations can occur in young and preterm infants. Fever is usually absent in uncomplicated neonatal pertussis. Tachypnea,

BOX 118.3 Pertussis Complications

Periorbital edema
Subconjunctival hemorrhage
Petechiae
Epistaxis
Hemoptysis
Subcutaneous emphysema
Pneumothorax
Pneumomediastinum
Diaphragmatic rupture
Umbilical and inguinal hernias
Rectal prolapse

apnea, and cyanotic and bradycardic episodes may be the predominant symptoms.[13] Older children and adults who have partial protection from vaccination or previous illness may have a long-lasting intractable dry cough that is frequently misdiagnosed as bronchitis. Post-tussive vomiting in adults is highly suggestive of pertussis.[9,14]

Physical findings are nonspecific. Tachypnea is variably present and may be related to the degree of pulmonary involvement. Low-grade fever, conjunctival injection, and rhinorrhea are common during the catarrhal phase. Fever during other stages of illness suggests secondary infection. Petechiae above the nipple line, subconjunctival hemorrhages, pneumothorax, and epistaxis may occur because of increased intrathoracic pressure during coughing paroxysms.[9,12] Chest examination may reveal rhonchi; the presence of rales suggests pneumonia.

Complications of pertussis are listed in Box 118.3. Secondary pulmonary infection may result from decreased respiratory clearance cause by the *Bordetella* organism and its toxins on bronchial and lung mucosa. Bacterial or viral pneumonia superinfection complicating pertussis is a leading cause of death, especially in infants and young children. Aspiration of gastric contents and respiratory secretions may occur during paroxysm of coughing, whooping, and vomiting. A fever during the paroxysmal phase should alert the physician to a possible superinfection.[9,10,12]

Seizures and encephalopathy occur in approximately 1% of patients but are more common in infants. This may be due to hypoxia, hypoglycemia, cerebral petechiae, toxin effect, or secondary infection by neurotropic viruses or bacteria. Central nervous system (CNS) hemorrhages may occur from increased cerebrovascular pressures during paroxysm of coughing. Sudden increases in intrathoracic and intra-abdominal pressures can result in other complications.[9,12] Bradycardia, hypotension, and cardiac arrest can occur in neonates and young infants with pertussis. Severe pulmonary hypertension has been recognized in this age group and can lead to systemic hypotension, hypoxia, and increased mortality.[13] Intensive care monitoring is recommended for these patients, regardless of how well they appear on admission.

Differential Diagnoses

The differential diagnosis includes acute viral upper respiratory tract infection, pneumonia, bronchiolitis, cystic fibrosis, tuberculosis, exacerbation of chronic obstructive pulmonary disease, and foreign body aspiration. The marked leukocytosis may suggest leukemia.

Diagnostic Testing

Pertussis should be considered in patients with cough lasting longer than 2 weeks with paroxysms, whoops, or post-tussive emesis, regardless of previous vaccination status.[13] Up to 27% of adults in the United States with a prolonged cough have serologic evidence of pertussis.

Ancillary studies are of limited value in the emergency department (ED). During the late catarrhal and early paroxysmal phases, a marked leukocytosis and a characteristic lymphocytosis are often present. A white blood cell (WBC) count of greater than 20,000/mL is common in pediatric patients.[12] Adults with pertussis frequently do not have the characteristic leukocytosis and lymphocytosis, and some infants and immunocompromised hosts may not mount this response. The chest radiograph (CXR) may show peribronchial thickening, atelectasis, or pulmonary consolidation.

BOX 118.4 Pertussis Case Definition

Clinical Case

Cough and illness for more than 2 weeks with no apparent other cause *plus* one of the following:

- Paroxysms of coughing
- Inspiratory "whoop"
- Post-tussive emesis

Probable Case

All of the following:

- Meets clinical case definition
- Not laboratory confirmed (Only PCR and culture are considered laboratory confirmation.)
- Not epidemiologically linked to a laboratory confirmed case

Confirmed Case

One of the following:

- Acute cough illness of any duration with a positive culture for *Bordetella pertussis*
- A case that meets the clinical case definition and is confirmed by PCR for *B. pertussis*
- A case that meets the clinical case definition and is epidemiologically linked directly to a case confirmed by either culture or PCR

PCR, Polymerase chain reaction.

Laboratory confirmation is important for epidemiologic purposes. Nasopharyngeal aspirate or swab (synthetic, non-cotton) should be obtained for culture and PCR, if both are available; sputum and throat swabs are inadequate because ciliated respiratory epithelial cells are required.[12] The *Bordetella* organism is fastidious, and isolation requires a medium impregnated with antibiotics to reduce overgrowth of competing bacteria. Colonies of *B. pertussis* take 3 to 7 days to appear. Pertussis cultures are 30% to 50% sensitive, and this drops to less than 3% three weeks after the onset of cough. Direct fluorescent antibody techniques are useful as a rapid screening test for pertussis but are variably specific and should not be relied upon as laboratory confirmation of *B. pertussis.* Adults generally come to medical attention late in the disease when cultures are rarely positive. PCR is more likely to identify the organism during the first 3 weeks of illness, but it has a high false-positive rate for various reasons, including asymptomatic carriers, recent vaccination, or contamination. Serologic testing is often performed as well. Most laboratories use enzyme-linked immunosorbent assay, which rises 2 to 3 weeks after infection or primary immunization. Paired serologic tests showing a twofold increase are considered positive, but they are reported as "probable" cases by the CDC unless performed at the CDC or the Massachusetts state laboratory. See Box 118.4 for the case definition.

Management

Acute Treatment

Treatment of pertussis is supportive and includes oxygen, frequent suctioning, appropriate hydration, parenteral nutrition as needed, and avoidance of respiratory irritants. Patients with suggested pertussis and

associated pneumonia, hypoxia, CNS complications, or those experiencing severe paroxysms should be hospitalized. Children younger than 1 year old should also be admitted, because they are not yet fully immunized and have the greatest risk for morbidity and mortality. Neonates with pertussis should be admitted to a neonatal intensive care unit (NICU) because apnea and significant cardiac complications can occur without warning.[9,12]

Antibiotic treatment does not reduce the severity or duration of illness at any phase. The goal of antibiotic therapy is to decrease infectivity and carriage.[14] The CDC recommends macrolides; erythromycin, clarithromycin, and azithromycin are preferred for pertussis in persons 1 month of age and older. Erythromycin estolate ester 40 to 50 mg/kg/day (maximum of 2 g/day) has previously been recommended for four divided doses for 14 days, but a 7-day course of erythromycin estolate ester at 1 g/day is just as effective at eradicating *B. pertussis* with better compliance. Azithromycin 10 mg/kg/day for 5 days is recommended in infants younger than 1-year-old because of an association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS). Alternative treatments include azithromycin (10 mg/kg on day 1, followed by 5 mg/kg on days 2 to 5) or clarithromycin (15 mg/kg/day; maximum of 1 g/day in two divided doses). Trimethoprim-sulfamethoxazole (8 mg/kg/day of trimethoprim) is an alternative for macrolide-allergic patients two months of age or older, but efficacy is unproven. Patients should be considered infectious for 3 weeks after the onset of the paroxysmal phase or until at least 5 days after antibiotics are started.[9] Droplet isolation is recommended during this period.

Corticosteroids, especially in young critically ill infants, may reduce the severity and course of illness, but effectiveness has not been established. Inhaled beta$_2$-adrenergic agonists do not reduce the frequency or severity of paroxysmal coughing episodes but may help patients with reactive airway disease. Past trials with pertussis immune globulin are limited and do not show benefit. Standard cough suppressants and antihistamines are ineffective.[15]

Postexposure prophylaxis with an appropriate macrolide is recommended for those at high risk for developing severe pertussis, including household contacts of a pertussis case, infants and women in their third trimester of pregnancy, persons with preexisting health conditions that may be exacerbated by a pertussis infection, and close contact with any of the above-listed people. This includes but is not limited to those who work in NICUs, childcare settings, and maternity wards. Women in their third trimester of pregnancy may be a source of pertussis to their newborn infant.[16]

Vaccination

Whole-cell and acellular pertussis vaccines are distributed in combination with diphtheria and tetanus toxoids as DPT and DTaP, respectively. The whole-cell vaccine is 70% to 90% effective at preventing serious pertussis infection. Pediatric recipients have fever, irritability, behavioral changes, and local discomfort at the site of inoculation. Moderately severe reactions are uncommon but include temperature above 104°F (40°C), persistent, high-pitched crying, and seizures. Severe neurologic complications (prolonged seizures and encephalopathy) occur rarely but led to decreased use of the whole-cell form of the vaccine and the development of DTaP.[17]

The acellular pertussis vaccines contain inactivated pertussis toxin and one or more other bacterial components; they are less effective than the whole-cell vaccine but have fewer reported adverse reactions.[18,19] DTaP has replaced DPT for childhood immunizations in the United States and is approved for children ages 6 weeks to 6 years old.[12,] Current American Academy of Pediatrics (AAP) guidelines state that acellular pertussis vaccinations are as safe as whole-cell vaccines, but new data suggest the latter provide a better, longer-lasting serologic response. There has also been a correlation between acellular vaccination and food allergies. Further studies are needed to guide future recommendations.

Pertussis immunity wanes 5 to 10 years after immunization and 15 years after natural infection, resulting in an increased incidence in people older than 15 years. Tetanus, diphtheria, acellular pertussis (Tdap) (with reduced diphtheria toxoid and pertussis antigens) is indicated as a booster vaccine in persons 11 to 18 years old. It is safe and effective in adults, including pregnant women and those over 65 years of age. Persons older than 65 years old who have never received Tdap and anticipate close contact with infants younger than 12 months old should receive a single dose of Tdap, regardless of interval since last Td vaccination. A live attenuated nasal vaccine has completed phase one trials in humans showing greater than 99.9 nasopharyngeal colonization and is undergoing further clinical development.[20]

TETANUS

Foundations

Background and Importance

Tetanus is a toxin-mediated disease characterized by severe uncontrolled skeletal muscle spasms. Respiratory muscle involvement leads to hypoventilation, hypoxia, and death. Dramatic descriptions of this disease date to ancient Egypt, when physicians recognized a frequent relationship between tissue injury and subsequent fatal spasm.[21] Prophylactic injection of tetanus antitoxin provided passive immunity to wounded soldiers during World War I. In 1924, an effective vaccine was developed, and large-scale testing during World War II indicated that the tetanus toxoid confers a high degree of protection against disease.[22] Despite the availability of an effective vaccine, tetanus remains endemic worldwide. It is more common in warm, damp climates and relatively rare in cold regions. The global annual incidence of reported cases of tetanus has declined with the introduction of vaccination programs (Fig. 118.3A). The WHO reported 15,103 cases of tetanus in 2018 but estimates that thousands of unreported cases occur annually resulting in approximately 34,000 neonatal deaths. Most of these cases occur in countries with low immunization rates.[23]

Since the introduction of vaccination programs in the United States, the incidence of tetanus has steadily declined from 4 cases per million population in the 1940s to fewer than 0.01 cases per million population in 2010 (see Fig. 118.3B).[24] The highest incidence occurs in people older than 65 years old (0.23 case per million population). Half of cases occur in injection drug users. The overall case fatality rate is 18% but approaches 50% in patients over 70 years old (Fig. 118.4). Cases have been reported in fully vaccinated patients, but no deaths occurred.[24]

Tetanus classically occurs as a result of a deep penetrating wound. A history of injury is present in more than 70% of patients, but the injury may be trivial. The remainder may have another identifiable condition or no apparent source.[21] The most common portals of entry are puncture wounds, lacerations, and abrasions. Tetanus has also been reported in association with chronic skin ulcers, abscesses, otitis media, foreign bodies, corneal abrasions, childbirth, and dental procedures. Postoperative tetanus has been reported in patients who have undergone intestinal operations and abortions. In these cases, the source of bacteria is probably endogenous because up to 10% of humans harbor *Clostridium tetani* in the colon. Inadequate primary immunization and waning immunity continue to be the primary risk factors for tetanus in the United States. As tetanus vaccination of children has improved, older people have accounted for an increasing percentage of reported cases.

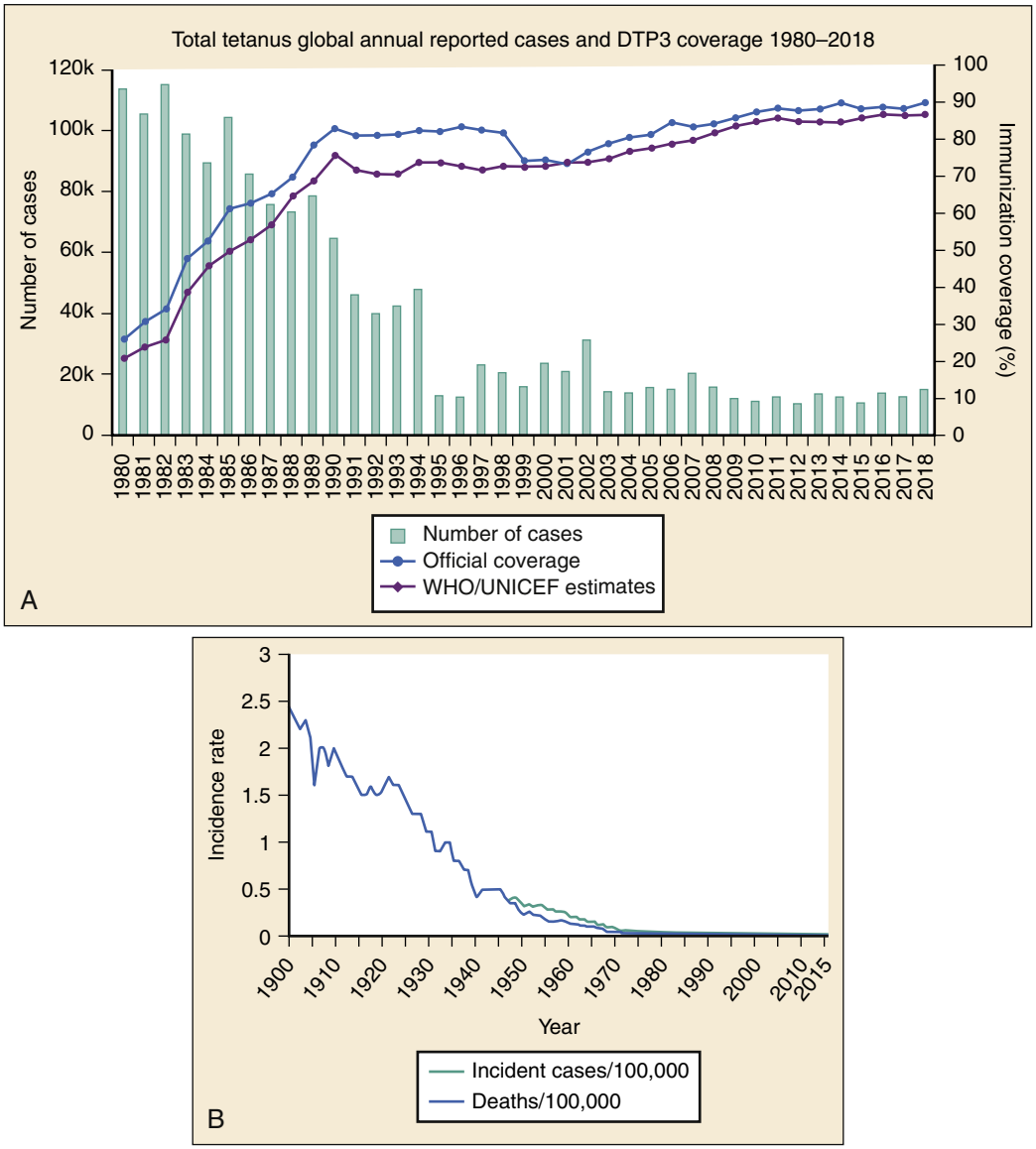

Fig. 118.3 (A) Global annual reported cases of tetanus compared with percentage of immunization coverage. (B) Incidence of reported tetanus cases in the United States by year. *DTP3,* third dose of diphtheria-tetanus-pertussis vaccine; *UNICEF,* United Nations Children's Fund; *WHO,* World Health Organization. (A, From: World Health Organization. Immunization, vaccines and biologicals: tetanus. Available at: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html. B, From: Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System. Available at: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html.)

Anatomy, Physiology, and Pathophysiology

C. tetani is a spore-forming, motile, rod-shaped, obligate anaerobic bacillus. It stains gram-positive in fresh culture but has a variable staining pattern in culture and tissue samples. *C. tetani* is ubiquitous in soil and dust and is also found in the feces of animals and humans. Spores are resistant to heating and chemical disinfectants and can survive in the soil for months to years. When introduced into a wound, spores may not germinate for weeks because of unfavorable tissue conditions. When injury favors anaerobic growth, the spores germinate into mature bacilli, which form a single spherical terminal endospore to produce a characteristic drumstick appearance. Only these mature bacilli produce the tetanus toxin that causes clinical disease.[21]

C. tetani is a noninvasive organism. The development of clinical disease requires a portal of entry and tissue conditions that promote germination and growth in a susceptible host. Tetanus-prone wounds have damaged or devitalized tissue, foreign bodies, or other bacteria. Under these conditions, *C. tetani* produces the neurotoxin that causes clinical illness. Germination and replication of *C. tetani* can occur without clinical signs of wound infection.

C. tetani produces the neurotoxin tetanospasmin at the site of tissue injury. Tetanospasmin binds the motor nerve ending and moves by retrograde axonal transport and trans-synaptic spread to the CNS. It binds preferentially to inhibitory (GABAergic and glycinergic) neurons and blocks the presynaptic release of these neurotransmitters. Interneurons afferent to alpha motor neurons are affected first. Without inhibitory control, the motor neurons undergo sustained excitatory discharge, resulting in the muscle spasm characteristic of tetanus.[25] Tetanospasmin may also affect preganglionic sympathetic neurons and

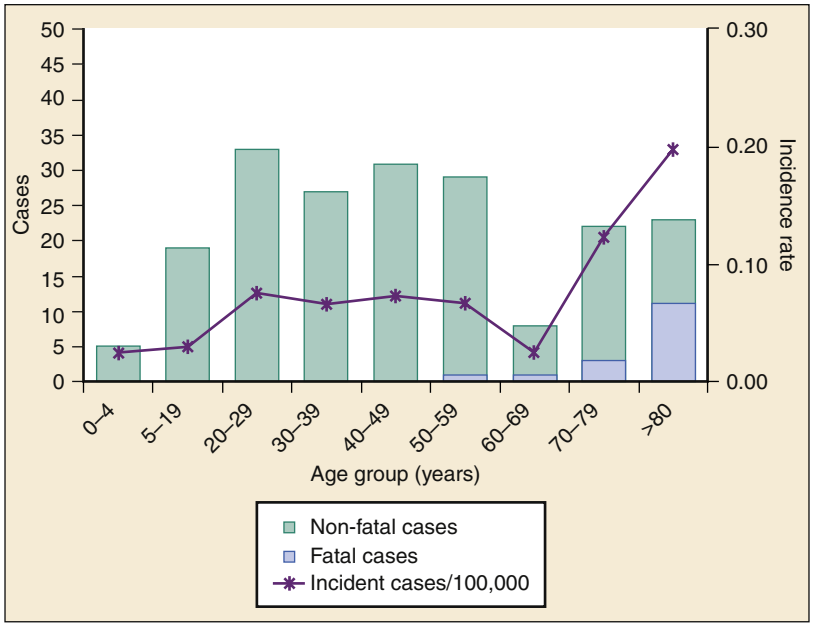

Fig. 118.4 Incidence of and mortality from tetanus by age group in the United States, 2009 to 2015. (Centers for Disease Control and Prevention. Manual for the surveillance of vaccine-preventable diseases. Available at: www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html.)

parasympathetic centers, resulting in autonomic nervous system dysfunction. The clinical manifestations include dysrhythmias and wide fluctuations in blood pressure and heart rate. The binding of tetanospasmin at the synapse is irreversible; recovery occurs only when a new axonal terminal is produced.[21]

Clinical Features

The incubation period for tetanus ranges from 1 day to several months. Shorter incubation periods portend a worse prognosis.[21] The duration of the incubation period is not useful in making the diagnosis of tetanus because many patients have no history of an antecedent wound. Four types of clinical tetanus have been described.

Generalized Tetanus

Generalized tetanus, the most common form of the disease, results in spasms of agonist and antagonist muscle groups throughout the body. The classic presenting symptom is trismus or "lockjaw," caused by masseter muscle spasm, and is present in 50% to 75% of patients. As the other facial muscles become involved, a characteristic sardonic smile (risus sardonicus) appears. Other early symptoms include irritability, weakness, myalgias, muscle cramps, dysphagia, hydrophobia, and drooling. As the disease progresses, generalized uncontrollable muscle spasms occur spontaneously or as a result of minor stimuli, such as touch or noise. Spasms can cause vertebral and long-bone fractures and tendon rupture. Opisthotonos is prolonged tonic contraction that resembles decorticate posturing. Spasms of laryngeal and respiratory muscles can cause ventilatory failure and death. Autonomic dysfunction is the major cause of death in patients who survive the acute phase and is manifested by tachycardia, hypertension, hyperpyrexia, cardiac dysrhythmias, and diaphoresis. The illness progresses over 2 weeks. If the patient survives, recovery is complete after 4 weeks or more. Throughout this illness, patients remain completely lucid unless they are chemically sedated.[21]

Localized Tetanus

Localized tetanus is a form of the disease characterized by persistent muscle spasms close to the site of injury. Symptoms may be mild or severe, but mortality is lower than with generalized tetanus. Local tetanus may progress to generalized disease. This form of illness may reflect partial immunity to tetanospasmin and may be present for weeks to months before resolution.[21]

Cephalic Tetanus

Cephalic tetanus, a rare variant of localized tetanus, results in cranial nerve palsies and muscle spasms. Palsies precede the spasm in many cases, resulting in misdiagnosis. The most commonly involved cranial nerve is the facial nerve (VII), mimicking Bell palsy. Most cases occur after facial trauma or otitis media. Patients have trismus and palsies of cranial nerve III, IV, VII, IX, X, or XII ipsilateral to the site of local infection. The clinical course is variable. In one-third of cases, resolution of symptoms is complete. The remainder progress to generalized tetanus with an overall mortality rate of 15% to 30%.[18,21]

Neonatal Tetanus

Neonatal tetanus is generalized tetanus of the newborn and occurs almost exclusively in countries where maternal immunization is inadequate and contaminated material is used to cut and dress umbilical cords. Symptoms begin during the first week of life and include irritability and poor feeding. Mortality approaches 100% because of the high toxin load for body weight and inadequate medical support. Even with limited resources, mortality can be reduced to less than 50% with medication and experienced medical personnel.

Complications

Acute respiratory failure results from respiratory muscle spasms or laryngospasms and airway obstruction. If patients survive the acute onset of illness and have adequate ventilatory support, autonomic dysfunction becomes the leading cause of death. Autonomic instability occurs several days after the onset of generalized spasms. Disinhibition of the sympathetic nervous system predominates and causes dysrhythmias, hypertension, myocarditis, and pulmonary edema. Dysrhythmias and myocardial infarction are the most common fatal events during this phase.

Forceful tetanic muscle spasms can cause vertebral subluxations and fractures, long-bone fractures, and shoulder and temporomandibular joint dislocations. Rhabdomyolysis occasionally occurs and can cause acute renal failure. Renal failure may also result from dehydration and sympathetic nervous system hyperactivity.

Secondary infection may occur in the initial inoculating wound or as a complication from invasive treatment modalities, such as mechanical ventilation. Hyperthermia may also result from muscle spasms and sympathetic hyperactivity. Prolonged immobility can lead to deep venous thrombosis and pulmonary embolism. Gastrointestinal complications include peptic ulcers, ileus, intestinal perforation, and constipation. The syndrome of inappropriate secretion of antidiuretic hormone occurs in a small number of patients. Hemolysis has also been reported.

Mortality is a function of the previous immunization status, incubation period, severity and rapidity of onset of illness, comorbid disease, age, and sophistication of medical treatment available. With appropriate intensive care treatment, older patients may fare as well as their middle-aged counterparts. Long-term physical complications in survivors are rare. The most common persistent problem is psychological trauma related to the disease and its treatment.[21]

Differential Diagnoses

Strychnine poisoning is the only clinical condition that truly mimics generalized tetanus. Strychnine, like tetanospasmin, antagonizes glycine release, but unlike tetanospasmin, it has no effect on GABA release. Patients have opisthotonos while remaining alert. The annual incidences of tetanus and strychnine poisoning are similar in the United States, and serum and urine tests for strychnine should be performed when tetanus is considered.

In patients who present with diffuse generalized spasms, the diagnosis is unlikely to be missed, but ideally the disease should be considered and diagnosed in the early stages to minimize complications and decrease mortality. Some conditions with clinical similarities to tetanus are listed in Box 118.5. Trismus is most commonly caused by intraoral infections. These can be excluded with careful history and physical examination. Mandibular dislocation can be ruled out with appropriate radiographs of the mandible and temporomandibular joints. Dystonic reactions can be differentiated from tetanus by medication history and symptoms alleviated by benztropine or diphenhydramine. Patients with encephalitis usually exhibit an altered mental status. Meningitis can be excluded by examination of the cerebrospinal fluid (CSF). Rabies should be considered when there are symptoms of brainstem dysfunction, including dysphagia and respiratory muscle dysfunction. A history of exposure to secretions of an infected animal is the most helpful historical point. In addition, rabies does not cause trismus.

Cephalic tetanus is especially difficult to diagnose when the cranial nerve palsy precedes trismus. The differential diagnosis of cephalic tetanus includes Bell palsy, botulism, cranial nerve palsies, and facial cellulitis with facial nerve compression and ophthalmoplegia.

Diagnostic Testing

The diagnosis of tetanus should be made on clinical grounds. Wound cultures are of little value and are positive in only one-third of cases. A positive culture does not indicate whether the bacterium is a toxin-producing strain. There are no laboratory tests to confirm or to exclude the diagnosis of tetanus. Lumbar puncture may be indicated to exclude meningitis in the neonate when the diagnosis of tetanus is uncertain. A computed tomography (CT) scan helps assess for intracranial disease. A serum calcium level is helpful to exclude hypocalcemia. Electromyography may be useful if the diagnosis of cephalic or localized tetanus is in doubt.

BOX 118.5 Differential Diagnosis of Tetanus

Acute abdomen
Black widow spider bite
Dental abscess/infection
Dislocated mandible
Dystonic reaction
Encephalitis
Head trauma
Hyperventilation syndrome
Hypocalcemia
Meningitis
Peritonsillar abscess
Progressive fluctuating muscle rigidity (stiff-man syndrome)
Psychogenic
Rabies
Sepsis
Status epilepticus
Strychnine poisoning
Subarachnoid hemorrhage
Temporomandibular joint syndrome

The spatula test involves touching the oropharynx with a tongue blade. With a negative test, the patient gags and expels the tongue blade. With a positive test, the patient has reflex masseter muscle spasm and bites the spatula. This test is 94% sensitive and 100% specific for tetanus.

Management

The four treatment strategies for patients with tetanus should be undertaken simultaneously: supportive care, elimination of unbound tetanospasmin, prevention of further toxin production, and active immunization.[22]

Supportive Care

Supportive care begins with controlling muscle spasms. Reflex spasms result from stimulation of the patient caused by any movement or loud noises. Unnecessary stimulation should be avoided. Benzodiazepines are the mainstay of symptomatic therapy. These drugs are GABA agonists and indirectly antagonize many of the effects of tetanospasmin, but they do not affect the glycine release inhibition by tetanospasmin. Diazepam is the most extensively studied, but lorazepam and midazolam are equally effective. Diazepam has a rapid onset of action, wide safety margin, and can be given orally, rectally, or IV. It is inexpensive and available in most parts of the world. Its long cumulative half-life and active metabolites can cause prolonged sedation and respiratory depression. The IV formulations of diazepam and lorazepam contain propylene glycol, which, at high doses, can produce lactic acidosis. Gastrointestinal delivery of these agents is limited by motility problems associated with tetanus. Midazolam has a short half-life and does not contain propylene glycol; it should be given by continuous infusion and is cost-prohibitive in many areas of the world. Propofol infusion is effective and expensive, but patients may not tolerate the lipid vehicle. Neuroleptics, barbiturates, and intrathecal baclofen have no advantage over benzodiazepines. Dantrolene is a direct muscle relaxant without CNS activity. It has been reported as an adjunctive agent for muscle spasms and may decrease the need for mechanical ventilation.[19] Magnesium sulfate infusion has been advocated as both adjuvant and first-line therapy for tetanus, with recent data showing effectiveness as first-line therapy to control spasms and muscle rigidity in mild-to-moderate tetanus.[26]

If spasms cannot be controlled with these regimens or airway compromise develops, the patient should receive neuromuscular blockade and mechanical ventilation. Succinylcholine should not be the first-line neuromuscular blockade because there is a risk of severe hyperkalemia resulting from its use in any neuromuscular disease. This effect does not begin until about 4 days after the onset of disease. Long-acting nondepolarizing agents are preferred. Vecuronium and rocuronium are shorter acting and lack significant cardiovascular side effects but require continuous infusion. Adequate sedation should be provided, and neuromuscular blockade should be withheld daily to assess the patient's status. All intubated patients should be considered for early tracheostomy to decrease reflex spasms caused by the endotracheal tube.

Autonomic instability requires monitoring and treatment. Sympathetic hyperactivity can be treated with combined alpha- and beta-adrenergic antagonists, such as labetalol and propranolol. The use of beta-antagonists alone can lead to unopposed alpha-activity, resulting in severe hypertension. If beta-antagonists are necessary, a short-acting agent such as esmolol should be used. Clonidine has variable success at modulation of sympathetic outflow in these cases. Morphine and magnesium sulfate infusions as well as spinal anesthesia and intrathecal baclofen have been shown to improve autonomic dysfunction.[21] Diuretics should be avoided for blood pressure control as volume depletion can worsen autonomic instability. Bradydysrhythmia should be treated with temporary pacing. Atropine and sympathomimetic drugs should be used with caution because the autonomic instability is essentially due to catecholamine excess.

Elimination of Unbound Toxin and Active Immunization. Passive immunization with human tetanus immune globulin (HTIG) and active immunization with Td should be initiated as soon as possible in all patients with suspected tetanus. HTIG neutralizes circulating toxin and reduces mortality. It does not neutralize toxin already present in the nervous system, nor does it treat any existing symptoms. HTIG should be administered at a site separate from the Td; 500 units is as effective as higher doses. Adult and pediatric doses are the same. Administration of a portion of the HTIG proximal to the site of inoculation is often recommended but has not been studied. The preparation of HTIG available in the United States is not licensed for intrathecal administration, which is of questionable benefit.[21]

Prevention of Further Toxin Production. Toxin production is eliminated by treatment of the *C. tetani* infection. Wound débridement and antibiotic administration can cause transient release of tetanospasmin, so these measures should be delayed until after the HTIG is administered. Metronidazole (500 mg orally or IV every 6 hours) is the antibiotic of choice for *C. tetani*. Table 118.1 lists pediatric doses of metronidazole based on age and weight.

Penicillin has good in vitro and in vivo activity against *C. tetani,* but it also has GABA antagonistic activity and may potentiate the effects of tetanospasmin. Metronidazole has better penetration into devitalized tissue and abscesses than penicillin and is superior in terms of recovery time and effect on mortality. Macrolides, doxycycline, chloramphenicol, and tetracycline are effective alternatives in metronidazole-allergic patients.[21]

Vaccination

Tetanus toxoid is an inactivated form of tetanospasmin. Vaccination confers protective antibody levels in nearly 100% of people who receive three doses. Immunity wanes between 5 and 10 years after completion of the series. In high-risk patients such as older patients, injection drug users, and immunocompromised patients, immunity wanes more quickly, and the response to the vaccine is slower.

Adults with uncertain primary immunization status should receive a primary series of three tetanus toxoid doses, followed by booster doses every 10 years. Age-specific guidelines for tetanus prophylaxis have been developed by the Advisory Committee on Immunization Practices (ACIP) and published by the CDC (Tables 118.2 and 118.3). Tetanus vaccination should be updated for all patients who present for wound management. Those younger than 7 years old should receive diphtheria-tetanus or DTaP. Patients 7 years old or older should receive Tdap.

HTIG prophylaxis (250 units IM) is recommended for unimmunized and underimmunized patients with high-risk wounds (>6 hours old, >1 cm deep, contaminated, stellate, denervated, ischemic, infected). When tetanus toxoid and HTIG are given concurrently, separate injection sites should be used. The only contraindication to tetanus and diphtheria toxoids is a history of a neurologic or severe hypersensitivity reaction to a previous dose. The most common side effects of tetanus vaccine are minor: local swelling, pain, erythema, pruritus, fever, nausea, vomiting, malaise, and nonspecific rash. Local reactions do not preclude future use of toxoid. Serious anaphylactic reactions are rare. If a patient who requires toxoid gives a history suggestive of a neurologic or severe anaphylactic reaction, HTIG should be administered alone to protect the patient from development of tetanus as a result of the present injury. HTIG does not confer active immunity, and such patients should be referred to an allergist for measurement of antibody levels, antitoxin desensitization, and immunization. No evidence exists that tetanus and diphtheria toxoids are teratogenic and HTIG is not contraindicated in pregnancy. For inadequately immunized patients of any age, referral should be made to ensure that the patient receives the remainder of the immunizations required.

TABLE 118.1 Pediatric Doses of Metronidazole Based on Age and Weight

Weight and Age	Dosage
Neonates <1200 g and 0 to 7 days	7.5 mg/kg IV or orally every 24 hours
Neonates <1200 g and 8 to 28 days	7.5 mg/kg IV or orally every 12 hours
Neonates >1200 g and 0 to 7 days	7.5 mg/kg IV or orally every 12 hours
Neonates >1200 g and 8 to 28 days	25 to 30 mg/kg/day IV or orally every 12 hours
Infants and children	30 mg/kg/day IV divided every 6 hours, maximum 4 g/day

IV, Intravenous.

BOTULISM

Foundations

Background and Importance

Botulism is a rare life-threatening paralytic illness caused by neurotoxins produced by *Clostridium botulinum*. The disease occurs in one of five forms: food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism.[27] Since the approval of botulinum toxins A and B by the FDA for cosmetic and therapeutic uses in the United States, cases of iatrogenic botulism have been reported.[28]

The term *botulism* comes from the Latin *botulus,* meaning "sausage," because of an association noted between sausage ingestion and the paralytic illness. Botulism first received attention in the United States during World War I when women were encouraged to preserve fruits and vegetables. The recommended heating methods for home canning did not destroy spores, leading to epidemics of botulism. Wound botulism was first described in 1943, the CDC began surveillance of this form of the disease in 1950. Infant botulism, now the most common form of the illness, was first described in 1976.

TABLE 118.2 Routine Diphtheria, Tetanus, and Pertussis Vaccination Schedule for Children and Adults—United States

Dose	Customary Age	Age/Interval	Product
Primary 1	2 months old	6 weeks or older	DTaP
Primary 2	4 months old	4 to 8 weeks after first dose[b]	DTaP
Primary 3	6 months old	4 to 8 weeks after second dose[b]	DTaP
Primary 4	15 to 18 months old	6 to 12 months after third dose[b]	DTaP
Booster	4 to 6 years old, not needed if fourth vaccination administered after birthday[a]		DTaP
Additional booster	11 to 18 years old		Tdap
Adult booster	>18 years old All pregnant women	Every 10 years	Tdap or Td[c]

[a]If primary immunizations are started after the age of 6 years, the series should begin and continue with Tdap.
[b]Prolonging the interval does not require restarting of the series.
[c]Td should be given to adult patients who have previously received Tdap. Tdap can be given regardless of interval since Td.
DTaP, Diphtheria, tetanus, and acellular pertussis; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.
Modified from: Recommended childhood immunization schedule—United States, 2020. Available at www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html and *MMWR.* 2019;68(5):112.

TABLE 118.3 Summary Guide to Tetanus Prophylaxis in Routine Wound Management

History of Absorbed Tetanus Toxoid (Doses)	CLEAN MINOR WOUNDS		ALL OTHER WOUNDS[a]	
	Tdap[b] or Td	TIG	Tdap[b] or Td	TIG
Unknown or less than three	Yes	No	Yes	Yes
Three or more[c]	No[d]	No	No[e]	No

[a]Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
[b]For children younger than 7 years old, DTaP is preferred. For persons older than 7 years old, Tdap is preferred to tetanus toxoid alone. Td is preferable in adults who have previously received one dose of Tdap.
[c]If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
[d]Yes, if greater than 10 years old since last dose.
[e]Yes, if greater than 5 years old since last dose. (More frequent boosters are not needed and can accentuate side effects.)
HTIG, Human tetanus immune globulin; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.
Modified from: Centers of Disease Control and Prevention. Pink Book. National enteric disease surveillance: botulism annual summary in 2017. Available at: www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html.

A total of 182 confirmed cases of botulism were reported to the CDC in 2017, a decrease from 205 cases in 2016. Of these, 77% were infant botulism, 10% were food-borne botulism, 10% were wound botulism, two cases were iatrogenic, and one was suspected adult intestinal colonization.[29] Despite the ubiquitous nature of botulinum spores and the variety of possible routes of toxin entry, the incidence of disease is low.

Typical food-borne botulism results from the ingestion of preformed heat-labile toxin rather than from the ingestion of spores or live bacteria. Food-borne botulism usually results from exposure to home-canned foods that are inadequately preserved and undercooked; large outbreaks occasionally occur after the ingestion of contaminated food at restaurants or from commercial sources. A variety of preserved foods have been implicated, and botulism has also been reported to result from ingestion of improperly prepared and stored fresh foods.

Infant botulism occurs in children younger than 1 year old with a peak incidence between the ages of 6 weeks and 6 months. In contrast to food-borne botulism in adults, infant botulism is caused by the ingestion of spores with in vivo production of toxin. Honey and to a lesser extent corn syrup have been implicated as sources of *C. botulinum* spores in infant botulism. Soil and vacuum cleaner dust have also been implicated, but the source of ingestion remains unknown in most cases. Types A and B botulinum toxins have been responsible for almost all infant cases. There appears to be no relationship between infant botulism and sudden infant death syndrome.

Wound botulism once accounted for approximately one botulism case per year, but the increased use of black tar heroin has resulted in a dramatic increase in cases. Most cases occur in California among injection drug users, with two confirmed cases in Los Angeles county associated with heroin injection. Toxin type A is the most frequent causative agent.[29,30]

Unclassified or adult infectious botulism is a rare illness that is analogous to infant botulism. The *Clostridium* bacterium produces toxin in vivo. Patients with compromised gastric acidity, disturbances of gastrointestinal motility, or abnormal gastrointestinal bacterial flora may be susceptible to in vivo production of botulinum toxin.

Inadvertent botulism is an iatrogenic form of the disease that occurs in patients who have been treated with botulinum toxin injections for dystonia and other movement disorders and for cosmetic purposes. Inadvertent generalized weakness as well as unintentional focal weakness may be seen.[31]

The potential exists for botulinum toxin to be used as a biologic weapon. It is highly potent and easy to produce. The Aum Shinrikyo, responsible for the 1995 sarin gas attack on the Tokyo subway,

produced and dispersed aerosolized botulinum toxin in Japan on at least three occasions between 1990 and 1995. In 1995, Iraq admitted to the United Nations that it had produced 19,000 L of concentrated botulinum toxin and loaded approximately 10,000 L into warheads. These 19,000 L are not fully accounted for and constitute three times the amount needed to kill the entire human population by inhalation.

Anatomy, Physiology, and Pathophysiology

C. botulinum is an anaerobic, gram-positive, rod-shaped organism. It forms spores that germinate under certain environmental conditions. It produces a potent exotoxin that is responsible for the disease. Each strain of *C. botulinum* produces a specific toxin type—A through G. Only types A, B, E, and F produce disease in humans.[32] Botulinum toxins are the most potent known biologic compounds. Doses as small as 0.09 to 0.15 μg IV or 0.7 to 0.9 μg inhaled can cause death in a 70-kg human.[33] Heating at 185°F (85°C) for 5 minutes destroys any botulism toxin, and heating of toxin-contaminated food just before ingestion prevents food-borne botulism. Conversely, spores are highly heat resistant and can survive a temperature of 212°F (100°C) for several hours.

Food-borne botulism results from ingestion of food that contains preformed toxin. Toxin-contaminated food may have a normal appearance and taste or exhibit signs of spoilage. Because of the potency, one bite can expose a person to enough toxin to cause illness. Digestive enzymes do not destroy preformed toxin.

Infant and adult infectious botulism results from in vivo bacterial elaboration of toxin in the gastrointestinal tract. Achlorhydria and recent antibiotic use predispose the gastrointestinal tract to colonization with *C. botulinum*. Wound botulism results from in vivo bacterial elaboration of toxin in a wound. Inadvertent or iatrogenic botulism results from injection of preformed toxin for medical purposes.[32] Primate studies indicate that aerosolized botulinum toxin can also be absorbed systemically through the respiratory tract.[33]

The botulinum neurotoxin is similar in structure and function to the tetanospasmin toxin produced by *C. tetani,* but the clinical effects differ dramatically. Tetanospasmin targets inhibitory interneurons in the CNS, causing generalized muscle spasm, whereas botulinum toxin targets peripheral neuromuscular junctions and autonomic synapses, causing flaccid paralysis. When botulinum toxin is absorbed, it circulates until it reaches the neurons. The toxin binds to the presynaptic nerve membrane, becomes internalized, and inhibits the release of acetylcholine predominantly at the cholinergic synapses of the cranial nerves, autonomic nerves, and neuromuscular junction. Clinically, this is manifested by cranial nerve palsies, parasympathetic blockade, and descending flaccid paralysis. Once affected with type A toxin, the nerve is permanently damaged, and recovery requires axonal regeneration and the formation of new synapses, which may take several months. Recovery after type F toxin is substantially faster.[27]

Clinical Features

Food-borne botulism is the prototype for understanding the clinical signs and symptoms of all forms of botulism. Symptoms begin 6 hours to 8 days after the ingestion of toxin-containing food. A shorter incubation period is associated with a more severe form of illness. Early symptoms include weakness, malaise, lightheadedness, nausea, vomiting, and constipation. These symptoms are generally not severe and occur in fewer than half of the patients.

Neurologic symptoms may begin immediately or be delayed for several days. The cranial nerves are first affected. Patients experience diplopia, blurred vision, dysphonia, dysphagia, dysarthria, and vertigo. Next, a symmetrical descending muscle weakness occurs, involving the upper and lower extremities and the muscles of respiration. Blockade of the cholinergic fibers of the autonomic nervous system leads to a variety of symptoms. Decreased salivation causes a dry mouth, which may be so severe that the patient complains of a painful tongue and sore throat. Ileus and urinary retention may occur.

The patient with botulism is usually alert and afebrile unless a secondary infection is present. Postural hypotension may be present. Ocular signs include ptosis, extraocular palsies, and markedly dilated and fixed pupils; the absence of ocular abnormalities does not exclude the diagnosis. The oropharynx may be erythematous, with dry mucous membranes. The gag reflex is depressed or absent. Muscle weakness is usually present and varies from mild to severe. Neck muscles are often weak. Upper extremity muscles are affected more than those of the lower extremity, and proximal muscles are weaker than distal muscles. Deep tendon reflexes may be normal, symmetrically decreased, or absent. The sensory examination is normal. The abdomen may be distended with hypoactive or absent bowel sounds. Bladder distention may be apparent on examination. Respirations may be tachypneic and shallow or normal. In advanced illness, signs of respiratory failure may be present. Atypical presentations of food-borne botulism have been reported, and certain serotypes produce distinct variations in the pattern of symptoms. Type A disease may be more severe and is more commonly associated with bulbar findings and upper extremity weakness. Type A and type B disease may rarely cause a decreased level of consciousness. Type E is associated with a greater incidence of gastrointestinal symptoms.[27]

The presentation of *infant botulism* is different from that of food-borne botulism. Constipation is a common presenting complaint, followed by several days to weeks of poor feeding, weak cry, loss of head control, and hypotonia. Patients have decreased muscle tone and depressed deep tendon reflexes. Cranial nerve involvement causes alterations in facial expression, ptosis, and extraocular palsies. Respiratory failure occurs in 50% of patients. Fever is absent unless a secondary infection is present.[34]

Wound botulism has notable differences from food-borne botulism. The incubation period is longer, from 4 to 14 days, because the toxin must be produced within the wound after the spores have germinated. If the wound is infected, the patient may be febrile. Gastrointestinal symptoms are absent in wound botulism. Recurrent episodes are well described.[30]

The clinical presentation of *unclassified (adult infectious) botulism* is similar to food-borne botulism, although the mortality rate is significantly greater. Recovery from botulism is slow, and survivors are hospitalized for several weeks to months.

Complications from botulism include respiratory failure and problems associated with prolonged intensive care management. Aspiration of oral secretions and gastric contents because of loss of protective airway reflexes can occur. In the past 50 years, the overall mortality rate has decreased from 50% to less than 1% with modern intensive care. Mortality rates are higher in wound botulism patients (15% to 17%) and lower in infant botulism patients (<1%). For those who recover, muscle strength and endurance may not return to normal for up to 1 year, and persistent psychological problems are common.[29]

Differential Diagnoses

The differential diagnosis of *adult botulism* includes a wide variety of illnesses. The first presenting case is often misdiagnosed because early symptoms suggest pharyngitis or gastroenteritis, both of which can affect several members of a single household. Only after one or more cases progress to classic botulism is the diagnosis usually suggested.

Botulism should be differentiated from other illnesses that cause paralysis. In Guillain-Barré syndrome, weakness usually starts distally and ascends, paresthesias may be present, and the CSF protein level may be elevated. Tick paralysis is an ascending paralysis, which

is notable for a lack of bulbar involvement and the presence of a tick. In myasthenia gravis, eye signs are also prominent, but pupillary response is preserved, no autonomic symptoms are present, and weakness responds to the administration of edrophonium or ice applied to the affected muscle group. Of note, minimal improvement in weakness after the administration of edrophonium has been reported in botulism.[35] Poliomyelitis causes fever, asymmetrical neurologic signs, and CSF abnormalities. Diphtheria can be distinguished by the prolonged interval between pharyngitis and neurologic symptoms. Eaton-Lambert syndrome does not usually involve bulbar muscles. Strokes of the brainstem have an acute onset and asymmetrical, neuroanatomically localizing signs and symptoms.

Certain toxins should be considered in the differential diagnosis of botulism. Anticholinergics (atropine, belladonna, jimson weed) cause pupillary dilation and dry, red mucous membranes but also cause delirium. Organophosphate insecticides cause hyperthermia and altered mental status. Dystonic reactions are self-limited and respond to diphenhydramine or benztropine. Neuromuscular blockade from the administration of aminoglycosides is distinguished by medication history. Heavy metal poisoning produces changes in mental status. Magnesium toxicity may mimic botulism, but history and serum magnesium levels distinguish these entities. In paralytic shellfish poisoning, paresthesias are prominent, a history of shellfish ingestion is present, and recovery occurs within 24 hours.

Infant botulism has a broader differential diagnosis. Common illnesses that can mimic infant botulism include sepsis, viral illnesses, dehydration, encephalitis, meningitis, and failure to thrive. Neurologic illnesses such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis should also be considered.[34] Hypothyroidism, hypoglycemia, diphtheria, and toxin exposures are all part of the differential diagnosis, as are less common conditions such as inborn errors of metabolism, congenital muscular dystrophy, and cerebral degenerative diseases.

Diagnostic Testing

Botulism is a clinical diagnosis that should be considered in any patient who presents with the constellation of gastrointestinal, autonomic, and cranial nerve dysfunction. Bilateral cranial nerve involvement and the progression of neurologic findings should increase clinical suspicion. Routine laboratory studies are of no value in the diagnosis. If a lumbar puncture is performed, the CSF may show only a slight elevation of protein.[32]

The diagnosis is confirmed by detecting botulinum toxin or *C. botulinum* in gastric contents, stool, or wound of the patient, botulinum toxin in the patient's blood, or toxin or organisms in the suspected food source. Local health departments and the CDC should be notified for instruction on the handling of specimens. Ideally, the specimens should be obtained before administering antitoxin, but treatment should not await laboratory confirmation. Serial measurements of the patient's vital capacity are helpful in recognizing deteriorating ventilatory function.[27]

Electromyography (EMG) can detect abnormalities consistent with the diagnosis of botulism and may be useful in differentiating botulism from other paralytic illnesses. The EMG signature of botulism is decreased amplitude of the compound muscle action potential in response to a supramaximal stimulus and facilitation of the muscle action potential with repetitive nerve stimulation. Not all motor units are affected, and normal test results do not exclude the diagnosis.

Management

The treatment of botulism consists of supportive care and specific treatment with antitoxin and other medications to block the effects of the toxin. All patients with suspected botulism should be admitted to an intensive care unit (ICU) because respiratory failure may develop rapidly. A decrease in vital capacity to less than 30% of predicted or less than 12 mL/kg is an appropriate criterion for intubation. Ileus should be treated with nasogastric suction and urinary retention with an indwelling urinary catheter. The autonomic dysfunction of botulism is much less severe than that of tetanus and rarely requires intervention.

Saline enemas and cathartics have been recommended to cleanse the gastrointestinal tract of residual toxin, but no evidence supports these treatments. Cathartics should not be given in the presence of ileus. Magnesium-containing cathartics should be avoided because elevated serum magnesium levels can exacerbate muscle weakness. Special care should be taken with use of gastrointestinal clearance in infants with botulism. Because the source of toxin is outside the gastrointestinal tract in wound botulism, bowel decontamination is not indicated.

Equine antitoxin contains antibodies to toxin types A, B, and E. It should be administered as soon as possible after appropriate laboratory specimens have been obtained. It neutralizes circulating toxin but does not affect bound toxin. Early administration prevents illness progression, decreases hospital length of stay, prevents respiratory failure, and shortens the duration of respiratory failure in patients with severe disease. Antitoxin can be obtained from the CDC or state health department. After skin testing for hypersensitivity, one 10-mL vial should be given IV. The serum half-life is 5 to 8 days. Contrary to the information in the package insert, only one vial of antitoxin is required. Repeated doses are unnecessary and increase the risk of hypersensitivity reactions, which occur in approximately 9% of patients.[29]

Infant botulism is treated with human botulism immune globulin (BabyBIG), which is pooled plasma from immunized adults with high titers of antibodies to toxins A and B.[35] BabyBIG shortens hospital length of stay by a mean of 3.1 weeks and mechanical ventilation by a mean of 1.7 weeks. It can be obtained by calling the Infant Botulism Treatment and Prevention Program (IBTPP) on-call physician at 510-231-7600 (24/7/365).[34,35]

Antibiotics are not currently recommended for food-borne botulism and may increase cell lysis and promote toxin release. Because the source of toxin is in vivo production within an infected wound, débridement and antibiotic administration should be considered only after antitoxin has been administered. Otherwise, the use of antibiotics should be limited to treatment of secondary infections that may develop. Antibiotic treatment of both infant and wound botulism has no proven benefit. If antibiotics are used for any reason in a botulism patient, attempts should be made to avoid the aminoglycosides and tetracyclines because they can impair neuron calcium entry and worsen the effects of botulinum toxin.[27] Guanidine hydrochloride may enhance acetylcholine release from terminal nerve fibers and has been recommended as an experimental component of botulism therapy.[35]

Disposition

All patients with possible botulism should be admitted to an ICU because respiratory failure may develop rapidly and insidiously. An infectious disease specialist should be consulted for management issues. The CDC should be called for assistance in any case of suggested botulism. The CDC can be reached by calling 404-639-3311 (days) and 404-639-2540 (nights, weekends, and holidays). State and local health departments may also be helpful in investigating and preventing major epidemics. Area emergency departments should be alerted so that clinicains can be aware of possible subsequent cases.

PNEUMOCOCCEMIA

Foundations

Background

Streptococcus pneumoniae is a significant cause of morbidity and mortality worldwide. Pneumococcemia is defined as the presence of *S. pneumoniae* in the blood. The clinical presentation ranges from a mild illness to a fulminant, life-threatening, systemic syndrome. *S. pneumoniae* also causes myriad localized infections, including otitis media, pneumonia, meningitis, and, less commonly, endocarditis, septic arthritis, and peritonitis.[31,36]

S. pneumoniae was discovered in 1881 by Sternberg in the United States and simultaneously by Pasteur in France. The first pneumococcal vaccine was licensed for use in the United States in 1977, and today there are two forms available: one for infants younger than 2 years old and individuals with impaired host defenses, and one for otherwise healthy individuals older than 2 years old.[37-40] *S. pneumoniae* remains a substantial cause of serious illness despite the availability of antibiotics and vaccines. Infection appears sporadically in normal individuals and in patients with impaired host defenses. Most cases of pneumococcal infections are community acquired, with a peak incidence in winter. Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site (blood, pleural fluid, CSF). Pneumococcemia occurs in less than 2% of all hospitalized patients with community-acquired pneumonia, but up to 7.3% of those admitted to the ICU, 11.5% of those with multilobar infiltrates, 15% of those with a temperature 104°F (40°C) or higher or 95°F (35°C) or lower, 20% of those with a systolic blood pressure below 90 mm Hg, and 22% of those with HIV. Other sources include the meninges (8%) and the sinuses or middle ear (4%).

Bacteremia is primary in 18% of adults but is much higher in children. People at higher risk for pneumococcemia include those with chronic respiratory or cardiovascular disease, chronic alcohol abusers, patients with cirrhosis, diabetes mellitus, or an absent or functionally impaired spleen (postsplenectomy or sickle cell disease), those receiving immunosuppressive therapy, those with chronic renal failure, nephrotic syndrome, organ transplantation, lymphoma, Hodgkin disease, multiple myeloma, and acquired immunodeficiency syndrome (AIDS).[39] Pneumococcus is spread from person to person by close contact, and crowded living conditions are associated with epidemics. The mortality rate from pneumococcemia is 10% to 20% for young adults and much higher for older patients, those with underlying disease, and those with localized infections, such as meningitis.[40-41] The case fatality rate is significantly lower for children.

Anatomy, Physiology, and Pathophysiology

Pneumococcemia is caused by *S. pneumoniae,* an encapsulated, gram-positive, facultative anaerobic coccus. Antigenic differences in the polysaccharide capsule separate *S. pneumoniae* into 90 serotypes.[31] In the United States, seven serotypes account for most of invasive disease in children younger than 6 years old and 50% of invasive disease in people older than 6 years old. Worldwide, 10 capsular types account for two-thirds of invasive disease while in western industrialized nations, seven capsular types account for two-thirds of invasive disease.

S. pneumoniae enters the blood by one of two routes: (1) It begins as a pulmonary infection that spreads to mediastinal lymph nodes, the thoracic duct, and into the circulation; (2) it colonizes or causes infection in the upper respiratory tract and spreads to the subarachnoid space through the arachnoid villi to the venous sinus and into the blood (with or without meningeal involvement).

S. pneumoniae bacteremia causes a clinical picture that ranges from a minor febrile illness to life-threatening septic shock. Multiple virulence factors contribute to adherence to tissues, inhibition of phagocytosis, activation of complement, and stimulation of cytokines.[31] Host defenses rely heavily upon antibody and complement production, and people who have impaired humoral immunity are more susceptible to IPD. In patients with pneumococcal infections, antibodies specific to the capsule serotype develop within several days of onset of infection. This response occurs approximately 30 days after a patient receives the pneumococcal vaccine. Patients who demonstrate substantial host resistance are able to develop active immunity, and some children can spontaneously clear culture-proven pneumococcemia.

Clinical Features

The clinical presentation of pneumococcemia ranges from mild illness to fulminant disease, progressing to death within several hours. Occult bacteremia begins as a febrile illness in which the only direct indication of pneumococcemia is a positive blood culture (often at 24 to 48 hours). Sepsis is indicated by 2 or more systemic inflammatory response syndrome (SIRS) criteria or the quick SOFA (qSOFA) assessment[42] (see Chapter 127). Patients may present with lethargy, signs of poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Either occult bacteremia or sepsis can occur in conjunction with a localized infection.

Symptoms include fever, chills, cough, shortness of breath, headache, and rash. The clinical presentation of pneumococcemia is similar to that of other common febrile illnesses. Although signs of focal infection, such as pneumonia, may be present, often the only indication of pneumococcemia is fever or other signs of bacterial toxicity. Most adult patients have fever or hypothermia. Cough, rigors, pleuritic pain, and gastrointestinal symptoms occur in about one-third of adult patients. Fever (temperature >101.3°F [38.5°C]) occurs in 90% of younger patients but in less than 60% of those older than 65 years old. Patients with signs of sepsis have an increased risk for a fulminant course with rapid deterioration. Physical examination findings vary with the site of primary infection. A focal primary source of infection is more common in adults than in children. Clinicians should evaluate for signs of otitis media, sinusitis, and meningitis. Pneumococcemia is considered primary in 18% of adults and 30% of children, so lack of localized infection as a source does not rule out IPD.

Cardiovascular collapse can occur with fulminant pneumococcal sepsis. Patients who develop severe illness from pneumococcemia may have end-organ damage from inadequate perfusion, disseminated intravascular coagulation (DIC), septic emboli, respiratory failure, meningitis, gastrointestinal bleeding, hepatic coma, renal failure, and myocardial infarction.

Pneumococcemia occasionally results in hematogenous seeding, causing peritonitis, arthritis, endocarditis, meningitis, and cellulitis. Adults and children with functional or anatomic asplenia may have fulminant pneumococcemia, or *overwhelming postsplenectomy infection (OPSI),* characterized by septic shock, adrenal hemorrhage, and DIC. Although the incidence of OPSI is unknown, studies demonstrate that it is substantial and that the risk for it does not decrease over time after splenectomy. Most invasive pneumococcal infections occur in the first 2 years postsplenectomy, and about two-thirds occur between 5 and 20 years. OPSI may arise with symptoms indistinguishable from those of common viral illnesses.[43,44] The 100-fold increased incidence of pneumococcal bacteremia and meningitis in children with sickle cell disease is likely primarily due to splenic dysfunction, but complement abnormalities may also play a role.[45]

Differential Diagnoses

Pneumococcemia is challenging to distinguish from other causes of febrile illness. The presence of fever and shock, with or without a

characteristic rash, suggests the possibility of sepsis caused by *Haemophilus influenzae, Neisseria meningitidis,* and other streptococcus types. The presence of confirmed pneumococcemia does not exclude other diagnoses, such as influenza.

Diagnostic Testing

The only test specific for pneumococcemia is a blood culture that grows *S. pneumoniae.* Ancillary testing should include a complete blood count with differential, blood and urine cultures, electrolyte values, glucose concentration, serum creatinine level, serum lactate, and blood urea nitrogen level. A CXR may demonstrate pneumonia. The results of sputum Gram stain, culture, and sensitivity testing may help direct later inpatient care. Sputum specimens should be collected before antimicrobial therapy is instituted if possible; however, therapy should not be delayed to obtain sputum. Antigen testing of urine for pneumococcal polysaccharide is up to 100% sensitive in IPD.[45]

If the patient appears toxic or has signs of respiratory compromise, an arterial blood gas, serum lactate, and coagulation profile should be obtained. If signs of meningitis or alterations in mental status are present, a lumbar puncture should be performed. Gram stain of the buffy coat may be positive in cases of overwhelming pneumococcal sepsis. The WBC count is usually elevated. A normal or low WBC count is suggestive of more serious disease, as are hypoxemia and hypercarbia. Increased mortality occurs in patients with serum creatinine levels higher than 2.0 mg/dL, bilirubin levels higher than 1.5 mg/dL, and albumin levels below 2.5 g/dL.

Management

Acute Treatment

Management of pneumococcemia consists of stabilization of life-threatening conditions, eradication of the infection, and treatment of predisposing or coexisting conditions. All septic patients should be managed with sepsis-directed therapy (see Chapter 127).[46,47] The decision to initiate antibiotic therapy is often made with limited objective data, which include the clinical findings, age of the patient, underlying conditions, and preliminary laboratory studies. Prompt initiation of antibiotics is essential to reduce the morbidity and mortality of pneumococcal infection, and should begin in the ED. To simplify selection of a treatment strategy, patients can be divided into two groups:

1. Bacteremia or sepsis suggested by clinical findings; organism not identified: Patients in this group are given antibiotics based on the most likely organism, patient's age, immune status, presence of coexisting disorders, and local patterns of antibiotic resistance. The antibiotic regimen is altered after identification of the organism and its sensitivities.
2. *S. pneumoniae* growth is reported from blood cultures (usually 1 to 2 days prior): The treatment regimen for occult bacteremia is guided by the patient's age, history, physical examination, general appearance, and ancillary test results. The antibiotic selected on initial visit may be sufficient to treat pneumococcal bacteremia subsequently identified by the laboratory. The patient should be reevaluated promptly. Repeated blood culture should be obtained if the patient has not been taking an antibiotic. For well-appearing children, a 7- to 10-day course of an appropriate oral antibiotic is reasonable. The decision to admit a child is based on the findings at the time of reevaluation.

Adult patients with laboratory-proven pneumococcemia may be treated with penicillin G if susceptibility has been documented: 2 to 4 million units IV every 4 hours if local penicillin resistance patterns are still low. Meningitis is treated with 4 million units of penicillin G every 4 hours. In children, the dosage for meningitis is 250,000 units/kg per 24 hours in divided doses every 4 hours IV up to a maximum of 20 million units.

S. pneumoniae susceptibility to penicillin in the United States continues to decline.[48] Unless penicillin susceptibility has been documented, treatment should begin with ceftriaxone (1 to 2 g IV every 12 to 24 hours; 50 to 100 mg/kg/day in children) or cefepime (1 to 2 g IV every 8 to 24 hours; 50 mg/kg every 8 hours in children). When meningitis is suspected, higher doses should be given. In areas where ceftriaxone resistance has emerged, vancomycin (weight-based loading dose 20 mg/kg, maintenance dose based on renal function in children) should be administered.

Ceftriaxone is commonly administered to children with suggested occult bacteremia treated as outpatients while blood, urine, and CSF culture results are pending. Ceftriaxone (initial dose of 50 to 100 mg/kg IM or IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (200 mg/kg/day in divided doses every 6 hours IV, up to a maximum of 12 g) are excellent antibiotics for *N. meningitidis* and *H. influenzae*. Alternative initial treatment of pneumococcemia in penicillin- or cephalosporin-allergic patients includes vancomycin, imipenem, and chloramphenicol.

Patients with pneumococcemia may not respond to treatment for the first 24 to 48 hours of therapy. This may be attributed to the normal course of the disease, an incorrect diagnosis, the underlying illness, or an antibiotic regimen that does not treat the infection sufficiently.

Vaccination

Pneumococcal vaccine is effective in preventing infection; the 23-valent vaccine contains the purified polysaccharide antigens of the serotypes that cause 70% to 88% of pneumococcemia infections in the United States. Although it is only 60% to 70% effective at preventing invasive disease, it is safe, inexpensive, and of substantial value for well-defined groups at risk.[37,39] The 23-valent pneumococcal vaccine has limited immunogenicity in children younger than 2 years. The heptavalent conjugate vaccine PCV7, licensed in 2000, linked the polysaccharide to proteins, resulting in an improved immunogenic response in children younger than 2 years old.[49] This vaccine significantly decreased IPD caused by the included serotypes, but an increase in disease caused by non-vaccine serotypes prompted the development of a 13-valent conjugate vaccine. PCV13 was licensed in the United States in 2010 and has replaced PCV7.[37] Recommendations for the use of the PVC13 and 23-valent (PPSV23) vaccines are given in Tables 118.4, 118.5, and 118.6.[50,51]

Approximately 50% of IPD in children with comorbidities is caused by serotypes not included in either the 13-valent or 23-valent vaccine.[52] Other preventive measures for pneumococcemia include passive immunization with immunoglobulins for patients with congenital or acquired immunodeficiency diseases and daily antibiotic prophylaxis for children with functional or anatomic asplenia.[53]

Disposition

Toxic-appearing patients of any age should be treated with antibiotics and admitted to the hospital. Patients with underlying or coexisting conditions and those with an unclear course of illness should also be admitted or observed. Children who are afebrile and appear well on initial examination are unlikely to have serious sequelae. The decision to treat a febrile child with antibiotics on an outpatient basis is based on clinical findings, vaccination history, medical history, the ability of the parents to follow the discharge instructions, and availability of timely follow-up.

MENINGOCOCCEMIA

Foundations

Background

Few clinical situations in emergency medicine produce greater concern than meningococcal infection. Virtually all emergency clinicians

TABLE 118.4 Centers for Disease Control and Prevention Recommendations for the Use of the PVC13 and PPSV23 in Adults

		PCV13	PPSV23[a]	
Risk Group	Underlying Medical Condition	Recommended	Recommended	Revaccination at 5 Years After First Dose
Immunocompetent persons	Chronic heart disease[b]		✓	
	Chronic lung disease[c]		✓	
	Diabetes mellitus		✓	
	CSF leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓
Immunocompromised persons	Congenital or acquired immunodeficiencies[d]	✓	✓	✓
	HIV infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression[e]	✓	✓	✓
	Solid organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

[a]All adults 65 years old or older should receive a dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine.
[b]Including congestive heart failure and cardiomyopathies.
[c]Including chronic obstructive pulmonary disease, emphysema, and asthma.
[d]Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).
[e]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.
CSF, Cerebrospinal fluid; *HIV,* human immunodeficiency virus.

TABLE 118.5 Centers for Disease Control and Prevention Recommendations for the Use of the PCV13 Vaccine Among Infants and Children Who Have Not Received Previous Doses of PCV7 or PCV13, by Age at First Dose

Age At First Dose	Primary PCV13 Series[a]	PCV13 Booster Dose[b]
2 to 6 months old	3 doses	1 dose at age 12 to 15 months old
7 to 11 months old	2 doses	1 dose at age 12 to 15 months old
12 to 23 months old	2 doses	—
24 to 59 months old (healthy children)	1 dose	—
24 to 71 months old (children with certain chronic diseases or immunocompromising conditions	2 doses	—

[a]Minimum interval between doses is 8 weeks except for children vaccinated at age <12 months old for whom minimum interval between doses is 4 weeks. Minimum age for administration of first dose is 6 weeks old.
[b]Given at least 8 weeks after the previous dose.
Advisory Committee on Immunization Practices (ACIP), United States, 2019.

practicing before the meningitis vaccine have had a patient who appeared relatively well on initial presentation, only to be moribund with fulminant infection a few hours later. Vieusseux initially described "Epidemic cerebrospinal fever" in 1805, and Weichselbaum identified the causative bacterial agent in 1887. The introduction of sulfonamide therapy in 1937 dramatically improved outcomes. Sulfonamide prophylaxis was also effective at eradication of the carrier state and was used to prevent epidemics that occurred in military barracks. In the 1940s, sulfonamide resistance began to emerge. In 1963 an outbreak of resistant meningococcal disease occurred in the United States, which

TABLE 118.6 Underlying Medical Conditions That Are Indications for Pneumococcal Vaccination Among Children, by Risk Group

Risk Group	Condition
Immunocompetent children	Chronic heart disease[a] Chronic lung disease[b] Diabetes mellitus CSF leaks Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection Chronic renal failure and nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation Congenital immunodeficiency[c]

[a]Particularly cyanotic congenital heart disease and cardiac failure.
[b]Including asthma if treated with prolonged high-dose oral corticosteroids.
[c]Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
CSF, Cerebrospinal fluid; *HIV,* human immunodeficiency virus.
Advisory Committee on Immunization Practices (ACIP), United States, 2010.

spurred efforts to develop a vaccine. Subsequent worldwide resistance has resulted in continued efforts to develop safe and effective vaccines.[53]

Humans are the only reservoir for *N. meningitidis*. In 2013, 564 cases of meningococcal disease were reported in the United States. Active Bacterial Core surveillance by the CDC reports an incidence of 0.14 per 100,000 population, a marked decrease since the licensing of the first conjugated meningococcal vaccine in 2005 (Fig. 118.5). Of the more than 13 serogroups, groups A, B, C, Y, and W-135 cause most infections. Most cases occur sporadically, with occasional outbreaks, notably on college campuses in dormitories or other crowded living situations. More than half of the cases in infants are caused by serogroup B, for which there is no effective vaccine. Serogroups C, Y, and W-135 cause 75% of meningococcal disease in patients older than 11 years old.[54]

The incidence of meningococcal disease peaks in the winter. Superimposed on this annual variation are cyclic peaks of disease every 5 to 15 years. Approximately every 10 years, massive outbreaks of serogroup A occur in sub-Saharan Africa (the "meningitis belt"). The last outbreak was in 2013 with over 9000 cases and close to 900 deaths.[55] During nonepidemic periods, children younger than 5 years old have the highest incidence of infection. During epidemics, the incidence increases among children aged 5 to 9 years, an observation that may be of value in predicting the beginning of an epidemic. Crowded living conditions increase the risk for spread of meningococcal disease. The incidence of disease and the carrier state are several times higher among military recruits in the first few weeks of service than in the general public. This is also true of first-year college students, particularly those living in dormitories. Other risk factors for development of invasive meningococcal disease include close contact with an infected patient, complement deficiency, properdin deficiency, asplenia, chronic alcohol abuse, active and passive smoking, corticosteroid use, and recent respiratory illness. The mortality rate of meningococcemia is 40% in the United States. Septicemia without meningitis carries a much higher mortality rate (up to 70%) than meningitis alone (less than 10%).[53,54,56]

Anatomy, Physiology, and Pathophysiology

Meningococcal disease is caused by *N. meningitidis,* a fastidious, aerobic, gram-negative diplococcus. *N. meningitidis* is an encapsulated organism classified into at least 13 serogroups based on the capsular polysaccharides.[53] *N. meningitidis* is an obligate human pathogen. It attaches to nonciliated epithelial cells in the nasopharynx. It may remain on the epithelial surface, causing an asymptomatic carrier state or producing mild upper respiratory tract infection symptoms. The carrier state acts as an immunizing process. In certain patients, the bacteria enter the bloodstream and cause localized infection, bacteremia, sepsis, or fulminant infection. Multiple host and microorganism characteristics determine whether clinical disease develops, but the presence of bactericidal antibodies is protective. Complement deficiency plays a role in a host's inability to fight this infection. The capsule is required for *N. meningitidis* to adhere to epithelium, but only unencapsulated meningococci enter epithelial cells; capsular biosynthesis has been shown to stop as the bacteria enter the epithelial cell.[53] The release of lipo-oligosaccharide (LOS) and endotoxin by autolysis of the *N. meningitidis* cell is the initial event in the development of meningococcal sepsis. LOS stimulates a massive host mediator response.

All of the major pathophysiologic events of meningococcal sepsis are caused by the host's inflammatory response to the organism causing functional and histologic damage to the microvasculature, resulting in increased vascular permeability, pathologic vasoconstriction and vasodilation, loss of thromboresistance, DIC, and profound myocardial dysfunction.[53]

Clinical Features

Presentation of meningococcemia ranges from a mild febrile illness to fulminant disease progressing to death within hours. Most patients have fever on presentation. Other complaints include headache, irritability, lethargy, myalgias, emesis, diarrhea, cough, and rhinorrhea. Anywhere from 27% to 77% of patients present with the classic hemorrhagic skin lesions.[53] These patients can rapidly progress to purpura fulminans, with hypotension, adrenal hemorrhage, and multiorgan failure. The following categories detail the five patterns of presentation.

Occult Bacteremia

This is a febrile illness in which the only direct indication of meningococcemia is a positive blood culture. In its mildest form, meningococcal bacteremia cannot clinically be distinguished from more benign febrile illnesses. Initial diagnoses include common childhood infections, such as otitis media, acute viral upper respiratory infections, and gastroenteritis. For some patients the illness resolves after treatment with an oral regimen of antibiotics; others experience spontaneous resolution without antibiotic treatment. *N. meningitidis* accounts for less than 1% of occult bacteremia cases, but these patients are much more likely to develop meningitis (up to 58%) than are those with *S. pneumoniae*. Despite the total absence of clinical clues to meningococcal infection at initial presentation, some untreated patients subsequently deteriorate rapidly.

Meningococcal Meningitis

Patients with meningococcal meningitis present similarly to those with meningitis of other causes, with headache, photophobia, vomiting, fever, and signs of meningeal inflammation. This classic triad of fever,

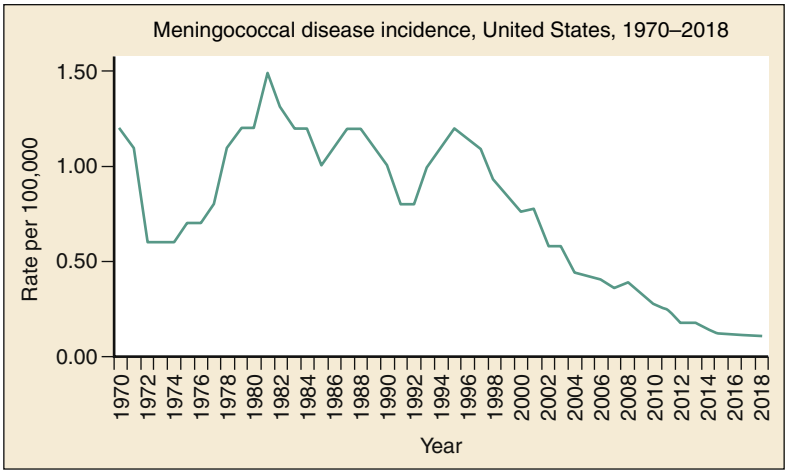

Fig. 118.5 Meningococcal disease incidence by year in the United States from 1970 to 2018. (Centers for Disease Control and Prevention. Manual for the surveillance of vaccine-preventable diseases. Available at: https://www.cdc.gov/meningococcal/surveillance/index.html)

neck stiffness, and altered mental status is present in less than 30% of patients.[57] Infants and small children may present with fever, irritability, and vomiting as the only complaints. More than half of patients with meningococcal meningitis have rash on presentation, and 20% present with seizures. Onset of symptoms is less abrupt (usually during 24 hours), and the prognosis is better for patients with meningococcal meningitis than for patients with meningococcemia without clinical signs of meningitis.

Meningococcal Septicemia

Patients with meningococcal septicemia present with lethargy, poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Hemorrhagic skin lesions are present in 28% to 77% of patients, but a macular or maculopapular rash may occur and be mistaken for a variety of viral exanthems. Petechiae generally appear on the extremities and under pressure points, such as the elastic bands of socks and underwear. They may progress to involve almost any body surface, including the mucosa and sclera, but typically spare the palms, soles, and head. Macular lesions may progress to purpura and ecchymoses in fulminant meningococcemia.

Purpura fulminans, the most advanced form of meningococcal septicemia, occurs most often in children and is usually associated with DIC. This condition is characterized by rapidly spreading ecchymoses and gangrene of the extremities. Mucosal and gastrointestinal bleeding as well as oozing from IV sites may occur. Clinical signs of meningitis and CSF pleocytosis may not be present, even when diplococci are isolated from the CSF, likely because the systemic progression of the disease is so rapid that it precludes a host meningeal inflammatory response to the organism in the CSF. Shock can result from distributive shock, intravascular volume loss, and heart failure, probably related to myocarditis. Renal failure, coma, and bilateral adrenal hemorrhage often occur.[53]

Fever and a Nonblanching Rash

Up to 30% of patients present without signs of meningitis or septicemia. They are typically admitted for fever and a nonblanching rash and no other specific findings. If left untreated, meningitis or fulminant septicemia and shock can develop.[50,56]

Chronic Meningococcemia

This syndrome is characterized by fever, rash, and arthritis in conjunction with a positive blood culture for *N. meningitidis*. Headache and upper respiratory symptoms are often present. This is the rarest form of meningococcal disease, accounting for less than 2% of cases. It may progress to meningitis, endocarditis, or fulminant meningococcemia regardless of treatment.

Complications

Circulatory collapse is a common complication of meningococcemia and the most common cause of death. Many of the inflammatory mediators released during sepsis cause peripheral vasodilation, capillary leak, and myocardial dysfunction. Acidosis, hypoglycemia, hypokalemia, hypocalcemia, hypophosphatemia, and hypoxia also contribute to myocardial dysfunction, which may become unresponsive to inotropic medications.

Acute respiratory failure occurs from capillary leak, DIC, and large volume requirements in the setting of decreased cardiac function. Patients frequently require mechanical ventilation. Renal failure is common due to impaired renal perfusion. If meningitis accompanies meningococcemia, focal neurologic deficits and seizures may occur but are less common than with pneumococcal meningitis. Long-term neurologic sequelae include hearing loss, visual deficits, neurodevelopmental impairment, cranial nerve palsies, and hemi- and quadriparesis. Purpura fulminans may result in skin lesions and loss of digits or limbs from gangrene. Purulent or immune complex arthritis and pericarditis with tamponade may also occur.

Poor prognostic indicators include seizures, hypothermia, hyperpyrexia, total peripheral WBC count of less than 500/mm^3, platelet count of less than 100,000/mm^3, metabolic acidosis (pH <7.30), development of purpura fulminans, onset of petechiae within 12 hours of admission, absence of meningitis, presence of shock, low sedimentation rate, and extremes of age. In one study, all patients who developed organ system failure had one or more of the following at the time of initial presentation: circulatory insufficiency (hypotension or shock), peripheral WBC count of less than 10,000 cells/mm^3, or a coagulopathy.[51]

Differential Diagnoses

It is difficult to distinguish the clinical signs of meningococcemia from bacteremia caused by *S. pneumoniae,* other streptococcal groups, *H. influenzae,* and *Neisseria gonorrhoeae.* A hemorrhagic rash is more commonly associated with meningococcal disease. The differential diagnosis of meningococcemia also includes viral exanthems, Rocky Mountain spotted fever, typhus, typhoid fever, endocarditis, vasculitis

syndromes (polyarteritis nodosa and Henoch-Schönlein purpura), toxic shock syndrome (TSS), acute rheumatic fever, dengue fever, drug reactions, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura.

Diagnostic Testing

The tentative diagnosis of meningococcemia is based on clinical findings and confirmed by the isolation of *N. meningitidis* from blood cultures or any other usually sterile site, such as CSF or synovial, pleural, or pericardial fluid. Ideally, blood culture specimens should be obtained before the administration of antibiotics unless this delays the patient's treatment. Blood cultures are positive in approximately 50% to 80% of cases. A lumbar puncture should be performed in stable patients without evidence of DIC. The CSF shows either gram-negative diplococci on Gram stain or a positive culture in about 46% to 94% of cases. Even patients without clinical signs of meningitis frequently have the organism grown from the CSF. Gram stain of petechial scrapings may show gram-negative diplococci in up to two-thirds of cases, and the organism can rarely be seen in the peripheral blood buffy coat. Highly specific antigen tests for CSF are available but have a high false-negative rate. PCR of the buffy coat or CSF is more sensitive and specific than any of the preceding tests and is not affected by prior antibiotic therapy.[53,54]

Ancillary laboratory tests are of little value in establishing a specific diagnosis of meningococcal sepsis but may be useful in ruling out other disease, determining prognosis, and monitoring complications. The WBC count may be high, low, or normal, but a bandemia is typically present. The symptoms and signs of CNS infection may be nonspecific in the infant and child younger than 2 years old. If meningitis is present, the CSF opening pressure is usually elevated, the protein level is increased, and the glucose concentration is decreased. Pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes. Gram-negative diplococci may be seen on microscopy. Early in the disease or with fulminant disease, the CSF may be free of inflammatory cells. Serologic evidence of DIC is frequently present.[54,55] A CXR is useful in evaluation for pneumonia and acute respiratory distress syndrome. An echocardiogram helps assess for myocardial dysfunction and pericardial effusion. Serum lactate may help direct therapy.

Management

Acute Treatment

Morbidity and mortality in meningococcemia are reduced with prompt recognition and intravenous antibiotic therapy. Patients can be divided into two general groups:

1. Bacteremia or sepsis suggested by clinical findings; no organism identified: Patients should receive empirical antibiotics based on factors that include the most likely organism, patient's age and immune status, presence of coexisting disorders, and local patterns of antibiotic resistance. A narrower-spectrum agent is selected after identification of the organism and its sensitivities.
2. *N. meningitidis* growth is reported from prior blood cultures: Treatment for occult bacteremia is guided by the patient's age, history, physical examination, general appearance, and ancillary test results. The antibiotic selected at the time of the initial visit may be sufficient to treat the meningococcal bacteremia subsequently identified by the laboratory. The decision to hospitalize the patient is based on the findings at the time of reevaluation and the risk of sequelae. We recommend repeating blood cultures, considering lumbar puncture, and admitting the patient to the hospital until results of repeated cultures are obtained.

The standard antibiotic regimen for laboratory-proven meningococcemia is penicillin G (4 million units every 4 hours IV for adults) and penicillin (250,000 to 300,000 units/kg/day in divided doses every 4 hours IV for children, up to a maximum of 20 million units). Penicillin resistance in *N. meningitidis* remains low in the United States but has been reported in Spain and the United Kingdom.[53]

Although appropriate first-line therapy, penicillin is rarely given as the initial agent in patients with suspected meningococcal sepsis or meningitis. Ceftriaxone (100 mg/kg IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (100 mg/kg/day IV in divided doses every 6 hours, up to a maximum of 12 g) are appropriate initial antibiotics as well. The cephalosporins are safe and have rapid onset of action and excellent coverage for *S. pneumoniae* and *H. influenzae*. Chloramphenicol (100 mg/kg/day divided every 6 hours to a maximum of 4 g/day) should be considered in penicillin- and cephalosporin-allergic patients. IM ceftriaxone is occasionally administered to children with suspected bacteremia treated as outpatients while culture results are pending. Several reports have demonstrated the efficacy of ceftriaxone (80 to 100 mg/kg IV) in a single daily dose; however, twice-daily dosing remains the standard recommendation at this time. Ceftriaxone-treated patients have more rapid sterilization of the CSF and a lower incidence of hearing loss than conventionally treated patients.

Patients with fulminant meningococcemia often require airway management, IV fluid resuscitation, and vasopressor support. Fluid requirements may be high. In the setting of frequent myocardial dysfunction, intensive cardiovascular monitoring is required. Electrolyte and acid-base abnormalities should be corrected. If the patient is oliguric or anuric, hemodialysis may be necessary to correct these abnormalities. Fresh frozen plasma should be considered for patients with bleeding complications.

The role of steroids in the treatment of meningococcemia without meningitis is controversial. Although corticosteroids were once widely recommended to treat the adrenal insufficiency associated with fulminant meningococcemia, recent studies demonstrate that adrenal function is not impaired in all patients. If patients have persistent shock despite vigorous fluid resuscitation and vasopressor therapy, glucocorticoid therapy and adrenal function testing should be considered as this subgroup of patients may benefit.[57]

The use of corticosteroids in patients with bacterial meningitis is currently recommended for adults and children. Corticosteroid administration before antibiotic administration decreases long-term neurologic sequelae in adults and children. There is also a mild decrease in mortality. In neonates, there are limited data of low quality that suggest steroids decrease morbidity from hearing loss and may decrease mortality. Although these benefits are not seen in patients with meningococcal meningitis, the organism is typically not identified when steroids are initiated. Dexamethasone (0.4 to 0.6 mg/kg/day every 6 hours for 4 days) should be given to patients with bacterial meningitis. The first dose should be given before the first dose of antibiotics if possible.[58,59] Plasmapheresis, blood exchange, and extracorporeal membrane oxygenation have been described, but data are limited.

Antibiotic Prophylaxis and Vaccination

Close patient contacts (household, nursery schools, daycare centers, military recruits, college dormitories, teammates) should receive antibiotic prophylaxis. Intimate contacts and health care workers with intimate exposure (e.g., mouth-to-mouth resuscitation, intubation, or suctioning) should receive rifampin, 10 mg/kg (up to 600 mg) orally every 12 hours for four doses. The dose for neonates is 5 mg/kg. Patients should be warned that rifampin discolors the urine and secretions; contact lenses should be removed to avoid permanent staining.

IM ceftriaxone (125 mg for children younger than 15 years old and 250 mg for those older than 12 years old) is an effective alternative for pregnant women and for people in whom compliance with an oral regimen cannot be ensured. Ciprofloxacin (500 mg orally) is another alternative for adults.[56]

Meningococcal vaccine should be considered an adjunct to prophylaxis in epidemics and for close contacts in sporadic cases if one of the serotypes contained in the vaccine is identified as the causative agent. The currently available vaccines are quadrivalent vaccines for serogroups A, C, Y, and W-135. No vaccine is licensed for group B, a serogroup that causes a significant portion of meningococcal infection in the United States, but trials are currently underway.[60] The conjugate vaccines (MCV4: Menactra and Menveo) produce a superior immune response compared to the polysaccharide vaccine (MPSV4: Menomune). Routine vaccination with MPSV4 is not recommended and should be limited to patients over 55 years old, or when MCV4 is unavailable. Routine vaccination with MCV4 is recommended for persons 11 or 12 years old with a booster at 16 years old. Vaccination is also recommended for those at increased risk of meningococcal disease, including microbiologists who are routinely working with *N. meningitides*, military recruits, children with functional or anatomic asplenia, and people traveling to endemic areas of the world, such as sub-Saharan Africa.[54]

Disposition

All patients with possible or confirmed meningococcemia should be placed in respiratory isolation and hospitalized, preferably in an ICU, because they can decompensate rapidly and without warning. A possible exception is the well-appearing child who has culture-proven *N. meningitidis* and has been taking appropriate antibiotics as an outpatient. This child should have a lumbar puncture performed to determine CSF involvement if one was not performed at the initial evaluation. Antibiotics should be continued on an inpatient basis, but an ICU may not be necessary if the child appears well.

TOXIC SHOCK SYNDROME

Foundations

Background and Importance

Toxic shock syndrome (TSS) is a toxin-mediated systemic inflammatory response syndrome that was first described in 1978 in a series of seven children 8 to 17 years old who had high fever, rash, headache, confusion, conjunctival injection, edema, vomiting, diarrhea, renal failure, hepatic dysfunction, DIC, and shock. *S. aureus* was cultured from various body sites but not from the blood in five of the seven cases. The disease gained notoriety in the early 1980s when many cases were reported in association with tampon use in young, healthy menstruating women. The term *toxic shock syndrome* was coined to describe the constellation of signs and symptoms. Investigators noted positive vaginal cultures for *S. aureus,* recurrence of illness during subsequent menses, and the value of antistaphylococcal antibiotics in preventing recurrences. Nonmenstrual cases were also recognized in both men and women due to a variety of predisposing conditions, and a case definition was published in 1982 (Box 118.6).[61-64]

In the late 1980s, several reports described group A streptococcus infection (*S. pyogenes*) associated with shock and multisystem organ failure. This is called *streptococcal toxic shock syndrome* because it shares many features with staphylococcal TSS. Box 118.7 shows the case definition for streptococcal TSS.[65]

The peak incidence of TSS occurred in 1980, when 890 cases were reported, 91% of which were associated with tampon use. Since then, the reduction in cases of the menstrual form of TSS has followed an active effort to decrease the absorbency of tampons and to change their composition. Menstruation remains the most common setting for TSS, but nonmenstrual TSS accounts for just under half of the reported cases. TSS has also been reported in association with barrier contraceptives and childbirth. Nonmenstrual TSS occurs in people of all ages and both sexes. The CDC reported an average of about 300 cases a year between 2010 and 2015, with a steady increase in the incidence of streptococcal TSS and a decrease in the incidence of staphylococcal TSS. The age and sex distribution reflects the association with menses. Streptococcal TSS accounts for two-thirds of the cases.[63]

Nonmenstrual staphylococcal TSS is associated with superinfection of various skin lesions, including burns, surgical sites, dialysis catheters, and lung (influenza-associated). It may also occur in association with staphylococcal respiratory infections or even with colonization by a toxigenic strain of the organism, without an obvious infectious source. Streptococcal TSS is classically associated with more severe soft tissue infections, such as necrotizing fasciitis and myositis, as well as with pneumonia, peritonitis, myometritis, and osteomyelitis.

The mortality rate from staphylococcal TSS has declined since the disease was first described. The case fatality rate in 1980 was 10% and is

BOX 118.6 Case Definition of Toxic Shock Syndrome (Revised)

Clinical Case Definition

Fever: Temperature >102°F (38.9°C)

Rash: Diffuse macular erythroderma

Desquamation 1 to 2 weeks after onset of illness, particularly of palms and soles

Hypotension: Systolic blood pressure <90 mm Hg for adults or below fifth percentile by age for children younger than 16 years old, orthostatic drop in diastolic blood pressure >15 mm Hg from lying to sitting, orthostatic syncope, or orthostatic dizziness

Multisystem involvement—*three* or more of the following:

- Gastrointestinal: Vomiting or diarrhea at onset of illness
- Muscular: Severe myalgia or creatine kinase level at least twice the upper limit of normal for laboratory
- Mucous membrane: Vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: BUN or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (>5 leukocytes/high-power field) in the absence of urinary tract infection
- Hepatic: Total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory
- Hematologic: Platelets <100,000/mm^3
- CNS: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:

Blood, throat, or CSF cultures (blood culture may be positive for *Staphylococcus aureus*)

Rise in titer to Rocky Mountain spotted fever, leptospirosis, or rubeola

Case Classification

Probable: A case that meets the laboratory criteria and in which four of the five clinical findings are present

Confirmed: A case that meets the laboratory criteria and in which all five of the clinical findings are present, including desquamation, unless the patient dies before desquamation occurs

ALT, Alanine transaminase; *AST,* aspartate transaminase; *BUN,* blood urea nitrogen; *CNS,* central nervous system; *CSF,* cerebrospinal fluid.

BOX 118.7 Case Definition of Streptococcal Toxic Shock Syndrome

Clinical Case Definition

Hypotension: Systolic blood pressure ≤90 mm Hg for adults or below fifth percentile by age for children younger than 16 years old

Multisystem involvement—*two* or more of the following:

- Renal: Creatinine >2 mg/dL (177 μmol/L) for adults or more than twice the upper limit of normal for age or more than twofold elevation above baseline for patients with preexisting renal disease
- Hematologic: Platelets <100,000/mm^3 or DIC, defined as prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
- Hepatic: Total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory, or a twofold increase in patients with preexisting liver disease
- Acute respiratory distress syndrome: Defined by acute onset of pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
- Generalized erythematous maculopapular rash that may desquamate
- Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene

Laboratory Criteria for Diagnosis

Isolation of group A streptococcus

Case Classification

Probable: A case that meets the clinical case definition in the absence of another identified cause of the illness and with isolation of group A streptococcus from a nonsterile site

Confirmed: A case that meets the clinical case definition and with isolation of group A streptococcus from a normally sterile site (e.g., CSF or joint, pleural, or pericardial fluid)

ALT, Alanine transaminase; *AST,* aspartate transaminase; *CSF,* cerebrospinal fluid; *DIC,* disseminated intravascular coagulation.

now 5%. Streptococcal TSS remains a highly fatal disease, with a mortality rate of 30% to 70%.

Anatomy, Physiology, and Pathophysiology

Staphylococcal TSS is caused by colonization or infection with toxigenic strains of *S. aureus*, which produce toxic shock syndrome toxin 1 (TSST-1). *S. aureus* is present in virtually all cases of both forms of the illness. Because the organism is often not invasive, the blood cultures are often negative. Streptococcal TSS is caused by invasive infection with toxigenic strains of group A streptococcus.[61,62,64]

The effects of various exotoxins produced by *S. aureus* and group A streptococcus cause the shock and multiorgan dysfunction associated with TSS. *S. aureus* produces TSST-1 and enterotoxin B. TSST-1 is identified in more than 90% of menstrual cases and 60% of nonmenstrual cases. Other toxins may play a role in nonmenstrual TSS. Antibodies to these toxins are protective against disease. Group A streptococcus produces streptococcal pyrogenic exotoxins A and B. These exotoxins are absorbed into the bloodstream through inflamed or traumatized mucous membranes or from areas of focal infection. Absorbed toxins act as superantigens, inducing mononuclear cells to synthesize and to release cytokines, tumor necrosis factor alpha (TNF-α), and interleukins at a rate and magnitude many fold greater than with the normal antigen presentation, which begin the cascade of systemic vasculitis and the multisystem manifestations of the disease. Host immune factors are important in the pathogenesis of TSS. Group A streptococcus is an invasive organism and circulating group A streptococcus organisms induce the production of TNF-α and other cytokines by mononuclear cells.[64]

BOX 118.8 Risk Factors for Toxic Shock Syndrome

Use of superabsorbent tampons
Postoperative wound infections
Postpartum period
Nasal packing
Cancer
Common bacterial infections
Ethanol abuse
Infection with influenza A virus
Infection with varicella virus
Diabetes mellitus
Human immunodeficiency virus (HIV) infection
Chronic cardiac disease
Chronic pulmonary disease
Nonsteroidal antiinflammatory drug (NSAID) use (may mask symptoms rather than be a risk factor)

Clinical Features

The clinical presentations of streptococcal TSS and staphylococcal TSS are similar. The primary difference is that an identifiable infectious source is virtually always present with streptococcal TSS, and colonization alone may be the source in staphylococcal TSS.

TSS should be considered in patients who present with fever, rash, hypotension, and evidence of end-organ damage, such as respiratory failure or altered mental status. Patients may have a prodromal illness with fever, chills, nausea, vomiting, watery diarrhea, headache, myalgias, and pharyngitis, which can last 2 to 3 days before progression to frank sepsis and organ dysfunction. Other patients may become abruptly symptomatic within hours. Rapid progression is more typical of streptococcal TSS. Patients may complain of pain at a site of infection more often with streptococcal TSS. Risk factors for TSS are listed in Box 118.8.

The fever is usually high and abrupt in onset, although patients may have hypothermia. The classic rash is a nonpruritic, diffuse, blanching, macular erythroderma. It develops in the first few days of the illness and may be faint, evanescent, and mistaken for the flush associated with a fever. It is usually diffuse but may be localized to the trunk, extremities, or perineum. After about a week, fine flaky desquamation occurs on the face, trunk, and extremities, followed by full-thickness peeling of the palms, soles, and fingers. This classic rash progression is much more common in staphylococcal TSS and is present in less than 10% of patients with streptococcal TSS. Patients with streptococcal TSS may have a scarlet fever–like rash, petechiae, or maculopapular lesions. Mucosal involvement may also occur, including conjunctival and scleral hemorrhages, "strawberry tongue," and mucosal ulceration.

Altered mental status such as confusion, somnolence, agitation, and combativeness are present in 55% of patients with streptococcal TSS and in even more patients with staphylococcal TSS. Other findings on physical examination include pharyngeal and conjunctival erythema and peripheral edema. Vaginal mucosal erythema and purulent vaginal discharge may be present in menstrual TSS but are not required make the diagnosis. As multiple organ systems become involved, a wide constellation of signs and symptoms may be seen. Gastrointestinal involvement is manifested by vomiting, diarrhea, and severe abdominal pain. Hepatomegaly may be present. Acute respiratory distress syndrome

(ARDS) develops in more than half of patients and is manifested by rales on pulmonary examination and hypoxia (see Chapter 2). Comparisons between staphylococcal and streptococcal TSS are presented in Table 118.7.

Complications of TSS include shock, gangrene, DIC, and a constellation of neuropsychiatric symptoms. Renal failure occurs in 80% of patients but is irreversible in only 10%. Less common findings in staphylococcal TSS include rhabdomyolysis, seizures, pancreatitis, pericarditis, and cardiomyopathy. Women with the menstrual form of TSS may experience recurrent episodes; recurrences of the nonmenstrual form are rare. Complication rates are higher with streptococcal TSS. Rhabdomyolysis occurs in up to 63% of patients with streptococcal TSS and is usually related to the underlying soft tissue infections.

Differential Diagnoses

The differential diagnosis of TSS includes any septic illness with exanthems. Other diseases to consider include heatstroke, cellulitis, Kawasaki disease, staphylococcal scalded skin syndrome, scarlet fever, drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Rocky Mountain spotted fever, clostridial gas gangrene, leptospirosis, meningococcemia, gram-negative sepsis, atypical measles, and viral illnesses.

Kawasaki disease occurs almost exclusively in children, usually does not progress to shock, lacks multisystem involvement, is manifested with a protracted fever, and is associated with thrombocytosis later in its course.[65] Staphylococcal scalded skin syndrome presents with a desquamating rash acutely, whereas the desquamation of TSS occurs in the convalescent phase. Staphylococcal scalded skin syndrome does not progress to shock, is not associated with multisystem illness, and lacks mucous membrane involvement. Scarlet fever differs in its clinical course by lack of shock and multisystem involvement, positive cultures for group A streptococcus, and a rise in the convalescent titer. Stevens-Johnson syndrome usually occurs after drug administration, has characteristic mucous membrane lesions, and lacks desquamation. TEN may be challenging to distinguish from TSS; TEN patients are typically febrile, are in shock, and can progress to multisystem failure. The desquamation of TEN occurs early in the course of the disease, and it usually occurs after administration of a drug.[66] Rocky Mountain spotted fever occurs after a tick bite, has a distinctive rash, and is associated with a severe headache without an altered mental status or hypotension. Leptospirosis occurs in endemic areas and may be distinguished by positive serologic studies and cultures. Petechiae and purpura occurring anywhere on the skin characterize the rash of meningococcemia.

Diagnostic Testing

Diagnosis of TSS does not require a positive culture for *S. aureus,* but isolation of *Streptococcus* organisms is a criterion. The case definitions (see Boxes 118.6 and 118.7) are useful, but they are neither specific nor foolproof. Suspecting the disease is key rather than meeting all CDC criteria for diagnosis.

No specific laboratory changes are associated with TSS, but many abnormalities are common. Leukocytosis or leukopenia with bandemia is common, and myelocytes and metamyelocytes may be seen. Elevated creatinine levels and hemoglobinuria occur in most patients. Renal dysfunction occurs before hypotension in half of the patients. Hypoalbuminemia (85%) and life-threatening hypocalcemia (79%) are prominent initially and persist throughout the disease. Other abnormalities include anemia, thrombocytopenia, prolonged prothrombin and activated partial thromboplastin times, hyper-bilirubinemia, elevated transaminase levels, severe metabolic acidosis, and sterile pyuria. Creatine phosphokinase (CPK) levels may be elevated in patients with necrotizing fasciitis and myonecrosis.[64]

TABLE 118.7 Comparison of Staphylococcal and Streptococcal Toxic Shock Syndrome

Feature	Staphylococcal	Streptococcal
Age	Primarily 15 to 35 years old	Primarily 20 to 50 years old
Sex	Greatest in women	Either
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, packing, NSAID use?	Cuts, burns, bruises, varicella, NSAID use?
Thrombocytopenia	Common	Common
Mortality rate	<3%	30% to 70%

NSAID, Nonsteroidal antiinflammatory drug.

Blood cultures are positive for bacteria in 60% of cases associated with group A streptococcus but are rarely positive in staphylococcal TSS. Gram stains and cultures from wounds may identify the organism. Culture of the cervix or vagina is positive in 90% of menstrual cases of TSS, even in the absence of local infection.

A CXR may reveal bilateral heterogeneous opacities, consistent with ARDS, or a pulmonary source of the organism. Plain radiographs of any infected skin or soft tissue site typically show only soft tissue swelling but may reveal a retained foreign body or air in the soft tissue. A lack of air in the soft tissue does not rule out a necrotizing soft tissue infection.

An ECG may reveal evidence of ischemia, arrhythmias, and varying degrees of atrioventricular block associated with sepsis. A blood gas analysis may indicate metabolic acidosis secondary to hypotension or hypoxia. A lumbar puncture should be performed in febrile patients with altered mental status to evaluate for meningitis. It is prudent to wait for the results of a coagulation profile before the lumbar puncture is performed because these patients may have DIC at presentation. The CSF is normal in patients with TSS.

Management

Patients with TSS should receive fluid resuscitation with crystalloids due to severe volume depletion and third spacing from capillary leaking. Supplemental oxygen should be administered to treat an Spo_2 less than 95%, and mechanical ventilation with low tidal volumes may be necessary in patients with ARDS. The source of bacteria, such as tampons, nasal packs, and other foreign bodies, should be removed. Prompt surgical consultation should be obtained to débride wounds. If specimens are sent for culture, the laboratory should be informed of the suspected diagnosis. Patients who do not respond to fluid resuscitation require vasopressors, such as norepinephrine, vasopressin, and epinephrine (see Chapter 3).

Antibiotics should be initiated early in the treatment of TSS because the clinical presentation of the disease is similar whether the source is staphylococcal or streptococcal. For septic patients without an identified organism, broad-spectrum antibiotics should be administered. Although the penicillinase-resistant penicillins (nafcillin, oxacillin) have been widely used in TSS treatment, we recommend clindamycin as

a first-line agent. Clindamycin is a potent suppressor of bacterial toxin synthesis; it also facilitates phagocytosis of streptococci by inhibiting M protein synthesis, decreases monocyte synthesis of cytokines, and has a more prolonged post-antibiotic effect than the β-lactams. The dose is 900 mg IV every 8 hours. (The pediatric dose is 20-40 mg/kg/day divided every 6 to 8 hours.)[64] Linezolid in combination with clindamycin may be better than either agent alone based on isolated case reports.

Patients who do not respond to appropriate fluid resuscitation, antibiotics, and vasopressors should be considered for intravenous immune globulin (IVIG) treatment, especially if pulmonary edema develops and mechanical ventilation is required. Pooled immune globulin has high titers for antibodies to TSST-1 and other exotoxins, and significant improvement has been reported with its use in streptococcal TSS. Because the data in staphylococcal TSS are inconclusive, and the mortality is relatively low, immunotherapy should be reserved for life-threatening cases. If used, the recommended dose is 1 to 2 g/kg on day 1 administered intravenously during several hours, followed by 400 to 500 mg/kg/day for up to 5 days.[61]

Hemodialysis or hemoperfusion may be necessary because more than half of streptococcal TSS patients develop renal failure. Both modalities may reduce concentrations of circulating toxins, and a study in Sweden demonstrated the lowest mortality rate ever recorded for strep TSS.[64]

The value of corticosteroids in TSS is unresolved. They are not currently recommended to treat staphylococcal or streptococcal TSS, but should be given to patients thought to have adrenal insufficiency related to underlying disease or chronic steroid use.

Disposition

All patients thought to have TSS should be admitted to an ICU. Prompt surgical consultation should be obtained for patients with a wound source.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 118: QUESTIONS AND ANSWERS

1. An 18-year-old male recent immigrant presents with acute-onset sore throat, fever, and weakness. He has no past medical history. Examination is remarkable for a grayish white exudative coat over both tonsils and the posterior pharynx. There is modest neck swelling with cough, low-grade fever, and hoarseness. Rapid strep testing and monospot results are negative. Which of the following statements regarding this patient's disease is *true?*

a. Antibiotics and corticosteroids are the main therapy.
b. Neuromuscular examination is critical.
c. Rapid treatment will obviate the need for intubation.
d. The electrocardiogram (ECG) is a sensitive indicator of myocarditis.

Answer: B. Diphtheria can be a more benign upper respiratory/nasal infection or a "malignant" process with airway obstruction, myocarditis, and neuropathy (palate is involved first; the only cells spared are cortical). Antibiotics stop further organism growth, but diphtheria equine antitoxin is the key to therapy. Death is usually from myocarditis or airway obstruction, with the highest mortality seen in patients with the "bull neck" appearance. The ECG is an insensitive indicator of myocarditis.

2. An 11-year-old child presents with coughing paroxysms for 10 days. This was preceded by a mild upper respiratory tract infection. The paroxysms occur multiple times per day and have occasionally caused vomiting. The child is relatively well between paroxysms. Vaccination history is unknown. Which of the following statements regarding this patient's disease is *true?*

a. Antibiotics will shorten illness duration.
b. Erythromycin should be given to unimmunized contacts.
c. Fever is expected.
d. Thoracic petechiae should prompt a septic evaluation.

Answer: B. Pertussis, caused by a gram-negative bacterium, is a three-phase illness: catarrhal (upper respiratory tract infection), paroxysmal, and convalescence of weeks to months. The coughing phase is characterized primarily by complications related to the paroxysms, such as subconjunctival hemorrhage, pneumomediastinum, headache, rectal prolapse, chest wall petechiae, and even seizures. Fever is rare unless there is secondary infection. Antibiotics only reduce the carrier state. Corticosteroids may help younger children. Antibiotic prophylaxis is indicated for nonimmunized contacts. Nasal culture is diagnostic. Standard cough suppressants are ineffective.

3. After which of the following circumstances has tetanus been reported?

a. Childbirth
b. Chronic skin ulcers
c. Corneal abrasion
d. All of the above

Answer: D. It has also been reported after dental procedures, abortions, and intestinal operations. In these cases, the source of the bacteria is endogenous because up to 10% of humans harbor *Clostridium tetani* in the colon.

4. Which of the following statements concerning the tetanus neurotoxin (tetanospasmin) is *true?*

a. A shorter incubation period portends a better prognosis.
b. It blocks presynaptic release of gamma-aminobutyric acid (GABA).
c. Sensory nerves are blocked, followed by motor nerves.
d. Synaptic binding is reversible and overcome by acetylcholinesterase therapy.

Answer: B. The toxin migrates in the motor nerve from the injury site to the central nervous system (CNS). Presynaptic release of the

inhibitory neurotransmitter GABA and glycine is diminished. The unopposed excitatory action results in muscle spasm. Presynaptic inhibition of the autonomic nervous system is also lost, and wide heart rate and blood pressure fluctuations are seen. The toxin binding is irreversible and diminishes only with axon synaptic regeneration. A shorter incubation period is a harbinger of a worse outcome.

5. A 62-year-old male farmer with no medical problems presents with leg pain and muscle spasms. He reports moderate to severe pain and muscle spasms in the calf that have occurred and worsened during 3 days. Two weeks prior, he suffered a puncture wound to his ankle just above his boot top with a piece of metal. Examination is remarkable for a heart rate of 115 beats/minute, blood pressure of 170/110 mm Hg, and a healing clean wound above the medial malleolus with no evidence of active infection. The calf is in active spasm with some increased tone in the peroneal musculature also. Which of the following statements regarding this patient's disease is *true?*

a. A radiograph should be obtained to assess for subcutaneous air.
b. Admission for intravenous (IV) antibiotics is indicated.
c. Outpatient management is indicated.
d. Tetanus immune globulin is indicated.

Answer: D. Localized tetanus reflects a local neuromuscular process with pain and spasm. It is likely due to a partial immunity. Immune globulin is indicated. Although mortality is lower, it can progress to generalized tetanus, and admission is warranted.

119

Viruses

Raghu Seethala, Sukhjit S. Takhar, Jeffrey Bullard-Berent, and Laura L. Banks

KEY CONCEPTS

- Recent outbreaks of vaccine-preventable childhood infections have occurred secondary to unvaccinated individuals and travel to areas where disease is still endemic. Emergency clinicians should recognize the possibility of these once rare diseases.
- Herpes simplex encephalitis is fatal if untreated. Clinicians should suspect this diagnosis when evaluating severely ill patients for suspected meningitis or encephalitis and promptly institute empirical therapy with IV acyclovir while awaiting diagnostic results.
- Primary varicella can be dangerous in select populations, including older children, adults, and pregnant patients. These patients require treatment with acyclovir.
- Zoster patients should be treated with acyclovir if they present within 72 hours of symptoms onset or if they are immunocompromised regardless of duration of illness. Disseminated zoster should be treated with IV acyclovir.
- In healthy patients with influenza infection, the duration of illness can be shortened by almost 1 day if antiviral treatment is administered within 48 hours of symptom onset. Hospitalized patients with influenza infection should be treated with antiviral medication regardless of duration of symptoms, because it may decrease mortality and influenza complications.
- Rabies has the highest case fatality rate of any recognized infectious disease.
- Almost 60,000 deaths per year worldwide are caused by dog-mediated human rabies, and this burden falls disproportionately on children and the poor in rural areas.
- Globally, human rabies results from bites by infected dogs. In North America human rabies results predominantly from wildlife exposures (bat, raccoon, and skunks).
- Treatment is rarely effective once symptoms of human rabies occur.
- Rabies postexposure prophylaxis (PEP) given strictly according to the World Health Organization (WHO) or US Centers for Disease Prevention and Control (CDC) guidelines is extremely effective. Discussion with public health officials is recommended to guide decisions regarding when PEP should be considered. The CDC clinician information line is 877-554-4625 or 800-CDC-INFO.
- Many emerging viral infections, including SARS-CoV2 and Ebola, should be considered in febrile patients. It is important to identify patients at risk by determining travel history and exposure history to individuals with confirmed infection. Once a patient is deemed at risk, the patient should be promptly isolated according to established guidelines while further investigation occurs. It is also important to immediately inform the hospital infection control program and public health agencies.

FOUNDATIONS

The vast majority of viral infections, such as the common cold, are minor and self-limiting. However, some are highly pathogenic, contagious, and have the potential to cause devastating illness. In addition to centuries-old infections such as chicken pox, there are also newer infections such as avian influenza, Middle East respiratory syndrome (MERS), enterovirus D68 (EV-D68), as well as SARS-CoV2 (see Chapter 120). With increasing international travel, emergency clinicians should be familiar with emerging infections spreading beyond their endemic origins. In addition to recognizing symptoms and knowing the treatment for these infections, emergency clinicians should be familiar with isolation and reporting practices vital to preventing global pandemics.

Advances in molecular biology have increased our knowledge of these infections, improved our diagnostic ability, and allowed more treatment options. Viruses are classified according to the type and structure of nucleic acid, capsid, and presence or absence of an envelope (Table 119.1). In practice, it is useful to group viruses based on clinical syndromes. This chapter reviews select viral illnesses with high morbidity and mortality, those with specific treatments, and those with major public health consequences. The chapter begins by reviewing several preventable diseases reemerging because of decreasing immunization rates caused by unfounded fears of complications or side effects.

VACCINE-PREVENTABLE INFECTIONS OF CHILDHOOD

Childhood immunization is among the most important public health measures globally. Immunizations save 2 to 3 million children per year from serious illness, disability, and death. However, there has been a troubling trend of people in industrialized nations refusing routine immunizations. These groups advocate for nonmedical exemptions from mandated school-entry vaccines in developed nations, and routine immunizations have been rejected by some over questions of safety and the lack of perceived threat for serious vaccine-preventable diseases.[1] The emergency clinicians may therefore play a significant role in educating parents on the safety and efficacy of childhood immunizations. The United States (US) Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians recommend a specific childhood immunization schedule each year. Table 119.2 summarizes the currently available viral vaccines and recommended schedule.

Mumps

Mumps is an RNA virus that is a member of the *Paramyxoviridae* family. It causes a febrile illness with swelling and tenderness of the parotid gland. Since the advent of the mumps vaccine in 1967, there has been a 99% decrease in mumps in the United States. Despite the vaccine, recent outbreaks in industrialized nations, even in vaccinated individuals, raised concerns about resurgence of mumps.[2]

Mumps is spread via infected respiratory secretions that enter a susceptible respiratory tract. The incubation period is typically 16 to 18

TABLE 119.1 Classification of Viruses

DNA Viruses		
Poxviridae	Variola	Smallpox
	Orf	Contagious pustular dermatitis
Herpesviridae	HSV-1, HSV-2	Mucocutaneous ulcers, herpes encephalitis
	Cytomegalovirus	Pneumonitis in immunocompromised patients
	VZV	Chickenpox, shingles
	HHV-6	Roseola infantum
	EBV	Mononucleosis
	Kaposi sarcoma herpesvirus	Kaposi sarcoma
Adenoviridae	Adenovirus (50+ species)	Upper respiratory tract infections, diarrhea
Papillomaviridae	Papillomavirus (80+ species)	Warts (e.g., plantar, genital)
Polyomaviridae	JC virus	PML
Hepadnaviridae	Hepatitis B	Hepatitis
Parvoviridae	Parvovirus B19	Aplastic anemia
RNA Viruses		
Reoviridae	Colorado tick fever	Fever and rash
	Rotavirus	Gastroenteritis
Togaviridae	Eastern equine encephalitis	Epidemic encephalitis
	Rubella	German measles
Flaviviridae	Yellow fever	Hemorrhagic fever
	Dengue	Dengue hemorrhagic fever
	Zika	Fever, rash, arthralgias
	West Nile virus	West Nile encephalitis
	Hepacivirus, hepatitis C	Chronic hepatitis
Coronaviridae	Coronavirus	Upper respiratory tract infections
	SARS-CoV	SARS
	MERS-CoV	MERS
	SARS-CoV-2	COVID-19
Paramyxoviridae	Respiratory syncytial virus	Bronchiolitis
	Measles	Measles (rubeola), SSPE
	Parainfluenza	Croup
Rhabdoviridae	Rabies	Rabies
Filoviridae	Ebola	Hemorrhagic fever
Orthomyxoviridae	Influenza A, B	Influenza
Bunyaviridae	La Crosse	Encephalitis
	Hanta	Hemorrhagic fevers, ARDS
Arenaviridae	Lassa	Hemorrhagic fever
	Lymphocytic choriomeningitis virus	Meningoencephalitis
Retroviridae	HIV	AIDS
Picornaviridae	Poliovirus	Polio
	Coxsackie B	Myocarditis
	Hepatitis A	Enteric hepatitis
	Rhinovirus (115+ species)	Upper respiratory infections
Caliciviridae	Norwalk virus	Gastroenteritis
Unclassified viruses	Hepatitis E	Enteric hepatitis

AIDS, Acquired immunodeficiency syndrome; *ARDS,* acute respiratory distress syndrome; *COVID-19*, coronavirus disease 2019; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *MERS-CoV*, Middle East respiratory syndrome coronavirus; *PML,* progressive multifocal leukoencephalopathy; *SARS-CoV,* severe acute respiratory syndrome–coronavirus; *SSPE,* subacute sclerosing panencephalitis; *VZV,* varicella-zoster virus.

TABLE 119.2 Viral Vaccines

Virus	Vaccine	Type	Indication	Recommended Schedule
Smallpox	Vaccinia	Live	For persons at risk or for emergency responders	Once, before anticipated risk of exposure
Polio	Oral polio vaccine (Sabin)	Live	During outbreaks Unvaccinated travelers	Inactivated polio vaccine preferred in almost all cases
	Inactivated polio vaccine (Salk)	Inactivated	All children	At 2, 4, 6–18 months, and at 4–6 years
Measles	Measles, mumps, rubella (MMR)	Live	All normal children	At 12–15 months and 4–6 years
Mumps	MMR	Live	All normal children	Same as for measles
Rubella	MMR	Live	All normal children	Same as for measles
Hepatitis A	HAV vaccine	Inactivated	Persons at risk (e.g., travelers, persons living in areas of high prevalence)	Two doses, 6 months apart. Ideally should be given one month prior to travel. Immune globulin should be given if travel is imminent
Hepatitis B	HBV vaccine	Inactivated or recombinant	All children	At birth, 1–2 months, and 6–18 months
			Persons at risk of exposure (e.g., health care workers)	Hepatitis B immune globulin (HBIG) should be given in addition in case of high-risk exposure
Influenza A and B	Influenza vaccine	Inactivated	In 2010, CDC expanded recommendation for annual influenza vaccination to include all persons aged 6 months and older	One dose yearly in the fall or winter
	Intranasal vaccine	Live, cold adapted	As above, for persons 2–49 years of age. Avoid if pregnant, immunosuppressed, young children with asthma, allergic to eggs	As above
Rabies	Human diploid cell vaccine (HDCV)	Inactivated	Postexposure prophylaxis or for preexposure prophylaxis in high-risk individuals	Postexposure: HDCV or PCEC 1.0 mL IM in the deltoid region on days 0, 3, 7, and 14. Rabies immune globulin (RIG) 20 IU/kg should be administered around the wound site, as possible, with the remainder given IM at an anatomically distant site. Preexposure: HDCV or PCEC 1.0 mL IM in the deltoid region on days 0, 7, 21, and 28.
	Purified chick embryo cell (PCEC)	Inactivated	Postexposure prophylaxis or for preexposure prophylaxis in high-risk individuals	As above
Yellow fever	17D virus strain	Live	Persons 9 months to 59 years of age traveling to endemic areas. Contraindicated in children younger than 6 months of age, precaution in age 6–8 months and 60 years or older	Boosters every 10 years
Rotavirus	RV1	Live	All healthy children	2 dose series, at 2 months and 4 months of age
	RV5	Live	All healthy children	3 dose series, at 2, 4, and 6 months of age
Varicella	Varicella	Live	All healthy children	At 12–15 months and 4–6 years
			At-risk adults (those without evidence of immunity and high risk for exposure or transmission)	Persons older than 13 years should receive two doses 4–8 weeks apart
Zoster	Zoster	Live	Anyone 60 years of age and older, contraindicated in severe immunodeficiency	A single one time dose in adults aged 60 years or older

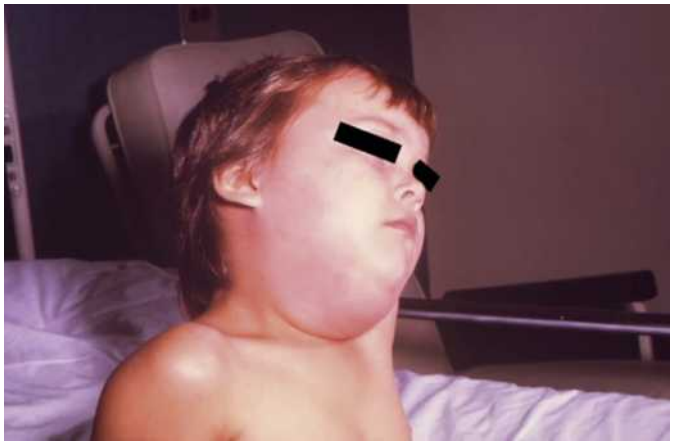


Fig. 119.1 Mumps infection demonstrating parotitis. (Courtesy of CDC website: http://phil.cdc.gov/phil/details.asp?pid=130)

days, ranging from 12 to 25 days. Infected patients are most contagious 1 to 2 days before onset of disease but can be contagious as early as 7 days before symptoms and up to 9 days after symptoms start.

Clinical Features

Parotitis, either unilateral or bilateral, is the hallmark of this infection, occurring in over 95% of symptomatic patients (Fig. 119.1). Other salivary glands are not commonly affected. Symptoms usually begin with fever, malaise, and headache, but about one-third of mumps infections are asymptomatic. Up to 30% of mumps infections cause orchitis, which usually occurs 1 week after the onset of parotitis and is more commonly seen in older patients. Orchitis is usually unilateral but can occur in both testes in up to one-third of the cases. There is a high incidence of cerebrospinal fluid (CSF) pleocytosis in patients with mumps, but less than 10% have symptomatic meningitis, and less than 1% have encephalitis. The mortality from mumps is very low, and the majority of morbidity and mortality associated with mumps occurs in cases complicated by encephalitis.

Differential Diagnosis

During an outbreak, mumps can be easy to diagnose. Other viral infections that can cause parotitis (Epstein-Barr virus [EBV], parainfluenza, influenza A virus, coxsackievirus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, and human immunodeficiency virus [HIV]), bacterial infections, facial cellulitis, and tumor are all other diagnoses that should be considered.

Diagnostic Testing

Mumps can be confirmed by detection of viral RNA, via reverse transcription polymerase chain reaction (RT-PCR), detection of the virus itself from clinical specimens, or detection of antibodies (immunoglobulin M [IgM] or a fourfold rise in immunoglobulin G [IgG] between acute and convalescent serum specimen). This entails collecting a buccal or oral swab specimen for virus isolation and blood sample for serologic testing. Collecting samples early improves yield as virus isolation greatly diminishes after the first week of symptoms.

Management and Disposition

The mainstay of treatment is supportive care with antipyretics and analgesics. There is no specific antiviral treatment. Most cases have a benign, self-resolving course and do not require admission to the hospital. In the hospital setting, these patients should have droplet precautions observed. Patients should be isolated for 5 days after the onset of parotid swelling. Individuals with close contact with the infected patient should receive vaccinations if not immunized.

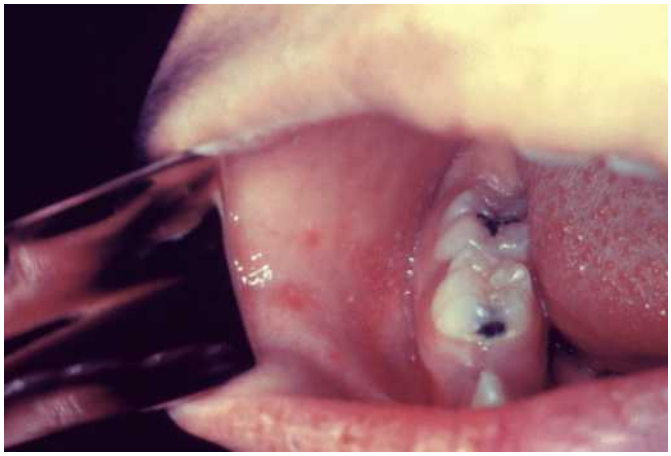


Fig. 119.2 Koplik spots. (Courtesy of CDC website: http://phil.cdc.gov/phil/details.asp?pid=6111.)

Measles (Rubeola)

Measles is an RNA virus thought to be the most contagious infection known to humans. It was a common childhood illness, causing 3 to 4 million cases per year in the United States the 1960s, but the number of cases has dramatically decreased since the advent of the measles vaccine. Despite introduction of the measles vaccine in the 1960s, measles remains common in developing countries, mostly in parts of Africa and Asia. Global health initiatives aimed at eliminating measles focus on reaching and maintaining over 95% coverage with two doses of measles-containing vaccination. Progress has been made toward measles elimination; the World Health Organization (WHO) reported that from 2000 to 2018, the annual measles incidence decreased by 66% and measles-related deaths decreased by 73%.[3]

Measles still occurs in the United States and other developed nations, mostly among unvaccinated or incompletely vaccinated individuals who have exposures to individuals infected from an endemic region. In 2011, France had a measles outbreak with nearly 15,000 cases. A recent outbreak in New York City was linked to an unvaccinated child returning home from Israel with measles with over 600 cases occurring.[4]

Clinical Features

The incubation period for measles is 7 to 21 days. The first symptoms manifest during the prodromal phase, which lasts approximately 3 days. During this phase patients have fever, malaise, and the classically taught three Cs (cough, coryza, and conjunctivitis). Koplik spots, small raised bluish white spots on the buccal mucosa, often opposite the lower first and second molars, or the roof of mouth (Fig. 119.2), are pathognomonic for the diagnosis and can be seen during the prodromal phase. The patient will then develop the typical rash; a nonpruritic maculopapular rash beginning on the head and face and spreading down the entire body over the next 2 to 3 days (Fig. 119.3). Patients are contagious 4 days before and 4 days after the onset of the rash.

Complications of measles include otitis media, laryngitis, tracheobronchitis, bronchiolitis, pneumonitis, severe diarrhea, and acute encephalitis. The virus itself can also cause pneumonia. Bacterial superinfection can also occur. The populations that are at high risk for severe disease or complications include children younger than 5 years old, adults older than 20 years old, pregnant women, and the immunocompromised.

Subacute sclerosing panencephalitis (SSPE) is a rare but fatal complication of measles. SSPE is a slow progressive infection of the central nervous systems (CNS) that results from a prior measles infection. It is

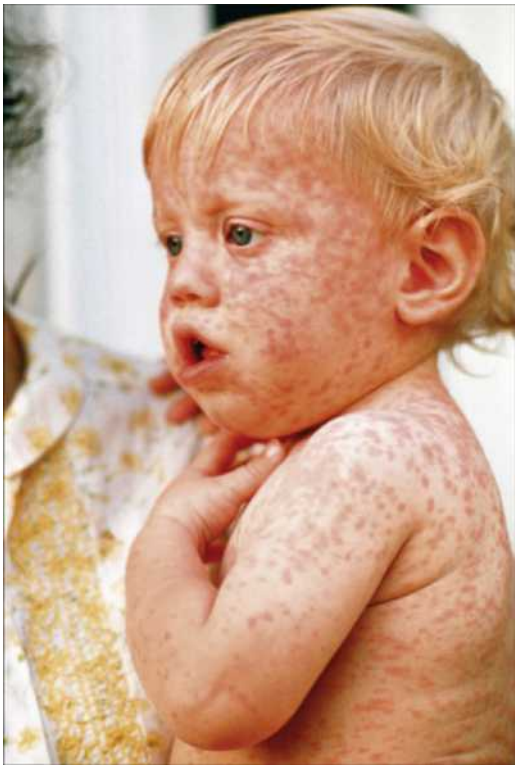


Figure 119.3 Typical rash associated with measles infection. (Kremer JR, Muller CP. Measles in Europe—there is room for improvement. *Lancet*. 2009;373(9661):356-358.)

thought to be due to continual measles infection of the CNS. The mean time of onset of SSPE is 7 years after measles infection. Symptoms include behavior change, decreased intellect, ataxia, and myoclonic seizures followed by progressive neurologic deterioration and death. Since the development of measles vaccine, this disease has almost disappeared in the United States.

Differential Diagnosis

Measles can be mistaken for other acute respiratory viral illnesses with rash or even noninfectious illnesses that present with fever and rash. Other diagnoses to consider include rubella, roseola, dengue, Kawasaki disease, and drug rash. Measles should be considered in patients that have traveled to endemic regions and return with fever and rash.

Diagnostic Testing

The diagnosis was usually made clinically by visualizing both Koplik spots and the characteristic rash along with cough, coryza, and conjunctivitis. However, the disease is not common in the developed world, and it may be mistaken for other illnesses. Clinicians suspecting a diagnosis of measles should contact local health departments. They can help instruct practitioners to obtain the necessary samples for diagnosis and surveillance. The most common methods of confirmation are serologic testing for measles-specific IgM antibody and detection of measles RNA from a nasopharyngeal specimen, blood, or urine by RT-PCR.

Management

The mainstay of treatment is supportive care. Bacterial superinfection should be treated appropriately. Postexposure prophylaxis is important in individuals who do not have evidence of measles immunity and have a measles exposure, because it can provide protection or lessen the severity of disease. Postexposure prophylaxis consists of either the measles, mumps, and rubella (MMR) vaccine within 72 hours, or immunoglobulin within 6 days. Healthy infants should receive 0.25 mL/kg of immunoglobulin intramuscularly, and immunocompromised children should be given 0.5 mL/kg intramuscularly, up to 15 mL. Children and malnourished patients who are hospitalized with severe measles may benefit from vitamin A.

Disposition

Patients with measles require admission to the hospital based on the severity of illness. Uncomplicated measles patients should be treated at home to prevent spread of the disease. It is important, however, to observe appropriate isolation precautions in the hospital setting. All suspected cases of measles should be evaluated with airborne isolation precautions in place. Infected individuals should have airborne isolation for 4 days after they develop the rash, and those who are immunocompromised should remain on airborne precautions until complete recovery.

Rubella (German Measles)

Rubella is a single-stranded RNA virus that is a member of the *Togaviridae* family. Since the wide-scale implementation of the vaccine, cases have dropped by greater than 99%. As a result, rubella is no longer endemic in the United States. The virus is spread via contact with respiratory droplets. In pregnant patients, the virus spreads to the placenta with subsequent infection of fetal organs.

Clinical Features

Acquired rubella is a mild febrile illness associated with a diffuse maculopapular rash, malaise, headache, and arthritis. Encephalitis and thrombocytopenia are rare complications. Rubella is generally a mild disease, but consequences in pregnant patients can be devastating. It can cause miscarriage, intrauterine death, premature delivery, or congenital rubella syndrome. Congenital rubella syndrome is characterized by severe birth defects, including hearing impairment, cataracts, retinopathy, developmental delay, microcephaly, and a variety of congenital heart defects.

Differential Diagnosis

The diagnosis of rubella on a clinical basis can be difficult because of the overlap with many other illnesses. Diseases that share common features include measles, roseola, erythema infectiosum (fifth disease), toxoplasmosis, and scarlet fever.

Diagnostic Testing

The diagnosis of rubella can be made by virus detection or serologic testing. The most common method is detection of IgM antibodies or fourfold increase in IgG antibody titer between acute and convalescent specimen. Virus culture and RT-PCR can also be isolated from blood or the nasopharynx.

Management and Disposition

There is no specific antiviral treatment for rubella. The management centers on symptom control with antipyretics and analgesics. The course of this disease is short and benign. These patients can generally be treated at home but should be educated about the risks to pregnant women.

VIRAL INFECTIONS WITH VESICULAR RASH

Herpes Simplex

Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are double-stranded DNA viruses of the *Herpesviridae* family. Herpes simplex infections primarily involve the skin or mucosal

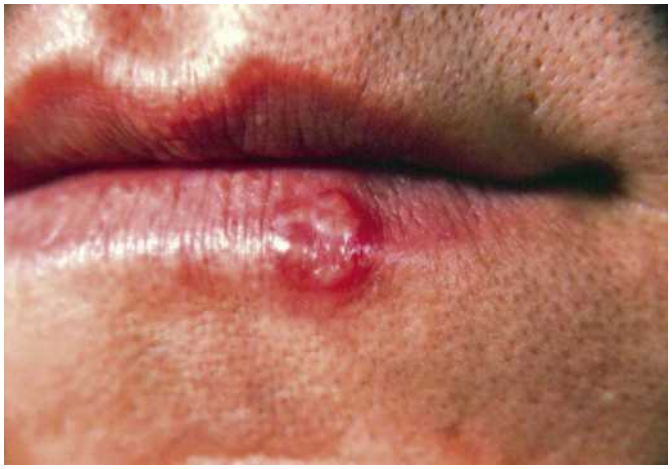


Fig. 119.4 Herpes labialis. (Courtesy of CDC website: http://phil.cdc.gov/phil/details.asp?pid=1573.)

surfaces with occasional severe involvement of organs. Herpes simplex virus (HSV) infections range in acuity from asymptomatic to life-threatening. HSV-1 typically causes orofacial infections but can affect liver, lung, eye, genitalia, and the CNS. HSV-2 typically causes genital herpes but can also affect the other systems as well. HSV infections are common; the seroprevalence of HSV-1 has been reported to be 57.7% in persons aged 14 to 49 years old in the United States, and the seroprevalence of HSV-2 has been reported to be 17.0% in the same population.

Initial HSV-1 infection usually occurs in childhood. HSV gains entry via breaks in the skin or mucosal surfaces. Viral replication is then initiated in epidermal and dermal cells. The infection then spreads to the nervous system, where it lays latent in the sensory nerve ganglia. Any stressor such as acute illness, emotional stress, trauma, intense sunlight, or fever can trigger reactivation of the virus. Recurrence rates are high for herpes infections. HSV-2 infections usually are acquired in adolescence or adulthood through sexual contact. Neonatal HSV-2 infections occur during childbirth via contact with the infected mother's birth canal.

Clinical Features

Oral Infection. The first episode of HSV-1 infections usually occurs early in life and manifests as a gingivostomatitis and pharyngitis. Symptoms include fever, malaise, and vesicular lesions anywhere in the mouth or oropharynx. Infections typically last between 10 to 14 days. Reactivation is usually much less severe and occurs as herpes labialis, small vesicles at the vermilion border of the lip (Fig. 119.4). These vesicles usually crust over within 48 hours.

Genital Herpes. This infection is characterized by painful vesicles and ulcers on the external genitalia. The first infection is usually the most severe and can be accompanied by systemic symptoms like fever, headache, malaise, and myalgias. It is also common to have dysuria and tender inguinal lymphadenopathy. Infections can also spread to the perianal and rectal region as well.

Central Nervous System Infection. HSV-1 is a common cause of infectious encephalitis; it causes necrotizing hemorrhagic encephalitis, typically involving the temporal lobes. Herpes simplex encephalitis is characterized by acute onset of symptoms, including fever, headache, altered mental status, seizures, and focal neurologic deficits resulting from frontal and temporal lobe necrosis. If left untreated, mortality is greater than 70%. HSV-2 can cause meningitis in over 25% of patients with primary infection, more commonly in women. In contrast to HSV encephalitis, HSV meningitis has a benign course. Neonatal HSV encephalitis is caused by HSV-2 acquired during vaginal delivery of an infected mother.

Other Infections. Herpes can cause a variety of cutaneous manifestations. They typically present with the classic painful grouped vesicles on an erythematous base on the affected area. Herpetic whitlow refers to these vesicles occurring on the finger. Herpes gladiatorum is a skin infection that can arise anywhere on the body and is associated with contact sports. Herpes can also cause ocular infections, including keratitis, conjunctivitis, and acute retinal necrosis. Immunocompromised patients are at risk for rare infections like HSV pneumonitis, esophagitis, or hepatitis.

Differential Diagnosis

When suspecting orofacial HSV infection, considerations include other diseases with vesicles and ulcers, such as aphthous ulcers, coxsackievirus infections (herpangina and hand-foot-and-mouth disease), infectious mononucleosis, Stevens-Johnson syndrome, or Behçet disease. The differential diagnosis for genital herpes infection should include other sexually transmitted infections with ulcers and vesicles, such as syphilis or chancroid or noninfectious diseases like Behçet disease. HSV encephalitis can be difficult to distinguish from other acute CNS emergencies like bacterial meningitis, brain abscess, other viral encephalitides, brain tumor, or stroke.

Diagnostic Testing

Frequently, clinicians diagnose oral or genital HSV infections clinically, given the classic appearance of the vesicles and ulcers. However, because of the risk of transmission and the impact of this diagnosis on a patient, testing should be performed if possible. Definitive diagnosis can be made by viral culture, direct fluorescent antibody (DFA), or polymerase chain reaction (PCR) from vesicles, ulcers, or mucocutaneous sites. PCR is more sensitive than viral culture. Tzanck smear has a low sensitivity and specificity and is mainly of historical interest. Serology can differentiate between acute infection and reactivation.

The diagnosis of HSV encephalitis is made by PCR from the CSF. The routine laboratory tests sent after a lumbar puncture (LP) to assess for bacterial meningitis do not adequately assess for HSV encephalitis. Classically, CSF analysis shows an elevated white blood cell (WBC) count, with lymphocyte predominance. Depending on the degree of brain necrosis, an elevated red blood cell (RBC) count can also be seen. Although it is rare, CSF results can be normal in HSV encephalitis, particularly in immunocompromised individuals.[5] This underscores the importance of waiting for PCR results before considering discontinuation of treatment in suspected cases of HSV encephalitis. In cases of negative CSF PCR with a high suspicion of HSV encephalitis, especially those with who present early in their illness, we recommend continuing empirical treatment and resending CSF PCR in 72 hours. Neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) can be highly suggestive of HSV encephalitis, but imaging can be negative early in the course of illness (Fig. 119.5).

Management

Antiviral agents are the mainstay of treatment. The treatment dose and duration for herpes simplex depends on the clinical syndrome that is present. Acyclovir, valacyclovir, and famciclovir are the commonly used antiviral drugs with activity against HSV. These drugs are nucleoside analogues that work by inhibiting viral DNA synthesis. Acyclovir is the only agent that is available in an intravenous (IV) formulation.

Herpes gingivostomatitis or labialis: First episodes are treated with oral acyclovir 200 mg five times a day (alternative regimen: 400 mg three times a day), valacyclovir 1 g twice daily, or famciclovir 250 mg three times a day for 7 days. Recurrent infections are treated with

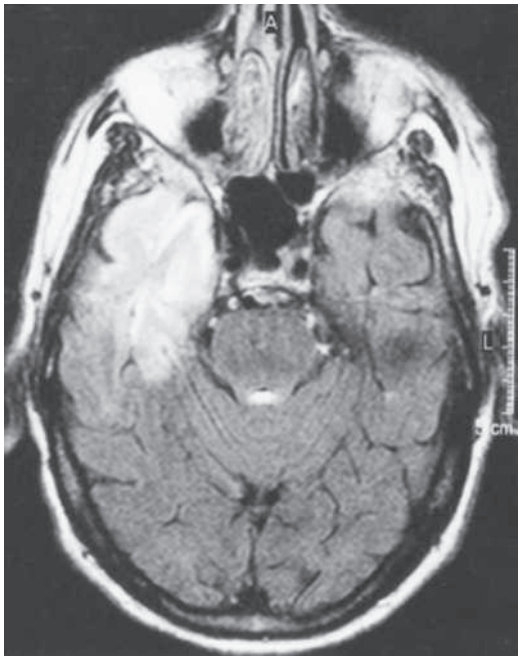


Fig. 119.5 T-2 weighted MRI with gadolinium demonstrating temporal lobe enhancement secondary to HSV-1 encephalitis. (Martin K, Franco-Paredes C. Herpes encephalitis. *Lancet*. 2002;360(9342):1286.)

acyclovir 400 mg five times a day for 5 days, valacyclovir 2 g twice daily for 1 day, or famciclovir 1500 mg as a single dose.

Genital herpes: First episodes are treated with oral acyclovir 200 mg five times a day (alternative regimen: 400 mg three times a day), valacyclovir 1 g twice daily, or famciclovir 250 mg three times a day for 7 to 10 days. A shorter course is usually adequate for treatment of recurrence. For suppression of recurrent episodes, acyclovir 400 to 800 mg twice daily or valacyclovir 500 mg daily can be used.

Herpetic whitlow and other mucocutaneous manifestations: Administer acyclovir 200 mg five times a day or 400 mg three times a day for 5 days.

Herpes keratitis: Administer acyclovir 400 mg five times a day or valacyclovir 500 mg three times a day. Topical antiviral therapy with trifluridine, acyclovir, or ganciclovir are all equally effective.[6]

HSV encephalitis: Administer IV acyclovir 10 mg/kg every 8 hours for 14 to 21 days. Given the high mortality associated with this condition, antiviral therapy should be started as soon as the diagnosis is suspected.

Disposition

The majority of herpes infections can be treated with oral antiviral therapy on an outpatient basis. Patients who are immunocompromised and have severe mucocutaneous disease or disseminated disease benefit from inpatient admission with IV acyclovir treatment. All patients with suspected encephalitis should be admitted for empirical treatment and diagnostic testing. Intensive care unit (ICU) admission may be necessary depending on the severity of neurologic symptoms. For HSV encephalitis patients, we recommend early involvement of infectious disease consultants to help guide treatment and neurology for management of cerebral edema and severe neurologic symptoms.

Varicella-Zoster Virus

The varicella-zoster virus (VZV) is another double-stranded DNA virus that is a member of the *Herpesviridae* family. VZV causes two common infections: varicella (chicken pox) and zoster (shingles). Transmission occurs via the respiratory tract through respiratory droplets and also by direct contact with virus present in the fluid-filled vesicles. VZV initially infects the nasopharynx and spreads to the lymphoid tissue. The virus is present in vesicles that develop on the skin and then infects the nerve endings in the skin and migrates to the dorsal ganglia where it lays latent.

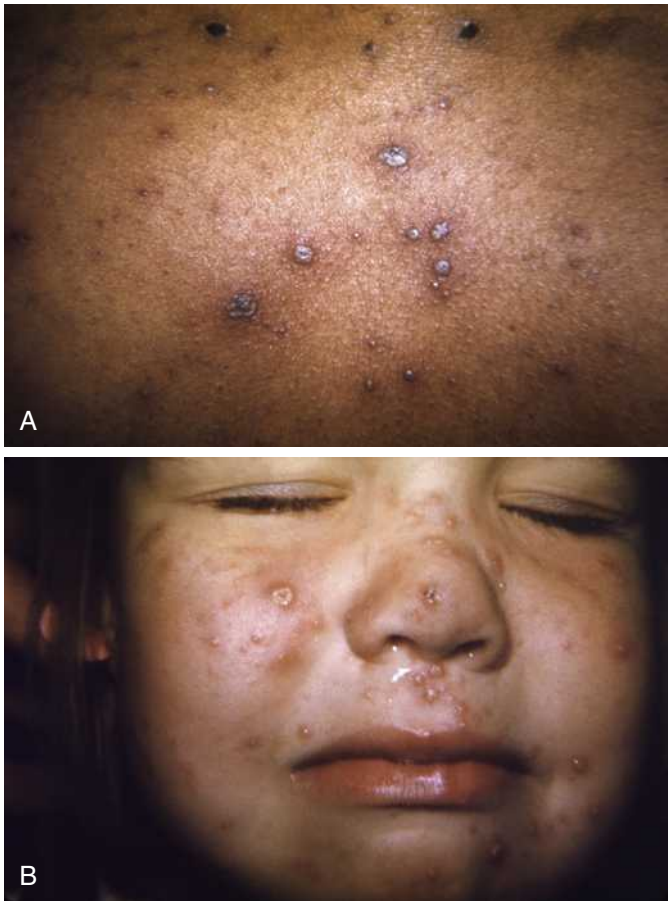


Fig. 119.6 (A and B) Varicella infection demonstrating the typical rash with lesions in different stages of healing. (Courtesy of CDC website: http://phil.cdc.gov/phil/details.asp?pid=10484 http://phil.cdc.gov/phil/details.asp?pid=10486.)

Primary infection of VZV occurs as varicella (chicken pox). Varicella is highly contagious and historically occurred year round with a predilection for winter and spring months. Prior to the development of the varicella vaccine in 1995, most people would develop this infection in childhood. After widespread uptake of the vaccine, the incidence of varicella has decreased by 90%, with a subsequent decline in mortality. Zoster (shingles) is a result of reactivation of the latent virus. Risk factors for developing shingles include older age and immunosuppression.

Clinical Features

Varicella. Chicken pox is a febrile illness characterized by malaise and rash. The rash begins first on the scalp and face and then spreads to the trunk and extremities. The lesions start as maculopapular, and progress to fluid-filled vesicles that eventually crust over and form scabs (Fig. 119.6). The lesions occur as crops at various stages of development. Patients are contagious until all lesions are scabbed over, which can typically take 1 to 2 weeks.

This disease typically has a benign course, although adults have a more severe course than children. The most common complication is a secondary bacterial infection of the skin lesions. VZV has been

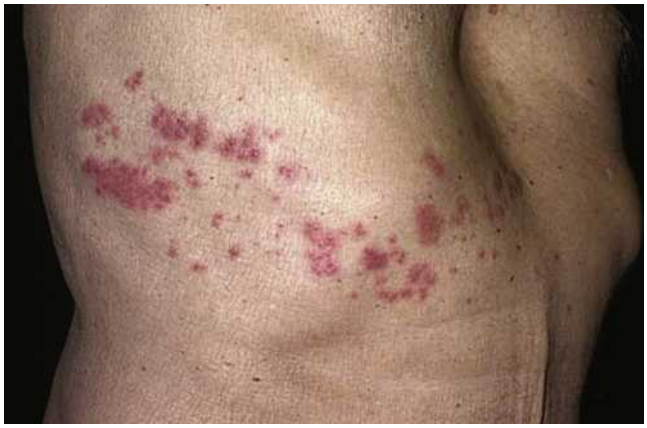


Fig. 119.7 Herpes zoster infection.

associated with invasive group A streptococcal infections and necrotizing fasciitis.[7] Immunocompromised patients are at risk for disseminated disease and visceral organ involvement. Pregnant patients are also at risk for severe disease. Varicella pneumonia accounts for most of the morbidity related to this disease. Neurologic complications are rare but can include encephalitis, aseptic meningitis, transverse myelitis, and Reye syndrome. Although exceedingly rare, it is important to recognize the association of aspirin use with Reye syndrome, a progressive encephalopathy with acute liver injury. Thus aspirin and other salicylates should be avoided in varicella treatment, especially in children.

Zoster. Herpes zoster typically causes a vesicular rash with an erythematous base that occurs unilaterally in a single dermatome (Fig. 119.7). The rash is often painful and preceded by paresthesias or hypesthesia. In immunocompetent individuals, the rash crusts in 7 to 10 days, and at that time patients are no longer contagious. Postherpetic neuralgia, defined as pain that persists for more than 90 days, is the feared complication. Risk factors for post-herpetic neuralgia include older age and severity of pain at onset.[8]

Herpes zoster ophthalmicus is viral reactivation within the trigeminal nerve ganglion. Ocular involvement occurs in over 50% of these cases. The Hutchinson sign, a vesicle on the tip of the nose, is associated with ocular involvement. Herpes zoster oticus (Ramsay Hunt syndrome) is characterized by facial nerve palsy, pain, and vesicular rash on the ear and in the auditory canal. Disseminated zoster involving multiple dermatomes can occur in immunocompromised patients.

Differential Diagnosis

Classic varicella is distinctive, but the other major diagnoses to consider are other febrile illnesses with rashes like disseminated HSV infection, coxsackievirus infection, measles, or rickettsialpox. Prior to eradication, smallpox was a consideration, presenting with lesions in the same stage of development. The rash of zoster is also usually very characteristic. Other diagnoses to consider include herpes simplex infection or contact dermatitis.

Diagnostic Testing

The majority of chickenpox and shingles diagnosis is made clinically. Confirmatory diagnosis can be made through viral culture, DFA, or PCR testing of the vesicle fluid.

Management

Varicella. The management is mainly supportive care with antipyretics and antihistamines to decrease the pruritus caused by the skin lesions. Salicylates should be avoided in children because of the association with Reye syndrome. Antiviral therapy with acyclovir has been shown to decrease the duration of fever and total number of lesions in healthy children. It does not reduce the number of varicella-related complications, however. Therefore, we typically do not recommend treatment of otherwise healthy children with varicella. We recommend treating high-risk groups with acyclovir, including those older than 12 years old, pregnant patients, persons with chronic cutaneous or pulmonary disorders, persons on long-term salicylate therapy, persons on aerosolized corticosteroids, and immunocompromised patients. The treatment should be initiated within 24 hours after the rash appears for the most benefit. The dose of acyclovir for VZV treatment is higher than that of HSV, 800 mg orally four times a day for 5 days. If the patient is immunocompromised and has severe disease, IV acyclovir should be administered.

Zoster. The goals of treatment for zoster are to treat the viral infection and control the pain that occurs with the rash. Uncomplicated zoster in the immunocompetent host can be treated with the following regimens for 1 week: acyclovir 800 mg five times a day, famciclovir 500 mg three times a day, or valacyclovir 1 g three times a day. Antiviral treatment should be initiated within 72 hours of the onset of rash because the efficacy beyond 72 hours is unclear. Immunocompromised patients should be treated regardless of time of onset of rash. Zoster involving more than one dermatome or disseminated zoster should be treated with IV acyclovir. The disease is often painful enough to require opioid agents. Currently, there are no treatments that have reliably shown a reduction in the occurrence of post-herpetic neuralgia. Antiviral treatment has shown mixed results and is likely not useful in preventing post-herpetic neuralgia.[9] Corticosteroids have been studied extensively, but a recent review did not support their use in preventing post-herpetic neuralgia.[10]

Disposition

Most patients with varicella and zoster can be treated at home. Patients with varicella are highly contagious and should be instructed to avoid people who have not been fully vaccinated or never had the disease, immunocompromised persons, or pregnant individuals until all of their lesions have crusted over. Immunocompromised patients, patients with disseminated zoster, or patients with complications require admission to the hospital.

In general, patients with varicella should be under contact and airborne precautions until all of the lesions have crusted over. An immunocompetent localized zoster patient only requires standard precautions, whereas an immunocompromised or disseminated zoster patient is treated like a patient with varicella, requiring contact and airborne precautions.

VIRAL INFECTIONS CAUSING NONSPECIFIC FEBRILE ILLNESS

Epstein-Barr Virus

EBV is a member of the *Herpesviridae* family. It is classically known for causing infectious mononucleosis. It is also associated with several types of cancer, including Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin disease, and B cell lymphoma. EBV is ubiquitous, with most individuals testing positive for antibodies by adulthood. One British study demonstrated that 70% of 0- to 5-year-olds had antibodies to EBV, whereas 95% of 20- to 25-year-olds tested positive.[11] EBV is spread via salivary secretions. The virus infects the oropharynx and then spreads through the bloodstream and infects B lymphocytes resulting in proliferation of infected B lymphocytes and T lymphocytes, leading to enlargement of lymphoid tissue.

Clinical Features

EBV infection in young children is usually asymptomatic or presents as mild pharyngitis. Adolescents and young adults tend to have the classic infectious mononucleosis (fever, exudative pharyngitis, lymphadenopathy, myalgias, and fatigue). Splenomegaly is common, seen in up to 50% of cases. Hepatomegaly and jaundice occur less than 10% of the time. The symptom duration is typically 1 to 3 weeks, with some cases having malaise and fatigue for several months. Splenic rupture is rare, occurring in less than 0.5% of patients. It should be suspected in patients with left upper quadrant pain and is more common during the first 3 weeks of illness. Airway obstruction occurs in less than 5% of children with mononucleosis and is one of the common causes of hospital admission. Rare neurologic complications include encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, retrobulbar neuritis, and peripheral neuropathies. Patients treated with amoxicillin or ampicillin for presumed streptococcal pharyngitis may develop a nonallergic maculopapular rash.

Differential Diagnosis

EBV causes 90% of infectious mononucleosis; the remaining 10% is caused by cytomegalovirus (CMV). Acute HIV infection, streptococcal pharyngitis, toxoplasmosis, and other viral pharyngitis causes should be considered in potential mononucleosis patients.

Diagnostic Testing

It is difficult to diagnose mononucleosis based on history and physical examination alone. Laboratory data can help confirm the diagnosis. Historically, the heterophile antibody test (monospot) has been the test of confirmation for primary EBV infection. The test has a sensitivity ranging from 63% to 84% and specificity ranging from 84% to 100%. The test is often not positive in younger children. The WBC count typically demonstrates lymphocyte predominance with many atypical lymphocytes. A lymphocyte count less than 4×10^9/L in adults is highly predictive of a negative monospot test. Health care providers can test for antibodies to EBV viral capsid and nuclear antigen if other testing is equivocal.

Management

Infectious mononucleosis typically has a self-limiting course. The treatment is supportive care with rest, antipyretics, and analgesia. Glucocorticoids have been used to decrease severity of symptoms, but there is insufficient evidence to support this practice. Antiviral treatment with acyclovir does not reduce the clinical symptoms of the disease. It is important to advise patients to avoid contact sports for at least 3 weeks to avoid the feared complication of splenic rupture. Abdominal ultrasound for assessment of spleen size may have a role in determining when it is safe to return to sports.[12]

Disposition

The majority of patients can be treated at home. Admission is necessary for airway obstruction and in patients with significant complications, such as splenic rupture.

Cytomegalovirus

CMV is a double-stranded DNA virus that belongs to the *Herpesviridae* family. Depending on geographic location, the seroprevalence ranges from 66% to 90%.[13] The spectrum of illness caused by CMV ranges from asymptomatic to severe disseminated disease in the immunocompromised patient. CMV is particularly harmful in pregnant patients because it can lead to congenital infection, causing profound neurologic defects and permanent hearing loss. CMV is present in breast milk, saliva, feces, urine, semen, cervical secretions, and blood. The virus spreads via prolonged exposure to these body fluids. After primary infection, CMV establishes a lifelong latent infection.

Clinical Features

The primary CMV infection is subclinical in most individuals. Some immunocompetent adults develop a mononucleosis-like syndrome. The illness can last from 2 to 6 weeks and is characterized by fever, fatigue, malaise, myalgia, and headache. Unlike EBV mononucleosis, exudative pharyngitis and lymphadenopathy are less common. Although it is rare, CMV can cause severe disease in the immunocompetent individual. CMV colitis and CNS infection (meningitis, encephalitis, transverse myelitis) are the most frequent forms of severe CMV infection in the immunocompetent host. Up to one-third of critically ill immunocompetent patients have evidence of CMV reactivation.

The majority of newborns who are infected with congenital CMV appear healthy or normal at birth. Common problems caused by congenital CMV infection include premature birth, intrauterine growth retardation, microcephaly, seizures, thrombocytopenia, hepatosplenomegaly, or pneumonitis. Sequelae of congenital CMV infection can present up to 2 years after birth. Frequent complications that occur are hearing loss, neurologic impairment, and ocular disturbances.

CMV can cause life-threatening disease in immunocompromised patients. CMV infection occurs in over 40% of solid organ transplant patients during the first 3 months when immunosuppressive therapy is the strongest. Transplant patients that are CMV seronegative and receive a CMV seropositive donor are at highest risk. HIV patients with CD4 count less than 100/μL are at high risk of CMV infection as well. In the immunocompromised host, CMV manifests initially as fever, malaise, and myalgias. The infection can then progress to cause leukopenia, pneumonia, esophagitis/gastritis, hepatitis, colitis, encephalitis, polyradiculopathy, and retinitis. CMV retinitis is the most common cause of blindness in patients with AIDS.

Differential Diagnosis

It is difficult to make the diagnosis of CMV infection solely on a clinical basis. Infectious mononucleosis caused by EBV presents very similarly. In the perinatal phase, infants with apparent infections should be evaluated for the other common congenital infections: toxoplasmosis, rubella, herpes simplex, syphilis, VZV, and parvovirus B19. Because the CMV infection can cause a wide array of disease in the immunocompromised host, the differential diagnosis should be broad and include other viral pathogens, bacterial infections, *Pneumocystis* infection, and fungal infections.

Diagnostic Testing

Making the diagnosis of CMV is unlikely in the ED. Confirmation of this diagnosis centers on either virus isolation, serologic testing, or histopathology. Common methods involve PCR, viral culture, or antibody testing. The WBC count may show lymphocyte predominance with more than 10% atypical lymphocytes, much like EBV infections.

Management

For the most part, CMV infection in the immunocompetent host only requires symptomatic care for the mononucleosis-like syndrome. The treatment recommendations for critically ill immunocompetent patients with CMV infection are less clear.[14] Immunocompromised patients with CMV infection are treated more aggressively. Antiviral treatment is necessary in sight and life-threatening infections.

Ganciclovir is an IV agent that is used to treat CMV infections. The treatment for CMV retinitis is induction therapy: 5 mg/kg/dose every 12 hours for 14 to 21 days followed by 5 mg/kg/dose once daily maintenance therapy for a prolonged course. Fever, diarrhea, and thrombocytopenia

are common adverse reactions. Valganciclovir is an oral prodrug that is metabolized to ganciclovir. The treatment regimen is induction: 900 mg twice daily for 21 days followed by maintenance of 900 mg once daily. Foscarnet and cidofovir are IV agents used to treat CMV resistant to ganciclovir, and both can also be used to treat HSV resistant to acyclovir. The primary limiting toxicity of these drugs is renal toxicity.

Disposition

Most immunocompetent patients with CMV infection can be managed at home. In contrast, immunocompromised patients with CMV infection will usually require admission to the hospital, and depending on the extent of end-organ damage, may require ICU admission.

Enteroviruses

Enteroviruses are a group of single-stranded RNA viruses that can multiply within the gastrointestinal tract. Most infections are asymptomatic or mild undifferentiated illnesses. Despite their name, their major manifestation is not gastroenteritis. There are many enteroviruses; common ones include poliovirus, coxsackievirus A and B, echovirus, and enterovirus. These viruses are found globally and are transmitted via the fecal-oral route. Vaccination exists for poliovirus; in the United States and other industrialized nations, the disease has been declared eradicated.

Clinical Features

Most of the infections caused by enteroviruses are asymptomatic or self-limiting febrile illnesses. More of the severe infections are discussed in the following sections.

Poliovirus. The poliovirus causes a nonspecific febrile illness with malaise, myalgias, headache, and sore throat. The most feared presentation of the poliovirus infection is paralytic poliomyelitis. This manifests as aseptic meningitis followed by back, neck, and muscle pain and then the development of motor weakness. The paralysis is usually asymmetrical and affects proximal muscles more. Usually some recovery of motor function occurs months later, but approximately two-thirds of patients have some form of permanent weakness.

Non-Polio Enteroviruses. Most enterovirus infections are subclinical, but they can also cause a variety of symptoms and syndromes. Enteroviruses account for most causes of viral meningitis and encephalitis. Enteroviruses commonly cause pericarditis and myocarditis, particularly coxsackievirus B. Symptoms usually include chest pain, fever, dyspnea, and can progress to severe heart failure. Enteroviruses are a common cause of viral exanthems as well. Herpangina is caused by coxsackievirus A and presents with fever, sore throat, odynophagia, and vesiculopapular lesions on the cheeks and soft palate (Fig. 119.8). Hand-foot-and-mouth disease is caused by coxsackievirus A or enterovirus 71 and commonly manifests as fever and malaise, followed by vesicles in the mouth, and vesicles on the hands and feet (Fig. 119.9). Pleurodynia is a painful illness characterized by fever and spasms of the chest wall and abdomen that occur in paroxysms.

In 2014, there was an outbreak across the United States of EV-D68.[15] The virus affected mostly children and was severe in children with asthma. Typically EV-D68 causes mild respiratory illness, rhinorrhea, sneezing, cough, and myalgias but occasionally causes severe disease with wheezing and respiratory distress. There has also been an association with flaccid paralysis with anterior myelitis with EV-D68 infection.[16]

Differential Diagnosis

Clinicians should consider other diagnoses depending on the specific symptoms and syndrome caused by enterovirus infection. For the

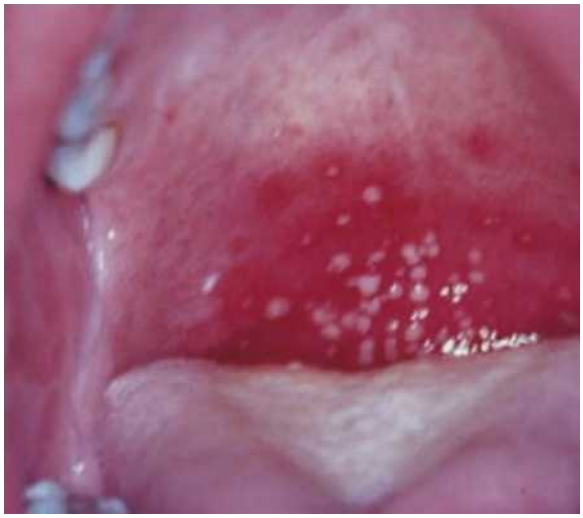


Fig. 119.8 Herpangina. (Originally from: Cohen J, Powderly WG. *Infectious Diseases*, ed 2. St. Louis: Mosby; 2004. Also found in: Bennett, JE. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, ed 8. Philadelphia: Elsevier; 2015.)

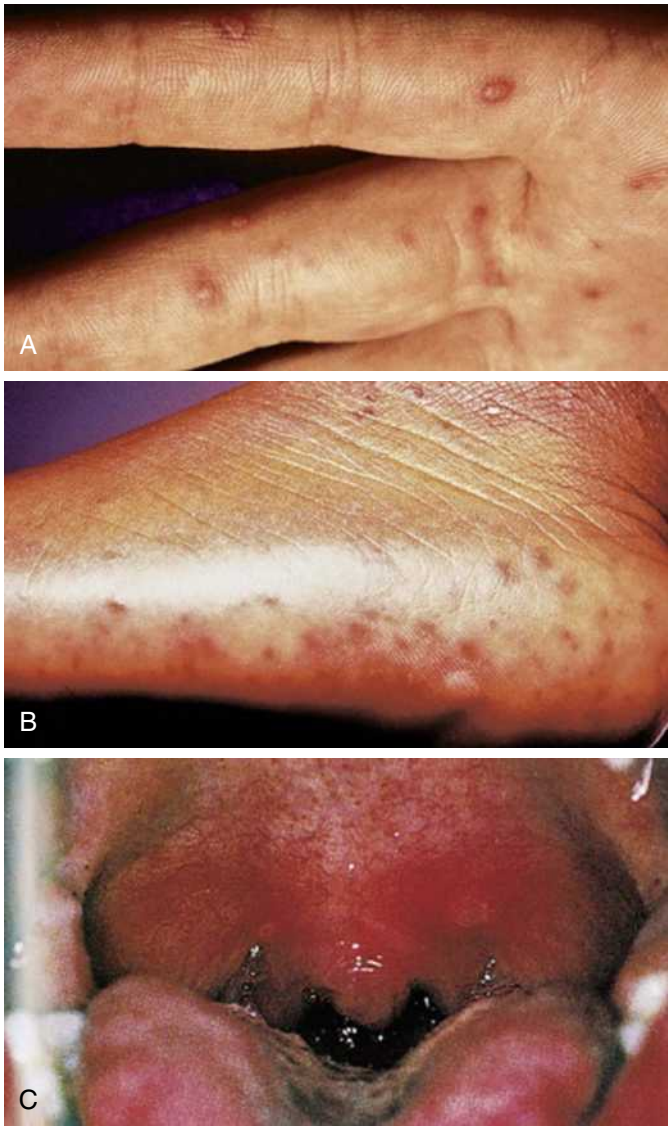


Fig. 119.9 Hand-foot-and-mouth disease. (From: Cohen BA. *Pediatric Dermatology*, ed 4. Philadelphia: Elsevier; 2013: 110.)

diseases with skin and oropharyngeal lesions, herpes simplex, aphthous stomatitis, mononucleosis, and bacterial pharyngitis should be considered. The diseases with primary neurologic manifestation present similarly to bacterial meningitis and other causes of viral meningitis or encephalitis, including herpes simplex encephalitis. Myopericarditis can present similar to pulmonary embolism, myocardial infarction, or pneumonia (see Chapter 68).

Diagnostic Testing

Diagnosis is confirmed by viral culture, serology, or PCR. Samples can be sent from nasopharynx or oropharynx via swabs or washings, CSF, serum, stool, or pericardial fluid. Other diagnostic testing should be tailored toward the symptoms, such as ECG, chest x-ray, and cardiac biomarkers for evaluation of myopericarditis. Lumbar puncture should be performed for meningitis or encephalitis evaluation.

Management

The treatment is primarily symptomatic, because currently, there are no recommended specific antiviral therapies for enteroviruses. Hand-foot-and-mouth disease can cause severe dehydration, because children refuse to eat secondary to the painful lesions in the mouth. This illness is typically treated with analgesia and encouragement of oral intake. Topical analgesia with diphenhydramine, aluminum hydroxide, and magnesium hydroxide can be used. Viscous lidocaine and topical benzocaine should be avoided in young children because of the risk of systemic toxicity and questionable efficacy. If there is concern for meningitis, empirical therapy for bacterial meningitis and herpes simplex encephalitis should be instituted while awaiting culture and PCR results because both of the aforementioned diseases have significantly higher morbidity and mortality with delayed treatment.

Disposition

The majority of enteroviruses cause a benign disease, and patients can be treated at home and expect no sequelae. Depending on the severity of symptoms, some patients may require hospitalization for dehydration, severe respiratory illness, or neurologic infection. Viral myocarditis can cause severe heart failure and dysrhythmias requiring hospitalization and ICU care. The outcome after viral myocarditis can be variable and range from return of normal heart function to severe cardiomyopathy requiring heart transplantation (see Chapters 66 and 67).

VIRUSES ASSOCIATED WITH RESPIRATORY INFECTIONS

Influenza

Influenza is an RNA virus from the *Orthomyxoviridae* family that causes acute respiratory symptoms. This virus is highly contagious and is transmitted through large-particle respiratory droplets. Transmission usually requires close contact between individuals less than 1 meter apart. Epidemics and outbreaks occur almost annually, with the peak influenza activity usually occurring in the winter months in the United States. Influenza occasionally causes devastating pandemics. During the 1918 influenza pandemic, approximately 50 to 100 million people were killed across the globe. The most recent pandemic occurred in 2009, when a new strain of H1N1 influenza emerged, killing over 284,000 globally.

There are three major types of influenza: A, B, and C. The majority of human infections are caused by influenza A and B. Influenza can be further subdivided based on the two major surface glycoproteins present, hemagglutinin (H) and neuraminidase (N). Influenza A is responsible for most of the severe epidemics and pandemics because of its ability of surface antigens to undergo periodic changes. This is known as *antigenic drift* when the changes are minor and *antigenic shift* when the changes are major.

BOX 119.1 Conditions that Increase Risk for Severe Influenza and Influenza-Related Complications

- Age less than 2 years
- Age 65 years and older
- Chronic pulmonary disorders, including asthma
- Chronic cardiovascular disorders except hypertension alone
- Chronic renal insufficiency
- Chronic hepatic disorders
- Chronic hematological conditions including sickle cell disease
- Metabolic and endocrine disorders including diabetes mellitus
- Neurologic disorders including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, seizure disorders, stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury
- Immunosuppression, including that caused by medications or by HIV infection
- Pregnancy or postpartum state (within 2 weeks after delivery)
- Ethnicity belonging to American Indians/Alaska Natives
- Morbid obesity (i.e., body mass index is equal to or greater than 40)
- Residency in nursing homes and other chronic care facilities

Adapted from Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2017–18 influenza season. *MMWR Recomm Rep* 2017;66:1–20.

Clinical Features

Influenza typically presents as fever with constitutional (headache, malaise, and myalgias) and respiratory symptoms (cough, sore throat, rhinitis). These symptoms typically last for 3 to 7 days. Individuals are usually contagious 1 day prior to symptom onset and up to 1 week after. The majority of influenza is a benign self-limited disease, but some patients are at risk for severe influenza and influenza-related complications (Box 119.1). The common influenza-related complications are bacterial pneumonia (typically due to *Staphylococcus aureus*), sinusitis, and otitis media. Influenza can also assert its pathogenic effects by exacerbating underlying cardiopulmonary and other chronic health conditions. Occasionally influenza itself can cause a rapidly progressing pneumonia that leads to acute respiratory distress syndrome (ARDS).

Differential Diagnosis

The differential diagnosis is broad, because many different infectious diseases can present with similar symptoms. Other respiratory viruses like RSV, rhinovirus, or coronavirus can have a similar presentation. Additionally, bacterial infections, like pneumonia and meningitis, can present similarly.

Diagnostic Testing

Influenza can be diagnosed clinically based on signs and symptoms, especially during influenza season, but the accuracy of clinical diagnosis in the absence of supportive tests is not high because influenza

shares common features with many viral and bacterial infections. Clinical diagnosis alone is poor, with a sensitivity less than 50% and a specificity near 70%.[17]

There are several diagnostic tests available to emergency clinicians. Rapid influenza diagnostic tests are based on immunochromatographic assays that detect specific influenza antigens, yielding results in less than 30 minutes. The sensitivity of these tests can vary from 50% to 65%, with specificities above 95%.[18] Molecular assays, such as RT-PCR or rapid antigen tests, are far more sensitive than traditional rapid influenza tests. RT-PCR is the most sensitive test and, if available, is preferred. However, rapid molecular tests have sensitivity and specificity that approach RT-PCR, and results can be back in less than 20 minutes. Rapid molecular tests have sensitivities of over 90%.

Management

The management of influenza centers on symptom control with antipyretics, analgesics, and hydration. Several antiviral agents are available to treat influenza, but some controversy surrounds treatment with these agents.

Neuraminidase Inhibitors. Oseltamivir, zanamivir, and peramivir are the currently available neuraminidase inhibitors. They work by inhibiting the release of viral progeny from infected cells. These drugs are active against both influenza A and B.

Oseltamivir is available orally as a capsule or suspension. The treatment dose in adults and children weighing more than 40 kg is 75 mg twice daily for 5 days. For children younger than 1 year old, the dose is 3 mg/kg twice daily. For children 1 year or older, the dose varies by weight: for those weighing less than or equal to 15 kg the dose is 30 mg twice daily, for those weighing more than 15 to 23 kg it is 45 mg twice daily, and for those weighing more than 23 to 40 kg it is 60 mg twice daily. The dosing does require adjustment in renally impaired individuals based on creatinine clearance. The main side effects reported have been nausea and vomiting.

Zanamivir is available as an aerosol powder and is administered via inhalation through a specialized inhaler. It is approved for use in patients 7 years old and older. The treatment dose is two inhalations twice daily for 5 days. It is not recommended in patients with underlying asthma and chronic obstructive pulmonary disease (COPD), because it can cause bronchospasm. Peramivir is the first IV neuraminidase inhibitor available for treatment in influenza patients. The treatment dose is 600 mg IV administered once as a single dose.

Adamantane Antivirals. Amantadine and rimantadine are the currently available adamantane antivirals. They prevent or greatly reduce the uncoating of the viral RNA of influenza A after attachment and endocytosis by host cells. They have no activity against influenza B. In the past, they have been used for prophylaxis and treatment for influenza A. In recent years, the circulating influenza strains have demonstrated greater than 90% resistance to these drugs. They are not recommended for use for influenza treatment.

Other Antivirals. Baloxavir is a novel antiviral that gained US Food and Drug Administration (FDA) approval to treat influenza A and B in patients 12 years of age and older in 2018. Its unique mechanism of action is inhibition of influenza cap-dependent endonuclease. Studies have demonstrated similar efficacy to oseltamivir.[19] The treatment is a single oral dose based on weight. For 40 kg to less than 80 kg, it is 40 mg as a single dose within 48 hours of the onset of influenza symptoms. For 80 kg or greater, it is 80 mg as a single dose within 48 hours of the onset of influenza symptoms.

The controversy surrounding the use of antivirals for treatment of influenza, specifically neuraminidase inhibitors (NIs) has centered on its modest effect with treatment. The most recent Cochrane review found that oseltamivir reduced symptom duration by 16.8 hours in those treated within 48 hours of symptom onset but did not affect hospitalization or reduce severe influenza complications.[20] However, another recent meta-analysis found that treatment with oseltamivir was associated with accelerated symptom improvement, reduced risk in lower respiratory tract complications, and decreased admission to hospital.[21] Investigations have also found that treatment of hospitalized patients with NIs is associated with reduced hospital length of stay and mortality.[22,23] The greatest benefit is in very early treatment, but some studies have demonstrated benefit up to 5 days after symptoms onset in hospitalized patients.[24] The Infectious Diseases Society of America (IDSA) recommendations are to treat all patients as early as possible who are hospitalized, have severe progressive illness regardless of duration, or are at high risk for influenza-related complications.[25]

Disposition

The majority of patients with influenza are discharged home with symptomatic treatment instructions, although this depends on the specific virulence of the circulating strain of the season. Patients with severe influenza require admission. These patients usually have accompanying cardiopulmonary comorbidities. A small number of influenza patients will require ICU admission because of primary influenza or acute exacerbation of an underlying illness. Influenza can cause rapidly progressive ARDS with refractory hypoxemic respiratory failure. These patients with rapidly progressive ARDS may benefit from transfer to centers that perform extracorporeal membrane oxygenation (ECMO). During the 2009 H1N1 pandemic, some centers had success with managing ARDS patients on ECMO.

Coronavirus

Coronaviruses are single-stranded RNA viruses that typically cause respiratory illness. They are covered in detail in Chapter 120.

Rhinovirus

Human rhinovirus is the most common cause of the common cold. Infections peak in the fall and spring but can occur all year. The infection is spread via infected respiratory secretions and direct contact with infected patients. The virus can remain contagious on surfaces for several hours. Hand-to-face inoculation is likely one of the predominant mechanisms of spread, underscoring the importance of frequent handwashing to decrease transmission.

Clinical Features

Symptoms of rhinovirus infection are usually limited to the nose, nasopharynx, and pharynx. The common symptoms that occur are sore throat, nasal congestion, low-grade fever, sneezing, and cough. Less commonly in children, rhinovirus can cause lower respiratory tract infections like pneumonia and tracheobronchitis.

Differential Diagnosis

Other viruses that cause respiratory illness, such as coronaviruses, respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses, adenoviruses, and enteroviruses, can produce clinical syndromes similar to those produced by the rhinoviruses.

Diagnostic Testing

Definitive diagnostic testing is usually not necessary for rhinovirus. Viral panels do exist that use nucleic acid testing to detect rhinovirus.[26] Samples are typically taken from nose, nasopharynx, or oropharynx.

Management and Disposition

The cornerstone of treatment is symptomatic relief with analgesics and antipyretics. Cough medicines should be avoided in children younger

than 6 years old. This infection has a benign course and can be treated at home.

Adenovirus

Adenoviruses are double-stranded DNA viruses consisting of 7 species (A–G) and greater than 100 types. They commonly cause upper respiratory tract infections, gastrointestinal symptoms, and conjunctivitis. Infection is spread via respiratory droplets and close contact. Outbreaks have been reported in crowded settings such as military personnel undergoing training and students living in dormitory style housing. In 2018 to 2019 there was a multistate outbreak on 5 college campuses, resulting in 168 infections, 11 hospitalizations, and 2 deaths.[27]

Clinical Features

The most common presentation of adenovirus is as a URI with sore throat, cough, and fever. Gastroenteritis and conjunctivitis are also common manifestations. Other syndromes less frequently caused by adenoviruses include hemorrhagic cystitis, urethritis, infantile diarrhea, myocarditis, encephalitis, and meningoencephalitis. In infants and immunocompromised patients, particularly hematopoietic stem cell transplant and solid organ transplant patients, adenovirus can cause severe life-threatening illness.

Differential Diagnosis

Other pathogens causing similar atypical pneumonia syndromes include influenza and parainfluenza viruses and *Mycoplasma pneumoniae*. Diarrheal syndromes may be similar to those caused by rotaviruses.

Diagnostic Testing

Because adenovirus mostly causes a benign self-limiting disease, routine diagnostic testing is unnecessary. If testing is required, qualitative or quantitative PCR from serum, tissue, or body fluid is the most diagnostic method.

Management and Disposition

The majority of these infections require only symptomatic treatment. There is no specific antiviral therapy that is routinely recommended. There have been reports of using cidofovir in immunocompromised patients with life-threatening adenovirus infection, but this is not routinely recommended. The majority of these patients will be treated at home. The most severe cases may require admission.

Parainfluenza

Parainfluenza is a single-stranded RNA virus that belongs to the *Paramyxoviridae* family. This infection is usually acquired in childhood. In the United States, parainfluenza infections have been reported to account for up to a quarter of respiratory disease in children. In adults, the burden of illness caused by parainfluenza is much less. Parainfluenza is transmitted by close contact via infected respiratory secretions. There are four types, each with its own clinical presentation.

Clinical Features

Parainfluenza type 1 is the most common cause of croup. Parainfluenza type 2 is also associated with croup but causes less morbidity. Croup symptoms usually worsen at night and are characterized by a barky cough. Typically patients have a fever and URI symptoms 1 to 2 days before the cough. Tachypnea and hoarse voice are common as well. In severe cases, stridor at rest may be present. Parainfluenza type 1 and 2 also cause lower respiratory tract infections in children. Parainfluenza type 3 more often causes bronchitis, bronchiolitis, and pneumonia. Parainfluenza type 4 is less common and causes a mild respiratory illness. In adults and older children, parainfluenza infections are mild and present as a simple URI.

Differential Diagnosis

Adenoviruses, rhinoviruses, influenza viruses, RSV, echoviruses, coxsackieviruses, and coronaviruses all can cause similar URI symptoms. If the primary presentation is croup, it is important to differentiate this from epiglottitis as a potential diagnosis.

Diagnostic Testing

Diagnosis is made from viral culture, rapid antigen test, or nucleic acid testing, either rapid testing or RT-PCR. Specimens are usually obtained from nasal swabs, throat swabs, or nasopharyngeal washings.

Management

There is no specific antiviral treatment for parainfluenza infection. The treatment is mainly symptomatic. For mild and moderate croup, a single dose of oral dexamethasone (0.15–0.6 mg/kg, maximum dose 20 mg) or oral prednisolone (1 mg/kg) can be given.[28] For severe croup, nebulized racemic epinephrine should be administered in addition to oral or intramuscular dexamethasone (0.6 mg/kg, maximum dose 20 mg). Glucocorticoids improve symptoms, reduce rates of return visits, admissions, and readmissions.[29]

Respiratory Syncytial Virus

RSV is an RNA virus that belongs to the *Paramyxoviridae* family. RSV causes significant morbidity in children. It is an important cause of death in young children in the low- and middle-income countries. In the United States, RSV is associated with approximately 20% of hospitalizations and 18% of ED visits in children younger than 5 years old. RSV is also a significant cause of respiratory illness in older patients, affecting 3% to 10% of the population over age 65 each year. RSV is spread via contact with infected individuals, by exposure to respiratory secretions and fomites.

Clinical Features

RSV causes a range of respiratory disease. The illness is most severe in infants, causing pneumonia and bronchiolitis. Newborns with RSV can present with apnea. Symptoms usually begin with nasal congestion, rhinorrhea, low-grade fever, and cough. Then 1 to 2 days after symptom onset, patients develop wheezing and increased respiratory effort. Symptoms can last up to 2 weeks. In adults and older children, RSV usually causes a benign URI typically lasting less than 5 days. Geriatric patients, immunosuppressed patients, and adults with chronic medical problems can develop severe lower respiratory tract disease.

Differential Diagnosis

The clinical presentation caused by RSV infections is similar to other upper and lower respiratory tract pathogens, including rhinovirus, parainfluenza, influenza, enteroviruses, coronaviruses, and bacterial causes of pneumonia. It is important to consider noninfectious causes of hypoxemia in infants, such as foreign body aspiration and asthma.

Diagnostic Testing

The common methods of diagnosis include viral culture, molecular assays, and rapid antigen detection tests. Specimens are typically obtained from nasopharyngeal swabs or washings. Other routine diagnostic testing is generally unnecessary and should be symptom targeted.

Management

The mainstay of treatment is supportive care. Beta-agonist bronchodilators are not recommended by the most recent guidelines published

by the AAP.[30] The authors agree that routine inhaled bronchodilators should not be used for RSV bronchiolitis given the lack of evidence of improved outcomes. However, it is reasonable to administer a trial of inhaled albuterol for severe disease, because most of these patients were excluded from studies and some of the patients may actually have viral-induced asthma exacerbation. Corticosteroids have not been shown to provide any benefit. Supplemental oxygen should be provided for pulse oximetry less than 90%. Nebulized hypertonic saline can be used as an inpatient, but currently data do not support use in the ED. For severe cases, nasal continuous positive airway pressure (CPAP) can be trialed to avoid intubation. It is also important to treat dehydration associated with the disease with IV or nasogastric fluids if the patient cannot maintain oral intake. For prevention of RSV infection in high-risk patients, the AAP recommends the use of palivizumab, a monoclonal anti-RSV antibody preparation, during the first year of life for infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants younger than 32 weeks' gestation who require more than 21% oxygen for at least the first 28 days of life.

Disposition

Healthy adults and older children have a short disease course that is mild and can be treated at home. The majority of infants with RSV may also be treated at home but may have prolonged illness. Infants younger than 1 year old that visit the ED for bronchiolitis have a median duration of symptoms of 15 days, and over one-third of them have a subsequent unscheduled medical visit. Approximately 1% to 3% of infants with RSV require hospitalization for hypoxemia, respiratory distress, or dehydration. Approximately 15% of geriatric patients requiring ICU care with an acute cardiopulmonary diagnosis are diagnosed with RSV infection.

VIRUSES ASSOCIATED WITH DIARRHEAL ILLNESS

Norovirus and Rotavirus

Norovirus is a member of the *Caliciviridae* family and is the most common cause of nonbacterial gastroenteritis. It is highly infectious because only a few particles are necessary to transmit the disease. Norovirus is spread through direct transmission from person to person via the fecal-oral route. Transmission can also occur through contaminated water, food, and surfaces. Because of its structure as a nonenveloped RNA virus, norovirus is very stable in the environment and is resistant to most disinfectants, including alcohol hand wash. Outbreaks of norovirus occur in areas where people are in proximity, including long-term care facilities, restaurants, hospitals, schools, and cruise ships. ED visits for norovirus peak in the winter months.

Rotaviruses are double-stranded RNA viruses that belong to the *Reoviridae* family. These viruses are ubiquitous, and by 5 years old most children have been exposed to them. They are the leading cause of severe gastroenteritis in children. The introduction of rotavirus vaccine in industrialized countries has dramatically decreased encounters for this disease.[31,32]

Clinical Features

Norovirus. The disease causes a severe gastroenteritis, with vomiting, diarrhea, and abdominal cramping. In infants and children, vomiting is the primary symptom, whereas adults more commonly have diarrhea. The gastrointestinal symptoms can be accompanied by fever, headache, and myalgias as well. The diarrhea is typically nonbloody, watery, and profuse. The acute illness usually lasts for half a day to 3 days.

Rotavirus. The illness manifests as sudden onset of nausea, vomiting, and profuse watery diarrhea, with fever, headache, and myalgias. The disease course is usually 3 to 7 days. The spectrum of disease can range from asymptomatic to severe and fatal dehydration.

Differential Diagnosis

Other causes of viral gastroenteritis include adenovirus, enterovirus, and certain coronaviruses. *Clostridioides difficile* infection and some bacterial gastroenteritis can present similarly.

Diagnostic Testing

Norovirus diagnosis can be confirmed by PCR of stool or vomit specimen. Rapid antigen detection test, enzyme-linked immunosorbent assay (ELISA), and PCR of stool specimen are the methods of diagnosis for rotavirus.

Management

There is no specific treatment for these viral gastrointestinal infections. Management centers on ensuring that patients are adequately hydrated and correcting significant electrolyte derangements. Most patients can be treated with oral rehydration alone. Patients with severe dehydration warrant IV rehydration. Meticulous attention to standard precautions and hand hygiene is important to prevent spread of these diseases.

Disposition

The majority of patients can be managed at home with oral therapy. Very young patients or patients with chronic illness may be at risk for more severe disease and benefit from IV therapy and monitoring. Depending on the severity of illness, these patients could be managed in an observation unit or may require inpatient admission.

VIRAL INFECTIONS WITH NEUROLOGIC MANIFESTATIONS

Rabies

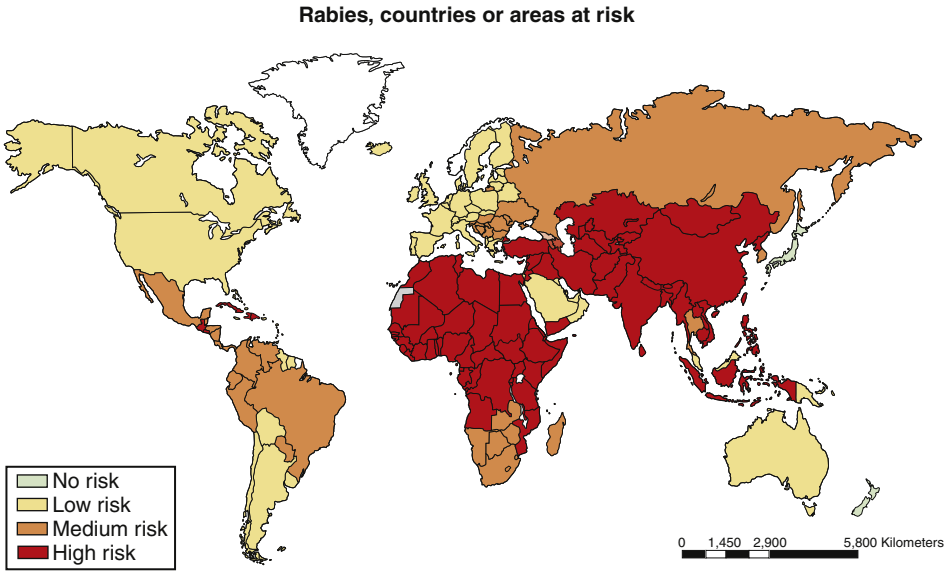
The natural history and clinical course of rabies disease is complex. After a bite from a rabid animal, the risk of developing clinical disease is unknown and depends on viral inoculation or migration into nerve tissue. The risk of death following untreated clinical disease, however, is almost 100%, and the risk of developing clinical disease following proper treatment approaches 0%.[33] Rabies remains a huge public health problem worldwide, particularly affecting vulnerable populations in poor and rural areas (Fig. 119.10). Human rabies disproportionately affects children, with an estimated 40% of rabid bites occurring in those 15 years of age and younger.[34]

Emergency medicine clinicians should be prepared to evaluate bites and other exposures for the risk of rabies inoculation as well as diagnose or rule out rabies disease in patients presenting with neurologic symptoms. The diagnosis of rabies requires a thorough medical history, noting the course of illness, and multiple laboratory tests. Likewise, the management of animal bites requires appropriate wound care, risk analysis in conjunction with local or state public health authorities, patient and physician decision making regarding the need for and timing of postexposure treatment, and appropriate bite reporting to animal control or public health authorities.[35]

The signs of rabies in all species of animals are extremely variable and cannot be used alone to determine the likelihood of rabies. Additionally, the incubation period for rabies (i.e., the time between when a human or animal is bitten by a rabid animal and the development of clinical signs) is highly variable, ranging from days to months or rarely years in both humans and animals.[36] For these reasons, thorough risk assessment based on environmental, historical, and clinical conditions is essential for every animal bite and exposure.

Epidemiology

All mammals are physiologically capable of becoming infected with rabies and transmitting the virus to humans, but globally the domestic



In countries of categories 1, 2 and 3, contacts with suspect rabid animals including bats should be followed by rabies post-exposure prophylaxis.

No risk: no risk at all.
Low risk: pre-exposure immunization recommended for people likely to have contact with bats.
Medium risk: pre-exposure immunization recommended for travellers and other people for whom contact with bats and other wildlife is likely.
High risk: pre-exposure immunization recommended for travellers and other people for whom contact with domestic animals particularly dogs and other rabies vectors is likely.

Fig. 119.10 Rabies—countries or areas at risk. (Courtesy of World Health Organization (WHO).)

dog is the highest-risk species for rabies exposure.[37] In many countries, endemic dog rabies still occurs, and the cycle of dog-to-dog transmission spills into the human population. The global burden of human rabies from dogs is high, with an estimated 59,000 deaths and the equivalent of over $8.5 billion (US) in economic losses from premature death and postexposure treatment.[38] Although the United States was declared free of endemic canine rabies in 2007, travelers to countries where canine rabies is endemic can be exposed to rabies and subsequently express symptoms after returning to the United States. Since 2003, all fatal cases of canine-attributed human rabies in the United States have been acquired outside the continental United States.[39]

In the United States, certain wildlife species are high-risk for human exposure. This risk is due to shared habitats, interactions between humans and wildlife, and human proximity to locations of endemic rabies in certain species, including the bat, raccoon, skunk, and fox. Small rodents such as squirrels, hamsters, guinea pigs, chipmunks, rats, and rabbits are almost never found to be infected and have not been known to transmit rabies to humans.[39]

Other modes of transmission are rare but exist. Human rabies disease has been caused via organ transplantation and aerosolization (in laboratories or high-concentration environments such as caves).[40,41] Other than through organ transplantation, person-to-person transmission of rabies has not been reported.

Pathophysiology

Rabies is caused by an RNA virus from the genus lyssavirus, in the family Rhabdoviridae. The rabies virus (RABV) is responsible for most human and animal rabies cases worldwide, but other lyssavirus have been implicated. RABV is found extensively throughout the world in terrestrial carnivores, but non-RABV lyssavirus is rarely encountered in nonflying carnivores.[37,42]

Bites through the dermis allow the virus to enter tissues and initiate infection. The virus spreads from muscle tissue to the peripheral nervous system via the neuromuscular junction and then travels to the spinal cord and brain. Host cell machinery is usurped, and rapid replication occurs, resulting in clinically apparent disease. Infection of the brain is followed quickly by peripheral viral dissemination. For the reservoir species, transmission to the salivary glands proceeds through the parasympathetic and sympathetic nervous systems. The associated aggressive behavior and hypersalivation promotes transmission to new hosts.[43,44]

Clinical Features

Two forms of clinical rabies are described, encephalitic and paralytic. The encephalitic form predominates and represents approximately 80% of all human rabies presentations.[45] It is believed that the burden of infection is in the brain in the encephalitic form, whereas the burden is in the spinal cord in the paralytic form. The initial symptoms of rabies infection are vague and may be confused with other flu-like illnesses. Presenting symptoms of rabies include headache, malaise, pharyngitis, and weakness which are followed by or concomitant with pruritus and paresthesia at the site of inoculation. Fever, tachycardia, and tachypnea foretell the acute behavioral changes characteristic of rabies: agitation, aerophagia, hydrophobia, seizures, and coma.[36] The image of a patient in the final stages of rabies delirium with agitation and foaming of the mouth is aptly described by the genus name lyssavirus, named for Lyssa, a Greek goddess of rage, fury, madness, and frenzy (Fig. 119.11). Infection in the central and peripheral nervous systems leads to multiorgan failure.

Encephalitic Rabies. Encephalitic rabies progresses rapidly over days, and the presenting signs and symptoms are supplanted rapidly by diffuse neurologic involvement. A brief period of anxiety, confusion, insomnia, and cerebellar dysfunction are soon replaced by frank delirium, hallucinations, and the clinically defining behavioral changes: hydrophobia, aerophobia, aggressive behavior, and seizures. These are the clinical symptoms most associated with rabies infection,

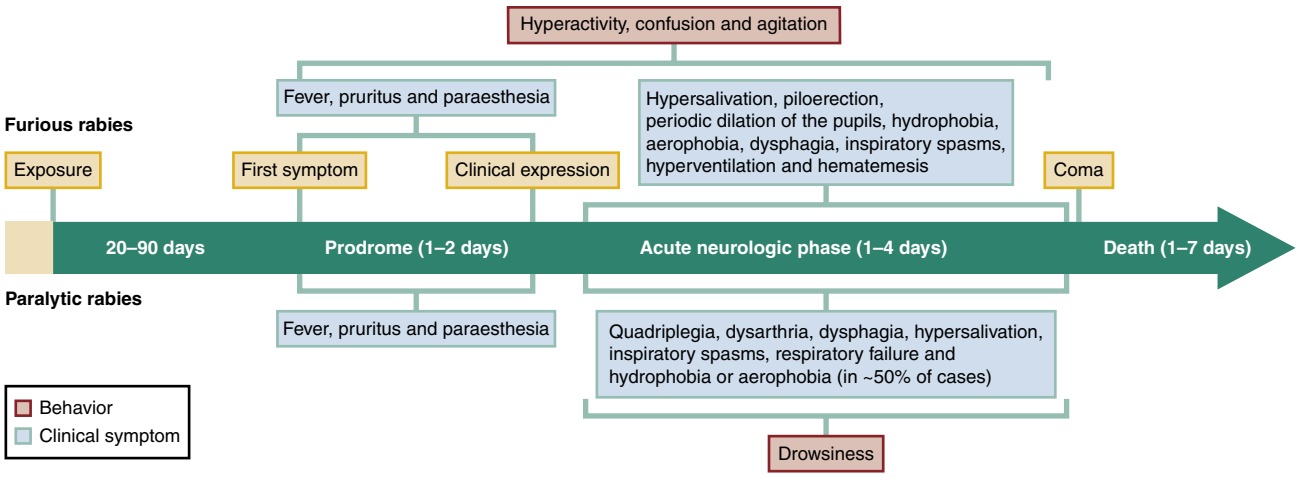


Fig. 119.11 Spectrum of clinical rabies. (From: Fooks AR, Cliquet F, Finke S, et al. Rabies. *Nat Rev Dis Primers.* 2017;3:17091.)

and these portend death.[45] In the final stage of encephalitic rabies, the patient has difficulty swallowing from involuntary muscle spasms of the pharynx, and hypersalivation occurs. If offered water, the patient may develop pharyngeal spasm with resultant gagging. Patients are unable to handle salivary secretions, leading to characteristic drooling and foaming of the mouth. The findings of hydrophobia with resultant gagging and hypersalivation are so characteristic of rabies infection that in many developing countries, water is offered to the patient as a diagnostic test. Coma and death follow rapidly, usually within 5 days of presentation.[36]

Paralytic Rabies. Paralytic rabies accounts for approximately 20% of human rabies infections. The presenting symptoms are similar to encephalitic rabies and include headache, weakness, and malaise. Muscle weakness and paresthesia occur at the site of the bite and, over days to weeks, an acute flaccid paralysis ensues. Unlike the encephalitic form, the patient does not develop agitation, hypersalivation, or hydrophobia. Rather, muscle weakness occurs over days to weeks, and the progression to coma and death takes longer than in the encephalitic form.[45] The paralytic form develops more often in patients who have been bitten by rabid bats than dogs and those who have had incomplete PEP, without a clear explanation. Exposed patients receiving the nerve cell–derived vaccine that is still used in a few countries are also at greater risk of developing the paralytic form.

Differential Diagnoses

The prodromal phase of rabies presents similarly to many common infections including mononucleosis, bacteremia, and meningitis. In its early stages, rabies may appear similar to other infectious encephalitis including herpes simplex, cerebral malaria, and West Nile infections. Noninfectious toxic or metabolic encephalopathies, including serotonin syndrome, alcohol withdrawal, organophosphate poisoning, elapid or scorpion envenomation, may mimic early rabies. On rare occasion, psychiatric disease, such as schizophrenia and conversion disorders, may resemble rabies.[46,47] Tetanus, dystonia, and strychnine poisoning all present with muscular rigidity which may appear similar to rabies. Once aerophagia, hydrophobia, or dysphagia appear, however, the diagnosis of rabies becomes clear.

The early presentation of paralytic rabies may mimic Guillain-Barré syndrome, but is distinguished by the onset of encephalitis, asymmetry of limb involvement, persistent fever, bladder incontinence, and intact sensory function. Percussion myoedema is the mounding of muscle at the site of percussion and is characteristic of rabies.[33] It is best elicited on the chest, deltoid, and thigh (Box 119.2).

BOX 119.2 Rabies Rigidity/Paralysis: Differential Diagnosis

Muscular Rigidity
Tetanus
Dystonia
Strychnine poisoning

Paralysis
Guillain-Barré
Acute flaccid paralysis
Envenomation
Hypokalemia

In atypical presentations of encephalitic rabies or paralytic rabies, the diagnosis may not be clear and may delay institution of appropriate public health and infection control measures. As improved antemortem techniques arise, more timely diagnosis will provide more opportunity for appropriate prophylaxis to family members, and more timely discussions with patient and family regarding prognosis.[42]

Diagnostic Evaluation and Testing

The diagnosis of human rabies requires clinical acumen, understanding of local capabilities of treatment, and public health issues in the community.[36] The emergency clinician must consider rabies in two scenarios: possible exposure to rabies and the diagnosis of clinical rabies. The decision to initiate postexposure prophylaxis requires understanding of the type of exposure and the local vector demographics. Because the risk assessment of the exposure is intricately tied to its management, this topic is addressed in the management section.

Clinical cases of human rabies are categorized as suspected, probable, or confirmed. A suspected case is one that is compatible with clinical findings, probable cases have a reliable history of contact suspected, probably or confirmed rabid animal as well as suspected clinical findings, and confirmed case definition indicates laboratory confirmation.[36] The WHO definition of confirmed rabies requires at least one of the laboratory criteria in Box 119.3.

Typical laboratory tests are rarely helpful in the diagnosis of rabies. Complete blood count often demonstrates a leukocytosis, and cerebrospinal fluid findings include lymphocytic pleocytosis with elevated protein and normal glucose. Neither of these studies and their findings are specific for rabies. MRI imaging may demonstrate T2 signals

BOX 119.3 Laboratory Criteria Used to Confirm Rabies

- Presence of viral antigens in samples (e.g., brain tissue, skin);
- Isolation of virus from samples in cell culture or in laboratory animals;
- Presence of viral-specific antibodies in the cerebrospinal fluid or serum of an unvaccinated person; and/or
- Presence of viral nucleic acids in samples (e.g., brain tissue, skin, saliva, concentrated urine).

The WHO definition of rabies requires at least one of the criteria to be met.[35]

in the hippocampus, hypothalamus, and brainstem, but is not clearly diagnostic.[33]

Effective antemortem testing remains elusive, particularly in endemic regions with limited laboratory capability. Patients with suspected rabies who have not been vaccinated may not have rabies antibodies in serum or CSF until obvious clinical signs are apparent, but positive titers are then diagnostic. Patients who have received rabies vaccine or rabies immunoglobulin (RIG) have serum titers of rabies antibody but require subsequent testing in 7 days to assess if titers are rising. Various forms of molecular methods-reverse transcription (RT) and polymerase chain reaction (PCR) assays have demonstrated high sensitivity for RABV in dog brain tissue. In humans, real-time PCR testing of cerebral spinal fluid, nuchal skin, and saliva using the TaqMan probes has demonstrated excellent sensitivity and specificity.[48] Consultation with local public health authorities to determine which tissues should be sampled and how to obtain and transport safely is paramount.[35]

Postmortem testing of fresh brain samples remains the gold standard for the diagnosis of rabies in all animal species. The WHO and World Organization for Animal Health (OIE) recommend fluorescent antibody testing (FAT) of brain smears or touch impressions.[49] FAT provides sensitive and specific results within a few hours. The best results are obtained with fresh brain tissue, but saline-washed tissue preserved in 50% glycerol saline also works well.

The direct rapid immunohistochemical test (dRIT) was developed in 2006 at the CDC. The dRIT assay is an immunohistochemical diagnostic assay that utilizes polyclonal or monoclonal antibody that is directly labeled, and is performed after a touch impression of brain tissues. A streptavidin reagent catalyzes the formation of a colored precipitate when bound to the rabies virus, making it visible with simple light microscopy. dRIT provides results in 1 hour, does not require expensive fluorescent-labeled antibodies, and has been field-tested in endemic areas with 100% sensitivity and specificity when compared to FAT.[50] The use of dRIT allows regions with limited resources to obtain important incidence data, as well as the possibility of carrying out more informed postexposure prophylaxis. However, one significant drawback of dRIT is that the reagents used for the test are only available through the CDC.

Management

The treatment of rabies exposure and rabies disease is divided into preexposure (PreP) recommendations in high-risk groups, animal bite or exposure assessment, wound care, postexposure prophylaxis, and treatment of human rabies (Fig. 119.12).

Preexposure Prophylaxis. Pasteur described the first rabies vaccine in 1885.[51,52] Nerve tissue–derived vaccines similar to Pasteur's were used worldwide until the 1940s, when they were replaced by cell culture–derived vaccines (CCVs) that were safer and more immunogenic. The nerve cell–derived vaccines contain myelin basic protein, which may cause a severe immune response resulting in devastating neurologic adverse reactions. Despite warnings from WHO, some countries continue to manufacture and use nerve tissue–derived vaccines.[36]

All US-licensed rabies vaccines are inactivated cell culture vaccines that can be administered to immunocompromised individuals. Patients with immunosuppressive disorders and those taking corticosteroids, immunosuppressive agents, or antimalarials may have a reduced response to the vaccine, necessitating a 5-dose regimen. In this setting, serologic testing for neutralizing rabies antibody may be considered 4 weeks after the last vaccine dose to determine if a booster is necessary.[36]

Adverse reactions to rabies vaccines include local reactions, mild systemic reactions, and immediate hypersensitivity reactions. Typical local reactions include pain, swelling, redness, and induration at the injection site.[52] These symptoms are reported by 60% to 85% of recipients of the human diploid cell vaccine (HDCV) and by 11% to 57% of recipients of the purified chick embryo vaccine (PCEV). From 6.8% to 55.6% and up to 31% of recipients of HDCV and PCEV, respectively, have reported systemic reactions, including gastrointestinal symptoms, headache, dizziness, and fever. Immediate hypersensitivity occurs in 1.2% of previously unimmunized HDCV recipients and in up to 6% of those previously immunized receiving HDCV as a booster. No deaths have been reported from recipients of the human diploid cell vaccine or purified chick embryo cell vaccine.[53]

Preexposure vaccine (PrEP) is recommended for travelers to endemic areas and those in high-risk professions (e.g., veterinarians, laboratory staff handling the virus). The PrEP regimen recommended by the WHO and CDC are not currently aligned, with WHO recommending a 2-dose strategy and CDC recommending a 3-dose regimen.[36,52]

Intramuscular or intradermal administration of vaccine is recommended.[36,52] In the United States, the CDC recommends the intramuscular route only. The intradermal method, common in many countries, uses less total vaccine in multidose vials and is thus less expensive while still being highly efficacious.[54] While some recommend preexposure prophylaxis for children younger than 15 years old in endemic areas, due to this group being responsible for approximately 50% of rabies deaths,[33,55] the current 3-dose PrEP regimen is cost-prohibitive in endemic areas, even with the lower-cost intradermal method. A PrEP regimen that induces immunity with a single injection is needed.[36]

Numerous serologic studies have provided evidence of robust production of neutralizing antibody in response to cell culture–derived vaccines. Following the use of WHO-approved vaccines, 100% of healthy individuals were found to have a significant antibody response. No individuals with circulating neutralizing antibody levels above 0.5 IU/mL have ever contracted rabies.

Animal Bite Risk Assessment. An animal bite or potential rabies exposure is a medical urgency, not an emergency. In the emergency department, PEP is either administered at the time of presentation after consultation with public health authorities or is postponed until the rabies risk of the biting animal is determined (Table 119.3). Discharge instructions for patients with postponed PEP should reflect the on-going nature of the risk assessment. Because of periodic national shortages of vaccine and immune globulin used in PEP, clinicians should consult with local or state public health authorities and complete a risk assessment before administering internal stocks of PEP supplies.

Bats are responsible for the greatest number of rabies exposures in the United States.[38] Because of the difficulty in identifying the very small bite wounds created by bats, the CDC classifies all bats found indoors with a person who was asleep or incapacitated, or a bat found near an unattended child or an adult who cannot reliably attest to their

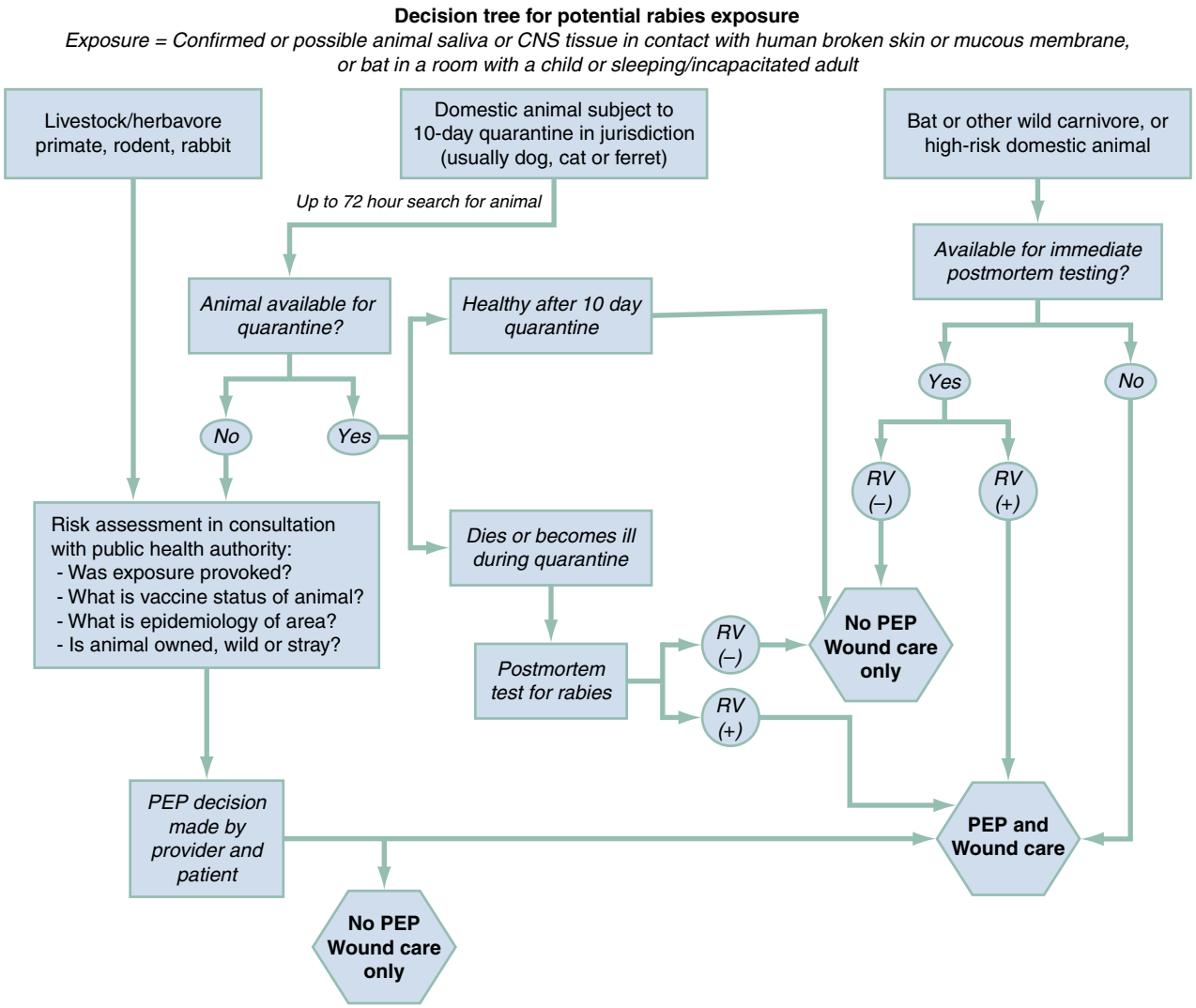


Fig. 119.12 Decision tree for potential rabies exposures.

physical contact with the bat, as an exposure. PEP is recommended under these conditions unless the bat is available for immediate testing and tests negative. In the United States, PEP always includes four doses of rabies vaccine and rabies immunoglobulin.[56]

Bites and exposure require a thorough history including geographic location where, when, and what type of exposure occurred (species, bite, scratch). Outside of the United States, WHO categorizes exposures in areas enzootic for rabies into three categories.[36] Category I includes touching or feeding animals, licks on intact skin, and contact of intact skin with secretions or excretions of a rabid animal or human. These are not regarded as significant exposures, and postexposure prophylaxis is not required. Category II includes nibbling of uncovered skin, minor scratches, or abrasions without bleeding. If these are caused by a bat, treat as category III. Vaccine should be injected as soon as possible, but RIG is not recommended for Category II. Category III includes single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks, and indoor exposure to bats. Category III contact requires full rabies prophylaxis including vaccine and rabies immunoglobulin.

Within the United States, most jurisdictions (state or local) require rabies vaccination of dogs and cats, and some require vaccination of pet ferrets. In addition, some livestock owners choose to vaccinate their animals against rabies. These variations in vaccination implementation result in different postexposure treatment recommendations among state public health officials for humans bitten by domestic animals. Each state and territory maintains a contact phone number for consultation for potential rabies exposure. The list of contacts is available from the U.S. Centers for Disease Control and Prevention at www.cdc.gov/rabies or by calling the CDC's information line, 877-554-4625 or 800-CDC-INFO, 24 hours/day, 7 days/week. In addition to seeking consultation for PEP, in some jurisdictions, emergency medicine clinicians must comply with mandated reporting of PEP administration to public health authorities. Clinicians should be familiar with their local regulations. Clinicians are also mandatory reporters of animal bites to animal control authorities in many states and local jurisdictions. This bite reporting initiates the process of animal location and testing or quarantine.[35,54] These PEP and bite reporting requirements are not generally waived for people bitten by their own animals.

The only species for which the shedding period has been scientifically determined are the domestic dog, cat, and ferret. A 10-day quarantine, based on the viral shedding period, is used in lieu of postmortem testing to determine the rabies risk of domestic animals in geographic areas with high rates of vaccination. Quarantine establishes that if a dog, cat, or ferret is alive on the tenth day after biting

TABLE 119.3 Assessment of Rabies Exposure

Exposure	Rationale	Action/Timing
Bite by a wild terrestrial mammal other than small rodent or lagomorph	Rabies is abundant in wildlife and cross-species transmission occurs. Many small rodents and lagomorphs paralyze and die before salivary excretion of virus occurs.	Animal will be sacrificed and submit head to public health authorities to test brain for rabies. Urgent PEP pending test results[a] If animal unavailable for testing, prepare for PEP and consult public health authorities for risk assessment.
Unprovoked bite by a pet (dog, cat, or ferret)	Pet vaccination is imperfect. Cross-species transmission occurs. Incubation periods are well-defined.	Report to animal control authorities as required. Observation for 10 d[b,c] Urgent PEP if animal is determined to have rabies
Unprovoked bite by a domestic mammal (horse, cow, or other pet)	Vaccinations exist for horses, cattle, and sheep, but efficacy and incubation period are poorly defined.	Report the incident to the local public health department. The animal may be sacrificed and the head submitted for testing.[b] Urgent PEP pending test results.
Dog or cat brings fresh prey to their master.	Without direct bite by the prey, there is no human exposure. The dog or cat is exposed.	Refer the pet to a veterinarian for assessment and treatment.
Dog or cat brings dead, desiccated prey to their master.	Virus is rapidly inactivated by desiccation or sunlight—no exposure.	No action
Physical contact with a bat	Bat bites are hard to appreciate or find by examination. Most American deaths from bat rabies have no known exposure, so known exposure confers very high odds for death from rabies.	Animal will be sacrificed and submit for testing. If positive or if animal cannot be tested, urgent PEP
Bat seen in the same room as a responsible child (>6 y) or adult	Physical contact can be reliably excluded—no exposure	No action
Bat seen in the same room as a young child (<7 y),[d] sleeping, intoxicated or cognitively impaired person	Eight percent of bats found indoors are rabid. Physical contact CANNOT be reliably excluded—exposure occurred	Animal will be sacrificed and submit for testing. If positive or if animal cannot be tested, urgent PEP
Bat found in a room that was previously occupied or seen in a hallway or room adjacent to persons who cannot report physical contact with a bat.	Risk of undetected contact is substantially lower—no exposure	No action

WHO Expert Consultation on Rabies, third report: WHO Technical Series Report No. 1012. Geneva; 2018. ISBN 978-92-4-121021-8.

a human, it did not have virus *in its saliva* on the day of the bite.[57] All other species that potentially expose a human to rabies, including domestic-wild animal hybrids, must be evaluated on a case-by-case basis without quarantine.

Wound Care. All mammal bites require meticulous wound care, and if rabies prophylaxis is considered the initial wound care is critical. Rabies virus is very sensitive to sunlight, soap, and drying. When performed within 3 hours of inoculation, scrubbing and flushing with benzalkonium chloride, 20% soap solution, or Ivory soap is nearly 100% protective. Wounds from high-risk animals should be scrubbed with soap, water, and a virucidal agent (e.g., povidone-iodine) and then flushed with saline or water.[33] As with other mammalian bites, bacterial infection, cosmetic results, and tetanus prophylaxis need to be considered, but any indicated wound closure should be sutured loosely with delayed scar revision as needed. The bite location is a significant determinant of disease potential. Wounds to the face are at highest risk, as well as other highly vascular areas, including the head, neck, genitals, and hands.

Postexposure Prophylaxis. PEP is almost 100% effective when administered according to CDC or WHO guidelines. Treatment failures usually occur when local wound care is not complete, immunoglobulin is not given, or nerve cell–derived vaccine is used. No postexposure prophylaxis failures have occurred in the United States, but scattered reports worldwide do occur. These are typically associated with variance from the WHO PEP protocol.

Once the decision to initiate PEP has been made, it should be started immediately. Currently, WHO describes 6 different protocols using 2 different routes for postexposure treatment of unimmunized individuals, 4 intradermal and 2 intramuscular to accommodate clinical care settings and preferences in different countries.[36] In the United States, the CDC recommends the intramuscular route only and 4 vaccinations over 14 days[56] (Table 119.4). Both the CDC and WHO recommend an intramuscular dose of 1.0 mL/injection, and an intradermal dose of 0.1 mL. Effective intradermal injections must form a bleb at the site. Two vaccines are currently available in the United States, RabAvert (Novartis, Chiron Behring GmbH) and Imovax (Sanofi Pasteur).

The CDC Advisory Committee on Immunization Practices (ACIP) recommends the 4-dose vaccine schedule for postexposure prophylaxis in previously unvaccinated individuals.[58] This regimen should start as soon as possible after the exposure, day 0, and should then be followed by repeated doses on days 3, 7, and 14. The dose is 1 mL of vaccine administered intramuscularly. The deltoid is the preferred site for adults; the anterolateral thigh is the preferred site in children. There is a diminished immunologic response to gluteal injection of vaccine, so this site should be avoided. The intradermal vaccination regimes recommended by the WHO are shorter in duration, but require may require two ID injections at each visit.[59]

In addition to vaccination, in the United States, once a decision to start PEP is made, rabies immunoglobulin (RIG) should be given promptly in patients not previously vaccinated. WHO only

TABLE 119.4 Postexposure Vaccination Comparison of WHO and CDC Protocols

Vaccine Regimen	Protocol Organization	Number of Vaccinations per Clinic Visit (Days 0, 3, 7, 14, 21, 28)	Route
If no previous rabies vaccinations:			
1 week, 2 sites	WHO	2-2-2-0-0	Intradermal
2 week, 1 site	WHO	1-1-1-1-0	Intramuscular
3 weeks, 1 site	WHO	2-0-1-0-1	Intramuscular
1 month, 2 sites	WHO	2-2-2-0-2	Alternative Intradermal
1 month, 4 sites	WHO	4-0-2-0-1	Alternative Intradermal
1 week, 4 sites	WHO	4-4-4-0-0	Alternative Intradermal
2 weeks, 1 site	CDC	1-1-1-1-0	Intramuscular
If previously vaccinated: 1 day, 4 sites	WHO	4-0-0-0-0	Intradermal
If previously vaccinated:3 day, 2 sites	CDC	1-1-0-0-0	Intramuscular

Center for Disease Control and Prevention: Rabies Post Exposure Prophylaxis https://www.cdc.gov/rabies/medical_care/index.html. O'Brien KL, Nolan T, on behalf of the SAGE WG on Rabies. The WHO position on rabies immunization—2018 updates. *Vaccine*. 2019;37(Suppl 1): A85-A87. PMC [article]PMCID:PMC6863036. PMID:30342901DOI:10.1016/j.vaccine.2018.10.014.

recommends RIG for Category III wounds, which differs from US practice. RIG may be derived from equine or human sources (human rabies immunoglobulin). RIG inhibits viral spread during the interval when antibodies are produced in response to the rabies vaccine.[33] Human rabies immunoglobulin produced by Grifols (HyperRAB) is available, but equine immunoglobulin[60] or monoclonal antibodies to rabies may be necessary for passive immunization if human RIG is not available.[36] Human rabies immunoglobulin, 20 IU/kg, should be administered soon after the bite occurs and not more than 7 days after the first dose of rabies vaccine. As much RIG is injected into and around the wound site as the patient will tolerate, with the remainder injected intramuscularly at a distance from the vaccine administration site.

Adverse reactions to human RIG are common, but these are primarily local reactions. Pain, induration, swelling, and erythema have been reported in 30% to 100% of injections. Headache is the most common systemic reaction to HRIG occurring in more than 50% of recipients. No deaths have been reported from human RIG.

Postexposure vaccination for previously vaccinated individuals requires wound care and a 2-dose intramuscular vaccination (days 0 and 3) or 4-dose intradermal vaccination (all on day 0). RIG is not needed in previously vaccinated individuals who have received ACIP- or WHO-approved PrEP or PEP or other vaccinations with documented rabies virus–neutralizing antibody response.[56]

Outside the United States, RIG is in short supply, and some countries do not use WHO-approved vaccines.[61] Exposed travelers from these areas may require further vaccination on return to their native country, and it is imperative that providers clarify what patients have actually received in the originating country.

Management

Reversal of the disease process in rabies remains elusive. RABVs ability to evade neuro and humoral immune responses and cross the blood-brain barrier without causing axonal apoptosis, is not completely understood, but it results in neuronal dysfunction rather than neuronal death. Without a clear understanding of the pathogenesis of this disease, targeting treatment is difficult.

Regardless of new developments, management remains focused on palliative care. Because the vast majority of human rabies occurs in low-income and rural areas, one must be cognizant of the local medical capabilities, and the local culture. Care focuses on comfort through sedation, analgesia, and rehydration in a calm, draft-free environment. The patient and family require support during the death process in a culturally sensitive manner. In resource-poor areas, the decision to initiate aggressive intensive care therapy should consider these factors: rabies vaccination prior to onset of disease, young age, rabies in previously healthy and immunocompetent individuals, initiation of treatment when neurologic signs are mild, New World bat variant rabies virus, and early detection of neutralizing anti–rabies virus antibodies in the serum and cerebrospinal fluid.[36]

Aggressive critical care management is rarely successful. In recent years, India reported survival in 6 individuals with aggressive therapy, but all suffered severe neurologic impairment.[62,63] Fifteen well-documented cases of survival with better cognitive outcomes were reported, but in all of these cases the patients had receive at least one preexposure vaccination.[45] The heralded Milwaukee Protocol, successful in treatment of a 15-year-old in Wisconsin in 2004, has not been replicated in spite of numerous attempts and should be abandoned.[64] Clinical trials for new protocols are limited. Thus, even in the ICU setting, sedation and analgesia with benzodiazepines, ketamine, haloperidol, and opiates remain the mainstay of therapy.

Disposition

Unfortunately, the survival of patients with rabies remains dismal and the disposition should focus on supportive therapy. Newer therapies may provide hope for patients in the future, but for now, prevention of canine rabies remains the single most important treatment for rabies and the best hope for eradication.

Arboviruses

Arboviruses are a group of viruses that are transmitted via arthropod vectors, generally mosquitoes and ticks. Encephalitis is a common manifestation of arboviral infection. Most of these viruses are primarily transmitted from the arthropod vector to another animal, and humans are only incidentally infected. The arboviral viruses that cause encephalitides belong to the following families: *Flaviviridae, Togaviridae, Bunyaviridae,* and *Reoviridae.*

St. Louis encephalitis virus, West Nile virus (WNV), Powassan virus, and Japanese encephalitis virus belong to the *Flaviviridae* family. Most of these viruses are maintained in a natural cycle of bird-mosquito-bird transmission. Given the mosquito vector, in North America and other temperate climates, these infections have a higher incidence in the summer months. WNV was popularized at the turn of the 20th century

because of its first-time appearance in the western hemisphere. WNV emerged in New York City in 1999 and since then has spread to the Pacific coast, as far south as Argentina, and as far north as Canada. Now WNV is the leading cause of domestically acquired arboviral infection in the United States.[65] Powassan virus is maintained in a natural cycle of ticks to rodents. In Asia, Japanese encephalitis virus is the most prevalent cause of viral encephalitis with the greatest morbidity as well.

La Crosse virus and California encephalitis virus belong to the *Bunyaviridae* family. According to reports from the CDC, La Crosse virus is the most common cause of encephalitis among children in the United States.[65] Eastern equine encephalitis (EEE) virus, Western equine encephalitis virus, and Venezuelan equine encephalitis virus belong to the *Togaviridae* family and cause infections in certain parts of North and South America.

Clinical Features

Arboviral infections cause a wide range of presentations, including subclinical disease, nonspecific febrile illness, hemorrhagic fever, meningitis, acute flaccid paralysis, and severe encephalitis. Typically encephalitis patients begin with a nonspecific febrile illness accompanied by malaise, sore throat, and respiratory symptoms. Headache, photophobia, meningismus, lethargy, somnolence, and altered mental status will then follow. Severe disease can manifest as paralysis, coma, and seizures. Depending on the virus, it can be common for patients that recover to have some neurologic sequelae.

West Nile Virus. The majority of people who become infected with WNV are asymptomatic. The most common presentation of symptomatic WNV is West Nile fever, a self-limiting illness characterized by fever, headache, malaise, and myalgias. Patients can also experience gastrointestinal symptoms. Between a quarter to half of the patients can also have an accompanying maculopapular rash on the chest, back, and arms. It is estimated that around 1% of WNV causes neuroinvasive disease. The neuroinvasive disease manifests as meningitis, encephalitis, or flaccid paralysis. WNV neuroinvasive disease carries with it a 10% mortality rate. Age and immunosuppression have been identified as a risk factor for more severe neuroinvasive disease and mortality for WNV infections.[66]

Eastern Equine Encephalitis Virus. EEE virus is the most dangerous of the viruses that cause equine encephalitides. It occurs along the Gulf and Atlantic coast with predominance in the late summer months. The usual manifestation is fever, chills, headache, and myalgias lasting 1 to 2 weeks, typically followed by resolution. A small portion of patients will go on to develop encephalitis with headache, nausea, vomiting, altered mental status, and focal neurologic deficits. Approximately 2% to 6% of infected patients develop rapidly deteriorating severe encephalitis that results in coma. EEE virus infection that results in encephalitis is associated with 30% mortality.

St. Louis Encephalitis Virus. The majority of infections are asymptomatic, but as patients get older the rate of symptomatic infections increases dramatically. The incubation period varies from 4 to 21 days. Symptomatic disease presents as fever, myalgias, and headaches. Patients older than 60 frequently present with encephalitis, with mental status ranging from lethargy to coma. Acute flaccid paralysis occurs in approximately 6% of patients with encephalitis.

Powasson Virus. The infection usually presents as fever with neurologic complaints including headache, confusion, weakness, paralysis, lethargy, or even seizures. The mortality rate is near 10%, and survivors are often left with long-term neurologic impairment.

Differential Diagnosis

The diagnosis of arboviral encephalitis is difficult based on clinical presentation alone. It shares many features with other arboviral infections, other viral causes of encephalitis, bacterial meningitis, HSV encephalitis, leptospirosis, Lyme disease, and brain abscess.

Diagnostic Testing

The primary method of diagnosis is CSF analysis for serologic markers or PCR. WNV encephalitis is diagnosed by detecting IgM antibody in CSF. Viral culture is not commonly used for these diagnoses. There is often a broad differential diagnosis when evaluating these patients, so it is crucial to elicit travel and potential exposure history to narrow the differential diagnosis. When performing a lumbar puncture, it can be helpful to obtain an extra tube or vial of CSF to put on hold. This extra CSF sample is useful because testing for arboviral infections is often sent after the initial evaluation, assessing for more common etiologies of neurologic infection, such as bacterial meningitis or HSV encephalitis, is completed. CSF demonstrates an elevated WBC count with lymphocyte predominance. Early during a WNV infection there may be a neutrophil predominance. Ancillary testing with CT or MRI may be indicated, depending on the severity of neurologic symptoms.

Management

The treatment for these entities remains largely symptomatic. There is no specific antiviral therapy or immunoglobulin treatment with proven benefit. In patients that develop cerebral edema, the therapies focus on preventing secondary brain injury and treatment of cerebral edema by maintaining adequate cerebral perfusion pressure, treating seizures, and avoiding hypoxemia, high fever, and hypoglycemia or hyperglycemia (see Chapter 4).

Disposition

Patients with neurologic symptoms should be admitted to the hospital. These patients often require neurology and infectious disease specialists to consult in their care. Arboviral infections are reportable diseases. Long-term outcomes for these patients can vary. Full recovery can usually be expected in patients with WNV meningitis. WNV encephalitis patients often have residual effects, with over half of them reporting some type of persistent symptoms (fatigue, muscle aches, decreased activity, memory difficulty, concentration difficulty) beyond 6 months.[67]

Other Arboviral Infections

Dengue Virus

Dengue is the most common virus in the *Flaviviridae* family to cause human infection. It can be found all over the world, with most infections occurring in Southeast Asia, the Western Pacific, and Central and South America. It is one of the most important causes of fever in the returned traveler. It is transmitted via the mosquito vector, *Aedes aegypti* and *Aedes albopictus,* and humans are the natural host.

Clinical Features. Dengue can cause a wide spectrum of disease. Many infected individuals with dengue are asymptomatic. Dengue fever is a self-limited illness characterized by fever, headache, retroorbital pain, severe myalgias, and arthralgias. Symptoms can last up to 1 week. Dengue hemorrhagic fever (DHF), a more severe syndrome, occurs when the following four criteria are present: (1) increased vascular permeability (pleural effusion, ascites, hemoconcentration), (2) thrombocytopenia, (3) fever lasting 2 to 7 days, and (4) hemorrhagic tendency or spontaneous bleeding. Dengue shock syndrome (DSS), the most severe presentation of dengue infection, is present when DHF occurs with circulatory shock.

Differential Diagnosis. Other diagnoses to consider in suspected dengue patients include Zika, malaria, chikungunya, rickettsial infections, leptospirosis, and other viral hemorrhagic fevers, including Ebola, Marburg, yellow fever, or bunyaviruses. It is also important to consider the diagnosis of measles in a returned febrile traveler with

a rash, because many countries that have endemic dengue also have endemic measles.

Diagnostic Testing. The diagnosis can be made via serologic testing with IgM assay, antigen testing of the viral antigen nonstructural protein 1 (NS1), or viral RNA detection with RT-PCR. Early in the course the IgM is often negative. Other laboratory findings that may be present with dengue infection include leukopenia, thrombocytopenia, elevated hematocrit (due to hemoconcentration from fluid loss), and abnormal liver function tests. In DHF, coagulopathy can be present.

Management. There are no specific antiviral agents that treat dengue. The treatment is mainly supportive. Dengue fever is usually a self-limited illness and can be treated with rest, antipyretics, analgesics, and fluid replacement therapy. Nonsteroidal antiinflammatory drugs and aspirin should be avoided given the bleeding tendencies associated with these medications. Patients with DHF and DSS require close monitoring, IV fluid replacement therapy, and organ support as indicated. Hemorrhagic sequelae are treated with blood product transfusions as needed. Steroid therapy for severe dengue has been evaluated in several low-quality studies, but the evidence to date is inconclusive, and steroid treatment cannot be recommended at this time. The control of epidemics revolves around reducing the mosquito vector population and preventing humans from being bitten by mosquitoes.

Disposition. Depending on the severity of illness, patients with dengue fever can be treated as outpatients, but some may require admission for rehydration therapy. Patients with DHF will require admission to the hospital for monitoring and IV fluid resuscitation, and patients with DSS will require admission to the ICU.

Zika Virus. Zika virus is an arbovirus in the *Flaviviridae* family that is transmitted to humans via the *Aedes* species mosquitos. Although transmission is predominantly from mosquitos, there have been reports of perinatal, in utero, sexual, and blood product transfusion–related transmission as well. In 2016 there was a large uptake in cases reported in the United States. Over 5000 cases of Zika virus were reported, with most travelers returning from Zika endemic regions.[68] Over 200 cases were reported from local transmission within the United States. Although the case fatality is low, Zika virus infection during pregnancy has been linked to severe congenital anomalies including microcephaly and other neurologic defects. This has led to the CDC issuing travel advisories to avoid Zika endemic regions for pregnant women, women planning on pregnancy, men with a pregnant partner, or men with a partner planning pregnancy.

Clinical Features. The majority of patients infected with Zika virus are asymptomatic. For those who do develop symptoms, the clinical manifestations include maculopapular rash, fever, nonpurulent conjunctivitis, headache, retro-orbital pain, myalgias, arthralgias, and vomiting. The most commonly reported symptom is an erythematous maculopapular rash (Fig. 119.13).[69] The course of the disease is typically mild with resolution within 2 weeks. Although rare, Zika infection has been associated with a variety of neurologic complications, including Guillain-Barré syndrome, meningoencephalitis, and myelitis.[70,71]

Differential Diagnosis. Other diseases with fever, rash, myalgias, and travel history should be considered, including dengue, chikungunya, malaria, rickettsial infections, leptospirosis, measles, rubella, and meningococcal disease.

Diagnostic Testing. The diagnosis of Zika virus infection can be made with RT-PCR or serology. In nonpregnant symptomatic patients with symptoms for less than 7 days, serum RT-PCR is the preferred method for diagnosis. If symptoms are present for more than 7 days, then serology is the preferred method. In pregnant symptomatic patients, RT-PCR and IgM antibody testing on a serum specimen and RT-PCR on a urine specimen are recommended.[72] It is important to test for dengue as well, as there is significant overlap in symptoms. Obtaining a CBC in severely symptomatic patients can be useful because significant thrombocytopenia has been reported in Zika infections.[73]

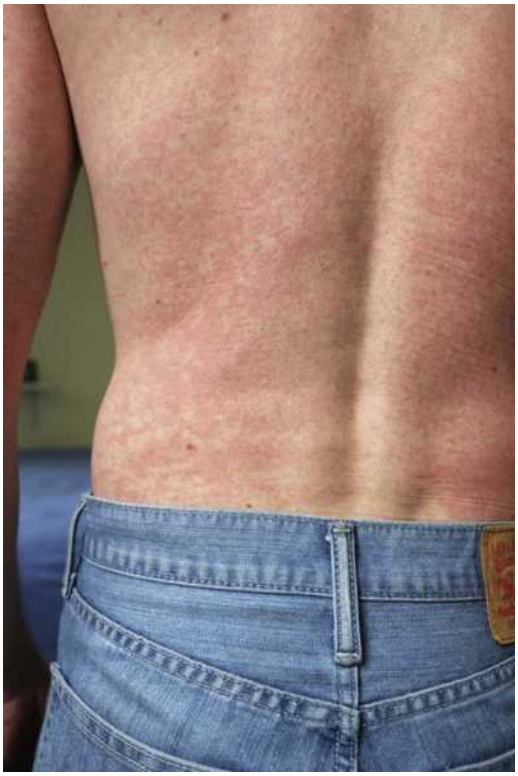


Fig. 119.13 Typical rash associated with Zika virus. (Courtesy of CDC website: https://phil.cdc.gov/Details.aspx?pid=21385)

Management and Disposition. Similar to other flavivirus infections, treatment largely consists of symptom management and supportive care. Antipyretics, analgesics, and hydration are the cornerstone of management. Acetaminophen is the agent of choice. If there is concern for severe thrombocytopenia or dengue infection, aspirin and NSAIDs should be avoided. Most of these patients can be discharged, and treatment can continue at home. Pregnant patients should have definite follow-up with their OB/GYN providers, given the risk of fetal anomalies. Typically, this follow-up will entail psychosocial support as well

Chikungunya Virus. Chikungunya is an arbovirus in the *Alphaviridae* family that was originally endemic to West Africa. Since early this millennium, the infection has spread broadly, responsible for multiple outbreaks in Asia, Europe, and the Indian subcontinent. In 2013, local transmission was identified in the Americas for the first time. The vectors are the same as dengue, the *Aedes aegypti* and *Aedes albopictus* mosquitoes.

Clinical Features. Chikungunya causes a self-limiting disease very similar to dengue. Fever, myalgias, and polyarthralgias are the hallmark of this disease. The joint pain can be so severe that ambulation is impaired. Symptoms typically last for 7 to 10 days. More than half of infected individuals develop a maculopapular rash several days after fever onset. Risk factors for severe disease with higher mortality include age older than 65, diabetes, and underlying cardiopulmonary disorders.

Differential Diagnosis. Other febrile illnesses with rash, myalgias, and arthralgias should be considered, including dengue, Zika, malaria, African tick bite fever, leptospirosis, measles, rubella, relapsing fever,

EBV, and meningococcal disease. Noninfectious disorders such as adult-onset Still disease and other rheumatologic disorders should also be considered.

Diagnostic Testing. The diagnosis can be confirmed via enzyme-linked immunosorbent assay (ELISA) testing for antibodies, RT-PCR for detecting viral RNA, or viral culture. Lab abnormalities associated with acute infection include abnormal liver function tests, thrombocytopenia, and lymphopenia.

Management and Disposition. Treatment is mainly supportive. Antipyretics, antiinflammatory agents, and analgesics play an important role in symptom control. IV fluids may be necessary, depending on disease severity. Prevention of disease centers on reducing mosquito exposure. Most patients can be treated at home. Patients that present with severe disease may require admission for IV hydration and observation until they are stable.

VIRAL HEMORRHAGIC FEVERS

Yellow Fever Virus

Yellow fever virus is an arbovirus in the *Flaviviridae* family that can cause a viral hemorrhagic fever. Prior to the discovery of its mosquito vector transmission, there were multiple yellow fever epidemics in Africa, Europe, and the Americas. The vector is the *Aedes* or *Haemagogus* mosquito. Vector control and development of a vaccine have significantly reduced the burden of this disease over the past several decades. Currently yellow fever occurs in tropical regions of Africa and South America.

Clinical Features

The incubation period is between 3 to 6 days. Patients present with an acute febrile illness accompanied by chills, malaise, headache, myalgias, nausea, and dizziness. Patients can have a much lower heart rate than expected in reference to the high fever that is present. This acute febrile phase of the illness can last between 3 to 6 days. Patients then experience a short period of remission, lasting up to 24 hours; some patients recover completely, whereas others go on to have a more severe recurrence of illness with fever, vomiting, jaundice, acute liver injury, acute renal failure, and hemorrhagic manifestations. The hallmark feature of yellow fever is jaundice with hemorrhagic fever. The mortality of patients with hepatorenal involvement ranges from 20 to 50%.

Differential Diagnosis

One must consider other febrile illnesses that occur in these endemic areas, including leptospirosis, relapsing fever, viral hepatitis, malaria, and other viral hemorrhagic fevers, including dengue.

Diagnostic Testing

Laboratory diagnosis is usually made by detecting IgM and neutralizing antibodies in the serum. There are a number of laboratory abnormalities that occur in this illness, including elevated aspartate transaminase (AST), alanine transaminase (ALT), and direct bilirubin. Patients with severe disease also have hematologic labs consistent with disseminated intravascular coagulation (DIC).

Management

There are no specific antiviral treatments for yellow fever. The treatment is supportive. Fluids, antipyretics, and analgesia are the main symptomatic treatments. Given the risk of hemorrhagic fever, aspirin and nonsteroidal antiinflammatory drugs should generally be avoided. If severe disease with shock develops, patients may require IV fluid resuscitation, blood product resuscitation, vasopressors, mechanical ventilation, and renal replacement therapy.

Because there is no specific treatment for yellow fever, much attention has been placed on prevention. Personal protection measures to avoid mosquito bites and vector control at the community level are important in preventing disease. The live-virus vaccine is recommended for individuals 9 months old and older who live in or are traveling to endemic areas. Many countries where yellow fever is endemic require a certificate of vaccination for entry.

Disposition

Depending on the severity of illness, patients can be treated at home or may require admission to the hospital. Severe illness may require ICU admission given the high mortality associated with severe forms of yellow fever.

Ebola

Ebola virus is an RNA virus that belongs to the *Filoviridae* family. Ebola virus disease (EVD) causes severe viral hemorrhagic fever. Ebola was first described in 1976 in Sudan and what is now the Democratic Republic of the Congo (Zaire at that time). Since then, there have been several outbreaks occurring in rural areas in Africa. The 2014 to 2016 Ebola outbreak in West Africa was the most severe in history. It began March 2014 in Guinea and then spread to Sierra Leone and Liberia. Nigeria, Senegal, and Mali have also been affected. At the close of this outbreak, 28,652 cases were identified, and 11,325 lives were claimed.[74] Prior to this outbreak, the largest recorded outbreak had resulted in fewer than 300 deaths. This outbreak also resulted in the first cases of Ebola acquired outside of Africa. A nurse assistant in Spain acquired the disease after caring for an Ebola patient transported from Sierra Leone to Spain. Subsequently, two nurses contracted Ebola in the United States after caring for an Ebola patient who contracted the virus in Liberia.[75]

The mortality rate for Ebola infections ranges from 25% to 90%. Transmission of the virus occurs by direct contact of infected tissue or infected bodily fluids, including blood, saliva, vomit, feces, or semen. Individuals are not contagious until they show symptoms. The usual incubation time is 5 to 7 days but can range from 2 to 21 days.

Clinical Features

The initial symptoms include high fever, headache, myalgias, malaise, sore throat, and profuse vomiting and diarrhea. After 5 to 7 days, patients can progress to develop the hemorrhagic manifestations, which include spontaneous bleeding, ecchymosis, and petechia. It is also common for patients to not develop any hemorrhagic complications.[76] An erythematous maculopapular rash can occur during that time that eventually desquamates. Patients can become hypovolemic and develop severe metabolic derangements secondary to fluid losses via the gastrointestinal tract. Eventually patients advance to shock and multiorgan failure.

Differential Diagnosis

The symptoms of Ebola are initially nonspecific and overlap with other diseases. Other more common infections from the endemic regions include malaria, typhoid fever, other viral hemorrhagic fevers (i.e., Marburg, bunyaviruses), meningococcemia, leptospirosis, or other bacterial illnesses.

Diagnostic Testing

Testing should only be conducted for patients that meet clinical criteria of having exposure history *and* signs or symptoms of EVD. The hospital should also have a protocol for handling lab specimens of potential EVD patients. The risk of acquiring EVD through lab testing is low but not zero. RT-PCR assay using a plasma specimen is currently the main

method of Ebola diagnosis. A rapid antigen point-of-care test with a turnaround time of 15 minutes has been developed with good sensitivity and specificity as compared to RT-PCR.[77] Laboratory findings that can accompany Ebola infection include thrombocytopenia, anemia, coagulopathy, transaminitis, elevated creatinine, hypocalcemia, and hypokalemia. All patients should have testing for malaria performed with thin and thick smear of the blood. Malaria is much more likely than Ebola in the endemic population and returned travelers. Coinfection is also common; in one study of Ebola patients in Guinea, 11% of the patients had concomitant malaria infection.[76]

Management

When managing a suspected EVD case, the important guiding principles are to treat the patient and prevent the spread of the infection. The CDC has developed practical algorithms for evaluating suspected EVD cases in United States EDs (www.cdc.gov/vhf/ebola/pdf/ed-algorithm-management-patients-possible-ebola.pdf). The basic tenets are to identify, isolate, and inform.

The main therapy for Ebola victims is supportive care. Patients are empirically managed with malaria treatment, broad-spectrum antibiotics, and antipyretics. They also require rehydration therapy, preferably with IV fluid and electrolyte repletion. Additionally, many EVD patients require support for organ failure, including renal replacement therapy, mechanical ventilation, vasopressors, or blood product administration.

Currently there are no clinically proven medical therapies against EVD. A number of therapies have been investigated, including monoclonal antibodies against Ebola viral antigens, convalescent plasma, and nucleotide analogue antiviral drugs. Unfortunately, many of these therapies have not shown clinical efficacy in studies.[78,79] The most promising therapies to date are a single monoclonal antibody, MAb114, and a triple monoclonal antibody, REGN-EB3.[80] Although specific therapies against Ebola are currently limited, a landmark breakthrough for the public health response was reached in 2019 when the FDA approved the first vaccine for prevention of EVD.[81]

Disposition

It is paramount that providers caring for potential EVD patients be familiar with proper isolation practices. The CDC stresses that health care providers should receive extensive training and demonstrate competency in Ebola-related infection control procedures, specifically in putting on and removing the PPE. Many hospitals have developed internal guidelines, but the CDC website is a useful resource and gives comprehensive guidance regarding how to deal with potential EVD patients in the United States health care setting (www.cdc.gov/vhf/ebola/healthcare-us/index.html).

The CDC has also developed a strategy to help hospitals prepare for suspected EVD cases (www.cdc.gov/vhf/ebola/pdf/preparing-hospitals-ebola.pdf). There is a tiered system categorized by frontline health care facilities, Ebola assessment hospitals, and then Ebola treatment centers. All hospitals should have and follow infection control protocols, ensure that staff is trained and competent in safe PPE practices, and have a system to manage waste disposal, cleaning, and disinfection. Patients with suspected EVD are admitted to hospital isolation rooms, and many of them will need ICU care. The mortality of EBV is high, but patients are likely to have much better outcomes than previously reported with access to medical facilities with ICUs. Of note, the Ebola patients treated in Europe and the United States had a mortality rate of 18.5%, much lower than reported in endemic regions.[82]

Marburg

Marburg virus is an RNA virus that belongs to the *Filoviridae* family. It is an important cause of viral hemorrhagic fever in central Africa. Marburg cases have occurred in Uganda, Zimbabwe, the Democratic Republic of the Congo, Kenya, and Angola. Cases have been reported outside Africa, including Germany, the former Yugoslavia, Netherlands, and the United States, all with confirmed exposure to an African source. The virus was described first in 1967 after an outbreak occurred in Marburg, Germany, when laboratory personnel working with African Green monkeys developed fever and hemorrhagic shock. Direct transmission occurs with contact with blood, secretions, or solid organs of infected individuals. It is currently thought that the natural host of the Marburg virus is the African fruit bat. The incubation period is 3 to 9 days. The disease carries a similar fatality rate to Ebola, with case fatality rate ranging from 24% to 88%.

Clinical Features

Marburg and Ebola virus cause a very similar clinical syndrome. Marburg virus illness initially causes fever, headache, malaise, and myalgias. After the third to fifth day, severe abdominal pain, cramping, vomiting, and diarrhea occurs. Around the same time, a maculopapular rash may develop. Half of the patients will also develop hemorrhagic manifestations during this time. Hematemesis, diarrhea, oropharyngeal bleeding, and bleeding from venipuncture sites can all occur. Death usually occurs because of acute blood loss and septic shock.

Differential Diagnosis

The differential diagnosis of Marburg infection is very similar to that of Ebola infection in that the symptoms are initially nonspecific and overlap with other diseases. Other more common infections from the endemic regions include malaria, typhoid fever, other viral hemorrhagic fevers (i.e., Marburg, bunyaviruses), meningococcemia, leptospirosis, or other bacterial illnesses.

Diagnostic Testing

Diagnosis requires laboratory testing, because the clinical features overlap with many other viral hemorrhagic fevers. Diagnosis can be made via RT-PCR, ELISA, antigen detection tests, serum neutralization tests, and viral culture.

Management

The priorities of managing a suspected Marburg hemorrhagic fever (MHF) case are similar to a suspected EVD case. Early recognition is key for controlling the spread of this infection. It is important to consider this disease in potential patients by assessing the patient for travel history to countries with endemic MHF or contact with someone who has had MHF within the past 3 weeks and then assessing if symptoms consistent with MHF are present. Patients identified at risk by the screening process should be isolated to a private room with private bathroom. Public health authorities and hospital infection control personnel should be immediately informed. Please refer to the Ebola section of this chapter for further details.

There is no specific treatment for MHF. The treatment is mainly supportive and directed at the patient's symptoms. Patients initially require large fluid volume resuscitation and antipyretics. Patients who develop end-organ failure need advanced therapies, such as vasopressors, mechanical ventilation, and renal replacement therapy. Patients with hemorrhagic manifestations also require blood product resuscitation with packed red blood cells (PRBCs) and fresh frozen plasma.

Disposition

Patients with MHF require hospital admission, and many will require ICU admission. It is important to observe strict isolation practices and ensure that staff use PPE when caring for the patient. When appropriate, patients should be transferred to specialized treatment centers that

are prepared for and designated to care for patients with viral hemorrhagic fevers.

Lassa Fever

Lassa virus is an *Arenavirus* that is endemic to West Africa. Its reservoir is the African rodent *Mastomys natalensis.* Humans contract the disease by exposure to urine or feces of *Mastomys natalensis.* Human-to-human transmission can occur via contact with blood or bodily secretions from infected humans. The incubation period is usually around 10 days, but can range from 3 to 21 days. Unlike Ebola and Marburg, the majority of Lassa infections are asymptomatic. The case fatality rate is less than 2%.

Clinical Features

When patients are symptomatic with Lassa fever, symptoms usually begin with gradual onset of fever and malaise. Headache, myalgias, sore throat, cough, chest pain, abdominal pain, nausea, vomiting, and diarrhea can all occur after a few days. Patients can also develop facial edema, pleural effusion, myocarditis, and encephalitis. Less than 20% of symptomatic patients progress to develop hemorrhagic manifestations. Patients that do go on to have full-blown hemorrhagic fever have a much higher mortality rate. Third-trimester pregnancy is associated with more severe disease with higher mortality as well.

Differential Diagnosis

The differential diagnosis is broad and includes that of other viral hemorrhagic fevers.

Diagnostic Testing

Diagnosis on clinical grounds alone is difficult, because Lassa fever shares features with many other diseases. Diagnosis can be made via RT-PCR, ELISA, antigen detection tests, and viral culture.

Management

Ribavirin has been shown to decrease overall mortality. The greatest effect occurs when treatment is initiated early within the first 6 days after fever onset. The remainder of treatment is supportive care with volume resuscitation, antipyretics, and blood product administration if hemorrhagic disease occurs. As with other viral hemorrhagic fevers, organ failure support with mechanical ventilation, vasopressors, and dialysis may also be needed. Although high-quality evidence does not exist, guidelines do recommend ribavirin as postexposure prophylaxis for definitive high-risk exposures.[83] Prevention of Lassa fever at the community level centers on good hygiene and rodent control.

Disposition

Symptomatic patients with Lassa fever require hospital admission. The same principles of the other viral hemorrhagic fevers of prompt recognition, identification, isolation, and informing authorities apply to Lassa fever as well. Please refer to the sections in this chapter on Ebola and Marburg for more details.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 119: QUESTIONS AND ANSWERS

1. In which of the following patients is antiviral treatment not recommended by the CDC for confirmed influenza infection?
   - **a.** 1-year-old male with 24 hours of symptoms
   - **b.** 22-year-old otherwise healthy female with symptoms for 3 days
   - **c.** 65-year-old male with history of asthma, coronary artery disease, and congestive heart failure with 2 days of mild symptoms
   - **d.** 35-year-old male with no significant past medical history with symptoms for 5 days, intubated with severe hypoxemic respiratory failure, admitted to the ICU

Answer: B. The 22-year-old female with no risk factors for influenza-related complications does not require antiviral treatment because her symptoms have been present for 3 days. The CDC recommends treating all patients as early as possible who are hospitalized, have severe illness, or are at risk for influenza-related complications. The greatest efficacy for antiviral treatment is within 48 hours of symptom onset, but admitted patients with severe disease should be treated regardless of symptom onset.

2. A 19-year-old female presents to the ED with fever, altered mental status, and seizures. She is a college student and lives in a dormitory. Her only past medical history is occasional cold sores. She had been in her usual state of health until 2 days ago when she developed fevers up to 38.5°C and headache. Today she became more lethargic and had two generalized seizures prior to ED arrival. What is the next best course of action?
   - **a.** Administer 1000 mg of intravenous acetaminophen, 2 liters of intravenous crystalloid fluids, and admit to the observation unit with the diagnosis of viral syndrome.
   - **b.** Prescribe 1 g valacyclovir twice daily for 10 days and 650 mg acetaminophen every 4 to 6 hours as needed and discharge home.
   - **c.** Administer 2 g intravenous ceftriaxone, 1 g intravenous vancomycin, intravenous acyclovir 10 mg/kg every 8 hours, order CT scan of head, and then perform lumbar puncture.
   - **d.** Order MRI of the brain, administer 1 g phenytoin, and consult neurology.

Answer: C. This patient has HSV encephalitis. Given the high mortality associated with this condition, antiviral therapy should be started as soon as the diagnosis is suspected. There is significant overlap in the clinical presentation of bacterial meningitis and HSV encephalitis, so patients should empirically be treated for both diagnoses while awaiting CSF results. HSV encephalitis cannot be treated as an outpatient and requires 14 to 21 days of treatment with intravenous acyclovir. An MRI may be necessary eventually to look for temporal lobe involvement but is not necessary at the time of ED presentation and can be negative early in the course of disease.

3. A 32-year-old emergency medicine intern crawls into bed after a 24-hour shift in the medical intensive care unit. Her 36-week pregnant spouse and 18-month-old daughter are asleep as she climbs into their bed. She is awakened from a dead sleep 3 hours later when her wife asks, "What is that brown thing on the ceiling?" Using a tennis racket, the bat is successfully encouraged out of the window. The intern calls you and asks if they need to be vaccinated. Your recommendations should include which of the following?
   - **a.** PEP (postexposure prophylaxis) is contraindicated in the pregnant spouse.
   - **b.** The 18-month-old and intern need PEP.
   - **c.** The spouse needs PEP.
   - **d.** They need better screens on their windows.

Answer: B. In spite of little evidence for a bite or scratch, the intern and 18-month-old fulfill requirements for PEP. Per CDC recommendations, based on developmental staging, the 18-month-old girl cannot know whether an exposure may have happened. The intern does not explicitly meet the requirements for PEP because she is not a child, developmentally challenged, or intoxicated but, after a 24-hour shift, she was likely in a state of deep sleep and would not have been aware of her surroundings. Initiating PEP for her should be seriously considered. Although there is no contraindication for PEP during pregnancy, at 36 weeks, her spouse probably was not sleeping well and was certainly more aware of her surroundings than the intern. PEP should be considered for her but, if she is adamant that no bite or scratch occurred, it may be held.

4. An 18-year-old male who arrived from Sierra Leone 2 weeks ago presents with fever, headache, vomiting, and rash. He has a temperature of 39.5°C and erythematous maculopapular rash over his trunk, back, and arms. He appears ill and severely dehydrated. Which of the following is immediately indicated?
   - **a.** Isolation and contact the public health department
   - **b.** Thin and thick smear to check for malaria
   - **c.** Ribavirin
   - **d.** Intravenous acyclovir for 10 days

Answer: A. This is a classic presentation for Ebola virus disease (EVD). The exposure history is important. Patients should be asked if they have lived or travelled to a country with Ebola or had contact with a confirmed EVD patient in the past 21 days. If the answer is yes, then the next task is to assess for any signs or symptoms compatible with Ebola, including fever, headache, weakness, myalgias, vomiting, diarrhea, abdominal pain or hemorrhage. Once a patient has been screened positive as a potential EVD patient, he or she should be immediately isolated and hospital infection control and the health department should be notified at once.

5. Which of the following viruses is not transmitted by a mosquito vector?
   - **a.** Dengue virus
   - **b.** Chikungunya virus
   - **c.** West Nile virus
   - **d.** Lassa fever virus

Answer: D. The reservoir for the Lassa virus is an African rodent, *Mastomys natalensis*. Humans contract the disease by exposure to urine or feces of *Mastomys natalensis*. Human-to-human transmission can occur via contact with blood or bodily secretions from infected humans. The other viruses are all arboviruses transmitted via a mosquito vector.

Coronaviruses

Raghu Seethala and Sukhjit S. Takhar

KEY CONCEPTS

- Coronaviruses infect humans and animals and have the ability for recombination, generating novel viruses.
- Most human coronaviruses cause mild disease. Three coronaviruses, severe acute respiratory syndrome (SARS) associated virus, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have caused severe disease in humans.
- The hallmark presentation of severe disease in coronavirus patients is respiratory failure, usually manifesting as acute respiratory distress syndrome (ARDS).
- Public health measures, including social distancing, wearing face masks, limiting social gatherings, and vaccinations, remain integral to controlling the COVID-19 pandemic.
- The vast majority of children have a benign disease course. However, a small number may develop a severe hyperinflammatory illness called multisystem inflammatory syndrome in children (MIS-C).
- Treatment for COVID-19 is rapidly evolving with the available data. Management of nonsevere illness is largely supportive and can occur at home. Treatment of moderate to severe disease occurs in the hospital and focuses on supporting oxygenation and ventilation. These patients may benefit from antiviral and corticosteroid therapies. At this point, the remainder of therapeutics remain mostly investigational.

FOUNDATIONS

Coronaviruses (CoVs) are pathogens that cause a variety of human and veterinary diseases. Seven members of the coronavirus family infect humans, and three lethal CoVs have crossed species barriers over the last twenty years as the causative agents of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19). Two (SARS-CoV and MERS-CoV) have caused dangerous epidemics. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19, was identified as the causative pathogen in a cluster of unusual pneumonia cases in Wuhan, China, in late 2019, leading to a worldwide pandemic with profound social, economic, and political consequences.[1] As of late December 2020, it has infected over 77 million and killed over 1,700,000 people globally with continued rapid spread.[2] Advances in molecular biology have increased our knowledge of these infections and have contributed to the massive scale-up of testing, development, and distribution of vaccines at an unprecedented pace. At the time of this chapter's writing, several SARS-CoV-2 vaccines are being distributed in a massive worldwide campaign.

Severe acute respiratory syndrome–coronavirus (SARS-CoV), resulting in SARS, is a virulent coronavirus that first appeared in China in November 2002. SARS affected at least 8098 individuals in 29 countries across Asia, Europe, and North and South America. Most of the cases were from China and Hong Kong, with a mortality rate near 10%. As the last reported case of SARS occurred in 2003, SARS will be discussed only briefly in this chapter.

In 2012, another novel coronavirus, *Middle East respiratory syndrome–coronavirus (MERS-CoV),* emerged, causing international concern. The majority of cases have been reported from Saudi Arabia and the United Arab Emirates, but cases have been reported in the United States, Europe, and Asia. All reported cases have been associated with direct or indirect exposure to travel or residence in the following countries: Saudi Arabia, the United Arab Emirates, Qatar, Jordan, Oman, Kuwait, Yemen, Lebanon, and Iran. MERS is still circulating in the animal population in the Middle East, causing intermittent, sporadic cases and community clusters.[3]

Coronaviruses (CoVs) are large and spherical, enveloped positive-sense RNA viruses. The virus has four major structural proteins: membrane protein (M), envelope protein (E), nucleocapsid protein (N), and the spike protein (S) (Fig. 120.1). The spike protein gives the virus its characteristic look, binds with human cells, and is also the target of novel vaccines.

SARS-CoV-2, SARS-CoV, and MERS-CoV typically cause severe disease, whereas the other human coronaviruses (HCoVs)—HKU1, NL63, OC43, and 229E—are associated with mild illness. HCoVs cause about 15% of all colds (Table 120.1).

SARS-CoV-2 is under the genus beta-coronavirus, which includes a diverse group isolated from bats. Natural selection rather than laboratory manipulation is almost certainly the origin of SARS-CoV-2.[4] Potentially, this pathogen arose from genetic reassortment. The sizeable genetic composition, along with the possibility of reassortment, increases the probability of novel coronaviruses emerging.

Transmission

Knowledge of the transmission of SARS-CoV-2 continues to evolve. Person-to-person transmission occurs primarily during close contact with an individual infected with SARS-CoV-2 via respiratory droplets. These respiratory droplets, produced by sneezing, coughing, or even talking, can land on mucous membranes, starting the infective process. Transmission is much less likely to occur through contact with contaminated surfaces. The evidence that SARS-CoV-2 is spreading via aerosols in the community is mixed, and droplet transmission is likely much more important than the aerosol route. Transmission is highly overdispersed—80% of secondary infections arose from 8.9% of index cases.[5] Nasal viral concentration is usually highest in early and presymptomatic disease, and patients are most infectious during this time. Asymptomatic and presymptomatic spread of the virus has contributed to the difficulty in controlling outbreaks; asymptomatic or

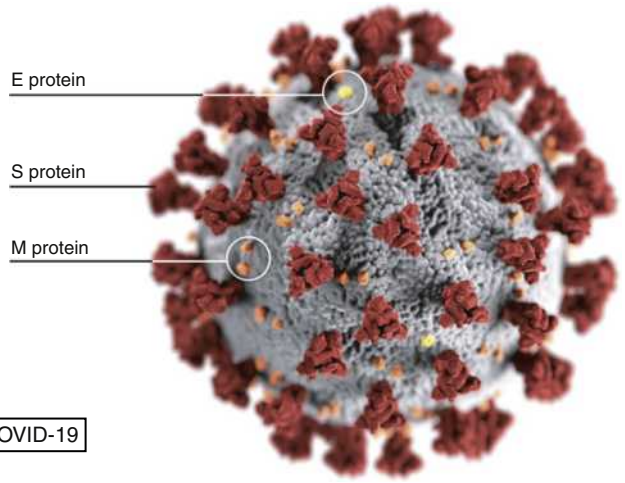

Fig. 120.1 Illustration of morphology exhibited by coronaviruses. Spikes are the S protein. (Courtesy of CDC website: https://phil.cdc.gov/Details.aspx?pid=23313.)

TABLE 120.1 Coronaviruses

Virus	Representative Disease	Clinical Features
SARS-CoV	SARS	Fevers, malaise, myalgias, chills, rigors, cough, dyspnea, tachypnea, pleuritic pain, ARDS
MERS-CoV	MERS	Fever, cough, dyspnea, sore throat, myalgias, GI symptoms, ARDS
SARS-CoV-2	COVID-19	Cough, fevers, chills, dyspnea, headaches, myalgias, diarrhea, nausea, anosmia, ageusia, ARDS
NL63, OC43, HKU1,229E	"Common cold"	Sore throat, rhinorrhea, nasal congestion, cough

presymptomatic individuals may cause as many as 50% of cases.[6-8] The duration of infectious viral shedding is unclear. Prolonged detection of viral RNA by PCR has been observed but does not necessarily mean that patients are infectious.[5] Patients are rarely contagious 10 days after symptom onset. However, those who are immune-compromised and those with severe disease can be contagious for much longer.[9] SARS-CoV-2 RNA has been detected in stool, blood, semen, and ocular secretions, but transmission via these routes is unlikely.

In health care settings, respiratory (either droplet or airborne) and contact precautions are recommended for COVID-19 patient contacts, with surgical or N95 mask, eye protection, gown, and gloves. Aerosolization can occur during certain procedures such as intubation or noninvasive ventilation. An N95 mask, powered air-purifying respirator (PAPR), or equivalent respirator, is recommended for aerosolizing procedures.

Emergency departments should screen patients with symptoms suggestive of COVID-19 so appropriate precautions can be quickly initiated. Because of the risk of asymptomatic spread during the pandemic, all persons entering medical facilities (both patients and visitors) should be masked. Persons in waiting areas and lines should be situated to maintain an adequate distance of 2 meters or more from each other. Health care workers should also be masked in the workplace to decrease the risk of asymptomatic spread to co-workers during the pandemic. In most health care settings, severe restrictions have been placed on patient visitors and accompanying family members.

MERS virus has a high mortality rate and shares many features with SARS-CoV. The mode of transmission has not been elucidated fully, but the most likely route is via direct droplet transmission. There have been case reports of transmission in the health care setting via a less than 10-minute encounter, maintaining 3 feet distance, but without any personal protective equipment (PPE). On the other hand, investigations have also revealed minimal transmission among close contacts at home, indicating that the viral load is higher in those who are more ill and in the hospital. In MERS and SARS, patients become more infectious as the illness progresses through the initial phase as viral replication increases. This contrasts with the early replication and infectivity of SARS-CoV-2, which makes the eradication of COVID-19 much more difficult.

CLINICAL FEATURES

Coronavirus Disease 2019

The incubation period for SARS-CoV-2 is up to 14 days from the time of exposure with a median of 4 to 5 days.[10] Patients present with a spectrum of illness, from minimally symptomatic, to a nonspecific influenza-like illness, with some developing a severe form requiring mechanical ventilation. Initial reports from China show 81% of individuals had mild or moderate disease, 14% had severe disease, and 5% were critical.[11] The most common presenting symptoms for patients who require medical care are cough, fevers or chills, and shortness of breath. Headaches, myalgias, diarrhea, and nausea also commonly occur. Anosmia and ageusia are also often reported.

Patients often worsen as the illness progresses, with a median time to dyspnea of 5 days after initial symptoms and acute respiratory distress syndrome (ARDS) occurring a few days after this.[12] Severe disease can occur in anyone, with the highest risk of fatal outcomes in people aged 65 years or older and those living in a nursing home or long-term care facility. Others at higher risk include those with comorbid conditions such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease, cancers, renal disease, and obesity.[12] The COVID-19 pandemic has highlighted the disparities along several social determinants of health, including race, ethnicity, and socioeconomic status. Thrombotic complications are described in COVID-19 patients, leading to acute kidney injury, stroke, deep vein thrombosis, and pulmonary embolism.

Multisystem Inflammatory Syndrome in Children

Most children with COVID-19 infection have mild symptoms. Clinicians in the United Kingdom reported previously healthy children who presented with cardiovascular shock, fever, and hyper inflammation, which was later called multisystem inflammatory syndrome in children (MIS-C) (Box 120.1).[13] MIS-C has been reported to occur weeks after initial COVID-19 infection. MIS-C is also frequently associated with some degree of cardiac dysfunction. Cases of multisystem inflammatory syndromes have been reported in adults as well (MIS-A).[14] Features of MIS-C and MIS-A include cardiac dysfunction, abdominal pain, significantly elevated inflammatory markers, including C-reactive protein (CRP), D-dimer, ferritin, and interleukin-6. MIS-A is distinguished from severe COVID-19 by having minimal respiratory symptoms, hypoxemia, or radiographic abnormalities.

Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome

SARS and MERS both initially cause high fevers, malaise, myalgias, chills, and rigors. As with COVID-19, initial symptoms can be followed by cough, shortness of breath, tachypnea, and pleuritic pain. The reported incubation time for MERS-CoV is between 2 to 14 days, with a median incubation of 7 days.[3] MERS can rapidly deteriorate to acute respiratory

failure. Close to half of the patients evaluated in the hospital setting will require ICU admission. Similar to COVID-19, age, diabetes mellitus, and other chronic health problems are risk factors for poor prognosis.

Sore throat and fever were less commonly manifested in SARS, and diarrhea can occur later in the course of the disease. About one-third of patients will have improvement in symptoms after the initial febrile illness. Approximately 20% to 30% go on to require mechanical ventilation secondary to hypoxemia. Severe respiratory failure, sepsis, and multiorgan failure are the common causes of death in these patients. Risk factors for mortality include age older than 60 years old, the presence of diabetes mellitus, and heart disease.

DIFFERENTIAL DIAGNOSES

The less severe, more common coronaviruses have similar presentations to the other benign upper respiratory tract infections like rhinovirus, adenovirus, parainfluenza, and other viral causes of upper respiratory infection (URI). For SARS, MERS, and COVID-19, other diagnoses to consider include bacterial pneumonia, influenza, other viral pneumonias, or other causes of ARDS.

DIAGNOSTIC TESTING

Coronavirus Disease 2019

The most common test for the diagnosis of COVID-19 is the reverse transcriptase-polymerase chain reaction (RT-PCR) test of nasopharyngeal (NP), mid-turbinate, or anterior nasal swabs.[15] The true sensitivity and specificity of available tests is difficult to establish in the absence of an established gold standard. Testing of induced sputum samples may be more sensitive than NP swab, but collection carries risk of aerosolization.[16] RT-PCR tests can remain positive for weeks after infection but may not indicate an ongoing risk of transmission as it can detect noninfectious viral RNA fragments. Semi-quantitative methods in RT-PCR, which can identify the cycle threshold (CT), may prove useful in identifying who may be contagious, those with a low CT count being infectious. Antigen testing may be an alternative—though being less sensitive, it may be adequate in those who are contagious. Additionally, newer technology such as CRISPR may allow for widespread and cheaper testing.[17]

Serologic testing with IgM and IgG enzyme-linked immunosorbent assay (ELISA) can help determine community prevalence. (Refer to Table 120.2 to compare the various diagnostic tests.) IgM and IgG typically become detectable several days to a few weeks after symptom onset and are often negative when patients are evaluated during acute illness. Currently available tests have a range of sensitivity and specificity. There is a risk of a high proportion of false-positive tests when performed on a low-prevalence population. It is not known how long antibody levels remain detectable, and the level of immunity conferred by detectable antibodies is also unknown. The CDC does not recommend any change in personal protective equipment (PPE) use for health care workers who test positive for SARS-CoV-2 antibody.

Laboratory findings of hospitalized individuals commonly include lymphopenia, elevated levels of C-reactive protein, D-dimer, LDH, IL-6, and ferritin. There is a correlation between inflammatory marker elevation and progression to more serious illness, although the strength of associations and individual test thresholds are still being determined. Chest radiographs often show patchy bilateral infiltrates with a peripheral and basilar predominance (Figs. 120.2 and 120.3), and ground-glass opacifications in a peripheral and subpleural distribution are typically found on CT (Fig. 120.4). Lung point-of-care ultrasound has characteristic findings, including B-lines, pleural thickening, pleural irregularities, and focal consolidation (Fig. 120.5). Some early studies have demonstrated the ability of ultrasound in the ED to risk stratify the severity of illness for COVID-19 patients.[18]

Multisystem Inflammatory Syndrome in Children

As mentioned previously, patients with MIS-C have severely elevated inflammatory markers. Diagnostic testing involves measuring the degree of inflammation and assessing the severity of cardiac involvement. If MIS-C is suspected, clinicians should measure C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), and interleukin 6 (IL-6). Troponin, B-type natriuretic peptide (BNP) or NT-proBNP, electrocardiogram, and echocardiogram assess the severity of cardiac involvement.

BOX 120.1 Case Definition of Multisystem Inflammatory Syndrome in Children (MIS-C)

Age less than 21 years
Evidence of infection with SARS-CoV-2
Fever for at least 24 hours
Laboratory evidence of inflammation
Multisystem organ system inflammation or dysfunction
Serious illness requiring hospitalization
No alternative plausible diagnosis

From Centers for Disease Control and Prevention (CDC). MIS, multisystem inflammatory syndrome. "Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C)." 2020. https://www.cdc.gov/mis/mis-c/hcp/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis%2Fhcp%2Findex.html. Accessed Sept 21, 2021.

TABLE 120.2 Diagnostic Testing for SARS-CoV-2

Test Type	Use	Type of Specimen	Comments
Nucleic acid amplification tests (NAATs) (including RT-PCR)	Diagnosis of current infection	Respiratory tract specimens (e.g., nasopharyngeal, oropharyngeal, nasal mid turbinate, anterior nasal, saliva)	Highly sensitive and specific. Often positive for weeks after initial diagnosis
Antigen tests	Diagnosis of current infection	Respiratory tract specimens	Less sensitive than NAAT. Potentially useful to identify those who are contagious.
Serology (antibody testing)	Diagnosis of prior infection	Blood	Potentially useful in the diagnosis of Multisystem inflammatory syndrome in children (MIS-C). Unclear if positive test means they are immune.

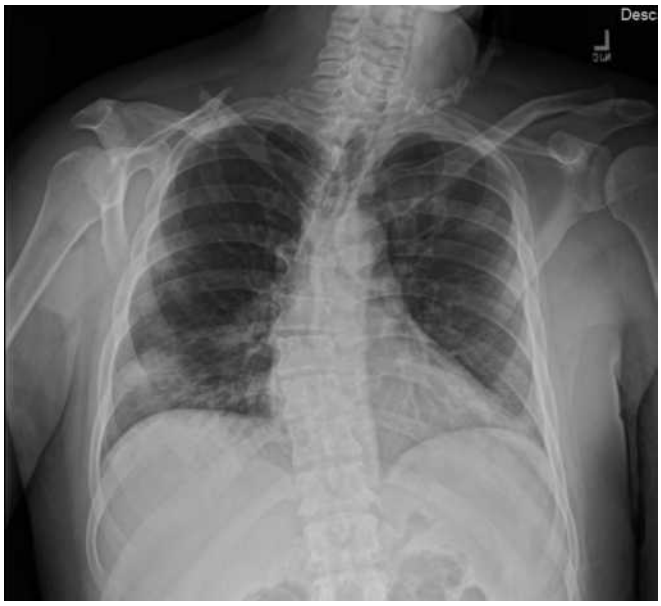

Fig. 120.2 Chest x-ray in mild disease demonstrating multifocal patchy bilateral airspace opacities.

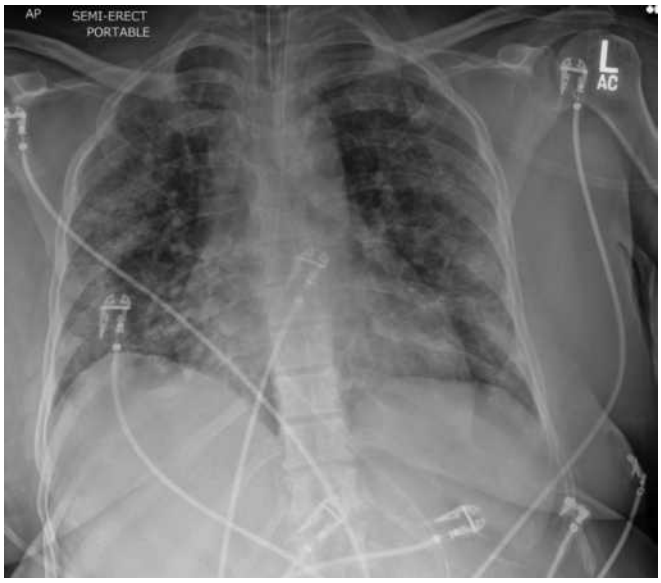

Fig. 120.3 Chest x-ray in severe disease demonstrating ground-glass opacities throughout the lungs, with the more coalescent opacities in the mid and lower zone subpleural regions.

Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome

The diagnosis of MERS can be also be confirmed by RT-PCR from upper or lower respiratory tract samples. MERS patients tend to have leukopenia, lymphocytopenia, and elevated transaminases as well. Over 80% of MERS patients have abnormalities on chest x-ray ranging from subtle findings to extensive bilateral infiltrates. SARS is thought to have been eradicated, but RT-PCR can be used to make the diagnosis.

MANAGEMENT

Coronavirus Disease 2019

Evidence on the management of COVID-19 is evolving, but treatment is largely supportive. The ED management of COVID-19 focuses on early identification, isolation, and risk stratification to decide which patients require further treatment and hospitalization. For patients that do not require hospitalization, management centers on symptom control and is similar to other nonspecific febrile viral illnesses (rest, hydration, antipyretics, and analgesics). The most important therapeutic interventions are supporting oxygenation and ventilation. At the time of this writing, only corticosteroids have been shown to decrease mortality. Some antiviral agents are thought to decrease hospital length of stay, although the data for this finding are mixed.

Oxygenation and Ventilation

Hypoxemia requiring supplemental oxygen or other ventilatory support is the most common reason for hospitalization. Patients should be given supplemental oxygen to target oxygen saturations of 92% to 96% as with other disease processes. There should be stepwise escalation to achieve this goal, starting with 1 to 6 L/min of oxygen via nasal cannula. If this support is not sufficient, oxygen therapy should be escalated to an Oxymizer or venturi mask. Patients with hypoxemic respiratory failure despite these measures should be tried on high-flow nasal cannula (HFNC).

Another therapeutic maneuver that has shown some promise is "awake proning" or "self-proning." This is the action of placing the nonintubated patient in the prone position. Proning increases oxygenation by improving ventilation-perfusion matching and increasing the recruitment of lung. This is typically done in moderate to severe ARDS patients who are intubated, but early on during the pandemic, multiple reports described an improvement in oxygenation with proning nonintubated patients with COVID-19 respiratory failure.[19] However, it is not clear that self-proning prevents the need for intubation.

Intubation and Mechanical Ventilation

Patients with COVID-19 may have rapid progression to respiratory failure, and these patients often meet criteria for ARDS. One study reported that approximately 12% of patients admitted to the hospital for COVID-19 required mechanical ventilation.[20] Intubation is an aerosol-generating procedure that can put the intubating clinician and other staff at increased risk. It is important to approach this procedure with caution. Guiding principles for intubation of a COVID-19 patient include reducing aerosolization of virus particles, maximizing the first attempt success rate, and reducing health care workers' exposure.[21] Intubations should be performed in a closed room, ideally a negative-pressure room, if available. All staff in the room should be protected with an N95 respirator, eye protection, gowns, and gloves. We recommend the use of high-dose neuromuscular blockade, with rocuronium 1.5 mg/kg or succinylcholine 2 mg/kg to reduce the risk of slow-onset or incomplete relaxation.[21] We also recommend videolaryngoscopy as a first-line approach to the airway, to maximize first-pass success and maintain distance between the intubating clinician and the patient.[21]

Because these patients typically meet moderate to severe ARDS criteria, postintubation management is similar to typical ARDS management. We recommend lung-protective ventilation with low tidal volumes (4–6 mL/kg/ideal body weight) targeting plateau pressures less than 30 cm H_2O (see Chapter 2). These patients usually require a moderate amount of PEEP. To tolerate these settings, these patients may need large doses of sedatives and analgesics.

Therapeutics

Medical treatments for COVID-19 are aimed at inhibiting viral replication, mitigating the inflammatory cascade, and augmenting immunity with antibodies to SARS-CoV-2. Patients may have sepsis, and treatment for bacterial pneumonia is also reasonable. Early optimism

about various treatments has typically faded once results from trials have become available; these include lopinavir/ritonavir, hydroxychloroquine, with or without azithromycin, and interferons.[22-24]

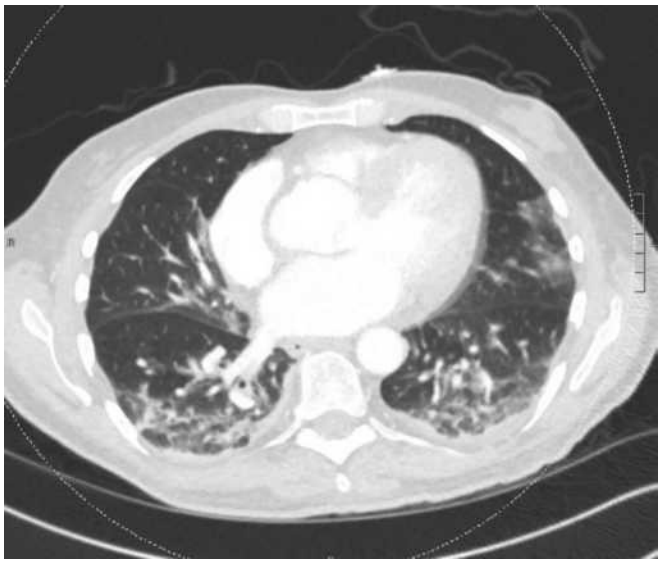

Fig. 120.4 CT scan demonstrating bilateral peripheral and peribronchovascular ground-glass opacities.

Most of the following treatments are primarily given to inpatients and are usually not administered in the ED. Symptoms can be treated with acetaminophen or NSAIDs as needed.

Antivirals. Remdesivir, an adenosine nucleotide analog active against a wide variety of RNA viruses including SARS-CoV-2, shows some promise in early studies and has gained FDA authorization for treatment of SARS-CoV-2. It may be more effective when started early in the course of infection.[25] The dose of remdesivir is 200 mg intravenously on day one and 100 mg a day for an additional 4 days days, depending on severity. The greatest benefits of remdesivir appear to be in hospitalized patients requiring low-flow supplemental oxygen and within 10 days of symptom onset.[25] A shorter course of 3-day remdesivir may be used for patients who are positive, largely symptomatic, but at high risk of developing severe disease. Results of ongoing trials continue to inform the role of remdesivir. However, due to the viral dynamics, we suspect that the benefit of remdesivir in hospitalized patients will be minimal, much like giving oseltamivir in those with later presentations of influenza.

Convalescent Serum and Monoclonal Antibodies. Convalescent serum has been used for over a century for viral infections and even bacterial infections. Studies are underway for pooled and concentrated antibodies specific for COVID-19, and for monoclonal antibodies that target SARS CoV-2. Serum obtained from people who have recovered from COVID-19 appears to be safe but likely will not prove to be effective. A monoclonal antibody targeting the spike protein recently obtained emergency use authorization for treatment of mild

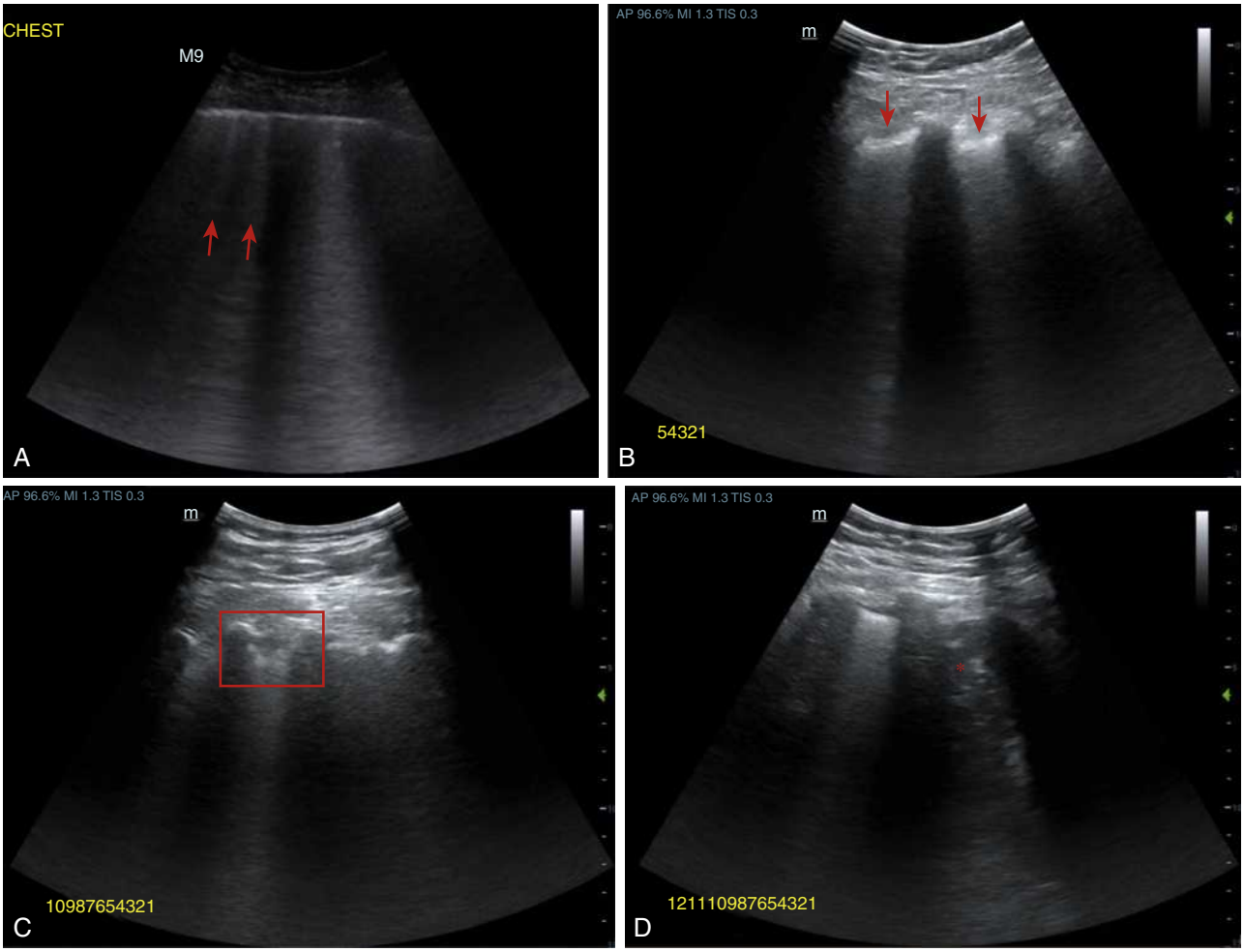

Fig. 120.5 Lung ultrasound demonstrating typical findings in COVID-19. (A) Isolated B-lines (*red arrow*). (B) Confluent B-lines (*red arrow*). (C) Irregular and thickened pleura (*red box*). (D) Subpleural consolidation (*red star*).

to moderate COVID-19.[26] Monoclonal antibodies are being evaluated for those early in their course and emergency departments may be a site where they are infused. We are hoping for a safe, oral medication for COVID-19, but at this time, there are no approved medications. Attempts at treatment with hydroxychloroquine, azithromycin, ivermectin, and zinc showed initial promise in small, uncontrolled studies but were found to be ineffective in more robust investigations.

Immunomodulatory Drugs Including Corticosteroids. Cytokine storm may trigger severe COVID-19 morbidity. Monoclonal antibodies targeting IL-6 and other components of the inflammatory cascade have been attempted as treatments, but preliminary data suggest they are not useful. In June 2020, data from the RECOVERY trial in England suggested that dexamethasone 6 mg daily orally or intravenously for up to 10 days is beneficial in patients with severe COVID-19, defined as those with oxygen saturations of less than 94% on room air and those who require supplemental oxygen, mechanical ventilation, or ECMO.[27-29] These data were the first to show any mortality benefit in treatments for patients hospitalized with COVID-19. Recently, hydrocortisone and other steroids have also been shown to improve mortality in critically ill patients, indicating a class effect.[30,31]

Several IL-6 pathway inhibitors are being studied in patients with severe COVID-19. Trials at this time have not shown a benefit of either tocilizumab, sarilumab, nor siltuximab, contrasting with observational studies.

Anticoagulation. Patients with COVID-19 are at risk for thrombotic complications, and those exhibiting evidence of thrombotic complications should undergo appropriate imaging and occasionally receive empirical anticoagulation. However, studies of empirical anticoagulation for COVID-19 patients without evidence of thrombosis have not shown better outcomes than DVT prophylaxis alone.[32] DVT prophylaxis with low-molecular-weight heparin does not have to be started in the ED, but should be initiated within 48 hours of admission. We do not recommend routine therapeutic anticoagulation in admitted patients without another indication. We also do not recommend anticoagulation in those who are discharged.

Prevention and Vaccination

Over one hundred first-generation COVID-19 vaccines are being developed, and several vaccines have been successfully brought to market, with aggressive roll out campaigns in the United States and Europe in December 2020. However, a SARS-CoV-2 vaccine is unlikely to lead to sterilizing immunity. The virus has a short incubation period and does not have a viremic phase, unlike measles. A variety of vaccine approaches are being used, either via a protein- or gene-based approach. The mRNA and DNA vaccines are not grown in cell cultures or eggs, which consumes time, making them theoretically easier to develop quickly. These genetic platforms have positive results but need to be refrigerated at −80°F.[33] This need for refrigeration presents a challenge to global scalability and a significant barrier to extending availability to low- and middle-income countries.

At this time, public health measures, such as physical distancing, wearing a mask, hand hygiene, and limiting gathering size, remain the most important factors in decreasing transmission. The best measures to control human coronaviruses rely on a strong public health system along with rapid diagnosis and isolating those who are infected.

Multisystem Inflammatory Syndrome in Children

The mainstay of treatment is supportive care and attenuating the inflammatory response. Patients typically require fluid therapy. More severe cases may require vasopressors, inotropes, mechanical ventilation, and in cases of refractory cardiogenic shock, ECMO. Patients are treated with immunomodulatory therapies such as IVIG, glucocorticoids, or interleukin antagonists.

Middle East Respiratory Syndrome

Obtaining an accurate travel history in febrile patients with an unknown respiratory illness, with a negative MERS-CoV-2 PCR, is key to early identification of MERS cases. Nosocomial outbreak was a critical component of the 2003 SARS outbreak as well as MERS outbreaks.

There is no specific antiviral treatment for MERS. The mainstay of treatment is supportive care. For the benign URI, nothing more than rest, antipyretics, and analgesics are needed. However, patients with MERS may require more invasive supportive measures. The diagnosis of MERS will not be immediately apparent, so patients should be treated initially with antibiotics covering community-acquired or health care–associated pneumonia. If mechanical ventilation is required, they should be ventilated with a lung-protective strategy with low tidal volumes to limit additional lung injury.

Prevention of transmission is an essential component of MERS management. This involves early identification of cases and prompt isolation of suspected cases. Obtaining an accurate travel history in all febrile patients with a respiratory illness is key to early identification of MERS cases. CDC guidelines on infection control measures for these infections can be found at www.cdc.gov/sars/infection/index.html and www.cdc.gov/coronavirus/mers/infection-prevention-control.html.

DISPOSITION

Most patients with coronaviruses can be treated at home. Those with moderate to severe COVID-19 will require hospitalization. Patients who have hypoxemia with an oxygen saturation of less than 94% on room air and those requiring oxygen or ventilatory support are classified as severe disease and require hospitalization. Children with suspected MIS-C should be admitted. All patients who are discharged should be counseled on infection control practices and self-isolation. Return precautions should be given. Patients should be counseled to return for dyspnea and confusion. If possible, we recommend providing patients who are discharged with a pulse-oximeter and clear instructions for use and interpretation.

Patients with MERS have a case fatality rate of 35% and will likely require admission to the hospital and ICU, depending on the severity of illness. Patients with suspected MERS should be isolated with contact precautions and airborne isolation, as are those with COVID-19. The hospital infection control team and department of public health should be notified immediately for patients under investigation for MERS.

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CHAPTER 120: QUESTIONS AND ANSWERS

1. Which of the following viruses are not known to be currently circulating in the wild?

a. Middle East respiratory syndrome–related coronavirus (MERS-CoV)
b. Severe acute respiratory syndrome coronavirus (SARS-CoV)
c. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)
d. Measles

Answer: B. The last reported case of SARS was in 2003. There are still sporadic cases of MERS in the Middle East. Currently there is a global pandemic caused by SARS-CoV-2. SARS carried a high mortality and similarities of SARS-CoV-2 to SARS informed some of the original pandemic response to COVID-19.

2. What are classic CXR findings of SARS-CoV-2 (COVID-19)?

a. Patchy, ground-glass opacities
b. Pneumothorax
c. Lobar consolidation
d. Pleural effusion

Answer: A. Ground-glass opacities, particularly in the lower lobes, are the most common findings of COVID-19 on CXR and on CT scans. In fact, early diagnosis of COVID-19 in many areas relied on radiographs because the results of PCR testing were often delayed.

3. Which of the following medications has proven to reduce mortality in those with severe COVID-19?

a. Dexamethasone
b. Hydroxychloroquine
c. Lopinavir/ritonavir
d. Low-molecular-weight heparin

Answer: A. Dexamethasone was the first agent to show a mortality benefit in those who were hospitalized with COVID-19. Hydroxychloroquine and many other medications showed some in vitro activity against the virus, but well controlled studies did not show any benefit.

HIV

Bhakti Hansoti

KEY CONCEPTS

- HIV/AIDS can affect any organ system, and the nonspecific complaints seen with viral illness are common. Consider acute HIV infection in the evaluation of patients with mononucleosis-like syndromes in the presence of risk factors.
- The presenting illness may originate from acute HIV infection, opportunistic infections, medication side effects, inflammation, and immune reconstitution inflammatory syndrome (IRIS).
- Patients with CD4+ count above 500 cells/μL tend to have illnesses similar to those without HIV infection.
- Opportunistic infections are more frequent as the CD4+ count declines but can occur at any stage of HIV infection.
- The patient's immune status should guide formulation of the differential diagnosis, considering the CD4+ count, viral load, current medications, and prior opportunistic infections.
- The current medications used for the treatment of HIV infection (especially ART) can interact with many commonly prescribed drugs.
- The role of the emergency physician has expanded beyond the management of acute HIV-related presentations, but also the facilitation of PreP, PEP, ART initiation, and linkage to care.

FOUNDATIONS

Background and Importance

Acquired immunodeficiency syndrome (AIDS) is a pandemic caused by the human immunodeficiency virus (HIV). HIV has caused tremendous human suffering and has had an immeasurable impact on demographics, cultures, economics, and politics in most societies around the globe. There are an estimated 37.9 million people living with HIV infection worldwide, and approximately 770,000 deaths annually.[1] Significant strides have been made in areas of prevention and treatment. Since 2010 the number of new HIV infections has decreased by 16%, and the number of AIDS-related deaths by 33%.[1,2] Decline in the incidence of new cases of HIV infection and AIDS-related deaths is mostly due to the widespread use of highly active antiretroviral therapy (ART) and the treatment as prevention paradigm, resulting in a decline in the overall HIV incidence worldwide. Recent advances in HIV management have focused on the scale-up of preventative strategies such as preexposure prophylaxis (PreP), universal ART, and even same-day initiation (SDI). However, there is no cure for HIV and significant treatment gaps in at-risk populations have resulted in an increase in global HIV prevalence. Therefore, a significant number of patients in the ED may present with HIV coinfection, as well as ART-related or AIDS-related complications (Figs. 121.1 and 121.2).

Pathophysiology

HIV, a retrovirus from the lentivirus subfamily, is the cause of AIDS. There are two main subtypes of HIV, HIV-1 and HIV-2. Worldwide, the predominant virus is HIV-1. HIV-1 accounts for around 95% of all infections worldwide. HIV-2 is estimated to be more than 55% genetically distinct from HIV-1. The relatively uncommon HIV-2 virus is concentrated in West Africa but has been seen in other countries with links to West Africa. It is less infectious and progresses more slowly than HIV-1, resulting in fewer deaths. HIV-1 can be further divided into four groups; group M is the strain responsible for the global HIV epidemic and can be further divided into nine genetically distinct subtypes. The individual characteristics of each of the subtypes are beyond the scope of emergency medicine, but clinicians should be aware that most ART is largely tested on populations with subtype B, and tests used to diagnose HIV may not be sensitive to all subtypes. This is a concern in places where diverse subtypes are prevalent.

The mature HIV virion is a spherical structure with an outer envelope and inner core (Fig. 121.3). The core contains two copies of the RNA genome, enzymes (reverse transcriptase and integrase), and regulatory proteins. Surrounding the core is the viral membrane, containing the glycoproteins responsible for the attachment and entry of the virus into a CD4+ cell. In a multistep process, the HIV virion invades the host cell and integrates its genetic material into the host's chromosome (Fig. 121.4). The infection begins with the binding of the virus to the CD4+ host cell. The virus enters the cell by fusing its envelope with the target cell membrane. After internalization, reverse transcriptase forms viral DNA from the original RNA. The viral enzyme integrase then transports the newly formed viral DNA into the nucleus, where it integrates with human chromosomal DNA. Viral polyproteins and RNA are formed, and new infectious viral particles are created. This cycle continues with HIV infecting more CD4+ cells. Major targets of ART include reverse transcriptase, protease, integrase, and the CCR5 coreceptor.

The hallmark of HIV infection is CD4+ T cell destruction, leading to a deficient cell-mediated arm of the immune system. Humoral immunity is also impaired through B cell proliferation and the production of abnormal antibodies, making HIV-infected individuals more vulnerable to infections by encapsulated bacteria. HIV infection also leads to chronic immune activation. Ongoing viremia, along with pro-inflammatory cytokines, B cell proliferation, and hypergammaglobulinemia leads to a chronic inflammatory state that contributes to cardiovascular disease, cancer, and other chronic diseases in HIV-infected individuals.[2] Increased immune activation persists, even in patients with immune reconstitution on antiretroviral therapy.

HIV has been isolated from a wide range of body fluids, including semen, vaginal secretions, lymphocytes, cell-free plasma, cerebrospinal fluid (CSF), tears, saliva, urine, and breast milk.[3] However, only semen,

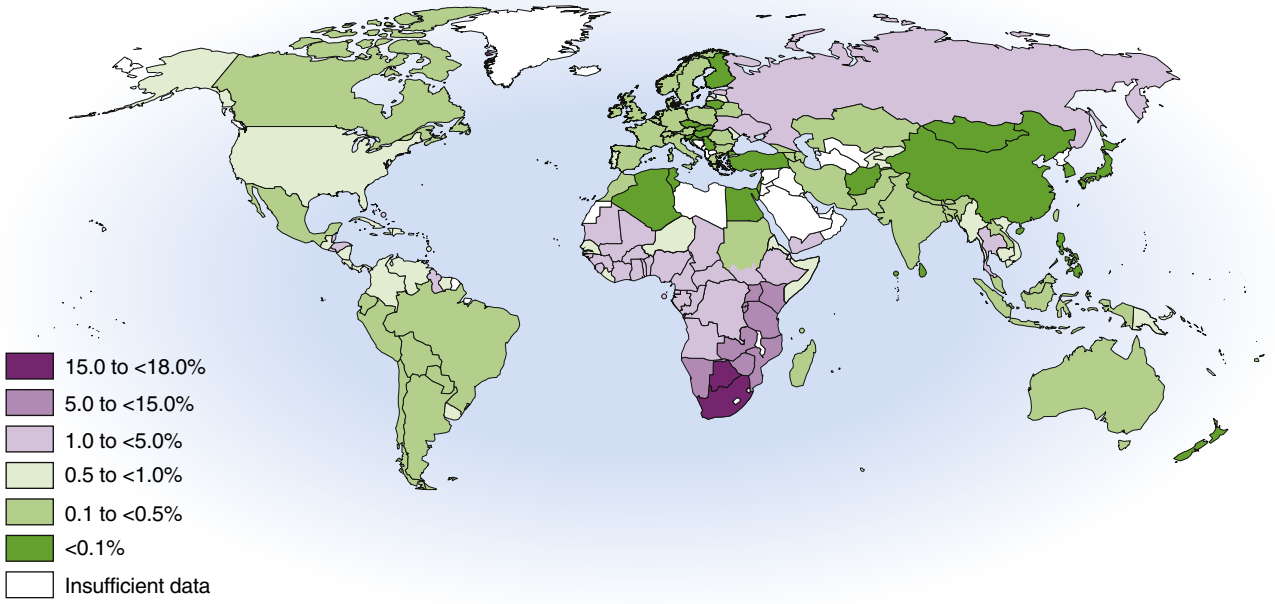

Fig. 121.1 Human immunodeficiency virus prevalence by country. (From Bennett JE, et al, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, ed 8. Philadelphia: Elsevier/Churchill Livingstone; 2015.)

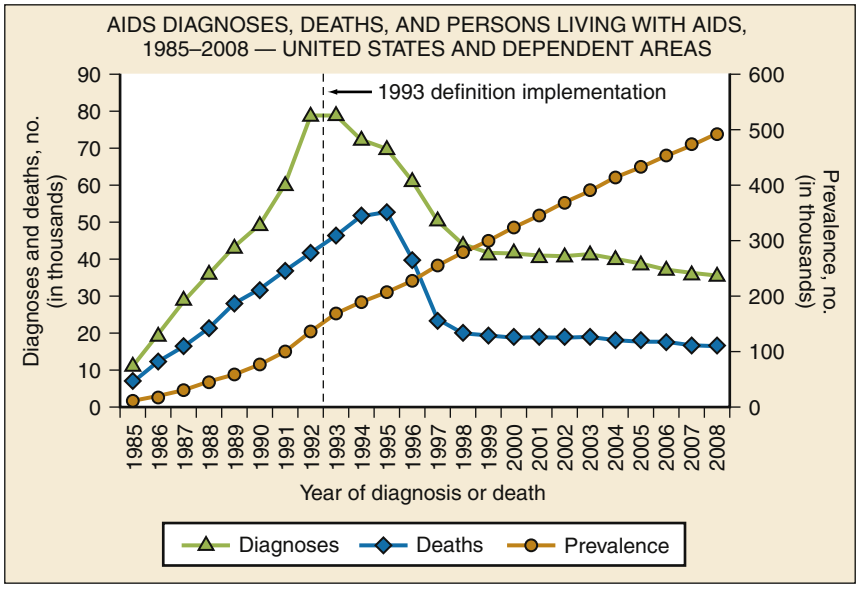

Fig. 121.2 AIDS diagnoses, deaths, and persons living with AIDS—United States. (From: Centers for Disease Control and Prevention. AIDS surveillance—trends [1985–2009]. www.cdc.gov/hiv/topics/surveillance/resources/slides/trends/index.htm.)

blood, vaginal secretions, and breast milk are significantly infectious. For transmission to occur, these fluids must come into contact with damaged tissue or with a mucous membrane or be directly injected into the bloodstream. After transmission, the virus replicates in the mucosal surface or lymphoid tissue at the site of entry in lymphocytes and macrophages. If enough cells are infected, the virus spreads to draining lymph nodes and infection is established, usually within 48 to 72 hours.

Means of transmission of HIV and the demographic distribution of the virus vary from country to country. Unprotected heterosexual intercourse with subsequent transmission of HIV to newborns and breast-fed babies (mother-to-child transmission) is the dominant mode of transmission worldwide, accounting for about 85% of all HIV infections. The main pattern of transmission in the higher-income countries of North America and western and central Europe is in men who have sex with men (MSM) and direct injection into the bloodstream in patients with intravenous drug use (IVDU).

The risk of transmission varies by modality. The average risk of HIV infection after a needlestick or cut exposure to HIV-infected blood is

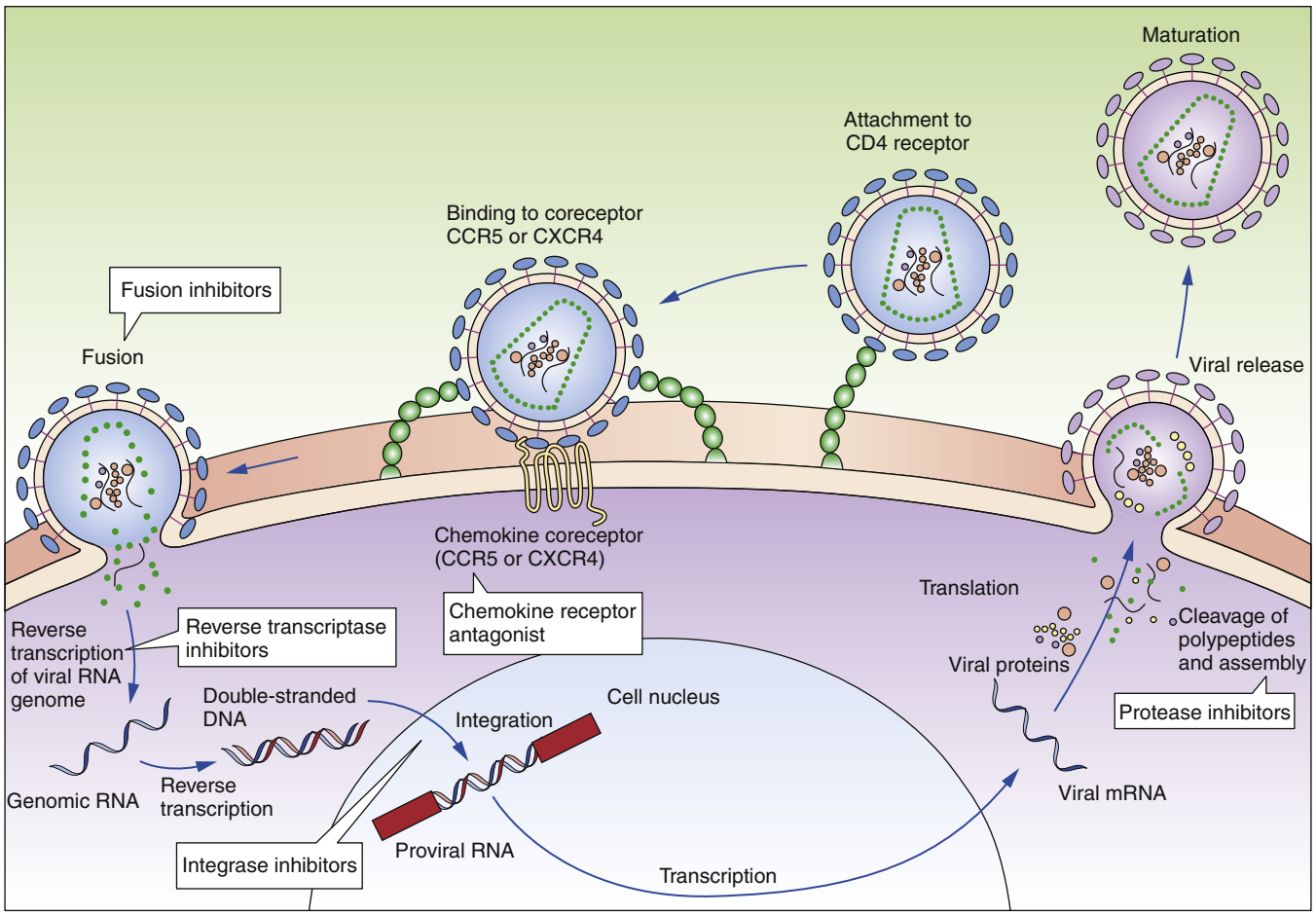

Fig. 121.3 Replicative cycle of the HIV virion. (Adapted from: Maartens G, et al. HIV infection: epidemiology, pathogenesis, treatment, and prevention. *Lancet.* 2014;384:258-271.)

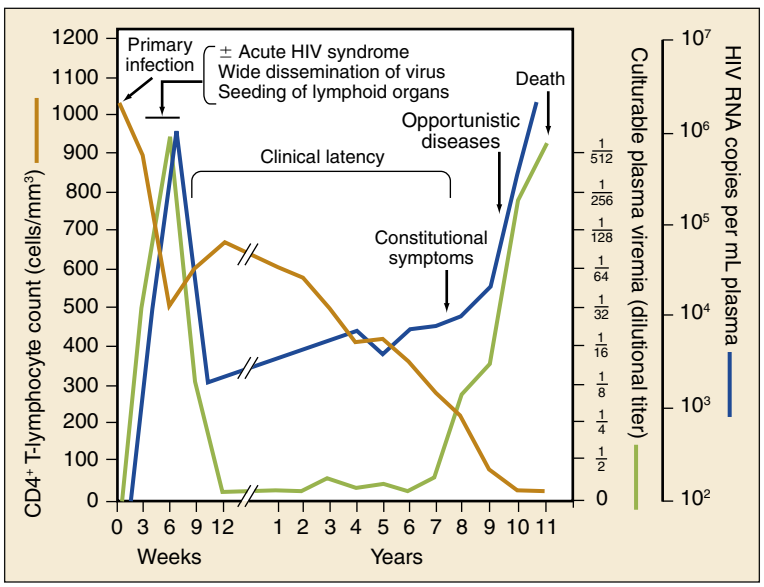

Fig. 121.4 Natural history of HIV infection in the absence of therapy in a hypothetical patient. (Adapted from: Fauci AS, et al. Immunopathogenic mechanisms of HIV infection. *Ann Intern Med.* 1996;124:654-663.)

0.3% while the risk after exposure of the eye, nose, or mouth to HIV-infected blood is estimated to be, on average, 0.1%. For people who inject drugs, the risk of transmission per injection from a contaminated needle has been estimated to be between 0.7% and 0.8%.[3] The risk estimates for the sexual transmission of HIV, per act, vary from 0.5% to 3.38% for receptive anal intercourse; 0.06% to 0.16% for insertive anal intercourse; 0.08% to 0.19% for male-to-female vaginal intercourse; and approximately 0.05% to 0.1% for female-to-male vaginal intercourse. Notably, the risk of HIV transmission is reduced by 99.2% with the combined use of condoms and antiretroviral treatment of the HIV-infected partner.

CLINICAL FEATURES

The clinical manifestations of HIV infection are varied. Patients may present to the emergency department (ED) with acute HIV infection, medication side effects, opportunistic infections, or other AIDS-related illnesses. The natural history of the disease has been altered significantly with the advent of ART. However, there still is no cure. In addition to causing progressive immune dysfunction, chronic HIV infection causes a constant inflammatory state, leading to the development of numerous manifestations that have not been classically thought of as HIV disease. These include malignant neoplasms, coronary artery disease, and neurocognitive disorders. The dramatic immune recovery seen with modern ART can also cause an inflammatory syndrome, immune reconstitution inflammatory syndrome (IRIS). IRIS can result in a paradoxical worsening of any preexisting infections. Overall, the spectrum of HIV infection is changing because of longer life expectancy and better treatment. However, many patients still have undiagnosed HIV infection and can present with acute HIV infection.

Acute HIV Infection

Acute HIV infection, also referred to as primary HIV infection, describes the earliest stage of infection with the HIV virus. Patients present with symptoms consistent with an acute, self-limited viral infection, including fever, fatigue, sore throat, pharyngitis, lymphadenopathy, muscle aches, diarrhea, and a rash. They can occur within a few days of exposure or up to 6 weeks after, and usually last about 14 days. Acute HIV infection can be complicated by encephalitis, Guillain-Barré syndrome, and mononeuritis. $CD4^+$ counts also transiently drop, occasionally to the level at which opportunistic infections can occur. Among others, *Pneumocystis jiroveci* pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV) infection, and thrush may occur in this stage.

During this time, the virus is actively replicating and antibodies to HIV have not been produced. The virus has many potential targets and viral loads are often enormous. The diagnosis of acute HIV infection has significant public health benefits. Patients with acute HIV infection transmit the infection disproportionately; these patients often do not know that they are infected, and their viral load may be in the range of millions of RNA copies per milliliter.

Diagnosis of acute HIV infection requires remembering the constellation of symptoms and understanding the pitfalls of laboratory testing for early infection. The results of routine HIV antibody testing may be negative for several weeks or even months after exposure. The diagnosis of acute HIV infection is confirmed with the presence of high titers of viral RNA and a negative antibody screen. Assay reactivity is dynamic; a plasma RNA test will detect HIV infection approximately one week before the ability to detect the p24 antigen and 12 days before antibodies to HIV develop (Table 121.1). A viral load test in the absence of symptoms of acute HIV infection is not recommended because false-positive results occur, and the test is costly.

Chronic HIV Infection

The second stage of HIV infection is chronic HIV infection (also known as asymptomatic HIV infection or clinical latency). Many patients have few or no clinical manifestations of HIV infection. There are several host and viral factors that are involved and affect the rate of progression. As a result, the asymptomatic period is variable; the average onset to AIDS from seroconversion is approximately 8 to 10 years. People who are taking ARTs may be in this stage for decades. Approximately 5% of patients are long-term nonprogressors (LTNP), sometimes also called elite noncontrollers; they are individuals who do not take ARTs and still maintain CD4 counts in the normal range indefinitely.

AIDS

AIDS is the final and most severe stage of HIV infection. Due to a severely immunocompromised state ($CD4^+$ count <200 cells/μL), the body is unable to fight off opportunistic infections, which for diagnostic purposes are reported as AIDS-defining conditions (Box 121.1). The types and frequency of opportunistic infections are more severe as the $CD4^+$ count continues to deteriorate. Some infections are so common in patients with AIDS that primary prophylaxis is indicated and is cost-effective.[4] Prophylaxis is started for PCP when $CD4^+$ counts are less than 200 cells/μL, for toxoplasmosis when $CD4^+$ counts are less than 100 cells/μL and, for *Mycobacterium avium* complex (MAC) infection when $CD4^+$ counts are less than 50 cells/μL (Table 121.2).

TABLE 121.1 HIV Testing by Laboratory Stage

	LABORATORY MARKER				
Stage	**RNA**	**p24 Antigen**	**Third-Generation Antibody (EIA)**	**Western Blot**	**HIV Stage**
1	+	–	–	–	Acute HIV infection
2	+++	+	–	–	Acute HIV infection
3	+++	+/–	+	–	Seroconversion
4	+++	+/–	+	Intermediate	Seroconversion
5	++	+/–	+	+	Seroconversion
6	+–+++	+/–	+	+	Chronic HIV infection (all Western blot bands are positive, older antibody tests react)

EIA, Enzyme immunoassay.

Adapted from: Fiebig EW, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS.* 2003;17:1871-1879.

BOX 121.1 AIDS-Defining Conditions

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Lymphoma, Burkitt (or equivalent term)
Kaposi sarcoma
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 mo
Wasting syndrome attributed to HIV

Furthermore, isoniazid preventative therapy is given to all patients with a positive tuberculin skin test (TST) to prevent latent TB.

Clinical Manifestations by Organ System

Manifestations of HIV infection vary greatly, depending on the patient's immune status and whether the patient is receiving ART. Some of the clinical manifestations are secondary to severe immunocompromise state and secondary opportunistic infections, and others are due to the proinflammatory pathology of the disease process.

Cardiac Manifestations

Patients with advanced HIV infection can have a constellation of cardiac manifestations, including pericarditis, myocarditis, cardiomyopathy, pulmonary vascular disease, pulmonary hypertension, valvular disease, and neoplastic involvement of the heart. Purulent pericarditis and cardiac tamponade are potentially lethal clinical manifestations of cardiovascular disease in patients with AIDS; *Mycobacterium tuberculosis* is often the causative organism, especially in low-resource countries.

The success of ART has led to prolonged survival in patients with HIV. Cardiovascular disease is now the major cause of morbidity and mortality. HIV-infected patients have a 50% increased risk of acute coronary syndrome compared to the general population, after adjustment for risk factors. Patients receiving ART also suffer from a number of metabolic abnormalities (e.g., hyperglycemia, hyperlipidemia, lipodystrophy) and accelerated atherosclerosis, which increases their cardiovascular risk profile. Protease inhibitors, particularly ritonavir in higher doses, are strongly associated with dyslipidemia. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are associated with increases in low-density lipoprotein cholesterol and total cholesterol but also a significant increase in high-density lipoprotein cholesterol. Discontinuing ART has been shown to result in systemic inflammation, coagulation cascade activation, an increase in biomarkers associated with endothelial activation, and increased risk of major

TABLE 121.2 Prophylaxis to Prevent First Episode of Selected Opportunistic Infections

Pathogen	Indication	First-Choice Therapy	Alternative
Pneumocystis jiroveci pneumonia (PCP)	• $CD4^+ < 200$ cells/μL or oropharyngeal candidiasis • $CD4^+ < 14\%$ or history of AIDS-defining illness • $CD4^+ > 200$ cells/μL but <250 cells/μL if monitoring is not possible every 1–3 mo	TMP-SMZ	TMP-SMZ Dapsone Dapsone + pyrimethamine + leucovorin Aerosolized pentamidine Atovaquone Atovaquone + pyrimethamine + leucovorin
Toxoplasma gondii encephalitis	• *Toxoplasma* IgG–positive patients with $CD4^+$ count < 100 cells/μL • Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have *Toxoplasma* serology retested if $CD4^+$ count declines to < 100 cells/μL • Initiate prophylaxis if seroconversion occurs.	TMP-SMZ	TMP-SMZ Dapsone + pyrimethamine + leucovorin Dapsone + pyrimethamine + leucovorin Atovaquone ± pyrimethamine + leucovorin
Disseminated *Mycobacterium avium* complex (MAC) disease	• $CD4^+$ count < 50 cells/μL (after active MAC infection is ruled out)	Azithromycin or Clarithromycin	Rifabutin (adjust dose on basis of ART interactions); rule out active TB before rifabutin is started.

ART, Antiretroviral therapy; *TB,* tuberculosis; *TMP-SMZ,* trimethoprim-sulfamethoxazole.
Adapted from: Kaplan JE, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm.

cardiovascular events. Studies have also shown that the virus alone is associated with dyslipidemia, endothelial damage, inflammation, and hypercoagulability.

Pulmonary Manifestations

Noninfectious and infectious pulmonary diseases are more common in those with HIV infection compared to uninfected individuals. Although the incidence is greatly reduced in the era of ART, pulmonary manifestations of Kaposi sarcoma and non-Hodgkin lymphoma can occur. HIV-infected patients also appear to be at increased risk for lung cancer, emphysema, cryptogenic organizing pneumonia, sarcoidosis, drug hypersensitivity, primary effusion lymphoma, foreign body granulomatosis, and lymphocytic interstitial pneumonitis.

The most frequent respiratory infections in people with HIV infection are upper respiratory tract infections and acute bronchitis. The incidence of lower respiratory tract infections increases as CD4⁺ counts decline. Potential causes of lower respiratory tract infections include viruses (influenza, respiratory syncytial, parainfluenza), bacteria, and fungi (*P. jiroveci*; Table 121.3). Bacterial pneumonia is more frequent in people infected with HIV than in uninfected persons (most commonly caused by *Streptococcus pneumoniae)*. In patients with a CD4⁺ count below 200 cells/μL, the prevalence of pneumocystis pneumonia (PCP) increases. The clinical presentation of PCP is characterized by the gradual onset of fever (79% to 100% of cases), cough (95%), and progressive dyspnea (95%). The cough is nonproductive, although sputum production does not exclude this diagnosis, and patients can be coinfected with bacterial pneumonia. Some patients, especially those taking nonsystemic prophylaxis (e.g., aerosolized pentamidine), may have extrapulmonary manifestations of PCP, such as hepatosplenomegaly, skin lesions, and ocular lesions. The most common associated laboratory abnormalities are a CD4⁺ count below 200 cells/μL and elevated lactate dehydrogenase level. Although chest radiographs can be normal, they usually show diffuse, bilateral, interstitial, or alveolar infiltrates (Fig. 121.5). High-resolution computed tomography (CT) has a high sensitivity for PCP and often reveals ground glass or cystic lesions (Fig. 121.6). The definitive diagnosis is made by isolation of the organism, commonly from respiratory specimens obtained by sputum induction, bronchoalveolar lavage, or endotracheal aspiration. Trimethoprim-sulfamethoxazole (TMP-SMZ) is also the preferred treatment of PCP; the route is dependent on the severity of the disease. There are a number of other possible regimens for those who are intolerant (Table 121.4). Patients with severe (partial pressure of oxygen 70 mm Hg or less or an alveolar-arterial oxygen gradient 35 mm Hg or

TABLE 121.3 Differential Diagnosis of Respiratory Infections in HIV-Infected Patients by CD4⁺ Count

CD4⁺ Count and Stage	Differential Diagnosis
Present at any stage	Acute bronchitis
	Bacterial pneumonia
	Tuberculosis
>500 cells/μL	Bacterial pneumonia[a]
Early HIV infection	PCP[a]
	HHV-8–related Kaposi sarcoma
200–500 cells/μL	Bacterial pneumonia[a]
	PCP[a]
<200 cells/μL	Bacterial pneumonia[a] (consider bacteremia)
AIDS	PCP[a]
	Histoplasma capsulatum or *Coccidioides immitis* pneumonia
	Cryptococcus neoformans pneumonia
	Extrapulmonary or disseminated tuberculosis[a]
≤50 cells/μL	Bacterial pneumonia[a]
Advanced HIV infection	PCP[a]
	Toxoplasma gondii pneumonia
	Pulmonary Kaposi sarcoma
	Histoplasma capsulatum or *Coccidioides immitis* pneumonia
	Mycobacterium avium complex pneumonia

HHV-8, Human herpesvirus 8; *PCP*, *Pneumocystis jiroveci* pneumonia.
[a]Occurs more frequently as immune function declines.

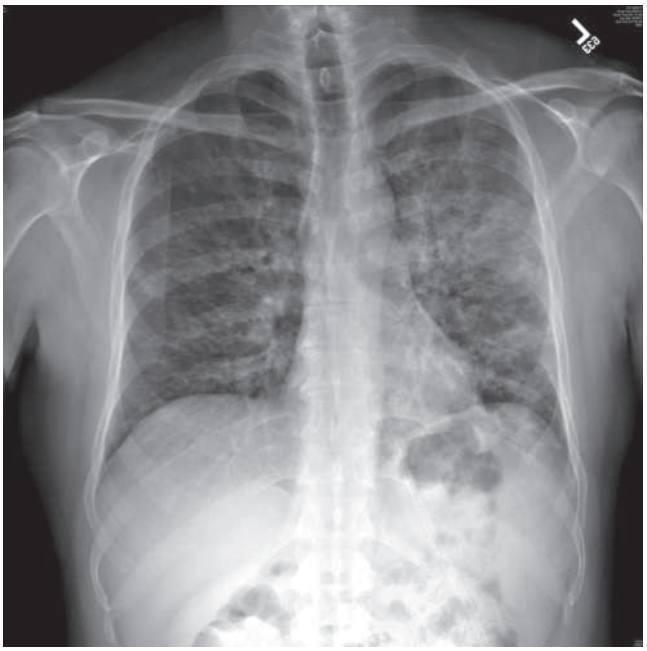

Fig. 121.5 Chest radiograph of *Pneumocystis* pneumonia. (From Mocroft A, et al: Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 362:22–29, 2003.)

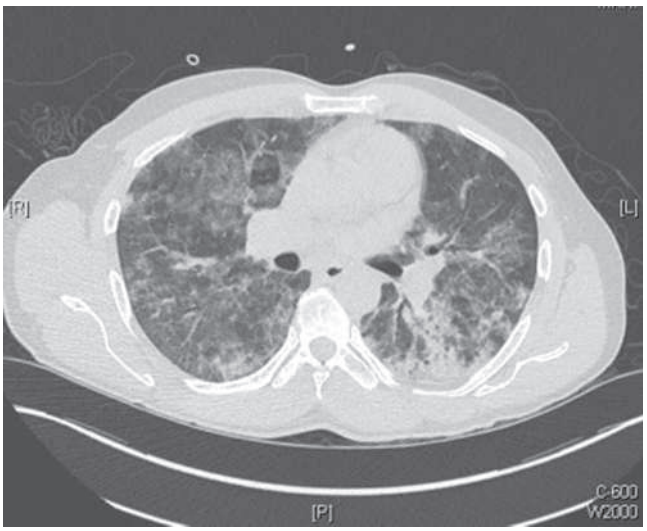

Fig. 121.6 Chest computed tomography scan of *Pneumocystis* pneumonia.

greater) PCP receive significant benefit from concurrent corticosteroid treatment and should receive a 21-day prednisone taper in addition to antibiotic therapy.

Pulmonary TB is so commonly found as a coinfection in HIV-positive patients that patients are recommended to take isoniazid preventative therapy (IPT). Patients with early HIV infection and TB have presentations similar to those of individuals without HIV infection; they often have classic symptoms of pulmonary TB, such as fever, cough, weight loss, malaise, and night sweats, with plain films showing upper lobe cavitations. In patients with advanced disease, atypical radiographic findings are more common, such as pulmonary infiltrates without preference for the upper lung fields. Patients with advanced HIV infection and severe immunosuppression may also present with extrapulmonary and disseminated TB. All patients with a clinical suspicion of TB should be placed in respiratory isolation. In addition to plain films and sputum samples, evaluation of extrapulmonary disease includes specimens of suspected areas of involvement (e.g., CSF, lymph nodes, pleural fluid, pericardial fluid, blood, urine). The treatment of TB in people with HIV infection is complicated, and drug interactions between ART and anti-TB therapy are severe and common. After initiation of anti-TB therapy, the patient requires close monitoring for assessment of adequate treatment response and for observation of signs of IRIS, a complication more common in patients with $CD4^+$ counts below 200 cells/μL.

Diagnostic evaluation of patients with HIV infection who present with respiratory complaints should be based on their HIV disease stage, as well as their clinical presentation (Table 121.5). Specific algorithms are difficult because of geographic differences in epidemiology. The evaluation includes pulse oximetry, chest radiography, and complete blood count. Additional tests may include arterial blood gas analysis to determine the need for corticosteroids in patients with PCP, levels of serum lactate dehydrogenase (elevated in PCP), 1,3-β-D-glucan (elevated in PCP), serum cryptococcal antigen, urine *Histoplasma capsulatum* antigen, and sputum studies (including Gram staining, acid-fast bacillus, and staining for *P. jiroveci*) if available. Blood cultures should be obtained before antibiotic therapy initiation. A thorough search for the pathogen is recommended in patients with HIV infection.

TABLE 121.4 Treatment of *Pneumocystis jiroveci* Pneumonia in Patients with HIV Infection

Severity of Illness	Preferred Therapy	Alternative Therapy
Moderate to severe	TMP-SMZ, IV; switch to oral administration after clinical improvement 21-day therapy	Pentamidine *or* Primaquine + clindamycin
Mild to moderate	TMP-SMZ	Dapsone + trimethoprim *or* Primaquine + clindamycin *or* Atovaquone

TMP-SMZ, Trimethoprim-sulfamethoxazole.

US Department of Health and Human Services. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. www.aidsinfo.nih.gov.

Oropharyngeal and Gastrointestinal Manifestations

HIV-infected patients with GI symptoms may present with common abdominal diseases or may have opportunistic infections, malignant neoplasms, or medication side effects. Patients receiving ART may suffer treatment-related adverse gastrointestinal events, including pancreatitis, hepatic steatosis, lactic acidosis, and drug-induced hepatotoxicity. Furthermore, a number of patients with HIV infection have concomitant hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and may also have GI manifestations from these causes as well. Although improvements have been noted, end-stage liver disease remains a common cause of mortality in HIV-infected patients.

Patients with primary HIV infection often present with thrush (secondary to candida is most often the first manifestation of HIV

TABLE 121.5 Pulmonary Manifestations of Disease in HIV-Infected Patients

Disease	Presentation	Diagnostic Evaluation	Treatment
Bacterial pneumonia	Acute onset (<1 wk) Cough Purulent sputum Fevers, chills, rigors	Elevated white blood cell count Chest radiograph—unilateral focal consolidation $CD4^+$ count variable	Antibiotic therapy targeting *Streptococcus pneumoniae* and *Haemophilus influenzae* Also cover atypical bacterial pathogens
Pneumocystis jiroveci pneumonia (PCP)	Gradual onset (>2 wk) Nonproductive cough Dyspnea Fever	Exercise-induced hypoxia Elevated serum lactate dehydrogenase level Chest radiograph—bilateral reticular or interstitial pattern Computed tomography scan—ground glass opacity (56%) $CD4^+ < 200$ cells/μL	Trimethoprim-sulfamethoxazole for 21 days If $Pao_2 < 70$ mm Hg at room air or alveolar-arterial oxygen gradient > 35 mm Hg, give prednisone; taper over 21 days.
Mycobacterium tuberculosis infection (TB)	Gradual onset (>2 wk) Cough Fever Night sweats Weight loss Lymphadenopathy	Chest radiograph—alveolar pattern (±cavitation), miliary pattern, nodules, adenopathy, effusions $CD4^+$ count variable	Determine antituberculosis therapy with infectious disease consultant. Consider possibility of drug resistance. Multiple drug interactions exist between TB medications and antiretroviral therapy.
Kaposi sarcoma	Gradual onset (>2–4 wk) Cough Dyspnea Fever	Chest radiograph—bilateral perihilar nodules, opacities, effusions, adenopathy $CD4^+ < 200$ cells/μL	Cryotherapy, radiation therapy Infrared coagulation Sclerosing agents, intralesional vinblastine Systemic chemotherapy

infection), pharyngitis, and severe aphthous ulcers. Less commonly, oral hairy leukoplakia, caused by Epstein-Barr virus (EBV), is manifested as raised white lesions on the side of the tongue. Unlike in thrush, the lesions cannot be scraped off and are not responsive to topical antifungal agents. Kaposi sarcoma, which can occur in the mouth, is usually found on the palate.

Patients with $CD4^+$ counts below 100 cells/μl are particularly prone to esophagitis, presenting with dysphagia or odynophagia. The most common cause of esophagitis in patients with HIV infection is *Candida*, followed by herpes simplex virus, CMV, and deep aphthous ulcers. Diagnosis can be confirmed by endoscopic biopsy. Given the invasive nature of the testing, most patients are empirically treated by a 5- to 7-day course of fluconazole. However, the decision to start treatment is usually made in conjunction with the patient's infectious disease physician.

Gastroesophageal reflux is another common complaint, and treatment is with antacids. However, atazanavir requires an acidic environment to aid in absorption, and thus close monitoring is required post-treatment initiation.

Abdominal pain, diarrhea, cramping, and fever may be due to bacterial enteritis affecting the small or large bowel; causative organisms include *Clostridium difficile*, *Salmonella, Shigella, Campylobacter,* and *Yersinia* spp. Patients with advanced immunosuppression can have chronic diarrhea, often from opportunistic infections with *Cryptosporidium, Isospora,* and microsporidia. CMV is known to cause large bowel enteritis and generally occurs in severely immunosuppressed hosts with $CD4^+$ counts below 50 cells/μL. In developing countries, extrapulmonary TB should also be on the differential for abdominal disease in HIV-positive patients. The evaluation for diarrhea involves laboratory stool studies (ova and parasite, *C. difficile* toxin, bacterial culture, modified acid-fast staining) and, occasionally, colonoscopy. For patients with mild to moderate symptoms, this can be arranged as an outpatient. For patients with severe cases, dehydration, or electrolyte abnormalities, these should be performed as an inpatient. Treatment is often supportive, maintaining hydration; symptoms often persist until immune reconstitution.

Rarely, malignancies such as Kaposi sarcoma or lymphoma, have been known to result in massive GI bleeding and bowel obstruction. Disseminated opportunistic infections such as MAC and *Bartonella* may cause secondary liver failure. AIDS-related cholangiopathy, biliary obstruction from infection-associated strictures of the biliary tract, is seen with severe immunosuppression.

Central Nervous System Manifestations

Common neurologic complications of HIV infection include aseptic meningitis, cryptococcal meningitis, toxoplasmosis, primary central nervous system (CNS) lymphoma, and progressive multifocal leukoencephalopathy. Patients present with a constellation of findings, including headaches, possible focal neurologic deficits, altered mental status, and fever.

HIV itself is a neurotropic virus, and patients with an acute infection can present with aseptic meningitis with complaints of fever, headaches, and meningismus. There usually is lymphocyte-predominant, moderate pleocytosis in the CSF. *Cryptococcus neoformans* is the most common cause of meningitis in patients with AIDS. It usually affects patients who are profoundly immunosuppressed, with $CD4^+$ counts below 100 cells/μL. The disease is subacute, and patients present with fevers, malaise, and headache. Later in the course, because of increased intracranial pressure, patients experience vomiting and altered mental status. *Cryptococcus* often does not cause a significant inflammatory response, and meningeal signs are frequently absent. A lumbar puncture is diagnostic, demonstrating elevated opening pressures (70% with pressures > 200 mm Hg), presence of cryptococcal antigen (CRAG), and low white blood cell count in the CSF (typically, <50/μL). Serum CRAG testing is readily available, sensitive, and especially useful in resource-poor settings. If the serum CRAG is negative, it will not likely be positive in the CSF and not the cause of cryptococcal meningitis. Poor prognostic factors for cryptococcal meningitis are altered mental status, absence of CSF pleocytosis, CSF antigen titers greater than 1:1024, and a positive serum fungal culture. These signs are indicative of a high organism burden, elevated CSF pressure, and lack of an inflammatory response. If left untreated, cryptococcal meningoencephalitis is fatal. Therapy involves three phases: induction, consolidation, and maintenance. Two weeks of amphotericin B and flucytosine is the recommended initial treatment. Fluconazole is used for the consolidation phase and is continued until immune reconstitution ($CD4^+$ count > 100 cell/μL for more than one year). Elevated intracranial pressure is treated with repeated lumbar punctures; occasionally, a lumbar drain is needed. Cryptococcal meningitis immune reconstitution syndrome, a clinical deterioration in the setting of cryptococcal disease after the reversal of immune deficiency, can cause rapid clinical deterioration. A multicenter randomized trial has shown improved survival when ART is started five weeks after antifungal treatment compared to 1 to 2 weeks in those with risk factors.

Severely immunocompromised hosts ($CD4^+$ count < 200 cells/μL) are likely to have opportunistic infections or AIDS-associated tumors (Table 121.6). In developed countries, common causes of mass effect are toxoplasmosis and EBV-related primary CNS lymphoma; in developing countries, the cause is more likely to be tuberculomas. Toxoplasmosis is caused by reactivation of latent infection by the parasite *Toxoplasma gondii*. Most infected patients have a $CD4^+$ count below 100 cells/μL. Patients present with signs of increased intracranial pressure, such as headaches, confusion, lethargy, and seizures. Lesions are typically multiple and ring-enhancing on CT. Although the definitive diagnosis is made after a brain biopsy, patients who are serologically positive for toxoplasmosis are usually treated empirically with pyrimethamine and sulfadiazine, keeping in mind that toxoplasmosis is much less common in patients who have been receiving TMP-SMZ prophylaxis for PCP. Most patients will show radiographic improvement in 2 weeks; response to treatment obviates the need for a brain biopsy (Fig. 121.7).

Primary CNS lymphoma often looks identical to toxoplasmosis on magnetic resonance imaging (MRI) or CT scans. It also occurs with profound immunosuppression ($CD4^+$ count < 50 cells/μL). EBV is the cause of primary CNS lymphoma, and a polymerase chain reaction (PCR) analysis of the CSF, looking for the virus, has become an integral step in the evaluation of mass lesions. Treatment involves ART and chemotherapy.

Progressive multifocal leukoencephalopathy, caused by the JC virus, is characterized by demyelinating lesions in the CNS. The diagnosis is suggested by nonenhancing, hypodense lesions on CT or MRI, with a CSF PCR assay positive for the JC virus. Advanced imaging with positron emission tomography, MRI, and single-photon emission CT can help differentiate among toxoplasmosis, lymphoma, and progressive multifocal leukoencephalopathy.

The gold standard for the diagnosis of CNS mass lesions remains brain biopsy. Corticosteroid therapy can cause false-negative results on brain biopsies in patients with lymphoma, and therefore the use of corticosteroids should be limited to patients with life-threatening mass lesions.

Renal Manifestations

The two main categories of HIV-related kidney disease are HIV-associated nephropathy (HIVAN) and HIV immune complex kidney

TABLE 121.6 Differential of Focal Central Nervous System Lesions in Patients With HIV Infection

	Common Clinical Presentation	Imaging and Diagnostic Testing
Toxoplasma encephalitis	Fever Headache Altered mental status Focal neurologic findings Seizure Evolves during days to weeks	Ring enhancing (≈90% of the time) CNS lesions Frequent edema and mass effect Toxoplasma antibodies (reflects past exposure) CD4+ often <100 cells/μL PCR detection of *Toxoplasma gondii*
Primary CNS lymphoma (PCNSL)	Confusion Lethargy Memory loss Hemiparesis Aphasia Seizure Fever Night sweats Weight loss Evolves during months	CNS lesion or lesions (may have mass effect) Solitary lesions are often large (>4 cm) Some ring enhancement may occur but less regular PCR assay for Epstein-Barr virus (associated with PCNSL)
Progressive multifocal leukoencephalopathy (PML)	Progressive focal neurologic deficits (during months) Hemiparesis Visual field defects Ataxia Aphasia Cognitive impairment	Multifocal areas of demyelination primarily involving white matter Less frequent mass effect or ring-enhancing PCR assay for DNA of JC virus (causes PML)
HIV encephalopathy	Memory and psychomotor speed impairment Depressive symptoms Movement disorders	Multiple hyperintense signals in T2-weighted images Often symmetrical; not well demarcated
Cytomegalovirus encephalitis	Delirium Confusion Focal neurologic abnormalities	Magnetic resonance imaging shows multifocal scattered micronodules and ventriculoencephalitis. $CD4^+ < 50$ cells/μL
Brain abscess	Focal neurologic deficit Headache Bacteremia or craniofacial infection	Often concomitant evidence of disseminated infection
Tuberculoma	Focal neurologic deficit Headache Tuberculosis infection	Single or multiple mass lesions Can be manifested as focal lesion or meningeal infection

CNS, Central nervous system; *PCR,* polymerase chain reaction.

disease. HIVAN is a form of focal glomerulosclerosis that usually occurs in untreated individuals of African descent. Proteinuria, often severe, and an elevated creatinine concentration occur. Some patients recover renal function with ART, but many progress to end-stage renal disease and require dialysis. Transplantation is now widely accepted for patients with stable HIV infection.

ART can also affect the kidney. Indinavir, although less commonly used in industrialized countries, is associated with renal calculi. Tenofovir can cause acute renal failure, a Fanconi-like syndrome, and nephrogenic diabetes insipidus. Medications used to treat opportunistic infections can cause acute renal failure; amphotericin, pentamidine, and foscarnet are especially notorious.

Rheumatologic and Orthopedic Manifestations

HIV-infected patients are susceptible to the same types of orthopedic injuries and musculoskeletal disorders as patients without HIV infection. However, a few conditions specific to HIV infection are worth mentioning. Disseminated TB is more common in HIV-infected patients and can present with septic arthritis, spondylitis, osteomyelitis, and bursitis. Risk factors include injection drug use and hemophilia. The most common causative organism involved is *Staphylococcus aureus*. Disseminated gonococcus causing septic arthritis is another possibility, especially in sexually active individuals. In late-stage AIDS, bacillary angiomatosis secondary to *Bartonella henselae* and *Bartonella quintana* can cause disseminated disease affecting the skin, lymph nodes, liver, and CNS and can also cause long-bone osteomyelitis.

Fractures of the hip, spine, and wrist are more common in HIV-infected individuals because they have lower bone mineral density than that of age-matched controls. Osteonecrosis, especially of the femoral head, is common. Predisposing factors include corticosteroid use, ethanol abuse, and hypertriglyceridemia.

HIV-related polymyositis can occur at any stage of infection. These patients may have proximal muscle weakness, myalgias, and fatigue. Medications, especially nucleotide reverse transcriptase inhibitors (NRTIs), such as azidothymidine (AZT), can be toxic to the mitochondria and are common causes of polymyositis. Myopathies, spondylarthritis, pyomyositis, and HIV-associated arthritis are also common musculoskeletal problems. Reactive arthritis and other seronegative

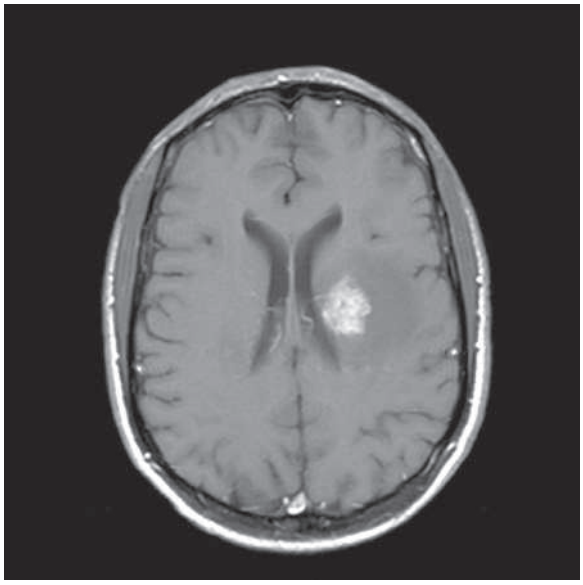

Fig. 121.7 Brain magnetic resonance image of a 38-year-old man with AIDS and *Toxoplasma* encephalitis. (From: Mandell GL, et al, ed. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, ed 7. Philadelphia: Elsevier/Churchill Livingstone; 2010.)

arthropathies are common, although it is unclear if these are because of sexual activity, generalized immune suppression, or the inflammatory response from the virus itself.

Hematologic Manifestations

HIV infection is known to cause anemia, thrombocytopenia, and leukopenia. While anemia and leukopenia occur in later stages of HIV infection, thrombocytopenia can occur at any stage. Anemia and leukopenia are often secondary to medication-associated (AZT, TMP-SMZ, and ganciclovir) bone marrow toxicity. Thrombocytopenia is often immune-related, presenting as a disease process similar to idiopathic thrombocytopenic purpura; the treatment is ART. Thrombotic thrombocytopenic purpura is also well described in HIV-infected patients and tends to occur at later stages of the disease. Lastly, systemic fungal infections and mycobacterial disease such as disseminated MAC disease can infect the bone marrow and decrease all three cell lines, as can nutritional deficiencies, such as folate and vitamin B_{12}, which are also common.

AIDS-related lymphoma (Hodgkin and non-Hodgkin) occurs more frequently in patients with advanced HIV infection. Most non-Hodgkin's lymphomas are of B cell origin and tend to be more aggressive in HIV-infected than in noninfected patients. CNS lymphomas and Burkitt's lymphoma are almost always associated with EBV, and primary effusion lymphoma is associated with human herpesvirus 8. The treatment involves standard chemotherapy and ART.

Cutaneous Manifestations

Dermatologic manifestations of HIV infection are extremely common, occurring throughout the course of HIV infection. Some skin findings are manifested early in the disease; others, found later, can be suggestive of profound immunosuppression (Box 121.2). Skin problems increase as HIV infection progresses. Recognition of HIV-related dermatologic conditions can lead to early diagnosis and can help the emergency clinician gauge the patient's immune status (Box 121.3).

Acute HIV infection often is manifested with a generalized maculopapular or morbilliform rash shortly after the onset of fevers. Oral ulcers, lesions on the palms and soles, and mucosal lesions can all be present. Aside from HIV itself, a variety of viruses can involve the skin.

BOX 121.2 Dermatologic and Mucocutaneous Manifestations of WHO Stage 4 HIV Disease

Chronic herpes simplex virus ulcers
Extrapulmonary tuberculosis
Kaposi sarcoma
Extrapulmonary cryptococcosis
Disseminated mycosis
Atypical disseminated leishmaniasis
Disseminated nontuberculous mycobacterial infection
Extrapulmonary cryptococcosis including meningitis

WHO, World Health Organization.

BOX 121.3 Cutaneous Findings Highly Suggestive of HIV Disease

Any WHO criteria for stage 4 HIV disease
Facial molluscum in an adult
Proximal subungual onychomycosis
Herpes zoster scarring
Oral hairy leukoplakia
Bacillary angiomatosis
Widespread dermatophytosis
Severe seborrheic dermatitis

WHO, World Health Organization.

Herpes simplex virus infections are often more severe and recur frequently. Chronic ulcerating herpes simplex occurs later in the disease course and is an AIDS-defining opportunistic infection. Other common viral diseases include molluscum contagiosum, human papillomavirus infection, and oral hairy leukoplakia.

Kaposi sarcoma, a vascular neoplasm, is the most common AIDS-related malignant disease in the United States, and the skin is the most commonly involved organ. Lesions are violaceous patches, nodules, or plaques (Fig. 121.8). Bacillary angiomatosis is manifested with lesions that resemble those of Kaposi sarcoma.

Disseminated fungal infections are often signs of severe immunosuppression, and patients can present with skin manifestations. Disseminated cryptococcosis can be manifested with centrally umbilicated skin lesions resembling those of molluscum contagiosum. Other fungi (e.g., *Histoplasma capsulatum*, *Coccidioides immitis, Blastomyces dermatitidis*, *Penicillium marneffei*) can cause cutaneous disease and are a significant cause of morbidity and mortality.

Noninfectious skin disorders are common. Seborrheic dermatitis, characterized by greasy, scaly patches that are often located on the nasolabial folds, eyebrows, and scalp, affects up to 80% of patients with AIDS. Cutaneous drug reactions occur with increased frequency and severity, such as toxic epidermal necrolysis. Often, the reaction is from sulfa-containing drugs. Abacavir can cause a hypersensitivity reaction that can be fatal if not recognized.

DIFFERENTIAL DIAGNOSES

Initial Evaluation

HIV-infected patients are at risk for some of the same infections and medical problems as noninfected patients, but they are more vulnerable to opportunistic and unusual infections. Knowledge of the $CD4^+$ count, along with the patient's clinical presentation, is critical in ED management. Before ART, patients were primarily hospitalized for

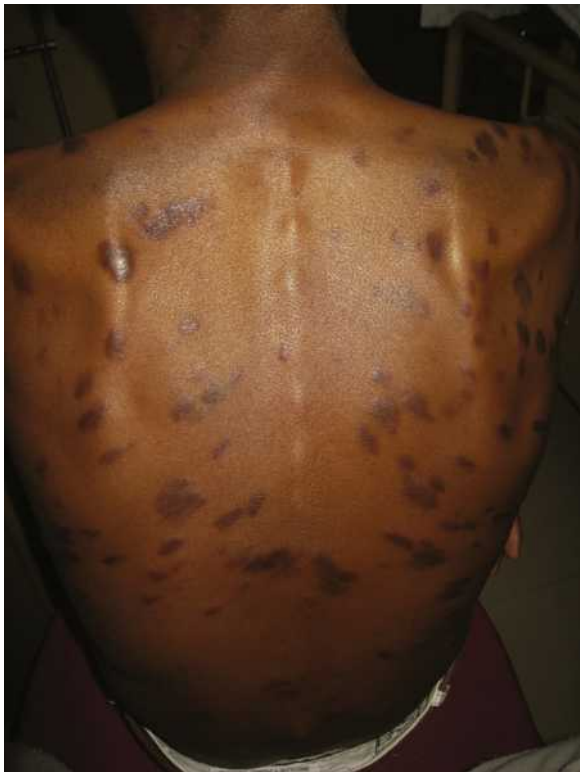

Fig. 121.8 Kaposi sarcoma lesions.

opportunistic infections. Patients with HIV infection are now dying of diseases that were not traditionally considered diseases of AIDS, such as heart disease, liver failure, and non–AIDS-related cancers.

The current $CD4^+$ count is a marker of the degree of immunosuppression and is critical background information for the interpretation of signs and symptoms. However, many ED patients have undiagnosed HIV infection or are medication noncompliant and may present with acute HIV infection, incidental HIV infection, or in later stages of the disease. Diagnostic clinical patterns are key to making an accurate diagnosis as to the stage of the disease. In lieu of a $CD4^+$ count, the total lymphocyte count may provide a rough approximation; a count between 1000 and 2000 cells/μL appears to be a reasonable surrogate of significant immunosuppression. Acute illness decreases peripheral lymphocyte counts and thus limits the value of the peripheral lymphocyte count as a diagnostic aid in an acute setting. However, an ED study has shown that patients with a peripheral lymphocyte count below 950 cells/μL are highly likely to have AIDS.

The possibility of HIV infection in patients presenting to the ED must be considered on a case by case basis. HIV infection should be considered in any patient who presents with unusual or recurrent serious infections without another explanation, especially patients with risk factors for HIV infection, such as IV drug users (IVDUs) and high-risk sexual practices. Although the opportunistic infections associated with AIDS can occur in the absence of HIV infection, they usually develop in patients with some form of immunosuppression. HIV infection should also be considered in younger patients who develop conditions that typically do not occur until later in life, such as herpes zoster.

Diagnostic Testing

HIV Testing

The diagnosis of HIV infection involves the detection of specific antibodies or viral antigens (see Table 121.1). Laboratory detection of HIV infection is a two-step process. The first step is a screening test; if the result is positive, a confirmatory test is performed.

The balance between public health and patient confidentiality has been an issue surrounding HIV testing and reporting. Most states and hospitals have developed policies related to these concerns. Regardless, testing should be done in a confidential manner, with appropriate follow-up and counseling.

With improved testing capabilities as well as efforts to diagnose existing cases of HIV infection in underserved populations, some experts have recommended routine screening tests. The advantages of testing in the ED include increased detection of HIV infection in difficult-to-reach populations and earlier diagnosis of HIV infection, allowing earlier ART implementation and therefore decreased viral transmission.

In 2006, the CDC published revised recommendations for HIV testing in health care settings, including hospital EDs.[5] This report recommended the use of diagnostic HIV testing and opt-out HIV screening in routine clinical care. Routine screening is recommended for 13- to 64-year-old patients, all patients who require TB treatment, those seeking treatment for sexually transmitted infections, and all pregnant women. Repeat annual screening is recommended for people at high risk. Recommendations specify that consent should be obtained for HIV testing, pretest information should be shared with patients, and those responsible for the patient's care should be notified verbally of the planned testing. The recommendations also call for reducing barriers to HIV testing. In April 2013, the U.S. Preventive Services Task Force issued similar recommendations.[3] Screening tests can include self-testing or provider-initiated testing. In emergency departments, given the resource constraints, there is a trend towards opt-out testing where the consent process is truncated and performed during triage. Testing can be in the form of a rapid point of care test, such as the INSTI©, or an oral test such as the Oraquick©. Local institutional availability and strategies for implementing testing in the ED will vary. Most rapid tests and self-tests are antibody tests; thus, it is recommended that patients with an initial negative test should retest at three months and, in the meantime, implement transmission reduction strategies such as condoms. The window period for a fourth-generation (antigen/antibody) test is still about four weeks.

MANAGEMENT

The care of the HIV-infected patient in the emergency department has evolved significantly, as has the management of HIV worldwide. In addition to the management of acute HIV infection, HIV-associated complications, and ART side effects, the modern ED physician may also be tasked with providing preexposure prophylaxis (PreP), postexposure prophylaxis, ART initiation, and linkage to care.

The clinical management of acute HIV infection is supportive. Management of opportunistic infections in the ED should be guided by the presumptive causative organism and may require consultation with Infectious Diseases.

Side effects of antiretroviral medications are extremely common. Protease inhibitors are notorious for GI side effects; most cause nausea and diarrhea. The NRTIs are mitochondrial toxic and can cause pancreatitis and hepatitis. Nevirapine, an NNRTI, can cause hepatic necrosis. Atazanavir causes Gilbert-like syndrome. Efavirenz is commonly associated with self-limited neuropsychiatric problems

Preexposure Prophylaxis

The CDC guidelines for preexposure for the prevention of HIV infection in the United States were updated in 2017. Daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF)

300 mg and emtricitabine (FTC) 200 mg is safe and effective in reducing the risk of sexual HIV acquisition in adults. It is recommended for patients with a substantial risk of HIV infection and for patients with HIV-positive partners. Currently, the data on the efficacy and safety of PrEP for adolescents are insufficient. Acute and chronic HIV infection must be excluded by symptom history and HIV testing immediately before PrEP is prescribed. Patients should be counseled that HIV infection should be assessed at least every three months, and renal function should be assessed at baseline and monitored every six months while on PrEP. Furthermore, when PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction services. Because high medication adherence is critical to PrEP efficacy but was not uniformly achieved by trial participants, patients should be encouraged and enabled to use PrEP in combination with other effective prevention methods.

Postexposure Prophylaxis

Postexposure prophylaxis (PEP) using ART significantly decreases the risk of transmission. Potentially infectious body fluids include CSF and synovial, pleural, peritoneal, pericardial, and amniotic fluids. Unless they contain blood, the following fluids are not considered infectious for HIV: vomitus, feces, nasal secretions, saliva, sputum, sweat, tears, and urine. Low-risk injuries are those involving solid needles (e.g., suture needles), those that are superficial, and those involving a low-risk source patient or body fluid. High-risk injuries include those involving hollow bore needles with visible blood and percutaneous injury from a needle that was in an artery or vein of the source patient. Unless a mucocutaneous exposure involves large volumes of blood from a source patient with a plasma HIV viral load more than 1500 copies/μL, mucocutaneous exposures are considered to be low risk.

The US Public Health Services updated guidelines on managing occupational exposures to HIV are as follows: (1) PEP is initiated when occupational exposures to HIV occur; (2) the HIV status of the exposure source patient should be determined, if possible, to guide need for HIV PEP; (3) PEP medication regimens should be started as soon as possible after occupational exposure to HIV, and they should be continued for a 4-week duration; (4) PEP medication regimens should contain 3 (or more) antiretroviral drugs for all occupational exposures to HIV; (5) expert consultation is recommended for occupational exposures to HIV, especially in cases of delayed exposure report, pregnancy or breastfeeding status of exposed individual, known or suspected resistance of source virus, underlying medical illness in the exposed individual, and unclear source (e.g., needle in sharps disposal container or laundry); (6) close follow-up for exposed personnel should be provided that includes counseling, baseline, and follow-up HIV testing, and monitoring for drug toxicity; follow-up appointments should begin within 72 hours of an HIV exposure.[6] Most institutions have specific guidelines that specify treatment regimens and follow-up plan through occupational health.

In addition to PEP, the initial response to exposure is immediate cleansing of the exposed or injured site; soap and water can be used for intact skin, and viricidal antiseptic agents, such as alcohol-based hand hygiene agents, can be used for small punctures and wounds. Mucosal surfaces and eyes should be flushed with copious amounts of water. Efforts should be made to document clinical information about the source patient, including risk factors and previous test results for HIV, HBV, and HCV, as well as to provide a description of the exposure and the time it occurred.

In situations where local expertise is unavailable, the Clinician Consultation Center (PEPline) can be contacted at 888-448-4911 for rapid, expert guidance in managing health care worker exposures to HIV and hepatitis B and C, including recommendations on when and how to initiate PEP through an online Quick Guide.[7]

Some patients may present after possible exposure to HIV/AIDS with concern about the potential of transmission. Possible means of exposure include sexual contact, injection drug use, and exposure to body fluids through broken skin or mucous membranes. The CDC recommends PEP for persons presenting within 72 hours after an exposure to a source known to be HIV-positive if contact of body fluid contaminated with blood (including semen, vaginal secretions, rectal secretions, and breast milk) was made with the vagina, rectum, eye, mouth or other mucous membranes, or nonintact skin or by percutaneous injection. Efforts should be made to determine the current HIV status of the source.

All persons offered PEP should be prescribed a 28-day course of a 3-drug antiretroviral regimen. The preferred regimen for otherwise healthy adults and adolescents is tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily plus raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg daily.[4] RAL is preferred if the woman is pregnant. A modification of this regimen is recommended for children, persons with decreased renal function, and pregnant women.

Whereas most seroconversions will occur in the first three months after the exposure, these patients should be checked for HIV at six weeks, 12 weeks, and six months. The PEPline is also available to provide advice (see earlier). In addition, all persons evaluated for possible nPEP should be provided any indicated prevention, treatment, or supportive care for other exposure-associated health risks and conditions (e.g., bacterial sexually transmitted infections, traumatic injuries, hepatitis B virus, and hepatitis C virus infection, or pregnancy). Persons who report behaviors or situations that place them at risk for frequently recurring HIV exposures (e.g., injection drug use, or sex without condoms) or who report receipt of 1 course or less of nPEP in the past year should be provided risk-reduction counseling and intervention services, including consideration of preexposure prophylaxis

ART Initiation and Linkage to Care

Immediate antiretroviral therapy (ART) refers to starting HIV treatment as soon as possible after the diagnosis of HIV infection, preferably on the first clinic visit (and even on the same day the HIV diagnosis is made). This strategy also is known as "rapid ART," "same-day ART," and "treatment upon diagnosis." Immediate ART initiation may bring earlier benefits in personal health and reductions in the risk of further transmission of HIV. For persons with acute infection, immediate ART may limit the HIV viral reservoir. In pilot studies in the United States and in randomized controlled trials in resource-limited settings, rapid ART initiation has been shown to reduce time to linkage to care and viral load suppression.[8,9]

As such, same-day initiation (SDI), has not only been piloted but is the standard of care at numerous institutions in the United States. Local institutional guidelines must be followed. To support this practice, the ED clinician should identify patients suitable for ART initiation, provide counseling, complete baseline laboratory testing, and prescribe a blister pack with a locally recommended treatment regimen. ART is started before the results of baseline testing (including HIV RNA, CD4 count, genotype, HLA-B*5701, and creatinine) are available. Thus, the ART regimens must be potent and effective in the setting of high viral load and/or transmitted NRTI resistance. The preferred recommended regimens are dolutegravir (Tivicay) + TAF/FTC (Descovy) or darunavir (Prezista) + booster (ritonavir or cobicistat) + TAF/FTC.[10]

ART initiation will be successful only if closely tied to linkage to care. Patients will need additional HIV-related education, information regarding the importance of medication adherence, counseling about preventing HIV transmission, and encouragement about living healthy lives with HIV. Most institutions will have a partnership with their local infectious disease clinic. It is recommended that patients have a

phone call scheduled within 2 to 3 days of the index visit, and a clinic follow-up appointment at 1 to 2 weeks.

DISPOSITION

The widespread use of ART among HIV-positive individuals has dramatically changed the course of the disease; individuals often have sustained and lasting immune reconstitution and live relatively normal lives. Knowledge of their immune status is critical for disposition and treatment; patients with a normal or near-normal $CD4^+$ count should be treated like non–HIV-infected patients. Drug interactions are common. Patients with AIDS, unlike immunocompetent patients, often suffer from multiple, simultaneous underlying pathologic processes, making evaluation and treatment decisions even more difficult; a unifying diagnosis is not the norm. These patients are at greater risk of morbidity and mortality from common disease entities, as well as from complications of HIV/AIDS. Emergency clinicians who approach these patients with background knowledge of the potential manifestations of HIV/AIDS will be poised to deliver the best emergent care.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 121: QUESTIONS AND ANSWERS

1. A 52-year-old man with acquired immunodeficiency syndrome (AIDS) presents with dysphagia. The pain radiates to his chest. He does not appear toxic. There is white plaque on his tongue and oropharynx, which is easily scraped off. His $CD4^+$ count was 52 cells/μL. He was just recently started on highly active antiviral therapy (HAART) and is taking atazanavir-ritonavir, tenofovir, and emtricitabine. What is the most appropriate treatment?

a. Acyclovir
b. Fluconazole
c. Ganciclovir
d. Immediate endoscopy

Answer: C. Odynophagia with a $CD4^+$ count less than 100 cells/μL and oral thrush suggests esophageal candidiasis. If the patient can tolerate oral therapy, fluconazole is first-line treatment. Endoscopy is reserved for treatment failure or those with an atypical presentation. Cytomegalovirus and herpes simplex virus can cause esophagitis but are less common. They are diagnosed with endoscopy, often after treatment failure with fluconazole. Patients with HIV can have esophagitis due to reflux but, in this setting, empirical treatment for candidiasis is the most appropriate. Proton pump inhibitors can decrease the absorption of atazanavir and should not be prescribed without first discussing the case with the patient's human immunodeficiency (HIV) physician.

2. Which of the following is not an AIDS-defining condition?

a. Cellulitis
b. Extrapulmonary *Cryptococcus*
c. Invasive cervical cancer
d. Recurrent pneumonia

Answer: A. All the answers except A are AIDS-defining conditions.

3. A 52-year-old male patient presents with 3 days of confusion, fever, and headache. He was diagnosed with HIV 3 weeks ago and is not currently taking antiretroviral medications. His $CD4^+$ count at that time was 32 cells/μL. He has lived in the United States all his life. A head CT scan with contrast on this visit reveals multiple ring-enhancing lesions. Which of the following is the most likely cause of this central nervous system (CNS) lesion?

a. Cytomegalovirus encephalitis
b. HIV encephalopathy
c. *Mycobacterium* tuberculosis
d. *Toxoplasma gondii*

Answer: D. *Toxoplasma* encephalitis presents over days to weeks with fever, headache, altered mental status, focal neurologic findings, and/or seizures. In 90% of cases, there are ring-enhancing CNS lesions. the $CD4^+$ count is typically less than 100 cells/μL, and often the count is much lower. The main differential diagnosis in developed countries is CNS lymphoma. Patients with ring-enhancing CNS lesions are often empirically treated for *Toxoplasma,* and then a repeat CT scan is performed. A brain biopsy is diagnostic. Tuberculoma must be considered in patients with an exposure to tuberculosis and in those who live in areas highly endemic for tuberculosis.

4. A 36-year-old woman presents with a warm, red, painful lower leg. She has multiple other dermatologic concerns, including flesh-colored, dome-shaped lesions on her face, a new dark pigmented lesion on her arm, cold sores, and facial erythema. Which of her cutaneous findings suggests HIV disease?

a. Cellulitis
b. Facial molluscum
c. Melanoma
d. Oral herpes

Answer: B. HIV has many cutaneous manifestations. In this case, her facial molluscum is highly suggestive of HIV disease.

5. A 35-year-old man with AIDS presents with fever and a productive cough for 1 day. His last known $CD4^+$ count 1 month ago was 538 cells/μL. He has a lobar pneumonia in the left lower lobe on his chest radiograph. There is no evidence of lymphadenopathy. What is the most likely culprit pathogen in this case?

a. *Cryptococcus neoformans* pneumonia
b. *Pneumocystis jiroveci* pneumonia (PCP)
c. Pulmonary tuberculosis
d. *Streptococcus pneumoniae*

Answer: D. It is critical to have an understanding of diseases relative to the absolute $CD4^+$ T cell count. Patients with CD4 counts higher than 500 cells/μL typically develop illnesses similar to the general population. This patient presents with a lobar pneumonia, and *S. pneumoniae* is the most common cause. PCP is the most common opportunistic pathogen in AIDS patients, usually occurring in those with a $CD4^+$ T cell count lower than 200 cells/μL. It would be extremely unusual for PCP to cause a lobar pneumonia in someone who is immune-reconstituted. Tuberculosis can occur at any stage of HIV infection. However, the symptoms tend to be more gradual in onset, and a lobar pneumonia is unlikely.

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Parasites

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KEY CONCEPTS

- Parasitic diseases may manifest with almost any constellation of signs and symptoms.
- The combination of presenting signs and symptoms and a history of recent travel to specific geographic regions can lead to early diagnosis and the initiation of pharmacotherapy, decreasing morbidity and mortality and increasing the probability of eradication of the infection.
- Parasitic coinfections are particularly common in patients with HIV infection and AIDS. A travel history is essential because the clinical presentation may be atypical, morbidity and mortality are more severe, and treatment is often prolonged.
- Acute malaria should be suspected in patients with irregular high fevers associated with headache, abdominal pain, or respiratory symptoms. Falciparum malaria, which has a unique morphology easily identifiable on the peripheral blood smear, is the predominant species of malaria that causes coma and death. *P. falciparum* is the most highly resistant to chemotherapy, demanding close observation and clinical follow-up of patients. Patients who are clinically ill or who are suspected of having falciparum malaria should be hospitalized.
- Cysticercosis should be considered in the differential diagnosis of the patient with new-onset seizures, especially in patients who have been living in Central and South America.
- Giardiasis should be suspected in patients with diarrhea who have recently been camping or drinking unfiltered mountain spring water. Patients may have tolerated several weeks of severe bloating, flatulence, eructation, and weight loss without fever before seeking medical attention.
- *Trypanosoma cruzi* infection results in Chagas disease, most notable for the development of acute and chronic myocarditis. Cardiomyopathy can be severe, at times even necessitating heart transplant.

FOUNDATIONS

Parasitic infections are caused by a diverse group of eukaryotic organisms distributed across the globe, although the highest prevalence of these infections is found in tropical regions. Box 122.1 outlines the taxonomy of human parasites. Protozoal agents are unicellular, while the helminths are multicellular. These infectious organisms demonstrate complex life cycles that often include intermediate stages that target (human) hosts, along with stages of development in which they live freely in the environment. The modes of transmission to humans may include insect bites, the consumption of raw or undercooked and "infected" meat or seafood, the ingestion of water or food contaminated by human feces, or skin exposure to water or soil containing parasites at the infectious stage of development. The spectrum of clinical parasitic disease can vary from acute, life-threatening infection to chronic, progressive illness. Other infections may present with acute illness that can recover without sequalae and some cause asymptomatic infections that may manifest years later or never.

An understanding of parasitology has become increasingly crucial for emergency clinicians. In the last few decades, there has been a dramatic increase in immigration across the globe, including regions where parasitic infections are highly endemic. There has also been an increase in business and adventure travel to tropical regions, bringing immunologically naïve and vulnerable hosts to sites rich in parasitic disease. Patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) who travel to or emigrate from countries where parasitic illnesses are endemic are at higher risk of infection with these illnesses. In addition, there continues to be an increase in the prevalence of endemic parasitic diseases in many rural areas of the southeastern and southwestern United States, and in some parts of Europe. Climate change has been extending the habitat of what were previously known as tropical parasites and vectors to previously temperate regions. Thus, a growing population of patients with parasitic illness now present to emergency departments, requiring the emergency clinician to consider these unusual but important diseases.

Many parasitic infections follow an indolent course or present with nonspecific symptoms, posing a challenge to diagnosis especially in the ED setting. While correct diagnosis and pharmacologic treatment of parasitic infections usually leads to a rapid and complete recovery, delayed treatment or mismanagement of parasitic diseases can have severe long-term consequences. To diagnose parasitic infection, the emergency clinician must obtain a thorough travel history, including questions summarized in Box 122.2, perform a detailed physical examination, and order appropriate laboratory studies. This information must be integrated with an understanding of the basic life cycles of parasites, incubation periods between inoculation and clinical presentation, and intersecting geography of the organism and host. Physicians must have the ability to recognize both the classical and atypical presentations of particular parasitic infections and institute appropriate therapy (Table 122.1).

Parasitic illness should be considered in the differential diagnosis of patients who have spent time in areas of the world with endemic parasitic illnesses (Table 122.2). For patients who have recently immigrated to the United States, the emergency clinician should elicit additional information specific to the country of origin, also summarized in Box 122.2. The incubation period for the development of symptoms for parasitic diseases ranges from days (falciparum malaria) to months (vivax malaria) to years (filariasis).

Parasite biochemical pathways are generally different from those of their human host, permitting selective metabolic interference by using relatively small doses of chemotherapeutic agents. New and more effective antiparasitic agents continue to be developed. The list of

BOX 122.1 List of Conditions and Taxonomy

Protozoa

Apicomplexan/Coccidia

- Malaria
- Babesia
- Cryptosporidia
- Cyclospora
- Cystoisospora
- Sarcocystis
- Toxoplasma

Amoebae

- *Entamoeba histolytica*
- *Naegleria fowleri*
- *Acanthamoeba spp.*
- *Balamuthia mandrillaris*

Flagellates

- *Leishmania*
- *Trypanosoma cruzi*
- *Trypanosoma brucei*
- *Giardia lamblia*
- *Trichomonas vaginalis*

Ciliates

- *Balantidium coli*

Helminths

Nematodes

- Hookworm (*Necator/Ancyclostoma*)
- *Trichuris*
- *Ascaris*
- *Enterobius*
- *Filaria* (Wuchereria/Brugia/Onchocerca/Loa loa/Mansonella)
- *Strongyloides*
- *Capillaria*
- Anisakiasis
- Dracunculiasis
- Trichinella

Trematodes

- *Schistosoma*
- *Fasciola* spp.
- *Paragonimus*
- *Clonorchis*
- *Opisthorchis*
- *Fasciolopsis/Echinostoma*

Cestodes

- *Taenia solium*
- *Taenia saginata*
- *Diphyllobothrium latum, D. pacificum*
- *Hymenolepis nana/diminuta*
- *Echinococcus granulosus, E. multilocularis*
- *Spirometra* (sparganosis)—eyes, brain, other
- *Sparganum* (proliferative sparganosis)

Zoonotic Helminths

- *Baylisascaris*
- *Angiostrongylus costaricensis, cantonensis*
- *Gnathostomiasis*
- *Toxocara*
- Hookworm (*Ancylostoma caninum, A. braziliense, Uncinaria*)

BOX 122.2 Comprehensive Travel History for Evaluation of Parasitic Disease in the Emergency Department

Questions for All Patients

- What were the exact dates of travel?
- What countries did the patient visit?
- How much time was spent in each country?
- What was the patient doing in the country, and where was he or she living?
- Was the patient a tourist, an adventure traveler, or a worker?
- Did the patient stay in cities or rural villages?
- Was the patient sleeping in hotels or tents?
- Did the patient engage in protected or unprotected sexual intercourse?
- What did the patient eat and drink?
- What were the patient's activities (e.g., swimming in fresh water leads to schistosomiasis)?
- Did the patient receive prophylactic immunizations before travel?
- Did the patient take malaria chemoprophylaxis and comply with the regimen?
- Did the patient use mosquito repellent and netting?
- Does the patient have underlying chronic medical problems?
- What medications does the patient take?
- When did symptoms start, and what has been the chronology of symptoms, particularly fever and diarrhea?

Questions for Patients Who Are Recent Immigrants to the United States

- When did the patient arrive, and from where?
- What acute and chronic illnesses did the patient have previously while living in the country of origin?
- What treatment did the patient receive there?
- If a refugee or immigrant, what countries did the patient pass through, and what were the living conditions (especially relevant for persons who have lived in numerous refugee camps)?
- What was the season during the patient's stay or travel in the countries (e.g., monsoon vs. dry)?
- What animal exposures and bites has the patient experienced?
- Has the patient had exposure to fresh water in work or recreational activities?

drugs used to treat parasitic infestations is long and varied. Table 122.3 includes recommended agents. The newer antiparasitic drugs tend to be less toxic and more efficacious. In many cases, single-dose treatment can eradicate an entire parasite burden, thus supporting effective public health initiatives that include mass treatment programs for populations with a large burden of infection in endemic areas.

MALARIA

Background and Importance

More than 41% of the world's population lives in malarial areas where plasmodia are endemic (e.g., parts of Africa, Asia, Oceania, Central America, and South America). The World Health Organization (WHO) has estimated that in 2013, malaria was responsible for 198 million clinical episodes and 500,000 deaths. Most of these deaths were the result of infection with *Plasmodium falciparum*.[1] Immigrants and returning travelers presenting with malarial symptoms warrant particular consideration as acute falciparum malaria, if left untreated, carries a high mortality. Although it is classically associated with cyclical fevers, malaria presents various symptoms, including headache and diarrhea. Fever is common but not universal at initial presentation. When fever is present, it is often continuous early in the course of illness. Some studies in low endemicity areas have suggested that the presence of fever or headache has a sensitivity greater than 95%. In recent years there has been an increase in the diagnosis of falciparum malaria in travelers returning to the United States; the most common region from which these travelers return is West Africa. Patients who have had a longer duration of travel and neglected to take prophylactic medications or who failed to adhere to prescribed regimens are at the greatest risk.

Most people contract malaria after being bitten by an infected vector mosquito in an endemic region. Other mechanisms of transmission have been reported, including blood transfusions, injection drug use with contaminated syringes, maternal-fetal perinatal transmission, transmission from infected organs after transplantation (worsened by immunosuppression), and what has been described as "airport malaria." This occurs when the infected mosquito is transported from the endemic region and released at the airport when the plane arrives, surviving long enough to transmit the parasite to a human host and then dying without establishing itself in its new location.

Pathophysiology

Malaria is caused by one of five species of the protozoan parasite *Plasmodium*: *P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*. Of these species, *P. falciparum* poses the greatest risk of

TABLE 122.1 Drug Classes and Modes of Action of Agents Used for Treatment of Parasitic Diseases

Type of Drug	Examples[a]	Useful in the Treatment of:	Likely Target in the Parasite	Proposed Effects on Targets
Anthelmintic	Thiabendazole Mebendazole Albendazole	*Ascaris, Enterobius,* hookworm, *Strongyloides, Trichuris,* hydatid disease (long-term therapy)	Tubulin polymerization	Blocks cellular structural integrity and egg production; secondary effects on mitochondrial fumarate reductase and glucose uptake
	Ivermectin (Stromectol)	Many nematodes of humans (except hookworms) Filariasis Onchocerciasis	GABA-sensitive neuromuscular interface	Flaccidity or contraction (tight-binding drug effective at low dose)
Trematodicide	Praziquantel (Biltricide)	Schistosomes Most other flukes, such as *Clonorchis, Paragonimus, Fasciolopsis* (many tapeworms of humans)	Surface structure Carbohydrate metabolism	Vacuolization and surface disruption followed by immune attacks by the host; contraction of the muscles due to flooding of calcium through a permeable tegument; initial increase of glucose metabolism followed by shutdown
Antiprotozoal	Metronidazole (Flagyl) Tinidazole Niridazole	Amebiasis Balantidiasis Giardiasis *Schistosoma haematobium*	Molecular electron transport systems Acetylcholine recycling systems	Failure to sustain energy-producing systems Binds to acetylcholinesterase, inactivating normal neuromuscular function
Antimalarial	Chloroquine phosphate (Aralen)	Many species of susceptible malaria	Parasite digestive vacuole hemoglobinase	Local pH is changed so enzyme becomes inoperative
	Mefloquine	Many species of susceptible malaria		
	Proguanil-atovaquone	Many species of susceptible malaria	Mitochondrial electron transport prevents the normal function of the apicoplast	Works on erythrocytic and hepatic stages
	Doxycycline	Many species of susceptible malaria		Kills *Plasmodium falciparum*

[a]Some drugs may be available only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA 30333; telephone: 404-639-3670 (nights, weekends, and holidays: 404-639-2888).
GABA, γ-aminobutyric acid.

TABLE 122.2 Parasites Causing Human Disease: Geographic Location and Portal of Entry

Parasite	Geographic Distribution	Common Infective Stage and Portal of Entry
Protozoa Apicomplexan Amoeba Flagellate Ciliate		
Entamoeba histolytica	Especially prevalent in warm climates	Cyst via mouth
Balantidium coli	Warm climates	Cyst via mouth
Giardia lamblia	Found throughout temperate and warm climates	Cyst via mouth
Trichomonas vaginalis	United States	Trophozoite via vulva or urethra
Leishmania tropica	Mediterranean area to western India	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania infantum	Southern Europe and Mediterranean	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania donovani	China, India, Africa, Mediterranean area, continental Latin America	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania chagasi	South America	Bite of sandfly introducing promastigote via skin, leading to visceral disease
Leishmania braziliensis	South America and Central America	Bite of sandfly introducing promastigote via skin, leading to cutaneous or mucocutaneous disease
Leishmania major, L. tropica	Africa and Asia	Bite of sandfly introducing promastigote via skin, leading to cutaneous disease

TABLE 122.2 Parasites Causing Human Disease: Geographic Location and Portal of Entry—cont'd.

Parasite	Geographic Distribution	Common Infective Stage and Portal of Entry
Leishmania mexicana, L. amazonensis, L. guyanensis, L. costaricensis	Central and South America	Bite of sandfly introducing promastigote via skin, leading to cutaneous disease
Trypanosoma brucei gambiense	West and Central Africa	Trypanosome via skin from bite of the tsetse fly
Trypanosoma brucei rhodesiense	Central and East Africa	Trypanosome via skin from bite of the tsetse fly
Trypanosoma cruzi	Continental Latin America	Trypanosome via skin from reduviid bug
Plasmodium vivax	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium ovale	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium malariae	Warm climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium knowlesi	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium falciparum *Babesia microti* *Cryptosporidium parvum* *Cyclospora cayetanensis* *Cystoisospora belli* *Toxoplasma gondii* *Sarcocystis hominis* *Naegleria fowleri* *Acanthamoeba* spp. *Balamuthia mandrillaris*	Warm climates	Sporozoite via skin from *Anopheles* mosquito
Nematodes		
Trichinella spiralis	Cooler and temperate climates	Encysted larva in pork or bear via mouth
Trichuris trichiura	Warm, moist climates	Embryonated egg via mouth
Strongyloides stercoralis	Warm, moist climates	Filariform larva via skin
Necator americanus	Common in warm climates	Filariform larva via skin
Ancylostoma duodenale	Common in warm climates	Filariform larva via skin
Enterobius vermicularis	Common in the United States	Embryonated egg via mouth
Ascaris lumbricoides	Global distribution; common in the United States	Embryonated egg via mouth
Wuchereria bancrofti	Prevalent in warm climates	Filariform larva via skin from bite of *Anopheles* or *Culex* mosquito
Brugia malayi	Asia	Filariform larva via skin from bite of *Anopheles* or *Culex* mosquito
Onchocerca volvulus	Tropical Africa, Mexico, Central America, and northern South America	Filariform larva via skin from bite of the blackfly
Loa loa	Tropical West Africa	Filariform larva via skin from bite of the *Chrysops* fly
Dracunculus medinensis *Capillaria philippinensis* *Anisakis simplex* *Baylisascaris procyonis* *Angiostrongylus cantonensis* *Gnathostoma spinigerum/binucleatum* *Toxocara canis* *Ancylostoma braziliense*	Increasingly rare	Ingestion of larva by copepod via mouth
Cestodes		
Taenia saginata	Global distribution; uncommon in the United States	Cysticercus in beef via mouth
Taenia solium	South America, Central America, Mexico, East Africa, India, China, Indonesia	
• Adult worm		Cysticercus in pork via mouth
• Cysticercus stage		Eggs in human infections via mouth
Echinococcus granulosus	Mediterranean, Russian Federation and neighboring countries, China, Central Asia, North and East Africa, and South America	Eggs from canines via fecal-oral transmission
Echinococcus multilocularis	Central Europe, northern Asia, Alaska	Eggs from foxes, dogs, and cats via fecal-oral transmission
Hymenolepis nana	Warm climates	Eggs in human infections via mouth

Continued

TABLE 122.2 Parasites Causing Human Disease: Geographic Location and Portal of Entry—cont'd.

Parasite	Geographic Distribution	Common Infective Stage and Portal of Entry
Hymenolepis diminuta	Warm climates	Larva in arthropod host via mouth
Diphyllobothrium latum *Diphyllobothrium pacificum* *Spirometra spp.* *Sparganum proliferum*	US Great Lakes region and Alaska, Scandinavia, Russia, Japan, Pacific Coast of South America, and Uganda	*Sparganum* larva in fish flesh via mouth
Trematodes		
Fasciola hepatica	Sheep-raising countries	Larva on vegetation via mouth
Fasciolopsis buski	Asia	Larva on water nuts
Clonorchis sinensis	Asia	Larva encysted in freshwater fish
Opisthorchis felineus	Europe, Asia	Larva encysted in freshwater fish
Opisthorchis viverrini	Thailand	Larva encysted in freshwater fish
Paragonimus westermani	Primarily Asia; also South America and Africa	Larva encysted in crabs or crayfish via mouth
Schistosoma japonicum	China, Southeast Asia, Philippines	Cercarial larva in water via skin
Schistosoma mansoni	Africa, Latin America, Middle East, Caribbean	Cercarial larva in water via skin
Schistosoma haematobium *Echinostoma hortense*	Africa, Middle East	Cercarial larva in water via skin

Adapted from: Beaver PC, Jung RC, Eddie Wayne Cupp EW. *Clinical Parasitology*, ed 9. Philadelphia: Lea & Febiger; 1984.

TABLE 122.3 Drug Regimens for Treatment of Parasitic Infections

		DOSAGE	
Infection	**Drug**[a]	**Adults**	**Children**
Amebiasis (*Entamoeba histolytica*)			
Asymptomatic			
	DRUG OF CHOICE	650 mg tid × 20 days	30 mg/kg/day in 3 doses × 20 days
	• Iodoquinol		
	ALTERNATIVES	500 mg tid × 10 days	25–35 mg/kg/day in 3 doses × 7 days
	• Diloxanide furoate *or*		
	• Paromomycin	25–30 mg/kg/day in 3 doses × 7 days	25–30 mg/kg/day in 3 doses × 7 days
Mild to Moderate Intestinal Disease			
	DRUG OF CHOICE	750 mg tid × 10 days	35–50 mg/kg/day in 3 doses × 10 days
	• Metronidazole *followed by* • Paromomycin or iodoquinol		
	ALTERNATIVES	2 g/day × 3 days	50 mg/kg (max, 2 g) qd × 3 days
	• Tinidazole *followed by* • Paromomycin or iodoquinol		
Severe Intestinal Disease, Hepatic Abscess			
Drainage of liver abscess	DRUG OF CHOICE	750 mg IV or PO tid × 10 days	35–50 mg/kg/day in 3 doses × 10 days
	• Metronidazole *followed by* • Paromomycin or iodoquinol		
	ALTERNATIVES		
	• Tinidazole *followed by* • Paromomycin or iodoquinol	2 g/day × 5 days	50 mg/kg or 60 mg/kg (max, 2 g) qd × 3 days
Amebic meningoencephalitis, primary (*Naegleria* spp.)	DRUG OF CHOICE • Amphotericin B	1 mg/kg/day IV, uncertain duration	1 mg/kg/day IV, uncertain duration
Anisakiasis (*Anisakis*)			
Treatment of choice	Surgical or endoscopic removal		

TABLE 122.3 Drug Regimens for Treatment of Parasitic Infections—cont'd.

Infection	Drug[a]	DOSAGE: Adults	DOSAGE: Children
Ascariasis (*Ascaris lumbricoides*)			
Roundworm	DRUGS OF CHOICE		
	• Mebendazole	100 mg bid × 3 days	100 mg bid × 3 days
	• Albendazole	400 mg × 1 dose	>6 yr, same dose as for adult
	• Nitazoxanide	500 mg bid × 3 days	200 mg bid × 3 days
	• Ivermectin	150–200 μg/kg for 1 dose; should be avoided in pregnant women	Should be avoided in young children
Balantidiasis (*Balantidium coli*)			
	DRUG OF CHOICE		
	• Tetracycline	500 mg qid × 10 days	40 mg/kg/day in 4 doses × 10 days (max, 2 g/day)
	ALTERNATIVES	650 mg tid × 20 days	40 mg/kg/day in 3 doses × 20 days
	• Iodoquinol		
	• Metronidazole	750 mg tid × 5 days	35–50 mg/kg/day in 3 doses × 5 days
Cutaneous Larva Migrans			
Creeping eruption	DRUG OF CHOICE		
	• Ivermectin	200 μg/kg once daily × 1 or 2 days	
Dracunculus medinensis			
Guinea worm; worm also needs to be extracted	DRUG OF CHOICE		
	• Metronidazole	750 mg tid × 5–10 days	25 mg/kg/day (max, 750 mg/day) in 2 doses × 10 days
	ALTERNATIVE		
	• Thiabendazole	50–75 mg/day bid × 3 days	50–75 mg/kg/day in 2 doses × 3 days
Enterobius vermicularis			
Pinworm	DRUGS OF CHOICE		
	• Albendazole	Single dose of 400 mg; repeat after 2 wk	11 mg/kg once (max, 1 g); repeat after 2 wk
	• Mebendazole	Single dose of 100 mg; repeat after 2 wk	Single dose of 100 mg; repeat after 2 wk
Filariasis (*Wuchereria bancrofti, Brugia malayi*)			
	DRUG OF CHOICE		
	• Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4–21: 6 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1–2 mg/kg tid Days 4–21: 6 mg/kg/day in 3 doses
Loa loa	DRUG OF CHOICE		
	• Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4–21: 9 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1–2 mg/kg tid Days 4–21: 6 mg/kg/day in 3 doses
Onchocerca volvulus	DRUG OF CHOICE		
	• Ivermectin	150 μg/kg PO once, repeated every 3–12 mo	150 μg/kg PO once, repeated every 3–12 mo
Hermaphroditic Fluke			
Clonorchis sinensis (Chinese liver fluke)	DRUG OF CHOICE		
	• Praziquantel	25 mg/kg/day in 4–6 doses × 1 day	25 mg/kg/day in 4–6 doses × 1 day
Fasciola hepatica (sheep liver fluke)	DRUG OF CHOICE	30–50 mg/kg on alternate days × 10–15 doses	30–50 mg/kg on alternate days × 10–15 doses
	• Bithionol		

Continued

TABLE 122.3 Drug Regimens for Treatment of Parasitic Infections—cont'd.

Infection	Drug[a]	DOSAGE: Adults	DOSAGE: Children
Fasciolopsis buski (intestinal fluke)	DRUG OF CHOICE		
	• Praziquantel	25 mg/kg/day in 4 to 6 doses × 1 day	25 mg/kg/day in 4 to 6 doses × 1 day
Opisthorchis felineu	DRUG OF CHOICE		
	• Praziquantel	25 mg/kg/day in 4 to 6 doses × 1 day	25 mg/kg/day in 4 to 6 doses × 1 day
Paragonimus westermani (lung fluke)	DRUG OF CHOICE		
	• Praziquantel	25 mg/kg/day in 4 to 6 doses × 2 days	25 mg/kg/day in 4 to 6 doses × 2 days
	ALTERNATIVE	30–50 mg/kg on alternate days × 10–15 doses	30–50 mg/kg on alternate days × 10–15 doses
	• Bithionol		
Giardiasis (*Giardia lamblia*)	DRUG OF CHOICE		
	• Metronidazole	250 mg tid × 5 to 7 days	15 mg/kg/day in 3 doses × 5 to 7 days
	ALTERNATIVES		
	• Nitazoxanide *or*	500 mg bid × 3 days	200 mg PO bid × 3 days (>4 yr)
	• Tinidazole	2 g as a single dose	50 mg/kg as a single dose
Hookworm Infection (*Ancylostoma duodenale, Necator americanus*)			
	DRUGS OF CHOICE		
	• Albendazole *or*	400 mg × one dose	
	• Mebendazole *or*	500 mg × one dose	500 mg × one dose
	• Pyrantel pamoate	11 mg/kg (max, 1 g) × 3 days	11 mg/kg (max, 1 g) × 3 days
LEISHMANIASIS			
Leishmania braziliensis, Leishmania mexicana, Leishmania tropica, Leishmania donovani (kala-azar, black fever)	DRUGS OF CHOICE		
	• Miltefosine *or*	Not indicated in those ≤12 yr	2.5 mg/kg/day PO × 28 days
	• Stibogluconate sodium	20 mg/kg/day IV or IM × 20–28 days	20 mg/kg/day IV or IM × 20–28 days
	ALTERNATIVE		
	• Amphotericin B	0.25–1 mg/kg by slow infusion daily or every 2 days for 8 wk	0.25–1 mg/kg by slow infusion daily or every 2 days for 8 wk
Malaria, Treatment of (*Plasmodium falciparum, P. ovale, P. vivax, P. malariae*) *All* Plasmodium *Species (Except Chloroquine-Resistant* P. falciparum*)*			
Oral	DRUG OF CHOICE		
	Chloroquine phosphate	600 mg base (1 g), then 300 mg base (500 mg) 6 hr later, then 300 mg base (500 mg) at 24 and 48 hr	10 mg base/kg (max, 600 mg base), then 5 mg base/kg 6 hr later, then 5 mg base/kg at 24 and 48 hr
Parenteral	DRUGS OF CHOICE		
	• Quinine dihydrochloride *or*	20 mg/kg loading dose in 10 mg/kg 5% dextrose during 4 hr, followed by 10 mg/kg during 2–4 hr q8h (max, 1800 mg/day) until oral therapy can be started	Same as adult dose
	• Quinidine gluconate *or*	10 mg/kg loading dose (max, 600 mg) in normal saline slowly during 1–2 hr, followed by continuous infusion of 0.02 mg/kg/min for 3 days max	Same as adult dose
	• Artesunate for treatment failure or adverse reactions from quinidine or quinine (available from the CDC)		
	ALTERNATIVE		
	• Chloroquine hydrochloride	200 mg base (250 mg) IM q6h if oral therapy cannot be started	0.83 mg base/kg/hr × 30 hr continuous infusion or 3.5 mg base/kg q6h IM or SC

TABLE 122.3 Drug Regimens for Treatment of Parasitic Infections—cont'd.

Infection	Drug[a]	DOSAGE: Adults	DOSAGE: Children
***Chloroquine-Resistant* P. falciparum**			
Oral	DRUGS OF CHOICE		
	• Quinine sulfate *plus*	650 mg tid × 3 days	25 mg/kg/day in 3 doses × 3–7 days
	• Doxycycline *or*	100 mg bid × 7 days	
	• Clindamycin	900 mg tid × 3–5 days	20–40 mg/kg/day in 3 doses × 3–5 days
	ALTERNATIVES		
	• Mefloquine	1250 mg once	25 mg/kg once (<45 kg)
	• Atovaquone-proguanil	1000/400 mg qd × 3 days	
	• Artemether-lumefantrine	4 tabs bid × 3 days	
Parenteral	DRUGS OF CHOICE		
	• Quinine dihydrochloride *or*	Same as above	Same as above
	• Quinidine gluconate *or*	Same as above	Same as above
	• Artesunate	Same as above	Same as above
Prevention of relapses—*P. vivax* and *P. ovale* only	DRUG OF CHOICE		
	• Primaquine phosphate	15 mg base (26.3 mg)/day × 14 days or 45 mg base (79 mg)/wk × 8 wk	0.3 mg base/kg/day × 14 days
Malaria, Prevention of			
	DRUG OF CHOICE		
	• Chloroquine phosphate	300 mg base (500 mg salt) PO, once/wk beginning 1 wk before and continuing for 4 wk after last exposure	5 mg/kg base (8.3 mg/kg salt) once/wk, up to adult dose of 300 mg base, same schedule as for adults
Chloroquine-resistant areas	DRUGS OF CHOICE		
	• Mefloquine *or*	250-mg tablet PO once/wk × 4 wk, then every other wk, continuing for 4 wk after last exposure	Same schedule as for adults with the following dosing guidelines: 15–19 kg, ¼ tablet; 20–30 kg, ½ tablet; 31–45 kg, ¾ tablet; >45 kg, 1 tablet
	• Atovaquone-proguanil *or*	250/100 mg qd 1 day before travel, each day in endemic region, and for 1 week afterward	
	• Doxycycline	100 mg daily during exposure and for 4 wk afterward	>8 yr: 2 mg/kg/day PO, up to 100 mg/day
Schistosomiasis			
Schistosoma haematobium	DRUG OF CHOICE		
	• Praziquantel	40 mg/kg/day in 4–6 doses × 1 day	20 mg/kg/day in 4–6 doses × 1 day
Schistosoma japonicum	DRUG OF CHOICE		
	• Praziquantel	40 mg/kg/day in 4–6 doses × 1 day	20 mg kg/day in 4–6 doses × 1 day
Schistosoma mansoni			
	DRUG OF CHOICE		
	• Praziquantel	60 mg/kg/day in 4–6 doses × 1 day	20 mg/kg/day in 4–6 doses × 1 day
	ALTERNATIVE		
	• Oxamniquine	15 mg/kg once	20 mg/kg/day in 2 doses × 1 day
Schistosoma mekongi	DRUG OF CHOICE		
	• Praziquantel	60 mg/kg/day in 4–6 doses × 1 day	20 mg/kg/day in 4–6 doses × 1 day
Strongyloidiasis (*Strongyloides stercoralis*)			
	DRUGS OF CHOICE		
	• Ivermectin *or*	200 μg/kg/day × 1–2 days	200 μg/kg/day × 1 or 2 days
	• Thiabendazole	50 mg/kg/day in 2 doses (max, 3 g/day) × 2 days	50 mg/kg/day in 2 doses (max, 3 g/day) × 2 days

Continued

TABLE 122.3 Drug Regimens for Treatment of Parasitic Infections—cont'd.

Infection	Drug[a]	DOSAGE: Adults	DOSAGE: Children
Tapeworm Infection			
Adult (Intestinal Stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)	DRUG OF CHOICE Praziquantel	5–10 mg/kg once	5–10 mg/kg once
Hymenolepis nana (dwarf tapeworm)	DRUG OF CHOICE • Praziquantel	25 mg/kg once	25 mg/kg once
Tapeworm Infection, Larval (Tissue) Stage			
Echinococcus granulosus (hydatid cysts)	DRUG OF CHOICE • Albendazole	400 mg bid × 28 days, repeated as necessary	15 mg/kg/day × 28 days, repeated as necessary
Echinococcus multilocularis—treatment of choice	Surgical excision		
Cysticercus cellulosae (cysticercosis)	DRUG OF CHOICE • Praziquantel ALTERNATIVE • Surgery	50 mg/kg/day in 3 doses × 15 days	50 mg/kg/day in 3 doses × 15 days
Trichinosis (*Trichinella spiralis*)	DRUGS OF CHOICE • Steroids for severe symptoms *plus* • Mebendazole	200–400 mg tid × 3 days, then 400–500 mg tid × 10 days	Same as adult dose
Trichomoniasis (*Trichomonas vaginalis*)			
	DRUG OF CHOICE • Metronidazole	2 g once or 250 mg tid or 375 mg bid PO × 7 days	15 mg/kg/day PO in 3 doses × 7 days
Trichuriasis (*Trichuris trichiura*, Whipworm)			
	DRUGS OF CHOICE • Mebendazole *or* • Albendazole	100 mg bid × 3 days 400 mg once	100 mg bid × 3 days 400 mg once
Trypanosomiasis			
Trypanosoma cruzi (South American trypanosomiasis, Chagas disease)	DRUG OF CHOICE • Nifurtimox	10–15 mg/kg/day PO in 4 doses × 120 days	1–10 yr: 15–20 mg/kg/day in 4 doses × 90 days 11–16 yr: 12.5–15 mg/kg/day in 4 doses × 90 days
	Alternative • Benznidazole	5–7 mg/kg/day × 30–120 days	Same as adult dose
Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense (African trypanosomiasis, sleeping sickness), hemolymphatic stage	DRUG OF CHOICE • Suramin	100–200 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21 Weight based: 2 mg/kg test dose followed by 10–15 mg/kg/day on days 1, 3, 7, 14, and 21	20 mg/kg on days 1, 3, 7, 14, and 21
	ALTERNATIVE • Pentamidine isethionate	4 mg/kg/day IM × 10 days	4 mg/kg/day IM × 10 days

TABLE 122.3 Drug Regimens for Treatment of Parasitic Infections—cont'd.

Infection	Drug[a]	DOSAGE: Adults	DOSAGE: Children
Late disease with central nervous system involvement	DRUG OF CHOICE		
	• Melarsoprol (Trypanosoma brucei rhodesiense)	2–3.6 mg/kg/day IV × 3 days; after 1 wk, 3.6 mg/kg/day IV × 3 days; repeat again after 10–21 days	18–25 mg/kg total during 1 mo; initial dose of 0.36 mg/kg IV, increasing gradually to max, 3.6 mg/kg at intervals of 1–5 days for total of 9 or 10 doses
	ALTERNATIVES (*T. b. gambiense* only)		
	• Tryparsamide	One injection of 30 mg/kg (max, 2 g) IV every 5 days to total of 12 injections; course may be repeated after 1 mo	Unknown
	• Eflornithine *plus*	400 mg/kg/day in 4 doses × 14 days injections; course may be repeated after 1 mo	Same as adult dose
	• Suramin	One injection of 10 mg/kg IV every 5 days to total of 12 injections; course may be repeated after 1 mo	Unknown
Visceral Larva Migrans			
Toxocariasis	DRUG OF CHOICE		
	• Diethylcarbamazine	6 mg/kg/day in 3 doses × 7–10 days	6 mg/kg/day in 3 doses × 7–10 days
	ALTERNATIVES		
	• Mebendazole *or*	100–200 mg bid × 5 days	Same as adult dose
	• Albendazole	400 mg bid × 3–5 days	400 mg bid × 3–5 days

[a]Some drugs may be available only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta; telephone, 404-639-3670 (nights, weekends, and holidays: 404-639-2888).
CDC, Centers for Disease Control and Prevention; *max,* Maximum.
Adapted from: Drugs for parasite infections. *Med Lett Drugs Ther.* 1995;37:99-108.

severe disease and death to the infected host. The female Anopheles mosquito is the arthropod vector that transmits malaria. The female ingests plasmodial gametocytes from ingesting a blood meal from an infected source. The gametocytes reproduce in the gut of the mosquito, transitioning to their sporozoite phase and migrating to the salivary glands in preparation for transmission. The plasmodia parasites enter the bloodstream of their next human host from the salivary glands of the female *Anopheles* mosquito during her blood meal. The sporozoites are trophic for human liver parenchymal cells; in hepatocytes, they undergo multiple replication rounds to form liver (extraerythrocytic) schizonts. The hepatocytes rupture, usually within 2 to 10 days after infection, releasing merozoites into the bloodstream. The merozoites invade red blood cells (RBCs), transforming into trophozoites and feeding on the hemoglobin in RBCs. Trophozoites mature into erythrocytic schizonts, which divide asexually into additional merozoites. Eventually, the erythrocyte undergoes lysis, releasing merozoites capable of infecting additional red blood cells. Although some merozoites are destroyed by the host's immune system, many enter new erythrocytes. As this cycle repeats itself, there is amplification of the number of infected erythrocytes. After several repetitions of the erythrocytic cycle, the process changes, and male or female macrogametocytes develop instead of merozoites. These gametes ingested by the mosquito, subsequently complete the reproductive cycle by fusion, which is accomplished sexually within the gut of a new female *Anopheles* mosquito after she feeds on the infected human.

Infection with *P. vivax* or *P. ovale* can manifest a dormant stage in human hepatocytes; this stage is known as the hypnozoite. Hypnozoites are metabolically inactive and thus less susceptible to standard pharmacologic therapies. Hypnozoites can eventually release merozoites into the blood stream weeks to months or even years after initial infection, initiating relapse in the host unless specific treatment for the hypnozoite stage was anticipated by the clinician treating the patient. Recrudescent infection occurs when primary blood stages of any species of *Plasmodium* are immunologically or pharmacologically controlled without being fully eradicated and the liver phase persists, thus leading to latent multiplication at a higher rate. This may occur later due to immune suppression or overlying acute illness. *P. malariae* can sometimes cause an initial asymptomatic infection, and clinical symptoms develop years or decades later.

Initial parasite replication cycles are asynchronous, as multiple liver schizonts may rupture and release merozoites into the bloodstream. The host immune response to these parasites can lead to cytokine production with fever and rigors, malaise, headache, and myalgia, in addition to a variety of other symptoms. Over time, cycles of parasite reproduction become synchronized, with 24-hour (*P. knowlesi),* 48-hour (*P. falciparum, P. vivax, P. ovale)*, or 72-hour (*P. malariae)* intervals of fever. Erythrocytes parasitized by *P. falciparum* express the parasitic protein PfEMP1, which binds to several host endothelial proteins, leading to cytoadhesion. RBC adherence to the endothelium leads to stasis of blood flow and microvascular occlusion, which can cause hypoperfusion of end organs. End-organ hypoperfusion in the brain can led to seizure, coma, and cerebral edema, which can be fatal. Hypoperfusion of other organs may lead to lactic acidosis or renal failure. Cytoadherence of parasitized RBCs may also result in low

measured levels of parasitemia or even false-negative blood smears due to sequestration of infected erythrocytes in capillary beds.

Clinical Features

Patients presenting with a fever or acute illness who have returned from travel in a region endemic for malaria should be evaluated for the possibility of malaria. Other signs and symptoms including anemia, headache, nausea, chills, lethargy, abdominal pain, and upper respiratory complaints should also be considered as manifestations of malaria.

P. falciparum is the malarial species most morbid to humans; it infects a larger percentage of the host's RBCs and is trophic for neural tissue leading to cerebral edema, seizures, encephalopathy, hypoglycemia (especially in children), metabolic acidosis, severe anemia, high-output cardiac failure, renal failure, pulmonary edema, disseminated intravascular coagulation, and death. In chronic malarial infection, increased cellularity from the host's exuberant immune response may lead to hepatosplenomegaly. Within the liver, parasites and malarial pigment distend the Kupffer cells. Parasitized RBCs also adhere to the sinusoidal system of the spleen, reducing its immunologic effectiveness. Anemia results from acute and chronic hemolysis. Hemoglobinuria caused by severe hemolysis leading to renal failure, known as blackwater fever, may occur in patients with chronic or acute falciparum malaria.

Signs of severe malaria requiring immediate IV antimalarial treatment include prostration, altered mental status (Glasgow coma scale <11), more than two generalized seizures, severe anemia (hemoglobin < 7 g/dL), acute renal failure (creatinine > 3 mg/dL or blood urea > 20 mmol/L), hyperbilirubinemia or clinical jaundice (total bilirubin > 3 mg/dL), respiratory distress or pulmonary edema, shock, hypoglycemia (glucose < 40 mg/dL), spontaneous bleeding or DIC, acidosis (bicarbonate < 15 mmol/L or lactate > 5 mmol/L), hemoglobinuria, and greater than 2% parasitemia on blood smear (i.e., more than 2% of the patient's RBCs contain malarial schizonts).

Cerebral malaria is a life-threatening complication of *P. falciparum* infection. Parasitized RBCs express malarial cell surface glycoproteins called knobs which adhere to capillary walls, resulting in sludging in the cerebral microvasculature. Impaired circulation leads to localized ischemia, capillary leakage, and petechial hemorrhages. Clinical manifestations of cerebral malaria include fever, altered mental status including obtundation and coma, and, not uncommonly, seizures. A careful history, rapid diagnosis, and immediate initiation of therapy are essential to prevent severe morbidity and death.

Differential Diagnosis

The emergency medicine clinician will most successfully diagnose parasitic infections by correlating historical features, such as exposure and travel history, with presenting symptoms that may be more nonspecific, including fever, anemia, peripheral edema, visual impairment, skin complaints, and symptoms related to the pulmonary, cardiovascular, and gastrointestinal (GI) systems. Other diagnostic considerations in at-risk travelers returning with febrile illness include more common conditions such as viral infections such as influenza or viral respiratory infections, and bacterial infections such as infectious diarrhea, urinary tract infections, and pneumonia. Cerebral malaria may manifest with confusion and mental status changes and should be differentiated from meningitis and encephalitis.

Malarial infection is often associated with anemia, particularly in children younger than 5 years. Anemia may develop quickly, from massive hemolysis in acute infection, or may have a more insidious onset, developing over months. Mature merozoites lyse parasitized RBCs. Uninfected RBCs undergo immune destruction from cell surface antibodies produced in response to parasite-associated changes in RBC surface proteins. This process of destruction is abetted by increased reticuloendothelial activity. The inhibition of erythropoietin secretion blunts the reticulocyte response in infected persons. Concomitant iron deficiency contributes to the severity of the anemia.

Diagnostic Testing

Microscopic examination of thick and thin blood films remains the gold standard for the diagnosis of malaria. Peripheral blood smears are stained with Giemsa or Wright stain and examined with ordinary light microscopy. The morphology of the intraerythrocytic schizonts allows the experienced clinician to determine the plasmodial species. In particular, *P. falciparum* has a very specific morphology, and the diagnosis can be made in a simply equipped laboratory. Even if the parasite is not visualized in the smear, treatment of malaria is indicated if the disease is suspected. The US Food and Drug Administration (FDA) has approved the use of an antigen-based rapid diagnostic test to screen patients. The Alere BinaxNOW kit provides qualitative testing for all four species and is available for approximately $5 per test. The test is not as sensitive as microscopy, which should still be performed for all patients with positive antigen test results to determine the species and severity of parasitemia.

Management

Untreated falciparum malaria can lead to coma and death; early treatment reduces morbidity and mortality. In the past, chloroquine phosphate was the treatment of choice for acute uncomplicated attacks of malaria. Resistance to chloroquine has been steadily increasing, and the drug is now recommended only in regions of known chloroquine sensitivity—Haiti, Dominican Republic, Central America north of the Panama Canal, and limited regions of the Middle East. For uncomplicated malarial infections in patients from chloroquine-resistant regions, oral quinine is given with doxycycline or clindamycin. Another suitable alternative combination is proguanil-atovaquone.

For severe *P. falciparum* infection or in patients unable to tolerate oral medication, intravenous (IV) artesunate is the recommended first-line treatment. It is available only as an expanded-access investigational new drug and must be obtained via request from the CDC (call CDC Malaria Hotline at 770-488-7788, Monday-Friday, 9 a.m. to 5 p.m. EST; at other hours call 770-488-7100). The artemisinin agents are excellent antimalarials and are available as enteral and parenteral preparations. They have a rapid onset of action and are well tolerated. An oral agent known as artemether-lumefantrine (Coartem) is now available for uncomplicated malaria, though other artemisinins are not approved for use in the United States.

Although not currently available in the United States, IV quinine or quinidine is another option for treatment of severe cases. Rapid infusion of IV quinine can cause profound hypoglycemia, as well as hyponatremia and coma vigil, a neurologic impairment due to high rates of parasite destruction. Patients should not receive IV quinine without cardiac monitoring.

Primaquine is used to eliminate the hepatic phases of *P. ovale* and *P. vivax* to prevent disease relapse. Primaquine therapy is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency because it can precipitate severe hemolysis.

Cerebral malaria is treated with IV quinine, quinidine, or artemisinin (as available), and supportive care, including mechanical ventilation for comatose patients and patients with noncardiogenic pulmonary edema, antiepileptics, and correction of acidosis and hypoglycemia. Hypoglycemia results from the high-grade falciparum parasitemia, as the protozoan is metabolically active, and the patient is often anorectic from the disease process or the quinine infusion and may be malnourished at baseline. The mortality rate is high, especially

in children, but neurologic sequelae are rare if the patient recovers. Corticosteroids, including dexamethasone, provide no benefit and can worsen outcomes. A second antimalarial, such as doxycycline or clindamycin, should always be administered in conjunction with artemisinin or quinine in these cases.

BABESIOSIS

Background and Importance

Babesiosis is a malaria-like illness that is becoming increasingly prevalent in the Northeastern United States (*Babesia microti*), northwestern United States (*Babesia gibsoni*), and Europe (*Babesia divergens*). Babesiosis is particularly endemic to Long Island, Cape Cod, Martha's Vineyard, Nantucket, and Block Island. Babesiosis must be suspected, along with ehrlichiosis/anaplasmosis and Lyme disease, in patients who live or have traveled in these regions who present with flu-like illness (see Chapter 123). *Babesia* is a protozoan, similar in structure and life cycle to plasmodia. It is transmitted by the deer tick *Ixodes dammini,* which also is the vector of Lyme disease, ehrlichiosis, and anaplasmosis. Several cases of babesiosis have been correlated with transfusions with infected blood.

Clinical Features

Patients with babesiosis experience fatigue, anorexia, malaise, and emotional lability, with myalgia, chills, high spiking fevers, sweats, headache, and dark urine. Other manifestations include hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, elevated liver enzyme levels (particularly the transaminases), and signs of hemolysis, with hyperbilirubinemia and decreased haptoglobin. In an otherwise healthy person, the disease may remit spontaneously. In asplenic, older, and immunocompromised patients, especially patients with AIDS and those taking corticosteroids, up to 85% of RBCs may contain organisms and infections may be fatal with vascular collapse and a septic shock-like presentation due to massive hemolysis, jaundice, renal failure, disseminated intravascular coagulation, hypotension, and adult respiratory distress syndrome (ARDS).

Diagnostic Testing

Diagnosis is based on clinical suspicion, multiple thin and thick blood smears (*Babesia* organisms resemble plasmodia in blood smears), and serologic testing (convalescent titers may not be positive for several weeks after infection).

Management

The treatment of choice consists of atovaquone (750 mg BID orally) plus azithromycin (500–1000 mg once followed by 250 mg once daily orally) or, for severe illness, quinine (650 mg TID orally) plus clindamycin (1.2 g bid IV or 600 mg TID). Patients infected with *B. divergens* tend to be sicker and require more supportive care. Coinfection with *Borrelia burgdorferi,* the agent of Lyme disease, results in a more severe and prolonged illness.

SCHISTOSOMIASIS AND KATAYAMA FEVER

Background and Importance

The acute phase of schistosomiasis infection causes Katayama fever. Schistosomiasis is a trematode infection acquired through skin contact with freshwater habitats of snail species that are the intermediate host for the parasite. Motile cercariae are released from the snail and penetrate the skin of a person wading in the water. In the human host, the cercariae mature into schistosomulae, which migrate through the bloodstream to the host's lungs, and, subsequently, to the venous plexi of the gastrointestinal or genitourinary organs where they mature into adult worms and begin laying eggs. One to three months after the host is exposed to the parasite during the migration and early egg-production phases of infection, patients who have experienced prior infection develop nocturnal fever, diaphoresis, cough, wheezing, myalgia, headache, or abdominal pain. Infected patients may report brief exposures to fresh water in endemic areas.

Diagnostic Testing

Diagnosis depends upon positive schistosome serology and appropriate exposure history, correlated with the detection of eggs in urine or stool. Initial serology and egg examination may be falsely negative at the time of initial presentation and should be repeated at three-month intervals. Lab tests often reveal eosinophilia. Radiographs may reveal diffuse pulmonary infiltrates or nodules.

Management

Treatment should be initiated based on clinical suspicion because initial testing may provide false-positive results. In returning travelers with isolated exposure and low infectious burden, the most concerning result of untreated schistosomiasis is the embolization of schistosome eggs to small venules in the central nervous system creating intense inflammation, fibrosis, and tissue destruction manifesting as transverse myelitis or central nervous system lesions. Treatment consists of praziquantel in single dose or three-day course, as well as corticosteroids to reduce the severity of the inflammatory reaction.

CYSTICERCOSIS

Background and Importance

Cysticercosis is caused by the larval form of *Taenia solium,* a tapeworm, which is neurotrophic and endemic in many tropical areas. Ingestion of undercooked pork containing *T. solium* cysterici leads to tapeworm infection in the human intestine. Human cysticercosis is acquired via the fecal-oral route through accidental ingestion of stool containing eggs shed by the adult tapeworm. Autoinfection may occur when an individual unknowingly infected with a tapeworm fails to practice adequate hand hygiene, and household infection may occur through contamination of the environment, or of food and water sources. Once the egg is ingested, it hatches in the small intestine, releasing a larva that penetrates the gut wall and migrates throughout the host's body with particular trophism for the CNS, muscle, and soft tissue. The larvae encyst, and the ensuing local inflammation and fibrosis create a nidus for seizure activity in the brain. Neurocysticercosis is the leading cause of acquired epilepsy worldwide.

Clinical Features

In the brain, a *T. solium* larva forms an expanding cyst that induces an intense immunologic reaction, including inflammation, edema, fibrosis, and, ultimately, calcification. Cysts may be single or multiple. Neurologic abnormalities develop when neural tissue cannot accommodate the enlarging cyst. Seizure activity is often the first indication of cysticercosis, which should be considered in the differential diagnosis of new-onset seizures in adults. Racemose cysticercosis occurs when cysterici lodge in the cerebral ventricles or subarachnoid space, leading to hydrocephalus, cranial nerve deficits, vasculitis, and stroke.

Diagnostic Testing

The diagnosis of cysticercosis can be made by pairing the finding of characteristic cysts with scolices on noncontrast cranial computed tomography (CT) or magnetic resonance imaging (MRI) with positive serology for *T. solium*. Stool may reveal eggs of *T. solium* if the patient

has a living worm in their gut. Brain lesions can mimic a CNS abscess, metastatic malignant disease, or primary tumor such as glioblastoma multiforme.

Management

Treatment of neurocysticercosis consists of a 10- to 14-day course of albendazole 400 mg BID alone, or albendazole with praziquantel 50 to 100 mg/kg/day, divided q8hr, depending on the number of cysts present. Consultation with an infectious disease specialist is appropriate. Corticosteroids and antiepileptics are important adjunct medications during therapy, because CNS cysts can release highly antigenic inflammatory material as they die and necrose. We recommend dexamethasone 10 mg and levetiracetam 1000 mg for most adult patients. Neurosurgical consultation is warranted for ventricular or subarachnoid cysts, or in the presence of hydrocephalus, elevated ICP, or mass effect.

AFRICAN TRYPANOSOMIASIS

Background and Importance

African sleeping sickness is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. This infection is endemic in limited areas of West and East Africa. Several recent cases have been reported in travelers who have returned from safari in East Africa. The motile organisms are transmitted by the bite of the *Glossina* (tsetse) fly, which introduces the infective form of the trypanosome into the host's blood. A small lesion or boil may develop and persist for several days. The flagellated organism travels throughout the bloodstream, invading the lymph nodes and spleen.

Clinical Features

The patient generally is febrile, and a maculopapular rash can often be seen. Once the parasite invades the CNS, cerebral inflammation causes severe headache. The Winterbottom sign, which is posterior cervical lymphadenopathy, usually is apparent at the time of initial presentation. Patients may display altered mental status, psychiatric symptoms, and eventually, extreme sleepiness and lethargy. Coma and death from starvation and trypanotoxins are inevitable in untreated patients.

Diagnostic Testing

An appropriate exposure history and characteristic symptoms should prompt the clinician to obtain diagnostic studies. The diagnosis is established when trypanosomes are found in peripheral blood, CSF, or lymph node and bone marrow aspirates. The presence of parasites in the CSF indicates advanced progression of the disease.

Management

Suramin sodium, given as 100 to 200 mg IV for a test dose, then 1 g IV on days 1, 3, 7, 14, 21, is the treatment of choice for early infection with *T. b. rhodesiense*. Pentamidine isethionate 4 mg/kg IM a day is the preferred treatment for early *T. b. gambiense* infection. Melarsoprol is used in CNS disease from *T. b. rhodesiense*; eflornithine is used in combination with nifurtimox in CNS disease from *T. b. gambiense* infection.

TOXOPLASMOSIS

Background and Importance

Toxoplasma gondii is a zoonotic protozoan that is estimated to infect one-third of the human population globally; however, clinically significant infection is rare, and is most often seen in congenitally acquired infection or in immunocompromised individuals, particularly those with HIV. CNS disease includes cerebral mass lesions, encephalitis, and chorioretinitis. Infections rarely occur in immunocompetent individuals.[3]

Clinical Features

Toxoplasma oocysts are infectious forms in the intestines of the usual host, members of the cat family. Oocysts shed in cat feces often contaminate food and water ingested by other mammals, leading to the formation of cysts in a variety of tissues. Humans generally become infected by one of two routes: ingestion of oocysts through environmental contamination in proximity to cats, or ingestion of raw or undercooked meat harboring tissue cysts. Upon ingestion of cysts, tachyzoites are released and disseminated through the blood or lymphatics, leading to an acute phase of infection. Acute infection manifests as fever, malaise, headache, myalgia, and lymphadenopathy, and can cause posterior uveitis in immunocompetent patients. Eventually, the host's immune system controls the acute infection, but cysts in tissues persist, supporting dormant infections. In immunocompromised hosts, the cysts release bradyzoites initiating reactivation. CNS toxoplasmosis has been a significant cause of morbidity and mortality in patients with advanced AIDS.

Diagnostic Testing

Serologic testing identifying IgM (acutely) or serially rising IgG levels support the diagnosis. The general population worldwide has a large prevalence of seropositivity with IgG titers, thus one positive titer does not suggest infection. PCR performed on body fluids or specific tissues is highly specific for infection and has a sensitivity of 70% to 95%. The classical finding in immunocompromised patients with CNS disease is a ring-enhancing lesion on contrast-enhanced CT.

Management

Therapeutic options include pyrimethamine 50 to 75 mg a day with sulfadiazine 1 to 1.5 gm QID or clindamycin 450 mg q6 to 8 hours. Pyrimethamine is a folate antagonist, so folic acid is often given with prolonged courses.

EOSINOPHILIC MENINGITIS

A number of helminths, including those that typically complete their life cycles in animal hosts, only infecting humans incidentally, can migrate to the brain and cause severe disease, including meningitis and intracerebral hemorrhage.

Angiostrongylus cantonensis, the rat lung worm, typically infects rats, and has snail species as intermediate hosts. Larvae may infect humans, either through ingestion of undercooked snail, which may be part of dietary practice in some cultures, or as has been reported in teens responding to a prank or dare, or through ingestion of vegetables that have been contaminated by snail slime. In infected humans, larvae migrate to the brain causing headaches, vomiting, and altered mental status. *Baylisascaris procyonis* is an intestinal roundworm found in racoons. Raccoon "latrines," sites of frequent raccoon urination and defecation, are often teeming with *B. procyonis* eggs. Geophagia or hand contamination and subsequent ingestion, especially among young children, can lead to significant human infection, with tropism for the brain and eye leading to severe neurologic sequelae and death.

Gnathostoma spinigerum is a roundworm that incidentally infects humans consuming raw or undercooked freshwater fish, including ceviche. Most cases occur in Southeast Asia and Latin America, initially manifesting as a migratory inflammatory swelling of the skin with subcutaneous hemorrhages. Migration to the brain and spinal cord causes eosinophilic meningitis, coma, cranial nerve deficit, and massive subarachnoid hemorrhage from erosion into cerebral arterioles. Cases of

CNS involvement with *Trichella spiralis* have been reported and are associated with cerebral edema and CNS vasculitis. *Toxocara canis* can also cause CNS disease. *Paragonimus westermani* occasionally causes eosinophilic meningitis or focal neurologic findings that demonstrate a classic cluster of ring-enhancing lesions on contrast-enhanced CT, with a "soap bubble" appearance.

Eosinophilic meningitis is diagnosed by CSF pleocytosis (>10 WBC/hpf) with at least 10% eosinophils, though up to 50% eosinophils may be seen. CT or MRI findings may suggest a particular helminthic infection, but serologic testing will be confirmatory. Treatment consists of appropriate antihelminthic therapy and corticosteroids. Albendazole is used for *Angiostrongylus, Baylisascaris, Gnathostoma,* and *Toxocara.* Ivermectin, in weight-based dosing, is an alternative for *Gnathostoma.* Praziquantel treats *Paragonimus* whereas mebendazole 100 mg PO q12hr or thiabendazole 500 mg PO are the drugs of choice for *Trichella.* The clinician should obtain neurosurgical consultation if there is evidence of mass or hemorrhage.

PARASITES ASSOCIATED WITH FEVER

Other parasitic illnesses that commonly present with fever include visceral leishmaniasis, and toxoplasmosis. Fascioliasis and amoebic liver abscess also generally present with fever.

Leishmaniasis

Leishmaniasis is spread to humans by the sandfly and is found in the Middle East, India, East Africa, Brazil, and along the Mediterranean coast. Although leishmaniasis can involve the skin (cutaneous) and mucosa (mucosal), fever is seen only in visceral leishmaniasis in immunocompetent persons. Patients present with massive hepatosplenomegaly, neutropenia, and weight loss.

Amebic Abscess

Amebic abscess of the brain or meningoencephalitis is a rare complication of infection with *E. histolytica* after ingestion of amebic cysts. Spread of amebae to the brain or meninges from the colonized large bowel wall is rare but should be considered in any patient with amebiasis and neurologic signs or symptoms. The diagnosis may be made by microscopic identification of trophozoites (motile amebae) in CSF; however, biopsy of affected tissue is more specific. CNS amebiasis is treated with IV metronidazole but may require neurosurgical intervention.

Naegleria fowleri, *Acanthamoeba* spp., and *Balamuthia mandrillaris* are free-living freshwater amoebae that infect patients swimming and diving in ponds and lakes. These organisms invade the CNS through the olfactory neuroepithelium or compromised corneal epithelium that has been violated by abrasion or contact lens wear, often resulting in devastating amebic meningoencephalitis. Cases of *Balamuthia* amoebic encephalitis are often preceded by skin lesions or rhinitis. Due to the rarity of the condition, there is little data on the efficacy of different therapeutic agents, but a pharmacologic regimen of five drugs is generally recommended. Therapeutic options include amphotericin B, miltefosine, fluconazole or miconazole, rifampin, azithromycin, flucytosine, and sulfadiazine. Treatment is initiated when motile amoebae are identified in CSF.

Strongyloides

Strongyloides stercoralis infection is a common disease in the tropics. The worm enters through the host's skin and migrates to their small bowel. Infection with *Strongyloides* is more clinically significant in immunosuppressed patients, particularly transplant patients or those with autoimmune disease who are treated with high-dose corticosteroids. Patients will manifest larval dissemination, with subsequent encephalitis and pyogenic meningitis. *Strongyloides* infection is treated with thiabendazole or albendazole. Ivermectin has recently been found to be as effective with fewer side effects, and we recommend this as a first-line agent.

WHIPWORM AND HOOKWORM

Infestation by the whipworm *Trichuris trichiura,* and especially by the two human hookworms *Necator americanus* and *Ancylostoma duodenale,* is a major cause of iron deficiency anemia worldwide. Adult worms penetrate intestinal mucosa and feed using mouthparts consisting of hooks or biting plates, causing significant luminal blood loss. Eggs are shed in the feces and mature in the soil, hatching to release a rhabditiform larva that subsequently develops into the infective filariform larva. These larvae penetrate the human skin, usually through the feet. In trichuriasis, anemia is seen only with massive parasite infestation. Ova from the whipworm are ingested through food and water contaminated with feces. Diagnosis of these infections requires identification of characteristic ova in the stool. As with most helminthic infections, peripheral eosinophilia is common. Mebendazole or albendazole effectively controls trichuriasis and hookworm infections in adults and children. Anemic patients should be further worked up and receive iron supplementation.

TAPEWORM

Infection with the fish tapeworm, *Diphyllobothrium latum,* is associated with pernicious anemia. This tapeworm competes with the human host, absorbing vitamin B_{12} from the host's intestine. Infection is acquired when the host ingests raw freshwater fish that contains the plerocercoid larvae in its muscle fiber. The larva develops in the human small intestine into an adult tapeworm that can grow to be longer than 15 meters and can live up to 20 years. The diagnosis is made by identification of the ova in the feces. Praziquantel is the drug of choice for adults and children.

PARASITES ASSOCIATED WITH CUTANEOUS MANIFESTATIONS

Elephantiasis

Elephantiasis, a manifestation of lymphatic filariasis, is the development of massive peripheral edema, with distention and thickening of the overlying epidermis, which acquires the appearance and texture of elephant skin. Elephantiasis is caused by infection with the filarial worm *Wuchereria bancrofti* or *Brugia malayi*. The infection is confined to humans and is widely distributed in the equatorial regions of the world, including Africa, Asia, South America, and Oceania. More than 90% of all infections are found in Asia, where the disease has reached epidemic proportions. Even in endemic regions in which most residents are infected, the disease is rare among travelers. Infected mosquitoes introduce larvae into the bloodstream of the human host during a blood meal. After infecting the host, the worms migrate into the lymphatic system and mature into coiled gravid adults. The adult worm triggers a robust inflammatory reaction in the lymphatic vessels, particularly in the lower extremities and genitalia. The macrophages, lymphocytes, plasma cells, giant cells, and eosinophils migrate to the inflamed and fibrotic lymphatic vessels, which becomes erythematous, edematous, and tender, suggesting the diagnosis of filariasis.

Chronic manifestations of filariasis include fibrosis of a lymphatic vessel containing a dead or calcified worm. Subsequent mechanical

blockage of the lymphatic system leads inevitably to severe lower extremity and genital edema accompanied by thickening of the skin. Recurrent cellulitis is common in these patients; prevention of superinfection requires meticulous skin care.

Diethylcarbamazine 50 mg orally rapidly clears the microfilariae from the peripheral blood and slowly sterilizes the gravid female nematode. Combined therapy with diethylcarbamazine and albendazole, or ivermectin and albendazole, may be more effective. Treatment with doxycycline eradicates *Wolbachia,* a symbiotic bacterium of the filarial parasite, increasing rates of eradication of the adult worm. Established elephantiasis of the scrotum can be successfully treated surgically. Chronic lymphatic obstruction of the limbs rarely responds to operative intervention.

Cutaneous Leishmaniasis

Cutaneous leishmaniasis is one of the most important causes of painless, chronic, ulcerating skin lesions globally. *Leishmania braziliensis* and *Leishmania mexicana* are responsible for New World leishmaniasis; *Leishmania tropica* and *Leishmania major* commonly cause Old World leishmaniasis. During a blood meal, a female sandfly of the species *Phlebotomus* or *Lutzomyia* transmits the promastigotes, which are then ingested by host macrophages and survive in their amastigote form in the skin.

Skin papules and nodules are seen early in the course of infection at the insect bite site. A raised lesion also can appear, which subsequently develops painless central ulceration and a raised border. Lymphocyte and macrophage invasions of the epidermis and dermis cause the induration that occurs at the ulcer border. Secondary bacterial infection of these ulcers increases the risk of associated scarring. *L. braziliensis braziliensis* (subspecies of *L. braziliensis*) can lead to spread of parasites from the primary lesion to the mucocutaneous skin borders (i.e., in tissues of the nose and mouth). Mutilation of the face occurs after massive tissue and nasal cartilage destruction. The soft palate, larynx, and trachea also can be involved, compromising the airway. Disseminated cutaneous leishmaniasis (*L. mexicana amazonensis* in South America and *L. tropica aethiopica* in Ethiopia) is characterized by diffuse nodules and papules resembling those of lepromatous leprosy (Fig. 122.1). Persons with this manifestation of leishmaniasis are thought to have a defect in their cell-mediated immune response.

Definitive diagnosis of leishmaniasis is made by direct visualization of the parasite with light microscopy. Diagnosis can also be made by an indirect fluorescent antibody test. Results of intradermal skin testing with parasite antigen often are negative during the acute stages of the disease.

Many forms of cutaneous leishmaniasis, especially *L. tropica* and *L. mexicana* infection, are self-limited and require no treatment unless the wounds become secondarily infected. Treatment options for advanced disease include sodium stibogluconate, meglumine antimonate, amphotericin B, miltefosine, fluconazole, and paromomycin. These treatments are rarely initiated in the ED setting.

Cutaneous Larva Migrans

Cutaneous larva migrans (CLM), the creeping eruption, occurs in the host's epidermis when the skin is penetrated by *Ancylostoma braziliense* (dog or cat hookworm) larvae. Exposure usually occurs after the host walks barefooted or lies directly on beaches or other warm soil contaminated by animal feces. The diagnosis is visual with a characteristic meandering erythematous track on the skin surface caused by larval migration. Visceral larva migrans occurs in young children after the ingestion of soil containing ova from the dog ascarid *Toxocara canis*. Thiabendazole, ivermectin, or albendazole may be used for treatment of cutaneous larva migrans, and antipruritics give symptomatic relief. Diethylcarbamazine treats visceral larva migrans. An alternative is thiabendazole.[2]

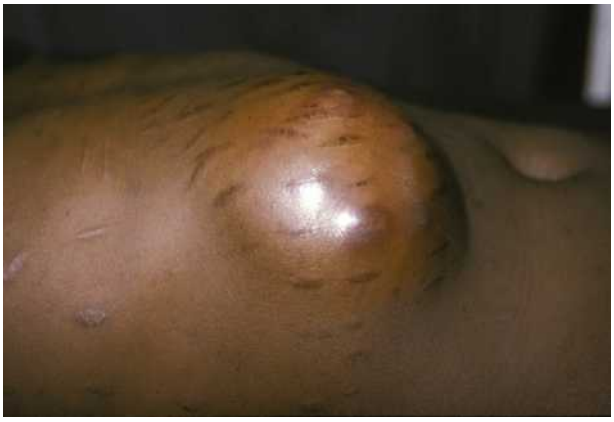

Fig. 122.1 Cutaneous leishmaniasis.

Swimmer's Itch (Cercarial Dermatitis)

Swimmer's itch is a dermatitis that occurs when skin is penetrated by a schistosome that is trophic for avians and nonhuman mammals while the patient usually was swimming in northern US freshwater lakes. The infection spontaneously resolves when the human host's immune system destroys the schistosome. A similar dermatitis also can occur after infection with schistosome species that are trophic for humans. Treatment is symptomatic.

Strongyloides

Strongyloides can cause a transient pruritic rash known as larva currens that may appear and then disappear within hours. *Taenia solium* can cause cysts in the soft tissues and muscles. These cysts often are an incidental finding. Onchocerciasis (from *Onchocerca volvulus*), common in West Africa and parts of South America, can cause severe pruritus and nodules overlying bony protuberances.

Dracunculus medinensis

Dracunculus medinensis, the fiery serpent, commonly referred to as Guinea-worm disease (GWD), is a parasite known since antiquity, which was once widely distributed in Africa and the Middle East. As the worm develops, it migrates to the subcutaneous tissues of the leg, where a painful blister forms; when the overlying skin is compromised, the worm emerges to release eggs into water. GWD has been eradicated and is currently primarily of interest for the success of this worldwide campaign, which has brought case numbers worldwide down from over 3 million in the 1980s to fewer than 100 per year over the last five years. While public health experts expect that GWD will be the first parasitic disease to be globally eradicated, COVID-19 has interrupted treatment programs and threatened years of progress.

PARASITES ASSOCIATED WITH OCULAR MANIFESTATIONS

Many different worms migrate to or through the eye, causing inflammation, tissue destruction, and blindness.

Onchocerciasis

Onchocerciasis is a major cause of blindness in the world; 95% of cases occur in Africa. The parasite is found only in humans and is transmitted by the bite of the *Simulium* fly. These flies live near rivers—hence, the common name of the disease, river blindness. Microfilariae of *O.*

Fig. 122.2 Patient with onchocerciasis (river blindness).

volvulus are released by adult nematodes, which coil in subcutaneous nodules in the infected host; the microfilariae then migrate through the dermis and epidermis. The presence of adult worms stimulates a brisk immune response, including the infiltration of lymphocytes, macrophages, plasma cells, and eosinophils.

The skin becomes chronically edematous and pruritic; it then atrophies, resulting in loose, thin folds of skin, known as lizard skin. River blindness is more likely to develop in patients with nodules close to the eyes. When the microfilaria dies during its migration in the eye, the immunologic response to parasitic antigens leads to sclerosing keratitis, which is the major cause of ocular destruction and subsequent blindness (Fig. 122.2). Posterior ocular disease can also occur, leading to subretinal fibrosis.

Onchocerciasis is diagnosed by identifying characteristic microfilariae in skin snipped from the patient. Ivermectin is the therapeutic drug of choice. Surgical excision of the subcutaneous nodules is recommended when they are located on the head.

Loiasis

Loiasis is confined to forest areas in West and Central Africa. Transmission of *Loa loa* occurs through the bite of flies of the genus *Chrysops*. The disease is caused by migration of the adult worm in the subcutaneous tissue. The edema initially associated with migration of the worm is called a Calabar swelling. The adult worm occasionally migrates through the subconjunctival tissues of the eye and can be surgically excised from the conjunctiva. Although it is upsetting to the patient, the disease is generally fairly benign. The adult worm releases sheathed microfilariae into the peripheral bloodstream during the daytime.

Microfilariae can be detected in a thick blood smear, securing the diagnosis of loiasis. The treatment of choice for *L. loa* infection is diethylcarbamazine. Albendazole is also effective. Corticosteroids or antihistamines should be used to supplement specific chemotherapy because of the intense allergic reaction when the dead adult worms and microfilariae disintegrate. Heavy infections require plasmapheresis before administering antihelminthic treatment to avoid encephalitis precipitated by dying microfilaria.

Toxocara canis (Dog Roundworm)

Toxocara canis (dog roundworm) has a trophism for the host's eyes. Toxocariasis is a roundworm infection found in urban dogs. Humans ingest eggs by the fecal-oral route. The larvae migrate and often enter the retina, where they become trapped. They stimulate an immune response that culminates in granuloma formation. These granulomas can impair vision and sometimes are mistaken for retinal tumors. There is no means of direct diagnosis except tissue biopsy. Although serologic tests are available, results may be unreliable. Infection is treated with albendazole and steroids; larvae visible in the retina can be destroyed with a laser.

PARASITES ASSOCIATED WITH PULMONARY MANIFESTATIONS

A number of parasitic infections may be associated with pulmonary symptoms, although the presence of pulmonary findings may not be sufficient to differentiate between various forms of parasitic diseases. Patients with *P. falciparum* malaria initially may seek treatment for fever and cough, further necessitating the consideration of malaria in travelers with apparent respiratory symptoms. Early in the course of treatment for severe malaria, noncardiogenic pulmonary edema or ARDS may develop, necessitating mechanical ventilation with positive end-expiratory pressure.

E. histolytica can cause sympathetic pleural effusions, pulmonary or pleural involvement by direct extension or rupture of an amebic liver abscess, or direct hematogenous seeding of the lungs, leading to considerable additional morbidity and mortality among patients with underlying amebic infection.

Löffler syndrome, characterized by persistent and nonproductive cough, substernal chest pain, wheezing, rales, pulmonary infiltrates on the chest radiograph, and marked eosinophilia, often is seen when larvae from the roundworm *Ascaris lumbricoides,* the hookworms *N. americanus* and *A. duodenale,* and the threadworm *Strongyloides stercoralis* transit the lungs as part of their developmental cycles. *Ascaris* larvae penetrate the small intestinal wall to gain entry into the small venules of the GI tract and then migrate to the lungs. *Strongyloides* and hookworm filariform larvae penetrate through the skin of the feet, entering small cutaneous venules before migrating to the lungs. The pulmonary infiltrates and symptoms are transient, resolving within 2 weeks. Diagnosis depends on the discovery of larvae in sputum or gastric aspirates. Negative stool examinations initially are nondiagnostic because eggs do not appear in the stool for at least one month after initial infection.

Tropical pulmonary eosinophilia is a syndrome that can result from the patient's immune response to the microfilariae of *W. bancrofti* and *B. malayi*. Affected patients present with malaise, weight loss, new-onset nocturnal wheezing and asthma, shortness of breath, and chest discomfort. Chest radiographs may show nodular or interstitial infiltrates, consolidations, or cavitation, but are sometimes normal. Untreated infection may result in obstructive or restrictive lung disease. Patients have marked eosinophilia and elevations of serum immunoglobulin E levels. Serologic testing demonstrates antibodies to filaria, and microfilaria can be seen on nocturnal blood smears. Young men are more commonly affected.

Paragonimus westermani and echinococcal species are trophic for the lungs in their human hosts. *P. westermani* eggs are shed in stool, hatch in fresh water, and, as miracidia, infect a snail intermediary. After further development, cercariae are released from the snail, penetrating and encysting in freshwater crabs or crayfish. If the human host consumes raw or undercooked shellfish, the metacercariae excyst within the host's duodenum, penetrating the duodenal wall into the abdominal cavity. The larvae migrate from the peritoneal cavity through the diaphragm into the pleural cavity, finally migrating to the lungs, where they cause hemorrhage, necrosis, and a granulomatous response. Early in the process, patients may have infiltrates and eosinophilia; later disease is marked by bronchiectasis, chronic bronchitis, fever, hemoptysis, and cachexia. Pulmonary nodules and cysts may cavitate. Many of these patients may have a positive result on purified protein derivative (PPD) testing, and their symptoms and chest radiographic findings may mimic those of tuberculosis. Sputum often is blood-streaked and

flecked with dark brown particles containing ova. Radiography, stool examination, and immune testing of sputum and blood are all helpful in making the diagnosis, and finding ova in sputum is diagnostic. Praziquantel is the therapeutic agent of choice.

E. granulosus causes pulmonary hydatid cyst disease; the host often remains asymptomatic until a cyst grows large enough to cause a mass effect or becomes superinfected. Pulmonary hydatid cysts also may be associated with cough, expectoration of cyst contents, chest pain, and/or hemoptysis. A thoracic CT scan may show a unilocular lung cyst; on a plain radiograph, a cyst with detached germinal membrane is said to resemble a water lily, a pathognomonic finding. Lung cysts can be treated with careful surgical excision or pharmacotherapy, depending on size.

PARASITIC DISEASES WITH CARDIOVASCULAR MANIFESTATIONS

Chagas Disease

Trypanosoma cruzi infection often leads to acute and chronic myocarditis. *T. cruzi* is endemic in South and Central America and causes Chagas disease. The vector is the reduviid bug (kissing bug) that inhabits the walls and roofs of thatched dwellings built adjacent to forests. Urban transmigration has expanded the epidemiologic scope of Chagas disease, which was previously a disease of rural populations. The disease is not seen commonly in travelers. The reduviid bug's bite is no longer the only source of *T. cruzi* infection; transfusion with blood containing live trypanosomes from infected hosts has been a growing source of infection. Oral transmission also has been reported through consumption of infected fruit.

The reduviid bug bites the patient, often around the eye, and excretes feces containing the trypomastigote of *T. cruzi*. The trypomastigote enters the inflamed bite wound or other mucosal or conjunctival surfaces, causing a local swelling called a chagoma. The Romaña sign (painless unilateral periorbital edema) is pathognomonic but rarely seen. The trypomastigote migrates to trophic tissues, including smooth muscle, cardiac muscle, and autonomic ganglia in the heart, esophagus, and colon, causing local inflammation and tissue destruction.

Acute infection is heralded by fever, facial and dependent extremity edema, hepatosplenomegaly, lymphadenopathy, malaise, lymphocytosis on peripheral blood smear, and elevated liver transaminase levels. At this stage, fatal left ventricular dysfunction and dysrhythmias are uncommon. Early illness lasts 1 to 2 months and resolves spontaneously, resulting in a latency known as the indeterminate phase, which can persist throughout the patient's lifetime.

In approximately 25% of cases, the infection progresses to chronic Chagas disease, principally with cardiomyopathy and GI pathology. Amastigotes invade cardiac muscle and the cardiac conduction system, causing chronic inflammation, mononuclear cell infiltration, and fibrosis. Involvement of the conduction system may lead to atrial bradydysrhythmias, right and left bundle branch blocks, complete heart block, and ventricular dysrhythmias, including ventricular fibrillation (see Chapter 65). Fibrosis and scarring from cardiac muscle infection leads to the development of right and left ventricular dysfunction and dilated cardiomyopathy. Mural thrombi are common, and the first indication of long-standing asymptomatic infection may be thromboembolic disease, such as stroke, pulmonary embolism, or peripheral arterial embolism. Heart failure is generally rapidly progressive and fatal within months unless treated with pharmacologic intervention and transplantation[4] (see Chapter 67).

Acute Chagas disease can be diagnosed by the presence of motile trypomastigotes in anticoagulated blood specimens. The organism also can be cultured in special liquid media. Chronic Chagas disease can be diagnosed by one of several serologic tests, including complement fixation, enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence testing. The assays are nonspecific, and cross-reaction may occur in the presence of underlying malaria, syphilis, leishmaniasis, and some collagen vascular diseases. Polymerase chain reaction (PCR) is the gold standard for diagnosing acute or congenital infection, or immunosuppression-induced reactivation.

Nifurtimox 8 to 10 mg/kg/day orally divided every 6 to 8 hours and benznidazole 5 to 7 mg/kg/day orally every 12 hours are used for treatment of *T. cruzi* infection. Cure rates rarely exceed 50%. The duration of treatment with nifurtimox is prolonged, and the drug has many serious side effects. Benznidazole has fewer side effects, is FDA approved in children ages 2 to 12, and is now recommended for indeterminate-phase treatment. Nifurtimox is available under investigational protocols from the CDC. (It can be obtained by calling 404-639-2888).

Late complications of chronic diseases are modulated by autoimmune activity and do not respond to antiparasitic pharmacotherapy. Chronic Chagas disease of the heart, esophagus, or colon is treated symptomatically. Automated implantable cardioverter-defibrillators decrease the incidence of sudden death in infected patients. Patients receiving immunosuppressive therapy to prevent rejection after cardiac transplantation have developed recurrent disease in the transplanted myocardium.

PARASITIC DISEASES WITH GASTROINTESTINAL MANIFESTATIONS

Diarrhea

Diarrhea is one of the most common symptoms motivating travelers to seek medical attention. Diarrhea also is the leading cause of death in children younger than 5 years in developing countries and a major source of morbidity for older children and adults. Most diarrheal disease is viral or bacterial; however, some clinically significant diarrheal disease is caused by parasites.

Cryptosporidium and Cyclospora

Cryptosporidium parvum and *Cyclospora cayetanensis* are foodborne and waterborne coccidians that cause watery diarrhea. Both are particularly significant causes of morbidity in malnourished children and patients with AIDS. Cryptosporidial oocysts can be seen in stool when an acid-fast stain is used. ELISA and immunofluorescent assays of stool also are available for this organism. Paromomycin 25 to 30 mg/kg/day in 3 doses decreases diarrheal frequency in patients with AIDS with cryptosporidial infections; without treatment, patients have prolonged, disabling symptoms. Severe infections in immunocompetent patients can be treated with nitazoxanide 500 mg twice daily. *Cyclospora* oocysts can be detected in stool samples with a Ziehl-Neelsen stain. Trimethoprim-sulfamethoxazole treats this infection.

Entamoeba histolytica

E. histolytica causes an invasive or inflammatory diarrhea. Patients complain of fever, tenesmus, abdominal pain, and watery stool containing blood and mucus. Untreated disease can progress to widespread colitis and perforation of the bowel wall, with peritonitis and death. Stool examination reveals mobile trophozoites containing ingested RBCs. Cysts noted on stool studies do not necessarily reflect active infection because there are nonpathogenic ameba species occasionally found in the bowel of healthy adults. However, nonpathogenic entamoeba do not contain host RBCs. Immune assays of stool can now differentiate between *E. histolytica* and these nonpathogenic ameba

species. Serologic tests may be useful for an infected patient from a nonendemic region, but patients will not have a positive test result for one month after initial infection. Metronidazole 750 mg every 8 hours is the drug of choice for treatment of amebiasis.

Entamoeba histolytica can also cause hepatic abscesses. The patient presents with high fevers, elevated white blood cell counts, right upper quadrant pain, weight loss, anorexia, but no jaundice. Affected patients typically do not have amebic dysentery and do not shed *Entamoeba* in their stool, but results of serologic studies are almost always positive. These patients are treated with metronidazole or tinidazole 2 g/day and a luminal amebicide, such as iodoquinol 650 mg three times a day or paromomycin. Drainage of the abscess is not indicated but will yield a viscous liquid often described "anchovy paste."

Balantidium coli

Balantidium coli is another protozoan that can cause invasive diarrhea. The usual hosts are pigs. It has tropism for the terminal ileum, sometimes causing a clinical picture suggestive of appendicitis. It can also infect the colon, causing abdominal pain, fever, diarrhea, and occasionally colonic perforation. Tetracycline, metronidazole, and iodoquinol are active against *B. coli*.

Giardia lamblia

Giardia lamblia can cause persistent diarrhea, abdominal bloating, cramps, flatulence, and significant weight loss. The organism is ingested and reproduces exponentially in the small bowel. In severe infection, the entire jejunum becomes covered with organisms, and the patient has malabsorption with steatorrhea. The organisms are rarely seen in fresh stool preparations because they quickly break down and become indiscernible. Accordingly, an antigen test often is used to confirm the diagnosis. *Giardia* has many animal reservoirs, including the beaver—thus the lay term, "beaver fever." Campers who drink unfiltered, "pure" mountain spring water in the United States commonly contract *Giardia* infection. Men who have sex with men are also at high risk from a fecal-oral route of transmission. Metronidazole, tinidazole, or nitazoxanide treats the disease.

S. stercoralis, *Capillaria philippinensis*, *T. trichiura*, and *Schistosoma* infections can cause diarrhea. Hyperinfection or dissemination of *Strongyloides* can cause persistent diarrhea, weight loss, and abdominal pain. *Trichuris* causes diarrhea when the parasite load in the intestine is high. Schistosomiasis can cause a chronic granulomatous colitis, which may resemble inflammatory bowel disease, or an acute, bloody, febrile colitis associated with Katayama fever in the immunologically naïve patient.

In chronic schistosomiasis, worm pairs in patients' mesenteric and portal venous systems lay eggs that become ensnared in the liver, causing intense local inflammation, scarring, and classic "pipestem" cirrhosis, with periportal fibrosis. Clinical manifestations in these patients include portal hypertension, ascites, and esophageal varices (Figs. 122.3 and 122.4). Upper GI bleeding is not as common as in patients with alcoholic cirrhosis; however, many patients are infected with schistosomiasis in endemic regions, so variceal bleeding is an important cause of GI hemorrhage in these populations.

Fig. 122.3 Pipestem cirrhosis with extensive ascites in a patient with chronic schistosomiasis.

Fig. 122.4 Extensive ascites in a child, which may be from schistosomiasis or kala-azar (leishmaniasis).

Echinococcosis

Echinococcus granulosus is a tapeworm capable of causing disease in a number of organs, most commonly the liver, lung, bone, and CNS. The *Echinococcal* life cycle usually occurs outside of humans, with dogs and other canid species harboring the adult tapeworm in their intestinal tract. Sheep and other grazing animals ingest eggs shed in the stool of dogs in pastural areas. In the sheep, eggs hatch, penetrate the intestine, and migrate to other tissues where they form cysts. The life cycle is completed when infected viscera of sheep are consumed by dogs. This usually occurs when sheep are slaughtered for food, and the discarded offal is fed to dogs. Humans become incidental end hosts when they ingest eggs from an environment (often food or water) contaminated by the feces of infected dogs.

In humans, infection results in the liberation of the embryonic oncosphere into the small intestine. *Echinococcal* larva then penetrate the intestinal wall and migrate to many organs, where they form enlarging hydatid cysts. Hydatid cysts are loculated structures containing a germinal epithelium, which produces the multiple infectious protoscoleces (heads) of the adult worm, as well as daughter cysts. The liver is the target organ in more than two-thirds of cases, with 20% occurring in the lungs, 6% in the spleen, and 2% or fewer in the heart, kidney, and brain.[5] Hydatid cysts typically grow slowly at a rate of 1 to 10 mm per year. The host immune response leads to a fibrous capsule around the cyst.

Fig. 122.5 Hydatid cysts removed surgically.

Fig. 122.6 Additional hydatid cysts removed surgically.

Over time, the metabolically active germinal layer can separate from the acellular laminar layer leading to cessation of growth and eventual involution and calcification. Hydatid cysts, especially larger ones, can rupture spontaneously or from direct trauma spilling cyst contents and initiating the proliferation of daughter cysts. This spilling and proliferation can lead to a disastrous seeding of the peritoneum or pleural space with metastatic growth which is very difficult to treat (so-called "white cancer") as well as the possibility of secondary bacterial infection of the ruptured cyst cavity, bronchopleural fistula, and anaphylactoid reactions to parasite antigens. When a pulmonary cyst ruptures, it may lead to the expectoration of salty cyst fluid, a phenomenon known as "hydatid vomica." *Echinococcus multilocularis,* the cause of human alveolar echinococcosis, is a related parasite found in the northern hemisphere, with relatively high incidence in China, Siberia, and central Europe. Like hydatid echinococcosis, *E. multilocularis* has a canid definitive host (foxes, coyotes, domestic dogs). Its intermediate host is a number of rodent species. When humans are incidentally infected, they develop proliferative multiloculated liver cysts that can resemble hepatic neoplasms.

The diagnosis of hydatid cyst disease is suggested by the appearance and localization of the cyst on ultrasound examination or CT scan. The Gharbi classification scheme describes ultrasonographic stages of hydatid cyst development and involution, which is important for determining treatment modality. Serologic evaluation of serum or cerebrospinal fluid (CSF) may help confirm the diagnosis. Simple aspiration of the cyst should not be attempted because of the risk of seeding the host's body with metastatic cysts.

Treatment options include albendazole, praziquantel, and surgical resection. PAIR (puncture, aspiration, instillation, re-aspiration) is a procedure that can be used on larger hydatid liver cysts and uses instillation of 95% alcohol to inactivate the germinal layer of an active cyst. Resection of the cyst may cause an anaphylactoid reaction if there is spillage of hydatid sand, which contains parasite antigenic proteins (Figs. 122.5 and 122.6). Treatment of alveolar hydatid disease is primarily with albendazole.

Fascioliasis, caused by the liver fluke *Fasciola hepatica,* is endemic on all continents except Antarctica and has been found in over 50 countries, especially where sheep or cattle are reared. Infection begins with ingestion of the metacercariae often found in watercress. Within 6 weeks, patients exhibit right upper quadrant abdominal pain, fever, nausea and vomiting, jaundice, tender enlarged liver, and elevated transaminase levels. This syndrome can mimic viral hepatitis; however, eosinophilia and urticaria are often present. Imaging studies, including CT, show the tracks of burrowing flukes. Serologic testing establishes the diagnosis; the patient's stool may not contain eggs for several months after ingestion.

Several parasites have been identified in the pathologic examination of appendices of patients diagnosed with tropical appendicitis. These infections have included enterobiasis, amebiasis, ascariasis, trichuriasis, and taeniasis.

A. lumbricoides (roundworm) can cause significant persistent or recurrent abdominal pain in adults and partial intestinal obstruction in children with significant worm loads. Antihelminthics and conservative supportive therapy usually eliminate this infestation, thereby avoiding surgical intervention. Clinicians diagnose ascariasis by identifying eggs in the stool. Patients with large worm loads may excrete adult worms, especially after therapy is started. Severe intestinal amebiasis can be complicated by colonic perforation and peritonitis.

Angiostrongylus costaricensis, a species of rat lung worm, is common in Central America. Infected children may appear clinically to have Meckel diverticulum or acute appendicitis. Manifestations of the infection include nausea, vomiting, fever, abdominal pain localized to the right lower quadrant, and a tender mass. Surgical exploration may uncover abscesses, obstruction, or intestinal infarction. Anisakiasis is characterized by severe abdominal pain that occurs within hours of ingestion of raw fish (sushi and sashimi primarily). It is caused by *Anisakis simplex,* a nematode that burrows into the wall of the stomach or intestine. Treatment requires endoscopic removal of the worm.

Jaundice may result from hemolysis secondary to direct infection of RBCs with *Plasmodium* or *Babesia* or from biliary obstruction with pigmented stones. *Ascaris* can cause biliary colic, pyogenic cholangitis, pancreatitis, or liver abscess. Dead worms can be the nidus for gallstone formation. Biliary imaging and endoscopic retrograde cholangiopancreatography show worms in the biliary tree. Mechanical removal by endoscopy combined with antihelminthic therapy is curative. *Clonorchis sinensis* and *F. hepatica* are trophic for the biliary tree. Infection with these worms may be asymptomatic for years before eventually precipitating cholecystitis, cholangitis, or cholangiocarcinoma.

Enterobius vermicularis

Enterobius vermicularis, or pinworm, causes pruritus ani, a syndrome of intense perianal itching occurring primarily in children. Autoinfection is common, because children (and adults) scratch the pruritic anal area and then bite their nails or put their fingers in their mouth. The worm has a worldwide distribution. Diagnosis is clinical and is confirmed by finding the small adult worms wriggling the anal verge. Eggs are rarely seen in the stool but can be visualized by the tape test—transparent tape touched to the perianal region collects eggs, which can be seen with light microscopy. Albendazole or mebendazole is the drug of choice.

PARASITIC COINFECTIONS IN PATIENTS WITH HIV INFECTION AND AIDS

HIV infection is prevalent in developing countries. Heterosexual transmission and perinatal transmission are common; children and young adults of both sexes are primarily infected. Patients presenting to the ED may be coinfected with HIV and any other infectious agent, including all the parasites discussed in this chapter. HIV coinfection may worsen the symptoms and outcome, alter the presentation, increase the virulence, or assist the infective process.

AIDS causes abnormalities in almost every aspect of a host's immune response to infection; cell-mediated immunity, which is important in combating parasitic infection, is most affected. The diagnosis and response to therapy of many parasitic infections are monitored serologically. HIV infection interferes with this response, rendering many of these tests unreliable. Therapies that are extremely effective in the normal host may be ineffective in a patient with HIV infection. Pharmacologic agents may have to be given for long periods or the duration of the patient's life.

Specific Parasitic Coinfections

Malaria is not an opportunistic infection in patients with AIDS; however, many patients, especially children, with recurrent malaria and anemia from hemolysis have required transfusions from blood supplies not screened for HIV and have become infected. In regions where malaria is endemic, it is a common practice to treat most febrile patients with antimalarials. Some antimalarials are sulfonamides. Patients with AIDS have more severe allergic reactions to drugs, especially sulfonamides. Fever alone is not predictive of malaria in patients with AIDS; therefore, diagnosis should precede therapy.

Patients with HIV infection are at greater risk for severe clinical manifestations of babesiosis.

Visceral leishmaniasis is usually disseminated and often fatal in patients with AIDS. Latent leishmanial infections may be reactivated, and a prolonged febrile illness in an HIV-positive patient with a lifetime history of travel in leishmaniasis-endemic areas of the world should prompt consideration of this coinfection. Cutaneous infection also may become disseminated in these patients. Several clinical trials are examining the role of chemoprophylaxis for leishmaniasis in HIV-positive persons who live in endemic regions.

Chagas disease in the indeterminate phase can be reactivated in patients infected with HIV. These patients frequently have CNS involvement, with meningoencephalitis and severe myocarditis. Single-drug therapy may be insufficient because benznidazole penetration into the CSF is minimal. *T. gondii* infection is well recognized throughout the world as a common opportunistic infection for patients with AIDS, with a particular trophism for the CNS.

The coccidial organisms *Isospora belli, C. parvum,* and *C. cayetanensis* have been associated with prolonged diarrhea in patients with AIDS. These organisms cause difficult to treat infections and are almost impossible to eradicate in patients with AIDS. The diarrhea is extremely debilitating and can be as profuse as that seen in cholera. *E. histolytica* has a high prevalence among men who practice unprotected anal intercourse; however, invasive amebiasis is not an opportunistic infection associated with HIV infection.

Schistosomiasis may enhance the pathogenesis of HIV infection and is more difficult to treat and eradicate in patients who are HIV positive. Despite initial concerns, *S. stercoralis* infection does not appear to manifest more frequently as hyperinfection and disseminated disease in HIV-positive patients. In patients at risk for HIV infection and parasitic illness, it is essential to consider coinfection in the differential diagnosis. While many HIV-positive patients in industrialized countries are taking suppressive medication (HAART) and have fairly normal immune function, many patients who emigrate from developing countries may not have access to testing or HAART and thus may be HIV positive with active AIDS and parasitic coinfection.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 122: QUESTIONS AND ANSWERS

1. A 33-year-old man presents with irregular fevers, shaking chills, intermittent abdominal pain, and fatigue. The fever comes in cycles during approximately 2 or 3 days. He has no medical history and takes no medications. He works as a baggage handler in Miami, Florida. Physical examination reveals a low-grade fever and mildly tender hepatosplenomegaly. Laboratory evaluation is remarkable for hemoglobin 9.6 g/dL, leukocytosis, lactate dehydrogenase 1850 IU/dL, elevated bilirubin, and urine dipstick "blood positive" but no red blood cells or white blood cells. He has had no international travel. Peripheral smear reveals few possible parasites with fragmented red blood cells. What is this patient's most likely infection?

a. Babesiosis
b. Early sepsis
c. Leishmaniasis
d. Malaria

Answer: D. Airport malaria has been reported in people who have never been in endemic areas but who work in or live near an international airport. The infected mosquito is transported from the endemic region and released when the plane arrives. Babesiosis is a parasitic illness with a clinical picture like that of malaria. It is tickborne and is endemic in the northeastern United States.

2. Parasite-induced loss of vision would be suggested by which of the following?

a. Cardiomegaly
b. Edematous and pruritic skin
c. Fever
d. Hepatosplenomegaly
e. Iron deficiency anemia

Answer: B. Onchocerciasis is a major cause of blindness worldwide. Ninety-five percent of cases occur in Africa. The biting flies are found near rivers, and humans are the only host for the parasite. It occupies the skin, resulting in pruritus, edema, and later atrophy with redundant skin folds. The following are other causes of parasite-induced visual loss: *Toxoplasma* can cause retinal hemorrhages, *Toxocara* can cause inflammatory retinal granulomas, and *Acanthamoeba* may cause a keratitis in contact lens wearers.

3. A macrocytic anemia would suggest infection from which parasite?

a. Ancylostoma duodenale
b. Diphyllobothrium latum
c. Falciparum malaria
d. Necator americanus

Answer: B. The fish tapeworm is associated with pernicious anemia. Hookworm and whipworm are associated with gastrointestinal iron loss and microcytic anemia. Malaria causes hemolytic anemia.

4. A 42-year-old man from Ethiopia presents with complaints of skin nodules and skin ulcerations. He has no known past illnesses, exposures, medication use, or systemic symptoms. Examination is remarkable for four 2- or 3-cm cutaneous ulcers on the arms and legs and scattered 1-cm nodules. Vital signs are normal, and physical examination is otherwise unrevealing. Which of the following statements regarding this infection is TRUE?

a. Respiratory tract symptoms would suggest an alternative diagnosis.
b. The lesions always require treatment.
c. The lesions are likely painful to touch.
d. The skin pattern may be confused with leprosy.

Answer: D. Leishmaniasis is transmitted by the sandfly bite. Skin papules and macules develop at bite sites. These may ulcerate into painless ulcers. A microcutaneous variant may be seen, and the inflammatory process may involve the larynx and trachea. Disseminated cutaneous leishmaniasis may resemble lepromatous leprosy.

5. Which of the following is the correct association between the type of parasitic infection and pulmonary symptoms?

a. Hookworm—positive PPD response
b. Leishmaniasis—pulmonary nodules
c. Löffler syndrome—ascariasis
d. Pneumocystis—90% of opportunistic infections in Africa

Answer: C. Ascariasis and hookworm may cause Löffler syndrome of chest pain, fever, rales, wheezing, and eosinophilia. The following are the other correct associations:

- Pneumocystis—less than 10% of pulmonary opportunistic infections in Africa
- *Paragonimus westermani*—positive tuberculin skin test response and chest radiograph resembling tuberculosis
- Echinococcus—anaphylaxis from leakage of cystic contents
- Schistosomiasis—diffuse pulmonary nodules (Katayama fever)

123

Tickborne Illnesses

Edward B. Bolgiano and Joseph Sexton

KEY CONCEPTS

- Tickborne illnesses frequently are misdiagnosed as common viral or bacterial infections. Diagnosis can be facilitated by considering tickborne illnesses in patients who recently have been in endemic areas and routinely asking for a history of recent tick or insect bites in patients with febrile illnesses.
- Lyme disease should be suspected in patients who present with signs of a viral illness, monarticular arthritis, meningitis, multiple neurologic abnormalities, or heart block. Diagnosis can be confirmed with serologic testing of acute and convalescent serum samples.
- Normal physiologic changes from tick bites should not be confused with erythema migrans.
- Relapsing fever should be suspected in patients who present with recurrent viral-like illness associated with high fever. The diagnosis can be confirmed by identifying spirochetes on a blood smear obtained during a period of rising temperature.
- Ulceroglandular tularemia should be suspected in patients with slow-healing extremity ulcers associated with large lesions of regional adenopathy (buboes). The diagnosis can be confirmed with serologic testing.
- Rocky Mountain spotted fever should be considered in patients who present with an unexplained febrile illness, even in the absence of a rash or known tick exposure. Delayed diagnosis and late initiation of specific antirickettsial therapy may lead to a fatal outcome. Treatment never should be delayed pending laboratory diagnosis.

OVERVIEW

Ticks are hematophagous parasites of humans and animals, distributed worldwide. They transmit rickettsial, bacterial, spirochetal, viral, and protozoal diseases and cause disease employing their own toxins (Table 123.1). As vectors of human disease, ticks rank second in importance only to mosquitoes. Although it is generally understood that people who travel during the summer months may return from endemic areas with tickborne disease, increasing reports of infection acquired within urban areas emphasize the need to consider tickborne illness even in the absence of a history of travel to high-risk areas. In addition, tularemia and Q fever are now considered by the Centers for Disease Control and Prevention (CDC) to be significant threats during biologic warfare, adding to the importance of research on ticks and tickborne diseases.

Reports on ticks, their feeding habits, and their possible relation to disease can be found from early human history. Tickborne illness was first recognized on the North American continent by Native Americans. The causative association of the tick vector with Rocky Mountain spotted fever (RMSF) was noted by missionaries and early settlers, who named the affliction tick fever, and physicians in Idaho and Montana recorded the classic clinical descriptions of the disease in 1899.

The majority of tickborne diseases in the United States occur east of the Mississippi River (Fig. 123.1). The reported cases of these diseases have nearly doubled since 2008, led by Lyme disease, the ehrlichioses, and the Rocky Mountain or other spotted fever rickettsioses (Table 123.2).

Identification of Ticks

Ticks are arthropods but not insects. They have eight legs instead of six and generally two fusing body parts—a capitulum (head) and opisthosoma (abdomen)—instead of three. Identification of an arthropod as a tick is not difficult (Figs. 123.2 and 123.3), but speciation requires a trained acarologist. However, tick identification has limited importance in clinical decision making. Color, which varies seasonally, and size, which varies by amount of blood ingested at the time of presentation, are unreliable criteria for identification purposes.

Physiology of Tick Feeding

An understanding of the physiology of feeding in arthropods is helpful when assessing the risks of disease transmission. Blood-sucking (hematophagic) arthropods are divided into two groups according to their method of acquiring blood. The solenophagic feeders insert their mouthparts directly into capillaries to obtain blood. Telmophagic feeders insert their mouthparts indiscriminately, lyse tissue along with capillaries, and feed on the resultant pool of blood, extracellular fluid, and tissue. Ticks and deer flies, for example, are telmophagic feeders, whereas mosquitoes are mostly solenophagic.

Argasid ticks (soft-bodied ticks) are short, rapid feeders with preformed distensible endocuticles. They therefore need to feed for only minutes to hours to acquire a full meal. As a result, they tend to be found in nests and burrows where their hosts visit frequently. The soft tick genus *Ornithodoros* is the vector for relapsing fever. Ixodid ticks (hard-bodied ticks) include the genera *Ixodes, Dermacentor, Amblyomma,* and *Rhipicephalus,* which are those responsible for the remainder of human tickborne diseases in the United States discussed in this chapter.

Two mechanisms prevent many species of tick from being removed from the skin—the barbed hypostome, or a calcified mouth-piece that anchors the tick to the skin, and a cement-like salivary secretion from the base of the hypostome, composed of lipoproteins and glycoproteins. This allows ixodid ticks to remain attached for as long as 2 weeks. Because argasids are much faster feeders, they secrete no cement substance.

During a bite, trauma and salivary gland products can cause local inflammation, hyperemia, edema, hemorrhage, and skin thickening. Hard and soft ticks produce a histolytic secretion injected during feeding that liquefies tissue, which is then sucked into the gut. Eventually, the secretion breaks down the walls of the dermal blood vessels and the released blood is ingested. To prevent hemostasis, the saliva contains

TABLE 123.1 Tickborne Illnesses

Type	Disease	Pathogen	Arthropod Vector	Geographic Distribution
Bacterial (including spirochetal)	Lyme disease	*Borrelia burgdorferi*	*Ixodes scapularis*	Northeastern United States
			Ixodes pacificus	Upper Midwestern United States
			Ixodes ricinus	Pacific Coast Europe
	Tularemia	*Francisella tularensis*	*Ixodes scapularis*	Southwest central United States
			Amblyomma americanum	
			Dermacentor variabilis	
Rickettsial	Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor andersoni* *Dermacentor variabilis*	Predominantly southeastern United States
			Rhipicephalus sanguineus	Arizona
	Q fever	*Coxiella burnetii*	*Dermacentor andersoni*	Worldwide
	Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	South central and southeastern United States
	Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis*	New England and north central United States
			Ixodes pacificus	Northern California
Parasitic (protozoal)	Babesiosis	*Babesia microti*	*Ixodes scapularis*	Coastal New England
Viral[a]	Colorado tick fever	Orbivirus	*Dermacentor andersoni*	Mountain areas of western United States and Canada
Miscellaneous	Tick paralysis	Ixobotoxin	*Dermacentor andersoni* *Dermacentor variabilis* *Amblyomma americanum* *Ixodes scapularis* *Ixodes pacificus* *Ixodes holocyclus*	Worldwide

[a]Many other viruses are transmitted to humans by ticks. In the United States, only Colorado tick fever occurs with any significant frequency.

a thrombokinase inhibitor, apyrase, which prevents platelet aggregation by depleting adenosine diphosphate, prostaglandin E_2, and prostacyclin (prostaglandin I_2) to prevent vasoconstriction, and cytolysins. *Ixodes scapularis* also secretes a carboxypeptidase that destroys other inflammatory mediators, such as anaphylatoxins and bradykinin, as well as anti–complement C3 factor. These other mediators normally would cause further inflammation, which would enhance hemostasis. The neurotoxins responsible for tick paralysis also are found in tick saliva. All infectious agents and excretory liquids from some argasids are transmitted through this saliva. Transmission of a disease from *Ixodes* ticks is unlikely if the tick is not yet engorged with blood at the time of removal.

The local physiologic changes associated with tick feeding produce the characteristic 1- to 4-mm erythematous mark typically seen on the skin after a tick bite. This is a common finding from most blood-sucking arthropods. The mark should not be confused with certain rashes associated with disease progression—for example, erythema migrans. Informing patients of this difference may be reassuring.

LYME DISEASE

Lyme disease, the most common vector-borne disease in the United States, is a tickborne illness caused by six species in the spirochete family Borreliaceae. In North America, infection is caused primarily by *Borrelia burgdorferi*. The recognition of Lyme disease began in 1975, when health officials at the Connecticut State Department of Health and physicians at Yale University were alerted by two skeptical mothers to an unusually large number of cases of apparent juvenile rheumatoid arthritis occurring in their small coastal community of Old Lyme, Connecticut. Investigation led to the description of a new entity called Lyme arthritis. The causative agent of Lyme disease was isolated in 1982.

Lyme disease occurs worldwide and has been reported on every continent except Antarctica. It now accounts for more than 95% of all reported cases of US vector-borne illness. The incidence of Lyme disease is unknown because many cases go unreported. Lyme disease occurs in people of all ages but is more common in children younger than 15 years and in adults 30 to 60 years of age. Persons at greatest risk live or vacation in endemic areas. In the United States, three distinct endemic foci are recognized—the northeastern coastal, Mid-Atlantic, and north central states. Twelve states (Connecticut, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Washington, and Wisconsin) account for 92% of US cases reported (Fig. 123.4).[1]

The principal tick vectors are *I. scapularis* in the Northeast and Midwest and *Ixodes pacificus* in the West. The *I. scapularis* population density depends on that of its preferred hosts, the white-footed field mouse, *Peromyscus leucopus,* for the larval and nymphal forms, and the white-tailed deer, *Odocoileus virginianus,* for the adult form. The white-footed mouse readily becomes infected after being bitten by infected ticks and remains highly infectious for periods that approach its life span, thereby providing an important reservoir for *B. burgdorferi*. Adult *I. scapularis* ticks feed primarily on deer, which are key hosts in the tick life cycle and in whose fur the adult tick may survive the winter. The repopulation

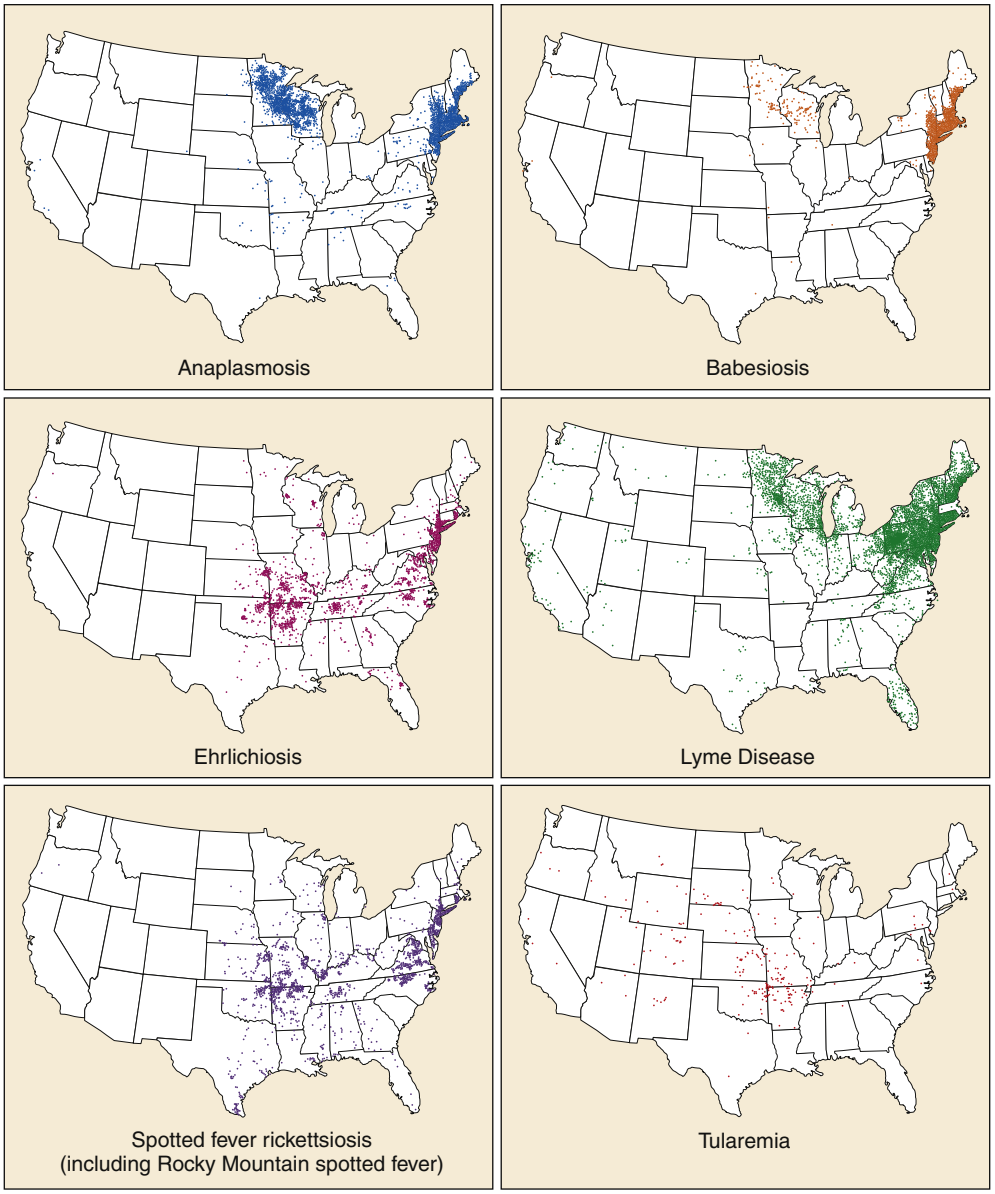

Fig. 123.1 Selected tickborne diseases reported to CDC, United States, 2016. (From: Centers for Disease Control and Prevention (CDC). Tickborne diseases of the United States: Overview of tickborne diseases. Available at: http://www.cdc.gov/ticks/tickbornediseases/overview.html. Accessed May 11 2021.)

TABLE 123.2 Tickborne Disease Surveillance Data Summary

Reported Tickborne Diseases, US	2016	2017	2018
Lyme disease (confirmed and probable)	36,429	42,743	33,666
Anaplasmosis/ehrlichiosis	5,750	7,718	6,123
Spotted fever rickettsisosis	4,269	6,248	5,544
Babesiosis	1,910	2,368	2,160
Tularemia	230	239	229
Powassan virus	22	33	21
Total	48,610	59,349	47,743

From: Centers for Disease Control and Prevention. Ticks: tickborne disease surveillance data summary. https://www.cdc.gov/ticks/data-summary/index.html.

of several areas in the United States by white-tailed deer preceded the recent emergence of Lyme disease in those regions.

Although all stages of the tick may feed on humans, the nymph is primarily responsible for transmitting Lyme disease. It is not surprising that more than two-thirds of patients with Lyme disease do not recall a tick bite, given the small size (1–2 mm) of nymphs (Fig. 123.5). The nymph feeds in the spring and summer, correlating with a peak incidence of early Lyme disease between May and August. In addition, recreational and occupational exposure is greatest during this time. Later manifestations of Lyme disease may appear throughout the year.

The spirochete *Borrelia burgdorferi* persists and multiplies in the midgut of its tick vector, *I. scapularis*. Transmission of the spirochete to humans occurs during feeding, generally about 2 days after attachment. The mechanism of transmission probably is inoculation with infectious saliva or with tick gut fluids periodically regurgitated during the feeding process.

After an incubation period that lasts several days to weeks, spirochetemia develops, and *Borrelia* organisms may migrate outward in the blood or lymph to virtually any site in the body. The spirochete appears to be tropic for synovial tissue, skin, and cells of the nervous system, but the mechanism of this tropism is not yet understood. Infection by the spirochete itself accounts for early clinical manifestations. It remains unclear whether late disease manifestations require the continued presence of viable spirochetes or whether an ongoing host immune response to initial infection is sufficient to cause some late disease effects, but persistent live spirochetes are likely responsible for most later manifestations of the disease. The variable severity of Lyme disease may in part result from genetic variations in the human immune system. For example, patients with chronic Lyme arthritis have an increased frequency of human leukocyte antigen (HLA) specificity, in particular for HLA-DR4 and, less often, for HLA-DR2.

Clinical Features

Lyme disease, a multisystem disorder, can be classified into three stages—early localized, early disseminated, and late disease. Virtually any clinical feature may occur alone or recur at intervals, and some patients who had no early symptoms may have late symptoms. The disorder usually begins with a rash and associated constitutional signs and symptoms, suggesting a viral syndrome (early Lyme disease). Neurologic, joint, or cardiac manifestations may emerge weeks to months later (early disseminated Lyme disease), and chronic arthritic and neurologic abnormalities may appear weeks to years later (late Lyme disease). The time course for the clinical features of untreated Lyme disease is illustrated in Fig. 123.6.

Early Lyme Disease

Ticks may attach to human hosts at the initial point of contact, generally around ankle level, or move about until they encounter an

Fig. 123.2 Scanning electron micrographs of two tick species. (A) Dorsal view of adult female, *Dermacentor variabilis*. (B) Dorsal view of adult female, *Ixodes scapularis*. (C) Dorsal close-up view of *D. variabilis* head. (D) Dorsal close-up view of *I. scapularis* head. (Courtesy Dr. J. E. Keirans, Georgia Southern University, Statesboro, Georgia.)

obstruction. The groin, popliteal fossae, gluteal folds, axillary folds, and earlobes are common sites of attachment. With transmission of *B. burgdorferi* through a tick bite, the initial site of infection is the skin at the site of the bite. After an incubation period of approximately 1 week (range, 1–36 days), the spirochetes cause a gradually spreading localized infection in the skin and a resultant skin lesion, erythema migrans.

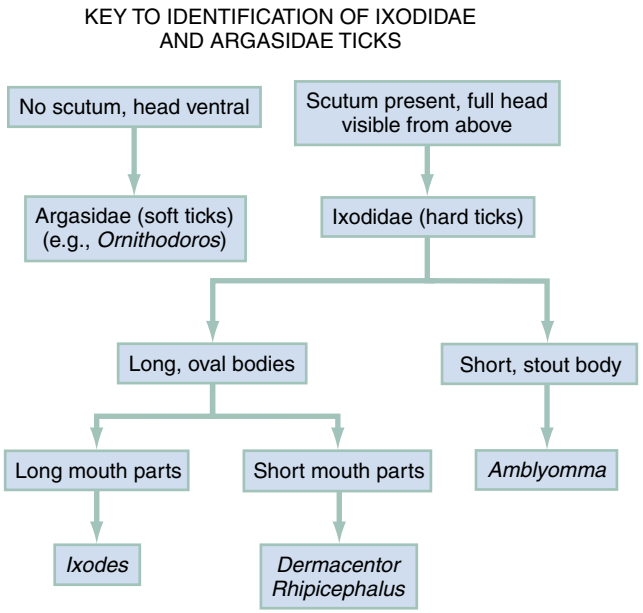

Fig. 123.3 Identification scheme for Ixodidae and Argasidae genera, the two primary disease-transmitting families of ticks.

Erythema migrans (EM) is the most characteristic clinical manifestation of Lyme disease and is recognized in 90% or more of patients. EM may go unnoticed if the entire skin surface is not examined. The characteristic rash begins at the site of the tick bite with an erythematous papule or macule. The lesion expands gradually (1–2 cm/day, a rate of expansion slower than cellulitis). The patch of erythema may be confluent or may have bands of normal-appearing skin. Central clearing may occur but is not an invariable feature. The lesion borders usually are flat but may be raised. The lesions generally are sharply demarcated and blanch with pressure. Most lesions are oval or round, but triangular and elongated patches may occur. In patients presenting 1 to 7 days after the appearance of lesions, the average lesion size is approximately 8 by 10 cm (range, 2 by 3 cm to 25 by 25 cm). In some cases, the center of some early lesions becomes red and indurated or vesicular and necrotic. The lesion is warm to the touch and may be described by the patient as nontender to minimally tender (Figs. 123.7 and 123.8).

Hematogenous spread of viable spirochetes (not additional tick bites) may result in one or more secondary lesions. These secondary lesions are smaller, migrate less, and typically spare the palms and soles. In all, 10% to 15% of patients have more than 20 such lesions; on rare occasions, they may number more than 100. Blistering and mucosal involvement do not occur. The primary and secondary skin lesions generally fade after approximately 28 days (range, 1 week to 14 months) without treatment and within several days of antibiotic therapy. Recurrent lesions may develop in patients who do not receive antibiotic therapy but not in those who receive appropriate antibiotics.

Constitutional signs and symptoms commonly appear in early Lyme disease (Table 123.3). Malaise, fatigue, and lethargy are most common (seen in ≈80% of patients) and may be severe. Fever typically is low grade and intermittent. Lymphadenopathy usually is regional in

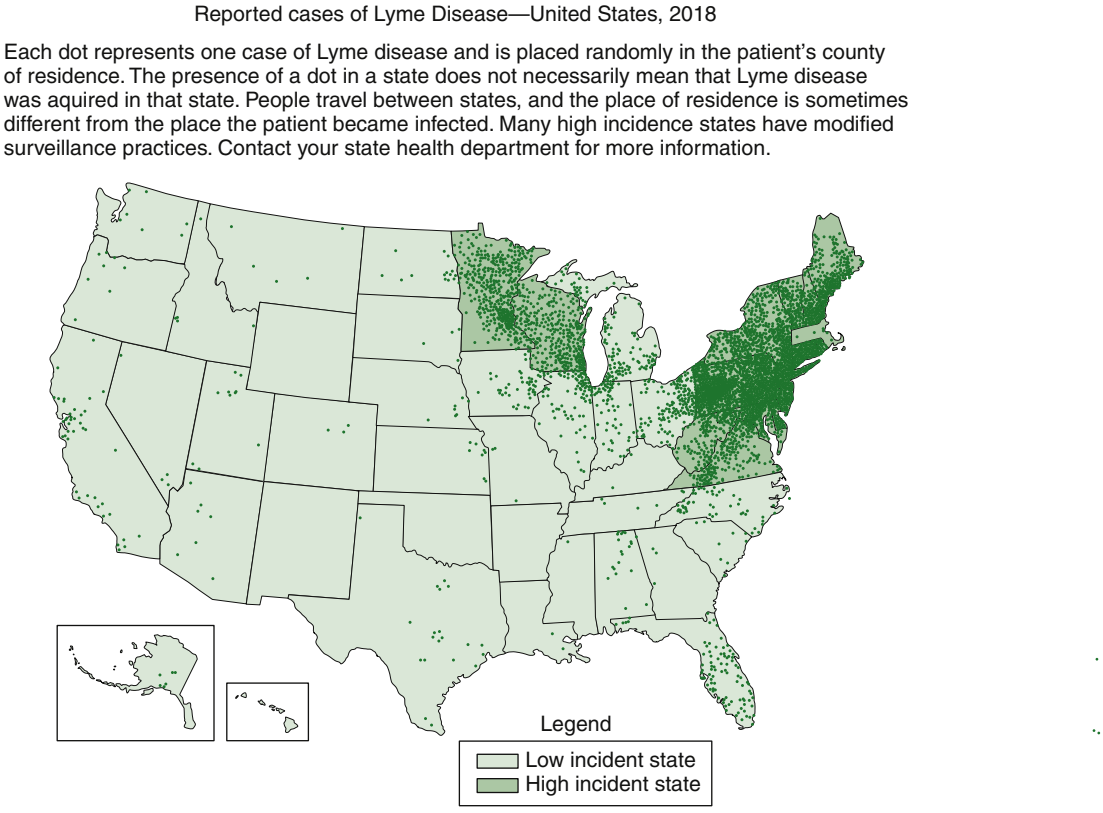

Fig. 123.4 Reported cases of Lyme disease cases by county in the United States in 2018. The number of confirmed cases totaled 23,558. (Adapted from: Centers for Disease Control and Prevention: Lyme disease maps. https://www.cdc.gov/lyme/stats/maps.html.)

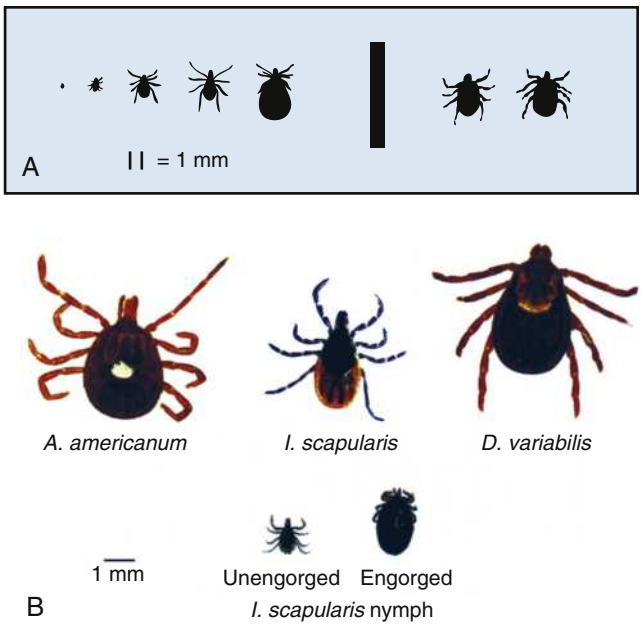

Fig. 123.5 (A) *Left to right,* Larva, nymph, adult male, adult female, and engorged adult female *Ixodes* ticks and adult male and female *Dermacentor* ticks; actual size. (B) Adult female *Amblyomma americanum* (Lone Star tick), adult female and nymphal *Ixodes scapularis* (deer tick), and adult female *Dermacentor variabilis* (dog tick). (From: Hayes EB, Piesman J, How can we prevent Lyme disease? *N Engl J Med.* 2003;348:2424-2430.)

the distribution of EM or may be generalized; splenomegaly may occur. Musculoskeletal complaints, such as arthralgias and myalgias, are common, and the discomfort typically is short-lived and migratory, sometimes lasting only hours in one location. Frank arthritis may occur at this stage but is rare.

Clinical manifestations of meningeal irritation are frequently seen. Headache, the most common symptom, usually is intermittent and localized. Nausea, vomiting, and photophobia occasionally accompany the headache. Kernig and Brudzinski signs typically are absent, and neck stiffness usually is noted only on extreme forward flexion. At this stage, the neurologic examination and cerebrospinal fluid (CSF) assessment usually yield normal findings.

Signs and symptoms of hepatitis, including anorexia, abdominal pain, right upper quadrant tenderness, nausea, and vomiting, may be present. Mild pharyngitis also may be present, but other upper respiratory symptoms, such as rhinorrhea, do not occur. Although the systemic symptoms of early Lyme disease often are described as flulike, that term can be misleading because clinically significant cough usually does not occur. Conjunctivitis develops in approximately 10% of patients.

The incidence of Lyme disease without EM appears to be approximately 10%. Because of the variety of nonspecific signs and symptoms at this stage, in the absence of the characteristic rash or history of tick bite, early Lyme disease may be easily confused with a viral or collagen vascular disease. The intermittent and rapidly changing nature of the early signs and symptoms of Lyme disease may be a helpful distinguishing feature, especially in a patient from an endemic area. In untreated disease, early symptoms usually last for several weeks but may persist for months.

Acute Disseminated Infection

Shortly after disease onset, hematogenous spread can cause various systemic signs and symptoms and result in secondary sites of infection. Organ systems commonly affected are the nervous system, heart, and joints. Less commonly, the eyes, liver, skeletal muscle, subcutaneous tissue, and spleen are infected.

Neurologic Manifestations. A relatively symptom-free interval usually occurs between early and disseminated infection; however, neurologic signs and symptoms may be the presenting manifestations of Lyme disease or may overlap with early or late manifestations. Beginning at an average of 4 weeks (range, 0–10 weeks) after the onset of erythema migrans, neurologic involvement occurs in approximately 15% of untreated patients.

The most common neurologic manifestation of Lyme disease is a fluctuating meningoencephalitis, with superimposed symptoms of cranial neuropathy, peripheral neuropathy, or radiculopathy. A triad of lymphocytic meningitis, cranial neuropathies (usually Bell palsy), and radiculoneuritis (motor or sensory or both) has been described, but each entity may occur alone. Headache of variable intensity usually is present; other signs and symptoms of a mild meningoencephalitis may be noted, including lethargy or irritability, sleep disturbances, poor concentration, and memory loss. At this point, the disease often is misdiagnosed as viral meningitis. As in early disease, Kernig and Brudzinski signs are absent and computed tomography (CT) findings are normal. Unlike in early disease, however, findings on CSF examination often are abnormal, with a lymphocytic pleocytosis and moderately elevated protein level. CSF glucose concentration usually is normal. Intrathecal *B. burgdorferi* antibody (usually immunoglobulin G [IgG] or IgA) is present in 80% to 90% of patients. CSF polymerase chain reaction (PCR) assay results are positive in less than 50% of patients, probably reflecting the low number of organisms usually present in spinal fluid. Routine testing of CSF by PCR assay is not recommended.

Cranial neuropathies are common, occurring in approximately 50% of patients with Lyme meningitis; the seventh nerve is usually involved. Other cranial nerves are affected less often. Bell palsy is bilateral in approximately one-third of patients. Its duration usually is weeks to months, and the condition generally resolves spontaneously without treatment.

Peripheral nervous system manifestations also may occur in early disseminated Lyme disease. The spinal root and plexus and peripheral nerves may be involved in the form of thoracic sensory radiculitis, brachial plexitis, mononeuritis, and motor and sensory radiculoneuritis in the extremities. Patients may complain of weakness, pain, or dysesthesia. Examination may reveal loss of reflexes. Involvement of the extremities usually is asymmetrical, but cervical and thoracic dermatomes may be affected. Radiculoneuritis can mimic a mechanical radiculopathy (such as sciatica) and should be considered in endemic areas in patients without an apparent mechanical cause. Other rare neurologic abnormalities described in association with Lyme disease include chorea, transverse myelitis, ataxia, and pseudotumor cerebri. Cerebral vasculitis associated with Lyme disease also has been reported.

Cardiac Manifestations. Cardiac involvement in Lyme disease is uncommon, with an estimated incidence in untreated patients ranging from 4% to 10%. Carditis occurs during the early disseminated phase of the disease. The average time from initial illness to the development of carditis typically is 3 to 5 weeks (range, 4 days to 7 months). Direct myocardial invasion has been demonstrated with endomyocardial biopsy. Electrophysiologic testing has demonstrated widespread involvement of the conduction system.

The most common cardiac manifestation of Lyme disease is atrioventricular (AV) block, although conduction defects may involve any level of the conducting system.[2] Myopericarditis, tachydysrhythmias including atrial fibrillation,[3] and ventricular impairment occur less often. In a review of 105 reported cases of Lyme carditis, 49% of cases were third-degree, 16% were second-degree, and 12% were first-degree AV block. The degree of AV block seen in a specific patient may fluctuate rapidly.

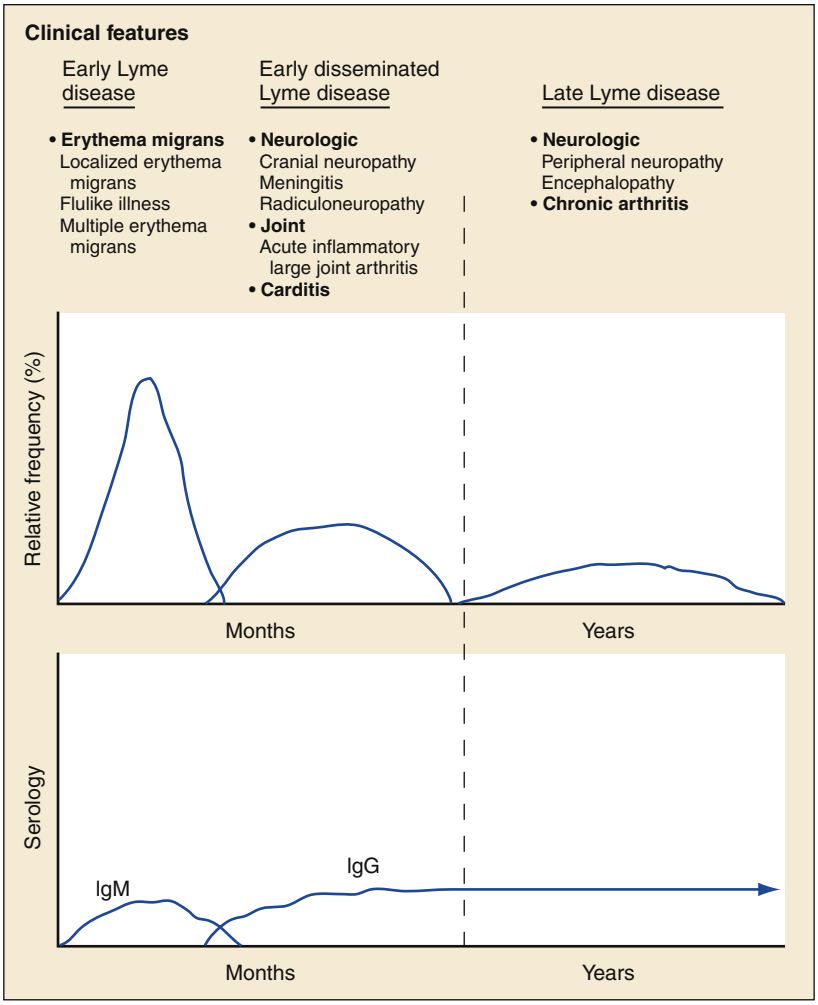

Fig. 123.6 Natural history of serologic response, with clinical features, in untreated Lyme disease. *IgG,* Immunoglobulin G; *IgM,* immunoglobulin M. (Adapted from: Rahn DW. Natural history of Lyme disease. In Rahn DW, Evans J, eds. *Lyme Disease*. Philadelphia: American College of Physicians; 1998, pp 35-48.)

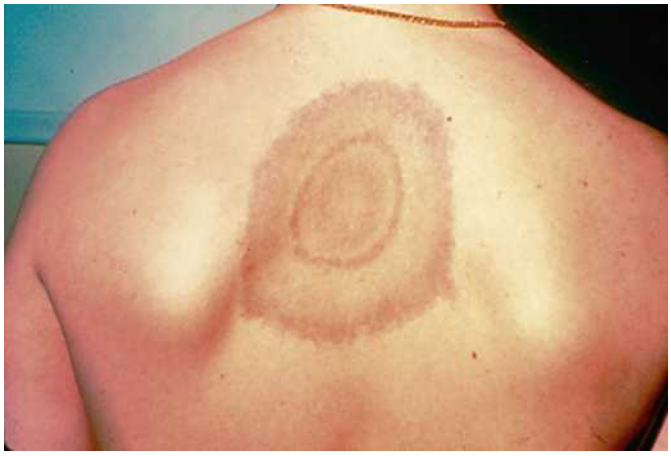

Fig. 123.7 Lyme disease usually begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite. The classic bull's-eye or target lesion has partial central clearing, a bright red outer border, and a target center. (From: Bhate C, Schwartz RA. Lyme disease. Part I. Advances and perspectives. *J Am Acad Dermatol*. 2011;64:619-636.)

A commonly observed feature of AV block in patients with Lyme carditis is its gradual resolution, resembling that occurring after an acute inferior wall myocardial infarction and presumably related to the resolution of inflammation. Assessment of the level of the AV block is important to determine the prognosis of a patient with Lyme carditis. In most cases, the block appears to be at or above the AV node; therefore, the prognosis is favorable. However, infranodal AV block does occur and may be characterized by slow escape rhythms of wide QRS pattern, asystole, or fluctuating left and right bundle branch block. Other electrocardiographic findings include nonspecific ST and T wave abnormalities and intraventricular conduction delay.

Patients with high-degree AV block usually are symptomatic. Symptoms include lightheadedness, palpitations, syncope, chest pain, and dyspnea on exertion. The physical examination may reveal flow murmurs and murmurs of mild mitral regurgitation, pericardial friction rub, or evidence of congestive heart failure. Associated left ventricular dysfunction may be present and has been documented by two-dimensional echocardiography and radionuclide studies; in most reported cases, it has been mild and transient. Sudden cardiac death attributable to Lyme disease has also been reported.

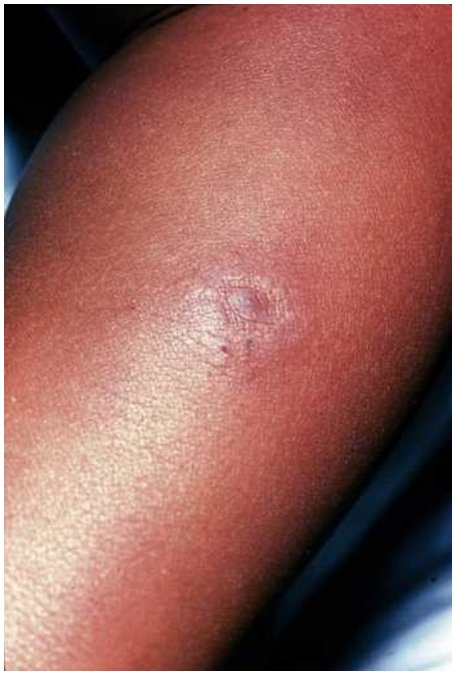

Fig. 123.8 Early erythema migrans on the lower leg. The erythematous nodular appearance could lead to misdiagnosis as a spider bite or MRSA cellulitis. (From: Bhate C, Schwartz RA. Lyme disease. Part I. Advances and perspectives. *J Am Acad Dermatol.* 2011;64:619-636.)

TABLE 123.3 Early Clinical Manifestations of Lyme Disease

Manifestation	No. of Patients (%)
Signs	
Erythema chronicum migrans[a]	314 (100)
Multiple annular lesions	150 (48)
Lymphadenopathy	
Regional	128 (41)
Generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41 (13)
Erythematous throat	38 (12)
Conjunctivitis	35 (11)
Symptoms	
Malaise, fatigue, lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
Dysesthesia	35 (11)
Vomiting	32 (10)

[a]Required for inclusion in this study.
From: Steere AC, Bartenhagen NH, Craft JE, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med.* 1983;99:76-82.

Arthritis. Although it is generally considered a sign of late Lyme disease, acute arthritis may begin during the acute disseminated stage. Monarticular or oligoarticular arthritis, primarily affecting large joints, especially the knee, may develop weeks to months after the onset of initial illness. In an early study of the natural history of Lyme arthritis, approximately 50% of untreated patients experienced one episode or multiple intermittent attacks of arthritis. Acute arthritis typically is monarticular, with involvement of only one knee. The shoulder, elbow, temporomandibular joint, ankle, wrist, hip, and small joints of the hands and feet are involved less commonly. Episodes of arthritis typically are brief (lasting weeks to months) and are separated by variable periods of remission.

Arthrocentesis generally is nondiagnostic, yielding an inflammatory synovial fluid with a mean white blood cell count of approximately 25,000 cells/μL (75% polymorphonuclear leukocytes). Higher white blood cell counts have been reported, simulating septic arthritis. The synovial glucose concentration usually is normal, and protein levels are variable, ranging from 3 to 8 g/dL. Cultures of the fluid rarely identify the causative spirochete. The complement level generally is greater than one-third that of serum. Synovial biopsy reveals hypertrophy, vascular proliferation, and a mononuclear cell infiltrate. Findings, therefore, are similar to those in rheumatoid arthritis, except that rheumatoid factor and antinuclear antibody assays yield a negative result in Lyme arthritis. Radiography may reveal nonspecific abnormalities such as juxtaarticular osteoporosis, cartilage loss, cortical or marginal bone erosions, and joint effusions.

Ophthalmic Manifestations. Ocular involvement also may be seen in early disseminated disease; manifestations include conjunctivitis, keratitis, choroiditis, retinal detachment, optic neuritis, and blindness. These findings also may be seen in late disease.

Late Lyme Disease

The chronic phase of Lyme disease is characterized by arthritic and, less commonly, neurologic symptoms. Over time, the pattern of episodic inflammation in early disease transitions to a more indolent persistent inflammation. The term *chronic* (or *late*) *Lyme disease* describes continuous inflammation in an organ system for more than 1 year.

A pattern of exacerbation and remission of arthritis may extend for several years, with a gradual tendency toward less frequent and less severe occurrences. The spontaneous long-term remission rate approximates 10% to 20% annually in untreated patients. However, patients commonly have episodes of periarticular involvement, arthralgias, or fatigue interspersed between attacks of frank arthritis. During the second or third year of illness, attacks of joint swelling sometimes become longer in duration, lasting months rather than weeks. Chronic arthritis eventually develops in approximately 10% of patients.

Late neurologic complications include a wide variety of abnormalities of the central and peripheral nervous systems and fatigue syndromes. Diagnosis may be difficult because of the large number of other neurologic conditions that Lyme disease may imitate and because late neurologic symptoms may be the first symptoms of the disease. The manifestations of chronic neuroborreliosis (the neurologic manifestations of Lyme disease) usually appear months to years after the onset of infection.

The most common late neurologic manifestation of Lyme disease is a chronic encephalopathy manifested as a mild to moderately severe impairment of memory and learning. Hypersomnolence and mild psychiatric disturbances (depression, irritability, paranoia) also may develop.[4]

Peripheral nervous system manifestations often are seen in late disease, with involvement of cranial nerves, spinal roots, spinal plexuses, and peripheral nerves. A predominantly sensory

polyradiculoneuropathy that is manifested as radicular pain or distal paresthesia is common. Significant overlap occurs with early symptoms. Less commonly, a demyelinating condition resembling multiple sclerosis may appear in late disease. Symptoms are variable and, as in multiple sclerosis, may undergo exacerbations and remissions. CT and magnetic resonance imaging (MRI) may reveal multiple white matter lesions.

Chronic inflammation also may occur in the skin, causing a seldom-recognized late cutaneous manifestation of Lyme disease, acrodermatitis chronica atrophicans. This condition usually involves the skin of distal extremities at the site of a tick bite. It is characterized in its initial stages by an edematous infiltration, which progresses to an atrophic lesion resembling localized scleroderma in its more established form. *B. burgdorferi* has been demonstrated in the skin of patients with acrodermatitis chronica atrophicans and positive findings on serologic studies.

Differential Diagnoses

The diagnosis of Lyme disease should be considered based on clinical and epidemiologic features. Identification of the disorder often is difficult, however, especially in the early stage. Although Lyme disease manifests in many ways, each stage has characteristic clinical findings that narrow the differential diagnosis. Early Lyme disease (EM and associated constitutional symptoms) may be easily confused with various other diseases, especially if the characteristic rash of EM is absent. A common clinical presentation is an influenza-like illness with headache, nausea, fever, chills, myalgias, arthralgias, stiff neck, and anorexia, occurring during the summer months. Even in endemic areas during the summer months, most patients with such symptoms do not have Lyme disease. When headache and stiff neck are the predominant symptoms, the principal diagnostic distinction to be made is between Lyme disease and the enteroviral diseases (and other causes of aseptic meningitis). The enteroviral diseases also have their peak incidence during the summer months; however, diarrhea, commonly associated with enteroviral infection, is not a feature of Lyme disease. Abdominal pain, anorexia, and nausea suggest hepatitis, sore throat, adenopathy, and fatigue suggest mononucleosis, and myalgias and arthralgias suggest connective tissue diseases. In many areas where Lyme disease is endemic, *Ixodes* ticks can be infected simultaneously with *B. burgdorferi*, *Anaplasma phagocytophilum*, and *Babesia microti*. Coinfection with more than one of these agents can occur.[5]

The rash of EM is characteristic of but not pathognomonic for Lyme disease. Some patients are not aware of having had such a rash and, in others, its appearance is atypical. An EM skin lesion is frequently misdiagnosed as a spider bite or community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) cellulitis, resulting in treatment with ineffective antibiotics. Other cutaneous entities in the differential diagnosis for EM include fungal infection, plant dermatitis, and fixed drug eruptions. Secondary lesions may be confused with the target lesions of erythema multiforme, which generally are smaller and nonexpanding. Erythema multiforme also may involve the mucous membranes, palms, and soles; EM does not. The presence of a malar rash in association with Lyme disease suggests systemic lupus erythematosus. Erythema nodosum generally causes more painful induration than EM and has a predilection for the extensor surfaces of the legs. Erythema marginatum of acute rheumatic fever also is in the differential diagnosis for EM; the Lyme disease rash differs in comprising generally fewer, larger, less evanescent lesions that migrate more slowly. Atypical EM manifesting as an urticarial rash may suggest hepatitis B infection or serum sickness. Lyme disease should be considered in a patient with an atypical rash accompanied by a viral syndrome or meningitis-like illness, especially during the months of peak incidence.

Acute rheumatic fever, coronary artery disease, or viral myocarditis may be suggested by the cardiac manifestations of Lyme disease. The carditis of Lyme disease, like the carditis of rheumatic fever, may follow pharyngitis and migratory polyarthritis. Erythema marginatum usually occurs with the onset of arthritis, in contrast with EM, which usually precedes the carditis. Although some patients with Lyme disease may satisfy the clinical aspects of the Jones criteria for acute rheumatic fever, they lack evidence of a preceding streptococcal infection; in addition, valvular involvement is not a prominent feature of Lyme carditis.

The differential diagnosis of the neurologic manifestations caused by Lyme disease is extensive. Considerations include aseptic meningitis, herpes simplex encephalitis, Bell palsy of other causes, radiculopathy due to mechanical causes, multiple sclerosis, Guillain-Barré syndrome, dementia, primary psychosis, cerebral vasculitis, and brain tumor. Neurologic symptoms often occur in the absence of any epidemiologic clues or preceding clinical symptoms suggestive of Lyme disease, making the diagnosis particularly challenging.

Lyme arthritis may mimic other immune-mediated disorders. The arthritis of Lyme disease generally is asymmetric, oligoarticular, and episodic. In contrast to patients with rheumatoid arthritis, those with Lyme arthritis rarely have symmetric polyarthritis, morning stiffness, a positive result on rheumatoid factor assay, or subcutaneous nodules. Lyme arthritis is commonly mistaken for seronegative rheumatoid arthritis; however, Lyme arthritis is most similar to the spondyloarthropathies, particularly reactive arthritis. Lyme disease and reactive arthritis both commonly cause huge knee effusions but, in Lyme disease, absence of the extra-articular features of reactive arthritis (conjunctivitis, urethritis or cervicitis, balanitis, keratosis blennorrhagica) at the time of the onset of arthritis helps distinguish it from reactive arthritis. In children, Lyme arthritis may mimic juvenile rheumatoid arthritis, but joint involvement in Lyme disease usually occurs in short intermittent attacks, and iridocyclitis typically is absent. Rheumatoid factor titers will be negative in juvenile rheumatoid arthritis and Lyme disease. The diseases resemble one another closely enough to have been confused at the time of the initial description of Lyme disease. Other diseases in the differential diagnosis for Lyme arthritis include acute gouty arthritis, septic arthritis, gonococcal arthritis, rheumatic fever, polymyalgia rheumatica, and temporomandibular joint syndrome.

Diagnostic Testing

Results of routine laboratory studies are nonspecific, and such studies generally are not helpful in the diagnosis of Lyme disease. Abnormalities may include an elevated erythrocyte sedimentation rate, mild anemia, total white blood cell count in the normal range with a decreased absolute lymphocyte count, microhematuria, proteinuria, and mildly elevated hepatic transaminases. Cultures of blood, tissue, and body fluids (including CSF and synovial fluid) for *B. burgdorferi* and direct visualization techniques are difficult to perform properly and have such a low yield that they are not clinically useful.

Serologic testing measuring the host's antibody response (for IgG and IgM) to *B. burgdorferi* is the most useful means of confirming a clinical diagnosis of Lyme disease, but is not without limitations. Results of serologic tests should be interpreted within the context of symptoms, considering the presumed stage of Lyme disease. These tests should be regarded only as adjuncts in the diagnostic process. Limitations of the tests' performance and the interpretation of their findings often result in diagnostic confusion. False-negative and, especially, false-positive results are common. The antibody response to *B. burgdorferi* develops slowly. The peak of IgM titers appears between 3 and 6 weeks after the onset of illness. Earlier in the course of the illness, IgM titers may be negative. IgM antibody usually returns to nondiagnostic

levels 4 to 6 weeks after the peak, but elevations may persist. IgG antibody may be detectable 2 months after exposure and peaks at approximately 12 months. Early antibiotic therapy may blunt or even abolish the antibody response.

A two-tier strategy is recommended for serologic testing—a sensitive enzyme immunoassay (EIA) followed by a Western blot (immunoblot). Positive or equivocal EIA results should be followed by a Western blot. If the EIA is negative, no further testing is necessary. Several Lyme disease serologic assays have recently been cleared by the Food and Drug Administration (FDA) allowing use of an EIA rather than Western blot as the second test in a Lyme disease testing algorithm.[6] IgM and IgG immunoblots should be obtained if early disease is suspected. If late disease is suspected, IgG Western blot alone should be obtained. Criteria for positive Western immunoblotting (requiring the presence of bands at particular locations) have been adopted by the CDC.

About one-third of patients with early localized Lyme disease (erythema migrans) are seropositive at the time of presentation by the two-tier method. Patients with skin lesions typical of EM do not require confirmatory serologic testing, and the rash itself is sufficient for the diagnosis to be made. If the cause of the rash is uncertain, acute and convalescent phase serologic testing may be considered, with the convalescent sample drawn 2 to 4 weeks after the acute sample. In contrast to early localized disease, most patients with early disseminated Lyme disease or late Lyme disease are seropositive.

IgG (and occasionally IgM) antibody may persist for several years after adequate treatment and symptom resolution. Persistent seropositivity is not diagnostic of ongoing infection. Even an IgM response cannot be interpreted as a demonstration of recent infection or reinfection unless the appropriate clinical characteristics are present. IgG antibody that developed after natural infection does not always confer immunity against future infection by *B. burgdorferi*. Patients who are treated for EM may become reinfected; patients with Lyme arthritis, however, usually have high antibody titers to many spirochetal proteins and seem not to become reinfected. Thus, the expanded immune response of late disease appears to be protective against reinfection, at least in most patients, whereas the immature immune response of early disease does not.

False-positive enzyme-linked immunosorbent assay (ELISA) results are common. Serologic cross-reactivity can occur between *B. burgdorferi* and other spirochetes, most notably *Treponema pallidum*. False-positive results for Lyme disease also can occur with relapsing fever, gingivitis, leptospirosis, enteroviral and other viral illnesses, rickettsial diseases, autoimmune diseases, malaria, and subacute bacterial endocarditis. In addition, it is estimated that up to 5% of the normal population will test positive for Lyme disease by ELISA. Bayes theorem states that if the pretest likelihood of the disease is low, the positive predictive value is low: a positive test result is more likely to be a false-positive result. For this reason, screening serologic tests are not indicated in the absence of objective clinical evidence of Lyme disease.

Patients suspected of having acute Lyme neuroborreliosis should be evaluated with serologic tests and routine CSF examination, including cell counts and differential, protein, glucose, Gram stain, and culture. Most patients with neuroborreliosis have positive results on serum serologic testing, thereby making additional laboratory confirmation with CSF serology unnecessary. The PCR assay has low sensitivity when performed on CSF and is not routinely recommended. However, the PCR assay is superior to culture for detecting *B. burgdorferi* in synovial fluid and has a sensitivity of 73% and specificity of 99% in untreated Lyme arthritis.

Management

Prompt treatment of early disease can shorten the duration of symptoms and prevent progression to later stages of disease. Most manifestations of Lyme disease can be treated successfully with oral antibiotic therapy, with the exception of neurologic abnormalities, which usually require intravenous (IV) therapy. Treatment of Lyme disease is summarized in Table 123.4.

Early Disease

Prompt antibiotic therapy is essential in early Lyme disease because it generally shortens the duration of the rash and associated symptoms and, more importantly, prevents later illness in most patients. Some patients with severe early disease, however, progress to later stages, despite appropriate antibiotic regimens.

The drug of choice for men, nonpregnant and nonlactating women, and children older than 8 years is doxycycline, 100 mg bid for 3 weeks. An advantage of doxycycline is that it also is effective for the treatment of human granulocytic anaplasmosis, which is transmitted by the same tick that transmits Lyme disease. Pregnant or lactating women and children younger than 8 years should receive amoxicillin, 500 mg three times daily orally (20 to 40 mg/kg/day in three doses for children). Cefuroxime axetil has been shown to be as effective as doxycycline and may be used in children of any age, but cephalexin is ineffective in Lyme disease.

Macrolide antibiotics are not recommended as first-line agents for therapy for early Lyme disease. They should be reserved for patients who cannot tolerate doxycycline, amoxicillin, and cefuroxime axetil. Macrolide regimens for adults include azithromycin, 500 mg orally daily for 7 to 10 days, erythromycin, 500 mg orally qid for 14 to 21 days, and clarithromycin, 500 mg orally bid for 14 to 21 days.

A Jarisch-Herxheimer type of reaction may occur in the first 24 hours of antibiotic treatment, consisting of fever, chills, myalgias, headache, tachycardia, increased respiratory rate, and mild leukocytosis. Defervescence usually takes place within 12 to 24 hours. The pathogenesis of this reaction is controversial, but it probably is caused by the killing of spirochetes, with the release of pyrogens. The Jarisch-Herxheimer reaction occurs more commonly with penicillin and doxycycline than with erythromycin, probably because of their superior spirocheticidal activity.

Early Disseminated Infection

Neurologic Disease. For patients with relatively mild symptoms (e.g., solitary facial nerve palsy with normal findings on CSF examination), doxycycline or amoxicillin can be used in the same dosage as for early disease, but the duration of therapy should be extended to 28 days. The use of prednisone for facial nerve palsy from Lyme disease has been suggested but is not currently recommended.

Parenteral antibiotic therapy is required for patients with other objective neurologic abnormalities (e.g., meningitis or encephalitis, peripheral neuropathies, cranial neuritis other than facial nerve palsy) or evidence of the spirochete in the CSF. Ceftriaxone, 2 g/day IV for 14 days (75 to 100 mg/kg/day for pediatric patients), or penicillin G, 18 to 24 million units every 4 hours daily IV for 10 to 14 days, may be used. Ceftriaxone may be more effective than penicillin, and many experts recommend longer courses (e.g., up to 4 weeks). In cases of penicillin or cephalosporin allergy, oral doxycycline may be used for 28 days.

Cardiac Disease. Patients with mild cardiac conduction system involvement, such as a first-degree AV block with a PR interval less than 0.30 second, and no other significant symptoms usually can be treated safely on an outpatient basis with oral doxycycline or amoxicillin for 21 to 30 days.[7] Patients with higher degrees of AV block, including first-degree block with a PR interval of more than 0.30 second or evidence of global ventricular impairment, should be hospitalized for cardiac monitoring and treatment with parenteral antibiotics. Penicillin G, 18 to 24 million units IV in 4 divided doses, or ceftriaxone, 2 g daily for 21 days (50 to 80 mg/kg/day for children), may be used.

TABLE 123.4 Treatment of Lyme Disease

Syndrome and Manifestation	Drug	Adult Dosage	Pediatric Dosage[a]
Early Lyme disease	Doxycycline[b]	100 mg PO bid for 21 days	
	or		
	Amoxicillin	500 mg PO tid for 21 days	50 mg/kg/day tid
	ALTERNATIVE		
	Cefuroxime axetil	500 mg PO bid for 21 days	15 mg/kg/day bid (max dose of 250 mg bid)
	or		
	Erythromycin (less effective than doxycycline or amoxicillin)	500 mg PO qid for 14–21 days	
Neurologic disease			
• Facial nerve paralysis	With an isolated deficit, oral regimens for early disease, used for at least 28 days, may suffice. For a deficit associated with other neurologic manifestations, intravenous therapy is warranted (see below).		
• Lyme meningitis	Ceftriaxone	2 g IV by single dose for 14–28 days	75–100 mg/kg/day IV
	Penicillin G	20 million units daily in divided doses for 10–14 days	300,000 units/kg/day IV
	ALTERNATIVE		
	Chloramphenicol	1 g IV qid for 10–21 days	
Cardiac disease			
• Mild	Doxycycline[b]	100 mg PO bid	
	or		
	Amoxicillin	500 mg PO tid	50 mg/kg/day tid
• More severe	Ceftriaxone	2 g IV daily by single dose for 14–21 days	75–100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses every 4 hours for 14–21 days	300,000 units/kg/day IV
Arthritis	ORAL		
	Doxycycline[b]	100 mg PO bid for 30 days	
	or		
	Amoxicillin	500 mg PO tid for 30 days	50 mg/kg/day divided tid
	PARENTERAL		
	Ceftriaxone	2 g IV by single dose for 14–21 days	75–100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14–21 days	300,000 units/kg/day IV

[a]Pediatric dosage should not exceed adult dosage.
[b]Tetracycline, 250 to 500 mg PO qid, may be substituted for doxycycline. Neither doxycycline nor any other tetracycline should be used for children younger than 8 years or for pregnant or lactating women.
[c]Regimens for radiculoneuropathy, peripheral neuropathy, and encephalitis are the same as those for meningitis.
[d]Oral regimens are reserved for mild cardiac involvement (see text).
Adapted from: New drugs for allergic conjunctivitis. *Med Lett Drugs Ther.* 2000;42:39-40; and Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43:1089-1134.

The benefit of the adjuvant use of aspirin or prednisone in the treatment of Lyme carditis is uncertain and not currently recommended. Temporary cardiac pacing may be necessary in patients who have severe heart block with hemodynamic instability. The block generally resolves entirely with antibiotic treatment, so the recognition of Lyme carditis in young patients with unexplained heart block is critical for avoidance of unnecessary permanent pacemaker implantation.

Late Infection

Arthritis. In established Lyme arthritis, the response to antibiotic therapy may be delayed for several weeks or months. An oral regimen for 30 days, such as doxycycline, 100 mg orally bid, or amoxicillin, 500 mg tid, usually are effective and, for reasons of cost and convenience, may be selected as first-line therapy given on an outpatient basis before parenteral antibiotic therapy is considered. Persistent or recurrent joint swelling after recommended courses of antibiotic therapy can be treated with another 4-week course of oral antibiotics or with a 2- to 4-week course of IV ceftriaxone. A small percentage of patients with Lyme arthritis, particularly those with HLA-DR4 specificity or antibody reactivity with OspA, may have persistent joint inflammation, despite treatment with oral or IV antibiotics. Such patients often do not respond to any antibiotic therapy and may require arthroscopic synovectomy.

Neurologic Disease. Patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once daily IV for 2 to 4 weeks). Alternative parenteral therapy may include cefotaxime (2 g IV three times a day) or penicillin G (18–24 million units IV daily, given in divided doses every 4 hours). Response to treatment is usually slow and may be incomplete.

Lyme Disease and Pregnancy

Similar to the spirochetal agents of syphilis and relapsing fever, *B. burgdorferi* can be passed transplacentally. In rare cases, Lyme disease acquired during pregnancy may lead to infection of the fetus and possibly to stillbirth, but adverse effects on the fetus have not been documented conclusively. Counseling about the termination of a pregnancy because of maternal Lyme disease is unwarranted.

Lyme disease contracted during pregnancy can be treated and cured. Treatment of pregnant patients can be identical to that of nonpregnant patients with the same disease manifestations, except that doxycycline should be avoided. Most women give birth to normal infants despite documented Lyme borreliosis during their pregnancies.

Vaccination

No vaccine against Lyme disease is currently available in the United States. The LYMErix vaccine (SmithKline Pharmaceuticals, Philadelphia), initially licensed in 1999, was withdrawn from the market in 2002. The vaccine, directed against the outer surface protein A of *B. burgdorferi* (OspA), was apparently safe but required repeated doses for optimal protection. Ongoing questions about its safety and cost-effectiveness dampened demand for the vaccine.

A history of vaccination with the previously licensed vaccine should not change the approach to management. Because protective immunity produced by the vaccine is short-lived, it is unlikely that previous vaccination will provide any residual protective effect. Vaccination may cause a persistently positive ELISA result but a negative Western blot result.

Prophylaxis and Asymptomatic Tick Bites

A well-designed trial found that a dose of doxycycline given within 72 hours after a bite by a deer tick (*I. scapularis*) effectively prevented Lyme disease. A single 200-mg dose of doxycycline therefore should be considered for adult patients and children 8 years of age and older (4 mg/kg, up to a maximum dose of 200 mg) when all the following criteria are met: (1) the tick is an adult or nymphal *I. scapularis*; (2) the tick has been attached for 36 hours or more, as indicated by certainty of the time of exposure or degree of engorgement; (3) prophylaxis can be started within 72 hours after tick removal; (4) the local rate of infection of these ticks with *B. burgdorferi* is 20% or greater; and (5) doxycycline is not contraindicated. *B. burgdorferi* infects 20% or more of ticks in highly endemic areas such as New England, parts of the Mid-Atlantic region, and parts of Minnesota and Wisconsin. Most other areas of the United States do not have infection rates high enough to warrant prophylaxis.

The efficacy of single-dose doxycycline in patients who present more than 72 hours after removing a tick is unknown. In children, the dosing and efficacy of prophylactic treatment have not been evaluated. The effectiveness of doxycycline for preventing other infections transmitted by *I. scapularis* ticks (e.g., babesiosis, human granulocytic anaplasmosis) is unknown and should not be assumed. Other antimicrobial agents effective for treating Lyme disease (e.g., amoxicillin) and even other regimens of doxycycline (e.g., 100 mg bid) have unknown efficacy for Lyme disease prophylaxis. Anyone who has been bitten by a tick should be instructed to seek medical evaluation if symptoms of tickborne illness develop.

SOUTHERN TICK-ASSOCIATED RASH ILLNESS

A rash similar to erythema migrans (EM) has been described in humans following bites of the lone star tick, *Amblyomma americanum,* found from central Texas and Oklahoma eastward across the southern states and along the Atlantic coast as far north as Maine. The rash may be accompanied by fatigue, fever, headache, muscle and joint pains. This condition has been named southern tick-associated rash illness (STARI).[8] The cause of STARI is not known.

STARI is diagnosed based on symptoms, geographic location, and possibility of tick bite. Because the cause of STARI is unknown, no diagnostic blood tests are available.

It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI. Because STARI resembles early Lyme disease, patients are often treated with oral antibiotics.

RELAPSING FEVER

Relapsing fever is caused by bacteria of the *Borrelia* species, order Spirochaetales. Human *Borrelia* infections occur worldwide, and all are associated with arthropod vectors. The epidemic (louseborne) form of relapsing fever is caused solely by *Borrelia recurrentis* and is found mostly in Africa, where mortality rates can reach 70% with outbreaks. The endemic form, tickborne relapsing fever (TBRF), is caused by a group of closely related *Borrelia* species, their names derived from the species names of *Ornithodoros* tick vectors that carry them. The more common species in North America are *Borrelia hermsii, Borrelia turicatae,* and *Borrelia parkeri*. *B. burgdorferi* has been recognized as the causative agent of the third and most recently described borrelial disease, Lyme disease.

TBRF is maintained in an animal reservoir consisting primarily of wild rodents, including squirrels, mice, rats, chipmunks, and rabbits. It is found predominantly at altitudes of 2000 to 7000 feet in coniferous forest habitats. The tick vectors are argasids (soft ticks) belonging to several species of the genus *Ornithodoros,* which routinely reside in the nests and burrows of their mammalian hosts. Ticks acquire the infection by feeding on a spirochetemic rodent. The borreliae remain viable in the ticks for several years and can be passed transovarially to the next generation. In addition, soft ticks—unlike hard ticks—can survive up to 10 years, making removal of all infested nests imperative.[9] Two unique characteristics make this genus a significant reservoir and vector. These soft ticks feed for brief periods (15–20 minutes), usually at night, and their painless bite generally is unnoticed by the sleeping victim. Transmission occurs by injection of infected saliva through the bite site or intact skin. Less common modes of transmission (e.g., venipuncture equipment in injection drug users) have been reported.

In the United States, TBRF occurs primarily in the western Mountain and Pacific states, including Montana, Wyoming, Nevada, Colorado, California, and Washington. Between 1990 and 2011, the CDC received 504 reports of TBRF. The groups most commonly affected were males and people between the ages of 10 to 14 and 40 to 44 years. Of all reported cases, 70% were collectively from California, Washington, and Colorado. Most cases involved visitors to those states. Although TBRF is not nationally reportable, it was reported in 12 states in 2011.[4] Outbreaks have been reported among groups of persons sleeping overnight in hunting cabins inhabited by wild rodents. In Texas, most cases were reported in the winter months among people who had been exploring caves.

Clinical Features

In TBRF, the initial febrile episode lasts 3 days. This is followed by an asymptomatic period of variable duration, usually, approximately 7 days. During this time, patients generally feel better and may return to their usual daily activity levels under the assumption that they have recovered from another viral illness. Relapse then occurs, with symptoms that mimic those of the original illness. With TBRF, this cycle repeats itself three to five times. Each successive relapse usually is less severe. Relapse is caused by the spirochete's unique ability to undergo

antigenic variation within the body of the infected host. Each successive antigenic variation is cleared from the bloodstream by specific host antibodies, and a characteristic relapsing febrile course results.

Clinical illness is manifested in two classic stages as each fever episode resolves. The first stage is called the chill phase (high fevers with reported temperatures of up to 106.7°F (41.5°C), mental status changes, tachycardia, and tachypnea), lasting approximately 30 minutes, followed by a flush phase (rapid temperature decrease, sweats, and hypotension), which can be confused with a Jarisch-Herxheimer reaction.[5]

After a postbite incubation period of 4 to 18 days, during which time the host concentration of spirochetes increases, fever of abrupt onset occurs, often accompanied by shaking chills, headache, arthralgias, myalgias, nausea, and vomiting. On occasion, a pruritic eschar may be noted at the site of the tick bite, but this usually is absent by the onset of clinical symptoms. Consequently, the nonspecific nature of the clinical presentation may lead to misdiagnosis of the disease as a viral illness. The patient's temperature is high, and generalized muscle weakness and lethargy are common. Hepatomegaly, splenomegaly, and jaundice are sometimes seen. Neurologic involvement is less common but can be manifested as delirium, nuchal rigidity, peripheral neuropathy, or pupillary abnormalities. Uveitis, iritis, and other cranial neuropathies can present acutely or, rarely, as long-term sequelae. A macular or petechial rash, more apparent on the trunk than on the extremities, may be present. There is evidence that febrile illness caused by relapsing fever might cause *Plasmodium vivax* malaria relapse.

Severe cases of TBRF resulting in acute respiratory distress syndrome (ARDS) in California and Nevada near the Lake Tahoe area and in the state of Washington prompted a comprehensive epidemiologic investigation of cases in those areas during a 10-year period. This study showed that ARDS may be more common than was previously suspected. Reported occurrence rates for Jarisch-Herxheimer reaction varied between 6% and 21%, 16% for hypoxia, 8% for elevated liver function test values, and 6% for ARDS; 46% of patients with TBRF required hospitalization.

Differential Diagnoses

On initial presentation, the differential diagnosis is extensive; however, it narrows with the occurrence of relapse. A history of possible soft tick exposure together with recurrent fever should suggest the diagnosis. Other conditions that initially may be considered include malaria, typhus, dengue, yellow fever, Colorado tick fever, and tularemia. Careful examination of blood smears, together with clinical data and other laboratory tests, aid in making the correct diagnosis.

A recently discovered Borrelia species, phylogenetically related to those responsible for relapsing fever, is now known to cause a new tickborne illness called Borrelia miyamotoi disease (BMD). It has been found in the Upper Midwest, mid-Atlantic, and Northeast states and tends to occur in late summer months as opposed to Lyme disease, which tends to occur in midsummer. Caused by the spirochete of the same name, BMD resembles Lyme disease and human granulocytic anaplasmosis (HGA), but the vectors consist of several species of the hard tick genus Ixodes. Headache, fever, and myalgias are the most common symptoms and tend to be more severe than those associated with Lyme or HGA. Diagnosis can be made using blood PCR samples and antibody titers. Giemsa-stained acute blood smears may reveal spirochetemia. Lab tests often show leukopenia, thrombocytopenia, and elevated liver enzymes. Both amoxicillin and doxycycline are effective treatments.[10,11]

Diagnostic Testing

In contrast to other spirochetal diseases, the definitive diagnosis of relapsing fever depends on the demonstration of spirochetes in peripheral blood smears during a febrile episode. In most cases, spirochetes are readily visible on a routine blood smear prepared with Wright or Giemsa stain. Thick or thin blood smears, such as those prepared for malaria evaluation, also are satisfactory. The organisms are seen within the plasma spaces between blood cells or may overlie the blood cells. Several organisms per high-power field typically are visible in smears from febrile patients with relapsing fever. Blood specimens for the smears should be obtained as the temperature curve increases. Repeated samples may be required before a positive result is observed because sensitivity approaches only 70%.

Spirochetes also may be visible in wet mounts with the use of phase contrast microscopy. Culture, although it is the most sensitive diagnostic method available, requires a special medium, does not yield rapid results, and therefore is not commonly performed. Genus-specific PCR testing has been used successfully and may be higher in sensitivity than serology or blood smear, especially in the acute phase of disease. Serologic testing is available through public and private health facilities but is not useful for immediate diagnosis. Nonspecific laboratory findings may include mildly increased bilirubin and liver function levels, thrombocytopenia, and an elevated erythrocyte sedimentation rate.[5]

Management

Relapsing fever is effectively treated with tetracycline or erythromycin. Tetracycline should be avoided in children younger than 8 years and in pregnant women. Tetracycline or erythromycin should be given in an oral dose of 500 mg four times daily for 10 days. Other treatment regimens have been recommended, including doxycycline and chloramphenicol. Treatment with penicillin G has been associated with an increased rate of relapse. Success with ceftriaxone has been reported in a patient with relapsing fever who did not respond to penicillin. Prophylaxis with doxycycline for TBRF in exposed subjects in high-risk infested areas is effective.

As many as one-third of patients experience a Jarisch-Herxheimer type of reaction during treatment with antibiotics. The reaction can be severe, especially with louseborne relapsing fever, and has been associated with high levels of cytokine intermediaries and endogenous opioids, and accelerated phagocytosis of spirochetes.[12] Approximately 4 hours after antibiotic treatment, and coinciding with the clearance of spirochetes from the blood, the patient usually experiences an increase in temperature and severe rigors, accompanied by a drop in the leukocyte and platelet counts and onset of hypotension. Anticipation of this reaction is crucial because volume expansion with saline solution may be required to maintain the blood pressure; the reaction can be more threatening than the disease itself.

The prognosis is good for treated patients with relapsing fever; approximately 95% achieve complete recovery. Poor prognostic signs include the presence of jaundice, high spirochete counts in the blood, and hypotension. Transplacental transmission can occur in infected pregnant women. Spontaneous abortions occur in nearly 50% of cases in pregnant women. Death is rare in TBRF and is limited to infants and older adults.

TULAREMIA

Tularemia was first characterized in 1837 by Soken, who described a febrile illness with generalized lymphadenopathy in people who had eaten infected rabbit meat. In 1912, McCoy first isolated *Bacterium tularense,* now known as *Francisella tularensis,* from rodents in Tulare County, California, giving rise to the name of the disease.

Tularemia occurs worldwide and is endemic between 30 and 71 degrees north latitude. The incidence of tularemia is low. There were between 180 and 314 yearly reported cases of tularemia in the United

States between 2014 and 2018, and it is a nationally notifiable disease.[13] Tularemia has been seen in every state except Hawaii but is most common in the southwest central region. During this period, most cases have come collectively from Missouri, Oklahoma, South Dakota, Colorado, Kansas, and Arkansas. It is more common in men than in women. Persons at increased risk for infection include hunters, trappers, butchers, agricultural workers, campers, sheep herders, mink farmers, and laboratory workers.

Ticks, lagomorphs (hares, rabbits), and rodents (mice, rats) are believed to be the most important sources of transmission to humans; however, the organism has been recovered from animals of more than 100 species. Significant epidemics have been linked to contact with a variety of them, including domestic cats. In 2002, a large number of commercially distributed prairie dogs from Texas died of tularemia.

The ticks most commonly involved in transmission of tularemia in the United States are from the hard tick family Ixodidae, specifically the Lone Star tick (*A. americanum*) and the dog tick (*D. variabilis*), both of which have been associated with other tickborne illnesses. Ticks were responsible for approximately half of tularemia cases in the United States between 2004 and 2014.[14] Whereas mosquitoes are major vectors in many European countries, horse fly and deer fly bites have been implicated in endemic situations in the United States. In 2007, an outbreak in Utah was associated with deer fly bites.

While transmission to humans most commonly occurs through tick bites or handling of infected animals, it also can occur with ingestion of infected food or water, inhalation of dust or water aerosol, and insect bites. Nonimmune laboratory workers who work with *F. tularensis* can acquire the disease. Person to person transmission is rare. Tularemia has a bimodal prevalence in the United States; an increased incidence in May to August is associated with tickborne transmission, and a December to January peak is associated with hunting and skinning of infected mammals (primarily rabbits). *F. tularensis* has been found to coexist in reservoir populations harboring the agent responsible for Lyme disease. Eleven cases of pneumonic tularemia, found to be from aerosolization of contaminated vegetation clippings, were discovered in Martha's Vineyard, Massachusetts. Outside the United States, tularemia has been confirmed in hundreds of cases in Kosovo through rodent contamination of food. Sweden has reported a high number of cases, usually associated with aquatic environments and mosquitoes.[15]

Tularemia is manifested in different ways, depending on the portal of entry of the organism. The primary route of infection by *F. tularensis* is through the skin. Entry can occur through hair follicles or small cuts and abrasions that may be contaminated by exposure to an infected animal; tick exposure can also introduce the bacteria. Because the bacterium has not been isolated from the salivary glands of ticks, it is thought that they transmit the organism through their feces. Scratching after a tick bite introduces the infected feces into the skin. Inhalation or ingestion of the organism or transmission through the conjunctivae also can cause infection. The incubation period is approximately 2 to 6 days, depending on the size of the inoculum.

After penetration of the skin or epithelial membrane, the organism usually spreads to the regional lymph nodes. An erythematous tender papule develops at the primary infection site, followed by inflammation and skin ulceration. The regional nodes enlarge, necrose, and may rupture. The necrotic, purulent, painful lymph node is termed a *bubo*. In the ulceroglandular form of the infection, the organism may not spread farther than the regional lymph nodes. If the inoculum is sufficiently large or host defenses are inadequate, bacteremia ensues, with dissemination to phagocytic cells of the reticuloendothelial system.

Pulmonary tularemia may result from inhalation of small-particle aerosols containing *F. tularensis* or from hematogenous dissemination. Small areas of localized pneumonitis are most commonly seen, although chest radiographic findings are nonspecific; lobar consolidation or abscess formation is rare. Oculoglandular tularemia occurs when the conjunctiva becomes infected from contact with material from an ulcer or contaminated finger. Typhoidal tularemia follows the systemic spread of *F. tularensis* from the oropharynx and probably the gastrointestinal tract when a large inoculum is swallowed.

Clinical Features

Presentations

Tularemia has six clinical presentations, depending on whether disease is localized to an entry site and its regional lymph nodes—ulceroglandular, glandular, oculoglandular, and oropharyngeal forms—or is more invasive and generalized—typhoidal and pulmonary forms. Ulceroglandular and glandular are the most common manifestations of tickborne tularemia.

Ulceroglandular Tularemia. This accounts for approximately 80% of cases. Typically, a skin lesion on an extremity at the site of primary inoculation begins as an erythematous papule, which then ulcerates 2 to 3 days later. The ulcer is slow to heal and often is still present when the subsequent regional lymphadenopathy and fever develop. The distribution of the regional adenopathy reflects the primary entry site; patients with tickborne tularemia usually have inguinal or femoral adenopathy, whereas those who acquire rabbit-associated tularemia have axillary or epitrochlear nodal involvement. Generalized lymphadenopathy also may be seen. On occasion, nodes suppurate and drain.

Glandular Tularemia. This is the second most common form. It is characterized by the development of lymphadenopathy (usually cervical) without an associated skin ulcer.

Oculoglandular Tularemia. This is seen in less than 2% of cases. It is characterized by unilateral conjunctivitis, with regional adenopathy involving preauricular lymph nodes.

Oropharyngeal Tularemia. This is manifested as severe exudative pharyngitis, with associated cervical lymphadenitis. It has been known to cause acute glaucoma.

Typhoidal Tularemia. This is a systemic form of the disease in which no obvious entry site can be found; it occurs in approximately 10% of cases. Only 10 to 50 organisms are required to induce disease; incubation time is 2 to 10 days. Symptoms and signs may include fever, chills, constipation or diarrhea, abdominal pain, and weight loss. A 30% to 60% case fatality rate is associated with untreated typhoidal tularemia.[16]

Pulmonary Tularemia. This has symptoms similar to those of other bacterial pneumonias—fever and chills, cough (usually nonproductive), substernal burning, dyspnea, malaise, and prostration. It may result from direct inhalation of aerosolized organisms or bacteremic spread from another site.

Other Considerations

Uncommon complications of tularemia include pericarditis, meningitis, endocarditis, peritonitis, appendicitis, perisplenitis, and osteomyelitis. Guillain-Barré syndrome associated with tularemia also has been reported.

Tularemia is one of the most widely studied diseases with respect to potential biologic warfare. The United States developed an aerosolized form in the 1950s, and the Japanese allegedly contaminated prisoners with the disease in the 1930s. It was removed from the national list of notifiable diseases in 1995 but then was reinstated in view of the heightened biologic weapons threat. It is classified by the CDC as one of the six category A critical biologic diseases.[7,13] An aerosolized form of the bacterium would be the most likely delivery mechanism used in biologic warfare. With the release of aerosolized particles, disease would

be manifested clinically as acute fever, progressive pneumonia, pleuritis, and hilar lymphadenopathy, beginning as early as 3 to 5 days after delivery. The mortality rate for untreated tularemia in general ranges from 5% to 30%, but the rate for the pulmonary form can reach 60%. With appropriate antibiotic treatment, death is rare (mortality rate < 1%). Only approximately 55% of emergency departments (EDs) have been adequately educated on the recognition of and preparedness for tularemia.

Diagnostic Testing

The diagnosis of tularemia is based on clinical findings and serologic testing. Antibody titers begin to rise approximately 7 to 10 days after exposure and peak in 3 to 4 weeks. In a patient with a clinical presentation suggesting tularemia, an antibody titer of 1:160 or higher in a single specimen is diagnostic. Confirmatory evidence is provided by a fourfold or greater rise in titer in a second sample obtained 2 weeks later. Unfortunately, titers of IgG and IgM can continue to be high for up to 10 years, and cell-mediated immunity can be maintained for up to 25 years. Rapid testing with PCR assay is available, and point of care analysis using an immunochromatographic approach has proven useful in testing water sources.

As for most infectious organisms, culture is the gold standard for diagnosis; however, aspiration of affected lymph nodes for culture is not routinely recommended because of the associated risk to laboratory personnel. If tularemia is suspected, the laboratory should be alerted so that appropriate precautions can be taken in specimen handling and enriched culture medium can be used. The risk of tularemia transmission lies in the danger of any handling that might produce aerosols or droplets.

Management

Isolation of patients with tularemia is not required because it is not transmitted from person to person. Streptomycin is the drug of choice for the treatment of all forms of tularemia but is not widely available. When given intramuscularly in a dose of 10 mg/kg (pediatric: 30 to 40 mg/kg/day) bid, streptomycin usually produces symptomatic improvement and resolution of fever in 1 to 2 days. After the third treatment day, half of the dose is given for a total course of 7 to 14 days. With this regimen, relapses are unusual.

Gentamicin is effective for treatment, especially in children (3 to 5 mg/kg/day for 10 to 14 days) and is more readily available than streptomycin. Tetracycline and chloramphenicol are also effective; however, the risk of relapse is greater than that associated with the aminoglycosides. Imipenem-cilastatin, an antibiotic without nephrotoxicity, has been used successfully to treat pulmonary tularemia in a patient with acute renal failure. Ceftriaxone is not effective against *F. tularensis* infections. Prophylaxis for possible exposure requires doxycycline, 100 mg bid for 14 days. Doxycycline or ciprofloxacin prophylaxis is recommended for a large biologic attack.

Ulcers and tender lymph nodes usually heal within 7 to 10 days; however, enlarged nodes occasionally develop into fluctuant sterile buboes, requiring incision and drainage after completion of the course of antibiotics. The unique ability of *F. tularensis* to attenuate host inflammatory responses has been emerging as a basis for research investigating the use of immunomodulatory agents or antibodies for adjunctive treatment. There continues to be no approved vaccine for tularemia. Because of recent interest in biologic warfare, however, research on tularemia vaccines has resurged.

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF) is an acute, febrile, systemic tickborne illness caused by *Rickettsia rickettsii*. The genus *Rickettsia* is divided into the spotted fever group and typhus group. *R. rickettsii* is considered the typical representative of the spotted fever group. Twenty-six species have been described.

RMSF is found in North, South, and Central America and is a nationally reportable disease. All cases are to be registered with the respective state department. As of 2010, reported cases of RMSF are categorized in the broader name of spotted fever rickettsiosis (Box 123.1).[16] The number of reported cases in the United States more than tripled between 2000 and 2007, especially in suburban areas.[17] The increase during this period was thought to be due to more widespread use of ELISA. Use of the assay has also resulted in a significantly lower

BOX 123.1 Diagnostic Criteria for Spotted Fever Rickettsiosis (*Rickettsia* spp.)

- Clinical criteria
  - Any reported fever and one or more of the following: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or hepatic transaminase level elevation
- Laboratory-confirmed
  - Serologic evidence of a fourfold change in immunoglobulin G (IgG)–specific antibody titer reactive with *Rickettsia rickettsii* or other spotted fever group antigen by indirect immunofluorescence assay (IFA) between paired serum specimens (one taken in the first week of illness and a second 2 to 4 weeks later) *or*
  - Detection of *R. rickettsii* or other spotted fever group DNA in a clinical specimen via amplification of a specific target by PCR assay, *or*
  - Demonstration of spotted fever group antigen in a biopsy or autopsy specimen by immunohistochemistry (IHC), *or*
  - Isolation of *R. rickettsii* or other spotted fever group *Rickettsia* from a clinical specimen in cell culture
- Laboratory-supportive
  - Has serologic evidence of elevated IgG or immunoglobulin M (IgM) antibody reactive with *R. rickettsii* or other spotted fever group antigen by IFA, enzyme-linked immunosorbent assay (ELISA),[a] dot ELISA, or latex agglutination
- Exposure
  - Exposure is defined as having been in a potential tick habitat within the 14 days preceding the onset of symptoms. The patient's occupation should be recorded if relevant to exposure. A history of a tick bite is not required.
- Case classification
  - Suspected: A case with laboratory evidence of past or present infection but no clinical information available (e.g., laboratory report)
  - Probable: A clinically compatible case (meets clinical evidence criteria) that has supportive laboratory results
  - Confirmed: A clinically compatible case (meets clinical evidence criteria) that is laboratory-confirmed

[a] NOTE: Current commercially available ELISA tests are not quantitative, cannot be used to evaluate changes in antibody titer, and hence are not useful for serologic confirmation. IgM tests are not strongly supported for use in the serodiagnosis of acute disease because the response might not be specific for the agent (resulting in false-positives) and the IgM response might be persistent. Complement fixation (CF) tests and older test methods are neither readily available nor commonly used. CDC uses in-house IFA IgG testing (cutoff ≥ 1:64), preferring simultaneous testing of paired specimens, and does not use IgM results for routine diagnostic testing.
From: Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System: Spotted fever rickettsiosis (*Rickettsia* spp.) 2010 case definition. www.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=853&DatePub=2010-01-01.

case fatality rate, which could be related to the high cross-reactivity of serologic tests with more benign rickettsioses. Higher awareness and more aggressive empirical treatment of RMSF might also have contributed to the decreased fatality rate. In 2016, there were 4,269 reported spotted fever cases in the United States, which included all spotted fever rickettsioses, not just RMSF, in accordance with the surveillance changes mentioned.[18] Another rare rickettsiosis that emerged in North America in 2004 was caused by *Rickettsia parkeri*, transmitted through the Gulf Coast tick, *Amblyomma maculatum*. It is distinguished from RMSF by sometimes causing eschars or a vesicular rash.

RMSF ranges in clinical severity from mild or even subclinical illness to fulminant disease, with vascular collapse and death within several days of onset. It is the only rickettsiosis still associated with significant mortality, causing approximately 40 deaths in the United States each year, with a mortality rate ranging from 3% to 5%, despite appropriate treatment. Before tetracycline and chloramphenicol were available, death occurred in as many as 30% of cases in the 1930s. The highest mortality rates occur in patients between the ages 5 and 9 years or older than 70 years, among Native Americans, and among immunosuppressed patients. In the South Atlantic United States, mortality reaches 9% in patients older than 70 years. The median time between onset of illness and death is 9.5 days, whereas death occurs in hospitalized patients in a median time of 3 days.

The recorded history of RMSF suggests that the disease was present at least before the European settlement of western North America among inhabitants of wooded Rocky Mountain regions. Early terms used to name the disease included *tick fever* and *black measles*. In 1899, RMSF was described as "an acute, endemic, noncontagious but probably infectious, febrile disease, characterized by a continuous moderately high fever, severe arthritic and muscle pains, and a profuse petechial or purpuric eruption in the skin, appearing first on the ankles, wrists, and forehead, but rapidly spreading to all parts of the body."

Although RMSF was first described in Montana and Idaho, it is now relatively rare in the Rocky Mountain states. Endemic in all 48 contiguous states except Maine, the disease continues to be most prevalent in the southeastern United States. RMSF has been reported in Canada, Central America, Mexico, and South America but never outside the Western Hemisphere. Recently, RMSF has become increasingly common in certain areas of Arizona, with 21 fatalities reported between 2003 and 2016. In 1987, four cases of RMSF were reported among residents of the Bronx in New York City; none of the affected persons had recently traveled to an area known for endemic disease, raising the possibility that other urban foci of RMSF may exist.

RMSF also tends to be focally endemic, with clustering of cases within a larger endemic area that may correspond to islands of infected ticks. These areas, ecologically distinct from surrounding areas, may be ideally suited to ticks; they usually consist of wild open fields, deciduous forests with thick ground cover and poor water drainage, or uncultivated areas. Geographic clusters of severe disease have been reported. In areas with frequent occurrence of RMSF (Oklahoma, North and South Carolina, Tennessee, Pennsylvania, Missouri, Arkansas, Arizona), an infectivity rate of 2% to 15% of the tick population has been reported. North Carolina and Oklahoma carry the highest incidence rates (35% of all cases) for RMSF.

R. rickettsii organisms are obligate intracellular bacteria with tropism for human endothelial cells. They often occur in pairs and possess a cell wall similar in structure and chemical composition to that of gram-negative bacteria. *R. rickettsii* contain RNA and DNA and, in contrast with other rickettsial organisms, can invade the nucleus as well as the cytoplasm.

The American dog tick, *Dermacentor variabilis,* and the Rocky Mountain wood tick, *Dermacentor andersoni,* have been the vectors responsible for human RMSF cases in the United States to date. However, the common brown dog tick, *Rhipicephalus sanguineus,* has emerged as a third vector. *R. sanguineus* has been the main RMSF vector in Mexico, Central America, and the southwestern United States. *Amblyomma imitator,* in the genus of the Lone Star tick, has been implicated as yet another vector because *R. rickettsii* has been found in its eggs.

Ticks feed on virtually any available warm-blooded animal and human; the occurrence of *R. rickettsii* in the United States does not depend on the presence of any given order of mammal. Domestic dogs infected with *R. rickettsii* can demonstrate clinical illness similar to that seen in humans. Although dogs do not play an important role in the amplification cycle of RMSF, they can serve as a conduit for infected ticks, carrying them into close contact with pet owners. Dogs may serve as sentinels for RMSF in humans. A high prevalence of rickettsial antibodies in stray dogs in Arizona was thought to be a major factor in the 70 cases and 8 deaths from RMSF reported there between 2003 and 2008. The deadliest spotted fever, Brazilian spotted fever, is also caused by *R. rickettsia*. The capybara, a common mammal in Brazil, appears to be the main reservoir through the vector tick *Amblyomma cajennense*.

Communication between physicians and veterinarians is important when cases of zoonotic diseases are detected. Humans serve only as accidental participants in the cycle of infection. A retrospective study has revealed that none of 10 recipients of blood products found to be from donors with confirmed or probable RMSF contracted the disease.[15]

Pathophysiology

After introduction of *R. rickettsii* into the host by the tick vector, the organisms invade and multiply in the vascular endothelial cells. They then enter deeper areas of the vessel walls and infect vascular smooth muscle. Rickettsial organisms move from cell to cell by actin-based motility. Damage to endothelial cells not only exposes subendothelium but also releases tissue plasminogen activator and von Willebrand factor, thereby causing microhemorrhage, microthrombus formation, and increased vascular permeability. In addition, antibody forms, with antigen activating the complement system (type III immune response), and a cellular response is recruited.

These widespread vascular lesions form the basis for most of the clinical features associated with RMSF. Hypotension, edema, and increased extravascular fluid space result from the increased small-vessel permeability. The early rash results from the vasculitis and associated changes in permeability; later petechial and hemorrhagic lesions are secondary to the vasculitis and thrombocytopenia. Microinfarcts and focal lesions develop in various organs, including the brain, heart, lungs, kidneys, adrenal glands, liver, and spleen. Rickettsial encephalitis and diffuse microinfarcts are usual features of central nervous system involvement. An interstitial pneumonitis caused by direct lung invasion by the organism may occur, and ARDS can ensue. Acute renal failure and hypovolemic shock, the primary causes of death, can occur as early as the second week of illness.

Clinical Features

Children from 5 to 9 years of age are the most common victims of RMSF. Two-thirds of all cases are in children younger than 15 years. More than 90% present with a fever and rash. A history of tick bite or presence in possible tick-infested areas is elicited in 60% to 70% of all patients with RMSF, although only 49% of the pediatric population reports a bite. The incubation period ranges from 2 to 14 days, with a mean of 7 days. A short incubation period may indicate a more severe infection. Factors that bring a higher risk of death include delayed onset of rash, glucose-6-phosphate dehydrogenase deficiency, hepatomegaly,

TABLE 123.5 Symptoms and Signs of Rocky Mountain Spotted Fever[a]

	FREQUENCY DURING ILLNESS (%)	
Symptom or Sign	**Any Time**	**First 3 Days**
Fever (temperature of 37.8°–38.9°C [100°–102°F])	99	73
Headache, mild to moderate	91	71
Fever (≥102°F [38.9°C])	90	63
Any rash	88	49
Myalgia, mild to moderate	83	57
Rash, maculopapular	82	46
Rash, palms and soles	74	28
Triad of fever, rash, history of tick exposure	67	3
Nausea and vomiting	60	38
Headache, severe	57	40
Abdominal pain	52	30
Rash, petechial and hemorrhagic	49	13
Myalgia, severe	47	25
Conjunctivitis	30	13
Lymphadenopathy	27	13
Stupor	26	6
Diarrhea	19	9
Edema	18	3
Ataxia	18	7
Meningismus	18	5

[a]In 262 patients.
From: Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. *J Infect Dis*. 1984;150:480-488.

neurologic deficits, renal insufficiency, increased period between symptoms and antibiotic treatment, and lack of tick bite history.

Onset of symptoms usually is abrupt but may be gradual in approximately one-third of patients. Early symptoms are nonspecific and similar to those of many acute infectious diseases, making early diagnosis difficult. Typical patients experience sudden onset of fever, severe headache, myalgias, prostration, nausea, and vomiting. Tenderness may be noted in large muscle groups (Table 123.5). As many as 80% of patients may have gastrointestinal symptoms secondary to myositis of the abdominal wall. Fever (temperature usually > 102°F [39°C]) is nearly always present during the first 2 to 3 days of illness and may precede other signs by 1 week or more. On occasion, the onset of illness is mild, with lethargy, headache, anorexia, and low-grade fever; these patients may remain ambulatory. Although the triad of fever, rash, and tick exposure traditionally was seen in only approximately 3% to 18% of cases, more recent data have shown that it is found in up to 45% of children with the disease. An extreme complication of RMSF is gangrene, which probably is induced by small-vessel occlusion.

Cutaneous Manifestations

Vasculitis secondary to rickettsial invasion of vascular endothelial cells causes the rash commonly associated with RMSF; however, the rash reportedly is absent in 4% to 16% of laboratory-confirmed cases, referred to as Rocky Mountain spotless fever. In addition, the rash may go unnoticed in dark-skinned patients. It usually appears on the third to fifth febrile day but can emerge as early as the second and as late as the sixth day. The initial lesions generally are restricted to the ankles and wrists, sometimes spreading to the palms and soles. The rash then spreads centripetally to the forearms, arms, legs, thighs, and trunk. The face can be involved, although it is usually spared. Despite the common belief that the palms and soles are critical for diagnosis, they are not consistently involved; rash on the palms and soles is reported in approximately 50% of cases. Involvement of the scrotum or vulva can be an evasive clue for RMSF. The rash of RMSF typically begins as 1- to 5-mm blanchable pink to bright red discrete macules that may be pruritic. At this initial stage, the lesions fade when pressure is applied and are not palpable. A warm compress applied to the area enhances the rash.

After 6 to 12 hours, the rash spreads centripetally. After 2 to 3 days, the rash becomes maculopapular and changes to a deeper red; at this stage, skin changes can be appreciated on light palpation. By approximately the fourth day, the rash becomes petechial and no longer fades with applied pressure. Applying tourniquets for several minutes or taking the blood pressure may cause additional petechiae to form distal to the site of occlusion (Rumpel-Leede phenomenon). The lesions occasionally coalesce to form large ecchymotic areas that may slough and form indolent ulcers (Fig. 123.9).

Prompt institution of specific therapy can cause the initial nonfixed lesions to disappear rapidly, unlike the later fixed lesions. Patients who have had the typical rash may exhibit brownish discolorations at the site during the convalescent period.

Cardiopulmonary Manifestations

Echocardiographic evidence of decreased left ventricular contractility secondary to myocarditis is commonly seen and often is detectable even before clinical signs of RMSF appear. Clinical manifestations of left ventricular dysfunction are uncommon, however, and hypotension and pulmonary edema, when present, usually have noncardiogenic causes. Chest radiographs may demonstrate cardiac enlargement. Electrocardiographic changes include low-voltage, nonspecific ST-T changes, first-degree AV block, dysrhythmias (e.g., sinus and nodal tachycardia, paroxysmal atrial tachycardia, atrial fibrillation), and left ventricular hypertrophy. Most cardiac abnormalities are transient, but persistent echocardiographic changes have been described. Decreased systolic function, elevated serum cardiac markers, no finding of vascular lesions, and a fourfold rise in antibody titers are consistent with myocarditis from RMSF.

Interstitial pneumonitis and increased pulmonary capillary permeability may result from infection of the pulmonary capillaries with rickettsiae. Nonproductive cough and dyspnea secondary to pneumonitis are sometimes seen on presentation. Chest radiographic abnormalities are identified in approximately 25% of patients. These abnormalities include interstitial infiltrates, patchy alveolar infiltrates, pleural effusions, and cardiomegaly with pulmonary edema. Pulmonary consolidation is rare. In severe cases, progression to noncardiogenic pulmonary edema and ARDS may occur.

Neurologic Manifestations

Neurologic manifestations of RMSF range from mild headache and lethargy to seizures and coma. Acute disseminated encephalomyelitis has been described. Headache, generally severe, is common, occurring in 50% to 90% of cases. Meningismus is present in 16% to 29% of patients. The CSF may be normal or show a slight protein elevation and pleocytosis of lymphocytes and polymorphonuclear cells (usually 8 to 35 cells/mL). The CSF glucose level and opening pressure usually are normal. Resolution of eosinophilic meningitis during RMSF after appropriate antibiotic treatment has been reported. Less than 40% of patients have a positive CSF finding.

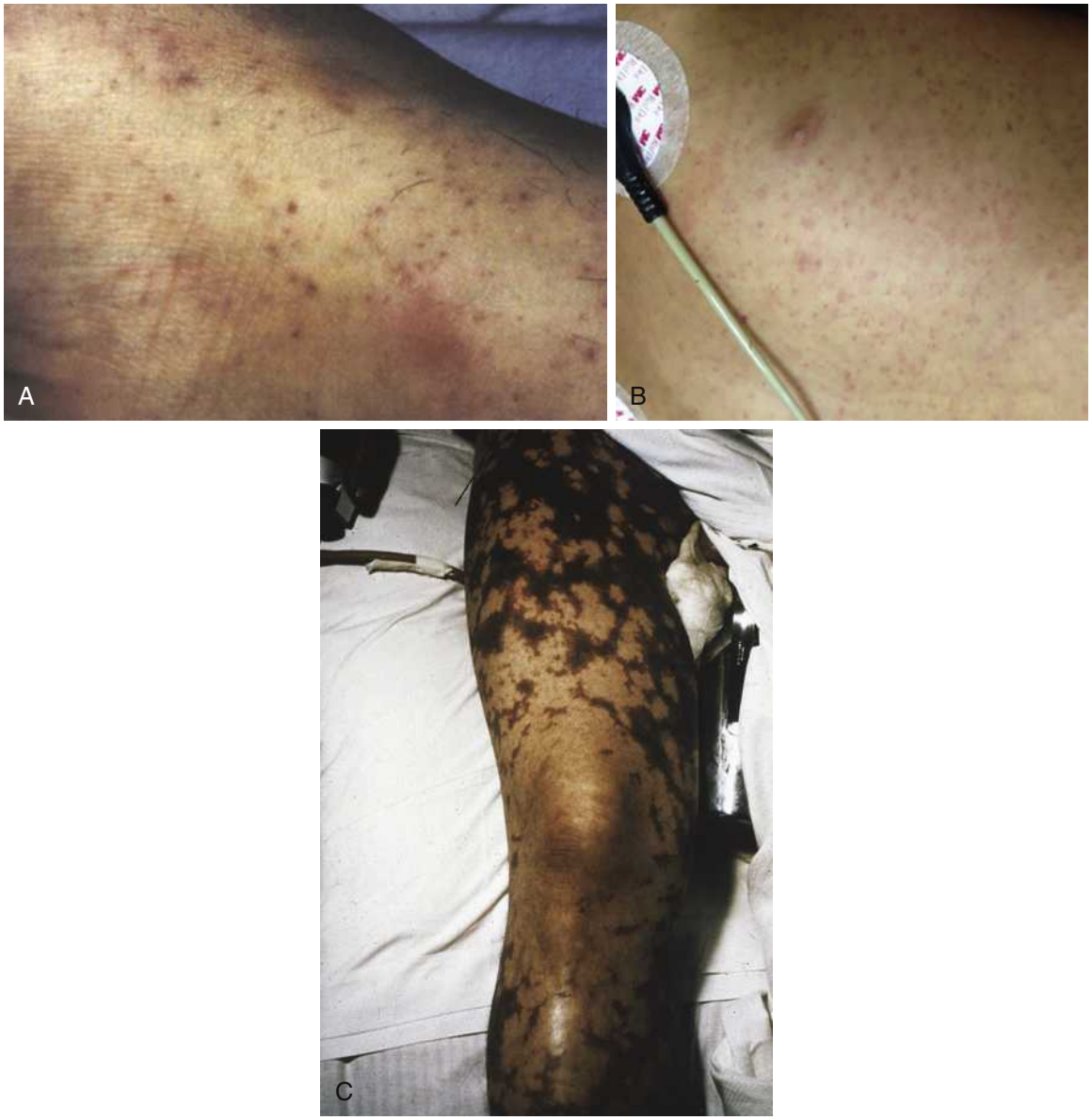

Fig. 123.9 Progression of rash of Rocky Mountain spotted fever. (A) Early, 2–4 days : Macular, maculopapular; small, flat, pink or red macules, usually on the wrists, forearms, and ankles. (B) Mid-stage, 5–7 days: Maculopapular, early petechia; progresses to maculopapular with petechiae, spreading centripetally to trunk. May involve palms and soles. (C) Late-stage, 7–9 days: Petechial, purpuric, necrosis; larger red to purple spots (petechiae) are considered a sign of progression to severe disease. These become diffuse, coalescing to form purpura. Areas of necrosis may occur. (A, From McGinley-Smith DE, Tsao SS. Dermatoses from ticks. *J Am Acad Dermatol*. 2003;49:363-392; B, From Centers for Disease Control and Prevention. RMSF training module: clinical diagnosis and treatment for healthcare providers [continuing education]. Accessed at: https://www.cdc.gov/rmsf/resources/module.html; Courtesy of Gerardo Álvarez; C, Courtesy Dr. Theodore Woodward.)

Cerebral thrombovasculitis may cause focal neurologic deficits, which usually are transient. Seizures can occur, especially during the acute phase of the illness. Generalized cerebral dysfunction ranging from lethargy to coma can occur secondary to systemic toxicity (e.g., fever, hypotension, hyponatremia) or vasculitic lesions involving the central nervous system. Coma is a late finding in patients with severe disease and is seen in less than 10% of cases. Some reports have described patients who remain alert but are amnesic for their illness after recovery. Other reported neurologic manifestations include transient deafness, tremor, rigidity, athetoid movements, paralysis, ataxia, opisthotonos, aphasia, and blindness. In general, neurologic signs abate without residual deficits, and permanent neurologic deficits are rare. Behavioral disturbances and learning disabilities have been reported after recovery from RMSF-associated coma in children.

Differential Diagnoses

Delayed diagnosis or misdiagnosis is the principal reason for the historically significant mortality associated with RMSF. Clinical diagnosis is difficult, especially early in the course of the illness, because of its nonspecific presentation. For avoidable deaths to be prevented, a diagnosis of RMSF should be considered in any patient with an unexplained febrile illness, with or without a rash and headache, even in

the absence of a history of tick bite or travel to an area known to be endemic for the disease. The emergency clinician should remember to ask routinely about recent tick bites, especially when assessing children with unexplained febrile illness, because parents do not always spontaneously provide this important information. An atypical presentation or manifestation of RMSF also should be considered during the differential diagnosis, including the following: (1) absence of a rash (Rocky Mountain spotless fever) or late appearance of a rash; (2) predominant gastrointestinal features or abdominal pain suggestive of an acute condition in the abdomen; (3) cough and pulmonary congestion suggestive of pneumonitis; and (4) meningismus suggestive of viral meningitis. A presumptive diagnosis is advised, with the initiation of specific therapy, well before specific confirmatory laboratory values are available.

A wide variety of other infections with similar exanthems can be confused with RMSF.[19] The most common include meningococcal infection, measles (rubeola) and atypical measles, gonococcemia, infectious mononucleosis, toxic shock syndrome, and enteroviral infections. Less common diseases include dengue fever, leptospirosis, murine typhus, and epidemic typhus. *R. parkeri* rickettsiosis should be considered.

Diagnostic Testing

Most immediately available laboratory tests provide little help in the diagnosis of RMSF. Early in the course of the illness, the diagnosis is based primarily on the history and physical exam, so epidemiologic features should be correlated with clinical signs and symptoms. The initial presentation of RMSF is similar to that of many acute febrile infectious diseases, and almost invariably a therapeutic decision must be made on clinical grounds alone, without the luxury of confirmatory laboratory evidence. Abnormalities such as thrombocytopenia, hyponatremia, and acute renal failure may be detected by routine laboratory tests, but they are nonspecific and unhelpful diagnostically. Up to 30% of patients present with anemia. A definitive diagnosis of RMSF requires positive results on one or more of several tests—skin biopsy, serologic study, or direct isolation and identification of the organism (see Box 123.1).

Skin Biopsy

Identification by immunofluorescent assay (IFA) and immunoperoxidase staining of *R. rickettsii* in biopsy specimens of the rash from patients with suspected RMSF are the best rapid diagnostic tests currently available. In experienced laboratories, the diagnosis of RMSF can be confirmed as soon as 4 hours after the specimen is obtained. The organisms can be detected as early as day 3 of clinical illness and as late as day 10. Unfortunately, this technique can be used only when a rash is visible for accurate localization of the biopsy site. Biopsy specimens generally are obtained with a 3-mm punch in the center of the skin lesion. Immunofluorescent demonstration of rickettsiae in frozen sections of skin biopsy specimens has a sensitivity of 70%. Results of immunohistochemical staining of tissues at autopsy were positive in all fatal cases in one study, whereas IFA results were negative in most cases. Failure to obtain a biopsy specimen of a rickettsial cutaneous lesion or failure to obtain sections through its center is associated with false-negative results. Treatment with anti-rickettsial drugs for 24 hours does not appreciably alter the sensitivity of the test; however, after 48 hours, rickettsiae are substantially reduced in number. Detection of rickettsial DNA in a skin biopsy specimen by PCR assay is available through the CDC, some state health departments, and other clinical laboratories.

Serologic Studies

Rickettsial infection can be confirmed by demonstration of an antibody rise in paired sera. Even with the most sensitive serologic tests, however, elevations in antibody titers do not occur until approximately 5 to 7 days after the onset of initial symptoms. Especially given the need to start treatment when RMSF is suspected, serodiagnosis is retrospective. It is achieved by comparing acute serum, which typically yields negative findings, with convalescent serum, which yields positive results for antibodies. The indirect IFA generally is considered to be the reference standard for RMSF diagnosis and is the test currently used by the CDC and most state public health laboratories. It has a high specificity and sensitivity (94%). IFA can be used to detect IgG or IgM antibodies. An RMSF latex agglutination test with results in less than 24 hours is available in selected laboratories.[15]

A prior study has shown a 12% seroprevalence, with antibody titers of 1:64 or higher, in the pediatric population in the southeastern and south central regions of the United States. Accordingly, clinical correlation with titers in these regions is critical.

Convalescent-stage blood samples are best obtained 2 to 3 weeks after the onset of clinical illness. Antibiotic therapy does not affect the time of appearance of antibodies or titers if initiated several days after the onset of illness. However, if antibiotic therapy is started earlier in the course of the illness, the rise in titers can be delayed for 4 weeks or more. Under these circumstances, antibody titers should be tested again at 4 to 6 weeks after the onset of illness.

Nested PCR testing with a turnaround time between 1 and 2 days has been used but is not specific for individual rickettsial species. Real-time PCR assays that can be completed in 1 hour and are 100% specific for RMSF have been developed but are not readily available.

Isolation of Organism

For most pathogenic infections, the standard diagnostic criterion is isolation and identification of the causative organism from the patient's blood or tissues. This is seldom attempted in rickettsioses, however, because the isolation procedures are time-consuming, expensive, and hazardous to laboratory personnel. In addition, primary isolation of rickettsiae by inoculation in the yolk sac of a chick embryo usually fails because of the small number of organisms in the patient's blood.

Management

Treatment of RMSF consists of antibiotic therapy, supportive care, and possibly steroids. An understanding of the underlying pathophysiologic changes and appreciation of the systemic complications that can occur in the patient afflicted with RMSF are necessary for the formulation of a balanced therapeutic regimen. The course of the disease can be complicated by electrolyte imbalances, renal failure, circulatory collapse, and coma. Although these complications are often absent in the mildly ill patient, for whom antibiotic therapy alone usually suffices, they should be anticipated in the seriously ill patient, especially if the patient is first seen late in the disease course.

The most important factor contributing to the persistent case fatality rate of 5% is the delayed administration of specific antibiotic therapy. Without appropriate treatment, the fatality rate rises to 25%. For a select group of early-stage, mildly ill patients, outpatient therapy with oral antibiotics can be successful if the patient is reliable and close follow-up observation is arranged. More severely ill patients in whom the diagnosis is uncertain should be hospitalized for the administration of IV antibiotics.

As part of an effort to improve physician awareness and timely treatment for RMSF, the CDC offers a free online training module that includes a rash comparison tool and case-based exercises.[20]

Supportive Care

Major complications of RMSF, such as shock, congestive heart failure, disseminated intravascular coagulation, and ARDS, should be

TABLE 123.6 Antibiotic Therapy for Rocky Mountain Spotted Fever[a]

Patient	Doxycycline[b] (Oral or IV)	Chloramphenicol[c] (Oral or IV)
Adult	100 mg bid; consider initial loading dose of 200 mg IV for seriously ill patients	50–75 mg/kg/day, divided q6h
Child (<45 kg)	2.2 mg/kg PO q12h	50–75 mg/kg/day, divided q6h

[a]Continue treatment at least 3 days after fever subsides or until unequivocal clinical improvement is seen; minimum course, 7 to 14 days.
[b]Doxycycline should not be given to pregnant women.
[c]Chloramphenicol should not be given to patients with thrombocytopenia; maximum of 1 g/day for children.
From: Centers for Disease Control and Prevention, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases: Rocky Mountain spotted fever, www.cdc.gov/rmsf/symptoms/index.html#treatment; and Cunha BA. Clinical features of Rocky Mountain spotted fever. *Lancet Infect Dis.* 2008;8:143-144.

anticipated and standard supportive measures instituted when appropriate. Circulatory collapse is common in patients with severe illness and is a major contributor to morbidity and mortality in RMSF. Hypotension unresponsive to fluid administration may require the use of vasopressors. In the critically ill patient with widespread vasculitis, however, a delicate balance exists between maintaining effective circulating volume and excessive leakage of fluids into the tissues, including the lungs and brain. Under these circumstances, the excessive administration of IV fluids can be deleterious. Isolation of the patient is unnecessary unless the diagnosis is still uncertain and other highly communicable illnesses, such as meningococcemia and measles, have not been excluded.

Antibiotics

Antibiotic therapy is most effective when initiated during the early stages of disease, coincident with the initial appearance of the rash. Although data from randomized clinical trials about antibiotic selection for RMSF are lacking, doxycycline is still widely regarded as the therapeutic agent of choice for most patients, including children.[21] Chloramphenicol should be considered only for patients in whom tetracyclines have caused significant adverse events and for pregnant women, except for those who are near term. The recommended doses of doxycycline and chloramphenicol are summarized in Table 123.6.

The American Academy of Pediatrics and CDC recommend doxycycline as the agent of choice for treatment of RMSF in children of all ages. The risk of cosmetically perceptible tooth staining appears to be minimal for a single course of treatment and is subordinate to the potential lethality of this illness.[22]

The effectiveness of therapy depends on the duration of therapy and interval between the onset of illness and the initiation of therapy. Treatment should begin as early as possible and continue for 7 to 10 days or until the patient is afebrile for 2 to 5 days. Response to treatment, as manifested by decreasing fever and subsiding rash, generally occurs 36 to 48 hours after antibiotic therapy is begun. Resistance to chloramphenicol or tetracyclines has not been reported. Penicillin, erythromycin, cephalosporins, aminoglycosides, clindamycin, and sulfonamides are ineffective against RMSF. In fact, empirical use of these agents for presumed bacterial infections could permit progression of the illness.

Symptom overlap between early meningococcal infection and RMSF frequently leads to both diagnoses being considered simultaneously. After blood and CSF culture specimens are obtained, empirical antibiotic coverage with ceftriaxone plus doxycycline should be administered.

On occasion, secondary bacterial infection from the RMSF rash may occur. Although sulfonamides have become a mainstay for the empirical treatment of MRSA skin infections, the use of these agents should be avoided in RMSF patients because their mechanism of inhibiting *p*-aminobenzoic acid may worsen the primary RMSF infection. The role of the new quinolones as potential replacements for doxycycline and chloramphenicol in the treatment of RMSF is as yet unproved. At present, no vaccine is available for RMSF.

Corticosteroids

The use of steroids in RMSF is controversial and is not routinely recommended. However, along with concomitant specific antibiotic therapy, short-term, high-dose steroid therapy should be considered for severe cases of RMSF complicated by extensive vasculitis, encephalitis, and cerebral edema, although there are no robust data to support this recommendation.

Q FEVER

Q fever, or "query fever," was first described in 1937 in Australia as an occupational disease of abattoir workers and dairy farmers. Cattle, sheep, goats, and ticks are the primary reservoirs of the causative rickettsiae, *Coxiella burnetii,* but many other species may be infected. The disease is now endemic worldwide, although it is rare in Scandinavian countries. The southern area of the Netherlands experienced a serious outbreak and reported more than 4000 cases since 2007 and 500 cases, with 11 deaths, in 2010 alone. France and Australia have significantly more cases than the United States. Africa presently is hyperendemic with Q fever. In the United States, the Midwest and California have had the highest incidences of Q fever. More than 30 cases have been seen in US military personnel deployed in Iraq and Afghanistan. Approximately 80% of cases of Q fever occur in males.[23]

Pathophysiology

C. burnetii is an obligate intracellular gram-negative coccobacillus bacterium, with multiple strains having been identified. Although most Q fever infections are transmitted by particle inhalation, tick transmission does occur. Besides being a vector of the disease, extremely high levels of *C. burnetii* in the feces of infected ticks are found on ruminant animals on which they feed. The Rocky Mountain wood tick, *D. andersoni*, is the main tick vector in the United States, although the bacterium has been isolated in more than 40 hard tick and 14 soft tick species.

Q fever historically has been characterized as either an acute or chronic presentation, although the exact definitions and criteria are controversial, with some authors suggesting phases of infection, akin to tuberculosis.[24] The most common foci of infection are endocarditis, vascular infections, osteoarticular infections, or lymphadenitis. Both the type of bacterial strain and patient risk factors play a role in the course of illness.[24] It is extremely infectious for humans and animals; a single inhaled organism is likely sufficient to initiate infection. The Q fever rickettsiae are extremely resistant to desiccation, physical and chemical agents, and can survive for long periods in an inanimate environment. Consequently, it is classified as a category B biologic warfare agent by the CDC and has been a nationally notifiable disease since 1999.[25] The organism's infectivity and estimated casualty rate have been judged to be comparable with those of anthrax. Humans most commonly are infected by inhalation of aerosolized particles from contaminated environments. Patients with Q fever rarely recall a history of tick bite.

Clinical Features

The incubation period of Q fever ranges from 14 to 39 days, with an average of 20 days. Up to 60% of initial infections are asymptomatic. The acute form of the disease includes clinical manifestations such as severe retrobulbar headache, fever with temperatures to 40°C (104°F) or higher, shaking chills, general malaise, myalgia, and chest pain. Although Q fever is widely regarded as primarily a respiratory disease, the reported incidence of pulmonary involvement varies, ranging from 0% to 90%. The reasons for this reported variation are unclear, but explanations include geographic strain variation, plasmids that may regulate virulence, and source, route, and dose of the agent. Mild hepatic involvement is common. Osteomyelitis in children, acute renal failure, and lymphocytic meningitis secondary to *C. burnetii* have been described.

Rarely, Q fever may present as a "chronic infection," occurring in less than 5% of cases, with or without an antecedent acute episode. Clinical syndromes that historically have been labeled as a chronic form of the disease include granulomatous hepatitis and culture-negative endocarditis. Endocarditis has been documented in up to 68% of patients with chronic Q fever; the mortality rate for this group approaches 25%. Most patients with Q fever in whom endocarditis develops have a history of valvular heart disease, particularly affecting the aortic valve. These patients should be especially cognizant of the potential hazards of Q fever infection and should be restricted from certain at-risk occupational settings. Patients with aneurysms and vascular grafts also are at risk.

Human fetal demise and deaths have been attributed to *C. burnetii* infection. Persons infected with human immunodeficiency virus (HIV) are at increased risk for Q fever.

Diagnostic Testing

The diagnosis of Q fever should be suspected in any patient with a severe febrile illness without an obvious cause, especially someone who has had recent contact with sheep, cattle, goats, or animal byproducts. Few patients with this disease recall a tick bite. Because of the laboratory hazards associated with the cultivation of Q fever rickettsiae, isolation of *C. burnetii* is not recommended for routine diagnosis. Rather, serologic studies such as IFA, PCR, and ELISA are the preferred diagnostic tests, but the results are not identifiable until 2 to 3 weeks after the onset of illness.

C. burnetii displays an antigenic phase variation. In patients with acute Q fever, phase II antibodies dominate the humoral immune response and are detectable by the second week of illness, whereas phase I antibodies are prominent only in patients with chronic (persistent) Q fever. Confirmation of a Q fever case requires (1) a fourfold increase in IgG titers between acute and convalescent samples or the presence of IgM phase II antibodies, (2) a positive PCR test result, (3) the culture of *C. burnetii* from a clinical specimen, or (4) the positive immunostaining of the organism in tissue. Measurement of IgA and IgG together has been useful in the diagnosis of endocarditis. The finding of granulomatous changes on bone marrow biopsy can be characteristic of Q fever in patients with osteomyelitis.

Management

Uncomplicated acute Q fever is treated with doxycycline (200 mg once daily for 2–3 weeks). Acute disease with concomitant valvular heart disease is treated with doxycycline (200 mg once daily) plus hydroxychloroquine (600 mg once daily) for 1 year. Fluoroquinolones have also been successful in this situation. Patients with persistent infections should be continued on the same regimen for 1.5 to 3 years. Combination therapy with doxycycline and hydroxychloroquine is effective for treatment of endocarditis in HIV-infected patients. Strong evidence has recommended combination therapy for endocarditis for 18 and 24 months in patients with native valves and prosthetic valves, respectively, with evidence of persistent infection. Cotrimoxazole is the recommended alternative treatment. Some macrolides and rifampin may also be effective. Treatment of pregnant women with Q fever with long-term cotrimoxazole, although not always curative, has been shown to decrease complications to the fetus.

In mass casualty situations, prophylaxis is recommended by treating with 5 to 7 days of doxycycline. Most acute Q fever infections resolve without treatment, but the risk of persistent infection makes treatment advisable. The mortality rate is less than 1% in untreated patients and lower still in those treated with antibiotics. The prognosis is worse in patients with protracted illness and hepatic involvement or endocarditis. Inactivated whole-cell vaccines for Q fever have proven to be effective for as long as 5 years. Vaccination can afford considerable protection to slaughterhouse and dairy workers and others at risk. Information on the handling of suspected or confirmed exposure to *C. burnetii* or bioterrorist threats can be found on the CDC website.

EHRLICHIOSES

There are currently two major forms of human ehrlichiosis in the United States—human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), caused by the bacteria *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum,* respectively. In 2001, restructuring of the *Ehrlichia* phylogenetic branches placed the previously known bacteria of human granulocytic ehrlichiosis into the genus *Anaplasma*—hence, the revised name. Both genera, *Ehrlichia* and *Anaplasma,* are now considered to be in the tribe Ehrlichieae, family Anaplasmataceae, but are still collectively referred to as being in the group of diseases called ehrlichioses. A total of seven different species are now thought to be possible human pathogens.[26] HME was discovered in 1986 and HGA (previously human granulocytic ehrlichiosis) in 1994. Both have been identified as emerging diseases by the CDC and are nationally notifiable diseases, reportable through the appropriate state departments.

More than 1650 cases of *E. chaffeensis* were reported in the United States between 2016 and 2017 (Fig. 123.10).[27] Dramatic increases in seroprevalence rates in both diseases during the past decade suggest that these diseases have previously been highly underdiagnosed, underreported, or both. Misclassification from failure to confirm *Anaplasma* serologically likely has led to underreporting of this disease.

Both diseases peak around June through August. High-risk populations are similar to those at high risk for Lyme disease, including those living in endemic areas or having frequent contact with wildlife or rural wooded areas. HME has been reported predominantly in the south-central and southeastern United States; HGA mostly is found in the upper Midwest, New England, parts of the Mid-Atlantic states, northern California, and many parts of Europe.

Pathophysiology

The causative agents in the ehrlichioses are gram-negative, obligate, intracellular, rickettsia-like coccobacilli. Transmitted from the midgut and salivary glands of their tick vectors, these organisms reside in specific circulating leukocytes in human and other mammalian hosts. Reservoirs include the white-tailed deer and white-footed mouse. *Ehrlichia canis* is the common pathogenic species in dogs. The species *Ehrlichia equina* has been isolated in California elk. HME, transmitted by the Lone Star tick, *A. americanum,* is most often caused by the organism *E. chaffeensis* (named for Fort Chaffee, Arkansas), which invades monocytes. *Ehrlichia ewingii* and *Ehrlichia muris* are also now known to be definite causative organisms.[28] *E. chaffeensis* has been isolated

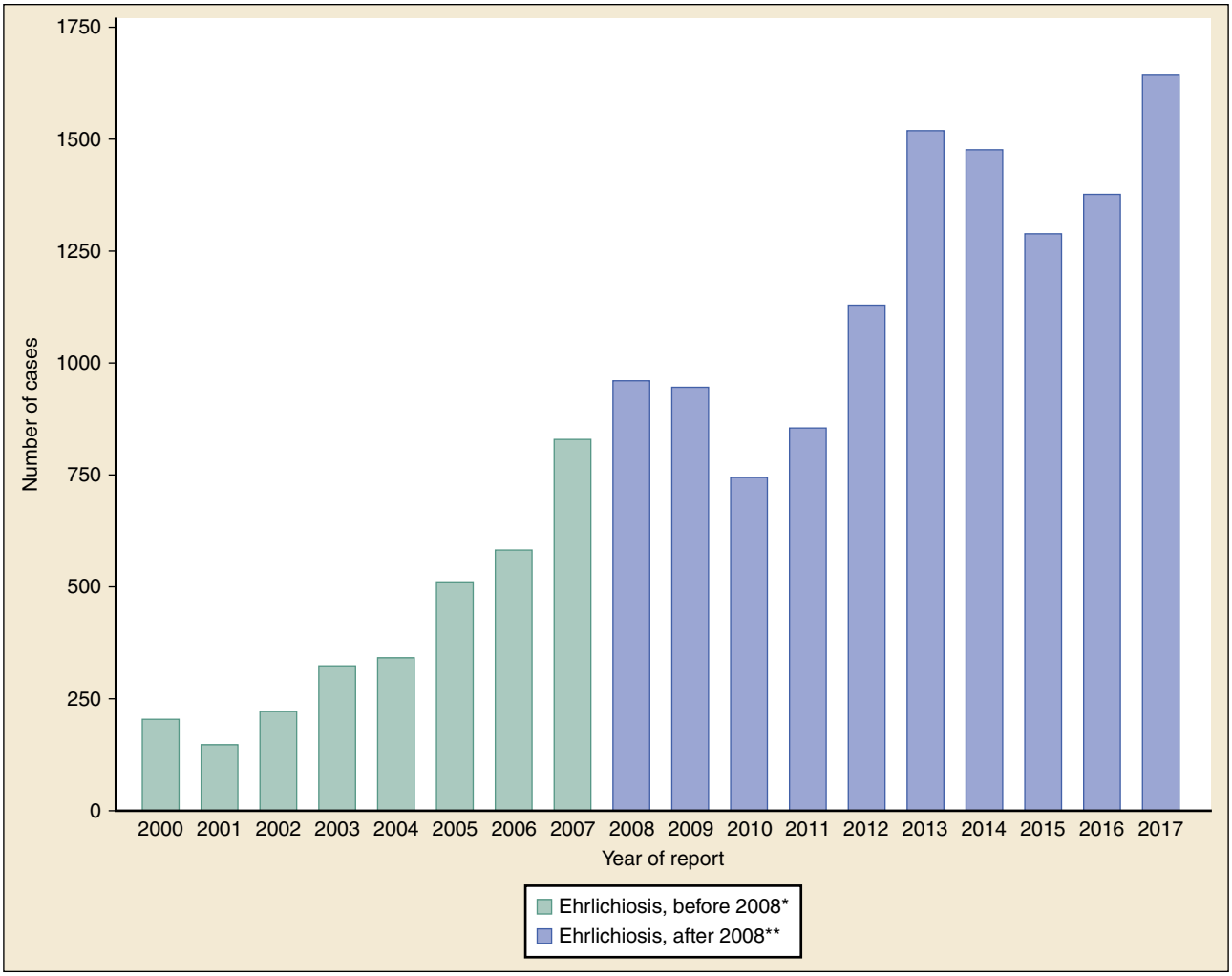

Fig. 123.10 More than 1650 cases of *Ehrlichia chaffeensis* were reported in the United States between 2016 and 2017.

from *I. pacificus* ticks in California. As of 2017, Missouri, Arkansas, New York, and Virginia are responsible for over half of reported HME cases.[27] *A. phagocytophilum* invades neutrophils (granulocytes), causing HGA and, in the United States, is transmitted by the black-legged tick, *I. scapularis*, and its West Coast counterpart, the western black-legged tick, *I. pacificus*. Deer, elk, and wild rodents are the main reservoirs for *Anaplasma*. Both ticks also are the vectors for Lyme disease. *A. phagocytophilum* has been detected in significant numbers in various *Ixodes* human tick species in mainland Portugal, Italy, and Japan.

Clinical Features

The clinical presentations of HME and HGA are similar and, for management, it is not necessary to differentiate between the two illnesses. The average time to onset of symptoms (for HME) from tick discovery is 9 days but ranges from 0 to 34 days. More than 90% of patients with HME report a history of tick bite or tick exposure. Ehrlichiosis characteristically is manifested with abrupt onset of fever, headache, myalgia, and shaking chills. Other, less frequent manifestations include nausea, vomiting, diarrhea, abdominal pain, cough, and confusion. Leukopenia, thrombocytopenia, and elevated liver function test values can be seen in 50% to 90% of patients.

Rashes occur in approximately one-third of patients with HME but in only 2% to 11% of those with HGA. In a small series of pediatric patients (average age, 7.4 years) with HME, a rash rate of 67% was found. Most of these patients suffered permanent cognitive or other neurologic damage.

Ehrlichiosis (HME) also has been associated with optic neuritis. ARDS, meningitis, pancarditis, renal failure, and disseminated intravascular coagulation have been associated with both ehrlichioses. Case fatality rates vary between studies but range from 0.5% to 3% for both diseases, with HGA usually reported as the lower of the two. Historically, data support only a 0.2% concurrence of lumbar puncture–proven meningitis or encephalitis with patients diagnosed with HGA who have a headache and/or stiff neck.[28] Approximately 45% of patients with HGA require hospitalization, although almost all recover without residual problems. HME has been associated with hemophagocytic lymphohistiocytosis.

Diagnostic Testing

For HME and HGA, the initial diagnosis is based largely on clinical presentation. With most tests, the diagnosis will be retrospective; results are rarely available immediately. The most common mode of diagnosis is confirmation of acute and convalescent antibodies with IFA. Enzyme immunoassay and confirmatory tests with Western blot have been developed but are not readily available. They provide only positive or negative results without titers. PCR testing for DNA fragments, although also not as readily available in most institutions, probably is most reliable in the acute phase of illness (at 1 week after onset of symptoms). Diagnostic serologic testing is available at the CDC through state health departments.

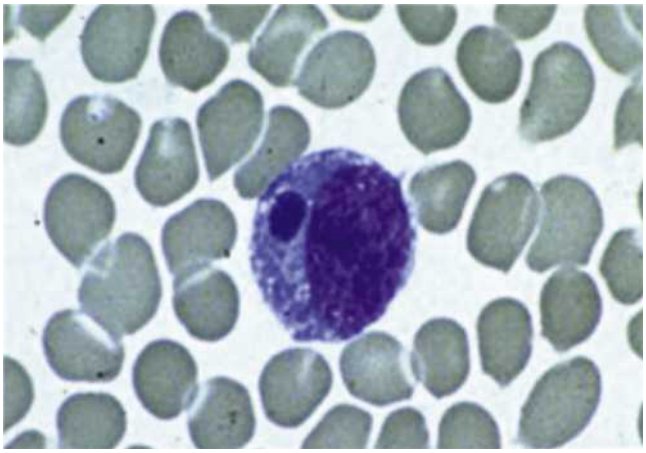

Fig. 123.11 Morulae detected in a monocyte on a peripheral blood smear associated with *Ehrlichia chaffeensis* infection (Wright stain; ×1000). (From: Centers for Disease Control and Prevention. Ehrlichiosis: symptoms, diagnosis, and treatment. www.cdc.gov/Ehrlichiosis/symptoms/index.html.)

Laboratory criteria required in the CDC's 2008 case definition to establish the presence of HME or HGA include detection of *E. chaffeensis* or *A. phagocytophilum,* respectively, through the use of the following diagnostic tests: (1) fourfold change in antibody titer to the organism antigen by IFA in paired serum samples; (2) positive result on PCR assay and confirmation of organism-specific DNA; (3) identification of morulae in leukocytes and a positive titer to the organism antigen; (4) immunostaining of the organism's antigen in a biopsy or autopsy specimen; or (5) culture of the organism from a clinical specimen. All tests require compatible clinical findings. Most patients with acute ehrlichiosis have antibody titers higher than 1 : 160.[29]

Cytopenia and abnormal liver function usually resolve after the acute phase of illness by 14 to 28 days. Microscopic identification of mulberry-like clusters (morulae) inside leukocytes on peripheral blood smears is helpful (Fig. 123.11). This finding, however, usually disappears after the first week of illness with HGA,[28] especially if the patient has been treated with doxycycline. Cultures take up to 2 weeks to grow the organisms.

Management

Doxycycline (100 mg bid; 2.2 mg/kg body weight bid for children weighing < 45 kg) and tetracycline regimens for 7 to 14 days are curative. Most patients respond rapidly after treatment is begun, and fever subsides within 24 to 48 hours. Tooth staining from doxycycline is no longer considered a concern for children and should not be a reason to withhold therapy. Rifampin is an effective alternative in children with human ehrlichiosis. Data supporting the use of chloramphenicol are inconclusive. The same ticks that transmit HGA (*Ixodes* spp.) also are responsible for Lyme disease and babesiosis. Each disease entity requires a full diagnostic evaluation because amoxicillin treats Lyme disease but not HGA or babesiosis, and doxycycline alone does not treat babesiosis. Failure of fever to resolve beyond 6 or 7 days of treatment of a suspected tickborne disease should heighten suspicion for another disease organism. There are no vaccines presently available for either of the ehrlichioses.

BABESIOSIS

Babesiosis is a tickborne, malaria-like, acute febrile illness caused by intraerythrocytic protozoal parasites of the genus *Babesia*. Babesiosis has long been recognized as an important veterinary disease and probably was known in ancient times; it has been proposed that the fifth plague described in the book of Exodus was likely babesiosis. The species almost solely causing the disease is the protozoan *Babesia microti,* which is transmitted via the tick *Ixodes scapularis. B. microti's* main reservoirs are the white-footed mouse, *Peromyscus leucopus*, and the white-tailed deer, *Odocoileus virginianus*.

The first human cases of babesiosis were reported in Montana in 1904. Investigators seeking the cause of RMSF examined blood smears from local inhabitants and described parasitic forms now known to be characteristic of *Babesia*. Since the late 1950s, several widely scattered cases (mostly in Europe) of human babesiosis have been reported in splenectomized persons. *Babesia divergens,* a species primarily infecting cattle, is the most common agent reported in Europe, but other species have been implicated as well, including *Babesia bovis, Babesia equi,* and a single case of *Babesia caucasia* infection. Two strains, WA1, related to a canine pathogen, *Babesia gibsoni,* and MO1, related to *B. divergens,* also have been found to cause disease in humans. In all these reported cases, the course was fulminant and the disease usually fatal.

In 2011, babesiosis became a nationally reportable condition. In 2013, 1762 cases of babesiosis were identified by the 27 states mandated to report. This count reached 2358 in 2017. Almost all these cases were caused by *Babesia microti,* a rodent parasite, and occurred in the coastal regions of southern New England, where *B. microti* is endemic. New Jersey and the eastern part of Long Island were found to be endemic with babesiosis. Ninety-five percent of cases came from seven states—Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin—and 85% of these patients presented with symptoms in June through August, coinciding with the nymphal feeding period and time of maximal human exposure in endemic areas.[30] The average age for cases reported was 62 and two-thirds were male.[31] This disease has been particularly on the rise within the last 8 years in the lower Hudson Valley in New York and in eastern Pennsylvania.[32]

These cases differ from the European cases in that most (≈80%) occurred in persons with intact spleens. Significant morbidity has been low in the United States, despite lack of specific therapy. Asplenic persons, older adults, and otherwise immunosuppressed patients usually have more severe disease.

Pathophysiology

B. microti is associated with mice and deer rather than with cattle. The ecology of *B. microti* is similar to that of *B. burgdorferi,* the causative agent of Lyme disease, with the same major vector, *I. scapularis,* and the same mammalian reservoirs—predominantly the white-footed mouse, which hosts the larval and nymphal stages of the tick, and the white-tailed deer, which hosts the adult ticks.

Human babesiosis results from accidental human intrusion on the natural cycle of infection. The nymphal form of the *Ixodes* tick most commonly transmits the disease to humans, although babesiosis also can be transmitted by the adult tick. *I. scapularis* nymphs measure only 1 to 2 mm long and thus are easily overlooked by the patient (see Fig. 123.5). In more than 50% of all cases of babesiosis, patients cannot recall tick exposure. Babesiosis acquired through blood transfusion has been well documented.

Clinical Features

Babesiosis has an incubation period of 1 to 4 weeks after tick exposure. A nonspecific influenza-like illness, with fever, chills, headache, fatigue, and anorexia, is characteristic. Less common manifestations are nausea, diaphoresis, depression, photophobia, myalgias, arthralgias, dark urine, emotional lability, and hyperesthesias. Unlike in Lyme disease, rash is not a feature of this illness; however, erythema figuratum, a

widespread exanthem with well-established annular lesions, has been associated with septic babesiosis. The physical examination usually reveals normal findings, except for fever, which typically is present, and splenomegaly, which occurs in some patients. Meningeal signs are absent. More severe disease occurs in splenectomized patients; hypotension, severe hemolytic anemia, hemoglobinuria, jaundice, renal insufficiency, ARDS, and disseminated intravascular coagulation can be seen in these cases. Some patients with babesiosis are only mildly ill, and asymptomatic infection also may occur, as demonstrated by serologic surveys in endemic areas. The diagnosis of babesiosis should be considered in any febrile patient from an endemic area during the tick season and should be part of the differential diagnosis for post-transfusion infections. Mortality rates for hospitalized patients historically range from 6% to 9%, and up to 21% in immunocompromised patients.

Diagnostic Testing

The diagnosis may be established through microscopy, antibody detection through IFA staining, or PCR assay. Microscopic examination is done with thick and thin Giemsa-stained blood smears. Characteristic intraerythrocytic forms (piriform, ring, tetrad) may be present. Babesiosis has been known to be misdiagnosed as malaria. Malaria may be excluded by the absence of intracellular pigment granules, schizonts, and gametocytes. The presence of parasites in budding tetrad formation, resembling a Maltese cross, is more suggestive of babesiosis. Contrary to what is commonly taught, this finding is uncommon. Because parasitemia may vary, serial smears over the course of several days may be necessary in suspected cases. An immunohistochemical assay has been developed that further allows easier microscopic differentiation between babesiosis and malarial organisms.

The diagnosis can be confirmed by serologic studies. IFA antibody to *B. microti* is available through the CDC, and titers usually rise to 1:1024 or greater within the first few weeks of illness. IgM–indirect IFA is sensitive and specific in acute babesiosis. Serologic tests for Lyme disease, which shares a common tick vector with babesiosis, also should be performed; concurrent Lyme disease has been reported in up to 50% of cases of babesiosis. ELISA and IFA sensitivities rise significantly after 5 days of illness, whereas PCR is more useful in the earlier days of sampling.

Parasitemia observed at 1 to 4 weeks after inoculation of blood from infected patients into gerbils or hamsters supports the diagnosis. Other nonspecific laboratory findings include mild to moderate hemolytic anemia, which is present in most patients, and resultant mild elevations in bilirubin and serum lactate dehydrogenase levels.

Management

Patients who have not undergone splenectomy generally recover without specific therapy, although prolonged malaise and fatigue are common. In patients with severe disease and those who have had splenectomies, the combination of clindamycin (1.2 g bid IV or 600 mg tid orally) plus quinine (650 mg tid orally) has been shown to be effective and is the treatment of choice. An alternative regimen that may be better tolerated, especially by children and infants, consists of atovaquone (750 mg bid orally) plus azithromycin (500–1000 mg once followed by 250 mg once daily orally); up to 25% of patients may have an adverse effect from quinine. Pediatric doses need to be adjusted accordingly. Therapy should be continued for a minimum of 7 to 10 days. Development of resistance during treatment with azithromycin-atovaquone in immunocompromised patients has been described.

Other antimalarial drugs, such as chloroquine and quinacrine, are not effective. Fulminantly ill patients with marked degrees of parasitemia and hemolysis have benefited from exchange transfusion or apheresis.[33] Effective live vaccines have been developed for bovine babesiosis but have not been developed yet for human disease.[34]

COLORADO TICK FEVER

Endemic to the Rocky Mountain area, Colorado tick fever is an acute, tickborne viral infection characterized by headache, back pain, biphasic febrile course, and leukopenia. The causative agent of Colorado tick fever is a small RNA virus of the genus *Coltivirus,* family Reoviridae. It is one of more than 500 viruses in the heterogeneous group of arthropod-borne viruses (arboviruses). Colorado tick fever has a sharply defined endemic zone encompassing mountainous and highland areas, from an altitude of approximately 4000 to more than 10,000 feet, in the Canadian provinces of British Columbia and Alberta and in at least 11 western states (California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, South Dakota, Utah, Washington, and Wyoming). The largest number of cases has been reported in Colorado. The distribution of the virus coincides with that of its principal tick vector, *D. andersoni,* the Rocky Mountain wood tick. Although RMSF is transmitted by the same vector, that disease is far less common in Colorado. The cases of RMSF are outnumbered at least 20-fold by cases of Colorado tick fever.

Pathophysiology

The Colorado tick fever virus has been isolated from at least eight species of ticks, but *D. andersoni* is the only proven vector for humans. The tick is a significant reservoir for the virus because trans-stadial transmission (from larva to nymph to adult) occurs, and the tick remains infected and infectious for life, up to 3 years. The primary vertebrate host species for Colorado tick fever virus maintenance are the chipmunk, *Tamias minimus,* and golden-mantled ground squirrel, *Spermophilus lateralis*; many other vertebrate hosts have been identified as well, including a species of porcupine in Colorado in Rocky Mountain National Park. Larval and nymphal stages of *D. andersoni* ticks are responsible for the transmission of Colorado tick fever virus among rodents, and overwintering of the virus is accomplished by nymphal and adult *D. andersoni*. Only adult ticks transmit Colorado tick fever virus to humans.

The CDC indicates that there were 83 cases reported between 2002 and 2012 in the United States. The actual incidence undoubtedly is much higher because many cases are diagnosed as nonspecific viral illness, and other cases may be mild or entirely subclinical. Human susceptibility to Colorado tick fever is universal, but it occurs most commonly in young men, reflecting greater occupational and recreational tick exposure. This disease is not notifiable nationally, but is in some states.

Clinical Features

After an incubation period of approximately 3 to 5 days (range, 0–14 days), a moderate to severe influenza-like illness occurs abruptly, with signs and symptoms similar to those in early-stage RMSF. Fever, chills, headache, retrobulbar pain, myalgia, lethargy, anorexia, and nausea are common; vomiting and abdominal pain are reported occasionally. Early physical findings are nonspecific. A macular or maculopapular rash has been reported in 5% to 12% of patients but, unlike the rash of RMSF, the rash of Colorado tick fever is not a prominent feature of the illness.

A distinct feature of the illness is a biphasic course that occurs in approximately 50% of patients, causing a characteristic saddleback fever curve. Initial symptoms resolve after 2 to 3 days, and the patient feels relatively well for 1 or 2 days, after which the fever, headache, and myalgias return. The second phase may be more intense than the first

phase and generally lasts 2 to 4 days. There may even be a third febrile period. Alternatively, a single prolonged febrile illness may occur. Recovery from Colorado tick fever usually occurs within 2 weeks, but convalescence can be prolonged, especially in patients older than 30 years.

Colorado tick fever is a self-limited disease, and virtually all patients recover without sequelae. Reports of severe complications, such as meningoencephalitis and hemorrhagic diathesis, have been limited to children. Only a few fatal cases have been recorded.

Diagnostic Testing

The peripheral leukocyte count often is depressed during the acute phase of illness to as low as 1000/μL, with a relative lymphocytosis. Transient thrombocytopenia can accompany the leukopenia and, less often, a mild anemia can occur. These hematologic abnormalities normalize during convalescence, but persistence of the virus in red blood cells causes a prolonged viremia, even when clinical recovery is complete. Transfusion-acquired infection has been reported and is caused by this persistent viremia in asymptomatic blood donors.

The diagnosis of Colorado tick fever can be confirmed by serologic testing (IFA, neutralizing antibody, complement fixation, enzyme immunoassay) of acute and convalescent samples, but serologic study is of little help early because of the slow rise of titers. The most rapid confirmation of Colorado tick fever, with corresponding elimination of concern about possible RMSF, is provided by direct immunofluorescent staining of virus in red blood cells in peripheral blood smears. RT-PCR testing is available for more rapid diagnosis. ELISA has shown promising sensitivity in detection of the Colorado tick fever virus.

Management

The treatment of Colorado tick fever is supportive only. Although not commonly a fatal disease, up to 30% of patients require hospitalization. If RMSF remains a diagnostic possibility, initial treatment with tetracycline or chloramphenicol and a period of observation are necessary until the diagnosis of RMSF can be ruled out.

OTHER TICKBORNE VIRUSES

In addition to the virus responsible for Colorado tick fever, at least 40 viral species have been transmitted to humans by ticks and caused illness, approximately 25 of them in the United States. Tickborne viruses are found predominantly in the RNA virus families. Historically, the most severe cases involved the tickborne encephalitis virus and Crimean-Congo hemorrhagic fever virus, but these have not been reported in the United States. A few tickborne viral illnesses have received notable press in the United States because of their mortality rates—the Heartland virus, a phlebovirus (family Bunyaviridae); the Bourbon virus, a thogotovirus (family Orthomyxoviridae); and Powassan virus (POWV). Recently, the exotic tick *Haemaphysalis longicornis* has been identified in several East Coast states in the United States. This tick is responsible for severe hemorrhagic fever in China and Japan and, so far, two cases in the United States have been confirmed.[35]

Eight cases of Heartland virus (RNA) disease were found among residents of Tennessee and Missouri as of March 2014. Four patients were hospitalized, and there was one death. All cases presented with leukopenia, thrombocytopenia, and fever. The Bourbon virus, named after the county of its discovery, caused the death of a man in Kansas. POWV, named after Powassan, Ontario, where a young boy died from this flavivirus, is transmitted by several *Ixodes* tick species, including *I. scapularis*. It can cause a severe encephalitis and up to 50% of subjects acquire permanent neurologic deficits.[36] Presentations and laboratory results of these new viral syndromes resembled those of other tickborne illnesses and were treated with antibiotics empirically and unsuccessfully. Other neurologic symptoms and encephalitis have been well-described with tickborne viral illnesses. As with most viral illnesses, treatment remains mostly supportive. The emergence and discovery of these newer tickborne diseases suggests that they have been underreported.[19,37]

TICK PARALYSIS

Tick paralysis occurs when an adult female tick attaches to a host and releases a neurotoxin that can produce cerebellar dysfunction or an ascending paralysis. Tick paralysis was recognized as early as the beginning of the 19th century. Hovell, while traveling through Australia, wrote in 1824 of "the small insect called the tick, which buries itself in the flesh, and would in the end destroy either human or beast if not removed in time."

Tick paralysis has been reported worldwide, but most cases occur in the southeastern and northwestern regions of the United States, western Canada, and Australia. Cases have been reported to occur in clusters; 43 species of ticks have been found to cause tick paralysis in humans, other mammals, or birds. Most cases in North America and Canada are caused by *D. andersoni* (Rocky Mountain wood tick) and *D. variabilis* (American dog tick). Species responsible for paralysis cases that also are associated with other tickborne diseases include *A. americanum* (Lone Star tick), *I. scapularis* (black-legged tick), and *I. pacificus* (western black-legged tick); in Australia, *Ixodes holocyclus* is primarily associated with this disorder. Family Argasidae ticks (soft ticks) also have been implicated. Tick paralysis usually occurs in the spring and summer months and most reported cases are in children, primarily girls, probably because ticks are more easily concealed in longer hair. Among adults, however, more men than women acquire the disease.

Pathophysiology

Tick paralysis is thought to be caused by a toxin secreted from the salivary glands of the tick during a blood meal. The toxin, ixobotoxin, affects sodium flux across axonal membranes without affecting the neuromuscular junction itself. The mechanism of action of the toxin is poorly understood, but it appears to produce a conduction block in the peripheral branches of motor fibers, resulting in a failure of release of acetylcholine at the neuromuscular junction. Electrophysiologic studies have confirmed a rapid reversal of significant impairment of motor nerve terminal function after tick removal, indicating that the disturbance is not a result of a neuromuscular junction defect. Possible central sites of action of the toxin have been postulated to explain cases in which the clinical picture is dominated by cerebellar dysfunction.

Clinical Features

The onset of symptoms usually occurs 4 to 7 days after the tick attaches. Initial manifestations include restlessness and irritability, followed by ascending flaccid paralysis, acute ataxia, or both. Deep tendon reflexes are almost invariably lost. These signs and symptoms can progress rapidly during a few days to bulbar involvement, respiratory paralysis, and ultimately death if the tick is not detected and removed.

The ascending nature of tick paralysis has been noted in most descriptions; however, ataxia and associated cerebellar abnormalities in the absence of muscle weakness may be seen. Thus, tick paralysis may sometimes be manifested as so-called tick ataxia. Isolated facial paralysis has been reported in patients with ticks embedded behind the ear. Fever, other systemic symptoms, and sensory deficits are unusual. Concomitant infection with Colorado tick fever has been reported.

Differential Diagnoses

Tick paralysis should be considered in the differential diagnosis for any patient thought to have Guillain-Barré syndrome, Eaton-Lambert syndrome, myasthenia gravis, poliomyelitis, botulism, diphtheritic polyneuropathy, or any disease with an acute onset of ascending flaccid paralysis or acute ataxia. Ocular findings, such as decreased convergence, unresponsive dilated pupils, and nystagmus (horizontal and vertical), seen early in tick paralysis can help distinguish this disease from Guillain-Barré syndrome.

Diagnostic Testing

No diagnostic tests to confirm tick paralysis are available other than the combination of the clinical scenario, presence of a tick, and improvement after its removal. The Tensilon test yields a negative result in patients with this condition, and CSF is normal.

Management

Treatment in the United States consists simply of removing the tick; improvement generally is seen within a few hours and complete recovery within 48 hours. Supportive care, including mechanical ventilation, may be necessary. The mortality rate is approximately 10%; nearly all patients who die are children. The recommended procedure for the removal of any tick, including ticks causing tick paralysis, is summarized in Box 123.2. Traditional methods, such as burning, forceful removal, and application of petroleum, viscous lidocaine, or gasoline, are not consistently successful and do not guarantee removal of mouthparts, where the salivary glands and toxin may remain. Retained mouthparts also may cause infection.

Tick paralysis in Australia is often more devastating than in the United States. Symptoms and signs of illness caused by the Australian tick, *I. holocyclus,* do not resolve and often worsen after tick removal. Hyperimmune serum is available in Australia and often is needed because symptoms may worsen up to 48 hours after removal.

TICK BITE PROPHYLAXIS WITH INSECT REPELLENTS

Insect repellents have long been used to prevent mosquito bites. With recent increased public awareness of and concern about tickborne illness, especially Lyme disease, skin and clothing repellents are now also being marketed for tick protection. Three active ingredients in repellents have been shown to be effective against blood-sucking arthropods, including ticks—*N,N*-diethyl-*m*-toluamide (DEET), picaridin in KBR 3023 (known as Bayrepel, Hepidanin, and Autan Repel outside the United States), and *p*-menthane-3,8-diol (PMD) in oil of lemon eucalyptus. The most effective and most studied is DEET. Formulation percentages of DEET vary widely, ranging from 4.75% to 23.8%, giving 1.5 to 5 hours of protection, respectively.[38] A long-acting 35% DEET formulation (US Army Extended Duration Topical Insect/Arthropod Repellent [EDTIAR]), available in the United States as Ultrathon (3M), provides protection for 6 to 12 hours. Picaridin is as effective as the 35% DEET formulation. Despite some earlier concerns, toxic and allergic reactions to DEET have been uncommon, and serious adverse effects are rare. Used as directed, concentrations up to 50% appear to be safe, even in young children, although toxic encephalopathy rarely can occur. Use for infants younger than 2 months is not recommended.

Permethrin is actually a contact insecticide rather than a repellent. It can be used as a clothing spray for protection against ticks. Applied to the clothing as an aerosol, it is nonstaining, nearly odorless, and resistant to degradation by light, heat, or immersion in water. Permethrin is toxic to the nervous system of insects, but in mammals it is poorly absorbed and rapidly inactivated. Reported adverse effects have been limited to the skin and are uncommon.

Topical DEET and clothing impregnated with permethrin are effective in field trials when each is used alone. Wearing protective clothing treated with permethrin in addition to the use of DEET on exposed skin provides the greatest degree of protection against tick bites.

The references for this chapter can be found online at ExpertConsult.com.

BOX 123.2 Recommended Method for Tick Removal

1. Remove an embedded tick by grasping it with blunt forceps or tweezers as close to the point of attachment as possible.
2. Do not use bare fingers to remove ticks from animals or humans; when tweezers are unavailable, fingers should be shielded with a tissue, paper towel, or rubber glove.
3. Apply gentle, steady, upward traction with the forceps; do not twist or jerk the tick. Avoid squeezing or crushing the tick.
4. Do not handle the tick with bare hands. After removal of the tick, thoroughly disinfect the bite site and wash hands with soap and water.
5. Dispose of ticks by placing them in a container of alcohol or flushing them down the toilet.

Adapted from: Needham GR. Evaluation of five popular methods for tick removal. *Pediatrics.* 1985;75:997-1002.

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CHAPTER 123: QUESTIONS AND ANSWERS

1. What is the most common vector-borne disease in the United States?
- **a.** Babesiosis
- **b.** Cysticercosis
- **c.** Lyme disease
- **d.** Malaria

Answer: c. Lyme disease accounts for 95% of cases.

2. Which of the following statements regarding erythema migrans (EM) is true?
- **a.** The incidence with Lyme disease is 70%.
- **b.** The lesion center may become necrotic.
- **c.** The lesion is tender and warm to touch.
- **d.** The rash does not begin at the tick bite site.

Answer: b. EM occurs in 90% of cases. It begins at the bite site and expands. There may be central clearing, skipped areas, central necrosis, vesicles, and marked erythema. It is warm but not tender. Satellite and secondary lesions may occur due to hematogenous seeding by spirochetes. They are smaller, nonmigratory, and spare the palms and soles. All lesions fade after approximately 1 month.

3. Which of the following clinical pictures is not seen with Lyme disease?
- **a.** Conjunctivitis
- **b.** Hepatitis
- **c.** Meningitis
- **d.** Pleuritis

Answer: e. Clinical pictures consistent with hepatitis, conjunctivitis, and meningitis may be seen with Lyme disease.

CHAPTER 123: QUESTIONS AND ANSWERS—cont'd

4. A 26-year-old woman presents complaining of muscle and joint aches. She has no past history and takes no medications except over-the-counter analgesics. She describes a pattern of migratory and intermittent muscle aches, which she reports as lasting only hours at any single location and then migrating. The physical examination reveals a mild pharyngitis and conjunctivitis and is otherwise normal. Which of the following statements is true?

a. A history of tick bite should be sought.
b. A rheumatoid factor (RF) level should be determined.
c. An erythrocyte sedimentation rate (ESR) would be confirmatory.
d. Creatine phosphokinase (CPK) levels are likely elevated.

Answer: a. The migratory, short-lived, and intermittent nature of the Lyme-related arthralgias is sometimes the best clue to the diagnosis. The ESR, RF, and CPK values will likely be normal. Both rheumatoid arthritis and fibromyalgia present with progressive and usually symmetrical symptoms. Conjunctivitis, pharyngitis, meningitis, and hepatitis pictures may be part of the Lyme presentation.

5. Which of the following statements regarding Lyme carditis is true?

a. Cardiac involvement is uncommon.
b. Electrocardiographic changes are stable and persistent.
c. Onset time from initial illness is 2 or 3 months.
d. The most common manifestation is bundle branch block.

Answer: a. Cardiac involvement is uncommon. The most common manifestation is atrioventricular block, which may fluctuate significantly but often resolves as the cardiac inflammation recedes. Onset time from illness is an average of 3 to 5 weeks.

Tuberculosis

Peter E. Sokolove and Robert W. Derlet

KEY CONCEPTS

- Early recognition of patients with risk for TB should begin at ED triage. Patients with possible active pulmonary TB should be placed in respiratory isolation promptly.
- TB should be considered in the differential diagnosis of patients who present with fever, cough, and weight loss.
- Risk factors for TB include HIV infection, immunosuppression, age older than 60 years, being from an endemic country, being undomiciled, and close contact with known cases.
- In addition to pulmonary manifestations, a variety of extrapulmonary manifestations may occur, including involvement of lymph nodes, pleura, bones, joints, genitourinary, gastrointestinal, and central nervous systems.
- Therapy should be determined based on consultation with infectious disease specialists. The most commonly used agents are isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Resistant strains, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR), have been increasing in frequency.

FOUNDATIONS

Background and Importance

The emergency department (ED) serves as the front line of contact for many persons with untreated tuberculosis (TB) in the United States. Undiagnosed patients, incompletely treated patients, or those with active disease who develop complications may first seek medical care in EDs. For this reason, emergency clinicians must fully understand the complexities of the disease, including the multiple presentations of undiagnosed disease, complications, and initial therapeutic options.

TB is currently the world's second leading infectious cause of death, and one-third of the world's population has been infected by TB. Each year, more than 8 million people acquire active TB infection globally, and over 1.5 million die of the disease. In the United States, close to 10,000 new cases of TB are diagnosed each year, and 65% of these cases are in patients from endemic countries.[1] The largest numbers of people with TB originate from Eastern Europe, Africa, and Asia. Ongoing challenges of the 21st century include increasing occurrence of TB in institutional living settings, increasing rates of poverty, and substance use disorders. Being undomiciled and urban crowding also have contributed to the spread of TB in the United States and globally.

The HIV/AIDS epidemic has increased the incidence of TB in the United States. The pandemic of HIV-related TB also increased TB cases among non–HIV-infected people owing to the higher numbers of source cases in the community. The rate of clinical TB among patients who are HIV-infected and have a positive TB skin test is higher the cohort of non–HIV-infected patients.

Pathophysiology

One microorganism, *Mycobacterium tuberculosis* (MTB), causes human TB in nearly all cases. Humans constitute the sole known reservoir for MTB. Two other pathogenic mycobacteria, *Mycobacterium bovis* and *Mycobacterium africanum* have, on rare occasions, been implicated in causing TB. *M. bovis* is transmitted by drinking milk from diseased cows, which is rare in industrialized nations. *M. africanum* also is a rare cause of human TB in rural Africa.

MTB is an intracellular, aerobic, nonmotile, non–spore-forming bacillus with a waxy lipid coat. This coating makes MTB resistant to decolorization with acid alcohol after staining—hence, the term *acid-fast bacillus* (AFB). MTB grows slowly. Its generation time is 15 to 20 hours, compared with less than 1 hour for some common bacteria, and cultures take 4 to 6 weeks to grow on standard solid media. MTB produces neither endotoxins nor exotoxins. Its cell components are immunoreactive: some are immunosuppressive, and others are the agents of granuloma formation, macrophage activation, host toxicity, and modification of the immune response.

Transmission

TB is transmitted with rare exception by the respiratory route, including droplet spread and true aerosolization into microparticles. Patients with active disease expel MTB in liquid droplets during coughing, sneezing, and vocalizing. A single cough or 5 minutes of talking can produce 3000 infectious droplets, and sneezing can produce an even higher number. The droplets rapidly evaporate, and the desiccated bacilli circulate airborne for prolonged periods. These infective particles, or droplet nuclei, measure 1 to 5 μm in diameter, contain one to three tubercle bacilli and, when inhaled, can travel to the distal alveoli. Transmission by nonrespiratory routes, such as direct inoculation, occurs primarily among health care workers.

The susceptible host may become infected when only a few of the droplet nuclei are inhaled. Fomites are not important in the transmission of the disease, and patients' rooms, eating utensils, and bedding do not require special decontamination procedures. Because the infectious droplet nuclei are airborne, exchange of contaminated air is the most important environmental control. In addition, MTB is susceptible to ultraviolet radiation, so transmission rarely occurs outdoors because of the dilution of infectious particles and exposure to ultraviolet radiation.

The risk for TB transmission increases when source patients have airway and cavitary disease. Infectivity correlates with the number of organisms seen on sputum smear, extent of pulmonary disease, and frequency of coughing. Currently, there is no clear epidemiologic evidence to define a patient's contagiousness once they have started effective therapy. Most patients who initially had AFB-negative sputum smears are noncontagious after 2 weeks of chemotherapy. In contrast, patients who initially were smear-positive may still have viable

MTB detectable in their posttreatment sputum cultures after 2 weeks of treatment. Patients with extensive disease may still have AFB detectable on their post-treatment sputum smears; these two groups should be considered contagious. The Centers for Disease Control and Prevention (CDC) has published guidelines requiring the presence of three negative smears on different days as the criteria for removal of a patient from respiratory isolation, but debate about this recommendation is ongoing.

Extrapulmonary TB also may be infectious, but only if it is in the oral cavity or open skin lesion. Transmission of MTB to health care workers caring for patients with skin ulcers and draining tuberculous abscesses has been reported. Irrigation of the abscess may aerosolize the bacilli, forming infectious droplet nuclei.

Pathogenesis

When infectious droplet nuclei are inhaled, the airflow through the bronchial tree tends to deposit them in the midlung zone on the respiratory surface of the alveoli. The deposition launches a complex series of immunologic events. The pathogenesis of TB is divided into four stages.

Stage 1

The first stage begins when an alveolar macrophage phagocytoses the recently inhaled bacillus. A macrophage from a resistant host can immediately destroy a less virulent bacillus. In these cases, no tuberculous infection develops, and the process ends. If a virulent bacillus can overcome a macrophage's microbicidal capability, the infection may progress to the next stage.

Stage 2

When the alveolar macrophage is unable to destroy the inhaled tubercle bacilli, the bacilli replicate until the macrophage lyses. Circulating monocytes are attracted to the site of infection by the released bacilli, cellular debris, and various chemotactic factors. The monocytes differentiate into macrophages and ingest the free bacilli. Initially, these new macrophages are not activated and cannot destroy or inhibit the mycobacteria. The bacilli multiply logarithmically within macrophages and accumulate at the primary focus of infection, called a tubercle. The infected macrophages also may be transported through lymphatics to regional lymph nodes, from which they can reach the bloodstream, with subsequent spread. During this lymphohematogenous dissemination, the pathogens tend to distribute preferentially to lymph nodes, kidney, epiphyses of long bones, vertebral bodies, meningeal areas, and apical posterior areas of the lungs.

Stage 3

The third stage of TB begins 2 to 3 weeks after the initial infection, with development of the immune response that terminates the unimpeded growth of MTB. Cell-mediated immunity occurs through $CD4^+$ helper T cells. These T cells secrete cytokines that attract and activate monocyte-macrophages. Once activated, the macrophages, containing previously ingested mycobacteria and their progeny, kill the bacilli. Mild fever and malaise may develop in association with the immune response at 4 to 6 weeks, but the primary infection is generally insignificant clinically. Eventually, in the immunocompetent host with strong cell-mediated immunity, the caseous center inspissates (thickens) while the primary lesion is effectively walled off by epithelioid cells and is arrested. This sequence of events, from stage 1 to stage 3, represents the pathogenesis of primary TB in the immunocompetent patient. In most cases, primary TB is subclinical and self-limited. Clinically active TB develops in 8% to 10% of otherwise healthy persons. By contrast, in persons also infected with HIV, progression to acute primary TB occurs at a rate of 37% within 6 months.

Stage 4

The final stage usually occurs months to decades after an apparent recovery from the initial infection. TB may progress to stage 4 even in immunocompetent persons. Usually, host factors lead to decreased resistance and reactivation of dormant foci of MTB. Reactivation of dormant foci is responsible for the major clinical manifestations of TB. Exogenous reinfection of patients with well-documented previous TB infection causes clinical disease indistinguishable from that of reactivation TB. Because it may be incorrect to label all late-onset cases as reactivation disease, the preferred term is *postprimary TB*. Postprimary TB is active or chronic disease in a patient previously infected. In the United States and other developed countries, reactivation is thought to be the primary mechanism of postprimary TB. The primary walled-off tubercle eventually may erode through the bronchial wall and drains its contents, forming a cavity. The liquefied caseous material, teeming with mycobacteria, enters other parts of the lung and outside environment. The spilling of this liquefied material within the lung may produce a caseous bronchopneumonia.

CLINICAL FEATURES

Patients with TB may present with a primary infection or, more commonly, reactivation of an old infection. TB should be included in the differential diagnosis of common presenting complaints, such as isolated fever, chronic weakness, weight loss, failure to thrive, and night sweats.

Clinically significant pulmonary TB often is indolent, and signs and symptoms are absent or minimal until the disease advances. The constitutional symptoms of anorexia, weight loss, fatigue, irritability, malaise, weakness, headache, chills and, most commonly, fever can be caused by many other diseases. The fever usually develops in the afternoon; defervescence occurs during sleep, leading to the classic night sweats of TB.

Cough is the most common symptom of pulmonary TB patients presenting to the ED. It may initially be a dry nonproductive cough or, less commonly mucopurulent in nature. Hemoptysis, caused by caseous sloughing or endobronchial erosion, usually is minor but often indicates extensive lung involvement. Many otherwise asymptomatic MTB patients present for medical attention because they are alarmed by an episode of sudden hemoptysis. Patients also may complain of pleuritic chest pain, caused by parenchymal inflammation adjacent to the pleural surface. Dyspnea with chest pain may indicate a spontaneous pneumothorax. Shortness of breath from parenchymal lung involvement is unusual, however, and, if present, indicates extensive parenchymal disease or tracheobronchial obstruction.

The clinical manifestations of TB in patients presenting to the ED may be especially challenging. In one study, only one-third of ED patients with active pulmonary TB had pulmonary chief complaints. Any vague systemic disorder or fever of unknown cause may represent TB. Atypical presentations are particularly common in infants, older adults, and immunocompromised persons. In infants and young children, the development of large hilar lymph nodes is common. Pulmonary TB should be considered in older adults with chronic cough and failure to thrive. Young adults often show the adult pattern of apical pulmonary disease, including cavity formation, suggesting reactivation. Because of reduced immunocompetence, older adults typically have disease manifestations similar to those in young children.

Clinical manifestations of TB in patients coinfected with HIV are even more subtle and nonspecific, especially because these patients are vulnerable to opportunistic infections and neoplasms that can cause the same constitutional symptoms as TB. A synergy between MTB and HIV leads to a greatly increased viral load. Active TB with HIV

coinfection has been associated with an increased risk for opportunistic infections and death. Patients with advanced HIV infection commonly have extrapulmonary involvement (seen in 30%) as well as combined pulmonary and extrapulmonary TB (in 32%).

Risk Factors

All ED patients who have been coughing should be screened for the presence of TB risk factors (Box 124.1). Individuals from endemic countries and those living with persons who recently emigrated from endemic areas are at risk, as are patients with unexplained weight loss or cachexia. One of the most important risk factors is HIV/AIDS with $CD4^+$ levels below 500 cells/μL.[10] Overseas, coinfection with HIV and TB is common and results in an increased TB mortality rate. Risks for acquiring TB may also be stratified by age. Because infants and toddlers have poorly developed cell-mediated immunity, they have a much higher incidence of TB than adults. Patients on immunosuppressant medications such as steroids or antiarthritic immunosuppressant agents are at increased risk. Patients with a history of purified protein derivative (PPD) conversion should be asked about the presence of immunosuppressive medical conditions, which are associated with an increased risk for the development of active postprimary disease through reactivation. Household contacts also have increased risk of TB infection. Health care providers should ask patients with a history of active TB about all antituberculosis medications previously or currently taken and about compliance. Failure to improve after 2 months with an appropriate regimen may signal nonadherence to therapy or the presence of a resistant strain.

Physical Examination

A wasted patient with a cachexic appearance is a hallmark of advanced disease. The patient may show signs of dyspnea or tachypnea. The mental status examination may show subtle abnormalities. Examination of the chest can reveal abnormalities, but is unlikely to establish the extent of disease. Over areas of infiltration, rales may be heard when the patient breathes in after a short cough (posttussive rales), and bronchial breath sounds may be present over areas of lung consolidation. Distant, hollow breath sounds (amphoric breath sounds) may be heard over cavities. Most physical findings are a result of complications of TB or from the extrapulmonary forms of the disease (see section on "Extrapulmonary Tuberculosis").

Complications of Pulmonic Tuberculosis

Hemoptysis

Minor hemoptysis is a common complication of acute infection. The destruction of lung parenchyma leads to the rupture of blood vessels. TB also may cause massive hemoptysis. An uncommon complication is the erosion of a tuberculous lesion or cavity into a pulmonary artery, leading to pseudoaneurysm formation (Rasmussen aneurysm), with potentially fatal hemoptysis. Alternatively, superinfection of cavities by invasive organisms or tumor development in the scarred lung may cause erosion of bronchial or pulmonary vessels, with resultant major hemorrhage. Affected patients often require emergency surgical resection or selective embolization.

Pneumothorax

Spontaneous pneumothorax is uncommon (affecting <5% of patients with severe cavitary disease) but may occur when a tuberculous cavity ruptures and creates a bronchopleural fistula or when a bleb ruptures into the pleural space (Fig. 124.1). If treatment with tube thoracostomy and suction is delayed, progressive infection and fibrosis of the pleura can lead to air trapping in the pleural space.

Pleural Effusion

Pleural extrapulmonary TB may occur early after primary infection with MTB and is manifested as pleurisy with effusion. More rarely, it may occur late in postprimary cavitary disease and arise as an empyema. Tuberculous pleural involvement often causes no symptoms and resolves spontaneously; however, a 65% relapse rate has been reported in untreated patients, with development of active pulmonary or extrapulmonary TB within 5 years. The diagnosis usually is confirmed by microscopic and chemical examination of pleural fluid or pleural biopsy tissue. White blood cell counts usually range from 500 to 2500 cells/mL. The fluid is an exudate with protein usually exceeding 50% of the serum protein, and the glucose concentration may be normal to low. Because there are few bacilli, AFB smears rarely are positive, and cultures grow MTB for only 25% to 30% of patients known to have the disease. Pleural biopsy can confirm the diagnosis in most patients.

Empyema

An empyema, characterized by extensive, progressive parenchymal disease and cavitation, may develop in patients with TB. Although it is rare, empyema is more common late in the course of the disease in debilitated patients. Rupture of a cavity into the pleural space usually is catastrophic and often is associated with bronchopleural fistula

BOX 124.1 Population Groups with Increased Risk for Tuberculosis

- Close contacts of known case
- Persons with HIV infection
- From Eastern Europe, Asia, Africa, Latin America
- Medically underserved, low-income populations
- Older adults
- Residents of long-term care facilities (e.g., nursing homes, correctional facilities)
- Injection drug users
- Undomiciled
- Persons who have occupational exposure

HIV, Human immunodeficiency virus.

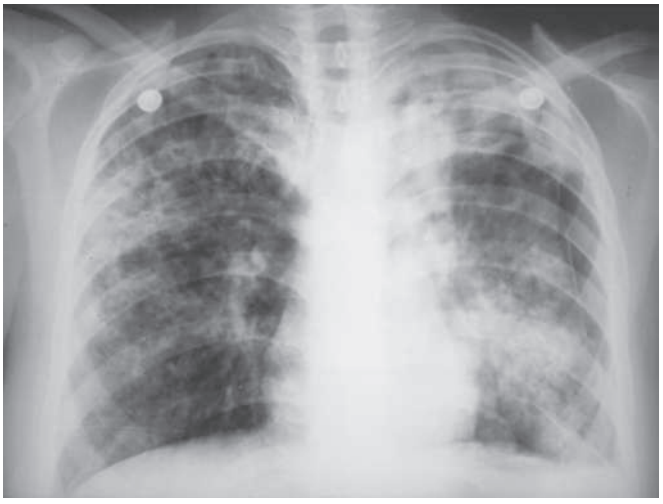

Fig. 124.1 Chest radiograph demonstrating cavitary tuberculosis with left-sided pneumothorax. The underlying cause of the pneumothorax was later determined to be a bronchopleural fistula. (Courtesy Dr. John Pearce.)

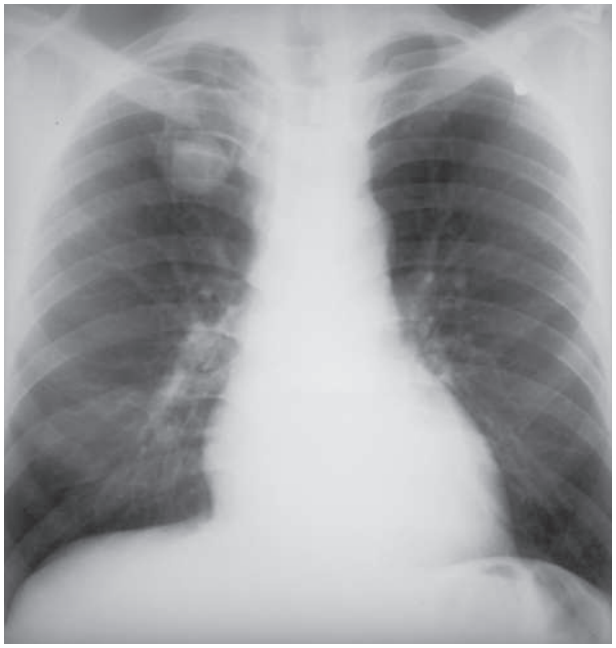

Fig. 124.2 Chest radiograph showing superinfection of healed tuberculous cavity. An aspergilloma can be seen in the right upper lung. (Courtesy Dr. John Pearce.)

formation. An untreated empyema can result in spontaneous pleurocutaneous fistula formation, presence of a chest wall mass on the radiograph, or rib and vertebral destruction.

Airway Tuberculosis

When a cavity drains its highly infectious material into the bronchial tree, the airways not only spread the infection but also develop endobronchial TB. Bronchiectasis commonly complicates endobronchial TB. Bronchial stenosis may result from extensive damage caused by endobronchial TB or from direct extension of infection by tuberculous adenitis or lymphatic dissemination to the airway. Tuberculous bronchostenosis may appear radiographically as persistent segmental or lobar collapse, lobar hyperinflation, and obstructive pneumonia. Tracheal and laryngeal TB are less common than endobronchial TB. Laryngeal disease is the most infectious form; it results from the proximal extension of lower airway disease, pooling of infected secretions in the posterior larynx, or hematogenous dissemination to the anterior larynx. Patients with laryngeal TB also usually have active pulmonary disease.

Superinfection with Fungi

Extensive TB infection often heals with open cavities and areas of bronchiectasis. Superinfection may occur with a wide variety of organisms, including *Aspergillus fumigatus*. The characteristic finding on chest radiographs is the aspergilloma or so-called fungus ball (Fig. 124.2). Aspergillomas are of particular clinical significance because they may cause massive and fatal hemoptysis.

Primary Tuberculous Pericarditis

Primary tuberculous pericarditis usually results from direct extension of infection from the tracheobronchial tree, mediastinal or hilar lymph nodes, sternum, or spine. Pericardial involvement also may result from hematogenous spread secondary to acute miliary TB or from another focus elsewhere in the body. TB is the leading cause of pericarditis among HIV-infected patients in the United States. The predominant symptoms are cough, chest pain, and dyspnea, and the most common signs are cardiomegaly, audible rub, fever, and tachycardia. Complications of pericardial TB include pericardial effusion, constrictive pericarditis, myocarditis, and cardiac tamponade. Cardiac tamponade may result from the accumulation of pericardial fluid or rupture of enlarging lymph nodes into the pericardium. Emergency echocardiography reliably confirms the presence of pericardial fluid.

DIFFERENTIAL DIAGNOSES

Pulmonary Tuberculosis

Bacterial Pneumonia

Segmental or lobar infiltrates on chest radiographs in bacterial pneumonia may easily be confused with those seen in TB, especially primary disease. Compared with TB, however, bacterial pneumonias usually arise with more profound symptoms of systemic toxicity, more acute onset, and elevated white blood cell count. In pulmonary TB, there is no prompt response to antibiotics, as often seen in bacterial pneumonia.

Fungal and Nontuberculous Mycobacterial Infections

Histoplasmosis, coccidioidomycosis and blastomycosis, as well as nontuberculous mycobacterial infections—mainly with *Mycobacterium avium* complex and *Mycobacterium kansasii*—may be radiologically indistinguishable from TB. The incidence of these infections is influenced by geographic location; therefore the ED physician must take into account travel history and local epidemiologic risks. Nontuberculous mycobacterial infection usually involves chronic pulmonary infection in HIV-infected patients. Immunocompetent persons also may become infected with MTB, especially patients with chronic lung disease, such as cystic fibrosis. Other important risk factors include work in the mining industry, warm climate, advancing age, and male sex.

Pneumonias in Patients with HIV Infection

Bacterial pneumonias including upper lobe *Pneumocystis* pneumonia (due to *Pneumocystis jiroveci*) and, rarely, *Nocardia* and *Rhodococcus* infections may mimic TB in patients with HIV infection.

Cavitary Lesions

Lung abscess or cavitating pneumonia caused by *Klebsiella pneumoniae, Staphylococcus aureus,* or aspiration may appear similar to cavitary TB on chest radiographs. In older patients, especially smokers, bronchogenic carcinoma may mimic TB. This is particularly true of squamous cell carcinoma, which tends to cavitate. Because cancer may cause a focus of TB to spread, the two diseases may be present simultaneously. Other causes of nontuberculous cavitary lesions include *M. avium* complex infection in HIV-negative patients, pulmonary infarction secondary to pulmonary embolus, Wegener granulomatosis, and upper lobe bullous disease secondary to emphysema or neurofibromatosis.

Mediastinal Lymphadenopathy

The main considerations in the differential diagnosis for adenopathy include lymphoma and sarcoidosis. In sarcoidosis, lymphadenopathy usually is bilateral, symmetrical, and asymptomatic. Lymphadenopathy tends to be unilateral in TB; if it is bilateral, it is asymmetrical and associated with parenchymal lung disease. Lymphoma tends to involve bulky mediastinal lymphadenopathy.

Extrapulmonary Tuberculosis

Tuberculous infection involving multiple sites is usually seen in populations of patients less capable of containing MTB infection, such as infants, older adults, and immunocompromised persons.

Extrapulmonary TB may occur in multiple sites, with decreasing relative frequencies in lymphatic, pleural, bone or joint, genitourinary, meningeal, peritoneal, and other sites. The lymph nodes are the most common site of extrapulmonary TB for otherwise normal and HIV-infected patients. Involvement of the meninges is more common in young children than in other age groups (present in ≈4% of children with TB), and the incidence of TB in the remainder of the extrapulmonary sites increases with age. Less commonly involved locations for extrapulmonary TB include the skin, heart, pericardium, thyroid gland, mastoid cells, sclerae, and adrenal glands.

Lymphadenitis

Tuberculous lymphadenitis (scrofula) is the most common form of extrapulmonary TB. Scrofula is most commonly seen in young women but is also seen in children. The patient usually has an enlarging, painless, red, firm mass in the region of one or more lymph nodes, most commonly in the anterior or posterior cervical chain or supraclavicular fossa. Early on, the nodes are discrete rubbery masses that are freely mobile and the overlying skin is normal. Eventually, the nodes may become matted and harder and the overlying skin inflamed. Fluctuance as well as an abscess or sinus tract may be present if a node erodes through the skin. Systemic signs and symptoms are uncommon, except in HIV-positive patients, in whom lymphadenitis usually is generalized. Pulmonary infection is present in a minority of cases. Considerations in the differential diagnosis include lymphoma, metastatic cancer, fungal disease, cat-scratch disease, sarcoid, toxoplasmosis, reactive adenitis, and bacterial adenitis.

The diagnosis of scrofula usually is made by fine-needle aspiration of an affected lymph node. Although AFB smears are positive in only approximately 20% of cases, granulomatous inflammation may be obvious. Overall, fine-needle aspiration has a sensitivity of 77% and specificity of 93% for TB infection. First-line treatment of scrofula consists of antituberculosis drugs, but surgical excision may be performed when medical therapy has failed or if the diagnosis is unclear. Incision and drainage should not be done because permanent sinuses and prolonged drainage can result.

Bone and Joint Infection

Bone and joint TB remains a disease of older children and young adults in developing countries, and it is increasingly a disease of adults in developed countries. Skeletal TB presumably develops from reactivation of dormant tubercles originally seeded during stage 2 of the primary infection or, in the case of spinal TB, from contiguous spread from paravertebral lymph nodes to the vertebrae. In general, spinal TB (Pott disease) accounts for 50% to 70% of the reported cases; the hip or knee is involved in 15% to 20% of cases, and the ankle, elbow, wrists, shoulders, and other bones and joints account for 15% to 20% of cases. Approximately 50% of patients have a previous history or concurrent case of pulmonary TB, but the chest radiograph is normal in appearance in up to 50% of cases.

Patients with Pott disease may simply complain of back pain or stiffness. Early changes of spinal TB can be difficult to detect on plain radiographs and include loss of the so-called white stripe of the vertebral endplate subsequent to destruction of subchondral bone. Thus, computed tomography (CT) and magnetic resonance imaging (MRI) should be used when the disease is suspected. Paraspinal cold abscesses develop in 50% or more of cases, with occasional formation of sinus tracts. The abscess can spread the infection up and down the spine, sometimes sparing vertebral bodies along its course, forming the so-called skip lesions. These skip lesions can easily be missed in imaging of the spine for Pott disease. The main complication of Pott disease is spinal cord compression.

Renal Disease

The kidney is highly vascularized, and hematogenous dissemination to that organ can occur. After the typical tuberculous lesions develop within the parenchyma, infection can spread into the calyces, renal pelvis, ureters, and bladder. As a result, tuberculous granulomas, scarring, and obstruction can occur anywhere along the urinary tract. Advanced renal disease and destruction may occur before the diagnosis is made. The urinalysis often reveals pyuria, hematuria, and albuminuria. Sterile pyuria is a classic finding in renal TB but, in many cases with this finding, cultures will be positive for other urinary pathogens. The finding of pyuria in an acidic urine with no organisms isolated should increase clinical suspicion for TB. Complications of renal TB include nephrolithiasis, ureteral obstruction or reflux, recurrent bacterial infections, hypertension, papillary necrosis, renal insufficiency, autonephrectomy and, rarely, development of transitional cell cancer.

Genital Disease

Male genital TB is usually associated with coexistent renal TB. Spread of infection from the kidney may involve the prostate, seminal vesicles, epididymides, and testes. A painless or slightly painful scrotal mass is a typical finding, and the patient may have symptoms of prostatitis, epididymitis, or orchitis. Epididymal or prostatic calcifications may be clues to the diagnosis. TB involvement of the seminal vesicles may lead to infertility.

In women, genital TB disease usually begins with a hematogenous focus in the fallopian tubes. The infection then spreads to the endometrium (in 50% of cases), ovaries (30%), cervix (5%–15%), and vagina (1%). Clinical manifestations may include abdominal or pelvic pain, ascites, infertility, menstrual irregularities and, rarely, vaginal discharge. An ulcerating mass may be present on the cervix. Genital TB may be confused with ovarian or endometrial cancer, Meigs syndrome, vulvar or vaginal ulcer, pelvic abscess, cervicitis, or cervical carcinoma. Sexual transmission of TB by persons with active genital TB has been described.

Multisystem Disease

The term *acute disseminated tuberculosis* refers to active hematogenous spread of MTB to several organs in the body. The term *miliary tuberculosis* was first used to describe the pathologic lesions, which resemble small millet seeds. This is now used as a clinical term referring to the massive dissemination that leads to systemic illness. Miliary TB occurs when the host is unable to contain a recently acquired or dormant TB infection. In the past, miliary TB occurred mainly in young children after primary infection; today, it is more common in older adults and in persons infected with HIV. Miliary TB often is a subtle disease associated with alcohol use disorder, cirrhosis, neoplasm, pregnancy, collagen vascular disease, or use of corticosteroids or immunosuppressive medications. A presumptive diagnosis can be made rapidly if chest radiographs show a miliary infiltrate (Fig. 124.3). Unfortunately, the classic miliary pattern is absent on radiographs in approximately 50% of cases. Routine laboratory tests generally are not helpful. Hyponatremia from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is common and often is associated with meningitis. Cultures of sputum, urine, draining lesions, and blood should be sent to the infectious disease laboratory.

Mortality rates for miliary TB are higher than for the other forms of TB, with one case series reporting a rate of 21%. The high mortality rate often is caused by delay in treatment, which should be initiated immediately on the basis of clinical suspicion and not delayed until confirmation of the diagnosis. A fulminant form of miliary TB may cause acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC).

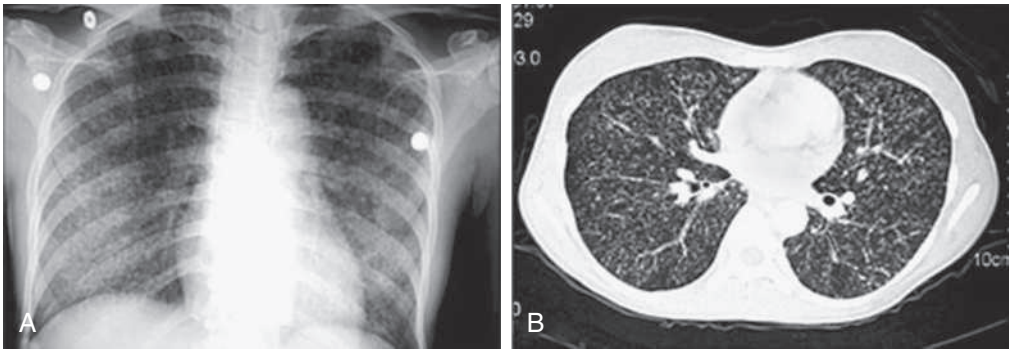

Fig. 124.3 Chest radiograph (A) and computed tomography scan (B) demonstrate a miliary pattern. (Reprinted with permission from: Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. *Am Fam Physician*. 2005;72:1761. Copyright 2005, American Academy of Family Physicians. All rights reserved.)

Central Nervous System Disease

Approximately 6% of all cases of extrapulmonary TB involve the central nervous system (CNS), and CNS involvement remains a grave consequence of tuberculous infection. The peak incidence of CNS TB occurs in newborns to 4-year-old children.

Tuberculous meningitis usually results from the rupture of a subependymal tubercle into the subarachnoid space rather than from direct hematogenous seeding of the CNS. When it is a complication of miliary TB, meningitis usually develops within several weeks of infection. In children, it is an early postprimary TB event, usually appearing within 6 months. Tuberculous cerebral involvement is most marked at the base of the brain, and vasculitis of local arteries and veins may lead to aneurysm formation, thrombosis, and focal hemorrhagic infarction. The vessels to the basal ganglia are usually involved, leading to formation of lacunar infarcts or deficits associated with movement disorders. Involvement of other vessels, such as the middle cerebral artery, may lead to hemiparesis or hemiplegia. Tuberculous meningitis begins with a prodrome of malaise, intermittent headache, and low-grade fever. In 2 to 3 weeks, a protracted headache develops. Vomiting, confusion, meningismus and focal neurologic signs, and coma may follow. Nuchal rigidity may be absent. Diplopia resulting from basilar exudate is present in up to 70% of patients. Hyponatremia may be present because SIADH is common. The cerebrospinal fluid (CSF) white blood cell count varies widely, from 0 to 1500 cells/mL, with a predominance of lymphocytes when WBCs are present; however, polymorphonuclear cells may predominate early in the course of the disease. The CSF protein concentration usually is elevated, and the CSF glucose concentration typically is low. The classic triad of neuroradiologic findings in patients with TB meningitis consists of basal meningeal enhancement, hydrocephalus, and cerebral or brainstem infarction. CT or MRI also may reveal rounded lesions typical of evolving parenchymal tuberculomas (Fig. 124.4).

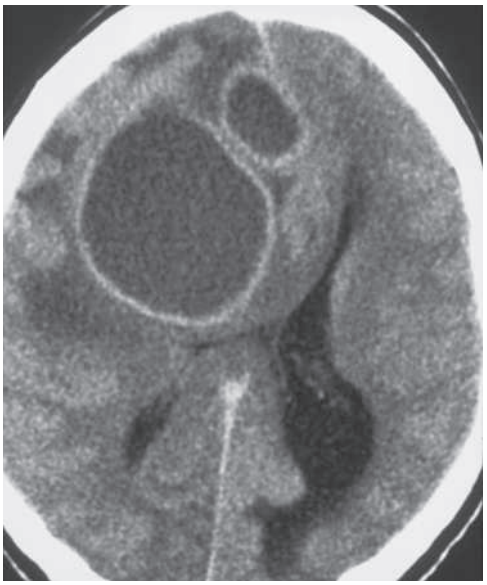

Fig. 124.4 Head CT scan demonstrating tuberculomas in a patient with AIDS.

Gastrointestinal Disease

The most common clinical manifestations of gastrointestinal TB are abdominal pain, fever, weight loss, anorexia, nausea, vomiting, and diarrhea. Gastrointestinal TB infection usually is secondary to hematogenous or lymphatic spread but also may result from swallowed bronchial secretions or direct spread from local sites, such as lymph nodes or fallopian tubes. TB may occur in any gastrointestinal location from the mouth to the anus, but lesions proximal to the terminal ileum are rare. The ileocecal area is the most common site of involvement, producing signs and symptoms of pain, anorexia, diarrhea, obstruction, hemorrhage and, often, a palpable mass. The nonspecificity of these findings, as well as of those on the physical examination, may lead to the misdiagnosis of gastrointestinal TB as an acute abdomen, appendicitis, intestinal obstruction, or cancer. The clinical manifestations of anal TB include fissures, fistulae, and perirectal abscesses.

Tuberculous peritonitis may develop from local spread of MTB infection from a tuberculous lymph node, intestinal focus, or infected fallopian tube. In addition, peritonitis can develop from seeding of the peritoneum in miliary TB or from the reactivation of a latent focus. The patient with tuberculous peritonitis commonly has pain and abdominal swelling associated with fever, anorexia, and weight loss. Diagnosis may be confounded by the similarity of this disease to alcoholic hepatitis and by the fact that this disease often coexists with other disorders, especially cirrhosis with ascites. Paracentesis is thus essential. The peritoneal fluid is exudative, with a cell count of 500 to 2000 cells/mL. Lymphocytes usually predominate, with rare exceptions early in the process, when polymorphonuclear leukocytes may predominate. AFB smears of the fluid have a low diagnostic yield. Peritoneal biopsy often is necessary to confirm the diagnosis. Treatment is the same as for pulmonary TB, with a 6-month therapeutic regimen.

DIAGNOSTIC TESTING

Laboratory Tests

Routine laboratory studies generally are not useful in suggesting or establishing the diagnosis of TB in the ED. Normochromic normocytic anemia, elevated erythrocyte sedimentation rate, elevated C-reactive protein (CRP) and serum globulin levels, hyponatremia, and hypercalcemia can occur in active pulmonary TB, but these findings are nonspecific.

White Cell Stimulation Tests

The patient's blood can be tested for sensitivity of its T cells to tuberculin antigens. These tests are called interferon-gamma (IFN-γ) release assays (IGRAs). The QuantiFERON-TB Gold (Quest Diagnostics) and T-Spot (Oxford Immunotec) tests are the most widely available IGRAs. They use an enzyme-linked immunosorbent assay (ELISA) to measure the amount of IFN-γ released in response to PPD. IFN-γ is a cytokine associated with cell-mediated immunity. Determination of IFN-γ levels also can be used as a diagnostic test for tuberculous pleural effusions, ascites, and pericardial effusions. Clinical studies have reported sensitivity ranges from 90% to 100%. TB infection can be rapidly confirmed in an individual in 2 days, compared with several weeks for a traditional culture. However, a normal study does not completely exclude TB; therefore, cultures should be sent when a person thought to have TB has a negative QuantiFERON-TB Gold test result.

Serology

Although ELISAs have been developed for several MTB serum antigens, in practice no serodiagnostic approach to the diagnosis of TB currently is in widespread clinical use in the United States. Other countries have discouraged the use of serology. Limitations of the ELISA include inadequate accuracy and reproducibility, inability to distinguish active from latent infection, poor discrimination between MTB and other mycobacteria, and relative cost.

Diagnostic Imaging

Plain radiography of the chest is the most useful study for a presumptive diagnosis of pulmonary TB. The availability of chest CT scans in most EDs has enhanced the sensitivity of detecting classic TB in the ED. A normal appearance on the chest radiograph has a high negative predictive value and is therefore useful in screening ED patients for active pulmonary TB. However, the low false-negative rate among immunocompetent adults increases significantly in HIV-positive patients. Therefore, depending on the clinical circumstances, the absence of specific abnormalities on the chest radiograph does not always exclude active TB, especially in patients with concomitant endobronchial disease and HIV infection.

Primary Tuberculosis

Chest radiographic manifestations of primary disease in adults often are not recognized as TB. Primary tuberculous infiltrates can occur in any lobe. In any age group, a pneumonic infiltrate with enlarged hilar or mediastinal nodes should strongly suggest the diagnosis. The infiltrate usually is homogeneous and most commonly involves a single lobe. Thus, primary TB may appear radiographically identical to a bacterial pneumonia, with associated lymphadenopathy, if present, being the only distinguishing feature.

Lymphadenopathy is considered the radiologic hallmark of primary TB in children but is seen less commonly in adults. When present, adenopathy usually is unilateral and associated with parenchymal infiltrate (Fig. 124.5). It may occur bilaterally or, less commonly, may be an isolated finding on chest radiography. Other primary TB chest radiographic findings include a moderate to large pleural effusion, which often is an isolated finding whose prevalence increases with age, and miliary TB characterized by the presence of innumerable, 1- to 3-mm noncalcified nodules dispersed throughout both lungs with mild basilar predominance. When the healed primary focus is visible on the chest radiograph as a calcified scar, it is known as the Ghon focus. Calcified secondary foci of infection in the lung apex are known as Simon foci. A Ghon focus associated with calcified hilar nodes is called a Ranke complex. A right-sided predominance in the distribution of the Ghon foci and Ranke complexes is well recognized and probably reflects the likelihood that an airborne infection will affect the right lung. Calcification seen on the chest radiograph indicates healing, but viable bacilli may still exist in a partially calcified lesion.

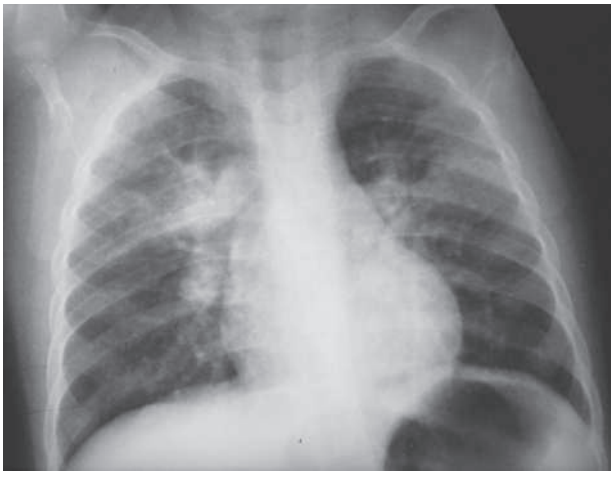

Fig. 124.5 Chest radiographic findings in a child with primary tuberculosis. Note the active Ghon focus, with associated hilar adenopathy and presence of bilateral infiltrates. (Courtesy Dr. John Pearce.)

Postprimary Tuberculosis

Postprimary TB typically appears as an upper lung infiltrate or consolidation, with or without cavitation. The lesion may be small or extensive and usually is located in the apical or posterior segment of the upper lobe but may appear in the superior segment of the lower lobe. Postprimary disease also occurs in the lower lung. In addition, bronchogenic spread can occur, leading to the involvement of multiple lobes (Fig. 124.6). Patients with bilateral upper lobe disease are extremely likely to have TB. The other important recognizable characteristics of postprimary disease are fibrosis and cavitation. These lesions are not purely exudative in that they are associated with a fibrotic pattern of nodules and a few fine, linear densities. Fibroproductive lesions often are irregular and angular in contour, have strands extending toward the hilum, and demonstrate calcification of one or more nodules and distortion of vascular and mediastinal structures. Severe fibrosis with upper lobe volume loss may eventually lead to retraction of the interlobar fissure and upward displacement of the hilum. The chest radiographic appearance at this stage has been variably referred to as "old scarring," "no active disease," or "fibrotic, apparently well-healed TB." Cavitation should alert one to the potential for high infectivity of the patient and associated complications, such as bronchogenic spread of TB (see Fig. 124.4). The walls of the cavities initially are thick and rough and become thinner and smoother with healing. Chest radiographs of patients with pulmonary TB and HIV infection may be atypical in approximately one-third of cases. Patients with late HIV infection more often demonstrate

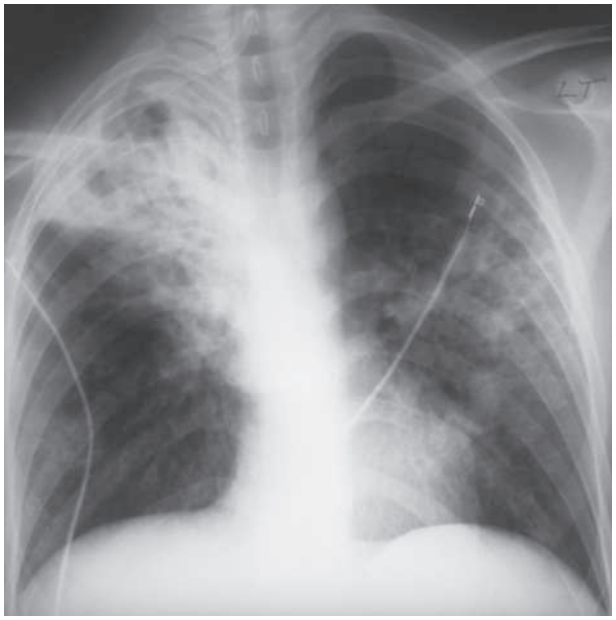

Fig. 124.6 Chest radiograph showing evidence of right upper lobe cavitary disease. Also note the left-sided infiltrate, secondary to endobronchial spread.

mediastinal adenopathy or atypical infiltrates and less often have cavitation. Severe immunosuppression has been reported to be associated with a miliary pattern of disease on chest radiographs.

Microbiologic Testing

Sputum Studies

If the clinical or chest radiographic findings suggest the diagnosis of pulmonary TB, mycobacteriologic studies of the patient's sputum should be ordered. A positive smear supports a presumptive diagnosis, and the number of bacilli seen correlates with infectivity. For patients who are not producing sputum, nebulized induction of sputum is the method of choice for the collection of samples. Induction of sputum with nebulization may increase the risk of TB transmission to health care workers and should be performed only in specially ventilated rooms, preferably not in the ED. When the sputum is not diagnostic in adults, fiberoptic bronchoscopy with bronchial washings, bronchoalveolar lavage, brushings, or transbronchial biopsy may be necessary for the laboratory diagnosis of TB.

Direct Microscopy. Direct microscopic examination of a stained sputum specimen for AFB (i.e., an AFB smear) is the most rapid laboratory test widely available to support a presumptive diagnosis of TB and results usually are available from hospital laboratories within 24 hours. Negative findings on an AFB smear, however, do not rule out active pulmonary TB because microscopy is relatively insensitive when performed on samples with small numbers of bacilli. At least 5000 bacilli/mL of sputum must be present for a positive result by microscopy. Overall, AFB smears have a sensitivity of 20% to 80% and a specificity of 90% to 100%. Despite limitations, microscopy remains an essential diagnostic test because of its ease of performance, low cost, rapid turnaround time, and reasonable diagnostic yield.

Nucleic Acid Amplification Tests. Nucleic acid amplification (NAA) tests are performed on sputum and take only 24 to 48 hours to yield results. Their overall positive predictive value is about 95%. In some cases, patients with positive TB sputum smears have had negative NAA test results because of inhibitors that may prevent amplification. This has been a rapidly growing field in TB diagnostics, although most EDs do not yet have bedside capabilities. The best role of NAA is to aid emergency clinicians in decision making for patients thought to have active TB. It should not be ordered routinely when the clinical suspicion for TB is low.

Culture. Sputum culture is more sensitive than microscopy for the detection of MTB and is still considered the gold standard diagnostic modality. Liquid culture can detect 10 to 100 bacilli/mL, compared with 5000 to 10,000 bacilli/mL for an AFB smear. When the presence of mycobacteria is established, the specific identification of MTB may be accomplished by subjecting the initial mycobacteria to various isolation techniques. These include the detection of pigmentation on solid culture media, various biochemical tests, high-performance liquid chromatography, and nucleic acid probes. A presumptive diagnosis of TB based on a positive sputum smear usually is confirmed by isolation of MTB by culture. Traditional culture methods using solid media require 3 to 8 weeks for colony formation. The development of liquid culture systems has shortened the detection time to 7 to 14 days.

Tuberculin Skin Test

Although newer serologic diagnostic tests have become widely used in most US hospitals, the tuberculin skin test continues to be the diagnostic workhorse for the detection of exposure to MTB. The tuberculin test is based on the principle that MTB infection induces sensitivity to certain antigens of the bacillus. These antigens are contained in the tuberculin preparation called PPD. In a person infected with TB, the PPD test result usually turns positive 3 to 8 weeks after the infection, when the immune response is developed. The standard 0.1-mL dose used in skin testing contains 5 tuberculin units (TU). A properly placed needle should leave a blanched distinct wheal 6 to 10 mm in diameter. If the tuberculin dose is incorrectly administered, the test may be repeated immediately at a site several centimeters away. Test results are read 48 to 72 hours after administration of PPD. The largest diameter of palpable induration is measured and recorded in millimeters; erythema by itself is not measured. The precise measurement that denotes a positive test result depends on the patient's other clinical factors. The current CDC guidelines use 15 mm of induration as a positive test response for people without TB risk factors. Persons with previous TB immunization (see later, "Vaccines for *Mycobacterium tuberculosis*") may have a positive PPD result even though they are not infected with TB. However, a significant reaction to PPD and a long time interval between bacilli Calmette-Guérin (BCG) vaccination and the current skin test make it more likely that the reaction is due to MTB infection. Because the BCG vaccine is imperfect in protecting against MTB infection, and because most vaccinated persons come from areas of high TB prevalence, the CDC recommends that tuberculin skin test results be interpreted without regard to BCG vaccination status.

MANAGEMENT

Initial Management in the Emergency Department

Hemoptysis

The most emergent presentation of pulmonary TB is massive hemoptysis, defined as loss of at least 600 mL of blood in 24 hours. Exsanguination rarely occurs, and the major morbidity is due to asphyxiation from aspirated blood. Secure the airway with a large-diameter (8-mm) endotracheal tube that can accommodate a fiberoptic bronchoscope. The patient is positioned with the bleeding lung in a dependent position, and one should consider selective main bronchus intubation to allow ventilation of the unaffected lung and minimize the spread of blood from the affected lung. Emergency consultation for bronchoscopy,

surgical resection, or angiography with selective embolization is required. Patients thought to have active pulmonary TB should be immediately placed in respiratory isolation.

Fever or Wasting

Patients with fever and wasting generally should be admitted for an in-hospital evaluation. Patients should be placed in respiratory isolation until the diagnosis of TB has been excluded.

History of Tuberculosis, Therapy Discontinued

In patients with vague symptoms and a history of TB, consider reactivation. Given the numerous considerations in resuming therapy, we recommend consulting a local TB health officer or an infectious diseases specialist.

Antituberculosis Medications

Three basic therapeutic principles govern the treatment of TB: (1) any treatment regimen must contain multiple drugs to which the MTB organism is susceptible; (2) the therapeutic agents must be taken regularly; and (3) therapy must continue for a sufficient period. In clinical practice, the last principle is the most problematic. The most up-to-date recommendations for the treatment of TB are available from the CDC through online publications or at the CDC website. Medications used to treat MTB generally are divided into first-line and second-line agents. Of these, 10 have been approved by the US Food and Drug Administration (FDA) for the treatment of MTB. The most commonly used first-line agents are isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).

First-Line Agents

INH demonstrates extremely potent early bactericidal activity and can rapidly decrease the patient's infectiousness. A small risk of hepatitis (<3%) occurs with long-term treatment. Supplemental pyridoxine is recommended for these patients. RIF also demonstrates strong early bactericidal activity. This agent causes orange discoloration of body fluids, including urine, tears, sweat, and sputum. PZA works against organisms contained in the acid environment of the macrophage. The chief side effect is hepatotoxicity, but this risk is very low at daily doses of 25 mg/kg or less. Polyarthralgias occur commonly (up to 40% of patients) but usually respond to nonsteroidal antiinflammatory drugs or aspirin. EMB is a first-line agent that helps prevent the emergence of RIF resistance during TB treatment. Retrobulbar neuritis can occur, resulting in decreased visual acuity to the point of blindness.

Second-Line Agents

Streptomycin must be given parenterally and has a peak of action 1 hour after the intramuscular dose is given. The chief side effects of this potentially teratogenic agent are ototoxicity and nephrotoxicity. Amikacin, kanamycin, and capreomycin also are injectable agents used for drug-resistant TB. As with streptomycin, ototoxicity and neurotoxicity are their major adverse effects. TB strains resistant to streptomycin usually are sensitive to amikacin and kanamycin, and resistance to these last two drugs usually is linked. Cycloserine, ethionamide, and *p*-aminosalicylic acid (PAS) are oral agents used for the treatment of patients with drug-resistant TB when the strain is presumed or known to be sensitive to these agents. The main adverse effect of cycloserine is psychosis or seizures, which occur in 3% to 16% of patients. Ethionamide is similar to INH in structure and toxicity. Major adverse effects of PAS include gastrointestinal distress (most common), hypothyroidism, and hepatitis. Fluoroquinolones have played a more recent role in the treatment of TB. They are less effective than the first-line agents and are used mainly in the treatment of drug-resistant disease.

Corticosteroids

Corticosteroids may prevent constriction in tuberculous pericarditis and decrease the neurologic sequelae in all stages of tuberculous meningitis, especially if they are given early in the disease. The CDC strongly recommends corticosteroids for MTB pericardial or CNS infections. Corticosteroids may provide some benefit to children with bronchial obstruction caused by enlarged lymph nodes. In addition, in patients with pulmonary TB, prednisone, 20 to 60 mg/day may benefit those who continue to experience temperature spiking and lose weight, despite a good bacteriologic response to appropriate antituberculosis therapy. In cases of miliary TB, 60 mg of prednisone should be added to the treatment regimen.

Initial Therapy

Emergency clinicians generally will not initiate treatment prior to consulting public health and infectious diseases specialists. To be successful, treatment must be continuous, ongoing, and monitored closely. A one-time dose of medications is fruitless in a patient who could be lost to follow-up. In some locations, this will require hospital admission with appropriate respiratory isolation.

Initial administration of anti-TB drugs in the ED is appropriate and necessary in certain circumstances, such as TB sepsis or miliary TB, critically ill HIV patients with TB, or life-threatening conditions. The CDC website should be reviewed for the most up-to-date treatment guidelines.[2,3] The goals of therapy are to rapidly kill large numbers of bacilli (bactericidal activity), prevent emergence of drug resistance, and prevent relapse by elimination of dormant or slowly dividing bacilli (sterilizing activity). In-person or telephone consultation with an infectious diseases specialist is critical, and they may recommend regimens that include INH, RIF, PZA, and/or EMB.[7]

Adequate treatment of active TB in patients coinfected with HIV is critical. It has been observed that immune activation from TB enhances systemic and local HIV replication and may accelerate the natural progression of HIV infection. Active TB in HIV-infected patients has been associated with increased risk for opportunistic infections and death. TB treatment alone leads to a reduction in viral load in these patients. Current recommendations for the initial treatment of MTB in HIV-infected patients are the same as those for patients who are not HIV-infected, with exceptions for complex drug interactions.[10] For example, significant drug interactions between rifamycins used for TB and antiretroviral drugs (protease inhibitors and nonnucleoside reverse transcriptase inhibitors [NNRTIs]) used for HIV infection complicate the treatment of patients with active TB who are coinfected with HIV. For treatment of MTB in patients who are taking protease inhibitors, rifabutin can be used instead of the other rifamycins. When TB treatment is initiated in HIV-positive patients, a paradoxical reaction to medical therapy may develop in some cases. The reaction is manifested with the development of fever, new or enlarging lymph nodes, or worsening of radiographic disease. Severe paradoxical reactions may be managed with a 2-week tapering course of prednisone or methylprednisolone.

Drug-Resistant Tuberculosis

Two types of drug-resistant MTB have emerged as a result of spontaneous mutations. Multidrug-resistant TB (MDR-TB) is defined as TB in which the mycobacteria are resistant to two or more first-line antituberculosis agents.[8] Extensively drug-resistant TB (XDR-TB) is TB characterized by resistance to first-line and at least three second-line drugs. Patients at high risk for MDR-TB and XDR-TB include those with HIV, those who have been treated in the past for TB, and those who live or lived in certain high-risk countries.

BOX 124.2 Risk Factors for Drug-Resistant *Mycobacterium tuberculosis* Infection

- Previous unsuccessful antituberculosis treatment
- Failure to respond or adhere to a treatment regimen
- Human immunodeficiency virus infection
- Injection drug abuse
- Close contact with source cases
- Recent immigration from area with a high prevalence of drug resistance
- Cavitary lung disease
- Undomiciled
- Imprisonment
- Drug malabsorption due to gastrectomy or ileal bypass surgery

Multidrug-Resistant Tuberculosis

The World Health Organization (WHO) has estimated the worldwide number of MDR-TB cases at close to one-half million persons. Airborne transmission of MDR-TB is a threat to those who come in contact with infected individuals, including family members, contacts in crowded living situations, and health care personnel. The spread of primary drug resistance is faster when HIV infection is highly prevalent in a population. Because initial TB infection in HIV-infected patients progresses rapidly to active disease, newly infected persons can quickly become source cases for further transmission of the resistant bacilli. In reports on hospital outbreaks of MDR-TB, more than 90% of patients had coinfection with HIV, and case fatality rates were as high as 70% to 90%. However, patients without HIV infection demonstrate excellent clinical responses when treated for MDR-TB.

For the identification of potential cases, health care workers should know the prevalence of drug resistance in their community and the risk factors for drug resistance (Box 124.2). Rapid identification and prompt isolation of these patients, along with other control measures, can reduce the nosocomial transmission of MDR-TB to patients and health care workers. Failure to control drug resistance may lead to wide dissemination of MDR-TB and to a public health crisis that physicians may confront without effective medications.

Treatment of drug-resistant TB can be challenging and requires familiarity with second-line agents. For MDR-TB, specialist consultation is essential. A general principle that applies in such cases is to use at least three drugs to which the organism is susceptible and that have not been used previously. In general, one of these medications should be an injectable agent. TB infection with strains that are resistant only to INH can be managed with shorter courses of RIF, PZA, and EMB.

Extensively Drug-Resistant Tuberculosis

XDR-TB was first recognized in patients coinfected with AIDS in South Africa in 2005 and is a major threat in Africa, Asia, and areas of the former Soviet Union. XDR-TB is found in 10% of patients presenting with MDR-TB. The strain has virulence similar to that of MTB, and disease does not progress faster in the absence of antibiotics. As resistance to so many antibiotics has developed, however, this strain has become a major threat, especially in patients with AIDS. Most alarming is a report that as many as 33% of patients with TB coinfected with HIV and MDR-TB had the XDR-TB strain. Mortality rates for this population of patients are high, because few alternative drugs exist. The CDC has reported cases in in the United States and has isolated patients as soon as they are identified. EDs could become a major focus for spread of this disease because of overcrowding, initial lack of recognition, and long wait times, exposing other patients to XDR-TB. Reports from Africa have shown that XDR-TB also can be transmitted directly to health care workers. Of great concern is the potential for transmission of the disease within the ED by a previously undiagnosed patient with XDR-TB, who presents for treatment of TB-related symptoms or an unrelated condition.

Vaccines for *Mycobacterium tuberculosis*

The BCG vaccine has been used since 1921, but its overall efficacy, duration of protective immunity, and optimal age for administration are debated. Nonetheless, 100 million children receive BCG vaccine each year outside the United States (US). In developing countries, BCG is credited with reducing the incidence of the most severe forms of pediatric TB and death, and some hospitals overseas require that staff have a BCG vaccination as a requirement for work. In the United States, BCG is rarely recommended because of the belief that it may undermine the epidemiologic and diagnostic value of PPD skin testing. BCG use in children is common in some countries. Tuberculin skin tests in patients given previous BCG vaccination usually demonstrate less than 10 mm of induration. Thus, previous BCG vaccination status should be ignored in the interpretation of skin test results. Institutional outbreaks of TB and the emergence of MDR-TB have been sparking reassessment of the BCG issue in the United States. Reports of BCG vaccine efficacy range from 0% to 80%. A meta-analysis of international data reported the efficacy of BCG vaccine to be approximately 50%. This is consistent with an American study conducted over 60 years in a Native American population which showed a 50% reduction in the development of TB in persons receiving BCG vaccine.

BCG vaccine is currently recommended in the United States only for tuberculin-negative infants and children who cannot take INH and have ongoing exposure to a persistently untreated or inadequately treated patient with active TB, who are continuously exposed to persons with INH- and RIF-resistant TB, or who belong to groups with rates of new MTB infection exceeding 1% per year. WHO recommends that all infants in developing countries receive the vaccine.[6]

BCG vaccine is strongly contraindicated in persons with HIV infection or another immunosuppressive disease.

New vaccines against MTB are being researched, including those using attenuated strains of the MTB complex, recombinant mycobacteria, subunit proteins, and DNA vaccines. Vaccines are also under development for treatment of occult TB. A recent trial tested an adjuvanted recombinant protein vaccine, M72/AS01, in adults with a positive interferon-gama release assay, but without evidence of clinical disease.[4] Conducted in 3 African countries, a nearly 50% reduction in progression to active clinical disease was found in those receiving the vaccine.

DISPOSITION

Acutely ill or older patients may require hospitalization during the first few days of treatment because adverse reactions to TB chemotherapy are common and may occasionally be life-threatening. In addition, severely ill patients may require parenteral drug administration. Patients with TB have a high rate of HIV coinfection, and the comorbid illnesses associated with HIV infection, complex synergy between MTB and HIV, and potentially harmful drug interactions between the antiretroviral agents and rifamycins may favor inpatient treatment for the initial management of these complicated cases.

Hospital admission also is indicated for patients with active or suspected MDR-TB. These patients commonly require observation during initiation of therapy because of the complexity of the treatment regimens, toxicity of the drugs, and need for close monitoring to ensure adherence to treatment and isolation measures. Finally, social issues such as being undomiciled, presence of infants or immunocompromised persons in the household, substance abuse, and inability for

self-care may necessitate hospitalization. The recalcitrant patient constitutes a potential threat to public health, and legal measures for involuntary hospitalization may be required.

Patients who are otherwise well but have suspected TB may be eligible for outpatient treatment in consultation with local county health officials, who agree to assume responsibility for ongoing care of the patient and investigate contacts for possible exposure to TB.

PREVENTION OF TRANSMISSION IN THE EMERGENCY DEPARTMENT

EDs often care for patients at increased risk for active pulmonary TB, such as those who are undomiciled, from endemic areas, recently incarcerated, or chronically ill. Accordingly, ED personnel can be at high risk for occupational TB infection. Increased hospital occupancy and ED crowding can lead to extended waiting periods for ED beds and hospital beds. Some EDs may lack an adequate number of TB isolation rooms.

Early Identification

For the most effective minimization of infectious exposures among health care workers and other patients, ideally, all patients with active pulmonary TB would be placed in respiratory isolation when they initially present. The CDC has recommended screening for TB at triage. Triage screening protocols can detect patients with more classic presentations of TB, but reported protocols are only moderately sensitive and somewhat cumbersome. Immediate respiratory isolation should be considered for patients with high-risk chief complaints, such as the HIV-positive patient with cough, the person with hemoptysis, or the patient with a history of TB presenting with cough or fever. The best guideline is to initiate respiratory isolation as soon as TB is considered a possible diagnosis. Masks should be placed on these patients before chest radiography is performed.

Isolation and Environmental Control

In addition to triage screening, the use of proper isolation facilities and environmental control measures can help prevent TB exposures. Airflow in the ED plays a central role, and inadequate ventilation has been a contributing factor in many nosocomial outbreaks of TB. Ideally, there should be single-pass airflow from waiting rooms to outside the facility. Within the ED, air should flow from clean areas to less clean areas, rather than vice versa. For EDs that frequently see patients with TB, at least one true respiratory isolation room should be available. The CDC recommends that respiratory isolation rooms have at least 12 air changes per hour and have negative pressure (air flows into the room from other ED areas). Other engineering approaches to TB infection control include the use of high-efficiency particulate air (HEPA) filters and upper room ultraviolet light irradiation.

Personal Respiratory Protection

ED personnel should be familiar with the appropriate use of respiratory protection against TB. Surgical masks (e.g., string tie masks) should be placed on potentially contagious patients to decrease the release of infectious droplets into the air. Air can leak around such masks, however, so they may not adequately prevent health care workers from inhaling infectious droplet nuclei. Thus, surgical masks are used only for source control, not for health care worker protection. More advanced personal respiratory protection devices include N95 particulate respirators. HEPA-filtered masks can also be used for health care worker respiratory protection; these masks were used more extensively before development of the N95 masks.

Preventive Therapy After Inadvertent Exposure

Health care workers who are exposed to patients with active pulmonary TB require referral to their primary care physicians or employee health services for follow-up testing and treatment. Tuberculin skin testing or IGRA blood testing usually is performed within days following exposure to establish whether the health care worker was previously infected with MTB. If the baseline test result is negative, a follow-up is performed 3 months later to determine whether conversion has occurred. The CDC has developed guidelines for the treatment of exposed personnel, which can be found on the CDC website.[9]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 124: QUESTIONS AND ANSWERS

1. Which of the following is not a typical vehicle for tuberculosis transmission?
- **a.** Coughing
- **b.** Eating utensils
- **c.** Parenteral transmission
- **d.** Sneezing

Answer: B. Bedclothes and eating utensils do not require special decontamination. Parenteral transmission is largely a risk of health care workers (e.g., skin ulcers, draining wounds). Talking, coughing, and sneezing all may produce significant droplet spread.

2. Which of the following anatomic areas is not a site of preferential organism spread during stage 2 spread of TB?
- **a.** Kidneys
- **b.** Long-bone epiphyses
- **c.** Lung bases
- **d.** Lymph nodes

Answer: C. Lung apices are favored rather than the bases. These sites are preferred, possibly because of high oxygen tension.

3. Clinically active TB develops in what percentage of immunocompetent purified protein derivative (PPD) converters?
- **a.** 5%
- **b.** 10%
- **c.** 15%
- **d.** 20%

Answer: B. TB develops in 10%: 3% to 5% in the first 2 years (acute primary) and 5% later in life (reactivation). Patients with HIV infection develop primary TB at a rate of 37% within 6 months and then develop active TB at a rate of 7% to 10%/year.

4. Which of the following statements regarding chest radiography findings in pulmonary tuberculosis is true?
- **a.** Adenopathy may distinguish TB from bacterial pneumonia.
- **b.** Primary TB typically appears as an upper lobe cavity lesion.
- **c.** The false-negative rate is 10% in immunocompetent patients.
- **d.** The false-negative rate is 40% in HIV-infected patients.

Answer: A. Hilar adenopathy may be the only way to suspect TB as opposed to a typical bacterial pneumonia. Primary TB is usually a single-lobe infiltrate with a homogenous appearance. It is postprimary TB that has a predilection for the upper lobes, with or without cavitation. The false-negative rate for chest radiography in immunocompetent patients is very low, 1%. The rate increases to 7% to 15% in HIV-infected patients and those with endobronchial disease.

5. Which of the following statements regarding the radiographic appearance of tuberculosis and infectivity is true?
- **a.** Chronic fibrotic changes are unlikely to be infective.
- **b.** Normal radiographs are uncommon with HIV infection.
- **c.** Only the presence of adenopathy can determine active disease.
- **d.** The presence of cavitation implies high infectivity.

Answer: D. Cavitation suggests high infectivity. Chronic fibrotic changes cannot differentiate old versus active disease, and many of these patients will have positive sputum. Active disease can only be determined radiographically by serial radiographs. Patients with late HIV infection are more likely to have mediastinal adenopathy and less likely to show cavitations. Normal radiographs are common with HIV infection.

Bone and Joint Infections

Neha P. Raukar and Brian J. Zink

KEY CONCEPTS

- Skeletal infection should be considered in the differential diagnosis of all patients who present with bone or joint pain.
- Laboratory evaluation is of little value in the diagnosis of bone and joint infections, with the exception of the ESR and CRP level, which are elevated in approximately 90% of cases of bone and joint infections.
- Joint aspiration is the definitive diagnostic procedure, and intraoperative synovial culture is the only reliable joint fluid test for establishing a diagnosis. When limited fluid is available, it should be sent for a cell count.
- With suspected septic arthritis, joint fluid and blood culture specimens are obtained before IV antibiotics are administered. With suspected osteomyelitis, blood culture specimens are obtained, and IV antibiotics are administered while plans are made for further imaging studies, surgical aspiration, or resection of bone.
- The most important aspect of antibiotic treatment of suspected bone and joint infections is to provide potent bactericidal activity against *S. aureus* with additional empirical antibiotic coverage aimed at suspected organisms on the basis of age, risk factors, and regional variability.

FOUNDATIONS

Background and Importance

Historically, bone and joint infections (BJIs) have been described in grim terms. *Aids to Surgery,* written in 1919, noted that "acute infective osteomyelitis … is a very fatal disease." With septic arthritis, "the patient becomes exhausted from toxaemia or pyemia," and "ankylosis is the usual most favourable termination." Advances in diagnostic methods, antibiotic therapy, and surgical techniques have resulted in better patient outcomes; however, new challenges are arising. The emergence of resistant bacteria endangers the efficacy of antibiotics, and antibiotic choices need to be informed by resistance patterns. Furthermore, there are increasing subsets of patients with reduced host immunity. This combination results in greater complexity in the management of BJIs than was previously encountered. The management focuses on prompt diagnosis, initiation of treatment, and avoidance of the complications and morbidity associated with bone or joint infections.

The overall occurrence of BJIs has remained constant during the past 4 decades.[1] In hospitalized patients in the United States, the incidence is approximately 1%. Osteomyelitis in children younger than 13 years occurs in 1 in 5000, whereas the incidence of septic arthritis ranges from 5.5 to 12/100,000 individuals.[1] In contrast to global patterns, socioeconomic factors or race do not affect the incidence of BJI in the United States. Both bone and joint infections show a bimodal age distribution, occurring most commonly in people younger than 20 years or older than 50 years. In children, BJIs usually occur in previously healthy individuals, with boys having a slightly increased susceptibility to bone infections. In adults, there are several known risk factors that lead to a higher risk of BJIs.

Orthopedic infections can be classified according to the site of involvement and include osseous (osteomyelitis), articular (septic, pyogenic, or suppurative arthritis), bursal (septic bursitis), subcutaneous (cellulitis or abscess), muscular (infectious myositis or abscess), and tendinous (infectious tendinitis or tenosynovitis) infections. The term *osteomyelitis* literally means inflammation of the marrow of the bone, but it is colloquially used to refer to infection in any part of the bone.

Infectious processes can also be categorized by their onset and are generally designated as acute, subacute, or chronic. An acute infection is one that is diagnosed within 2 weeks after disease onset, a subacute infection is one diagnosed after one to several months, and chronic infections after a few months. Periprosthetic infections follow a similar nomenclature, using time of onset after surgery. Chronic osteomyelitis is also used to define a bone infection that fails to respond to a normal course of antibiotic therapy.

For the emergency clinician, the most practical way to classify osteomyelitis is as hematogenous, which is more common, or contiguous, which is further subdivided based on the presence or absence of vascular insufficiency. This method of classification assists in the interpretation of diagnostic imaging examinations and helps guide management, including antibiotic therapy and surgical intervention.

Anatomy, Physiology, and Pathophysiology

Histologically, bone is composed of compact and trabecular tissue. Compact bone forms the shaft of long bones and also covers the epiphysis. Trabecular or spongy bone is found within the epiphysis and makes up irregular bones. Compact bone is dense and without cavities and consists of longitudinally running Haversian systems, which contain Haversian canals that house vasculature and nerves. Spongy bone, conversely, consists of a bony lattice, the trabeculae, which is located within the medullary cavity and contains marrow, making it more metabolically active. The central Haversian canals in spongy bone run parallel to the long axis of the bone and contain the blood supply and reticular connective tissue for the Haversian system.

The gross structure of long bones is divided into several sections. The diaphysis is the shaft of the bone and contains the compact cortical bone with an overlying periosteum and a medullary canal containing marrow. The metaphysis is the junctional region between the epiphysis and diaphysis. The metaphysis contains abundant trabecular bone, but the cortical bone thins here relative to the diaphysis. Finally, the epiphysis is the area at either end of a long bone and is made up of abundant trabecular bone and a thin shell of cortical bone (Fig. 125.1). In the skeletally mature individual, the epiphysis of most bones is involved in articulation and, instead of being covered by a periosteum, is covered with a thin layer of articulating cartilage. This cartilage is composed of a thin layer of secretory cells that sits on a loose fibrous stroma and allows frictionless movement of the bones.

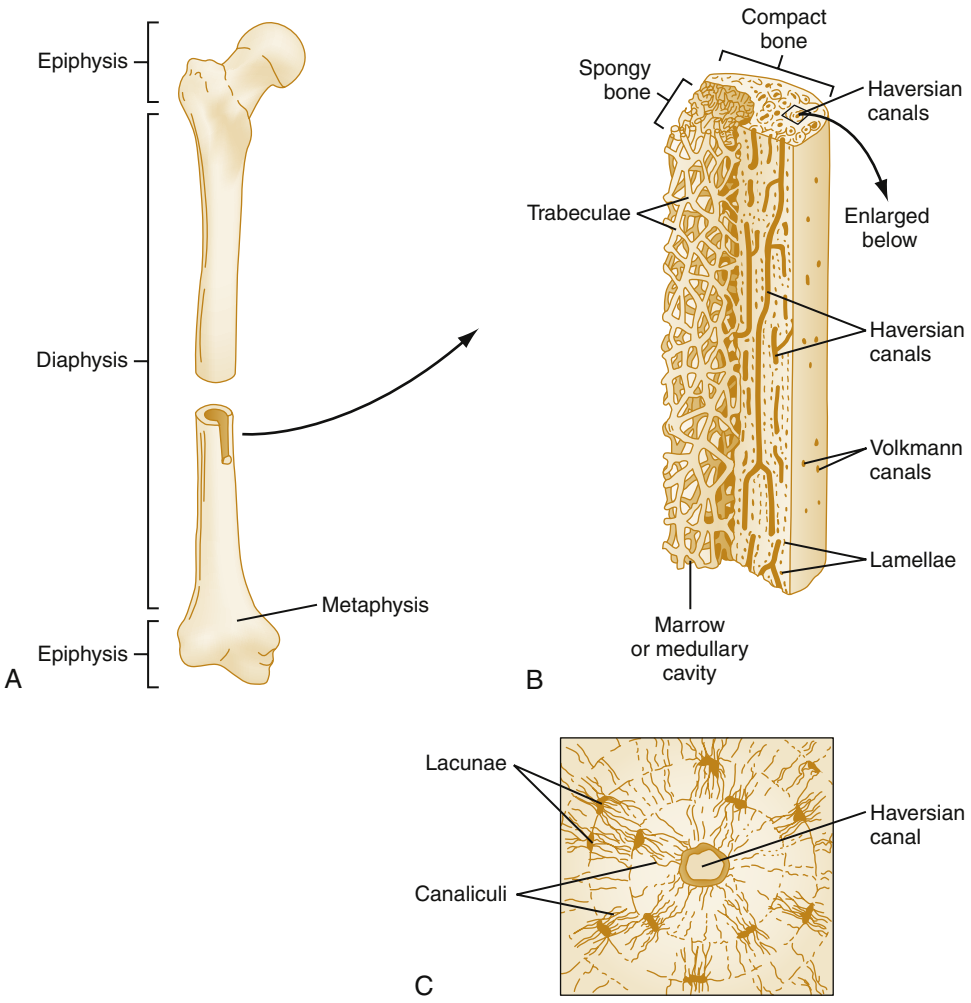

Fig. 125.1 Schematic drawing of long bone. (A) Regions of long bone. (B) Cross-sectional structure of long bone. (C) Microscopic structure.

Joints are enclosed by a synovial capsule. This layer of dense fibrous connective tissue offers structural integrity and is lined with synovial cells that secrete synovial fluid. This forms a sleeve around the articulating bones to which it is attached. The synovial membrane of the shoulder, hip, and knee joints extends beyond the epiphysis and attaches to the metaphysis allowing bacteria to spread directly from the metaphysis into the joint.

Osteomyelitis is an infection of the bone and medullary cavity. Bone is typically resistant to infection unless it is subjected to trauma, disruption of blood flow that deprives the bone of normal host immunity, a large inoculum of blood-borne or external microorganisms, or a foreign body. Hematogenous inoculation usually starts in the metaphysis, given the slow flow of blood in the sinusoidal blood vessels. Acute inflammatory cells migrate to the area, causing edema, vascular congestion, and small vessel thrombosis, which then leads to an increase in the intraosseous pressure compromising blood flow to the bone. The significantly reduced blood supply to this necrotic bone tissue makes bacterial infection difficult to eradicate with medication alone and, frequently, chronic osteomyelitis requires a combination of surgical debridement and antibiotic therapy. Eventually, lack of blood supply to the medullary canal and periosteum leads to areas of necrotic bone termed *sequestra*. Bony tissue attempts to compensate for the tensile stresses caused by infection by creating new bone around the areas of necrosis. This new bone deposition is called an involucrum.

The normal development of blood flow patterns at the metaphyseal-epiphyseal junction helps to explain the pathologic features of hematogenous osteomyelitis seen in the different age groups. In neonates and infants, osteomyelitis readily advances from the metaphysis to the epiphysis and adjacent joint space, leading to septic arthritis. After the first year of life, the infection usually spreads laterally through Volkmann canals, breaks through the cortex, and lifts the periosteum to form a subperiosteal abscess. In the adult, after the epiphyseal plate ossifies, anastomoses form between the metaphyseal and epiphyseal blood vessels and infection can once again spread from the metaphysis to the epiphysis and eventually into the synovium and joint space. In addition, because the periosteum becomes firmly attached to the underlying bone in adults, this limits subperiosteal abscess formation.

Bacteria congregate in a highly structured community, the biofilm, which plays an important role in the pathogenesis of septic arthritis and osteomyelitis. Within the biofilm, the bacteria are at varying stages of metabolism—some are active, some are slow-growing, and some are dormant. Antibiotics target metabolically active bacteria, such as those in the single cell state (planktonic state), and bacteria in other stages in the biofilm community are more resistant to the effects of antibiotics. Furthermore, Gram staining only identifies planktonic bacteria, which helps explain why Gram stains of aspirated synovial fluid in a suspected septic joint are often negative; therefore, a definitive diagnosis is made only by culture of the synovial fluid aspirate or synovial tissue. Biofilm

formation also explains why optimal treatment of a septic joint, especially of prosthetic joints, involves complete surgical débridement.

Hematogenous spread of bacteria causes almost all cases of osteomyelitis in children and in the subset of adults who have vertebral osteomyelitis. In the appendicular skeleton of adults, such as in the foot, hand, skull, maxilla, and mandible, osteomyelitis usually occurs by spread of the pathogens from a contiguous source of infection or direct implantation. Head and neck osteomyelitis is usually caused by sinus disease and odontogenic infection.

Infections from direct implantation of bacteria are caused by deep puncture wounds, such as by an animal bite, and tend to occur in the hands and feet. Although cats account for only 10% of animal bites, significant infection results from 20% to 50% of cat bites versus only 5% of dog bites because of the morphology of feline teeth. Most human bite injuries are related to fistfights and contamination of the metacarpophalangeal joints and metacarpals, with infection due to oral flora. Direct implantation of pathogens is also common with open fractures and surgical instrumentation.

Septic arthritis is usually a consequence of hematogenous spread unless there is direct injection of bacteria into the joint. The lack of a basement membrane makes the highly vascular synovium vulnerable to bacterial seeding. Infection occurs first in the synovium, spreads into joint fluid, and finally affects the articular cartilage. Bacterial enzymes and toxins directly damage cartilage. The synovial membrane responds to infection by increasing synovial fluid production, resulting in a large joint effusion. In response to infection, synovial cells and polymorphonuclear leukocytes release lysosomal enzymes, which irreversibly degrade articular cartilage, creating a painful joint with limited range of motion. This is amplified by the damage produced by bacterial enzymes and toxins. Even a small bacterial load in the joint space elicits profound and persistent inflammatory and immune responses. Bacteria can be cleared from the joint, resulting in a sterile-appearing inflammatory response. In addition, other structures that are enclosed within or adjacent to the synovium, such as bursae, tendons, and bone, may also become damaged in those with septic arthritis.[2]

Causes and Microbiology

Typically, hematogenous osteomyelitis or septic arthritis is caused by a single strain of bacterium, with gram-positive organisms being responsible for most infections. Even though gram-negative organisms account for 43% of cases of community-acquired bacteremia, they result in only about 10% of septic arthritis cases. Trauma predisposes patients to osteomyelitis by environmental pathogens. Patients who are wounded or sustain open fractures in fresh water are susceptible to infections with the gram-negative bacillus *Aeromonas hydrophila*. People who are bitten by animals, particularly dogs and cats, are at risk for the development of osteomyelitis from *Pasteurella multocida*. Osteomyelitis caused from human bites is most common in the hand and involves human oral flora, such as *Streptococcus anginosus, Fusobacterium nucleatum,* and *Eikenella* spp. In the population of injection drug users, *Staphylococcus aureus* is the most likely cause of infection, followed by *Pseudomonas* spp. *Pseudomonas aeruginosa* is also an important cause of osteomyelitis in puncture wounds, postsurgical wounds, and patients with sickle cell anemia.

Certain underlying disease states predispose a patient to BJI. These conditions include diabetes mellitus, sickle cell disease, HIV, alcohol use disorder, injection drug use, chronic corticosteroid use, preexisting joint disease (especially rheumatoid arthritis), and other immunosuppressed states. Postsurgical patients are also susceptible to BJIs, especially those who have implanted prosthetic devices.

Although most BJIs are bacterial, other pathogens include viruses, fungi, and parasites. The microbiology of osteomyelitis and septic arthritis is a function of several host and environmental factors. A patient's living environment also has some role in determining the incidence of BJIs. For example, people living in crowded conditions where tuberculosis is prevalent are at increased risk for tubercular BJIs, whereas older patients in hospitals and institutions may be more susceptible to infections with gram-negative bacteria. A summary of the organisms that cause osteomyelitis and septic arthritis is presented in Tables 125.1 and 125.2.

When considering the offending organism, *S. aureus* is the leading cause of osteomyelitis in all age groups except neonates. In neonates, group B streptococci, *Escherichia coli* and other gram-negative coliforms, and *Staphylococcus epidermidis* are the most common pathogens responsible for BJIs. Since the introduction of the vaccine, *Haemophilus influenzae* type b, once a common cause of septic arthritis and osteomyelitis in children younger than 2 years, has essentially disappeared as a pathogen in vaccinated children but cases of septic arthritis are being reported from other serotypes of *H. influenzae*. Another gram-negative coccobacillus in the Neisseriaceae family, *Kingella kingae* has been encountered with increasing frequency.[3] *K. kingae* can be part of the normal flora of the nasopharynx and can be spread hematogenously to bones and joints. It is a fastidious organism and may be mistaken for *Haemophilus* or *Neisseria* spp. and often requires PCR for diagnosis.[4] In older adults and patients with diabetes, gram-negative bacteria account for a higher percentage of cases of bone and joint infections.

P. aeruginosa has been reported as a cause of cervical spine osteomyelitis in injection drug users and lumbar spine osteomyelitis in patients

TABLE 125.1 Microbiology of Bacterial Septic Arthritis as Related to Age of the Patient

Organism	Child (%)[a]	Young Adult Engaging in High-Risk Sexual Behavior (%)	Adult (%)	Older Adult (%)
Staphylococcus aureus	10–20	15–20	60–0	45–65
Streptococcus species	5–10	1–5	15–20	10–15
Gram-negative bacterium	1–5	Rare	10–5	15–35
Haemophilus influenza	Rare[b]	Rare[b]	Rare[b]	Rare[b]
Neisseria gonorrhoeae	1–5	60–80	1–5	Rare

[a]Ages 6 months to 5 years.
[b]With widespread immunization.
Reprinted with permission from: Esterhai JL Jr, Rao N. The epidemiology of musculoskeletal infections. In: Cierny G 3rd, McLaren AC, Wongworawat MD, eds. *Orthopaedic Knowledge Update: Musculoskeletal Infection*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2009.

TABLE 125.2 Microbiology and Initial (Empirical) Antibiotic Treatment of Bone and Joint Infection

	OSTEOMYELITIS		SEPTIC ARTHRITIS	
Age Group	**Common Organisms**	**Antibiotic Regimen**	**Common Organisms**	**Antibiotic Regimen**
Neonate to <3 mo	*Staphylococcus aureus* Group B streptococcus Enterobacteriaceae Gram-negative rods	Ceph 3 PRP + gentamicin Consider vancomycin instead of PRP for MRSA.	*S. aureus* Group B streptococcus Enterobacteriaceae	PRP + Ceph 3 Alt—PRP + APAG Consider vancomycin instead of PRP for MRSA.
3 mo–14 yr	*S. aureus* Group A streptococcus *Haemophilus influenzae*	PRP + Ceph 3 Alt: vancomycin + Ceph 3, chloramphenicol PRP or Ceph 3 with allergy to penicillin or clindamycin with allergy to penicillin + Ceph 3	*S. aureus* Group A streptococcus *Streptococcus pneumoniae* *H. influenzae*	PRP + Ceph 3 Alt—vancomycin + Ceph 3
14 yr–adult	*S. aureus*	PRP Alt—vancomycin	*S. aureus* Streptococcal spp. Enterobacteriaceae	PRP or Ceph 3 Alt—vancomycin + Ceph 3 *or* penicillin + aminoglycoside or Ceph 3
Infection Subsets				
Sexually active adolescents or adults with acute arthritis			*Neisseria gonorrhoeae*[a]	Ceph 3 Alt—spectinomycin *or* penicillin if sensitive
Chronic osteomyelitis and diabetic foot infections	*S. aureus* Enterobacteriaceae Anaerobic bacteria	PRP + FLQ + metronidazole Alt—PRP + Ceph 3 + clindamycin		
Infected orthopedic joint prosthesis	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	Vancomycin + FLQ Alt—imipenem	*S. aureus* *S. epidermidis* *P. aeruginosa*	Vancomycin + FLQ Alt—PRP + APAG
Sickle cell disease	*Staphylococcus aureus* *Salmonella* sp.	PRP + Ceph 3 Alt—FLQ	*S. aureus* *Salmonella* spp.	PRP + Ceph 3 Alt—FLQ
Injection drug abuse	*Staphylococcus aureus* *Pseudomonas aeruginosa* Enterobacteriaceae	Ceph 3 + aminoglycoside Alt—Ceph 3	*P. aeruginosa* *S. aureus* Enterobacteriaceae	PRP + APAG or FLQ Alt—vancomycin + FLQ
Plantar puncture wound	*Pseudomonas aeruginosa*	AP Ceph Alt—FLQ	*P. aeruginosa*	AP Ceph Alt—FLQ
Human or animal bites	*Eikenella corrodens* *Pasteurella multocida*	Penicillin ± AC Alt—Ceph 3, TS	*E. corrodens* *P. multocida*	Penicillin ± AC Alt—Ceph 3, TS

Alt, Alternative antibiotics; *APAG,* antipseudomonal aminoglycoside; *AP Ceph,* antipseudomonal cephalosporin (ceftazidime or cefepime); *Ceph 3,* third-generation cephalosporin (e.g., ceftriaxone, cefotaxime, cefamandole, ceftizoxime, ceftazidime, cefazolin, moxalactam); *FLQ,* fluoroquinolone; *MRSA,* methicillin-resistant *S. aureus*; *PRP,* penicillinase-resistant penicillin (oxacillin, nafcillin, methicillin, amoxicillin-clavulanate [*AC*]); *TS,* trimethoprim-sulfamethoxazole.

[a]Concurrent treatment of *Chlamydia trachomatis* infection should be given to patients with suspected *N. gonorrhoeae* septic arthritis.

with chronic urinary catheters. *Pseudomonas* colonizes the rubber and plastic inserts in footwear and is therefore seen in soft tissue infections and osteomyelitis of the foot after a puncture wound through footwear.

Methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis,* and vancomycin-resistant enterococci (VRE) pose significant microbiologic problems. In fact, MRSA has become the most prevalent cause of acute hematogenous osteomyelitis in pediatric patients.[5] Traditional therapies, including vancomycin and clindamycin, remain effective for the treatment of much of pediatric AHO. Multiresistant enterococci pose the greatest potential danger in that bacteriocidal antibiotic regimens are limited.

The rise in injection opioid use in the United States since 2000 has also resulted in a rise in invasive bacterial infections, including osteomyelitis. One study found that those who inject heroin were 16 times more likely to develop MRSA than those who did not inject drugs.[6]

Diabetic foot osteomyelitis, posttraumatic osteomyelitis, and chronic septic arthritis or osteomyelitis are often polymicrobial. Anaerobic bacteria can complicate polymicrobial infections and may be present more often than is commonly identified because standard culture techniques may be inadequate to identify them. Anaerobic bacteria are reportedly discovered in up to 40% of cases of chronic osteomyelitis.

Mycobacterium tuberculosis may infect bones and joints, usually in the axial skeleton. The two most common forms of skeletal infection are vertebral osteomyelitis (Pott disease), in which the spine is affected in 50% of cases, and tubercular arthritis, which manifests as a chronic,

low-grade inflammatory process that resembles rheumatoid arthritis more than acute septic arthritis.

Patients with human immunodeficiency virus (HIV) infection and AIDS are predisposed to various common and opportunistic pathogens. Although *S. aureus* is still the most likely cause of bone and joint infections in patients with AIDS, fungal and other atypical organisms should be considered. One unusual but particularly characteristic form of osteomyelitis in HIV-positive patients is bacillary angiomatosis. This infection is caused by a gram-negative, rickettsia-like organism that frequently causes osteolytic bone lesions.

OSTEOMYELITIS

Clinical Features

History and Physical Examination

The symptoms and signs of osteomyelitis in adults vary. Patients with osteomyelitis often present with fever, rigors, and may even appear toxic. Systemic complaints of headache, fatigue, malaise, and anorexia are inconsistently reported and are less likely with chronic osteomyelitis. In children with lower extremity osteomyelitis, a sudden limp or inability to bear weight, localized warmth, swelling, and erythema may be reported. A careful review of the patient's past medical history should be performed to identify risk factors that may predispose to bone infection.

The predominant physical exam finding of osteomyelitis is point tenderness over the infected segment. Palpable warmth and soft tissue swelling with erythema may be present, but these findings are variable. In chronic osteomyelitis, the involucrum or sequestrum (fragments of necrotic bone separated from healthy bone) may be palpated, and sinus tracts that fistulize to the skin may be noted. A sympathetic effusion in the adjacent joint may develop in patients with osteomyelitis, even when the joint is not infected.

Complications

In addition to the development of chronic osteomyelitis, complications of acute osteomyelitis include bacteremia and sepsis. Depending on the location of osteomyelitis, local extension of an invasive suppurative process can lead to septic arthritis, brain abscess, meningitis, spinal cord compression, pneumonia, and empyema. In children, osteomyelitis damages the developing skeleton. If the infection involves the epiphysis, permanent growth alterations can occur, resulting in a shorter or deformed extremity on the affected side. Pathologic fractures may occur through sites of osteomyelitis.

Clinical Subsets of Osteomyelitis

Osteomyelitis in Children. Osteomyelitis in children tends to be acute, usually arising from hematogenous seeding of bone, and can often be treated with antibiotics alone. Acute hematogenous osteomyelitis (AHO) is seen in children as young as 3 months and as old as 16 years. *S. aureus* is the most common infecting organism in children of all ages, except neonates (see Tables 125.1 and 125.2) with MRSA being most common in AHO. As noted, *H. influenzae* is no longer a common cause of AHO.

AHO has a well-established male preponderance (male-female ratio of 2 : 1 to 3 : 1) and involves long bones approximately 80% of the time. The site of infection is usually the distal metaphysis because of its increased vascularity, but up to 30% of AHO occurs in other parts of the bone. Children with AHO may have fever, chills, vomiting, dehydration, and malaise, but they usually do not appear toxic. Most children have characteristic pain, limited use of the limb, and are point tender. The diagnostic evaluation for AHO is shown in Fig. 125.2. Blood cultures are positive for the bacterial cause of osteomyelitis in about 40%

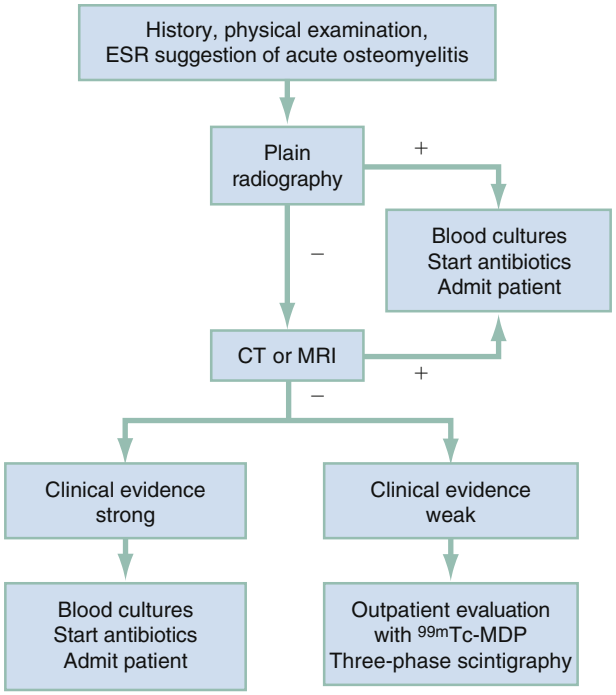

Fig. 125.2 Algorithm for the use of imaging studies in the emergency department diagnosis of osteomyelitis. *CT,* Computed tomography; *ESR,* erythrocyte sedimentation rate; *MRI,* magnetic resonance imaging; *^{99m}Tc-MDP,* technetium Tc-99m–labeled methylene diphosphonate.

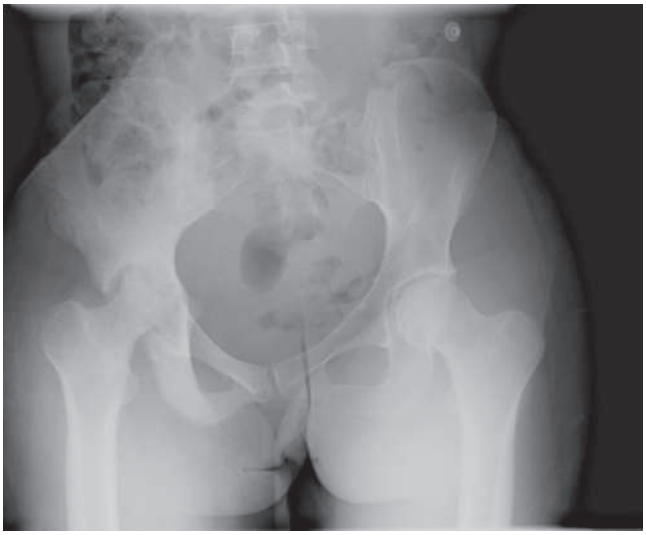

Fig. 125.3 Radiograph of chronic osteomyelitis. Diffuse sclerosis of the right hemipelvis includes the ischium and iliac bone, with extension to the right sacroiliac joint. The right acetabulum demonstrates whittling of the femoral head and neck, with marked loss of bone stock. Abutting the right symphysis pubis is increased cortical lucency suggestive of subchondral cystic changes. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

of pediatric patients[7] with AHO while tissue cultures are positive 86% of the time. A positive blood culture and physical examination consistent with osteomyelitis may be sufficient to diagnose AHO. Figs. 125.3 and 125.4 show typical radiographs of AHO.

Neonatal osteomyelitis is more commonly seen after an abnormal pregnancy or delivery and often accompanies other acute illnesses

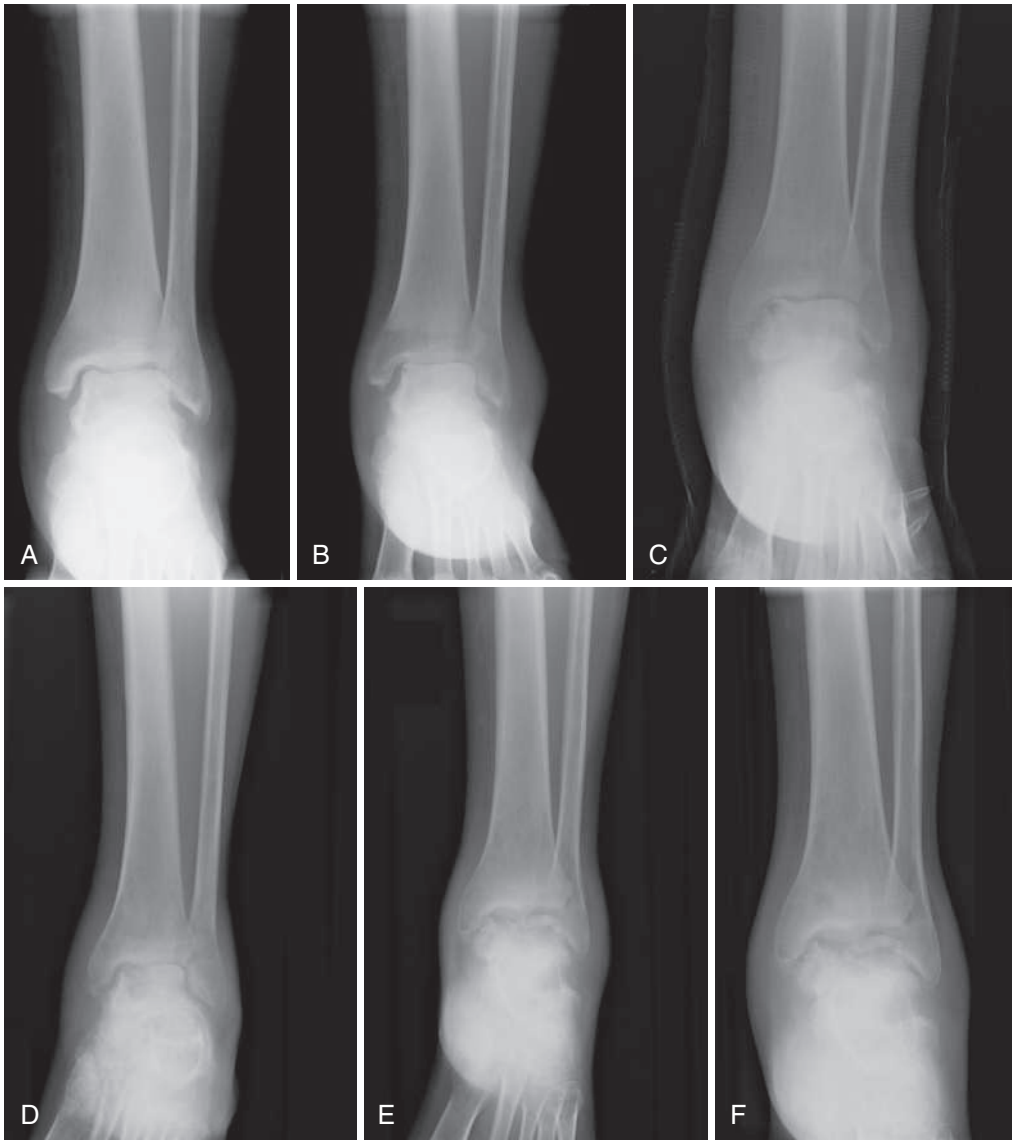

Fig. 125.4 Radiographic progression of acute osteomyelitis. (A) Soft tissue swelling at the medial and lateral aspects of the ankle, with a moderately sized effusion (August 2, 2006). (B) Large ankle effusion with extensive soft tissue swelling. There is complete loss of the tibiotalar joint space and widening of the medial joint space, suggesting chondrolysis. There are lucent areas in the distal tibia and fibula, suggestive of hyperemia, and the talus is diffusely sclerotic (September 11, 2006). (C) Increased erosion of the medial aspect of the talar dome, with increased joint effusion (October 12, 2006). (D) Talar bone destruction with demineralization involving all the osseous structures. There is also a small joint effusion (January 2, 2007). (E) Avascular necrosis of the talus and destruction of the articular surfaces of the tibia and talus is present, consistent with chronic osteomyelitis. There is diffuse osteopenia and loose bodies within the joint (April 19, 2007). (F) There is continued irregularity of the articular surface of the tibia and collapse of the talus. Loose bodies are still present within the joint, and there is a persistent joint effusion and soft tissue swelling (June 14, 2007). (Courtesy Dr. Thomas Egglin, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

but is difficult to diagnose because of a paucity of systemic findings. Multiple sites of bone involvement are found in approximately 50% of reported cases. Because of the unique vascular anatomy of the neonate, septic arthritis often accompanies osteomyelitis. Osteomyelitis of the flat bones, such as the facial bones, is more common among neonates than any other age group. Group B streptococcus is the leading causative bacterium in neonatal osteomyelitis, but staphylococcal species are still common. As with adults, plain radiographs are a good initial test because abnormalities are identified within days of development of neonatal osteomyelitis, and radiographs are usually abnormal when the disease is suspected. In the presence of a normal radiograph, the next step for the emergency clinician who suspects neonatal osteomyelitis is magnetic resonance imaging (MRI) in consultation with the orthopedic surgical service.

Two less common forms of osteomyelitis, subacute osteomyelitis and chronic recurrent multifocal osteomyelitis (CRMO), can occur in children, particularly older children (6–10 years) and adolescents. Subacute osteomyelitis refers to a form of the disease in which clinical symptoms and signs are slow to appear, and radiographs show small areas of osteomyelitis, usually in the metaphysis of long bones. Cultures

of blood and bone are negative more than 50% of the time but usually implicate staphylococcal species when they are positive.

CRMO is characterized by small foci of infection at various sites in the skeleton. The disease is defined by multiple episodes of indolent infection. Diagnosis is made by radiography because culture of the bone sites is almost always negative. This disease may be associated with certain psoriatic subtypes.

Vertebral Osteomyelitis. Vertebral osteomyelitis usually affects older adults and is increasing in frequency as the population ages and has more chronic medical diseases. Risk factors in older adults include intravenous (IV) access devices, indwelling lines, and asymptomatic urinary infections, whereas in younger individuals risk factors include injection drug abuse. The spine is particularly susceptible to bacterial infection because the venous system surrounding vertebral bodies is valveless, permitting two-way flow of blood, and has transverse and longitudinal anastomoses. This anatomy allows bacteria to readily spread to adjacent vertebral bodies. Vertebral osteomyelitis usually results from hematogenous seeding, direct inoculation at the time of spinal surgery, or contiguous spread from an adjacent infection. A clear source of bacterial hematogenous seeding with positive blood cultures occurs in approximately 40% of cases of vertebral osteomyelitis. *S. aureus* (including MRSA) is the most common offending agent, followed by aerobic gram-negative rods from urinary or gastrointestinal sources.

Vertebral infections occur in the lumbar (58%), thoracic (30%), and cervical (11%) spine. Only 10% of patients with vertebral osteomyelitis appear septic or toxic; most patients present with insidious symptoms, leading to delays in diagnosis of up to 4 months. Back pain, seen in roughly 90% of patients, is the most common presenting symptom, and physical examination often reveals tenderness over the spinous process. Neurologic deficits are reported in less than 40% of patients with vertebral osteomyelitis and often coincide with a concomitant epidural abscess. Up to 60% of patients with these abscesses present without fever or leukocytosis. On laboratory testing, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are elevated in 98% and 100% of cases, respectively. Blood culture specimens should be obtained before antibiotic treatment is initiated. Rapid diagnosis and treatment of this medical emergency start with the initiation of empiric antibiotics, immediate imaging, and early orthopedic (or spine service) involvement. Diagnostic delay is an independent risk factor for an unfavorable outcome.

Similar to osteomyelitis in other parts of the body, findings on plain radiographs are not seen until at least the second week of vertebral infection and are nonspecific. MRI has largely replaced bone scintigraphy for imaging in suspected vertebral osteomyelitis. Although computed tomography (CT) is good for defining bone destruction and is often used to assist needle aspiration of the lesion, MRI can identify an epidural abscess and rule out other noninfectious vertebral conditions. MRI has a sensitivity of 90% for vertebral osteomyelitis, with T2-weighted images most valuable in establishing the diagnosis. When suspected, an MRI of the complete spine, with and without contrast, is the imaging study of choice.

Cervical spine osteomyelitis can cause a retropharyngeal abscess, whereas lumbar spine osteomyelitis may be complicated by a psoas muscle abscess. Vertebral osteomyelitis can cause spinal cord ischemia if the vertebral infection causes septic thrombosis or compression of local blood vessels. When osteomyelitis affects the thoracic spine, infection can spread to the chest. Paraspinal abscesses, reactive pleural effusions, and empyema have been reported as complications of vertebral osteomyelitis and may mislead the emergency clinician. The most dreaded complication of vertebral osteomyelitis is the spread of infection into the spinal canal, development of an epidural abscess, and progression of the infection to cause spinal cord injury and permanent paralysis. Fortunately, this occurs in less than 15% of cases of vertebral osteomyelitis, and risk factors for this include older adults, those with cervical spine osteomyelitis, and those with serious underlying diseases (e.g., rheumatoid arthritis, diabetes mellitus).

Patients who present with a clinical picture consistent with vertebral osteomyelitis require rapid diagnostic confirmation to avoid progression and spinal cord compression. The diagnosis is suspected in patients who have recently undergone a spinal procedure or injection and have focal severe pain that is not relieved by rest. It can also result from hematogenous spread, making diagnosis elusive. The diagnostic procedure of choice for vertebral osteomyelitis is a spinal MRI with contrast, and needle biopsy may be indicated to identify the causative organism.

Patients with vertebral osteomyelitis initially require IV antibiotic therapy and can usually be successfully treated with antibiotics alone. Surgery may be required when there is spinal cord compression, for abscess drainage or débridement, for correction of the progressive anatomic deformity, and if the infection recurs after adequate treatment.

Diskitis is a variant of vertebral osteomyelitis. The disk is an avascular structure that depends on nutrient diffusion from adjacent blood vessels from the vertebral body and endplates. The avascular disk creates a rich environment for the bacteria to flourish. Due to the vascular anatomy, diskitis often coexists with vertebral osteomyelitis in adults while isolated diskitis is more common in children. The patient often complains of back pain and may refuse to walk. MRI demonstrates the anatomy of diskitis, whereas CT is used to guide aspiration. Cultures of the disk from needle aspiration are reported to be positive for bacteria 30% to 60% of the time, usually for *S. aureus*. The disease typically resolves with nonoperative treatment.

Posttraumatic Osteomyelitis. Posttraumatic osteomyelitis is a form of osteomyelitis that results from open fractures, burns, bites, puncture wounds, and surgery and invasive procedures. Open fractures are typically graded according to the Gustillo classification, which takes into account wound length and amount of soft tissue damage; this helps guide antibiotic treatment. Overall, the rate of osteomyelitis in open long-bone fractures is reported to be around 0.05%.[8] The fracture site may be contaminated directly from the environment or iatrogenically secondary to emergency procedures or surgery. When there is damage to soft tissues, a necrotic nidus of infection is created, and the bacteria can spread to bone. Polymicrobial infection is more common in this scenario. The imaging of posttraumatic osteomyelitis is complicated by changes induced by surgery and new bone formation in the fracture; therefore, the optimal imaging modalities are MRI and CT.

The intraoperative implantation of prosthetic devices increases the chance of infection. The rate of prosthetic joint infection is 0.5% to 1% for hips,[9] 0.5% to 2% for knees, and less than 1% for shoulder replacements. Osteomyelitis due to direct inoculation associated with joint arthroplasty and implantation of prosthetic devices typically becomes evident about 12 weeks after surgery. These patients generally do not report relief of their pain after surgery. Patients who have symptoms of infection more than 12 weeks after surgery and who have postoperative improvement of their pain are considered to have a hematogenous source of infection. Techniques to retain implanted prosthetic devices in the setting of an acute infection after total joint arthroplasty are evolving. Débridement and irrigation with prosthetic retention followed by antibiotic therapy is the treatment of choice in infections following total knee arthroplasty.[9,10] Postsurgical osteomyelitis should be considered in the postoperative patient with a painful joint. The prevalence of infection after total knee or hip arthroplasty is estimated to be approximately 1% to 2%, with infections within 3 months of injury likely the result of surgical contamination, and those that occur longer than 3 months postoperatively due to hematogenous seeding.

S. aureus and *S. epidermidis* account for 75% of postsurgical and prosthesis-related cases of osteomyelitis. Radiographs are often normal but may show subtle signs of bone resorption and loosening of the prosthetic components. It is difficult to distinguish mechanical from infectious loosening, so joint aspiration, synovial fluid analysis, and bone biopsy—all performed in a sterile operative setting—are undertaken to establish a diagnosis. Other imaging techniques such as CT and MRI are used but may be difficult to interpret because of scatter from the metallic components and postsurgical changes.

Puncture wounds to the feet have approximately a 2% incidence of development of osteomyelitis. The causative organism is usually *S. aureus* or beta-hemolytic streptococcus. *P. aeruginosa* is commonly associated with plantar wounds that occur while a person is wearing rubber-soled shoes. Invasive procedures that produce puncture wounds, such as venipuncture for central lines, intraosseous devices for intravascular access, and fetal scalp monitoring, may introduce infection that can lead to osteomyelitis. Proper antiseptic skin cleansing and avoiding punctures through infected skin will reduce the chance of contiguous bone infection.

Diabetic Foot Osteomyelitis. Diabetic foot infections lead to osteomyelitis 20% of the time, while diabetic ulcers have underlying osteomyelitis 15% of the time. This rate increases in ulcers greater in size than 2 cm^2. The pathologic changes induced by long-standing diabetes mellitus, such as compromised vascularity, encourage the development of osteomyelitis. Over 60% of patients report polyneuropathy, leading to repetitive trauma and subsequent foot ulcers. Once the skin has been violated and infected, the altered host defenses of diabetic patients make it easier for infection to occur and spread. Hyperglycemia resulting from the infection allows bacteria to proliferate, impairs leukocyte function, and results in defective chemotaxis, abnormal phagocytosis, decreased bactericidal function, defective antibody synthesis, and decreased complement levels, all of which impair healing and exacerbate osteomyelitis. The infection typically starts in the periosteum, spreads to the cortex, and eventually disrupts medullary bone.

Local findings in diabetic foot infections include swelling, erythema, and sometimes pain. Indolent ulcers and frank cellulitis are seen in more than 50% of cases. Laboratory testing cannot definitively diagnose osteomyelitis, though an ESR over 70 mm/h is associated with an 11-fold greater risk. Surgical biopsy of the bone is the only reliable way for the bacteriologic diagnosis to be made. The probe-to-bone (PTB) test can be performed by exploring the wound for palpable bone with a sterile blunt metal probe. The pretest probability plays a significant role in using PTB to diagnose osteomyelitis and the PTB result should be interpreted with the results of clinical, laboratory, and imaging findings.

Diabetic osteomyelitis is often chronic, so radiographic changes are often notable. Osteopenia, periosteal thickening, cortical erosions, new bone formation, and mottled lytic lesions are typical, and air may be present in the soft tissues. Bone biopsy for diabetic foot osteomyelitis has a reported sensitivity of 94%. Diabetic foot osteomyelitis is usually polymicrobial and often includes gram-negative bacteria. *S. aureus* is the most common pathogen; other organisms include streptococci, Enterobacteriaceae, and anaerobes. Surgical treatment with amputation had been the mainstay of treatment; however, a 10-week antibiotic treatment regimen, including IV administration followed by oral antibiotics, can be successful in select patients.[11]

Osteomyelitis in Sickle Cell Disease. Patients with sickle cell disease (SCD) are at increased risk for hematogenous infection, including osteomyelitis, often due to reduced or absent splenic function. In children, the difference in the vasculature of immature bone increases susceptibility to osteomyelitis. In contrast to AHO in non–sickle cell patients, AHO in children with sickle cell disease usually affects the diaphysis instead of the metaphysis. Also, although *S. aureus* is the most common bacterium in children without sickle cell disease, *Salmonella* spp. is the most common infecting organism in patients with SCD.[9,12] Reasons for this are not completely understood, although it has been postulated that microinfarcts in the bowel allow *Salmonella* bacteremia to seed the bloodstream and lead to hematogenous osteomyelitis.

The differentiation of bone infection from bone infarction and vaso-occlusive crisis in sickle cell patients is a challenge. Vaso-occlusive pain is typically consistent and far more common than either infarcts or infection. Fever, toxic appearance, and elevated ESR are more commonly associated with osteomyelitis than with bone infarction. Plain radiographs are not helpful in distinguishing between the entities, but MRI has been proving useful in differentiating between bone infarction and infection. Another approach is to note the response to conservative therapy; bone infarctions usually improve within 24 to 48 hours, whereas bone infections worsen. Empiric antibiotic treatment of osteomyelitis in the sickle cell patient should include coverage against *S. Aureus, Salmonella,* as well as other gram-negative bacteria with vancomycin and ciprofloxacin.

Chronic Osteomyelitis. Most chronic bone infections occur as a complication of posttraumatic infection, surgical procedures, or diabetic foot infections. The inflammatory response to infection triggers bone resorption and cartilage destruction and ultimately leads to bone death (see Fig. 125.3). The necrotic bone provides an inanimate surface to which microorganisms adhere. Clinical signs that the infection has become chronic include the formation of sequestra and presence of draining tracts or fistulas. Chronic infection is almost always polymicrobial and commonly involves anaerobes. Because sinus tract culture is not a reliable method to predict which bacteria are active in the underlying bone infection, direct biopsy of bone is the only option for the accurate diagnosis of most cases of chronic osteomyelitis. Chronically established infections can be remarkably persistent or evolve even in the face of prolonged antibiotic therapy; therefore, treatment commonly involves surgery.

Differential Diagnoses

Many processes involving bone may masquerade as osteomyelitis. Bone tumors, such as osteoid osteomas and chondroblastomas, metastatic bone tumors, and lymphoma may produce local pain and radiographic changes consistent with osteomyelitis, such as small, round, radiolucent lesions. Ewing sarcoma is a tumor of bone marrow in children that can be mistaken for osteomyelitis. Finally, occult fractures, such as buckle fractures in children, present with point tenderness that may be mistaken for osteomyelitis.

Diagnostic Testing

Laboratory Tests

Initial evaluation in the emergency department (ED) often involves laboratory and radiographic evaluation, but the gold standard to confirm diagnosis is bone biopsy and culture, which also helps guide treatment. Laboratory data are not specific and can only suggest the diagnosis of osteomyelitis. In acute osteomyelitis, the white blood cell (WBC) count can be elevated—typical values range from normal to 15,000/mm^3—whereas in chronic osteomyelitis the WBC count is often normal.

The ESR, a nonspecific measure of inflammation, is more helpful than the WBC count. The ESR is a relatively sensitive marker for infection, and many series have reported elevated ESR and CRP values in patients who have confirmed osteomyelitis. An elevated ESR in the presence of pertinent physical findings should lead one to suspect osteomyelitis, but a normal or slightly elevated ESR does not eliminate the diagnosis. Other inflammatory conditions, such as cellulitis, can

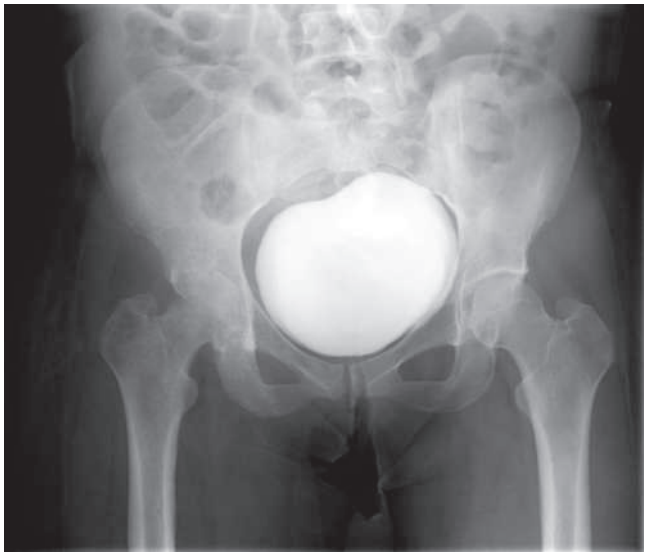

Fig. 125.5 Radiograph of right hemipelvis and proximal femur demonstrate permeative moth-eaten changes, with resultant femoroacetabular joint space narrowing consistent with osteomyelitis. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

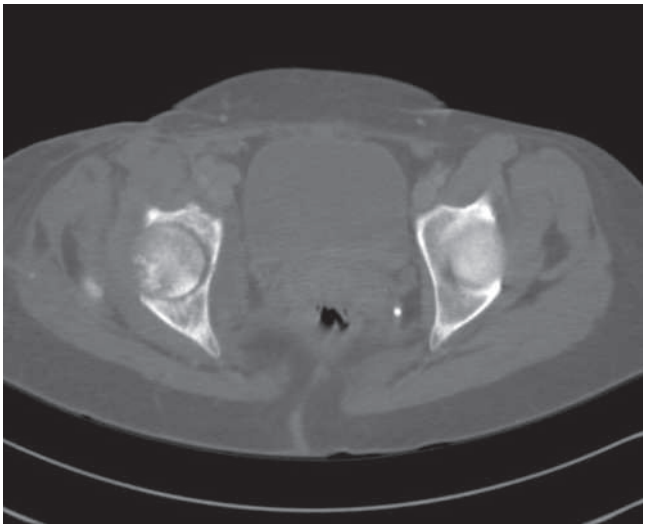

Fig. 125.6 CT scan of osteomyelitis. There is a diffuse moth-eaten appearance involving the right hemipelvis and right femoral head, with abundant periosteal reaction. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

cause an elevated ESR, although the degree of elevation of the ESR is often higher with osteomyelitis. In evaluating a diabetic foot infection, an ESR greater than 70 mm/hr predicts the presence of an underlying bone infection.

The CRP level, another nonspecific marker of inflammation, increases within the first 24 hours of infection, peaks within approximately 48 hours, and is usually normal within 1 week of therapy. The CRP level may be a better early indicator of disease, but the ESR is most valuable in following response to treatment. Typically, the ESR falls steadily as osteomyelitis resolves and increases should it recur. However, it is common to see elevations in one and not the other parameter, especially when there is development of a concurrent illness or the infection has progressed so that the ESR rises and stays elevated while the CRP rises and falls. In children, an elevated ESR or CRP level is seen in all cases of osteoarticular infection; sensitivity of the use of both the ESR and CRP value is 98%, but a leukocytosis is reportedly seen in only 35% of cases.

Diagnostic Imaging

Conventional Radiography. Conventional radiography is the initial modality of choice to evaluate osseous changes and, in most cases, will be the only imaging technique used to aid in the diagnosis of osteomyelitis.

Conventional radiography is readily available, relatively inexpensive, and useful in the differentiation of infection from trauma and tumors. The characteristic findings of early osteomyelitis on the plain radiograph are lucent lytic areas of cortical bone destruction (see Fig. 125.4). However, lucency is not detected on radiographs until approximately 50% of bone mineral is lost, which often takes up to 2 weeks from the onset of infection. Although these findings are often difficult to identify on plain radiographs, soft tissue edema, distorted fascial planes, and altered fat interfaces may be present within 3 to 5 days from the onset of infection and can serve as a clue to osteomyelitis in the underlying bone. A periosteal reaction, hypertrophy or elevation of the periosteum, and presence of an involucrum can also be seen, especially in children, given their thinner periosteum (Fig. 125.5). In advanced disease, the lytic lesions are surrounded by dense sclerotic bone, and sequestra may be noted. By 28 days from the onset of osteomyelitis, 90% of the plain radiographs are abnormal.

Radionuclide Bone Scanning. Radionuclide skeletal scintigraphy (bone scanning) is more sensitive than plain radiography for the early diagnosis of osteomyelitis, and is especially useful in the presence of prosthetics or other hardware. Radionuclide scans can detect osteomyelitis within 48 to 72 hours after the onset of infection. A radioactive tracer is injected into the bloodstream and given time to bind or accumulate in body tissues, after which a camera is used to determine released radioactivity. An image is created that is evaluated for an increase or decrease in expected uptake of the radionuclide. Given the radiation burden associated with this modality, however, in the past 3 decades, there has been a movement away from skeletal scintigraphy to MRI to diagnose osteomyelitis. The amount of time this study requires makes this less than ideal in the emergency department.

Computed Tomography. Even though MRI is the best imaging modality to diagnose osteomyelitis because it can identify early changes in the bone, when it is not available, or is contraindicated, CT is a useful alternative. The bony cortex is seen particularly well on CT, and involucrum and sequestrum formation are easily identified. CT is generally used to detect and define areas of possible infection in bones that are difficult to visualize on plain radiographs, such as the sternum, vertebrae, pelvic bones, and calcaneus. On CT scan, osteomyelitis appears as lucent areas (Fig. 125.6), and gas may be seen in bony abscess cavities. The limitation of CT for the early diagnosis of osteomyelitis is the same as that for plain radiography, in that the disease must be present for more than 1 week for changes to be apparent. When required, the CT scan can guide the surgeon in débridement of infected bone and in choosing a site for diagnostic biopsy. However, the rate of a positive culture even with a CT guided bone biopsy is low and infrequently changes the course of the patient's care,[13] therefore, antibiotics should not be withheld while waiting for this procedure.

Magnetic Resonance Imaging. The use of bone scans and CT for the evaluation of osseous anatomy has been decreasing as the availability and image quality of MRI improves while its cost decreases. MRI findings are often evident before other modalities detect an abnormality with earlier detection of bone marrow involvement and medullary or cortical destruction, periosteal reaction, edema, soft tissue extension, joint

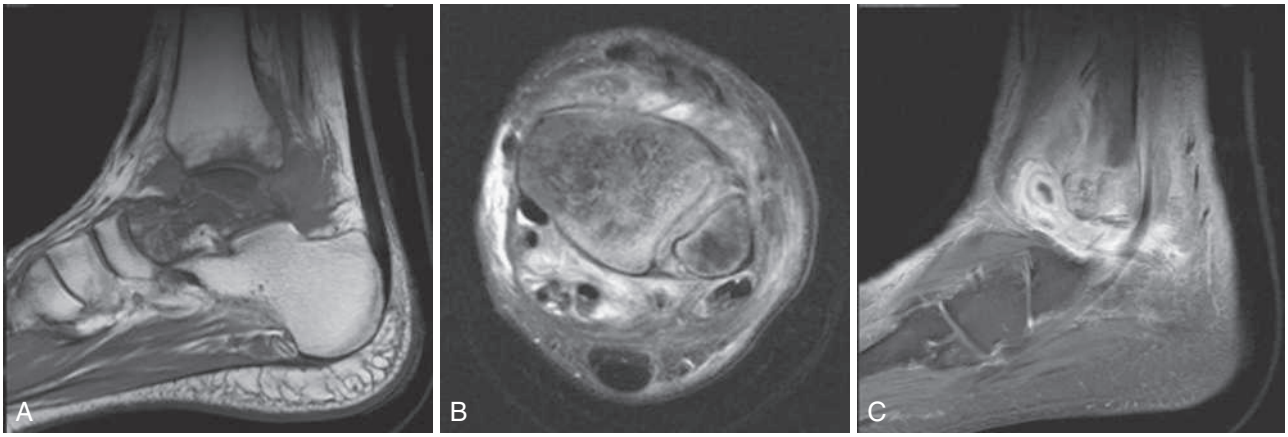

Fig. 125.7 MRI scan of osteomyelitis. (A) Sagittal T1 image shows decreased signal within the talus, suggesting osteomyelitis. (B) Axial T2 image demonstrating increased signal throughout the talus and distal fibula consistent with osteomyelitis (fat-suppressed image). (C) Sagittal T1 image after the administration of gadolinium demonstrates a small focus of nonenhancing fluid just anterior to the distal fibula, suggestive of an abscess. (Courtesy Dr. Thomas Egglin, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

effusion, articular damage, and complications of osteomyelitis, such as abscess formation. Whereas the presence of ferromagnetic material is a contraindication to the use of MRI, most materials used in orthopedic surgery, such as titanium and chrome cobalt, do not interfere with this imaging modality. Metal may cause distortion of the signal in the area adjacent to a joint prosthesis, but this does not exclude MRI in this group of patients. Osteomyelitis produces a diminished intensity of the normal marrow signal on T1-weighted images and a normal or increased signal on T2-weighted images (Fig. 125.7). These findings, however, are not specific to osteomyelitis; the differential diagnoses for the MRI findings in acute osteomyelitis are trauma, noninfectious inflammatory and metabolic lesions, and cancer. In cases in which a surgical procedure will be done to obtain a microbiologic diagnosis or is needed to treat osteomyelitis, MRI has obvious advantages over other modalities in detailing the anatomy for the surgeon.

The administration of gadolinium as a contrast agent enhances the interface between normal and abnormal marrow, helps distinguish devitalized bone from normally perfused bone, helps identify sinus tracts, and helps differentiate between an abscess and a phlegmon. Gadolinium becomes localized in areas of increased vascularity and blood flow and also helps distinguish soft tissue infections, such as abscesses and cellulitis from osteomyelitis (Fig. 125.8). Contrast improves the specificity of the images on MRI and if there are no contraindications, gadolinium should be used.

Microbiologic Diagnosis

The most definitive way to diagnose osteomyelitis is to obtain infected bone by needle aspiration or surgical resection. This also helps guide antimicrobial therapy. Cultures from draining fistulas or sinus tracts are not an acceptable substitute because these cultured organisms often differ from those in the underlying infected bone. Because osteomyelitis may be polymicrobial or due to unusual microorganisms, especially in immunocompromised patients, cultures for fungal and anaerobic organisms should be included.

Particularly in cases of hematogenous osteomyelitis, cultures of blood, urine, cerebrospinal fluid, when necessary, and pus from other sites of infection can help identify the infecting bacteria. Blood cultures in patients with acute untreated osteomyelitis are positive for the offending bacteria approximately 50% of the time, while in chronic osteomyelitis, blood cultures are almost always negative.

The emergency clinician's diagnostic approach in suspected osteomyelitis is presented as an algorithm in Fig. 125.2. A few key points should be considered with use of this algorithm:

- Radiographs lag behind the clinical picture.
- In infants and children, the amount of radiation exposure with imaging techniques must be considered.
- If the clinical presentation strongly suggests osteomyelitis, a lengthy diagnostic evaluation should not delay empirical treatment. Culture specimens of blood, urine, and other appropriate sites should be obtained and antibiotic treatment started.
- Early osteomyelitis is best identified on MRI with contrast. Other imaging modalities are useful later in the disease course and play an important role, especially when MRI is unavailable or contraindicated, and in concert with other clinical and laboratory findings.

Management

The goal of therapy is to contain the infection before bone necrosis occurs because cure rates fall dramatically once this happens. Medical management with antibiotics is usually sufficient for asymptomatic osteomyelitis that is coincidentally discovered during the evaluation of a patient with fever, weight loss, or bacteremia, hematogenous infection caused by sensitive microbacteria or fungi, or hematogenous vertebral osteomyelitis caused by sensitive pathogens.

For all other types of osteomyelitis, including contiguous focus osteomyelitis, diabetic foot infections, posttraumatic osteomyelitis, and implant-related infection, definitive care is frequently surgical. In these cases, a discussion with an infectious disease or orthopedic surgery specialist, depending on the scenario and available services, is appropriate to plan surgical and medical therapy.

The ideal antibiotic in the treatment of osteomyelitis should be able to penetrate through the bone or the synovial membrane. While most antibiotics fulfill these criteria, penicillin and metronidazole do not penetrate bone as well as other antibiotic classes.[14] Penicillin is reserved for bone contaminated with soil to cover *Corynebacterium* which causes gas gangrene, and penicillin with gentamycin and metronidazole is reserved for bone infections that are contaminated with fecal content. Effective antibiotics should also be bactericidal against the offending bacteria, such as beta-hemolytic streptococci and staphylococci (including MRSA), have low toxicity, be chemically stable at the site of infection, and be relatively inexpensive. The low pH of infected

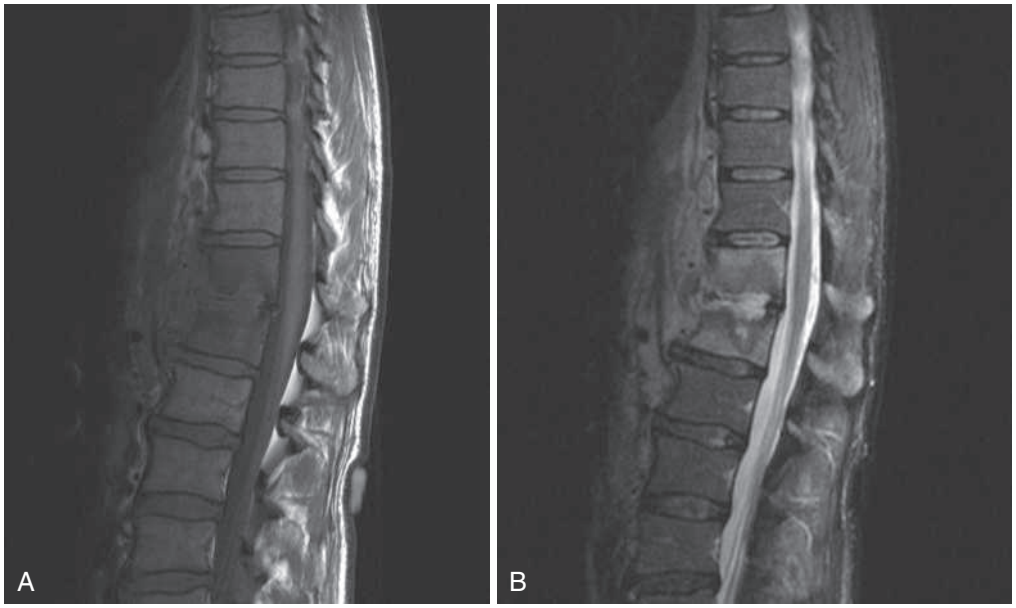

Fig. 125.8 MRI scan of osteomyelitis. (A) There is diffuse, abnormal, decreased T1 signal increase. (B) There is an increased STIR signal through the T12 and L1 vertebral bodies, with loss of the normal disk space and enhancement of these vertebral bodies consistent with osteomyelitis and diskitis. (Courtesy Dr. Peter Evangelista, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University, Providence, RI.)

bone limits the bactericidal action of some antibiotics, particularly the aminoglycosides. Cephalosporins are stable in this environment.

In the ED, the first treatment priority is adequate coverage of *Staphylococcus* spp. with a penicillinase-resistant penicillin, such as oxacillin or nafcillin, or first-generation cephalosporin. In patients with a penicillin allergy, vancomycin is an acceptable alternative. Vancomycin is an often first-line antibiotic when MRSA is considered to be the causative organism. Retrospective studies have demonstrated higher relapse rates after vancomycin compared with those after a β-lactam for non-MRSA bone infections and in those with methicillin-sensitive *S. aureus* (MSSA), so vancomycin should be reserved for those patients with an actual type I penicillin allergy or in whom MRSA is strongly suggested.

Nonenterococcal streptococci are usually sensitive to antibiotics used to combat staphylococci. Gram-negative bacteria, including Enterobacteriaceae, *E. coli, Proteus mirabilis,* and *Serratia marcescens,* are rare causes of osteomyelitis. Third-generation cephalosporins, aminoglycosides, imipenem-cilastatin, and ampicillin are the usual choices for broad gram-negative coverage if this is identified on prior or current cultures. Beyond this initial broad-spectrum therapy, treatment for gram-negative anaerobic bacteria, *Pseudomonas,* and fungal organisms should be based on existing risk factors.

Antibiotics should be dosed to ensure a serum level eight times greater than its minimum inhibitory concentration. Table 125.2 lists common treatment regimens for the variety of bacteria that cause osteomyelitis. The standard recommendation is parenteral antibiotics for 4 to 6 weeks, then transition to an oral course of antibiotics.

Treatment of chronic osteomyelitis is a difficult surgical problem. A variety of adjunctive therapies have been investigated, such as installation of antibiotic-containing beads into infected bone and hyperbaric oxygen therapy.[15,16]

Prevention of posttraumatic osteomyelitis as can occur with an open fracture depends on reducing the concentration of bacteria on exposed bone. The proper management of open fractures in the field is to cut away surrounding clothing, pour sterile saline or water over the exposed bone, and cover the wound with moist sterile gauze bandages or a sterile sheet. Only in the case of severe vascular compromise to the distal limb should an open fracture site be manipulated or realigned because of the danger of introducing bacteria deeper into the wound. Wound surface cultures in the ED setting are not reliable in predicting future pathogens in bone infections and should not be performed. Even a single dose of antibiotics dramatically reduces the bacterial load and should be routinely administered in the emergency department.

Disposition

Patients with osteomyelitis are admitted for IV antibiotic treatment and some will also need operative débridement. After steady-state serum antibiotic levels have been achieved, patients can receive outpatient IV or oral antibiotic therapy.

SEPTIC ARTHRITIS

Foundations

Septic arthritis is an orthopedic emergency, and the incidence appears to be increasing. Even with prompt recognition and appropriate care, septic arthritis leads to a loss of function in 25% to 50% of patients. In the United States, the incidence of septic arthritis in native joints ranges from 2 to 10/100,000 and, in the subset of patients with rheumatoid arthritis, the incidence jumps to 30 to 70/100,000.

Septic arthritis usually results from hematogenous migration of bacteria into a joint and is often a monoarticular process. Like osteomyelitis, septic arthritis may also result from the spread from a contiguous focus of infection, direct inoculation from trauma, or iatrogenically after joint aspiration or injection. The synovial membrane extends beyond the epiphysis and attaches to the metaphysis in the knee, hip, and shoulder joints, allowing bacteria to spread easily from the metaphysis of the femur or humerus into the joint. This explains why septic arthritis may occur concomitantly with osteomyelitis, with infection spreading from bone to joint, and osteomyelitis may also be the result of septic arthritis with infection spreading from joint to bone. The most commonly isolated organism is *S. aureus.* Polyarticular involvement is present in less than 10% of pediatric cases and less than 20% of adult cases.[17] An adjacent infection, such as osteomyelitis and intramuscular

abscesses can also occur. A reactive arthritis, which is more common than bacterial arthritis, is a sterile secondary inflammation of a joint, with no identifiable infecting microorganisms in the synovial fluid. Commonly, reactive arthritis occurs after a systemic viral infection but can also develop after a group A streptococcal infection.

Clinical Features

History and Physical Examination

Septic arthritis is usually more acute in onset than osteomyelitis. The predominant symptom of septic arthritis is joint pain, exacerbated with range of motion. The lower extremity is more commonly affected in all populations. In adults, the knee is the site of septic arthritis 50% of the time, followed by the hip (25%) and shoulder (15%). Immunosuppressed patients, especially those receiving corticosteroids, may have septic arthritis with minimal joint pain. It is important in obtaining the patient's history to identify underlying joint disease, such as osteoarthritis, gout, rheumatoid arthritis, or joint surgery or a past medical history for chronic systemic disease, immunodeficiency, prolonged steroid use, or history of injection drug use. In these patients, a careful history may help differentiate chronic joint pain from the acute pain associated with septic arthritis.

On presentation, more than 80% of children and 40% of adults with septic arthritis have a fever; constitutional symptoms such as weakness, malaise, anorexia, nausea, and diffuse myalgias are inconsistently reported. If the hip is infected, the patient may present with referred pain to the thigh or knee. Many children who have septic arthritis will not use the involved limb.

On physical examination, tachycardia and hypotension may indicate a generalized septic process. In the neonate or infant, there may be a so-called pseudoparalysis of the affected limb. This can be mistaken for a neurologic problem; however, an isolated true paralysis is far less common than septic arthritis. The inability of a child to bear weight on a lower extremity or to move any joint spontaneously should be considered a sign of septic arthritis and should be investigated.

In the older child and adult, signs may be more localized. The extremity will usually be held in the position of greatest comfort, which is slight flexion. Palpation of the septic joint will cause exquisite pain, and any maneuver that stretches the synovium, such as flexion and extension, will cause severe pain. The cardinal signs of inflammation—swelling, erythema, and warmth—are commonly found in the infected joint. Joint pain is 80% to 100% sensitive for septic arthritis, and tenderness is 100% sensitive. Periarticular processes such as bursitis, tendinitis, and cellulitis may produce erythema, warmth, and tenderness, but a thorough physical exam can help differentiate from septic arthritis. Palpation of the joint line and maneuvers that stretch the synovium and joint are usually not painful in cellulitis. Periarticular processes also do not commonly produce an effusion. In general, the triad of fever (seen in 45% to 60% of cases), pain (seen in 75% of cases), and impaired range of motion suggests septic arthritis. One caveat with the physical examination is that an increasing number of patients have been receiving chronic immunosuppressive drugs; in these patients, the classic history and examination findings are significantly less dramatic than in their immunocompetent counterparts.

Complications

Septic arthritis leads to two types of serious complications, those involving the joint itself and those that are systemic. The introduction of bacteria into a joint triggers a profound immune response that leads to destruction of the articular cartilage. Bacteria, host synovial cells, chondrocytes, neutrophils, and macrophages all release enzymes and inflammatory chemicals such as collagenase, elastase, hyaluronidase, lipase, and lipoproteinase, which are destructive to the joint. Damaged articular cartilage has limited repair capacity, and a common result of articular cartilage destruction is arthritis or ankylosis, which results in a stiff and immobile joint.

Children are at great risk for epiphyseal damage if the infection extends through subchondral bone. This can progress to growth impairment and limb length discrepancy.

Other tissues adjacent to the joint can be invaded, leading to suppurative destruction of bursae, tendons, ligaments, or muscles. Sinus tracts may lead the infection out through the skin. In the hip, the pressure and edema of a septic synovial effusion can occlude the tenuous blood supply to the femoral head, resulting in avascular necrosis, especially in neonates.

The hematogenous spread of bacteria from an infected joint can produce sepsis, septic shock, and death. Seeding of other sites with bacteria is also a possibility, though less common, and this can produce endocarditis, pneumonia, and systemic sepsis.[18]

Clinical Subsets of Septic Arthritis

Bites. The human mouth is a polymicrobial environment comprised of aerobic organisms, such as *Staphylococcus*, oral gram-negative rods, such as *Eikenella corrodens*, and anaerobes, such as *Fusobacterium*, making bone and joint infections caused by human bites difficult to treat. Similarly, animal bites also lead to a polymicrobial infection, with *Pasteurella multocida* an important additional organism seen in cat bites. Antibiotics should be empirically started, but treatment may also require drainage and débridement.

Infants and Children. Septic arthritis is more common in children than in adults, and the incidence of septic arthritis is twice that of osteomyelitis in children. Two-thirds of pediatric cases occur in children younger than 2 years, and boys are affected twice as often as girls. The offending agent in septic arthritis varies with age. In the post–*H. influenzae* vaccine era, overall, *S. aureus* (methicillin-sensitive more than methicillin-resistant) is the most common infecting organism in all pediatric and adult age groups, followed by group A streptococci and *Streptococcus pneumoniae*. In neonates, group B streptococci, *S. aureus,* and gram-negative enteric bacilli are usual pathogens. *Candida albicans* should also be considered in neonates and premature infants. *K. kingae* has been emerging as an important cause of septic arthritis and osteomyelitis in children younger than 2 years and often appears concurrent or shortly after an oropharyngeal infection. Prior trauma or skin infection may be more common with staphylococcal septic arthritis.

In the pediatric population, the hip and knee have equal rates of infection, with each accounting for about one-third of infections. Patients may have concurrent osteomyelitis, and this diagnosis impacts management.[17,19,20]

Laboratory work, including complete blood count and determination of the ESR and CRP level, are part of the routine evaluation of the limping child but, individually, do not have adequate sensitivity or specificity to rule in or rule out the diagnosis. The Kocher criteria of fever (temperature ≥38.5°C [101°F]), non–weight-bearing on the affected side, ESR greater than 40 mm/hr, and peripheral blood WBC count more than 12,000 cells/mm^3 (Table 125.3), can be used to help identify children with septic arthritis of the hip and when combined with the CRP, can help determine which patients require arthrocentesis and orthopedic consultation. When all 5 markers are negative, patients were found to have less than a 1% chance of having septic arthritis.

A synovial fluid analysis should be performed if there is any suspicion for septic arthritis. Even when cultures of synovial fluid and blood are tested, a causative organism is not discovered in up to 30% of cases of septic arthritis in children. Prior antibiotic treatment in children decreases the yield on synovial fluid cultures from 80% to 38%.

TABLE 125.3 Kocher Criteria

No. of Kocher Criteria Met	Likelihood of Septic Arthritis of the Hip
1	3
2	40
3	93
4	99

Gonococcal Septic Arthritis. In the United States, *N. gonorrhoeae* is the most common cause of septic arthritis in sexually active patients. A person with gonorrhea of the urethra, cervix, rectum, or pharynx has a 1% to 3% chance to develop disseminated gonococcal infection (DGI). More than 75% of cases of DGI occur in women, possibly because of their increased risk of asymptomatic infection. DGI is common during pregnancy or after menstruation, when the alkaline vaginal environment makes the organism more resistant to host defenses in the bloodstream and therefore more likely to disseminate. Septic arthritis develops in approximately 40% of patients with DGI.

The classic triad of gonococcal bacteremia is migratory polyarthritis, tenosynovitis, and dermatitis. Asymmetric polyarthralgia, which may be migratory, is the most common presenting complaint, occurring in two-thirds of cases; 25% of patients have monoarthralgia. Polyarthralgia is usually asymmetric and most frequently involves the knee, although the elbow, wrist, metacarpophalangeal, and ankle joints are also affected. The sacroiliac and sternoclavicular joints may be involved, although these sites are far less common. The patient will present with classic signs of a septic joint, including a joint effusion, warmth, tenderness, decreased range of motion, and marked erythema. There is usually no clear progression of DGI and polyarthralgias to purulent monarticular arthritis, and many patients are afflicted with dermatitis and tenosynovitis without the development of true arthritis. Some strains of *N. gonorrhoeae* that produce DGI favor the development of tenosynovitis and dermatitis, whereas others favor the development of purulent arthritis.

Hemorrhagic pustules on the skin, scattered, painless, nonpruritic, small (0.5- to 0.75-cm) papules distributed below the neck that can involve the palms and the soles, are seen in 41% of cases. These papules can turn into pustules on a broad erythematous base with a necrotic or hemorrhagic center. There are usually fewer than 50 lesions, distinguishing DGI from the rash of meningococcus.

The diagnosis of gonococcal arthritis is difficult. In patients who present with localized purulent arthritis, *N. gonorrhoeae* will be isolated in only about 50% (range of 25% to 75%) of synovial fluid specimens.

In septic arthritis due to gonorrhea, the synovial fluid WBC count is often less than 50,000 cells/mm^3, Gram stains of aspirated joint fluid are positive for bacteria only 25% of the time, and cultures of the joint fluid are negative in approximately 50% of cases. This may be due to poor culture techniques or because a suppurative reactive process can occur in the joint in DGI, even when bacteria are no longer present. When gonococcal arthritis is suspected, cultures for *N. gonorrhoeae* should be obtained from mucosal surfaces, because these may be the only places where bacteria are readily recovered. Cultures of the genital tract, pharynx, or rectum will be positive in 80% of cases of gonococcal arthritis. Nucleic acid amplification testing of either urine specimens in both men and women or vaginal swabs in women is preferred, if available. This has a sensitivity over 75% and should be performed if gonococcal arthritis is considered.

Gonococcal septic arthritis responds rapidly to antibiotic treatment and, unlike other types of bacterial arthritis, rarely causes permanent damage to the joint. Patients with gonococcal septic arthritis require hospital admission, with antibiotic coverage against the likely pathogens until laboratory results are available. With the rise in fluoroquinolone-resistant gonorrhea, the recommended treatment of gonococcal arthritis is a third-generation cephalosporin, such as ceftriaxone, ceftizoxime, or cefotaxime. Patients are given the first dose via the IV route or intramuscularly in the ED and admitted until culture results are available. A presumptive diagnosis of gonococcal arthritis, or disseminated gonorrhea, is best treated with inpatient therapy involving intravenous administration of 1 gm of ceftriaxone every 24 hours.

Lyme Arthritis. Lyme disease, the most common tickborne disease in the United States, is caused by infection with a spirochete, *Borrelia burgdorferi*. Transmitted by the *Ixodes* tick, it is an important cause of arthritis in endemic areas, and its incidence has been increasing. Lyme disease has been reported in all 50 states, but endemic areas, including Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Wisconsin, Connecticut, Delaware, and Rhode Island, account for 93% of all cases annually. There is a bimodal age distribution in children aged 5 to 9 years and adults aged 55 to 59 years. Children infected by *B. burgdorferi* are more likely than adults to have arthritis as the initial manifestation of the disease. Although it is important to determine a history of a tick bite, up to 30% of people do not remember being bitten.

Arthritis, which is the most distinguishing feature of late-stage Lyme disease, develops in up to 60% of untreated Lyme patients and is manifested months after disease onset. After infection, spirochetes are disseminated and invade synovial joints, resulting in a profound immune response, similar to that seen in bacterial arthritis. Patients with Lyme arthritis present with migratory polyarthralgia that also involves bursae and tendons. This typically evolves into a monarticular process and usually involves single large joints. More than 90% of patients report knee inflammation, but other affected joints include the wrist, elbow, ankle, and hip.

The rash is often overlooked by patients and is generally not present in patients when they present with arthritis. However, fever is noted in up to 50% of all children who have Lyme arthritis. Clinically, the arthritis is similar to other inflammatory processes of the joint and includes warmth, erythema, swelling, and pain on motion of the joints; however, the effusion is usually large and out of proportion to the patient's complaints. The effusion also generally recurs after aspiration, even when the joint is appropriately treated.

The most widely used test for the diagnosis of Lyme disease is the serum antibody titer, including enzyme-linked immunosorbent assay (ELISA) and Western blot testing, but serum testing does not differentiate between acute and past infections. Synovial fluid analysis is not helpful in distinguishing Lyme arthritis and cultures are typically negative, but it usually reveals an inflammatory process with WBC counts that have been reported to have a very wide range, from 500 to 98,000 cells/μL. Arthrocentesis cannot differentiate between bacterial and Lyme arthritis because serologic analysis is similar. Testing of synovial fluid with ELISA or Western blot methods for Lyme disease is not recommended because no consensus exists on how to interpret these data. Lyme arthritis can be successfully treated with oral doxycycline, amoxicillin, or cefuroxime for 30 days. If this is unsuccessful, patients can be re-treated with the same oral regimen for another 30 days, or the antibiotic can be changed to IV ceftriaxone for 14 to 30 days.

Fortunately, Lyme arthritis has an excellent prognosis. Up to 95% of children remain asymptomatic after a single course of antibiotics; adults may show an increased incidence of persistent joint swelling months to years after the initial infection, even after appropriate antibiotics.

Periprosthetic Joint Infections. Infections occurring after joint replacement are a challenging and dangerous complication of arthroplasty, with rates reported to be 0.5 to 2% for knee replacements, 0.5 to 1% for hip replacements, and less than 1% for shoulder replacements. The prosthesis and cement are foreign bodies and are ideal sites for bacterial colonization. The most common infectious agents are *S. epidermidis* (40% of cases), *S. aureus,* methicillin-sensitive and methicillin-resistant (20%), and streptococcal species (20%). Risk factors for periprosthetic joint infections have been identified and include rheumatologic disease, preoperative anemia, coagulopathy, diabetes, depression, and low socioeconomic status. The American Academy of Orthopaedic Surgeons clinical practice guideline summary recommends that patients who present to the ED should initially be stratified to high or low probability for a periprosthetic joint infection. As with many diagnostic maneuvers performed in the ED, a pretest probability helps guide the evaluation.

On history and physical examination, the patient will complain of pain that is constant and present at rest, along with impaired function of the joint secondary to loosening of the hardware. Radiographs may also reveal movement of the prosthesis, bone erosion, new subperiosteal bone growth widening, or more than a 2-mm lucency at the bone-cement interface. The laboratory data should include an ESR and CRP level; if both test results are negative, a periprosthetic infection is unlikely (negative likelihood ratio, 0–0.06); when both test results are positive, a periprosthetic infection must be considered (likelihood ratio, 4.3–12.1). However, many inflammatory processes can result in an elevation of the ESR and CRP level, and these are not specific tests. The use of either test alone is less reliable, and no definitive conclusion can be drawn with just one result. In patients with an elevated ESR or CRP level in whom a prosthetic joint infection is suspected, consultation with the patient's orthopedic surgeon about the decision to perform joint aspiration in the ED and the selection and timing of antibiotics in suspected periprosthetic joint infection is advisable.

A synovial WBC count more than 1100 cells/mm^3 with more than 64% neutrophils is a sensitive and specific marker for periprosthetic joint infection in a patient with an elevated ESR (>30 mm/hr) and CRP level (>10 mg/L). Because of the difficulty in isolating infectious organisms from the prosthetic joint, even if done intraoperatively, in stable patients, antibiotics should not be started until after culture specimens are obtained.

Patients With Existing Joint Disease. Patients with underlying joint disease, especially rheumatoid arthritis or a crystal arthropathy, are at increased risk for septic arthritis. If septic arthritis is suspected, laboratory and radiographic evaluation are of lower yield in patients with these conditions compared to those without joint pathology. To reduce mortality, antibiotics are started immediately after synovial fluid is sent for testing. In patients with a crystal arthropathy, neutrophil invasion secondary to septic arthritis also leads to increased precipitation and release of crystals. Therefore, the emergency clinician who discovers crystals on joint fluid aspiration should not abandon the search for an infectious agent.

Atypical Joints. Septic arthritis can be particularly difficult to diagnose and treat if it occurs in fibrocartilaginous joints, such as the sternoclavicular, acromioclavicular, sacroiliac, or symphysis pubis. Septic arthritis of the axial skeleton, especially of the sternoclavicular joint, is commonly seen in injection drug users, with *Pseudomonas* a common infecting agent. In patients who are not injection drug users, the most common bacterial causes are *S. aureus* and *S. epidermidis*. The presentation is usually pain and point tenderness over the involved joint. Fever and an elevated ESR are commonly reported, although they are not always present because of the often suppressed immune status of the patient. As with other cases of septic arthritis and osteomyelitis, MRI with contrast is the preferred imaging modality and is helpful in the diagnosis of septic arthritis in the fibrocartilaginous joints.

Differential Diagnoses

Many disease processes can be confused with septic arthritis. Toxic or transient synovitis, an inflammatory process common in children, especially after an upper respiratory infection, can be confused with septic arthritis. It occurs in the 3-month to 6-year age range, usually affects the hip, and is a self-limited disease, with no long-term morbidity. Children with transient synovitis have less pain with passive joint motion than patients with septic arthritis; they do not usually have a fever or appear ill but tend to favor the unaffected leg, as in septic arthritis. The diagnostic evaluation typically reveals a normal WBC count and ESR and no radiographic abnormalities.

Metaphyseal osteomyelitis may mimic septic arthritis because the adjacent joint may develop an effusion, and the two infections can be concurrent. Juvenile rheumatoid arthritis is usually more gradual in onset and produces polyarticular arthritis in children younger than 16 years but may be manifested as a monoarticular process that mimics septic arthritis.

Other diseases of the hip in children that are included in the differential diagnoses are Legg-Calvé-Perthes disease (avascular necrosis of the femoral head) and slipped capital femoral epiphysis; however, these processes are not as acutely disabling as septic arthritis. Rheumatic fever commonly presents with a migrating polyarthritis and may mimic gonococcal bacteremia. Patients with Lyme arthritis are not as debilitated as those with septic arthritis. In endemic areas, serum antibody titers for Lyme should be obtained early in the evaluation of the patient with an effusion.

In the adult, osteoarthritis, gout, and pseudogout may produce findings on joint examination similar to the findings of septic arthritis. Other arthropathies, such as psoriatic arthritis, arthritis associated with inflammatory bowel disease, ankylosing spondylitis, crystal-induced arthritis, and drug-induced arthritis should also be considered in the differential diagnosis of septic arthritis. Collectively, these are known as the seronegative spondyloarthropathies. Trauma to the joint can produce synovitis and hemarthrosis, which may be mistaken for septic arthritis. In a patient with hemophilia, hemarthrosis causes joint inflammation and destruction, and there may be superimposed infection.

Reactive arthritis has traditionally been considered to be a sterile inflammatory response to a distant infection. However, antigens from the infectious trigger are often present in the joint. Several viral and bacterial microorganisms can produce reactive arthritis. The most recognized syndrome is poststreptococcal reactive arthritis. Some other common organisms that cause reactive arthritis are *Chlamydia, Salmonella, Shigella, B. burgdorferi* (Lyme disease), *Yersinia,* human T-lymphotropic virus type 1, rubella virus, hepatitis B virus, adenoviruses, parvovirus, and Epstein-Barr virus. Reactive arthritis can usually be distinguished from septic arthritis because it tends to involve multiple joints in a migratory pattern, the inflammatory process is less severe with reactive arthritis, there is less effusion, the joint is not as hot or tender as it is with septic arthritis, and joint fluid cell counts are usually below 50,000 cells/mm^3.

Diagnostic Testing

Serum and Urine Tests

Blood tests are not consistently helpful in making a diagnosis of septic arthritis. Serum leukocytosis is nonspecific and nonsensitive for diagnosis of septic arthritis. Traditionally, a serum WBC count more than 10,000 cells/mm^3 may suggest a systemic illness but is present in only 50% of patients with septic arthritis, and many sterile inflammatory

processes create a similar leukocytosis. The ESR is elevated in approximately 90% of cases and, along with the CRP level, can be used to help diagnose the infection and track resolution. When low thresholds are used in the ED, the sensitivity of ESR is reported to be 98%, with a cutoff of 10 mm/hr or more, and the sensitivity of CRP is 92%, with a threshold of 20 mg/L or more. A sensitivity of 96% for an ESR higher than 30 mm/hr has been demonstrated. A procalcitonin level more than 0.5 ng/mL is another possible serum marker for septic arthritis, but is also nonspecific and is often not readily available in the ED.[21] Synovial presepsin is another potential biomarker that seems to be both specific and sensitive in septic arthritis but needs to be tested further.[22]

Two sets of blood culture specimens should be obtained; however, blood cultures reveal the infecting organism in the minority of cases of both osteomyelitis and septic arthritis.[7,23] Cultures of infectious foci, such as the throat, cervix, and urine, may demonstrate the bacteria responsible for septic arthritis. Synovial leukocyte esterase has been studied as a possible new indicator for a septic arthritis; it is especially sensitive and specific in prosthetic joints, with initial studies showing a high sensitivity and specificity.[24]

Joint Fluid Analysis

The diagnosis of septic arthritis requires joint fluid for culture and analysis. The knee joint is the most likely to be infected and is the easiest to aspirate. Aspiration of other joints, such as the hip, often requires interventional radiology or orthopedic surgical consultation. When violating the joint capsule, aseptic technique should always be practiced. This has resulted in reducing the risk of introducing infection into a joint during intraarticular aspiration or injection, reported to be between 1 in 2000 to 1 in 15,000 injections,

Because joint fluid analysis is not performed as often as other diagnostic tests in the ED, a joint fluid protocol is useful to ensure that all necessary tests are prepared and ordered properly. To increase the bacterial yield from joint fluid, blood culture bottles should be inoculated with joint fluid immediately after joint aspiration. This allows some bacteria, which would normally die before being inoculated on culture media in the laboratory, to survive and grow in the blood culture bottle (brain-heart infusion broth). The sample should include special media to test for fastidious organisms such as *N. gonorrhoeae.* Anaerobic and fungal organisms should be cultured in patients with risk factors for these infections.

When only a small volume of synovial fluid is recovered from a joint aspiration, the single most important test is a cell count. If extra fluid is available after a cell count is obtained, other tests should be performed, including Gram stain and culture, crystal analysis, and joint fluid glucose level. The definitive test to determine bacterial arthritis is synovial culture. Tissue cultures from the operating room are more useful than fluid for identifying the offending organism and its susceptibility, but administration of antibiotics should not be delayed for these results.

Even with an adequate joint fluid sample, proper culture techniques, and the presence of fastidious organisms, synovial Gram staining results in clinically suspected septic arthritis are negative 45% to 71% of the time, likely due to the planktonic state of the bacteria in the joint. A positive result of Gram staining can be used to guide antibiotic treatment; however, empirical treatment should not be delayed if the result is negative.

Traditionally, a synovial fluid leukocyte count of more than 50,000 cells/mm^3 with a predominance of polymorphonuclear leukocytes was used to define septic arthritis, but other processes can produce similar cell counts. Up to 30% of patients with septic arthritis have been documented to have counts well below 50,000 cells/mm^3.

Many studies have not supported the idea that a specific range of elevation of the synovial fluid leukocyte count can be reliably used to diagnose septic arthritis. One large study found that a synovial fluid WBC count higher than 17,500 cells/mm^3 has a sensitivity of 83% and specificity of 67% for septic arthritis. The positive likelihood ratio at this level was 2.5, with a negative likelihood ratio of 0.25. A synovial fluid leukocyte differential count with at least 90% neutrophils suggests septic arthritis, with a likelihood ratio of 3.4; a count of less than 90% decreases the likelihood ratio. There is mounting evidence that one cannot rely solely on the synovial fluid leukocyte count to exclude or include the diagnosis of septic arthritis; this value should be used with the clinical, radiographic, and laboratory findings to help guide therapy as Gram staining and culture results become available.

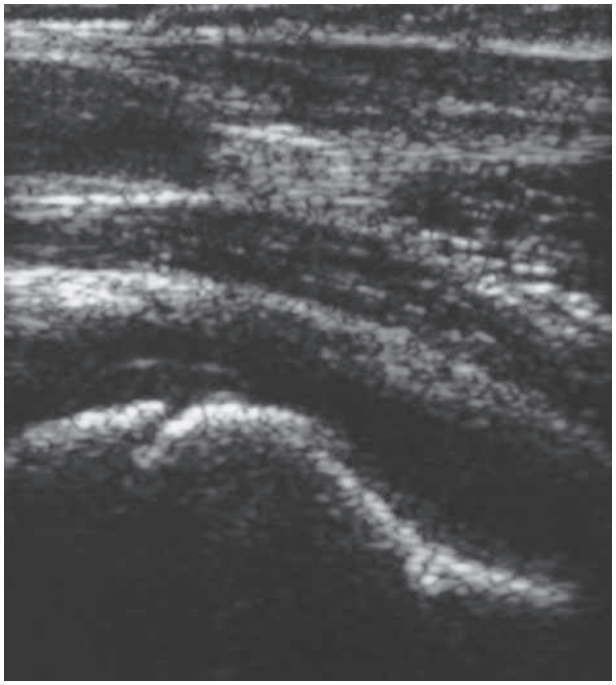

Fig. 125.9 Ultrasound image of the right hip in an 8-year-old girl with septic arthritis. A significant joint effusion can be seen just superior to the round contour of the femoral head. Joint aspiration revealed purulent fluid, with a white blood cell count of 71,000/mm^3.

The examination of synovial fluid under polarizing microscopy for the presence of crystals may be useful in the differentiation of inflammatory from noninflammatory joint disease but is not helpful in identifying infection in this population because the two often coexist. The identification of crystals does not rule out an infectious cause of the joint pain.

Imaging

Plain radiography is not an effective tool for the early evaluation of septic arthritis but may detect surrounding osteomyelitis. In most joints, the small areas of attachment of the synovial membrane to bone are devoid of cartilage. These so-called bare areas at the margins of the joint appear as lucencies or erosions early in the course of septic arthritis. Bone beneath the articular cartilage may start to erode 1 to 3 weeks into the disease. Air in the joint may be a sign of infection with gas-forming organisms but may be the result of a previous joint aspiration. In patients with existing joint disease, radiographs provide minimal assistance in the diagnosis of septic arthritis.

For joints that are not visualized, other than a physical examination, a variety of modalities are available to help detect a joint effusion, which under the right circumstances could suggest septic arthritis. Ultrasonography is a useful modality to help detect a joint effusion and assist in joint aspiration, particularly of the hip[25] (Fig. 125.9). CT and MRI provide detailed anatomic images of the joint, and MRI can also help

TABLE 125.4 Guidelines for Choice of Empirical Antibiotic Based on Gram Staining Results

Gram Stain or Clinical Condition	Probable Organism	Preferred Antibiotics	Alternative Antibiotics
Gram-positive cocci	*Staphylococcus aureus* Streptococci	Nafcillin or cefazolin	Clindamycin Trimethoprim-sulfamethoxazole Vancomycin
Gram-negative cocci or negative stain Healthy, sexually active patient	*Neisseria gonorrhoeae*	Ceftriaxone	Doxycycline
Gram-negative bacilli	*Pseudomonas aeruginosa* Enterobacteriaceae	Piperacillin ± gentamicin	Fourth-generation cephalosporin
Gram-positive bacilli	*Propionibacterium acnes*	Penicillin G	Nafcillin Vancomycin

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determine if septic arthritis is complicated by concurrent osteomyelitis. CT and MRI can identify joint fluid but not necessarily an effusion, because a volumetric analysis cannot be done to assess the amount of fluid. In adult patients with an antalgic gait and painful internal and external rotation of the hip, MRI findings of bone marrow edema led to a diagnosis of septic arthritis only 6% of the time.

Skeletal scintigraphy (bone scanning) has been used in the diagnosis of septic arthritis, but its use has been decreasing. The main advantage of skeletal scintigraphy is for the detection of septic arthritis earlier than with other imaging techniques. In septic arthritis, scintigraphy shows symmetrical areas of increased uptake on both sides of the joint. In a three-phase ^{99m}Tc scan, all three phases will be hot with septic arthritis. In general, skeletal scintigraphy is used only when there is enough uncertainty about the diagnosis to warrant further investigation. However, in joints where aspiration is easier, skeletal scintigraphy has little role in diagnosis.

Management

Septic arthritis is an orthopedic emergency and, once synovial fluid is obtained, empirical antibiotics should be promptly administered based on Gram stain results, when possible (Table 125.4). Whereas many joint infections require surgical joint irrigation and débridement, there are a few cases in which medical management will suffice, such as gonococcal septic arthritis and Lyme arthritis.

Unlike most other infectious emergencies encountered in the ED, when time to antibiotic administration decreases morbidity and mortality, definitive management for most cases of septic arthritis requires surgical intervention and a prolonged course of antibiotics. Therefore, it is more important to obtain synovial fluid for Gram staining and culture than to start antibiotics, because this will guide appropriate long-term antibiotic treatment. In the hemodynamically stable patient in whom septic arthritis is a strong consideration, antibiotics should be held until blood and synovial fluid cultures are obtained.

The selection of antibiotics for the treatment of septic arthritis is outlined in Table 125.2. In most cases, because the emergency clinician does not know the identity of the causative organism, treatment should be tailored to the most likely causative agents based on the patient's age, history, and immune status, as well as results from the gram stain.

In general, if the initial Gram stain of synovial fluid demonstrates gram-positive cocci, empirical treatment starts with vancomycin whereas empirical treatment of gram-negative bacilli starts with a cephalosporin. In cases where pseudomonas is suspected, the antibiotic regimen should consist of two antipseudomonal agents such as ceftazidime with ciprofloxacin or gentamycin. Empirical antibiotic choices when the initial Gram stain is negative but there is still a high index of suspicion for a septic joint typically start with vancomycin.

S. aureus accounts for 44% of cases and remains the predominant pathogen for all age groups. Unless gonococcal arthritis, the most common cause of arthritis in young adults, is confirmed, the antibiotic selected should be bactericidal against *S. aureus*. Empirical antibiotics active against MRSA should be considered but should be based on the prevalence of this pathogen in the community. Group B streptococci have emerged as invasive pathogens in older adults, especially those with diabetes mellitus, cirrhosis, and neurologic disease. Penicillin- and fluoroquinolone-resistant strains of gonorrhea have become more prevalent, and a third-generation cephalosporin is the best choice for gonococcal arthritis. In older adults, gram-negative septic arthritis is more common, and agents such as the third-generation cephalosporins and aminoglycosides are added to the antistaphylococcal regimen. Establishment of good bactericidal serum levels of antibiotics will ensure that the levels in joint fluid are also bactericidal. In pediatrics, the use of dexamethasone to accelerate clinical improvement is no longer recommended.[26]

Disposition

Any patient thought to have septic arthritis requires joint aspiration. Patients for whom septic arthritis is considered to be the diagnosis should be given an initial parenteral dose of antibiotics after joint aspiration in the ED and admitted for culture results and continued management. If the joint fluid aspirate is not consistent with septic arthritis and clinical findings are equivocal, the patient can be discharged and reevaluated in 24 hours. In immunosuppressed patients, patients with preexisting joint disease, and patients with a joint replacement, septic arthritis can be difficult to detect. A conservative approach with in-hospital observation and treatment should be considered if there is any possibility of septic arthritis in these patients.

The prognosis for the patient with septic arthritis is favorable in most cases. From 50% to 75% of afflicted patients can expect to recover completely and achieve full painless range of motion of the joint. About one-third of patients have complications such as decreased mobility or ankylosis, pain on joint movement, chronic infection, or overwhelming sepsis and death. The patients most likely to do poorly include those who have had a delay in diagnosis and treatment, patients with underlying joint disease (especially rheumatoid arthritis), those with polyarticular septic arthritis, and those who have positive blood cultures. Despite many advances in diagnosis and treatment, the overall morbidity for patients with septic arthritis has not decreased in the last 3 decades. A general rule is that if the diagnosis of septic arthritis is made

and treatment is initiated within 1 week of the onset of symptoms, the outcome is almost always favorable. Diagnosis and rapid treatment of septic arthritis have proven to be most elusive in two groups of patients, infants and people with existing joint disease. In infants and children, early symptoms can be nonspecific and difficult to assess; consequently, children with septic arthritis, especially of the hip, who experience a delay in diagnosis and treatment have a disappointingly high rate of complications. In patients with existing joint disease, septic arthritis may be mistaken for an acute exacerbation of the underlying disease process, so emergency clinicians must remain vigilant in their pursuit of the correct diagnosis.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 125: QUESTIONS AND ANSWERS

1. Which of the following associations between osteomyelitis and pathogenic organism is true?

a. Dog bite—*Pasteurella*
b. Freshwater wounds—*Pseudomonas*
c. Human bite—*Aeromonas*
d. Intravenous drug use—*Fusobacterium*

Answer: A. The following are correct associations: freshwater—*Aeromonas hydrophila*; intravenous drug use (IVDU)—*Staphylococcus aureus*; sickle cell—*Pseudomonas* and *Salmonella*; cat or dog bite—*Pasteurella multocida*; human bite—mixed with *Fusobacterium*, *Eikenella*, and *Streptococcus anginosus*.

2. Which of the following statements regarding septic arthritis is true?

a. Despite vaccination, *Haemophilus influenzae* remains a frequent pathogen in children.
b. *Pseudomonas aeruginosa* is associated with IVDU-related osteomyelitis.
c. *Pseudomonas aeruginosa* is not associated with prosthetic device joint infection.
d. The most common organism in neonates is *Staphylococcus aureus*.

Answer: B. *Pseudomonas* is associated with IVDU-related cervical osteomyelitis and lumbar osteomyelitis in cases of prolonged urinary catheterization. *H. influenzae* has largely disappeared as a joint pathogen in vaccinated children. The most common neonatal joint pathogens are group B streptococci, *Escherichia coli,* and *Staphylococcus epidermidis*. The most common cause of septic arthritis in people younger than 30 years is gonococcal.

3. Which of the following statements regarding acute hematogenous osteomyelitis in children is ***not*** true?

a. Blood cultures are not usually positive.
b. Skeletal scintigraphy is indicated in neonates.
c. The child usually appears toxic.
d. The most common site is the long-bone epiphysis.

Answer: C. Children may be ill but not usually toxic. There is a 2:1 or 3:1 male predominance, with the most likely site being the distal metaphysis. Blood cultures are positive in 60% of cases. Scintigraphy is not useful in neonates due to a limited inflammatory response. Radiographs are more useful and sensitive early on than in adults.

CHAPTER 125: QUESTIONS AND ANSWERS—cont'd

4. Which of the following statements regarding vertebral osteomyelitis is true?
   - **a.** Children are less prone to isolated diskitis.
   - **b.** Of the cases of epidural abscesses, 30% are due to osteomyelitis.
   - **c.** The diagnostic procedure of choice is a magnetic resonance imaging scan.
   - **d.** The most common location is the lumbar spine.

Answer: D. The incidence of associated epidural abscess is 15%. The most common location of vertebral osteomyelitis is the thoracic, lumbar, and cervical spine. The diagnostic procedure of choice is needle biopsy. The disease usually involves two vertebrae and the disk in between. Children are more prone to isolated diskitis, although it may also occur in adults.

5. An 18-year-old woman with known sickle cell disease presents with leg pain of 2 days' duration. Her typical pain syndrome is lower extremity tibial and femur pain. Today's episode is primarily right tibial. She complains bitterly of pain, but there are no gross findings other than trace bilateral anterior tibial swelling, with no discernible warmth or erythema. Vital signs are remarkable for a low-grade fever and heart rate of 110 beats/min. Which of the following statements regarding this patient's condition is true?
   - **a.** Bony infection would be expected in the bony metaphysis.
   - **b.** Plain radiography can differentiate bony infarction from infection.
   - **d.** *Staphylococcus aureus* would be the most likely infectious cause.
   - **d.** MRI is not necessary as it will not differentiate infection from infarction.

Answer: A. Sickle cell osteomyelitis is more typically seen in the diaphysis than in non–sickle cell situations, which more often involve the metaphysis. Fever, toxicity, and an elevated ESR suggest infection. The most likely infectious cause is now *Salmonella*, followed by *Staphylococcus aureus*. Often, observation and response to therapy (e.g., analgesics, hydration) ultimately help differentiate the two. When in question, an MRI should be pursued.

Skin and Soft Tissue Infections

Michael Pulia and Larissa S. May

KEY CONCEPTS

- Bacterial skin infections such as cellulitis and abscess are common and are rarely life-threatening.
- Necrotizing infection is suggested by pain out of proportion to physical findings, crepitance, gas seen on imaging studies, or clinical instability. Suspected necrotizing infection should be managed with prompt broad-spectrum antibiotics and surgical consultation.
- Emergency clinicians should be familiar with toxic shock syndrome and Rocky Mountain spotted fever, which are rare, life-threatening, systemic infections with skin manifestations.
- Antibiotics reduce treatment failure after surgical drainage of uncomplicated abscesses.
- Current recommendations for the treatment of uncomplicated cellulitis suggest selection of an agent effective against streptococci and methicillin-sensitive *Staphylococcus aureus* (MSSA) (e.g., cephalexin at maximal doses). The addition of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) coverage does not improve outcomes for uncomplicated cellulitis.
- Clindamycin is no longer recommended for routine treatment of purulent SSTIs due to increasing rates of both MSSA and CA-MRSA resistance.
- White blood cell count should not be routinely measured in patients with uncomplicated skin infections.
- Blood cultures are not necessary to evaluate skin infections, except in cases of sepsis, necrotizing infections, immunocompromised hosts, and multifocal infections suggesting hematogenous seeding.
- Mimics such as venous stasis dermatitis are often misdiagnosed as cellulitis. These conditions are termed *pseudocellulitis* and novel tools are being developed that may assist clinicians improve diagnostic accuracy (e.g., ALT-70 and surface thermal imaging).

FOUNDATIONS

Background and Importance

Skin and soft tissue infections (SSTIs) exist on a clinical spectrum from common and typically mild bacterial infections, such as cellulitis and abscess, to relatively rare conditions with high mortality, such as necrotizing fasciitis and toxic shock syndrome. As a group, SSTIs are the third most common type of infection treated in the emergency department (ED), accounting for approximately 2.5% of all encounters.[1] The epidemiology of skin infections remained relatively stable over the past decade since the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) as the predominant cause of purulent SSTIs in the early 2000s.

Anatomy and Physiology

The skin is the largest organ in the body and accounts for about 15% of total body weight. It has three layers, the hypodermis, dermis, and epidermis (Fig. 126.1). Hair is present throughout the body except on glabrous skin, which is the heavily keratinized skin found on the palms, soles, and parts of the genitals.

The skin has a rich supply of blood vessels, lymphatics, and nerves, although the epidermis is entirely avascular and relies on the dermis for nourishment. The main cell type in the epidermis is the keratinocyte, which has a cytoskeleton composed of keratin filaments, which are proteins. Also living in the epidermis is the Langerhans cell, a motile, macrophage-like, antigen-presenting member of the immune system that originates in the bone marrow. Melanocytes in the epidermis produce melanin.

The epidermis contains the pilosebaceous follicles and sweat glands, known collectively as epidermal appendages. The combination of the hair apparatus and sebaceous gland is known as a pilosebaceous follicle. The epidermal appendages are important as sites of infection because they provide a break in the otherwise continuous protective layer of keratinocytes and create a potential space for bacterial replication. There are two types, sweat glands and follicles. Sweat glands take three forms—eccrine, apocrine, and apoeccrine.

The dermal-epidermal junction is a complex basement membrane whose disruption results in vesicles and bullae. The dermis consists of cells, fibers, and ground substance, which is an acellular material composed of glycoproteins and other macromolecules. The hypodermis, or subcutaneous tissue, is composed largely of adipocytes. The lymphatic system drains interstitial fluid, and its disruption leads to interstitial fluid accumulation and edema.

Pathophysiology

The source of a skin infection may not always be evident. Skin infections may arise from nonvisible breaks in the protective epidermal layer or more obvious portals of entry such as injections, abrasions or lacerations. Hematogenous seeding from another infected site is a less common source. Venous blood and lymph drain from the orbits and skin around them into the cavernous sinuses; thus, bacterial infections in this area can lead to central nervous system infection.

CLINICAL FEATURES

Overview

Most skin infections present with redness (erythema), warmth, and induration. Erythema, caused by microvascular dilation due to the immune response, can present differently depending upon the patient's pigmentation. Thus, emergency clinicians should familiarize themselves with pathology on different skin types. Confluent erythema is typical of most skin infections; discrete macules and morbilliform (measles-like) eruptions are not typical. Induration means hardening and is a common finding with many inflammatory lesions of the skin. Skin that is indurated from cellulitis may become engorged with interstitial fluid and

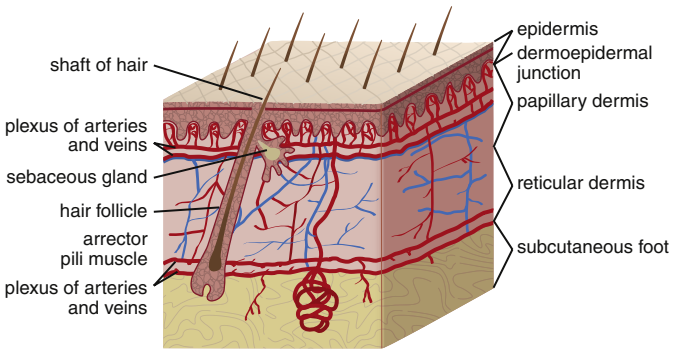

Fig. 126.1 Anatomy of the skin. (From Amirlak B: Skin anatomy. Available at http://emedicine.medscape.com/article/1294744-overview#a1.)

take on the texture of an orange peel due to dimpling where the skin is anchored by hair follicles. This classic finding is known by the French phrase *peau d'orange*. Fluctuance describes a fluid collection palpated on examination. "Pointing" or "coming to a head" conveys a sense of imminent rupture. Crepitance describes skin that feels crackly when palpated and suggests gas is present in the soft tissues.

Many skin infections have characteristic appearances. Well-demarcated erythema with a raised border, particularly on the face, is typical of erysipelas, a streptococcal cellulitis. Linear erythema tracking distally to proximally along a vascular pathway suggests lymphangitis or phlebitis. This usually represents the action of cytokines combating the infection, although proximal spread of the infection is a possibility. Vesicles suggest contact dermatitis, herpes simplex, varicella-zoster, or impetigo. Pruritic serpiginous (snakelike) lesions that are not particularly tender suggest an intracutaneous parasite, such as scabies (hands, intertriginous areas), hookworm larvae (feet or buttocks), or strongyloidiasis. Parasitic nematodes (e.g., Guinea worm) and insects (e.g., botfly) should be considered in the setting of a nodule after exposure to fresh water or insects in developing countries.

Other systemic infections may present with significant skin manifestations. Less common color changes associated with infection stem from small hemorrhages, vasculitis, or septic emboli. Janeway lesions are painless red, purple, or brown spots, usually seen on the hands or feet, due to septic emboli from infective endocarditis. Painless discolorations of the palms and soles may indicate secondary syphilis or Rocky Mountain spotted fever. Petechiae and purpura can indicate overwhelming bacterial infection, as with meningococcemia. When the diagnosis of infection is not clear, vasculitides such as Kawasaki syndrome in children and granulomatosis with polyangiitis should be considered. Intracutaneous pustules on the palms or soles of the feet are often due to a form of psoriasis called palmoplantar pustulosis, which can be uncomfortable for the patient, but is benign.

Fever is present in approximately 20% of patients with abscesses and 50% of patients with cellulitis presenting to the ED. Febrile skin infections are more common in children; in adults, fever may indicate a more serious infection. Skin infections can suggest underlying systemic illness. For example, a young man who presents with balanitis may have diabetes as the underlying problem. Disseminated varicella (other than the primary episode of chickenpox) suggests an immunocompromised state.

CELLULITIS

Clinical Features

Cellulitis is an inflammatory condition of skin and subcutaneous tissue caused by bacterial infection. Cellulitis may be purulent or nonpurulent and may occur in the setting of wounds, foreign bodies, or impaired perfusion. Purulent cellulitis drains freely, in contrast to abscesses, which are walled off by fibrous tissue and epidermis. CA-MRSA is the leading cause of purulent skin and soft tissue infections in ED patients but is not a common cause of nonpurulent cellulitis.

The cardinal feature of cellulitis is inflammation with increased local blood flow. Pain may be variable, but most patients without neuropathy have some degree of tenderness. The inflammation of cellulitis is typically confluent, although it may be patchy. The borders are typically poorly defined and irregular. Linear or circular lesions should prompt a search for other underlying causes, such as contact dermatitis or Lyme disease. In some cases of cellulitis, there are streaks of inflammation extending proximally from the main area of inflammation along vascular tracts. This finding is known as lymphangitis and is commonly seen with cellulitis due to streptococci and bite wound–associated *Pasteurella multocida*.

When localized edema becomes severe, epidermal layers can separate, leading to vesicles or bullae. This can make it challenging to distinguish cellulitis from other infectious and noninfectious causes of dermatitis. When the border of an area of cellulitis becomes well-demarcated, raised, and palpable, the term *erysipelas* is used. This form of cellulitis is most often caused by *Streptococcus pyogenes*. The bacterial causes of cellulitis vary according to body site, comorbidities, and environmental exposures (Table 126.1).

Diabetic Foot Infections

Diabetic foot infections are the most common cause of hospitalization for patients with diabetes, and an infected wound precedes two-thirds of lower extremity amputations in patients with diabetes. Neuropathy, vascular insufficiency, and hyperglycemia are important factors in the development of diabetic ulcers and foot infections. Although early antibiotic therapy is important in diabetic infections, to avoid antibiotic overuse, uninfected ulcers should not be treated with antibiotics. In addition to antibiotics, diabetic foot infections require careful wound care and, in some cases débridement, revascularization, or amputation.

The most likely organisms in an acute diabetic foot infection are *S. aureus* and streptococci. Chronic wounds are more likely to be polymicrobial with gram-positive and gram-negative organisms, as well as anaerobes. Chronic wounds that have previously been treated with antimicrobials are more likely to involve multidrug-resistant organisms. *Pseudomonas* is uncommon, although is more likely to occur in patients with diabetes than those without. Deep tissue specimens for aerobic and anaerobic culture or bone samples should be obtained at the time of débridement if deep tissue infection or osteomyelitis is suspected. Organisms cultured from superficial swabs are not reliable for identifying pathogens responsible for deeper infection. Osteomyelitis should be considered a potential complication of any deep or extensive ulcer, especially one that is chronic or overlies a bony prominence.

Bite Wounds

A high proportion of cat bites become infected and presumptive antibiotic treatment is appropriate in the absence of signs of infection. The typical agent is *Pasteurella multocida*. Human bites also become infected frequently (≈25%) with polymicrobial (mixed aerobic and anaerobic) being the predominant pattern. Typical pathogens included oral flora (e.g. *Eikenella, Fusobacterium*, group A *Streptococcus*) and skin flora (e.g., *S. aureus*). Dog bites become infected infrequently (≈16%) and do not require routine antibiotic prophylaxis.[2] However, certain circumstances warrant prophylaxis, including those on the hands, face, genitals, or areas with poor perfusion, or in immunocompromised patients.

TABLE 126.1 Skin Infections: Bacteriology and First-Line Antibiotic Therapy

Anatomic Variant or Predisposition	Likely Bacterial Cause	First-Line Therapy (Nontoxic and Immunocompetent)[a]
Uncomplicated cutaneous abscess	CA-MRSA	Incision and drainage, consider antibiotics
Nonpurulent bacterial skin infections	Various *Streptococcus* spp., *Staphylococcus aureus*	Cephalexin or clindamycin; adjunctive measures
Purulent cellulitis and wound infections	CA-MRSA, *Streptococcus* spp.	TMP-SMX or doxycycline monotherapy; adjunctive measures
Diabetic foot infection	Mixed gram-positive, gram-negative, and anaerobes	Amoxicillin–clavulanic acid plus trimethoprim-sulfamethoxazole; avoid antibiotics for uninfected ulcers.
Any cat bite or infected dog bite	*Pasteurella multocida*, others	Amoxicillin–clavulanic acid
Human bite (treat presumptively)	Oral anaerobes, others	Amoxicillin–clavulanic acid
Erythema migrans	*Borrelia burgdorferi* (Lyme disease)	Doxycycline
Puncture wound through sole of shoe (treat presumptively)	*Pseudomonas aeruginosa*	Levofloxacin
Buccal cellulitis	*Haemophilus influenzae* type b (vaccine serotype)	Ceftriaxone or ampicillin-sulbactam
Balanitis	*Candida albicans* or group A streptococcus	Fluconazole plus penicillin or amoxicillin; consider diabetes
Liposuction	*Peptostreptococcus* (anaerobe), group A streptococcus	Ampicillin–clavulanic acid ± trimethoprim-sulfamethoxazole
Saltwater exposure	*Vibrio vulnificus*	Doxycycline
Freshwater exposure	*Aeromonas* species	Ciprofloxacin
Butcher, clam handler, veterinarian	*Erysipelothrix rhusiopathiae*	Amoxicillin
Black necrotic eschar with raised border and severe surrounding edema	*Bacillus anthracis* (anthrax)	Ciprofloxacin

[a]For life- or limb-threatening infections, use IV equivalents and add vancomycin.
CA-MRSA, Community-associated methicillin-resistant Staphylococcus aureus.

Water-Borne Infections

Exposure and travel history are important considerations in the evaluation of skin and soft tissue infections. *Vibrio* spp., in particular *Vibrio vulnificus*, are associated with exposure to seawater and can cause severe soft tissue infections and sepsis. Patients with liver disease, such as cirrhosis, are particularly at risk. Infection occurs from contamination of open wounds by seawater or shellfish and rarely by hematogenous spread from the ingestion of contaminated seafood, such as raw oysters. *Edwardsiella tarda* is a rare cause of wound infection after seawater exposure; it has been implicated in serious soft tissue infections, including myonecrosis, particularly in patients with liver disease. *Erysipelothrix rhusiopathiae* is usually associated with a localized erysipeloid eruption with minor trauma, often on the hands of seafood workers.

Aeromonas myonecrosis is associated with exposure to fresh water by penetrating trauma or exposure to aquatic animals. It causes rapidly progressive suppurative infections that often require surgical drainage. *Mycobacterium marinum* causes so-called fish tank granuloma. It typically is manifested weeks after exposure as a papule or nodule that may ulcerate and drain serosanguineous fluid. Multiple nodular lesions may develop along the lymphatics.

Differential Diagnosis

Consideration of potential mimics (i.e., pseudocellulitis) is critical when assessing potential cellulitis because the misdiagnosis rate may be as high as 30% in the ED. Common examples of pseudocellulitis include venous stasis dermatitis, burns, viral infections, fixed drug eruptions, lymphedema, venous thrombosis, gout, and contact dermatitis.[3,4] Venous stasis dermatitis in particular may appear similar to cellulitis. It is typically located above the ankle and is often (but not always) circumferential. Persistent erythema despite elevating the affected limb suggests cellulitis. Cellulitis is rarely bilateral and alternative diagnosis should strongly be considered with this presentation. Symmetric venous stasis dermatitis in the afebrile patient should not be confused with cellulitis. The ALT-70 (asymmetry, leukocytosis, tachycardia, age ≥70 years) scoring system has recently been proposed to help differentiate cellulitis from pseudocellulitis but requires further validation before utilization in clinical practice.[5,6] When any dermatologic presentation is accompanied by fever or lymphangitis, co-occurring cellulitis should be considered. Cellulitis must always be distinguished from more severe necrotizing infections, as discussed later.

Lyme disease causes a rash known as erythema chronicum migrans which can mimic cellulitis. It a bright red, round lesion, usually larger than 5 cm, with central clearing that gives a targetoid appearance. It occurs in only 80% of cases of Lyme disease. When the rash is observed in an endemic area, Lyme disease can be diagnosed and treated without further testing. Lyme disease is transmitted by the deer tick, *Ixodes scapularis*, and attachment of the tick for at least 24 hours is necessary for infection. Noninfectious, localized bite reactions from insects, arthropods, and hymenoptera can be mistaken for cellulitis despite their rapid development. In contrast, cellulitis typically develops over a period of days. The time course should be considered before initiation of antibiotics.

Diagnostic Testing

Wound Cultures

For nonpurulent cellulitis, needle aspiration, superficial swabs, and skin biopsy are unlikely to reveal the cause and are not recommended for typical cases. These can be considered in complex cases involving purulent cellulitis, immunocompromised patients, immersion injuries, surgical wound infections, or animal bites.[2]

Blood Cultures

Blood cultures are not indicated in patients with uncomplicated cellulitis. They are recommended in cases involving immunocompromised patients or those with systemic infection (e.g., sepsis). In the past, blood cultures were recommended for facial cellulitis, due to concern over *Haemophilus influenzae* bacteremia. However, the relevant strain (type b) is now covered by childhood vaccination, leading to a revision of this recommendation.

Radiographic Studies

Radiographic studies are not part of the standard diagnostic process for cellulitis but should be utilized in certain clinical scenarios. When a foreign body is suspected, plain radiographs are obtained, although they occasionally miss small or radiolucent foreign bodies. Ultrasonography can detect many foreign bodies. The location and extraction of foreign bodies can be challenging, however, and emergency clinicians must use their judgment in deciding when to use plain films, ultrasound, or both.

If necrotizing infection is suspected, plain radiographs or computed tomography (CT) may reveal soft tissue gas or inflammation along fascial planes, but cannot rule out necrotizing infection. Ultrasound examination is useful for differentiating abscess from cellulitis, as discussed later.

Plain radiographs are used to evaluate for evidence of osteomyelitis for chronic skin infections, especially in patients with diabetes, peripheral vascular disease, and secondarily infected nonhealing ulcers. Plain films are not definitive, and magnetic resonance imaging (MRI) has higher sensitivity for detecting osteomyelitis. CT with intravenous contrast is helpful when there is concern that a skin infection is an extension of a deeper infection (e.g., post-surgery).

Surface Thermal Imaging

Specialized cameras capable of measuring skin surface temperature have been proposed as a means to help differentiate cellulitis from pseudocellulitis by replacing the subjective assessment of tissue temperature through touch with quantitative data. In a recent study, temperature gradients between affected and unaffected limbs were observed to be significantly greater for cellulitis cases as compared to pseudocellulitis.[7] The use of surface temperature gradients in the diagnosis of cellulitis will require further validation before use in routine practice.

Management

Fig. 126.2 is a universal treatment algorithm for skin and soft tissue infections. The algorithm assumes no prior treatment as previously treated infections failing therapy generally require broader spectrum antibiotic coverage and customized management decisions. Table 126.2 summarizes the most commonly used antibiotics for skin and soft tissue infections. As *Streptococcus* spp. and *Staphylococcus aureus* are the predominant organisms causing cellulitis, first-line therapy is cephalexin 500 mg, four times daily for at least 5 days, or an equivalent oral β-lactam (e.g., penicillin VK, dicloxacillin). Trials examining the addition of CA-MRSA coverage for uncomplicated, nonpurulent cellulitis found no reduction in treatment failure and is not recommended.[8,9] CA-MRSA coverage should be added for all cases of purulent cellulitis and cases of treatment failure. The most common strain of CA-MRSA is highly susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), making this the first-line empiric therapy. Critically ill patients (e.g., severe sepsis/shock) with suspected skin infection source should receive broad-spectrum empiric antibiotics, vancomycin plus piperacillin/tazobactam, and the emergency clinician should assess for a necrotizing soft tissue infection. Vancomycin is the recommended parenteral agent for MRSA.[2]

Two long-acting, broad-spectrum antibiotics, oritavancin and dalbavancin, recently have been approved for skin and soft tissue infections. These novel lipoglycopeptides cover all major cellulitis pathogens, including MRSA, and have extremely long half-lives. This results in oritavancin requiring only a single IV infusion for an entire treatment course and dalbavancin using a single IV infusion per week regimen. Clinical experience with these agents is limited but they have been proposed as a cost-effective alternative to hospital admission for complicated skin and soft tissue infections without an absolute need for admission (e.g., sepsis) or when concerns exist about medication compliance.[10-12] Due to the cost and logistical concerns (i.e., infusion time, follow-up plan) associated with these agents, we recommend using them only as part of an established ED pathway developed in partnership with pharmacy and infectious diseases.

We recommend amoxicillin–clavulanic acid for 3 to 5 days as a prophylactic regimen for high-risk bite wounds (i.e., cat or human source, puncture wound, immunocompromised patient, wounds to the hands/face, or penetrating the periosteum/joint capsule.) It is also the first-line agent for infected bite wounds. Doxycycline and moxifloxacin are second-line alternatives.[2] For severe infections, ampicillin-sulbactam is the first-line IV agent.

Patients allergic to penicillin may safely take cephalosporins in most cases due to limited cross-reactivity.[13] For patients with a cephalosporin or life-threatening penicillin allergy (e.g., anaphylaxis), clindamycin is the first-line alternative.

Although adjunctive measures are commonly recommended in the treatment of cellulitis. Extremity cellulitis responds dramatically to compression and elevation. Patients with cellulitis complicating venous stasis or lymphedema should be educated about the importance of compression with elastic socks, sleeves, or wraps. This is helpful for the acute infection and to prevent future episodes. Nonsteroidal antiinflammatory drugs (NSAIDs; e.g., ibuprofen) are helpful for pain control in the absence of contraindications.

Table. 126.1 summarizes the common skin and soft tissue infections, including causative organisms and first-line treatment. Recommendations in the table assume no treatment failure, necrotizing infection, or systemic illness. Cases involving these scenarios require broader-spectrum antibiotic coverage and customized management decisions.

Disposition

Immunocompetent patients with cellulitis who can take oral medications and adjunctive measures can be managed as outpatients. Hospitalization is generally required for patients with systemic symptoms (i.e., fever), immunosuppression, diabetic foot infections, infected lymphedema, or large, multifocal cellulitis. In severe cases, such as sepsis, broad-spectrum IV antibiotics are initiated in the ED prior to admission. ED infusion of novel lipoglycopeptides may represent an alternative option to admission for patients without an absolute indication for hospitalization.

ABSCESS

Clinical Features

An abscess begins when bacteria multiply beneath the epidermis. Neutrophils are drawn to the site of infection, and various cytokines combine with bacterial toxins to promote the development of purulence. A furuncle, or boil, is an abscess of the hair follicle. A carbuncle comprises multiple furuncles with loculations and connecting sinuses, often with multiple sites of drainage. Carbuncles are more likely to occur on the back of the neck and are more prevalent in diabetics.

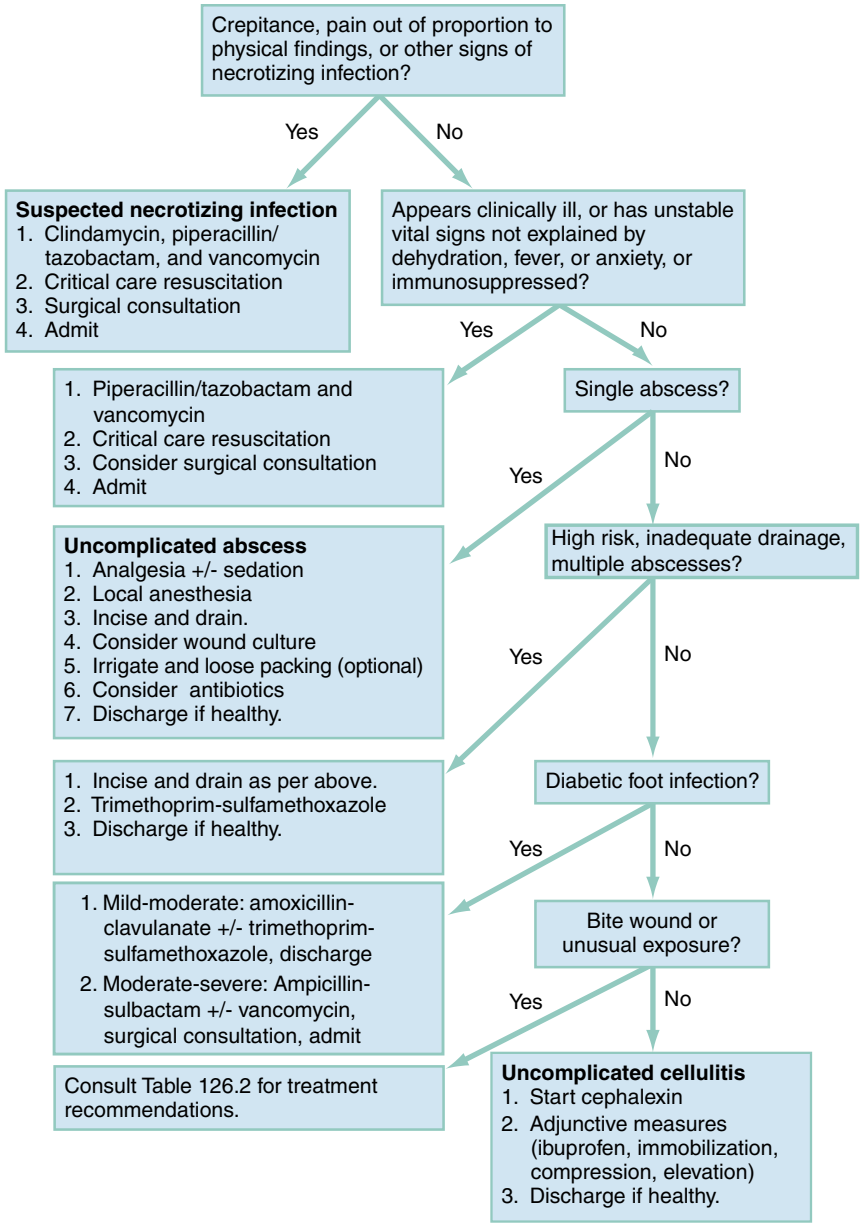

Fig. 126.2 Universal algorithm for skin and soft tissue infections, assuming no prior treatment.

In cutaneous abscesses, the overlying epidermis often prevents drainage and a painful, warm, and erythematous mass is usually seen. Skin abscesses rarely lead to systemic illness and most will eventually rupture through the epidermis and drain spontaneously. Historically, abscesses were caused by MSSA or mixed flora, but today CA-MRSA accounts for the majority of cases in the United States. Whirlpool baths at nail salons have been implicated in mycobacterial furunculosis.

Bartholin gland abscess is caused by an obstructed Bartholin duct. Bartholin gland is located at the upper part of the lower third of the labium majus, and its duct opens onto the mucosa in this area medially but externally to the labium minus. Bacteria cultured are usually a mixture of aerobic and anaerobic flora from the vagina. *Chlamydia trachomatis* or *Neisseria gonorrhoeae* is isolated approximately 10% of the time.

A pilonidal abscess is an abscess at the superior aspect of the gluteal cleft between the buttocks. Because they result from an infected pilonidal cyst, these abscesses are typically recurrent. Acute treatment is the same as for other cutaneous abscesses but patients should be referred for surgical excision of the cyst in recurrent cases.

A stitch abscess is a collection of pus around a suture. Stitch abscesses are generally caused by an inflammatory response in the suture tract and sterile. However, deeper wound infection can be confused with a stitch abscess.

Differential Diagnosis and Diagnostic Testing

The differentiation of abscess from cellulitis can be challenging. Bedside ultrasound examination with a high-frequency linear probe is the best option, improving diagnostic accuracy and management.[14] Abscesses are seen as hypoechoic areas with posterior acoustic enhancement. The hypoechoic areas are pus and may be heterogeneous, with some bright signals (Fig. 126.3A). Cellulitis is seen as a uniformly hyperechoic area or as hyperechoic areas separated by curvilinear hypoechoic areas (see Fig. 126.3B). This appearance is known as cobblestoning and results from interstitial edema.

TABLE 126.2 First-Line Oral Antibiotics for Skin and Soft Tissue Infection

Drug	Mechanism of Action	Pediatric Dose (Mg/Kg; Adult Dose Is Max)	Adult Dose (Mg)	Frequency (Doses/Day)	Special Instructions	Strep	MSSA	MRSA	Anaerobes
Cephalexin	Cell wall synthesis, bactericidal	12.5 qid	500 (max dose 2000 per day)	4		+	+	–	–
Dicloxacillin	Cell wall synthesis, bactericidal	10	250–500	4	Empty stomach	+	+	–	–
Amoxicillin	Cell wall synthesis, bactericidal	15	500	3		+	+	–	±
Amoxicillin–clavulanic acid	Cell wall synthesis, bactericidal	25 bid[a]	875 or 2000 for extended release formulation[a]	2		+	+	–	+
Clindamycin	Ribosome, bacteriostatic	10	300–450	3		+	+	±	±
Trimethoprim-sulfamethoxazole	DNA synthesis (folate metabolism), bacteriostatic	10[b]	160[b]	2	Warfarin interaction, avoid with glucose-6-phosphate dehydrogenase or folate deficiency	–	+	+	±
Doxycycline	Ribosome, bacteriostatic	2.2[c]	100	2	Empty stomach, sun sensitivity	±	+	+	–

[a]Dose by amoxicillin component.
[b]Dose by trimethoprim.
[c]Only for ≥ 8 years old.
MRSA, methicillin-resistant *S.* aureus; *MSSA*, methicillin-sensitive *S.* aureus.

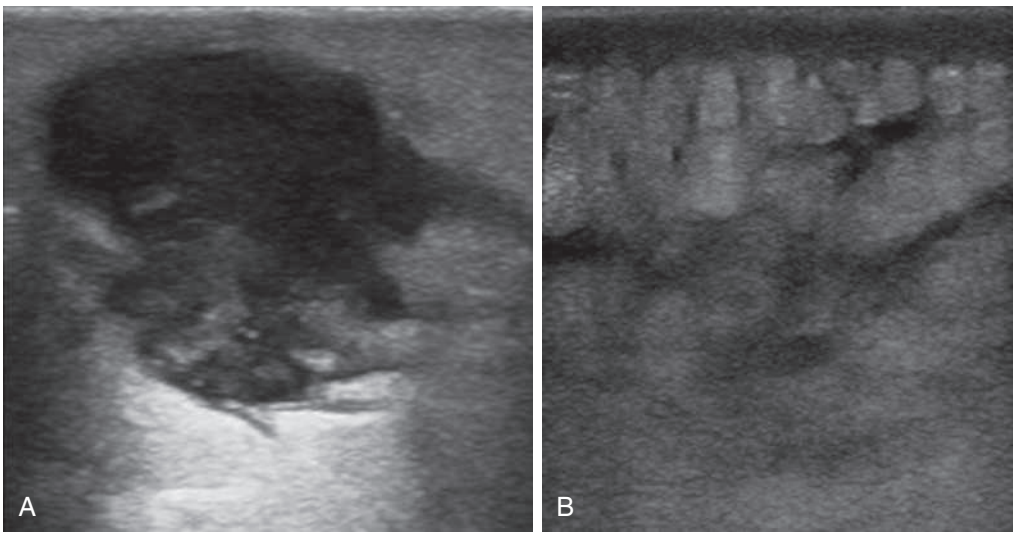

Fig. 126.3 Ultrasound examination to distinguish abscess from cellulitis. (A) Abscess visualized with 8-MHz linear probe demonstrating dark areas (pus) with posterior acoustic enhancement. (B) Cellulitis visualized with 8-MHz linear probe demonstrating cobblestoning. (Courtesy Dr. Mark W. Byrne, Department of Emergency Medicine, Brigham and Women's Hospital, Boston.)

Necrotizing fasciitis is always a consideration, although it is extremely rare relative to cellulitis. Fistula should be considered when perianal, perirectal, or perivaginal infections are evaluated, and the mucosa should be examined digitally. When perirectal abscess recurs, a deep abscess may be the source, and external examination may be unreliable. In this case, CT scanning should be performed.

The epidermoid cyst represents another diagnostic challenge. These lesions, formerly known as sebaceous cysts, are benign cystic tumors resulting from the pathologic accumulation of keratinaceous material. Patients report a long history of a cutaneous mass, often intermittently painful. These lesions become inflamed periodically and sometimes rupture spontaneously. With rupture, they drain a pearly white or yellowish, glistening, waxy material. Pus, which appears dull and viscous rather than waxy, may indicate an infected epidermoid cyst. Isolated mild inflammation of an epidermoid cyst does not contraindicate primary excision, although primary excision is more difficult during an

episode of inflammation. A brief course of antibiotics and NSAIDs with delayed excision is also an option.

Vascular aneurysms and enlarged lymph nodes can be misdiagnosed as abscesses. Ultrasound examination is helpful to distinguish the pathology, and a color Doppler study should be used to investigate perivascular abscesses. When there is doubt, needle aspiration should be used to confirm the presence of pus and absence of blood.

Inflamed cutaneous nodules and cystic masses in returning travelers and immigrants from developing countries present special diagnostic challenges. Typical staphylococcal abscesses are most common, but parasitic causes, such as dracunculiasis and myiasis, should be considered.

Management

The primary treatment of abscess is surgical drainage. Needle aspiration alone has not been found to be an adequate alternative to incision and blunt dissection.

Abscess incision and drainage is a nonsterile procedure, but the operator and all environmental fomites should be protected from contamination and transmission of infectious material. The main challenge is to attain adequate analgesia. Injection of local anesthetics into the skin overlying an abscess is difficult because the skin is usually edematous and tense. Also, superficial anesthesia is often inadequate for blunt dissection. An alternative is to administer procedural sedation. Another excellent option is regional anesthesia with a nerve block. Oral analgesia plus a ring block may also provide adequate anesthesia and analgesia. The following medications are safe together and have additive effects: ibuprofen, acetaminophen, oxycodone, and low-dose diazepam. The ring block is performed with a 25-gauge needle (3.5-inch spinal needle for large areas) to inject bupivacaine in a ring around the abscess, with as few punctures through the skin surface as possible and with care taken that the injection not spread bacteria from infected to healthy tissue. At least 20 minutes should be allowed for this to take effect.

Once anesthesia has been attained, incision and drainage of an abscess involves four steps—incision, blunt dissection to disrupt loculations, irrigation, and packing. The skin is prepared with povidone-iodine, although this is a nonsterile procedure and expensive sterile gloves are not needed. A single incision across the abscess is made, but there is little evidence to guide us in determining how large to make the incision. Incisions parallel to cutaneous tension lines will leave smaller scars. A small clamp is used to probe the cavity and disrupt loculations by opening the clamp through the loculations. Blunt dissection rarely risks injury to vessels and nerves, but the initial sharp incision should be made with such structures in mind. The drained cavity can be irrigated to break loculations further, although there is no evidence to support the practice. Traditionally, the abscess is then packed and left to heal without closure; however, packing may increase pain and the evidence to support this practice is lacking. The loop technique, which involves placing a tied sterile rubber tube through the central incision and a secondary lateral incision, allows continuous drainage and has been proposed as a less painful alternative to traditional packing.[15,16] There is insufficient evidence to institute routine use of loop drainage or primary closure of abscesses immediately after incision and drainage, although these can be considered on a case by case basis.

Bartholin abscesses are drained from the mucosal rather than from the cutaneous surface. The Word catheter is a device used to keep the surgical wound from closing (Fig. 126.4) because the abscess will recur if the wound is allowed to close. A very small incision (≈3 mm) is made, and the cavity is drained. The catheter is inserted and inflated with about 4 mL of water or saline. The catheter should be left in place for 4 to 6 weeks so that a sinus tract will have time to form. Sitz baths may help keep the area clean and draining. Marsupialization is used in recurrent cases to prevent further recurrences and is usually deferred

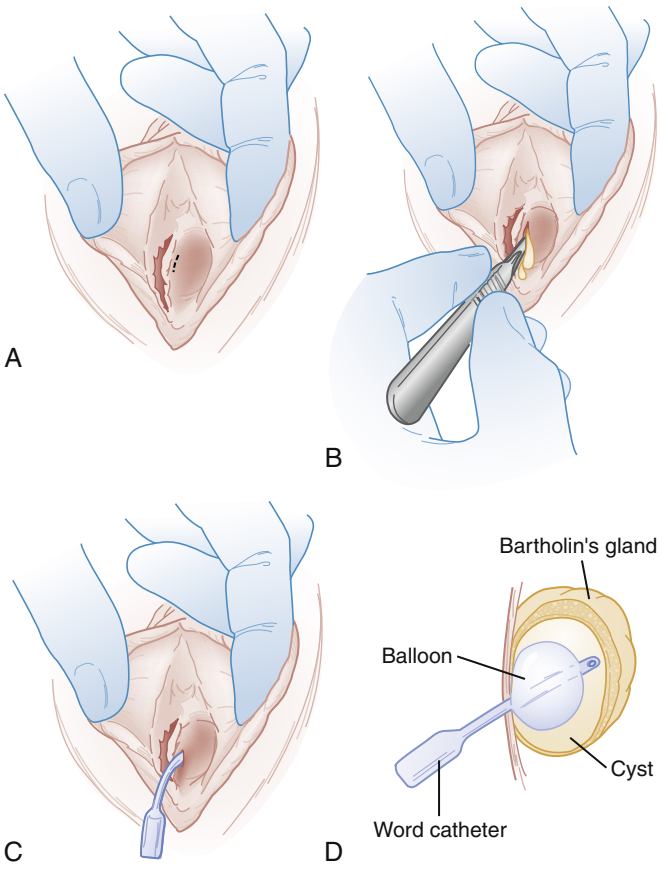

Fig. 126.4 (A–D) Drainage of Bartholin abscess and use of a Word catheter.

until the acute inflammation has subsided. A large incision is made, and the interior of the abscess is then sutured to the surrounding mucosa so that the abscess is sutured open.

The optimal approach to adjunct antibiotics following an adequate incision and drainage of abscesses is a matter of ongoing controversy.[17,18] Two recent, large randomized controlled trials focused on uncomplicated abscesses demonstrated a reduction in treatment failure (including recurrent abscesses) with antibiotic therapy. However, the numbers needed to treat ranged from 7 to 26 depending on how treatment failure was defined. A majority of patients in the control groups had clinical cure without antibiotics (70% to 90%).[19,20] Subgroup analysis of one trial demonstrated that patients with history of MRSA, MRSA as the causative organism, or fever derived the most benefit from antibiotic therapy.[21] Expert consensus suggests antibiotic decisions following incision and drainage for uncomplicated abscesses include an individualized patient risk/benefit assessment and shared decision making.[17,18] Routine antibiotics are recommended in patients with limited access to follow-up care and in severe or complicated cases, including: multiple sites of infection, associated cellulitis, systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, genitalia), septic phlebitis, and poor response to incision and drainage alone (see Fig. 126.2).

Universal wound cultures for uncomplicated abscesses are not recommended but they should be considered in cases of recurrent infections, treatment failure, or when considering treating with more than one antibiotic to facilitate tailoring of therapy. Although not widely implemented, rapid (≈90 minute) MSSA/MRSA polymerase chain reaction assays are available and can assist in tailoring of therapy to a single agent when providers are considering dual antibiotic coverage.[22]

Disposition

Patients can be discharged to home after incision and drainage of an uncomplicated abscess. It is traditional to schedule one or more visits for wound checks, but many patients can remove the packing themselves after 2 to 4 days and be instructed to return for reevaluation only in cases of persistent or worsening pain or other symptoms indicative of treatment failure. Admission can be considered for severe or complicated cases as defined previously.

IMPETIGO

Impetigo is a common superficial skin infection that is most prevalent in children aged 2 to 5 years, but it can occur at any age. It is communicable, spread by person to person transmission, autoinoculation, and fomites. It may be manifested as an infection of previously intact skin or may infect skin that has been damaged from minor trauma or atopic dermatitis.

Impetigo rarely progresses to systemic illness. However, most cases of poststreptococcal glomerulonephritis are believed to be caused by impetigo and not pharyngitis. Its onset is usually 10 days after the onset of impetigo but may occur up to 5 weeks later.

Clinical Features and Management

The two main forms of impetigo are nonbullous and bullous. Nonbullous impetigo, or impetigo contagiosa, is the most common. It was believed for many years that group A streptococci were the primary cause of this disorder, but studies have subsequently shown that most cases are due to *S. aureus*. Approximately one-third of cases have *S. pyogenes* isolated, usually in combination with *S. aureus*. The lesions begin as thin-walled vesicles that progress to pustules; subsequent rupture results in the characteristic so-called honey crusted lesions, typically found on the face or extremities. Associated lymphadenopathy is common.

Bullous impetigo is caused by *S. aureus,* including CA-MRSA. The bacteria produce an epidermolytic toxin that causes separation of the dermal-epidermal junction, resulting in bullae. The lesions in bullous impetigo are fewer and larger (0.5–3 cm) but rupture less readily than the vesicles of the nonbullous form. After rupture, the bullae leave a thin brown crust.

Ecthyma, or deep impetigo, is a less common ulcerative form of impetigo that extends through the epidermis into the dermis. It is manifested as ulcers with a punched-out appearance, with raised reddened margins covered with thick crust. It has a predilection for the lower extremities. Unlike impetigo, ecthyma can result in cutaneous scarring. Impetigo can be confused with contact dermatitis, varicella, herpes simplex, bullous pemphigoid, and Stevens-Johnson syndrome. It does not affect mucous membranes.

Nonbullous impetigo should be treated with topical mupirocin, which is active against most MRSA strains; however, extensive disease or multiple lesions should be treated with oral agents effective against MRSA. Bullous impetigo should be treated with systemic antibiotics active against MRSA and streptococcus (e.g., cephalexin plus trimethoprim-sulfamethoxazole). Ecthyma should also be treated with oral antibiotics, but it is rarely caused by CA-MRSA. Therefore, we recommend 7 days of either cephalexin or dicloxacillin as first-line treatment.

FOLLICULITIS

Folliculitis is a superficial inflammation of the hair follicle that is limited to the epidermis. It has many causes, including eosinophilic and drug-related factors, but it is usually an infection due to *S. aureus*.

Clinical Features and Management

Folliculitis is diagnosed clinically by its characteristic appearance of a small (2–5 mm), raised, erythematous, painful, tender lesion(s) that is typically pruritic. It can affect any hair-bearing area of the skin and is often associated with shaving. Folliculitis barbae involves the shaved beard area of the face or shaved scalp. Hot tub folliculitis is a pruritic condition caused by *Pseudomonas aeruginosa* that develops within 48 hours of bathing in a contaminated hot tub or swimming pool or from use of contaminated sponges. The rash consists of larger pustules and may have well-demarcated margins, typically involving the area of skin that was under the bathing suit. Candidal folliculitis occurs primarily in immunosuppressed patients and in individuals treated with broad-spectrum antibiotics. Eosinophilic folliculitis is a noninfectious recurrent disorder of unknown cause. It is more likely to occur in immunocompromised patients and is considered an AIDS-defining illness.

Folliculitis usually resolves on its own but can be treated with warm compresses or topical mupirocin. Multiple sites or a large cluster can warrant systemic antibiotics, although no randomized trials have been conducted on the efficacy of this treatment. Shaving of the involved area should be avoided. Hot tub folliculitis usually resolves on its own without specific treatment, but antihistamines and ciprofloxacin are treatment options. Fungal folliculitis is treated with topical antifungal agents. AIDS-associated folliculitis may be eosinophilic or fungal and may be treated with isotretinoin topically or systemic antifungals, respectively.

ACNE VULGARIS AND HIDRADENITIS SUPPURATIVA (ACNE INVERSA)

Acne vulgaris is a common cutaneous disorder involving the face, neck, or proximal upper extremities. It has an increased prevalence in adolescence with a male predominance. The exact pathogenic mechanism of acne is unknown but it is thought to originate in the sebaceous glands via androgen-mediated increased production of sebum and subsequent overgrowth of bacteria. An immune response then results in the formation of inflammatory papules, pustules, and nodules. Hidradenitis suppurativa (acne inversa) is an exquisitely painful condition usually seen in the axilla. It may also occur in other apocrine gland–bearing skin, including the perineum, breasts, and inner thighs. It is about three times more common in females than in males. There is some familial predisposition. The typical onset is between puberty and 40 years. It is currently believed to be an acneiform disorder that begins with follicular occlusion, rather than infection of the sweat glands. This has led to suggestions that the term *hidradenitis suppurativa,* which means suppurative inflammation of the sweat glands, be replaced with the term *acne inversa,* which implies an origin of follicular obstruction. The pathophysiologic mechanism remains incompletely understood and is likely to be a complex interaction of hormonal, environmental, and genetic factors.

Clinical Features and Management

Acne vulgaris manifests as papules, pustules, and nodules of varying severity. It is not typically associated with cellulitis or abscess formation. Acne fulminans is a rare complication involving large nodular lesions with associated ulcerations that can have systemic manifestations. Additional known complications include folliculitis, scarring, hyperpigmentation, and adverse psychosocial effects. The clinical course of hidradenitis varies from intermittent isolated inflamed nodules to recurrent draining cysts and sinuses that can progress to a chronic and debilitating condition that is difficult to treat. Recurrences can lead to scarring, sinus tract formation, and disfigurement. This is

a debilitating disease, and patients suffer not only from pain but also from social stigma due to the odor that may accompany the lesions and may suffer reactive depression.

Recommended therapies for acne vulgaris include oral doxycycline, topical clindamycin, or topical retinoids. Acne fulminans is managed with systemic steroids initially followed by isotretinoin, and dermatology consultation is recommended.

For hidradenitis, incision of painful nondraining lesions can be considered for symptomatic relief although it is uncertain whether this accelerates healing. Systemic antibiotics are usually prescribed for symptomatic lesions and should cover CA-MRSA. Perianal and vulvar manifestations of Crohn disease can mimic hidradenitis and should be considered as part of the differential for lesions in these areas. Perianal and vulvar hidradenitis lesions should be treated more broadly with agents active against CA-MRSA, gram-negative organisms, and anaerobes. Amoxicillin–clavulanic acid plus trimethoprim-sulfamethoxazole is recommended in this scenario.

The optimal approach to long-term management of hidradenitis is unclear. Options include immunomodulators (e.g., steroids, cyclosporine), hormones, and en bloc resection. All patients should be instructed to stop smoking and keep the affected area(s) clean and dry. Pain control is essential. Patients rarely show signs of systemic illness and thus can be discharged and referred to a plastic surgeon or dermatologist.

NECROTIZING SKIN AND SOFT TISSUE INFECTIONS

Clinical Features

Necrotizing infections progress rapidly, cause extensive tissue destruction, and can be fatal despite prompt treatment. Clinical manifestations that suggest a necrotizing infection are signs of systemic toxicity, including abnormal vital signs, severe pain or pain out of proportion to physical findings, altered mental status, rapidly advancing infection, crepitus, hemorrhage, sloughing, and blistering. Some patients appear well at presentation, and overlying skin may not be involved initially. Extensive tissue destruction occurs eventually; the mortality rate is 20%.

Risk factors include diabetes, vascular insufficiency, and immunosuppression, although healthy people are vulnerable. Inciting events include penetrating trauma, recent surgery, varicella infection, injection drug use, burns, and childbirth.

Typical bacterial isolates include group A beta-streptococci, *S. aureus*, including CA-MRSA, enterococci, Enterobacteriaceae, and the anaerobes *Bacteroides* and *Clostridium*. Most cases are polymicrobial. The classification schemes historically used for necrotizing infections are less important than optimizing early identification and pursuing prompt surgical treatment.

Necrotizing fasciitis is an aggressive infection of subcutaneous tissues that spreads rapidly along fascial planes. In the operating room, the fasciae are inflamed, and tissue layers separate friably. It is caused by direct extension from a skin lesion in 80% of cases. Two types are described. Type I is polymicrobial, with aerobes and anaerobes; it is more common in diabetics and immunocompromised individuals. Type II is caused by a single organism, and occurs in any age group and in patients who are not chronically ill. Group A streptococci are most common, and CA-MRSA is also a cause, although it appears to be less virulent. Initial symptoms may be vague (e.g., malaise, fever, body aches, nausea, diarrhea). There may initially be diffuse or fusiform swelling of an extremity, or it may appear to be a simple cellulitis or wound infection. Physical findings may not be obvious initially, and pain out of proportion to physical findings can be an early clinical indicator. Eventually, the skin turns violaceous or ecchymotic. Anesthesia may develop over the involved tissue because of infarction of superficial nerves. Subsequent inflammation may result in the classic sign of "woody" subcutaneous tissues.

Skin infections in the perineum warrant extra caution. *Fournier gangrene* is the term given to necrotizing polymicrobial infections of the perineum. Fournier gangrene progresses rapidly to extend to the entire perineum or abdominal wall. It can be recognized by severe pain, tenderness, and induration.

Myonecrosis, myositis, and pyomyositis refer to infections of muscle, which are rare. They may result from local spread of an adjacent infection, penetrating trauma, vascular insufficiency, or hematogenous spread. Clostridial myonecrosis, also known as gas gangrene, has two forms, a more common traumatic form and a rare spontaneous form. The traumatic form typically occurs from an injury that results in an interruption in the blood supply, and crush injuries are often implicated. The infection is most commonly due to *Clostridium perfringens,* a gram-positive spore-forming bacillus that is ubiquitous in nature, including the human body. Inoculation of the organism into tissue with low oxygen tension allows proliferation. Exotoxins destroy tissue, contribute to shock, and may cause intravascular hemolysis, with anemia and disseminated intravascular coagulation (DIC). Patients present with severe pain. The skin may initially be pale, then bronze, and eventually purplish red. Hemorrhagic bullae may develop. Soft tissue gas may not be present initially. Systemic toxicity and shock ensue when aggressive treatment is not initiated early and sometimes occur despite aggressive treatment. The spontaneous form of clostridial myonecrosis is very rare and occurs without any inciting wound. It is usually due to *Clostridium septicum* and occurs in patients with bowel disease, such as colon cancer. Synergistic nonclostridial myonecrosis is a related syndrome, usually seen in the immunocompromised.

Anaerobic streptococcal myositis usually results from trauma or is a postoperative complication. It resembles clostridial myonecrosis but has a more insidious course. It is caused by anaerobic streptococci, including *Peptostreptococcus,* but the infection may also include group A streptococci and *S. aureus*.

Spontaneous gangrenous myositis—also known as spontaneous streptococcal gangrenous myositis, group A streptococcal necrotizing myositis, or streptococcal myonecrosis—is rare but aggressive and fatal in most cases. It occurs spontaneously, without trauma, in immunocompetent hosts. Gangrenous necrosis of skeletal muscle then results in severe pain, with tense local swelling.

Pyomyositis is a deep abscess within striated muscle resulting from the hematogenous spread of bacteria in the setting of muscle injury. It is usually due to *S. aureus,* including CA-MRSA, and is more common in those who are immunocompromised. Mortality is less than 10%.

Differential Diagnosis and Diagnostic Testing

A necrotizing infection should be considered when a patient with a skin or soft tissue complaint presents with a rapidly progressing course or pain out of proportion to clinical findings. It should also be considered when the patient appears systemically ill (tachypnea, hypotension) or has tachycardia not explained by fever or dehydration. Crepitance or radiographic air is diagnostic of a necrotizing infection unless there is another explanation (e.g., recent surgery).

Phlegmasia cerulea dolens is iliofemoral vein thrombosis, which can be confused with necrotizing fasciitis. Arterial insufficiency causes gangrene, and it may be difficult to determine whether infection is present in severe or chronic cases. Similarly, compartment syndrome can be confused with necrotizing infection or coexist with it.

The diagnostic gold standard is the characteristic appearance of the tissue by direct visualization in the operating room. Some surgeons may elect to perform an exploration at the bedside.

The use of blood tests as part of scoring systems to help differentiate necrotizing infections from other skin infections has been proposed (e.g., Laboratory Risk Indicator for Necrotizing Fasciitis [LRINEC]). While laboratory values and scoring systems can assist in risk stratification, given the catastrophic consequences of delayed diagnosis and lack of validation, they should not be used alone to guide clinical decision making. The diagnosis of necrotizing infection remains clinical. Universal laboratory screening of well-appearing patients with uncomplicated skin and soft tissue infections is not recommended to evaluate for this rare condition.

Plain radiographs may show air in the soft tissues, but absence of this finding does not rule out necrotizing infection. Ultrasound examination can visualize the abscess of pyomyositis and evaluation for subcutaneous thickening, air, and fascial fluid (STAFF exam) has been proposed as a rapid modality for diagnosis, especially in unstable patients. CT and MRI may show compelling evidence of a necrotizing infection but can be time-consuming and delay definitive management. There is no established optimal use of imaging in these cases. The decision to pursue imaging depends on a patient's clinical status and the consistency of their presentation with a necrotizing soft tissue infection. If clinical suspicion is high, the diagnosis should not be ruled out solely based on any imaging modality.

Management and Disposition

Patients with suspected necrotizing infections should be treated for sepsis, with IV fluids as indicated by their hemodynamics and prompt administration of broad-spectrum antimicrobials. A good empiric regimen is clindamycin plus a broad-spectrum β-lactam such as piperacillin-tazobactam (gram negatives, anaerobes, *Streptococcus* spp., *Pseudomonas aeruginosa*) plus vancomycin (*S. aureus*, MRSA). Clindamycin, in addition to providing bacterial coverage, may reduce bacterial toxin (virulence proteins) synthesis and reduce disease severity.[23] Maximal doses of all antibiotics should be used.

When a necrotizing infection is suspected, a surgeon should be consulted in tandem with the diagnostic workup. The patient should be prepared for the operating room by being made NPO, ordering coagulation studies, and a type and screen. Repeated operative débridement is often needed. Fasciotomies are often necessary because these syndromes are associated with elevated compartment pressures, which contribute to myonecrosis. The efficacy of hyperbaric oxygen in the management of necrotizing infections is unproven, and treatment should not delay surgery.

TOXIC SHOCK SYNDROMES

Clinical Features

The main systemic, toxin-mediated, bacterial skin syndromes are streptococcal toxic shock syndrome, staphylococcal toxic shock syndrome, and staphylococcal scaled skin syndrome. These are caused by bacterial exotoxins known as superantigens because they cause a severe and pathologic host immune system response by stimulating T lymphocyte activation and functioning as mitogens in vitro. Systemic disease results from the immune system's response to the toxin, but may be accompanied by or simply resemble bacteremic septic shock (Table 126.3).

Streptococcal Toxic Shock Syndrome

Streptococcal toxic shock syndrome (TSS) is a severe, toxin-mediated syndrome that rapidly progresses to shock, with multiorgan failure and death. Identified in the mid-1980s, this syndrome is caused by group A streptococci, often in the setting of a severe soft tissue infection. Most victims were previously healthy. Rarely, TSS can occur as a complication of disseminated varicella (chickenpox).

Invasive group A streptococcal infections are often due to M-type isolates with potent exotoxins. Signs and symptoms are caused by pyrogenic exotoxins A and B. These act as superantigens and cause overactivation of T cells with a massive release of cytokines, including interleukins and tumor necrosis factor.

Patients may have an influenza-like prodrome with nausea, vomiting, diarrhea, myalgias, and chills. High fever, hypotension, and tachycardia are typical. Altered mental status with confusion is common. A diffuse rash is present in 10% of cases, which may make differentiation from staphylococcal TSS more difficult.

On presentation, the patient has a severe streptococcal infection; necrotizing fasciitis is present in 50% of cases. Pain is often out of proportion to physical findings. Most patients present with shock or develop it within 4 to 6 hours. Bacteremia is common, with positive blood cultures in about 60% of cases. Serious multisystem complications are common, including DIC, acute renal failure, and acute respiratory distress syndrome. In contrast to staphylococcal TSS, which is infrequently fatal, about 30% to 80% of patients diagnosed with streptococcal TSS die. Epidermolysis, typical of staphylococcal TSS, is not characteristic of the streptococcal variety.

TABLE 126.3 Comparison of Features of Streptococcal Toxic Shock Syndrome (TSS), Staphylococcal Toxic Shock Syndrome, and Staphylococcal Scalded Skin Syndrome (SSSS)

Parameter	Streptococcal TSS	Staphylococcal TSS	SSSS
Organism	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Staphylococcus aureus*
Toxin	Pyrogenic exotoxins	TSS type 1; enterotoxins A, B, C	Epidermolytic toxin A or B
Patient	Previously healthy	Previously healthy	Infant
Source	Necrotizing infection	Nasal or wound packing, tampon; infection not obvious	Skin flora
Rash	Erythematous rash in only 10%; stigmata of necrotizing infection present; exfoliation weeks later	Initially diffuse erythroderma, with exfoliation after 1–2 wk; mucosal hyperemia	Tender erythematous rash, localized blisters, extensive exfoliation if no antibodies to toxin; mucosa spared
Systemic illness	Hypotension, shock, multiorgan failure likely	Hypotension, shock, sometimes multiorgan failure	Fever, irritability
Mortality	30%–80%	<5%	<5%
Treatment	Critical care resuscitation, operative debridement	Critical care resuscitation	Wound care, hydration

Staphylococcal Toxic Shock Syndrome

Although staphylococcal TSS is not as severe as the streptococcal variety, it remains a life-threatening systemic illness. The classic presentation is of fever, rash, and hypotension, often in previously healthy patients. It was first described in 1978 and, beginning in 1980, there was an epidemic of cases associated with the use of highly absorbent tampons. Menses-associated cases have since declined dramatically when these tampons were eliminated from the market, although tampon use remains a risk factor.

Nonmenstrual cases, which currently account for about 50% of cases, are associated with various conditions, including surgical procedures (e.g., rhinoplasty, abortion), nasal packing, burns, injection drug use, and the postpartum state. To the emergency clinician, menstrual and nonmenstrual staphylococcal TSS appear similar, and the source infection is often not readily apparent. Of note, prevention of TSS was a traditional indication for systemic antibiotic therapy after nasal packing for epistaxis, but recent evidence has suggested that this is not necessary, and topical antibiotics may be a preferred approach.

S. aureus exotoxins are superantigens that can activate large numbers of T lymphocytes, resulting in the massive release of inflammatory mediators, including interleukins, tumor necrosis factors, and interferon. Toxic shock syndrome toxin 1 (TSST-1) is associated with most menstrual cases. A lack of antibody against this toxin has been demonstrated in patients with menstrual staphylococcal TSS. Episodes of recurrent staphylococcal TSS have been reported in patients who do not mount a long-term antibody response, and it has been postulated that the toxin may interfere with antibody generation against itself.

Patients often have an acute onset of fever, chills, malaise, myalgia, muscle tenderness, and diffuse blanching macular rash that is not pruritic. There may be nausea, vomiting, or diarrhea. Patients may have fever and altered mental status.

Severe hypotension may ensue as a result of massive vasodilation and fluid shifts out of the intravascular space. Toxic cardiomyopathy may also contribute to low blood pressure. Hypotension or rhabdomyolysis may cause acute tubular necrosis. Anemia, thrombocytopenia, and leukocytosis are common, and DIC may develop. Desquamation of the skin, including the palms and soles, eventually occurs 7 to 14 days after onset. The overall mortality is below 5% with aggressive supportive care.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a desquamating skin disorder caused by exfoliating toxins produced by *S. aureus*. A disease of infants, it is rare in older children and adults. It can cause outbreaks in nurseries and daycare centers. SSSS was historically known as fourth disease and as Ritter's disease in newborns.

SSSS is caused by certain strains of *S. aureus,* including CA-MRSA, that produce epidermolytic toxin A or epidermolytic toxin B. These toxins probably act as proteases that target the protein desmoglein 1 on the stratum granulosum layer of the epidermis. Whether they meet the T lymphocyte mitogenic criterion for a superantigen has been a subject of debate.

The severity of the disease ranges from a few blisters at the site of infection to exfoliation of most of the body. People with preexisting toxin antibodies develop the localized form, in which toxin is found in the wound periphery; those without preexisting toxin antibodies develop the generalized form, in which toxin spreads through the bloodstream. Cultures of the bullae are negative unless they are contaminated or secondarily infected.

Typically, a young child presents with fever, irritability, and tender red rash. The erythema progresses to bullae formation and subsequent exfoliation of the affected skin. The skin exhibits the Nikolsky sign, which is separation of the epidermal layer of skin on gentle stroking. Desquamation may be patchy or sheet-like, leaving the skin denuded, with a red moist base and predisposing it to secondary infection. Perioral, perianal, and flexural skin may be affected more severely. Mucous membranes are spared. SSSS is not associated with multisystem illness and typically does not lead to shock. Mortality is usually a result of complications from comorbid conditions or superimposed infection.

Differential Diagnosis and Diagnostic Testing

Streptococcal TSS should be suspected in any patient presenting with shock, especially if the patient was previously healthy. Diagnostic criteria for streptococcal TSS include the presence of group A streptococcal infection, hypotension, and two of the following: renal impairment, liver abnormalities, acute respiratory distress syndrome, coagulopathy, necrotic soft tissue infection, and rash. These criteria were developed for epidemiologic purposes; failure to meet all criteria should not exclude the clinical diagnosis in suspicious cases.

Staphylococcal TSS should be considered in any patient presenting with diffuse rash and hypotension. The diagnosis is made on the basis of the clinical presentation. The characteristic rash often raises suspicion and ultimately aids in establishment of the diagnosis. Isolation of *S. aureus* is not necessary for the diagnosis to be made; in fact, blood cultures are positive in a small minority of cases. In severe cases, laboratory abnormalities are those resulting from shock and organ damage.

Early SSSS may be difficult to differentiate from bullous impetigo. The lack of mucosal involvement helps differentiate SSSS from toxic epidermal necrolysis and Stevens-Johnson syndrome. Other differential considerations include Kawasaki syndrome, Rocky Mountain spotted fever, meningococcemia, leptospirosis, and heatstroke.

Management

Streptococcal and staphylococcal TSS require critical care resuscitation. In streptococcal TSS, immediate surgical consultation for operative débridement of necrotizing infections is critical. In staphylococcal TSS, any potential source of infection should be removed, such as tampons or wound packing, and all postoperative wounds should be explored for infection. Clindamycin and vancomycin should be administered. Gram-negative coverage should be added when the diagnosis of TSS is uncertain because the clinical picture overlaps with that of septic shock.

IV immune globulin has theoretical benefit, but its efficacy has not been shown in clinical trials. It is a reasonable option in cases of presumed staphylococcal TSS unresponsive to IV fluids and vasopressors, but is not commonly employed in the ED setting. There has been conflicting evidence on its efficacy for the treatment of streptococcal TSS. SSSS is treated with antibiotics active against *S. aureus,* including MRSA. Wound care and hydration are important.

Disposition

Patients with suspected TSS should be admitted, usually to the intensive care unit, for IV fluids, antibiotics, and close monitoring due to the potential for decompensation. Patients with necrotizing soft tissue infections associated with streptococcal TSS usually require surgical débridement.

Children with mild SSSS may be considered for outpatient management with oral antibiotics and close follow-up. Those with more severe skin involvement often need admission for pain control, temperature regulation, and fluid and electrolyte management. Severely affected patients may need intensive or burn center care. With proper supportive care and antibiotic treatment, the prognosis is excellent, with an overall mortality of less than 5%. Scarring is rarely severe.

OTHER INFECTIONS WITH SKIN MANIFESTATIONS

Borrelia burgdorferi is the spirochete that causes Lyme disease, endemic in the United States, especially in New England. It produces a characteristic targetoid rash known as erythema migrans, which emerges one week on average after the infecting tick bite. The targetoid appearance results from central clearing of the erythema. However, 20% of Lyme disease patients do not report a rash, and the rash does not always have the characteristic round and targetoid appearance.

Another spirochete, *Treponema pallidum* (syphilis), is an increasingly rare cause of rash. The primary lesion of syphilis is a painless ulcer at the inoculation site, known as a chancre, with raised borders and regional lymphadenopathy. The chancre appears days to months after infection and resolves in approximately 1 month. Secondary syphilis develops weeks to months later in about 25% of infected patients. It involves a rash that can take any form other than vesicular and includes the palms and soles; there is usually diffuse lymphadenopathy. Syphilis is uncommon in the United States, although about 10,000 cases still occur annually.

Rocky Mountain spotted fever, caused by *Rickettsia rickettsii,* is even more uncommon, diagnosed only about 2000 times each year in the United States. A few days after a bite by a dog tick or wood tick, the characteristic rash begins on the wrists and spreads everywhere, including the palms and soles. It starts macular and becomes petechial and then dusky. Of those infected, 10% never develop a rash. The untreated mortality for Rocky Mountain spotted fever approaches 25%, but treated patients do well.

Cutaneous anthrax is transmitted from animal products of infected animals, such as wool or pelts, to exposed areas of veterinarians and farmers. A spore of the gram-positive anaerobe *Bacillus anthracis* enters a break in the skin and, after an incubation period of about 1 week, a vesicle forms. This ruptures, leaving a shallow-based ulcer with a raised border. The lesion progresses to painless necrosis and the characteristic eschar. Severe surrounding edema is due to bacterial toxins. The lesions may be confused with recluse spider bites. Unlike the case with inhalational anthrax, treated cases do well, and even untreated cases have a mortality rate of less than 20%.

Tularemia is a rare disease resulting from exposure to animals such as rodents, rabbits, and hares and is endemic in much of the United States, especially the south central states. The ulceroglandular form is most common and involves an influenza-like illness with a single raised ulcer that has a mild central eschar formation. The lesion itself is raised, rather than the border, which might suggest anthrax.

The floor of the mouth is a dangerous location for soft tissue infections. Severe infections may progress to Ludwig angina, in which the floor of the mouth becomes severely indurated. Ludwig angina can be fatal due to airway obstruction. Broad-spectrum antibiotics are indicated. Steroids may reduce swelling. Intubation should be considered and a difficult airway anticipated.

Scabies is a skin infestation of the parasitic mite *Sarcoptes scabiei*. It is endemic worldwide and can cause institutional outbreaks. Lesions are most prominent on the dorsal aspect of the hand and in intertriginous areas. It is diagnosed by visualization of characteristic burrows and, in ambiguous cases, by microscopy of skin scrapings. It is treated with topical permethrin or a single dose of oral ivermectin (200 μg/kg). Norwegian scabies, also known as crusted scabies, is an aggressive infestation in the immunocompromised; it is treated with permethrin and ivermectin.

Cat-scratch disease results from *Bartonella henselae* infection after a cat bite or scratch. Its hallmark is regional lymphadenopathy that appears weeks after a primary lesion at the site of inoculation. Treatment is with a standard 5-day course of azithromycin, with a double dose on day 1.

Strongyloidiasis is caused by infection with the parasitic helminth *Strongyloides stercoralis*. Skin lesions can appear years after infection and are urticarial or serpiginous. A rapidly extending burrow that is pruritic and erythematous is diagnostic; this finding, due to rapid migration of larvae in the skin, is known as larva currens (running larva). Such findings or unexplained eosinophilia in people who have lived in Southeast Asia or tropical Africa should prompt consideration of strongyloidiasis. Diagnosis is by an enzyme-linked immunosorbent assay performed on serum. Detection is important because, unlike other nematodes, strongyloides can complete its life cycle in the human host, leading to lifelong infection. When the infected patient becomes immunosuppressed by medications or illness, the strongyloides hyperinfection syndrome can result and is often fatal.

Cutaneous larva migrans is another serpiginous skin lesion caused by migrating larvae. In this case, the organism is hookworm, and the site is typically the foot or buttock; it is often seen after a vacation on the beach in Mexico. Treatment is with a single dose of ivermectin 200 mg/kg.

Cutaneous leishmaniasis is common in many parts of the world and is found on every continent except Australia and Antarctica. It is caused by protozoans of the genus *Leishmania* and is transmitted by sandflies. Lesions are most common on the face and are painless, ulcerative, and disfiguring. Papules in returning travelers and immigrants should raise suspicion of myiasis (botfly) and, rarely, dracunculiasis (Guinea worm).

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 126: QUESTIONS AND ANSWERS

1. Which of the following statements regarding cellulitis is true?

- **a.** Bilateral cellulitis of the lower extremities is a common bacterial infection.
- **b.** Computed tomography (CT) can rule out necrotizing fasciitis.
- **c.** Fever and leukocytosis are key to the diagnosis.
- **d.** Needle aspiration of the uncomplicated cellulitis is unlikely to identify the causative organism.
- **e.** Ultrasound evaluation cannot rule out a large abscess.

Answer: D. Needle aspiration and even biopsy are rarely able to identify a causative organism in nonpurulent cellulitis. Necrotizing fasciitis is a clinical diagnosis and cannot be ruled out with a CT. Fever and leukocytosis are often absent, and measurement of the white blood cell count is not indicated. Ultrasound evaluation is sensitive and specific and can rule out a large abscess, although distinguishing small abscesses from the cobblestoning of cellulitis can be difficult. Bilateral lower extremity inflammation is usually venous stasis dermatitis, which can be confused with cellulitis. Bilateral cellulitis is rare and suggests hematogenous dissemination.

2. A 53-year-old woman presents with fever and painful swelling of the left side of her face. The physical examination is remarkable for a toxic-appearing woman with a sharply demarcated, raised, bright red, and extremely tender eruption involving the left side of her face. Which of the following statements regarding this patient's condition is true?

- **a.** Echocardiography is indicated.
- **b.** Fluoroquinolones are first-line antibiotics.
- **c.** Penicillin G monotherapy is the correct treatment.
- **d.** The face is the most commonly involved site.
- **e.** There is an association with glomerulonephritis.

Answer: E. Erysipelas is an acute cellulitis typically caused by group A streptococci. It presents with an angry red area of inflammation that is well-demarcated from the surrounding skin and has a raised border. Like other group A streptococcal skin infections, erysipelas can give rise to poststreptococcal glomerulonephritis. Penicillin G is probably the ideal therapy, but any toxic-appearing patient should be treated

more aggressively, with goal-directed therapy and broad-spectrum antibiotic coverage. *H. influenzae* is a classic cause of facial cellulitis but is more common in children, is rare in the era of HiB vaccination, and typically causes transdermal cellulitis, rather than the more superficial form of cellulitis known as erysipelas. The lower extremities are usually involved.

3. A 5-month-old girl presents with fever and a diffuse dermatitis characterized by bulla formation, with surrounding vesicles leading to the loss of large sheets of epidermis. She has no past medical history and has been on no medications. The areas of desquamation are tender and red. Which of the following statements regarding this patient's condition is true?
   - **a.** Antibiotics are not indicated.
   - **b.** Corticosteroids will help prevent progression.
   - **c.** Culture of the bullae is not indicated.
   - **d.** Mortality is greater than 30%.
   - **e.** Mucous membranes are likely affected.

Answer: C. Staphylococcal scalded skin syndrome is a toxin-mediated process occurring in the very young (6 months–6 years) and older adults. The cornerstone of treatment is resuscitation and prompt administration of antistaphylococcal antibiotics. Culture of bulla fluid is generally negative. Mucous membranes are spared. This condition is rarely fatal.

4. A 7-year-old boy presents with a left leg rash. The mother describes an initial sequence of a patch of small red papules that rapidly became vesicular, then pustular, and then crusted over. The emergency physician observes a 2- × 3-cm area on the left thigh with heavily crusted erythematous macules. There is moderate left inguinal lymphadenopathy. The lesions are not tender, and the child is not toxic-appearing. Which of the following statements regarding this patient's condition is true?
   - **a.** Acute rheumatic fever is a risk.
   - **b.** Corticosteroids are indicated.
   - **c.** Systemic antibiotics are necessary.
   - **d.** The streptozyme test is highly reliable.
   - **e.** Topical mupirocin is indicated.

Answer: E. Impetigo involves a blistering eruption with a honey-colored crust. It may be caused by streptococci or staphylococci. For limited disease, topical mupirocin is the treatment of choice. Oral or systemic antibiotics are only indicated for more severe cases. Corticosteroids are not indicated. No laboratory test is useful. Acute rheumatic fever does not occur after impetigo, but poststreptococcal glomerulonephritis may occur.

5. Which of the following statements about antibiotic therapy for skin infections is true?
   - **a.** Dual coverage of CA-MRSA and *Streptococcus* spp. reduces treatment failure for uncomplicated cellulitis.
   - **b.** Uncomplicated abscesses should always be treated with dual antibiotic therapy covering CA-MRSA and *Streptococcus* spp. after incision and drainage.
   - **c.** Single-dose intravenous antibiotics are recommended prior to discharge for uncomplicated cellulitis to reduce treatment failure.
   - **d.** Clindamycin should be included in the antibiotic regimen for necrotizing infections.
   - **e.** Mammalian bites should routinely receive CA-MRSA coverage.

Answer: D. Multiple trials suggest that dual antibiotic therapy does not improve outcomes for uncomplicated cellulitis. Recent data suggest a margin of benefit for systemic antibiotic after incision and drainage but there is no support for routine dual antibiotic therapy. Single intravenous doses prior to ED discharge have not been demonstrated to reduce outpatient treatment failure. Given its potential to mediate toxin production, clindamycin should be included in the initial antibiotic regimen for necrotizing infections, along with agents providing broad-spectrum gram-positive and gram-negative coverage. CA-MRSA is not considered a common pathogen in mammalian bites and amoxicillin–clavulanic acid is first-line therapy.

6. A young woman presents complaining of a painful itchy rash. She has just returned from a vacation in the Caribbean, where she was snorkeling. Examination reveals streaks of erythema with slight vesiculation along the lateral aspect of the right leg. The lesions are oriented diagonally, not along vascular lines, and are about 15 cm long. What is the most appropriate next step in this patient's management?
   - **a.** Obtain a CT scan to assess for necrotizing fasciitis.
   - **b.** Perform a Tzanck smear on an unroofed vesicle.
   - **c.** Treat with acyclovir.
   - **d.** Treat with corticosteroids.
   - **e.** Treat with trimethoprim-sulfamethoxazole.

Answer: D. This is an example of contact dermatitis, likely from seaweed or jellyfish stings. Nothing in the presentation is suggestive of an infection. Trimethoprim-sulfamethoxazole monotherapy is rarely appropriate because abscesses generally do not require antibiotics, and streptococci are thought to be covered poorly by this antibiotic. A Tzanck smear and acyclovir treatment would be appropriate if herpetic infection were suspected, but neither herpes simplex nor varicella zoster would present with 15-cm streaks.

Sepsis Syndrome

Nathan I. Shapiro and Alan E. Jones

KEY CONCEPTS

- Sepsis is a progressive disease due to a dysregulated inflammatory cascade, leading to organ dysfunction and circulatory compromise in severe cases.
- Older adults, immunocompromised and neutropenic patients, and patients with multiple comorbidities are at increased risk for the development of sepsis syndromes.
- A thorough history, physical examination, and laboratory testing should guide the diagnostic evaluation.
- Early treatment should focus on appropriate identification, improvement of tissue perfusion (through the administration of fluids and vasopressor medications), improvement of tissue oxygenation (through administration of oxygen and positive-pressure ventilation), administration of antibiotics, and early identification of infections requiring surgical management.
- Prompt administration of antibiotics is essential and should be based on the suspected source of infection.

FOUNDATIONS

Background

Sepsis syndrome represents the body's host response to an infection. The causative agent and host's activated inflammatory cascade overwhelm the body's defenses and regulatory systems, leading to disruption in homeostasis. Tachycardia, tachypnea, fever, and immune system activation are common manifestations. If the body is unable to overcome this insult, cellular injury, tissue damage, shock, multiorgan failure, or death may ensue.

In 1992, the American College of Chest Physicians and Society of Critical Care Medicine issued a consensus statement to establish uniform criteria defining the sepsis syndromes. The goal was to create a common nomenclature for disease classification and systematic comparisons across studies of septic patients. The term *systemic inflammatory response syndrome* (SIRS) is defined as two or more of the following: tachycardia, tachypnea, hyperthermia or hypothermia, high or low white blood cell count, or bandemia. Sepsis is the combination of infection plus SIRS, severe sepsis is sepsis plus organ dysfunction, and septic shock is sepsis plus hypotension, defined as a systolic blood pressure below 90 mm Hg, not responsive to a fluid challenge (Box 127.1). This nomenclature is intended to provide clinicians and researchers with a common classification. Efforts to validate this classification scheme in the emergency department (ED) population have demonstrated that the term *sepsis,* when characterized by fulfilling the SIRS criteria alone, is overly sensitive and nonspecific and does not convey an increased mortality risk. SIRS is not specific because it can be present in noninfectious inflammatory states and in localized infections that are not inclined to lead to sepsis, such as streptococcal pharyngitis or viral illnesses. However, organ dysfunction and shock have been shown to portend worse outcomes.

The Third International Consensus Definitions Task Force (SEP-3) is a group who revisited the sepsis definitions and published a set of revised definitions.[1] The quick SOFA (qSOFA) score emerged as a risk stratification tool for the Emergency Department (ED).[2] The qSOFA score uses three clinical criteria with each receiving one point if present: respiratory rate of 22 breaths or less per minute, altered mental status, and hypotension defined by a systolic blood pressure (SBP) 100 mm Hg or less. A qSOFA score of two or greater was associated with an increased risk of mortality. The definitions group proposed using a suspected infection plus a qSOFA of 2 or greater to help identify patients with potential sepsis in the non-ICU setting. Subsequent validation studies have called the accuracy into question; ultimately it appears that it is a reasonable tool that is less sensitive and more specific than the original sepsis criteria. However, consensus is lacking as to whether it should be used to define sepsis.[3]

Bacteremia may be present, but positive cultures are not obligatory in the diagnosis of sepsis. Culture-negative and culture-positive septic populations have similar outcomes in patients with similar illness severity. Pneumonia, abdominal abscess with viscus perforation, and pyelonephritis are common primary causes of sepsis. Gram-positive organisms account for 25% to 50% of infections, gram-negative organisms for 30% to 60%, and fungi for 2% to 10%. The distribution varies with the study and, more importantly, with host factors such as the status of the host immune system, age of the patient, recent hospitalizations, and presence of indwelling vascular catheters.

The health status of the host is an important risk factor in the development and progression of sepsis. Older adults and those with multiple comorbidities may be more susceptible to developing a systemic infection. Chemotherapy-induced neutropenia, acquired immunodeficiency syndrome, and steroid dependency increase susceptibility to sepsis. Increased use of indwelling devices such as intravascular catheters, prosthetic devices, and endotracheal tubes also contribute to the risk of systemic infection and sepsis.

Pathophysiology

Sepsis results from the complex interaction of detection molecules, signaling molecules, and numerous inflammatory and coagulation mediators in response to infection. Although our understanding of the pathophysiologic process of sepsis has evolved, it remains incomplete. The initial host response is to mobilize inflammatory cells, particularly neutrophils and macrophages, to the site of infection. These inflammatory cells then release circulating molecules, including cytokines, which trigger a cascade of other inflammatory mediators that result in a coordinated host response. Synthesis of the components of the cascade is increased at many steps along the pathway. If these mediators are not appropriately regulated, sepsis will occur. In the setting of

BOX 127.1 Definitions of Sepsis

- Bacteremia (fungemia)—presence of viable bacteria (fungi) in the blood, as evidenced by positive blood cultures
- Systemic inflammatory response syndrome (SIRS)—at least two of the following conditions: oral temperature > 38°C (100.4°F) or < 35°C (95°F); respiratory rate > 20 breaths/min or partial pressure of arterial carbon dioxide ($Paco_2$) < 32 mm Hg; heart rate > 90 beats/min; leukocyte count > 12,000/dL or < 4000/dL; or >10% bands
- Sepsis—systemic inflammatory response syndrome (SIRS) that has a proven or suspected microbial source
- Septic shock—sepsis with hypotension that is unresponsive to fluid resuscitation plus organ dysfunction or perfusion abnormalities, as listed for severe sepsis
- Multiple organ dysfunction syndrome (MODS)—dysfunction of more than one organ, requiring intervention homeostasis

Adapted from: Bone R, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The APP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101:1644-1655.

ongoing toxin release, a persistent inflammatory response occurs, with ongoing mediator activation, cellular hypoxia, tissue injury, shock, multiorgan failure, and potentially death.

Mediators of Sepsis

Host response and pathogen characteristics are both important in the pathogenesis of sepsis. More than 100 discrete markers have been identified and attributed to the sepsis cascade, but the true culprits have not been clearly identified.[1] A pathogen is sensed by pattern recognition receptors, most notably Toll-like receptors, located on the surface of the white blood cell. The resulting host-pathogen interaction activates the inflammatory and coagulation cascades. The subsequent inflammatory signaling occurs through cytokines, chemokines, and other soluble mediators, including increased circulating levels of the interleukins IL-1, IL-6, and IL-8 and tumor necrosis factor alpha (TNF-α). Activation of the clotting cascade may result in increased D-dimer levels and decreased circulating levels of protein C.

In benign conditions, a self-limited response helps clear the pathogen. If the innate immune response is inadequate, mediators create a procoagulant state. Coagulation and fibrinolytic components are proinflammatory, precipitating a worsening cycle of procoagulant and proinflammatory mediators. Propagation of this cascade ultimately contributes to end-organ damage and often to disseminated intravascular coagulation (DIC). If it is not effectively reversed, the process leads to cellular hypoxia, organ dysfunction, shock, and death.

The primary mediators are cytokines that are primarily proinflammatory, antiinflammatory, or growth-promoting. The molecular mechanisms whereby they are regulated are not well understood. An initial cytokine, TNF-α, is found in serum approximately 90 minutes after the administration of endotoxin to healthy volunteers. IL-6 and IL-8 reach peak levels at approximately 120 minutes. The main proinflammatory cytokines include IL-1, TNF-α, and IL-8. The primary antiinflammatory cytokines are IL-10, IL-6, transforming growth factor-β, soluble receptors to TNF, and IL-1 receptor antagonist (IL-1RA). If the resultant inflammatory response is adequate, the infection is controlled and cleared. If the response is deficient or excessive, however, a persistent and worsening cascade is produced, ultimately leading to (once again) shock, organ failure, and potentially death.

Instability in vascular tone has become increasingly important in understanding the pathophysiologic mechanism of sepsis. Vasopressin, also known as antidiuretic hormone, is a naturally occurring hormone that is essential for cardiovascular stability. It is produced as a prohormone in the hypothalamus. The hormone is stored in the pituitary gland and released in response to stressors such as pain, hypoxia, hypovolemia, and hyperosmolality. In severe sepsis, there is a brief rise in circulating vasopressin levels followed by a prolonged and severe suppression. This pattern of secretion is different from other forms of shock, in which vasopressin levels remain elevated. Vasopressin has numerous physiologic effects, including vasoconstriction of the systemic vasculature, osmoregulation, and maintenance of normovolemia.

Nitric oxide (NO) is a gas that has an important role in septic shock, regulating vascular tone by an indirect effect on smooth muscle cells. NO also contributes to platelet adhesion, insulin secretion, neurotransmission, tissue injury, and inflammation and cytotoxicity. Its half-life is short (6–10 seconds), and it easily diffuses into cells. Although its mechanisms of action are not well understood, it seems to be a key mediator of sepsis. Animal data have shown that nitric oxide synthase, the enzyme that produces NO, is upregulated in cases of sepsis. Enhanced NO production is thought to contribute to the profound vasodilation found in patients in septic shock.

In the setting of ongoing inflammatory activation, the mediators of sepsis continue to be produced, and the cascade is perpetuated. Unless it is appropriately and rapidly controlled, the ultimate effect is a sequence of events starting with cellular dysfunction and ultimately leading to tissue damage, organ dysfunction, and death.

Organ System Dysfunction

The organ dysfunction that results from sepsis is central to the pathogenesis of the disease. The mortality of patients with sepsis increases as the number of failing organs increases (Fig. 127.1A). In one large study, the mortality rate was 1% for sepsis patients with no organ dysfunction, whereas the rates for patients with dysfunction of a single organ, two organs, three organs, and four or more organs were 6%, 13%, 26%, and 53%, respectively (see Fig. 127.1B).

Neurologic Impairment. Patients with sepsis may display neurologic impairment manifested by altered mental status and lethargy, commonly referred to as septic encephalopathy. The incidence has been reported as between 10% and 70%. The mortality rate in patients with septic encephalopathy is higher than that in septic patients without significant neurologic involvement. Although the pathophysiologic process has not been clearly defined, contributing factors may include direct bacterial invasion, endotoxemia, altered cerebral perfusion or metabolism, metabolic derangements, multiorgan system failure, and iatrogenic injury. In addition, impaired renal or hepatic function in the absence of overt organ failure has been shown to correlate with encephalopathy.

Cardiovascular Dysfunction. Cardiovascular dysfunction is common with sepsis. The cardiovascular dysfunction and failure arise from direct myocardial depression and distributive shock. Gram-negative, gram-positive, and killed organisms can cause myocardial depression. The direct insults of the toxic mediators as well as the mobilization of host mediators of sepsis produce a distributive shock. Early in sepsis, a hyperdynamic state develops, characterized by increased cardiac output and decreased systemic vascular resistance. Although the cardiac output is increased, it is at the expense of ventricular dilation and decreased ejection fraction (EF). Vigorous fluid resuscitation usually increases preload and, secondarily, EF, thereby improving the cardiac index. Much of the cardiovascular compromise from septic shock is reversible, and normal cardiovascular function usually returns within 10 days.

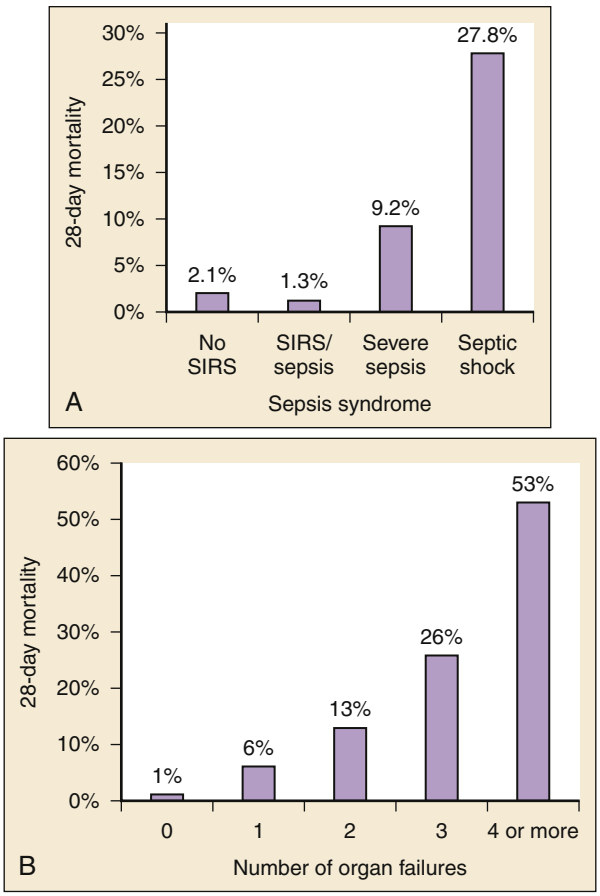

Fig. 127.1 Mortality rates by sepsis syndrome (A) and number of organ dysfunctions (B). *SIRS,* Systemic inflammatory response syndrome.

Pulmonary Involvement. Involvement of the lung is often seen in the inflammatory response to infection. These effects are apparent, irrespective of the primary infection that caused sepsis. Early infiltration with neutrophils, surfactant dysfunction, and edema gives way to monocyte infiltration and fibrosis. Significant right-to-left shunting, arterial hypoxemia, and intractable hypoxemia occur. The resulting morbidity is high and is a common endpoint to sepsis-related deaths.

Sepsis produces a highly catabolic state and places significant demands on the respiratory system to maintain the acid-base status. At the same time, airway resistance may be increased, and muscle function is impaired. Irrespective of whether pneumonia is the cause of sepsis, a common pulmonary endpoint is acute respiratory distress syndrome (ARDS). ARDS is defined clinically and correlates with the pathologic finding of diffuse alveolar damage (see Chapter 2). Because of alveolar-capillary membrane damage, fluid accumulates in the alveoli. Rather than being a diffuse disease, ARDS is a heterogeneous process that results in interspersed damaged and normal alveoli.

Gastrointestinal Effects. Splanchnic blood flow is dependent on mean arterial pressure because there is relatively little autoregulation. Therefore, hemodynamic dysfunction may have a profound effect on viscus metabolism. A shock state causes significant deleterious effects on a hollow viscus and its oxygen supply. A prolonged ileus may accompany hypoperfusion and persist beyond the perfusion deficit.

Solid organ involvement is also common. Even in the previously normal host, elevations in aminotransferases and bilirubin levels are common early in sepsis. The liver has also been implicated in the pathogenesis of sepsis; some of the mediators of sepsis are produced by the liver.

Endocrine Disorders. An absolute or relative adrenal insufficiency is common in sepsis. Depending on the balance of circulating cytokines, augmentation or suppression of the hypothalamic-pituitary axis is possible. IL-1 and IL-6 both activate the hypothalamic-pituitary-adrenal axis. TNF-α and cortistatin depress pituitary function. Other factors that may contribute to adrenal insufficiency in sepsis include decreased blood flow to the adrenal cortex, decreased pituitary function, and decreased pituitary secretion of adrenocorticotropic hormone due to severe stress. As a result of these interactions, the hypothalamic thermoregulatory mechanism may be reset, and temperature fluctuations may develop.

Hematologic Abnormalities. Sepsis causes abnormalities in many parts of the coagulation system. Endotoxin, TNF-α, and IL-1 are the key mediators. Pathologic activation of the extrinsic (tissue factor–dependent) pathway, protein C, protein S, and fibrinolysis lead to consumption of essential coagulation factors, causing DIC. The activation of the coagulation cascade produces fibrin deposition and microvascular thrombi. If these depositions are not corrected, they can compromise organ perfusion and contribute to organ failure. Tissue factor expression on monocytes is increased. This results in fibrin deposition and perhaps contributes to an increased incidence of multiorgan failure due to microvascular thrombi.

Protein C has been identified as an important modulator of inflammation and coagulation in patients with sepsis. Impairment of the protein C–dependent anticoagulation pathway is critical to the development of the thrombotic complications of sepsis. In healthy people, protein C is activated by a combination of thrombin and thrombomodulin. The activation of protein C results in the downregulation of many portions of the coagulation cascade, including release of tissue factor, inactivation of factors VIIIa and Va, and stimulation of fibrinolysis. It is possible that protein C activation in early sepsis is impaired because of an inflammatory cytokine–mediated downregulation of thrombomodulin. As a result, a consumptive coagulopathy ensues. This leads to increased fibrin deposition and a resulting upregulation of the fibrinolytic pathway, as identified by low plasma levels of the fibrinolytic proteins and increased fibrin split products. This sequence of events leads to consumption of coagulation factors and DIC. In late sepsis, the fibrinolytic system is suppressed.

Genetic Factors

There has been increasing evidence that genetics are a risk factor for the outcome of sepsis. An individual may contain a set of individual characteristics or polymorphisms that may affect the ways in which he or she responds to sepsis in general, or perhaps there may be differences in response to specific sepsis therapeutics. Identifying and understanding these differences in an individual's genetic makeup is likely to lead to tailored approaches to diagnosis and therapy. The impact of genetics on future treatment modalities for sepsis remains unclear, but the prospect of customized genetic therapy for sepsis is a promising early development.

CLINICAL FEATURES

Symptoms and Signs

The approach to a patient with sepsis relies on identification of the presence of a systemic infection and localization of the source of the initial infection. This allows appropriate treatment directed to the source of infection. Often, the source is not readily apparent, but early identification of the septic state allows implementation of broad-spectrum antibiotics.

The septic patient may manifest signs of systemic infection through tachycardia, tachypnea, hyperthermia or hypothermia and, if severe, hypotension. Very early in the patient's presentation, vital sign changes such as tachycardia and tachypnea may be first indicators of sepsis. If the patient is in shock, a rapid assessment that excludes other causes, such as hypovolemic or cardiogenic shock, is essential to the proper initial treatment. A septic patient will often have flushed skin with warm, well-perfused extremities secondary to the early vasodilation and hyperdynamic state. Alternatively, the severely hypoperfused patient with advanced shock may appear cyanotic. A complete detailed clinical examination will help the emergency clinician determine the cause of the shock state (see Chapter 3). These are classic signs; however, these findings may not be manifested in a septic patient, and signs and symptoms may be subtle or absent.

Both underlying comorbidities and the cause of sepsis should be considered. Risk factors such as immunocompromised states (e.g., acquired immunodeficiency syndrome, malignant disease, diabetes, splenectomy, concurrent chemotherapy), older age, debilitation, high-risk environments for iatrogenic infections (e.g., acute care hospitalizations, long-term care facilities), and multiple comorbidities should be considered.

The respiratory system is the most common source of infection in the septic patient (see Chapter 62). A history of a productive cough, fevers, chills, upper respiratory symptoms, sore throat, or ear pain should be sought. Physical examination should also include a detailed evaluation for focal infection, such as exudative tonsillitis, sinus tenderness, tympanic membrane injection, and crackles or dullness on lung auscultation. Also, pharyngeal thrush should be noted as a potential marker of an immunocompromised state.

The gastrointestinal system is the second or third (depending on the study) most common source of sepsis. A history of abdominal pain, including its description, location, timing, and modifying factors, should be sought. Further history, including the presence of nausea, vomiting, and diarrhea and time of the last bowel movement should be noted. A careful physical examination, looking for signs of peritoneal irritation, abdominal tenderness, and hyperactive or hypoactive bowel sounds, is critical in identifying the source of abdominal sepsis. Particular attention should be paid to physical findings suggestive of common sources of infection or disease—Murphy sign indicating cholecystitis, pain at McBurney point indicating appendicitis, left lower quadrant pain suggesting diverticulitis, or rectal examination revealing a rectal abscess or prostatitis.

The neurologic system should be evaluated for signs of meningitis, encephalitis, or epidural abscess, including nuchal rigidity, fevers, and change in consciousness (see Chapter 95). Lethargy or altered mentation may indicate primary neurologic disease or may be the result of decreased brain perfusion.

The genitourinary (GU) history includes queries about the presence of flank pain, dysuria, polyuria, discharge, Foley catheter placement, and genitourinary instrumentation. However, one must also remember that GU infection is a common source of infection in older patients and is a common offender in patients with nonspecific symptoms. Obstructed nephrolithiasis with associated urinary tract infection is a potentially lethal source of infection that can advance rapidly without decompression by nephrostomy.

Rarely, sexually transmitted infections may be the cause of sepsis. The genital examination could reveal ulcers, discharge, penile or vulvar lesions, or the woody induration of Fournier gangrene. Cervical motion tenderness indicates pelvic inflammatory disease, and adnexal tenderness in a toxic-appearing woman may represent a tubo-ovarian abscess. Tampons are rarely a cause of toxic shock syndrome, but when no other source of septic shock is found, a retained tampon should be considered.

The musculoskeletal history includes the presence of any localizing symptoms to a particular joint. Redness, swelling, and warmth over a joint, especially if there is a decreased range of motion in that joint, may be signs of septic arthritis and may mandate arthrocentesis. The skin should be examined for evidence of cellulitis, abscess, wound infection, or traumatic injury. Deep injuries, foreign bodies, and fasciitis may be difficult to identify clinically. The emergency clinician should look for crepitus, bullae, or skin edema extending beyond areas of erythema that may indicate the presence of an aggressive, gas-forming organism (see Chapter 126). Back pain and fever may be signs of an epidural abscess. Local lymphadenopathy, swelling, and streaking should also be noted as signs of an advancing infection. Petechiae and purpura may represent a *Neisseria meningitidis* infection or DIC. Generalized erythroderma and rash may represent an exotoxin from pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*.

A history of fevers or chills in the setting of injection drug use, artificial heart valve, or mitral valve prolapse should increase the suspicion for endocarditis. The emergency clinician should suspect endocarditis in the presence of a murmur or other stigmata of endocarditis (e.g., splinter hemorrhages, Roth's spots, Janeway's lesions) (see Chapter 69).

Emergency clinicians must identify the severity of illness in patients with infection and initiate early resuscitation for those with the potential of becoming critically ill. Although a patient may meet SIRS criteria, this alone has little predictive value in determining the severity of illness and mortality. There are many scoring systems that have been developed to risk-stratify illness severity. Most scoring systems are not clinically relevant and not routinely used. The Mortality in Emergency Department Sepsis (MEDS) score is one proposed method to risk stratify ED patients with sepsis. The MEDS prediction rule assigns point values to specific clinical characteristics (Table 127.1). The total score can be used to assess risk of death. Thus, the greater the number of risk factors, the more likely a patient is to die during hospitalization. Although typically not calculated for all patients, the elements of the score may be identified and considered as a red flag when risk-stratifying a patient.

TABLE 127.1 Mortality in Emergency Department Sepsis (MEDS) Prediction Rule

Risk Factor	Odds Ratio for Death	Meds Score (Points)
Terminal illness (death within 30 days)	6.1	6
Tachypnea or hypoxia	2.7	3
Septic shock	2.7	3
Platelet count < 150,000/mm^3	2.5	3
Bands > 5%	2.3	3
Age > 65 yr	2.2	3
Pneumonia	1.9	2
Nursing home resident	1.9	2
Altered mental status	1.6	2

Risk of Death	Total Meds Score (% of Sepsis Deaths)
Very low	0–4 (1.1%)
Low	5–7 (4.4%)
Moderate	8–12 (9.3%)
High	13–15 (16.1%)
Very high	>15 (39%)

DIAGNOSTIC CONSIDERATIONS

Differential Diagnoses

The sepsis syndromes represent a spectrum of disease and clinical presentations. Often, noninfectious sources can cause a syndrome that mimics that of sepsis; thus, one must keep in mind a broad differential diagnosis when approaching these patients (Box 127.2). A detailed history and physical examination are the first steps in narrowing the differential diagnosis to identify the true source.

Diagnostic Testing

Diagnostic studies are used to identify the type and location of the infecting organisms and define the extent and severity of the infection to assist in focusing therapy. As a result, the diagnostic approach should be tailored to the particular patient.

BOX 127.2 Differential Diagnosis of Sepsis and Septic Shock

Sepsis

Dehydration
Acute respiratory distress syndrome
Anemia
Ischemia
Hypoxia
Congestive heart failure
Vasculitis
Toxicologic
- Poisonings
- Overdose
- Drug-induced
- Neuroleptic malignant syndrome

Pancreatitis
Hypothalamic injury
Disseminated intravascular coagulation
Anaphylaxis
Metabolic
Hyperthyroidism
Diabetic ketoacidosis
Adrenal dysfunction
- Environmental
- Burn
- Heat exhaustion or stroke

Trauma
Blood loss
Cardiac contusion

Septic Shock

Hypovolemic shock
Acute blood loss
Severe dehydration
Cardiogenic shock
Pulmonary embolus
Myocardial infarction
Pericardial tamponade
Tension pneumothorax
Vasogenic shock
Anaphylaxis
Paralysis

Laboratory Testing

Hematology. The white blood cell count can be an indicator of inflammation and activation of the inflammatory cascade. Leukocytosis is associated with infection and is incorporated in the consensus definition of sepsis; however, it is often insensitive and nonspecific, limiting its value in the ED. The febrile neutropenic patient has been shown to be at increased risk for severe infection. Thus, a neutrophil count of less than 500 cells/mm^3 should prompt consideration for admission, isolation, and empirical intravenous (IV) antibiotics in most chemotherapy patients. A bandemia (≥5%–10% bands on a peripheral smear) represents the release of immature cells from the bone marrow and may be a sign of infection and inflammation. Like the white blood cell count, it is an imperfect indicator of infection. The absence of leukocytosis or bandemia does not preclude the possibility of severe sepsis nor does their presence confirm it. The hemoglobin level should be determined to ensure adequate oxygen delivery in shock. Platelets are an acute-phase reactant and may be elevated in the presence of infection. Conversely, a low platelet count may be seen in patients with sepsis and septic shock. Thrombocytopenia, elevated prothrombin time, elevated activated partial thromboplastin time, decreased fibrinogen, and increased fibrin split products are associated with DIC and severe sepsis syndrome.

Blood Chemistry. Electrolyte abnormalities should be identified and corrected. A low bicarbonate level suggests acidosis and inadequate perfusion. An elevated anion gap acidosis in the setting of sepsis syndrome commonly represents lactic acidosis or diabetic ketoacidosis, but other causes need to be ruled out. An elevated serum creatinine concentration or decreased glomerular filtration rate signals renal dysfunction or failure, which, if due primarily to sepsis, indicates organ failure and a worse prognosis. Calcium, magnesium, and phosphorus levels should be checked.

An elevated lactate level is associated with inadequate perfusion, shock, and poorer prognosis. In one study, the mortality rate correlated with the venous lactate level—a lactate level of 0 to 2.5 mg/dL was associated with a 5% mortality rate, a lactate level of 2.5 to 4.0 mg/dL, 9% mortality, and a lactate level greater than 4 mg/dL, 28% mortality. A blood gas assessment is helpful in identifying and classifying acid-base disturbances, with metabolic acidosis suggesting inadequate tissue perfusion. Liver function tests can be used to identify liver failure or dysfunction. An elevated bilirubin level may suggest the gallbladder as a cause of sepsis. An elevated lipase level may represent pancreatitis as the cause of SIRS. Procalcitonin and C-reactive protein are biomarkers sometimes used in the diagnosis and prognosis of sepsis. The literature primarily supports procalcitonin in serial measurements and for antibiotic stewardship, but the role for procalcitonin in the ED has not been clearly delineated.

Urinalysis. Urinalysis is another essential laboratory test, especially in older patients with higher risk of urinary tract infection who may not manifest localizing symptoms of infection. Urinalysis is likewise important to rule out infection in patients with renal colic or ureteral obstruction.

Microbiology. Proper blood, urine, sputum, cerebrospinal fluid, and other tissue culture samples are important in guiding therapy. Although the results of culture are not helpful in the initial management, culture samples ideally should be obtained before the administration of antibiotics in the patient with sepsis. The initiation of antibiotic therapy should not be delayed significantly while waiting for culture samples to be obtained. Studies have suggested that the yield of initial blood cultures is low (5%–10%), but this is probably an artifact of the lack of reliable discriminatory guidelines for obtaining blood culture samples in the ED. Among patients with clinical sepsis, only 30% to 40% of patients will have positive cultures. The results of initial microbiologic

tests, including Gram staining whenever possible, will help guide subsequent antibiotic treatment. Initial empirical therapy should be broad spectrum to allow early treatment of all likely organisms.

Special Procedures

Historically, a central venous pressure (CVP) line was thought helpful in guiding fluid resuscitation in sepsis patients. We do not recommend the routine use of CVP to determine fluid responsiveness. When available, arterial lines can be useful for close monitoring of hypotensive patients, especially when one or more vasopressors are being titrated to maintain an adequate blood pressure. However, they are not routinely placed in the ED. The technology of noninvasive or minimally invasive cardiac output monitoring is evolving and, where available, may help guide fluid administration by evaluating cardiac output alone or in conjunction with a fluid challenge or passive leg raise approach. Cardiac ultrasound, while unproven, is also commonly used to assess volume status and cardiac function.

Radiology

Imaging studies are generally used to identify the source of infection. A chest radiograph should be considered in patients with suspected sepsis syndrome, looking not only for a focal infiltrate representing pneumonia but also for the bilateral infiltrates indicative of ARDS. An upright chest radiograph should be considered for suspected bowel perforation to detect free air under the diaphragm. The presence of pneumomediastinum is suggestive of esophageal perforation and current or impending mediastinitis.

Soft tissue plain radiographs of infected areas can be obtained, looking for air in the soft tissues associated with necrotizing or gas-forming infection, although plain x-rays are not sensitive for tissue infection. Periosteal thickening or bone erosion may be seen on plain radiographs of patients with osteomyelitis; a bone scan may be diagnostic. Computed tomography (CT) of superficial infections may be more helpful to quantify the extent of infection further and identify abscesses that are not readily evident on physical examination. A CT scan of the abdomen and pelvis may identify abdominal or pelvic pathologic lesions, provided there is no clear clinical indication for immediate operative intervention. Suspected disease, such as diverticulitis, appendicitis, necrotizing pancreatitis, microperforation of the stomach or bowel, or formation of an intra-abdominal abscess, may be best diagnosed by a CT scan. A head CT scan can identify septic emboli from endocarditis or increased intracranial pressure from a mass and should be considered before a lumbar puncture is performed. An abdominal ultrasound examination may be indicated for suspected cholecystitis, and a pelvic ultrasound examination may be indicated for tubo-ovarian abscess or endometritis. If endocarditis is suspected, a transesophageal cardiac ultrasound study may be performed for the detection of any valvular vegetations. Magnetic resonance imaging (MRI) can be useful to identify soft tissue infection, such as necrotizing fasciitis or epidural abscess.

MANAGEMENT

Early detection and appropriate treatment can reduce the mortality from sepsis. The primary goal is timely administration of appropriate antimicrobial therapy—or interventional source control as required—and maintenance of adequate tissue oxygenation and perfusion through titrated resuscitation. With early detection and early resuscitation there is increasing evidence that the natural history of sepsis can be altered. Initial resuscitation, including appropriate airway management, IV access, oxygen, early and appropriate antibiotics, fluid resuscitation, and vasopressor support, remains the foundation on which new efforts may be applied.

From a historical perspective, Rivers and associates[2a] provided compelling evidence supporting the importance of this concept when they published a protocol of standardized timely and titrated care being used to guide resuscitation in the ED. This randomized, double-blind, placebo-controlled study showed a 16% mortality reduction in patients with severe sepsis and septic shock. The protocol, termed *early goal-directed therapy* (EGDT), measures targeted goals and uses a resuscitation algorithm to guide the resuscitation. The theory behind the protocol was to normalize preload and blood pressure and prevent tissue hypoxia by matching oxygen delivery with consumption. Use of this protocol, which facilitated earlier and more aggressive fluid resuscitation through the use of increased fluids, increased blood products, increased use of dobutamine, and greater degree of normalization of tissue hypoxia, reduced mortality at their center. The interventions in combination were likely responsible for the better outcomes in the intervention group.

The principles of EGDT, as well as efforts such as the Surviving Sepsis Campaign, helped underscore the importance of early identification and timely resuscitation.[3] However, until 2014, the evidence in support of the formal EGDT protocol was only in the form of the original single- center trial and subsequent observational efforts. Subsequently, the ProCESS, ProMISE, and ARISE studies were large multicenter trials that sought to validate the value of EGDT.[4,5] Each of the trials showed no mortality benefit to EGDT as compared to usual resuscitation measures; thus, although EGDT is one strategy to consider, it is not a superior approach. It is important to underscore, however, that the usual care groups in these newer trials were all identified early, received antibiotics, and received generous amounts of fluids (on average, approximately 40–60 mL/kg in the first 6 hours across the trials), supporting the principle that early identification of sepsis, early antibiotics, and carefully titrated resuscitation should remain a core tenant.

Respiratory Support

Altered mental status is common in patients in septic shock, and patients may require rapid airway protection. Because patients with impending respiratory failure use a disproportionately large amount of energy for the muscles of respiration, improved oxygen delivery to other organs may be achieved by mechanical ventilation, sedation, and paralysis. Although there are no clear intubation guidelines, hypercapnia, persistent hypoxemia, airway compromise, and profound acidosis are valid indicators for intubation.

In addition to airway protection, intubation and mechanical ventilatory support provide positive-pressure ventilation. Pulmonary compliance is often low in ARDS, resulting in increased airway pressures to maintain oxygen delivery. The ARDSNet trial established the benefit of low tidal volumes (6 mL/kg) and plateau pressures of 30 cm H_2O or below in mechanically ventilated patients to prevent iatrogenic lung damage (see Chapter 2). Maintenance of a relatively low plateau pressure with higher positive end-expiratory pressure is an effective way to increase arterial oxygen delivery.

Cardiovascular Support

Fluid Resuscitation

Patients with sepsis are often administered IV fluid to maintain adequate perfusion. The primary reasons for this intravascular hypovolemia are venodilation and diffuse capillary leak. Initial therapy for adults with septic shock should generally be up to 30 mL/kg of isotonic crystalloid. Additional fluid replacement should be titrated to clinical parameters such as heart rate, blood pressure, change in mental status,

capillary refill, cool skin, and adequate urine output (0.5–1 mL/kg/hr). Colloids are as effective as crystalloids, but they are more expensive and less readily available. Balanced salt solutions (e.g., lactated Ringers) have been shown to have beneficial effects over normal saline, due primarily to adverse renal effects associated with normal saline. Evidence suggests that balanced solutions are likely as good or better than normal saline; thus, we recommend the use of balanced solutions for sepsis resuscitation.

Although one should be increasingly vigilant in watching for fluid overload in patients who are predisposed, such as older adults, those with congestive heart failure (CHF), or those with renal impairment, these patients are not precluded from volume resuscitation as described previously. Efforts to identify ways to measure regional perfusion more directly, such as direct measurement of splanchnic blood flow, have been proposed, but are not commonly used in clinical practice. Even in the absence of global hypoxia and impaired tissue perfusion, there is evidence that regional hypoperfusion and ischemia exist.

Vasoactive Drug Therapy

Use of mean arterial pressure alone as an indicator of overall efficacy of therapeutic intervention is not always sufficient. A mean arterial pressure of 65 mm Hg has been recommended in otherwise healthy, normovolemic adult patients but must be correlated with other indicators of adequate perfusion, such as mental status and urine output. Patients with previously uncontrolled hypertension may require a mean arterial pressure of 75 mm Hg or even higher. If appropriate fluid resuscitation has failed to maintain end-organ perfusion, vasopressor support may be required (Table 127.2).

The 2016 Surviving Sepsis Campaign guidelines provided consensus recommendations for treatment of septic shock.[6] Norepinephrine should be used as the initial vasopressor, with the addition of epinephrine or vasopressin to norepinephrine as adjuncts. Vasopressin has not been shown to improve outcomes when added to norepinephrine in refractory septic shock, but there is no evidence of harm. As such, the optimum role for vasopressin is unclear. Once the mean arterial pressure is adequately supported, dobutamine should be used as the primary inotropic agent if myocardial dysfunction is evident. Patients requiring vasopressors and inotropes require frequent reassessment and medication titration, as needs can change greatly during the first few hours of resuscitation.

Norepinephrine. Norepinephrine is predominantly α-agonist with some β_1-agonism with minimal β_2 activity and primarily functions to increase systemic vascular resistance and cardiac output. In a large study examining patients with varied causes of shock, norepinephrine was associated with fewer adverse events (particularly arrhythmias) compared with dopamine. Dopamine was also associated with a higher mortality rate in patients with cardiogenic shock. In another meta-analysis, norepinephrine was shown to be superior to dopamine in both in-hospital and 28-day mortality. Compared with dopamine in septic patients, norepinephrine increases glomerular filtration and urine output equally well. We recommend norepinephrine as the first-line vasopressor for septic shock, either as a sole vasopressor or in conjunction with other agents. Norepinephrine can be started at 3 to 5 μg/min and titrated to achieve the goal mean arterial pressure.

TABLE 127.2 Dosing of Vasoactive Therapy

Drug	Dosage
Dobutamine	2–15 μg/kg/min
Epinephrine	5–20 μg/min
Norepinephrine	3–30 μg/min
Phenylephrine	2–300 μg/min
Vasopressin	0.01–0.04 units/min

Dopamine. Dopamine is the immediate precursor of norepinephrine and epinephrine. It is primarily an α-, β_1-, and dopaminergic agonist. Dopamine was previously thought to improve renal outcomes, but it has not been shown to reduce mortality or decrease dialysis dependence, and should not be used for these indications. Persistent tachycardia, decreased partial pressure of arterial oxygen, and increased pulmonary artery occlusion pressure are common side effects of dopamine use. We do not recommend the routine use of dopamine if other vasopressors are available.

Vasopressin. Vasopressin is a naturally occurring peptide that is synthesized as a large prohormone in the hypothalamus. In states of septic shock, there is an early surge of vasopressin followed by a profound drop in circulating vasopressin levels. In a well-designed randomized trial, investigators demonstrated no change in mortality for patients with severe sepsis when vasopressin was added to catecholamine vasopressors. Vasopressin should not be used as the sole initial therapy for refractory septic shock. However, vasopressin does not increase pulmonary vascular resistance, making it a useful adjunct in patients with pulmonary hypertension, obstructive shock secondary to PE, or right ventricular dysfunction.

Epinephrine. Epinephrine is a potent mixed α- and β-agonist. Epinephrine infusion is also associated with increased oxygen consumption, increased systemic lactate concentrations, and decreased splanchnic blood flow. The rise in the lactate level is short term, and there is no evidence regarding its long-term effects. As a result of all the possible adverse effects of epinephrine, it is currently recommended only for those patients who are unresponsive to other vasopressors. Epinephrine can be a good adjunct for patients with combined septic and cardiogenic shock, given its vasopressor and inotropic activity.

Phenylephrine. Phenylephrine is a selective α_1-agonist, increasing systemic vascular resistance without significant changes in cardiac output. It can produce reflexive bradycardia or suppression in cardiac output. A single small study has shown that phenylephrine is effective in restoring perfusion in patients with septic shock refractory to dopamine or dobutamine. Another small study has demonstrated that phenylephrine is less effective than norepinephrine in the treatment of hypotension in septic patients; however, there was no difference in other measured hemodynamic parameters, including oxygen delivery. Phenylephrine does not impair cardiac and renal function and may be a good choice when significant tachyarrhythmia limits the use of other agents.

Dobutamine. Dobutamine is a mixed α- and β-agonist. In dosage ranges from 2 to 28 μg/kg/min, the cardiac index is increased at the expense of heart rate. In addition, decreased splanchnic blood flow is common. Dobutamine should be used in patients with depressed cardiac index and persistent hypoperfusion in spite of adequate volume expansion and the use of other vasopressor agents. Dobutamine decreases systemic vascular resistance, and therefore should not be used as the sole agent in a hypotensive patient. One study has suggested that survival in sepsis is associated with the patient's increase in stroke volume in response to dobutamine.

Bicarbonate

Bicarbonate supplementation was previously the standard treatment for patients with presumed lactic acidosis. Current consensus is that it should be reserved for severe acidemia (pH < 7.0–7.2) because there

TABLE 127.3 Suggested Initial Antibiotic Management[a]

Infection	Modifying Factors	Antibiotic
Sepsis, unknown source	Immunocompetent	Antipseudomonal cephalosporin *plus* aminoglycoside or fluoroquinolone, *or* antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone, *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Anaerobic infection	Add metronidazole or clindamycin to above regimen.
	Methicillin-resistant *Staphylococcus aureus* (MRSA)	Add vancomycin to above regimen.
	Neutropenia	Antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone, *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Splenectomy	Cefotaxime *or* ceftriaxone
Pneumonia	Immunocompetent	Second- or third-generation cephalosporin *plus* second-generation macrolide *or* fluoroquinolone
	Legionella suspected	Azithromycin, fluoroquinolone, or high-dose erythromycin
Abdominal infection	Immunocompetent	Ampicillin *plus* aminoglycoside *plus* metronidazole
	Multidrug-resistant organism suspected	Carbapenem, *or* piperacillin-tazobactam *plus* aminoglycoside
	Urinary tract source	Fluoroquinolone, *or* third-generation cephalosporin, *or* ampicillin *plus* aminoglycoside
Cellulitis	Nonnecrotizing fasciitis	Cefazolin *or* nafcillin
	MRSA possible	Vancomycin
	Necrotizing fasciitis (surgical drainage)	Ampicillin-sulbactam, piperacillin *plus* aminoglycoside *plus* clindamycin, *or* carbapenem
Intravenous catheter infection (remove catheter)	Outpatient-acquired	Third-generation cephalosporin
	MRSA suspected	Add vancomycin.
	Fungal infection	Amphotericin B
Cerebrospinal infection	Immunocompetent	Ceftriaxone *plus* vancomycin
	Older adult or immunocompromised patient	Add ampicillin.
Injection drug abuse	MRSA not suspected	Cefazolin *or* nafcillin *plus* aminoglycoside
	MRSA suspected	Vancomycin *plus* aminoglycoside

[a]Pending microbiologic identification of organism and sensitivity.

may be a paradoxical decrease in intracellular pH as a result of diffusion of soluble carbon dioxide across the cell membrane. Alternatively, hyperventilation has been suggested to help increase systemic pH.

Antibiotics

Early antibiotic therapy should target the nidus of infection if known. If the patient's condition permits, appropriate culture specimens should be obtained before the administration of broad-spectrum antibiotics (Table 127.3). Surgically correctable conditions, such as intra-abdominal abscesses, perforated viscus, retained products of conception, or retained foreign body (e.g., a tampon), should be treated concurrently. Antibiotics should be administered as soon as possible in patients with serious infections. Although some observational studies and national benchmarks have called for the administration of antibiotics within a predefined time period of 3 hours from ED presentation, a comprehensive meta-analysis failed to support an association between antibiotics administered after 3 hours and mortality.[7] Thus, early antibiotics are important, but their exact timing remains undefined.

In the absence of an obvious source of infection, the use of broad-spectrum antibiotics is recommended. The specific agent depends on many variables, including institutional preference and local resistance patterns. As results from cultures become available, therapy should be modified. There is no consensus about the need for double or triple antibiotic coverage for particular organisms, although it is common practice to double-cover virulent organisms, such as *Pseudomonas aeruginosa,* as well as areas commonly infected with multiple organisms, such as the peritoneum. With increasing rates of methicillin-resistant organisms, combinations that include nonpenicillin choices may be warranted.

Steroid Therapy

It has been nearly 40 years since the first treatment attempts to block inflammation in sepsis. Because sepsis involves a systemic inflammatory response, corticosteroids are a logical treatment modality as anti-inflammatory agents. Physicians have been working for decades to prove or disprove their value. Steroids appear to be more effective in reducing the amount of time patients spend in a hypotensive state, and moderate-quality evidence suggests a mortality benefit, especially in the most critically ill patients.[8-10] However, the optimum timing, dose, drug, and method of administration (continuous or bolus dosing) remains unknown. At this time, we believe that the role of steroid therapy in sepsis remains controversial and recommend their use when there is refractory cardiovascular insufficiency, despite fluid and vasopressor therapy.

DISPOSITION

Once ED management is complete, patients who are deemed at increased risk should be admitted to the hospital into a setting that is deemed appropriate for the severity of the patient's condition. For

example, in patients who remain hypotensive, are on vasopressors, or who are unstable and require more frequent monitoring, the intensive care unit may be appropriate. Other patients who are more stable but still require monitoring and perhaps IV therapy may be admitted to a hospital ward. Finally, in certain cases, patients initially meeting sepsis criteria but who are not severely ill (e.g., young patients with pharyngitis) may be appropriate for discharge.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 127: QUESTIONS AND ANSWERS

1. Which of the following patients meets the criteria for systemic inflammatory response syndrome (SIRS)?
- **a.** 6-year-old boy with pneumonia, temperature 39.0°C (102.2°F)
- **b.** 53-year-old man with respirations 30 breaths/min, white blood cell (WBC) count 16,000 cells/mm^3
- **c.** 74-year-old woman with chest pain, heart rate 130 beats/min
- **d.** 81-year-old man with WBC count, 2700 cells/mm^3, heart rate, 73 beats/min

Answer: B. SIRS is defined as two or more of the following—tachycardia, tachypnea, temperature higher than 38°C (100.4°F) or lower than 35°C (95°F), high or low WBC count, or bandemia. Sepsis is SIRS with infection. Severe sepsis includes organ dysfunction. Septic shock involves systolic blood pressure below 90 mm Hg.

2. Sepsis is characterized by which of the following?
- **a.** Depression of tumor necrosis factor levels
- **b.** Increased endogenous anticoagulant levels
- **c.** Prolonged suppression of nitric oxide levels
- **d.** Increased inflammatory cytokine levels

Answer: D. Clinical sepsis is induced by sustained levels of proinflammatory and procoagulant mediators. Cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-α) and prostaglandins are primary mediators. Nitric oxide synthase is upregulated, resulting in sustained elevations of the serum nitric oxide level, with subsequent vasodilations. Sustained suppression of vasopressin adds to this sometimes refractory vasodilated state.

3. Which of the following statements regarding septic shock is true?
- **a.** Cardiac output is always decreased.
- **b.** Much of the cardiac decompensation is reversible.
- **c.** Systemic vascular resistance is high.
- **d.** The ejection fraction is always increased.

Answer: B. Sepsis affects myocardial function and peripheral vascular tone. The systemic vascular resistance is usually markedly depressed. Cardiac output is generally increased because of a compensatory tachycardia that can at least partially overcome the ventricular dilation and depressed ejection fraction. The myocardial effects are typically reversible.

4. What are the two most common sources of infection in cases of sepsis?
- **a.** Genitourinary > respiratory
- **b.** Musculoskeletal > genitourinary
- **c.** Respiratory > gastrointestinal
- **d.** Respiratory > genitourinary

Answer: C. Epidemiology studies show that pneumonia is the most common cause of sepsis, followed by an intra-abdominal source. However, a careful investigation to identify the source of infection should occur.

5. In most chemotherapy patients, which neutrophil count should prompt admission, isolation, and empirical antibiotics?
- **a.** <250 cells/mm^3
- **b.** <500 cells/mm^3
- **c.** <750 cells/mm^3
- **d.** <1000 cells/mm^3

Answer: B. Patients with an ANC <500 cells/mm^3 are at increased risk of infection; thus, a conservative approach should be taken in these patients.

6. Among patients with clinical septic shock, which percentage will have positive blood cultures?
- **a.** 0%–30%
- **b.** 30%–60%
- **c.** 60%–90%
- **d.** 90%–100%

Answer: B. Although blood cultures are perhaps a gold standard for identification and isolation of bacteria, they may be negative even when the etiology of illness is clearly infectious. Empirical antibiotic treatment in the ED remains a standard approach.

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Hypothermia, Frostbite, and Nonfreezing Cold Injuries

Ken Zafren and Daniel F. Danzl

ACCIDENTAL HYPOTHERMIA

KEY CONCEPTS

- Patients with hypothermia should be actively rewarmed whenever possible. Specific indications for active rather than passive rewarming include trauma, cardiovascular instability, temperature below 32°C (89.6°F), poor rate of passive rewarming, and endocrine insufficiency.
- Rewarming methods should be chosen to minimize core temperature afterdrop.
- If tachycardia is out of proportion to core temperature then hypoglycemia, hypovolemia, or an overdose should be considered.
- The effects of most medications are temperature dependent. Overmedication to achieve an effect when the patient is cold could cause toxicity during rewarming.
- Laboratory coagulation tests are performed at 37°C (98.6°F). Despite clinically obvious coagulopathy, measures of coagulation will be deceptively normal. Treatment for coagulopathy is to rewarm the patient.
- There are no safe predictors of serum electrolyte levels. Hypothermia enhances the cardiac toxicity of hyperkalemia and obscures premonitory electrocardiographic changes.
- Failure to rewarm despite good technique should suggest infection, endocrine insufficiency, or a futile resuscitation.

Foundations

Background and Importance

Reported reanimations of profoundly cold victims in prolonged cardiac arrest and the emergence of targeted temperature management (formerly called "therapeutic hypothermia") after cardiac arrest have made hypothermia a compelling topic. The lowest recorded core temperature in accidental hypothermia with successful resuscitation in an adult is 13.7°C (56.7°F) in a 29-year-old Norwegian physician. Cardiopulmonary resuscitation was initiated at the scene. The 9-hour resuscitation included 179 minutes of cardiopulmonary bypass. The lowest recorded core temperature with successful resuscitation in a child is 11.8°C in a 2-year-old boy who had an unwitnessed cardiac arrest. CPR was administered for 135 minutes. He was weaned off ECMO after 22 hours.[1] Profoundly cold patients have been resuscitated with full neurologic recovery after CPR for as long as 9 hours.[2] The lowest possible temperature with neurologically intact survival in accidental hypothermia is not known. The lowest temperature in a survivor of induced hypothermia was long considered to be 9°C (48.2°F). Recently rediscovered journal articles from the early 1960s document survival after much lower induced core temperatures, as low as 4°C (39.2°F) measured using esophageal probes.

The treatment of accidental hypothermia has been controversial throughout history. The Bible recounts the truncal rewarming of King David by a damsel. Various remedies, including rubbing extremities with hot oil, were mentioned by Hippocrates, Aristotle, and Galen.

Cold weather has had a major impact on military history. Hannibal lost nearly half of his army of 46,000 while traversing the Alps in 218 BCE. The winter of 1777 took its toll on Washington's troops at Valley Forge. Napoleon's chief surgeon, Baron Larrey, reported that only 350 of the 12,000 men in the 12th division survived the cold during their retreat from Russia in 1812. Those soldiers who were rapidly rewarmed closest to the campfire died. Many lessons were relearned during World Wars I and II when pilots and U-boat crews perished in the cold waters of the North Atlantic.

Cold-related tragedies also affect civilians, including hunters, skiers, climbers, boaters, swimmers, and survivors of natural disasters. Hypothermia can occur in a wide range of climates and seasons. Large numbers of cases occur in urban settings. Indoor hypothermia in elderly patients is an increasing problem.[3] Primary hypothermia fatalities can be classified as accidental, homicidal, or suicidal. Death certificate data have underreported mortality from secondary hypothermia, in which cold complicates systemic diseases. As a result, the overall impact of cold on mortality from cardiovascular and neurologic disorders is greatly underestimated.

Anatomy, Physiology, and Pathophysiology

Hypothermia is defined as a core temperature below 35°C (95°F). Many variables contribute to the development of accidental hypothermia. Exposure, old age, poor health, inadequate nutrition, and various medications and intoxicants can decrease heat production, increase heat loss, or interfere with thermoregulation. Compensatory responses to heat loss through conduction, convection, radiation, and evaporation are often overwhelmed by exposure, even in healthy persons. Medications and central nervous system problems can also interfere with thermoregulation.

Temperature Regulation

Human basal heat production increases with ingestion of food or calorie containing fluids, muscle activity, fever, and acute cold exposure. Cold stress increases preshivering muscle tone, potentially doubling heat production. Maximal heat production, primarily due to shivering, lasts only a few hours because of fatigue and glycogen depletion.

Shivering thermogenesis increases the basal metabolic rate up to five times, markedly increasing oxygen consumption. Shivering begins at a normal core temperature when the skin is cooled. Shivering intensity is modulated by the posterior hypothalamus and the spinal cord. The preoptic anterior hypothalamus orchestrates nonshivering heat conservation and dissipation. Heat loss occurs by radiation, conduction, convection, respiration, and evaporation. The most common causes of accidental hypothermia are convective heat loss to cold air and conduction and convection in cold water. Heat loss increases up to five times in wet clothing. Conduction and convection in cold water can increase heat loss by a factor of 25.

Individuals with greater amounts of subcutaneous fat lose heat more slowly than thin people. Convective losses increase with shivering. Respiration and evaporation cause heat loss in the warming of inspired air and by insensible evaporation from the skin and lungs.

Cutaneous and respiratory heat losses are markedly influenced by the ambient temperature, air motion, and relative humidity. Greater losses occur in cool, dry, windy environments. When there is no sweating, most heat loss is through radiation and convection. Convective losses are significant in immersion-induced hypothermia. Children cool faster than adults because they have higher ratios of surface area to mass. Chronic cold exposure may result in thermal acclimatization (Fig. 128.1).

When the core temperature ranges from 37°C to 30°C (98.6°F to 86°F), vasoconstriction, shivering, and nonshivering basal and endocrine thermogenesis generate heat. From 30°C to 24°C (86°F to 75.2°F), the basal metabolic rate decreases, and shivering is absent. At temperatures below 24°C (75.2°F), autonomic and endocrine mechanisms for heat conservation become inactive. The pathophysiologic characteristics of hypothermia are described in Table 128.1.

Cardiovascular System

Initial tachycardia is followed by progressive bradycardia, although periods of tachycardia sometimes occur. The pulse decreases by 50% at 28°C (82.4°F). If the degree of tachycardia is inconsistent with the core temperature, consider associated conditions such as hypoglycemia, drug ingestion, and hypovolemia.

The bradycardia of hypothermia results from decreased spontaneous depolarization of cardiac pacemaker cells and is refractory to atropine. The electrocardiographic features of hypothermia include the

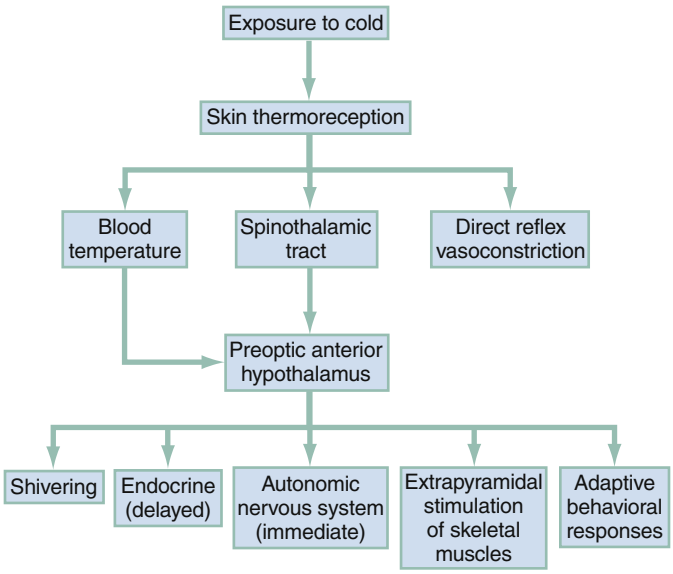

Fig. 128.1 Physiology of cold exposure.

TABLE 128.1 Physiologic Characteristics of the Four Zones of Hypothermia

State	Core Temperature °C (°F)	Characteristics
Cold-stressed	37–35 (98.6–95)	Shivering and increased metabolism
Mild	35 (95)	Increased shivering thermogenesis; increase in metabolic rate
	34 (93.2)	Normal blood pressure; maximum respiratory stimulation; ataxia, and apathy
	33 (91.4)	Amnesia
Moderate	32 (89.6)	Stupor; 25% decrease in oxygen consumption
	31 (87.8)	Increased shivering thermogenesis
	30 (86)	Atrial fibrillation and other dysrhythmias; poikilothermia; pulse and cardiac output two-thirds normal; insulin ineffective; Progressive decrease in level of consciousness; loss of consciousness can be seen
	29 (85.2)	Progressive decrease in pulse, and respiration; pupils dilated
Severe	28 (82.4)	Ventricular fibrillation susceptibility; 50% decrease in oxygen consumption and pulse
	27 (80.6)	Loss of reflexes
	26 (78.8)	Major acid-base disturbances; no reflexes or response to pain
	25 (77)	Cerebral blood flow one-third normal; cardiac output 45% normal; pulmonary edema may develop
	23 (73.4)	No corneal or oculocephalic reflexes
	22 (71.6)	Maximum risk of ventricular fibrillation; 75% decrease in oxygen consumption
	20 (68)	Lowest resumption of cardiac electromechanical activity; pulse 20% of normal
	19 (66.2)	Flat electroencephalogram
	13.7 (56.7)	Lowest accidental hypothermia survival in an adult
	11.8 (53.2)	Lowest accidental hypothermia survival in a child
	4.2 (39.6)	Lowest therapeutic hypothermia survivor

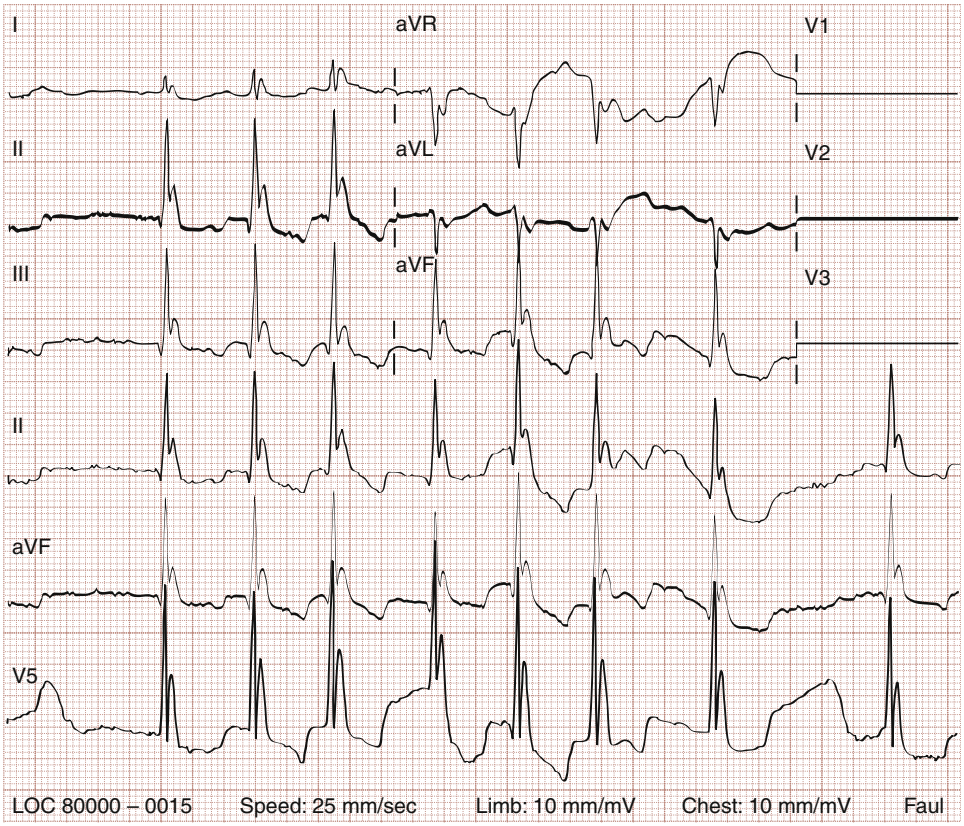

Fig. 128.2 Hypothermic J waves.

Osborn (J) wave seen at the junction of the QRS complex and ST segment with core temperatures below 32°C (89.6°F; Fig. 128.2). J waves are neither unique to hypothermia nor of any prognostic value. J waves are normally upright in aVL, aVF, and the left precordial leads. J waves can also be seen during local cardiac ischemia, with sepsis or CNS lesions, and hypercalcemia. J waves may resemble myocardial injury current and may not be recognized by ECG computer interpretations. This can result in misguided thrombolysis, which could exacerbate preexistent coagulopathies. Hypothermia can also cause electrocardiographic changes that mimic Brugada syndrome.

Atrial and ventricular dysrhythmias are common in moderate or severe hypothermia. Because the conduction system is more sensitive to the cold than the myocardium, cardiac cycle prolongation occurs. As hypothermia worsens, the PR interval, then the QRS interval, and finally the QTc interval become prolonged. Even in the absence of shivering, increased muscle tone may obscure P waves or produce artifacts. Atrial fibrillation is common when the core temperature is below 32°C (89.6°F). Sinus atrial or junctional rhythms also occur. Atrial fibrillation usually converts spontaneously during rewarming, but mesenteric embolization is a hazard. Ventricular fibrillation (VF) may be caused by tissue hypoxia, physical jostling, electrophysiologic or acid-base disturbances, or autonomic dysfunction. Asystole and VF can occur spontaneously when the core temperature falls below 25°C (77°F), but vital signs may persist well below 24°C (75.2°F).

The term *core temperature afterdrop* refers to a decrease in an individual's core temperature after removal from the cold. Temperature equilibration by conduction of heat from the core to the cooler peripheral tissue contributes to afterdrop, but countercurrent cooling of blood perfusing cold tissues in the periphery before returning to the warmer core results in a greater decrease in the core temperature. Active external rewarming of the extremities abolishes peripheral vasoconstriction and reverses arteriovenous shunting. In one human experiment, cooling followed by immersion in a warm bath produced a 30% fall in mean arterial pressure, with a 50% decrease in peripheral vascular resistance.

Core temperature afterdrop is clinically relevant in the treatment of patients with large temperature gradients between the core and periphery. Large afterdrops can occur in severely hypothermic patients if frostbitten extremities are thawed before the core is rewarmed.

Central Nervous System

Hypothermia progressively depresses the CNS. Significant alteration of brain electrical activity begins below about 33.5°C (92.3°F). The electroencephalogram becomes silent at about 19°C to 20°C (66.2°F to 68°F). Cerebral autoregulation is maintained with an increase in vascular resistance until about 25°C (77°F). In severe hypothermia, there is a redistribution of blood flow to the brain. Like the heart, the brain has a critical period of tolerance to hypothermia.

Renal System

Exposure to cold induces diuresis, regardless of the state of hydration. The kidneys excrete a large amount of dilute urine that is essentially glomerular filtrate and does not clear nitrogenous waste products. Severe hypothermia causes relative central hypervolemia due to peripheral vasoconstriction. Cold diuresis may act as a volume regulator to diminish the capacitance vessel overload. Cold water immersion can further increase urinary output by 3.5 times.

Respiratory System

Hypothermia initially stimulates respiration, followed by a progressive decrease in the respiratory minute volume. Carbon dioxide production decreases 50% with an 8°C (14.4°F) decrease in temperature. Stimuli for respiratory control are altered in severe hypothermia and carbon dioxide

BOX 128.1 Factors Predisposing to Hypothermia

Decreased Heat Production
Endocrine failure
Hypopituitarism
Hypothyroidism
Diabetes
Insufficient fuel
Hypoglycemia
Malnutrition
Marasmus
Kwashiorkor
Extreme exertion
Neuromuscular inefficiency
Age extremes
Impaired shivering
Inactivity
Lack of adaptation

Increased Heat Loss
Environmental
Immersion
Nonimmersion
Induced vasodilation
Pharmacologic
Toxicologic
Erythrodermas
Burns
Psoriasis
Ichthyosis
Exfoliative dermatitis
Iatrogenic
Emergency deliveries
Cold infusions
Heatstroke treatment

Impaired Thermoregulation
Peripheral failure
Neuropathy
Acute spinal cord transection
Diabetes
Central neurologic failure
Central nervous system trauma
Cerebrovascular accident
Toxicologic
Metabolic
Subarachnoid hemorrhage
Pharmacologic
Hypothalamic dysfunction
Parkinson disease
Anorexia nervosa
Cerebellar lesion
Neoplasm
Congenital intracranial anomalies
Multiple sclerosis

Miscellaneous Associated Clinical States
Recurrent hypothermia
Episodic hypothermia
Sepsis
Pancreatitis
Carcinomatosis
Cardiopulmonary disease
Vascular insufficiency
Uremia
Paget's disease
Giant cell arteritis
Sarcoidosis
Shaken baby syndrome
Multisystem trauma
Shapiro's syndrome
Wernicke-Korsakoff syndrome
Hodgkin disease

retention with respiratory acidosis can occur. Hypercapnia increases core temperature cooling during snow burial. Other pathophysiologic factors that adversely affect the respiratory system include viscous bronchorrhea, decreased ciliary motility, and noncardiogenic pulmonary edema.

Predisposing Factors

Factors that predispose to hypothermia include decreased heat production, increased heat loss, and impaired thermoregulation (Box 128.1). Hypothermia can occur even in warm conditions.

Decreased Heat Production. Decreased thermogenesis may be due to endocrine dysfunction, such as hypopituitarism, hypoadrenalism, or myxedema. Myxedema coma is several times more common in women and up to 80% of women with myxedema coma are hypothermic. Hypothyroidism is often occult, with no history of lassitude, dry skin, arthralgias, or cold intolerance. Hypoglycemia can predispose to hypothermia. Another cause of decreased heat production is malnutrition, with a decrease in subcutaneous fat. Severe malnutrition with wasting contributes to heat loss. Kwashiorkor is less of a risk due to the insulating effect of hypoproteinemic edema.

Neonates are at particular risk of hypothermia due to large surface area–to–mass ratio, relatively little subcutaneous tissue, and inefficient shivering. Additionally, neonates do not have behavioral defense mechanisms. Acute neonatal hypothermia is common after emergency delivery or resuscitation and has also been reported after abandonment of infants. Hypothermic neonates are lethargic, fail to thrive, and have a weak cry. Many have paradoxically rosy cheeks. Hypothermia that occurs after 72 hours of life is often due to septicemia. Hypothermia can occur in shaken baby syndrome and may be a factor in some cases of sudden infant death syndrome.

Most older adults are capable of normal thermoregulation, but conditions such as immobility and systemic disease may interfere with heat production and conservation. Geriatric autonomic dysfunction may cause an inability to sense cold, abnormal adaptive behavioral responses, and decreased peripheral blood flow.

Increased Heat Loss. Patients with erythrodermas, such as psoriasis, exfoliative dermatitis, ichthyosis, eczema, and burns, can have increased peripheral blood flow. Iatrogenic causes of heat loss include exposure during resuscitation, cold or room temperature

infusions, overcooling of patients with heatstroke, and overzealous burn treatment.

Ethanol is metabolized slowly in hypothermia and interacts with thermoregulatory neurotransmitters. Ethanol may directly suppress the activity of the posterior hypothalamus and mammillary bodies. Cutaneous heat loss increases through vasodilation and shivering thermogenesis is decreased. Ethanol is the most common cause of excessive heat loss in urban settings. Aging is associated with an increased sensitivity to the hypothermic actions of ethanol. Intoxicated persons may be incapable of adaptive behavior to avoid cold and can be impaired by hypothermic alcoholic ketoacidosis.

Impaired Thermoregulation. Thermoregulation can be impaired centrally, peripherally, or metabolically. Skull fractures, particularly basilar fractures, and chronic subdural hematomas are associated with central impairment. Other causes include strokes, neoplasms, anorexia nervosa, and Hodgkin and Parkinson diseases. The final common pathway in these disorders may be centrally mediated vasodilation. Cerebellar lesions can produce choreiform inefficient shivering.

In therapeutic or toxic doses, antidepressants, mood stabilizers, antipsychotics, anxiolytics, and general anesthetics interfere with thermoregulation by impairing centrally mediated vasoconstriction. Other overdoses, including by organophosphates, opioids, sedative hypnotics, barbiturates, and carbon monoxide, predispose to hypothermia.

Peripheral thermoregulatory failure occurs in neurogenic shock after acute spinal cord transection. In spinal cord injury, disruption of the autonomic nervous system eliminates vasoconstriction. The patient effectively becomes poikilothermic and can rapidly become hypothermic. Neuropathies and diabetes are also peripheral causes of heat loss. Abnormal plasma osmolality may cause hypothalamic dysfunction in uremia, lactic acidosis, diabetic ketoacidosis, and hypoglycemia.

Trauma

After trauma, hypotension, immobility in a cold environment, and hypovolemia predispose to hypothermia. In patients with major injuries, shivering is decreased or absent, causing skin and core temperatures to fall. Thermoregulation is impaired, and heat production decreases.

Hypothermia may exacerbate blood loss by inducing coagulopathy due to impaired activity of coagulation factors and enhanced plasma fibrinolytic activity, with decreased function and sequestration of platelets. Hypothermia in trauma is a risk factor for multiorgan dysfunction. Traumatic injuries may be missed if hypotension or neurologic findings such as areflexia or paralysis are misattributed to hypothermia. Major risk factors for hypothermia in trauma patients include extremes of age, severe injury, intoxication, large transfusion requirements, and prolonged field, emergency department (ED), and operating room times.

Hypothermia can protect the brain from ischemia only when induced before shock develops. This reduces adenosine triphosphate (ATP) use while ATP stores are nearly normal. In trauma patients, ATP stores are already depleted.

Clinical Features

Appreciation of subtle presentations facilitates the early diagnosis of mild to moderate hypothermia. Vague symptoms include hunger, nausea, confusion, dizziness, chills, pruritus, and dyspnea (Box 128.2). During outdoor activities, individuals may simply become uncooperative, uncoordinated, moody, or apathetic. Indoors, older patients may exhibit confusion or become less communicative and may display lassitude or a flat affect. Progression of mental deterioration or motor skill impairment may mimic dementia. Symptoms such as slurred speech and ataxia may resemble symptoms of stroke or intoxication. Some older adults have a decreased ability to sense cold and fail to take adaptive action.

Paradoxical undressing has been widely reported in hypothermic patients. This final preterminal effort may be related to peripheral vasoconstrictive changes of hypothermia. Hypothermic patients who have paradoxically undressed have been mistaken for victims of sexual assault or thought to have a psychiatric disorder. In urban settings, hypothermia is most commonly associated with alcohol consumption or underlying illness. Other causes include stroke, drug overdose, psychiatric emergency, and major trauma.

Neurologic manifestations vary widely. A progressive decrease in the level of consciousness is usually proportional to the degree of hypothermia. Some patients, however, continue to be verbally responsive and display intact reflexes at 27°C to 25°C (80.6°F to 77°F).

Eye movement abnormalities and extensor plantar responses do not correlate directly with the degree of hypothermia. Cranial nerve signs may be seen with bulbar damage from central pontine myelinolysis. Above 22°C (71.6°F), it should be assumed that nonreactive dilated pupils reflect inadequate tissue perfusion rather than hypothermia.

Neuromuscular examination may reveal stiff posture, pseudo–rigor mortis, or opisthotonos. Reflexes are usually hyperactive to 32°C (89.6°F) and then become hypoactive, disappearing around 26°C (78.8°F). Cremasteric reflexes are absent because the testicles are already retracted. The plantar response usually remains flexor until 26°C (78.8°F). The knee jerk reflex is the last reflex to disappear and the first to reappear with rewarming. Diagnosis of CNS disorders, including spinal cord lesions, may be obscured by hypothermia. From 30°C to 26°C (86°F to 78.8°F), both contraction and relaxation phases of the reflexes are equally prolonged. If intact, the ankle jerk is helpful to diagnose hypothermic myxedema. Myxedema characteristically prolongs the relaxation phase more than the contraction phase.

Psychiatric disorders do not improve when the patient is cold. Mental status alterations can include anxiety, perseveration, neurosis, and psychosis. Individuals who are functional in warm conditions may decompensate in cold weather. Hypothermia-induced psychiatric presentations and suicide attempts are commonly misdiagnosed.

Differential Diagnoses

The differential diagnosis of hypothermia is broad and includes hypothyroidism, hypopituitarism, diabetes, hypoglycemia, malnutrition, intracranial and spinal cord injuries, and sedative-hypnotic and alcohol intoxication (see Box 128.1). Hypothermia is also common in patients with Wernicke encephalopathy. Hypothermia can mask the usual clinical triad of ophthalmoplegia, confusion, and truncal ataxia. Intravenous thiamine can be diagnostic and therapeutic.

Hypothermia occurs in conjunction with infections, most commonly overwhelming gram-negative sepsis, pneumonia, meningitis, and encephalitis. Other infections that can lead to hypothermia include bacterial endocarditis, brucellosis, malaria, syphilis, typhoid, miliary tuberculosis, and trypanosomiasis.

Medical conditions associated with hypothermia include carcinoma, pancreatitis, peritonitis, and cerebrovascular disease. Low cardiac output resulting from myocardial infarction can induce hypothermia. Fetal and maternal bradycardia and hypothermia may result from magnesium sulfate infusion during preterm labor. Hypothermia can cause delayed recovery from neuromuscular blockade. Although many conditions can cause or be associated with accidental hypothermia, there is no true differential diagnosis of accidental hypothermia once the diagnosis has been established by core temperature measurement.

BOX 128.2 Presenting Signs of Hypothermia

Head, Eye, Ear, Nose, Throat
Mydriasis
Decreased corneal reflexes
Extraocular muscle abnormalities
Erythropsia (altered color perception)
Flushing
Facial edema
Epistaxis
Rhinorrhea
Strabismus

Cardiovascular
Initial tachycardia
Subsequent bradycardia
Dysrhythmias
Decreased heart tones
Hepatojugular reflux
Jugular venous distention
Hypotension

Respiratory
Initial tachypnea
Adventitious sounds
Bronchorrhea
Progressive hypoventilation
Apnea

Gastrointestinal
Ileus
Constipation
Abdominal distention or rigidity
Poor rectal tone
Gastric dilation in neonates or in adults with myxedema

Genitourinary
Anuria
Oliguria
Polyuria
Testicular torsion

Neurologic
Depressed level of consciousness
Ataxia
Hypesthesia
Dysarthria
Antinociception
Amnesia
Initial hyperreflexia
Anesthesia
Hyporeflexia
Areflexia
Central pontine myelinolysis

Psychiatric
Impaired judgment
Perseveration
Mood changes
Flat affect
Altered mental status
Paradoxical undressing
Neuroses
Psychoses
Suicide
Organic brain syndrome

Musculoskeletal
Increased muscle tone
Shivering
Rigidity or pseudo–rigor mortis
Paravertebral spasm
Opisthotonos
Compartment syndrome

Dermatologic
Erythema
Pernio
Pallor
Frostnip
Cyanosis
Frostbite
Icterus
Popsicle panniculitis (inflammation of the cheeks; also called "cold panniculitis")
Sclerema (hardening of subcutaneous tissue)
Cold urticaria
Ecchymosis
Necrosis
Edema
Gangrene

Diagnostic Testing

Except in mild cases of hypothermia, initial laboratory evaluation should include glucose level, complete blood cell count, comprehensive metabolic panel, serum lipase level, and coagulation studies. Blood urea nitrogen and creatinine levels should be checked because renal failure may occur after rewarming in patients with chronic hypothermia. Arterial or venous blood gases, if obtained, should not be temperature-corrected. A serum ethanol level and urine toxicology screen may be helpful based on history or when a depressed level of consciousness is inconsistent with the degree of hypothermia. Thyroid function studies, cardiac markers, and serum cortisol levels may also be indicated.

Acid-Base Balance. Blood gas analyzers warm blood to 37°C (98.6°F), increasing the partial pressure of dissolved gases. This results in arterial blood gases with higher oxygen and carbon dioxide and lower pH than in vivo values. Attempting to maintain a corrected pH at 7.4 and arterial partial pressure of carbon dioxide ($Paco_2$) at 40 mm Hg during hypothermia depresses cerebral and coronary blood flow and cardiac output and increases the incidence of VF. The ideal acid-base goal is an uncorrected pH of 7.4 and $Paco_2$ of 40 mm Hg.

Cold blood buffers poorly. In normothermia, pH decreases by 0.08 unit for every 10-mm Hg increase in $Paco_2$. At 28°C (82.4°F), the decrease in pH doubles. Because the neutral point of water at 37°C (98.6°F) is a pH of 6.8, the normal 0.6-unit pH offset between blood and intracellular water should be maintained at all temperatures (Fig. 128.3). Intracellular electrochemical neutrality ensures optimal

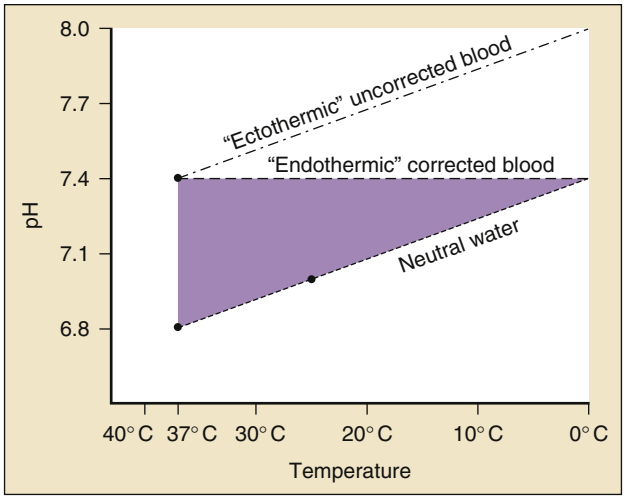

Fig. 128.3 Neutrality reflects the pH of water at any given temperature. The pH of water is 6.8 at 37°C (98.6°F) and 7.0 at 25°C (78.8°F). The physiologically ideal intracellular-to-extracellular, 0.6-unit pH offset will be maintained if the arterial pH is kept at 7.42, uncorrected for temperature.

enzymatic function at all temperatures. Relative alkalinity affords myocardial protection and improves the heart's electrical stability.

Hematologic Evaluation. The hematocrit can be deceptively high due to decreased plasma volume. The hematocrit increases 2% for every 1°C (1.8°F) fall in temperature. A low-normal hematocrit level in a moderately to severely hypothermic patient should suggest acute or chronic blood loss.

Splenic, hepatic, and splanchnic sequestration in hypothermia decreases leukocyte and platelet counts. As in normothermia, a normal white blood cell count does not exclude infection, especially if the patient is debilitated, alcoholic, myxedematous, or at either extreme of age.

Frequent evaluation of serum electrolyte levels during rewarming is essential. There are no safe predictors of values or trends. Changes occur in membrane permeability and in the sodium-potassium pump. The patient's preexisting physiologic status, severity and chronicity of hypothermia, and method of rewarming alter the serum electrolyte values.

The plasma potassium level is independent of hypothermia. Hyperkalemia can be associated with metabolic acidosis, rhabdomyolysis, or renal failure. Hypothermia enhances the cardiac toxicity of hyperkalemia and obscures premonitory electrocardiographic changes. Hypokalemia is most common with chronic hypothermia. It results from potassium entering muscle, rather than potassium diuresis. A decline in the serum potassium level despite a decreasing serum pH is caused by intracellular pH fluxes greater than extracellular pH fluxes.

Conditions associated with hypokalemia include preexisting diabetic ketoacidosis, hypopituitarism, inappropriate secretion of antidiuretic hormone, previous diuretic therapy, and alcoholism. If the serum potassium level is less than 3 mEq/L, provide supplementation during rewarming.

Blood urea nitrogen and creatinine levels are elevated with preexisting renal disease or decreased clearance. Because of hypothermic fluid shifts, hematocrit and blood urea nitrogen levels are poor indicators of actual fluid status.

The blood glucose level may provide a subtle clue to the chronicity of hypothermia. Acute hypothermia initially elevates the blood glucose level by catecholamine-induced glycogenolysis, diminished insulin release, and inhibition of cellular membrane glucose carrier systems. Subacute and chronic hypothermia produce glycogen depletion, leading to hypoglycemia. Hypoglycemia can also develop during rewarming in acute hypothermia. Symptoms of hypoglycemia can be masked by hypothermia. A cold-induced renal glycosuria neither implies hyperglycemia nor guarantees normoglycemia.

When hyperglycemia persists during rewarming, suspect hemorrhagic pancreatitis or diabetic ketoacidosis. Actively rewarm patients with diabetic ketoacidosis past 30°C (86°F) because insulin is ineffective below 30°C (86°F). Correction of hypoglycemia corrects the level of consciousness only to the level consistent with the degree of hypothermia.

Severe hypothermia also causes serum enzyme level elevation because of the ultrastructural cellular damage. Rhabdomyolysis is commonly associated with cold exposure. Ischemic pancreatitis may result from the microcirculatory shock of hypothermia. Decreased pancreatic blood flow then activates proteolytic enzymes, increasing the serum lipase level.

Hypothermic Coagulation. A physiologic hypercoagulable state can occur with hypothermia and can be associated with a disseminated intravascular coagulation (DIC)–type syndrome. The cause may be catecholamine or steroid release, circulatory collapse, or release of tissue thromboplastin from cold, ischemic tissue.

Coagulopathies also occur because the enzymatic activity of the activated clotting factors is depressed by the cold. Clotting prolongation is proportional to the number of steps in the cascade. Because kinetic tests of coagulation are performed in the laboratory at 37°C (98.6°F), there is a disparity between clinically evident coagulopathy in vivo and deceptively normal prothrombin times, partial thromboplastin times, and international normalized ratios reported by the laboratory. The only effective treatment is rewarming, not administration of clotting factors.

Leukopenia and thrombocytopenia usually reverse with rewarming. Clinically significant coagulopathies can still occur, particularly in association with trauma and volume resuscitation. Cold-induced thrombocytopenia may be from direct bone marrow suppression or from splenic and hepatic sequestration. Platelet thromboxane B2 production is also temperature dependent, which can result in decreased platelet function and adhesion.

Elevated blood viscosity seen in hypothermia may be exacerbated in patients with cryoglobulinemia or cryofibrinogenemia, especially in older patients. Cryofibrinogen, a cold-precipitated fibrinogen, is associated with collagen vascular diseases, carcinomas, and coliform sepsis. Cold hemagglutination from cold agglutinins produces hemolysis or agglutination with thrombosis, which might explain the increase in coronary and cerebral thromboses in winter.

Imaging

If the patient is not alert and there is suspicion of trauma, standard trauma imaging is indicated, including an extended focused assessment with sonography in trauma (eFAST) and computed tomography (CT) scan of the head. CT scanning of the abdomen and pelvis may show pancreatic calcifications, unsuspected pneumoperitoneum, small bowel dilation from hypothermia-induced mesenteric vascular occlusion, or colonic dilation associated with myxedema coma.

Management

General Measures

Patients who are cold, stiff, and cyanotic, with fixed pupils, inaudible heart tones, and no visible thoracic excursions, can still be successfully resuscitated. Unexpectedly, a few patients have revived in the morgue while awaiting autopsy.

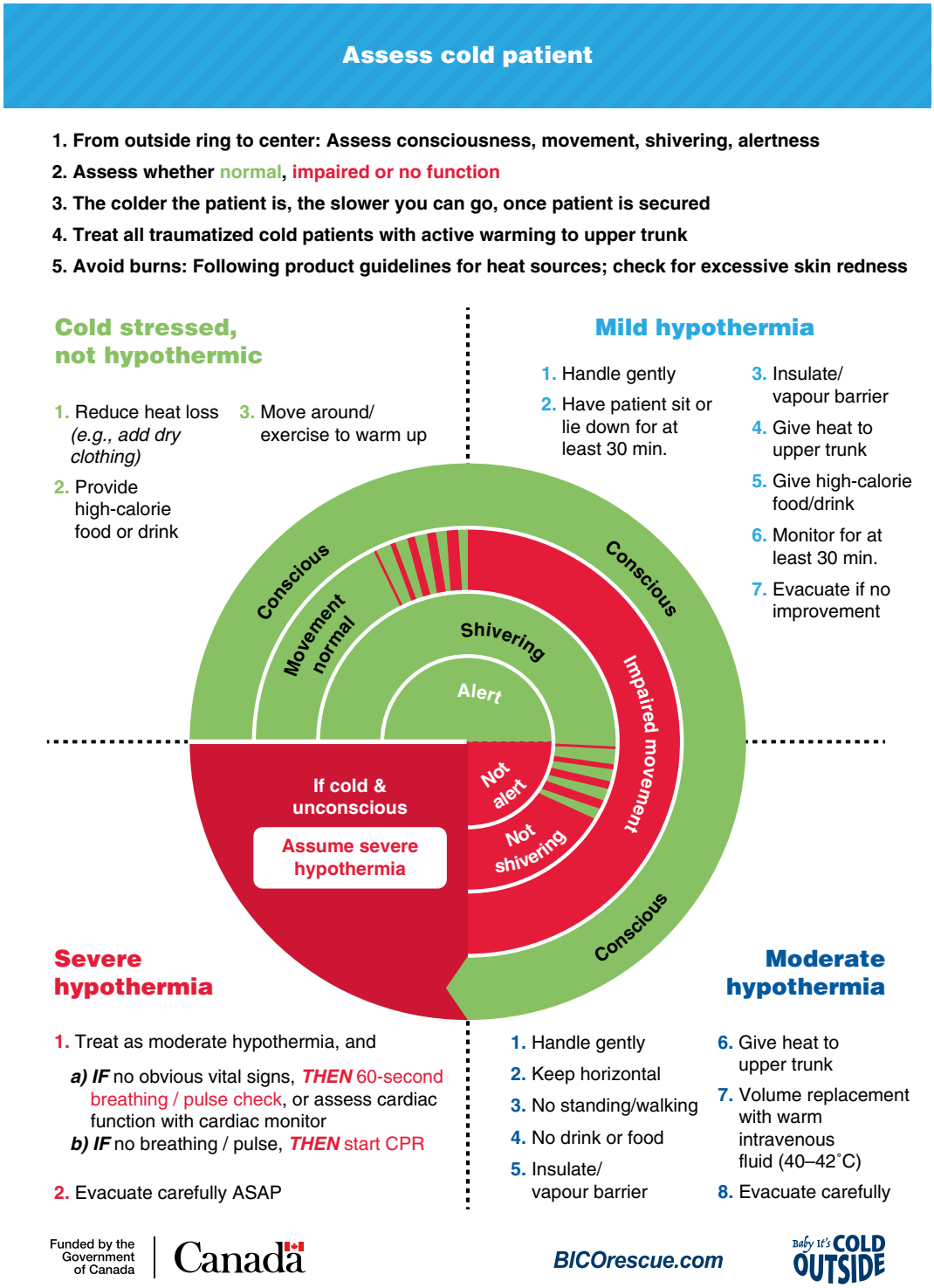

Fig. 128.4 "Cold card" for treatment of cold patients.

Pertinent history includes information about preexisting cardiac, pulmonary, neurologic, or endocrine disease. The duration of exposure, outdoor conditions, circumstances of discovery, associated injuries, and predisposing conditions should be documented. Initial management should emphasize prevention of further heat loss. Specific goals of prehospital care include adequate insulation, avoidance of core afterdrop, gentle handling, and transport in a horizontal position.[4] Hypothermic patients should be actively rewarmed in the field, if possible.[4] A graphic flowchart to assist with clinical staging of hypothermia and to guide treatment is available as a "cold card" (Figure 128.4).[5]

A patient who is unresponsive and not shivering should be treated for severe hypothermia. At core temperatures below 32°C (89.6°F), expect an irritable myocardium, a large temperature gradient between the core and periphery, and relative hypovolemia.

In the ED, hypothermia should be confirmed and monitored with continuous core temperature evaluation. Clinically, the rectal

temperature is most widely used. However, it lags behind core temperature changes and is influenced by lower extremity temperatures and probe placement. The probe should be inserted to 15 cm and not placed into cold feces. Epitympanic temperature equilibrates rapidly with core temperature and is closest to the hypothalamic temperature. Most epitympanic probes are not suitable for field use.[4] Infrared thermography (tympanic temperature) is too unreliable be used, except to exclude hypothermia. So-called temporal artery thermometers are often random number generators and unreliable for clinical use. If the airway is protected, an esophageal probe placed in the lower third of the esophagus, an average of 24 cm below the larynx in adults, is the ideal method for continuous core temperature monitoring. If the probe is placed higher, the reading can be falsely elevated by inhalation of heated oxygen. An esophageal probe without markings can have tape placed on the proximal part to mark the correct depth of insertion.

Hand-held Doppler may be useful to establish the presence of a spontaneous pulse. Bedside echocardiography should precede chest compressions. Pulse oximetry is usually unreliable in hypothermia with peripheral vasoconstriction. It is often not possible to obtain an accurate reading. End-tidal carbon dioxide measurements accurately assess tissue perfusion and tracheal tube placement, but only at normal temperatures. Commercially available devices do not function when humidified air is used for airway rewarming. Endotracheal intubation or placement of a supraglottic airway may be indicated unless the patient has intact protective airway reflexes. Cold depression of ciliary activity allows for the accumulation of secretions with frothy sputum and chest congestion. It may be hard to differentiate between bronchorrhea and pulmonary edema. Fiberoptic or blind nasotracheal intubation can be useful to avoid a surgical airway when cold-induced trismus is present.

Dysrhythmias during intubation are rare. These may be due to failure to preoxygenate, mechanical jostling, acid-base changes, and electrolyte level fluctuations. A nasogastric tube is indicated after endotracheal intubation because decreased gastric motility and gastric dilation are common. Physical examination of the abdomen is unreliable because cold can induce rectus muscle rigidity. Many moderately and severely hypothermic patients have decreased or absent bowel sounds. It is important to evaluate the patient for an associated ileus, pancreatitis, or occult trauma.

In moderate and severe hypothermia, indwelling urinary catheters are useful to monitor urine output and help determine the severity of vascular fluid shifts.

Cardiac monitoring should be continuous. If central venous access is required, avoid insertion of the catheter tip into the heart, which can irritate the myocardium and precipitate dysrhythmias. Arterial catheters for continuous monitoring of intra-arterial blood pressure may be helpful in profoundly hypothermic patients. Placement of a pulmonary artery catheter risks perforation of a cold, stiff, pulmonary artery and is not recommended in the emergency department.

Volume Resuscitation

Patients with moderate or severe hypothermia are usually volume depleted. They are prone to thromboembolism resulting from increased viscosity. During rewarming, the total plasma volume is usually high, but the circulatory plasma volume is usually low due to increased peripheral vascular resistance. Rapid volume expansion can be lifesaving, especially in hypothermic neonates. Adult patients with moderate or severe hypothermia should initially receive a 500-mL fluid challenge of warmed normal saline. Avoid lactated Ringers solution because the cold liver metabolizes lactate poorly. Fluids administered via the intravenous (IV) route should be warmed to 40°C to 42°C (104°F to 107.6°F). If a commercial fluid or blood warmer is not available, IV fluids can be heated in a standard microwave. Shake the fluid bag before administration to avoid hot spots. Avoid rapid central venous administration, which may produce myocardial thermal gradients. Another option in vasoconstricted patients is administration via the intraosseous route. Countercurrent heat exchangers effectively heat crystalloids and blood from 10°C to 35°C (50°F to 95°F). There can be significant conductive heat loss through IV tubing, especially with long lengths of tubing at slow flow rates. It is preferable to administer fluids as boluses to effect rather than as drips.

Normally, hypothermia increases natriuresis. Preexisting gastrointestinal losses or previous diuretic treatment can also contribute to sodium loss. Patients with a normal sodium level and osmolality may have preexisting sodium overload as a result of cirrhosis, nephrosis, or congestive heart failure. However, most patients will be free-water depleted, elevating the sodium level and osmolality. Hemoconcentration due to decreased plasma volume, fluid shifts, and increased vascular permeability usually is present. Hemodilution can occur from parenteral crystalloid administration, but a low hematocrit can also result from acute hemorrhage or preexisting anemia.

Advanced Life Support

During hypothermic cardiac arrest, cardiac output and cerebral and myocardial blood flows are much less than those during normothermic closed chest compressions. Metabolic demands, however, are also less during hypothermia.

Blood flow during cardiopulmonary resuscitation (CPR) in patients with hypothermia differs from flow during normothermia. In normothermia, some flow results from phasic alterations in the intrathoracic pressure rather than from direct cardiac compression. In hypothermia, the heart is a passive conduit, and phasic alterations in the intrathoracic pressure are exerted equally on all cardiac chambers. The mitral valve remains patent during systole, and blood continues to circulate through the left side of the heart. This explains an observation of a thoracotomy in a patient who ultimately survived severe hypothermia: "the heart was found to be hard as stone and it is hardly conceivable how effective external cardiac massage could have been." There have been many neurologically intact survivors after prolonged closed chest compressions.

Chest wall elasticity and pulmonary compliance are decreased with cold. More force is needed to depress the chest wall sufficiently to generate adequate intrathoracic pressure gradients. Powered thoracic compression devices are useful during prolonged resuscitations pending decisions about extracorporeal rewarming.

Apparent rigor mortis and fixed dilated pupils are not reliable criteria for withholding CPR in a hypothermic patient. Accurately diagnosed dependent lividity is a sign of death even in hypothermia, although previous guidelines have stated the contrary. Because intermittent flow may provide adequate support during evacuation, CPR should not be withheld just because continuous compressions cannot be ensured.[6]

Rescuers should initiate CPR in accidental hypothermia unless do-not-resuscitate status is known, obviously lethal injuries are present, chest wall depression is impossible, signs of life are present, or rescuers are endangered.[4] If possible, verify that there is no spontaneous mechanical cardiac activity with bedside ultrasonography before chest compressions are initiated.

Pharmacologic Treatment

The efficacy of most medications is temperature dependent. Protein binding increases during hypothermia. Liver metabolism is decreased. Large doses could be required to achieve a therapeutic response. Toxic levels could develop with rewarming. In severe hypothermia, withhold

medications until the patient is warmed, and then leave longer intervals between doses. No medication should be given orally because of the patient's decreased gastrointestinal motility. Intramuscular medications are also contraindicated because of poor absorption from vasoconstricted sites.

Cardiovascular Medications. The effects of hypothermia on the autonomic nervous system are variable. In primates, sympathetic response increases rapidly to cooling from 37°C to 31°C (98.6°F to 87.8°F) and then switches off at about 29°C (84.2°F). This suggests that modest catecholamine support might be useful below 29°C (84.2°F).

Pharmacologic manipulation of the pulse and blood pressure should be avoided. Epinephrine and other vasoconstrictors may be dysrhythmogenic and have a minimal effect on the maximally constricted peripheral vasculature. There are no clear indications for vasopressors although, in animal models, the return of spontaneous circulation after induced VF below 30°C (86°F) is higher after the administration of vasopressors.

Inotropes are usually not necessary to support blood pressure. Inotropic support may be considered in disproportionately hypotensive patients who do not maintain a mean arterial pressure of 60 mm Hg in response to volume replacement and rewarming.

Atrial dysrhythmias are common below 32°C (89.6°F), associated with a slow ventricular response. Atrial fibrillation is common but self-limited and typically converts spontaneously during rewarming. Beta blockers and calcium channel blockers are contraindicated unless there is a rapid ventricular response.

Preexisting, chronic, premature ventricular contractions can be suppressed during hypothermia and recur during rewarming. Most hypothermia-induced dysrhythmias convert spontaneously during rewarming. Asystole that develops during rewarming is not as ominous as asystole in normothermic patients. For VF, defibrillation should be attempted at the usual energy level. Successful defibrillation has been reported at 20°C (68°F) but attempted defibrillation is often unsuccessful until the core temperature is above 30°C (86°F). If a defibrillation attempt is unsuccessful, active rewarming should be initiated while continuing CPR. Defibrillation can be attempted occasionally during rewarming. Once the core temperature is above 30°C (86°F), further attempts can be made.[7]

The ideal approach to ventricular dysrhythmias in the hypothermic patient has not been well studied. Lidocaine and propranolol have minimal hemodynamic effects during hypothermia. Their efficacy in the treatment of ventricular dysrhythmias appears limited. In a canine model of severe hypothermic VF, neither amiodarone nor bretylium was effective. Human chemical defibrillations with bretylium tosylate in cases of severe hypothermia have been reported. Recurrent VF was controlled by isoproterenol in one reported case.[8] Amiodarone can cause torsades de pointes by QT prolongation and its safety during accidental and induced hypothermia is not known.

In hypothermia, at least one Group 1 antidysrhythmic agent, procainamide, increases the incidence of VF. Another drug in the same group, quinidine, can prevent VF during induced profound hypothermia and during cardiac manipulation at 25°C to 30°C (77°F to 86°F). Transvenous cardiac pacing is hazardous for bradydysrhythmias in hypothermia. External pacing may be worth trying in the rare setting of profoundly disproportionate bradycardia. Transcutaneous pacing has been used to facilitate continuous arteriovenous rewarming in perfusing patients by raising the systolic blood pressure above 60 mm Hg. Other active rewarming techniques do not require specific pressure gradients.

Antibiotics. Hypothermia compromises host defenses and predisposes to infection. In hypothermia, the usual signs of infection, including fever, are absent. Shaking chills from sepsis may be mistaken for shivering. Suspect CNS injury or infection if a patient's mental status remains altered, despite rewarming.

In hypothermic children younger than 3 months, empirical antibiotics are indicated after cultures have been obtained. There are no reliable clinical or laboratory indicators of infection, but bradycardia, anemia, uremia, and high serum glucose levels, as well as leukocyte abnormalities, are common clues. The role of empirical antibiotics in adults is less clear. Although gram-negative septicemia may cause hypothermia, coexistent infections from gram-positive cocci, Enterobacteriaceae, and oral anaerobes are common.

Older adults with thermoregulatory failure have a high risk of mortality and should be considered septic until proven otherwise. Routine empiric antibiotics are warranted in hypothermia only in geriatric patients. Administer antibiotics if the clinical picture is consistent with septic shock or if there is failure to rewarm. Cellulitis, myositis, bacteriuria, or infiltrate on chest x-ray warrants immediate antimicrobial therapy. In an urban setting, infection is the leading cause of failure to rewarm and subsequent mortality.

Failure to Rewarm. Cold abolishes adrenal responsiveness to adrenocorticotropic hormone (ACTH). A false diagnosis of decreased adrenal reserve is possible. The increase in ACTH level seen in hypothermic individuals may be a neurogenic or emotional response to the cold.

Acute cold stress initially stimulates cortisol secretion. There may already be a very high level as a result of underlying stress. In clinical series, total serum cortisol levels are commonly elevated; however, the active free fraction is decreased due to increased protein binding. Failure to rewarm may be due to adrenocortical insufficiency or steroid dependence. If either condition is suspected, administer 100 mg IV of hydrocortisone.

Empirical treatment with thyroxine is reserved for patients thought to have myxedema. Thyroid hormone should be replaced if there is a history of hypothyroidism, suggestive neck scar, or failure to rewarm. After thyroid function study samples have been drawn, levothyroxine, 250 to 500 µg IV, can be slowly administered over several minutes. Daily injections of 50 to 100 µg are necessary for 5 to 7 days. Hydrocortisone (100–200 mg) should be added to the first several liters of crystalloid fluid. The absorption of oral or intramuscular levothyroxine is variable. IV administration has a smooth effect after the onset of action at 6 to 12 hours. This will be manifested by improvement in vital signs and rewarming rate. Half the dose is converted by the peripheral tissues into L-triiodothyronine (T_3). An underlying infection can also compromise thermogenesis.

Rewarming

There are no published controlled studies comparing rewarming methods in hypothermia. Rigid treatment protocols are not evidence-based. The emergency clinician should choose specific methods on a case-by-case basis, taking into account availability, institutional resources, and clinical experience.

Passive External Rewarming. Spontaneous passive external rewarming is noninvasive. It is the treatment of choice for patients with mild hypothermia when active rewarming is not available. The patient should be able to generate sufficient metabolic heat to maintain an acceptable rate of spontaneous rewarming. Older adults are commonly glycogen-depleted, have central hypovolemia, and are not capable of normal cardiovascular or metabolic homeostasis.

The normal processes of heat dissipation are minimized by passive external rewarming. Cessation of evaporation and convection is coupled with insulation against further radiation of heat. This technique simply involves covering the patient with an insulating material in a favorable atmospheric condition. The ambient temperature should exceed 21°C (69.8°F). When the air is stationary, less heat is lost to conduction, convection, and radiation.

BOX 128.3 Indications for Active Rewarming

Cardiovascular instability
Mild to severe hypothermia
Inadequate rate of rewarming or failure to rewarm
Endocrine insufficiency
Trauma
Traumatic or toxicological peripheral vasodilation
Secondary hypothermia impairing thermoregulation

Shivering is the most effective thermoregulatory neuromuscular response to cold in humans. Without shivering, endogenously generated metabolic heat is insufficient to raise the core temperature. When the core temperature exceeds 32°C (89.6°F), unless complete glycogen depletion occurs, the major source of heat production is shivering thermogenesis.

Recommended rewarming rates vary between 0.5°C and 2.0°C/hr (0.9°F and 3.6°F/hr). The rewarming rate should be rapid enough to avoid prolonged exposure to dysrhythmias. Below 32°C (89.6°F), humans are functionally poikilothermic. Shivering is ineffective below 32°C (89.6°F) and absent below 30°C (86°F).

Active Rewarming. Active rewarming is the direct transfer of exogenous heat to the patient. It can be accomplished by external or internal techniques. Active rewarming is useful in mild hypothermia to decrease metabolic requirements of rewarming and improve thermal comfort.

In moderate to severe hypothermia, cardiovascular instability and decompensation require prompt elevation of the core temperature while minimizing afterdrop (Box 128.3). Defibrillation is rarely successful at temperatures below 28°C (82.46°F). Active rewarming is indicated with strokes and other conditions that impair CNS control of thermoregulation. Active rewarming is also indicated for patients when endogenous thermogenesis is insufficient or when glycogen depletion is present, usually from endocrine causes that include hypopituitarism, adrenal insufficiency, hypothyroidism, and Wernicke encephalopathy. Active rewarming is recommended in diabetic ketoacidosis because the core temperature must be elevated above 30°C (86°F) before insulin becomes effective.

Pharmacologically induced peripheral vasodilation or acute spinal cord transection prevents sufficient thermogenesis and requires active rewarming. Patients with severe hypothermia do not necessarily require invasive extracorporeal rewarming techniques, especially if they have a sustained perfusing rhythm.

Aggressive treatment of hypothermia is indicated in infants. Rapid rewarming is advantageous because it minimizes energy expenditures. Hypothermic neonates have been successfully rewarmed using minimally invasive methods. A neonate with a core temperature of 14.8°C (58.6°F) receiving CPR made a full neurologic recovery after being rewarmed by active external rewarming (AER), warmed IV fluids, and heated, humidified ventilator gases.

Active External Rewarming. Early concern with AER was sparked after a 1961 study, in which 20 of 23 patients died. Retrospective analysis of clinical series has shown widely varying mortality rates with AER. Various methods conduct heat directly to the skin. Rewarming options include plumbed garments that circulate warm fluids, hot water bottles, heating pads, forced air warming systems, and radiant sources. Thermal injury to vasoconstricted hypoperfused skin is a potential hazard with local heat application.

Forced air warming systems efficiently transfer heat. They can be used in field conditions or in the ED. These devices circulate hot air through a blanket. The air flows through apertures on the patient's side, allowing convective transfer of heat. Hypotension and core temperature afterdrop are not seen in forced air warming for accidental hypothermia in the ED. Like all active methods, forced air warming decreases shivering and is able to transfer large amounts of heat while minimizing afterdrop. Other options include thermoregulatory systems that circulate warm water through energy transfer pads.

Arteriovenous anastomosis (AVA) rewarming is a unique, noninvasive, AER technique. Exogenous heat is provided by immersion of distal extremities (upper extremities to the elbows and lower extremities to the knees) in hot (44°C to 45°C [111.2°F to 113.6°F]) water. The heat opens the AVAs, which are 1 mm below the epidermal surface in the digits. As a result, there is an increased flow of warmed venous subcutaneous blood returning directly to the heart. The forearms and calves must be included for this technique to be effective. The AVA technique was designed for use on ships and is not practical in most situations. In addition, many patients cannot tolerate the very hot water. Burns of vasoconstricted skin are a potential hazard.

Previously healthy patients with acute hypothermia are optimal candidates for AER. They have minimal dehydration and pathophysiologic circulatory changes. If AER is used, and the extremities are vasoconstricted, the heat source should be applied preferentially to the thorax rather than to the extremities. Application of heat to the extremities increases the cardiovascular load by increasing the metabolic requirements of the peripheral musculature. The depressed cardiovascular system may not be able to meet the demands, resulting in cardiovascular collapse.

Combining truncal AER with core rewarming can also be successful. The provision of heated humidified oxygen and warmed IV fluids, in addition to AER, may help prevent hypoxia, metabolic acidosis, core temperature afterdrop, and hypotension. If AER is used to treat moderate or severe hypothermia, it can be combined with one or more active core rewarming techniques.

Active Core Rewarming. Many methods achieve active rewarming of the core. These techniques minimize the risk of rewarming collapse in patients with core temperatures below 32°C (89.6°F).

Airway Rewarming. Airway rewarming with heated humidified oxygen is a simple and inexpensive method that can be used as an adjunct to other forms of active rewarming in moderate or severe hypothermia, although it is ineffective on its own. Airway rewarming improves oxygenation, helps avoid afterdrop, stimulates pulmonary cilia, decreases viscosity of pulmonary secretions, and reduces cold-induced bronchorrhea. Pulmonary absorption of moisture does not adversely affect surfactant or increase pulmonary congestion.

The respiratory tract is a limited site for heat exchange, but heated humidified oxygen increases blood oxygen content and temperature in the pulmonary circulation. The myocardium is perfused by warmer oxygenated blood, decreasing intermittent temperature gradients.

Sufficient minute volume and complete humidification are necessary for maximal heat delivery. Because dry air has low thermal conductivity, ventilation with warm dry air provides negligible heat. Increases in rewarming rates from 1°C to 4.5°C/hr (1.8°F to 8.1°F/hr) have been reported with heated humidified oxygen. The larger increases are unlikely to be true. Increases in warming rates with endotracheal intubation are higher than those with a mask. Positive-pressure ventilation with a mask can be used but has not been studied.

Maintenance of sufficient oxygenation is important in moderate to severe hypothermia. In patients on cardiopulmonary bypass cooled to 28°C to 30°C (82.4°F to 86°F), the capacity of hemoglobin to unload oxygen to the tissue is less than half that found in normothermic patients. Despite lower metabolic requirements, this decreased functional hemoglobin, combined with a depressed respiratory minute volume, results in minimal oxygen reserves. Some patients maintain a level of spontaneous respiration appropriate to depressed carbon

dioxide production. This may not be the case in patients with coexisting toxicologic, traumatic, or metabolic depression of the respiratory center.

Providing heated, humidified oxygen to a patient with spontaneous respiration requires a heated cascade nebulizer. An immersion heater can be connected to a hose with a warming wire. Because patients with a depressed level of consciousness do not complain of pain, it is essential to check the temperature of the inspired air frequently with an in-line temperature probe. The gas temperature should be maintained at 42°C to 45°C (107.6°F to 113°F). Most heater modules require modification to allow the temperature to reach 42°C to 45°C (107.6°F to 113°F). Modified heater modules should be labeled to avoid routine use. Most humidifiers will not exceed 41°C (105.8°F) close to the patient outlet with a 2-m tubing length. Strategies to circumvent the 41°C (105.8°F) ceiling include reduction of tubing length, addition of more heat sources, disabling of the humidifier safety system, and placement of the temperature probe outside the patient circuit. Because of the modest clinical benefit in stable patients, it is probably not worth the effort to circumvent the 41°C (105.8°F) ceiling. The only report of thermal airway injury was in a patient ventilated by endotracheal tube for 11 hours with 80°C (176°F) inhaled gas.

Peritoneal Dialysis. Peritoneal dialysis delivers dialysate at 40°C to 45°C (104°F to 113°F). Heat is conducted directly to intraperitoneal structures through the posterior parietal peritoneum and the solid viscera and through the hemidiaphragms to the heart and lungs. A double-catheter system with suction at the outflow can theoretically increase flow to about 6 L/hr. Two liters are infused, retained for 20 minutes, and then aspirated. In practice, it can be difficult to recover all of the infused fluid. This lowers the achievable flow rate. Rewarming rates average 1°C to 3°C/hr (1.8°F to 5.4°F/hr).

An additional benefit of peritoneal dialysis is hepatic rewarming, which reactivates detoxification and conversion enzymes. Serum electrolyte levels should be monitored because peritoneal dialysis can exacerbate preexisting hypokalemia. Peritoneal lavage is useful primarily in severe cases in combination with other rewarming techniques for patients without spontaneous perfusion but has also been used alone in patients undergoing CPR for whom extracorporeal circulation was thought to be contraindicated due to coagulopathy or was not available.

Heated Irrigation. Heat transfer from irrigation fluids is usually limited due to the minimal surface area available for heat exchange. Gastric or colonic irrigation can cause fluid and electrolyte level fluxes and are not recommended. An esophageal heat transfer device with closed circulation of heated water is practical and has been used successfully for rewarming in hypothermia.[9]

Closed thoracic lavage can be useful in severe hypothermia. Two large-bore thoracostomy tubes are inserted into one or both hemithoraces. One is inserted anteriorly in the second or third intercostal space at the midclavicular line, the historical classic site for needle thoracostomy. The other is inserted between the fifth and sixth intercostal spaces in the posterior axillary line, the usual site for tube thoracostomy. Normal saline heated to 40°C to 42°C (104°F to 107.6°F) is infused into the superior tube. The inferior tube is used for drainage. Left-sided tube insertion in perfusing patients risks causing VF. Efficiency of the heat transfer varies with flow rate and dwell times. Pleural adhesions can prevent adequate infusion and can result in a tension hydrothorax. Adequate drainage should be ensured to prevent intrathoracic hypertension.

Thoracic lavage is usually reserved for the severely hypothermic patient who does not respond to standard techniques or the patient with another indication for a chest tube. It should be combined with other rewarming modalities in potentially salvageable cardiac arrest patients. However, thoracic lavage has been used successfully in patients requiring CPR when extracorporeal circulation was not available. The rate of rewarming averages 3°C/hr (5.4°F/hr).

Mediastinal irrigation and direct myocardial lavage should be considered only in patients without spontaneous perfusion. The procedure requires a standard left lateral thoracotomy incision. The pericardium is not incised unless an effusion or tamponade is present. The heart is bathed in 1 to 2 L of an isotonic solution heated to 40°C (104°F) for several minutes. The fluid is removed and the lavage is repeated. Internal defibrillation is attempted at intervals of 2°C (3.6°F) after the myocardial temperature exceeds 26°C to 28°C (78.8°F to 82.4°F). When a perfusing rhythm is achieved, lavage is continued until the myocardial temperature exceeds 32°C (89.6°F). A median sternotomy approach allows ventricular decompression in addition to direct defibrillation. Open cardiac massage of a cold, rigid, and contracted heart may not generate flow.

Endovascular Rewarming. Another active core rewarming option uses endovascular warming devices that are intended for therapeutic cooling and subsequent rewarming of comatose, resuscitated, cardiac arrest patients.[10] These systems involve femoral vein catheterization with a closed-loop catheter that has a thermostat at the tip. If the core temperature is below 30°C (86°F), the fail-safe feature on the console must be circumvented to allow rewarming.

Diathermy. Truncal diathermy involves the conversion of energy waves into heat. Large amounts of heat can be delivered to deep tissues with ultrasonic and low-frequency microwave irradiation. Frostbite, burns, significant edema, and the presence of all types of metallic implants and pacemakers are contraindications. In spite of successes in piglets, infants, and a few adults, diathermy is still experimental.

Extracorporeal Blood Rewarming. The four common extracorporeal techniques to rewarm blood are venovenous rewarming, hemodialysis, continuous arteriovenous (AV) rewarming, and extracorporeal circulation–cardiopulmonary bypass (CPB and extracorporeal membrane oxygenation [ECMO]); Table 128.2).

In venovenous rewarming, blood is removed, ideally by a large peripheral venous catheter, heated to 40°C (104°F) and returned through a second venous catheter. Flow rates are 150 to 400 mL/min. The circuit is simple and efficient. There is no oxygenator, and the system does not provide circulatory support. Volume infusion is an option to augment inadequate cardiac output.

Standard hemodialysis is a widely available, practical rewarming technique. It is portable and efficient and can also be used to treat electrolyte abnormalities, renal failure, or intoxication with a dialyzable substance (e.g., ethylene glycol, methanol).

Continuous AV rewarming is an option if the blood pressure is at least 60 mm Hg, which may be maintained, if necessary, with CPR. AV rewarming involves the use of percutaneously inserted femoral arterial and contralateral femoral venous catheters. Heparin-bonded tubing circuits obviate the need for systemic anticoagulation. The blood pressure of a spontaneously perfusing, traumatized, hypothermic patient creates a functional arteriovenous fistula by diverting part of the cardiac output from the femoral artery through a commercially available countercurrent heat exchanger. The heated blood is then returned with admixed heated crystalloids through the femoral vein. Continuous AV rewarming avoids the need for specialized equipment and a perfusionist, which are necessary for cardiopulmonary bypass. The average rate of rewarming is 3°C to 4°C/hr (5.4°F to 7.2°F/hr). Because the catheters are 8.5 Fr, the patient should weigh at least 40 kg.

Extracorporeal circulation, also called *extracorporeal life support* or ECLS, refers to cardiopulmonary bypass or ECMO. In one review, the

TABLE 128.2 Extracorporeal Blood Rewarming Options

Options	Considerations
Venovenous circuit	Central venous catheter to central venous or peripheral catheter rewarming
	No oxygenator, circulatory support
	Flow rates, 150–400 mL/min
	Rate of rewarming 2°C–3°C/hr (3.6°F–4.5°F)
Hemodialysis circuit	Single- or dual-vessel cannulation; stabilizes electrolyte or toxicologic abnormalities
	Exchange cycle volumes 200–500 mL/min
	Rate of rewarming 2°C–3°C/hr (3.6°F–5.4°F/hr)
Continuous arteriovenous rewarming circuit	Percutaneous 8.5-Fr femoral catheters
	Requires blood pressure of 60 mm Hg systolic
	No perfusionist, pump, anticoagulation
	Flow rates, 225–375 mL/min
	Rate of rewarming, 3°C–4°C/hr (5.4°F–7.2°F/hr)
Cardiopulmonary bypass circuit	Full circulatory support with pump and oxygenator
	Perfusate-temperature gradient, 5°C–10°C/hr (9°F–18°F/hr)
	Flow rates, 2–7 L/min (average, 3–4 L/min)
	Rate of rewarming up to 9.5°C/hr (18.9°F/hr)

Adapted from: Danzl DF. Hypothermia and frostbite. In Kasper D, Fauci A, Hauser S, et al, eds. *Harrison's Principles of Internal Medicine*, ed 20. New York: McGraw-Hill; 2018.

mean temperature increase was 9.5°C/hr (17.1°F/hr) with CPB. ECMO appears to reduce the risk of intractable cardiorespiratory failure or severe pulmonary edema after rewarming.

The major advantage of extracorporeal circulation in perfusing patients is the preservation of flow if mechanical cardiac activity is lost during rewarming. Other candidates are patients who do not respond to less invasive rewarming techniques, those with completely frozen extremities, and those with rhabdomyolysis accompanied by major electrolyte disturbances. In some European centers, severely hypothermic patients without obvious trauma are admitted directly to the operating suite for extracorporeal circulation.

Very rapid rates of rewarming do not necessarily improve survival, but slow rewarming increases hospital mortality.[11] Complications of rapid rewarming include DIC, pulmonary edema, hemolysis, and acute tubular necrosis. Extracorporeal circulation can provide cardiovascular support in hemodynamically unstable patients.

Extracorporeal rewarming should be considered in hypothermic cardiac arrest patients if there are no contraindications to CPR.[12] A realistic assessment of the risk-benefit ratio for debilitated patients with secondary hypothermia should be made. Discontinue resuscitation if frozen or clotted intravascular contents are identified.

Disposition

Previously healthy patients who have mild primary accidental hypothermia (35°C to 32°C [95°F to 89.6°F) usually rewarm easily. They can be safely discharged if a warm environment is available. Patients with mild hypothermia associated with trauma are more difficult to rewarm and require admission.

Patients with severe hypothermia (<32°C [89.6°F]) generally require admission to an intensive care setting. These patients should be evaluated for the presence of underlying medical disorders (see Box 128.1). Cardiac monitoring should be considered for patients with persistent toxicologic or metabolic abnormalities and should be used for patients with cardiovascular instability or an inadequate rate of rewarming. Transfer of patients to tertiary care centers is generally not mandatory, but severely hypothermic patients may be most easily managed in facilities capable of extracorporeal circulation.

Because human physiologic responses are variable, it is difficult to predict outcomes. The type and severity of the underlying or precipitating disease process are major determinants.[13] The age of the patient is a weak predictor of mortality. Trauma, infection, and toxin ingestions unpredictably affect survival. Outcome prediction based on the Glasgow Coma Scale score is unreliable. Significant predictors of poor outcome include asphyxia, prehospital cardiac arrest, low or absent blood pressure, elevated blood urea nitrogen level, and need for endotracheal or nasogastric intubation in the ED. Patients with hypothermic cardiac arrest due to alcohol intoxication may have better neurologic outcomes than patients with hypothermic cardiac arrest from other causes.

In the past, the treatment dictum was that "*no one is dead until they are warm and dead.*" Now we realize that some patients are cold and dead. It would be useful and humane if they could be safely identified. The search for a valid triage marker of death continues. Grave prognostic indicators include evidence of intravascular thrombosis (fibrinogen < 50 mg/dL), ammonia levels greater than 250 mmol/L, and cell lysis (hyperkalemia > 10–12 mEq/L). In hypothermia with asphyxia in avalanche victims, hyperkalemia greater than 7 mEq/L is a reliable indicator of death.[14]

FROSTBITE AND NONFREEZING COLD INJURIES

KEY CONCEPTS

Frostbite

- Premature termination of thawing in 37°C to 39°C (98.6°F to 102.2°F) water is a common error. Reperfusion of completely frozen tissue may be painful, requiring parenteral analgesia.
- The early formation of clear blebs is more favorable than delayed formation of hemorrhagic blebs, which reflect damage to the subdermal vascular plexi.
- Advise patients that accurate prediction of eventual tissue loss is not always possible at presentation, despite imaging.
- Thrombolysis may salvage severely frostbitten tissue if given within 24 hours of thawing.

Nonfreezing Cold Injuries

- Immersion injuries should be rewarmed slowly and not above 30°C (86°F).
- Gentle cooling of nonfreezing cold injuries may be helpful to relieve pain and edema.
- Pernio can be treated by drying and gentle massage. The skin should not be warmed above 30°C (86°F).

FROSTBITE

Foundations

Background and Importance

Unlike other mammals that live outside the tropics, humans are susceptible to local cold injuries. Local cold injuries may occur in conjunction with systemic hypothermia. Frostbite involves tissue freezing with formation of ice crystals in the tissues. Immersion injury (trench foot) is a nonfreezing injury that results from exposure to wet cold.

Pernio (chilblains) is a nonfreezing injury that occurs in susceptible individuals, usually after repetitive exposure to dry or damp cold.

Historically, frostbite has been a disease of wars. Frostbite caused over 1 million casualties in World Wars I and II and the Korean War. Trench foot was common in the world wars and during the conflict in the Falkland Islands. Frostbite and immersion injuries are risks for anyone who ventures outdoors in severely cold conditions for recreation or work. Homeless or displaced people are also at risk, especially during cold winter months and disasters.

Anatomy, Physiology, and Pathophysiology

The human body attempts to maintain a core temperature of about 37°C (98.6°F). Skin cooling activates the anterior hypothalamus, causing catecholamine release, thyroid stimulation, shivering thermogenesis, and peripheral vasoconstriction. People are physiologically adapted to tropical conditions. In cold conditions, humans have a limited ability to protect themselves against decreased core temperature. Behavioral responses are far more effective if adequate clothing or shelter is available.

Cutaneous circulation is one of the keys to maintenance of a constant core temperature. Baseline cutaneous circulation greatly exceeds nutritional requirements. In warm conditions, the skin acts as a radiator to shed excess heat. Cold-induced vasoconstriction can reduce flow to as low as 10% of baseline without damage to the skin.

During cold stress, peripheral vasoconstriction limits radiant heat loss. Acral skin structures (including fingers, toes, ears, and nose) contain a plethora of arteriovenous anastomoses. These anastomoses shut down in the cold, causing drastic reductions in blood flow. This so-called life-versus-limb mechanism is a means of preventing systemic hypothermia.

Cooling of digits to about 15°C (59°F) results in maximal peripheral vasoconstriction, with minimal blood flow. Continued cooling to about 10°C (50°F) produces cold-induced vasodilation (CIVD, also called "the hunting response"), a counterbalance to cold-induced vasoconstriction. Vasodilation follows 5- to 10-minute cycles, interrupting vasoconstriction and protecting the extremity. Inuits, Lapps, and other northern peoples have stronger CIVD than do individuals from tropical regions. There is evidence of adaptation, with more robust CIVD in response to cold, in addition to genetic control.

Frostbite occurs only when the tissue is supercooled to well below 0°C (32°F). The required temperature is at least −4°C (24.8°F) and may be as low as −10°C (14°F) under some conditions. Tissue injury occurs due to structural damage to cells from ice crystal formation and due to microvascular thrombosis and stasis. In the prefreeze phase, tissue temperatures drop below 10°C (50°F), and cutaneous sensation is lost. Before ice crystals form, microvascular vasoconstriction can occur, with endothelial leakage of plasma into the interstitium. In the freeze-thaw phase, the timing, location, and rate of ice crystal formation depend on conditions. Wind and moisture increase the freezing rate. The phases vary with the extent and rapidity of the cold response and may overlap (Box 128.4).

Except in extremely cold conditions, ice crystal formation initially occurs extracellularly. Water then exits the cells to maintain osmotic equilibrium. Cellular dehydration increases the intracellular osmolarity and electrolyte concentrations. After approximately one-third of the cellular volume is lost, the cell collapses and dies, even if there was no direct structural damage from ice crystals. Extracellular crystallization increases the tissue pressure on cell membranes and vascular structures. Sludging, stasis, and cessation of flow occur at the capillary level.

A third phase, progressive microvascular collapse, first affects venules, then arterioles. Red blood cells sludge and form microthrombi during the first few hours after the tissues are thawed. Factors that decrease flow include hypoxic vasospasm, hyperviscosity, and direct endothelial cell damage. Ischemic conditions extend the surrounding injury. Plasma leakage and arteriovenous shunting result in thrombosis, increased tissue pressure, ischemia, and necrosis.

BOX 128.4 Freezing Injury Cascade

Prefreeze Phase
Superficial tissue cooling
Increased viscosity of vascular contents
Microvascular constriction
Endothelial plasma leakage

Freeze-Thaw Phase
Extracellular fluid ice crystal formation
Water movement across cell membrane
Intracellular dehydration and hyperosmolality
Cell membrane denaturation or disruption
Cell shrinkage and collapse

Vascular Stasis and Progressive Ischemia
Vasospasticity and stasis coagulation
Arteriovenous shunting
Vascular endothelial cell damage and prostanoid release
Interstitial leakage and tissue hypertension
Necrosis, demarcation, mummification, or slough

[a]Extremely rapid cooling produces more initial intracellular than extracellular ice crystallization.

Progressive dermal ischemia is partially mediated by thromboxane. Prostaglandins are found in clear vesicles. When subdermal vascular plexi are injured, hemorrhagic blisters develop, which also contain prostaglandins. Arachidonic acid breakdown products released from underlying damaged tissue into blister fluid include prostaglandins and thromboxane. These mediators produce platelet aggregation, vasoconstriction, and leukocyte immobilization.

Injury to the microvasculature is the ultimate determinant of progressive tissue damage. Endothelial cells are very susceptible to freezing injury. After thawing, the vasculature may be temporarily patent. Platelet and erythrocyte aggregates promptly clog and distort the vasculature. Intense vasoconstriction and arteriovenous shunting occur at the interface between normal and damaged tissue. Injured viable vasculature remains distorted. Local arteritis, medial degeneration, and intimal proliferative thickening occur. Nerve and muscle tissues are more susceptible than connective tissue to cold injury. Nonviable hands and feet can be moved after thawing if the tendons are intact.

Edema progresses for 48 to 72 hours after tissue is thawed. Necrosis becomes apparent as edema resolves. The dry gangrene carapace of frostbite is superficial in comparison to arteriosclerosis-induced, full-thickness gangrene. Although the historical surgical aphorism was "frostbite in January, amputate in July," advances in imaging modalities can accelerate the identification of the demarcation between viable and nonviable tissue.

The extent of peripheral cold injury is determined by the type and duration of cold contact with the skin (Box 128.5). Risk factors include physiologic, mechanical, psychological, environmental, and cardiovascular factors.

Any condition affecting judgment can jeopardize a physiologically tropical human. Cold injuries are often due to psychiatric impairment or intoxication, primarily ethanol intoxication. Ethanol also produces peripheral vasodilation, which increases heat loss. Blunting of self-protective instincts can cause people to put themselves at increased risk by not wearing appropriate clothing or finding shelter in cold conditions.

Although air is a poor thermal conductor, the combination of cold and wind (wind chill index) markedly increases heat loss. Direct skin contact with good thermal conductors such as metal, water, and volatile liquids

BOX 128.5 Predisposing Factors

Physiologic
Genetic
Core temperature
Previous cold injury
Lack of acclimatization to altitude
Dehydration
Overexertion
Trauma—multisystem, extremity
Dermatologic disease
Physical conditioning
Diaphoresis, hyperhidrosis
Hypoxia

Mechanical
Constricting or wet clothing
Tight boots
Vapor barrier, neoprene liners
Inadequate insulation
Immobility or cramped positioning

Psychological
Mental status
Fear, panic
Attitude
Peer pressure
Fatigue
Intense concentration on tasks
Hunger, malnutrition
Intoxicants

Environmental
Ambient temperature
Humidity
Duration of exposure
Wind chill factor
Altitude and associated conditions
Quantity of exposed surface area
Heat loss—conductive, evaporative
Aerosol propellants
Cardiovascular
Hypotension
Atherosclerosis
Arteritis
Raynaud syndrome
Anemia
Sickle cell disease
Diabetes
Vasoconstrictors, vasodilators

increases the rate and extent of tissue destruction. Commercial aerosol spray propellants, such as propane and butane, and carbon dioxide in fire extinguishers are potentially hazardous. Liquid oxygen and Freon can also cause frostbite. Overenthusiastic application of ice or frozen gel packs for soft tissue injuries can cause frostbite, with tissue loss. Contact with dry ice or vapor coolant sprays such as chloroethane can also cause frostbite.

Clinical Features

The term *frostnip* refers to a superficial freezing injury manifested by transient numbness and tingling that resolves after rewarming. No tissue destruction occurs. The most common, nearly universal, presenting symptom of frostbite is numbness. All patients have initial sensory deficits of light touch, pain, or temperature. Anesthesia is produced by intense vasoconstrictive ischemia and neurapraxia, usually in acral areas and distal extremities. Fingers, toes, nose, ears, and penis are the specific areas at the greatest risk. Patients often complain of clumsiness and report so-called "block of wood" sensations in the extremities. Complete anesthesia in a cold digit suggests a severe injury.

Initial presentation of frostbite is often deceptively benign. Most patients do not arrive in the emergency department (ED) with frozen insensate tissue. Frozen tissue feels hard and appears mottled or violaceous white, waxy, or pale yellow (Fig. 128.5). In severe cases, it is not possible to roll the dermis over bony prominences. Rapid thawing in warm water results in an initial hyperemia, even in severe cases (Fig. 128.6). After thawing, there is usually partial return of sensation until blebs form.

Favorable initial symptoms after rewarming include normal sensation, warmth, and color. Soft pliable subcutaneous tissue suggests a superficial injury. A residual violaceous hue after rewarming is ominous (Figs. 128.7 and 128.8). Early formation of large blebs with relatively clear fluid that extend to the tips of the digits (Fig. 128.9) is more favorable than a delayed appearance of smaller, more proximal hemorrhagic vesicles that are produced by damage to subdermal vascular plexi (Fig. 128.10). Bullae and vesicles usually form in 1 to 24 hours.

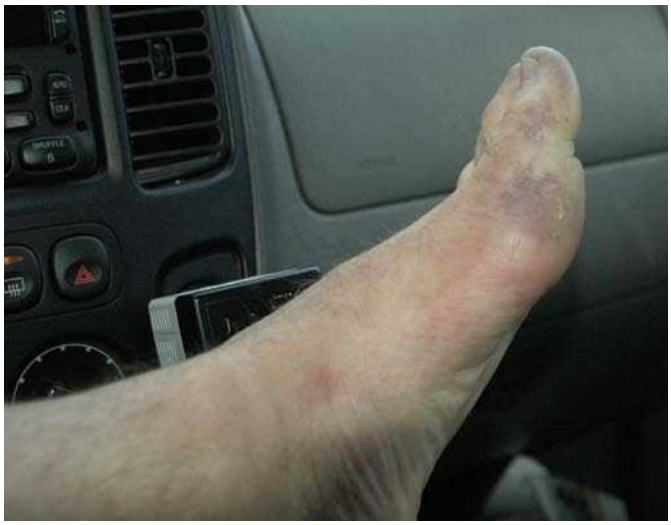

Fig. 128.5 Frostbite that is still frozen. The victim is thawing the foot using a car heater. This technique is not advisable due to a high likelihood of causing further damage. (Courtesy Dr. Nicholas Kanaan.)

Lack of edema formation suggests significant tissue damage. Post-thaw edema usually develops within 3 hours. In severe cases, frostbitten skin forms a black dry eschar that mummifies, with demarcation between living and dead tissue (Figs. 128.11 and 128.12). The appearance may be misleading as live tissue often extends distally deep to the eschar.

Historically, frostbite, like burns, was classified into degrees of injury. Anesthesia and erythema were considered to be first-degree frostbite. Superficial vesiculation surrounded by edema and erythema indicated second-degree frostbite. Third-degree frostbite produced deeper hemorrhagic vesicles. Fourth-degree injuries extended into subcutaneous tissues, including bones and muscles.

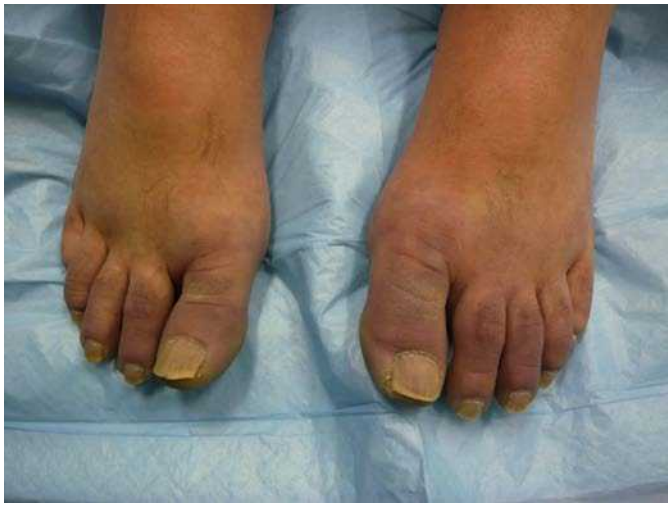

Fig. 128.6 Severe frostbite of the toes immediately after thawing. The injury appears deceptively benign. (Courtesy Dr. Ken Zafren.)

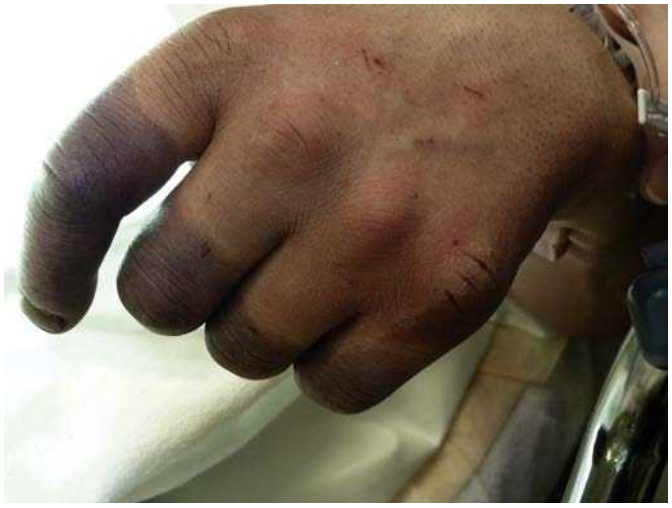

Fig. 128.7 Early appearance of severe frostbite of the hand after thawing. A purple color and absence of blisters are very unfavorable prognostic signs. (Courtesy Dr. Ken Zafren.)

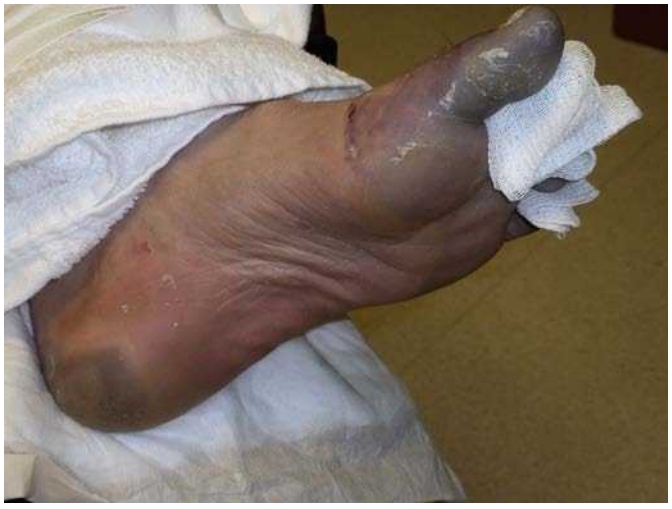

Fig. 128.8 Early appearance of severe frostbite of the foot. A purple color and absence of blisters are very unfavorable prognostic signs. (Courtesy Dr. Ken Zafren.)

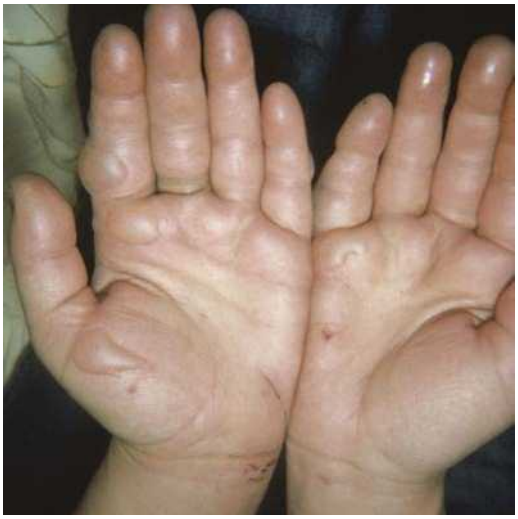

Fig. 128.9 Frostbite with clear vesiculations. (Courtesy Dr. William Mills, Jr.)

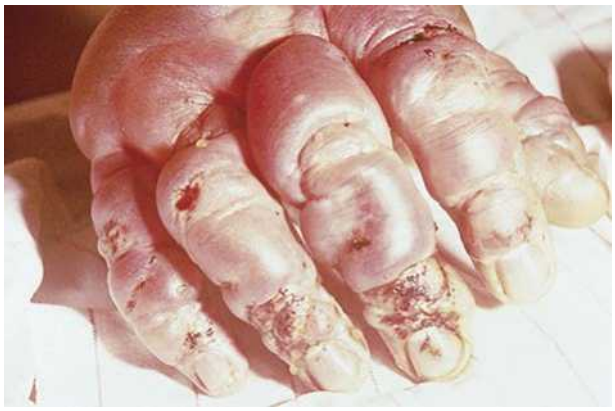

Fig. 128.10 Severe frostbite with early hemorrhagic vesicles. (Courtesy Dr. William Mills, Jr.)

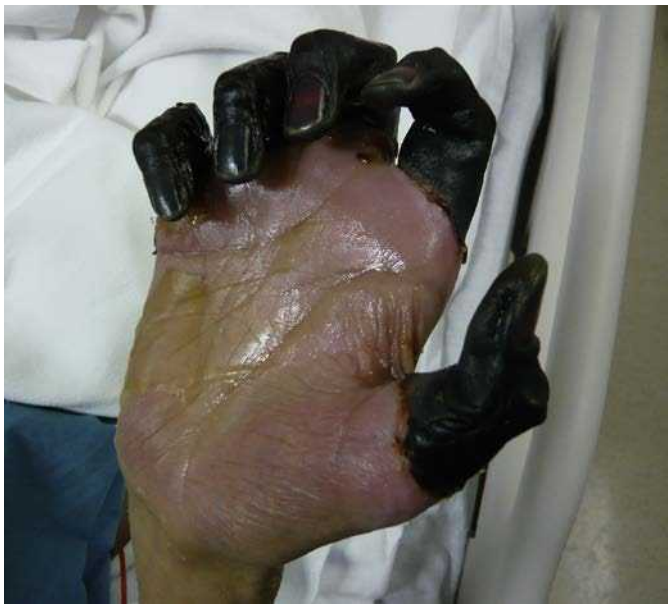

Fig. 128.11 Severe frostbite of the hand. Dry gangrene is clearly demarcated. There was significant tissue loss. (Courtesy Dr. Ken Zafren.)

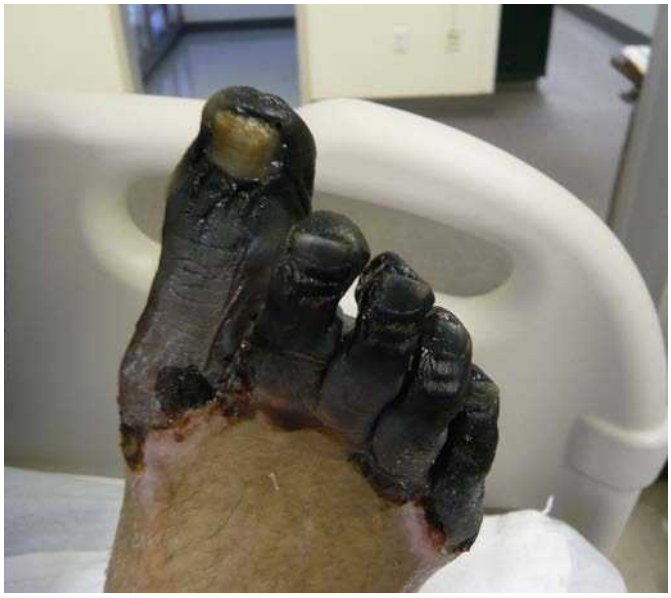

Fig. 128.12 Severe frostbite of the foot. Dry gangrene is clearly demarcated. There was significant tissue loss. (Courtesy Dr. Ken Zafren.)

Classification by degrees is a poor method of predicting the amount of tissue damage and is therapeutically misleading. A simpler, more useful classification divides frostbite into superficial (mild) frostbite, which does not result in tissue loss, and deep (severe) frostbite, which causes loss of tissue. It is difficult to predict the amount of tissue loss at the time of initial presentation. The best method is clinical staging using the extent of cyanosis immediately after rapid thawing in warm water (Table 128.3). In Grade 1 frostbite there is no cyanosis, predicting no amputation and no sequelae. In Grade 2, cyanosis limited to the distal phalanx predicts only soft tissue amputation and sequelae involving the nails. In Grade 3, cyanosis of the intermediate and proximal phalanges predicts bone amputation and functional sequelae. In Grade 4, cyanosis over the carpal or tarsal bones predicts limb amputation with severe functional sequelae.

Significant pain usually accompanies reestablishment of perfusion. A dull continuous ache evolves into a throbbing sensation in 48 to 72 hours. This may persist until tissue demarcation occurs weeks later. Short-term and long-term sequelae are common (Box 128.6).

Differential Diagnoses

The differential diagnosis of frostbite is limited. Burns, cellulitis, gangrene from causes other than freezing, vascular injuries, diabetic neuropathies, and pressure necrosis can resemble frostbite, but can usually be distinguished based on history. Severe, nonfreezing, cold injuries that have been complicated by pressure necrosis with or without infection, can also mimic frostbite. After spontaneous thawing, before edema develops, frostbitten areas may appear deceptively normal for a few hours.

Diagnostic Testing

Except in patients being considered for thrombolytic therapy, diagnostic imaging has a limited role in the emergency care of patients with frostbite. Ancillary diagnostic imaging techniques can be used to help grade the severity of injury, but no technique consistently predicts tissue loss at the time of initial examination.

Patients with frostbite should undergo laboratory testing and imaging, as indicated for coexisting conditions and injuries. Plain radiographs of frostbitten extremities can be used to diagnose fractures due to trauma. Follow-up radiographs may begin to demonstrate abnormalities due to frostbite 4 to 10 weeks after injury.

Patients being considered for thrombolytic therapy may undergo computed tomography angiography (CTA), magnetic resonance angiography (MRA) or Doppler ultrasound, for intra-arterial therapy or radionuclide scanning for intravenous (IV) therapy. Otherwise, angiography or scintigraphy should be delayed. In pediatric patients, magnetic resonance imaging (MRI) of developing hyaline cartilage can demonstrate physial injury, which has the largest impact on longitudinal growth.

Management

Prehospital

Napoleon's Surgeon General, Baron Larrey, first recorded the disastrous effects of the freeze-thaw-refreeze cycle. During the 1812 to 1813 Russian campaign, soldiers would thaw frozen extremities directly over open fires, only to burn them or have them refreeze, with resulting tissue destruction. Unfortunately, the formation of gangrene was misattributed to rapid thawing. Gradual thawing, often including friction massage with snow, became the standard treatment regimen until the 1950s. In 1961, William Mills, Jr., popularized rapid thawing in warm water after extensive research with severe Alaskan frostbite cases.

Field rewarming of frozen tissue is rarely practical. If possible, remove wet or constricting clothing and immobilize and insulate affected areas. Massage is not efficacious and increases tissue loss. Frozen parts should be kept away from dry heat sources, such as heated forced air during transport.

In general, the longer tissue has been frozen, the greater the extent of cellular damage. However, rewarming should not be initiated in the field if there is any possibility that thawing will be interrupted

TABLE 128.3 Frostbite Classification System

Frostbite injuries of the extremities	Grade 1	Grade 2	Grade 3	Grade 4
Extent of initial lesion at day 0 after rapid rewarming	Absence of initial lesion	Initial lesion on distal phalanx	Initial lesion on intermediary and proximal phalanx	Initial lesion on carpal/tarsal
Bone scanning at day 2	Useless	Hypofixation of radiotracer uptake area	Absence of radiotracer uptake area on the digit	Absence of radiotracer uptake area on the carpal/tarsal
Blisters at day 2	Absence of blisters	Clear blisters	Hemorrhagic blisters on the digit	Hemorrhagic blisters over carpal/tarsal
Prognosis at day 2	No amputation	Tissue amputation	Bone amputation of digit	Bone amputation of the limb ± systemic involvement ± sepsis
	No sequelae	Fingernail sequelae	Functional sequelae	Functional sequelae

From: Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wilderness Environ Med.* 2001;12:248.

BOX 128.6 Sequelae of Frostbite and Nonfreezing Cold Injuries

Neuropathic
- Pain
  - Phantom pain
  - Complex regional pain syndrome
  - Chronic pain
- Sensation
  - Hypesthesia
  - Dysesthesia
  - Paresthesia
  - Anesthesia
- Thermal sensitivity
  - Heat
  - Cold
- Autonomic dysfunction
  - Hyperhidrosis
  - Raynaud syndrome

Musculoskeletal
- Atrophy
- Compartment syndrome
- Rhabdomyolysis
- Tenosynovitis
- Stricture
- Epiphyseal fusion
- Osteoarthritis
- Osteolytic lesions
- Subchondral cysts
- Necrosis
- Amputation

Dermatologic
- Edema
- Lymphedema
- Chronic or recurrent ulcers
- Epidermoid or squamous cell carcinoma
- Hair or nail deformities

Miscellaneous
- Core temperature afterdrop
- Acute tubular necrosis
- Electrolyte fluxes
- Psychological stress
- Gangrene
- Sepsis

or incomplete or that tissue will refreeze during evacuation. Tissue refreezing is disastrous. It is better to walk to safety on frozen feet if rescue will be delayed. When evacuation is not possible, rapid field rewarming, preferably in water at 37°C to 39°C (98.6°F to 102.2°F), may be the best option.

Emergency Department

Prethaw. Stabilize hypothermia and other life-threatening conditions before warming frostbitten extremities.[15] Do not delay treatment while waiting for the results of laboratory and radiographic studies. Most patients are volume-depleted, partly due to poor oral intake and hypothermia-induced cold diuresis, and volume replacement with crystalloid at 40°C (104°F) to decrease blood viscosity and sludging is indicated.

Thawing by Immersion in Warm Water

Rapidly rewarm completely frozen or partially thawed tissue by immersion in gently circulating water that is carefully maintained at a temperature of 37°C to 39°C (98.6°F to 102.2°F). A whirlpool is ideal, but any large container can be used for the hands or feet. Do not let frostbitten areas bump or rub against the side of the container. Water warmer than 39°C (102.2°F) does not thaw significantly faster but causes more pain. Tissue can suffer thermal injury when the water temperature exceeds 42°C (107.6°F). Rewarming should be continued until distal erythema is noted. The part should have return of color and feel pliable, which usually requires 15 to 30 minutes of submersion. Active gentle motion is encouraged during rewarming, but the tissue should not be massaged. Premature termination of rewarming results in a partial thaw, with increased tissue damage.

Parenteral analgesia is often indicated during rewarming. Reperfusion may be intensely painful, with throbbing, burning pain and tenderness. Sensation is usually diminished after thawing until it disappears with bleb formation.

Patients with completely frozen extremities are usually hypothermic and at risk for significant fluid and electrolyte fluxes during rewarming. The acute thawing of large amounts of distal musculature can extinguish peripheral vasoconstriction, resulting in a sudden return of cold, hyperkalemic, acidotic blood to the central circulation. This can produce core temperature afterdrop, with ventricular fibrillation. In the most severe cases, extracorporeal rewarming should be used (Box 128.7). Rewarm frostbitten extremities only after the hypothermic patient has been stabilized.

Postthaw. We elevate injured extremities to minimize edema formation, apply sterile dressings loosely, and handle frostbitten areas gently. Due to cold-induced anesthesia, soft tissue injuries are often not appreciated by the patient or emergency clinician. Persistent cyanosis in the extremities after a complete thaw may reflect increased compartment pressure. Tissue should be monitored carefully, although decompressive fasciotomies are usually not necessary during initial treatment.

Although there is no definitive supporting evidence, we recommend the use of topical aloe vera with oral aspirin or ibuprofen. Topical aloe vera every 6 hours inhibits thromboxane when applied directly to frostbitten areas. Aspirin and ibuprofen inhibit the arachidonic acid cascade, although there is no evidence of efficacy for either agent. Some experts prefer ibuprofen because it may also cause fibrinolysis. However, aspirin is also used widely. There is no convincing data showing improved tissue salvage with any of these agents.

Large clear blisters can be left intact, débrided or aspirated. We débride broken or intact nonhemorrhagic blisters. Hemorrhagic blisters are aspirated rather than débrided. When hemorrhagic blisters are débrided, secondary desiccation of deep dermal layers may extend the injury.

Although there is no demonstrated benefit of penicillin for streptococcal prophylaxis, it is used routinely in some centers. We recommend against prophylactic antibiotics for frostbite unless there is associated gross contamination or crush injury. Tetanus can occur after frostbite. Administer tetanus prophylaxis per usual wound care guidelines.

Thrombolytic therapy has been used to treat microvascular thrombosis in frostbite. In one retrospective study, IV tissue plasminogen activator (tPA) and heparin reduced predicted digit amputations in severe

BOX 128.7 Emergency Department Rewarming Protocol

Prethaw

Assess Doppler pulses and appearance.
- Protect part—no friction massage.
- Stabilize core temperature.
- Address medical and surgical conditions.
- Administer volume replacement as indicated.

Thaw

Provide parenteral opiate analgesia as needed.
- Administer ibuprofen 400–600 mg (or aspirin, 325 mg).
- Immerse part in circulating water at 37°C–39°C (98.6°F–102.2°F), monitored by thermometer.
- Encourage gentle motion, but do not massage.

Postthaw

Dry and elevate.
- Aspirate or débride clear vesicles.
- Débride broken vesicles and apply topical antibiotic or sterile aloe vera ointment every 6 hours.
- Leave hemorrhagic vesicles intact.
- Administer tetanus prophylaxis if indicated.
- Provide streptococcal prophylaxis if high risk.
- Consider phenoxybenzamine in severe cases.
- Perform imaging, including angiography, if thrombolysis may be indicated.
- Carry out thrombolysis, if indicated and available.
- Obtain admission photographs.

frostbite. In other studies, intra-arterial tPA decreased the incidence of amputations when administered within 24 hours of thawing.[16,17]

Thrombolysis should be reserved for patients with severe injuries (Grade 3 or 4) likely to produce significant tissue loss. Frostbite that has not undergone freeze-thaw-refreeze can be treated using tPA within 24 hours of thawing if there are no contraindications to thrombolysis. There is no standard dosing regimen. With intra-arterial tPA, angiography is performed with intra-arterial vasodilators, such as papaverine,[18] nitroglycerin,[17] and nicardipine.[19] If flow is not reestablished, intra-arterial, catheter-directed tPA can be infused with a bolus of 2 to 4 mg followed by an infusion of 0.5 to 1 mg/hr. Heparin is also given at 500 units/hour via the intra-arterial catheter. Angiograms are repeated every 8 to 12 hours. Treatment is stopped when perfusion is restored or up to 48 hours.

Intra-arterial thrombolysis should only be performed in centers that have intensive care capabilities and are familiar with the technique. An alternative approach that appears to have equal efficacy uses systemic IV thrombolytic therapy. After thawing, a technetium-99m triple phase bone scan can be performed. One regimen uses a loading dose of alteplase 0.15 mg/kg IV over 15 minutes followed by an infusion of 0.15 mg/kg/hour for 6 hours. If technetium scanning is available, a repeat technetium scan can be used to evaluate reperfusion. Treatment with alteplase is followed by enoxaparin 1 mg/kg subcutaneously twice daily for 14 days. Intravenous tPA for frostbite is an option at smaller hospitals where tPA is available for myocardial infarction or stroke.

Prostacyclin has vasodilatory properties that mimic a chemical sympathectomy. The risk of amputation was significantly lower in a controlled trial of patients with severe frostbite who received IV Iloprost (a prostacyclin analog not currently available in the United States) with aspirin after thawing. Selected patients with severe frostbite were also treated with recombinant tPA. We recommend treatment with Iloprost, if available for Grade 2 to 4 frostbite injury. It should be infused within 48 hours of thawing, combined with tPA in appropriate settings for Grade 3 to 4 frostbite injury in patients seen within 24 hours who meet the indications for tPA. Iloprost is safe enough that it can be used in prehospital settings if necessary.

There are many unproven therapies for frostbite, including low-molecular-weight dextran, vasodilator therapy, and phenoxybenzamine. Hyperbaric oxygen may accelerate demarcation but has not been shown to increase tissue salvage in severe frostbite.[20]

Chemical or surgical sympathectomies do not decrease tissue loss. Surgical sympathectomy produces a smoother initial clinical course but no long-term benefits, with the possible exception of decreased long-term pain. Forearm nerve blocks produce a chemical sympathectomy that increases finger skin temperature. Although prehospital wrist blocks may achieve rapid pain control with rewarming, there have been no systematic studies of outcomes.

Disposition

Patients with superficial frostbite can be safely discharged to a warm place unless there is another indication for admission. Consult social services if the patient is undomiciled. All other patients with significant frostbite are best admitted for further evaluation and treatment. Transfer or further consultation is indicated when the admitting service lacks experience in the care of frostbite. At hospitals not capable of giving intravenous tPA, patients who meet the criteria for thrombolysis should be transferred to a suitable facility if thrombolysis can be initiated after transfer within 24 hours of thawing.

NONFREEZING COLD INJURIES

Foundations

Background and Importance

Nonfreezing cold injury occurs when tissue fluids have not frozen. The most common nonfreezing cold injury is immersion injury, often referred to as *trench foot*, although the hands may also be affected. This is a significant threat during recreational activities and military expeditions in cold wet climates.

Anatomy, Physiology, and Pathophysiology

Trench foot is produced by prolonged exposure to wet cold at temperatures too high to cause frostbite. It usually develops slowly over several days and results in neurovascular damage. Immersion injury commonly develops while a person is wearing socks that are wet from immersion in water.

Immersion injury can also occur from sweat, especially with the use of neoprene socks, vapor barrier boots, or constrictive gaiters. People who soak their feet for hours in cool water for pain relief are also at risk. Bullae and tissue loss in immersion injury are due to pressure necrosis with or without infection rather than to cold injury. Most patients with severe immersion injury are military personnel who have worn boots continuously for days or weeks. Prevention of immersion injury may require frequent drying of feet and socks.

Pernio (chilblains) is a form of cold injury that often follows repetitive exposure to cold in susceptible individuals. Chilblains can also occur without exposure to cold in individuals who have underlying diseases, such as systemic lupus erythematosus (SLE).

Clinical Features

Immersion Injury

Immersion injury is classically described as progressing through four stages. In the first stage (during cold exposure), numbness is the most

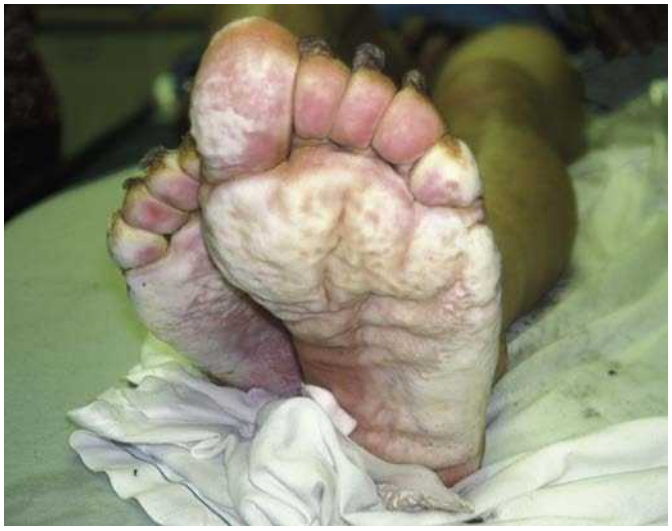

Fig. 128.13 Nonfreezing cold injury (trench foot, immersion foot) in a homeless man in the emergency department, shortly after removal of wet socks and shoes. (Courtesy Dr. Ken Zafren.)

common symptom. The extremities may appear bright red, but soon become pale or white due to extreme vasoconstriction (Fig. 128.13). There is no pain or swelling at this stage.

In the second stage (following cold exposure) after removal from a cold environment and during rewarming, peripheral blood flow slowly returns, and the extremities become a mottled pale blue. This change may be subtle in highly pigmented skin. The extremities remain cold and numb, although pain and edema can result from active rewarming. This stage usually lasts for a few hours, but occasionally persists for several days.

In the third stage (hyperemia), blood flow increases markedly. The extremity suddenly becomes hot and red, with bounding pulses, while the microcirculation is sluggish, as evidenced by prolonged capillary refill. Dependent redness (rubor) with pallor on elevation may occur due to vasomotor paralysis. At the same time, numbness gives way to severe pain with hyperalgesia, even to light touch. Edema often develops. In severe cases associated with pressure necrosis, bullae, like those seen in frostbite, can form. In cases associated with tissue loss, necrosis becomes evident. The third stage may last weeks to months.

In the fourth stage (following hyperemia), the limb generally appears normal except in cases with tissue loss, but pain may persist. Tissue that was necrotic in the third stage becomes gangrenous and is lost. This stage can last from weeks to years or be permanent. Most cases of immersion injury present to the ED during the first or second stage, but pain that is often resistant to usual pain medications may be a presenting complaint during later stages.

Short- and long-term sequelae of cold immersion injury are similar to those of frostbite, although only the most severe immersion injuries are associated with tissue loss (see Box 128.6).

Pernio

Chilblains, or cold sores, appear within 24 hours of exposure and most often affect the face, dorsa of the hands and feet, and pretibial areas (Fig. 128.14). Young women with Raynaud phenomenon, SLE, or antiphospholipid antibodies are at increased risk. Persistent vasospasm and vasculitis result in burning, pruritus, erythema, and mild edema. Plaques, blue nodules, and ulcerations can develop. These painful lesions usually last 1 to 2 weeks but can persist much longer if there are repeated exposures to cold.

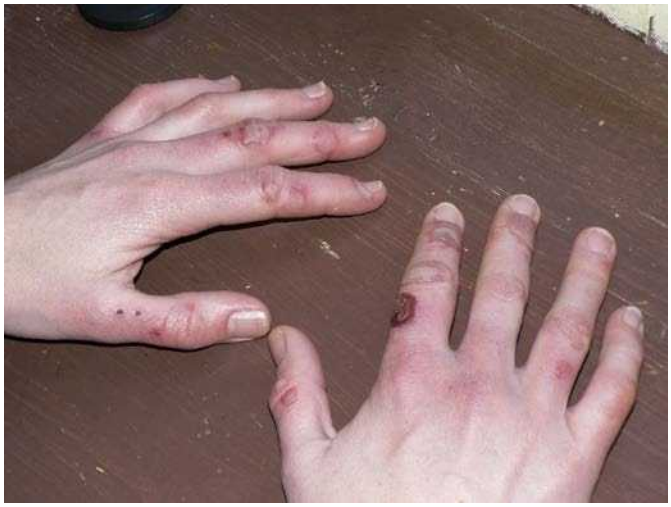

Fig. 128.14 Pernio in a woman who was working in an unheated high-altitude clinic. (Courtesy Dr. Alice Murray.)

Differential Diagnoses

Frostbite can mimic nonfreezing cold injury but can usually be diagnosed by history. Frostbite and nonfreezing cold injuries can also occur together. Warm immersion injuries, including jungle foot (paddy foot) or tropical immersion foot, may appear similar to immersion injuries due to wet cold, but resolve with drying and elevation within a few days.

Pernio has a wide differential diagnosis. The diagnosis is usually clear when pernio is associated with recent cold exposure. Cases of suspected pernio with uncertain cause should prompt a search for underlying conditions, such as SLE.

Diagnostic Testing

Intraepidermal nerve fiber density measurement can be used to assess the severity and guide management of immersion injury in patients with neuropathic symptoms. Diagnostic testing in patients with pernio is directed toward finding an underlying condition.

Management

Immersion Injury

Treat hypothermia, if present, before treating nonfreezing cold injuries. Provide volume replacement with warm IV fluids if the patient is clinically volume depleted. Immersion injuries should be allowed to rewarm slowly to room temperature. Rapid rewarming or rubbing may worsen the injury. No medications are known to be helpful. Local cooling, often in a cool room with a fan, lowers metabolic requirements and improves pain and edema. Cooling should be continued until hyperemia resolves. Pain after rewarming is common and usually responds poorly to most pain medications. Amitriptyline (50–100 mg orally at bedtime) is the treatment of choice.

Pernio

There is no standard treatment for pernio. We recommend drying the skin if it is damp and gentle massage if the patient can tolerate it. Avoid warming the skin above 30°C (86°F). Pernio is very painful and may require opioid analgesia. Nifedipine (20–60 mg daily) is the only

medication that has been shown to be potentially effective in the treatment of severe pernio.

Disposition

Many patients with significant immersion injury require admission for pain control, as well as social service assistance with activities of daily living. Patients with mild immersion injuries can be discharged if there are no other indications for admission and the patient can be released to a warm environment. Patients with pernio are usually managed as outpatients.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 128: QUESTIONS AND ANSWERS

1. Emergency medical services (EMS) notifies your emergency department (ED) that an unknown male who was "found down" is being transported. No history is available. Paramedics report that the patient's pulse is 42 beats/min and blood pressure is difficult to obtain. Spontaneous respirations are present at a rate of 10 breaths/min. The electrocardiogram (ECG) showing sinus bradycardia is faxed before the patient's arrival. What treatment should you administer when the patient arrives?
   a. Intravenous epinephrine
   b. Normal saline bolus
   c. Synchronized cardioversion
   d. Warm the patient

Answer: D. Warm the patient. When this hypothermic patient arrives in the ED, after assessment of the airway, the top priority is rapid rewarming. Patients with hypothermia should be actively rewarmed whenever possible. Specific indications for active rather than passive rewarming include trauma, cardiovascular instability, temperature below 32°C (89.6°F), poor rate of passive rewarming, and endocrine insufficiency.

2. Rapid rewarming is the mainstay of treatment for hypothermia. However, rewarming can cause complications. Which of the following complications should be anticipated and prevented when rewarming a hypothermic patient?
   a. Hyperkalemia
   b. Hyponatremia
   c. Hypotension
   d. Rhabdomyolysis

Answer C: Hypotension should be anticipated and prevented when rewarming a hypothermic patient. Patients with moderate or severe hypothermia are usually volume depleted. During rewarming, the total plasma volume is usually high, but the circulatory plasma volume is usually low due to increased peripheral vascular resistance. Rapid volume expansion can be lifesaving, especially in hypothermic neonates. Adult patients with moderate or severe hypothermia should initially receive a 500-mL fluid challenge of warmed normal saline. Avoid lactated Ringers solution because the cold liver metabolizes lactate poorly. Fluids administered via the intravenous (IV) route should be warmed to 40°C to 42°C (104°F to 107.6°F).

3. A 30-year-old woman in cardiac arrest is brought to the ED by emergency medical services. She was intubated in the field, and chest compressions have been continuously performed. Her temperature is 25°C (77°F). When placed on the cardiac monitor, she is noted to be in ventricular fibrillation. A defibrillation attempt is made at the appropriate setting, but she remains in ventricular fibrillation. A nurse resumes providing chest compressions and asks for further instructions. What should be done next?
   a. IV amiodarone
   b. IV lidocaine
   c. IV procainamide
   d. Warm the patient

Answer: D. Warm the patient. This severely hypothermic patient needs further rewarming before subsequent defibrillation attempts are made to treat her ventricular fibrillation. Most hypothermia-induced dysrhythmias convert spontaneously during rewarming. Asystole that

CHAPTER 128: QUESTIONS AND ANSWERS—Cont'd.

develops during rewarming is not as ominous as asystole in normothermic patients. For VF, defibrillation should be attempted at the usual energy level. Successful defibrillation has been reported at 20°C (68°F) but attempted defibrillation is often unsuccessful until the core temperature is above 30°C (86°F). If a defibrillation attempt is unsuccessful, active rewarming should be initiated while continuing CPR. Defibrillation can be attempted occasionally during rewarming. Once the core temperature is above 30°C (86°F), further attempts can be made.

4. A 27-year-old homeless man presents complaining of numb feet. He reports sleeping outdoors overnight. The temperature was consistently below −20°C (−4°F). The feet appear white and waxy. They are cold and hard to the touch. What is the best way to rewarm the feet?
   - **a.** Room temperature air convection
   - **b.** Room temperature water immersion
   - **c.** Warm air convection
   - **d.** Warm water immersion

Answer: D. This patient is suffering from frostbite of the feet. The treatment of choice in this scenario is rapid warm water immersion. Rapidly rewarm completely frozen or partially thawed tissue by immersion in gently circulating water that is carefully maintained at a temperature of 37°C to 39°C (98.6°F to 102.2°F). A whirlpool is ideal, but any large container can be used for the hands or feet. Water warmer than 39°C (102.2°F) does not thaw significantly faster but causes more pain. Tissue can suffer thermal injury when the water temperature exceeds 42°C (107.6°F). Rewarming should be continued until distal erythema is noted. The part should have return of color and feel pliable, which usually requires 15 to 30 minutes of submersion.

5. What is the most common error made when treating frostbite injury?
   - **a.** Débridement of broken blisters
   - **b.** Premature termination of thawing
   - **c.** Use of nonsteroidal antiinflammatory drugs (NSAIDs) for analgesia
   - **d.** Use of thrombolytic agents to restore blood flow

Answer: B. Premature termination of thawing in 37°C to 39°C (98.6°F to 102.2°F) water is a common error. Reperfusion of completely frozen tissue may be painful, requiring parenteral analgesia.

Heat Illness

Melissa A. Platt and Timothy G. Price

KEY CONCEPTS

- Classic heatstroke is generally diagnosed in older patients with comorbidities during heat waves, whereas exertional heatstroke is more common in young athletic patients or military personnel.
- Heat exhaustion and heatstroke are a continuum of the same pathophysiologic process. Neurologic dysfunction is a hallmark of heatstroke, and cerebral edema is common.
- In heat stroke, morbidity and mortality are directly related to the duration of core temperature elevation. Rapid cooling should be initiated without delay.
- The evaporative technique and ice water immersion are the 2 forms of primary cooling measures. Other cooling measures are secondary and considered adjunct therapy.
- Antipyretics are ineffective and should not be used to control environmental hyperthermia.
- Heatstroke can cause right-sided cardiac dilation and elevated central venous pressure and clinically resemble pulmonary edema but may still require crystalloid resuscitation.

FOUNDATIONS

Background and Importance

Humans have been plagued by heat illness throughout recorded history. Heat illness has the potential to affect all age groups and population types. Older adults and the poor (who often lack adequate air conditioning and nutrition) are susceptible to heat illness during environmental extremes and heat waves. Those with preexisting disease are also prone to heat illness. It is estimated that at least 10 times as many heat aggravated illnesses occur in patients with comorbid conditions such as coronary artery disease, cerebrovascular disease, and diabetes.[1] Children are also susceptible to heat stressors because of their higher surface area-to mass ratios. They also have lower sweat rates per gland. Military personnel, athletes, including American football players, and those who occupationally exert themselves in heat, are also at risk.

For an accurate heat illness diagnosis, information about living conditions, occupation, access to water, strenuous physical activity, acclimatization, and current environmental temperatures need to be ascertained. Heat illness is often associated with military exercises, athletic events, occupation, and recreational activities. A recognition of the microclimates conducive to heat illness including military tanks, tents in the sun, engine rooms, mines, hot tubs, saunas, and automobile interiors, is also important. In the United States, nearly 40 children die each year from hyperthermia after being left alone in a motor vehicle.[2]

Anatomy, Physiology, and Pathophysiology

Heat Production

Humans are essentially biochemical furnaces that burn food to fuel with a complex array of metabolic functions. These chemical reactions consume substrate, generate usable energy, and produce byproducts that must be eliminated for continued operation of the system. Water and carbon dioxide are produced and eliminated in large quantities, as well as urea, sulfates, phosphates, and other chemical byproducts. These reactions are exothermic and combine to produce a basal metabolic rate that amounts to approximately 100 kCal/h for a 70-kg person. In the absence of cooling mechanisms, this baseline metabolic activity would result in a 1.1°C (2°F) hourly rise in body temperature.

Heat production can be increased 20-fold by strenuous exertion. Rectal temperatures as high as 42°C (107.6°F) have been recorded in trained marathon runners, without ill effects. Metabolic factors (hyperthyroidism and sympathomimetic drug ingestion) can dramatically increase heat production. Environmental heat not only adds to the heat load but also interferes with its dissipation. The physics of heat transfer as it relates to human physiology involves four mechanisms—conduction, convection, radiation, and evaporation.[3]

Conduction. This is the transfer of heat energy from warmer to cooler objects by direct physical contact. Air is a good insulator; therefore, only approximately 2% of the body heat loss is by conduction. In contrast, the thermal conductivity of water is at least 25 times that of air.

Convection. This is heat loss to air and water vapor molecules circulating around the body. As the ambient temperature rises, the amount of heat dissipated by convection becomes minimal. Once the air temperature exceeds the mean skin temperature, heat is gained by the body. Convective heat loss varies directly with wind velocity. Loose-fitting clothing maximizes convective, and also evaporative, heat loss.

Radiation. This is heat transfer by electromagnetic waves. Although radiation accounts for approximately 65% of heat loss in cool environments, it is a major source of heat gain in hot climates. Up to 300 kCal/h can be gained from radiation when someone is directly exposed to the hot summer sun.

Evaporation. Evaporation is the conversion of a liquid to the gaseous phase. Evaporation of 1 mL of sweat from the skin cools the body by 0.58 kCal. In humans, heat loss through sweat evaporation is the principal means of heat loss during exercise and the dominant means of dissipating heat via the skin when ambient air temperatures exceed skin temperature. Panting mammals such as dogs have an oropharyngeal countercurrent flow mechanism *(carotid rete mirabile)* that results in selective cooling of the brain. In humans, respiratory and countercurrent mechanisms are minimal sources of heat loss.

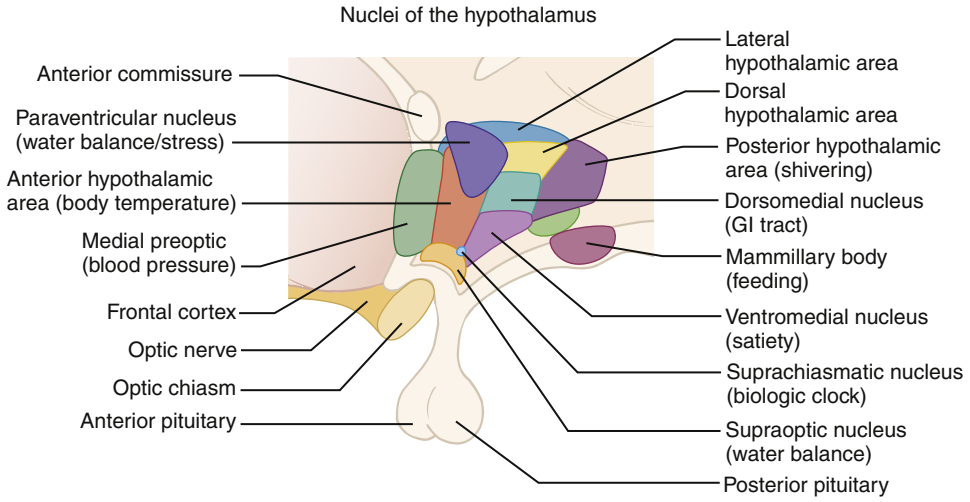

Fig. 129.1 Preoptic Anterior Hypothalamus. (Adapted from Nuclei of the hypothalamus. bhavanajagat.files.wordpress.com/2012/07/nuclei-of-hypothalamus.jpg.)

Heat Regulation

The regulation of body temperature involves three distinct functions—thermosensors, a central integrative area, and thermoregulatory effectors.

Thermosensors. Temperature-sensitive structures are located peripherally in the skin and centrally in the body. However, skin temperature changes correlate poorly with changes in the rate of heat loss. Thermosensitive neurons, located in the preoptic anterior hypothalamus, are activated when the temperature of the blood circulating through that area exceeds a set point (Fig. 129.1).

The skin temperature affects heat loss when a person resting in a warm environment initiates sweating, even though the core temperature remains constant. In contrast, changes in core temperature are more dominant than skin temperature changes in producing heat-dissipating responses.

Central integrative area. The central nervous system (CNS) interprets information received from the thermosensors to instruct thermoregulatory effectors properly. The concept of a central thermostat where an alteration shifts effector thresholds in the same direction fits a variety of clinical situations. For example, fever, the circadian rhythm of temperature variation, and the difference in rectal temperature after ovulation can be explained by variation of a thermal set point.

Thermoregulatory effectors. Sweating and peripheral vasodilation are the major mechanisms whereby heat loss can be accelerated. In a warm environment, evaporation of sweat from the skin is the most important mechanism of heat dissipation. Heat loss from the skin by convection and radiation is maximized by increased skin blood flow to facilitate sweating.

Humans possess apocrine and eccrine sweat glands. Apocrine glands are concentrated in the axillae and produce milky sweat, rich in carbohydrate and protein. They are adrenergically innervated and respond to emotional stress as well as to heat. Most glands producing so-called thermal sweat are eccrine glands. These are cholinergically innervated and distributed over the entire body, with the largest number on the palms and soles. Eccrine sweat is colorless, odorless, and devoid of protein. Individuals exercising in hot environments commonly lose 1 or 2 L/h of sweat. A loss of up to 4 L/h is possible with strenuous exercise.

Cooling is best achieved by evaporation from the body surface; sweat that drips from the skin does not cool the body. Each liter of completely evaporated sweat dissipates 580 kCal of heat. The ability of the environment to evaporate sweat is termed *atmospheric cooling power* and varies primarily with humidity, but also with wind velocity. As humidity approaches 100%, evaporative heat loss ceases.

The vascular response to heat stress is cutaneous vasodilation and compensatory vasoconstriction of the splanchnic and renal beds. These vascular changes are under neurogenic control and allow heat to be dissipated quickly and efficiently, but they place a tremendous burden on the cardiovascular system. To maintain blood pressure, cardiac output increases dramatically. For this reason, saunas and hot tubs may be dangerous for patients with cardiac disease. Cardiovascular and baroreceptor reflexes also affect skin blood flow. Reduced forearm sweating and vasodilation have been observed in severely dehydrated subjects exercising in a warm environment.

Acclimatization

Acclimatization is the constellation of physiologic adaptations that occur in a normal person as the result of repeated exposures to heat stress. Daily exposure to work and heat for 100 min/day results in near-maximal acclimatization within 7 to 14 days.[4] This is characterized by an earlier onset of sweating (at a lower core temperature), increased sweat volume, and lowered sweat sodium concentration. Acclimatization is hastened by modest salt deprivation and delayed by high dietary salt intake.

The cardiovascular system plays a major role in acclimatization and endurance training, largely resulting from an expansion of plasma volume. Heart rate is lower and associated with a higher stroke volume. Other physiologic changes include earlier release of aldosterone, although acclimatized individuals generate lower plasma levels of aldosterone during exercise heat stress. Total body potassium depletion of up to 20% (500 mEq) by the second week of acclimatization can occur as a result of sweat and urine losses, coupled with inadequate repletion.

Although many similarities exist among thermoregulatory responses to heat and exercise, the well-conditioned athlete is not necessarily heat-acclimatized. For heat and exercise-induced adaptive responses to be maintained, heat exposure needs to continue intermittently, at least on 4-day intervals. Plasma volume decreases considerably within 1 week in the absence of heat stress.

Predisposing Factors

Advanced age, psychiatric conditions, chronic disease, obesity, and certain medications increase the risk for classic heatstroke during periods of high heat and humidity. Adequate fluid intake is essential. Older adults often overdress during hot weather conditions. Heat loss is maximized by light, loose-fitting garments.

Exertional heatstroke is most likely to occur in young healthy people involved in strenuous physical activity, especially if they have not acclimatized to environmental factors that overwhelm heat-dissipating mechanisms. For example, wrestlers frequently fast, restrict food and fluid intake, and exercise vigorously wearing vapor-impermeable clothing in an effort to maintain or drop their current weight class. Pre-existing illness may not increase the risk of exertional heat stroke.[5] Fluid intake is the most critical variable. Dehydration can be minimized by education on work-rest cycles and fluid consumption, and through provision of cool flavored fluids.

The goal is to maximize voluntary fluid intake and gastric emptying so that fluid can rapidly enter the small intestine, where it is absorbed. Gastric emptying is accelerated to 25 mL/min by large fluid volumes (500 to 600 mL) and cool temperatures (10°C to 15.8°C [50°F to 60.4°F]). High osmolality inhibits gastric emptying; osmolality of less than 200 mOsm/L is optimal. Most commercially available electrolyte solutions contain excessive sugar. Hydration can be monitored by measurement of body weight before and after training or athletic competition. An athlete with a loss of 2% to 3% body weight (1.5 to 2 L in a 70-kg man) should drink extra fluid and be permitted to compete only when his or her body weight is within 0.5 to 1 kg (1 or 2 pounds) of the starting weight on the previous day. A weight loss of 5% or 6% represents a moderately severe deficit and usually is associated with intense thirst, scant dark-colored urine, tachycardia, and increase in rectal temperature of approximately 2°C (3.6°F). These athletes should be restricted to light workouts after hydration until they return to normal weight. A loss of 7% or more of body weight represents severe water depletion; participation in sports should not be permitted until the athlete is evaluated by a physician or sports trainer. The administration of salt tablets during strenuous exercise can cause delayed gastric emptying, osmotic fluid shifts into the gut, gastric mucosal damage, and hypernatremic dehydration. A 6-g sodium diet is sufficient for successful adaptation for work in the heat, with sweat losses averaging 7 L/day. Excessively high salt intake in relation to salt losses in sweat during initial heat exposure can impair acclimatization because of the inhibition of aldosterone secretion. Excessive salt ingestion can also exacerbate potassium depletion.

Evaporative cooling can be lost when clothing inhibits air convection and evaporation. Water evaporated from clothing is much less efficient for body cooling than water evaporated from the skin. Loose-fitting clothing or ventilated fishnet jerseys allow efficient evaporation. Light-colored clothing reflects rather than absorbs light.

The heat dissipation mechanisms of the body are analogous to the cooling system of an automobile (Fig. 129.2). Coolant (blood) is circulated by a pump (heart) from the hot inner core to a radiator (skin surface cooled by the evaporation of sweat). Temperature is sensed by a thermostat (CNS), which alters coolant flow by a system of pipes, valves, and reservoirs (vasculature). Failure of any of these components can result in overheating.

Effective circulation requires an intact pump and adequate coolant levels. β-adrenergic blocking agents or calcium channel blockers may prevent an increase in cardiac output sufficient to produce the necessary peripheral vasodilation to dissipate heat. Dehydration caused by gastroenteritis, diuretics, or inadequate fluid intake predisposes to heat illness. Individuals working in the heat seldom voluntarily drink as much fluid as they lose and replace only approximately two-thirds

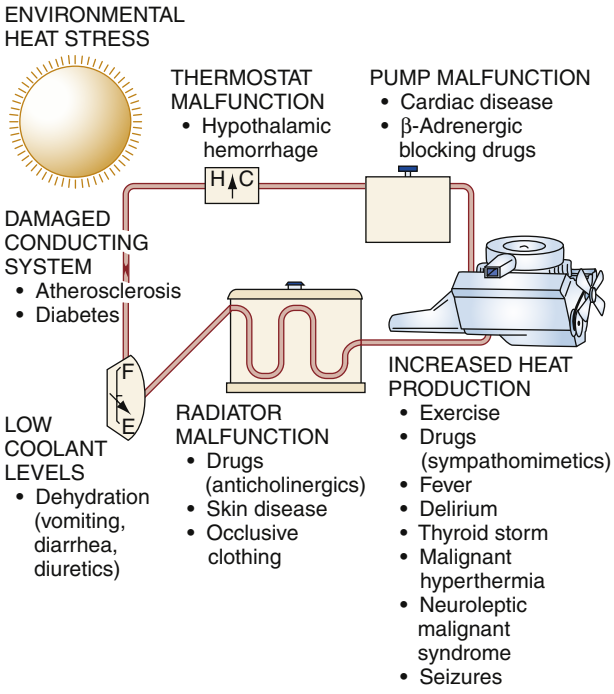

Fig. 129.2 Predisposing factors for heat illness, an automotive analogy.

of net water loss (so-called voluntary dehydration). Dehydration alone increases body temperature at rest by increasing the work of the sodium-potassium adenosine triphosphatase pump, which accounts for 25% to 45% of the basal metabolic rate. This is particularly true in cases of hypernatremic dehydration. The pipes and valves of the coolant system may be abnormal in diabetic or older patients with extensive atherosclerosis.

Radiator function depends on the skin and sweat glands. Occlusive, vapor-impermeable clothing hinders evaporative and convective cooling. Anticholinergic medications and stimulant drugs of abuse interfere with sweating and contribute to heat illness. Various skin diseases, including miliaria (prickly heat rash), extensive burns, scleroderma, ectodermal dysplasia, and cystic fibrosis, are risk factors. Anhidrosis can also be secondary to central or peripheral nervous system disorders.

Increased heat production causing heat illness most often accompanies exercise in a hot humid environment. When heat and humidity are extreme, exertion is not necessary to produce heat-related problems. Several indices help objectify heat strain. These indices can be divided into two categories, heat scales based on meteorologic parameters and those that combine environmental and physiologic parameters.

The wet bulb globe temperature heat index is an excellent meteorologic measure of environmental heat stress (Box 129.1). It measures the effects of temperature, humidity, and radiant thermal energy from the sun. When climatic conditions exceed 25°C (77°F) wet bulb, even healthy people are at high risk during exercise. Above 28°C (82.4°F), exercise and strenuous work should be avoided or limited to extremely short periods of time.

Fever Versus Hyperthermia

It is diagnostically and therapeutically important to identify patients suffering from a febrile response rather than heat illness. Fever does not cause primary pathologic or physiologic damage to humans and does not require primary emphasis in the therapeutic regimen, which is directed at the underlying disease state. If temperature-related physiologic changes such as febrile seizures and tachycardia compromise

BOX 129.1 Wet Bulb Globe Temperature

$$WBGT = 0.7\ T_n + 0.2\ T_g + T_a$$

T_n = "Natural" wet bulb temperature—the temperature achieved by a thermometer covered with a moistened white wick and left exposed to the ambient environment

T_g = Globe temperature—the temperature inside a blackened hollow copper sphere exposed to the ambient environment

T_a = Ambient temperature

These measurements can be done manually or calculated automatically with the help of computer algorithms.

a patient with marginal cardiac reserve, the temperature should be artificially regulated with antipyretics. In contrast, antipyretics are not effective against heat illness and are **not** recommended to control environmental hyperthermia.

MINOR HEAT ILLNESSES

Miliaria Rubra

Miliaria rubra, also known as prickly heat, lichen tropicus, and heat rash, is an acute inflammatory disorder of the skin that occurs in hot and humid climates. It is the result of the blockage of sweat gland pores by macerated stratum corneum and secondary staphylococcal infection. The acute phase is characterized by vesicles in the malpighian layer of the skin, caused by dilation and rupture of the obstructed sweat gland ducts.

Clinical Features

Miliaria produces intensely pruritic vesicles on an erythematous base. The rash is confined to clothed areas, and the affected area is often completely anhidrotic. During the next week, a keratin plug develops and fills these vesicles, causing a deeper obstruction of the sweat gland duct. The obstructed duct then ruptures a second time, producing a deeper vesicle within the dermis. This is known as the profunda stage, and it can persist for weeks. Profunda vesicles are not pruritic and closely resemble the white papules of piloerection. Chronic dermatitis is a common complication (Fig. 129.3).

Differential Diagnoses

Alternative diagnoses include contact dermatitis, cellulitis, and allergic reactions. A heat exposure history and distribution of the rash will solidify the diagnosis.

Diagnostic Testing

Laboratory data is not indicated with miliaria.

Management and Disposition

Miliaria rubra can be prevented by wearing light, loose-fitting, clean clothing and avoiding situations that produce continuous sweating. Avoid routine use of talcum or baby powder. Gentle exfoliation may help to remove debris that occlude the eccrine sweat ducts. However, soap may cause additional skin irritation. Topical corticosteroids, such as hydrocortisone 2.5% or triamcinolone 0.1% twice a day for one to two weeks, may decrease pruritus and inflammation but is not required for the resolution of miliaria. Patients can be discharged with dermatologic or primary care follow-up.

Heat Cramps

Heat cramps are brief, intermittent, and often severe muscle cramps occurring typically in muscles that are fatigued by heavy work or

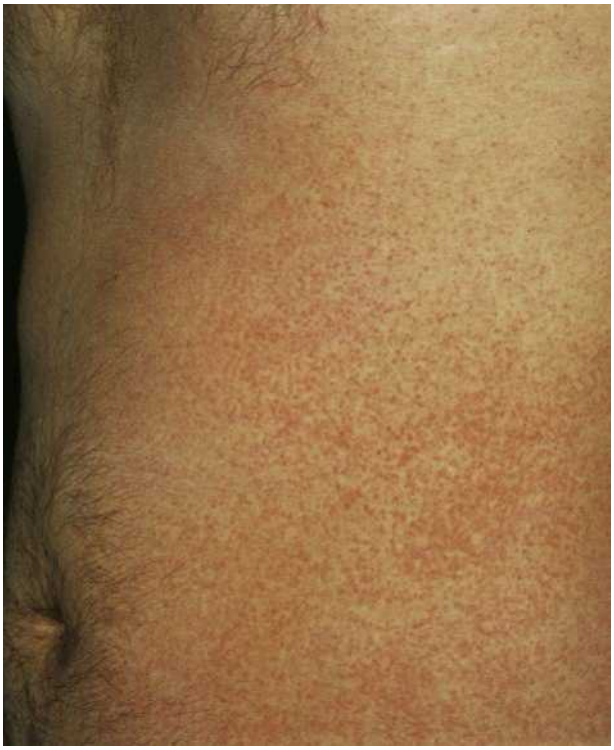

Fig. 129.3 Prickly Heat. (From Habif TP. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 3rd ed. St. Louis: Mosby; 1996.)

BOX 129.2 Heat Cramps: Essentials of Diagnosis

Cramps of most worked muscles
Usually occur after exertion
Copious sweating during exertion
Copious hypotonic fluid replacement during exertion
Hyperventilation not present in cool environment

prolonged exercise. Heat cramps appear to be related to a salt deficiency. They usually occur during the first days of work in a hot environment and develop in persons who produce large amounts of thermal sweat and subsequently drink copious amounts of hypotonic fluid.

Clinical Features

Athletes, roofers, steelworkers, coal miners, field workers, and boiler operators are among the most common victims of heat cramps. Heat cramps tend to occur after exercise, when the victim stops working and is relaxing (Box 129.2). In this respect, they differ from the cramps experienced by athletes during exercise, which tend to last for several minutes, are relieved by massage, and resolve spontaneously.

Differential Diagnoses

Heat cramps are occasionally confused with hyperventilation tetany, which can occur during heat exhaustion. Hyperventilation tetany can be distinguished by the presence of carpopedal spasm and paresthesias in the distal extremities and perioral area.

Diagnostic Testing

Heat cramps accompanied by systemic symptoms may be part of salt depletion heat exhaustion. Check serum electrolyte levels as heat cramp victims often exhibit hyponatremia and hypochloremia.

Rhabdomyolysis or resultant renal damage is not present with isolated heat cramps.

Management and Disposition

Heat cramps are rapidly relieved by salt solutions. Many commercially available flavored electrolyte solutions are available. Mild cases without concurrent dehydration are treated orally with a 0.1% or 0.2% salt solution (two to four 10-grain salt tablets [56 to 112 mEq] or ¼ to ½ teaspoon of table salt dissolved in 1 quart of water), which is the general limit of palatability. Severe cases respond rapidly to an infusion of normal saline. Salt tablets are gastric irritants, delay gastric emptying, and are not recommended as treatment. Although most patients do not seek medical treatment, most patients with heat cramps may be safely discharged after the administration of balanced salt solutions and clinical improvement.

Heat Edema

It is presumed that hydrostatic pressure and vasodilation of cutaneous vessels, combined orthostatic pooling, lead to vascular leak and accumulation of interstitial fluid in the lower extremities. Simultaneously, the aldosterone level increases in response to the heat stress and perceived central volume deficit.

Clinical Features

Swollen feet and ankles are often reported by non-acclimatized individuals, especially older adults, who encounter climatic stresses of tropical and semitropical areas. They commonly have schedules that involve long periods of sitting or standing. The edema is usually minimal, is not accompanied by any significant impairment in function or ambulation, and often resolves after several days of acclimatization.

Differential Diagnoses

Differentiate heat edema from congestive heart failure, liver disease states, nephrosis, lower extremity infections, and deep venous thrombosis.

Diagnostic Testing

Awareness of this clinical presentation prevents overly vigorous diagnostic and therapeutic intervention. A brief diagnostic evaluation to rule out thrombophlebitis, lymphedema, or congestive heart failure may be appropriate, but invasive diagnostic techniques are not indicated.

Management and Disposition

Pharmacologic therapy is not indicated, and diuretic therapy is not effective. Simple leg elevation or thigh-high support hose should be used. In most individuals, the problem resolves through adequate acclimatization or with the individual's return to a temperate climate. Given its benign nature, patients with heat edema can be safely discharged with outpatient follow-up.

Heat Syncope

Individuals adapt to a hot, humid environment by dilation of cutaneous vessels to deliver heat to the body surface. Thus, an increased portion of the intravascular pool is located in the periphery at any given time. Increasing blood flow to compliant cutaneous veins raises skin vascular volume at the expense of thoracic blood volume. The combination of volume loss and peripheral vasodilation can result in inadequate central venous return, a concomitant drop in cardiac output, and cerebral perfusion inadequate to maintain consciousness.

Clinical Features

Heat syncope is a multifactorial disorder that results in a temporary loss of consciousness in the presence of heat exposure. Older adults have a special predilection for this disorder, due to reduced cardiovascular reserve and blunted baroreceptor reflexes.

Differential Diagnoses

The diagnosis of heat syncope requires the appropriate clinical setting and exclusion of other possible causes of syncope, given a patient's age and underlying medical disorders such as cardiovascular and neurological causes (see Chapter 11).

Diagnostic Testing

Heat syncope can be precipitated by an underlying metabolic or cardiac disorder, so cardiac monitoring, electrocardiography, and hemoglobin determination are warranted. Other tests are individualized based on clinical suspicion following a thorough history and physical examination (see Chapter 11).

Management and Disposition

This disorder is self-limited and placing the patient in a horizontal position is generally curative. Older patients with comorbidities may require admission to address cardiac or neurologic etiologies. These individuals are at risk for recurrent heat syncope and should be advised to move around often, flex leg muscles repeatedly when standing stationary, avoid protracted standing in hot environments, and assume a sitting or horizontal position when prodromal warning symptoms or signs occur.

MAJOR HEAT ILLNESSES

Heat Exhaustion

Foundations

Background and importance. Heat exhaustion (heat prostration) is a clinical syndrome characterized by volume depletion that occurs under conditions of heat stress. Two types of heat exhaustion are classically described, water depletion and salt depletion.

Anatomy, physiology and pathophysiology. Water depletion heat exhaustion results from inadequate fluid replacement by individuals working in a hot environment and incapacitated individuals without free access to water. Those working in the heat seldom drink as much as they lose, and this voluntary dehydration results in progressive hypovolemia. Left untreated, heat exhaustion caused water depletion will progress to heatstroke because they are a continuum of the same disease.

Salt depletion heat exhaustion takes longer to develop than the water depletion form. It occurs when large volumes of thermal sweat are replaced by water with too little salt. It differs from heat cramps in that systemic symptoms occur. Symptoms are similar to those seen in water depletion heat exhaustion; the body temperature usually remains normal or minimally elevated.

Clinical Features

The symptoms and signs associated with both types of heat exhaustion are variable and include weakness, fatigue, frontal headache, impaired judgment, vertigo, nausea and vomiting and, occasionally, muscle cramps (Box 129.3). Orthostatic dizziness and syncope can occur. Sweating persists and may be profuse. The core temperature is only moderately elevated, usually below 40°C (104°F). Signs of severe CNS dysfunction (e.g., altered mental status) are not present.

Differential Diagnoses

Mild heat exhaustion and full-blown heatstroke represent extremes of the spectrum of heat illness, and intermediate cases may prove difficult to differentiate. Heat exhaustion should not be diagnosed in the

BOX 129.3 Heat Exhaustion: Diagnosis

- Vague malaise, fatigue, headache
- Core temperature often normal; if elevated, <40°C (104°F)
- Mental function essentially intact; no coma or seizures
- Tachycardia, orthostatic hypotension, clinical dehydration (may occur)
- Other major illness ruled out
- If in doubt, treat as heatstroke.

BOX 129.4 Heat Exhaustion: Management

Rest

Cool environment

Assessment of volume status—orthostatic changes, blood urea nitrogen level, hematocrit, serum sodium concentration

Fluid replacement—normal saline to replete volume if the patient is orthostatic; replace free water deficits slowly to avoid cerebral edema.

Healthy young patients are usually treated as outpatients; consider admission if the patient is older, has significant electrolyte abnormalities, or would be at risk for recurrence if discharged.

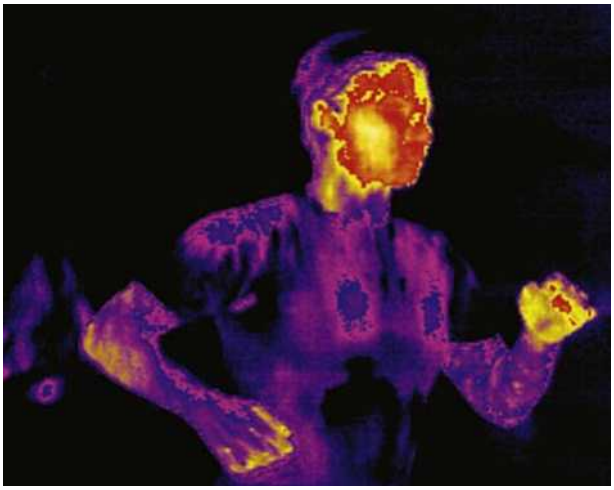

Fig. 129.4 Human Infrared Image. Note that the palms and face are substantially warmer than the rest of the body. (From Auerbach PS. *Wilderness Medicine.* 6th ed. Philadelphia: Mosby/Elsevier; 2012.)

presence of major CNS dysfunction (e.g., seizures, coma) or severe hyperthermia (40.5°C [105°F]).

Diagnostic Testing

This syndrome is characterized by hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. Determine a serum creatine kinase (CK) level and renal function. Measurement of hepatic transaminase levels may prove helpful. Elevations to several thousand units can be seen in patients with heat exhaustion or in healthy runners after a marathon.

Management

Pure forms of either type of heat exhaustion are rare, and most cases of heat exhaustion involve mixed salt and water depletion. Heat exhaustion is primarily a volume depletion problem, and rapid recovery follows fluid administration. Decisions regarding the type of fluid and electrolyte replacements should be based on serum electrolyte level measurements and the estimation of hydration status by clinical and laboratory parameters.

Patients with significant volume depletion or electrolyte abnormalities require IV fluids. If the patient is orthostatic, normal saline should be administered until vital signs normalize. Free water deficits should be replaced slowly over 48 hours to avoid a decrease of serum osmolality of more than 2 mOsm/h. Overly rapid correction of hyponatremia can result in cerebral edema and seizures.

Disposition

Young, otherwise healthy patients who do not have significant laboratory abnormalities and who respond rapidly to hydration do not require hospitalization. These patients should be instructed to drink plenty of fluids and avoid heat stress for 24 to 48 hours. Older patients, particularly those with cardiovascular disease or other chronic diseases, may benefit from more cautious inpatient fluid and electrolyte replacement and frequent reassessment (Box 129.4).

Heatstroke

Foundations

Background and importance. In the previously discussed forms of heat illness, although the body temperature rises, homeostatic thermoregulatory mechanisms remain intact. Heatstroke is the catastrophic life-threatening emergency that occurs when these mechanisms fail. This results in the elevation of body temperature to extreme levels, usually higher than 40.5°C (105°F), producing multisystem tissue damage and organ dysfunction.

Anatomy, physiology and pathophysiology. As heatstroke develops, energy will be insufficient to sustain thermoregulatory mechanisms, resulting in dramatic increases in core temperature and the clinical manifestations of heatstroke. Tissue damage is a function of a complex interaction of body temperature, exposure time, workload, tissue perfusion, and individual factors. The exact temperature at which cellular damage begins to occur in an individual patient varies. With rapid intervention, full recovery is possible, despite rectal temperatures up to 46.5°C (115.7°F).

Neurologic dysfunction is a hallmark of heatstroke, and cerebral edema is common. Other pathologic changes include petechiae in the walls of the third and fourth ventricles and marked cerebellar Purkinje cell damage.[6,7] Interestingly, the hypothalamus, the predominant site of central thermoregulatory control, is usually not damaged. Long term neurological impairment, such as motor, cerebellar or cognitive, is common.[6,7]

Heat stress creates tremendous demands on the cardiovascular system, and patients who succumb to heatstroke show signs of circulatory failure. Although such pathologic changes are common, cardiac damage alone is not lethal.

Prolonged heat stress produces impressive increases in skin blood flow (peripheral vasodilation) and a reduction of the thermal gradient between the core and the skin (Fig. 129.4). Functional hypovolemia is avoided by compensatory vasoconstriction of the splanchnic and renal vasculatures. The resulting splanchnic and renal ischemia may explain the nausea, vomiting, and diarrhea observed in runners after a marathon. Hepatic damage is a consistent feature of heatstroke, and its absence should cast doubt on the diagnosis.

If severe heat stress continues, compensatory splanchnic vasoconstriction will eventually fail, resulting in reduced mean arterial pressure and a continued cascade of exaggerated systemic inflammatory responses. Failure to perfuse the skin with heated blood from the core results in a dramatically increased rate of heat storage. This produces elevated intracranial pressure, which, in combination with the reduction in mean arterial pressure caused by failure of compensatory

BOX 129.5 Heatstroke: Diagnosis

- Exposure to heat stress, endogenous or exogenous
- Signs of severe central nervous system dysfunction (coma, seizures, delirium)
- Core temperature usually >40.5°C (105°F), but may be lower
- Hot skin common, and sweating may persist
- Marked elevation of hepatic transaminase levels

TABLE 129.1 Characteristics of Classic Versus Exertional Heatstroke

Exertional	Classic
Healthy	Predisposing factors or medications
Younger	Older
Exercise	Sedentary
Sporadic	Heat wave occurrence
Diaphoresis	Anhidrosis
Hypoglycemia	Normoglycemia
DIC	Mild coagulopathy
Rhabdomyolysis	Mild CK level elevation
Acute renal failure	Oliguria
Marked lactic acidosis	Mild acidosis
Hypocalcemia	Normocalcemia

CK, Creatine kinase; *DIC,* disseminated intravascular coagulation.

TABLE 129.2 Medications Associated With Heat Stroke

Drug Class	Examples
Anticholinergics	Atropine
	Benztropine
	Oxybutynin
	Scopolamine
Antidepressants	Tricyclics
Antiemetics	Metaclopramide
	Prochlorperazine
	Promethazine
Antiepileptics	Topiramate
	Zonisamide
Antihistamines	All
Antihypertensives	Beta blockers
	Calcium channel blockers
Antipsychotics	All
Diuretics	Hydrochlorothiazide
	Furosemide
	Spironolactone
Ergogenic Aids	Anabolic steroids
	Creatine
	Ephedra
Sympathomimetics	Amphetamines
	Cocaine
	Methylphenidate

splanchnic vasoconstriction, conspires to produce a decrease in cerebral blood flow. This results in the major CNS dysfunction characteristic of heatstroke.

Clinical Features

The onset of heatstroke is sudden, and the patient's level of consciousness is altered. Prodromal symptoms lasting minutes to hours occur in approximately 20% of cases. These are non-specific and may include weakness, dizziness, nausea, vomiting, anorexia, frontal headache, confusion, drowsiness, disorientation, muscle twitching, ataxia and signs of cerebellar dysfunction, along with possible psychiatric symptoms, ranging from anxiety and irritability to psychosis. These prodromal symptoms are reminiscent of the description of heat exhaustion. Heat exhaustion, particularly the water depletion variety, can progress to heatstroke if untreated.

The usual manifestations of heatstroke include hyperpyrexia above 40.5°C (105°F), profound CNS dysfunction, and hot skin (Box 129.5). Persistent sweating can be observed in patients with rectal temperatures of 41.5°C to 42.4°C (106.7°F to 108.3°F). Importantly, the cessation of sweating is not the cause of heatstroke, and continued sweating does not preclude the diagnosis.

Although in heatstroke the core temperature is elevated above 40.5°C (105°F), significant cooling may occur in the out-of-hospital setting, and the first temperature obtained in the emergency department (ED) may not represent the original maximum core temperature.

Classic heatstroke versus exertional heatstroke. The two forms of heatstroke, classic (epidemic) heatstroke (CHS) and exertional heatstroke (EHS), may have significantly different presentations and manifestations (Table 129.1).

CHS occurs during periods of sustained high ambient temperatures and humidity, such as during summer heat waves. Victims are often fixed income older adults who live in underventilated dwellings without air conditioning. Debilitated patients who have limited access to oral fluids may develop heat exhaustion due to water depletion, which progresses to heatstroke if untreated. Victims of CHS commonly suffer from chronic diseases, substance abuse, or psychiatric conditions which predispose to heat illness. Such patients are often prescribed medications (diuretics, antihypertensives, neuroleptics, anticholinergics) that impair the ability to tolerate heat stress (Table 129.2). Sweating ceases in most CHS patients. The central venous pressure (CVP) is usually elevated. The combination of elevated CVP with right-sided cardiac dilation suggests high output cardiac failure. These changes are expected because skin blood vessels dilate to dissipate heat; however, this low peripheral vascular resistance can persist in patients after reduction of body temperature to nearly normal. Pulmonary edema may also be present. Factors such as advanced age, hypotension, altered coagulation status, lactic acidosis, and the necessity for endotracheal intubation on arrival at the ED predict a poor outcome, despite successful cooling measures.

In contrast, patients with EHS are usually young and healthy individuals whose heat-dispelling mechanisms are overwhelmed by endogenous heat production. Athletes and military recruits are typical victims. Rhabdomyolysis and acute renal failure, rarely seen in patients with CHS, are common in patients with EHS. Sweating is present in 50% of cases of EHS. Hypoglycemia may occur as the result of increased glucose metabolism and hepatic damage, resulting in impaired gluconeogenesis. Coagulopathy is common. Hyponatremia

with serum sodium levels of less than 130 mmol/L has been detected in summer hikers in the Grand Canyon; many were found to have neurologic symptoms or seizures.

Patients with heatstroke usually have hyperdynamic cardiovascular systems with low peripheral vascular resistance, tachycardia (up to 180 beats/min), and an elevated cardiac index. Elevation of cardiac troponin is not uncommon with CHS; however, it is rarer in EHS. Respiratory alkalosis is a physiologic response to active or passive heating and may be severe enough to produce tetany. Although most patients with CHS have respiratory alkalosis, those with EHS usually have a relatively pure lactic acidosis. Lactic acidosis is associated with a poor prognosis in cases of CHS but not necessarily with EHS.

Signs of profound CNS dysfunction dominate the early course of CHS and EHS. Delirium or coma is characteristic, but virtually any neurologic abnormality, including bizarre behavior, opisthotonos, hallucinations, decerebrate rigidity, oculogyric crisis, and cerebellar dysfunction, can be seen. Convulsions occur in up to 75% of patients and can be precipitated by therapeutic cooling maneuvers. Profound muscle rigidity with tonic contractions, coarse tremor, and dystonic movements can mimic seizures. Pupils may be fixed and dilated, and the electroencephalogram may be isoelectric. All of these changes are potentially reversible with rapid intervention, although permanent damage, including cerebellar deficits, hemiplegia, dementia, and personality changes, may still occur in severe cases.[6,7]

Both CHS and EHS cause the hemoglobin-oxygen dissociation curve to shift to the right. An increase in the temperature denatures the bond between oxygen and hemoglobin, decreasing the concentration of oxyhemoglobin. Aberrations in coagulation are common in patients with severe heatstroke, and their presence is a poor prognostic sign.[8] Abnormal hemostasis is manifested clinically by purpura, conjunctival hemorrhage, melena, bloody diarrhea, hemoptysis, hematuria, myocardial bleeding, or hemorrhage into the CNS. Pancreatitis is described, with elevated serum amylase and lipase levels. Diarrhea, probably caused by intense splanchnic vasoconstriction, is commonly seen. Cooling aggravates the diarrhea, creating an unpleasant treatment dilemma.

Differential Diagnoses

Heatstroke occurs when the thermoregulatory responses are overwhelmed and fail. If the patient is evaluated as this is occurring, differentiation between heat exhaustion and heatstroke is difficult. If heatstroke cannot be excluded, efforts to cool the patient should begin immediately. Only after the initial assessment and cooling are initiated is the differential diagnosis relevant. When a history of collapse under conditions of heat stress is present, rapid improvement in mental status and blood pressure with cooling essentially eliminates alternative diagnoses. Consider other causes of fever and coma such as infectious causes if the temperature does not respond, and the patient does not recover neurologically (Box 129.6).

Meningitis and encephalitis. These can masquerade as heatstroke. In patients with heatstroke, the spinal fluid should be clear, with occasional lymphocytic pleocytosis and elevated protein levels. Cerebral falciparum malaria, which has a clinical picture of high fever and encephalitis, is seen in tropical areas where heat illness can also occur.

Thyroid storm. In patients with thyroid storm, the clinical symptoms resemble those of heatstroke. It should be suspected if the thyroid gland is enlarged or nodular, but a normal thyroid gland does not exclude the diagnosis. Thyroid function test results are elevated, but these may not be available on an emergency basis. Fortunately, thyroid storm is rare, and some critical aspects of treatment, such as rapid cooling, coincide with those for heatstroke.

BOX 129.6 Differential Diagnoses of Heatstroke

- Central nervous system hemorrhage
- Toxins, drugs
- Seizures
- Malignant hyperthermia
- Exercise-induced hyponatremia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Thyroid storm
- High fever, sepsis
- Encephalitis, meningitis

Drug-induced heat illness. This is an important consideration, particularly anticholinergic poisoning. Differentiation may be difficult because heatstroke and anticholinergic poisoning cause hyperpyrexia, hot and dry skin, tachycardia, and abnormal mental status. Constricted pupils are present in many heatstroke patients. Mydriasis should be present in patients with anticholinergic poisoning, and its absence argues strongly against this diagnosis. Typhoid fever, typhus, delirium tremens, and hypothalamic hemorrhage all produce a symptom complex similar to that of heatstroke.

Drug overdose of sympathomimetics or stimulants, such as amphetamines, cocaine, and phencyclidine, can cause fatal hyperpyrexia. A high ambient temperature is associated with a significant increase in mortality from cocaine overdose. Many younger patients who die of hyperthermia test positive for cocaine. Heatstroke can occur with delirium resulting from ethanol withdrawal. Aspirin and clopidogrel attenuate the skin vasodilatory response and shifts the onset of peripheral thermoeffector mechanisms toward a higher body temperature during exercise heat stress. Heatstroke occurs in well-trained military soldiers and athletes who ingest dietary supplements containing ephedra or the ergogenic aid creatine. Some antipsychotics also cause suppression of thirst recognition. Individuals with a history of heatstroke, with or without an inherent aberration that predisposed them to the initial episode, are at increased risk for a recurrence.

Exercised associated hyponatremia. Symptoms of hyponatremia, especially exercised associated hyponatremia, can be mistaken for heat exhaustion or heat stroke. Although not a true heat related illness, it may be difficult to differentiate from exertional heat illnesses due to overlapping symptoms of collapse, dizziness, weakness, and in severe cases, mental status changes. However, severe hyperthermia (40.5°C) should not be present.[9]

Neuroleptic malignant syndrome. This disorder is induced by antipsychotic medications and is characterized by muscle rigidity, severe dyskinesia or akinesia, hyperthermia, tachycardia, dyspnea, dysphagia, and urinary incontinence. Although the so-called "lead pipe rigidity" and hyperthermia are reminiscent of malignant hyperthermia, the putative mechanism is different. Dopamine receptor blockade in the corpus striatum caused by butyrophenones (e.g., haloperidol) and similar agents produces severe muscle spasticity and dystonia, leading to the overproduction of heat in patients with NMS (see Chapter 150).

Serotonin syndrome. This can also mimic heatstroke because of the elevated body temperature tremors, clonus, and CNS alterations that occur. Serotonin syndrome is classically a triad of mental status

changes, autonomic hyperactivity, and neuromuscular abnormalities (e.g., clonus) secondary to increased CNS serotonergic activity. A history of recent exposure to an illicit drug or interaction with a therapeutic medication is an important clue.

Diagnostic Testing

Most standard measurements of body temperature vary significantly from the actual core temperature. Oral thermometry is affected by mouth breathing and is a poor approximation of the body's core. Rectal thermometry is less variable but responds to changes in core temperature slowly. Thermistors that are inserted 15 cm into the rectum, and not within stool, offer continuous monitoring of temperature and have less variability. Although rectal measurements are slower to respond to changes in core temperature than tympanic temperature readings, rectal measurements are not biased by head skin temperature. An esophageal thermistor positioned adjacent to the heart is another option. Do not use alternative methods such as oral, aural canal, tympanic, or skin to measure body temperature in patients with heatstroke.

The hematologic evaluation should include arterial blood gas determination, complete blood cell and platelet counts, liver transaminases, electrolyte values (including calcium), glucose, blood urea nitrogen, and serum creatinine levels. Hypoglycemia with a serum glucose level less than 65 mg/dL is often found in cases of EHS. With the risk of acute rhabdomyolysis, serum creatine kinase and myoglobin levels should be measured, and urinalysis performed. Severe heatstroke can induce disseminated intravascular coagulation (DIC). Measure prothrombin and partial thromboplastin times, international normalized ratio, and fibrin degradation products. Obtain serum cardiac troponin levels. Metabolic acidosis is common, especially in patients with EHS. Serum lactate levels are usually elevated and may persist or even worsen with improved extremity perfusion.

Acute renal damage is common. The initial urine specimen, usually obtained by catheterization, is a scant, brownish, turbid fluid resembling machine oil. Microscopic examination reveals proteinuria, with abundant granular casts and red blood cells. Acute oliguric renal failure complicates 25% to 30% of EHS cases and 5% of CHS cases. The glomerular filtration rate, renal plasma flow, urine flow, and sodium excretion diminish markedly during exercise. Heavy physical exertion in hot climates produces acidic and maximally concentrated urine, which can result in acute oliguric renal failure in combination with hypotension and myoglobinuria.

Because heatstroke patients are prone to liver failure, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), and liver other enzyme levels should be monitored. Elevation typically occurs within 24 hours. Hepatic transaminase level elevations may be diagnostically helpful. In most febrile states that include altered mental status or coma, these enzyme levels will be normal or minimally elevated, although they are usually dramatically elevated early in the course of heatstroke. Hepatic damage is consistently featured in heatstroke. Hepatic injury is evidenced by markedly elevated levels of hepatic aminotransferases (serum AST and ALT). Elevation can be into the tens of thousands. Early experimental models have shown that high-mobility group box 1 (HMGB1) as a mediator of systemic inflammation is elevated in heatstroke, and its inhibition may be liver-protective. Jaundice typically appears 24 to 72 hours after the onset of severe heatstroke and gradually precedes if the victim survives. Survivors generally have no permanent impairment of liver function.

Management

Cooling. Immediate cooling is the cornerstone of treatment. If heatstroke cannot be excluded, begin cooling immediately. In EHS, it is usually best to follow the "cool first, transport second" guideline.[10,11]

BOX 129.7 Cooling Modalities to Lower Body Temperature in Heatstroke

Preferred

Evaporative cooling with large circulating fans and skin wetting
Ice water immersion

Adjuncts

Ice packs to axillae and groin
Cooling blanket
Peritoneal lavage (unproven efficacy in humans)
Rectal lavage
Gastric lavage
Cardiopulmonary bypass

Cooling should not be delayed in order to remove all clothing; this can be done simultaneously with cooling efforts.[12] Patients who present to the hospital with heatstroke have high mortality rates ranging from 20% to 65%, and mortality increases significantly when cooling is delayed. Insert a rectal thermistor probe as soon as possible and monitor the patient's temperature continuously.

Immersion in ice water results in a rapid reduction of core temperature to below 39°C within 10 to 40 minutes. Vigorous skin massage to maintain cutaneous circulation has been advocated, but there is no evidence that this is clinically efficacious. Ice water immersion presents many logistical challenges and may hamper resuscitative efforts especially in the ED. The lack of adequate space or drainage, the need for monitoring, rapid facilitation of patient entry and exit from the immersion tank create unique challenges. Environmental safety concerns surrounding management of spilled ice and water in proximity to electrical equipment is an additional concern. For EHS, it is most beneficial when it is preplanned and available for mass participation events during the warm season such as in medical tents in close proximity to the participants.[13] The military has recognized the difficulties with ice water immersion in remote military exercises and have adapted to ice water sheets draped over the patient. It can be initiated at the scene using skin lavage with ice water slurry and chilled intravenous saline.[14]

Evaporative cooling is also recommended because it is effective, easy to perform, noninvasive, and less likely to interfere with other patient care activities than other cooling techniques. The patient is stripped of all clothing, and tepid tap water is sprayed while fans blow air continuously over the body, causing evaporative cooling. One reported method of evaporative cooling uses a body cooling unit on which the patient lies suspended on a net surface while being sprayed with atomized 15°C (59°F) water from above and below. Air warmed to 45°C to 48°C (113°F to 118.4°F) is blown over the skin surface at a rate of 3 m/min. This approach maximizes evaporative and convective cooling by maintaining cutaneous vasodilation and avoiding heat generation caused by shivering. Vasoconstriction from ice water immersion may be beneficial to hypotensive patients and may be better than evaporative cooling for victims in shock who have poor peripheral circulation. Discontinue cooling measures when the patient's body temperature reaches 39°C (102.2°F) to avoid "hypothermic overshoot."[15] Continuous monitoring is necessary to maintain the core temperature at 37°C to 38°C (98.6°F to 100.4°F).

Cooling modalities other than evaporation and immersion are considered adjunctive treatments (Box 129.7).[16] Application of ice packs to high heat transfer areas (e.g., neck, groin, axillae) is commonly used. Cooling blankets may be a useful adjunct but will not produce rapid cooling if used exclusively. Cold irrigant gastric or rectal lavage will not provide significant heat exchange if used as the primary cooling

modality. Antipyretics have no role in the treatment of heat-related illness. The clinical efficacy of dantrolene has not been established in the setting of heat stroke.

Resuscitation. Mortality correlates with the elevated temperature duration and number of dysfunctional organ systems, with an increased risk of death if patients present with anuria, coma, or cardiovascular failure. Aspiration and seizures are common in patients with heatstroke, and airway control is indicated. Hypoxemia may occur because of aspiration, pneumonitis and pulmonary infarction, hemorrhage, or edema. Metabolic demands are high, and normal pulmonary ventilation may be inadequate in this setting.

Crystalloid fluid resuscitation is essential. Circulatory fluid requirements are modest in some cases, averaging 1200 mL of isotonic crystalloid solution in the first 4 hours. Pulmonary edema occurs in patients with heatstroke and can be exacerbated by overzealous fluid administration. The use of a CVP catheter to monitor fluid resuscitation may be deceptive. Most patients have a hyperdynamic circulation with a high cardiac index, low peripheral vascular resistance, and elevated CVP as a result of high output cardiac failure. These patients may require only modest IV fluids because cooling produces vasoconstriction and increases blood pressure. Hypotension is common in patients with heatstroke and is usually caused by peripheral vasodilation resulting in high-output cardiac failure in addition to dehydration. Blood pressure usually rises with cooling. If this does not occur, or if the invasively monitored patient has a low CVP, a fluid challenge of 250 to 500 mL of isotonic intravenous fluid should be given rapidly while blood pressure, pulse, and urine output are monitored. Fluid replacement is continued until the blood pressure reaches 90/60 mm Hg or the CVP exceeds 12 mL H_2O. On occasion, patients exhibit hypodynamic responses with a low cardiac index, elevated CVP, and hypotension. These patients may be cyanotic, whereas patients with hyperdynamic circulation are initially pink. This clinical observation can be helpful in identifying patients who may respond to catecholamines.

A variety of tachyarrhythmias commonly occur during heatstroke. These usually resolve with cooling, and electrical cardioversion should be avoided until the myocardium is adequately cooled. The use of α-adrenergic agents such as norepinephrine is not recommended because they promote vasoconstriction without improving cardiac output or perfusion, decrease cutaneous heat exchange, and may exacerbate ischemic renal and hepatic damage. Atropine and other anticholinergic drugs that inhibit sweating should be avoided.

The pathophysiologic processes of heatstroke and fever differ, so antipyretics are not indicated and may be harmful. Salicylates, particularly in large doses, may worsen hyperthermia by uncoupling oxidative phosphorylation and aggravating coagulopathies. Large doses of acetaminophen can result in further hepatic damage.

If rhabdomyolysis is present, maintenance of urinary output of at least 2 mL/kg/h is recommended. Consider urinary alkalinization (higher than a pH of 6.5) early in patients with acidemia, dehydration, or underlying renal disease. After volume repletion, administration of mannitol may be considered to increase intravascular volume and increase the glomerular filtration rate. Mannitol, however, should not be used in an oliguric patient. Persistent anuria, uremia, or hyperkalemia is an indication for consideration of hemodialysis.

Cooling modalities that drastically lower skin temperature may induce violent shivering; this increases metabolic heat production and may impede cooling. Intravenous benzodiazepines are the treatment of choice for shivering. The administration of neuroleptics, like chlorpromazine, should be avoided. These agents have anticholinergic properties that can interfere with sweating and cause hypotension or precipitate seizures. Many patients are extremely agitated during the initial cooling period. Short-acting benzodiazepines can be used for sedation and to control seizures. Barbiturates are less desirable as their metabolism is altered by hepatic dysfunction and they may exacerbate hypotension.

Coagulopathies can occur during the first day of illness but are more common on the second and third days. Initial treatment after cooling should include replacement therapy with fresh- frozen plasma and platelets while monitoring for laboratory signs of DIC (hypofibrinogenemia, elevated fibrin split products, prolonged prothrombin time, and thrombocytopenia). The bleeding diathesis seen in patients with heatstroke may be the result of fibrinolysis. Although α-aminocaproic acid can impede fibrinolysis, administration of this compound is associated with rhabdomyolysis, and its use is not recommended.

Disposition

Admission to an intensive care setting may be necessary. Heat stroke victims can have long term sequela from heat stroke that may not be readily apparent in the initial stages. Follow-up after hospitalization is needed. Patients with more complex end-organ damage (e.g., renal failure requiring dialysis) will require transfer to a center with more comprehensive tertiary care capabilities.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 129: QUESTIONS AND ANSWERS

1. An 18-year-old female marathon runner presents to the medical aid station during a hot summer race. She is extremely irritable and diaphoretic. She is complaining of generalized weakness, dizziness, nausea, and headache. The physical examination reveals an oral temperature of 40.5°C (105°F), heart rate of 120 beats/min, muscle twitching, and ataxia. What is the most appropriate management?

a. Assess her volume status and immediately start normal saline to replete volume loss before transfer to a hospital.
b. Encourage her to drink cold water to replace her free water deficit rapidly.
c. Immediately remove her from the hot environment and begin cooling before transfer to a hospital.
d. Prescribe immediate rest, after which she may be allowed to finish the race.

Answer: c. The onset of heatstroke is sudden. Prodromal symptoms lasting minutes to hours can occur that are nonspecific and similar to those of heat exhaustion. Signs and symptoms may include weakness, dizziness, nausea, frontal headaches, confusion, muscle twitching, ataxia and signs of cerebellar dysfunction, and psychiatric symptoms, ranging from anxiety and irritability to psychosis. Heat exhaustion can progress to heatstroke if it is untreated. If the patient is evaluated as this is occurring, differentiation between heat exhaustion and heatstroke is difficult. If heatstroke cannot be excluded, begin cooling the patient immediately.

Whereas rest is part of the treatment for heat exhaustion, it is not the only treatment. She must be removed from the hot environment, not be allowed to finish the race, and assessed for her volume status. Normal saline is used to replete volume if the patient is orthostatic; free water deficits are replaced slowly to avoid cerebral edema.

2. Which of the following statements regarding heat exhaustion is true?

a. It causes body temperatures that often exceed 40.5°C (105°F).
b. It only exists in two discrete forms, either salt depletion or water depletion.
c. It is associated with systemic symptoms.
d. It is characterized by hyponatremia and hyperchloremia.
e. It occurs when muscles are fatigued by heavy work.

Answer: c. Heat exhaustion is a clinical syndrome. Whereas there are typically two types of heat exhaustion, water depletion and salt depletion, pure forms of either type are rare. Most cases of heat exhaustion involve mixed salt and water depletion. In salt depletion heat exhaustion, the syndrome is characterized by hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. The symptoms and signs associated are variable and nonspecific but usually systemic, such as weakness, fatigue, frontal headache, vertigo, nausea, and vomiting. The body temperature usually remains nearly normal.

3. Despite cooling measures, poor outcomes are seen in heatstroke patients with which of the following?

a. Altered coagulation status
b. History of schizophrenia
c. Need for supplemental oxygen
d. Presentation with acute renal failure
e. Presentation with acute rhabdomyolysis

Answer: a. Factors such as advanced age, hypotension, altered coagulation status, and the necessity for endotracheal intubation on arrival at the emergency department predict a poor outcome, despite successful cooling measures.

CHAPTER 129: QUESTIONS AND ANSWERS—cont'd.

4. The usual characteristics of classic heatstroke include which of the following?
   - **a.** Diaphoresis
   - **b.** Disseminated intravascular coagulation
   - **c.** Hypoglycemia
   - **d.** Marked lactic acidosis
   - **e.** Usual occurrence during heat waves

Answer: e. Usual characteristics of classic heatstroke include predisposing factors or medication, older population, sedentary lifestyle, anhidrosis, normoglycemia, mild coagulopathy, mild elevation in creatine kinase level, oliguria, mild acidosis, and occurrence during heat waves. Diaphoresis, hypoglycemia, disseminated intravascular coagulation, and marked lactic acidosis are characteristics of exertional heatstroke.

5. Which of the following is associated with heat cramps?
   - **a.** Excessive salt intake
   - **b.** Drinking copious amounts of hypertonic fluids
   - **c.** Carpopedal spasms with distal extremity paresthesias
   - **d.** Hyponatremia and hypochloremia
   - **e.** Rhabdomyolysis

Answer: d. Heat cramps are brief, intermittent, and often severe muscle cramps occurring typically in muscles that are fatigued by heavy work. Heat cramps appear to be related to a salt deficiency. Heat cramps are occasionally confused with hyperventilation tetany. Hyperventilation tetany can be distinguished by the presence of carpopedal spasm and paresthesias in the distal extremities and perioral area. Heat cramps accompanied by systemic symptoms may be part of salt depletion heat exhaustion. Heat cramp victims exhibit hyponatremia and hypochloremia, so serum electrolyte levels should be measured. Rhabdomyolysis or resultant renal damage is not present with isolated heat cramps.

Electrical and Lightning Injuries

Paul Chen and Alice Kidder Bukhman

KEY CONCEPTS

- Electrical current follows the path of least resistance, which is often along neurovascular bundles. Deep tissue injuries and organ damage are often more extensive than indicated by examination of the overlying skin.
- Testing is not indicated for victims of low-voltage electrical injuries who are asymptomatic or have minimal local symptoms and physical evidence of burn injury. These patients may be discharged home after emergency department (ED) evaluation.
- Patients exposed to high-voltage sources or lightning strikes who present with syncope, altered mentation, focal neurologic abnormality, significant burns, entry and exit wounds, or persistent symptoms should have testing including electrocardiography, complete blood count, basic chemistry panel, myoglobin and troponin level determination, and urinalysis. Additional testing is directed at suspected areas of injuries.
- Patients with electrocardiographic signs of cardiac injury or dysrhythmias, or with evidence of significant local injury, should be monitored for 12 to 24 hours in the ED, observation unit, or inpatient setting.
- The enormous current of a lightning strike may cause critical injury or death, or the current may be directed superficially over the patient to the ground, resulting in no injury and minor burns.
- Electrocardiography is indicated for all patients evaluated for lightning strike. Additional testing should be based on specific signs and symptoms.
- Lightning strike patients who present without symptoms or signs of injury, or with only minor first-degree burns, and with a normal ECG can be discharged home from the ED after evaluation.
- Lightning strike can cause fixed, dilated pupils in the absence of irreversible brain injury.

FOUNDATIONS

Background and Importance

Electrical injuries are uncommon but can cause significant morbidity and mortality. Toddlers and younger children experience low-voltage injuries in the household as the result of contact with electric sockets and cords. Adolescents and young adults more frequently experience high-voltage injury from contact with electric lines outside of houses. Another peak occurs in the third to fourth decade of life, almost exclusively in men with occupational injuries due to high-voltage encounters with power lines and, to a lesser extent, from electric tools. Worldwide, electrical injuries comprise less than 5% of admissions to burn units, but in developing countries this proportion is much higher at 25%.[1] Forensic reports of deaths caused by electrical injury show that the overwhelming majority of victims are men and most deaths are accidental, with a minority attributed to suicide or homicide.[2]

Anatomy, Physiology, and Pathophysiology

Electrical Injury

Current and Voltage. *Joule's law*, which describes the amount of thermal energy applied to tissues from electricity, is described by the formula

$$P = I^2RT$$

where P is thermal energy, I the current, R the resistance, and T is the duration (time) that the electricity is applied. Current is the flow of electrons down an electrical gradient and is measured in units of amperage. Current is the most important factor in determining the degree of energy transmitted, but it is rarely known in a given exposure. Instead, voltage is used as a proxy for current. According to *Ohm's law*, current (I) is directly proportional to the voltage (V) of the source and inversely proportional to the resistance (R) of the material through which it flows (I = V/R).

Injuries are conventionally classified as being caused by high- or low-voltage sources, with 1000 V as the dividing line. In North America, household sources are low voltage, typically 120 or 240 V. High-voltage injuries, such as those caused by electrical power lines or occupational accidents, are characterized by partial to full-thickness skin burns, deep tissue destruction, and potential cardiac or respiratory arrest. High-voltage injuries are associated with higher rates of death, and more associated traumatic injuries, such as extremity fractures, blunt head injuries, and spinal cord injuries.[1,2] Low-voltage exposure causes less surface damage, but may be equally lethal, particularly in cases in which skin resistance is low, such as when immersed or exposed to water.

Current Type. Electrical sources create current that flows in one direction (*direct current, DC*) or alternates direction cyclically at varying frequencies (*alternating current, AC*). The few systems in the United States that use DC include batteries, automobile electronics, and railroad tracks. Exposure to DC most frequently causes a single, strong, muscular contraction. This may throw the victim back from the source in a way that limits duration of exposure but can result in other traumatic injuries. AC is more commonly used (e.g., household currents) because it conveniently allows for an increase or decrease of power at transformers. It is more dangerous than DC of similar voltage because amperage above the so-called "let-go" current will cause muscular tetanic contractions. Because the flexor muscles of the upper extremities are stronger than extensor muscles, these contractions pull the victim closer to the source resulting in prolonged exposure. Box 130.1 shows the physical effects of different amperage levels at a common 60-Hz AC exposure.

Capacitors store electric charge in circuits, and discharge from these devices may result in sudden bursts of very large amounts of electrical

BOX 130.1 Physical Effects of Different Amperage Levels[a]

1 mA—barely perceptible
6–9 mA—usual range of let-go current
16 mA—maximum current that an average person can grasp and let go
20 mA—paralysis of respiratory muscles
100 mA—ventricular fibrillation threshold
2 A—cardiac standstill and internal organ damage

[a] At 60-Hz AC exposure.
From Centers for Disease Control. Worker deaths by electrocution: a summary of NIOSH surveillance and investigative findings. www.cdc.gov/niosh/docs/98-131/pdfs/98-131.pdf.

BOX 130.2 Resistance of Body Tissues[a]

Lowest
Nerve
Blood vessels
Muscle
Skin
Tendon
Fat
Bone
Highest

[a] Lowest to highest.

energy. Injury from a capacitor may occur even when the electrical device is not energized or plugged in into an electrical source.

Resistance of Tissue Affected. Resistance is the degree to which a substance resists the flow of current; when resistance goes down, current increases. Resistance varies among body tissues. Neurovascular tissues are good conductors of electricity, whereas skin, tendons, fat, and bone are relatively poor conductors (Box 130.2). Current that is initially unable to pass through skin will create thermal energy and cause significant burns. As the skin blisters and deteriorates, its resistance decreases. Once current is through the skin, it can pass easily along lower resistance structures, causing deep tissue injury which may not be immediately evident. As a result, the degree of burns seen on the surface of the skin typically underestimates the damage occurring below the surface. As current strength increases, the relative resistance of tissues ceases to determine the pathway of current, and the entire body functions as a conductor. Current may also jump across skin surfaces in a behavior termed *arcing*, resulting in prominent burns across flexor surfaces.

Within a given tissue, resistance differs based on the fluid and electrolyte content of cells. Dry skin offers the largest resistance, up to 100,000 ohm (Ω) in thick, calloused skin, but dermal resistance decreases to as little as 1000 Ω when wet. This explains why electrical injuries are generally worse in the setting of water.

Path Taken by Current Through the Body. The pathway followed by electrical current determines morbidity and mortality. The entrance and exit sites of the electrical current typically demonstrate greater evidence of skin damage, with full-thickness burns commonly encountered. These sites are properly referred to as the *source and ground contact points*. A patient may have one or multiple source and ground contact points. The most common points of source contact are the hands, wrists, and arms, but children also present with burns from oral contact with electric cords or sockets. The most common ground contact points are the heels of the feet.

Electrical current passing through a limb causes greater local tissue damage than current passing through the trunk because the smaller cross-sectional area limits the ability to dissipate heat. However, current passing through the trunk results in greater mortality due to the involvement of more vital cardiothoracic organs. Transthoracic pathways (arm to arm) are more likely to generate dysrhythmias and have higher mortality rates than vertical currents (leg to arm) or straddle pathways (leg to leg).

Duration of Contact. The degree of tissue damage is directly proportional to the duration of exposure for all voltage levels. Exposure times greater than the length of one cardiac cycle tend to generate dysrhythmias, likely in a manner analogous to the R-on-T phenomenon.

Lightning Injury

Although the same basic scientific principles of electricity apply to lightning, there are several major differences. Lightning strikes involve hundreds of millions of volts, significantly more than those from electrical sources. In contrast, the duration of contact is drastically shorter, averaging 30 microseconds. As a result, current flow is altered, with most of the energy passing over rather than through a victim (termed the "flashover effect"). This reduction in penetration explains why lightning strikes paradoxically result in less destruction to tissues compared with lower-voltage electrical injuries.

Lightning takes various forms, described as streaked, forked, ribbon, sheet, or beaded. The most unusual form is ball lightning, which appears as a globe, rolls along structures, and may even pass through open doors or windows. Strikes occur from cloud to cloud, cloud to ground, and less commonly, ground to cloud.

Lightning may strike a person directly or indirectly. A person's chances of being struck are increased by wearing or carrying metal objects (such as golf clubs or umbrellas) or other conductors. Current from lightning may reach the body indirectly by traveling through a tree or other object (contact voltage), through the ground or even through the air from a struck object (side flash, or splash injury). Side flashes may travel as far as 30 meters.

The risk of injury from a ground strike is increased when one contact point on the victim (e.g., the right foot) is closer to the strike than a second contact point (e.g., the left foot), thus creating a potential difference. This is referred to as the "stride voltage" and is likely responsible for cattle deaths in a pasture after a thunderstorm. Hence, when out in the open during a storm, risk of a lightning strike can be reduced by placing an insulating material, such as a raincoat, between the ground and the body and assuming the lightning position, a squatting configuration with the feet together, or by curling up in a ball on the ground to reduce the number of contact points. Box 130.3 lists safety tips for avoiding lightning strikes.

Injury occurs from the force of a strike, blunt trauma when the victim is thrown, the superheating of metallic objects in contact with the patient, barotrauma, or penetrating trauma from shrapnel.

Conducted Energy Weapons

Conducted energy weapons (CEW), commonly known as Tasers or stun guns, are now widely used in law enforcement. These weapons deliver brief bursts of high-voltage, low-amperage direct current. Although CEWs have been associated with several high-profile police-involved fatalities, a clear causal link between their use and a death has not been established.

The most commonly known CEWs are the Taser (Axon Enterprise, Inc.) (Fig. 130.1). These weapons consist of a hand-held unit with two barbs (Fig. 130.2) with connecting cables that are deployed by the user at distances of up to 25 feet. The units typically lodge in the skin or

BOX 130.3 Tips to Avoid Lightning Strike

- Seek shelter inside an enclosed building or metal-topped automobile.
- Avoid large flat, open areas or hilltops.
- Avoid contact with metal objects and remove metal objects, such as jewelry or hairpins.
- Avoid trees, boats, and open water.
- If caught on open ground, curl up on your side with hands and feet close together to reduce contact points, or squat with feet together. If possible, place a rubber raincoat under your body or feet to reduce ground current effects.
- If in a forest, seek shelter under a thick growth of shorter trees.
- If indoors, avoid the use of wired phones and contact with plumbing or electrical appliances.

Fig. 130.1 Commonly used conducted energy weapon—Taser X26.

Fig. 130.2 Taser barbs that deliver electrical burst, causing neuromuscular incapacitation.

clothing and then automatically deliver a 5-second burst of energy. Further energy bursts can be delivered at the user's discretion. When these barbs lodge in the person at a distance from one another, they cause an energy arc that results in general muscle contraction and neuromuscular incapacitation (NMI). Newer devices have been developed to create a larger barb spread at close range to maximize the arc distance and more readily induce NMI.

BOX 130.4 Types of Burns Associated With Electrical Injury

Entrance and exit site burns
Arc burns, kissing burns
Thermal burns
Flash burns

CEWs may also include a touch-stun mode, in which direct contact of the weapon to the person is required to deliver an electrical energy pulse. In these cases, the barbs are not deployed, and the subject experiences localized pain but will not undergo NMI.

CLINICAL FEATURES

Electrical Injury

At the cellular level, current causes damage to cell membranes and alters membrane solubility, leading to electrolyte abnormalities and cellular edema. This process, termed *electroporation*, eventually leads to irreversible cell damage and death. At the tissue and organ levels, electrical current produces damage when electrical energy is converted to thermal energy. Electrical injury rarely causes immediate death, but when it does, it is often due to current-induced cardiac arrest (ventricular fibrillation or asystole), respiratory arrest due to respiratory muscle paralysis, or brainstem injury. Commonly reported delayed complications of electrical injuries include sepsis, acute renal failure, wound infections, and amputations.[3]

Lightning Injury

In contrast to electrical injury, lightning injuries involve very brief exposure to high-voltage energy. General effects are thus quite different than electrical injury, with deep muscle injury being much less common. Instead, lightning more commonly causes blunt traumatic injuries or cardiopulmonary arrest from transient stunning and disruption of the pacemaker cells and brainstem.

Skin

Electrical Injury. Most electrical injuries result in skin burns, which fall into one or more of four patterns (as described in Box 130.4). The relatively high resistance of skin in many cases leads to significant partial- or full-thickness burns at entrance and exit sites, most commonly seen over the upper extremities, particularly at the hand and wrist. The skull is another common source contact point. Visible burns may be insignificant in comparison to the damage that occurs beneath the surface and, as a result, are associated with significantly greater morbidity than simple thermal burns involving a similar surface area. Because of this, use of the Parkland formula or other fluid resuscitation equations tend to under-resuscitate these patients. Burns at entrance and exit sites will typically have a punctate appearance, with central depression and necrosis surrounded by a hyperemic border.

Arc burns, or so-called "kissing burns" (Fig. 130.3), occur when electricity jumps from skin surface to skin surface, typically across flexed areas of the body. Temperatures may reach 3500°C (6332°F) and cause severe damage. Arc burns are usually noted across the volar forearm and elbow and along the inner arm and axilla.

In cases in which clothing ignites and catches fire, patients also experience thermal burns. Flash burns are skin burns caused by brief, intense flashes of light, electrical current, or thermal radiation. Cutaneous burns across the chest and upper abdomen indicate a transthoracic current and portend a worse prognosis.

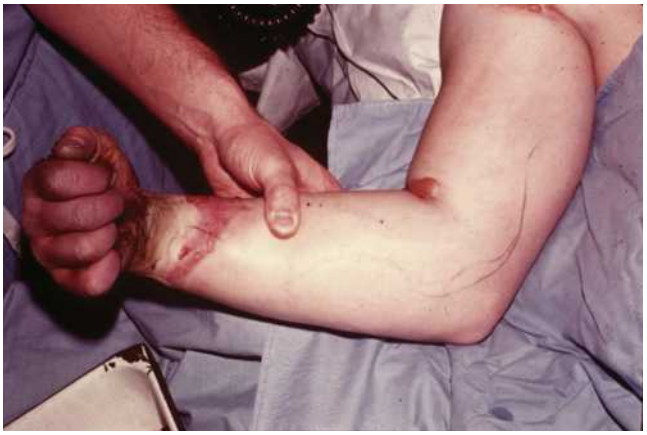

Fig. 130.3 Kissing burn. (Courtesy Dr. Mary Ann Cooper.)

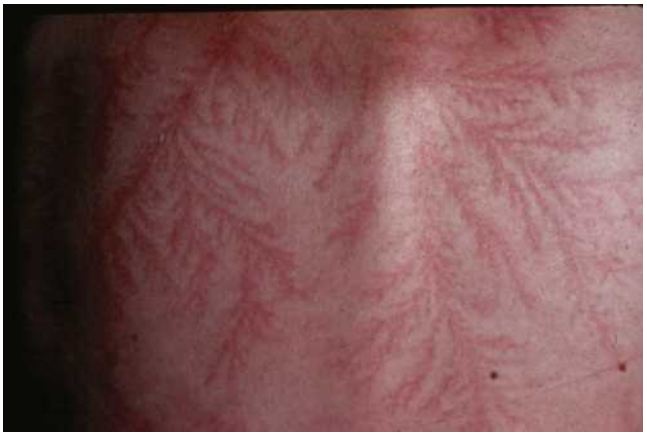

Fig. 130.4 Lightning burn. (Courtesy Dr. Mary Ann Cooper.)

Lightning Injury. Roughly 90% of lightning strike victims suffer skin burns, but less than 5% are deep burns. Although the voltages involved in a strike are substantial, most of the voltage will pass over rather than through the body in what is called a flashover effect. Moreover, the duration of contact is so brief that significant damage does not usually occur. Skin resistance is typically lessened by rain or perspiration, contributing to the flashover effect, where current preferentially flows over the integument rather than through it (i.e., following the path of least resistance). The result is the arborescent or fernlike patterns of erythematous streaks (typically first-degree burns) that have been termed *Lichtenberg figures* (Fig. 130.4). Deeper burns may occur at the direct point of contact or wherever metal is involved (due to superheating), such as with a belt buckle or jewelry. Clothing may catch on fire, resulting in thermal burns. Unlike conventional high-voltage electrical exposures, exit wounds are generally not seen, and the overall effects are much less severe.

Cardiovascular

Electrical Injury. Cardiac or respiratory arrest is the most common cause of death immediately following electrical injury. High-voltage exposures are associated with higher rates of cardiac complications, although low-voltage exposures can also cause cardiac arrest.[2] Traditionally, it is believed that AC causes ventricular fibrillation and DC causes asystole. In reality, exposure to either type of circuit is associated with both dysrhythmias, especially at higher voltages. Respiratory arrest may occur as a result of tetanic paralysis of the thoracic respiratory muscles and diaphragm or as a result of damage to the brainstem respiratory centers. Prolonged apnea in these situations can lead to hypoxic cardiac arrest.

Most dysrhythmias are seen immediately following electrocution. These include life-threatening dysrhythmias, but more frequently involve sinus tachycardia or bradycardia, atrial fibrillation, and ectopic beats. A variety of electrocardiographic abnormalities may be present, including transient ST elevation or depression that does not correlate with myocardial ischemia or infarction. Injury to coronary arteries or directly to the myocardium may result in infarction, but this is rare. Nonspecific cardiac biomarker levels (e.g., creatine kinase) are frequently elevated in the period following electrical injury, but this is usually due to skeletal muscle injury and is only rarely related to cardiac damage. Dysrhythmias may also appear in a delayed fashion, with case reports of fatal dysrhythmias, although the limited available studies suggest the risk is very low.[4,5,6]

Lightning Injury. The most severe effects of lightning strike are cardiac and respiratory arrest. The massive surge is analogous to defibrillation and can result in asystole or nonperfusing ventricular rhythms, with the latter likely more common than previously thought.[7] The actual pacemaker cells are typically not permanently damaged. Thus, with recovery, the intrinsic pacemaker activity of the heart brings about a resumption of cardiac activity. However, a lightning strike can result in stunning of the respiratory center of the medulla and brainstem, causing central apnea. This respiratory arrest is thought to often last longer than the cardiac standstill itself, which may lead to hypoxic cardiac arrest. Research into the actual effects of lightning on humans is limited but it has been hypothesized that the strike leads to a state of suspended animation and cessation of metabolism in all cells, including the brain. This may explain reports of successful resuscitation and full recovery of lightning strike victims after being apneic and pulseless for up to 15 minutes and following resuscitations lasting up to 8 hours. This observation has led to the practice of treating the "apparent dead" first at the scene of a multiple-victim lightning strike because early resuscitative efforts may prevent death.

Lightning has also been linked to a variety of less ominous dysrhythmias, such as atrial fibrillation, most of which resolve with time. Lightning strikes can also cause QT prolongation which can persist for weeks after the incident.[7] A lightning strike in close proximity to a patient with an automatic implantable cardioverter defibrillator can cause firing of the device. The longer-term effect of a strike on the integrity of the device is not clear.[7]

A number of electrocardiographic changes, usually with gradual resolution, have been reported (Box 130.5). ST segment elevation and depression and T wave inversions suggestive of myocardial ischemia have been widely reported, and may be the result of cardiac contusion, hypoxia-induced infarction, transient coronary vasospasm or actual coronary thrombosis. Given this wide differential diagnosis, the role of immediate coronary interventions is not yet established.[7]

Head and Neck

Electrical Injury. Ocular involvement is common following exposure to electrical current, with cataracts being the most frequent manifestation. Other forms of injury include vitreous and anterior chamber hemorrhages, retinal detachment, macular lacerations, ocular foreign bodies, and corneal or conjunctival burns. Injury to structures of the ear is less common, but sensorineural deafness can be seen as a result of nerve damage. Patients frequently develop vertigo, which may be transient or persistent. Toddlers and young children sustain orofacial injuries after chewing or sucking on electrical cords or from lingual contact with sockets. Full-thickness burns may be sustained on the mucous membranes and lips, with destruction to the tongue and teeth as well. Injuries to the oral commissure produce cosmetic

BOX 130.5 Electrocardiographic Changes Seen with Lightning Strike

ST segment elevation
QT interval prolongation
Atrial fibrillation
Inverted or flattened T waves
Myocardial infarction pattern without cardiac sequelae

difficulties and, more significantly, delayed labial artery bleeding which typically occurs 2 to 3 days after injury when the resultant eschar separates from the wound.

Lightning Injury. The most common ocular event after lightning strike is the development of cataracts, occurring immediately or in a delayed fashion. Damage to almost every part of the eye has been described. Fixed and dilated or asymmetrical pupils due to autonomic dysfunction may accompany a strike, a finding that by itself should not obviate the need for resuscitative efforts.

The tympanic membranes of patients involved in lightning events are commonly ruptured due to the shock wave and blast effect produced by the rapid expansion of the air as lightning passes through it. Bleeding and cerebrospinal fluid leaks may accompany this injury. Other effects include hearing loss, tinnitus, vertigo, and nystagmus. Specific injuries include avulsion of the mastoid process, ossicle damage, rupture of the Meissner membrane, and strial degeneration.

Extremities

Electrical Injury. Neurovascular bundles have low resistance and are particularly prone to damage from electrical current. Muscle necrosis occurs primarily or is secondary to compromise of the blood supply. Vascular injury is most prominent at the intimal and medial layers. Involvement of the intima results in immediate coagulative necrosis and thrombosis. Injury to the media causes aneurysmal dilation, and occasionally artery rupture and hemorrhage, and may occur months after the injury. Decreases in tissue perfusion lead to edema and tissue death. Areas of infarction may be distributed sporadically throughout the injured region, with areas of surviving tissue adjacent to necrotic tissue.

Muscle that initially appears viable may deteriorate over days and weeks, especially in the periosteal regions. Rhabdomyolysis may occur from muscle breakdown and patients should be aggressively hydrated to prevent acute kidney injury (see "Management" section). Endothelial and smooth muscle function are depressed for many weeks following the initial injury, contributing to a hypercoagulable state that increases the risk of delayed deep venous thrombosis. The combination of tissue edema and perfusion defects makes compartment syndrome likely, necessitating emergent fasciotomy or possible amputation. Compartment syndrome and rhabdomyolysis are risk factors for late arterial rupture.[8] Cyanosis or pulselessness may be transient or may indicate permanent damage; in a similar fashion, limbs that appear initially well perfused may later necrose. Bony injury is common because bone is highly resistant to electrical current flow. This generates large amounts of heat resulting in periosteal burns and osteonecrosis. Fractures and dislocations often occur as a result of the patient being thrown or propelled (particularly with DC current) or from the strength of muscular contractions (AC current).

Nervous System

Electrical Injury. Electrical injury damages the central and peripheral nervous systems. The most common immediate central symptoms are altered mentation, seizure, or coma. Seizures may occur as an isolated event or as a chronic seizure disorder. Vascular injury may cause cerebral infarction, and secondary trauma may result in intracranial hemorrhage. Cerebral venous sinus thrombosis has been reported.

Patients may experience transient spastic paralysis with accompanying sensory deficits immediately following electrical injury. Delayed and chronic manifestations include ascending paralysis, transverse myelitis, and amyotrophic lateral sclerosis (ALS). Peripheral neuropathies are a common result, most often involving the median and ulnar nerves.

Unlike other complications, rates of neuropsychological sequelae are equal in low- and high-voltage injuries. Immediately after injury, sleep disturbances and anxiety are particularly common. Other short-term complications include depressed mood, flashbacks, dizziness, nightmares, and memory and concentration impairments. Longer-term neuropsychiatric sequelae include posttraumatic stress disorder and major depressive disorder.[9] A post–electrical and lighting injury syndrome has been described and features both prominent memory and executive function deficits as well as other miscellaneous features such as depression and social withdrawal.[10]

Lightning Injury. A wide variety of very serious neurologic effects follow lightning strike. Apnea, due to effects on the medullary respiratory center, may persist for several hours. Direct trauma may result in skull fractures, intracerebral and extracerebral hematomas and hemorrhages, cerebral edema, and elevated intracranial pressure. More common findings include transient loss of consciousness, amnesia of the event, and transient paresthesias and paralysis of the extremities. This later phenomenon, called *keraunoparalysis* is characterized as a flaccid paralysis, usually accompanied by marked vasomotor changes that result in extremities that appear cyanotic, mottled, and pulseless. The lower extremities are more commonly involved, and the typical prognosis is recovery within minutes to days.

Prolonged loss of consciousness may be related to trauma or hypoxia. "Miracle" recoveries have been documented, despite prolonged cardiac arrest and apnea. Conversely, death may occur rapidly from massive brain edema and herniation. Permanent peripheral nerve damage can occur. Other neurologic sequelae include seizures, cerebellar ataxia, Horner syndrome, cognitive dysfunction, facial nerve palsy, neuritis, and neuralgia.

Some psychiatric effects are predictable, usually anxiety and a logical fear of thunderstorms. Other negative effects are similar to those experienced with electrical injury, including memory loss and concentration deficits, prolonged depression, sleep disturbances, nightmares, nocturnal enuresis, and separation anxiety. Hysterical blindness, deafness, and muteness have been described.

Other Viscera

Electrical Injury. Extensive muscle damage may result in significant myoglobinuria, subsequent renal failure, and life-threatening hyperkalemia. These complications are more likely in patients who are hypotensive or volume-depleted. Stress ulcers are a common gastrointestinal complication. Uncommon but severe intra-abdominal injuries include a ruptured hollow viscus and necrosis of the pancreas or gallbladder. Pulmonary edema is rare. Although early fatalities are due to respiratory and cardiac arrest, delayed deaths occur from sepsis, pneumonia, and renal failure. For obstetric patients, the overall risk to the fetus is low, but a spontaneous abortion can occur. Secondary trauma may lead to placental abruption.

Lightning Injury. The lungs, gastrointestinal tract, and other internal organs may suffer injury from blunt trauma or a blast effect. Strikes to the face may produce damage to the tongue and oral structures, esophagus, and trachea. Various fractures, dislocations, and soft tissue

injuries occur. Myoglobinuria is relatively unusual due to the brief duration of contact.

Vasomotor changes may occur at the time of the strike and can last for variable periods. Mottling or cyanosis appears, and pulses may be absent. Although dramatic in appearance, these typically resolve without intervention. Vascular changes mimic those seen in compartment syndromes, but fasciotomy is generally not indicated. When pregnant women are struck by lightning, the effects on the fetus are not predictable therefore, depending on the dates of gestation, maternal-fetal monitoring is generally recommended.

Conducted Electrical Weapon. Patients who present after receiving a CEW barb discharge may have local injury to the skin and nearby superficial structures, such as vessels, nerves, and bones. Most barbs penetrate the chest or back, but barbs may also lodge in the face, eyes, or genitals. These patients may also sustain injuries from muscle contraction or falls due to NMI. Traumatic brain injury and spinal compression fractures in osteopenic patients as a result of CEW discharge have been described. However, the overall occurrence of injuries due to this mechanism is rare, occurring in less than 0.5% of CEW deployment subjects.[11] Patients who have received CEW touch-stun exposure may develop skin irritation or minor contact burns.

Current literature indicates that there is no evidence of cardiac ischemia, dysrhythmias, or structural cardiac damage to patients who have received CEW exposure of less than 15 seconds, and who are otherwise asymptomatic, awake, and alert. Most CEW exposures from law enforcement are less than 15 seconds, suggesting that the risk of cardiac complications is very low.[11]

DIFFERENTIAL DIAGNOSES

Electrical Injury

Most electrical injuries are self-evident, except in unwitnessed water-related exposures where there may be no skin burns. In such cases, patients may present with cardiac arrest, dysrhythmias, or altered mentation. Victims of known electrical injury who present with altered mentation may be suffering from electrical injury of the central nervous system, associated traumatic brain injury, or underlying metabolic disease.

Lightning Injury

In cases in which lightning strikes are not witnessed, these injuries should be suspected in patients presenting from the outdoors with altered mentation or cardiac arrest in the setting of a recent thunderstorm. Other clues include the presence of typical skin burn patterns, clothing that has been blasted off, singed or has melting of metal pieces such as zippers or grommets. Other suggestive findings are listed in Box 130.6. Differential diagnoses of altered mentation in lightning strike victims are the same as with other high-voltage injuries.

BOX 130.6 Findings Suggestive of a Lightning Strike

- Clothing wet from rain
- Tears or disintegration of clothing
- Multiple victims
- Typical arborescent pattern of erythema or superficial linear or punctate burns
- Tympanic membrane injury
- Cataracts, especially in a younger patient
- Magnetization of metallic objects on the body or clothing
- Electrocardiographic changes

DIAGNOSTIC TESTING

Electrical Injury

No evidence-based guidelines direct the ancillary testing of electrical injury victims. Testing is not required for victims of low-voltage electrical injuries who are asymptomatic or have minimal localized symptoms. Evaluation for underlying injury should be undertaken in patients who have been exposed to high-voltage sources. In addition, those victims who have lost consciousness or present with altered mentation or neurologic deficits, have entrance and exit wounds or more than superficial partial-thickness burns, cardiac dysrhythmias or other significant symptoms should be fully evaluated, regardless of the source voltage. Because the location and extent of injury cannot be predicted clinically, we recommend electrocardiography, a complete blood count, basic serum electrolytes, serum myoglobin and troponin, blood urea nitrogen, serum creatinine levels, and urine analysis, testing for myoglobinuria. Patients with suspected intra-abdominal injury from electrical current or associated trauma should have hepatic transaminases and pancreatic enzyme levels (lipase) measured and coagulation studies performed. Radiographs of injured extremities are indicated if there is significant pain, deformity, swelling or bony tenderness following trauma. Computed tomography or magnetic resonance imaging should be used when intracranial, spinal, intra-abdominal or pelvic injuries are clinically suspected. There is little evidence to guide further workup of patients with significant troponin elevations, but we recommend 12 to 24 hours of telemetry monitoring and an echocardiogram for those with a troponin rise thought to signify myocardial damage.[5] The utility of prolonged cardiac monitoring in patients with an electrical exposure is unclear, as most studies show delayed cardiac dysrhythmias are rare.[4] However, we recommend a period of observation for 12 to 24 hours in any patient who sustained a high-voltage electrocution as well for those who suffered loss of consciousness, or have a dysrhythmia or abnormal ECG on arrival to the ED.

Lightning Injury

The Wilderness Medical Society has recommended that an electrocardiogram (ECG) be obtained on lightning strike victims with high-risk indicators, such as suspected direct strike, loss of consciousness, focal neurologic complaint, chest pain or dyspnea, associated traumatic injuries, pregnancy, or burns of the cranium or legs or on more than 10% of the total body surface area. Cardiac markers are often elevated in victims of lightning strikes, but they do not correlate with myocardial injury and are not prognostic. Patients will often have been thrown or propelled by the force of the lightning and a detailed examination looking for signs of secondary trauma is indicated. Compared to electrical injuries, lightning strikes are much less likely to result in compartment syndrome or rhabdomyolysis and when these occur, it is often a result of a traumatic injury rather than from the strike itself. A thorough eye and ear exam should be performed because lightning current can affect the lens as well as the tympanic membranes, which can often burst due to the acoustic blast wave.

Patients without any obvious sequalae should still receive follow-up care, as a large percentage of lightning survivors will experience some neurocognitive sequelae. Regional burn centers are often equipped to further evaluate and refer these patients.

Conducted Electrical Weapon

In patients who are awake and alert, asymptomatic, and have had CEW exposure of less than 15 seconds, no specific diagnostic testing is required to evaluate for cardiac injury, electrolyte imbalance, renal abnormalities, or acid-base disturbances. Similarly, evidence has not shown any clinically significant rise in lactate or CK levels, and we do not recommend testing in this patient population. Additionally, routine

EKG, cardiac monitoring, or echocardiography are not recommended in this patient population. However, patients may have underlying conditions that precipitated the use of the CEW, including but not limited to altered mental status, intoxication, or psychiatric conditions, and they should undergo diagnostic testing as guided by their presentation and past medical history. Additionally, patients should be evaluated for secondary traumatic injury and undergo appropriate trauma evaluation.

MANAGEMENT

Electrical Injury

Low-voltage electrical injuries associated with minimal signs and symptoms generally require only local wound treatment and patient reassurance. The treatment of other patients is directed at the organ systems involved.

Patients who present in cardiopulmonary arrest should be resuscitated, regardless of cardiac rhythm, because favorable outcomes have been documented even with patients presenting in asystole. Patients with electrocardiographic signs of cardiac injury or dysrhythmias and patients with more than minimal local signs and symptoms should be monitored in the emergency department (ED), observation unit, or inpatient setting, depending on the extent and severity of associated injuries. Dysrhythmias are treated according to advanced cardiovascular life support (ACLS) guidelines. Hypotensive patients should be evaluated for possible blood loss from associated traumatic injuries. Hypotension may also be caused by third spacing of intravascular volume secondary to electrical injury of deep tissues, so fluid management is similar to that of crush injuries, often requiring more fluid than typically recommended by thermal burn wound protocols. Intravenous crystalloid fluids are given to maintain adequate urine output (over 100 mL/hr in adults and 1.5 to 2 mL/kg/hr in young children). Serum potassium levels should be closely monitored in patients with acute renal injury or myoglobinuria.

Although AC causes thrombotic injury to blood vessels, DC can result in transient vasospasm that results in extremities that appear cyanotic, mottled, and pulseless. This should be kept in mind when deciding when vascular surgical intervention is indicated. Skin and vascular findings are likely to resolve with supportive care only but, if significant thrombosis (immediate or delayed) develops, amputation may be required. The presence of pulseless and mottled extremities may limit the ability to detect hypotension with standard devices, and central monitoring or arterial lines may be required to accurately assess volume status.

Patients with myoglobinuria should be monitored with determination of serial serum myoglobin levels and renal function studies. The management of rhabdomyolysis is discussed in Chapter 116. Injured extremities require burn wound management (see Chapter 54). These injuries should be monitored for the development of compartment syndromes (see Chapter 41).

Lightning Injury

Lightning strike victims who present without symptoms or signs of injury, including those with minor first-degree burns, do not require treatment in the ED unless their electrocardiograms show signs of ischemia or concerning dysrhythmias. Patients who present with altered mentation or significant symptoms are approached in a manner similar to that used for victims of high-voltage electrical injury. However, a few differences should be noted. Lightning strikes can result in a spectrum of peripheral and central neurologic injuries, including pupils that are fixed and dilated in the absence of irreversible brain injury. This factor should be kept in mind when deciding when to discontinue resuscitative efforts in patients who present in cardiac arrest. Lightning strikes can cause extensive catecholamine release or autonomic stimulation, resulting in transient hypertension and tachycardia that can be treated with β-adrenergic blockers and hydralazine or with alpha-2 adrenergic agonists such as clonidine, to reduce adrenergic excesses.

Conducted Electrical Weapon

Patients injured by CEWs rarely require intervention. Patients with barb injury should have evaluation of the barb penetration site, and most will not require additional treatment beyond removal and localized wound care. For those who sustain barbs to the face, eyes, or genitals, specialist consultation and operative removal may be required. In those patients with touch-stun exposure, local wound care is recommended.

DISPOSITION

Electrical Injury

Asymptomatic patients who present after low-voltage exposures may be safely discharged home. Other patients are monitored and treated in the ED, observation unit, or inpatient setting, depending on their clinical status and extent and severity of identified injuries. There is some debate around the need for prolonged cardiac monitoring of patients, with most studies showing that the risk of delayed dysrhythmia is very low. A reasonable approach is to observe patients with loss of consciousness, dysrhythmia, high-voltage exposure, ECG abnormality or significant troponin increase on telemetry for 12 to 24 hours. Patients with significant burns should be stabilized and transferred to a burn unit, if available.

Pediatric patients with oral electric injuries are usually hospitalized for hydration, wound and pain management, and plastic surgery consultation. Patients with minor burns confined to the oral commissure can be discharged with close follow-up but should be provided with information regarding the possibility of delayed labial artery bleeding, which can be managed by the parents with direct wound pressure and return visit instructions.

Pregnant patients should receive a period of fetal monitoring when gestational age–appropriate. Women who are subsequently discharged should be counselled regarding the remote risk of spontaneous abortion and referred for high-risk obstetric follow-up care.

Patients may experience delayed neuropsychiatric sequelae, so discharge instructions with a neurologic referral may be provided.

Lightning Injury

The Wilderness Medical Society has recommended that victims of direct lightning strikes and those with an abnormal ECG be monitored with telemetry for a minimum of 24 hours. Other patients can be discharged but should be counselled regarding the need to seek further care if they develop delayed-onset symptoms, which can be cardiopulmonary, neurologic, psychiatric, ophthalmologic, or otolaryngologic in nature.

Conducted Electrical Weapon

Unless there is a concomitant condition present that requires further care or admission, routine cardiac monitoring, ED observation, or hospitalization is not recommended for patients who are awake, alert, and asymptomatic who have had CEW exposure less than 15 seconds.

For patients who have had CEW exposure for greater than 15 seconds, there is limited experience and no clear guidelines exist, so an observation period of 6 to 8 hours is a reasonable approach.

ACKNOWLEGMENTS

The authors wish to acknowledge and thank Kelly P. O'Keefe and Rachel Semmons for their valuable contributions, expertise, and authorship of this chapter in previous editions.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 130: QUESTIONS AND ANSWERS

1. A 37-year-old woman presents with blurred vision. Her vision has been progressively worsening for approximately 2 months. She denies eye pain or direct eye trauma. She reports that approximately 2 months ago, just before the beginning of her vision problems, she was struck by lightning while playing golf. She states that she went to an emergency department (ED) at that time, had no major injuries, and seems to have recovered well. What is the most likely cause of her decreased vision?

a. Cataracts
b. Glaucoma
c. Iritis
d. Macular degeneration
e. Retinal detachment

Answer: A. Cataracts are a well-known complication of electrical injury, either from artificial electrical sources or from lightning. They may occur immediately or have a delayed presentation. Glaucoma is due to elevated intraocular pressure and is often painful. Iritis and retinal detachment can be caused by electrical injury but are manifested acutely. Macular degeneration is a chronic condition of older adults with central vision loss and is not associated with electrical injury. Macular holes may occur acutely with lightning injury.

2. Which of the following patients presenting to the emergency department should have consultation by the burn surgery service?

a. 22-year-old female who presents after receiving a taser shock who is awake and alert. She has barb wounds in her abdomen that were removed by law enforcement prior to arrival and has mild erythema at the barb sites, but no other injuries.
b. 47-year-old male who presents after a lightning strike, who complains of chest pain and EKG shows sinus tachycardia.
c. 34-year-old male who presents after an occupational accident, in which he received an electrical shock to the right hand from a high-voltage source. He is awake and alert, with normal vital signs and no complaints other than a small area of hyperemia to his right palm and pain to his right arm.
d. 3-year-old female, brought in by parents for concern that she put her finger into an electrical socket. On exam, she is awake and alert, has normal behavior, and has no skin or soft tissue findings.
e. 67-year-old female who presented unresponsive after a lightning strike, but is now awake and alert, but reports hearing difficulties.

Answer: C. Electrical injuries, especially high-voltage injuries, can cause deep tissue burns and damage that may not be readily apparent on the surface, due to decreased resistance of neurovascular bundles. In severe cases, tissue edema and decreased perfusion may require fasciotomy. Often, fluid resuscitation calculations using the Parkland formula are underestimated, as visible injury may be insignificant compared to damage beneath the surface. Patients who receive a taser shock do not require further management beyond local wound care. The victims of lightning strikes may require further evaluation for cardiac and HEENT abnormalities, but skin and soft tissue damage in these patients is less likely as the electrical energy often passes over rather than through them. The 3-year-old does not require further management beyond reassurance.

3. A 42-year-old man suffers an electrical injury while working on power transmission lines near your hospital. Paramedics report that he is unresponsive and initially in ventricular fibrillation but spontaneously converted to sinus tachycardia before treatment. His initial electrocardiogram (ECG) from the field shows ST segment elevation in the inferior leads. An ECG repeated in the ED shows continued inferior ST segment elevation but with decreased magnitude. Creatine kinase (CK) and CK-MB levels are markedly elevated and troponin levels are slightly above normal range. While he does have pulses, he continues to be unresponsive, has no spontaneous respirations, and has bilateral fixed and dilated pupils. What is the appropriate next action?

a. Brain death testing
b. Cardiac catheterization
c. Mannitol infusion
d. Intubation and supportive care
e. Thrombolytic administration

Answer: D. Electrical injury can cause a variety of cardiac manifestations, including multiple dysrhythmias, transient ST elevation, and conduction blocks. Myocardial infarction, although reported, is rare. Extensive skeletal muscle damage can be seen in electrical injuries and

CHAPTER 130: QUESTIONS AND ANSWERS—cont'd.

results in marked elevations of CK and CK-MB levels. Respiratory muscle paralysis and ocular injuries often occur. This patient is probably not brain-dead, nor has he suffered a myocardial infarction. Mannitol is used in cases of impending cerebral herniation, which is not expected in this patient. Supportive care, including mechanical ventilation and treatment of dysrhythmias per ACLS protocols as needed is most appropriate.

4. A 22-month-old female is brought to the emergency department by parents after she was found chewing on an electrical cord. She has minor burns to the lips and oral commissure. Upon discharge, what condition should the parents be warned about as a reason to return to the ED?
   - **a.** Facial compartment syndrome
   - **b.** Cardiac dysrhythmias
   - **c.** Delayed dental eruption
   - **d.** Rhabdomyolysis
   - **e.** Delayed labial artery bleeding

Answer: E. Delayed labial artery bleeding usually occurs two days after the initial injury, when the initial eschar separates. When this occurs, there can be significant bleeding from the labial artery. Traditionally, admission for observation has been advocated for these patients but, if there is good social support, discharge with specific return instructions and close follow-up are appropriate. These types of electrical injury have only local effects, so dysrhythmias, cataracts, and rhabdomyolysis are not complications. Contractures are common and may require reconstructive surgery, but this complication is not life-threatening.

5. A 53-year-old male is brought to the emergency department by law enforcement after they incapacitated him with a taser. There are no visible signs of traumatic injury, but he is not responsive. The most appropriate next step is:
   - **a.** Supportive care as most patients quickly arouse after a taser shock.
   - **b.** Evaluate for burns around the taser barb site.
   - **c.** Perform EKG to evaluate for STEMI.
   - **d.** Evaluate the patient for other etiologies of altered mental status.
   - **e.** Discharge the patient with law enforcement to be taken to jail.

Answer. D. There have been a number of high-profile deaths associated with taser shocks by law enforcement. However, the cause of these deaths has not been linked to the electrical effect of the taser shock itself, and patients who present after a taser shock with altered mental status should be evaluated for other etiologies, including but not limited to infection, toxic/metabolic etiologies, and traumatic injuries. Burns evaluation and EKG alone would not be sufficient evaluation for this patient.

Scuba Diving and Dysbarism

David A. Peak

KEY CONCEPTS

- The majority of dive injuries are diagnosed on the basis of the focused dive history and physical examination and are best differentiated into disorders of descent, disorders of depth, and disorders of ascent.
- The *U.S. Navy Diving Manual* and the Divers Alert Network (DAN) are valuable resources for the clinician presented with a diving emergency. DAN provides a 24-hour medical emergency hotline at 1-919-684-9111 (see Table 131.4).
- Treatment with 100% oxygen is the initial therapy for *all* diving emergencies until the diagnoses can be determined. It has been demonstrated to reduce the morbidity and mortality related to decompression illness and can be helpful in patients with pneumothorax.
- Diagnostic imaging and laboratory studies are generally not useful for ruling in or out decompression illness and should not delay transfer for recompression therapy.
- Recompression treatment is recommended for patients with decompression sickness (DCS) and arterial gas embolism (AGE).

FOUNDATIONS

Background and Importance

Underwater free diving has been practiced for more than 5000 years both commercially and for recreation. Diving bells physically provided access to air and protection from pressure at depths to divers and have been described as far back as the 4th century BCE. The earliest artificial underwater breathing devices were restrictive to shallow water because of pressure constraints. In the 1940s, Cousteau and Gagnan introduced a self-contained underwater apparatus (SCUBA) and buoyancy control device (BCD), which revolutionized the ability of divers to safely dive to moderate depths. Diving has increased exponentially since that time among commercial, military, and especially recreational activities which now account for approximately 9 million participants per year in the United States alone, with several hundred thousand new divers trained per year. As a result of its recreational popularity, injuries related to diving have also increased.[1,2] According to the Divers Alert Network (DAN), which is the diving industry's largest association dedicated to diving safety, there are approximately three injuries of any kind per 100 dives and up to 10% of these are fatal. This represents a small but clinically relevant subpopulation of dives.

The symptoms and signs of diving-related illness, also known as *dysbarisms,* began to be recognized as diving became increasingly accessible. The ailment became known as *caisson disease,* named after the large diving bell commonly used for submersion. Construction workers on the Brooklyn Bridge (constructed between 1870–1880) termed the disorder "the bends," because the symptoms often caused the victim to bend forward in pain. The first clinical description by Bert in 1878 correctly attributed the disease to nitrogen gas coming out of solution in the tissues during decompression, which led to the recommendation of slow ascents for pressurized workers and the development of the first recompression chambers.

Most divers use compressed air, open-circuit scuba equipment at depths of less than 130 feet of seawater (fsw). Systems with artificial mixtures of various gases, however, are used to extend the depths to which divers can descend or the duration that a diver may safely remain submerged. Other variations of supplying air for divers include closed-circuit and semiclosed-circuit diving apparatus (called "rebreathers") that use calcium hydroxide to absorb expired carbon dioxide and add oxygen to the decarboxylated gas before rebreathing and allow more efficient and safe diving.

Physiology and Pathophysiology

The leading cause of death among divers is from drowning accidents. Scuba divers may also encounter emergencies common to environmental exposures (e.g., hypothermia, sun exposure, motion sickness, bites, envenomation, and physical trauma). They are also subject to the unique injuries related to pressure at depth.[3] The pathophysiologic mechanism of diving or dysbarisms can be separated into two broad categories: (1) Barotrauma which is related to pressure and; (2) Decompression illness which is related to gas bubbles. Barotrauma can be related to the speed of descent and ascent but is almost completely independent of time of depth. Bubble formation (primarily nitrogen) during and immediately after ascent as well as nitrogen narcosis are both dependent on being at depth for an extended period of time. Therefore, it is useful when treating a patient with an acute diving injury to know the recent dive history because it can assist the clinician in narrowing down the differential diagnoses. For instance, a recreational diver who was at a moderate depth for only a few minutes can still have a major barotrauma-related dive injury but would not have had time to accumulate enough gas or nitrogen in their tissues to cause symptoms.

Familiarity with several of the laws of physics that define the properties of liquids and gases (Table 131.1; Figs. 131.1 to 131.5) is useful when discussing diving pathophysiology. Boyle's law explains diver-related barotrauma and states that at constant temperature, the absolute pressure, and the volume of gas are inversely proportional ($PV = k$). In other words, as pressure increases (with descent), the gas volume is reduced; as the pressure is reduced (with ascent), the gas volume increases. A diver needs to descend only 33 feet in seawater to double the atmospheric pressure, an increase of 23 mm Hg per foot of depth. Abrupt changes in the volume of air-containing parts of the body (e.g., ears, sinuses, and lungs) are at risk of barotrauma with the extreme pressure changes of the environment. These include barotrauma associated with an inability to equalize, mask squeeze, or

TABLE 131.1 Laws of Physics

Gas Law	Formula	Significance
Pascal's law: A pressure applied to any part of a liquid is transmitted equally throughout.	$\Delta P = \varrho g (\Delta h)$ ΔP is the hydrostatic pressure. ϱ is the fluid density. g is acceleration due to gravity. Δh is the height of fluid.	Pressure increases in a contained space are transmitted throughout; significant for IEBT and MEBT (see Fig. 131.1)
Boyle's law: At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.	P1 • V1 = P2 • V2	Relates to change in the volume of a gas caused by the change in pressure due to depth, which defines the relationship of pressure and volume in breathing gas supplies (see Fig. 131.2)
Charles' law: At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.	V1/T1 = V2/T2	Increasing pressure (filling a scuba tank) causes heat; cooling a tank decreases the pressure (see Fig. 131.3)
The general gas law combines these concepts to predict the behavior of a gas when the factors change.	P1 • V1/T1 = P2 • V2/T2 P1 is the initial pressure. V1 is the initial volume. T1 is the initial temperature. P2 is the final pressure. V2 is the final volume. T2 is the final temperature.	A means of relating pressure, volume, and temperature together in one equation when variables are not constant
Dalton's law: The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume.	PTotal 3 P1 + P2 + P3 + … + Pn	Nitrogen under pressure acts as if other gases are not present (see Fig. 131.4)
Henry's law: The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas.	$e^p = e^{kc}$ *e* is approximately 2.7182818 (the base of the natural logarithm). *p* is the partial pressure of the solute above the solution. *c* is the concentration of the solute in the solution. *k* is the Henry's law constant.	More nitrogen is taken into solution (e.g., serum) at high pressures than comes out of solution at lower pressures (see Fig. 131.5)

IEBT, Inner ear barotrauma; *MEBT,* middle ear barotrauma.

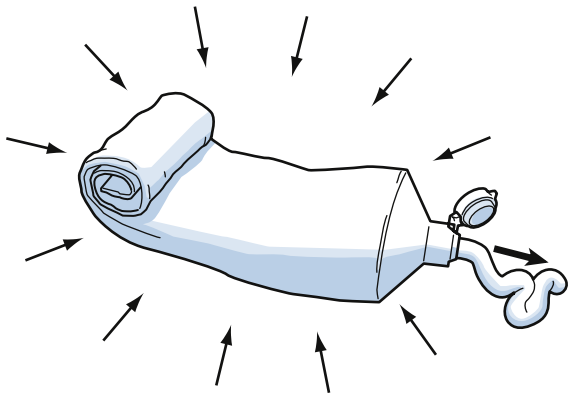

Fig. 131.1 Pascal's law. A pressure applied to any part of a liquid is transmitted equally throughout.

barotrauma to the ears and sinuses during descent, as well as barotrauma related to ascent (usually associated with breath-holding) including pneumomediastinum, pneumothorax, and arterial gas embolism. Fractional changes in volume are greater near where the proportional pressure changes are highest, which is generally in more shallow water.

Henry's law explains decompression illness and states that the amount of any gas that dissolves in a liquid at a given temperature is directly proportional to the partial pressure of that gas. At higher ambient pressures, an increasing concentration of each component gas of the inhaled air will dissolve in solution until a new steady-state concentration is achieved. Therefore, the length of time the diver is breathing the gas at the increased pressure and the inherent solubility of the gas also govern the quantity of a particular gas that dissolves. The dissolved gas remains in solution as long as the pressure is maintained. As the diver ascends, however, increasingly more of the dissolved gas comes out of solution. A rapid ascent may reduce the pressure at a rate higher than the body can accommodate, and the bubbles (particularly nitrogen) may accumulate and disrupt body tissues and systems, a phenomenon termed *decompression sickness* (DCS). This is similar to the rapid opening of a bottle of a carbonated beverage which allows bubbles of carbon dioxide to rapidly come out of solution.

Safe diving practice includes a controlled ascent rate (i.e., through the use of safe decompression tables or submersible dive computers), during which the gas is carried to the lung vascular bed and is exhaled before it accumulates to form significantly large or numerous bubbles in the tissues. This is similar to how opening of a soda bottle slowly reduces agitated bubbling of the contained carbonated liquid.

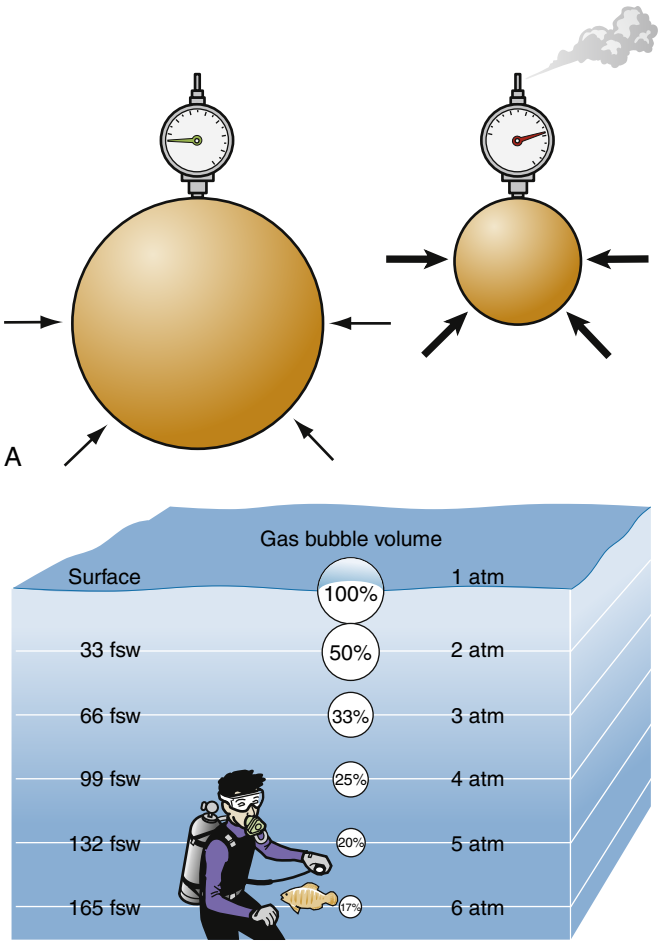

Fig. 131.2 Boyle's law. (A) At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. (B) As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases. *fsw,* Feet of seawater.

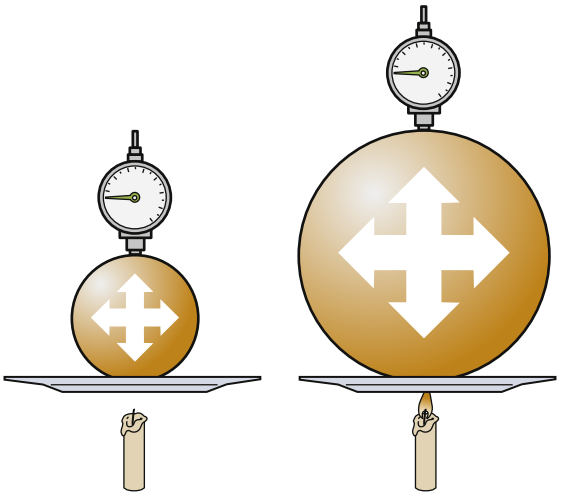

Fig. 131.3 Charles' law. At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.

CLINICAL FEATURES

The clinical features of the injuries and maladies related to diving will be presented in this section based on when the symptoms are likely to start during a dive, first those that occur on descent, then those that occur at depth, and finally those that occur upon surfacing. This organization is used to help the clinician stratify the likelihood of a specific disorder based on when the symptoms started during the dive. Box 131.1 lists the recommended components of a focused dive history.

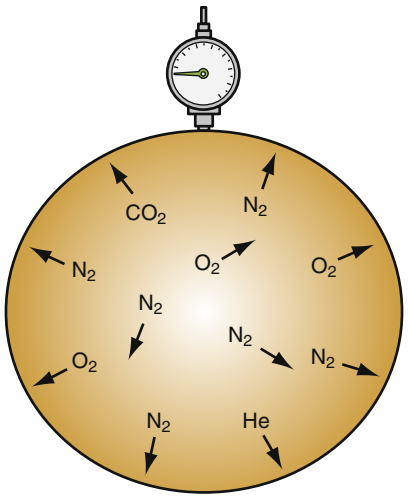

Fig. 131.4 Dalton's law. The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume. *CO2,* Carbon dioxide; *He,* helium; *N2,* nitrogen; *O2,* oxygen.

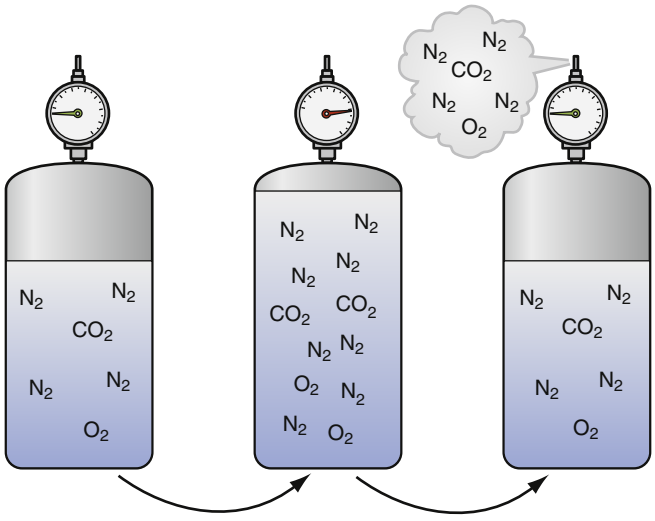

Fig. 131.5 Henry's law. The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas. *CO2,* Carbon dioxide; *N2,* nitrogen; *O2,* oxygen.

Disorders Related to Descent/Barotrauma

Middle Ear Barotrauma

Middle ear barotrauma (MEBT), also known as *barotitis or ear squeeze,* is the most common complaint of scuba divers. In a survey of over 750 recreational divers, over half experienced pain related to mild ear barotrauma multiple times during their dives. Most of these were minor pains associated with descent that resolve with equalization maneuvers with no long-term effects.[4-6]

The middle ear is an air-filled space with solid bone walls except for the tympanic membrane (Fig. 131.6). In the auditory system, the eustachian tube is the only anatomic passage to the external environment. During descent, there is an increase in external pressure that

BOX 131.1 Focused Dive History

When was the first onset of symptoms?
What type of equipment was used? Compressed air, mixed gas, enriched air, rebreather? What was the source of the gas?
Did the dive approach or exceed decompression limits? Was a dive computer used?
What were the number, depth, bottom time, total time, and surface intervals for all dives in the 72 hours preceding symptoms (the dive "profiles")?
Were decompression stops used? Was in-water decompression attempted?
What was the time delay from the last dive to air travel?
Did the diver experience difficulty with ear or sinus equilibration? Did the pain occur on descent or ascent?
Was the diver intoxicated? Dehydrated? Working strenuously?
How long after the dive did symptoms present? Were they present at surfacing? Delayed? Progressive?
Is a medical history of ear or sinus infections or abnormalities present? Emphysema or asthma? Coronary artery disease? Patent foramen ovale (PFO)? Neurologic illness?

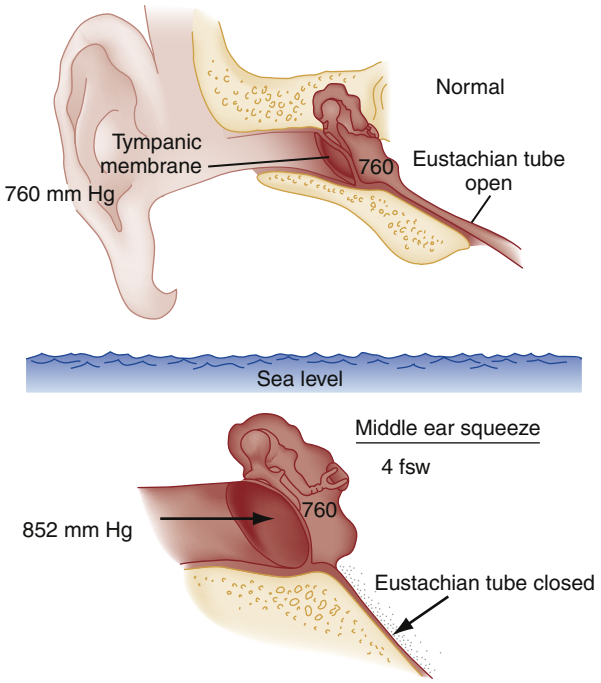

Fig. 131.6 Middle ear barotrauma symptoms include fullness and pain caused by stretching of the tympanic membrane. (From: Van Hoesen KB, Bird NH. Diving medicine. In Auerbach PS, ed. *Wilderness Medicine*, ed 6. Philadelphia: Elsevier; 2012: 1529.)

exerts inward pressure against the tympanic membrane (TM). This occurs when the eustachian tube (ET) does not effectively allow air to flow into the middle ear space to equalize pressure. The ET can become blocked and eventually locked in place by a combination of pressure differential and tissue inflammation or edema.

During a diving descent, there is increasing external and inward pressure against the tympanic membrane unless air enters the middle ear via the eustachian tube (ET) to maintain equal pressure across the tympanic membrane. Typically, a diver performs various equalization maneuvers to force air into the middle ear through the ET. The ET may become blocked or collapse related to the pressure differential or inflammation, making subsequent attempts at equalization virtually impossible. This is typically painful and may be associated with tinnitus; some patients develop transient vertigo. Further descent without successful equalization can cause the TM to collapse inward and rupture. The pain may or may not resolve as the TM ruptures. Rupture of TM can cause asymmetric caloric stimulation by exposure of the middle ear to cold water, inducing a transient nystagmus and vertigo. This can become life-threatening if the diver panics or becomes disoriented. The pressure of the water in the middle ear may also lead to a facial palsy in certain individuals where the seventh cranial nerve passes through this space.

External Ear Barotrauma

External ear barotrauma is less common than MEBT and can be caused by an obstruction of the external auditory canal (e.g., cerumen, ear plugs) which can trap air in the canal instead of filling with water. This may lead to localized pain or hemorrhages within the wall of the external auditory canal on examination. These symptoms are generally self-limited.

Inner Ear Barotrauma

IEBT is trauma occurring as a result of a pressure differential between the middle and inner ear spaces. Inner ear barotrauma (IEBT) results in damage to the cochleovestibular apparatus. It is less common than MEBT (reported as 0.5% lifetime incidence in divers) but is associated with greater morbidity. If the diver is unable to equalize the middle ear during descent, pressure is transmitted across the labyrinthine windows (oval and round) leading to inner ear hemorrhage. Intralabyrinthine membrane tears which effect the Reissner, tectorial or basilar membranes can also occur or cause a tear of the labyrinthine windows, leading to perilymphatic fistula formation (PLF). Fifty percent of these injuries are mixed cochlear and vestibular, 40% are isolated cochlear, and 10% isolated vestibular.

Symptoms associated with IEBT include variable hearing loss, severe vertigo, nausea, tinnitus, and fullness in the affected ear. Signs include severe nystagmus, positional vertigo, ataxia, and vomiting. The degree of sensorineural hearing loss is variable. Distinguishing IEBT from inner ear DCS can be challenging but should not delay recompression in a patient in whom the diagnosis is unclear.

Reverse Middle Ear Squeeze

Reverse middle ear squeeze is the opposite of middle squeeze and occurs during ascent. As the pressure lessens, a pressure gradient can cause the TM to bulge outward and even rupture causing pain. This is much less common than middle ear squeeze during descent.

Barosinusitis

After ear barotrauma, the second most common diving-related physical disturbance is sinus barotrauma. In a survey of over 750 recreational divers, 35% experienced sinus pain related to barotrauma on more than one occasion while diving. Most of these were minor pains associated with descent that resolve with equalization maneuvers and have no long-term effects. The air-filled maxillary, frontal, and ethmoidal sinuses are susceptible to volume-pressure changes on ascent or descent; the most commonly affected is the maxillary sinus, followed by the frontal. The most common symptoms are facial pain and epistaxis. Obstruction of the sinus ostia for any reason (e.g., mucosal thickening, polyps, pus, or deviated septum) predisposes to the inability to equalize and sinus barotrauma.[5-6]

Alternobaric Vertigo

Alternobaric vertigo is a common but usually transient, self-limited vertigo secondary to asymmetric ear pressure transmitting from the middle ear to the inner ear. It is not thought to have long-term effects.

Facial Barotrauma or Mask Squeeze

During descent, a negative pressure develops within the diving mask that may increase to the point of damaging surrounding tissues if the diver does not exhale into the mask in order to equalize the pressures within and outside the mask. "Mask squeeze" is a type of facial barotrauma injury that occurs more commonly in novice divers or in masks that cannot be exhaled into (e.g., free diving masks) The difference in pressure inside and outside the mask can lead to barotrauma to the contents inside the mask leading to injury of blood vessels and tissue of the eyes and face. This can lead to facial and conjunctival edema, diffuse petechial hemorrhages on the face, and subconjunctival hemorrhages which are generally self-limited. Rarely, optic nerve damage can result from severe facial barotrauma. Recent eye surgery or preexisting glaucoma may increase the risk of injury.

Disorders Arising at Depth

Nitrogen Narcosis

Nitrogen narcosis (known as *rapture of the deep*) is a phenomenon that occurs when exposed to the intoxicating increases of partial pressures of nitrogen and is considered a significant contributing factor in diving-related accidents. Narcosis is characterized by an impairment of psychomotor coordination and alterations in mood (such as euphoria or increased anxiety) and behavior (lowering of inhibitions and impairment in reasoning). Symptoms require time at depth and may become apparent at a depth of 100 ft (30 m) and increase with further increases in depth. Use of mixed gases with lower concentration of nitrogen is recommended for technical, military, commercial or sport diving to deeper depths. The effects of nitrogen narcosis resolve with gradual and controlled ascent to shallower depths.

Oxygen Toxicity

At elevated partial pressures for extended periods, oxygen can be toxic to the central nervous system (CNS) or lungs. Oxygen becomes toxic to the CNS when its partial pressure exceeds 1.6 atmosphere absolute (ata). Oxygen partial pressures below 1.4 ata are unlikely to produce CNS toxicity. A diver breathing compressed air would attain a partial pressure of 1.6 ata of oxygen at a depth of 218 fsw. This far exceeds the depth to which most recreational divers would dive. Most professional divers prevent oxygen toxicity by breathing mixed gases with decreased oxygen and nitrogen content to decrease the possibility of oxygen toxicity (and nitrogen narcosis). This requires special equipment and advanced training.

Pulmonary oxygen toxicity (low-pressure oxygen poisoning) can occur after 24 hours of exposure to partial pressures of oxygen in excess of 0.6 ata. The symptoms of pulmonary oxygen toxicity include a burning sensation or pain on inspiration and coughing. Pulmonary function gradually becomes normal after the exposure is terminated, but pneumonitis and permanent fibrosis are possible. CNS oxygen toxicity symptoms include headache, dizziness, irritability, anxiety, visual changes, extremity tingling or twitching, tinnitus and hearing abnormalities, nausea, and seizures. It can cause drowning and death. It is extremely unlikely that a sport diver would ever be exposed for the duration that is required to produce toxicity; however, long exposures to higher levels of oxygen, such as those administered for certain recompression protocols, may lead to oxygen toxicity. In a 20-year single hyperbaric center study of over 18,000 patients, only 0.02% of patients experienced seizure activity.[5] Most hyperbaric centers use intermittent "air breaks" during hyperbaric treatment sessions in which the patients breath air with a normal Pao_2 to give their bodies a break from high oxygen levels and prevent toxicity.

Contaminated Air

Rarely, other gases, such as carbon monoxide and carbon dioxide, can contaminate the air that is compressed into a tank. This can happen if the compressor intake is placed too close to the compressor's engine exhaust. As in the case of oxygen and nitrogen, the partial pressure of these contaminants in the tissues increases dramatically with depth, potentiating their clinical effects. The symptoms of hypercarbia or carbon monoxide poisoning are thus more severe at elevated partial pressures. Hypercarbia will also increase a diver's susceptibility to CNS oxygen toxicity.

Rebreathers are used by recreational divers to recirculate the gas used by the diver after replacing oxygen and removing carbon dioxide. The major advantages are extended dive times and diminished accumulation of bubbles. Rebreathers use absorbent material to remove carbon dioxide from the circuit. A hose rupture allowing seawater contamination of the circuit may create a caustic alkaline-based liquid containing calcium or sodium hydroxide, which can cause burns to the mouth, throat, and airways.

Disorders Arising on Ascent

Alternobaric Vertigo

Alternobaric vertigo (ABV) results from an inability to equalize pressure within the middle ear during ascent and affects up to 25% of divers. ABV is based on asymmetrical pressure changes in the middle ear that are transmitted through the oval and round window to the vestibular system, resulting in a sensation of spinning and loss of orientation. This profound but transient sense of vertigo during ascent may be associated with nausea and vomiting but is not thought to lead to major morbidity or mortality. Unlike those of IEBT, the symptoms are self-limited.

Barodontalgia

On occasion, air that is trapped beneath a poorly filled dental cavity or within a dental abscess and expands on ascent, leading to dental pain. This condition affects up to 10% of divers but is relatively benign and self-limited.

Gastrointestinal Barotrauma

Serious gastrointestinal barotrauma is a rare condition in scuba divers. It results from the expansion of bowel gas in the small intestine and colon on ascent after diving. Predisposing factors include consumption of carbonated beverages, large meals, or gas-producing foods before diving, as well as performance of the Valsalva maneuver in the head-down position. Symptoms include eructation, flatulence, bloating, and crampy abdominal pain. In divers with inguinal or other abdominal hernias, the potential for expansion of trapped gas within the hernia exists, and expansion may result in incarceration or strangulation. Gastric rupture has been reported. Although gastrointestinal barotrauma is a rare entity, it should be suspected in the diver-patient with a provocative history and acute abdominal pain.

Pulmonary Barotrauma

Without continuously expiring on ascent, the lungs of a scuba diver who takes a full breath at 33 fsw would have to expand to double their volume by the time they reached the surface (based on Boyle's law). However, expansion of the alveoli is limited. Breath-holding during ascent with resultant expansion of lung volumes and pressure can force gas bubbles across the alveolar-capillary membrane and cause the wall of the alveoli to rupture. This can occur with as little a change in depth from 3 to 4 feet (or pressure difference of 80 mm Hg) and *does not* require being at depth for a prolonged time period.

BOX 131.2 Factors That Increase Pulmonary Barotrauma Risk in Asthmatics

1. Bronchospasm and mucus plugging predispose local regions of lung to injury.
2. When air is compressed, it becomes denser. This may contribute to greater turbulent flow through narrow airways.
3. During scuba diving, there is a reduction in breathing capacity related to the effects of immersion. At 33 feet underwater, the maximum breathing capacity of a normal scuba diver is only 70% of the surface value. At 100 feet underwater, the reduction is approximately 50%.
4. When compressed air (from the scuba tank) expands in the regulator before delivery to the lungs, it cools (Charles' law). Breathing of chilled air may trigger bronchospasm in asthmatics who have a cold-induced component of their disease.
5. Scuba diving takes some effort; asthmatics who have an exercise-induced component of their disease may experience bronchospasm.
6. Compressed air may be contaminated by pollen and other allergens.

BOX 131.3 Recommendations for Asthmatic Patients

A thorough history and physical by a trained physician
The patient's asthma should be well controlled
Normal spirometry: FEV_1 ≥80%, FEV_1/FVC ≥75%
Successful completion of a bronchial provocation challenge
Cold-, exercise-, or emotion-induced asthmatics should not dive
Asthmatics requiring rescue medication with 48 hours should not dive

FEV1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity. Adapted from: Coop CA, Adams KE, Webb CN. SCUBA diving and asthma: clinical recommendations and safety. *Clin Rev Allergy Immunol.* 2016;50(1):18-22.

In fact, the greatest risk for pulmonary barotrauma occurs in less than 10 feet of water. Therefore, it is important for the clinician to consider this disease entity in patients with symptoms even after exposure to shallow depths for a short period. Pulmonary barotrauma can result in the following four conditions: pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage. Risk factors elicited from the dive and medical history may suggest the diagnosis of pulmonary barotrauma. In most cases, fast ascent, panic, problems in regulating proper buoyancy, or running out of air precipitates an uncontrolled ascent with breath-holding.

Patients with restrictive and obstructive lung diseases are at increased risk. Asthmatics have a twofold-increased risk for pulmonary barotrauma compared with the general diver population. Box 131.2 lists six mechanisms that contribute to the increased risk in asthmatics,[8] who should be instructed not to dive unless they are completely free of symptoms. Box 131.3 summarizes the recommendations from the multiple national scuba governing agencies, as well as expert consensus.[6]

Pneumomediastinum and subcutaneous emphysema result when air crosses the alveolar endothelium and dissects into the pulmonary interstitium. Most commonly, air travels into the neck, mediastinum, or pericardium. The manifestations of pneumomediastinum may include fullness or pain in the neck, palpable subcutaneous crepitance, and a change in voice quality. Unless evidence of either hemodynamic instability or airway compromise exists, interstitial air or subcutaneous emphysema is not a life-threatening condition.

Pulmonary barotrauma-induced pneumothorax occurs when air from alveoli crosses the visceral pleura. A tension pneumothorax is a rare complication. The symptoms and signs of a pneumothorax secondary to pulmonary barotrauma are similar to a pneumothorax of any other cause.

Pulmonary barotrauma can also cause alveolar hemorrhage. Patients may present with hemoptysis coincident with chest pain and dyspnea. Chest radiography may reveal an interstitial infiltrate. If alveolar gas invades the pulmonary veins and enters the systemic circulation it can cause arterial gas embolism (AGE) which is discussed later.

Decompression Sickness

The term *decompression sickness (DCS)* refers to a spectrum of clinical illnesses resulting from the formation of small bubbles of nitrogen gas in the blood and tissues on ascent. The clinical expression of DCS depends on the location, destination, and degree of nitrogen bubble formation in blood and tissues. Small, usually asymptomatic venous gas emboli are common in the ascending diver after ascent and for the first several hours after ascent and are usually filtered by the lungs without apparent permanent damage. Persistent intravascular bubbles, however, may elicit inflammatory cascades, cytokines, the complement system, platelet aggregation, and thrombosis. They can also induce mechanical obstruction leading to ischemia and hypoxia resulting in major pathology and even death. Nitrogen is highly fat soluble, and the heavily myelinated white matter of the CNS is at particular risk for DCS.

The incidence of DCS ranges from 1 per 1000 dives to 1 in 20,000 dives based on previous studies, but may be underreported because some divers may not present to a health care professional. The potential for development of DCS increases with the length and depth of diving. Other risk factors may include age, obesity, fatigue, heavy exertion, dehydration, fever, cold ambient temperatures after diving, diving at high altitude or flying soon after diving. The risk of DCS is 2.5 times greater for men than for women, possibly due to risk-taking behaviors. A patent foramen ovale (PFO) or other left-to-right shunt (e.g., atrial septal defect) is a risk factor for increased susceptibility to DCS and larger defects are likely to be more relevant.[7,8,9] Sixty-five percent of divers who present with serious DCS have a PFO. Most sport divers do not undergo screening for PFO with echocardiographic bubble studies.

The United States Navy dive tables estimate the amount of nitrogen that accumulates in the body during a dive to a particular depth and duration. The tables calculate a maximal dive time, called the *no-decompression limit.* If the no-decompression limits are exceeded, underwater decompression stops are recommended. Many sport scuba divers use submersible dive computers to calculate maximum dive times in lieu of the tables. These tables and computers are meant to reduce the likelihood of exceeding the solubility of nitrogen at sea level to produce DCS. The diver still must ascend in a slow, controlled manner to allow the gradual release of nitrogen. Off-gassing continues after the diver has surfaced. Repetitive dives within several hours result in accumulation of tissue nitrogen and shorter no-decompression limits. Because dive tables are based on several assumptions about nitrogen elimination, even strict adherence to these tables does not guarantee that DCS will not occur. It is important for emergency clinicians to realize that divers can develop DCS even when they are within these calculated no-decompression limits.

DCS typically is manifested within hours after surfacing. Approximately 40% of symptoms occur within 1 hour after diving, 60% within 3 hours, 80% within 8 hours, and 98% within 24 hours. Flying shortly after diving or ascending to altitude, however, may cause symptoms in patients later than expected, and some patients may present days after diving with DCS.

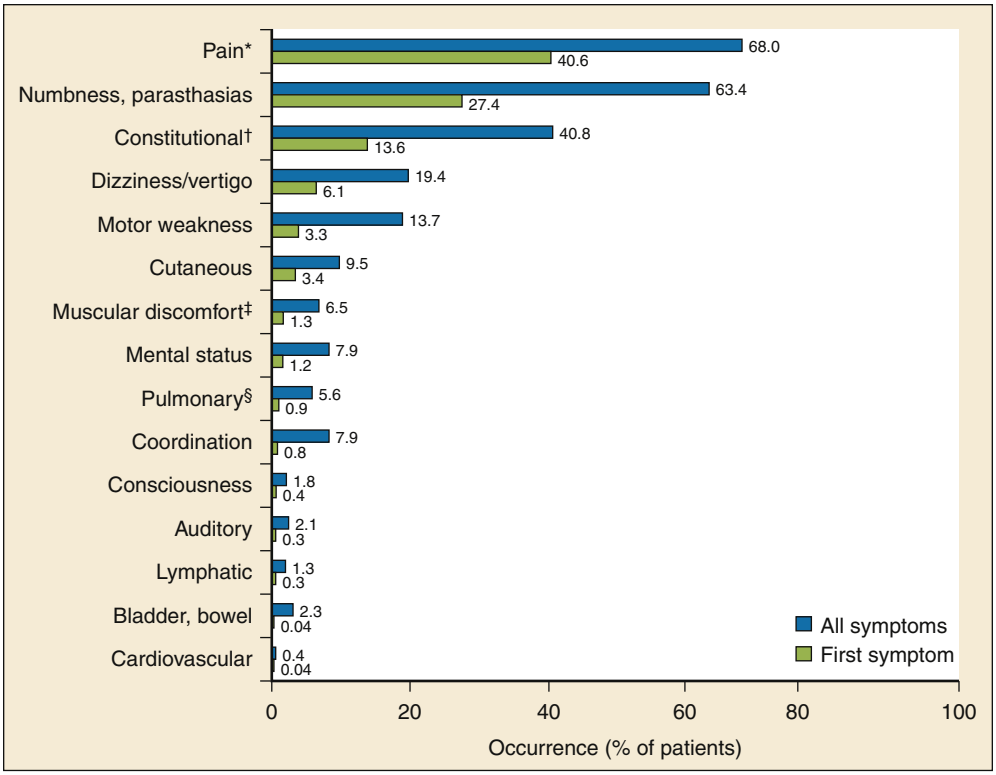

Fig. 131.7 Classification of initial and of all eventual manifestations of decompression illness in 2346 recreational diving accidents reported to the Divers Alert Network (DAN) from 1998 to 2004. *For all instances of pain, 58% consisted of joint pain, 35% muscle pain, and 7% girdle pain. Girdle pain often portends spinal cord involvement. †Constitutional symptoms included headache, lightheadedness, inappropriate fatigue, malaise, nausea or vomiting, and anorexia. ‡Muscular discomfort included stiffness, pressure, cramps, and spasm but excluded pain. §Pulmonary manifestations included dyspnea and cough. (From: Vann RD, Butler FK, Mitchell SJ, et al. Decompression illness. *Lancet*. 2011;377:153-164.)

Traditionally, DCS has been divided into two categories, type I and type II. Type I DCS is considered less severe and affects the musculoskeletal system, skin, and lymphatic vessels. Type II DCS involves any other organ system and typically involves neurologic, vestibular or pulmonary symptoms. The more inclusive decompression illness (DCI) or "decompression-related illness" is now also used to encompass DCS I, DCS II, and arterial gas embolism (AGE). This simplified DCI terminology can aid clinicians to more rapidly select the necessary intervention since all types of decompression illness require recompression. DCS I, DCS II, and AGE can also coexist. The symptoms of DCS may be subtle and resolve by the time of evaluation. A distribution of the initial most common symptoms is presented in Figure 131.7.

Divers experiencing more minor type I DCS generally experience joint pains. The elbow and shoulder joints are most commonly affected. Local tenderness and erythema are uncommon. The placement of a blood pressure cuff inflated to 150 to 200 mm Hg on an affected joint produces relief of pain and helps confirm the diagnosis; however, the sensitivity of this maneuver has been reported to be as low as 60%. Mild skin irritation or pruritus may also be consistent with more minor type I DCS. Lymphatic obstruction by air bubbles can also occur, causing extremity edema, but is still considered type I DCS. (Fig. 131.8).

Patchy cyanotic marbling of the skin, known as *cutis marmorata* was previously considered as part of type I DCS, but more recent literature suggests that this reticular rash may be related to CNS-related changes in vasomotor regulation and may be more closely related to type II DCS.[10] This update has been reflected in the Divers Alert Network website information as well. Cutis marmorata may begin as

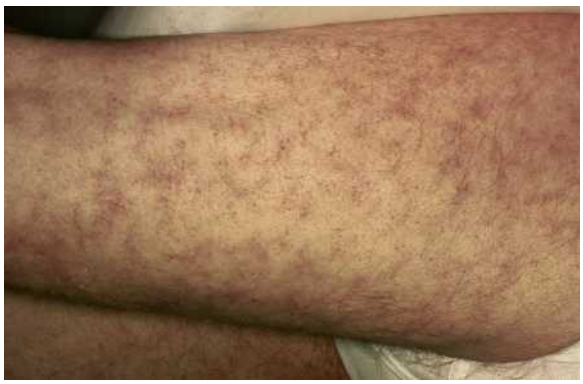

Fig. 131.8 Marbling of the thigh in cutaneous decompression sickness (DCS). (From: Maeyens E. Aquatic skin disorders. In: Auerbach PS, ed. *Wilderness Medicine*. ed 6. Philadelphia: Elsevier; 2012: 1665.)

severe pruritus and progress into an erythematous rash and then skin mottling which commonly involves the trunk and torso but does not follow a dermatomal distribution. Type II DCS includes symptoms that can involve the CNS, the inner ear, and the lungs. The CNS is particularly susceptible to decompression illness because of its high lipid content. The spinal cord, especially the upper lumbar area, is more often involved than cerebral tissue. Symptoms of spinal DCS include limb weakness or paralysis, paresthesias, numbness, with low back and abdominal pain. Limb symptoms often begin as a distal prickly

sensation that advances proximally, followed by progressive sensory or motor loss. Urinary retention, bladder and fecal incontinence, and priapism may also occur. Unlike patients with spinal cord trauma, patients experiencing DCS may have patchy or unequally distributed sensory and motor findings.

Spinal DCS can occur alone or in combination with cerebral, inner ear, or pulmonary symptoms. Cerebral symptoms include mild to moderate headache, blurred vision, diplopia, dysarthria, unusual fatigue, inappropriate behavior, dizziness and a sense of detachment. Loss of consciousness in CNS DCS is rare (in marked contrast to AGE).

Inner ear DCS is commonly called *the staggers*. Approximately one-third of patients that present with DCS report cochlear vestibular symptoms. The symptoms of inner ear DCS are the same as those of IEBT and include nausea, dizziness, vertigo, nystagmus, and hearing loss. Vestibular symptoms predominate with only about a quarter of patients experience hearing loss or tinnitus. This can usually be distinguished from IEBT because the onset occurs during ascent or after surfacing.

Pulmonary DCS is commonly called *the chokes*. All divers are exposed to some degree of microbubble emboli to the lungs on ascent. The progression to symptoms depends on the number and volume of bubbles. The deposition of venous gas emboli in the pulmonary arterial circulation produces progressive dyspnea, cough, and chest pain. The cough may progress to paroxysmal fits with worsening pain. This is usually a progressive process after ascent as opposed to pulmonary barotrauma-related pathology which generally occurs immediately after ascent.

The physical examination of patients suffering from pulmonary DCS may reveal cyanosis and hypotension in association with increased central venous pressure and pulmonary arterial pressure. The condition may progress to respiratory arrest.

DCS may be particularly dangerous to a developing fetus of a scuba diving mother because the majority of the fetal circulation bypasses the pulmonary bed through the foramen ovale and the ductus arteriosus. This bypass prevents the fetal lungs from acting as a filter for microbubbles. In addition, venous gas emboli may appear in the fetal circulation before they are apparent in the maternal circulation. Data on the effects of diving on pregnant women suggest a higher incidence of low-birth-weight infants, prematurity, congenital malformations, stillbirths, and spontaneous abortions. There are no safe-diving tables that would protect a fetus from DCS; therefore, pregnant women should be advised to refrain from scuba diving.

Arterial Gas Embolism

AGE can be caused by barotrauma with air forced across the alveolar-capillary membrane through the pulmonary venous circulation into the arterial system. Alternatively, venous bubbles can cross into the arterial circulation from a left-to-right shunt. Barotrauma-related AGE from air bubbles forced across the alveolar-capillary membrane into the pulmonary venous circulation through the left atrium and ventricle and then into the arterial circulation can be immediately life-threatening. It is one of the most common causes of death in divers and is usually related to an uncontrolled ascent with breath-holding and does not require a significant time at depth. Even at a relatively shallow depth, a diver can elicit significant barotrauma with rapid surfacing, especially with breath-holding. Clinical symptoms and signs are the result of mechanical obstruction by gas bubbles. AGE can also result from a right-to-left shunt of venous bubbles, such as in a diver with a PFO, and often presents with symptoms consistent with type II DCS. AGE may occur alone or in conjunction with DCS.

Although air bubbles may embolize to any organ, the coronary and cerebral arteries are associated with the most serious consequences. Emboli to the coronary arteries may cause cardiac ischemia, myocardial infarction, dysrhythmias, or cardiac arrest. Dysrhythmias may also be indirectly caused by centrally mediated autonomic dysfunction from cerebral emboli. Mechanical occlusion of the cerebral vasculature from emboli, most commonly to the anterior and middle cerebral arteries, causes a variety of symptoms and signs similar in appearance to an acute stroke. Large volumes of intracardiac bubbles can mechanically displace blood in the ventricles, leading to a precipitous fall in cardiac output with resultant hypotension and cardiac arrest.

The clinical manifestations of AGE may be sudden, dramatic, and life-threatening. Any diver breathing compressed air at any depth underwater and who surfaces unconscious or who loses consciousness within 10 minutes of reaching the surface should be assumed to be suffering from AGE. The most common presentation of AGE includes a global alteration of consciousness, headache, dizziness, convulsions, and visual changes. Other common presenting symptoms and signs include cranial nerve symptoms, unilateral weakness, unilateral or bilateral sensory loss, ataxia, and speech changes. Pulmonary symptoms, including dyspnea, pleuritic chest pain, and hemoptysis, occur in up to a quarter to half of cases.

Pulmonary Edema

Pulmonary edema while scuba diving was first reported in the 1980s. An increase in afterload (from vascular hyper-reactivity, possibly triggered by cold water) combined with an increase in preload (from the hyperbaric underwater environment) are likely causes.

DIFFERENTIAL DIAGNOSES

Most diving injuries have limited differential diagnoses that include medical disorders and trauma unrelated to dysbarism. The differential diagnoses of IEBT include inner ear DCS, ABV, and isolated MEBT with a rupture of the tympanic membrane. It is relatively easy to distinguish IEBT from MEBT and ABV because the vestibular symptoms associated with the last two entities are transient and self-limited (Table 131.2). When IEBT occurs simultaneously with MEBT, the presence of both may be documented by an audiogram, which demonstrates both a conductive and a sensorineural hearing loss.

The differentiation of IEBT from inner ear neurologic DCS is crucial because the treatments differ. IEBT is considered classic when symptoms begin during descent or the diver relates a history of difficulty equilibrating or performing a vigorous Valsalva maneuver. Inner ear DCS usually presents within 15 minutes to 2 hours after ascent, and usually includes a dive profile which approached no-decompression limits. A trial of recompression therapy is prudent if concerns for DCS exist.

Differential diagnoses of pulmonary DCS include AGE. Table 131.3 provides factors that differentiate the two conditions. Although the treatment of both requires recompression therapy, they can be differentiated by the timing of the onset of symptoms. Almost all cases of AGE present within the first 10 minutes of surfacing, whereas DCS presents more typically well after 10 minutes upon surfacing: 40% of pulmonary DCS symptoms begin within 1 hour of surfacing, 60% within 3 hours, 80% within 8 hours, and almost all within 24 hours.

Diagnostic Testing

Most diagnostic imaging and laboratory studies are not useful in diving- and dysbarism-related injuries and should not delay transfer for definitive recompression therapy. Focused history concerning the dive profile, including the depth and length of the dive and other details of the dive profile (including rapid ascent) and a careful assessment of when the symptoms first occurred, may provide

TABLE 131.2 Middle Ear Barotrauma, Inner Ear Barotrauma, and Alternobaric Vertigo

	Middle Ear Barotrauma	Inner Ear Barotrauma	Alternobaric Vertigo
Symptoms	Ear pain during descent	Ear pain during descent	Ear pain during ascent
	Hearing loss	Hearing loss	Transient hearing loss
	Possible transient vertigo	Severe vertigo and nausea	Nausea
Signs	Conductive hearing loss	Nystagmus	Nystagmus
	TM injury	Emesis	Emesis
	Unilateral face paralysis	Ataxia	TM injury
		Romberg sign	
		Neural hearing loss	

TM, Tympanic membrane.

TABLE 131.3 Decompression Sickness Versus Arterial Gas Embolism

Decompression Sickness	Arterial Gas Embolism
Dive History	
Depth and length dependent	Independent of dive profile
Decompression limits approached	Rapid ascent
Flying after diving	Inexperience
Diving at altitude	Out of air
Risk Factors	
Fatigue	Obstructive lung disease
Dehydration	Emphysema
Fever, hypothermia	Mucus plugging
Obesity	Patent foramen ovale (PFO)
Strenuous activity	
Symptoms and Signs	
Progressive onset	Rapid onset
Spinal symptoms predominate	Cerebral symptoms predominate
Headache	Headache
Unusual fatigue	Loss of consciousness
Limb weakness or paralysis	Confusion
Paresthesias	Convulsions
Abdominal pain	Motor or sensory loss
Urinary retention	Cardiac dysrhythmias or arrest
Fecal incontinence	
Periarticular joint pain	
Skin marbling	
Vertigo or nystagmus	
Treatment	
Recompression	Recompression

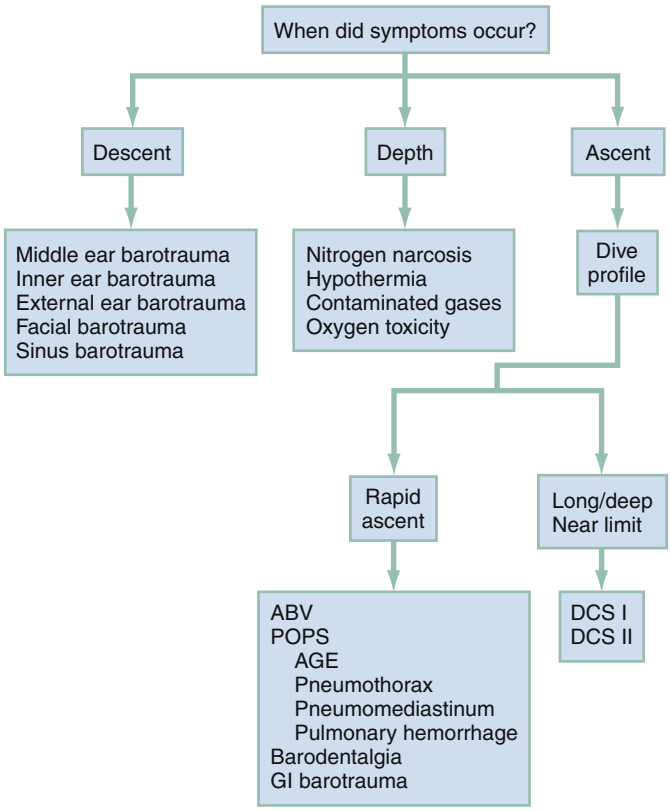

Fig. 131.9 The approach to the injured diver. *ABV,* Alternobaric vertigo; *AGE,* arterial gas embolism; *DCS,* decompression sickness; *GI,* gastrointestinal; *POPS,* pulmonary overpressure syndrome.

important diagnostic clues (see Box 131.3). In making the diagnosis of a dive injury, it is helpful to think of the injuries in terms of occurring during descent, while at depth, or during ascent (Fig. 131.9). Because recompression therapy is time sensitive, it is more important to concentrate on treatment decisions rather than on securing a definitive diagnosis.

Pulmonary barotrauma can also cause alveolar hemorrhage. Patients may present with hemoptysis coincident with chest pain and dyspnea. Chest radiography may reveal an interstitial infiltrate or pneumothorax. An untreated pneumothorax is considered an absolute contraindication for recompression therapy and will need to be managed prior to treatment. Magnetic resonance imaging (MRI), computed tomography (CT), and single-photon emission CT with technetium (Tc-99m)–labeled hexamethyl propylene amine can identify the bubbles of CNS DCS. However, *no* imaging studies are sensitive enough to exclude DCS, and normal imaging results should not delay transfer for definitive therapy. DCS can cause right-sided strain on an electrocardiogram and decreased end-tidal carbon dioxide level. Even after ascent from very shallow saturation dives, microbubbles in the venous circulation can be routinely detected by M-mode ultrasonography; however, their presence does not necessarily correlate with symptoms.

TABLE 131.4 Important Contact Information

Divers Alert Network Head Quarters	Phone Number	Website
DAN America Emergency Hotline	1-919-684-9111	www.diversalertnetwork.org
DAN America nonemergency line (Monday to Friday 8:30 a.m. to 5:00 p.m. Eastern time)	1-919-684-2848 or 1-800-446-2671	
DAN Europe	+3906-4211-5685	www.daneurope.org
DAN South Africa	+27-10-209-8112	www.dansa.org
DAN Asia-Pacific	+61-39886-9166	www.danap.org
DAN Japan	+81-3-3812-4999	www.danjapan.gr.jp

DAN, Divers Alert Network.

MANAGEMENT

Patients with stable vital signs and suspected dive injuries should receive 100% oxygen until the clinician can exclude pulmonary barotrauma or decompression illness. Normobaric 100% oxygen can improve outcomes and should be provided until the patient can be treated definitively. Patients with unstable vital signs or in cardiac arrest should be treated according to advanced cardiac life support (ACLS) guidelines. The clinician should conduct a focused history, including elements summarized in Box 131.1, and then perform a thorough physical examination.

Diving-related illnesses are diagnosed and treated on the basis of the history and physical examination, with several resources available for emergent advice. The Divers Alert Network (DAN), located at Duke University in Durham, North Carolina, is a membership association that provides courses on diving-related emergencies and publishes data on diving accidents and fatalities. DAN provides a 24-hour medical emergency hotline at 1-919-684-9111 (collect calls are accepted) and a nonemergency advisory line Monday through Friday, 8:30 a.m. to 5 p.m. Eastern time, at 1-919-684-2948 or 1-800-446-2671 (Table 131.4). In addition, DAN international contacts are in Europe, Brazil, Japan, Asia Pacific, and southern Africa. DAN maintains a website with links to key information at www.diversalertnetwork.org. DAN uses a telephone intake form, the DAN On-Site Neurological Assessment for Diver's History (Fig. 131.10).

The United States Navy has its current diving manual (6th edition) available at its website, www.usu.edu/scuba/navy_manual6.pdf. This manual contains readily accessible information describing diving principles, equipment, operations, and recompression.

Diving Disorders Requiring Recompression Therapy

Diving disorders that require recompression therapy are listed in Box 131.4. Early consultation with a hyperbaric specialist is recommended. Treatment with 100% normobaric oxygen during recovery, assessment, and transfer is recommended. Treatment with 100% oxygen replaces inert gases in the lungs with oxygen by establishment of a large gradient from the tissues to the alveoli, removal of inert gases is enhanced, and bubble size is reduced. In addition, oxygen administration treats the tissue hypoxia created by the accumulation of gas bubbles.

Dehydration may increase the seriousness of DCS. Diving appears to be associated with dehydration and hemoconcentration in many studies. Intravenous fluids may be administered to divers suspected of having nonpulmonary ("chokes") DCS. Overly aggressive hydration in divers with pulmonary DCS may worsen pulmonary edema and is discouraged. Similarly, fluid overload should be avoided in patients with suspected cerebral or spinal cord edema or AGE. If given, fluids should be administered to ensure a urinary output of 0.5 mL/kg per hour.

The goals of recompression therapy are to reduce the mechanical obstruction of air bubbles, to facilitate the washout of nitrogen by increasing the tissue-blood nitrogen gradient, and to increase oxygen delivery to ischemic tissue. Recompression is the only definitive treatment of DCS and AGE and is most effective if administered early. Treatment of DCS or AGE should not be withheld even if a significant time delay in transferring a patient to a hyperbaric chamber is anticipated. Although delayed recompression is less effective than immediate recompression in serious cases, the time beyond which recompression offers no benefit is not well documented.

Hyperbaric therapy for AGE is also considered time sensitive. Patients with AGE who are recompressed within 5 hours of surfacing have a mortality rate of 5%, and there is an extremely low risk of morbidity among the survivors. If recompression is delayed by 5 hours or more, the mortality rate increases to 10%, with 50% morbidity. Although spontaneous resolution of symptoms may occur in patients with AGE, all patients should be recompressed. The rationale is that although microbubbles may clear from the cerebral circulation, secondary capillary edema and swelling may be further ameliorated by recompression.

Similarly, the prognosis for DCS when it is treated with recompression is generally good but depends on the severity of symptoms at onset, and the delay to recompression. A delay to definitive recompression treatment is associated with a worse outcome in cases of severe DCS. Patients can obtain some benefit from recompression, however, even if treatment is initiated more than 24 hours after the dive. Recompression therapy for DCS initiated as late as 10 to 14 days after exposure has been associated with improved outcomes.

Recompression for DCS and AGE may be performed in a multiplace chamber with one or more in-chamber attendants or within a monoplace chamber. Monoplace chambers are compact, lightweight, and more widely available than multiplace chambers, but most monoplace chambers cannot be pressurized beyond 3 ata (100 fsw) or deliver air-oxygen mixtures. The most common recompression schedule is the United States Navy treatment (or an equivalent procedure). With this protocol, the diver is compressed to 2.8 bar (60 fsw pressure) while breathing 100% oxygen. The time to complete treatment is 4 hours 45 minutes, not including descent and ascent time.

Ground transport to a hyperbaric facility is preferred to air transportation, if feasible, because an increase in altitude lowers the ambient pressure and allows microbubbles to expand. If air transportation must be used, it is recommended maintain cabin pressure at less than 1000 feet. Commercial aircraft are typically pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight (30,000 feet). Many of these aircraft are capable of near–sea level cabin pressures if flying no higher than 15,000 to 20,000 feet. Because helicopters are not pressurized, it is recommended that they maintain an altitude of no more than 500 feet during transport of a diving accident victim.

DAN On-Site Neurological Assessment for Diver's History

Last Name: _____ **First Name:** _____ **MI:** _____

Date: (mm/dd/yy): _____ **Time: (hh:mm)** _____

COMPLETED BY: _____

How do you feel? _____

Symptoms? _____

Did symptoms start during descent, on bottom, during ascent, or after surfacing? _____

_____

Dive profile, breathing gas, ascent and time of surfacing, recent dive history _____

_____

_____

_____

Unusual features of dive (eg, out of air, rapid ascent) _____

Decompression computer, table _____

Difficulty with middle ear equalization? _____

Numbness, tingling? Where? _____

Pain? Where? What makes it better or worse? _____

Rate the pain on a scale of 0 (no pain) to 10 (the worst pain imaginable) _____

Shortness of breath? _____

Ringing or buzzing in ear? _____ Decreased hearing? _____

Dizziness? Vertigo? _____

"Vertigo" implies a sensation of the world spinning around. Vague "dizziness" is not vertigo.

Weakness? _____

Difficulty walking? If so, is this due to difficulty with balance or leg weakness? _____

Nausea, vomiting? _____ Able to urinate? _____

From "observer" (eg, dive buddy, companion) _____

Confirm dive profile _____

His/her version of events _____

_____

_____

Did the diver breach safe procedures (eg, ascent rate, out of air, was he/she breathing during ascent)?

_____

Has the diver been acting inappropriately? _____

Was there loss of consciousness, seizure? _____

Fig. 131.10 The Divers Alert Network (DAN) On-Site Neurological Assessment for Diver's History.

BOX 131.4 Diving Disorders That Require Recompression Therapy

Decompression sickness type I
Decompression sickness type II
Arterial gas embolism (AGE)
Contaminated air (carbon monoxide poisoning)

In addition to recompression therapy, several adjunctive treatments are proposed in the treatment of DCS and AGE. The treatment or prevention of hypothermia may increase tissue perfusion and prevent off-gassing. Anticoagulants to prevent deep venous thromboembolism may be considered in patients with paralysis with long transport times. Intermittent pneumatic compression devices are alternative therapeutic measures. Seizures may be managed with standard doses of benzodiazepines; however, mannitol should be avoided. Spinal DCS patients often develop urinary retention requiring bladder catheterization.

BOX 131.5 Diving Disorders That Do Not Require Recompression Therapy

Middle ear barotrauma (MEBT)
External ear barotrauma
Inner ear barotrauma (IEBT)
Barosinusitis
Facial barotrauma
Nitrogen narcosis
Oxygen toxicity
Pneumothorax
Pneumomediastinum
Subcutaneous emphysema
Alveolar hemorrhage
Alternobaric vertigo (ABV)
Barodontalgia
Gastrointestinal barotrauma
Avascular osteonecrosis

Urinary catheter (and endotracheal tube) balloons should be inflated with saline (not air) before recompression therapy is initiated.

The head-down position (Trendelenburg) has traditionally been advocated to prevent migration of intra-arterial bubbles to the brain, however, it may actually result in worsening cerebral edema and intracranial pressure and is no longer recommended. Transport of the patient with AGE in a flat supine position is recommended to maximize arterial-venous flow.

Suspected carbon monoxide poisoning from contaminated air supplies in a diving environment should be treated immediately with high-flow normobaric 100% oxygen and may require hyperbaric oxygen therapy if neurologic symptoms are present. Consultation with a hyperbaric specialist or medical toxicologist is recommended.

Diving Disorders Not Requiring Recompression Therapy

Diving disorders that do not require recompression therapy are summarized in Box 131.5.

External Ear Barotrauma

Treatment of external ear barotrauma includes cleaning of the external canal and removal of foreign bodies. Earplugs should not be worn when diving.

Middle Ear Barotrauma

Prevention of MEBT requires that the diver equalize the pressure in both middle ears. Any diver who cannot clear both ears on the surface should not dive. The diver should not perform a forceful Valsalva maneuver during descent or ascent to clear the ears because of the risk of ABV, round or oval window rupture (descent), or pulmonary barotrauma (ascent). The prophylactic use of pseudoephedrine (60 mg taken orally 30 minutes before diving) or oxymetazoline nasal spray may reduce the incidence and severity of MEBT. The use of these medications to facilitate diving with symptoms of an upper respiratory infection, however, is not recommended. Antihistamines should be avoided before diving because these agents induce dry mouth when breathing compressed air and drowsiness. Sinusitis and upper respiratory infections increase the likelihood of suffering barotitis. Diving should be avoided during and for 2 weeks after the resolution of an upper respiratory infection. Persistent symptoms may require otolaryngology consultation.

Treatment of uncomplicated serous otitis from MEBT includes topical nasal vasoconstrictors, such as phenylephrine and oxymetazoline hydrochloride, and repeated Frenzel maneuvers to displace the fluid through the eustachian tube. The *Frenzel maneuver* is performed by pinching the nose, placing the tongue on the roof of the mouth, as far forward as possible, and gently moving the back of the tongue upward, as when starting to swallow. This is repeated as many times as necessary until equalization occurs. If the physical examination reveals a ruptured tympanic membrane, prophylactic treatment should also include an oral antibiotic. Oral steroids (prednisone) may speed recovery when a seventh nerve palsy is diagnosed in conjunction with a perforated tympanic membrane, although this disorder is typically self-limited. Diving must also be suspended until the tympanic membrane heals to prevent calorically induced vertigo. Outpatient follow-up with an otolaryngologist is recommended.

Internal Ear Barotrauma

A conservative treatment approach to IEBT includes bed rest for 5 to 7 days with the head elevated, avoidance of straining or the Valsalva maneuver, and decongestants to facilitate drainage of the middle ear. Early surgical intervention may benefit patients with total or near-total hearing loss but is not effective in isolated high-frequency hearing loss.[11] All patients with suspected IEBT should be referred to an otolaryngologist, because IEBT suggests significant injury to the cochleovestibular system.

Barosinusitis

Treatment of barosinusitis is typically conservative, including the use of decongestants and occasionally, antibiotics. If symptoms persist, referral to an otolaryngologist should be considered. The patient should be advised not to dive until any underlying respiratory infection or acute inflammatory process has resolved.

Facial Barotrauma

The victim of facial barotrauma may have a dramatic appearance, but the condition is usually benign and requires no specific treatment. The patient should be advised not to resume diving until facial edema resolves.

Nitrogen Narcosis

Nitrogen narcosis symptoms should resolve on ascending as the partial pressure of nitrogen decreases. Persistent symptoms should prompt a search for other causes, such as DCS, cerebral AGE, contaminated air, and near drowning.

Pulmonary Barotrauma

With the exception of AGE, none of the pulmonary barotrauma disorders (pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage) require recompression therapy. Treatment with 100% oxygen may aid in the resolution of these disorders. Tube thoracostomy may be required for divers undergoing recompression therapy to prevent a tension pneumothorax. Catheter aspiration of the pneumothorax may be an acceptable alternative to tube thoracostomy if the patient does not receive positive-pressure ventilation or recompression therapy.

The evaluation and management of pneumomediastinum includes observation, monitoring, and serial chest radiographs to ensure that no coexisting pneumothorax develops. One hundred percent oxygen therapy may hasten the resolution of symptoms.

Alternobaric Vertigo

Oral and intranasal decongestants may be indicated if symptoms persist. Myringotomy is occasionally required. Outpatient follow-up with otolaryngology is recommended for persistent symptoms.

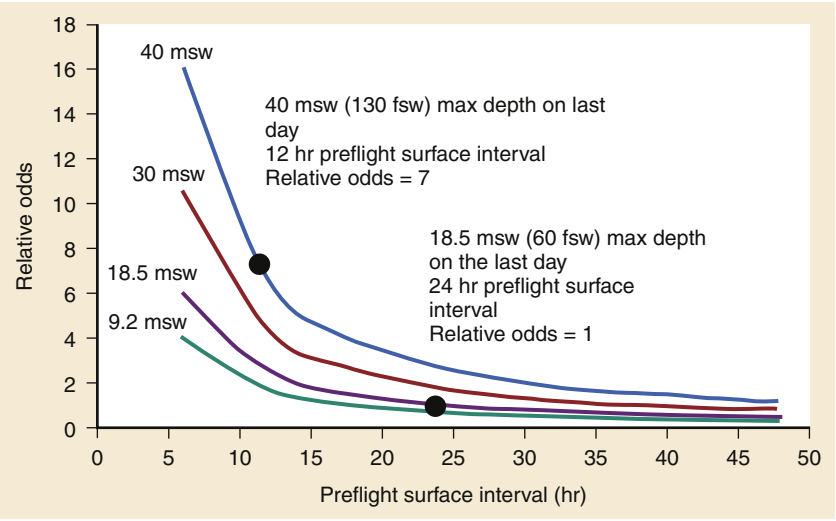

Fig. 131.11 The risk of decompression sickness (DCS) relative to flying. *fsw,* Feet of seawater; *msw,* meters of seawater. (From: Freiberger JJ, et al. The relative risk of decompression sickness during and after air travel following diving. *Aviat Space Environ Med.* 2002;73:983.)

DISPOSITION

Divers should be aware that commercial airliners may be pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight. Many cases of DCS have a delay in the onset of symptoms in divers who fly after diving even if they are symptom-free before departure. Divers who experience DCS symptoms before departure and still elect to fly, are more likely to have type II DCS, less likely to achieve complete relief after recompression, and more likely to have residual symptoms for at up to 3 months.

The relative risk for development of DCS increases with longer dive times at significant depth and shorter preflight surface intervals (Fig. 131.11). Flying should be delayed for at least 12 hours after diving if less than 2 hours of total dive time was accumulated in the preceding 48 hours. For multiple-day, unlimited diving, flying should be delayed for at least 24 hours. Patients recompressed after DCS or AGE should not fly for at least 72 hours.

United States Navy guidelines recommend that the patient not return to diving for 7 days after recompression for type I DCS and for 4 weeks after type II DCS. Divers who experiences DCS type II symptoms or AGE should be discouraged from future diving again and may referred to dive specialist for further recommendations.

After treatment for pulmonary barotrauma or DCS, divers should be referred to a dive specialist to consider if they require further evaluation to determine if there are any preexisting conditions (e.g., bullae, PFO or left-to-right shunts) prior to diving. A history of any major diving-related injury is a clear risk factor for future events.

The author wishes to thank Richard L. Byyny and Lee W. Shockley for their valuable contributions and expertise in previous chapter editions.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 131: QUESTIONS AND ANSWERS

1. When is a diver most likely to suffer barotrauma?

a. When the diver also suffers from decompression sickness (DCS)
b. When the diver is at extreme depth
c. When the diver is closest the surface
d. When the diver stays at depth for an extended period of time
e. When the diver uses specialized gas mixtures with decreased partial pressure of nitrogen

Answer: C. Barotrauma refers to injuries due to pressure changes. Boyle's law states that pressure and volume are inversely proportional ($P \times V = k$ or $P_1V_1 = P_2V_2$). As the pressure decreases, the volume of gas increases and can damage gas-filled structures (sinuses, inner/middle ears, lungs, and intestines). The incremental changes in pressure (and therefore volume) are greatest at the surface, so barotrauma most commonly occurs near the surface (either at the beginning or at the end of a dive). Long or deep dives are not required for barotrauma but predispose to decompression illness due to the build-up of tissue nitrogen which comes out of solution during ascent.

2. A 55-year-old man presents with the acute onset of left-sided weakness and confusion. Family members report that they are on vacation and had just finished scuba diving when the patient complained of chest pain, became confused, and stopped moving his left arm and leg. This happened 30 minutes ago. The patient has no known medical history and takes no medications. Physical examination reveals a drowsy and confused male who follows commands but does not move his left arm or leg. His blood pressure is 162/98 mm Hg, and his other vital signs are within normal limits. What is the appropriate treatment?

a. Computed tomography (CT) of the brain
b. Endotracheal intubation
c. Intravenous labetalol
d. Intravenous tissue plasminogen activator
e. Recompression in a dive chamber

Answer: E. This patient has suffered an arterial gas embolism (AGE). In AGE, air bubbles gain access to the arterial circulation and can cause mechanical obstruction of the artery. Symptoms can mirror an acute thrombotic or embolic event including myocardial infarction or stroke. Treatment with 100% oxygen should be instituted immediately, but the only definitive treatment is emergent recompression.

3. Which of the following individuals should be advised not to dive?

a. A 10-year-old boy with no known medical problems
b. A 19-year-old woman with no medical problems but who just landed from an intercontinental commercial flight
c. A 20-year-old man with well-controlled asthma
d. A 27-year-old woman who is 20 weeks pregnant
e. A 70-year-old man with asymptomatic coronary artery disease

Answer: D. Upon surfacing, small nitrogen bubbles form in the circulation of all divers. If proper technique is followed, these bubbles are small and asymptomatic. They form in the venous circulation and are eliminated in the lungs. However, if these bubbles are transmitted into the arterial system, embolization with serious consequences can occur. The fetus has a patent foramen ovale (PFO) and ductus arteriosus, both of which would allow air to bypass this filtering effect of the lungs and proceed into the systemic circulation. Asthmatics can dive as long as symptoms are well controlled. There are no definite age recommendations for diving. Flying immediately after diving should be avoided; flying prior to diving is of less concern.

4. A 24-year-old woman presents with complaints of severe chest pain and shortness of breath. The symptoms started approximately 1 hour ago while surfacing from a dive. She denies loss of consciousness or other symptoms. Physical examination reveals decreased breath sounds in the right chest and crepitus in her neck; otherwise, it is normal. Vital signs are normal except for a slight tachypnea. A chest radiograph shows a moderate right-sided pneumothorax and a pneumomediastinum. She has no other symptoms or signs. You place a chest tube on her right side. What is the next course of action?

a. Computed tomography (CT) of the brain
b. CT of the chest
c. Observation and supportive care
d. Pericardiocentesis
e. Recompression in a dive chamber

Answer: C. This patient has suffered from pulmonary barotrauma. Although this injury does predispose one to arterial gas embolism (AGE), the diagnosis of AGE is clinical. The treatment for a pneumothorax from pulmonary barotrauma is the same as for a pneumothorax from another cause—that is, aspiration, catheter insertion, or chest tube placement. Management of pneumomediastinum is supportive. Recompression is only necessary for decompression sickness (DCS) or AGE, not for barotrauma.

CHAPTER 131: QUESTIONS AND ANSWERS—cont'd.

5. A 32-year-old man presents with bilateral lower extremity numbness and weakness. The patient reports several days of scuba diving without incident until after his most recent dive, when the symptoms started. Physical examination reveals bilateral lower extremity weakness and decreased sensation to pinprick and light touch. Priapism is also noted. The remainder of the physical examination and all vital signs are within normal limits. You decide that recompression therapy is indicated, but your emergency department does not have a dive chamber and the nearest chamber is 50 miles away. The patient has been accepted in transfer. What is the most appropriate way to transfer this patient?

a. Air ambulance, lying flat
b. Air ambulance, Trendelenburg position
c. Ground ambulance, lying flat
d. Ground ambulance, Trendelenburg position
e. This patient has not yet been stabilized for transport; he should remain at the current hospital.

Answer: C. This patient is suffering from spinal decompression sickness (DCS II). Recompression therapy is the treatment of choice. Unless an inordinate delay to the recompression chamber would result, anything that further decreases ambient pressure should be avoided (e.g., flying). If a patient must be flown, the aircraft should fly at the lowest possible altitude or pressurize the cabin at the highest possible pressure. Traditionally, the Trendelenburg position was advocated because it was believed that it would decrease the incidence of AGE to the brain. This is not the case. In addition, the Trendelenburg position increases cerebral edema and the incidence of coronary artery air embolism. Therefore, the Trendelenburg position should not be used for patients with diving injuries.

6. You decide that a 27-year-old patient with an arterial gas embolism (AGE) following scuba diving requires recompression therapy. Which of the following treatments should be initiated before hyperbaric therapy?

a. Administer 40% oxygen.
b. Administer steroids.
c. Ensure that the endotracheal tube and urinary catheter balloons are filled with water, rather than air.
d. Place prophylactic thoracostomy tubes bilaterally.
e. Place the patient in the Trendelenburg position.

Answer: C. 100% normobaric oxygen is standard of care during evaluation, treatment and transport. Inflate endotracheal tube and urinary catheter balloons with sterile saline. There is no evidence that steroids are effective. The Trendelenburg position increases intracranial pressure and facilitates coronary gas embolization.

High-Altitude Medicine

N. Stuart Harris

KEY CONCEPTS

- All forms of altitude illness can be treated with oxygen and rapid descent.
- The diagnosis of acute mountain sickness requires the presence of headache in the setting of a recent elevation change to greater than 8,000 feet. Additional nonspecific symptoms may include nausea, anorexia, and fatigue. Those with significant symptoms should not ascend further until symptoms improve.
- Patients with mild high-altitude pulmonary edema may be treated in place if experienced providers and treatment options exist. Patients with moderate high-altitude pulmonary edema or high-altitude cerebral edema should descend immediately.
- Dyspnea at rest is an early symptom of high-altitude pulmonary edema. More advanced findings include rest tachypnea, cough productive of frothy sputum, and altered mentation. Treatment involves oxygen and descent.
- Altered consciousness and cerebellar ataxia are early signs of high-altitude cerebral edema. Failure to initiate immediate treatment with oxygen, descent, and dexamethasone can result in permanent disability or death.
- Acute mountain sickness may be prevented by using acetazolamide or dexamethasone. Symptoms can be controlled with analgesia and antiemetics. High-altitude pulmonary edema may be prevented using nifedipine. In patients unable to use nifedipine, consider inhaled salmeterol, and oral phosphodiesterase type 5 inhibitors (sildenafil [50 mg every 8 hours] and tadalafil [10 mg every 12 hours]). Temazepam (7.5 mg qhs) can safely improve sleep quality.

FOUNDATIONS

Background and Importance

Acute high-altitude illnesses result from exposure to low oxygen states caused by low atmospheric pressure (hypobaria). Syndromes of the brain and lung are the primary clinical manifestations of high-altitude illness. They result from ascent too rapid to allow for adequate acclimatization. Cerebral forms of altitude illness occur as a continuum, from common and benign acute mountain sickness (AMS), to rare, but potentially lethal high-altitude cerebral edema (HACE). High-altitude pulmonary edema (HAPE) is the primary lung syndrome. HAPE is the leading cause of death from altitude illness.

All forms of altitude illness have their origins in acute oxygen insufficiency due to hypobaria. All can be treated with oxygen and descent. Although the percentage of atmospheric oxygen is a constant 20.9%, as elevation increases, atmospheric pressure decreases and with it, oxygen availability. Human physiology is adaptable when given sufficient time to acclimatize by gradual ascent. Rapid ascent to elevations greater than 8,000 feet prevents adequate acclimatization and can lead to debilitating and deadly high-altitude illnesses. On the summit of Mt. Everest (8848 m), the partial pressure of inspired oxygen (Pio_2) is only 29% of the sea-level value. Although gradual ascents (over weeks) of Mt. Everest without oxygen are not uncommon, a rapid ascent to the same summit would result in loss of consciousness and death. Gradual ascent reduces symptoms and can save lives. Serious altitude illness typically follows from unheeded warning symptoms of mild altitude illness. The importance of patient and public education to reduce the morbidity and mortality of serious altitude illness cannot be overstated.[1]

Epidemiology

It is estimated that approximately 40 million individuals worldwide live above 8,000 feet. These individuals do not suffer acute altitude illness. Instead, it is the individual who rapidly travels to high altitude (whether for skiing, climbing, or travel) who is at the greatest risk. In the United States alone, approximately 35 million visitors travel to high-altitude recreation areas every year. Internationally, millions more travel to high mountain ranges in Europe, Asia, Africa, and South America, placing these transient sojourners at risk.[2]

The incidence and severity of altitude illness are directly related to elevation and rapidity of ascent. Other variables include prior acclimatization, individual genetic susceptibility, sleeping elevation, and duration of stay. Rapid ascent to 8000 feet is associated with an approximately 25% incidence of AMS, whereas a rapid ascent (1 or 2 days) to 14,410 feet on Mt. Rainier has rates as high as 67%. Rapidity and mode of ascent also matter; trekkers who fly into the Khumbu region to explore the Mt. Everest region are more likely to develop AMS (47%) than those who trek in from lower elevations (23%).

HACE is much less common than AMS, occurring in less than 1% of rapid ascents to more than 14,000 feet. Although rare, it carries a grave prognosis if not quickly recognized and treated. The incidence of HAPE varies from 0.01% to 2% but may be as high as 15.5% if flown directly to 14,500 feet without a chance to acclimatize at a lower altitude. Both HAPE and HACE are more common with a longer duration of visit (more than 2 days) and higher sleeping altitude.

Age may be a relative risk factor. Most studies of children suggest that they have the same incidence of AMS as adults. Younger individuals (younger than 20 years old) are more likely to have HAPE, although HAPE is extremely rare in children younger than 2 years old. Gender does not affect the incidence of AMS; however, women may have less risk for development of HAPE. No relationship appears to exist between AMS development and timing of the menstrual cycle.

The number of older travelers visiting mountain resorts is increasing. Many of these individuals have underlying health problems, including lung disease, heart disease, and hypertension. Despite these conditions, the risk for AMS in adults older than 50 years old may be less than in younger age groups. Nevertheless, there are indications that elders may not react well to acute high-altitude exposure. Pulmonary vital capacity decreases by one-third in elders ascending from sea level

to 14,000 feet for 1 week, producing a large decrease in both oxygen saturation and maximal oxygen uptake during altitude-related exercise.

Definitions

Moderate altitude is between 5000 and 8000 feet of elevation. Rapid ascent to this altitude may result in mild, transient symptoms, but severe altitude illness is uncommon. *High altitude* is between 8000 and 14,000 feet. Although most people do not experience significant arterial oxygen desaturation until they reach higher altitudes, high-altitude illness is common with rapid ascent above 8000 feet, and individuals with underlying medical problems may be predisposed to develop altitude illness at lower levels. The pathophysiologic effects of high altitude begin when the oxygen saturation of the arterial blood begins to fall below the 90% level. The sigmoidal shape of the oxyhemoglobin dissociation curve prevents a significant fall of arterial oxygen saturation (Sao_2) in most individuals until an altitude of approximately 12,000 feet. At this altitude, the steep portion of the curve is encountered, and marked oxygen desaturation may occur with relatively small increases in altitude (Fig. 132.1). Some predisposed individuals may desaturate to less than 90% at altitudes as low as 8000 feet. *Very high altitude* is between 14,000 to 18,000 feet. At this elevation, the likelihood of altitude illness is high, and the risk of serious altitude illness (HAPE and HACE) increases. *Extreme altitude* is above 18,000 feet. Although climbers using careful acclimatization schedules can transiently tolerate this elevation, complete acclimatization generally is not possible and long durations above this level result in progressive deterioration. Given limitations in physiologic reserves, climbers who become incapacitated at this elevation typically are dependent on others to survive.

Environmental Considerations

Barometric pressure decreases logarithmically as the altitude rises. The pernicious effects of altitude are due to hypobaric hypoxia; as atmospheric pressure decreases the partial pressure of oxygen (Po_2) decreases. Due to centrifugal forces, the earth is slightly flatter at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; therefore, at any one elevation the barometric pressure tends to be lower at higher latitudes than at the equator. Although subtle, the physiologic reserves are so limited at extreme elevations that it has been calculated that if Mt. Everest happened to be at a more northern latitude, it would be impossible to climb without supplemental oxygen.

The atmospheric envelope also undergoes seasonal variations in local thickness. In the winter, barometric pressures tend to be lower making "relative altitudes" physiologically higher. Local weather can also significantly affect the barometric pressure. A low-pressure front can reduce the barometric pressure 12 to 40 mm Hg and so increase the "relative altitude" by 500 to 2,500 feet. At extreme elevations these changes can be physiologically relevant. High-altitude illness can occur even where mountains appear distant. Although the South Pole is on a flat, barren plain, it rests at approximately 9300 ft and severe altitude illness caused by rapid transport from sea-level research facilities is not uncommon.[3]

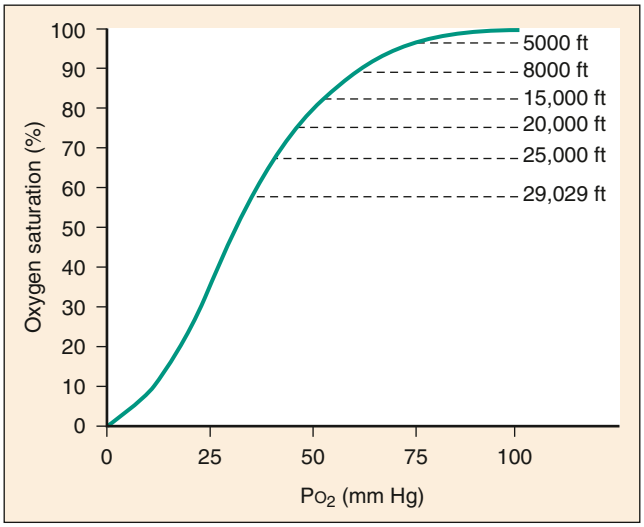

Fig. 132.1 Oxygen-hemoglobin dissociation curve. Approximate oxygen saturations are marked for several altitudes. Po_2, Partial pressure of oxygen. (Data for 15,000 to 29,029 feet from: Sutton JR, et al. Operation Everest II: oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309.)

Anatomy, Physiology, and Pathophysiology

Acclimatization

Exposure to acute hypobaric hypoxia results in myriad physiologic responses that act to improve oxygenation. *Acclimatization* is both immediate (within minutes the carotid bodies sense hypoxemia) and continuous over months (hemoglobin increases may continue over more than 6 weeks). It involves multiple systems from mitochondrial function, protein synthesis to respiratory, cardiovascular, renal, and hematologic responses. Acclimatization begins as the oxygen saturation of arterial blood falls below sea-level values. The altitude at which this occurs depends on the rate of ascent, the duration of exposure, and the individual's physiology. Individuals with preexisting conditions that limit cellular oxygen delivery and pulmonary reserves may have a decreased altitude tolerance. Most healthy, unacclimatized visitors to high altitude will not desaturate significantly (to less than 90%) until they reach elevations higher than 8000 feet.

The risk of high-altitude illness depends, in part, on an individual's inherent ability to acclimatize. Some people acclimatize easily without having any clinical symptoms. Others may transiently have AMS during acclimatization and a few develop severe altitude illness. This variability involves many genetic and epigenetic factors that influence acclimatization. Previous successful acclimatization may be predictive of future responses for adults in similar conditions, but this may not be the case for children.

One of the most fundamental physiologic changes that occurs during acclimatization is an increase in minute ventilation. Within minutes of exposure to high altitude, the peripheral chemoreceptors in the carotid bodies sense hypoxemia resulting from the decrease in the partial pressure of oxygen in alveoli (P_{AO_2}) and signal the respiratory control center in the medulla to increase ventilation. Increased minute ventilation causes a decrease in the partial pressure of carbon dioxide in alveolus (P_{ACO_2}). As described by the alveolar gas equation, for any given inspired oxygen tension, the level of ventilation determines alveolar oxygen: as the P_{ACO_2} decreases, P_{AO_2} correspondingly increases (Box 132.1). This increased ventilation in response to hypoxic challenge is known as the *hypoxic ventilatory response (HVR)*. The magnitude of the HVR varies among individuals and may be genetically predetermined. HVR may also be inhibited or stimulated by numerous

BOX 132.1 Alveolar Gas Equation

$P_{AO_2} = P_{IO_2} (P_{ACO_2}/R)$

P_{AO_2}	Partial pressure of oxygen in alveolus
P_{IO_2}	Partial pressure of oxygen in inspired air
P_{ACO_2}	Partial pressure of carbon dioxide in alveolus
R	Respiratory quotient

factors, including ethanol consumption, sleep medications, caffeine, cocoa, prochlorperazine, and progesterone.

As minute ventilation increases, carbon dioxide exhalation increases. Within minutes, a resulting respiratory alkalosis acts on the central respiratory center to limit further increases in ventilation. To compensate for this respiratory alkalosis, the kidneys begin to excrete bicarbonate. Acetazolamide enhances this excretion. Gradual, progressive renal excretion of bicarbonate allows ventilation to rise slowly, reaching a maximum after 6 to 8 days at a given altitude. An individual's HVR is related to their ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE. For the majority of people with intermediate HVRs, however, ventilatory drive appears to have no predictive value for AMS development.

The stress of acute hypoxia leads to rapid release of catecholamines. This results in increased cardiac output and elevations in heart rate, stroke volume, blood pressure, and venous tone. Except at extreme altitudes, acclimatization over weeks results in the gradual return of the resting heart rate to near sea-level values. Continued resting tachycardia is evidence of poor acclimatization. As the altitude increases, the maximal heart rate capacity decreases. At the limits of acclimatization, maximal and resting heart rates converge. Ultimately, for most individuals it is pulmonary, not cardiac reserves that limit high-altitude performance.

The hematopoietic response to high-altitude acclimatization includes an increase in both hemoglobin and the number of red blood cells. As a result of fluid shifts into the extravascular space, hemoglobin concentration increases up to 15% after rapid ascent to high altitude. Long-term acclimatization leads to an increase in plasma volume and total blood volume. Within hours of ascent, erythropoietin is secreted in response to hypoxemia which in turn stimulates the production of red blood cells, leading to new circulatory red blood cells in 4 or 5 days. During the next 2 months, red blood cell mass increases in proportion to the degree of hypoxemia.

Hypoxemia also results in an increase in 2,3-diphosphoglycerate, causing a rightward shift of the oxyhemoglobin dissociation curve, which favors a release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The net result is a negligible change in the oxyhemoglobin curve. Some individuals with mutant hemoglobin and high oxygen-hemoglobin affinity are found to acclimatize more efficiently than their normal counterparts at moderate altitudes.

Physiologic Response to Hypobaric Hypoxia

Although acute hypoxia elicits a broad array of physiologic responses, the clinical syndromes of high-altitude illness predominantly affect the brain and lungs. Hypobaric hypoxia's effects on central nervous system homeostasis give rise to AMS and HACE. AMS is the common, benign form that unheeded, can develop into rare, but potentially lethal HACE. HAPE results from overly exuberant increases in pulmonary arterial pressures that lead to stress failures of the delicate pulmonary capillary beds.

Although discrete physiologic responses occur within minutes of exposure to acute hypoxia, the clinical syndromes of high altitude typically require hours to days to manifest themselves. AMS can develop within 4 to 8 hours of acute exposure to hypobaric hypoxia. HACE and HAPE typically occur 2 to 4 days after exposure to high altitude. Because hypobaric hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness. Instead, it appears to be the initiating factor for a complex pathologic process that leads to the development of the various clinical syndromes. The proposed mechanisms for the development of AMS, HAPE, and HACE are represented schematically in Figure 132.2.

HVR is the first response to insufficient oxygen, leading to increased minute ventilation. A robust HVR tends to be protective by encouraging compensatory ventilation. A limited HVR leads to relative hypoventilation and inadequate response to the hypoxemia of high altitude.

Centrally mediated periodic breathing associated with high-altitude exposure may result in periods of apnea during sleep, causing severe arterial oxygen desaturation, which further exacerbates hypoxemia. Significant hypoxemia initiates multiple systemic responses that involve the circulatory, pulmonary, endocrine, and central nervous systems.

Hypoxemia alters fluid homeostasis, resulting in generalized fluid retention followed by the shift of fluid into the intracellular spaces. This is manifested by peripheral edema, decreased urinary output, decreased central vascular volume, and increased body weight in patients with AMS. Several different mechanisms may account for these fluid shifts, including arginine vasopressin levels and centrally mediated sympathetic stimulation. Arginine vasopressin levels are elevated in some cases of AMS and HAPE and decreased in others. Aldosterone, plasma renin, and atrial natriuretic levels are higher in people with AMS.

HAPE results from hypoxia-induced acute pulmonary hypertension leading to stress failure of pulmonary capillaries with consequent alveolar and interstitial edema. Although exercise and cold stress at altitude may increase hypoxemia and exacerbate pulmonary hypertension, the hypoxic pulmonary vasoconstrictive response (HPVR) acts as the primary mediator. HPVR results in pulmonary arterial smooth muscle contraction within the typically low-pressure pulmonary arterial system, with consequent increases in pulmonary arterial pressures within minutes. The HPVR can vary widely between individuals and can even vary widely in different regions of the lungs of the same individual. This unevenness of pulmonary vasoconstriction within the lung is thought to contribute to the pathophysiology of HAPE. In patients with HAPE, exaggerated pulmonary arterial pressures (mean pressure 36 to 51 mm Hg) occur. Uneven vasoconstriction forces the pulmonary hypertension to be transmitted to delicate capillary vessels in an asymmetrical fashion, leading to the failure of capillary endothelium with resultant alveolar and interstitial edema. This uneven edema explains the patchy nature of the infiltrate seen on a chest radiograph with HAPE. Although elevated pulmonary arterial pressure is the sine qua non of HAPE, even marked acute pulmonary hypertension is not alone sufficient to cause HAPE.

The mechanism for the uneven vasoconstriction in HAPE may be due to decreased nitric oxide bioavailability at the pulmonary tissue level. That HAPE has its origins in acute pulmonary hypertension and resultant over-perfusion is supported by studies revealing that pharmacologic agents that limit excessive rises in pulmonary artery pressure prevent HAPE.

Once mechanical injury and pulmonary edema occur, other factors come into play. Acute inflammatory mediators appear and likely contribute to worsening lung function. As alveolar fluid accumulates, impairment in a patient's transepithelial sodium transport may decrease their ability to clear alveolar fluid worsening HAPE. Sodium channel–mediated alveolar fluid clearance is upregulated by inhaled beta-adrenergic agonists, which have been proven to decrease risk of HAPE.

Preexisting inflammation may also be a risk factor for HAPE. Particularly in children, preexisting respiratory infection during ascent to high altitude increases susceptibility to HAPE. Inflammation may "sensitize" the pulmonary endothelium to mechanical injury and increase susceptibility to alveolar fluid accumulation and HAPE during ascent.

The definitive etiology of the cerebral forms of altitude illness remains unclear. Evidence suggests that clinical manifestations of AMS

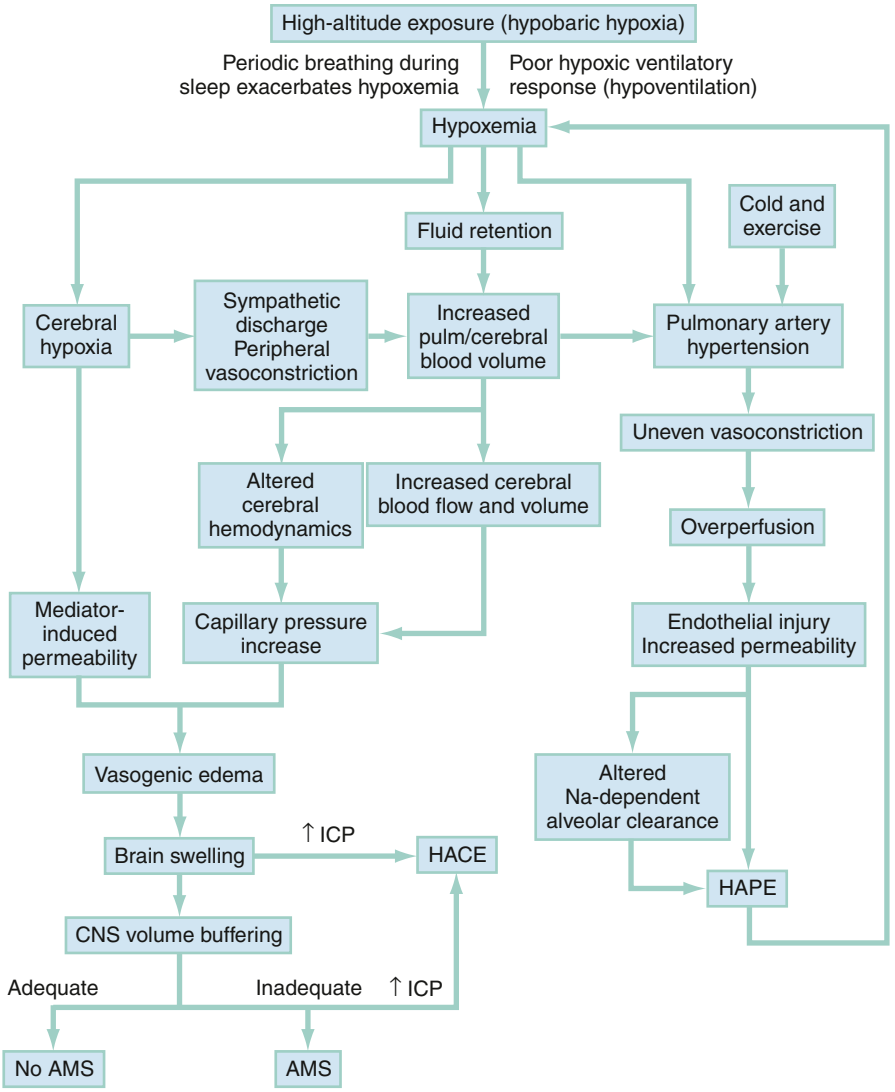

Fig. 132.2 Flowchart of proposed mechanisms for the development of acute mountain sickness *(AMS),* high-altitude pulmonary edema *(HAPE),* and high-altitude cerebral edema *(HACE). CNS,* Central nervous system; *ICP,* intracranial pressure.

and HACE result from the combined effects of altered cerebral hemodynamics and inflammatory mediators. Within minutes of exposure to hypoxia, cerebral vasodilation occurs with increased arterial blood velocity and volume. Hypocapnia (secondary to increased ventilation) creates a countervailing cerebral vasoconstriction, however, the overall effect is one of increased cerebral blood flow. Given the rigid confines of the skull, increases in intracranial blood volume require compensatory changes in the brain and cerebral spinal fluid or intracranial pressures will increase. CNS hypoxemia leads to impaired vascular autoregulation, causing increased pressures within the brain's capillary beds. In addition, systemic hypertension from strenuous exercise at high altitude may overwhelm the brain vasculature, resulting in transcapillary leakage and vasogenic edema. In susceptible individuals, these hemodynamic changes are likely to contribute to clinical manifestations of AMS and HACE.

Additional circumstances, however, may be necessary for the development of vasogenic edema and clinical symptoms. Inflammatory mediators may contribute to edema formation. Vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, mitochondrial dysfunction, and free radical formation may alter brain endothelial permeability. The roles that these play in the pathophysiologic process of altitude illness remain unclear.

The role of vasogenic edema in AMS is still under investigation. Magnetic resonance imaging (MRI) of subjects acutely exposed to hypoxia reveal similar signal changes in both subjects with and without clinical AMS. In patients with HACE, MRI studies reveal characteristic white matter changes consistent with vasogenic edema that correlate with symptoms. Although still an area of active research, AMS and HACE pathophysiology is likely due to disturbances in the blood-brain barrier through a combination of mechanical factors and biochemical mediation of permeability.

In severe AMS, MRI studies have revealed cytotoxic edema to present. Rather than being the primary mechanism of severe AMS or HACE, this cytotoxic edema is likely secondary to increased cell ischemia resulting from initial hemodynamic changes, vasogenic edema, biochemical mediators, and increased ratios of brain volume to intracranial space. Increasing data highlight the independent role of hypobaria in the development of AMS and on physiologic responses, including heart rate.[4] In experiments where subjects are exposed to identical levels of alveolar oxygen deprivation, subjects exposed to

normobaric hypoxia (by decreasing fraction of inspired oxygen [Fio_2]) alone have much lower AMS incidence than subjects exposed to a hypobaric hypoxia.

The "tight fit" hypothesis was proposed more than three decades ago to explain AMS development and its inherent individual susceptibility. This theory suggests that individuals are more susceptible to AMS and HACE as their ability to accommodate increased hypoxia-related intracranial blood volume and cerebral edema decrease. As brain volume increases from increased cerebral blood volume, the volume-buffering capacity of the central nervous system may prevent an immediate rise of intracranial pressure. As brain volume increases, the intracranial cerebrospinal fluid (CSF) is displaced through the foramen magnum into the spinal canal. Increased absorption of CSF by the arachnoid villi and decreased CSF production also occur. Individuals with less intracranial and intraspinal CSF buffering capacity have less compliance, and so experience larger increases in intracranial pressure, and become more symptomatic (i.e., manifested as AMS) from mild brain swelling. The tight fit hypothesis is supported by lumbar puncture, MRI, and computed tomography (CT) studies. More recently, optic nerve sheath ultrasonography has emerged as an early, noninvasive diagnostic tool to assess intracranial pressure. Increasing intracranial pressure correlates directly with optic nerve sheath diameter (ONSD). Studies have demonstrated that elevated intracranial pressure is associated with AMS and HACE.

ACUTE MOUNTAIN SICKNESS

Clinical Features

AMS is a clinical diagnosis. As defined by the Lake Louise Criteria, the diagnosis of AMS requires a patient to have recently ascended to an elevation to 8000 feet, with report of a headache *plus* at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, or dizziness or lightheadedness (Box 132.2).[5] The headache may vary from mild to severe, is generally bitemporal and throbbing in nature, and is worse during the night and on awakening or when suddenly becoming upright. Anorexia and nausea, with or without vomiting, are common, and the other symptoms described can range in severity from mild to incapacitating. The disturbance of sleep caused by periodic breathing is common in all visitors to high altitudes but may be exacerbated in the setting of AMS. The symptoms of AMS develop within a few hours after arrival at high altitude and generally reach maximum severity between 24 and 48 hours, followed by a gradual resolution. Most individuals become symptom-free by the third or fourth day. Patients with continued symptoms should not ascend until symptoms abate, and descent and alternative diagnoses should also be considered.

BOX 132.2 Acute Mountain Sickness

Incidence: 12% to 67%, varies widely with elevation, rate of ascent, and individual susceptibility; rare below 8000 feet, most common with rapid ascent to altitudes above 10,000 feet.

Symptoms and signs: Headache, anorexia, nausea, fatigue, dizziness.

Treatment: Mild cases are usually self-limited and do not require treatment; discontinue ascent, rest. For moderate cases, administer acetazolamide; ibuprofen, aspirin, or acetaminophen for headache; Zofran or prochlorperazine for nausea; supplemental oxygen if available; descend if persistent or severe; add dexamethasone in severe cases.

Prevention: Gradual ascent to allow acclimatization; high-carbohydrate diet, avoidance of ethanol or smoking; acetazolamide if ascent is rapid or known history of recurrent acute mountain sickness (AMS).

Given its subjective nature, AMS is difficult to definitively diagnose in infants and pre-verbal children. AMS may be manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance. Although AMS, or a change in environment, sleeping accommodation, or eating habits may result in a fussy, unhappy child, the differential diagnosis for these nonspecific findings must remain broad. If occult bacteremia or another serious illness is suspected in a young child, descent to lower altitude for an appropriate diagnostic and treatment regimen is recommended.

Differential Diagnoses

AMS is a clinical diagnosis without objective diagnostic physical findings, therefore a broad differential diagnosis when treating these nonspecific symptoms is prudent (Box 132.3). Less common, but lethal etiologies of headache, nausea, and fatigue must be considered before the relatively benign diagnosis of AMS is made. Any evidence of ataxia or altered mentation suggests HACE or other malignant etiology and mandates immediate descent. Benign focal neurologic findings and transient global amnesia have been described at altitude but should be assumed to be malignant in etiology until proven otherwise. Acute carbon monoxide (CO) poisoning should also be considered in high-altitude settings and is most commonly detected in poorly ventilated shelters near campfires, stoves or gas-powered generators used for heat, cooking, and fuel. Physiologically, when coupled with hypobaric hypoxia, carbon monoxide exposure is more dangerous in cold high-altitude locations than in other environments. Although dyspnea on exertion is universal and expected at high altitudes, dyspnea at rest suggests HAPE and warrants a careful examination for pulmonary edema.

Diagnostic Testing

Serial measurement of ONSD using ultrasound has demonstrated that subjects with symptoms and signs of worsening AMS or HACE have enlarged ONSDs on serial measurements, which may prove a useful adjunct in the diagnosis and monitoring of AMS and HACE (Fig. 132.3). Given significant individual variability in ONSD, isolated ONSD ultrasonography at a single point in time has little utility in the diagnosis of AMS.

Management

Patients with AMS should not ascend to a higher sleeping altitude until symptoms resolve to allow acclimatization to occur. Continued ascent exacerbates the underlying pathologic processes and may lead to severe AMS or lethal HACE. If patients develop neurologic abnormalities

BOX 132.3 Acute Mountain Sickness Differential Diagnosis

- Tension headache
- Viral syndrome
- Alcohol intoxication/toxidrome
- Carbon monoxide (CO) poisoning
- Dehydration
- Caffeine withdrawal
- Migraine headache
- Infectious (meningitis, encephalitis/viral syndrome)
- Intracranial hemorrhage or mass
- Central nervous system aneurysm
- Venous sinus thrombosis
- Abdominal process (e.g., gastroenteritis)
- Acute angle closure glaucoma/ocular process

Fig. 132.3 Diagnostic image of optic nerve sheath ultrasonography. (A) Probe positioning: This study is typically performed with the subject supine and with eyes closed. The probe is placed on the closed lid, lateral of the center of the pupil, and adjusted until a longitudinal, cross-sectional image of the optic nerve (deep to the retina) is obtained. For clarity, this figure does not show the use of ultrasound gel, occlusive dressing, or a high-frequency (7- to 10-MHz) linear probe. (B) Optic nerve sheath ultrasonogram with measurements. (Courtesy N. Stuart Harris, MD.)

(e.g., ataxia or altered mentation) or evidence of severe pulmonary edema, immediate descent is indicated.[6]

Mild AMS may be treated by symptom management and cessation of ascent until acclimatization occurs. This may take 1 to 4 days. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention necessitates descent. A descent of as little as 500 feet may be sufficient. Descent of 1500 to 3000 feet effectively reverses high-altitude illness in most cases. Descent should be continued until symptom improvement is seen, and efforts to minimize exertion should be instituted during the descent.[7]

Oxygen Therapy

All forms of altitude illness, including AMS, are effectively treated with supplemental oxygen. In mild AMS, supplemental oxygen may be helpful but is not essential. For severe forms of altitude illness, oxygen can be lifesaving. In resort settings, oxygen can often be rented directly from the hotel or condominium. For AMS, low flow oxygen (1 to 2 L/min), including small amounts during sleep, is often sufficient. In the wilderness, oxygen tanks are cumbersome, heavy, and are usually unavailable in adequate quantities. To overcome this, remote clinics often use solar-powered oxygen generators. In resource-limited settings, oxygen therapy is reserved for the more serious manifestations of high-altitude illness. Hyperbaric therapy with a portable fabric chamber that simulates descent is also effective.

Analgesics and Antiemetics

Symptomatic treatment of headache and nausea can be beneficial during the course of mild AMS. Aspirin, ibuprofen, and acetaminophen are useful for the treatment of high-altitude headache. Narcotic analgesics should be avoided because of depression of the hypoventilation response (HVR) and respiratory drive during sleep. For nausea and vomiting, prochlorperazine, unlike other antiemetics, stimulates the HVR and is preferred.

Acetazolamide

Periodic breathing causes insomnia, which is best treated with the respiratory stimulant acetazolamide.[8] Doses of acetazolamide as low as 62.5 mg to 125 mg bid may prevent intermittent breathing and eradicate insomnia.[9] Most benzodiazepines and other sedative-hypnotics should be avoided because of their tendency to decrease ventilation during sleep. Even individuals who have previously used diazepam at lower altitudes without difficulty describe unusual reactions, including agitation, hallucinations, and disorientation when this agent is used at high altitude. Studies suggest that low doses of benzodiazepines in combination with acetazolamide are safe at high altitude and can improve sleep quality and reduce episodes of nocturia without increasing oxygen desaturation. Nonbenzodiazepine sleep agents (such as zolpidem and zaleplon) do not depress ventilation and may prove useful in AMS-related insomnia.

Acetazolamide accelerates acclimatization and, if given early in the development of AMS, may rapidly resolve symptoms. Although the optimal dose has not yet been definitively established, a dose of 250 mg of acetazolamide at the onset of symptoms and repeated twice daily is effective therapy for AMS. The treatment of AMS in children is not formally studied, but anecdotal experience supports the use of acetazolamide in children. The dose for children is 2.5 mg/kg/dose every 6 to 8 hours or 125 mg given twice daily to a maximum of 250 mg.

Acetazolamide has myriad beneficial effects. By acting as a carbonic anhydrase inhibitor, it enhances renal bicarbonate diuresis and so improves renal correction of the ventilation-related respiratory alkalosis by causing continued increased ventilation and arterial oxygenation. It improves sleep by decreasing nocturnal period breathing. Acetazolamide also acts as a diuretic and so attenuates fluid retention common in patients with AMS. It lowers CSF volume and pressure, which may play an additional role in its therapeutic effect. In addition, it has positive effects beyond its role as a carbonic anhydrase inhibitor, with beneficial chemoreceptor effects on ventilatory drive, alterations of cerebral blood flow, relaxation of smooth muscles, and upregulation of fluid resorption in the lungs.

The most common adverse reactions to acetazolamide are paresthesias and polyuria. Less common reactions include nausea, diarrhea, drowsiness, tinnitus, and transient myopia. Carbonic anhydrase inhibition at the tongue causes dysgeusia, altering the flavor of carbonated beverages, including carbonated beers (of note, nitrogenated beers are unaffected). Acetazolamide is a sulfa compound and carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics. Patients with known sulfonamide allergy may consider administration of a trial dose of acetazolamide in a controlled environment before ascent. Acetazolamide is contraindicated in patients with a history of anaphylaxis or severe skin reactions to any sulfa-containing medication, and it should be avoided in breast-feeding mothers and pregnant women.

Dexamethasone

Dexamethasone is an effective alternative treatment of moderate to severe AMS. An initial dose of 8 mg followed by 4 mg every 6 hours is recommended. As a treatment option, concurrent use with acetazolamide is advocated by some to promote acclimatization. Dexamethasone is known to have antiinflammatory properties. Additionally, it may reduce cerebral blood flow and block the action of vascular endothelial growth factor. Reduction of AMS symptoms with the use of dexamethasone may be the result of these or its euphoric effects. Prophylactic use of dexamethasone should generally be reserved for use in individuals forced to rapidly ascend (e.g., professional mountain search and rescue operations). Although dexamethasone effectively relieves the symptoms of AMS, unlike acetazolamide, it does not enhance acclimatization. If used as a prophylactic agent to allow ascent beyond physiologic acclimatization, acute cessation can result in rapid onset of severe altitude illness. For treatment, use should be limited to patients with acetazolamide intolerance or more advanced cases of AMS, especially to help facilitate descent. Common side effects of dexamethasone include gastrointestinal irritation, gastritis, esophagitis, altered mood, and gastroesophageal reflux disease (GERD). Dexamethasone should not be used for more than 3 days for this indication because more serious side effects such as GI bleed and altered mental status with aberrant behavior have been described.

Disposition

Individuals with AMS may resume their ascent after symptoms resolve. Consider prophylactic acetazolamide if they are to further ascend. Further elevation gain should be halted if symptoms recur.

Prevention

The symptoms of mild AMS are generally benign and well-tolerated. For some, however, they are unpleasant and debilitating to the point that travel, business, or vacation plans are interrupted. Up to 50% of individuals with AMS report a decrease in activity.

The best method of prevention is a gradual or staged ascent that allows adequate time for acclimatization; however, the time constraints of many vacationers and inexperienced guides often make such an ascent profile unrealistic. The 19th-century climbing adage, "Climb high, sleep low," is born of experience: during acclimatization, hypoxic nadirs encountered during sleep are much greater than those during waking hours. Decreased respiratory drive during sleep can lead to increasing symptoms of poor acclimatization. Ideally, the first night should not be spent at an altitude higher than 9200 feet, with a subsequent increase (to a new sleeping altitude) of not more than 1600 feet each night. One extra night of acclimatization (at the same sleeping altitude) should be added for every 3000 to 5000 feet of altitude gain above 10,000 feet. Excursions to higher altitudes during the day with a return to a lower sleeping altitude aid in successful acclimatization.

Pre-exposure to artificially hypoxic environments to prompt acclimatization and to decrease symptoms of high-altitude illness have been studied. Pre-exposure regimens (typically in normobaric, hypoxic tents) lasting less than 8 to 12 hours appear to offer limited protection from subsequent altitude exposure.

Mild to moderate exercise likely aids acclimatization; however, overexertion can contribute to the development of AMS. Maintaining adequate hydration—targeting relatively clear (dilute) urine and normal urine output—is also recommended. No data support recommendations for hyperhydration that is sometimes promoted in the lay literature. In fact, consumption of excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness. Balanced electrolyte solutions are recommended (premixed or prepared with purified water).

The elevation goal, rate of ascent, and prior history of altitude illness should be considered in the assessment of the risk for development of altitude illness and the choice of prevention strategies (eTable 132.1). Individuals in low-risk situations should not need medications for prophylaxis. Ascent should be gradual to prevent illness. In some cases, such as arrival at a high-altitude airport (e.g., Lhasa, Tibet, 11,995 ft) or the immediate dispatch of rescue personnel to high altitude, a slow or staged ascent is not possible. Mountain climbers commonly ascend at rates that are higher than recommended, and some individuals continue to suffer AMS symptoms despite gradual ascent. Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical fall into the moderate- and high-risk categories and should consider prophylactic medication in addition to gradual ascent.

Numerous studies demonstrate the effectiveness of acetazolamide in prevention of AMS in adults. Lower dosages provide prophylaxis similar to that of higher dosages with fewer adverse reactions. A dose of 125 mg twice daily starting 24 hours before ascent and continuing for the first 2 days at high altitude is effective. When compared with higher doses, this dose has a lower likelihood of noxious side effects. Although it is unstudied, the recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose up to 125 mg total given twice daily, and this weight-based approach may reduce side effects in smaller adults. Ibuprofen compared with acetazolamide is equally efficacious in preventing headache.

Dexamethasone also prevents AMS. The lowest effective prophylactic dosage is 2 mg every 6 hours or 4 mg every 12 hours. Some patients experience the rapid onset of AMS after dexamethasone is discontinued. Dexamethasone does not facilitate acclimatization but rather reduces nausea and enhances mood. In most cases, dexamethasone use should be reserved for treatment of AMS rather than for prophylaxis. Military or rescue personnel rapidly ascending to high altitude and individuals with acetazolamide intolerance are candidates for prophylaxis with dexamethasone. The combination of acetazolamide and dexamethasone may be more effective than either drug alone.

Oxygen is an effective prophylactic modality for rescue personnel. Adequate supplies should be available to ensure the safety of all team members for the entire duration of the rescue. Air drops of oxygen can be lifesaving when weather or terrain prevents the immediate arrival of rescue personnel.

HIGH-ALTITUDE PULMONARY EDEMA

Clinical Features

HAPE is the most common fatal manifestation of severe high-altitude illness (Box 132.4). Although HAPE is uncommon below 10,000 feet, it can occur and even be fatal at altitudes below 8000 feet. Episodes occurring between 8000 and 10,000 feet are usually related to heavy exercise or comorbidities; but at higher altitudes, pulmonary edema can also occur at rest or with light activity.

Some individuals are susceptible and experience HAPE with each ascent to altitude, but many patients have a single episode of HAPE and subsequently are able to return to high altitude without a recurrence. Less commonly, those with multiple previously uneventful high-altitude exposures may still develop HAPE. Individuals, especially children and young adults, who have been residents at high-altitude locations for extended periods may have pulmonary edema develop on re-ascent from a trip to low altitude. This phenomenon has been termed *reentry HAPE*.

The initial symptoms of HAPE typically begin insidiously 2 to 4 days after arrival at high altitude. Most cases occur during the second night, but HAPE may develop rapidly, with early symptoms apparent after

ETABLE 132.1 Risk Categories for Acute Mountain Sickness[a]

Risk Category	Description
Low	Individuals with no prior history of altitude illness and ascending to ≤9200 feet
	Individuals taking ≥2 days to arrive at 8200 to 9800 feet with subsequent increases in sleeping elevation <1600 feet per day
Moderate	Individuals with prior history of AMS and ascending to 8200 to 9200 feet in 1 day
	No history of AMS and ascending to >9200 feet in 1 day
	All individuals ascending >1600 feet per day (increase in sleeping elevation) at altitudes above 9800 feet
High	History of AMS and ascending to ≥9200 feet in 1 day
	All individuals with a prior history of HAPE or HACE
	All individuals ascending to >11,500 feet in 1 day
	All individuals ascending >1,600 feet per day (increase in sleeping elevation) above >11,500 feet
	Very rapid ascents

[a]Altitudes listed in the table refer to the altitude at which the person sleeps. Ascent is assumed to start from elevations <4000 feet. The risk categories described pertain to unacclimatized individuals.
AMS, Acute mountain sickness; *HACE,* high-altitude cerebral edema; *HAPE*, high-altitude pulmonary edema.
Modified from: Luks AM, et al. Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness: 2019 update. *Wilderness Environ Med.* 2019;30(4S):S3eS18.

BOX 132.4 High-Altitude Pulmonary Edema

Incidence: 0.01% to 15%, varies with elevation and rate of ascent; rare below 8000 feet and more common above 14,500 feet; typically occurs 2 to 4 days after arrival at high altitude.

Symptoms and signs: Dyspnea at rest, cough, anorexia, cyanosis, rales, tachypnea, tachycardia.

Treatment: Patients with mild cases may recover with bed rest. Moderate cases can be treated with bed rest and supplemental oxygen if clinical monitoring is available. Severe cases require oxygen and descent; use hyperbaric therapy if available; if oxygen or descent is unavailable, then nifedipine 30 mg slow-release every 12 hours; consider acetazolamide (125–250 mg every 12 hours) and tadalafil 10 mg every 12 hours (limited data).

Prevention: Gradual ascent and recognition of early AMS symptoms so that ascent is stopped before HAPE develops; with previous HAPE history, use nifedipine 30 mg slow-release every 12 hours during ascent, then continue for 3 days (monitor for hypotension).

AMS, Acute mountain sickness; *HAPE,* high-altitude pulmonary edema.

just a few hours at high altitude. Marked dyspnea on exertion, fatigue with minimal-to-moderate effort, prolonged dyspneic recovery time, and dry cough are early manifestations of the disease. The symptoms of AMS usually occur concurrently with the development of HAPE.

As the HAPE patient deteriorates, usually through the night, the dyspnea intensifies with effort and is unrelieved by rest. Dyspnea at rest is a red flag warning. The cough may become productive of copious amounts of clear, watery sputum. Hemoptysis may be seen in severe cases. As the condition intensifies, cerebral edema or simply severe hypoxemia may cause central nervous system dysfunction, such as ataxia and altered mentation. Coma may follow and precede death in a few hours if immediate oxygen therapy and descent are not instituted.

The physical examination reveals a few rales in patients with mild HAPE, usually found in the region of the right middle lobe, progressing to unilateral or bilateral rales and then to diffuse bilateral rales, rhonchi, and gurgles audible without a stethoscope. Neck veins are not distended. Cyanosis of the nail beds alone may progress to severe central cyanosis. Tachypnea and tachycardia become more pronounced as severity increases. Elevated temperatures are common, and a concurrent respiratory tract infection is occasionally seen, especially in children.

Differential Diagnoses

It is prudent to maintain a wide differential diagnosis in assessing patients with acute dyspnea at high altitude (Box 132.5). Although HAPE occurs at high altitude, so does acute coronary syndrome, pulmonary embolism (PE), congestive heart failure (CHF), and pneumonia.

Pneumonia can be misdiagnosed in the setting of HAPE because the symptoms and signs of pneumonia are similar to those of HAPE. The incidence of pneumonia and the common organisms responsible for pneumonia at high altitude are understudied, but visitors to high altitudes may be predisposed to acquire bacterial infections because of impaired T-lymphocyte function. Treat patients for HAPE who present with symptoms compatible with pneumonia at high altitude. Initiate antibiotics if there is doubt about the diagnosis of HAPE versus pneumonia. Because of decreased respiratory reserves and mild immunosuppression coincident with high-altitude exposure, the treatment of any serious pulmonary infection at high altitude requires oxygen, descent, and antibiotics.

BOX 132.5 High-Altitude Pulmonary Edema Differential Diagnoses

- Carbon monoxide (CO) poisoning
- Pneumonia
- Pneumothorax
- Pleural effusion
- Pulmonary embolism (PE)
- Acute coronary syndrome
- Acute congestive heart failure (CHF)
- Acute exacerbation of preexisting pulmonary hypertension
- Acute flare of chronic obstructive pulmonary disease (COPD)
- Acute asthma flare
- Acute exacerbations of valvular disease (insufficiency and stenosis)

High-altitude bronchitis ("Khumbu cough") and pharyngitis are common problems among climbers. They may result from the increased ventilation of cold, dry air across the upper airway mucosa, causing mucosal inflammation. Copious sputum production is sometimes seen, and antibiotic therapy is rarely helpful. Coughing spasms may be severe and require treatment with antitussives. Other therapeutic measures include hydration, lozenges, and steam inhalation.

Death from PE at high altitude is described. Given frequent travel involving long plane flights prior to many vacations at high altitude, patients may often have increased risk of deep vein thrombus (DVT) and PE. Additional predisposing factors for DVT include acute hyperviscosity due to increased hematocrit, dehydration, and forced stasis due to sleeping and sheltering in confined spaces, particularly during inclement weather conditions. The symptoms and signs of PE can mimic those of HAPE; however, embolic disease tends to have a more rapid onset, and pleuritic chest pain is a more prominent feature.

Diagnostic Testing

Ultrasonography

Ultrasound machines are portable, require limited training for effective use in this setting, and use non-ionizing radiation. As a result, serial assessments can easily be performed to gauge response to treatment. Given their portability, limited power requirements, and instant access to diagnostic data, they are the preferred modality for many remote clinical settings.

Thoracic ultrasonography allows rapid, accurate assessment for acute pulmonary edema at the bedside (Fig. 132.4). The presence of "lung comet tails" (also called *B-lines*) on thoracic ultrasound indicates extravascular water, is reproducible, quantifiable, and has been inversely correlated with oxygen saturation and clinical status in HAPE patients. The use of ultrasonography to estimate pulmonary artery pressure is an established modality for early detection and diagnosis of HAPE. Demonstration of high pulmonary artery pressures with normal left ventricular function is associated with HAPE and HAPE susceptibility.

Chest Radiographs

In HAPE patients, chest films reveal patchy alveolar infiltrates with areas of clearing between the patches. Unilateral infiltrates may be present in mild cases; however, bilateral infiltrates are seen in more advanced cases, most commonly involving the right mid-lung fields (Fig. 132.5). Pleural effusion is rare but may be present in severe cases. The extent of the edema on the chest radiograph roughly parallels the clinical severity. Of note, the radiographic findings of cardiomegaly, bat-wing distribution of infiltrates, and Kerley B-lines, which are typical of cardiogenic pulmonary edema, are generally absent in cases of HAPE.

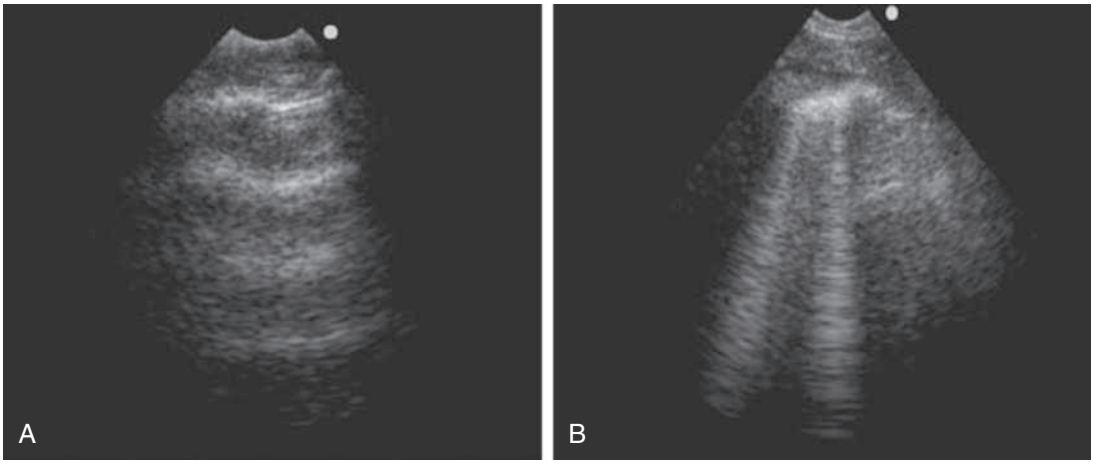

Fig. 132.4 Diagnostic image of thoracic ultrasound of lung with high-altitude pulmonary edema (HAPE). (A) Normal lung tissue is uniform "snowstorm." (B) B-lines, also known as "comet tails," are present in this patient with HAPE. They are defined as echogenic, coherent, wedge-shaped signals with a narrow origin in the near field of the image, arising from the pleural line and extending to the edge of the screen. B-lines indicate pulmonary interstitial fluid (edema). Views obtained using *low* frequency, curved probe and B-mode imaging. (Courtesy American College of Chest Physicians.)

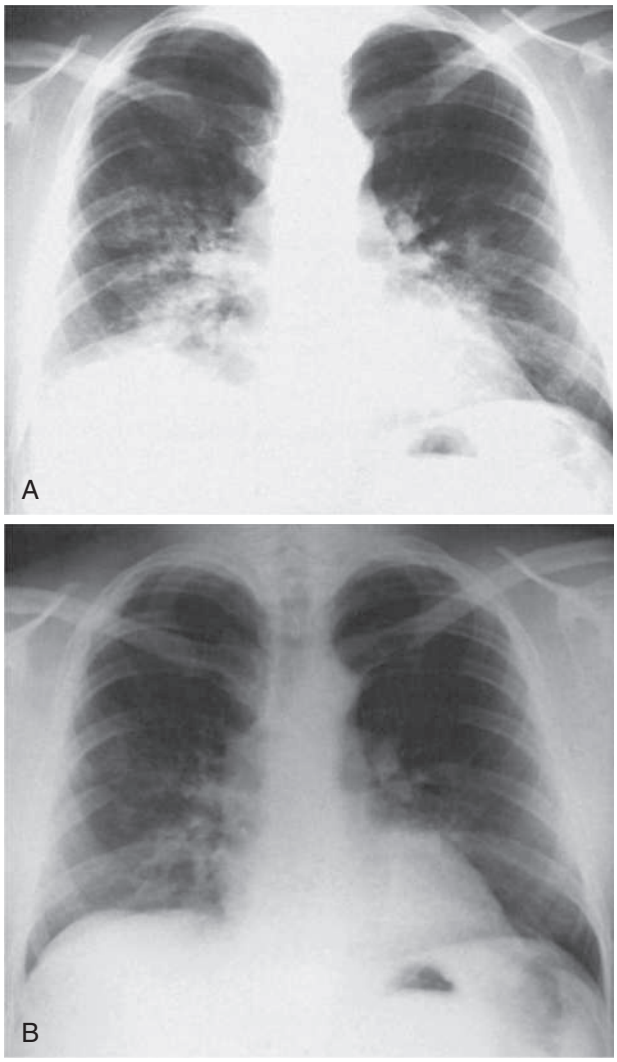

Fig. 132.5 Diagnostic image of chest radiograph of a patient with high-altitude pulmonary edema (HAPE). (A) Before treatment. (B) After treatment. (Courtesy Richard Nicholas, MD.)

Radiographic evidence of HAPE clears rapidly after initiation of treatment; some mild cases may clear in 4 to 6 hours, and most clear by 24 hours. Radiographs of patients with severe HAPE may reveal infiltrates that persist for as long as 2 weeks, even though the clinical symptoms have resolved.

Electrocardiogram and Echocardiogram

An electrocardiogram reveals tachycardia and evidence of right-sided heart strain, including right axis deviation, P wave abnormalities, tall R waves in the precordial leads, and S waves in the lateral leads. Hemodynamic studies reveal increased pulmonary vascular resistance, elevated pulmonary artery pressures, and normal pulmonary wedge pressures. Echocardiographic studies demonstrate high estimated pulmonary artery pressures, pulmonary vascular resistance, and normal left ventricular function.

Management

Descent

In remote settings, where oxygen and medical expertise may be unavailable, immediate descent to treat HAPE may be lifesaving. Delay of descent (e.g., waiting hours for rescue personnel to initiate evacuation) can lead to rapid HAPE progression and death. Descents of 3000 feet are generally adequate for a rapid recovery; however, descent should continue until symptoms resolve.

Oxygen Therapy

To minimize cold- or exercise-induced pulmonary hypertension, HAPE patients should be kept warm and should minimize exertion (Fig. 132.6). Patients with mild cases of HAPE under expert supervision have been successfully treated at altitude with oxygen, medications, and 1 or 2 days of bed rest. Oxygen administration increases the rate of improvement. Moderate cases can be treated without descent if bed rest, experienced providers, and adequate supplies of supplemental oxygen are available. Any treatment plan that does not include descent necessitates serial examinations by clinicians with experience in management of high-altitude illness.

If difficult terrain or weather conditions hamper efforts to descend, oxygen administration (or hyperbaric therapy) can be a lifesaving measure. If immediate evacuation to lower altitudes

Fig. 132.6 Clinical photograph of high-altitude pulmonary edema (HAPE) patient being treated with immediate descent in rural Nepal. Patient is provided with oxygen and descending with minimal exertion. (Courtesy Lara Phillips, MD.)

will be delayed, rescue personnel should air drop oxygen supplies. Deliver oxygen at rates of 6 to 8 L/min by mask to victims with severe HAPE until clinical improvement is seen. As patients improve, flow rates can then be lowered until recovery or descent is completed with a goal peripheral oxygen saturation greater than 90% likely sufficient. Delivery of oxygen with a continuous positive airway pressure mask will decrease work of breathing and improve alveolar fluid clearance.

Hyperbaric therapy simulates descent by increasing the available oxygen at a given altitude, as the amount of oxygen available is a function of the percentage of inspired oxygen multiplied by the barometric pressure. Although preferred with oxygen, if supplies are low, hyperbaric therapy may be employed without administration of supplemental oxygen. Several portable, lightweight (approximately 15 pounds), fabric hyperbaric chambers are available. They are pressurized manually (Fig. 132.7) and generate approximately 103 mm Hg (2 psi) above the ambient pressure. This simulates a descent of 4000 to 5000 feet at moderate altitudes, and at the summit of Mt. Everest it would simulate a descent of approximately 9000 feet. These devices can be lifesaving in patients with HAPE and HACE. They should only be used as a temporizing treatment when descent is not immediately feasible. Some previously nonambulatory patients are able to descend under their own power after a few hours of treatment in these hyperbaric chambers.

Most of the pharmacotherapies used for HAPE treatment derive their presumed efficacy from studies examining their abilities to prevent HAPE in a "HAPE-susceptible" subject population. There are few robust studies directly examining pharmacologic treatments for HAPE. Oxygen and descent remain the mainstays in treatment.

Fig. 132.7 Clinical photograph of Gamow bag, a lightweight, portable hyperbaric chamber used for rapid treatment of severe altitude illness. Note the attached foot-operated pressure pump. (Courtesy Reuben Tabner.)

Nifedipine

In addition to oxygen and descent to treat HAPE, medications that lower pulmonary artery pressure, pulmonary blood volume, and pulmonary vascular resistance or enhance alveolar fluid clearance may be useful adjuncts. Unlike pulmonary edema secondary to acute CHF, HAPE results from increased pulmonary vascular tone. It does not result from excessive intravascular volume or failed cardiac pump function. As such, diuretic therapy has no role in the treatment of HAPE and may further exacerbate volume loss in patients who are already intravascularly depleted.

One of the better studied agents for both prophylaxis and treatment of HAPE is the calcium channel blocker nifedipine. Acting as a pulmonary vasodilator, nifedipine is especially useful when oxygen is not readily available or descent is impossible. Nifedipine does not improve pulmonary hemodynamics as much as oxygen or descent do, and it does not have an additive effect when it is administered with oxygen. Treatment with 30 mg of a slow-release nifedipine preparation administered twice daily is recommended. Patients should be monitored for the development of hypotension during nifedipine administration.

Other Medications

Although phosphodiesterase type 5 inhibitors (including tadalafil and sildenafil) are known to be useful for HAPE prevention, are widely used, and are unlikely to cause acute harm in this indication, they remain unstudied for HAPE treatment. Alveolar fluid clearance is upregulated by beta-adrenergic agonists in animal models, and inhaled beta-agonists (salmeterol 125 μg inhaled twice daily) have been used anecdotally for therapy of HAPE.

The mainstay of HAPE treatment remains immediate oxygen administration (when available) and descent. Nifedipine treatment is recommended if these treatments are unavailable. No compelling evidence suggests the concurrent use of these medications with oxygen has additional benefit beyond the use of oxygen alone.

Disposition

Mild to moderate cases of HAPE can be treated with oxygen, rest, and careful monitoring. Experienced clinicians in recreational areas at moderate altitudes (e.g., Colorado ski resorts or dedicated high-altitude clinics in Nepal) administer oxygen and observe HAPE patients to ensure adequate oxygenation. These patients are then discharged to their local lodging with supplemental oxygen and monitored for improvement or deterioration. In severe HAPE, or milder cases that do

not improve with therapy, descent is warranted. Rapid recovery is usually seen after descent to lower altitudes, and observation of the patient in the emergency department to ensure adequate room air oxygenation is generally adequate. On occasion, admission to the hospital is indicated to maintain the Sao_2 greater than 90%. In the hospital, continuous positive airway pressure may improve gas exchange and decrease work of breathing in HAPE patients. Hypocapnia, alkalosis, and radiographic evidence of HAPE may persist for several days. Thoracic ultrasound allows for frequent reassessments and has been shown to closely follow resolving edema and increasing oxygen saturations.

If oxygen saturation can be maintained at greater than 90% on room air and clinical improvement is apparent, the patient can be discharged. If the patient requires air travel to return home (cabin pressures equal approximately 8000 feet), additional recovery time before travel or arrangement for supplemental oxygen administration is advised. Assessment for structural cardiac abnormalities with echocardiography is indicated if a heart murmur is detected in a patient with HAPE. An evaluation for underlying congenital heart disease is warranted after an episode of HAPE in a young child.[10]

Patients may be able to re-ascend (generally in 2 to 3 days) when symptoms resolve and oxygen levels remain acceptable off supplemental oxygen at rest and with mild exercise. Re-ascent with pulmonary vasodilator medication may be considered.

Prevention

As with all forms of serious altitude illness, two key teaching points are the most effective means of prevention and must be understood by the patient: (1) a gradual or staged ascent to allow sufficient time to acclimatize is critical, and (2) immediate cessation of further ascent at the onset of symptoms can be lifesaving. Individuals with a prior history of HAPE should also avoid extreme exertion during the first 2 days at altitude. Consider prophylactic therapy with nifedipine (30 mg extended release twice daily for 3 days) in patients with a prior history of HAPE. Less evidence exists to support the routine use of other pulmonary vasodilators for HAPE prevention.

Phosphodiesterase type 5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) have been found to be effective in preventing HAPE in HAPE-susceptible subjects. The phosphodiesterase type 5 inhibitors have the added benefit that they are less likely than calcium channel blockers to induce systemic hypotension. However, as with other indicated uses, they should not be administered to individuals concurrently taking nitroglycerin.

Although high-quality data are lacking, a few additional medication options may be considered for prevention. Dexamethasone (8 mg every 12 hours) started 2 days before ascent may prevent HAPE. To enhance alveolar fluid clearance, salmeterol 125 μg inhaled twice daily may be used as an adjunct to nifedipine in patients with a history of HAPE, although side effects are common at this high inhaled dose. Finally, clinical experience suggests that acetazolamide aids in acclimatization and prevents HAPE, with additional benefits of reducing hypoxic pulmonary vasoconstriction.

HIGH-ALTITUDE CEREBRAL EDEMA

Clinical Features

HACE is the least common but most lethal form of high-altitude illness (Box 132.6). Death from HACE typically occurs above 12,000 feet. Mild AMS can progress to severe HACE with coma in as few as 12 hours. Although severe symptoms usually develop within 1 to 3 days, they may not occur until 5 to 9 days. HACE is characterized by evidence of global cerebral dysfunction. The symptoms of severe AMS (headache, fatigue, and vomiting) as well as those of HAPE (cough and dyspnea) are often present. Patients with HACE invariably have had prior, unheeded symptoms of worsening AMS over hours to days. HACE-specific signs include ataxia, slurred speech, and altered mental status, which can range from mild emotional lability or confusion, to hallucinations and worsening obtundation that may advance to coma and death. Less commonly, generalized seizures and rarely, focal neurologic deficits may occur. HACE can also occur in children.[11]

Altered mental status and cerebellar ataxia are the most sensitive signs of early HACE. The early appearance of ataxia reflects the particular sensitivity of the cerebellum to hypoxia. Ataxia alone is an indication for immediate descent. Retinal hemorrhages are common and rarely of clinical significance. Papilledema and occasionally cranial nerve palsy also occur in the setting of increased intracranial pressure.

BOX 132.6 High-Altitude Cerebral Edema

Incidence: Lower than 1% or 2%, uncommon as a pure entity; usually associated with the presence of severe AMS and HAPE.

Symptoms and signs: Ataxia, severe headache, nausea and vomiting, altered mentation, seizures, coma.

Treatment: Immediate evacuation to a lower altitude; oxygen, bed rest, dexamethasone (8 mg PO or IV, then 4 mg q6h). Hyperbaric therapy if unable to immediately descend.

AMS, Acute mountain sickness; *HAPE,* high-altitude pulmonary edema.

BOX 132.7 High-Altitude Cerebral Edema Differential Diagnoses

- Acute cerebral vascular accident (CVA)/transient ischemic attack
- Intracranial hemorrhage
- Hypoglycemia
- Carbon monoxide (CO) poisoning
- Meningitis/encephalitis
- Hypothermia
- Intracranial mass
- Vertebral/carotid dissection or stenosis
- Acute toxidrome—alcohol, other
- Acute alcohol withdrawal/delirium tremens
- Seizure
- Transient global amnesia

Differential Diagnoses

Paroxysmal onset of symptoms should prompt consideration of other etiologies, such as hypothermia, hypoglycemia, CO poisoning, and acute cerebral vascular accidents (CVAs) (Box 132.7). A cerebral vascular lesion is suggested by abrupt onset, presence of a dense hemilateral palsy, a lack of preceding symptoms of AMS, or the persistence of signs despite adequate treatment of high-altitude illness.

Diagnostic Testing

Without advanced imaging, differentiating between HACE and acute CVA may be difficult – regardless, both are acute neurologic emergencies. Although not common, the occurrence of cerebral thrombosis and transient ischemic attacks, in the absence of high-altitude illness, have been documented at high altitude. Subsequent MRI studies of patients with HACE reveals white matter changes consistent with vasogenic edema (Fig. 132.8).[12]

Management

Successful therapy for HACE requires early recognition and immediate descent. Administer high-flow oxygen, if available. Oxygen alone reduces intracranial blood flow at high altitude. Steroid therapy is recommended and may result in recovery from HACE without neurologic deficits. The initial dose of dexamethasone is 8 mg parenterally or orally in mild cases, followed by 4 mg every 6 hours.

Patients with severely altered levels of consciousness require tracheal intubation. Increase oxygenation, both by increasing Fio_2 and barometric pressure by descent or hyperbaric treatment. Hyperventilation, diuretics (e.g., furosemide), and hypertonic solutions (e.g., mannitol) have been used to manage severely elevated intracranial pressure, but extreme caution is warranted. Many patients with HACE are already volume depleted from poor fluid intake; diuretic use could compromise adequate intravascular volume and reduce cerebral perfusion pressure.

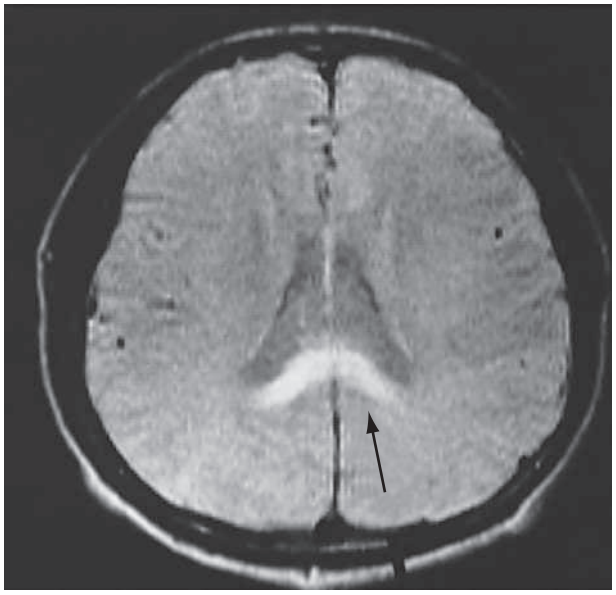

Fig. 132.8 Diagnostic image of axial proton-weighted magnetic resonance image of a mountain climber with high-altitude cerebral edema (HACE). The *arrow* demonstrates the markedly increased signal (edema) in the splenium of the corpus callosum. (Courtesy Peter Hackett, MD.)

Hyperbaric treatment of HACE is also effective and may result in temporary improvement and allow self-rescue and descent. Conversely, coma may persist for several days even after descent to lower altitudes.

Disposition

When safe and feasible, immediate descent is essential. If immediate descent to definitive care is an option, placing HACE patients in a hyperbaric device may only delay the more comprehensive care available in the hospital setting.

Long-term neurologic deficits including ataxia and cognitive impairment have been reported after recovery from acute episodes of HACE. Both transient and long-lasting neurobehavioral impairments can occur in mountaineers after climbing to extreme altitude without experiencing clinical HACE. Because of the potential for long-lasting neurologic injury, the clinician must maintain awareness of the early manifestations of HACE. Early treatment of HACE generally results in good outcomes, but after coma is present, the mortality rate exceeds 60%. Patients who have suffered HACE should be referred to a neurologist for further evaluation.

SPECIAL CONSIDERATIONS

High-Altitude Retinal Hemorrhage

High-altitude retinal hemorrhage (HARH) is the most common type of retinopathy in visitors to high altitude. These hemorrhages are common at altitudes above 17,500 feet, although they can occur at lower levels.

The exact incidence of HARH is unknown because most patients are asymptomatic, with HARH noted only on retinoscopy. HARH is not generally related to the presence of mild AMS but does seem to be related to strenuous exercise at high altitude. At any altitude, in the setting of severe HAPE or HACE, retinal hemorrhages are commonly noted, but the mechanism remains unclear.

Hemorrhages usually spare the macula (Fig. 132.9) and most often resolve without treatment in 2 or 3 weeks. With macular involvement, central scotomas may be noticed and only gradually resolve. In some cases, these visual defects are permanent. HARH is more likely to occur among individuals with a previous history of such hemorrhages and those on anticoagulation therapy. The underlying risk remains unclear. They usually do not pose a contraindication to return to high altitude unless the macular region is involved. Altitude related changes in intraocular pressure are not associated with AMS.

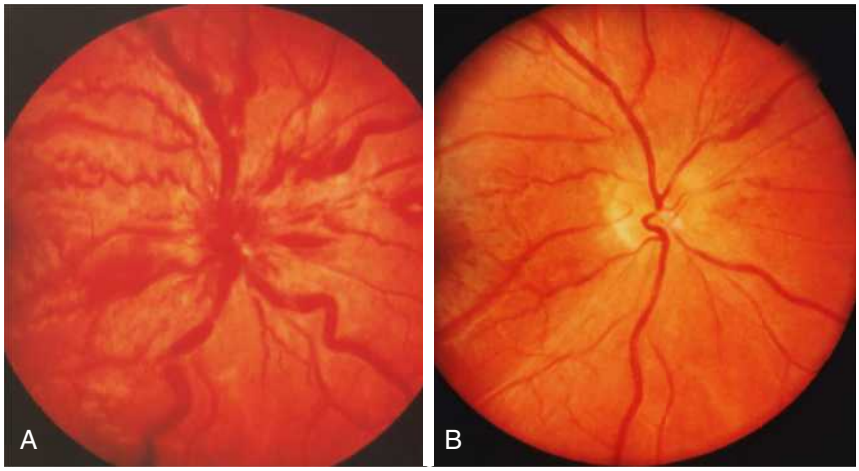

Fig. 132.9 Diagnostic image of high-altitude retinal hemorrhages (HARHs). (A) Acute. (B) After 1 week of resolution. (Courtesy Charles Houston, MD.)

Carbon Monoxide Poisoning

CO poisoning is not uncommon at altitude, typically from the use of fires and combustion stoves to keep warm or to prepare food in the high-altitude environment. CO poisoning at altitude can be more devastating because of preexisting hypobaria-induced hypoxia. As CO avidly binds to hemoglobin, it prevents oxygen transport and exacerbates tissue hypoxia. CO poisoning and AMS are clinically indistinguishable. If suspected, immediate removal of the patient from the potential CO source with assay of carboxyhemoglobin levels using cooximetry or lab testing is indicated. Importantly, empirical treatment with oxygen hyperbaria will benefit both conditions. If CO poisoning is suspected, test the patient's affected indoor space and assess other victims who may have been exposed. If testing is not available, the patient should not return to the enclosed space and should descend or use supplemental oxygen, if available.

ALTITUDE AND UNDERLYING MEDICAL CONDITIONS

Individuals with preexisting diseases such as sickle-cell disease, moderate to severe chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) may have a more difficult time acclimatizing, because these disease states can be aggravated by the hypoxic atmosphere at higher elevations. eBox 132.1 describes the risk associated with travel to altitude in individuals with a variety of underlying comorbidities.

Respiratory Illnesses

Travelers with COPD have underlying anatomic and physiologic changes that predispose them to development of hypoxemia, sleep apnea, pulmonary hypertension, and ventilation disorders at even moderate altitudes. COPD is a risk factor for the development of AMS. Although oxygen saturation remains more than 90% in a healthy, awake individual until an altitude of 8000 feet, patients with COPD may desaturate below 90% at lower altitudes. High altitude increases hypoxic pulmonary vasoconstriction and may potentiate the development of cor pulmonale, which is known to adversely affect survival at sea level. Individuals with chronic COPD should be advised of the potential need for oxygen supplementation when traveling to moderate altitude, especially if they are already using oxygen at sea level or if dyspnea or fatigue becomes worse. Use of a pulse oximeter can guide the need for increased oxygen supplementation.

Patients with asthma, on the other hand, may have fewer problems at altitude because of decreased ambient allergens and pollutants as well as decreased airflow turbulence. Even those with exercise-induced bronchospasm do not have worsening symptoms while exercising at 5000 feet. In addition, AMS incidence is not increased in asthmatics. People with asthma traveling to higher elevations should continue their usual medications and carry a rescue supply of bronchodilators and steroids.

Patients who ascend to high altitude with preexisting primary or secondary pulmonary hypertension are considered HAPE susceptible, and those with primary pulmonary hypertension are considered at increased risk for HAPE. Patients with known pulmonary hypertension should be advised against travel to higher elevations. If travel cannot be avoided, supplemental oxygen should be used. Prophylactic sustained release nifedipine, 30 mg twice daily for the duration of the stay at altitude, can decrease the risk of HAPE. Phosphodiesterase type-5 inhibitors and dexamethasone may also be used.

Cardiovascular

Individuals with a history of CHF, CAD, dysrhythmias, or coronary bypass surgery are infrequently studied in the high-altitude setting. In theory, people with diseased myocardium should avoid high altitude because of decreased environmental oxygen availability. No studies report increased mortality in visitors to these locations, however. To the contrary, long-term residents at high altitude may be protected from coronary artery disease (CAD) by increased collateral vessel formation or a decrease in the development of atherosclerosis.

All travelers have increased sympathetic activity on initial exposure to high altitude. In patients with heart disease, the resultant increase in heart rate and blood pressure increases cardiac work and myocardial oxygen consumption, which could increase angina symptoms and dysrhythmias. Although both cardiac rhythm abnormalities and ST segment and T wave electrocardiographic changes are reported, none of these changes are associated with clinical evidence of myocardial ischemia. Limited data suggest no increased risk for sudden cardiac death or myocardial infarction at altitudes up to 8000 feet in patients with asymptomatic CAD. When individuals with stable angina are exercised, there is conflicting evidence for the probability of inducing malignant dysrhythmias. Travelers with heart disease who ascend to moderate altitudes do not appear to have an increased incidence of AMS.

Travelers with mild stable CAD should be advised to ascend gradually, to limit activity especially in the first few days at elevation, and to continue anti-anginal and antihypertensive medications. Individuals who have more severe, symptomatic coronary disease or those in a high-risk group (low ejection fraction, abnormal stress test results, and high-grade ventricular ectopy) should avoid travel to high altitudes. Ascent to moderate elevations can be suggested on an individual basis with the previously mentioned precautions. Individuals with heart failure who travel to altitude may require increased use of diuretics to promote diuresis and acclimatization. Patients previously prescribed nitroglycerin should be instructed not to take phosphodiesterase type-5 inhibitors. Acetazolamide prophylaxis may be useful to speed acclimatization and to prevent AMS and its accompanying fluid retention.

Hypertension

High-altitude travel produces a rapid, mild increase in blood pressure and heart rate in healthy individuals because of increased sympathetic tone. This increase is maximal at 2 or 3 weeks, and returns to baseline values over time because of a downregulation of adrenergic receptors if one stays at high altitude or upon descent to sea level. No studies demonstrate an increased predisposition for altitude illness in patients with underlying hypertension.

The incidence of hypertension in sea-level dwellers traveling to high altitude is 10% to 25%. On travel from sea-level to low altitudes (3000 feet), no differences are noted in either normotensive or hypertensive individuals. Above 9800 feet, more significant increases may occur. This suggests that people with severe hypertension should travel to high altitude only under careful monitoring. For individuals who have mild preexisting hypertension, additional treatment is not routinely necessary. Monitor patients with moderate hypertension during the first few days at altitude and continue all antihypertensive medications. For hypertensive patients with a rapid rise in blood pressure who will be staying at altitude for several weeks, an alpha-blocker, nifedipine, or angiotensin-converting enzyme inhibitor are recommended agents to add to the patient's daily regimen.

Seizures

Numerous reports of altitude-provoked seizures exist, but compelling epidemiologic data are lacking. Seizures attributable to high altitude are typically generalized tonic-clonic in nature and a new-onset focal seizure at altitude should prompt a thorough evaluation for a structural brain lesion. Several pathophysiologic mechanisms are implicated. These include sleep deprivation from periodic breathing, hyperventilation, and the direct effect of hypobaric hypoxia. These mechanisms are postulated to induce a metabolic state that lowers the seizure threshold.

EBOX 132.1 Risk Associated With Travel to Altitude in Individuals With a Variety of Underlying Comorbidities

Advisability of Exposure to High Altitude for Common Conditions (Without Supplemental Oxygen)

Little Additional Risk

Young and old
Fit and unfit
Mild obesity
Diabetes
Previous coronary artery bypass grafting (without angina)
Mild chronic obstructive pulmonary disease (COPD)
Asthma
Low-risk pregnancy
Controlled hypertension
Controlled seizure disorder
Psychiatric disorders
Neoplastic diseases
Inflammatory conditions

Caution

Moderate COPD
Asymptomatic pulmonary hypertension
Compensated congestive heart failure (CHF)
Morbid obesity
Sleep apnea syndromes
Troublesome arrhythmias
Stable angina or coronary artery disease (CAD)
High-risk pregnancy
Sickle cell trait
Cerebrovascular diseases
Any cause of restricted pulmonary circulation
Seizure disorder (not taking medication)
Radial keratotomy

Contraindicated

Sickle cell anemia (with history of crises)
Severe COPD
Symptomatic pulmonary hypertension
Uncompensated CHF

Modified from: Luks AM, Hackett PH. High altitude and preexisting medicine conditions. In: Auerbach PS, Cushing, TF, Harris NS, eds. *Auerbach's Wilderness Medicine*, 7th ed. Philadelphia: Mosby/Elsevier; 2017: 29-39.

Seizures not responding to supportive care can be treated with benzodiazepines. Should an epileptic who is already taking seizure medicine experience a breakthrough seizure at altitude, standard seizure evaluation is warranted, and acetazolamide at 125 to 250 mg twice daily may be added. Acetazolamide itself has antiepileptic properties and may ameliorate the altitude-related metabolic derangements. As discussed previously, any patient with seizure activity at high altitude should also be assessed for possible HACE.

Sickle Cell Disease

In patients with sickle cell disease, exposure to even low to moderate altitudes (4000 to 6500 feet) will provide additional hypoxic stress. Up to 20% of patients with hemoglobin sickle cell and sickle cell–thalassemia disease may experience a vaso-occlusive crisis, even under pressurized aircraft conditions. Oxygen is therefore advised for air travelers who have sickle cell disease.

Although most people with sickle cell trait remain asymptomatic, this subgroup can experience the development of left upper quadrant pain as a result of splenic ischemia or infarction.

Pregnancy

Studies of permanent high-altitude residents in Colorado and Peru show an increased incidence of complications in maternal, fetal, and neonatal life. Infants born at high altitude have a lower birth weight compared with infants born at sea level because of a combination of factors, including altitude-related effects on fetal growth, changes in uterine blood flow, and increased premature births. As supported by evolutionary genetic studies, patient ethnicity is relevant. At the same elevation, newborns of recently immigrated Han Chinese have lower birth weights than indigenous Tibetans.

Pregnancy-induced hypertension, proteinuria, and peripheral edema (manifestations of toxemia and preeclampsia) are more common at high altitudes and may also be related to maternal and uterine hypoxemia. Although hypertension in pregnancy is more common at high altitudes, no evidence exists for an increase in spontaneous abortions, abruptio placentae, or placenta previa.

Travel by pregnant women to moderate altitudes appears to be safe, but caution is advised for lowland women with normal pregnancies who wish to travel above 13,000 feet, for pregnant women who wish to remain at high altitude for a prolonged period, and for women with complicated or high-risk pregnancies.

Radial Keratotomy

Patients with a history of radial keratotomy may experience hyperopic (farsighted) visual changes with ascent above 9000 feet. This results from corneal swelling from ambient hypoxia because the cornea is markedly sensitive to both systemic and ambient oxygen tension. In normal corneas, this swelling is uniform. After radial keratotomy, the swelling is exacerbated and inconsistent secondary to the pattern of the incisions. Photorefractive keratotomy and LASIK, which use laser techniques that do not produce incisions but instead shave the cornea and corneal stroma, respectively, do not result in similar problems.

ACKNOWLEDGMENT

The author would like to acknowledge Drs. Benjamin Honigman, Michael Yaron, Ryan D. Paterson, and Christopher B. Davis for their contributions to previous editions of this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 132: QUESTIONS AND ANSWERS

1. Which of the following individuals has the highest risk of developing high-altitude pulmonary edema (HAPE), assuming all are generally healthy, live at the same altitude, and travel to the same altitude?

a. A 16-month-old boy
b. A 19-year-old man
c. A 19-year-old woman
d. A 42-year-old man
e. A 42-year-old woman

Answer: B. Many factors contribute to the development of HAPE including total altitude, sleeping altitude, time at altitude, previous acclimatization, and the presence of comorbidities. However, in general, both females and the elderly have been found to be less likely to develop HAPE. Also, whereas younger males are more at risk, HAPE is extremely rare in individuals younger than 2 years old regardless of gender.

2. Which of the following symptoms must be present to establish a diagnosis of acute mountain sickness (AMS)?

a. Dizziness
b. Fatigue
c. Headache
d. Dyspnea
e. Nausea

Answer: C. To diagnose AMS, a patient must have a recent gain in altitude, be at that altitude for several hours, and have a headache. In addition, at least one of the following must also be present: gastrointestinal upset, fatigue, dizziness or light-headedness. Exertional dyspnea is common at high altitude. Resting dyspnea is concerning for potential HAPE.

3. Which of the following medications used to treat acute mountain sickness (AMS) actually accelerates acclimatization?

a. Acetazolamide
b. Ibuprofen
c. Dexamethasone
d. Oxygen
e. Prochlorperazine

Answer: A. Acetazolamide is a carbonic anhydrase inhibitor and induces a metabolic acidosis that results in increased ventilation. Ibuprofen is an appropriate treatment for the headache associated with AMS. Dexamethasone and oxygen both improve all symptoms of AMS but do not aid acclimatization. Prochlorperazine is appropriate treatment for the gastrointestinal upset caused by AMS and is preferred over promethazine because it does not depress the respiratory centers.

4. Which of the following conditions occurs more commonly at high altitude?

a. Congestive heart failure (CHF)
b. Myocardial infarction
c. Pericarditis
d. Pneumothorax
e. Pulmonary embolism (PE)

Answer: E. Altitude may contribute to hypercoagulability from hyperviscosity due to elevated hematocrit and dehydration. Venous stasis is also more common at altitude due to the relative immobility of sleeping in confined spaces (sleeping bags and small tents) and long flights that tend to precede vacations at altitude. Together, these facts lead to an increased risk of PE. Occasionally, PE may be misdiagnosed as high-altitude pulmonary edema (HAPE) and treated inappropriately.

5. The acute hypoxic stresses of high altitude can cause a range of symptoms suggestive of both cardiovascular and CNS dysfunction. Although high-altitude pulmonary edema (HAPE) and acute mountain sickness (AMS) share the same pathophysiologic trigger (decreased available oxygen), the treatment and prognosis are different. Which of the following features is indicative of HAPE as opposed to AMS?

a. Frequent urination
b. Dyspnea at rest
c. Headache
d. Lower-extremity edema
e. Symptom onset immediately after arrival at altitude.

Answer: B. Dyspnea on exertion is nearly universal at altitude and is not indicative of a pathologic process. Dyspnea at rest is not normal and is an early symptom of HAPE. Cough is common at altitude or any time when one breathes cold dry air. Fluid retention and peripheral edema are common manifestations of AMS, whereas an alkaline diuresis can be a sign of acclimatization. Neither AMS nor HAPE commonly occurs immediately after arrival at altitude. AMS usually occurs within 24 hours and HAPE usually occurs after 2 to 4 days.

6. The definitive treatment for high-altitude pulmonary edema (HAPE) is oxygen and descent to lower altitudes. Which of the following medications is also useful in the treatment of HAPE?

a. Hydrochlorothiazide
b. Metoprolol
c. Nifedipine
d. Nitroglycerin
e. Furosemide

Answer: C. Nifedipine is a nonselective pulmonary vasodilator and is useful in the treatment and prevention of HAPE. Sildenafil and

CHAPTER 132: QUESTIONS AND ANSWERS—cont'd.

tadalafil may also be useful in the prevention of HAPE. These phosphodiesterase–5 inhibitors increase cyclic guanosine monophosphate availability and result in pulmonary vasodilation. As a non-cardiac form of pulmonary edema, neither nitroglycerin or furosemide has a role in the treatment of HAPE.

7. Which of the following signs or symptoms is specific for high-altitude cerebral edema (HACE) as opposed to acute mountain sickness (AMS) or high-altitude pulmonary edema (HAPE)?

a. Ataxia
b. Dizziness
c. Dyspnea at rest
d. Headache
e. Vomiting

Answer: A. Ataxia, seizures, slurred speech, focal neurologic deficits, and altered mentation are all concerning to HACE and require immediate descent and treatment. Dizziness, headache, and vomiting can all be seen in AMS. Dyspnea at rest is nearly universal in HAPE.

8. You are the doctor on a group expedition to Denali. Recently, some of the climbers have complained of headaches, dyspnea, nausea, and difficulty sleeping. At breakfast this morning, one of the climbers, a 28-year-old female, is noted to have difficulty speaking and some slurred speech, which she attributes to a restless night's sleep. What treatment is mandated for this patient?

a. 24 hours of rest before further ascent
b. Acetazolamide
c. Descent to lower altitude
d. Nifedipine
e. Ibuprofen

Answer: C. This patient has an acute neurologic emergency, most likely high-altitude cerebral edema (HACE) until proven otherwise. Any hard neurologic finding (ataxia, slurred speech, focal neurologic deficits, seizure, or altered mentation) at altitude is suggestive of HACE, but acute CVA and other malignant etiologies must be considered. Unlike acute mountain sickness (AMS) or high-altitude pulmonary edema (HAPE), which can occasionally be treated without descent, descent is mandatory for all cases of HACE. Dexamethasone should also be given to all patients with HACE.

9. You are the doctor on a group expedition to Denali and are currently at an elevation of 10,000 feet. One of the members of the group experiences headache, lightheadedness, and nausea. You diagnose him with acute mountain sickness (AMS) and treat him with acetazolamide and oxygen. He wants to know when he can continue climbing the mountain. What do you tell him?

a. You may ascend if your oxygen saturation (as measured by pulse oximetry) is higher than 90%.
b. You may ascend when all your symptoms resolve.
c. You may never ascend any higher than this altitude.
d. You may not ascend any higher on this expedition but may try again in 1 or 2 months.
e. You may only sleep 1000 feet higher than your current altitude.

Answer: B. Management of AMS must adhere to the axiom, "After the symptoms of altitude illness occur, further ascent to a higher sleeping altitude is contraindicated."

Drowning

David B. Richards

KEY CONCEPTS

- Drowning is a leading cause of death and loss of years of life with over 90% of cases occurring in lower- and middle-income countries. Cost-effective prevention strategies have been developed for settings where resources limit treatment for drowning victims.
- Significant drowning injuries induce pulmonary injury and hypoxia in proportion to the amount of water aspirated and the duration of submersion.
- Pulmonary and neurologic support is essential to optimize the victim's chance of a favorable outcome.
- Electroencephalography is used in obtunded drowning victims to assess for subclinical seizures.
- No prognostic scale or clinical presentation accurately predicts long-term neurologic outcome after significant drowning injuries. Normal neurologic recovery is documented in patients despite prolonged submersions, persistent coma, cardiovascular instability, and fixed and dilated pupils on presentation.
- Hyperventilation, corticosteroids, diuresis, barbiturate coma, and neuromuscular blockade do not improve outcome following resuscitation of a drowning victim.
- Comatose patients who have been resuscitated after reasonable submersion time regardless of rhythm should not be rewarmed above 34°C.

FOUNDATIONS

Background and Importance

Traditionally, the terminology describing drowning injuries has been confusing and impractical. In the past, *drowning* referred to death within 24 hours of suffocation from submersion in a liquid, whereas *near-drowning* described victims who survived at least 24 hours past the initial event regardless of the outcome. The World Health Organization (WHO) published a new policy defining drowning to clarify documentation and to better track drowning injuries worldwide. *Drowning* was defined as "the process of experiencing respiratory impairment from submersion/immersion in liquid." Furthermore, the WHO policy states, "Drowning outcomes should be classified as: death, morbidity, and no morbidity; the terms wet, dry, active, passive, silent, and secondary drowning should no longer be used." Also, the term *near-drowning* should not be used, and the associated term *drowning with a fatal outcome* should be abandoned.

Immersion syndrome refers specifically to syncope resulting from cardiac dysrhythmias on sudden contact with water that is at least 5°C lower than body temperature. The risk is proportional to the difference between body temperature and water temperature. Wetting of the face and head before entrance into the water may prevent the inciting sequence of events. Putative mechanisms for the syndrome are vagal stimulation leading to asystole and ventricular fibrillation secondary to QT prolongation after a massive release of catecholamines on contact with cold water. The resultant loss of consciousness leads to secondary drowning.

Each year an estimated 360,000 people die of drowning worldwide, a rate of approximately 40 individuals an hour, most of whom are children. Low- and middle-income countries account for more than 90% of all drowning deaths and a disproportionate share of years of life lost. Drowning is among the top ten causes of mortality for children and young people worldwide.

In the United States, drowning is the tenth most common cause of unintentional death, accounting for 3709 deaths (1.1 per 100,000) in 2017. Among children 1 to 4 years old, drowning is the leading cause of injury mortality; for 5- to 9-year-olds, it is second only to motor vehicle crashes.[1]

The incidence of drowning with nonfatal outcomes is not well documented. The Centers for Disease Control and Prevention (CDC) estimates that for every child who dies by drowning in the United States, another five receive emergency department (ED) care for a drowning event, and half of these children require hospitalization.[2] Among all age groups, an estimated one to four hospitalizations secondary to nonfatal drownings occur for every drowning death. The economic implications of drowning injuries are profound. In Australia, drowning-related injuries have the highest average lifetime cost ($40,000 USD per patient) of any injury type.

Drownings occur in domestic settings such as swimming pools, hot tubs, bathtubs, large buckets, and rainwater tanks and in all forms of natural bodies of water. A review of all drowning deaths among individuals younger than 20 years old in the United States during a 1-year period revealed that 55% of infants younger than 1 year old drown in bathtubs, and nearly 16% drown in large household buckets. Most (56%) children 1 to 4 years old drown in artificial pools, whereas most (63%) deaths among older children occur in natural bodies of fresh water.

Because of natural disasters, the incidence of drowning injuries and fatalities is rising. In disasters such as floods and tsunamis, older populations are disproportionately affected. A study from hurricane Katrina found that 49% of fatalities were in people 75 years old or older.

Age, gender, and race affect incidence of drowning. Toddlers (1–3 years old) and those over 80 years old are at greatest risk of death by drowning, with annual incidences of 2.5 and 2.1 per 100,000, respectively. Males account for almost 75% of victims.[1] Indigenous American and Alaska Native children between 1 and 4 years old have the highest annual incidence of drowning mortality (3.8 per 100,000), and black teenagers between 11 and 12 years old drown in swimming

pools at ten times the rate of white children of the same age. The risk of death by drowning for all ages of the American Indigenous and Alaska Native population is 80% higher than the United States population as a whole.[3,4]

Ethanol consumption in proximity with water is a major risk factor for drowning. Acute ethanol intoxication may be a contributing factor in up to 50% of drownings among adults and adolescents.[5] The risk of death from drowning while using watercraft is directly proportional to an operator's blood ethanol concentration (BEC). The odds ratios of fatality from drowning follow a trend from 2.8 for a BEC of 1 to 49 mg/dL to 37.4 for a BEC of 150 mg/dL or greater compared with sober case controls.

Drowning in the United States is seasonal, with most occurring during the summer months. Two-thirds of pediatric deaths occur between the months of May and August. Drowning injuries are 48% more likely to occur on weekends than weekdays and drowning victims older than 20 years old are most often participating in water sports or using watercraft.[6]

The relationship between swimming ability and the risk of drowning is unclear. No direct evidence exists to suggest that inexperienced swimmers are more likely to drown. On the contrary, skilled swimmers have greater exposure time in water and may be more prone to drowning incidents.

Numerous medical conditions confer an increased likelihood of drowning injury. Seizure disorders increase the chance of drowning among children and adolescents nearly 20-fold and longitudinal studies of patients with epilepsy found that 10% of deaths were due to drowning. Autism and other developmental and behavioral disorders increase risk in children as well. Immersion in cold water extends the QT interval, thus increasing the risk of dysrhythmias in individuals with baseline prolonged QT syndrome.

Anatomy, Physiology, and Pathophysiology

Unexpected submersion triggers breath-holding, panic, and a struggle to surface. Air hunger and hypoxia develop, and the victim begins to swallow water. As breath-holding is overcome, involuntary gasps result in aspiration. The quantity of fluid aspirated, rather than the composition, determines subsequent pulmonary system derangement.

The pathophysiologic differences between freshwater and saltwater aspiration with respect to resultant electrolyte imbalance, hemolysis, and fluid compartment shifting do not occur until the amount of aspirated water is significantly more than the typical drowning victim aspirates. In one review of the hospital treatment of drowning victims, no patient required emergent intervention for a significant electrolyte abnormality. Aspiration of 1 to 3 mL/kg of either fresh water or saltwater destroys the integrity of pulmonary surfactant, leading to alveolar collapse, atelectasis, noncardiogenic pulmonary edema, intrapulmonary shunting, and ventilation-perfusion mismatch. Profound hypoxia and metabolic and respiratory acidosis ensue, leading to cardiovascular collapse, neuronal injury, and ultimately death.

The classic hypothesis was that 10% to 15% of drowning victims die without aspiration of a significant amount of water. Death from such dry drowning purportedly results from severe laryngospasm causing hypoxia, convulsion, and death without entry of fluid into the lungs. An exhaustive review of the literature failed to corroborate this hypothesis. Dry drownings more appropriately reflect deaths from other causes (e.g., fatal cardiac dysrhythmias and severe hypothermia) than from simple submersion.

Many factors may influence the pathophysiologic sequence of events in drowning and affect the chance of survival, including age, water temperature, duration and degree of hypothermia, diving reflex, and effectiveness of resuscitative efforts. Children have a lower ratio of body mass to surface area and, therefore, develop hypothermia more quickly and to a greater degree after immersion in cold water than adults do. Hypothermia lowers cerebral metabolic rate and is neuroprotective to some extent for victims of submersion injury. Despite dramatic case reports of patients surviving prolonged submersion in cold water with full neurologic recovery, hypothermia is generally a poor prognostic finding. Cold-water immersion speeds the development of exhaustion, altered consciousness, and cardiac dysrhythmia. The *diving reflex*, an involuntary physiologic response to cold submersion that includes apnea, bradycardia, and increased peripheral vascular resistance, may play a protective role in infant and child submersions. The diving reflex works to shunt blood centrally to the heart and brain, thereby prolonging the duration of submersion tolerated without central nervous system (CNS) damage. The evidence to date, however, has not shown a clear correlation between outcome and water temperature.

CLINICAL FEATURES

History and Physical Examination

Many drowning episodes are witnessed. Toddler drownings are an important exception, however, often occurring because of a lapse in supervision. Signs of pulmonary injury may be obvious in a drowning victim who is hypoxic, cyanotic, and in respiratory distress or arrest. More subtle clues, such as increased respiratory rate and audible rhonchi, rales, or wheezes on pulmonary auscultation, should alert the clinician to evolving respiratory compromise. Drowning victims swallow a significantly greater volume of water than is aspirated, and gastric distention from positive-pressure ventilation during rescue is common. As a result, 60% of patients vomit soon after a drowning event. Aspiration of gastric contents greatly compounds the degree of pulmonary injury and increases the likelihood that acute respiratory distress syndrome (ARDS) will ensue. In addition, aspiration of particulate contaminants such as mud, algae, sewage, and bacteria may obstruct the smaller bronchi and bronchioles and greatly increase the risk of infection (both bacterial and fungal in nature).

Victims with CNS injury may present with symptoms ranging from mild lethargy to coma with fixed and dilated pupils. CNS injury results from the initial hypoxic or ischemic insult and from the cascade of reperfusion injury that follows reestablishment of cerebral blood flow after a cardiopulmonary arrest. The release of inflammatory mediators and the generation of oxygen free radicals in the post-resuscitative period contribute to cytotoxic cerebral edema, compromise of the blood-brain barrier, and increased intracranial pressure.

Cardiac dysrhythmias may incite drowning or develop as a consequence. Hypoxemia, acidosis, and, potentially, hypothermia are the primary factors responsible for dysrhythmias ranging from ventricular tachycardia and fibrillation to bradycardia-asystole. Electrolyte disturbances are rarely significant enough to be dysrhythmogenic.

Other clinical sequelae of drowning may include acute renal injury, which is present on admission in approximately 50% of patients as the result of lactic acidosis; prolonged hypoperfusion; and, in some instances, rhabdomyolysis. Hypothermia-related coagulopathy or disseminated intravascular coagulation (DIC) may occur.

Prognostic Factors

Many factors help predict patients who will survive a drowning injury neurologically intact. Hypoxia, which is usually dependent on submersion time, is the most important factor related to outcome and subsequent quality of life in drowning victims. Drowning victims who arrive in the ED alert with normal hemodynamics are unlikely to experience neurologic impairment. Victims younger than 3 years old, submersion for longer than 5 to 10 minutes, and initiation of cardiopulmonary

resuscitation (CPR) more than 10 minutes after rescue portend a poor prognosis. Adverse neurologic findings on initial presentation do not preclude full neurologic recovery, although in general, patients whose duration of submersion or resuscitation exceeds 10 minutes have an unfavorable outcome.[7] With the exception of victim age, however, such measurements are often unknown or inaccurately estimated at the time of a patient's arrival in the ED. On arrival, objective findings associated with an unfavorable prognosis include hypothermia, severe acidosis, unreactive pupils, a Glasgow Coma Scale score of 3, and asystole or the need for ongoing CPR. Neurologically intact survival is reported for individual patients even with several of these factors present; however, none of the proposed scoring systems using combinations of these variables has 100% predictive power.

Children who present with an abnormal head computed tomography (CT) scan (e.g., intracranial bleed, cerebral edema) within the first 24 hours have a nearly 100% mortality rate. Furthermore, an abnormal head CT scan at any time is associated with poor outcome (persistent vegetative state (PVS), post-coma unresponsiveness (PCU) or death).

DIFFERENTIAL DIAGNOSES

The precipitants of a drowning, such as drug or ethanol intoxication, cardiac arrest, hypothermia, hypoglycemia, seizure, and attempted suicide or homicide, should be considered in patients found unresponsive in water. For pediatric victims, child abuse or neglect should also be considered a potential cause. Potential head or cervical spine injury is an important consideration in drowning associated with diving injuries or trauma.

DIAGNOSTIC TESTING

Initiate cardiac monitoring and obtain an electrocardiogram (ECG) to determine the presence of significant dysrhythmias, QT prolongation, or ischemia. Monitor pulse oximetry, capnography, and arterial or venous blood gases closely for signs of hypoxemia, hypercarbia, and acidosis. Blood glucose, serum creatinine, and electrolyte values should be obtained, although serum creatinine concentration and electrolyte levels are usually normal on initial presentation. Similarly, complete blood count is often normal with the exception of leukocytosis. Serum ethanol levels and urine toxicology screening may be appropriate for illicit drugs, depending on the circumstances of the drowning. Subsequently, evidence of renal failure, hepatic dysfunction, and DIC may be noted on laboratory testing.

The initial chest radiograph is often unremarkable and may underestimate the severity of pulmonary injury. Infiltrates or pulmonary edema may be evident within hours; therefore, repeat radiographs are indicted with persistent respiratory symptoms. Initial chest radiographs are often unremarkable even in the setting of serious and evolving pathologic processes.

Electroencephalography to assess for seizure activity should be performed, if available, in the obtunded drowning victim. Head CT scans are rarely initially contributory unless significant trauma or other pertinent injury is suspected. Magnetic resonance imaging (MRI) of the brain may predict neurologic outcome after drowning, but its prognostic value is not optimal until 3 or 4 days have elapsed and is therefore not indicated in the emergency setting.

MANAGEMENT

Salient details of the events surrounding the incident should be ascertained rapidly from family, friends, or EMS personnel. Resuscitation of pulseless and apneic patients should be attempted initially in most cases because bystander estimates of total submersion time are often inaccurate. The clinical presentation of severe hypothermia often mimics death, and functional recovery is possible for hypothermic individuals submerged for significant periods of time.

For a victim without measurable vital signs or signs of life, outcome depends on the interval preceding CPR.[8] Since most cases are hypoxia-driven cardiac arrests, CPR with assisted ventilations may be more effective than compression-only CPR, although this has not been well studied. Mouth-to-mouth ventilation while in the water should be attempted but not at the cost of prolonging the extrication.[9] Chest compressions are impractical before extrication but should be initiated as soon as the individual is placed on a solid surface, such as a boat deck, poolside, or beach.

Cervical spine injuries are rare in drowning victims. Patients more likely to have cervical spine injuries tend to have either clinical signs of serious trauma or a history of motor vehicle crash, fall from height, or diving into the water. Unless such factors are present, routine cervical spine immobilization for submersion victims is not warranted.

On arrival in the ED, cardiac monitoring and continuous pulse oximetry should be established. A core temperature obtained with a low-reading probe is indicated for any unstable or lethargic patient. Values obtained by use of infrared ear thermometry are unreliable in drowning victims. Rewarming of a hypothermic patient may suffice for hemodynamic stabilization and improvement in mental status. A spontaneously breathing patient should be monitored for signs of developing pulmonary injury.

As with any patient, expected clinical course, mental status and objective determination of the adequacy of oxygenation and ventilation should determine the decision for tracheal intubation. If an arterial blood gas is obtained, a partial pressure of carbon dioxide ($Paco_2$) greater than 50 mm Hg should warn the clinician that intubation and lung protective ventilation is likely needed. Patients unable to maintain oxygen saturation greater than 90% despite high-flow supplemental oxygen, require positive airway pressure to increase alveolar recruitment, decrease intrapulmonary shunting, and reduce ventilation-perfusion mismatch. In awake patients, this may be accomplished by face or nasal mask (continuous positive airway pressure), but the risk of potential gastric distention, vomiting, and aspiration should be considered. Otherwise, tracheal intubation and lung-protective ventilation are indicated. The hemodynamic consequences of positive end-expiratory pressure should be monitored carefully, because increased intrathoracic pressure may compromise venous return and cardiac output. Decreased cranial venous return may impede cerebral perfusion.

No consensus exists with regard to the appropriate length of resuscitative effort for hypothermic drowning victims in the ED. The safest parameter is to continue until the core temperature reaches at least 32°C to 35°C, because cerebral death cannot be diagnosed accurately in severely hypothermic patients with temperatures below this level. This parameter may not always be practical, however, because brain-dead patients are often poikilothermic.

The administration of corticosteroids in the setting of drowning and potential ARDS does not improve outcome. Barbiturate-induced coma, diuresis, neuromuscular blockade, and hyperventilation do not improve neurologic outcome and, particularly in the case of hyperventilation, may be harmful. Similarly, empirical antibiotics do not increase survival and should be administered only to the patient who was submerged in grossly contaminated water or who shows signs of infection or sepsis.

Interventions, such as induced or permissive hypothermia, aimed at attenuation of reperfusion injury after anoxic brain insult are the

focus of intense investigative effort. Drowning victims in cardiac arrest are usually colder than 30°C and require warming. Comatose patients who have been resuscitated after reasonable submersion time regardless of rhythm should not be rewarmed above 34°C. Rewarming only up to 34°C followed by a 24-hour mild hypothermic treatment before normothermia is reached may be advantageous because of decreased pulmonary reperfusion injury and reduced secondary brain injury. Emerging resuscitation literature indicates an emerging role for therapeutic hypothermia in drowning victims.[10]

DISPOSITION

Symptomatic patients should be admitted for treatment. Patients with a history of apnea, unconsciousness, intoxication, or hypoxia and any patients who manifest cardiac dysrhythmias or an abnormal chest radiographs also require admission. Patients who are asymptomatic on presentation to the ED, maintain normal room air oxygen saturation, and have no chest radiograph abnormalities can be discharged safely after an observation period of 8 hours.[11,12] Careful instructions about symptoms or signs of delayed pulmonary complications are necessary, and the patient should be discharged in the care of a competent adult.

Preventive Efforts and Discharge Education

For survivors of a drowning episode, discharge instructions with a focus on parental education and future preventative measures are critical. Canadian research has shown that drowning was in the top three causes of death and costs per hospitalization for youths under the age of 19 years and identified prevention of drowning as a high-yield priority.[13] An Australian study highlighted this by demonstrating a $830 million annual economic burden in Australia alone.[14] In low-income countries, drowning deaths (particularly in children) are on the rise. In high-income countries, drowning morbidity and mortality are on the decline although the exact causes of this decline are unclear. An increased public awareness of preventive measures and an emphasis on public education with regard to bystander CPR and the dangers of ethanol use in conjunction with water-related activities are contributing significantly to the reduction in fatalities, in some locations by over 80%.

Parental education about the danger of pediatric drowning is an important focus of preventive efforts. Inadequate supervision of children playing in or near water is one of the most common causes of pediatric submersion death, underscoring the importance of increasing awareness of the need for constant oversight of children in this setting. Most pediatric submersion injuries in swimming pools occur at the victim's home. In most cases, the child is last seen in the house, is left unattended for a moment, and enters the pool on an unfenced side closest to the home with no audible splash or screaming. Fully circumferential fencing with functioning door locks or latching mechanisms of residential pools is a current recommendation of the American Academy of Pediatrics (AAP). Drowning or submersion is 3.7 times more likely in a nonfenced pool than in a properly fenced pool. In Australia, safety legislation is associated with a 30% reduction in drowning rates in young children. Unfortunately, legislation requiring appropriate fencing is poorly adhered to, and only 40% of households are compliant. Legislation requiring personal floatation device usage in recreational boaters in Australia has resulted in a significant decrease in drowning deaths.

Effective approaches to prevention efforts in low- and middle-income countries differ from those in high-income countries.[15] Data from almost 100,000 children in Bangladesh either entered into swim lessons or kept in a common supervision area in the community showed relative risks of drowning of 0.072 and 0.181, respectively. Both interventions were found to be extremely cost effective.[16]

Emergency care providers are a vital resource for enhancement of public awareness of the importance of these measures. The literature supports the concept that education in the ED highlighting drowning prevention can have a positive impact on patient and family awareness of steps to lessen the likelihood of catastrophic drowning injury.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 133: QUESTIONS AND ANSWERS

1. Which of the following is the greatest risk factor for death from drowning?

a. Ethanol
b. Male gender
c. Poor swimming ability
d. Saltwater drowning
e. Warm water

Answer: A. Ethanol is a major risk factor for drowning and for death from drowning. Ethanol is a contributing factor in up to 50% of drowning incidents among adolescents and adults. More males drown than females, but male gender alone does not increase the risk of death from drowning. No direct evidence exists relating swimming ability to risk of death from drowning. Although frequently cited in older literature, there is no significant difference between saltwater and freshwater drowning. Although case reports of survival from cold-water drowning exist, overall mortality is greater in cold water than in warm water.

2. A 13-year-old boy is brought to the emergency department (ED) after an apparent drowning. Family and paramedics report the patient was submerged for approximately 4 minutes. Bystanders began cardiopulmonary resuscitation (CPR) immediately. Paramedics intubated the patient and continued CPR, which has now been ongoing for 10 minutes. On arrival in the ED, the patient has a Glasgow Coma Score (GCS) of 3, unreactive pupils, no pulse, and is in asystole on the cardiac monitor. What is the most appropriate next step?

a. Cessation of treatment/pronounce death
b. External cardiac pacing
c. Induction of hypothermia
d. Intravenous epinephrine
e. Unsynchronized defibrillation

Answer: D. Although this patient will likely have a poor outcome, asystolic victims of drowning have a higher incidence of full neurologic recovery than patients with asystole from other causes. Poor prognostic indicators are age younger than 3 years old, submersion greater than 5 minutes, delay in initiation of CPR greater than 10 minutes, hypothermia, severe acidosis, unreactive pupils, GCS of 3, and asystole. The decision to cease care must be made on a case-by-case basis, but initial treatment of asystole should be begun in drowning victims following standard advanced cardiac life support (ACLS) protocols and as in this case, administration of intravenous epinephrine. Experiments with induction of hypothermia are ongoing in drowning victims, but the results are not definitive.

3. A 16-year-old boy presents with tachypnea and coughing. Family members state that they were swimming in a nearby lake when they noticed the patient with the previously mentioned symptoms. The patient is awake and alert but in obvious distress. He has a respiratory rate of 35 breaths per minute, with the remainder of his vital signs within normal limits. His oxygen saturation as measured by pulse oximetry is 84% while on high-flow oxygen. Pulmonary examination reveals diffuse rales. There is no evidence of trauma. In addition to intubation, which of the following is indicated?

a. Administer intravenous diuretics.
b. Administer intravenous corticosteroids.
c. Obtain an electrocardiogram (ECG).
d. Perform maneuvers to remove fluid from the lungs.
e. Place the patient in cervical spine precautions.

Answer: C. Dysrhythmias are frequently associated with drowning, especially when no obvious cause is found. ECGs should be performed on all drowning patients. Antibiotics, steroids, and diuretics have all been studied in drowning victims, and none show any benefit. Cervical spine precautions are often initiated in all drowning victims but are not needed unless the patient has clinical signs of trauma or a history of motor vehicle crash, fall from height, or diving into the water. Maneuvers to remove fluid from the lungs (Heimlich, Patrick maneuvers) are ineffective and potentially dangerous.

CHAPTER 133: QUESTIONS AND ANSWERS—cont'd.

4. An 18-year-old man is brought to the emergency department (ED) after submersion in his swimming pool. Per witnesses, once the patient was brought out from the water, he initially had severe coughing and complained of shortness of breath. On arrival to the ED, the patient denies shortness of breath and is not coughing. Vital signs as well as oxygen saturation are all within normal limits. Electrocardiogram (ECG) and chest radiographs are normal. What is the appropriate disposition of this patient?

a. Admission to telemetry for 23-hour observation
b. Admission to the general hospital for 23-hour observation
c. Admission to the intensive care unit for 23-hour observation
d. Discharge home after observation in the ED for 8 hours
e. Discharge home now

Answer: D. Any symptomatic patients or patients with a history of apnea, unconsciousness, or hypoxia should be admitted. Likewise, patients with dysrhythmias or abnormal chest radiographs should be admitted. Some effects of drowning can be delayed, so asymptomatic patients should be observed for 8 hours in the ED but can be safely discharged if they continue to be asymptomatic and can maintain normal room air oxygen saturation. They should be discharged in the care of a responsible family member or friend.

Radiation Injuries

Jillian L. Theobald and J. Marc Liu

KEY CONCEPTS

- Patients contaminated with radiation pose minimal risk to health care providers when appropriate precautions and decontamination procedures are employed.
- Decontamination should not delay or impede emergency stabilization of patients with radiation exposure.
- Tissues with greater rates of cellular division, particularly the hematopoietic and gastrointestinal systems, are most radiosensitive. Children are more radiosensitive than adults.
- Vomiting, diarrhea, and skin burns occurring shortly following radiation exposure are predictors of severe radiation injury.
- The 48-hour absolute lymphocyte count is the most important prognostic indicator and should be drawn on suspected radiation exposure patients.
- Most therapy is supportive with symptomatic measures except for exposures involving the ingestion or inhalation of radioactive material, when directed therapy with blocking or chelating agents may be indicated.
- Formal consultation at the hospital, regional, and national levels is available 24 hours a day and should be used for assistance when managing patients with radiation injuries (Table 134.4).

FOUNDATIONS

Background and Importance

Radiation is energy that travels through space in the form of a particle or wave.[1] It is produced by radioactive decay of an unstable atom (radionuclide or radioisotope) or by the interaction of a particle with matter. *Particle radiation* consists of particles that have mass and energy and may carry an electric charge. Examples of particle radiation include alpha particles (helium nuclei), protons, beta particles (electrons ejected from the nucleus), and neutrons. *Electromagnetic radiation* consists of photons that have energy but no mass or charge. Radiation can be either ionizing or nonionizing depending on its energy and ability to penetrate matter. Electromagnetic radiation varies by frequency and wavelength as shown in Figure 134.1.

Radioactive decay (radioactivity) is the process by which a nucleus of an unstable atom loses energy by emitting ionizing radiation in the form of high-energy particles or rays. Radioactive decay can emit particles (e.g., alpha and beta) or rays such as gamma or x-rays. Gamma rays and x-rays are high-energy photons that differ in their place of origin: gamma rays are emitted from the nucleus, whereas x-rays are produced as the result of changes in the positions of electrons orbiting the nucleus.

The type and rate of radioactive decay varies by radionuclide. The rate of decay is measured by the radioactive half-life (the time for half the radioactive nuclei in any sample to undergo radioactive decay) and varies from a few microseconds to billions of years. Radiation exposure can be external (e.g., exposure to x-rays) or internal, resulting from the inhalation, ingestion, or injection of radioisotopes.

Radiation Measurements

The four different but interrelated units for measuring radiation (radioactivity, exposure, absorbed dose, and dose equivalent) are shown in Table 134.1. These units are also commonly expressed as fractions of whole units using the terms and abbreviations milli (m; 1/1000th) and micro (μ; 1/1,000,000th).[1]

Radiation Protection

The principles of radiation protection include time, distance, shielding, and quantity. Reducing the time of radiation exposure will reduce the absorbed dose. The intensity of radiation is a function of distance from the source and follows the inverse square law: the dose of radiation decreases inversely with the square of the distance. For instance, if you double the distance from the source you decrease the radiation exposure by a fourth. Shielding is the placement of an absorber (material that reduces radiation) between the person and the source. The effectiveness of shielding varies with the type of the radiation. For example, alpha particles can be stopped by a thin piece of paper or even the dermal cells in the outer layer of the skin, whereas thick, dense shielding like lead or concrete is necessary to protect against gamma rays. Limiting the quantity of radioactive material in the work area will also decrease exposure. National and international regulatory bodies set acceptable limits for occupational and population exposures to radiation.

Radiation Sources

Ionizing radiation and radioactive substances are natural and permanent features of the environment. The average annual radiation dose per person in the United States is 6.2 mSv (620 mrem). Fifty percent of this average dose comes from background radiation and 48% from medical procedures. The major sources of background radiation are radon and thoron (37%), cosmic radiation (5%), naturally occurring internal radioisotopes (e.g., potassium-40 [5%]), and terrestrial background radiation (3%). The major medical sources include computed tomography (CT; 24%), nuclear medicine (12%), interventional fluoroscopy (7%), and conventional radiography and fluoroscopy (5%). The remainder of the average annual radiation dose comes from occupational and consumer sources.[2]

Radon is a naturally occurring radioactive gas that is formed from the radioactive decay of uranium. Radon can accumulate in homes and is the second leading cause of lung cancer in the United States after tobacco exposure.[3] Radon exposure is estimated by measuring radon

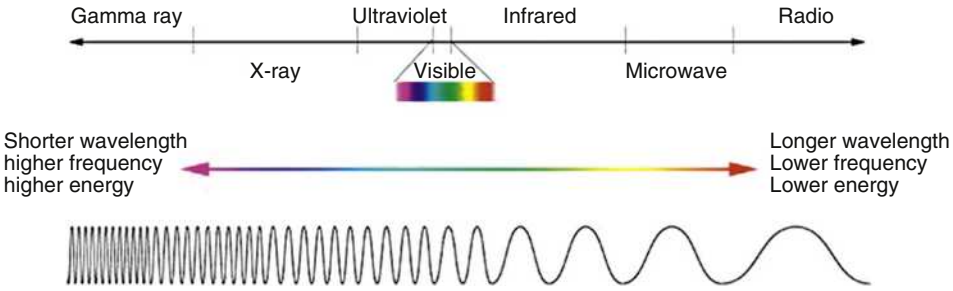

Fig. 134.1 Electromagnetic radiation varies by frequency and wavelength. (National Aeronautics and Space Administration: Imagine the universe: the electromagnetic spectrum. Available at: http://imagine.gsfc.nasa.gov/science/toolbox/emspectrum1.html.)

TABLE 134.1 Radiation Units Description and Conversion Factors

Measure	Description	United States Units	International Units	Conversion
Radioactivity	Amount of ionizing radiation released by a material	Curie (Ci)	Becquerel (Bq)	1 Bq = 2.7×10^{-11} C
Exposure	Amount of radiation traveling through air	Roentgen (R)	Coulomb (C)/kg	1 C/kg = 3875.9 R
Absorbed dose	Amount of radiation absorbed by a person	Radiation absorbed dose (Rad)	Gray (Gy)	1 Gy = 100 rad
Dose equivalent (effective dose)	Combines the amount of radiation absorbed with the tissue damaging potential of the type of radiation	Roentgen equivalent man (Rem)	Sievert (Sv)	1 Sv = 100 rem

levels in the air using inexpensive and readily available kits. If indoor levels of radon are 4 pCi/L or greater, then the US Environmental Protection Agency (EPA) recommends that the homeowner consult a certified radon mitigation specialist to reduce radon air levels in the home.

Although radiation-related incidents are rare, the consequences of exposure or significant internal contamination can be fatal. The Radiation Emergency Assistance Center at Oak Ridge National Laboratory maintains a worldwide registry of serious radiation incidents. Between 1944 and 2012, there have been 454 radiation incidents recorded worldwide. The greatest numbers of serious exposures have occurred with sealed sources, which include brachytherapy sources used in radiation oncology and industrial radiography devices (n = 214), followed by x-ray devices (n = 86). Radioisotopes used in medical diagnosis and therapy have caused approximately 10% of major radiation incidents.

Serious nuclear power incidents include the Fukushima Daiichi disaster (2011), the Chernobyl disaster (1986), Three Mile Island (1979), and the SL-1 accident (1961). The radioisotopes most commonly released from nuclear reactor accidents include iodine, cesium, and strontium. Chernobyl had the largest number of radiation-related injuries. About 150 individuals who received very high whole-body doses were treated for acute radiation sickness; 28 of these died within a relatively short time, and approximately 20 more have since died from radiation-related diseases.[4] Radiation to the thyroid from radioisotopes of iodine released during the Chernobyl event has caused several thousand cases of thyroid cancer, with children being the most susceptible population.

The detonation of nuclear bombs has the greatest potential to produce mass casualties. The acute and long-term effects following the bomb blasts in Hiroshima and Nagasaki in 1945 (18 and 22 kilotons) have been well documented. Today's nuclear weapons are orders of magnitude potentially more devastating. Another threat is the detonation of a low-yield nuclear bomb by terrorists. A 10-kiloton nuclear detonation within a city in the United States would result in a zone of destruction of more than 2 miles from ground zero and would expose hundreds of thousands of people to radiation.[5] A more likely terrorist scenario is the explosion of a *dirty bomb*. A dirty bomb is the combination of a conventional explosive with a radioisotope. The radioisotopes most likely to be used in a dirty bomb are cesium-137, cobalt-60, or strontium-90.[6] Although the acute radiation risks from a dirty bomb detonation are low, the localized residual radiation contamination would likely cause widespread panic.

Anatomy, Physiology, and Pathophysiology

The biologic effects of radiation exposure are determined by the type of radiation, the total dose, the dose rate, the volume of tissue or anatomic body part irradiated, and individual susceptibility factors. The amount of energy released in matter (linear energy transfer) varies by type of radiation. Different types of radiation are assigned a quality factor (QF) based on their ability to produce biologic damage in exposed tissue. The higher the QF, the more biologically damaging the radiation is. Gamma rays, x-rays, and beta particles have a QF of 1. Alpha particles (internal exposure only) have a QF of 20, whereas neutrons have a QF range of 3 to 20, depending on their energy.

Ionizing radiation includes particles and photons that have sufficient energy to detach electrons, thus causing ionization of the atoms that they encounter. Alpha particles, beta particles, and neutrons are examples of particle ionizing radiation. Only the high-frequency portion of the electromagnetic radiation spectrum (gamma rays, x-rays, and far-ultraviolet) has sufficient energy to produce ionization. Other frequencies and wavelengths (near-ultraviolet, infrared, microwaves, radio waves, and very or extremely low frequency radiation) are considered *nonionizing*. The health effects of exposure to nonionizing radiation depend on the frequency and wavelength. For example, ultraviolet light can produce sunburns, visible light (such as lasers), can produce corneal and retinal burns, and microwaves can produce heating of body tissues.

TABLE 134.2 Systemic Radiation Effects Based on Dose

Dose (gray)				
	12 +	→ Bone Marrow Suppression	Neurovascular syndrome onset	Multiple organ failure Probable death
	11			
	10			Consider stem cell transplants
	9			
	8			
	7			LD 50/60 with supportive care
	6		Gastrointestinal syndrome onset	
	5			LD 50/60 without treatment
	4			
	3			
	2			≈100% survival without treatment
	1		Hematopoietic syndrome onset	
	0			

Adapted from: The Medical Aspects of Radiation Incidents; originally published by ORISE and REAC/TS under contract number DE-AC05-06OR23100 between the US Department of Energy and ORAU, 2013.

The effects of ionizing radiation on tissue can be *direct* or *indirect*. Direct effects include single- and double-strand DNA breaks. Indirect effects act through generation of free radicals that then attack other molecules in the cell. Cells vary in their sensitivity to radiation. In general, cells that are undifferentiated, divide quickly, and have high metabolic activity are most radiosensitive. Examples of these types of cells include bone marrow stem cells, lymphocytes, spermatogonia, ovarian cells, intestinal crypt cells, and epidermal basal cells. Less radiosensitive tissues and organs are made up of cells with little or no turnover such as connective tissue or the central nervous system. The effects of radiation can be *deterministic* or *stochastic*. Deterministic effects are those in which the severity of injury is a function of dose (e.g., bone marrow suppression). Stochastic or probabilistic effects are those in which the probability of an effect, rather than its severity, is a function of dose. An example of a stochastic effect is the development of radiation-induced cancer.

For external exposure, the site of the body that is irradiated (e.g., bone marrow vs. upper extremity) is an important determinant of the resulting effects. For internal exposure, the biodisposition of the radioisotope, its radiologic and biologic half-lives, as well as the types of radioisotopes produced during radioactive decay are important determinants of the effects. *Biodisposition* refers to the absorption, distribution, metabolism, and excretion of a radioisotope.

The *effective half-life* reflects both the radiologic and biologic half-life and can be calculated as 1/effective half-life = 1/biologic half-life + 1/physical half-life.[7] For example, iodine-131 has an approximate biologic half-life of 57 days and a radiologic half-life of 8 days. The resulting effective half-life is approximately 7 days.

Radioisotopes will have their greatest effects at the sites in the body where they are concentrated. For example, radioiodine concentrates in the thyroid gland and the resulting effects, such as thyroiditis or thyroid cancer, occur at the site of concentration.

Routes of Exposure

An individual can be exposed to radiation by one or a combination of three processes: irradiation, incorporation, and contamination.

Irradiation occurs when an object or person is exposed to a radioactive source. An object does not become radioactive unless neutron activation occurs. When a person is irradiated, such as a patient who has just received a CT scan or x-ray, no hazard exists to medical personnel who come into contact with the patient.

Contamination is the presence of radioactive matter on or in an object. Contamination usually occurs externally but may be internal if the radioactive material is ingested or inhaled with continued radiation emitted by the contaminating substance. However, in almost all cases, contamination is not an acute threat to the life of the patient or the health care provider, and its presence should not preclude institution of lifesaving measures. The radioactive particulate matter may emit radiation with an effect that is directly related to the time of exposure, distance from the source, and type of contamination.

Incorporation occurs when a radioactive material is taken up by a tissue, cell, or organ. This can occur through ingestion, inhalation, or absorption via an open wound.

CLINICAL FEATURES

Acute Radiation Syndrome

Acute radiation syndrome (ARS) occurs after a patient is exposed to whole body radiation. ARS from external or internal exposure to radiation varies in nature and severity by dose, dose rate, dose distribution, and individual susceptibility. There are three phases to ARS: prodromal, latent, and manifest illness. The progression and patterns of symptoms and signs of the phases of ARS can overlap. The timing of the progression through the phases can be accelerated with increasing radiation doses.[8]

In the *prodromal phase,* initial symptoms are typically nonspecific, and include anorexia, nausea, vomiting, and fatigue. This phase is useful to help predict the severity of the radiation injury. The presence, onset, and frequency of nausea and vomiting, although nonspecific, can serve as a prognostic factor. Early onset or persistent nausea and vomiting as well as the presence of diarrhea, indicate a more severe radiation injury.

The *latent phase* is a period of initial symptom improvement. Patients may even become symptom-free. Those victims with lethal radiation doses may not have a symptom-free period and progress from the prodromal phase directly to the manifest illness phase.

The *manifest illness phase* has three sub-syndromes that may occur and overlap depending on the radiation dose received (Table 134.2). All organs are affected by radiation. However, the relative sensitivities of the organ systems exposed to radiation determines the clinical symptoms. Tissues with greater rates of cellular division, particularly the hematopoietic and gastrointestinal systems, are most radiosensitive.

TABLE 134.3 Local Irradiation Symptoms by Dose

Threshold Dose (Gy)	Symptoms	Time To Onset (Days)
3	Epilation	14 to 18
6	Early erythema	14 to 21
10	Dry desquamation	25 to 30
15	Wet desquamation	20 to 28
>20	Ulceration and necrosis	>21

The hematopoietic sub-syndrome is the first sub-syndrome seen. This sub-syndrome can appear at doses greater than 1 Gy and typically results in bone marrow suppression. At doses less than 1 Gy (100 rem), most cells survive but may be susceptible to radiation-induced cancer.[9] Lymphocytes are the first cell line to decrease and with high doses of radiation this drop will occur sooner and with greater severity. The hematopoietic system in children has been estimated to be more than twice as radiosensitive as in adults.[10]

The gastrointestinal sub-syndrome begins to occur at doses nearing 6 Gy, about 1 week after exposure. Patients will display nausea, vomiting, gastrointestinal bleeding, malabsorption, and fluid losses, potentially leading to hypovolemia and cardiovascular collapse. These symptoms are due to death of the intestinal epithelial precursor cells and resultant denuding of the intestinal epithelial surface. Thrombocytopenia and immunosuppression from the accompanying hematopoietic sub-syndrome also predispose patients to infection and bleeding.[11]

The neurovascular sub-syndrome results from doses greater than 10 Gy and is typically lethal. Patients will develop irritability, altered mental status, seizures, prostration, ataxia, and hypotension. Coma and death usually occur within a few hours. Because of the high dose of radiation needed to produce these findings, patients often die without experiencing a latent phase.[11]

Local Radiation Injury

Cutaneous involvement can occur following a radiation exposure. It can be one component of ARS with other organ involvement or it can occur alone.[11] Radiation injury limited to the skin and the tissues located directly beneath the area of injury is termed a *local radiation injury (LRI).*This injury typically happens after a patient handles or has close contact with an industrial radioactive source. LRI can also result from medical testing or therapy, such as fluoroscopy, nuclear medicine studies, and CT scans.[12] Inflammation, oxidative damage, and damage to the microvasculature are all involved in the pathophysiology of LRI. Hair loss occurs after exposure to 3 Gy, and erythema is seen after exposure to 6 Gy. Wet desquamation, a loss of epithelial thickness and integrity leading to fluid loss, occurs after 15 Gy, and necrosis occurs after 20 to 25 Gy of localized skin exposure (Table 134.3).[13,14]

DIFFERENTIAL DIAGNOSES

The initial signs and symptoms following radiation exposure are nonspecific and include anorexia, nausea, vomiting, and fatigue. In the absence of an exposure history, these symptoms in the prodromal phase of acute radiation sickness can be confused for gastroenteritis with its long list of differential diagnoses. Neutropenia seen after whole body radiation exposure also has many other etiologies, including viral infections, medication-induced, certain autoimmune or oncological disorders, and nutritional deficiency.

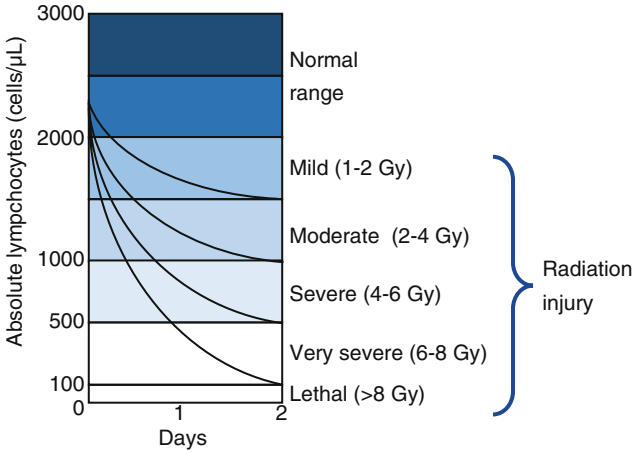

Fig. 134.2 Lymphocyte decrease over time following radiation injury. (Adapted from: Andrews GA, Auxier JA, Lushbaugh CC. The importance of dosimetry to the medical management of persons exposed to high levels of radiation. In: *Personal Dosimetry for Radiation Accidents.* Vienna: International Atomic Energy Agency; 1965.)

The severe symptoms following high-dose radiation injury resulting in the neurovascular sub-syndrome can occur with any catastrophic cardiovascular or neurologic event. Local radiation injuries can appear similar to thermal or sun exposure burns but differ in their progression over time.

DIAGNOSTIC TESTING

If contamination with radioactive material is a possibility, then the patient should be surveyed with a contamination survey instrument (e.g., Geiger Muller detector). These very sensitive detectors measure the presence of radioactive material in counts per minute. There are a variety of other radiation detection devices that are designed to measure field strength in units of mrem/hour or μSv/hour. These latter types of instruments are most often used to measure radiation fields at an incident scene or "hot zone." The hospital radiation safety officer should be consulted to assist in performing radiation surveys of potentially contaminated patients or objects.

Quantifying the absorbed dose of radiation can be challenging, especially in the emergency department (ED). Information on the radiation source, field strength, time of exposure, distance, shielding, and routes of exposure is often incomplete. Although radiation doses can be reconstructed at a later time by health physicists, emergency clinicians will most often rely on biodosimetric tools, such as time to vomiting and lymphocyte depletion kinetics. These online tools are available at www.remm.nlm.gov/ars_wbd.htm#vomit.

A baseline complete blood count (CBC) with differential and absolute lymphocyte count should be obtained and repeated every 6 hours for the first 24 hours and at least daily thereafter. The absolute lymphocyte count at 48 hours after exposure is a good predictor of radiation injury (Fig. 134.2). If the absolute lymphocyte count at 48 hours is greater than 1200 cells/μL, it is unlikely that the patient has received a clinically significant dose of radiation. If the absolute lymphocyte count falls between 100 and 500 cells/μL at 48 hours, a significant or even lethal dose of radiation should be suspected. A level in this range is an indication for neutropenic precautions.[11] Thrombocytopenia and anemia may develop weeks later because these cell lines are less radiosensitive. Serum lipase, liver function tests, and C-reactive protein (CRP) should also be obtained and repeated daily. If the patient has been internally exposed to radioisotopes, rather than just external radiation,

TABLE 134.4 Available Resources for Assistance and Consultation During a Radiation Incident and Informational Resources

Organization	Contact	Website
Consultative		
Radiation Emergency Assistance Center/Training Site (REAC/TS)	24-hour emergency number: (865) 576-1005	www.orau.gov/reacts
Armed Forces Radiobiology Research Institute	24-hour military emergency response resource: (301) 295-0530	http://afrri.usuhs.edu
Chemical/Biological Hotline of the National Response Center	24-hour federal point of contact: (800) 424-8802	http://nrc.uscg.mil/
Informational		
US Department of Human and Health Services: Radiation and Emergency Medical Management		http://remm.hhs.gov
Center for Disease Control and Prevention: Radiation Emergencies		http://emergency.cdc.gov/radiation/
World Health Organization: Radiation Emergencies		www.who.int/ionizing_radiation/a_e/en/

obtain nasal and mouth swabs and collect 24-hour urine and feces specimens for radiation bioassay.[7] Hospital nuclear medicine departments may have equipment that can be adapted and used for the diagnosis of internal contamination (e.g., thyroid scanners and gamma cameras).

MANAGEMENT

Prehospital Care

Gathered information regarding the exposure event includes: the numbers and types of patients potentially affected, the radionuclide involved, the route of exposure, and the estimated dose of radiation. Multiple triage guidelines exist to help guide transport and decontamination of individuals in the prehospital setting and are available to the public (Table 134.4).[15,16] Most communities will have a disaster plan for radiation incidents, which should be activated if a significant number of patients are involved.

Decontamination should be initiated at the scene. Patients with abnormal vital signs need partial decontamination, such as clothing removal, at the scene before expeditious transportation to an ED or medical facility. Unstable patients, however, should be rapidly transported in lieu of decontamination measures. Pre-arrival contact and up-to-date information should be provided to the receiving hospital as far in advance as possible to facilitate preparations and local safety measures. If the community disaster plan has a designated hospital for radiation-contaminated victims, patients should be transported directly to that facility, bypassing other hospitals less equipped to care for these complicated patients.

Emergency Department

Preparation

The chaos that occurs following radiation exposure incidents highlights the need for a community disaster plan with a predetermined incident command structure empowered to make decisions about evacuation and other issues concerning the at-risk population. On notification of the numbers and types of patients involved in a radiation exposure, incident commanders make a decision about implementation of a full disaster plan versus a limited response. The hospital radiation control officer should be contacted immediately. The radiation control officer monitors all patients and medical personnel with a radiation counter and supervises the "clean-up" and routing of patients to minimize "tracking," or spread, of contamination. Information dissemination to the public is critical. Timely and accurate information and instructions should be given to a public relations representative for dissemination to the news media to minimize the chaos and paranoia that inevitably result from such incidents.

External Contamination

Radiation contamination is *not* an acute threat to the life of the patient, first responder or health care provider, and its presence does not preclude institution of lifesaving measures. If standard precautions are taken, the risk to the health care providers is minimal. This was true for the providers caring for Alexander Litvinenko, a former agent of the Federal Security Service of the Russian Federation who was poisoned with a radioactive substance. It was 3 weeks before it was determined that he was internally contaminated with polonium 210.[17] Because the risk is minimal, care for life-threatening conditions and evaluation for severe traumatic injuries takes precedence over decontamination measures. A general approach to the patient exposed to radiation developed by the Radiation Emergency Assistance Center/Training Site of Oak Ridge Associates Universities is shown in Figure 134.3.

When a person is irradiated without any contamination, as in a patient who has just received a CT scan or x-ray, no hazard exists to medical personnel and the patient may be handled like any other emergency patient.

If a patient is determined to be contaminated with radioactive material by survey with a radiation counter (such as a Geiger counter), then they require decontamination. Universal precautions, including rubber gloves, eye protection, hair covers, shoe covers, and respirators (if airborne contamination is suspected), are effective in protecting personnel and the work area from contamination. The only variation from standard precautions is to wear two sets of gloves and to change the outer pair when appropriate to avoid cross-contamination.[15] Removing the patient's clothing and placing it in a plastic bag is paramount because exposed garments are responsible for 70% to 90% of the radiation from the patient.[15] If possible, soap and water cleansing of exposed skin should be performed. All materials, including wash water, should be placed in containers and labeled as radioactive waste. After decontamination, a repeat survey is performed. Decontamination is repeated until the patient's radiation reading is equal to or below two times the background radiation level. If decontamination methods are causing damage or injury to the skin, they should be discontinued regardless of the patient's radiation survey results.[7]

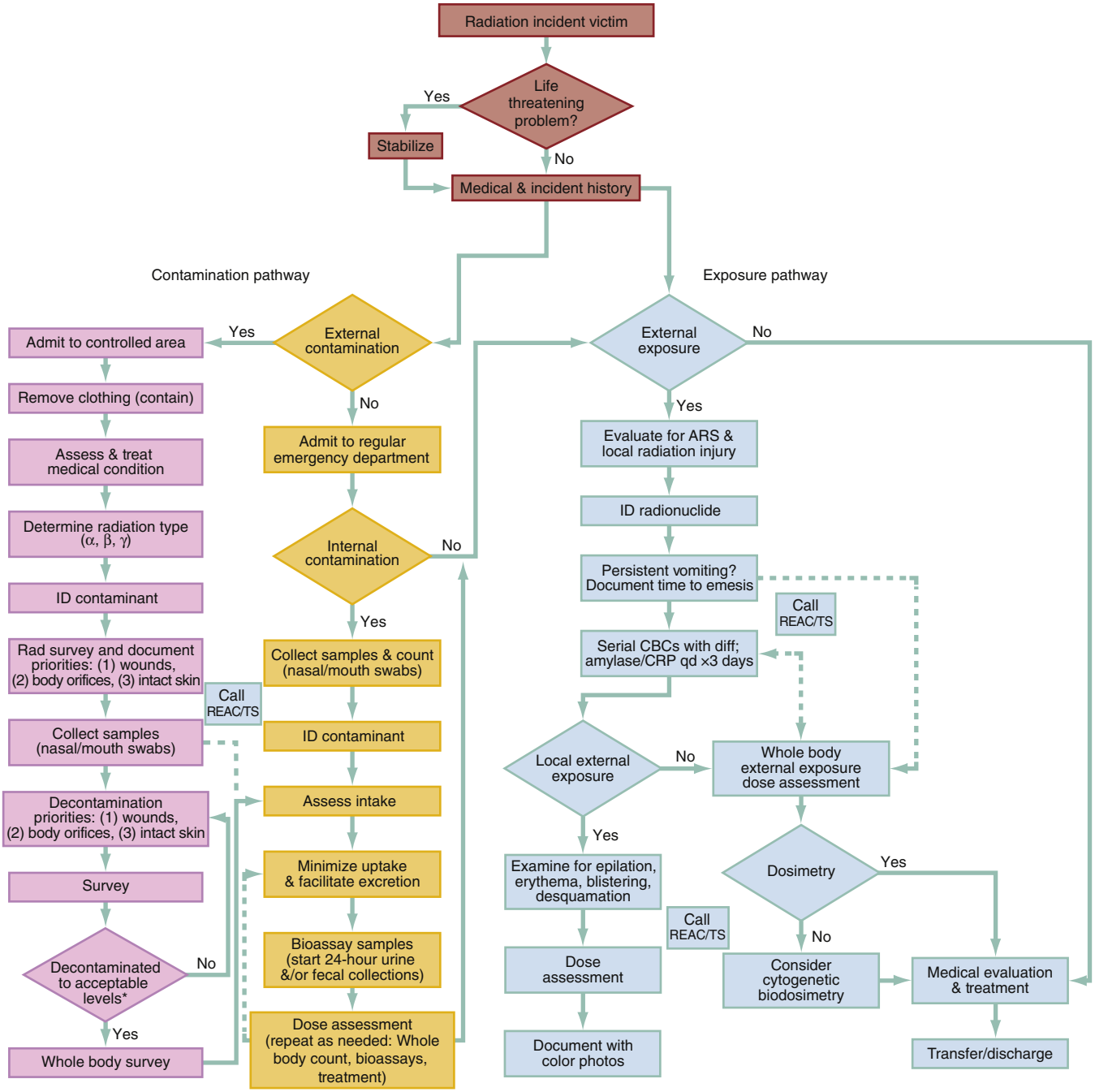

Fig. 134.3 Radiation patient treatment algorithm. *, <2–3× Natural background or no reduction in counts, medical priorities dictate stopping decontamination, health physics consultation warranted. *ARS,* Acute radiation syndrome; *CBC,* complete blood count; *CRP,* C-reactive protein; *diff,* differential; *ID,* identification; *qd,* on prescription; *REAC/TS,* Radiation Emergency Assistance Center/Training Site. (Used with permission and originally published by ORISE and REAC/TS under contract number DE-AC05-06OR23100 between the US Department of Energy and ORAU.)

Wounds can be decontaminated with saline or water. Using high pressure for irrigation is more important than the type of irrigation solution.[18] Remove foreign bodies and safely set these aside for further analysis. Repeat irrigation until the survey reveals decreased wound radiation. If further attempts at decontamination do not result in a decreased amount of radiation in the wound, then clinicians can proceed with standard medical treatment or surgical closure. Attempts to surgically decontaminate the wound should be avoided because this will potentially cause more localized damage.[19]

Internal Contamination

Assessing a patient for internal contamination can be difficult because most beta and alpha emitters will not be detectable with standard handheld survey devices. If a patient is externally contaminated, they have a higher risk of being internally contaminated. For internally contaminated patients, management focuses on decreasing absorption, enhancing elimination, and blocking distribution to target organs.[7] Treatment directed at internal contamination by particular radionuclides can include potassium iodide for radioactive iodine exposures,

TABLE 134.5 Radionuclides of Interest, Primary Decay Pattern, Half-Life, Major Routes of Exposure, and Recommended Treatment

	Name	Isotope	Decay	Half-Life	Route of Exposure	Treatment
University Five	Carbon 14	^{14}C	β	5700 years	Inhalation Ingestion	N/A
	Phosphorus 32	^{32}P	β	14 days	Inhalation Ingestion Skin	Phosphorus
	Iodine 125	^{125}I	γ	59 days	Inhalation Ingestion	KI
	Iodine 131	^{131}I	β, γ	8 days	Inhalation Ingestion	KI
	Californium 252	^{252}Cf	α, γ	2.6 years	Inhalation Ingestion	DTPA
Industrial Three	Iridium 192	^{192}Ir	β, γ	74 days	Inhalation Ingestion	DTPA
	Cesium 137	^{137}Cs	β, γ	30 years	Inhalation Ingestion	Prussian Blue
	Cobalt 60	^{60}Co	β, γ	5.3 years	Inhalation	DTPA
Military Five	Tritium	^{3}H	β	12 years	Inhalation Ingestion Skin	Water Diuresis
	Uranium 235	^{235}U	α	700 million years	Inhalation Ingestion	Bicarbonate
	Uranium 238	^{238}U	α	4.5 billion years	Inhalation Ingestion	Bicarbonate
	Plutonium 239	^{239}Pu	α	24,000 years	Inhalation	DTPA
	Americium 241	^{241}Am	α	430 years	Inhalation Skin	DTPA

DTPA, Diethylenetriaminepentaacetate; *KI,* potassium iodide.

bicarbonate for uranium, Prussian blue for cesium, and DTPA for plutonium and transuranics (Table 134.5).

Acute Radiation Syndrome

Hematopoietic Sub-Syndrome. Colony-stimulating factors (cytokines) that induce bone marrow hematopoietic cells to proliferate may have substantial benefit with little risk to victims who are predicted to have moderate or severe bone marrow failure. Cytokine therapy should be started for the following reasons: a greater than 2 Gy dose exposure, decrease in lymphocyte count, or if leukopenia is expected to last more than 7 days. Cytokines are started within 24 hours of exposure and continued until the absolute lymphocyte count is above 1000 cells/μL. Bone marrow transplant is considered for patients who continue to have prolonged leukopenia (2 to 3 weeks) in spite of cytokine treatment; however, the patients must not have other significant organ involvement.[11] Prophylactic antibiotics are given in accordance with the Infectious Disease Society of America recommendations for neutropenia.[19]

Gastrointestinal Sub-Syndrome. Treatment for the gastrointestinal sub-syndrome is largely supportive with antiemetics (preferably serotonin receptor antagonists such as ondansetron), antidiarrheals, fluid resuscitation, antibiotics, and monitoring for signs of gastrointestinal perforation.

Neurovascular Sub-Syndrome. Patients who develop signs and symptoms consistent with this sub-syndrome within the first 24 hours should be provided palliative comfort care, because they likely sustained a lethal dose of radiation.

Local Radiation Injury

Patients who sustained an LRI are managed in a manner similar to thermal burn patients.[14,20] Treatment at a burn center is preferred for débridement and wound care. Eventual extremity amputation may be necessary in patients who present with symptoms such as pain and erythema shortly after radiation exposure. Due to the chronic vascular injury and the potential for even minor trauma to the area to recapitulate the injury, the following are important in the treatment of LRI: topical corticosteroids, hyperbaric oxygen (HBO) therapy, pentoxifylline and vitamin E therapy, and appropriate wound care. New treatments currently under investigation include gene therapy, topical administration of growth factors, and laser therapy.[20]

Psychological Consequences

The general public harbors a profound fear of radiation and its effects on the body. Radiation is one of the most dreaded components of a terrorist attack or industrial disaster.[21] People are fearful of the long-term effects of radiation exposure, such as cancer, and especially with their children. This fear can lead to ostracizing people or things associated with the event. Furthermore, those who develop ARS or other illnesses related to radiation may have significant fear and depression requiring psychological posttraumatic support. Moreover, both health

care providers and communities as a whole are also at risk for psychological effects from a radiation incident. As a result, proper information dissemination to the public and incorporation of behavioral health professionals early into the disaster response are extremely important.

DISPOSITION

The disposition will depend in part on the scale of the event and the availability of medical resources. A mass casualty event may place a strain on surge capacity, requiring disaster triage and resource rationing. Fortunately, large-scale radiation events are rare, and most radiation incidents have generated small numbers of patients requiring emergency or intensive care. The time of onset to vomiting can be useful in determining likelihood of survival. Patients who experience vomiting within 2 hours of exposure will require hospitalization and careful medical observation, because they are likely to have sustained life-threatening doses of radiation. Patients with severe burns and those requiring surgical management should be transferred to a burn unit, preferably within 72 hours from the time of radiation exposure.

ADDITIONAL RESOURCES

Many resources are available for both assistance in diagnosing and managing radiation injuries and for reporting of incidents. Table 134.4 lists resources that can help guide diagnosis and treatment of radiation emergencies and provide evidence-based information for those without formal radiation medicine expertise.

The authors wish to thank and acknowledge Daniel O. Hryhorczuk for his expertise and contributions to this chapter in previous editions.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 134: QUESTIONS AND ANSWERS

1. Your Emergency Department receives a report of a "dirty bomb" explosion with multiple injuries and deaths on scene. Which injuries would you be *most* likely to see?

a. Cutaneous (local) radiation injuries
b. Gastrointestinal radiation injuries
c. Hematopoietic radiation injuries
d. Neurologic radiation injuries
e. Soft tissue and orthopedic injuries

Answer: E. "Dirty bomb" is a term for a traditional explosive device to which an amount of radioactive material has been added. The greatest risk of injury is from traditional blast/explosive effects. The risk of radiation injury and contamination from a "dirty bomb" is extremely low. The small amount of radioactive material that survives the explosion is concentrated in the area immediately around the explosion, where victims are likely killed by the blast itself.

2. Which of the following is the proper sequence for caring for patients from a mass casualty incident involving potential radiologic contamination?

a. Decontamination, assess with radiation meter, emergency stabilization, mass casualty triage
b. Assess with radiation meter, decontamination, mass casualty triage, emergency stabilization
c. Assess with radiation meter, decontamination, emergency stabilization, mass casualty triage
d. Mass casualty triage, emergency stabilization, assess with radiation meter, decontamination
e. Decontamination, emergency stabilization, mass casualty triage, assess with radiation meter

Answer: D. In radiation incidents, the immediate risk to patients and providers from radiation injury is low. The most immediate risks are from traditional ABCD compromises. Thus, mass casualty triage and emergency stabilization take precedence, followed by an assessment for radiologic contamination, and decontamination if needed. This is in contrast to chemical or biologic incidents, where decontamination takes precedence.

3. A worker in your hospital's blood bank comes into the emergency department (ED) complaining that he has been exposed to radiation on an ongoing basis for approximately 1 month. He reports his job duties include irradiating blood products to be used in the hospital and that he has not been wearing protective clothing. He reports a burning sensation in his hands. His physical examination is normal. What is the appropriate course of action?

a. Admit for observation
b. Decontaminate the patient, admit for observation
c. Decontaminate the patient, discharge home
d. Decontaminate the patient, place on isolation, admit for observation
e. Educate patient and arrange appropriate follow-up

Answer: E. This patient has been irradiated but not contaminated. Patients who are exposed to external beam radiation are not made radioactive and are not a hazard to others. Decontamination and isolation are not necessary. With a normal physical examination and minimal symptoms, this patient can be followed as an outpatient. The most important action in this instance is to educate the patient.

CHAPTER 134: QUESTIONS AND ANSWERS—cont'd.

4. What is the most important laboratory test to be performed 48 hours after exposure in determining the prognosis of a patient exposed to a significant radiation source?
   a. Absolute lymphocyte count
   b. Absolute neutrophil count
   c. Genetic karyotype
   d. Platelet count
   e. Aspartate aminotransferase

Answer: A. Monitoring the kinetics of lymphocyte depletion during the first 48 hours following a radiation exposure is very useful at estimating the radiation dose received. The 48-hour absolute lymphocyte count is the most important prognostic indicator. Levels greater than 1200/μL indicate a clinically insignificant dose of radiation and an excellent prognosis. Levels less than 500/μL indicate a significant and possibly lethal exposure. None of the other answer choices carry prognostic significance.

5. Which of the following symptoms within the first 24 hours after a significant radiation exposure would indicate a lethal dose of radiation?
   a. Bruising
   b. Gait ataxia
   c. Nausea and vomiting
   d. Skin burns
   e. Shortness of breath

Answer: B. The neurologic system is the most resistant to radiation injury, requiring at least a 10 Gy dose to be affected. The development of neurologic symptoms (such as altered mental status, focal weakness/paralysis, dizziness, ataxia, seizures) within 24 hours of exposure indicates a lethal dose of radiation. The hematopoietic system is the most radiosensitive (can be affected by as little as 0.5 to 1 Gy), followed by the gastrointestinal system (more than 5–7 Gy). The skin will be affected by local doses of radiation greater than 3 to 5 Gy.

6. A 45-year-old man is inadvertently exposed to a radiation field of 850 mSv/hour for 4 hours while working on the clean-up of a nuclear power plant. In addition to general supportive care, which of the following medications may improve his survival?
   a. Acyclovir
   b. Colony-stimulating factor (cytokines)
   c. Diethylenetriaminepentaacetate (DTPA)
   d. Erythropoietin
   e. Potassium iodide

Answer: B. This patient's radiation dose is sufficient to produce the hematopoietic component of acute radiation syndrome (ARS). Cytokines or colony-stimulating factors have shown modest effects in improving survival. Irradiated patients may develop oral herpes, and acyclovir can be used for treatment but does not affect survival. Anemia is present in most irradiated patients but is typically not clinically significant, and erythropoietin has no role. DTPA is a chelating agent that can be used for patients with internal exposure to plutonium or transuranics. Potassium iodine is useful if a patient is exposed to radioactive iodine, because it will compete with the radioactive iodine for uptake into the thyroid gland, resulting in overall less radioactive uptake.

135

Care of the Poisoned Patient

Timothy J. Meehan

KEY CONCEPTS

- Toxidromes are constellations of signs and symptoms based primarily on vital signs and neuropsychiatric functions that are characteristic manifestations of certain toxic exposures. Recognition of the presence of a toxidrome can suggest a potential intoxicant and guide early interventions and management strategies. Examples of toxidromes include sympathomimetic, antimuscarinic, cholinergic, sedative-hypnotic, and opioid categories.
- Qualitative urine drug assays have limited roles in the clinical setting and are inferior to quantitative serum levels in terms of guiding specific therapy.
- Syrup of ipecac is not indicated in the emergency department (ED) care of a poisoned patient. Gastric lavage is not part of routine care. When given in a timely fashion (1-hour post ingestion), activated charcoal may be indicated for potentially lethal agents in alert, cooperative patients as noted in Figure 135.1. Whole-bowel irrigation is rarely useful for management of poisoned patients but is potentially helpful for specific poisonings, such as metals, illicit drug packets, or sustained-release medications.
- Serum alkalinization enhances urinary drug elimination for certain drugs and is indicated for significant poisoning caused by salicylates, phenobarbital, and methotrexate.
- Hemodialysis is best suited to remove poisons of low molecular weight, low protein binding, and high water solubility; examples include methanol, ethylene glycol, lithium, and salicylates.
- Regional Poison Control Centers (US: 1-800-222-1222) or a medical toxicologist can assist with antidotal therapy and may help facilitate patient disposition.
- If the motivation behind the toxic exposure was self-harm, a psychiatric consultation is warranted. Patients with substance use disorders should be referred to a detoxification center or designated program.

PRINCIPLES OF TOXICITY

Most poisoned patients seen in the emergency department (ED) are adults with intentional drug overdoses. The second most common scenario involves accidental poisoning in children, which actually represents the majority of calls to regional poison control centers.[1] Additionally, other frequent causes of toxicity include: illicit drugs of abuse, accidental poisoning from pharmaceutical agents (drug-drug interactions as well as chronic toxicity), environmental exposures, and envenomations. Occupational chemical exposures, both industrial and agricultural, represent other important sources of potential toxicity. In the ED, it is important to evaluate and recognize scenarios where there may be immediate or delayed toxicity, in order to guide strategies for decontamination, enhanced drug elimination, and administration of antidotes when indicated.

When evaluating a patient with a particular ingestion, essential historical points include: the agent itself, the route of exposure, the amount ingested, possible co-ingestants, and the timing of the exposure. Knowing these facts can help make a determination regarding the expected course of care in the ED and help to mobilize diagnostic and therapeutic resources.

CLINICAL FEATURES

Toxicologic History and Physical

Oftentimes, the poisoned patient may be altered, obtunded, or uncooperative with the examiner. This leaves the history limited to that which can be gleaned from witnesses, such as paramedics or family, and the information generated from physical examination findings over which the patient does not have conscious control.

Historical information should be pulled from all available sources. A family member or friend may offer insight into the circumstances behind the patient's exposure (e.g., intentional or accidental). Information regarding what medications or substances were available to the patient, and the timing of ingestion also is important. Paramedics should bring in all medication bottles present at the scene, not just the patient's prescribed medications or alleged ingestion; if they do not, someone should be sent to the patient's dwelling to retrieve them. Frequently, confusion as to what exactly was ingested can occur (e.g., ibuprofen mistaken for aspirin or acetaminophen) and this can lead a provider down the wrong path. A patient attempting suicide may intentionally mislead the ED staff, or medications may have been stored in mislabeled containers. Other sources of potentially useful information include state controlled-substance registries, pharmacy records, and previous medical records. Accessing the patient's text-messaging history also may be helpful, if the patient consents to this or if friends and family provide this collateral information of their own accord.

For chemical exposures in either the home or workplace, avoid exposure to other individuals in the ED. Proper identification of the substance is important to initiate care and obtain product safety information, such as a Material Safety Data Sheet. Consequently, one could consider taking a picture of the label including any precise chemical

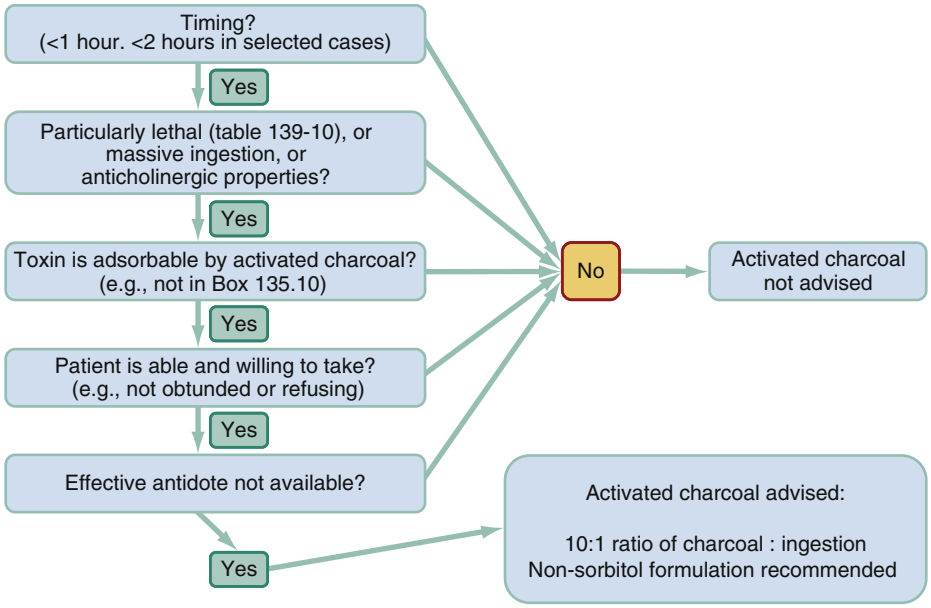

Fig. 135.1 Indications for early administration of activated charcoal 1 hr post-ingestion.

BOX 135.1 Agents Affecting Pupil Size

Miosis (COPS)
Cholinergics, clonidine, carbamates
Opioids, organophosphates
Phenothiazines (antipsychotics), pilocarpine, pontine hemorrhage
Sedative-hypnotics

Mydriasis (SAW)
Sympathomimetics
Anticholinergics
Withdrawal syndromes

Toxicology acronyms listed in Boxes (135.1–12) were created and previously published by Timothy B. Erickson (used and modified with permission.)

BOX 135.2 Agents Causing Coma or Seizures

Coma (LETHARGIC)
Lead, lithium
Ethanol, ethylene glycol, ethchlorvynol
Tricyclic antidepressants, thallium, toluene
Heroin, hemlock, hepatic encephalopathy, heavy metals, hydrogen sulfide, hypoglycemics
Arsenic, antidepressants, anticonvulsants, antipsychotics, antihistamines
Rohypnol (sedative hypnotics), risperidone
Gamma-hydroxybutyrate (GHB)
Isoniazid, insulin
Carbon monoxide, cyanide, clonidine

Seizures (OTIS CAMPBELL)
Organophosphates, oral hypoglycemics
Tricyclic antidepressants
Isoniazid, insulin
Sympathomimetics, strychnine, salicylates
Camphor, cocaine, carbon monoxide, cyanide, chlorinated hydrocarbons
Amphetamines, anticholinergics
Methylxanthines (theophylline, caffeine), methanol
Phencyclidine (PCP), propranolol
Benzodiazepine withdrawal, botanicals (water hemlock, nicotine), bupropion, GHB
Ethanol withdrawal, ethylene glycol
Lithium, lidocaine
Lead, lindane

numbers; if a substance is brought to the ED, take appropriate steps to avoid further exposure, such as sealing in an airtight container.

Poisoned patients are frequently unwilling or unable to participate in an interactive physical examination. The toxicologic physical examination, therefore, rests upon observing factors that do not require cooperation to elicit. Many ingested substances can cause derangement of the pulse, respiratory rate, as well as blood pressure. Rapid and accurate recording of the patient's vital signs, including pulse oximetry and a rectal core temperature, should be done and repeated at appropriate intervals depending on the suspected toxin. Patients with hemodynamic instability or obtundation should be considered for continuous monitoring, at least initially until stabilized. The overall level of consciousness, pupillary size, and presence or absence of seizure activity may suggest a particular agent (Boxes 135.1 and 135.2). Examination of the skin and mucous membranes with particular attention to discoloration and level of moisture may suggest poisoning by any of several agents (Box 135.3); it may also reveal evidence of injection drug abuse, such as "track marks" or ulcerations from "skin popping." A careful neurologic examination focusing on the level of muscle tone, clonus, or hyperreflexia can assist in the diagnosis of serotonin syndrome or neuroleptic malignant syndrome (NMS). Certain intoxicants may have particular odors associated with them; the presence of such an odor ought to alert the clinician to the possibility of poisoning by one of these agents (Table 135.1); however, the absence of a characteristic smell does not exclude it.

Toxidromes

Toxidromes are constellations of signs and symptoms based on autonomic and neurochemical processes that can suggest a particular class of exposure and direct management and therapy. The five traditionally described entities include the sympathomimetic, anticholinergic (antimuscarinic), cholinergic, sedative/hypnotic, and opioid toxidromes.

BOX 135.3 Agents Causing Skin Findings

Diaphoretic Skin (SOAP)
Sympathomimetics
Organophosphates
Acetylsalicylic acid or other salicylates
Phencyclidine (PCP)

Dry Skin
Antihistamines, anticholinergics

Bullous Lesions or Blisters
Barbiturates and other sedative-hypnotics
Mustard gas
Snakes and spiders

Flushed or Red Appearance
Anticholinergics, niacin
Boric acid
Carbon monoxide (in morbid states)
Cyanide (rare)

Cyanosis
Ergotamine
Nitrates
Nitrites
Aniline dyes
Phenazopyridine
Dapsone
Agent causing hypoxemia, hypotension, or methemoglobinemia

Acneiform Rash
Bromides
Chlorinated aromatic hydrocarbons

TABLE 135.1 Agents With a Characteristic Odor

Odor	Possible Source
Bitter almonds	Cyanide
Carrots	Cicutoxin (water hemlock)
Fruity	Diabetic ketoacidosis, isopropanol
Garlic	Organophosphates, arsenic, dimethyl sulfoxide (DMSO), selenium
Gasoline	Petroleum distillates
Mothballs	Naphthalene, camphor
Pears	Chloral hydrate
Pungent aromatic	Ethchlorvynol
Oil of wintergreen	Methylsalicylate
Rotten eggs	Sulfur dioxide, hydrogen sulfide
Freshly mowed hay	Phosgene

In addition, withdrawal disorders, serotonin syndrome, and NMS have been well described.

Sympathomimetic

This toxidrome is defined by a state of sympathomimetic excess, typically causing those effects expected from the "fight or flight" reaction. Patients are often in an altered state and may be delusional—especially with ingestion of substituted amphetamines, such as *N*-methyl-3,4-methylenedioxyamphetamine (MDMA: "ecstasy" or "molly") or synthetic cannabinoids. Patients typically present with hypertension, tachycardia, and tachypnea. They may also be hyperthermic as a consequence of an increased metabolic rate. Mydriasis and diaphoresis may also be present. In severe overdoses, derangement of cardiac output can occur. Decreased diastolic filling time coupled with dysrhythmogenesis can result in circulatory collapse and shock, which may be refractory to fluid resuscitation and pressor agents.

Anticholinergic

The anticholinergic toxidrome is frequently encountered, because many pharmaceuticals have antimuscarinic properties. It manifests as a consequence of blocking normal cholinergic tone, causing an alteration in the normal homeostatic balance between the sympathetic and parasympathetic arms of the autonomic nervous system. This allows the sympathetic side to function unopposed and generates a state of relative sympathomimesis. Therefore, many of the symptoms attributable to the anticholinergic toxidrome—delirium, hyperthermia, mydriasis, and cutaneous flushing—share similarity with the sympathomimetic toxidrome. In contrast, because the secretory glands of the skin and mucous membranes contain muscarinic acetylcholine receptors, these patients are typically dry and not diaphoretic as found in the sympathomimetic toxidrome. The typical signs and symptoms can be recalled by the mnemonic "mad as a hatter, hot as a hare, blind as a bat, red as a beet, and dry as a bone." Patients with severe anticholinergic toxicity are often altered and may be delusional, often requiring sedation in the emergency department (see Management section).

Cholinergic

The cholinergic toxidrome results from overstimulation of the parasympathetic portion of the autonomic nervous system, which maintains the "rest and digest" functions. These patients typically have "fluids coming from every orifice" as a consequence of increased glandular secretion, and present with diaphoresis, urination, miosis, bronchorrhea, emesis, lacrimation, lethargy, and salivation (Box 135.4). Agents of concern are primarily anticholinesterase agents, such as organophosphates and carbamate insecticides. These substances are readily available as pesticides; but they have also been engineered as weapons of mass destruction, typically referred to as nerve gases (e.g., sarin gas) and more recently the novel or *Novichok* agents. It is important to rapidly recognize this toxidrome because patients frequently die from excessive bronchorrhea, effectively drowning in their own secretions, unless timely antidotal therapy and cholinesterase regenerators are given.

Nicotine poisoning from tobacco can occur in children who ingest detritus, such as used cigarettes or chewing tobacco, as well as liquids from electronic cigarettes.[2] Nicotine stimulates the nicotinic acetylcholine receptors in the autonomic nervous system. This is the first postsynaptic step in both the sympathetic and parasympathetic subsystems. Given the role of nicotine in both the central and peripheral autonomic nervous systems, the clinical picture in these poisonings may resemble both sympathomimetic and cholinergic toxidromes as noted in Box 135.4.

Sedative/Hypnotic

This toxidrome primarily presents with sedation and occurs on a spectrum depending on the particular substance, route, and potency. In severe ingestions, a state of general anesthesia may be reached with loss of muscle tone and airway protective reflexes. Additionally, overdose can be severe enough to cause hypothermia through suppression of muscular thermogenesis. The sedative/hypnotic toxic syndrome is well known in the ED, largely because ethanol intoxication is frequently seen. Other agents such as benzodiazepines and barbiturates will also cause a similar picture, as will illicit substances such as

BOX 135.4 Toxidrome Symptoms

Cholinergic

Muscarinic (DUMBELLS)

Diarrhea, diaphoresis
Urination
Miosis
Bradycardia
Bronchorrhea
Emesis
Lacrimation
Lethargic
Salivation

Nicotinic: Days of Week

Mydriasis
Tachycardia
Weakness
Tremors
Fasciculations
Seizures
Somnolence

Anticholinergic

Hyperthermia (HOT as a hare)
Flushed (RED as a beet)
Dry skin (DRY as a bone)
Dilated pupils (BLIND as a bat)
Delirium, hallucinations (MAD as a hatter)
Urinary retention (DRY as a bone)
Tachycardia

Opioid

Acute Intoxication/Overdose

Miosis
Hypoventilation
Depressed mental status/coma

Withdrawal

Withdrawal
Diarrhea
Mydriasis
Goose flesh
Tachycardia
Lacrimation
Hypertension
Yawning
Cramps
Hallucinations
Seizures (with ethyl alcohol [ETOH] and benzodiazepine withdrawal)

Sympathomimetic

Hyperthermic
Flushed
Diaphoretic
Mydriatic
Agitated
Tachycardic
Seizures

gamma-hydroxybutyrate (GHB). The incidence of concomitant traumatic injuries (from falls or syncope) may be high in these patients, and providers should exclude their presence.

Opioid

Similar to sedative/hypnotics, the opioid toxidrome also involves sedation and a diminished respiratory drive. With the notable exception of pentazocine and propoxyphene, this toxidrome causes pupillary miosis. The diagnosis is confirmed by noting a rapid response to naloxone, a direct opioid receptor antagonist. However, because certain opioids have higher potencies, a lack of response to this reversal agent does not exclude opioid intoxication. Furthermore, this is a clinical diagnosis because not all opioids will be detectable by the standard drug screen (discussed later).

Serotonin Syndrome

A state of serotonergic excess defines this toxidrome, and it is often precipitated by the addition of a new serotonergic agent or a substance that interferes with the metabolism of a previously tolerated agent. Typically described with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), it has been reported with cyclic antidepressants, atypical antipsychotics; and nonpsychiatric medications such as tramadol and ondansetron. Serotonin syndrome typically occurs within hours to days of introduction of a new medication, although it has been described in a delayed fashion due to the prolonged half-lives of some antidepressants. The manifestations of serotonin syndrome include altered mental status, agitation, autonomic instability (hyperthermia, diaphoresis, hypertension), and most notedly, neuromuscular abnormalities (hyperreflexia and clonus).

BOX 135.5 Altered Mental Status

AEIOU

Alcohol/acidosis
Encephalopathy/electrolytes
Infection
Opioids/overdose
Uremia

Tips

Trauma
Insulin (hypoglycemia/hyperglycemia)
Psychosis
Seizure/stroke

Neuroleptic Malignant Syndrome

Similar to serotonin syndrome, NMS also presents with altered mental status, agitation, autonomic instability, severe hyperthermia, and neuromuscular abnormalities. Unlike serotonin syndrome, however, peripheral muscular effects tend toward rigidity and hyporeflexia rather than clonus and hyperreflexia. It is due to dopaminergic depletion secondary to chronic use of dopamine antagonists, such as antipsychotics.

DIFFERENTIAL DIAGNOSES

Frequently, poisoned patients have some level of delirium as part of their presentation. As such, excluding other causes of altered mental status while initiating appropriate toxicologic therapy is appropriate (Box 135.5). Any "intoxicated" patient presenting to the ED should

BOX 135.6 Predicting Toxicity from Vital Signs

Bradycardia (PACED)
Propranolol (β-blockers), poppies (opioids), propoxyphene, physostigmine
Anticholinesterase drugs, antiarrhythmics
Clonidine, calcium channel blockers
Ethanol or other alcohols
Digoxin, digitalis

Tachycardia (FAST)
Free base or other forms of cocaine, Freon
Anticholinergics, antihistamines, antipsychotics amphetamines, alcohol withdrawal
Sympathomimetics (cocaine, caffeine, amphetamines, phencyclidine [PCP]), solvent abuse, strychnine
Theophylline, tricyclic antidepressants (TCAs), thyroid hormones

Hypothermia (COOLS)
Carbon monoxide
Opioids
Oral hypoglycemics, insulin
Liquor (alcohols)
Sedative-hypnotics

Hyperthermia (NASA)
Neuroleptic malignant syndrome (NMS), nicotine
Antihistamines, alcohol withdrawal
Salicylates, sympathomimetics, serotonin syndrome
Anticholinergics, antidepressants, antipsychotics

Hypotension (CRASH)
Clonidine, calcium channel blockers
Rodenticides (containing arsenic, cyanide)
Antidepressants, aminophylline, antihypertensives
Sedative-hypnotics
Heroin or other opioids

Hypertension (CT SCAN)
Cocaine
Thyroid supplements
Sympathomimetics
Caffeine
Anticholinergics, amphetamines
Nicotine

Rapid Respiration (PANT)
Phencyclidine (PCP), paraquat, pneumonitis, phosgene
Acetylsalicylic acid (ASA) and other salicylates
Noncardiogenic pulmonary edema, nerve agents
Toxin-induced metabolic acidosis

Slow Respiration (SLOW)
Sedative-hypnotics (barbiturates, benzodiazepines)
Liquor (alcohols)
Opioids
Weed (marijuana)

have the reversible causes of altered mental status excluded, such as hypoglycemia and nutritional deficiencies.[3] Trauma is frequently coincident with intoxication, so a careful unclothed examination looking for evidence of head trauma and other traumatic injuries should be part of the initial evaluation.

The physical examination may also reveal findings that could suggest specific intoxicants, as noted in Box 135.6. The most important diagnostic approach is maintaining a broad differential diagnosis of both toxicologic and non-toxicologic causes for the patient's presentation and avoid making a premature conclusion to the case. In these cases, differential diagnoses may be extremely broad such as when ingestion of a toxin is not known or felt unlikely.

DIAGNOSTIC TESTING

Diagnostic testing is guided by the clinical findings and suspected toxin(s) involved. When a patient presents with altered mental status and hyperthermia, testing may focus on differentiating a toxic cause from thyrotoxicosis or acute infectious diseases. Patients with intoxication and evidence of trauma may require evaluation for head trauma as a cause of their altered mental status. In many instances, it is known that the patient has a potentially toxic exposure but some or all of the involved toxins have not been implicated or identified. The approaches to individual toxins and syndromes are outlined in the relevant chapters. In the setting of an unknown overdose or exposure, a broad array of laboratory testing is often used to screen for abnormalities and potentially elucidate the clinical picture. The diagnostic studies routinely checked are: complete blood count, serum chemistry with renal function, liver function tests, urinalysis (with a pregnancy test if appropriate), urine toxicology screen, serum ethanol concentration, arterial blood gas, serum lactate, and a bedside glucose.

BOX 135.7 Commonly Available Serum Drug Levels

Acetaminophen
Acetylsalicylic acid (salicylate)
Carbamazepine
Carbon monoxide
Digoxin
Ethanol
Ethylene glycol
Iron
Isopropyl alcohol
Lead
Lithium
Methanol
Methotrexate
Phenobarbital
Phenytoin
Valproic acid

Based on these results, or when the ingestion is known, other tests such as specific serum concentrations may be obtained; Box 135.7 lists those drug levels commonly available in most hospitals. When assays for a particular agent are not available, or are not performed on site, empirical treatment generally begins before results are available. Reference laboratories are available to analyze specific and unique assays, but the turn-around time is often delayed and not clinically applicable in the emergency department.

If the blood gas shows the presence of a metabolic acidosis, calculating the anion gap can further refine the possible etiologies.

The calculation is: [Na] − ([HCO_3] + [Cl]). The normal range is 8 to 12 mEq/L.

Metabolic acidosis without an anion gap typically results from loss of bicarbonate (diarrhea, renal tubular acidosis) or gain of chloride-containing compounds (ammonia, calcium chloride). Metabolic acidosis associated with an anion gap results from an increase in unmeasured serum anions and suggests several specific toxins and disease states (Box 135.8).

BOX 135.8 Substances Causing Wide Anion-Gap Acidosis

Metal Acid Gap

M Methanol, Metformin, Massive overdose
E Ethylene glycol
T Toluene
A Alcoholic ketoacidosis
L Lactic acidosis
A Acetaminophen (large overdose)
C CO, Cyanide, Colchicine
I Isoniazid (INH), Iron, Ibuprofen
D Diabetic ketoacidosis (DKA)
G Generalized seizure inducing drugs
A ASA (salicylates)
P Paraldehyde, Phenformin

When ingestion of a toxic alcohol (such as methanol, ethylene glycol, or isopropanol) is suspected, calculating the osmolal gap may be helpful because early in the poisoning course the patient may be minimally or non-acidemic. Furthermore, urine fluorescence is not sufficiently sensitive to be reliable and its absence cannot be used to "rule out" ethylene glycol ingestion. The osmolal gap is discussed in Chapter 136.

Toxicology "screens" may also be helpful in diagnosing an unknown ingestion, provided that the limitations of these panels are understood. Blood toxicology screens can be falsely negative if the ingested drug has a short half-life and the sample is not drawn soon enough after the exposure. Urine toxicology screens are more reliable, because they typically have a longer time period for positive detection, typically 24 to 72 hours. Urine toxicology screens typically include phencyclidine (PCP), cocaine, opioids, amphetamines, and cannabinoids; however, these can vary among institutions, so knowing what is available in one's facility is important in interpreting a positive or negative screen. The urine screen is also a qualitative, not a quantitative test; as such, a positive result does not necessarily imply acute toxicity. A urine toxicology screen can be falsely positive due to cross-reactivity between agents (such as a "positive" phencyclidine or PCP screen in the setting of dextromethorphan ingestion). Alternatively, urine screens can be falsely negative if the substance ingested does not cross-react with the tested analyte—such as methadone, which does not cross-react with the opiate component of the urine toxicology screen (Table 135.2). Ultimately, the diagnosis of intoxication is clinical; urine drug screening may be confirmatory but should

TABLE 135.2 Urine Drug Screen Limitations

Assay	False Positive	True Positive (Therapeutic Use)	False Negative
Amphetamines	Many; some clinically relevant ones include: Amantadine Bupropion Labetalol Promethazine Ranitidine Trazodone	ADHD medications: Dextroamphetamine, methamphetamine Phenylephrine Pseudoephedrine	"Designer amphetamines" Molly Ecstasy
Benzodiazepines	Sertraline Oxaprozin		Alprazolam Flurazepam Midazolam "Z" drugs (zolpidem, zaleplon, zopiclone, eszopiclone)
Cannabinoids	Dronabinol Efavirenz PPI	Medical marijuana CBD oil (contaminant)	Synthetic marijuana: K2/Spice
Opiates	Dextromethorphan Diphenhydramine Quinolones		Synthetic opioids: Demerol, fentanyl, methadone, propoxyphene Semisynthetic opioids (may have some cross-reactivity): Hydrocodone, hydromorphone, oxycodone
Phencyclidine (PCP)	Dextromethorphan Diphenhydramine Ibuprofen Tramadol	Ketamine	
Cocaine	Coca leaf tea	Cocaine-containing anesthetics (topical TAC)	

ADHD, Attention deficit hyperactivity disorder; *PPI,* proton pump inhibition; *TAC,* tetracaine, adrenaline (epinephrine), and cocaine.

not supplant clinical evaluation and judgment nor should it delay therapy.

In addition to the blood work discussed earlier, one should obtain an electrocardiogram (ECG) if the patient is tachycardic or bradycardic or may have ingested a cardiotoxic agent that can prolong the QRS complex or QT intervals, such as cyclic antidepressants, antimalarials (e.g., chloroquine), and antipsychotic agents. Table 135.3 provides guidance regarding for which patients an ECG should be obtained.

MANAGEMENT

The general management of a poisoned patient involves providing appropriate supportive care, undertaking decontamination, enhancing elimination, and providing specific antidotal therapy when indicated. Specific strategies will be discussed at length in the following chapters regarding specific poisons. However, the basic framework remains the same.

Antidotes do not exist for every potential poisoning, and thus supportive care is the cornerstone of managing the poisoned patient. Providing resuscitation by ensuring airway protection and adequacy of ventilation while maintaining the circulatory status of the patient with crystalloids and vasopressor support is the prime focus. If the airway is compromised or in danger of becoming so, or if the respiratory effort is insufficient to maintain appropriate ventilation, intubation is usually the preferred course (with special care in the situation of a salicylate poisoning, which is discussed in Chapter 139).

Vascular access needs to be obtained, with peripheral or central venous catheters, intraosseous lines are also viable access points from the toxicologic perspective, because there are no known contraindications to antidotal therapy through this route. Once supportive care has been initiated and the patient stabilized, one should then progress to a systematic assessment of decontamination strategies, enhanced elimination, focused therapy (antidotes), and obtaining consultation.

Decontamination

Decontamination is the process of preventing systemic absorption. In the case of ocular or dermal exposure, this is achieved by copious irrigation with water, after removal of contaminated clothing to expose the area. Water irrigation is not used for metallic potassium, magnesium, or sodium (found in "tracer" ammunition, for example), because these can ignite on contact with water. Instead, in these very rare exposures, the area should be covered with petroleum jelly or mineral oil.

SYRUP OF IPECAC

Inducing emesis with syrup of ipecac is not indicated in the care of any poisoned patient in the ED. Syrup of ipecac use is associated with significant side effects (e.g., dehydration due to intractable vomiting) and complications (e.g., aspiration pneumonitis, Mallory-Weiss tears, and gastric rupture). There are also insufficient data and evidence showing improvement in clinical outcomes with poisonings.[4]

GASTRIC LAVAGE

Gastric lavage, the process of directly removing an ingested substance from the stomach using a 30 Fr or larger orogastric tube, also has little data or evidence showing its efficacy and should not be performed routinely for the treatment of poisoned patients. Given the risks of aspiration and esophageal trauma, the American Association of Poison Centers suggests it only be employed "within an hour of ingestion of a potentially life-threatening poison which does not adsorb to activated charcoal or for which no antidote exists" and, even then, in a center with "sufficient expertise" to perform the procedure safely.[5] Only a rare overdose (such as colchicine) will meet all these criteria; and hence, despite its once widespread use, gastric lavage is mostly of historical interest only.

SINGLE-DOSE ACTIVATED CHARCOAL

Historically, single-dose activated charcoal (SDAC) has been the mainstay of gastric decontamination in medical toxicology. Activated charcoal is a carbonaceous substance that has been exposed to high heat and steam—i.e., "activated"—which results in a large surface area to volume ratio. This provides ample surface space for intralumenal ingested substances to adsorb, and thus decreases absorption into the body. Current understanding of the role of activated charcoal in poison management is based on pharmaco-toxicologic data (lethality, availability of antidotes, or alternative detoxification therapies); pharmacokinetics (area under the concentration versus time curve in controlled volunteer studies); clinical trials in patients with overdose; and collective, empirical clinical experience.[6] Studies involving healthy volunteers ingesting small (safe) doses of various agents do not accurately replicate the overdose (large ingestion) situation, so are of limited value. In addition, there are very few appropriately designed clinical studies assessing the benefit from SDAC. Therefore, due to the lack of convincing evidence demonstrating benefit in clinical outcome in human overdose, we do not recommend

TABLE 135.3 Toxicologic Electrocardiogram Manifestations

Segment/Interval	Appearance	Agent(s)	Segment/Interval	Appearance	Agent(s)
P wave	Absent	Digoxin Cholinergics Hyperkalemia	QT/QTc	Prolonged	Antipsychotics (typical and atypical), citalopram, hydrofluoric acid, methadone, ethylene glycol (oxalate byproduct)
	Notched	Quinidine			
PR interval	Prolonged	Beta-antagonists, calcium-channel antagonists, magnesium, lacosamide	T wave	Peaked	Hydrofluoric acid (hyperkalemia)
				Flattened	Lithium
QRS interval	Prolonged	Type 1 antidysrhythmics, cocaine, diphenhydramine, tricyclic antidepressants	U wave		Barium, beta-agonists, lithium, methylxanthines (caffeine, theophylline), toluene
ST segment	Scooped	Digoxin ("Salvador Dali's moustache")			

the routine use of activated charcoal following ingestion.[7] We do, however, recommend its use in certain overdose scenarios.

Although few studies have shown a reduction of morbidity or mortality attributable to activated charcoal administration, and there have been reports of pulmonary aspiration of activated charcoal with serious patient harm, these aspiration events have occurred in a minority of patients receiving activated charcoal; therefore it is considered a relatively low-risk intervention. With certain toxic exposures, SDAC administration may be reasonable after a consideration of the risk versus benefit for the patient in the context of the quantity and toxicity of the ingested substance, the time elapsed between ingestion and treatment, and the availability of alternative antidotes or decontamination procedures (e.g., hemodialysis). Benefits include decreasing primary absorption or binding during enterohepatic recirculation of a potentially toxic xenobiotic. These benefits are more likely to occur if:

- The activated charcoal is administered within one hour after ingestion, *and*
- The patient is alert, able, and willing to cooperate with administration, and anticipated to remain alert and protective of airway reflexes, *and either*
  - The substance ingested has high toxicity or is a toxic sustained-release agent, *or*
  - There is evidence of a massive ingestion of a toxic agent (e.g., salicylates)

If the patient is sedated, has an unprotected airway, or is unwilling to drink the charcoal suspension, administration is contraindicated. This may be particularly true for young children with limited ability to drink the slurry. Furthermore, one should not place a nasogastric tube solely to administer activated charcoal, because of the risk of aspiration or direct instillation of activated charcoal into the lungs, thus changing the risk-benefit ratio.

Considering all of this information, how does one decide whether activated charcoal is indicated in a specific overdose? First, the ingested drug must have a high potential for toxicity and lethality. These drugs are listed by class in Box 135.9. If the drug ingested has low toxicity (e.g., ibuprofen, diazepam), or there is an effective antidote available (e.g., *N*-acetylcysteine for acetaminophen, digoxin immune fab for digoxin), activated charcoal administration is not advised.

Second, the ingestion must be recent. For most overdoses, this means that the activated charcoal needs to be administered within one hour of the ingestion. For certain overdoses (sustained-release products, anticholinergic agents, massive ingestions), either because of pharmacokinetics or the quantity ingested, activated charcoal may be given up to 2 hours after ingestion. Many patients arrive at the ED more than 2 hours after the ingestion or ingest the drugs over a period of several hours, often with alcohol, and do not meet this time requirement. Third, the ingestion must be amenable to adsorption by activated charcoal. This eliminates rapidly absorbed toxins (e.g., alcohols) and those agents listed in Box 135.10. Fourth, the patient must be alert and anticipated to remain alert and be willing to take the activated charcoal slurry voluntarily. An algorithm guiding the administration of activated charcoal is shown in Figure 135.1. We recommend consultation with a regional poison center or medical toxicologist if there is uncertainty regarding the indications for activated charcoal.

Activated charcoal historically has most often been given in a dose of 50 to 100 grams (or 1.0 g/kg in young children), but we advise customizing the dose to the dose of the ingested agent by administering activated charcoal in a weight ratio of 10:1 (ratio of activated charcoal to drug).

BOX 135.9 Potentially Lethal Toxins Where Early Activated Charcoal Administration May Be Indicated

The Killer Cs
Cyanide
Colchicine
Calcium channel blockers
Cyclic antidepressants
Cardio glycosides
Cyclopeptide mushrooms *(Amanita phalloides)*
Cocaine
Cicutoxin (water hemlock)
Salicylates

WHOLE BOWEL IRRIGATION

In certain ingestions such as extended-release preparations, illicit drug packets, or metals (e.g., iron and lead), continuous whole-bowel irrigation may be indicated. Whole bowel irrigation (WBI) is performed with a balanced polyethylene glycol solution that does not participate in fluid exchange nor become absorbed into the body. To be effective, it requires a rate of 2 liters per hour in an adult; consequently, this will require nasogastric tube placement.[8] However, if a patient is critically ill, has hypoperfusion of the gut, or has obstruction of the bowel, WBI is contraindicated because there have been reports of increased morbidity and mortality in these clinical settings.

Enhanced Elimination

Once a toxin has been absorbed into the body, it undergoes metabolism and elimination primarily via hepatic and renal pathways. Certain substances are amenable to enhancing these elimination pathways either ex vivo as is the case with hemodialysis and its related therapies, or in vivo as is the case with multiple-dose activated charcoal (MDAC) and urinary alkalinization.

Hemodialysis and its related therapies are best suited to remove poisons of low molecular weight, low protein binding, and high water solubility; examples include toxic alcohols, lithium, and salicylates, as listed in Box 135.11. All forms of extracorporeal removal have been studied and found to be efficacious; the selection of a specific type of

BOX 135.10 Substances That Do *Not* Bind to Activated Charcoal

Phails
Pesticides
Heavy metals
Acids/alkalis
Iron
Lithium
Solvents

BOX 135.11 Dialyzable Toxins

Stumbled
Salicylates
Theophylline
Uremia
Metformin/methanol
Barbiturates
Lithium
Ethylene glycol
Depakote (valproic acid—in massive overdose)

elimination modality ought to be made based on patient-specific factors and early consultation with a nephrologist in conjunction with a medical toxicologist or poison control center.[9]

MULTIPLE-DOSE ACTIVATED CHARCOAL

Unlike preventing absorption of a drug as is the case for SDAC, multiple dose activated charcoal (MDAC) is intended to facilitate removal of a toxin that has already been absorbed. MDAC decreases xenobiotic absorption and elimination half-life when large amounts of the toxin are ingested and dissolution is delayed (e.g., concretions, bezoars, or extended release formulations). It also is believed to create a hemoperfusion substrate for the gut wall microcirculation to permit "gastrointestinal dialysis," which generates a concentration gradient into the stool for certain poisons, which are then eliminated by defecation. In addition, certain drugs are excreted in the bile, then reabsorbed by the gut, only to be re-excreted in the bile, a process called *enterohepatic circulation*. MDAC also may interfere with reabsorption of these drugs by binding them during their transit of the gastrointestinal tract. Drugs with significant enterohepatic circulation are listed in Box 135.12. As with SDAC, MDAC administration may cause pulmonary aspiration and intestinal obstruction. Aspiration is best avoided by applying the same conditions for administration as for SDAC—patient is awake, alert, and cooperating and is anticipated to remain so. Obstruction is more difficult to predict and prevent, although avoidance in situations with delayed gut motility (e.g., critical illness, opioid or anticholinergic effects) is recommended to reduce this risk.

When MDAC is indicated, the initial loading dose of an activated charcoal–to-xenobiotic ratio of 10:1 is followed by subsequent doses of 50% of the initial dose every 4 to 6 hours for up to 24 hours. MDAC may be discontinued when the patient's measurable serum levels are no longer considered in the toxic range. Take care to only use non-sorbitol containing formulations when administering MDAC; sorbitol, a non-absorbable sugar added to charcoal slurries to enhance palatability, can induce significant fluid shifts and cause profound electrolyte abnormalities (particularly in children) such as hypernatremia when a large amount is ingested, as in the case of MDAC.

SERUM ALKALINIZATION

Certain water-soluble drugs such as salicylates, methotrexate, and phenobarbital will undergo ion-trapping and enhanced urinary elimination if the serum is sufficiently alkalinized. This is especially important with salicylate poisonings, because alkalinization not only promotes elimination but also prevents salicylate crossing the blood-brain barrier into the central nervous system (CNS). Monitor the serum pH and bicarbonate level, as well as the urinary pH, with the goal being a serum pH of approximately 7.5 and a urinary pH of approximately 8.0. Also ensure that the serum potassium level is normal, because alkalinization will cause an intracellular shift of potassium and consequently increase urine reabsorption of potassium by excreting hydrogen ions into the urine; this will eliminate the pH gradient and dissipate the benefits of this process. To accomplish this, combine 150 mEq (3 amps) of 8.4% sodium bicarbonate into a liter of dextrose 5% in water (D5W) and add potassium (20 to 40 mEq total) to the intravenous fluid as well. This solution should be infused at a rate not to exceed 250 mL/hour. Barring concerns for fluid overload (particularly in elderly and renal failure patients) we recommend infusing at 250 mL an hour.

BOX 135.12 Substances Amenable to Multiple-Dose Activated Charcoal

ABCDQ
Aminophylline/theophylline
Barbiturates
Carbamazepine/concretion forming drugs (e.g., salicylates)
Dapsone
Quinine

INTRAVENOUS FAT EMULSION (INTRALIPID)

Intravenous fat emulsion (IFE) is utilized for poison-induced cardiogenic shock or intractable seizures. This therapy was first described for treatment of toxicity from local anesthetics, such as bupivacaine. IFE is proposed to work primarily by two separate mechanisms: (1) the lipid sink and (2) enhanced cardiac metabolism.[10] The lipid sink theory posits that fat-soluble drugs are "soaked up" and removed from the site of toxicity, effectively increasing the volume of distribution for a fat-soluble drug. This is the predominant theory behind the use of IFE. A second theory involves optimization of cardiac metabolism. The heart under physiologic circumstances prefers free fatty acids; in times of stress, it switches to glucose metabolism for energy. A dose of IFE theoretically provides a large supply of free fatty acids to optimize energy use in the heart. In addition to providing supplemental energy for myocytes, IFE may also enhance activation of cardiac calcium channels.

Indications for IFE are not universally agreed upon. In addition to anesthetic agents, successful resuscitations have been described with refractory B-blocker overdose, calcium channel blockers, cyclic antidepressants, and bupropion and cocaine toxicity. Although originally described as a treatment for overdose patients in cardiac arrest, several reports now exist describing the successful use of IFE in critically ill patients prior to circulatory collapse and cardiac arrest. Dosing for IFE also varies in the literature. If indicated, we recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given over 2 to 3 minutes followed by an infusion of 0.25 mL/kg/min over 30 to 60 minutes, based on the most commonly recommended and described protocols; this can be given via peripheral, central, or intraosseus access.

With the exception of local anesthetic systemic toxicity (LAST), where IFE is considered front-line therapy, intralipids should only be administered to overdoses when resuscitative efforts have been refractory to other more conventional therapies (e.g., vasopressor agents, sodium bicarbonate, calcium, high-dose insulin-dextrose therapy). When considering administration of IFE therapy to an unstable overdosed patient, consultation with a medical toxicologist or regional poison center is recommended.

Despite recent enthusiasm for IFE, its use has associated complications, including extreme lipemia resulting in lab interference with blood tests (complete blood counts, chemistries, and coagulations studies), as well as acute pancreatitis, and acute respiratory distress syndrome.[11]

Focused Therapy

Although the majority of poisonings require supportive care alone, in selected ingestions specific antidotal therapy may be available. Evidence and experience support the use of several antidotes, which should be available either immediately (e.g., hospital stocked) or rapidly accessed (e.g., transported within a few hours). These antidotes and their indications can be found in Table 135.4, and their use is discussed in the relevant chapters.[12]

Toxicology Consultation

Most poisoning cases are straightforward and appropriately handled by the emergency clinician. When the poisoning is severe, high risk,

TABLE 135.4 Selected Antidotes and Their Indications

Antidote	Indication (Poison)
N-acetylcysteine	Acetaminophen
Fomepizole (4-MP)/ethanol	Methanol/ethylene glycol
Oxygen/hyperbarics	Carbon monoxide
Naloxone	Opioids, clonidine
Physostigmine	Anticholinergics
Atropine/pralidoxime (2-PAM)	Organophosphates
Methylene blue	Methemoglobinemia
Nitrites/hydroxycobalamin	Cyanide
Deferoxamine	Iron
Dimercaprol (BAL)	Arsenic, lead
Succimer (DMSA)	Lead, mercury
CaEDTA	Lead
Fab fragments	Digoxin, crotalids
Glucagon	β-blockers
Sodium bicarbonate	Salicylates, tricyclic antidepressants
Insulin/Glucose, calcium	Calcium channel antagonists, B-blockers
Dextrose, glucagon, octreotide	Oral hypoglycemic agents
Pyridoxine (vitamin B_6)	Isoniazid (INH)
Intravenous fat emulsion	Local anesthetic systemic toxicity
	Certain fat-soluble medications

2-PAM, 2-pralidoxime; *4-MP,* 4-methylpyrazone; *BAL,* British antilewisite; *CaEDTA,* calcium ethylenediamine tetracetate; *DMSA,* dimercaptosuccinic acid.

involves unfamiliar or multiple toxins, or occurs in a patient with significant comorbidity, we recommend consultation with a Poison Control Center or, if available, a medical toxicologist. Consultation can assist the bedside clinician in the determination of an unknown ingestion, critical management decisions, or whether an antidote or invasive procedure, such as hemodialysis, is advisable.

In the United States, a national toll-free phone number has been established that will route a practitioner to their nearest Poison Control Center. This number is 1-800-222-1222.[1]

DISPOSITION

Patients with severe toxicity (for example seizures, persistent cardiovascular instability, airway compromise, or significant metabolic derangements) should be admitted to an intensive care setting. Patients who are asymptomatic on arrival but have ingested a potentially dangerous substance or an extended-release preparation that could cause significant deterioration in their clinical status, ought be admitted to either an inpatient setting or an observation unit for 24 hours, or until peak toxicity has passed and the patient is physiologically stable. For patients who are asymptomatic after an ingestion of a minimally toxic substance and for whom other ingestions and psychiatric issues have been addressed, discharge after the ED visit, which typically takes at least 4 to 6 hours, is appropriate.

If the motivation behind the ingestion, was suicidality, or self-harm, a psychiatric consultation is warranted. If a suicidal patient is to be admitted medically for observation, it is important to ensure that a dedicated sitter or other type of secure environment is available to prevent any further patient inflicted self-injury.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 135: QUESTIONS AND ANSWERS

1. A 23-year-old man presents with confusion. His vital signs are blood pressure 105/77 mm Hg, heart rate 69 beats per minute, respiratory rate 10 breaths per minute, temperature 37.0°C, and arterial oxygen saturation (SaO_2) 96% on 2 L NC. His eyes open only to pain, he localizes to pain, but he does not follow commands and his speech is confused. Otherwise, his physical examination is normal. After intravenous (IV) access is obtained and he is placed on continuous cardiac monitoring, what is the most appropriate next step?

a. Check arterial blood gases (ABG).
b. Check bedside serum glucose.
c. Give 50% dextrose 1 amp IV.
d. Give naloxone 2 mg IV.
e. Perform electrocardiogram (ECG).

Answer: B. All patients with altered mental status should have a rapid determination of their glucose. Although this patient has several abnormal vital signs, none necessitate immediate action. His Glasgow Coma Score (GCS) is 11, and it appears that his respiratory status is adequate. Dextrose should not be given unless hypoglycemia is documented. Naloxone is an opioid antagonist, and it could reverse the patient's confusion if it is caused by opioids. This drug could be considered once other more easily reversible causes of confusion (e.g., hypoglycemia) have been ruled out. ABG and ECG are both occasionally needed in patients with altered mental status, but neither is as urgent as glucose testing.

2. The odor on a poisoned patient can provide clues as to the substance causing the poisoning. If a patient smells of garlic, what should you be concerned about?

a. Cyanide
b. Hydrogen sulfide
c. Methyl salicylate
d. Organophosphates
e. Toluene

Answer: D. Arsenic, dimethyl sulfoxide (DMSO), yellow phosphorus, selenium, and tellurium can also have a garlic odor. Odors associated with the other answer choices are as follows: cyanide, bitter almonds; hydrogen sulfide, rotten eggs; methyl salicylate, wintergreen; and toluene, glue. Odors can aid in making the diagnosis but should not be relied on as completely diagnostic. Also, the lack of odors cannot be used to rule out a poisoning resulting from that substance.

3. A 17-year-old girl presents with delirium, tachycardia, dry skin, flushed face, decreased bowel sounds, dilated pupils, and urinary retention. A friend states that the patient had recently ingested some unknown medications in a suicide attempt. Which of the following medications is most likely responsible for the constellation of signs?

a. Alprazolam
b. Clonidine
c. Diphenhydramine
d. Hydrocodone
e. Pseudoephedrine

Answer: C. The patient is expressing the signs of classic antimuscarinic poisoning. Central nervous system (CNS) effects include the delirium and typical "picking movements" of the fingers. Suppression of the cholinergic system results in tachycardia. All secretory functions are inhibited, causing the dry, flushed skin, decreased bowel sounds, and urinary retention. Unopposed sympathetic activity results in dilated pupils. Alprazolam, clonidine, and hydrocodone can all cause the sedative toxidrome. Pseudoephedrine can lead to the sympathomimetic toxidrome, which typically has diaphoretic skin but can otherwise appear similar to an anticholinergic presentation.

4. A 27-year-old individual presents to the emergency department via emergency medical services after being "found down" with pinpoint pupils, slow breathing, and depressed mentation. The patient was given 2 mg of naloxone via the intranasal route and by the time of arrival in the ED is now awake, alert, and cooperative—and asking to leave. There is no evidence of trauma, and the patient has no other complaints. Based on your knowledge of the half-life of naloxone, when do you feel the patient will be safely dischargeable?

a. 30 minutes
b. 1 hour
c. 2 hours
d. 4 hours
e. 6 hours

Answer: D. The exact elimination half-life of naloxone is closer to 1.1 hours (1 hour 6 minutes). This is markedly shorter than the half-life of almost all opioids. For comparison, morphine has a half-life of approximately 2 hours, hydrocodone has a half-life of approximately 4 hours, and methadone has a half-life up to 30 hours. This means that repeat dosing of naloxone is often necessary when treating opioid overdose. A drug similar in action to naloxone, nalmefene, has a half-life of 10 hours and may sometimes be useful.

CHAPTER 135: QUESTIONS AND ANSWERS—cont'd.

5. You suspect a patient has a cholinergic syndrome. Which of the following, if found, would make you question your diagnosis?
   a. Confusion
   b. Diaphoresis
   c. Diarrhea
   d. Fasciculations
   e. Mydriasis (dilated pupils)

   Answer: E. The typical cholinergic patient is "wet." A common mnemonic used to remember the symptoms is SLUDGE—salivation, lacrimation, urination, defecation, gastrointestinal cramping, and emesis. Confusion can be present but is nonspecific. Frequently, cholinergic syndrome is caused by organophosphate poisoning, so fasciculations are common. Another common sign is miosis, not mydriasis.

6. Gastric decontamination with activated charcoal can decrease the absorption of certain toxins. However, before charcoal can be given, it must be determined that the risk of aspiration is low, the likelihood of reduction of toxicity or improved patient outcome is high, and that the ingestion occurred recently (within approximately 1 hour). Also, it must be determined that the substance ingested is actually adsorbed by charcoal. Which of the following substances is adsorbed by charcoal?
   a. Gasoline
   b. Hydrofluoric acid
   c. Iron
   d. Methanol
   e. Metoprolol

   Answer: E. Charcoal does not adsorb hydrocarbons (i.e., gasoline), ionic substances (i.e., strong acids or bases), metals (e.g., iron), or alcohols. It does adsorb most therapeutic drugs with potential major toxicity, such as β-blockers, calcium channel blockers, and cyclic antidepressants.

7. A 6-year-old boy is found playing with liquid pesticide by family members. The family states that he was drinking the solution. Paramedics find the child sitting in a puddle of liquid that smells strongly of pesticide. He is acting normally. During transportation to the hospital, the paramedics report that the child is now sleepier than previously but still easily aroused with a loud voice. His vital signs are within normal limits. They ask what they should do next. What do you advise?
   a. Administer IV atropine
   b. Administer oral activated charcoal
   c. Administer naloxone
   d. Perform rapid sequence intubation
   e. Remove the child's clothing and wash the skin

   Answer: E. This child's clothing has been impregnated with poison, and as long as the child is clothed, he will continue to absorb the poison. Ideally, all patients should be decontaminated on scene to expedite decontamination as well as to minimize the risk of contaminating others. Although this child may have ingested some poison, it is likely that far more is being absorbed from his skin than through his gastrointestinal tract. In addition, charcoal can cause complications, whereas removal of contaminated clothing is relatively safe. Although this child may eventually require intubation, he does not need it now. Most pesticides are organophosphates, so this patient may require atropine, but removal from the poison (taking off his clothing) will provide the greater immediate impact on his condition.

8. A patient suffering from serotonin syndrome will experience myriad physiologic abnormalities, including altered mental status, fever, agitation, tremor, and myoclonus. Many of the symptoms are nonspecific. Which of the following diagnoses is often mistaken for serotonin syndrome?
   a. Anticholinergic syndrome
   b. Brown recluse envenomation
   c. Opioid withdrawal
   d. Sepsis
   e. Sympathomimetic overdose

   Answer: E. Serotonin syndrome is characterized by altered mental status, fever, agitation, tremor, myoclonus, hyperreflexia, ataxia, incoordination, diaphoresis, shivering, and diarrhea. Similar symptoms are seen with overdoses of sympathomimetics, lithium, and monoamine oxidase inhibitors (MAOIs). Similar symptoms are also seen with neuroleptic malignant syndrome (NMS) and malignant hyperthermia. The antimuscarinic syndrome will give a "dry" patient without diaphoresis. Brown recluse envenomation produces local pain and possibly skin necrosis, as well as systemic symptoms of fever, nausea, and vomiting. Opioid withdrawal produces similar symptoms and will cause myalgias but without other musculoskeletal effects. Sepsis likewise can produce many of the systemic signs and symptoms seen in serotonin syndrome but without the musculoskeletal effects.

Toxic Alcohols

Michael E. Nelson

KEY CONCEPTS

- The classic finding of an elevated osmolar and anion gap should raise suspicion of methanol or ethylene glycol toxicity but may not be present depending on the timing of ingestion. Early ingestion has a high osmolar gap without acidosis, and late ingestion has acidosis without an osmolar gap.
- Serum osmolarity is calculated by the following equation:

$$\text{Calculated osmolarity (mOsm/kg)} = 2\text{Na}^+ + (\text{BUN}/2.8) + (\text{glucose}/18) + (\text{ethanol}/4.6)$$

The measured osmolar gap is the difference between the measured serum osmolality and calculated serum osmolarity, with a normal range of –15 to +10 mOsm.

- It is important to note that a normal osmolar gap does not exclude toxic alcohol ingestion.
- Initiate therapy based on strong clinical suspicion of exposure to methanol or ethylene glycol. Block alcohol dehydrogenase preferably with fomepizole, but ethanol can be used if fomepizole is unavailable.
- The main priorities in toxic alcohol exposure are correction of acidosis using bicarbonate solution and hemodialysis, inhibition of the production of toxic metabolites, and elimination of the parent alcohol and its toxic metabolites.
- The presence of acidosis indicates the accumulation of the toxic metabolites of methanol (formic acid) and ethylene glycol (glycolic and oxalic acid). Consult nephrology for emergent hemodialysis to correct acid-base disturbances and remove the parent compound as well as its toxic metabolites.
- Severe acidosis is a poor prognostic factor, with high mortality rates in methanol and ethylene glycol ingestions. A comatose state at the time of presentation also is associated with a higher mortality outcome.
- The findings of an elevated osmolar gap with ketonemia or ketonuria and no development of acidosis indicate isopropanol ingestion. Patients can have a prolonged period of inebriation and can be comatose. Alcohol dehydrogenase inhibition is not indicated in these cases.
- Hypotension and gastrointestinal bleeding are poor prognostic factors in isopropanol ingestion.
- Diethylene glycol can result in acidosis and renal failure and should be managed similarly to ethylene glycol poisoning with fomepizole and hemodialysis.

Ethyl alcohol (ethanol) is ubiquitously consumed worldwide on a daily basis and contributes to a multitude of acute and chronic disease processes and traumatic events. Although ethanol certainly can be viewed as a toxic alcohol, its use, abuse, and related conditions are discussed in Chapter 137. This chapter focuses on methanol, ethylene glycol (EG), and isopropyl alcohol (IPA; isopropanol).

METHANOL

Foundations

Methanol (methyl alcohol; CAS 67-56-1; H_3COH) is a clear, volatile, colorless, slightly sweet-tasting alcohol at room temperature. It is also known as wood alcohol due to methanol being produced from the destructive distillation of wood. Methanol is mainly used as a solvent or octane booster in gasoline. It is manufactured frequently as an intermediate in chemical reactions. As a solvent, it is present in many items found in the home, including cleaning solutions, adhesives, enamels, stains, dyes, and paint removers. Methanol is also commonly found in windshield washer fluid, antifreeze (particularly brake line antifreeze), embalming fluid, and fuel for camp stoves.

Many mass methanol poisonings have occurred throughout history, including outbreaks in Estonia (2001), Norway (2002–2004), the Czech Republic (2012), Libya (2013), Kenya (2014), Nigeria (2015), and Iran (2018).[1,2] Despite vast knowledge and experience with methanol, these outbreaks demonstrate the diagnostic challenge and difficulty in treating these patients. In 2018, 1828 single substance exposures to methanol were reported to US poison centers. The vast majority were unintentional exposures (89.4%), with few major complications (1.6%) and only 11 deaths.[3] These data, however, rely on voluntary reporting and likely underrepresent the true burden of methanol exposures and mortality outcomes from forensic data in the United States.

Principles of Toxicology

Methanol is rapidly absorbed from the gastrointestinal (GI) tract with an average absorptive half-life of 5 minutes and reaches peak concentration in 30 to 60 minutes. While the majority of exposures occur through oral ingestion, occupational and recreational inhalation of methanol from cleaning and cooling fluids has resulted in toxicity causing neurologic dysfunction and necessitating antidote therapy and hemodialysis (HD).[4–6] Transdermal exposure as well can lead to significant methanol toxicity. High-risk occupations for exposure to methanol include painting, varnishing, lithography, printing, and glazing.

Methanol itself has very low toxicity, but its metabolism results in toxic metabolites, in particular, formic acid, which dissociates into formate and hydrogen ions. Methanol is primarily metabolized in the liver by alcohol dehydrogenase (ADH) into formaldehyde. Formaldehyde is then metabolized by aldehyde dehydrogenase (ALDH) very rapidly, with a half-life of 1 to 2 minutes, into formic acid (Fig. 136.1). Formic acid can combine with tetrahydrofolate (THF) to form 10-formyl THF, which can be metabolized into carbon dioxide and water.

Elimination of methanol is mainly characterized via zero-order kinetics in the poisoned patient but does have first-order metabolism

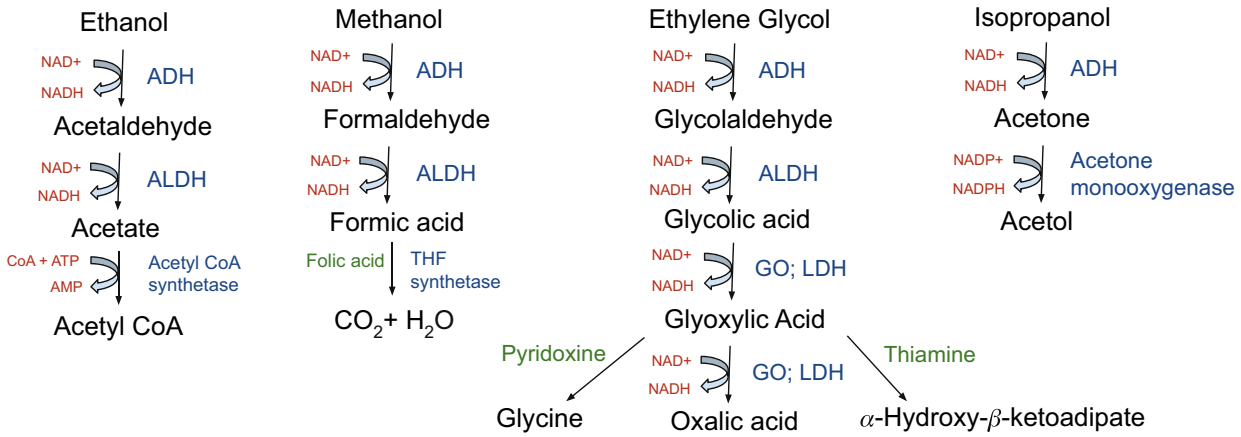

Fig. 136.1 Metabolism of alcohols. *ADH,* Alcohol dehydrogenase; *ALDH,* aldehyde dehydrogenase; *AMP,* adenosine monophosphate; *ATP,* adenosine triphosphate, *GO, Glycolate oxidase, LDH,* lactate dehydrogenase, *NAD+,* nicotinamide adenine dinucleotide; *NADH,* reduced form of nicotinamide adenine dinucleotide, *THF*, tetrahydrofolate.

at very low concentrations, with an elimination half-life of about 2 to 3 hours at low concentrations. Small amounts of methanol are eliminated by the renal and pulmonary systems.

At toxic concentrations, the elimination half-life of methanol is nearly 24 hours. The metabolite, formic acid, has a half-life of nearly 20 hours. With ADH inhibition by concurrent consumption of ethanol or administration of fomepizole, the half-life of methanol extends upward to more than 50 hours. With dialysis, the half-life of methanol is approximately 3 to 4 hours.

Formic acid will accumulate due to its slower metabolism as it exceeds the elimination rate. Formic acid binds iron efficiently, resulting in mitochondrial cytochrome oxidase inhibition, and interferes with oxidative metabolism in a manner similar to that of cyanide, carbon monoxide, and hydrogen sulfide. The dissociation of formic acid into formate and hydrogen ions leads to acidosis. The interference of oxidative metabolism, combined with acidosis, further promotes lactate production and worsens the acidotic state. Decreasing pH promotes formic acid diffusion across cell membranes, in particular to the central nervous system (CNS). Also, inhibition of cytochrome oxidase by formic acid is potentiated with decreasing pH. The net effect of this vicious cycle, coined the "*circulus hypoxicus*," is tissue hypoxia and inhibition of intracellular respiration.[7] Further mechanisms of toxicity include free radical formation, lipid peroxidation, and impairment of antioxidant reactions.

Formic acid uniquely targets the optic disk of the retina and retrolaminar optic nerve, potentially due to the high amount of blood and cerebrospinal fluid (CSF) flow through the choriocapillaris. These cells are more susceptible to cellular hypoxia due to low levels of mitochondria and cytochrome oxidase, making formic acid oxidation slower in the eye compared to the brain.[8] Inhibition of mitochondrial cytochrome oxidase results in decreased adenosine triphosphate (ATP) production, leading to myelin sheath damage and loss of vision. Worsening acidosis potentiates these effects by enhancing the diffusion of formic acid across cell membranes into the neurons.

The basal ganglia and subcortical white matter are affected by formic acid in a similar manner to the ocular toxicity. Neuroimaging and autopsy findings classically demonstrate putamen hypodensity, with hemorrhages and necrosis. Bilateral putamen changes are not specific to methanol toxicity and can be found in Wilson disease, Leigh disease, Kearns-Sayre syndrome, toxic encephalopathy (e.g., carbon monoxide, cyanide, hydrogen sulfide), hemolytic-uremic syndrome, and hypoxic-ischemic injury. The severity of findings and extent of necrosis on imaging do not necessarily correlate with clinical outcomes. The vulnerability of the basal ganglia to formic acid toxicity may be due to its high metabolic activity, with poor venous drainage and inadequate arterial flow.

Clinical Features

Clinical signs and symptoms of methanol intoxication typically involve the GI tract, CNS, and optic system. Shortly after exposure, patients appear similar to other alcohol ingestions, with GI irritation, inebriation, and CNS depression. Methanol has a less inebriating effect than ethanol but causes similar slurred speech, ataxia, confusion, and CNS depression. Abdominal discomfort and vomiting occur from mucosal irritation, and patients can develop acute pancreatitis. Severe mucosal irritation can also result in hemorrhagic gastritis. A latency period, ranging from 1 to 72 hours, depending on the amount ingested, can occur with the improvement of inebriation symptoms and development of visual symptoms as methanol metabolizes and formic acid accumulates.

As formic acid accumulates, the most characteristic feature is some degree of visual disturbance, including seeing spots with blurred vision (commonly referred to as "snowstorm vision"), altered visual fields, and blindness. Visual disturbances occur in 30% to 70% of patients.[9] Early ophthalmologic findings include reduced pupillary response to light and hyperemia of the optic disc. Peripapillary retinal edema and loss of optic disk cupping follow and often lead to decreased visual fields and central scotomata. Retinal dysfunction can be reversible. Blurred vision from formic acid induced retinal injury, is typically transient, and vision recovers. Optic atrophy and optic neuropathy suggest a poor prognosis for visual recovery. The incidence of ophthalmologic abnormalities correlates directly with the degree of acidosis. Long-term visual sequelae are associated with visual deficits at presentation, coma, and brain lesions on imaging.[10,11]

As acidosis progresses, compensatory tachypnea develops. Acidosis can be profound, with many patients presenting with an arterial pH less than 7.0 and serum bicarbonate level less than 10 mEq/L. Tachycardia is often noted, but patients rarely have significant cardiac dysrhythmias. Also, shock, seizures, myoglobinuria, and rhabdomyolysis have been reported. Death typically results from respiratory failure and sudden respiratory arrest, with cerebral edema and multiorgan failure.

TABLE 136.1 Causes of Elevated Osmolar and Anion Gaps

Osmolar Gap	Anion Gap (*A Cat Piles Mud*)	Double Gap	Distinguishing Features
Methanol	***A***lcoholic ketoacidosis	Methanol	Vision loss—methanol
Ethylene glycol	***C***yanide, carbon monoxide, colchicine	Ethylene glycol	Hypocalcemia and calcium oxalate crystalluria—ethylene glycol
Isopropanol	***A***cetaminophen (large ingestion)	Diabetic ketoacidosis	Hyperglycemia, ketonuria—diabetic ketoacidosis
Ethanol	***T***oluene	Alcoholic ketoacidosis	Normal or low glucose level, ketonuria—alcoholic ketoacidosis
Mannitol	***P***araldehyde	Uremia	Positive blood cultures, lactic acidosis—septic shock
Acetone	Propylene glycol	Septic shock	
Glycerol	Phenformin	Multiorgan failure	
Propylene glycol	***I***soniazid, iron, ibuprofen		
Sorbitol	***L***actic acidosis (e.g., sepsis, ischemia)		
Fructose	***E***thylene glycol		
Diatrizoate (IV dye)	***S***alicylates		
Acetonitrile	***M***ethanol, metformin		
Ethyl ether	***U***remia		
Hyperlipidemia	***D***iabetic ketoacidosis		
Hyperproteinemia			
Diabetic ketoacidosis			
Alcoholic ketoacidosis			
Sick Cell Syndrome			
Uremia			
Multiorgan failure			
Septic shock			

Prognosis after methanol ingestion correlates with the degree of acidosis, time to presentation, and initiation of treatment. The strongest predictor of morbidity and mortality is the degree of acidosis, with high mortality rates observed at a pH less than 7.0. A comatose state at presentation also portends a worse outcome with high mortality rates and long-term neurologic sequelae.[12] Aggregated data from mass methanol poisoning events demonstrate that a comatose state with a pH less than 6.74 has an 83% mortality rate and 100% of survivors had neurologic sequelae, while non-comatose patients with a pH greater than 7.0 had a 5% mortality rate and only 16% of survivors had neurologic sequelae.[12] Patients that survive the acute toxicity of methanol can have permanent complications, including blindness and neurologic deficits. A Parkinson-like extrapyramidal syndrome, with bradykinesia, tremor, and dementia, can occur. These findings are generally associated with necrosis of the putamen and subcortical white matter on neuroimaging studies. Other neurologic sequelae include polyneuropathy, encephalopathy, ataxia, and cognitive deficits. Permanent vision deficits and evidence of brain hemorrhages on magnetic resonance imaging (MRI) are associated with decreased quality of life in survivors of methanol poisoning.[13]

Differential Diagnoses

The differential diagnoses for methanol intoxication are broad, making it difficult to detect, particularly at the initial presentation. The inebriated state of the patient can easily be confused with ethanol intoxication. Further causes of altered mental status (AMS) include hypoglycemia, hypoxia, carbon dioxide narcosis, infections, trauma, seizures, metabolic disturbances, endocrinopathies, and encephalopathy. Poisoning or intoxication by other substances, including opiates, carbon monoxide, sedative-hypnotics, and benzodiazepines, often presents with AMS. The GI irritation can occur with ethanol intoxication and with other intra-abdominal pathologies, such as gastritis and pancreatitis.

After ingestion of methanol, serum osmolality will be elevated and can lead to an elevated osmolar gap. Other substances that contribute to an elevated osmolar gap include EG, isopropanol, ethanol, mannitol, glycerol, propylene glycol (PG), sorbitol, fructose, diatrizoate (IV dye), acetonitrile, and ethyl ether (Table 136.1). Additionally, hyperlipidemia, hyperproteinemia, and sick cell syndrome cause an increase in the osmolar gap by decreasing the measured sodium concentration.[14]

As the parent compound methanol is metabolized, the production of formic acid results in an elevated anion gap (AG) acidosis. In addition to methanol, causes of AG acidosis include lactic acidosis of varying causes (e.g., sepsis, ischemia), diabetic ketoacidosis, alcoholic ketoacidosis, uremia, inborn errors of metabolism, and toxins (e.g., salicylates, isoniazid, iron, carbon monoxide, cyanide, metformin, toluene, paraldehyde, PG, and EG; see Table 136.1). Worsening acidosis, despite adequate fluid hydration and no evidence of underlying ischemia producing lactic acidosis, should raise the concern for toxic alcohol ingestion.

The presence of a so-called double gap (elevated osmolar and AGs) is classically described for toxic alcohol ingestion. Many other situations, however, can cause a similar picture, including diabetic ketoacidosis, alcoholic ketoacidosis, renal failure, multiple organ failure, and septic shock (see Table 136.1). This double gap picture is also dependent on the timing of presentation because early presenters will have only an osmotically active parent compound and late presenters will have acidosis without an elevated osmolar gap (Fig. 136.2).[15]

The development of ocular manifestations with worsening acidosis is a strong indicator of methanol poisoning. Other toxins, however, can cause ophthalmologic conditions and blindness such as cinchonism with quinine intoxication, but this lacks the elevated osmolar and AGs. Cortical blindness can occur with various causes of toxic leukoencephalopathy, including carbon monoxide, hydrocarbons, steroids, metals (organic mercury), and various chemotherapeutic agents (e.g., carboplatin, cisplatin).

Diagnostic Testing

The classically described presentation of toxic alcohol ingestion includes an AG metabolic acidosis and an elevated osmolar gap. Due

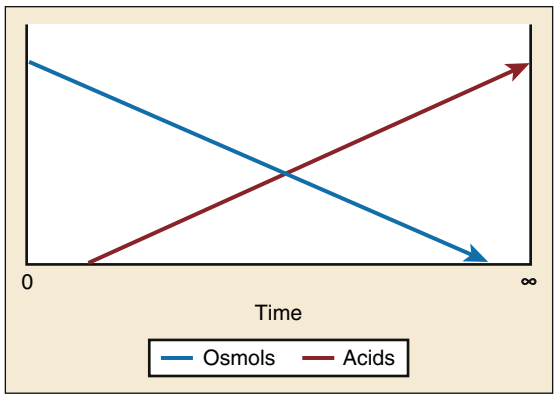

Fig. 136.2 Relationship of osmotically active parent alcohol to acid metabolite over time. (Adapted and modified with permission from Mycyk MB, Aks SE. A visual schematic for clarifying the temporal relationship between the anion gap and the osmol gaps in toxic alcohol poisoning. *Am J Emerg Med.* 2003;21:333–335.)

to the latency period of methanol metabolism, a normal AG does not exclude methanol ingestion. The AG is commonly calculated by the following equation:

$$AG = [Na^+] - ([HCO_3^-] + [Cl^-])$$

with a normal AG of 8 to 12 mEq/L. Decreased albumin can falsely elevate the AG; the AG can be corrected by using the Figge equation:

$$AG\ corrected = AG + (2.5 \times [44 - measured\ serum\ albumin]),\ (albumin\ expressed\ as\ g/dL)$$

Mortality correlates highly with the degree of acidosis and formate concentration rather than with a specific methanol concentration. Visual dysfunction occurs with a formate concentration greater than 20 to 30 mg/dL. Indicators for a poor prognosis include a formate concentration of more than 50 mg/dL and a pH less than 7.0

Many formulas exist for calculating serum osmolarity, but the most commonly used is the following:

$$Calculated\ osmolarity\ (mOsm/L) = 2Na^+ + (BUN/2.8) + (glucose/18) + (ethanol/4.6)$$

where blood urea nitrogen (BUN), glucose, and the ethanol concentrations are measured in mg/dL. The difference between measured serum osmolality and calculated serum osmolarity is as follows:

$$Osmolar\ gap = measured\ osmolality\ (mOsm/kg) - calculated\ osmolarity\ (mOsm/L)$$

If using the International System of Units (SI units), there are no corrections, and the various serum levels are simply added or subtracted. The normal osmolar gap has been arbitrarily defined as normal if it is less than 10 mOsm. However, a wide range of osmolar gaps is observed in the population, from −15 to +10 mOsm. As a result, individuals who begin with a negative osmolar gap can have significantly elevated concentrations of toxic alcohols but have a so-called normal osmolar gap. Many other substances can contribute to an osmolar gap and can be misleading. Also, if patients are acidotic, the parent compound (methanol, EG) has been metabolized into its respective acid and does not contribute to the osmotic load. Thus, a normal osmolar gap cannot exclude toxic alcohol ingestion. Methanol, however, is more likely than EG to have an elevated osmolar gap. An extremely elevated osmolar gap (>20–25 mOsm) however is highly suspicious for toxic alcohol ingestion.[16–18] In methanol ingestions, the metabolite formic acid can be measured using enzymatic analysis but this test is not routinely available.[14,19]

Neuroimaging with MRI and computed tomography (CT) can be performed for patients with AMS. The most consistent finding for methanol poisoning is bilateral necrosis of the putamen. However, this finding is not specific for methanol poisoning, and neuroimaging is typically normal in the first 24 hours after methanol exposure because findings typically lag behind clinical symptoms. Patients with evidence of putaminal necrosis on imaging are at risk for an irreversible Parkinson-like extrapyramidal syndrome and chronic disability limiting daily functioning.[13] The measurement of visual evoked potentials (VEP) is sensitive to detect impairment in the optic system.[8]

Ultimately, the definitive diagnosis requires laboratory confirmation of the presence of methanol. Once toxic alcohol ingestion is suspected, directly measure methanol and EG concentrations and begin empirical therapy. Peak methanol concentrations less than 20 mg/dL are generally not associated with toxicity, but peak methanol concentrations greater than 50 mg/dL indicate significant and serious exposure. Peak methanol concentrations occur shortly after ingestion due to rapid GI absorption. Due to the variability of the timing of patient presentation, the methanol level interpretation must be based on clinical findings (e.g., AMS, vision complaints) as well as additional laboratory findings (e.g., metabolic acidosis, elevated osmolar gap). Depending on the location of the practice and laboratory capabilities, specific serum concentrations of methanol or EG may not be readily attainable in most hospitals, and blood specimens may need to be transported to regional reference laboratories for emergent analysis.

Management

Alcohols are rapidly absorbed from the GI tract, so GI decontamination has limited to no value. Gastric suctioning via a nasogastric or orogastric tube may be considered in a large volume exposure (such as an entire bottle of windshield washer fluid or antifreeze) in someone who presents immediately after ingestion, but there is no evidence to support routine use and gastric lavage is generally not recommended. Activated charcoal is not indicated for toxic alcohol ingestions. Aside from standard stabilization and resuscitation, the main priorities in toxic alcohol exposure are correction of acidosis, inhibition of the production of toxic metabolites, and elimination of the parent alcohol and its toxic metabolites. Therapy should be initiated based on strong clinical suspicion. Treatment should not be delayed while waiting for specific serum concentrations to be determined.

Because the degree of acidosis correlates with severity and outcome, treat a serum pH less than 7.3 with intravenous (IV) sodium bicarbonate to normalize the pH. Worsening acidosis from formic acid accumulation potentiates mitochondrial cytochrome oxidase inhibition and anaerobic metabolism, also generating lactic acidosis. Based on supporting patient data, correction of acidosis likely improves outcomes and ophthalmologic symptoms. Bicarbonate can be administered via intermittent boluses, combination of a bolus and infusion, or infusion alone based on the severity of symptoms. Administer bolus sodium bicarbonate at 1 to 2 mEq/kg and infuse 150 mEq/L of sodium bicarbonate in 5% dextrose at 1.5 to 2 times the maintenance fluid rate until normalization of the serum pH (7.35–7.45). Large amounts of bicarbonate may be necessary for even partial correction of acidosis due to metabolism of the parent alcohol into its toxic acid. With bicarbonate administration, monitor for the development of hypernatremia and hypokalemia. The use of bicarbonate should not deter definitive elimination of the parent alcohol and its toxic metabolites via HD.

Prevent the further production of formic acid by inhibiting ADH with fomepizole (methylpyrazole, 4-MP) or ethanol. Fomepizole is preferable due to its safety profile and ease of administration, with a

BOX 136.1 Criteria for Initiation of Alcohol Dehydrogenase Blockade for Methanol or Ethylene Glycol Poisoning

Documented plasma methanol or EG concentration ≥20 mg/dL
or
History of ingestion of methanol or EG and an osmolar gap >10 mOsm/L
or
Strong clinical suspicion of ingestion of methanol or EG and at least two of the following:
1. Arterial pH <7.3
2. Serum bicarbonate <20 mEq/L (mmol/L)
3. Osmolar gap >10 mOsm/L
4. Urinary oxalate crystals present (for EG ingestion)

EG, Ethylene glycol.

BOX 136.2 Fomepizole Dosing

- Loading dose—15 mg/kg IV
- Maintenance dose—10 mg/kg IV every 12 h for up to 48 h
- After 48 h—15 mg/kg every 12 h
- If undergoing HD—same doses as above, but start maintenance schedule 6 h after loading dose and then administer every 4 h during HD

sevenfold reduction in adverse drug event rate versus ethanol.[9,18,20] No contraindication exists for fomepizole use except for a severe allergic reaction, but currently, there have been no reported cases.[18] Most adverse reactions to fomepizole are transient and do not require discontinuation of treatment.[21] Specific indications for initiating ADH blockade are a documented methanol or EG concentration more than 20 mg/dL, documented history of methanol or EG ingestion with an osmolar gap more than 10 mOsm/L, or suspected methanol or EG ingestion with an arterial pH less than 7.3, serum carbon dioxide (bicarbonate) level less than 20 mmol/L, or oxalate crystalluria (Box 136.1).

In clinical practice, however, initiate fomepizole therapy with a strong clinical suspicion for serious ingestion, and send for confirmatory levels, because a delay in ADH blockade can lead to the development of acidosis and deleterious consequences. Fomepizole dosing involves a loading dose of 15 mg/kg followed by 10-mg/kg doses every 12 hours, up to 48 hours. After 48 hours, give 15 mg/kg every 12 hours because repeated dosing of fomepizole induces its own cytochrome P-450 metabolism. Of note, the fomepizole dosing frequency does need to be adjusted with HD (Box 136.2). Side effects of fomepizole include headache, nausea, dizziness, phlebitis, and reversible liver transaminase level elevation. One case of hypotension and bradycardia due to the rapid infusion of fomepizole has been described.[15,20]

If fomepizole is not available, and ethanol therapy is used to inhibit ADH, maintain serum ethanol concentrations between 100 and 150 mg/dL. The affinity of ADH for ethanol is 10 times greater than for methanol. Ethanol dosing is complex, however, and can cause worsening CNS and respiratory depression, with hypotension, vomiting, phlebitis, and hypoglycemia, particularly in children or malnourished individuals.[18,20] Given the widespread availability of fomepizole and its safety profile versus that of ethanol, the dosing of IV ethanol is not discussed here because its routine use is not recommended with the exception of mass outbreaks or lack of fomepizole availability.[12,22] With ADH inhibition, the half-life of methanol is significantly extended upward of 50 hours. Patients who present early after methanol ingestion without acidosis can potentially be treated with ADH inhibition alone but may have prolonged hospitalizations due to the extended half-life of the parent compound.

Elimination of the parent alcohol via HD is the mainstay of therapy in severe toxic alcohol ingestions, and consultation with a regional poison center or medical toxicologist will help determine whether the patient is a candidate. HD serves multiple purposes in that it removes the parent alcohol and its metabolites, corrects acidosis, and aids in fluid management and cardiovascular stabilization. Additionally, it can shorten the course and cost of hospitalization, particularly in methanol ingestions, due to methanol's long half-life.[11] Intermittent HD is preferred over continuous renal replacement therapy (CRRT) but CRRT is acceptable if HD is not available[15,23]

HD is indicated for acidosis (pH < 7.3), renal failure, vision abnormalities with methanol exposure, electrolyte imbalances unresponsive to conventional therapy (i.e., hyperkalemia), hemodynamic instability, and methanol or EG concentration more than 50 mg/dL.[15] Traditional endpoints for discontinuing HD or ADH inhibition are a normal acid-base status and methanol-EG concentration less than 20 mg/dL.[15] Ophthalmologic disturbances are not an indication for continued dialysis after correction of the acid-base disturbance and removal of methanol. There is no specific treatment for methanol-induced persistent optic nerve injury. Formic acid is converted to carbon dioxide and water via THF synthetase; therefore, folinic acid (leucovorin) may aid in formic acid elimination, but there have been no human trials to support its efficacy. The recommended dose is 1 mg/kg (maximum dose: 50 mg) of folinic acid IV every 4 to 6 hours until methanol has been eliminated and the acidosis resolves. The use of folinic acid (leucovorin) should not deter emergent HD if indicated.

Disposition

Admission is generally necessary for patients being treated for methanol exposure. Consult with nephrology early for possible HD. If HD is not available, administer fomepizole and transfer the patient to an institution where emergent HD can be initiated. Consult the regional poison center (1-800-222-1222) or a medical toxicologist to guide management. Consult an ophthalmologist to evaluate visual fields and the retina for methanol-induced ocular injury within 24 hours. Patients with a methanol concentration less than 20 mg/dL and no clinical symptoms or laboratory abnormalities may be discharged. If the patient has psychiatric issues or intent of self-harm, a psychiatric consultation is indicated.

ETHYLENE GLYCOL

Foundations

EG (ethane-1,2-diol, CAS 107-21-1, $C_2H_6O_2$) is a colorless, odorless, sweet-tasting liquid. It is a common component of antifreeze and deicing solutions because it lowers the freezing point of water. Additional sources of EG include hydraulic brake fluids, industrial solvents, foam stabilizer, paints, and cosmetics. Because EG has a sweet taste, it is often substituted for ethanol and has led to mass poisonings historically. In 2018, 6599 single substance exposures to EG were reported to US poison centers. Most of these were unintentional (82%) but resulted in roughly 10.5% of patients having moderate to severe effects and a total of 19 deaths.[3] Like methanol, the data rely on voluntary reporting and likely underestimate the true burden of EG exposures and mortality outcomes.

EG is rapidly absorbed from the GI tract with peak blood levels occurring within 1 to 4 hours after ingestion. EG is highly water-soluble and, unlike methanol or isopropanol, is not volatile at room

temperature. Thus, transdermal and pulmonary absorption of EG are extremely limited, and toxicity from these routes of exposure is not expected or observed.

Metabolism of EG primarily occurs in the liver via the conversion of ADH into glycolaldehyde, which is rapidly converted by ALDH into glycolic acid. Glycolic acid is further metabolized into glyoxylic acid (glyoxylate) and oxalic acid (see Fig. 136.1). The conversion of glycolic acid into glyoxylic acid is slow, and the accumulation of glycolic acid generates a profound metabolic acidosis. Pyridoxine and thiamine are cofactors in the metabolism of glyoxylic acid; however, given the slow conversion of glycolic acid to glyoxylic acid, these cofactors likely do not contribute significantly to EG detoxification. A small amount of oxalate will precipitate with calcium to form calcium oxalate crystals. These metabolic oxidation steps result in the conversion of nicotinamide adenine dinucleotide (NAD^+) to nicotinamide adenine dinucleotide (NADH). The increase of NADH to NAD^+ converts pyruvate to lactate and generates lactic acidosis.

Calcium oxalate crystals precipitate in the proximal renal tubules and are the main contributing factor in the development of acute tubular necrosis and renal failure. Calcium oxalate deposits also occur in the brain, intestinal mucosa, lungs, heart, and spleen, although the contribution of these deposits to the clinical picture is less clear. Further findings of EG toxicity include diffuse petechial hemorrhages in the heart, lungs, and brain, as well as the development of cerebral edema. Myonecrosis and rhabdomyolysis can occur. The chelation of calcium by oxalate can lead to systemic hypocalcemia.

Elimination of EG occurs mainly in the liver, but roughly 20% to 25% of EG is excreted unchanged in the urine. The reported half-life of EG ranges from 3 to 9 hours, but when metabolism is inhibited by ethanol or fomepizole, the half-life increases up to 20 hours. With HD, the half-life of EG is about 2 to 3 hours, depending on flow rates.

Clinical Features

The clinical picture of EG toxicity is typically divided into three stages: (1) acute neurologic stage; (2) cardiopulmonary stage; and (3) renal stage. As with methanol, delayed neurologic sequelae are described. An extreme amount of clinical variability occurs, stages may overlap, and mortality may occur at any stage. Poor prognostic factors at admission include hyperkalemia, severe metabolic acidosis, renal failure, seizures, coma, and delays in treatment. Seizures are highly prognostic for death.[20] The co-ingestion of ethanol can delay the onset of symptoms.

EG is a gastric irritant and can produce nausea and vomiting shortly after ingestion. The acute neurologic stage occurs over 30 minutes to 12 hours after ingestion with EG, producing inebriation and euphoria similar to ethanol. In severe poisonings, CNS depression can progress to coma, hypotonia, and seizures. Additional findings include nystagmus, ataxia, and myoclonic jerks. Cerebral edema can develop from calcium oxalate crystal deposition and cytotoxic damage contributing to CNS depression.

The cardiopulmonary stage occurs 12 to 24 hours after ingestion, with patients developing tachycardia with severe metabolic acidosis and compensatory tachypnea. The acidosis occurs from the generation of glycolic acid. Hypoxia with pulmonary edema and acute respiratory distress syndrome (ARDS) can cause hypoxia. Multiorgan failure with circulatory collapse can occur, and most deaths ensue during this stage.

The renal stage occurs 24 to 72 hours postingestion with the development of acute renal failure (ARF) from calcium oxalate crystal deposition. Conscious patients may complain of flank pain and have costovertebral tenderness. Hematuria and proteinuria can occur. Renal failure can be anuric, oliguric, or nonoliguric. Renal dysfunction frequently necessitates HD and, in some cases, for months after exposure. Renal function usually returns to normal following EG intoxication, but occasionally renal damage can be permanent. Long-term HD is rarely necessary.

Delayed neurologic sequelae commonly present as bulbar palsy from 5 to 20 days after ingestion, with cranial nerve VII being most commonly implicated. Other cranial nerve involvement has been documented; clinical findings include ophthalmoplegia, diplopia, nystagmus, facial droop, facial sensory loss, hearing loss, dysphagia, and vertigo.[24] The term *facial auditory nerve oxalosis* has been used to describe this delayed syndrome and its predilection to affect cranial nerves VII and VIII noted on autopsy. In addition to the cranial nerves, an autonomic nerve dysfunction has been described, with postural hypotension and gastroparesis. The exact pathogenesis for these neurologic findings is unclear, but postulated mechanisms include calcium oxalate deposition resulting in mechanical nerve injury, inflammatory response causing nerve dysfunction, and depletion of thiamine and pyridoxine cofactors. Neuroimaging studies can demonstrate the focal infiltration of calcium oxalate with inflammation and necrosis of the basal ganglia. Despite significant MRI pathology, individuals with neurologic complications can have a full recovery.[25]

Differential Diagnoses

The differential diagnoses for EG intoxication are broad and similar to methanol. See earlier, "Methanol: Differential Diagnoses," for a more in-depth explanation, especially regarding the initial presentation of inebriation and AMS, proceeding through elevated osmolar and AGs (see Table 136.1).

Unlike methanol, however, the hallmark of EG toxicity involves renal failure with calcium oxalate crystalluria. Many other substances cause ARF, including antimicrobials (e.g., aminoglycosides, vancomycin, sulfa-based drugs, ciprofloxacin, penicillins, polymixins), nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, HMG-CoA reductase inhibitors, antivirals (e.g., acyclovir, foscarnet, antiretrovirals), amphotericin B, chemotherapeutics (e.g., methotrexate, cisplatin, ifosfamide), diethylene glycol (DEG), bisphosphonates, radiocontrast media, heavy metals, proton pump inhibitors, lithium, and acetaminophen. Calcium oxalate crystalluria is not specific for EG and is only present in up to 50% of cases of EG ingestion. Healthy individuals with excess dietary intake of vitamin C or foods rich in oxalate (e.g., garlic, tomatoes, spinach, rhubarb, and tea) may have incidental calcium oxalate crystalluria.

Xenobiotic-induced hypocalcemia can occur from proton pump inhibitors, bisphosphonates, other phosphate-containing substances (e.g., laxatives and sodium phosphate), loop diuretics, glucocorticoids, calcitonin, cisplatin, pentamidine, interferon-alfa, fluorides (e.g., hydrofluoric acid), citrate, phenytoin, phenobarbital, carbamazepine, estrogens, and ethylenediaminetetraacetic acid. Hypocalcemia, metabolic acidosis, ARF, and calcium oxalate crystalluria, however, strongly suggest EG toxicity. Ultimately, the definitive diagnosis requires laboratory confirmation of EG concentrations in blood or serum.

Diagnostic Testing

Diagnostic testing for EG is similar to that for methanol; for a more detailed discussion of AG acidosis and elevated osmolar gap calculations, see earlier, "Methanol: Diagnostic Testing." The contribution of EG to the osmolar gap is relatively small compared to other alcohols, and an EG concentration of 50 mg/dL will only cause an 8- to 10-mOsm rise in the osmolar gap. Thus, an elevated osmolar gap can suggest EG ingestion, but a normal gap does not exclude it.

Glycolic acid is structurally similar to lactate and can cause a false positive lactate elevation in laboratory equipment using a lactate oxidase-based system measuring hydrogen peroxide generated from the metabolism of lactate to pyruvate. These machines tend to be

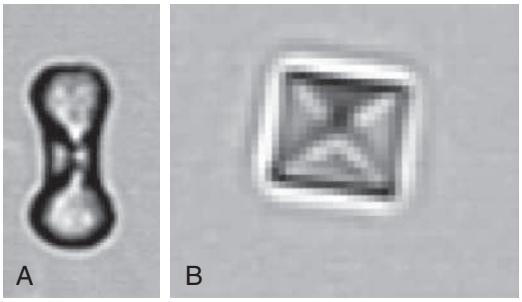

Fig. 136.3 Calcium oxalate crystals. Illustrated are calcium oxalate monohydrate (A) and dihydrate (B) crystals in the urine. The monohydrate whewellite crystals typically are needle-like or dumbbell-shaped and strongly birefringent, whereas the dihydrate weddellite crystals are octahedral, envelope-shaped, and weakly birefringent.

point-of-care tests such as whole blood arterial or venous blood gas analyzers. This can create a "lactate gap" in EG ingestion where a point-of-care lactate is extremely elevated but a formal laboratory analysis of lactate using a lactate dehydrogenase system is markedly less.[26,27]

Calcium oxalate crystalluria can be of two major forms, needle-shaped calcium oxalate monohydrate or polyhedron-shaped calcium oxalate dihydrate crystals. The calcium oxalate monohydrate crystals may be mistaken for hippuric acid crystals. Crystals can be found in the urine 4 to 8 hours after exposure. Additional urinary findings include hematuria and proteinuria (Fig. 136.3).

Fluorescein dye is often added to antifreeze agents to assist in the detection of automobile radiator leaks, so patients who ingest antifreeze EG-containing agents may exhibit urinary fluorescence under a Woods lamp. Urinary fluorescence, however, is neither specific nor sensitive for diagnosing or excluding EG intoxication. The fluorescence of gastric contents soon after EG ingestion may be more definitive.

The EG concentration itself does not predict severity as much as it depends on the timing of presentation and initiation of intervention. Serum EG concentrations greater than 50 mg/dL, however, are associated with serious ingestion and toxicity. The degree of acidosis (particularly a pH <7.2–7.3) does predict an increase in the creatinine level and mortality outcome. A peak EG concentration less than 20 mg/dL is generally not associated with significant toxicity.

In EG intoxication, the serum glycolic acid concentration is the driving force for acidosis. Glycolic acid concentrations greater than 99 mg/dL are strongly associated with severe CNS toxicity and mortality. Levels greater than 76 mg/dL have nearly 100% sensitivity for predicting ARF.[28] Glycolic acid levels greater than 60 mg/dL could be an indication for HD, but this is not well validated.[28] Serum glycolic acid concentrations typically are not readily available in a timely fashion to aid in most clinical situations and only a small percentage of reference laboratories perform this test.[28]

Management

Many of the management principles of EG toxicity overlap with those of methanol. EG, like methanol, is rapidly absorbed from the GI tract; thus, gut decontamination has a limited to no role in EG ingestion. Correction of metabolic acidosis with sodium bicarbonate (pH < 7.3) may increase the urinary excretion of EG and delay calcium oxalate-induced ARF. Initiate ADH blockade, preferably with fomepizole, as soon as possible to prevent the development of toxic metabolites (see Boxes 136.1 and 136.2). Ethanol therapy can be used if fomepizole is unavailable, although its routine use is not recommended. Consider HD for the indications stated earlier, particularly for an acid-base imbalance and renal failure. EG, however, has a shorter half-life than methanol, and patients without acidosis or renal compromise can be managed with fomepizole alone, thus preventing the need for HD in adult and pediatric patients. Continue treatment until serum EG concentrations are less than 20 mg/dL, and a normal acid-base status is present.

Pyridoxine and thiamine are cofactors in EG metabolism. Pyridoxine aids in the conversion of glyoxylic acid metabolism to glycine. Thiamine stimulates conversion of glyoxylic acid to α-hydroxy-β-ketoadipate (see Fig. 136.1). No clinical data, however, support the effectiveness of these cofactors in otherwise healthy patients with EG ingestion. These cofactors should be given to patients with vitamin deficiencies, such as alcoholics and malnourished individuals. The recommended adult doses are thiamine 100 mg IV daily, and pyridoxine 100 mg IV daily, for 2 days. If patients have symptomatic hypocalcemia (interval changes on the electrocardiogram and dysrhythmias), replete with calcium gluconate or calcium chloride as needed.

Disposition

Admission is generally necessary for patients being treated for EG exposure. Consult nephrology early for possible HD. If HD is not available, initiate ADH inhibition and transfer the patient to an institution where emergent dialysis is available. Consult the regional poison center (1-800-222-1222) or a medical toxicologist to guide management. Patients with an EG concentration less than 20 mg/dL and no laboratory abnormalities or clinical symptoms may be discharged. If the patient has psychiatric issues or intent for self-harm, a psychiatric consultation is indicated.

ISOPROPYL ALCOHOL

Foundations

IPA (isopropanol, 2-propanol, CAS 67-63-0, C_3H_7OH) is a clear, colorless liquid with a fruity odor and bitter taste. IPA is found in numerous household and commercial products, including rubbing alcohol, antifreeze, disinfectants, cleaning solutions, skin and hair products, and hand sanitizers. IPA is commonly used as a solvent for industrial applications. It is the second most commonly ingested alcohol after ethanol. Exposures to IPA, either as a single substance or combined with other substances, reported to US poison centers have ranged from about 15,000 to 21,000 cases/year.[3] In 2018, 12,730 single substance IPA exposures occurred, with 82% unintentional in nature, 1% having moderate to major effects, and zero deaths, reflecting a low case-fatality rate.[3]

Isopropyl alcohol is rapidly absorbed from the GI tract with peak plasma concentrations occurring within 30 minutes. Oral ingestion is the major route of exposure, but absorption can occur transdermally, rectally, or via inhalation. Children are especially susceptible to systemic symptoms from the dermal application of IPA used to reduce fever.

Metabolism occurs primarily in the liver by ADH into acetone. Acetone is metabolized to acetol (hydroxyacetone) by acetone monooxygenase (see Fig. 136.1). Further metabolic products include PG, methylglyoxal, lactate, formate, and acetate. Many of these minor metabolic products are then converted to glucose. Acetone reaches a peak plasma concentration from 7 to 30 hours postexposure and has a half-life of up to 24 hours. IPA follows first-order kinetics, with a half-life of 2.5 to 8 hours. ADH inhibition increases the half-life to 16 to 27 hours. Elimination primarily occurs via the kidneys, with up to 20% of IPA excreted unchanged in the urine.

Isopropyl alcohol directly acts as a CNS depressant and is considered to be twice as inebriating as ethanol. Acetone can also contribute to CNS depression. A concomitant respiratory depression can

occur with profound CNS depression. With larger doses, peripheral vasodilation and decreased cardiac inotropy can cause hypotension. Topical exposure leads to corneal de-epithelialization, with dermal irritation.

Clinical Features

Isopropyl alcohol irritates mucosal surfaces, and GI effects typically occur early after ingestion. Nausea, vomiting, and abdominal pain typically ensue, but hemorrhagic gastritis, hematemesis, and significant blood loss can result with larger ingestions. As with other alcohols, pancreatitis is a potential complication. Aspiration of IPA can cause hemorrhagic tracheobronchitis and pulmonary edema.

CNS depression ranges from lethargy to stupor or coma. Headache, dizziness, ataxia, hypotonia, hyporeflexia, dysarthria, and seizures have been reported. Pupil size is variable, but miosis is commonly observed. Loss of consciousness is associated with respiratory depression, hypoxia, and aspiration pneumonitis. Hypotension and hypothermia can occur with very large ingestions. Hypotension signifies severe poisoning with increased mortality risk. Injuries from prolonged immobilization with CNS depression can lead to compartment syndrome and rhabdomyolysis. Myoglobinuria can cause ARF. Hypoglycemia has not been reported with IPA as it has for other alcohols. Dermal contact causes a defatting dermatitis with drying and cracking of the skin, and pediatric patients can sustain chemical burns. Ketosis without acidosis is a classic finding in IPA ingestion.

Differential Diagnoses

Patients with significant IPA ingestion appear intoxicated similar to ethanol. IPA will elevate the osmolar gap but, unlike methanol and EG, not the AG. See earlier, "Methanol: Differential Diagnoses" for causes for AMS and an elevated osmolar gap. As IPA is converted to acetone, ketosis will occur. Ketosis is present in conditions such as diabetic ketoacidosis, alcoholic ketoacidosis, starvation ketosis, salicylism, and cyanide and acetone ingestion. Those chronically dependent on ethanol may consume IPA to prevent alcohol withdrawal and can have a mixed picture of alcoholic ketoacidosis with IPA ingestion.[29] ARF can develop from rhabdomyolysis but the differential for ARF is extensive.

Diagnostic Testing

The most common laboratory abnormality is ketosis without acidosis and euglycemia. As IPA is metabolized, acetone accumulates. Acetone does not elevate the AG, but IPA and acetone do contribute to the osmolar gap. Acetone can be detected within 30 minutes in serum and within 3 hours in urine postexposure. Acetone can interfere with the assay for creatinine and cause a pseudo-renal failure measurement with an isolated elevated creatinine but normal BUN level. If patients are hypotensive from a large IPA ingestion, lactic acidosis can occur, which can then cause a confounding AG acidosis.

The measurement of the IPA concentration is the definitive method of diagnosis. Occasionally, IPA can be detected in patients with acetonemia not exposed to IPA because acetone is converted to IPA in vivo. Serum concentrations of IPA do not correlate well with clinical outcomes—deaths have been reported with concentrations as low as 20 mg/dL. The scant data available suggest that a concentration of more than 50 mg/dL is associated with toxicity, and some authors suggest HD for levels greater than 400 mg/dL, hypotension, or lactic acidosis, although there has been no clear evidence for these recommendations[9]

Management

Supportive care is the mainstay of therapy for IPA ingestion. There is no role for GI decontamination. Wash the skin with soap and water for dermal contamination. Provide proton pump inhibitors (e.g., pantoprazole, 80 mg IV push and a drip at 8 mg/h for 72 hours, or until the patient can tolerate oral foods and fluids) for hemorrhagic gastritis. Consult gastroenterology for endoscopy to exclude other causes of upper GI bleeding or to intervene for persistent bleeding causing hemodynamic instability, necessitating transfusion, or worsening clinical condition. For deeply comatose patients, airway protection is indicated. Hypotension generally responds to IV crystalloid solution. For significant hypotension, initiate 1 to 2 L of normal saline as a bolus infusion, followed by repeated 500-mL boluses at 30-minute intervals until a mean arterial pressure (MAP) of 65 mm Hg is achieved. If the target MAP cannot be achieved or maintained with 4 L of normal saline boluses, start a norepinephrine infusion and titrate to the target MAP. Additional vasopressor support can be added with fluids, as needed. If the patient is persistently hypotensive, despite standard resuscitative measures, HD is indicated. ADH blockade with fomepizole or ethanol is not indicated because this will only prolong the hypotensive and CNS depressant effects of IPA.

Disposition

Due to IPA's rapid absorption on its onset of action, patients who are stable and alert 6 hours after ingestion are unlikely to develop significant complications and can be monitored until no longer clinically intoxicated and discharged from the emergency department (ED). Patients with significant inebriation or AMS should be admitted as an inpatient or placed in an observation unit for 24 hours. Consult gastroenterology for patients with hemorrhagic gastritis for endoscopy. Consult nephrology for patients with a comatose state or refractory hypotension for HD. Consult the regional poison center (1-800-222-1222) or medical toxicologist to help guide management.

OTHER ALCOHOLS OF CLINICAL SIGNIFICANCE

DEG is an odorless, viscous, sweet-tasting liquid commonly used as a solvent. It is found in brake fluid, antifreeze, lubricants, wallpaper strippers, and artificial fog machine solutions. Most exposures to DEG occur in epidemics in which DEG is substituted in pharmaceutical preparations for more expensive glycols. The first epidemic occurred in the United States in 1937, with DEG being used as a solvent for sulfanilamide, and led to the passing of the 1938 Federal Food, Drug, and Cosmetic Act requiring drug manufactures to demonstrate product safety prior to marketing. Other epidemics include those in South Africa (1969), Spain (1985), Nigeria (1990), Bangladesh (1990–92), Haiti (1996), India (1998), Panama (2006), and Nigeria (2008). DEG toxicity resembles that of EG, with initial GI irritation and CNS depressant effects, followed by metabolic acidosis. ARF without urinary calcium oxalate crystals occurs. Patients who survive ARF, unlike EG, typically require lifelong HD. Neurologic symptoms develop 5 to 10 days postingestion and can include lethargy, cranial neuropathies, peripheral polyneuropathies, and quadriparesis. DEG is metabolized into 2-hydroxyethoxyacetic acid and does not metabolize into EG, as once believed. Management is similar to that of methanol and EG and includes ADH blockade and early consideration for HD.[9,18]

PG is commonly used as a solvent in various pharmaceutical products and in antifreeze and hydraulic fluids. Common medications that use PG as a diluent include IV phenytoin, lorazepam, diazepam, etomidate, nitroglycerin, phenobarbital, hydralazine, and trimethoprim-sulfamethoxazole.[30] PG is metabolized to lactic acid and can produce metabolic acidosis. Also, it can contribute to an elevated osmolar gap. Because PG has a short half-life, the osmolar gap rapidly returns to normal once the medication diluent or exposure is discontinued.

Underlying renal insufficiency and hepatic dysfunction increase the risk for toxicity. Case reports have noted acute kidney injury from proximal tubular necrosis with PG toxicity. Additionally, PG toxicity can mimic a systemic inflammatory response syndrome and cause a confounding picture, with an elevated osmolar and AG triggering exploration for methanol and EG exposure. Approximately 20% of intensive care unit patients on continuous lorazepam infusions can have some degree of PG toxicity. Treatment typically involves stopping the offending agent, but HD and ADH blockade can be considered for severe acidosis and metabolic abnormalities.[9]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 136: QUESTIONS AND ANSWERS

1. A 24-year-old man presents after intentional methanol ingestion. The patient reports that 1 or 2 hours ago he drank approximately 8 ounces of windshield washer fluid in a suicide attempt. He is not sure of the product name. His only current complaint is slight nausea. His vital signs and physical examination are within normal limits. Serum chemistry reveals the following: sodium, 142 mEq/L, potassium, 4.5 mEq/L, chloride, 110 mEq/L, bicarbonate, 22 mEq/L, blood urea nitrogen (BUN), 18 mg/dL, creatinine, 1.5 mg/dL, and glucose, 111 mg/dL. Serum methanol levels are not obtainable at your hospital. The psychiatry service asks if the patient is medically cleared. Which of the following is the most appropriate response?

a. The patient is cleared; he has a normal anion gap, so no significant methanol ingestion occurred.

b. The patient is cleared; ingestion of 8 ounces is below the toxic level regardless of the concentration.

c. The patient is not cleared; he has an elevated anion gap and needs to receive treatment for methanol toxicity.

d. The patient is not cleared; he has evidence of renal failure and needs to receive treatment for methanol toxicity.

e. The patient is not cleared; not enough time has elapsed from the ingestion to determine if significant toxicity has occurred.

Answer: e. Windshield washer fluid can contain high concentrations of methanol. Methanol itself does not cause toxicity or an anion gap acidosis but its metabolites do, specifically formic acid. It can take 12 to 24 hours for acidosis to develop and even longer if a significant amount of ethanol has also been ingested. This patient should be observed and treated. This patient's anion gap is 10 mEq/L, which is within normal limits. Ingestion of very small amounts of methanol can be fatal or cause permanent neurologic or ophthalmologic damage. As little as 15 mL of 40% methanol can cause death in adults.

2. A 44-year-old woman complains of abdominal pain and headache. Her family reports that the patient drank "something" approximately 8 hours ago in a suicide attempt. The patient is sleepy but arouses with manual stimulation. Her speech is confused, but she follows all simple commands. Her vital signs are blood pressure,

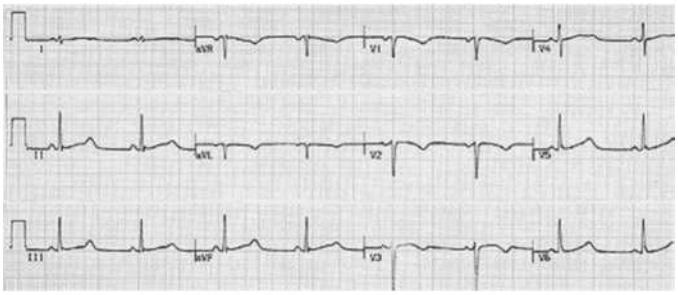
CHAPTER 136: QUESTIONS AND ANSWERS—cont'd.

124/82 mm Hg, heart rate, 108 beats/min, respiratory rate, 26 breaths/min, and temperature, 37.0°C (98.6°F). Her physical examination is unremarkable. Her serum chemistry reveals an anion gap of 24 mEq/L. Other laboratory work is pending. Which of the following treatments should be administered initially?

a. Diuresis
b. Hemoperfusion
c. Intravenous flumazenil
d. Intravenous fomepizole
e. Oral activated charcoal

Answer: d. Intravenous fomepizole should be administered. This patient has likely ingested methanol or ethylene glycol, both of which can cause these symptoms, as well as an anion gap metabolic acidosis. The definitive treatment for both ingestions is hemodialysis, which can take some time to arrange. Treatment should be started with fomepizole, even before a definitive diagnosis has been made. Fomepizole and ethanol act by inhibiting the conversion of methanol or ethylene glycol to toxic substances, thereby allowing elimination of the much less toxic parent compounds. Diuresis and hemoperfusion are not effective for methanol or ethylene glycol. Flumazenil will reverse the effect of benzodiazepine but should always be used with caution so as not to induce seizure activity in chronic users. Oral charcoal is not effective for methanol or ethylene glycol, especially after such a long delay.

3. A 20-year-old man presents after ingesting antifreeze. His electrocardiogram (ECG) is shown below. Which electrolyte abnormality is most likely responsible for the findings on the ECG?



a. Hypercalcemia
b. Hyperkalemia
c. Hypocalcemia
d. Hypokalemia
e. Hypomagnesemia

Answer: c. Hypocalcemia is a cause of QT prolongation. Ingestion of ethylene glycol can result in hypocalcemia, which is caused by calcium precipitation with oxalate. Although ethylene glycol ingestion can result in renal failure that can then cause hyperkalemia, it is not associated with QT prolongation. Hypokalemia and hypomagnesemia can both cause QT prolongation; neither is generally associated with ethylene glycol ingestion.

4. An otherwise healthy patient presents after suicidal ethylene glycol ingestion. He is drowsy. His serum pH is 7.1. You have started treatment with fomepizole and have contacted the nephrologist to arrange hemodialysis. In the meantime, what should be done about the patient's acidosis?

a. Normal saline should be administered to facilitate clearance of the acid.
b. Nothing should be done; dialysis will correct the acidosis.
c. Nothing should be done; the fomepizole will correct the acidosis.
d. Nothing should be done; the patient is not truly acidotic, but ethylene glycol interferes with the laboratory determination of pH.
e. Sodium bicarbonate should be administered to neutralize the exogenous acid.

Answer: e. Unlike lactic acid, which will be metabolized to bicarbonate, the acidic metabolites of methanol and ethylene glycol cannot be metabolized to bicarbonate and can cause severe acidosis if not treated. Dialysis will correct the acidosis, but the early treatment of the acidosis can reverse some of the adverse effects of methanol or ethylene glycol poisoning. Fomepizole prevents the conversion of methanol or ethylene glycol into toxic metabolites but does nothing to those toxic metabolites already produced. Forced saline diuresis is not beneficial and may increase the incidence of acute respiratory distress syndrome.

5. Which of the following is an indication for hemodialysis after methanol or ethylene glycol ingestion?

a. Metabolic acidosis
b. Blood level of 10 mg/dL
c. Elevated anion gap
d. Hypocalcemia
e. Hypokalemia

Answer: a. Metabolic acidosis, renal compromise, visual symptoms, deterioration despite intensive supportive care, and electrolyte abnormalities unresponsive to conventional therapy are all indications for hemodialysis. Although an anion gap is often associated with metabolic acidosis, an anion gap in and of itself is not an indication for hemodialysis. There is debate about the alcohol levels that indicate the need for hemodialysis. Recommendations have been made to dialyze patients with levels of methanol or ethylene glycol between 25 and 50 mg/dL.

6. Which of the following cofactors helps with the elimination of methanol and should be considered in patients with methanol poisoning?

a. Folinic acid (leucovorin)
b. Hydroxocobalamin (vitamin B_{12})
c. Niacin (vitamin B_3)
d. Pyridoxine (vitamin B_6)
e. Thiamine (vitamin B_1)

Answer: a. Folinic acid is a cofactor in the degradation of formic acid to carbon dioxide and water, the final step in the metabolism of methanol. Give folinic acid 50 mg IV every 4 hours to adults with methanol poisoning. Thiamine and pyridoxine are indicated for patients with ethylene glycol poisoning and should be considered. Niacin and hydroxocobalamin are antidotes but play no role in the treatment for ethanol or ethylene glycol poisoning.

7. Which of the following statements comparing the effects of isopropyl alcohol and ethylene glycol is true?

a. Isopropyl alcohol causes less CNS depression and is less toxic than ethylene glycol.
b. Isopropyl alcohol causes less CNS depression and is more toxic than ethylene glycol.
c. Isopropyl alcohol causes more CNS depression and is less toxic than ethylene glycol.
d. Isopropyl alcohol causes more CNS depression and is more toxic than ethylene glycol.
e. Isopropyl alcohol has the same effects as ethylene glycol.

Answer: c. Isopropyl alcohol causes twice the central nervous system (CNS) depression of ethanol, which causes more depression than ethylene glycol. Isopropyl alcohol is metabolized to acetone, which also causes CNS depression but is relatively nontoxic, except in very high doses.

CHAPTER 136: QUESTIONS AND ANSWERS—cont'd.

8. A patient presents with decreased mental status after drinking some homemade alcohol. Serum chemistry reveals sodium, 140 mEq/L, potassium, 4.5 mEq/L, chloride, 108 mEq/L, bicarbonate, 22 mEq/L, BUN, 28 mg/dL, creatinine, 1.0 mg/dL, glucose, 90 mg/dL, and serum osmolality, 320 mOsm/kg. Urinalysis is positive for ketones. Which of the following is the most likely alcohol ingested?

a. Ethanol
b. Ethylene glycol
c. Isopropyl alcohol
d. Methanol
e. On the basis of this information, the patient probably did not ingest an alcohol.

Answer: c. This patient has a normal anion gap of 10 but an elevated osmolal gap of 25. The osmolal gap equals the measured serum osmolarity minus the calculated serum osmolarity. The calculated osmolarity is

$$(\text{Sodium} \times 2) + (\text{BUN}/2.8) + (\text{glucose}/18)$$

In this case, it is 295 mOsm/kg. Ethylene glycol and methanol both cause a double gap or elevated anion and osmolal gaps. Ethanol and isopropyl alcohol generally elevate only the osmolal gap. Isopropyl alcohol ingestion causes more CNS depression than ethanol ingestion and results in ketonemia and ketonuria as it is metabolized to acetone.

137

Alcohol-Related Disease

John T. Finnell

As eloquently stated by Paracelsus in the 16th century, "all substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

KEY CONCEPTS

- Moderate alcohol consumption is defined as one or two drinks/day for men and one drink/day for women.
- DSM–5 integrates alcohol abuse and alcohol dependence into a single disorder called *alcohol use disorder* (AUD), with mild, moderate, and severe sub-classifications.
- Benzodiazepines are the main treatment of alcohol withdrawal and alcohol withdrawal-induced seizures. Minor alcohol withdrawal occurs as early as 6 h and usually peaks at 24–36 h after the cessation of or significant decrease in alcohol intake.
- Major alcohol withdrawal occurs after 24 h and usually peaks at 50 h (but may take up to 5 days) after the decrease or termination of drinking.
- Delirium tremens is the extreme end of the alcohol withdrawal spectrum; it consists of gross tremors, profound confusion, fever, incontinence, and frightening visual hallucinations.
- Alcohol withdrawal seizures occur 6–48 h after the cessation of drinking, with 60% of patients experiencing multiple seizures within a 6-h period.
- Alcohol withdrawal should be assessed and managed using a validated scale, such as the CIWA-Ar scale.
- Brief intervention and screening (SBIRT—***s***creening, ***b***rief ***i***ntervention, and ***r***eferral to ***t***reatment) can reduce alcohol consumption and is feasible and effective in the emergency department.

FOUNDATIONS

Excess alcohol consumption places a significant burden on individuals and society. Globally, alcohol consumption is the seventh leading risk factor for both death and the burden of disease and injury. 2016 data from the World Health Organization (WHO) state that 5.3% of all deaths globally were attributable to alcohol consumption.[1] The overall costs associated with alcohol use represent more than 1% of the gross national product in high- and middle-income countries, with the costs of social harm (e.g., violence and road accidents) being far greater than health costs alone. In short, except for tobacco, alcohol accounts for a higher burden of disease than any other drug.[2]

From 2002 to 2010,[3] the rate of emergency department (ED) visits for alcohol-related diagnoses increased by 38%. In addition to the number of visits, current National Hospital Ambulatory Care survey data indicates that the total time and the length of stay (LOS) for ethanol-related visits are increasing as well.[4]

Twenty-seven percent of the US population admits to alcohol misuse.[5] Alcohol misuse accounts for more than 100,000 deaths in the United States every year, making it the fourth leading preventable cause of death in the United States and the 12th leading cause of death overall and is associated with over 200 diseases.[5,6] Alcoholism permeates all levels of society. Studies reveal a complex association between alcohol consumption and socioeconomic status (SES),[7] where people of lower SES show greater susceptibility to the damaging effects of alcohol.

Alcohol use and misuse also have social and financial costs, with estimates of over $220 billion in societal costs in the United States annually.[8] The literature refers to harmful, hazardous, and risky drinking interchangeably as a pattern of drinking that increases the risk of harm for the person consuming alcohol or others. The International Classification of Disease 10th Revision (ICD-10), draft ICD-11, and the *Diagnostic and Statistical Manual of Mental Disorders 4th Edition* (DSM-4) use the term "alcohol dependence." Alcohol dependence is a result of repeated use leading to a person having impaired control over the use of alcohol despite physical, psychological, and social harms. The fifth edition of the Diagnostic and Statistical Manual (DSM-5) combines diagnostic criteria for alcohol abuse and dependence under the term "alcohol use disorder," with severity modifiers of "mild," "moderate," or "severe," based on the number of criteria met. DSM-5 AUD of moderate or greater severity is essentially equivalent to DSM-4 and ICD-10 criteria for alcohol dependence. DSM–5 integrates alcohol abuse and alcohol dependence into a single disorder called alcohol use disorder (AUD), with mild, moderate, and severe sub-classifications.

At least 24% to 31% of ED patients meet National Institute Alcohol Abuse and Alcoholism (NIAAA) criteria for "at-risk" or heavy drinking. At-risk drinking is defined as an average of 14 or more standard drinks/week or 5 or more per occasion for men and 7 or more drinks weekly or 3 or more per occasion for women and people older than 65 years. (Table 137.1: Terms and Definitions of Unhealthy Alcohol Use.[9])

Patients, their families, and society, in general, should be aware that AUDs are not a result of any individual weakness or moral failing but arise from a complex interaction of individual, social, cultural, and biological factors. Most people with AUD are difficult to identify because they are likely to have jobs and families and to present with general complaints, such as malaise, insomnia, anxiety, sadness, or a range of medical problems.

In 2013, the US Preventive Services Task Force (USPSTF) recommended that clinicians screen adults 18 years or older for alcohol misuse and provide brief behavioral counseling interventions to those engaged in risky or hazardous drinking behaviors.[10] Of the available screening tools, the USPSTF determined that 1-item to 3-item screening instruments have the best accuracy for assessing unhealthy alcohol use in adults 18 years or older. These instruments include the abbreviated Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) and the NIAAA-recommended Single Alcohol Screening Questionnaire (SASQ).[9] This high

TABLE 137.1 Terms and Definitions of Unhealthy Alcohol Use

Term	Source	Definition
Low-risk use/lower-risk use	ASAM	Consumption of alcohol below the amount identified as hazardous and in situations not defined as hazardous
Risky/at-risk use	NIAAA	Consumption of alcohol above the recommended daily, weekly, or per-occasion amounts but not meeting criteria for alcohol use disorder For all women and men 65 years or older: No more than 3 drinks/day and no more than 7 drinks/week for men (21 to 64 years): No more than 4 drinks/day and no more than 14 drinks/week Should avoid alcohol completely: Adolescents, women who are pregnant or trying to get pregnant, and adults who plan to drive a vehicle or operate machinery, are taking medication that interacts with alcohol, or have a medical condition that can be aggravated by alcohol For adolescents: NIAAA defines moderate- and high-risk use based on days of alcohol use in the past year, by age group: Moderate risk: Ages 12–15 years: 1 day/year Ages 16–17 years: 6 days/year Age 18 years: 12 days/year Highest risk: Age 11 years: 1 day Ages 12–15 years: 6 days Age 16 years: 12 days Age 17 years: 24 days Age 18 years: 52 days
Unhealthy use	ASAM	Any alcohol use that increases the risk or likelihood of health consequences (hazardous use [see below]) or has already led to health consequences (harmful use [see below])
Hazardous use	WHO	A pattern of substance use that increases the risk of harmful consequences; in contrast to harmful use, hazardous use refers to patterns of use that are of public health significance, despite the absence of a current alcohol use disorder ¡n the individual user
	ASAM	Alcohol use that increases the risk or likelihood of health consequences; does not include alcohol use that has already led to health consequences
Harmful use	WHO	A pattern of drinking that is already causing damage to health; the damage may be either physical (e.g., liver damage from chronic drinking) or mental (e.g., depressive episodes secondary to drinking) The description for *ICD-10* code F10.l, also labeled "Alcohol Abuse" in the 2018 *ICD-10-CM* codebook
	ASAM	Consumption of alcohol that results in health consequences in the absence of addiction
Alcohol use disorder	*DSM-5*	A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period: 1. Having times when the patient drank more, or longer, than intended 2. More than once wanted to cut down or stop, tried It, but could not 3. Spending a lot of time drinking or being sick/getting over the aftereffects of drinking 4. Wanting to drink so badly that they could not think of anything else 5. Found that drinking (or being sick from drinking) often interfered with taking care of home or family responsibilities, caused problems at work, or caused problems at school 6. Continuing to drink even though it was causing trouble with family and friends 7. Given up or cut back on activities that were important or interesting ¡n order to drink 8. More than once gotten into situations while or after drinking that increased the chances of getting hurt (e.g., driving, swimming, unsafe sexual behavior) 9. Continued to drink even though it was causing depression or anxiety, other health problems, or causing memory blackouts 10. Having to drink much more than previously ¡n order to get the desired effect, or finding that the usual number of drinks had much less effect than previously 11. Experiencing the symptoms of withdrawal after the effects of alcohol were wearing off, such as trouble sleeping, shakiness, restlessness, nausea, sweating, racing heart, or seizure Severity is determined based on the number of symptoms present: Mild: 2–3 symptoms Moderate: 4–5 symptoms Severe: ≥6 symptoms

(Continued)

TABLE 137.1 Terms and Definitions of Unhealthy Alcohol Use—cont'd.

Term	Source	Definition
Binge drinking/heavy drinking	NIAAA	A pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL, which typically occurs after 4 drinks for women and 5 drinks for men-in about 2 h
Episodes[3]	SAMHSA	Drinking ≥5 alcoholic drinks on the same occasion on at least 1 day in the past 30 days
Heavy drinking	SAMHSA	Drinking ≥5 drinks on the same occasion on each of ≥5 days in the past 30 days
Alcohol dependence	*WHO/ICD*-10-CM	≥3 of the following at some time during the previous year:
		A strong desire or sense of compulsion to take the substance
		Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use
		A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
		Evidence of tolerance, such that increased doses of the psychoactive substance are required ¡ή order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users)
		Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance, or to recover from its effects
		Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm
Abbreviations: ASAM. American Society of Addiction Medicine; *DSM-5. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-10-CM. International Classification of Diseases. Tenth Revision Clinical Modification* NIAAA. National Institute on Alcohol Abuse and		Alcoholism; SAMHSA. Substance Abuse and Mental Health Services Administration; WHO. World Health Organization.

[a] According to the American Society of Addiction Medicine, the preferred term; is "heavy drinking episode."
Data from US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening and Behavioral Counseling Interventions to Reduce Unhealthy Alcohol Use in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(18):1899–1909.

burden of alcohol-related injury and disease indicates a need to increase awareness of AUD and its effective treatment options (see Box 137.3).[11]

Metabolism of Alcohol

While some alcohol is absorbed in the stomach, the vast majority is absorbed in the small intestine. It is distributed uniformly to all organ systems, including the placenta. Although 2% to 10% of alcohol is excreted through the lungs, urine, and sweat, most is metabolized to acetaldehyde, primarily by alcohol dehydrogenase (ADH). The oxidation of alcohol is a complex process involving three enzyme systems, all contained in the hepatocyte. Acetaldehyde is then quickly converted to carbon dioxide and water, primarily through aldehyde dehydrogenase (ALDH). The common forms of ADH decrease the alcohol concentration in blood by about 4.5 mmol/L ethanol/h (the equivalent of about one drink/h):

$$\text{Ethanol ADH} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol hydrogenase}} \text{Acetaldehyde ADH} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol dehydrogenase}} \text{Acetyl coenzyme A} \xrightarrow[\text{Cycle}]{\text{Critical acid}} CO_2 + H_2O$$

where NAD is nicotinamide adenine dinucleotide and NADH is reduced nicotinamide adenine dinucleotide.

At least two variations of ADH genes (*ADH1B*2* and *ADH1C*1*) produce a slightly more rapid breakdown of alcohol and therefore potentially faster production of acetaldehyde, which is rapidly metabolized by *ALDH2*. However, about 40% of Asian people (Japanese, Chinese, and Koreans) have an inactive *ALDH2* mutation that results in much higher acetaldehyde levels after drinking than normal. About 10% of people who are homozygous for this gene form cannot drink alcohol without becoming sick and have almost no risk of AUD, whereas those who are heterozygous have a relatively low rate of AUD.

An alternative pathway, the microsomal ethanol-oxidizing system (MEOS), is induced by chronic alcohol exposure. The primary component of the MEOS is the molecule cytochrome P_{450}, which exists in several variants. The variant most important for alcohol metabolism is cytochrome P_{450} 2E1 (CYP2E1). Many effects of alcoholism are produced by the toxic byproducts (hydrogen, acetaldehyde), acceleration of the metabolism of other drugs, and activation of hepatotoxic compounds by these metabolic pathways.

Although the liver is the major site of ethanol metabolism, other tissues contribute to its metabolism. ADH is found in the gastric mucosa, but the gastric metabolism of alcohol is decreased in women and those of Asian descent. This increased bioavailability of ethanol or decreased first-pass metabolism may explain the greater vulnerability of women to acute and chronic complications of alcohol.

Alcohol metabolism has two elimination rates. The alcohol elimination rate approximates zero-order kinetics (constant rate) for lower

TABLE 137.2 Physiologic Effects and Blood Ethanol Levels

Blood Ethanol Concentration (mg/dL)	Effects[a]
20–50	Diminished fine motor control
50–100	Impaired judgment, impaired coordination
100–150	Difficulty with gait and balance
150–250	Lethargy, difficulty sitting upright without assistance
300	Coma in the novice drinker
400	Respiratory depression

[a]These effects are for the occasional drinker. Chronic drinkers can function at much higher alcohol concentrations because of tolerance. On the other hand, patients may become comatose with low levels of alcohol in mixed alcohol-drug overdose.

ethanol levels and first-order kinetics (amount of drug removed over time is proportional to the concentration of the drug) for higher levels, especially in chronic alcoholics; most likely, through induction of the MEOS pathway, the elimination rate is increased at higher blood levels.

The absorption and elimination rates of alcohol vary by individual and depend on many factors. There is enormous variation among patients in the rate of elimination of ethanol from the blood, ranging from 9 to 36 mg/dL/h in published data. Although the clearance rate may be as high as 36 mg/dL/h in some chronic drinkers, 20 mg/dL/h is a reasonable rate to assume in a typical intoxicated ED patient.

Physiologic effects vary directly with the blood alcohol level (Table 137.2). Diminished fine motor control and impaired judgment appear with alcohol concentrations as low as 20 mg/dL (0.02 mg%), but wide individual variability exists. Chronic alcoholics can exhibit impressive tolerance. The blood alcohol concentration of a person cannot be accurately determined without quantitative testing. More than 50% of the adult population is obviously intoxicated with a level of 150 mg/dL (0.15 mg%). As the ethanol level rises, the patient's level of consciousness declines, eventually ending in a coma. Death is caused by aspiration or respiratory depression.

CLINICAL FEATURES

Alcohol Withdrawal Syndrome

Alcohol is a central nervous system (CNS) depressant. Chronic alcohol use results in a down-regulation of γ-aminobutyric acid (GABA) receptor activity and disinhibition of the dopaminergic reward pathway.[12] This down-regulation of GABA receptors is thought to lead to an increase in the desirable effects of alcohol and vulnerability for dependence due to the presence of increased synaptic GABA. The hallmark of alcohol withdrawal is CNS excitation, with increased cerebrospinal fluid, plasma, and urinary catecholamine levels. Alcohol withdrawal syndrome (AWS) is a continuum of syndromes that begins after a decrease in the amount of intake of ethanol. Therefore, only a reduction, not the abrupt cessation, of ethanol intake may result in withdrawal.

AWS is often divided into three sets of symptoms. The first set consists of autonomic hyperactivity, which appears within hours of the last drink and usually peaks within 24 hours.

Symptoms may occur as early as 6 hours after cessation of or a significant decrease in alcohol intake and usually peaks at 24 to 36 hours. It is characterized by mild autonomic hyperactivity—anorexia, nausea, vomiting, anxiety, coarse tremor, tachycardia, hypertension, hyperreflexia, and sleep disturbances such as insomnia and vivid dreams.

BOX 137.1 DSM-5 Criteria for Withdrawal Delirium (Delirium Tremens)

Criteria for Alcohol Withdrawal

Cessation of or reduction in heavy and prolonged use of alcohol

At least two of eight possible symptoms after reduced use of alcohol:

- Autonomic hyperactivity
- Hand tremor
- Insomnia
- Nausea or vomiting
- Transient hallucinations or illusions
- Psychomotor agitation
- Anxiety
- Generalized tonic-clonic seizures

Criteria for Delirium

Decreased attention and awareness

Disturbance in attention, awareness, memory, orientation, language, visuospatial ability, perception, or all these abilities change from the normal level and fluctuate in severity during the day

No evidence of coma or other evolving neurocognitive disorders

From the American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington DC: American Psychiatric Publishing; 2013.

The second symptom set includes additional neuronal excitation, with epileptiform seizures and global confusion, usually occurring within 24 to 48 hours of abstinence and usually peaks at 50 hours after cessation of or a significant decrease in alcohol intake but occasionally takes up to 5 days. The syndrome is characterized by pronounced anxiety, insomnia, irritability, tremor, anorexia, tachycardia, hyperreflexia, hypertension, fever, decreased seizure threshold, visual and auditory hallucinations, and finally delirium.

The third set of symptoms features delirium tremens or alcohol withdrawal delirium (AWD). While only 5% of patients hospitalized for alcohol withdrawal have delirium tremens, this syndrome is a life-threatening manifestation of alcohol withdrawal and consists of gross tremor, frightening visual hallucinations, profound confusion, agitation, and a hyperadrenergic state characterized by a temperature above 101°F (≈38.5°C), blood pressure higher than 140/90 mm Hg, and tachycardia. It seldom appears before the third post abstinence day.

The criteria for withdrawal delirium, as described in Box 137.1, are delirium and alcohol withdrawal. Alcohol withdrawal is the most common alcohol-related illness that may require inpatient admission and is associated with adverse events such as uncontrolled agitation with the potential for over-sedation, generalized seizures, and prolonged hospital stay.[3] Emergency clinicians should be familiar with the commonly used withdrawal rating instrument known as the Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar). See Table 137.3.

Alcohol-Related Seizures

Patients presenting to the ED with seizures should be questioned about alcohol intake (Box 137.2). Of seizure patients presenting to an ED, 20% to 40% will have their seizures related to alcohol use or abuse. The primary consideration in the initial care of seizure patients who regularly consume alcohol is the recognition of treatable, life-threatening causes. Alcohol may act in one of several ways to produce seizures in

TABLE 137.3 Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Components of Scale	Most Severe Manifestations
Nine items[a]	
• Nausea or vomiting	Constant nausea with vomiting
• Tremor	Severe tremor, even with arms extended
• Paroxysmal sweats	Drenching sweats
• Anxiety	Acute panic
• Tactile disturbances (e.g., itching, numbness, sensation of bugs crawling on or under the skin)	Continuous hallucinations
• Auditory disturbances (e.g., sensitivity to sound, hearing things that are not there)	Continuous hallucinations
• Visual disturbances (e.g., sensitivity to brightness and color, seeing things that are not there)	Continuous hallucinations
• Headache, sensation of a band around the head	Extremely severe headache
• Agitation	Pacing during most of an interview with clinician or thrashing about
One item—orientation and clouding of sensorium[b]	

[a]Scored on a scale ranging from 0 (no symptoms) to 7 (most severe symptoms).
[b]Scored on a scale ranging from 0 (no symptoms) to 4 (disoriented with respect to place or person).
Adapted from Sullivan JT, Sykora K, Schneiderman, J, et al. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84:1353–1357.

BOX 137.2 Differential Diagnosis of Alcohol-Related Seizures

Withdrawal (alcohol or drugs)
Exacerbation of idiopathic or posttraumatic seizures
Acute intoxication (e.g., amphetamines, anticholinergics, cocaine, isoniazid, organophosphates, phenothiazines, tricyclic antidepressants, salicylates, lithium)
Metabolic (e.g., hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hepatic failure)
Infectious (e.g., meningitis, encephalitis, brain abscess)
Trauma (e.g., intracranial hemorrhage)
Cerebrovascular accident
Sleep deprivation
Noncompliance with anticonvulsants

patients by its partial or absolute withdrawal after a period of chronic intake by, an acute alcohol-related metabolic disorder (e.g., hypoglycemia, hyponatremia), an acute event leading to cerebral trauma, precipitation of seizures in patients with idiopathic or posttraumatic epilepsy, or lowering of the seizure threshold in patients with prior existing intracerebral disease states.

Alcohol Withdrawal Seizures

Withdrawal seizures may occur 6 to 48 hours after the cessation of drinking. Of patients with seizures, 90% have one to six generalized tonic-clonic seizures, and 60% experience multiple seizures within a 6-hour period. The incidence of partial seizures, common with posttraumatic epilepsy, is increased during alcohol withdrawal. The term *alcohol withdrawal seizure* is reserved for seizures with these characteristics. The term *alcohol-related seizure* is used to refer to all seizures in the aggregate associated with alcohol use, including this subset of alcohol withdrawal seizures.

Alcoholic Hallucinosis

Alcoholic hallucinosis is clinically distinct from delirium tremens and is characterized by hallucinations presenting within 12 to 24 hours of abstinence and resolve within 24 to 48 hours, in contrast to delirium tremens that presents at least 48 to 72 hours after abstinence. Hallucinations are typically visual, although tactile hallucinations have been described. Alcoholic hallucinosis is also generally not associated with autonomic instability such as tachycardia, hypertension, or hyperthermia.

Cardiovascular Effects

Acute and chronic ethanol consumption can affect the mechanical function of the heart, produce dysrhythmias, and exacerbate coronary artery disease (CAD). It may alter myocardial function by direct toxic effects, by associated hypertension, or indirectly by altering specific electrolytes. Acute intoxication can decrease cardiac output in alcoholic and nonalcoholic patients with preexisting cardiac disease (see Table 137.4).[13]

Studies have linked moderate alcohol consumption (two drinks/day in men and one drink/day in women) with a reduced risk of cardiovascular disease.[14–16] There is a strong biological plausibility that moderate wine consumption may have a positive effect on organs and systems. Whether the positive effect of wine on health is attributed to ethanol, to wine micro-constituents, or to their synergistic effect, is still unanswered.[17] Low to moderate alcohol consumption decreases platelet aggregation, raises plasma levels of endogenous tissue plasminogen activator, and lowers insulin resistance and likely poses little cardiovascular risk.[14]

Heavy alcohol consumption has a detrimental effect on those with preexisting CAD. It reduces exercise tolerance, induces coronary vasoconstriction, and raises heart rate and blood pressure. These patients also have a significantly higher incidence of peripheral arterial disease.[18] The additive cardiovascular effects of ethanol and nicotine contribute to dysrhythmias and sudden death in patients with CAD.[19]

Alcohol abuse is a known risk factor for the development of alcoholic cardiomyopathy which presents as a dilated cardiomyopathy that can lead to heart failure.[14,20] Heavy drinkers have increased odds of having a prolonged QTc interval and supraventricular dysrhythmias.[21] Supraventricular (usually atrial fibrillation) and ventricular (usually transitory ventricular tachycardia) dysrhythmias, commonly referred to as "holiday heart," have been documented in alcoholic patients who have been drinking heavily. Tachydysrhythmias as a result of episodic

TABLE 137.4 Cardiovascular Effects of Alcohol

Condition	Probable Relationship With Alcohol		Potential Epidemiological Consequences
	Lighter drinking[a]	Heavier drinking[b]	
Dilated Cardiomyopathy	Unrelated	One (of several) causes; ? requires cofactors	↑ risk of HF, AF, cardioembolic stroke and HS if on ACs
Systemic HTN	Little or none	Probably causal in susceptible persons	↑ risk of HF, AF, IS, and HS
CAD	Protective	? less protective or ↑ risk	↑ risk of HF, cardioembolic stroke, and AF; t risk of HS if on ACs
Supraventricular arrhythmia	Little or none	Probably a causal factor, especially with binges	↑ risk of cardioembolic stroke, and HS if on ACs
HS	? unrelated or slight ↑ risk	↑ risk	Disability and ↑ risk of VTE
IS	Protective	Probable ↑ risk; varies with subtype	Disability and ↑ risk of VTE
Heart failure	Indirectly protective	Varies with underlying CV condition	Disability and ↑ risk of VTE

AC, Anticoagulant; *AF*, atrial fibrillation; CAD, coronary artery disease; *HS*, hemorrhagic stroke; *HTN*, hypertension;; *IS*, Ischemic stroke; VTE, venous thromboembolism; cv, cardiovascular; t, increase; 4, decrease; ?, possibly.
[a]Less than three standard-sized drinks per day; [b]Three or more standard-sized drinks per day.
Data from Klatsky AL. Alcohol and cardiovascular diseases: where do we stand today? *J Intern Med*. 2015;278(3):238—250.

drinking commonly revert to sinus rhythm with abstinence and do not require immediate intervention if the patient is hemodynamically stable.

Pulmonary Effects

There is a clear and statistically significant relationship between alcohol consumption and the risk of community-acquired pneumonia (CAP). Consuming drinks that contain 10 to 20 g of alcohol per day is linked to an 8% increased risk of acquiring CAP.[22] Pneumococcal pneumonia is the most common type of pneumonia in both healthy individuals and heavy alcohol users. In addition, *Klebsiella pneumoniae* also is increased in people with AUD and seems to cause disproportionate rates of lung infection and high mortality in this population.[23]

For centuries, it has been known that people with AUD are more likely to have pulmonary infections such as pneumonia and tuberculosis. Over the past two decades, it has become clear that other conditions such as RSV and ARDS also are linked to high-risk alcohol consumption.[23]

Gastrointestinal and Hepatic Effects

Esophagus and Stomach

Alcoholic patients have a higher incidence of esophagitis, gastric cancer, and esophageal carcinoma than in the general population. Acute alcohol ingestion also decreases lower esophageal sphincter pressure, delays gastric emptying, and disrupts the normal gastric mucosal barrier. Alcohol consumption, because of its inherent toxicity, has been shown to eliminate infection of the gastric mucosa by *Helicobacter pylori*. Forceful or persistent emesis can lead to a Mallory-Weiss tear or more severely, Boerhaave syndrome.

Gastrointestinal Bleeding

Alcohol is closely associated with gastrointestinal (GI) bleeding. Causes and contributing factors include Mallory-Weiss tears, esophagitis, esophageal varices, acute and chronic gastritis, thrombocytopenia, portal hypertensive gastropathy, qualitative and quantitative platelet disorders, and prolonged clotting times. Alcohol may exacerbate gastric mucosal damage when it is combined with nonsteroidal antiinflammatory drugs (NSAIDs), but ethanol itself is not a risk factor for peptic ulcer disease. Peptic ulcer disease is the most common cause of bleeding in alcoholic patients with upper GI hemorrhage, as well as in those who do not regularly consume alcohol.

Liver Damage

Hepatic damage has been recognized for centuries as the hallmark of chronic alcohol abuse. Above a certain quantity, alcoholic consumption can elicit a spectrum of liver lesions among which steatosis is present in nearly all drinkers who consume in excess of 40 g/day regularly.[24] The activation of the immune system with the production of cytokines such as tumor necrosis factor-alpha is one of the earliest events in many types of liver injury. This cascade stimulates Kupffer cells and the production of other cytokines that together enlist inflammatory cells, kill hepatocytes, and initiate healing through fibrogenesis.

Alcoholic liver disease is the most common liver disorder in the Western Hemisphere and, along with hepatitis C (HCV), is a leading cause of liver transplantation. Alcohol use is associated with more persistent HCV infection and more extensive liver damage than no alcohol use because of interactions between alcohol use and HCV that affect immune responses, cytotoxicity, and oxidative stress.[2] No safe level of alcohol consumption has been determined for patients with HCV.[2]

Alcoholic Hepatitis

Alcoholic hepatitis is a pro-inflammatory chronic liver disease that is associated with high short-term morbidity and mortality (25% to 35% in 1 month) in the setting of chronic alcohol use.[25] It is a clinical syndrome characterized by right upper quadrant pain, a tender enlarged liver, fever, jaundice, leukocytosis, and altered liver function test results. aspartate transaminase (AST) levels are usually less than 400 IU/L, and ALT levels are typically less than half the AST level. It is associated with profound immune dysfunction with a primed but ineffective immune response against pathogens.[26]

Alcoholic hepatitis has a range of clinical manifestations from mildly symptomatic hepatomegaly to fulminant hepatic failure. The severity of the disease can be estimated in the ED by a prolonged prothrombin time/international normalized ratio (INR) or with the use of the Maddrey discriminant factor. The ABIC (***a***ge, ***b***ilirubin, *I*NR, ***c***reatinine) score and model for end-stage liver disease (MELD) are also helpful in predicting mortality in these patients.

Cirrhosis

The causal association between alcohol intake and alcoholic liver disease has been well documented, yet liver cirrhosis develops in only 10% to 20% of heavy drinkers.[2] Cirrhosis is the disruption of the normal architecture of the liver by scarring and regenerating nodules of parenchyma. Alcoholism is the most common cause of cirrhosis in the United States and is responsible for approximately 48% of all cirrhotic-induced deaths.[27] Alcoholic cirrhosis usually requires 10 to 15 years of chronic drinking, often punctuated by one or more episodes of acute alcoholic hepatitis. The clinical outcome is determined by the development of complications of portal hypertension and hepatic dysfunction. Alteration of the normal hepatic architecture by fibrosis and nodule formation may eventually lead to portal hypertension. Portal hypertension may be complicated by ascites and esophageal varices. Although cirrhosis is irreversible, its progression may be halted with abstinence.

Pancreatitis and Malabsorption

The association of ethanol with acute and chronic pancreatitis is well established, but the exact pathogenesis is unclear. Hypotheses include reflux of duodenal contents and bile into the pancreatic duct, obstruction by a plug of pancreatic juice rich in proteins, and a direct toxic effect of ethanol.

The diagnosis of alcoholic pancreatitis can be difficult because asymptomatic alcoholics may have an elevated amylase level. Conversely, up to 30% of patients with acute alcoholic pancreatitis have an amylase value within normal limits. The serum lipase level rises after amylase, remains elevated longer, and is a more reliable indicator of alcoholic pancreatitis, especially when it is more than three times the normal range.

Neurologic Effects

Neuropathy. A symmetric sensorimotor polyneuropathy is common with chronic alcohol abuse, usually in the lower extremities. It is thought to be a combination of nutritional deficiency with thiamine or vitamin B_{12} deficit and a direct neurotoxic effect of alcohol. Burning pain and paresthesia are common complaints. Findings on physical examination include loss of light touch, decreased pinprick sensation, and reduced lower extremity deep tendon reflexes. Distal muscle weakness is a delayed finding. The neuropathy may lead to nonhealing ulcers on the feet. Treatment of alcoholic neuropathy is abstinence, adequate diet, and thiamine. Complete recovery is rare.

So-called "Saturday night palsy" or "honeymooner's syndrome" is a wrist drop caused by radial nerve compression. The patient usually has spent the night with his or her arm drooped over the back of a chair, bench, or companion; compressing the radial nerve against the humerus producing neurapraxia. Loss of function due to radial nerve neuropraxia usually returns after a few weeks to months.

Wernicke-Korsakoff Syndrome. There are high rates of dementia reported in patients with AUD, and up to 25% when all types of severe cognitive impairment are considered. Previously, two main disorders were described: Wernicke-Korsakoff syndrome (WKS) and alcohol-related dementia (ARD). Now, the DSM-5 introduces major neurocognitive disorder as an alternative term to dementia, with a subtype related to substance or medication use. WKS and ARD could be a direct result of alcohol neurotoxicity or the consequence of a concurrent underlying pathology (such as thiamine deficiency) or both (neurotoxicity associated with nutritional deficiencies).[28]

Although they are similar pathologically and are caused by thiamine deficiency, Wernicke and Korsakoff syndromes are clinically distinct. Wernicke encephalopathy, a medical emergency with a mortality rate of approximately 17%, remains a clinical diagnosis and is often unrecognized. Contemporary criteria require two of these signs—dietary deficiencies, oculomotor abnormalities (nystagmus being the most common), cerebellar dysfunction, and an altered mental state or mild memory impairment. Mental abnormalities include lethargy, inattentiveness, abulia, and impaired memory, progressing without treatment to coma.

Korsakoff psychosis or amnesic state also called an alcohol-induced persisting amnestic disorder, is a disorder with recent memory impairment, inability to learn new information or recall previously learned information, apathy, and confabulation. Although it is common, confabulation is not essential for the diagnosis. Whereas 80% of patients with acute Wernicke's encephalopathy have Korsakoff syndrome, age older than 40 years and many years of heavy alcohol use are additional risk factors.

Treatment of WKS consists of abstinence, adequate diet, and thiamine. The ophthalmoplegia and nystagmus usually have a good response to thiamine administration within hours to days. The ataxia and mental changes may take days to weeks to improve and usually have a poorer prognosis. Less than 25% of patients show any real recovery, 50% show some recovery, and the remainder show no response, despite adequate thiamine replacement. Because magnesium is a cofactor for this enzyme system, its serum levels should be corrected. Patients with WKS require admission with thiamine and magnesium repletion.

Alcoholic Cerebellar Degeneration

Characterized by ataxia of the extremities, cerebellar ataxia of alcoholism results in a wide-based stance and uncoordinated gait. Lower extremity involvement predominates, although the arms may rarely be involved. Pathologic changes consist of the degeneration of elements in the cerebellum, especially the Purkinje cells. The diagnosis is based on history, physical examination, and findings on magnetic resonance imaging or computed tomography (CT), which shows severe cerebellar atrophy. Treatment consists of abstinence, adequate nutrition, and thiamine.

Infectious Disease

Chronic alcohol exposure depresses the development and expression of cell-mediated immunity. This depression may contribute to the high incidence of head, neck, and upper GI cancers in alcoholics. The suppression of macrophage function by alcohol reduces the reticuloendothelial system's ability to clear particles. This may contribute to spontaneous bacteremia, spontaneous bacterial peritonitis, pneumonia, and tuberculosis.

The most common infection in alcoholism is pneumonia. Although alcoholic patients may contract a variety of bacterial pneumoniae, *Streptococcus pneumoniae* is still the most common organism. Periods of alcoholic stupor with incomplete glottic closure and subsequent aspiration can lead to aspiration pneumonia or lung abscess. *K. pneumoniae,* classically associated with alcoholism, is currently more common in patients with cytotoxic chemotherapy, hematologic malignant disease, and transplantation than in the chronic alcoholic. Chronic alcohol consumption increases the risk and severity of chronic infections with HIV; hepatitis C virus (HCV); and *Mycobacterium tuberculosis*.[29]

Endocrine Effects

Alcohol dependence adversely affects many endocrine systems. Peripheral thyroid hormone dysfunction and central hypothalamic-pituitary-thyroid axis deregulation are seen. Male hypogonadism and feminism are seen in chronic male alcoholics. Alcohol's effects on the testes and hypothalamus decrease testosterone production in men. Alcohol may cause impotence by CNS sedation, secondary depression, or decreased testosterone production. Decreased testosterone, increased estrogen (in patients with liver disease), and

increased prolactin levels can lead to decreased libido, feminization, and gynecomastia in male alcoholics and to abnormalities in lactation and menstruation in women. In female alcoholics, increased levels of testosterone and estrogen are found. Estrogen replacement therapy may increase hormonal levels threefold and thus increase the risk of cholelithiasis and breast cancer.

Metabolic Effects

Carbohydrates

Alcohol-induced hypoglycemia occurs in up to 4% of chronic alcoholics. Coma, seizures, hemiparesis, and a variety of other neurologic signs have been described in patients presenting with alcohol-induced hypoglycemia. Starvation, depletion of liver glycogen stores, decreased plasma cortisol levels, the impaired release of growth hormone, and inhibition of gluconeogenesis contribute to this phenomenon.

Hyperglycemia and diabetes may be found in chronic alcoholism. Alcohol abuse can lead to chronic pancreatitis, resulting in the underproduction of insulin by the damaged pancreatic cells. Alcohol also impairs peripheral glucose utilization, causing relative insulin resistance (similar to type 2 diabetes).

Lipids

Ethanol increases the hepatic synthesis of triglycerides. Abstinence is necessary to reverse elevated triglyceride levels. Except for its relationship to fatty infiltration of the liver, the clinical significance of this hyperlipidemia is unknown.

Electrolytes

Ethanol has numerous effects on electrolytes and mineral metabolism, as summarized in Table 137.5. Hyponatremia and hypokalemia are common in active drinkers. Vomiting, diarrhea, magnesium depletion, malnutrition, and metabolic alkalosis contribute to these abnormalities.

Alcoholism is the most common cause of severe magnesium deficiency in adult outpatients. Magnesium deficiency is seen in 30% of alcoholics as a result of malabsorption, malnutrition, diarrhea, vomiting, and increased urinary losses. Oral magnesium supplementation in chronic alcoholics improves liver function test results, electrolyte balance, and muscle strength.

Hypocalcemia is common in alcoholic patients with magnesium depletion. The mechanism is related to diminished parathyroid hormone secretion, decreased tissue responsiveness to parathyroid hormone, decreased vitamin D metabolism, and decreased calcium release from bone, which is independent of parathyroid hormone. Correction of magnesium depletion is necessary to restore calcium to normal levels. Hypoalbuminemia, pancreatitis, or vitamin D deficiency also contribute to low serum calcium levels or low total-body stores of calcium in alcoholic patients.

Hypophosphatemia is found in up to 50% of hospitalized patients with alcoholism. Phosphorus depletion results from malnutrition, vomiting, respiratory alkalosis, diarrhea, enhanced release of calcitonin, phosphate-binding antacids, and urinary loss (related to vitamin D deficiency and secondary hyperparathyroidism). Hypophosphatemic patients often have low magnesium levels. Rehydration, carbohydrate repletion, and parenteral alimentation further exacerbate phosphorus depletion. Glucose bolus and infusions have been shown to produce a significant fall in serum inorganic phosphate levels. Severe hypophosphatemia (<1 mg/dL) has been associated with acute respiratory failure, myocardial depression, CNS irritability, dysfunction of erythrocytes, leukocytes, and platelets, and rhabdomyolysis.

Although chronic alcoholics who require admission often have potassium, magnesium, and phosphate depletion, empirical treatment with potassium and phosphate is discouraged. Serum levels and renal function should be determined first. Unintended hyperkalemia and hyperphosphatemia can produce significant morbidity, and phosphate infusion exacerbates hypocalcemia if present. Because most magnesium is intracellular, a normal serum magnesium level does not rule out decreased total-body magnesium stores. If the serum level is normal, total-body levels may still be low. As long as renal function is adequate, empiric magnesium treatment can be considered. Abstinence and a proper diet resolve electrolyte and nutritional deficiencies in the alcoholic patient who is healthy enough to be treated as an outpatient.

Alcoholic Ketoacidosis

Twenty-five percent of patients who are admitted to the hospital with an alcohol-related disorder develop alcoholic ketoacidosis.[30] Alcoholic ketoacidosis occurs most frequently in severe chronic alcoholics who have had a recent binge followed 1 to 3 days later by protracted vomiting, decreased food intake, dehydration, and abstinence. Nausea, vomiting, and abdominal pain are common presenting complaints. Serum glucose levels are usually less than 200 mg/dL. Normal blood pH may be found despite ketonemia because of coexisting respiratory alkalosis and metabolic alkalosis.

Treatment of alcoholic ketosis consists of the administration of normal saline, glucose, and thiamine with correction of hypokalemia. This can be accomplished with 5% dextrose in normal saline and 30 mEq of potassium chloride or 30 mEq of oral potassium. If no serious complicating illness is present, ketosis is often reversed within 12 to 24 hours of treatment.

Hematologic Effects

Chronic alcohol use is associated with significant alterations in the immune system that predispose people to viral and bacterial infections and cancer development. The alcoholic presents with myriad hematologic abnormalities. The direct toxic effect of ethanol and its metabolites, secondary nutritional deficiency, and hepatic disease, individually or in combination, affect red blood cells, white blood cells, platelets, hemostasis, and the immune system.

Anemia

Several mechanisms cause anemia, which is common in the alcoholic. Megaloblastic anemia resulting from folate deficiency is the most common anemia in alcoholics. The mean corpuscular volume (MCV) is typically increased but may be normal when iron deficiency coexists. Malnutrition, the inability of the cirrhotic liver to store folate, excessive urinary loss, and malabsorption decrease folate stores. Alcohol accelerates the development of megaloblastic anemia in individuals with depleted folate stores (MCV > 100 fL) by less clearly defined mechanisms.

Iron deficiency anemia is common and is usually a result of blood loss from the GI tract. With iron deficiency anemia, the serum iron level is decreased, total serum iron-binding capacity is elevated, and serum ferritin level is decreased. Alcoholics frequently have chronic inflammatory diseases that produce anemia of chronic disease.

Leukocyte Abnormalities

Leukopenia is common in alcoholic patients and has several possible causes. Sepsis, folate deficiency, and hypersplenism all lead to a decreased white blood cell count. Alcohol has a direct toxic effect on white blood cell production in the bone marrow. Granulocyte mobilization (chemotaxis) and adherence are also impaired, resulting in decreased inflammatory responses.

TABLE 137.5 Electrolyte Disturbances[30]

Disturbance	Mechanism or Cause	Comment	Treatment
Acid-Base			
Alcoholic ketoacidosis	Anion-gap metabolic acidosis due to decrease in insulin: glucagon ratio	Increased NADH:NAD ratio favors formation of/3-hydroxybutyric acid	Administer 5% dextrose in 0.9% (normal) saline and treat other disorders if present
Lactic acidosis	Increased NADH:NAD ratio due to ethanol metabolism	Average lactate level 3 mmol/L consider sepsis or thiamine deficiency with higher levels	Administer 5% dextrose in 0.9% (normal) saline and treat other disorders if present
Hyperchloremic normal-gap metabolic acidosis	Indirect loss of bicarbonate due to loss of ketoacid salts in urine	Regeneration of bicarbonate by kidneys repairs deficit	Provide conservative management
Metabolic alkalosis	Vomiting	Increase in anion gap greater than decrease in bicarbonate concentration when combined with alcoholic ketoacidosis	Restore volume of extracellular fluid with chloride-containing fluids, correct hypokalemia
Respiratory alkalosis	Alcohol withdrawal, chronic liver disease, pain, sepsis	Often the primary disorder in a mixed acid-base disturbance	Administer benzodiazepines for alcohol withdrawal; treat underlying disorders
Hypophosphatemia	Alcohol-induced urinary loss, magnesium deficiency, acidemia, increased parathyroid hormone level, nutritional deficiency, decrease in gastrointestinal absorption, cellular shift due to insulin release, respiratory alkalosis, β_2-adrenergic stimulation	Muscle weakness, rhabdomyolysis, tissue ischemia, hemolysis, cardiac dysfunction; urine phosphate excretion >100 mg/24 h r or fractional excretion ≥5% indicates renal wasting	Oral supplements preferred; for complications, administer 42–67 mmol phosphate over 6 to 9 hr, not to exceed 90 mmol/day to avoid decrease in calcium and magnesium levels
Hypomagnesemia	Alcohol-induced urinary loss, phosphate deficiency, nutritional deficiency, decreased gastrointestinal absorption, cellular shift due to insulin release, respiratory alkalosis, β_2-adrenergic stimulation	Persistent renal wasting can last several weeks, accounting for recurrence of hypomagnesemia after initial correction; urinary magnesium excretion >25 mg/ 24 h or fractional excretion >2% indicates renal wasting	Oral supplements preferred; intravenous magnesium indicated in patients with arrhythmias or neuromuscular irritability
Hypocalcemia†	Decrease in parathyroid hormone level and resistance due to magnesium deficiency, alcohol-induced urinary loss, vitamin D deficiency	Correct for a low albumin concentration as follows: corrected calcium=serum calcium in mg/dL + [0.8× (4.0-serum albumin in g/dL)]; bicarbonate therapy can decrease ionized fraction	Correct the magnesium deficit; correct the deficiency in vitamin D
Hypokalemia	Urinary loss due to coupling of increased distal sodium delivery and increased aldosterone level, magnesium deficiency, diarrhea, cellular shift due to insulin release, correction of acidosis, respiratory alkalosis, β_2 adrenergic stimulation	A low or normal potassium level in patients with rhabdomyolysis suggests a significant underlying total-body deficit of potassium; urinary potassium >30 mmol/24 h or urinary potassium: creatinine ratio >13 (in millimoles of potassium per gram of creatinine) indicates renal wasting	Oral supplements preferred; for complications, administer intravenous potassium chloride at 10–20 mmol/h; administer potassium before Bicarbonate in patients with acidemia
Hyponatremia	Increased release of vasopressin due to volume depletion; decreased solute excretion in beer potomanía	Increased risk of osmotic demyelination	Restore volume and increase protein intake; limit rate of correction to 6–8 mmol in first 24 hours, to slow rate with 5% dextrose in water, desmopressin, or both

Data from Palmer BF, Clegg DJ. Electrolyte Disturbances in Patients with Chronic Alcohol-Use Disorder. *N Engl J Med*. 2017;377(14):1368–1377.

Platelet Disorders

Thrombocytopenia can occur with folate deficiency, marrow suppression, sepsis, disseminated intravascular coagulation, or splenic sequestration. The direct toxic effects of alcohol decrease measured survival time and impair the production of platelets in the bone marrow, but marrow toxicity rarely reduces the platelet count below 30,000/mm^3. Qualitative platelet function is also impaired. Binge drinking is associated with a reactive thrombocytosis potentially responsible for acute stroke and sudden death.

Hemostasis

Alcoholic patients have a bleeding diathesis for many reasons, including thrombocytopenia, qualitative platelet disorders, deficient production of hepatic clotting factors, GI variceal formation, and vitamin K deficiency. Bleeding associated with coagulation abnormalities may require fresh-frozen plasma for the immediate correction of coagulation factor depletion; vitamin K (10 mg IV) takes 6 to 10 hours to reverse the vitamin K–dependent factors II, VII, IX, and X. Because of poor diet and impaired hepatobiliary function, alcoholics may have

insufficient vitamin K storage and benefit from vitamin K delivery. However, alcoholic patients with profound liver failure are unable to produce the precoagulation factors II, VII, IX, X, and IV, so vitamin K therapy is ineffective. Platelet transfusions should be started in the ED for adult patients with active bleeding when the platelet count is less than 50,000/mm^3.

Oncologic Effects

While alcohol itself is not carcinogenic, its metabolite, acetaldehyde, has emerged as an important contributor; it can form stable DNA adducts, trigger mutations in tumor suppressors and oncogenes, and interfere with DNA repair. Over 5% of all new cancer occurrences and 6% of all cancer deaths worldwide were estimated to be attributable to alcohol.[31,32]. Alcohol consumption has been highly associated with specific oncological diseases such as oral, pharyngeal, laryngeal, esophageal, hepatic, colorectal, and breast cancers.[31,32]

Hypothermia

Acute alcohol ingestion is one of the most common precipitating factors for accidental hypothermia and occurs in 33% to 75% of patients presenting with a core temperature below 35°C (95°F). Alcohol exacerbates hypothermia of other causes, with depressed hypothalamic thermoregulation, peripheral vasodilation producing heat loss, CNS depression, sepsis, inability to shiver, hypoglycemia, and increased risk of environmental exposure. Hypothermia may be the presentation of Wernicke syndrome, possibly caused by lesions of the posterior hypothalamus, hypoglycemia, or sepsis.

Psychiatric Effects

Depression and antisocial personality are the two most common psychiatric disorders that correlate with alcoholism, with a prevalence of 30% to 60% in most studies. Of alcoholic men admitted to a psychiatric ward, approximately 40% have another psychiatric disorder unrelated to substance abuse—in particular, antisocial personality disorder, schizophrenia, mood disorders, and anxiety disorders.

Mental illness and substance use often co-occur and heavy alcohol use and AUDs are known risk factors for violence.[33] Secondary depression may be caused by alcoholism, or the primary affective disorder may be present with secondary alcoholism. Mild depressive symptoms are also common in alcohol withdrawal. Alcoholism, major depression, and antisocial personality all predispose to suicide, and interaction among the three is particularly dangerous, but the acute risk on any given day is difficult to assess.[34] Alcohol increases the lifetime risk of suicide, with over 15% of all alcoholics eventually dying by suicide.

Toxicologic Effects

Alcohol has long been known to have additive or even synergistic effects with several drugs including opioids and sedative hypnotic agents. Acute intoxication decreases the rate of drug metabolism, which is partially explained by competition for the same enzymatic process in the liver. Ethanol increases aspirin-induced prolongation of bleeding time and reduces the metabolism of warfarin, leading to increased anticoagulant effects. There is an increased risk of upper GI bleeding when alcohol is combined with NSAIDs.

Disulfiram and Similar Reactions

Most patients pretreated with disulfiram (Antabuse) who then consume even small amounts of alcohol experience an extremely unpleasant reaction. These patients have a hypersensitivity to ethanol and experience a direct response within 15 minutes, lasting 30 minutes to several hours. The reaction consists of skin flushing on the head that spreads to the trunk, along with nausea, vomiting, headache, chest and abdominal discomfort, diaphoresis, vertigo, palpitations, and confusion. A severe reaction may produce hypotension, seizures, and dysrhythmias. The disulfiram-ethanol reaction is thought to occur by the accumulation of acetaldehyde secondary to inhibition of the ALDH enzyme, which may be deficient in many Asians, or another unknown toxic factor. The common ink cap mushroom *(Coprinopsis atramentatia)*, while nontoxic when ingested alone, causes a similar disulfiram reaction if consumed with alcohol. Treatment for disulfiram reaction is generally observation, cardiac monitoring, an antiemetic for symptoms, and intravenous (IV) fluids.

Other Considerations—Patient Groups Affected

Adolescents. Excessive high school and college drinking continues to be prevalent and problematic. Approximately 1.2 million youths aged 12 to 17 met the criteria for SUDs in 2015 (5% of this population).[35] Alcohol is by far the most commonly used substance among youth, with 37% of 18-year-olds endorsing alcohol use and 24 % reporting being drunk in the past month.[36] Alcohol is the most commonly used drug and is a common contributor to the leading cause of death, unintentional injury, homicide, and suicide among adolescents (10 to 20 years old) in the United States.

Adolescent onset of alcohol use has been associated with an increased risk for developing an AUD later in life.[37] Although underage youth may drink less often than adults, they typically drink in larger quantities than adults when they do drink, and often binge drink.[38] Binge drinking, as defined by the NIAAA, is a pattern of alcohol consumption that brings blood alcohol concentration to .08 g/dL, which typically occurs following the intake of five or more standard alcohol drinks by men and four or more by women over a period of approximately 2 hours. In 2011, the NIAAA produced a two-question Youth Alcohol Screening Tool which asks about the frequency of alcohol consumption and friends' alcohol use in the past year (Table 137.6).[39]

Older Patients. Alcohol use is a growing public health concern for elderly adults. Elderly patients, meaning patients ages 65 years and older, comprise the fastest-growing portion of the US population. By 2040, the elderly will comprise more than 20% of the total population. Compared with all other substances, alcohol is the most commonly used among the elderly, and thus, the risks of drinking by older individuals will undoubtedly become an increasing issue as this population rises over the coming decades.[40]

Common screening tests (e.g., the CAGE questionnaire) tend to be less sensitive in this age group. Alcohol may exacerbate underlying disease by masking anginal chest pain, worsening hypertension, and inducing dysrhythmias. Older adults who consume low to moderate levels of alcohol, however, may have a decreased risk for the development of dementia and heart failure.

Older patients are more likely to have neuropsychiatric complications of alcoholism, such as sleep problems, anxiety, depression, and dementia. Alcohol is involved in one-third of suicides in older adults. Older subjects also perform less well than younger subjects on tests of perception and attention when under the influence at all blood alcohol levels. This may result in an increased risk of fractures from falling and osteoporosis. However, evidence has suggested that compared with abstinence, consumption of up to one drink/day is associated with a decreased risk of osteoporotic hip fracture, and there is a beneficial effect of moderate alcohol consumption on bone density.

Pregnant Women. There is no known safe level of alcohol consumption during pregnancy. Alcohol is a known teratogen that can impact fetal growth and development during all stages of pregnancy. The current recommendation from the American College of Obstetricians and Gynecologists, Center for Disease Control (CDC),

TABLE 137.6 The NIAAA Youth Alcohol Screening Tool

Age:	First Question:	Second Question:
Elementary School (ages 9–11)	Friends: Any drinking? "Do you have any friends who drank beer, wine, or any drinking containing alcohol in the *past year?"*	Patient: Any drinking? "How about you —have you *ever* had more than a few sips of beer, wine, or any drink containing alcohol?
Middle School (ages 11–14)	Friends: Any drinking? "Do you have any friends who drank beer, wine, or any drinking containing alcohol in the *past year*	Patient: How many days? "How about you—in the *past year, on how many days* have you had more than a few sips of beer, wine, or any drink containing alcohol?"
High School (ages 14–18)	Patient: How many days? in the *past year, on how many days* have you had more than a few sips of beer, wine, or any drink containing alcohol?"	Friends: How much? "If your friends drink, *how many drinks* do they usually drink on an occasion?"

Surgeon General, and medical societies from other countries all recommend complete abstinence during pregnancy.[41]

Alcohol readily crosses the placenta with fetal blood alcohol levels approaching maternal levels within 2 hours of maternal intake. There are a wide variety of developmental defects that result from alcohol exposure, including brain abnormalities, CNS dysfunctions, and growth deficiencies of developing organs and body systems. These adverse effects on the developing fetus are known collectively as fetal alcohol spectrum disorders (FASDs).[42] FASDs cause dysfunctions in learning, emotion, cognition, motor performance, and can lead to behavioral as well as social problems.[42] FASDs are characterized by a triad of CNS defects, including mild to moderate mental retardation, dysmorphology, involving mostly facial structures, and growth deficiencies, usually consisting of short stature and microcephaly. FASDs are now considered the most common identifiable source of mental retardation. Children exposed to prenatal alcohol exhibit increased activity levels, cognitive and attention deficits, perseverative behavior, and language and motor problems, which persist into adulthood.

Alcohol has the ability to freely pass through a lactating mother's milk and thus lactating mothers who decide to continue to drink should avoid breastfeeding 3 to 4 hours after moderate to high consumption of alcohol.[41]

Trauma

Injury is a leading cause of death in those between the ages of 1 and 44 years, accounting for more than 50 million injuries/year and approximately 26,000 deaths/year. In the United States, alcohol is the major risk factor for virtually all categories of intentional and unintentional injury. In addition to increasing the frequency and severity of the injury, alcohol consumption significantly impacts the management of the trauma victim. Alcohol intoxication often complicates the initial assessment of injury severity, resulting in an increased need for invasive diagnostic and therapeutic procedures (e.g., intubation and ventilation, CT imaging, intracranial pressure monitoring).

Alcohol may diminish the patient's capacity to respond to hemorrhagic shock by altering hemodynamic effects and the acid-base balance. Volume depletion as a result of the diuretic effect of alcohol or vomiting can impair the reserve of the intoxicated trauma patient. Peripheral vasodilation caused by alcohol may contribute to hypotension and hypothermia. Although these effects may be transient, they underscore the need for early and adequate fluid resuscitation in these patients. Intoxicated patients with severe non-neurologic trauma may have lower blood pressures and carbon dioxide levels, indicative of compensatory hyperventilation, on hospital arrival compared with sober patients. More importantly, a poorly understood cardiac depressant effect also increases the depth of shock and volume requirements for resuscitation. Alcohol-induced skin vasodilation may be accompanied by an increase in skeletal muscle, mesenteric, and renal bed constriction and left ventricular stroke work. Thus, the overall effect on systemic vascular resistance and blood pressure may be balanced.

Intoxication renders the signs and symptoms of intra-abdominal and retroperitoneal injury less reliable than usual. If the risk of an intra-abdominal injury exists, further evaluation (e.g., diagnostic ultrasonography, CT imaging) should be considered. Alcohol intoxication predisposes to abdominal wall laxity and therefore less protection from blunt trauma. These patients are also likely to have full stomachs, increasing the risk of gastric injury after trauma and predisposing to vomiting and aspiration, especially during acute airway management. The fatty liver changes in alcoholism can result in hepatomegaly. Portal hypertension in alcoholics may produce splenomegaly. These organs can become more vulnerable to the effects of trauma because of their enlarged size, protrusion beneath the protection of the ribs, and increased intracapsular pressure.

The American College of Surgeons Committee on Trauma requires screening for problem drinking for designation at a level I or II trauma center. In addition, level I trauma centers must provide intervention for identified problem drinkers. Although many institutions use blood alcohol levels to determine at-risk drinking in trauma patients, the Alcohol Use Disorders Identification Test (AUDIT) offers a practical alternative (Box 137.3).[43]

DIFFERENTIAL DIAGNOSIS

Acute alcohol intoxication is a diagnosis of exclusion. Before it is assumed that a patient's behavior is caused only by alcohol, other conditions should be considered, particularly co-ingestion of other substances and pharmaceutical agents, head trauma, and infection. Hypoglycemia, hypoxia, carbon dioxide narcosis, mixed alcohol-drug overdose, ethylene glycol poisoning, isopropanol or methanol poisoning, hepatic encephalopathy, psychosis, severe vertigo, postictal state, and psychomotor seizures can be manifested in a manner similar to that of ethanol intoxication.

AWS can initially be confused with acute schizophrenia, encephalitis, drug-induced psychosis, thyrotoxicosis, anticholinergic poisoning, and withdrawal from other sedative hypnotic agents. Alcohol withdrawal and alcohol-induced hypoglycemia also present with similar clinical presentations.

DIAGNOSTIC TESTING

Determination of a blood ethanol level is not routinely necessary in caring for the intoxicated patient when there is clear evidence of

BOX 137.3 AUDIT-C Questions

1. How often did you have a drink containing alcohol in the past year?
   a. Never (0 points)
   b. Monthly or less (1 point)
   c. Two to four times a month (2 points)
   d. Two to three times per week (3 points)
   e. Four or more times a week (4 points)
2. How many drinks containing alcohol did you have on a typical day when you were drinking in the past year?
   a. 0–2 (0 points)
   b. 3–4(1 point)
   c. 5–6 (2 points)
   d. 7–9 (3 points)
   e. 10 or more (4 points)
3. How often did you have six or more drinks on one occasion in the past year?
   a. Never (0 points)
   b. Less than monthly (1 point)
   c. Monthly (2 points)
   d. Weekly (3 points)
   e. Daily or almost daily (4 points)

Adapted from Miller LB, Brennan-Cook J, Turner B, et al. Utilizing an Evidence-Based Alcohol Screening Tool for Identification of Alcohol Misuse. *J Addict Nurs*. 2018;29(2):90–95.

alcohol intake (e.g., confirmation by the patient). When the mental status is sufficiently altered that an adequate history cannot be obtained, there is evidence of head trauma, or the patient fails to improve (detoxify) as expected, a serum ethanol level or measurement by a breathalyzer should be determined. If the degree of obtundation is not commensurate with the measured (or breathalyzed) level, and other laboratory test results (e.g., toxicology screen, electrolyte levels, metabolic profile) do not explain the altered mental status, a head CT scan is indicated. Adequate history from paramedics, patient, and family members, serial physical examinations (especially mental status), and bedside testing, such as serum glucose level and oximetry, can help clarify the clinical situation and guide further testing.

Blood tests can be useful if the history is in doubt and can also help patients recognize that alcohol has adversely affected their health. The utilization of direct metabolites of ethanol is considered more accurate biomarkers of recent alcohol consumption. Three of these biomarkers, ethyl glucuronide (EtG), ethyl sulfate (EtS), and phosphatidylethanol (PEth), are gaining acceptance, although they are not currently available for routine testing.[5,44]

Tests of liver function that measure AST and ALT levels can identify heavy drinking and AUDs with sensitivities of 25% to 45% and specificities as high as 90%. A ratio of AST to alanine transaminase (ALT) higher than 2 suggests that alcohol is the cause of liver injury.

Laboratory Tests

In the apparently intoxicated patient with altered mental status, the serum glucose level, usually as a point of care test, should be measured to assess for hypoglycemia. In the alcoholic patient, electrolyte levels and acid/base status should be determined to look for hypomagnesemia, hypophosphatemia, hyponatremia, and metabolic acidosis. A complete blood count is obtained to evaluate for anemia, leukopenia, and thrombocytopenia and a serum lipase level to evaluate for pancreatitis if the patient has severe upper abdominal pain or tenderness, especially if accompanied by vomiting. A complete blood count, peripheral smear, platelet count, reticulocyte count, thrombin time, prothrombin time and INR, and partial thromboplastin time help evaluate episodes of significant alcohol disease-induced bleeding.

Liver function tests are followed in a serial manner in cases of alcoholic hepatitis. An electrocardiogram (ECG) is indicated for tachydysrhythmias or chest pain (e.g., holiday heart, acute ischemia). A CT scan of the head or cervical spine imaging may be indicated if head trauma or seizures are suspected or confirmed or if the patient's mental status does not improve in step with the metabolism of alcohol. A chest radiograph is obtained to rule out cardiomyopathy, infectious pneumonia, or aspiration pneumonitis.

Alcohol Screening Questionnaires

Detection of risky drinking behaviors can be through clinical history or the administration of short alcohol screening tools in the ED setting. The screening tools with superior sensitivity and specificity are the SASQ, AUDIT, and AUDIT-Consumption (AUDIT-C), see Box 137.3.

As part of the initial assessment and in alignment with national recommendations, computerized screening programs could be used as an effective method for detecting at-risk alcohol use in ED patients. Identification of AUD and brief, sentinel event advice in the ED can be an effective and cost-effective method to reduce levels of alcohol consumption and alcohol-related harm.

The SASQ From the NIAAA can be used to streamline the screening process—it includes only 1 question: "How many times in the past year have you had x or more drinks in a day?" (where x is 5 for men and 4 for women).

MANAGEMENT

Comatose or stuporous patients may require assisted ventilation and intubation. If the bedside serum glucose level identifies hypoglycemia, IV glucose, as $D_{50}W$ or an infusion of D_5W, is indicated. Patients with evidence of poor nutrition should receive thiamine, 100 to 250 mg IM or IV once daily for 3 to 5 days. If an opioid overdose is suspected, naloxone may be diagnostic and therapeutic. Because magnesium is a necessary cofactor for thiamine metabolism, consider administering magnesium, 2 g IV. When possible, hypoglycemia should be documented before the empirical administration of glucose. With the airway maintained and respirations supported, the patient's liver eventually metabolizes the alcohol, and most patients recover.

Intoxicated patients who do not appear capable of appropriate decision making require evaluation and treatment in the ED, regardless of their willingness to cooperate. It is incumbent on the emergency clinician to establish that the patient understands the nature of the problem, whether intoxication alone or intoxication in the context of acute illness or injury and is capable of making reasoned and responsible decisions about care. Inappropriate discharge and failure to diagnose are two common areas of liability in the treatment of the alcohol-dependent patient. Discharge can be considered when a patient is clinically sober enough to be able to dress, walk, make reasonable decisions, and function independently, as judged and well documented by the treating emergency clinician. When possible, it is ideal to have another sober adult who is willing to take responsibility for and remain with the patient for the next 24 to 48 hours. Once clinically sober and cleared for discharge, patients should be reminded not to drink and drive.

Alcohol Withdrawal Syndrome

Family, friends, bystanders, or paramedics often give more reliable historical data than the patient does. Accurate vital signs are essential; this may require a rectal temperature. Hyperthermia, hypothermia,

tachypnea, or tachycardia may suggest serious disorders that often accompany the alcohol-dependent patient. A rapid and thorough physical examination should be performed, with attention to the level of consciousness, signs of hepatic failure, or coagulopathy. Signs of trauma are sought, as well as a thorough neurologic examination.

The AWS should be promptly recognized and treated. The CIWA-Ar is a validated tool for symptom-based prescribing of benzodiazepines for alcohol withdrawal. Scores on the CIWA-Ar ranges from 0 to 67; scores lower than 8 indicate mild withdrawal symptoms that rarely require the use of medications, scores from 8 to 15 indicate moderate withdrawal symptoms that are likely to respond to moderate doses of benzodiazepines, and scores higher than 15 indicate severe syndromes that require close monitoring to avoid seizures and AWD (or delirium tremens).

Pharmacologic Treatment

Patients suffering from alcohol withdrawal should receive pharmacologic intervention along with supportive care. The ideal drug for alcohol withdrawal should have a rapid onset, a wide margin of safety, metabolism not dependent on liver function, and limited abuse potential. Although no one drug class meets all these requirements, benzodiazepines are clearly the mainstay of treatment.

Benzodiazepines. Benzodiazepines have anticonvulsant activity, dose-dependent respiratory and cardiovascular depressive effects, and and be given IV/IM if necessary. By interacting with receptors linked to the GABA-associated chloride ion channel, benzodiazepines substitute for the withdrawal of the GABA-potentiating effect of alcohol and abate withdrawal signs and symptoms. Numerous benzodiazepines have been studied, but there is no evidence of the clear superiority of any one benzodiazepine.

Lorazepam has good bioavailability with the oral, intramuscular, and IV routes. It may be given via an IM injection in agitated patients with no IV access. The half-life of lorazepam is ~12 hours and it does not have any active metabolites.. Excessive sedation, confusion, and ataxia are potential complications of all benzodiazepines with prolonged half-lives. Lorazepam is metabolized (conjugated) in the liver, yielding inactive products. Although the half-life of lorazepam increases in patients with cirrhosis or liver failure, it is much shorter than the increase with chlordiazepoxide. The elimination of lorazepam is only minimally altered in patients with renal failure and in older adults. Lorazepam may be given IV in a dose of 1 to 4 mg, depending on the severity of the withdrawal. Dosing can be repeated at 5 to 15-minute intervals for patients in severe withdrawal. Although it is not ideal, an intramuscular dose of 1 to 4 mg can be used every 30 to 60 minutes until the patient is calm and then every hour, as needed, for light somnolence.

Diazepam is another commonly used benzodiazepine to treat patients with alcohol withdrawal. When given IV, it has a rapid onset (1 to 3 mins) and a duration of 1 to 2 hours, though its half-life can be increased significantly in patients with liver dysfunction. Since diazepam has a more rapid onset than lorazepam, its dosing interval can be much shorter. One such dosing strategy involves giving diazepam 5 mg IV every 5 to 10 minutes for patients with major withdrawal symptoms. The dose can be repeated in 5 to 10 minutes. If the second dose of 5 mg is not working, consider 10 mg for the third and fourth doses every 5 to 10 minutes. If this is not effective, consider 20 mg for the fifth and subsequent dose until adequate sedation has been obtained.

Butyrophenones. Haloperidol, a dopamine antagonist, can be considered in patients with major alcohol withdrawal or delirium tremens and acute agitation or behavioral issues not responding to IV benzodiazepines. However, antipsychotics should never be used alone or as a first-line treatment for alcohol withdrawal as they do not treat the underlying pathophysiology. Haloperidol has little effect on myocardial function or respiratory drive, and its safety and efficacy by the IV, intramuscular, or oral route in the ED has been established. The typical dose is 2 to 5 mg q4–8h prn; q1h may be required with acute agitation; but not to exceed 20 mg/day. Haloperidol has no anticonvulsant properties; however, extrapyramidal effects may be seen. Caution should be used in patients who may be susceptible to a prolonged QTc interval. Droperidol has effects and risks similar to those of haloperidol and remains a safe and effective treatment for acutely agitated patients in the ED. The recommended adult dose is 2.5 mg IV/IM; additional doses of 1.25 mg may be given to a desired effect if the clinical benefit outweighs the potential risk.

Other Agents. Patients being treated for major alcohol withdrawal may be given thiamine (100 mg IV) and magnesium (2 g IV). Although magnesium sulfate does not decrease the severity of withdrawal symptoms, the incidence of delirium, or seizures, it carries no significant risk with adequate renal function. For patients who require intubation for refractory withdrawal or for other reasons, an infusion of propofol or a benzodiazepine should be initiated to treat the patient's alcohol withdrawal.

Neurologic Examination

New-Onset Seizures

Patients with new-onset, alcohol-related seizures should be thoroughly evaluated. This includes alcoholics who claim to have had seizures but for whom no documentation or appropriate evaluation is available. Metabolic disorders, toxic ingestion, infection, and structural abnormalities should also be considered.

If the initial physical examination findings, imaging studies, and laboratory test results are within normal limits, patients who remain seizure-free and symptom-free, with no sign of withdrawal after 4 to 6 hours of observation, may be discharged. It may be unclear whether the patient has had a pure alcohol withdrawal seizure or a new-onset seizure disorder in the setting of alcohol ingestion. Long-term treatment with antiepileptic drugs is not useful in unprovoked new-onset seizures that have resolved or when a clear relation to alcohol consumption can be identified.

Optimal outpatient treatment includes follow-up and referral to a detoxification or rehabilitation program. Ideally, the assistance of a reliable family member or friend who is not a drinking partner and can remain with the patient for at least 1 or 2 days is helpful.

Prior History of Seizures During Withdrawal

The risk of seizure increases significantly in alcoholic patients with manifestations of alcohol withdrawal who relate a history of alcohol withdrawal seizure. Detoxification with benzodiazepines reduces alcohol withdrawal seizures and should be initiated early because most seizures occur within the first 24 hours after alcohol withdrawal. An initial dose of 2 mg of lorazepam or 5 mg of diazepam can be given IV. These doses frequently need to be repeated, as noted in the Benzodiazepine section.

Abnormal Neurologic Examination

New-Onset Partial Seizures. Partial seizures account for up to 50% of alcohol-related seizures. Conversely, approximately 20% of patients with partial alcohol-related seizures have structural lesions—hematomas, tumors, vascular abnormalities, or stroke. These primary causes of partial alcohol-related seizure, such as prior head trauma, may be easily missed in the history taking. As a result, an emergent CT scan of the head is indicated to evaluate new-onset partial seizures. The patient with a history of a focal alcohol-related seizure who has been previously evaluated does not require an emergency CT scan provided a return to baseline occurs promptly.

Patients Taking Anticonvulsants. A patient currently taking antiepileptic drugs for an antecedent seizure disorder who presents with a seizure while intoxicated falls into a different category. Such

an episode could be an isolated event in a usually compliant patient without a history of chronic alcohol abuse. In this patient, a seizure in the setting of a subtherapeutic antiepileptic drug level may represent the consequences of noncompliance with antiepileptic medication, coingestants, or sleep deprivation versus alcohol withdrawal seizure.

DISPOSITION

Most patients with acute alcohol intoxication are managed in the ED or observation unit and then discharged home. Patients who achieve sufficient sobriety to be ready for discharge are offered detoxification or alcohol treatment programs. Most alcoholics suffer from a combination of medical, psychiatric, and social problems. Hospitalization may be necessary to diagnose and treat these multiple problems. Moreover, with alcoholics who are no longer able to care for themselves, hospitalization is often dictated for this reason alone. Unfortunately, many managed care and Medicaid plans limit or do not cover inpatient detoxification. In choosing medical versus psychiatric admission, a medical illness usually takes priority. Optimal outpatient therapy for chronic alcoholics includes the involvement of concerned family or friends to ensure that the patient takes his or her medications properly, keeps follow-up appointments, abstains from alcohol, and maintains an adequate diet. Alcoholic patients who undergo outpatient treatment need close supervision; therefore, a follow-up clinic appointment within 24 to 48 hours should be considered.

Acute Intoxication

Acute intoxication alone seldom requires admission. However, a combined alcohol-drug overdose or associated medical, psychiatric, or social problems may require hospitalization. Acute alcohol intoxication is a diagnosis of exclusion reached after adequate observation to ensure that the altered mental status resolves and that the patient is hemodynamically stable.

Alcohol levels that may be tolerated by an adult can be lethal in children. It is prudent to admit young pediatric patients with acute intoxication and ensure close psychosocial follow-up for adolescent patients. Children presenting with hypoglycemia or medical complications should be admitted. Child abuse or neglect should always be considered.

Alcohol Withdrawal

Outpatient treatment consists of lorazepam, 1 to 2 mg TID tapered over 3 to 6 days, chlordiazepoxide, 25 to 100 mg TID tapered over 3 to 6 days, or diazepam, 30 mg once daily tapered over 5 days, depending on the severity of symptoms. Adequate diet, abstinence, and participation in a rehabilitation program in the community are also desirable. Any patient requiring 300 mg of chlordiazepoxide or 60 mg of diazepam/day to control withdrawal should be considered for admission.

Patients with signs of major withdrawal (fever, hallucinations, confusion, extreme agitation) require admission for close monitoring, serial neurological checks, and repeated medication dosing. Risk factors for clinical deterioration in patients with moderate to severe withdrawal include older patients who may be at greater risk for delirium tremens and may not tolerate the systemic stress of major withdrawal. Patients with delirium tremens generally require ICU admission. Criteria for ICU admission may also include patients with hemodynamic instability, electrolyte or acid-base disturbance, persistent hyper or hypothermia, rhabdomyolysis, renal insufficiency, and co-morbid conditions such as severe infection or pancreatitis.

Patients with mild alcohol withdrawal can be observed in the ED. After 4 to 6 hours of observation and treatment, the alert-oriented patient whose vital signs, physical examination findings, and results of laboratory analysis are within normal limits may be released with appropriate medications and aftercare instructions. Nevertheless, the patient can benefit from treatment for the underlying disease of alcoholism and should be advised or referred accordingly.

Seizures

The alcoholic patient with a first-time, alcohol-related seizure may be discharged to a suitable social situation in these situations: (1) when the patient's alcohol withdrawal is mild and controlled by supportive care or low-dose benzodiazepines; (2) the diagnostic evaluation, including a head CT scan, is unremarkable; (3) the patient has had fewer than two seizures; and (4) the patient has been observed to be alert and oriented, with stable vital signs and physical examination findings, normalized laboratory study results since the last seizure, and appropriate outpatient follow-up can be ensured.

Patients with a documented history of alcohol-related seizures can be discharged if they have had no more than two alcohol-related seizures during a 6-hour period, with a lucid interval between seizures, and are observed to be seizure-free and at baseline mental and physical status for at least 6 hours after their last alcohol-related seizure. Three to five brief, self-limited seizures may occur with alcohol withdrawal seizures. We recommend prolonged observation in the ED or observation unit for patients with two or more seizures because of the potential for deterioration to status epilepticus. Such patients should be observed until at least 6 hours have passed since their last seizure and they have a normal mental status and neurologic examination.

Patients with partial seizures or focal neurologic findings on physical examination require admission unless these findings have been previously documented. Patients with seizures associated with head trauma or mixed alcohol-drug withdrawal are admitted. Status epilepticus or recurrent seizures during ED observation indicate a lack of seizure control and require further hospitalization, often in a critical care setting.

Psychiatric and Social Problems

Alcoholic patients requiring admission with acute intoxication, alcohol-related seizure, alcohol withdrawal, or medical or surgical disorders are usually best managed in acute care units rather than by a general psychiatric service. Some psychiatric and social conditions in the alcoholic can be better handled on a general psychiatric unit—psychosis, exacerbation of schizophrenia, depression with suicidal tendencies, any patient who is a danger to self or others, or alcoholic hallucinosis with an otherwise clear sensorium.

Patients who are no longer able to care for themselves may also require admission. Although these patients' ultimate destination is a rehabilitation center or a border care program, hospitalization may be necessary to rule out medical or psychiatric illness and treat impending withdrawal symptoms. Patients who wish to stop drinking are usually referred to a detoxification unit for treatment of impending withdrawal.

Psychosocial interventions are the basis of long-term treatment, but medications are also often used. However, the data surrounding the use of medications are weak.[45] The FDA has approved three medications for alcohol dependence in the United States: disulfiram, naltrexone, and acamprosate. A fourth drug, nalmefene (oral), is approved throughout the European Union and is taken on an "as needed" basis prior to anticipated drinking occasions.

Other medications for AUDs have shown limited efficacy, and there is a high degree of variability in treatment response. Baclofen for the long-term treatment of alcohol dependence shows no clear-cut evidence from randomized, double-blind studies.[1,45] Gabapentin is used as monotherapy or as an add-on pharmacotherapy in outpatient settings in the control of alcohol consumption and craving

and in helping patients achieve abstinence.[46] Ondansetron may show benefit in early-onset but not in late-onset alcoholics. Risperidone for agitation has minimal effects on vital signs with or without a benzodiazepine, suggesting that risperidone is a safe option for patients presenting with acute agitation even in the setting of alcohol intoxication.[47]

Brief intervention and screening (SBIRT—***s***creening, ***b***rief ***i***ntervention, and ***r***eferral to ***t***reatment) can reduce alcohol consumption and is feasible and effective in the ED.[48] An ultra-BI (less than 10 minutes face-to-face time) or employing technology such as computers and mobile phones reduces previously identified barriers to ED clinician utilization.[49] Internet-based interventions show promise for reducing alcohol consumption, especially among those meeting criteria for hazardous or harmful drinking. Telephone contact after the ED visit may be another effective tool to screen injured patients for hazardous drinking and offer a brief intervention while avoiding interruptions to patient flow. Providing internet-based interventions is more effective than no intervention at all to reduce binge drinking among college-aged students. The Internet could be an economic and acceptable form of delivering brief interventions and is a preferred approach to reach binge drinkers in college.[50]

Most communities have an Alcoholics Anonymous (AA) chapter or treatment center for anyone who desires help with alcohol. Sobering centers can have a prominent role in the care for those with acute alcohol intoxication, particularly those individuals with chronic public intoxication who are likewise homeless. In smaller communities, clergy or social workers can usually arrange rehabilitation. Psychosocial treatments such as brief counseling, motivational enhancement therapy, the community reinforcement approach, guided self-change, behavior contracting, and social skills training were among the top ten most effective interventions for AUDs, together with various pharmacological interventions.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 137: QUESTIONS AND ANSWERS

1. A 56-year-old man presents with alcohol intoxication. He is drowsy but arousable to painful stimuli. He is confused. Vital signs are within normal limits, and there is no evidence of trauma. Routine testing should include which of the following first?
   a. Basic metabolic panel
   b. Glucose
   c. Serum blood ethanol level
   d. Urine toxicology screen

Answer: b. Chronic alcoholics have decreased glycogen stores and frequently experience hypoglycemia. While a basic metabolic panel could provide you with additional information, the primary electrolyte of interest is glucose. Serum blood ethanol and urine drug screens may be helpful in the undifferentiated patient with altered mental status, but these patients still require a bedside glucose test first.

2. A 42-year-old woman presents with agitation, confusion, and fever. She is noted to experience visual hallucinations during your interview. Her vital signs reveal hypertension, tachycardia, and fever. Physical examination is otherwise unremarkable. Diagnostic studies (including head CT scan and lumbar puncture) are nonspecific. Which diagnosis is most consistent with this patient's presentation?
   a. Acute schizophrenia
   b. Alcohol withdrawal
   c. Anticholinergic poisoning
   d. Thyrotoxicosis

Answer: b. Patients are often confused and agitated and exhibit autonomic instability, resulting in hypertension, tachycardia, and, often, fever. Hallucinations are typically visual. Schizophrenia typically results in auditory hallucinations and, although patients are delusional, they are not typically confused. Patients with anticholinergic poisoning typically present with confusion but also have dry mouth, dry eyes, dry skin, hypoactive bowel sounds, and urinary retention. Thyrotoxicosis patients exhibit lid lag, tremor, and gastrointestinal complaints.

3. In addition to altered mental status (AMS), which of the following is a criterion for diagnosing Wernicke encephalopathy?
   a. Alcohol intoxication
   b. Fever
   c. Oculomotor abnormalities
   d. Seizure

Answer: c. Criteria to diagnoses Wernicke encephalopathy require two of the following: (1) dietary deficiencies; (2) oculomotor abnormalities; (3) cerebellar dysfunction; and (4) AMS or mild memory impairment. Although it is most often diagnosed in alcoholics, alcohol consumption is not required. Treatment is with replacement of dietary deficiencies, particularly thiamine. Magnesium levels should be checked and treated if low. Magnesium is a cofactor for thiamine and is often depleted in chronic alcoholics.

4. Given that brief intervention and screening (SBIRT—***s***creening, ***b***rief ***i***ntervention, and ***r***eferral to ***t***reatment) can reduce alcohol consumption and is feasible and effective in the emergency department, which of the following interventions are particularly effective and preferred for college students?
   a. AA meetings
   b. In-person counseling
   c. Internet-based interventions
   d. Pharmacologic-based interventions

Answer: c. Studies show that providing internet-based interventions is more effective to reduce binge drinking among college students. The Internet could be an economic and acceptable form of delivering brief interventions and is a preferred approach to reach binge drinkers in college. AA Meetings, counseling, and pharmacologic treatment are likely to occur later in the treatment process.

5. A 28-year-old man with alcohol use disorder presents with fever, chills, and a productive cough. The x-ray reveals right lower lobe pneumonia. Which of the following is the most likely etiology of this infection?
   a. *Klebsiella pneumoniae*
   b. *Mycobacterium tuberculosis*
   c. *Mycoplasma pneumoniae*
   d. *Streptococcus pneumoniae*

Answer: d. Pneumococcal pneumonia is the most common type of pneumonia in both healthy individuals and heavy alcohol users. Other infections such as *Klebsiella pneumoniae* and Mycobacterium are also increased in patients with alcohol use disorders and cause disproportionate rates of lung infection, but not the most common. *Klebsiella pneumoniae,* classically associated with alcoholism, is currently more common in patients with cytotoxic chemotherapy, hematologic malignant disease, and transplantation than in the chronic alcoholic.

Acetaminophen

Michael Ganetsky

KEY CONCEPTS

- Acetaminophen concentration should be measured in patients with intentional oral overdoses. Acetaminophen poisoning is relatively silent clinically until serious hepatotoxicity ensues.
- Repeated supratherapeutic dosing of acetaminophen can lead to life-threatening toxicity.
- Use the acetaminophen concentration on the nomogram at 4 hours or later post-ingestion to determine whether *N*-acetylcysteine (NAC) therapy is indicated for acute ingestions.
- IV NAC is preferable to PO NAC. When initiating NAC, continue it until the protocol is completed with adequate clearance of acetaminophen, and there is no evidence of liver injury. If there is evidence of liver injury or acetaminophen concentration remains >10 μg/mL, continue NAC until acetaminophen is undetectable, clinical signs of liver injury have resolved, and liver enzymes are declining (aspartate aminotransferase [AST] <1000 IU/L).
- For maximum benefit, NAC treatment should not be delayed beyond 8 hours after ingestion. If more than 8 hours have passed since ingestion, initiate treatment with ongoing assessment of the amount of ingestion (serial serum acetaminophen levels) and development of hepatotoxicity (elevated transaminases, coagulopathy, and encephalopathy).
- Late or prolonged administration of NAC is beneficial even with low or absent acetaminophen concentrations if hepatotoxicity is evident.
- NAC is safe in pregnancy and is used in the same protocol as for the nonpregnant patient.

FOUNDATIONS

Acetaminophen (known internationally as paracetamol) is one of the most important toxins encountered in emergency care because of its ready availability, high potential lethality, and absence of symptoms in the early period after acute ingestion, during which administration of the antidote is most effective. Acetaminophen is found as an isolated product or in combination medications for the treatment of pain and febrile illness. An intravenous (IV) formulation is also available. Given its widespread availability and occult clinical presentation, acetaminophen toxicity is a concern in the vast majority of intentional ingestions, as well as with repeated supratherapeutic dosing, prescription drug misuse, and use by patients with alcohol use disorder. Acetaminophen toxicity is one of the leading causes of hospital admission, antidote use, and fatalities from oral poisonings in the United States.[1]

Protocols have been established for the assessment and management of acute and chronic acetaminophen ingestion through decades of research and experience; however, controversy continues to exist, and management of acetaminophen exposures continues to evolve.

Acetaminophen is absorbed rapidly, with peak plasma concentrations generally occurring within 1 hour and complete absorption within 4 hours. Once absorbed, acetaminophen inhibits prostaglandin E_2 (PGE_2) synthesis, leading to antipyresis and analgesia. Inhibition of PGE_2 synthesis is either by direct cyclooxygenase-2 (COX-2) inhibition or inhibition of membrane-associated prostaglandin synthase.

In therapeutic doses, 85% to 90% of acetaminophen is conjugated or sulfated into nontoxic metabolites that are excreted in the urine (Fig. 138.1).[2] A small percentage (<5%) is oxidized by cytochrome P_{450} 2E1 (CYP2E1) (and to a lesser extent 1A4 and 3A4) to a highly cytotoxic metabolic intermediary, *N*-acetyl-*p*-benzoquinone imine (NAPQI).[2] In therapeutic doses, NAPQI is short-lived, combining rapidly with glutathione and other thiol-containing compounds to form nontoxic metabolites that are excreted in the urine. With typical therapeutic acetaminophen dosing, glutathione stores and the ability to regenerate glutathione easily detoxify any NAPQI that is produced.

After large acute ingestions or repeated supratherapeutic ingestions, the amount of NAPQI produced begins to overwhelm glutathione stores and the liver's ability to regenerate glutathione, leading to unbound NAPQI. The highly reactive electrophile NAPQI covalently binds to cell proteins in the liver, which initiates a cascade of events that leads to hepatic cell death. Renal injury may also occur with or without liver injury and may be mediated by renal cytochrome P_{450} (CYP) enzymes or activation of prostaglandin synthase.

Acetaminophen-induced liver damage initially occurs in hepatic zone III (centrilobular), because oxidative metabolism is concentrated in this area. With severe toxicity, necrosis of the entire liver parenchyma may occur. The clinical effects of acetaminophen toxicity are the result of fulminant liver failure rather than a direct acetaminophen effect. These effects include multiorgan failure, systemic inflammatory response syndrome, hypotension, cerebral edema, and death. In the setting of massive ingestions, patients can present with altered mental status and metabolic acidosis. They typically have serum acetaminophen concentrations greater than 300 to 500 mg/L, and are at increased risk of developing hepatotoxicity despite early NAC administration.[3,4]

The principal therapy for acetaminophen toxicity is *N*-acetylcysteine (NAC),[5] which is effective via two separate mechanisms. Soon after overdose, NAC serves as a glutathione precursor and a sulfur-containing glutathione substitute (see Fig. 138.1) binding to, and thereby detoxifying, NAPQI. NAC may also decrease NAPQI formation by enhancing acetaminophen conjugation with sulfate to nontoxic metabolites.

Even after acetaminophen hepatotoxicity is evident, NAC acts as a free-radical scavenger and an antioxidant and alters hepatic microcirculation and oxygen delivery. In patients with acetaminophen-induced hepatic failure, IV NAC decreases the rates of cerebral edema, hypotension, and death even when no detectable acetaminophen remains in the serum.[5,6]

CLINICAL FEATURES

Adolescent and adult patients typically present after an acute, intentional ingestion of acetaminophen, either alone, or in combination with other drugs. Patients with chronic toxicity fall into two main categories: persistent supratherapeutic dosing (>4 g/day over 48 to 72 hours) or therapeutic or regular use in the presence of comorbidities that predispose to acetaminophen-induced hepatic injury. This latter group includes chronic alcohol users, patients with dehydration, malnutrition, and those taking other potentially hepatotoxic agents (e.g., isoniazid, valproic acid). Patients with chronic toxicity typically present with abdominal pain, anorexia, nausea, vomiting or new onset of jaundice. Careful questioning about acetaminophen use in patients with unexpected transaminitis is important, particularly when the cause of the abnormalities is not clear. Early after acute acetaminophen ingestion, patients are asymptomatic or have mild nonspecific symptoms (e.g., nausea, vomiting, anorexia, malaise, and diaphoresis) (Table 138.1). Liver injury becomes evident after a period of 8 to 36 hours as an elevation in aspartate transaminase (AST).[2] Once liver injury has ensued, patients may develop right upper quadrant (RUQ) pain or tenderness, vomiting, and jaundice. AST concentrations continue to rise rapidly and usually peak in 2 to 4 days, corresponding to maximal liver injury. Alanine transferase (ALT), prothrombin time (PT), and bilirubin typically begin to rise and peak several hours after AST values. With severe toxicity, AST, ALT, and PT may all be elevated within 24 hours (Fig. 138.2). With maximal liver injury, patients develop signs and symptoms consistent with fulminant liver failure, including metabolic acidosis, coagulopathy, and hepatic encephalopathy. Death may occur from hemorrhage, adult respiratory distress syndrome, sepsis, multiorgan failure, or cerebral edema. The risk of renal injury increases with the severity of hepatic injury (known as the hepatorenal syndrome), occurring in 1% to 2% of patients without hepatotoxicity and in 25% of patients with severe hepatotoxicity.

If hepatotoxic patients recover, aminotransferases return to baseline concentrations over a 5- to 7-day period (see Fig 138.2), although complete histologic resolution of liver injury may take months. Once histologic recovery is complete, there are no long-term sequelae to the liver and patients are not at risk for chronic hepatic dysfunction.

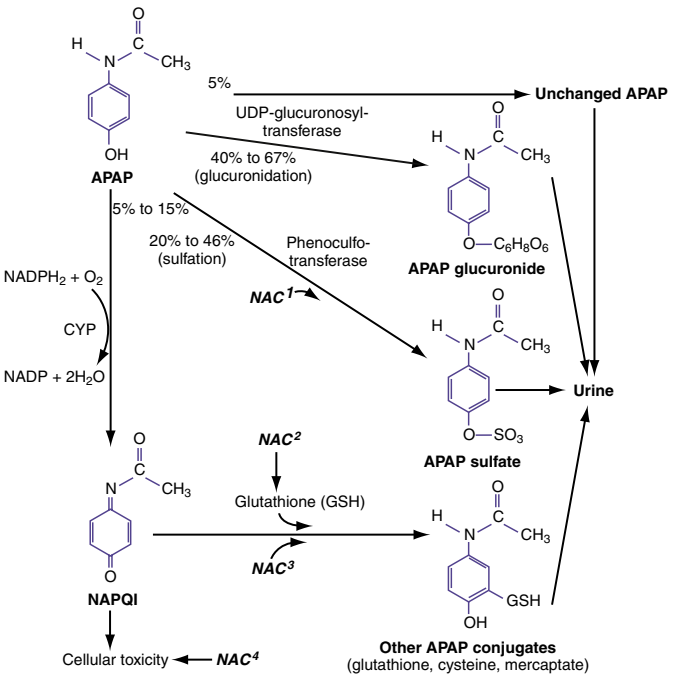

Fig. 138.1 Acetaminophen *(APAP)* metabolism and *N*-acetylcysteine *(NAC)* mechanisms of action. *NAC*[1] enhances sulfation; *NAC*[2] serves as a glutathione (GSH) precursor; *NAC*[3] is a GSH substitute; *NAC*[4] may reduce systemic toxicity. *CYP,* Cytochrome P_{450}; *NAPQI, N*-acetyl-*p*-benzoquinone imine; *UDP,* uridine 5′-diphospho. (Modified from Hendrickson RG: Acetaminophen. In Hoffman RS, et al, editors: *Goldfrank's Toxicologic Emergencies*, ed 10. New York: McGraw-Hill Education; 2015: 448.)

Differential Diagnoses

Until excluded, acetaminophen should be considered a co-ingestant in patients with intentional oral overdoses regardless of whether they state that they ingested acetaminophen. Other causes of injury in patients with elevations in aminotransferases, bilirubin, prothrombin time and international normalized ratio (PT/INR), or creatinine, include acute tubular necrosis, rhabdomyolysis, ischemic hepatitis, alcoholic hepatic disease, cyclopeptide-containing mushroom toxicity, viral hepatitis, and Wilson disease. Other hepatic toxins include valproic acid, isoniazid (INH), statins, herbal medications (such as chaparral and pennyroyal oil), vinyl chloride, and polychlorinated biphenyls.

DIAGNOSTIC TESTING

The goals of patient assessment after acetaminophen ingestion are (1) the determination of the patient's risk, (2) diagnostic testing, and (3) treatment with the antidote NAC when indicated.

We recommend serum acetaminophen testing for intentional ingestion patients, whether or not they report acetaminophen ingestion. Patients with a known acetaminophen exposure should have the following laboratory testing: serum acetaminophen concentration at four hours post-ingestion, serum salicylate concentration (since patients often confuse these over-the-counter analgesics), AST, ALT, bilirubin, PT/INR, bicarbonate (screening for metabolic acidosis), and creatinine (to assess renal function). If a patient has signs of liver injury (elevated

TABLE 138.1 Time Course and Clinical Stages of Acetaminophen Toxicity

Stage	Time Course	Name	Symptoms	Signs
1	0 to 12 (up to 24 to 36) hours	Preinjury	Nausea, vomiting, anorexia, malaise	Elevated serum acetaminophen concentration
2	8 to 36 hours	Liver injury	Nausea, vomiting, RUQ abdominal tenderness	Aminotransferase elevation (AST begins to rise 8 to 36 hours after ingestion)
3	2 to 4 days	Maximum liver injury	Liver failure (encephalopathy, coagulopathy, hemorrhage, acidosis)	Hemorrhage, ARDS, sepsis/SIRS, multiorgan failure, cerebral edema
4	>4 days	Recovery	None	Complete hepatic histologic recovery

ARDS, Acute respiratory distress syndrome; *AST,* aspartate transaminase; *RUQ,* right upper quadrant; *SIRS,* systemic inflammatory response syndrome.

AST or ALT), a venous blood gas and serum lactate should be measured. Acetaminophen exposures may be classified as acute or chronic, and each type requires different testing and risk assessment. An acute ingestion is defined as a single ingestion or a series of ingestions within an 8-hour period. All other ingestions, including accidental repeated supratherapeutic ingestions and intentional ingestions spread over longer than 8 hours, are considered to be chronic.

Risk Assessment With Acute Acetaminophen Ingestion

The initial diagnostic strategy of an acute ingestion is well-established. The first step is to determine the patient's risk of developing acute liver injury. Patients who report an acute intentional ingestion of acetaminophen should have laboratory risk stratification regardless of the reported amount ingested, because history alone is not reliable. In an otherwise healthy adult patient, ingestions of less than 10 grams in total or 150 mg/kg (approximately thirty 325 mg [regular strength] or twenty 500 mg [extra strength] tablets for an 70 kg adult) in an acute ingestion will not cause significant liver toxicity. A serum acetaminophen concentration should be checked in all intentional overdose patients, regardless of whether they report taking it, unless it is certain that the patient could not have had access to acetaminophen. Acetaminophen has been detected in the serum of up to 8% to 10% of patients with intentional ingestions who deny acetaminophen ingestion. Also, there is a high prevalence of unrecognized acetaminophen toxicity among subjects presenting with indeterminate acute liver failure.

Once an acute acetaminophen overdose is identified, establish the time of ingestion as accurately as possible using all available information. If no accurate time of ingestion can be determined, it is best to assume the earliest possible time of ingestion or to begin NAC therapy empirically if the time of ingestion is indeterminate.

A serum acetaminophen concentration 4 hours post-ingestion, or as soon as possible after 4 hours, determines the need for antidotal therapy by plotting the serum acetaminophen concentration against the time since ingestion on the treatment nomogram (Fig. 138.3). A serum acetaminophen concentration above the treatment line (that starts at 150 μg/mL at 4 hours and decreases to 4.7 μg/mL at 24 hours), indicates need for treatment with NAC. If the serum acetaminophen concentration is below the treatment line and the highest risk scenario has been assumed for the time of ingestion, then the patient requires no antidotal therapy. Use of the treatment line is indicated for otherwise healthy patients presenting after single acute ingestions. Alternative approaches in patients with alcohol use disorder, patients with co-ingestions of antimuscarinic agents, patients with unknown ingestion times, and after IV formulations have been suggested, but these are not supported by trial data.[2] In a patient with an antimuscarinic (i.e., diphenhydramine) co-ingestion who has an elevated serum acetaminophen concentration at 4 hours that does not meet criteria for treatment, we recommend rechecking an acetaminophen concentration at 8 hours to ensure that appropriate clearance has occurred with no delayed absorption.

Measurement of serum acetaminophen concentration prior to 4 hours post-ingestion is not indicated. There is insufficient evidence to support claims that a serum acetaminophen concentration of less than 10 μg/mL between 1 and 4 hours excludes significant ingestion of acetaminophen. Absorption of acetaminophen may not be complete prior to 4 hours, and serum acetaminophen concentrations measured prior to 4 hours cannot be plotted on the treatment nomogram. There is no known benefit to administering NAC before the recommended 4 to 8-hour window after ingestion. Patients treated with NAC within 8 hours after ingestion, even after very large overdoses, have no increased risk of hepatotoxicity regardless of their serum acetaminophen concentration. For patients who have developed hepatotoxicity at presentation, those with preexisting liver disease, or those in whom a serum acetaminophen concentration cannot be obtained prior to 8 hours after ingestion, a loading dose of NAC is recommended along with consultation with a medical toxicologist or poison center. (See Box 138.1 listing indications for a medical toxicology consultation)

Risk Assessment With Chronic Ingestion

With repeated or chronic exposure, risk assessment is more complex, and the treatment nomogram cannot be used. Determination of the need for NAC is based on assessment of the risk for hepatotoxicity and measurement of serum concentrations of acetaminophen and AST.

The risk of hepatotoxicity from chronic ingestion of acetaminophen increases with total dose of acetaminophen and the duration over which it has been ingested in supratherapeutic quantities. Laboratory testing for serum acetaminophen concentration and AST should be initiated in any patient who fits the criteria outlined in Table 138.2.

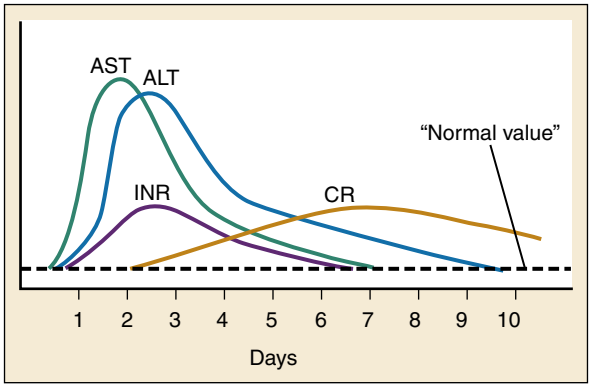

Fig. 138.2 A typical time course of rise, peak, and fall of laboratory values in patients with acetaminophen-induced hepatic dysfunction who survive. Peaks are not proportional. Not all laboratory abnormalities occur in all patients, and significant individual variation may occur. *ALT,* Alanine transaminase; *AST,* aspartate transaminase; *CR,* creatinine; *INR,* international normalized ratio. (Copyright Robert G. Hendrickson, MD.)

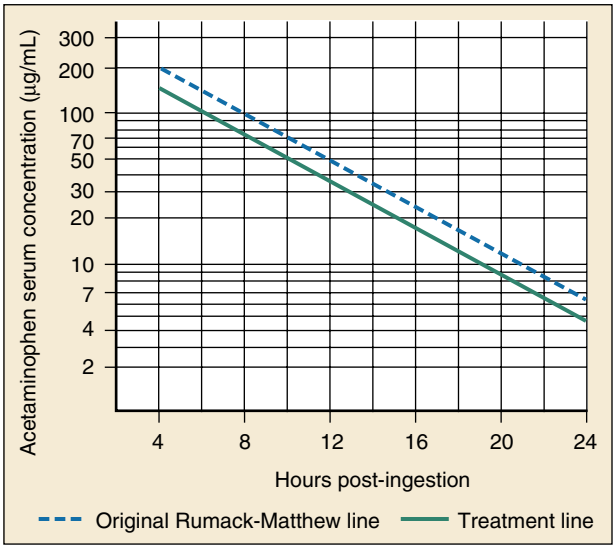

Fig. 138.3 Treatment nomogram for acute overdose. The lower treatment line should be used for treatment decisions. (Modified from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. *Pediatrics.* 1975;55:871.)

BOX 138.1 Indications for Medical Toxicology Consultation for Acetaminophen Toxicity

- Patients who have developed hepatotoxicity at presentation
- Patients with preexisting liver disease
- Patients in whom a serum acetaminophen concentration cannot be obtained prior to 8 hours after ingestion
- Patients with hepatotoxicity following a chronic acetaminophen ingestion where an acetaminophen concentration cannot be plotted on the treatment nomogram.
- Patients with massive ingestions (serum acetaminophen concentrations >900 mcg/mL)
- Patients with metabolic acidosis, hepatorenal syndrome, or hepatic encephalopathy

TABLE 138.2 Indications for Initiating Testing for Serum Acetaminophen Concentration and Aspartate Transaminase in Chronic Acetaminophen Ingestions

Age ≥6 years old;	Ingestion of >10 g/d (or >200 mg/kg/d) (whichever is smaller) over a 24-hour period
or	Ingestion of >6 g/d (or >150 mg/kg/d) (whichever is smaller) over a 48-hour period or longer
or	Symptomatic (e.g., RUQ pain/tenderness, jaundice, vomiting)
Children <6 years old;	Ingestion of >200 mg/kg/d over a 24-hour period
or	Ingestion of >150 mg/kg/d over a 48-hour period
or	Ingestion of >100 mg/kg/d over a 72-hour or longer period
or	Symptomatic (eg, RUQ pain/tenderness, jaundice, vomiting)

AST, Aspartate transaminase; *RUQ,* right upper quadrant.

Ingestion of therapeutic amounts of acetaminophen appears to be quite safe, although subclinical transaminitis can occur. Studies of patients presenting after taking 4 grams per day have shown ALT elevation of greater than 3 times the upper limit of normal in up to one-third of patients at one week, although no subject had clinical side effects, and all recovered without antidotal treatment. The implication of these findings is unclear but could be helpful to explain certain clinical scenarios. Some patients may be at increased risk for liver injury, possibly due to genetic variation or to specific risk factors. For example, patients who chronically ingest INH or ethanol may have increased CYP2E1 activity and may be at higher risk for chronic acetaminophen toxicity. Similarly, patients who are malnourished or have severe dehydration may be at higher risk for hepatotoxicity. Patients who ingest the liquid acetaminophen formulation may have lower risk of hepatotoxicity because the common diluent, propylene glycol, is a CYP2E1 inhibitor.[7]

Once serum acetaminophen concentration and AST are obtained, further risk assessment is necessary. Patients with chronic ingestions (e.g., >4 grams/day over a period of 48 to 72 hours) may benefit from antidotal therapy if they have evidence of liver injury (AST >2 times normal, or 120 IU/L) *or* if they have evidence of acetaminophen excess (serum acetaminophen concentration >30 mcg/mL) with a prolonged half-life that may lead to liver injury. After a typical therapeutic dose of acetaminophen, serum acetaminophen concentration peaks at less than 30 µg/mL and declines to less than 10 µg/mL at 4 hours. In patients who are asymptomatic, who have a minimal AST elevation, who do not report an intentional ingestion, we recommend a recheck of serum aminotransferases after 4 hours. If there is not a sharp increase as would be expected to occur with acetaminophen acute liver injury, NAC therapy is not indicated.

Risk Assessment in Pregnant Women

The risk assessment and diagnostic approach to pregnant women is the same as for nonpregnant women. In acute overdoses, a serum acetaminophen concentration should be drawn and plotted on the treatment nomogram. NAC therapy should be initiated if the serum acetaminophen concentration plots above the treatment line. With chronic exposure, the same criteria strategy as outlined earlier should be instituted.

MANAGEMENT

Stabilization and Supportive Care

The mainstay of management is antidotal therapy with NAC, complemented by supportive measures. Supportive care includes management of co-ingestions, nausea and vomiting, hepatic injury, and renal dysfunction related to acetaminophen poisoning. Treatment of these problems is based on general treatment principles and is not acetaminophen-dependent (see Chapters 76 and 83). When questions exist regarding initiation of NAC or there are confounding clinical issues present (e.g., preexisting liver disease), clinicians may consult with a regional poison center (1-800-222-1222 in the United States) or a medical toxicologist for advice.

Decontamination

Activated charcoal (AC) effectively binds acetaminophen in vitro, and some studies have suggested that early administration of AC (within 1 to 2 hours post-ingestion) may decrease the number of patients that require antidotal therapy. In massive ingestions (≥40 grams), AC was shown to decrease acetaminophen concentrations and rate of hepatotoxicity up to 4 hours after ingestion.[3] However, many patients have co-ingestions that may depress mental status, and patients with severe acetaminophen poisoning often develop vomiting and are not able to tolerate AC. Given the lack of demonstrated efficacy in terms of improved outcomes from single-dose AC and the existence and availability of a very effective antidote, we do not recommend the routine use of AC for acetaminophen overdose, except in circumstances where the patient is asymptomatic and AC administration may prevent need for NAC, such as pediatric accidental ingestions.

Enhanced Elimination

Hemodialysis is not routinely used for acetaminophen overdose, because there is a highly effective antidote with good clinical outcomes when given within 8 hours of ingestion. However, acetaminophen is removed by hemodialysis, which may be helpful when the absorbed acetaminophen burden is sufficient to cause hepatotoxicity despite standard doses of NAC.[4] We recommend consultation with a poison center or medical toxicologist and nephrologist for initiation of hemodialysis for patients presenting following an acute massive ingestion with the characteristics outlined in Box 138.2. These are based on consensus guidelines from the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup.[8]

Antidote Therapy

N-Acetylcysteine

NAC should be administered as early as possible when the acetaminophen concentration obtained at or after 4 hours post-ingestion is determined to be above the treatment line. NAC is also indicated when the liver function tests are noted to be elevated in a chronic

BOX 138.2 Indications for Emergent Hemodialysis Following Acute Acetaminophen Ingestion

- If the serum acetaminophen concentration >1000 mcg/mL and NAC is NOT administered
- If the patient presents with altered mental status, metabolic acidosis, an elevated lactate, and a serum acetaminophen concentration >700 mcg/mL and NAC is NOT administered
- If the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and a serum acetaminophen concentration >900 mcg/mL even if NAC is administered[a]

[a] NAC therapy should be continued during hemodialysis.

supratherapeutic ingestion. NAC is highly efficacious at preventing hepatotoxicity when administered at any time within 8 hours after an acute ingestion; delaying more than 8 hours after ingestion increases the risk of hepatotoxicity (Fig. 138.4).

NAC can be administered by mouth (PO) or IV. Both methods are efficacious in most situations, with advantages in favor of IV administration. All formulations of NAC (PO or IV) are effective when started within 8 hours of ingestion, with reductions in effectiveness when started between 8 and 24 hours post-ingestion. The risk of liver injury (i.e., AST >1000 IU/L) in patients treated with NAC within 8 hours is less than 1% and the mortality rate approaches zero (see Fig. 138.4).[9]

Once liver failure is evident (e.g., acidosis, coagulopathy, encephalopathy) NAC is given intravenously. IV NAC decreases the risk of hypotension, cerebral edema, and death in patients with acetaminophen-related hepatic failure. Oral NAC should only be used if IV NAC is not available. Even when there is no acetaminophen detectable in the serum, if a patient has AST greater than 1000 IU/L and there is a history or suspicion for acetaminophen ingestion or exposure, NAC should be started because there is evidence it decreases the need for liver transplantation and overall mortality.[6] There is an acetaminophen protein adducts assay in development that can discriminate liver injury due to acetaminophen and in the future may help to determine when NAC is indicated in the setting of liver failure with no detectable acetaminophen concentration in the serum.[10]

The main differences between IV and PO NAC are in their side effect profiles (Table 138.3). Approximately 5% of patients treated with IV NAC develop significant anaphylactoid reactions, although rates of up to 30% have been reported in prospective trials. The majority of these reactions are mild and self-limited consisting of sneezing, transient skin rashes, and flushing. More severe reactions have been reported in less than 1% of patients and include angioedema, bronchospasm, hypotension, and rarely death. Symptoms occur within 30 minutes of the start of the loading infusion. These anaphylactoid reactions are dose, rate, and peak NAC concentration dependent.[9]

Anaphylactoid reactions are less frequent with PO NAC. Skin rash, serious systemic reactions, and anaphylactic reactions are rarely reported with the PO formulation. However, approximately 15% of patients receiving PO NAC vomit (versus 7% with IV NAC), delaying timely antidote delivery. PO NAC is extremely unpalatable largely due to a sulfur or "rotten egg" odor and taste. Palatability may be improved by administering NAC diluted with either soda or juice and serving it in a covered container through a straw. Any dose that is vomited within 1 hour of administration should be repeated. If vomiting occurs, an antiemetic such as ondansetron can be trialed, but antiemetics administered prophylactically are not indicated.

Anaphylactoid reactions to IV NAC are typically mild (e.g., flushing) and occur during the initial loading infusion. Mild reactions can be managed with parenteral diphenhydramine, 25 mg IV, without stopping the infusion. If hypotension develops, we recommend slowing or pausing the infusion, giving a 500 mL fluid crystalloid bolus, and administering diphenhydramine, 25 mg IV, and restarting the NAC infusion at a slower rate. For reactions persisting despite these steps, administer methylprednisolone 80 mg IV and treat as indicated for severe allergic reaction. Epinephrine is rarely required. These reactions require observation and treatment, but do not preclude subsequent doses, and treatment with diphenhydramine should be continued.[11]

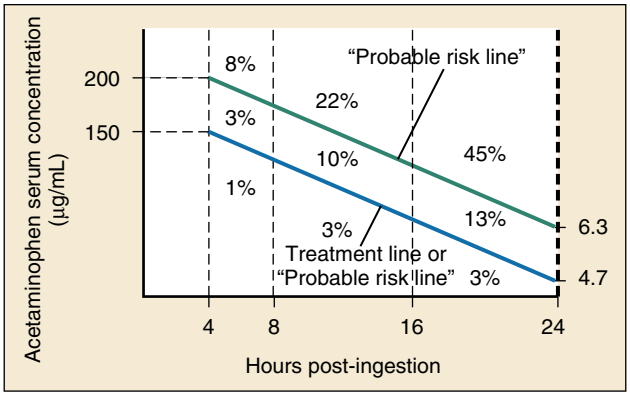

Fig. 138.4 Risk of liver injury (alanine transaminase >1000 IU) based on initial acetaminophen concentration and time to administration of oral *N*-acetylcysteine (NAC). (Adapted from Rumack BH: Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol.* 2002;40:3.)

TABLE 138.3 Side Effect Profile for *N*-Acetylcysteine Formulations

N-Acetylcysteine Formulation	Common Side Effects	Severe Side Effects
PO NAC	Vomiting (13%), inability to tolerate due to smell	Very rare
IV NAC	Mild anaphylactoid reactions (e.g., rash, flushing, pruritus, vomiting), 2% to 18%	Severe anaphylactoid reactions (e.g., hypotension, bronchospasm), <1%

IV, Intravenous; *NAC, N*-acetylcysteine; *PO, per os* (by mouth).

Use in Pregnancy

Acetaminophen crosses the placenta, but the fetus in the first trimester of development is only at risk for injury if the mother suffers hepatotoxicity because fetal CYP enzymes have not fully developed. If the fetus is near-term (third trimester of development), there is a risk for direct fetal and neonatal hepatotoxicity, because the liver is more developed at this stage. Treating the mother with NAC is safe and effective, and NAC effectively crosses the placenta. NAC is used with the same protocols as for the nonpregnant patient. We recommend IV NAC when treating a pregnant patient. IV administration circumvents first-pass metabolism, therefore likely delivering higher doses to the fetus via higher maternal serum concentrations.

Duration of Therapy

There are two well-established protocols for NAC administration in cases of acute acetaminophen toxicity, depending on the route of administration: a 21-hour IV protocol and a 72-hour PO protocol. The standard IV NAC protocol in adults is a loading dose of 150 mg/kg up to a maximum of 15 gm in 200 mL of dextrose 5% in water (D5W)

TABLE 138.4 Inpatient Predictors of the Severity of Illness in Patients With Acetaminophen Toxicity

Score	Predictive Variables	Outcome Predicted	Notes
Kings College Criteria	pH <7.3 *or All three:* • Cr >3.3 *and* • INR >5 (or PTT >100s) *and* • Encephalopathy more than grade III (patient comatose)	Death or transplant	Arterial pH is measured *after* fluid resuscitation. The presence of any one of the Cr, INR, encephalopathy variables alone has a lower specificity for transplant than all 3 combined, but still has significant sensitivity to prompt consideration of transfer to transplantation center.
APACHE II	APACHE II score >20	Death or transplant	Confounders include co-ingested medications that may alter the APACHE II score.
Lactate	Lactate >3.5 mmol/L prior to resuscitation	Death or transplant	Lactate was drawn a mean of 55 hours after ingestion. The predictive ability of an early lactate draw is unknown.

APACHE II, Acute Physiology and Chronic Health Evaluation II; *Cr,* creatinine; *INR,* international normalized ratio; *PTT,* partial thromboplastin time.

infused over 60 minutes followed by a first maintenance dose of 50 mg/kg (up to a maximum of 5 gm) in 500 mL D5W infused over 4 hours. This is followed by a second maintenance dose of 100 mg/kg (up to a maximum of 10 gm) in 1000 mL D5W infused over 16 hours (6.25 mg/kg/hour).

Oral NAC is given as a 140 mg/kg loading dose, either by mouth or by enteral tube. Starting 4 hours after the loading dose, 70 mg/kg is given every 4 hours for an additional 17 doses (total treatment duration of 72 hours).

Several other regimens, including 48 hours IV, 36 hours IV, 36 hours PO, and 20 hours PO protocols are described; however, none of these are generally accepted as standard of care.[9] Recently, a "two-bag" protocol has been developed as an alternative to the 21-hour IV NAC protocol: 200 mg/kg NAC (in 500 ml D5W or 0.9% saline) over 4 hours followed by 100 mg/kg NAC (in 1 L D5W or 0.9% saline) over 16 hours. This protocol has demonstrated fewer adverse reactions and fewer medication errors with similar efficacy as the 21-hour protocol and is now being used in many centers.[12-14] Until further clinical trials are conducted to prove the clinical efficacy of these alternative dosing regimens, we recommend using the traditional 21-hour IV protocol.

Patients with very large acetaminophen ingestions may develop hepatotoxicity despite early and appropriate NAC dosing, and we recommend early consultation with a medical toxicologist in such cases (see Box 138.1.) We also advise consultation with a nephrologist or transfer to a capable center for possible hemodialysis for patients with the characteristics outlined in Box 138.2. Patients with hepatic failure and persistently elevated serum acetaminophen concentrations that do not decrease as expected are also at risk of failing NAC therapy. There have been various recommendations to increase NAC dosing based on very elevated 4-hour concentrations, but none are universally accepted. One recommendation is to increase the NAC rate to 12.5 mg/kg/hr (200 mg/kg NAC in 1 L over 16 hours) when the concentration is greater than the 300 µg/mL at 4 hour treatment line.[15] We do not recommend routinely using this dosing regimen until further clinical trials are conducted proving its clinical efficacy or unless recommended in consultation with a medical toxicologist..

For delayed, chronic, or supratherapeutic dosing toxicity, NAC therapy should continue until acetaminophen is undetectable in the serum (<10 mcg/mL) and signs of liver injury have resolved (i.e., no encephalopathy, improvement of the coagulation profile with INR <2.0, resolution of metabolic acidosis, and AST less than 1000 IU/L with a downward trend).

DISPOSITION

Asymptomatic patients who meet criteria for treatment should be treated with NAC, which is started in the ED and continued in a medical inpatient unit or an ED observation unit. The motivation behind any ingestion needs to be evaluated, and psychiatric consultation obtained when appropriate.

Patients showing evidence of hepatotoxicity and those at risk for fulminant hepatic failure may require admission to a monitored bed or an ED or inpatient intensive care unit. These patients require frequent neurologic checks, monitoring of vital signs, and repeated laboratory studies.

Need for Transplantation

The King's College Criteria are the most commonly accepted decision rule for determining risk for needing liver transplantation.[16] Clinical rules for identifying patients at risk for developing fulminant hepatic failure are listed in Table 138.4, and patients meeting these criteria should be transferred to a tertiary care center that specializes in the management of patients with hepatic failure with potential need for liver transplant.

We would like to acknowledge the scholarly contributions of the previous edition authors, Robert G. Hendrickson and Nathanael J. McKeown

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 138: QUESTIONS AND ANSWERS

1. Which of the following is true regarding pregnant patients with an acute acetaminophen ingestion?

- **a.** All pregnant women should be treated with *N*-acetylcysteine (NAC) after any known ingestion of acetaminophen.
- **b.** Pregnant women in the third trimester should be treated with NAC if their acetaminophen concentration is ever elevated above 50 μg/mL.
- **c.** Pregnant women should be treated with NAC if their acetaminophen concentration is above the treatment line on the nomogram.
- **d.** Pregnant women should be treated with NAC if they ingest >75 mg/kg PO acetaminophen over less than 8 hours.
- **e.** The treatment line on the nomogram is lowered to a line starting at 100 μg/mL at 4 hours after ingestion.

Answer: C. Pregnant patients with an acute ingestion of acetaminophen should have the same initial treatment as nonpregnant patients. After measurement of an acetaminophen concentration, plotting of the acetaminophen concentration on the nomogram treatment with NAC should be given if the concentration is above the treatment line on the nomogram. Both acetaminophen and NAC do cross the placenta, but the fetus is at risk only if the mother becomes ill. Patients with first trimester pregnancies are at risk of miscarriage if the mother becomes ill, and fetuses that are near-term may be at risk for fetal/neonatal hepatotoxicity.

2. A 30-year-old woman presents with drowsiness, nausea, and vomiting. She reports taking several pills in a suicide attempt. Despite your best efforts, she cannot describe what she ingested or how many she ingested. She states she took the pills "last night" and refuses to be more specific. Currently, it is 6 a.m. A family member is present and found the patient vomiting at 4 a.m., at which time she informed the family member she took some pills. The family member further states that the patient was in an argument with a friend at 12 p.m. and may or may not have ingested the pills at that time. The family was with the patient at 8 p.m. and is sure that she had not ingested the pills at that time. What time should be used as the time of ingestion?

- **a.** 2 a.m.—the time that is 4 hours prior to presentation
- **b.** 4 a.m.—the time the patient was found abnormal
- **c.** 6 a.m.—the time of presentation
- **d.** 8 p.m.—the time the patient was last seen and known to be prior to the ingestion
- **e.** 12 p.m.—the time the patient was last seen prior to becoming symptomatic

Answer: D. If the exact time of ingestion cannot be determined, then the "worst case" scenario should be assumed. The longer a patient goes without therapy, the worse the outcome. Therefore, the time of ingestion should be assumed to be the last time the patient was seen normal prior to any possible ingestion.

3. A 20-year-old man is brought to the emergency department by family with a complaint of "overdose." The patient is drowsy but arousable. His vital signs are normal. His physical examination is normal except for appearing to be intoxicated. He has no complaints. The family reports the ingestion of unknown "pills" as well as alcohol and possibly "street drugs." The ingestion occurred approximately 6 hours ago after an argument. Routine supportive care is initiated. What test must be ordered on this patient because it may affect the immediate treatment plan?

- **a.** Acetaminophen concentration
- **b.** Chest radiograph
- **c.** Head computed tomography (CT) scan
- **d.** Serum alcohol concentration
- **e.** Urine drug screen

Answer: A. The antidote should be given within 8 hours of ingestion to prevent development of hepatotoxicity.

CHAPTER 138: QUESTIONS AND ANSWERS—cont'd

4. What is the typical peak serum acetaminophen concentration after a therapeutic oral ingestion?
   - **a.** Undetectable
   - **b.** 10 μg/mL
   - **c.** 30 μg/mL
   - **d.** 50 μg/mL
   - **e.** 100 μg/mL

Answer: C. This concentration is typically reached approximately 1 hour after ingestion. Four hours after a therapeutic ingestion, the concentration is typically less than 10 μg/mL. Concentrations higher than this should lead one to consider the possibility of chronic ingestion or a person who does not properly metabolize acetaminophen.

5. Two 20-year-old patients present to the emergency department 1 hour after ingesting 15 grams of acetaminophen each in a suicide pact. You are confident of the time of ingestion and that time is confirmed by text messages sent by the patients. Patient A has a 4-hour acetaminophen concentration of 130 mg/dL. Patient B's 4-hour acetaminophen concentration is 170 mg/dL. What is the appropriate treatment for both patients?
   - **a.** Neither patient requires treatment because the acetaminophen concentrations are below the treatment cutoff.
   - **b.** Neither patient requires treatment because they received activated charcoal (AC).
   - **c.** Patient A should receive immediate *N*-acetylcysteine (NAC); patient B should *not* receive NAC.
   - **d.** Patient A should *not* receive NAC; patient B should receive immediate NAC treatment.
   - **e.** Both patients should receive immediate NAC therapy.

Answer: D. In this case, your confidence of the time of ingestion is high. The treatment line crosses 150 mg/dL at 4 hours. Therefore, if the 4-hour acetaminophen concentration is >150 mg/dL, treatment is indicated. In the case above, patient A does not require NAC therapy, but patient B does require treatment with NAC.

6. What is the antidote for acetaminophen ingestion?
   - **a.** Dimercaprol
   - **b.** Hydroxycobalamin
   - **c.** *N*-acetylcysteine (NAC)
   - **d.** *N*-acetyl-*p*-benzoquinone imine (NAPQI)
   - **e.** Succimer

Answer: C. Hydroxycobalamin is an antidote for cyanide; succimer is an antidote for lead; and dimercaprol is an antidote for arsenic, lead, and mercury. NAPQI is the toxic metabolite of acetaminophen.

7. A 42-year-old man presents to the emergency department with complaints of nausea and vomiting. He has no other complaints. His symptoms started approximately 12 hours ago. His history is significant for "back pain," which has been worse than normal recently. He states that he finished a bottle of 60 "pain pills" during the past 2 days. His vital signs are normal. Other than right upper abdominal tenderness, his physical examination is normal. Routine laboratory tests including complete blood count, chemistry, and liver panel are normal except an aspartate transaminase (AST) concentration of 1265 IU/L. You are concerned for possible repeated supratherapeutic acetaminophen poisoning. What should you do next?
   - **a.** Admit the patient for observation and repeat AST testing; because this is a repeated supratherapeutic ingestion, treatment with *N*-acetylcysteine (NAC) is not beneficial.
   - **b.** Initiate treatment with activated charcoal (AC) now.
   - **c.** Initiate treatment with NAC now.
   - **d.** Obtain two serum acetaminophen concentrations 1 hour apart to determine the drug's elimination half-life to decide if treatment with NAC is indicated.
   - **e.** Plot the acetaminophen concentration on the acetaminophen treatment nomogram to determine if treatment with NAC is indicated.

Answer: C. Many prescription and nonprescription analgesics contain acetaminophen, so although a patient may deny use of acetaminophen, suspicion should remain high. A patient with chronic acetaminophen ingestion should have an AST and acetaminophen concentration checked. If the AST is significantly elevated, treatment with NAC should be initiated. Many patients with repeated supratherapeutic ingestion will not have a markedly increased acetaminophen concentration, and the treatment nomogram is not used with repeated supratherapeutic dosing. Regardless of how long ago the ingestion occurred, if a patient displays signs or symptoms of liver damage, NAC should be given because it will still have beneficial effects.

8. A 55-year-old man has taken 10 grams of acetaminophen per day over the last 8 days for a toothache. He arrives to the emergency department with severe right upper quadrant (RUQ) pain, jaundice, and hypoglycemia. His aminotransferases, bilirubin, and acetaminophen concentration are highly elevated, and he is resuscitated and started on intravenous (IV) *N*-acetylcysteine (NAC). Which of the following laboratory findings is a very poor prognostic indicator and indicates that he is a candidate for immediate liver transplant?
   - **a.** Aspartate transaminase (AST) >10,000 IU/L
   - **b.** Bilirubin >5 mg/dL
   - **c.** Lactate >5 mmol/L
   - **d.** Acetaminophen concentration >150mg/dL
   - **e.** pH <7.4

Answer: C. The patient has severe liver failure due to repeated supratherapeutic dosing of acetaminophen. Prognostic variables that are used to determine immediate hepatic transplant are the Kings College Criteria (a pH <7.3[or lactate >3.5 mmol/L] after resuscitation *or* the combination of Cr >3.3 and PTT >100s [or INR >5] and grade 3 or 4 encephalopathy). Other criteria that indicate high mortality are the APACHE II score >20. If a patient in the emergency department meets these criteria, transfer to a center with liver transplant capabilities is indicated.

9. A 27-year-old woman is brought to the emergency department by emergency medical service (EMS). The patient is lethargic and cannot provide a history. A suicide note indicates that she ingested 50 g of acetaminophen approximately 24 hours ago. The patient is noted to be jaundiced with right upper quadrant (RUQ) tenderness. General supportive care is initiated. Her aspartate transaminase (AST) is 1072 IU. A serum acetaminophen concentration is pending. Which of the following statements is true regarding treatment with *N*-acetylcysteine (NAC)?
   - **a.** Treatment with NAC should be delayed until the acetaminophen concentration is obtained.
   - **b.** Treatment with NAC should be initiated because an ingestion of 50 g of acetaminophen is potentially fatal.
   - **c.** Treatment with NAC should be initiated because the patient has liver injury secondary to acetaminophen poisoning.
   - **d.** Treatment with NAC will not alter the outcome; this patient will require a liver transplant.
   - **e.** Treatment with NAC will not be beneficial because the ingestion occurred more than 10 hours ago.

CHAPTER 138: QUESTIONS AND ANSWERS—cont'd

Answer: C. Ideally, NAC treatment is initiated within 8 hours of ingestion, but treatment with NAC is still beneficial even after hepatotoxicity has developed. An acetaminophen concentration should be obtained, but there is no reason to delay treatment. Ingestion of 50 g is potentially toxic, but decisions should be based on the patient's current condition. Occasionally, hepatotoxicity from acetaminophen is severe and liver transplant is required, but most cases of hepatotoxicity resolve with NAC treatment.

Aspirin and Nonsteroidal Agents

Benjamin W. Hatten

KEY CONCEPTS

- In the overdose setting, salicylates are profoundly toxic and can be fatal. Salicylate overdose requires vigilant assessment and treatment. The other nonsteroidal antiinflammatory drugs (NSAIDs) generally have self-limited toxicity and respond to supportive measures. There is no specific antidote for any of these drugs.
- Salicylism should be considered in the differential diagnosis of altered mental status, particularly in the elderly.
- Acidemia signifies loss of respiratory compensation and acceleration of toxicity.
- The Done nomogram is no longer used and is not recommended in the evaluation and treatment of salicylate toxicity.
- Salicylate concentrations and blood gas draws should occur every 2 hours until the serum salicylate level is less than 30 mg/dL and is steadily declining at least 10% between assays in the absence of measures to enhance elimination.
- Potassium stores are rapidly depleted in patients with salicylate intoxication and should be repleted with a goal serum level of 4.5 to 5.0 mEq/L (4.5–5.0 mmol/L).
- When possible, mechanical ventilation should be avoided in cases of severe salicylate poisoning. Acidosis may rapidly worsen due to loss of adequate ventilation during the intubation procedure, and it is difficult to maintain ventilation at the level of physiologic hyperventilation.
- If intubation is necessary, a bolus of sodium bicarbonate (50 to 100 mEq) should be given before intubation and post-intubation; minute ventilation should be increased to match pre-intubation respiratory compensation.
- Enhanced elimination through urinary alkalinization with an intravenous sodium bicarbonate drip should be initiated in acute toxicity with a serum level >30 mg/dL.
- Consultation with nephrology and preparation for emergent hemodialysis should occur if the salicylate concentration is above 80 mg/dL or is rising rapidly.
- Hemodialysis is recommended for signs of pulmonary or cerebral edema, coma, seizures, hepatic failure, renal failure, circulatory collapse, or refractory metabolic acidosis along with acute serum levels greater than 100 mg/dL and chronic levels over 40 mg/dL.
- Altered mental status in the setting of salicylate toxicity warrants IV dextrose supplementation.
- Most NSAID overdoses are asymptomatic or cause only minor gastrointestinal symptoms.
- Ibuprofen, along with other propionic acid derivatives, has been associated with sporadic cases of aseptic meningitis.
- The management of NSAID overdose is supportive, and there is no specific antidote. Hemodialysis is reserved for patients with massive overdose (>400–500 mg/kg) and pH <7.1.
- Patients who have ingested a pyrazolone or fenamate require observation for possible seizures for 8 to 12 hours following ingestion.

ASPIRIN

Principles of Toxicity

Overview

Aspirin, or acetylsalicylic acid, is widely consumed for its analgesic, antiinflammatory, and antiplatelet effects. Although its therapeutic use is ubiquitous, salicylate toxicity is not a benign condition and causes a complex set of life-threatening metabolic derangements with significant morbidity and mortality.

Epidemiology

In 2017, twenty-three deaths were reported to United States Poison Control Centers due to aspirin alone.[1] This is consistent with reports to Poison Control Centers of twenty to thirty deaths per year for the past decades. One analysis identified salicylate toxicity as the most common preventable death due to poisoning that reached medical attention, suggesting an opportunity to impact mortality through proper management.[2] Elderly patients with chronic medical problems and young patients diagnosed with an acute illness are particularly at risk for delay in diagnosis with consequent severe adverse clinical effects.[3] In addition, increasing age has been identified as an independent predictor of severe outcomes and has been associated with lower peak levels in fatal cases.[4,5]

Salicylate-Containing Products

Aspirin is the most common salicylate-containing product. Other potential sources of salicylate toxicity include topical salicylates, analgesic balms, oil of wintergreen, willow bark, Alka Seltzer®, and bismuth subsalicylate. Ingestion of oil of wintergreen is of particular concern given that 1 mL of 98% solution contains the equivalent of 1.4 grams of aspirin.[6]

Pathophysiology

Salts of salicylic acid are rapidly absorbed intact from the gastrointestinal (GI) tract with appreciable serum concentrations typically occurring within 30 minutes after ingestion of a therapeutic dose with peak levels delayed from 2 to 4 hours. Large ingestions frequently slow gastric emptying. Aspirin, particularly enteric-coated preparations, tends to form concretions or bezoars in the stomach. These properties often result in prolonged absorption with rising serum levels for 12 hours or more.[3]

In the intestinal wall, liver, and red blood cells, aspirin is hydrolyzed to free salicylic acid, which reversibly binds to albumin. Free salicylate is eliminated by renal excretion. At therapeutic salicylate concentrations, elimination follows first-order kinetics. Once serum salicylate concentrations are greater than 30 mg/dL, elimination follows zero-order kinetics. The metabolic pathways become saturated,

BOX 139.1 Acid-Base Disturbance and Progression of Toxicity in Acute Salicylate Overdose

Early (0 to 4 hours; level 20 to 60 mg/dL): Respiratory alkalosis with alkalemia; gastrointestinal (GI) distress, mild to moderate hyperpnea, tinnitus, lethargy

Moderate (2 to 12 hours; level 50 to 90 mg/dL): Respiratory alkalosis and metabolic acidosis with alkalemia or neutral pH; severe hyperpnea, lethargy or agitation, hyperthermia

Severe (6 to 24 hours: level >80 mg/dL): Respiratory alkalosis or acidosis and metabolic acidosis with acidemia; severe hyperpnea, coma or acute delirium, hyperthermia, pulmonary or cerebral edema, seizure, cardiovascular collapse

and the pH-sensitive urinary excretion of salicylic acid determines the half-life, prolonging significantly (up to 15 to 30 hours) with large overdoses.[3]

The initial physiologic effect of salicylates is direct stimulation of the medullary respiratory center. In addition, salicylic acid increases the sensitivity of the respiratory center to pH and partial pressure of carbon dioxide (P_{CO_2}). Hyperventilation develops early, subsequently becoming a compensatory mechanism for metabolic acidosis. Prolonged high serum concentrations eventually depress the respiratory center. Respiratory alkalosis is compensated by the buffering capacity of the hemoglobin-oxyhemoglobin system, the exchange of intracellular hydrogen ions for extracellular cations, and the urinary excretion of bicarbonate. Loss of bicarbonate decreases buffering capacity and exacerbates the degree of metabolic acidosis (Box 139.1).[3]

Toxicity results primarily from salicylate interference with aerobic metabolism by uncoupling of mitochondrial oxidative phosphorylation. Inhibition of the Krebs cycle increases production of pyruvic acid and increases conversion to lactic acid. Increased lipid metabolism generates ketone bodies. Metabolic rate, temperature, tissue carbon dioxide, and oxygen consumption are increased. Tissue glycolysis predisposes to hypoglycemia, particularly in children. Inefficiency of anaerobic metabolism results in decreased production of adenosine triphosphate, with energy released as heat causing the hyperthermia frequently attributed to salicylate poisoning.

Only nonionized particles can cross the lipophilic cell membrane and accumulate in the brain and other tissues. Because salicylic acid has a pK_a of 3.5, the majority of salicylate is ionized and unable to enter tissue at the physiologic pH of 7.4. However, as serum pH decreases, more particles become un-ionized and cross the cell membrane and blood-brain barrier, markedly increasing the movement of salicylate into the tissues and central nervous system (CNS).

The rapid depletion of potassium stores in salicylate toxicity is caused by multiple factors. Immediate losses occur due to vomiting, which is secondary to stimulation of the medullary chemoreceptor trigger zone. In addition, increased renal excretion of sodium, bicarbonate, and potassium occurs as a compensatory response to the respiratory alkalosis, and salicylate-induced increased permeability of the renal tubules causes further loss of potassium. A final factor is inhibition of the active transport system, secondary to uncoupling of oxidative phosphorylation.[6]

Salicylate-related decreases in renal blood flow or direct nephrotoxicity may cause acute nonoliguric renal failure. Drug-induced, inappropriate secretion of antidiuretic hormone may also affect renal function. The exact mechanism by which salicylates increase alveolar capillary membrane permeability is not clearly defined. Theories include inhibition of prostacyclin, changes in platelet-vessel interaction, and neurogenic influences.

In adults, risk factors for salicylate-induced pulmonary edema include age greater than 30 years old, long-term cigarette smoking, chronic salicylate ingestion, metabolic acidosis, neurologic symptoms, and serum salicylate concentration greater than 40 mg/dL. Risk factors in children include high serum salicylate levels (>80 mg/dL), large anion gap acidosis, decreased serum potassium concentration, and low pCO_2.

Salicylates severely affect the CNS in two ways. First, there is a poorly elucidated aspect of toxicity that ultimately results in cerebral edema. This pathway is presumably related to increased energy requirements, acidemia, and direct cellular toxicity. Second, the consumption of glucose in the brain may outpace the supply. This occurs even in the face of normal serum glucose. One or both of these mechanisms can cause altered mental status, seizures, and coma.

At moderate to high tissue burden, salicylates induce a classic finding of toxicity—tinnitus, or the sensation of ringing in the ears. This phenomenon is due to a combination of central and peripheral effects. Cochlear toxicity is thought to be the result of alterations in *N*-methyl-D-aspartate (NMDA) activity, decreased blood flow, and increased membrane permeability. Cochlear toxicity combines with hyperactivity in the auditory cortex to cause tonotopic shifts where upper and lower frequency sounds are perceived in the 10 to 20 hertz tinnitus range, and sounds within this range become hyperacute. Salicylate-induced hearing disturbance may take days to resolve after the tissue burden normalizes.

At therapeutic dosing, salicylates increase bleeding risk via irreversible inhibition of platelet cyclooxygenase (COX). In overdose, vitamin K epoxide reductase is inhibited in a manner similar to warfarin. This acquired coagulopathy prolongs prothrombin time measurements and is associated with a substantial risk of clinically significant bleeding.[7]

Physiologic changes of aging predispose elderly patients to toxicity from chronic therapeutic ingestion. Decreased liver blood flow limits biotransformation of salicylate, and decreased renal function reduces salicylate clearance. Chronic ingestion decreases albumin binding, increasing the free salicylate that can enter the cell, and allows salicylates more time to pass through the blood-brain barrier. Therefore, a patient with chronic salicylate toxicity and a serum concentration of 40 mg/dL may be more ill than a patient with an acute ingestion and serum concentration of 80 mg/dL.

Clinical Features

Salicylate toxicity initially generates gastrointestinal (GI) distress followed by tachypnea with an accompanying respiratory alkalosis, tinnitus, and hearing disturbances due to concentration-dependent reversible ototoxicity, diaphoresis, and an evolving anion gap acidosis. As the toxicity progresses, hyperthermia, coagulopathy, cerebral and pulmonary edema, cardiovascular collapse, and, ultimately, death occur. Chronic poisoning may be more subtle, manifesting as a waxing and waning combination of the above manifestations of toxicity.[6]

Differential Diagnoses

Salicylism mimics sepsis, CNS infection, withdrawal syndromes, and alcoholic or diabetic ketoacidosis. This is especially true in chronic toxicity given that the serum salicylate concentration is relatively low. Thus, the severity of poisoning is often not recognized or not fully appreciated. In addition, co-ingestion is common, so evaluation for other toxic exposures is warranted. Other pain relievers and fever reducers such as acetaminophen and ibuprofen are often confused with aspirin by patients. Other toxins that cause a metabolic acidosis with an elevated anion gap include colchicine, iron, isoniazid, methanol, ethylene glycol, metformin, and cyanide. Other toxins that can cause

tinnitus include aminoglycosides, loop diuretics, opioids, methotrexate, cisplatin, and antimalarial agents containing quinine.

Diagnostic Testing

The serum salicylate concentration, acid-base status, serum potassium, and glucose are key diagnostic studies. Be mindful of the laboratory units of measurement when interpreting salicylate levels. Serum salicylate concentrations are reported as mg/dL, mg/L, or mmol/L by various labs but are listed in mg/dL in this text. The Done nomogram, historically used for aspirin toxicity, should not be used to determine prognosis or treatment of the salicylate-poisoned patient.

Measure an initial salicylate concentration on arrival with a second sample obtained 2 hours later. A low initial salicylate level may be deceptive as early salicylate levels have not been shown to predict severity of outcome.[4] Obtain concentrations every 2 hours to monitor for continued absorption, which may be prolonged. Serum salicylate levels should be repeated every 2 hours until three consecutive levels are less than 30 mg/dL and are declining by at least 10% to 20% on each measurement while the patient is no longer undergoing therapy to enhance elimination. In one series, 3.5% of cases demonstrated peak serum levels greater than 30 mg/dl despite a nondetectable initial level with the longest interval from ingestion to detection of 225 minutes.[8] Thus, given sufficient clinical suspicion, continue to obtain salicylate levels up to 4 hours post-ingestion even if the initial level is undetectable.

Acid-base status can change quickly, and monitoring of pH every 2 hours is important to guide treatment. Use early and frequent arterial or venous blood gas determinations in symptomatic patients to rapidly assess acid-base and compensatory status. Developing acidemia portends severe disease. The pH begins to drop when the patient is unable to compensate for acidemia. Lactic acid accumulates, and serum bicarbonate is consumed. A serum lactate greater than 2.25 mmol/L is a predictor of severe outcome.[4] When serum pH is less than 7.4 and both P_{CO_2} and bicarbonate level are low, hemodynamic instability rapidly develops.[6]

A metabolic panel is necessary to guide electrolyte replacement (with a focus on serum potassium) and to assess renal function and glucose metabolism. However, anion gap determination on a metabolic panel is not a substitute for obtaining a salicylate level or measuring the pH. Measurement of protime/INR will assist in guiding vitamin K therapy in the setting of coagulopathy. A serum acetaminophen concentration should also be obtained to screen for ingestion of this common, clinically occult analgesic overdose.

Management

Stabilization and Supportive Care

Accurate ascertainment of vital signs is the initial step in assessment, including oxygen saturation, respiratory rate, and a reliable temperature. Chest auscultation can provide evidence of pulmonary edema, and altered mental status may suggest CNS toxicity. Dehydration occurs early in salicylate intoxication because of the hypermetabolic state, and initial fluid requirements may be as high as 4 to 6 L. Fluid administration should be guided by the patient's apparent deficit to maintain urine output of 2 to 3 mL/kg/hr. Correct potassium depletion to maintain a serum level between 4.5 and 5.0 mEq/L (4.5–5.0 mmol/L).[6]

Unless the patient is rapidly decompensating, early mechanical ventilation should be avoided in the aspirin poisoned patient. Similar to diabetic ketoacidosis, it is difficult to artificially achieve adequate minute ventilation that sufficiently matches the patient's own respiratory compensation. In addition, the loss of ventilation during the intubation procedure results in rapid loss of respiratory compensation and worsening acidemia. If the patient is critically ill and requires intubation, worsening of acidosis during apnea is potentially harmful. Thus, we recommend bolus administration of 50 to 100 mEq (1 to 2 amps) of sodium bicarbonate ($NaHCO_3$) immediately prior to the procedure irrespective of the serum pH to temporarily compensate for a respiratory acidosis in addition to the bicarbonate drip being administered for enhanced elimination. Attempt to adjust the tidal volume post-intubation to optimally match the pre-intubation P_{CO_2} level. In addition, establish an elevated minute volume and obtain frequent arterial blood gases to guide ventilator management to maintain respiratory compensation.[6]

BOX 139.2 Treatment of Acute Salicylate Poisoning

- Treat dehydration; maintain urine output at 2 to 3 mL/kg/hr.
- Correct potassium depletion with goal serum level of 4.5–5.0 mEq/L.
- Consider oral activated charcoal (AC); 25 grams every 2 to 4 hours for two to four doses if tolerated.
- Alkalinize urine with goal urine pH of 7.5 to 8.0.
  - Infuse bicarbonate drip: 132 to 150 mEq (three 50-mL ampules of 7.5% or 8.4% sodium bicarbonate ($NaHCO_3$) in 1 L of dextrose 5% in water (D5W) + 40 mEq of potassium chloride (KCl) running at 2 to 3 mL/kg/hr.
  - Allow serum pH up to 7.55.
  - Do not attempt forced diuresis.
- Initiate hemodialysis if any of the following occur:
  - Altered mental status, coma, seizure
  - Renal failure
  - Hepatic failure
  - Pulmonary edema or respiratory failure
  - Severe acid-base imbalance (pH <7.1 to 7.2)
  - Deterioration in condition
  - Need for intubation
  - Failure of urine alkalinization
  - Rapidly rising salicylate level
  - Serum salicylate concentration ≥100 mg/dL after acute ingestion
  - Serum salicylate concentration ≥40 mg/dL after chronic ingestion
- Administer intravenous (IV) dextrose 0.5 to 1 g/kg IV for any central nervous system (CNS) abnormalities (altered mental status, coma, agitation, seizure).

Decontamination

Activated charcoal (AC) has been shown to reduce salicylate absorption in both animal studies and human volunteer trials. Evidence in the overdose setting is less clear. We recommend administering multiple-dose oral AC (25 to 50 gm via a nasogastric tube) every 2 to 4 hours for 2 to 4 doses if the patient's GI distress, mental status, and hemodynamic stability can tolerate, because large salicylate ingestions tend to form gastric concretions. AC is not used in chronic salicylate poisoning because the presentation occurs long after absorption from the GI tract.[6]

Enhanced Elimination

Specific treatment of salicylate toxicity has two objectives: (1) to correct fluid deficits and acid-base abnormalities and (2) to increase excretion (Box 139.2). Because salicylates have a low pK_a and are renally excreted, alkaline urine traps the salicylate ion and increases excretion. Urine alkalinization is advisable in patients with salicylate levels greater than 30 mg/dL, significant acid-base disturbance, or increasing salicylate levels. This is most often achieved via administration of a bicarbonate drip: 132 to 150 mEq (three 50 mL ampules) of 7.5% or 8.4% $NaHCO_3$ in 1 L of dextrose 5% in water (D5W) plus 40 mEq

of potassium chloride (KCl) running at 2 to 3 mL/kg/hr. Salicylate clearance varies in direct proportion to renal flow rate but increases exponentially with pH. A urine pH of at least 7.5 to 8.0 is ideal to increase excretion. Urine alkalinization is difficult to achieve because the excretion of salicylic acid in the urine decreases urine pH. In addition, potassium depletion must be corrected to attain alkaline urine as the kidney exchanges hydrogen for potassium in the setting of hypokalemia, further acidifying the urine. In most patients, a serum pH of up to 7.55 is well tolerated. Forced diuresis should not be performed, because it does not significantly increase salicylate excretion and may potentiate fluid overload, as well as cerebral and pulmonary edema.[3,6]

Hemodialysis is highly effective in treating severe salicylate toxicity. It is indicated for patients with any of the following: serum salicylate levels greater than 100 mg/dL in acute and over 40 mg/dL in chronic salicylate poisoning; altered mental status, including coma; seizure; endotracheal intubation (other than for co-ingestions); renal or hepatic failure; pulmonary edema; severe acid-base imbalance (pH <7.1 to 7.2); rapidly rising serum salicylate level; and failure to respond to more standard treatments previously described. Of note, the levels recommended here are the maximum levels permissible for initiation of hemodialysis. Early consultation with nephrology to prepare for hemodialysis should occur prior to reaching a serum salicylate concentration of 100 mg/dL. In one series, over half of peak levels in fatal cases were less than 100 mg/dl. A concentration of 80 mg/dL, or even lower if concentrations are rising rapidly, should prompt nephrology consultation or transfer to a higher level of care with extracorporeal capabilities in anticipation of emergent hemodialysis.[3,5,6,9]

Greater salicylate concentration on the fetal side of the placenta and relative fetal acidemia contribute to fetal distress from maternal salicylate poisoning. Salicylate poisoning during pregnancy is associated with fetal demise, and therefore the mother should be treated expeditiously. Consultation with an obstetrician to facilitate delivery of the distressed fetus in the third trimester of pregnancy is indicated if the fetus is viable.[3]

Antidote Therapy

There is no specific antidote for salicylate toxicity. Central hypoglycemia may be responsible for altered mental status in the setting of salicylate toxicity. In all cases of altered mental status, even in the face of a normal serum glucose measurement, supplemental intravenous (IV) dextrose (0.5 to 1 gm/kg) should be administered. Additional glucose supplementation may be required and should be administered in response to recurrent altered mental status.[6]

In the setting of major bleeding with elevated protime/INR measurements, administer prothrombin complex concentrate along with vitamin K 5 to 10 mg IV. Platelet transfusion may also be helpful in the setting of bleeding to correct irreversible platelet inhibition.

Disposition

In patients with acute intoxication, hospital admission to an intensive care setting is recommended for pulmonary edema, CNS symptoms (other than tinnitus), seizures, pH less than 7.3, electrolyte disorders, dehydration, renal insufficiency, or increasing serum levels during serial testing. In patients with chronic intoxication, low serum salicylate concentrations (40 mg/dL) may accompany severe salicylism. These patients should be admitted to a monitored setting for observation, serial serum levels, and metabolic assessment. Consultation with a medical toxicologist may allow for emergency department (ED) observation management of the salicylate poisoned patient not requiring hemodialysis.

In patients with acute ingestion, repeated serum salicylate measurements are essential to determine that the serum concentration is decreasing before the patient is discharged. Serum salicylate levels should be repeated every 2 hours until three consecutive levels are both less than 30 mg/dL and decreasing by at least 10% to 20% on each measurement when no longer undergoing therapy to enhance elimination. In addition, the patient should not be symptomatic (aside from residual tinnitus) at the time of discharge. With any case of intentional overdose, psychiatric evaluation is recommended.[3,6]

NONSTEROIDAL AGENTS

Principles of Toxicity

The nonsteroidal antiinflammatory drugs (NSAIDs) have analgesic, antiinflammatory, and antipyretic activities. Ibuprofen and naproxen, both propionic acid derivatives, are available over the counter in the United States and are the most commonly encountered NSAIDs. The therapeutic antiinflammatory effect of the NSAIDs is achieved by inhibition of cyclooxygenase (COX) and consequent blockade of prostaglandin production.[10]

NSAIDs are almost completely absorbed from the upper small intestine after oral administration. NSAIDs are highly bound to plasma proteins and therefore have small volumes of distribution (0.10 to 0.17 L/kg). They are eliminated by hepatic biotransformation. Metabolites are typically inactive with the notable exception of phenylbutazone. Plasma half-lives are relatively short (1 to 4 hours), except for naproxen (12 to 15 hours), oxaprozin (25 to 50 hours), piroxicam (45 hours), and phenylbutazone (50 to 100 hours). Elimination half-lives are not substantially prolonged in overdose.[11]

Clinical Features

Most NSAID overdoses are asymptomatic or cause only minor gastrointestinal symptoms. Ibuprofen is the most common NSAID ingested in overdose. Such exposures typically follow a benign, self-limited course. Symptomatic overdose occurs only after ingestion of at least 100 mg/kg, and symptoms develop within 4 hours of ingestion. Life-threatening toxicity is rare with most cases limited to mild GI disturbance that resolves in hours. Less common clinical effects include metabolic acidosis, muscle fasciculations, mydriasis, diaphoresis, hyperventilation, bradycardia, hypotension, dyspnea, tinnitus, and rash. Rare cases of coma, seizure, hypotension, and metabolic acidosis have been reported in acute massive overdoses (>400–500 mg/kg).[11]

Renal dysfunction is seen only after large acute overdose and in association with a period of relative hypovolemia with hypotension. It is usually reversible and generally responds to supportive measures. There are sporadic cases of acute liver injury with a predominantly hepatocellular pattern. This occurs both in therapeutic and supratherapeutic NSAID exposure. Diclofenac was the most common agent identified in a North American acute liver injury registry whereas nimesulide presented the highest risk. Both ibuprofen and ketoprofen were also identified as culprits in a European study.[12,13]

All propionic acid derivatives have been associated with sporadic cases of aseptic meningitis. This complication is most common with ibuprofen. It occurs in an idiosyncratic fashion—both in overdose and with therapeutic dosing.

Mefenamic acid, a fenamate, is associated with a high rate of CNS toxicity in overdose compared to other NSAIDS. In particular, there is a high incidence of seizures, which occur 2 to 8 hours after supratherapeutic ingestion. Rapid recovery is the rule with supportive care and IV doses of benzodiazepines administered in the case of seizure activity.[14]

Phenylbutazone, a pyrazolone, is now rarely prescribed because of its association with aplastic anemia and agranulocytosis. Although phenylbutazone overdose is rare, the course is much more severe than with other NSAIDs. Severely poisoned patients have early onset of GI

distress, coma, seizure, hyperthermia, hyperventilation, alkalosis or acidosis, hypotension, electrocardiographic abnormalities, or cardiac arrest. Late sequelae of severe poisoning (2 to 7 days) include renal, hepatic, and hematologic dysfunction. The clinical course is prolonged compared with that of other NSAID poisonings, reflecting the long elimination half-lives of phenylbutazone and its principal metabolite, oxyphenbutazone.

Differential Diagnoses

Given that NSAID overdoses rarely cause substantial morbidity and are almost never fatal, the differential diagnosis should focus on toxicity due to possible co-ingestions. Patients often confuse NSAIDs with other pain relievers and fever reducers, including acetaminophen and salicylates. Other over-the-counter medications that can cause GI distress include iron preparations, vitamins, herbal supplements, as well as acetaminophen and salicylates.

Diagnostic Testing

Plasma NSAID concentrations are not clinically useful and are rarely available in the ED. With larger overdoses (>100 mg/kg), a complete blood count, metabolic profile, and assessment of renal function are recommended. Because patients often confuse and mix pain relievers, screening serum acetaminophen and salicylate levels are also recommended.

Management

Stabilization and Supportive Care

The management of NSAID overdose is largely supportive, and there is no specific antidote. Pyrazolone (e.g., phenylbutazone) and fenamate (e.g., mefenamic acid) toxicity is associated with significantly higher morbidity and may require more supportive care measures, including control of seizures with benzodiazepines, crystalloid fluid resuscitation, correction of electrolyte disturbances, and ventilatory support. Hypotension is managed with a 1 to 2 L bolus of normal saline or lactated Ringer solution, which may be repeated or supported by infusions at two to three times maintenance rate. If perfusion compromise persists, initiate a vasopressor, such as norepinephrine, and titrate to maintain an adequate mean arterial pressure for perfusion. Although it is rarely indicated and understudied, extracorporeal membrane oxygenation (ECMO) has been used to successfully manage refractory hypotension after massive ibuprofen overdose.

Decontamination

There is no evidence supporting the use of gastric emptying, AC or whole bowel irrigation in NSAID overdoses.

Enhanced Elimination

Because of high protein binding and rapid metabolism, enhanced elimination is not useful in most cases. In the rare case of a massive overdose (>400–500 mg/kg) with pH less than 7.1, hemodialysis should be considered to correct acidemia. Consultation with a nephrologist or transfer to a facility capable of emergently dialyzing the patient is indicated. In this situation, hemodialysis may also remove the free drug once protein binding is overwhelmed. Plasmapheresis has been attempted in severe phenylbutazone poisoning.

Antidote Therapy

There is no specific antidote for NSAID poisoning.

Disposition

Patients who are mildly symptomatic or asymptomatic for more than 4 hours after an NSAID overdose do not require further medical care. Patients who have ingested a pyrazolone or fenamate require observation for possible seizures for 8 to 12 hours after ingestion. Those with CNS symptoms, acidosis, or renal insufficiency and who require further supportive care should be admitted for ongoing treatment. Patients with mild to moderate symptoms may be observed in the ED until they are asymptomatic or improving. Patients for whom the ingestion represents a suicidal gesture should undergo psychiatric assessment.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 139: QUESTIONS AND ANSWERS

1. What type of acid-base disorder is caused by salicylate overdose?
- **a.** Metabolic acidosis and respiratory acidosis
- **b.** Metabolic acidosis and respiratory alkalosis
- **c.** Metabolic alkalosis and respiratory acidosis
- **d.** Metabolic alkalosis and respiratory alkalosis
- **e.** No acid-base disorder

Answer: B. Early in overdose, salicylates stimulate the respiratory center, causing hyperventilation and a respiratory alkalosis. Later, salicylates inhibit mitochondrial oxidative phosphorylation, resulting in anaerobic metabolism and a metabolic acidosis. This is the classic situation but is later followed by respiratory compensation, resulting in the possibility of a triple acid-base disorder.

2. A 22-year-old man presents 6 hours after an aspirin overdose in an attempt to commit suicide. His only complaint is of tinnitus, and his vital signs and physical examination are normal. His salicylate level is 47 mg/dL. His serum pH is 7.3, with an anion gap of 18 and a serum bicarbonate level of 17 mmol/L. Which of the following is the most appropriate therapy?
- **a.** Forced diuresis
- **b.** Hemodialysis
- **c.** Observation only
- **d.** Oral activated charcoal due to chronic poisoning
- **e.** Urinary alkalinization

Answer: E. Salicylates are acidic compounds and therefore readily ionize in an alkali environment. Only in the nonionized state can they traverse cell membranes. Thus, once ionized in the urine, they are effectively "trapped" and can be easily excreted. Urinary alkalinization is indicated in patients with a salicylate level greater than 30 mg/dL, significant acid-base disturbances, or increasing salicylate levels. Forced diuresis does not increase excretion, increases the risk for pulmonary and cerebral edema, and is never indicated. Hemodialysis is the ultimate treatment for salicylate poisoning but is generally reserved for patients with more severe signs or symptoms, more severe acid-base disturbances, or acute salicylate levels greater than 100 mg/dL. Observation alone would be indicated in a patient with a history of salicylate overdose but with no symptoms and normal laboratory values. AC can decrease the amount of salicylate absorbed if given within 1 hour of ingestion. Because large salicylate ingestions tend to form gastric concretions, multiple doses of AC may be indicated. AC is not used in chronic salicylate poisoning because the presentation occurs long after gastrointestinal absorption.

3. Which of the following patients does not require hemodialysis?
- **a.** A 9-year-old boy with acute salicylate ingestion and an initial salicylate level of 30 mg/dL
- **b.** A 20-year-old pregnant woman with acute salicylate overdose and an initial salicylate level of 100 mg/dL
- **c.** A 24-year-old man with acute salicylate overdose and salicylate level of 110 mg/dL despite urinary alkalinization
- **d.** A 30-year-old woman with chronic salicylate ingestion and salicylate level of 50 mg/dL
- **e.** A 42-year-old woman with acute salicylate overdose and salicylate level that has risen from 50 to 90 mg/dL despite urinary alkalinization

Answer: A. Indications for hemodialysis in the setting of salicylate toxicity include levels of 100 mg/dl or greater in an acute overdose, a rising level reaching values at or above 80 mg/dl despite urinary alkalinization in an acute overdose, or a level greater than 40 mg/dl in the setting of chronic toxicity. Fetal distress is associated with salicylate toxicity, although recommended salicylate concentration thresholds for hemodialysis are not different than the general population. Rather, discussion with obstetrics regarding emergent delivery should occur if the mother presents in the third trimester of pregnancy.

4. A 41-year-old man presents after an intentional ibuprofen overdose. He complains of epigastric pain, nausea, and one episode of vomiting. He reports that approximately 2 hours ago he took "a handful" of 200-mg ibuprofen tablets in a self-harm attempt. Which of the following is the appropriate next step?
- **a.** Hemodialysis
- **b.** Check serum acetaminophen and salicylate levels
- **c.** Observation for resolution of symptoms
- **d.** Oral activated charcoal (AC)
- **e.** Urinary alkalinization

Answer: B. Oftentimes, patients are unable to differentiate various over-the-counter analgesics. Obtaining salicylate and acetaminophen concentrations in the setting of a reported ibuprofen overdose is essential because occult toxicity due to those compounds may be life-threatening

CHAPTER 139: QUESTIONS AND ANSWERS—cont'd.

whereas nonsteroidal antiinflammatory drugs (NSAIDs) are generally safe in overdose. Specifically, ibuprofen overdose often results in mild self-limited gastrointestinal (GI) upset. Typically, at least 100 mg/kg of ibuprofen needs to be ingested to cause symptoms. All symptoms are treated with supportive care. Symptoms almost always develop within 4 hours of ingestion. In general, patients may be discharged in cases of small overdoses (<100 mg/kg), once symptoms resolve or after a 4-hour period of observation.

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Anticholinergics

Jason A. Hoppe and Andrew A. Monte

KEY CONCEPTS

- Anticholinergic (antimuscarinic) intoxication is common and can occur as a result of ingestion of a variety of plants and drugs, both prescription and over-the-counter.
- Most patients with antimuscarinic toxicity do well with supportive care and observation.
- Antimuscarinic syndrome varies in clinical presentation with either peripheral or central manifestations predominating.
- Central antimuscarinic delirium is most effectively treated with physostigmine.
- Contraindications to physostigmine administration include narrow angle glaucoma, atrioventricular (AV) blockade, bradycardia, and seizure precipitated by overdose.

PRINCIPLES OF TOXICOLOGY

Overview

Anticholinergic agents cause toxicity through inhibition of muscarinic, nicotinic, parasympathetic, or sympathetic acetylcholine receptors. Nicotinic receptor inhibition and ganglionic acetylcholine inhibition at parasympathetic and sympathetic locations are covered in Chapter 152. This chapter will focus on antimuscarinic effects and toxicity. The terms *anticholinergic* and *antimuscarinic* are used synonymously though the mechanism of toxicity is more accurately described by the term "antimuscarinic," and thus that term will be used in this chapter.

Antimuscarinic effects are due to competitive inhibition of acetylcholine at muscarinic receptors. Muscarinic receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle (intestinal, bronchial, and cardiac), the secretory glands (salivary and sweat), the ciliary body of the eye, and the central nervous system (CNS).

Antimuscarinic agents have been used medicinally from antiquity to the present day. Mandrake plant remains were found in the coffin of Tutankhamen, the Old Testament of the Bible references its use as an aphrodisiac, and antimuscarinic plants were used as anesthetics in Greek and Roman settlements in the 1st century. Atropine, hyoscyamine, and scopolamine are naturally occurring tertiary amine antimuscarinic agents that remain in wide clinical use today. The tertiary amine structure allows the agent to cross the blood-brain barrier; therefore, these agents may precipitate CNS toxicity. Quaternary amine antimuscarinic agents, such as the anti-sialagogue glycopyrrolate, have been developed to mitigate CNS side effects due to their limited ability to cross the blood-brain barrier, though mild delirium may occur in the setting of a large overdose.

CLINICAL FEATURES

Over 600 compounds contain antimuscarinic activity, including prescription drugs, over-the-counter drugs, and plants. The effects of muscarinic receptor blockade are utilized for clinical purposes including pupillary dilation, antispasmodics, sleep aids, treatment of motion sickness, allergic reactions, drying of airway secretions, reactive airway disease, treatment of bradycardia, treatment of Parkinsonism, and the management of urinary incontinence and bladder spasm. The agents that most commonly precipitate antimuscarinic toxicity, such as H1 antihistamines and some antipsychotics, often affect several neurotransmitters and receptor systems in addition to antagonism at muscarinic receptors. This may complicate the clinical presentation and some clinical symptoms may be unique to the specific etiologic agent (Box 140.1).

Antimuscarinic toxicity has both central and peripheral manifestations (Fig. 140.1). Peripheral muscarinic antagonism causes tachycardia, hypertension, hyperthermia, mydriasis, dry mouth, lack of sweating, skin flushing, decreased bowel motility, and urinary retention. Central nervous system blockade of muscarinic receptors may produce delirium characterized by confusion, mumbling speech, agitation, hallucinations, hand picking gestures, myoclonus, tremor, and coma. Manifestations of the toxidrome are frequently incomplete and either peripheral or central components may predominate depending upon which antimuscarinic agent is involved, the dose, and the individual patient (Table 140.1). In one large series of antimuscarinic poisoning, only 28% of patients had all three classic manifestations of tachycardia, dry skin/axilla, and mydriasis. Therefore, most patients will not present with all of these features.[1] Duration of toxicity may be prolonged (18–72 hours) depending on the specific agent, dose, and the pharmacologic effect of delayed gastric emptying.[1]

DIFFERENTIAL DIAGNOSES

The differential diagnosis of altered mental status is broad. Consider antimuscarinic toxicity when there is a history of exposure or if there are physical exam findings consistent with the antimuscarinic toxidrome (Box 140.2).

DIAGNOSTIC TESTING

Laboratory

Patients with mild toxicity, a reliable history of exposure, and symptoms consistent with antimuscarinic toxicity do not require specific laboratory testing. Patients with an unclear history of exposure, other potential etiologies, moderate to severe toxicity or hyperthermia should be evaluated for causes of altered mental status and end-organ toxicity including: serum glucose, electrolytes, cardiac biomarkers, renal function, creatinine kinase to evaluate for rhabdomyolysis, and acid-base status. Patients with an overdose of unclear history should be evaluated for co-ingestion since antimuscarinic agents are often formulated with other potentially toxic agents. Serum acetaminophen and

salicylate levels should be measured. Physostigmine may be used as a diagnostic test (see section on management).

Electrocardiogram

An electrocardiogram (ECG) should be obtained in cases of suspected tricyclic antidepressant or diphenhydramine toxicity to assess for possible sodium channel blockade (widened QRS interval > 120 ms or terminal R wave in lead aVR > 3 mm). Prior to the use of physostigmine, an ECG should be reviewed for bradycardia or atrioventricular (AV) block which would preclude the use of the antidote.

BOX 140.1 Signs and Symptoms of Antimuscarinic Toxicity

Mydriasis: "blind as a bat"
Altered mental status: "mad as a hatter"
Dry mucous membranes: "dry as a bone"
Dry, flushed skin: "red as a beet"
Hyperthermia: "hot as hades"
Urinary retention: "full as a flask"
Decreased bowel sounds/ileus
Tachycardia

MANAGEMENT

Stabilization

Initial management should focus on evaluation and stabilization of cardiovascular and neurologic toxicity. Sodium bicarbonate boluses of 50 mEq (1 amp) in adults and 1 to 2 mEq/kg in children should be given for evidence of sodium channel blockade with a QRS interval greater than 120 msec. Benzodiazepines should be considered for treatment of agitation and recurrent seizures. Patients with drug-induced hyperthermia should be treated with rapid cooling with progression to paralysis, ventilation and airway control, with sedation, when noninvasive cooling measures fail.

Decontamination

Most patients do well with symptomatic care alone. Gastric decontamination with activated charcoal may be considered though the risk of aspiration due to CNS depression or seizures generally outweigh the benefits. Activated charcoal may decrease ongoing absorption in patients that have ingested antimuscarinic plants or patients with decreased gastric motility. Theoretically this may decrease symptom duration. If considered, activated charcoal should only be administered early in the clinical course in awake, cooperative patients with a low risk of seizures or aspiration. There is little role for gastric lavage in antimuscarinic poisoned patients. There is no role for dialysis.

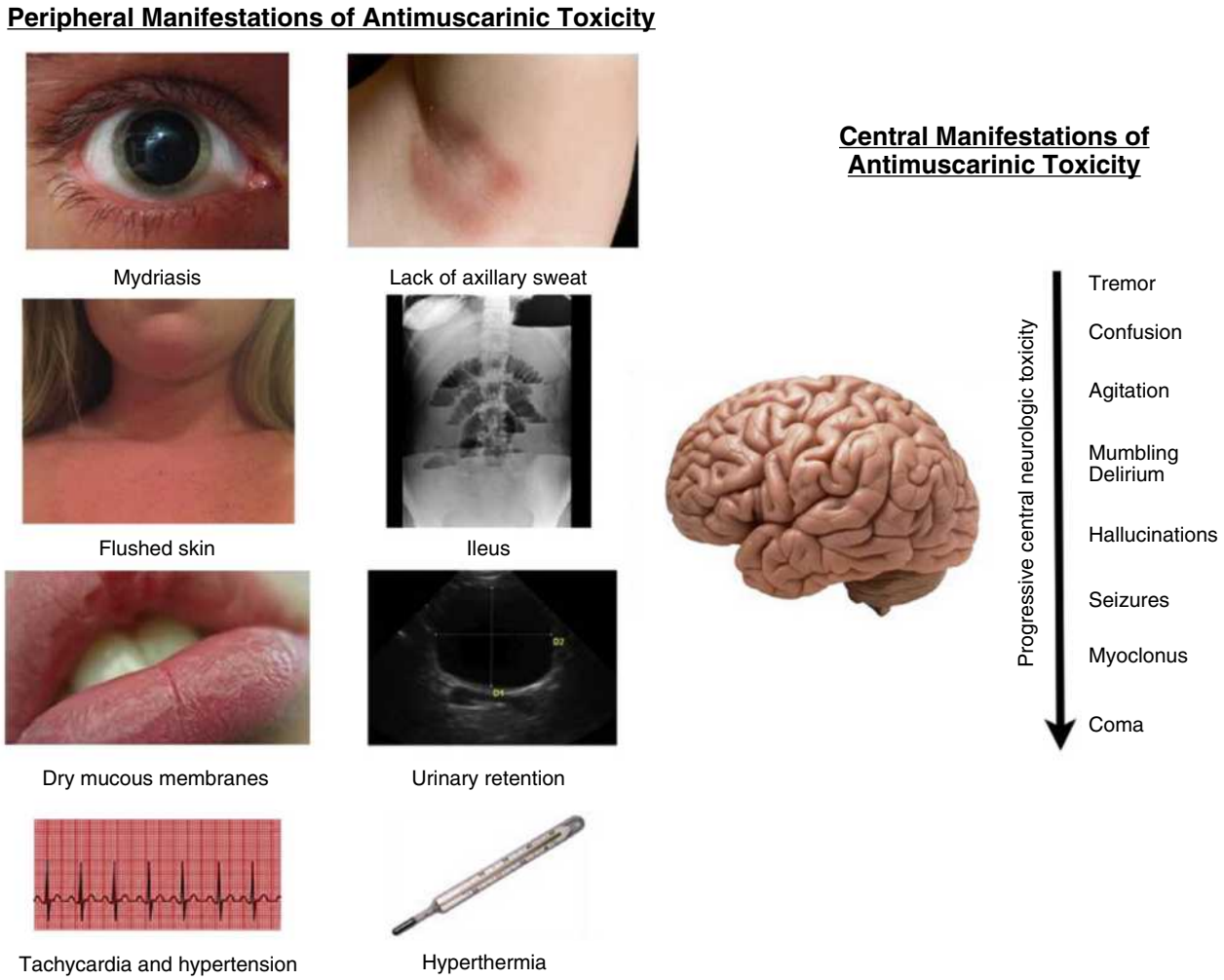

Fig. 140.1 Signs and symptoms of antimuscarinic toxicity.

TABLE 140.1 Specific Antimuscarinic Agents and Their Unique Clinical Manifestations

Antimuscarinic Agent	Toxic Dose	Unique Clinical Manifestations and Receptors Antagonized.
Datura spp.	Seeds contain high concentrations of hyoscyamine and scopolamine. The toxic dose depends upon the species and the mode of ingestion. In general 5 to 10 seeds may be toxic.	Classic peripheral and central antimuscarinic features M_1
Diphenhydramine	2.5 mg/kg, >10 mg/kg may result in cardiovascular and neurologic toxicity	CNS depression, QRS prolongation and ventricular dysrhythmias, seizures M_1, H_1, Na^+ channels
Doxylamine	>20 mg/kg associated with rhabdomyolysis	CNS depression, seizures, rhabdomyolysis M_1, H_1
Tricyclic antidepressants (TCA)	2.5 mg/kg, >10 mg/kg may result in cardiovascular and neurologic toxicity.	CNS depression, QRS prolongation, ventricular dysrhythmias, seizures, hypotension, antimuscarinic symptoms may manifest late in the course. M_1, H_1, α_1, Na^+ channels
Atypical antipsychotics	Varies depending upon agent.	CNS depression, hypotension, antimuscarinic symptoms may manifest late in the course. M_1, H_1, α_1, D_2, $5\text{-}HT_{2A}$

M_1, Muscarinic; D_2, dopamine; $5\text{-}HT_{2A}$, serotonin; H_1, histamine; α_1, alpha adrenergic.

BOX 140.2 Common Differential Considerations With Overlapping Signs and Symptoms of Antimuscarinic Toxicity

Differential Diagnosis Considerations

Toxicological

Sympathomimetic toxicity
Serotonin toxicity
Neuroleptic malignant syndrome
Lithium toxicity
Antidepressant toxicity
Antipsychotic toxicity

Central Nervous System

Intracranial hemorrhage
Seizure
Infectious
Sepsis
CNS infections

Metabolic

Hyperthyroid
Encephalopathy
Psychiatric
Delirium
Dementia
Bipolar disorder

BOX 140.3 Antimuscarinic Reversal Agent: Physostigmine

Physostigmine Salicylate

Indications: Diagnosis and treatment of antimuscarinic toxicity.
Contraindications: narrow angle glaucoma, AV blockade, bradycardia, and seizures due to current overdose.
Adverse effects: bradycardia, seizure, vomiting
Route: IV or IM.
Kinetics/dynamics: Time of onset: within 5 to 10 minutes following IV administration, 20 to 30 minutes following IM administration. Half-life: 16 ±3 minutes. Plasma cholinesterase inhibition 84 ±5 minutes.
Adult dosing: 1 to 2 mg bolus slowly (no faster than 1 mg/min). Start infusion at 1 mg/hour titrated every 30 minutes to clinical effect. Pediatric dose: 0.02 mg/kg (max 0.5 mg/dose) IV over 5 min, repeat every 5 min PRN (max total dose: 2 mg)

Pharmacologic Intervention and Antidote Treatment

Control of delirium is the most common reason for emergency intervention in antimuscarinic poisoned patients. Sedation or antidotal treatment should be considered in patients whose delirium places them at risk of physical harm; falling out of bed, becoming combative with staff, need for physical restraints, or pulling out intravenous (IV) access necessary for treatment. Sedation can be accomplished with IV benzodiazepines, such as lorazepam (0.05–0.1 mg/kg), midazolam (0.05–0.1 mg/kg), or diazepam (0.1–0.5 mg/kg), titrated every 15 minutes to sedation. However, benzodiazepines are inferior to physostigmine for control of delirium and agitation.[1]

Physostigmine salicylate is the antidote for antimuscarinic toxicity. It may be used for diagnostic and therapeutic purposes (see Box 140.3 for indications, contraindications, and dosing). Physostigmine is a tertiary amine carbamate that reversibly inhibits cholinesterases in both peripheral and central nervous systems.[1] This allows for acetylcholine accumulation and subsequent competition with the antimuscarinic blocking agent occupying the receptor. It has a short half-life, approximately 20 minutes,[1] though inhibition of the esterase, which yields the pharmacodynamic effects, lasts considerably longer with a half-life of 80 minutes.

When used diagnostically in an antimuscarinic poisoned patient, a response is expected rapidly, within 10 minutes. Near complete reversal of delirium is expected in a matter of minutes and may decrease the need for more invasive testing, such as lumbar punctures (to exclude meningitis) or neuroimaging. Therefore, if antimuscarinic poisoning

is considered, appropriate doses of physostigmine may be considered early in the course.

Physostigmine may be used for treatment of delirium. Multiple observational studies have found that patients with antimuscarinic poisoning have delirium controlled with physostigmine in a large proportion of cases, 79% to 96%.[2-4] Further, benzodiazepines controlled agitation in only 24%, were ineffective for reversal of delirium in antimuscarinic poisoned patients, and were associated with a longer time to recovery.[1] A prospective observational study of 154 poisoned patients reported the odds of delirium control with physostigmine were six times greater than non-antidotal treatment.[3] Importantly, a retrospective study of 1815 patients with antimuscarinic toxicity within a clinical toxicology registry found a significantly decreased rate of intubation (1.9% versus 8.4%, OR 0.21) with physostigmine alone when compared to other treatments.[4]

Repeat dosing of physostigmine may be necessary in severely symptomatic patients. In case series of patients with antimuscarinic poisoning receiving the antidote, 30% to 39% needed re-dosing within 5.5 hours and the longest time between the first and last dose was 6.5 hours.[5] This suggests patients that remain asymptomatic beyond 6.5 hours are unlikely to have recurrence of symptoms. Severely poisoned patients requiring frequent re-dosing, such as *Datura stramonium* poisoned patients, may benefit from an infusion of the antidote. We recommend that the dose for the intravenous infusion be the same dose required for reversal of delirium, given per hour. The infusion should be stopped every 4 to 6 hours to reevaluate for ongoing need of the antidote.

Adverse drug events associated with physostigmine are manifestations of excess acetylcholine at neuromuscular junctions and thus can approximate cholinergic poisoning.[5] Symptoms may include salivation, nausea, vomiting, diarrhea, bradycardia, bronchospasm, muscular weakness, or seizures.[2,5] Physostigmine use in antimuscarinic patients is associated with very low rates of adverse events (5% to 9%), with serious events attributable to the underlying overdose, rather than the antidote.[2,5] However, it is advisable to avoid physostigmine in patients who have had a seizure temporally related to the overdose. Adverse drug events may be more common in antimuscarinic poisoned patients treated with benzodiazepines compared with physostigmine, largely due to airway complications secondary to respiratory depression associated with high-dose benzodiazepines.

Physostigmine has traditionally been contraindicated in patients with tricyclic antidepressant (TCA) overdose. This is based on a few well-publicized case reports that subsequently discouraged use of the antidote. The consistent ECG manifestations in these cases were AV blockade and bradycardia. The role of physostigmine as an etiology of the subsequent cardiac dysrhythmias has been questioned given that tricyclic antidepressants have inherent cardiac toxicity. Many patients in case series examining the safety and efficacy of physostigmine were found to have ingested TCAs.[2,3] This suggests that the antidote may be used safely when tricyclic antidepressant toxicity is manifested as antimuscarinic delirium, which occurs at low doses or late in the course. We, however, do not recommend use of physostigmine in the treatment of acutely TCA poisoned patients with cardiovascular toxicity. Use of the antidote should be avoided in overdosed patients with bradycardia or AV block.

Overall, physostigmine should be considered as a safe diagnostic and therapeutic intervention in patients with antimuscarinic toxicity without overdose-induced seizure, AV blockade, or bradycardia, especially when the antimuscarinic-induced delirium places the patient or staff at risk.

DISPOSITION

Most patients do improve with supportive care alone (sedation, hydration, temperature control, and observation). Length of observation and need for admission depend on the agent, the dose, the intent, and the patient. Antimuscarinic agents slow gut motility, which increases the time to peak symptoms. As such, long-acting agents, plant seeds, or large ingestions should be considered for extended observation of up to 24 hours even if asymptomatic. Patients at extremes of age are at increased risk for toxicity and should be considered for observation over a similar period of time. Patients with an unreliable history or concern for self-harm should have extended observation and psychiatric consultation.

Observation at Home

Asymptomatic reliable patients with low-dose accidental exposures are safe to be observed at home by a trustworthy adult.

Emergency Department Observation

Patients with mild toxicity, normal mental status, normal vital signs, and small ingestions can potentially go directly home or may be observed in the ED for 4 to 6 hours for resolution of symptoms.

Hospital Admission

Patients with large ingestions or moderate toxicity (abnormal vital signs, altered mental status) should be observed for progression of toxicity or until symptoms improve. Ingestion of large amounts of pills or plant seeds should be expected to require prolonged observation (up to 24 hours) due to decreased gastrointestinal motility.

ICU Admission

Patients with agitated delirium, hyperthermia, dysrhythmia or seizures will benefit from intensive care unit admission for monitoring, redosing of reversal agents, and airway control if high doses of sedatives or additional physostigmine administration is necessary.

Consultations

Medical toxicology or poison center consultation should be considered when there are questions about exposure, diagnosis, or the appropriateness of antidotal therapy.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 140: QUESTIONS AND ANSWERS

1. A 21-year-old man presents after drinking an "herbal tea" with some friends. He reports visual hallucinations. He has a resting tachycardia and a mildly elevated temperature. On physical examination, he is noted to have dry mucous membranes, dry and flushed skin, and absent bowel sounds. In addition to certain plants, which of the following medications can also cause these symptoms?

a. Amiodarone
b. Clonidine
c. Diphenhydramine
d. Lidocaine
e. Morphine

Answer: C. This patient is experiencing the antimuscarinic toxidrome. In addition to the signs and symptoms described here, patients may also have mydriasis and bladder distention. Mental status can be agitated or depressed. Myoclonus or choreoathetoid movements can also be seen. Amiodarone can cause hypothyroidism or hyperthyroidism and skin discoloration, as well as several other long-term effects. Clonidine can cause dry mouth, drowsiness, bradycardia, and hypotension. Lidocaine can cause headaches, dizziness, confusion, tinnitus, and tremor, as well as bradycardia and hypotension. Morphine can cause respiratory cerebral depression, as well as miosis, bradycardia, and hypotension.

2. Many signs and symptoms of the antimuscarinic syndrome are similar to those of other toxic syndromes, including the sympathomimetic syndrome, serotonin syndrome, and neuroleptic malignant syndrome. Which of the following antimuscarinic findings is most likely to distinguish the antimuscarinic syndrome from the other syndromes listed?

a. Altered mental status
b. Altered movements
c. Dry skin
d. Fever
e. Mydriasis

Answer: C. All the other syndromes often have some degree of diaphoresis. Hyperthermia, altered mental status, and mydriasis can occur in all the named syndromes. Myoclonus can occur in the antimuscarinic syndrome, tremor in the serotonin syndrome, and rigidity in the neuroleptic malignant syndrome.

3. A 31-year-old woman presents with altered mental status after ingesting an unknown quantity of an unknown medication. Her vital signs are significant for tachycardia and hyperthermia. Her physical examination reveals mydriasis, dry mucous membranes, dry skin, decreased bowel sounds, and hypotension. Her electrocardiogram (ECG) reveals a wide QRS complex, at 130 msec, and prolonged QT interval. Which of the following medications is associated with this toxidrome?

a. Amitriptyline
b. Dextroamphetamine
c. Diphenhydramine
d. Fluoxetine
e. Lithium

Answer: A. This patient is experiencing many of the signs and symptoms of antimuscarinic syndrome. However, pure antimuscarinics rarely if ever cause cardiac dysrhythmias (other than sinus tachycardia). Tricyclic antidepressants (TCAs) frequently cause antimuscarinic signs and symptoms but also cause dysrhythmias. Although selective serotonin reuptake inhibitors, stimulants, and lithium can all cause similar signs and symptoms, electrocardiographic abnormalities such as those described here are rare.

4. Which diagnostic test should be performed in almost all patients presenting with the antimuscarinic syndrome?

a. Arterial blood gas analysis
b. Computed tomography (CT) scan of the brain
c. Electrocardiography
d. Electroencephalography
e. Urine drug screen

Answer: C. Patients with a clear presentation and mild symptoms do not necessarily require any diagnostic evaluation. However, patients with more severe symptoms should have measurements of serum electrolytes, renal function, creatine kinase, and glucose concentration performed. Electrocardiography is most helpful because cyclic antidepressants are a common cause of antimuscarinic symptoms and can cause fatal cardiac dysrhythmias. Arterial blood gas analysis might be helpful if the patient has respiratory depression. Head CT might be indicated in patients with altered mental status of unknown cause. Electroencephalography would be indicated only if there is a suspicion of unrecognized seizures. Urine drug screens are almost never helpful in determining treatment, especially in the case of antimuscarinic syndrome because they will not detect most of the medications responsible for this syndrome.

5. What is the best initial treatment of hyperthermia in patients with antimuscarinic syndrome?

a. Acetaminophen
b. Cooling blankets
c. Dantrolene
d. Evaporative cooling
e. Physical restraints

Answer: D. Evaporative cooling is the most effective and noninvasive way to decrease temperature. Death has occurred because of untreated hyperthermia in patients with antimuscarinic syndrome. Antipyretics such as acetaminophen are ineffective at reducing temperature because hyperthermia is not "fever." Dantrolene is useful in malignant hyperthermia but has no role in hyperthermia of other causes. Cooling blankets are ineffective. Physical restraints are likely to worsen the problem and to increase the risk of rhabdomyolysis and myoglobinuric renal failure. If a patient is dangerously agitated from antimuscarinic toxicity, physostigmine is the agent of choice to decrease agitation, muscle activity, and related metabolic activity that contribute to hyperthermia.

CHAPTER 140: QUESTIONS AND ANSWERS—cont'd

6. Which of the following medications crosses the blood-brain barrier and is potentially useful in the treatment of antimuscarinic syndrome?

a. Edrophonium
b. Metoclopramide
c. Neostigmine
d. Physostigmine
e. Pyridostigmine

Answer: D. Metoclopramide is an antiemetic and prokinetic medication that has no role in antimuscarinic syndrome. All of the other agents are acetylcholinesterase inhibitors, but only physostigmine crosses the blood-brain barrier and so it is the only drug that can reverse the central and peripheral effects of antimuscarinic medications. However, physostigmine can cause cardiac dysrhythmias and thus should be used carefully in patients with bradycardia or AV block.

7. Which of the following is a contraindication to physostigmine use in a patient with antimuscarinic syndrome?

a. Altered mental status
b. Bradycardia and atrioventricular (AV) blockade
c. Coexisting myasthenia gravis
d. Hyperthermia
e. Bladder distention and urinary retention

Answer: B. Physostigmine is an acetylcholinesterase inhibitor that is useful to reverse the effects of antimuscarinic medications. However, it is contradicted with narrow angle glaucoma, AV blockade, bradycardia, and seizures due to the causal overdose. The main benefit of physostigmine is to reverse the altered mental status and agitation caused by the antimuscarinic medication. Physostigmine is occasionally used to treat myasthenia gravis. Hyperthermia and urinary retention can occur as symptoms of the antimuscarinic syndrome, and although neither is directly treated with physostigmine, they are not a contraindication to its use.

Antidepressants

Michael D. Levine and Anne-Michelle Ruha

KEY CONCEPTS

- Although rarely used for depression, MAOIs are used in the treatment of Parkinson disease.
- Because serious symptoms can occur after a lengthy latent period, patients with reported MAOI overdose should be admitted for 24 hours, regardless of symptoms. Toxicity is characterized by tachycardia, hypertension, and CNS changes, and later cardiovascular collapse.
- The primary manifestations of TCA toxicity are seizures, tachycardia, hypotension, and intraventricular conduction delay. IV sodium bicarbonate should be administered for QRS prolongation.
- SSRIs are relatively benign in overdose and generally managed with supportive care alone.
- SNRI ingestions can result in seizures, tachycardia, and occasionally intraventricular conduction delay.
- The hallmark feature of serotonin syndrome is lower extremity rigidity with spontaneous or inducible clonus, especially at the ankles.
- Serotonin syndrome is primarily treated with supportive care, including discontinuation of the offending agent, and benzodiazepines.

PRINCIPLES OF TOXICITY

Depression is one of the most common medical conditions in the United States and is associated with significant morbidity. Worldwide, depression is the third leading cause of disability.[1] Whereas many treatment strategies are used in the management of depressed patients, pharmacotherapy remains a cornerstone of modern practice. Modern antidepressant therapy hinges on the monoamine hypothesis, which suggests that depressive symptoms are mediated through an imbalance of the dopaminergic, noradrenergic, and serotonergic systems.[1] Consequently, numerous antidepressant classes have emerged in an attempt to increase synaptic monoamine concentrations.

In the early 1950s, isoniazid and iproniazid were introduced for the treatment of tuberculosis. Shortly after, it was noted that these patients had improved mood, which was attributed to the ability of iproniazid to inhibit monoamine oxidase (MAO). Iproniazid subsequently became one of the first drugs used specifically as an antidepressant.[2] This led to the advent of other monoamine oxidase inhibitors (MAOIs). In 1956, the antidepressant effect of imipramine, a tricyclic agent, was recognized, and it was marketed the following year. The MAOIs and tricyclic antidepressants (TCAs) became the mainstay for treatment of depression for several decades until the advent of the safer selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

The morbidity of antidepressants in overdose varies greatly by specific class. Overall, however, there were more than 132,000 overdoses on antidepressants reported to United States poison control centers in 2017. Despite representing only 5.2% of calls, they accounted for 9.4% of fatalities.[3]

MONOAMINE OXIDASE INHIBITORS

MAO is located on the outer mitochondrial membrane and is responsible for breakdown of cytoplasmic catecholamines. Monoamine oxidase type A (MAO-A) primarily deaminates serotonin and norepinephrine; monoamine oxidase type B (MAO-B) primarily deaminates phenylethylamine.[2] Tyramine and dopamine are metabolized equally by both isoenzymes.[2] Whereas most tissues contain both isozymes, MAO-A is primarily found in the placenta, sympathetic nerve terminals, and intestinal mucosa; MAO-B is found primarily in platelets and the basal ganglia.

Drugs targeting the MAO system can act as specific or nonspecific inhibitors. The first-generation MAOIs are nonselective and irreversible. Drugs belonging to this class include phenelzine, isocarboxazid, and tranylcypromine. The second-generation MAOIs can preferentially inhibit either MAO-A or MAO-B.

MAOIs have fallen out of favor for treatment of depression due to side effects from adverse drug and food interactions. However, their use in treatment of Parkinson disease is increasing.

Drugs that selectively inhibit MAO-B disproportionately increase dopamine concentrations in the striatum.[2] Selegiline is an irreversible MAO-B inhibitor used in the treatment of Parkinson disease. Importantly, the selectivity for MAO-B is only present at low doses.[4]

Rasagiline is also an irreversible inhibitor of MAO-B and has similar clinical efficacy as selegiline.[5] Furthermore, unlike selegiline, which is metabolized to L-methamphetamine, rasagiline is not metabolized to an amphetamine derivative. Table 141.1 summarizes the MAO-inhibitors currently available for use in the United States. In addition to its antibiotic properties, linezolid, an oxazolidinone class antibiotic, is a reversible inhibitor of MAO, producing significant inhibition of MAO-A.

As a class, MAOIs are rapidly absorbed from the gastrointestinal tract and are bound extensively to plasma proteins. With overdose, the MAOIs initially stimulate release of neurotransmitters from the presynaptic neuron but later inhibit their release.

Clinical Features

Patients may develop toxicity from an MAOI either as a result of an interaction with a medication or food, or because of an overdose. Depending on the scenario that leads to toxicity, the clinical presentation may vary. Obtaining a thorough medication history is critical to establishing the diagnosis of MAOI toxicity. After acute overdose, a patient may remain asymptomatic for up to 24 hours before life-threatening toxicity develops. After this asymptomatic period, hyperadrenergic symptoms, including tachycardia, hypertension, and hyperthermia, can develop. Seizures, rhabdomyolysis, coma, and

TABLE 141.1 Summary of Monoamine Oxidase Inhibitor Agents Currently Available.

Generic Name	Route	Selectivity	FDA-Approved Uses
Tranylcypromine	Oral	Nonselective	Depression
Phenelzine	Oral	Nonselective	Depression
Isocarboxazid	Oral	Nonselective	Depression
Selegiline	Oral or transdermal patch	MAO-B at lower doses; MAO-A at higher doses	Depression, Parkinson disease

FDA, U.S. Food and Drug Administration; *MAO-A,* monoamine oxidase type A; *MAO-B,* monoamine oxidase type B.

ultimately cardiovascular collapse can occur once presynaptic catecholamines are depleted.

Patients who take nonselective MAOIs in therapeutic doses are at risk for food-drug interactions. Tyramine is an indirectly acting sympathomimetic amine that is present in foods including aged cheeses, red wine, smoked or pickled and aged meats. Usually, tyramine is metabolized in the gut and liver by MAO, rarely causing systemic effects. When MAO-A is inhibited, tyramine is absorbed systemically and enters presynaptic vesicles, ultimately causing release of norepinephrine and serotonin into the synapse, leading to a hypertensive crisis. This tyramine syndrome, which can occur within minutes to hours of ingestion of foods with high tyramine content, is characterized by headache, hypertension, flushing, and diaphoresis. This syndrome can occur up to 3 weeks after discontinuation of a nonselective MAOI. Although it is theoretically possible, this syndrome is rare with therapeutic use of MAO-B inhibitors. A drug-drug interaction may result when MAOIs are combined with other agents that have serotonergic effects. A variety of prescription and over-the-counter medications may interact with MAOIs to produce a constellation of symptoms referred to as *serotonin syndrome* (see later section). This syndrome may be life-threatening, therefore the use of medications with serotonin-potentiating activity should be avoided in patients taking MAOIs.

Differential Diagnoses

The differential diagnosis for MAOI toxicity includes sympathomimetic drugs of abuse such as cocaine and amphetamine derivatives, anticholinergic (or antimuscarinic) toxicity (e.g., diphenhydramine, cyclic antidepressants, anti-Parkinson drugs, and jimson weed), and methylxanthine toxicity (e.g., theophylline and caffeine). Other toxicologic considerations include acute withdrawal states (e.g., ethanol and benzodiazepines), neuroleptic malignant syndrome (NMS), and the serotonin syndrome from other serotonergic drug combinations. Nontoxicologic causes to consider include environmental hyperthermia or heatstroke, febrile illness from infectious causes (e.g., meningitis and encephalitis), pheochromocytoma, carcinoid syndrome, thyroid storm, and hypertensive emergency.

Diagnostic Testing

Laboratory abnormalities are nonspecific but can include hyperglycemia and leukocytosis, secondary to a hyperadrenergic state, and elevated creatine kinase due to rhabdomyolysis. Immunoassay urine drug screens that are commonly used in the emergency department do not detect MAOIs, and even gas chromatography–mass spectroscopy of urine may fail to detect the presence of an MAOI. Patients taking selegiline will test positive for methamphetamine because methamphetamine is a metabolite. Spectral analysis is needed to differentiate illicit methamphetamine from selegiline.

Symptomatic patients presenting after an MAOI overdose should have an electrocardiogram (ECG) to assess the QT and QRS intervals and for evidence of cardiac ischemia. Patients with chest pain should be evaluated for myocardial infarction. Measurement of serum glucose and electrolytes are indicated if the patient is obtunded. Because of the potential for intracranial hemorrhage in the setting of severe MAOI-induced hypertension, patients with a seizure or focal neurologic deficit should undergo a non–contrast-enhanced head computed tomography (CT) scan.

Management

As with most intoxications, supportive care is paramount. Central nervous system (CNS) excitation should be treated with intravenous (IV) administration of benzodiazepines such as lorazepam and diazepam in titrated doses. Lorazepam may be given IV in a dose of 1 to 4 mg, depending on the severity of symptoms. Dosing can be repeated at 5- to 15-minute intervals for patients with severe toxicity. Alternatively, diazepam, 5 mg IV every 5 to 10 minutes, can be given until the patient is stabilized. Hyperthermia should be treated with external cooling using evaporative techniques and strategic ice packing. Antipyretics such as acetaminophen or nonsteroidal antiinflammatory medications have no role in the management. Hyperthermia that persists, despite administration of benzodiazepines and external cooling measures, may need intubation, ventilation, and chemical paralysis with a nondepolarizing neuromuscular blocker, such as rocuronium (0.6 to 1.2 mg/kg IV). The use of succinylcholine is discouraged as this may cause hyperkalemia if rhabdomyolysis has occurred, and fasciculation from succinylcholine may further increase metabolic heat production. Furthermore, many of these patients are already acutely hyperkalemic, which is a relative contraindication to succinylcholine. Mild hypertension should not be treated, but sustained severe hypertension (e.g., systolic blood pressure exceeding 200 mm Hg or a diastolic exceeding 100 mm Hg) is best managed with a rapid onset, short-acting agent such as phentolamine (titrated slowly by repeated IV doses of 1 mg every 3 minutes) or nitroprusside (0.25 to 0.5 mcg/kg/min by IV infusion). Treatment should target a 25% reduction in the mean arterial pressure. Hypotension should first be managed by volume resuscitation with normal saline. Persistent or severe hypotension requires treatment with infusion of a direct-acting catecholamine such as norepinephrine or epinephrine. Because hypotension and cardiovascular collapse after MAOI overdose are due to catecholamine depletion, the use of indirect-acting agents such as dopamine are not likely to be beneficial. Extracorporeal elimination methods such as hemodialysis are also unlikely to be beneficial because of extensive protein binding and large volume of distribution of MAOIs.

Patients presenting with a tyramine reaction may have spontaneous resolution of symptoms within 6 hours. Severe hypertension higher than 200 mm Hg systolic with symptoms such as headache, flushing, or chest pain should be treated with phentolamine or nitroprusside. Patients with persistent severe headache and hypertension should have a head CT scan to assess for intracranial hemorrhage. Patients with chest pain should be evaluated for myocardial infarction (see Chapter 64).

Treatment of suspected serotonin syndrome is supportive (see later section) and consists primarily of benzodiazepine administration and active cooling measures.

Disposition

Patients presenting with an MAOI overdose should be admitted to a monitored setting for 24 hours due to the risk of delayed, rapid deterioration and development of hyperadrenergic symptoms. Asymptomatic patients chronically taking an MAOI who present out of concern for a possible drug-food interaction can be discharged after 6 hours if no signs of toxicity develop over that period. The care of any patient with suspected toxicity from an MAO inhibitor should be discussed with a medical toxicologist or poison control center (800-222-1222).

TRICYCLIC ANTIDEPRESSANTS

Principles of Toxicity

In the 1950s, imipramine became the first TCA used for the treatment of depression. Until the introduction of the SSRIs, TCAs remained the primary agents for treatment of depression. The therapeutic benefit of TCAs results from monoamine reuptake inhibition.[6] Whereas use of TCAs for treatment of depression has waned, use for other conditions, including treatment of migraines, various neuropathies, trigeminal neuralgia, and nocturnal enuresis has increased.

Clinical Features

Cyclic antidepressant toxicity can result from overdose of a TCA or drug interactions. Overdose is more commonly associated with life-threatening toxicity, but toxic effects can also occur when a TCA is combined with drugs that impair its metabolism through cytochrome P450. Tertiary amine TCAs such as amitriptyline, imipramine, and clomipramine are substrates of CYP2C19 and CYP1A2. Doxepin is also a substrate for CYP2D6. Drug-induced inhibition of these enzymes as well as genetic polymorphisms of these isoenzymes can decrease metabolism of these drugs, resulting in unexpectedly high serum concentrations and clinical toxicity. Conversely, inhibition of CYP2D6 and other P450 enzymes by these TCAs can also lead to increased serum concentrations of other drugs metabolized by the same enzymes. Because desipramine and nortriptyline are only weak CYP2D6 inhibitors, they cause fewer drug interactions. Another toxicity that can occur with TCAs is serotonin syndrome, which can result when a TCA is combined with another serotonergic drug such as an MAOI or SSRI.

Following a TCA overdose, clinical toxicity typically begins within 1 to 2 hours. When smaller quantities are ingested, symptoms may be minimal and resolve quickly; patients who take large amounts may deteriorate rapidly soon after ingestion. Severely poisoned patients typically have symptoms within 1 to 2 hours after ingestion, but nearly always by 6 hours after ingestion. Early cyclic antidepressant toxicity (within the first 2 hours) is primarily characterized by anticholinergic effects. These findings include dry mucosal membranes, urinary retention, and hot dry skin. Despite having potent antimuscarinic properties, the pupils are often small due to competing *alpha* effects. Patients may be alert and confused, severely agitated, hallucinating, or even deeply comatose. Speech is often rapid and mumbling in character. Seizures may occur and are likely to be multifactorial, resulting from increased synaptic monoamines, sodium channel inhibition, and gamma-aminobutyric acid (GABA) receptor antagonism. Early hypertension is common from the anticholinergic effects of the TCA and excess norepinephrine in the synapse from blockade of norepinephrine reuptake, but hypotension may also be due to alpha-receptor antagonism and also norepinephrine depletion.

Later (2 to 6 hours post ingestion), myocardial depression resulting from severe sodium channel antagonism may also lead to hypotension and bradycardia. Significant sodium channel blockade is associated with widening of the QRS interval. The degree of widening is prognostic for both arrhythmias and seizures.[7] Tricyclic antidepressants also block potassium efflux, which leads to a prolonged QT interval. Clomipramine and amitriptyline are especially associated with QT prolongation. Furthermore, clomipramine is associated with significant QT dispersion, which has been shown to be a risk for ventricular arrhythmias and mortality.[8] With severe poisoning, the combined effects of the TCA on various receptors and ion channels lead to depressed level of consciousness, seizures, hypotension, and wide-complex cardiac arrhythmias.

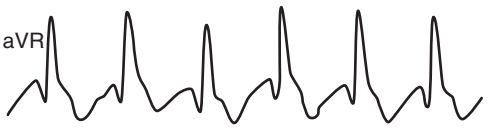

Fig. 141.1 Augmented vector right *(aVR)* demonstrating tall R wave.

Chronic toxicity from drug interactions or decreased ability to metabolize the drug because of genetic polymorphism may be manifested in a less evident fashion. Confusion, urinary retention, and prolonged corrected QT (QTc) interval are common. Chronic toxicity presents more gradually and should be considered in any confused patient taking therapeutic doses of a cyclic antidepressant.

Differential Diagnoses

Many agents with anticholinergic properties produce similar clinical features as TCAs. Diphenhydramine and carbamazepine, in particular, can also produce seizure and sodium-channel blockade. Agents that produce sympathomimetic toxicity (e.g., cocaine, amphetamines) or serotonin syndrome (e.g., SSRIs, MAOIs) should be included in the differential diagnosis. Other drugs with sodium channel blockade, and hence a wide QRS complex, include the Vaughn-Williams class IA antidysrhythmics (e.g., procainamide, disopyramide, quinidine) and class IC antidysrhythmics (e.g., flecainide, encainide, and propafenone), along with amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine. Propoxyphene and propranolol can also cause an intraventricular conduction delay by sodium channel blockade but typically cause a bradycardic rhythm rather than a tachycardic rhythm. The constellation of early anticholinergic symptoms, decreased level of consciousness followed by seizures, wide QRS and cardiovascular collapse, is highly suggestive of acute TCA overdose.

Diagnostic Testing

After overdose, the ECG can yield prognostic information. Early anticholinergic effects cause sinus tachycardia, which occurs uniformly before other effects. Whereas the serum tricyclic concentrations are not particularly beneficial in predicting adverse events, the ECG is prognostic. Historically, it is felt that QRS duration longer than 100 milliseconds is predictive of seizures, whereas QRS duration longer than 160 milliseconds is predictive of ventricular dysrhythmias, but hard evidence does not exist for either of these assertions. Additional findings on the ECG include a rightward shift of the terminal 40 milliseconds of the QRS complex seen as an R wave in augmented vector right (aVR) longer than 3 milliseconds. Figure 141.1 demonstrates lead aVR following a tricyclic ingestion. QT prolongation has less prognostic value than the QRS duration.

Urine drug of abuse screens commonly test for the presence of TCAs, but a positive test result suggests only use of a TCA or another xenobiotic that cross-reacts with the screen (e.g., antipsychotic medications, antimuscarinic agents, carbamazepine, or the muscle relaxant cyclobenzaprine). Quantitative serum tricyclic levels do not correlate well with severity of illness.

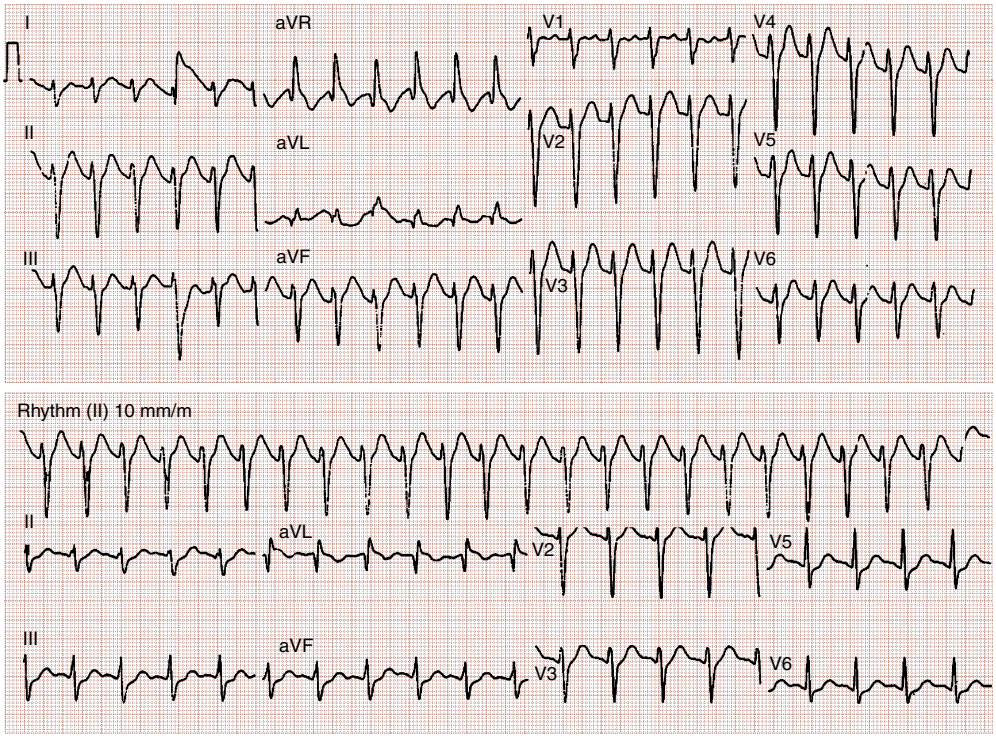

Fig. 141.2 *Top,* Initial 12-lead electrocardiogram (ECG) demonstrating substantial intraventricular conduction delay (QRS 141 milliseconds). *Bottom,* Repeated ECG after bicarbonate therapy. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

Management

Ensuring stability of the airway, with adequate ventilation, and volume repletion are of primary importance. There are no randomized controlled trials demonstrating improved patient-oriented outcomes and decreased mortality with activated charcoal administration in patients with cyclic antidepressant overdose. Nonetheless, because of the high lethality of the acute overdose, a patient who presents within 1 hour after an overdose and who is awake, alert, and cooperative and is not exhibiting any signs of toxicity (e.g., no tachycardia or intraventricular conduction delay) can be given oral activated charcoal. Patients who are not cooperative or who are not willing to drink charcoal should not have a nasogastric tube inserted for the sole purpose of administering charcoal. Due to risk of seizures with subsequent aspiration, activated charcoal is not routinely recommended in patients with an unprotected airway who are already exhibiting toxicity. There is no role for gastric lavage.

Patients with sinus tachycardia alone do not need specific treatment but should be monitored to detect QRS widening early in the clinical course. Early hypertension should not be treated. Hypotensive patients should first receive fluid resuscitation with an isotonic crystalloid. Patients who remain hypotensive should be treated with direct-acting vasopressors such as norepinephrine and epinephrine.

Hypertonic sodium bicarbonate is given only to treat specific evidence of sodium channel blockade such as a wide QRS and ventricular dysrhythmias.[7] Sodium bicarbonate should not be given strictly to treat tachycardia. Recommendations regarding the specific administration of sodium bicarbonate vary. We recommend a conservative approach by administering a bolus of 1 to 2 mEq/kg hypertonic sodium bicarbonate intravenous push (IVP) if the QRS interval exceeds 100 milliseconds. This dose may be repeated in 5 to 10 minutes if the QRS does not narrow. After IV bolus, a sodium bicarbonate infusion can be used to maintain a serum pH between 7.50 and 7.55. Such an infusion can be created by the addition of 150 mEq sodium bicarbonate and 850 mL of dextrose 5% in water (D5W). The infusion should be created with a 5% dextrose solution, and not normal saline, due to the risk of hypernatremia with the latter. The infusion should be administered at twice the normal maintenance rate, titrating to QRS width and serum pH. Alternatively, infusions of 1 mEq sodium bicarbonate per milliliter of fluid may be used if volume overload is a concern. Additional IV boluses of sodium bicarbonate may be necessary if the QRS widens. The use of a bicarbonate-containing infusion should not be a substitute for IV sodium bicarbonate boluses for the initial treatment of intraventricular conduction delay. Figure 141.2 demonstrates a 12-lead ECG from a patient poisoned with a TCA before and after sodium bicarbonate therapy. If ventricular dysrhythmias persist despite maximal alkalinization (pH > 7.55), 3% hypertonic saline (in an adult) can be used. Class Ia or Ic antidysrhythmics should be avoided. Seizures are best treated with an IV benzodiazepine (lorazepam 1 to 4 mg IVP; diazepam 5 to 10 mg IVP) along with sodium bicarbonate. Refractory seizures can be treated with phenobarbital (15 to 20 mg/kg IV loading dose). Because seizure leads to acidosis and worsens the cardiac status, patients with intractable seizures who do not respond to benzodiazepines or phenobarbital should be rapidly paralyzed, intubated, and mechanically ventilated to prevent increasing metabolic acidosis.

Physostigmine, the antidote of choice for pure anticholinergic toxicity (see Chapter 140), is considered by many experts to be relatively contraindicated in the management of TCA overdose. Asystole has been reported after physostigmine use in TCA toxicity, particularly in patients with bradycardia and AV block. It is not advised to administer this agent to patients with QRS or QTc prolongation following TCA overdose. However, we recommend it be considered in patients with delirium of unclear etiology who are therapeutically taking anticholinergic agents and in whom toxicity is suspected, but only if there is no

bradycardia, no history of seizures, and the PR, QRS, and QTc intervals are normal. Physostigmine (1 to 2 mg slow IV infusion over 5 minutes in adults) should be given with caution in a monitored setting, because it may exacerbate bradycardia, AV block, and seizures related to the overdose (see Chapter 140).

Intravenous lipid emulsion (ILE) therapy has gained interest recently for reversal of toxicity caused by lipophilic drugs, including TCAs.[9-10] Although the exact mechanism of ILE is not clearly defined, it likely involves redistribution of a lipophilic drug from the tissue receptors back into the vascular compartment in the context of a large bolus of concentrated lipid solution, the so-called *lipid sink phenomenon.*[10] Other mechanisms such as enhanced cardiac metabolism are also possible explanations. Because not all studies reveal beneficial effects from ILE in the treatment of TCA toxicity and due to the potential for iatrogenic harm, its use is currently reserved for life-threatening toxicity that remains refractory to sodium bicarbonate administration.[11] ILE should be administered only on advice of a medical toxicologist or regional poison center. If ILE is to be administered, there are several different dosing strategies. We recommend 1.5 mL/kg of a 20% lipid solution over 2 to 3 minutes. This bolus can be repeated once in 5 minutes if there is no clinical improvement. If clinical improvement does occur, the bolus may be followed by an infusion of 0.25 mL/kg/min.[12]

Complications of ILE include extreme lipemia resulting in interference with laboratory blood tests (complete blood counts, chemistries, and coagulation studies), as well as acute pancreatitis, and acute respiratory distress syndrome.[13]

Disposition

If the heart rate has not exceeded 100/minute for a sustained period of time (at least 10 to 15 minutes), ECG intervals are normal, level of consciousness is normal, and no seizures have developed within 6 hours of a TCA overdose, it is unlikely that toxicity will occur. The patient can be medically cleared from the ED for psychiatric evaluation and disposition if needed. Patients with signs of cyclic antidepressant cardiotoxicity, seizures, or coma should be admitted to an intensive care unit.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Principles of Toxicity

In recent years, SSRIs have become the mainstay for treatment of depression. As implied by their name, these drugs prevent the presynaptic reuptake of serotonin without affecting the synaptic concentration of other monoamines. Some of the more commonly used SSRIs available today include escitalopram and its enantiomer citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

SSRIs have a wide therapeutic index. Most SSRIs undergo hepatic metabolism. There is considerable variability in their half-life; however, paroxetine has one of the shortest half-lives (17 hours) compared with fluoxetine, which has one of the longest half-lives (53 hours for parent drug, 240 hours for active metabolite).

Clinical Features

Overdoses of SSRI agents alone are usually well-tolerated and rarely fatal, with ingestions of up to 30 times the daily dose associated with few or no symptoms. Gastrointestinal upset and mild CNS depression can occur with large overdoses. Coma and seizures are rare, with incidences of approximately 2% for each. The incidence of serotonin syndrome after SSRI overdose is variable, but remains relatively uncommon in most series.

Citalopram overdose deserves special mention because of a reported higher rate of QTc prolongation and seizures compared with other SSRIs.[14] There has been some suggestion that the QT prolongation may be delayed with citalopram ingestion. However, there are not convincing data to support this delayed onset of toxicity. The risk of QT prolongation at therapeutic dosing may be over-stated.[15] In overdose, however, QT prolongation does appear to be dose-dependent. Despite a risk of QT prolongation, torsade de pointes associated with citalopram is relatively rare.[16] Escitalopram appears to be less toxic than citalopram, with a lower incidence of seizure and QT prolongation. Therapeutic administration of SSRIs may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Most cases of hyponatremia develop shortly after commencing use. The overall incidence is not well documented. Studies have documented that approximately 12% of elderly patients taking an SSRI may have SIADH.

Abrupt discontinuation of an SSRI may be associated with a mild withdrawal state, in which individuals feel anxious, jittery, and have some gastrointestinal upset. This withdrawal syndrome is not life-threatening.

Differential Diagnoses

The differential diagnosis for SSRI toxicity includes toxicity due to cyclic antidepressants, MAOIs, sedative hypnotics (e.g., benzodiazepines, barbiturates), SNRIs, neuroleptic agents, and atypical antipsychotics.

Diagnostic Testing

Diagnosis of SSRI toxicity is often dependent on obtaining a history of overdose. Clinical features of toxicity are similar to those seen after overdose of many other toxicants. An ECG can assess for conduction disturbances, especially QT prolongation. Specific SSRI levels are not performed by most hospital laboratories and do not influence management, although they may help confirm overdose retrospectively. A standard urine drug of abuse screen will not detect an SSRI.

Management

Treatment of an SSRI overdose is largely supportive. Activated charcoal has not been demonstrated to change outcomes following SSRI overdose but may be considered if the patient presents alert and cooperative within an hour of ingestion. Only rarely will patients require tracheal intubation because of loss of airway reflexes. For adult patients with a QTc interval greater than 500 msec, 2 grams of IV magnesium sulfate should be administered. IV administration of benzodiazepines (1 to 4 mg/kg of lorazepam via IV push; or 5 to 10 mg/kg diazepam via IV push) should be used to treat agitation and seizures.

Disposition

Patients who overdose with an SSRI who are asymptomatic after 6 hours of monitoring are unlikely to have toxicity. A patient who presents following an SSRI ingestion can be medically cleared after a six-hour observation period, assuming the patient has remained asymptomatic with a normal ECG. For citalopram or escitalopram, we recommend a repeat ECG be performed at the six-hour mark prior to providing medical clearance. Some advocate for extending this observation period to 12 hours following ingestions of more than 1000 mg of citalopram or escitalopram. Symptomatic patients should be admitted to a monitored care setting. Those patients with an intent of self-harm should be evaluated by a psychiatric service.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS AND NOREPINEPHRINE REUPTAKE INHIBITORS

Principles of Toxicity

Duloxetine, venlafaxine, desvenlafaxine, milnacipran, and levomilnacipran are collectively referred to as *serotonin-norepinephrine*

reuptake inhibitors (SNRIs). All of these agents, except milnacipran, are approved for use in the United States for treatment of major depression. Milnacipran, despite being used as an antidepressant in Europe, is only approved for treatment of fibromyalgia in the United States. Some of these agents are also approved for other disorders. For example, venlafaxine can be used to treat panic disorder, generalized anxiety disorder, or social phobia, whereas duloxetine is also used to treat chronic musculoskeletal pain, diabetic neuropathy, fibromyalgia, and generalized anxiety disorder. Venlafaxine and its active metabolite desvenlafaxine are both available medicinally. The SNRIs may also produce dose-dependent inhibition of sodium channels. Reboxetine is an isolated norepinephrine reuptake inhibitor. It is also used for the treatment of depression.

Clinical Features

Unlike the SSRIs, which are relatively benign in overdose, ingestion of any of the SNRIs can be dangerous. Fatal ingestions have been described with virtually all of the SNRIs. The SNRIs may produce hyperadrenergic symptoms, including tachycardia and hypertension.[16] Rarely, hypotension can be observed after massive overdose.[17] Acute cardiac dysfunction, including impaired biventricular function, has been demonstrated following acute overdose.[17-18] Seizures can occur following ingestion of the SNRIs.[16] Unlike bupropion, however, which can have delayed onset of seizures, the onset of seizures following an SNRI ingestion is expected to occur within the first several hours post ingestion.

Rhabdomyolysis has been reported independent of seizure activity following ingestions of venlafaxine. Venlafaxine and desvenlafaxine overdoses can result in cardiovascular toxicity, manifesting as intraventricular conduction delay and ventricular dysrhythmias. Venlafaxine has also been associated with QT prolongation. In addition, based on their mechanism of action, serotonin syndrome may develop after ingestion of these agents.[16]

Differential Diagnoses

The differential diagnosis for SNRI toxicity includes toxicity due to cyclic antidepressants, MAOIs, sedative hypnotics, SSRIs, neuroleptic agents, bupropion, and atypical antipsychotic medications.

Diagnostic Testing

Specific drug levels are not rapidly available and do not aid management. An ECG can detect QRS or QT interval prolongation. SNRIs are not detected by urine drug of abuse screens, but venlafaxine and desvenlafaxine may be associated with a false-positive phencyclidine screen.[19] In cases of a venlafaxine ingestion, creatinine kinase and renal function tests should be obtained to assess for acute rhabdomyolysis. As with any multidrug ingestion, serum acetaminophen and salicylate levels should be measured.

Management

Care of the patient with an SNRI overdose is supportive, with focus on ensuring airway patency and adequate ventilation. While oral activated charcoal has not been clearly demonstrated to be beneficial in the setting of an SNRI overdose, if the patient presents within an hour and is awake and alert and cooperative, the use of charcoal can be considered. Hypotension (systolic blood pressure <90 mm Hg) should first be treated with a 20 cc/kg bolus of 0.9% normal saline. This bolus can be repeated if necessary. If hypotension still persists, a direct-acting vasopressor (such as epinephrine or norepinephrine) should be used. Intraventricular conduction delay with a widened QRS on ECG should be treated with sodium bicarbonate infusions (as previously described in the tricyclic antidepressants section). First-line treatment of seizures is the IV administration of a benzodiazepine such as lorazepam, diazepam, or midazolam.

Disposition

Patients who are asymptomatic with a normal 12-lead ECG after an observation period of 6 hours can be cleared for discharge after appropriate psychiatric consultation. Patients with an intentional ingestion who develop manifestations of neurologic or cardiovascular toxicity (such as sedation, hypotension, or tachycardia) should be observed in a monitored setting. Those with profound CNS depression or hemodynamic instability warrant intensive care unit admission.

SEROTONIN MODULATORS AND STIMULATORS

Vilazodone and vortioxetine belong to a new class of antidepressants, referred to as serotonin modulators and simulators (SMS). While both of these drugs inhibit serotonin reuptake, they are also partial agonists at various serotonin receptors.[20-21] Clinical experience with these drugs in overdose is relatively limited. Unlike the SSRIs, in which serotonin syndrome is unlikely to occur with a single-agent ingestion, there are multiple case reports in which serotonin syndrome has been reported following isolated vilazodone ingestions.[21] In addition, gastrointestinal upset (e.g., vomiting), tachycardia, central nervous system depression, and seizures have been reported.[21-22]

The toxicologic differential diagnoses of these agents includes toxicity from the SNRIs, tricyclic antidepressants, bupropion, and trazodone. The primary aspects of management include ensuring the patient has adequate airway patency. Severe central nervous system depression may warrant intubation and mechanical ventilation. Seizures, should they occur, should be treated with benzodiazepines (e.g., lorazepam, diazepam, or midazolam). Hypotension should be first treated with rapid crystalloid fluid resuscitation. Refractory hypotension should be treated with a direct-acting vasopressor, such as norepinephrine or epinephrine. Patients who remain asymptomatic after a six-hour observation period can be medically cleared for psychiatric disposition.

MISCELLANEOUS ANTIDEPRESSANTS

Bupropion

Bupropion is an atypical antidepressant, belonging to a unique class (aminoketone).[23] It is widely used not only as an antidepressant, but also for smoking cessation. The primary mechanism of action is inhibition of dopamine and norepinephrine reuptake, but it also acts as a noncompetitive inhibitor of nicotinic acetylcholine receptors.[23]

Seizure activity is a dose-dependent phenomenon and can occur with therapeutic dosing or overdose of bupropion.[24] Seizures are relatively common after overdose and occur in approximately 30% of cases, the majority of which are initially tachycardic.[24-26] Sinus tachycardia, tonic-clonic seizures, and agitation are common after overdose.[24-26] Unlike many agents that produce seizures acutely following overdose, ingestion of extended-release bupropion can produce delayed onset seizures. The risk of seizures is not only dose dependent, but also preparation dependent; the immediate release is the least likely to cause seizures, whereas the XL preparation is the most likely.[27] Both QRS and QT prolongation can occur with toxicity.

Treatment is primarily supportive. Activated charcoal has not been clearly demonstrated to be beneficial in this setting, but its use can be considered if the patient is awake and alert and presents within one hour of ingestion. Patients with large overdoses may require endotracheal intubation and mechanical ventilation because of CNS and respiratory depression. Lorazepam, diazepam or midazolam are effective for terminating seizures. If seizures persist, phenobarbital or other GABA

agonists may be used. Sodium bicarbonate (150 mEq IV or 3 mEq/kg for pediatric patients) should be administered for any QRS prolongation, although because the mechanism of action of intraventricular conduction delay appears to be related to gap junction inhibition, rather than to sodium channel blockade, it tends to be less responsive to sodium bicarbonate therapy. Resuscitative ILE therapy, as well as extracorporeal membrane oxygenation (ECMO), has been described in anecdotal case reports of severely poisoned patients who are refractory to standard management measures.[28] Intravenous lipid emulsion should be undertaken only on the advice of a medical toxicologist or regional poison center (as described in the tricyclic antidepressant section).

Although pediatric patients may have seizures with accidental or exploratory ingestions, the risk of seizures is much less than in older children, where the exposure is typically the result of a suicidal attempt.[29] Nonetheless, because of the risk of delayed seizures, we recommend admission and monitoring for adult patients who ingest more than 450 mg of an ER or XL preparation or more than 8 mg/kg in pediatric patients.

Trazodone

Trazodone is an atypical antidepressant that is used for its hypnotic and anxiolytic properties. In addition to weakly inhibiting serotonin reuptake, it is a relatively strong blocker of the alpha$_1$ receptor.[30] Its use as an antidepressant has been historically somewhat limited by adverse effects, including orthostatic hypotension, priapism, and sedation. Priapism is probably a result of trazodone's alpha-antagonism, with an incidence of 1/100 to 1/10,000. Whereas many drugs are associated with priapism, particularly those with alpha-antagonism or inhibition of type 5 phosphodiesterase, trazodone is responsible for a disproportionate number of reported cases.

After overdose, sedation and hypotension due to vasodilation are expected. Priapism is not typically associated with overdose of trazodone. Prolongation of the QT interval may occur. Management is supportive, with airway protection, IV fluid resuscitation, and use of alpha-adrenergic agonists such as norepinephrine as needed for refractory hypotension. Activated charcoal has not been clearly demonstrated to be beneficial in this setting. If the patient is awake and alert, however, and presents within one hour of ingestion, its use can be considered.

Nefazodone

Nefazodone, a phenylpiperazine antidepressant, is structurally similar to trazodone. It acts as an antagonist at the 5-HT$_{2A}$ receptor, and chronic administration is associated with receptor downregulation. Nefazodone is associated with weak inhibition of norepinephrine and serotonin reuptake. It is metabolized to several active metabolites. After overdose, most patients remain asymptomatic. Antagonism of the alpha$_1$ receptor is responsible for the orthostatic hypotension that can occur. Treatment is primarily supportive.

SEROTONIN SYNDROME

Principles of Toxicity

Serotonin syndrome is a potentially lethal condition resulting from excess serotonin accumulation in the synaptic cleft.[31] This syndrome may occur after an isolated overdose of an SSRI, but it is more commonly a result of drug interactions, especially with drug combinations that raise synaptic serotonin concentrations by different mechanisms. Agonism of the 5-HT$_{2A}$ receptor appears to be largely responsible for this condition in humans.[31] Whereas numerous xenobiotics have been implicated in causing serotonin syndrome, some of the most common are the SSRIs, SNRIs, TCAs, MAOIs, dextromethorphan, amphetamines, and designer amphetamines, including methylenedioxymethamphetamine ("ecstasy"), cocaine, meperidine, lithium, tramadol, buspirone, lysergic acid diethylamide (LSD), and linezolid (Box 141.1). Serotonin syndrome is more likely to develop when drugs from different classes are combined, resulting in increased serotonin in the synaptic cleft from different mechanisms (e.g., increased release and impaired uptake).

BOX 141.1 Xenobiotics Commonly Implicated in Serotonin Syndrome

Analgesics: Tramadol, meperidine, pentazocine
Drugs of abuse: Cocaine, amphetamine derivatives (e.g., methylenedioxymethamphetamine), lysergic acid diethylamide (LSD)
Monoamine oxidase inhibitors (MAOIs) (e.g., isocarboxazid, linezolid, phenelzine, moclobemide, selegiline)
Miscellaneous: Dextromethorphan, lithium, metoclopramide, St. John's wort
Selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., milnacipran, venlafaxine)
Tricyclic antidepressants (TCAs) (e.g., amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline)

Clinical Features

Serotonin syndrome is described as a triad of mental status changes, autonomic instability, and increased neuromuscular activity, but the condition exists along a spectrum; some patients have only mild tremor and diarrhea, whereas others exhibit life-threatening manifestations. Clinical features may include tremor, akathisia, gastrointestinal illness, clonus (inducible or spontaneous), rigidity, fever, seizures, and autonomic instability. The clonus is typically more pronounced in the lower extremities (most notably the ankles) than in the upper extremities. After an acute overdose of a serotonergic agent, symptom onset typically begins within several hours. With proper treatment, symptoms usually resolve within 24 hours but can persist for several days in severe cases.

Differential Diagnoses

The differential diagnosis of serotonin syndrome includes NMS, malignant hyperthermia, sympathomimetic toxicity, anticholinergic toxicity, strychnine toxicity, bupropion toxicity, and GABA withdrawal. Nontoxicologic considerations include thyroid storm, meningitis, idiopathic seizure, intracranial hemorrhage, and hypoglycemia.

Diagnostic Testing

There is no "gold standard" for the diagnosis of serotonin syndrome. Laboratory studies cannot be used to confirm or to exclude the diagnosis of serotonin syndrome. Rhabdomyolysis and hyperkalemia can occur as a result of increased neuromuscular activity, and these should be screened for as indicated on the basis of the clinical examination.

The Sternbach criteria were developed in the 1990s and became the first widely used diagnostic algorithm. Additional criteria, including the Hunter criteria and the Boyer and Shannon criteria, have been developed. The Hunter criteria (Box 141.2) appear to be more sensitive than the Sternbach criteria, with fewer false positives.

In general, a history of overdose or of recently starting an additional serotonergic agent along with clinical findings consistent with this diagnosis should raise the concern for serotonin syndrome.

BOX 141.2 The Hunter Criteria for Serotonin Syndrome

In the setting of exposure to a known serotonergic agent, serotonin syndrome can be diagnosed by the presence of any of the following:

- Spontaneous clonus
- Inducible clonus *and* agitation or diaphoresis
- Ocular clonus *and* agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonic with temperature >38°C *and* ocular clonus or inducible clonus

Management

Management is supportive, with removal of the offending agents being paramount. Mild cases may require only discontinuation of the agent and low-dose benzodiazepines (e.g., 5 to 10 mg of IV diazepam) for rigidity. More severe cases may require IV fluid resuscitation and large doses of benzodiazepines (e.g., 10 to 20 mg of IV diazepam, with titration in 10 mg aliquots) or other sedative-hypnotic agents to gain control of symptoms. Cyproheptadine, a 5-HT_{2A} antagonist, is an adjunctive therapy for more severe cases, but there are no randomized controlled trials demonstrating improved benefit with cyproheptadine over supportive care and benzodiazepines alone. If cyproheptadine is available, the syndrome is severe or refractory to treatment, and the clinician is confident with the diagnosis, we recommend a single oral dose of 12 mg of cyproheptadine for patients with serotonin syndrome. If anticholinergic toxicity remains on the differential diagnosis, cyproheptadine should not be given, because it can worsen anticholinergic toxicity. Patients with hyperthermia that does not respond promptly to sedation with benzodiazepines should receive a nondepolarizing neuromuscular blocking agent (e.g., rocuronium) during rapid sequence intubation. Typically, only a single dose of a long-acting neuromuscular blocking agent is required. If additional doses are required, we recommend a single IV dose of 10 mg of vecuronium.

Disposition

Patients with all but the mildest forms of serotonin syndrome should be admitted to a monitored care setting. Those with unresponsiveness, autonomic instability, hyperthermia, and rigidity should be admitted to an intensive care unit.

DISCONTINUATION SYNDROMES

After the abrupt discontinuation of certain antidepressants, patients can experience a withdrawal, or discontinuation, syndrome. Unlike potentially life-threatening GABA withdrawal from ethanol or benzodiazepines, the discontinuation syndrome from antidepressants is rarely life-threatening but can result in significant discomfort. One notable exception involves neonates born to mothers using TCAs, who can have serious, potentially life-threatening withdrawal. Antidepressant discontinuation syndrome does not always develop, but when it does, it typically starts within the first 3 days after therapy is stopped. This syndrome is difficult to distinguish from recurrence of the underlying depression, which has overlap of some symptoms.

Antidepressant discontinuation syndrome occurs with all major classes of antidepressants. Withdrawal from SSRIs involves both physical and psychological symptoms, most commonly nausea, lethargy, headache, and dizziness. The symptoms can be divided into six general categories: dysequilibrium (e.g., dizziness, ataxia), sleep disturbances, gastrointestinal symptoms, affective symptoms (e.g., irritability, anxiety), sensory symptoms (e.g., electric shock–like sensation, paresthesias), and general somatic symptoms (e.g., headache, tremor, anorexia, diaphoresis). The syndrome is more common after discontinuation of drugs with shorter half-lives (e.g., paroxetine) than of drugs with longer half-lives (e.g., fluoxetine). TCA withdrawal is similar to SSRI withdrawal, although sensory abnormalities and equilibrium disturbances are rare with TCA discontinuation. Non–life-threatening arrhythmias are rare after discontinuation of the TCAs.

Patients with mild withdrawal symptoms do not require any specific therapy. For those patients with more severe symptoms, treatment involves restarting of the antidepressant, followed by a gradual tapering dose.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 141: QUESTIONS AND ANSWERS

1. A 42-year-old woman presents after ingesting an unknown number of pills in a suicide attempt. She does not know the name of the medication she ingested but knows it is an antidepressant. She denies taking any co-ingestants. Currently, she has no complaints; her vital signs, physical examination findings, and electrocardiogram (ECG) are normal. To receive a psychiatric evaluation, she must be transferred off-site. How long should she be observed in the emergency department before transfer to a psychiatric facility?

a. 1 hour
b. 2 hours
c. 6 hours
d. 12 hours

Answer: C. The most dangerous class of antidepressants is the cyclic antidepressants. Typically, peak plasma concentrations and therefore peak effect occur in 2 to 4 hours. However, in overdose, the anticholinergic effects of these agents may result in delayed gastric emptying and delay peak absorption to 6 hours. Most serious signs and symptoms occur within 30 to 60 minutes of ingestion. If the patient has tachycardia or seizure or decreased level of consciousness at 6 hours, she should be admitted for medical observation. If any of these pills were a monoamine oxidase inhibitor (MAOI), however, the patient should be admitted to the hospital for 24 hours.

2. After sinus tachycardia, what is the most common electrocardiographic abnormality seen in cyclic antidepressant overdose?

a. Left bundle branch block
b. PR prolongation
c. QRS prolongation
d. QT prolongation
e. Right bundle branch block

Answer: C. After sinus tachycardia, QRS prolongation of more than 100 milliseconds is the most common specific finding and results from sodium channel–blocking effects of the cyclic antidepressant. Prolonged PR and QT intervals, as well as a right bundle branch block, can also occur but are less common.

CHAPTER 141: QUESTIONS AND ANSWERS—cont'd

3. Which of the following treatment options would be the most appropriate to consider in the awake, asymptomatic patient who presents within 1 hour of a large overdose of a tricyclic antidepressant (TCA)?
   a. Activated charcoal
   b. Endotracheal intubation
   c. Gastric lavage
   d. Physostigmine
   e. Sodium bicarbonate

   Answer: A. Physostigmine should never be prophylactically administered and its use in TCA overdose is generally considered contraindicated, particularly in patients with bradycardia, AV block, and seizures related to the overdose. Sodium bicarbonate should not be prophylactically administered either, but it should be administered as an intravenous (IV) bolus for patients with intraventricular conduction delay and QRS widening. Endotracheal intubation is indicated for patients with significant central nervous system (CNS) depression who are not able to protect their airway. Gastric lavage is not indicated. Activated charcoal can be considered in an awake individual presenting within one hour of ingestion. It should not be "forced" on someone who will not voluntarily drink it (e.g., by placement of a nasogastric tube for the purpose of administering charcoal) because of the increased risk of aspiration and subsequent charcoal pneumonitis.

4. A 23-year-old man presents after an ingestion of a cyclic antidepressant. His initial vital signs are normal. During your initial evaluation, the patient begins to seize. Which agent should be administered first?
   a. Lorazepam
   b. Phenobarbital
   c. Phenytoin
   d. Propofol
   e. Valproic acid

   Answer: A. Lorazepam or any other benzodiazepine is the first-line treatment of toxin-induced seizures. Intravenous phenytoin can increase the incidence of ventricular tachycardia and is not generally effective in controlling toxin-induced seizures. Phenobarbital and propofol are effective but take longer to give and typically are used after benzodiazepines. Valproic acid is not likely to be effective.

5. A 57-year-old woman presents with altered mental status. A friend states that the patient takes antidepressant medications and has recently been complaining of symptoms of an upper respiratory tract infection. The patient is noted to have a temperature of 39.2°C and a pulse of 135 beats/minute. Otherwise, her vital signs are within normal limits. On examination, she has a tremor, myoclonus, and diaphoresis. Which of the following is the most consistent with this presentation?
   a. Anticholinergic syndrome
   b. Cocaine intoxication
   c. Cyclic antidepressant overdose
   d. Neuroleptic malignant syndrome (NMS)
   e. Serotonin syndrome

   Answer: E. Symptoms of serotonin syndrome include altered mental status, agitation, ataxia, diaphoresis, diarrhea, hyperreflexia, hyperthermia, myoclonus, shivering, and tremor. Many of the symptoms are similar to symptoms caused by NMS and sympathomimetic overdoses; however, myoclonus is unique to the serotonin syndrome. Additional historical features consistent with the serotonin syndrome are the fact that the patient is taking an antidepressant, possibly a selective serotonin reuptake inhibitor (SSRI), and has likely added an over-the-counter "cold" medication. Many of these medications contain dextromethorphan, which also decreases serotonin reuptake and can precipitate the serotonin syndrome in patients taking SSRIs.

6. A 24-year-old man presents after taking an overdose of his antidepressant. He does not know the name of the drug. He has no complaints, and his vital signs and physical examination findings are normal. Soon after completing your evaluation, the patient experiences a tonic-clonic seizure. Which of the following antidepressants is most likely to produce seizures without other symptoms of severe toxicity?
   a. Amitriptyline
   b. Bupropion
   c. Fluoxetine
   d. Phenelzine
   e. Trazodone

   Answer: B. Bupropion can induce seizures even at therapeutic levels. Other adverse effects include tachycardia, tremulousness, hallucinations, and QRS prolongation. Cyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (SSRIs; fluoxetine), and monoamine oxidase inhibitors (MAOIs; phenelzine) can also cause seizures but less frequently than bupropion and usually with other symptoms of serious intoxication such as central nervous system (CNS) depression or QRS prolongation.

7. A patient is prescribed a new medication that he takes each night. After 4 days, he is drowsy and noted to have orthostatic hypotension, nausea, vomiting, and priapism. What medication is most likely involved?
   a. Amitriptyline
   b. Bupropion
   c. Fluoxetine
   d. Phenelzine
   e. Trazodone

   Answer: E. Trazodone and nefazodone may cause orthostatic hypotension and lethargy. Priapism is a relatively unique complication of trazodone and is more common with therapeutic use rather than in acute overdose.

8. A patient presents after a substantial accidental overdose of her monoamine oxidase inhibitor (MAOI), which she confused with her megavitamin therapy. There is no need for psychiatric evaluation. She is asymptomatic and has normal vital signs and a normal physical examination. What is the appropriate disposition?
   a. Admit to intensive care unit for a minimum of 24 hours of observation
   b. Admit to ward for a minimum of 24 hours of observation
   c. Discharge home
   d. Observe for 6 hours, then discharge home
   e. Observe for 12 hours, then discharge home

   Answer: A. All patients who overdose on MAOIs should be admitted for at least 24 hours of observation because symptom onset is often delayed. In addition, the effects of overdose may be severe and require aggressive therapy.

142

Cardiovascular Drugs

Jon B. Cole

CARDIOACTIVE STEROIDS (DIGOXIN)

KEY CONCEPTS

- Digoxin toxicity is often occult and should be considered in any patient who is on digoxin and presents with gastrointestinal or visual disturbance and a new dysrhythmia, conduction disturbance or hemodynamic instability, particularly in the setting of ingestion of a natural weight-loss supplement.
- Digitalis Fab is the specific antidote for digoxin toxicity and is dosed based on chronicity of poisoning; most patients require only 1 (chronic poisoning) or 2 (acute poisoning) vials. If full reversal is needed for patients in extremis, dosing is based on total body load of digoxin, not by patient weight.
- Indications for digitalis Fab include progressive and hemodynamically significant bradydysrhythmias and serum potassium >5.0 mEq/L, as summarized in Box 142.4. Of note, Fab therapy should be used before pacing or antidysrhythmic drugs.
- Hyperkalemia in acute digoxin toxicity is best treated with Fab fragments. Conventional treatment as for any other cause of hyperkalemia is also appropriate when Fab fragments are not immediately available. Hyperkalemia in chronic poisoning is likely multifactorial and should be treated with Fab fragments followed by usual hyperkalemia treatments as needed.

Foundations

Digoxin is derived from the Grecian foxglove plant, *Digitalis lanata* (Fig. 142.1); the trade name for digoxin (Lanoxin) is derived from the Latin name of this plant. Digitoxin, which is no longer in clinical use in the United States, comes from *Digitalis purpurea* (Fig 142.2).[2] Despite centuries of experience with digitalis preparations, chronic and acute poisonings still occur. Medication errors, including failure to account for drug-drug and disease-drug interactions (particularly kidney disease), account for a substantial number of poisonings.[3] Though the use of digoxin continues to be controversial, it is still commonly prescribed, particularly for patients with concomitant heart failure and atrial fibrillation.[4]

Digoxin is used therapeutically (1) to increase the force of myocardial contraction to increase cardiac output in patients with heart failure and (2) to decrease atrioventricular (AV) conduction to slow the ventricular rate in atrial fibrillation. The basis for its first effect is inhibition of membrane sodium-potassium–adenosine triphosphatase (Na^+, K^+-ATPase) pumps; this inhibition results in increased intracellular sodium and extracellular potassium concentrations.[5] This increase in intracellular sodium concentration results in dysfunction of the sodium-calcium ion exchanger, which normally extrudes intracellular calcium after systole. This subsequent increase in intracellular calcium concentration results in a larger amount of calcium pumped into the sarcoplasmic reticulum so that upon calcium release during subsequent action potentials, a larger amount of calcium is released into the cell, causing a more powerful contraction and thus increased stroke volume and subsequent cardiac output. Molecules containing an aglycone steroid moiety with this specific effect are classified as cardioactive steroids.[6] Cardiac glycosides (such as digoxin) are merely cardioactive steroids with additional sugar moieties attached to their steroid nucleus.[5] At therapeutic doses, the effects of digoxin on serum electrolytes are minimal. With toxic concentrations, digoxin paralyzes the Na^+, K^+-ATPase pump, potassium cannot be transported into cells, and serum potassium concentration can rise as high as 13.5 mmol/L.

Digoxin exerts direct and indirect effects on sinoatrial (SA) and AV nodal fibers. At therapeutic concentrations, digoxin indirectly increases vagal activity. At toxic concentrations, digoxin can directly block the generation of impulses in the SA node, depress conduction through the AV node, and increase the sensitivity of the SA and AV nodes to catecholamines. Catecholamines, whether endogenous or administered to treat bradydysrhythmias or hypotension, play an important role in digoxin toxicity. Because bradydysrhythmias and tachydysrhythmias can appear and alternate in the same patient, administration of antidysrhythmic agents to treat tachycardias may later contribute to more refractory bradycardias and AV block.

Digoxin also exerts three primary effects on Purkinje fibers: (1) decreased resting potential, resulting in slowed phase 0 depolarization and conduction velocity; (2) decreased action potential duration, which increases sensitivity of muscle fibers to electrical stimuli; and (3) enhanced automaticity resulting from increased rate of phase 4 repolarization and delayed after-depolarizations. These mechanisms account for an increase in premature ventricular contractions, which is the most common electrocardiographic manifestation of digoxin toxicity. At extremes of toxicity, these effects result in a hypersensitivity to mechanical and electrical stimulation. Interventions with pacemaker wires, catheters, and cardioversion can result in asystole, ventricular tachycardia, and ventricular fibrillation.

Unlike most cardiovascular drugs, digoxin can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias (Box 142.1). However, none is unique to digoxin, and because they can all occur in the setting of ischemic and other heart disease, digoxin toxicity remains a clinical rather than an electrocardiographic diagnosis.

The volume of distribution (V_d) of digoxin is 5 L/kg for adults but varies from 3.5 L/kg in premature infants to 16.3 L/kg in older infants. This indicates that only a small fraction of digoxin remains in the intravascular space, and the drug is highly concentrated in cardiac tissue. The myocardial-to-serum ratio at equilibrium ranges from 15 : 1 to 30 : 1.

The elimination half-life of digoxin, which is primarily excreted in the urine, is 36 hours.

Protein binding varies from 20% to 30% for digoxin. The significant protein binding and large volumes of distribution of digoxin suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective. The long half-lives have therapeutic implications for

temporizing measures such as pacemakers, atropine, and antidysrhythmic drugs compared to the more definitive treatment of Fab fragments.

Multiple drugs and disease states can alter absorption, V_d, protein binding, and elimination, rendering the heart more susceptible to digoxin toxicity. The factors listed in Box 142.2 are especially important risk factors in chronic intoxication.

Fig. 142.1 The Grecian foxglove plant, *Digitalis lanata*, the source of digoxin. (Photos courtesy of Gary Bebeau and Friends of the Eloise Butler Wildflower Garden, Minneapolis, Minnesota.)

Clinical Features

The symptoms and signs of chronic digoxin toxicity are nonspecific. The most common symptoms are nausea, anorexia, and fatigue; but a variety of gastrointestinal, neurologic, and ophthalmic disturbances also occur (Box 142.3). Visual disturbances include decreased visual acuity, scotomata, photophobia, and chromatopsia (aberrations of color vision, classically yellow, but may occur in a variety of colors). Digoxin intoxication should be considered in any patient receiving maintenance therapy who has consistent symptoms, no matter how vague, particularly if presenting with new conduction disturbances or dysrhythmias.

There are significant differences between acute and chronic toxicity (Table 142.1). Chronic poisoning has an insidious onset and is accompanied by a higher mortality rate that is likely due in part to underlying heart disease and chronic accumulation of the toxin. In cases of chronic intoxication, the level with a 50% mortality (LL_{50}) is only 6 ng/mL. The LL_{50} for acute poisoning is much higher, especially in children. Although toxicity increases with greater body load, there is no clear correlation with amount ingested, especially in children, and many patients with large acute ingestions or high serum levels become only mildly symptomatic. The association of hyperkalemia with acute toxicity is more apparent given the mechanism of digoxin; either hypokalemia or hyperkalemia may occur with chronic toxicity.

Pediatric Considerations

Children with healthy hearts can tolerate massive acute oral ingestions and may not require Fab treatment. This excludes therapeutic errors, children who are taking digoxin therapeutically, and children with heart disease.

Medication errors account for the most common causes of preventable iatrogenic cardiac arrests. Therapeutic errors, especially accidental IV overdoses, often result in death within 1 to 4 hours.

Fig. 142.2 The common foxglove plant *Digitalis purpurea*, the source of digitoxin. The flowers are typically purple but may also be white. White flowers may mature to purple or may remain white. (Photos courtesy of Ann Arens, MD.)

BOX 142.1 Dysrhythmias Associated With Digoxin Toxicity

Nonspecific Dysrhythmias
PVCs, especially bigeminal and multiform
AV heart blocks of all degrees
Sinus bradycardia
Sinus tachycardia
SA block or arrest
Atrial fibrillation with slow ventricular response
Atrial tachycardia
Junction (escape) rhythm
AV dissociation
Ventricular bigeminy and/or trigeminy
Ventricular tachycardia
Ventricular fibrillation

More Specific but Not Pathognomonic
Atrial fibrillation with slow, regular ventricular rate (AV dissociation)
Nonparoxysmal junctional tachycardia (rate usually 70–130 beats/min)
Atrial tachycardia with block (atrial rate usually 150–200 beats/min)
Bidirectional ventricular tachycardia

AV, Atrioventricular; *PVCs*, premature ventricular contractions; *SA*, sinoatrial.

BOX 142.2 Factors Associated With an Increased Risk of Digoxin Toxicity

Concomitant kidney injury or underlying kidney disease
Concomitant or underlying heart disease
- Congenital heart disease
- Ischemic heart disease
- Heart failure
- Myocarditis

Electrolyte disturbances
- Hyperkalemia
- Hypokalemia
- Hypomagnesemia
- Hypercalcemia

Alkalosis
Hypothyroidism
Sympathomimetic drugs (e.g., cocaine)
Cardiotoxic co-ingestions
- Beta-blockers
- Calcium channel blockers
- Class IA or IC antidysrhythmics (e.g., flecainide)
- Tricyclic antidepressants

Drug interactions (may increase serum digoxin concentration)
- Quinidine
- Amiodarone
- Erythromycin
- Nifedipine

Drug Interactions (may increase serum digoxin concentration and cause synergistic bradycardia)
- Verapamil
- Diltiazem

Signs and symptoms in children with digoxin poisoning are different than in adults (Table 142.2). Vomiting, somnolence, and obtundation are more common than in adults. Conduction disturbances and bradycardias are more common than ventricular dysrhythmias in children, especially following acute ingestion.

BOX 142.3 Noncardiac Symptoms of Cardioactive Steroid Intoxication

General
Weakness
Fatigue
Malaise

Gastrointestinal
Nausea and/or vomiting
Anorexia
Abdominal pain
Diarrhea

Ophthalmologic
Blurred or snowy vision
Photophobia
Chromatopsia (yellow, green, red, brown, blue vision changes)
Transient amblyopia, diplopia, scotomata, blindness

Neurologic
Dizziness
Headache
Confusion, disorientation, delirium
Visual and/or auditory hallucinations
Somnolence
Abnormal dreams
Paresthesias and/or neuralgia
Aphasia
Seizure

TABLE 142.1 Acute Versus Chronic Digoxin Poisoning

Acute	Chronic
Lower mortality	Higher mortality (LL_{50} = 6 ng/mL)
Bradycardia and AV block more common	Ventricular dysrhythmias more common
Typically, younger patients	Typically, elderly patients
Underlying heart disease generally less common, decreased morbidity and mortality	Underlying heart disease more common, increased morbidity and mortality

AV, Atrioventricular; *LL_{50}*, level with a 50% mortality.

Differential Diagnoses

No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so its differential diagnosis is broad. Intrinsic cardiac disease as well as other cardiotoxic drugs should be considered, particularly beta-blockers and calcium channel blockers. Cardioactive steroid poisoning from plants is rare in the United States but presents similarly to digoxin toxicity. Common examples include oleander (*Nerium oleander*) and lily-of-the-valley (*Convallaria majalis;* Fig. 142.3). Recently, there has been an increase in the use of natural products containing cardioactive steroids for the purpose of weight loss.[7] Several cardioactive-steroid containing plants have been purported to be "natural" agents for weight loss, including pong-pong seeds (*Cerebra odollam*) and yellow oleander (*Thevetia peruviana*), both of which have resulted in fatal poisonings.[8,9] Yellow oleander is particularly problematic in that its seeds bear a physical resemblance to the seeds of another minimally toxic plant

(that does not contain cardioactive steroids but is also purported to aid in weight loss) commonly called candle nuts (*Aleurites moluccana*). The substitution of yellow oleander for candle nuts has resulted in at least one accidental fatality; it is likely other cases have gone unrecognized.[9] In some parts of the world, such as Southeast Asia and India, ingestion of plants containing cardioactive steroids (e.g., pong-pong or yellow oleander seeds) is a common method of suicide[10]; ingestion of 1 or 2 yellow oleander seeds has resulted in death.[6] Aconitine, a sodium-channel opening poison found in common Monkshood plants *(Aconitum napellus),* may also mimic digoxin poisoning.[11]

Central nervous system (CNS) depression or confusion may be due to various depressant drugs (e.g., opioids, sedative hypnotic agents, alcohol) and toxins, as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances caused by digoxin are binocular and are often not reported by the patient; they are not specific to digoxin poisoning. Methanol, metformin, ethambutol, ethyl chloride, quinine, and other antimalarial medications are all capable of producing visual disturbances. Gastrointestinal disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

TABLE 142.2 Age Difference in Digoxin Intoxication

Adult	Pediatric
Toxic at lower concentrations	Asymptomatic at higher concentrations
Nausea, fatigue, and visual disturbances more common	Obtundation and vomiting more common
Tachydysrhythmias as common as blocks and bradydysrhythmias	Bradydysrhythmias and blocks more common
Allergic reactions to Fab fragments uncommon (<1%)	Allergic reactions extremely rare
V_d less variable (5–7.5 L/kg)	V_d more variable (3.5–6.0 L/kg in premature infants, 8.0–16.3 in infants 2–24 months old)

V_d, Volume of distribution.

Diagnostic Testing

Diagnosis and management rely on serum digoxin concentrations, but it is the steady state, rather than peak concentration, that correlates with tissue toxicity and is used to calculate antidote dosages. Peak concentrations after an oral dose of digoxin occur in 1.5 to 2 hours, with a range of 0.5 to 6 hours. Steady-state serum concentrations are not achieved until after alpha distribution, or 6 to 8 hours after a therapeutic or toxic dose and may be only 20% to 25% of the peak concentration. The ideal serum digoxin concentration for patients with heart failure is considered to be 0.7 to 1.1 ng/mL, although laboratory "normal ranges" are often reported up to 2.0 ng/mL. Serum steady-state digoxin concentrations of 1.1 to 3.0 ng/mL are difficult to interpret; that is, concentrations as low as 1.1 ng/mL have been associated with toxicity, and patients with levels up to 3.0 ng/mL can be asymptomatic. The incidence of digoxin-incited dysrhythmia reaches 10% at a concentration of 1.7 ng/mL and rises to 50% at a concentration of 2.5 ng/mL. Determination of a serum digoxin concentration measured too early after the last maintenance dose falsely suggests toxicity, especially in cases of chronic intoxication, in which significant morbidity and mortality can occur at levels of 2 to 6 ng/mL. After an acute massive overdose in a patient who is rapidly becoming symptomatic, however, it is impractical to wait 6 to 8 hours for the first measurement. It is unlikely that early concentrations exceeding 10 to 20 ng/mL will fade to clinical insignificance at 6 to 8 hours after ingestion.

Management

Fab Fragments (DigiFab)

The primary treatment of significant digoxin poisoning is the administration of digoxin-specific fragment antigen-binding (Fab) antibodies (DigiFab); all other interventions are considered complementary.

The mortality rate of digoxin poisoning before Fab fragment therapy was 23% despite all of the interventions described in this section.

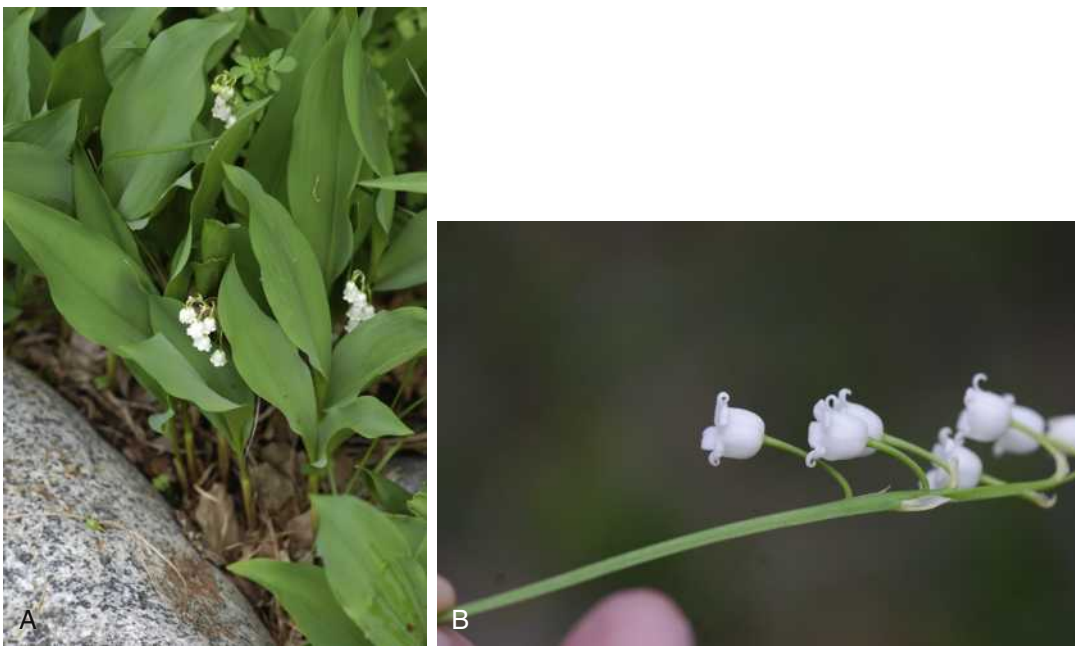

Fig. 142.3 Lily-of-the-valley (*Convallaria majalis*), which contains the cardiac glycoside convallatoxin. (Photos courtesy of Gary Bebeau and Friends of the Eloise Butler Wildflower Garden, Minneapolis, Minnesota.)

Fig. 142.4 A vial of digoxin antibody fragments (DigiFab) next to a cutting of *Digitalis purpurea*, demonstrating the darkening of the purple flowers as they age. (Photo courtesy of Laurie Wilhite, PharmD, CSPI.)

Fab fragment treatment is well established in both chronic and acute poisonings, with a successful response rate approaching 90%. Nonresponders usually receive Fab fragments too late, have concomitant poisoning, or are compromised by underlying comorbidities.

Digoxin antibodies are derived from sheep. Allergic reactions occur in less than 1% of cases but are slightly more common in patients with asthma. Reactions have included erythema, urticaria, and facial edema, all of which are responsive to the usual treatments for allergic reactions (e.g., diphenhydramine, corticosteroids, epinephrine). Other infrequent reactions when Fab fragments neutralize digitalis include hypokalemia, heart failure exacerbation, and increase in ventricular rate with atrial fibrillation. Two Fab fragment preparations were previously available; however, DigiFab is the only available product in the United States (Fig. 142.4). Previous products required a 0.22-μm membrane filter for proper use; such a filter is not required for DigiFab.

Fab fragment treatment is best reserved for cases of serious cardiovascular toxicity rather than for routine or prophylactic administration with higher than expected serum concentrations. Fab fragments should be used for a serum potassium level above 5.0 mEq/L or unstable dysrhythmias such as symptomatic bradycardia, ventricular dysrhythmias, or second- or third-degree heart block unresponsive to atropine. Fab fragment therapy should be used before transvenous pacing, because the latter is believed to carry a higher risk of ventricular dysrhythmia, although the evidence for this is mixed. Large acute overdoses (>0.1 mg/kg in a child or 10 mg in a healthy adult) are also likely to require Fab fragments.

The median time to initial response is 19 minutes after completion of the Fab infusion, but complete resolution of digitalis-induced toxic dysrhythmias may require hours. Late administration of Fab fragments has resuscitated up to 54% of patients who have suffered cardiac arrest secondary to digoxin toxicity. Fab fragments should be administered whenever hemodynamic compromise occurs in the setting of a digoxin-induced toxic dysrhythmia or heart block; a full list of indications is included in Box 142.4.

Dosing of Fab fragments is based both upon the patient's clinical status and acuity of poisoning. Patients in cardiac arrest, or in the midst of a life-threatening ventricular dysrhythmia, generally require full reversal. In chronic poisoning, however, the benefit of Fab fragments is less clear. Recently published prospective data on chronic digoxin-poisoned patients shows that small doses (median dose 1.5 vials) results in complete binding of free digoxin, with minimal improvement in clinically important parameters such as heart rate, blood pressure, or serum potassium.[12,13] These prospective data, which compared chronically digoxin-poisoned patients with similar physiologic parameters receiving Fab fragments with those who received supportive care only, showed no difference in vital signs, potassium, or mortality, despite complete binding of all available free digoxin. These data call into question the utility of Fab fragments in chronically poisoned patients. Nevertheless, in hemodynamically unstable patients, such as those with hypotension, treatment with Fab fragments is still considered the standard of care.

If the patient is in cardiac arrest, the maximum number of vials of Fab fragments available (up to 10) should be administered undiluted as an intravenous (IV) bolus. If, in acute or chronic toxicity, the patient is in a life-threatening ventricular dysrhythmia or heart block and the serum digoxin concentration *is unknown* but the amount of digoxin ingested is known, we recommend full reversal based upon the following concept: one vial of DigiFab contains 40 mg of Fab fragments, which bind 0.5 mg of digoxin (Box 142.5). In the same patient, if the steady-state serum digoxin concentration *is known*, we recommend full reversal with Fab fragments based upon the digoxin concentration utilizing the formula in Box 142.6. An exception to the above regimens is the case of yellow oleander poisoning, where a high case fatality rate and poor cross-reactivity of Fab fragments with the offending cardioactive steroids necessitates higher dosing. Therefore, with acute yellow oleander poisoning, 20 to 30 vials (if available) are recommended.

In hemodynamically stable patients, we recommend a more conservative dosing regimen of Fab fragments. The total body burden of digoxin is often overestimated. Furthermore, the incidence of life-threatening dysrhythmias, even in reported large ingestions, is low,

BOX 142.4 Recommendation for Administration of Digoxin Antibody Fragments

1. Ventricular dysrhythmias more severe than PVCs
2. Progressive and hemodynamically significant bradydysrhythmias unresponsive to atropine
3. Serum potassium >5.0 mEq/L
4. Rapidly progressive rhythm disturbances or rising potassium
5. Co-ingestion of cardiotoxic drugs (for examples, see Box 142.2)
6. Ingestion of plant known to contain cardioactive steroids plus severe dysrhythmia or potassium >5.0 mEq/L
7. Acute ingestion of >10 mg or 0.1 mg/kg in a child *plus* any one of factors 1 through 6
8. Steady-state digoxin concentration > 6 ng/mL *plus* any one of factors 1 through 6

BOX 142.5 Sample Calculation of Digitalis Fab Fragments based on Ingested Dose

Case: A toxic-appearing 40-year-old woman has acutely ingested fifty 0.25-mg digoxin tablets.

$$\text{Body load} = \text{amount ingested} \times 0.8\ (\text{bioavailability of digoxin tablets}) = 12.5\ \text{mg} \times 0.8 = 10\ \text{mg}$$

$$\text{Dose of digoxin Fab fragments (in vials)} = 10\ \text{mg} \div 0.5\ \text{mg bound per vial} = 20\ \text{vials}$$

BOX 142.6 Sample Calculation of Digitalis Fab Fragments Based on Steady-State Digoxin Concentration

Case: A toxic-appearing 4-year-old child weighing 20 kg has a digoxin level of 16 ng/mL 8 hours after ingestion of an unknown number of digoxin tablets.

Dose (in number of vials) = (serum digoxin concentration × weight in kg) ÷ 100
= (16 × 20) ÷ 100
= approximately 3 vials

suggesting most patients do not require Fab fragments.[13] Pharmacokinetic modeling of digoxin toxicity suggests smaller doses of Fab fragments than previously recommended are adequate to reverse toxicity.[14] Therefore, in acute digoxin poisoning, if the patient has an indication for Fab fragments (see Box 142.4) but is not in an immediately life-threatening ventricular dysrhythmia or heart block, we recommend two vials, repeated as needed using clinical markers of toxicity such as evidence of shock or severe dysrhythmias. For similar patients with chronic poisoning, the recommended dose is one vial with a repeat dose at 60 minutes if the patient remains symptomatic. Earlier repeat dosing is reasonable if the patient becomes unstable.

Because most assays measure both bound and unbound drug, digoxin concentrations will be elevated for up to one week after Fab fragments administration, with values often greater than 100 ng/mL once Fab fragments have been administered. If laboratory measurement of free serum digoxin is available, these levels more accurately follow a patient's clinical status.

Electrolyte Correction

In cases of chronic toxicity, which may be exacerbated by hypokalemia, normalization of the serum potassium is an important early treatment. Potassium can be administered orally in the alert patient (which is safer) or intravenously at a rate of 20 mEq/hr or less.

In acute poisoning, serum potassium concentration may begin to rise rapidly within 1 to 2 hours of ingestion. Potassium should be withheld, even if mild hypokalemia is measured initially. The initial serum potassium concentration may in fact be a better predictor of mortality than the initial digoxin concentration. Before Fab fragments were available, up to 50% of the patients with serum potassium concentrations between 5.0 and 5.5 mEq/L died. In the setting of acute digoxin poisoning, we recommend initiating Fab fragment treatment based solely on a serum potassium concentration greater than 5 mEq/L.

The decision to administer calcium to patients with hyperkalemia and digoxin poisoning represents a clinical dilemma. Classic teaching is that in the setting of the increased intracellular calcium concentration from digoxin poisoning, administration of exogenous calcium will result in a "stone heart" (cardiac tetany) from excessive intracellular calcium. This concept has been in the literature since 1927, based primarily on animal studies. Documented cases of cardiac arrest after calcium administration are exceedingly rare, and the temporal relationship is dubious. More recent human data indicate that the IV administration of calcium for hyperkalemia in the setting of digoxin toxicity is safe. Unequivocally, however, the best treatment of hyperkalemia due to acute digoxin toxicity is Fab fragments. The treatment of hyperkalemia in a patient with chronic digoxin toxicity and renal failure is less clear. Patients with hyperkalemia and chronic digoxin poisoning often have multiple reasons for hyperkalemia in addition to digoxin toxicity (e.g., acute worsening of renal function, concomitant use of potassium-sparing diuretics). Furthermore in chronic digoxin-poisoned patients, even when full digoxin reversal is performed, potassium levels rarely decline further than with supportive care alone.[13] Regardless, the evidence that calcium salts will be harmful in chronic digoxin poisoning is lacking. As such, treatment of hyperkalemia related to digoxin toxicity is similar in indication and approach to that for hyperkalemia from other causes after Fab fragments have been administered (see Chapter 114).

Hypomagnesemia enhances the effects of cardioactive steroids. Therefore, any patient with suspected poisoning should have serum magnesium concentrations measured. This is further supported by evidence of magnesium reversing digoxin-induced tachydysrhythmias. If significant magnesium depletion is present, 1 to 2 g of magnesium sulfate should be administered over 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hr until magnesium concentrations are normal, accounting for concomitant kidney injury. We do not recommend administration of magnesium in digoxin-induced bradydysrhythmias and conduction blocks, because hypermagnesemia can impair impulse formation and AV conduction.

Atropine

Atropine is generally used for symptomatic bradycardia (pulse < 50 beats/min) and advanced AV block. We recommend using atropine as a temporizing measure for symptomatic patients while Fab fragments are being administered. We also recommend atropine for bradycardia refractory to Fab fragments. Standard dosing (0.02 mg/kg in children with a minimum of 0.1 mg; 1 mg IV in adults) should be used. Doses can be repeated every 3 to 5 minutes. In general, an external pacemaker should be readied once atropine has been administered.

Pacing and Cardioversion

Transvenous pacing is a mainstay of treatment for severe bradycardia. There is some evidence that the catheter may induce ventricular tachydysrhythmias in a myocardium made irritable by digoxin, although convincing studies on this question are lacking. Iatrogenic accidents of cardiac pacing are frequent (36%) in one study and can be fatal (up to 13%). Transvenous pacing should be used only if external pacing fails. Pacing usually is required only temporarily while waiting for Fab fragments to take clinical effect. Cardioversion in the setting of digoxin poisoning should be reserved for life-threatening dysrhythmias such as pulseless ventricular tachycardia or ventricular fibrillation.

Phenytoin and Lidocaine

Fab fragments are the preferred therapy for dysrhythmias, but a dysrhythmia may require intervention while Fab fragments are readied or until they begin to have effect after infusion.

Although both phenytoin and lidocaine are believed to be safe for control of tachydysrhythmias in the setting of digoxin toxicity, we prefer phenytoin. Indications for phenytoin include unstable tachydysrhythmias when Fab fragments are unavailable and unstable tachydysrhythmias that occur while waiting for Fab fragments to take effect. Phenytoin may enhance AV conduction. We recommend administering phenytoin in 100 mg boluses every 5 minutes until dysrhythmias improve or until the standard loading dose of 18 mg/kg is reached. No data exist to support or refute the substitution of fosphenytoin for phenytoin in this scenario. We recommend lidocaine only if the patient has a contraindication to phenytoin or if the maximum dose of phenytoin has been reached. When given, we recommend a loading dose of 1.5 mg/kg IV push, followed by an infusion of 1 to 4 mg/min (30 to 50 μg/kg/min), started at 1 mg/min and titrated up based on response to therapy. Most other cardiac drugs (isoproterenol, procainamide, amiodarone, beta-blockers, calcium antagonists) may worsen dysrhythmias or depress AV conduction in digoxin poisoned patients and should not be administered in this setting.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO has been successfully used to treat cardioactive steroid poisoning, though cases are rare and data are limited.[15] Due to the relatively high survival rate in patients with cardiac arrest from digoxin poisoning treated with Fab fragments, we recommend ECMO in this instance only if Fab fragments are ineffective in establishing return of spontaneous circulation, or in the rare instance of cardiac arrest or refractory cardiogenic shock at an institution where ECMO is readily available, but high doses of Fab fragments are not.

Disposition

Patients who are symptomatic from digoxin toxicity with hyperkalemia, dysrhythmia, AV block, or significant comorbidity should be admitted to an intensive care unit after treatment with Fab fragments. Asymptomatic patients reporting an acute ingestion of digoxin should be observed for at least 12 hours of continuous cardiac monitoring. Chronically poisoned patients should be admitted to a monitored setting because they often have concomitant comorbidities and underlying heart disease.

BETA-BLOCKERS

KEY CONCEPTS

- Beta-blocker intoxication causes bradydysrhythmias and occasionally AV block.
- Noncardiac symptoms such as obtundation, seizures, and hypoglycemia may occur early in the course and are classically associated with propranolol toxicity.
- Volume expansion, atropine, calcium, and glucagon are early treatment measures, but absent a response, begin a high-dose insulin (HDI)/glucose infusion.
- When using HDI/glucose infusions, concentrated glucose solutions are recommended to avoid fluid overload.

Foundations

Principles of Toxicity

Beta-adrenergic blocking drugs (commonly referred to as beta-blockers) became widely used in Europe in the 1960s for treatment of dysrhythmias. Their antihypertensive effects were later appreciated. By the 1970s, they were one of the most widely prescribed classes of drugs in the United States. Current indications include supraventricular dysrhythmias, hypertension (although the drugs have fallen out of favor for this indication), angina, thyrotoxicosis, migraine, and glaucoma. Of the numerous beta-blockers available, overdose with propranolol has the highest fatality rate. In 2018, United States poison centers received more than 26,000 calls regarding beta-blocker exposures.[1] Over 1000 of these calls were regarding patients with life-threatening symptoms. While the vast majority of beta-blocker overdoses have favorable outcomes,[16] deaths from isolated ingestions still occur regularly.

Pathophysiology

Beta-blockers structurally resemble isoproterenol, a pure beta-agonist. They competitively inhibit endogenous catecholamines such as epinephrine at beta-adrenergic receptors, blocking the catecholamine effects of inotropy (increased myocardial contraction), dromotropy (enhanced cardiac conduction), and chronotropy (increased heart rate). These are all β_1 effects. Complex β_2 effects include vascular (smooth muscle relaxation and vasodilation), liver (glycogenolysis, gluconeogenesis), lung (bronchodilation), adipose tissue (release of free fatty acids), and uterus (smooth muscle relaxation) effects. Important additional properties, which vary from one beta-blocker to another, include cardioselectivity (β_1 selectivity), membrane-stabilizing activity (fast cardiac sodium channel blocking properties), lipophilicity, and intrinsic sympathomimetic activity (Table 142.3). Although cardioselectivity is masked in overdose, cardioselective beta-blockers such as atenolol, metoprolol, and esmolol still have lower mortality rates than that of propranolol.[1]

Beta-blockers are rapidly absorbed after oral ingestion, with peak effects varying among drugs (Table 142.3). Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing than with IV injection (e.g., 1 : 40 for propranolol, 1 : 2.5 for metoprolol). Because volume of distribution for most beta-blockers generally exceeds 1 L/kg, hemodialysis is not efficacious for most beta-blocker overdoses.

Clinical Features

The most common initial clinical sign is bradycardia. Hypotension and unconsciousness are also common. While unconsciousness may be from a lack of brain perfusion due to cardiotoxic effects, beta-blockers (particularly propranolol) may also cause direct CNS depression and apnea. Hypoglycemia, due to blockade of the counter-regulatory effects of epinephrine, is often described, but rare. Though uncommon in all patients, hypoglycemia is more common in children than adults. In overdose, signs and symptoms are identical among beta-blockers, with the exception of propranolol which tends to cause seizures.[16] Much of propranolol's unique toxicity derives from its lipophilic nature combined with its membrane-stabilizing activity, which allows it to penetrate the CNS, causing obtundation, respiratory depression, and occasionally seizures. Of note, bronchospasm is rarely a problem in beta-blocker overdose, even with nonselective beta-blockers. The few cases of symptomatic bronchospasm respond to usual doses of nebulized bronchodilators.

Propranolol, nadolol, betaxolol, and acebutolol have membrane-stabilizing activity that impairs SA and AV node function and leads to bradycardia and AV block. Ventricular conduction is also depressed secondary to membrane-stabilizing activity (similar to tricyclic antidepressants or class IA/IC antidysrhythmics), which manifests as QRS widening on ECG, with ventricular dysrhythmias and cardiogenic shock. The intrinsic sympathomimetic activity of some beta-blockers (e.g., pindolol, oxprenolol, acebutolol, carteolol) can lead to some unusual manifestations such as ventricular dysrhythmias and tachycardia instead of bradycardia. Labetalol and carvedilol also block α_1-adrenergic receptors, giving an additional mechanism for hypotension and distributive shock, however clinically they present similarly to other beta blockers due to their respective $\beta : \alpha$ blockade ratios. Labetalol's beta-blockade is three times more potent via the oral route, and seven times more potent intravenously than its α-blockade. Carvedilol is even more beta-selective; its blockade of β_1 and β_2 receptors is 10 times more potent than α_1.

In contrast to digoxin, beta-blocker toxicity has a more rapid onset. Life-threatening CNS and cardiovascular effects can occur 30 minutes after oral overdose. With the exception of sotalol, which causes QT prolongation and torsades de pointes, toxicity from beta-blocker poisoning is usually apparent within 6 hours of ingestion. Patients ingesting delayed-release preparations, however, may remain asymptomatic for several hours, followed by a prolonged period of toxicity of up to 24 hours. For additional clinical features, see Table 142.5.

TABLE 142.3 Selected Pharmacologic Characteristics of Common Beta-Blockers

Drug	Time to Peak (hrs, oral form)	T1/2 (hrs)	V_d (L/kg)	Lipophilicity	Protein Binding (%)	MSA	ISA	Comments
Non-Selective Beta-Blockers								
Propranolol	1–4 (6–14 ERF)	4.0	4.0	+	93	Yes	No	Most fatalities
Nadolol	3–4	10–20	1.9	0	20	No	No	Dialyzable
Timolol	1–2	3–5	1.4–3.4	+	10	No	No	Dialyzable; available as ocular drops
Pindolol	1	3–4	3–6	+	51	Yes	Yes	
Labetalol	1–2	4–6	10	0	50	Yes	No	α_1-blockade
Oxprenolol	3	2	1.3	+	78	Yes	Yes	
Sotalol	2–4	7–18	1.6–2.4	+	0	No	No	Dialyzable, QT prolongation & risk of torsades de pointes
Carvedilol	5	6–10	1.5–2	+	95	No	No	α_1-blockade
Selective Beta-Blockers								
Metoprolol	1–2 (4–5 ERF)	3–4	5.5	+	12	No	No	
Atenolol	2–4	5–8	0.7	0	5	No	No	Dialyzable
Esmolol (IV only)	rapid	0.13	2	0	55	No	No	
Acebutolol	2–4	2–4	1.2	+	26	Yes	Yes	Dialyzable, QT prolongation & risk of torsades de pointes
Bisoprolol	2–4	10–12	2.9	0	30	No	No	
Betaxolol	1.5–6	12–22	5 - 13	0	55	No	No	

V_d, Volume of distribution; *T1/2*, elimination half-life; *MSA*, membrane stabilizing activity; *ISA*, intrinsic sympathomimetic activity; *ERF*, extended-release formulations.

Differential Diagnoses

The combination of bradycardia and hypotension suggests beta-blockade, calcium channel blockade, or digoxin poisoning. Centrally acting α_2-adrenergic agonists such as clonidine and tizanidine or imidazoline receptor agonists such as tetrahydrozoline and oxymetazoline may also cause this constellation of symptoms. Without a history of beta-blocker ingestion, the diagnosis can be challenging, especially when non-cardiac effects such as CNS depression and seizures predominate. Sodium channel poisoning with QRS widening can occur, suggesting other antidysrhythmic drugs or cyclic antidepressants. The differential diagnoses also include sedative-hypnotic drug overdose, hypoglycemic drug ingestion, opioid overdose, CNS injury or infection, various endocrine and metabolic disorders, sepsis, and acute myocardial infarction.

Diagnostic Testing

Diagnosis and management depend entirely on the clinical picture, and the only essential testing is a point-of-care glucose monitoring and a 12-lead electrocardiogram (ECG) with continuous ECG monitoring. Serum concentrations of beta-blockers correlate poorly with severity of intoxication and are not readily available. Most urine toxicology screens do not identify antidysrhythmic drugs and are not helpful. Known access of the patient to a beta-blocker and consistent clinical features such as bradycardia and hypotension should lead the clinician to consider beta-blocker intoxication and begin empirical treatment. Whereas some authors believe that a serum lactate concentration can help predict mortality in overdose patients,[17] this has not held true in pure beta-blocker ingestions.

Management

Immediate measures include IV fluids for hypotension, supplemental oxygen as needed for hypoxia, and monitoring of cardiac rhythm and respirations. Whole-bowel irrigation is cumbersome and because there is a lack of evidence for efficacy in clinical trials, we recommend against its use in beta-blocker poisoning.[18] The clinical efficacy of gastric lavage is also unproven, the procedure is cumbersome, and benefit is outweighed by procedural risks. Please see Chapter 135 for further information on gastrointestinal decontamination, including the use of activated charcoal.

Hypotension, Bradycardia, and Atrioventricular Block

The first step in the treatment of beta-blocker overdose is bolus administration of crystalloid fluids. In hypotensive patients, 20 to 40 mL/kg of normal saline or lactated Ringers solution can be infused. Further doses of isotonic fluids, however, can lead to pulmonary edema and should be avoided particularly in older patients with underlying

TABLE 142.4 Selected Pharmacologic Characteristics of Calcium Channel Blockers

Drug	Time to Peak (hrs, oral form)	T1/2 (hrs)	V_d (L/kg)	Protein Binding (%)	Comments
Non-dihydropyridines					
Verapamil	1–2 (5–11 ERF)	3–12	4	90	Most lethal in overdose; impairs contractility and AV conduction more than most other calcium channel blockers
Diltiazem	2–4 (10–18 ERF)	3–7.9	1.7–5.3	70–80	AV node suppression similar to verapamil, contractility inhibition generally less than verapamil
Dihydropyridines					
Amlodipine	6–12	30–50	21	98	Vasodilation; additional vasodilation from nitric oxide production
Nifedipine	1 (6–11 ERF)	1–5	1.4–2.2	92–98	Vasodilation
Nimodipine	1	1–2	0.94–2.3	95	Vasodilation
Nicardipine	0.5–2 (1–4 ERF)	8–9	0.64	95	Vasodilation
Clevidipine (IV only)	Rapid	0.25	0.17	>99.5	Formulated in lipid emulsion for infusion
Felodipine	2.5–5	10	10	99	Vasodilation
Isradipine	1–1.5	1.9–16	3	95	Vasodilation
Nisoldipine	4–14	7–12	4–5	99	Vasodilation
Amine Calcium Channel Blocker					
Bepridil	2–6	33–42	8	99	Blocks sodium channels as well; QT prolongation & risk of torsades de pointes; no longer sold in United States

V_d, Volume of distribution; *T1/2*, elimination half-life; *AV*, atrioventricular; *ERF*, extended-release formulations.

TABLE 142.5 Clinical Characteristic of Poisoning from Beta-Blockers and Calcium Channel Blockers

Organ System	Beta-Blockers	Calcium Channel Blockers
Cardiovascular	Bradycardia & hypotension	Bradycardia & hypotension in non-DHPs, tachycardia & hypotension with DHPs
Pulmonary	Apnea (likely central) Bronchospasm (rare)	Pulmonary edema
Neurologic[a]	Drowsiness/coma in lipophilic BBs, seizures possible, preserved consciousness in non-lipophilic BBs until shock ensues	Generally preserved mental status until shock ensues
Endocrine	Hypoglycemia (rare)	Hyperglycemia

[a]Regardless of lipophilicity, both classes may cause obtundation once shock ensues.
BB, Beta-blocker; *DHP*, dihydropyridine.

cardiac disease. Frequent monitoring of volume status, such as with point-of-care ultrasound (by measuring the diameter and collapsibility of various large vessels including the inferior vena cava and common carotid artery) is recommended to avoid volume overload. Atropine at standard doses noted earlier may be used for bradycardia but is rarely effective. We recommend atropine for a heart rate of less than 50 beats per minute with concomitant hypotension and symptoms of severe bradycardia such as weakness, drowsiness, or obtundation. Infusion of more potent drugs or cardiac pacing is often necessary, and we recommend that atropine is best used as a temporizing measure to the therapies noted later.

Calcium

The final common pathway for stimulation of beta-adrenergic receptors is an increase in intracellular calcium concentration, and deleterious effects on calcium transport may contribute to beta-blocker toxicity. Therefore, IV administration of calcium can be used for treatment of hypotension. One gram of calcium gluconate contains 4.65 mEq of elemental calcium, whereas 1 g of calcium chloride contains 13.4 mEq. Calcium chloride is an acidifying salt and can cause significant tissue damage and necrosis if extravasation at the IV site occurs. Thus, it should be administered through a central venous catheter (or a secure large-bore antecubital peripheral line if the patient is in extremis). Indications for calcium include hypotension unresponsive to crystalloid fluids or symptomatic bradycardia. Typically, the heart rate should be less than 60 beats per minute, while considering whether the patient may have relative bradycardia. We recommend an initial dose of 13 to 25 mEq of calcium in adults (1 to 2 g calcium chloride, 3 to 6 g calcium gluconate) infused over 10 minutes. Patients in extremis may receive the initial dose over one minute. If a response is observed, repeated

doses may be given in 20 minutes, and a constant infusion may be started at 20 mg/kg/hr of calcium chloride (60 mg/kg/hr of calcium gluconate). If ionized calcium is measured instead of total calcium, we recommend not to exceed 1.5 times the upper limit of normal. The total serum calcium concentration can be as high as 18 mg/dL within 15 minutes after a bolus of just 5 mL of 10% calcium chloride, so calcium concentrations should be measured at least 30 minutes after bolus dosing has finished.

Glucagon

Glucagon has both inotropic and chronotropic effects and does not depend on beta-adrenergic receptors for its action; therefore, it has long been used for beta-blocker toxicity. It stimulates the production of intracellular cyclic adenosine monophosphate independently of the beta-adrenergic receptor. Furthermore, it helps counteract the hypoglycemia induced by beta-blocker overdose. Although not well studied, the initial recommended dose of glucagon is a 3- to 10-mg IV bolus (0.05 mg/kg for children). If a response occurs to glucagon, specifically if heart rate, blood pressure, or symptom improvement is observed, an infusion can be started at 3 to 5 mg/hr. Because glucagon is rarely used in large quantities, many hospitals may not stock enough glucagon to facilitate a long-term infusion. Additionally, glucagon is only available in 1 mg/1 mL vials that must be reconstituted, and preparation of it is labor-intensive and may be prolonged. Thus, clinicians administering glucagon should simultaneously ready themselves for additional therapies, such as high-dose insulin (HDI). We recommend glucagon for patients with bradycardia or hypotension not responsive to crystalloid fluids, atropine, and an initial bolus of calcium. In addition to stocking problems in most facilities, glucagon has a short (20-minute) half-life, and its effect is often transient. Vomiting is a common complication of glucagon, particularly if administered too rapidly, so the airway should be secured or monitored closely to prevent aspiration. With cumulative large doses, glucagon should be diluted in 5% glucose in water for constant infusion. Side effects also include hypokalemia. The response to glucagon alone is often inadequate, and glucagon is likely to be less effective than HDI for severe poisoning. From clinical experience, we find glucagon most useful as a transient therapy to bridge patients to HDI therapy, unless a glucagon bolus effectively resolves symptoms.

High-Dose Insulin

Despite glucagon's longer history for treatment of beta-blocker toxicity, HDI is a superior therapy. HDI is not a vasopressor; it is a potent inotrope with vasodilating properties.[19] The mechanism for HDI is not fully elucidated but probably involves both optimization of the use of carbohydrates for fuel by cardiac myocytes and modulation of intracellular calcium. HDI improves cardiac output significantly in beta-blocker toxicity from an increase in stroke volume more than heart rate.[20] Dosing of HDI is not universally agreed on; dosing in humans successfully treated with HDI has ranged from 0.5 to 22 U/kg/hr.[21] Human evidence for years was limited to case reports and small case series, however recommendations for HDI use with beta-blocker poisoning is increasing.[22] Multiple centers have reported favorable outcomes with HDI.[22,23] In the largest HDI study to date of 199 patients (103 of which were poisoned with beta-blockers), the overall survival was 84%. In this study, 21% of patients suffered cardiac arrest; however, of those experiencing arrest, 25% survived. Median peak HDI infusion in this study was 8 U/kg/hr. In beta-blocker poisoning, we recommend a bolus of 1 U/kg of regular insulin IV, followed by an infusion at 1 U/kg/hr titrated up by 2 U/kg/hr every 10 minutes (up to a maximum of 10 U/kg/hr) based on hemodynamic response to achieve adequate end-organ perfusion. Regardless of HDI dosing, we recommend that patients receive a bolus of 25 g glucose (1 traditional "amp" of D50) prior to insulin administration unless the serum glucose is greater than 200 mg/dL. A dextrose infusion (preferably a concentrated solution such as D50)[22] is administered via a central line because patients receiving HDI therapy are at higher risk of fluid overload.[24] Glucose concentration should be monitored as frequently as every 15 minutes until a steady state of glucose use is achieved. Although glucose requirements in HDI are typically higher with beta-blockers than with calcium channel blockers,[22] in neither scenario do glucose requirements increase with increasing doses of insulin.[23] Potassium concentration should also be monitored closely and replaced as needed because patients may become hypokalemic. Clinicians should be aware that metabolic abnormalities are common in HDI; hypoglycemia occurs in 31% to 73% of patients and hypokalemia occurs in 29% to 82% of patients, though in both cases careful monitoring and replacement prevents adverse outcomes.[22,23] In addition, hypoglycemia is less common if concentrated glucose infusions are used.[22] We recommend HDI for patients experiencing hypotension despite crystalloid fluid, atropine, and a single bolus of calcium. We also recommend a central venous catheter and an arterial catheter be placed upon the decision to initiate HDI. Of note, the inotropic effects of HDI do not typically occur until 20 minutes after the insulin bolus. As such, patients may need the bridging therapies described above, while HDI takes effect.

Sodium Bicarbonate

Sodium channel blockade from beta-blockers with membrane-stabilizing activity such as propranolol occasionally causes QRS widening, which mechanistically should respond to sodium bicarbonate. Bicarbonate should be dosed at 1 to 2 mEq/kg IV as a bolus repeated every 3 to 5 minutes until the QRS narrows to less than 120 ms. It is our experience that this is typically a late or even moribund finding in propranolol overdose. We recommend sodium bicarbonate for patients poisoned with a membrane-stabilizing beta-blocker who have an acute change in QRS duration to greater than 120 ms and demonstrate clinical signs of shock.

Vasopressors and Other Inotropes

Catecholamines are indicated when mean arterial pressure (MAP) cannot be maintained at 60 mm Hg or above, despite use of crystalloid infusion, calcium, atropine, glucagon, and HDI. We recommend against the use of vasopressors before HDI, because animal data show worse outcomes with vasopressors than HDI,[25] or even placebo.[26] A clinical conundrum exists regarding the use of vasopressors for toxin-induced shock in that animal studies generally show no benefit or even harm, while human data (which is limited to case reports and case series) show generally favorable outcomes.[27] Recent data in pigs poisoned with propranolol demonstrate rapid death with a combination of norepinephrine and epinephrine, and that HDI was a superior therapy in terms of mortality.[25] HDI, however, did not confer universal survival, and in fact both survival and brain perfusion improved when norepinephrine was added to HDI.[25] Given the extensive body of evidence demonstrating the safety and effectiveness of norepinephrine in other forms of shock, we recommend it as our first-line vasopressor, titrated to a MAP of 60 mm Hg up to a dose of 0.5 mcg/kg/min. In the selection of cardioactive medications to supplement HDI, glucagon, and norepinephrine, we recommend early assessment of cardiac contractility with bedside echocardiography. If contractility and heart rate are adequate, therapeutic focus should shift to providing support with vasopressors. Our second-line vasopressor of choice is vasopressin, dosed at a constant infusion of 0.01 to 0.04 U/min. If the clinical picture is still uncertain, an assessment of systemic vascular resistance and cardiac output by either indirect or direct measurements

is recommended to determine if either cardiogenic or distributive shock exists. We recommend third-line vasopressors or inotropes be chosen based upon these measurements used in conjunction with bedside echocardiography. Refractory cases of bradycardia may respond to an external or transvenous pacemaker. A pacemaker is particularly useful when cardiac contractility is vigorous, but bradycardia is persistent.

Intravenous Fat Emulsion (Intralipid)

Intravenous fat emulsion (IFE) is an adjunctive therapy for cardiotoxic shock. This therapy was first described for treatment of toxicity from local anesthetics such as bupivacaine.[28] The pharmacologic rationale for the use of IFE is discussed in Chapter 135. Enthusiasm for IFE for beta-blocker poisoning was high after the publication of positive animal studies and several case reports describing good outcomes,[29] but subsequent larger studies cast significant doubt on the effectiveness of IFE for oral overdoses, as in beta-blockers.[30,31] One study found that in 91% of published IFE cases, a concomitant resuscitative therapy was administered that could also explain the observed positive outcome.[30] A recent systematic review and collaborative expert panel found the evidence for non-local anesthetic poisoning to be of very low quality, and did not recommend in favor or against the use of IFE, even as a salvage therapy.[32] A national toxicology organization's position statement recently stated there is no standard of care to use or not use IFE for oral overdoses, and that in circumstances where there is significant hemodynamic instability secondary to a lipid-soluble drug, that IFE is a reasonable consideration for therapy. As such, we recommend IFE in patients with persistent bradycardia or hypotension not responding to IV fluids, calcium, HDI, and at least three vasopressors or inotropes at maximum recommended infusion rates and if extracorporeal membrane oxygenation (ECMO) is unavailable. Dosing for IFE is also not universally agreed upon.[33] We recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given over 2 to 3 minutes, followed immediately by an infusion of 0.25 mL/kg/min. If a response occurs at this infusion rate, the infusion dose may be decreased to 0.025 mL/kg/min (1/10th the initial rate) to sustain lipemic serum for a longer period of time.[33,34] The 1.5 mL/kg bolus can be repeated up to two additional times for refractory shock or cardiac arrest, although clinicians should avoid exceeding 10 mL/kg unless hemodynamic compromise requires otherwise. Response, when it occurs, is typically within minutes of the bolus.

The use of IFE is associated with several complications, including extreme lipemia resulting in lab interference with blood tests (complete blood counts, chemistries, and coagulation studies), as well as acute pancreatitis, acute kidney injury, acute respiratory distress syndrome, fat overload syndrome, and cardiac arrest.[35]

Ventricular Dysrhythmias

Although it is uncharacteristic, ventricular tachydysrhythmias can occur following beta-blocker toxicity. Cardioversion and defibrillation are indicated for ventricular tachycardia and ventricular fibrillation, respectively, following American Heart Association guidelines. Pulsatile ventricular tachycardia can most safely be treated with lidocaine. For dosing recommendations, please see the Management of Cardioactive Steroids section of this chapter. Antidysrhythmic drugs, especially of classes IA and IC, should be avoided because they may potentiate AV block or be prodysrhythmic because of additive membrane-stabilizing activity. Sotalol, unlike other beta-blockers, has class III as well as class II effects causing prolongation of the QT interval and can induce torsades de pointes and other ventricular dysrhythmias. Overdrive pacing with isoproterenol or a pacemaker and magnesium sulfate are specific therapies for torsades de pointes.

Extracorporeal Elimination and Circulatory Assistance

Hemodialysis or hemoperfusion may be beneficial for beta-blockers with lower V_d, lower protein binding, and greater hydrophilicity (see Table 142.3), though due to limited evidence[36] we recommend hemodialysis only if another indication for hemodialysis is present (e.g., severe metabolic acidosis, acute renal failure, fluid overload, hyperkalemia, or other electrolyte disturbances).

Unlike overdoses of other drugs, toxicity from cardiovascular drugs do not destroy tissue, and if circulation can be supported, complete recovery can be expected. Intra-aortic balloon pumps,[22] percutaneous left ventricular assist devices,[36-38] and cardiopulmonary bypass have all been successfully employed as salvage therapies. However, with the proliferation of extracorporeal cardiopulmonary resuscitation (eCPR) programs[39] the availability of ECMO for poisonings has increased substantially in the past decade.[15,40-43] As such, ECMO is our recommended mechanical support therapy in cases where patients have hypotension refractory to HDI, and at least three vasoactive agents or in cases with bradycardia or cardiogenic shock unresponsive to inotropes and a pacemaker.

Pediatric Considerations

Severe pediatric beta-blocker poisonings are rare. In the cases reported, CNS, cardiac, and metabolic toxicities are similar to those in adult overdoses. Symptomatic hypoglycemia, however, is more common in children and occurs even after therapeutic doses. Therefore, serum glucose concentration should be measured in children. Risk factors include young age, fasting state, and diabetes mellitus. Obtunded children should receive empirical glucose, 1 to 2 mL/kg of 25% glucose IV. In general, 5% glucose infusions have been sufficient to maintain euglycemia, especially with concomitant use of glucagon and catecholamines, which stimulate glucose release.

Seizures also occur in cases of pediatric beta-blocker overdose; hypoglycemia may be a contributing factor. They are more common with the lipid-soluble beta-blocker propranolol. Benzodiazepines in standard doses are generally effective. Children generally fare well after beta-blocker ingestion, with symptoms in only 2% of potential beta-blocker exposures.

Sequential Approach to Beta-Blocker Poisoning

The management of beta-blocker poisoning begins with a 20 mL/kg bolus of IV fluid, repeated once if needed (Table 142.6). Symptomatic bradycardia, typically a heart rate of 50 bpm or less in adults, should be treated with atropine, 1 mg every 3 minutes up to a total of 3 mg. If hypotension (systolic pressure <90 mm Hg) persists, 3 to 6 g of calcium gluconate should be infused over 10 minutes. If hypotension persists after calcium infusion, HDI should be initiated. Glucagon, given as a 5-mg bolus, can be used to bridge to HDI. One "amp" of D50 should be administered followed by 1 U/kg of regular insulin as a loading dose. An infusion of 25 g/hr of concentrated glucose should be initiated in addition to an infusion of insulin at 1 U/kg/hr. The insulin infusion should be increased by 2 U/kg/hr every 10 minutes until hypotension resolves or a maximum rate of 10 U/kg/hr is reached. Glucagon may be repeated during HDI titration if hypotension persists. If HDI does not resolve hypotension, norepinephrine should be administered starting at 0.1 mcg/kg/min and titrated up until hypotension resolves or until a maximum dose is reached. After maximal norepinephrine is reached, the clinician should reassess using bedside echocardiography and measurement of cardiac

TABLE 142.6 Sequential Treatment Recommendations for Poisoning from Beta-Blockers and Calcium Channel Blockers

Phase of Treatment	Beta-Blockers	Calcium Channel Blockers
Phase 1 (initial resuscitation; primarily bolus dose therapies)	Activated charcoal as indicated Isotonic fluid bolus 20–40 mL/kg Atropine Calcium Glucagon	Activated charcoal as indicated Isotonic fluid bolus 20–40 mL/kg Atropine Calcium
Phase 2 (stabilization; place central & arterial lines, consider cardiac output & SVR monitoring)	Place central & arterial lines HDI infusion Norepinephrine Vasopressin 3rd agent based on type of shock Pacemaker for bradycardia	Place central & arterial lines HDI infusion Norepinephrine Vasopressin 3rd agent based on type of shock Pacemaker for bradycardia
Phase 3 (salvage therapies)	IFE ECMO Other mechanical devices if ECMO not available	IFE Methylene blue ECMO Other mechanical devices if ECMO not available

HDI, High-dose insulin; *IFE*, intravenous fat emulsion; *SVR*, systemic vascular resistance; *ECMO*, extracorporeal membrane oxygenation.

output and systemic vascular resistance to determine if the patient needs additional inotropy, chronotropy, or vasotropy. If bradycardia is contributing to decreased cardiac output, we recommend a pacemaker; a transvenous approach will likely be necessary. Additional inotropes or vasopressors such as vasopressin, phenylephrine, epinephrine, dopamine, or dobutamine should be selected and titrated up based upon the patient's cardiac output and systemic vascular resistance. We recommend vasopressin as the second-line vasopressor at a steady-state infusion of 0.01 to 0.04 U/min. Once the patient has reached maximal doses on HDI and three vasopressors or catecholamines, depending on institutional availability we next recommend either IFE or ECMO; if ECMO is readily available, ECMO is preferred. If used, IFE may be dosed at 1.5 mL/kg IV of 20% lipid solution followed by an infusion as noted above. The bolus may be repeated; however, a maximal dose of 1000 mL of lipid solution should not be exceeded. A concern exists that if IFE and ECMO are used in tandem, clogging and malfunction of the membrane oxygenator from lipemia and fat agglutination is a concern.[44] Case reports[45] and in vitro data suggest this can occur, along with cracking of stopcocks and increased blood clotting in the circuits.[44] Nonetheless, the use of IFE is not a contraindication to ECMO. If IFE is used prior to ECMO, the infusion should be discontinued once the decision to cannulate has been made, and the perfusionist alerted that clogging of the oxygenator may occur so they may anticipate this complication.

Disposition

Patients who remain completely asymptomatic for 6 hours after an oral overdose of normal-release preparations can be safely discharged home if the overdose was accidental or referred for psychiatric evaluation if it was intentional. We recommend consultation with a poison control center or standard pharmacologic reference to confirm that peak effect of the beta-blocker in question has passed before psychiatric disposition (see Table 142.3). Patients ingesting sustained-release preparations should be admitted to a monitored bed; however, those who remain asymptomatic 8 to 12 hours after ingestion are unlikely to have toxicity. Patients with second or third-degree AV heart block, hypotension not responding to IV fluid administration, or who have hemodynamically significant dysrhythmias should be admitted to an intensive care unit.

CALCIUM CHANNEL BLOCKERS

KEY CONCEPTS

- Signs and symptoms of calcium channel blocker intoxication often occur early after overdose but may be significantly delayed with sustained-release products.
- AV block and bradydysrhythmias predominate with verapamil and diltiazem; dihydropyridine calcium channel blockers often present with tachycardia.
- Treatment is similar to beta-blockers, except glucagon is not recommended, and methylene blue is a reasonable option for vasoplegia unresponsive to maximum doses of norepinephrine and vasopressin.

Foundations

Principles of Toxicity

Verapamil and nifedipine, the earliest calcium channel antagonists, were introduced in Europe in the 1970s and in the United States in the early 1980s. Calcium antagonists have found many clinical applications: angina pectoris, hypertension, supraventricular dysrhythmias, hypertrophic cardiomyopathy, and migraine prophylaxis. Verapamil is the most lethal in overdose, but severe toxicity and death have been reported for most drugs of this class. In 2018, United States poison control centers received nearly 14,000 calls about calcium channel blockers.[1] Nearly 1200 of these calls were regarding patients with life-threatening symptoms.[1] In general, calcium channel blockers are more toxic than beta-blockers, likely because they cause both cardiogenic shock and vasoplegia.

Pathophysiology

Calcium channel antagonists block the slow L-type calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation. They also reduce cardiac contractility, depress SA nodal activity, and slow AV conduction. In cases of overdose, verapamil has the deadliest profile, combining severe myocardial depression and peripheral vasodilation. Both verapamil and diltiazem act on the heart and blood vessels, whereas dihydropyridine calcium channel blockers (e.g., amlodipine) cause primarily vasodilation and

subsequent reflex tachycardia due to subtle binding differences in the α1c subunit of L-type calcium channels. As with beta-blockers, selectivity is lost after overdose and toxicity is in four domains: negative effects on heart rate, contractility, conduction, and vascular tone, with the exception of dihydropyridine calcium channel blockers, which tend to result in tachycardia until severe toxicity occurs, when bradycardia ensues.

All calcium channel blockers are rapidly absorbed, although first-pass hepatic metabolism significantly reduces bioavailability (see Table 142.4). Onset of action and toxicity may occur as early as 30 minutes after ingestion. In contrast, the poisoning from sustained-release verapamil may not manifest for 12 hours or more. High protein binding and V_d greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective with calcium antagonists.

Clinical Features

Severe calcium antagonism eventually affects multiple organ systems, but cardiovascular toxicity is primarily responsible for morbidity and mortality. Hypotension and bradycardia occur early, and other rhythm disturbances include AV block of all degrees, sinus arrest, AV dissociation, junctional rhythm, and asystole. Dihydropyridine calcium channel blockers (e.g., amlodipine) often cause reflex sinus tachycardia from peripheral vasodilation. Calcium channel blockade has little effect on ventricular conduction; therefore, QRS widening is not seen early on. Ventricular dysrhythmias are also uncommon. A unique feature of calcium channel blocker poisoning is endocrine dysfunction. Like many drugs, calcium channel blockers lose specificity in overdose and thus interfere with other calcium channels within the body. As calcium influx triggers the release of insulin, patients poisoned with calcium channel blockers are often hyperglycemic. In addition, edema is a common side effect of calcium channel blockers at therapeutic doses. Edema occurs because of selective dilation of vessels on the afferent side of the capillary bed while suppressing normal regulatory responses that protect capillaries from hydrostatic pressure. At therapeutic doses, peripheral edema from calcium channel blockers is common; however, pulmonary edema may occur in overdose, which is likely due to a combination of drug effect and iatrogenic volume overload.[46,47] Nearly half of patients with severe amlodipine poisoning have non-cardiogenic pulmonary edema.[48] As with digoxin and beta-blocker overdose, nausea and vomiting are common but not specific. For additional clinical features, see Table 142.5. Like beta-blockers, calcium channel blockers cause early toxicity, and symptoms commonly occur within 6 hours of ingestion of normal-release preparations. Toxicity can be delayed 12 to 24 hours with sustained-release preparations.

Differential Diagnoses

Differential diagnoses are similar to that of digoxin and beta-blocker overdoses. Until characteristic rhythm disturbances supervene, many other toxic, metabolic, traumatic, and cardiovascular disorders can cause hypotension but less commonly bradycardia. The reflex tachycardia and distributive shock seen with dihydropyridine calcium channel blockers can mimic sepsis, volume depletion, or anaphylaxis.

Diagnostic Testing

Serum levels of calcium antagonists are not readily available nor do urine toxicology screens reliably detect this class of drugs. Glucose and electrolytes (including calcium and magnesium) should be measured. Hyperglycemia secondary to insulin inhibition occurs and correlates with severity of verapamil and diltiazem poisoning; it is unknown if the same is true in dihydropyridine overdose. If hyperglycemia is present with concomitant hypotension, we recommend HDI. Please see specific dosing recommendations later. A metabolic (lactic) acidosis can occur with prolonged hypotension and hypoperfusion.

An ECG should be promptly obtained, with special attention to atrial and ventricular rates and PR, QRS, and QT intervals. The ECG should be repeated when the patient's hemodynamic status changes.

Management

Initial management includes rapid establishment of vascular access, cardiac monitoring, and frequent blood pressure measurement. Please see Chapter 135 for further information on gastrointestinal decontamination, including the use of activated charcoal. For an algorithmic approach to management, see Table 142.6.

Hypotension and Bradycardia

Hypotension can be caused by myocardial depression, inadequate heart rate, or peripheral vasodilation. Atropine may be used for bradycardia but is rarely effective. We recommend atropine at the doses noted earlier for a heart rate of less than 50 beats per minute with concomitant hypotension and symptoms of severe bradycardia such as weakness, drowsiness, or obtundation. Atropine's effect has often been minimal and short-lived, and it is at best a temporizing intervention. A bolus of crystalloid (20 to 40 mL/kg or more) should also be infused early; however, care should be taken to avoid fluid overload given the additional risk of pulmonary edema with calcium channel blocker poisoning, particularly in elderly patients or those with underlying heart disease.

After the basic supportive therapies noted previously, expert consensus recommendations include calcium salts, HDI, and norepinephrine.[49] We recommend these three agents be administered in the sequential fashion noted for beta-blocker poisoning. We do not recommend glucagon in calcium channel blocker poisoning. It has no mechanistic advantage over epinephrine or other beta-agonists, and no good evidence exists to support its use in calcium channel blocker poisoning.

IFE (e.g., Intralipid) has been described in the use of calcium channel blockers. The proposed mechanisms are discussed in Chapter 135. Similar to beta-blockers, early animal studies and case reports were promising, while larger follow-up studies showed poor outcomes in human poisoning. The same collaborative expert panel on IFE noted earlier did not recommend in favor or against the use of IFE in calcium channel blocker poisoning, even as a salvage therapy.[32] As such, we recommend IFE in patients with persistent cardiogenic shock not responding to IV fluids, calcium, HDI, and at least three vasopressors or inotropes at maximum recommended infusion rates if extracorporeal membrane oxygenation (ECMO) is not immediately available.

Methylene blue is an emerging therapy for calcium channel blocker poisoning.[50] Although traditionally used as a reducing agent for the treatment of methemoglobinemia, methylene blue is also a vasoconstrictor. Specifically, it inhibits the enzyme guanylyl cyclase, resulting in decreased production of cyclic guanosine monophosphate (cGMP) and inhibition of endothelial smooth muscle relaxation, causing an increase in systemic vascular resistance.[51] Methylene blue is particularly intriguing for the treatment of amlodipine poisoning, because amlodipine specifically causes an increase in nitric oxide production, which leads to increased cGMP and vasodilation as noted earlier. Data are limited to a small number of animal studies and human case reports,[52,53] and thus far suggest improvement is limited to hemodynamic parameters and not overall mortality.[51] Methylene blue was inferior to IFE in a rat model of amlodipine poisoning,[54] nor did it improve outcomes when compared to norepinephrine in a pig model of amlodipine poisoning.[55] We recommend the use of methylene blue only as an alternative salvage therapy for vasoplegic shock refractory to infusions of HDI, maximal norepinephrine, and vasopressin. Dosing

involves a 1- to 2-mg/kg bolus of a 1% methylene blue solution followed by an infusion of 1 mg/kg for up to 6 hours. Recently angiotensin II was FDA-approved for the treatment of vasodilatory shock;[56] its use in poisoning from calcium channel blockers (and poisoning in general) is limited to case reports requiring further study.[57] The use of angiotensin II would be a reasonable treatment for refractory vasodilatory shock in lieu of methylene blue, or as an additional therapy for profound vasoplegia refractory to maximal infusions of an α_1-adrenergic agonist (e.g., norepinephrine, phenylephrine) and vasopressin.

Pediatric Considerations

Nifedipine, verapamil, and probably other drugs in its class join the short list of medications that can kill a child with ingestion of a single tablet. Seizures may be more common in children than in adults and should be treated with benzodiazepines. Overall, death after calcium antagonist ingestion in children is rare. The IV route of administration, as with digoxin, is much more dangerous. Even therapeutic doses of IV verapamil are considered contraindicated in infants with supraventricular tachycardia because of cardiovascular collapse and cardiac arrest after injection which have been documented in case reports.[58]

Hyperglycemia occasionally occurs in children, but the elevation is usually short-lived. Although insulin has been administered in a small number of cases, it is generally not necessary unless HDI is required for hemodynamic compromise, because the hyperglycemia usually resolves spontaneously within 24 to 36 hours.

There are case reports of children in refractory shock secondary to drug toxicity who have been treated with intra-aortic balloon counterpulsation or cardiac bypass, though ECMO has gained favor as the mechanical support device of choice.[58] Aside from the differences previously noted, the presentation in children is similar to that in adults: rapid onset of toxicity with CNS depression, bradydysrhythmias (except for dihydropyridine calcium channel blockers), and hypotension.

Disposition

Because the peak effect of normal-release calcium channel blockers commonly occurs in 90 minutes to 6 hours, patients who are totally asymptomatic for 6 hours after an ingestion of immediate-release medication can be safely discharged if accidental, or according to psychiatric recommendations if intentional. Symptomatic patients or those who ingested delayed-release preparations should be admitted for at least 24 hours of continuous cardiac monitoring. Persistently hypotensive, bradycardic patients who do not respond to conventional therapy require intensive care monitoring.

CLONIDINE AND OTHER CENTRAL ALPHA-2 AGONISTS

KEY CONCEPTS

- Clonidine poisoning may mimic opioid poisoning and is best treated with crystalloid fluids followed by an infusion of norepinephrine.
- In patients at low risk for opioid dependence, naloxone, given as a 10 mg bolus from a single syringe, is recommended for obtundation.

Foundations

Clonidine is a central acting α_2-adrenergic and imidazoline agonist initially approved by the FDA as a treatment for hypertension in 1974. Since that time, its use has expanded to treat conditions such as attention deficit hyperactivity disorder (ADHD), pheochromocytoma, and withdrawal from opioids, ethanol, and nicotine. It is also used in spinal and epidural anesthesia. Based on its mechanism of action, it mimics clinical features of both opioid poisoning and poisoning from digoxin, beta-blockers, or calcium channel blockers. In 2018 United States poison centers received over 10,000 calls regarding clonidine exposures with over 2,000 suffering life-threatening effects.[1] Clonidine poisoning appears to be increasing in children.[59]

Clinical Features

Clonidine exerts its effects by binding to presynaptic α_2-adrenergic receptors in the brain, inhibiting neurons in the nucleus tractus solitarius, causing decreased norepinephrine release. This leads to bradycardia, hypotension, decreased mental status, miosis, and occasionally hypothermia. Clonidine is also an agonist at imidazole receptors; imidazoline receptors are located throughout the body, but their activation in the brain, specifically in the rostral ventrolateral medulla, causes unconsciousness, bradycardia, and hypotension, potentially exacerbating the α_2-adrenergic effects of clonidine.[60] Although clonidine overdose presents with bradycardia, hypotension, and coma, most cases have favorable clinical outcomes.[61]

Differential Diagnoses

There is a wide overlap between the clinical effects of central α_2-agonists such as clonidine and imidazole agonists. Individual drugs that are agonists at either or both receptors may belong to disparate classes. Therefore, antihypertensive medications (e.g., guanabenz, α-methyldopa), ADHD medications (e.g., guanfacine), muscle relaxers (e.g., tizanidine), and topical vasoconstrictors in dermatologic (e.g., brimonidine),[62] ocular, and nasal settings (e.g., tetrahydrozoline, oxymetazoline, and naphazoline)[63] all have similar systemic effects in overdose. The presentation of miosis and obtundation may be mistaken for opioid or sedative-hypnotic overdose, and the combination of bradycardia and hypotension may mimic digoxin, beta-blocker, or calcium channel blocker poisoning. Pontine hemorrhage should also be considered in the differential diagnoses.

Diagnostic Testing

Clonidine and other similar drugs are not routinely screened for in most blood or urine drug screens. Clonidine poisoning is a clinical diagnosis. An ECG should be obtained to evaluate for heart block and to evaluate the QRS and corrected QT (QTc) intervals, and the patient should be placed on continuous cardiac monitoring and pulse oximetry. Small doses of naloxone may help differentiate clonidine poisoning from opioid poisoning; however, if large doses are required, this may be less helpful diagnostically because large doses of naloxone have been reported to reverse clonidine toxicity.

Management

Supportive care is the mainstay of therapy for clonidine poisoning. Monitoring as described earlier is essential. Hypotension should be treated with boluses of 20 mL/kg of isotonic fluid. The concern for pulmonary edema is less than with beta-blocker or calcium channel blocker poisoning, thus the clinician can be more liberal with IV fluid administration in clonidine poisoning. We recommend treating hypotension with up to 60 mL/kg of isotonic fluid. If hypotension is worsening or persistent at a level of inadequate organ perfusion despite adequate fluid resuscitation, a catecholamine is indicated. There are no human randomized trials comparing various catecholamines in clonidine poisoning; however, because the underlying pathophysiology is a lack of systemic norepinephrine, we recommend norepinephrine initiated as 0.1 mcg/kg/min and titrated to a MAP of 60 mm Hg. When blood pressure stabilizes, downward titration of norepinephrine is initiated, with a goal of maintaining adequate organ perfusion with the

least necessary dose, ultimately weaning the patient off the vasopressor entirely.

Several authors have suggested naloxone may be a useful therapy in clonidine poisoning. Clonidine causes the spontaneous release of β-endorphin, an endogenous opioid. It is likely naloxone's antagonism of β-endorphin's opioid effects that causes reversal of CNS depression in clonidine poisoning. Although case reports of naloxone successfully reversing clonidine poisoning exist, they are rare and inconsistent. Our clinical experience is that naloxone is rarely effective for clonidine poisoning in adults, however recent data suggest clonidine may be an effective treatment in children. In a study of 51 somnolent children poisoned with clonidine, 40 (78%) woke upon administration of naloxone.[64] The authors noted greater success when 10 mg of naloxone was administered as a bolus from a single syringe, rather than a titrated approach. Because the precipitation of opioid withdrawal can be dangerous, in patients at high risk for opioid dependence we recommend escalating doses of naloxone of 0.2 mg, 0.4 mg, 2 mg, and then 10 mg if the patient is obtunded. If there is no concern for opioid dependence, we recommend naloxone be given as a 10-mg rapid bolus from a single syringe, regardless of the patient's age or size.

Disposition

Clonidine's peak effects occur 2 to 4 hours post-ingestion. Its half-life is between 5 and 13 hours. Therefore, patients with normal vital signs and mental status 4 hours post-ingestion may be discharged home if the overdose was accidental or to an appropriate psychiatric facility if intentional. Patients with persistent vital sign abnormalities or altered mental status should be admitted to a unit capable of continuous cardiac and oximetry monitoring. Patients requiring vasopressor support or with severe obtundation should be admitted to a critical care unit.

NITRATES, NITRITES, AND METHEMOGLOBINEMIA

KEY CONCEPTS

- Nitrates are contraindicated in patients who have recently taken phosphodiesterase inhibitors for erectile dysfunction.
- Patients with a methemoglobin concentration of 25% and symptoms of anemia should be treated with methylene blue.

Foundations

Principles of Toxicity

Nitrates (nitroglycerin, isosorbide mononitrate and dinitrate) are widely used as vasodilators in the treatment of heart failure and ischemic heart disease. They augment coronary blood flow, as well as reduce myocardial oxygen consumption by reducing afterload. At lower doses nitrates primarily dilate veins, but at higher doses they also dilate arteries. In addition, many exposures occur in young adults, usually male, who inhale various alkyl nitrites (amyl, butyl, isobutyl, or ethyl nitrite) in the hope of enhancing or prolonging sexual pleasure. Because of the sound they make when broken open, these products are commonly known as "poppers."[65]

Nitrates are occasionally found in rural well water contaminated by livestock or fertilizer runoff. Oral nitrates may be converted to nitrites in the gastrointestinal tract, especially in infants up to 4 months old. Nitrites, and to a lesser extent, nitrates themselves, have substantial oxidizing power and may oxidize the ferrous (Fe^{2+}) ion in hemoglobin to its ferric (Fe^{3+}) state, causing methemoglobinemia. Methemoglobin is incapable of carrying oxygen, thus it alters the shape of the hemoglobin-dissociation curve shifting it to the left, causing functional anemia via impaired oxygen delivery.

Clinical Features

Hypotension is a common complication. Typically, it is accompanied by reflex tachycardia unless the patient also has taken another agent such as a beta-blocker that slows chronotropy. Even in therapeutic doses, rapid dilation of meningeal arterioles causes headache, often leading to patient noncompliance.

Patients suffering nitrate-induced methemoglobinemia have symptoms related to impaired oxygen delivery. The concentration of methemoglobinemia and the speed with which it is achieved are directly proportional to symptom severity. Cyanosis occurs commonly when the percentage of methemoglobin exceeds 10%. Inspection of the patient's blood upon venipuncture reveals "chocolate-colored" blood due to the spectrum of light absorbed by methemoglobin; this typically occurs at a methemoglobin concentration greater than 15%. Higher concentrations of methemoglobin may result in fatigue, dyspnea, weakness, dizziness, drowsiness, syncope, coma, seizures, and death.

Differential Diagnoses

The differential diagnosis of nitrate poisoning includes all other vasodilating drugs such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, and dihydropyridine calcium channel blockers, as well as oxidative phosphorylation uncouplers such as cyanide and carbon monoxide. Non-toxicologic conditions capable of mimicking nitrate poisoning include sepsis and anaphylaxis. The differential diagnosis of methemoglobinemia includes hypoxia, as well as other hemoglobinopathies such as sulfhemoglobinemia.

Diagnostic Testing

No specific mandatory diagnostic testing is recommended for nitrate poisoning. For patients with suspected methemoglobinemia, an oxygen challenge should first be attempted. If the patient is cyanotic and high-flow oxygen at 15 L/min by non-rebreather mask does not improve cyanosis, blood co-oximetry should be performed to determine the percentage of methemoglobin in the blood. If methemoglobinemia is confirmed, a hemoglobin concentration should be obtained. If anemia is present, smaller concentrations of methemoglobin may be clinically significant because the functional anemia of methemoglobinemia is synergistic with absolute anemia. Most humans have, at baseline, a methemoglobin percentage of 1% to 3%. Symptoms do not typically occur until concentrations of 10% or more.

Clinicians should be wary of interpreting pulse oximetry in the setting of methemoglobinemia. Pulse oximeters function by reading the absorbance of light at wavelengths of 660 and 940 nm, which are selected to separate oxy and deoxyhemoglobin. Methemoglobin absorbs light at both these wavelengths more than either oxy or deoxyhemoglobin. This results in unreliable pulse oximetry that typically reads near 85%, regardless of the patient's oxygenation status.

Management

Nitrate poisoning usually responds to supine positioning, IV fluids, and reduction of dose or removal of the offending agent. Hypotension is usually transient. Low-dose vasopressors are occasionally needed, but it is best to avoid them in the setting of acute coronary syndrome.

Review of the therapeutic use of nitrates offers insight into poisoning. For example, IV nitroglycerin infusions are used commonly in patients with acute pulmonary edema for afterload reduction. Infusions are usually initiated at 5 to 10 μg/min, but rates of 300 mcg/min or greater may be used. These doses may be beneficial in patients with pulmonary edema accompanied by acute hypertension, but

hypotension may develop suddenly. IV nitroglycerin has a rapid offset of action, so excessive fall in blood pressure usually responds to reduction or termination of the infusion.

Use of nitrates is contraindicated in patients who have recently taken certain drugs for erectile dysfunction, such as sildenafil (Viagra) or tadalafil (Cialis). These drugs inhibit type 5 phosphodiesterase, relaxing vascular smooth muscle, which can prolong and intensify the vasodilating effects of nitrates causing severe hypotension. If blood pressure does not normalize with IV fluids and cessation of the nitrate infusion, norepinephrine should be cautiously titrated to a MAP of 60 mm Hg, beginning at 0.1 mcg/kg/min.

Treatment of patients with methemoglobinemia involves supportive care such as supplemental oxygen and IV fluids as needed. More severely poisoned patients should be treated with IV methylene blue. Methylene blue is an oxidizing agent. However, in the presence of the red blood cell enzyme nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase, it is reduced to leukomethylene blue, which then reduces methemoglobin back to hemoglobin. We recommend an intravenous dose of 1 to 2 mg/kg of 1% methylene blue solution for patients with a methemoglobin concentration greater than 25% and any symptoms of functional anemia. The infusion should be given over 5 minutes to reduce pain at the IV access site. A clinical response should occur within minutes of infusion. If cyanosis does not resolve in 1 hour, a second infusion of 1 mg/kg can be repeated. At doses exceeding 7 mg/kg, the oxidizing power of methylene blue becomes great enough that it may paradoxically worsen methemoglobinemia or cause hemolysis; thus, multiple or excessive doses are not recommended.

Disposition

Patients with refractory hypotension despite therapeutic measures discussed in the preceding section should be admitted to a monitored setting. We recommend all patients receiving methylene blue be admitted, as some poisons that cause methemoglobinemia have half-lives that exceed that of methylene blue. If the patient remains unstable and persistently cyanotic or hypoxic, or requires repeat doses of methylene blue, they should be admitted to a critical care setting.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 142: QUESTIONS AND ANSWERS

1. A 72-year-old man presents with a chief complaint of nausea. He also complains of blurred vision and general weakness. His vital signs and physical examination are normal. He has a past medical history significant for myocardial infarction, congestive heart failure, hypertension, and diabetes. He states that he takes all prescribed medications regularly and just took all of his medications as prescribed approximately 1 hour ago. Reviewing his medication list, you note that one of his medications is digoxin. Which of the following should be done?
   a. Administer oral potassium.
   b. Give digoxin-specific Fab fragment antibodies now.
   c. Give digoxin-specific Fab fragment antibodies only if he has an abnormal electrocardiogram (ECG).
   d. Obtain a serum digoxin level in 6 hours.
   e. Obtain a serum digoxin level now.

Answer: D. The steady-state (as opposed to peak) digoxin level is most closely correlated with toxicity. Peak level is reached in 1.5 to 2 hours, whereas steady-state levels are not reached until 6 to 8 hours after ingestion. As long as a patient is stable and a chronic ingestion is suspected, digoxin levels taken soon after ingestion are not helpful. Other diagnostic studies should be undertaken while waiting for the digoxin level, including, but not limited to, an electrocardiogram (ECG) and serum electrolyte determination.

2. In a patient with a known digoxin overdose, which of the following is an indication for administration of digitalis antibody fragments?
   a. Acute ingestion of 10 mg of digoxin
   b. Atrial fibrillation with rapid ventricular response
   c. First-degree heart block
   d. Ingestion of oleander *(Nerium oleander)*
   e. Serum potassium greater than 5 mEq/L

Answer: E. Hyperkalemia is an indication for treatment with digitalis antibody fragments. Other indications include severe ventricular dysrhythmias; hemodynamically significant bradydysrhythmias unresponsive to atropine; rapidly progressive rhythm disturbances or rising potassium level; co-ingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or cyclic antidepressants; or ingestion of a plant known to contain cardiac glycosides in the setting of severe dysrhythmias.

3. A 27-year-old man presents after ingesting 8 mg of digoxin in a suicide attempt. He has ventricular tachycardia on his electrocardiogram (ECG). His blood pressure is 93/54 mm Hg. Laboratory results are not available. You decide to treat with digitalis antibody fragments. How many vials would bind the entire ingestion?
   a. 2 vials
   b. 4 vials
   c. 8 vials
   d. 16 vials
   e. 20 vials

Answer: D. Each vial contains enough digitalis antibody fragments to neutralize 0.5 mg of digoxin; therefore, the patient should be given 16 vials of Fab fragments to fully treat his ingested dose.

CHAPTER 142: QUESTIONS AND ANSWERS—cont'd.

4. A 5-year-old girl presents after taking some of her grandmother's heart medications. She has sinus bradycardia and a slightly low blood pressure. The remainder of her vital signs and physical examination are nonspecific. A bedside glucose test reveals hyperglycemia. The child is not responsive to calcium therapy. The next therapeutic intervention that is likely to treat both the endocrine and cardiovascular pathology would be:
   a. Dobutamine
   b. Epinephrine
   c. High-dose insulin (HDI)
   d. Intravenous fat emulsion (IFE)
   e. Glucagon

Answer: C. Calcium channel blocker toxicity may result in bradycardia and hypotension, much like beta-blocker toxicity. Unlike beta-blocker toxicity, which can cause hypoglycemia, calcium channel blockers can cause hyperglycemia via blockade of calcium channels on beta islet cells. HDI therapy treats calcium channel blocker toxicity via increasing inotropy, as well as normalizing glucose.

5. A 60-year-old man has taken an overdose of his beta-blocker medication. He is awake but lightheaded and has a pulse of 50 beats per minute and a blood pressure of 92/60 mm Hg. Which of the following is the most appropriate initial treatment?
   a. Atropine, crystalloid fluids, calcium salts, glucagon
   b. Atropine, crystalloid fluids, insulin
   c. Atropine, norepinephrine, glucagon
   d. Norepinephrine, crystalloid fluids, insulin
   e. Norepinephrine, glucagon, insulin

Answer: A. Atropine, crystalloid fluids, calcium salts, and glucagon are the initial treatments of choice for beta-blocker toxicity. If these agents are ineffective, high-dose insulin (HDI) is reasonable as next-line therapy for cardiogenic shock. If HDI is ineffective, catecholamines are a reasonable option. The catecholamine choice may vary depending on the type of shock the patient is in, and the dose needed for a response may be greater than for other conditions.

6. A patient presents after an apparent overdose of diltiazem. Which of the following findings would lead you to suspect a co-ingestant in addition to the calcium channel blocker?
   a. Atrioventricular (AV) block on electrocardiogram (ECG)
   b. Hyperglycemia
   c. Metabolic acidosis
   d. Prolonged QRS complex on ECG
   e. Pulmonary edema

Answer: D. Prolonged QRS and QT intervals are generally not seen in calcium channel blocker overdose and should prompt the search for co-ingestants. One exception is the calcium channel blocker bepridil, which can cause QRS or QT prolongation, though bepridil is no longer sold in the United States. All the other listed abnormalities are typical of calcium channel blocker overdose.

7. Treatment for beta-blocker overdose is most similar to the treatment for overdose from which other class of medications?
   a. Anticholinergics
   b. Calcium channel blockers
   c. Cyclic antidepressants
   d. Digoxin
   e. Nitrates

Answer: B. Symptoms from overdose of calcium channel blockers and beta-blockers are similar, as are the therapeutic strategies. Severe anticholinergic toxicity may respond to physostigmine administration, cyclic antidepressants to intravenous (IV) sodium bicarbonate boluses, digoxin poisoning to antibody Fab fragments, and nitrate toxicity to methylene blue therapy.

8. Which of the following drugs is most likely to kill a toddler with ingestion of a single tablet?
   a. Atenolol
   b. Chlorthalidone
   c. Lisinopril
   d. Nitroglycerin
   e. Verapamil

Answer: E. Verapamil and other calcium channel blockers can kill a toddler with the ingestion of a single tablet. Appropriate medical treatment, however, is extremely effective, and very few children die from calcium channel blocker overdose. Although beta-blockers have the potential to cause serious toxicity, propranolol is the beta-blocker most likely to cause serious toxicity. Educating parents and caregivers of young children about the potential effects of these medications is important.

143

Caustics

Christopher Hoyte

KEY CONCEPTS

- Health care workers caring for patients with caustic exposures should adhere to universal precautions to prevent additional exposure.
- All symptomatic patients should undergo endoscopy and be should be observed for at least 24 hours.
- Asymptomatic patients can undergo endoscopy in the emergency department or be discharged with close follow-up monitoring.
- Gastric emptying or GI decontamination is not indicated for the majority of caustic ingestions.
- Concentration and pH are the most important characteristics of a substance to predict esophageal and gastric injury.
- Button batteries lodged in the airway or esophagus require endoscopic retrieval.

FOUNDATIONS

Caustic or corrosive agents have the potential to cause tissue injury on contact with mucosal surfaces. Both strong acids and alkalis are capable of causing corrosive chemical injury. Alkalis are proton acceptors and result in the formation of conjugate acids and free hydroxide ions. Lye is an example of an alkali and refers to both sodium hydroxide (NaOH) and potassium hydroxide (KOH). Ammonia (NH_3) is another common alkaline corrosive. Acids are proton donors; they dissociate into conjugate bases and free hydrogen ions in solution. Acidic caustics include hydrochloric acid (HCl) and sulfuric acid (H_2SO_4). The injury from caustic agents typically increases with a pH below 3 or above 11. Other chemicals that have caustic properties include phenol, formaldehyde, iodine, and concentrated hydrogen peroxide. This chapter discusses oral exposure. Dermal and inhalational exposures are discussed in Chapter 55 and Chapter 148, respectively.

More than 40,000 exposures involving caustic agents occur in the United States every year.[1] Nearly 75% of reported caustic ingestions are intentional for the purpose of self-harm.[1] Accidental ingestions occur typically among the pediatric and elderly populations. Transfer and storage of cleaners in alternative containers that may not be "child proof," such as jars, soda bottles, and sports drink containers, contribute to unintentional ingestion. Intentional ingestions may have a greater degree of oropharyngeal sparing because of rapid swallowing but have a higher likelihood of serious injury.

Principles of Toxicity

Some household products, such as liquid drain cleaners, continue to have high concentrations of alkali (30% KOH) or acid (93% H_2SO_4) (Table 143.1). These products often do not have concentration or content information available on the label, making it difficult for clinicians to determine the severity of exposure. Industrial, agricultural (dairy pipeline cleaners containing liquid NaOH and KOH in concentrations of 8% to 25%), and swimming pool chemicals also contain caustics in high concentrations.

Crystals and solid particles can have prolonged tissue adherence, causing more severe injury. Household detergents such as laundry powders and detergent pods (LDPs) and dishwasher detergents containing silicates, carbonates, and phosphates have the potential to induce caustic burns and strictures, even when ingested unintentionally. These ingestions are limited by immediate oral pain, usually causing them to be spit out sooner than a liquid agent. The ingestion of granular automatic dishwashing detergents or brightly colored laundry detergent capsules or "pods" can be associated with devastating injuries.[2] Compared to children with traditional non-LDP exposures, LDP exposures are associated with a higher incidence of toxicity including central nervous system depression and respiratory compromise with failure. Whether the toxicity observed with LDP exposures is due to other ingredients in the products, pH, concentration, tensile strength, or the delivery vehicle remains unclear.

Crystal drain cleaners have lye concentrations as high as 74% NaOH and may cause proximal esophageal injury. Liquid dishwashing detergents and laundry detergents have a pH higher than 12, but because the titratable alkaline reserve is low, tissue equilibration occurs quickly, and there is less risk of injury after ingestion.

Liquid household bleach typically contains dilute (3% to 5%) sodium hypochlorite (NaOCl), and ingestion rarely causes consequential injury. Industrial-strength bleach, however, contains significantly higher concentrations of NaOCl, which are more likely to cause esophageal necrosis. Toilet bowl cleaners contain HCl concentrations as high as 26%. General-purpose anticorrosive cleaners, such as 31% hydrochloride acid (HCl), are sold in gallon containers for home use and as swimming pool cleaners.

The alkali powder in air bags can cause ocular burns. Perfume unintentionally sprayed in the eyes can be caustic. Cement is alkaline and causes topical burns, typically on the knees and hands. Although hair relaxer creams contain NaOH and have a pH of 11.2 to 11.9, injuries after ingestion are usually mild.

Caustic ingestions may occur when methamphetamine is produced from over-the-counter medications and household chemicals. H_2SO_4, HCl, NaOH, ammonium hydroxide, anhydrous ammonia, and metallic lithium are all used in the clandestine production of methamphetamine. Severe caustic injuries occurring from ingestion of these agents can cause stricture formation, esophageal resection, and the need for colonic interposition.

Many medication pills can cause injury when they come in contact with the esophageal mucosa for prolonged periods. Patients who take medications in the supine position or who take pills without water are at higher risk of pill esophagitis. The pills most likely to adhere are doxycycline, tetracycline, potassium chloride, antimalarials, and aspirin.

TABLE 143.1 Household Cleaning Products That Contain Caustic Chemicals

Application	Product (Manufacturer), Chemical
Drain cleaner, liquid	Heavy Duty Liquid Drain Opener (Share), H_2SO_4 93%
	Drain Out Extra (Iron Out), KOH 30%
	Liquid-Plumr (Clorox), NaOH 0.5% to 2%, NaOCl 5% to 10%
	Maximum Strength Drain Opener (Enforcer), KOH 1% to 10%, NaOCl <5%
	Drain Care Professional Strength Drain Opener, NaOH 5% to 15%
Drain cleaner, crystals	Heavy Duty Crystal Drain Opener (Roebic), NaOH 100%
	Crystal Drain Opener (Rohyme), NaOH 74%
	Crystal Drain Out (Iron Out), NaOH 30% to 60%
	Drano Pipe Cleaner (Johnson), NaOH 54%
Oven cleaner	Easy-Off Heavy Duty Oven Cleaner (Reckitt), NaOH 4% to 6%
Rust remover	Rust Remover/Carpet Care (Johnson Wax Professional), HCl 10%
	Rust Stain Remover (Whink), hydrofluoric acid 2.5% to 3%
	Rust Stripper (Certified), NaOH 50% to 75%
	Naval Jelly Rust Dissolver (Loctite), phosphoric acid 25% to 30%
Toilet bowl cleaner	Instant Power Toilet Bowl Cleaner (Scotch), HCl 26%
	Bowl and Porcelain Cleaner (Cleanline), HCl 0.10%
	Bowl/Tile/Porcelain Cleaner (Share), phosphoric acid 15% to 25%
	Husky 303 Toilet Bowl Cleaner, HCl 23%
	Misty Bolex Bowl Cleaner, HCl 26%
Swimming pool cleaner	Muriatic acid, Aqua Chem (Recreational Water), HCl 31%

H_2SO_4, Sulfuric acid; *HCl,* hydrochloric acid; *KOH,* potassium hydroxide; *NaOCl,* sodium hypochlorite; *NaOH,* sodium hydroxide.

Although uncommon, potassium chloride is particularly dangerous and can cause esophageal perforation with devastating communication with the aorta, left atrium, and bronchial artery.[3]

Pathophysiology

Factors that influence the extent of injury from a caustic exposure include type of agent, concentration of solution, volume, viscosity, duration of contact, pH, and presence or absence of food in the stomach. The titratable acid/alkaline reserve of an alkali or acid correlates with the ability to produce tissue damage. Concentrated forms of acids and bases generate heat, resulting in superimposed thermal injury.

Acidic compounds desiccate epithelial cells and cause coagulation necrosis. An eschar is formed that limits further penetration. Because acids tend to have a strong odor and cause immediate pain on contact, the quantity ingested is usually limited. Because of resistance of squamous epithelium to *coagulation necrosis*, acids are thought to be less likely to cause esophageal and pharyngeal injury, although severe esophageal and laryngeal injury still occur, particularly with intentional ingestions.[4] In many case series, acid ingestion results in equal esophageal and gastric mucosal injury.[4] Acids can also be absorbed systemically, causing metabolic acidosis as well as damage to the spleen, liver, biliary tract, pancreas, and kidneys from perforation and direct local contact.

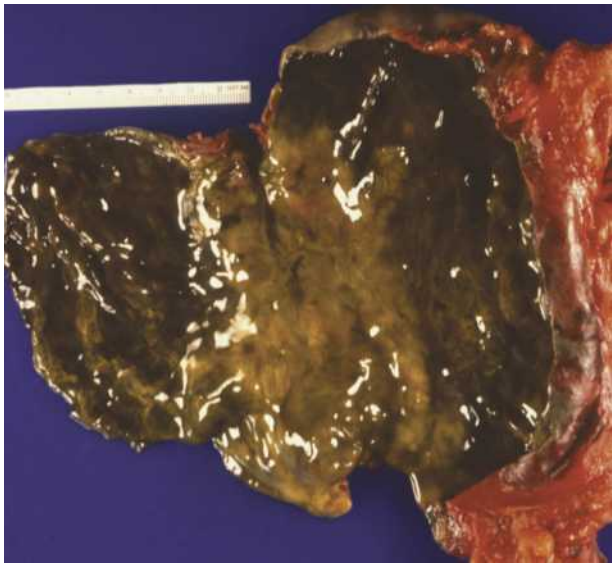

Fig. 143.1 Gastric mucosa after ingestion of 35% potassium hydroxide (KOH).

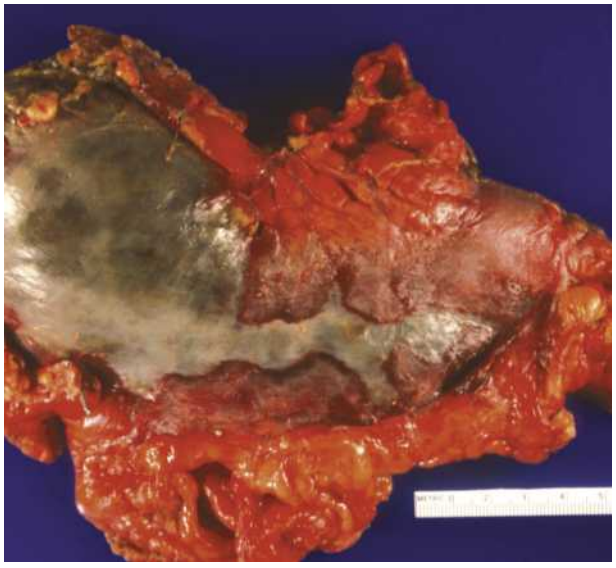

Fig. 143.2 Gastric serosa after ingestion of 35% potassium hydroxide (KOH).

Alkaline contact, in contrast to acids, causes *liquefaction necrosis*, fat saponification, and protein disruption, allowing further penetration of the alkaline substance into the tissue. The depth of the necrosis depends on the concentration of the agent. A concentration of 30% NaOH in contact with tissue for one second results in a full-thickness burn. Alkalis are colorless and odorless, and unlike acids, they do not cause immediate pain on contact. Alkaline ingestions typically involve the squamous epithelial cells of the oropharynx, hypopharynx, and esophagus. The narrow portions of the esophagus, where pooling of secretions can occur, are also commonly involved. Alkalis may also cause gastric necrosis (Figs. 143.1 and 143.2), intestinal necrosis, and perforation. The esophagus can also be injured (Fig. 143.3). Burns below the pylorus carry a 50% mortality compared with 9% for burns above the pylorus.[5]

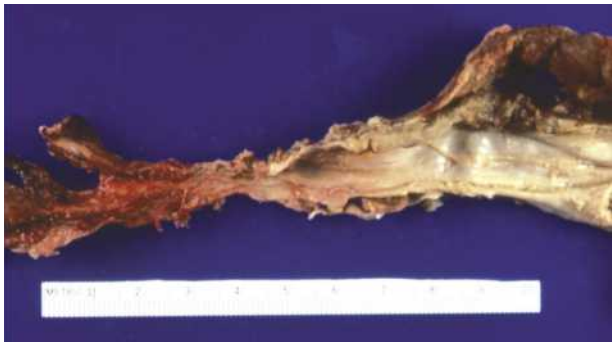

Fig. 143.3 Esophagus after ingestion of 35% potassium hydroxide (KOH).

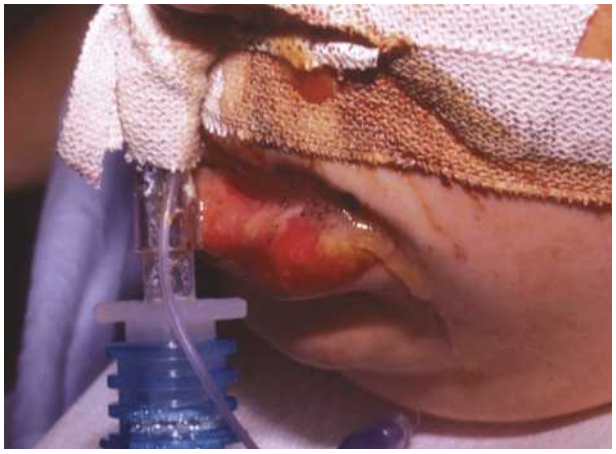

Fig. 143.4 Lip burn after exposure to 35% potassium hydroxide (KOH).

Caustic damage occurs in four phases. Initially, necrosis occurs, with invasion by bacteria and polymorphonuclear leukocytes. Vascular thrombosis follows, increasing the damage. During the next two to five days, superficial layers of injured tissue begin to slough. The tensile strength of the healing tissue may be low for up to three weeks after the caustic exposure, greatly increasing the chance of delayed perforation in some cases. Between one week and several months, granulation tissue forms, collagen is deposited, and reepithelialization occurs in the burn area. Esophageal strictures may form during a period of weeks to years from contraction of the scar.

Caustic injury is categorized as first, second, and third degree, similar to a thermal burn, by appearance on endoscopy. The initial depth of injury found on esophagoscopy correlates with the risk of stricture formation. Grade I injury consists of edema and hyperemia. Grade II injury can be further divided into grade IIa, which is non-circumferential, and grade IIb, which is nearly circumferential. Overall, grade II injuries are characterized by superficial ulcers, whitish membranes, exudates, friability, and hemorrhage. Grade III injury is associated with transmural involvement with deep injury, necrotic mucosa, or perforation of the stomach or esophagus. Although grade I injuries do not progress to stricture, 15% to 30% of all grade IIa injuries and up to 75% of circumferential grade IIb injuries of the esophagus develop strictures. With grade III injury, up to 90% result in stricture. Recently, the formation of strictures is decreasing for both grade II and grade III injury, possibly because of the type and caustic intensity of the substance ingested.[4]

CLINICAL FEATURES

Airway edema and esophageal or gastric perforations are the most emergent issues. Laryngeal edema begins in minutes and occurs over several hours. Systemic toxicity, hypovolemic shock, and hemodynamic instability with hypotension, tachycardia, fever, and metabolic acidosis are ominous signs. Small ingestions of potent substances can be as serious as larger ingestions. More than 40% of patients reporting to have "only taken a lick or sip" have esophageal burns. Patients with acid or alkali ingestions present with similar initial constellation of signs and symptoms. Oral pain, abdominal pain, vomiting, and drooling are common. Patients can have wheezing and coughing, respiratory distress, hoarseness, odynophagia, dysphagia, stridor, and dysphonia. Chest pain is common. Visible burns to the face, lips, and oral cavity may be seen (Fig. 143.4), although these signs are not always clinically reliable.[5,6] Skin burns can occur from spillage or secondary contamination after vomiting. Peritoneal signs suggest hollow viscus perforation or contiguous extension of the burn injury to adjoining visceral areas. Oropharyngeal burns alone are not predictive of more distal injury, but drooling, odynophagia, dysphagia, vomiting, and stridor, especially in combination, are highly predictive of significant lesions. Tracheal necrosis is one of the most frequent causes of death after caustic ingestion.

Dysphagia usually subsides in three to four days. Patients with significant esophageal burns, particularly those that are circumferential, may develop esophageal stricture; 80% of strictures become apparent in 2 to 8 weeks. Symptoms include dysphagia and food impactions. Strictures that become symptomatic early are generally more severe. In one study of 86 adults admitted to the hospital after caustic ingestion, 18 had complications with strictures and 6 died.

Patients with significant esophageal injury have a thousand-fold increase in esophageal carcinoma, which develops 40 to 50 years after the caustic ingestion. Long-term, 2% of patients who ingest caustics develop esophageal cancer and nearly 3% of esophageal cancer patients have a history of caustic ingestion.

Significant acid ingestions may be devastating and result in a higher mortality rate than alkali ingestions. The fulminant course of some acid ingestions may be due to systemic absorption of the acid, resulting in metabolic acidosis (which may also be the result of extensive tissue necrosis), hemolysis, and renal failure. Ingestion of glacial acetic acid (80% acetic acid) is common among certain ethnic populations as a suicidal gesture or accidental ingestion during food preparation, resulting in systemic complications, including renal and hepatic insufficiency, hemolysis, and disseminated intravascular coagulation. Ingestion of H_2SO_4 and HCl typically does not cause these systemic complications.

On clinical evaluation, the goal is to identify the extent and severity of the burn. In evaluation of a patient, the history should include the time, amount, type of product ingested, and presence of suicidal intent, if any. Patients who are suicidal may minimize their symptoms or understate the ingestion. Physical examination addresses all of the above described features and should focus on the oropharynx, supraglottic area, airway, and gastrointestinal (GI) tract.

DIFFERENTIAL DIAGNOSES

The ingestion of a caustic agent is most often reported upon presentation by patient or family member. When this is not known, the differential diagnosis is essentially that of abdominal discomfort, nausea, and vomiting, until typical mucosal injury becomes apparent. Mucosal injuries can be the result of various causes. The presence of early shock or altered mental status soon after ingestion of a caustic agent should prompt the search for other causes. Gastroenteritis from the ingestion of heavy metals (e.g., iron, arsenic, inorganic mercury) and hydrocarbons can result in similar clinical effects as seen in caustic ingestions. Other GI conditions such as gastric perforation, esophageal rupture, esophagitis, and gastroesophageal reflux disease should be considered.

Patients suffering from allergic reactions progressing to anaphylaxis and angioedema can present with irritation and inflammation of the throat and larynx mimicking a caustic ingestion. Infectious sources such as aspiration pneumonitis, croup (laryngotracheobronchitis), and epiglottitis can present in a similar manner as well.

DIAGNOSTIC TESTING

Product labels are important in confirming the concentration of chemicals. If the product with the label is brought by the patient or family, call the regional poison center for product information, look up the contents, or test the pH with litmus paper.

Evaluation of the severity of caustic ingestion and determination of the likelihood of deterioration or serious injury is based on examination of the upper airway, the esophagus, and the chest and abdomen. Examination of the oral pharynx is optimized by direct visualization. Nasopharyngoscopy, after appropriate application of a vasoconstrictor (e.g., phenylephrine) and local anesthesia (e.g., 4% lidocaine), determines the extent of injury and edema posterior to the tongue and in the supraglottic area and the glottis itself. Flexible endoscopy is used to evaluate the esophagus and stomach, after completion of the airway evaluation. Computed tomography (CT) scan is much more sensitive than plain radiography for identification of perforation of the GI tract, and both chest and abdomen are scanned when there is concern for serious injury (see earlier criteria). CT scan of the chest and the abdomen is able to detect evidence of perforation, such as mediastinal and extraluminal air, with high sensitivity.[7,8,9] Another benefit of CT is the ability to evaluate surrounding tissues that cannot be directly visualized during endoscopy due to technical challenges or safety.[7,8] Although chest and abdominal radiography are often used in the early stages to determine whether perforation has occurred, they are insensitive and these tests are not indicated if CT scanning is available.

Patients with significant injury (such as grades IIb or III) may have perforations difficult to detect during endoscopic evaluation. Thus, delayed (approximately 24 hours post ingestion) esophagram with water-soluble contrast medium may detect perforations by the presence of extravasation of contrast. If there is a high clinical suspicion, we recommend barium in the case of a nondiagnostic water-soluble contrast study that does not demonstrate a leak because barium is more radiopaque. Esophageal dilation, widening of the pleuroesophageal line, and pleural reflection displacement all portend impending perforation.

Laboratory studies should evaluate for metabolic acidosis, coagulation profile, hemoglobin, and electrolyte derangements. Some ingested acids are absorbed from the gastric mucosa and subsequently hydrogen ion disassociation occurs. The accumulation of the anionic species in the vascular space contributes to an elevation in ion gap. Ingestion of acids such as HCl result in a non-anion gap metabolic acidosis because both the dissociated hydrogen and chloride ions contribute in the measurement of the anion gap. Typically, alkalis are not absorbed from the gastric mucosa into the vascular space. A lactic acidosis can result, however, due to esophageal or gastric injury and necrosis. Therefore, in the setting of significant acid or alkali ingestion, serum pH and chemistry for serum bicarbonate analysis are indicated to determine the degree of acidosis. In cases of intentional overdose, co-ingestants should be considered and measured diagnostically if levels are available and clinically indicated.

Hydrofluoric acid exposures, whether by inhalation, ingestion, or dermal contact (hand size or larger), are notorious for the effect of absorbed fluoride, resulting in hypocalcemia, and require immediate cardiac monitoring to assess for corrected QT (QTc) prolongation, torsades de pointes, or other ventricular dysrhythmias. Rapid cardiac deterioration can occur in these cases. Serum calcium, potassium, and magnesium levels should also be determined in these cases.

The depth and extent of injury cannot be predicted based on signs and symptoms alone. Patients with signs and symptoms (vomiting, drooling, stridor, or dyspnea) of intentional ingestion should undergo endoscopy within 12 to 24 hours to define the extent of the disease. Endoscopy is contraindicated, however, in patients with likely or known perforation. Endoscopy performed too early may miss the extent or depth of tissue injury. Wound softening in the subacute phase when the likelihood of perforation is greatest makes late endoscopy (after 24 hours) more hazardous. Wound strength is weakest between day 5 to day 14 and the time of greatest risk for perforation. Early endoscopy has been studied and shown to be beneficial. Early endoscopy and GI tract evaluation permits more rapid administration of nutritional support. However, it is advised that the endoscopy be terminated at the level of the most proximal circumferential burn, particularly if the burn is severe, to avoid iatrogenic perforation. A soft feeding tube or silk string can be placed in the esophagus, when burns are present, for future dilation.

MANAGEMENT

Early and continuous hemodynamic monitoring is indicated. All contaminated clothing should be removed to prevent ongoing injury to the patient as well protection of health care personnel. Appropriate personal protective equipment (PPE) and hazardous waste disposal should be used.

After a caustic ingestion, little can be done to attenuate the severity of the tissue injury. Early endotracheal intubation or upper airway endoscopic examination is warranted when there are indications of upper airway injury on nasopharyngoscopy. If there are significant symptoms or signs, such as respiratory distress, stridor, or voice alteration (hoarseness, muffling), intubation is often necessary early in the course of evaluation, before edema and secretions both threaten the airway and make intubation difficult or impossible. For this reason, upper airway examination is often done with an intubating bronchoscope so that if significant injury and edema are identified, intubation can be accomplished during performance of the bronchoscopic examination. Blind nasotracheal intubation is contraindicated. When oral intubation is planned, a video laryngoscope should be used to provide optimal view with the least amount of tissue trauma. If significant symptoms and signs are present, intubation can be anticipated to be difficult, and awake flexible endoscopy is the method of choice.

After the airway is secured, persistent hypoxia and an increasing arterial-alveolar gradient warrant early bronchoscopy. Patients should have intravenous fluid resuscitation (20 to 40 mL/kg 0.9% normal saline bolus). Oropharyngeal and GI injury secondary to caustic ingestion can result hypotension because of fluid shift from the intravascular to the interstitial space. Intravenous access should be established and a bolus of 30 mL/kg of isotonic crystalloid, usually normal saline, should be administered. Standard measures of resuscitative progress such as heart rate and urine output should be monitored closely. In alert patients who are not vomiting and can tolerate liquids, small volumes (1 to 2 cups) of water or milk can be considered within the first 5 minutes after ingestion. Because injuries occur almost immediately, later dilution is not warranted. Forcing of fluids is never indicated. Attempts to neutralize the ingested corrosive with weak acids or alkalis can cause possible thermal reactions and worsen the injury.

GI decontamination after caustic ingestion is generally not indicated and can be hazardous. Inducing emesis is absolutely contraindicated given the risk of re-induction of the caustic agent into the esophagus, oropharynx, and airway. Activated charcoal is contraindicated as well, because it has little effect and will interfere with the endoscopist's view and assessment.

Careful nasogastric aspiration may decrease the amount of acid absorbed and may be useful in the setting of significant (massive) acid ingestions presenting within 30 to 45 minutes after the event, given the ominous natural history of many of these cases and the lower risk of esophageal perforation compared with alkali ingestion.

Exceptions to the general rules of gastrointestinal decontamination regarding caustics are noted in the management of zinc chloride ($ZnCl_2$) and mercuric chloride ($HgCl_2$). Both may result in severe systemic toxicity due to cationic metal injury. The local caustic effects, while of concern, are less consequential than the effects after systemic absorption. Thus, prevention of systemic absorption should be the primary action followed by direct assessment and management of the local effects. Initial management to prevent systemic absorption includes decontamination with gentle nasogastric tube aspiration and administration of activated charcoal.

Surgical consultation is indicated for free air, peritonitis, increasing and severe chest and abdominal pain, and hypotension. The decision to perform surgery in patients with caustic ingestions is generally clear. Endoscopic or diagnostic imaging evidence of perforation, severe abdominal rigidity, or persistent hypotension are all indications for surgical intervention. Hypotension is a grave clinical finding and often indicates perforation or significant blood loss. Additionally, elevations in prothrombin and partial thromboplastin times, as well as acidemia, are associated with severe caustic injury.

There remains controversy regarding the use of corticosteroid therapy in the management of grade IIb circumferential esophageal burns due to caustic injury. A dated prospective study of 83 children with grade IIb esophageal burns compared a short (3 day) course of high-dose methylprednisolone to placebo and found a statistically significant decrease in stricture formation in the high-dose steroids group. Prior to this study, the medical literature suggested no benefit of corticosteroids because there was no demonstrated significant decrease in stricture formations after grade IIa, IIb, or III esophageal burns, but there was increased risk for hemorrhage, infectious complications, severe esophagogastric necrosis, and prepyloric ulcer formation. Steroids can also mask early signs of inflammation and inhibit resistance to infection. Accordingly, they are not indicated to reduce the extent of esophageal injury. Controversy also surrounds the administration of steroids in patients with airway edema secondary to caustic ingestion. There are no controlled studies evaluating this practice, and the same downside risks exist as for steroid use for esophageal stricture. Airway edema can be fatal, however, and a single dose of a potent corticosteroid might mitigate some of the edema with minimal risk to the patient. We recommend dexamethasone 10 mg IV when there is indication of airway edema.

Prophylactic antibiotics are not indicated. Patients with proven perforation should have an emergent surgical consultation.

The risk of perforation from esophageal dilation is decreased if the initial procedure is delayed beyond 4 weeks post-ingestion. At this time, healing, remodeling, and potential stricture formation in the esophagus have already taken place. Following perforation, patients develop clinical symptoms such as dyspnea or chest pain in the setting of associated subcutaneous emphysema or pneumomediastinum. Diagnostic imaging is recommended to identify the perforation and provide information for emergent surgical repair. Patients with stricture formation require long-term endoscopic follow-up for the presence of neoplastic changes of the esophagus that may occur with a delay of several years to decades.

DISPOSITION

Asymptomatic patients can undergo endoscopy in the emergency department. Those patients with grades 0 or I injury may be discharged home after 4 to 6 hours of observation with close follow-up monitoring with appropriate gastroenterology or otolaryngology consultants.[9] They can have a liquid diet for 24 hours and then gradually transition to soft food over the next 3 days and to a full diet thereafter if progressing well.

Surgical intervention is required in cases of hollow viscus perforation; early exploration may also be warranted in cases of suggested full-thickness burns.[9] Symptomatic patients, particularly those with potential for airway compromise, or high-grade esophageal or gastric injuries, require admission to an intensive care unit. If endoscopy is unavailable, the patient should be transferred to a tertiary care facility where it can be performed. Psychiatric evaluation is indicated in patients with intentional ingestion.

SPECIAL CASES

Ocular alkali exposures are true ophthalmologic emergencies. Immediate irrigation with at least 2 L of normal saline per eye is indicated in almost all cases except frank perforation. Management is described in Chapter 57. Dermal caustic exposures can also result in significant burn injuries (see Chapter 55). Clothing removal, copious irrigation, and local wound débridement are the most important initial treatment measures.

Povidone-Iodine

Povidone-iodine (Betadine) is used as a surgical scrub and is not a caustic agent, but ingestion of tincture of iodine can cause severe GI injury and is potentially life-threatening. Gastric irrigation with starch or milk in these cases may convert iodine to the much less toxic iodide. Either of these agents is most likely to be effective if administered within the first 30 to 45 minutes post ingestion. The goal is to convert the gastric effluent to a dark blue or purple hue.

Phenol and Formaldehyde

Ingestion of phenol or formaldehyde can also cause severe caustic injury to the GI tract. Both phenol and formaldehyde are general protoplasmic poisons and can cause protein denaturation and coagulation necrosis. Systemic symptoms, including dysrhythmias, hypotension, seizures, and coma, may also result from phenol ingestion. Acidosis may be prominent after formaldehyde ingestion because of its metabolism to formic acid. Phenol is well absorbed through the skin, and dermal exposure may result in burns and systemic toxicity. Although dermal decontamination of phenol exposures with low–molecular-weight polyethylene glycol has been suggested, there is no evidence that it is superior to irrigation with water, which is more readily accessible.

Hydrogen Peroxide

Ingestion of concentrated (>30%) hydrogen peroxide (H_2O_2) may cause GI burn injuries and the formation of gas emboli. Radiographic evaluation for the presence of gas in the chest or abdominal cavities, including the portal system, should be performed in symptomatic patients or those who ingest concentrated H_2O_2. Hyperbaric oxygen has been used successfully to treat gas emboli from H_2O_2 ingestion.

Button Batteries

Button (disk) batteries and conventional alkaline cylindrical batteries pose potential obstructive and chemical hazards if they are ingested. Ingestion of large (25-mm) wafer-sized button batteries was a common problem in the past, but the smaller button batteries of today are less likely to cause esophageal obstruction. Button batteries are usually made of a metallic salt (lithium, mercury, nickel, zinc, cadmium, or silver) bathed in NaOH or KOH. Obstruction can cause pressure necrosis, caustic

injury due to leakage of alkaline medium, or electrical injury. Caustic injury is much less common. Ulceration, perforation, and possible fistula formation occur but are uncommon. Heavy-metal toxicity in this setting has not been reported with newer-generation of disk batteries.

Evaluation of button battery ingestions includes radiography to assess the position of the foreign body. Batteries lodged in the airway or esophagus require expeditious removal. Single gastric or intestinal batteries can be treated with watchful waiting, generally in the patient's home. Checking the stool for passage of the batteries is recommended. Follow-up radiographs should be obtained one week after ingestion if the battery has not passed. If the patient becomes symptomatic with acute abdominal pain or exhibits GI bleeding, expedited reassessment is indicated.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 143: QUESTIONS AND ANSWERS

1. A patient presents after the intentional ingestion of hydrochloric acid (HCl). He complains of mouth, throat, and chest pain, as well as painful swallowing and nausea. His vital signs are normal. Physical examination reveals oral burns without edema. The remainder of the examination is normal. You decide that in addition to psychiatric consultation, the patient should have upper endoscopy. What is the best time for the patient to have the endoscopy?

a. Immediately
b. In 2 to 4 hours
c. In 4 to 12 hours
d. In 12 to 24 hours
e. In 2 or 3 days

Answer: D. The ideal time for endoscopy is 12 to 24 hours. Endoscopy done too soon may miss the extent or depth of injury, whereas endoscopy after 24 hours is actually more likely to cause perforation because the wounds have softened. All patients with signs or symptoms of strong acid ingestion as well as patients with intentional ingestion should have endoscopy performed.

2. A patient presents immediately after the ingestion of bleach. The patient is awake and alert and complaining only of mouth pain. His vital signs and physical examination findings are normal. You consider having the patient drink fluids to dilute the bleach. Which of the following statements regarding this therapy is *true?*

a. Dilution is beneficial only if it is done very soon after ingestion.
b. In cases of alkali ingestions, dilution with a mild acid such as acetic acid is best.
c. Large volumes of fluid should be used.
d. Milk should always be used instead of water.
e. Patients should also be encouraged to eat solids.

Answer: A. Dilution, if it is done at all, should be done early because injuries from caustics occur almost immediately. Water and milk are equally beneficial and are the agents of choice. Weak acids or alkalis should never be used for dilution, because they can cause thermal reactions that worsen the injury. Small volumes up to approximately 500 mL should be used. Solids are not beneficial and can complicate the situation and increase the risk of aspiration.

3. A patient presents after an intentional caustic ingestion. She complains of hoarseness, with mouth, throat, and chest pain. Burns are present on her lips and oral mucosa and she is drooling. Her vital signs are normal, as is the remainder of her physical examination. Which of the following is the most appropriate treatment?

a. Administer 500 mL water orally
b. Administer intravenous Solu-Medrol
c. Endotracheal intubation
d. Obtain electrocardiogram
e. Upper endoscopy

Answer: C. Early intubation is indicated if there is any evidence of airway compromise, such as hoarseness, throat pain, drooling, or edema. Because edema and secretions can both increase rapidly and can make intubation difficult or even impossible, preparations should be made for a difficult airway. Fluids for oral dilution should not be given if the patient has difficulty swallowing. Corticosteroids have been studied to decrease the incidence of stricture formation, but evidence for their benefit is lacking and serious side effects can occur. With the exception of hydrofluoric acid, an electrocardiogram is not routinely needed for caustic ingestions, and endoscopy should be performed 12 to 24 hours after the ingestion and after the airway has been secured.

4. What empirical treatment is indicated to prevent systemic toxicity from hydrofluoric acid ingestions?

a. Calcium chloride
b. Magnesium chloride
c. Potassium chloride
d. Sodium bicarbonate
e. Sodium chloride

Answer: A. Calcium chloride is indicated in significant hydrofluoric acid exposures. Although hydrofluoric acid is a weak acid, the fluoride ion is extremely electronegative and will bind with multiple cations, specifically calcium and magnesium. Profound hypocalcemia is responsible for most deaths from hydrofluoric acid exposure and can occur before a serum calcium concentration can be measured.

CHAPTER 143: QUESTIONS AND ANSWERS—cont'd.

5. A 3-year-old boy presents after swallowing a button battery. What is the most appropriate management?
   a. Endoscopic removal
   b. Inpatient observation
   c. Radiograph to assess anatomic location
   d. Surgical removal
   e. Whole-bowel irrigation

Answer: C. Outpatient observation is warranted for button batteries that are located in the stomach or intestines, which can be assessed by plain radiographs. Batteries lodged in the esophagus require endoscopic removal. Examination of the stool for passage of the battery is recommended. If it is not passed in one week, repeated radiographs should be obtained. Inpatient observation is not needed as long as close follow-up can be ensured. Surgical removal and whole-bowel irrigation are not beneficial and are potentially deleterious.

6. A patient presents after a self-harm attempt with 3% household bleach (sodium hypochlorite). The patient has normal vital signs and is asymptomatic. His physical examination is unremarkable. Which is the most appropriate treatment?
   a. Administer 500 mL water orally
   b. Administer intravenous Solu-Medrol
   c. Endotracheal intubation
   d. Obtain electrocardiogram
   e. Upper endoscopy

Answer: E. This patient is high risk for significant esophageal or gastric injury due to the self-harm attempt. Several studies evaluating for the presence or absence of oropharyngeal burns as a predictor of distal esophageal of gastric injury had found these finding to be poorly predictive. Thus, endoscopy should be a standard diagnostic tool used in the management of intentional caustic ingestions.

7. A 45-year-old female presents after an intentional caustic ingestion. She has severe chest pain, and is tachycardic, stridulous, drooling, and hoarse. She has a normal blood pressure. Due to concerns about her airway, she is intubated without difficulty. Which of the following diagnostic imaging modalities is most appropriate for this patient?
   a. Plain chest radiograph
   b. Ultrasound
   c. MRI chest
   d. CT chest
   e. Contrast esophagram

Answer: D. CT scanning is considerably more sensitive than radiography and ultrasound for detecting hollow viscus perforation, for which the patient is at high risk. MRI does not add significant benefit over CT and typically takes longer to obtain.

Cocaine and Other Sympathomimetics

Michael A. Chary and Timothy B. Erickson

KEY CONCEPTS

- Excessive use of stimulants can lead to *sympathomimetic toxicity*, manifesting as tachycardia, hypertension, mydriasis, diaphoresis, hyperthermia, hyperreflexia, and agitation. If untreated, sympathomimetic toxicity can lead to seizures, coma, and death.
- Administration of benzodiazepines is the key therapeutic intervention for sympathomimetic toxicity. Ketamine, olanzapine, and butyrophenones are alternative adjuncts if the cause of severe agitation is not clearly sympathomimetic toxicity.
- Worsening hyperthermia portends imminent death. Reduce body temperature rapidly by external cooling, sedation, and, if needed, paralysis.
- Anti-hypertensives are adjuncts to benzodiazepines. Antihypertensives do not treat as many aspects of sympathomimetic toxicity as do benzodiazepines, however, and short-acting antihypertensive agents (e.g., phentolamine, nitroglycerin, nicardipine, clevidipine) are preferred.
- Wide-complex rhythms secondary to stimulants (cocaine, bupropion) may respond to intravenous sodium bicarbonate administration.
- Cocaine body packers who develop toxicity need emergent surgical intervention to limit bowel necrosis and life-threatening sequelae caused by leaking packets.
- Novel psychoactive substances (e.g., MDMA, bath salts) combine stimulant, hallucinogenic, and psychedelic effects. They generally produce longer-lasting and more intense effects than cocaine or amphetamine.
- Screen for hyponatremia in patients with sympathomimetic or serotonin toxicity.
- If the clinical presentation does not fit the history (e.g., ingested cocaine but hypoxic and somnolent), consider a contaminant or alternate cause. Contaminants change rapidly and vary by geographic region. Consult a medical toxicologist or regional poison control center.

FOUNDATIONS

Sympathomimetics are substances that activate the sympathetic nervous system (Box 144.1). These substances stimulate release (amphetamine, phenethylamines) or decrease reuptake (cocaine, amphetamine, phenethylamines) of neurotransmitters (serotonin, norepinephrine, dopamine, epinephrine). As a result, these neurotransmitters remain in synapses longer and activate neuronal pathways more strongly and persistently.[1] Stimulants cause an acute upper effect—euphoria and increased energy. Excessive use can lead to sympathomimetic toxicity—tachycardia, hypertension, mydriasis, diaphoresis, hyperthermia, hyperreflexia, and agitation. If untreated, sympathomimetic toxicity can lead to seizures, coma, and death.

This chapter reviews the epidemiology, pathophysiology, and treatment of stimulant toxicity. Over the past two decades, many designer chemicals have emerged with properties that combine traditional drug classes. Some are stimulants and hallucinogens. Others are stimulants and sedatives. Toxicity from a stimulant, whatever its pedigree, manifests as overactivation of the nervous and cardiovascular systems. The primary goals of clinical intervention are to decrease activation of the sympathetic nervous system by sedating the patient, identify end-organ toxicity, and involve a medical toxicologist to guide further management for more complicated cases.

Cocaine

Cocaine is the canonical ubiquitous stimulant drug of abuse. The indigenous people of South America chew the cocoa leaf *(Erythroxylon coca)* for energy. Spanish colonists initially banned chewing cocoa leaves, but soon acknowledged their ergogenic properties, legalizing and taxing cocoa leaf production in the 16th century. In 1855, Friedrich Gaedcke isolated pure cocaine. This three-century delay partly reflects the difficulty in keeping cocaine warm and dry while shipping it across the Atlantic Ocean. Soon after, cocaine became a popular ingredient in beverages, pharmaceuticals, and tonics. In the 19th century, physicians such as Carl Koller and William S. Halsted explored the use of cocaine as an anesthetic, exploiting its unique ability to block sodium channels and constrict blood vessels. Victorian literature mentions cocaine's ability to "stave off the ennui of existence," and it was notably used by the character Sherlock Holmes to keep him stimulated between cases. In 1914, the U.S. Congress passed the Harrison Narcotics Tax Act, which required a physician's order to dispense cocaine and narcotics.

Epidemiology

General statistics on drug use may not distinguish between people who have ever used cocaine, those who have used in the last year, or those who have used in the last week. As a result, these studies combine different populations: the regular user, the sporadic user, the heavy user, the sampler, adults, and adolescents. Any of these groups may experience an overdose of cocaine, although anecdotal experience suggests that inexperienced drug users with psychiatric comorbidities are the population most at risk for cocaine toxicity. Regular use of cocaine accelerates vascular pathology, including coronary artery arteriosclerosis. It is more useful for the clinician to consider incidence or prevalence in terms of the at-risk population. Most information on novel psychoactive substances comes from observational studies on social media, which rarely can identify the exposure or fully define the population.

The prevalence of people in the world who reportedly used cocaine was 13 million in 2012 (0.18%), increasing to 18 million (0.24%) in 2016.[2] The fraction of 8th graders in the United States who reportedly used cocaine was 0.9%, nearly four times the global average. The fraction of 12th graders who used cocaine was 3.8%, again, nearly four times the global average.[3]

In the emergency department (ED), cocaine use is associated with up to 20% of drug misuse-related deaths in the United States[4,5] and between 20% and 50% in the European Union. These data may underestimate the incidence of morbidity and mortality attributable to cocaine, especially in trauma patients.[6] In 2017, drug overdose deaths involving cocaine increased by more than 33%, with almost 14,000 Americans dying from an overdose involving cocaine. From 2016 to 2017, the largest relative and absolute rate changes for cocaine-involved overdoses among racial/ethnic groups were highest among non-Hispanic Blacks. The highest death rate for overdoses involving cocaine in 2017 also occurred among Non-Hispanic Blacks.[7]

Formulation

Unpurified cocaine paste is converted to more usable forms of cocaine. The crystallized freebase of the cocaine alkaloid is known as crack cocaine. It is inhaled with a "crack pipe" designed to tolerate the high temperature required to volatilize pure cocaine. The high lipid solubility and rapid transport from the lungs into the brain contribute to crack's rapid onset of action (Table 144.1). The water-soluble salts of cocaine (i.e., cocaine hydrochloride and cocaine sulfate) are available as a white crystalline powder that is inhaled intranasally or dissolved and injected intravenously. Oral administration is rare except for among those patients who are smuggling or concealing drugs.

Pathophysiology

Cocaine decreases the clearance of dopamine, epinephrine, norepinephrine, and serotonin from synapses between nerve cells or between nerve cells and muscle cells (Fig. 144.1). Decreased clearance allows these neurotransmitters to stay bound to post-synaptic receptors longer, leading to autonomic stimulation (all four neurotransmitters), euphoria (dopamine and serotonin), and a sensation that things are more salient, or important, than they might be otherwise (dopamine) (see Box 144.1). Norepinephrine causes vasoconstriction by stimulation of alpha-adrenergic receptors on vascular smooth muscle. Epinephrine increases myocardial contractility and heart rate through stimulation of $beta_1$-adrenergic receptors. In addition to catecholamine release, the reuptake of these stimulatory neurotransmitters from synaptic clefts is inhibited, altering the normal balance between excitatory and inhibitory tones in the central nervous system (CNS). Subsequent stimulation propagates peripheral catecholamine release. Reuptake of serotonin is similarly inhibited and can cause serotonergic excess, as well.

Cocaine is also a local anesthetic. It blocks sodium channels, slowing nerve impulses from neuronal pain fibers by prolonging the upstroke of the action potential. Along with adrenergic stimulation, this can precipitate tachydysrhythmias such as supraventricular or, with severe sodium channel blockade, ventricular tachycardia. A clinical marker for heart sodium channel blockade is the duration of the QRS on a 12-lead electrocardiogram (ECG). QRS durations longer than 100 ms in a patient with a previously unremarkable ECG suggests sodium channel blockade. The prognostic value of the QRS in patients with preexisting bundle branch blocks or who are actively paced is less known.

The half-life of cocaine is approximately 90 minutes. Cholinesterases in the plasma and liver metabolize cocaine to the inactive metabolites—ecgonine methyl ester and benzoyl ecgonine. In the presence of ethanol, cocaine is metabolized to cocaethylene, which has the same effects as cocaine,[8] giving rise to the observation that ethanol prolongs rather than counteracts cocaine's effects. Genetic differences in the phenotypic expression of plasma cholinesterases may explain the variation across individuals in susceptibility to cocaine toxicity. Most standard urine drug screens in the ED test for benzoylecgonine, which is a metabolite only of cocaine. It can be detected in the urine within 4 hours after using cocaine and remains detectable, depending on the laboratory threshold, for up to 7 days after use.

BOX 144.1 Clinical Effects of Sympathomimetics

Central nervous system (CNS) excitation
Diaphoresis
Hypertension
Hyperthermia
Increased motor tone
Mydriasis
Tachycardia

Amphetamine and Its Derivatives

Amphetamines are structurally distinct from cocaine even though they have similar effects. They are in fact structurally more similar to dopamine than cocaine. The word "amphetamine" is an abbreviation of **a**lpha-**m**ethyl**ph**en**et**hyl**amine**. Phenethylamine is the parent compound from which amphetamines, catecholamines, cathinones (bath salts), and novel psychoactive substances such as methylenedioxymethamphetamine (MDMA) can be derived.

Amphetamines were discovered while chemists John K. Smith and Mahlon Kline were trying to develop a cheaper alternative nasal decongestant to ephedrine. Beginning in 1929, dextroamphetamine was sold as Dexedrine. It was made a prescription drug in 1959, however, owing to concerns over its addictive potential. The racemic mixture is sold as Adderall. Amphetamine-based psychostimulants with abuse potential include illicit drugs, such as methamphetamine and ecstasy, and prescription stimulants, as well. Prescription stimulants, used to treat conditions such as attention-deficit/hyperactivity disorder (ADHD), are commonly misused.

Epidemiology

Rates of overdose deaths from all psychostimulants have been increasing since 2010. More than 10,000 Americans died from an overdose involving psychostimulants with abuse potential in 2017, which was a

TABLE 144.1 Cocaine Pharmacology by Route of Administration

Route	Formula	Onset of Action	Peak Effect	Duration
Inhalation	"Crack"	8–12 s	2–5 min	10–20 min
Intranasal	Cocaine HCl	2–5 min	5–10 min	30 min
Intravenous	Cocaine HCl	Seconds	10–20 min	60–90 min
Oral	Cocaine HCl	30–60 min	60–90 min	Unknown
"Skin popping"	Cocaine HCl	Unknown	Unknown	Unknown

HCl, Hydrogen chloride.

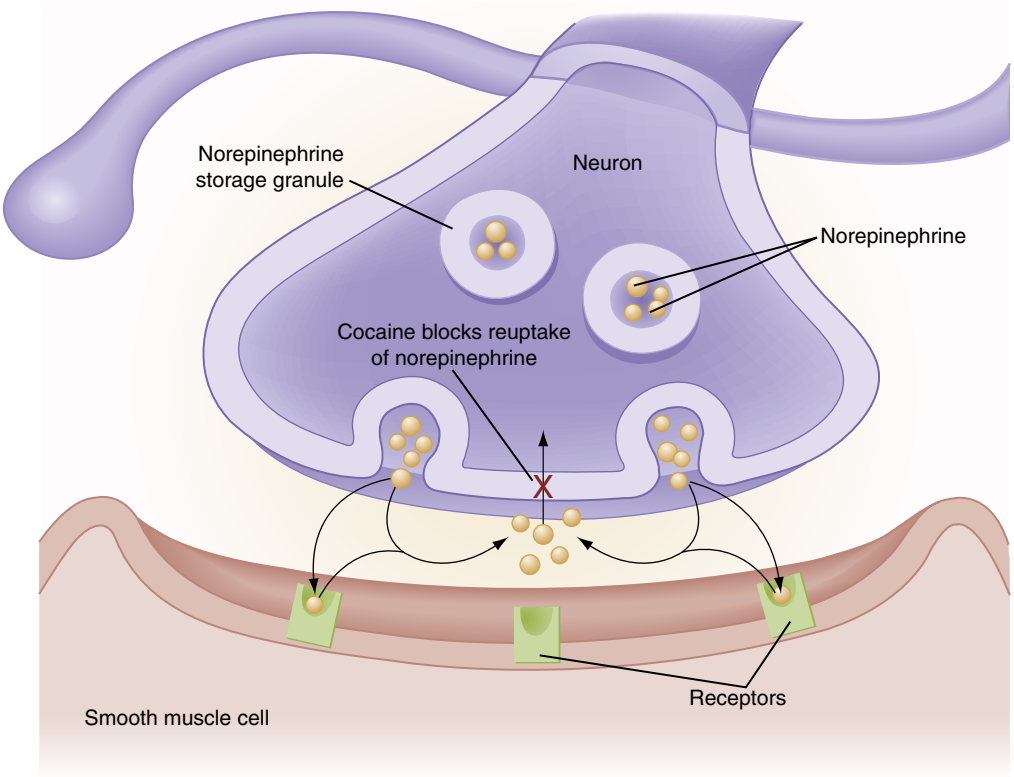

Fig. 144.1 How cocaine increases sympathetic tone by increasing neurotransmitters in the synapse.

nearly 40% increase over the previous year. From 2016 to 2017, non-Hispanic whites had the greatest percent increase in the death rate for overdoses involving psychostimulants, while the largest absolute rate change in psychostimulant-involved overdoses was in American Indian/Alaska Native (AI/AN) populations. AI/AN also experienced the highest death rate for overdoses involving psychostimulants in 2017.

The highest rate increases of psychostimulant-related overdose deaths were in the Midwest region in 2017, while the overall rate was highest in the West. However, the highest overdose death rates were in West Virginia and Alaska.[7]

Methamphetamine

Methamphetamine (methyl amphetamine) was discovered shortly after amphetamine, also as an alternative to ephedrine. Like amphetamine, it was extensively used during the Second World War, to the point that German soldiers called it "Stuka-Tabletten," referring to the pilots of the Stuka dive bombers. The effects of methamphetamine, also known as "crank" and "crystal meth," last longer. Some paranoid delusions persist for 24 hours. The production of methamphetamines requires metal salts. Lead toxicity from the drug being inappropriately produced has been reported. Injuries during illicit methamphetamine production or police raids include exposure to anhydrous ammonia, hydrochloric acid, sodium hydroxide, ether, and ephedrine, as well as burns and explosions in "meth labs." Amphetamines are usually ingested orally as pills, but can be crushed and injected, as well.

Pathophysiology

Amphetamines act by multiple mechanisms to increase norepinephrine, epinephrine, dopamine, and serotonin levels in the brain. They increase the amount of neurotransmitter released per action potential, decrease the rate of clearance from the synaptic cleft, and decrease the rate of enzymatic inactivation. The subsequent CNS stimulation results in sympathomimetic effects nearly identical to those from cocaine, but the effects generally last longer and are less intense. Patients are at risk for hyperthermia, hypertensive emergencies, dysrhythmias, myocardial ischemia, and hyperkalemia associated with rhabdomyolysis.[9] In contrast to cocaine, amphetamines do not block sodium channels. Although urine drug screens can identify amphetamines, they are of little utility in the treatment of an intoxicated patient.

Phenylethylamines, which are closely related in molecular structure to amphetamines, include the "2C" and "NBOMe" drugs, named for the location of specific structural elements along the amphetamine backbone.[10] These have powerful serotonergic, hallucinogenic effects, and patients can present with adrenergic toxicity and behavioral agitation. The brominated form (street-named "Bromo-DragonFLY" due to its structural similarity to a dragonfly) is associated with a necrotizing angiitis that can compromise blood flow to the limbs.[11] Limb or digit pain in such patients warrants comprehensive monitoring and evaluation for vasospasm and tissue ischemia.

Ephedrine and Ephedra

Ephedra is a plant-based medicinal preparation from the herb Ephedra sinica. It is an evergreen shrub-like plant native to Asia and also grows in southwestern United States. Ephedra, also known as the Chinese herbal product Ma Huang, has been associated with strokes and deaths in adolescent users. People have used ephedra for centuries in China for colds, fever, flu, headaches, asthma, nasal congestion, and wheezing. Ephedrine is the main active ingredient in ephedra. In 1997, in response to mounting concern over cardiovascular side effects, the U.S. Food and Drug Administration (FDA) banned products containing 8 mg or more of ephedrine alkaloids and required all ephedra-containing products to disclose the health risks of heart attack, stroke, and death.

Ephedra is widely used by athletes as a performance-enhancing drug, despite a lack of evidence that it improves athletic performance.

Its use has been completely banned from all sports competitions since 2003. Bitter orange is marketed as a "safer" herbal alternative to ephedrine. It contains p-synephrine, which is demethylated ephedrine. At the dose amounts generally available, bitter orange appears to have neither stimulant nor cardiotoxic effects.[12] Ephedrine (and its diastereomer pseudoephedrine) can also be used as a precursor in the manufacture of methamphetamine by dehydrating it. Ephedrine and its stereoisomer, norpseudoephedrine, cross the blood-brain barrier and lead to the release of noradrenaline and dopamine in the substantia nigra.

Caffeine

Caffeine (1,3,7-trimethylxanthine) is a widely consumed psychoactive substance noted for its ergogenic and prokinetic effects. It is a common component of energy drinks and weight loss supplements. It is also a reported adulterant in cocaine, MDMA, and many novel psychoactive substances. In one analysis of 512 street samples of cocaine from Brazil, caffeine concentration ranged between 40% and 60% by weight.[13] Caffeine potentiates the euphoric effects of cocaine in mice.[14] Caffeine is an adenosine antagonist, binding to post-synaptic adenosine receptors throughout the body. Toxic doses of caffeine (greater than 100 mg/kg, or roughly one cup of coffee per kilogram) may induce status epilepticus and tachydysrhythmias refractory to standard treatment regimens requiring hemodialysis.[15]

Novel Psychoactive Substances

Novel psychoactive stimulants are structural variants of amphetamine that combine hallucinogenic, euphoric, and stimulant properties to strike balances between auditory hallucinations, visual hallucinations, paranoia, euphoria, dysphoria, and dissociation.[16] A general rule of thumb used by informal chemists is that aromatic substitutions increase the hallucinogen/entactogen effects and aliphatic substitutions increase the stimulant effects.

Novel psychoactive stimulants are often combined with ethanol or sedatives to mitigate anxiety or dysphoria, or to prolong the perceptual alteration.[17] Novel psychoactive substances are a broader category including synthetic cannabinoid receptor agonists (K2, synthetic marijuana). This chapter does not discuss those substances as they are conceptually closer to cannabis than stimulants.

Data on the usage of most novel psychoactive substances are lacking. Epidemiologists have used wastewater analysis to quantify exposure,[18] but it is difficult to estimate usage from this method. From questionnaires, the use of mephedrone, a bath salt (cathinone), seems more prominent in the United Kingdom than the United States, where 0.5% of people aged 16 to 59 reported using mephedrone at least once in 2015 to 2016.[19]

There is a similar trajectory between derivatives of amphetamine overtaking amphetamine and derivatives of fentanyl overtaking the parent compound fentanyl. In both cases, the derivatives are often more potent than the unmodified compounds, have narrower therapeutic indices, and are generally not detected on standard drug screens. In addition, novel combinations such as methamphetamine contaminated with fentanyl (street named "goofballing") are emerging.

Ecstasy

MDMA (ecstasy, Molly) is a derivative of amphetamine. It is the canonical entactogen. An entactogen produces experiences of emotional communion, oneness, relatedness, emotional openness—that is, empathy or sympathy. The molecular structure of MDMA is in between amphetamine and serotonin, explaining its combination of sympathomimetic and serotonergic features. The term "Molly" (short for molecular) is used to describe a product with a higher concentration of MDMA, although these products may contain merely caffeine or placebos. User reports are, therefore, often unreliable in determining true exposure.

MDMA can precipitate hyponatremia via drug-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). MDMA and its metabolite increase the release of vasopressin (anti-diuretic hormone), which in the setting of high free water intake, results in free water retention.[20] Patients with MDMA-induced hyponatremia demonstrate urine with high osmolality and sodium. Chronic use of MDMA and its variants (MDA) may cause irreversible neurologic damage to serotonergic neurons in mice.[21]

Bath Salts

Bath salts are derivatives of cathinone, an active ingredient in the leaves of khat or qat *(Catha edulis)*. Cathinone is, itself, a phenethylamine derivative. Khat leaves also contain methcathinone, a similarly potent sympathomimetic.

Bath salts were first encountered in Japan in the early 2000s. The ease of synthesis and modification of specific functional groups of the parent cathinone make these drugs particularly difficult to regulate.[22,23] This led to a cat-and-mouse dynamic between internet vendors and regulatory agencies. Most initial bath salts contained mephedrone (4-methyl methcathinone). Once regulatory agencies developed tests for mephedrone, the composition of bath salts rapidly changed to include methylone, ethylone, butylone, pyrovalerone, methylenedioxypyrovalerone (MDPV), methcathinone, and ethcathinone. One cathinone, bupropion (Wellbutrin), is approved for medical use in the United States.

Bath salts may be ingested, inhaled, or injected and can result in severe agitation, sympathomimetic effects, hyperthermia, and rhabdomyolysis. One in vitro study suggests that cathinones and MDMA may have direct myotoxic effects by increasing the permeability of the outer mitochondrial membrane.[24] Smoking khat typically results in little toxicity because cathinone is heat labile. Numerous fatalities have been reported, causing the U.S. Drug Enforcement Administration (DEA) to categorize these agents as illegal Schedule I substances.[25] Synthetic cathinones are usually not detectable on routine urine drug screens. Treatment is similar to that of cocaine and amphetamine toxicity and includes adequate dosing of benzodiazepines for agitation with diazepam, lorazepam, or butyrophenone antipsychotic agents, such as haloperidol and droperidol (see Management, Pharmacologic Sedation for Agitation section).

Some users of synthetic methcathinone demonstrate an extrapyramidal syndrome similar to Parkinson disease with elevated manganese concentrations, presumably resulting from contamination during production. Chelation therapy is, in general, not useful in treating the parkinsonism associated with manganese toxicity.

Kratom

Kratom is a tropical tree *(Mitragyna speciosa)* native to Southeast Asia. Its leaves contain psychotropic compounds, the most studied of which are mitragynine and 7-hydroxymitragynine. Kratom is not currently an illegal substance and can be readily acquired over the internet. It is sometimes sold as an extract, gum, or green powder in packets labeled "not for human consumption." Kratom was traditionally chewed or brewed in a tea in a fashion similar to coca leaves. Mitragynine and 7-hydroxymitragynine exert opioid effects at low doses and stimulant effects at higher doses. This has led to the usage of kratom as a means to treat opioid withdrawal or to address problematic opioid use. There is one report of possible kratom use presenting as opioid intoxication requiring sedation after naloxone, similar to cocaine "speedballing," or cocaine contaminated with heroin.[26]

Clinical Features

The treatment of sympathomimetic toxicity begins with recognition of high-risk symptoms. The imminent life-threatening nature may necessitate treatment before the most likely cause is established. Risk-stratification begins with recognition of high-risk features of sympathomimetic toxicity, which are described in this section.

The sympathomimetic toxidrome refers to the constellation of tachycardia, hypertension, hyperthermia, tachypnea, mydriasis, diaphoresis, tremor, hyperactive bowel sounds, agitation, psychosis, and seizures. These clinical signs reflect overactivation of the sympathetic nervous system by sympathomimetic substances.

Sympathomimetic toxicity is an acute phenomenon with abnormal vital signs. Ingestions that do not develop abnormal vital signs after an appropriate period of monitoring may be medically cleared. Toxicity can range from mild tachycardia or agitation, depending on the amount ingested and the potency of the medication.

A patient with mild toxicity is alert and awake but may be diaphoretic, tachycardic, mydriatic, or hypertensive without organ damage. A patient with severe toxicity may be agitated, combative, or hyperthermic. Patients may present with focal acute pain syndromes, circulatory abnormalities, acute hypertension, coronary vasospasm, or seizures.

Additives, contaminants, or other drugs may create a mixed picture. Patients may combine intravenous (IV) heroin and cocaine ("speedballing"), presenting with signs of opioid toxicity but manifesting signs of cocaine toxicity after they receive naloxone. Patients may combine cocaine or crack cocaine with ethanol to elongate cocaine's euphoric effects.

The clinical presentation of sympathomimetic toxicity depends on the dose, route of administration, coingestants, and time elapsed between ingestion and presentation. Initial assessment should focus on rapidly fatal complications including hyperthermia, hypertensive emergencies, cardiac dysrhythmias, and hyponatremia.

Hyperthermia

Cocaine-toxic patients have increased motor tone and generate excessive heat. Vasoconstriction and salt and water depletion can compromise cooling, resulting in life-threatening hyperthermia with core temperatures exceeding 106°F (41°C). Delay in recognition and management increases the likelihood of death. Even with a normal temperature, increased motor tone can release intramuscular (IM) creatine kinase (CK), with rhabdomyolysis and its attendant renal and electrolyte complications. Acute psychomotor agitation with delirium increases the risk of hyperthermia.

Hypertensive Emergencies

Acute cocaine-induced hypertension can injure the cardiovascular and CNS systems. Reported sequelae include aortic dissection, pulmonary edema, myocardial ischemia and infarction, intracranial hemorrhage, stroke, and infarction in the distribution of the anterior spinal artery.[27] Vasospasm can also compromise perfusion. Intestinal infarctions and mesenteric ischemia can occur, particularly in body packers with large oral ingestions. Other local ischemic events include retinal vasospasm, renal infarctions, and placental insufficiency and infarction in the gravid uterus.

Cardiac Dysrhythmias

Sinus tachycardia is the most common rhythm. Atrial fibrillation and other supraventricular tachycardias can occur as a result of the surge in catecholamines. Life-threatening dysrhythmia may occur suddenly, heralded by abrupt diminution of cardiac output and loss of consciousness. Torsades de pointes from hypokalemia due to potassium shifting into the cells or wide-complex tachycardias from blockade of fast sodium channels on the myocardium may deteriorate into poorly perfusing or fatal ventricular rhythms. Transient conduction abnormalities consistent with a Brugada-type pattern are associated with cocaine, although some cases may be unmasking previously undiagnosed pathology. Hyperkalemia from rhabdomyolysis and myocardial ischemia can also cause dysrhythmias.

Cocaine Use Disorder, Stimulant Use Disorder

Cocaine's effects on the CNS can lead to craving behavior and cocaine use disorders that lead to secondary harm (cellulitis from injection, trauma, and sexually transmitted infections due to accessing drugs by risky means). Paranoia, either drug-induced or from underlying psychiatric illness, may occur even after the acute effects of the drug subside. Similar to phencyclidine (PCP), the neuropsychiatric effects of cocaine can alter behavior and judgment, increasing the risk of violent injuries.

Cardiomyopathy

Cocaine may precipitate heart failure by increasing the risk of myocardial ischemia and by direct injury to the myocardium.[28] The incidence of cardiomyopathy attributable to cocaine use is not well known, but case studies suggest that one should treat cardiomyopathy due to cocaine use just as cardiomyopathy from any other cause and encourage cessation of sympathomimetics.[29]

Washout

Those who binge on sympathomimetics have a prolonged activation of the sympathetic nervous system and reward pathways. This prolonged activation depletes catecholamine stores, disrupts salt/water balance, and may lead to malnutrition as eating falls to the wayside in the face of desire for cocaine. After a cocaine binge, users may experience cocaine washout, an obtunded state where the user is profoundly sedated but arousable and oriented when aroused, with normal vital signs or a mild sinus bradycardia. Users of MDMA report "suicide Sundays," where those who reported using MDMA on Friday night felt profoundly depressed on Sunday.

Nontoxicologic sequelae

Complications also arise from the route of administration. Inhalation may cause oropharyngeal burns. Inhaling and suppressing the cough reflex may precipitate spontaneous pneumothorax, pneumopericardium, or pneumomediastinum. Intranasal cocaine use is associated with sinusitis and nasopalatine necrosis or perforation. IV users have a high risk of infection with blood-borne viruses, local abscesses, and systemic bacterial infections, including *Clostridium botulinum* and endocarditis**.** Transdermal injection of cocaine, or "skin popping," has similar types of complications, especially skin abscesses. For chronic users, addiction or psychological dependence is mediated through specific dopaminergic neurotransmitter pathways. Although there are no well-defined syndromes constituting cocaine withdrawal, patients have strong cravings for the drug or a general feeling of dysphoria that is not physiologically life-threatening.

Some of the toxicity associated with cocaine is due to the unintentional ingestion of adulterants, rather than the formulation of cocaine or route of administration. Of a case series of 97 patients with serum cocaine levels, 31 had one of the following: atropine, phenacetin, hydroxyzine, ketamine, lidocaine, or tetramisole.[30] An analysis of 615 samples from two drug seizures in the United States identified the following contaminants: caffeine (31%), quinine/quinidine (25%), levamisole (12%), acetaminophen (8%), and procaine (8%).[31]

Levamisole is an older adulterant, related to tetramisole, used to dilute cocaine. Neither levamisole nor tetramisole is psychoactive;

rather, they have a similar consistency to cocaine. Levamisole was used to treat pediatric nephritic syndrome and rheumatoid arthritis until it was withdrawn from the market due to hematological complications and vasculopathy. Agranulocytosis, vasculopathy with thrombosis, dermal ulcers, and purpura, often affecting the earlobes, occurred from unintentional exposure to levamisole. A case series of 50 patients reports the development of long-lasting anti-levamisole antibodies that contribute to a serum sickness-like illness.[32] Clenbuterol is a beta-agonist with a similar appearance to cocaine that is used to dilute the amount of cocaine to sell more units. Clenbuterol inhalation or injection may precipitate tachydysrhythmias and hypokalemia.

DIFFERENTIAL DIAGNOSES

The differential diagnoses of the sympathomimetic toxidrome can be split into toxicologic and non-toxicologic causes. One useful rule of thumb is that all vital signs are "revved-up" in frank sympathomimetic toxicity. The heart rate, blood pressure, core temperature, and respiratory rate are all elevated.

Other causes of tachycardia are usually normotensive or hypotensive, for example tachydysrhythmias or hemorrhage. Thyroid storm presents similarly to the sympathomimetic toxidrome because thyroxine also activates the sympathetic nervous system.

A current medication list can help identify possible coingestants. Thought disorders and auditory hallucinations are not typically present, unlike acute psychotic or manic episodes (Box 144.2). It can be difficult to distinguish cocaine toxicity from withdrawal from sedative-hypnotics (benzodiazepines, ethanol, baclofen, gamma-hydroxybutyrate). A history of abstinence from sedative-hypnotics after heavy use may suggest sedative-hypnotic withdrawal if there is documented prior use and no other compelling explanation.

Toxicity from other sympathomimetic agents such as amphetamines, amphetamine derivatives, and PCP can present similarly to cocaine toxicity. Cocaine toxicity generally causes more frequent cardiotoxic effects (acute myocardial infarction, cardiac dysrhythmia, aortic dissection) than amphetamines or PCP.[33] One should also include myocardial ischemia, hyperkalemia, and drug-induced sodium channel blockade (e.g., cyclic antidepressants) in the differential for cocaine-induced wide-complex tachycardia.

Designer amphetamines such as MDMA are more likely than cocaine to cause hyponatremia, either from SIADH or excessive intake of free water. Patients abusing methamphetamine also tend to have more muscle wasting, malnutrition, and poor dental hygiene than chronic cocaine users. PCP toxicity may be distinguished by the presence of multidirectional nystagmus and highly combative behavior.

Like cocaine, patients with antimuscarinic poisoning (such as diphenhydramine, atropine, and jimsonweed; see Chapter 140) may present with agitation, tachycardia, hypertension, and mydriasis. Findings of acute urinary retention and dry mucous membranes distinguish the anticholinergic from the sympathomimetic toxidromes.

The hyperthermic state induced by cocaine toxicity should be further differentiated from classic and exertional heat stroke. Heat stroke tends to have more ambient environmental factors, dehydration, and more profound changes in mental status than cocaine toxicity. Serotonin toxicity (previously called serotonin syndrome) is often precipitated by the addition of a new serotonergic agent or a substance that interferes with the metabolism of a previously tolerated agent. Serotonin toxicity is most commonly reported with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), but it has also been reported with cyclic antidepressants and atypical antipsychotics. The cardinal signs of serotonin toxicity include altered mental status and autonomic instability (hyperthermia, diaphoresis, labile blood pressure) with hyperreflexia and clonus. The neuromuscular findings in serotonin toxicity are more prominent in the lower extremities, in contrast to many motor disorders, which prefer the upper extremities or spread diffusely. The agitation described with serotonin syndrome is less organized and the patient is unlikely to be ambulatory or severely combative. The onset is typically abrupt in the setting of serotonergic drug interactions or overdose. The finding of clonus is an important differentiating feature, because this is present in serotonin syndrome but absent in cocaine toxicity. Similar to serotonin toxicity, neuroleptic malignant syndrome (NMS) also presents with altered mental status, hyperthermia, and agitation. However, unlike serotonin toxicity, peripheral muscular effects tend toward rigidity and decreased reflexes rather than clonus and hyperreflexia. This is due to dopaminergic depletion from the use of dopamine antagonists, such as the older or classic antipsychotic agents. Patients presenting with NMS generally have a gradual course of hypokinesis and increasing resting muscle tone in the setting of escalating antipsychotic use. The alteration in mental status is more commonly a catatonic state.

BOX 144.2 Differential Diagnosis of Agitated Delirium

- Endocrine disease
  - Thyrotoxicosis
- Heatstroke
- Infections
  - Bacterial or viral meningitis or encephalitis
- Psychiatric
  - Acute mania
  - Acute schizophrenia
- Metabolic causes
  - Electrolyte abnormalities
  - Hyperammonemia
  - Hypoglycemia
  - Hypoxia
  - Uremia
- Postictal state
- Structural lesions of the CNS
  - Hemorrhage
  - Mass
  - Stroke
  - Trauma
- Toxicologic causes
  - Amphetamines and derivatives
  - Anticholinergics
  - Caffeine
  - Cocaine
- Lithium
- Neuroleptic malignant syndrome (NMS)
  - PCP, ketamine
  - Sedative-hypnotic withdrawal
  - Serotonin toxicity
  - Sympathomimetics, stimulants
  - Synthetic cannabinoid receptor agonists

CNS, Central nervous system; *PCP,* phencyclidine.

DIAGNOSTIC TESTING

Urine drug screening (UDS) for cocaine is accurate but unlikely to change treatment in the ED, except to provide diagnostic clarity when cocaine toxicity is suspected (e.g., young, otherwise healthy adult with

chest pain) to substantiate exposure in cases of abuse or neglect, to confirm cocaine as the unknown substance in body packers, or to exclude acute cocaine toxicity in an acutely paranoid patient. Most urine drug screens in the ED for cocaine are an immunoassay for benzoyl ecgonine, a chemical produced only by the metabolism of cocaine. Benzoyl ecgonine persists in the urine for 3 to 7 days after last use, depending on the detection limits. Despite popular belief, the local anesthetic lidocaine does not produce a false-positive cocaine screen.[34]

Urine Drug Screening for Amphetamines and Amphetamine Derivatives

The urine drug screen for amphetamine is less useful for providing diagnostic clarity in the ED than the urine drug screen for cocaine. In contrast to cocaine's unique structure, amphetamine, as described above, serves as a starting point for many FDA-approved medications (Adderall [amphetamine salts], Vyvanse [lisdexamfetamine], Wellbutrin [bupropion]) and novel psychoactive substances (cathinones [bath salts], NBOMes, and methamphetamine). The common starting point of these medications and novel psychoactive substances may lead to a false positive result, more accurately termed a cross-reaction. As an example, some beta blockers such as metoprolol are reported to cause a false-positive amphetamine screen.[35]

Electrocardiogram

An ECG screens for dysrhythmias, conduction abnormalities, and ischemia, and can provide insights into hyperkalemia or hypokalemia, as well as sodium channel blockade. Sodium channel blockade, which manifests as a QRS duration longer than 100 milliseconds, can precipitate wide-complex tachycardia by slowing myocardial depolarization. Cyclic antidepressants and cocaine share class IA antidysrhythmic effects with QRS widening and resultant QT prolongation. The prognostic value of QRS widening in the context of a bundle branch block is not known.

The evaluation of chest pain in cocaine ingestion is challenging because cocaine toxicity can precipitate myocardial ischemia via coronary vasospasm. Chronic cocaine use also accelerates arteriosclerosis, which itself can precipitate myocardial ischemia. Young patients may also demonstrate early repolarization, further complicating interpretation. Serial ECGs may be helpful to identify dynamic processes.

A chest radiograph may identify aspirated foreign bodies, pneumothorax, or pneumomediastinum from inhalational barotrauma when these are suspected, but is not required in most cases.

CK, a nonspecific marker for muscle injury, is often elevated with cocaine use. In users with myalgias, a serum CK and urine for myoglobin is checked to screen for rhabdomyolysis. Original data on cocaine-related coronary syndromes used CK-MB as a cardiac marker. This is now supplanted by troponin I, T, or the newer generation high sensitivity troponin assays, as for all patients evaluated for possible ischemic chest pain. Most patients presenting with troponin elevation and chest pain after cocaine use had angiographically proven obstructive coronary disease, often of a single vessel, but almost 20% have normal angiography.[36]

Even though the sensitivity and specificity of troponin cardiac markers for cocaine-related chest pain is unknown, we recommend that patients with cocaine use be evaluated for chest pain in a similar fashion as chest pain patients without cocaine use. Decisions regarding further investigation are based on the characteristics and course of the chest pain and results of serial troponin measurements and ECGs. We do not recommend routine use of diagnostic coronary computed tomographic angiography (CTA) in the evaluation of patients with chest pain in the context of acute cocaine use.

BOX 144.3 Initial Evaluation of Patients With Sympathetic Stimulation

Rapid assessment of vital signs, especially core temperature
Exclude hypoxia, hypoglycemia, and hyponatremia
Pharmacologic sedation with benzodiazepines
Electrocardiogram (ECG)
Urinalysis
Serum creatine kinase (CK)

Severe persistent headache despite normalization of blood pressure may be caused by a subarachnoid hemorrhage (SAH) and warrants evaluation (see Chapters 16 and 33).

In the rare event that a cocaine user presents with agranulocytosis or digital discoloration suggestive of levamisole, a "send-out" or reference laboratory evaluation for urine levamisole by gas chromatography–mass spectrometry can be performed. The sample is ideally obtained within 48 hours after last use.

MANAGEMENT

The altered mental status associated with the sympathomimetic toxidrome ranges from agitated to belligerent behavior. A severely poisoned patient may be combative and unable to cooperate in assessment of vital signs. Agitated delirium is associated with up to a 10% mortality rate. Actions taken during these first stages of the encounter are crucial (Box 144.3) even though the patient remains undifferentiated. Sedation with benzodiazepines serves multiple purposes. It treats agitation and reduces heat production by muscle, heart rate, blood pressure, and the overall adrenergic surge of cocaine or sympathomimetic toxicity.

In the severely agitated patient, immediate administration of IM benzodiazepines while the patient is transiently restrained may be necessary. Once more under control, staff can obtain a complete set of vital signs (including temperature), a bedside glucose measurement, and IV access. If a chest restraint is used, a mesh vest is preferred over a jacket to help limit hyperthermia. Immediate pharmacologic sedation with IM or IV administration of benzodiazepines may be necessary (see next section), which, in adequate doses, restores inhibitory tone to the CNS and decreases excessive sympathetic outflow to peripheral tissues. Sedation also facilitates measurement of vital signs (particularly core temperature), continuous electrocardiographic monitoring, and completion of the physical examination.

Pharmacologic Sedation for Agitation

Benzodiazepines are the mainstay of treatment of cocaine-induced agitation. Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Diazepam can be administered intravenously in increments of 5 to 10 mg every 5 minutes in adults until sedation is achieved. Lorazepam, administered 1 to 2 mg intravenously every 5 minutes, is also an acceptable option. Midazolam in 1 to 2 mg doses IV is more rapid in onset with a shorter duration of effect. The endpoint of benzodiazepine administration in sympathomimetic toxicity is normalization of vital signs and motor tone. Persistently increased motor tone reflects an inadequate benzodiazepine dose, even if the patient appears somnolent. In that case, additional doses of diazepam, lorazepam, or midazolam can be given, with close monitoring of the patient's respiratory status.

If IV access is not possible because of agitation, IM midazolam 5 to 10 mg is the preferred approach and may be repeated every 10 to 20 minutes until the patient can be controlled. Lorazepam is a less-preferred alternative because it takes longer to reach peak

concentration (5 vs. 15 minutes) and clears less rapidly than midazolam, increasing the risk of respiratory depression. Ethanol is a common coingestant. The combination of ethanol and benzodiazepines depresses respiration more than either alone. A prudent course is to give the medication and observe for an objective response, redosing after an appropriate interval. In all patients, titration of the benzodiazepine is important, allowing the clinician to observe the effects of one dose (usually 5 minutes) before an additional dose is given. After sedation is achieved, the patient is closely observed to ensure that the patient's respiratory status is stable when peak sedation effect is achieved.

Benzodiazepines provide the cleanest pharmacologic approach to treating the agitated patient as they bind to one receptor system. However, benzodiazepines may precipitate paradoxical reactions in the pediatric and geriatric populations and may be suboptimal treatments if the ultimate diagnosis of the agitated patient is a psychotic disorder that might benefit from an antipsychotic agent.

Ketamine has been used to treat the acutely agitated patient in the ED[37] and in the prehospital setting.[38–40] Ketamine, like midazolam and haloperidol, can be administered intramuscularly with reliable onset and duration of action. Ketamine is an NMDA-antagonist that induces a dissociative state. It also produces modest increases in heart rate (on the order of 10 beats/min) and blood pressure (10 to 20 mm Hg systolic) when used in 0.3 to 0.5 mg/kg doses. Aripiprazole and ketamine reduced the time to seizure in a mouse model of cocaine toxicity.[41] A systematic review identified 330 subjects with amphetamine toxicity treated with an antipsychotic and documented a low incidence of adverse effects, including two episodes of coma and QT prolongation, with one episode of each: hypotension, NMS, cardiac arrest, and death.[42]

If the cause of delirium is unclear, careful attention to the patient's respiratory status avoids the respiratory depression caused by excessive benzodiazepine administration in the presence of other sedating agents, such as ethanol or opioids.

Most cocaine-induced agitation responds to adequate doses of benzodiazepines. The dose of benzodiazepine required to treat excessive sympathetic tone may exceed 10 times the typical dose used for anxiolysis or relaxation of musculature. Butyrophenone antipsychotic agents (e.g., haloperidol and droperidol) are rapidly effective and generally safe for drug-induced psychosis or agitation states from sympathomimetic agents, including cocaine, amphetamines, and PCP when used in patients with stable vital signs (also discussed in Chapters 13 and 90). They may, however, worsen hyperthermia and tachydysrhythmias, because of their anticholinergic properties. Haloperidol, given 2 to 5 mg IM, may be repeated every 20 to 30 minutes with consideration of other agents after a total of 10 mg. Although not approved for IV use, this route is widely used but should only be considered in the psychotic patient with stable vital signs with close cardiac monitoring in 5-mg doses to a maximum dose of 15 mg. The sedative dose for droperidol is 2.5 to 5 mg IM. Droperidol has a box warning from the FDA for QT prolongation and potentially torsades de pointes. However, most reported cases of butyrophenone-induced dysrhythmias have been in individuals receiving large doses for prolonged periods, such as hours to days, or in elderly populations (older than 60 years). These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when rapid sedation is required. For these reasons, the butyrophenones remain effective agents for treatment of drug and sympathomimetic-induced agitation in carefully selected patients.

Hyperthermia

Cocaine-induced hyperthermia must be treated with rapid cooling (Box 144.4). Patients who sustain elevated core temperatures above 106°F (41°C) for more than 20 minutes will likely develop disseminated intravascular coagulation (DIC) followed by fatal multisystem organ failure. It is crucial to reduce core temperature to 102°F (38.8°C) as soon as clinically possible, ideally within 20 minutes or less. Cooling blankets are insufficient. Ice water submersion in a portable tub is preferred when available, although some favor wet sheets with large circulating fans.[43] These patients require continuous temperature monitoring and fluid resuscitation as judged by standard measures. Invasive cooling techniques are often delayed and inadequate against the vasoconstrictive effects of cocaine and other adrenergic agents. Patients should have continuous monitoring of their core temperature with a rectal probe. Heat generated by agitation and increased muscle tone can be terminated by adequate use of benzodiazepines, as described earlier, with neuromuscular paralysis and intubation as required. If paralysis is needed, we recommend rocuronium, 1 mg/kg, over succinylcholine. Succinylcholine and cocaine are metabolized by the same plasma enzyme—plasma cholinesterase. Concomitant use may prolong the effects of each drug. Succinylcholine may also worsen hyperkalemia due to rhabdomyolysis.

BOX 144.4 Management of Stimulant-Induced Hyperthermia

Cooling

Early identification of elevated core temperature
Large-bore IV access with rapid infusion of crystalloid
Sedation and muscle relaxation with benzodiazepines
Rapid cooling within 20–30 minutes[a]
Paralysis and intubation if necessary

Monitoring and Diagnostics

Urine output via Foley catheterization
Laboratory analysis for organ function
- Serum chemistries, creatinine, CK
- Liver function
- PT, PTT, fibrin split products
- Bacterial cultures
- Urinalysis for myoglobinuria

Neuroimaging if etiology unclear[b]

[a]Ideally with ice water immersion.
[b]Consider lumbar puncture or antibiotic therapy, especially in injection drug users.
CK, Creatine kinase; *IV,* intravenous; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

Acute Hypertensive Emergencies

The goal in cocaine-induced hypertensive emergencies is to lower blood pressure by counteracting alpha-adrenergic vasoconstriction. Benzodiazepines are the first line treatment. These agents restore the CNS inhibitory tone throughout the body, including the heart. We also recommend phentolamine, a direct alpha-adrenergic antagonist, given as repeated IV doses of 1 mg every 3 minutes with continuous blood pressure monitoring. If two doses fail to reduce the mean arterial pressure by at least one-third, increase each following dose by 1 mg up to 5 mg/dose until the mean arterial pressure is reduced by at least one-third. Phentolamine lasts roughly 45 minutes. Alternative agents include hydralazine, nitroglycerin, and short-acting IV calcium channel antagonists like nicardipine or clevidipine (see Chapter 70). We prefer shorter-acting antihypertensives because they can be discontinued as toxicity subsides without risk of overshoot, which may be deleterious if the patient also has a SAH or aortic dissection attributable to cocaine.

It had been previously recommended to avoid beta-adrenergic antagonists (beta blockers) in treating cocaine-induced hypertension because unopposed α-receptor activity would precipitate coronary artery spasm and hypertension. This concern was based on data that patients undergoing cardiac catheterization demonstrated decreased coronary artery diameter in the presence of injected (mainlined) cocaine and beta-adrenergic antagonists. In two retrospective studies, beta-blocker use was not associated with clinically significant hypertension, troponin elevation, or adverse events in patients presenting with acute cocaine toxicity.[44,45] A meta-analysis of five studies found no differences between patients treated with or without beta-blockers for either myocardial infarction or overall-cause mortality. Another meta-analysis found no significant difference in the odds of myocardial infarction or overall-cause mortality in patients who received a beta-blocker versus not. This second meta-analysis did not explicitly control for whether the patients were currently prescribed a beta-blocker and shared one study with the first meta-analysis.

One way to reconcile previous concerns with the evidence is to recognize that most beta blockers are also alpha-adrenergic antagonists. Beta-blockers may be a useful adjunct in treating cocaine-associated hypertension, but the clinician should be aware that beta-blockers do not treat the other toxic effects of cocaine, which are generally responsive to adequate doses of benzodiazepines. As a result, while not contraindicated, we do not postulate that beta-blockers provide a clinical benefit in this setting and do not recommend their routine use in patients presenting with cocaine-induced hypertension.

Dysrhythmias

Dysrhythmias from cocaine may be atrial or ventricular. Atrial fibrillation and supraventricular tachycardias attributable to cocaine will respond to benzodiazepines. Calcium channel blockers or beta blockers can be used if rapid atrial rhythms fail to respond to sedation, cooling, and volume resuscitation, but negative ionotropic agents (e.g., beta-1 preferential antagonists, verapamil, diltiazem) should be used with caution as cocaine is directly cardiotoxic.

Important considerations in the differential diagnosis of a wide-complex tachycardia include hyperkalemia, sodium channel blockade (cyclic antidepressants and cocaine), and myocardial ischemia. In cocaine body packers or patients presenting with cocaine-induced adrenergic toxidrome, abrupt development of a wide-complex tachycardia with a pulse should be treated with empirical sodium bicarbonate, 1 to 2 mEq/kg IV bolus, with closely recorded cardiac monitoring to observe for QRS narrowing.[46] If hypotension and QRS prolongation do not improve with sodium bicarbonate, consult a medical toxicologist to discuss possible intravenous lipid emulsion therapy. Intravenous lipid emulsion therapy was reported as "life-saving" in case reports of cocaine toxicity. However, the absence of rigorous trials prevents the American Association of Clinical Toxicologists (AACT) from recommending routine use in these cases.[47] Fluid and electrolytes should be corrected as indicated. Close monitoring is required for patients with a preexisting or unmasked Brugada-type conduction pattern.

Hyponatremia

Treatment for sympathomimetic-induced hyponatremia (e.g., MDMA) is the same as that for SIADH from other causes and includes fluid restriction and hypertonic saline (if seizing). Normal saline may worsen hyponatremia by inadvertently increasing free water retention. To our knowledge, treatment with V2-receptor antagonists has not been described for these patients.

Cocaine-Related Chest Pain

The causes of cocaine-related chest pain are diverse (Box 144.5), including aspirated foreign bodies or pneumothorax or pneumomediastinum from inhalational barotrauma. Fever and shortness of breath should prompt consideration of pneumonia, pulmonary infarction, or endocarditis with septic pulmonary emboli in IV drug abuse.

BOX 144.5 Causes of Stimulant-Induced Chest Pain

Cardiac Chest Pain
- Coronary stent thrombosis
- Endocarditis
- Ischemia, infarction
  - During acute intoxication
  - After acute intoxication
- Left ventricular apical ballooning
- Pericarditis

Noncardiac
- Aortic dissection
- Foreign body aspiration
- Infection
- Pneumomediastinum
- Pneumopericardium
- Pneumothorax
- Pulmonary infarction
- Intestinal ischemia or infarct

Cocaine acutely induces coronary vasoconstriction while increasing myocardial oxygen demand. Platelet aggregation is enhanced through thrombogenic and antifibrinolytic pathways. These cumulative effects can result in coronary insufficiency. Cigarette smoking acutely exacerbates these conditions. Chronic cocaine use may accelerate atherogenesis and induce left ventricular hypertrophy.[48] All of these factors contribute to myocardial ischemia or infarction. Of nonfatal myocardial infarctions in patients aged 18 to 45 years, 25% are attributed to cocaine, even after adjustment of other known cardiac risk factors.[49]

Identification of a patient with a cocaine-related coronary syndrome is difficult. Patients may present hours to days after use, possibly because of vasoactive metabolites. The patient may deny drug use and have atypical chest pain. Almost one-third of cocaine-using patients with elevated serum enzymes have pleuritic chest pain. There are no clear predictors for patients at risk for cocaine-related coronary syndrome, including the patient's age, route of drug use, time to presentation, and preexisting risk factors for coronary artery disease. In the setting of cocaine-related chest pain, risk stratification by thrombolysis in the myocardial infarction (TIMI) score may not adequately identify patients at risk for 30-day adverse outcomes. Cocaine history alone, however, in low-risk asymptomatic patients assessed by coronary CTA is generally not associated with increased risk of coronary artery disease. Patients with positive serum biomarkers for myocardial infarction often have significant angiographic stenosis. Of patients without positive serum markers, up to 20% may still have significant disease by angiography. Other predictors of significant disease in this group included elevated cholesterol concentration and prior diagnosis of coronary disease or myocardial infarction. Patients with previous coronary stent placement are at higher risk of thrombosis with cocaine use.

As for most complications of cocaine use, benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation and should be given early to patients presenting with cocaine-induced chest pain, especially when signs of adrenergic excess are present. Aspirin and nitrates should be administered as for any case of suspected ischemic chest pain. In patients meeting electrocardiographic criteria for myocardial infarction with persistent chest pain and hypertension and a clear history of acute cocaine intoxication, coronary vasodilation

with IV phentolamine (1 mg) can be given slowly over 3 minutes if available. This dose can be repeated, if needed, as long as the patient's blood pressure remains stable. Morphine sulfate can be used to treat chest pain. Patients with persistent chest pain and ST segment changes strongly suggestive of myocardial infarction can be considered for percutaneous intervention or thrombolytic therapy, assuming there are no contraindications, such as uncontrolled severe hypertension.[48]

In contrast to non-cocaine-induced myocardial ischemia or infarction, beta-adrenergic antagonists, including labetalol, are generally not recommended with acute cocaine toxicity because coronary vasoconstriction may be exacerbated. In patients with cocaine-related coronary syndromes who are not acutely toxic, alpha-adrenergic vasoactive metabolites may be responsible. Outcomes of uncomplicated chest pain due to cocaine are generally good. Current guidelines for care of the patient with an acute coronary syndrome that is unrelated to cocaine do not recommend immediate administration of beta-adrenergic antagonists, but rather within the first 24 hours. As such, in patients with known or suspected cocaine-related myocardial infarction with or without ST segment elevation, there is little role for beta-adrenergic antagonists in the ED and we do not recommend their routine use. Such patients warrant further evaluations of coexisting atherosclerotic heart disease and clinical reevaluation prior to consideration of this therapy. Administration of beta-adrenergic antagonists on discharge is controversial, especially if cocaine use is likely to continue, and we advise against this routine practice.[44]

Heparin can be given, but fibrinolytic therapy is not well studied. Some mechanisms of cocaine-induced myocardial infarction would be expected to respond to fibrinolytic agents. Patients failing to respond to treatment with nitrates and phentolamine who have a known coronary artery disease or a previous ECG confirming new ST segment elevations are candidates for cardiac catheterization or fibrinolysis, if necessary. The same contraindications apply as those for non-cocaine-induced myocardial infarction. Nuclear imaging studies also may provide more diagnostic information, but their use is best considered in consultation with cardiology. Patients presenting with chest pain after cocaine use and an ECG with definitive or new ST elevations should have prompt evaluation by a cardiologist for potential cardiac catheterization intervention when such services are available.

Antiplatelet and glycoprotein IIb/IIIa inhibitors and calcium channel antagonists seem to be of benefit to some patients with myocardial infarction or ischemia of atherosclerotic origin. Theoretically, these agents may counter some of the platelet aggregation enhanced by cocaine, but data investigating their use are lacking.

Patients with cocaine-related chest pain without other cardiac risk factors who have normal ECGs and cardiac biomarkers are at low risk for myocardial infarction. The role of provocative testing in these patients is not well established.

In summary, cocaine-induced coronary ischemia is managed with benzodiazepines, nitrates, and vasodilators, preferably phentolamine. As with non-cocaine-using patients presenting with acute ischemic chest pain, we recommend use of aspirin, heparin, and antiplatelet agents in conjunction with interventional therapy as indicated.

Interventions to cease cocaine use are warranted. For patients with documented coronary artery disease, cessation of cocaine use is imperative. In studies, cocaine users presenting with chest pain who subsequently continued cocaine use after ED discharge were more likely to have recurrent ED visits than were those who stopped subsequent use.

SPECIAL TOPICS

Body Packers

A body packer is an individual who intentionally ingests a large amount of an illicit substance in multiple carefully wrapped packages to transport that substance from an area of production to an area of distribution or consumption. The substances are often wrapped tightly into condoms or other latex products and sometimes coated in wax.

Body packing is most extensively described with cocaine. Each packet can contain nearly 10 g of cocaine. Packers may swallow as many as 150 packets. To quiet peristalsis, the packer may be forced to take antimotility drugs (loperamide, diphenoxylate-atropine). On arrival at the patient's destination, a cathartic is often taken to stimulate gastrointestinal passage of the product for subsequent delivery and distribution. Body packers are likely to know the exact number of packets they ingested but may be reluctant to share that information. Treatment should be specific for each group of drugs, whether it is opioids, cocaine, or amphetamine. Surgical interventions are indicated for obstruction of the intestines or package rupture. Legal consultation should be obtained because of the legal complexity of body packing cases.

A body packer may present without symptoms to the ED. Diagnosis is made by history. The patient may not be forthcoming, owing to the presence of law enforcement or fear of retribution by the packer's handlers. The patient should be placed on continuous cardiac monitoring, with large-bore IV access. An abdominal radiograph may qualitatively confirm foreign bodies, but cannot be used to count packets. Plain radiographs do not reliably detect small or loosely packed packets; computed tomography may be warranted if suspicion is high.

The main step in body packer management is to ensure that the patient passes all of the swallowed packages.[49] We recommend whole-bowel irrigation with polyethylene glycol to facilitate passage. Endoscopic retrieval is generally discouraged because the packets may rupture during the procedure, but it has been done on occasion.[50] Patients stating that they swallowed a larger number of packets than are passed or who refuse to reveal the number ingested should have continued bowel irrigation, observation, and repeated studies. Subsequent computed tomography (CT) scans or contrast studies may be required to evaluate for remaining packets.[50] However, these radiographic studies may fail to detect isolated packets that contain potentially fatal quantities of cocaine.

Rupture of a single cocaine packet can be fatal. Each packet contains almost 10 times the lethal dose. Cocaine body packers with retained packets should be admitted to a monitored setting with a plan to facilitate removal of the packets via whole bowel irrigation. There is no indication for surgical intervention to remove drug packets from the gastrointestinal tract of an asymptomatic patient.[2] If the patient develops sympathomimetic toxicity and abdominal pain or signs of a bowel obstruction, surgery should be consulted for evaluation of urgent removal.[51,52] When evidence of cocaine toxicity is manifested, rapid surgical intervention may be the only way to rescue these patients. Benzodiazepines, neuromuscular blockade, or sodium bicarbonate administration (for wide-complex tachycardia) do not address the imminently ischemic gut.

All packets passed in the stool, through endoscopic procedures, or in the operating room should be counted carefully and promptly given to law enforcement officials. If law enforcement is not yet involved, hospital legal counsel or risk management and the hospital ethics committee may be helpful in determining the handling of the packets. If the patient fails to improve after passage of all packets intact, one should consider alternative diagnoses. As an example, one case identified a body packer with HIV who presented with tachypnea, tachycardia, mydriasis, and a temperature of 102° F. He was found to have pulmonary infiltrates on computed tomography and was eventually diagnosed with pneumococcal pneumonia.[53]

Body Stuffers

A "body stuffer" attempts to conceal evidence of possession of illicit substances by internally concealing the drug while being pursued by

law enforcement officials. Stuffing usually is by ingestion. It may also involve vaginal or anal concealment. In contrast to packing, stuffing is usually an unplanned event that involves a spontaneous insertion of small amounts of poorly packaged material. The substances are often swallowed in poorly sealed vials or glassine packets that may not be evident on radiographs. In general, patients ingest nonlethal doses and are asymptomatic. For cooperative asymptomatic oral body stuffers, the role of gastric decontamination is not well studied. We recommend activated charcoal if presenting within 3 hours after ingestion to bind and sequester any contents leaking into the GI tract. Monitoring, as described earlier with body packers, should be performed if the quantity ingested is of concern or if signs of toxicity develop. Due to lower doses and less potential lethality, the vast majority of body stuffers will not require whole bowel irrigation therapy as do body packers. Body stuffers rarely have fatal events, and these patients usually have symptoms in the first 8 hours. Asymptomatic patients who are unwilling to disclose events or cooperate with care should have monitoring in the ED regardless of status of police custody. However, if the patient is not under arrest, they are free to decline therapy and leave the ED against medical advice if they can demonstrate clear understanding of the risks, including sudden death, of leaving with retained packets. Although the ideal period of observation is uncertain, 8 to 12 hours is reasonable with admission if the patient develops signs or symptoms of toxicity. Patients with suspected vaginal or anal concealment who are asymptomatic and without signs of toxicity who refuse a physical examination should be assessed for capacity and observed in the ED as outlined earlier. Any judicial warrants for an invasive examination against the patient's will should carefully involve risk management and hospital legal counsel, because these are forensic requests and not medically emergent in the asymptomatic patient.

DISPOSITION

Most patients with sympathomimetic toxicity are young adults with a clear history of single substance ingestion. If there are no signs of end-organ damage, they may be discharged once vital signs and mental status return to baseline after a period of observation of 4 to 6 hours.

Patients who respond quickly to one to two doses of sedation, have no concerning elements in their history or presentation, and exhibit no evidence of end-organ toxicity may be safely discharged once their vital signs and mental status return to baseline. Concerning elements in the history include the presence of coingestants, concern for drug packing, human trafficking, or prior episodes of endocarditis. Some patients may be extremely lethargic from catecholamine depletion, even if not in frank washout. It is prudent to discharge them with a responsible adult. Patients may be open to drug counseling and referral while in the ED.

Patients with chest pain (Box 144.6) and who show dynamic changes on the ECG, troponin elevation, dysrhythmias, or pulmonary edema and patients requiring vasodilators or reperfusion should be admitted to a coronary care unit or a telemetry unit. These patients require further evaluation of the extent of preexisting reversible ischemia and intervention to encourage cessation of drug use. Patients in whom the chest pain is felt to be less likely attributable to cocaine (e.g., frequent user with no change in pattern of use with chest pain) may be treated and risk-stratified according to standard screening for risk factors as with non-cocaine chest pain (see Chapter 64).

BOX 144.6 Admission Criteria for Cocaine-Related Chest Pain

Cardiogenic shock
CHF
Dysrhythmias or conduction abnormalities
Electrocardiographic changes
Elevated myocardial enzymes
Multiple risk factors for CAD
Persistent chest pain, dyspnea, or abnormal vital signs
Preexisting CAD or stent placement
Requiring vasodilating pharmacotherapy
Persistent symptoms

CAD, Coronary artery disease; *CHF,* congestive heart failure.

In patients with no other risk factors for cardiovascular disease, cocaine use is not associated with an increased likelihood of coronary disease after adjustment for age, race, sex, and other risk factors for coronary disease.[48] Complications such as congestive heart failure and ventricular dysrhythmias typically manifest within the first 4 to 6 hours. Young patients who present after resolution of chest pain with normal and unchanging ECGs, no dysrhythmias and few or no risks of coronary artery disease are likely to have a good outcome. Prior studies have demonstrated that these low- to intermediate-risk patients with cocaine-associated chest pain can be safely discharged after 8 to 12 hours of observation. The goal of a more recent study was to determine the safety of an 8-hour protocol for ruling out myocardial infarction in patients who presented with cocaine-associated chest pain. Application of an abbreviated cardiac enzyme protocol (at 0, 2, 4, and 8 hours) after presentation with continuous cardiac monitoring, resulted in the safe and rapid discharge of patients presenting to the ED with cocaine-associated chest pain.

Body packers need to be observed until all packets have passed. Ideally, these patients have had several packet-free stools, a reliable packet count consistent with the ingestion, and a normal CT scan or contrast radiographic study. Body stuffers who receive activated charcoal, have normal ECGs, and remain asymptomatic with normal vital signs after 6 to 12 hours of observation may be discharged.

There are special considerations for the pediatric patient. There should be a low threshold to admit the pediatric patient in whom the intent of the ingestion is unclear, even if the patient demonstrates no current sympathomimetic toxicity. An unintentional ingestion by an adolescent of one to two short-acting sympathomimetics (e.g., Adderall) may be treated as above. An intentional ingestion not for suicidal purposes of a similar amount may be similarly discharged if evaluation by social work uncovers no other concerns and the clinician of records feels that it is a safe discharge. Any toddler presenting with sympathomimetic toxicity should be evaluated by social work and may require admission until a safe discharge can be assured. Involve a medical toxicologist early to guide clinical care and to provide insight with critically ill patients or when expanded testing is needed for forensic or medicolegal concerns.

We would like to acknowledge the scholarly efforts and expertise of the previous edition authors Drs. Rama B. Rao and Robert S. Hoffman.

The references for this chapter can be found online at ExpertConsult.com

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CHAPTER 144: QUESTIONS AND ANSWERS

1. How long does a typical urine drug screen result remain positive after use of cocaine?
   a. 1 day
   b. 3-7 days
   c. 2 weeks
   d. 1 month

Answer: b. Urine drug screens typically detect the cocaine metabolite benzoylecgonine, which is typically present in the urine for 3 to 7 days after the last use.

2. A 24-year-old man is seen by police to be smoking crack cocaine on a street corner. On the way to jail, the patient reports a severe headache, so the police bring him to the emergency department (ED) for medical clearance. The patient is awake with normal mental status but continues to complain of diffuse head pain. His vital signs are blood pressure (BP), 195/99 mm Hg; heart rate (HR), 102 bpm; respiratory rate (RR), 18 rpm; and temperature, 37.2°C. His physical examination is normal. How should his headache be evaluated?
   a. Acetaminophen administration, discharge if headache resolves
   b. Blood pressure reduction, discharge if headache resolves
   c. Head computed tomography (CT) scan, discharge if normal
   d. Head CT scan, lumbar puncture if normal, discharge if both are normal
   e. No evaluation needed; cocaine is not associated with headache

Answer: d. Cocaine is associated with subarachnoid hemorrhage (SAH). Patients complaining of a severe headache after cocaine use should receive a complete evaluation for SAH, including head CT and lumbar puncture. In addition, elevated blood pressure should be lowered while the evaluation is being performed.

3. What is the preferred primary method for controlling a combative patient suffering from a sympathomimetic overdose?
   a. Chlorpromazine
   b. Diazepam
   c. Droperidol
   d. Haloperidol
   e. Physical restraints

Answer: b. Diazepam and other benzodiazepines are the best agents to sedate and establish control of an agitated patient. They cause sedation as well as decrease muscle tone, which can ameliorate hyperthermia. In addition, they can lower the acutely increased blood pressure often seen with sympathomimetic use. In the agitated patient when intravenous (IV) access may be difficult to establish, lorazepam is more predictably absorbed than diazepam. Chlorpromazine can be given intramuscularly to provide rapid sedation but is associated with anticholinergic effects that may exacerbate hyperthermia. Butyrophenone agents (e.g., haloperidol and droperidol) are reserved for more severe agitation and are considered secondary methods of treatment after adequate doses of benzodiazepines. Also, they may have associated dysrhythmic effects that are additive to those of cocaine. Physical restraints may be necessary initially but are not desirable, because they can also increase the risk of hyperthermia as well as increase agitation, which is associated with sudden death.

4. A 27-year-old woman presents with severe chest pain that began soon after use of a large amount of cocaine. She describes the pain as "tearing from my chest to my back." Her vital signs are blood pressure (BP), 210/112 mm Hg; heart rate (HR), 142 bpm; respiratory rate (RR) 22 rpm; and temperature, 38.0°C. A BP measurement taken in the other arm is 147/86 mm Hg. An electrocardiogram (ECG) is normal. You are highly suspicious that the patient is suffering from an aortic dissection and order a transesophageal ultrasound examination while contacting the cardiothoracic surgeon. In the meantime, what should you use to lower her blood pressure?
   a. Labetalol
   b. Nitroglycerine
   c. Nitroprusside
   d. Phentolamine
   e. Treatment should be withheld until a definitive diagnosis is made.

Answer: d. Phentolamine is a direct alpha-adrenergic antagonist and is the drug of choice for sympathomimetic-induced hypertension with end-organ damage. Labetalol and beta-blockers are not recommended, because they have little clinical benefit in this setting. Nitroprusside and nitroglycerine are acceptable agents if phentolamine is not available. Treatment should not be withheld because rapid blood pressure control could be lifesaving.

5. A 35-year-old man presents with chest pain that started approximately 2 hours ago, soon after he smoked crack cocaine. The pain occurred with exertion and has not resolved. He has no previous medical history. His vital signs are blood pressure (BP), 182/99 mm Hg; heart rate (HR), 122 bpm; respiratory rate (RR) 18 rpm; and temperature, 38.2°C. His electrocardiogram (ECG) shows sinus tachycardia with ST depression in the anterior leads. The chest radiograph is normal. Laboratory results are significant for elevations in troponin I. What is the likely explanation for his elevated serum cardiac markers?
   a. He has a completely occluded coronary artery causing ischemia.
   b. He has coronary artery spasm without ischemia.
   c. He has coronary stenosis causing ischemia.
   d. He has fever and rhabdomyolysis but no cardiac disease.
   e. His elevated blood pressure is causing cardiac strain but not ischemia.

Answer: c. Although cocaine can cause coronary spasm with resultant chest pain, patients with positive serum markers are likely to have significant angiographic stenosis. Cocaine users who have complete coronary occlusion typically develop ST elevation just as non-cocaine users do. His elevated blood pressure and fever are certainly increasing the workload on the heart but are not causing his elevated cardiac markers. Cocaine patients may suffer from rhabdomyolysis, and although the resultant renal failure can slow the clearance of the cardiac markers, it does not cause the elevation.

6. A 24-year-old man is brought to the emergency department (ED) in police custody after he admitted to swallowing multiple packets of cocaine to smuggle them through an airport. The patient has no complaints. His physical examination is normal. An abdominal radiograph shows multiple slightly radiopaque areas consistent with packets of cocaine. An electrocardiogram (ECG) is normal. What is the most appropriate management of this patient?
   a. Endoscopic removal of packets
   b. No therapy needed; the patient may be discharged
   c. Observation alone to watch for elimination of packets
   d. Surgical removal of packets
   e. Whole bowel irrigation to remove packets

Answer: e. Whole bowel irrigation with polyethylene glycol facilitates passage of the packets and is safe and effective. Endoscopic removal should be avoided, because there is increased risk of packet rupture. Emergent surgical removal is indicated if there is evidence of packet leak and the patient becomes symptomatic. The patient needs to be observed with cardiac monitoring at a center capable of emergent surgery until all packets have passed.

CHAPTER 144: QUESTIONS AND ANSWERS—cont'd

7. Which unique life-threatening electrolyte abnormality is seen with the use of *N*-methyl-3,4-methylenedioxyamphetamine (MDMA)?
   a. Hyperkalemia
   b. Hypernatremia
   c. Hypokalemia
   d. Hypomagnesemia
   e. Hyponatremia

Answer: e. Hyponatremia can occur with MDMA use and can be severe and life-threatening. MDMA alters the release of vasopressin and will induce a clinical syndrome resembling the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The patients have concentrated urine with high urine sodium content. Seizures can occur and should be treated with hypertonic saline. In the absence of seizures or other life-threatening conditions, general supportive care with water restriction is adequate treatment.

THC and Hallucinogens

Whitney Barrett and Janetta L. Iwanicki

KEY CONCEPTS

- Hallucinogens include many types of drugs and chemicals with different associated effects, including action at serotonin receptors, dopamine receptors, and glutamate *N*-methyl-D-aspartate receptors.
- Diagnosis and management are based primarily on the history and physical examination, with hallmarks of therapy including supportive care, a calm quiet environment, and sedation with benzodiazepines such as diazepam or lorazepam. Severely agitated patients may benefit from butyrophenone antipsychotic agents such as haloperidol and droperidol.
- Screening tests for hallucinogenic drugs of abuse are of limited value in the acute management of intoxicated patients.
- Novel synthetic hallucinogens continue to emerge and may have effects from hallucinogenic, serotonergic, and dissociative toxidromes. These drugs are rarely detected by screening tests, and cases of toxicity may occur in regional outbreaks.
- Patients with phencyclidine (PCP) toxicity can have unpredictable, violent behavior, and may sustain traumatic injuries. Extreme agitation, although possible, is less common with abuse of ketamine and methoxetamine.
- Extremely agitated, violent PCP-intoxicated patients may require rapid sedation to decrease danger to the patient and health care providers. For hyperthermic patients, sufficient sedation to decrease neuromuscular hyperactivity may require intubation, paralytics, and active external cooling to decrease the risk of multiorgan failure and mortality.
- The care of patients intoxicated from cannabis and synthetic cannabinoids consists of prevention of injury and reassurance for those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines or antipsychotics. High doses of antiemetics may be necessary to treat the nausea and vomiting associated with synthetic cannabinoids and heavy daily cannabis use, referred to as the "cannabinoid hyperemesis syndrome."
- The central nervous system and physiologic effects of mescaline use are similar to those of lysergic acid diethylamide (LSD) derivatives, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects.

Hallucinogens include many types of drugs and chemicals with different associated effects, including action at serotonin receptors, dopamine receptors, and glutamate N-methyl-D-aspartate receptors. Diagnosis and management are based primarily on the history and physical examination, with hallmarks of therapy including supportive care, a calm quiet environment, and sedation with benzodiazepines. Severely agitated patients may benefit from butyrophenone antipsychotic agents such as haloperidol and droperidol.

Screening tests for hallucinogenic drugs of abuse are of limited value in the acute management of intoxicated patients. Novel synthetic hallucinogens continue to emerge. These drugs are rarely detected by screening tests, and cases of toxicity may occur in regional outbreaks. Patients with phencyclidine (PCP) toxicity can have unpredictable, violent behavior, and may sustain traumatic injuries. They may require rapid sedation to decrease danger to the patient and health care providers. For hyperthermic patients, sufficient sedation to decrease neuromuscular hyperactivity may require intubation, paralytics, and active external cooling. Extreme agitation is less common with abuse of ketamine and methoxetamine. The care of patients intoxicated from cannabis and synthetic cannabinoids consists of prevention of injury and reassurance for those who have panic reactions. High doses of antiemetics may be necessary to treat the nausea and vomiting associated with synthetic cannabinoids and heavy daily cannabis use, referred to as the "cannabinoid hyperemesis syndrome." The central nervous system and physiologic effects of mescaline use are similar to those of lysergic acid diethylamide (LSD) derivatives, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects.

The term *hallucinogen* is used to describe a variety of xenobiotics causing altered perception. A hallucination is defined as perception of an object or sensation that does not exist in reality. However, most drugs do not produce actual hallucinations. Drugs that are classified as hallucinogens are more likely to cause illusions, or misperceptions of real objects. Some hallucinogens are called psychedelics, a subset that alters cognition and perception. Hallucinogens work by several mechanisms, including stimulating the serotonergic 5-HT_{2A} receptor, hyperactivation of the dopamine D2 receptor, and blockade of the glutamate N-methyl-D-aspartate (NMDA) receptors. This chapter describes serotonergic agents, dissociative agents, and selected plants and fungi. Sympathomimetic agents are discussed in Chapter 144.

SEROTONERGIC AGENTS

Principles of Toxicity

Serotoninergic agents are a broad category of compounds that share structural similarities with serotonin (5-hydroxytryptamine [5-HT]) or enhance serotonergic tone within the body, predominantly by their action at the 5-HT_{2A} serotonin receptor subtype. These agents include various lysergic acid derivatives (lysergamides) and tryptamines (indolealkylamines). Serotonin-like agents produce changes in thought, mood, perception, and consciousness. Orientation to person, place, and time is usually preserved, but severe intoxication may cause delirium, disorientation, and altered levels of consciousness. Patients may present to the emergency department (ED) because of an acute panic reaction, excessive ingestion, or accidental exposure (e.g., children or adults who have ingested the drug unknowingly). Unlike opioids, there is no addictive component in psychedelics and no euphoria-dysphoria cycle, as occurs with sympathomimetic drugs such as cocaine. The rapid development of tolerance also limits the effect of repeated doses.

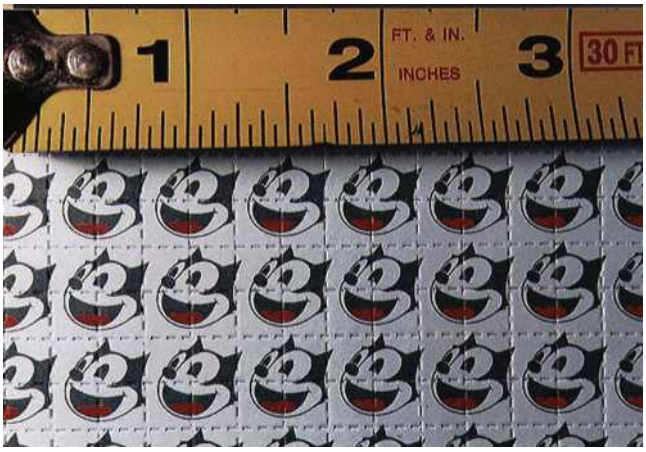

Fig. 145.1 LSD blotters (Felix the Cat). (Photo by Jon, copyright 2001, Blotterart.com. Accessed at www.erowid.org.)

Lysergamides

Lysergic acid diethylamide (LSD), or acid, is a potent psychedelic drug. Doses of 1 to 1.5 µg/kg produce psychedelic effects. The typical dose taken for an "acid trip" is approximately 25 to 100 µg. LSD is sold as a tablet (microdot), liquid, powder, gelatin square (or "windowpane"), and blotter acid. Sheets of blotting paper are sprayed with LSD, dried, and perforated into small squares. Graphics are incorporated onto the blotting paper in designs that include cartoon characters (e.g., Felix the Cat, Bart Simpson) and geometric designs (Fig. 145.1). Each sheet is composed of hundreds of squares that are placed sublingually or eaten whole. Massive ingestions are rare. Drug paraphernalia recently sold and touted as "LSD" does not actually contain lysergic acid diethylamide but synthetic cannabinoids.

In addition to synthetic LSD, several plants contain lysergic acid amide (LSA) similar in structure and action to LSD. These plants include the Hawaiian baby wood rose (*Argyreia nervosa*), Hawaiian wood rose (*Merremia tuberosa*), morning glory (*Ipomoea violacea*), and ololiuqui (*Rivea corymbosa*). Intoxication may result after ingestion of the seeds, extract, or tea.

Tryptamines

Tryptamines may be synthetic or natural compounds. For centuries, Native Central and South Americans have used tryptamine-containing beverages such as ayahuasca in their religious ceremonies. This beverage is brewed from a combination of plants containing dimethyltryptamine (DMT) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), as well as harmine alkaloids with monoamine oxidase inhibitor effects that increase the bioavailability of orally ingested DMT. Ayahuasca has gained recent popularity in Europe and North America.

Psilocybin and psilocin are naturally occurring tryptamines found in some species of *Psilocybe* (Fig. 145.2), *Panaeolus,* and *Conocybe* mushrooms. Psilocybin remains active when the mushrooms are dried or cooked. Street psilocybin sold as pills or capsules is frequently substituted with phencyclidine (PCP) or LSD. Naturally occurring tryptamines are also found in the parotid glands of the *Bufo* toad species. The venom of the Sonoran Desert or Colorado River toad (*Bufo alvarius*) contains 5-MeO-DMT. Smoking of the dried venom results in psychoactive effects.

Designer tryptamines such as α-methyltryptamine, diisopropyltryptamine, and diisopropyl-5-methoxytryptamine (street named foxy or foxy methoxy) have been synthesized and are orally active. The effects of these synthetic derivatives are similar to those of naturally occurring tryptamines.

Fig. 145.2 *Psilocybe cubensis* mushroom. (Photo by Gweedo, copyright 2003. Accessed at www.erowid.org.)

Clinical Features

In Western society, psychoactive agents are taken for internal mental exploration or, more commonly, for recreation. Effects include loss of boundaries between the user and environment, the sensation that colors and sounds are distorted and intensified, the sensation that perceptions are occurring via unusual pathways such as synesthesia, and the perception that usual objects appear novel, fascinating, or awe-inspiring. Users are usually aware that they are under the influence of the drug. A sense of euphoria is common, but it may alternate with an intense dysphoric experience that is accompanied by paranoia (e.g., illusions of dying or being born).

Acute panic reaction is a common adverse reaction to psychedelics. Paranoid delusions and fear of impending death can also occur. Behavior may be agitated or withdrawn. Sympathomimetic effects include mydriasis, tachycardia, hypertension, and in severe cases, hyperthermia. Mydriasis seems to parallel the intensity of the trip. The individual's altered perceptions may result in lack of awareness of dangers in the environment, resulting in injury. Psychosis after LSD trips has been reported, and schizophrenia (overt or borderline) may worsen. Transient depression sometimes occurs after LSD use. Flashbacks, or posthallucinogen perceptual disorder, are transient episodes of altered consciousness that occur months or years after LSD ingestion. Hyperactivity may also be seen, with marked auditory and visual hallucinations. Massive ingestions may result in coma and decreased responsiveness to painful stimuli. Fixed and dilated pupils, diaphoresis, vomiting, hyperthermia, rhabdomyolysis, coagulopathy, and seizures may result.

Euphoria and a distortion of reality usually occur after ingestion of one to five *Psilocybe cubensis* mushroom caps. In contrast to peyote (discussed later), vomiting is unusual. Larger doses (5–20 *P. cubensis* mushrooms) produce colorful visual hallucinations. Few adverse reactions occur, and the incidence of bad trips or panic reactions is lower than with LSD. Rarely, seizures, coma, and hyperthermia have been reported after psilocybin use.

Differential Diagnoses

Alcohol, other drugs and mixed ingestion are a possible source of the patient's symptoms, especially with coma or marked physiologic changes. Cocaine, PCP, amphetamines, and anticholinergic agents

should be considered. Acute psychosis and schizophrenic breaks may also appear similar to a psychedelic reaction. Finally, nontoxicologic diagnoses are crucial to rule out, including central nervous system infection, intracranial mass or bleed, and partial complex seizures.

Diagnostic Testing

Often, patients are in a panic or are brought in by a worried companion who may be aware of the use of hallucinogenic substances. A focus on history, especially from collateral information sources, and physical exam are important to make the diagnosis. Most patients require no laboratory testing, but a basic metabolic profile, serum ethanol, and serum glucose levels may be helpful in patients with unclear ingestions, co-ingestants, or underlying psychiatric disorders. Toxicology screening and specific testing for psychedelics is not available in a timely fashion in most clinical settings, and rarely changes management.

Management

Reassurance and supportive care are the cornerstones of management. If patients are a danger to themselves or others, they may need to be sedated with benzodiazepines (see below) or physically restrained temporarily to permit sedation. There is no specific antagonist to the effects of serotonergic agents. Empathetic reassurance in a calm, quiet environment with decreased external stimuli is an effective therapeutic modality. The drug effects typically last for hours, but most patients return to baseline after the acute effects.

Benzodiazepines are the mainstay of treatment for hallucinogenic drug-induced agitation. Diazepam, lorazepam, and midazolam have all been successfully used in this setting. Diazepam can be administered via the intravenous (IV) route in increments of 5 to 10 mg every 5 minutes in adults until sedation is achieved. Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Lorazepam, 1 to 2 mg IV every 5 minutes is also an acceptable option. Additional doses of lorazepam or diazepam should be titrated to effect, until the patient is calm and relaxed. There is no true maximum dose of these medications. For an adult patient in whom IV access is not possible because of agitation, intramuscular (IM) midazolam, 5 to 10 mg, can be administered to facilitate subsequent interventions. In all patients, titration of the benzodiazepine is important. The emergency clinician should observe the effects of one dose (usually 5 minutes) before an additional dose is given. After sedation is achieved, the patient should be closely observed to ensure that respiratory status is stable when the peak sedation effect is achieved.

The vast majority of patients with hallucinogen-induced agitation respond clinically to adequate doses of benzodiazepines. Butyrophenone antipsychotic agents, such as haloperidol and droperidol, are rapidly effective and generally safe for drug-induced psychosis or agitation states from other drugs, including cocaine, amphetamines, and phencyclidine (also discussed in Chapters 144 and 150). Haloperidol, given 2 to 5 mg IM, may be repeated every 20 to 30 minutes with consideration of other agents after a total of 10 mg. Although not approved for IV use, this route is widely used but may be considered in the psychotic or severely agitated patient with stable vital signs with cardiac monitoring in 5-mg doses to a maximum dose of 15 mg. The recommended sedative dose for droperidol is 2.5 to 5 mg IM. Of note, droperidol has a black box warning from the U.S. Food and Drug Administration (FDA) for QT prolongation and potentially torsade de pointes. However, most reported cases of butyrophenone-induced dysrhythmias have been in individuals receiving large doses for prolonged periods, such as hours to days, or in elderly populations (older than 60 years). These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when rapid sedation is required. For these reasons, the butyrophenones remain effective agents for treatment of more severe hallucinogenic-induced agitation in carefully selected patients.

Disposition

The majority of patients with anxiety or panic reactions can be verbally deescalated, with little clinical intervention. Acutely toxic patients who respond to sedation and do not have complications can be discharged after the acute toxicity stage resolves. We recommend discharging them accompanied by a non-intoxicated, responsible family member or friend. Patients who persist with confused or paranoid behavior should be observed until their mental status returns to baseline. Patients with altered mental status that does not normalize after 8 to 12 hours of observation in the ED, or who present after a massive ingestion with medical complications, require admission to a monitored setting for serial reassessments. Patients with self-destructive behavior or in need of addiction counselling may benefit from psychiatric intervention.

DISSOCIATIVE AGENTS

Principles of Toxicity

Dissociative hallucinogens describe a cohort of agents that result in symptoms that include dissociation from the environment that frequently have analgesic and amnestic properties. The agents in the category of dissociative hallucinogens have effects on multiple receptors that result in their unique properties, but the common thread among this group is their activity at the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor is found on neurons and normally functions as an ion channel that is activated by glutamate or glycine but modulated by various other substances that bind to the receptor. When open, it allows cations to flow into the nerve cell and propagate an impulse. The NMDA receptor in the brain is thought to play an important role in neuronal plasticity and memory. Phencyclidine (PCP) and ketamine are the two main agents included in the class of dissociative hallucinogens, although dextromethorphan and methoxetamine have emerged as drugs of abuse and have some similar symptoms of toxicity. All of these are similar in chemical structure and pharmacologic effects and at least part of their activity is on the NMDA receptor and more specifically as channel blocking agents. Despite being simple molecules, PCP, ketamine, dextromethorphan, and methoxetamine have complex pharmacology that includes activity on the NMDA receptor, dopamine-norepinephrine-serotonin reuptake pump, sigma opioid receptor, and cholinergic receptors. The combination of these pharmacologic effects, duration of the effects, and amount of agent used all contribute to the ultimate presentation and management of these patients.

Phencyclidine

PCP was initially marketed for use as a general anesthetic; however, severe emergence reactions rapidly led to its recall. In 1978, PCP was classified as a Schedule I drug. Despite well-described negative sensory effects and psychiatric effects, PCP became a common drug of abuse in the 1960s. PCP was sold as the PeaCePill, which was consumed orally and also as Angel Dust. In the mid-1970s, PCP was the most common cause of recreational drug–related emergencies, and in some regions it resulted in more hospitalizations than alcohol and schizophrenia combined.[1] Its popularity eventually decreased because of unpredictable effects, long clinical course, dysphoria, and association with violence; however, over the past decade, there has been a resurgence of PCP use.

PCP causes variable effects depending on dose. At low doses, users can experience sight and sound distortion as well as feelings of invulnerability. At high doses, users can experience hallucinations and catatonia. Violent behavior and profound psychiatric effects can be seen initially or as part of an emergence phenomenon. PCP is well absorbed

from any oral, nasal, or rectal mucous membrane and can be insufflated or smoked. It can be injected IM, subcutaneously, or IV. Ingested PCP is well absorbed, with an onset of action between 15 and 60 minutes. When smoked, PCP produces symptoms within 5 minutes, with peak activity in 15 minutes. Intoxication with PCP usually lasts 8 to 16 hours but can be prolonged in chronic users. Although enterohepatic recirculation has been proposed, a more likely cause of these prolonged effects in chronic users is gastrointestinal concretion or delayed release from lipid stores.

Ketamine

Ketamine was developed shortly after PCP in an effort to find a sedative with similar hemodynamic stability and properties as PCP that was shorter acting and without the severe emergence phenomenon commonly seen with PCP. It was first trialed in humans in 1964 and since then has become a relatively common medication with multiple indications, including as a sedative for procedural sedation, an induction agent for rapid sequence intubation (RSI), treatment of acute agitation, and treatment of depression. As a drug of abuse, ketamine is known as Vitamin K, Special K, kit kat, and cat valium; however, preparations available on the street are often adulterated with various stimulants. The most common route of use of street ketamine is by insufflation, but subcutaneous and IM injection and even rectal infusions are performed to achieve a level of intoxication or high, known as the K-hole. Similar to PCP, effects of ketamine are dose dependent and can range from mild disorientation and illusions to catatonia or complete dissociation. Ketamine is approximately an order of magnitude less potent than PCP. With ketamine, the intensity of intoxication is less pronounced, although in larger doses the effects may parallel those of PCP. Duration of action of ketamine is typically shorter, with symptoms lasting approximately 1 hour after insufflation but up to 4 to 8 hours after an oral dose. It is important to point out that chronic ketamine users, even at low doses, can experience persistent psychiatric symptoms similar to schizophrenia.[2] In addition, chronic users of ketamine both as a substance of abuse and under medical direction, have a high incidence of urologic complications such as urinary frequency and nocturia. PCP and ketamine are both highly lipid-soluble agents that undergo extensive metabolism in the liver and are eventually excreted in the urine.

Methoxetamine

Methoxetamine is a derivative of ketamine known as Special M, MXE, Mexxy, and ROFLcopter, and has been sold as a legal high and an alternative to ketamine, with reports of a lower risk of the urologic complications seen with chronic ketamine use which may make it preferable to a minority of users.[3] It is readily available on the internet as an agent often labeled as "research chemicals" and with the warning "not for human consumption." Symptoms of intoxication are similar to those seen with ketamine but may also have an increased risk of neuronal toxicity.[4] Methoxetamine appears to have a slower onset and longer duration of action than ketamine.

Dextromethorphan

Dextromethorphan is not truly a dissociative agent, but at higher doses than medically indicated dextromethorphan and its major metabolite, dextrorphan, act as an NMDA receptor antagonist that produces dissociative hallucinogenic effects similar to ketamine and PCP. With the availability of concentrated pill formulations, abusers of dextromethorphan can ingest large doses without having to drink large volumes of the less palatable cough syrup formulation. Particularly popular in the adolescent community, dextromethorphan is known as DXM, robo, skittles, triple C, and red hots. Although dextromethorphan is typically classified as an opioid, it also has a complex pharmacology. Structurally, DMX is similar to the opioids and is the methylated dextroisomer of the opioid analgesic levorphanol. Dextromethorphan not only antagonizes the NMDA receptor, resulting in its dissociative effects, but it also inhibits the uptake of serotonin, and drug interactions with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors have been reported. At high dosages, dextromethorphan is an agonist at the sigma opiate receptor, and naloxone has been reported to reverse intoxication.

Clinical Features

The desired effects of dissociative agents include changes in and pleasant intensification of sensory perceptions such as a euphoric "out of body experience." In this setting, patients seldom come to the attention of emergency care providers. However, more distressing symptoms are very common, especially with PCP, and frequently result in patients or friends seeking emergency treatment. Patients with PCP intoxication presenting to EDs can have a wide spectrum of findings, including sympathomimetic signs and symptoms. Behavior may be bizarre, lethargic, agitated, confused, or violent. A blank or catatonic stare is relatively common. Vital signs frequently demonstrate moderate tachycardia and hypertension, with some patients also having hyperthermia. Physical exam can demonstrate pupils that are midsized and reactive, although there may be miosis or mydriasis. Vertical and horizontal nystagmus are often present and considered a hallmark sign of PCP intoxication. Less commonly, rotary nystagmus may be noted with PCP toxicity but should prompt a consideration for another etiology such as head injury or intracranial lesion. Additionally, bizarre posturing, grimacing, and writhing may be seen.

In more severe intoxications, other findings include ataxia, muscle rigidity, increased deep tendon reflexes, increased secretions, bronchospasm, hyperthermia, and seizures. Up to 40% of PCP patients may be violent and combative, and control of these patients may be one of the most challenging encounters in the ED. Superhuman strength is possible because of the dissociative and analgesic action of PCP. Rarely, severe hypertension with PCP overdose has caused intracerebral hemorrhage.

Hyperthermia from PCP can range from mild to life-threatening and high-output congestive heart failure has been reported. Acute rhabdomyolysis and acute myoglobinuric renal failure are also seen due to muscle damage from seizures, extreme muscle activity such as struggling against restraints, or prolonged immobility. Respiratory depression, apnea, and cardiac arrest have also been described.

Although dextromethorphan has activity at opioid receptors, the typical triad of opioid intoxication—miosis, respiratory depression, and mental status depression—is not generally encountered. Similar to meperidine, dextromethorphan may result in mydriasis through paralysis of the ciliary body with intoxication. Typical clinical findings include lethargy, agitation, slurred speech, ataxia, diaphoresis, hypertension, nystagmus, nausea, vomiting, and hallucinations.

Differential Diagnoses

PCP, ketamine, methoxetamine, and dextromethorphan intoxication can mimic other drugs of abuse and intoxicants or can mimic organic causes of the behavior. Sympathetically mediated vital sign changes can be found with numerous other agents, including cocaine, amphetamine, and LSD. Antimuscarinic compounds, such as diphenhydramine, benztropine, and tricyclic antidepressants, can also produce the tachycardia and altered mental status found with PCP or ketamine.

There are many organic causes of symptoms such as altered mental status, tachycardia, and agitation commonly found with dissociative hallucinogens. Trauma and specifically head injuries and intracranial hemorrhage should be considered. Medical etiologies include

meningitis (viral or bacterial), heatstroke, salicylate poisoning, thyrotoxicosis, and sepsis. Underlying psychiatric disease, especially if it exists in combination with substance abuse, can be very difficult to distinguish. The provider should be cautious about ascribing symptoms to substance use or abuse without considering other etiologies.

Diagnostic Testing

Many hospital laboratories use radioimmunoassays that can detect urinary PCP with a detection limit of 5 ng/mL. Urine may be positive for PCP for 2 to 4 days after use and can be positive for more than 1 week. Serum screening for PCP is of little clinical benefit because levels correlate poorly with symptoms. Several substances, including dextromethorphan, may cross-react with urine screens for PCP because of their structural similarities. Chlorpromazine, methadone, mesoridazine, ketamine, diphenhydramine, venlafaxine, meperidine, and tramadol may also cross-react with some assays, causing false-positive results. If the ingestion is known or suspected to be dextromethorphan because of the prevalence of combination medications, a serum acetaminophen level should be obtained.

If patients have not been hyperthermic and have no signs of trauma, laboratory or other diagnostic tests are generally not needed. With acutely symptomatic patients, a complete metabolic profile, renal function, and creatine phosphokinase (CPK), serum glucose, and ethanol levels should be measured. Workup for any other disease processes should also be pursued as directed by presentation. For patients with acute mental status changes that persist beyond the expected natural course, computed tomography of the head is indicated.

Of particular note, because dextromethorphan is typically formulated as a hydrobromide salt, chronic use may result in spurious hyperchloremia with a low or negative anion gap due to interference of chloride analysis by the bromide ion in the laboratory autoanalyzer.

Management

Prehospital treatment should follow usual protocols for management of agitated patients. The threat of violence to prehospital care providers from patients with PCP intoxication is important to recognize and prehospital systems should have both chemical and physical restraint protocols in place that maximize the safety of providers, patients, and bystanders. Sometimes, awaiting more help or awaiting providers who can use chemical sedation is better than engaging with these patients without adequate support. Extreme agitation, although possible, is less common with ketamine and methoxetamine. Especially when these patients have been sedated prior to hospital arrival, prehospital providers can often provide critical information regarding the patient and notify ED providers of potential trauma or other issues associated with patient care and presentation at the scene.

Sedation of patients under the influence of dissociative hallucinogens is often the first challenge. Chemical sedation is preferred to physical restraint with PCP or ketamine intoxication to reduce the incidence of rhabdomyolysis. Temporary physical restraint may be necessary to ensure patient and medical staff safety until chemical restraint has been achieved. A well-coordinated team with security personnel involvement should apply restraints simultaneously to all four extremities and the body. Assessment of mental status may not be as reliable after chemical sedation, but the benefits of protecting the patient, staff, and other patients in adjacent rooms far outweigh the disadvantages.

As discussed earlier with hallucinogenic agents, butyrophenones such as haloperidol and droperidol can be given IM with a rapid response, avoiding the danger of IV establishment. Haloperidol, 5 to 10 mg IM or IV, is usually effective but can be titrated at 10- to 15-minute intervals until the patient is calm. The sedative dose for droperidol is 2.5 to 5 mg IM. These agents may antagonize the CNS receptor sites that are responsible for much of the violent behavior in these individuals. These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when sedation is required. Droperidol and haloperidol are sometimes withheld because of the FDA black block warning about QT prolongation. It is important to note that most cases of this have been seen in patients receiving higher doses than those recommended here, given repeatedly over a longer period of time, and in patients greater than 60 years old. For these reasons, butyrophenones are still considered safe and effective agents in controlling agitated patients. Benzodiazepines such as lorazepam, 2 to 4 mg IV or IM, or diazepam, 5 to 10 mg IV, or midazolam 5 to 10 mg IM may also be used to treat agitation (see Chapters 144, 150, and 185).

Any effects of dissociative hallucinogens should be managed with symptomatic and supportive care. Hyperthermia and seizure are two of the more common severe complications. Hyperthermia is common in severe cases of PCP poisoning. All patients with significant symptoms, psychosis, or history of violent behavior should have their core temperature measured. Individuals with hyperthermia should be treated with rapid sedation to decrease neuromuscular hyperactivity and heat production. Rapid sequence intubation may be required to allow for adequate sedation and active, evaporative cooling measures (see Chapter 129). Renal status and creatine kinase level should also be monitored to detect rhabdomyolysis and myoglobinuric renal failure.

Dextromethorphan poisoning may cause agitation, or it can present with somnolence due to the opiate effects of the agent. Respiratory depression may respond to IV administration of naloxone; however, the dissociative effects of the drug do not typically respond to naloxone. Similar to mild cases of other dissociative hallucinogens, patients generally improve within 4 to 6 hours post ingestion.

Disposition

For nonviolent patients with dissociative agent intoxication, a quiet holding room is ideal for 4 to 6 hours of observation. Patients with violent behavior or obtundation sometimes require admission to the hospital, especially if they have developed significant renal insufficiency, rhabdomyolysis, require respiratory monitoring, or if their temperature does not normalize. Many of these patients, even when presenting with significant symptoms, can be medically cleared within 12 to 24 hours.

CANNABIS AND SYNTHETIC CANNABINOIDS

Principles of Toxicity

Cannabis (marijuana) is the most common federally illegal drug in the United States. It was used medicinally in ancient times for conditions such as colic and asthma and has been federally illegal since 1937. However, as of 2020, fifteen states (Alaska, Arizona, California, Colorado, Illinois, Maine, Massachusetts, Michigan, Montana, Nevada, New Jersey, Oregon, South Dakota, and Washington) and the District of Columbia have passed legislation to legalize recreational cannabis, and 29 additional states have legalized medical cannabis.

Cannabis sativa and *Cannabis indica* plants are some of the earliest plants grown by humans. Bioactive substances derived from these plants are collectively called cannabinoids. The seedless flowering tops of the female plant are referred to as sinsemilla and are the commonly grown form of cannabis in the United States. The resin from the flowers is made into hashish. Cannabis is smoked, vaporized, or eaten blended into foods. Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive agent of the more than 61 cannabinoid compounds and approximately 300 other substances present in the cannabis plant, and cannabidiol (CBD) is the major nonpsychoactive component. THC has been associated with some of the adverse effects of cannabis use, including

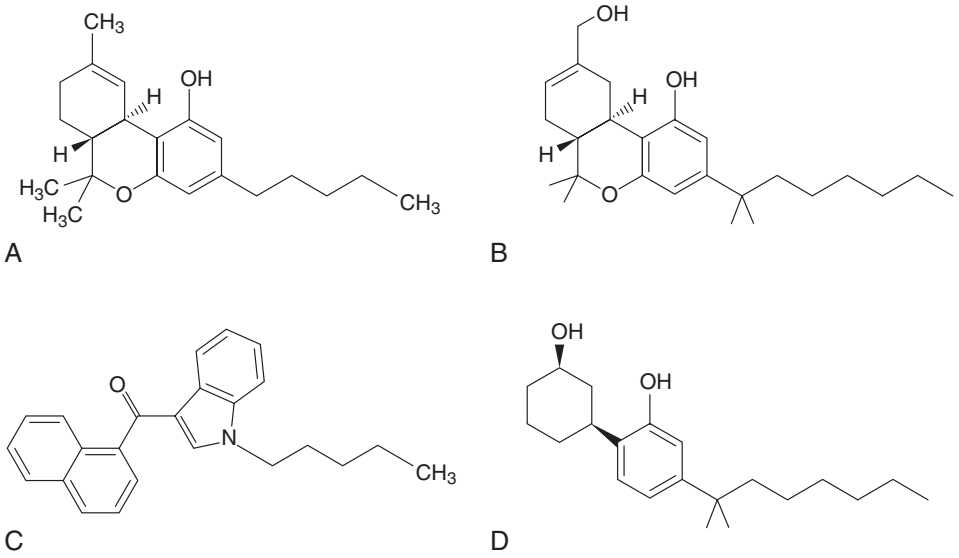

Fig. 145.3 Cannabinoid structures. (A) Δ^9-Tetrahydrocannabinol. (B) HU-210. (C) JWH-018. (D) CP-47,497.

increased agitation, anxiety, and potential for psychosis. Neuroimaging studies have shown that co-ingestion with CBD may modulate and decrease some of these effects, leading to concerns that newer, high-potency, THC-predominant strains of cannabis may lead to a higher-risk chemical profile of these plants.[5]

Synthetic cannabinoids have also become readily available. These products are often marketed as novelty herbal incense and labeled "not for human consumption." They typically come in resealable foil packages and contain various plant leaves sprayed with a solvent mixture of one or several synthetic cannabinoid compounds. Products have names such as Spice, K2 Summit, Banana Cream Nuke, Yucatan Fire, Genie, Black Mamba, Crazy Clown, and many others depending on the region of the country. The Drug Enforcement Administration (DEA) issued an order in 2011 to list five synthetic cannabinoids—JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol—into Schedule I of the Controlled Substances Act (CSA) to avoid an imminent hazard to public safety. Previously, only one synthetic cannabinoid (HU-210), a structural analogue of THC, was listed as such. In 2014, another four compounds—PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA—were also listed as Schedule I after outbreaks of severe illness in several states. Because numerous synthetic cannabinoids are available, producers of spice products can simply replace a scheduled cannabinoid with others that are not on the Schedule I list, which minimizes the impact of scheduling by the DEA on long-term availability because the demand for the cannabinoid products remains high.

Cannabinoids act primarily at cannabinoid receptors CB1R, found mostly in the CNS, and CB2R, found primarily on peripheral immune cells. Discovery of these cannabinoid receptors and experiences in states with medical cannabis availability have led to interest in further exploration of the therapeutic potential of cannabinoids (Fig. 145.3).

Clinical Features

Smoking cannabis, either in the dried plant form or by smoking or vaporizing resins, extracts, or oils, leads to rapid and predictable signs and symptoms. Ingestion can cause delayed and sometimes unpredictable effects. The most common effects from smoking of cannabis include alteration of mood and usually relaxation and euphoria. The only reliable physiologic effects are a mild increase in heart rate and conjunctival injection. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure. Short-term memory is impaired, and the ability to perform complex tasks may be adversely affected. Many users report excessive appetite after cannabis use. Peak blood levels occur within 8 minutes of inhalation, with rapid distribution into tissues, especially tissues with a high lipid content. The duration of perceived effects is usually 2 to 4 hours when the drug is smoked.

Oral ingestion of cannabis edibles may be associated with longer duration of effect (≥6–12 hours), and patients with a massive oral cannabis ingestion may develop profound ataxia, vomiting, agitation, anxiety, and CNS depression requiring medical care. Edible products often carry high concentrations of THC in relatively small portion sizes and, due to a delayed onset of effect up to 4 hours after ingestion, patients may ingest escalating amounts of product while awaiting the onset of psychoactive effects.[6]

Pediatric exposures to cannabis may lead to hypothermia, ataxia, nystagmus, tremor, tachycardia, injected conjunctiva, and labile affect. Oral ingestion of potent cannabis in children can produce rapid onset of drowsiness, hypotonia, lethargy, and less commonly seizures. Large ingestions can lead to coma and airway obstruction and respiratory compromise requiring intubation and ventilatory assistance.[7] Pediatric exposures have been rising with the legalization of cannabis in several states.[8]

Whereas intoxications with cannabis and synthetic cannabinoids may have some similarities, significant differences have been described. First-generation synthetic cannabinoids such as JWH-018, JWH-073, HU-210, and CP-47 were commonly associated with tachycardia, agitation, nausea and vomiting, altered mentation, and hallucinations. Seizures were also noted with this group of cannabinoids. Second-generation synthetic cannabinoids such as ADB-PINACA and AB-FUBINACA have been associated with more profound agitation and aggression followed by CNS depression, seizures, tachycardia followed by bradycardia, hypertension followed by hypotension, and, less commonly, ischemic stroke and cardiac toxicity.

Additionally, synthetic cannabinoid use has been associated with an outbreak of anticoagulant toxicity.[9,10] In these cases, patients were exposed to brodifacoum and similar long-acting vitamin K antagonist anticoagulants that contaminated synthetic cannabinoids and presented with bleeding from multiple sites and bruising. Over 160 cases presented to hospitals in Illinois alone, with 4 reported deaths. Many

other patients required long-term management with vitamin K supplementation and close follow-up.[9]

Differential Diagnoses

The presentation that most closely resembles that of cannabis and synthetic cannabinoid intoxication is acute psychosis. Some individuals with underlying and preexisting psychiatric disorders may progress to overt psychosis after heavy or first-time cannabis use. Because cannabis is so readily available, it is commonly a co-intoxicant used with ethanol and other psychotropic agents. Pediatric patients with unknown unintentional exposures may appear similar to patients with opioid or sedative hypnotic agent overdose, sepsis, meningitis, or metabolic disorders. Rarely, cannabis can be adulterated with other substances, such as PCP and other illicit drugs used concomitantly.

Diagnostic Testing

Cannabis screening is rarely helpful in the ED. Urinary metabolites of THC are detectable within 1 hour after smoking cannabis, but a positive result on a routine urine toxicology screen does not correlate with acute intoxication. Smoking a single "joint" can be detected for 72 hours when a cutoff level of 100 ng/mL is used, and positive urine levels may persist for 3 months after chronic cannabis use. Inadvertent or passive exposure to large amounts of second-hand cannabis smoke in enclosed areas may produce positive urine test results, depending on the laboratory cutoff levels used. False-positive urine screen results may be produced by efavirenz, ibuprofen, and naproxen. An exception to the utility of a urine drug screen for cannabis exposure in pediatric patients may be an unclear cause of altered mental status.

Of the synthetic cannabinoids, only HU-210 should trigger a positive THC immunoassay screen as a result of structural homology. The majority of other synthetic cannabinoids are structurally distinct from THC and do not result in positive THC immunoassay screens.

Management and Disposition

Care of patients intoxicated from cannabis and synthetic cannabinoids consists of prevention of injury and reassurance for those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines or antipsychotics. Antiemetics (e.g., ondansetron 4–8 mg IV, or metoclopramide, 10–20 mg IV) or butyrphenones (e.g., haloperidol or droperidol 0.625–2.5 mg IV) may be used to treat nausea and vomiting induced by the cannabinoid hyperemesis syndrome associated with the synthetic cannabinoids and heavy, daily cannabis use. Hot showers are often recommended for patients suffering these symptoms. The precise mechanism whereby hot bathing produces a rapid reduction in the symptoms of CHS is not clear, but thought to be related to a peripheral tissue receptor called TRPV1, a G-protein coupled receptor that has been shown to interact with the endocannabinoid system.[11] Capsaicin cream may also have some benefit in these cases through a similar mechanism and activation of TRPV1 receptors, although discomfort with its use may limit its utility. Children who are significantly symptomatic may require admission for a 24-hour observation period.

Other Agents

Mescaline

Mescaline is a naturally occurring phenylethylamine usually consumed in the form of peyote buttons, which are derived from the small, blue-green cacti *Lophophora williamsii* and *Lophophora diffusa* (Fig. 145.4). They grow in the deserts of the southwestern United States and Mexico.

Peyote has been used in religious ceremonies for 8000 years. Mescaline is also contained in the San Pedro cactus (*Trichocereus pachanoi*) of South America and is used ritualistically by Andean Native Americans.

Fig. 145.4 *Lophophora williamsii* (peyote cactus). (Photo by Christopher B., copyright 2000. Accessed at www.erowid.org.)

These cacti contain many other alkaloids, some of which are also psychoactive. The use of peyote is legal for members of the Native American Church in some states. Adverse reactions (e.g., panic attacks) to peyote are rare in structured religious use. Mescaline has an onset of action of 45 to 60 minutes, with a duration of effect lasting 4 to 8 hours. The CNS and physiologic effects of mescaline use are similar to those of LSD, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects, which is an important aspect of the cleansing spiritual ritual.

Nutmeg

Nutmeg is a spice derived from the seed of the nutmeg tree, *Myristica fragrans*. Use of nutmeg as a natural and legal psychotropic agent was popularized in the 1960s. Despite lack of any in vivo human studies, myristicin and elemicin have been suggested as the agents responsible for intoxication because their chemical structure resembles that of mescaline. Reports of intoxication are uncommon. Ingestion of 5 to 30 g (1–4 tablespoons) of the spice is said to induce euphoria and hallucinations but is more likely to cause gastroenteritis.[12]

Salvia

Salvia divinorum, a perennial herb cultivated outdoors in mild climates, is a member of the mint (Lamiaceae) family. Common names for *S. divinorum* are diviner's sage, mystic sage, magic mint, sage of the seers, Sally-D, ska, and Maria Pastora. Although the plant has been used for divination and shamanism by the Mazatec Indians of Oaxaca, Mexico, *S. divinorum* has become popular in the past 20 years for recreational purposes because of its recognized hallucinogenic properties and hallmark "uncontrollable laughter" side effect. In 2004, the DEA listed *S. divinorum* as a drug of concern but, to date, *S. divinorum* and salvinorin A are not currently controlled under the CSA in the United States. Several states, however, have instituted or are considering legislation making possession, cultivation, and use of *S. divinorum* or its extracts illegal.

The active ingredient in *S. divinorum* is salvinorin A, a neoclerodane diterpene with selective agonist activity for kappa opioid receptors. Salvinorin A appears to have no activity at delta or mu opioid receptors. The threshold dose of salvinorin A to produce hallucinations is comparable to that of LSD. However, salvinorin A is distinct from more traditional hallucinogens because it does not bind to the 5-HT_{2A} serotonin receptors, as is the case with LSD.

Salvia is usually chewed and spit out or swallowed, and it seems to be absorbed more readily from the oral mucosa than from the rest of

the gastrointestinal tract. Effects produced as a result of oral mucosal absorption may persist for 1 hour. Dried leaves can also be smoked. Inhalation of smoke can produce symptoms within 1 minute that subside after 20 to 30 minutes. Sensations experienced are variable but include distortions of color and vision, laughter, and synesthesias, which are confusions of the senses, such as "seeing sounds or smelling colors." Salvinorin A is not detected by typical drug screening tests and is not known to cause interference with routine drug screens used in the clinical setting. Management of intoxication from *S. divinorum* is mainly supportive, with emphasis on injury prevention.[13] Use of naloxone, a nonspecific opioid receptor antagonist, may theoretically be helpful for the reversal of psychotropic manifestations.

Kratom

Mitragyna speciosa, or kratom, is a tree found in tropical and subtropical regions of Asia and Africa. The popularity of kratom has grown because of reports of its successful use to attenuate symptoms of opioid withdrawal. Because kratom remains easily obtainable, individuals are able to self-administer the perceived remedy, obviating the need for physician supervision. The safety of such a practice is unknown.

Although kratom extract contains more than 25 alkaloids, mitragynine is the most abundantly found in the plant. Mitragynine is an indole alkaloid with structural analogy similar to that of yohimbine and has agonist activity at mu and delta opioid receptors, producing euphoric, analgesic, and respiratory depressant effects. The respiratory depressant effects are more likely to occur when combined with opioids or other respiratory depressants. Despite its structural similarity to yohimbine, a selective antagonist of presynaptic α_2-adrenergic receptors, animal studies have suggested that mitragynine is also an agonist at postsynaptic α_2-adrenergic receptors and blocks 5-HT_{2A} receptors.

Often, kratom is ingested in powder or capsule form. The leaves may also be chewed, smoked, or brewed into a tea. Psychotomimetic effects occur within 5 to 10 minutes of use and may persist for 1 hour, with stimulatory effects at lower doses and opioid effects at higher doses. Opioid properties include analgesic, antitussive, antidiarrheal, and emetogenic effects.[14]

Currently, there are no clinical diagnostic tests available to detect the presence of kratom alkaloids. Treatment of intoxication is supportive. Although coma and opioid activity have been demonstrated with kratom, the effectiveness of opioid antagonists in reversing its effects is inconsistent. A withdrawal syndrome characterized by anxiety, restlessness, and nausea treated with an opioid agonist and lofexidine (an α_2-agonist related to clonidine) has also been reported.

The issues regarding the safety and efficacy of kratom and its mitragynine constituent require additional research. The DEA classification of the Mitragyna alkaloids as Schedule I controlled substances is likely to impede further studies on kratom.[15]

Ibogaine

Ibogaine is a naturally occurring indole alkaloid found in the roots of the African rain forest shrub *Tabernanthe iboga*. For many centuries, iboga has been ingested by the indigenous peoples of western Africa as a remedy for fatigue, hunger, and thirst and as a sacrament in religious ceremonies. As with many plant-derived agents, ibogaine's physiologic effects are highly complex and may involve opioid, dopaminergic, serotonergic, glutaminergic, γ-aminobutyric acid (GABA)–ergic, glutamatergic, adrenergic, and cellular ion channel signaling systems.

Although ibogaine is classified as a Schedule I drug, it is still sought after as a treatment to ease opioid withdrawal and diminish craving of other abused drugs. The intensity of visual hallucinations from ingestion of iboga, in contrast to other hallucinogens, is described to be more pronounced with eyes closed. Since the first report in 1990, there have been reported fatalities due to sudden cardiac death within 72 hours of ibogaine use. The mechanism appears to be blockage of the hERG/IKr channel, leading to marked QT prolongation and tachyarrhythmias. There are no specific detection tests for ibogaine, and diagnosis is dependent on a history of exposure because clinical findings are largely nonspecific. Management is predominantly supportive, although patients with markedly prolonged QT intervals and evidence of risk for torsades de pointes may require admission to a monitored setting, treatment with IV magnesium supplementation (magnesium sulfate, 2–4 g IV), electrolyte repletion, and overdrive pacing (either chemical with isoproterenol, or electric via transdermal or transvenous pacing) in severe cases.

Fig. 145.5 *Amanita muscaria* mushroom. (Photo by Mark Shubert, copyright 2004. Accessed at www.erowid.org.)

Isoxazole Mushrooms

Isoxazole-containing mushrooms include *Amanita muscaria*, *Amanita pantherina*, *Amanita gemmata*, and *Amanita cothurnata*. *A. muscaria* has a red or yellow cap, with white warty structures on its surface, and grows in forests of aspen, birch, fir, or pine trees (Fig. 145.5). It has been used in Siberia for centuries and is often described in folklore and fairy tales (also see Chapter 153).

The active ingredients are the isoxazole derivatives ibotenic acid and its decarboxylation product, muscimol, which are structural analogues of the endogenous neurotransmitters glutamic acid (excitatory) and GABA (inhibitory) and are thought to act at these respective receptor sites. The excitatory effects characterized by elation, giddiness, hyperactivity, muscle tremors, and distortion of space and time begin approximately 30 minutes to 2 hours after ingestion and are likely to be mediated by ibotenic acid. Following is a phase of tiredness and deep sleep, in which it may be difficult to arouse the patient. During this phase, vivid hallucinations and manic excitement may oscillate with periods of deep sleep. The duration of effect is up to 12 hours. Management of the excitatory phase is similar to that of other hallucinogens previously described in this

chapter, consisting of supportive care, a low stimulus environment, and benzodiazepine administration. Prolonged sleep with *A. muscaria* ingestion requires only observation and supportive care. Tonic-clonic seizures are reported, but occurrences are rare. In general, adult patients more often experience GABA-dominant symptoms, and pediatric patients more often experience glutamic acid-dominant symptoms.

Paradoxically, there has been a high incidence of mistreatment of *A. muscaria* ingestion with atropine because the name implies that it contains muscarine, a cholinergic toxin. However, the amount of muscarine is miniscule. Atropine may exacerbate the anticholinergic effects associated with isoxazole mushrooms. It is important to differentiate isoxazole-containing *Amanita* mushrooms from the potentially deadly hepatotoxic cyclopeptide-containing *Amanita* mushrooms, of which *Amanita phalloides* is a member.

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CHAPTER 145: QUESTIONS AND ANSWERS

1. Intoxication with morning glory seeds will mimic intoxication with which of the following hallucinogens?
   a. Ecstasy
   b. Ketamine
   c. LSD
   d. Cannabis
   e. PCP

Answer: C. Several plants contain alkaloids similar to LSD, including morning glory and Hawaiian baby wood rose.

2. A 14-year-old boy presents with altered mental status. On examination he has mydriasis, nystagmus, and lethargy. There is a history of exposure to "skittles." His urine drug screen for drugs of abuse is presumptively positive for PCP. Which toxicant did he ingest?
   a. Dextromethorphan
   b. Ecstasy
   c. LSD
   d. Psilocybin
   e. Synthetic cannabinoids

Answer: A. Dextromethorphan presents with more of a dissociative clinical pattern than opioids. "Skittles, red hots, and triple Cs" are street names for over-the-counter tablets of dextromethorphan. Most immunoassays for PCP cross-react with dextromethorphan to give a false-positive PCP report. Ketamine can also give a similar clinical picture, so the history is also necessary to determine which is the most likely intoxicant in the differential.

3. Which of the following is likely to be detected on a typical urine immunoassay drug screen?
   a. LSD
   b. Kratom
   c. Salvia
   d. Cocaine
   e. Synthetic cannabinoids

Answer: D. The immunoassay screen for cocaine detects its metabolite, benzoylecgonine. Unlike immunoassays for amphetamines, benzodiazepines, phencyclidine, and THC, which may be highly unreliable, inconsistent, or nonspecific, the immunoassay for benzoylecgonine does not typically result in false-positives or false-negatives. Detection of benzoylecgonine is a specific indication of cocaine use in the past 3 days. LSD, kratom, salvia, and synthetic cannabinoids do not typically cross-react with immunoassays that are commonly used.

4. Which of the following mushroom species has hepatotoxic but not hallucinogenic properties?
   a. *Amanita muscaria*
   b. *Amanita pantherina*
   c. *Amanita phalloides*
   d. *Conocybe smithii*
   e. *Psilocybe cubensis*

Answer: C. *A. phalloides* mushrooms do not have hallucinogenic properties. Their toxicity is mainly hepatic due to a number of cyclopeptide toxins contained in all parts of the mushroom. *C. smithii* and *P. cubensis* contain psilocybin and psilocin tryptamines. *A. muscaria* and *A. pantherina* contain the isoxazole compounds ibotenic acid and muscimol, which are analogues of glutamic acid (excitatory) and γ-aminobutyric acid (GABA; inhibitory) neurotransmitters, respectively.

5. Which of the following agents have been used to treat acute withdrawal syndromes and chronic drug dependence?
   a. Kratom
   b. Ibogaine
   c. Buprenorphine
   d. Clonidine
   e. All of the above

Answer: E. Kratom, ibogaine, buprenorphine, and clonidine have all been used to treat acute opioid withdrawal and chronic drug dependency with varying effects and long-term outcomes.

146

Iron and Heavy Metals

Jillian L. Theobald and Mark B. Mycyk

KEY CONCEPTS

- Asymptomatic patients seeking emergency department (ED) care for an abnormal metal test need follow-up evaluation arranged with a medical toxicologist.
- Metal testing in the ED should be ordered in consultation with a medical toxicologist or regional poison center.
- Acute ingestion of the salts of most metals causes rapid severe gastrointestinal pain and emesis.
- Abnormal neurologic signs in a patient with any metal exposure warrants admission for further evaluation and chelation therapy.
- Acute iron poisoning can result in gastrointestinal symptoms, metabolic acidosis, and hepatoxicity. Serum iron levels at 3 and 6 hours after ingestion determine toxicity and need for therapy.
- The chelation agent of choice for severe iron poisoning is deferoxamine, which is indicated for peak serum iron concentrations greater than 500 μg/dL and in patients with severe signs and symptoms regardless of the iron level.
- The most important intervention for lead poisoning is removal from the source of exposure.
- The gastrointestinal decontamination method of choice for iron and lead toxicity with radiographic presence of pills or paint chips is whole bowel irrigation (WBI).
- The chelation agent of choice for acute arsenic poisoning is intramuscular British antilewisite (BAL) or oral succimer.
- Elemental mercury is nontoxic to the gastrointestinal tract but may cause pulmonary and central nervous system (CNS) toxicity from inhalation of volatilized vapors.

IRON

Foundations

Iron poisoning used to be the leading cause of poisoning death in children. In 1997 the U.S. Food and Drug Administration (FDA) required warning labels and implemented changes in the packaging of iron supplements after which there was an abrupt decrease in the number of poisonings and deaths. Although the FDA rescinded its strict packaging restrictions on iron supplements in 2003, iron poisoning currently remains relatively uncommon. In 2017, there were 6033 calls to poison centers concerning iron exposures and there were two deaths. Calls regarding multivitamins containing iron were much more common, resulting in 11,157 calls but no deaths.[1]

Iron is an important metal that is essential to the function of hemoglobin, myoglobin, and many cytochromes and enzymes. Certain disease states result from too much or too little iron, such as hemochromatosis and anemia, respectively. Iron is absorbed mostly in the small intestine. Depending on total body stores, as little as 10% or as much as 95% of the ingested iron is taken into cells. In the cell, iron has three pathway options: storage bound to ferritin, transfer to the serum where it is bound to transferrin, or loss when the intestinal cell is sloughed off. Under normal conditions only 15% to 35% of the iron-binding capacity of transferrin is used. The total iron-binding capacity (TIBC), a crude measure of the ability of serum proteins (including transferrin) to bind iron, ranges from 300 to 400 μg/dL. Normal serum iron concentrations range from 50 to 150 μg/dL. When iron concentrations rise after a significant overdose, transferrin becomes saturated. Excess iron circulates free and unbound in the serum. Unbound iron is directly toxic to target organs.

Iron has two distinct toxic effects: (1) direct caustic injury to the gastrointestinal mucosa, and (2) impaired cellular metabolism, primarily of the heart, liver, and central nervous system (CNS). The caustic effects of iron on the gut cause the initial symptoms of vomiting, diarrhea, and abdominal pain. Hemorrhagic necrosis of gastric or intestinal mucosa can lead to bleeding, perforation, and peritonitis. Metabolic acidosis occurs when unbound iron moves into cells and localizes near the mitochondrial cristae, resulting in uncoupling of oxidative phosphorylation and impairment of adenosine triphosphate synthesis. Hydration of the iron molecule creates an excess of unbuffered protons, worsening metabolic acidosis. Cell membranes are injured by free radical–mediated lipid peroxidation. Hypotension occurs as iron increases capillary permeability and leads to both arteriolar and venodilation. Direct myocardial toxicity decreases cardiac output. These effects, combined with severe gastrointestinal fluid losses, can lead to shock, cardiovascular collapse, and death.

In an iron overdose, determining the amount of elemental iron ingested is most important, because cellular toxicity depends on the effects of elemental iron. Different formulations of iron salts contain different percentages of elemental iron (Table 146.1). The total amount of elemental iron ingested can be approximated by multiplying the estimated number of tablets by the fraction of elemental iron contained in the tablet. Ingestions of less than 20 mg/kg of elemental iron usually causes no symptoms. Ingestion of 20 to 60 mg/kg results in mild to moderate symptoms, and ingestion of more than 60 mg/kg may lead to severe morbidity and mortality. Newer forms of iron are carbonyl iron and iron polysaccharide: both are non-ionic and associated with lower toxicity. Neither form is directly corrosive. The conversion to the iron ion, which is responsible for toxicity, is very slow in these newer preparations. There are no reported cases of serious toxicity or death from the ingestion of the non-ionic compounds.

Clinical Features

The clinical effects of acute iron poisoning have traditionally been divided into five stages (Table 146.2). The timing of each stage varies

for individual patients. The severity of phase 4 is primarily dose-related, and it is usually during this phase that fatality occurs.

Differential Diagnoses

Many toxins are irritating to the gastrointestinal tract and can cause nausea, vomiting, and diarrhea. Hemorrhagic gastroenteritis in the setting of an ingestion history should raise suspicion for caustic ingestions, ethanol, toxic alcohols, salicylates, ibuprofen, colchicine, and other heavy metals, such as arsenic, inorganic mercury, and iron.

Diagnostic Testing

The presence of early gastrointestinal symptoms suggests a potentially serious ingestion, whereas absence of gastrointestinal symptoms is usually reassuring. A serum iron concentration measured at 3 to 5 hours after ingestion is the most useful laboratory test to evaluate the potential severity of an iron overdose. Sustained-release or enteric-coated preparations may have erratic absorption, so the serum concentration should be repeated at 6 to 8 hours after ingestion. Peak serum iron below 350 µg/dL is generally associated with minimal toxicity; 350 to 500 µg/dL with moderate toxicity; and above 500 µg/dL with severe toxicity. Because iron is rapidly cleared from the serum and deposited in the liver, the concentration of iron after a substantial ingestion may be deceptively low if it is measured several hours after its peak absorption. TIBC is an inaccurate test and is not useful to gauge the severity of iron poisoning.

A screening abdominal radiograph may also be helpful to confirm a recent large ingestion and should be interpreted in the context of serum levels, as described later. Most tablets that contain a significant amount of elemental iron are radiopaque (Fig. 146.1). False-negative radiographs may occur with chewable, liquid, and completely dissolved iron compounds, so negative radiography should not be used to exclude iron ingestion in cases of suspected or witnessed ingestion. Repeated radiographs can also demonstrate the efficacy of gastrointestinal decontamination efforts.

TABLE 146.1 Common Iron Preparations

Compound	Percentage of Elemental Iron
Ionic Compounds	
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
Non-Ionic Compounds	
Carbonyl iron	100
Iron polysaccharide	46

Management

Stabilization and Supportive Care

Early hypotension is often due to GI losses and should be treated with intravenous fluids. Later, direct toxic effects on the cardiovascular system occur and are best treated with vasopressors. Patients with mental status depression and concern for airway protection should be intubated and mechanically ventilated.

Decontamination

Oral activated charcoal does not bind iron. Gastric lavage and ipecac are ineffective and not recommended. Iron tablets clump together as their outer coatings dissolve, often forming large pharmacobezoars. Whole bowel irrigation (WBI) is the preferred method of decontamination for significant iron tablet ingestions, especially when confirmed by radiograph, but WBI is not useful in cases of liquid or chewable iron.[2] Early, rapid decontamination of the gastrointestinal system may obviate the need for or shorten antidotal therapy duration.

For significant ingestions, especially when the number of tablets identified by abdominal radiography indicates a likely toxic dose, WBI with a polyethylene glycol–electrolyte solution (PEG-ELS) should be initiated.[2] The solution should be administered through a nasogastric tube. The recommended rate of administration of PEG-ELS is 500 mL/hr in children 9 months to 6 years old, 1000 mL/hr in children 6 to 12

TABLE 146.2 Clinical Manifestations of Iron Toxicity Following an Acute Overdose[a]

	Phase	Clinical Features	Mechanism of Toxicity
1	Gastrointestinal (6 hours)	Vomiting Diarrhea Hematemesis Hematochezia	Corrosive effect of iron on the gastrointestinal mucosa
2	Latent (6 to 24 hours)	Resolution of gastrointestinal symptoms Tachycardia Acidosis Depressed mental status	Ongoing cellular toxicity and organ damage
3	Systemic (12 to 24 hours)	Return of gastrointestinal symptoms Acidosis Leukocytosis Coagulopathy Renal failure Lethargy or coma Cardiovascular collapse	Iron distributes to the tissues with worsening cellular toxicity and organ damage
4	Hepatic (2 to 5 days)	Fulminant liver failure Coagulopathy	Rapid absorption from portal system with resultant oxidative damage
5	Obstructive (3 to 6 weeks)	Pyloric or bowel scarring Obstruction	Healing of the injured gastrointestinal mucosa

[a]Typical duration of symptoms post-ingestion is also given.

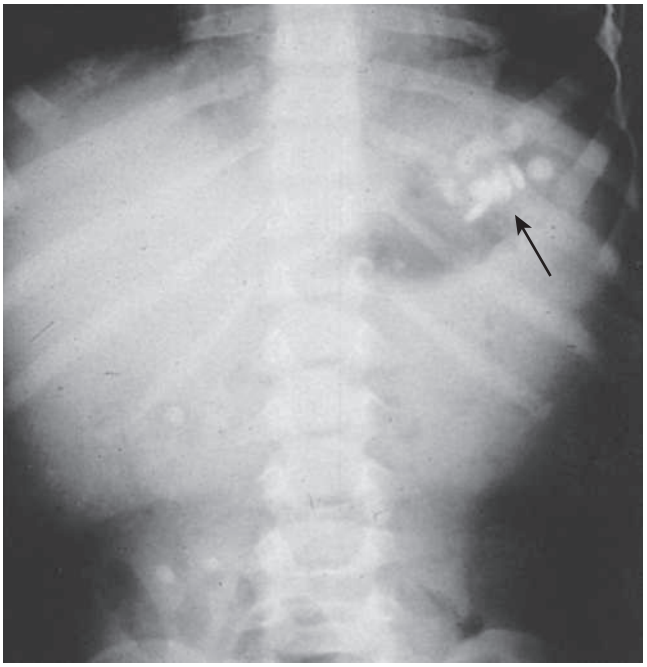

Fig. 146.1 Radiopaque iron tablets *(arrow)* seen on abdominal radiograph. (From: Craig SA. Radiology. In: Ford MD, Delaney KA, Ling LJ, et al, editors. Clinical Toxicology. Philadelphia: WB Saunders: 2001; p 62.)

years old, and 1.5 to 2 L/hr in adolescents and adults. WBI is continued until the rectal effluent is clear and there is no radiographic evidence of pill fragments.[2] This technique has been used in children, adolescents, and pregnant women without serious complications or electrolyte disturbances. Common side effects include nausea, vomiting, abdominal cramping, and bloating. WBI is contraindicated in the presence of bowel obstruction, perforation, ileus, or hemodynamic instability.[2]

Enhanced Elimination

Hemodialysis and hemoperfusion are not effective in the removal of iron because of its large volume of distribution. Early exchange transfusions have been used with some success for severely symptomatic patients. However, this should only be considered in patients who are not responding to standard chelation therapy.

Antidotal Therapy

Deferoxamine is the antidote for iron toxicity. Deferoxamine chelates iron to form the water-soluble compound ferrioxamine, which is renally excreted. Deferoxamine binds to free iron and will not chelate iron from hemoglobin, transferrin, or ferritin. Patients with an iron concentration above 500 µg/dL and those who, regardless of level, are exhibiting severe signs and symptoms of iron toxicity (metabolic acidosis, lethargy, hypotension, or signs of shock) require chelation. Pregnancy is not a contraindication to deferoxamine therapy. However, the prepregnancy weight should be used to calculate the ingested dose. Because of its short half-life, deferoxamine is administered as a continuous intravenous infusion starting at 5 mg/kg/hr and titrated to the typical goal rate of 15 mg/kg/hr, as tolerated, for 24 hours. Infusion rates of up to 35 mg/kg/hr have been reported, but this should only be considered following consultation with a toxicologist. More rapid administration of deferoxamine can lead to hypotension, which is managed by reducing the initial rate of the infusion and then slowly increasing it to the desired rate. Prolonged deferoxamine infusion has been associated with acute respiratory distress syndrome (ARDS) and also with *Yersinia* sepsis. The pulmonary complications are usually related to high dose deferoxamine for durations longer than 24 hours.

TABLE 146.3 Sources of Lead Exposure

Category	Source
Pediatric	Lead dust Paint in old homes Parent's occupation Imported toys or candies Foreign body ingestion (fishing weights, toys)
Occupational	Construction, particularly old home remodeling Lead smelters Battery recycling, repair, and manufacturing Firing range instructors Automobile mechanics Plastics manufacturing
Recreational	Moonshine Ceramics Home and car remodeling Painting
Other	Herbal remedies Retained lead bullets

Disposition

The asymptomatic patient who is reliably known to have ingested less than 40 mg/kg of elemental iron does not need additional therapy and can be discharged home after appropriate poison prevention counseling with reliable care takers. In patients who ingest more than 40 mg/kg, an iron concentration should be obtained at 3 to 5 hours post-ingestion and also 6 to 8 hours post-ingestion. If peak iron remains less than 300 µg/dL, is not rising, and the patient is asymptomatic during 6 hours of observation, the patient can be discharged home. If the patient is exhibiting signs of severe toxicity, even if the ingested dose is unknown, or meets criteria for deferoxamine chelation therapy, admission to an intensive care unit with poison center or toxicologist consultation is advised. If indicated, a psychiatric consultation should be requested.

LEAD

Foundations

Lead poisoning remains one of the most common and preventable environmentally mediated problems in the United States. The elimination of leaded gasoline and the ban on leaded paint in households in the 1970s exponentially reduced the number of lead poisonings in the United States. However, the Center for Disease Control and Prevention (CDC) estimates that approximately 535,000 children, aged 1 to 5 years old, still have elevated blood lead levels (BLLs) from various environmental exposures.[3] Immigrant and refugee children are at much greater risk for lead poisoning than children born in the United States because of exposures prior to arrival in the United States.[4,5] Adult lead poisoning has been decreasing over time and the CDC reported that in 2013, 20.4 per 100,000 adult workers had BLLs of 10 mcg/dL or greater, down from 26.6 in 2010.[6] Given the continued wide use of lead in industry, there are many potential sources of exposure. Retained bullet fragments are another important source to investigate[7] (Table 146.3).

Most lead exposures occur by ingestion in children and workplace inhalation in adults. Dermal absorption may also occur but is much less significant. Children and pregnant women absorb almost four times the amount of ingested lead than other adults. Once absorbed, lead is bound to red bloods cells and slowly distributes to the soft tissues where it is eventually stored, primarily in bone. The half-life of lead in the red blood cell is approximately 30 days, but once in the bone, the half-life can last decades. Lead easily crosses the placenta,

TABLE 146.4 Typical Blood Lead Levels and Correlative Signs and Symptoms in Children and Adults

	SYMPTOMS	
Level (μg/dl)	**Adults**	**Children**
10	None	Decreased IQ Decreased hearing Decreased growth
20	Increased protoporphyrin No symptoms	Decreased nerve conduction velocity Increased protoporphyrin
30	Increased blood pressure Decreased hearing	Decreased vitamin D metabolism
40	Peripheral neuropathies Nephropathy Infertility (men)	Decreased hemoglobin synthesis
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia Encephalopathy Nephropathy
100	Encephalopathy	Death

IQ, Intelligence quotient.

and maternal blood levels correlate with umbilical cord blood levels.[8] Neonatal lead exposure also occurs through breast milk. Most lead is ultimately excreted in the urine and bile.

There is no biologic role for lead in the human body. Lead complexes with sulfhydryl groups of proteins, which can alter enzyme and receptor function and distort structural proteins. Lead is also structurally similar to calcium and interferes with calcium-dependent cellular processes. Its toxic effects are most prominent in the hematopoietic and neurologic systems.

Clinical Features

The clinical features of lead poisoning are broad and often nonspecific (Table 146.4). Symptoms depend on the BLL, whether the patient is an adult or child, and whether the exposure is acute or chronic. Although all organ systems are affected, the most sensitive are the hematologic, vascular, and nervous systems. Lead inhibits heme biosynthesis, and the classic manifestation of hematopoietic lead toxicity is anemia. Anemia may be either normochromic or hypochromic. Chronic kidney disease and hyperuricemic gout ("saturnine gout") can also result from elevated BLLs. Chronic kidney disease consequently may worsen underlying anemia. Lead poisoning is associated with chronic hypertension. In the peripheral nervous system, segmental demyelination and degeneration of motor axons result in peripheral neuropathies. Wrist-drop and foot-drop are characteristic of adult lead poisoning but rarely seen today.[9] Importantly, lead toxicity can cause neuropsychiatric disorders. Many are difficult to distinguish during an emergency department (ED) evaluation, so collaboration with a primary care physician is essential to identify new cognitive deficits. In children, elevated BLL is associated with decreased intelligence quotient (IQ) scores, hyperactivity, decreased attention span, overaggressive behavior, learning disabilities, and criminal behavior. Severely high BLLs may present with lead encephalopathy associated with increased capillary permeability and cerebral edema.

Differential Diagnoses

The differential diagnoses of lead poisoning are broad, and because the symptoms of early poisoning are nonspecific, lead poisoning today is often initially not considered or misdiagnosed. Lead poisoning could be confused for neuropathies (such as carpal tunnel or Landry-Guillain-Barré syndrome) or abdominal or urologic pathologies (such as gastroenteritis, nephrolithiasis, or appendicitis).[9,10] The subtle neuropsychiatric signs in children can also be misdiagnosed as attention deficit hyperactivity disorder or other behavioral disturbances. Therefore, it is necessary to consider lead poisoning in the appropriate circumstance, particularly where another diagnosis is not established as the primary cause of the presentation.

Diagnostic Testing

Lead toxicity rarely presents primarily to the ED. Most patients encountered in the ED have been referred for management of an elevated screening BLL measured in a clinic or workplace surveillance program. Some patients may seek ED care following an ingestion of a leaded foreign body or with worrisome symptoms following a possible environmental exposure. Diagnostic testing should consist of a venous BLL, including those cases referred in for an abnormal screening test. Capillary screens (such as finger or heel sticks) may be falsely elevated. If the patient is symptomatic, other tests include a complete blood cell count, basic metabolic panel, liver and renal function tests, and urinalysis. A peripheral smear classically shows basophilic stippling, but this finding is relatively rare. Because lead-containing objects and paint chips are radiopaque, abdominal radiographs can confirm acute ingestion and determine the need for bowel decontamination. In cases of altered mental status, seizures, or coma, a computed tomography (CT) scan of the head may show cerebral edema associated with acute lead encephalopathy and can assist in ruling out other causes of these neurologic signs. In children, plain radiographs of the wrist and knees classically demonstrate increased metaphyseal activity termed *lead lines* that are characteristic of chronic exposures. However, such x-rays are not routinely obtained in the ED.

Management

Stabilization and Supportive Care

The most important treatment step in lead poisoning is removing the patient from the source. This is the only treatment needed in most cases of lead poisoning. Determining the exact source often requires the collaborative assistance of a primary care physician, social worker, and the

department of public health. Recent data suggest urban patients at risk for lead poisoning are also at risk for asthma; the environmental evaluation for lead and asthma risks is similar, so ensuring follow-up with a primary care provider to assess the risk for both problems is essential.

Decontamination

Oral activated charcoal does not bind lead. If an abdominal radiograph demonstrates lead within the gastrointestinal tract—particularly the stomach and small intestine—then bowel decontamination should be performed. This can be done with WBI or repeated doses of polyethylene glycol (see the Iron section for dosing regimen).

Antidotal Therapy

Children. Treatment for lead toxicity rarely is commenced in the ED, but the decision to admit for chelation or source control may be indicated after consultation with the poison control, a medical toxicologist, or the primary care provider. Regardless of the BLL, eliminating the source of exposure remains the most important priority. Evidence indicates no significant benefit from chelation for children with a BLL lower than 45 µg/dL as long as the source of exposure is controlled. A BLL less than 44 µg/dL in a patient who is asymptomatic or minimally symptomatic requires a medical and environmental evaluation to identify the source, stop further exposure, and have scheduled repeat BLLs done as per current Centers for Disease Control (CDC) and public health guidelines. Caregiver education about concerning symptoms and sources of lead exposure should be coupled with close follow-up with a primary caregiver for all patients with a detectable BLL. An environmental evaluation can often be arranged with the local public health department.

Blood lead levels of 45 to 69 µg/dL in patients without vomiting or CNS symptoms can be managed in the outpatient setting with oral succimer (2,3-dimercaptosuccinic acid [DMSA]; Chemet). The initial dose of succimer is 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days (maximum 500 mg per dose for children). The most common adverse reactions include nausea, vomiting, diarrhea, and transient elevations in liver transaminase levels. Although succimer has been FDA-approved only for children, it is effective and can be used in adults with lead poisoning. Table 146.5 summarizes available chelating agents with indications and doses. Any patient treated on an outpatient basis should be discharged to a lead-free environment.

Patients with a BLL of 69 µg/dL or higher require hospitalization and parenteral chelation therapy, even if asymptomatic. Evidence of encephalopathy, regardless of BLL, requires admission for parenteral chelation therapy. Consultation with a medical toxicologist, regional poison center, and pediatrician is indicated. Dimercaprol (or British antilewisite [BAL]) is given via a deep intramuscular injection as 4 mg/kg every 4 hours for children and adults. Adverse reactions to BAL include nausea, vomiting, urticaria, pyrexia, hypertension, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Because BAL is diluted in peanut oil, it is contraindicated in patients with peanut allergies. In cases of encephalopathy, intravenous calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) should be initiated with the second dose of BAL. Starting treatment with $CaNa_2EDTA$ may paradoxically increase lead transport across the blood-brain barrier. The dosage of $CaNa_2EDTA$ for adult and pediatric patients with acute lead encephalopathy is 1500 mg/m^2/day (approximately 50 to 75 mg/kg/day) given by continuous intravenous infusion for 5 days (maximum of 1000 mg per day for children and 3000 mg per day for adults). Adverse reactions include renal tubular injury and chelation of other metals, especially iron and zinc. $CaNa_2EDTA$ should be given only with adequate urine flow or with hemodialysis in the patient with renal failure. For patients with a BLL more than 69 µg/dL but no signs of encephalopathy, the dosage of $CaNa_2EDTA$ is 50 mg/kg/day or 1000 mg/m^2/day, given in two to four divided doses for up to 5 days without the need for concurrent BAL therapy.

Adults. The treatment of adults with chronic poisoning is based primarily on symptoms and threshold BLLs established by workplace regulatory agencies. In the asymptomatic adult or the patient with only mild clinical symptoms, the only intervention needed is cessation of exposure. According to the Occupational Safety and Health Administration (OSHA) lead standard, workers with serum lead levels above 40 µg/dL should be removed from work. If encephalopathy or severe symptoms are present, then hospitalization and chelation therapy with combined BAL and $CaNa_2EDTA$, as with children described previously, are indicated. Pregnant women should be treated in accordance with adult treatment guidelines. Lead does cross the placenta and can accumulate in the fetus. Newborn infants of exposure mothers may require chelation as well.

Disposition

Families of asymptomatic children with BLLs less than 45 µg/dL and asymptomatic adults should be counseled on how to avoid further exposure and given close follow-up with their primary care provider for a repeat BLL and exposure risk evaluation.

Patients who require oral chelation can be discharged home if they can tolerate succimer and if it can be ensured they do not return to a lead-contaminated environment. The health department should conduct an environmental assessment and testing of other family members so that the primary source of lead exposure can be identified, and further exposure prevented. Follow-up should be arranged with a pediatrician, medical toxicologist, or occupational medicine physician.

Patients who are significantly symptomatic, have worrisome CNS symptoms, and any children with a BLL of 69 µg/dL or higher require hospitalization for environmental exposure evaluation and parenteral chelation therapy.

ARSENIC

Foundations

Arsenic has an infamous history as an agent of homicide and been implicated in mass environmental poisonings.[11] Currently, arsenic exposure is primarily environmental and occupational. Arsenic is found in smelters and electric power plants that burn arsenic-rich coal; in the production of glass and microcircuits; and in rodenticides, fungicides, insecticides, paint, tanning agents, defoliants in the cotton industry, and wood preservatives. Arsenic is also still used for medicinal purposes in the treatment of trypanosomiasis, amebiasis, and leukemia. Importantly, significant concentrations of heavy metals including arsenic, lead, and mercury have been found as contaminants in ayurvedic medications.[12] Arsenic has also been reported in resource challenged countries with large environmental poisonings via well water.

Arsenic exists in different forms: elemental, organic, inorganic, and gaseous. Elemental arsenic (As) is a metal that is poorly water soluble and considered nontoxic. Organic arsenic, found in shellfish, is also generally nontoxic to humans. Of the two inorganic forms, trivalent arsenite (As^{3+}) is more toxic than the pentavalent arsenate (As^{5+}) form.[13] Absorbed arsenic is bound by hemoglobin, leukocytes, and plasma proteins. It is cleared from the intravascular compartment within 24 hours and concentrates in the liver, kidneys, spleen, lungs, and gastrointestinal tract. Arsenic crosses the placenta and can also accumulate in the fetus. Inorganic arsenic interferes with normal cellular metabolic function, energy generation, and induces apoptosis. Arsenic also generates reactive oxygen species and induces oxidative damage in the cell.[13] Gaseous arsenic in the form of arsine (AsH_3) is colorless, almost odorless, and extremely toxic. It is lethal at 250 ppm

TABLE 146.5 Chelators

Chelator	Dosage	Indications	Contraindications	Adverse Effects
Deferoxamine	15 mg/kg/hr up to 24 hours (titrate up slowly because of hypotension)	*Iron* level >500 g/dL or systemic symptoms	Severe renal disease Anuria	Rate-related hypotension Pulmonary complications if given for >24hrs Increased incidence of *Yersinia* and *Mucormycosis* infections
Dimercaprol (BAL)	*Lead encephalopathy:* 4 mg/kg deep IM injection every 4 hours for 5 days in children and adults *Arsenic (severe):* No established regimen; consider 3 mg/kg IM every 4 hours for 48 hours, then twice daily for 7 to 10 days *Mercury:* 5 mg/kg IM first, then 2.5 mg/kg every 12 to 24 hours for 10 days	*Lead* level >70 μg/dL or encephalopathy *Arsenic:* Symptomatic patient with known exposure *Mercury:* Inorganic	Peanut allergy Organic mercury poisoning Hepatic insufficiency	Pain at injection site Hypertension and tachycardia Nausea, vomiting Headache Fever (especially in children) Nephrotoxicity in the setting of an acidic urine
$CaNa_2EDTA$	1500 mg/m^2/day continuous intravenous infusion 50 mg/kg/day or 1000 mg/m^2/day in two to four divided doses for up to 5 days if less severe symptoms	*Lead* level of 70 μg/dL or encephalopathy (given after first dose of BAL)	Severe renal disease Anuria Hepatitis	Nephrotoxicity Transient increase in AST/ALT
Succimer (DMSA)	10 mg/kg every 8 hours for 5 days, then every 12 hours for 14 days (maximum 500 mg per dose for children)	*Lead* level of 45 to 69 μg/dL *Arsenic*: If tolerated orally for subacute and chronic toxicity *Mercury*: Acute and chronic	None	Nausea, vomiting Diarrhea Metallic taste Transient increase in AST/ALT
D-Penicillamine	*Lead*: 1–1.5 g/d (children: 20–30 mg/kg/d), in 3 or 4 divided doses for 1–6 months. To minimize adverse reactions, start at 250 mg/d (children: 10 mg/kg/d) and increase to 50% during week 2 and to a full dose by week 3. The maximum adult daily dose is 2 g. *Elemental or Inorganic Mercury (not effective for Organic)*: 250 mg (5 mg/kg) every 6 hours for 1–2 weeks *Arsenic*: 25 mg/kg every 6 hours for 5 days	*Lead* level of 45 to 69 μg/dL, succimer not tolerated *Arsenic*: Only if BAL and DMSA are unavailable *Mercury*: If BAL and DMSA are unavailable or not tolerated	Penicillin allergy	Leukopenia Thrombocytopenia Enuresis Abdominal pain
DMPS (investigational)	*Oral*: 100–200 mg (50–100 mg in children) every 6–8 hours, tapered over days to weeks *Parenteral (preferred for acute ingestions)*: 5 mg/kg/dose IM or slow IV push every 6–8 hours; day 1, every 8–12 hours; day 2, every 12–24 hours; day 3, until 24-hour urine is <50 mcg/L	*Lead* (chronic) *Arsenic* *Mercury*		Nausea, vomiting Headache Fatigue Rash, pruritis

Note: Indications for chelation and dosing regimens may change. Consult with a medical toxicologist or regional poison center for the most up-to-date recommendations.

BAL, British antilewisite; *$CaNa_2EDTA$,* calcium disodium ethylenediaminetetraacetic acid; *DMPS,* dimercapto-1-propanesulfonic acid, *DMSA,* 2,3-dimercaptosuccinic acid; *IM,* intramuscular; *AST*, alanine transaminase; *ALT*, aspartate transaminase.

and causes massive hemolysis. The excretion of arsenic and its metabolites occurs primarily through the kidneys.

Clinical Features

Acute Arsenic Toxicity

Gastrointestinal effects including nausea, vomiting, abdominal pain, and diarrhea predominate as the initial manifestations of acute exposure to inorganic arsenic. The diarrhea has often been described as "rice water-like" and difficult to differentiate from diarrhea induced by *Vibrio cholerae* infection. These symptoms can be so severe that they progress to hematemesis and hematochezia. The patient can also develop multisystem organ failure and cardiac conduction disturbances (Box 146.1). In cases of severe poisoning, cardiovascular collapse and death ensue. Early arsenic poisoning may be misdiagnosed as gastroenteritis or sepsis. For those who survive the initial gastrointestinal illness, chronic effects of arsenic poisoning appear weeks to months later. These include characteristic white lines that transverse the nailbeds running parallel to the lunula (also known as Aldrich-Mees lines; Fig. 146.2), painful sensorimotor neuropathy, and hyperkeratosis of the palms and soles.

BOX 146.1 Acute Effects of Arsenic Poisoning

Gastrointestinal
Severe gastroenteritis; hematemesis or hematochezia
Jaundice
Pancreatitis
Dysphagia
Hepatomegaly

Cardiovascular
Third spacing with shock
Sinus or ventricular tachycardia
Prolonged QT interval, ST depression, T wave inversion
Torsades de pointes
Pericarditis

Respiratory
Pneumonia
Pulmonary edema
Acute respiratory distress syndrome
Respiratory failure

Renal
Proteinuria
Hematuria
Oliguria
Renal failure

Neurologic
Headache
Drowsiness
Delirium
Coma
Encephalopathy
Seizures

Chronic Arsenic Toxicity

Chronic exposure to arsenic, typically through contaminated drinking water or occupational exposure, is associated with cardiovascular disease, diabetes mellitus, and both benign and malignant dermatologic disease.[14,15] Patients chronically exposed to arsenic have an increased risk of bladder, kidney, liver, and lung cancer.[16]

Arsine Gas

Acute exposure to arsine gas is characterized by severe hemolysis that is also associated with renal tubular injury. Signs of toxicity are usually evident within minutes to hours after exposure. Gastrointestinal symptoms are common, and CNS and liver dysfunction can occur.

Differential Diagnoses

Acute arsenic poisoning is often misdiagnosed as viral or bacterial gastroenteritis or gastrointestinal bleeding. Hemorrhagic gastroenteritis in the setting of an ingestion history should raise suspicions for caustic ingestions, ethanol, toxic alcohols, colchicine, heavy metals, and iron. Obtaining an environmental and occupational exposure history is important to help discern the etiology of the patient's symptoms.

Diagnostic Testing

To diagnose arsenic poisoning accurately, a 24-hour urine collection should be done. Spot urine samples are inaccurate and should not guide therapy. Normal arsenic concentrations are 5 μg/L or less in blood or less than 50 μg/day in a 24-hour urine collection. Any urine level above

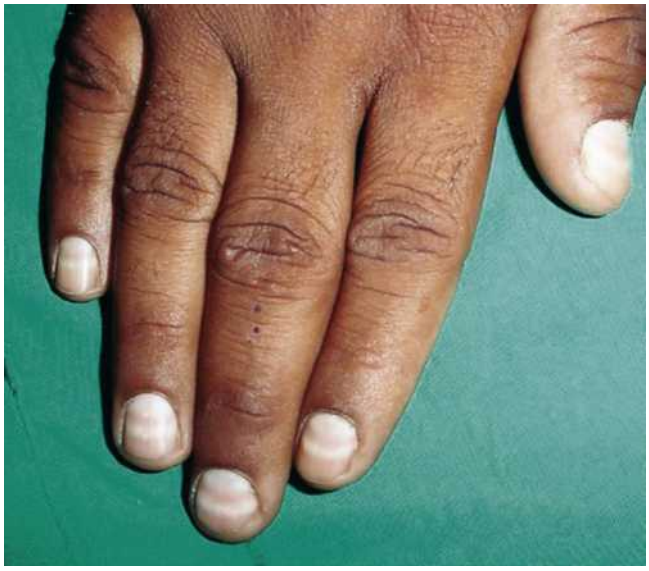

Fig. 146.2 Aldrich-Mees lines seen on the fingernails of a patient. (From: Chauhan S, D'Cruz S, Singh R, et al. Mees' lines. Lancet. 2008;372[9647]:1410.)

100 μg/day or 50 μg/L necessitates treatment. Seafood contains organic arsenic (arsenobetaine), which can significantly increase total urine arsenic concentrations, but arsenobetaine does not result in human toxicity. For this reason, patients should refrain from eating seafood, specifically shellfish, before testing, and the laboratory should be asked to specify the type of arsenic measured. Most patients referred to the ED for management of abnormal urine arsenic tests are not arsenic toxic; their urine tests are falsely abnormal because laboratories do not routinely differentiate between organic and inorganic arsenic. In cases of chronic arsenic poisoning or remote exposure, the serum and urine arsenic levels may no longer detect abnormal concentrations of arsenic.

Other laboratory results may suggest arsenic poisoning. Anemia, leukocytosis or leukopenia, and erythrocyte basophilic stippling may be seen. The results of renal function tests may be abnormal, demonstrating proteinuria, hematuria, and pyuria. Serum alanine transaminase, aspartate transaminase, and bilirubin levels may be elevated.

Arsenic in the gastrointestinal tract is radiopaque and can appear on a radiograph, although sensitivity is limited by its rapid absorption and the ensuing gastroenteritis.

Management

Stabilization and Supportive Care

Initial management of arsenic poisoning should address life-threatening conditions with supportive care of shock, dysrhythmias, and seizures. Fluid resuscitation helps maintain kidney perfusion early after arsine gas exposures.

Decontamination and Enhanced Elimination

As is the case with other metals, oral activated charcoal does not adsorb arsenic and is not recommended. Hemodialysis may remove some arsenic in the setting of acute renal failure. Exchange transfusions or plasma exchange can be done early after a severe arsine exposure. These treatments should be initiated in the intensive care setting for critically ill patients and in consultation with a medical toxicologist and nephrologist.

Antidotal Therapy

Acute Arsenic Poisoning. With a confirmed history of exposure in a symptomatic patient, chelation should start as early as possible without waiting for laboratory confirmation. Intramuscular BAL is

the preferred chelator in patients who are critically ill as described for lead poisoning. Succimer can be given orally, but its use is often limited by the severe gastroenteritis resulting from arsenic poisoning. D-Penicillamine has a high side effect profile and is much less effective than BAL or succimer, so should be used only when BAL or succimer are unavailable. Table 146.5 summarizes available chelating agents with indications and doses. Chelation is not useful for arsine gas exposures. With arsine gas poisoning, exchange transfusion, continuous venovenous hemodialysis, and plasma exchange have been used to remove arsine, which is tightly bound to erythrocytes.[17]

Chronic Arsenic Poisoning. Treatment of chronic arsenic toxicity should begin in a symptomatic patient after confirmation of elevated urinary arsenic levels. Oral chelation with succimer (DMSA) is the treatment of choice. Workers should modify their habits to avoid further exposure, and repeated monthly 24-hour urine collections can follow arsenic excretion dynamics. Prolonged chelation treatment in patients with chronic exposure but no detectable arsenic in blood or urine has not been proven to be effective.

Disposition

Patients who are severely ill and those receiving parenteral chelation for acute arsenic toxicity should be admitted to an intensive care setting. Patients with chronic arsenic exposure who are mildly symptomatic can be discharged home after removal from the source of exposure. Close follow-up with occupational medicine or a medical toxicologist should be arranged. Patients who are asymptomatic with a normal physical examination and vital signs can be discharged home.

MERCURY

Foundations

Mercury is a shimmering silver metal, familiar to most as one of the few metals that is liquid at room temperature in its elemental form. It has a long history of medicinal uses as an antiparasitic, a diuretic, a cathartic, an antiseptic, and a preservative in many older vaccines.

Significant poisoning can occur in the home and in the workplace.[18] Mercury has many industrial uses that include the manufacture of fluorescent lights, batteries, polyvinyl chloride, and in paints as a biocide. Recently, artisanal small-scale gold mining has become a significant source of global mercury pollution and toxicity.[19] For these reasons, mercury is a common environmental pollutant of air and water.[20] This has led to restrictions in the consumption of fish caught in many local waters, especially by pregnant women and children.

Like other metals, mercury exists in different forms: elemental, organic, and inorganic. Toxicity depends on the form of mercury. The most familiar form of mercury is elemental or metallic mercury, also known as *quicksilver.* A common route of exposure to elemental mercury is the inhalation of volatilized vapor during the goldmining extraction process or after vacuuming up a spill. After inhalation, metallic mercury is retained in the lungs and can result in pneumonitis and acute respiratory distress syndrome. Later systemic absorption may also occur leading to CNS and renal toxicities.[21] Subcutaneous and intravenous injections also cause poisoning from systemic absorption.[22] Elemental mercury is not well absorbed by the gastrointestinal tract and toxicity is unlikely by this route.[23]

Inorganic mercury salts have two different valences: Hg^{1+} (mercurous) and Hg^{2+} (mercuric). Ingestion of either salt leads to significant gastrointestinal and renal toxicity. Inorganic salts have a direct corrosive effect on the gastrointestinal tract resulting in third spacing and hemorrhage.

The organic mercury compounds are categorized as either short chain (alkyl) or long chain (aryl). The major route of exposure to organic mercury is through ingestion, but these compounds are also readily absorbed through the skin. Organic forms classically result in delayed neurotoxicity, and most documentation describing this form of toxicity comes from large population exposures.[24] Concerns about mercury poisoning from excessive fish consumption are extrapolations from those exposures.

Like lead, mercury has no known physiologic role in the human body. Mercury binds covalently to sulfhydryl groups, disturbing multiple cellular enzyme functions. Nephrotoxicity results from oxidative damage, cytoskeletal alterations, and increased autophagy in the kidney.[25] Mercury exposure affects both the cardiovascular system and the CNS. Mercury may lead to hypertension and other cardiovascular problems.[26] Mercury also increases reactive oxygen species in the nervous system, leading to cellular damage.[24] Although mercury was previously used as a preservative in various vaccines, it is important to note the dose in those vaccines was relatively low, and mercury has not been proven to be a cause of autistic spectrum disease.

TABLE 146.6 Mercury Poisoning and Clinical Manifestations Based on Route of Exposure and Form of Mercury

Type of Mercury and Route of Exposure	Signs and Symptoms
Inhalation of elemental mercury	Hypoxemia, dyspnea, chest tightness Fever, chills Burning in mouth and throat Nausea, vomiting, bloody diarrhea Renal tubular necrosis
Subacute or chronic inhalation of metallic mercury	Metal fume fever Neuropsychiatric symptoms Renal dysfunction Skin changes
Ingestion of inorganic mercury salts	Severe hemorrhagic gastroenteritis, shock, hypovolemia, third spacing Acute tubular necrosis
Subacute or chronic inhalation of mercury	Neurasthenia, erethism, acrodynia
Organic mercury exposure (methyl-, diethyl-)	Delayed neurologic problems (ataxia, tremor, dysarthria) Visual field constriction Hearing loss Spasticity Hyperreflexia

ARDS, Acute respiratory distress syndrome.

Clinical Features

The clinical manifestations of mercury poisoning depend on the acuity of the exposure, the route of exposure, and the chemical form of mercury (Table 146.6).

Differential Diagnoses

Hemorrhagic gastroenteritis in the setting of an ingestion history should raise suspicions for caustic ingestion, heavy metals, and iron. Respiratory distress from elemental mercury inhalation can also be mistaken for pneumonia, asthma, or influenza. The vague neurotoxic symptoms of mercury may also be confused with lead-induced neurocognitive deficits and encephalopathy. Obtaining an environmental and occupational exposure history is important to help discern the etiology of the patient's symptoms.

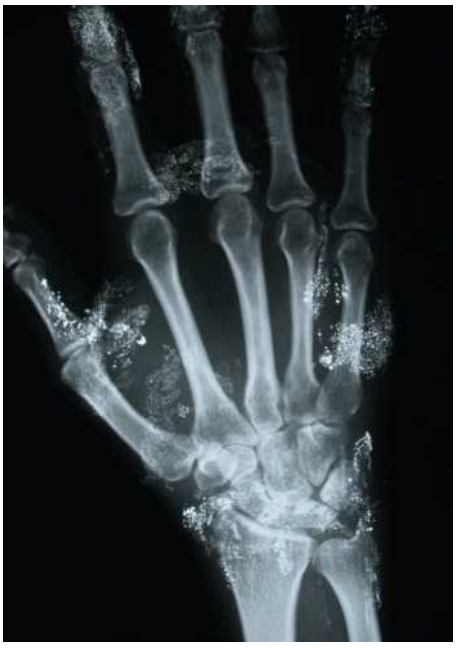

Fig. 146.3 Radiograph of the hand showing elemental mercury deposits in the subcutaneous tissue of a patient who was injecting chronically subcutaneously. (Courtesy Dr. Steven Aks.)

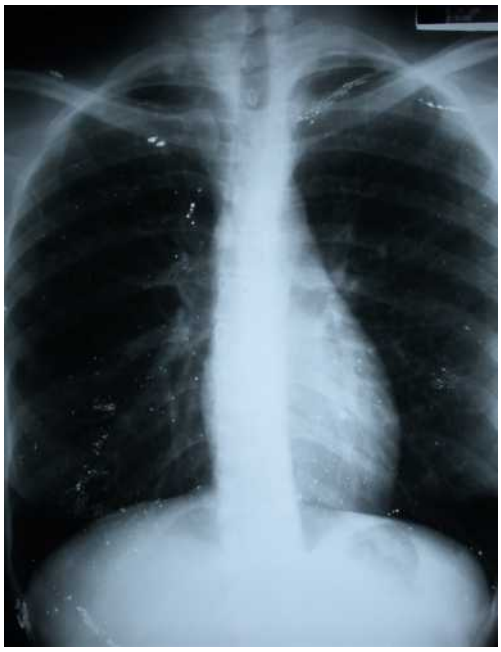

Fig. 146.4 Radiograph of the chest showing elemental mercury deposits in a patient who was chronically injecting the metal subcutaneously. (Courtesy Dr. Steven Aks.)

Diagnostic Testing

Measurement of a 24-hour urine mercury concentration is the most helpful test in confirming exposure and monitoring the effectiveness of chelation therapy. For organic mercury compounds, which undergo little urinary excretion, serum concentration should be used to confirm the diagnosis. A "normal" mercury concentration is considered to be less than 10 µg/L in the blood or less than 20 µg/L in the urine. Blood concentrations above 35 µg/L and urine concentrations above 150 µg/L require intervention. Fish can be contaminated with mercury, especially larger predatory fish and those from certain bodies of water known by local health departments to be most polluted. Individuals eating these locally caught fish may have elevated mercury levels. Elemental (metallic) mercury is radiopaque on plain radiographs, which can be ordered in cases of ingestion or dermal injection of elemental mercury (Figs. 146.3 and 146.4).

Management

Stabilization and Supportive Care

Initial management in the acutely poisoned patient is removal from the source and supportive care regardless of the type of mercury or route of exposure. There is no role for prophylactic antibiotics or steroids.

Decontamination

Oral activated charcoal and other gastrointestinal decontamination strategies are not recommended.

Enhanced Elimination

For acute inhalational exposures, the patient should be removed from the source of exposure and supportive management provided. Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury. Self-injection of metallic mercury may require surgical débridement of infiltrated tissue.[22]

Antidotal Therapy

BAL is used for clinically significant acute inorganic mercury intoxication. BAL is contraindicated for patients poisoned with organic methylmercury compounds because it may increase transport of mercury across the blood-brain barrier.[27] Succimer (DMSA) has been used for both acute and chronic mercury poisoning and may be the best available chelator for methylmercury. D-Penicillamine may also be used but should only be administered if no additional mercury is present in the gastrointestinal tract, because mercury absorption from the intestinal lumen may be enhanced by the penicillamines. Table 146.5 summarizes available chelating agents for mercury poisoning with indications and doses.

Disposition

Ingestion of inorganic mercury in patients with any symptoms warrants admission for further evaluation and supportive treatment. Patients who self-inject metallic mercury may need surgical consultation for surgical débridement; this may be done as an outpatient if no symptoms or signs are evident. Patients with signs of neurotoxicity from organic mercury require admission. Asymptomatic patients with exposure to any form of mercury warrant environmental counseling, and those with exposure from excessive fish consumption need primary care or medical toxicology follow-up as outpatients for dietary counseling and further testing as indicated.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 146: QUESTIONS AND ANSWERS

1. An 18-month-old female presents to the emergency department with her mother after they were informed of an elevated venous blood lead level of 38 mg/dL by their pediatrician. The child is asymptomatic and has a normal physical exam. She is an only child, does not attend daycare, and spends her time in the family home which was built in 1942. Which of the following would be the most appropriate initial management?

a. Admit for parenteral chelation
b. Start oral chelation and discharge home
c. Admit or secure alternative housing to limit exposure
d. Discharge home to follow-up with their pediatrician
e. Obtain an abdominal x-ray to determine if leaded foreign bodies are present

Answer: E. The most important treatment for all heavy metal poisonings is to limit further exposure. The source of lead in this case is likely from leaded paint in the home. Evaluating if the child currently has paint chips or other leaded foreign bodies in her gastrointestinal tract is important. If present, she will require decontamination to prevent absorption. After confirming the absence or presence of leaded foreign bodies, environmental control is paramount. To limit any further exposure, parents should ensure alternative housing (i.e., staying with a relative) or the child should be admitted to the hospital until the local public health entities can inspect and remediate the home. Discharging home with primary care follow-up is not appropriate because the child will continue to be exposed. Parenteral chelation is required for children with a lead level of 69 mg/dL and above or for severely symptomatic patients. Oral chelation is for children with blood lead levels above 44 mg/dL. This asymptomatic child does not meet criteria for chelation with a level of 38 mg/dL.

2. A 20-year-old man presents after an iron overdose. An abdominal radiograph shows many radiopaque objects in his stomach, consistent with iron tablets. You decide to try to decrease the gastrointestinal absorption of the iron. Which of the following methods is most effective?

a. Activated charcoal
b. Gastric lavage
c. Surgical removal
d. Syrup of ipecac
e. Whole bowel irrigation (WBI)

Answer: E. WBI is the preferred method to minimize iron absorption. WBI should not be routinely used in small overdoses or with mild symptoms, but it should be considered when a significant ingestion is suspected or when multiple tablets are identified by radiography. Iron

CHAPTER 146: QUESTIONS AND ANSWERS—cont'd.

is not adsorbed to oral activated charcoal. Gastric lavage and syrup of ipecac do not remove significant amounts of iron. Open surgical removal of tablets has been used in the past and is effective, but it is invasive and has a higher rate of adverse outcomes than WBI.

3. A healthy 26-year-old female was helping her great aunt clean out her home when she spilled a large tray of old mercury thermometers on the floor. She then attempted to vacuum up the mercury. She is now presenting to the emergency department 3 hours later with cough, fever, and shortness of breath. Her oxygen saturation is 93% on room air and her respiratory rate is 24 breaths per minute. A chest x-ray shows bilateral patchy infiltrates. Which of the following would be the most appropriate initial management?
   a. Provide supplemental oxygen and intravenous fluid resuscitation and admit for further monitoring.
   b. Give oral activated charcoal.
   c. Consult nephrology for potential acute kidney injury.
   d. Administer antibiotics and admit for further monitoring.
   e. Call the department of public health to evaluate the home for hazardous material clean-up.

Answer: A. This patient is exhibiting acute inhalation elemental mercury toxicity. After an inhalation exposure where mercury is volatilized and inhaled, patients can have fever, shortness of breath, and cough that can rapidly progress to ARDS. This may occur hours after exposure. Later, as the mercury is absorbed patients are at risk for inorganic mercury poisoning resulting in nephrotoxicity. The best approach to these patients is supportive care and close monitoring of their respiratory status. There are no roles for activated charcoal or antibiotics as activated charcoal does not bind heavy metals and this is a pneumonitis. Nephrology may ultimately need to be consulted but now the focus should be on the patient's cardiorespiratory status. Answer choice E is also reasonable to prevent further exposure at the home given the large amount of elemental mercury spilled, however it is not the most emergent management step.

4. A 5-year-old boy presents with abdominal pain, nausea, vomiting, and bloody diarrhea. The boy was found rummaging through his grandmother's medicine cabinet and says he swallowed some of her medications. His vital signs are significant for hypotension and tachycardia. An electrocardiogram (ECG) shows sinus tachycardia. Laboratory tests are significant for an anion gap acidosis, hyperglycemia, and moderate leukocytosis. Which of the following medications did he most likely ingest?
   a. Digoxin
   b. Diltiazem
   c. Iron
   d. Metformin
   e. Metoprolol

Answer: C. Iron toxicity typically presents with gastrointestinal symptoms including occasional bleeding soon after ingestion. The previously mentioned laboratory findings are also typical. Digoxin toxicity can also be manifested with gastrointestinal symptoms, but there is usually no gastrointestinal bleeding and there are also typically ECG changes. Beta-blocker toxicity, such as with metoprolol, is manifested with hypotension and bradycardia, as well as with hypoglycemia. Calcium channel blocker toxicity, such as with diltiazem, can be manifested with gastrointestinal symptoms, acidosis, and hyperglycemia. However, patients typically have bradycardia, and gastrointestinal bleeding is not expected. Metformin toxicity is manifested with gastrointestinal upset, typically without bleeding. Lactic acidosis can result, but the vital sign abnormalities and other laboratory results are not expected.

5. A 57-year-old woman with hypothyroidism presents to the emergency department with painful, burning circumferential bilateral lower leg pain. She states that over the last 2 weeks the pain has gotten progressively worse so that she feels as though she cannot even wear socks. She lives in a rural community, works part-time at the public library, and denies alcohol use or taking any herbal supplements. Her only medication is levothyroxine. She denies fevers or chills, polyuria, chest pain or shortness of breath. Her exam is remarkable for hyperalgesia in the bilateral lower extremities. Looking through her chart you notice that she was in the ED 2 weeks ago for gastroenteritis, was given IV fluids and then discharged home. As you leave her room, she tells you she is convinced her husband is poisoning her. You then decide to order a complete blood count, a basic metabolic panel, and a:
   a. Neurology consult
   b. Venous blood lead level
   c. Vitamin B_{12}
   d. 24-hour urine collection for arsenic testing
   e. Ethylene glycol level

Answer: D. Acute inorganic arsenic poisoning is characterized by cholera-like diarrhea followed weeks to months later by peripheral neuropathy and nail and skin changes. Arsenic was commonly used as a rodenticide until the mid-19th century when it was no longer produced. It can still be found in rural areas, stored in old barns. A 24-hour speciated urine arsenic test to determine the amount of inorganic and organic arsenic is the gold standard for determining the need for chelation. Although lead poisoning can cause peripheral neuropathy, this is typically motor in nature and not preceded by nausea, vomiting, and diarrhea. Constipation and colicky abdominal pain are characteristic for lead poisoning. Vitamin B_{12} deficiency can lead to a peripheral neuropathy however in this patient it is not the most likely diagnosis.

Hydrocarbons

George Sam Wang and Jennie Alison Buchanan

KEY CONCEPTS

- Aspiration is the major toxic risk of hydrocarbon poisoning.
- Hydrocarbons may cause systemic toxicity, burns, cardiac dysrhythmias, altered mentation, and seizures depending upon the specific agent, dose, and duration of exposure.
- Gastrointestinal decontamination is potentially harmful in cases of hydrocarbon ingestion and is contraindicated.
- Hydrocarbon inhalant abuse can cause central nervous system (CNS) and cardiotoxic effects.
- In most cases of hydrocarbon ingestion or inhalation, symptomatic care with observation and monitoring are the cornerstones of management. There are no specific antidotes for hydrocarbons. Patients with pulmonary symptoms should have a chest radiograph.
- Symptoms of toxicity, especially aspiration, can be delayed, so asymptomatic patients should be observed for 6 hours and given instructions to return if symptoms develop after discharge.

FOUNDATIONS

Overview

Hydrocarbons are a diverse group of organic compounds that contain hydrogen and carbon (Table 147.1). Most hydrocarbons (such as gasoline) are byproducts of crude oil and are therefore called *petroleum distillates.* Essential oils such as turpentine or wormwood are derived from plants. Hydrocarbons are used as solvents and diluents in many products, including household cosmetics and chemicals, pesticides and fuels. The two main categories of hydrocarbons are aliphatic (straight chain structures, such as propane) and aromatic (cyclic structures, such as toluene). Hydrocarbons can also have multiple nonorganic side chains. For example, halogenated hydrocarbons will have at least one bromide, chloride, fluoride, or iodide moiety (e.g., carbon tetrachloride). Finally, hydrocarbons are used as a solvent base for many toxic chemicals, such as insecticides, carburetor cleaner (methanol), and heavy metals, which in turn can cause separate distinct syndromes of poisoning. Although there is a wide variety of toxic hydrocarbons, the majority of human exposures are confined to petroleum distillates.

Human exposure, both intentional and unintentional, to hydrocarbons is a common problem. In 2018, U.S. poison centers reported over 28,500 exposures to hydrocarbons accounting for over 1% of all calls with 121 major outcomes and 20 deaths.[1] Over the prior decade, there were approximately 4000 pediatric exposures to hydrocarbons per year, and almost 10% were hospitalized.[2] It is estimated that nearly 10% of the United States population aged 12 years and older have used an inhalant for its psychoactive properties.[3] Toxic exposure to hydrocarbons is dermal, inhalational, or via ingestion (with potential for aspiration). Inhalational exposures are typically due to either intentional abuse of volatile hydrocarbons (huffing, sniffing, dusting or bagging) or household and workplace exposures. Ingestions are mostly accidental pediatric exposures, which can lead to aspiration pneumonitis. Dermal exposures are from household or workplace use of hydrocarbon-based agents and are rarely intentional.

Pathophysiology

Hydrocarbons are local gastrointestinal irritants, but acute toxicity usually manifests through effects on three main target organs: lungs, heart, and central nervous system (CNS). Most ingestions of hydrocarbons do not lead to serious systemic toxicity but localized gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea may occur. Exceptions include halogenated or aromatic hydrocarbons, and hydrocarbons containing metals or pesticides, which are capable of causing significant CNS, hepatic, or renal toxicity. Despite the fact that there are thousands of different types of hydrocarbons, their potential for acute toxicity depends on a few physical properties:

- Viscosity is the capacity to resist flow or change. Low-viscosity hydrocarbons, such as gasoline, lamp oil, and furniture polish, spread rapidly into the airway, with high risk of aspiration toxicity. Lubricants and mineral oil, conversely, have high viscosity and low aspiration potential.
- Volatility is a measure of a liquid's ability to evaporate to a gas or vapor. Hydrocarbons with high volatility can displace alveolar oxygen and cause hypoxia. Butane and propane are examples of hydrocarbons with high volatility.
- Surface tension is the capacity for a liquid to adhere to a surface. Low surface tension, like low viscosity, enables a substance (e.g., turpentine) to disperse easily and may lead to pulmonary toxicity.
- Chemical side chains or substitutions often increase potential toxicity. These include metals (e.g., lead), halogens (e.g., the chloride ions in carbon tetrachloride), and those found on aromatic structures (e.g., the CH_3 groups in toluene and xylene). Halogenated hydrocarbons may cause cardiotoxicity.
- Lipophilicity enhances blood brain barrier penetration resulting in CNS effects.

Pulmonary Pathophysiology

The primary target organ for direct toxicity is the lung. Fatalities after ingestion usually occur because of accompanying aspiration. As noted above, hydrocarbons with high volatility, low viscosity, and low surface tension are especially dangerous (Box 147.1).[2-4]

Hydrocarbons penetrate into the lower airways, producing bronchospasm and direct injury to pulmonary alveoli and capillaries leading to an inflammatory response and pneumonitis.[2,4] Hydrocarbons

TABLE 147.1 Spectrum of Hydrocarbon Toxicity

Type	Example	Use	Pathophysiology	Comments
Aliphatic petroleum distillates	Methane, propane, butane, gasoline, kerosene, mineral spirits, mineral oil, naphtha, mineral seal oil, diesel oil, *n*-hexane	Fuels, liquid fuels, solvents, furniture polish, degreasers, multiple uses in chemical industry	Asphyxiants causing hypoxia and CNS depression Abused inhalants Pneumonitis when aspirated CNS depression *n*-Hexane causes peripheral neuropathy	Sudden death from inhalation abuse Viscosity and volatility determine spectrum of toxicity Mineral seal oil has high aspiration potential Poor gastrointestinal absorption
Aromatic petroleum distillates	Toluene, xylene, benzene	Used in plastics, pharmaceutical, rubber, chemical, and solvent industries, degreasers	Highly volatile, lung aspiration Absorbed from gastrointestinal tract Abused inhalants	Inhaled toluene causes renal tubular acidosis Benzene causes aplastic anemia, leukemia
Essential oils	Turpentine, pine oil, oil of wintergreen, pennyroyal	Solvents, household disinfectants, incense	Well absorbed from gastrointestinal tract	Gastrointestinal and CNS toxicity Wintergreen with methylsalycylates Pennyroyal can lead to hepatotoxicity
Halogenated hydrocarbons	Methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, Freon, methylbromide, lindane, DDT	Solvents cleaning fluids, degreasers, fire extinguishers, paint strippers, fumigants	Multisystem toxicity (CNS, renal, hepatic, cardiac) Inhalant abuse Highly lipid soluble	Methylene chloride metabolized to carbon monoxide after ingestion, absorbed through the skin resulting in burns Carbon tetrachloride is radiopaque and can lead to hepatotoxicity Insecticides absorbed through skin
Related chemicals	Phenol, creosols	Disinfectants	Very corrosive	Phenol causes severe skin burns, and systemic toxicity including metabolic acidosis

CNS, Central nervous system; *DDT,* dichlorodiphenyltrichloroethane.

BOX 147.1 Qualities of Hydrocarbon That May Lead to Aspiration and Pneumonitis

- High volatility
- Low viscosity
- Low surface tension

also impair surfactant lipid production and function, leading to alveolar instability and collapse, decreased compliance, and impaired gas exchange. These mechanisms lead to alveolar dysfunction, ventilation-perfusion mismatch, and hypoxemia, which can progress to respiratory failure. Lipoid pneumonia can also develop after hydrocarbons coalesce in alveoli and become encapsulated by fibrous tissue. This has been reported in adults siphoning gasoline and from fire-eating performances and is known as "fire-eater's lung."[5-7]

Central Nervous System Pathophysiology

Most inhalant forms of hydrocarbons cause CNS depression. Products used for recreational mood alteration include glues and adhesives, aerosols, anesthetics, cleaning agents, solvents, and gases. After respiratory exposure, hydrocarbons passively diffuse through the pulmonary alveolus, are absorbed in blood and tissues, and cross the blood-brain barrier. Experimental data suggest that effects occur through binding of hydrocarbons with various neurotransmitter receptors, including glutamate/N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), dopamine, and opioids.[3] The inhalation route avoids hepatic first-pass metabolism and generates high CNS concentrations. With an isolated single exposure, these effects usually have a rapid onset of intoxication and short duration of effect. Chronic use of inhaled hydrocarbons can cause severe abnormalities in nervous system function, which include deficits in memory, attention, and judgment, peripheral neuropathy, cerebellar degeneration, neuropsychiatric disorders, chronic encephalopathy, and dementia. More than 50% of patients who abuse toluene for greater than 10 years will have cerebral cortical atrophy (Fig. 147.1) with histologic changes that include loss of neurons, diffuse gliosis, and axonal degeneration.[3] CNS depression can also occur through ingestion of some hydrocarbons, such as tea tree oil.

Cardiac Pathophysiology

Hydrocarbons can precipitate sudden death, usually in the setting of intentional inhalation. These compounds are thought to produce myocardial sensitization to endogenous and exogenous catecholamines by inhibition of calcium signaling, which precipitates ventricular dysrhythmias and myocardial dysfunction. Hypoxemia is also thought to be a contributing factor. Cardiac dysrhythmia occurs disproportionately among those using halogenated and aromatic hydrocarbons (e.g., difluoroethane). Halogenated hydrocarbons can be found in refrigerant propellants and air spray cleaners commonly used for computer keyboard cleaning. Prolonged use can lead to cardiac structural damage and may impede normal cardiac electrical function

Other Organ Systems

Toxicity related to hydrocarbons also has been reported for other organ systems. Recognized syndromes include toluene-induced renal tubular acidosis, benzene-induced bone marrow toxicity and leukemia, delayed methylene chloride–induced carbon monoxide poisoning, and chlorinated hydrocarbon–induced centrilobular hepatic necrosis.[1] Direct skin exposure to certain hydrocarbons can cause defatting dermatitis, contact dermatitis, or chemical burns. Intentional intravenous injection of hydrocarbons such as kerosene has led to both localized caustic and necrotic effects, and systemic effects including renal or

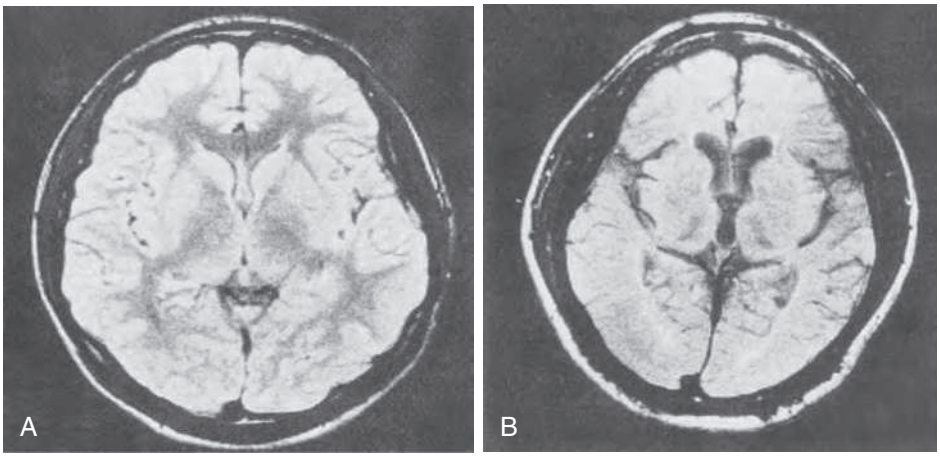

Fig. 147.1 Brain magnetic resonance imaging (MRI) of an individual with no history of inhalant abuse (A) and a patient with a history of chronic toluene abuse (B). (From NIDA Research Report [NIH 05-3818].)

hepatic toxicity, systemic inflammatory response syndrome (SIRS), hemolysis, seizures, pulmonary injury, cardiovascular toxicity, and death.[8] Huffing can lead to localized increased vascular permeability, which can lead to angioedema, or localized frostbite when refrigerants or freon are abused (Fig. 147.2).[9]

CLINICAL FEATURES

After oral ingestion of hydrocarbons, severe poisoning is most often related to aspiration. This manifests with progressive respiratory symptoms, including cyanosis, coughing, grunting, noisy respirations, and increased work of breathing. A patient may initially have mild symptoms and then develop tachypnea, dyspnea, bronchospasm, wheezing, rales, and fever after several hours.[2,4] A change in mental status can be a manifestation of hypoxia or hypercapnia, but it is also a direct effect of the hydrocarbon itself. In extreme cases, respiratory failure can require intubation. Various additives or solutes can produce symptoms independently (e.g., seizures from camphorated hydrocarbons, cyanosis from nitrite-induced methemoglobinemia, or delayed carbon monoxide poisoning from methylene chloride exposure[10]). Pesticides are often dissolved in a hydrocarbon base. With pesticide exposures, it can be difficult to distinguish acute respiratory distress syndrome induced by hydrocarbon aspiration from bronchorrhea induced by organophosphate toxicity (see Chapter 152).

Hydrocarbon solvent abuse is common and associated with various paraphernalia, such as plastic bags used for "bagging" (a method of pouring or spraying hydrocarbons in a bag or container and then inhaling deeply) and hydrocarbon soaked cloth used for "huffing" (a method in which abusers inhale through a saturated cloth).[9] Patients often have the distinctive odor associated with organic hydrocarbons. A characteristic coloration from spray paint (usually silver or gold because these paint colors contain higher concentrations of toluene) may be present over the mouth and nose or localized angioedema may occur, resulting in a "glue-sniffer's rash" (Fig. 147.3). These patients generally present to the emergency department (ED) with CNS intoxication and exhibit euphoria, agitation, hallucinations, confusion, or bizarre behavior. This may progress to CNS depression and seizures. In extreme cases, an individual who has inhaled solvents and then engaged in physical exertion, such as an altercation, may suddenly collapse in cardiac arrest, likely due to cardiac sensitization of endogenous catecholamines by hydrocarbons with ensuing dysrhythmias.[3] Chronic hydrocarbon inhalers may be brought to medical attention for behavioral problems or nonspecific medical symptoms caused by long-term exposure. These patients may share traits with the chronic ethanol user, with peripheral neuropathy (caused by, for example, *n*-hexane), cerebellar degeneration, and encephalopathy.[11]

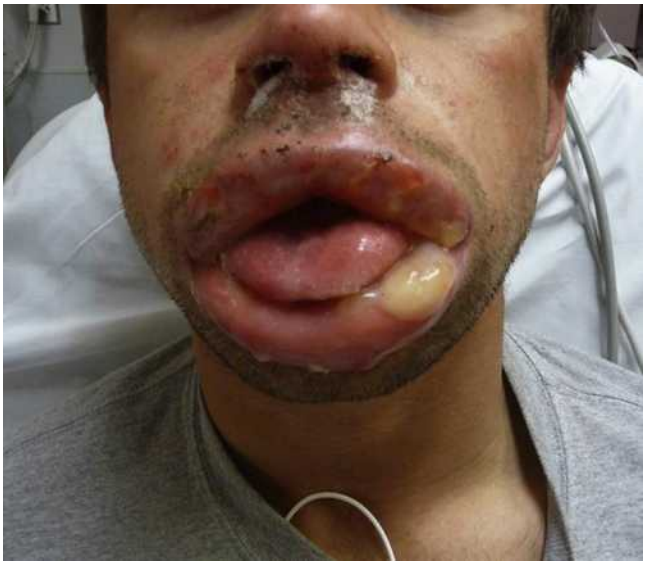

Fig. 147.2 Angioedema resulting from huffing computer cleaner. (From: Kurniali PC, Henry L. Inhalant abuse of computer cleaner manifested as angioedema. *Am J Emerg Med.* 2012;30:265.e3-5.)

Accidental dermal or inhaled (non-aspiration) respiratory exposure to hydrocarbons may occur in the workplace or home. Such exposures are rarely life-threatening. Most cases do not present for medical care.[1] The few patients who present to the ED typically will be asymptomatic or have transient nonspecific symptoms, such as headache, dizziness, or nausea. Those with significant respiratory exposure may have persistent pulmonary complaints and physical findings, such as coughing, wheezing, and cyanosis. Patients with significant acute dermal exposures may have localized pain and evidence of chemical burns consisting of erythema, swelling, angioedema, blistering, and dermal destruction (e.g., exposure to phenol).[3,9]

In the absence of aspiration, large-volume ingestion, or co-ingestion of another toxic substance, oral ingestion of most commonly available hydrocarbons is not associated with significant morbidity or mortality. Cough or tachypnea may be an early sign of pneumonitis or aspiration.

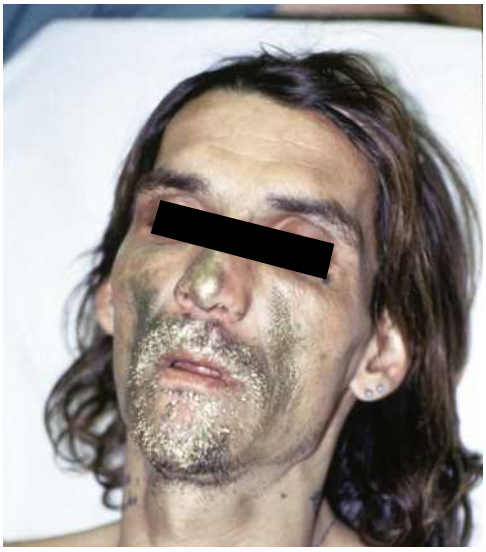

Fig. 147.3 Presentation of paint sniffer ("huffer") with paint around the face and sedation. (Courtesy Chris Tomaszewski, MD.)

DIFFERENTIAL DIAGNOSES

The history of exposure to a hydrocarbon, and the route or method of that exposure is usually straightforward. Additional history and examination should focus on other ingredients and possible aspiration, especially if the agent is ingested. Symptoms of aspiration include cough, dyspnea, and shortness of breath. Signs of significant pulmonary exposure include tachypnea, tachycardia, wheezing, and hypoxemia. Differential diagnosis depends upon the route of exposure, which primarily includes inhalation and ingestion, and the likelihood of co-intoxicants. CNS depressants such as ethanol and sedative-hypnotics can mimic the altered mental status of hydrocarbon ingestion. For hydrocarbon pneumonitis, pulmonary irritants; organophosphates, salicylates, and paraquat poisonings; and viral or bacterial pneumonia, may all produce a similar clinical presentation, but a focused history usually will lead to the correct diagnosis. In the scenario of the recreational abuser inhaling a particular agent, multiple drugs of abuse are often present, which can confound the clinical evaluation. Furthermore, hydrocarbon products may contain other constituents leading to specific toxicities. Behavioral disorders and confusion can be caused by hypoxia and respiratory compromise, as well as by the drugs themselves. Hypoglycemia, electrolyte abnormalities, and trauma should be considered as an etiology of altered mentation in these patients.

DIAGNOSTIC TESTING

The diagnosis is usually self-evident, and the exposure is often reported by the patient, supported by history of exposure and chemical odor. Ideally, the offending agent and container are brought to the ED. The local poison control center, medical toxicologist or material safety data sheet (MSDS) may identify and verify substances containing hydrocarbons. Hydrocarbons often are vehicles for other chemicals, and other exposures should be investigated.

CHAMP is a long-standing mnemonic used to help identify hydrocarbons and their additives with systemic toxicity (Box 147.2).

We do not recommend laboratory identification of specific hydrocarbons, which is difficult, time-consuming, and does not alter ED management. Other laboratory tests including electrolytes, complete blood count, and liver function tests can be performed to assess for renal tubular acidosis, electrolyte abnormalities (e.g., hypokalemia), bone marrow suppression, or liver injury caused by various hydrocarbons.[3] If essential oils such as oil of wintergreen (salicylates) or pennyroyal (liver toxicity) are ingested, specific relevant testing is performed. We recommend an electrocardiogram (ECG) in patients with a history of halogenated hydrocarbon use, dysrhythmias, syncope, or hemodynamic instability. Abnormal ECG findings may include premature ventricular contractions, QTc interval prolongation, or, in extreme cases, ventricular tachycardia or fibrillation.

Patients with pulmonary symptoms should have a chest radiograph and be observed for at least 6 hours with a repeat chest radiograph if there is worsening of their pulmonary status.[2,3]

BOX 147.2 CHAMP Mnemonic

*C*amphor can cause neurotoxicity and seizures
*H*alogenated hydrocarbons can cause dysrhythmias and hepatotoxicity
*A*romatic hydrocarbons can cause bone marrow suppression and leukemia
*M*etals (e.g., arsenic, mercury, and lead) can cause neurotoxicity
*P*esticides can cause cholinergic crises, seizures, and respiratory depression

MANAGEMENT

Dermal exposures to hydrocarbons can cause extensive burns, and exposed patients require early decontamination. Contaminated clothing should be removed, and the skin should be washed with soap and copious lukewarm water. Thermal injuries and chemical injuries are treated as described in Chapters 54 and 55.

In most cases of hydrocarbon ingestion or inhalation, symptomatic care along with observation and monitoring are the cornerstones of management. Gastrointestinal decontamination with gastric lavage or activated charcoal is not indicated. Most hydrocarbons are much more toxic to the lungs than to the gastrointestinal tract, and emesis or attempts at gastric emptying or decontamination may lead to aspiration and pulmonary toxicity.

Cardiac abnormalities are treated according to standard advanced cardiac life support (ACLS)/pediatric advanced life support (PALS) resuscitation with the exception of epinephrine administration. It is postulated that catecholamines worsen or precipitate cardiac dysrhythmias. This had led to recommendations for using short-acting beta blockers, such as esmolol, for hydrocarbon-induced refractory tachydysrhythmias. We recommend an initial bolus of 1 mg/kg IV over 30 seconds followed by an infusion starting at 50 mcg/kg/min (maximum of 300 mcg/kg/min) until resolution of the tachydysrhythmia. Epinephrine should be avoided in the acutely intoxicated patient for concern of precipitating an arrhythmia.[3] Patients with any history or ECG abnormalities concerning for cardiac involvement should be monitored on cardiac telemetry until symptoms resolve.

Significant hydrocarbon toxicity may lead to early and rapid decompensation of a patient's pulmonary, cardiac, and CNS functions. Monitoring in an intensive care or appropriate ED observation setting is indicated for patients with respiratory distress, significant oxygen requirements, those needing positive-pressure assistance or mechanical ventilation, tachydysrhythmias, cardiac conduction disturbance, or CNS depression. Patients with mild pulmonary symptoms (cough, minimal work of breathing, or low oxygen requirement) may be admitted to an inpatient unit for further observation. All other asymptomatic or minimally symptomatic patients should be observed with cardiac monitoring and pulse oximetry for a minimum of 6 hours and until asymptomatic. Indications for positive-pressure ventilation or mechanical ventilation include hypercarbia, severe respiratory distress, hypoxia unresponsive to noninvasive measures, or CNS depression. There are case reports and animal models using high-frequency jet ventilation, and extracorporeal membrane oxygenation in severe

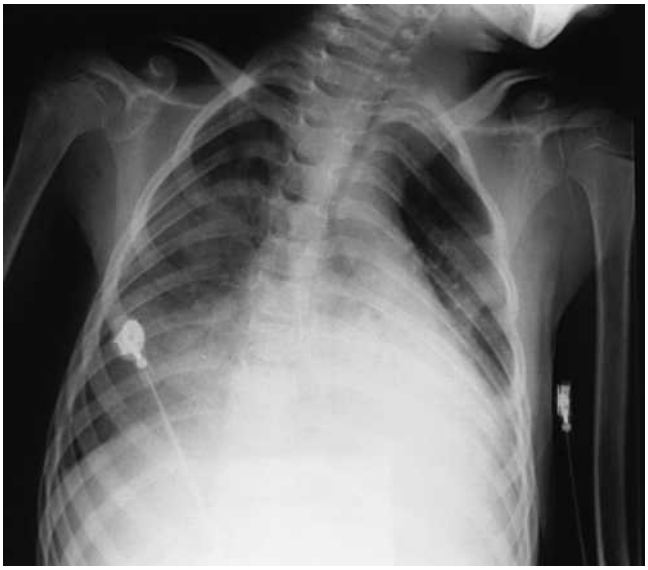

Fig. 147.4 Chest radiograph of a patient with hydrocarbon ingestion 6 hours after exposure.

cases of pneumonitis, with unproven clinical efficacy. Clinical decisions regarding these novel therapies should be made as in any other case of severe lung disease.[2-4] We recommend consideration of intrapulmonary administration of surfactant for severe hydrocarbon pneumonitis, using elevated oxygenation index, Pao_2/Fio_2 ratios, or poor lung compliance as indicators for use.[12] Consultation with a pulmonologist is advised for surfactant administration. Corticosteroids and antibiotics have not been shown to improve outcomes and are not indicated.[3]

DISPOSITION

Exposures to known, relatively benign hydrocarbons with minimal symptoms should have a 6-hour period of observation. Asymptomatic patients can be discharged home after appropriate psychiatric clearance, if indicated. If signs of pulmonary or systemic toxicity develop during the observation period (such as tachypnea and hypoxia), and a chest radiograph shows evidence of pneumonitis (Fig. 147.4), patients will require observation or hospital admission for at least 24 hours until symptoms have improved. Patients with CNS depression, history of dysrhythmia, significant respiratory distress including cyanosis, coughing, grunting, noisy respirations, and increased work of breathing should be monitored in the intensive care unit (Box 147.3).

BOX 147.3 Disposition

- Observation
  - Patients should be monitored for minimum 6 hours.
  - Discharge criteria: Asymptomatic without chest x-ray findings after 6 hours
- Inpatient admission
  - Mild CNS depression, tachypnea, hypoxia, chest x-ray findings not resolved after 6 hours
- Intensive care monitoring
  - Moderate to severe CNS depression
  - Significant respiratory distress
  - Significant hypoxia or hypercarbia
  - Requiring significant respiratory support (positive-pressure ventilation/mechanical ventilation)
  - History of cardiac dysrhythmias
  - Hemodynamic instability

CNS, Central nervous system.

Recreational inhalational users of hydrocarbons should be observed until clinical symptoms are improving or resolved. In most cases, if asymptomatic without complaints, the patient may be discharged after medical clearance for drug abuse counseling. Patients exposed to hydrocarbons with chemical side chains or substitutions have an increased incidence of systemic toxicity. These include metals (e.g., lead), halogens (e.g., the chloride ions in carbon tetrachloride), those found on aromatic structures (e.g., the CH_3 groups in toluene and xylene) and halogenated hydrocarbons, which can cause cardiotoxicity. These types of hydrocarbon exposures should be managed in conjunction with a poison control center or a medical toxicologist.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 147: QUESTIONS AND ANSWERS

1. Hydrocarbons can affect many organ systems, but derangements in which organ system most commonly lead to death after hydrocarbon exposure?

a. Cardiac
b. Gastrointestinal
c. Nervous
d. Pulmonary
e. Renal

Answer: D. Most fatalities from hydrocarbon ingestion occur because of aspiration. Hydrocarbons cause direct lung injury, as well as displace oxygen and disrupt surfactant. Hydrocarbons can sensitize the myocardium to catecholamines, which can result in ventricular dysrhythmias and sudden death. Although an important consideration, death is more frequently caused by pulmonary complications. Gastrointestinal complications from hydrocarbon exposure are rare unless related to aspiration potential. Chronic hydrocarbon abuse or exposure causes nervous system dysfunction, including peripheral neuropathy, cerebellar degeneration, and neuropsychiatric disorders, but typically does not result in death. Several hydrocarbons cause renal failure, particularly toluene, but rarely result in death.

2. A healthy 20-year-old man presents after accidentally ingesting furniture polish that was stored in a plastic container that he mistook for a beverage. The ingestion occurred approximately 1 hour ago. He has no complaints. His vital signs and physical examination are normal. Which is the most appropriate course of action?

a. Carbon monoxide level
b. Careful gastric decontamination using nasogastric tube
c. Drug screen
d. Observe for 6 hours and discharge if condition does not change
e. Serum electrolytes

Answer: D. Furniture polish is typically a mixture of nontoxic chemicals with a hydrocarbon base. The primary toxicity from hydrocarbon is from aspiration. Gastric decontamination is not recommended. Serum electrolytes and drug screens are rarely helpful in acute asymptomatic hydrocarbon exposures. Wood strippers often contain methylene chloride, which can cause carbon monoxide poisoning, but this chemical is not found in furniture polish.

3. A 4-year-old boy with a history of asthma is brought to the emergency department (ED) following an accidental hydrocarbon ingestion 2 hours ago. He initially was noted to be coughing. His vital signs are normal. His physical examination reveals mild bilateral wheezing but with good air movement. His oxygen saturation is 99% on room air. A chest radiograph is normal. The child is placed on a cardiac monitor and intravenous (IV) access is obtained. What is the most appropriate treatment plan?

a. Admission and observation
b. Endotracheal intubation
c. Intravenous sodium bicarbonate
d. Racemic epinephrine
e. Oral activated charcoal

Answer: A. Patient is symptomatic after a hydrocarbon exposure. Hydrocarbon pneumonitis can worsen over the next 24hours. Typically, they will cause few symptoms when ingested. Any therapy that risks inducing vomiting should be avoided (i.e., gastric lavage and oral activated charcoal). Patient is not ill enough to get intubated. Racemic epinephrine may be helpful if stridor or upper airway swelling is evident. Sodium bicarbonate has no role in hydrocarbon toxicity.

4. A 16-year-old male presents by emergency medical services (EMS) paramedics with sudden cardiopulmonary arrest after being found unresponsive by friends at a high school beach party. In the emergency department (ED), he is unresponsive with no gag reflex. When you attempt to orally intubate the patient, you note gold metallic colorations inside his oral cavity. What else are you immediately concerned about clinically?

a. Airway obstruction from anaphylactic shock
b. Cardiac arrest from ventricular dysrhythmias
c. Sedative hypnotic toxicity and respiratory arrest
d. Toxic alcohol poisoning and acute renal failure
e. Traumatic intracranial hemorrhage

Answer: B. This adolescent has likely abused a hydrocarbon (such as toluene from gold spray paint) for recreational and euphoric reasons. Cardiac arrest could occur from primary asphyxia if they huffed using a bag over their head or possible direct cardiotoxicity from the inhaled hydrocarbon resulting in ventricular dysrhythmias.

Inhaled Toxins

Christopher W. Meaden and Lewis S. Nelson

KEY CONCEPTS

- An asphyxiant is any gas that displaces sufficient oxygen from the breathable air. Treatment consists of removal from exposure, supplemental oxygen, and supportive care.
- Highly water-soluble gases produce rapid irritation and predominantly upper respiratory tract effects, such as airway irritation. Poorly water-soluble gases, like phosgene, often produce delayed lower respiratory tract findings, such as bronchospasm or acute respiratory distress syndrome (ARDS).
- Carbon monoxide (CO) poisoning is confirmed by co-oximetry measurement. Cyanide poisoning is treated empirically when cardiovascular instability (e.g., hypotension), altered mental status, or a serum lactate greater than 10 mmol/L are present in a patient with a concerning history, such as a fire victim.
- Hydroxocobalamin is the preferred antidote for most cyanide-poisoned patients due to its efficacy, ease of use, and safety in patient with concomitant CO poisoning. Sodium thiosulfate may be administered concomitantly and may provide additional benefits.
- Patients with hydrogen sulfide poisoning generally respond to removal from exposure and ventilatory support.
- Normobaric oxygen therapy is sufficient to many patients with CO poisoning, but we recommend consultation with a hyperbaric (HBO) facility, poison control center, or medical toxicologist for consideration of HBO therapy under specific conditions. Indications for consultation and HBO treatment include patients with a carboxyhemoglobin (COHb) greater than 25% in the absence of clinical findings, a COHb greater than 15% or signs of fetal distress in pregnancy, or an elevated COHb level with one or more of the following: syncope, coma, altered mental status, abnormal cerebellar function, or a prolonged CO exposure with minor clinical findings.

Inhalational exposure to systemic toxins can be covert and indolent (as in occupational exposure to irritant photochemical smog) or overt and fulminant. The circumstances of the exposure, the presence of combustion or odors, and the number and condition of victims assist in the management. Despite the array of possible toxic inhalants, identification of a specific inhalant is generally unnecessary because therapy is based primarily on the clinical manifestations (Table 148.1).

SIMPLE ASPHYXIANTS

Foundations

Simple asphyxiants are inert and produce toxicity only by displacement of oxygen and lowering the fraction of inspired oxygen (FiO_2). Exposed patients remain asymptomatic if the FiO_2 is normal. Carbon dioxide and nitrogen are exceptions in that both can produce narcosis at elevated partial pressures, even though their predominant toxicological effect is simple asphyxiation. Since the introduction of catalytic converters, most deaths from the intentional inhalation of automotive exhaust result from simple asphyxiation, due to hypoxia, and not from carbon monoxide (CO) poisoning. Emerging methods of suicide secondary to gas inhalation are the inhalation of helium and charcoal burning.[1]

Clinical Features

Acute effects occur within minutes of the onset of hypoxia and are manifestations of ischemia. A fall in the FiO_2 from normal, 0.21 (i.e., 21%), to 0.15 results in autonomic stimulation (e.g., tachycardia, tachypnea, and dyspnea) and cerebral hypoxia (e.g., ataxia, dizziness, incoordination, and confusion). Dyspnea is not an early finding because hypoxemia is not nearly as potent a stimulus to the medullary respiratory center as are hypercarbia and acidemia. Lethargy from cerebral edema occurs as the FiO_2 falls below 0.1 (10%), and life is difficult to sustain at an FiO_2 below 0.06 (6%). Because removal from exposure terminates the simple asphyxiation and allows restoration of oxygenation and clinical improvement, most patients present with resolving symptoms. Failure to improve suggests complications of ischemia (e.g., seizures, coma, and cardiac arrest) and is associated with a poor prognosis.

Differential Diagnoses

Because the presenting complaints offered by most exposed patients are nonspecific (e.g., dizziness, syncope, and dyspnea), the differential diagnosis is extensive. A consistent history, particularly of a setting in which asphyxia is expected to occur such as in an enclosed space, an appropriate spectrum of complaints and a rapid resolution on removal from exposure are generally sufficient to establish the diagnosis.

Diagnostic Testing

Minimally, symptomatic patients do not require chest radiography or arterial blood gas (ABG) analysis. There is no need for toxicology testing unless the asphyxiation was an act of deliberate self-harm, in which in this case, we recommend selected screening for acetaminophen and any other relevant toxin implicated by history, physical examination, or observation. A definitive diagnosis ultimately requires scene investigation by a trained and suitably outfitted team with personal protective equipment (PPE). Determination of the exact nature of the gas is of limited clinical value but may have important public health implications.

Management

Management rarely requires specific therapy other than removal from exposure, administration of supplemental oxygen, and supportive care. Neurologic injury or cardiorespiratory arrest should be managed with standard advanced cardiac life support (ACLS) resuscitation protocols. Psychiatric consultation is indicated when the exposure was an act of deliberate self-harm.

TABLE 148.1 Common Inhaled Toxins

Inhalant	Source or Use	Predominant Class
Acrolein	Combustion	Irritant, highly soluble
Ammonia	Fertilizer, combustion	Irritant, highly soluble
Carbon dioxide	Fermentation, complete combustion, fire extinguisher	Simple asphyxiant; systemic effects
Carbon monoxide (CO)	Incomplete combustion, methylene chloride	Chemical asphyxiant
Chloramine	Mixed cleaning products (e.g., hypochlorite bleach and ammonia)	Irritant, highly soluble
Chlorine (Cl_2)	Swimming pool disinfectant, cleaning products	Irritant, intermediate solubility
Chlorobenzylidene malononitrile (CS), chloroacetophenone (CN)	Tear gas (Mace)	Pharmacologic irritant
Hydrogen chloride	Tanning and electroplating industry	Irritant, highly soluble
Hydrogen cyanide	Combustion of plastics, acidification of cyanide salts	Chemical asphyxiant
Hydrogen fluoride	Hydrofluoric acid	Irritant, highly soluble; systemic effects
Hydrogen sulfide	Decaying organic matter, oil industry, mines, asphalt	Chemical asphyxiant; irritant, highly soluble
Methane	Natural gas, swamp gas	Simple asphyxiant
Methylbromide	Fumigant	Chemical asphyxiant
Nitrogen	Mines, scuba diving (nitrogen narcosis, decompression sickness)	Simple asphyxiant; systemic effects
Nitrous oxide	Inhalant of abuse, whipping cream, racing fuel booster	Simple asphyxiant
Noble gases (e.g., helium)	Industry, laboratories	Simple asphyxiant
Oxides of nitrogen	Silos, anesthetics, combustion	Irritant, intermediate solubility
Oxygen	Medical use, hyperbaric conditions	Irritant, free radical; systemic effects
Ozone	Electrostatic energy	Irritant, free radical
Phosgene	Combustion of chlorinated hydrocarbons	Irritant, poorly soluble
Phosphine	Hydration of aluminum or zinc phosphide (fumigants)	Chemical asphyxiant
Smoke (varying composition)	Combustion	Variable, but may include all classes
Sulfur dioxide	Photochemical smog (fossil fuels)	Irritant, highly soluble

Disposition

Patients with manifestations of mild asphyxia, who recover after removal from the exposure can be discharged after 6 hours of observation if they are asymptomatic or minimally symptomatic with improvements. Patients at risk for complications of hypoxia, such as those presenting with significant signs or symptoms (e.g., altered mental status, coma, chest pain, electrocardiogram [ECG] changes) or with exacerbating medical conditions (e.g., cardiac disease, asthma), should be observed for 24 to 48 hours for the development or progression of post-hypoxic complications.

PULMONARY IRRITANTS

Foundations

The pulmonary irritant gases are a large and diverse group of agents that produce a common toxicological syndrome when they are inhaled in moderate concentrations. Although many of these gases can be found in the home, significant poisoning from consumer products is uncommon because of restrictions designed to reduce their toxicity. However, catastrophes such as the 1984 release of methyl isocyanate in Bhopal, India, which resulted in more than 2000 fatalities and 250,000 injuries, remain as an environmental risk. On a different scale, industrialization has increased ambient concentrations of sulfur dioxide, ozone, and oxides of nitrogen. These irritant gases frequently exacerbate chronic pulmonary disease.

Irritant gases dissolve in the respiratory tract mucus and alter the air-lung interface by invoking an irritant, or inflammatory response.[2] When these gases are dissolved, most of them produce an acid or alkaline product, but several generate oxygen-derived free radicals that produce direct cellular toxicity (Fig. 148.1). The clinical effects of pulmonary irritants can be predicted by their water solubility (see Table 148.1).

Clinical Features

Highly, water-soluble gases rapidly impact the mucous membranes of the eyes and upper airway causing lacrimation, cough and nasal burning. Although their pungent odor and rapid onset of symptoms tend to limit significant exposure, massive or prolonged exposure can result in life-threatening laryngeal edema, laryngospasm, bronchospasm, or acute respiratory distress syndrome (ARDS). In contrast, because poorly water-soluble gases do not readily irritate the mucous membranes at low concentrations and some have a pleasant odor (e.g., phosgene's odor is similar to that of newly mown hay or freshly cut grass), prolonged breathing in the toxic environment allows time for the gas to reach deep into the alveoli. Even moderate exposure causes delayed irritation of the lower airway, alveoli, and parenchyma 2- to 24-hour after exposure. Initial effects may be mild, only to progress to overt respiratory failure and delayed ARDS during the ensuing 24 to 36 hours.[3] Gases with intermediate water solubility tend to produce syndromes that are a composite of the clinical features manifested with the other gases, depending on the extent of exposure. Massive exposure is most often associated with rapid onset of upper airway irritation and more moderate exposure with delayed onset of lower airway symptoms.

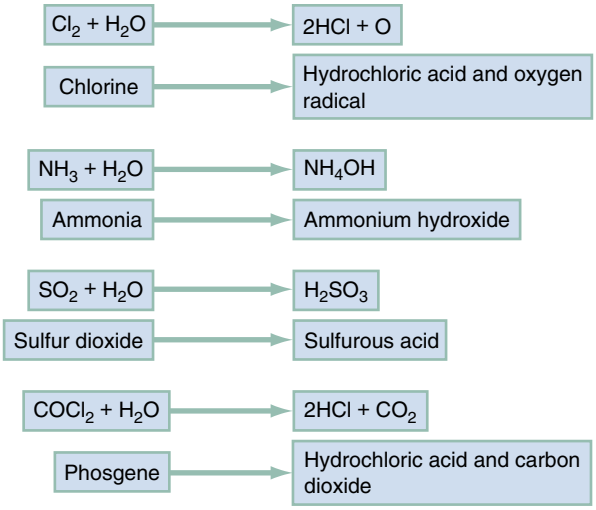

Fig. 148.1 Sample Reactions of Pulmonary Irritants Reacting With Water in the Lung. *Cl_2,* Chlorine; *CO_2,* carbon dioxide; *$CoCl_2$,* cobalt (II) chloride; *H_2O,* water; *H_2SO_3,* sulfurous acid; *HCl,* hydrochloric acid; *NH_3,* ammonia; *NH_4OH,* ammonium hydroxide; *O,* oxygen; *SO_2,* sulfur dioxide.

Differential Diagnoses

The typical symptoms of pulmonary exposure to an irritant gas are bronchospasm, cough, chest tightness, and acute conjunctival irritation. Presentation may mimic non-toxicological causes of pulmonary disease, but the history generally confirms the exposure to the irritant (Box 148.1). History may be particularly important if the patient presents with severe or advanced findings, such as ARDS, which can occur after many physiologic insults, including trauma and sepsis.

Diagnostic Testing

Inhalation of respiratory irritants may affect the upper airway, the lower airways and lungs, or both. Upper airway evaluation proceeds as described in the following Management section. Radiographic and laboratory studies are not useful in the evaluation of upper airway symptoms.

Oxygenation and ventilation are assessed by serial chest auscultation, pulse oximetry, and continuous capnography. Chest radiography is indicated for patients presenting with cough, dyspnea, hypoxia, or abnormal findings, such as rales or wheezes, on pulmonary examination. ABGs are reserved for patients who are more severely symptomatic, have hypoxia, or do not improve readily with oxygen therapy.

In general, it is neither possible nor necessary to test for the specific agent. There are no clinical tests that will differentiate the irritant to which a patient was exposed, although testing at the site by public health authorities may be performed for epidemiologic purposes. Knowing that an agent is highly water soluble will shorten the observation period for symptom development, whereas patients exposed to poorly water-soluble agents will require a more prolonged period of observation.

Management

Patients with no upper airway symptoms, normal voice, and no evidence of irritation (erythema) or burns on examination of the oral pharynx require no further upper airway evaluation but should be reexamined if symptoms or signs develop after the initial evaluation. Those with evidence of tissue irritation, such as oral or tongue edema, altered voice (raspy or muffled), stridor, or significant odynophagia or dysphagia require early examination by laryngoscopy and if severe, should undergo early intubation because rapid progression of these injuries is expected. Laryngoscopy may be performed using a flexible laryngoscope, rigid video, or conventional laryngoscope with appropriate topical anesthesia and sedation as indicated (see Chapter 1). Patients with evidence of mild irritation of the larynx or supralaryngeal area (erythema, no edema, normal glottis) may be observed. Those with more severe findings are considered not to require early intubation, such as erythema with mild edema, should undergo repeat examination from 30 to 90 minutes after the initial examination or earlier, if symptoms or signs are worsening.

Bronchospasm generally respond to inhaled beta-adrenergic agonists. Data regarding the use of corticosteroids are limited and do not support clinical benefits in humans. Therefore, corticosteroids are not recommended unless the patient has underlying reactive airways disease.[3–5]

Patients exposed to chlorine or hydrogen chloride gas receive symptomatic relief from nebulized 2% sodium bicarbonate solution.[6] This solution is prepared by diluting a given volume of standard 8.4% sodium bicarbonate solution with three equivalent volumes of sterile water and administering it in 3 to 5 mL aliquots with standard nebulizer equipment. There are no studies on the recommended dosing regimen, but if successful after its first use, providing it every 30 minutes as needed for symptom relief, for up to 6 hours, is a reasonable approach. Nebulized bicarbonate will not alter the inflammatory cascade so it will not have significant effect on the progression of pulmonary injury. ARDS, if identified, is managed as described in Chapter 2.

BOX 148.1 Differential Diagnoses for Pulmonary Irritant Exposure

1. Acute respiratory distress syndrome
2. Congestive heart failure
3. Pulmonary embolism
4. Pneumonitis (e.g., aspiration, chemical, viral)
5. Asthma exacerbation
6. Metal fume fever
7. Inorganic dust exposure
8. Chronic obstructive pulmonary disease exacerbation
9. Allergic response/hypersensitivity pneumonitis

Disposition

Patients exposed to highly water-soluble gases (see Table 148.1) can be discharged if they are asymptomatic or symptoms are minimal and improving. After exposure to intermediate or poorly water-soluble gases, asymptomatic patients should be observed for increasing dyspnea for 6 hours before final disposition. Regardless of the solubility, patients with prolonged gas exposure, exposure to highly concentrated gases, exposure in a closed space or those with high-risk medical conditions (e.g., underlying pulmonary disease, extremes of age, and poor follow-up) should be observed in an inpatient setting or observation unit for 24 hours. Patients with upper airway findings on examination should be observed in the emergency department (ED) or an intensive care unit (ICU) until there is clear evidence that the process is subsiding. All discharged patients should receive instructions for signs and symptoms of pulmonary deterioration.

SMOKE INHALATION

Foundations

According to a 2019 report by the National Fire Protection Association, an average of 2,620 deaths and 11,220 injuries occur per year in residential fires in the United States.[6] Many of these casualties do not

suffer serious cutaneous burns but rather die of smoke inhalation. This is a variant of irritant injury in which heated particulate matter and adsorbed toxins injure normal mucosa. In addition, CO and cyanide are systemic toxins often considered in conjunction with the smoke inhalation syndrome because of their common origin.

Even at temperatures between 350°C and 500°C, air has such a low heat capacity that it rarely produces lower airway damage. The greater heat capacity of steam (approximately 4000 times than that of air), or heated soot suspended in air (i.e., smoke) can transfer heat and cause injury deep within the respiratory tract.

The nature of the fuel determines the composition of its smoke, and because fires involve variable fuels and burning conditions, the character of fire smoke is often undefined to the emergency clinician. Irritant toxins produced by the fire are adsorbed onto carbonaceous particles that are deposited in the airways and damage the mucosa through mechanisms similar to those of the irritant gases.

Clinical Features

Thermal and irritant-induced laryngeal injury may produce cough, voice alteration, or stridor, but these findings are often delayed. Soot and irritant toxins in the airways can produce early cough, dyspnea, and bronchospasm. Subsequently, a cascade of airway inflammation results in ARDS with failure of pulmonary gas exchange. The time between smoke exposure and the onset of clinical symptoms is highly variable and dependent on the nature of the exposure. Deaths that occur rapidly after exposure are caused by asphyxia, airway compromise, or metabolic poisoning (e.g., CO and cyanide). Singed nasal hairs and soot in the sputum suggest substantial exposure, but significant exposure and injury can occur with neither of these being present.

Differential Diagnoses

With the obvious exposure history to smoke inhalation, the differential diagnosis is limited, however, cyanide and carbon monoxide should always be considered as discussed below. Although it is often unclear whether smoke inhalational injuries are thermal or irritant, the differentiation is clinically irrelevant, as the management approach remains the same. Concomitant physical injuries such as "burns" or trauma may complicate the metabolic picture.

Diagnostic Testing

Airway patency should be evaluated early. Airway management is as described earlier for inhaled pulmonary irritants. If evidence of significant airway exposure is present, such as carbonaceous sputum or a hoarse voice, the airway should be examined by laryngoscopy and secured if signs of injury or compromise are noted. Pulmonary injury is assessed through auscultation and chest radiography for signs of alveolar filling or hyperinflation. Oxygenation should be assessed by co-oximetry, because blood gas analysis and pulse oximetry may be inaccurate in CO-poisoned patients (see discussion in the Carbon Monoxide section later). Co-oximetry will provide a blood carboxyhemoglobin (COHb) level, and we recommend testing for every patient, unless the smoke exposure was brief and in an open space. Metabolic acidosis, particularly when serum lactate concentration is greater than 8 mmol/L and the COHb is not significantly elevated, suggests concomitant cyanide poisoning.[7]

Management

The acute management of a patient with smoke inhalation, is identical to that with other irritant inhalational injuries. Early assessment of the airway and early intubation, as indicated, are critical because deterioration may be occult and rapid. Patients with no upper airway symptoms, normal oropharyngeal, nasopharyngeal examination, no voice alteration, and normal swallowing, may be observed and reevaluated if symptoms develop. Patients with symptoms or findings should be evaluated early stage by laryngoscopy. Simply observing these patients for deterioration can result in airway compromise requiring rapid and potentially difficult airway intervention. Despite a lack of evidence supporting their effectiveness, inhaled beta-adrenergics are widely used for patients with dyspnea or wheezing. Because these agents may provide benefit with little likelihood of harm, we recommend at least one dose of a beta-adrenergic agonist for patients with symptoms of bronchospasm. Both subjective (patient-reported) and objective (respirometry) assessment may be used to determine whether these agents appear to benefit a particular patient, and guide the use of additional doses. Optimal supportive care and maintenance of adequate oxygenation (e.g., suctioning and pulmonary toilet) are the most important aspects of care. Bronchoscopy with bronchoalveolar lavage is frequently recommended to clear debris and toxins from the distal airways. We do not recommend the use of corticosteroids, by inhalation or systemically, because there is no evidence of clinical benefit and they are potentially harmful in patients with cutaneous burns. Ibuprofen, antioxidants, exogenous surfactant, and high-frequency ventilation yield, variably improved survival in experimental and clinical trials but none are considered as standard care.[8] Antibiotics should be used only in patients with suspected bacterial infection.

Disposition

Patients who are intubated should be admitted to the ICU or burn unit, depending on the extent of the cutaneous burns or respiratory tract injury. Patients with upper airway symptoms or signs, but without concerns for airway loss, should undergo repeat airway examination for 6 hours, preferably in an ICU. Patients with prolonged closed-space exposure or lower airway findings, such as rales or carbonaceous sputum, should be admitted to an ICU, and observed for at least 24 hours while assessing for the development of signs of lower respiratory tract injury. Transfer considerations to a higher level of care at another institution or to a burn center should be based on local resources, consultation with the specialty center, an assessment of the risks of transfer, and existing protocols. Patients that should be considered for transfer include those with burns greater than 10 percent body surface area, burns that involve the face, hands, genitalia, perineum, or major joints, and those with third degree burns. See Chapter 54 for further discussion.

CYANIDE AND HYDROGEN SULFIDE

Foundations

Instead of directly affecting the airway and lungs, these poisons cause effects at the cellular level. Hydrogen cyanide is a gas with many commercial uses, particularly in synthetic fiber manufacture and fumigation. Gaseous hydrogen cyanide is occasionally noted to have the odor of bitter almonds. Cyanide in its salt form (e.g., sodium or potassium) is important in metallurgy (e.g., jewelry) and photography and is much safer to work with because of its low volatility. When cyanide salts are dissolved in water, hydrogen cyanide, a gas, can be produced, particularly under acidic conditions. Cyanide is metabolically released *in vivo* from precursors (cyanogens) such as amygdalin, found in apricot and other *Prunus* species pits, and from nitriles, a group of chemicals with many commercial uses.

H_2S poisoning most often occurs in petroleum refinery and sewage storage tank workers. A more recent means of suicide involves generation of H_2S from sulfur-containing products, such as detergent, mixed with acids in an enclosed space, such as an automobile.[9] On occasion, well-intentioned but ill-prepared pre-hospital rescuers become victims

emphasizing the need for proper training and equipment. H_2S has a noxious odor similar to that of a rotten egg, which becomes unnoticeable with extremely high concentrations or prolonged exposure (a process called "olfactory fatigue").

Gaseous cyanide is rapidly absorbed after inhalation and is immediately distributed to the body tissues. Inhibition of oxidative metabolism by binding to cytochrome c oxidase (or Complex IV) of the electron transport chain within the mitochondria which occurs within some seconds. The poisoned tissue rapidly depletes its adenosine triphosphate (ATP) reserves and ceases to function (Fig. 148.2). Cyanide has no evident effect on other oxygen-binding enzyme systems, most notably hemoglobin. This is probably explained by the oxidation state of its iron moiety; cyanide binds only to oxidized iron (Fe^{3+}), whereas deoxyhemoglobin contains reduced iron (Fe^{2+}).

H_2S exerts its toxic effects both as a pulmonary irritant, and as a cellular poison. Its deadly metabolic effects are produced by a mechanism identical to that of cyanide.[10] However, H_2S's spontaneous dissociation from the mitochondria is rapid, allowing most patients to survive after brief exposure.

Clinical Features

Tissue hypoxia occurs within minutes, with the exact onset dependent on the route, dose or concentration, and nature of the exposure. Dysfunction of the heart and the central nervous system that is the organ systems most sensitive to hypoxia and it is a characteristic of cyanide poisoning, manifested as coma, seizures, dysrhythmias, and cardiovascular collapse. Metabolic acidosis develops as a result of diffuse cellular dysfunction and this is associated with an elevated serum lactate concentration. Despite popular belief, cyanosis is not a characteristic clinical finding. Given the extreme toxicity of cyanide, mild acute poisoning is uncommon. Patients with acute H_2S poisoning have similar clinical manifestations, although generally recover by the time of arrival to the ED due to its spontaneous mitochondrial dissociation.

Because cyanide and H_2S prevent tissue extraction of oxygen from the blood, the oxygen content of venous blood remains high, approaching that of arterial blood. Clinically, this may appear as the "arterialization" or brightening of venous blood to resemble arterial blood. A comparison of the measured (by co-oximetry) venous and arterial oxygen contents may assist in the diagnosis of cyanide poisoning. A

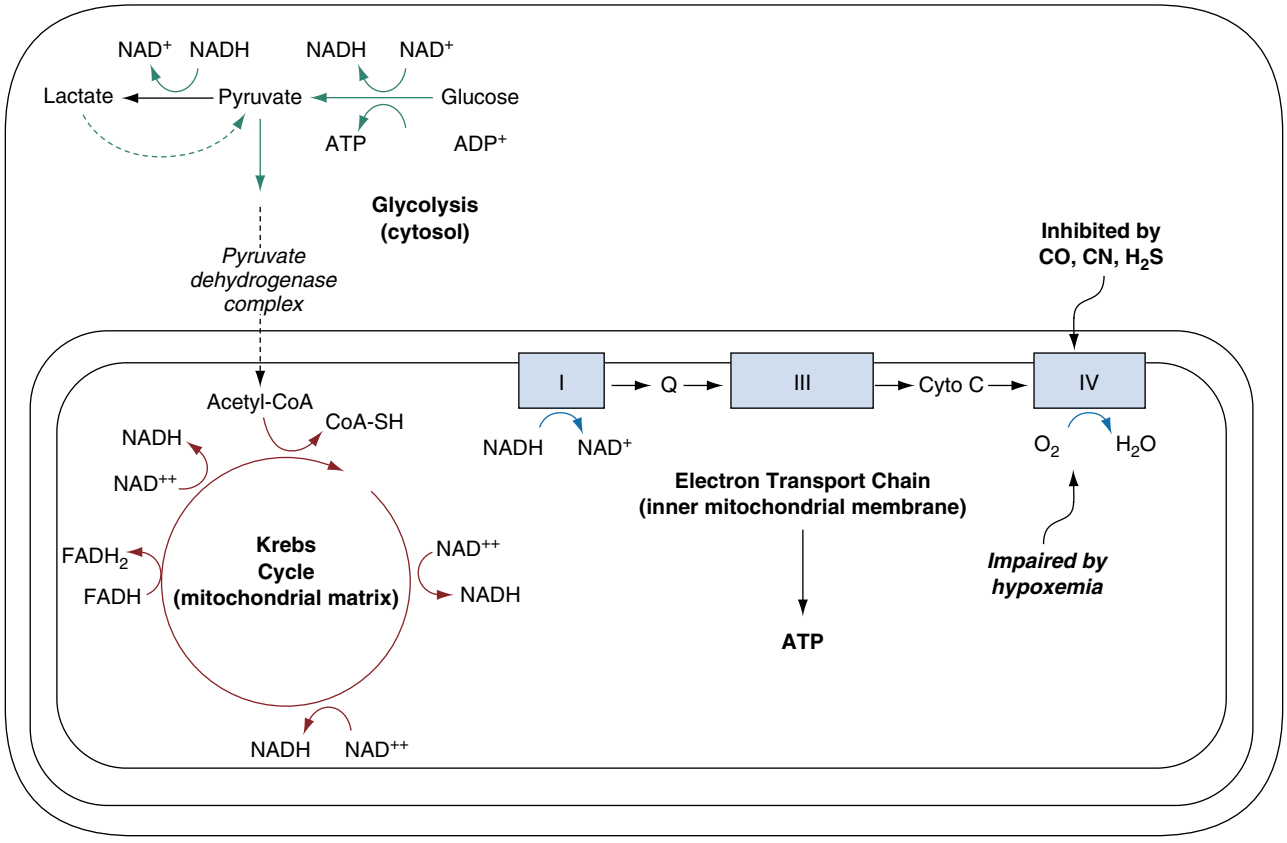

Fig. 148.2 The Complete Metabolism of a Molecule of Glucose to Energy Is Complex but Occurs in Two Broad Steps. The first step, anaerobic glycolysis, which occurs in the absence of oxygen, generates pyruvate, nicotinamide adenine dinucleotide *(NADH),* and adenosine triphosphate *(ATP).* Pyruvate then enters the Krebs cycle to create potential energy in the second step, through the reduction of NAD^+ to NADH and flavin adenine dinucleotide *(FADH)* to $FADH_2$. Fatty acid metabolism and protein metabolism produce $FADH_2$ and NADH, which also requires conversion to ATP. These conversions occur in the mitochondrial membrane, where oxidative phosphorylation is linked to the electron transport chain, the last phase of which involves the transfer of electrons to molecular oxygen to form water. Cyanide *(CN),* hydrogen sulfide *(H_2S),* and carbon monoxide *(CO)* bind to and inhibit the last step, the Fe^{3+}-containing cytochrome-aa_3 oxidase in Complex IV, preventing further oxidation of NADH. This in turn hinders the Krebs cycle because the required regeneration of NAD^+ does not occur, and glucose metabolism is forced to end at pyruvate. For energy production to continue, NADH donates its electrons to pyruvate, creating lactate, and sufficient NAD^+ is regenerated for glycolysis to progress. Ultimately, energy failure and end-organ damage occur. *CoA,* Coenzyme A; *H_2O,* water; *IV,* intravenous; *O_2,* oxygen.

low arterial-venous oxygen difference is suggestive, but not pathognomonic of cyanide poisoning and its absence does not exclude the diagnosis.

Patients surviving cyanide or H_2S poisoning may have persistent or delayed-onset neurologic syndromes identical to those noted in patients with CO poisoning or post-cardiac arrest.

Differential Diagnoses

Rapid cardiovascular collapse, hypotension, bradycardia, ventricular dysrhythmias, and seizures in a fire victim should suggest profound hypoxia, cyanide poisoning, severe CO poisoning, or a combination.[11] In patients without an exposure history, the differential diagnosis is vast and includes CO poisoning, asphyxiants, and other toxicologic and non-toxicologic causes.

Diagnostic Testing

Unlike with CO poisoning, pulse oximetry and ABG analysis are accurate in cases of isolated cyanide or H_2S poisoning. An increased anion gap metabolic acidosis and hyperlactatemia are usually present. A lactate concentration greater than 8 mmol/L is highly predictive of cyanide poisoning in the appropriate clinical context.[6,12] CO and cyanide are fellow travelers, so an elevated COHb level in a fire victim warrants consideration of concomitant cyanide poisoning. The presence of severe clinical findings and metabolic acidosis with a low COHb level is particularly concerning for cyanide poisoning. The result of a blood cyanide determination is usually delayed, to be of use in the ED, but it can be useful for confirmation and documentation purposes. Technology exists for immediate cyanide determination but is not widely available. Testing for H_2S is not clinically available, and support for the diagnosis of H_2S exposure would come primarily from on-scene testing.

Management

The diagnosis of cyanide poisoning usually cannot be confirmed rapidly, and therapy is almost always empirical. Treatment should not be delayed pending the COHb level or other laboratory tests in patients with suspected acute cyanide poisoning. Patients removed from a fire environment who have cardiovascular instability, altered mental status, or a serum lactate greater than 8 mmol/L should receive cyanide treatment regardless of the COHb concentration.

Hydrogen Cyanide

The accepted goal of therapy is to reactivate the cytochrome oxidase system by providing an alternative binding site for the cyanide ion. There are two types of antidotal therapy for cyanide. The preferred antidote is hydroxocobalamin, which takes advantage of the high affinity of cobalt for cyanide. On binding of cyanide, cyanocobalamin, or vitamin B_{12}, is formed. The initial dose is 5 g intravenously (IV) over 15 minutes for adults and 70 mg/kg IV for children, up to an adult dose, and can be repeated once if an incomplete response is noted. Thiosulfate, 12.5 g in adults (250 mg/kg in children), can be considered in combination with hydroxocobalamin (via a separate IV line) in severe cases of cyanide toxicity, but the benefit of this is not well established. The known adverse effects of hydroxocobalamin are mild and include hypertension in those not cyanide poisoned and a bright red discoloration of the patient's skin and urine. Inexperienced clinicians often mistake this side effect as an "allergic" reaction to the drug. The drug's red color can interfere with certain spectrophotometric laboratory tests, including COHb and possibly serum lactate. Therefore, blood samples should be obtained before the administration of the first dose of hydroxocobalamin.

The cyanide antidote kit, an alternative therapy for toxicity, contains three components (amyl nitrite, sodium nitrite, and sodium thiosulfate). The cyanide antidote kit produces a high-affinity source of ferric ions (Fe^{3+}) for cyanide to bind. Its administration can be impractical or dangerous, particularly for nonhospital providers due to the means by which it is administered (i.e., amyl nitrite capsules are crushed between the fingers and placed under the victim's nose and may be inadvertently inhaled by rescuers). Because animal models and clinical evidence in humans demonstrate that sodium thiosulfate alone in combination with oxygen offers substantial protection, this should be the initial therapy administered by paramedics and during mass poisoning events if ample supplies of hydroxocobalamin are not available. Antidotes should not completely replace other resuscitation measures, including high-flow oxygen and removal of the patient from the source of exposure.

Methemoglobin (MetHb) formation results from the nitrites found in the kit. Inhaled amyl nitrite and IV sodium nitrite are both effective, but amyl nitrite should only be administered to patients in the absence of IV access. Caution should be taken to minimize the provider's exposure to the volatile amyl nitrite because dizziness, hypotension, or syncope may occur. The dose of sodium nitrite for a previously healthy adult is 300 mg (10 mL of a 3% solution) given over 2 to 4 minutes. Dosing instructions for anemic patients and children are supplied with the kit. Cyanide has a high affinity for MetHb and readily leaves cytochrome oxidase to form cyanmethemoglobin, which is metabolically inactive. Additionally, the nitrites are vasodilators, and this may be mechanistically important in their therapeutic effect by enhancing blood flow to the liver for clearance. However, hypotension may complicate a rapid infusion.

Both free serum cyanide and cyanmethemoglobin are converted by sulfur transferase (rhodanese) to thiocyanate, which is renally eliminated. Because the rate of rhodanese function increases with the availability of a sulfur donor, the third component of the antidote kit is the sulfur-containing compound sodium thiosulfate. The adult dose is 12.5 g IV, which is provided as 50 mL of a 25% solution (250 mg/kg sodium thiosulfate up to an adult dose in children). In general, few if any adverse effects are associated with proper doses. The nitrite components of the cyanide antidote kit should be avoided in fire victims with known or suspected simultaneous CO and cyanide poisoning because both CO and MetHb reduce oxygen delivery to the tissues. The use of the thiosulfate component alone in this subset of patients is recommended if hydroxocobalamin is not available (Box 148.2).

There are insufficient clinical data to fully support the use of one cyanide antidote over the other. We recommend hydroxocobalamin because of its ease of use and presumed superior safety in CO-poisoned fire victims.[12] Direct comparison to thiosulfate alone in this population has not been and likely never will be performed, but animal models and case reports suggest that hydroxocobalamin is superior.[13] When possible, we recommend administering both hydroxocobalamin and thiosulfate, with the priority given to hydroxocobalamin, and not administering them through the same IV due to incompatibility.[14]

Hydrogen Sulfide

Because the bond between H_2S and cytochrome oxidase is rapidly reversible, removal from exposure and standard resuscitative techniques are usually sufficient to reverse H_2S toxicity. Use of the nitrite portion of the cyanide antidote kit is suggested to create MetHb for patients with severe or prolonged toxicity. Sodium thiosulfate is unnecessary because H_2S is not detoxified by rhodanese. Hydroxocobalamin also binds sulfide, and has been shown to decrease sulfide concentrations, but has not been shown to be clinically effective for H_2S poisoning. There is no defined role for hyperbaric oxygen (HBO) therapy in cases of H_2S toxicity.

BOX 148.2 Cyanide Antidotes

Hydroxocobalamin[a]
Adults: 5 g IV over 15 min[b]
Children: 70 mg/kg up to 5 g[b]

Cyanide Antidote Kit (Two Parts)
1. MetHb inducers[c]
   Amyl nitrite (inhalational, prehospital) *or*
   Sodium nitrite ($NaNO_2$) 3% solution IV over 2–4 min IV
      Adults: 10 mL (300 mg)
      Children: See labeling information with kit
2. Cyanide detoxification
   Sodium thiosulfate ($Na_2S_2O_3$) 25% solution IV
      Adults: 50 mL (12.5 g)
      Children: 250 mg/kg up to 12.5 g

[a] Thiosulfate (see text) can be concomitantly administered for patients with severe clinical effects.
[b] A second dose may be administered in patients with an incomplete response.
[c] Withhold nitrites if an elevated blood carboxyhemoglobin (COHb) is suspected to be present (e.g., fire victims).
IV, Intravenous; *MetHb,* methemoglobin.

Disposition

Patients with symptomatic cyanide or H_2S poisoning should be admitted to a critical care unit and observed for complications of tissue hypoxia. These patients should also be evaluated for delayed neuropsychiatric findings.

CARBON MONOXIDE

Foundations

CO remains a common cause of morbidity and mortality worldwide with an estimated incidence of 137 cases per million annually.[15] CO is generated through incomplete combustion of virtually all carbon-containing products. Structure fires (e.g., wood), clogged vents for home heating units (e.g., methane), and use of gasoline-powered generators indoors are examples of the myriad means through which patients are poisoned by CO. Appropriate public health authorities (e.g., fire department and Department of Health officials) should be informed immediately about any potential public health risks that are identified during the care of a CO-exposed patient.

CO interacts with deoxyhemoglobin to form COHb, which cannot carry oxygen. Hemoglobin binds CO tightly and forms a complex that is only slowly reversible. This allows the exposed individual to accumulate CO, even with exposure to low ambient concentrations. Although binding of hemoglobin is historically described as the mechanism of CO poisoning, it is relevant only in profoundly CO-poisoned patients because a simple reduction in oxygen-carrying capacity due, for example, to anemia would not cause similar symptoms. However, for pregnant patients, the fetus is at increased risk because it is relatively hypoxic compared with the mother. CO shifts the oxyhemoglobin dissociation curve to the left in such a way that even if oxygen is bound to hemoglobin, its unloading to tissues is impaired. In muscle, CO binds myoglobin, preventing its normal function. This likely contributes to the development of atraumatic rhabdomyolysis.

CO affects cellular oxygen use at the tissue level. Similar to cyanide, it inhibits the final cytochrome complex involved in mitochondrial oxidative phosphorylation. This results in a switch to anaerobic metabolism and ultimately in cellular death.

Delayed-onset neurologic complications may be a manifestation of the hypoxic insult, and reperfusion injury and lipid peroxidation related to platelet-induced nitric oxide release may play a significant role.[16] By alteration of the platelet-associated nitric oxide cycle, the microvascular endothelium of the central nervous system undergoes free radical–mediated injury, resulting in localized inflammation and dysfunction. Animal models and human reports suggest that loss of consciousness during CO exposure is a risk factor for the development of delayed neurologic sequelae.

Clinical Features

Severe CO toxicity and cyanide poisoning have identical clinical presentations of chemical asphyxia: altered mental status, including coma and seizures; unstable vital signs, including hypotension and cardiac arrest; and metabolic acidosis. Unlike cyanide poisoning, however, mild CO poisoning occurs frequently, with headache, nausea, vomiting, dizziness, myalgia, and confusion as common presenting complaints. The neurological assessment in these patients may yield normal findings or may demonstrate focal findings or subtle perceptual abnormalities. The often-touted "cherry-red" skin color in patients with cyanide or CO poisoning is a postmortem finding and is not noted in living patients.

Delayed neurologic sequelae is a well-documented phenomenon after CO exposure; the frequency varies from 10% to 30%, depending on the definition and the sensitivity of the test used for their detection. Patients have a variety of neurologic abnormalities after an asymptomatic period, ranging from 3 to 240 days.[17] The delayed neurologic effects can be divided into those with readily identifiable neurologic syndromes (e.g., focal deficits and seizures) and those with primarily psychiatric or cognitive findings (e.g., apathy and memory deficits). Although the delayed neuropsychiatric sequelae require formal neuropsychiatric testing to be detected, the impact of these abnormalities on the patient's daily function may be significant. Risk factors that predict the development of delayed neurologic sequelae include extremes of age and loss of consciousness. Because most CO-poisoned patients reaching the ED survive with minimal intervention, prevention of delayed neurologic and neuropsychiatric sequelae is a major goal of therapy.

Differential Diagnoses

Mild-to-moderate CO poisoning is a difficult diagnosis to establish clinically, and patients are easily misdiagnosed as having a benign headache syndrome or viral illness. CO poisoning should be suspected in patients with persistent or recurrent headache, especially if a group of people have similar symptoms or if the headache improves soon after the person leaves an exposure site.

Patients with severe CO poisoning may present with coma or cardiovascular collapse, both of which have a broad toxicologic, metabolic, infectious, medical, and traumatic differential diagnosis. The medical history, physical examination, and standard laboratory testing are easily able to exclude many of these diagnoses. Given the relatively protean manifestations of CO poisoning and the potentially serious consequences of misdiagnosis, particularly if the patient returns to the contaminated environment, we recommend specific measurement of CO by co-oximetry of an arterial or venous blood sample when the clinician considers CO poisoning as a possible cause for the patient's presentation.

Diagnostic Testing

Suspicion of CO poisoning relies on the history and physical examination findings. Co-oximetry, an inexpensive and readily available spectrophotometric laboratory method that can distinguish between normal hemoglobin, COHb, and MetHb, confirms exposure to CO.

Other laboratory tests only exclude other diagnoses. Severity of poisoning may not correlate with COHb levels because prolonged exposure to low levels can be fatal with a low measured COHb, but a brief, high-concentration exposure can produce a high COHb level with minimal symptoms.

The standard blood gas (ABG or venous blood gas [VBG]) analysis is a poor screening test for CO poisoning other than to identify the presence of a metabolic acidosis and a normal partial pressure of oxygen (Po_2). CO impairs binding of oxygen to hemoglobin but does not affect the amount of oxygen dissolved in blood. Because the Po_2 is a measure of dissolved oxygen, it is normal in patients with CO poisoning. The calculated oxygen saturation will be normal even in the presence of significant CO poisoning. Most pulse oximeters are unable to identify CO poisoning because COHb is misinterpreted as oxyhemoglobin. Newer pulse co-oximeters are capable of noninvasively detecting COHb as well as methemoglobinemia.[18]

Management

Treatment begins with oxygen therapy, which serves two purposes. First, the half-life of COHb is inversely related to the Po_2; it can be reduced from approximately 5 hours at room air to 1 hour by providing supplemental 100% oxygen. HBO therapy (at 3 atmospheres) further reduces the half-life to approximately 30 minutes. Alteration of the kinetics of COHb is relevant only to patients with extremely elevated COHb levels (e.g., over 50%). Even then, only a minority of patients can be treated sufficiently and rapidly enough for HBO to be lifesaving. A sufficient Po_2 can be achieved with HBO to sustain life in the absence of adequately functioning hemoglobin, but this is helpful only when the COHb is extremely elevated. Thus, the primary indication for HBO is not to prevent mortality but rather to prevent delayed neurologic sequelae.

There is controversy regarding the benefit of HBO because the effect is not immediate (as with life and death) and outcome assessment requires close follow-up and sophisticated testing. Several evidence-based reviews have asserted the limited role for HBO, although this conclusion is disputed.[17] Evidence suggests that HBO helps prevent the development of delayed neuropsychiatric and neurologic sequelae after CO poisoning, with a decrease of delayed neurologic sequelae from approximately 12% to less than 1% with its use. When HBO administration is delayed for more than 6 hours after exposure, its efficacy appears to decrease, suggesting the need for rapid implementation. A meta-analysis performed on randomized controlled trials showed a lower risk of impaired memory in patients who received HBO versus those who did not. The meta-analysis also revealed that HBO treated patients had an improvement in their neuropsycholic scores of block design and trail making when compared to patients treated with normobaric oxygen.[19]

Given the implications of poor tissue oxygenation with COHb and the relative safety of HBO, a patient with a neurologic abnormality or cardiovascular instability (e.g., syncope, altered mental status, seizures, myocardial ischemia, and dysrhythmias) is a candidate for HBO (Box 148.3). This should be tempered by the need for transport, often over long distances, for HBO therapy to be obtained. The decision about HBO therapy should not be strictly based on the COHb level, which correlates only weakly with poisoning. Patients with prolonged low-level exposure have a "soaking" phenomenon, in which extremely high tissue concentrations of CO occur with relatively low COHb levels. Thus, patients with consequential clinical findings that are considered to be related to CO poisoning should receive HBO despite relatively low COHb levels.

In addition to the use of HBO in patients with obvious signs of tissue hypoxia or syncope, we recommend referral for HBO for asymptomatic patients with a COHb level of 25% or greater. The decision to perform HBO therapy should be made in the context of transport and other medical requirements, including need for transfer to a burn center which may delay or prevent HBO therapy unless implemented at the burn center. If doubt remains, consultation with a medical toxicologist, poison center, or the HBO treatment specialist will guide decision-making. Because fetal CO poisoning is associated with dysfunction and death and HBO therapy appears to be safe in pregnancy, we recommend HBO therapy in a pregnant woman with a COHb level of 15% or greater regardless of symptoms. Further study is still needed to define the optimal duration, pressure, and frequency, as well as the cost-benefit and risk-benefit relationships of HBO therapy. At this time, discussion with a regional HBO center or poison control center is advisable. Patients with elevated COHb levels who do not require HBO should be treated with normobaric oxygen delivered by a tight-fitting non-rebreather face mask at a flow rate of 15L/min until the symptoms resolve and the COHb levels fall to normal.

BOX 148.3 Recommendations for Hyperbaric Oxygen

Carboxyhemoglobin (COHb) (varies by local standards) independent of clinical findings
- >25% with normal clinical findings
- >15% in pregnancy or fetal distress

or an elevated COHb with one or more of the following findings:
- Syncope
- Coma
- Seizure
- Altered mental status (GCS < 15) or confusion
- Abnormal cerebellar function
- Prolonged CO exposure with minor clinical findings ("soaking")

CO, Carbon monoxide; *GCS,* Glasgow Coma Score.

Simultaneous Carbon Monoxide and Cyanide Poisoning (Fire Victims)

Concurrent toxicity from CO and cyanide is widely reported and a major factor in the mortality associated with smoke inhalation.[20] Victims who present with coma and metabolic acidosis can have severe CO poisoning, cyanide poisoning, or both. Nitrite-induced methemoglobinemia, which further reduces the tissue oxygen delivery, may be detrimental to patients with elevated COHb levels or otherwise impaired oxygen delivery.

Sodium thiosulfate, administered without nitrites, or hydroxocobalamin should be given to all smoke inhalation victims with coma, hypotension, severe acidosis, or cardiovascular collapse in whom cyanide poisoning cannot be rapidly excluded.

Disposition

The decision to transfer a patient to an HBO facility should consider the time delay to therapy, patient issues (e.g., hemodynamic instability, burns, and age), and potential transport-related complications. Patients with minor clinical effects that resolve can be discharged with dedicated follow-up. Those with signs of end organ effects, such as chest pain or altered mental status, if not transferred for HBO, should be admitted for observation. All patients exposed to CO require close follow-up for delayed neurologic sequelae.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 148: QUESTIONS AND ANSWERS

1. A laboratory worker is brought to the emergency department (ED) after being found unconscious. His colleague reports that the patient was found in his vehicle with its windows closed which he was using to transport dry ice. The patient is now awake but reports feeling tired and confused. He has no other complaints. His vital signs and physical examination are normal. What toxin-specific diagnostic test should be ordered for this patient?

a. Carboxyhemoglobin (COHb)
b. Chest radiograph
c. Electrocardiogram
d. Methemoglobin (MetHb)
e. No tests are indicated

Answer: e. Carbon dioxide is primarily a simple asphyxiant, meaning that its major consequential adverse effects stem from its displacement of oxygen in the lungs. Once patients are removed from the source, they generally recover completely. Patients should be observed until this time. COHb measurement would be indicated if there is a suspicion of carbon monoxide (CO) exposure. Chest radiographs should be ordered if patients have pulmonary complaints after an unknown exposure. Electrocardiograms should be ordered if patients are exposed to known cardiac toxins. MetHb levels should be checked when there is suspicion for oxidative stress on the red blood cells.

2. A 32-year-old woman presents following exposure to an irritant gas at her job site. She reports cough, burning eyes, and shortness of breath. She has mild tachypnea, with the remainder of her vital signs within normal limits. Her oxygen saturation is 96% on room air. She is noted to have stridor on physical examination. What is the preferred method to evaluate her upper airway symptoms?

a. Arterial blood gas (ABG)
b. Chest radiograph
c. Computed tomography of the neck
d. Fiberoptic laryngoscopy
e. Soft tissue neck radiograph

Answer: d. Fiberoptic or direct laryngoscopy is the preferred method to evaluate upper airway symptoms after exposures to irritant gases. Radiographs and laboratory tests have no role and should not influence the decision to provide a definitive airway. Symptoms can progress rapidly, so patients with upper airway symptoms require either placement of a definitive airway or close observation with frequent serial examinations.

3. A 52-year-old man is brought to the emergency department (ED) after being rescued from a house fire. He has not suffered any cutaneous burns. He complains of a sore throat, hoarse voice, and cough. Vital signs are normal. Physical examination reveals soot in his oropharynx and carbonaceous sputum. What therapy should be instituted first?

a. Endotracheal intubation
b. Intravenous (IV) methylprednisolone
c. Nebulized albuterol
d. Nebulized sodium bicarbonate
e. Saline bronchoalveolar lavage

Answer: a. Endotracheal intubation should be performed early in patients with signs and symptoms of significant airway burns (as with this patient). Corticosteroids are not beneficial and can worsen associated injuries. Inhaled beta-agonists are commonly used, but there is no evidence of improved outcome. Inhaled sodium bicarbonate plays no role in the management of smoke inhalation. Bronchoalveolar lavage can be performed if there is suspicion of inhaled debris or toxins, but the airway should first be secured.

CHAPTER 148: QUESTIONS AND ANSWERS—cont'd.

4. A 47-year-old woman is brought to the emergency department (ED) after being rescued from a house fire. She was found unconscious at the scene and intubated before arrival. Her vital signs are significant for hypotension and tachycardia. Physical examination is significant for soot in the oropharynx. No cutaneous burns are noted. You suspect that she is suffering from cyanide poisoning. What is the most appropriate immediate therapy?
   a. Hyperbaric oxygen (HBO)
   b. Intravenous (IV) hydroxocobalamin
   c. IV methylene blue
   d. IV sodium nitrite
   e. Observation and supportive care

Answer: b. One of the two major treatments for cyanide poisoning is hydroxocobalamin (the other is the traditional cyanide antidote kit). The nitrite compounds in the cyanide antidote kit convert hemoglobin to methemoglobin (MetHb), which in turn binds to cyanide. However, nitrites produce hypotension and the MetHb prevents proper oxygen deliver, which may compound the reduction in oxygen delivery associated with carbon monoxide (CO) poisoning. HBO has no role in acute cyanide poisoning. Methylene blue has been used for cyanide poisoning in the past but is not as useful as the cyanide kit. Its primary use is in treating methemoglobinemia. General supportive care is not appropriate because there is an effective antidote for this patient's poisoning.

5. A 22-year-old man is brought to the emergency department (ED) after being found unconscious in a car with an intentionally prominent suicide note visible in the window. By the time he arrives in the ED, he has regained consciousness and is complaining of headache and nausea. Paramedics report that the car engine was not running when the patient was discovered. His vital signs and physical examination are normal. Which of the following therapies should be instituted?
   a. Hyperbaric oxygen (HBO)
   b. Intravenous (IV) methylene blue
   c. IV sodium nitrite
   d. IV sodium thiosulfate
   e. Observation and supportive care

Answer: e. This patient has been exposed to hydrogen sulfide (a common form of suicide in some parts of the world), which has similar effects on the mitochondria as cyanide. However, hydrogen sulfide is rapidly removed from the body; and as long as patients are recovering, removal from the source is usually all that is necessary. HBO and methylene blue have no role in hydrogen sulfide poisoning. Sodium nitrite can be used in patients who are not recovering once removed from the source or for severe exposures. Sodium thiosulfate is not necessary because hydrogen sulfide is detoxified by a different pathway than cyanide and does not need a sulfur donor.

6. A worker at a chemical plant was exposed to a cloud of chlorine gas (Cl_2). On examination in the emergency department you note a normal oxygen saturation, increased respiratory rate, and wheezing on lung auscultation. In addition to administration of inhaled beta-adrenergic agonists, which of the following can be administered for symptomatic relief?
   a. Nebulized hypertonic saline
   b. Systemic corticosteroids
   c. Nebulized 2% sodium bicarbonate solution
   d. Antibiotics
   e. Intravenous magnesium sulfate

Answer: c. This patient was exposed to chlorine gas which is an intermediate water-soluble gas that combines with water in the respiratory tract to form hydrochloric acid. Patients may have improvement of their symptoms with the administration of nebulized 2% sodium bicarbonate solution. Systemic corticosteroids have not shown a benefit in these patients. Antibiotics should not be administered routinely in these patients unless an overlying infectious process is suspected.

7. What is the major benefit of hyperbaric oxygen (HBO) therapy for patients suffering from carbon monoxide (CO) poisoning?
   a. Decreased rate of hospitalization
   b. Improvement of 24-hour mortality
   c. Improvement of 30-day mortality
   d. Prevention of delayed cardiovascular complications
   e. Prevention of delayed neuropsychiatric complications

Answer: e. There is controversy regarding the role of HBO therapy for patients with CO poisoning, but the best evidence suggests that it can significantly decrease the incidence of delayed neuropsychiatric complications. There is no change in rate of hospitalization, nor on overall mortality, either short term or long term. There are no delayed cardiovascular symptoms associated with CO poisoning.

8. Assuming that all patients have similar vital signs and complaints of headache and nausea, which of the following patients suffering from carbon monoxide (CO) poisoning should be considered highest priority for hyperbaric oxygen (HBO) therapy?
   a. A 22-year-old otherwise healthy man with a carboxyhemoglobin (COHb) level of 30%
   b. A 25-year-old otherwise healthy pregnant woman with a COHb level of 25%
   c. A 30-year-old otherwise healthy man also suffering from cyanide poisoning with a COHb level of 15%
   d. A 35-year-old otherwise healthy woman with second-degree burns to 20% of her body and with a COHb level of 20%
   e. A 67-year-old asymptomatic woman with coronary artery disease and with a COHb level of 25%

Answer: b. Pregnant patients should be considered for HBO therapy. CO binds more strongly to fetal hemoglobin than to adult hemoglobin and can cause severe hypoxia to the fetus. There is controversy about an absolute level of COHb that requires HBO therapy. HBO does not benefit cyanide victims, nor is it indicated in uncomplicated burn patients or those with stable comorbidities.

9. You successfully treat a patient for cyanide poisoning. Several hours after improvement of the patient's hemodynamics, you are alerted that the patient has developed a bright red skin discoloration. Which of the following is the most likely explanation for this new physical exam finding?
   a. Administration of hydroxocobalamin
   b. Concomitant carbon monoxide toxicity
   c. An anaphylactic reaction
   d. Development of hyperthermia
   e. Peripheral vasodilation

Answer: a. Patient presented with cyanide toxicity for which the antidote, hydroxocobalamin, was given. Hydroxocobalamin has only mild adverse effects, although it can cause hypertension in those without cyanide toxicity and it can cause a bright red discoloration of the patient's skin. This discoloration can often be mistaken as an allergic reaction and it can interfere with spectrophotometric laboratory assays including COHb level. Cherry red skin discoloration in the setting of CN or CO poisoning is a postmortem finding.

149

Lithium

Jillian L. Theobald and Steven E. Aks

KEY CONCEPTS

- The clinical pattern of acute and chronic lithium toxicity is different. Gastrointestinal symptoms occur early, and neurologic toxicity manifests late in acute toxicity. Neurologic findings (e.g., tremors, altered mental status and seizures) often are presenting signs of chronic lithium toxicity, whereas gastrointestinal symptoms often are absent.
- Neither activated charcoal nor whole bowel irrigation (WBI) is indicated in the routine management of acute or chronic lithium toxicity.
- Serial lithium concentrations should be obtained every 2 to 4 hours initially to determine the peak level and the need for hemodialysis.
- Fluid hydration with crystalloid is essential to enhance renal excretion of lithium. Diuretics are contraindicated.
- We recommend hemodialysis for acute lithium concentrations greater than 5 mEq/L or for patients with signs of severe neurologic lithium toxicity, particularly tremor, clonus, altered mental status, and seizure, regardless of the serum concentration.

FOUNDATIONS

Lithium has been used therapeutically since the mid-1800s, when it was initially prescribed to treat gout. Lithium compounds were also historically used therapeutically: lithium bromide as a hypnotic, lithium iodide to treat syphilis, and lithium chloride introduced as a table salt alternative for heart failure patients in the 20th century. Ultimately, multiple deaths led to removal of lithium chloride from the US market. In 1970, lithium was approved for the treatment of bipolar disorder, and it remains one of the most effective agents for both depressive and manic symptoms. Lithium is the only drug treatment for bipolar disorder that is associated with a reduced risk of suicide.[1]

Lithium is a monovalent cation with a narrow therapeutic range, and significant toxicity can result when outside of this range. Lithium largely has no effect when given in therapeutic doses to patients without mood disorders. Despite its long history of therapeutic use, the complex and multimodal mechanism of action of lithium is still not fully understood. Its efficacy in the treatment of psychiatric illnesses is thought to be due to the modulation of neurotransmitters, which has downstream effects through cell signaling and molecular mechanisms.[2]

Lithium is rapidly absorbed from the gastrointestinal tract and peaks in the serum 1 to 2 hours after ingestion of immediate-release preparation and 4 to 5 hours with sustained-release preparations. Absorption and peak concentrations can be delayed in overdose situations, with ingestion of sustained-release formulations, or when concretions form in the gut. Once absorbed, lithium enters the serum followed by a delayed distribution to the tissues. In therapeutic dosing, lithium reaches a steady state within 6 hours after the last dose. Therefore lithium levels must be interpreted in the context of the patient's last dose. Lithium is not metabolized and is excreted unchanged in the urine. Any decreases in renal excretion because of conditions such as dehydration, hyponatremia, or renal dysfunction will lead to increases in serum lithium levels.

CLINICAL FEATURES

Lithium toxicity is categorized into acute, acute on chronic, or chronic toxicity. Evaluation of the potentially lithium toxic patient requires knowledge of whether the patient was previously taking lithium, the timing of the last dose, and the amount of drug ingested. The clinical features of lithium toxicity depend on whether it is acute or chronic in nature (Table 149.1). Acute toxicity usually follows a recent ingestion in a patient who is not therapeutically taking lithium and manifests early with gastrointestinal symptoms such as vomiting and diarrhea. Neurologic consequences of an acute lithium overdose include seizures, altered mental status, tremors, hyperreflexia, clonus, or fasciculations. They occur several hours later, after lithium redistributes to the central nervous system. In some cases with delayed-release lithium, neurologic symptoms may occur 12 or more hours after ingestion. These neurologic consequences are similar to chronic lithium toxicity. Chronic toxicity is caused by a relatively gradual increase in serum lithium level in a patient who is regularly taking lithium. This can either be from reduced excretion, renal insufficiency, or a dose adjustment. Chronic lithium toxicity causes predominantly neurologic symptoms with minimal to no gastrointestinal symptoms. Acute-on-chronic toxicity occurs when a patient with a stable steady-state lithium level takes a substantial additional amount of lithium, intentionally or accidentally. These patients present with signs and symptoms of both acute and chronic toxicity. Either acute or chronic toxicity can result in cardiac conduction abnormalities with T-wave inversions being the most common electrocardiogram (ECG) finding.[3]

Long-term chronic use of lithium can lead to nephrogenic diabetes insipidus and hypothyroidism. Both conditions are reversible with discontinuation of the medication and respond well to conventional management.[4] Hypercalcemia and hyperparathyroidism also can occur and reverse upon discontinuation of lithium.[5] Patients chronically taking lithium can develop the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). Patients with SILENT will often have persistent cerebellar and brain stem dysfunction, dementia, and extrapyramidal signs even after lithium use has been discontinued for days to weeks. [6] Use of lithium during early pregnancy may increase the risk for cardiovascular abnormalities in the fetus.[7]

DIFFERENTIAL DIAGNOSES

Lithium toxicity is nonspecific and may present in a manner similar to many systemic and neurologic disorders, so obtaining a history of lithium use or ingestion is critical to making the diagnosis. Nausea and vomiting are common with viral or bacterial gastrointestinal

TABLE 149.1 Clinical Features of Lithium Toxicity

Clinical Features	TYPE OF TOXICITY	
	Acute	Chronic
Gastrointestinal[4]	Nausea Vomiting Diarrhea	Mild or nonexistent
Neurologic[8]	Similar to chronic toxicity, occurs several hours after lithium distribution to the brain	Tremors Clonus Hyperreflexia Extrapyramidal symptoms Altered mental status Somnolence Coma Seizures
Cardiac[2]	Sinus node dysfunction AV blockade Brugada pattern on ECG Ischemic changes on ECG QTc prolongation	

AV, Atrioventricular; *ECG,* electrocardiogram.
Modified from Won E, Kim YK. An oldie but goodie: lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. *Int J Mol Sci.* 2017;18(12):2679. https://doi.org/10.3390/ijms18122679; Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. *BMC Nephrol.* 2018;19(1):305; Thanacoody R, Caravati EM, Troutman B, et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. *Clin Toxicol.* 2015;53(1):5–12.

syndromes, early pregnancy, various abdominal pathologies, acute neurologic events, and other toxic ingestions. The neurologic manifestations of lithium toxicity (tremors, hyperreflexia, altered mental status, and seizures) may prompt consideration of withdrawal syndromes (alcohol or benzodiazepines), sympathomimetic toxicities (cocaine and amphetamines), and serotonin syndrome.

DIAGNOSTIC TESTING

Serum lithium levels should be obtained in all patients who are taking lithium, or have access to lithium, and present with potential toxicity. Because of the insidious and nonspecific nature of chronic lithium toxicity, a serum lithium level is also advisable in any patients who is on lithium maintenance therapy, regardless of their reason for presentation (Box 149.1). Therapeutic serum concentrations of lithium are between 0.6 and 1.2 mEq/L. Serum lithium levels are in a steady state approximately 6 hours after ingestion of a therapeutic dose and should be interpreted in the context of when the last dose was taken. In overdose situations, peak concentrations can occur beyond 6 hours. We recommend obtaining serum lithium concentrations every 2 to 4 hours until two consecutive declining measurements are observed. Serum electrolytes should be obtained because lithium can cause alterations in calcium and sodium, most commonly hypercalcemia and hypernatremia. An assessment of the patient's renal function either by a serum creatinine concentration or a glomerular filtration rate should also be performed. If there is clinical concern for thyroid dysfunction, then thyroid studies should be obtained. In patients presenting with an acute intentional ingestion, both acetaminophen and aspirin levels should be sent to evaluate for possible coingestants. Finally, an ECG

BOX 149.1 Diagnostic Testing for Lithium

Serum lithium level
Serum electrolytes
Creatinine concentration or a glomerular filtration rate (GFR)
Electrocardiogram (ECG)
If the clinical picture dictates:
Acetaminophen/salicylate levels
Thyroid function tests

should be obtained and cardiac monitoring initiated in patients presenting with an acute or chronic overdose. An ECG also should be obtained for patients on chronic lithium therapy, given the propensity of lithium to cause conduction abnormalities.

MANAGEMENT

Stabilization and Supportive Care

No specific antidote exists for lithium toxicity therefore supportive care and enhanced elimination are the mainstays of treatment. Most patients who are lithium-toxic are dehydrated because of gastrointestinal losses in acute toxicity or from underlying dehydration and lithium-induced diabetes insipidus, leading to chronic toxicity. Crystalloid solution (lactated Ringers solution) should be infused as a 1 L bolus followed by a continuous infusion at 150% of the calculated maintenance rate if there are no contraindications, such as congestive heart failure. Volume expansion also enhances renal elimination of lithium. Electrolyte abnormalities, such as hypernatremia and hypercalcemia, if significant, should be corrected (see Chapter 114).

Decontamination

Activated charcoal does not bind lithium. Furthermore, we do not recommend the use of whole bowel irrigation (WBI) in routine lithium ingestions. Although a position paper suggests that WBI can be considered after massive overdose, there is only scant evidence that WBI can decrease the amount of lithium absorbed in nontoxic doses, and there is no clinical evidence of benefit in overdose.[8] Similarly sodium polystyrene resins (e.g., Kayexalate) have been proposed to assist in the elimination of lithium by sodium-lithium exchange; however, due to limited binding capacity, large volumes are needed to have any significant reduction in lithium levels. There are no studies demonstrating an actual impact on clinical outcome, the risks outweigh the benefit, and we do not recommend the use of ion-exchange resins in lithium poisoning.[9]

Enhanced Elimination

Because lithium is primarily excreted unchanged by the kidney, early initiation of intravenous crystalloid solution, as described earlier, enhances elimination. Diuretics are contraindicated, because they can cause worsening dehydration, with further impairment of renal function, and also can enhance renal reabsorption of lithium.

Lithium is highly dialyzable, and hemodialysis is indicated for patients exhibiting signs of severe lithium toxicity (Box 149.2). Patients with severe neurologic toxicity (e.g., altered mental status, clonus, hyperreflexia, and seizures) should undergo hemodialysis to reduce serum lithium levels to less than 1.0 mEq/L.[10] In addition, hemodialysis is indicated for patients with impaired renal function or those who cannot tolerate intravenous fluids. There is little high-quality evidence in favor of dialysis based solely on serum lithium concentration. A Cochrane review concluded that there is insufficient evidence to determine which lithium-intoxicated patients might benefit from hemodialysis.[11] Based on our experience and available evidence, we recommend

BOX 149.2 Indications for H Somnolence

Hemodialysis in Lithium Poisoned Patients

Severely symptomatic patients
Unable to tolerate crystalloid fluid resuscitation
Renal impairment
Acute or chronic toxicity: Levels >5 mEq/L
Neurotoxicity including tremors, clonus, altered mental status, somnolence, seizures

dialysis for serum levels greater than 5 mEq/L[12] or for patients with signs of severe neurologic lithium toxicity, particularly tremor, clonus, altered mental status, and seizure, regardless of the serum concentration. Serum lithium concentrations can rise or rebound after dialysis sessions; therefore a steady state concentration should be determined at 6 hours post procedure.

DISPOSITION

Disposition depends largely on the extent of clinical toxicity and the psychiatric status of the patient. Patients manifesting clinical signs of neurotoxicity such as tremors, altered mental status, and seizures should be admitted. Patients with an acute overdose complicated by significant cardiologic or neurologic symptoms and high (>5 mEq/L) or increasing supratherapeutic serum lithium levels should undergo hemodialysis. Patients with significant altered mental status or seizures, and those requiring dialysis should be monitored in an intensive care which may require early transfer to a hospital with this capability. In these cases, we recommend consultation with a regional poison center or medical toxicologist. Patients with overdoses of sustained-release lithium should also be placed in an observation unit or hospitalized for serial monitoring of lithium concentrations until at least two consecutive declining serum levels are documented. Patients who remain asymptomatic with normal physical examination findings and serum lithium levels in the therapeutic range 6 hours after ingestion of immediate-release lithium preparations or 12 hours after a sustained-release preparation can be discharged or cleared for psychiatric evaluation. Women taking lithium who present to the emergency department with newly diagnosed pregnancy should be referred to an obstetrician for fetal evaluation and monitoring and to discuss the risk benefit profile of lithium use during pregnancy.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 149: QUESTIONS AND ANSWERS

1. What are the two most common electrolyte abnormalities seen in chronic lithium toxicity?

a. Hyperkalemia and hypernatremia
b. Hypernatremia and hypercalcemia
c. Hypokalemia and hypercalcemia
d. Hypomagnesemia and hyponatremia
e. Hyponatremia and hypercalcemia

Answer: b. Chronic lithium use can cause hypernatremia due to the development of diabetes insipidus. Prolonged therapy with lithium alters cellular calcium sensing and leads to elevated parathyroid hormone levels and hypercalcemia. Magnesium and potassium levels are typically normal, and abnormalities are not caused by lithium. Hyponatremia and hypercalcemia are frequently seen in cases of acute lithium overdose.

2. Which of the following conditions is most frequently seen in patients with chronic lithium use?

a. Anticholinergic syndrome
b. Diabetes insipidus
c. Hyperthyroidism
d. Hypoparathyroidism
e. Syndrome of inappropriate antidiuretic hormone

Answer: b. Diabetes insipidus commonly occurs in patients on chronic lithium therapy or with chronic overdose. Diabetes insipidus can cause dehydration and a further increase in lithium concentration and is a frequent contributory cause to chronic lithium toxicity. Rarely, hypothyroidism can also develop. Lithium use is also associated with neuroleptic malignant syndrome and serotonin syndrome but none of the other listed conditions.

3. Which of the following drugs should be used with caution in patients taking lithium?

a. Acetaminophen
b. Hydrochlorothiazide
c. Metformin
d. Metoprolol
e. Penicillin

Answer: b. Hydrochlorothiazide, other diuretics, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) can increase lithium levels and consequently cause chronic lithium toxicity by interfering with renal elimination. Lithium has also been implicated in serotonin syndrome when combined with other serotonergic drugs, such as monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRIs), and dextromethorphan. None of the other drugs listed causes significant interactions with lithium.

4. A 26-year-old woman presents following a witnessed seizure. She was found with an empty bottle of lithium and a suicide note. Her vital signs reveal hypotension and tachycardia. She is lethargic and her only response is to withdraw from painful stimuli. The remainder of her physical examination is normal. Laboratory tests including a serum lithium level are pending. Which of the following treatments is the most appropriate?

a. Activated charcoal
b. Forced diuresis
c. Hemodialysis
d. Urinary alkalinization
e. Whole bowel irrigation (WBI)

Answer: c. Hemodialysis is the most effective way to remove lithium. It can remove lithium at a rate five to seven times the rate of typical renal elimination. Common indications for dialysis include decreased level of consciousness and seizures. Activated charcoal does not adsorb lithium. Lithium overdose patients are often dehydrated and occasionally hypernatremic and should be fluid resuscitated, but once dehydration is corrected, forced diuresis is of no benefit and can be detrimental. Urinary alkalinization has no role in lithium toxicity. Because this patient has already experienced a seizure, the administration of WBI is not advised. In addition, the seizure suggests that the brain concentration of lithium is already toxic and this is not improved by WBI.

Antipsychotics

Jessica Monas and Aaron B. Skolnik

KEY CONCEPTS

- Antipsychotics are commonly categorized into typical, or first-generation antipsychotics (FGAs) with primary antagonism to dopamine receptors, and atypical, or second-generation antipsychotics (SGAs) which include serotonin receptors as a target. Aripiprazole is an example of a third type of antipsychotic that acts as a partial agonist at dopamine sites.
- Extrapyramidal symptoms are common side effects of antipsychotics. First line treatment is benztropine or diphenhydramine. Lorazepam may be used in refractory cases.
- The most common presentation of an antipsychotic overdose is central nervous system (CNS) depression. Treatment focuses on supportive care, airway management, and cardiac monitoring.
- QT prolongation and *torsades de pointes* are potential complications of antipsychotic overdose but may also occur with therapeutic use.
- Clozapine is associated with potentially life-threatening agranulocytosis. Treatment includes cessation of the medication, treating potential infections, and supportive care.
- Neuroleptic malignant syndrome (NMS) is characterized by altered mental status, hyperthermia, muscle rigidity, and autonomic instability. Treatment includes supportive care with airway management, benzodiazepines, muscular rigidity management, and evaporative cooling methods for hyperthermia.

FOUNDATIONS

Background

In 1950, promethazine was synthesized in an effort to develop antihistamines, but it was also found to potentiate the effects of anesthetics and was widely used. An attempt to derive similar drugs led to the synthesis of chlorpromazine. It was discovered that patients treated with this became sedate and apathetic and it was termed a *neuroleptic*. Chlorpromazine was first used to successfully treat a patient with psychosis in 1952 and helped to pave the way for the modern treatment of mental illness. Prior to the development of antipsychotics, pharmacotherapy for psychosis had focused on tranquilization rather than modification of disease.

In 1956, clozapine was synthesized. It demonstrated that a drug could treat psychosis without significant extrapyramidal effects and became the precursor of the *atypical* antipsychotics. Clozapine was initially removed from market in 1974 due to agranulocytosis but was reintroduced in 1990 with mandatory monitoring because of its clinical efficacy in treatment-resistant schizophrenia.[1]

The term *neuroleptic* has since been replaced with *antipsychotic*, because newer agents are less sedating. Antipsychotic use has expanded beyond schizophrenia and schizoaffective disorders to include supplemental treatment for major depressive disorder, bipolar disorder, anxiety disorders, behavioral changes associated with dementia, and psychoses related to substance use disorders and withdrawal. In the past decade, antipsychotic prescribing has dramatically increased, including off-label and nonpsychosis use.[2–5] In 2018, nearly 50,000 exposures attributable to antipsychotics were reported to poison control centers in the United States. In conjunction with sedatives and hypnotics, antipsychotics comprised the group of drugs with the greatest increase per year in serious adverse outcomes and human ingestions.[6]

Pathophysiology

Antipsychotics have been categorized according to their mechanism of action as well as their clinical effect. All antipsychotics have dopamine receptor antagonism. Typical, or first-generation antipsychotics (FGAs) focused on dopamine blockade as a primary target with subsequent adverse extrapyramidal effects. FGAs are sometimes classified as low-potency or high-potency based on their affinity for the dopamine D_2 receptor subtype (Box 150.1). Atypical, or second-generation antipsychotics (SGAs) were developed to combine with serotonin receptor antagonism (5-hydroxytryptamine type 2A) to decrease neurologic side effects and also treat negative symptoms of thought disorders. More recent development of partial dopamine agonism, such as aripiprazole and brexpiprazole, led to the phrase "third-generation" antipsychotic, but this term has not been readily accepted.[7,8] In 2019, the US Food and Drug Administration (FDA) approved a novel first-in-class antipsychotic, lumateperone, that acts synergistically though serotonergic, dopaminergic, and glutaminergic modulation.[9] Lumateperone has been shown to improve depressive as well as psychotic symptoms.[10] In general, low-potency FGAs are the most sedating. Movement disorders are a significant adverse effect of this class of medication, with SGAs having lower frequency. Although neuroleptic malignant syndrome (NMS) can occur with all antipsychotics, it occurs less often with SGAs.[11]

Antipsychotic medications are widely used for both psychiatric and nonpsychiatric purposes. The antiemetic effects of prochlorperazine, promethazine, and droperidol result from blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla. Prochlorperazine and droperidol are thought to improve migraine headaches by inhibiting dopamine-mediated trigeminovascular activation. Olanzapine has been used for fibromyalgia and the treatment of other chronic pain.[12,13] Chlorpromazine is the historical drug of choice for singultus or intractable hiccups, although other antipsychotics are also used.[14] Although haloperidol, pimozide, and aripiprazole are the only FDA-approved treatments for Tourette syndrome, other SGAs have been recommended.

Toxicity

Toxicity of antipsychotic drugs can be divided into three categories: exaggerated pharmacologic effects seen in acute overdose, undesired clinical effects seen in therapeutic use such as extrapyramidal syndromes, and idiosyncratic effects such as NMS.

BOX 150.1 Classification of US Food and Drug Administration Approved Antipsychotics*

Low Potency (First-Generation Antipsychotics)
Chlorpromazine (Thorazine)
Fluphenazine (Prolixin)
Perphenazine (Trilafon)
Promethazine (Phenergan)
Thioridazine (Mellaril)

High Potency (First-Generation Antipsychotics)
Droperidol (Inapsine)
Haloperidol (Haldol)
Loxapine (Loxitane)
Pimozide (Orap)
Thiothixene (Navane)
Trifluoperazine (Stelazine)

Atypical (Second-Generation Antipsychotics)
Aripiprazole (Abilify)
Asenapine (Saphris)
Brexpiprazole (Rexulti)
Cariprazine (Vraylar)
Clozapine (Clozaril)
Iloperidone (Fanapt)
Lurasidone (Latuda)
Olanzapine (Zyprexa)
Paliperidone (Invega)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Ziprasidone (Geodon)

Atypical (Third-Generation Antipsychotics)
Aripiprazole (Abilify)
Brexpiprazole (Rexulti)
Cariprazine (Vraylar)

Atypical (Other)
Lumateperone (Caplyta)

*Current as of March, 2020.

In addition to D_2 receptor antagonism, most antipsychotics take effect at other receptors and ion channels. These include alpha-1 adrenergic, muscarinic, and histamine H_1 receptor antagonism, as well as fast voltage-gated sodium, and delayed potassium rectifier channel blockade.

Alpha antagonism may result in orthostatic hypotension. Muscarinic antagonism can produce minor side effects in therapeutic use or anticholinergic toxicity in acute overdose including cognitive impairment. Histaminergic blockade can produce sedating effects in both therapeutic use and overdose.

Phenothiazine antipsychotics such as chlorpromazine are structurally related to tricyclic antidepressants (TCAs), exhibiting sodium channel blockade that may lead to wide complex dysrhythmias. Many agents inhibit potassium rectifying currents resulting in QT prolongation and, potentially, torsades de pointes. The degree of prolongation varies between antipsychotics and can increase in a dose-dependent manner, with ziprasidone and iloperidone having the highest risk, and aripiprazole and brexpiprazole the lowest.[15] QT prolonging effects may be worsened in chronically ill patients and with concomitant use of other QT-prolonging drugs.[15,16] Although a direct correlation between degree of QT prolongation and risk of torsades de pointes has not been well established, antipsychotics are associated with increased risk of sudden death that is worsened with comorbid cardiac disease and in elderly patients.[17] In addition, psychotic disorders alone increase the risk of sudden death.[18] Therapeutic use of clozapine has been linked to myocarditis and cardiomyopathy that may be accompanied by eosinophilia.[19]

Antipsychotic drugs block dopamine receptors at multiple regions within the brain. Mesolimbic D_2 blockade produces the desirable effect of reducing positive symptoms of schizophrenia. However, similar degrees of D_2 receptor blockade in the nigrostriatal pathway also produce the undesirable extrapyramidal symptoms (EPSs). This includes dystonia, akathisia, and drug-induced parkinsonism, which may be immediate or delayed in onset. SGAs have lower affinity for the dopamine receptors and add-in serotonin receptor antagonism, both of which are thought to reduce EPSs. The propensity of antipsychotics to produce EPSs is also inversely proportional to the agent's muscarinic receptor antagonism.[20] Rapid dissociation from the D_2 receptor has been hypothesized to reduce the risk of EPS; however, data suggest that association rates may also play a factor.[21,22]

Tardive syndromes (TSs) encompass the hyperkinetic and hypokinetic movements that result after delay from exposure to dopamine-blocking drugs. Tardive dyskinesia (TD) may develop after prolonged use of these medications and has been reported with all antipsychotics. One proposed pathophysiological mechanism is chronic dopamine receptor blockade in the nigrostriatal pathway leading to D_2 receptor upregulation and hypersensitivity to dopamine. Genetic factors are also thought to play a significant role in the development of TD.

NMS is a rare, idiosyncratic reaction to antipsychotic medications, the pathophysiology of which is less understood. It can be severe and, if unrecognized or undertreated, can lead to permanent neurologic sequalae and death. NMS is thought to result from D_2 receptor blockade in the nigrostriatum and hypothalamus, which can lead to rigidity and hyperthermia, with downstream dysregulation of the autonomic nervous system. It has more recently been suggested that NMS may be due to a direct toxic effect of the drug on the musculoskeletal fibers.

Clozapine-associated agranulocytosis is rare, with an incidence of approximately 1%, which drops to 0.38% with routine white blood cell count monitoring.[23] A more recent meta-analysis found that this does not occur more frequently with clozapine than with other antipsychotics.[24] The classic proposed mechanism is a direct cytotoxic effect on bone marrow mesenchymal stromal cells. An alternate suggested etiology is that it may be related to an autoimmune process.

Antipsychotic use has also been associated with weight gain, dyslipidemia, glucose intolerance, metabolic syndrome, and new-onset diabetes mellitus.[23] Numerous observational and case-control studies indicate an increased risk of venous thromboembolism (VTE) with antipsychotic use. Multiple hypotheses regarding the mechanism include drug-induced sedation, weight gain, enhanced platelet aggregation, antiphospholipid antibody level increase, and the possibility that thought disorders may cause a predisposition. The risk of VTE may also be highest within the first 3 months of antipsychotic therapy initiation.

CLINICAL FEATURES

Acute Overdose

In overdose, antipsychotics produce signs and symptoms that are exaggerations of their pharmacologic profile. Most patients develop symptoms within a few hours post ingestion. Paliperidone has a unique delayed-delivery system, and late onset of symptoms has been reported.[25] Central nervous system (CNS) depression is common, ranging from mild sedation to coma. Anticholinergic delirium and agitation may result from drugs with antimuscarinic effects (Box 150.2). Airway reflexes can be impaired and respiratory depression can occur after overdose. Pupils may be of variable size; anticholinergic effects

BOX 150.2 Antipsychotics With Antimuscarinic Effects

Typical Antipsychotics
Chlorpromazine (Thorazine)
Loxapine (Loxitane)
Mesoridazine besylate (Serentil)
Thioridazine (Mellaril)

Atypical Antipsychotics
Clozapine (Clozaril)
Olanzapine (Zyprexa)
Quetiapine (Seroquel)

Data from Levine M, Ruha AM. Overdose of atypical antipsychotics: clinical presentation, mechanisms of toxicity and management. *CNS Drugs*. 2012;26:601–611; Richelson E. New antipsychotic drugs: how do their receptor-binding profiles compare? *J Clin Psychiatry* 2010;71:1243–1244.

promote mydriasis, whereas miosis, resulting from alpha-antagonism, may mimic opioid toxicity. Orthostatic hypotension is also a common finding resulting from alpha-adrenergic blockade. Variable evidence suggests that antipsychotics lower seizure threshold; however, with the exception of clozapine, seizures rarely occur in overdose. Acute EPSs have also been reported in overdose.

Acute Extrapyramidal Syndromes

Acute dystonia presents with involuntary spasms of antagonistic muscle groups most often involving facial, neck, back, or limb muscles. This results in trismus, facial grimacing, dysarthria, tongue and lip distortion, torticollis, or oculogyric crisis. Half of patients who develop acute dystonia do so within 48 hours of receiving the implicated drug. Symptoms may develop rapidly or may be delayed hours to days, although most acute dystonia develops within 5 days of drug administration. Recurrent dystonic reactions may occur, even following a single dose of an antipsychotic. *Laryngeal dystonia,* a rare but life-threatening form of dystonia, manifests as dyspnea, stridor, choking sensation, or respiratory distress and has been reported with both FGAs and SGAs.[26] Increased risk of death due to choking has been reported in patients treated for schizophrenia; both FGAs and SGAs have been associated with dysphagia.

Akathisia (from Greek, *"unable to sit"*) is characterized by subjective feelings of internal restlessness associated with objective motor findings, including repetitive foot shuffling, truncal shifting, or pacing. Akathisia usually develops within hours to days of initiating or increasing the dose of an antipsychotic. Studies of emergency department (ED) patients have demonstrated a lower incidence of akathisia and other EPSs with SGAs. *Rabbit syndrome* is a perioral, tongue-sparing dyskinesia in which rhythmic lip and nose movements resemble the chewing movements of a rabbit. Rabbit syndrome is primarily associated with FGA drugs but has also been case reported with SGAs.

Drug-induced parkinsonism, manifest by bradykinesia, masklike facies, shuffling gait, rigidity, and tremor, may occur in up to 60% of patients treated with antipsychotics and frequently develops 2 to 4 weeks after initiating treatment. Ninety percent of cases develop within 3 months.

Tardive Syndromes

TSs refer to delayed-onset motor and nonmotor syndromes induced by prolonged use of dopamine antagonists, including antipsychotic medications. TSs include dystonia, akathisia, motor, sensory syndromes, and classic TD. TD refers to the repetitive, rapid, involuntary orofacial, limb, trunk, or pelvic movements first described in 1964. The risk of TD with sustained antipsychotic treatment is estimated to be approximately 5% per year and may be higher in the elderly. Prevalence is estimated at approximately 20% of psychiatric patients undergoing long-term treatment. Reduction of the antipsychotic dose or a change to an alternative agent should be considered, in consultation with the patient's psychiatrist. Two drugs, valbenazine and deutetrabenazine, were FDA approved for the treatment of TD in 2017.

Neuroleptic Malignant Syndrome

NMS is a serious idiosyncratic drug reaction that is potentially life threatening. NMS typically develops during the first 2 weeks of therapy but has occurred during long-term drug regimens. The incidence of NMS has been reported to range from less than 1% to 3% among patients exposed to antipsychotics. The unadjusted mortality rate of NMS has been estimated at approximately 5%. Males are approximately 50% more likely to develop NMS, with peak overall incidence between the ages of 20 and 25 years old. Other risk factors include recent dose changes, cumulative drug dosage, high-potency antipsychotics, parenteral formulations, polypharmacy, prolonged physical restraint, dehydration, hyperthermia, prior brain injury, family history of catatonia, muscle channelopathies, and previous episodes of NMS. Cotreatment with two antipsychotics is associated with increased risk for NMS.[27] Although highly potent FGAs are most frequently the culprit in NMS, all antipsychotics have been implicated, including SGAs. NMS caused by SGAs is associated with a lower incidence, decreased severity, and lower mortality than that caused by FGAs.[11] Abrupt withdrawal from dopaminergic agents used to treat Parkinson disease (i.e., levodopa/carbidopa) may cause a potentially fatal syndrome that is clinically indistinguishable from NMS, termed the parkinsonism-hyperpyrexia syndrome.

NMS is characterized by the tetrad of altered mental status, muscular rigidity, hyperthermia, and autonomic instability (Table 150.1). Other features of NMS may include sialorrhea, dysarthria, dysphagia, metabolic acidosis, generalized slowing on electroencephalogram (EEG), coagulopathy, rhabdomyolysis, deep venous thrombosis, pulmonary embolism, and acute kidney injury. Laboratory studies are typically notable for markedly elevated creatinine kinase (>1000 IU/mL), leukocytosis, and nonspecific elevation of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Most patients have the cardinal features of NMS within 1 to 2 weeks after starting an antipsychotic or abruptly increasing the dose. Of note, the signs of NMS may develop gradually and in any order. Clinicians should discontinue all antipsychotics, other dopamine antagonists, and other psychotropic drugs in patients with suspected NMS. Acute care in the ED includes airway management as required, intravenous (IV) fluid resuscitation, correction of metabolic disturbances, and supportive care with rapid cooling methods for hyperthermia. Administration of benzodiazepines is also indicated depending on the patient's clinical severity and response to treatment (see dosing recommendations in Management section). Most episodes of NMS resolve with appropriate care within 2 weeks after cessation of the offending medication; however, symptoms may wax and wane for months.

Cardiovascular Toxicity

The most common cardiac effect of these medications is sinus tachycardia with a normal QRS duration. A few FGAs can cause QRS prolongation; however, coingestions should be considered. QT prolongation was once considered a "class effect" of all antipsychotic medications. More recent literature has identified significant differences among the antipsychotics with respect to potential for QTc prolongation and torsades de pointes during therapeutic dosing or in overdose. At therapeutic doses, the highest risk of QT prolongation occurs with pimozide and sertindole. The only antipsychotics without any effect on QT in therapeutic use are brexpiprazole, cariprazine, and lurasidone.[28]

TABLE 150.1 Prevalence of Suggested Diagnostic Criteria for Neuroleptic Malignant Syndrome

Criterion	Prevalence
Exposure to a dopamine antagonist or withdrawal of a dopamine agonist within 72 h:	
Hyperthermia (>38°C) on at least two occasions, measured orally	98%
Rigidity	97%
Mental status alteration	97%
Creatinine kinase elevation (at least 4 times the upper level of normal)	95%
Sympathetic nervous system lability, defined as at least two of the following:	
Blood pressure elevation (SBP or DBP ≥25% above baseline)	61%[a]
Blood pressure fluctuation (≥20% DBP change or ≥25% SBP change in 24 h)	
Diaphoresis	98%
Urinary incontinence	
Hypermetabolic state (heart rate ≥25% and respiratory rate ≥50% above baseline)	88%[b]
Negative evaluation for other toxic, metabolic, infectious, or neurologic causes	

[a]Elevated or labile blood pressure.
[b]Tachycardia.
DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.
Modified from Gurrera RJ, Caroff SN, Cohen A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. *J Clin Psychiatry*. 2001;72:1222–1228.

Antipsychotic use has also been associated with an overall increased risk of cardiopulmonary arrest and death.[17]

Myocarditis has been reported in less than 1% of patients taking clozapine. The majority of cases develop in the first 2 months of treatment, with the incidence decreasing 10-fold over 12 months of treatment. A nonspecific, flulike prodrome frequently precedes the onset of myocarditis by days to weeks. The spectrum of disease ranges widely, from subclinical, asymptomatic disease to decompensated heart failure with case-fatality reported between 10% and 30%.

Agranulocytosis

Clozapine can produce life-threatening agranulocytosis in approximately 1% of exposed patients; the highest risk occurs between 1 and 5 months after starting the drug and decreases with subsequent duration of treatment. By 1 year, the risk of agranulocytosis approaches that of chlorpromazine (0.1%). With monitoring and treatment, attributable mortality is approximately 1 in 10,000. Agranulocytosis has not been reported after acute clozapine overdose. Agranulocytosis and neutropenia have been reported with many FGAs and SGAs. A recent meta-analysis of controlled trials suggests that the risk of neutropenia associated with clozapine is not greater than that associated with other antipsychotics.[24] With early recognition, antipsychotic-induced neutropenia typically resolves within 3 to 4 weeks of discontinuing the drug.

Seizures

The risk of new-onset seizures among patients treated with antipsychotics is up to 2.5-fold higher than the background rate in the untreated population, suggesting antipsychotic medications lower the seizure threshold.[29] The prevalence of psychosis in persons with epilepsy may be threefold greater than that of nonepilepsy controls, with a pooled prevalence estimate of 6%. The prescription of antipsychotic drugs to persons with epilepsy is therefore necessary and safe when indicated, even though most antipsychotics may reduce the seizure threshold.

DIFFERENTIAL DIAGNOSES

Antipsychotic toxicity may present similarly to clinical conditions and agents that produce altered mental status, seizures, anticholinergic toxidrome, orthostatic hypotension, QT prolongation, or torsades de pointes, such as TCAs. The differential diagnosis of NMS includes malignant catatonia, serotonin syndrome, heatstroke, sympathomimetic toxicity, acute salicylate poisoning, and other medical conditions (Table 150.2). Consider malignant hyperthermia in patients receiving inhalational anesthetics or succinylcholine.

DIAGNOSTIC TESTING

Quantitative blood levels of antipsychotics are neither readily available nor helpful in the ED setting. As with any patient who presents with suspected drug toxicity, blood glucose concentration, serum acetaminophen level, and directed toxicologic screening are recommended. Aspiration is common among patients with depressed mentation; chest radiography should be performed in hypoxic patients.

An electrocardiogram (ECG) should be obtained in all patients with suspected overdose and in those taking antipsychotics therapeutically with symptoms concerning for cardiotoxicity, because the ECG may predict adverse cardiovascular events.[30] If QT prolongation is present, serum sodium, potassium, calcium, and magnesium levels should be measured.

Patients who have NMS, EPSs with marked muscle rigidity, or prolonged seizures are at risk for rhabdomyolysis. In such patients we recommend serum creatinine kinase, assessment of renal function, and urine myoglobin measurements.

Patients who are severely hyperthermic (>40°C) are at risk for multi-system organ failure and disseminated intravascular coagulation. Because severe salicylate poisoning can cause CNS toxicity and hyperthermia due to uncoupling of oxidative phosphorylation, we recommend a serum salicylate level, in addition to serum transaminases and coagulation studies.

Patients taking antipsychotic medications who present with unusual infections or fever without a source should be evaluated for neutropenia, as the (low) risk appears to be similar for clozapine and other antipsychotics.[24]

Second-generation antipsychotics are associated with new-onset diabetes mellitus (including adult diagnosis of previously latent autoimmune diabetes) and diabetic ketoacidosis (DKA). This typically occurs within 1 year from the onset of treatment and may occur in the absence of weight gain. Most of these patients will subsequently require insulin for long-term blood glucose management.[31] Patients in whom DKA is clinically suspected should have blood glucose and pH, serum electrolytes, and serum or urine ketone testing. Salicylism can also produce a clinical picture that mimics DKA.

Other tests, such as brain computed tomography, lumbar puncture, and drug screens may be helpful in some cases to exclude other diagnoses or establish a comorbid condition but are not indicated when

TABLE 150.2 Differential Diagnoses of Neuroleptic Malignant Syndrome[a]

Disease	Proposed Mechanism	Differentiating Factor	Time Course	Treatment
Neuroleptic malignant syndrome (NMS)	Impaired thermoregulation in hypothalamus and basal ganglia due to due to dopamine blockade Downstream autonomic nervous system dysfunction	Antipsychotic use Muscle rigidity	Gradual over several days Waxing and waning course	Stop offending medication Hydration Active cooling IV benzodiazepines Nondepolarizing neuromuscular blockade Limited evidence: Dantrolene Dopamine agonists (e.g., bromocriptine) Consider ECT for refractory cases
Serotonin syndrome	Excess serotonin levels in CNS	Medications (usually a combination) that increase serotonin levels (e.g., SSRIs, MAOIs, lithium, dextromethorphan, meperidine, tramadol) Muscle rigidity (lower > upper extremities) Muscular or ocular clonus	Usually rapid after introduction of new medication or increase in dose	Stop offending medication Hydration Active cooling IV benzodiazepines Cyproheptadine
Malignant or lethal catatonia	Severe manifestation of schizophrenia, mood disorders, other psychiatric disorders, or neurological conditions Multiple mechanisms proposed	Occurs in absence of antipsychotic administration May be clinically indistinguishable from NMS	Gradual, typically over several days	Hydration Active cooling IV benzodiazepines ECT
Sympathomimetic toxicity	Hyperadrenergic state Extreme psychomotor agitation	Occurs in absence of antipsychotic administration Cardiovascular toxicity may be prominent Muscular hyperactivity in lieu of rigidity	Subacute, typically over hours	Hydration Active cooling IV benzodiazepines Alpha-antagonists Vasodilators
Malignant hyperthermia	Mutations in ryanodine receptors or dihydropyridine receptors allow uncontrolled calcium release from sarcoplasmic reticulum	Occurs after administration of inhalational anesthetic or succinylcholine Muscle rigidity	Sudden Provoked by administration of anesthetic	Stop anesthetic Hyperventilation with 100% oxygen Active cooling Dantrolene
Heatstroke	Impaired physiologic mechanisms for heat dissipation (classical) Environment or exercise elevates body temperature beyond range of cooling mechanisms (exertional)	Environmental exposure History Muscle rigidity rare	Subacute, typically over hours	Hydration Active cooling Prevent shivering

[a]Other clinical entities to consider in the differential diagnosis of NMS include CNS infection, status epilepticus (including nonconvulsive status), alcohol or sedative hypnotic withdrawal, hypocalcemia, hypoglycemia, hyponatremia, intracranial hemorrhage, other poisoning (e.g., anticholinergics, nicotine, salicylates, strychnine, theophylline), sepsis, tetanus, thalamic infarct, thyroid storm, and psychotic agitation.
CNS, Central nervous system; *ECT,* electroconvulsive therapy; *IV,* intravenous; *MAOI,* monoamine oxidase inhibitor; *SSRI,* selective serotonin reuptake inhibitor.

the historical context and presentation support uncomplicated antipsychotic toxicity as the cause.

MANAGEMENT

General

Treatment of antipsychotic overdose is supportive. Endotracheal intubation and mechanical ventilation may be required in patients with severe CNS depression or respiratory distress. Dextrose should be given to patients with hypoglycemia. Neither gastric emptying nor activated charcoal is indicated for antipsychotic toxicity. See Chapter 135 for a discussion of the roles of activated charcoal and other methods of gastric decontamination.[32]

If sedation and miosis suggest possible opioid intoxication, a trial of intranasal or IV naloxone is warranted. We recommend administering naloxone 0.04 to 0.4 mg intravenous push (IVP) every 2 to 3 minutes in escalating doses and, if effective, titrating to return of normal oxygenation and ventilation. If a naloxone infusion is required, it may be

started at two-thirds of the total dose required to restore respiration per hour and titrated to clinical effect.

Anticholinergic Toxidrome

Physostigmine has been used to treat anticholinergic (antimuscarinic) delirium from antipsychotic overdoses. Contraindications to physostigmine include reactive airway disease and cardiovascular disease (including any intraventricular conduction delay, QRS widening, bradycardia, or heart block). Physostigmine will usually cause a decrease in heart rate through enhanced vagal tone. We recommend avoiding its use in patients who present with seizures, because physostigmine may precipitate additional seizures. In adult patients who have obvious central anticholinergic delirium with agitation, we use physostigmine 1 to 2 mg IV, infused over 5 minutes in the absence of contraindications. In patients in whom agitated delirium is present but the toxidrome is unclear, we recommend lorazepam 1 to 2 mg IV every 10 to 15 minutes titrated to mild sedation. The delirium reversal effect of physostigmine is usually short lived (45 to 60 minutes), with delirium recurring in 30% to 90% of complete responders. The use of physostigmine for reversal of anticholinergic delirium does not preclude the use of benzodiazepines for agitation and vice versa.

Seizures

Antipsychotic-induced seizures may be short and self-limited and may not require pharmacologic treatment. For multiple seizures or status epilepticus, first line treatment is lorazepam 0.1 mg/kg (maximum 4 mg) given intravenously. This dose may be repeated in 5 minutes if seizures have not terminated. Refractory seizures unresponsive to lorazepam can be treated with phenobarbital (10 to 20 mg/kg IV loading dose) or propofol infusion may be administered (80 to 200 mcg/kg/min in healthy adults <55 years old). Use of phenobarbital or propofol in these dosages will likely require endotracheal intubation and initiation of continuous EEG monitoring, if available.

Acute Extrapyramidal Syndromes

Dystonia will often respond within 30 minutes to diphenhydramine (25 to 50 mg) or benztropine (1 to 2 mg) intravenously, intramuscularly, or orally. Lorazepam (1 to 2 mg IV) may also be effective in patients who do not respond within 1 hour to diphenhydramine or benztropine. IV lorazepam may be repeated in 15 to 20 minutes if dystonia is not improved. The first line treatment for akathisia is modification of the antipsychotic regimen. In the acute setting, clinicians may start by giving benztropine (1.5 to 8 mg total daily dose, divided) until symptoms improve. If sufficient improvement in symptoms is not achieved, propranolol (40 to 80 mg total daily dose, divided) or mirtazapine (15 mg/day) can be added.[33] Treatment of drug-induced parkinsonism includes minimizing the effective antipsychotic dose. Acute therapy begins with an anticholinergic agent, dosed as for dystonia and akathisia.

Cardiotoxicity

Cardiac monitoring is recommended in patients who are symptomatic or those with ECG abnormalities until the symptoms are resolving or ECG intervals have normalized. Sinus tachycardia with normal ECG intervals is expected in overdose and does not need to be treated unless secondary cardiac injury is present. Widening of the QRS due to sodium channel blockade is uncommon and is managed similarly to cyclic antidepressant toxicity. We recommend sodium bicarbonate 1 to 2 mEq/kg IVP, which may be repeated every 3 to 5 minutes until QRS narrowing occurs. Boluses may be repeated or an infusion of 150 mEq/L of sodium bicarbonate in 5% dextrose in water may be infused at 1.5 times the calculated maintenance rate and titrated to a goal blood pH of 7.45 to 7.55.

Hypotension is generally mild and typically responds to IV sodium chloride bolus and infusion. We prefer sodium chloride as the crystalloid in these cases because the sodium ion may be beneficial in the context of sodium channel blockade. If hypotension is severe, or persists after 2 L of isotonic crystalloid, a direct-acting vasopressor with alpha-adrenergic agonism should be initiated. We recommend a norepinephrine IV infusion, started at 0.1 mcg/kg/min and titrated to maintain mean arterial pressure greater than 65 mm Hg.

Correction of hypokalemia, hypomagnesemia, and hypocalcemia shortens the QT interval. Adults with a QTc greater than 500 msec or transient torsade de pointes should be given 1 to 2 g of magnesium sulfate IV. Treatment of sustained torsades de pointes includes IV magnesium sulfate up to 4 g total, defibrillation, overdrive pacing, or isoproterenol (see Chapter 65).[34] Any drugs that prolong the QT interval should be avoided.

ED treatment of clozapine-induced myocarditis is supportive. Clozapine treatment should be discontinued when the diagnosis is suspected.

Neuroleptic Malignant Syndrome

Treatment of NMS consists of supportive care and discontinuation of all dopamine-blocking medications. Agitation, psychomotor hyperactivity, and muscle rigidity should be treated with liberal doses of IV benzodiazepines. Lorazepam is administered at a dose of 1 to 2 mg IV every 5 to 10 minutes, until muscle rigidity improves. Refractory cases or patients at risk for aspiration can be managed with intubation and neuromuscular blockade with a nondepolarizing agent (e.g., rocuronium). Hyperthermia should be managed with IV fluids and evaporative cooling. To facilitate evaporative cooling, the patient's bare skin is continually misted with water while a cooling fan blows air continuously across the skin surface. The goal of cooling is a reduction in core temperature to less than 39°C within 30 minutes. If rhabdomyolysis is present, it is treated as described in Chapter 116 with IV fluids, urinary alkalinization, and mannitol depending on the clinical severity.

The dopamine agonists bromocriptine and amantadine (both available only in enteral formulations) have been successfully used in the treatment of NMS, although the quality of evidence is low. Dopamine agonists also carry a theoretical risk of worsening psychosis and are not recommended as a first line treatment. Dantrolene has also been used for the treatment of muscle rigidity. However, as rigidity in NMS is believed to originate in the CNS rather than in myocytes, dantrolene offers no mechanistic advantage over benzodiazepines and nondepolarizing neuromuscular blockade. We do not recommend dantrolene as part of routine treatment of NMS, although it may be administered for refractory, severe rigidity.

Electroconvulsive therapy (ECT) may be used in cases of NMS refractory to pharmacologic treatment. Evidence for efficacy is limited, although it is proposed as a treatment of choice in malignant catatonia, which may be indistinguishable from NMS. One of the primary advantages of ECT is that it may continue to be used when use of antipsychotic drugs is precluded by possible NMS.

Venous thromboembolism (VTE) disease is a prominent cause of morbidity and mortality in NMS. Patients with NMS should receive pharmacologic VTE prophylaxis.

DISPOSITION

Patients with NMS and overdose patients with hemodynamic instability, coma, torsades de pointes, or airway compromise should be admitted to an intensive care unit. Patients with a prolonged QT interval of

any magnitude should have at least 12 hours of cardiac monitoring to ensure that the interval prolongation is resolving and QTc is less than 500 ms. Patients with minimal signs of toxicity should be observed for at least 6 hours from the time of ingestion, with hospitalization for persistent or worsening signs and symptoms. Criteria for hospital discharge include return of baseline mental status and normalization of vital signs with resolution of metabolic and electrocardiographic abnormalities. Psychiatric consultation may be necessary to assess the risk of harm to self or others. Patients with acute dystonia resolved by diphenhydramine or benztropine should continue the drug for 48 hours to prevent recurrence. Patients with drug-induced parkinsonism who must continue antipsychotic medications may need to use anticholinergic agents long term. Such patients should be discharged with benztropine 1 to 2 mg by mouth twice daily for at least 48 hours and should be referred to their treating physician, who may reduce the antipsychotic dose or change treatment regimens as necessary. Patients should be informed that benztropine, diphenhydramine, and other antipsychotic medications have anticholinergic effects, so combination therapy may increase symptoms of dry mouth, blurred vision, and urinary retention.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 150: QUESTIONS AND ANSWERS

1. Which of the following is a second-generation atypical antipsychotic?
   a. Aripiprazole
   b. Haloperidol
   c. Lumateperone
   d. Olanzapine

Answer: d. Olanzapine is an atypical second-generation antipsychotic. Aripiprazole is an atypical psychotic but would be considered a third generation. Haloperidol is a first-generation, high-potency antipsychotic. Lumateperone is a newer unique antipsychotic that affects multiple systems including serotonergic, dopaminergic, and glutamatergic.

2. A 19-year-old woman presents with urinary frequency, urgency, and dysuria. She had a urinalysis which demonstrated 20 to 40 white blood cells per high-power field. She has schizophrenia for which she takes haloperidol. You diagnose her with an uncomplicated urinary tract infection. Which of the following antibiotics could cause a life-threatening arrhythmia if administered to this patient?
   a. Amoxicillin/clavulanic acid
   b. Ciprofloxacin
   c. Cephalexin
   d. Nitrofurantoin

Answer: b. Antipsychotics can cause QT prolongation, so other drugs that cause QT prolongation should be avoided. Macrolides, fluoroquinolones, and trimethoprim-sulfamethoxazole are common antibiotics that can all cause QT prolongation.

3. A 32-year-old man presents complaining of neck pain. His neck is turned to the right and he states that he has difficulty moving it. He denies any trauma and has not had a fever. He has no previous similar episodes. He has schizophrenia but cannot recall the names of his medications. His vital signs are normal and his examination reveals a palpable spasm of the right trapezius and sternocleidomastoid muscles. What is the most appropriate treatment?
   a. Bromocriptine
   b. Cyclobenzaprine
   c. Diphenhydramine
   d. Morphine

Answer: c. This patient has an acute dystonic reaction to an antipsychotic medication best treated with an anticholinergic medication, such as diphenhydramine or benztropine. Bromocriptine is a dopamine agonist used to treat pituitary disorders and can worsen psychosis. Cyclobenzaprine can be used for typical muscle spasms but will not significantly improve acute dystonia. Morphine may help but does not resolve the underlying problem.

4. A 52-year-old man presents to the emergency department with a cough. He is tachycardic with a temperature of 38.6°C. His chest x-ray has a left lower lobe infiltrate. His lab work is significant for a leukopenia with an absolute neutrophil count of 250 cells/μL. His past medical history is significant for psychiatric illness. Which of the following medications is he most likely to be taking?
   a. Clonidine
   b. Clozapine
   c. Fluoxetine
   d. Lithium

Answer: b. Clozapine is an antipsychotic associated with agranulocytosis and neutropenia. Clonidine is an alpha-adrenergic agonist with no known association with this condition. Fluoxetine is a selective serotonin reuptake inhibitor commonly used in the treatment of depression and is not known to cause neutropenia. Lithium is used as a mood stabilizing medication such as in bipolar disorder and not known to cause an alteration in cell counts.

5. A 23-year-old woman is brought to the emergency department by her boyfriend with a change in mental status. He reports that the patient had her psychiatric medications adjusted 3 days ago and has been confused since then. The patient's vital signs are: blood pressure: 162/100 mm Hg; heart rate: 140 beats/min; respiratory rate: 22 breaths per minute; and temperature: 40.2°C. On physical examination, the patient is noted to have muscle rigidity. Laboratory tests are pending. Intravenous (IV) access is obtained, and balanced crystalloid fluids are started. Cool mist and fans are applied to the patient. What therapy is indicated next?
   a. Acetaminophen
   b. Cyproheptadine
   c. Dantrolene
   d. Lorazepam

Answer: d. The patient has neuroleptic malignant syndrome (NMS) and the best first line treatment option is a benzodiazepine, such as lorazepam. Acetaminophen is ineffective in treating the hyperthermia, which should be treated with active cooling measures. Cyproheptadine can be used in serotonin syndrome but does not improve NMS. Dantrolene can be used in malignant hyperthermia and for refractory, severe muscle rigidity but has no mechanistic indication in NMS, and evidence for its use is of low quality. Diphenhydramine is used for acute dystonia and does not affect the course of NMS.

Opioids

Jenna Karagianis Nikolaides and Trevonne M. Thompson

KEY CONCEPTS

- The opioid toxidrome includes three prominent findings—central nervous system depression, miosis, and, most importantly, respiratory depression—but presentations may be variable.
- A negative urine screen is often unreliable, and absence of detection should not deter a diagnosis of opioid intoxication when clinical findings support it.
- Airway protection, oxygenation, ventilation, and early administration of the reversal agent naloxone are the cornerstones for management of patients with opioid toxicity.
- The duration of action of many opioids, especially after overdose, is significantly longer than that of naloxone. Patients responsive to naloxone should be observed for recurrence of respiratory depression because they may require additional doses of naloxone.
- Naloxone distribution, prescription drug monitoring programs, and initiation of buprenorphine with a referral to addiction treatment programs are ways in which the medical profession is trying to combat the epidemic of opioid-related deaths.
- Opioid withdrawal syndrome does not include altered cognition. Patients with known or suspected opioid withdrawal who also have altered mental status should be evaluated for an alternative cause of altered cognition.

PRINCIPLES OF TOXICITY

Opiate is the term for natural agents derived from the poppy plant that have morphine-like pharmacological effects. Examples of opiates include morphine and codeine. Opioid is the more inclusive term, which refers to any synthetic, semisynthetic, or natural agent that has morphine-like properties. Some common semisynthetic opioids are heroin, hydrocodone, oxycodone, hydromorphone, oxymorphone, and buprenorphine. Some common synthetic opioids are fentanyl, methadone, and meperidine. Both "opiate" and "opioid" are terms derived from "opium," which was the Greek word for the juice of the poppy plant (Papaver somniferum).

Opioids are among the world's oldest known drugs. The therapeutic use of opioids has been a practice since ancient times, with the primary goals being sedation and analgesia. Opioids act on receptors in the central nervous, cardiovascular, pulmonary, and gastrointestinal systems and can also be used therapeutically for their antitussive and antidiarrheal effects.

Pain is a common reason why patients present to the emergency department (ED). Since the Joint Commission placed increased attention on pain management and hospitals increased their emphasis on patient satisfaction, there has been a proliferation in the number of opioid prescriptions written by physicians, including emergency providers. This trend did not lead to an actual improvement in overall patient satisfaction, but rather led to a flood of available opioids into the wider population.[1] According to the Centers for Disease Control and Prevention (CDC), there was a 300% increase in the sale of opioid analgesics from 1999 to 2011. As the medical profession recognized the severity of the subsequent epidemic of deaths due to opioids, the CDC issued new opioid prescribing guidelines[2] in 2016 and prescription rates began to decline.[3]

Opioid-related fatalities continued, however, because of a concomitant rise in illicit heroin use, and a heroin supply that has been mixed with a family of synthetic opioids such as fentanyl. According to the CDC, the death rate from heroin overdose increased five-fold from 2010 to 2017.[4] There has also been a change in demographics of heroin use. Formerly involving primarily inner-city minority populations, in recent years, the use of heroin has spread geographically beyond urban areas[5] and has increased among men and women, in most age groups and at all income levels. Some of the greatest increases have occurred in women, the privately insured, and people with higher incomes.[6] It is now believed that prescription analgesics can be a gateway to heroin use. During 2000 to 2013, approximately three out of four new heroin users reported having misused prescription opioids prior to using heroin.[5]

The wider availability of opioids has affected each population group. This has been especially concerning for pediatric patients, because analgesic prescriptions written for adults can end up in the hands of children and adolescents. From 1999 to 2016, there was an approximate threefold rise in the mortality rate of pediatric opioid poisonings, resulting in the deaths of nearly 9000 children and adolescents.[7] Unintentional opioid overdose is also a growing concern among chronic pain patients, geriatric patients, and obese patients because risk is increased by polypharmacy, medical comorbidities, and sleep apnea.

Opioids come in three forms: synthetic, semisynthetic, and natural opiates. There are prescription versions of all three forms, which are available in many different preparations, including tablets, liquids, patches, and even lollipops. Prescription opioids are commonly packaged as combination preparations with acetaminophen, ibuprofen, and aspirin, and have historically existed in combination with atropine and camphor. Other prescription oral preparations are formulated with opioid-receptor antagonists, such as naloxone, which has little oral bioavailability to prevent illicit use and intentional alteration for intravenous (IV) misuse. There are also prescription drugs that are not chemically classified as opioids, but which have opioid receptor agonist properties, such as tramadol and tapentadol.

Illicit opioids also exist in all three forms. Table 151.1 details some of the known street names for opioids sold illicitly.[8,9] Street names are often unreliable, however, because they tend to be regional and are subject to dealers who attempt to market or rebrand their product to cater to their target population. Heroin (diacetylmorphine), a semisynthetic opioid, is the most widespread street preparation, but recent years have seen a rise in synthetics, such as fentanyl, fentanyl analogues, and other novel substances such as U-47700, often mixed with or mislabeled as heroin. Synthetic opioids have also proliferated in the form of counterfeit pills due to increased demand for prescription opioids on the illicit

TABLE 151.1 Street Names for Illicitly Obtained Opioids

Opioid	Street Names
Heroin	Dope, Smack, H, Horse, Junk, Skag, Skunk, Brown Sugar, White Horse, China White
Heroin + acetaminophen and diphenhydramine	Cheese
Codeine ± acetaminophen	Captain Cody, Cody, Lean, Schoolboy, T-threes, cough syrup
Codeine + promethazine + soft drinks and hard candy	Purple Drank, Sizzurp
Codeine + glutethimide	Doors & Fours, Loads, Pancakes and Syrup
Fentanyl	China White, China Girl, Apache, Dance Fever, Friend, Goodfella, Jackpot, Murder 8, Tango and Cash, TNT
Hydrocodone ± acetaminophen	Vike, Watson-387
Hydromorphone	D, Dillies, Footballs, Juice, Smack
Meperidine	Demmies, Pain Killer
Methadone	Dollies, Amidone, Fizzies
Methadone + MDMA	Chocolate Chip Cookies
Morphine	M, Morph, Miss Emma, Monkey, White Stuff
Oxycodone ± acetaminophen	O.C., Oxycet, Oxycotton, Oxy, Hillbilly Heroin, Percs
Oxymorphone	Biscuits, Blue Heaven, Blues, Mrs. O, O Bomb, Octagons, Stop Signs
Pentazocine	Yellow Footballs

MDMA, N-methyl-3,4-methylenedioxyamphetamine.

drug market.[10] Consequently, the U.S. Drug Enforcement Administration (DEA) added "Fentanyl-Related Substances" to the list of Schedule I drugs in 2018, making it illegal to manufacture, distribute, or possess fentanyl analogs.[11]

Illicit opioid preparations can be contaminated by the byproducts from the manufacturing process, adulterated with additives to change the preparation's pharmacological effects, and diluted with inert substances to increase bulk. The most commonly found additional substances are sugars and starches, talcum powder, caffeine, over-the-counter medications (such as diphenhydramine), prescription medications (including other opioids, quinine, benzodiazepines, and other psychoactive medications such as antipsychotics),[12,13] other illicit drugs (such as cocaine), heavy metals, and spore-forming infectious agents.[14,15] Toxicity can occur as a consequence of intentional overdose, recreational misuse, or as an adverse effect of therapeutic use. Although different opioids have receptor preferences in therapeutic doses, this specificity is lost at higher doses.

Opioids are well absorbed via gastrointestinal, IV, intramuscular (IM), mucocutaneous, and subcutaneous routes of administration. Depending on the lipid solubility of the specific opioid, they can also be absorbed through nasal, buccal, pulmonary, or a specifically formulated transdermal delivery system.[16] In general, toxicity is less pronounced but more prolonged when ingested than with parenteral administration. In therapeutic doses, an ingested opioid is absorbed in the small intestine within 1 to 2 hours. In toxic doses, delayed gastric emptying prolongs the absorption and clinical effects of the opioid.

Most opioids have a large volume of distribution. Different opioids and their metabolites cross into the blood-brain barrier due to variations in lipid solubility. All opioids undergo hepatic metabolism and renal elimination. Thus, changes in hepatic or renal function will alter drug clearance, which could prolong clinical and toxic effects of the specific opioid.

CLINICAL FEATURES

The hallmarks of the opioid toxidrome are central nervous system (CNS) depression, respiratory depression, and miosis. Miosis is caused by stimulation of μ receptors in the Edinger-Westphal nuclei of the third cranial nerve. This effect may be unreliable or masked by coingestants and, thus, respiratory depression is the essential feature of opioid intoxication. Respiratory depression is caused by opioids' effect on the medullary respiratory center via suppressing its sensitivity to hypercapnia and overriding the hypoxic drive. When combined with CNS depression, prolonged hypopnea can lead to hypoxia, causing further neurologic complications and death. Long-term opioid use is known to cause dependence and appears to contribute to central sleep apnea, as well as structural and functional changes in the brain.

Acute lung injury can be seen in opioid overdose, and pulmonary edema can cause further hypoxia. This manifests as desaturations on pulse oximetry, despite an adequate respiratory rate, with rales auscultated on lung examination. The cause of acute lung injury in opioid overdose is not clearly elucidated but may be related to a capillary leak phenomenon.

Other signs and symptoms commonly associated with opioids include relative bradycardia, mild hypotension, pruritus, skin flushing, nausea, vomiting, and bowel dysfunction. Hypotension, pruritus, and flushing are caused by nonallergic histamine release—an effect more pronounced with morphine. Nausea and vomiting are frequently seen, even in therapeutic doses of opioids, and are responsive to antiemetics and more potent opioids. Decreased gastrointestinal motility, delayed gastric emptying, constipation, and ileus are all commonly described with the spectrum of opioid-induced bowel dysfunction.

The skin should be examined in a patient exhibiting the opioid toxidrome because it may give diagnostic clues as to which opioids have been used. Look for the presence of fentanyl patches over the entire body, including in the oropharynx and other bodily orifices. If IV puncture sites or scars from "skin popping" (a process where opioids are injected subcutaneously) are detected, these findings could be signs of illicit opioid use.

Certain opioids have unique clinical findings due to their chemical structure or to their route of exposure (Table 151.2). Propoxyphene is associated with sodium channel blockade properties, causing QRS widening, in addition to PR and QT interval prolongation, which led to its withdrawal from the market. Methadone is known to block the human ether-a-go-go-related gene (hERG) as well as potassium channels, causing QTc prolongation. Propoxyphene, meperidine, and tramadol have been associated with hypertonicity, myoclonus, and seizures. Meperidine, methadone, tramadol, and fentanyl inhibit serotonin reuptake and are associated with serotonin syndrome. Sensorineural hearing loss has been reported with both acute and chronic use of heroin, methadone, and hydrocodone, thought to be due to direct ototoxicity. Heroin has also been found to be associated with Parkinsonian-like symptoms. A practice known as "chasing the dragon," where heroin is heated in aluminum foil and the vapor inhaled, has been found to be associated with spongiform leukoencephalopathy, with symptoms including psychomotor retardation, dysarthria, ataxia, and tremor.

Patients who hastily ingest loosely packaged bags of illicit drugs are known as "body stuffers." Patients who internally conceal dense and meticulously packaged packets of illicit drugs for the purpose of trafficking across international borders are known as "body packers." Heroin is a common drug seen in both stuffers and packers. Both populations are at risk for severe and prolonged opioid toxicity if the

TABLE 151.2 Special Clinical Properties of Certain Opioids

Effect	Opioid
QRS widening, sodium channel blockade	Propoxyphene
QT widening, potassium channel blockade	Methadone
Seizures	Propoxyphene, meperidine
Serotonin syndrome	Meperidine, methadone, tramadol, fentanyl
Hearing loss, ototoxicity	Methadone, hydrocodone, heroin
Spongiform leukoencephalopathy Parkinsonism	Heroin via "chasing the dragon" or inhalation of heroin vapor

packets leak or rupture. Heroin "stuffers" however, generally do not ingest enough to cause serious effects when compared to "packers," who may have several-fold lethal amounts of concentrated product in their gastrointestinal tract.

DIFFERENTIAL DIAGNOSES

The diagnosis of opioid intoxication is usually based on history, vital signs, and physical examination, with recognition of its characteristic toxidrome: hypopnea, stupor, and miosis. All of these findings are not consistently present, and the clinical picture may be complicated by cointoxicants. The essential finding in opioid intoxication is respiratory depression. Other intoxications may present similarly, such as clonidine, guanfacine, tetrahydrozoline, valproic acid, gamma-hydroxybutyrate, ethanol, sedative hypnotics, and atypical antipsychotics. Nontoxicologic considerations include pontine stroke or hemorrhage.

DIAGNOSTIC TESTING

No laboratory test or drug screen should be relied upon by the emergency clinician to make the diagnosis of opioid toxicity. The presence of the toxidrome and rapid response to naloxone are the two most important diagnostic clues. End-tidal carbon dioxide and oxygen saturation monitoring may be helpful for recognition of respiratory depression and hypoxia but are not as necessary as observation of the patient's respiratory rate.

A 12-lead electrocardiogram is a useful diagnostic for identifying QRS widening, as seen in propoxyphene use, or for QTc prolongation, as seen in methadone use. If the patient exhibits audible pulmonary rales on examination, then a chest radiograph is useful to evaluate for the presence of acute lung injury. If the opioid preparation is unknown, then acetaminophen and salicylate levels should be measured, because many prescription opioids are sold as combination preparations with these pain relievers. Hypoglycemia is the only consistent laboratory abnormality found in opioid toxicity. It is generally mild but can contribute to the decreased level of consciousness seen in opioid overdose. In addition, a serum ethanol level should be measured.

If needed for confirmation, a urine drug screen can be obtained once the patient has been stabilized. Nonetheless, a negative urine screen can be unreliable, and absence of detection should not deter a diagnosis of opioid intoxication when clinical findings support it. Opiates or opioids that metabolize to opiates, such as morphine, codeine, and heroin, are reliably detected on most qualitative antibody-based enzymatic immunoassay urine toxicology screens. Some semisynthetic and synthetic opioids, such as oxycodone, methadone, and fentanyl, however, are often missed on typical urine drug screens unless they are specifically measured. A urine test result can remain positive for up to 72 hours after last use, depending on the half-life of the drug used. A large poppy seed ingestion can lead to a positive opiate screen, although federal workplace testing guidelines have raised the confirmatory morphine concentration threshold to 2000 ng/mL to avoid positive screens for commonplace poppy seed ingestions in food sources. Advanced screening methods detecting for 6-monoacetylmorphine, a specific metabolite of heroin, can be used to confirm heroin use, although this test is generally not available in the ED setting.

MANAGEMENT

Stabilization and Supportive Care

The ED clinician should direct efforts at stabilizing the patient's airway, oxygenation, and ventilation. This can be accomplished with a combination of basic supportive measures and titrated use of naloxone. Patients with acute lung injury may require oxygen and positive-pressure modalities, such as bi-level positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), or mechanical ventilation with positive end-expiratory pressure (PEEP).

Decontamination

Because many opioids are extended-release preparations and can also delay gastric motility, activated charcoal has been used in the past but there are no data to support or refute the effectiveness of this practice. Additionally, naloxone is a highly effective antidote for opioid overdose, and sedation from opioid intoxication could conceivably lead to charcoal aspiration. Hence, activated charcoal administration should be considered on a patient-specific basis, but we generally discourage its use in patients with opioid intoxication. Gastric lavage similarly is not recommended because the risks outweigh the benefits. Whole bowel irrigation is not generally useful, but it can be considered for body packers (see Chapter 135).

Enhanced Elimination

As mentioned previously, most opioids have a large volume of distribution. There are no clinically effective techniques for enhanced or extracorporeal elimination of opioids.

Antidote Therapy

Naloxone is a competitive opioid antagonist that rapidly reverses the effects of opioid intoxication. Because of the rapid clinical response, it can also aid in the diagnosis of opioid overdose. Naloxone is ineffective orally because its bioavailability is minimal due to first-pass hepatic metabolism. It is effective via IV, subcutaneous, intramuscular (IM), intranasal (IN), inhalational, and endotracheal routes. It is indicated when an opioid-intoxicated patient has significant CNS or respiratory depression.

In the ED, naloxone is usually administered intravenously with empirical dosing. The dose widely ranges from 0.04 to 15 mg, depending on the amount and formulation of the opioid taken, the patient's weight, and whether the patient is opioid dependent. In general, it is best to start with low doses and to increase each subsequent dose as needed to alleviate respiratory depression. The exception to this rule is the arrest or near-arrest situation where opioids are the suspected cause. In this scenario, recommended starting doses are 0.4 to 4.0 mg IV. In chronic opioid users, the minimal effective naloxone dose should be used so as not to precipitate acute withdrawal. In this population, when respiratory status is adequate, we recommend starting with doses of 0.04 mg of naloxone, followed by titration of subsequent doses. Acute opioid withdrawal can be unpleasant for the habituated patient, but it is not considered life-threatening. Furthermore, naloxone has an excellent safety profile. The clinician should not be reluctant to dose

naloxone as needed, even if opioid withdrawal symptoms develop, in order to ensure adequate patient oxygenation and ventilation.

Naloxone's onset of action, when administered intravenously, is less than 2 minutes, and the duration of action is anywhere between 20 minutes and 2 hours, which is shorter than the duration of action of most opioids. Reversal of respiratory depression usually occurs at low doses, but dosing may be repeated until the desired effect is achieved. If respiratory depression is not reversed after the administration of high doses of naloxone (10 to 15 mg), then it is unlikely that opioid intoxication is the cause of the symptoms. If naloxone does reverse the symptoms but the patient later develops recurrent respiratory depression, then repeated naloxone doses, a continuous naloxone infusion, or endotracheal intubation should be considered. When starting a naloxone infusion, one-half to two-thirds of the bolus dose that effectively reversed intoxication is given hourly, although individual patient responses may vary depending on dose, tolerance, and dependency. This is usually enough to maintain an adequate respiratory effort without producing withdrawal.

In situations where IV access is not easily obtained, naloxone can also be given via IM, IN, IO, or nebulized routes. IN naloxone has proved a viable alternative to IV administration, especially for prehospital providers and nonmedical bystanders. It is available as 0.4 mg/mL and 1 mg/mL solutions, in vials or prefilled syringes, delivered into each nostril using an atomizer device, or as a 4 mg/0.1 mL prepackaged nasal spray.[17] Nebulized naloxone—2 mg of naloxone is mixed with 3 mL of saline—has also been shown to be a safe, effective, and gradual way to reverse opioid intoxication in both the ED and prehospital settings. Care must be taken in selecting the optimal patient for nebulized naloxone. A patient with profound respiratory depression, such as a respiratory rate of less than six breaths per minute or cyanosis, will not receive enough naloxone via a nebulizer to obtain the desired clinical effect.

Nalmefene and naltrexone are opioid antagonists with longer half-lives and duration than naloxone. Nalmefene's duration of action is 4 to 10 hours. Naltrexone is available in an oral preparation, with a duration of action between 24 to 72 hours, and as an extended-release injectable solution, with a duration of action of up to 30 days. We do not recommend their use in the ED because of concern for inducing a prolonged withdrawal state. Naloxone bolus and titration remains the treatment of choice for opioid reversal in the acutely intoxicated patient.

DISPOSITION

Patients who present with heroin toxicity can be successfully treated in the ED. Opioid intoxicated patients who use longer-acting opioids may require an admission to an observation unit. Body stuffers who remain asymptomatic after 6 hours of observation may be discharged. Asymptomatic body packers, however, require admission until all packets have been successfully passed or retrieved. If an overdose is severe, involves multiple drugs, or requires multiple doses of naloxone, naloxone infusion, or endotracheal intubation, then intensive care unit (ICU) admission is appropriate.

The observation period following the administration of naloxone is dependent on the opioid implicated in the poisoning. Overdoses of long-acting opioids or sustained-released opioid preparations will require longer observation periods. In cases of heroin-only overdose, an observation period of up to 4 hours is generally sufficient. After an appropriate observation period, if there are no signs of recurrent toxicity and no concerns for longer-acting coingestants, the patient may be discharged. When indicated, the patient may require a psychiatric evaluation or be referred for substance misuse counseling and an appropriate treatment program.

In recent years, as the opioid overdose epidemic has grown, there have been increased efforts to expand access to naloxone as a public health measure intended to save lives. Most states have passed laws to widen the availability of naloxone to family, friends, and other potential bystanders of an overdose.[18] Community and hospital-based initiatives have worked to educate opioid users and bystanders on signs of overdose, train them for out-of-hospital naloxone use, and then distribute or prescribe naloxone directly to patients or bystanders.[19,20] Both IN and IM auto-injector delivery methods have been used.[21] The number of naloxone prescriptions dispensed from retail pharmacies increased substantially from 2012 to 2018.[22] These programs are showing that providing overdose education and naloxone distribution has decreased opioid overdose mortality.[19,23] Prescribing take-home naloxone is one intervention that the emergency provider can provide to reduce the harm caused by opioids.

Another evolving public health effort is the use of prescription drug monitoring programs (PDMPs), which are currently available in 49 U.S. states, the District of Columbia, and Guam.[24] To decrease the opioid burden in the community, the emergency provider can use these programs to access a patient's prescription opioid history prior to prescribing a new opioid upon discharge. However, while there is some evidence to suggest that states with more robust PDMPs have less overdose deaths,[25] inconsistent implementation has resulted in mixed results regarding the impact PDMPs have on prescribing[26] and on overdose deaths.[27] There have been several proposed solutions, such as improving the technology and its integration into electronic medical records, which may make PDMPs a more useful public health tool in the ED setting.[28]

WITHDRAWAL

Withdrawal occurs in tolerant patients when opioids are abruptly withheld or an antagonist is administered. In withdrawal, the patient goes into a hyperadrenergic state. The symptoms include yawning, piloerection, CNS excitation, tachypnea, mydriasis, tachycardia, hypertension, nausea, vomiting, diarrhea, abdominal cramps, and myalgias. CNS excitation takes the form of restlessness, agitation, dysphoria, and insomnia. Cognition and mental status are usually unaffected. In general, opioid withdrawal is uncomfortable but not life-threatening. As with opioid toxicity, no diagnostic test exists for acute opioid withdrawal. It is diagnosed based on the patient's symptoms, signs, and a history of prior opioid use.

Treatment for the withdrawing patient in the ED has historically been supportive and symptom-based: IV fluids, electrolyte replacement, and antiemetics. Clonidine, an alpha$_2$-agonist, can be used to suppress sympathetic hyperactivity and shorten the duration of withdrawal. However, there are now increased efforts by EDs to use buprenorphine, a long-acting partial opioid agonist approved by the U.S. Food and Drug Administration (FDA) for opioid use disorder, to not only control withdrawal, but to also initiate as a maintenance therapy in the ED as a bridge to long-term addiction treatment.[29] For an emergency provider to be able to prescribe buprenorphine at discharge, additional training to get an X-waiver applied to his or her DEA license is required. Methadone, a full opioid agonist, can also palliate withdrawal and has federal prescribing restrictions, as well. Even without a waiver, emergency providers are permitted to initiate the administration of either buprenorphine or methadone for 72 hours to patients under their care for the purposes of transitioning patients to outpatient treatment through an opioid treatment program or addiction medicine specialist.[30] Opioid withdrawal alone typically does not require inpatient treatment, but some patients with severe symptoms and other comorbidities may require admission. It has been documented that patients who ultimately die from an opioid overdose sharply increase their ED utilization prior to their death.[31] Therefore, treating withdrawal in the ED setting gives emergency providers a sentinel opportunity to engage patients in treatment and long-term recovery.[32]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 151: QUESTIONS AND ANSWERS

1. Most opioids cause mild hypotension related to histamine release and bradycardia. Which of the following opioids can also cause sodium channel blockade and QRS widening?
   a. Hydromorphone
   b. Hydrocodone
   c. Morphine
   d. Oxycodone
   e. Propoxyphene

Answer: e. Propoxyphene and its metabolite norpropoxyphene can cause QRS widening. None of the other listed opioids has significant effects on the cardiac conduction system.

2. Which of the following laboratory abnormalities is most commonly seen in opioid overdose?
   a. Hypocalcemia
   b. Hypochloremia
   c. Hypoglycemia
   d. Hypokalemia
   e. Hyponatremia

Answer: c. Hypoglycemia is the only consistent laboratory abnormality found in opioid overdose. It is generally mild but can contribute to the decreased level of consciousness seen in opioid overdose.

3. A 32-year-old man presents with confusion, nausea, vomiting, diarrhea, and abdominal pain. His friends report that he is withdrawing from heroin. Vital signs reveal mild hypertension, tachycardia, and tachypnea. Physical examination is significant for confusion, mydriasis, diaphoresis, lacrimation, piloerection, and mild diffuse abdominal tenderness. Which of the following signs and symptoms makes you concerned that this may not be a simple opioid withdrawal case?
   a. Confusion
   b. Diarrhea
   c. Mydriasis
   d. Piloerection
   e. Tachycardia

Answer: a. Opioid withdrawal almost always causes restlessness, agitation, and anxiety. Cognition and mental status are not affected in simple opioid withdrawal and, if present, should prompt the clinician to search for other causes instead of, or in addition to, withdrawal.

4. A 20-year-old woman is brought to the emergency department (ED) after being found with decreased mental status at a club. Vital signs indicate mild hypotension and bradycardia. She is drowsy but arousable, and she has an otherwise normal physical examination. Upon receiving naloxone 2 mg IV, her mental status immediately improves and soon thereafter she vomits. She now reports nausea but has no other complaints. She states that she took some "pain pills" to get high but does not know what they were. What diagnostic tests should be performed?
   a. Acetaminophen
   b. Arterial blood gas
   c. Chest radiograph
   d. Lactate
   e. Urine drug screen

Answer: a. Because many prescription opioid medications are combinations of an opioid and acetaminophen, ibuprofen, or salicylate, concentrations of acetaminophen and salicylate should also be ordered. Acetaminophen overdose might otherwise remain undiagnosed but, if identified, can be treated with an existing antidote, *N* acetylcysteine. The chest radiograph is not indicated unless a pulmonary complication is suspected. Lactate and a urine drug screen would not change patient management.

5. Which of the following medications can be used to treat opioid withdrawal?
   a. Clonidine
   b. Dextromethorphan
   c. Diphenhydramine
   d. Nalmefene
   e. Valproic acid

Answer: a. Clonidine suppresses the sympathetic hyperactivity of opioid withdrawal. Dextromethorphan is an opioid derivative used as a cough suppressant, but it does not treat the symptoms of opioid withdrawal. Diphenhydramine is not the most commonly used antihistamine for a patient in withdrawal. Valproic acid has no role in opioid withdrawal. Nalmefene is an opioid antagonist similar to naloxone but with a longer duration of action. Administration of nalmefene is longer-acting than naloxone and would worsen opioid withdrawal symptoms.

6. A 14-month-old child is brought to the emergency department (ED) 4 hours after he was found with his grandmother's antidiarrheal medication bottle. A pill count identifies that only one Lomotil tablet is missing. The child is playful, has a normal respiratory rate and pattern, and has a soft abdomen with normal bowel sounds. Appropriate management includes which of the following?
   a. Administration of activated charcoal
   b. Administration of naloxone
   c. Admission to a monitored unit
   d. Discharge home
   e. Gastric lavage

Answer: c. Activated charcoal and gastric lavage are means of gastrointestinal decontamination and are not routinely recommended in opioid toxicity. Opioid intoxicated patients with central nervous system (CNS) and respiratory depression should be treated with naloxone, but asymptomatic patients do not require antidote administration. Asymptomatic patients with known or suspected Lomotil (diphenoxylate/atropine) ingestion should be observed in a monitored setting for delayed onset of toxicity from the metabolite of diphenoxylate.

7. An 18-year-old male is driven to the emergency department (ED) by friends and carried into the triage area. He has agonal respirations and is cyanotic. Immediate resuscitative measures include bag-valve-mask (BVM) ventilation, establishment of an intravenous (IV) line, and administration of 0.4 mg of naloxone. The patient's respiratory status improves and, although sleepy, he is able to answer some questions. During subsequent monitoring, the patient's respiratory status again declines, and he requires two additional doses of naloxone. Additional treatment should include which of the following?
   a. Nalmefene
   b. Naloxone infusion
   c. Hemodialysis
   d. Naltrexone
   e. Narcan nasal spray

Answer: b. This patient likely has toxicity from a long-acting opioid agent, and a continuous infusion of naloxone will be necessary for ongoing reversal of toxicity. Nalmefene and Naltrexone are a longer-acting opioid antagonists but are not preferred over naloxone infusion because naloxone allows for dose titration. Once multiple doses of IV narcan are given, there is no role for narcan nasal spray. Opioids are not dialyzable due to large volumes of distribution.

CHAPTER 151: QUESTIONS AND ANSWERS—cont'd

8. A 26-year-old female is brought to the emergency department (ED) from the local airport by law enforcement. She is sleepy, with small pupils, and mumbles incoherently in a foreign language. Vital signs include the following: blood pressure, 104/66; respiratory rate, 14 breaths/min; and temperature, 98.6°F. Which of the following tests might identify the cause of this patient's symptoms?

a. Abdominal radiograph
b. Electrocardiogram (ECG)
c. Electroencephalogram (EEG)
d. Head computed tomography (CT)
e. Urine drug screen

Answer: a. An abdominal radiograph would likely reveal multiple packets of illicit opioid in the gastrointestinal tract of this body packer. One or more of the packets has leaked, producing the opioid toxicity. A urine drug screen may not identify an opioid but would not identify the internal packets. A head computed tomography (CT) scan would not be helpful unless associated head trauma is suspected. An EEG and ECG would not provide specific information to identify the internal packets.

152

Pesticides

Katherine Louise Welker and Trevonne M. Thompson

KEY CONCEPTS

- Organophosphates cause symptoms by accumulation of acetylcholine.
  - Treat cholinergic symptoms with atropine.
  - Reverse the inhibition of acetylcholinesterase with oximes.
- Aging, which results in prolonged toxicity, occurs with organophosphate poisoning, but not with carbamates.
- Chlorinated hydrocarbons can present with seizures and cardiac toxicity.
- Substituted phenols are found in weight loss products and exert their toxicity by uncoupling oxidative phosphorylation. These products can cause cardiac, liver, and renal injury.
- Chlorophenoxy compounds cause muscular injury. Measure creatinine kinase; assess for acute rhabdomyolysis, kidney injury, and liver injury.
- Bipyridyl compounds (paraquat and diquat) cause pulmonary and renal injury.
  - Paraquat concentrates in lungs; supplemental oxygen therapy should be limited, since this will exacerbate pulmonary toxicity.
  - Diquat causes renal injury.
- Pyrethrins and pyrethroids cause local dermatologic symptoms.
- Acute toxicity with glyphosate is likely related to the surfactant included in the product.
- DEET (N, N-Diethyl-meta-toluamide) should not be used in infants younger than 2 months old. DEET in concentrations of more than 30% should not be used in children and may result in neurotoxicity and self-limited seizure activity if used in excessive amounts.
- Most rodenticide exposures will be superwarfarin compounds.
  - For large exposures, International Normalized Ratio (INR) should be checked at a minimum of 2 days after ingestion.
  - Vitamin K should be used for reversal; blood products should be used for active bleeding.

Pesticide is a general term that refers to all pest-killing agents. It includes insecticides, herbicides, rodenticides, and fungicides. In this chapter, several classes of pesticides will be discussed, as well as their importance in the emergency department (ED) setting (Table 152.1).

ORGANOPHOSPHATE INSECTICIDES

Foundations

Organophosphates are a class of insecticide that work by inhibiting cholinesterases, including acetylcholinesterase and pseudocholinesterase. This is both the mechanism of their efficacy as insecticides, as well as their toxicity in humans. Inhibition of cholinesterases results in accumulation of acetylcholine at multiple receptors within the autonomic nervous system, such as the sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites (Fig. 152.1).[1]

Organophosphates are lipid soluble and are absorbed through dermal, gastrointestinal, and respiratory routes. This can lead to deposition in fat tissues, allowing for possible toxicity from acute and chronic, low-level exposures. Some organophosphates have active metabolites that can result in delayed toxicity.

For a discussion of chemical warfare nerve agents (e.g., sarin gas and novel "*Novichok*" agents), see Chapter 55.

Clinical Features

Organophosphate toxicity is represented by the "SLUDGE" or "DUMBELS" syndrome (these are acronyms, which are explained in Box 152.1) manifested by accumulation of acetylcholine at receptor sites. The clinical features in any given case are attributable to the location of the receptors affected, the properties of the specific organophosphate product (predominance of nicotinic versus muscarinic effects), and the dose of the exposure. Muscarinic acetylcholine accumulation leads to salivation, lacrimation, urinary incontinence, defecation, emesis, bronchospasm, bronchorrhea, and bradycardia. Nicotinic acetylcholine accumulation leads to tachycardia, tachydysrhythmias, and skeletal muscle fasciculations.

At the neuromuscular junction, excess acetylcholine causes hyperstimulation of the muscles with secondary paralysis, and when the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest. Sympathetic stimulation can lead to diaphoresis. A combination of sympathetic stimulation, involvement of the *N*-methyl-D-aspartate (NMDA) receptor, and enhanced acetylcholine concentrations can induce seizures.[2,3]

Pulmonary edema can occur in organophosphate poisoning and should not be confused with bronchorrhea or bronchospasm. Pulmonary edema results from many factors, including the release of inflammatory mediators and increased vascular permeability. Bronchospasm and bronchorrhea are mediated by both central and local mechanisms involving acetylcholine. Pulmonary edema, bronchospasm, bronchorrhea, and the aforementioned respiratory muscle paralysis all contribute to respiratory failure.

Although the classic clinical picture of acute organophosphate poisoning is more apparent, toxicity from gradual, cumulative exposure may be subtle. These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.

A unique feature of organophosphate insecticides is the process called *aging,* the irreversible conformational change that occurs when the organophosphate is bound to the cholinesterase enzyme for a prolonged time. This causes the clinical effects to persist for periods of days to weeks. The time to aging varies by the specific product involved. Once an enzyme has aged, an oxime antidote (as discussed under Antidote Therapy) cannot regenerate the cholinesterase.

Differential Diagnoses

Differential diagnoses for acetylcholinesterase inhibitor poisoning are limited. Carbamate pesticides, carbamate medications (e.g., rivastigmine), nicotine and other nicotine alkaloids, and cholinomimetics (e.g., pilocarpine) are xenobiotics that can cause a similar constellation of symptoms. There are few medical conditions included in the differential diagnosis: viral and bacterial gastroenteritis, as well as conditions causing exaggerated vagal response (e.g., inferior wall myocardial infarction with pulmonary edema) and conditions that cause exaggerated sympathetic responses (e.g., thyroid storm or pheochromocytoma).

Diagnostic Testing

Patients who present with the classic cholinergic toxidrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity. Known or suspected exposures to organophosphates can be evaluated by assessing plasma and erythrocyte (red blood cell [RBC]) cholinesterase concentrations. These concentrations are not generally available in real-time clinical settings and are usually sent out to regional reference laboratories for analysis.

In acute toxicity, plasma cholinesterase levels decrease first. In chronic, low-level exposure, however, plasma enzyme levels may be normal, but RBC cholinesterase may still be decreased. This is because plasma cholinesterases can recover in 4 to 6 weeks, whereas RBC cholinesterases can take as long as 12 weeks to recover. Other laboratory studies should focus on the evaluation of pulmonary, cardiovascular, and renal function, as well as fluid and electrolyte balance. A measurement of acid-base status should be performed, because patients with metabolic acidosis have higher mortality rates.[1] Both initial hyperglycemia and hypoglycemia in organophosphate-poisoned patients have been shown to be associated with increased mortality and severity of toxicity.[3] Other prognostic tools such as the Glasgow Coma Scale or the Poison Severity Score vary by type of organophosphate and are generally of little clinical utility.[2]

Management

Treatment of organophosphate poisoning is directed toward four goals: (1) decontamination, (2) supportive care with an emphasis on respiratory stabilization, (3) reversal of acetylcholine excess, and (4) reversal

TABLE 152.1 Pesticide Classes and Examples

Pesticide Class	Example(s)
Organophosphates	Parathion, malathion
Carbamates	Aldicarb, carbaryl
Chlorinated hydrocarbons	Dichlorodiphenyltrichloroethane (DDT), gamma-hexachlorocyclohexane (lindane)
Substituted phenols	2,4-dinitrophenol (DNP)
Chlorophenoxy pesticides	2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4-dichlorophenoxyacetic acid (2,4-D)
Bipyridyl pesticides	N, N′-dimethyl-4,4′-bipyridinum dichloride (paraquat), 1,1′-ethylene-2,2′-bipyridyldiylium dibromide (diquat)
Pyrethrins/pyrethroids	Permethrin
Glyphosate	N-(phosphonomethyl)glycine
Insect repellent	N, N-Diethyl-meta-toluamide (DEET)

BOX 152.1 Cholinergic Toxidrome (SLUDGE DUMBELS)

Salivation
Lacrimation
Urinary incontinence
Diarrhea
Gastrointestinal cramps
Emesis
Diarrhea/diaphoresis
Urination
Miosis
(Killer) **B**s: **B**radycardia/bronchorrhea/bronchospasm
Emesis
Lacrimation
Salivation

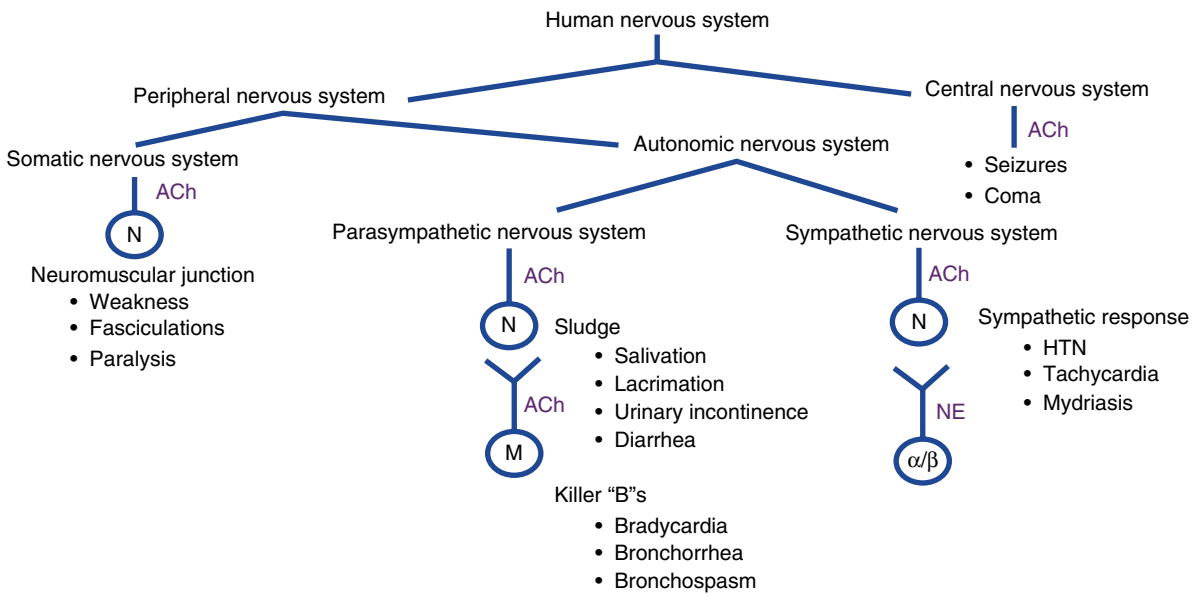

Fig. 152.1 Cholinergic Effects on Nervous System. *ACh,* Acetylcholine; *HTN,* hypertension; *M,* Muscarinic; *N,* nicotinic; *NE,* norepinephrine.

of toxin binding at receptor sites on the cholinesterase molecule. The severity of the patient's signs and symptoms, as well as antidote availability, will guide management.

Decontamination

Decontamination begins in the out-of-hospital setting to prevent further absorption and to protect care providers. Because dermal absorption is likely, removal and destruction of clothing and thorough flushing of exposed skin limits absorption and toxicity. Alternatively, dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite. Due to availability and ease of flushing with water, we recommend this as the primary method of decontamination. Caregivers are at risk for contamination from splashes or handling of contaminated clothing. Personnel may be rotated to limit their exposure to either multiple contaminated patients or patients extensively contaminated (or contaminated with a high concentration product). Caregivers should use universal precautions (level C PPE), which includes a full-face air purifier cartridge mask, eye shield, and protective clothing including a chemical-resistant suit, boots, and nitrile or butyl rubber gloves. In the case of ingestion, neither gastrointestinal decontamination procedures (such as gastric lavage) nor activated charcoal are of benefit. Cholinergic agents are rapidly absorbed and profuse vomiting and diarrhea are seen early in ingestion, negating any beneficial effect of additional gastrointestinal decontamination. Equipment, but not skin, may be washed with a 5% hypochlorite solution.

Stabilization and Supportive Care

Because death is a result of airway and respiratory failure, supportive care should be directed primarily toward airway management and should include suctioning of secretions and vomitus, oxygenation, and ventilatory support. Succinylcholine, 1.5 mg/kg, is commonly used as a paralytic drug for rapid-sequence orotracheal intubation. Succinylcholine, however, is metabolized by cholinesterases and may have a prolonged duration of effect (4 to 6 hours) in the setting of organophosphate poisoning. If succinylcholine is used as a paralytic drug, anticipate the need for prolonged sedation and ventilatory support. We prefer a nondepolarizing paralytic drug not metabolized by cholinesterases (e.g., rocuronium, 1 mg/kg). Tachycardia and tachydysrhythmia generally resolve by treating the underlying cholinergic excess and should not be treated symptomatically (e.g., with beta blockers). Patients with agitation, seizures, and coma should be treated with adequate doses of a benzodiazepine after the airway has been secured and ventilatory support established.

Enhanced Elimination

There is no role for enhanced elimination or extracorporeal techniques of removal, such as hemodialysis, in organophosphate poisoning.

Antidote Therapy

Definitive treatment for organophosphate poisoning is focused on decreasing the amount and effect of acetylcholine at its various receptor sites. This begins with atropine, which is a competitive inhibitor of acetylcholine at muscarinic receptors. The atropine dose for the treatment of organophosphate poisoning is 1 to 3 mg (0.05 mg/kg in children) intravenously with doubling of each subsequent dose every 5 minutes until there is control of the muscarinic effects, particularly reduction in airway secretions. Atropine may initially be administered intramuscularly until intravenous or intraosseous access is obtained. Depending on the specific organophosphate product involved and the degree of poisoning, patients may require as much as 200 to 500 mg of atropine during the first hour. Once the patient has been stabilized with appropriate "atropinization," an infusion is initiated to provide 10% to 20% of the total cumulative dose needed to obtain symptom control per hour. Tachycardia and mydriasis may occur at these atropine doses but are not an indication to discontinue therapy. However, excessive administration of atropine may cause the typical symptoms of the anticholinergic toxidrome. The endpoint of atropinization is drying of respiratory secretions, easing of respiratory effort, and normalization of respiratory rate. Early and rapid atropinization is associated with better control of seizures and reduced mortality in animal models. The recommended atropine dosing regimen can easily exhaust available hospital supplies, and arrangements for alternative sources should be discussed with the appropriate hospital personnel early in the case of an organophosphate poisoning. Other anticholinergic medications, such as diphenhydramine and anticholinergic ophthalmic drugs, have been studied in rodents and may be considered a "last resort" alternative in humans if intravenous atropine is scarce or exhausted. Atropine is not active at nicotinic receptor sites and will not reverse skeletal muscle effects, such as respiratory muscle paralysis.

The second part of the treatment of organophosphate poisoning is the use of an oxime to regenerate acetylcholinesterase function. Oximes bind to the organophosphate-cholinesterase complex, causing a conformational change that allows for the cholinesterase to resume normal function. There are currently five oximes in common use worldwide: pralidoxime (2-PAM), trimedoxime (TMB-4), obidoxime chloride (Toxogonin), methoxime, and asoxime chloride (HI-6). Pralidoxime is the product commonly available in the United States. There are controversies regarding the use of oximes related to dosing, duration of treatment, time to therapy initiation, and effectiveness in treating neurologic symptoms. Despite these controversies, we recommend oximes for the treatment of moderate or severely poisoned patients, defined as those who require multiple, large doses of atropine. Indications for oxime treatment include respiratory depression or failure, muscle fasciculations, seizures, dysrhythmias, hemodynamic instability, or the use of large amounts or repeated doses of atropine to completely control signs and symptoms of organophosphate intoxication. We recommend administering pralidoxime as a 1 to 2 g bolus (25 to 50 mg/kg in pediatric patients) over 30 minutes, which can be repeated as needed (up to hourly) based on response (improved mental status and respiratory and heart rate, as well as decreased secretion). Even higher doses may be required. Alternative dosing options are 2 g bolus over 20 minutes followed by an infusion of 500 mg/h for up to 7 days; 1 g/h every 4 hours; or 30 mg/kg followed by infusion of 8 mg/kg/h (Table 152.2). Oximes can be given intravenously or intramuscularly (as with standard military autoinjectors).

Novel treatments for organophosphate and nerve agent poisoning are under investigation. At present, pyridostigmine is the most commonly used prophylactic drug. Other prophylactics include tablets containing pyridostigmine, trihexyphenidyl and benactyzine, as well as a transdermal patch containing H-series oximes (HI-6).

Disposition

Most patients who present to the ED after significant organophosphate exposure should be admitted to a monitored setting. The effects of organophosphate intoxication can be prolonged. If plasma cholinesterase levels are available, they may be useful for treatment and disposition decisions. Asymptomatic or minimally symptomatic patients with normal or minimally depressed cholinesterase levels may be discharged after 6 hours with close outpatient follow-up to ensure that progressive toxicity does not occur. Patients who present with significant symptoms (e.g., seizures, acute respiratory compromise associated with depressed cholinesterase levels) require admission and continuous monitoring, usually to an intensive care unit (ICU). Patients may have rebound toxicity several days after apparently

TABLE 152.2 Specific Treatment Dosing

Agent	Indication	Adult Dose	Pediatric Dose	Route	Comments
Atropine	Organophosphate toxicity	1–3 mg	0.05 mg/kg	IV, IM	Double dose every 5 min until effect
Pralidoxime	Organophosphate toxicity	1–2 g bolus	25–50 mg/kg	IV, IM	Given over 30 min Dose can be repeated based on response

IM, Intramuscular; *IV,* intravenous.

satisfactory response to initial treatment. This may occur for many reasons, including persistent release of organophosphates from lipid stores. Poisoning with fenthion is of particular concern because initial symptoms could be mild and progress to life-threatening intoxication over time.

The intermediate syndrome (IMS) can occur after the acute intoxication from organophosphates has resolved. IMS manifests with delayed muscle paralysis, including in respiratory muscles, which can occur 24 to 96 hours after the resolution of the cholinergic crisis. The precise cause of IMS is not well documented. Delayed peripheral neuropathy may occur 7 to 21 days after acute organophosphate intoxication.[4] Therefore, close patient follow-up, including a neurological evaluation, is important after stabilization. Finally, those patients with acts of self-harm or suicidal intent require psychiatric consultation once medically stabilized.

Carbamate Insecticides

Carbamates are acetylcholinesterase inhibitors whose toxicological picture is similar to organophosphates. There are two important differences: (1) short duration of effect (minutes to 48 hours) and (2) the process of aging does not occur. Decontamination, supportive care, airway management, and atropinization are usually adequate for treating patients poisoned with these compounds. Severe toxicity, including respiratory depression and seizures, can occur. Because carbamates do not cross the blood-brain barrier as readily as organophosphates, neurotoxicity is less likely. Dosing of atropine is the same as for organophosphates, but the duration of treatment is usually less. There is controversy regarding the use of oximes in carbamate poisoning. We recommend the use of oximes only when the poisoning is severe (as defined for organophosphates) or if the provider cannot differentiate carbamate from organophosphate poisoning.

Chlorinated Hydrocarbons Insecticides

Foundations

Dichlorodiphenyltrichloroethane (DDT) is the best-known example of chlorinated hydrocarbon insecticides. This class is also known as *organochlorine insecticides.* DDT was developed in the late 1800s and first used widely in World War II to reduce mosquito populations in an attempt to prevent transmission of typhus and malaria. It was found to be effective and stable and led to the development of other similar insecticides that were used in agricultural, industrial, and residential settings. Their widespread and indiscriminate use, long half-life, and persistence in the environment resulted in adverse ecologic effects that lead to a ban on most chlorinated hydrocarbons. In the United States, gamma-hexachlorocyclohexane (also known as *lindane*) is a chlorinated hydrocarbon insecticide available as a pharmaceutical drug for the second-line treatment of head lice and scabies. Many U.S. states have banned lindane and restricted its use to physician prescription only.

Principles of Toxicity

Chlorinated hydrocarbon insecticides are highly lipid soluble. They are readily absorbed via dermal, respiratory, and gastrointestinal routes and are stored in fatty tissues. This storage allows for toxicity from repeated, low-level exposure. Lindane toxicity often occurs from excessive dermal exposure or accidental oral exposure.

Chlorinated hydrocarbon insecticides affect neuronal voltage-gated sodium channels. They are also gamma-aminobutyric acid (GABA) antagonists. This results in hyperexcitability and irritability of both central and peripheral neurons. Chlorinated hydrocarbons increase susceptibility to ventricular tachydysrhythmias, as well, because of increased myocardial sensitivity to circulating catecholamines.

Clinical Features

The primary clinical feature of chlorinated hydrocarbon insecticide toxicity is neurologic excitation. This includes muscle fasciculations, ataxia, tremors, delirium, weakness, paresthesias, and, in severe toxicity, paralysis, seizures, and death. Mild premonitory symptoms are not always present prior to serious neurological manifestations; patients can present initially with seizure activity. Hyperthermia can result from muscle fasciculations and seizures. Metabolic acidosis, respiratory failure, and acute renal failure can also occur. Chronic exposure can cause liver toxicity, arrhythmias, menstrual changes, and neuropsychological effects. The most important clue to diagnosing exposure to chlorinated hydrocarbons is a detailed history because there is no specific clinical toxidrome.

Differential Diagnoses

The defining features of chlorinated hydrocarbon insecticide toxicity are neuro-excitation and seizure. Differential diagnoses are broad, including any disorder or toxic exposure that can lead to seizures (e.g., organophosphates, isoniazid, theophylline, sympathomimetic agents, lead, ethanol, and benzodiazepine or alcohol withdrawal).

Diagnostic Testing

The diagnosis of chlorinated hydrocarbon insecticide poisoning is determined by history and clinical features. Some reference laboratories can measure chlorinated hydrocarbons from fat or plasma samples, but this will not be readily available during emergency treatment. An electrolyte panel, creatinine kinase, and blood gas should be measured on patients with known or suspected acute poisoning.

Management

Decontamination

The first step in chlorinated hydrocarbon insecticide toxicity is decontamination. Remove all clothing and wash the skin and hair with soap and water. Ingested chlorinated hydrocarbons are rapidly absorbed by the gastrointestinal tract; therefore, decontamination with activated charcoal has no clinical effectiveness.

Stabilization and Supportive Care

The main objective in treating chlorinated hydrocarbon toxicity is cessation of seizures. Benzodiazepines and barbiturates are the mainstays of therapy to treat seizures. Chlorinated hydrocarbons can cause myocardial sensitization that can lead to ventricular

tachydysrhythmias, which are most commonly seen around the time of seizure activity due to a catecholamine surge. Beta-adrenergic antagonists (e.g., intravenous metoprolol, 5 mg boluses every 5 minutes) are recommended for treating any life-threatening tachydysrhythmias (e.g., ventricular tachycardia and fibrillation). Prolonged seizures can lead to hyperthermia. Seizure control with benzodiazepines and external cooling with evaporative cooling methods should be implemented if severe hyperthermia is present. Other complications such as metabolic acidosis, rhabdomyolysis, and acute kidney injury are treated with intravenous crystalloid hydration and, in the case of rhabdomyolysis, alkalinization, as described in Chapter 116.

Enhanced Elimination

There is no role for enhanced elimination of chlorinated hydrocarbon insecticides in the ED.

Antidote Therapy

There is no known antidotal therapy for chlorinated hydrocarbon insecticides.

Disposition

Patients who present symptomatic with chlorinated hydrocarbon insecticide poisoning require admission for evaluation, monitoring, and treatment of neurologic and metabolic derangements.

SUBSTITUTED PHENOLS

Foundations

Dinitrophenol (DNP), pentachlorophenol, and dinitrocresol belong to a class of compounds called *substituted phenols* and have been used as dyes, wood preservatives, photograph developers, and insecticides. DNP was previously used as a weight loss medication but has not been available by prescription since the 1930s because of fatalities associated with its use. DNP is currently used as a weight loss supplement and is readily available over the internet. It can be easily obtained from online nutritional supplement retailers and is available in powder, capsule, and crystalline form. The most common route of exposure is oral, but substituted phenols can also be absorbed dermally or inhaled.

Principles of Toxicity

Substituted phenols uncouple oxidative phosphorylation. This results in decreased adenosine triphosphate (ATP) formation and increased heat generation, which is the mechanism of action for DNP in weight loss because calories are burned excessively. DNP also stimulates glycolysis, which, along with the uncoupling of oxidative phosphorylation, increases lactic acid production.

Clinical Features

Patients with acute toxicity from substituted phenols present with hyperthermia, tachycardia, diaphoresis, and tachypnea. Neurologic signs and symptoms include confusion, agitation, seizures, and coma. Rhabdomyolysis, myocardial injury, acute kidney injury, and hepatic damage can occur in acute toxicity. These patients can progress to cardiovascular collapse and death. Dermal exposure can cause a yellow discoloration of the skin and corrosive injury.

Differential Diagnoses

Patients suffering from the toxic effects of substituted phenols will appear to have sympathomimetic excess. This leads to a broad differential diagnosis that includes toxicologic, infectious, and environmental considerations, such as cocaine and amphetamine toxicity, encephalitis, and heat stroke (Table 152.3). Since substituted phenols act by uncoupling oxidative phosphorylation, salicylate toxicity should also be considered in the differential diagnosis. An accurate history is important to the diagnosis of substituted phenol intoxication.

TABLE 152.3 Differential Diagnoses for Substituted Phenol Poisoning

Toxicological	Infectious	Environmental
Cocaine	Meningitis	Hyperthermia
Salicylates	Encephalitis	Heat stroke
Amphetamines/MDMA	Sepsis	
Caffeine		
Other sympathomimetics		

MDMA, N-methyl-3,4-methylenedioxyamphetamine.

Diagnostic Testing

Diagnostic testing focuses on the metabolic disturbances and potential organ damage associated with acute substituted phenol toxicity. Serum electrolytes and renal function are to be assessed. Liver studies should be performed, and creatinine kinase is measured to assess for rhabdomyolysis. An electrocardiogram (ECG) and laboratory assessment for myocardial injury with serial cardiac markers (troponin) is advised for any patient with symptoms consistent with myocardial ischemia.

Management

Decontamination

Patients who present with dermal exposure should have their clothing removed and skin washed with soap and water. Because of the potential lethality of phenol-containing compounds with no effective antidote, a patient presenting within 1 hour of an acute oral ingestion who is alert and cooperative should be given oral activated charcoal (at least 100 g in adults).

Stabilization and Supportive Care

Supportive care is the mainstay of treatment for substituted phenol toxicity. Patients with hyperthermia (temperature >102.5°F) should be cooled with evaporative cooling, a cooling blanket, cold intravenous fluids, and strategically placed ice packs. Patients should be given adequate crystalloid fluid resuscitation and electrolyte derangements should be corrected. This is especially important in hyperthermic patients. Agitation and seizures should be treated with benzodiazepines, such as lorazepam (1 to 2 mg intravenous push [IVP]) or diazepam (5 to 10 mg IVP).

Enhanced Elimination

There is no known role for enhanced elimination in substituted phenol toxicity.

Antidote Therapy

There is no known antidote for acute phenol poisoning.

Disposition

Patients who manifest symptoms after substituted phenol exposure should be admitted for intensive cardiac and neurologic monitoring and treatment. A patient who presents asymptomatically after an exposure should be observed for 8 to 12 hours and may be safely discharged if they remain asymptomatic over that period of time.

CHLOROPHENOXY HERBICIDES

Foundations and Principles of Toxicity

Chlorophenoxy compounds are effective herbicides for broad-leaved weeds. This class of herbicides includes 2-methyl-4-chlorophenoxyacetic acid (MCPA), methylchlorophenoxypropionic acid (MCPP), and 2,4-dichlorophenoxyacetic acid (2,4-D). Chlorophenoxy herbicides are widely used in both commercial and residential settings.

Chlorophenoxy herbicides are absorbed through the gastrointestinal tract, skin, and respiratory tract. Most cases of toxicity, however, result from ingestion. Skeletal muscle is the primary organ of toxicity, although the exact mechanism of action is not well defined. Proposed mechanisms of action include direct cell membrane damage, forming analogues of acetyl-CoA and acting as false cholinergic messengers, and at high doses, uncoupling of oxidative phosphorylation.[5]

Clinical Features

Ingestion of chlorophenoxy herbicides can result in gastrointestinal symptoms that include vomiting, abdominal pain, diarrhea, oropharyngeal burning, and gastrointestinal hemorrhage. Other symptoms include muscle fasciculations, weakness, myotonia, and decreased tendon reflexes. Myotonia and fasciculations may lead to rhabdomyolysis and metabolic acidosis.[5]

Differential Diagnoses

Severe toxicity from chlorophenoxy herbicides is rare. When symptoms are present, other possible diagnoses include other causes of acute myopathy. When gastrointestinal symptoms are present, viral and bacterial gastroenteritis, ingestion of caustic substances, organophosphate, and carbamate exposure are other considerations.

Diagnostic Testing

Testing for chlorophenoxy herbicides is not available in the emergency setting. Diagnostic testing should focus on assessing skeletal muscle damage and its consequences. Measurement of creatinine kinase, electrolyte profile, renal function, liver function, and acid base status are indicated.

Management

Decontamination

In the case of a dermal exposure, remove the clothing and wash the skin with soapy water. Because chlorophenoxy herbicides are rapidly absorbed via the gastrointestinal tract and vomiting may occur early, activated charcoal is not indicated.

Stabilization and Supportive Care

Supportive care with fluid resuscitation is the mainstay of treatment for patients symptomatic after chlorophenoxy herbicides.

Enhanced Elimination

In the rare event of a critically ill patient (patients requiring ventilator, hemodynamic support, and those with seizures, hyperthermia, or significant metabolic derangements) who presents after chlorophenoxy herbicide poisoning, urinary alkalinization or hemodialysis can be used to enhance elimination.

Antidote Therapy

There is no known antidote for chlorophenoxy herbicide toxicity.

Disposition

A patient who presents with muscular symptoms after chlorophenoxy herbicide toxicity should be admitted and carefully monitored for progression of symptoms. A patient who is asymptomatic at presentation should be monitored for 6 hours. If no symptoms develop, the patient can be safely discharged home.

BIPYRIDYL HERBICIDES

The bipyridyl (also called *dipyridyl*) herbicides paraquat and diquat are extremely effective contact herbicides that are widely used throughout the world. Paraquat is particularly toxic to humans and is under strict regulation in the United States. Diquat is less toxic and is subject to less regulation.

Foundations and Principles of Toxicity

Paraquat causes the production of superoxides created during cyclic oxidation-reduction reactions in tissues. This causes oxygen radical damage that results in cell death.[6] Paraquat selectively concentrates in the lungs, regardless of the route of exposure, because of an uptake mechanism in alveolar cells. High concentration of oxygen in the pulmonary system increases the extent of paraquat-induced oxygen radical injury; therefore, the lungs are the major target in paraquat poisoning. Paraquat exposure can lead to adult respiratory distress syndrome, progressive pulmonary fibrosis, and respiratory failure. Paraquat damages other organ systems by the same oxygen radical injury effect, including the liver, kidneys, heart, and central nervous system. Diquat has a similar mechanism of action but does not accumulate in the lungs as does paraquat. Diquat concentrates in the kidneys and often results in renal failure. Paraquat is absorbed through the skin, gastrointestinal tract, and respiratory tract. Diquat is poorly absorbed through intact dermis.

Clinical Features

Paraquat and diquat are corrosive and can cause vomiting and caustic injury to the oropharynx, esophagus, and gastrointestinal tract. Dermal exposure can cause corrosive injury to the skin. Systemic toxicity from both paraquat and diquat poisoning will often progress to multiorgan failure and death. This is especially true for paraquat, which can be fatal in small amounts. Patients who survive systemic toxicity from paraquat often develop a progressive pulmonary fibrosis 1 to 3 weeks after the exposure. The clinical course, however, is dependent on the dose of the exposure.

Differential Diagnoses

Bipyridyl herbicides are corrosive and the differential diagnosis encompasses other caustic agents (e.g., acids and alkalis), insecticides (organophosphates and carbamates), and pulmonary toxic chemotherapy agents (e.g., bleomycin). The subsequent systemic toxicity and multiorgan failure with bipyridyl herbicide poisoning could be attributable to other sources of similar symptoms, such as sepsis and acute respiratory distress syndrome (ARDS).

Diagnostic Testing

The cornerstone of diagnosing bipyridyl herbicide poisoning lies in the history of exposure. There is a colorimetric test to detect diquat and paraquat in urine that can be useful but is not readily available in the United States. Serum concentrations of bipyridyl herbicides can be measured but are generally not available in a time frame useful in the ED; however, the concentration paired with the time of ingestion can be used for mortality prognostication.

Multiorgan failure is possible after bipyridyl herbicide poisoning. Laboratory evaluation for respiratory, renal, hepatic, metabolic, and cardiovascular toxicity is indicated. Serial chest radiographs and arterial blood gases are recommended for symptomatic patients.

Management

Decontamination

Dermal exposure should be treated by removing soiled clothing and washing the skin with water. In general, gastrointestinal decontamination is not indicated in the case of caustic ingestions. Because bipyridyl herbicides, particularly paraquat, can cause systemic toxicity in small amounts, gastrointestinal decontamination may be warranted in these cases of ingestion. We recommend at least 100 g activated charcoal or Fuller's earth (in certain international settings) if an alert patient presents early, within 1 hour of the ingestion, because this toxicity has high morbidity and mortality without any antidotal therapy.

Stabilization and Supportive Care

Upper airway corrosive injury can lead to an obstructed airway. Orotracheal intubation is necessary when there is any concern for pending obstruction. Because of the oxygen radical damage, supplemental oxygenation should be targeted to an oxyhemoglobin saturation of 90% to 95%, and excessive supplemental oxygen should be avoided. Supportive care for multiorgan failure is indicated based on the clinical circumstances.

Enhanced Elimination

The use of hemodialysis to increase the elimination of paraquat or diquat is controversial. If renal failure, metabolic acidosis, or electrolyte imbalance develops as a result of the poisoning, hemodialysis is indicated.

Antidote Therapy

There is currently no specific antidotal therapy for bipyridyl herbicide poisoning. Antioxidants, immune modulators, and corticosteroids have been incompletely evaluated as options for therapy to prevent the delayed pulmonary fibrosis. There is currently insufficient data to recommend specific antidotal treatment in the ED.

Disposition

Due to potential high lethality, patients presenting with bipyridyl poisoning require admission to an ICU setting. As with any pesticide or herbicide exposure, those patients with acts of self-harm or suicidal intent require psychiatric consultation once medically stabilized.

PYRETHRIN AND PYRETHROID INSECTICIDES

Pyrethrins are naturally occurring insecticides derived from the chrysanthemum plant. Pyrethroids are synthetic derivatives of pyrethrins that are more stable in the environment.

Foundations and Principles of Toxicity

In humans, pyrethrins block voltage-gated sodium channels, voltage-gated calcium channels, and the chloride channels on GABA receptors. Toxicity in humans, however, is not common. Pyrethrins and pyrethroids are used both as commercial insecticides and pharmaceutically to treat human infestations of scabies and lice (e.g., permethrin). Pyrethrins and pyrethroids are poorly absorbed dermally but are well absorbed via gastrointestinal and respiratory routes.

Clinical Features

Toxicity from pyrethrins and pyrethroids is rare. Allergic and sensitivity reactions can be seen with exposure. Skin exposure can result in erythema. Inhalation can result in rhinitis, sneezing, oral mucosa irritation, cough, dyspnea, wheezing, and chest pain. Nausea, vomiting, abdominal pain, and diarrhea can occur after ingestion; in severe cases, this can contribute to metabolic acidosis.[7] With massive ingestions, the patient is at risk for neurological symptoms, such as numbness, tremors, ataxia, paralysis, seizures, and cerebral infarction.[8]

Differential Diagnoses

Sensitivity reactions seen with exposure to pyrethrins and pyrethroids can mimic allergic reactions or contact dermatitis from other etiologies.

Diagnostic Testing

There are no laboratory or diagnostic tests specific to poisoning from pyrethrins and pyrethroids in the ED setting.

Management

Decontamination

In the case of dermal exposure, clothing should be removed and skin washed with water.

Stabilization and Supportive Care

Skin reactions should be treated symptomatically with histamine blockers, such as diphenhydramine. Wheezing should be treated with beta agonists. Neurologic symptoms can be treated with benzodiazepines as needed (lorazepam, 1 to 2 mg IVP; diazepam, 5 to 10 mg IVP).

Enhanced Elimination

There is no role for enhanced elimination in pyrethrin and pyrethroid poisoning.

Antidote Therapy

There is no known antidotal therapy for pyrethrin and pyrethroid poisoning.

Disposition

Most cases of pyrethrin and pyrethroid exposure will not demonstrate signs of toxicity and can be safely discharged from the ED. Patients with massive ingestions should be observed for 24 hours for the development of neurologic symptoms. Any patient with neurologic symptoms should be admitted to a monitored setting.

GLYPHOSATE

Glyphosate is one of the most commonly used pesticides in the United States. It is a nonselective, contact herbicide that interferes with amino acid synthesis in plants. Recent in vitro studies have shown that glyphosate causes DNA damage and mitochondrial-driven apoptosis, resulting in potential human toxicity.[9] There is much controversy regarding whether glyphosate is associated with cancer in humans; however, this issue is less pertinent to the ED management in an acute exposure.[10,11]

Foundations and Principles of Toxicity

Glyphosate is poorly absorbed dermally. It is absorbed through the gastrointestinal tract. Concentrated solutions (40%) can cause mucosal injury. The residential concentration is 1%. Human acute toxicity is thought to be due to the surfactant included in the glyphosate preparation. Unintentional ingestion of glyphosate generally results in mild

gastrointestinal symptoms. Hypotension, renal failure, respiratory distress, and death can occur from intentional, massive ingestions.

Clinical Features

Patients who present with dermal exposure to glyphosate will likely have no signs of toxicity. However, one case of a large exposure (unclear if inhalational or dermal) resulted in vasculitic peripheral neuropathy.[12] Most ingestions of dilute preparations cause only mild gastrointestinal symptoms. Patients ingesting large volumes of dilute solutions or moderate volumes of concentrated solutions may develop sore throat, nausea, vomiting, abdominal pain, hyperthermia, respiratory distress, acute lung injury, renal failure, and coma. Metabolic acidosis may develop as a result of cardiovascular compromise. Poor prognostic features include altered mental status, hyperkalemia, and renal failure.

Differential Diagnoses

The differential diagnosis of glyphosate poisoning includes caustic ingestions and other causes of respiratory distress or cardiovascular compromise from other pesticides (e.g., organophosphates and carbamates) and herbicides (e.g., paraquat and diquat).

Diagnostic Testing

The key to the diagnosis of glyphosate poisoning is to obtain an accurate history of exposure. An electrolyte profile is recommended to assess for hyperkalemia. A creatinine concentration assesses for renal injury. If respiratory distress is present, a chest radiograph should be performed. We recommend measuring acid-base status with a venous or arterial blood gas to assess extent of respiratory compromise and for comparison with serial measurements to ascertain whether the patient is clinically improving or deteriorating.

Management

Decontamination

With dermal exposure, remove the clothing and wash the skin with water. Gastrointestinal symptoms are generally present with significant ingestions, and activated charcoal is not indicated.

Stabilization and Supportive Care

The mainstay of management of acute glyphosate exposure is supportive care. Provide airway management and cardiovascular support as indicated by the symptom profile. Hyperkalemia can be managed by standard measures.

Enhanced Elimination

There is no role for enhanced elimination in the management of glyphosate poisoning.

Antidote Therapy

There is no known antidote for glyphosate poisoning.

Disposition

Patients who demonstrate symptoms after glyphosate ingestion should be admitted for further management. Patients who present after unintentional exposures of small amounts or low concentrations of glyphosate can be discharged from the ED after a 6-hour observation period.

DEET

N, N-diethyl-m-toluamide, or DEET, is not technically a pesticide. It is the most widely used insect repellant used throughout the world. DEET is available in concentrations ranging from 5% to 100%, and it primarily repels mosquitoes and ticks. The American Academy of Pediatrics recommends 30% as the maximum concentration for use in children and does not recommend use of DEET in infants younger than 2 months old. It is available as lotions, aerosols, pump sprays, roll-on applicators, and impregnated towelettes. Concentrated DEET solutions (up to 100%) can cause plastic products, such as sunglasses and water bottles, to melt with contact.

Foundations and Principles of Toxicology

DEET is lipid soluble and is well absorbed when applied to the skin or ingested. Repeated exposure, skin wounds or abrasions, sweating, and elevated skin temperature increase absorption. DEET affects the central nervous system at the GABA receptors in humans.

Clinical Features

Most exposures to DEET result in minimal or no symptoms. Prolonged skin contact may lead to contact dermatitis, and prolonged contact with higher concentrations can lead to skin blisters. Ingestion of DEET can result in nausea, vomiting, and oral mucosal irritation. Ingestion or excessive skin exposure can lead to headache, liver injury, lethargy, respiratory depression, seizures, and coma.

Differential Diagnoses

The differential diagnosis for DEET poisoning includes any infectious (malaria, encephalitis) toxicological (pesticides, organophosphates, carbamates), metabolic, or neurologic abnormality that could cause seizures and depressed mental status.

Diagnostic Testing

There is no specific test for DEET poisoning that is useful in the ED.

Management

Decontamination

In patients with excessive or prolonged skin exposure to DEET, wash the skin with water. Gastrointestinal decontamination has no role in DEET ingestions because of rapid absorption and the potential for seizure activity.

Stabilization and Supportive Care

Supportive care is the mainstay of treatment for a DEET-poisoned patient. Seizures should be treated with benzodiazepines (lorazepam, 1 to 2 mg IVP; diazepam, 5 to 10 mg IVP) and are generally self-limited.

Enhanced Elimination

There is no role for enhanced elimination with DEET exposure.

Antidote Therapy

There is no known antidote for DEET poisoning.

Disposition

Any patient with acute neurologic symptoms after DEET exposure should be admitted. An asymptomatic patient after an oral ingestion or a patient with localized skin reaction can be discharged after a 6-hour observation period.

RODENTICIDES

Foundations

There are hundreds of rodenticides available throughout the world with variable toxicity (Table 152.4). Rodenticides are implicated in self-harm attempts, malicious poisonings, and accidental ingestions. In the United States, anticoagulants, or superwarfarin-type, are the most common rodenticides, accounting for over 90% of exposures. They are

TABLE 152.4 Rodenticides (Acronym: RATS PANIC)

R SUPER WARFARINS	AT FLUORACETAMIDE	S STRYCHNINE	P PHOSPHORUS	A ALUMINUM[1]	NIC NICOTINAMIDE
Rodenticide	SMFA, fluoroacetamide 1080–1972; banned in 1972 Today: Sheep collars	Moles, gophers, pigeons Adulterant in heroin and cocaine	Yellow (white) phosphorus	Aluminum and zinc phosphide ("rice tablet")	Vacor: 2% PNU banned in 1979
Mechanism	Irreversible TCA cycle inhibitor (fluorocitrate is "suicide inhibitor")	Competitive inhibitor of glycine binding (increased neuronal excitability)	Corrosive, cellular poison Combusts at room temp	Unknown (inhibit electron transport chain, release phosphine gas with moisture and gastric acid)	Unknown (antagonizes nicotinamide axons and injures pancreatic cells)
Effects	GI: Nausea/vomiting/diarrhea/pain Respiratory distress Seizures Cardiotoxicity Hypotension	"Awake seizure" Risus sardonicus Opisthotonus Hyperthermia, rhabdomyolysis	Respiratory "Phossy jaw" GI ("smoking" stool), liver failure Neuro, cardio Eye Skin (burns)	Delayed pulmonary edema, ARDS, GI, neurologic, cardio, hepatic, adrenal Refractory hypotension Metabolic acidosis	Nausea/vomiting Orthostatic hypotension Diabetes mellitus Neuropathy, coma
Diagnosis	Electrolytes, BUN/Cr, calcium, LFTs ECG, MRI Levels not helpful acutely	Cramps, awake seizure, electrolytes, BUN/Cr, CPK, ABG, serum levels do not correlate with toxicity	Garlic odor Burns (skin fluoresces) BUN/Cr, calcium, LFTs UA ABG, chest x-ray, ECG	Fishy/garlic odor BUN/Cr, electrolytes, LFTs ABG, chest x-ray	History Sudden orthostatic hypotension or DM Electrolytes, glucose, BUN/Cr
Treatment	Decontaminate Activated charcoal Supportive care	Stabilization and supportive care Limit stimulation Benzodiazepines for seizures, analgesia	PPE Decontaminate Sand or water over solid phosphorus	Benzodiazepines for seizures, steroids for adrenal dysfunction, magnesium for refractory arrhythmia	IVFs, activated charcoal Nicotinamide Insulin Steroids
Disposition	ICU for CNS, CV symptoms—more than rapid death	ICU if symptomatic Symptoms several hours (supportive care)	Likely ICU admission if significant exposure Isolation (patient and secretions)	Observe at least 72 hours for delayed effects	Admit for delayed neurologic symptoms Neuropathy/DM after several days

Modified from the original acronym created by Jack Snyder, MD.

ABG, Arterial blood gas; *ARDS,* acute respiratory distress syndrome; *BUN/Cr,* blood urea nitrogen/creatinine; *CNS,* central nervous system; *CPK,* creatine phosphokinase; *CV,* cardiovascular; *DM,* diabetes mellitus; *ECG,* electrocardiogram; *GI,* gastrointestinal; *ICU,* intensive care unit; *IVF,* intravenous fluids; *LFT,* liver function test; *MRI,* magnetic resonance imaging; *PNU,* N-3-pyridylmethyl-N′-*p*-nitrophenyl urea; *PPE,* personal protective equipment; *SMFA,* sodium monofluoroacetate; *TCA,* tricarboxylic acid; *UA,* urine analysis.

Hassan NAM, Madboly AG. Correlation between serum creatine phosphokinase and severity of acute organophosphorus poisoning: a prospective clinical study (2012–2013). *IOSR J Environ Sci Toxicol Food Tech*. 4(5):18–29, 2013.

long-acting, anti-vitamin K anticoagulants. Examples are brodifacoum, diphacinone, bromadiolone, chlorophacinone, and difenacoum.

Principles of Toxicology

Superwarfarins competitively inhibit vitamin K and the hepatic synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X. These anticoagulants can also damage capillary walls, increasing permeability and fragility and exacerbating bleeding. Effects are prolonged in these long-acting anticoagulants—half-life of 150 hours versus 15 hours in first generation warfarins, leading to toxic effects that can last for months. All significant toxicological exposures are via ingestion, and all warfarins are well absorbed orally.

Clinical Features

Initially, patients can by asymptomatic and remain so for as long as 72 hours after ingestion, even with large ingestions. Alternatively, signs of gastrointestinal irritation can predominate early in the course of poisoning, and symptoms appear as early as 8 hours after exposure. They can then present with bleeding anywhere in the body, as evidenced by ecchymosis, epistaxis, hemarthrosis, gingival bleeding, menorrhagia, and hematuria. Life-threatening effects are massive gastrointestinal bleeding and intracranial hemorrhage.

Differential Diagnoses

The differential diagnosis includes supratherapeutic doses of warfarin, advanced stages of hepatic failure, disseminated intravascular coagulation, hemophilia, oncological diseases, and other hematological disorders that can present with similar bleeding symptoms.

Diagnostic Testing

Measure hemoglobin/hematocrit, platelets, prothrombin time (PT)/international normalized ratio (INR), and partial thromboplastin time (PTT). Additionally, obtain blood type and screen as well as crossmatch (if actively bleeding). PT/INR might not be abnormal until 48 hours after ingestion; a normal INR at 48 hours essentially excludes a significant ingestion. Although most rodenticides are not commonly

measurable, brodifacoum level is available at many reference labs (<4 to 10 ng/mL is normal and generally does not cause coagulopathy).

Management

Decontamination

If a patient presents within 1 hour after reported massive ingestion of superwarfarin, we recommend oral activated charcoal in a 10:1 activated charcoal to poison ratio. If the dose ingested is unknown, 100 g is an appropriate dose. Do not perform gastric lavage, because, in addition to a lack of clinical efficacy, it adds the additional risk of inducing gastrointestinal bleeding with insertion of a large orogastric tube.

Stabilization and Supportive Care

With massive blood loss, fluid resuscitation and transfusion are necessary. Packed RBCs to replace blood loss, fresh frozen plasma to improve coagulation profile, and four-factor prothrombin complex concentrate (PCC) are proven to be beneficial and are considered first-line treatments. Another option shown to be beneficial is recombinant activated factor VII.

Enhanced Elimination

There is no role for enhanced elimination in superwarfarin toxicity.

Antidote Therapy

Vitamin K_1, (as opposed to K_3 or K_4), is the preferred antidote, or reversal agent, because other forms are not effective and have potential for toxicity. Although vitamin K_1 will reliably reverse anticoagulation, it should not be given prophylactically; toxicity is determined by derangement in INR. This therapy requires 6 hours to take effect and, therefore, is not used for immediate reversal. This pharmacokinetic principle explains the usual vitamin K dosing regimen of every 6 hours. Prolonged treatment with doses as high as 800 mg daily has been required in massive overdoses.

Disposition

The majority of patients with small warfarin-based rodenticide ingestions (e.g., children tasting two to three pellets) can be discharged home with outpatient follow-up in 48 to 72 hours. Patients presenting with reported large intentional ingestion of superwarfarins (i.e., an entire box or bait tray) should be admitted for at least 48 hours, at which time an INR should be checked (minimum time after ingestion to check INR is 48 hours). In patients with coagulopathy, admission is required until all bleeding has subsided, and the patient is maintained on a vitamin K regimen for desired INR. On an outpatient basis, these patients may require monitoring of their coagulation profile for 4 to 6 weeks with the longer-acting superwarfarin products. Patients with acts of self-harm or suicidal intent require psychiatric consultation once medically stabilized.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 152: QUESTIONS AND ANSWERS

1. A 37-year-old man arrives at the emergency department (ED) after exposure to an organophosphate. He is severely symptomatic, and atropine is given. When should atropine treatment be discontinued?

a. After 100 mg has been given
b. When fasciculations stop
c. When mydriasis occurs
d. When secretions have stopped
e. When tachycardia occurs

Answer: d. Patients with organophosphate poisoning may require very large doses of atropine (up to 500 mg). Proper dosing is 1 or 2 mg intravenously, with doubling of the dose every 5 minutes until the drying of secretions. Atropine has no effect at the neuromuscular junction. Mydriasis may occur before secretions have dried. Tachycardia is likely, but it is not a contraindication for continued atropine treatment. The tachycardia often improves as the pulmonary status improves.

2. A 30-year-old agricultural worker arrives at the emergency department (ED) with confusion, abdominal pain, nausea, vomiting, and shortness of breath. His coworkers report that he was spraying plants with an insecticide. The patient's vital signs are significant for hypotension, bradycardia, and tachypnea. Physical examination reveals miosis, wheezing, vomiting, diarrhea, and urinary incontinence. Which clinical finding is associated with higher mortality?

a. Hyperglycemia
b. Hypoglycemia
c. Glasgow Coma Scale (GCS) ≤3
d. Acidosis
e. Poison Severity Score (PSS) 4

Answer: d. This patient has symptoms of the cholinergic syndrome (SLUDGE symptoms) and was likely exposed to an organophosphate or carbamate pesticide. Patients poisoned with organophosphate or carbamate pesticides that are acidotic have a higher mortality than those with normal acid-base status. Elevated and decreased glucose concentrations have both been associated with increased morbidity and mortality. As for PSS and GCS, these vary by type of poisoning and cannot reliably be used to determine risk of fatality.

3. A 4-year-old boy arrives at the emergency department (ED) after drinking a medication that was being used to treat his sister's head lice. An unknown amount was consumed, and the bottle is not available. The patient's only complaint is of nausea. Vital signs and physical examination findings are normal. Which of the following symptoms should be anticipated?

a. Gastrointestinal hemorrhage
b. Hallucinations
c. Hypotension
d. Paralysis
e. Seizure

Answer: e. Lindane is a chlorinated hydrocarbon insecticide that is used for the topical treatment of head lice and scabies. It is rapidly absorbed and can result in difficult-to-control seizures requiring high doses of benzodiazepines or barbiturates and that may require sedation, paralysis, and intubation. Because lindane is a hydrocarbon, it can sensitize the cardiac membrane and predispose to ventricular dysrhythmias. It can also cause pulmonary compromise if it is aspirated.

4. An 18-year-old woman arrives at the emergency department (ED) complaining of feeling generally weak. She reports reading online about a pesticide that can help in weight loss, and she has recently tried this. Her vital signs are blood pressure, 110/70 mm Hg; heart rate, 121 bpm; respiratory rate, 22 rpm; and temperature, 104°F (40.0°C). Her physical examination reveals dry mucous membranes and yellow staining on her abdomen. Which of the following laboratory findings can you anticipate?

a. Hypoglycemia
b. Hypokalemia
c. Hyponatremia
d. Hypoxia
e. Methemoglobinemia

Answer: a. Substituted phenols, such as dinitrophenol, are pesticides that uncouple oxidative phosphorylation. This causes an increased metabolism, which in turn consumes glucose and generates heat, often causing an increased body temperature. For this reason, they have been used as diet aids. They can be applied topically, and the yellow skin staining is considered pathognomonic for nitrogen compounds. Treatment is supportive and should be aimed at stopping further exposure; providing the needed substrates of oxygen, water, and glucose; and applying active cooling measures.

5. What organ system is most affected by paraquat ingestion?

a. Cardiac
b. Gastrointestinal
c. Nervous
d. Pulmonary
e. Renal

CHAPTER 152: QUESTIONS AND ANSWERS—cont'd.

Answer: d. Paraquat is concentrated in the lungs and directly damages the alveolar capillary membrane. This results in surfactant loss, adult respiratory distress syndrome, pulmonary fibrosis, and respiratory failure and is accelerated with supplemental oxygen. All the other organ systems listed are affected but to a much lesser degree.

6. A patient arrives at the emergency department (ED) after an intentional paraquat ingestion complaining of severe mouth, throat, and chest pain. What potentially fatal complication of paraquat ingestion should be suspected?
- **a.** Aortic dissection
- **b.** Esophageal rupture
- **c.** Myocardial infarction
- **d.** Pneumothorax
- **e.** Pulmonary embolism

Answer: b. Paraquat is extremely corrosive and can cause severe burns to the oropharynx, as well as to the esophagus. Frequently, esophageal rupture occurs, leading to mediastinitis and death. None of the other listed conditions occurs with any frequency in paraquat poisoning.

7. How do pyrethrins cause toxicity?
- **a.** Sensitivity or allergic reactions
- **b.** Bone marrow suppression
- **c.** Cardiovascular instability
- **d.** Inhibition of coagulation
- **e.** Uncoupling of oxidative phosphorylation

Answer: a. Pyrethrins are naturally occurring substances from the yellow chrysanthemum and commonly cause allergic reactions in humans. These reactions can be mild or life-threatening, with bronchoconstriction and laryngeal edema. They also affect gamma-aminobutyric acid (GABA)-mediated chloride channels in the nervous system, but this typically results in only a mild headache and paresthesias.

8. DEET is a commonly used insect repellant that can cause contact dermatitis and more severe neurologic complications, including seizures with high doses that are absorbed through the skin. Which of the following methods will minimize DEET absorption through the skin?
- **a.** Apply to skin at night
- **b.** Cover skin with clothing
- **c.** Expose skin to direct sunlight
- **d.** Keep skin dry
- **e.** Remove from skin with oil-based products

Answer: d. DEET absorption and toxicity increase with repeated applications, with increased ambient temperatures, with sweating, when it is applied to abraded or thin skin, and when it is covered with tight-fitting clothing. Oils or lipophilic substances applied to the skin also increase absorption of DEET.

9. A patient has long-standing depression that was exacerbated by the recent COVID-19 pandemic. During the isolation of the pandemic, the patient was cleaning their attic and found an old box of rat poison. During a particularly challenging time, the patient attempted suicide by consuming the contents of the rat poison container. The patient woke up the next day and was asymptomatic. Two days later, the patient noted bruising and hematuria. Which class of pesticides likely represents the overdose in this situation?
- **a.** Bipyridal compounds
- **b.** Organophosphates
- **c.** Pyrethrins
- **d.** Superwarfarins
- **e.** Chlorophenoxy compounds

Answer: d. Superwarfarins were developed from warfarin for rodenticides, after increasing numbers of rats developed resistance to warfarin. They act by inhibiting vitamin K, which is a cofactor in the synthesis of clotting factors II, VII, IX, and X. The therapeutic and toxic effects require significant reduction of these clotting factor concentrations, thus taking at least 15 hours to present. While warfarin has a half-life of 35 hours, the duration of action can be up to 5 days. Superwarfarins are 100 times more potent than warfarin, leading to increased and prolonged toxicity, which can manifest as superficial, as well as internal, bleeding (such as bruising and hematuria). Bipyridal compounds, such as paraquat and diquat, are pesticides that are not used in the United States. Organophosphates are insecticides that are highly regulated in the United States. Pyrethrins are insecticides derived from chrysanthemums, commonly used to treat scabies. Chlorophenoxy compounds are herbicides, and not used as rodenticides.

153

Plants, Herbal Medications, and Mushrooms

Christopher S. Lim and Steven E. Aks

KEY CONCEPTS

- Most botanical exposures result in minimal toxicity and management is largely supportive.
- Most serious toxicities result from exposure to plants with anticholinergic, antimitotic, cardiovascular or convulsive properties.
- Most cases of mushroom ingestion in which gastrointestinal (GI) symptoms begin within the first 2 h will prove to involve a non–life-threatening substance.
- Delayed GI symptoms with an onset of more than 6–8 h after exposure suggest a potentially life-threatening ingestion, such as the cyclopeptide and gyromitrin mushroom groups.
- Regional poison control centers, mycologists, and botanists can assist in identifying potentially toxic plants and mushrooms. We recommend smart phone digital photography with expert consultation.
- Herbal medications are largely unregulated and may have inherent toxicity, herb-drug interactions, or contaminants. Clinicians should advise against the routine use of herbal medications.

PLANTS

FOUNDATIONS

The nutritional, therapeutic, psychoactive and toxic properties of botanicals have made their usage pervasive since antiquity. The earliest documented use of plants for medicinal purposes can be found in Sumerian clay tablets that describe the use of over 200 different plants in the treatment of various maladies. Ancient Greeks recognized the lethal effects of botanicals, sentencing Socrates to death by ingestion of a poison hemlock-based liquid. The recreational abuse and medicinal use of opium poppies highlight the wide-ranging role plants have played throughout history.

Exposures to plants comprise over 42,000 calls nationally to US poison centers, with over half of cases involving pediatric patients less than 6 years of age. Over 85% of plant exposures are accidental ingestions. The overwhelming majority of plant exposures result in minimal toxicity and death is exceedingly rare.[1] Plant exposures reported to US poison centers have been decreasing over the past three decades, ranking 3rd and comprising 9% of all exposures in 1983, but ranking 22nd and making up only 2% of all exposures in 2018. The most common plant exposures resulting in severe and occasionally fatal poisonings involve those with anticholinergic, antimitotic, cardiotoxic or convulsive properties.[1]

CLINICAL FEATURES

The vast majority of plants are considered non-toxic (Table 153.1). However, serious toxicity can result from certain plant exposure (Table 153.2). Toxicity does not correlate well with taxonomy, and plants within the same genera may have varying toxic profiles. Further complicating matters, the severity of exposure may depend on the method of exposure (chewed, swallowed, smoked or injected) and which part of the plant was ingested (berries, leaves, or stems). For example, although all parts of the water hemlock plant are considered toxic, cicutoxin is most concentrated in the root of the plant. The majority of serious or fatal outcomes occur when adults intentionally consume botanicals for suicidal or recreational intent. A focused history and physical exam should be aimed at identifying the etiology of the present illness and to identify any toxidrome common to botanical exposures.

DIFFERENTIAL DIAGNOSES

Patients with plant ingestions present with vomiting and diarrhea and should be differentiated from food poisoning, viral or bacterial gastroenteritis, and pesticide poisoning (often sprayed on plants). Those patients presenting with altered mental status should be differentiated from patients co-ingesting hallucinogenic, stimulant, or opioid drugs of abuse.

DIAGNOSTIC TESTING

Although specific concentrations of botanical toxins are not routinely available at most institutions, evaluation of electrolytes, renal and liver functions, transaminases, and complete blood count should be performed in patients with potentially toxic exposures. An electrocardiogram (ECG) and cardiac monitoring should be performed to identify any dysrhythmias. Efforts at botanical identification should be made to determine the potential toxicity of any exposure. Patients should not be routinely relied upon for botanical identification. Mistaken identification by patients and family members is a frequent cause of accidental ingestion of toxic botanicals and can lead to toxicity and inappropriate disposition from the emergency department (ED).[2–4] Most emergency medical staff struggle to correctly identify even common house plants. Instead, family members or friends should be asked to bring in or send digital photographs of the involved plant, which can then be compared to reliable reference photographs or sent to local botanical experts or regional poison centers for proper identification.

MANAGEMENT

Ipecac for forced emesis and gastric lavage in botanical poisoning is not indicated. There is little evidence of clinical benefit of activated charcoal, and we do not recommend its routine use in botanical poisoning. A few exceptions can be made in patients who present within 1 hour of ingestion of a potentially life-threatening exposure (see Table 139.12).

TABLE 153.1 Non-toxic Plants

Common Name	*Botanical Name*
Abelia	*Abelia spp.*
African daisy	*Gerbera jamesonii*
African violet	*Saintpaulia ionantha*
Aglaonema	*Aglaonema spp.*
Aluminum plant	*Pilea cadierei*
Alyssum	*Slyssum spp.*
Aralia	*Dizygotheca elegantissima*
Areca palm	*Chrysalidocarpus lutescens*
Artillery plant	*Pilea spp.*
Asparagus fern	*Asparagus setaceus*
Aspidistra	*Aspidistra spp.*
Aster	*Callistephus chinensis, Townsendia sericea*
Astilbe	*Astilbe japonica*
Baby's breath	*Gysophila paniculate*
Baby's tears	*Hypoestes phyllostachya, Soleirolia soleirolii*
Baby's toes	*Centaurea cyanus*
Bachelor's buttons	*Centaurea cyanus*
Balsam	*Impatients spp.*
Bamboo	*Phyllostachys aurea*
Basket vine	*Aeschynanthus spp.*
Beauty bush	*Kolkwitzia amabilis*
Begonia	*Begonia goegoensis, Cissus spp.*
Bird's nest fern	*Asplenium nidus*
Bleeding heart vine	*Clerodendrum spp.*
Blood leaf plant	*Iresine spp.*
Boston fern	*Nephrolepis spp.*
Bromeliad	*Vriesea hieroglyphica*
Brunch berry	*Cornus canadensis*
Butterfly bush	*Buddleia davidii*
Button fern	*Pellaea rotundifolia*
Calathea	*Calathea spp.*
Camellia	*Camellia japonica, Thea japonica*
Candle plant	*Plectranthus oetendahlii*
Cape primrose	*Streptocarpus spp.*
Cast iron plant	*Aspidistra elatior*
Cattail	*Typha latifolia*
China doll	*Leea spp.*
Chinese evergreen	*Aglaonema modestum*
Christmas cactus	*Cactaceae*
Coleus	*Coleus spp.*
Columbine	*Aquilegia spp.*
Coral bells	*Kalanchoe uniflora*
Cordyline	*Cordyline spp.*
Corn plant or cornstalk plant	*Dracaena fragrans*
Creeping Charlie (houseplant)	*Pilea nummulariifolia, Plectranthus australis*
Creeping Jennie	*Lysimachia nummularia*
Crocus (Spring ONLY)	*Crocus spp.*
Dahlia	*Dahlia spp.*
Dandelion	*Taraxacum officinale*
Day lily	*Hermocallis spp.*
Donkey's tail	*Sedum morganianum*
Dracaena	*Dracaena spp., Cordyline spp.*
Dragon tree	*Dracaena draco*
Easter lily	*Lilium longiflorum*
Echeveria	*Echeveria spp.*
Emerald feather	*Asparagus densiflorus sprengeri*
Eugenia	*Eugenia cyanocarpa, Syzgium cuminii*
False aralia	*Dizygotheca elegantissima*
Fatsia	*Fatsia japonica*
Ferns	*Davallia canariensis, Davallia fejeensis, Rumohra adiantiformis, Asplenium spp.*
Ficus	*Ficus benjamina*
Fig	*Ficus carica*
Fingernail plant	*Aregelia spp.*
Firecracker flower	*Crossandra spp.*
Firecracker vine	*Menettia bicolor*
Fittonia	*Fittonia spp.*
Florida beauty	*Dracaena spp.*
Flowering quince	*Chaenomeles spp.*
Forsythia	*Forsythia spp.*
Friendship plant	*Billbergia spp., Pilea involucrate*
Fuchsia	*Fuchsia spp.*
Gardenia	*Gardenia jasminoides*
Gazania	*Gazania spp.*
Geranium	*Pelargonium spp.*
Glory tree	*Clerodendrum thomsoniae*
Gloxinia	*Gloxinia perennis, Sinningia speciosa*
Golddust plant	*Alyssum spp., Aucuba japonica*
Goldfish plant	*Hypocyrta spp.*
Hawthorn	*Crataegus spp.*
Hemlock tree	*Tsuga spp. (not to be confused with Conium or Cicuta spp.)*
Hens and chicks	*Echeveria spp., Sempervivum tectorum*
Hibiscus	*Hibiscus spp.*
Honey locust	*Gleditsia triacanthos*
Honeysuckle	*Lonicera fragrantissima*
Hosta	*Hosta spp.*
Hoya	*Hoya spp.*

Continued

TABLE 153.1 Non-toxic Plants—cont'd

Common Name	*Botanical Name*
Ice plant	*Aptenia cordifolia, Lampranthus spp., Mesembryanthemum cordifolium*
Impatients	*Impatients spp.*
Iron plant	*Aspidistra spp.*
Jade plant	*Portulacaria afra*
Janet Craig plant	*Dracaena deremensis*
Japanese aralia	*Fatsia japonica*
Japanese lantern	*Hibiscus schizopetalus*
Japanese snowbell	*Styrax japonica*
Kalanchoe	*Kalanchoe spp.*
King and queen fern	*Asplenium spp.*
Lavendar	*Lavandula officinalis*
Lilac	*Syringa spp.*
Linden tree	*Tilia americana*
Lipstick plant	*Aeschynanthus spp.*
Magnolia	*Magnolia spp.*
Maidenhair fern	*Adiantum decorum*
Maple tree	*Acer spp.*
Maranta	*Calathea spp., Maranta spp.*
Marigolds (except Marsh Marigolds)	*Calendula spp.*
Maternity plant	*Kalanchoe spp.*
Mexican snowball	*Echeveria spp.*
Mimosa	*Albizia julibrissin*
Mock orange	*Philadelphus spp., Pittosporum tobira*
Monkey plant	*Ruellia makoyana*
Mosaic plant	*Fittonia argyroneura*
Mother fern	*Asplenium spp.*
Mother of thousands	*Kalanchoe pinnata*
Mountain grape	*Mahonia spp.*
Mulberry tree or bush	*Morus spp.*
Nasturtium	*Tropaeolum spp.*
Neanthebella	*Chamaedorea elegans*
Nerve plant	*Fittonia spp.*
Norfolk Island pine	*Araucaria heterophylla*
October plant	*Sedum sieboldii*
Old man of the mountains	*Hymenoxys grandiflora*
Orchid	*Cattleya spp., Cymbidium spp., Epidendrum spp., Oncidium spp.*
Painted lady	*Echeveria spp.*
Panda plant	*Kalanchoe tomentosa*
Parlor palm	*Chamaedorea elegans*
Passion vine, purple	*Gynura aurantiaca*
Patient Lucy	*Impatients spp.*

Common Name	*Botanical Name*
Peacock plant	*Calathea makoyana, Kaempferia spp.*
Peperomia	*Peperomia spp.*
Petunia	*Petunia spp.*
Phlox	*Phlox spp.*
Piggyback plant	*Tolmiea menziesii*
Pilea	*Pilea spp.*
Pine trees	*Pinus spp.*
Pitcher plant	*Darlingtonia californica*
Pittosporum	*Pittosporum spp.*
Plantago	*Plantago major*
Plush plant	*Echeveria spp., Kalanchoe spp.*
Pocketbook plant	*Calceolaria spp.*
Poinsettia	*Euphorbia pulcherrima*
Polka Dot plant	*Hypoestes phyllostachya*
Pony Tail plant	*Beaucarnea recurvata*
Potentilla	*Potentilla spp.*
Prayer plant	*Maranta leuconeura*
Pregnant plant	*Kalanchoe pinnata*
Propeller plant	*Crassula cultrate*
Purple passion	*Gynura aurantiaca*
Pyracantha	*Pyranchantha spp.*
Queen's tears	*Billbergia spp.*
Rabbit's foot	*Maranta leuconeura*
Rainbow plant	*Billbergia spp.*
Red bud	*Cercis canadensis*
Red hot poker	*Kniphofia spp.*
Resurrection plant	*Selaginella lepidophylla*
Rex-begonia vine	*Cissus discolor*
Ribbon plant	*Dracaena sanderiana*
Rosary vine	*Ceropegia woodii, Crassula rupestris*
Rose, rosehips	*Rosa spp. (except Rosa rugose)*
Rose of Sharon	*Hibiscus syriacus*
Rubber plant	*Ficus elastica*
Salvia	*Salvia spp.*
Sedum	*Sedum spp.*
Sensitive plant	*Mimosa pudica*
Sentry palm	*Howea forsterana*
Silk tree	*Albizia julibrissin*
Silver bell	*Halesia spp.*
Silver berry	*Elaeagnus spp.*
Silver dollar plant	*Astrophytum asterias, Crassula arborscens*
Silver evergreen	*Aglaonema spp.*
Silver king	*Aglaonema spp.*

TABLE 153.1 Non-toxic Plants—cont'd

Common Name	*Botanical Name*
Silver vine	*Actinidia polygama*
Snapdragon	*Antirrhinum majus*
Snowball bush	*Viburnum spp.*
Spider aralia	*Dizygotheca elegantissima*
Spider flower	*Cleome spp., Hermocallis spp., Tibouchina spp.*
Spiraea	*Astilbe japonica*
Spirea	*Spirea spp.*
Spruce tree	*Picea spp.*
Staghorn fern	*Platycerium spp.*
Starfish flower	*Stapelia spp.*
Stone face	*Lithops spp.*
String of buttons	*Crassula rupestris*
Striped inch plant	*Callisia spp.*
Swedish ivy	*Plectranthus australis*
Sword fern	*Polystichum munitum*
Teddy bear plant or vine	*Cyanotis kewensis*
Tiger lily	*Lilium spp.*
Tulip tree	*Liriodendron tulipifera, Spathodea campanulata*
Umbrella plant	*Eriogonum umbellatum*
Umbrella tree	*Magnolia tripetala*
Velvet plant	*Gynura aurantiaca*
Viburnum	*Viburnum spp.*
Wandering Jew	*Zebrina pendula*
Wax flower	*Stephanotis floribunda*
Wax plant	*Hoya spp.*
Wild strawberry	*Fragaria spp.*
Willow	*Salix spp.*
Yellow wood	*Cladrastis lutea, Rhodosphaera rhodanthema*
Yucca plant	*Yucca spp.*
Zebra plant	*Aphelandra squarrosa, Calanthea zebrina, Cryptanthus zonatus*
Zinnia	*Zinnia spp.*

TABLE 153.2 Toxic Plants

Common Name	*Botanical Name*	Toxic Effects
Ackee tree	*Blighia sapida*	Hypoglycemia, gastrointestinal, neurologic
Almond, apricot, cherry, plum, peach	*Prunus spp.*	Cyanogenic
American mistletoe	*Phoradendron spp.*	Gastrointestinal
Angel trumpet	*Brugmansia suaveolens*	Anticholinergic
Autumn crocus, meadow or wild saffron	*Colchicum autumnale*	Gastrointestinal, multi-organ
Azalea	*Azalea spp.*	Cardiovascular
Betel nut	*Areca catechu*	Cholinergic
Bird-lime, blue thistle	*Atractylis gummifera*	Hepatic
Bitter orange	*Citrus aurantium*	Cardiovascular, neurologic
Black locust	*Robinia pseudoacacia*	Gastrointestinal
Buckeye	*Aesculus glabra*	Gastrointestinal, neurologic
Calabar bean	*Physostigma venenosum*	Cholinergic
Cassava	*Manihot exculentus*	Cyanogenic
Castor bean	*Ricinus communus*	Gastrointestinal, multi-organ
Cayenne pepper	*Capsicum spp.*	Dermatologic, mucosal irritant
Chysanthemum, dandelion	*Chrysanthemum spp.*	Dermatologic
Cinchona	*Cinchona spp.*	Cardiovascular, cinchonism
Common, white or pink oleander	*Nerium oleander*	Cardiovascular[a]
Deadly nightshade	*Atropa belladonna*	Anticholinergic
Dumbcane, mother-in-law plant	*Dieffenbachia spp.*	Dermatologic, mucosal irritant
Elderberry	*Sambucus nigra*	Gastrointestinal, metabolic
Elephant ear, angel wings, heart of Jesus	*Caladium spp.*	Dermatologic, mucosal irritant
Ergot	*Claviceps purpurea*	Cardiovascular, neurologic, oxytocic

Continued

TABLE 153.2 **Toxic Plants—cont'd**

Common Name	*Botanical Name*	Toxic Effects
Eucalyptus	*Eucalyptus spp.*	Dermatologic, gastrointestinal
European or true mandrake	*Mandragora officinarum*	Anticholinergic
Fava bean	*Vicia fava*	Hematologic
Foxglove	*Digitalis spp.*	Cardiovascular[a]
Glory lily	*Gloriosa superba*	Gastrointestinal, multi-organ
Golden chain or rain	*Laburnum anagyroides*	Gastrointestinal, neurologic
Grass pea	*Lathyrus sativus*	Neurologic, skeletal
Green tomato	*Lycopersicon spp.*	Gastrointestinal, neurologic, anticholinergic
Guarana	*Paullinia cupana*	Neurologic, cardiac
Henbane, hyoscyamus	*Hyoscyamus niger*	Anticholinergic
Holly	*Ilex spp.*	Gastrointestinal
Ipecac	*Cephaelis ipecacuanha, Cephaelis acuminata*	Gastrointestinal
Jequirity pea, rosary or prayer bead	*Abrus precatorius*	Gastrointestinal, neurologic
Jimsonweek, angel's trumpet	*Datura Stramonium*	Anticholinergic
Khat	*Catha edulis*	Cardiovascular, neurologic
Larkspur	*Delphinium spp.*	Cardiovascular, neurologic
Lily of the valley	*Convallaria majalis*	Cardiovascular[a]
Mad honey	*Rhododendron spp.*	Gastrointestinal, cardiac
Madagascar periwinkle, vinca	*Catharanthus roseus*	Gastrointestinal
Marijuana, hashish, pot	*Cannabis*	Neurologic
Mayapple	*Podophyllum emodi, Podophyllum peltatum*	Multi-organ
Milkweed	*Asclepias spp.*	Cardiovascular[a]
Monkshood, Wolfsbane	*Aconitum napellus*	Cardiovascular, neurologic
Nightshade (various), potato	*Solanum spp.*	Anticholinergic
Opium poppy	*Papaver somniferum*	Neurologic, respiratory
Peace lily	*Spathiphyllum spp.*	Dermatologic, mucosal irritant
Peyote, mescal	*Lophophora williamsii*	Neurologic
Philodendron	*Philodendron spp.*	Dermatologic, mucosal irritant
Pilocarpus	*Pilocarpus jaborandi, Pilocarpus pinnatifolius*	Cholinergic
Pink-eyed cerbera, sea mango, suicide tree, pong pong tree	*Cerbera spp.*	Cardiovascular[a]
Poison hemlock	*Conium maculatum*	Neurologic, pulmonary
Poison ivy, poison oak, poison sumac	*Toxicodendron spp.*	Dermatologic
Pokeweed	*Phytolacca americana*	Gastrointestinal
Poplar	*Populus spp.*	Salicylism
Pothos	*Epipremnum aureum*	Dermatologic, mucosal irritant
Queen sago, indu	*Cycas circinalis*	Neurologic
Rattlebox	*Crotalaria spp.*	Hepatotoxic
Red squill	*Urginea maritima, Urginea indica*	Cardiovascular[a]
Spider plant	*Chlorophytum comosum*	Dermatologic, mucosal irritant
Tansy	*Tanacetum vulgare*	Neurologic
Tobacco	*Nicotiana spp.*	Gastrointestinal, neurologic
Tonka beans	*Dipteryx odorata, Dipteryx oppositifolia*	Hematologic

TABLE 153.2 Toxic Plants—cont'd

Common Name	*Botanical Name*	Toxic Effects
Tubocurare, curare	*Chondrodendron spp., Curarea spp., Strychnos spp.*	Neurologic
Tullidora, buckthorn	*Karwinskia humboldtiana*	Neurologic, respiratory
Umbrella tree	*Schefflera spp., Brassaia spp.*	Dermatologic, mucosal irritant
Water hemlock	*Cicuta maculata*	Neurologic
Water hemlock	*Oenanthe crocata*	Neurologic
White cedar	*Thuja occidentalis*	Neurologic
Wormwood, absinthe	*Artemisia absinthium*	Neurologic
Yellow oleander	*Thevetia peruviana*	Cardiovascular[a]
Yew	*Taxus spp.*	Cardiovascular

[a]Cardioactive steroid.

of the plant is not immediately known and treatment should be focused on symptom-based, supportive care. This includes maintenance of a patent airway, intravenous fluids and vasopressors for hypotension, active cooling for hyperthermia, and benzodiazepines for agitation and seizures. Management of specific categories of botanicals is outlined in the following sections.

DISPOSITION

Any patient with signs of severe toxicity, especially those involving the cardiovascular and neurologic systems, should be managed in the ED until symptoms and signs are resolving, or they are admitted to an intensive care setting. Patients with exposure to unknown plants can be discharged after 6 hours of cardiac monitoring if they are hemodynamically stable and otherwise asymptomatic. This period of observation should be extended to 24 hours if pre-existing cardiovascular or other concerning medical problems exist or an exposure to a plant of serious toxicity is suspected.

Fig. 153.1 *Datura stramonium* (jimson weed). (Courtesy Steven Setzer.)

PLANT CATEGORIES

Anticholinergics

Foundations

Principles of toxicity. *Datura stramonium* (Jimson weed, angel's trumpet) (Fig. 153.1) and *Atropa belladonna* (deadly nightshade) are the most frequently encountered plants with anticholinergic toxins. They contain scopolamine, hyocyamine and atropine. All parts of the plant contain toxic alkaloids, but they are most concentrated in the seeds of *D. stramonium* and the fruit and leaves of *A. belladonna*.

Clinical features. Ingestion can cause the antimuscarinic syndrome of agitation, diminished gastrointestinal (GI) motility, dry skin, flushing, hallucinations, hyperthermia, mydriasis, tachycardia, and urinary retention.[5,6] *D. stramonium* is commonly abused for its hallucinogenic properties, whereas berries from *A. belladonna* have been mistaken for the common blueberry *(Vaccinium arctostaphylos)* resulting in poisonings.

Differential diagnoses. The differential diagnosis of antimuscarinic toxicity includes toxicity from pharmaceutical agents such as diphenhydramine, benztropine, cyclic antidepressants, antipsychotics, and antiparkinson medications. Sympathomimetic drugs such as cocaine and amphetamines will also cause similar toxic symptoms but typically present with diaphoresis instead of dry skin, which is typical of the antimuscarinic toxidrome.

Diagnostic testing. Symptomatic patients with altered mental status or abnormal vital signs should have a screening ECG to assess corrected QT (QTc) and QRS intervals, serum electrolytes, glucose, creatinine phosphokinase (CPK) and renal function.

Management. Management should be focused on supportive care, including active cooling for hyperthermia and benzodiazepines for agitation. Recommended agents include diazepam, 5 to 10 mg IV, or lorazepam, 1 to 2 mg IV. Additional doses can be administered every 10 minutes until the patient is calm and able to cooperate with care. The use of a cholinesterase inhibitor, such as physostigmine (0.5 to 2 mg in adults; 0.02 mg/kg in children), is recommended for severe anticholinergic toxicity (see Chapter 140).[6]

Disposition. Mildly symptomatic patients can be observed in the ED for 6 to 8 hours and discharged from the ED. Severely poisoned patients with refractory antimuscarinic symptoms should be admitted to a monitored setting for 24 hours.

Antimitotic Toxins

Foundations

Principles of toxicity. *Colchicum autumnale* is also known as autumn crocus, meadow saffron, or wild saffron, and contains the toxic alkaloid colchicine. Colchicine inhibits microtubule formation, leading to disruption of mitosis, intracellular transport mechanisms and cell structure. *C. autumnale* is often mistaken for *Allium ursinum* (wild garlic), leading to fatal, unintentional ingestions. Pharmaceutical colchicine is most commonly used to treat acute gouty arthritis. Serious

toxicity from pharmaceutical colchicine is seen at doses greater than 0.5 mg/kg, and it is invariably lethal at doses of 0.8 mg/kg.

Clinical features. The clinical course of colchicine poisoning is typically divided into three phases of illness.[7] The first phase is marked by GI symptoms, such as severe vomiting, diarrhea, abdominal pain, hypovolemia, and electrolyte disturbances. Multi-organ failure ensues in the second phase, with manifestations of cardiac dysrhythmia, adult respiratory distress syndrome (ARDS), pancytopenia, liver failure, rhabdomyolysis, and sepsis. Death usually occurs during this second phase. The third phase is recovery from the poisoning.

Differential diagnoses. Patients presenting in the first phase of illness may be misdiagnosed as having gastroenteritis or food poisoning. In the second phase, colchicine poisoning mimics many serious disorders and is treated similarly with supportive interventions based on the type and severity of the patient's presentation. Obtaining a history of ingestion is critical to making the correct diagnosis but will not significantly alter the treatment plan. Patients with pancytopenia should be differentiated from patients with sepsis, leukemia, or oncological disorders—obtaining the history of ingestion may avoid invasive testing, such as a bone marrow biopsy.

Diagnostic testing. Laboratory data should include a complete blood count to assess for pancytopenia. Additional labs include serum electrolytes, renal and liver function tests as well as a screening ECG. Serum colchicine levels can be sent out to reference laboratories for analysis, but the results are time consuming and should not alter or delay emergency care.

Management. There is no specific therapy for colchicine poisoning, and management consists primarily of supportive care. There is no commercially available antidote for colchicine poisoning in the United States, and supportive care is ineffective in those who ingest a lethal dose. Thus, efforts to prevent gastric absorption by administration of activated charcoal should be made for those who ingest a potentially lethal dose of colchicine and present within 1 hour of ingestion.

Disposition. Patients presenting with GI symptoms but normal laboratory testing may be discharged home after 6 to 8 hours of hydration and observation in the ED. Patients with cardiac dysrhythmias, pancytopenia, liver dysfunction or renal failure require admission to a monitored setting. Patients with pancytopenia require admission and isolation precautions to avoid sepsis and secondary nosocomial infections.

Cardiac Glycosides

Foundations

Principles of toxicity. Cardiac glycosides bind to cell transmembrane Na^+-K^+-ATPases, which, in turn leads to a rise in intracellular Ca^{2+} concentrations, causing decreased automaticity and increased contractility. Common plants that contain cardiac glycosides include *Convallaria maalis* (lily of the valley), *Digitalis* spp. (foxglove) (Fig. 153.2), *Nerium oleander* (common, pink or white oleander) (Fig. 153.3), and *Thevetia peruviana* (yellow oleander).

Clinical features. Similar to digoxin poisoning, patients with exposure to cardiac glycosides can present with GI symptoms, generalized weakness, altered mental status, bradydysrhythmias, tachydysrhythmias, and hypotension. Toxicity and treatment of cardiac glycosides are also discussed in Chapter 142.

Differential diagnoses. The differential diagnoses of cardiac glycoside plant poisoning is broad and includes pharmaceutical toxicity with digoxin, calcium channel blockers, beta blockers, and clonidine. Additionally, other cardiogenic bradydysrhythmias (atrioventricular [AV] blocks and sick sinus syndromes) should be considered.

No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so the differential diagnosis is broad. Intrinsic cardiac disease, as well as other cardiotoxic drugs, should be considered. Cardioactive steroid poisoning from plants is rare but presents similarly to digoxin toxicity. Common examples include oleander (*N. oleander*, see Fig. 147.2) and lily of the valley (*Convallaria majalis*, see Fig. 147.3). Aconitine, a sodium-channel opening xenobiotic found in common monkshood *(Aconitum napellus)*, may also mimic digoxin poisoning. Central nervous system (CNS) depression or confusion may be due to various depressant drugs (opioids, major tranquilizers, sedative hypnotic agents) and toxins, as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances caused by digoxin are binocular and are often not reported by the patient; unfortunately,

Fig. 153.2 *Digitalis purpurea* (foxglove). (Courtesy Christopher Lim.)

Fig. 153.3 Nerium oleander. (Courtesy Steven Setzer.)

they are not specific to digoxin poisoning. Methanol, metformin, ethambutol, ethyl chloride, quinine, and other anti-malarial medications are all capable of producing visual disturbances. GI disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

Diagnostic testing. Patients should have an ECG performed, and serum electrolytes should be evaluated with attention to potassium because cardiac glycoside-poisoned patients are susceptible to hyperkalemia. A serum digoxin concentration can be measured, but correlates poorly with the degree of toxicity and should be used only to confirm exposure.

Management. The cornerstone of therapy is digoxin-specific antibody fragments (Fab) and should be administered in any patient displaying serious toxicity (heart rate <40 beats/min, sinus arrest or exit block, atrial tachydysrhythmia, ventricular dysrhythmia, second- or third-degree AV block, hypotension, and/or serum potassium level >5.0 mEq/L).[8] The optimal dose is not established and may be dependent on several variables (e.g., plant species, amount, route of exposure, and part of plant ingested).[8,9] Studies from yellow oleander poisoning suggest higher dose requirements of digoxin immune Fab with plant cardiac glycoside poisoning than with pharmaceutical digoxin poisoning. A reasonable approach considers the patient's clinical status. If the patient is in cardiac arrest or unstable, we suggest an initial 20 vials IV of Fab fragment. For stable patients, we recommend an initial 10 vials IV. Patients should be re-evaluated every hour for the need of additional doses. Cardiac pacing, atropine, beta-adrenergic agents are without demonstrated benefit and should only be considered adjunctive therapies.

Disposition. Symptomatic patients with bradycardia, hypotension, altered mental status, or hyperkalemia are admitted to a monitored setting. Those requiring digoxin-specific Fab should be admitted to an intensive care setting with cardiology and medical toxicology consultation.

OTHER CARDIOTOXIC PLANTS

Rhododendron species contain grayanotoxin, which can be found in concentrated levels in the honey that is produced from the nectar. Often referred to as "mad honey," poisonings can result in GI symptoms, hypersalivation, diaphoresis, and cardiac effects. Grayanotoxin binds to cell membrane sodium channels, preventing voltage-dependent inactivation, thereby holding cells in a depolarized state. This is thought to increase the vagal tone. The cardiac manifestations mainly consist of bradydysrhythmias (including sinus bradycardia, AV blocks, and atrial fibrillation with slow ventricular response) and hypotension, leading to symptoms of dizziness and syncope.[10,11] It has even been implicated as a cause of myocardial infarction.[12] In addition to IV fluids for hypotension, atropine and cardiac pacing have been used successfully in the treatment of mad honey toxicity.[10,11]

Taxus species (Fig. 153.4), commonly known as yew, are coniferous trees and shrubs that are often cultivated for ornamental landscaping. They contain several toxic components, including taxine pseudoalkaloids that cause sodium and calcium channel blockade. The most serious effects are on the cardiovascular system, and manifestations include hypotension, dysrhythmias, and cardiac arrest.[13,14] Management of toxicity is largely supportive. The successful use of extracorporeal membrane oxygenation (ECMO) for severe and refractory cardiotoxicity and hypotension has been reported.[13,15]

Aconitium spp. (monkshood, wolfsbane) contain aconitine and other related alkaloids. Similar to grayanotoxins, aconitine binds and prevents inactivation of voltage-gated sodium channels of myocardial and neural cells. Thus, the main features of poisoning are neurological (paresthesias, weakness) and cardiovascular (hypotension, dysrhythmias).[16] Management includes supportive care and standard therapy for dysrhythmias.[17]

Cicutoxin

Principles of Toxicity

Both *Cicuta* spp. (Fig. 153.5) and *Oenanthe crocata* are commonly known as water hemlock and contain toxins responsible for the hallmark presentation of intractable and life-threatening seizure activity. Seizures are thought to occur from non-competitive gamma-aminobutyric acid (GABA) antagonism.

Clinical Features

Initial features of poisoning may include vomiting, abdominal pain, confusion, weakness, and dizziness. Prolonged seizures can further complicate the clinical course, leading to rhabdomyolysis, hyperthermia, acidosis, hypoxia, cerebral edema, and eventual cardiopulmonary arrest.

Fig. 153.4 *Taxus media* (yew). (Courtesy Christopher Lim.)

Fig. 153.5 *Cicuta maculata* (water hemlock). (Courtesy Steven Setzer.)

Differential Diagnoses

Water hemlock is often confused for edible plants (e.g., carrots, parsnips, turnips), leading to unintentional poisonings. Other neurotoxic agents should be considered including organophosphates, isoniazid (INH), cyclic antidepressants, methyl xanthines, tramadol, sympathomimetic toxicity, and ethanol and benzodiazepine withdrawal. Seizure disorders, hypoglycemia, head trauma, and brain lesions are also diagnostic considerations.

Diagnostic Testing

History is essential to identify the toxin as the cause of the new onset seizure, thus obviating the need for further diagnostic testing. Serum electrolytes exclude hypernatremia, hyponatremia, hypocalcemia, or hypoglycemia as a cause of the confusion or seizures and hypokalemia as a cause of the weakness. Serum CPK and creatinine evaluate for rhabdomyolysis and renal impairment. A toxicology screen, especially a serum ethanol level, help identify or exclude alternate causes of the confusion. An ECG should be performed to assess intervals if an electrolyte disturbance or overdose is suspected.

Management

The mainstay of management is seizure control with benzodiazepines (lorazepam, 1 to 2 mg IV, or diazepam, 5 to 10 mg IV, repeated every few minutes until seizure activity ceases). If seizure activity is not controlled with benzodiazepines, treatment is similar to that of other toxicologic causes of status epilepticus (see Chapter 88).

Disposition

Patient with altered mental status and seizures should be admitted to an intensive care setting. Those who are asymptomatic after 6 to 8 hours of observation in the ED may be discharged home.

OTHER TOXIC PLANTS

Nicotinic toxin

Conium maculatum (poison hemlock) (Fig. 153.6), *Nicotian tabacum* (Fig. 153.7), and *Nicotiana glauca* (wild or tree tobacco) contain alkaloids capable of producing nicotinic-cholinergic poisoning. They contain the toxins coniine and coniceine (*C. maculatum*), and anabasine (*N. glauca*) that stimulate nicotinic acetylcholine receptors on the autonomic nervous system and neuromuscular junction. Clinical effects can include hypersalivation, vomiting, diarrhea, muscle fasciculation, and agitation; toxicity can progress to profound weakness, paralysis, respiratory failure, hypotension, rhabdomyolysis, and renal failure.

Fig. 153.6 *Conium maculatum* (poison hemlock). (Courtesy Steven Setzer.)

There is no specific antidote, and treatment should be aimed at ventilatory support for those with respiratory distress or muscle fatigue and those who cannot adequately oxygenate. Treatment should be continued until resolution of respiratory muscle fatigue and airway stabilization.[18,19]

Raphides

Raphides are needle-shaped, calcium oxalate crystals and have been observed in over 200 plants. Common plants that contain calcium oxalate crystals include the species from the genera *Dieffenbachia* (dumb cane, mother-in-law plant) (Fig. 153.8), *Philodendron*, *Spathiphyllum*, and *Brassaia* spp. Dieffenbachia plants are commonly found in homes and offices due to their attractive appearance, low cost and resistance to neglect. Ingestions can result in vomiting, and mucosal irritation,

Fig. 153.7 *Nicotiana tabacum* (tobacco). (Courtesy Christopher Lim.)

Fig. 153.8 *Dieffenbachia amoena* (dumb cane). (Courtesy Christopher Lim.)

ulceration and edema that can lead to compromise of the airway in severe ingestions. Dermal exposures may lead to contact dermatitis.[20]

Treatment is supportive including maintenance of a patent airway. The use of corticosteroids and antihistamines are considered adjunctive therapies, but they have not been shown to improve outcomes in mild cases of exposure. However, we recommend the administration of diphenhydramine (25 to 50 mg intravenous push [IVP]) and dexamethasone (4 to 8 mg IVP) for the rare cases of respiratory distress with significant airway edema following ingestion of specific raphide plants.

Toxalbumins

Abrus precatorius (jequirity pea, rosary, or prayer bead) (Fig. 153.9) and *Ricinus communis* (castor oil plant) contain the toxins abrin and ricin, respectively, that inhibit ribosomal protein synthesis, leading to cell death. Seeds of *A. precatorius* are distinctive, bright red or orange seeds with black caps that are often used in jewelry or rosaries. Castor beans are light brown and mottled, with dark brown spots. Seeds or beans swallowed whole with the hard outer shell intact typically prevent absorption of significant toxin. Chewed or crushed seeds or beans may release the toxin and cause local toxicity in the GI tract, leading to gastroenteritis, abdominal pain, dehydration, and electrolyte disturbances.[21,22]

Rarely, abrin or ricin is absorbed systemically, and symptoms may progress to severe neurologic toxicity (seizure, coma, cerebral edema, demyelinating encephalitis), multi-organ failure, and death. Purified ricin derived from the castor bean is highly toxic and lethal in small doses. It has been used historically as a biologic weapon, implicated in the assassination of Bulgarian journalist Georgi Markov in the 1970s, and discovered at a Washington DC postal service facility in 2001. There is no effective antidote, vaccine, or other therapy for the treatment of prevention of abrin or ricin poisoning. Treatment consists of fluid resuscitation, vasopressor agents for hypotension, and correction of electrolyte imbalances with neurotoxic symptom precautions.

Fig. 153.9 *Abrus precatorius* (jequirity pea or rosary pea). (Courtesy Steven Setzer.)

MUSHROOMS

FOUNDATIONS

Mushrooms represent a wide range of species with regional variation. In this section, we will consider the mushrooms of toxicologic significance. The categories of poisonous mushrooms are grouped according to the types of illness or organ-specific toxicity. Another important perspective is that the most common species of toxic mushrooms belong to the GI irritant group and generally do not cause life-threatening illness. Distinguishing the GI irritant group from the more serious groups is the challenge for the treating emergency clinician.

According to data from 2018 as reported by the American Association of Poison control centers, there were a total of 6318 mushrooms exposures. The majority of the ingested mushrooms were never identified (5138). Four mushrooms from the cyclopeptide group, nine from the hallucinogenic group, one from the muscimol-containing group, and one from the orellarine group resulted in major effects. There were five fatalities from mushroom exposures in this database.[1]

CLINICAL FEATURES

An important clinical consideration is the onset of symptoms after a mushroom ingestion. In general, the GI irritants will develop symptoms in the first 2 to 3 hours after ingestion. Some of the most lethal mushrooms will cause symptoms on a delayed basis, such as *Amanita phalloides*, or *Gyromitria esculenta,* at 6 to 8 hours after ingestion.[23] There are some exceptions that are highlighted later in the chapter.

DIFFERENTIAL DIAGNOSES

Many mushrooms are edible and considered delicacies, such as puffballs or morels. However, there are many look-alikes, and foragers must be certain that they identify correct species to avoid morbidity and mortality. The differential diagnosis with mushroom poisoning includes gastroenteritis, pancreatitis, hepatitis, acute renal failure, hallucinogenic poisonings, anticholinergic and cholinergic poisonings, disulfiram toxicity, and food poisoning.

DIAGNOSTIC TESTING

Identifying the mushroom ingested is extremely helpful to the treating team. It is beyond a realistic scope for emergency clinicians to be able to identify mushrooms, and it is wise to coordinate with poison control centers and local mycologists to identify mushrooms in real time. Smart phone digital identification by sending images to mycologists via a poison control center model has been shown to be accurate in identifying mushrooms. Attempts at mushroom identification should be made, particularly if a patient presents with a delayed onset of symptoms.

Routine testing includes complete blood count, urinalysis, and basic metabolic profile with specific attention to renal function and measures of dehydration. Liver enzyme and tests of liver function should be obtained if cyclopeptide or gyromitrin poisoning is suspected.

MANAGEMENT

The general management of mushroom poisoning focuses on symptom-based supportive care. There is no proven outcome benefit from administration of activated charcoal for patients with mushroom ingestion. We recommend activated charcoal only if it can be administered within 1 hour of the ingestion and the clinician suspects

ingestion of a potentially life-threatening mushroom (e.g., cyclopeptide- or gyromitrin-containing species). We do not recommend gastric emptying by any method. Because many toxic mushrooms can cause vomiting or diarrhea, it is important that these patients are fluid resuscitated and rehydrated until they can tolerate oral liquids.

DISPOSITION

Patients should be admitted for 24 hours when the ingestion of a potentially life-threatening mushroom has occurred. For hepatotoxic mushrooms, transferring the patient to a tertiary care center with liver transplantation capabilities should be considered. For suspected or confirmed GI irritant mushroom ingestion the patient can be safely discharged after the GI symptoms are controlled and oral fluids are tolerated.

MUSHROOM CATEGORIES

Hepatotoxic Mushrooms

Principles of Toxicity

The two major categories of mushrooms that can cause life-threatening hepatotoxicity include cyclopeptide-containing mushrooms such as *A. phalloides*, or certain *Lepiota* species of mushrooms. The *Gyromitra* species also cause hepatotoxicity but have other symptoms distinct from the cyclopeptide-containing mushrooms.

Clinical Features

The cyclopeptide-containing mushrooms will cause an onset of GI symptoms 6 to 8 hours after ingestion. This includes nausea, vomiting, diarrhea, and abdominal pain. Over the next 1 to 2 days, the patient will develop increasingly severe hepatic injury and encephalopathy.

Differential Diagnoses

In patients with cyclopeptide-containing mushroom toxicity with elevations in liver aminotransferases, bilirubin, partial thromboplastin time (PTT)/international normalized ratio (INR), or creatinine, other sources of injury should be considered, including acute tubular necrosis, rhabdomyolysis, ischemic hepatitis, alcoholic hepatic disease, viral hepatitis, and Wilson's disease. Other hepatotoxic considerations include poisoning with acetaminophen, valproic acid, INH, statins, herbal medications (e.g., pennyroyal oil, pyrrolizidine alkaloids), vinyl chloride, and polychlorinated biphenyls.

Diagnostic Testing

Poisoning is evidenced by rising liver enzymes and worsening measures of liver function (rising bilirubin and increased INR). Hyperammonemia can also be seen in severe toxicity. These markers should be followed serially during the hospital course. Also, because patients may develop a hepatorenal syndrome, creatinine and blood urea nitrogen should be measured.

Management

Many therapies have been tried for cyclopeptide-containing mushrooms. Initial decontamination measures with oral activated charcoal are recommended if the patient presents within 1 hour of ingestion and has not already vomited. Suggested therapies in the literature that may be immediately available include *N*-acetylcysteine (NAC), high dose IV penicillin, and early hemodialysis or hemoperfusion.[23] NAC is thought to work via hepatoprotective effects, and animal studies indicate that amatoxins deplete glutathione stores. IV NAC dosing regimens are similar to those administered to acetaminophen poisoned patients (see Chapter 138). High dose penicillin is thought to work by displacing amatoxin uptake by the hepatocytes. Experimental antidotes such as thioctic acid, silibinin, and *polymyxin* B, have been more commonly used in Europe. Silibinin, the main isomer of silymarin, found in milk thistle, is currently available as an investigational agent. It works as an antioxidant, free radical scavenger, and can restore glutathione stores.[24] If a cyclopeptide-containing mushroom has been ingested, we suggest mobilizing silibinin by calling the regional poison control center to coordinate management and prioritization of agents. The use of oral milk thistle extract, a common health supplement product, has been reported in areas where the IV formulation is not available. However, its use has not been adequately studied to be routinely recommended as a therapeutic option. Patients who progress to fulminant hepatic failure despite appropriate supportive care may ultimately require liver transplantation.[25] Consultation with a transplant center should be initiated early in the course of management.

Disposition

Patients showing evidence of severe hepatotoxicity and those at risk for fulminant hepatic failure should be admitted to an intensive care unit. These patients require frequent neurological checks, continuous vital sign monitoring, and serial laboratory studies. If a patient presents with established hepatotoxicity, transferring to a tertiary-care center that specializes in the management of patients with hepatic failure with liver transplant capabilities is recommended.

Gyromitrin-containing Mushrooms

Principles of Toxicity

Gyromitrin-containing species are also known as the *false morel*. Like the cyclopeptide-containing mushrooms, these can also cause significant hepatotoxicity[26] but may also cause neurotoxicity, particularly seizures and altered mental status. The mechanism for seizures is similar to INH by causing deficiency of pyridoxine and inhibiting the action of glutamic acid decarboxylase. This prevents the formation of GABA, an inhibitory neurotransmitter.[27] These mushrooms can also induce some degree of oxidant stress, which can clinically manifest as methemoglobinemia.

Clinical Features

Similar to the cyclopeptide-containing group, gyromitrin mushrooms can cause delayed nausea, vomiting, diarrhea, and hepatotoxicity, but most notably manifest with generalized seizure activity.

Differential Diagnoses

The highly sought-after *true morel* is an edible delicacy and is considered nontoxic. The *false morel* has a close resemblance and can be found in similar regions. Other causes of seizures and neurotoxicity should be considered, including INH poisoning, sympathomimetic toxicity, intracranial bleeds, brain mass lesions, and underlying seizure disorders. Other causes of methemoglobinemia include ingestion of nitrate and nitrate-containing compounds, local anesthetic agents, dapsone, and inborn errors in metabolism.

Diagnostic Testing

In patients presenting with seizure activity, obtaining a history of toxic ingestion obviates the need for most diagnostic testing. Because there is potential for hepatoxicity, serial liver transaminases should be monitored. Serum electrolytes should be monitored for protracted vomiting or diarrhea. A screening methemoglobin level is also recommended.

Management

Management of gyromitrin-induced seizures should include IV pyridoxine, as recommended for INH poisoning, with 5 g as an empirical dose (see

Chapter 124). Clinically significant methemoglobinemia can be managed with methylene blue, although this is a rare occurrence. Methylene blue dosing is typically 2 mg/kg IV, which can be repeated within 30 to 60 minutes as needed. (See Chapters 55 and 148 for dosing of methylene blue.)

Disposition

Patients with altered mental status and seizures requiring pyridoxine therapy should be admitted to an intensive care setting. Those who are asymptomatic after 6 to 8 hours observation the ED may be discharged home.

OTHER MUSHROOM CLASSES

Cholinergic Agonists

True cholinergic agonists are rarely encountered in the clinical setting. *Clitocybe dealbata*, also known as "the sweater," is one of these mushrooms. If ingested, clinical symptoms of cholinergic excess may be seen. Muscarinic effects recalled by the mnemonic SLUGBAM, can be useful. **SLUGBAM** stands for **S**alivation, **L**acrimation, **U**rination (excessive), **G**astrointestinal effects (nausea, vomiting, and diarrhea), **B**radycardia/bronchorrhea/**b**ronchospam, **A**bdominal cramps, and **M**iosis. Treatment is supportive, but atropine can be used for excessive cholinergic symptoms, as described in Chapter 152. Unlike organophosphates, there is no role for oxime therapy.

Disulfiram Reaction-Inducing Mushrooms

Coprinus atramentarius and other *Coprinus* species contain the toxin coprine that can inhibit aldehyde dehydrogenase similar to disulfiram. If ingested along with ethanol, it can lead to a disulfiram-like reaction including nausea, vomiting, diarrhea and flushing. Treatment is generally supportive, including IV hydration and antiemetics, such as prochlorperazine, or ondansetron (Fig. 153.10).

Hallucinogenic Mushrooms

There are a wide variety of mushrooms that can lead to hallucinations. Some common examples include the *Psilocybe* and *Conocybe* species. These are direct hallucinogens and contain psilocybin and related compounds. Psilocybin is found in a wide range of mushrooms. These are well known to be available for purchase online and in "grow at home" kits.[28] Possession of these types of mushrooms has recently been decriminalized in the State of Colorado.

Fig. 153.10 Coprinus atramentarius (Courtesy Joe McFarland.)

The ibotenic acid and muscimol containing mushrooms can also lead to hallucinations. *Amanita muscaria* is an important example of this class. Others include *Amanita pantherina* and *Gemmata* species. Ibotenic acid acts similarly to glutamate and can have excitatory effects. Muscimol has inhibitory effects and works as a GABA agonist. These mushrooms are used for their hallucinogenic effect and both CNS excitation and depression can be seen.

Overdose of these mushrooms can lead to nausea, vomiting, diarrhea, abdominal pain, dry mouth, dilated pupils, tachycardia, agitation, delirium, coma and seizures.[29] The mainstay of treatment of hallucinogenic mushrooms is providing a low-stimulus environment where the effects can dissipate. Benzodiazepines are generally effective in treating the agitation and tachycardia (lorazepam, 1 to 2 mg IVP; diazepam, 5 to 10 mg IVP). Antipsychotic agents can be used for prolonged hallucinations not improved with benzodiazepines (e.g., haloperidol, 2 to 5 mg IM or droperidol, 1.25 to 2.5 mg IM).

Gastrointestinal Irritants

There are hundreds of species of mushrooms that are GI irritants. These mushrooms will cause irritation to the GI tract within 2 to 3 hours of ingestion. Some commonly encountered species of GI irritants include *Boletus* sp., *Chlorophyllum molybdites, Lactarius* sp, and *Omphalotus* sp. Nausea, vomiting, diarrhea, and crampy abdominal pain will be the typical presenting symptoms. The course is generally self-limited, but care should be taken to monitor patients with prolonged symptoms or with significant fluid losses.

Another consideration with mushrooms ingested that cause GI symptoms is that the mushroom will be contaminated with pesticides or metals. Therefore, the symptoms may not be from the mushroom itself but from the chemical contaminant.

Renal Insufficiency

Two species of mushrooms can potentially lead to direct renal toxicity. In Europe, the *Cortinarius* species of mushrooms have been associated with renal failure.[30] Similar to the deadly cyclopeptide and gyromitirin-containing mushrooms, symptoms commonly occur on a delayed basis and as long as 2 weeks after ingestion. This mushroom is not generally found in the US.

A more problematic mushroom that is found in the Pacific Northwest is the *Amanita smithiana* mushroom. The toxin contained in this mushroom is allenic norleucine, which can have serious nephrotoxic effects. This mushroom leads to GI symptoms early after ingestion, and thus violates the general rule that serious poisoning follows delayed onset of GI symptoms. GI symptoms can begin between 2 and 12 hours after ingestion. Treatment is generally supportive, including fluid bolus followed by maintenance. However, with acute renal failure, metabolic acidosis, and electrolyte imbalances, hemodialysis may be required.

Rhabdomyolysis-Inducing Mushrooms

Another mushroom that can cause toxicity on a delayed basis is *Tricholoma equestre* (commonly referred to as the "man on horseback" or "yellow knight" mushroom). It can cause weakness, fatigue, and muscle pain 24 to 72 hours after ingestion. This mushroom can cause clinically significant rhabdomyolysis. Serial serum CPK levels should be followed to monitor for rhabdomyolysis and development of renal failure. Treatment is supportive with IV hydration and alkalinization therapy.

HERBAL MEDICATIONS

Although much of the world's population has used herbal products as medicine for centuries, its growing popularity in the United States has

been a relatively recent trend. Since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, the number of herbal products on the market has sharply increased from 4000 to 90,000 in 2014.[31] It is estimated that nearly 40 million US adults use herbal products with sales exceeding $5 billion annually.

PRINCIPLES OF TOXICITY

The DSHEA established herbal products as food, and unlike pharmaceuticals, they are not subject to rigorous regulations and do not need to demonstrate efficacy or safety for commercial sale. As a result, ingredients and their concentrations are often unknown, and controlled clinical trials and toxicologic testing are not routinely performed. The consumer may believe that herbal medications undergo strict regulation and testing, and are safer and more efficacious than pharmaceuticals. This misperception, combined with a lack of proper dosing and scheduling regimen, may lead to misuse and over-use of herbal medications. Factors that further contribute to adverse events include inherent toxicity, contamination and adulteration of products, and herb-drug interaction.[32] Studies show that most people who use herbal medications in addition to prescribed medications will do so without consulting or notifying their health care providers.

Clinical research in the area of herb-drug interaction is lacking.[33] Most pharmaceutical drugs undergo hepatic biotransformation and inactivation via the cytochrome P_{450} enzymes. Herb-drug interactions typically stem from alteration of this system, leading to increased or decreased drug concentration. Herbal medications may also affect drug transporters, such a p-glycoprotein, and further modify pharmacodynamics. Herb-drug interactions are best documented in the use of St. John's Wort *(Hypericum perforatum)* (Fig. 153.11).[34] It induces cytochrome P_{450}, family 3, subfamily A (CYP3A), which metabolizes approximately 50% of available US pharmaceuticals, leading to decreased drug concentrations.

CLINICAL FEATURES

Many herbal medications possess toxicity inherent to the botanical from which they are derived (Table 153.3). Adverse effects can range from allergic reactions to cardiovascular and hepatic toxicity.[35–39] The Food and Drug Administration (FDA) banned the sale of Ma Huang *(Ephedra sinica)* in 2004 after reports of serious cardiovascular events and death related to its sympathomimetic effects. Many herbal medications, including Germander *(Teucrium chamaedrys)*, Pennyroyal oil (*Mentha pulegium*

Fig. 153.11 *Hypericum perforatum* (St. John's wort). (Courtesy Christopher Lim.)

TABLE 153.3 Mushrooms

Early Onset Symptoms (First 2–3 h)

Clinical Category	Symptoms	Treatment
Gastrointestinal irritants (*Boletus* sp., *Chlorophyllum* sp., *Lactarius* sp.)	Nausea, vomiting, diarrhea	Supportive care
Hallucinogens (*Psilocybe* and *Conocybe* sp., *Amanita muscaria, Amanita pantherina*)	Agitation, hallucinations	Benzodiazepines Low stimulus environment
Disulfiram (*Coprinus* sp.)	Nausea, vomiting, diarrhea, abdominal cramping, flushing	Supportive
Cholinergic (*Clitocybe* sp.)	SLUGBAM (Salivation, lacrimation, Urination, GI Distress, Bronchorrhea, Bradycardia, Bronchospasm, Abdominal cramps, Miosis)	Atropine
Renal *(Amanita smithiana)*	Renal insufficiency (GI symptoms early)	Supportive Hemodialysis

Late Onset Symptoms (>4–5 h)

Mushroom Group Hepatotoxic	Symptoms	Treatment
Cyclopeptide-containing (*Amanita phalloides, Amanita bisporigera, Lepiota* sp.,*Galerina* sp.)	Hepatic failure, symptoms begin 6–8 h post-ingestion	Supportive, NAC, Dialysis, Penicillin, Thioctic acid Silibinin, Liver transplant
Gyromitrin *(Gyromitra esculenta)*	Hepatic failure, Seizures, Supportive, Vitamin B6, Methylene blue	Methemoglobinemia
Renal (*Cortinarius* sp.)	Delayed onset renal failure	Supportive, Dialysis
Rhabodomyolysis *(Tricholoma equestre, Russula subnigricans)*	Muscle pain, weakness, fatigue	Supportive, hydration, Hemodialysis

and *Hedeoma pulegoides*), and those containing pyrrolizidine alkaloids are associated with hepatotoxicity.[39] Most herbal medications that possess inherent toxicity can have adverse maternal-fetal effects, and we advise against the routine use of herbal medications during pregnancy.

Some herbal medications increase bleeding risk by altering the pharmacokinetics of anticoagulants, such as warfarin, or having a synergistic effect with antiplatelet agents and anticoagulants.[40] The concurrent use of several herbal medications, such as St. John's wort, with other serotonergic drugs can potentially contribute to the development of serotonin syndrome. Kava Kava *(Piper methisticum)* and Valerian *(Valerian officinalis)* have been shown to potentiate the GABA-mediated CNS depression from alcohol consumption.

DIFFERENTIAL DIAGNOSES

Due to the unregulated nature of herbal medications, contaminants and adulterants are often present and sometimes result in toxicity. In addition to fillers and substituents, contamination with heavy metals, pesticides and other harmful materials has been found in herbal medications. Certain metals are believed to have therapeutic properties. Lead is the most commonly reported heavy metal contaminant, but arsenic, cadmium, and mercury poisoning after herbal medication use have been described as well.[32] Additionally, there are many examples reported in the literature of toxicity from herbal medications adulterated with pharmaceuticals.

DIAGNOSTIC TESTING

Diagnostic studies in patients presenting with herbal medication toxicity include a complete blood count, coagulation profile, serum electrolytes, glucose, hepatic, and renal function tests. In addition, acetaminophen and salicylate levels should be measured along with urinary heavy metal screens, targeting lead, arsenic, and mercury.

MANAGEMENT

Treatment is largely supportive, with hydration, bleeding control if coagulopathic, cardiac dysrhythmia treatment, and targeted antidote therapy (e.g., NAC, heavy metal chelation therapy; see Chapter 146).

DISPOSITION

The majority of patients with herbal medication toxicity will be mildly symptomatic with GI symptoms and normal diagnostic testing. These patients can be observed and hydrated in the ED and safely discharged home. Patients with systemic toxicity including hepatic, renal, cardiac or multi-organ failure require admission for monitoring and consultation from appropriate services.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 153: QUESTIONS AND ANSWERS

1. A 52-year-old man presents after ingestion of water hemlock complaining of nausea but no other symptoms. He reports that he ate the water hemlock in a suicide attempt but has since changed his mind. His vital signs and physical examination are normal. What is the most appropriate initial treatment of this patient?
   a. General seizure precautions
   b. Hemodialysis
   c. Neutralization with milk
   d. Supportive care only
   e. Whole bowel irrigation

Answer: a. Water hemlock is very toxic, with fatality rates as high as 70%. Because this patient is at risk for seizures, oral activated charcoal and gastric lavage are contraindicated. Hemodialysis, whole bowel irrigation, and milk are not beneficial. Supportive care is not adequate with water hemlock ingestion. Most deaths are caused by intractable seizures, so this complication should be anticipated.

2. A family of four presents to the emergency department feeling ill after consuming a homemade stew containing Datura stramonium (Jimsonweed). Which of the following can be expected upon physical examination?
   a. Bradycardia
   b. Confusion
   c. Diaphoresis
   d. Miosis
   e. Respiratory depression

Answer: b. Jimsonweed contains atropine, hyoscyamine, and scopolamine, all of which have anticholinergic properties. Anticholinergic signs include confusion, dry skin and mucous membranes, mydriasis, tachycardia, urinary retention, confusion. In severe cases, physostigmine can be used to reverse effects.

3. Oleander contains cardiac glycosides similar to digoxin. Which of the following should be considered when treating oleander ingestion?
   a. Activated charcoal should be avoided.
   b. Serum digoxin levels correlate with degree of toxicity.
   c. Treatment is supportive.
   d. Treatment with digoxin-specific Fab fragments is beneficial, but a higher dose may be necessary.
   e. Treatment with digoxin-specific Fab fragments is not beneficial.

Answer: d. Treatment is with digoxin-specific Fab fragments, but much higher doses are necessary compared with those needed to treat digoxin toxicity. Activated charcoal is useful if the ingestion was recent. A serum digoxin level should be measured, but it is not a reliable indicator of level of toxicity. An elevated level confirms oleander ingestion, but a negative level cannot rule out ingestion.

4. A husband and wife present to the emergency department (ED) complaining of nausea and vomiting after eating mushrooms that they picked while hiking. They report eating the mushrooms on a salad approximately 1 hour ago. Each is complaining of severe nausea, vomiting, and diffuse abdominal pain. There is no hematemesis. Vitals signs and physical examination are normal. You inform them that they will be symptomatically treated and observed, but there is likely nothing to worry about. Why are you not concerned about their ingestion?
   a. Early onset of gastrointestinal symptoms
   b. No hematemesis
   c. No right upper quadrant tenderness
   d. Normal mental status
   e. Normal vital signs

Answer: a. The vast majority of severely toxic mushrooms have delayed onset of symptoms (>6 hours from ingestion). Occasionally, people will ingest two different types of mushrooms—one benign and causing early onset of symptoms and one more toxic. Therefore, patients should be observed and rechecked.

5. What is the most common cause of death after mushroom ingestion?
   a. Gastrointestinal hemorrhage
   b. Heart failure
   c. Liver failure
   d. Renal failure
   e. Respiratory failure

Answer: c. The *Amanita* species of mushrooms are very toxic and cause fulminant liver failure often necessitating liver transplant. Hepatotoxic mushrooms account for about 90% of all mushroom fatalities. Although certain mushrooms (*Cortinarius* spp. and *Amanita smithiana*) can cause renal failure, death is uncommon with these mushrooms. Mushrooms generally do not affect the other listed organ systems.

6. A 46-year-old man presents after waking in the night with headache and severe nausea and vomiting. For dinner the night before, he consumed some mushrooms that he had gathered from a nearby forest. He felt fine immediately after dinner. His vital signs are normal. While conducting your physical examination, he begins to seize. Benzodiazepines are administered without improvement. What treatment is indicated?
   a. Phenobarbital
   b. Phenytoin
   c. Propofol
   d. Pyridoxine
   e. Vecuronium

Answer: d. Most mushrooms do not cause seizures, but gyromitrin-containing mushrooms are an exception. They are commonly mistaken for edible morels because they look quite similar. They contain an isoniazid-like toxin that causes seizures. Traditional seizure medications can be used (because they are typically more readily available), but seizures can be intractable until pyridoxine is given.

7. A 54-year-old male with a history of depression presents to the emergency department with confusion. He is prescribed nortriptyline only, but his wife reports that he has recently started taking an herbal supplement. His vital signs are temperature 100.3°F, blood pressure 130/75, pulse 124, respiratory rate 20, oxygen saturation 96%, You note spontaneous clonus to his lower extremities and diagnose him with serotonin syndrome. Which of the following herbal supplements did he most likely start taking?
   a. Ephedra
   b. *Hypericum perforatum*
   c. *Gingko biloba*
   d. *Piper methisticum*
   e. Saw palmetto

Answer: b. *Hypericum peforatum* (St. John's wort) is a non-selective serotonin reuptake inhibitor and is thought to also upregulate post-synaptic serotonin receptors. Combination therapy with other anti-depressants that increase serotonin has been reported to cause serotonin syndrome. Ephedra is no longer commercially available as it was banned by the FDA for its association with cardiovascular disease. *Gingko biloba* may have antioxidant properties and inhibit platelet aggregation. *Piper methisticum* can increases GABA-mediated CNS depression when combined with alcohol. Saw palmetto is a remedy for benign prostatic hypertrophy and is thought to work by inhibiting 5-α-reductase.

Sedative-Hypnotics

Daniel L. Overbeek and Timothy B. Erickson

KEY CONCEPTS

- Supportive care, with a focus on respiratory depression, is the foundation of management of all sedative-hypnotic ingestions.
- Benzodiazepines are commonly used medications both medically and recreationally. Coingestions with other sedative-hypnotic agents can potentiate their neurologic and respiratory effects.
- Barbiturate medications are less commonly prescribed, and intoxications are infrequent. Most patients recover with supportive care alone.
- A positive urine toxicology screen for benzodiazepines or barbiturates does not prove a causal linkage between the drug and the current clinical condition.
- We do not recommend routine use of flumazenil for benzodiazepine toxicity, particularly in chronic benzodiazepine users in whom flumazenil can precipitate seizures. Due to the short duration of action of flumazenil, when administered, patients should be monitored closely for recurrence of respiratory depression.
- Chloral hydrate toxicity may result in sedation and cardiotoxicity, principally in the form of supraventricular tachycardias, which are best treated with a short-acting beta blocker.
- Withdrawal from sedative-hypnotic use, including benzodiazepines, barbiturates and gamma hydroxybutyrate (GHB), can be life threatening. Management often requires high doses of benzodiazepines or barbiturates.

FOUNDATIONS

The sedative-hypnotic toxidrome encompasses depressed mental status, decreased respiratory rate, and suppressed response to stimuli. Within this chapter, we will discuss a variety of medications and agents that can induce a sedative-hypnotic toxidrome at therapeutic or toxic doses. Also, the general treatment recommendations and specific considerations for individual agents will be presented.

Most sedative-hypnotics have effects mediated through the gamma-aminobutyric acid (GABA) neurotransmitter system. GABA is the primary inhibitory neurotransmitter, and the GABA-A receptor is a protein complex found on postsynaptic membranes in the CNS. Structurally, it consists of several distinct receptor sites surrounding a chloride ion (Cl^-) channel (Fig. 154.1), which is opened by GABA binding. The resulting flow of Cl^- into the cell increases the negative resting potential, hyperpolarizing and stabilizing of the membrane. The net effect is a diminished ability of the nerve cell to initiate an action potential, inhibiting neural transmission. There are separate receptor sites for barbiturates and for benzodiazepines and a third site that binds GABA, ethanol, and meprobamate. Increasing either the frequency or duration of GABA stimulation in the nervous system causes most of the effects seen in the sedative-hypnotic toxidrome, including blunted responses to stimuli and sedation.

Sedative-hypnotic drugs, especially benzodiazepines, are among the most widely prescribed classes of drugs[1] (Table 154.1) and are the most commonly prescribed drugs used in suicide attempts. Pediatric patients comprise 10% of benzodiazepine overdose cases. With the significant proliferation of opioid usage, prevalence of combined benzodiazepine and opioid toxicity with significant risk of respiratory compromise has increased significantly.[2]

BENZODIAZEPINES

Clinical Features

Benzodiazepines are widely used medically for their antiepileptic, sedative, and anxiolytic properties. Prior to benzodiazepines, barbiturates were the primary sedative-hypnotics used, but they have been overwhelmingly supplanted by benzodiazepines and other, newer agents.

Benzodiazepines produce sedative, hypnotic, anxiolytic, and anticonvulsant effects by potentiating the GABA-A receptor in the presence of GABA.[3–5] In contrast, barbiturates can directly increase Cl^- conductance. This may account for the relative safety of benzodiazepines in comparison with barbiturates.

At therapeutic dosage, the GABA effects of benzodiazepines cause euphoria, anxiolysis, and drowsiness. Mild toxicity includes CNS depression, ataxia, slurred speech, nystagmus, and impaired cognition. Most benzodiazepine overdoses follow a relatively benign clinical course. Larger overdoses may cause respiratory depression, which may require intervention. The respiratory depression is less severe than with barbiturates, especially if benzodiazepines are the only substance ingested. Coingestants with sedative properties, particularly ethanol or opioids, can markedly potentiate the respiratory depression caused by benzodiazepines.[6] Loss of muscle tone leads to upper airway obstruction and increased airway resistance. Hypoventilation is often the first sign of severe respiratory depression, and may be masked by oxygen supplementation, which can maintain adequate oxyhemoglobin saturation. Capnography can be useful in detecting early signs of hypoventilation.

Cardiac toxicity or hypotension from pure benzodiazepine overdose is rare. Other potential complications include aspiration pneumonia and pressure necrosis of skin and muscles. Intravenous solutions of diazepam and lorazepam contain the diluent propylene glycol, which is metabolized to lactate, and prolonged or high-dose infusions of these preparations can cause lactic acidosis. Patients with renal or hepatic insufficiency are at increased risk for this complication.

Most pediatric patients have symptoms within four hours of benzodiazepine ingestion. Ataxia is the most common sign of toxicity, occurring in 90% of pediatric patients. Respiratory depression occurs in fewer than 10% of pediatric cases, and hypotension is rarely reported in children.

Benzodiazepines were previously identified as pregnancy category D, noting some risk, but that they should be used when indicated based on a risk-benefit analysis (see Chapter 175 regarding drug therapy for the pregnant patient). There are some studies showing risks, but these are difficult to analyze as most patients involved were also exposed to other psychiatric medications.[7] In the acute setting, when needed for management of emergent conditions including seizures, the benefits of short term acute use likely outweigh the complications to the mother and fetus.[8,9] Management of seizures during pregnancy is discussed in Chapter 173. The management of benzodiazepine toxicity during pregnancy follows the standard approach, including supportive care and respiratory support, with the recognition of an increased risk of respiratory and mental status depression in the fetus if delivery is required.

Novel synthetic benzodiazepines are procured from a variety of internet sites or other illicit sources, and the true content of the product received is unknown to the user. Limited information is available about many of these agents. Management should be similar to the known pharmaceutical benzodiazepines, recognizing the increased likelihood of coingestants, as discussed in the following.[10,11]

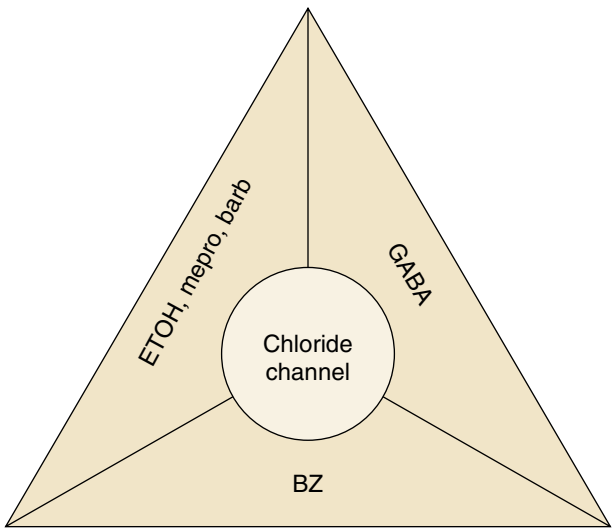

Fig. 154.1 The gamma-aminobutyric acid (GABA) receptor complex. *BZ,* Benzodiazepine binding site; *GABA,* GABA binding site; *ETOH, mepro, barb,* binding sites for ethanol, meprobamate, and barbiturates, respectively.

Pharmacokinetics

Benzodiazepines are rapidly absorbed orally. Intramuscular use of chlordiazepoxide and diazepam is limited by erratic absorption, but lorazepam and midazolam are predictably absorbed after intramuscular injection. Parenteral and rectal administration of benzodiazepines provide faster time to onset than oral ingestion and can be used for antiepileptic and sedative indications. After absorption, benzodiazepines distribute readily, and rapidly penetrate the blood-brain barrier. In plasma, benzodiazepines are highly protein bound.[12,13]

Benzodiazepines are metabolized in the liver. Lorazepam, oxazepam, and temazepam are directly conjugated to an inactive, water-soluble glucuronide metabolite that is excreted by the kidney. Other benzodiazepines must first be converted by the hepatic cytochrome P450 system. Many benzodiazepines, including chlordiazepoxide and diazepam, are metabolized to active compounds that are then conjugated and excreted. The long elimination half-lives of up to 120 hours of these intermediates can cause accumulation in the body with repeated dosing and prolong the sedative effects of these benzodiazepines.[13] Alprazolam and midazolam are converted to hydroxylated intermediates that are rapidly conjugated and excreted, but do not contribute significantly to the overall effect of the drug.[12]

Cytochrome P450 metabolism may be significantly impaired in elderly patients or those with liver disease, leading to prolonged elimination of benzodiazepines. Coingestion of drugs that inhibit P450 metabolism (e.g., cimetidine, ethanol) also prolongs the half-lives of benzodiazepines.[12]

Differential Diagnoses

Benzodiazepine overdose is usually suspected or diagnosed by clinical presentation. Many patients are able to interact appropriately with providers and can provide supporting information. Atypical or focal neurological findings suggest the presence of other conditions, such as intracranial events (e.g., intracerebral hemorrhage, cerebral ischemia). Profound coma or cardiopulmonary instability is rare with pure benzodiazepine overdose and should prompt the search for coingestants, such as opioids, ethanol, phenobarbital, choral hydrate, or a cyclic antidepressant. Non-toxicologic metabolic causes of CNS depression,

TABLE 154.1 Benzodiazepines

Name	Usual Dose	Oral Peak (Hours)	Half-Life (Hours)	Parent Metabolite Activity
Alprazolam (Xanax)	0.25–0.5 mg	1–2	6–27	Inactive
Chlordiazepoxide(Librium)	5–25 mg	0.5–4	5–30	Active
Clonazepam (Klonopin)	0.25–0.5 mg	1–2	18–50	Inactive
Clorazepate (Tranxene)	7.5–15 mg	1–2	1–3	Active
Diazepam (Valium)	2–10 mg	0.5–1	20–50	Active
Estazolam (Prosom)	1–2 mg	2	8–28	Inactive
Flurazepam (Dalmane)	15–30 mg	0.5–1	2–3	Active
Halazepam (Paxipam)	20–40 mg	1–3	14	Active
Lorazepam (Ativan)	0.5–2 mg	2–4	10–20	Inactive
Midazolam (Versed)	10–20 mg	1–2	1.5–3	Active
Oxazepam (Serax)	10–30 mg	2–4	5–20	Inactive
Quazepam (Doral)	7.5–15 mg	2	39–41	Active
Temazepam (Restoril)	7.5–30 mg	1–2	3–19	Inactive
Triazolam (Halcion)	0.125–0.25 mg	1–2	1.5–5.5	Inactive

such as hypoglycemia or hyponatremia should also be considered. The broader differential of CNS depression includes conditions described in Chapters 12 and 13.

Diagnostic Testing

Sedative-hypnotic toxidromes are clinical diagnoses, and most laboratory testing will not be helpful in determining the appropriate care for the patient. Any patient with altered mental status should have a blood glucose level rapidly determined. Qualitative immunoassays for benzodiazepines in urine are available, but do not aid management decisions and cannot provide definitive information regarding the cause of the altered mental status. Because most screening tests detect a specific benzodiazepine metabolite, including nordiazepam or oxazepam glucuronide, some benzodiazepines (including clonazepam, lorazepam, midazolam, and alprazolam) will not be detected on many standard urine drug tests. A positive urine drug screen for benzodiazepines indicates exposure or use but does not identify intoxication or indicate a specific agent and does not confirm benzodiazepine exposure as the cause of the clinical presentation. The positive screen also does not provide information regarding the timing of the benzodiazepine exposure. Serum drug concentrations are not routinely available and do not correlate with clinical severity.[14]

Adjunct testing should be used as clinically indicated, including computerized topography (CT) imaging when concerned for head trauma or intracranial hemorrhage. The benzodiazepine antagonist flumazenil should not be routinely administered to patients with suspected benzodiazepine overdose or coma of unknown origin solely for diagnostic purposes.[15]

MANAGEMENT

Stabilization and Supportive Care

Initial stabilization, including endotracheal intubation when necessary, should not be delayed by the administration of an antidote. Most benzodiazepine overdoses can be managed expectantly with observation and supportive care alone. Neither gastrointestinal (GI) decontamination or administration of activated charcoal is indicated in benzodiazepine ingestion. Close respiratory monitoring is indicated to guide respiratory interventions and end tidal carbon dioxide (CO_2) monitoring can be a useful adjunct. Naloxone should be administered in cases of suspected opioid coingestion (see further discussion of opioid overdoses in Chapter 151).

Antidote Therapy

Flumazenil, a nonspecific competitive antagonist at the benzodiazepine receptor, can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and confirmed benzodiazepine overdose. However, the risks of flumazenil usually outweigh the benefits in patients with benzodiazepine toxicity. Therefore, flumazenil is not recommended for the routine reversal of sedative overdose in the ED.[15] Theoretic benefits of flumazenil use include cost savings and avoidance of procedures and tests (such as endotracheal intubation and CT scans). However, several clinical studies have failed to demonstrate these benefits in practice.[15] Benzodiazepine toxicity has a low mortality rate with supportive care, shifting the risk benefit analysis away from the use of flumazenil in routine cases.

There are also risks associated with flumazenil; it can precipitate acute withdrawal in patients who are chronically dependent on benzodiazepines, leading to significant complications including status epilepticus. Similarly, this antidote is hazardous when it is given to patients who have coingested seizure-inducing drugs (such as cocaine or a tricyclic antidepressant) because of loss of the benzodiazepine's protective anticonvulsant properties and the subsequent ineffectiveness of benzodiazepines to abort a seizure if one occurs. Seizures after the administration of flumazenil should be treated with the administration of barbiturates or propofol. Cardiac dysrhythmias (principally paroxysmal supraventricular tachycardia [PSVT]) can occur after flumazenil administration. Coingestants that cause dysrhythmias, such as carbamazepine or chloral hydrate, may increase the likelihood of cardiac effects. Fatalities after flumazenil administration have been reported.[15] Other risk factors are summarized in Box 154.1.

BOX 154.1 Use of Flumazenil

Indications

Isolated benzodiazepine overdose in non-habituated user (e.g., accidental pediatric exposure)

Reversal of conscious sedation

Absolute Contraindications

Suspected coingestant that lowers seizure threshold (e.g., tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate)

Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures)

Concurrent sedative-hypnotic withdrawal

Seizure activity or myoclonus

Hypersensitivity to flumazenil or benzodiazepines

Patient with neuromuscular blockade

Relative Contraindications

Chronic benzodiazepine use, not taken for control of life-threatening condition

Known seizure disorder not treated with benzodiazepines

Head injury

Chronic alcoholism

When benzodiazepine-naive patients ingest benzodiazepines alone in overdose (as occurs in young children), the risks associated with flumazenil are lower.[15] In cases of benzodiazepine overdose by a non-benzodiazepine habituated patient, flumazenil use combined with close monitoring and repeated or infusion-based dosing, may obviate the need for intubation and mechanical ventilation. We recommend basing this decision on a balance of risks/benefits for the particular patient and the reliability that the patient is a novice benzodiazepine user. This approach extends to the setting of unintended over-sedation by benzodiazepines for procedural sedation. In these cases, as patients are often nonbenzodiazepine-dependent, flumazenil would likely have a lower risk of complications.

The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2 mg dose at 1-minute intervals to a total of 1 mg. In children, the initial dose is 0.01 mg/kg (up to 0.2 mg). Because the duration of action of flumazenil is short (45 to 75 minutes), re-sedation occurs in up to 65% of patients and requires either re-dosing or continuous infusion (0.25 to 1.0 mg/h). It is important to note that flumazenil reverses the CNS depressant effects of benzodiazepines more than it reverses the respiratory depression.

In summary, benzodiazepine overdose requires primarily supportive care, assisted ventilation, and if severe, intubation. Flumazenil may precipitate seizures or acute withdrawal and should be used only in highly selected cases (such as to reverse procedural sedation, or to treat young children with a clear history of inadvertent benzodiazepine ingestion). When flumazenil is used, close monitoring of

oxy-hemoglobin saturation and overall ventilatory status (ideally including end-tidal CO_2) is necessary because of the risk for recurrent respiratory depression or resedation.[15]

Disposition

Patients remaining asymptomatic after 4 to 6 hours of ED observation following benzodiazepine ingestion may be medically cleared. For cases of deliberate overdose, appropriate psychiatric consultation should be obtained. Patients presenting with respiratory depression and coma should be given oxygen, ventilatory support, and admission to a monitored setting, such as an ED Observation Unit, or monitored inpatient unit.

Benzodiazepine Withdrawal Syndrome

Abrupt discontinuation of a benzodiazepine in a chronic user results in a characteristic constellation of symptoms similar to ethanol withdrawal (Box 154.2). Risk for withdrawal is a function of both the dose of benzodiazepine and the duration of its use. Continuous treatment for more than 3 to 4 months is generally required before a patient is at risk for withdrawal. With abrupt discontinuation of a benzodiazepine, the most severe withdrawal symptoms occur within several days to a week. Treatment of withdrawal consists of restarting benzodiazepines in the acute setting and, if refractory, phenobarbital or propofol administration to treat withdrawal symptoms. Patients who have experienced withdrawal symptoms after cessation of benzodiazepine use may require benzodiazepine tapers to avoid symptomatic withdrawal.

BARBITURATES

Clinical Features

Barbiturates, once commonly prescribed as sedative-hypnotic agents, are generally used now only for management of some seizure disorders and withdrawal states. Mortality from barbiturate poisoning declined from approximately 1500 deaths per year in the 1950s to fewer than five fatalities in 2017.[16]

Barbiturates are addictive, producing physical dependence and a potentially life-threatening withdrawal syndrome similar to that of benzodiazepines. Whereas tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects including respiratory depression develops more slowly, and the risk of severe toxicity increases with the dose escalation that often accompanies continued use.

Barbiturates depress the activity of excitable cells, especially those in the central nervous system (CNS), by enhancing the activity of GABA. In acute overdose, barbiturates decrease neural transmission in autonomic ganglia, the myocardium, and the GI tract, also inhibiting the response to acetylcholine at the neuromuscular junction.

Barbiturates produce dose-related depressive effects ranging from mild sedation to coma and respiratory arrest. Mild barbiturate toxicity manifests with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability, and impaired cognition. In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest. The life threat in severe barbiturate toxicity is respiratory depression, from direct barbiturate action on the respiratory centers in the medulla. Because respirations can be rapid but shallow, the degree of hypoventilation may not be apparent on clinical examination, and pulse oximetry or capnography may be needed to detect the ventilation compromise. Barbiturate-induced respiratory depression can be significantly potentiated by the addition of other respiratory depressants, particularly opioids. High barbiturate levels depress GI motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise again.

Therapeutic doses cause anxiolysis and euphoria, and mild decreases in pulse rate and blood pressure, similar to sleep. With toxic doses, more significant hypotension occurs from direct depression of the myocardium along with pooling of blood in a dilated venous system. Peripheral vascular resistance is usually normal or increased, but barbiturates interfere with autonomic reflexes, which then do not adequately compensate for the myocardial depression and decreased venous return. Barbiturates can precipitate severe hypotension in patients whose compensatory reflexes are already maximally stimulated, such as those with heart failure or hypovolemic shock. Barbiturates also decrease cerebral blood flow and intracerebral pressure. Although hypnotic doses of barbiturates do not affect gastric emptying, higher doses can decrease GI smooth muscle tone and peristaltic contractions, delaying gastric emptying.

Hypotension is common in patients with severe intoxication, along with a normal or increased heart rate. Barbiturate overdose is also associated with noncardiogenic pulmonary edema or acute lung injury. Altered pulmonary capillary permeability can be caused by hypoperfusion, hypoxia, or a direct effect of the drug.

Barbiturates are classified according to their onset and duration of action (Box 154.3). Only long-acting preparations have anticonvulsant effects in doses that do not cause sedation. Short- and intermediate-acting preparations are almost completely metabolized to inactive metabolites in the liver, whereas 25% of a phenobarbital (long-acting) dose is excreted unchanged through the kidney.

Barbiturates cross the placenta with fetal levels approaching those of the mother. They are also excreted in low concentration in breast milk. Use during pregnancy is associated with birth defects (category D).

Barbiturate withdrawal syndrome includes tremors, hallucinations, seizures, and delirium, which is similar to the delirium tremens of ethanol withdrawal or benzodiazepine withdrawal discussed previously. However, severe withdrawal occurs only after dependence on short- or intermediate-acting barbiturates (e.g., pentobarbital, secobarbital, amobarbital, or butalbital). Because these drugs are less commonly used, this syndrome is now rare.

Differential Diagnoses

Mild barbiturate toxicity mimics ethanol intoxication and that of other sedative-hypnotic agents such as benzodiazepines. Barbiturate intoxication causes relatively more respiratory depression and hypotension than ethanol compared to benzodiazepine toxicities. Chloral hydrate overdose is marked by greater cardiotoxicity (discussed later in this chapter). Gamma-hydroxybutyrate (GHB) produces coma just like barbiturates, but resolution of the coma occurs much more rapidly. Opioids cause similar sedation with a greater degree of respiratory depression, which reverses rapidly with the administration of naloxone. Other common antiepileptic agents (such as, carbamazepine, phenytoin, and valproic acid) will cause sedation similar to barbiturates with acute overdose. As with any patient exhibiting depressed mental status, metabolic causes (such as, hypoglycemia or hyponatremia) and intracranial events (such as, cerebral ischemia or hemorrhage) should be excluded.

BOX 154.2 Benzodiazepine Withdrawal Symptoms

Nonspecific
Anxiety, depression, insomnia, tremor, tachycardia, sweating

Severe (Rare)
Visual hallucinations, delirium, seizures

BOX 154.3 Barbiturates

Ultrashort Acting
Methohexital (Brevital)
Thiopental (Pentothal)

Short and Intermediate Acting
Pentobarbital (Nembutal)
Secobarbital (Seconal)
Amobarbital (Amytal)
Aprobarbital (Alurate)
Butabarbital (Butisol)
Butalbital (Fiorinal)

Long Acting
Phenobarbital (Solfoton, Luminal)
Mephobarbital (Mebaral)

Diagnostic Testing

Generally, laboratory testing is not helpful in the acute management of barbiturate toxicity, except to exclude metabolic or electrolyte disorder. A positive urine screen establishes only qualitative exposure to a barbiturate but does not prove that the drug is present in toxic amounts and should not be relied on to explain decreased mental status. A quantitative serum phenobarbital level can be obtained to document toxicity (therapeutic levels range 10 to 40 mcg/mL) but rarely guide management. Other than phenobarbital, barbiturates have high volumes of distribution, so serum levels do not accurately reflect CNS concentrations or correlate with clinical severity and these levels are not rapidly available.

A chest radiograph can detect noncardiogenic pulmonary edema, acute lung injury or aspiration pneumonia. Computed tomography (CT) of the head may be helpful in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or no otherwise identifiable cause of stupor and coma.

Because the electroencephalogram may be silent as a result of barbiturate overdose, in patients with coma, brain death should not be determined if phenobarbital is present in the serum at therapeutic levels or higher.[17]

MANAGEMENT

Supportive Care and Stabilization

Barbiturates have no specific antidote, and management is supportive care, particularly with respect to the cardiovascular and respiratory systems. Severely intoxicated patients are unable to protect their airway and have a decreased ventilatory drive. Supplemental oxygen may suffice for patients with mild to moderate overdose, but intubation and mechanical ventilation is often required. Fluid replacement should be limited to maintain a systolic blood pressure above 90 mm Hg and adequate urine output as patients may be at risk of pulmonary edema.

Gastrointestinal Decontamination

Gastric emptying by lavage is not indicated. High barbiturate levels depress GI motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to again rise. Although multidose activated charcoal increases clearance of phenobarbital via hepato-enteric circulation and may shorten the duration of clinical toxicity, there is no convincing evidence it results in improved outcome over supportive care alone and we do not recommend its routine use.

Enhanced Elimination

Because phenobarbital is a weak acid (pKa 7.2), alkalinization of the urine will increase the amount of drug present in ionized form, minimizing tubular reabsorption and increasing drug clearance. Short- and intermediate-acting barbiturates are not significantly affected by pH changes in this range. Alkalinization may interfere with the ability of the drug to diffuse across intestinal mucosa from the gut into the blood. There is limited evidence, regarding the clinical benefits of alkalinization in the setting of barbiturate toxicity,[18] and we do not recommend its routine use.

Despite a lack of compelling data demonstrating, its benefit in acute phenobarbital overdose, hemodialysis is a legitimate option for severe phenobarbital toxicity.[19,20] Phenobarbital is 40% to 60% protein bound, and newer, high-efficiency dialyzers using high blood flow rates provide drug clearance greater than that achieved by hemoperfusion. Cases with pharmacokinetic data have documented significant elimination of barbiturates with hemodialysis. Although rarely indicated, we recommend hemodialysis for acute phenobarbital toxicity (persistent serum levels over 100 mcg/mL) in the presence of prolonged coma, refractory hypotension, renal or cardiac failure, metabolic acidosis, or inadequate response to less invasive measures (such as supportive care and mechanical ventilation).[19] Although potentially efficacious with severe toxicity, we are not aware of studies assessing the role of extracorporeal membrane oxygenation (ECMO) in cases of refractory barbiturate poisoning, and until further studied, would not recommend its use over hemodialysis.

Disposition

Asymptomatic patients presenting after barbiturate ingestion should be observed for 6 hours for mental status changes, slurred speech, ataxia, hypotension, and respiratory depression. Symptoms generally occur within 1 hour of ingestion. Patients who remain asymptomatic and have no significant complicating coingestants can be discharged or referred for psychiatric evaluation. Patients who are symptomatic after 6 hours should be admitted to a monitored setting in hospital or an ED observation unit for respiratory monitoring and supportive care. Those with persistent hypotension, severe depression of mental status, or respiratory depression requiring intubation and ventilator support will need intensive care monitoring. Psychiatry or social services consultation is undertaken when the patient with intentional ingestion is medically cleared.

INDIVIDUAL MEDICATIONS

Zolpidem, Zaleplon, and Zopiclone

Zolpidem (Ambien), zaleplon (Sonata), and zopiclone (Imovane) differ in structure from the benzodiazepines and act selectively at the benzodiazepine receptor, producing sedation without many of the side effects seen with benzodiazepines. They have modest anxiolytic, muscle relaxant, and anticonvulsant properties. Significant drug interactions are rare.[21] Transient visual disturbances, transient global amnesia, hallucinations, and somnambulism can occur in patients with normal levels of consciousness with both zolpidem and zaleplon. Over ingestion of zolpidem is limited by vomiting, which may occur after a supratherapeutic dose. Both zolpidem and zaleplon are rapidly eliminated and lack active metabolites. A controlled-release formulation of zolpidem (Ambien CR) is also available. The dual-layered tablet releases an immediate dose of zolpidem, followed by a slow, extended release from the inner layer to maintain plasma zolpidem concentrations. Overdoses with the controlled-release formulation mirror those of the immediate-release preparation, with only small differences in the likelihood of drowsiness, hallucinations, and ataxia. Of the three "Z-drugs," zopiclone has the longest duration of action, and may have longer duration of symptoms in toxic ingestions.

Zolpidem overdose is managed by supportive care. Fatalities from isolated zolpidem overdose are rare[21] and are associated with coingestants, particularly other sedative-hypnotics or antipsychotics. Drowsiness is the most common symptom; coma and respiratory failure are rare, despite overdoses of up to 40 times the normal dose. Intubation may be required for airway protection or ventilatory support, particularly if there are coingestants that exacerbate respiratory depression. Zolpidem overdose in children which generally follows a similarly benign course. Drowsiness, ataxia, and hallucinations generally resolve within eight hours. Patients who remain asymptomatic after six hours can be discharged.

Adverse effects with therapeutic zaleplon use include headache, anterograde amnesia, and transient visual hallucinations. Overdose information is limited, but patients generally experience CNS depression and mild hypotension. Flumazenil administration is not advised.[21] The blue-green discoloration of gastric contents, oral cavity, and urine after zaleplon overdose is attributed to the indigo carmine dye present in zaleplon's capsule shell.

Minimal data are available on the toxicity of zopiclone, which is not currently available as a commercial product in the United States. There have been multiple reported deaths with zopiclone ingestion;[23] however most of these have associated coingestants. Zopiclone has a notably high prevalence of toxicity in areas where its prescription is uncontrolled. General principles should follow the sedative-hypnotics discussed previously, including supportive care with respiratory intervention when indicated.

Eszopiclone

Eszopiclone (Lunesta) has been marketed in the United States for treatment of insomnia. It is the S-isomer of racemic zopiclone, which has been used for decades outside the United States. Eszopiclone has a structure unrelated to that of benzodiazepines or barbiturates.

The mechanism of eszopiclone's action involves a specific GABA-A receptor close to or coupled with the benzodiazepine receptor. Eszopiclone is rapidly absorbed, with a peak serum level at 1 hour and a half-life of 6 hours. It is metabolized in the liver to minimally active metabolites. The maximum hypnotic dose is 3 mg. It is recommended that elderly patients and those with hepatic insufficiency be treated with a lower (1 mg) dose.

Adverse effects with therapeutic use of eszopiclone include drowsiness, dizziness, dry mouth, unpleasant taste, nausea, and vomiting. Auditory and visual hallucinations have been reported. Experience with eszopiclone overdose is limited. Treatment is supportive. CNS depression may be prolonged and pronounced in elderly patients. Most reported eszopiclone ingestions had mild to moderate symptoms.

Buspirone

Buspirone (BuSpar) is often prescribed for generalized anxiety disorder because of its lack of sedative effect. Even when combined with ethanol, CNS depression is minimal. Buspirone acts on the serotonin (5HT-1A) receptor and antagonizes dopamine (D2) receptors, unlike the mechanism of action of benzodiazepines discussed above. There are rare case reports of toxicity in overdose, including a death reported in single-drug buspirone overdose.[16] A withdrawal state after discontinuation has not been reported. Due to the low toxicity in most situations, supportive care is sufficient for buspirone overdose.

Flunitrazepam

Flunitrazepam (Rohypnol) has been used in Europe, Asia, and Latin America for insomnia and preoperative sedation. Although it has never been manufactured or sold commercially in the United States, flunitrazepam has been documented in many sexual assaults or "date rape" incidents. Flunitrazepam has been an active agent in the illicit drug market, where it is used to alter the effects of other drugs, including ethanol, heroin, and cocaine.

Flunitrazepam has 10 times more affinity than diazepam for benzodiazepine receptors. CNS depression occurs within 30 minutes. The drug is most frequently ingested with alcohol, producing additional disinhibition and amnesia. Despite marked CNS depression, patients can usually be aroused with noxious stimuli. The half-life of the drug is 16 to 36 hours, but coma can be prolonged for up to 48 hours. Management should include monitoring for hypoxia, hypoventilation, and aspiration; airway protection and ventilatory support can be provided when indicated. Flunitrazepam is easily obtained outside the United States and on the Internet. The drug is not detected on routine urine drug screens, but if needed as evidence, a urine sample should be obtained and the local or state police crime laboratory contacted to arrange specific testing. Metabolites of flunitrazepam can be detected in the urine up to 72 hours after exposure.

Chloral Hydrate

Clinical Features

Chloral hydrate has a low therapeutic ratio and can produce significant, potentially fatal toxicity. It is used in rare cases, but chloral hydrate is occasionally prescribed as a sedative in the elderly and for children undergoing hospital and outpatient procedures.[24,25] The use has decreased significantly with the availability of other procedural sedation medications with wider therapeutic indices. The oral hypnotic in adult is of dose 0.5 to 1.0 g. The pediatric sedation dose is 25 to 50 mg/kg orally 30 minutes prior to the procedure, with a maximum dose of 1000 mg.

The toxic oral dose is approximately 10 g in adults and may be as little as 1.5 g in children. The toxic effects of chloral hydrate include CNS and respiratory depression, GI irritation, cardiovascular instability, hepatitis, and proteinuria.[24] The combination of deep coma and cardiac dysrhythmia without hypoxia is characteristic of severe cases. Chloral hydrate decreases myocardial contractility, shortens the cardiac refractory period, and increases the sensitivity of myocardium to catecholamines. Dysrhythmias can be fatal, and include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, multifocal premature ventricular contractions, torsades de pointes, ventricular fibrillation, and asystole.

A citrus or pear-like odor to the patient's breath or gastric contents may suggest the diagnosis. Findings consistent with chloral hydrate toxicity include miosis, muscle flaccidity, diminished deep tendon reflexes, hypoventilation, hypotension, and hypothermia. Chloral hydrate is a GI irritant and causes nausea, vomiting, esophagitis, hemorrhagic gastritis, and, rarely, GI perforation or necrosis. Transient hepatic or renal dysfunction can also occur.

Chloral hydrate is rapidly absorbed from the GI tract. The primary active metabolite of chloral hydrate, trichloroethanol, has a barbiturate-like effect on GABA-A receptors and is responsible for most of the CNS depression seen with significant overdose. Metabolism to trichloroethanol occurs via the enzyme alcohol dehydrogenase with an onset of action of 20 to 30 minutes. Trichloroethanol is long acting, and its half-life can be significantly prolonged after overdose as the metabolic pathways become saturated.

Chloral hydrate and ethanol in combination (historically referred to as a "Mickey Finn") potentiate each other's effects to produce rapid loss of consciousness. Chloral hydrate increases the half-life of ethanol by competitively inhibiting the enzyme alcohol dehydrogenase, and the metabolism of ethanol generates nicotinamide adenine dinucleotide (NADH), a cofactor for the conversion of chloral hydrate to trichloroethanol.

Differential Diagnoses

Mild chloral hydrate toxicity can mimic many other sedative-hypnotics, including ethanol, benzodiazepines or barbiturates, with drowsiness, ataxia, and lethargy. More severe toxicity can mimic other cardiotoxic agents, including tricyclic antidepressants and cocaine. Hypomagnesemia can also induce torsades de pointes, as can QTc prolonging agents such as antipsychotics or methadone.

Management

The key to management is support of cardiorespiratory functions. Intubation may be required for airway protection, or to support ventilation, and oxygenation if there is significant depression of respiratory function. Avoid naloxone or flumazenil, which may precipitate ventricular dysrhythmias and will not have reversal effects. Because chloral hydrate, like other chlorinated hydrocarbons, sensitizes myocardium to catecholamines, epinephrine and norepinephrine should also be avoided. Standard type I antidysrhythmic agents, such as quinidine (1a) and lidocaine (1b), do not appear effective against chloral hydrate–induced cardiac ectopy. The treatment of choice for chloral hydrate-induced tachydysrhythmias is a beta-blocker. A short-acting agent, such as esmolol, can be used with an initial bolus of 1 mg/kg IV over 30 seconds followed by an infusion starting at 50 mcg/kg/min (maximum of 300 mcg/kg/min) as an intravenous infusion until resolution of the tachydysrhythmia. Torsades de pointes should be treated with intravenous magnesium or overdrive pacing, as described in Chapter 65. Patients with refractory hypotension or persistent unstable dysrhythmia despite supportive therapy can be treated with hemodialysis.

Disposition

Patients with acute chloral hydrate overdose should be observed in the ED until clinically stable, alert, oriented, and ambulatory. In cases of prolonged altered mental status, respiratory depression, hypoxia, or evidence of cardiotoxicity (e.g., PSVT, QRS widening, QTc prolongation, torsades de pointes), the patient should be admitted to a monitored setting. If the intent of the overdose was self-harm, psychiatric consultation is indicated once the patient is medically stabilized.

OVER-THE-COUNTER SLEEP AIDS

Over-the-counter (OTC) sleep aids, currently available in the United States, contain either diphenhydramine or doxylamine. Many preparations also contain acetaminophen or aspirin, added to achieve nighttime pain relief. The availability and frequent use of these agents may explain why overdose is so common. Diphenhydramine and doxylamine are first generation H-1 antihistamines that also have hypnotic, antimuscarinic, and weak local anesthetic properties. They act as competitive antagonists of H-1 histamine receptors and cause sedation by inhibiting the actions of acetylcholine on muscarinic receptors in the CNS. They also have sodium channel blocking effects which can cause QRS prolongation. Patients generally experience anticholinergic toxidromes, including tachycardia, dilated pupils, red and dry skin, and delirium. Further discussion of antimuscarinic toxicity is found in Chapter 140.

GAMMA-HYDROXYBUTYRATE

Clinical Features

Originally synthesized in the 1960s as an anesthetic, GHB was later discovered to be a naturally occurring metabolite of GABA. GHB had been used clinically to treat narcolepsy, alcohol addiction, opioid withdrawal, and depression.[26] GHB quickly distributes across the blood-brain barrier where it exerts its main toxic effects.[27]

The FDA approved GHB for the treatment of narcolepsy under the trade name Xyrem (sodium oxybate, 0.5 mg/mL) as a schedule III drug. The sale and manufacture of GHB is otherwise banned in the United States yet illicit use of GHB has increased, along with its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). There is a wide variety of "street names" that have been associated with GHB (Box 154.4).

GHB remains a popular drug of abuse. Some individuals take GHB for its purported muscle-building and fat-burning actions, others for its psychoactive effects. The drug's euphoria-producing properties make it popular at "raves" (large, crowded parties with energetic dancing to rhythmic music). Self-treatment of insomnia with GHB has been reported and can cause dependence. CNS depression, amnesia, and disinhibition caused by mixing of GHB with ethanol make this combination a potential agent in "date rape" situations. After overdose, a call for medical assistance is often delayed because of the false belief that victims need only to "sleep off" their intoxications. Death occurs most often in the prehospital setting, both from direct effects of the drug and increased the risk for fatal traumatic accidents. Combined intoxication with ethanol occurs in most fatal cases.

GHB binds to specific GHB receptors and at high concentrations to GABA-B receptors. The complex interaction between these two receptors may explain the paradoxical manifestations of GHB toxicity with somnolence alternating with agitation.

GHB is lipophilic and rapidly absorbed. Onset of symptoms occurs within 15 to 30 minutes, and peak plasma levels are reached within 20 to 60 minutes. Unlike GABA, GHB readily crosses the blood-brain barrier. The half-life of GHB is 30 minutes but may increase at high doses.

As underground clandestine laboratories often synthesize liquid GHB by mixing and heating butyrolactone and sodium hydroxide, careless preparation can result in residual unreacted alkali, causing significant caustic injury when the liquid is ingested.

Chemical precursors to GHB are also commonly abused with similar toxic effects. GBL is an industrial solvent that is rapidly absorbed after ingestion and it is metabolized within minutes to GHB by peripheral and hepatic lactonases. Before conversion to GHB, GBL itself is inactive and has no sedating effects. It produces a clinical syndrome similar to that of GHB ingestion, but its effects are more pronounced and prolonged.

1,4-BD is converted after ingestion to GHB by the enzyme alcohol dehydrogenase. Like GBL, it is used as an industrial solvent. Clinical findings are similar to those of GHB. When 1,4-BD and ethanol are ingested together, ethanol acts as a competitive inhibitor of alcohol dehydrogenase, so the toxic effects of 1,4-BD are delayed and prolonged, and the risk of death is increased.

BOX 154.4 Gamma-Hydroxybutyrate Street Names

Grievous bodily harm (GHB)	Liquid G
Georgia home boy (GBH)	Somatomax
Gib	Soap
Natural sleep-500	Salty water
Gamma-OH	Scoop
Gamma hydrate	Sodium oxybate
Liquid X	Easy lay
Organic Quaalude	Cherry menth
Liquid E	Fantasy
Liquid ecstasy	G-Riffick

Differential Diagnoses

The differential diagnoses of GHB intoxication is broad including other sedative-hypnotics (such as barbiturates or benzodiazepines), OTC sleep aids, antimuscarinic agents, opioids, ethanol, ketamine, chloral hydrate, and designer amphetamines.

Poisoning with other sedative-hypnotics can produce a similar clinical picture. Unique to GHB, however, is the relatively rapid resolution of symptoms. In the absence of a coingestant such as ethanol, most patients will be functionally awake within 3 to 4 hours. Nearly all patients recover fully within 8 hours. Prolonged coma should prompt a search for another toxicological or non-toxicological cause. Cardiac effects and refractory seizures are rare and suggest the presence of other agents or etiologies.

Diagnosis of GHB intoxication is based on the history and clinical course, as clinical laboratory testing is not readily available. Rapid recovery from coma or periods of agitation alternating with periods of decreased level of consciousness is its characteristic. Hypothermia may occur with prolonged coma. In the presence of coma, bradycardia with or without hypotension can occur and may respond to auditory or tactile stimulation alone. Miosis with or without nystagmus may be seen. Because emesis occurs in about 50% of cases, obtunded patients are at risk for aspiration pneumonitis. Apparent seizure activity may actually represent random myoclonic movements of the face and extremities. Severity is dependent on the dose and the concurrent use of alcohol or other psychoactive drugs.

Diagnostic Testing

GHB is not detected on routine urine toxicology screens. If laboratory confirmation is required, specimens must be collected early in the clinical course, and sent for gas chromatography–mass spectroscopy. The drug may be detected in urine up to 12 hours after ingestion. In most cases, the toxicology laboratory test is not available for patient management. Pulse oximetry and end-tidal capnometry can be used to monitor respiratory status, and adjunct testing can be used to rule out alternative diagnoses.

Management

The management strategy for GHB toxicity follows the same principles as the other sedative-hypnotics discussed previously. Supportive care including respiratory and ventilatory support is critical. Because of rapid absorption and the high incidence of emesis with GHB overdose, there is no indication for gastric decontamination. Intubation for airway protection may be required by patients with significant CNS depression or hypoxia. There is a high prevalence of coingestants with recreational use of GHB. Physostigmine should not be used for GHB intoxication, based on reported adverse events, particularly in the setting of polydrug use.

Disposition

Because of GHB's short half-life, symptoms of intoxication generally resolve while the patient is still in the ED. The patient generally regains consciousness spontaneously within 3 to 4 hours. No delayed toxicity is expected unless there are coingestants. Patients should be counseled about the seriousness of GHB intoxication, withdrawal potential with chronic use, and discharged home with reliable caretakers.

Additional monitoring and observation for up to 12 to 24 hours should be provided in the setting of ingestions of either GBL or 1,4-BD as toxicity can be prolonged and more severe, as well as less predictable.

Withdrawal

Patients who abruptly stop GHB or its precursors after chronic frequent use can experience a severe and potentially life-threatening withdrawal syndrome. Because of the short half-life of GHB, symptoms of withdrawal begin within several hours of the last dose. The typical patient will have been using these products for weeks or months, in frequent repetitive doses, to avoid withdrawal symptoms.[28]

Withdrawal symptoms are similar to withdrawal from other sedative-hypnotics, including benzodiazepines. Mild withdrawal is manifested with anxiety, tremor, and insomnia. This can progress to confusion, delirium, overt psychosis, paranoid ideation, hallucinations (visual, aural, or tactile), and autonomic instability. Diagnosis relies on a history of symptoms beginning after abrupt cessation of use of these products. The differential diagnosis includes withdrawal from other sedative-hypnotic agents, delirium tremens, sympathomimetic toxicity, serotonin syndrome, neuroleptic malignant syndrome, CNS infection, and thyroid storm.

Initial treatment begins with high-dose benzodiazepines with doses escalated as required for agitation. However, GHB withdrawal may involve depleted levels of GABA. Because the effect of benzodiazepines requires the presence of GABA, they may be less effective in control of GHB withdrawal. Barbiturates, such as pentobarbital or phenobarbital, which do not need GABA to be effective, are often required in cases of severe withdrawal. These patients often require admission to an intensive care unit for titrated sedation, as well as to observe for development of seizures, rhabdomyolysis or hyperthermia.

ACKNOWLEDGMENTS

We would like to acknowledge the valuable contributions of the previous edition authors Drs. Andrea Carlson and Leon Gussow.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 154: QUESTIONS AND ANSWERS

1. All of the following patients have depressed mental status, decreased respiratory drive, and mild hypotension. Supportive care has been initiated. All of the patients have a confirmed benzodiazepine overdose by a reliable historian. For which patient is it most reasonable to consider the use of flumazenil?

- **a.** A 5-year-old boy with no known medical problems who took his mother's medication
- **b.** A 22-year-old woman with no known medical problems
- **c.** A 30-year-old man who is known to abuse cocaine
- **d.** A 43-year-old man with depression and anxiety
- **e.** A 79-year-old woman with congestive heart failure, coronary artery disease, and diabetes who takes benzodiazepines for insomnia

Answer: a. Flumazenil variably reverses the effects of benzodiazepines but can cause dysrhythmias and intractable seizures. Contraindications for flumazenil include history or suspected chronic benzodiazepine use (which are the vast majority of benzodiazepine overdose patients), coingestants that lower the seizure threshold, tricyclic antidepressants, cocaine, history of seizure disorder, chronic alcoholism, and head trauma. Its use should be for a known non-habituated patient (e.g., the pediatric patient described here). Because flumazenil's duration of action is short compared with the benzodiazepine and it has variability to reverse respiratory depression, patients require close, monitored observation, repeated dosing or continuous infusion, and preparations to manage the airway. Because benzodiazepine overdose is rarely lethal and patients recover with supportive care, using an antidote requires a careful benefit/risk analysis.

CHAPTER 154: QUESTIONS AND ANSWERS—cont'd.

2. How do barbiturates affect peripheral and cerebral blood flow?
   - **a.** Decrease peripheral pressure and have no effect on intracranial pressure
   - **b.** Decrease peripheral pressure and increase intracranial pressure
   - **c.** Decrease peripheral and intracranial pressure
   - **d.** Increase peripheral and intracranial pressure
   - **e.** Increase peripheral pressure and decrease intracranial pressure

Answer: c. Barbiturates cause direct cardiac depression with decreased cardiac output. In addition, they cause venous pooling and blunt the normal compensatory increase in system vascular resistance that would occur with decreased cardiac output. They also decrease cerebral blood flow and lower intracranial pressure. These effects are particularly pronounced in individuals with an already low cardiac output, such as in congestive heart failure or hypovolemic shock.

3. Other than general supportive care, which of the following is most useful in the management of a severe phenobarbital overdose with hemodynamic instability?
   - **a.** Flumazenil
   - **b.** Hemodialysis
   - **c.** Multidose activated charcoal
   - **d.** Urinary alkalinization
   - **e.** Whole bowel irrigation

Answer: b. Although rarely indicated, hemodialysis is effective for acute phenobarbital toxicity (persistent serum levels over 100 mcg/mL) in the presence of prolonged coma, refractory hypotension, renal or cardiac failure, metabolic acidosis, or inadequate response to conventional measures and ventilatory support. These patients often require mechanical ventilation, so the patient's airway should be secured prior. Although there is evidence that multi-dose activated charcoal (MDAC) increases clearance of phenobarbital and may shorten duration of clinical toxicity, there is no evidence it results in improved outcomes over supportive care alone. Flumazenil will reverse the effect of benzodiazepines but has no effect on barbiturates. Urinary alkalinization has traditionally been used to "trap" the acidic barbiturates in the urine to increase excretion, However, a recent comprehensive review concluded that there is little clinical role for urine alkalinization in acute barbiturate poisoning. Whole bowel irrigation is not beneficial.

4. Which of the following sedative-hypnotics is most likely to cause fatal cardiac dysrhythmias in overdose?
   - **a.** Buspirone
   - **b.** Chloral hydrate
   - **c.** Eszopiclone
   - **d.** Flunitrazepam
   - **e.** Zolpidem

Answer: b. Chloral hydrate sensitizes the myocardium to catecholamines and also independently induces dysrhythmias. Treatment of choice of dysrhythmias from chloral hydrate is beta-blockers. None of the other listed medications cause significant cardiac toxicity.

5. A 53-year-old woman presents with decreased mental status and mild hypotension. She is arousable to pain. Her husband reports that approximately 4 hours ago she had been complaining of insomnia and said she was going to take something to help her sleep. He then found her in her present state with an empty bottle of "sleeping pills" on the counter. He does not remember the name of the sleeping pills. Supportive care is initiated. Which of the following laboratory tests would be the most helpful to manage this patient?
   - **a.** Acetaminophen level
   - **b.** Arterial blood gas
   - **c.** Serum chemistry
   - **d.** Serum myoglobin
   - **e.** Urine drug screen

Answer: a. Many over-the-counter (OTC) sleep aids contain acetaminophen or salicylates. The active ingredient in OTC sleep aids is an antihistamine, typically diphenhydramine or doxylamine. Both have anticholinergic effects in addition to causing sedation. Toxicity is typically mild and can be successfully managed with supportive care. It is rare that an antihistamine overdose results in rhabdomyolysis, and a serum creatine phosphokinase level, urinalysis, and urinary myoglobin level can be checked if there is concern. Myoglobin is cleared rapidly from the serum and is not a useful diagnostic test. Arterial blood gases, serum chemistries, and urine drug screens can be ordered if there is a complicated clinical course—but only rarely alter treatment.

6. A 21-year-old woman is brought to the emergency department (ED) by her friends after they found her unconscious in the bathroom of a local bar. The friends report that she had only had one or two alcoholic drinks. The patient's vital signs show bradycardia, hypotension, and bradypnea. Physical examination reveals short periods of apnea with hypoxia. She wakens briefly to noxious stimuli. You suspect that she may be suffering from gamma-hydroxybutyrate (GHB) poisoning. What is the most appropriate next step in management?
   - **a.** Atropine
   - **b.** Electrocardiogram
   - **c.** Endotracheal intubation
   - **d.** Flumazenil
   - **e.** Naloxone

Answer: c. GHB frequently causes emesis and aspiration because patients are unable to protect their airways. Patients with significant GHB overdose should be intubated, but supportive care alone is all that is required for most GHB overdoses. The half-life is short, and many patients will return to baseline mental status in several hours. Bradycardia is common, usually mild, and does not typically require atropine, but this can be used if bradycardia is severe. GHB does not generally cause dysrhythmias. Neither flumazenil nor naloxone has any effect on GHB.

7. A 30-year-old man presents with anxiety and insomnia. He is agitated and has a tremor on physical examination. His vital signs are as follows: blood pressure, 200/124 mm Hg; heart rate, 123 beats/min; respiratory rate, 22 breaths/min; and temperature, 37.5°C. On further questioning, he reports that he chronically uses gamma-hydroxybutyrate (GHB) for muscle building but has not been able to take any for approximately 24 hours. Lorazepam is given in two escalating doses without response. Which of the following should be given next?
   - **a.** A barbiturate
   - **b.** Additional lorazepam
   - **c.** Clonidine
   - **d.** GHB
   - **e.** Labetalol

Answer: a. GHB withdrawal is severe, and deaths have been reported. GHB acts as a central nervous system (CNS) depressant, so withdrawal causes CNS excitement and autonomic instability. Chronic GHB abuse can lead to GABA depletion in the CNS. Because benzodiazepines require the presence of GABA, they may not be effective. Barbiturates act independently of GABA and are therefore more effective in GHB withdrawal. Clonidine can be used in opioid withdrawal but is not useful in GHB withdrawal. Labetalol would improve the vital signs but would have no effect on the underlying cause of the autonomic instability.

155

Care of the Pediatric Patient

Stephen John Cico and Derya Caglar

KEY CONCEPTS

- Patterns of illness and injury vary by age, and a number of anatomic and physiologic characteristics affect the presentation and management of pediatric emergencies.
- A basic understanding of normal development will aid the emergency clinician in assessment of the pediatric patient.
- The pediatric assessment triangle (PAT) can be used as a tool for rapid evaluation of the patient's overall status.
- Tachypnea in children should be evaluated relative to age norms and is often a sign of increased metabolic demands. A child with tachypnea despite normothermia should be evaluated for respiratory and nonrespiratory causes (e.g., hypoperfusion, acidemia).
- Maintenance of a neutral thermal environment is necessary for critically ill infants.
- Child abuse should be considered when injuries are inconsistent with history, when details of the history change, or with certain injury patterns.
- A joint guideline of the American College of Emergency Physicians, American Academy of Pediatrics, and Emergency Nurses Association summarizes the role of pediatric emergency care coordinators, development of pediatric policies, and recommended equipment, supplies, and medications for emergency departments (EDs).
- EDs that comply with the national guidelines for pediatric readiness have improved outcomes for care of critically ill children.
- The family's presence should be encouraged for pediatric procedures and resuscitations.
- A variety of pharmacologic and nonpharmacologic techniques are available to decrease procedural pain and anxiety.

FOUNDATIONS

Emergency clinicians assess and manage pediatric patients from newborns to adolescents. Of the 146 million annual US emergency department (ED) visits, 27.4 million (19%) are for children younger than 15 years.[1] Twenty-two percent of children have at least one ED visit per year. Infants have higher per capita ED utilization than other age groups, with 98.7 visits/100 infants.[1] More than 80% of pediatric patients are seen in general EDs, requiring all emergency clinicians to be skilled in the assessment, treatment, and stabilization of pediatric illnesses and injuries.[2]

Children can present diagnostic and management challenges due to their anatomic, physiologic, and developmental differences from adult patients. Understanding these differences is crucial to the recognition and appropriate treatment of many pediatric emergencies. In addition, caring for the pediatric patient also involves active participation from caregivers.

Pathophysiology

Children exhibit different patterns of illness and injury because of their unique physiologic and anatomic characteristics. Illness and injury patterns not only differ between pediatric and adult patients, but also vary in children by age. In addition to changes in cognitive and behavioral development, temperature regulation, airway anatomy, cardiovascular physiology, immune function, and the musculoskeletal system all change as children grow. Furthermore, pediatric patients may present to the ED with previously undiagnosed congenital disorders. Drug dosing and choice of medications also depend on patient size and physiology.

Assessment should begin with a review of vital signs, evaluating for early signs of physiologic decompensation. Normal heart rate and respiratory rate vary by age (Table 155.1). Normal blood pressure also varies by age, height, and gender (Box 155.1; Table 155.2). Abnormal vital signs should be repeated and persistently abnormal vital signs quickly addressed.

Temperature Regulation

Infants and young children have a larger surface area–to–mass ratio, resulting in more heat loss to the environment than in adolescents and adults. Maintenance of a stable body temperature can be a significant metabolic demand for young infants, especially those stressed by injury or illness. Maintain a neutral thermal environment for children during the physical examination and while performing procedures. Patients exposed briefly for examinations and interventions should be covered as soon as possible to avoid excessive heat loss. Critically ill young infants should be placed under radiant warmers. Overhead warming lights are useful for older infants and children who require prolonged exposure for resuscitation and procedures.

Airway

The pediatric airway differs in a number of ways from an adult airway.[3,4] Compared to the adult airway, the pediatric larynx is more

TABLE 155.1 Normal Pediatric Vital Signs

Age (Years)	Respiratory Rate (Breaths/Min)	Heart Rate (Beats/Min)
<1	30–60	100–160
1–2	24–40	90–150
2–5	22–34	80–140
6–12	18–30	70–120
>12	12–16	60–100

From Dieckmann R, Brownstein D, Gausche-Hill M, eds. *Pediatric Education for Prehospital Professionals*. Sudbury, MA: Jones & Bartlett; 2013.

BOX 155.1 Hypotension in the Pediatric Population by Age

0–28 days: 60 mm Hg
1–12 months: 70 mm Hg
1–10 years: 70 mm Hg + (2× age in years)

From American Heart Association: American Heart Association emergency cardiovascular care (ECC) guidelines, 2010. https://www.ahajournals.org/doi/10.1161/circ.102.suppl_1.I-291.

TABLE 155.2 Pediatric Blood Pressure by Age

Age (Years)	50TH PERCENTILE (MM HG)		HYPERTENSION–95TH PERCENTILE (MM HG)	
	Girls	*Boys*	*Girls*	*Boys*
1	86/40	85/37	104/58	103/56
5	93/54	95/53	110/72	112/72
10	102/60	102/61	119/78	119/80
15	110/65	113/64	127/83	131/83

[a]For children at the 50th percentile for height.
Modified from The National High Blood Pressure Education Program Working Group on Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074640/ and https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf

anterior and cephalad, and the epiglottis is composed of more flexible cartilage, making it floppy. The relatively larger occiput in infants and young children can cause neck flexion in the supine position, leading to potential airway obstruction. To open the airway, particularly during intubation attempts, a towel roll placed under the shoulders may be needed to align the laryngeal, pharyngeal, and oral airway axes (Fig. 155.1). Infants and young children also have relatively large tongues, which may lead to airway obstruction during periods of changes in muscle tone, such as during a seizure. Use of a nasopharyngeal airway can alleviate the obstruction by allowing a clear passage of inhaled gases. In addition, airways in children are much smaller in diameter and much more easily obstructed with secretions. Because young infants preferentially breathe through their noses, respiratory distress can develop from copious nasal secretions. Thus, suctioning the nose and upper airway can dramatically diminish an infant's work of breathing.

Cardiovascular System

Healthy children have compensatory mechanisms to maintain blood pressure, even when cardiac output is decreasing. Children have the ability to increase their heart rate and vasoconstrict peripherally to shunt blood centrally, while very young children have limited ability to increase their cardiac contractility. Hypotension is a late finding of shock in previously healthy children, and interventions should ideally occur before the onset of hypotension.[5] The earliest sign of cardiovascular compromise in most patients is tachycardia. Unfortunately, tachycardia is nonspecific and may be due to fever, pain, or anxiety. Repeated assessment of the heart rate can be helpful. In a crying child, a true resting heart rate can be obtained by leaving the pulse oximeter on until the child is calm. Unexplained tachycardia in a calm or sleeping child should be investigated for the cause of the tachycardia. The quality of the pulse is also helpful. A thready peripheral pulse associated with tachycardia should be considered a sign of shock. Bradycardia in ill children is especially ominous and may signal impending cardiopulmonary failure.

Musculoskeletal System

Growing children have musculoskeletal injury patterns different from those of adults. Ligaments are stronger relative to the immature bone, so children are more likely to fracture bones than sprain ligaments. The weakest part of a growing child's bone is the physis, or growth plate. If tenderness is present on examination, physeal injuries should be considered in children with normal radiographs. Treatment of fractures in children should consider future growth potential. For example, certain physeal injuries can lead to long-term growth disturbances, whereas greater degrees of angulation are acceptable in many fractures due to the increased potential for bone remodeling.

Immunologic System

Due to their immature immune system, young infants are at increased risk of serious bacterial infections. Febrile infants younger than 1 month are a particularly high-risk group and have a 10% or higher rate of serious bacterial infection.[5] For this reason, the evaluation of infants with fever differs from the evaluation of older children and adults; the evaluation varies by age and vaccination status (see Chapter 161).

Pharmacologic Considerations

Medications for children are calculated using weight-based dosing, with attention to the maximum medication dose. Suggested safeguards to prevent calculation-based dosing errors in children include pharmacy review of medication orders, computerized order entry, use of templated order forms, and length-based resuscitation tapes to reduce calculation errors.[6] One easily remedied potential error is the inadvertent calculation of a drug dose on the basis of weight in pounds, not kilograms, leading to a more than twofold overdose. Therefore, ED scales and electronic charts should be programmed to report weight only in kilograms.[7]

In addition to potential dosing errors, certain frequently used medications in older children and adolescents should not be given to young infants. For example, ceftriaxone is not recommended for infants younger than 28 days because it can displace bilirubin from albumin, leading to kernicterus or bilirubin-induced neurologic dysfunction (BIND). Although not well studied, the use of ibuprofen in infants younger than 6 months has not been approved by the US Food

Fig. 155.1 Infant With Neck in Flexed Position (A) and After Placement of a Shoulder Roll (B). (From Santillanes G, Gausche-Hill M. Pediatric airway management. *Emerg Med Clin North Am.* 2008;26:961–975.)

and Drug Administration because of the theoretical risk of kidney and liver injury.

Developmental Considerations

Assessment of pediatric patients requires an understanding of normal developmental milestones. Table 155.3 lists basic developmental milestones in the first 2 years of life. Variation in the rate at which children develop can be normal or may signal neurodevelopmental delays. Therefore, the parent's report of the child's developmental history and normal behavior is extremely important. Injuries identified should also fit the developmental milestones of a child. Injuries that fall outside of the normal developmental patterns should raise the consideration of non-accidental trauma/child abuse.[8]

Young Infants

Infants younger than 2 months are especially challenging to assess because they have a limited behavioral repertoire. They may not make eye contact nor have a social smile. Normal behavior includes sleeping, crying, quiet alert time, feeding, and stooling. A change in any of these activities may indicate serious disease. Increased sleeping or crying or decreased interest in feeding may herald a serious illness, such as sepsis or an underlying cardiac or metabolic disorder.

Infants (<12 Months)

Infants typically develop a social smile and track close objects by 2 to 3 months of age. After 6 months, infants may develop significant stranger anxiety, making the physical examination challenging. Whenever possible, examining the infant in the parent's lap, with the infant initially facing away from the examiner, can mitigate anxiety and facilitate physical examination. Bubbles or interactive toys can distract infants and may help keep them calm.

Toddlers (1- to 2-Year-Olds)

Toddlers have variable reactions to a physical examination. A toddler may provide a limited history due to their narrow expressive language skills (e.g., only pointing to the location of pain). Some are fearful and will not cooperate, whereas others are curious and cooperate more easily with the examination. In a stable patient, begin the encounter standing or sitting at a distance from the child while taking the history. Speaking in a soothing voice and distracting the child with toys or other interesting objects can facilitate the examination. Emergency clinicians should interact with the parents, because this will be perceived by the child as a sign of endorsement and indicate that the parents are involved with the emergency care. Conversely, toddlers will often negatively react to parental anxiety.

TABLE 155.3 Developmental Milestones in Typically Developing Children Up To 2 Years of Age

Age (Months)	Gross Motor	Visual-Motor, Social, and Language
1	Raises head from prone position	Visually follows to midline, alerts to sound, regards face
2	Lifts chest off table	Smiles socially, recognizes parent, follows object past midline
4	Rolls over	Laughs, orients to voice
6	Sits unsupported	Babbles
9	Pulls to stand, cruises	Says "mama" and "dada" indiscriminately, plays games such as pat-a-cake
12	Walks alone	Two words other than "mama" and "dada"
15	Creeps upstairs, walks backward	Uses 4–6 words
18	Runs	Uses 7–10 words, knows five body parts
24	Walks up and down stairs independently	50-word vocabulary, two-word sentences

Adapted from Engorn B, Flerlage J. *The Harriet Lane Handbook*. 20th ed. Philadelphia: Elsevier Saunders; 2015.

Preschoolers (3- to 5-Year-Olds)

Preschool-age children have increasing language skills. Like toddlers, their receptive language skills exceed their expressive language skills, and they often understand more than is realized. Preschoolers should be included in the conversation when possible. Emergency clinicians should be cautious about talking to the parents about procedures or diagnoses in front of the preschool child, even if the child seems not to be paying attention or not to understand. Like toddlers, preschool children vary greatly in their cooperation with the physical examination. Providing limited options, such as sitting with the parent or on the gurney, or choosing which ear should be examined first, may give the child a sense of control and improve cooperation. Distraction with stories, videos, or games on a smartphone or other devices can also facilitate the physical examination. The young child will build up anxiety awaiting a procedure. For this reason, clinicians should provide

children with simple concrete explanations of procedures only immediately before and during the procedure. Preschool children may perceive illness or painful procedures as punishment for their actions, making simple explanations of what and why it is occurring even more important.

School-Age Children

Some questions during the history should be directed at the school-age child, because many can provide much of the history themselves. At this age, children are often cooperative with the examination, but may regress when they are frightened or in pain. Additionally, children at this age become increasingly modest, and conscious attempts should be made to provide privacy.

School-age children may develop anxiety and attempt to negotiate or stall when a painful or unpleasant examination or procedure is planned, particularly if there is a long delay between the explanation and procedure. Firm but reassuring explanations of what will happen are important. Appropriate concrete explanations include the sequence of events and what physical sensations the patient will experience. It is also crucial to involve parents in the process to provide not only a candid explanation of the procedure itself, but also anticipated reactions from their child. When available, child life specialists are particularly helpful with this age population, using play and education to prepare children for anxiety-provoking procedures.

Adolescents

Adolescents will be able to provide much, if not all, of the history. However, despite desired independence from their parents, adolescents may regress in times of stress. It is therefore important to elicit the concerns of the adolescent and parent, and to ensure that both understand the diagnosis and plan. The adolescent should be given a chance to speak to the emergency clinician without the parent in the room. Any sensitive questions, such as those about drug use, alcohol consumption, tobacco and vaping, and sexual activity should be asked privately. State laws vary on confidentiality and ages of consent, so it is important for emergency clinicians to know those specifics which may be applicable to their patients.

Adolescents can generally be examined in a manner similar to that for adults. They may or may not prefer to have a parent present during the physical examination, and providers should clarify the patient's preference. Adolescents are often extremely modest, and attempts should be made to preserve privacy with the examination in a private room, when possible, with exposure of only the body part being examined.

EVALUATION

Triage

Pediatric-specific triage systems are important to avoid overtriage and undertriage of children. The application of adult-specific vital signs to children will lead to an inappropriate triage level classification or inadvertently trigger inappropriate sepsis alerts. In addition, signs and symptoms of serious illness may be subtle in infants and very young children, requiring those providing the initial triage assessment to be familiar with normal pediatric physiology and development.

Triage systems with pediatric modifications include the Emergency Severity Index, Paediatric Canadian Triage and Acuity Scale, Manchester Triage System, and Australasian Triage Scale. No triage system has been clearly demonstrated to be superior, and data on reliability and validity are limited for all triage systems. The Emergency Severity Index, Manchester Triage System, and Paediatric Canadian Triage and Acuity Scale have been demonstrated to be valid for pediatric patients.

BOX 155.2 Focused Sample History

Signs and symptoms
Allergies
Medications
Past medical problems
Last food or liquid
Events leading to injury or illness

Modified from Dieckmann R, Brownstein D, Gausche-Hill M, eds. *Pediatric Education for Prehospital Professionals*. Sudbury, MA: Jones & Bartlett; 2013.

The Emergency Severity Index has been updated by the Emergency Nurses Association and has pediatric specific resources.[9]

History

In critically ill or injured patients, the SAMPLE history can be used to obtain a focused history quickly (Box 155.2). The SAMPLE history reminds providers to ask for ***S***igns and symptoms, ***A***llergies, ***Me***dications, ***P***ast medical history, ***L***ast meal, and ***E***vents surrounding the illness or injury.

A more detailed history will be guided by the patient's presenting complaint. In preverbal children, symptoms will often be inferred by the caregiver based on the child's behavior. Parents are often very perceptive and may notice subtle changes in behavior that are not immediately evident to a healthcare provider.

Additional age-specific questions may be indicated. In neonates, pregnancy and birth history will help identify risk factors for conditions such as hyperbilirubinemia (e.g., prematurity, ABO incompatibility), infection (e.g., maternal fever during labor, early or prolonged rupture of membranes, maternal group B streptococcus [GBS] status), and respiratory illnesses (e.g., prematurity, meconium aspiration, need for supplemental oxygen or mechanical ventilation). The emergency clinician should also inquire about results of the newborn screen if available. Each state screens for a different panel of disorders determined by their public health board. Most of the conditions included in newborn screening can lead to serious health problems if not recognized and treated shortly after birth. Prompt identification and management of these conditions may be able to prevent life-threatening complications.

In infants and toddlers, urine output, quantified by the number of wet diapers, helps determine hydration status. This can be especially helpful in breast-feeding newborns, whose intake is difficult to quantify. Vaccination status is important in infants and children presenting with symptoms such as fever (e.g., risk of bacteremia) and rash (e.g., risk of varicella, measles). Drug, alcohol, and e-cigarette use, as well as the sexual history, become important in adolescents who have increased risk-taking behaviors and should be questioned in a private setting, not in front of the caregiver.

Pediatric Assessment Triangle

Rapid recognition of the critically ill child is a crucial skill. The pediatric assessment triangle (PAT) assists emergency clinicians in assessing children quickly and is an orderly approach for formulating an initial impression of the child's overall status from the door of the examination room (Fig. 155.2). The three components of the PAT are (1) appearance, (2) work of breathing, and (3) circulation to the skin. On the basis of the initial PAT, the emergency clinician can distinguish the "sick" from the "well" child rapidly. Table 155.4 summarizes the findings that may be noted on each of the three sides of the triangle, and Table 155.5 summarizes interpretation of the PAT.

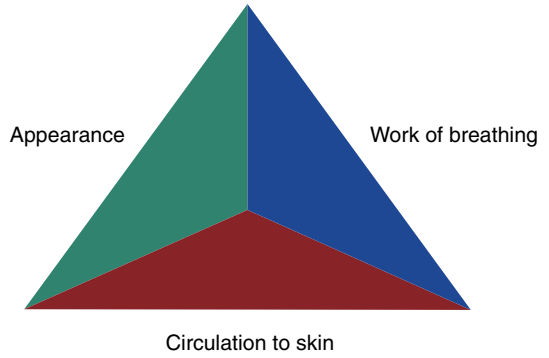

Fig. 155.2 Pediatric Assessment Triangle.

TABLE 155.4 Pediatric Assessment Triangle Abnormal Findings

Appearance	Work of Breathing	Circulation to the Skin
Tone—poor tone, floppy infant	Abnormal sounds—stridor, grunting, snoring, wheezing	Pallor
Interactiveness—irritability, poor responsiveness to surroundings	Abnormal positioning—sniffing, tripoding, refusal to lie down	Delayed capillary refill time (>2 s) Mottling
Consolable—inability to be consoled by parent	Retractions	Cyanosis
Look, gaze—poor attention, lack of normal tracking	Head bobbing	Petechiae
Speech, cry—weak cry, or no cry with environmental stimuli	Nasal flaring	

Adapted from Dieckmann R, Brownstein D, Gausche-Hill M, eds. *Pediatric Education for Prehospital Professionals*. Sudbury, MA: Jones & Bartlett; 2013.

Appearance

Observation of the child from a distance allows the provider to assess the patient's overall status without upsetting the child. The mnemonic TICLS (***t***one, ***i***nteractiveness, ***c***onsolability, ***l***ook and gaze, ***s***peech and cry) summarizes the components of the assessment of overall appearance. Observation of the infant or child interacting with his or her parents provides many clues about the child's overall status. An ill infant with a vacant or glazed look can be distinguished from an alert infant who responds to environmental stimuli. An infant who is awake but lying motionless on a gurney is much more concerning than an active infant who moves all the extremities. Irritability is an early sign of inadequate brain perfusion. This may be followed by lethargy and then coma as perfusion is further compromised.

The quality of the cry is another helpful clue. A persistently high-pitched or irritable cry is concerning for central nervous system disease, such as meningitis. A normal overall appearance suggests that oxygenation, ventilation, and perfusion are adequate.

TABLE 155.5 Interpretation of the Pediatric Assessment Triangle General Impression of Condition

Physiologic State	Appearance	Work of Breathing	Circulation to the Skin
Respiratory distress	Normal	Abnormal	Normal
Respiratory failure	Abnormal	Abnormal	Normal-abnormal
Compensated shock	Normal	Normal	Abnormal
Decompensated shock	Abnormal	Normal-abnormal	Abnormal
Brain injury or dysfunction	Abnormal	Normal	Normal
Cardiopulmonary failure	Abnormal	Abnormal	Abnormal

Adapted from Dieckmann R, Brownstein D, Gausche-Hill M, eds. *Pediatric Education for Prehospital Professionals*. Sudbury, MA: Jones & Bartlett; 2013.

Work of Breathing

The work of breathing should be observed ideally when the child is calm. Children may have increased work of breathing with retractions without facial signs of respiratory distress, therefore, the emergency clinician should ask the parent to remove the clothing so the chest wall can be observed for retractions. Infants and children with respiratory distress may assume the sniffing position in an attempt to decrease their work of breathing. The tripod position is an ominous sign of severe respiratory distress.

The quality of the voice or cry may be a clue to airway and respiratory disease or compromise. For example, children with croup have a hoarse voice, and children with peritonsillar abscesses may have a have muffled or so-called "hot potato" voice. Abnormal breath sounds may be audible without a stethoscope.

Signs of respiratory compromise include stridor, audible wheezing, retractions, grunting, and snoring respirations. Retractions may be seen in the suprasternal, supraclavicular, intercostal, and subcostal areas (Fig. 155.3). Nasal flaring is an attempt to decrease airway resistance (Fig. 155.4). Head bobbing (the use of neck muscles to assist respiration) and seesaw breathing (ineffective breathing pattern, in which the abdomen moves outward while the chest moves inward during inspiration) are signs of impending respiratory failure. As the child tires and nears complete respiratory failure, the respiratory rate falls and the work of breathing may diminish.

Normal pediatric respiratory rates are inversely related to age due to younger children's increased metabolic rates and lower tidal volume reserves. Because children normally function near their maximum tidal volume capacity, relatively small increases in metabolic demands (e.g., fever) can result in an elevated respiratory rate. As a result, abnormal respiratory patterns may provide clues about a nonrespiratory illness. Effortless tachypnea may be a sign of shock from any cause, whereas deep rapid breathing without other auscultative findings may be compensation for a metabolic acidosis. Children who are tachypneic despite normothermia should be evaluated for respiratory and nonrespiratory causes. Neurologic disorders may also lead to abnormal respiratory patterns (e.g., bradypnea and irregular respiration in the setting of increased intracranial pressure).

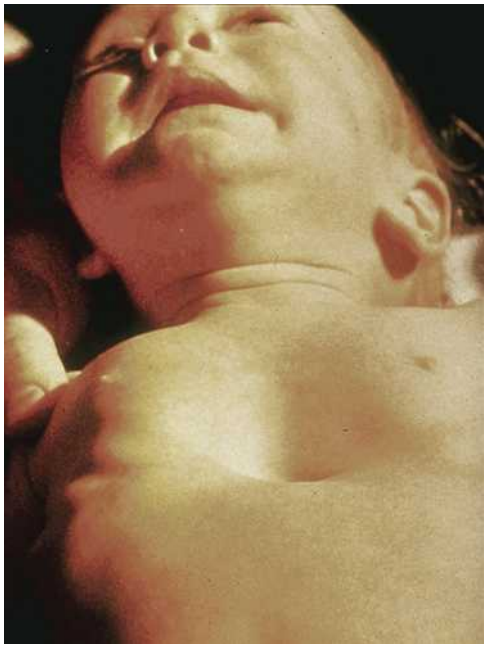

Fig. 155.3 Intercostal Retractions in a Child With Respiratory Distress.

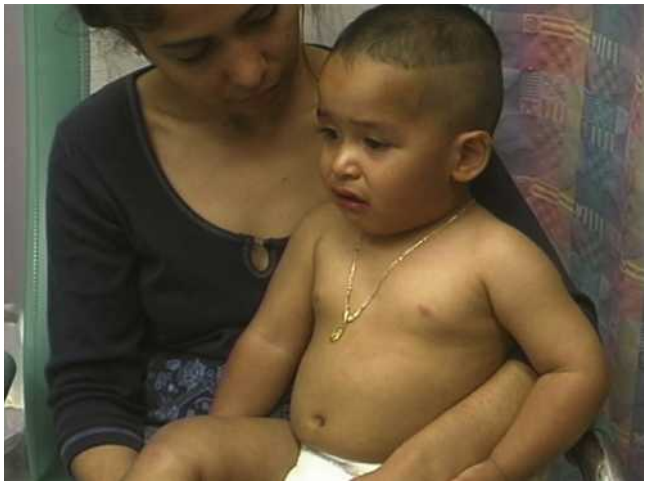

Fig. 155.4 Nasal Flaring in a Child With Respiratory Distress From Lower Airway Obstruction.

Circulation to the Skin

Visual inspection of the skin can provide clues to overall cardiovascular status. Early compensated shock is characterized by peripheral vasoconstriction and shunting of blood to the brain and other vital organs. At this stage, skin appears pale but remains warm to the touch with delayed capillary refill time (>2 seconds). If the shock state is not corrected, the patient may become mottled, with cold extremities (Fig. 155.5A). Mottling is a random pattern of vasoconstriction in adjacent capillary beds in the skin. This is not to be confused with cutis marmorata, a regular lacy pattern on the skin caused by vascular instability (see Fig. 155.5B). Cutis marmorata is a normal finding in young infants in a cool environment. In contrast to infants with mottling, infants with cutis marmorata will be otherwise well-appearing, and the skin findings will diminish or disappear if the infant is placed in a warm environment. Cyanosis may be present normally in children with congenital heart disease but, if cyanosis is a new finding for the patient, it is almost always indicative of respiratory failure or decompensated shock.

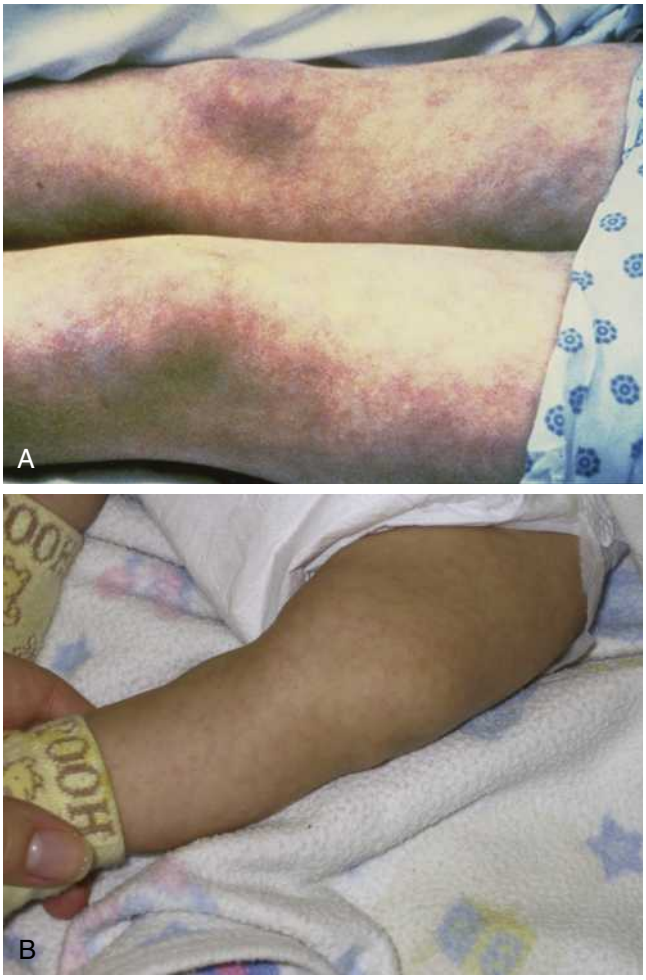

Fig. 155.5 Infant with skin mottling (A) and cutis marmorata (B).

Length-Based Resuscitation Tape

Ideally an actual body weight in kilograms should be used for determination of medication dosing in children. An accurate weight may not be available for critically ill children especially for those that require immediate resuscitation. Use of a color-coded, length-based resuscitation tape gives an estimate of the child's weight. Each color on the tape corresponds to a weight range that corresponds to an ideal body weight for length. Medication doses and appropriate equipment are listed on the tape for each weight range. Use of the length-based resuscitation tape avoids error-prone calculations of medication dosages and equipment sizes in the high-stress setting of a pediatric resuscitation. In addition, pediatric resuscitation equipment organized by weight ranges minimizes the need to search for appropriately sized equipment.

Physical Examination

As in adults, the physical examination in critically ill or injured children will focus initially on airway, breathing, and circulation, with abnormalities in these systems corrected before a complete physical examination is performed. In any infant or toddler with respiratory complaints, observing the child breathing with the shirt removed will allow the most reliable assessment of the work of breathing. The respiratory rate should be manually counted for a minimum of 30 seconds, due to periodic breathing, and also because the rate on the monitor

Fig. 155.6 Toddler Being Held for Otoscopic Examination of the Ears.

can be unreliable. In infants and young children with some degree of respiratory distress, observation of respiratory status and pulse oximetry during feeding or sleeping can be helpful when deciding on further observation and admission.

In infants and young children, the physical examination should not be performed in a head-to-toe fashion. Auscultation of the heart and lungs and palpation of the abdomen should be performed before other more frightening or uncomfortable parts of the examination. Although, ideally, the emergency clinician should palpate the child's abdomen, occasionally a fearful child will cry so much it is impossible to determine if the child has abdominal tenderness or guarding. In these cases, observing the parent palpate the abdomen may be helpful. Although parents cannot be relied on to examine for masses or organomegaly, they can elicit pain with palpation and feel for guarding.

Examination of the ears, oropharynx, or area of injury should occur toward the end of the physical examination. Providers can try to ease a child's fear by first demonstrating the examination on a parent, older sibling, or stuffed animal. For the ear examination, the parent can hold the young child in his or her lap, with one arm around the head and one arm around the child's body and arms (Fig. 155.6). Young children can often be coaxed into opening the mouth wide enough for examination of the oropharynx without use of a tongue depressor. The examination can be turned into a game by asking the child to open his mouth and pant "like a puppy" or see if she or he can touch the tongue to the chin. The exam of the groin in young girls or boys can be facilitated by having them sit in a frog leg position in the parent's lap. Children should be reassured of the safe environment with the provider and caregiver but also should be counseled to understand the difference between the examination and inappropriate touching by others.

SPECIFIC DISORDERS

The most common reasons for infants and children to present to EDs are respiratory illness, fever, and injury. Causes of serious illness and injury vary by age. Respiratory illnesses are the most common reason for infant hospitalization after the immediate neonatal period. Asthma and appendicitis are the most common reasons for hospitalization of school-age children, and affective disorders are the most common cause of adolescent hospitalizations.

This section focuses on complaints specific to the pediatric population and complaints in which the differential and approach vary significantly from those in adult populations.

Common Neonatal Complaints

Neonates may present with a variety of previously undiagnosed genetic, anatomic, and metabolic conditions. In addition to the very limited behavioral cues displayed by newborns, parents of newborns are frequently anxious and may not know what behaviors or patterns are normal.

Concerns about feeding are common. Neonates typically feed every 2 to 3 hours. Bottle-fed neonates take about 2 to 3 ounces per feed, whereas breast-feeding neonates typically spend 10 to 15 minutes on each breast each feed. Newborns, especially those who are exclusively breast-fed, can lose up to 10% of their birth weight during the first 7 days of life. Birth weight should be regained by day 10, with a subsequent weight gain of 20 to 30 g/day for the first 3 months of life. Providers should clarify feeding routines with caregivers. Infants with excessive weight loss or failure to gain weight may have underlying metabolic, cardiac, or infectious causes or be victims of abuse or neglect.

Small amounts of regurgitation of breast milk or formula are normal in infants and generally are not concerning if the amount is stable, the infant is gaining weight, and emesis is not bilious. Larger volume emesis should be evaluated. Common benign causes include overfeeding and inadequate burping, but providers should consider other serious causes, such as pyloric stenosis, malrotation with volvulus, intussusception, and nonaccidental trauma (head or abdominal). Bilious emesis in a neonate should always prompt further investigation with imaging.

Another common concern is the frequency and consistency of bowel movements. Although infants typically have soft stools multiple times a day, it can be normal for exclusively breast-fed infants to stool as infrequently as once every 5 to 7 days. Straining during a bowel movement is also commonly seen and may occur after transition from breast milk to formula. In infants presenting with constipation, a history of failure to stool in the first 24 hours of life is concerning for Hirschsprung's disease—aganglionic segments of the colon that fail to relax.

Urate crystals may also form in the first week of life. Families often come to the ED with concerns for neonatal hematuria upon seeing these reddish "brick stained" deposits in the diaper. Though benign, these are most commonly seen in babies who have some degree of dehydration, especially in mothers who are breastfeeding and have not quite established a good milk supply.

Neonatal Intensive Care Unit Graduate

Gestational rather than chronologic age is typically used for premature infants in whom development is often delayed. Due to their immature immune function relative to infants of the same chronologic age, premature infants are at increased risk for recurrent respiratory infections. Chronic lung disease is a common complication in extremely premature infants (gestational age <28 weeks). Such infants frequently have a baseline tachypnea and increased work of breathing and may

require supplemental home oxygen. Parental report of changes in work of breathing, activity, feeding pattern, and level of alertness can be clues to serious illness, such as sepsis or underlying metabolic abnormalities.

Respiratory syncytial virus (RSV) immunoglobulin (palivizumab) prophylaxis is recommended for certain high-risk infants during peak season.[10] During RSV season, the timing of the last RSV immunoglobulin injection given should be ascertained when a premature infant presents with fever, cough, or rhinorrhea. Palivizumab is administered monthly and, if a dose has been missed, the physician should have a higher level of suspicion for RSV infection.

Children With Special Health Care Needs

The assessment of children with chronic illnesses and other special health care needs is especially challenging. Although specialty care is often provided at pediatric EDs affiliated with tertiary children's hospitals, a greater absolute number of the most complex pediatric patients are cared for within general EDs, likely due to regional proximity and easier access to care. This emphasizes the need for general EDs to be prepared to care for this vulnerable population[3,11]. Parents or other daily caregivers can provide helpful information on baseline behavior and mental status, and the caregiver's input should be sought.

However, a parent's knowledge and recollection of detailed medical information may be limited, especially during times of high stress. Parents may forget medication names or concentrations, details of previous hospital admissions, and current treatment plans. An Emergency Information Form (EIF) that summarizes chronic medical conditions, medications, medical devices, and other critical information can be used for children with special health care needs.[12] These forms can quickly provide critical information to the ED provider, assisting in the early management and stabilization of the child until more detailed records are obtained. ED staff can request that specialists affiliated with their hospitals provide EIFs for complex patients to facilitate rapid and appropriate emergency treatment.

Children with autism or sensory processing disorders may have a particularly difficult time in the loud and unpredictable environment of the ED. Day-to-day life for a child with an autism spectrum disorder can become extremely regimented, and knowing what is going to happen may help the encounter go more smoothly and decrease patient and family stress. Asking what sensory sensitivities the child experiences with touch, noise, and lighting will help guide the best approach to evaluating and treating the patient.[13]

Child Abuse

Nonaccidental trauma should be in all patients presenting with injuries and complaints, such as altered mental status and apparent life-threatening events. Unfortunately, abusive injuries are frequently not recognized at the initial health care encounter, leaving children at high risk for future and more serious injuries and death. Historical clues to nonaccidental trauma include mechanisms inconsistent with the injury pattern or a history inconsistent with the developmental level of the child (Box 155.3). Physical examination clues for abuse include presence of bruises in young precruising or nonambulatory infants and unusual locations of bruises, such as the trunk, ear(s), and neck (the so-called TEN regions) (Box 155.4). The TEN-4 Rule for bruising states that bruising in children under the age of four in any of the TEN regions, or any bruising under 4 months of age, should raise suspicion for non-accidental trauma. Fractures in children younger than 12 months without a significant witnessed trauma mechanism are especially concerning (see Chapter 172).

BOX 155.3 Historical Features Causing Concern for Child Abuse

- History lacking in details
- Inconsistency—details change with repeated questioning
- History inconsistent with child's developmental status
- Reported mechanism inconsistent with injury

BOX 155.4 Physical Examination and Radiologic Findings Concerning for Abuse

- Any bruises in young precruising infants
- Patterned ecchymosis, burns, or skin marks (abrasions, lacerations)
- Bruises on the ears, trunk, inner thighs, neck, or groin
- Posterior oropharynx bruising or lacerations
- Posterior rib fractures
- Classic metaphyseal fractures
- Any fracture in a nonambulatory child
- Fractures in different stages of healing

OTHER CONSIDERATIONS

Consent for Emergency Care

In general, parent or guardian consent is required for the evaluation and treatment of minors, and emergency clinicians should attempt to notify parents or guardians and obtain consent. However, in emergency situations, evaluation and stabilization cannot be delayed while awaiting consent. The Emergency Medical Treatment and Active Labor Act has mandated that patients presenting for emergency care receive a medical screening examination and, if an emergency medical condition is identified, patients should receive the care required to stabilize the condition (see Chapter e7). Thus, all minors presenting to the ED require an examination to determine if an emergency medical condition exists. If a condition that is threatening to life or health exists, treatment should be provided under the doctrine of implied consent. If an emergency medical condition is not suspected after a screening examination, nonemergent care should be delayed until guardian consent is obtained, unless the minor is legally able to consent for care. Patients in foster care or who are in child protective services custody should have a medical screening examination, but consent for treatment beyond emergency medical conditions may need to be obtained from a state representative.

The circumstances under which minors can consent for their own care vary from state to state, but minors can generally consent if they are emancipated or if they are seeking treatment for mental health issues, drug or alcohol abuse, contraception, pregnancy, or testing for or treatment of sexually transmitted infections. Minors are generally considered emancipated if married, on active duty in the military, or living independently and economically independent from their parents. Some states recognize minors as emancipated if they are pregnant or a parent. Many states recognize that a mature minor, generally 14 years or older, can consent for care if sufficient intelligence and maturity is displayed to make a reasonable and voluntary choice. The process for determining mature minor status varies from state to state.

Pediatric-Ready Emergency Department

Preparation to care for infants and children of all ages involves not only ED staff training but also stocking pediatric medication formulations, equipment, and supplies in appropriate sizes for the premature neonate

to the adult-sized adolescent. The American College of Emergency Physicians, American Academy of Pediatrics, and Emergency Nurses Association have developed joint guidelines for the care of children in the ED.[14–16] The guidelines include recommendations for necessary personnel, protocols, medications, equipment, and supplies. Surveys have found that EDs frequently lack the items recommended in the guidelines.[3] One strong recommendation in the guidelines is the appointment of physician and nurse coordinators for pediatric emergency care.[14–16]

Pediatric emergency readiness also requires a plan for continuing care of critically ill and injured children. Small community hospitals often do not have pediatric intensive care units or access to pediatric subspecialists. Therefore, a plan for transfer of patients whose needs exceed available resources is necessary. Receiving hospitals and a mechanism for transporting critically ill pediatric patients should be identified in advance. Overall mortality for critically ill children is reduced in pediatric ready facilities.[17]

Pediatric-Friendly Emergency Department

One topic that has received increasing attention is pain and anxiety management in pediatric patients. Procedural pain is frequently undertreated in infants. Appropriate use of sedation, anesthesia, analgesia, and nonpharmacologic methods of pain management can increase the patient's cooperation and increase visit satisfaction for the child and parent. Children have significant anxiety and fear surrounding medical procedures, leading to additional challenges in performing procedures successfully. In addition to reducing pain and anxiety during the acute visit, adequate pain control is likely to have long-term benefits. Multiple studies have demonstrated that inadequate procedural pain control can lead to increased pain perception with future painful procedures.

A variety of options are available to minimize pain associated with blood draws and intravenous line starts, including vapocoolants, topical anesthetics, and needle-free jet injection of anesthetics.[18] Topical anesthetics can also decrease the pain of an anesthetic injection before a lumbar puncture and other procedures. Topical application of a lidocaine, epinephrine, and tetracaine mixture has been shown to have comparable efficacy to injected anesthesia for facial and scalp lacerations. The combination of sucrose and radiant warmth can provide effective analgesia to newborns.[19] Child life specialists are particularly helpful and, when available, should be used to provide play therapy and education to frightened children, allowing the provider to focus on the procedure. Child life providers are trained in the developmentally appropriate use of nonpharmacologic distraction techniques such as bubbles, songs, books, videos, and video games to decrease anxiety, tools that can also be adopted by department staff.[18] In young children, the use of anxiolytic medications or procedural sedation may be appropriate for procedures that could be accomplished with local anesthesia in older patients.

Providers should encourage and support the family's presence during pediatric procedures and resuscitations.[20] Children are stressed when separated from their parents and their presence can reassure and calm the child. Studies have shown that a family's presence also decreases anxiety levels in family members.[20] Their presence during unsuccessful cardiopulmonary resuscitation is perceived by families as beneficial in the grieving process. Studies have shown that with well-implemented policies, a family's presence does not interfere with resuscitation.[20]

Families present during resuscitations should have a family support person assigned who can explain procedures and answer questions. Ideally, families are briefed on what to expect before entering the resuscitation room. Social workers and Child Life specialists can provide expertise and support, helping families understand what is happening to their child, guide them through procedures, and support them through critical illness and death. Guidelines have been developed to assist emergency clinicians in implementing family presence protocols at their institutions.[21]

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CHAPTER 155: QUESTIONS AND ANSWERS

1. Which of the following respiratory signs is characteristic of a child in compensated or decompensated shock?

a. Grunting with abnormal breath sounds
b. Tachypnea with nasal flaring
c. Tachypnea with clear breath sounds on auscultation
d. Tripoding with stridor
e. Wheezing with retractions

Answer: c. Effortless tachypnea, or rapid respirations with clear breath sounds, is characteristic of a child in compensated or decompensated shock. Grunting, nasal flaring, tripoding, stridor, wheezing, and retractions are all signs of increased work of breathing and would be more indicative of pulmonary or airway disease.

2. As the pediatric physician coordinator for your emergency department, you decide to institute new policies to prevent pediatric medication errors. Which of the following strategies will be most effective in decreasing risk of dosing errors?

a. Pharmacy review of medication orders
b. Use of length-based resuscitation tapes
c. Use of resuscitation calculators
d. Weighing and recording the weight in kilograms

Answer: d. Weights should be measured and recorded in kilograms, not pounds, to avoid inadvertent dosing calculations using pounds instead of kilograms. The use of length-based resuscitation tapes and resuscitation calculators and pharmacy review of medication orders have also been suggested to reduce medication dosing errors, but the most effective measure is to weigh and record the weight in kilograms.

3. You have written an order for a blood draw and placement of an intravenous line in a nervous 3-year-old boy. Which of the following is least likely to be helpful in decreasing the patient's procedure-related distress?

a. Application of a lidocaine-epinephrine-tetracaine mixture
b. Having the patient blow bubbles prior to the needle stick
c. Needle-free jet injection of local anesthetic
d. Use of a vapocoolant

Answer: a. The formulation of lidocaine-epinephrine-tetracaine only works on broken skin (i.e., lacerations). Unlike eutectic mixture of local anesthetic (EMLA) and 4% liposomal lidocaine preparations which are effective on intact skin, it will not work on intact skin. The use of vapocoolants and a needle-free jet infection of local anesthetic may decrease the patient's pain. Distraction techniques such as blowing bubbles, singing a song, or watching a video may relieve procedure-related anxiety.

Pediatric Airway Management

Joshua Nagler and Nathan W. Mick

KEY CONCEPTS

- Pediatric advanced airway management is a relatively rare skill to perform in most emergency departments (EDs), and skill maintenance is difficult based solely on clinical practice.
- There are several anatomic differences that impact pediatric airway management, and these occur mostly in the very young child (<2 years of age). Infants have a large occiput and a high, anterior airway, which impacts positioning during intubation. The narrowest portion of the pediatric airway is at the level of the cricothyroid membrane which means a foreign body could be lodged below the cords. They are also more dependent on diaphragmatic excursion for ventilation, thus gastric insufflation can result in difficulty with rescue ventilation.
- Children are prone to desaturation due to their high metabolic rate and their lungs' small functional residual capacity, making preoxygenation and maintenance of oxygenation during intubation attempts crucial.
- The cognitive burden inherent in dealing with the large age/size spectrum in pediatrics can be overcome with reference aids that organize equipment selection and drug dosing based on length/age/size. Formulas have been developed to aid in selection of the correct endotracheal tube (ETT) size and determine appropriate depth of ETT insertion. For estimation of uncuffed tube sizes in children older than 1 year old: ETT size = 4 + (age in years/4). Subtract 0.5 in size for cuffed tubes. To estimate the depth of ETT insertion (the so-called "lip to tip" distance), multiply the ETT size × 3 (e.g., a 5.0 ETT would be inserted to 15 cm at the lip).
- Rapid sequence intubation (RSI) is the preferred method of airway management in the vast majority of pediatric cases in the ED.
- Compared to adults, children are more prone to desaturation over the time it takes for a neuromuscular blocking agent (NMBA) to take effect. Use of high-flow nasal cannula during the apneic period of RSI has not been well studied in children in the emergency setting, but we recommend its use at 1 to 2 L/min/year of age to a maximum of 15 Lpm. Because children desaturate more rapidly than adults, we recommend that assisted ventilation (coordinated with the child's respiratory efforts if not yet fully paralyzed) be initiated if oxygen saturation drops below 95%.
- Video laryngoscopy is an evolving technology for use in pediatrics and assists in visualization of the airway but may prolong time to intubation.
- Surgical airway techniques differ in infants and young children, necessitating a needle technique that is different from the older child or adult. This technique provides a mechanism to oxygenate the "can't intubate, can't ventilate" child, but should not be relied on as a definitive airway.

FOUNDATIONS

Background and Importance

Pediatric airway management is an uncommon, but critical resuscitation skill. Acquisition and retention of necessary skills is difficult when relying solely on clinical practice. Although the skills required to perform advanced airway management between adults and children are similar, there are anatomic and physiologic nuances of pediatric patients. These differences are most prevalent in the first 2 years of life and necessitate modifications to the "typical" intubation approach in older adolescents and adults. Additionally, because of the size and weight spectrum inherent in the pediatric patient population, there is a large spectrum of equipment and medication dosages.

Even in large children's hospitals, there are few opportunities to perform endotracheal intubation as part of clinical practice. Of 1000 pediatric emergency department (ED) patients, 1 to 3 will require intubation, compared to 1 out of 100 adults. Many providers will leave residency training with fewer than 10 pediatric intubations and will not routinely intubate children as part of their clinical practice after training. At the same time, pediatric intubation success and skill mastery improves with increasing experience. Operating room studies demonstrate first-pass intubation success rates are less than 50% after 10 airways but rise to more than 90% after 50 intubation attempts. Fortunately, through experience with older patients, most emergency clinicians can recognize critical illness and have the skills necessary to manage the pediatric airway. These translational skills can be augmented using a simulated environment or with dedicated training in the operating room. Developing a systematic approach to pediatric airway management, while recognizing the anatomic and physiologic differences in the young child, is critical to success and will help to eliminate much of the anxiety associated with performing a time-dependent, infrequent critical procedure.

ANATOMY

There are several anatomic differences in pediatric patients that directly impact airway management (Table 156.1). These differences are most notable in the first 2 years of life; children 2 to 8 years old represent a transitional stage where the anatomy becomes more adult-like, yet there remains variability with medication dosing and equipment size selection.

By correctly positioning the patient, the oral, pharyngeal, and laryngeal axes can be aligned to visualize the glottis during direct laryngoscopy. The small infant has a relatively large head and occiput in relation to their body size. This can cause slight flexion at the neck when the patient is lying supine, impeding the ability to visualize the glottis. The patient should be positioned so that a line drawn through the external auditory canal and the anterior shoulder is horizontal and parallel to the bed (Fig. 156.1). In the infant (younger than 6 months old), this is accomplished by placing a towel roll under the patient's shoulders, elevating the body, and overcoming the neck flexion associated with their large occiput. In the small child (6 months to 5 years old), correct positioning can likely be achieved without the need for support. In the older child/adolescent, the head is smaller in relation to the size of the body, and the head may need to be elevated. As long as cervical spine

TABLE 156.1 Anatomic Differences in Pediatric Airway Management

Anatomic Difference	Implications for Airway Management	Solution
Large occiput and head	Neck position flexed when lying supine and flat on stretcher	Shoulder roll required for optimal positioning of young infant
Large tongue	May occlude airway in the unconscious or obtunded patient	Jaw thrust and oral or nasopharyngeal airway useful adjuncts during airway management
High, anterior airway	Visualization of the vocal cords may be difficult	Correct positioning prior to laryngoscopy critical
Upper airway anatomy and narrow subglottic region	Upper airway prone to dynamic collapse and inflammation (e.g., croup)	Cuffed tubes safe, and sometimes preferred, as long as cuff pressure monitored
Large tonsils and adenoids	Prone to bleeding with manipulation	Blind nasotracheal intubation relatively contraindicated younger than 10 years old
Small cricothyroid membrane	Surgical cricothyrotomy difficult	Needle cricothyrotomy recommended in infants and young children
Large stomach, dependence on diaphragmatic excursion for ventilation	Insufflation of the stomach during BMV can compromise ventilation	Use orogastric or nasogastric tube for decompression

BMV, Bag-mask ventilation.

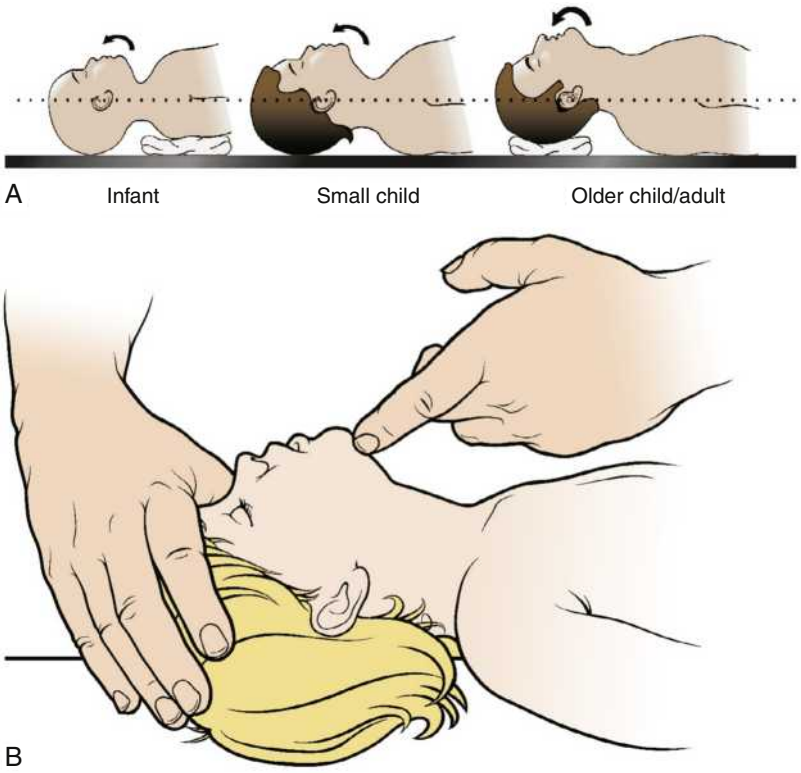


Fig. 156.1 Correct positioning of a pediatric patient to ensure optimal airway alignment utilizing a line passing through the external auditory canal and the anterior shoulder. (A) The small infant requires a shoulder roll to achieve optimal positioning, the small child typically requires neither a shoulder roll nor head support, and the older child/adolescent may require head support. (B) In this small child, a line drawn through the external auditory canal and the anterior shoulder reveals the child to be in good position without support. Slight extension of the head results in the achievement of the sniffing position. (Used with permission: Walls R, Murphy M. *Manual of Emergency Airway Management*, ed 4. Philadelphia: Lippincott Williams & Wilkins; 2012.)

injury is not suspected, correct positioning combined with slight head extension will optimize conditions for direct laryngoscopy.

Infants and children have large tongues relative to the size of their mouths and tend to have a large, floppy epiglottis. Because of these differences in anatomy, they are prone to obstruction when sedated or obtunded, and manipulation of the epiglottis during direct laryngoscopy is frequently required to achieve intubation. Practically, these differences may necessitate the use of an oral or nasopharyngeal airway during bag-mask ventilation (BMV) to bypass the large tongue. Furthermore, a straight (Miller) laryngoscope blade may better manipulate the floppy epiglottis.

The vocal cords and glottic opening are situated at the level of the first cervical vertebrae in infants, gradually dropping to the C3 to C4 level by age 7, and further descending to the C6 level by late

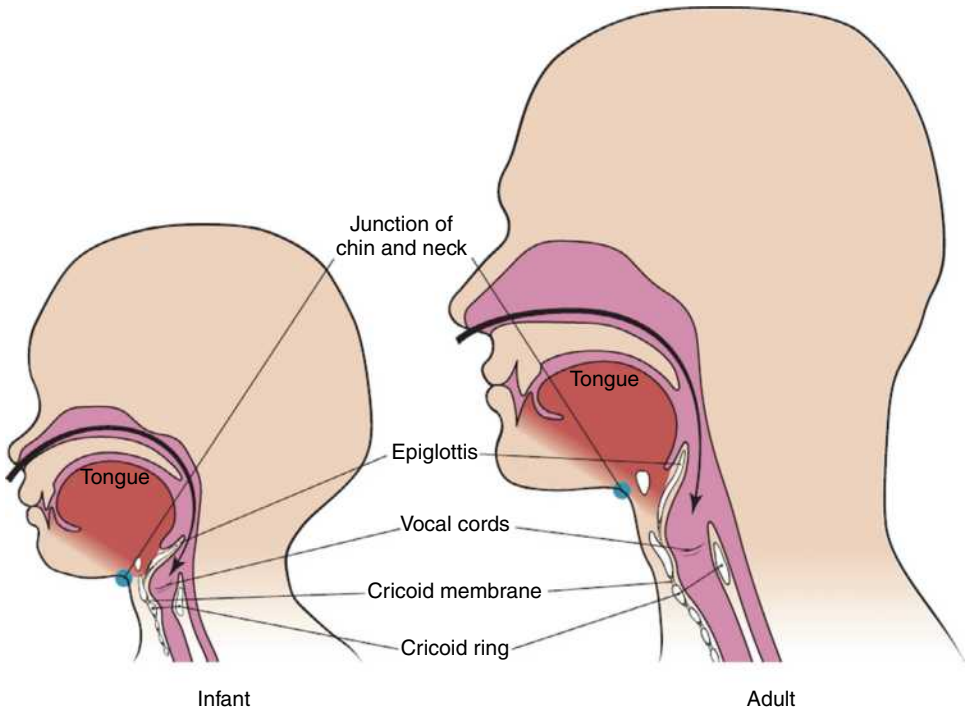


Fig. 156.2 High, anterior airway of the small child. Anatomic difference in the relation of the glottis in the small child compared with the adult.

adolescence. Therefore, the airway is higher and more anterior in small infants than what is encountered in adults, making correct positioning prior to direct laryngoscopy critical to ensure success of intubation (Fig. 156.2).

Historically the narrowest portion of the pediatric trachea was felt to be subglottic at the cricoid ring. However, recent studies using airway CT in anesthetized pediatric patients have confirmed prior MRI and bronchoscopy findings demonstrating anatomic narrowing at the level of the vocal cords and an elliptical-shaped subglottic region.[1,2] Because of the non-distensible nature of the cricoid cartilage, the subglottic region functionally remains the narrowest in the spontaneously breathing child.

The unique anatomy of the pediatric upper airway has traditionally led to the use of uncuffed endotracheal tubes (ETTs) in the small child. Support for uncuffed tubes came at a time when the cuffs were relatively stiff and there was not a reliable, easy way to identify high cuff pressures that can lead to subglottic tracheal injury. Current cuff technology can accurately measure cuff inflation pressures, and we recommend using cuffed tubes for intubation of children, particularly in instances of high airway pressures or poor compliance (e.g., asthma, pneumonia, and acute respiratory distress syndrome [ARDS]).[3-5] Utilizing a cuffed ETT may obviate the need to replace and upsize a tube when there is significant air leak that impacts ventilation, avoiding the risk of losing an already secured airway.

The pediatric trachea is more flexible and prone to dynamic collapse. In addition to implications with positioning during assisted BMV and intubation, the trachea can narrow due to upper airway pathology (e.g., croup, bacterial tracheitis). In cases of upper airway pathology, keeping the patient in a calm and quiet environment is important. Children with "complete" upper airway obstruction often respond well to positive pressure via BMV, which can act to stent open the upper airway. Heliox, typically a 70% to 30% mixture of helium to oxygen, can help decrease a child's work of breathing by increasing laminar flow in partially obstructed airways. Where available, a trial of heliox may be considered in cases of partial upper airway obstruction (e.g., croup), although it has been found no more effective than racemic epinephrine or humidified oxygen in reducing the level of distress in these patients.[6]

The anatomic variations in children impact recommendations in pediatric airway management. Children have relatively prominent tonsillar and adenoidal tissue that is prone to bleeding with even minor trauma. Thus, blind nasotracheal intubation is relatively contraindicated and not routinely recommended in pediatric patients younger than 10 years old. Anatomic landmarks in the neck may be difficult to identify in young infants and children with short necks, and the cricothyroid membrane is small. Thus, needle cricothyrotomy is the recommended invasive airway of choice rather than surgical cricothyrotomy in emergency department settings when the airway cannot otherwise be managed with BMV, intubation or supraglottic device.

Finally, small children are dependent on diaphragmatic excursion for ventilation and have relatively large stomachs and low gastroesophageal sphincter tone. They are predisposed to gastric insufflation during BMV, which can impede diaphragmatic motion and compromise ventilation. Use of cricoid pressure in infants and young children is controversial and not well supported in the literature. If gentle cricoid pressure is used during BMV to reduce gastric insufflation and chest rise is poor, we recommend release of cricoid pressure to see if effective ventilation can then be maintained. We recommend placement of a nasogastric or orogastric tube and aspiration of air immediately following endotracheal intubation, or before intubation attempts if the abdomen is becoming distended and impeding ventilation during BMV.

PHYSIOLOGY

Owing to a high metabolic rate and low functional residual lung capacity, young children are prone to quick desaturation once apneic, even with adequate preoxygenation. Whereas a fully preoxygenated adult with healthy lungs may not desaturate below 90% for a full 6 minutes, a

normal healthy 10-kg child may fall below 90% in half that time and a sick infant may desaturate in less than 1 minute. Thus, careful attention to preoxygenation is crucial. Additionally, use of nasal cannula (1–2 L/min/year of age to a maximum of 15 L/min) during the apneic period may help support oxygenation until intubation can be achieved. BMV should be provided between intubation attempts when oxygen saturation levels start to decline below 95%.

Children have a large extracellular fluid volume compared with adults. Many of the drugs used to facilitate endotracheal intubation (sedatives and paralytics) need higher per kilogram doses and their duration of action may also be shorter when compared with adults.

EQUIPMENT

The cognitive burden that occurs when caring for a critically ill child is significant. Equipment selection and medication dosing should be calculated based on weight and size, which can vary tremendously across the spectrum of pediatric patients, from the 3 kg newborn to the 100 kg adolescent. Every ED that cares for pediatric patients should have airway equipment stocked, accessible, and organized by age and size to facilitate easy use. There are numerous mobile device and computer applications, as well as color-coded length-based systems, which can be utilized to simplify medication and equipment selection (Fig. 156.3). Regardless of method, elimination of the reliance on rote memorization lessens the cognitive burden of caring for pediatric patients across the age/size spectrum, particularly during periods of high stress.

There are several "formulas" that are useful in selecting the appropriate equipment for pediatric patients. To determine ETT size, a number of methods are used. Measure the length of the child with a length-based resuscitation tape that has tube sizes based on length and weight recorded on the tape, or use of age-based formulas for a child older than 1 year old:

$$4 + (\text{age in years}/4)$$

Example: 4-year-old patient

$$4 + (4\ \text{years}/4) = 5.0\ \text{uncuffed ETT}$$

or

4.5 *cuffed* ETT (subtract 0.5 from above formula for cuffed tube sizing)

ETT depth of insertion (lip to tip distance) can be visualized during intubation by watching the vocal cord marker go past the vocal cords, or estimated by use of the Broselow-Luten tape or by the following formula:

$$3 \times \text{uncuffed tube size} = \text{lip to tip distance (midtrachea)}$$

Example: 5.0 ETT

$$3 \times 5.0 = 15\ \text{cm depth of insertion}$$

MANAGEMENT

Decision Making

For a child who is effectively stabilized using noninvasive means (such as BMV), the additional benefit of a secure airway needs to be weighed against the risk of potential difficulty or complications. Failure to successfully oxygenate or ventilate a child by other means forces immediate action, whereas other conditions allow medical interventions and recurrent assessments over time to determine if advanced airway management is required.

Overall, an equal number of pediatric intubations in the ED are performed on trauma and nontrauma patients.[7] Indications for pediatric intubation can be placed into four categories: (1) inability to oxygenate and ventilate; (2) inability to maintain or protect the airway; (3) potential for clinical deterioration; and (4) facilitation of necessary diagnostic studies, procedures, or for safe patient transport (e.g., high risk of decompensation on route).

Respiratory compromise is a leading contributor to morbidity and mortality in the pediatric population, and more likely than a primary cardiac disease to be the cause of arrest. Respiratory failure can result from intrinsic pulmonary disease or from conditions with infectious, neuromuscular, traumatic, toxicologic, or environmental etiologies. Respiratory failure is a clinical diagnosis, identified by characteristic examination findings and supported by noninvasive measurement of oxygenation (pulse oximetry) and ventilation (capnography). Blood gas analysis can also be informative but should not be relied upon to determine need to perform necessary advanced airway management.

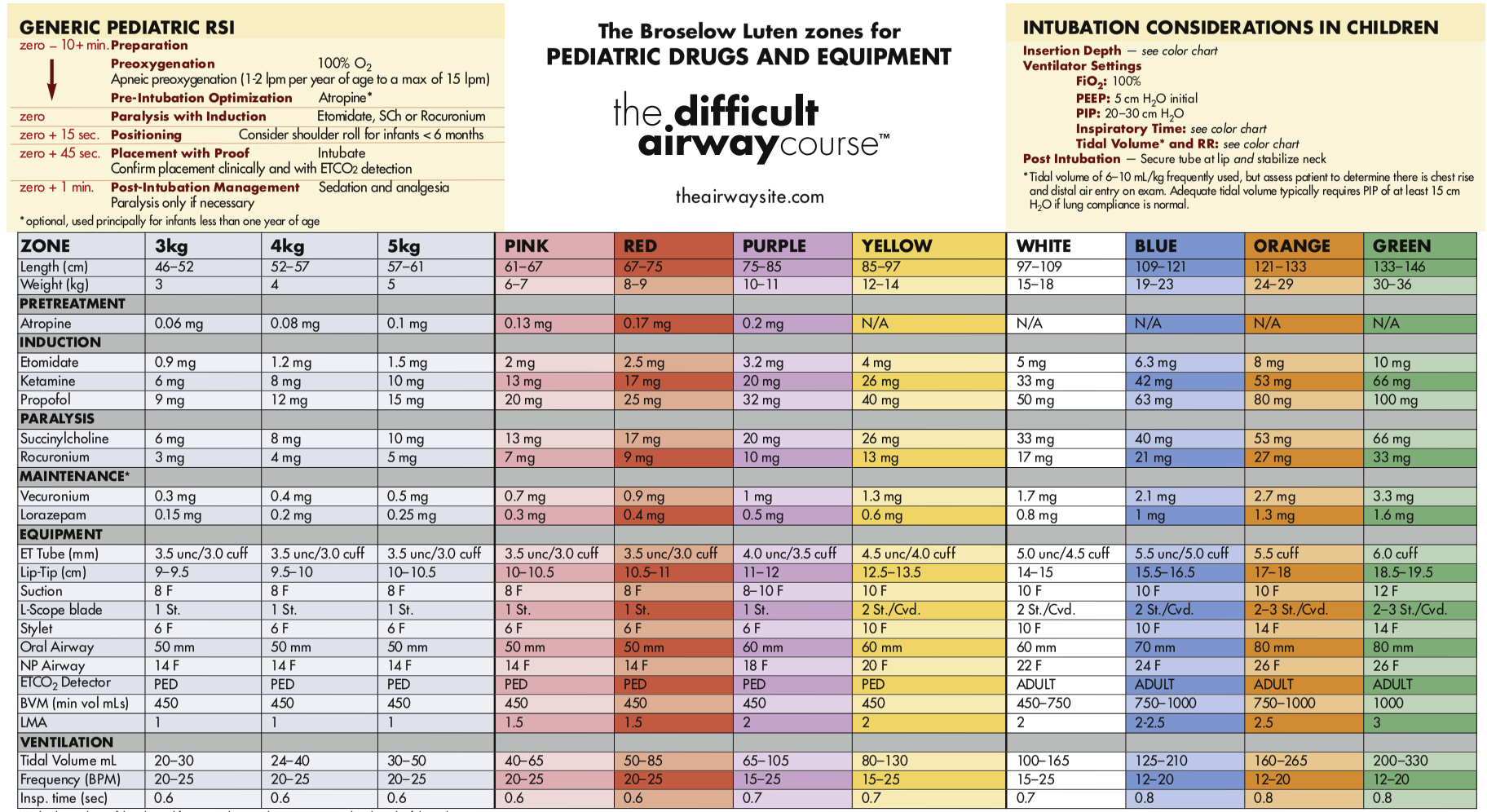
Signs of partial obstruction (sonorous or stridulous airway noises) or complete obstruction (inability to phonate or produce audible breath sounds in a patient with adequate respiratory effort) suggest an inability to maintain the airway and should prompt immediate basic airway maneuvers, including airway repositioning or insertion of oral and nasal airways to help stent open the upper airways. Suctioning and removal of any foreign material might also be required. When these efforts are ineffective, patients may require an advanced airway. For patients with severely depressed mental status, the loss of protective airway reflexes may necessitate airway control, regardless of the ability to maintain the airway. For example, the use of a Glasgow Coma Score (GCS) of 8 or less is often cited as an indication for intubation in head-injured patients. Systemic illness, toxicologic exposure, and other etiologies of central nervous system (CNS) depression may also increase risk of aspiration; the presence of a gag reflex correlates poorly with GCS and the risk of aspiration. Thus, testing for a gag is not recommended, because it may increase the risk of vomiting and subsequent aspiration.

When airway compromise is progressive (e.g., from acute thermal injury), airway management should be initiated early to avoid increased difficulty later in securing the airway. Similarly, patients with systemic illnesses (e.g., sepsis) may require intubation to maximize oxygen delivery and decrease the metabolic demands of increased work of breathing.

Children often require sedation to perform diagnostic testing, such as computed tomography (CT), magnetic resonance imaging (MRI), or invasive procedures. The risk of airway compromise during procedural sedation is greater in patients with significant illness or medical instability. Therefore, securing the child's airway may be necessary to ensure safety during the procedure, particularly in circumstances where accessibility for assessment and intervention may be compromised (e.g., a patient under surgical drapes or tunneled into a CT or MRI scanner). Because many acutely ill and injured children will require transfer to a pediatric tertiary care center, the stability of the patient's overall condition and risk of airway compromise should be carefully considered. Securing the airway prior to transfer can obviate the need for emergent advanced airway management in a less controlled setting.

Rapid Sequence Intubation

Rapid sequence intubation (RSI) is the preferred method to perform endotracheal intubation in children, provided no contraindications exist. We do not recommend attempting emergency pediatric endotracheal intubation with sedation only as studies have demonstrated higher success and lower complications rates with RSI. A small number of medications are used for pretreatment, sedation/induction, and neuromuscular blockade during ED pediatric RSI (Table 156.2).



ZONE	3kg	4kg	5kg	PINK	RED	PURPLE	YELLOW	WHITE	BLUE	ORANGE	GREEN
Length (cm)	46–52	52–57	57–61	61–67	67–75	75–85	85–97	97–109	109–121	121–133	133–146
Weight (kg)	3	4	5	6–7	8–9	10–11	12–14	15–18	19–23	24–29	30–36
PRETREATMENT											
Atropine	0.06 mg	0.08 mg	0.1 mg	0.13 mg	0.17 mg	0.2 mg	N/A	N/A	N/A	N/A	N/A
INDUCTION											
Etomidate	0.9 mg	1.2 mg	1.5 mg	2 mg	2.5 mg	3.2 mg	4 mg	5 mg	6.3 mg	8 mg	10 mg
Ketamine	6 mg	8 mg	10 mg	13 mg	17 mg	20 mg	26 mg	33 mg	42 mg	53 mg	66 mg
Propofol	9 mg	12 mg	15 mg	20 mg	25 mg	32 mg	40 mg	50 mg	63 mg	80 mg	100 mg
PARALYSIS											
Succinylcholine	6 mg	8 mg	10 mg	13 mg	17 mg	20 mg	26 mg	33 mg	40 mg	53 mg	66 mg
Rocuronium	3 mg	4 mg	5 mg	7 mg	9 mg	10 mg	13 mg	17 mg	21 mg	27 mg	33 mg
MAINTENANCE*											
Vecuronium	0.3 mg	0.4 mg	0.5 mg	0.7 mg	0.9 mg	1 mg	1.3 mg	1.7 mg	2.1 mg	2.7 mg	3.3 mg
Lorazepam	0.15 mg	0.2 mg	0.25 mg	0.3 mg	0.4 mg	0.5 mg	0.6 mg	0.8 mg	1 mg	1.3 mg	1.6 mg
EQUIPMENT											
ET Tube (mm)	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	3.5 unc/3.0 cuff	4.0 unc/3.5 cuff	4.5 unc/4.0 cuff	5.0 unc/4.5 cuff	5.5 unc/5.0 cuff	5.5 cuff	6.0 cuff
Lip-Tip (cm)	9–9.5	9.5–10	10–10.5	10–10.5	10.5–11	11–12	12.5–13.5	14–15	15.5–16.5	17–18	18.5–19.5
Suction	8 F	8 F	8 F	8 F	8 F	8–10 F	10 F	10 F	10 F	10 F	12 F
L-Scope blade	1 St.	1 St.	1 St.	1 St.	1 St.	1 St.	2 St./Cvd.	2 St./Cvd.	2 St./Cvd.	2–3 St./Cvd.	2–3 St./Cvd.
Stylet	6 F	6 F	6 F	6 F	6 F	6 F	10 F	10 F	10 F	14 F	14 F
Oral Airway	50 mm	50 mm	50 mm	50 mm	50 mm	60 mm	60 mm	60 mm	70 mm	80 mm	80 mm
NP Airway	14 F	14 F	14 F	14 F	14 F	18 F	20 F	22 F	24 F	26 F	26 F
$ETCO_2$ Detector	PED	PED	PED	PED	PED	PED	PED	ADULT	ADULT	ADULT	ADULT
BVM (min vol mLs)	450	450	450	450	450	450	450	450–750	750–1000	750–1000	1000
LMA	1	1	1	1.5	1.5	2	2	2	2-2.5	2.5	3
VENTILATION											
Tidal Volume mL	20–30	24–40	30–50	40–65	50–85	65–105	80–130	100–165	125–210	160–265	200–330
Frequency (BPM)	20–25	20–25	20–25	20–25	20–25	15–25	15–25	15–25	12–20	12–20	12–20
Insp. time (sec)	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.7	0.8	0.8	0.8

** Midazolam and propofol can be used for post-intubation sedation. Dosing is on the other side of the card.*

Fig. 156.3 The Broselow-Luten zones for pediatric drugs and equipment. *BVM*, bag-valve mask; *$ETCO_2$*, end-tidal carbon dioxide; *ETT*, endotracheal tube; *FiO_2*, fraction of inspired oxygen; *LMA*, laryngeal mask airway; *NP*, nasopharyngeal; *PED*, pediatric; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *RR*, respiratory rate; *RSI*, rapid sequence intubation; *SCh*, succinylcholine. (Reproduced with permission from the Airway Management Education Center, The Difficult Airway Course: Emergency 2020.)

TABLE 156.2 Common Rapid-Sequence Intubation Medications in Children[a]

Medication	Dosage	Comments
Premedications		
Atropine	0.02 mg/kg	Not routinely used in RSI. Consider use in young infants (<1 year of age) Should be given for preexisting or periprocedure bradycardia not responsive to oxygenation and ventilation
Lidocaine	1.5 mg/kg	Not routinely used in RSI. Very limited pediatric-specific data to support use in increased ICP Needs to be given 3 minutes prior to laryngoscopy No data for bronchodilatory effect in children
Induction Agents		
Etomidate	0.3 mg/kg	Rapid and reliable sedation Preserves hemodynamics Known to cause adrenal suppression even with single dose, although limited data on impact on clinical outcome Consider stress dose hydrocortisone with use No analgesic properties
Ketamine	1 to 2 mg/kg	Causes release of endogenous catecholamines May support hemodynamics in hypotensive patients Beta-agonist effect may help with bronchodilatation, favoring its use in asthma Preserves airway reflexes and respiratory drive Can be used without NMBA for "awake sedated look" in suspected difficult airways
Propofol	3 mg/kg	Rapid onset, short acting May cause hypotension Apnea possible Higher dose recommended in infants No analgesic properties
Midazolam	0.3 mg/kg	Higher dosing required than used for antiepileptic dosing or anxiolysis At induction dosing, may cause hypotension Often used concomitantly with opioids No analgesic properties
Fentanyl	1 to 5 mcg/kg	Often used with midazolam Lower dosing (1–2 mcg/kg) recommended for shock or hemodynamic concerns
Paralytics		
Rocuronium	1 to 1.2 mg/kg	Nondepolarizing agent Equivalent onset as succinylcholine but longer duration of action No specific contraindications in patients suitable for RSI
Vecuronium	0.1 mg/kg	Nondepolarizing agent Slower onset of action than rocuronium Suitable alternative for rocuronium if more readily available
Succinylcholine	0–11 years: 2 mg/kg >11 years: 1.5 mg/kg Double the dose when given IM	Fasciculations without clinical relevance in children Shorter duration than rocuronium Very low risk of bradycardia with IV induction agents used in ED (see earlier) Risk of hyperkalemia and arrest in patients with known and undiagnosed myopathies and neuromuscular disease
Sugammadex	16 mg/kg (full reversal dose)	Rapid reversal agent for rocuronium or vecuronium Neuromuscular blockade generally reversed within 3 minutes

[a]RSI medications can be given intraosseous (IO) when IV access cannot be obtained.
ED, Emergency department; *ICP,* intracranial pressure; *IM,* intramuscular; *IV,* intravenous; *NMBA,* neuromuscular blocking agent; *RSI,* rapid sequence intubation.

Pretreatment

The goal of pretreatment medications is to attenuate the physiologic responses to laryngoscopy and intubation, or to mitigate the adverse effect of pharmacologic agents used for sedation or neuromuscular blockade; however, data are limited with regard to the benefit of pretreatment medications in children. Use of these agents needs to be weighed against the potential for procedural delays and drug errors that can occur with the administration of medications requiring weight-based dosing. This is particularly relevant during high stress situations, such as the management of critically ill children. Two drugs

have been used for pretreatment in pediatrics: (1) atropine to prevent bradycardia related to vagal tone, and (2) lidocaine to attenuate the reflex sympathetic response in patients with concern for increased intracranial pressure (ICP); however, their use today is not routinely recommended.

Infants, particularly younger than 1 year old, have higher intrinsic vagal tone than older children or adults. Atropine serves as a vagolytic and can reduce the risk of bradycardia resulting from laryngoscopy in this age group. There is an association between the use of succinylcholine and bradycardia. Data suggest that this risk may be tied to use with select inhaled anesthetics (e.g., halothane) and with newer induction agents the incidence of succinylcholine-related bradycardia is very low.[8] Given the limited available evidence, routine use of atropine for patients receiving succinylcholine during RSI is not necessary.[9] Atropine may be helpful for bradycardia that exists prior to intubation, but it should only be considered once hypoxia-induced bradycardia is excluded and maximal oxygenation achieved.

Data on the effectiveness of lidocaine in blunting the sympathetic response to laryngoscopy in patients with suspected elevated ICP are limited to case series and extrapolated from adult experience. Literature reviews have failed to identify a benefit in adult head injured patients, and no supporting data exist in pediatric populations. Therefore, we do not recommend the routine use of lidocaine.

Sedatives

Sedatives rapidly induce unconsciousness and facilitate intubation. Providers should choose sedatives based on their efficacy, adverse effect profile, and clinical situation. In particular, providers should pay careful attention to the hemodynamic profile of these agents, to minimize the risk of clinical deterioration during RSI.

Etomidate is a common sedative used for pediatric RSI. It has reliable efficacy and pharmacokinetics and a stable hemodynamic profile. Etomidate may suppress adrenal corticosteroid synthesis transiently. However, no convincing data exist to suggest that administration of a single dose during intubation influences clinical outcome. Pediatric advanced life support (PALS) guidelines have included precautions against "routine use" in septic shock, and suggest consideration of stress dose hydrocortisone when etomidate is used.

Ketamine is a dissociative anesthetic with reliable and rapid onset. Its use is well established for procedural sedation and analgesia in pediatrics. It causes an endogenous release of catecholamines, making it appealing for patients with hypotension or shock. Adverse reactions to ketamine include vomiting, laryngospasm, myoclonus, and emergence phenomenon. Although ketamine is a known sialagogue, the coadministration of atropine is unlikely to be of help during RSI given that the onset of action for the drying effects of atropine may take up to 20 minutes. Ketamine has been shown to increase ICP, although the significance of this on clinical outcome is unclear, as it can also support cerebral perfusion pressure.[10,11] The catecholamine release with ketamine may lead to the beta-agonist effect of bronchodilation, making it an ideal drug for patients with bronchoconstriction. This same benefit may not apply to conditions such as bronchiolitis, in which airway edema and debris are the primary etiology of airway obstruction. Ketamine is the preferred sedative for children in septic shock requiring RSI because of its ability to maintain mean arterial pressure.[12]

Propofol has rapid and profound sedative properties, that when combined with its short duration of action, make it an ideal induction agent. However, as a vasodilator and myocardial depressant, propofol is not recommended in patients with tenuous hemodynamics, including hypovolemia or shock. Propofol may also compromise cerebral perfusion if mean arterial pressure is rapidly reduced.

Benzodiazepine dosing is higher for RSI induction than when used as an anticonvulsant or during procedural sedation. For example, 0.3 to 0.4 mg/kg of midazolam may be required to achieve sufficient sedation. Alternatively, benzodiazepines may be used in conjunction with opioids, such a fentanyl, but the combination can compromise hemodynamics.

Neuromuscular Blocking Agents

Neuromuscular blocking agents (NMBAs) are used to relax airway musculature and block airway protective reflexes during laryngoscopy to facilitate the passage of an ETT. The aim is rapid onset of action to limit the time without spontaneous or assisted ventilation. Succinylcholine and rocuronium are the most commonly used NMBAs for emergent pediatric RSI.[13] Understanding the specific benefits and risks of each is helpful in creating an airway management plan.

Succinylcholine has a rapid onset of action of 30 to 60 seconds and duration of action of 3 to 8 minutes. It is the oldest, and often the most familiar, NMBA for emergency clinicians, and has a long track record of safe and effective use. Higher doses (2 mg/kg) are recommended in neonates and infants compared to 1.5 mg/kg for adolescents. Providers should be aware of several side effects and potential risks of succinylcholine. Muscle fasciculations result from the depolarizing effect of this agent, although young children may not have large enough muscle mass to result in clinically observable effects. Succinylcholine can cause hyperkalemia, which can be fatal in a number of clinical conditions (see Table 156.2). In many patients, high-risk diagnoses are known or suspected; however, published case series have described succinylcholine use in infants with undiagnosed myopathies leading to hyperkalemia arrest. As a result, a US Food and Drug Administration (FDA) black box warning exists for the use of succinylcholine in children, although given the rarity of these conditions, exception has been allowed for emergency use. Given this waiver, succinylcholine is still the most commonly used NMBA in pediatric emergency airway management.[7] Other serious but rare adverse effects of succinylcholine use in children include masseter spasm and malignant hyperthermia, which are most commonly associated with concurrent halothane use. Masseter spasm is a rare side effect of succinylcholine administration in children and can be terminated by the administration of a competitive neuromuscular blocking agent (NMBA).

Rocuronium is the most common nondepolarizing NMBA used in emergency pediatric airway management. Pediatric data suggest that rocuronium at a dose of 1.2 mg/kg has equivalent efficacy in time to intubation conditions as succinylcholine. The duration of action, however, is much longer with a time to return of spontaneous respirations of anywhere from 20 to 90 minutes. The primary advantage of nondepolarizing agents is the absence of the risks (e.g., hyperkalemia) associated with depolarizing agents. The longer duration of action can be of concern if the airway cannot be secured or in patients in whom rapid return of examination findings (e.g., neurologic examination) is important. However, it may also have advantages if subsequent management may include imaging, additional vascular access, initial ventilator management, or other procedures. A reversal agent (sugammadex) for rocuronium exists that can limit its duration of action to less than that of succinylcholine.

DEVICES AND TECHNIQUES

Basic Airway Management

The priority in pediatric airway management is establishing effective oxygenation and ventilation. For children with hypoxemia but effective ventilation and without concern for increased work of breathing, passive supplemental oxygen delivery may be sufficient. For

mild hypoxemia in children who will not tolerate a nasal cannula or face mask, "blow-by" oxygen using a mask, shovel, or plastic funnel attached to oxygen tubing aimed toward the face are options. Nasal cannula can provide more consistent oxygen delivery, particularly in infants who are preferential nasal breathers. High-flow nasal cannula is increasingly being used to deliver supplementary oxygen to pediatric patients. The heated and humidified delivery allows higher flow rates without discomfort, and the absence of a need for a tight seal makes application easier than other forms of noninvasive ventilation.[14] Simple face masks can be used, whereas non-rebreather masks provide maximal passive oxygen delivery in spontaneously breathing patients.

When ventilation is of concern or a child's work of breathing is excessive, assisted ventilation may be required with a bag and mask. Effective assisted ventilation requires: (1) a patent airway and (2) an effective mask seal. Opening the airway is accomplished with positioning of the child, avoiding flexion of the neck from a large occiput or from downward pressure on the face when applying the mask. Application of basic airway maneuvers including a head tilt–chin lift maneuver or a jaw thrust can be of further help. Placement of nasopharyngeal and oral airways can be of value when the airway is being partially or completely obstructed, often by the tongue or soft palate. Oral airways are only tolerated in patients with depressed mental status, either pharmacologically induced or related to underlying pathophysiology. To create an effective mask seal, the provider first needs to select the appropriate size mask. An ideal fitting mask is large enough to cover the nose and open mouth but should not allow air leak across the bridge of the nose or off the base of the chin. Emergency clinicians should deliver appropriate volume and pressure breaths. There may be a tendency in an acute situation to deliver a much larger tidal volume than is appropriate for the size of the child, which may result in barotrauma. Gentle rise of the chest accompanied by clinical improvement are key clinical features of effective BMV. The bag-mask device should be squeezed just until chest rise is initiated and then released. The emergency clinician may time ventilation by stating "squeeze, release, release" which slows ventilation rate and may reduce complications from hyperventilation and gastric insufflation during rescue ventilation. Cricoid pressure has limited utility, primarily in reducing gastric insufflation, and should be used with caution in children. Too much cricoid pressure can compress the pliable pediatric trachea, leading to iatrogenic upper airway obstruction. Cricoid pressure should be lightened or released if felt to impede BMV.

Advanced Airway Management

Chapter 1 covers a detailed approach to RSI. The general approach to the procedure is identical to that of an adult, although there are several pediatric considerations worthy of mention.

Preparation

Passive oxygen delivery devices, self-inflating bags and masks, oral and nasal airways, laryngoscope blades, ETTs, stylets, and rescue devices all come in varying sizes to match the anatomy of the child. Generally having at least two sizes of ETTs (estimated size as well as a half size smaller) available during the procedure is prudent. Having a systematic approach to identifying the correct equipment prior to initiating the procedure can eliminate errors and failed attempts in critical situations. Potential resources include a length-based resuscitation system, pediatric resuscitation cards (Fig. 156.3), print or online textbooks, and mobile device applications.

Preoxygenation

As described earlier, young children desaturate much more quickly than adolescents or adults. In a patient with sufficient respiratory effort, preoxygenation with maximal passive oxygen delivery (i.e., a non-rebreather mask) for 2 to 3 minutes may be sufficient in healthy children. However, patients requiring emergency intubation often have compromised pulmonary function or respiratory effort and may benefit from a more prolonged preoxygenation time. A technique of using vital capacity breaths for more rapid preoxygenation will be difficult to accomplish in children who may not be cooperative with this technique. Even with appropriate preoxygenation, a significant percentage of young children will desaturate during intubation attempts, particularly those with underlying respiratory illness or when intubation attempts are prolonged (Fig. 156.4).[15] Due to children's propensity to quickly drop oxygen saturations during intubation attempts, we recommend utilizing apneic oxygenation using nasal cannula during RSI. A number of nasal cannula flow rates for apneic oxygenation in children have been proposed.[8] As a simplified approach in infants and children, we recommend 1 to 2 L/min/year of age to a maximum of 15 L/min for children to help prevent the drop in oxygen saturation during the apneic period of RSI. Positive-pressure ventilation with bag-mask device should be considered at the first sign of desaturation, and we recommend it be initiated when oxygen saturation drops below 95%. Once oxygen saturation has improved, additional attempts can begin.

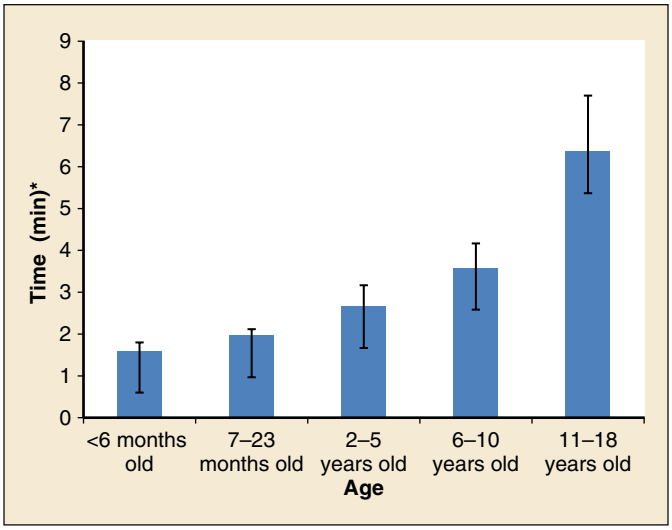


Fig. 156.4 Time to desaturation in preoxygenated healthy children. (American Society of Anesthesiologists Classification 1 [ASA 1] patients undergoing elective surgery.) *Time from administration of neuromuscular blocking agent (NMBA) to desaturation to 90%, with no ongoing supplemental oxygen or respiratory support. (Adapted from: Patel R, Lenczyk M, Hannallah RS, et al. Age and the onset of desaturation in apnoeic children. *Can J Anaesth*. 1994;41:771-774.)

Positioning

As described previously, age-appropriate positioning is required during laryngoscopy and endotracheal intubation. Alignment of the oral, pharyngeal, and tracheal axes greatly facilitates visualization. In neonates and infants, a shoulder roll is often required; toddlers and school-age children are usually best aligned in the neutral recumbent position; and adolescents will often require elevation of the head similar to adults.

Placement of Tube

When performing direct laryngoscopy, straight blades placed beneath the epiglottis are preferred in infants and younger children to lift the larger pediatric epiglottis and bring the vocal cords into line of sight. Alternatively, an appropriately sized laryngoscope blade placed into the

TABLE 156.3 Common Post-Intubation Sedation/Analgesia in Children

Medication	Bolus Dosing	Drip	Comments
Lorazepam	0.05 to 0.1 mg/kg		Long-acting sedative/amnesic Often used in combination with analgesic
Midazolam	0.5 to 2 mg/kg	0.05 to 0.1 mg/kg/h	Short-acting sedative/amnestic Often used in combination with analgesic
Fentanyl	1 to 2 mcg/kg	1 to 3 mcg/kg/h	Short-acting analgesia Preserves hemodynamic stability
Morphine	0.05 to 0.1 mg/kg	0.05 to 0.1 mg/kg/h	Longer-acting analgesic May cause histamine release
Ketamine		0.1 to 1 mg/kg/h	Bolus dosing not recommended for prolonged ongoing sedation May be helpful in status asthmaticus
Propofol	0.5 to 1 mg/kg	25 to 250 mcg/kg/min	No analgesic properties Prolonged infusion in children can lead to profound acidosis and rhabdomyolysis
Dexmedetomidine		0.2 to 0.7 mcg/kg/h	Associated with significant cardiovascular effects (including bradycardia, hypotension, AND hypertension) Limited data on safety in infants (<5 kg)

vallecula can engage the hyoepiglottic ligament to elevate the epiglottis in most pediatric patients.[7] In younger children, emergency clinicians may tend to insert the laryngoscope blade too deeply, resulting in retroglottic or esophageal placement and unnecessary airway trauma. With this in mind, emergency clinicians should start the intubation procedure by placing the laryngoscope blade just to the base of the tongue and lift up to view the airway anatomy. Identify structures progressively, first directly identifying the base of the tongue and the epiglottis prior to insertion of the straight blade underneath the epiglottis or the curved blade into the vallecula to visualize the vocal cords. If no laryngeal structures are identified due to inadvertent deep insertion, the blade should be slowly withdrawn under visualization, and the cords or the epiglottis will often fall into view.

Given the superior position of the larynx in children, use of a stylet is often helpful in guiding the ETT into the glottic opening. This is particularly true during videolaryngoscopy, where the delivery of the endotracheal tube to the glottic opening is often performed under *indirect* visualization. Given the relatively small size of the oropharyngeal cavity, the tube should be placed from the 3 o'clock position, often with an assistant applying lateral traction to the child's lip to provide more room for tube insertion.

There is a tendency to insert the ETT too far in the young child in whom the distance from the vocal cords to the tracheal carina may just be a few centimeters.[16] Right mainstem intubation is difficult to appreciate on auscultation, particularly in the infant whose breath sounds are easily transmitted throughout the chest. Using a pediatric resuscitation resource as described earlier, or the formula (tube size × 3 = depth [cm] at the lip) can approximate insertion depth. Under direct visualization, the vocal cord markers on the tube should rest just below the glottic opening, or the cuff observed to pass just beyond the vocal cords.

Post-Intubation Management

Optimally, the ETT should be visualized to pass into the glottic opening. If vocal cords are not seen, passage of the tube below the epiglottis and above the posterior cartilages indicates ETT placement into the glottic aperture, but should be subsequently assessed clinically in conjunction with other confirmatory tests. Visible chest wall rise, auscultation of breaths sounds in both axillae, absence of gurgling noise in the epigastrium (i.e., exclusion of esophageal placement), and improving oxygenation are all used to confirm tube position. However, end-tidal carbon dioxide ($ETCO_2$) detection, either with a colorimetric device or capnography, is the most reliable and accurate measure of correct tube placement. Waveform capnography is preferred for monitoring pediatric ventilation and for determination of correct airway placement.

If waveform capnography is not available, then pediatric colorimetric $ETCO_2$ detectors are available for children weighing less than 15 kg in whom smaller tidal volumes may result in less apparent detection using adult-sized devices. Detection of $ETCO_2$ confirms the ETT is in the tracheobronchial tree; however, it does not discriminate between intubation of the trachea and the right mainstem bronchus. In patients in cardiac arrest, CO_2 delivery to the lungs is markedly reduced and gas exchange is compromised, therefore CO_2 may not be detectable. Here, an esophageal detector device or bulb may be used to confirm tracheal placement in children who weigh more than 20 kg. Point-of-care ultrasound has been introduced as a real-time modality for detecting bilateral lung sliding, diaphragm excursion, and cuff position in the trachea.[16] However, a chest radiograph is still considered standard of care to confirm appropriate position.

Even small movements of the child's head can result in accidental displacement of the tube: flexion of the neck can advance the tube into a mainstem bronchus, whereas neck extension can lead to unintended extubation. After intubation, the ETT should be secured and, as much as is possible, the child's head and neck kept still. Most sedatives used for induction will wear off before rocuronium; therefore post-intubation sedatives should be administered after the airway has been secured. Table 156.3 lists common drugs used for post-intubation sedation in the pediatric population. Decisions regarding continued neuromuscular blockade can be made based on clinical context, including desire for return of clinical examination, ventilation management strategies, need for additional procedures or diagnostics studies, and need for interfacility transfer.

Video Laryngoscopy

Video laryngoscopy is an emerging approach to pediatric airway management. Much as in adults, data support improved laryngeal views with video laryngoscopes, with particular benefit in cases where there is difficulty visualizing the vocal cords, or Cormack-Lehane airways classified as grade 3 (only epiglottis seen) or grade 4 (neither epiglottis nor glottis seen). In addition, video laryngoscopy allows for shared

TABLE 156.4 Video Laryngoscopy Devices for Use in Pediatrics

Device	Description	Monitor	Disposable	Recording	Sizes
C-MAC	Traditional Miller and Macintosh shaped blades Allows for direct or indirect (video projection) laryngoscopy	7″ LCD monitor or 2.4″ pocket monitor	Reusable blades or disposable blades	SD card in 7″ monitor Pocket monitor also allows recording	Miller (size 0, 1, 2) Macintosh (size 0, and 2 to 4) D-Blade (pediatric and adult sizes)
GlideScope	Blades with 60-degree angulation Different models GVL, AVL (advanced video technology) GlideScope Go (handheld)	7″ LCD monitor or 3.5″ portable screen	Reusable blades Video batons with single use blades	DVR or USB depending on model	Newly available Miller 0 and 1 blades GVL Blades (size 0, 1, 2, 2.5, 3, and 4) Macintosh blades (size 3 and 4)
Airtraq	Different models Disposable blade with reusable optics Fully disposable optical laryngoscope, no electronics Channeled device (provides guide for ETT to pass around curvature of airway)	Direct view eyepiece or 2.6″ camera hood with wi-fi capabilities	Disposable single-use devices Reusable optics with disposable blades available in adult sizes only	Phone adapter or wi-fi camera	Size 0 (infant) Size 1 (pediatric) Size 2 (small) Size 3 (regular)
King Vision	Handheld videolaryngoscope, disposable channeled and unchanneled blades	2.4″ LCD display	Reusable display and video adapter, disposable blades	Video output capability, no internal recording	Size 1 (unchanneled) Size 2 and 3 (channelled and unchanneled)

AVL, Advanced video laryngoscopy; *DVR,* digital video recording; *ETT,* endotracheal tube; *GVL,* GlideScope video laryngoscope; *LCD,* liquid crystal display; *SD,* secure digital; *USB,* universal serial bus.

viewing by multiple providers, which permits real-time guidance and supervision during tracheal intubation. Currently, data on the use of video laryngoscopy in pediatric patients are largely limited to the anesthesia literature or performance in simulated scenarios, although emergency medicine studies focused on use in children are emerging. Data consistently show that video laryngoscopy improves visualization, and newer data suggest it may also improve first-pass success.[18,19] Importantly, video laryngoscopy has been shown to have a faster learning curve than direct laryngoscopy. This may be particularly important for airway management in children, given the infrequency with which pediatric airway management is performed in the ED.

Video laryngoscopes for use in pediatrics are becoming increasingly available. Many are smaller adult models, which permit use in older children. Currently, there are a limited number of devices available with a complete range of sizes that allow for use across all pediatric ages, from neonates to adolescents. There are unique advantages, potential drawbacks, and subtleties in technique for using each (Table 156.4). The decision regarding which device to use is ultimately based on availability, operator preference, operator experience, and patient-specific attributes that may favor a given approach.

Airway Rescue Devices for Children

The overall success rate for advanced airway management in children is more than 99%, so the need for rescue device use is fortunately rare. Nonetheless, it is imperative to have a contingency plan for circumstances in which a provider cannot secure the airway. Bag-mask ventilation is a critical, and often underestimated, skill for establishing adequate oxygenation and ventilation in pediatric patients. A recent retrospective study on nontraumatic out-of-hospital pediatric cardiac arrest found improved survival to hospital discharge among children who received BMV by emergency medical services (EMS) compared to children who received either endotracheal intubation or supraglottic device (SGD).[20] Additionally, a study of children with in-hospital cardiac arrest found no difference in survival to hospital discharge among children receiving either ETI or BVM.[21] Alternative strategies to manage the airway when intubation cannot be accomplished using traditional techniques include SGDs or optical approaches to improve glottic visualization.[22,23] SGDs have been demonstrated to be a reliable way to establish oxygenation and gas exchange in the normal and difficult pediatric airway, as well as during resuscitation. First-generation devices have been used in anesthesia for decades. Newer, second-generation devices often include a channel that allows gastric decompression. In addition to the gastric channel, some current SGDs have alternative construction that may be advantageous in pediatrics.[24] For example, the Air-Q does not have aperture bars and uses a shorter wider tube to allow passage of an ETT through the lumen. The I-gel uses a thermoplastic elastomer that molds to the airway as it warms from body temperature. This allows a tighter seal and avoids complications related to cuff hyperinflation.

In most cases, SGDs are easily and rapidly placed, with more than 90% success rate on first attempts; devices sized for neonates and young infants are the most difficult to place. Placement technique is similar to adults with two potential differences: (1) some studies have demonstrated improved placement success and fewer complications when using a rotational approach with traditional laryngeal mask airways (LMAs); and (2) insertion of the SGD with the cuff partially inflated may facilitate placement and help it mold to the shape of the pharynx. SGDs are available in all sizes from neonatal to adolescent ages but data are limited on their use in emergency settings. The Combitube is not recommended for those under 4 feet tall.[25,26]

Pharyngeal sealers, also called *esophageal blockers,* are double-balloon devices in which the tip is placed into the upper esophagus, and ventilation occurs between one balloon occluding the proximal esophagus and another occluding the airway above the glottis. In small children, laryngeal tubes (and laryngeal mask airways) may cause folding of the epiglottis, leading to iatrogenic airway obstruction and

significant air leaks, requiring repositioning or another modality to secure the airway.

A number of pediatric devices beyond video laryngoscopes are available to facilitate visualization and intubation in cases of difficult airways. Flexible fiberoptic scopes can be effective, although extensive experience is required, and young children may not be cooperative with awake approaches. This approach is most commonly used by anesthesia or otorhinolaryngology, often in the operating room. Similarly, fiberoptic stylets are available in pediatric sizes to facilitate visualization with intubation. As with video laryngoscopes, gaining experience with the technique for a given device prior to use in the stressful scenario of a difficult or failed airway is critical.

Pediatric Surgical Airway Techniques

In the rare case of the "can't intubate, can't ventilate" child, a surgical airway represents the final airway option. This can occur if direct/video laryngoscopy has failed and the emergency clinician is unable to maintain oxygenation and ventilation via BMV or a rescue device, such as an SGD. In this case, direct access to the airway through the neck is the only option. Surgical techniques are challenged by limited optimal visualization or palpation of anatomic landmarks in infants and young children; therefore, we recommend needle cricothyrotomy in these children.

Experience in surgical airway techniques is limited in small children, with most of the published literature representing case reports, operating room experience, or animal studies. Needle-based rescue procedures should be considered an "oxygenation" strategy rather than a "ventilation" strategy, because progressive hypercarbia will inevitably ensue, limiting the utility of this technique for long-term use. Animal models suggest that a needle cricothyroidotomy will provide approximately 30 to 45 minutes of adequate oxygenation.

To perform a needle cricothyroidotomy, the provider places a large needle catheter (e.g., 14-gauge) through the anterior neck into the airway, ideally entering through the cricothyroid membrane. However, difficulty identifying landmarks by palpation or even ultrasound in young children with short, adipose-rich necks may make determination of the exact level of airway entry difficult. The needle is then removed, and the catheter can be connected to the adaptor from a 3.0-mm ETT, which is then connected to a standard bag device. If a 3.0-mm ETT is not available, an adaptor from a 7.0-mm ETT can be placed into a 3-mL syringe with the plunger removed; this can then be attached directly to the catheter. The bag is then squeezed to provide oxygen delivery, allowing prolonged time between breaths for the passive exhalation phase. Alternatively, commercially available oxygen tubing set-up (e.g., ENK modulator, Cook Inc.) can be used with oxygen flow set at 1 L/min for every year of age. These techniques are preferred to true "jet" ventilation, which uses a much higher-pressure oxygen source and has a greater potential for iatrogenic injury. Open surgical cricothyrotomy or percutaneous Seldinger-based cricothyrotomy, performed in the same way as in an adult, is reserved for children *in whom anatomic landmarks can be found* and in whom the cricothyroid membrane is larger. The literature does not support a specific age cutoff for needle cricothyrotomy versus surgical cricothyrotomy, but needle cricothyrotomy should be performed when indicated in infants and small children (<6 years of age or older depending on anatomic landmarks).

OUTCOMES

The majority of pediatric intubations performed in the ED are successful. Despite the relative rarity of the procedure, there is significant overlap in the techniques and strategies used in adult airway management. There are a limited number of anatomic and physiologic differences that can be learned and mastered. The cognitive burden associated with the procedure can be overcome by length/size-based systems or readily available electronic applications to allow the clinician to focus on the critical actions necessary to successfully manage the airway.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 156: QUESTIONS AND ANSWERS

1. Which of the following is a correct formula for use in airway management of children?

- **a.** Cuffed ETT size (1 to 10 years old) = 4 + (age in years/2)
- **b.** ETT depth = 3 × ETT size
- **c.** ETT depth = 4 × ETT size
- **d.** Uncuffed ETT size (1 to 10 years old) = (16/age in years) + 4

Answer: B. Correct formulas are as follows:

Uncuffed ETT size = 4 + (age in years/4)

Cuffed ETT size = subtract 0.5 from formula for uncuffed ETT; (4 + (age in years/4)) − 0.5

ETT depth = 3 × uncuffed tube size

2. Which of the following should be used for proper positioning of the pediatric patient during endotracheal intubation?

- **a.** The chin should be tilted and the head lifted.
- **b.** The infant younger than 6 months old should have a towel roll placed under the occiput to align the airway axes.
- **c.** The neck should be placed in slight flexion and the shoulders extended.
- **d.** The patient should be positioned so that a line drawn through the external auditory canal and the anterior shoulder is parallel to the bed.

Answer: D. The relatively large head and occiput of the infant results in slight flexion at the neck when supine, impeding the ability to visualize the glottis. The infant is correctly positioned so that a line drawn through the external auditory canal and the anterior shoulder is horizontal and parallel to the bed. In the infant (<6 months old), this is accomplished by placing a towel roll under the patient's shoulders, elevating the body and overcoming the flexion associated with their large occiput. A head tilt–chin lift may open the airway.

CHAPTER 156: QUESTIONS AND ANSWERS—cont'd

3. Relative to rapid sequence intubation (RSI) in adults, children undergoing RSI:
   - **a.** Are less affected by stomach pressures.
   - **b.** Are more likely to develop bradycardia in response to hypoxia.
   - **c.** Have less missed intubations.
   - **d.** Have less pliable airways.
   - **e.** Maintain their oxygen saturations longer after paralytics are administered.

Answer: B. Children have a higher metabolic rate and thus a higher oxygen demand. In the absence of respiratory support, children will drop their oxygen saturations more quickly than adults due to their relatively greater consumption of oxygen. Hypoxia is the most common reason for bradycardia during intubation in children. The more pliable pediatric thorax combined with children's lower ventilatory reserve make stominflation a significant impediment to effective respiratory support. Pediatric intubations are infrequent and multiple pediatric intubation attempts are more common in children than in adults.

4. Which of the following does *not* characterize the pediatric airway relative to adults?
   - **a.** A straight blade is used to pick up the floppy epiglottis.
   - **b.** Infants may require a shoulder roll to align airway axes.
   - **c.** The airway is more pliable.
   - **d.** The airway is more superior and posterior.
   - **e.** The epiglottis is larger and omega-shaped.

Answer: D. Small infants have a large occiput and a high, anterior airway, which impacts positioning during intubation, often requiring a shoulder roll to align airway axes. The airway is also more pliable and the membranes thinner, necessitating needle cricothyroidotomy for surgical airways in children younger than 10 years old. Blade choice is age dependent, and a straight blade is recommended in young children; this blade lifts the relatively larger epiglottis to visualize the vocal cords.

5. Following the administration of succinylcholine in a 7-year-old boy with respiratory distress, severe masseter spasm is noted. Which of the following medications should be administered to terminate this spasm?
   - **a.** Diazepam
   - **b.** Fentanyl
   - **c.** Repeated dose of succinylcholine
   - **d.** Rocuronium
   - **e.** Thiopental

Answer: D. Masseter muscle spasm is a rare side effect of succinylcholine administration. It primarily occurs in pediatric patients and is typically terminated by the administration of a competitive neuromuscular blocking agent (NMBA), such as rocuronium, vecuronium, or pancuronium. Failure to respond to such therapy should prompt consideration of malignant hyperthermia.

Pediatric Sedation and Analgesia

Huma Shaikh and Corrie E. Chumpitazi

KEY CONCEPTS

- Patients of all ages experience pain, including infants, neonates, and premature babies.
- Oligoanalgesia, the inadequate treatment of pain, has many short-term and long-term consequences: worse patient outcomes, increase in patient's pain threshold, and development of chronic pain.
- Pain management may include a combination of techniques: analgesics, topical anesthetics, local anesthetic injections, oral sucrose in infants, and nonpharmacologic interventions.
- Nonpharmacologic interventions to decrease pain or anxiety include parental presence; physical measures, such as heat or cold therapy and splinting for musculoskeletal injuries; and behavioral or cognitive measures, such as distraction and play therapy.
- Topical anesthetics are recommended to decrease the pain of minor procedures, such as venipuncture or IV cannulation.
- Techniques for decreasing the pain of intradermal injections include topical agent prior to the intradermal injection; slowly injecting warmed, buffered local anesthetic solution from within the wound with the smallest gauge needle possible; and limiting the number of needle punctures.
- When using large amounts of local anesthetics in small children or infants, calculate the drug dose to avoid toxicity; a 1% solution = 1 g/100 mL or 10 mg/mL.
- Procedural sedation and analgesia (PSA) requires pre-sedation evaluation; sufficient monitoring (during and after the procedure) by qualified individuals capable of dealing with any adverse events that may occur; age-appropriate equipment (including airway equipment) and medications (including reversal agents and advance life support drugs); and discharge criteria for when the patient is fully awake, returns to baseline with normal vital signs, and is able to be discharged in the care of a responsible adult.
- Overall, preprocedural fasting is not necessary for most emergency patients, because large studies show no clinically significant differences with airway complications, emesis, or other adverse effects between groups of patients stratified by their preprocedural fasting status.
- Choice of sedative and analgesic for PSA depends on many variables including patient factors and the procedure to be done. Slow titration of medications can achieve the desired level of sedation and analgesia while minimizing risk of adverse events.

SEDATION

Foundations

Sedation is a controlled reduction of environmental awareness. Sedation is a continuum that begins with minimal, moving to moderate, then deep sedation, and may proceed to general anesthesia.

Definitions[1,2]

- *Anxiolysis* is a state of decreased apprehension concerning a particular situation in which the patient's level of awareness does not change.
- *Analgesia* refers to the relief of pain without the intentional alteration of mental status, such as occurs in sedation. An altered mental state may be a secondary effect of the medications administered for this purpose.
- *Minimal sedation* (e.g., anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive functions and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- *Moderate sedation/analgesia* (formerly called "conscious sedation") refers to a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. Reflex withdrawal from the painful stimulus is NOT considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
- *Dissociative sedation* is a trancelike cataleptic state induced by the dissociative agent ketamine and characterized by profound analgesia and amnesia, while protective airway reflexes, spontaneous respirations, and cardiopulmonary stability are maintained.
- *Deep sedation/analgesia* describes a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
- *General anesthesia* is a drug-induced loss of consciousness during which patients are not arousable, even with painful stimulation. The ability to independently maintain ventilatory function is usually impaired. Patients require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.
- *Procedural sedation and analgesia (PSA)* are techniques of administering a sedative or dissociative agent, usually along with an analgesic, to induce a state that allows the patient to tolerate painful or unpleasant procedures while maintaining adequate spontaneous cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously.

The goal of PSA is to alleviate the anxiety, pain, and suffering associated with medical procedures. PSA is an essential part of emergency medicine practice and part of the core curriculum for emergency medicine training programs. Providers should be prepared to appropriately manage the airway and in rare instances intubate if sedation becomes deeper than expected.

Specific Issues

Preparation

The patient's American Society of Anesthesiology (ASA) physical status classification should be calculated prior to procedure (Table 157.1) and airway assessed, for example, using the Mallampati score (see Chapter 1) to identify potential difficulties. Children with special needs, anatomic airway abnormalities, moderate to severe tonsillar hypertrophy, and current or recent upper respiratory illness present increased risk and require additional consideration.[1,3] ASA classes I and II are considered appropriate candidates for minimal, moderate, or deep sedation.[1–3] Staff are encouraged to consult with appropriate subspecialists (e.g., pediatric anesthesiologist) if there is a question of sedation adverse events because of an underlying medical/surgical condition (e.g. Pierre Robin syndrome). Those aged less than 3 months or with weight less than 5 kg are at increased risk for sedation adverse events.

There should be at least one provider, in addition to the provider performing the procedure, who is responsible to monitor appropriate physiologic parameters and assist in any needed supportive or resuscitation measures.[1–3] Pulse oximetry and capnography readings should be continuously monitored; depth of sedation, heart rate, blood pressure, and respiratory rate should be recorded at regular intervals. Although there are scales for assessing the depth of sedation in pediatric patients, continuous monitoring is more important than any specific measurement on a sedation scale. Although there is no evidence of benefit in young healthy individuals, cardiac monitoring has been shown useful in those with a cardiac history and older patients. Thus, we recommend continuous cardiac rhythm monitoring, especially for high-risk patients (e.g., preexisting cardiovascular disease or a history of dysrhythmias) or high-risk procedures (e.g., cardioversion).

Providers administering pediatric procedural sedation should have training and skills in airway management and be ready to rescue the patient from a deeper level than intended for the procedure, since it is common for children to pass easily into a deeper level of sedation. In addition to monitoring equipment and oxygen, age-appropriate suction, bag-valve-mask, and intubating equipment should be available and readied prior to administering medications. The SOAP-ME mnemonic provides an equipment checklist for sedation[3]:

Size-appropriate suction catheters (connected, checked, and with suction turned on)

Oxygen supply (connected to bag and turned on)

Airway: Size-appropriate airway equipment (appropriate size mask and intubation supplies)

Pharmacy: Advanced life support medications and antagonists

Monitors: Size-appropriate oximeter, end-tidal carbon dioxide monitor, and blood pressure cuff

Equipment or drugs for a particular case

Children over age 4 can benefit from simple information about what to expect for their procedure. Explaining the steps, as well as what they might see or feel, being shown the medical supplies (e.g., irrigation solution), and offering realistic options for their procedure help them feel in control. Similarly, parents should be prepared for where to sit and how they can assist with positioning or distraction. A child's ability to control behavior and cooperate for a procedure depends on chronologic age and cognitive/emotional development.

TABLE 157.1 American Society of Anesthesiologists Physical Status Classification

Class	Description	Examples	Sedation Risk
I	Normal and healthy patient	No past medical history	Minimal
II	Mild systemic disease without functional limitations	Mild asthma, controlled diabetes	Low
III	Severe systemic disease with functional limitations	Pneumonia, poorly controlled diabetes mellitus, hypertension or seizure disorder	Intermediate
IV	Severe systemic disease that is a constant threat to life	Advanced cardiac disease, renal failure, sepsis	High
V	Moribund patient who may not survive without procedure	Septic shock, severe trauma	Extremely high
VI	A declared brain-dead patient whose organs are being removed for donor purposes		

Preprocedural Fasting

The ASA has guidelines for preoperative fasting in healthy patients of all ages undergoing elective procedures. In patients undergoing PSA in the emergency department (ED), the evidence indicates that preprocedural fasting does not decrease the risk of emesis or aspiration, as noted in the American College of Emergency Physicians (ACEP) clinical policy.[1,2] Recent studies in pediatric patients do not find any evidence of association between vomiting and shortened fasting time, and no patients were found to have aspiration.[4] Therefore, adherence to the ASA preoperative fasting guidelines for procedures is not necessary in ED patients undergoing PSA.

Supplemental Oxygen and Capnography During Procedural Sedation and Analgesia

Use of supplemental oxygenation has been shown to decrease the incidence of desaturation in pediatric patients from 17% to 10%, although it may delay the recognition of hypoventilation or apnea. Oxygen desaturation and delay in assisted ventilation events can be significantly reduced with the use capnography.[5] Close capnography monitoring can detect hypoventilation early, prior to a drop in pulse oximetry, irrespective of use of supplemental oxygen.[3] ACEP and AAP clinical policy recommend capnography be routinely used to monitor ventilation in children undergoing PSA.[1–3]

Specific Medications

Table 157.2 details specific PSA sedative agents commonly used in infants and children. Patient age, preexisting conditions, and anticipated level of pain or anxiety should guide choice of sedative. Providers should administer drugs by slow intravenous (IV) titration to decrease the risk of adverse events, including hypotension and respiratory depression. For intranasal medications or nitrous oxide use, employing a Child Life specialist or the parents to assist with

TABLE 157.2 Commonly Used Sedatives for Procedural Sedation in Children and Infants

Sedative[a]	Route	Dose[b]	Usual Dose[c]	Maximum Dose	Onset	Duration	Side Effects	Advantages/Comments[a]
Dexmedetomidine	IN	2–4 mcg/kg/dose	3 mcg/kg/dose	200 mcg (100 mcg/nare)	30 min	60–90 min	Decreased HR and BP	Contraindication with heart block, severe renal or hepatic impairment or use of beta blockers
Etomidate	IV	0.1–0.3 mg/kg	0.2 mg/kg PSA	0.4 mg/kg	<1 min	3–10 min	Pain on injection, myoclonic movements, adrenal insufficiency (prolonged use)	Minimal CV/respiratory depression
Ketamine[d]	IV	1–2 mg/kg initial (repeat 0.5–1 mg/kg for longer procedures)	1.5 mg/kg initial PSA		1 min	15 min	Sympathomimetic effects (↑HR, ↑BP) Nausea, vomiting Emergence reaction Laryngospasm (rare)	Warn parents of nystagmus as an expected effect. Has analgesic effect CV/respiratory stability bronchodilator (use in asthmatics) Battlefield use/disasters
Ketamine	IM	4 mg/kg	4 mg/kg 2 mg/kg if <2 years old		5 min	30 min	(Same as above) Higher risk of nausea	(Same as above)
Ketamine	IN	3–9 mg/kg			10 min	60 min	(Same as above)	(Same as above)
Midazolam[e]	IV	0.05–0.1 mg/kg (6 months to 5 years old or adult) 0.025–0.05 mg/kg (≥6 years old) Give slowly 1–2 mg over ≥ 2 min and titrate to effect	If giving with fentanyl, may dose at 0.02 mg/kg	0.6 mg or 6 mg if ≤5 years old and 10 mg if >6 years old	5 min	30 min	Paradoxical agitation, vomiting, coughing, hiccups, dizziness, respiratory depression, apnea so use lower dose if given with opioids or respiratory depressants	Protective in seizure patients ↓ ICP, CBF, ↓ LV filling pressure may benefit cardiac patients Mild CV effects unless hypovolemic Reversed by antagonist flumazenil
Midazolam	IN	0.2–0.5 mg/kg	0.2 mg/kg	10 mg	<10 min		(Same as above)	(Same as above)
Pentobarbital[f]	IV	1–6 mg/kg	1–2 mg/kg initial, repeat 3–5 min to desired effect or max dose	100 mg/dose	1–2 min	15–60 min	CV/respiratory depression, paradoxical agitation, extravasation can cause tissue necrosis Contraindication: Porphyria	↓ IOP, ↓ ICP , used to treat status epilepticus Use in head injury/neurology patients Can use if malignant hyperthermia

Propofol	IV	0.5–1.5 mg/kg (repeat 0.5 mg/kg every 3–5 min for longer procedures)	Variable, may be 1 mg/kg	None	<1 min	5–15 min (mean 8 min)	CV/respiratory depression Use with caution if shock/low BP/impaired cardiac function Caution if allergy to eggs, soybean oil, EDTA[g]	Rapid onset/recovery No dose change if renal or liver disease Can use if malignant hyperthermia
Nitrous oxide	Inhalation	Dose is 30%–70% mixture	Commercially available in 50%:50% mixture	70%	1–2 min	15–20 min	Contraindications: Trapped air (bowel obstruction, pneumothorax, emphysema, air emboli)	Need a scavenger system and proper ventilation, potential for abuse, chronic exposure may have adverse effects

[a]Other agents used for sedation, e.g., DPT (meperidine [Demerol], promethazine [Phenergan], and chlorpromazine [Thorazine]) IM should be avoided because there are better, newer agents for sedation with fewer side effects. Chloral hydrate has been used in the past but is used infrequently at present because there are other better options.

[b]Doses will vary with the individual patient; these are some generally recommended starting doses. Some patients will need greater than the typical maximum dose, whereas others may be sedated with less than the usual dose. It is best to titrate the dose in all patients.

[c]Be especially cautious in at-risk patients. At-risk patients include those patients with significant heart disease, including heart failure or pulmonary hypertension, liver disease, renal failure, and patients at the extremes of age (infants, particularly neonates and the geriatric patient). It may be prudent in these patients, to "start low and go slow."

[d]Ketamine's effect on ICP is discussed in the text. Previously ketamine was thought to be contraindicated if there was an increase in ICP. However, recently, this concept has been challenged. If ketamine is given PO or PR, higher doses are needed with less predictable effect and increased side effects so PO and PR routes are not recommended.

[e]Midazolam may be given by several routes including IV, IM, IN, PO, and PR. The PO and especially PR routes of administration have more variable absorption and effects, so they are not commonly used.

[f]Pentobarbital can be given PO or PR or IM, but onset and duration are longer with more variable effect, so IV is preferred.

[g]Although the manufacturer's labeling lists egg allergy as a contraindication, available studies (mostly retrospective) and an American Academy of Allergy, Asthma, and Immunology statement have suggested that propofol may be used safely in soy- or egg-allergic patients (AAAAI [Lieberman 2015]; AAAAI 2019; Asserhoj 2016; Dziedzic 2016; Murphy 2011). In patients with more severe soy or egg allergy, some experts recommend the use of an alternative anesthetic or a small trial dose of propofol prior to full dose administration (Sicherer 2020).

BP, Blood pressure; *CBF,* cerebral blood flow; *CV,* cardiovascular; *EDTA,* ethylenediaminetetraacetic acid; *HR,* heart rate; *ICP,* intracerebral pressure; *IM,* intramuscular; *IN,* intranasal; *IOP,* intraocular pressure; *IV,* intravenous; *LV,* left ventricular; *PO, per oz.* (by mouth); *PR,* per rectum; *PSA,* procedural sedation and analgesia; *RSI,* rapid sequence intubation.

distraction, music, or other cognitive behavioral modalities may be advantageous.

Propofol. Propofol has several advantages for PSA; it has a rapid onset in 30-60 seconds, is short acting, and has antiemetic properties. Its side effects include hypotension and respiratory depression. However, studies have shown safe administration in the ED for sedation by physicians who are skilled in airway management and resuscitation of patients that may enter deeper sedation or respiratory distress.[6] Although the dosing of propofol varies from 0.5 to 2 mg/kg, an initial dose of 0.5 to 1.0 mg/kg should be administered and titrated to effect with additional doses, usually in increments of 0.5 mg/kg.

Ketamine. Ketamine, a dissociative anesthetic, has sedative, amnestic, and analgesic properties. Ketamine maintains cardiovascular and respiratory stability, has minimal respiratory depression, and maintains protective airway reflexes in patients with spontaneous respirations. Ketamine's sympathomimetic effects include increased blood pressure, heart rate, cardiac output, and bronchodilation, making it the preferred sedative in patients with asthma.

Apnea is rare with ketamine (0.8% incidence), but has been associated with very high doses, rapid administration, and co-administration with narcotics or other respiratory depressants. Ketamine increases salivary secretions, which may increase the incidence of laryngospasm, especially in oral procedures; however laryngospasm can typically be resolved with simple airway maneuvers.[7] Laryngospasm is usually transient and responds to repositioning of the head, supplemental oxygen administration, gentle suctioning if secretions are the irritant, and positive pressure ventilation with a bag-valve mask. Although rarely needed, the use of a paralytic at lower doses than required for intubation (e.g., succinylcholine given at 10% of a paralytic dose) has been shown to break laryngospasm when the above measures fail. Rapid sequence intubation is rarely needed, but a last resort option to treat laryngospasm.

Ketamine may be given intravenously, intramuscularly, per os (by mouth; PO), or intranasal (IN). For IV administration in pediatric patients, initial doses range from 1.0 to 2.0 mg/kg, with further bolus doses of 0.5 to 1 mg/kg titrated to desired effect. Intramuscular (IM) dosing is an option when IV access is unobtainable; dosing ranges from 4 to 5 mg/kg. The disadvantages of IM ketamine include a higher rate of vomiting, longer recovery time, and lack of IV access in the event of complications requiring IV medication administration (e.g., paralytics). IN ketamine can be used in dosing ranges from 3-9 mg/kg/dose with onset of action between 5 and 10 minutes. As with all intranasal medications, the optimal intranasal dose per nare is 0.5 to 1 mL.[8]

Use of Ketamine in Patients With Head Injury. Multiple studies have dispelled the myth that ketamine increases intracranial pressure (ICP). Ketamine may even have beneficial effects on the brain, including protection against seizures, cerebral ischemia, and secondary brain injury related to hypotension.[9]

Ketamine Recovery Agitation: Use of Benzodiazepines. Emergence reaction or recovery agitation refers to agitation (which may include floating sensation, vivid pleasant dreams, nightmares, hallucinations or delirium) that can occur after waking up or emerging from ketamine. Pediatric studies have not demonstrated benefit in routine use of benzodiazepines to prevent recovery agitation, likely due to their own adverse effects; although rare, they can cause paradoxical agitation. A large pediatric study showed no significant difference in the report of agitation in patients receiving ketamine and benzodiazepine versus ketamine alone.[10] As no pediatric studies to date have shown benefit, we do not recommend that midazolam be routinely given as an adjunct to ketamine in children. However, when recovery agitation occurs, children can be treated with midazolam (0.03 mg/kg; up to a maximum of 5 mg for ages 6 months to 5 years old, or a maximum cumulative dose of 10 mg for children greater than 5 years old).

Emergence reactions occur more frequently in patients greater than 16 years of age, females, shorter operative procedures, large doses, and individuals with psychiatric disorders. Providers should consider an alternate agent or ketamine plus midazolam for older teens and children with psychiatric illness; schizophrenia is an absolute contraindication. Children typically emerge from the sedated state in the format that they achieve sedation; all children, but teenagers especially, may benefit from the use of positive visualization, music, massage, or other distraction techniques in preparation for sedation.

Use of Anticholinergics With Ketamine. Ketamine stimulates tracheobronchial and salivary secretions. However, studies have shown that the co-administration of anticholinergic medications is associated with an increase in the odds of adverse events.[9] Providers may consider anticholinergics for children undergoing an airway examination (e.g., fiberoptic laryngoscopy) to improve visibility, or in patients with clinically significant hypersalivation or an impaired ability to mobilize secretions, but it should not routinely be used.

Glycopyrrolate is the preferred anticholinergic over atropine; it is a more potent anti-sialagogue and has fewer tachy-dysrhythmias. Unlike atropine, glycopyrrolate does not cross the blood brain barrier, so has no central nervous system (CNS) side effects. CNS side effects of atropine range from drowsiness to coma and include headache, nervousness, insomnia, excitement, dizziness, disorientation, hallucinations, and ataxia. Headache is the only CNS side effect listed for glycopyrrolate.

Use of Antiemetics with Ketamine. Vomiting with ketamine sedation in children is common.[10] Vomiting usually develops during recovery, when patients are alert and can clear their airways. Slow IV administration over several minutes may mitigate this response. Risk is higher among adolescents and patients receiving high doses or IM administration. Although ondansetron is associated with a small decrease in the incidence of vomiting associated with ketamine sedation in children, ondansetron is also associated with other adverse effects, including QT prolongation and serotonin syndrome. We recommend reserving treatment with ondansetron for patients who develop nausea or vomiting during recovery from ketamine.

Ketofol: Ketamine Plus Propofol. The combination of ketamine with propofol has the potential to provide benefits of both sedatives. The combination allows for lower doses of each medication, which may theoretically minimize adverse effects of either sedative alone. The incidence of hypotension from propofol alone has been shown to be lessened when combined with ketamine.[10,11] However, studies have not shown significant differences in rates of respiratory depression between co-administration versus either sedative alone.[10–12]

Ketamine and propofol (ketofol) can be dosed at 0.5 mg/kg to 0.75 mg/kg for each drug via separate syringes. For short procedures, re-dosing is usually not needed. For longer procedures, if the sedation is wearing off, propofol is usually re-dosed (due to its shorter half-life) at 0.1 to 0.5 mg/kg IV.

Dexmedetomidine. Dexmedetomidine is an effective sedative, anxiolytic and analgesic that does not cause respiratory depression.[13]A loading dose poses the risk of bradycardia and hypotension due to α_2-agonist effects on the sympathetic ganglia.[13] Lack of amnesia can be a concern in certain situations, however, this can be managed with the addition of low dose benzodiazepines. Use of dexmedetomidine in addition to propofol has been shown to decrease cardiovascular, respiratory, and agitation-related adverse effects.[14] Dexmedetomidine can be used intranasally at 2 to 3 mcg/kg/dose (max 100 mcg/nare). An additional 1 mcg/kg/dose may be administered in 30 minutes (max cumulative dose 4 mcg/kg). Contraindications include heart block, severe renal or hepatic impairment, or use of a beta blocker.

Nitrous Oxide

The use of inhaled nitrous oxide in the pediatric emergency setting has been well established for mildly painful or distressing procedures. Although the exact mechanism of action is not known, sedation is likely achieved due to a noncompetitive inhibition of the NMDA-receptor and analgesia via central opioid and opioid-like receptors. Concentrations between 50% and 70% are commonly used, with best effect to side effect ratios seen with inhalation times less than 30 minutes. The combination of inhaled nitrous oxide and IN fentanyl obviates painful and time-consuming IV access insertions and delivers a short recovery time.[15] Another study in a pediatric emergency department found fewer adverse reactions and lower length of stay in patients treated with inhaled nitrous oxide and IN fentanyl, as compared to ketamine and midazolam, with no difference in efficacy between groups.[16]

Post-Sedation Monitoring

Once the procedure is complete and the painful stimuli are removed, patients are at risk of hypoventilation or hypoxia. Monitoring should continue until the patient has met predetermined discharge criteria, which should include normal vital signs and baseline mental and physical status. Once fully awake, patients should be discharged to the care of a responsible adult. Patients should receive predeveloped age-appropriate PSA discharge instructions.

Outcomes

Adequately treating anxiety and pain results in greater procedural success rates; improved patient and caregiver satisfaction; decreased likelihood of the patient developing chronic pain; and improved patient outcomes. Patients at increased risk of adverse events during PSA include the following: the very young or very old; those with comorbidities (e.g., cardiopulmonary diseases) or craniofacial abnormalities (e.g., Down syndrome and Pierre Robin syndrome); the morbidly obese; and those with a higher ASA physical status classification (see Table 157.1).

PAIN MANAGEMENT

Foundations

Pain is defined as an unpleasant visceral or somatic experience or sensation associated with actual, potential, or perceived tissue damage. Pain receptors, termed *nociceptors,* are the free nerve endings of a sensory neuron that convert mechanical, thermal, or chemical stimuli into electrical activity, and initiates an impulse that travels along the neuron and then on to the dorsal horn of the spinal cord (Fig. 157.1). Input from various peripheral nerves and additional sensory stimuli are processed, undergoing integration and modulation in the dorsal horn of the spinal cord, and then transmitted up the spinal cord to the CNS (Fig. 157.2).

There are two types of pain: nociceptive or neuropathic. Nociceptive pain occurs when tissue injury or inflammation stimulates intact pain receptors. Nociceptive pain can be further divided into visceral pain (i.e., of internal organs) and somatic pain (i.e., of the skin, soft tissue, and musculoskeletal structures). Neuropathic pain occurs when there is abnormal functioning or stimulation of damaged sensory nerves. Children with severe developmental impairment may have central neuropathic pain or pain secondary to visceral hyperalgesia.

Neuropathic pain is typically burning, searing, tingling, shooting, or electric in quality. Nociceptive somatic pain is generally described as sharp and well localized. However, pain in deeper structures (e.g., bones, joints, or tendons) can cause achy, diffuse, or radiating pain. Nociceptive visceral pain is typically poorly localized, deep, and aching. Chronic pain is a maladaptive response in which the pain persists after the original injury or illness has resolved.

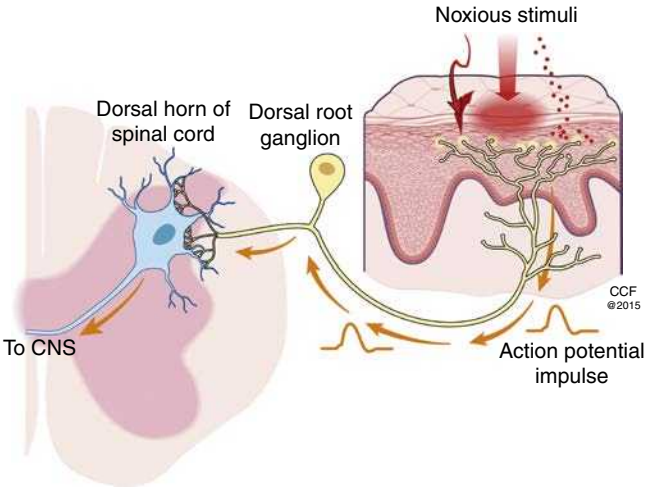

Fig. 157.1 Nociceptors. *CNS,* Central nervous system. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

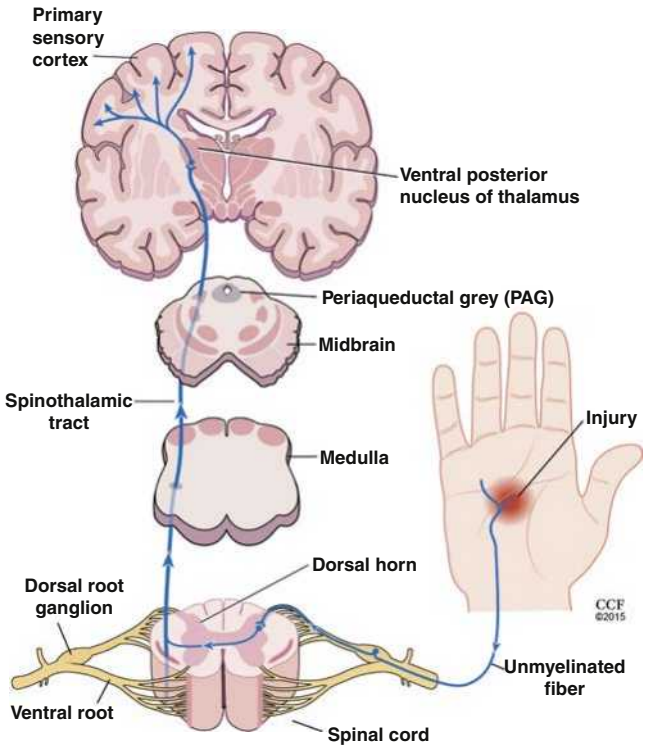

Fig. 157.2 Pain Pathway. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

Specific Issues

Pain Assessment

Patient self-report is the most accurate measure of pain severity. Pain assessments can be used to guide pain management. Pain scales should be age-specific; subjective or self-reporting scales can start being used at 3 years of age, depending on developmental level. Children younger than 3 years old do not have the cognitive or verbal skills needed to communicate levels of pain and, thus, require behavioral or psychological pain scales. Behavioral pain scales rely on the observation of specific child or infant behaviors. Some of the parameters used in behavioral pain scales include facial expressions, consolability, interaction level, limb responses, trunk motor responses, and verbal

responses. Behavioral and physiologic pain scales combine behavioral observations and physiologic parameters (e.g., vital signs) to obtain a score.

The numeric rating scale (NRS) and the visual analogue scale (VAS) are commonly used self-report scales that have been found to have reliability and validity. With the VAS, patients are asked to place a mark on a 10-cm line with descriptors along the line. With the NRS, patients are asked to rate their pain severity on a scale from 0 to 10 or 0 to 100, with 0 being no pain and 10 or 100 the worst pain possible. Horizontal lines are preferred rather than vertical lines because scores are more normally distributed. Patients with poor hand-eye coordination, visual acuity or hand dexterity have difficulty completing the VAS.

As noted, the use of pain scales is based on age. Adolescents and adults can rate their pain using an NRS or VAS. Older children (8 to 11 years old) can also use an NRS or VAS. Younger children (3 to 8 years old) can quantify their pain using a faces pain scale, most commonly, the Faces Pain Scale–Revised (FPS-R)[17]. The Premature Infant Pain Scale (PIPP) is used to assess pain in premature infants. The Crying, Requires oxygen, Increased vital signs, Expressions, and Sleeplessness (CRIES) scale is for infants. The Faces, Legs, Activity, Cry, Consolability (FLACC) pain scale can be used for infants and toddlers. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and the Observational Scale of Behavioral Distress (OSBD) may be used for toddlers and young children.

Nonverbal children with neurological impairment, irrespective of age, cannot self-report their pain. The child's caregiver generally knows his or her typical behavior patterns, both at baseline and in response to stimuli or needs. Behaviors that may indicate pain include facial expressions (e.g., grimacing), vocalizations (crying or moaning), inconsolability, increased movement, increased tone or posture (e.g., stiffening or arching), and uncharacteristic or atypical behaviors (e.g., withdrawal, lack of expression, or even laughing). The revised FLACC (r-FLACC) scale is one pain scale designed for use in children with cognitive impairment.

We recommend that all patients have a pain assessment and that the FLACC scale be used in infants to age 3 years of age and those with developmental delay and nonverbal of any age, the FPS-R scale be used in children 3 to 8 years of age, and the NRS used in children 8 years of age or older.

Nonpharmacologic Techniques

Nonpharmacologic interventions should be routinely used with pharmacologic therapy for pain management; this includes physical comfort measures and distraction techniques. Patients should be given basic first measures, including the application of splints or immobilization to stabilize fractures and dislocations; cold packs can help reduce swelling and provide topical analgesia. Hypnosis is accepted by the American Medical Association as a medical therapy and has been used to treat anxiety, as well as acute and chronic pain. Children may be more easily hypnotized compared to adults. Studies indicate that hypnosis is efficacious in pediatric patients for painful medical procedures, headaches, sickle cell disease, chronic pain, and even in cancer treatment.[18] In non-ED settings, acupuncture and acupressure has also been used as a nonpharmacologic method for pain management.

Techniques that distract from pain should be tailored to patients based on their age and developmental stage.[19] Younger children may not yet comprehend verbal reassurance, and thus benefit more from distraction techniques. Distractions include playing games, blowing bubbles or looking at books. Older children can use music, video games, cartoon videos, and books to distract from pain and reduce anxiety. Preliminary research suggests that the high-tech virtual reality that uses multiple sensory inputs may be effective in decreasing pain.

Educated in human growth, development, and psychology, Child Life specialists are invaluable team members of any pediatric ED. Child Life specialists help children effectively cope with illness or injury and the emotional stressors of healthcare and hospitalization through play, preparation, education, and distraction. A study of children undergoing suturing in the ED found that having a Child Life specialist involved lessened the emotional distress for children.[20] Child Life services have resulted in lower self-reported pain in children receiving peripheral IV placement and greater family satisfaction with the ED visit.[21]

Perhaps one of the most important and common nonpharmacologic methods for limiting the anxiety and pain of the child or infant is parental presence during the procedure. Techniques used in infants include nonnutritive sucking, breastfeeding, skin-to-skin contact (kangaroo care), and oral sucrose. Skin-to-skin care is a safe, effective measure to reduce distress in term and preterm neonates based on composite pain scores. Sucrose water (2mL of 25% glucose solution) administered by pacifier or oral syringe has been shown to effectively decrease pain in infants 3 months old and younger undergoing painful procedures. To optimize pain reduction and recovery in infants, a combination of interventions should be used before, during, and after painful procedures.

Pharmacologic Techniques

Topical Anesthetics. Used in conjunction with other methods for decreasing pain, topical anesthetics may decrease the need for systemic analgesics or local anesthesia. Topical anesthetics can be used for venipuncture, IV cannulation, minor surgical procedures, wound care, suturing, and lumbar puncture. Topical anesthetics are painless to apply and do not distort tissue (e.g., for cosmetically important facial lacerations). Needleless, they also avoid the risk of needle sticks.

Different topical anesthetics can be used on intact skin or broken skin (Table 157.3), as well as mucosal surfaces. Vasoconstrictors, such as epinephrine, increase anesthetic efficacy and duration of effect. While traditionally not used at an end-arteriolar blood supply (e.g., fingertip), the risk of irreversible ischemia is very low. Common formulations used for intact skin (e.g., prior to venipuncture) are eutectic mixture of local anesthetics (EMLA), liposome encapsulated lidocaine (LMX), and vapo-coolants. Lidocaine, epinephrine (adrenaline), tetracaine (LET), and cocaine (TAC) can be used for open wounds. Due to the potential for cocaine toxicity, we recommend using other topical anesthetics instead of TAC. EMLA has been associated with methemoglobinemia, seizures, and respiratory depression with excessive skin application. Methemoglobinemia is associated with the prilocaine component of EMLA and is more likely to occur in patients with glucose-6-phosphate dehydrogenase (G6PD) and those on methemoglobinemia-inducing medications.

The use of topical anesthetic agents (e.g., lidocaine and benzocaine) on mucosal surfaces for teething pain or stomatitis has been associated with overdose toxicity, including seizures, respiratory depression, cardiovascular events, and death. These adverse events have led to a recent black box warning for viscous lidocaine, and the U.S. Food and Drug Administration (FDA) recommendation against using over-the-counter (OTC) topical anesthetics for teething pain. We recommend not using topical anesthetics on mucosal surfaces in infants and young children. For teething pain, use a chilled (not frozen) teething ring or have the caregiver gently massage the gums with a finger. Children with stomatitis can be treated with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).

The topical vapo-coolants or refrigerant anesthetic sprays have similar uses to topical anesthetics (Table 157.4). Two commonly used vapo-coolants are ethyl chloride, which is flammable, and 1,1,1,3,3 pentafluoropropane/1,1,1,2 tetrafluoroethane, which is nonflammable

TABLE 157.3 Topical Anesthetic Agents for Application to Intact Skin or Open Wounds

Topical Agent[a,b,c]	Composition	Sites	Time to Efficacy	Administration	Comments	Contraindications
Eutectic mixture of local anesthetic agents (EMLA)	Lidocaine 2.5% Prilocaine 2.5% 1 : 1 mixture	Intact skin	Onset: 60 min Peak: 120 min Max ≤ 4 h Max 1 h in children ≤ 3 months	Apply 5–10 g in thick layer Cover with semiocclusive dressing	Dose[d]: 0–3 months old or <5 kg: maximum 1 g per 10 cm^3 3–12 months and >5 kg: maximum 2 g per 20 cm^3 1–6 years and >10 kg: maximum 10 g per 100 cm^3 7–12 years and >20 kg: maximum 20 g per 200 cm^3	Infants EGA <37 weeks, <1 year if susceptible to methemoglobinemia or on methemoglobin-inducing agents (sulfonamides, nitrates, primaquine, others) Use with caution if age <3 months old, heart block, or severe hepatic disorder
Liposome encapsulated lidocaine (LMX)	Lidocaine 4% (LMX4) or 5% (LMX5) (previous name: ELA Max)	Intact skin	Onset: 30–60 min	Apply 2.5 grams in thick layer Cover with semiocclusive dressing	Max dose: 4.5 mg/kg/dose, not to exceed 300 mg/dose	Same as for lidocaine
Lidocaine, epinephrine, and tetracaine (LET)	Lidocaine 4% Epinephrine 0.1% Tetracaine 0.5%	Open dermis	20–30 min	Apply 5 mL to cotton ball, place in wound, cover with semiocclusive dressing, apply gentle pressure to infiltrate tissue		Area of compromised blood supply, or end-arteriolar blood supply
Vapo-coolant (PainEase) (other common vapo-coolant is ethyl chloride)	1,1,1,3,3 pentafluoropropane, 1,1,1,2-tetrafluoroethane (nonflammable and ozone friendly so is preferred over ethyl chloride)	Intact dermis Open dermis	Almost instantaneously, 4–10 s	Hold the spray can 3–7 inches from site, spray for 4–10 s or until blanching occurs	Inexpensive Can use on intact or open dermis (such as, laceration) Should perform procedure quickly since effect wears off rapidly (within 1 min) Can be reapplied	Area of compromised blood supply, insensitive skin cold intolerance or hypersensitivity

[a]Tetracaine, adrenaline (epinephrine), and cocaine (TAC) is a topical anesthetic used on open dermis, but because of the potential toxicity due to the cocaine component as well as for legal and regulatory issues, it has been replaced by other topical anesthetics.
[b]Tetracaine topical (Ametop) has been used in adults and reported in the literature in pediatric patients, but according to Pediatric and Neonatal Lexi-drugs for tetracaine topical under dosing, "Children: safety and efficacy has not been established" so it is not included in this list.
[c]Use of topical anesthetic agents on mucosal surfaces in infants and young children, as for teething pain or stomatitis, has been associated with serious adverse events, including seizures, respiratory depression, and death, so they are not included on this list. The American Academy of Pediatrics (AAP) recommends using a chilled (not frozen) teething ring or gently rubbing/massaging with the caregiver's fingers for teething pain. The U.S. Food and Drug Administration (FDA) recommends against using topical over-the-counter (OTC) medicines for teething pain. Such OTC products may contain up to 20% local anesthetic, such as 20% benzocaine, which is 200 mg/mL. This can be compared with the usual concentration of local anesthetics for subdermal injection for suturing, such as 2% lidocaine, which is 20 mg/mL for a tenfold increase to 200 mg/mL for 20% concentration.
[d]The dose of EMLA® varies by age and weight, with the maximum amount of intact skin in cm^3 over which the cream can be applied and the length of time allowed for skin contact specified.
EGA, Estimated gestational age.

and ozone friendly. A meta-analysis study showed that vapo-coolant spray significantly reduced pain during IV cannulation in comparison to placebo spray or no treatment.[22] To be effective, application should include correct distance 3 to 7 inches from the skin site, a steady spray covering the specific area (about as large as a quarter for a venipuncture or IV cannulation), and adequate spray time for 4 to 10 seconds or until the skin begins to turn white, whichever comes first. Vapo-coolants have also been used to alleviate myofascial pain, muscle pain, and musculoskeletal injury pain. Vapo-coolants have immediate onset. Although the anesthetic effect subsides within a minute, it can be reapplied.

The J tip is a needleless jet injector that uses pressurized gas for the delivery of local anesthetic. J tip lidocaine delivery has been found effective in decreasing the pain of peripheral IV catheter insertion. In one study of neonatal patients in the ED requiring lumbar punctures, jet delivered lidocaine was not found to be more effective in reducing pain than topical anesthetic cream, however, advantages included quick onset of action and increased success rate.[23] Devices used for

TABLE 157.4 Common Local Anesthetics

Local Anesthetics[a]	Maximum Dose[b] (mg/kg)	Onset (min)	Duration[c] (Average) (min)
Amides[d]			
Long Duration			
Bupivacaine (Marcaine)	2	10	200
Etidocaine (Duranest)	3	3	200
Moderate Duration			
Lidocaine (Xylocaine)	4–4.5	5	100
Mepivicaine (Carbocaine)	4–4.5	3	100
Prilocaine (Citanest)	5	5	100
Amides With Epinephrine			
Lidocaine with epinephrine	7	5	120
Mepivicaine with epinephrine	7	5	120
Esters[d]			
Short Duration			
Chloroprocaine (Nesacaine)	8	5	45
Procaine (Novocain)	7	18	40
Long Duration			
Tetracaine (Pontocaine)	1.5	15	200

[a]Use of commercially available brand names does not imply endorsement of any medication or product. They are included because individuals may be more familiar with commercial or brand names than the specific drug or category of drugs.
[b]Maximum dose is based on ideal body weight.
[c]Duration is affected by binding (e.g., ↑ protein binding produces ↑ duration) and concentration (↑ concentration ↑ duration). 2% lidocaine has greater duration than 1% lidocaine.
[d]In case of a true immunoglobulin E (IgE) anaphylaxis, which is very rare, to one class of local anesthetics the other class may be used (e.g., if allergy to esters, then one can use amides and vice versa). If there is an allergy to all "caines" (both amides and esters), then one can use benzoyl alcohol or diphenhydramine. Benzoyl alcohol is preferred over diphenhydramine.
Derived from multiple sources including Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, Cohen NH, Eriksson LI, et al., eds. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier; 2015:1028–1054.

injection of local anesthetics are often associated with minor local skin side effects (such as, erythema or bruising) and may produce an audible "pop" when used, which could frighten a young child. One study in pediatric patients found that a vibrating cold device showed equal effectiveness in reducing pain and distress during IV cannulation as 4% topical lidocaine cream and is an acceptable alternative due to speedy time to onset.[24]

Local Anesthetics

Local anesthetics reversibly block sodium channels, which inhibits the propagation of nerve impulses (Fig. 157.3). Local anesthetics fall into one of two classes: amides and esters. Amides can be remembered as the prefix before the ending "caine" will have the letter "I" (e.g., lidocaine and bupivacaine). Local anesthetics are also classified by duration

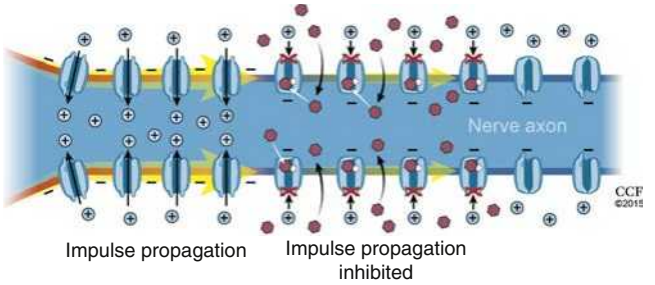

Fig. 157.3 Local Anesthetics Mechanism of Action. Local anesthetics reversibly block sodium channels. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

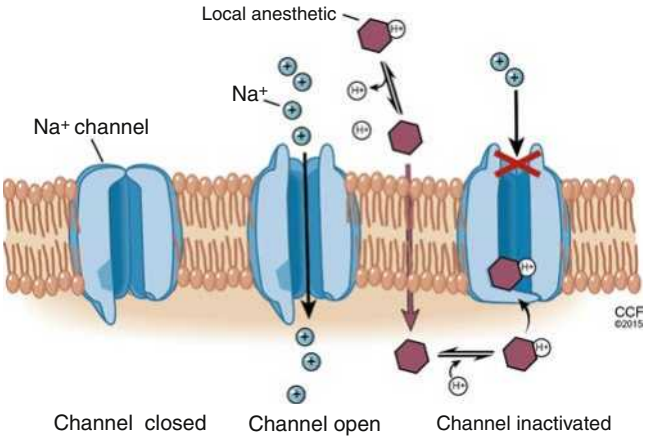

Fig. 157.4 Local Anesthetics Mechanism of Action. Local anesthetics blocks transmission of nerve impulse by binding to the receptor within the sodium channel and inactivating it. *H+*, Hydrogen ion; *Na+*, sodium ion. (Figure illustration by Department of Medical Art and Photography—Cleveland Clinic and Mr. Dave Schumick with permission.)

of action. Local anesthetics that are tightly protein bound to a receptor in the sodium channel (e.g., bupivacaine and tetracaine) have a longer duration of action than less tightly bound anesthetics (e.g., procaine and prilocaine). Greater concentrations of the local anesthetic will also increase the duration of action.

Potency refers to the degree to which the individual local anesthetic blocks transmission in the neural tissue (Fig. 157.4).

When added to a local anesthetic, epinephrine lengthens the duration of the anesthesia, slows systemic absorption, and aids in controlling local bleeding Although the risk is currently being questioned for epinephrine-containing local anesthetics, we recommend generally avoiding in end-arterial fields (e.g., digits) and in patients with vascular pathology (e.g., Buerger's disease or digital vascular injury) who are at high risk for ischemia. Techniques for decreasing injection pain are described in Box 157.1.

The vasoconstrictor reaction is the most common adverse reaction to a local anesthetic. It occurs when an epinephrine-containing local anesthetic is injected into a highly vascular space. The patient suddenly feels a rapid heartbeat and becomes anxious and panicky from rapid absorption of epinephrine. This reaction ends quickly and is not a true allergy.

True immunoglobulin E (IgE)-mediated anaphylaxis to local anesthetics is very rare, especially to the amide class. Reported allergies to amides are more likely to be a reaction to epinephrine or an allergy to one of the preservatives (e.g., methylparaben). There is no cross-reactivity between amides and esters, and they contain

BOX 157.1 Techniques to Decrease the Pain of Local Anesthetics

Use a topical agent prior to the injection
Use smallest gauge needle possible (generally, a 27- to 30-gauge needle)
Use warmed solution: Warmed to 98.6°F–102°F (37°C–39°C)
Inject slowly
Inject into the subcutaneous space, not the dermis
Minimize the number of punctures
Inject from within open wounds, do not inject through the adjacent intact skin
Buffer the local anesthetic: Mix 1% lidocaine with 8.4% sodium bicarbonate solution in a ratio of 9 parts lidocaine to 1 part sodium bicarbonate (Mixing bupivacaine with bicarbonate can cause precipitation of the anesthetic and is not recommended.)

different preservatives. For patients with a known true allergy to lidocaine, a benzyl alcohol solution (made by adding 0.2 mL of 1:1000 epinephrine to a 20 mL vial of normal saline containing 0.9% benzoyl alcohol) can be used. Diphenhydramine is no longer recommended because it is a tissue irritant and can cause local necrosis.

Serious toxicity from local anesthetics is due to their effects on the CNS and to the cardiovascular system (CVS). Early signs of toxicity include numbness or tingling of the lips, metallic taste, muffled hearing, and tinnitus. These symptoms often portend the onset of drowsiness, seizures, status epilepticus, and coma. Direct myocardial depression and pump failure can occur, especially if the patient is on beta blockers or calcium channel blockers; heart block and asystole can also occur. If cardiac arrest is known or presumed to be from local anesthetic toxicity, length of resuscitation should take into consideration time for the negative cardiac effects to wear off. Any of the local anesthetics can have these adverse effects, especially when exceeding recommended doses.

Compared to the amides, the esters have a higher incidence of allergic reactions. Procaine and benzocaine are metabolized to para-aminobenzoic acid (PABA), which has been associated with rare anaphylactic reactions. The metabolites of prilocaine and benzocaine have been associated with methemoglobinemia. Bupivacaine has a higher cardiac toxicity profile than other local anesthetics, but bupivacaine is still widely used and generally safe and effective when used as recommended. In general, the choice of local anesthetic depends more on duration and personal preference than a marked advantage of one specific drug or anesthetic class.

Nerve Blocks. A nerve block is regional anesthesia attained by the injection of a local anesthetic agent near a nerve, nerves, or nerve plexus supplying a particular area. There may be a fairly well circumscribed region of anesthesia (e.g., a wrist or ankle block) or an entire limb, termed *major regional anesthesia.* Nerve blocks are often used to provide anesthesia prior to procedures (e.g., reduction of fractures or dislocations and suturing large lacerations). This approach has the advantage of limiting the amount of lidocaine or other anesthetic needed, decreasing the possibility of reaching toxic levels of the local anesthetic. The use of ultrasound-guided nerve blocks in the ED has been increasing due to the increased safety and efficacy found with sonographic visualization of structures. Although there has been much literature on the use of nerve blocks for adults in the ED, there are relatively few studies dealing with the use of nerve blocks for pediatric patients in the ED.

Complications that can occur with any nerve block include needle breakage (more likely with very small and long needles or if needles are bent to perform the block; e.g., posterior superior alveolar block), needle damage to anatomic structures (e.g., nerves, vessels, viscera, pleura, other structures), neurotoxicity, vascular complications (e.g., hematoma formation, intra-arterial injection), infection, and bleeding. With any nerve block, providers should review the appropriate anatomy (particularly if performed infrequently), be careful not to exceed maximum doses of anesthetics, and calculate the maximum dose based on actual, not ideal, body weight. Mixing lidocaine and bupivacaine will give both a rapid onset and longer duration nerve block.

Nonopioid Systemic Analgesics. Nonopioid systemic analgesics (Table 157.5) include acetaminophen (paracetamol), which has analgesic and antipyretic effects but does not have any anti-inflammatory effects. There is no need for any dosage change for mild renal or hepatic impairment. If therapeutic doses are used and there is no alcohol abuse or preexisting liver disease, then hepatic toxicity is rare. Acetaminophen is an excellent choice for the treatment of mild pain, in combination with opioids for moderate to severe pain, and has several methods of administration, including the IV route. Indications for the IV use of acetaminophen include patients with pain or fever who are unable to take oral medications and those who have impaired gastrointestinal (GI) absorption.

The NSAIDs have analgesic and antiinflammatory properties. NSAIDs inhibit cyclooxygenase (COX)-1 and COX-2, which decreases the synthesis of prostaglandins, thereby elevating the threshold for nociceptor activation. Nonselective NSAIDs inhibit both COX-1 and COX-2. Side effects of COX-1 inhibition include GI bleeding, renal failure, and platelet dysfunction. In pediatric patients, ibuprofen is the NSAID of choice, because it has fewer side effects than other NSAIDs. NSAIDs may be more effective than acetaminophen at reducing pain from inflammation associated with tissue injury.

Aspirin has analgesic, antipyretic, and anti-inflammatory effects. However, aspirin is not recommended in children and infants due to risk of Reye syndrome, a rapid-onset encephalopathy associated with hepatic dysfunction and seizures; for this reason, aspirin should not be used in any individual with chicken pox or flu symptoms.

Opioid Analgesics. Opioids, previously termed *narcotics,* produce analgesia by binding to opioid receptors in the brain, brainstem, spinal cord, and peripheral nervous system. The main adverse effect of opioids is a dose-dependent respiratory depression with blunting of the responses to hypoxia and hypercarbia; this effect is potentiated when co-administered with other sedative medications. Other side effects are primarily GI (e.g., constipation, nausea, vomiting), urinary retention, and pruritus.

There are many routes of administration of opioids. IM is not recommended secondary to injection pain and variable IM absorption. IN administration is useful for quick pain relief in children who have moderate-to-severe pain without established IV access. IN fentanyl has been shown to be effective in treatment of acute pain in children as young as 6 months.[25] IV is used for patients with severe pain and titrated to effect to avoid adverse events.

Morphine and fentanyl are the commonly used opioids used to treat acute and breakthrough pain in pediatric patients. Hydromorphone, though less commonly used, is useful to treat children with chronic pain or opioid tolerance, such as in sickle cell disease. Codeine is a weak opioid that has an increased incidence of side effects compared to other opioids. It is no longer recommended in children because of genetic variability in the metabolism and risk of respiratory depression in fast metabolizers. Meperidine is not recommended due its possible CNS toxicity (e.g., seizures, hallucinations, and psychosis) at therapeutic doses and its risk of serotonin syndrome.

Opioid Prescribing and Use. In 2017, the Department of Health and Human Services declared a public health emergency due to the opioid crisis. Although there is no evidence-based literature documenting

TABLE 157.5 Systemic Analgesics

Systemic Analgesic[d,e]	Route[c,f]	Dose (Pediatric)[a]	Dose (Adult)[b]	Maximum Dose[c]	Formulations and Notes	Comments
Nonopioid[b]						
Acetaminophen (Paracetamol) (Tylenol)	PO	Child/infant 10–15 mg/kg dose every 4–6 h Child 6–11 years old: 325 mg dose every 4–6 h	≥12 years old/ adults 650 mg every 4–6 h 1000 mg every 6 h (maximum 4000 mg daily)	Child single dose 15 mg/kg Total daily dose: Lesser of 75 mg/kg or 4000 mg Not more than 5 doses daily	PO solution or suspension: 160 mg/5 mL, 500 mg/15 mL Tablets/gelcaps: 325 mg, 500 mg Chewable or ODT: 80 mg, 160 mg, 325 mg	Analgesic Antipyretic No anti-inflammatory effect has been associated with liver failure Hepatotoxicity is usually associated with excessive dose Do not exceed maximum daily dose
	PR	10–20 mg/kg dose every 4–6 h	325–650 mg every 4–6 h	Child total daily dose: Lesser of 75 mg/kg/day or 1625 mg/day	80, 120, 325, 650 mg	(Same as above)
Acetaminophen (Ofirmev)	IV	Adolescents >50 kg: 650 mg every 4 hours or 1000 mg every 6 hours	≥50 kg: 650 mg every 6 h or 1000 mg every 6 h	If <50 kg: Single dose 15 mg/kg, total daily dose <75 mg/kg/day ≥50 kg: Single dose 1000 mg daily Total daily dose: 4000 mg	10 mg/mL (100 mL vial)	(Same as above) More expensive, can be used in NPO patients
Ibuprofen (Advil, Motrin)	PO	6 months old to 5 years old: 5–10 mg/kg dose every 6–8 h	≥12 years old/ adults 400–600 mg every 4–6 h or 800 mg every 8 h	<12 years old Single dose: 400 mg Total daily dose: 40 mg/kg up to 1600 mg Adults: Total daily dose 3200 mg	Suspension: 50 mg/1.25mL, 100 mg/5 mL Tablets: 100, 200, 400, 600, 800 mg Chewable tab: 100 mg	Analgesic Antipyretic Anti-inflammatory Side effects: GI bleeding, renal failure, and platelet dysfunction; most side effects occur with the chronic use of nonselective NSAIDs
Ketorolac (Toradol)	IV or IM	0.5 mg/kg dose every 6–8 h	Child >50 kg and adult 15 mg	15 mg/dose Total daily dose: 120 mg	Doses up to 60 mg can be given but are not recommended because doses higher than 15 mg have no greater efficacy but have more incidence side effects	(Same as for ibuprofen) Therapy should not be more than 5 days
Opioids: Oral With or Without Acetaminophen[b]						
Hydrocodone	PO	0.1–0.2 mg/kg dose every 4–6 h Usual dose: 0.15 mg/kg	Child ≥50 kg and adult: 5–15 mg every 4–6 h, usual dose 10 mg	No more than 6 doses/day 60 mg total daily dose	24-h extended-release tablets: 20, 30, 40, 60, 80, 100, 120 mg capsules 12-h extended-release tablets: 10, 15, 20, 30, 40, 50 mg	Weak opioid Preferred over codeine Generally hydrocodone is given in combination with acetaminophen

TABLE 157.5 Systemic Analgesic—cont'd.

Systemic Analgesic[d,e]	Route[c,f]	Dose (Pediatric)[a]	Dose (Adult)[b]	Maximum Dose[c]	Formulations and Notes	Comments
Hydrocodone and acetaminophen[j] (Lorcet, Vicodin)	PO	0.1–0.2 mg/kg dose every 4–6 h (based on hydrocodone component) Usual dose: 0.15 mg/kg	Child ≥50 kg and adult: 10 mg hydrocodone every 4–6 h	No more than 6 doses/day or recommended acetaminophen daily dose, 60 mg hydrocodone total daily dose	Elixir: hydrocodone 10 mg/acetaminophen 300 mg/15 mL Solution: Hydrocodone 7.5 mg/acetaminophen 325 mg/15 mL Tablets: Hydrocodone 2.5 mg/acetaminophen 325 mg Hydrocodone 7.5 mg/ acetaminophen 325 mg Hydrocodone 10 mg/ acetaminophen 325 mg Hydorcodone 5 mg/ acetaminophen 300 mg Hydrocodone 7.5 mg/ acetaminophen 300 mg Hydrocodone 10 mg/ acetaminophen 300 mg	Weak opioid Preferred over codeine Generally hydrocodone is given in combination with acetaminophen
Oxycodone	PO	Age >6 mo: 0.1–0.2 mg/kg dose every 4–6 h Usual dose: 0.15 mg/kg	Child ≥50 kg and adult: Immediate release: 5–10 mg every 4–6 h	Initial: 5 mg/dose oxycodone	Solution: 5 mg/5 mL Concentrate: 100 mg/5 mL Capsule: 5 mg Tablets: 5, 7.5, 10, 15, 20, 30 mg 12-h extended-release tablets: 9, 10, 13.5, 15, 18, 20, 27, 30, 36, 40, 60, 80 mg	Strong opioid Preferred over hydrocodone Generally oxycodone is given in combination with acetaminophen Sustained release form is available but is usually not given for acute pain in the ED setting
Oxycodone and acetaminophen[j] (Endocet, Percocet, Roxicet)	PO	Age >6 mo: 0.1–0.2 mg/kg dose every 4–6 h Usual dose: 0.15 mg/kg (based on oxycodone component)	Child ≥50 kg and adult: Immediate release: 5–10 mg every 4–6 h	Initial: 5 mg/dose oxycodone Total daily dose: Based on acetaminophen component	Solution: Oxycodone 5 mg/ acetaminophen 325 mg/5 mL (Roxicet), oxycodone 10 mg/acetominophen 300 mg/5 mL Tablets: Oxycodone 5 mg/ acetaminophen 325 mg (Roxicet5), oxycodone 2.5 mg/acetaminophen 325 mg, oxycodone 7.5 mg/acetaminophen 325 mg, oxycodone 10 mg/ acetaminophen 325 mg, oxycodone 2.5 mg/ acetaminophen 300 mg, oxycodone 5 mg/ acetaminophen 300 mg, oxycodone 7.5 mg/ acetaminophen 300 mg, oxycodone 10 mg/ acetaminophen 300 mg	Strong opioid Preferred over hydrocodone Generally oxycodone is given in combination with acetaminophen
Opioids: Oral[b]						
Hydromorphone (Dilaudid, Exalgo)	PO	Child <50 kg: 0.03–0.08 mg/kg dose every 3–4 h	Child ≥50 kg and adults; opioid naive: 1–2 mg every 3–4 h	Varies: Depends on whether opioid naive or opioid tolerant	Oral liquid: 1 mg/mL Tablets: 2, 4, 6, 8 mg 12-h Extended release tablets: 8, 12, 16, 32 mg	More potent (×5) than morphine No histamine release and fewer side effects than morphine Sustained release form is available but is usually not given for acute pain in the ED setting

Continued

TABLE 157.5 Systemic Analgesic—cont'd.

Systemic Analgesic[d,e]	Route[c,f]	Dose (Pediatric)[a]	Dose (Adult)[b]	Maximum Dose[c]	Formulations and Notes	Comments
Morphine (Duramorph, Kadian, MS Contin)	PO	Child <50 kg: 0.2–0.5 mg/kg/dose every 3–4 h (immediate release)	Child ≥50 kg and adults: 15–20 mg every 3–4 h		Solution: 10 mg/5 mL, 20 mg/5 mL, 20 mg/mL Tablets: 15 mg, 30 mg 12-h Extended-release tablets: 15, 30, 60, 100, 200 mg 24-h Extended release tablets: 10, 20, 30, 45, 50, 60, 80, 100, 120 mg	Potent opioid Side effect: May cause histamine release (some prefer other opioids for this reason) May be the most commonly use opioid in pediatric patients Sustained release forms available but generally not given for acute pain in the ED
Tramadol (Synapryn, Ultram)	PO	Child ≥ 4 years old: 1–2 mg/kg dose every 4–6 h	Adolescents and adults: 50–100 mg every 4–6 h	Maximum of 100 mg/dose Total daily dose: lesser of 8 mg/kg/day or 400 mg/day	Solution: 5 mg/mL Tablets: 50, 100 mg 24-h extended-release tablets or capsules: 100, 200, 300 mg	Weak opioid; related to codeine; preferred over codeine Less respiratory depression than other opioids Mechanism of action: Central inhibition of norepinephrine and serotonin reuptake, weak affinity for mu receptors
Opioids: Parenteral[b]						
Fentanyl (Abstral, Actiq, Duragesic, Fentora, Lazanda, Onsolis, Subsys)	IV	<50 kg: 1–2 mcg/kg every 1–2 h	Child ≥50 kg and adults: 25–100 mcg/dose every 1–2 h	1–2 μg/kg/dose	Note: Fentanyl is μg or micrograms/kg dose (unlike other opioids which are milligrams or mg/kg per dose), also shorter half-life so given more frequently	More potent (70–100×) than morphine Side effect: Chest wall rigidity with high doses given rapidly More rapid onset and shorter duration than morphine and other opioids
Hydromorphone (Dilaudid, Exalgo)	IV	<50 kg: 0.015 mg/kg every 3–6 h	Child ≥50 kg: 0.2–0.6 mg every 2-4 h	May need higher doses in opioid tolerant patients		More potent (×5) than morphine No histamine release and fewer side effects than morphine
Morphine (Duramorph, Kadian, MS Contin)	IV	<50 kg: 0.05 mg/kg every 2–4 h	Child ≥50 kg and adults: 2–5 mg every 2–4 h	Infants: 2 mg/dose Children 1–6 years: 4 mg/dose Children 7–12 years: 8 mg/dose Adolescents: 10 mg/dose		IM is not recommended because of painful administration, variable absorption, and lag time to peak effect Repeated subcutaneous causes local pain, irritation and induration (see also PO)

[a]Typical doses and maximums are listed. This may not apply to all individuals. Patients differ greatly in their responses to medications, especially opioids. Response may vary due to many factors including age (very young and elderly), previous or chronic exposure to opioids (opioid naive or opioid tolerant), and initial pain severity, so opioids should be titrated to effect.

[b]Use of commercially available brand names does not imply endorsement of any medication or product. They are used because health care providers may be more familiar with brand names than the specific drug name or category or drugs.

[c]There are many routes of administration of opioids, but IM is not recommended, because the injection is painful and has variable absorption and, thus, variable efficacy and unpredictable side effects.

[d]Codeine and meperidine are not included in this table, because they are not preferred and other options are available with fewer side effects.

[e]Oral transmucosal fentanyl is not included in the table, because the fentanyl lollipop was associated with a high incidence of side effects, including nausea, vomiting, and respiratory depression, so it was removed from the market.

[f]Rectal suppositories are available for hydromorphone but are not recommended due to variable absorption.

[g]Other analgesics, such as remifentanil, have been administered for analgesia as part of procedural sedation and analgesia (PSA) but has not yet gained widespread popularity so is not included in the table.

[h]Transdermal patches are available for various medications including lidocaine (Lidoderm), opioids, fentanyl (Duragesic), and buprenorphine (Butrans), but these are generally for chronic pain. They may be encountered in patients with chronic pain, such as cancer patients, but are not generally used for the treatment of acute pain in the ED.

[i]If hydrocodone, oxycodone, or morphine are in the extended release or sustained form, which is for chronic pain, the tablets should be swallowed whole and should not be moistened, dissolved, cut, crushed, broken, or chewed, because this changes the formulation from sustained release to immediate-acting, which can lead to an acute overdose.

[j]Note: Both hydrocodone (Hysingla ER, Zohydro) and oxycodone (Oxecta, OxyContin, Roxicodone) are available in formulations without the acetaminophen component, with the same dosage of hydrocodone or oxycodone, respectively, as for the combinations with acetaminophen. However, they are not frequently prescribed in these formulations without the acetaminophen.

ED, Emergency department; *GI,* gastrointestinal; *IM,* intramuscular; *IV,* intravenous; *NPO, nil per oz.* (nothing by mouth); *NSAID,* nonsteroidal anti-inflammatory drug; *ODT,* orally disintegrating tablets; *PCA,* patient-controlled analgesia; *PO, per oz.* (by mouth); *PR,* per rectal.

a clear superiority of opioid versus nonopioid analgesics, there are multiple adverse effects and consequences for both the individual and the community associated with opioid use, misuse, and abuse. Thus, we recommend that opioids be reserved for more severe pain or pain refractory to other analgesics rather than for routine prescription. If opioids are indicated, they should be given at the lowest effective dose for a limited duration (e.g., 3 days), and the prescriber should consider the patient's risk for opioid use, abuse, or diversion.[26]

Low Dose Ketamine for Treatment of Pain. Low dose ketamine has been successfully used in adults and pediatric patients for the treatment of acute pain.[27] Doses for the treatment of acute pain are lower than those used for sedation and vary. A commonly used dose is 0.15 mg/kg (range 0.1 to 0.2 mg/kg). Higher doses (e.g., 0.3 mg/kg) have been associated with a higher incidence of side effects. Continuous infusions have also been used, in the range of 0.1 to 0.2 mg/kg/h. A randomized control study in children with vaso-occlusive pain crises showed that low dose ketamine had a rapid decrease in pain when compared to morphine.[28] Low dose ketamine was more likely to develop side effects (37.5% vs 3.3% with morphine), with nystagmus and dysphoria being the most common; all side effects were transient and non-life threatening.

Reversal Agents. Naloxone is used for the reversal of opioids effects on the mu receptors (e.g., sedation and respiratory depression). Although the half-life is about 1 hour, the clinically effective duration of action may be much less (e.g., 20 to 60 minutes). Due to longer half-lives of many opioids, re-dosing or an infusion of naloxone is often needed with opioid overdoses. The usual dose for full reversal of opioid intoxication is 0.1 mg/kg/dose with an initial maximum dose of 2 mg. The dose may be repeated every 2 to 3 minutes if there is no response. The IV route is preferred, but intraosseous (IO) can be used if there is no IV line. It may also be given intramuscularly or subcutaneously, but the onset of action may be delayed, especially if there is poor perfusion. Naloxone may be administered intranasally at a dose of 2 mg (1 mg per nare) for adolescents (13 years old and older) and is often given by emergency medical service (EMS) in the field or at home for acute opioid overdoses. Naloxone can also be administered endotracheally at 2 to 3 times the initial IV dose. For reversal of respiratory depression with therapeutic opioid doses, lower doses may be used with an initial dose of 0.001 to 0.005 mg/kg/dose with some recommending 0.001 to 0.015 mg/kg/dose intravenously, intramuscularly, or subcutaneously; the dose is titrated to effect or repeated every 2 to 3 minutes as needed until the desired response is obtained.

Flumazenil antagonizes the action of the benzodiazepines at the gamma-aminobutyric acid (GABA) receptor. It has a half-life of about 1 hour, but the clinically effective duration of action may be much less (20 to 60 minutes). Flumazenil can only be given intravenously. Flumazenil may be given when there is an acute overdose of benzodiazepines which were administered for clinical reasons, and only in a patient who is not benzodiazepine habituated. In individuals who overdose on benzodiazepines, it is likely that they are habituated and on benzodiazepines chronically. In these cases, flumazenil can precipitate benzodiazepine withdrawal with status epilepticus and even death. Thus, except in the acute iatrogenic overdose setting, the use of flumazenil is not recommended. Patients who co-ingest benzodiazepines and tricyclic antidepressants may develop intractable seizures after flumazenil administration. Thus, use of flumazenil should be reserved for patients with an uncomplicated benzodiazepine overdose, no evidence of tricyclic antidepressant use (e.g., no electrocardiogram [ECG] findings and no anticholinergic signs and symptoms), no history of seizure disorder, and no history of benzodiazepine habituation. For benzodiazepine reversal with procedural sedation or anesthesia, the initial dose of flumazenil for infants, children, and adolescents is 0.01 mg/kg (maximum 0.2 mg), which may be repeated after 45 seconds and then every minute up to 4 additional doses. The maximum total cumulative dose is 1 mg or 0.05 mg/kg, whichever is lower. Flumazenil is used infrequently and has a black box warning; we recommend its use only for patients requiring benzodiazepine reversal with procedural sedation or anesthesia (e.g., airway compromise due to oversedation).

Outcomes

There are moral, ethical, legal, and regulatory reasons to adequately treat pain. Oligoanalgesia, the failure to adequately treat pain, continues despite increasing literature demonstrating that pain is too often undertreated. Children and infants, the elderly, individuals with limited cognitive ability, and ethnic and social minorities have a greater risk of oligoanalgesia. The negative consequences of undertreating pain include decreasing the patient's pain threshold and predisposing patients to developing chronic pain syndromes. Inadequate analgesia may lead to harmful physiologic consequences, including an increase in stress hormones and increased sympathetic outflow. This results in an increase in catabolism, myocardial oxygen consumption, production of carbon dioxide, and peripheral vascular resistance, as well as an impaired immune response.

The Joint Commission (TJC) mandates that hospitals adapt a pain management quality improvement program, which includes the measurement, documentation, and therapy for pain. Patient satisfaction and the patient experience are gaining greater importance, and the Centers for Medicare and Medicaid Services (CMS) and the National Committee on Quality Assurance require public reporting of patient satisfaction data for participating health plans. In the future, hospital and physician payment will be based on patient outcomes, as well as patient satisfaction. The positive relationship between adequate treatment of pain and patient satisfaction has been documented for all ages of patients, including children and infants. Eliminating or minimizing the pain of medical procedures can also lead to greater procedural success rates.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 157: QUESTIONS AND ANSWERS

1. When do most adverse events associated with emergency department (ED) procedural sedation occur?

a. During the manipulation or intervention
b. 5 to 20 minutes after the last sedative dose
c. 20 to 30 minutes after the last sedative dose
d. 30 to 60 minutes after the last sedative dose
e. 60 to 90 minutes after the last sedative dose

Answer: b. High-risk times are 5 to 20 minutes after the last medication administration and at the completion of the procedure when there is no longer a painful stimulus, but the patient remains sedated.

2. Which of the following modalities has proven most effective for monitoring patients undergoing procedural sedation?

a. Capnometry or capnography
b. Cardiac rhythm monitoring
c. Continual direct visual observation of qualitative clinical signs
d. Documented respiratory rate
e. Pulse oximetry

Answer: c. The patient's ability to follow commands in response to varied levels of stimulation and direct observation of the ventilatory status have been the most reliably documented methods of assessing the level of consciousness during procedural sedation. Pulse oximetry is a reliable adjunct, but it identifies hypoventilation late, especially when used with supplemental oxygen. Cardiac monitoring has been shown to be helpful in older patients or in those with a history of cardiac disease, but there is no evidence that it is of any benefit in young healthy patients. End-tidal carbon dioxide monitoring has been shown to be useful to detect inadequate ventilation earlier than oximetry, especially when direct observation of the patient is difficult, but no studies have demonstrated an effect on clinical outcome to date. Recently, the American Society of Anesthesiologists (ASA) updated its procedural sedation standards to include capnography during moderate or deep sedation, in addition to the continual observation of qualitative clinical signs. Respiratory rate alone is an insensitive indicator of adequacy of ventilation.

CHAPTER 157: QUESTIONS AND ANSWERS—cont'd

3. Which of the following agents is matched with the correct associated side effect?
   - **a.** Etomidate—longer (>30-minute) duration of sedation
   - **b.** Ketamine—laryngospasm
   - **c.** Methohexital—venoirritation
   - **d.** Pentobarbital—seizures
   - **e.** Propofol—myoclonus

Answer: b. Ketamine has been associated with laryngospasm in children younger than 3 months old and those with a respiratory infection. The following are the other correct associations:

- Etomidate—myoclonus
- Methohexital—seizures
- Pentobarbital—longer (>30-minute) duration
- Propofol—venoirritation

4. Which of the following statements regarding the use of ketamine is false?
   - **a.** Benzodiazepine administration may be useful for emergence phenomenon in children that are not improved by removing stimulation and providing calming interventions.
   - **b.** Despite increased secretions, airway reflexes are generally well maintained.
   - **c.** Hypotension is common.
   - **d.** Profound analgesic and sedative effects occur with minimal respiratory depression.
   - **e.** Repeat doses are well tolerated in longer procedures.

Answer: c. Ketamine increases the release of catecholamines upon administration and supports blood pressure well. It also decreases smooth muscle tone in the bronchial tree and may have a benefit in patients with reactive airways disease. Several studies have failed to show benefit with the concurrent administration of low-to-moderate dosages of benzodiazepines in preventing emergence phenomenon in children. These studies have shown a slightly increased risk of side effects. Their routine use is discouraged and should be reserved for the actual treatment of severe emergency phenomenon that are not improved by removing stimulation and providing calming interventions.

5. Which of the following statements regarding the use of propofol is true?
   - **a.** Propofol has a long duration of action and provides significant analgesia.
   - **b.** Propofol has significant antiemetic properties.
   - **c.** Propofol can be easily reversed with a reversal agent.
   - **d.** Propofol is well tolerated in volume-depleted patients.
   - **e.** The use of "ketofol" (ketamine in combination with propofol) is clinically superior to the use of propofol alone.

Answer: b. Propofol is an ultra–short-acting, sedative-hypnotic, cerebroprotective agent with no analgesic but profound antiemetic properties. Its adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Preload-dependent patients are particularly susceptible to hypotension. Its combined use with ketamine is common. The two agents are felt to have synergistic effects that balance each other's deficits. The combined use has been shown to improve provider satisfaction, sedation quality, and decrease emesis but has not been shown to be clinically superior to either agent used alone regarding respiratory depression, airway complications, or improved recovery times.

6. Which of the following statements is true regarding the need for fasting before procedural sedation?
   - **a.** A 6-hour period of fasting is required after the ingestion of liquids or solids before procedural sedation.
   - **b.** Preprocedural fasting is required in all circumstances.
   - **c.** The recommendation for preprocedural fasting is based on controlled trials involving patients undergoing procedural sedation.
   - **d.** The risk of vomiting and the loss of the airway protective reflexes is an extremely rare occurrence during procedural sedation.
   - **e.** There is an increased risk of aspiration during procedural sedation after a liquid or solid meal.

Answer: d. The American College of Emergency Physicians organized a multidisciplinary Consensus Statement on Unscheduled Sedation that recommends the assessment of the timing and nature of recent oral intake. The urgency of the procedure will dictate the necessity of providing sedation without delay, regardless of fasting status. For patients with established risk factors for aspiration (e.g., serious underlying illness, obstructive sleep apnea, obesity, age less than 12 months, upper endoscopy as the procedure, or bowel obstruction), consider the risks versus benefits of delaying procedural sedation after recent ingestion of a substantial meal. American Society of Anesthesiologists (ASA) currently recommends a period of 2 hours after ingestion of clear liquids, a period of 4 hours after ingestion of breast milk, and a period of 6 hours after ingestion of other liquids or solids before the performance of procedural sedation. This recommendation is based on expert consensus and extrapolated from data on patients receiving general anesthesia and manipulation of the airway during intubation and extubation. There are no published studies showing increased risk of aspiration after a liquid or solid meal, nor benefits of fasting before procedural sedation. There are large studies showing no clinically significant differences with airway complications, emesis, or other adverse effects between groups of patients stratified by their preprocedural fasting status. Adherence to the ASA preoperative fasting guidelines for procedures is not necessary in emergency department (ED) patients undergoing procedural sedation and analgesia (PSA).

Pediatric Resuscitation

Joshua S. Easter

KEY CONCEPTS

- Unlike adults, most cardiac arrests in children arise from respiratory etiologies. Therefore, emphasis is first on oxygenation and ventilation.
- Detection of a child's pulse may be difficult; if a brachial pulse is not definitively present after 10 seconds of palpation, initiate cardiopulmonary resuscitation (CPR).
- Hypotension is a late finding in pediatric shock and requires immediate intervention to prevent cardiac arrest. Progression from tachycardia to bradycardia in a child is often a harbinger of imminent arrest.
- Although few studies support recommendations for exact rate, depths, and ratios of compressions to ventilations in pediatric CPR, emergency clinicians should perform rapid compressions over the lower sternum with minimal interruptions. The hand encircling technique is recommended for infants requiring chest compressions and the two-hand approach in mid sternum for older children. In the emergency department (ED), we recommend 15 compressions to 2 ventilations for children less than 8 years and 30 compressions to 2 ventilations for older children.
- Verbal and quantitative feedback improves compressions and ventilations.
- Advanced airway management (i.e., endotracheal intubation) may be harmful for children in arrest in the ED. If attempted, physicians should strive for minimal interruptions in compressions and to ventilate at 8 to 10 breaths/min. High quality bag-mask ventilation is a reasonable alternative to advanced airway maneuvers.
- If ventricular fibrillation or pulseless ventricular tachycardia arise, defibrillate at 2 J/kg as soon as possible. While preparing the equipment and charging, continue to perform high quality compressions. Administer subsequent defibrillations at escalating energy doses of 4 J/kg and then 10 J/kg.
- Early administration of epinephrine for non-perfusing rhythms may improve survival.
- Empiric administration of medications to children in arrest worsens outcomes. Reserve medications for specific indications, for example, bicarbonate administration for hyperkalemia.
- Knowledge of the child's approximate weight is necessary to administer the appropriate medication doses and to utilize the appropriate equipment. Determine actual weight in kilogram and estimate weight based on parental report or the child's length.
- Prompt vascular access is critical in a resuscitation. Intraosseous access tends to be the easiest and fastest, but care should be taken that the needle is not residing in the subcutaneous tissue. Central venous access is resource intensive and not necessary in the first few hours of a resuscitation.
- Except in specific circumstances, resuscitations greater than 30 minutes are unlikely to yield favorable outcomes for pediatric arrest.
- After return of circulation, maintain normothermia and avoid hypotension.
- Current definitions of sepsis are based on consensus and primarily for research purposes.
- Systemic inflammatory response syndrome (SIRS) criteria are sensitive but not specific for identifying sepsis in children.
- Hypotension should prompt administration of 20 to 60 mL/kg fluids and likely vasopressors.
- Most children with septic shock have cold shock and therefore epinephrine (0.05 mcg/kg/min) is the first line vasopressor.
- Protocols bundling intravenous fluids, antibiotics, and blood culture acquisition in septic children improve outcomes.
- Brief resolved unexplained events (BRUEs) involve alterations in breathing, tone, or behavior that last less than 1 minute before resolving spontaneously. Children appear well on presentation to the ED, and there are no elements of the history that suggest a particular etiology for the event.
- Low-risk BRUEs occur in children that were born greater than 32 weeks, are greater than 60 days of age, have had no prior BRUEs, and CPR was not required during the event. These children require an assessment and brief observation in the ED, little or no diagnostic testing, and may be discharged with close follow-up.

CARDIAC ARREST

Foundations

Background

Pediatric cardiac arrest is rare, but the consequences are dire when considering lost years of life and productivity. The incidence and survival of pediatric cardiac arrest varies with the location of the arrest, the patient's age, and the mechanism (Table 158.1). Most cardiac arrests encountered in the emergency department (ED) occur outside the hospital, from medical causes in infants and traumatic causes in older children. In children, cardiac arrest is most prevalent in infants, occurring primarily in children less than 3 months of age. The incidence of atraumatic cardiac arrest in older children is 30 to 50 times less common than infants and adults. Overall, survival following cardiac arrest in children is low; however, it is improving, and certain groups have higher likelihoods of survival. Infants survive infrequently (6%) but older children survive (14%) comparably to adults (11%).[1] The frequency of survival with good neurologic outcome has been estimated at 6% to 12%.

Pediatric resuscitations are relatively rare, limiting clinicians' proficiency. In a review of resuscitations at a busy pediatric ED, less than half of emergency physicians had completed any critical care procedures

TABLE 158.1 Differences in Cardiac Arrest Pathophysiology, Presentation, and Management by Age

	Infant	Child	Adult
Incidence (per 100,000)	75	5	141
Survival (%)	6	14	11
Etiology	Respiratory	Respiratory > Trauma	Cardiac
Rhythm	Asystole, bradycardia	Asystole	Ventricular fibrillation or tachycardia
Early Focus	Compressions, Ventilations		Defibrillation
Location for pulse check	Brachial	Carotid	Carotid
Compression technique	Hands encircling chest	2 hands	2 hands
Compression depth	1.5 inches	2 inches	2 inches
Defibrillation dose (monophasic)	2J/kg, then 4J/kg, and then 10 J/kg		200 J
Epinephrine dose	0.1 mg/mL		0.1 mg/mL

(e.g., cardioversion, intubation, intraosseous line placement) in the preceding year. No physicians had performed cardiac pacing, needle cricothyroidotomy, diagnostic peritoneal lavage, thoracentesis, arterial line placement, and venous cutdown line placement. In the absence of actual clinical experience, emergency clinicians often rely on didactic resuscitation courses. However, knowledge retention after these courses is poor. As a result, many emergency clinicians remain uncomfortable managing critically ill children.[2–4] This discomfort can lead to insufficient interventions for fear of harming a child, or alternatively, excessive interventions that stress resources, families, and clinicians.

Pathophysiology

Most atraumatic cardiac arrests in children arise from respiratory etiologies, particularly respiratory failure, drowning, and asphyxia. Children commonly progress from respiratory failure to shock, and finally to bradycardia and loss of circulation. Pediatric advanced life support (PALS) guidelines have largely focused on the treatment of these respiratory emergencies. However, population-based studies suggest cardiac causes account for approximately a third of pediatric medical arrests. Another 21% of pediatric arrests follow trauma. These frequencies are in stark contrast to adults, where two-thirds of arrests are attributed to cardiac etiologies. The differences in the etiology of arrests between adults and children have significant implications for management; arrests from respiratory causes require an emphasis on ventilatory support, oxygen delivery, and maintenance of perfusion, whereas arrests from cardiac causes require a more directed emphasis on restoring perfusion and treatment of underlying dysrhythmias (see Table 158.1).

The most common presenting pediatric arrest rhythm is asystole, occurring in two-thirds of children. Pulseless electrical activity and bradycardia are the next most common presenting rhythms. Unlike adults, ventricular fibrillation and tachycardia are rare, occurring in 9% of children in cardiac arrest. These dysrhythmias can arise with prolonged resuscitation and are more common in adolescents and children with congenital heart disease.

With return of circulation after cardiac arrest, reperfusion induces a cascade of physiologic changes that increase morbidity. During the initial minutes after return of circulation, there is not adequate substrate for aerobic metabolism leading to accumulation of free radicals and cellular necrosis. Children may also develop a sepsis like syndrome, with increased cytokines and endotoxin producing capillary leak and coagulopathy. This may lead to hypotension and multiple organ dysfunction. In the hours following return of circulation, nearly half of children may also develop reversible myocardial dysfunction, producing pulmonary edema, hypotension, or arrhythmias.[5]

Clinical Features

The absence of a pulse, respiratory effort, and responsiveness constitute cardiac arrest. While identifying respiratory effort and responsiveness are relatively straightforward, detecting a pulse in a pediatric patient can be difficult. Physicians identified the presence of a pulse when one was not present in one quarter of children undergoing extracorporeal membrane oxygenation (ECMO). Moreover, emergency clinicians require extended time to determine if a pulse is present in a child, with an average of 9 (±6) seconds to detect a brachial pulse and 29 (±14) seconds to determine that a pulse was not present. Current guidelines suggest lay people should initiate cardiopulmonary resuscitation (CPR) in children without performing a pulse check; any child that is unresponsive and apneic should receive CPR. For emergency clinicians, if no pulse is detected in 10 seconds, CPR should be initiated without delay; the adverse effects of delayed CPR outweigh the effects of CPR for an apneic, unresponsive child with a weak pulse.

The ideal location for palpation of a child's pulse is unclear. There are few studies comparing sites, and they are conducted in the operating room with conflicting results. In infants, the carotid pulse can be difficult to detect compared to the brachial or femoral pulse. In adolescents, the carotid is the easiest location to identify a pulse. In children in cardiac arrest, auscultation of the heart or palpation of the apical impulse can be misleading; patients with pulseless electrical activity can have an apical impulse or auscultated heartbeat without central pulses or adequate perfusion.

Recognizing Imminent Arrest

Anticipating impending cardiac arrest allows for early interventions that may prevent progression. Abnormal vital signs, based on age-specific norms, are often the best indicator of imminent arrest in an ill child. These values can be difficult to remember, but physicians can recognize several key features (Box 158.1). While tachycardia and tachypnea are commonly present in children with relatively benign febrile illnesses, hypotension or ill appearance should prompt immediate intervention.

Management

The paucity of pediatric out-of-hospital cardiac arrests limits available evidence on its management. Most pediatric guidelines are consensus-based and much is extrapolated from adult data.[6–8] The American Heart Association (AHA) guidelines for management are illustrated in

BOX 158.1 Worrisome Vital Sign Findings in Children

Blood Pressure

Systolic blood pressure <70 mm Hg + (2 × age in years) is hypotension (less than fifth percentile for age)

Respiratory Rate

Respiratory rate >60 breaths/min is tachypnea

Declining respiratory rate in previously tachypneic patient can represent improvement *or* fatigue and imminent respiratory failure

Fever

Each 1°C (1.8°F) of fever increases heart rate by only 10 beats/min and respiratory rate by 2–5 breaths/min

End-Tidal Carbon Dioxide

Progressive increase or decrease precede desaturation and respiratory failure

Fig. 158.1. Neonatal resuscitation guidelines (see Chapter 159) should be used for newborns and for neonates within the first weeks of life, after which these pediatric guidelines are applicable for children until puberty (i.e., axillary hair in males and breasts in females).

Compressions-Airway-Breathing

During the initial no-flow state of cardiac arrest, the priority is initiation of flow. This priority has prompted a change in the sequence of "airway-breathing-compressions (A-B-C)" to "compressions-airway-breathing (C-A-B)." This avoids delays in the initiation of blood flow and may render bystanders to an arrest more likely to provide CPR. This is particularly helpful in children; bystander CPR improves pediatric survival but is infrequently administered.[9] Although the A-B-C approach is still considered preferred in children, it is feasible to begin with the C-A-B approach and still provide timely ventilations; a simulated pediatric respiratory arrest model found no delays in the initiation of ventilations with the C-A-B approach compared to the A-B-C approach. Moreover, the C-A-B approach led to prompter recognition of cardiac arrest. If untrained bystanders are reluctant to provide ventilations, children with out-of-hospital cardiac arrest should still receive chest compressions without delay. In the ED, with multiple professionals available, compressions should be administered concurrently with ventilations.

Compressions. High quality compressions improve outcomes but are rarely performed. When administered appropriately, compressions generate one-third of a child's normal cardiac output and a coronary artery perfusion pressure of 10 mm Hg. In a prospective, observational study of in-hospital pediatric arrest, one half of children received the recommended rate of chest compressions and one fifth received the recommended depth per AHA guidelines. In an academic pediatric ED study, 87% of compressions exceeded 100 per minute. However, only 40% complied with recommended compression to ventilation ratios, and there were frequent pauses in compressions.[10]

The location of compressions influences cardiac output. Infants' hearts reside inferior to the lower third of their sternums. In these younger children, encircling the chest with both hands and compressing the lower part of the sternum with the thumbs while squeezing the thorax with the remaining fingers yields greater cardiac output than compression with two fingers. In video review of infant CPR, this approach yielded more accurate compression rates compared to a one handed technique.[11] The AHA suggests utilizing the one hand approach to administer compressions to children 1 to 8 years old, but a study of simulated compressions suggested a two-handed technique, identical to that performed on adults, is easier and generates higher pressures. When feasible, a resuscitation board placed under children receiving chest compressions improves compressions; at a minimum, the child should be supine on a firm surface.

The ideal compression depth and rate is unknown, but the AHA recommends pushing "hard and fast." Compressions should be deep enough to achieve optimal cardiac output without being so deep as to cause injuries to other vital organs. Attempts to increase depth excessively can result in leaning, which reduces coronary artery perfusion pressure and cardiac output. Guidelines suggest compressing the chest an estimated one-third of the anteroposterior diameter of the child. However, this estimating method has led to relatively deeper compressions than recommended in adults, and it can be extremely difficult to assess proportional anteroposterior compression depth during CPR. As a result, it is more practical to focus on absolute depths; we recommend 1½ inches in infants and 2 inches in older children.

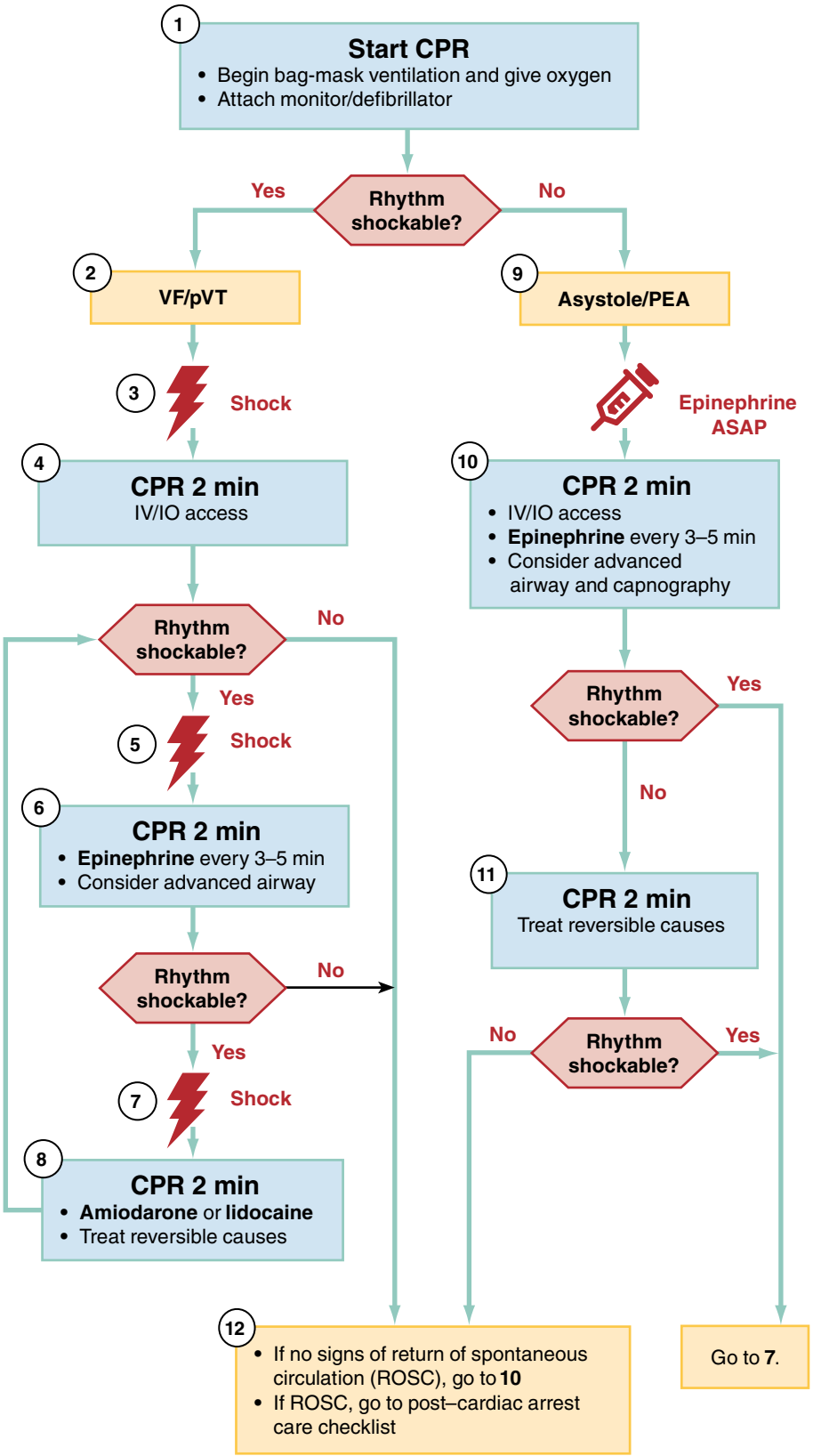
Similarly, the exact rate of compressions to generate ideal cardiac output is unclear. Rates more than 100 compressions per minute improve cardiac output, coronary artery perfusion pressure, and survival compared with rates less than 90 compressions per minute in children. However, attempts to exceed 120 compressions per minute diminish perfusing pressures.[12] High quality compressions diminish after 2 minutes. At this point, emergency clinicians may deny fatigue and be able to maintain the rate of compressions, but depth of compressions decreases substantially. This reduction in quality worsens with time. In adults, pauses in compressions yield substantial drops in coronary artery perfusion pressure, and pauses more than 20 seconds increase the odds of mortality by 50%. A recent study of in-hospital pediatric arrest found that brief pauses (median of 2.4 seconds) did not lead to significant reductions in intra-arterial pressures.[13] Nevertheless, pauses in compressions should be minimized. When pauses are necessary to switch compressors, check rhythms, or provide defibrillation, they should be kept as brief as feasible.

Finally, the appropriate ratio of compression to ventilations is unknown. Animal models indicate the amount of ventilation required during CPR is much lower than with a normal perfusing rhythm, likely due to the lower cardiac output in CPR. The AHA recommends 30:2 compressions to ventilations for single rescuers and 15:2 for two rescuers. However, 15:2 ratios may yield insufficient compressions per minute in older children, and we recommend 30:2 ratios for children greater than 8 years. If an advanced airway is in place, ventilations should be delivered at 8 to 10 breaths per minute and should not interrupt compressions. Overventilation can be dangerous, but is common; in an observational study at a busy pediatric ED, 70% of CPR involved ventilations in excess of recommendations.[10]

Notably, although resuscitation guidelines provide exact rates, depths, and ratios of compressions to ventilations, these recommendations are largely based on consensus. There are no randomized control studies comparing the impact of exact ratios, frequencies, or depths of compressions on survival. Rather than focusing on strict adherence to exact guidelines, we recommend focusing on promptly recognizing the need for compressions and then administering rapid compressions over the lower sternum with minimal interruptions. Practice is critical to maintaining quality, as most individual clinicians have limited real patient experience; in a busy pediatric ED, clinicians averaged 3 minutes of compressions per year.[14,15]

The AHA recommends feedback, as it improves the quality of compressions. Quantitative feedback is most helpful because qualitative assessments can be difficult. During simulated arrests, emergency clinicians significantly overestimated compression depth and rate while underestimating pauses. Accelerometers and force

Pediatric cardiac arrest algorithm – 2020 update



CPR quality

- Push hard (≥⅓ of anteroposterior diameter of chest) and fast (100–120/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Change compressor every 2 minutes, or sooner if fatigued
- If no advanced airway, 15:2 compression-ventilation ratio
- If advanced airway, provide continuous compressions and give a breath every 2–3 seconds

Shock energy for defibrillation

- First shock 2 J/kg
- Second shock 4 J/kg
- Subsequent shocks ≥4 J/kg, maximum 10 J/kg or adult dose

Drug therapy

- **Epinephrine IV/IO dose:** 0.01 mg/kg (0.1 mL/kg of the 0.1 mg/mL concentration, max dose 1 mg). Max dose 1 mg. Repeat every 3–5 minutes. If no IV/IO access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of the 1 mg/mL concentration).
- **Amiodarone IV/IO dose:** 5 mg/kg bolus during cardiac arrest. May repeat up to 3 total doses for refractory VF/pulseless VT
  or
  Lidocaine IV/IO dose: Initial: 1 mg/kg loading dose

Advanced airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement

Reversible causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypoglycemia
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Fig. 158.1 The American Heart Association (AHA) Guidelines Algorithm for Management of Infants and Children in Cardiopulmonary Arrest. *CPR,* Cardiopulmonary resuscitation; *ETT,* endotracheal tube; *IO/IV,* intraosseous/intravenous; *PEA,* pulseless electrical activity; *ROSC,* return of spontaneous circulation; *VF/VT,* ventricular fibrillation/pulseless ventricular tachycardia.

sensors provide real-time data on compression rate and force. These feedback devices improve adherence with compression guidelines amongst children in simulated cardiac arrest.[16] The presence of a coach providing verbal feedback augments feedback devices in simulated arrests.[17–19] End-tidal carbon dioxide ($ETCO_2$) also serves as an adjunct measure of the adequacy of compressions.[20,21] In the low-flow state of CPR, the flow of venous blood to the lungs serves as the rate-limiting step for the elimination of CO_2 as opposed to ventilation. As a result, exhaled CO_2 increases with cardiac output, and the AHA recommends titration to greater than 20 mm Hg, although an observational study of in-hospital pediatric arrest found levels greater than 20 mm Hg were not associated with survival.[22] Despite proven benefits, less than 5% of hospitals employ feedback devices regularly during resuscitation.

Ventilation. Although life-threatening airway emergencies in children are rare, most critical illness in children stems from respiratory etiologies; therefore, focus is largely on effective ventilation and oxygenation. The appropriate method to ventilate children in arrest is unclear, as advanced airway management with endotracheal intubation may not improve outcomes compared to bag-mask ventilation. A randomized trial of intubation versus mask ventilation in the pre-hospital setting found no difference in survival to hospital discharge (OR = 0.82; 95% CI, 0.61 to 1.1) for tracheal intubation versus bag-mask ventilation alone. A large observational study in Japan confirmed these results.[23] In contrast, a retrospective review of an airway registry suggested endotracheal intubation was associated with reduced survival (OR = 0.39; 95% CI, 0.26 to 0.59). While this may stem from complications associated with pre-hospital pediatric intubation, results are similar for in-hospital pediatric arrest. An observational study of 2294 children found intubation was associated with reduced survival (RR = 0.89; 95% CI, 0.81 to 0.99).[24] The lack of benefit of pre-hospital advanced airway management may extend to supraglottic devices, with a retrospective study showing reduced survival (OR = 0.32; 95% CI, 0.12 to 0.84).[25] Advanced airway management may reduce survival by leading to interruptions in compressions; a review of pediatric ED intubation attempts found pauses in over half of attempts with a median duration of 25 seconds.[26]

As a result of this evidence, the 2019 PALS update recommends bag-mask ventilation for pre-hospital arrest.[6] While the AHA found insufficient evidence to create a guideline for the ED, we extrapolate from the pre-hospital and in-hospital evidence and recommend emergency physicians focus on delivering high quality bag-mask ventilation. This requires the appropriate equipment (mask size and airway adjuncts) as well as deliberate practice.[7] If advanced airway management is attempted during resuscitation, care should be taken to avoid prolonged interruptions in compressions. In addition, patients should receive only 8 to 10 breaths/min via the advanced airway without interruptions in compressions. A more in-depth discussion of pediatric airway management can be found in Chapter 156.

Compression-Only Cardiopulmonary Resuscitation

Compression only CPR is utilized in adults, but the benefits in children are less apparent. For arrests secondary to ventricular fibrillation, as are common in adults, patients often have a reservoir of oxygen in their lungs and can maintain adequate arterial partial pressure of oxygen (PaO_2) for 5 minutes with compressions alone. In contrast, animal studies of arrests from respiratory causes show that compression-only CPR leads to rapid depletion of oxygen reservoirs and increased CO_2 and lactate. In a large observational study of children, conventional CPR was associated with improved survival compared to compression-only CPR.[27] For children with cardiac etiologies to their arrest, survival was similar with both approaches. As children commonly suffer respiratory etiologies for their arrest, and there are multiple providers available in the ED, conventional CPR should be the norm.

Bystander CPR improves outcomes, but only half of children receive it. Bystanders may be more willing to perform compression-only CPR, and this should be encouraged compared to no CPR. Compression-only CPR improved survival compared to no CPR (OR = 3.3, 95% CI, 1.9 to 5.7).[9,28]

Defibrillation. Although ventricular fibrillation and pulseless ventricular tachycardia are rarely the presenting rhythm in children, they arise at some point during one quarter of pediatric resuscitations. Children with these rhythms are more likely to survive. Defibrillation applies asynchronous current to the heart to restore a perfusing rhythm. While out-of-hospital arrest studies demonstrated that shorter durations between onset of a shockable rhythm and defibrillation improved survival, a recent observational study of in-hospital pediatric arrest found time to defibrillation was not associated with survival (RR = 0.99; 95% CI, 0.94 to 1.1).[29] This may reflect the abrupt recognition of arrest and initiation of CPR in-hospital, which may mitigate the survival benefit of rapid defibrillation. In the setting of conflicting evidence, in the ED we recommend prompt defibrillation as soon as a shockable rhythm is identified. Delays in defibrillation of over 3 minutes arise in nearly half of simulated shockable arrests. These delays stem from failure to recognize the shockable rhythm and difficulty operating the defibrillator.[30] While awaiting defibrillation, emergency clinicians should focus on administering high quality compressions without interruptions until the defibrillator is placed and charged.

Pediatric specific equipment is available for defibrillation. Both paddles and pads provide adequate energy, assuming gel is placed on the paddles and pads are firmly attached to the chest wall. Optimal pad size has not been well defined in the pediatric population; pads can be used according to the manufacturer's size recommendations and should fit on the child's chest without touching. Anteroposterior and anterolateral positioning of pads provide equivalent energy to the heart. If pediatric pads are not available, apply adult-sized pads anteroposteriorly and minimize contact between the pads.

The optimal energy dose for defibrillation in children is uncertain. The AHA recommends administering 2 to 4 J/kg initially, whereas the European Resuscitation Council recommends 4 J/kg. Dosing based strictly on weight often leads to lower than anticipated energy delivery. Theoretically, a higher dose per kilogram may overcome this variability and ensure adequate energy reaches the heart. However, multiple small studies have not identified any association between energy dose and survival.[31] The primary disadvantage of higher energy doses is damage to the myocardium, but animal studies suggest long-term myocardial necrosis only occurs with doses more than 10 J/kg. The only circumstance where a child would receive such high doses is if adult pads are utilized with an infant. Nevertheless, when presented with an infant in ventricular fibrillation and no other equipment, we recommend employing the adult pads.[32] We also recommend starting defibrillation at 2 J/kg, increasing to 4 J/kg with the second defibrillation, and increasing to 10 J/kg for third and subsequent shocks. There is no difference in survival between monophasic and biphasic defibrillation in children.

Pharmacology

There are no high-quality randomized control studies showing improvement in survival to hospital discharge or neurologic outcome with any medications administered during pediatric cardiac arrest. Observational studies suggest that prompt administration of epinephrine may improve return of circulation and mortality for non-traumatic out-of-hospital cardiac arrest in children; each minute from emergency medical service (EMS) arrival until administration of epinephrine reduced

TABLE 158.2 Medications for Pediatric Cardiac Arrest

Medication	Indications	Dose (mg/kg)	Comments
Epinephrine	Asystole, PEA, bradycardia, VF, pulseless VT	0.01	0.1mg/mL formulation Higher doses of epinephrine may decrease survival May increase harm with bradycardia
Atropine	Bradycardia	0.02	Not for routine use in PEA, asystole 0.02 mg/kg
Amiodarone	VF, VT, SVT	5	Unclear if superior to lidocaine for VF, VT
Lidocaine	VF, VT	1	Avoid in WPW
Procainamide	SVT refractory to adenosine, stable VT	10–15	First line for SVT in WPW May be more effective than amiodarone for SVT Do not give in patients receiving amiodarone, torsades de pointes, or prolonged QT Can cause hypotension
Adenosine	SVT	0.1	First line therapy for stable SVT Avoid in WPW, wide complex tachycardia, long QT Potentially unreliable through IO route
Dextrose	Hypoglycemia	0.5–1 g/kg, maximum 25 g	D10W: 5 mL/kg, D25W: 2 mL/kg, D50W: 1 mL/kg Do not administer empirically
Calcium chloride	Hyperkalemia, hypocalcemia, calcium channel blocker overdose	20	Not for routine use Calcium chloride provides more bioavailable calcium but requires central line
Sodium bicarbonate	Hyperkalemia, TCA overdose	1 mEq/kg	Not for routine use
Magnesium sulfate	Torsades de pointes, hypomagnesemia	Maximum single dose: 2g	Not for routine use

D10W, Dextrose 10% in water; *D25W,* dextrose 25% in water; *D50W,* dextrose 50% in water; *PEA,* pulseless electrical activity; *SVT,* supraventricular tachycardia; *TCA,* tricyclic antidepressant; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White.

survival 9%.[33–36] Doses of epinephrine greater than 0.01 mg/kg do not improve survival. Pre-filled code cart epinephrine syringes may lead to substantial overdoses in infants.[37] The benefits of epinephrine may not extend to *non*-pulseless events, with a recent observational study showing decreased survival (RR = 0.79; 95% CI, 0.74 to 0.85) with epinephrine administration within the first 10 minutes of resuscitation for children with bradycardia and poor perfusion.[38]

There is mounting evidence to suggest that certain commonly administered medications are associated with decreased survival and poorer neurologic outcome. Bicarbonate continues to be used in two thirds of pediatric in-hospital arrests despite evidence suggesting empiric administration is associated with decreased survival (OR = 0.80; 95% CI, 0.65 to 0.97).[39] Similarly, calcium is administered in nearly half of pediatric in-hospital cardiac arrests, despite an association with decreased survival and poorer neurologic outcome. Atropine is also often administered inappropriately, including in 1 of every 5 out-of-hospital pediatric arrests.[40] These drugs should be reserved for specific indications (Table 158.2).

The ideal drug for ventricular tachycardia and pulseless ventricular tachycardia remains unclear, with recommendations extrapolated from adult data. A prospective study of in-hospital pediatric arrest with shockable rhythms found that there were no differences in return of circulation or mortality (RR = 1.0; 95% CI 0.63 to 1.6) between lidocaine and amiodarone.[41] The implications of this study for out-of-hospital cardiac arrest are uncertain. Without further evidence or consensus, either agent seems appropriate.

Dosing of medications during pediatric cardiac arrest can be difficult; accurate administration requires correct estimation of weight, determination of weight-based dose, and conversion of weight to volume. Time spent on these tasks increases clinicians' cognitive load and errors. Estimations based on length (Broselow-Luten) or upper extremity circumference (Mercy TAPE) are better than estimates based on appearance or age, but may underestimate weight in obese children or overestimate in underweight children.[42] Parents tend to be more accurate than these estimation methods.[43] Regardless, these estimates do not eliminate all dosing errors because clinicians still have to calculate volumes of medications. Utilization of color coded, prefilled syringes corresponding to the weight, or precalculated medication charts or applications based on a standardized formulary may mitigate these dosing errors.[44]

Confirmation of weight estimates reduces errors. Often in the rush of resuscitation, inaccurately estimated weights result in inappropriate equipment and medications. The finger counting method can confirm an estimated weight. The clinician counts age on the left hand, starting with 1 on the thumb and counting by odd numbers to 9 on the small finger (i.e., 1–3–5–7–9 years of age). Weight in kilograms is counted on the right hand, starting with 10 kg and counting by 5 to 30 kg on the small finger (i.e., 10 kg–15 kg–20 kg–25 kg–30 kg). Fingers are matched between hands to estimate weight based on age. To prepare appropriate equipment and medications, emergency clinicians should ask EMS providers for the child's approximate weight.

Vascular Access. The particular site of vascular access is less important than its timely acquisition. Peripheral venous and intraosseous drug administration produce similar onset of drug action and peak levels for the commonly administered resuscitation drugs.[45] Prolonged delays are common in the ED; nearly half of children in the resuscitation area of an ED required greater than 90 minutes to obtain vascular access.[46]

For children in arrest or imminent arrest, an immediate attempt to obtain intraosseous access saves time. Intraosseous access is more successful and faster with minimal complications compared to peripheral or central access in critically ill patients.[47] Directing the needle away

TABLE 158.3 Monitoring After Return of Circulation

Parameter	Assessment	Goal	Action
Oxygen	Arterial blood gas; continuous pulse oximetry	SpO_2 94%–99% PaO_2 80–200 mm Hg	Titrate FiO_2
Carbon dioxide	Continuous capnography	$PaCO_2$ 35–45 mm Hg	Adjust respiratory rate
Perfusion	Arterial line; lactate; urine output	Avoid SBP <70 + 2 × age	20 mL/kg of isotonic fluid; norepinpehrine 0.1–2 mcg/kg/min
Heart rhythm	Continuous cardiac monitor	Avoid arrhythmias	Treat if arise; no prophylaxis
Glucose	Blood glucose	Avoid glucose <60	Dextrose
Temperature	Continuous core temperature	<38	Antipyretics; cooling blanket
Sedation		Avoid shivering	Fentanyl; midazolam
Seizure	EEG	Termination of seizure	Midazolam; phenytoin or levetiracetam

EEG, Electroencephalogram; *SBP,* systolic blood pressure.

from the growth plate during insertion reduces the risk of injury to the growth plate; long-term follow up has shown minimal adverse impact on bone growth from intraosseous placement alone. Monitoring of the insertion site allows detection of compartment syndrome, which can arise from excessive insertion of fluids into a needle misplaced in the subcutaneous tissue. Powered intraosseous insertion devices, such as the EZ-IO (Vidacare), may decrease insertion times and improve the frequency of successful insertion; although, other powered devices that require calibration, such as the Bone Injection Gun (WaisMed) may delay insertion and reduce the frequency of success. Manual placement may avoid insertion through the posterior cortex in children less than 8 kg.[48] In young children, the tibia and femur are preferred, because their marrow cavity is well developed. When administering fluid through an intraosseous line, manual pressure is helpful to overcome the resistance of the marrow cavity. Multiple injections of smaller (10 mL) syringes of fluid (i.e., "flushes") can resuscitate infants and small children through an intraosseous needle. Surveys suggest physicians often unnecessarily delay attempts at intraosseous access while attempting peripheral or central access. Central line access should typically be reserved for children requiring prolonged vasopressors. The femoral vein is the easiest site of cannulation in young children.

Termination of Resuscitation. There are no universal criteria to guide the termination of a pediatric resuscitation. Emergency clinicians are less comfortable terminating efforts in children than adults, often resulting in prolonged, futile resuscitations that increase stress on families and staff. There are anecdotal reports of children surviving with good neurologic outcome after prolonged resuscitations, but these often involve in-hospital arrests or arrests with prompt access to extracorporeal membrane oxygenation (ECMO). Several variables, including length of resuscitation, unwitnessed arrest, initial cardiac rhythm, administration of multiple doses of epinephrine, administration of atropine, and $ETCO_2$ less than 10 mm Hg have been associated with low survival and poor neurologic outcome.[49,50] However, none of these variables possess sufficient discriminative ability to provide absolute cutoffs for termination of resuscitation. Perhaps the most predictive variable is duration of resuscitation; a multicenter retrospective analysis indicated that for every additional minute of pediatric CPR, the frequency of survival decreased by 2.1%. For traumatic arrest, guidelines suggest prehospital termination after 30 minutes of unsuccessful resuscitation.[51] A recent large retrospective study of pediatric arrest following traffic accidents found that when CPR was necessary for greater than 15 minutes, less than 1% of children survived and all had poor neurologic outcome.[52] Such guidelines do not exist for atraumatic arrest. Guidelines designed for adults, such as the Termination of Resuscitation rule, fail to predict survival in children adequately and should not be employed.[53] Outside of family wishes and specific clinical situations where prolonged resuscitation may be beneficial (e.g., hypothermia with drowning or electrocution, in-hospital arrest, or prompt access to ECMO), we recommend considering termination of resuscitation after 30 minutes for atraumatic causes and 15 minutes for traumatic causes. This approach can minimize suffering for the patient, family, and staff.

E-CPR

When readily available, physicians should also consider ECMO early in an arrest course. Although initial studies suggested ECMO provided greater benefits for patients with underlying cardiac disease, a retrospective analysis also identified benefits for children with non-cardiac etiologies of their arrest. Pediatric critical care centers performing high volumes of ECMO and with rapid response teams to initiate timely cannulation have better outcomes. ECMO also should be considered for children with return of circulation but refractory shock, particularly cardiogenic shock.

Post-Arrest Care

For children with return of circulation, several actions may improve survival and neurologic outcome. Focus should shift to treating the underlying etiology of the arrest, minimizing brain injury, and improving end-organ perfusion. This requires monitoring oxygen, carbon dioxide, blood pressure, temperature, glucose, and urine output (Table 158.3).

Blood Pressure

Hypotension develops in over half of children following in-hospital cardiac arrest and predicts increased mortality. A single episode of hypotension (<5th percentile for age) within the first 6 hours after arrest is associated with decreased survival (OR = 0.39; 95% CI, 0.20 to 0.74).[54] More frequent episodes of hypotension further reduce survival. Arterial pressure monitoring facilitates early detection of hypotension; we recommend it for children with hypotension or protracted courses in the ED. While avoidance of hypotension (<5th percentile for age, estimated as systolic blood pressure <70 + age × 2) reduces mortality, the ideal blood pressure target is unknown.

It is also not clear if augmentation of blood pressure with intravenous fluids or vasopressors mitigates the mortality risk. Although vasopressors can help maintain end-organ perfusion in the setting of post-arrest myocardial dysfunction, in observational studies their use has not improved survival. There are no randomized studies of comparing the performance of particular vasopressors for pediatric post-arrest care. In the absence of strong evidence, we administer intravenous fluid

boluses and norepinephrine or push dose epinephrine to maintain systolic blood pressure greater than 5th percentile. Norepinephrine causes fewer arrhythmias than dopamine in adults and is the preferred first-line vasopressor in the post-arrest period. Push dose epinephrine can augment blood pressure while a norepinephrine drip is prepared. Concurrent administration of dobutamine may be necessary to achieve hemodynamic stability in patients with refractory cardiogenic shock.

Ventilation and Oxygenation

Significant alterations in oxygenation and ventilation may also increase mortality. These are quite common; less than one fifth of children have normal oxygen and carbon dioxide levels when measured during the first 6 hours after return of circulation. Confirming the results of a prior smaller study focused on pediatric cardiac arrest, a recent large study of 6250 critically ill children found that severe hyperoxemia ($PaO_2 \geq$ 300 mg Hg) increased mortality (OR = 1.5, 95% CI, 1.1 to 2.1) and recurrent hyperoxemia further increased mortality (OR = 2.5, 95% CI, 1.6 to 3.9).[55] Ventilator settings should be adjusted to maintain oxygen saturations above 94%, while avoiding PaO_2 levels greater than 300 mm Hg. Hypocapnia induces cerebral vasoconstriction, exacerbating ischemia. Meanwhile, hypercapnia leads to vasodilation and cerebral edema. While end tidal CO_2 measurement may allow assessment of trends in carbon dioxide levels, alteration in alveolar dead space in the post arrest period may lead to end tidal CO_2 not accurately representing $PaCO_2$. Therefore, we measure CO_2 directly with a blood gas. Notably, studies of post-arrest oxygenation and ventilation are limited by the timing of oxygen and carbon dioxide measurement, and therefore the true impact of abnormalities on survival is not clear. Nevertheless, in the absence of strong evidence, we recommend adjusting ventilator settings in the post-arrest period to normalize carbon dioxide and oxygen levels.

Targeted Temperature Management

Maintaining normothermia is most important. Theoretically, hypothermia reduces many of the complications seen with reperfusion after cardiac arrest by reducing metabolic demand and free radical production. However, two large randomized control trials of targeted temperature management in children failed to show benefit for children who received induced hypothermia. In a randomized trial of 260 children with out-of-hospital cardiac arrest, targeted temperature management to 33°C (range of 32°C to 34°C) with automated cooling blankets for 120 hours demonstrated no difference from therapeutic normothermia (target temperature of 36.8°C, range of 36°C to 37.5°C) in survival or favorable neurologic outcome (RR = 1.59; 95% CI, 0.89 to 2.85).[56] A subsequent randomized controlled study of 329 children with in-hospital cardiac arrest was terminated early because targeted temperature management to 33°C with the same protocol did not improve survival (RR = 0.92; 95% CI, 0.67 to 1.3).[57] When the in-hospital and out-of-hospital studies were combined to increase the power of the study, targeted temperature management to 33°C continued to show no benefit on survival or favorable neurologic outcome, including in subgroup analyses.[58] These studies were multicenter without standardization regarding other elements of post-arrest care, potentially limiting the conclusions. The 2019 PALS update endorses targeted temperature management or avoidance of hyperthermia as "reasonable" options.[6] In the absence of strong evidence, we recommend monitoring core temperature and focusing on the avoidance of hyperthermia (target temperature of 36°C to 37.5°C) with external cooling and antipyretic medications. If cooling is employed, children should not be allowed to reach temperatures less than 32°C, which increases mortality.[59]

Glucose

In response to the stress of cardiac arrest, alterations in glucose levels are also common. In theory, significant hyperglycemia produces an osmotic diuresis, which impairs perfusion. In critically ill children not suffering from cardiac arrest, hyperglycemia worsens outcomes. However, in pursuit of euglycemia with insulin administration, children often become hypoglycemic. Critically ill children randomized to a lower target glucose (80 to 110 mg/dL) had more frequent episodes of profound hypoglycemia but similar mortality and duration of intensive care unit (ICU) stay compared to higher glucose levels (150 to 180 mg/dL).[56] In the absence of strong evidence in post-arrest care, we recommend targeting modest glucose control (80 to 180 mg/dL) and vigilant avoidance of hypoglycemia.

Arrhythmia and Seizures

Children may develop arrhythmias or seizures following reperfusion. Premature atrial or ventricular contractions are most frequent, particularly with vasopressor administration, and do not require therapy. In contrast, ventricular arrhythmias may arise and require prompt administration of antiarrhythmics (see Table 158.3). Seizures arise in 10% of children, with over two thirds of cases evolving into status epilepticus.[60] As seizures are associated with poor neurologic outcome, consensus guidelines recommend continuous electroencephalogram (EEG) monitoring as soon as possible to detect non-convulsive status, which is common.[61–63] While there are no randomized trials in children seizing after arrest, we recommend benzodiazepines, followed by fosphenytoin or levetiracetam, for seizures.

Family Presence

We endorse the recommendation from the American College of Emergency Physicians (ACEP) and American Academy of Pediatrics (AAP) that physicians offer family the opportunity to be present during their child's resuscitation. The limited evidence to support this recommendation is primarily descriptive or survey-based. Most families want to be present for the resuscitation of their child, and when asked after being present, they report that they would repeat the experience, even if their child died. Families report their presence helps them appreciate the efforts of clinicians, facilitates their understanding of the gravity of the situation, and facilitates the grieving process. In contrast, surveyed physicians frequently are reluctant to have families present, often mistakenly assuming families will impede care. In the only randomized study of family presence during trauma resuscitations in a pediatric ED, 93% of physicians reported increased stress from family presence. However, the adverse effects of family presence seemed limited to stress on the physician. No differences were detected in clinical care, and other studies have confirmed that family presence rarely hinders care. In most situations, the benefits to the family of being present outweigh the increased stress on clinicians.

Structured programs for family presence during resuscitations are helpful. Families should be counseled on anticipated events prior to entering the resuscitation. They should be informed that their presence in the resuscitation is their decision; although, they can be asked to leave if they impede medical care. Designated nurses or social workers with training in grief counseling and free of clinical responsibilities should focus on the family, explaining steps in the resuscitation and answering questions.

SEPTIC SHOCK IN THE PEDIATRIC PATIENT

Foundations

Background

Sepsis is the leading cause of death in children worldwide. Globally, 8% of children in the ICU have severe sepsis with mortality approaching 25%.[64] Young age (<1 month), immunosuppression, chronic debilitating disease, presence of invasive devices, and genitourinary anomalies

increase the risk of sepsis and severe disease.[65,66] Rates of sepsis have increased over time, likely due to increased recognition. Mortality has decreased, likely a result of immunizations and the implementation of consensus recommendations. While these guidelines are not grounded in strong evidence, EDs in the United States implementing these guidelines have reduced mortality and length of stay. Nevertheless, variation and uncertainty persist for multiple elements of ED sepsis management, particularly the optimal approaches to screening, diagnosis, fluid administration, and vasoactive therapy.

Pathophysiology

Sepsis arises when immune dysregulation following an infection promotes pro and anti-inflammatory cascades that may manifest in vasodilation, myocardial depression, activation of the complement system, disseminated intravascular coagulation, and increased production of nitric oxide. Infection tends to arise from common bacterial and viral pathogens in the lungs, blood, urine, or the skin, with the most likely organism depending on the location of the infection and patient risk factors. Immunosuppressed children may develop less common bacterial or fungal infections. Unchecked, infections progress to shock with end-organ hypoperfusion and then multisystem organ failure.

Clinical Features

The diagnosis of sepsis is difficult, with numerous definitions in the literature. Definitions were derived from consensus only and were primarily established for research purposes. For example, the presence of SIRS criteria (abnormal temperature or white blood cell count and tachycardia or tachypnea) plus infection constitutes sepsis per guidelines, but many children with non-life threatening infections display SIRS criteria.[67] Differentiating these patients from patients with early sepsis is crucial, as delays in treatment of sepsis adversely impact outcomes. While definitions of sepsis were revised in adults to improve clinical application during the latest consensus conference (Sepsis-3), pediatric definitions have not been significantly revised in the last fifteen years. We extrapolate from the adult evidence and recommend strong consideration of sepsis in children with concern for infection, SIRS criteria, and any physical examination or laboratory findings of decreased perfusion or organ dysfunction.[68] Systematic screening allows for early detection of sepsis, but clinician assessment is necessary to confirm concern for sepsis and the need for treatment.

Most individual physical examination findings demonstrate poor diagnostic accuracy for sepsis. Hypotension is the most reliable indicator of septic shock and impending organ dysfunction, but it tends to develop late in the disease course, as children are able to maintain their blood pressure through tachycardia and vasoconstriction. In contrast to adults, hypotension is not universally present with pediatric septic shock. Other potential signs of organ dysfunction may be present, including toxic appearance, altered mental status, loss of consciousness, seizures, or respiratory failure. The combination of hypotension and delayed capillary refill together portended the highest mortality in a large study of patients transported to a pediatric ICU. Other findings, such as dry mucus membranes, sunken eyes, decreased urine output, height of fever, or rigors, have poor diagnostic accuracy for sepsis or shock.

Multiple scoring systems exist to identify early sepsis and predict outcomes. Similar to adults, the Quick Sequential Organ Failure Assessment (qSOFA) score may help identify patients with organ dysfunction. qSOFA includes altered mental status, hypotension, and tachypnea. In two large retrospective studies, an age adjusted qSOFA had lower sensitivity but much better specificity compared to SIRS for predicting mortality from pediatric sepsis.[69,70] Other scoring systems, such as the quick Pediatric Logistic Organ Dysfunction-2 Score (qPELOD2) have poorer diagnostic accuracy.[71]

Consensus guidelines define septic shock as hypotension refractory to administration of ≥40 mL/kg of intravenous fluids in one hour. From a practical perspective, we recommend considering any child with hypotension (blood pressure <5th percentile for age) to be in shock. While children may develop cold or warm shock, it is difficult to differentiate these processes without invasive monitoring. Laboratory testing may augment the diagnosis, but treatment should not be delayed if there is high clinical suspicion for sepsis. Venous blood gas can identify a metabolic acidosis and elevated lactate. In an observational study of children with SIRS, lactate greater than 4 mmol/L in the ED was associated with increased 30 day mortality (OR = 3.3; 95% CI, 1.2 to 9.2).[72] Efforts should be made to identify the source of the infection in order to target therapy. Bacteremia and urinary tract infections are common, so blood and urine cultures should be obtained from all patients. Risk-stratification strategies in a research setting include RNA expression profiling and novel serum biomarkers. These techniques hold promise in the future for more objective and systematic assessment to enable clinicians to distinguish children with more benign viral illness from those with early septic shock.

Management

The pillars of emergency treatment of pediatric sepsis are: (1) timely establishment of intravascular access; (2) rapid fluid resuscitation titrated to patient condition; (3) appropriate, broad-spectrum antibiotics; and (4) individualized vasoactive agents directed to reverse shock (Table 158.4).

The 2020 pediatric Surviving Sepsis Campaign guidelines strongly recommend **antibiotic** administration as soon as possible and within 1 hour of recognition of septic shock.[73] Delays in appropriate antimicrobial therapy increase mortality and prolong organ dysfunction in pediatric patients with severe sepsis or septic shock.[74] For children with sepsis-associated organ dysfunction but not shock, guidelines recommend antibiotic administration as soon as possible and within 3 hours of recognition. This allows time to acquire laboratory studies to help differentiate sepsis from other infections. Acquisition of blood cultures should not delay administration of antibiotics. While host factors, suspected source, and local susceptibility patterns should guide antibiotic selection, children with septic shock or organ dysfunction typically require broad spectrum antibiotic therapy in the ED. For otherwise healthy children with community acquired sepsis, a third-generation cephalosporin, such as ceftriaxone, is often appropriate. For chronically ill children or hospital acquired sepsis, an antipseudomonal cephalosporin, such as cefepime; a carbapenem, such as meropenem; or extended spectrum penicillin, such as piperacillin/tazobactam is appropriate. Additional antibiotics may be required in children at risk for drug resistance. Antibiotics can later be tailored to culture results. There is not strong evidence to suggest that children with sepsis require multiple antibiotics targeting the same organism, although multiple antibiotics may be appropriate in certain high-risk scenarios, such as septic shock in immunocompromised children. If available, an infectious disease physician can help guide antibiotic therapy for complex patients.

Septic shock in children is most frequently marked by relative or absolute hypovolemia; outcomes from shock in children are improved when the shock state is reversed as early as possible. Cohort studies have demonstrated improved mortality and hospital length of stay in septic children with hypotension or organ dysfunction treated with 40 to 60 mL/kg of **intravenous (IV) fluid** in the first hour. A highly publicized randomized controlled trial in African children with severe infection, but not hypotension, demonstrated increased mortality in patients receiving 20 to 40 mL/kg in the first hour compared to no fluid. This outcome likely is specific to the setting, as there were limited

resources and a high frequency of malaria and anemia. In another single, small study, rapid administration of fluid bolus in less than 10 minutes increased the risk of needing mechanical ventilation. We follow the 2020 Surviving Sepsis guidelines and administer up to 40 to 60 mL/kg in the first hour.[75,76] Fluid resuscitation should be goal-directed and continue until vital signs and signs of perfusion improve, which may necessitate administration of multiple 10 to 20 mL/kg boluses.

TABLE 158.4 Bundled Management of the First Hour of Septic Shock

	Key Features	Sample Regimen
Antibiotics	Broad spectrum; MRSA coverage if indwelling catheter; Pseudomonas coverage if nosocomial infection	Cefepime 50 mg/kg +/– Vancomycin 20 mg/kg
Fluids	Large bore intravenous access; Bolus isotonic fluid; Monitor fluid responsiveness	20 mL/kg lactated Ringers over 10 min
Vasopressors	Hypotension refractory to fluids	Epinephrine 0.05 mcg/kg/min
Cultures	Blood, urine cultures; Viral testing based on clinical suspicion; Should not delay antibiotics	2nd blood culture if indwelling line
Monitoring	Frequent bedside assessments for signs of fluid overload	Cardiorespiratory monitoring; arterial line for hypotension; not routinely need central venous pressure, mixed venous saturation

MRSA, Methicillin-resistant Staphylococcus aureus.

Concomitant with fluid administration, clinicians should monitor children for signs of fluid overload and reduce or stop fluids for any signs of pulmonary edema (e.g., tachypnea) or new hepatomegaly. Notably, hypoperfusion may persist despite correction of hypotension. Similarly, tachycardia may persist despite restoration of perfusion. In resource limited settings, clinicians should be cautious about reflexively administering excessive amounts of fluid, and guidelines recommend a maximum of 40 mL/kg over the first hour.[73] Most children will not require invasive monitoring in the ED to assess fluid responsiveness.

We recommend prompt acquisition of large bore intravenous access via an intravenous or intraosseous line and fluid bolus administration early in presentation. Fluid can be administered using a "push-pull" inline syringe, rapid infuser, or pressure bag to achieve a goal of administering each 20 mL/kg crystalloid fluid bolus over 10 to 20 minutes, followed by reassessment and potentially additional boluses (Fig. 158.2). There is conflicting evidence from two large retrospective studies about the benefits of balanced fluids, such as lactated Ringers, versus normal saline.[77,78] When data from these studies was combined it showed decreased mortality with balanced fluids. Based on this result and other studies in adults, the 2020 pediatric guidelines recommend administration of balanced fluids.[73] There is *insufficient* evidence to support routine administration of albumin or starches in the resuscitation of children in septic shock in the ED.

If shock does not improve with administration of 60 mL/kg of isotonic fluid, or if signs of fluid overload develop in the setting of ongoing hypoperfusion, children should receive **vasoactive agents**. Epinephrine or norepinephrine may serve as the first-line agent in pediatric septic shock. In two small studies, epinephrine was associated with more rapid resolution of shock and decreased mortality compared to dopamine.[79,80] Therefore, epinephrine (0.05 mcg/kg/min) is our standard first-line agent. If the child's status does not improve with the initial agent, then a second vasopressor should be administered. There is no evidence to guide the choice of the second agent. We initiate vasoactive agents in any pediatric patient with septic shock and hypotension lasting more than 1 hour, regardless of the amount of fluid delivered.

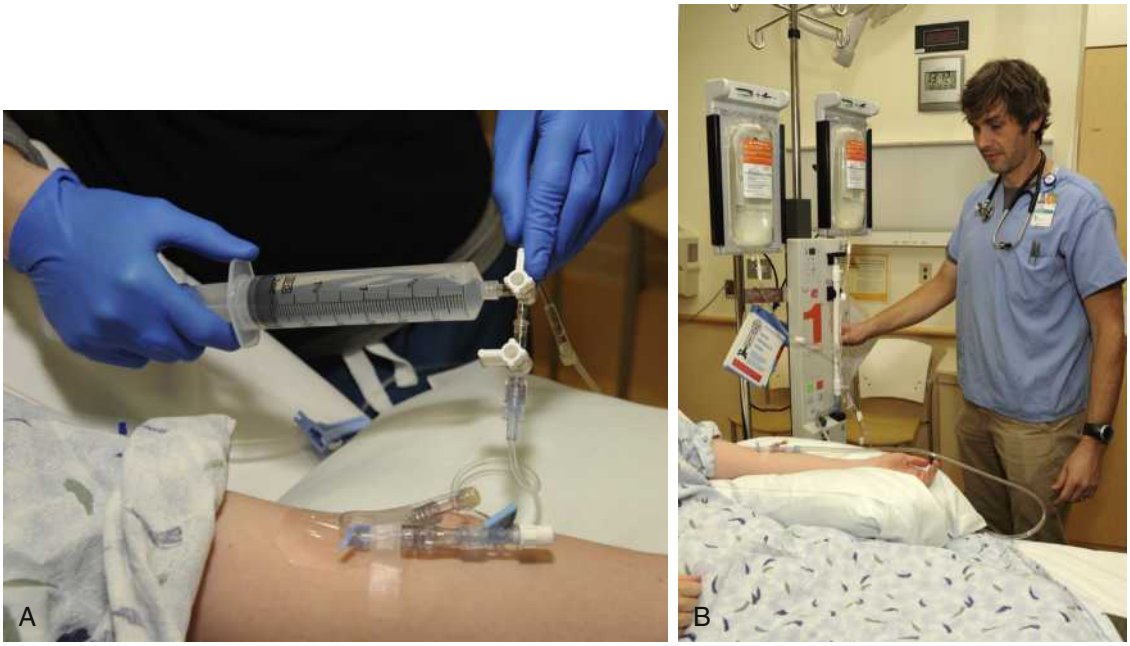


Fig. 158.2 (A) Using a 60-mL syringe with an inline three-way stopcock is an effective way to deliver rapid fluid boluses, particularly in patients less than 25 kg where a bolus is not easily dosed by a standard fluid bag. (B) Rapid infusers and pressure bags rapidly deliver fluid boluses when a full bag is an appropriate dose. (Courtesy Tia Brayman, Children's Hospital Colorado.)

Obtaining central venous access in an ill child is an uncommon procedure in most EDs, and it is a frequent source of delayed care in pediatric septic shock. Instead, we recommend rapid vascular access in critically ill children with large bore peripheral IV catheters or an intraosseous device. Vasoactive infusions can be administered through a peripheral IV catheter to correct shock until a central venous catheter can be placed safely.

Critical illness-related corticosteroid insufficiency is moderately prevalent in pediatric sepsis, and nearly half of septic children receive exogenous **corticosteroids**.[64] However, there is insufficient evidence to support or refute this practice. A small retrospective study found increased mortality with hydrocortisone administration to children with catecholamine resistant shock.[81] Nevertheless, based on larger studies in adults, we administer hydrocortisone (50 to 100 mg/m^2 or 1 to 2 mg/kg, maximum 100 mg/dose) for children in shock refractory to fluids and vasoactive agents. The 2020 pediatric sepsis guidelines state hydrocortisone may be considered under these circumstances.[73]

Although, like adults, children with sepsis may be prone to stress hyperglycemia, they are also prone to hypoglycemia due to their limited glycogen stores. Tight and conventional **glycemic control** has shown equivalence in critically ill children; a large trial is currently underway to determine optimal glucose control strategies. We recommend correction of hypoglycemia and cautious use of insulin with frequent glucose monitoring for blood glucose levels more than 180 mg/day (10.0 mmol/L).

Combining the aforementioned therapies into a **bundle** appears to improve outcomes. A large prospective, multicenter, observational study found that administration of a bundle of antibiotics and fluids coupled with acquisition of blood cultures within one hour reduced mortality (OR = 0.59; 95% CI, 0.38 to 0.93).[82] Notably, administration of each individual element within one hour was not associated with decreased mortality. The 2020 pediatric Surviving Sepsis guidelines recommend a bundled approach for children with signs of organ dysfunction.[73] EDs should establish protocols to ensure acquisition of a blood culture and administration of a fluid bolus and antibiotics within one hour. Despite a mandate at participating hospitals in the aforementioned study to complete the bundle within one hour, less than one in four children met this mandate. Therefore, EDs should have continuing quality improvement measures which facilitate and encourage use of a bundled protocol.

Monitoring Response to Therapy

There are limited options to assess response to therapy beyond the physical examination. Clearance of lactate may reflect reversal of tissue hypoxia. In a small prospective observation study, children whose lactate decreased to less than 2 mmol/L within 3 to 4 hours had less organ dysfunction (RR = 0.46; 95% CI, 0.29 to 0.73).[83] Passive leg raise may predict fluid responsiveness, but there are no large studies in pediatric sepsis. Transthoracic echocardiography may establish a role in refractory septic shock in the future; small studies suggest between 41% and 71% of children have myocardial dysfunction.[84,85] Currently there is insufficient evidence to support routine ED utilization of other modalities for treatment response, including mixed venous oxygen saturation monitoring, central venous pressure, biomarkers, or non-invasive cardiac output monitors.[86]

Brief Resolved Unexplained Events

Background

In 2016, the American Academy of Pediatrics published consensus guidelines creating a new term, BRUE, to describe infants less than 1 year of age presenting with transient alterations in their breathing, appearance, or behavior that cannot be explained based on their history or physical examination.[87] BRUE has supplanted apparent life-threatening event (ALTE), a term that was too broad in scope to be clinically useful. BRUE is more precise and allows for the establishment a low-risk group of infants that do not require further evaluation. The hallmark of a BRUE is that the cause for the event is unclear. As a result, children with potential explanations for their presentation are not classified as having BRUEs, e.g., a child with a transient episode of cyanosis in the setting of congestion is not a BRUE.

TABLE 158.5 Brief Resolved Unexplained Event Compared to Apparent Life-Threatening Event

	BRUE	ALTE
Defining characteristics	Change in breathing, tone, color	
Other elements	Possible alteration in consciousness	Apnea; possible choking, gagging
Perception	Concerning to clinician	Concerning to lay observer
Etiology	Unexplained	Unexplained or GERD, seizure, infection, etc.
Age	<1 year	<1 year
Duration	<1 min	Any
History	Unrevealing	May identify etiology
Vital signs	Normal	May be abnormal
Physical examination	Normal	May identify etiology

ALTE, Apparent life-threatening event; *BRUE,* brief resolved unexplained event.

Clinical Features

With a BRUE, a child may have changes in breathing, tone, or responsiveness. Breathing may be absent, decreased, or irregular, potentially leading to central cyanosis or pallor. This does not include acrocyanosis, perioral cyanosis, rubor, or periodic breathing, which are commonly encountered in healthy infants. Infants may have increased or decreased tone, although this does not include hypertonia with crying or straining, which is normal.

There are multiple differences between BRUEs and ALTEs (Table 158.5), but the primary distinction is that the emergency clinician cannot determine any potential etiology for a BRUE. On presentation to the ED, the infant appears well without any examination abnormalities. Therefore, to determine if an event constitutes a BRUE, clinicians should focus on historical circumstances before, during, and after the event. Certain features may suggest a common or dangerous etiology and indicate the event does not represent a BRUE (Table 158.6).

If no etiology for the event is apparent, BRUEs can be classified further into high or low risk events. Low-risk infants are those born ≥32 weeks and greater than 60 days of age with no prior BRUEs, and CPR (by a health care provider) was not performed during the event. If these features are present, infants are potentially at higher risk of recurrent events or adverse outcomes. Several retrospective studies have confirmed the diagnostic accuracy of these criteria.[88,89]

Management

As the concept of BRUE is relatively new, there is not strong evidence to guide management. However, evidence extrapolated from children with ALTEs suggests that testing low-risk BRUEs is low yield, and we recommend limiting routine testing to an electrocardiogram, which

TABLE 158.6 Presenting Features of Common Conditions Leading to Transient Alterations in Breathing, Responsiveness, or Color in Infants

Condition	Potential Features
GERD	Choking, gagging, vomiting, after feed; Often turn red; Brief apnea
Respiratory infection (RSV, pertussis)	Congestion, cough; Tachypnea; Adventitial lung findings
Seizure	Convulsions; Altered consciousness; Eye deviation
NAT (brain hemorrhage)	Delayed presentation; Inconsistent history; Signs of trauma; Head circumference >95th percentile
Bacterial infection (UTI, bacteremia, meningitis)	Fever; Lethargy; Irritability

GERD, gastroesophageal reflux disease; *NAT,* nonaccidental trauma; *RSV,* respiratory syncytial virus; *UTI,* urinary tract infection.

displayed high sensitivity for arrhythmias and structural heart disease in children with ALTE. While cardiac abnormalities are rare causes of BRUEs, an electrocardiogram is safe, inexpensive, and easy to obtain. For children with signs of central apnea during their event, we consider pertussis testing, as infants may develop apnea before they manifest other respiratory symptoms.

Guidelines explicitly discourage routine acquisition of other tests, including blood, CSF, radiography, EEG, echocardiogram, or testing for gastroesophageal reflux disease (GERD). Moreover, typically viral respiratory testing, urinalysis, or neuroimaging are not necessary for low-risk infants. These guidelines appear to have reduced testing over time.[90,91] There is no definitive evidence about the benefit of ED observation or pulse oximetry measurement, but we observe low-risk infants for 2 to 4 hours in the ED with intermittent pulse oximetry assessments.

There is little evidence for the management of high-risk BRUEs. We agree with a recently proposed tiered approach.[92] To determine occult etiologies for a high-risk BRUEs, we recommend obtaining a respiratory viral panel, hematocrit, glucose, bicarbonate, and lactic acid, as well as a feeding evaluation and screen for non-accidental trauma, to be completed by a social worker. If the evaluation is unrevealing, we recommend the patient be admitted for further evaluation and continued monitoring. Where ED resources are limited or in high demand, some children may require admission to complete this evaluation. This approach is derived from consensus and has not been studied.

Disposition

Low-risk BRUEs are unlikely to benefit from hospitalization and therefore guidelines recommend discharge from the ED with outpatient follow-up within 24 hours. Parents may be reluctant to return home, but a recent meta-analysis may provide reassurance.[93,94] Pooling of data from 3,005 infants found no increased risk of death following a BRUE.[95] There is no evidence to support outpatient cardio-respiratory monitoring.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 158: QUESTIONS AND ANSWERS

1. You are treating a 4-month-old with bronchiolitis. While being observed in the ED, the child becomes bradycardic and then loses pulses. What should be the primary focus of your initial minutes of the resuscitation?
   - **a.** Preparing to insert an endotracheal tube to improve oxygenation and ventilation
   - **b.** Correction of potential acidosis with bicarbonate
   - **c.** Vascular access to administer epinephrine
   - **d.** Uninterrupted compressions with ventilations via bag-mask device

Answer: d. At the beginning of the arrest, the most important elements are restoration of perfusion and ventilations with compressions and ventilations. Early insertion of an endotracheal tube is likely to impede compressions, and initial ventilations should occur with a bag valve mask and oral airway. Vascular access will be needed but is not as time sensitive. Bicarbonate should be given only if there is a clear indication.

2. After return of circulation, which action is most critical to improve a child's prognosis?
   - **a.** Empiric amiodarone to prevent arrhythmias
   - **b.** Avoidance of hypotension
   - **c.** Induced hypothermia to 33°
   - **d.** Strict glucose control less than 110 mg/dL with an insulin drip
   - **e.** Maintenance of oxygen saturation at 100%

Answer: b. A single episode of hypotension increases mortality and therefore efforts should be made to avoid it. Induced hypothermia does not appear to improve outcomes in pediatric arrest. Strict glucose control, hyperoxemia, and empiric amiodarone are not beneficial and may induce harm.

3. A 6-year-old male with Trisomy 21 presents with decreased responsiveness and not eating. His temperature is 39°C, heart rate is 150, blood pressure is 80/55, respiratory rate is 24, oxygen saturation is 98%, and glucose is 90 mg/dL. He receives cefepime and 20 mL/kg of lactated Ringers but his vital sign abnormalities persist. On examination, he is lethargic with a neck that is supple, lungs that are clear to auscultation, cool extremities, and capillary refill of 3 seconds. What is the next best step in the management?
   - **a.** Hydrocortisone 50 mg/m^2
   - **b.** Vancomycin 50 mg/kg
   - **c.** Epinephrine 0.05 mcg/kg/min
   - **d.** Lactated Ringers 20 mL/kg

Answer: D. This child is in septic shock. He received an initial fluid bolus but has ongoing signs of decreased perfusion. In the absence of signs of pulmonary edema, the next step should be to administer another bolus of isotonic fluids. He may benefit from epinephrine and vancomycin but after a second bolus is initiated.

4. A 4-month-old girl presents after changing color and tone at home. She was feeding and started to choke. She turned red-purple in her face and upper body while her arms stiffened. After 30 seconds, she spit up some formula, and the episode resolved. She was born full-term and has no other medical issues. In the ED she is asymptomatic and has a normal physical examination. What is your next step in the management of this patient?
   - **a.** Discharge after 2 hours of observation
   - **b.** Classify the event as a high-risk BRUE and admit to the hospital
   - **c.** Obtain a pH probe to assess for GERD
   - **d.** Obtain an ECG and blood glucose

Answer: a. Choking in the setting of feeding with complete resolution of the symptoms after vomiting suggests reflux. As a potential etiology is apparent based on the history, this event should not be classified as a BRUE. Diagnostic testing is not necessary; pH probes are not specific for GERD and are rarely helpful in the ED.

5. Which of the following medications have shown a mortality benefit for children in arrest without a clear etiology?
   - **a.** Calcium chloride 20 mg/kg
   - **b.** Sodium bicarbonate 1 mEq/kg
   - **c.** Epinephrine 0.01 mg/kg
   - **d.** Normal Saline 20 mL/kg

Answer: c. There are no randomized control trials of medications in pediatric arrest. However, observational studies suggest that epinephrine is beneficial. Other medications are only beneficial for specific indications, such as glucose for hypoglycemia.

Neonatal Resuscitation

Ryan D. Kearney

KEY CONCEPTS

- Resuscitation should be anticipated for all deliveries; 10% of newborns will require some resuscitation, and 1% will require advanced life support interventions after birth.
- Predictable indications for resuscitation include hypoxia, hypothermia, hypoglycemia, hypovolemia, prematurity, maternal infection, and adverse effects of maternal medication.
- Drying, warming, positioning, and stimulating the infant are sufficient resuscitative measures for most deliveries.
- Adequate ventilation will reverse most bradycardia, while oxygenation with more than 21% fraction of inspired oxygen (FiO_2) is not indicated for most neonatal resuscitations.
- The Neonatal Resuscitation Program (NRP) resuscitation algorithm provides a proven guide for management and its implementation has shown to improve short- and long-term outcomes, including neurodevelopment.
- Routine tracheal suctioning of vigorous and nonvigorous infants born through meconium-stained amniotic fluid is no longer recommended.
- Weight-based epinephrine and volume expanders are rarely required.
- Significant hypovolemia is rare in neonates. Hemorrhage is one of the few predictable situations in which volume expansion improves newborn outcome.
- Preterm infants and those born to mothers with suspected infection, including chorioamnionitis, should receive empirical antibiotic therapy. An acceptable regimen includes dual therapy with ampicillin and gentamicin.
- Any neonate with persistent cyanosis or signs of respiratory distress (e.g., grunting, nasal flaring, and tachypnea) should be assisted by continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV). Endotracheal intubation should be performed in several situations, such as when bag-mask ventilation is ineffective or prolonged, chest compressions are performed, an extremely low birth weight infant is born, and tracheal suctioning for meconium in infants results in failure to improve, despite effective PPV.
- Chest compressions are rarely required, because bradycardia generally responds to effective ventilation. However, compressions should be started for a heart rate (HR) less than 60 beats/min despite oxygen and adequate ventilation for 30 seconds.
- The umbilical vein is the preferred route of immediate vascular access, followed by peripheral veins, peripherally inserted central catheter lines, and the femoral vein. Intraosseous (IO) line placement can be problematic in neonates.
- No reliable and widely adopted set of parameters has been identified for newborns who should not receive resuscitative efforts. Unless there is clear family, parent, and health care provider agreement, resuscitation efforts should ensue.
- Infants receiving appropriate resuscitation efforts nonetheless showing no signs of life after 10 minutes may have further efforts withheld, particularly when this decision is in accord with parental preference.
- All newborns requiring intravenous (IV) line placement, medication administration, chest compressions, or endotracheal intubation should be transferred to an appropriate neonatal intensive care unit.

FOUNDATIONS

Approximately 10% of newborns require some assistance at birth, with 1% requiring extensive resuscitative measures.[1] Knowledge of neonatal physiology, appropriate equipment, and procedural skills is essential to successful resuscitation. Preparation for neonatal resuscitation requires an understanding of how it differs from pediatric and adult resuscitation:

1. Newborns have rapidly changing, dynamic cardiopulmonary physiology, with a unique range of normal vital signs.[2,3]
2. Neonatal resuscitation is almost entirely respiratory (not cardiac) management.[2]
3. Neonates require special and dedicated equipment.

TRANSITION FROM FETAL TO EXTRAUTERINE LIFE

The successful transition from fetal to extrauterine life requires three major cardiorespiratory changes: (1) removal of fluid from unexpanded alveoli to allow ventilation; (2) lung expansion and establishment of functional residual capacity (FRC); and (3) redistribution of cardiac output to provide lung perfusion. Failed development of adequate ventilation or perfusion leads to persistent shunting, hypoxia and, ultimately, a deleterious reversion to fetal physiology.[2]

In utero, fetal nutrient and gas exchange is dependent on the placenta, a temporary organ with remarkably low vascular resistance, as well as the maternal circulation. As a result of its low resistance, the placenta receives approximately 30% of total fetal cardiac output between 18 and 41 weeks of gestation. In contrast, fluid-filled fetal alveoli have increased vascular resistance, leading to poor perfusion of the developing lung. The pulmonary arterial bed is so vasoconstricted that the fetal lung receives only 40% of right ventricular output and approximately 10% of total cardiac output; most of the right ventricular output is shunted from the pulmonary artery through the ductus arteriosus to the descending aorta.[4,5] An additional right-to-left shunting occurs at the level of the foramen ovale, with relatively oxygen-rich blood shunted from the right to left atrium. Fig. 159.1 illustrates normal intracardiac fetal circulation. Reversal of these two shunts is essential to the successful transition into extrauterine life and is facilitated by the significant drop in pulmonary vascular resistance that occurs at birth. The first step in this process is alveolar fluid clearance.

Removal of this fluid is partially accomplished by vaginal delivery, which provides some compression of the fluid out of the alveoli into the bronchi, trachea, and pulmonary capillary bed. The remaining fluid is largely evacuated by the first few breaths, with the quality of the first few breaths crucial to establishing adequate ventilation. Alveolar expansion requires the generation of high intrathoracic pressures and the presence of surfactant to maintain alveolar patency. Because the lung is one of the last organs to reach structural and functional maturity,

Fig. 159.1 Meconium Aspirator With Suction and 3.0 Uncuffed Endotracheal Tube (ETT) Attached. (Courtesy Seattle Children's Hospital, Seattle, WA.)

interruptions in this coordinated physiologic process, although rare, should be nonetheless anticipated in all deliveries, particularly those outside of the delivery room.[6]

After the first few breaths, pulmonary vascular resistance decreases as a result of alveolar oxygen exposure. Simultaneously, clamping of the umbilical cord removes the placenta from circulation, predictably increasing systemic vascular resistance. Shunting through the ductus arteriosus reverses as systemic vascular resistance increases; this usually ceases altogether by 15 hours of age as the ductus arteriosus also constricts. This reversal of flow redirects all right ventricular output to the lungs. However, hypoxia or acidosis can cause the pulmonary vascular bed to constrict again, and, when severe or prolonged, recurrent pulmonary vascular constriction can cause the ductus arteriosus to reopen. The reinstitution of fetal circulation, with its attendant shunting, leads to ongoing hypoxia and is termed *persistent fetal circulation*.[2] When indicated, resuscitation facilitates the first few breaths, prevents and reverses ongoing hypoxia and acidosis, and assists the newborn in the transition to extrauterine life.

SPECIFIC ISSUES

Indications for Resuscitation

At least one person, whose exclusive role is to ensure safe transition of the newborn, should be present for all deliveries, including those that occur outside the delivery room. Any infant born outside of a delivery room should be anticipated to need resuscitation.[1–3] Although minimal intervention may be required, a standardized approach should still be followed. Some specific conditions increase the likelihood that additional resuscitative efforts will be required.

Hypoxia

Even in the uncompromised newborn, it can take 10 minutes for blood oxygen saturation to reach normal extrauterine levels.[1] Pulse oximetry may assist in determining hypoxemia, but it may take several minutes for a reliable waveform to be achieved.[7,8] In utero or intrapartum asphyxia (pathologic lack of oxygen to the fetus before or during delivery) can precipitate a sequence of events that results in primary or secondary apnea. With initial hypoxia, rapid gasps are followed by cessation of respirations (primary apnea) and, if prolonged, decreased heart rate (HR). Ostensibly normal respiratory effort does not ensure adequate ventilation. However, bradycardia in the newborn (HR < 100 beats/min) almost always reflects inadequate ventilation and oxygenation. As such, bradycardia is a major indicator of hypoxia.[1,2] Simple stimulation is required at the onset of primary apnea to stimulate ventilation and reverse bradycardia. If asphyxia persists, the newborn takes several final deep, gasping breaths, followed by cessation of respirations (secondary apnea); this is accompanied by worsening bradycardia, refractory to simple stimulation, and eventually hypotension. For newborns with secondary apnea, more vigorous and prolonged resuscitation is needed to restore ventilation and adequate circulation.[2]

Hypothermia

Drying and warming the newborn are vital to initial resuscitation because the newborn's inability to maintain normothermia (>36.5°C [97.7°F]) has potentially dire consequences. Newborns cannot generate heat by shivering, cannot retain heat due to low fat stores, and have excess heat loss due to their large surface-to-volume ratio. Exacerbating these challenges in the immediate postpartum period, newborns have an acutely elevated metabolic rate, are covered with amniotic fluid, and are suddenly exposed to a relatively cool environment. Body temperature rapidly decreases, with hypothermia accelerating metabolic acidosis, oxygen consumption, hypoglycemia, and apnea.[1–3] Prematurity and very low birth weight status exacerbate these consequences and require extra efforts to mitigate.[1]

Hypoglycemia

Poor glycogen stores, coupled with immature hepatic enzymes, place the normal newborn at increased risk for hypoglycemia. Hypoglycemia is particularly common in premature and small-for-gestational-age newborns, as well as those born to diabetic mothers. Hypoglycemia may also be a response to other factors, including respiratory illness, hypothermia, polycythemia, asphyxia, and sepsis. Hypoglycemia can be asymptomatic or may cause an array of symptoms, including apnea, color changes, respiratory distress, lethargy, jitteriness, seizures, acidosis, and poor myocardial contractility.[9,10] A low blood glucose level, particularly when prolonged, recurrent, or associated with hyperinsulinism, has been associated with adverse neurologic outcomes[9]; correction of hypoglycemia, if detected expeditiously, improves outcomes.[11] Neonatal hypoglycemia is generally defined as a blood glucose level less than 40 mg/dL, although this number serves as more of a guideline than a strict cutoff. All newborns exhibiting signs of hypoglycemia, with glucose levels less than 40 mg/dL, should receive intravenous (IV) glucose. *Of note, bedside glucometers tend to underestimate plasma glucose levels by approximately 10 mg/dL.*[10]

Hypovolemia

Clinically significant hypovolemia is rare and usually secondary to blood loss. Risk factors include known maternal hemorrhage during delivery, prematurity, newborns with overt shock, and initiation of cardiopulmonary resuscitation (CPR).[1–3,12] Hemorrhage can lead to respiratory depression and overt shock in the newborn, whether secondary to abruptio placentae, placenta previa, umbilical cord accident, or trauma. In the newborn, hemorrhage is one of the few situations in which fluid resuscitation and volume expansion improves outcomes. At the time of birth, mean arterial pressure should be equivalent to known or estimated gestational age. Examination findings consistent with hypovolemia or hemodynamically significant hemorrhage include pallor, despite oxygenation, weak pulses with a rapid HR, and poor response to resuscitation.[1–3]

Prematurity

Premature infants, especially those born before 34 weeks of gestational age, are uniquely at risk due to their pulmonary immaturity and susceptibility to hypothermia. Those requiring delivery room CPR have increased risk of mortality, intraventricular hemorrhage, periventricular leukomalacia, early sepsis, and retinopathy of prematurity.[13] For these reasons, in utero transfer of high-risk pregnant women to tertiary centers possessing expertise and experience with premature infant resuscitation has been associated with improved neonatal outcomes.[14] Intubation should be performed for the premature newborn in respiratory distress, which is clinically suggested by retractions, desaturation, or tachypnea.[15] In certain cases, surfactant may be delivered via an endotracheal tube (ETT) shortly after birth.

MECONIUM-STAINED AMNIOTIC FLUID

Meconium-stained amniotic fluid (MSAF) indicates potentially significant newborn stress prior to delivery. Aspiration of meconium and its consequences can be avoided, or at least significantly limited, by rapid intervention. Previous recommendations stipulated suctioning meconium from the newborn's airway after delivery of the head but before delivery of the shoulders (intrapartum suctioning). However, there appears to be no benefit from intrapartum suctioning.[16,17] Therefore current recommendations no longer advise routine intrapartum suctioning of newborns with MSAF. To prevent aspiration of meconium, previous recommendations also stipulated tracheal suctioning of all nonvigorous newborns with MSAF immediately on delivery and before any other resuscitative efforts (including drying and stimulation). However, routine endotracheal intubation in nonvigorous and vigorous term, meconium-stained newborns has shown no benefit, including the incidence of meconium aspiration syndrome (MAS), pneumothorax, oxygen need, stridor, seizure, or hypoxic ischemic encephalopathy.[18] Standard measures to support adequate ventilation and oxygenation should be initiated for all infants born through MSAF, with a small subset eventually needing endotracheal intubation, as warranted.[1]

The most recent recommendations from the American Heart Association for the practice of tracheal suctioning after delivery for meconium aspiration is that it should be performed only if indicated for signs of airway obstruction secondary to meconium that do not improve despite standard resuscitative measures, including warming and drying and initiation of effective positive pressure ventilation (PPV). When performing tracheal suctioning, a meconium aspirator (see Fig. 159.1) should be attached to the appropriate-sized ETT and connected to wall suction at 100 mm Hg or less. On intubation by direct laryngoscopy, the ETT is then withdrawn while suction is applied. Serial reintubation with suctioning should be repeated to remove obstructing meconium or until the infant becomes vigorous, which is usually accomplished after two rounds. If bradycardia or apnea persists beyond two passes, ongoing resuscitation should include bag-mask ventilation (BMV) and consideration of endotracheal intubation to secure the airway. In tertiary centers with skilled providers, eventual lung lavage with surfactant for babies born through MSAF is likely to reduce duration of hospital stay, mechanical ventilation, and need for extracorporeal membrane oxygenation.[19]

Maternal Factors

Infection

Maternal infection (chorioamnionitis) is a particularly common trigger for premature delivery; premature infants are themselves more susceptible to infection. Therefore IV antibiotics should be administered after obtaining blood cultures, and a complete blood count should be carried out in all infants born before 37 weeks of gestation.

Medications

Medications provided to the mother during labor or illicit drugs taken before delivery, usually opioids, can promote newborn respiratory depression. Maternal opioid administration or antenatal drug abuse should be considered in any newborn with isolated respiratory depression that persists, despite a seemingly successful initial resuscitation. As in adults, opioid-induced respiratory depression could be reversed with naloxone.[1,20] However, naloxone may precipitate acute withdrawal and seizures in the newborn of an opioid-dependent mother; thus naloxone is not recommended in the initial resuscitation of the newborn.[3,21] Suspected opiate toxicity in the newborn should be treated with support of oxygenation and ventilation rather than pharmacologic reversal. This should include use of a bag-mask device and, if necessary, intubation.

Withholding and Discontinuing Resuscitation

No reliable and widely adopted set of parameters has been identified for newborns who should not receive resuscitative efforts.[22] A recent systematic review attempted to identify international consensus surrounding this medically and ethically complex scenario—worldwide, resuscitation is not typically recommended for neonates with a confirmed gestational age less than 23 weeks.[23] In high-income countries, there is increasing resuscitative efforts and postnatal intervention for babies with confirmed trisomies 18 and 13, highlighting the importance of timely counseling to ascertain parental values and expectations.[24] Parental request has been shown to be the most important factor determining resuscitative efforts for newborns at 22 to 25 weeks of gestation; most neonatologists consider a gestational age more than 25 weeks of gestation as the cutoff for obligatory resuscitation, even with parental refusal.[23] In the setting of uncertain gestational age and unclear or conflicting parental wishes, the recommendation is to initiate resuscitation. Similarly, if prognosis is uncertain at the time of delivery, resuscitation should be attempted until additional data can be obtained and parental wishes have been considered. Outside the delivery room, every attempt should be made to stabilize the neonate until further resuscitation would clearly not improve the likelihood of survival with acceptable morbidity. Neonates with no signs of life (asystole, apnea) after 10 minutes of resuscitation have high mortality or severe lifelong developmental delay, and resuscitation can be terminated.[25] This is a rare and inherently challenging decision to make and should account for availability of local resources and personnel skill, transportation needs and options, and parental preference. However, enhanced resuscitation techniques and postresuscitation therapeutic hypothermia have recently shown promise, even for neonates with a 10-minute APGAR score of zero.[26,27] In one notable cohort of term neonates receiving CPR and subsequent hypothermia, more than 50% were found to have normal developmental trajectory by 18 months of age,[26] highlighting the importance of dialogue with the parent(s) and acknowledgment of their feelings regarding the risks of morbidity. Parents should actively participate in the decision to continue or withdraw resuscitative efforts in cases in which there is prognostic uncertainty. For infants with a low 10-minute APGAR score but showing some signs of life, especially when aligned with parental preference, resuscitation efforts should continue until futility is determined. Although not absolute, we recommend considering terminating resuscitative efforts for infants with no signs of life after 10 minutes of resuscitation.

SPECIAL ANATOMIC ANOMALIES

Diaphragmatic Hernia

In addition to pulmonary hypoplasia, neonates with diaphragmatic hernias have exquisitely reactive pulmonary vascular beds, predisposing them to potentially fatal pulmonary vasospasm in the immediate and late postnatal period.[28] Examination findings concerning for congenital diaphragmatic hernia include barrel chest, ipsilateral absence of breath sounds, tracheal or point of maximum cardiac impulse displacement, and scaphoid abdomen. BMV will distend the stomach, which is usually intrathoracic, further worsening respiratory distress. The neonate should be immediately intubated if a prenatal diagnosis of diaphragmatic hernia is known or if a diaphragmatic hernia is diagnosed on the chest radiograph (Fig. 159.2).

Myelomeningocele and Omphalocele

Infants with myelomeningocele should never be placed supine but instead be placed prone or on the side to avoid pressure on the defect

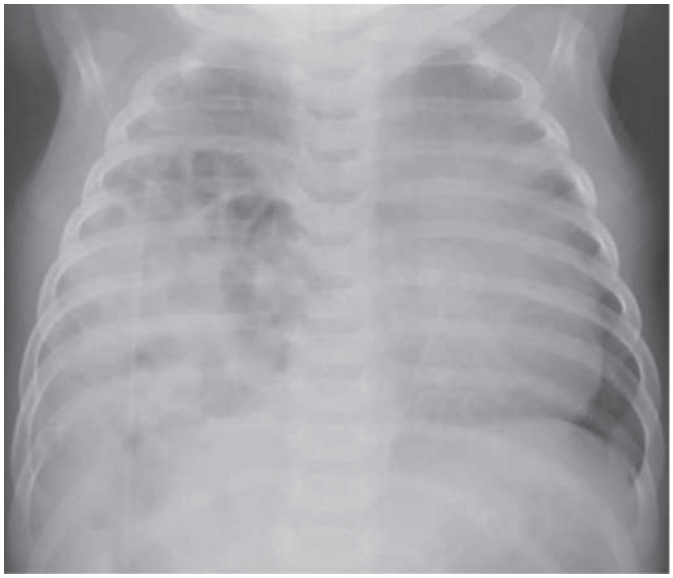

Fig. 159.2 Chest Radiograph Reveals Right-Sided Congenital Diaphragmatic Hernia. (Courtesy Seattle Children's Hospital, Seattle, WA.)

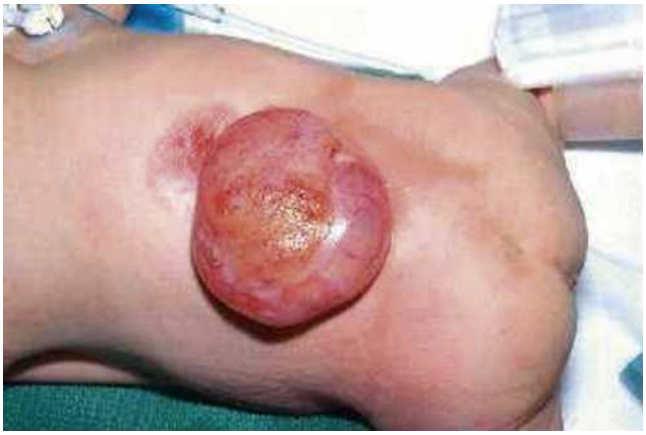

Fig. 159.3 Preoperative myelomeningocele, highlighting the obvious anatomic challenges and sensitivities required in resuscitation of neonates with this condition. (From Elbabaa SK, Luciano MG. Myelomeningocele and associated anomalies. In: Benzel E, editor. *Spine Surgery: Techniques, Complication Avoidance and Management,* 3rd edition. Philadelphia: Saunders; 2012. Figure 117-1.)

(Fig. 159.3). Resuscitation should proceed from this modified position. For unclear reasons, myelomeningocele seems to be associated with an elevated risk for latex allergy, usually necessitating efforts to avoid latex sensitization in these neonates.[29] The spinal defect should be gently wrapped with sterile gauze pads soaked in warm sterile saline and enclosed with plastic wrap.[30] Infants with gastroschisis or omphalocele should be resuscitated as needed, and these defects should also be covered with an occlusive plastic wrapping to decrease water and heat loss.[31] These newborns often require parenteral maintenance fluid infusion, orogastric tube for gastric decompression, and antimicrobial prophylaxis with IV antibiotics.[31]

Choanal Atresia

Because newborns are obligate nose breathers, bilateral choanal atresia causes upper airway obstruction and often severe respiratory distress. Choanal atresia can be rapidly diagnosed by the inability to pass a catheter through either naris into the posterior oropharynx. An oral airway device can bypass the obstruction. Special attention should be paid to a thorough physical examination of these infants because they often have multiple congenital anomaly syndrome.

Pierre Robin Sequence

The hallmark of this abnormality is profound micrognathia, resulting in glossoptosis (retraction or downward displacement of the tongue) and cleft palate. Therefore Pierre Robin sequence confers a high risk for significant upper airway obstruction. A nasal or oral airway should be able to bypass the obstruction; if not, intubation may be necessary. Given the technical challenges of performing endotracheal intubation on a patient with Pierre Robin sequence, fiberoptic intubation is often needed, although prone positioning and a laryngeal mask airway (LMA) or other supraglottic airway device can be attempted to support ventilation.[32] Consultation with anesthesiology or otolaryngology may be required.

Congenital Cardiac Disease

Echocardiographic evidence of congenital heart disease (CHD) is as high as 5% for term newborns.[33] However, critical CHD, defined as requiring surgery, catheter-based intervention, or death in the first 28 days of life, is present in only 1 to 2 per 1000 term births.[33] Stereotypic examination findings seen in critical CHD include a blood pressure gradient between the upper and lower extremities, weak femoral pulses, central cyanosis, pathologic murmur, and hepatomegaly. These signs of cardiogenic shock in a newborn may be fairly indistinguishable from those of severe sepsis and respiratory failure. Resuscitation of a newborn with known or suspected critical CHD should therefore include standard ventilatory management, as well as empiric antimicrobial therapy.[34] Cardiomegaly on a chest radiograph is more likely consistent with cardiogenic shock. Some common laboratory findings include polycythemia and unexplained acidosis. Many newborns with critical CHD have a ductal-dependent lesion and are likely to experience profound physiologic decompensation—defined by severe metabolic acidosis, seizure, cardiac arrest, or renal or hepatic injury—on closure of the ductus arteriosus.[35] Prostaglandin E_1 (PGE_1) should be used in lesions with ductal-dependent systemic or pulmonary blood flow (Box 159.1).[36] In case of an uncertain diagnosis or in preparation for transport to a specialized facility, prostaglandin should be started via continuous IV infusion. A second peripheral IV is recommended to treat the possible adverse effects of prostaglandin: hypotension, tachycardia, and apnea. Continuous alprostadil should begin soon after birth,[36] with gradual dose titration to a maximum of 0.1 μg/kg/min. For a more in-depth discussion on CHD, see Chapter 165.

Newborn Resuscitation Algorithm

Preparation

To maximize the effectiveness of resuscitation, all emergency departments should have an age- and weight-appropriate prestocked drug pack, standardized equipment (Box 159.2), and staff trained on newborn resuscitation.[1,3] There are several pediatric length-based resuscitation tape (e.g., Broselow, PAWPER) that can be used to determine equipment size and drug dosages for newborn resuscitation of infants weighing 3 kg or more.[37,38] A dedicated neonatal resuscitation cart, organized according to the Neonatal Resuscitation Program (NRP) algorithm, increases the speed of equipment retrieval and is preferred by providers to other organizing schemes.[39] When available, additional maternal information (Box 159.3) can help to anticipate resuscitation needs so that appropriate staff, equipment, and disposition plans can be expeditiously managed.

Universal precautions, including gown, gloves, and eye protection, should be followed during neonatal resuscitations. An external heat source should be turned on early and the table warmed prior to the

BOX 159.1 Ductal-Dependent Congenital Cardiac Lesions

Ductal-Dependent Pulmonary Blood Flow
Critical pulmonary stenosis, atresia
Severe tricuspid stenosis, atresia
Severe tetralogy of Fallot

Ductal-Dependent Systemic Blood Flow
Hypoplastic left heart syndrome
Critical aortic stenosis
Interrupted aortic arch

BOX 159.2 Equipment Checklist for Neonatal Resuscitation

1. Gown, gloves, and eye protection (universal precautions)
2. Timing device
3. Blankets (to warm and dry infant)
4. Plastic wrap (for omphalocele, gastroschisis, possibly premature infant)
5. Radiant warmer
6. Bulb syringe
7. Suction and suction catheters (sizes 5, 8, and 10 Fr)
8. Self-inflating (450 and 750 mL) and flow-inflating (250 and 450 mL) bags
9. Masks (premature, newborn, and infant sizes)
10. Laryngoscope with straight blades (nos. 00, 0, and 1)
11. Endotracheal tubes with stylets (2.5, 3.0, 3.5, and 4 mm), uncuffed
12. Scissors and tape to stabilize endotracheal tube
13. Pediatric CO_2 detector
14. Meconium aspirator
15. Umbilical catheters (3.5 and 5 Fr)
16. Hemostats, sterile drapes and gloves, povidone-iodine solution, scalpel, umbilical tape, suture, and three-way stopcock for umbilical vessel catheterization

BOX 159.3 Maternal History Questions

1. What is the estimated gestational age?
2. Is this a multiple gestation?
3. Is meconium present?
4. Is there a history of vaginal bleeding?
5. Were medications given or drugs taken?
6. Was there documented maternal fever?
7. Did mother have routine prenatal care? If so, were any abnormalities seen on prenatal ultrasonography?

start of resuscitation. Hypothermia is an independent risk factor for neonatal mortality worldwide.[40–42] Similarly, hyperthermia is a risk factor for neonatal encephalopathy and correlates with respiratory depression, cerebral palsy, and mortality. Correct equipment size is essential; in particular, respiratory supplies are most likely to be used and key to most resuscitative efforts. Appropriately sized self-inflating devices (Fig. 159.4) decrease complications from overventilation, prevent injury, and limit the inability to ventilate due to improper mask fit. When available, and in the hands of experienced providers, flow-inflating devices have the added ability to deliver continuous positive airway pressure (CPAP), control ventilation pressure with greater precision, and ensure a proper fit. Table 159.1 lists the recommended ETT sizes by birth weight and gestational age.

Fig. 159.4 Appropriate Self-Inflating Resuscitator With Appropriate Neonatal-Sized Mask Attached. This device has additional functionality with manometer and single-use positive end-expiratory pressure (PEEP) valve attachments. (Courtesy Seattle Children's Hospital, Seattle, WA.)

TABLE 159.1 Endotracheal Tube Size by Birth Weight and Gestational Age

Birth Weight (kg)	Gestational Age (Weeks)	ETT Tube Size (mm, Uncuffed)	Depth of Insertion (cm)
<1	<28	2.5	7
1–2	28–34	3	8
2–3	34–38	3.5	9
3+	38+	3.5–4	10

ETT, Endotracheal tube.
Adapted from American Academy of Pediatrics; American Heart Association. *Neonatal Resuscitation Textbook*. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

As part of their shared NRP curriculum, the American Heart Association and American Academy of Pediatrics, with the International Liaison Committee on Resuscitation, have developed a newborn resuscitation algorithm (Fig. 159.5). This stepwise approach is detailed later.[1–3] However, if a term neonate is crying and appears to have good tone, she or he can be warmed, dried, and returned to the mother for ongoing care and evaluation, without any additional resuscitation efforts.[1]

Dry, Warm, Stimulate, Position, Suction, and Assess Need for Further Intervention

Hypothermia increases metabolic demand and oxygen consumption, which can render seemingly effective resuscitation efforts futile. To prevent hypothermia and its more subtle sequelae, all newborns should be dried immediately on delivery and placed under a radiant heat source. In the case of crying term infants with normal tone, this may be accomplished by simple drying and skin to skin contact with the mother.[1] Wet blankets should be replaced with dry blankets and preferably warm linens, but the baby should be left uncovered to facilitate radiant warming and team access. All resuscitation techniques are designed to be performed with these temperature-controlling efforts in place.[1] The supine neonate should be further positioned to maximize air entry and avoid obstruction of airflow. Due to a relatively large occiput and anterior glottic opening, airway patency is best achieved with the neck in slight extension. A slightly extended position that aligns the posterior pharynx, larynx, and trachea is best accomplished by placing a rolled diaper or small towel under the infant's shoulders. Placement under the neck is not useful. However, a towel that is too large and under the shoulders can also lead to airway occlusion due to hyperextension of the neck.

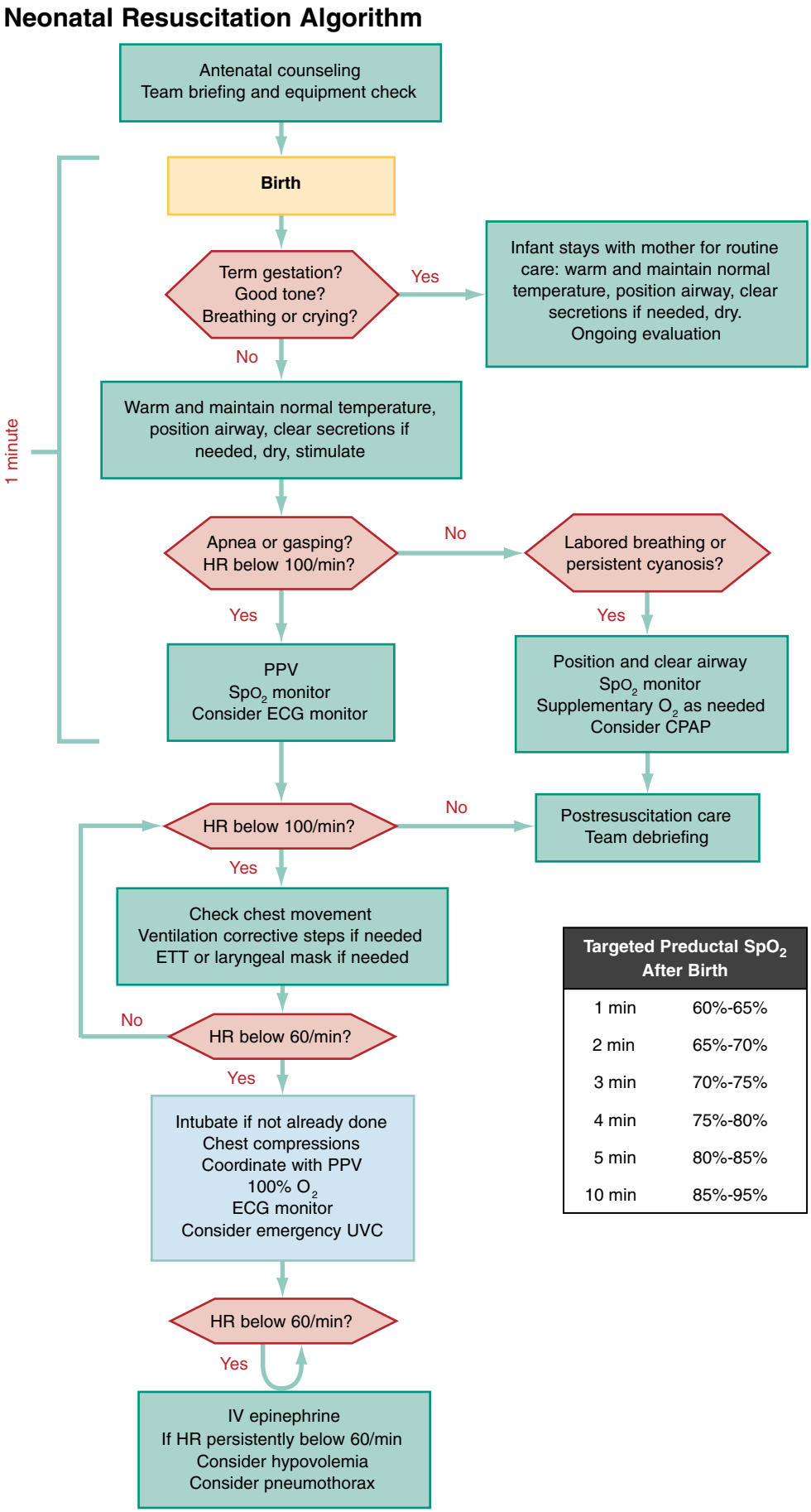

Fig. 159.5 Algorithm for Neonatal Resuscitation. *ECG,* Electrocardiogram; *ETT,* endotracheal tube; *HR,* heart rate; *PPV,* positive pressure ventilation; *UVC,* umbilical vein cannula. (Adapted from Wyckoff MH, Aziz K, Escobedo MB, et al: Part 13: neonatal resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132:S543–S560.)

Only if meconium is present and the newborn has poor tone, poor respiratory effort, or bradycardia (HR < 100 beats/min) after 1 minute of appropriate PPV should the trachea be suctioned with an ETT and meconium aspirator attachment. Poor respiratory effort and obvious obstruction from secretions should otherwise be treated with bulb or mechanical suction (~100 mm Hg wall suction). Upper airway suctioning, including that performed with a bulb syringe, should be reserved only for newborns with these signs because suctioning has been associated with decreased lung compliance, bradycardia, and lowered cerebral blood flow velocity.[1] When suction is indicated, the NRP protocol should be followed, with the mouth suctioned first, followed by the nose. This sequence helps to avoid aspiration of oral secretions if the neonate inspires after nasal suctioning. Overly vigorous or deep suctioning should be avoided because it can cause significant vagal stimulation, and subsequent bradycardia or apnea.[2,43] Because NRP recommendations stipulate suctioning with less than 100 mm Hg, emergency clinicians should be judicious with syringe use because even standard delivery bulb syringes produce a negative pressure that can easily exceed this threshold.[43]

For most term neonates, these measures stimulate breathing sufficiently and may be all that is required to resuscitate a newborn. If adequate respirations are still not present, additional stimulation should be given. This is best done by flicking the soles of the feet and rubbing the back; more forceful efforts could prove harmful. If stimulation and warming efforts prove inadequate, PPV is required, followed by intubation, if necessary.

Time is an important component of NRP guidelines. Within the first 60 seconds of life, the newborn should be assessed with simultaneous warming, drying, and stimulation; if necessary, upper airway clearance should be performed (see Fig. 159.5). If the HR is less than 100 beats/min or if the newborn has primary apnea or respiratory distress, PPV and pulse oximetry should be initiated within the first minute of life. If bradycardia worsens (HR < 60 beats/min), despite adequate ventilation, chest compressions should be initiated. HR calculation can be manual—by palpation of the pulse at the base of the umbilicus or auscultation of cardiac sounds—with pulse oximetry, or most accurately with a standard electrocardiography (ECG) lead.[44] Three-lead ECG is more acute in identifying true bradycardia, as pulse oximetry and palpation of the umbilical pulse have been found to underestimate a newborn's HR.[1] Persistent bradycardia is usually secondary to inadequate ventilation. Thus intubation is recommended in the event that chest compressions are indicated.

Routinely counted at 1, 5, and 10 minutes of life, the APGAR score (Table 159.2) is a composite that reflects HR, respiratory effort, muscle tone, reflex irritability, and color. The score is primarily for assessing the need for (1 minute) and efficacy of (5 minute) ongoing resuscitative measures. In the setting of modern algorithm-based resuscitation, low 5- and 10-minute APGAR scores are associated with increased mortality because they identify infants who are failing medical management.[44] Muscle tone and reflex irritability do not significantly aid in the assessment of the newborn during resuscitation.[44,45]

Instead, HR and respiratory effort are the important indicators and should be continuously monitored. Skin color is a poor indicator of oxyhemoglobin saturation during the first several minutes of life while the transition from fetal to infant circulation ensues.[46–48] In this brief period, pulse oximetry may be a useful tool to assess the oxygenation status of the newborn.[8] However, level of oxygen saturation should take into account normal postductal saturations after birth. An oxygen saturation of 60% would be the targeted normal preductal saturation for 1 minute of life and may not reach 90% or more until 10 minutes of life (see Fig. 159.5). Pulse oximeter should be placed on the baby's right wrist or hand to measure preductal saturations after birth. NRP guidelines recommend pulse oximeter use in only a few select situations—anticipated resuscitation, prolonged PPV use, persistent central cyanosis, and use of supplemental oxygen.[1] We recommend preparing pulse oximetry and ECG monitoring as a standard approach for all ED neonatal resuscitations. Precipitous deliveries are infrequent, yet high-risk presentations and newborns are likely to require accurate HR and pulse oximeter measurements to guide resuscitation.

TABLE 159.2 APGAR Score[a]

	POINTS		
Sign	**0**	**1**	**2**
Heart rate (beats/min)	Absent	Slow (<100)	≥100
Respirations	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active, good flexion
Reflex irritability	No response	Grimace	Cough, sneeze
Color	Blue, pale	Pink body, blue hands and feet	Pink

[a]Calculate at 1, 5, and 10 minutes of life.

Ventilation, Oxygen, Intubation

Any neonate with persistent cyanosis or signs of respiratory distress (e.g., grunting, nasal flaring, tachypnea) should be assisted by CPAP or PPV. For apnea, severe respiratory distress, or HR less than 100 beats/min, BMV (with a manometer, if available) should be initiated. The first breaths often require higher pressures (30 to 40 mm Hg) to remove lung fluid, with the adequacy of ventilation assessed by chest rise. An initial sustained breath of 2 to 5 seconds may further increase FRC and promote clearance of lung fluid, but several clinical trials and meta-analyses have yet to prove the efficacy and safety of this technique.[49–52] Subsequent breaths generally require 20 mm Hg of peak inspiratory pressure.[1,2] To minimize barotrauma and the incidence of pneumothorax, excessive pressures (defined as more than needed to achieve adequate chest rise) should be avoided. An appropriately sized mask with a tight seal (covering the mouth and nose, but not the eyes), proper positioning of the newborn, and use of pressure to attain correct chest wall movement are essential for effective ventilation. Unless otherwise dictated by blood gas levels, recommended ventilation rates are 40 to 60 breaths/min, aimed at achieving a HR greater than 100 beat/min. Current NRP guidelines recommend PPV but do not delineate between CPAP and positive end-expiratory pressure (PEEP). However, preterm neonates (<33 weeks' gestation) receiving single-inflation CPAP (pressure-controlled inflation at 20 cm H_2O for 10 seconds) appear less likely to be intubated at 72 hours of age, receive more than one dose of surfactant, or develop bronchopulmonary dysplasia (BPD). When BMV is required for more than 2 minutes, an orogastric tube should be placed to prevent respiratory compromise from gastric distention.[2]

Resuscitation with 100% oxygen is no longer recommended.[3,53–56] There is reduced mortality in infants resuscitated on room air, with no obvious evidence of harm.[54] Resuscitation-induced hyperoxia results in increased oxidative stress, including direct cardiac and renal injury.[57] Neurologic outcomes appear improved by resuscitation with room air versus 100% oxygen, likely due to a reduction in cerebral free radical generation.[1,3,56,58] Current NRP guidelines recommend initiating resuscitation with room air and then blending to increasing oxygen concentrations, as needed. An updated guideline suggests it is reasonable to initiate resuscitation in preterm newborns (less than 35

BOX 159.4 Intubation Corrective Action and Deterioration Mnemonics

MR SOPA
M: Mask adjustment
R: Reposition airway
S: Suction mouth and nose
O: Open mouth
P: Pressure increase
A: Airway alternative

DOPE
D: Displacement of ETT
O: Obstruction of ETT
P: Pneumothorax
E: Equipment failure

ETT, Endotracheal tube.

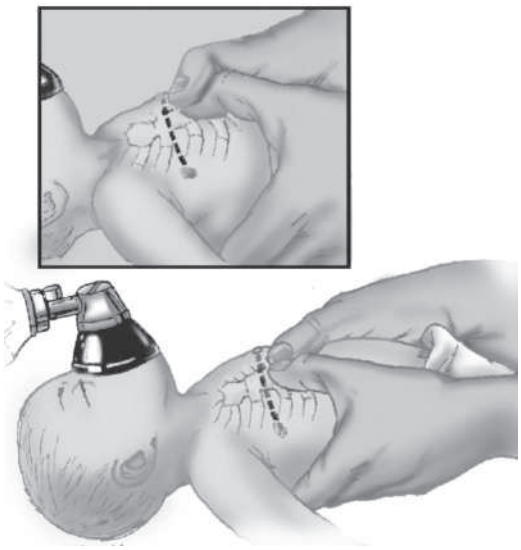

Fig. 159.6 The preferred way to provide chest compressions on a newly born neonate is called two thumbs-encircling hands. This method is best when one rescuer can provide chest compressions and another can ventilate the patient. The two thumbs are placed over the sternum and below an imaginary line between the nipples. If the newborn is very small, the two thumbs can overlap. (From From Gregory GA: In: *The Anesthesiology, The Mother and Newborn.* Edited by Shinder SM, Moya F. Baltimore, Williams and Wilkins, 1974.)

weeks' gestation) with 21% to 30% fraction of inspired oxygen (FiO_2) and titrate to goal saturations.[3] Unless needed to achieve target oxygen saturations, 100% oxygen should be used only for newborns with bradycardia of less than 60 beats/min after 90 seconds (see Fig. 159.5). Attempts to restore adequate ventilation are often more beneficial than increasing the oxygen concentration.

Endotracheal intubation is indicated at several points during neonatal resuscitation—tracheal suctioning for meconium in infants with failure to improve, despite effective PPV; if BMV is ineffective or prolonged; when chest compressions are performed; and for extremely low birth weight infants or infants with anatomic anomalies (e.g., diaphragmatic hernia). Traditional direct laryngoscopy and video laryngoscopy are both reasonable options, with video-assisted techniques consistently having improved views but slightly longer total intubation times.[59–61] Confirmation of proper ETT placement should include detection of expired carbon dioxide using capnography. Although ultrasonography can show appropriate ETT positioning in the term infant, the gold standard remains plain radiography.[62–66]

If acute deterioration occurs shortly after intubation, equipment should be immediately checked. Consider the DOPE and MR SOPA mnemonics when trying to determine the cause of the deterioration (Box 159.4). In the absence of an obvious explanation, it is safest to extubate the newborn and promptly ventilate with a BMV device by an experienced provider. Needle aspiration of the chest may be considered for treatment of a possible pneumothorax, particularly if unequal breath sounds are appreciated upon extubation, ventilatory pressures are inexplicably high, or a neonate's condition fails to improve with effective ventilation.

If ETT intubation is indicated but is technically challenging, the LMA has been shown to be effective for ventilating full-term newborns.[67–69] However, there are limited data on LMA use in preterm infants (<2000 g or <34 weeks' gestation) in the setting of MAS or during CPR.

Chest Compressions

Bradycardia (HR < 100 beats/min) is a reliable indicator of clinically significant hypoxia. Fortunately, most neonates with bradycardia respond promptly to effective ventilation. If a neonate has an HR less than 60 beats/min, despite oxygen and adequate ventilation (good air movement and chest rise) for at least 30 seconds, chest compression should be started.[1,2,70] Compressions should be performed at a rate of 90/min, coordinated with 30 breaths/min for a total of 120 events/min. The preferred neonatal resuscitation compression-to-ventilation ratio is 3:1. If the provider is certain that the cardiac arrest has a primary cardiac cause, a compression-to-ventilation ratio of 15:2 may be considered.[1,3] The preferred method for performing chest compressions, the two thumb-encircling hands technique, is as follows: the fingers of both hands encircle the chest and support the back, with the thumbs of both hands placed side by side or one over the other on the sternum, just below the nipple line (Fig. 159.6).[71,72]

The depth of compression is one-third the anteroposterior diameter of the chest.[2] Spontaneous respirations and HR should be assessed every 30 seconds, attempting to minimize interruptions, when possible, with coordinated chest compressions and ventilation continuing until the HR is at least 60 beats/min.[1,2] A yellow color change on a colorimetric CO_2 monitor or increase in end-tidal CO_2 values during PPV administration often precedes a significant rise in HR and should be used, when available.

Vascular Access

The umbilical vein is the preferred route of immediate vascular access because it can be easily identified and cannulated. Umbilical vein access can have serious complications (e.g., infection, portal vein thrombosis), so the umbilical vein cannula (UVC) should be removed by the accepting neonatologist after the infant has been stabilized and additional venous access has been obtained.[73] Other vascular access routes include peripheral veins, peripherally inserted central catheters, and the femoral vein.[74] Intraosseous (IO) access can be problematic in neonates (especially premature infants) because of bone fragility and the small size of the IO space. However, in simulated resuscitation, placement of an IO line has been shown to be almost 1 minute faster than a UVC, even for skilled providers. Preferred IO access sites in newborns include the distal femur (midline; ≈1 cm above the superior border of the patella, with the leg in extension) and the proximal tibia (≈2 cm below the tuberosity and 1 cm medially on the tibial plateau). If vascular access cannot be achieved, certain drugs including epinephrine, can be given through the ETT, although this is not the optimal route.

TABLE 159.3 Resuscitation Medications

Medication	Concentration	Dose	Route	Comments
Epinephrine	0.1 mg/mL	0.01–0.03 mg/kg (0.1–0.3 mL/kg)	IV (preferred) or ETT	
Dopamine	Varies	Continuous infusion at 5 µg/kg/min; increase to 20 µg/kg/min as needed.	IV	
Glucose	$D_{10}W$	2–4 mL/kg	IV	Avoid higher concentrations
Volume expanders	O-negative packed RBCs	10 mL/kg	IV	Give over 5–10 min for acute bleeding; repeat as needed
	Normal saline	10 mL/kg	IV	Give over 5–10 min; repeat as needed
	Lactated Ringers	10 mL/kg	IV	Give over 5–10 min; repeat as needed
Ampicillin	Varies	100 mg/kg	IV, IM	
Gentamicin	Varies	4 mg/kg	IV, IM	If neonate less than 35 weeks gestational age: 5 mg/kg
Cefotaxime	Varies	50 mg/kg	IV, IM	

$D_{10}W$, 10% dextrose in water; *ETT,* endotracheal tube; *IM,* intramuscular; *IO,* intraosseous; *IV,* intravenous.

Medications

Few neonates require pharmacotherapy during resuscitation. Medications (Table 159.3) are primarily indicated for bradycardia or asystole unresponsive to effective ventilation and chest compressions, as well as hemorrhage (maternal, fetal, or placental) that necessitates fluid resuscitation.[1–3]

Epinephrine. Epinephrine is indicated for asystole and persistent bradycardia (<60 beats/min) despite effective ventilation with 100% oxygen and ongoing coordinated chest compressions. Although it may be given by ETT, IV is the preferred epinephrine administration route. The recommended IV dose is 0.01 to 0.03 mg/kg, or 0.1 to 0.3 mL/kg, of a 0.1 mg/mL solution. Unlike epinephrine use in adult patients, weight-based dosing with no known minimum is required for neonates. Repeat doses may be given every 3 to 5 minutes.[1,2] If administered via an ETT, higher doses (0.05 to 0.1 mg/kg) with a 0.1 mg/mL solution are indicated, but the safety and efficacy of this practice have not been rigorously evaluated.[1,2,74–76] Unlike many adult resuscitations, sodium bicarbonate is not routinely used,[77,78] although it may be beneficial in the neonatal intensive care unit (NICU) setting when ventilation is known to be adequate.[1,79]

Volume Expanders. When indicated, volume expansion is accomplished with packed red blood cells (Rh-negative type O blood), normal saline, or Lactated Ringers solution given in IV boluses of 10 mL/kg over 5 to 10 minutes. During resuscitation of premature infants, rapid administration of volume expanders should be avoided because this practice has been associated with increased incidence of intraventricular hemorrhage.[2] Higher-volume (e.g., 20 mL/kg) fluid boluses are recommended for full-term infants. Boluses may be repeated several times, as indicated by the ongoing response to resuscitative efforts.

Antibiotics. Antibiotics are not indicated in the initial resuscitation phase but may be required once the neonate has been stabilized. When suspected, sepsis should be treated with broad-spectrum antimicrobial therapy directed against the most likely pathogens. The most common bacterial pathogens implicated in early-onset neonatal sepsis are a heterogeneous group that includes group B *Streptococcus* (GBS), *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Listeria*. In the United States, where GBS and *E. coli* represent the most common newborn pathogens, a recommended empirical antibiotic regimen is ampicillin (100 mg/kg IV) plus an aminoglycoside (usually gentamicin, 4 mg/kg).[80] Reasonable alternative regimens include ampicillin with a third-generation cephalosporin, but there is evidence that several members of the latter group predispose a neonate to invasive candidiasis. Because ceftriaxone can increase the risk of kernicterus, cefotaxime (50 mg/kg IV) is preferred.

Glucose. Concomitant hypoglycemia should be considered and promptly treated in a neonate requiring ongoing resuscitation. Hypoglycemia is most easily diagnosed by rapid bedside glucose testing or serum glucose level measurement. Neonates with a glucose level less than 40 mg/dL and with symptoms of hypoglycemia—irritability, tremors, jitteriness, apnea, tachypnea, seizures, cyanosis, lethargy, poor feeding—require treatment with IV glucose. Standard therapy is 2 to 4 mL/kg of 10% dextrose in water ($D_{10}W$)/kg as well as starting a continuous infusion of $D_{10}W$ at 80 to 100 mL/kg/day.[10] Higher concentrations of glucose (e.g., 25% dextrose in water, $D_{25}W$) are hyperosmolar and should be avoided. If the newborn can safely tolerate feeds, oral glucose solution, maternal breast milk, or formula should be given by mouth (PO) on demand. Repeat glucose measurement should be obtained 10 to 20 minutes after glucose administration. Asymptomatic neonates with hypoglycemia should be encouraged to feed more often and are treated with IV glucose only if glucose levels fall precipitously (<25 mg/dL at birth to 4 hours of age or <35 mg/dL at 4 to 24 hours of age).[10]

Dopamine. Dopamine is indicated only when signs of shock (e.g., poor peripheral perfusion, weak pulses) are still present, despite adequate volume replacement. Given as a continuous infusion beginning at 5 µg/kg/min, dopamine may be increased to 20 µg/kg/min as necessary, before additional inotrope support is indicated.

Therapeutic Hypothermia

When moderate to severe hypoxic-ischemic encephalopathy is suspected, selective cerebral hypothermia in asphyxiated infants may protect against brain injury.[1,81–89] Therapeutic hypothermia of 33.5°C to 34.5°C (92.3°F to 94.1°F) in this population can lower mortality and improve the likelihood of normal neurologic outcome at 18 months. Current NRP guidelines recommend therapeutic hypothermia for patients with suspected early neonatal asphyxia. Symptoms of possible evolving brain injury include abnormal levels of consciousness, seizures, hypotonia, and hyporeflexia. Established protocols generally recommend the initiation of cooling within 6 hours of birth, for a total of 72 hours, followed by gradual rewarming over at least 4 hours. Neonates meeting eligibility criteria should be transferred to facilities capable of providing this specialized care. Emergency clinicians and families should be aware that the risks associated with therapeutic hypothermia include thrombocytopenia and hypotension.

DISPOSITION

Early consultation with a neonatologist can assist in the resuscitation and postresuscitation phases of care. Once a neonate is stabilized, the monitoring of oxygenation, ventilation, perfusion, temperature, and glucose level continues. Neonates who require extensive resuscitation (i.e., obtaining venous access, medication requirement, or endotracheal intubation) should be transported to a NICU by personnel skilled in neonatal resuscitation. If feasible and safe, parents should be allowed to see, touch, and hold the newborn before transport.

OUTCOMES

Safety

Advanced life support skills are critical for successful neonatal resuscitation yet are far from routine for most emergency clinicians. For example, in a cohort of almost 5000 births in Norway, only 19 infants required intubation and 10 were given chest compressions.[90] An important step toward improving outcomes is team adherence to NRP guidelines. Highlighting the importance of safety, an essential component of the new NRP curriculum is the inclusion of simulation.[91] Simulation in neonatal resuscitation allows for a multidisciplinary team to practice behavioral and teamwork skills, not only individual technical skills, in a safe environment.[92] Implementation of an integrated Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) and NRP curriculum improves communication and helps to prevent incorrect medication dosing and inadequate chest compression depth. Furthermore, routine (and unannounced) simulation-based neonatal resuscitation training has been shown to improve provider self-confidence, knowledge, and both technical and nontechnical skills.[93,94]

Effectiveness

In the hands of trained emergency clinicians, neonates requiring advanced resuscitative efforts receive improved PPV, decreased time to vascular access, and shortened time to first IV medication. Deliberate training has been shown to improve ability to perform the key first steps of resuscitation—stimulation, positioning and neck-extension, PPV effectiveness, and HR assessment.[95] Provider level improvements are seen worldwide with the implementation of guideline-based care.[96] Analyses of the NRP program, which has now trained more than 5 million providers in the United States alone, suggests fewer high-risk infants experience a drop in APGAR score from 1 to 5 minutes, with many actually showing an improvement since implementation. However, resuscitation is not without potential pitfalls.

Complications

Relatively common complications post neonatal resuscitation include hypoglycemia, transient tachypnea of the newborn, MAS, pneumothorax, electrolyte disturbances, significant hyperbilirubinemia, and sepsis. These conditions are associated with increased NICU admission rates, as well as morbidity and mortality.[97,98] Additional perinatal risk factors relevant to resuscitation that are associated with length of NICU stay include: placental abruption, assisted delivery, small for dates, gestational age less than 37 weeks, low 5-minute APGAR score, and need for intubation at birth.

The need for chest compressions and CPR is a known prognostic marker for increased rates of morbidity and mortality in neonates.[99] Undergoing CPR at delivery increases the likelihood of pneumothorax, sepsis, severe intraventricular hemorrhage, and death.[100] Unfortunately, these complications have also been associated with poor long-term neurodevelopment outcomes.[100] However, the implementation of neonatal resuscitation protocols appears to improve neurodevelopment outcomes, but data from randomized trials are lacking.[101]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 159: QUESTIONS AND ANSWERS

1. With most neonatal deliveries, which resuscitative measures are usually sufficient?
   a. Administer fluids.
   b. Bag-mask ventilation.
   c. Intubate.
   d. Warm, dry, stimulate, and position.

   Answer: d. Drying, warming, positioning, and stimulating the infant are usually sufficient resuscitative measures in most deliveries.

2. For a term newborn with cyanosis, respiratory distress, and a heart rate more than 100 beats/min, which of the following is not initially indicated?
   a. Apply 100% oxygen.
   b. Position airway.
   c. Suction.
   d. Warm, dry, and stimulate.

   Answer: a. 100% oxygen is not indicated for initial resuscitation in all neonates born at 35 weeks' gestation or later; avoiding unnecessary supplemental oxygen is thought to minimize free radical creation in the brain and decreases the incidence of retinopathy of prematurity. Initial resuscitation with room air is recommended. For select newborns less than 35 weeks' gestation, initial FiO_2 of 21% to 30% may be required to achieve normal oxygen saturations.

3. In a typical neonatal resuscitation, what is the preferred compression-to-ventilation ratio?
   a. 3:1
   b. 5:1
   c. 10:2
   d. 15:2
   e. 30:2

   Answer: a. Unlike pediatric or adult cardiopulmonary resuscitation (CPR), neonatal CPR is performed at a ratio of three compressions to one breath, with a goal of approximately 90 compressions with 30 synchronized breaths (120 "events") per minute. If the cause of the bradycardia is known to be cardiac, a ratio of 15:2 is acceptable.

4. A nonvigorous and crying newborn is delivered with copious meconium-stained fluid. What is the correct recommended resuscitative measure?
   a. Bag-mask ventilate.
   b. Intubate.
   c. Suction at maternal perineum before cutting umbilical cord.
   d. Gentle mouth suctioning if needed, followed by warming, drying, and stimulation.

   Answer: d. For infants born with meconium-stained amniotic fluid, routine intubation and endotracheal tube suctioning are no longer recommended because they have shown no consistent benefit. Vigorous and nonvigorous infants born through even thick meconium should instead have gentle mouth suctioning, if needed, followed by warming, drying, and stimulation.

5. After drying, stimulating, and bag-mask ventilation, what is the next step in resuscitation of a newborn that appears floppy and apneic and with a heart rate of 50 beats/min?
   a. Give a normal saline bolus of 20 mL/kg.
   b. Give epinephrine (0.1 mg/mL) intravenous (IV) at a dose of 0.1 mg/kg.
   c. Intubate.
   d. Start with a chest compression-to-ventilation ratio of 3:1.

   Answer: d. With a heart rate less than 60 beats/min in a neonate, intubation may be considered, but compressions should be started. If the low heart rate persists, IV epinephrine (0.1 mg/mL) may be considered at a dose of 0.01 mg/kg.

Pediatric Trauma

Sonia Singh and James F. Holmes

KEY CONCEPTS

- Trauma is the leading cause of death in children in the United States.
- Avoid hypoxia and hypotension by early administration of oxygen and assisted ventilation, and fluid resuscitation with crystalloid at 20 mL/kg increments. Initiate transfusion of 10 mL/kg of packed red blood cells (pRBCs) if hypotensive or signs of hypovolemic shock after 40 mL/kg of crystalloid is infused.
- Key pediatric anatomic and physiologic differences include:
  - Children are smaller, so bodily force is more widely distributed, making multi-system injuries more likely.
  - The infant's head-to-body ratio is greater, creating a relatively higher center of gravity. This, combined with a less myelinated brain and thinner cranial bones, predisposes infants to more serious head injury.
  - Children have a higher anatomic fulcrum in the cervical spine (C2 to C3 in children <8 years old), resulting in higher cervical spine injuries.
  - Children have greater laxity of the cervical column ligaments, leading to a greater risk of spinal cord injury without radiographic abnormalities (SCIWORA).
  - Children have more horizontally positioned ribs, resulting in a more upward movement during inspiration; this leads to a limited ability to increase tidal volume and risk for respiratory failure with chest or diaphragmatic injury.
  - Children have more elastic ribs, allowing for pulmonary injury without skeletal injury.
  - Children have thinner abdominal walls and a more anterior location of the liver and spleen; this results in a greater chance of injury to those organs.
  - Despite large intravascular volume loss, children are able to substantially increase their systemic vascular resistance to remain normotensive; hypotension is a very late sign.
- Most minor head trauma may be managed with observation and without computed tomography (CT) imaging. When applied, clinical decision rules may reduce imaging and radiation exposure.
- In major trauma patients, indications for intubation include respiratory failure or a Glasgow Coma Scale ≤8.
- The diagnostic test of choice for the evaluation of intra-abdominal injury in a stable patient with high suspicion for injury is abdominal CT.
- Solid organ injuries are generally treated nonoperatively in children.

FOUNDATIONS

Injury is the leading cause of death among children 1 to 18 years of age in the United States, accounting for over 10,000 deaths and 9 million annual emergency department (ED) visits.[1] Motor vehicle collisions (MVCs) account for more than half of all pediatric trauma deaths, whereas nonfatal injuries are primarily due to unintentional falls.[1] Mechanisms of injury vary by patient age, and certain mechanisms result in specific injury patterns (e.g., sports and concussions). Blunt mechanisms account for over 95% of childhood injuries. The trauma history, as well as the initial response, determine injury risk and response required. Criteria for trauma center transport (primary triage) and trauma team activation (secondary triage) are primarily based on expert consensus and an area ripe for further research. Although the examination of the injured patient is standardized, diagnostic testing should be tailored to avoid unnecessary testing while assessing for important injuries.

Anatomy and Physiology

Children have distinct anatomy and unique physiology that impact their evaluation and management (Box 160.1). Force is more widely distributed throughout the child's body, making multi-system injuries more likely in children. The younger a patient is, the higher their surface area to weight ratio, resulting in a greater potential for heat loss. As injured patients are at increased risk of hypothermia, this is especially true in children.

Normal ranges for pediatric vital signs vary greatly and should be readily available in the ED (Chapter 155). A child's physiologic response to injury is different from the adult's, depending on the age and maturation of the child and severity of the injury. Children have a high capacity to maintain blood pressure despite significant hemorrhage; hypotension is a late finding with blood loss exceeding 30% of total blood volume. The younger the child is, the less their ability to increase cardiac contractility. Thus, a young child's cardiac output is primarily determined by heart rate and systematic vascular resistance. Compensated shock should be considered and promptly addressed when a child is tachycardic, especially if capillary refill is delayed. Changes in heart rate, blood pressure and extremity perfusion commonly precede cardiorespiratory failure and should prompt resuscitation.

CLINICAL FEATURES

Initial Assessment and Primary Survey

Most children evaluated in the ED are minimally injured and require limited diagnostic evaluation after the standard history and physical evaluation. In those with *major* trauma, cardiac and pulse oximetry monitoring, supplemental oxygen, frequent vital sign measurements, intravenous (IV) access, and laboratory testing are often needed. Immediately after prehospital notification, preparation should include assigning team member functions, preparing necessary equipment, and donning protective clothing. Color-coded length-based tape measures are often used to provide initial estimates of patient weight, equipment size and medication dosages, but important equipment sizes are in Box 160.2.

The initial trauma assessment is designed to rapidly identify and treat life- or limb-threatening injuries. Treatment of these injuries

BOX 160.1 Important Anatomic Differences in Adults and Children: Implications for Pediatric Trauma Management

- The child's head-to-body ratio is greater, the brain is less myelinated, and cranial bones are thinner, resulting in more serious head injuries.
- The child's internal organs are more susceptible to injury based on more anterior placement of the liver and spleen, and less protective musculature and subcutaneous tissue mass.
- The child's kidney is less well protected and more mobile, making it susceptible to deceleration injury.
- The elasticity of the child's chest wall allows for pulmonary injury without rib fracture.
- Children have a more tenuous spinal cord blood supply and a greater elasticity of the vertebral column, predisposing them to unique spinal cord injuries including SCIWORA.

SCIWORA, Spinal cord injury without obvious radiographic abnormality.

BOX 160.2 Specific Equipment Size Estimates for Pediatric Trauma

Endotracheal Tube (ETT) Size Estimates (Sizing in Millimeters Internal Diameter) and Depth

- Endotracheal (cuffed) tube size (mm) = (Age in years/4) + 3.5
- An ETT 0.5 mm larger and 0.5 mm smaller than the calculated size should also be ready at the bedside
- ETT tube depth = tube size × 3

Chest Tube Size (Diameter) = 4 × the ETT Size

Orogastric, Nasogastric, or Foley Size (Diameter) = 2 × ETT Size

precedes the continuation of the evaluation. The initial assessment and resuscitation occur simultaneously over the initial 5 to 10 minutes of care. Similar to adults, the elements of the primary survey for children are remembered as *A, B, C, D, E,* and *F*.[2] Patient deterioration warrants repeat of the primary survey to identify the cause and institute treatment.

A—Airway and Cervical Spine Stabilization

Children have important anatomic considerations that impact the management of the pediatric airway (Chapter 156). The patient is initially evaluated for possible airway obstruction or inability to maintain their airway. Gurgling or stridor may indicate upper airway obstruction. Maxillofacial trauma, blood, swelling, or vomitus may also obstruct the airway, and efforts are made toward clearing the oropharynx of debris. Initial attempts to open the airway include a jaw-thrust maneuver. If an open airway cannot be established and maintained by noninvasive means, endotracheal intubation (ETI) should be performed. Unless the neck has been cleared of injury, cervical spine immobilization should be maintained with in-line immobilization when airway maneuvers are performed.

Indications for ETI in a pediatric trauma patient include (1) inability to ventilate with bag-mask ventilation (BMV) or the need for prolonged airway control, (2) Glasgow Coma Scale (GCS) score ≤8, (3) respiratory failure from hypoxemia or hypoventilation, and (4) worsening decompensated shock resistant to initial fluid resuscitation. Rapid sequence intubation is the preferred method for ETI in severely injured children, and includes both sedative medications (e.g., ketamine or etomidate) and paralytic medications (e.g., succinylcholine or rocuronium), see Chapter 156. Although unlikely to do harm, premedication with fentanyl or lidocaine to blunt the rise of intracranial pressure (ICP) is not evidence-based, and we do not recommend its use for this purpose.

B—Breathing and Ventilation

Breath sounds and adequacy of chest rise should be assessed. Adequate ventilation is dependent upon airway patency and sufficient air exchange. Pulse oximetry measures the adequacy of oxygenation, but not ventilation. Continuous end-tidal carbon dioxide capnography better informs ventilatory status but should be interpreted in conjunction with the respiratory wave form. For example, a child with a low capnography reading could either be taking slow shallow breaths (e.g., hypoventilation), or may be breathing deeply and rapidly (e.g., hyperventilation). Many factors may compromise ventilatory function in an injured child, including depressed sensorium, airway obstruction, painful respirations, diaphragmatic fatigue, and direct pulmonary injury.

In a young child, chest rise occurs in the lower chest and upper abdomen, and both should move concordantly. Discordant motion or *paradoxical breathing* is a sign of impending respiratory failure. Respiratory rates that are very fast or very slow may indicate impending respiratory failure; tachypnea may also be due to shock or inadequate pain control. If assisted ventilation is necessary, BMV should be initiated with only the volume necessary to cause the chest to rise. In addition to a potential increased risk of vomiting and aspiration, excessive bagging volumes (i.e., hyperventilation) can lead to gastric distension (Fig. 160.1). As the stomach distends, the diaphragm can push into the thoracic cavity, causing increased intrathoracic pressures, decreased venous return, and hypotension. Gastric decompression may be performed with either an orogastric tube or nasogastric tube (if no evidence of facial trauma).

C—Circulation and Hemorrhage Control

Shock occurs when the body is unable to maintain adequate tissue perfusion. Normal systolic blood pressure does not exclude shock. The pediatric vasculature maintains normal blood pressure by constricting peripheral arteries and progressively increasing systemic vascular resistance. Signs of poor perfusion (cool distal extremities, decreased peripheral pulse quality, and delayed capillary refill) are signs of pediatric shock, even when blood pressure is normal (Box 160.3). External hemorrhage should be sought and controlled with direct pressure. IV access should be established and blood collected for laboratory testing (see following).

Vascular access is best obtained by placing two large-bore IV lines, ideally in the upper extremities (lower extremity sites may be used if needed). If obtaining vascular access is unsuccessful or delayed in the critically injured patient, intraosseous (IO) access is a safe, quick, and reliable procedure to access the vascular space and is recommended prior to attempting a central line. The preferred site for IO placement is the proximal medial tibia, just below (and directed slightly away from) the growth plate; other potential locations include the proximal humerus, the flat area of the anterior distal femur, or the distal tibia. Once IO access is obtained, it should be stabilized and secured. More than one IO needle may need to be placed (in separate bones); IV access may be easier after initial fluid resuscitation and vascular volume expansion. IO placement in a fractured extremity is contraindicated. Medications and blood products can be administered through an IO line similar to an IV. Central line placement in young children is difficult, with frequent complications, and should be avoided if possible. If absolutely necessary, ultrasound-guided femoral line placement is our preferred initial option. Much less commonly used vascular access techniques include a venous cut-down, or a central line into the intrajugular, supraclavicular, or subclavian vein. Venous cutdown is a

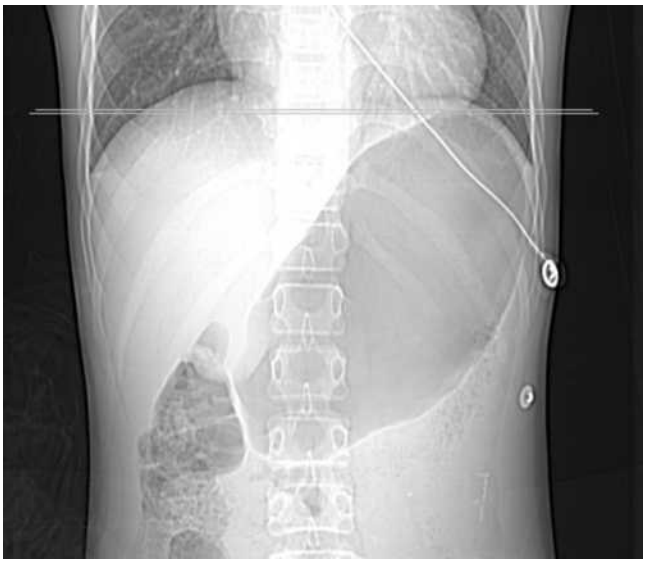

Fig. 160.1 CT (Scout) Demonstrating Gastric Distention in a Child Having Swallowed Large Amounts of Air from Crying. Severe Gastric Distention Can Harm Diaphragmatic Excursion and Impact Ventilation.

BOX 160.3 Circulation Assessment and Treatment in Critical Pediatric Trauma Patients

Assessment

- Tachycardia, delayed capillary refill, decreased peripheral pulses, tachypnea or bradypnea, and altered sensorium may indicate volume loss prior to hypotension.
- Vital signs, monitored every 5 min during the initial assessment.
- Continuous oximeter and cardiac monitor.

Treatment and Interventions for Hypovolemic Shock from Trauma

- Place two large-bore IV lines (above and below diaphragm if indicated).
- Intraosseous line placement if peripheral venous access is difficult.
- Bolus with 20 mL/kg of warm normal saline/lactated Ringers and repeat if necessary.
- Consider intubation and ventilation to decrease work of breathing.
- Transfuse 10 mL/kg pRBC for hemorrhagic shock secondary refractory to crystalloid.

IV, Intravenous; *pRBC,* packed red blood cells.

skill not often performed and is rarely needed to obtain vascular access in the pediatric trauma patient. If performed, the greater saphenous vein at the ankle is the preferred site. In the rare occasion that a neonate presents after trauma, an umbilical vein cannulation can be attempted in infants up to 10 days old if there is enough of an umbilical stump to perform the procedure.

Fluid resuscitation in pediatric trauma patients begins with a 20 mL/kg bolus of warm isotonic crystalloid solution over 10 minutes. A second bolus of 20 mL/kg of warm isotonic crystalloid is given for those who do not initially improve or stabilize. If the patient continues to require fluid resuscitation after two boluses, warmed, packed red blood cells (pRBCs) at 10 mL/kg should be transfused, while identifying and treating any sources of hemorrhage. In cases of massive transfusion (blood products >40 mL/kg in an adolescent or >50 mL/kg in a child/infant), it is important to add plasma and platelets to correct coagulopathy. Adult patients undergoing massive transfusion are

BOX 160.4 Disability: Neurologic Assessment and Treatment

Assessment

- Level of consciousness: Use AVPU scale and age-appropriate GCS
- Pupil size and reactivity
- Movement in all extremities and tone
- Posturing and reflexes

Treatment and Interventions

- Stabilize spinal column with spinal immobilization techniques.
- Rapid Sequence intubation for GCS scores ≤8
- Cranial CT scan all with GCS scores less than 15 and neurosurgical consultation as needed.
- With signs of herniation, elevate head of the bed and 3% hypertonic saline 2–5 mL/kg IV (or mannitol 0.5–1.0 g/kg IV).
- Maintain CPP of at least 40 mm Hg in children.

AVPU, Alert, verbal, painful, unresponsive; *CPP,* cerebral perfusion pressure; *CT,* computed tomography; *ETI,* endotracheal intubation; *GCS,* Glasgow Coma Scale; *IV,* intravenous; Pco_2, partial pressure of carbon dioxide, *RSI,* rapid sequence induction.

resuscitated with plasma, platelets, and pRBCs in a 1:1:1 ratio.[3] Less data exists for this strategy in the pediatric trauma population as data is conflicting,[4,5] although many centers now resuscitate children with a 1:1 plasma: pRBC ratio. In adult patients with significant traumatic hemorrhage, tranexamic acid is now routinely used to stabilize clot and limit blood loss. Although frequently used in non-traumatic pediatric surgery, use of tranexamic acid in injured children is rare.[6] The dosage in injured children (15 mg/kg over 20 minutes, then 2 mg/kg/h for 8 hours or 30 mg/kg over 20 minutes, then 4 mg/kg/h for 8 hours) is currently under study.[7]

D—Disability Assessment

A rapid neurologic and mental status evaluation is performed to assess neurologic status. The assessment of disability in pediatric trauma patients is described in Box 160.4. The alert, verbal, painful, unresponsive (AVPU) system and the GCS (Table 160.1) are utilized to assess neurologic status. The modified pediatrics GCS (used in pre-verbal children) performs similarly to the standard GCS in older children (see Table 160.1). Children's higher metabolic demands result in higher oxygen consumption and glucose utilization; a rapid bedside glucose level should be checked in any child with altered mental status after trauma.

E—Exposure and Environment

Trauma patients should have each body area fully exposed for evaluation; preverbal children are particularly high risk for missed injuries. However, children are often embarrassed or shy about physical exposure. In the stable patient, body areas can be examined in sections, keeping other parts covered from view. Compared to adults, children are also more susceptible to insensible heat and fluid loss due to their greater surface to mass ratios and should be kept normothermic, as hypothermia increases morbidity and mortality. Hypothermia contributes to metabolic acidemia and has direct adverse effects on cardiac inotropy, chronotropy, catecholamine responsiveness, platelet function, and both renal and hepatic drug clearance.

Interventions to maintain normothermia include increasing ambient temperature, administering warmed humidified oxygen, and warming all infused fluids, especially all blood products. Head wraps and convective warmers or radiant heat sources are adjuncts in

TABLE 160.1 Glasgow Coma Scale Score and Modified Pediatric Glasgow Coma Scale (For Those <2 Years)

BEST EYE OPENING RESPONSE		
Score	**>2 Years Old**	**<2 Years Old**
4	Spontaneous	Spontaneous
3	To verbal command	To voice
2	To pain	To pain
1	None	None
BEST MOTOR RESPONSE		
Score	**>2 Years Old**	**<2 Years Old**
6	Follows commands	Spontaneous movement
5	Localizes pain	Withdraws to touch
4	Withdraws to pain	Withdraws to pain
3	Abnormal flexion to pain (decorticate)	Abnormal flexion to pain (decorticate)
2	Abnormal extension to pain (decerebrate)	Abnormal extension to pain (decerebrate)
1	None	None
BEST VERBAL RESPONSE		
Score	**>2 Years Old**	**<2 Years Old**
5	Oriented and converses	Coos/babbles
4	Confused conversation	Irritable/cries
3	Inappropriate words	Cries to pain
2	Incomprehensible sounds	Moans
1	None	None

[a]Total score key for traumatic brain injury: severe, ≤8; moderate, 9 to 12; mild, 13 to 15.

newborns and infants, as well as older children with mild hypothermia (temperature <36°C). The exposure phase of the survey is often the appropriate time to concurrently begin initial imaging and further diagnostic testing (see following).

F—Family

We recommend the option of family members present during the initial resuscitations, a practice often preferred by families in both traumatic and non-traumatic pediatric resuscitations. A social worker or other qualified staff member dedicated to the family should be available to help explain treatments, answer questions, and provide emotional support.

Secondary Survey

A systematic secondary survey should follow the primary survey and necessary interventions, and should consist of an organized, complete head to toe assessment to detect additional injuries. Significant historical findings are collected at this time and can be remembered by the mnemonic *AMPLE* (Box 160.5). Key points of the ongoing assessment of the patient, after the secondary assessment, are summarized in Box 160.6.[2]

BOX 160.5 Ample History

A—*A*llergies
M—*M*edications
P—*P*ast medical history
L—*L*ast meal
E—*E*vents and *E*nvironment

BOX 160.6 Tasks to Be Completed After the Secondary Survey

- Continuous monitoring of vital signs
- Provision of analgesia, and continuous reassessment of pain
- Antibiotics and tetanus as appropriate
- Ensure urine output of 1 mL/kg/h
- Begin transport process if the patient will obviously need transport

If patient instability prohibits completion of the secondary survey, this should be communicated to the next caregivers. Tertiary surveys are now completed on all trauma patients within 24 hours of admission.

Physical Examination

During the secondary survey, a head-to-toe examination should be carefully performed. Specifics of the head examination include inspection and palpation of the skull (fontanelle) and facial bones, assessing pupillary size and reactivity, and evaluation of extraocular movements. In possible nonaccidental trauma, funduscopic examination may reveal retinal hemorrhages. A fluorescein examination may reveal occult eye injury in the crying child.

Cervical spine immobilization should be maintained until the patient's neck is cleared of injury. Patients in spinal immobilization should be removed from the backboard with spinal motion restriction maintained. When the patient is log-rolled for backboard removal, the thoracic and lumbar spinous processes are individually palpated, evaluating for tenderness or step-offs. To protect them from further injury, obtunded patients and those with signs or symptoms of thoracic or lumbar spine injuries should be carefully moved and positioned until imaging or clinical assessment provides a more definitive assessment.

Chest assessment involves visual inspection for wounds and flail segments, palpation for tenderness or crepitus, and auscultation for breath sounds. The abdominal examination consists of inspection for evidence of abdominal wall trauma and palpation for the presence of tenderness. A "seat belt sign," consists of erythema, abrasions, or ecchymosis extending across the chest or abdomen from the seat belt (see below). Abdominal tenderness is present in approximately 75% of alert children with an intra-abdominal injury; however, the reliability of the abdominal examination decreases drastically in patients with GCS scores less than 14. Digital rectal examination should only be performed to evaluate rectal tone in suspected spinal cord injury, or if the integrity of the rectum is in question. Testing the injured child's stool for occult blood is not useful and we do not recommend this. All pelvic bones should be assessed for stability and tenderness. Although rare in children, urethral injuries may result in perineal, scrotal, penile, or lower abdominal hematomas, or blood at the urethral meatus. If there is a concern for urethral injury, a retrograde urethrogram should be completed prior to insertion of a urinary catheter to avoid further injury.

Extremity examination evaluates for deformities, skin disruptions, neurologic deficits, and abnormal perfusion. Fractures may be stabilized with splinting before definitive management. Careful and

recurrent vascular and neurologic examinations should be performed and documented, especially after interventions such as splinting or reduction.

Trauma patients should be reexamined throughout their time in the ED to ensure their condition is stable, their pain is controlled, and no injuries are missed. When possible, ambulation can expose additional injuries not identified with previous examinations. Up to 70% of injuries with delayed diagnosis in pediatric trauma are orthopedic.[8]

Pain Assessment

Pain assessment and control is an essential part of any trauma patient's management. Analgesic medications, immobilization of injured extremities, and non-pharmacologic techniques should all be considered. Please refer to Chapter 157 for further discussion of pain control in children.

DIAGNOSTIC TESTING

Laboratory Testing

Laboratory testing is used to guide resuscitation, monitor blood loss, and screen for particular injuries, but should be tailored to avoid unnecessary testing. Patients at risk for hemorrhage should have a type and screen in addition to hemoglobin measurements. In acute hemorrhage, hemoglobin requires time to equilibrate and does not initially correlate with severity of blood loss. Serial hemoglobin measurements are not useful to screen for occult injuries; however, serial measurements may identify ongoing blood loss in patients with undifferentiated hypotension. In children with solid organ injuries, serial hemoglobin measurements are routinely performed, but the exact timing and utility is unclear.[9,10] Liver transaminases are useful to screen for hepatic injury, as they immediately elevate following liver injury. Children with GCS scores ≤13, hypotension, open or multiple bony fractures, or major tissue wounds are at risk for coagulopathy and should be screened with coagulation studies (INR and aPTT). Urinalysis is used to assess for blood (see below). Older pediatric trauma patients should be assessed for substance abuse and depression as contributing factors to the traumatic event. Post-pubertal females or those Tanner stage greater than 3 should be tested for pregnancy. Other than glucose testing in patients with altered mental status, serum electrolytes are routinely measured, but of limited initial use.

Radiologic Imaging

In the severely injured patient, we recommend performing an anteroposterior chest radiograph and a focused assessment with sonography for trauma (FAST), particularly if hypotensive. Plain films should be performed following the primary survey (routinely after the patient is rolled to their side, backboard removal and radiograph plates placed under the patient). An initial chest radiograph screens for immediate life-threatening thoracic injuries, but misses more subtle thoracic injuries. The FAST can be performed after the primary survey (or in conjunction if multiple providers), and evaluates for the presence of intraperitoneal and pericardial fluid. In hemodynamically unstable children, the FAST has good test characteristics for detecting intra-abdominal hemorrhage and can guide further management. The extended FAST (eFAST) examination incorporates the addition of lung views to evaluate for pneumothorax or hemothorax, but has yet to be proven useful in children. A plain pelvis radiograph may identify major pelvic disruptions, but should only be performed in patients who are hypotensive or have unstable pelvic bone examinations. In these patients, the pelvic radiograph may guide the use of a pelvic binder to limit further hemorrhage.

Further imaging should be obtained based on findings from the history and physical examination. Computed tomography (CT) has substantially changed the trauma patient evaluation, as it provides rapid injury identification and details to guide treatment. However, CT carries the risk of radiation-induced malignancy, which is greater in children than adults due to their higher organ sensitivity and longer life expectancy. Data suggests the risk of radiation-induced malignancy is 1 per 5000 to 10,000 cranial CT scans and 1 per 300 to 600 abdominal CT scans. Girls are more sensitive to CT radiation than boys. CT use has rapidly increased in injured children and is highly variable, and CT scans are more commonly obtained in children treated at adult or mixed trauma centers than pediatric trauma centers.[11] In an effort to improve and provide evidence-based care, investigators have developed clinical decision instruments that align CT use in injured children with need (see following).

DISPOSITION

The primary role of the emergency physician is to evaluate and stabilize the severely injured patient before admission or transfer to a facility able to provide the necessary care. Moderately to severely injured pediatric patients of all ages have improved outcomes in pediatric trauma centers.[12,13] For patients requiring transport to a pediatric trauma center, the emergency clinician should not delay transfer for extensive radiologic testing. There should be direct communication between the emergency physician and the accepting doctor, and all radiologic imaging, notes and laboratory results should accompany the patient. Technology now allows images to be transported via the cloud for immediate review by a trauma specialist, which has the potential to decrease unnecessary trauma transfers. Parents should be informed of the reason for the transfer and the exact location to which the child is being taken.

SPECIFIC INJURIES

Head Injury

Traumatic brain injury is the leading cause of death and disability in children older than 1 year of age in the United States.[14] Infants and toddlers are more prone to falls from standing height; school-age children are involved in sports injuries and MVCs; and children of all ages are subject to the sequelae of assault or abuse.

Important anatomic variations lead to differences in pediatric and adult head trauma. The cranial vault of a child is larger and heavier in proportion to the total body mass, predisposing young children to high degrees of torque that are generated by forces along the cervical spine axis. Sutures within the pediatric skull are both protective and detrimental to the outcome of head injury; although the cranium may be more pliable relative to traumatic insult, forces transmitted internally can result in parenchymal injury in the absence of skull fractures. The pediatric brain is less myelinated, with higher water content, predisposing it to shearing forces and higher risks for diffuse axonal injury and post-traumatic seizures.

Clinical Features

The height of the fall and the quality of the surface at the point of impact are important risk factors associated with severity of injury. Most children fall from standing height, but impact with an object can increase the localized force despite the short distance. In MVCs, the type of restraint used should be evaluated because unrestrained and improperly restrained children are at increased risk of serious injury. Several methods are available for evaluating mental status of head-injured patients, including the AVPU system and the GCS score.[15] The

GCS score should be modified for preverbal children (see Table 160.1). The "pediatric" GCS performs similarly to the adult GCS in verbal children.[16] In addition to assessing the child's mental status and examining the head for signs of trauma (including hematomas, lacerations and signs of skull fracture), the child and parents should be questioned on risk factors for intracranial hemorrhage, including loss of consciousness, mechanism of injury, behavior since the event, vomiting, and headache.

A brief seizure that occurs immediately after an insult (with a rapid return to a normal level of consciousness) is commonly called an *impact seizure*. Most children with post-traumatic seizures should undergo cranial CT scanning, but if the CT and the child's mental status are both normal, the child may be safely discharged home.[17]

The examination of a moderate to severely head-injured child includes strict attention to the ABCs (airway, breathing, and circulation). As the pediatric brain is highly sensitive to hypoxia and hypoperfusion, maintenance of oxygenation and blood pressure reduces further insult and optimizes the chance of functional recovery. Cerebral perfusion pressure (CPP) is adequate only in the face of a normal mean arterial pressure (MAP). Conceptually, CPP is equal to MAP minus ICP: CPP = MAP – ICP. As MAP is reduced, so is CPP. Therapy should target a CPP greater than 40 mm Hg and ICP less than 20 mm Hg.[18] Localized CPP at the site of injury and surrounding areas may vary greatly and be difficult to detect. Common symptoms and signs of raised ICP in infants and children are listed in Box 160.7. Herniation syndromes in children are similar to those in adults and described in Chapter 33.

Concussion. A *concussion* is a functional brain injury seen after a blow to the head or body, a fall, or another injury that "shakes" the brain within the skull. Radiographic studies should be obtained if there are findings suggestive of intracranial hemorrhage, but imaging solely for concussion is not recommended, as standard structural radiographic studies are normal, and current imaging for concussion is primarily experimental.[19]

Patients who sustain concussive insults may have somatic, cognitive, affective, or sleep symptoms. All children with concussive symptoms should be monitored for progression of symptoms by their primary care physician or a concussion recovery specialist. Treatment recommendations for concussion are a source of current research, as prior recommendations of bed rest are not beneficial.[20] Currently, we recommend a period of 24 to 48 hours of rest followed by increasing physical activity.

Scalp injuries. Bleeding from scalp wounds is often profuse and can lead to hemodynamic compromise in infants and small children if not quickly controlled. Early hemostasis prevents ongoing blood loss and should be addressed during the initial examination of the trauma patient. Scalp injuries in infants and children may also involve the development of three injury complexes. For these injury complexes to be better understood, the layers of the *s*kin, *c*onnective tissue, *a*poneurosis, *l*oose areolar tissue, and *p*eriosteum (SCALP) should be considered (Fig. 160.2). *Caput succedaneum* refers to a hematoma in the connective tissue layer. This is freely mobile and crosses suture lines. A *subgaleal hematoma* refers to a hematoma that is within the loose areolar tissue above the periosteum. Lastly, *cephalohematoma* refers to a collection of blood under the periosteum. Because the periosteum adheres tightly to the various suture lines, cephalohematomas do not cross them.

Skull fractures. In children, skull fractures occur in many different configurations. Simple linear non-depressed fractures rarely require therapy, are associated with good outcomes, and do not routinely require hospitalization in isolation. Factors associated with poor outcomes include the presence of a fracture overlying a vascular channel (especially the middle meningeal artery), a depressed fracture, or a diastatic fracture. Diastatic fractures are defects which extend through suture lines and can lead to leptomeningeal cysts and "growing fractures." Leptomeningeal cysts are more common in children younger than 3 years old and may form after a skull fracture with a dural tear. "Growing fractures" develop when leptomeninges herniate through a dural tear, causing bony erosion around the fracture site.

Signs of basilar skull fractures in children are similar to adults and include the presence of periorbital subcutaneous hematoma (raccoon eyes), posterior auricular ecchymosis (Battle's sign), and CSF rhinorrhea or otorrhea. Both raccoon eyes and Battle signs take hours to days to develop, and therefore an absence of these signs does not rule out basilar skull fracture.

Cerebral contusions. Cerebral contusions are often the result of coup and countercoup forces and manifest as multiple microhemorrhages. Patients often have associated symptoms, which include an altered level of consciousness, severe headache, vomiting, or focal deficits on neurologic assessment.

Epidural hematoma. Epidural hematomas are typically caused by bleeding from the meningeal vessels and are often associated with overlying skull fractures. The classic presentation of an epidural hematoma is the triad of head injury, followed by a lucid interval, and rapid deterioration as the hematoma expands and compresses the brain.

Subdural hematoma. Subdural hematomas are often secondary to the rupture of bridging veins. Subdural hematomas most commonly occur in patients younger than 2 years of age, and less than half have associated skull fractures. Chronic subdural hematomas are associated with nonaccidental injury or "shaken baby syndrome," the result of accelerating and decelerating forces within the cranial vault

BOX 160.7 Symptoms and Signs of Increased Intracranial Pressure in Infants and Children

- Headache
- Stiff neck
- Photophobia
- Altered state of consciousness
- Persistent emesis
- Cranial nerve abnormalities
- Papilledema
- Hypertension, bradycardia, and hypoventilation
- Infants: paradoxical irritability, split sutures, full fontanelle, and "setting sun sign"
- Decorticate or decerebrate posturing

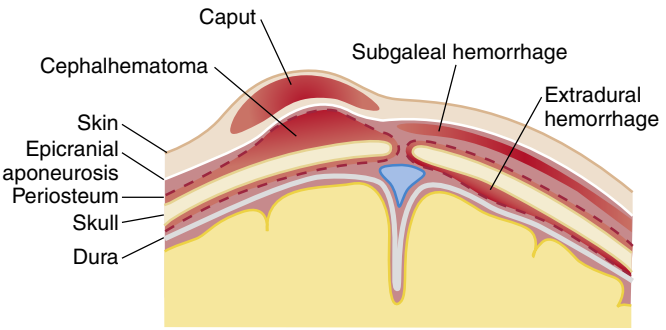

Fig. 160.2 Sites of Extracranial Hemorrhages in the Infant. (From Volpe JJ. *Neurology of the Newborn*. 4th ed. Philadelphia: WB Saunders; 2001.)

from the violent shaking of a child. Subdural hematomas at multiple sites, over areas other than the convexities, in the posterior fossa, or the posterior interhemispheric fissure should raise suspicion for nonaccidental trauma. See Chapter 172 for a more in-depth discussion on nonaccidental trauma.

Diagnostic Testing

Skull radiographs. Clinicians have historically used skull radiographs as a screen for skull fractures in young patients with scalp hematomas. Due to the limited sensitivity of skull radiographs and the increased use of CT scanning in head trauma, skull radiographs are now rarely obtained. Skull radiographs may be considered for part of a skeletal survey in the evaluation of child abuse; to evaluate functioning of a ventricular peritoneal shunt; or to identify suspected foreign bodies underlying scalp lacerations.

Cranial computed tomography. Cranial CT provides substantial information but should be balanced with the risk of radiation. Substantial research has now identified various risk factors for intracranial hemorrhage. The Pediatric Emergency Care Applied Research Network (PECARN) head injury decision instrument was derived in over 42,000 children and validated in a separate population of over 15,000 children.[21] The decision instrument provides evidence based guidelines for children with blunt head trauma (Fig. 160.3). Patients with no risk variables are at very low risk for intracranial injury and should not undergo cranial CT imaging. Furthermore, most patients with only a single risk variable can be observed in the ED and safely discharged after improvement, decreasing CT utilization. However, as the number of PECARN variables increase, risk increases and CT scanning becomes warranted.

Management and Disposition

Alert patients with normal cranial CT scans and normal neurologic examinations may be discharged home. Those with no PECARN risk variables, and those with a single risk factor who clinically improve after a period of observation, can also be discharged home. Reliable caretakers should be given specific return precautions for any focal

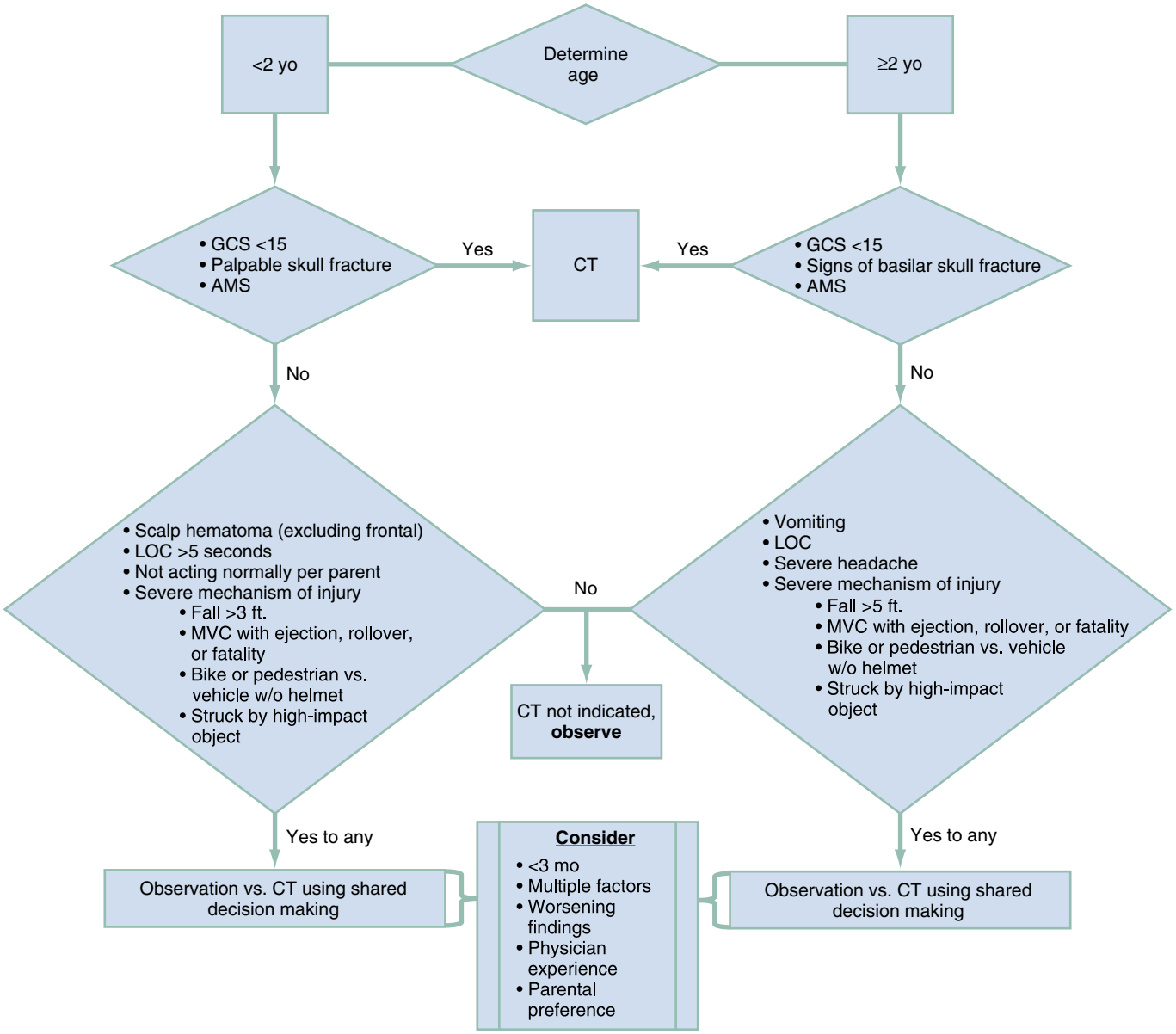

Fig. 160.3 PECARN Head Injury Chart. *AMS,* Altered mental status; *CT,* computed tomography; *GCS,* Glasgow Coma Scale; *LOC,* loss of consciousness; *MVC,* motor vehicle collision.

deficit, lethargy, worsening of symptoms, or alteration of consciousness. Children with intracranial hemorrhage or skull fractures should be evaluated by a neurosurgeon.

Skull fractures. Historically, children with skull fractures are routinely admitted to the hospital. However, alert children with linear, non-depressed skull fracture are unlikely to benefit from hospitalization. In selected cases after neurosurgical consultation, discharge with close outpatient follow-up and return precautions may be acceptable.[22] Skull fractures depressed more than the width of the skull are often repaired surgically. Basilar skull fractures require observation, but no specific therapy unless a persistent CSF leak is identified.

Severe traumatic brain injury. Prehospital BVM is recommended over ETI for support of ventilation and oxygenation. In the ED, ETI is performed in those with rapid deterioration, inability to protect their airway, or GCS scores ≤8. Recommendations for the treatment of children with moderate to severe head injuries are provided and regularly updated by the Brain Trauma Foundation (Box 160.8).[18] Standardization of care with early identification of impending herniation, emergency management of raised ICP, neuroimaging and neurosurgical involvement for appropriate use of ICP monitors improves outcomes.[18] In patients with suspected intracranial hypertension, treatment measures should include elevation of the head of the bed to 30 degrees, appropriate analgesia and sedation, controlled mechanical ventilation with $PaCO_2$ 35 to 40 mm Hg, hemoglobin maintained greater than 7 g/dL, normothermia (35 to 38°C), correcting any coagulopathy, and adequate intravascular volume with normal saline boluses.[18] Management of suspected acute herniation includes administering 3% hypertonic saline between 2 and 5 mL/kg over 15 minutes.[18] Mannitol (0.5–1 g/kg IV) is also used in this setting, but data is insufficient in the pediatric population to support its use. Serial neurologic examinations are the most reliable indicators of clinical deterioration and impending herniation. Repeat cranial CT scanning should be based on clinical assessments and not routinely performed.[18] We recommend a 7-day course of anticonvulsants (phenytoin or levetiracetam) for children with moderate to severe head injury to prevent early post-traumatic seizures. Prophylaxis beyond 7 days is not warranted. If a seizure does occur, rapid treatment with benzodiazepines is indicated.

Vertebral and Spinal Cord Injury

Foundations

Due to anatomic differences in the cervical spine, vertebral and spinal cord injury patterns vary with the age of the patient (Box 160.9) and are most commonly from falls, followed by MVCs. Thoracic and lumbar spine fractures are more common and characterized by compression fractures, whereas burst fractures are rare in children.[23] Cervical spine fractures are rare, especially in children less than 8 years. In this age group, cervical spine injuries are usually C3 or above.[24] As anatomic features of the cervical spine approach adult patterns between ages 8 and 10 years, injuries are more common in the lower cervical spine, and by age 15 years, the injury spectrum is similar to adult patients.

The anatomic differences between children and adults (see Box 160.9) lead to higher cervical cord injuries and an increased incidence of cord injury without bone involvement.[25] Thus, spinal cord injury without obvious radiographic abnormality (SCIWORA) is more common in children.[26] SCIWORA is a misnomer in this era of magnetic resonance imaging (MRI), because most injuries traditionally described as SCIWORA are identified on MRI but not plain radiographs. Treatment and prognosis of cervical spine injury depend on the neurologic presentation and extent of MRI findings. Whenever a cervical spinal injury is identified, careful attention should be paid to the entire spine as multilevel injuries occur frequently.[23]

BOX 160.8 Emergent Management of Severe Traumatic Brain Injury Pertinent to the Emergency Department

- ICP monitoring is suggested for severe TBI with a threshold for treatment of less than 20 mm Hg.
- Excluding increased ICP based on a normal cranial CT in comatose children is not recommended.
- Target CPP is 40–50 mm Hg.
- Bolus 3% hypertonic saline for increased ICP at 2–5 mL/kg IV over 15 min.
- Avoid fentanyl and midazolam boluses during ICP crises.
- Seizure prophylaxis to prevent early post-traumatic seizures with (phenytoin or levetiracetam).
- Avoid prophylactic hyperventilation (PaCO2 <30 mm Hg).
- Prophylactic hypothermia and corticosteroids are not recommended.

CPP, cerebral perfusion pressure; *ED,* emergency department; *ICP,* intracranial pressure; *IV,* intravenously; *$Paco_2$,* arterial carbon dioxide partial pressure; *TBI*, traumatic brain injury.
Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. *Pediatr Crit Care Med*. 2019;20:280-289.

BOX 160.9 Anatomic Differences in the Pediatric Cervical Spine

- Cervical spine fulcrum changes from C2 to C3 in toddlers to C5 to C6 by 8–12 years old.
- Relatively larger head size, resulting in greater flexion and extension injuries.
- Relatively large occiput in children younger than 2 years old leads to flexion of cervical spine if they are laid flat on standard backboard without support under their scapula and pelvis.
- Smaller neck muscle mass with ligamentous injuries more common than fractures.
- Anterior wedge appearance of cervical vertebral bodies is common.
- Increased flexibility of interspinous ligaments.
- Flatter facet joints with a more horizontal orientation.
- Incomplete ossification, making interpretation of bony alignment difficult (synchondrosis).
- Uncinate processes do not calcify until approximately 7 years old.
- Basilar odontoid synchondrosis fuses at 3–7 years old.
- Apical odontoid epiphyses radiographically apparent at 7 years old but may not fuse until approximately 12 years old.
- Posterior arch of C1 fuses at 4 years old.
- Anterior C1 arch may not be visible until 1 year old and fuses at 7–10 years old.
- Neural arches fuse to body by approximately 7 years old.
- Posterior arches fuse by 3–5 years old.
- Epiphyses of spinous process tips may mimic fractures.
- Predental space less than 5 mm in those less than 8 years and less than 3 mm in those ≥8 years.
- Pseudosubluxation of C2 on C3 seen in 40% of children up to 10 years and can be identified by an intact Line of Swischuk (Fig. 160.4).
- Prevertebral space size varies with phase of respiration.

Clinical Features

Although all trauma patients should be examined for vertebral injuries, significant head, neck, or back trauma, high-speed MVCs, or falls from a height onto the head should heighten suspicions. After the initial evaluation and stabilization, the cervical region can be definitively examined. Gentle palpation of the spine for tenderness or bony deformity can be performed to clinically assess the spine in alert children

with otherwise normal neurologic exams. The facial response of a younger child to pain is often more indicative of injury than their verbal response. The neurologic examination in a pediatric patient can be difficult, but several factors should be evaluated in a patient with suspected spinal cord injury. Paralysis, paresthesia, and priapism are highly correlated with spinal cord injuries. Symptoms of paralysis or paresthesia, even if completely resolved at the time of examination, should be considered an indication of spinal cord injury. Spontaneously resolved deficits from an initial stretching of the cord with a rapid deceleration mechanism may return several days later from subsequent cord edema (as commonly described in patients with SCIWORA).[26]

Pediatric presentations of spinal cord injury syndromes are similar to adults and are detailed in Chapter 35. Spinal cord injuries are described as complete or incomplete, depending on the presence or absence of sensory and motor function. Incomplete lesions have preservation of some sensory or motor function below the injury level. Incomplete cord injury has a better prognosis.

Diagnostic Testing

Radiographic recommendations for potential cervical spine injuries are a source of current research and substantial variability. The National Emergency X-Radiography Utilization Study (NEXUS) criteria are often used to clear the cervical spine in adults (see Chapter 35). However, of the 34,069 patients enrolled in NEXUS, only 3065 (9.0%) were less than 18 years of age, and only 30 (0.98%) of these children had cervical spine injuries. Although the NEXUS decision rule identified all patients less than 18 years of age with cervical spine injury, only four children with injuries were younger than 9 years of age, and none were younger than 2 years of age. In a retrospective case-control study, the PECARN reviewed 540 records of children less than 16 years of age with cervical spine injury to identify 8 factors associated with cervical spine injury: altered mental status (including intoxication), focal neurologic findings, any neck pain, torticollis, substantial torso injury, conditions predisposing to cervical spine injury, diving mechanism, and high-risk motor vehicle crash. Children with none of these factors were at very low risk of cervical spine injury.

With limited research to direct pediatric cervical spine clearance, emergency physicians have developed reasonable practice variations in the use of specialist consultation and choice of imaging modalities. We recommend institutions develop multidisciplinary agreements on pediatric cervical spine clearance; establishing protocols has been shown to decrease time to clinical clearance and reduce unnecessary radiation exposure in children. We believe it is reasonable to follow a recent consensus statement and diagnostic algorithms published by the Pediatric Cervical Spine Clearance Working Group, consisting of 15 pediatric orthopedic surgeons, 3 pediatric emergency medicine physicians, 3 pediatric neurosurgeons, 2 pediatric trauma surgeons, and 2 pediatric radiologists.[27] Based on literature and expert opinion, the authors recommend clinical clearance in children with GCS scores 14 to 15, with minor mechanisms of injury (see following), no midline spine tenderness with full range of motion, normal head position, no associated neurological deficits, no painful distracting injuries, hypotension, or intoxication.[27] Patient not meeting all of these criteria should receive cervical spine imaging, starting with plain radiographs that should include a lateral view at minimum. We also agree with this group that a child who is able to maintain focus during an examination can have their cervical spine clinically cleared, despite other significant injuries. However, any child with a visible or known "substantial" injury to the chest, abdomen, or pelvis should have imaging.[27] High risk mechanisms of injury that should prompt imaging include an axial load, clotheslining injury, high-speed MVCs, suspected nonaccidental trauma, or a fall from a height of more than 10 feet. Thus, any alteration of mental status, focal sensory or motor abnormalities, neck pain, the presence of midline neck

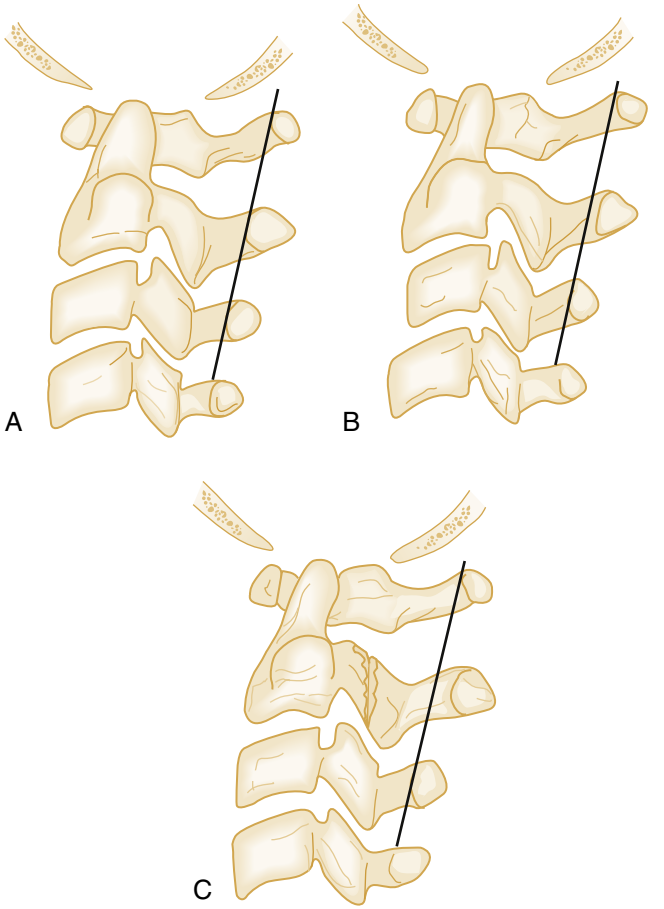

Fig. 160.4 Spinolaminar Line. Use only to access anterior displacement of C2 on C3. A line is drawn from the cortex of the spinous process of C1 to the cortex of the spinous process of C3, and the relationship of the spinous process of C2 is noted. (A) Normal line passing through the cortex of C2. (B) Normal line passing within 1.5 mm of the cortex of C2. (C) Abnormal line passing more than 1.5 mm anterior to the cortex of C2, suggesting underlying fracture of posterior elements of C2. (From American Academy of Pediatrics and American College of Emergency Physicians. *APLS: The Pediatric Emergency Medicine Resource*. 4th ed. Sudbury, MA: Jones and Bartlett Publishers; 2004.)

tenderness or torticollis, limited cervical range of motion or substantial distracting injuries on physical examination, warrant further imaging.[27] To reduce radiation exposure from CT, plain cervical spine radiographs are initially recommended in children with GCS scores 14 to 15 whose cervical spines cannot be clinically cleared.[27] Plain radiographic evaluation consists of lateral and anteroposterior views. In children older than 8 years, an open-mouth odontoid view should be added. The sensitivity of cervical spine plain radiographs is variable, as interpretation in children may be challenging due to the anatomic changes occurring with growth (see Box 160.9).

An essential criterion for radiographic clearance of the cervical spine is complete visualization of all seven cervical vertebrae to the C7 to T1 interface. The pre-dental space should be less than 5 mm in children younger than 6 years old, and the prevertebral soft tissue space should not be greater than one-half the vertebral body width above C4, and not greater than the width of the vertebral body at C6. The four cervical radiographic lines should be evaluated and the atlanto-occipital alignment assessed for dislocation (Fig. 160.4). Pseudo-subluxation of C2 on C3 in children up to age 10 years, occurs in approximately 40% of patients. Subluxation can be differentiated from pseudo-subluxation by the posterior cervical line and the relationship of the spinolaminar line

(line of Swischuk) to the anterior cortical margin of the spinous process at C2 (see Fig. 160.4). This line should maintain its integrity with no more than 1.5 mm of deviation. Although exceptions to this occur, an abnormal line of Swischuk is usually a pathologic finding and should prompt further investigation, typically with specialist consultation.

In children with GCS scores less than 14, we recommend cervical spine CT be obtained at the time of cranial CT imaging.[27] Alternatively, in children less than 3 years of age with GCS scores less than 14, cervical spine CT of C1–C2/C3 can be obtained with plain radiographs of the remaining cervical vertebral. Spine consultation should be obtained in children with injuries found on initial imaging. MRI may be obtained for ongoing concerns or to further delineate spinal cord injury.

Young children are at risk for occipital cervical junction injuries (atlanto-occipital disassociation). Although many of these injuries are immediately fatal, early detection and immobilization are important to prevent further morbidity and mortality. A Power's ratio greater than 1 on imaging indicates atlanto-occipital dislocation (Fig. 160.5). Traumatic atlantoaxial rotatory subluxation should be suspected in an injured child with torticollis. Classically, it is differentiated from muscular, non-traumatic torticollis by history, time course, and the absence of palpable spasm of the sternocleidomastoid muscle on the side contralateral to the direction in which the chin is pointing. When an atlantoaxial rotatory subluxation is suspected, plain radiographs or CT of the cervical spine are indicated. In children with upper cervical spine tenderness, it is prudent to consider a fracture of the synchondrosis between the odontoid and C2. This can be difficult to diagnose on plain radiographs, but it is often recognized as a subtle anterior tilt to the odontoid on C2. A CT scan with sagittal reconstructions can confirm the diagnosis. Children with peripheral neurologic abnormalities should be initially screened with CT or plain radiographs, but undergo MRI if findings persist. If a cervical spine ligamentous or cord injury is suspected with a negative CT scan, we recommend obtaining an MRI. Depending on the scenario and resources, patients with continued neck pain or tenderness despite negative plain radiographs or CT may require spine consultation, MRI, or treatment with a cervical collar and 1 to 2 week outpatient follow-up. The use of cervical spine flexion and extension radiographs to evaluate for ligamentous injury in the acute setting is often limited by the child's pain with neck ranging.

Management

Direct spinal cord injury results in a potentially irreversible injury. Indirect injury results from preventable or reversible injury secondary to ischemia, hypoxemia, and cord edema. Resuscitation of a patient with spinal cord injury should focus on prevention or minimization of the indirect causes of injury to the cervical spine. Spinal injury management begins prehospital, and most injured children arrive with adequate spine immobilization. In transport, the child who requires spinal immobilization should be placed in a stiff cervical collar, a rigid backboard, and external fixation using head blocks, cloth tape, or straps to provide adequate precautions. Appropriate padding should be placed under the shoulder blades of the patient to approximate neutral alignment of the cervical spine and help prevent pressure-related injury. Smaller children can be immobilized in their car seats.

In the ED, spinal immobilization should be maintained throughout the initial trauma evaluation. However, even when thoracic or lumbar fractures exist, patients should be expeditiously removed from the backboard to prevent discomfort and morbidity. Sliding boards (smooth movers) can be used to move patients onto scanner tables and back to their trauma beds.

Breathing should be assessed to determine the presence of hypoventilation, as patients with spinal cord injury may have diminished diaphragmatic activity or intercostal muscle paralysis. Supplemental oxygen should be provided, and ventilatory assistance considered in patients with hypoventilation or altered mental status.

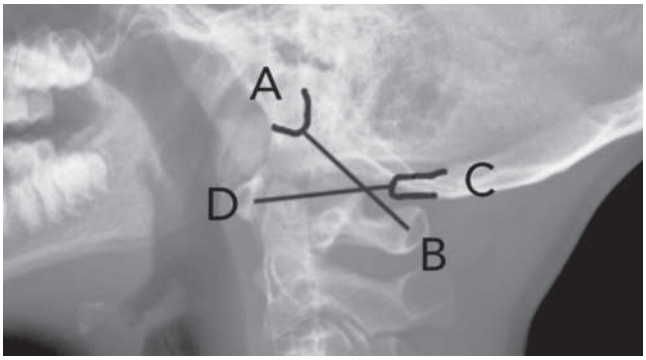

Fig. 160.5 Power's Ratio is Calculated as the Ratio of the Distance From the Basion (Midpoint of the Anterior Margin of the Foramen Magnum) *(A)* to the Anterior Cortex of the Posterior Arch of the Atlas *(B)* Divided by the Distance From the Opisthion (Midline Point of the Posterior Margin of the Foramen Magnum) *(C)* to the Posterior Cortex of the Anterior Arch of the Atlas *(D)*. A Ratio of Ab:cd Greater than 1 Indicates an Atlanto-Occipital Dislocation. The Figure Shows a Normal Power's Ratio.

Spinal shock is the loss of spinal reflexes below the site of injury, and generally resolves in 1 to 24 hours as spinal reflexes return below the site of injury. Neurogenic shock typically occurs with spinal cord injuries above the mid-thoracic level, and should only be considered once hemorrhagic shock has been excluded. Patients with neurogenic shock lose their sympathetic tone, manifested as hypotension and bradycardia. Treatment includes fluid administration, parasympathetic receptor blocking agents (e.g., atropine), and vasopressors with chronotropic, vasoactive, and inotropic characteristics (e.g., norepinephrine). Corticosteroids are no longer recommended in spinal cord injury. Early spine consultation is critical in children with potential spine injury to determine the need for further imaging and treatment, including possible need for transfer with continued spinal immobilization.

Cardiothoracic Injury

Foundations

Thoracic injuries are the second leading cause of death in injured children.[1] Most serious pediatric thoracic injuries are caused by blunt trauma (MVCs or pedestrian accidents). Considering the typical forces associated with blunt trauma, isolated chest injury is relatively infrequent in children. Those with penetrating chest trauma often die from primary vascular injuries which are rare following blunt mechanisms.

Pediatric ribs are less calcified than adults, resulting in more rib flexibility. This results in fewer rib fractures and more energy from the trauma transmitted internally. The presence of actual rib fractures in children suggests high energy and substantially increases the risk of morbidity and mortality. Pediatric rib fractures are generally treated with supportive care, but additional injuries should be sought. Rib fracture in infants should raise suspicion for abuse.[28]

Because of their unique anatomy and respiratory physiology (see Chapter 155), children have an increased risk for early decompensation after chest injury. A child's chest wall circumference does not change substantially during respiration, impairing their ability to increase forced vital capacity. Due to this and their increased metabolic demands, children normally function near maximum tidal volume capacity. As a result, children primarily increase ventilation by increasing their respiratory rate. Thus, anything that impedes a child's ability to increase ventilatory rate can significantly compromise ventilation,

as with diaphragmatic impairment from gastric over-inflation (see Fig. 160.1). Finally, infant diaphragmatic muscle fibers predispose them to muscle fatigue and sudden apnea.

Diagnostic Testing

Plain chest radiography is the initial screening test for thoracic injury and is indicated in children with hypotension, tachypnea, or abnormal thoracic examinations, including any auscultatory abnormalities. This diagnostic test, however, fails to identify 50% of thoracic injuries. Chest CT has greater sensitivity, but exposes the child to substantial radiation, results in increased costs, and has demonstrated limited impact on outcomes.[29] Indications for contrast enhanced chest CT include the need to evaluate for trachea-bronchial or aortic/great vessel injury.[29] Unfortunately, further indications for thoracic CT are not well identified.

Pneumothorax. Traumatic pneumothoraces are less common in children and often associated with a hemothorax. Patients present with symptoms of chest pain, shortness of breath with evidence of chest wall abrasions or ecchymosis. Decreased breath sounds may not be appreciated in children with a pneumothorax because of the extensive transmission of breath sounds in the chest and upper abdomen. Initial anteroposterior supine chest radiography fails to identify half of pneumothoraces. Thoracic ultrasound has higher sensitivity, and chest CT is the gold standard.

Pneumothorax treatment includes the placement of an appropriately sized tube thoracostomy (see Box 160.2) in the mid-axillary line. Chest radiographs should confirm the eyelets of the chest tube are within the chest wall cavity. The chest tube is then attached to an under-water sealed suction device to drain the pneumothorax. A small, simple pneumothorax (<20% volume) in a spontaneously breathing alert, hemodynamically stable child may be observed. Occult pneumothoraces (visualized only on CT or ultrasound and not on plain radiography) are also routinely observed. All pneumothoraces undergoing observation should be treated with high flow oxygen to speed resolution. Children with occult pneumothoraces under positive pressure ventilation may also be observed, but rapid treatment should be available for any decompensation.

Pulmonary air leaks occurring through a one-way valve can cause a tension pneumothorax (Fig. 160.6). Increasing amounts of trapped air within the pleural cavity force the mediastinal structures toward the opposite side, compromising cardiac output. The mediastinal shift forces the trachea to the opposite side, with distention of the neck veins from the decreased venous return to the heart. This results in hypoxia, hypotension, and fluid-refractory shock. Most patients with tension pneumothorax have severe respiratory distress, decreased breath sounds (often bilaterally), and a shift in the point of maximal cardiac impulse. Immediate treatment includes angiocatheter (14 gauge) decompression in the second intercostal space in the midclavicular line or a tube thoracostomy in the fourth intercostal space anterior to the mid-axillary line.

An open pneumothorax occurs when the injured chest wall allows the bi-directional flow of air through the wound. The equalization of pressures between the atmosphere and the chest cavity prevents adequate lung expansion. As a result, ventilation and oxygenation can be severely impaired. In the prehospital setting, a bandage applied over an open pneumothorax wound and taped on three sides, as a temporizing measure, allows air to escape during expiration but not to enter during inspiration.

Management of an open pneumothorax is determined by the size of the chest wall defect and the amount of respiratory compromise. A simple, small, open pneumothorax in a breathing patient may be treated by covering the chest wall defect with an occlusive dressing, such as sterile petroleum gauze, and performing a separate incision for the chest tube. Defects that are too large to seal adequately and patients with ventilatory failure are candidates for intubation with mechanical ventilation in addition to the chest thoracostomy.

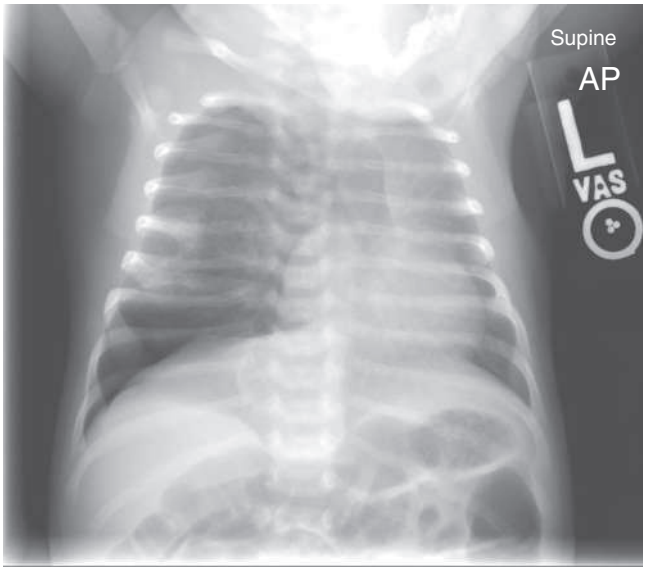

Fig. 160.6 Plain radiograph demonstrating a right sided tension pneumothorax with shift of the mediastinal structures to the left. The mediastinum is more mobile in children resulting in rapid ventilatory and circulatory collapse when under tension.

Hemothorax. Significant bleeding may occur as a result of injury to intercostal vessels, the internal mammary vessels, or lung parenchyma. Clinically, patients have decreased breath sounds and dullness to percussion on the affected side. Approximately 50% of pneumothoraces have concomitant hemothoraces. As hemothoraces collect in the most dependent portion of lung, they are better visualized on upright films as opposed to the standard anteroposterior radiograph. The only sign of hemothorax on a supine radiograph may be a slightly less radiolucent appearance on the affected side of the chest. Although small hemothoraces are observed, significant hemothoraces are treated with tube thoracostomy. In the supine patient with a simple pneumothorax, chest tubes are directed superiorly; in hemopneumothorax, however, they are directed posteromedially. Repeat chest radiographs should be obtained to confirm tube position and document lung expansion.

Massive hemothorax is rare in children and is associated with severe mechanisms of injury (high-velocity MVCs, falls from extreme heights, or gunshot wounds). Indications for open thoracotomy include evacuated blood volumes greater than 15 mL/kg of blood immediately on placement of the chest tube, persistent blood loss (exceeding 2 to 4 mL/kg/h over 3 hours), persistent hemodynamic instability or continued air leak.

Pulmonary contusion. Both penetrating and blunt thoracic trauma may cause pulmonary contusions, the most common thoracic injury in children. The compliance of the rib cage in children makes them susceptible to the development of pulmonary contusion, even in the absence of external signs of chest trauma. Injury to capillary membranes allows blood to collect within the interstitial spaces, resulting in hypoxia and respiratory distress. If bleeding is severe, both oxygenation and ventilation can be impaired. Initial chest radiographs underestimate the degree of injury and chest CT better delineates the insult. Treatment includes close monitoring, as these injuries evolve and patients can progress to respiratory distress over hours. The majority can be treated, however, with observation and supplemental oxygen as needed. Most resolve without sequelae, but those that progress can

require positive pressure ventilation or even extracorporeal membrane oxygenation. Prophylactic steroids and antibiotics are of no known benefit.

Traumatic diaphragmatic hernia. Traumatic diaphragmatic hernias are exceedingly rare. Mechanisms causing these injuries usually involve a sudden increase in intra-abdominal pressure. The degree of symptoms is dependent on the extent of abdominal herniation into the pulmonary space. Most commonly, the herniation occurs on the left side, as the liver hinders the herniation of bowel on the right (Fig. 160.7). Initial management involves placement of a nasogastric tube to decompress the stomach. In cases of severe respiratory distress, intubation with mechanical ventilation is indicated. BMV should be avoided whenever possible, as this can cause distension of the herniated contents in the chest. Surgery is required for definitive repair.

Cardiac and vascular injuries. Although cardiac injuries following trauma are rare, cardiac contusion is the most common injury of the heart but is frequently without symptoms and not diagnosed. Patients often have chest wall tenderness or may report generalized chest pain; tachycardia is the most common finding. No consensus exists on the need and type of evaluation, but most providers screen those at risk with an electrocardiogram. In symptomatic patients (unexplained hypotension) an echocardiogram is indicated and may be diagnostic. Screening with cardiac enzymes is generally not warranted, but normal high sensitivity troponin measurements make the diagnosis unlikely. Patients with significant myocardial contusions should be monitored closely for the development of dysrhythmias and impaired myocardial function; however, in most cases no sequelae occur.

Cardiac tamponade is an immediately life-threatening condition, as extravasated blood fills the pericardial space and impairs cardiac filling during diastole. It presents with tachycardia, distant heart sounds, narrow pulse pressure, jugular venous distention, and pulsus paradoxus. In the scenario of profound hypovolemia, venous distention may be absent. The final common pathway involves the development of cardiopulmonary failure and pulseless electrical activity. The FAST examination (or dedicated echocardiogram) can rapidly identify tamponade (Fig. 160.8), provide an estimate of the pericardial effusion and diastolic dysfunction, and guide therapy. In critical patients with tamponade, emergency pericardiocentesis should be performed to drain the fluid from the pericardial sac. However, this is often inadequate, depending on the volume of blood and the presence of a subpericardial clot. Therefore, a definitive thoracotomy or pericardial window is often required to evacuate the pericardium adequately and repair the primary injury. Penetrating cardiac wounds and tamponade are survivable if recognized early.

Commotio Cordis results from blunt trauma to the anterior chest wall, which causes cessation of normal cardiac function. The patient may have an immediate dysrhythmia or ventricular fibrillation that is refractory to resuscitation efforts. Significant morbidity and mortality are associated with this disorder. Although most patients recover completely, some require extended treatment with antiarrhythmic agents, cardiac pacemaker placement, inotropic agents, or an intra-aortic balloon pump. In patients with prolonged cardiac instability, cardiogenic shock and death may occur despite maximal therapeutic intervention. Aortic and large vessel injuries are fortunately quite rare in young children but begin to increase in adolescents as mediastinal and vascular anatomy more closely resembles adults.

ED thoracotomy is more effective for penetrating trauma; it may be considered for patients with thoracic trauma who deteriorate to cardiopulmonary arrest despite maximal resuscitation. Because their injuries are more likely to be from penetrating mechanisms, adolescents have the best response to intervention.[30] In patients with penetrating chest trauma with cardiopulmonary resuscitation (CPR) for less than 15 minutes, a left anterior thoracotomy may be warranted. Suggested contraindications to ED resuscitative thoracotomy after out-of-hospital CPR include (1) blunt trauma with CPR for longer than 10 minutes with asystole and no signs of life on presentation without ultrasound evidence of cardiac tamponade and (2) penetrating trauma with CPR for greater than 15 minutes and asystole with no signs of life on arrival without ultrasound evidence of cardiac tamponade.

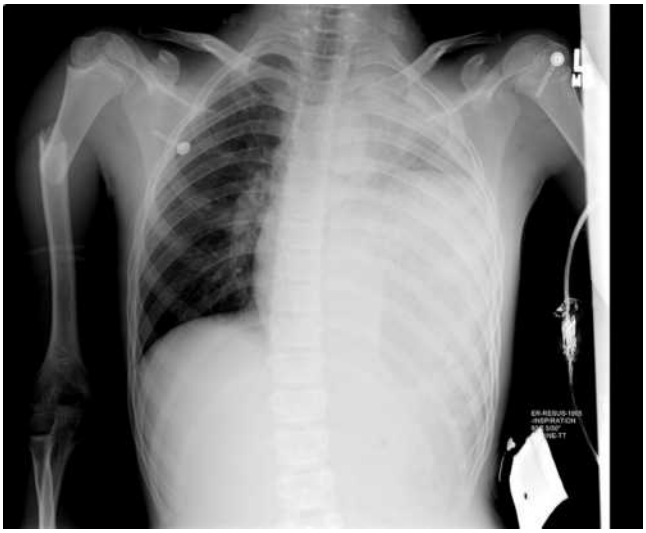

Fig. 160.7 Chest Radiograph with Herniation of the Stomach into the Left Thoracic Cavity. Care should be taken in these patients as the absence of breath sounds on the left may be mistaken for a pneumothorax. Chest tube placement could be complicated if the stomach was punctured during the procedure.

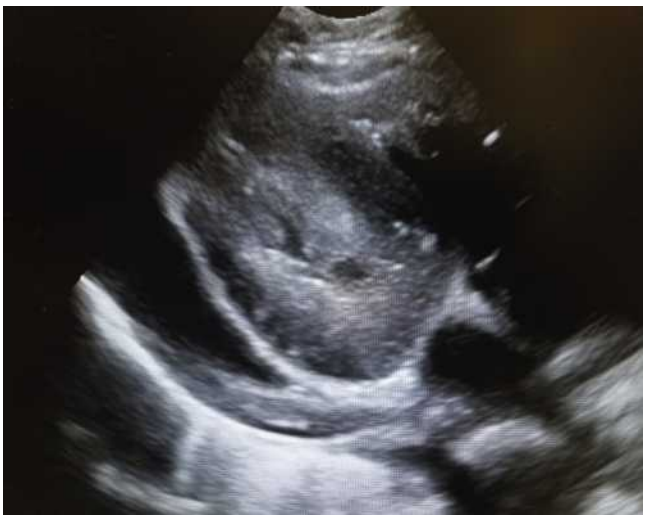

Fig. 160.8 FAST Examination Demonstrating Pericardial Tamponade in a Young Child with unexplained hypotension following a motor vehicle collision. This image resulted in immediate transport to the operating suite for life saving repair of a right atrial perforation in an otherwise uninjured child.

Abdominal and Pelvic Injury

Foundations

After head and thoracic injuries, abdominal injury is the third leading cause of traumatic death in children.[1] Blunt trauma in MVCs is most lethal, causing more than half of abdominal injuries. Certain injury patterns are more common in children due to their unique activities

or anatomy. These range from handlebar-inflicted abdominal injuries (Fig. 160.9) to crush injuries from television toppling. "Lap belt" injuries are most common in children and adolescents, and are characterized by intestinal injuries and "Chance" (horizontal) spinal fractures. Sports-related abdominal injuries often involve an isolated organ, as a result of a direct blow. Finally, abdominal injury is second only to head injury as a cause of death in child abuse cases.

A child's anatomy lends protection from some abdominal injury patterns, while predisposing children to other types of injuries. Children have proportionally larger solid organs, less subcutaneous fat, and less protective abdominal musculature than adults. Children have relatively larger kidneys with fetal lobulations, predisposing to renal injury. Children also have a flexible cartilaginous rib cage that allows for significant excursion of the lower chest wall, permitting compression of the abdominal organs. The combination of these factors provides the basis for the differences in abdominal injury patterns seen between children and adults.

Clinical Features

The rate of abdominal tenderness in alert children with intra-abdominal injuries is similar to that in adults, suggesting that the reliability of the abdominal examination is no different. However, the abdominal examination does become increasingly unreliable in children with significant head injuries (GCS scores <13).

Signs and symptoms of abdominal injury in children include tachypnea (from impaired diaphragmatic excursion and increased metabolic demands), abdominal tenderness, and signs of shock. Patients with abdominal wall injury (e.g., erythema, ecchymosis, abrasions) are much more likely to have intra-abdominal injuries. Abdominal distention is a common nonspecific finding that is often the result of swallowing air (e.g., from crying) after a painful event and not usually from massive hemorrhage (see Fig. 160.1).

Pelvic injuries are uncommon in young children due to their pliable pelvis and relatively larger shielding intraabdominal organs. To exclude injury, pelvic bone stability should be assessed in cases of abdominal trauma, including a genital examination searching for signs of injury. Rectal examination should only be performed in patients with a concern for specific injuries: spinal injury to assess rectal tone; or lower abdominal/pelvic trauma to evaluate rectal integrity.

Diagnostic Testing and Management

In patients with suspected abdominal injuries, management and resuscitation should be carefully planned to balance identification of all clinically important injuries and avoiding unnecessary testing. A careful history and physical examination can risk stratify patients for further evaluation. The PECARN abdominal injury rule risk stratifies children with abdominal trauma for intraabdominal injuries (Fig. 160.10). Children without any PECARN risk variables should not undergo abdominal CT, whereas CT is indicated for most with high risk variables. We recommend that children at intermediate to low risk undergo a period of observation, laboratory screening and FAST examination. Screening laboratory tests considered useful in children include elevated liver enzyme levels (serum aspartate aminotransferase [AST] >200 U/L or serum alanine aminotransferase [ALT] >125 U/L, hematuria, or an initial hematocrit <30%).

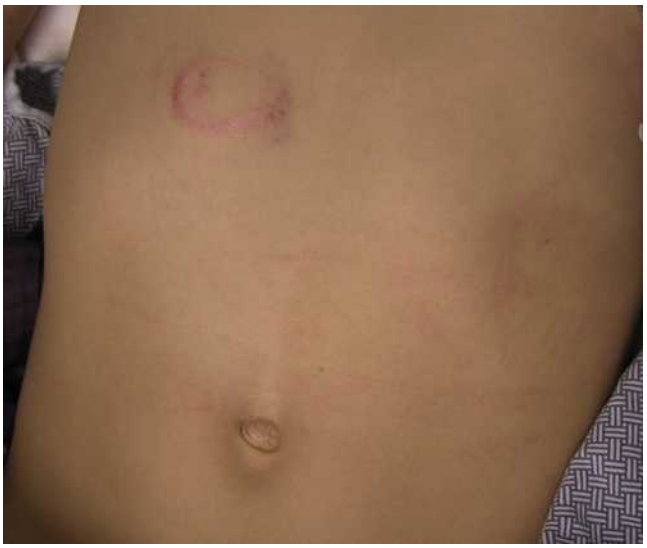

Fig. 160.9 Handlebar Injury in a Child Who Fell Off a Bike. Due to the location, the child sustained a liver laceration, but this mechanism often results in pancreatic or duodenal injuries when striking the epigastrium.

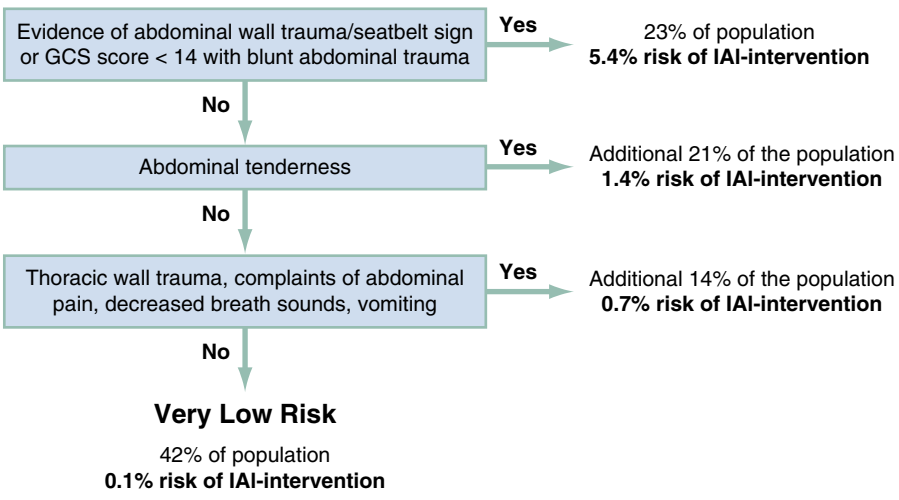

Fig. 160.10 PECARN abdominal injury rule provides evidence-based guidance for abdominal CT use in children. Children at 5.4% risk of injury undergoing intervention are considered at high risk, whereas those at 1.4% or 0.7% are considered at intermediate and low risk, respectively. Children without any risk factors are unlikely to benefit from CT. (Holmes JF, Lillis K, Monroe D, et al. Identifying children at very low risk of clinically important blunt abdominal injuries. *Ann Emerg Med.* 2013;62:107–16.e2)

The FAST examination evaluates the right upper quadrant (Morison's pouch), left upper quadrant and pelvis for intraperitoneal fluid. Although Morison's pouch is the most sensitive location for intraperitoneal fluid in adults, fluid is equally identified in the pelvis and Morison's pouch in children. Unfortunately, FAST has a lower sensitivity for intraperitoneal fluid in children than in adults, leading to uncertainty in its appropriate use.[31] Observational data suggests FAST safely decreases CT in children, however, the single randomized controlled trial in children did not demonstrate any clinical benefit with FAST.[32] Use of the FAST, however, did appropriately decrease the clinical suspicion of intra-abdominal injury, suggesting further study is warranted.[32] The finding of intraperitoneal hemorrhage on FAST does not mandate laparotomy, but if positive, ED abdominal CT is warranted. In hemodynamically unstable children, FAST quickly identifies an abdominal source of hemorrhage and can expedite care.[31]

The diagnostic test of choice to assess for intra-abdominal injury in stable patients at significant risk of intra-abdominal injury is abdominal CT. Abdominal CT scans should be performed with IV contrast; oral contrast is not necessary.[33]

Non-operative management of patients with solid organ injuries was pioneered in children. Now, patients with known sources of bleeding are routinely treated with observation, transfusion, and even arterial embolization instead of surgery.[34,35] Indications for laparotomy include intra-abdominal injuries with hemodynamic instability unresponsive to fluid resuscitation, transfusion greater than 50% of total blood volume, treatment of gastrointestinal injuries, penetrating abdominal trauma, and peritonitis.

Pelvic bone imaging is indicated in children with hemodynamic instability, decreased levels of consciousness, pelvic bone tenderness or instability, hematuria or significant distracting injuries (e.g. femur fracture).[36] If abdominal CT scan is already planned, plain pelvic radiographs are unnecessary, as the sensitivity of plain pelvic radiographs is less than 80%[37] with no additional information to CT. A CT should be considered for children with a strong suspicion for pelvic fracture (severe pain, inability to walk) but normal plain pelvic radiographs.

Splenic injury. The spleen is the most commonly injured abdominal organ. Findings include left upper quadrant abdominal pain that may radiate to the left shoulder. The presence of costal margin tenderness increases the risk of splenic injury, although isolated costal margin tenderness is very low and further evaluation is usually unnecessary.[38] Splenic injuries are best identified and characterized by abdominal CT scans.

Most splenic injuries are managed with simple observation, but surgical consultation should be obtained.[34,35] Almost all patients with splenic injury are admitted, but those with minor (Grade I or II injuries) managed on the ward.[39] Patients with more severe injuries are typically observed in the intensive care unit.[39] Delayed splenic hemorrhage occurs in a small subset of patients, and includes rupture of subcapsular hematomas. To maintain immunocompetency, every effort is made to avoid splenectomy and salvage the spleen.

Hepatic injury. The liver is the second most commonly injured abdominal organ. Abdominal tenderness especially in the right upper quadrant suggests injury. Similar to the left costal margin, tenderness to the right costal margin is associated with hepatic injury, but when present in isolation does not warrant CT imaging.[38] Patients with low-grade injuries are managed on the ward, while high grade injuries are typically admitted to the intensive care unit.[39] Following hepatic injuries, AST levels are usually greater than ALT levels. However, since AST degrades faster than ALT, AST will often be lower than ALT in hepatic injuries greater than 12 hours old.

Renal injury. Due to unique anatomic differences, the pediatric kidney is more susceptible to injury: potential remnant fetal lobules; increased organ mobility with rapid deceleration mechanisms; and lack of protective abdominal musculature. Because of its retroperitoneal location, signs and symptoms of kidney injury are often less obvious and more diffuse than those of other abdominal organ injuries. Flank pain and posterior costal margin tenderness increase risk of injury. Fortunately, patients are readily screened for renal injury by urinalysis. Those without hematuria are unlikely to have significant urinary system injury. Gross hematuria requires abdominal CT scanning as the risk of intra-abdominal injury is approximately 50%. The degree of microscopic hematuria warranting imaging, however, is controversial, as investigators have suggested cutoffs ranging from 5 to 100 RBC/hpf. We recommend ED providers consider hematuria in context with other findings, as isolated asymptomatic microscopic hematuria is unlikely to yield an important injury on CT. For most patients, initial CT scan of the abdomen to assess for genitourinary injury is indicated when there is gross hematuria, microscopic hematuria with additional risk variables (e.g., abdominal pain or evident pelvic trauma), and penetrating injury to the abdomen (with or without hematuria).

Gastrointestinal injury. Approximately 15% of children with intra-abdominal injuries will have gastrointestinal injuries. These injuries range from simple serosal tears or intestinal wall hematomas that often do not require specific intervention, to intestinal perforation and bowel devascularization which require prompt surgical therapy. Fortunately, alert children with severe gastrointestinal injuries have significant abdominal examination findings. Historically, CT had insufficient sensitivity to identify children with gastrointestinal injuries. With improvement in CT technology, abdominal CT now demonstrates abnormalities in approximately 95% of children with gastrointestinal injuries. Abdominal CT findings suggestive of gastrointestinal injuries include intraperitoneal air, bowel wall thickening, bowel wall enhancement, mesenteric infiltration, and vascular contrast extravasation. With improved CT technology, isolated intraperitoneal fluid, once thought to be an ominous sign, is now known to be a common finding in children without diagnosed intra-abdominal injury. Asymptomatic children with normal abdominal examinations and small amounts of isolated intraperitoneal fluid may be observed and ultimately discharged from the ED with appropriate return precautions.

Pancreatic injury. Fortunately, pancreatic injury is rare, occurring in 5% of children with intra-abdominal injuries, but less than 1% of children undergoing abdominal CT scanning. Despite improvements in CT technology, this injury remains difficult to diagnose, as CT has a sensitivity of only 50% for pancreatic injury and fails to correctly grade the injury. Lipase and amylase are poor initial screening labs but increase 24 to 48 hours after pancreatic injury. Most injuries are managed non-operatively, but significant morbidity can occur in those with severe pancreatic trauma.

Penetrating injury. Penetrating wounds to the abdomen usually require rapid evaluation by a surgeon and consideration for operative intervention. Gunshot wounds generally result in more damage and higher mortality than stab wounds. With hemodynamic instability or peritonitis, urgent laparotomy is indicated. Depending on clinical findings, management options for the hemodynamically stable patient include further evaluation with abdominal CT scan; local wound exploration to determine violation of the peritoneum; diagnostic laparoscopy; and observation. In modern practice, diagnostic peritoneal lavage has been supplanted by other diagnostic modalities, including CT and diagnostic laparoscopy.

Straddle injuries. Straddle injuries occur when the child falls, striking their genitals and perineum on a hard object, most commonly bicycles and playground equipment. Injuries are typically localized to the genitalia and perineum, and physical examination is usually

sufficient to identify the extent of injury. Pain and anxiety, however, may limit the ability to adequately examine the area, often requiring sedation. Child abuse should be ruled out, especially if the injury is unlikely from blunt trauma (e.g., rectal or posterior fourchette tears). We recommend observing children with straddle injuries to confirm the ability to void and assess for hematuria. Scrotal ultrasound is recommended for significant scrotal edema or tenderness. Children who should receive referral for definitive care include those with extensive lacerations, vaginal bleeding, large hymenal tears, scrotal laceration through the dartos layer, or evidence of urethral injury.

Pelvic fractures. While pelvic fractures are less common in children than adults, pelvic avulsion fractures are significantly more common in children, especially as related to sports. More severe pelvic fractures are the result of high energy mechanisms, and frequently associated with other injuries. Genitourinary injuries are found in 10% of children with pelvic fractures. Orthopedic consultation is recommended to determine further treatment.

MUSCULOSKELETAL INJURIES

Musculoskeletal injuries are a common ED complaint for children. Pediatric injury patterns differ substantially from those of adults, as children have strong ligaments and growing, less dense bones covered in a thicker periosteum. The Salter-Harris fracture classification characterizes fracture patterns unique in children. In cases where the skin is disrupted at the site of the fracture, the fracture is considered open; the wound should be irrigated and IV antibiotics covering gram-positive skin flora administered. Antibiotics with gram-negative coverage are added in those with more complicated fractures. Fractures with vascular deficits require emergent reduction and splinting, but those with normal neurovascular examinations should be splinted until definitive care. A detailed discussion of these types of injuries is found in Chapter 170.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 160: QUESTIONS AND ANSWERS

1. A 5-year-old male is struck by a car while riding a bicycle with no helmet, presents with heart rate of 92 beats/min, blood pressure 60/30 mm Hg, cervical spine immobilized with a collar, and quadriplegia. The patient has no evidence of hemorrhage on examination or diagnostic testing. You suspect neurogenic shock and attempt to correct the hypotension with fluids but are not successful. Which of the following should be your first choice for a vasopressor?
   a. Dobutamine
   b. Dopamine
   c. Epinephrine
   d. Norepinephrine

Answer: d. Patients with neurogenic shock lose their sympathetic tone, manifested as the triad of hypotension, bradycardia and peripheral vasodilation. Treatment includes fluid administration, parasympathetic receptor blocking agents (e.g., atropine), and vasopressors with chronotropic, vasoactive, and inotropic characteristics (e.g., norepinephrine).

2. A 6-month-old infant is brought to your emergency department (ED) by his mother after he reportedly fell 3 feet from his changing table approximately 45 minutes ago. His mother reports that the child did not lose consciousness but is fussy and has a large scalp hematoma on the right side of head. On exam, the Glasgow Coma Scale (GCS) is 14 (spontaneous eye and motor, irritable cries). The patient has a right sided 4 cm scalp hematoma in the temporal area but otherwise the examination is normal. What is your most important intervention at this point?
   a. Consulting a social worker to help screen for child abuse
   b. Cranial computed tomography (CT) scan
   c. Ice packs for the scalp hematoma
   d. Observation in the ED for 4 hours
   e. Skull radiographs

Answer: b. A 6-month-old infant with a GCS 14 has a 4% risk of clinically important traumatic brain injury (TBI) by the Pediatric Emergency Care Applied Research Network rules. Additionally, the temporal scalp hematoma is associated with a 1.6% risk of clinically important TBI while a severe mechanism of injury carries a 0.5% risk of clinically important TBI. Solely on the GCS 14 score, the infant needs a non-contrast cranial CT to rule out TBI. If the infant had a GCS 15, and was acting normally, based on the severe mechanism alone, shared decision-making with the parents to observe the infant in the ED is a reasonable alternative to an immediate cranial CT scan.

3. Which of the following is the most commonly injured solid organ in pediatric patients with abdominal trauma?
   a. Bladder
   b. Duodenum
   c. Kidney
   d. Liver
   e. Spleen

Answer: e. Injuries to the spleen are the most common injuries in pediatric abdominal trauma. Children involved in motor vehicle collisions (MVCs), sudden deceleration injuries, and contact sports–related injuries may sustain splenic trauma. Clinical exam findings include left upper quadrant abdominal pain that may radiate to the left shoulder. Splenic injuries are best identified and characterized by abdominal computed tomography (CT) scans. Treatment includes fluid resuscitation and blood transfusion as needed. Splenic salvage is important for immunocompetence in children and operative intervention is avoided as long as the patient can be stabilized with fluid resuscitation.

4. A 4-year-old female is brought to your emergency department (ED) from the scene of a motor vehicle collision. Paramedics intubated the child in the field because she was unresponsive at the scene. On arrival, her vital signs are within normal limits. Before transport to the computed tomography (CT) scanner, however, you note that she is becoming mildly bradycardic and hypertensive. Her left pupil becomes dilated and nonreactive. You elevate the head of bed 30 degrees and maintain $ETCO_2$ at 35 mm Hg with controlled ventilation. Which of the following should be your next immediate action?
   a. Mannitol or 3% hypertonic saline IV
   b. Nicardipine infusion
   c. Phenytoin administration
   d. Proceed immediately to the CT scanner

Answer: a. The sudden onset of a dilated, nonreactive pupil, along with bradycardia and hypertension, is indicative of acute brain herniation from raised intracranial pressure. Controlled ventilation to keep $ETCO_2$ greater than 30 mm Hg, a hyperosmolar agent, such as mannitol or hypertonic saline given intravenously, and raising the head of the bed 30 degrees are recommended strategies. Phenytoin can be considered for seizure prophylaxis in this patient, but not before the other measures are instituted. Nicardipine and other antihypertensive agents have no place in the management of a head-injured child. Hypertension is a physiologic response to brain herniation, where increasing the mean arterial pressure (MAP) preserves cerebral perfusion pressure (CPP).

5. A 7-year-old girl is brought into the emergency department (ED) by emergency medical service (EMS) personnel from the scene of a motor vehicle collision (MVC). On your primary survey, she is noted to have a patent airway, decreased breath sounds in the right lung field, and subcutaneous emphysema. She has hypotension and weak distal pulses. What is your next step in stabilizing this patient?
   a. Airway control with endotracheal intubation (ETI)
   b. Bag-mask ventilation (BMV)
   c. Immediate needle thoracostomy in the second midclavicular space on the right
   d. Portable chest radiograph to confirm diagnosis

Answer: c. This patient is presenting with signs of tension pneumothorax. In this case, immediate decompression with a needle thoracostomy, followed by the placement of an appropriately sized chest tube or immediate chest tube placement is required to avoid cardiovascular collapse. A portable chest radiograph should be performed to confirm chest tube placement.

6. Which of the following statements regarding chest injuries in children is correct?
   a. Aortic transection is more likely in a pediatric patient than in an adult patient.
   b. Multiple rib fractures without significant underlying lung injury are common in children.
   c. Penetrating chest trauma is more common than blunt chest trauma in pediatric patients.
   d. Significant pulmonary contusions may be present in the absence of rib fractures in children.

Answer: d. The pediatric rib cage has more compliance than an adult rib cage. Thus children are predisposed to pulmonary injury in the absence of rib fractures. Blunt chest trauma is more common than penetrating chest trauma in pediatric patients and concurrent chest and abdominal injuries are common. Aortic transection is more common in adults.

CHAPTER 160: QUESTIONS AND ANSWERS—cont'd.

7. A 12-year-old male fell while climbing over a 12-foot barbed-wire fence and sustained a deep 10-cm laceration to his medial left thigh. Parents bring him to the ED directly from the scene. There is active oozing from the laceration. What is the first step in the management of this patient?

a. Apply a tourniquet to the leg.
b. Begin with a primary survey and assess the patient's airway and breathing.
c. Obtain intravenous (IV) access and begin blood transfusion immediately.
d. Pack the wound to decrease hemorrhage.

Answer: b. The primary survey should quickly assess the airway, breathing, and circulation (ABCs). Approaching trauma patients in a systemic fashion will ensure that large, obvious injuries do not distract from the detection of other injuries. Oftentimes multiple interventions would be done simultaneously. Jaw thrust to open an airway and then another health care providers quickly applying pressure on the wound for hemorrhage control. The child in the question fell from a fence and may have other fall-related injuries that should be identified during the secondary survey.

8. Which of the following statements regarding imaging of a multitrauma pediatric patient is correct?

a. A negative computed tomography (CT) scan of the cervical spine rules out spinal cord injury, and if normal, immobilization can be discontinued.
b. A negative focused assessment with sonography in trauma (FAST) examination rules out traumatic intra-abdominal injury, making a CT scan unnecessary.
c. In a hemodynamically stable pediatric trauma patient, CT imaging should be completed before transfer to a pediatric trauma facility, even if it delays transfer.
d. In a hemodynamically stable pediatric patient with a high level of concern for intra-abdominal trauma, CT scan is the imaging test of choice.

Answer: d. CT scan is the diagnostic test of choice for evaluation of intra-abdominal trauma in children. Spinal cord injury without radiologic abnormality (SCIWORA) is more common in pediatric patients, and a normal cervical spine CT scan does not rule out ligamentous injuries or spinal cord edema. Although often a useful adjunct, a FAST examination does not rule out intra-abdominal injury. In a hemodynamically stable patient, CT imaging does not need to be completed before transfer to a pediatric trauma center and definitely should not delay transfer.

Pediatric Fever

Nathan W. Mick

KEY CONCEPTS

- Fever is the most common complaint among pediatric patients presenting to the emergency department (ED). Although rates of bacterial illness are lower since the advent of universal vaccination for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, serious bacterial infection (SBI) should be considered in the under-vaccinated or unvaccinated child.
- Viruses cause the vast majority of childhood febrile illnesses and are generally self-limited and benign.
- SBI is the growth of pathogenic bacteria in a previously sterile site, such as urinary tract infection (UTI), bacteremia, meningitis, osteomyelitis, bacterial gastroenteritis, bacterial pneumonia, cellulitis, or septic arthritis.
- The rate of SBI in infants younger than 3 months old with fever is between 6% and 10%.
- Infants 28 days old and younger are at much higher risk for bacterial illness with fever because of their immature immune systems and incomplete vaccination status.
- Empirical treatment of a febrile neonate is indicated, and appropriate antibiotic regimens include ampicillin plus either gentamicin or cefotaxime, which cover the bacterial organisms likely in this age group.
- Empiric treatment for herpes simplex virus (HSV) in neonates with a maternal history of genital herpes, ill appearance, fever and seizure, cutaneous vesicles on physical examination, transaminitis, or evidence of coagulopathy is recommended.
- The most common cause of SBI in children continues to be UTI. In infants who are not toilet-trained, bladder catheterization is the best method for collecting uncontaminated urine. However, for select patients, bagged urine may be obtained, and if results do not indicate infection, no further studies are needed. Suprapubic aspiration may be considered when a urine sample cannot otherwise be obtained.
- Bacterial meningitis can occur at any age, but most commonly presents in a relatively small proportion of febrile infants younger than 3 months old (3/1000).
- Respiratory syncytial virus (RSV) and influenza are common viral causes of fever and respiratory distress in infants, but the presence of viral infection does not lower the risk of concomitant SBI in children younger than 28 days old.
- In older infants and children, the documented presence of RSV or influenza significantly reduces the incidence of SBI and can be used to modify the evaluation. Because UTI is still common in this population, a urinalysis should be obtained.
- There are numerous risk-stratification strategies (e.g., Boston, Rochester, and Philadelphia criteria) reported in the literature that have similar performance characteristics. All involve a laboratory evaluation designed to identify a subset of febrile infants younger than 3 months old that can safely be managed as outpatients with or without antibiotics.
- Standardization and adoption of a clinical practice guideline for the evaluation of the febrile infant have been shown to reduce variation and cost.
- Due to universal vaccination against pneumococcus, the evaluation of highly febrile children 3 to 36 months old has evolved from one of universal screening for occult bacteremia to one where clinical assessment determines the need for bloodwork.
- Inflammatory markers, such as C-reactive protein (CRP) and procalcitonin, have been shown to predict bacterial illness in febrile children more accurately than the white blood cell (WBC) count but does not solely rule out SBI.
- Traumatic lumbar punctures occur relatively commonly in young infants and can make interpretation of cell counts difficult. The use of various formulas to account for the protein and WBCs in the cerebrospinal fluid (CSF) after a traumatic tap should be used with caution.
- As the risk of meningitis is exceedingly low, we do not recommend lumbar puncture in well-appearing children with a simple febrile seizure.
- Children presenting with fever and petechiae are at risk for infection with meningococcus; blood should include a complete blood count (CBC) and culture and, if available, CRP and procalcitonin (>0.5 ng/mL). Children with an abnormal CRP, WBC count (<5000/mm^3 or >15,000/mm^3), or bandemia should be treated with parenteral antibiotics and admitted. Lower risk, well-appearing children with normal laboratory parameters can be considered for close outpatient follow-up.
- Children with fever who also are receiving cytotoxic chemotherapy for cancer are at high risk for bacteremia and sepsis and should receive prompt broad-spectrum antibiotic therapy after appropriate diagnostic evaluation (at minimum, a CBC and blood culture).
- Patients with fever and a history of sickle cell disease are at risk for bacteremia from encapsulated organisms due to functional asplenia and should be considered high risk, admitted, and treated.

FOUNDATIONS

Background

Fever is the most common chief complaint of pediatric patients presenting to the emergency department (ED). Most cases of fever are viral in origin, benign in course, and resolve spontaneously. Management of children with fever varies by the age of the child, with the following common divisions: 0 to 28 days old, 1 to 2 months old, 2 to 3 months old, 3 to 6 months old, 6 to 36 months old, and 3 years old to adulthood. Understanding that risk is a continuum, these divisions reflect differing immunologic and vaccination milestones, as well as a spectrum of age-specific pathogens.

Anatomy, Physiology, and Pathophysiology

Fever is defined as any elevation in body temperature of 100.4°F (38.0°C) or above. The most reliable method to measure temperature is with a rectal thermometer and is the preferred method of measurement in high-risk groups, such as infants 0 to 3 months old. However, the rectal route should not be used in patients who are potentially immunocompromised (e.g., children receiving cytotoxic chemotherapy) because of the risk of mucosal damage leading to bacteremia. The cutoff for a clinically significant fever (i.e., one that may trigger a laboratory evaluation) varies with the age and immunologic status of the child. A rectal temperature of 100.4°F (38.0°C) is considered a clinically significant fever in an infant younger than 3 months, often warranting laboratory evaluation; however, a toddler with a temperature of 103.1°F (39.5°C) and an upper respiratory infection may not need any evaluation beyond a thorough history and physical examination.

Causes of fever vary with the age of the child (Table 161.1). The majority of pediatric fever is due to infections, and most infections are attributable to a viral source. (See Chapter 120 for a discussion of COVID-19 in children) Upper respiratory infections, viral gastroenteritis, croup, bronchiolitis, stomatitis, roseola, infectious mononucleosis, and varicella are all known causes of fever. Most viral illnesses are benign and self-limited, but infection with measles, herpes simplex virus (HSV), or respiratory syncytial virus (RSV) can lead to significant morbidity and mortality, particularly in the first month of life.

Bacterial disease is also an important cause of fever in children. Serious bacterial infection (SBI) is defined as the presence of pathogenic bacteria in a previously sterile site and includes urinary tract infection (UTI), bacteremia, meningitis, osteomyelitis, bacterial gastroenteritis, bacterial pneumonia, cellulitis, and septic arthritis. The risk of SBI in febrile infants younger than 3 months old with a temperature of at least 100.4°F (38.0°C) is between 6% and 10%; children younger than 28 days old have the highest incidence.[1] Hyperpyrexia (rectal temperature ≥40.0°C) is associated with a higher risk of SBI.[2] Pathogens change during early infancy, with vertical transmission of organisms such as group B streptococcus, *Listeria monocytogenes,* and HSV more common in neonates. By 1 to 2 months of age, organisms such as *Streptococcus pneumoniae, Neisseria meningitidis,* and urinary pathogens *(Escherichia coli* or *Enterococcus)* become more common. In all children younger than 3 months old, the urinary tract is the most common site of infection, followed by bacteremia and meningitis.

Children younger than 3 months old may present with an apparent viral syndrome and still harbor SBI. Levine and colleagues studied 1248 infants younger than 60 days old who had temperatures above 100.4°F (38.0°C). Of these children, 22% were positive for RSV. Overall, children with documented RSV had a lower incidence of concomitant SBI than those without RSV (12.5% vs. 7%), but there was no significant difference in rates of SBI in those younger than 28 days old (14.2% in RSV-negative vs. 10.1% in RSV-positive). Most of the bacterial infections were UTIs. Older children 3 to 36 months old with recognizable viral syndromes (e.g., croup, bronchiolitis, varicella, stomatitis) have a very low incidence of bacteremia; in over 1300 patients with a temperature above 102.2°F (39.0°C) who had a recognizable viral syndrome, the risk of bacteremia was 0.2%.

Occult bacteremia describes the presence of pathogenic bacteria in the bloodstream of a well-appearing febrile child in the absence of a focus of infection; it was first described as a clinical entity in the 1970s. The term typically refers to children 3 to 36 months old who are highly febrile (>102.2°F [39.0°C]) but appear well. Before the adoption of the conjugate vaccines against *Haemophilus influenzae* type b and *S. pneumoniae,* the incidence of bacteremia in this population was approximately 5%. Vaccination has proved remarkably effective, nearly eradicating *H. influenzae* type b as a significant pathogen and greatly reducing the burden of pneumococcal disease (Fig. 161.1).[3,4] Currently, the rate of occult bacteremia is less than 1%, with pathogens such as *N. meningitidis* becoming proportionally more prevalent. Urinary pathogens, occurring in 5% of febrile children younger than 2 years old, continue to be a common source of bacterial illness in infants and children. Risk factors include female sex, absence of another apparent source of infection, fever higher than 102.2°F (39.0°C), white race, and for boys, uncircumcised status.

Bacterial illness in school-age children and adolescents includes focal infections, such as streptococcal pharyngitis, cellulitis, and pneumonia, as well as bacteremia and meningitis. *N. meningitidis* has a bimodal distribution, with the highest incidence in children younger than 12 months old (9.2/100,000 population). A second peak occurs

TABLE 161.1 Etiology of Fever in Children

Age	Bacterial Causes	Viral Causes	Other
0–8 days old	Group B streptococcus	HSV	Bundling (skin temperature only)[a]
	Listeria monocytogenes	Varicella	Environmental
	Escherichia coli	Enteroviruses	
	Chlamydia trachomatis	RSV	
	Neisseria gonorrhoeae	Influenza	
1–3 months old	*Haemophilus influenzae*	Varicella	
	Streptococcus pneumoniae	Enteroviruses	Environmental
	Neisseria meningitidis	RSV	
	E. coli	Influenza	
3–36 months old	*S. pneumoniae*	Varicella	Leukemia
	N. meningitidis	Enteroviruses	Lymphoma
	E. coli	RSV	Neuroblastoma
		Influenza	Wilms' tumor
		Mononucleosis	
		Roseola	
		Adenovirus	
		Norwalk virus	
		Coxsackievirus	
3 years old to adulthood	*S. pneumoniae*	Varicella	Leukemia
	N. meningitidis	Enteroviruses	Lymphoma
	E. coli	RSV	Neuroblastoma
	Group A streptococcus	Influenza	Wilms' tumor
		Mononucleosis	Juvenile rheumatoid arthritis
		Roseola	
		Adenovirus	
		Norwalk virus	

[a]Bundling may raise skin temperature but does not change rectal temperature. Irrespective of how measured, a fever in this high-risk population should not be attributed to bundling alone.
HSV, Herpes simplex virus; *RSV,* respiratory syncytial virus.

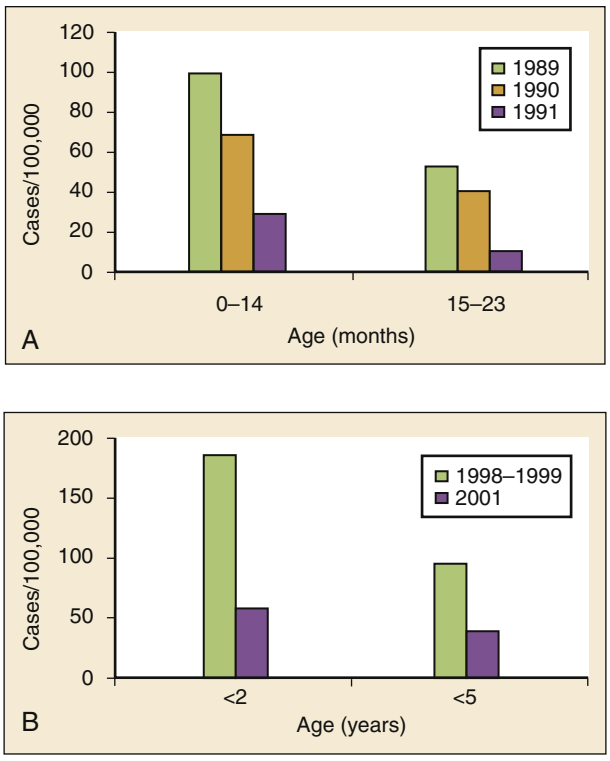

Fig. 161.1 Decline in incidence of occult bacteremia after the introduction of the conjugate vaccine against *Haemophilus influenzae* (A) and *Streptococcus pneumoniae* (B).

during adolescence, when the rate of illness is 1.2/100,000 population, with a significant proportion of cases occurring in college students who reside in a dormitory setting (3.2/100,000 population).

Although it is much less common than in viral or bacterial infection, fever can also be a presenting sign of autoimmune diseases, such as juvenile rheumatoid arthritis or Kawasaki disease. Central nervous system (CNS) lesions such as brain tumors also can infrequently manifest with fever.

The body's ability to fight infection varies with age. Maternal antibodies confer some protection after birth, but the infant's immune system is initially inadequate, particularly T-cell function and the ability to mount an immunoglobulin G response to infection. Their immature immune system and exposure to certain pathogens during the birthing process (e.g., group B streptococcus, *Chlamydia trachomatis, Neisseria gonorrhoeae*) places the newborn at particularly high risk for SBI. Young infants are also at risk for disseminated infection because they are unable to mount the immune response needed to prevent bacterial spread. Thus, a simple cellulitis, mastitis, omphalitis, or, rarely, gonococcal eye disease, can lead to sepsis or seeding of the CNS. Immune function improves during the first 2 to 3 months of life, as does the ability to assess a child clinically. Infants begin the primary series of vaccinations against acquired infections, such as *S. pneumoniae* and *H. influenzae,* at 2 months of age, providing further protection against common bacterial pathogens. As a result, empirical testing and treatment give way to more selective evaluations above 2 to 3 months old.

Clinical Features

History taking should focus on the length of illness, localizing symptoms (e.g., headache and neck pain [meningitis or encephalitis] or ear pain [otitis media]), exposure to ill contacts, travel history, and pertinent past medical history. For infants younger than 28 days old, document birth history, including gestational age and the presence of potentially transmittable maternal infections (HSV or group B streptococcus). Document immunization status, sick contacts, use of antipyretics before evaluation, and prior use of antibiotics. Defervescence after acetaminophen administration has not been shown to reliably exclude bacteremia in children of any age. Prior antibiotic use may mask the classic findings in diseases, such as meningitis. Cough and congestion may suggest pneumonia or viral upper respiratory infection, whereas a harsh, barking, or seal-like cough is often a predominant complaint in viral laryngotracheitis (croup). Parents may report vomiting and diarrhea as a component of gastroenteritis, or the presence of sore throat and lymphadenopathy with viral or streptococcal pharyngitis. Decreased oral intake or decreased urine output is a frequent complaint in gastroenteritis but may also be seen in patients with stomatitis because painful oral aphthous ulcerations prevent fluid intake. A history of lethargy, irritability, or altered mental status can occur with severe dehydration but should raise concern for meningitis or encephalitis. A rash occurs in many viral illnesses (e.g., roseola) but may be seen in life-threatening conditions, such as meningococcemia, Rocky Mountain spotted fever, and toxic shock syndrome (TSS).

The physical examination of the febrile child should begin with a complete set of vital signs, including pulse oximetry. Hypoxia or significant respiratory distress (e.g., tachypnea, grunting respirations, nasal flaring, or retractions) may accompany sepsis or pulmonary infection. Stridor can be seen with croup but also can occur with retropharyngeal abscess, epiglottitis, or bacterial tracheitis. Signs of shock, such as hypotension and poor peripheral perfusion, should be noted. Children typically mount a tachycardic response to fever, and hypotension is often a late and dire finding. Tachycardia is often due to the fever itself, but tachycardia out of proportion to the degree of fever can be seen with early shock, myopericarditis, and dehydration. Estimations of heart rate increase based on fever in infants younger than 12 months old (i.e., heart rate increases linearly by 9.6 beats/min with each 1°C increase in body temperature) should be used with caution and clinical signs of sepsis evaluated before attributing tachycardia to fever alone. Once oxygenation, ventilation, and perfusion have been assessed and deemed adequate, the physical examination should focus on a thorough search for focal infection. In young infants, particularly those younger than 3 months old, and in children who lack immunocompetence, fever may be the only presenting sign of SBI, including meningitis. The physical examination in this age group is insufficiently sensitive to exclude SBI, and emergency clinicians should not be falsely reassured by a normal physical examination in young children. Those who do appear toxic may have decreased tone, poor skin turgor, poor tracking, increased or decreased respiratory effort, a weak cry or suck, or delayed capillary refill times. The neonate who refuses to feed should have a full SBI evaluation, irrespective of temperature. See Chapter 155.

Diagnostic Testing

Numerous laboratory and radiographic studies can be used to evaluate the febrile child. In general, testing should be directed at the identification of the source and complications of infection. Several guidelines exist for the evaluation of febrile children, although there is marked variation in adherence to these guidelines. Office-based practitioners have been found to follow published guidelines only 42% of the time in the evaluation of febrile children. Clinicians with less experience and those based in the hospital tend to order more tests compared with more experienced clinicians and those practicing in an office setting, respectively. The use of institutional clinical decision rules and guidelines can help streamline appropriate testing.[5,6]

White Blood Cell Count

An elevated white blood cell (WBC) count (>15,000/mm^3) can be an indicator of bacteremia but is also present in many viral illnesses. Leukopenia (<5000/mm^3) can also be a sign of SBI or early sepsis. Pneumococcal infection is classically associated with leukocytosis, whereas infection with *N. meningitidis* and *H. influenzae* may be present even with normal WBC counts. In children with fever greater than 102.2°F (39.0°C), Lee and colleagues found that the rate of pneumococcal bacteremia increased from 0.5% with a WBC count between 10,000 and 15,000/mm^3 to 3.5% if the WBC count was 15,000 to 20,000/mm^3 and up to 18% with a WBC count above 30,000/mm^3. More extreme leukocytosis is associated with an increased risk of bacterial infection, particularly lobar pneumonia, and a WBC count of above 25,000/mm^3 should prompt consideration of a chest radiograph unless another definitive source is apparent.[7]

The WBC differential diagnosis has also been used to risk-stratify febrile children in various models; an increase in polymorphonuclear leukocytes increases the risk of bacterial disease. A rise in polymorphonuclear leukocytes is also seen early in some viral infections. An absolute neutrophil count (ANC) above 10,000/mm^3 suggests an increased risk of pneumococcal bacteremia in febrile children (0.8% for children with an ANC below 10,000/mm^3 vs. 8% for children with an ANC above 10,000/mm^3). Routine screening of all febrile children greater than 3 months of age with bloodwork has not been shown to be cost-effective in the post-vaccination era. The vast majority of acute febrile illness is due to self-limited viral infection. If the decision is made on clinical grounds to obtain a WBC and if it is abnormal (<5000/mm^3 or >15,000/mm^3) or the ANC is greater than 10,000/mm^3, then we recommend screening for occult bacteremia with a blood culture, understanding that leukocytosis is neither perfectly sensitive nor specific for bacterial illness. We also recommend treatment with ceftriaxone for incompletely immunized children who have a WBC of more than 15,000/mm^3.

Inflammatory Markers

Both C-reactive protein (CRP) and procalcitonin have been studied as markers of bacterial infection. The utility of the measurement of inflammatory markers is dependent on the cutoff level assigned for clinical significance with lower values having higher sensitivity but lower specificities. Procalcitonin greater than 0.5 ng/mL is highly specific for SBI, though some clinicians use a lower cutoff (>0.2 ng/mL) to increase sensitivity. Both CRP and procalcitonin appear to be more sensitive and specific than the WBC alone, although the lack of widespread availability limits the usefulness of procalcitonin clinically at this time.[8,9]

Blood Culture

Many centers obtain blood for culture during intravenous (IV) catheter placement after sterile preparation of the skin has been performed. Although this eliminates a second venipuncture solely to obtain blood for culture, in children, the rates of contamination with this technique are higher than a sterile straight stick (9.1% vs. 2.8%). The risks of contamination should be weighed against the ability to obtain blood through a separate venipuncture. The yield of a single blood culture in infants and small children is actually good. The routine sending of more than one sample is generally not needed, and bacteremia is often accurately detected even if only 0.5 to 1 mL of blood is obtained. The advent of automated blood culture systems has led to the identification of true pathogens more quickly than by traditional methods, often within 24 hours. Pathogens isolated in the first 24 hours are more likely to be true pathogens than are bacteria isolated after 24 hours.[10]

Urinalysis and Urine Culture

UTIs are common causes of bacterial illness in febrile children, occurring in 5% of infants 2 to 24 months old with fever 100.4°F (38.0°C) or higher. Accurate documentation of UTI is imperative both to diagnose the cause of a fever and to identify those infants who need follow-up radiographic imaging to exclude anatomic abnormalities that will predispose them to further infection. It is currently recommended that febrile infants with documented UTIs undergo renal ultrasonography to evaluate for urinary tract anomalies. For infants with signs of urosepsis or not improving within 24 hours of antibiotic administration, an ultrasound should be performed to evaluate for obstructive uropathy or rare complications, such as renal or perirenal abscesses. Voiding cystourethrography is not indicated after the first febrile UTI in children unless renal ultrasonography reveals evidence of high-grade vesicoureteral reflux or scarring.

The only reliable method to obtain urine in a non-toilet-trained child is bladder catheterization or suprapubic aspiration. Bladder catheterization is the preferred method in *almost all* cases. Bag collection of urine is notoriously unreliable; up to 85% of cultures from bag specimens will be falsely positive (defined as a culture growing a single organism with >10^5 colony-forming units [CFUs]/mL or a mix of two or more organisms), which then places these children at risk for unneeded, potentially painful, and expensive follow-up diagnostic testing and antibiotics. However, for select patients, bagged urine may be obtained, and if results do not indicate infection, no further studies are needed.[11] A clean catch urine specimen is appropriate for toilet-trained children.

UTI is defined as the combination of bacteriuria and pyuria. Bacteriuria in the absence of WBCs on microscopic examination represents asymptomatic bacteriuria. Urine is typically analyzed with a dipstick, followed by microscopic analysis of a centrifuged specimen of urine. An "enhanced" urinalysis, which is an examination with a hemocytometer of an unspun specimen of urine for pyuria (defined as >10 WBCs per high-power field) or the presence of any bacteria per high-power field in Gram stain of unspun urine has a negative predictive value of 99.8%, perhaps making urine culture unneeded if pyuria and bacteriuria are absent by use of the enhanced urinalysis method. However, many centers are not using this enhanced method. Because dipstick and microscopic analysis have lower sensitivities, most experts recommend sending urine for culture in high-risk groups (febrile girls <24 months old, uncircumcised boys <12 months old, and circumcised boys <6 months old).

A positive urine culture is defined as the growth of more than 50,000 CFU/mL of a single uropathogen in urine obtained via catheterization or suprapubic aspirate.

Lumbar Puncture

A sample of cerebrospinal fluid (CSF) should be obtained from any child with signs and symptoms of meningitis. Fluid should be obtained with the smallest spinal needle possible (typically a 22-gauge) and sent for cell counts, manual differential diagnosis, Gram staining, culture, and measurement of CSF protein and glucose concentrations. Meningoencephalitis due to HSV is a potential cause of fever, particularly in neonates; if suspected, CSF should be sent for HSV polymerase chain reaction (PCR) testing. Panel-based nucleic amplification tests that detect a wide array of viral and bacterial pathogens can also be useful but should be coupled with traditional CSF cultures as they do not identify every possible pathogen and do not give information on antibiotic susceptibility.[12,13] The CSF in bacterial meningitis typically contains more than 1000 WBCs/mL, although there is considerable overlap in the CSF profile of bacterial and viral meningitis, making a determination of viral or aseptic meningitis difficult on the basis of

CSF parameters, such as cell count, protein, and glucose; thus, CSF culture of a pathogenic bacterium is the "gold standard." A prediction rule has been developed and validated to differentiate bacterial from aseptic meningitis in children 29 days to 19 years old who have CSF pleocytosis. Children *without* any of the following criteria have a low risk (0.1%) of bacterial meningitis: positive CSF Gram stain, CSF ANC of 1000 cells/mL or more, CSF protein concentration of at least 80 mg/dL, peripheral blood ANC of 10,000 cells/mL or more, and history of seizure before or at the time of presentation. This may obviate the need for empirical antibiotic therapy and hospital admission in some children who are at low risk for bacterial meningitis.[14]

Contraindications to lumbar puncture include cellulitis over the proposed site of puncture, cardiopulmonary instability, bleeding diathesis, or platelet count below 50,000/μL, focal neurologic deficits, and signs of increased intracranial pressure, including papilledema. In these patients, lumbar puncture should be deferred until the child is stable, and blood should be obtained for culture while the child is treated empirically, recognizing that up to 50% of children with meningitis will not have bacteremia.

CSF contaminated by blood (i.e., a traumatic lumbar puncture) can make interpretation of cell counts and differential diagnoses difficult. In these cases, fluid should be obtained for Gram stain and culture and the child hospitalized and treated presumptively for meningitis until culture data are available.

Stool Studies

Stool studies are indicated in patients in whom bacterial gastroenteritis may be a cause of fever. A stool guaiac test for blood, as well as Gram stain for WBCs, should be performed. The presence of more than five WBCs per high-power field in the stool of a febrile child should trigger a culture of stool for *Salmonella, Shigella, Campylobacter,* enterotoxigenic *E. coli,* and *Yersinia* species. Patients with sickle cell disease are at particular risk for focal complications, such as osteomyelitis from *Salmonella* infection (see Chapter 167).

Chest Radiography

Chest radiographs may be useful in the evaluation of the febrile child and are indicated when hypoxemia, respiratory distress, tachypnea, or focal findings on lung examination are present. Children younger than 6 months old may present with tachypnea as the sole finding of bacterial pneumonia. Occult pneumonia can also occur in a small percentage of children, particularly in the highly febrile child (>102.2°F [39.0°C]) without an apparent source of fever and an elevated ANC. Studies done prior to universal vaccination against pneumococcus demonstrated a relatively high rate of pneumonia in highly febrile children who had leukocytosis more than 20,000/mm^3 (26%). Since the advent of universal vaccination, the number of occult pneumonias has declined (15% to 9%) but is not yet low enough to recommend not obtaining radiographs on highly febrile children with leukocytosis or elevated ANC and no other apparent source of infection. Point of care lung ultrasound has been shown to compare favorably to chest radiographs in multiple studies when used for the diagnosis of pneumonia.[15]

Rapid Viral Antigen Testing

Many clinical laboratories have the ability to perform rapid viral antigen testing, either individually or as part of a panel for such common pediatric viral illnesses as influenza A and B, parainfluenza, rhinovirus, and RSV. The presence of a viral "source" for the fever in an ill child may obviate the need for expensive, painful, and lengthy diagnostic evaluations for bacterial processes. Of patients aged 2 months to 21 years old who present with classic signs and symptoms of influenza, more than half have been shown to have positive rapid assays for influenza, leading to fewer antibiotics prescribed. A large multicenter trial of febrile infants 60 days old or younger revealed a decreased risk for SBI (2.5% vs. 11.7%) if the infant was influenza positive.

RSV is also a frequent cause of fever in children. As previously noted, RSV decreases but does not completely eliminate the risk of SBI in children. This is especially true of UTI in infants younger than 28 days old. Routine testing for RSV has not been shown to affect outcomes at the individual patient level.[16] Given the exceedingly low rates of bacteremia and meningitis, it is reasonable to consider a selective, de-escalated evaluation (i.e., urine and urine culture only) of well-appearing infants who have positive viral testing in the ED. Ill-appearing infants or neonates (28 days old and younger) should still undergo a full evaluation for SBI.

Management

Approach to the Febrile Infant and Child

The initial approach to any child with a febrile illness is a rapid assessment for evidence of cardiopulmonary compromise or shock. Significant respiratory distress, hypoxemia unresponsive to supplemental oxygen, or altered mental status may necessitate intubation by rapid sequence induction and mechanical ventilation. Evidence of shock (poor perfusion, hypotension, altered mentation) should be quickly treated with fluid resuscitation. An IV or intraosseous line should be placed, and the initial resuscitative fluid should be 20 mL/kg of isotonic crystalloid. This should be repeated to a total of 60 mL/kg over 60 minutes if signs of hypovolemia persist, followed by vasopressor therapy (dopamine 1 to 20 μg/kg/min or norepinephrine 0.05 to 2 μg/kg/min titrated to blood pressure) to maintain blood pressures.

Every effort should be made to obtain appropriate specimens for culture (blood and urine) before antibiotic administration, even in the critically ill child. Lumbar puncture may be deferred in the critically ill child until stabilization occurs. Empirical antibiotic therapy should be directed at the most likely causative organisms based on age. Sterilization of the CSF starts to occur once antibiotic administration has been initiated—within 15 minutes to 2 hours in patients with meningococcal meningitis and within 4 to 10 hours in patients with pneumococcal meningitis. However, antibiotics should not be delayed awaiting successful lumbar puncture. Antibiotics will not affect PCR or bacterial antigen test results.

Infants 0 to 28 Days Old

Children presenting with a temperature of 100.4°F (38.0°C) or higher who are younger than 28 days old are at particularly high risk for bacterial illness, with rates as high as 12%.[17] Often, fever is the only manifestation of potentially life-threatening disease, with other signs and symptoms that may be exceedingly subtle. This has led to a conservative approach to diagnostic testing, empirical antibiotic therapy, and hospitalization in this age group, even if the child appears well.

Children in this age group often present with nonspecific complaints, such as irritability, lethargy, poor feeding, and grunting. Besides fever, other signs of serious illness include a bulging fontanel, mottled extremities, petechiae, and tachypnea. Bacterial pathogens in this age group include *E. coli*, group B streptococcus, *L. monocytogenes, and less commonly, N. meningitidis, S. pneumoniae*. Viral pathogens, including RSV and HSV, are also important considerations. Neonatal HSV infection carries a high degree of morbidity and mortality and should be considered in any febrile neonate who appears ill, presents with fever and seizure, has cutaneous vesicles on physical examination, has evidence of transaminitis or coagulopathy, or has a maternal history of genital herpes. HSV meningoencephalitis should also be considered in patients with fever and CSF pleocytosis but a negative CSF Gram stain. The highest risk period for HSV disease is between 2 and 12 days old

(Fig. 161.2). Other noninfectious causes of a septic-appearing neonate include inborn errors of metabolism, the acute salt-wasting crisis associated with congenital adrenal hyperplasia, and undiagnosed ductal-dependent congenital heart disease.

Because of the high risk of bacterial pathogens and the difficulty in the clinical assessment of children younger than 28 days old (neonate), febrile neonates require a thorough diagnostic evaluation, including a complete septic evaluation. This consists of a complete blood count (CBC) with differential, blood culture, urinalysis and urine culture, and lumbar puncture. Lumbar puncture is indicated in this age group even in the presence of a UTI because of the risk of concomitant meningitis. All neonates should be admitted to the hospital with empirical antibiotics while awaiting culture results. Appropriate parenteral antibiotic regimens include ampicillin (50 to 100 mg/kg every 6 to 12 hours) plus either gentamicin (4 to 5 mg/kg every 24 to 48 hours) or cefepime (50 mg/kg every 8 to 12 hours). Ceftriaxone should be avoided in infants younger than 28 days old because ceftriaxone causes bilirubin to be displaced from its protein binding sites and has a theoretical risk of inducing acute bilirubin encephalopathy. Empirical acyclovir should be added if risk factors for HSV disease exist or a pleocytosis is found in the CSF (20 mg/kg every 8 hours if adequate renal function).

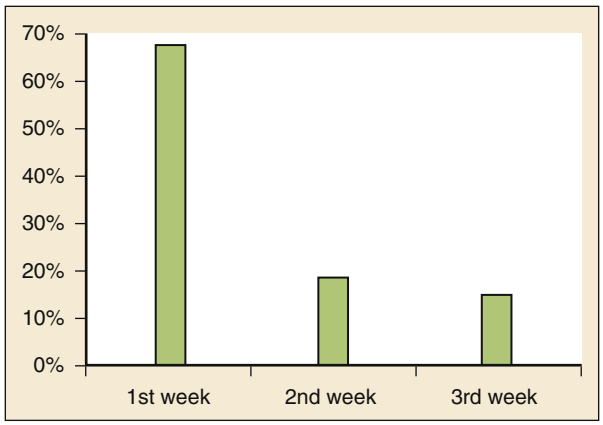

Fig. 161.2 Age at Presentation for Neonatal Herpes Simplex Virus (HSV) Infection.

Infants 29 to 90 Days Old

Although there is a relative consensus as to the evaluation and management of febrile infants younger than 28 days old, there is debate about the appropriate evaluation for slightly older febrile infants. Ill-appearing children of any age should have a complete sepsis evaluation performed and be admitted to the hospital with empirical antibiotic therapy. Appropriate antibiotic therapy for high-risk children includes coverage of neonatal pathogens, such as *L. monocytogenes* and group B streptococci, as well as coverage against *H. influenzae, N. meningitidis,* and *S. pneumoniae*. Ampicillin (50 to 100 mg/kg every 6 to 12 hours based on gestational age and renal function) plus ceftriaxone (50 mg/kg every 12 hours) are two reasonable options. Vancomycin, 10 to 20 mg/kg IV every 6 to 8 hours, should be considered if *S. pneumoniae* resistant to penicillins and cephalosporins is suspected.

Historically, various strategies (herein referred to as the *Rochester, Philadelphia, and Boston criteria*) for the evaluation of well-appearing children have been reported, compared, and retested in the literature. Each strategy has unique features, including the definition of fever (100.4°F [38.0°C] vs. 100.8°F [38.2°C]), the study population (0 to 3 months old, 1 to 2 months old, and 1 to 3 months old), the clinical and laboratory variables studied, and the disposition (hospitalization with or without antibiotics or outpatient treatment with or without antibiotics). Each strategy seeks to identify a set of low-risk criteria that, if met, identify patients that may forgo further testing or empirical antibiotic therapy. The three main strategies are highlighted in Table 161.2. Baraff synthesized the recommendations of the Rochester, Philadelphia, and Boston criteria into an algorithm for the management of the previously healthy febrile infant 29 to 90 days old (Fig. 161.3). To be low risk, the child had to have been previously healthy with an uncomplicated nursery stay, to be nontoxic clinically, and to have no focal source of bacterial infection. Low-risk laboratory criteria in this schema included a normal WBC count (between 5000 and 15,000 WBCs/mm^3), fewer than 1500 bands/mm^3, normal urinalysis (negative Gram stain and

TABLE 161.2 Summary of Major Strategies for the Management of Febrile Infants Younger Than 3 Months Old

	Philadelphia	Rochester	Boston
Age	29–60 days old	<60 days old	28–89 days old
Temperature	>100.8°F (38.2°C)	>100.4°F (38.0°C)	>100.4°F (38.0°C)
Examination	Well, no focus	Well, no focus	Well, no focus
Laboratory values (define low risk)	WBCs >15,000/mm^3 Band/neutrophil ratio <0.2 UA <10 WBCs/hpf (negative Gram stain) CSF <8 WBCs/hpf (negative Gram stain) Chest radiograph normal, stool negative (if obtained)	WBCs 5000–15,000/mm^3 Absolute band count <1500 UA <10 WBCs/hpf Stool <5 WBCs/hpf (if obtained)	WBCs <20,000/mm^3 UA <10 WBCs/hpf CSF <10 WBCs/hpf Chest radiograph normal (if obtained)
High risk	Admission + IV antibiotics	Admission + IV antibiotics	Admission + IV antibiotics
Low risk	Home, no antibiotics	Home, no antibiotics	Home, empirical antibiotics
Performance	Sensitivity 98% (92%–100%) Specificity 42% (38%–46%) PPV 14% (11%–17%) NPV 99.7% (98%–100%)	Sensitivity 92% (83%–97%) Specificity 50% (47%–53%) PPV 12% (10%–16%) NPV 98.9% (97%–100%)	Sensitivity not available Specificity not available PPV not available NPV 94.6%

CSF, Cerebrospinal fluid; *IV,* intravenous; *NPV,* negative predictive value; *PPV,* positive predictive value; *UA,* urinalysis; *WBC,* white blood cell; *WBCs/hpf,* white blood cells per high-power field.

<5 WBCs per high-power field), and negative CSF Gram stain and cell counts (<8 WBCs/mm^3), if obtained. When diarrhea was present, fewer than 5 WBCs per high-power field was the threshold for low risk. Since this publication, numerous variations of these historical criteria have been developed, modified, and tested.[18–21] All seek to identify criteria that categorize febrile young infants into "high risk" and "low risk" groups based on historical features (e.g., prematurity, prior antibiotic exposure, past medical history), physical examination findings (e.g., hyperpyrexia, focal infection) and laboratory parameters (e.g., elevated or depressed WBC, elevated procalcitonin, elevated CRP). Studies evaluating the various permutations of the evaluation of a febrile infant all perform similarly, emphasizing consistent use of a set of criteria is more critical than which set of criteria are used. The use of an evidence-based guideline to standardize the evaluation and disposition of young infants has been shown to reduce costs.

An infant who meets "low risk" criteria can be appropriately managed in several ways. For instance, one management strategy may call for a CBC, blood culture, urinalysis, and urine culture. If the results reveal the patient to be at low risk, the child may be discharged without antibiotics with close outpatient follow-up. If results are abnormal, the patient should receive a lumbar puncture and antibiotics. Another option, based on the Boston criteria, calls for a complete sepsis evaluation, including lumbar puncture, followed by empirical treatment with or without ceftriaxone (50 mg/kg IV or intramuscularly [IM]) and reevaluation within 24 hours. Generally, antibiotics should not be administered unless a complete sepsis evaluation is performed (including a lumbar puncture); children treated with antibiotics will not have reliable culture results if performed much later.

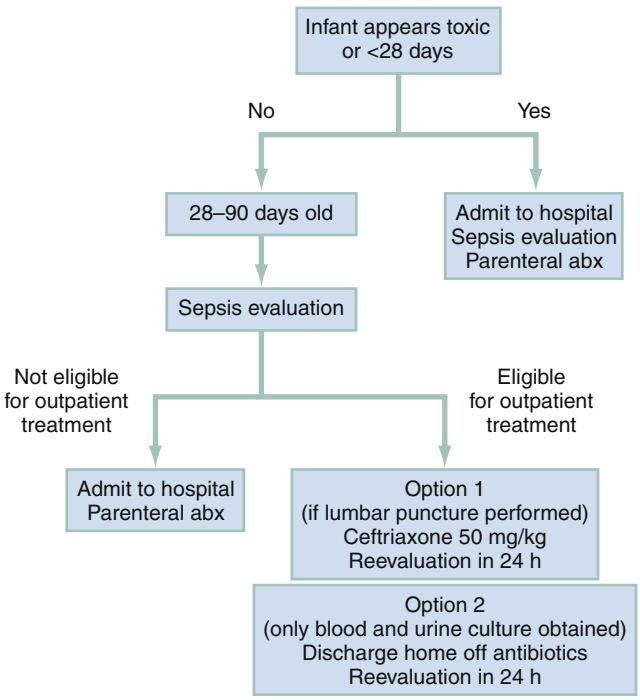

Fig. 161.3 Sample Algorithm for the Management of Febrile Infants Younger than 3 Months Old. To be eligible for outpatient treatment, the following should be met: white blood cell (WBC) count 5000 to 15,000 cells/mm^3, urinalysis is negative, lumbar puncture without pleocytosis or bacteria on Gram stain, able to return for care if necessary, reliable outpatient follow-up, no focal infection present (i.e., cellulitis, omphalitis), and chest radiograph and stool studies negative if obtained. *abx*, Antibiotics.

Infants 3 to 36 Months Old

Most cases of fever in children 3 to 36 months old represent self-limited viral illnesses. Common causes of fever in this age group include viral upper respiratory infections, croup, bronchiolitis, stomatitis (typically caused by HSV or coxsackievirus), gastroenteritis, roseola, and fifth disease (parvovirus B19 infection). Focal infections, such as pyelonephritis, periorbital cellulitis, bacterial pharyngitis (group A streptococcus), septic arthritis, retropharyngeal abscess, meningitis, and bacterial pneumonia, also become more common in this age group. Typically, these focal infections are apparent on the basis of history and physical examination findings, and diagnostic testing and treatment should be directed accordingly.

The history in this age group should focus on the duration of illness, associated symptoms that may focus the evaluation, immunization history (particularly vaccination for *H. influenzae* type B and pneumococcus), and sick contacts. A thorough physical examination is essential to rule out serious focal infection, such as meningitis. Young children may demonstrate inconsolable irritability or lethargy as the sole manifestation of meningitis; furthermore, classic meningeal signs, such as nuchal rigidity, are seen in less than 27% of infants (0 to 6 months old) with bacterial meningitis.

Prior research has focused on the assessment of children in this age group for the presence of occult bacteremia. It was found that a small percentage of highly febrile children (>102.2°F [39.0°C]) 3 to 36 months old were bacteremic. These children were noted to be highly febrile but lacked any localizing signs of infection. No historical or physical examination findings were sufficiently sensitive or specific to identify cases of occult bacteremia, making universal diagnostic testing necessary. A typical evaluation included a CBC and blood culture, and empirical antibiotic therapy was prescribed for children with WBC counts above 15,000/mm^3. Empirical antibiotics were justified on the basis of studies that revealed treatment with antibiotics prevented focal sequelae of bacteremia, such as meningitis, and shortened the duration of fever. Before almost universal immunization against *S. pneumoniae,* the rate of occult bacteremia was approximately 3%, and although pneumococcal bacteremia resolved without therapy up to 75% of the time, a small proportion of children had sepsis or focal infections, such as meningitis. Pneumococcal meningitis has a high degree of morbidity and mortality, including permanent neurologic disability, hearing loss, and death.

Since the advent of PCV7 (conjugate pneumococcal vaccine) and most recently PCV13, the number of invasive pneumococcal infections caused by vaccine-serogroup isolates among eight children's hospitals in the United States has decreased more than 75% among children younger than 24 months old. Because of the decline in invasive pneumococcal disease, young children with fever of unknown source no longer require blood culture; instead, clinical judgment should select high-risk populations that might benefit from testing and treatment. Although the incidence of pneumococcal bacteremia has declined in infants 3 to 36 months old because of the deliberate campaign to vaccinate, infants 3 to 6 months old have not yet completed the primary series of immunizations against *S. pneumoniae* and to a lesser extent against *H. influenzae*. Despite being "incompletely vaccinated" at this age, the rate of bacteremia is exceedingly low, and we do not recommend routine screening in this age group. The 13-valent conjugate pneumococcal vaccine (PCV-13) for routine childhood vaccinations provides expanded coverage. The additional six serotypes included in PCV13 were responsible for more than 60% of the cases of invasive pneumococcal disease in the years preceding the release of the updated vaccine schedule.[22] Despite these vaccine advances, there are approximately 90 serotypes that are capable of infecting humans, and

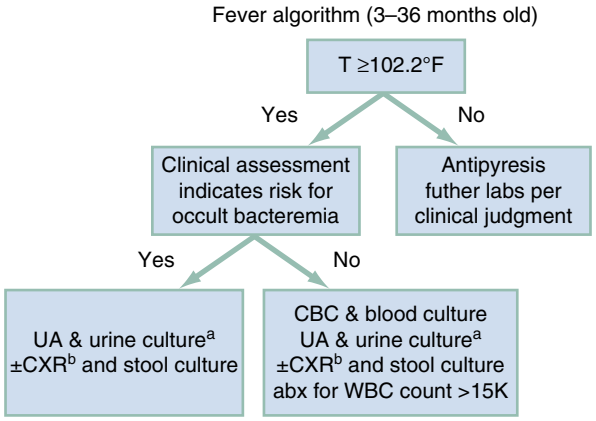

Fig. 161.4 Sample algorithm for the management of febrile infants 3 to 36 months old. [a]Females <24 months old; circumcised males <6 months old, uncircumcised males <12 months old. [b]CXR for symptoms or WBC >20,000/mm^3. *abx,* Antibiotics; *CBC,* complete blood count; *CXR,* chest x-ray; *T,* temperature; *UA,* urinalysis; *WBC,* white blood cell.

continued bacterial surveillance is necessary to ensure that other serotypes do not rise in incidence to fill the void left by vaccination.

No clinical prediction algorithm correctly identifies all patients with meningococcal disease. Additional signs and symptoms that may suggest meningococcemia are purpuric rash, bandemia, limb pain, and exposure to a person with the disease. A flow diagram for the evaluation of febrile infants 3 to 36 months old is presented in Fig. 161.4.

Children 3 Years Old to Adulthood

The incidence of occult bacteremia decreases after 3 years of age. Focal infections such as streptococcal pharyngitis, septic arthritis, pneumonia, peritonsillar abscess (most often in adolescents), and cellulitis become more common. Viral pathogens are also common, such as infectious mononucleosis. Infection with atypical pathogens, such as *Mycoplasma pneumoniae,* should also be considered in children presenting with pneumonia. Skin infections secondary to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) are also becoming more common and should be considered in children who present with pyogenic skin infection and skin abscesses. Community-acquired MRSA occurs in all age groups but has clustered among such children as wrestlers (associated with contaminated wrestling mats) and football players (infected equipment). Appropriate therapy includes incision and drainage of the abscess cavity. Based on recent studies that demonstrate improved primary resolution, decreased recurrences, and decreased spread, we recommend antibiotic therapy in addition to incision and drainage, especially for patients with large abscesses (>5 cm), cellulitis, or fever.[23] Antibiotic selections should be based on local resistance patterns but could include trimethoprim-sulfamethoxazole or clindamycin for younger children and doxycycline for children 8 years old or older.

There is a second peak in incidence of meningococcal disease in adolescent children with an attack rate of 1.2 infections per 100,000 population. As opposed to infants, adolescents with meningococcal infection are more likely to present with meningococcemia (40% vs. 20%) and shock (69% vs. 27%) and to have a fatal outcome (22.5% vs. 4.6%). Meningococcal infections often manifest with one of three clinical syndromes: meningitis, bacteremia, or a combination of the two. College students residing in dormitories are at particular risk for infection, with attack rates of 3.2/100,000 population.

Meningococcal infection is often rapidly progressive, presenting with fever, headache, and a stiff neck. Shock, altered mental status or frank coma, petechiae or purpura, seizures, and myalgias are also common. Some of the first signs of meningococcal infection include leg pain, cold hands and feet, and abnormal skin mottling. Children exposed to a patient with meningococcemia, particularly those with close contact with nasopharyngeal secretions, and who have any of the presenting signs, should receive a full septic evaluation, admission to the hospital, and empirical treatment with antibiotics until results of blood and CSF cultures. Appropriate initial therapy for children suspected of having meningococcal infection is ceftriaxone 100 mg/kg IV.

In January 2005, the U.S. Food and Drug Administration (FDA) approved the quadrivalent meningococcal conjugate vaccine (Menactra) for use in adolescents. This vaccine is a polysaccharide-protein conjugate directed against the four serotypes that cause most cases of invasive meningococcal disease in humans. The Advisory Committee on Immunization Practices recommends vaccination of adolescents at their 11- or 12-year-old well-child checkup, and the American Academy of Pediatrics (AAP) has also advised that all college freshmen living in dormitories be vaccinated. The use of the vaccine is associated with a 67% decrease in invasive disease and a 66% decrease in carriage rates. Younger children with anatomic or functional asplenia, those with complement component deficiencies, and children who travel reside in other countries where the disease is hyperendemic should be vaccinated. Based on age, a number of vaccines for the prevention of meningococcal disease are available (www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html).

SPECIFIC DISORDERS

Febrile Seizures

Febrile seizures are a common cause of convulsions in children younger than 5 years old.[24] They are defined as a seizure accompanied by a fever without the presence of CNS infection. They typically occur in infants and children 6 months to 5 years old. It is thought that the at-risk period is the rapid rise or defervescence of a fever rather than the absolute height of the fever. The subsequent risk of epilepsy after a febrile seizure is a common parental worry, although studies have shown that the risk is only slightly increased. The risk of epilepsy in the general population is thought to be 0.5% to 1%, whereas the risk in a patient who has had a febrile seizure is 1% to 2%. Although they are generally benign in course, febrile seizures can rarely be the presenting complaint of infants and children with CNS infection, such as meningitis. Febrile seizures are classified as either simple or complex. Simple febrile seizures are brief (<15 minutes), single, and nonfocal or generalized tonic-clonic. Complex febrile seizures are prolonged, recurrent (more than one within 24 hours), focal, prolonged, or occur outside the typical age range.

Differentiation of a benign febrile seizure from one that heralds CNS infection can be difficult. The AAP has published consensus guidelines for the evaluation and management of febrile seizures. Laboratory and radiographic evaluation should be directed at finding the source of the fever, not driven by the seizure itself. The AAP suggests that a lumbar puncture be performed in any child with signs of meningeal irritation after the first febrile seizure and be considered in symptomatic children who are incompletely immunized or have received prior antibiotic therapy.

Routine referral for neuroimaging or electroencephalography is not indicated. There is also no role for antiepileptic therapy after a single febrile seizure. Retrospective studies have shown that the incidence of meningitis after the simple or complex febrile seizures is exceedingly low and that infants with meningitis will demonstrate signs of sepsis or meningitis after the seizure, making empirical lumbar puncture based solely on a febrile seizure unnecessary.[25,26] Febrile status epilepticus, in contrast to a simple or even complex febrile seizure, carries a higher risk of meningitis and lumbar puncture should be performed in these cases. See Chapter 169 for a more in-depth discussion on pediatric seizures.

Fever and Petechiae

The presence of a petechial rash in the setting of a febrile illness is concerning for the possibility of meningococcal infection, although the vast

majority are due to a viral cause. The incidence of meningococcal infection has been found to be 7% to 11% in patients hospitalized with fever and petechiae. The rate of bacteremia of any cause was found to be much lower (1.9%) in an ED population. The differential diagnosis of fever and petechiae also includes disseminated intravascular coagulation, Rocky Mountain spotted fever, pneumococcal bacteremia, *Streptococcus pyogenes* infection, various viral infections, idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, and leukemia. Petechiae can also be caused mechanically by a tourniquet, retching, or violent coughing. Petechiae due to vomiting or coughing are typically confined to the skin above the nipple line, but petechiae caused by SBI can have any distribution.

Because of the risk of serious illness in children with fever and petechiae, blood should be obtained for CBC, CRP, and culture. Patients with associated pharyngitis should undergo testing for group A streptococcus infection. Among patients presenting to a pediatric ED with a temperature higher than 100.4°F (38.0°C) and petechiae, an abnormal WBC count (<5000 WBCs/mm^3 and >15,000 WBCs/mm^3) or abnormal coagulation studies have been shown to be predictive but not diagnostic of invasive bacteremia. We recommend that children with fever and petechiae and an abnormal WBC, high band count, or elevated CRP be admitted and treated for presumptive bacterial infection until blood cultures result. Well-appearing children with normal WBC, CRP, and coagulation studies are unlikely to have invasive bacteremia and can be discharged without antibiotic therapy with close outpatient follow-up.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki disease is one of the most common vasculitides in childhood and should be considered in any infant or child with prolonged fever (greater than 4 days).[27] Accurate diagnosis is important because the main complication of Kawasaki disease is the development of coronary artery aneurysms. Some patients will present with "incomplete Kawasaki disease," which occurs when not all diagnostic criteria are met. Despite the lack of classic findings, these children are still at risk for coronary complications. Laboratory abnormalities found in cases of Kawasaki disease include leukocytosis, thrombocytosis (platelet counts as high as 1,000,000/mm^3), and evidence of systemic inflammation with elevation in the erythrocyte sedimentation rate and CRP level.

Children with suspected Kawasaki disease should be hospitalized and receive therapy with intravenous immune globulin (IVIG; 2 g/kg infused during 10 to 12 hours) and aspirin (initial dose 80 to 100 mg/kg daily divided every 6 hours). Pediatric cardiology consultation for echocardiography is also indicated (see Chapter 165 for a more complete discussion of Kawasaki's Disease and Chapter 120 for a discussion on multi-inflammatory syndrome in children [MIS-C]).

Toxic Shock Syndrome

TSS refers to the toxin-mediated clinical syndrome that occurs from *S. aureus,* although a similar illness is caused by group A streptococcus. The toxin implicated in TSS is an exotoxin termed *TSS toxin 1.* The syndrome is classically associated with tampon use by menstruating women, although cases also occur in males and prepubertal girls from other sources of infection with *S. aureus*.

Clinical manifestations of TSS include fever (>102°F [38.9°C]), hypotension, diffuse erythroderma, and multisystem involvement. Patients may present with vomiting or diarrhea, severe myalgias, oropharyngeal hyperemia, or altered mental status. Laboratory abnormalities are common and include elevated creatine kinase, elevated blood urea nitrogen or creatinine, transaminitis, and thrombocytopenia. The Centers for Disease Control and Prevention (CDC) has developed a set of findings for case definition (Box 161.1).

Treatment of TSS involves fluid resuscitation because these patients typically have immense requirements and antistaphylococcal antibiotic therapy with clindamycin (20 to 40 mg/kg/day in three divided doses) and vancomycin (10 to 20 mg/kg IV every 6 to 8 hours).

BOX 161.1 Centers for Disease Control and Prevention Case Definition for Toxic Shock Syndrome

Fever: Temperature >102°F (38.9°C)
Hypotension: Systolic blood pressure 90 mm Hg for adults or less than fifth percentile by age for children <16 years old; orthostatic drop in diastolic blood pressure by 15 mm Hg
Orthostatic syncope or dizziness
Diffuse erythroderma
Desquamation: 1–2 weeks after onset of illness, particularly involving palms and soles
Multisystem involvement (three or more of the following organ systems):
- Gastrointestinal: Vomiting or diarrhea at onset of illness
- Muscular: Severe myalgia or creatine kinase elevation more than two times the normal upper limit
- Mucous membranes: Vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: Blood urea nitrogen or serum creatinine more than two times the normal upper limit, or pyuria (>5 WBCs/high-power field)
- Hepatic: Bilirubin or transaminases more than two times the normal upper limit
- Hematologic: Platelets <100,000/L
- CNS: Disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension

Negative results on the following tests, if obtained:
- Blood, throat, or CSF cultures for another pathogen (blood cultures may be positive for *Staphylococcus aureus*)
- Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Criteria for a probable case include a patient with temperature >102°F (38.9°C), hypotension, diffuse erythroderma, desquamation (unless the patient dies before desquamation can occur), and involvement of at least three organ systems. A probable case is a patient who is missing one of the characteristics of the confirmed case definition.

CNS, Central nervous system; *CSF,* cerebrospinal fluid; *WBC,* white blood cell.

Fever in Children With an Underlying Chronic Medical Illness

Oncology Patients

Children with cancer, particularly those undergoing treatment with cytotoxic chemotherapy, are at particular risk for sepsis and bacterial infection. These life-threatening infections are most common during periods of profound neutropenia. Neutropenia is defined as an ANC of less than 500/mL or an ANC of less than 1000/mL that is falling. Children with cancer also frequently have central venous catheters, predisposing them to central line-associated bloodstream infections.

Causative organisms include both gram-positive and gram-negative bacteria. Staphylococci and streptococci as well as *Pseudomonas* are frequent pathogens. Often, patients with focal infection may not present with classic signs because of their leukopenia. Focal infections specific to cancer patients include stomatitis and typhlitis, which is a necrotizing enterocolitis of the terminal ileum and cecum.

Children presenting with fever and possible neutropenia should receive a prompt evaluation with a goal of arrival to antibiotic therapy of fewer than 60 minutes.[28] Blood should be obtained for a CBC and manual differential diagnosis as well as culture. Once appropriate laboratory studies are obtained, empirical antibiotic therapy should be initiated without waiting for

the laboratory results. Appropriate monotherapy antibiotic regimens include cefepime, 50 mg/kg IV every 8 to 12 hours based on gestational age and renal function, or ceftazidime, 50 mg/kg IV every 8 hours. Vancomycin, 10 to 20 mg/kg every 6 to 8 hours, should be added for staphylococcal coverage in children with suspected central line infections or skin and soft tissue infections. Children with fever and neutropenia are rarely treated as outpatients; in very select cases and in consultation with an oncologist, ceftriaxone 50 mg/kg IV may be given every 24 hours with close follow-up.

Patients With the Acquired Immunodeficiency Syndrome

Children with the acquired immunodeficiency syndrome (AIDS) are at risk for bacterial infection due to a whole host of different organisms—some common, some uncommon. Infections specific to AIDS include cryptococcosis and infection with *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* and *Pneumocystis jiroveci (carinii)*. Viral infections, such as cytomegalovirus and Epstein–Barr virus infections, are also common.

Laboratory evaluation should be directed by the history and physical examination. Early initiation of broad-spectrum antibiotic therapy is warranted.

Sickle Cell Disease

Febrile children with sickle cell disease are at particular risk for overwhelming infection. In fact, infection is the most common cause of sickle cell-related death, occurring in up to 40% of patients with sickle cell disease who die. Recurrent episodes of splenic infarction lead to functional asplenia early in life. Thus, these patients are at particular risk for infection with encapsulated organisms, including *S. pneumoniae* and *H. influenzae*. Because of this risk of bacterial disease, it is recommended that all children with sickle cell disease be completely immunized. Prophylaxis with penicillin is recommended in children younger than 5 years old, after which it can be safely discontinued in children who have not had a prior severe pneumococcal infection or surgical splenectomy. The dose of penicillin is 125 mg orally twice daily until 3 years old (at about 14 kg) and 250 mg orally twice daily after 3 years old.

High-risk criteria for bacterial infection include toxic appearance, temperature higher than 104°F (40°C), abnormal WBC count (<5000 or >30,000 WBCs/mm^3), and noncompliance with penicillin prophylaxis. Sickle cell patients are at particular risk for *Salmonella* osteomyelitis. All patients presenting with a temperature higher than 100.4°F (38.0°C) and sickle cell disease should have a blood specimen drawn for CBC, reticulocyte count, and culture. A reticulocyte count is important because many infections (e.g., parvovirus B19) can induce a life-threatening aplastic crisis. Infection also predisposes children with sickle cell disease to acute chest syndrome. Common causes of infection include *C. pneumoniae, M. pneumoniae,* RSV, *S. aureus,* and *S. pneumoniae*. Further laboratory and radiographic evaluation should be directed by the presenting history and physical examination findings.

As defined earlier, high-risk patients should be admitted for further evaluation and antibiotic therapy. Low-risk patients may be treated with a single dose of IV or IM antibiotics, typically ceftriaxone 50 mg/kg, and discharged to close outpatient follow-up. All patients should be reevaluated within 24 hours or sooner if the clinical condition deteriorates.

Osteomyelitis typically manifests as fever and bone pain. As patients with sickle cell disease may have frequent bone pain due to vaso-occlusive crisis, the diagnosis can be difficult. All patients should have a blood specimen drawn for CBC with differential diagnosis, erythrocyte sedimentation rate, and culture; a radionuclide bone scan or magnetic resonance imaging (MRI) may help localize the infection. If *Salmonella* infection is suspected, a stool sample should be sent for culture.

Congenital Heart Disease

Children with congenital heart disease are at high risk for cardiovascular complications in the setting of febrile illness. Often, relatively minor viral illness can produce significant changes in cardiac function or make it difficult for children to be compliant with their oral medications. Children with congenital heart disease are also at risk for infective endocarditis. Infective endocarditis is heralded by fever and possibly a changing or worsening cardiac murmur. The modified Duke criteria for the diagnosis of endocarditis are presented in Box 161.2.

BOX 161.2 Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major Criteria

Blood cultures positive for IE
- Typical microorganism for IE from two separate blood cultures
  - Viridians streptococci
  - *Streptococcus bovis,* including nutritional variant strains
  - HACEK group: *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*
  - *Staphylococcus aureus*
- Community-acquired enterococci, in the absence of a primary focus; *or*
- Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood samples drawn more than 12 hours apart; *or*
- All of three or a majority of four or more separate blood cultures, with first and last samples drawn at least 1 hour apart
- Single blood culture positive for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800

Evidence of endocardial involvement

Echocardiogram positive for IE
- TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess); TTE as the first test in other patients[a]
- Definition of positive echocardiogram
- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; *or*
- Abscess; *or*
- New partial dehiscence of prosthetic valve

New valvular regurgitation (increase in or change in preexisting murmur not sufficient)

Minor Criteria

Predisposition: Predisposing heart condition or injection drug use

Fever: 100.4°F (38.0°C)

Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

Microbiologic evidence: Positive blood culture but not meeting major criterion (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

IE, Infective endocarditis; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

[a] Echocardiographic minor criteria eliminated.

Endocarditis is typically caused by *S. aureus,* viridans streptococci, *Streptococcus bovis,* enterococci, or infection with organisms from the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*). Children with suspected endocarditis should have blood culture specimens drawn and be admitted to the hospital for treatment and echocardiography. The American Heart Association recommends that initial antibiotic therapy be with ceftriaxone, 100 mg/kg IV or IM every 24 hours, or vancomycin, 10 to 20 mg/kg IV Q6-8H. Therapy is typically continued for at least 4 weeks. Ceftriaxone can be combined with gentamicin, 3 to 6 mg/kg IV divided every 8 hours (if renal function is normal), if shorter treatment duration (2 weeks) is desired. See Chapter 165 for a more complete discussion.

Ventriculoperitoneal Shunts

Children presenting with fever in the setting of ventriculoperitoneal shunts are at risk for shunt infection. If shunt infection is suspected, based on the presence of altered mental status or signs of meningismus, neurosurgical consultation should be obtained and a sample of CSF obtained. This is typically accomplished by sterile aspiration of fluid from the shunt reservoir. *S. aureus* and *Staphylococcus epidermidis* are the usual causative organisms. If an altered mental status is present, a computed tomography (CT) scan should be obtained to assess ventricular size. Children with suspected shunt infection are typically managed as inpatients, and antibiotics should begin as soon as possible.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 161: QUESTIONS AND ANSWERS

1. Which of the following are appropriate methods to obtain urine as part of a fever evaluation in a non-toilet-trained child?

a. Catheterized specimen
b. Clean catch, midstream
c. Suprapubic aspiration
d. A and C

Answer: d. The only reliable method to obtain sterile urine in a non-toilet-trained child is bladder catheterization or suprapubic aspiration if a catheter specimen cannot otherwise be obtained. Bag collection has a high rate of false-positive results and is not preferred in a child who is not toilet trained.

2. A 38-day old male infant presents to the emergency department (ED) after parents noted a fever at home today. In the ED, the temperature was noted to be 40.0°C. The child was born at 35 weeks gestation and 1 week ago was diagnosed with otitis media by his primary care physician and has been taking amoxicillin as treatment. Which of the following historical aspects places this child at higher risk for invasive bacterial infection?

a. Fever responsive to acetaminophen
b. Temperature of 40.0°C
c. Prior treatment with antibiotics
d. Prematurity
e. B, C, and D

CHAPTER 161: QUESTIONS AND ANSWERS—cont'd.

Answer: e. Risk for serious bacterial infection (SBI) varies with age. Children less than 3 months are at high risk for SBI, with those less than 28 days of age at highest risk. Hyperpyrexia, prior treatment with antibiotics, and prematurity have also been identified as risk factors for SBI. Response to antipyretics has not been linked to SBI risk.

3. Which of the following statements regarding occult bacteremia in children younger than 36 months old is *true?*
   - **a.** Children with no obvious source of fever and a temperature higher than 102.2°F (39°C) have an incidence of bacteremia of 5%.
   - **b.** Most patients appear toxic.
   - **c.** The most common pathogen is *Neisseria meningitidis.*
   - **d.** There has been a marked decrease in the incidence of occult bacteremia since the advent of universal vaccination against pneumococcus and *Haemophilus influenzae* type B.
   - **e.** With pneumococcal bacteremia, most patients remain febrile until antibiotic therapy is initiated.

Answer: d. Children younger than 36 months old with a fever higher than 102.2°F (39°C) and no obvious source have an incidence of occult bacteremia of less than 1%. Most patients appear nontoxic. The most common pathogen in positive cultures is *Streptococcus pneumoniae,* and the incidence of infection has dropped dramatically since the advent of universal vaccination. With pneumococcal bacteremia, most patients become afebrile in 3 or 4 days with or without antibiotic therapy.

4. A 3-year-old boy presents with a fever of 103°F. His mother reports that the fever started approximately 5 days ago, and he has an associated maculopapular rash. On examination, you find the patient also has bilateral conjunctival injection, a strawberry tongue, and swelling of his hands and feet. Which of the following medications should be included in the treatment of this patient?
   - **a.** Aspirin
   - **b.** Decadron
   - **c.** Penicillin G
   - **d.** Ceftriaxone

Answer: a. This patient has Kawasaki disease. Goals of treatment include amelioration of symptoms and prevention of coronary aneurysms, which are normally accomplished with aspirin and immunoglobulin. There are no indications for antibiotics or steroids.

5. A 2-year-old presents with a high fever and vomiting. On examination, you find an irritable child with a rectal temperature of 102°F rectal and a stiff neck. The patient's past medical history is significant for hydrocephalus with a ventriculoperitoneal shunt placement. You suspect the patient has a ventriculoperitoneal shunt infection. Which of the following is the most likely bacterial pathogen?
   - **a.** *Haemophilus influenzae*
   - **b.** *Neisseria meningitidis*
   - **c.** *Staphylococcus aureus*
   - **d.** *Staphylococcus epidermidis*

Answer**: d.** Patients with ventriculoperitoneal shunts and fever should be evaluated for shunt infection. The most common bacterial pathogen is *S. epidermidis*.

Pediatric Upper Airway Obstruction and Infections

Emily Rose

KEY CONCEPTS

Respiratory arrest precedes most pediatric cardiac arrests. Quick recognition of an airway problem and intervention in potentially life-threatening upper airway obstruction in children are critical.

Retropharyngeal Abscess

- This is a potentially life-threatening emergency in young children with signs of upper airway obstruction or meningismus; a retropharyngeal abscess is often related to oral trauma.
- Retropharyngeal abscess is most frequently caused by *Staphylococcus aureus*, group A streptococci, and anaerobes. Treatment is admission, IV antibiotics, and for more severe cases, surgical drainage.

Epiglottitis

- Epiglottitis may be caused by many bacteria or local injury. In the post–*Haemophilus influenzae* type b vaccine era, the incidence of pediatric epiglottitis has decreased, and epiglottitis is now more likely in older patients.
- Clinical features of epiglottitis are often subtle, such as in the older adolescent, (e.g., sore throat out of proportion to physical findings, anterior neck tenderness), but may also be dramatic, as in infants and young children (i.e., drooling, stridor, toxicity, severe respiratory distress).

Croup

- Viral croup is the most common infection of the upper airway in young children.
- Glucocorticoids (usually given as a single oral dose of dexamethasone) reduce symptoms, hospitalizations, and length of stay in the emergency department (ED).
- Treatment of moderate to severe croup includes vaporized epinephrine in addition to glucocorticoids. Patients can be discharged from the ED after a posttreatment observation period. We recommend discharge after a period of observation, if the child is free of resting stridor and distress and has access to follow-up care.

Bacterial Tracheitis

- Suspect bacterial tracheitis when an upper respiratory infection (URI) progresses to acute toxicity and marked respiratory distress and stridor. Standard treatment for croup may be tried, but usually does not significantly improve the patient's symptoms. Antibiotic therapy should include a cephalosporin plus coverage for *S. aureus*, which is the most common cause of this infection.
- Bronchoscopy is diagnostic and therapeutic and should be emergently performed.

Airway Foreign Body

- Complete obstruction due to an airway foreign body requires emergent life support procedures for removal of the foreign body.
- Plain films may be negative in aspirated foreign bodies. Bronchoscopy should be performed with a clinical suspicion of aspiration.
- Emergency cricothyroidotomy may be required for obstructed patients who cannot be intubated or ventilated as a lifesaving temporizing measure; needle cricothyroidotomy is preferred for infants and young children because of the challenges in identifying landmarks and associated complications of surgical cricothyrotomy.

FOUNDATIONS

Respiratory distress from upper airway obstruction is a rare but potentially a catastrophic emergency in young children. Causes include acute infectious processes, congenital anomalies, or a foreign body in the airway or esophagus. Children are predisposed to respiratory failure due to increased airway resistance (small, compressible airway), low functional residual capacity, high oxygen metabolism, which leads to quicker fatigue, and shorter safe apnea time, with precipitous hypoxia.

Clinical presentations of children with upper airway disease vary with cause, predisposing factors, and age at presentation:

- Acute infections of the upper airway range from relatively mild distress and self-limited signs and symptoms, to the abrupt onset of a rapidly progressive airway obstruction.
- Undiagnosed congenital anomalies of the airway and surrounding structures may be manifested as chronic or progressive stridor, or simply difficulty with feeding.
- An infant with a congenital airway anomaly in whom an acute airway infection develops is at higher risk for decompensation and respiratory failure.
- Upper airway obstruction from a foreign body in the airway or esophagus can cause partial or complete airway obstruction and may require urgent, advanced, airway management skills.

CLINICAL FEATURES

Recent history and observation of the child typically provide clues to the cause of the airway obstruction. Important items to elucidate in the history include the following:

- Onset and duration (acute vs. chronic)
- Associated symptoms (e.g., respiratory distress, fever, toxicity, drooling, cyanosis, neck stiffness, or torticollis)
- Progression with age (number of bouts and severity of "croup" with increasing age)

- Exacerbating factors (supine vs. prone position, upper respiratory infection [URI], crying)
- Feeding abnormality or dysphagia
- Prior airway procedures, such as intubation in the neonatal period
- Choking episode indicating possible foreign body aspiration
- Baseline noises, quality of cry and voice to assist the emergency clinician in pinpointing the location of obstructive lesion

Initial observation can be quickly assessed utilizing the Pediatric Assessment Triangle (see Chapter 155). Observation and physical examination should include vital signs (respiratory rate, heart rate, oxygen saturation) and indicators of increased work of breathing (retractions, flaring, grunting, stridor, wheezing) to gauge the severity of distress. Observe the character and timing of stridor, as well as the symmetry and quality of breath sounds. Respiratory failure is identified by the presence of extreme distress: hypoventilation or hyperventilation; altered mental status; pale, mottled, or cyanotic skin color; or hypotonia. Stridor may not be present in respiratory failure due to the lack of airflow.

Stridor (from the Latin, *stridulus,* indicating creaking, whistling, or grating) is the classic sound associated with upper airway obstruction. Stridor is a harsh vibratory sound of variable pitch caused by partial airway obstruction or collapse and the resultant turbulent airflow through some portion of the airway, from the nose to the trachea. Stridor is described by timing in the respiratory cycle (inspiratory, expiratory, biphasic) and quality (coarse or high-pitched; Table 162.1). Inspiratory stridor is usually associated with obstruction above the glottis, expiratory stridor with intrathoracic obstruction, and biphasic stridor typically with a critical or fixed obstruction at any level. Stridor character differs by cause and anatomic location (Fig. 162.1).

Snoring or stertor is low-pitched inspiratory noise caused by nasal or nasopharyngeal obstruction. Stertor and stridor can coexist. Stridor from the pharynx, such as from a peritonsillar abscess (PTA), tends to have a sonorous, gurgling, and coarse quality. The voice may be altered and have a muffled or "hot potato" quality to it. High-pitched inspiratory stridor occurs in the supraglottic and immediate subglottic trachea, as in croup and laryngomalacia. The voice may sound hoarse or weak, but a normal voice may be heard, even with a laryngeal cause of stridor.

Biphasic stridor is heard with inspiration and expiration and usually suggests a fixed lesion. Examples include laryngeal webs and vocal cord paralysis. Stridor from the lower part of the trachea is usually expiratory, such as in bacterial tracheitis or aspirated foreign bodies (Fig. 162.2).

TABLE 162.1 Causes of Stridor: Anatomic Location, Sound, and Quality

Features (Structures)	Supraglottic (Nose, Pharynx, Epiglottitis)	Glottic (Larynx, Vocal Cords)	Subglottic Trachea (Lower Trachea)
Sound	Sonorous (stertor)	Biphasic stridor	High-pitched stridor
	Gurgling		Inspiratory stridor
	Coarse		Expiratory stridor (if intrathoracic)
	Expiratory stridor		
Congenital	Micrognathia	Laryngomalacia	Subglottic stenosis
	Pierre Robin syndrome	Vocal cord paralysis	Tracheomalacia
	Treacher-Collins syndrome	Laryngeal web	Tracheal stenosis
	Macroglossia	Laryngocele	Vascular ring
	Down syndrome		Hemangioma cyst
	Storage diseases		
	Choanal atresia		
	Lingual thyroid		
	Thyroglossal cyst		
Acquired	Adenopathy	Papillomas	Croup
	Tonsillar hypertrophy	Foreign body	Bacterial tracheitis
	Foreign body		Subglottic stenosis
	Pharyngeal abscess		Foreign body
	Epiglottitis		
Positional stridor	Micrognathia, macroglossia		Laryngomalacia

Diagnostic Testing and Management

Definitive airway management takes precedence in an acute airway emergency. An individualized diagnostic evaluation can be undertaken in a less critical, stable patient with an uncertain diagnosis. Lateral and anteroposterior radiographs of the soft tissues of the neck may be helpful to assess the adenoid and tonsillar size, contour of the epiglottis, thickness of the retropharyngeal soft tissue space, vallecula, aryepiglottic folds, and tracheal air column (Fig. 162.3). The child's head should be positioned in extension and film taken during inspiration. However, plain radiographs are commonly misleading and may be normal, even with significant underlying pathology. Chest views assess the heart size, trachea and bronchi, location of the aortic arch, and presence of other pulmonary pathologic processes.

Additional studies may be indicated in specific settings. Bedside fiberoptic nasopharyngoscopy allows for the visualization and assessment of the supraglottic structures and vocal cords and can assist with intubation when indicated. Esophagography can define lesions compressing the airway and trachea; computed tomography (CT), magnetic resonance imaging (MRI), or bronchoscopy may be needed to evaluate the upper airway.

Specific Disorders

Supraglottic Airway Diseases

The supraglottic portion of the airway includes the nose, pharynx, epiglottis, and surrounding structures. Diseases of the nose and pharynx are commonly associated with noisy congested breathing and respiratory distress. Congenital lesions involving these structures may cause mild symptoms at baseline, but dramatic distress when there is a superimposed infectious process. Congenital lesions include choanal atresia, macroglossia, micrognathia, thyroglossal duct cyst, and lingular thyroid. Acquired causes of supraglottic disease include a nasal foreign body, nasal polyps, hypertrophic tonsils and adenoids, epiglottitis, retropharyngeal abscess (RPA), PTA, pharyngitis, mononucleosis, and upper airway foreign body. The most common conditions are discussed in the following sections.

Congenital Lesions

Choanal atresia. All infants are obligate nose breathers; they breathe nasally when the mouth is closed to allow breathing while feeding. In choanal atresia, the most common congenital anomaly of

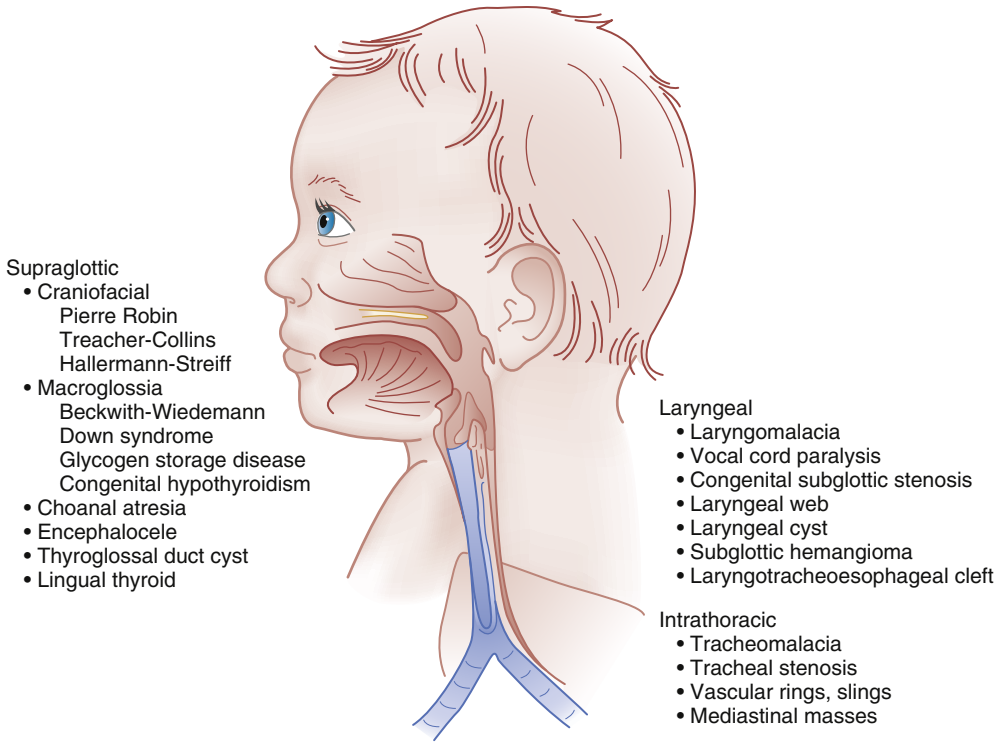

Fig. 162.1 Regions and Associated Diseases of the Pediatric Upper Airway. (From Simon NP, Simon N. Evaluation and management of stridor in the newborn. *Clin Pediatr [Phila].* 1991;30:211.)

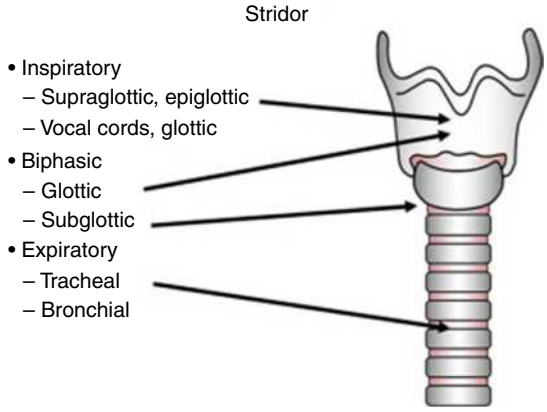

Fig. 162.2 Level of Obstruction Correlates with Phase of Stridor. (From Ida JB, Thompson DM. Pediatric stridor. *Otolaryngol Clin North Am.* 2014;47:795–819.)

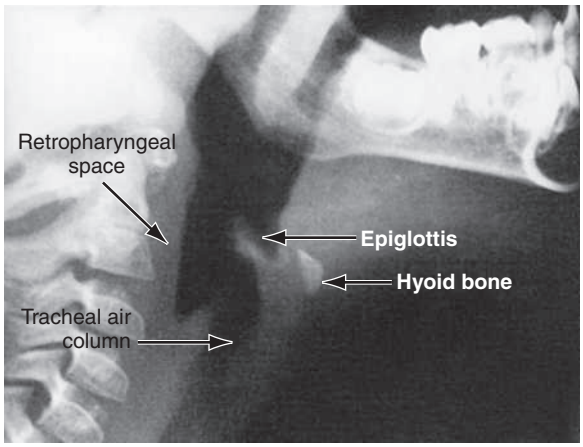

Fig. 162.3 Normal Appearance of Upper Airway Structures on a Lateral Neck Radiographic Study. Note the hyoid bone, epiglottis, retropharyngeal space, and tracheal air column.

the nose, there is persistence of the bucconasal membrane or a bony septum in the posterior naris. The posterior aspect of the infant's soft palate extends downward and contacts the tip of the epiglottis. Bilateral choanal atresia is a life-threatening emergency that is almost always identified early, as neonates become acutely distressed and cyanotic at birth. Immediate airway management is with oral airway and definitive surgical correction of the obstructing membrane. Unilateral choanal atresia is often initially undetected. Infants may present in respiratory distress with a URI when the normal patent naris is obstructed by swelling or secretions. Immediate nasal suction should be performed along with urgent referral for surgical repair.

Macroglossia. Macroglossia, an abnormally large tongue that protrudes posteriorly into the hypopharynx, is associated with conditions such as Down syndrome, glycogen storage disease, and congenital hypothyroidism. The increased secretions with a URI exacerbate underlying obstruction and may induce stridor or labored breathing. Good head positioning with nasal suctioning should be performed to relieve the obstruction.

Micrognathia. With micrognathia, an abnormally small mandible posteriorly displaces the normal-sized tongue (e.g., Pierre Robin and Treacher-Collins syndromes). Obstructive symptoms typically worsen when supine.

Pharyngitis

Infection is the most common cause of sore throat in children. Viruses cause the majority of infections. Certain viruses have characteristic features such as coxsackie A viruses that manifest as herpangina or

hand, foot, and mouth disease. Herpes simplex more commonly causes stomatitis and less commonly may cause pharyngitis. *Streptococcus pyogenes* (Group A streptococcus) is the most common bacterial infectious etiology (see Chapter 19). Diphtheria can cause a thick exudative tonsillar membrane. Acetaminophen (15 mg/kg/dose q4h) or ibuprofen (10 mg/kg/dose q6h) is sufficient supportive treatment for most causes of pharyngitis.

Peritonsillar Abscess

PTA is the most common deep neck infection and usually occurs in older children and teenagers. Drooling and a muffled, hot potato voice is common, but severe respiratory distress is unusual. PTA is associated with trismus (in two out of three patients), bulging or asymmetry of the tonsils, and deviation of the uvula away from the abscess side (in 50% of patients). Throat pain may radiate to the ear. Treatment involves antibiotics and incision and drainage or needle aspiration. Antibiotics alone are insufficient management for an abscess but may resolve a phlegmon or cellulitis.[1] Surgical intervention typically removes the majority of purulence, but additional antibiotics are recommended to clear the remaining infection.

PTAs are typically polymicrobial. Predominant bacterial species are *S. pyogenes* (group A streptococcus), *Staphylococcus aureus* (including Methicillin-resistant *S. aureus* [MRSA]), and respiratory anaerobes. Posterior pharynx ultrasonography can confirm the diagnosis and guide treatment.[2,3] A CT scan may be indicated if extension of infection is suspected. Any drainage effort should take great care to avoid puncture of the carotid artery (the carotid artery lies 25 mm posterolateral to the tonsillar pillar in children >12 years). Approximately 10% to 20% of patients have recurrent PTAs.

Mononucleosis

Infectious mononucleosis, caused by the Epstein-Barr virus (EBV), can lead to mucosal edema and an exudative pharyngitis. Uncommonly, massive tonsillar enlargement can occur and create upper airway distress. EBV IgM antibody is the preferred test for infective mononucleosis (>90% sensitive), particularly in children younger than 4 years who are less likely to generate heterophile antibodies with primary EBV infection. In older children and adults, the heterophile antibody can be detected in 50% of patients within the first week of illness and in 60% to 90% in weeks 2 and 3.

In addition to airway management and general supportive care, there may be additional benefits of steroids in reducing tonsillar edema and pain.[4] Although steroids decrease pharyngitis symptoms, it is important to consider an underlying lymphoid malignancy. Children often present with sore throat prior to malignancy diagnosis. Treatment with glucocorticoids prior to the diagnosis of leukemia may delay leukemia diagnosis, increase the risk of tumor lysis syndrome, complicate risk stratification, and ultimately result in fatal complications. Therefore, great caution should be exercised in using glucocorticoids in children and adolescents and should be avoided in children younger than 14 years or in a child who has any signs of possible lymphoid malignancy such as lymphadenopathy, hepatosplenomegaly, rash, or abnormal complete blood count.

Retropharyngeal Abscess

A RPA is a potentially life-threatening airway emergency resulting from infection of the retropharyngeal soft tissue space. The retropharyngeal space is a potential space between the posterior pharyngeal wall and prevertebral fascia that extends from the base of the skull to the level of T2. It is rich in lymph tissue that drains the nose, pharynx, sinuses, and ears. An abscess may result from direct trauma from a fall with a hard object in the mouth that penetrates the soft tissue, suppuration of lymph nodes, contiguous spread of infection, or hematogenous seeding. RPA is usually a disease of young children because the lymphatic chains are prominent in the young and atrophy before puberty; RPA in older children often occurs after inciting trauma. These infections are commonly polymicrobial, with *Streptococcus* and anaerobes being the most commonly isolated organisms. MRSA is increasing in incidence and is commonly associated with severe infections such as jugular venous thrombosis or mediastinal extension.

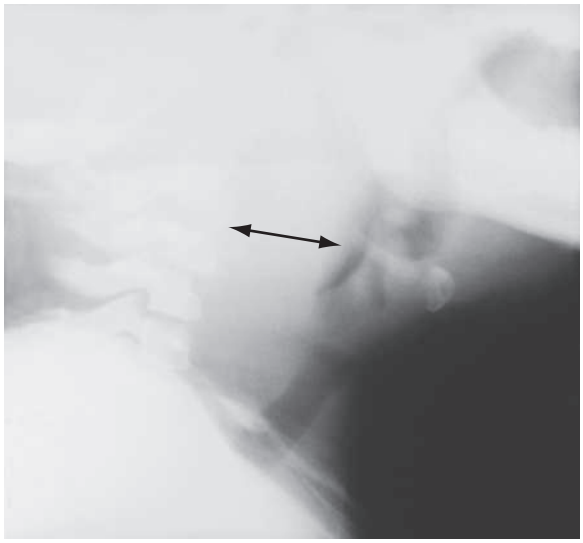

Fig. 162.4 Retropharyngeal Abscess. Note the widened retropharyngeal soft tissue space *(double arrow)*.

Clinical features. Retropharyngeal infections typically progress from cellulitis to organized phlegmon to mature abscess. Presenting symptoms may vary. Common signs and symptoms include fever, sore throat, neck stiffness or nuchal rigidity, torticollis, trismus, neck swelling, drooling, stridor, and muffled voice. Stridor and respiratory distress may occur if a large abscess compresses the trachea; the clinical appearance can resemble that of epiglottitis. Reluctance to extend the neck and an unwillingness to look side to side is often seen with RPA and may help differentiate it from other supraglottic infections. With less obvious signs of airway obstruction, patients can exhibit a mixture of symptoms, including fever, neck stiffness, and generalized toxicity, which may suggest meningitis or sepsis. Other serious complications of a RPA include aspiration pneumonia, mediastinitis, and empyema.

Diagnostic testing. Careful evaluation of airway patency takes precedence in the management of a child with a presumed RPA. Examination of the pharynx may reveal bulging of the posterior pharyngeal wall. A soft tissue lateral view of the neck may be helpful to establish the diagnosis; in the normal patient, the width of the retropharyngeal space should not exceed the diameter of the adjacent vertebral body (Fig. 162.4). The soft tissue width should not be larger than 7 mm at C2, regardless of the patient's age. At C6, this distance should not exceed 14 mm in children younger than 15 years and 22 mm in adults. Most patients will demonstrate retropharyngeal thickening on the lateral neck radiograph. An air-fluid level may be present with perforation or anaerobic infections. Redundant soft tissue of the retropharyngeal space complicates the interpretation of lateral neck films in young infants with an RPA. Artefactual widening of a normal retropharyngeal space is commonly seen when the radiograph is taken with the head and neck in flexion or during exhalation. CT scanning of the neck (thin cuts to T2) may be beneficial in delineating the size and extent of an abscess and determining possible impingement on airway

structures. The ability to tolerate lying supine should first be assessed, and staff and airway equipment should be immediately available.

Management. The size of the abscess, degree of airway obstruction, and overall toxicity of the patient dictate management. The need for intubation or surgical drainage is determined on an individual basis, and these patients generally benefit from the involvement of an otolaryngologist. Intubation can be complicated by distorted anatomy and can lead to abscess rupture. Some retropharyngeal infections respond to intravenous (IV) antibiotics and do not require surgical drainage.[5] Features that suggest abscess and require surgical intervention include imaging findings of scalloping of the abscess wall, rim enhancement, and lesions larger than 2 cm. The decision to admit and provide a trial of antibiotic therapy should be made between the emergency clinician and otolaryngology consultant. Clindamycin and a third-generation cephalosporin are recommended antibiotic therapy. Vancomycin or linezolid should be added with suspected MRSA infection, resistant cases, or with systemic illness.

Ludwig's Angina

Ludwig's angina is a rapidly spreading, woody induration or brawny cellulitis of the sublingual, submandibular, and submaxillary spaces, with the potential for airway obstruction. Most patients have dental sources of infection, which are usually polymicrobial. The spread of infection is direct and not via the lymphatics, so involvement is typically bilateral and without associated lymphadenopathy. Hallmark signs include enlargement and elevation of the tongue above the lower teeth, a tender woody induration in the sublingual space, trismus, and odynophagia. Ludwig's angina can create a functional upper airway obstruction or respiratory distress through significant swelling and direct airway compression. Subsequent abscess formation may occur. CT evaluates the extent of infection but MRI may better delineate soft tissue involvement. Treatment involves broad-spectrum IV antibiotics with anaerobic coverage, airway support, and admission for close monitoring. Otolaryngology and anesthesia consultants may facilitate planning and support if an emergent airway is required.

Epiglottitis

Although still a feared pediatric emergency, acute epiglottitis has declined markedly in incidence since the widespread administration of the *Haemophilus influenzae* type b vaccine in the 1980s.

Foundations. Epiglottitis is an invasive bacterial disease that causes inflammation and edema of the epiglottis, aryepiglottic folds, arytenoids, and surrounding supraglottic tissues. As these structures become inflamed and distended, they protrude downward and over the glottic opening. Supraglottic swelling reduces the upper airway caliber and causes turbulent airflow during inspiration (stridor). The epiglottis may also act as a ball valve, obstructing airflow during inspiration but permitting exhalation. This traditional profile of *H. influenzae* type b (Hib) in young children has changed; the overall incidence has decreased, and now epiglottitis is relatively more common in older children and adults. However, Hib is still the most common infectious cause of epiglottitis in children and can occur in fully immunized children. Additional causes include other *H. influenzae* types (A, F, nontypeable), streptococci, *S. aureus* (including methicillin-resistant strains), and *Neisseria meningitidis*.[6,7] Immunocompromised children may have other infections such as *Pseudomonas aeruginosa* and *Candida* spp. Noninfectious causes are rare and include thermal injury from swallowing hot liquids, steam inhalation, caustic ingestions, allergic reactions, foreign body and irritant injuries, and lymphoproliferative disorders.

Clinical features. Epiglottitis is classically acute in onset. It is marked by high fever, intense sore throat, toxicity, and rapid progression. Children with epiglottitis appear anxious and maintain a sniffing or tripod position, with the jaw jutting forward and the neck extended to maximize airway patency. As symptoms worsen, cough and phonation are usually absent. Drooling is prominent because of an inability to swallow. Toxicity, altered mental status, dyspnea, stridor, retractions, and fever are common initial symptoms; the diagnosis is often delayed and is associated with a significantly increased mortality rate. Croup is a common misdiagnosis made in young children and those without prominent drooling and difficulty swallowing. The older patient is less likely to show dramatic signs of upper airway obstruction compared with the younger child because the diameter of the airway is larger and thus takes a greater degree of swelling to produce symptoms. These patients often complain of a sore throat that is out of proportion to physical findings and may also exhibit tenderness on palpation of the anterior neck. Epiglottitis caused by bacteria other than *H. influenzae* tends to have a slower onset and is less likely to cause airway compromise. Epiglottic abscess may occur, particularly in adolescents. Patients with immunodeficiency may develop necrotizing epiglottitis.

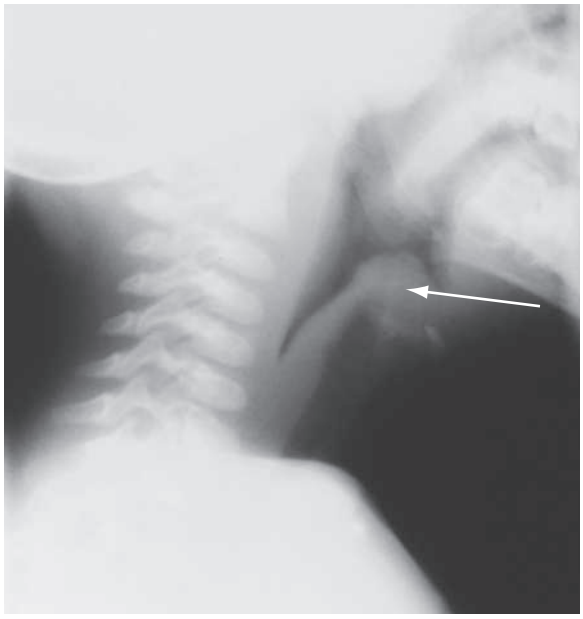

Fig. 162.5 Epiglottitis. Note the thumbprint sign of the epiglottis *(arrow)* and thickened aryepiglottic folds.

Diagnostic testing. When epiglottitis is strongly suspected, a lateral neck radiograph can be helpful to confirm the diagnosis and should be evaluated for an enlarged epiglottis (thumbprint sign; Fig. 162.5), thickened aryepiglottic folds, lack of air in the vallecula, and dilated hypopharynx. However, up to 70% of all patients with epiglottitis have normal radiographic findings. Careful observation of a child in consultation with an otolaryngologist is essential, and clinicians skilled in airway management should accompany the patient at all times; the risk of obstruction is particularly high in younger children with smaller airways.

Management. For the younger child, the importance of securing the airway takes precedence over diagnostic evaluation. A stable patient who is maintaining a patent airway and adequate oxygenation should not be moved or repositioned for examination, laboratory tests, or radiography. Such patients should be carefully transported to a setting where definitive airway management can be achieved in a controlled fashion, generally the operating room. Adolescents with epiglottitis generally have signs and symptoms of adults and do not often require airway stabilization. These patients can be managed as inpatients in a pediatric intensive care unit (PICU) setting with IV antibiotics but do

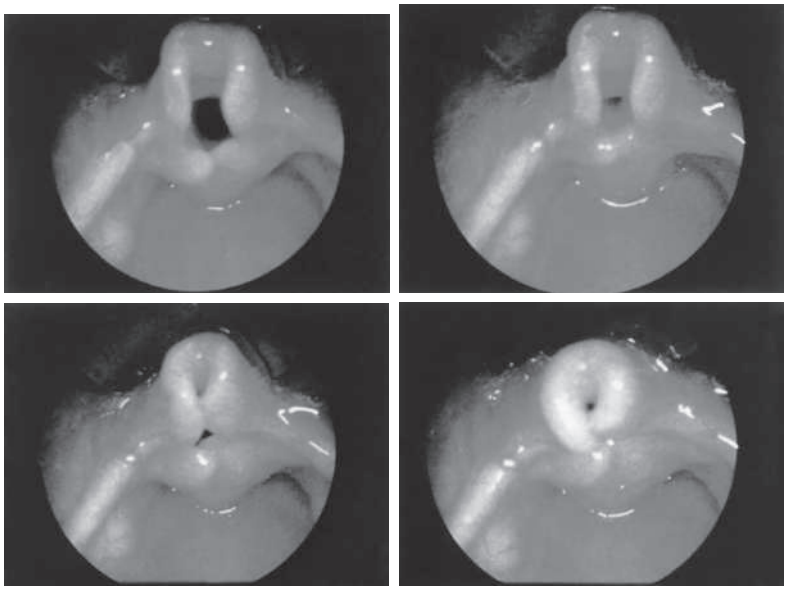

Fig. 162.6 Laryngomalacia. Note the progressive obstruction with inspiration as the epiglottis and surrounding structures collapse into the glottic opening.

not require immediate airway management unless signs and symptoms dictate that this is the case.

Unstable patients with respiratory failure require assisted ventilation. Bag-mask ventilation should be attempted first and, if successful, continued until intubation can be performed. If neither bag-mask ventilation nor intubation is successful, needle cricothyroidotomy or tracheostomy may be indicated. Regardless of the approach to securing the airway, it is prudent for the emergency clinician to consult other experts in airway management rapidly, such as an anesthesiologist (fiberoptic intubation), otolaryngologist, or general surgeon (surgical approaches), so that a plan of approach can be made and morbidity minimized. Patients often remain intubated for 3 to 5 days in order for antibiotic therapy to reduce inflammation and surrounding tissue edema. A second- or third-generation cephalosporin is recommended.

Trauma and Burns

Thermal injury from facial burns and inhaled smoke or steam and trauma to the face and neck can create physical findings similar to those of infectious epiglottitis. Rapidly progressive stridor, drooling, an unwillingness to lie flat, and a swollen inflamed epiglottis may occur. Aspiration of hot liquids is the most common cause of airway burns in infants and young children. Toddlers are particularly prone to inhalation of hot liquids because they can eat and drink independently without initially being attentive to temperature. The initial physical examination of the oropharynx may be relatively normal. The airway should be secured early in suspected laryngeal edema, as progression and obstruction can occur rapidly. Bronchodilators may help with bronchospasm; steroids are not recommended.

Allergic Reactions

Acute allergic reactions may cause rapid supraglottic edema with respiratory distress and stridor. Food is the most common precipitant in infants and children. Children with peanut allergies and those with atopy and asthma have higher mortality rates. The treatment of anaphylaxis is epinephrine. Intramuscular epinephrine (1 mg/mL solution) at 0.01 mg/kg up to 0.5 mg per dose is initial management and may be repeated twice. IV epinephrine (0.1 mg/mL solution) at a 0.001 mg/kg bolus followed by 0.1 to 1 mcg/kg/min up to 10 mcg/min may be necessary for patients in shock with anaphylaxis. IV fluids and oxygen should be administered. Racemic epinephrine may be given to reduce airway edema and other bronchodilators may be given for epinephrine-resistant bronchospasm. H1 and H2 antihistamines and steroids are commonly given for symptomatic relief but do not act rapidly enough to effectively treat anaphylaxis. Intubation may be required and should be considered early for acute airway obstruction unresponsive to epinephrine. On discharge from the hospital, all patients with anaphylaxis should be given a prescription for an epinephrine autoinjector (0.15 mg for children <30 kg; 0.3 mg for older children) and instructed in its use. Follow-up with the primary care physician for allergist referral and a medical alert bracelet is also recommended.

Diseases of the Larynx

The larynx and vocal cords are commonly involved with obstructing airway disease. Many obstructing conditions are congenital lesions, including laryngomalacia, laryngeal web, and vocal cord paralysis. Acquired lesions include laryngeal papillomas.

Congenital lesions. Laryngomalacia is the most common cause of chronic stridor in infants and accounts for 60% to 75% of congenital laryngeal anomalies. It is a result of incomplete development of the supporting cartilage of the larynx. With inspiration, the long floppy epiglottis, arytenoids, and aryepiglottic folds are drawn into the larynx and create a partial obstruction (Fig. 162.6). Baseline inspiratory stridor begins several weeks after birth and worsens with supine positioning, neck flexion, and increased respiratory effort (crying, URI). Laryngomalacia is rarely associated with significant respiratory distress, feeding difficulties, or failure to thrive. Most patients experience complete resolution of symptoms by 2 years of age and are treated conservatively. Fiberoptic bronchoscopy is used to confirm the diagnosis and identify the existence of coexisting or synchronous anomalies (e.g., subglottic stenosis, tracheomalacia). Surgical intervention is warranted in severe cases in which the child suffers from apneic events, respiratory compromise, pulmonary hypertension, or failure to thrive.[8]

Vocal cord paralysis is the second most common cause of chronic stridor in infants. Bilateral vocal cord paralysis results in severe respiratory distress and stridor and typically requires intervention for airway

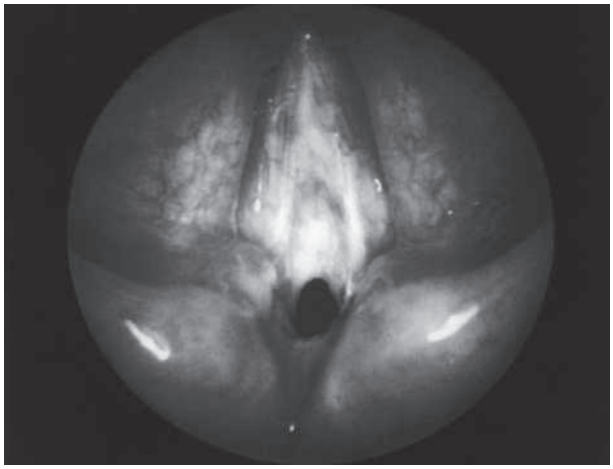

Fig. 162.7 Large Laryngeal Web.

protection; it is often associated with serious central nervous system abnormalities, such as Arnold-Chiari malformations. Unilateral vocal cord paralysis is usually left-sided and related to traction on the left recurrent laryngeal nerve at birth or compression from mediastinal structures. Infants with unilateral vocal cord paralysis have a hoarse weak cry, feeding difficulties, and aspiration. Stridor often worsens with distress and improves with positioning the affected side down. Most children improve with voice and speech therapy and do not require invasive treatment.

A laryngeal web results from failure of complete canalization of the airway. Most webs lie between the cords and appear as a partial anterior fusion (Fig. 162.7). The spectrum of symptoms reflects the size of the web. Small webs may cause a hoarse weak cry and mild stridor. Larger, more complete webs are associated with aphonia and severe respiratory distress.

Congenital laryngotracheal (subglottic) stenosis is a result of a congenital defect in canalization of the subglottic trachea. Deformity of the cricoid ring is usually seen. Infants with severe stenosis have stridor at birth. Milder lesions may be asymptomatic until additional obstruction from infection or inflammation occurs. Subglottic stenosis is also an acquired condition that occurs after prolonged intubation or blunt trauma to the neck.

A subglottic hemangioma is a less common cause of stridor and subglottic airway obstruction in infants. The infant is usually asymptomatic at birth, but stridor (which may be biphasic) and cough develop within the first few weeks to months of life. Symptoms generally peak at 6 months as a result of rapid growth of the infant and hemangioma during the first months of life. Respiratory symptoms worsen with crying and agitation. Cutaneous hemangiomas are seen in approximately 50% of cases (often in a beard distribution; Fig. 162.8). Hemangiomas of the airway may be seen on plain film as an asymmetric lesion along the tracheal air column. Endoscopy is diagnostic (Fig. 162.9).

Acquired lesions

Laryngeal papillomas. Laryngeal papillomas are the most common benign laryngeal neoplasm in children and the second most common cause of hoarseness. They are typically acquired after exposure to human papillomavirus via vertical transmission from an infected mother. Multiple lesions are generally present and usually occur in the vocal cords but may involve any part of the larynx. Hoarseness, abnormal cry, and inspiratory stridor commonly occur by 3 to 4 years of age. Symptoms can progress to severe respiratory distress as the lesions enlarge and obstruct the larynx. Multiple ablation procedures are often required and malignant transformation may rarely occur.

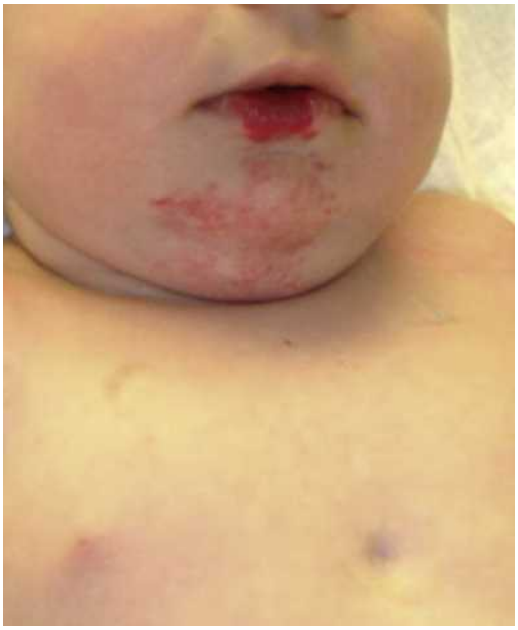

Fig. 162.8 2-month-old infant with a facial hemangioma in the beard distribution. This patient was also found to have a subglottic hemangioma. (From O-Lee TJ, Messner A. Subglottic hemangioma. *Otolaryngol Clin North Am.* 2008;41:903–911, viii–ix.)

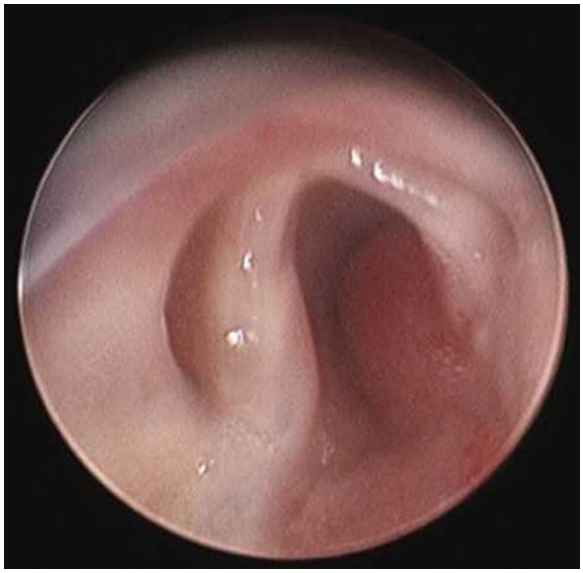

Fig. 162.9 Subglottic Hemangioma Seen on Endoscopy. (From Ida JB, Thompson DM. Pediatric stridor. *Otolaryngol Clin North Am* 2014;47:795–819.)

Subglottic tracheal disease. The subglottic trachea is the origin of the high-pitched inspiratory sound commonly associated with upper airway obstruction. The subglottic space is elliptical-shaped and completely surrounded by the cricoid ring. This anatomy predisposes this part of the airway to obstruction. Subglottic narrowing or stenosis can result from a congenital anomaly, inflammation from infection, and trauma associated with prolonged intubation.

Viral Croup

Foundations. Croup (laryngotracheobronchitis) is the most common infectious cause of upper airway distress and obstruction

TABLE 162.2 Simplified Differential Diagnosis of Upper Airway Symptoms

Condition	Distinguishing Features
Anaphylaxis	Abrupt onset, associated trigger, other organ system involvement
Croup	URI symptoms, acute onset of barky cough, stridor, no distinct positional preference
Bacterial tracheitis	Fever, toxicity, prolongation of symptoms, lack of response to croup treatment
Epiglottitis	Drooling a predominant symptom, patient desire to remain sitting. Muffled voice (but hoarseness typically absent), cough absent, anxiety
Retropharyngeal abscess	Fever, toxicity, torticollis, neck pain/stiffness, +/– drooling, +/– muffled voice
Foreign body aspiration	History of choking episode, absence of URI symptoms or hoarseness, +/– drooling
Peritonsillar abscess	Sore throat, trismus, muffled voice, pharyngeal erythema and edema, uvular deviation

URI, Upper respiratory tract infection.

in childhood. It accounts for more than 90% of all cases of stridor in children. It usually occurs between 6 and 36 months of age but can be seen from early infancy through school age. Croup is rare in children greater than 6 years of age. Parainfluenza virus accounts for 50% to 75% of cases; respiratory syncytial virus, influenza A and B viruses, and rhinovirus cause the remainder. Measles can also cause croup and should be considered in unvaccinated children. The clinical picture of croup associated with influenza is more severe than with parainfluenza. Croup is caused by inflammation, exudates, and edema of the loosely adherent mucosal and submucosal tissues of the subglottic space. The inflamed mucosa expands into the airway lumen because the cricoid cartilage forms a complete cartilaginous (nonexpanding) ring in this part of the trachea. In severe disease, the airway may be narrowed to as little as 1 to 2 mm.

Clinical features. Croup is diagnosed clinically. A 1- to 3-day prodrome of mild fever and URI symptoms is followed by a fairly abrupt onset of barky cough, hoarse voice, and high-pitched inspiratory stridor. The barky cough is the predominant presentation in infants and young children, whereas older children tend to present primarily with hoarseness. The cough lasts an average of 3 days and all symptoms typically resolve in 4 to 7 days. A simplified differential diagnosis for croup is shown in Table 162.2. Scoring systems have been developed for the assessment of croup; these include an evaluation of worsening stridor, retractions, cyanosis, heart rate, and respiratory rate. Although a formal croup score is often not assigned in many clinical settings, the determination of mild, moderate, or severe croup should be based on careful evaluation of these five signs as well as on mental status and air movement. See Fig. 162.10 for a clinical treatment algorithm based on croup severity.

Mild croup is characterized by an intermittent barky cough, stridor with agitation but not at rest, mild tachypnea, and tachycardia. A child with mild croup is minimally distressed and well hydrated and has normal mental status. Moderate croup is characterized by audible stridor at rest, worsening stridor with agitation, barky cough, and increased work of breathing (retractions, tachypnea, and tachycardia). A patient with moderate croup may be fussy but is alert, interactive, and comforted by parents. Hypoxia is rare in mild or moderate croup. When hypoxia is seen, it may signify concomitant lower respiratory disease, another disease process, or severe croup. Mild croup occurs in 85% of children; fewer than 1% of children have severe croup. Laboratory tests are nondiagnostic, and radiographic studies of the neck do not change management nor are they sensitive or specific. The classic x-ray finding is a steeple sign—a tapered narrowing of the normal shouldered appearance of the subglottic trachea—which can be seen in those with croup and also in patients without the disease.

Management. Glucocorticoids reduce symptoms, decrease the need for aerosolized epinephrine, and result in fewer readmissions to the ED and shorter ED and hospital stays. Oral dexamethasone (0.15 mg/kg to 0.6 mg/kg, max 10 to 16 mg) is the preferred agent and can improve symptoms within two hours. The IV form of dexamethasone is more concentrated than the oral formulation and can be given orally. Severe cases or patients with oral intolerance may be given the same dose IM/IV. Lower dosing (0.15 mg/kg) has been shown to be as effective as a higher dose (0.6 mg/kg) in most cases. However, there is some evidence that patients with more severe obstruction benefit from the higher dose.[15,16] Inhaled budesonide (2 mg/dose) is also effective but more expensive, so it is not routinely used. Prednisolone may be as effective as dexamethasone in milder cases but should not be used in patients with significant symptoms due to the shorter duration of action.[9]

Aerosolized epinephrine, which reverses edema and relieves acute symptoms through vasoconstriction in the subglottic mucosa, should be given to children with stridor at rest or with significant respiratory distress. It is a temporizing measure with a quick onset of action (<10 minutes) and a duration of up to 2 hours. The L form of epinephrine is the active isomer and has the same degree of safety and efficacy as racemic epinephrine; either form may be used. Nebulized L-epinephrine (1:1000 solution) dosing is 0.5 mL/kg (max, 5 mL) *or* racemic epinephrine (2.25% solution) is 1.125 mg/kg (max, 11.25 mg/dose or 0.5 mL/dose); either should be diluted in 2 to 3 mL of NS and given via nebulizer over 15 minutes. Patients with stridor at rest who receive inhaled epinephrine should be observed in the ED to ensure no recurrence of severe symptoms. The amount of time needed to observe these patients is controversial, but patients are unlikely to deteriorate beyond 3 hours. We recommend that patients be observed in the ED for 2 to 3 hours after epinephrine administration to ensure that stridor and respiratory distress do not recur.

Heliox (i.e., concentrations of helium: oxygen at 80:20, 70:30, or 60:40) may improve resistance to gas flow and thus decrease work of breathing in young children with moderate to severe croup. Heliox has been shown to improve symptoms temporarily (in the first hour), but the benefits are not sustained (after two hours). Heliox (with nebulized epinephrine) may be considered to avoid intubation in young children with moderate to severe increased work of breathing, although studies to date have not been powered to assess its effect on this rare outcome.[10] Cool mist has not been demonstrated to improve outcomes and there is insufficient evidence to support its routine use.

Most children with croup can be safely discharged, provided respiratory distress and resting stridor have resolved.[11] A small percentage of patients with croup require admission. Several factors may impact the decision to admit a child with moderate croup, such as the severity of symptoms at initial evaluation, persistence of respiratory distress, stridor at rest, hypoxia, poor response to treatment, dehydration, history suggesting airway disease or recurrent croup, young age (<6 months), difficulty with feeds, and poor social support (Box 162.1).

Severe croup is rare (<1%) and associated with signs of impending airway obstruction and respiratory failure—fatigue, hypoxia, hypercapnia, abnormal mental status, and extreme respiratory distress. In the rare case in which intubation is required, an endotracheal tube (ETT) at least a half-size smaller than expected for the child's size is often necessary. If the ETT that can be passed is too small to allow adequate ventilation, tracheostomy may be required.

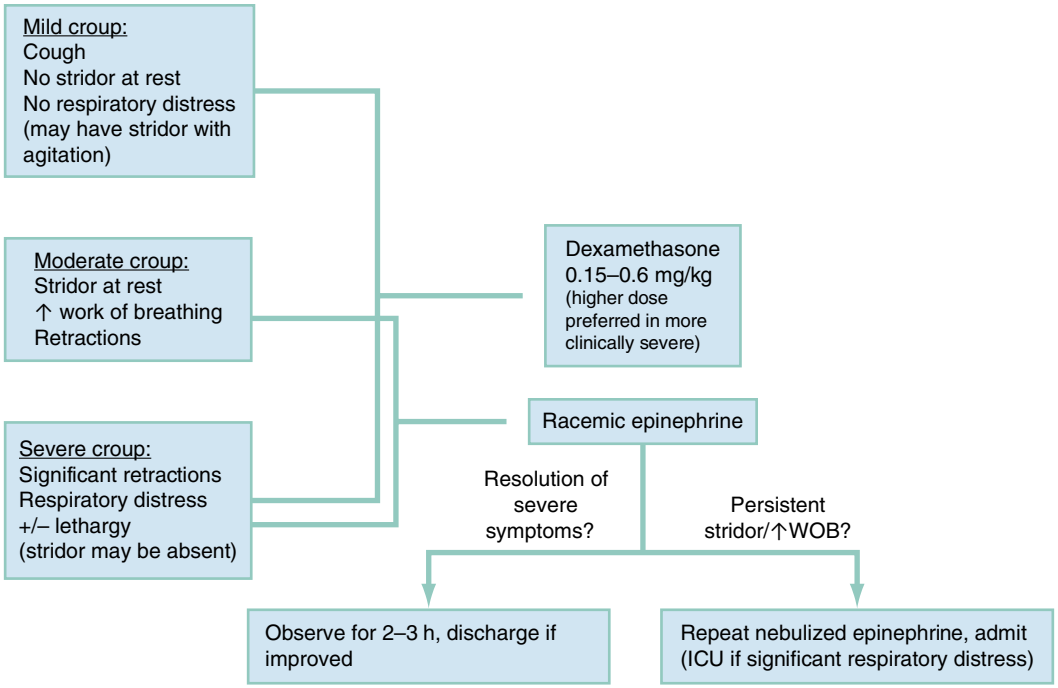

Fig. 162.10 Simplified Croup Treatment Algorithm Based on Presenting Signs, Symptoms, and Severity. (Rose E, ed. *Pediatric Emergencies: A Practical, Clinical Guide*. New York, NY: Oxford University Press; 2021)

BOX 162.1 Croup: Indications for Admission

Severe respiratory distress or failure
Unusual symptoms (hypoxia, hyperpyrexia)
Dehydration
Persistence of stridor at rest after aerosolized epinephrine and steroids
Persistence of tachycardia, tachypnea
Complex past medical history (prematurity, pulmonary, cardiac disease)

Spasmodic or Atypical Croup

Spasmodic or atypical croup is a somewhat indistinct clinical entity with many features that overlap those of viral croup. There is no consensus on the definition, but the term *atypical croup* is often used to describe numerous recurrent episodes or croup in children outside the expected age group. An association with allergy, atopy, airway hyperreactivity, asthma, and gastroesophageal reflux has been described. Airway lesions (most commonly subglottic stenosis) may be present and contribute to the pathophysiology.[12]

Diseases of the Trachea

Obstruction of the trachea distal to the subglottic space can be a result of congenital and acquired lesions.

Congenital lesions

Tracheomalacia. Tracheomalacia results from abnormally soft, undeveloped supporting cartilage of the tracheal rings. Primary or congenital tracheomalacia is seen in otherwise healthy term newborns, as well as in infants with conditions such as Down syndrome and DiGeorge syndrome. Healthy infants with isolated disease have a good prognosis because symptoms improve as the cartilage strengthens with growth. Secondary disease is associated with extrinsic compression of the trachea (e.g., vascular rings, tumor, nodes, and cysts). Tracheomalacia should be suspected in patients with a history of stridor that increases during the first few weeks of life and worsens with agitation, supine positioning, and infection. Plain radiographs are nondiagnostic but dynamic studies, such as fluoroscopy, may be helpful. Patients should follow up with primary care for outpatient monitoring of symptoms.

Tracheal stenosis. Tracheal stenosis is a congenital anomaly that results from complete tracheal rings. Infants have persistent stridor and respiratory distress. Because the tracheal diameter is fixed, symptoms worsen with agitation and age.

Tracheal compression. Tracheal compression may also occur externally from vascular anomalies or mediastinal lesions (Fig. 162.11). A vascular ring is an anomaly of the aortic arch and related vessels in which a ring of vessels encircles the trachea, esophagus, or both. Examples of vascular rings include a double aortic arch, right aortic arch with a persistent left ligamentum arteriosum, anomalous innominate artery and anomalous left common carotid artery, left pulmonary artery, or aberrant right subclavian artery. Stridor, wheezing, dyspnea, and cough are common initial symptoms and are frequently mistaken as a URI. Many patients with vascular rings have additional cardiovascular anomalies and further work up is often indicated. Other associated mediastinal lesions that can compress the trachea include esophageal duplication cysts, bronchogenic cysts, mediastinal cyst, teratomas, lymphomas, and lymphadenopathy.

Vascular rings. Infants with vascular rings typically present with persistent, unexplained respiratory and feeding problems. A chest radiograph revealing an abnormal (right-sided) aortic arch may suggest the diagnosis in the ED; barium esophagography has traditionally been considered to be the single most important diagnostic procedure in patients with complete vascular rings (Fig. 162.12). Additional studies, such as CT, MRI, angiography, or bronchoscopy, may be indicated based on symptoms and associated risk factors for co-morbidities.

Bacterial tracheitis

Foundations. Bacterial tracheitis, also referred to as bacterial laryngotracheobronchitis, pseudomembranous croup, is a serious cause of stridor and airway obstruction in children. The epidemiology of upper airway infections has changed since widespread immunization for *H. influenzae* and the use of steroids for croup. This has increased the relative frequency of bacterial tracheitis as a cause of respiratory

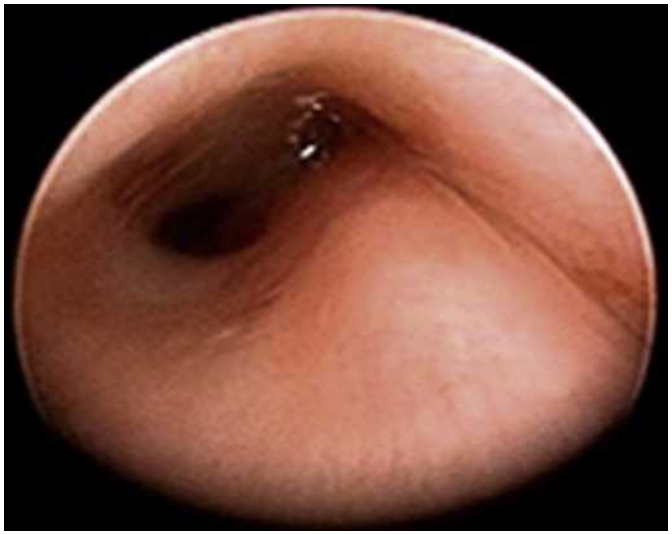

Fig. 162.11 External Vascular Compression of the Trachea Seen on Endoscopy. (From Ida JB, Thompson DM. Pediatric stridor. *Otolaryngol Clin North Am.* 2014;47:795–819.)

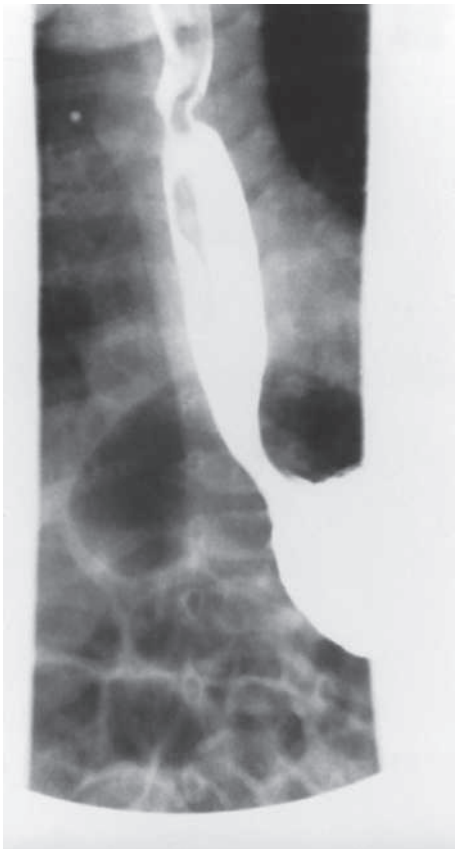

Fig. 162.12 Barium Esophagogram. Note the indentation of the esophagus caused by an encircling vascular ring.

failure from upper airway infection. Bacterial tracheitis is three times more likely to cause respiratory failure than epiglottis and viral croup combined. Bacterial tracheitis usually affects younger children but may occur at any age.

The pathogenesis of bacterial tracheitis is severe inflammation of the tracheal epithelium and the production of thick mucopurulent secretions. The lining of the trachea forms a loosely adherent membrane that may become necrotic and slough, occluding the lumen. Microabscesses may be present in the tracheal mucosa. Perforation and pneumomediastinum have been described. Traditionally, *S. aureus* (including MRSA) has been the organism primarily responsible for bacterial tracheitis, but many causative bacteria have been reported. Fungal tracheitis in immunocompromised individuals portends a grave prognosis.

Clinical features. The classic presentation of bacterial tracheitis is a toxic child with high fevers and rapidly worsening stridor that fails to improve with racemic epinephrine. Symptoms may overlap with those of croup and epiglottitis (Table 162.3). Most patients experience a viral prodrome of fever, barky cough, and stridor. These symptoms typically intensify as the bacterial superinfection grows on damaged tracheal epithelium. The child appears toxic, and signs of airway obstruction and respiratory failure may develop acutely. Less commonly, primary bacterial tracheitis may occur with a fulminant onset and rapid progression to acute respiratory distress. Features that suggest bacterial tracheitis include a viral prodrome followed by acute decompensation, symptoms atypical for croup (e.g., high fever, cyanosis, severe distress), poor response to the usual treatment of croup (e.g., nebulized epinephrine), and inspiratory and expiratory stridor. Changes in bacteriologic profiles have produced less virulent but more prolonged infections, increasing the diagnostic challenge.[13]

Diagnostic testing. The evaluation of a toxic-appearing child with bacterial tracheitis should be conducted expeditiously. Laboratory tests are nondiagnostic. The white blood cell count is often normal or slightly elevated, and blood cultures are rarely positive in bacterial tracheitis. Lateral and anteroposterior views of the neck and chest may be helpful. Findings on plain radiographs include subglottic narrowing, a ragged edge of the usually smooth tracheal air column, and a hazy density within the tracheal lumen, mimicking the appearance of airway foreign bodies. The epiglottis and supraglottic structures appear normal. In addition, the chest radiograph may reveal coexisting pneumonia. Bronchoscopy is both diagnostic and therapeutic and should be performed emergently (Fig. 162.13); this procedure allows visualization of the supraglottic structures and larynx, exclusion of other diseases, suctioning of tracheal secretions and debris, and establishment of an artificial airway.

Management. Severe distress may rarely require immediate intubation and suctioning in the ED, although airway management in the operating room is preferred. Endoscopic tracheal débridement may result in significant clinical improvement and allow the child to be managed without intubation. Serial endoscopy may be needed to manage secretions. Endotracheal intubation is required in children with respiratory distress and hypoxia. Patients should be admitted and receive supplemental oxygen, fluid resuscitation, and broad-spectrum antibiotics.

Broad antibiotic coverage is recommended with an antistaphylococcal agent (e.g., vancomycin, clindamycin) plus a third-generation cephalosporin (e.g., ceftriaxone). Alternatively, an antistaphylococcal agent plus ampicillin-sulbactam may be used. In penicillin-allergic patients, vancomycin or clindamycin plus a quinolone should be administered (ciprofloxacin if *Pseudomonas* is a concern or levofloxacin if *Streptococcus pneumoniae* is suspected). Although 7 to 10 days is usually sufficient, longer courses of antibiotics may be necessary for children with extra-tracheal infection or persistent tracheal inflammation. Complications of bacterial tracheitis include toxic shock syndrome, septic shock, renal failure, postintubation pulmonary edema, acute respiratory distress syndrome, and the need for reintubation. Residual subglottic stenosis has been described.

TABLE 162.3 Comparison of Croup, Epiglottitis, and Bacterial Tracheitis

Parameter	Croup	Epiglottitis	Bacterial Tracheitis
Peak age	6 months–3 years	5–7 years, but can be seen throughout childhood	3–5 years, but seen throughout childhood
Pathologic features	Subglottic inflammation, edema	Inflammation and edema of the epiglottis, aryepiglottic folds	Bacterial superinfection with inflammation of the tracheal mucosa, copious mucopurulent secretions obstructing the trachea
Organisms	Parainfluenza virus, RSV, adenovirus, influenza	*Haemophilus influenzae*, group A beta-hemolytic streptococcus, *Staphylococcus aureus, Streptococcus pneumoniae*	*S. aureus* or mixed flora
Clinical features	Onset follows URI prodrome consisting of croupy cough, hoarse voice, low-grade fever, inspiratory stridor	Rapid progression of high fever, toxicity, drooling, stridor	Several-day prodrome of croup-like illness progressing to toxicity, inspiratory and expiratory stridor, marked distress
Laboratory and radiographic findings	Steeple sign on PA view of the neck or normal	Thumbprint sign on the lateral aspect of the neck, thickened aryepiglottic folds, loss of air in the vallecula	Normal upper airway structures, shaggy tracheal air column
Management	Steroids uncommon, aerosolized epinephrine	Intubation, antibiotics	Intubation common, antibiotics rare, intubation

PA, Posteroanterior; *RSV,* respiratory syncytial virus; *URI,* upper respiratory infection.

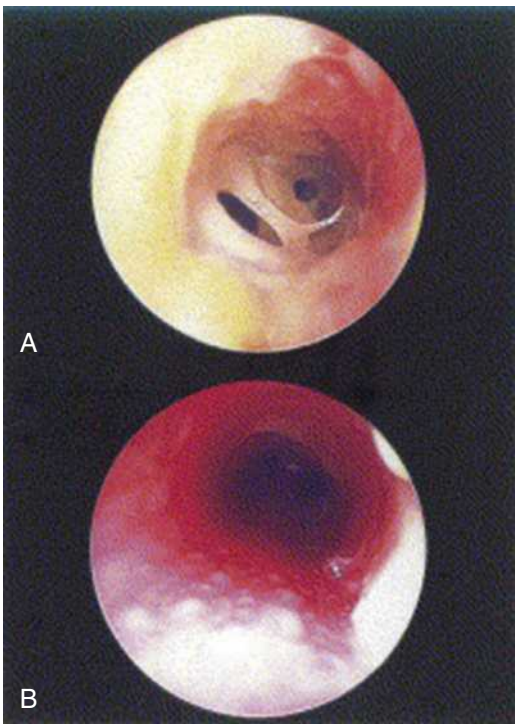

Fig. 162.13 Thick Tracheal Membranes Seen on Rigid Bronchoscopy in Bacterial Tracheitis. (A) Thick adherent membranous secretions. (B), The distal tracheobronchial tree is unremarkable. (From Salamone FN, Bobbitt DB, Myer CM, et al. Bacterial tracheitis reexamined: is there a less severe manifestation? *Otolaryngol Head Neck Surg.* 2004;131:871–876.)

Foreign Bodies

Airway foreign body

Foundations. Asphyxia from airway obstruction by an airway or esophageal foreign body is a common cause of death in children. Round foods (e.g., peanuts, grapes, raisins, and hot dogs) are especially common. Conformable objects are the most difficult to manage and remove, and balloons, including those made from hospital gloves, are the objects most likely to result in death.

Large objects that lodge in the upper airway and trachea cause dramatic signs of upper airway obstruction (e.g., dyspnea, drooling, stridor, cyanosis) and carry the worst prognosis. Objects that pass through the subglottic space typically will lodge in a bronchus, usually the right mainstem bronchus, or in a more terminal part of the airway. These objects may be "coughed up" again and cause sudden upper airway obstruction.

Clinical features. An upper airway foreign body can cause partial or complete obstruction. Clinical signs of complete obstruction include poor air exchange, inability to speak, ineffective cough, severe distress, and cyanosis. Foreign body aspiration that has settled in the lower airways may have subacute symptoms, such as unilateral wheeze, or may present later (days to years) as recurrent pneumonia. The sensitivity of a witnessed choking episode varies in the literature.

Diagnostic testing. In a child with an aspirated foreign body in the upper airway, there is often no time, nor is it prudent, to perform diagnostic imaging. In a stable patient, a portable lateral neck radiograph and chest radiograph may be obtained as long as the patient is allowed to maintain a position of comfort. Radiographic findings suspicious for foreign body aspiration include radiopaque materials, mediastinal shift, emphysema, and atelectasis. A normal chest radiograph cannot rule out a nonradiopaque foreign body. CT scan and virtual bronchoscopy (a reformatted three-dimensional CT image that generates intraluminal views of the airway and bronchi) may be used to aid diagnosis in equivocal cases. Diagnostic flexible bronchoscopy is indicated with significant clinical suspicion of foreign body aspiration, despite normal imaging.

Management. An acute obstructing upper airway foreign body requires emergent intervention with basic life support maneuvers. Choking infants younger than 1 year should be given five back blows delivered between the shoulder blades, followed by five chest thrusts with the head held below the trunk. Abdominal thrusts should not be performed in infants and may injure abdominal organs. Blind finger sweeps may push the object further into the airway and are no longer recommended.

The Heimlich maneuver is used in conscious children older than 1 year; chest compressions should be delivered to unconscious children. If there is no chest rise with assisted ventilation with a bag-mask device, advanced airway techniques are indicated. Laryngoscopy should be performed to attempt visualization and foreign body removal with pediatric Magill forceps. If the obstructing foreign body cannot be visualized, it may be pushed distally into the right mainstem bronchus with an ETT to ventilate the non-obstructed portion of the lung. Recruiting additional expertise from an otolaryngologist, anesthesiologist, or general surgeon may be needed.

A patient who is adequately oxygenated and is moving air should be initially allowed to maintain a preferred position, continue coughing to clear the obstruction, and breathe spontaneously until operative management can be arranged. Paralysis with rapid sequence induction should be avoided if the patient is maintaining a patent airway; with paralysis, the airway tone may be lost, and a partial obstruction can become complete.

Can't Intubate, Can't Ventilate Scenari. Surgical cricothyrotomy is not generally recommended for infants and young children younger than 8 to 10 years. The anatomy changes with growth (i.e., the larynx is high and cricothyroid membrane small), and it may be difficult to locate pertinent anatomy until a child is of school age.[14] Trachea compressibility also increases complication risk. Needle cricothyrotomy may be performed in children, but significant CO_2 retention limits its effectiveness; it is a temporizing measure used as a bridge to a more definitive, secure airway.

Commercial percutaneous transtracheal ventilation kits are available, but homemade kits can be constructed using tools readily accessible in the ED. A 14- to 18-gauge angiocatheter (the size of the catheter does not affect the rate of turbulent gas flow) is inserted in the cricothyroid membrane and connected to a 3-mL syringe (without the plunger) to a 7.5-mm ETT adaptor (or a 3.0-mm ETT connector directly to the angiocatheter). These homemade kits are rigid and may easily become dislodged. Alternative setups include using IV tubing—attaching IV tubing to the angiocatheter, cutting the tubing, and attaching a 2.5-mm ETT connector—or directly connecting oxygen tubing to the catheter with a Y connector or three-way stopcock. Bag-mask ventilation (recommended in children <5 years) can be performed through the ETT adaptor at 10 to 12 breaths/min to minimize barotrauma by allowing for passive exhalation. Percutaneous transtracheal ventilation (in children ≥5 years) is given at an oxygen flow rate of 1 L/min/year of age with a 1:4 inspiration-to-expiration ratio (I:E). Adults should receive oxygen from the wall source at 15 L/min (50 to 58 psi) and children at a rate of 10 to 12 L/min (25 to 35 psi). Complete airway obstruction does not allow for passive exhalation and necessitates a reduction of bag-mask ventilation rate to five or six breaths/min or an I:E ratio of 1:8 to 10 as a temporizing measure. Complications of needle cricothyrotomy include barotrauma and damage to adjacent structures. See Chapter 156 for further discussion.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 162: QUESTIONS AND ANSWERS

1. Which of the following is the most common cause of upper respiratory obstruction in childhood?

a. Airway foreign body
b. Bacterial tracheitis
c. Croup
d. Epiglottitis

Answer: c. Although all the choices may lead to symptoms of airway obstruction in children, the most common cause of upper airway obstruction is viral croup.

2. A 3-year-old girl presents at 2 AM with complaints of a barky cough, which started abruptly overnight. Vital signs are heart rate, 140 beats/min, respiratory rate, 40 breaths/min, and temperature, 100.1°F (38°C). She has no history of asthma or wheezing. She appears to be in moderate distress and has audible stridor. Indications for admission include which of the following?

a. Low-grade fever
b. Prior history of croup
c. Stridor at rest
d. Severe dehydration

Answer: d. Indications for admission of patients with croup include severe respiratory distress or failure, unusual symptoms (hypoxia and hyperpyrexia), anything but mild dehydration, persistence of stridor at rest after aerosolized epinephrine and steroids, persistence of tachycardia or tachypnea, and complex medical history (e.g., prematurity, pulmonary or cardiac disease).

3. A 5-year-old immunized boy presents with severe stridor at rest, low-grade fever, and nasal congestion. His family reports a barky-sounding cough. After initiating vaporized epinephrine, he appears well and is in no distress. The parents are asking about discharge. Which of the following would be the most appropriate next step in management?

a. Administer dexamethasone, observe the patient for 2 to 3 hours, and discharge if well.
b. Admit the patient for overnight observation.
c. Allow the patient to go home.
d. Allow the patient to go home with a prescription of steroids.

Answer: a. The child has croup and, after being treated with nebulized epinephrine, should be observed for recurrent stridor after 2 hours. If the child is well, is in no respiratory distress, has a good hydration status, and is able to access emergency and follow-up care, he or she can then be safely discharged.

4. What is the ideal head position to assess a pediatric soft tissue radiograph of the neck for upper airway pathology?

a. Extension during inspiration
b. Flexion
c. Flexion during inspiration
d. Neutral

Answer: a. Gentle extension of the head gives the most accurate images, avoiding the artificial soft tissue widening that can be seen in flexion. Inspiration, if possible, allows maximal distention of the pharynx and the best viewing of soft tissue structures defined by an air–soft tissue interface.

5. Which of the following factors is least consistent with the diagnosis of peritonsillar abscess?

a. Muffled, hot potato voice
b. Pain radiating to the ear
c. Patient 3 years of age
d. Patient 13 years old
e. Trismus

CHAPTER 162: QUESTIONS AND ANSWERS—cont'd.

Answer: c. Peritonsillar abscess more commonly occurs in older children and teenagers, whereas retropharyngeal abscess is more common in a younger population. All the other signs or symptoms listed are consistent with peritonsillar abscess, along with deviation of the uvula away from the abscess side.

6. A 3-year-old immunized girl presents after a brief viral illness with progressive dyspnea, ill appearance, and high fever. The child is relatively still, appearing as if she is trying not to cough. Stridor is heard, and she does not respond to croup therapy. You notify the operating room, where the patient undergoes bronchoscopy, with suctioning and airway placement. Culture results are most likely to grow which of the following organisms?

a. *Bacteroides fragilis*
b. *Candida albicans*
c. Parainfluenza
d. *Staphylococcus aureus*
e. *Streptococcus pneumoniae*

Answer: d. The case described is consistent with bacterial tracheitis. Although *Candida,* parainfluenza, and *Streptococcus* have all been reported, *S. aureus* is most common. Broad-spectrum antibiotics are appropriate, with an emphasis on covering *S. aureus*.

Pediatric Lower Airway Obstruction

Richard J. Scarfone and Jeffrey A. Seiden

ASTHMA

KEY CONCEPTS

- No single asthma score has been universally adopted to assess the degree of illness or treatment responses. However, most scores include some combination of respiratory rate, degree of wheezing, inspiratory-to-expiratory ratio, use of accessory muscles, and oxygen saturation.
- Chest x-ray (CXR) is not required for wheezing children, even for those who are febrile, are wheezing for the first time, or require hospitalization. CXR is indicated for those with a history of choking, focal chest findings, extreme distress, subcutaneous emphysema, diagnostic uncertainty relative to respiratory illness, or with clinical findings suggestive of a cardiac etiology.
- Albuterol delivered by metered-dose inhalers with spacers (MDI-S) is as effective as that delivered by nebulizers for children with acute asthma. The mode of delivery is largely chosen on the basis of cost and ability to achieve the goal of three treatments within the first hour of care. Per the 2007 National Heart Lung and Blood Institute guidelines, a high dose (4–12 puffs) of a short-acting beta-agonists (SABAs) metered-dose inhaler (MDI) with a spacer has "equivalent bronchodilation" to nebulized treatment.
- Levalbuterol does not lead to better emergency department (ED) outcomes compared with racemic albuterol. Racemic albuterol, at a substantially lower cost, should remain the drug of choice for children with acute asthma exacerbations.
- Dexamethasone is as effective as prednisone in the ED treatment of acute asthma. Dexamethasone is associated with fewer doses, less vomiting, and greater compliance.
- Continuously nebulized albuterol, corticosteroids, magnesium sulfate, and parenteral SABA are cornerstones of therapy for moderately to severely ill children with asthma.

Foundations

Background and Importance

A recent national survey found that one in 12 children had asthma; however, the prevalence among non-Hispanic black children was 16%.[1] Asthma is associated with significant morbidity, with approximately 17% of children with asthma requiring emergency department (ED) or Urgent Care management and 5% needing to be hospitalized annually[1]

Anatomy, Physiology, and Pathophysiology

Asthma is a lower airway disease marked by bronchoconstriction, mucosal edema, and pulmonary secretions. Upper respiratory infections (URIs) associated with copious rhinorrhea, a common trigger of an asthma exacerbation, may significantly increase airway resistance in young children. Because children have compliant chest walls and horizontally located ribs, their ability to use the thorax to increase tidal volume is limited; thus, ventilation is highly dependent on diaphragmatic movement. Also, as functional residual lung capacity increases with age, minute ventilation is largely rate-dependent in young children and may quickly lead to fatigue. An infant younger than 12 months has an oxygen consumption index that is double that of an adult. Increased airway resistance and a compliant chest wall predispose infants to tachypnea, increased work of breathing, and increased oxygen consumption. As a result, the infant with respiratory distress may rapidly develop hypoxemia, precipitating bradycardia and cardiopulmonary arrest.

Clinical Features

All acutely wheezing children arriving for ED care should be attached to a cardiorespiratory monitor and have oxygen saturation determined by pulse oximetry. For children with hypoxia, supplemental oxygen should be provided while the emergency clinician begins the clinical assessment.

History

To initiate appropriate therapy quickly, based on the degree of illness, a concise history should be obtained upon patient arrival, followed by a physical examination that focuses on the cardiopulmonary system. An abbreviated history should include questions about the child's age, duration and severity of symptoms, recent medication use, and hospitalizations, including the need for intensive care unit (ICU) care or intubation. The parents should be able to relate how the severity of this attack compares with that of previous exacerbations. A history of difficulty sleeping, eating, or speaking suggests a moderate to severe exacerbation. Names, doses, and frequency of asthma medications, as well as preexisting conditions, should be documented.

After starting therapy, a more comprehensive history should include questions about asthma triggers, such as URIs, cigarette smoke, allergies, and exercise. Frequent ED visits or hospitalizations due to asthma may indicate poorly controlled asthma. The impact of asthma on the child's life may be gauged by the monthly frequency of daytime or nighttime symptoms, including cough, as well as missed days of school or restricted activity. A child with persistent asthma marked by frequent symptoms should be receiving daily anti-inflammatory therapy. Family and social histories should focus on asthma, cystic fibrosis, or atopic disease, and on the adequacy of support systems at home.

Physical Examination

The targeted examination includes assessing vital signs, mental status, and cardiopulmonary systems. A child who is anxious, restless, or lethargic may be hypoxic. The oxygen saturation, sometimes referred to as the "fifth vital sign," should be determined soon after ED arrival for any child with respiratory distress, and supplemental oxygen should be provided for values 92% or less. No single asthma score has

TABLE 163.1 Differential Diagnosis of Asthma

Condition	Distinguishing Characteristics
Infectious	
Bronchiolitis	Infant, preceding upper respiratory infection, seasonal, no history of atopy, no family history of asthma
Laryngotracheobronchitis (croup)	Inspiratory stridor, barky cough, fever, response to humidified air or racemic epinephrine
Pneumonia	Focal wheezing, rhonchi, rales, grunting, fever
Tuberculosis	Diffuse adenopathy, weight loss, prolonged fever
Bronchiolitis obliterans	Prolonged cough or chest pain, inhalational exposure to toxin
Anatomic or Congenital	
Gastroesophageal reflux	Frequent emesis, weight loss, aspiration
Cystic fibrosis	Diarrhea, weight loss, chronic cough, salty sweat
Congestive heart failure	Rales, murmur, gallop, hepatosplenomegaly, cardiomegaly, or pulmonary vascular congestion on chest radiograph
Tracheoesophageal fistula	Choking, coughing, cyanosis with feeds
Mediastinal mass	Chest pain, mediastinal density on chest radiograph
Vascular ring	Stridor, cyanosis, apnea, high-pitched brassy cough, dysphagia
Acquired	
Foreign body aspiration	History of choking, toddler, asymmetric pulmonary examination, unilateral hyperinflation on chest radiograph
Anaphylaxis	Abrupt onset, urticarial rash, angioedema, sensation of throat "tightening," history of allergies

been universally adopted to assess the degree of illness or treatment responses. However, most scores include some combination of respiratory rate, degree of wheezing, inspiratory-to-expiratory ratio, use of accessory muscles, and oxygen saturation. These scores can assist in assessing the pretreatment degree of illness and tracking the response to therapy.

Assessing the work of breathing should include a careful inspection of the chest and neck; rarely, an associated pneumomediastinum or pneumothorax will produce subcutaneous air. Severely ill children may have wheezing that is audible without a stethoscope or have no wheezing ("silent chest") due to critically limited aeration. Asymmetric wheezing suggests pneumonia, pneumothorax, or a foreign body. More anxiety-provoking parts of the examination, such as otoscopy, should be delayed until treatment is well underway.

Differential Diagnoses

The differential diagnosis for childhood asthma includes bronchiolitis, laryngotracheobronchitis (croup), pneumonia, cardiac disorders (e.g., myocarditis), and gastroesophageal reflux (Table 163.1).

Bronchiolitis is the disease that is most commonly confused with asthma, and the two are not easily distinguished by examination findings alone. Children with bronchiolitis are typically younger and have symptoms associated with viral illness. Children believed to have bronchiolitis but who have some combination of food allergies, atopic dermatitis, or a strong family history of asthma should receive bronchodilator therapy to determine if their wheezing is reversible. Croup may have a viral or allergic cause and affects children from infancy through early school age. Clinical presentation is marked by an abrupt onset of a harsh barky cough and inspiratory stridor. Symptoms are typically worse at night. Asthma will not be manifested with stridor alone, but a subset of children with croup may present with stridor and wheezing. Children with pneumonia may sometimes present with a component of wheezing, although rales and rhonchi are the usual auscultative findings. Infants and young children with pneumonia may also have a high fever, cough, grunting, nasal flaring, retractions, and an asymmetric lung examination. Children with pulmonary edema secondary to congenital cardiac disease or myocarditis may present with wheezing and rales, often associated with a cardiac murmur and hepatomegaly. A history of weight loss and sweating with feeds may also indicate a cardiac etiology (see Chapter 165).

Diagnostic Testing

Most children with wheezing have asthma or bronchiolitis and do not need imaging or laboratory studies. Performing an arterial blood gas (ABG) analysis is rarely indicated for most children with acute asthma but may be useful among those with severe bronchospasm and signs of respiratory failure despite initial therapy. A high or apparently normal partial pressure of carbon dioxide ($Paco_2$ ≥40 mm Hg) in a child with hypoxia and retractions indicates impaired ventilation and impending respiratory failure. Alternatively, a young child who suddenly appears 'calm' with decreased respiratory effort may be developing hypercarbia and altered mental status from respiratory fatigue; an elevated $Paco_2$ helps differentiate this child from those finally able to rest from improved aeration. Measurement of the peak expiratory flow rate (PEFR) is a means of obtaining an objective assessment of exacerbation severity. However, up to two-thirds of children greater than 5 years are unable to complete PEFR testing during an asthma exacerbation. When feasible, the PEFR should be measured with the child standing and the best of three attempts recorded.

URIs marked by low-grade fever and coughing are common triggers of asthma exacerbations. These signs overlap with those found among children with pneumonia, making it difficult to determine the necessity of obtaining a CXR. No set of predictors has been found that can accurately identify children likely to have radiographic abnormalities. Emergency clinicians frequently obtain a CXR for children in the ED with asthma but rarely are pneumonia or other unsuspected diagnoses discovered, even if the child has never wheezed before.

It should not be routine practice to obtain a CXR for wheezing children, even for those who are febrile, wheezing for the first time, or requiring hospitalization. Performing chest radiography is indicated for those with a history of choking, focal chest findings, extreme distress, subcutaneous emphysema, or diagnostic uncertainty of respiratory versus or suspected cardiac etiology. Reassessment after SABA treatment to evaluate for resolution of focal findings may further decrease the need to obtain a CXR.

Management

Children can be stratified by degree of illness based on the physical examination (Fig. 163.1).

Mild Exacerbation

A mild exacerbation is characterized by alertness, slight tachypnea, expiratory wheezing only, a mildly prolonged expiratory phase, minimal accessory muscle use, and oxygen saturation of greater than 95%. Some children may have 1 or 2 of these features that are more

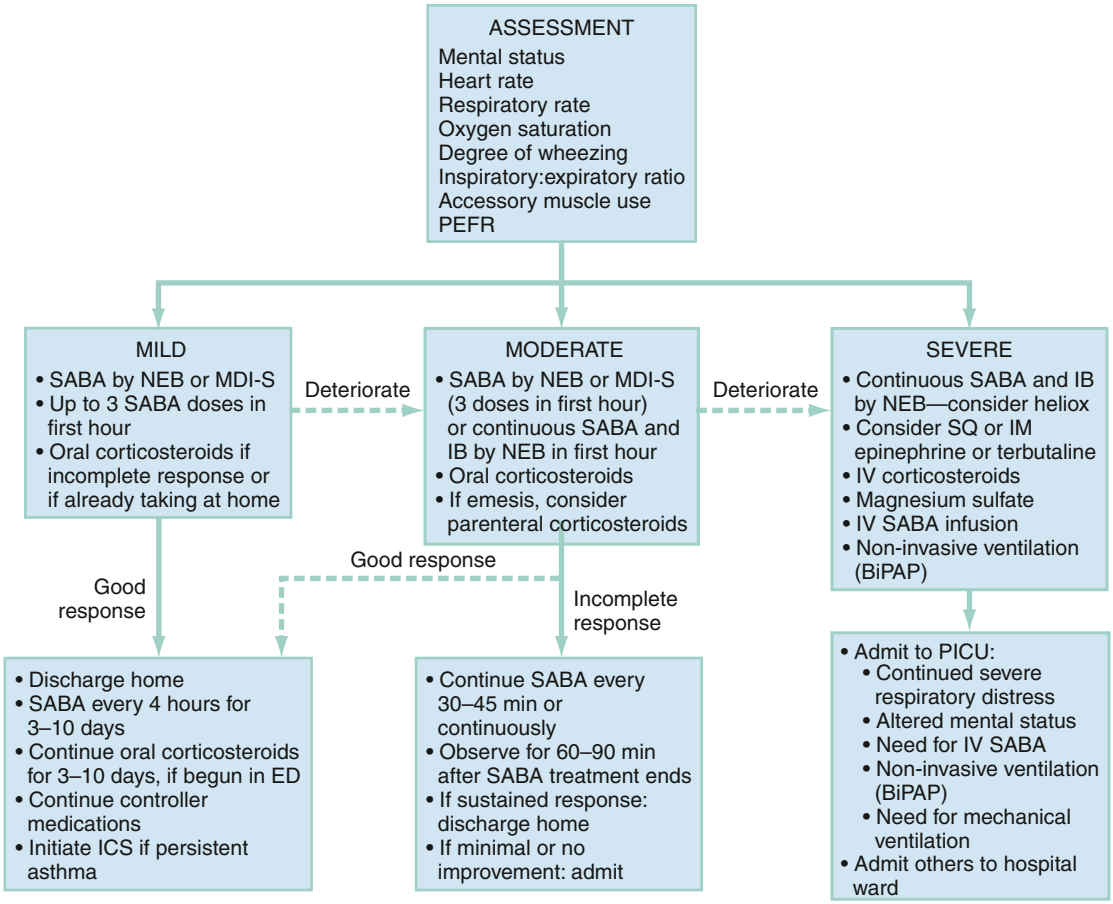

Fig. 163.1 Emergency Department Management of Acute Asthma. *ED,* Emergency department; *IB,* ipratropium bromide; *ICS,* inhaled corticosteroids; *IM,* intramuscular; *MDI-S,* metered-dose inhaler with spacer; *NEB,* nebulizer; *PEFR,* peak expiratory flow rate; *PICU,* pediatric intensive care unit; *SABA,* short-acting β_2-agonist: *SQ,* subcutaneous.

characteristic of a moderate exacerbation, yet still be judged as mildly ill overall. Usually, patients with a mild exacerbation will only require SABA therapy, and the Expert Panel of the National Heart, Lung, and Blood Institute (NHLBI) recommends that it be given every 20 minutes in the first hour of care. Children with mild exacerbations often improve promptly with just one or two SABA treatments and many are managed without corticosteroids (CS). However, CS may be given to mildly ill children who have received home SABA doses prior to presentation or to those who do not respond promptly to SABA therapy (see later, "Moderate Exacerbation").

Racemic albuterol has become the SABA of choice for the treatment of children with acute asthma. Options for the mode of delivery include a small-volume nebulizer (NEB) and metered-dose inhaler (MDI)-S. Most emergency clinicians use NEBs to administer SABA, regardless of illness severity. NEBs provide a passive means of receiving aerosolized medication because precise coordination between respiration and aerosol delivery is not needed; additionally, anticholinergic medication and humidified oxygen may be delivered concurrently. However, medication delivery via NEBs is inefficient, with only about 10% of the drug delivered to the small airways. Also, the administration takes about 10 minutes, increasing respiratory therapy time and costs.

On the other hand, spacers used with an MDI provide a reservoir of medication that is available to be inhaled. Therefore, precise coordination between actuation and inhalation is not needed, and there is no need for breath-holding. After each actuation, children should take five to eight breaths. Drug deposition in the oropharynx and systemic absorption are reduced with the use of a spacer and decreased administration time may result in reduced costs. Face mask–equipped spacers are available for children too young to use the spacer's mouthpiece, although mouthpieces are preferable for older children to decrease nasal filtering of the drug.

Numerous clinical trials and meta-analyses over the past three decades have consistently demonstrated that albuterol delivery by MDI-S is as effective as NEBs among children of all ages and degrees of illness[2]. In some studies, MDI-S use was associated with a greater reduction in wheezing and lower hospitalization rates. The American College of Chest Physicians and American College of Asthma, Allergy, and Immunology have concluded that either NEBs or MDI-S are appropriate for the delivery of SABA in the ED.

Nebulized racemic albuterol should be administered at a dose of 0.15 mg/kg with a maximum dose of 5 mg, while optimal dosing for albuterol administered by MDI-S is not as well defined. Multiple puffs of SABA delivered by MDI-S seem to be well tolerated, even by young children. Children 1 to 4 years of age treated with six puffs of albuterol by MDI-S have been shown to have less tachycardia than those treated with 2.5 mg of albuterol by NEB. Per the 2007 NHLBI guidelines, a high dose (4 to 12 puffs) of a SABA MDI with a spacer has "equivalent bronchodilation" to NEB treatment. We recommend two to eight puffs, depending on weight (Table 163.2).

Another consideration in the use of SABA is the potential role of levalbuterol. Racemic albuterol is an equal mix of the active *R*-albuterol and inactive *S*-albuterol. *R*-Albuterol produces bronchodilation as well

TABLE 163.2 Recommended Doses of Medications for Acute Asthma

Medication	Dosage
Albuterol	0.15 mg/kg/dose (0.03 mL/kg/dose, max, 5 mg)
Continuous albuterol	0.5–1.0 mg/kg/h by nebulization (max, 15 mg/h)
Albuterol by metered-dose inhaler	Dose not well established
• ≤10 kg	2–4 puffs
• 11–19 kg	4–6 puffs
• ≥20 kg	6–8 puffs
Levalbuterol	Half the recommended albuterol doses
Ipratropium bromide	
• ≤20 kg	250 μg/dose
• >20 kg	500 μg/dose
L-Epinephrine (1:1000) or terbutaline (1.0 mg/mL)	0.01 mg/kg (max, 0.5 mg) 0.01 mg/kg (max, 0.25 mg)
IV terbutaline	10 mcg/kg IV over 10 minutes Every 30 minutes, may increase infusion by 0.3 μg/kg/min to max of 5 μg/kg/min
Prednisone	2 mg/kg (max, 60 mg), in ED 1 mg/kg/dose bid (max, 30 mg/dose), home therapy
Dexamethasone	0.3–0.6 mg/kg PO, two or three doses 24 hours apart (max, 8–16 mg/dose)
IV methylprednisolone	1 mg/kg (max, 125 mg)
IV magnesium sulfate	50–75 mg/kg over 20 min (max, 2g)

IM, Intramuscular; *IV,* intravenous; *PO,* by mouth; *SC,* subcutaneous.

as tachycardia and tremors, and *S*-albuterol had been long thought to be inert. However, there is some evidence that *S*-albuterol may increase reactivity to histamine, have proinflammatory effects, and exhibit characteristics of a typical contractile agent. There is also preferential retention of *S*-albuterol in the lungs of healthy volunteers; this may account for diminished effectiveness with frequent dosing. On the other hand, levalbuterol is pure *R*-albuterol without the *S* component. In theory, levalbuterol should be more effective than racemic albuterol at 50% of the dose (same amount of *R*-albuterol) because there are no competing harmful effects from the *S* isomer. However, studies assessing the use of levalbuterol for the treatment of children with acute asthma have not consistently demonstrated this theoretic advantage.

In an early study, the ED use of levalbuterol was associated with a decreased need for hospitalization. Subsequently, other randomized trials comparing the ED use of the two drugs failed to find a levalbuterol benefit and at least one clinical trial failed to demonstrate benefit with continuously nebulized levalbuterol. The cost of levalbuterol is more than 10 times that of racemic albuterol. Until there are more compelling data to demonstrate conclusively that the additional costs of levalbuterol are offset by clinical benefits, racemic albuterol is the drug of choice for children with acute asthma exacerbations.

Children sustaining clinical improvement 60 minutes after the most recent SABA treatment may be discharged; SABA should be weaned over the next 3 to 7 days. If prednisone was administered in the ED, it may be continued as 3 to 5 days of prednisone (1 mg/kg once or twice per day; maximum, 60 mg); however, compliance is not as good as with dexamethasone. Children treated with dexamethasone in the ED should be provided either one or two additional doses to be taken 24 and 48 hours after the ED dose. The recommended dose is 0.3 to 0.6 mg/kg once per day with a maximum of 8 to 16 mg. Children should continue all other asthma controller medications, including inhaled corticosteroids (ICSs).

For those who are not already receiving ICSs, it is unclear if prescribing them at ED discharge leads to improved short-term outcomes, such as fewer ED relapses within 72 hours. Some have found "insufficient evidence that ICS therapy provides additional benefit" when added to systemic corticosteroids at ED discharge. Rather than prescribing ICS to prevent ED relapse, prescribing may be considered to help achieve longer-term symptom relief for patients with persistent disease marked by frequent coughing or wheezing, frequent exacerbations requiring the use of SABA, or recurrent visits to the ED. ICS are safe and well tolerated at recommended doses and may be given concurrently with systemic corticosteroids. In addition to prescribing medications, emergency clinicians should also provide asthma education at discharge. Some EDs provide standardized information to families with a video or DVD while they undergo ED therapy. Descriptions of how to identify and avoid asthma triggers, a written asthma action plan explaining proper steps to take in response to an asthma flare, a review of discharge medications, and instruction on proper MDI-S use should be included. Follow-up asthma care is recommended within 1 to 4 weeks.

Moderate Exacerbation

In general, a moderate exacerbation is characterized by alert tachypneic children who have wheezing throughout expiration, an inspiratory-to-expiratory ratio of 1:2, and significant use of accessory muscles. Typically, the oxygen saturation will be 92% to 95% and the PEFR will be 41% to 70% of personal best. As with children experiencing milder attacks, the cornerstone of therapy is SABA therapy. Other medications include ipratropium bromide and corticosteroids.

Ipratropium bromide, an anticholinergic agent, blocks reflex bronchoconstriction caused by stimulation of airway cholinergic receptors. It is available as an MDI and as an NEB solution for nebulization that may be mixed directly with albuterol. The combination therapy of a SABA with ipratropium bromide has been demonstrated to be more effective than a SABA alone (i.e., lower hospitalization rates and improvements in asthma scores and pulmonary function test results).

The clinical benefits of ipratropium bromide may be delayed for up to 60 minutes. However, it is inexpensive and free of adverse effects because less than 1% is systemically absorbed. Ipratropium bromide should be given to children with moderate to severe exacerbations. Two to three doses may be mixed with three doses of albuterol and delivered continuously by NEB for 1 hour (Table 163.3). This means of administration, although not superior in efficacy to delivery of albuterol and ipratropium bromide by MDI-S, more consistently achieves the goal of three treatments in the first hour of care, as opposed to giving intermittent treatments every 20 minutes. Alternatively, intermittent therapy may be provided for moderately ill children by giving 4 to 8 puffs of ipratropium bromide every 20 minutes in the first hour, along with albuterol via MDI-S.

Moderately ill children who continue with dyspnea or significant work of breathing or poor aeration after the first hour of albuterol and IB therapy need continued albuterol therapy. Children treated with continuously nebulized SABAs have lower rates of hospitalization, greater improvements in PEFR, and similar rates of adverse events compared with those treated intermittently. Additionally, continuous NEB therapy will result in less respiratory therapy, nursing time, and costs, has been shown to be safe, and may benefit the sickest patients the most.

The prompt use of corticosteroids can decrease the need for hospitalization and should be administered early for patients with moderate disease. Although oral prednisone has historically been the corticosteroids of

TABLE 163.3 Short-Acting β_2-Agonists in Acute Asthma.

	Mild	Moderate	Severe
Delivery method	Intermittent NEB or MDI-S	Intermittent by NEB or MDI-S (3 doses in first hour) or continuous by NEB for 1 hour	Consider subcutaneous or intramuscular therapy; continuous by NEB
Comments	Most patients will need one or two treatments; allows MDI-S teaching; no IB needed	Continuous is not superior to MDI-S; easier to adhere to NHLBI guidelines for the first hour of therapy: concurrent IB therapy more easily delivered	Better outcomes in severe asthma

IB, Ipratropium bromide; *MDI-S,* metered-dose inhaler with spacer; *NEB,* nebulizer; *NHLBI,* National Heart, Lung, and Blood Institute.

choice in the ED treatment of acute asthma, recent studies demonstrate that oral dexamethasone has equivalent efficacy.[3] Dexamethasone has the advantage of having a substantially longer half-life (36 to 72 hours) than prednisone (18 to 36 hours), permitting a shorter treatment course with less vomiting and greater compliance. At this point, the optimal dose and duration of dexamethasone therapy are being established. Dose ranges from 0.3 to 0.6 mg/kg/dose are commonly used, with maximum doses of 8 to 16 mg[4]. Following the initial ED dose, patients typically receive either one or two additional doses, each spaced apart by 24 hours.

Most children with moderate asthma exacerbation can be managed without the insertion of an IV line. Intramuscular therapy is a reasonable option for children who vomit orally administered corticosteroids. The use of ICS, in addition to systemic corticosteroids, for the ED treatment of acute asthma is an area of ongoing research; at this point, we do not recommend its routine use.

A suggested approach to the management of children with moderately acute asthma is summarized in Fig. 163.1. After 1 hour of therapy, a clinical reassessment should be made; evaluation at this time is more accurate than the assessment at ED arrival in predicting the need for hospitalization. Those who worsen despite the first hour of therapy are likely to need continuously nebulized albuterol and hospitalization. In contrast, children with markedly decreased wheezing and work of breathing with improved aeration may be monitored without SABAs to assess for clinical deterioration. The disposition decision can then be made after the child has been observed for 90 to 120 minutes from their last SABA dose. The disposition decision should take into consideration the frequency of prior hospitalizations and ED visits and issues regarding compliance and support systems. ED discharge medications and education are the same as outlined for those with mild exacerbations.

There is a third group of children who are improved after the first hour of therapy but are not well enough to be discharged home. In a study of children treated with prednisone and 2 hours of SABA therapy who met criteria for admission at the 2-hour point, less than 50% were hospitalized when SABA therapy was continued for an additional 2 hours, and none returned to the ED within 48 hours of discharge. To avoid unnecessary hospitalizations, we recommend observing patients who do not otherwise decline for a total of 3 to 4 hours from ED arrival prior to making the disposition decision.

Severe Exacerbation

A severe exacerbation is characterized by restlessness or lethargy, extreme tachypnea and tachycardia, audible wheezing, inspiratory-to-expiratory ratio exceeding 1:2, significant use of accessory muscles, and oxygen saturation less than 92%. Some older children with a severe exacerbation may have bradypnea due to a prolonged expiratory phase, and auscultated wheezing may be absent with markedly decreased aeration. The PEFR will typically be less than 40% predicted, although most children will be too ill to use a peak flow meter.

Fig. 163.1 outlines the approach to the management of severely ill children. They should be attached to a cardiorespiratory monitor and blood pressure cuff, with continuous monitoring of oxygen saturation by a pulse oximeter. As with moderately ill children, supplemental oxygen and continuously nebulized albuterol and ipratropium bromide should be provided soon after arrival. Nearly all severely ill children will require more prolonged therapy with continuously nebulized albuterol, as outlined above. To achieve an oxygen saturation of 92% or greater, it may be necessary to use a non-rebreathing facemask. Severely ill children may be too sick to tolerate oral medications and may need IV medications. A dose of methylprednisolone or dexamethasone should be given as soon as an IV line is established.

For children with very poor inspiratory flow, nebulized SABAs may not be effectively delivered to the smallest airways; short inspiratory time, low inspiratory pressures, and a prolonged exhalation phase will impair the delivery of inhaled medications. In these cases, subcutaneous or intramuscular terbutaline or epinephrine may be considered. Terbutaline has the advantage of being a more selective agent with fewer side effects, such as tremors, vomiting, or palpitations. This treatment can be of particular benefit for very ill and anxious young children who are uncooperative with the inhalation treatments. There are no data to suggest that one mode of administration is superior to the other, although intramuscular epinephrine therapy is recommended for children with bronchospasm due to anaphylaxis. If it is more readily available, an epinephrine autoinjector is effective for this subset of patients. Subcutaneous or intramuscular therapy may be repeated every 10 to 15 minutes, as needed, in extreme cases. If IV access is already established, instead of the subcutaneous or intramuscular therapy outlined above, the patient may be treated with a bolus of 10 μg/kg of IV terbutaline.

Meta-analyses have determined that the use of magnesium sulfate results in improved outcomes for adults and children. In particular, children with a suboptimal response to initial SABA therapy who are subsequently treated with magnesium have significantly greater improvements in pulmonary function compared with those treated with placebo. In contrast, magnesium has not been found to be efficacious as a component of initial therapy for children with moderate to severe exacerbation when given prior to judging the response to early albuterol therapy.

Magnesium is inexpensive and has minimal adverse effects. Hypotension may be minimized by slowly infusing the dose over 20 minutes. Magnesium (50 to 75 mg/kg over 20 minutes; maximum, 2 g) should be given to moderately ill patients who have a suboptimal response to SABAs, IB, and CS, as well as for all severely ill children.

There are insufficient data to make recommendations for the use of continuously infused IV SABAs. Potential adverse effects from use of continuously infused IV SABAs are substantial and include dysrhythmias, hypertension, and hypokalemia. Continuously infused IV SABAs should not be used except for impending respiratory failure, a situation in which the risk-benefit ratio shifts toward favoring their use.

Heliox is a low-density mixture of helium and oxygen that results in less turbulent flow through narrowed airways. Theoretically, heliox may decrease the work of breathing, resulting in less respiratory muscle fatigue and a lower likelihood of ventilatory failure. Heliox has not been found

beneficial in all asthma exacerbations, but it may be considered for severely ill children who are not responding to more conventional therapy.

Although there is little in the literature to support the use of noninvasive ventilation (NIV), such as bilevel positive airway pressure (BiPAP), in the management of severe asthma in children, clinicians have employed it with good success to avoid the need for mechanical ventilation. Theoretically, the positive pressure of NIV can ease inhalation and decrease the alveolar collapse associated with exhalation. For a child who remains severely ill despite the previously outlined treatment, the risk-benefit ratio favors the use of BiPAP. The need for mechanical ventilation of the severely ill patient should take into account the entire clinical picture, including illness severity, response to therapy, and ABG results. However, the ABG results should not be used solely to make this decision. The child with an initial pH of 7.10 and a $Paco_2$ of 55 mm Hg who shows marked improvement with IV SABA therapy may not require ventilatory assistance, whereas the child with a pH of 7.18 and $Paco_2$ of 50 mm Hg who appears fatigued and is not responding to therapy will likely need mechanical support. Ketamine is a bronchodilator and is the drug of choice for sedation and analgesia of the asthmatic child who requires intubation.

Since mechanical ventilation can result in air trapping and barotrauma, enough expiratory time should be allowed for air exit from the lungs. Permissive hypercapnia describes one strategy to prevent barotrauma; it minimizes tidal volumes and respiratory rates to decrease peak inspiratory pressures.

BRONCHIOLITIS

KEY CONCEPTS

- An infant younger than 12 months has an oxygen consumption index double that of an adult and with bronchospasm, may rapidly develop hypoxemia, bradycardia, and cardiopulmonary arrest.
- Bronchiolitis is a clinical diagnosis based on a history of prodromal upper respiratory infection symptoms in an infant or young child, followed by findings on physical examination of wheezing (often with shifting crackles) and increased work of breathing. The value of diagnostic imaging and laboratory evaluation is limited, and these measures should not be used routinely.
- All febrile infants in the first month of life should undergo testing and evaluation for serious bacterial infection and be empirically treated with antibiotics, regardless of respiratory syncytial virus (RSV) status or presence of clinical bronchiolitis.
- A urinalysis and culture should be performed for febrile infants between 1 and 3 months of age who are known to be RSV-positive or have clinical bronchiolitis. The decision to obtain blood or cerebrospinal fluid cultures and give empirical antibiotics should be made on an individual basis (see Chapter 161).
- The management of infants with bronchiolitis focuses largely on supportive measures, and most patients able to tolerate oral hydration can be managed as outpatients. There are currently no consistently effective pharmacologic therapies for bronchiolitis (including SABA, corticosteroids, or antibiotics).
- Despite reports that more than 50% of infants may be prescribed corticosteroids when diagnosed with bronchiolitis, well-designed controlled trials have demonstrated no benefit for their use in rates of admission, clinical scores, or any other clinical outcomes.
- High-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) may have some utility in preventing the need for endotracheal intubation, but the evidence is limited and so the use of these modalities should be reserved only for patients with moderate to severe bronchiolitis.
- Disposition from the ED for bronchiolitis depends on the assessment of multiple risk factors, including young age, prematurity, significant hypoxemia, and severe tachypnea, which may predict a more severe clinical course.

Foundations

Bronchiolitis is an acute infectious disease that results in inflammation of the small airways in children younger than 2 years of age. This process is manifested clinically as wheezing and crackles and increased work of breathing, along with the typical signs and symptoms of a URI. Nearly all children are affected by the viruses that cause bronchiolitis at least once during their first 2 years of life, but it is more common for infants younger than 12 months to manifest clinical signs of bronchiolitis.

Bronchiolitis is a seasonal disease, with most cases occurring between November and April in temperate climates. Bronchiolitis is rarely fatal, and severe cases are associated with a number of risk factors, including low birth weight, prematurity, chronic lung disease, and congenital heart disease. Many viruses are implicated as the underlying cause of bronchiolitis, but respiratory syncytial virus (RSV) is estimated to cause up to 70% of cases in previously healthy children. Other viruses commonly isolated are parainfluenza, human metapneumovirus, influenza, adenovirus, bocavirus, and rhinovirus.

Most respiratory viruses that cause bronchiolitis in children are transmitted from one host to another by fomites spread from hand to nose or by droplets produced by sneezing or coughing of respiratory secretions. Shedding of the virus often begins before the onset of significant clinical symptoms and can continue for 2 to 3 weeks in an immunocompetent infant. The typical incubation period is 2 to 8 days from the time of initial contact.

Anatomy, Physiology, and Pathophysiology

In an infected patient, viral replication often begins in the epithelial cells of the upper airway before spreading to the mucosal surfaces of the lower respiratory tract. The infected epithelial cells are generally destroyed by lysis or apoptosis, which results in the desquamation of these cells and the release of host inflammatory mediators. Affected lungs demonstrate epithelial cell necrosis, monocytic inflammation and edema of the peribronchial tissues, and mucus and fibrin plugging of the distal airways on histologic examination. These findings translate into the clinical findings of wheezing and lower airway obstruction in an infant with bronchiolitis. Younger infants, whose distal airways are of smaller caliber and who lack active immunity to most respiratory viruses, are prone to more severe clinical symptoms. Severe lower airway obstruction leads to air trapping and atelectasis, resulting in mismatched ventilation and perfusion and hypoxemia. In addition, younger infants are at increased risk for fatigue, leading to hypercarbia and respiratory failure.

Clinical Features

Infants with bronchiolitis are typically younger than 12 months and present during the winter months. The first symptoms are generally those of a URI, such as nasal congestion and copious rhinorrhea. This is followed within a few days by a tight cough, often associated with difficulty in feeding. Some parents will report audible wheezing as well. Approximately one-third of patients admitted with bronchiolitis will have a fever. Very young infants may present with a history of apnea, which may precede the onset of typical symptoms of respiratory infection. The emergency clinician should ascertain information about the infant's hydration status, including the amount and frequency of oral intake, urine output, vomiting, and diarrhea.

Comorbidities, such as congenital heart disease, chronic lung disease, and prematurity, can have a significant impact on the clinical course of bronchiolitis. A past history or family history of wheezing or atopy may make the diagnosis of asthma more likely, particularly in the older infant; daycare attendance and household contacts with respiratory symptoms favor a diagnosis of bronchiolitis.

TABLE 163.4 Suggested Bronchiolitis Assessment Tool

	DEGREE OF BRONCHIOLITIS		
Parameter	**Mild**	**Moderate**	**Severe**
Feeding	Normal	Less	Poor
Sao_2 in room air	≥95%	92%–94%	<92%
Respiratory rate (breaths/min)	<60	60%–70%	>70
Retractions	None or minimal	Intercostal	Substernal
Accessory muscle use	None	None	Neck or abdominal
Wheeze	None or minimal	Moderate expiratory	Severe inspiratory-expiratory; audible without a stethoscope
Air exchange	Good, equal breath sounds	Localized, decreased breath sounds	Multiple areas of decreased breath sounds

Common vital sign abnormalities include fever, tachycardia, tachypnea, and hypoxia. The oxygen saturation (Sao_2) of any moderately or severely ill infant should be obtained soon after ED arrival as an adjunct to the physical examination. With the use of pulse oximetry, an ABG analysis is generally unnecessary to assess a patient's oxygenation. Thus, carrying out ABG analysis should be reserved for those with severe disease and impending respiratory failure to measure the extent of hypercarbia and respiratory acidosis.

Nasal flaring and retractions are visible signs of respiratory distress. Lung auscultation often reveals decreased air movement, rales, rhonchi, wheezing, and a prolonged expiratory phase. Irritability or lethargy, particularly in young infants, indicates a more severe disease. Children can be stratified into mild, moderate, and severe categories based on the physical examination findings (Table 163.4). The combination of poor feeding and increased insensible fluid losses often has an impact on an infant's hydration status. A careful assessment of the anterior fontanel, mucous membranes, capillary refill time, and skin turgor can help identify dehydration.

The worst phase of the illness generally occurs in the first few days and children admitted for bronchiolitis have a median length of hospital stay of 2 to 3 days. However, the entire course of illness can last much longer, with a median duration of 12 days. Coughing and noisy breathing, in particular, can last for more than 4 weeks.

Acute bacterial otitis media is the most common associated illness, with a prevalence of up to 60%. The bacterial pathogens are similar to those recovered in other children with acute otitis media and should be treated accordingly. Other concurrent bacterial infections are rare.

Young infants with fever and bronchiolitis present a unique dilemma for the emergency clinician. The rate of serious bacterial infections (SBIs), defined as UTI, bacteremia, bacterial meningitis, or bacterial enteritis, among all febrile infants younger than 8 weeks is as high as 12%. However, in infants with documented RSV infection or clinical bronchiolitis at the time of ED presentation, the incidence of an SBI is substantially lower. Due to their particularly high level of SBI risk, all febrile infants in the first month of life should undergo a complete laboratory evaluation for SBI and be empirically treated with antibiotics, regardless of RSV status or presence of clinical bronchiolitis. For infants between 1 and 3 months of age who are known to be RSV-positive or have clinical bronchiolitis, we recommend catheterized urinalysis and culture for rectal temperatures above 38°C (100.4°F), since nearly all concomitant SBIs in this age group are UTIs. Urine testing should also be considered for febrile infants with bronchiolitis who are older than 3 months of age, particularly for those with high-risk features for a UTI: temperatures over 39°C (102.2°F), fever for greater than 24 hours, females, and nonblack race.[5] Additional testing to obtain culture specimens of cerebrospinal fluid and blood may be done selectively. Assuming a normal urinalysis and no concern for bacteremia or meningitis, these infants will not typically require empiric antibiotic therapy for presumed SBIs; decisions to treat with antibiotics should be made on an individual basis, considering the degree of ill appearance and comorbidities.

Apnea is commonly reported in young infants with bronchiolitis, especially among those who are hospitalized. Of admitted patients, nearly 5% will have apnea during the hospital stay. Risk factors for the development of in-hospital apnea include post-menstrual age ≤43 weeks, low birth weight, and a history of apnea reported by the caregiver.[6] The absence of all these risk factors has a high negative predictive value for the development of in-hospital apnea.

Differential Diagnoses

Asthma is the condition that has the most clinical overlap with bronchiolitis. Physical examination findings alone cannot often distinguish the two. Younger age, presentation during the winter months, antecedent URI symptoms, and absence of a prior or family history of atopic disease and wheezing suggest bronchiolitis as the cause of wheezing in an individual patient. Some infants will have clinical features consistent with both conditions. For example, a 12-month-old may present in July with a URI and wheezing for the first time. For this child, a clinician may choose to initiate SABA therapy in the ED but continue it only if the child has a favorable response. Conditions that should be differentiated from bronchiolitis are summarized in Table 163.1.

Diagnostic Testing

Bronchiolitis should be diagnosed primarily on the basis of history and physical examination findings. In general, expensive viral diagnostic testing is not warranted for the majority of patients, although confirmation of a viral cause of the illness may eliminate the need for further laboratory evaluation in young infants with fever. (See Chapter 161 for a comprehensive overview of recommendations for pediatric fever.)

There is tremendous variability in the use of diagnostic imaging, with some centers reporting that chest radiographs are obtained for more than 70% of infants hospitalized with bronchiolitis. In children with clinical findings typical for bronchiolitis, however, radiographic imaging is rarely helpful. Hyperinflation, atelectasis, and peribronchial cuffing are the radiography findings most commonly associated with bronchiolitis. In ambulatory patients with acute lower respiratory infections, obtaining a chest radiograph does not affect the clinical outcome but has been associated with increased use of unnecessary antibiotics. Furthermore, the chance of identifying an alternative diagnosis from a chest x-ray is less than 1%. Diagnostic imaging may be helpful in patients with severe distress, significant hypoxia, or an atypical presentation. We agree with the clinical practice guideline published by the American Academy of Pediatrics in 2014 that "when clinicians diagnose bronchiolitis on the basis of history and physical examination, radiographic or laboratory studies should not be obtained routinely."[7]

Management

Whereas the diagnosis of bronchiolitis is fairly straightforward, the management of children with the disease often presents emergency clinicians with confusing and controversial dilemmas. The literature

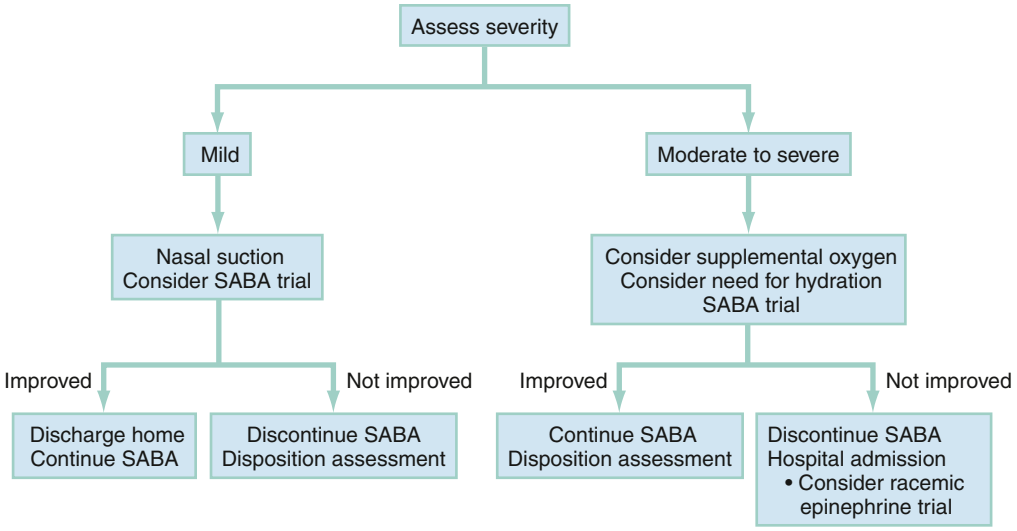

Fig. 163.2 Emergency Department Management of Bronchiolitis. *SABA,* Short-acting β_2-agonist.

is often contradictory, making it difficult to reach a consensus. As a result, there is wide practice variation in the management of bronchiolitis. However, it is clear that a consistent, evidence-based approach to this disease can lead to more efficient and effective care. Supportive care, such as nasal suctioning, providing hydration and supplemental oxygen, is the cornerstone of therapy for affected children A management strategy, stratified by the patient's initial degree of illness, is outlined in Fig. 163.2.

SABAs are the treatment of choice for children with wheezing due to asthma. However, the evidence supporting their use in wheezing caused by bronchiolitis is considerably less favorable. Treatment with SABAs has no significant effect on rates or duration of hospitalization. Conversely, adverse effects such as tachycardia, decreased oxygen saturation, flushing, and hyperactivity occur more frequently in children treated with SABAs. Thus, we do not recommend the routine use of SABAs for bronchiolitis; instead, we recommend a trial of such medications to determine if a patient has a beneficial clinical response *only* if it is unclear whether the patient has asthma or bronchiolitis.

Similar controversy exists with respect to the use of racemic epinephrine in the treatment of bronchiolitis. We recommend that a trial of nebulized epinephrine be considered for a select group of infants with moderate to severe distress who might otherwise require more invasive interventions (e.g., endotracheal intubation) secondary to disease severity. As with SABAs, nebulized epinephrine should be continued only for those patients who demonstrate a clinical benefit. There is currently no sufficient evidence to recommend the use of other bronchodilators, such as anticholinergic agents, for young children with wheezing and suspected bronchiolitis.

Many of the symptoms of bronchiolitis are a result of increased and thickened respiratory secretions. A great deal of literature supports the use of nebulized hypertonic saline in the treatment of cystic fibrosis, in which clearance of thickened secretions is vital. Although there is not yet enough evidence to recommend the routine use of nebulized hypertonic saline in the ED for bronchiolitis, several studies have suggested that it is a safe medication that may reduce the length of stay for some hospitalized children.

Systemic corticosteroids are a well-established and effective treatment of wheezing due to acute asthma. Despite reports that more than 50% of infants may be prescribed corticosteroids when they are diagnosed with bronchiolitis, well-designed controlled trials have demonstrated no benefit for their use in terms of rate of admission, clinical score, or any other outcome. Thus, our recommendation is that emergency clinicians not use corticosteroids for the treatment of bronchiolitis.

Whereas infants with severe bronchiolitis, who require intensive care and mechanical ventilation, frequently have concurrent or secondary bacterial infections, this is an uncommon complication for most children. There is no evidence for the routine use of antibiotics for bronchiolitis, and they should be reserved for patients with identified bacterial infections.

High-flow nasal cannula (HFNC) is a treatment modality that utilizes heated and humidified air flow with FiO_2 ranging from 21% to 100% to deliver variable degrees of positive airway pressure. By increasing the intraluminal diameter of airways, HFNC can stabilize unsupported airways and relieve air trapping and hyperexpansion. In addition, HFNC can improve alveolar gas exchange by increasing the transpulmonary pressure gradient. Finally, the delivery of heated and humidified air decreases the metabolic demand on the patient. While a few small studies suggest that non-invasive positive pressure ventilation (e.g., CPAP) may be helpful in avoiding endotracheal intubation in severe disease, a Cochrane meta-analysis failed to find sufficient evidence for its use in children with bronchiolitis.[8] A randomized trial of HFNC vs. standard oxygen therapy demonstrated that patients treated with HFNC had fewer escalations of care due to treatment failure.[9] However, the definition of treatment failure in this study is controversial and not widely accepted. A meta-analysis of the available literature regarding HFNC in bronchiolitis concluded that there is not sufficient evidence to show significant benefit from HFNC when compared with standard oxygen therapy or nasal CPAP.[10] While awaiting results from larger, well-designed clinical trials, we believe the risk/benefit ratio favors utilizing HFNC and other forms of non-invasive positive pressure ventilation for patients with moderate to severe disease and judging the response by assessing rate and work of breathing.

Prophylaxis

Although emergency clinicians generally do not have a role in the administration of preventive medications, they should be aware that selected infants will be receiving prophylactic management. Palivizumab (Synagis) consists of monoclonal antibodies against RSV. Whereas RSV-specific immune globulin is not effective for treating the acute disease process, palivizumab is effective in reducing hospitalization rates for RSV in certain high-risk populations; it is recommended for most children

younger than 24 months with chronic lung disease, congenital heart disease, or prematurity and is administered as a monthly intramuscular injection during the high-prevalence months. The emergency clinician should be aware that although preventive treatment has been initiated, treated infants with signs of bronchiolitis may still have RSV infections.

Disposition

Because bronchiolitis is a dynamic disease, evaluations at a single point in time may not be sufficient to estimate its severity fully; thus, serial examinations are necessary. A number of demographic and clinical features have been associated with a more severe clinical course. These factors include age younger than 12 weeks, history of prematurity, ill appearance, hypoxemia (Sao_2 <95%), tachypnea (>70 breaths/min), and significant atelectasis on the chest radiograph (when obtained). In addition to younger age and prematurity, a history of hemodynamically significant congenital heart disease, chronic lung disease, and immunocompromised state has been associated with higher morbidity and mortality among inpatients.

Ultimately, the emergency clinician should assess more than just the child's degree of respiratory distress. Patients should be admitted if they are unable to maintain oral hydration due to respiratory symptoms, difficulty with feeds due to increased work of breathing, or copious nasal secretions requiring frequent deep suctioning. The family or caregiver should be able to continue supportive measures at home and have access to medical care. Discharge instructions should include 24-hour follow-up with a primary care provider or emergency clinician for reevaluation. For the small subset of children who are treated with and had a sustained clinical improvement to SABA therapy, this treatment should be continued at home every 4 hours, as needed. Although home oxygen therapy for selected patients with mild to moderate disease has demonstrated success in reducing inpatient hospitalization, primarily in high-altitude conditions, this practice requires careful coordination of care and resources, which may not be feasible in all practice settings. Furthermore, its application to children at sea level is still unclear and thus is not recommended. Parents should be instructed to seek immediate medical care for signs of worsening respiratory distress, including poor feeding, retractions, increased tachypnea, lethargy, and irritability.

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CHAPTER 163: QUESTIONS AND ANSWERS

1. A 19-month-old girl with a history of asthma presents with severe respiratory distress marked by wheezing, tachypnea, deep retractions, and an oxygen saturation of 92% in room air. She fails to improve 10 minutes after nebulized short-acting β_2-agonist (SABA) therapy and repeatedly tries to pull off her face mask. Which strategy is likely to produce the most rapid clinical benefits in this setting?

a. Administering IM terbutaline
b. Administering IV methylprednisolone
c. Administering the SABA via metered-dose inhaler (MDI) instead of by nebulization
d. Doubling the dose of SABA in the nebulizer reservoir
e. Taking off her face mask and holding it close to her face to reduce her agitation

Answer: a. This patient's degree of bronchospasm and lack of cooperation makes it difficult to deliver aerosolized medication effectively. In this setting, IM terbutaline is most likely to result in rapid bronchodilation, making subsequent aerosolized therapy more effective.

2. A 6-month-old male infant presents to the ED with his father, who reports that the patient has been wheezing. His vital signs are a temperature of 39.7°C, respiratory rate 62 breaths/min, and oxygen saturation of 90%. On examination, you find diffuse wheezing and copious nasal secretions. While in the ED, the patient does not have a wet diaper; his father reports that he has had decreased oral intake for the past 2 days. Which of the following findings with bronchiolitis is not associated with the need for admission?

a. Age
b. Decreased oral intake
c. Oxygen saturation
d. Respiratory rate
e. Temperature

Answer: a. Patients often in need of admission for bronchiolitis include those with respiratory rates more than 70 breaths/min, O_2 saturation of 95% or less, age younger than 3 months, and poor feeding.

3. Which of the following side effects are seen with the use of intravenous magnesium in the treatment of asthma in children?

a. Change in serum pH
b. Development of a prolonged QT interval on the electrocardiogram
c. Hypercalcemia
d. Hyperkalemia
e. Hypotension

Answer: e. Most patients who receive a magnesium infusion at the recommended dose will experience a clinically insignificant decrease in blood pressure. This may be minimized by infusing the medication over 20 minutes and by concurrently administering normal saline solution.

4. You are about to treat a child with acute asthma with albuterol. Which of the following factors is most important when considering the method of aerosolized drug delivery?

a. About 20% to 30% of nebulized drug reaches the alveoli.
b. Children receiving β-agonists by nebulizer (NEB) have similar outcomes compared with those using a metered-dose inhaler (MDI-S).
c. Children weighing >20 kg should receive a maximum of four puffs of albuterol via MDI-S.
d. MDI-S therapy is more costly than NEB therapy.
e. The use of MDI-S for acute asthma is not supported by national guidelines.

Answer: b. Clinical trials and systematic reviews have repeatedly shown these two forms of therapy to be equivalent. With NEB treatment, less than 10% of nebulized drug reaches the alveoli. A recommended MDI-S dose for older children is eight puffs. Most studies demonstrate that MDI-S therapy is more cost-effective because of a slightly reduced need for hospitalization. National guidelines support the use of MDI-S to deliver albuterol to children with acute asthma.

5. A 7-month-old male infant was diagnosed 2 days ago with bronchiolitis. He continues to have wheezing and increased work of breathing, prompting his parents to bring him into the ED because of a new-onset fever. Which of the following is the most likely secondary bacterial infection in this infant with bronchiolitis?

a. Pneumonia
b. Acute otitis media
c. Meningitis
d. Urinary tract infection

Answer: b. Bacterial acute otitis media (AOM) is the most common condition associated with bronchiolitis, with a prevalence of up to 60%. The bacterial pathogens are similar to those recovered in other children with AOM; thus, it should be treated according to standard recommendations. Other concurrent bacterial infections are rare.

Pediatric Lung Disease

Eric R. Schmitt

KEY CONCEPTS

- Determining the causative agent of pneumonia by clinical presentation and radiographic findings is not reliable; empirical treatment is based on guideline recommendations and likely pathogens.
- Causative agents vary by age; viral agents predominate, especially in younger children, and *Streptococcus pneumonia* is the leading bacterial cause outside of the neonatal period.
- Infants and younger children with pneumonia may have subtle or nonspecific symptoms and signs on presentation, and fever may be the only sign of disease.
- First line therapy for the treatment of bacterial pneumonia in children is amoxicillin for an outpatient and ceftriaxone or ampicillin for an inpatient.
- Pertussis should be considered in a young infant with a staccato cough or episodes of cyanosis.
- In patients with cystic fibrosis, defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, which leads to an increased likelihood for pneumonia, especially that caused by *Pseudomonas aeruginosa.*
- Cystic fibrosis may respond favorably to bronchodilator therapy and mucolytics, such as inhaled *N*-acetylcysteine.
- Patients with bronchopulmonary dysplasia have increased airway resistance, decreased lung compliance, and obstructive lung disease; reactive airway disease and pneumonia are common in these patients.

SPECIFIC DISORDERS

Pneumonia

Foundations

Although upper respiratory tract infections are more common, children frequently develop lower respiratory tract infections, most notably pneumonia and bronchiolitis. Bronchiolitis (see Chapter 163– Pediatric Lower Airway Obstruction) is primarily seen in children younger than 2 years old and manifests as wheezing and congestion due to a viral infection. Pneumonia is an inflammation of the lung tissue that is most often due to an infection but occasionally may follow a noninfectious insult. The diagnosis of pneumonia is made by clinical signs and symptoms and is often aided by an abnormal chest radiograph demonstrating pulmonary infiltrates (Fig. 164.1).[1] The clinical presentation of pneumonia is variable, ranging from a mild illness to life-threatening disease. A specific organism may be suggested by clinical and radiographic findings, but determination of a precise causative agent is not always possible given the limitations of diagnostic testing, nor is it critical in an emergency setting, as initial treatment is empiric. Infection rates for pneumonia in children vary inversely with age, averaging 40/1000 in preschool-age children and decreasing gradually to 7/1000 in 12- to 15-year-olds.[2] Most deaths from pneumonia result from bacterial infections.

The causative organisms vary with the age of the child. Overall, viral agents cause up to 90% of all pneumonias and are more common in younger children.[3] Bacteria predominate in neonates but become less frequent in toddlers and older children. Outside the neonatal period, the incidence of bacterial agents is stable throughout different age groups. *Chlamydia trachomatis* is a unique cause of pneumonia in infants 3 to 19 weeks of age. *Bordetella pertussis* classically occurs in infants younger than 1 year but may occur in older children and adolescents. *Mycoplasma pneumoniae* is one of the most common causes of pneumonia among children older than 5 years but may also be seen in younger children.[3] *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* is also seen more often in children older than 5 years but may cause infection in younger children.

Among bacteria, group B streptococci and gram-negative bacilli predominate in neonates. Although rare, *Ureaplasma urealyticum* and *Listeria monocytogenes* may cause illness in infants younger than 2 months. *Streptococcus pneumoniae* is the leading bacterial cause of pneumonia in all age groups beyond the newborn period, whereas *Staphylococcus aureus* and *Haemophilus influenzae* are less common causative agents. A vaccine against *H. influenzae* type b first became available in 1985, and incidence of disease has decreased markedly with widespread immunization of infants and young children. In 2010, the 13-valent pneumococcal vaccine (Prevnar 13, Wyeth Pharmaceuticals, NY) replaced the heptavalent pneumococcal conjugate vaccine Prevnar (Wyeth). Prevnar 13 is recommended for the primary series at 2, 4, and 6 months of age, with a fourth booster dose given at 12 to 15 months of age. Vaccination is highly efficacious, with 85% protection against serotype-specific cases of pneumococcal pneumonia, decrease in carriage rates of the included serotypes in daycare settings, and even some protection against viral pneumonia (possibly due to frequent concomitant infection of viral pneumonia with pneumococcal infection).[2,4,5]

Less common bacterial agents include group A streptococci, *Neisseria meningitidis,* and anaerobic bacteria (usually in the setting of aspiration pneumonia). Unusual causes of pneumonia include *Pseudomonas aeruginosa, Legionella pneumophila, Pneumocystis jiroveci,* and rickettsial infections. The incidence of *Mycobacterium tuberculosis* has been increasing in the United States, particularly in urban and low-income areas and among non-White racial or ethnic groups. Infants and adolescents are at highest risk in the United States.[6] Respiratory syncytial virus (RSV) and parainfluenza are the most frequent viral agents in infants younger than 1 year.[3] Viruses that may be responsible for neonatal pneumonia include rubella, cytomegalovirus (CMV), and herpes simplex virus. Other viral agents include influenza, adenovirus, rhinovirus, enterovirus, measles, varicella, and Epstein-Barr virus. In addition, immunocompromised hosts are susceptible to mixed and opportunistic infections, including bacterial, viral (CMV, varicella), protozoan (*P. jiroveci*), and fungal disease (*Coccidioidomycosis*, etc.).

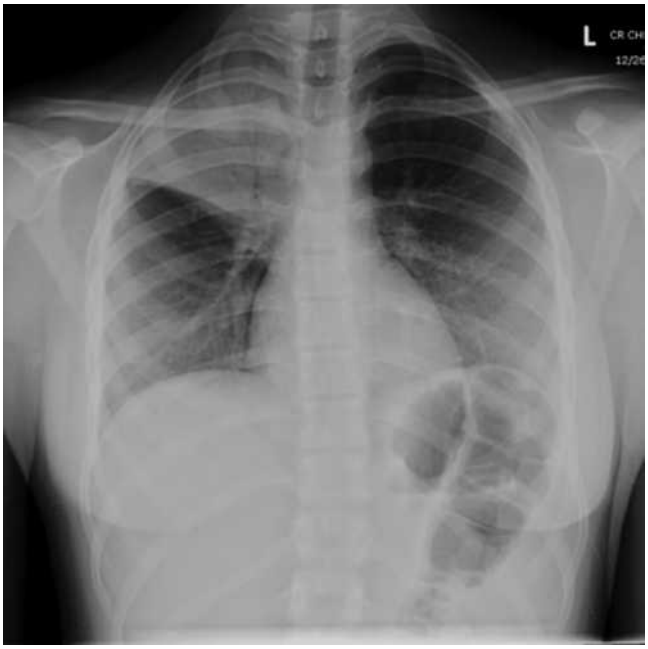

Fig. 164.1 Radiograph showing a right upper lobe consolidation with air bronchograms in a 13-year-old. (Courtesy Dr. Eric R. Schmitt.)

The lung is protected from infection by a variety of local and systemic immune mechanisms. Passively acquired maternal antibodies are important in protection against *S. pneumoniae* and *H. influenzae* infections during the first few months of life. Children with altered protective mechanisms are at increased risk for development of pneumonia; this includes children with congenital anatomic abnormalities (e.g., cleft palate, tracheoesophageal fistulas, pulmonary sequestration, congenital cystic adenomatoid malformation), immune deficiencies (e.g., congenital, acquired, medication induced), neurologic alterations that predispose to aspiration (e.g. coma, seizures, cerebral palsy, general anesthesia), and alterations in quality of secreted mucus (cystic fibrosis [CF]).

Bacterial pneumonia and mycoplasma infections are usually transmitted person to person by droplet aspiration. Asymptomatic upper airway colonization often occurs in children and may spread infection to other children. Much less commonly, bacterial pneumonia may result from hematogenous spread from a distant focus or during primary bacteremia. Viral agents that cause pneumonia proliferate in the upper respiratory tract and spread contiguously to involve the lower respiratory tract. Viruses such as varicella, CMV, herpes simplex, Epstein-Barr, measles, and rubella also may infect the lungs through hematogenous spread.

Clinical Features

Clinical symptoms and signs of pneumonia in pediatric patients vary with patient age, specific pathogen, and disease severity.[2] Infants younger than 3 months of age generally have respiratory symptoms, such as tachypnea, cough, retractions, and grunting, but may show only nonlocalizing symptoms, such as isolated fever or hypothermia, vomiting, poor feeding, irritability, and lethargy. Toddlers with *S. pneumoniae* infection may have nonspecific symptoms, such as high fever and lethargy, without significant respiratory symptoms. In general, signs and symptoms in children become more specific with increasing age, although pneumonia may have only subtle manifestations in any child.[1] Systemic symptoms include fever and chills, headache, rigors, and malaise. Symptoms of lower respiratory tract disease may include cough and wheezing. Pleural irritation often causes chest pain, but the child may also complain of pain in the abdomen or neck. Vomiting (often posttussive) and poor oral intake are common.

TABLE 164.1 Tachypnea as Defined by the World Health Organization for the Clinical Diagnosis of Pneumonia

Patient Age	Respiratory Rate
Younger than 1 year	Greater than 50 breaths/min
1–5 years old	Greater than 40 breaths/min
Older than 5 years	Greater than 30 breaths/min

Key historical factors include birth and immunization history (particularly pneumococcal and *H. influenzae* type b vaccination), sickle cell status, history of previous pneumonia or frequent infections, and presence of underlying chronic disease. Children with known respiratory (e.g., bronchopulmonary dysplasia [BPD], CF) or cardiac disease tend to have more severe courses of illness; children with a primary or acquired immunodeficiency are also prone to more severe and fulminant disease from common, uncommon, and opportunistic pathogens.

The physical examination should begin with the general appearance and breathing pattern. A full set of vital signs, including oxygen saturation, should be obtained on arrival. Fever is often present but may be low grade or absent. Important findings include hydration status, perfusion, and level of alertness and interaction. Abnormal cardiovascular parameters may indicate dehydration or, rarely, shock. Tachypnea, although not universal, is the most sensitive indicator of pneumonia and may be the only manifestation in younger children. The World Health Organization (WHO) has published guidelines for the clinical diagnosis of pneumonia in developing countries and cites tachypnea and retractions as indicators of lower respiratory disease (Table 164.1).

Other manifestations of lower airway disease include cough, wheezing, or signs of increased work of breathing: nasal flaring, retractions, grunting, and accessory muscle use. The characteristics of the cough may aid in the diagnosis; a staccato cough in an infant may indicate pneumonia caused by *C. trachomatis* or *B. pertussis*. The patient's lungs should be auscultated, and findings may include rales, wheezing, or diminished breath sounds. Although these may be present in younger children, the findings are much less consistent and may be masked by poor inspiratory effort or noisy upper airway sounds. Pleural irritation can cause abdominal tenderness or meningismus, and pulmonary hyperinflation may cause downward displacement of the liver and spleen. Extrapulmonary exam findings may include rhinorrhea, pharyngitis, or exanthem with viral infections. Conjunctivitis can be seen with chlamydial pneumonia, whereas pharyngitis and exanthems are associated with *M. pneumoniae.*

Several complications of pneumonia may result from local and systemic effects of the infection, with the most common systemic complication being dehydration. Pleural effusion or empyema is usually associated with bacterial pathogens (notably *S. pneumoniae, H. influenzae,* and *S. aureus*) but are occasionally seen with mycoplasma, viral, and tuberculosis pneumonia. Similarly, lung abscess, pneumatocele, and pneumothorax are local complications primarily seen with bacterial disease, particularly with *S. aureus*. Extensive pulmonary involvement, regardless of the causative agent, may lead to hypoxia, progressive respiratory deterioration, and multiple organ failure (Fig. 164.2). Apnea in isolation without other symptoms can occur in infants younger than 3 months and is usually associated with viral (especially RSV), chlamydial, and pertussis infections. Additional infectious foci may develop from concomitant bacteremia (e.g., meningitis, epiglottitis, pericarditis, septic arthritis, soft tissue infections). Viral or bacterial

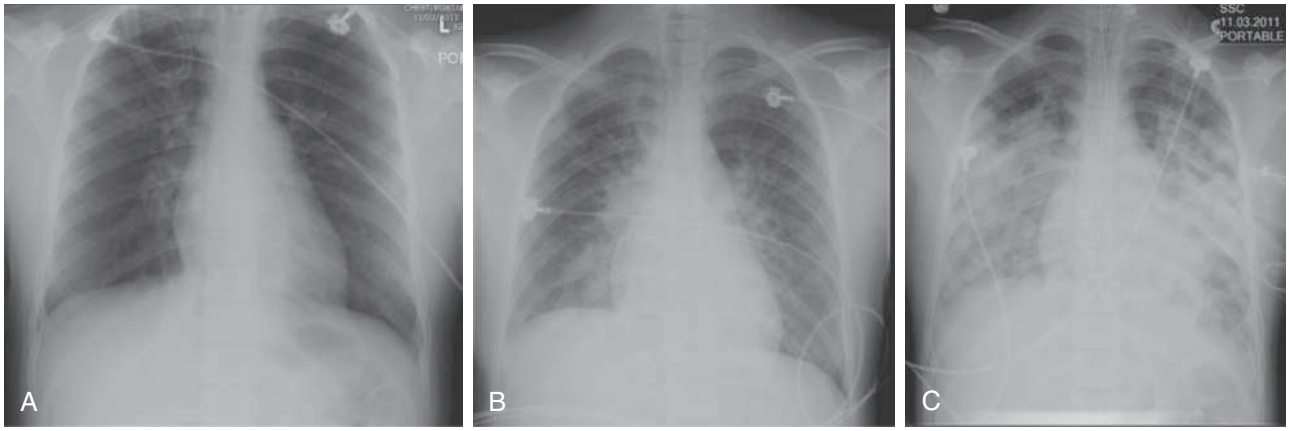

Fig. 164.2 An 11-year-old presented in respiratory distress; radiographs at presentation (A), 4 hours later following resuscitation (B) showing the development of diffuse bilateral infiltrates, and after intubation (C) as the patient rapidly progressed to respiratory failure. (Courtesy Dr. Eric R. Schmitt.)

pneumonia is rarely associated with meningitis, encephalitis, arthritis, rhabdomyolysis, and hemolytic uremic syndrome.

Differential Diagnoses

Unfortunately, no single finding can reliably differentiate pneumonia from other causes of respiratory distress in children.[7] The major conditions to be differentiated in children with pneumonia include bacterial pneumonias, viral disease, other unusual infectious causes (mycobacterial, protozoal, fungal), and noninfectious pathologic conditions (Box 164.1). Common infectious causes classically present with certain historical, clinical, and laboratory findings (Table 164.2). However, the broad spectrum of illness for each condition makes a definitive diagnosis difficult for any individual patient, and no specific feature can reliably differentiate bacterial from nonbacterial pneumonia. Providers should consider a bacterial cause in a child with a temperature higher than 39°C (102.2°F), clinical toxicity, lobar infiltrate, or pleural effusions (Fig. 164.3). Host factors, epidemiology, clinical presentation, and judicious use of diagnostic tests can establish a likely diagnosis and appropriate empiric management.

Bacterial Pneumonia

S. pneumoniae is one of the most frequently seen bacterial causes of pneumonia in children. Children with immunodeficiency, chronic renal disease, and functional or anatomic asplenia and Native Americans are at increased risk for *S. pneumoniae* infections. *S. aureus* pneumonia, although less common, tends to cause a more severe pneumonia and should be considered in any patient who is unusually ill appearing or presenting with respiratory failure or shock.[8] Children with foreign body aspiration, immunosuppression, or concomitant skin infections are at increased risk for *S. aureus* pneumonia. Progression of the disease is rapid, and empyema (90%), pneumatocele (50%), and pneumothorax (25%) are common complications (Fig. 164.4).

Before widespread immunization, *H. influenzae* type b was the second most common bacterial cause of pneumonia. However, its incidence has decreased by 90% since the advent of effective immunization. *H. influenzae* was previously considered a disease of younger children, but most cases now occur in older children.[9] Although clinically indistinguishable from *S. pneumoniae* pneumonia, *H. influenzae* pneumonia historically had a higher incidence of associated pleural effusions (25% to 75%) and bacteremia (75% to 95%).

Although still uncommon, the incidence of group A streptococcal pneumonia has increased since the 1980s. Group A streptococcal pneumonia may occur sporadically and may be a complication of varicella infection. It is typically a severe illness with abrupt onset, rapid progression to toxicity, and high fatality rate (30% to 60% fatality rate reported in a study of all ages).

In bacterial pneumonia beyond the neonatal period, fever is almost universal (often >39°C [102.2°F]). Patients usually have a cough and tachypnea disproportionate to fever and may also appear relatively toxic (e.g., pallor, poor tone, lethargy, delayed capillary refill). Focal lung findings (rales, wheezes, and decreased or bronchial breath sounds) are easier to appreciate in older children, whereas the physical examination in a younger child may be completely unrevealing.

BOX 164.1 Noninfectious Diagnoses for Patients Presenting With Lung Disease

Radiologic technique
- Inadequate inspiration
- Breast shadow
- Thymus
- Underpenetration

Primary pulmonary
- Asthma
- Bronchiectasis
- Atelectasis
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Pulmonary sequestration
- Congenital cystic adenomatoid malformation
- α_1-Antitrypsin deficiency

Aspiration
- Foreign body
- Chemical
- Recurrent, caused by anatomic or physiologic disorders

Primary cardiac
- Congenital heart disease
- Congestive heart failure

Pulmonary infarction
- Sickle cell vaso-occlusive crisis
- Pulmonary embolism

Collagen vascular disorders

Acute respiratory distress syndrome

Pleural effusion

Neoplasm

TABLE 164.2 Pneumonia Syndromes

	INFECTIOUS CAUSE			
Typical Feature	**Bacterial**	**Viral**	**Chlamydial**	**Mycoplasmal**
Historical				
Age	Any	Any	4–16 weeks	5–18 years
Fever	High (>39°C [102.2°F])	Low grade	Usually none	Low
Onset	Abrupt, often after upper respiratory infection	Gradual	Gradual	Gradual
Cough	Productive	Nonproductive	Staccato	Hacking
Associated symptoms	Chest pain; focal infarct	Myalgias, rash, sore throat, coryza	Conjunctivitis	Headache, sore throat, rash
Physical	Toxic appearance			
Lungs	Confined rales	Diffuse rales, wheeze, stridor	Diffuse rales, rare wheeze	Unilateral rales
Chest radiograph				
Infiltrate	Lobar or segmental	Interstitial	Diffuse, interstitial	Lobar or diffuse
Pleural effusion	Occasional	Rare	None	Rare
Other	Pneumatocele; abscess	Hyperinflation, atelectasis	Hyperinflation	
Laboratory test results	Increased WBC granulocytosis	Normal or increased WBC count, lymphocytosis	Normal WBC count, eosinophilia	Normal WBC count
Pathogens (common)	*Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus* <2 months—group B streptococcus; gram-negative enterics; *Listeria monocytogenes*	RSV, parainfluenza, influenza, adenovirus, enterovirus	*Chlamydia trachomatis*	*Mycoplasma pneumoniae*

RSV, Respiratory syncytial virus; *WBC,* white blood cell.

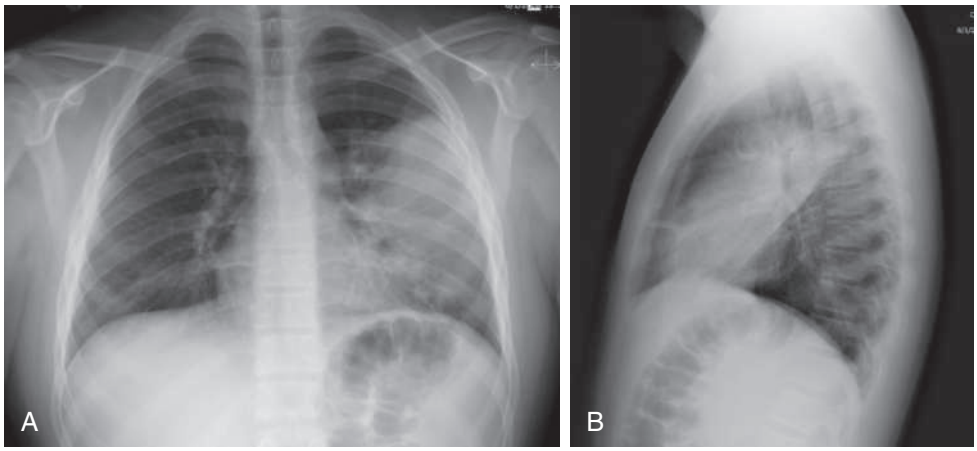

Fig. 164.3 Posteroanterior (A) and lateral (B) radiographs of a left upper lobe consolidation in a 15-year-old with pneumococcal pneumonia. (Courtesy Dr. Eric R. Schmitt.)

Viral Pneumonia

Viral pneumonia is more common in the winter season and generally has a gradual onset, often with associated cough, congestion, and low-grade fever. Tachypnea may be the only physical finding; however, retractions, rales, and wheezing are common. Grunting, cyanosis, lethargy, dehydration, and apnea are seen in more severely affected children.

Radiographic findings typically include hyperinflation and peribronchial thickening, with a diffuse increase in interstitial findings (Fig. 164.5). Patchy areas of consolidation may be present, representing lobular atelectasis or alveolar pneumonia (Fig. 164.6). Although lobar consolidation and small pleural effusions may occur in viral pneumonia, these findings are more consistent with a bacterial cause.

Children do not require chest radiography or viral testing to make the diagnosis of viral pneumonia, particularly in a child who presents during the winter months with fever, cough, congestion, and wheezing. Most viral pneumonias resolve without therapy; however, because of the possibility of secondary bacterial infection and the difficulty in differentiating between bacterial and viral pneumonia, antibiotics should be considered for a more severely ill child.[10] Complications seen with viral pneumonia include dehydration, local progression of the disease, bronchiolitis obliterans, and apnea (usually in the first 3 months of life).

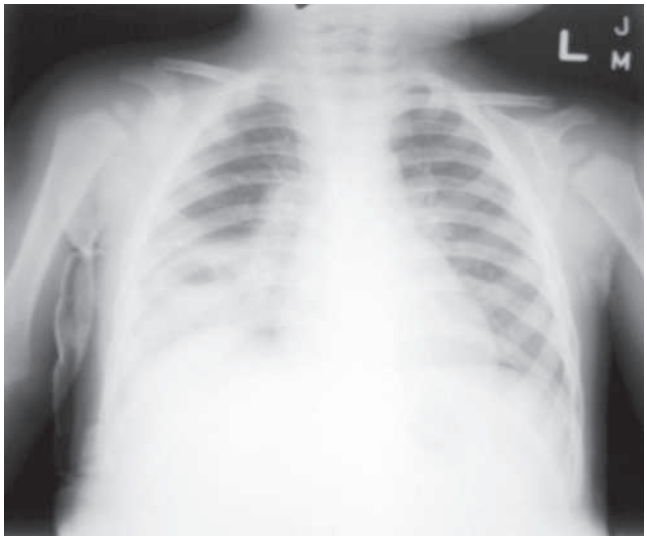

Fig. 164.4 Radiograph showing staphylococcal pneumonia, with empyema and abscess on the right. (Courtesy Dr. Brianna Enriquez and Dr. Marianne Gausche-Hill.)

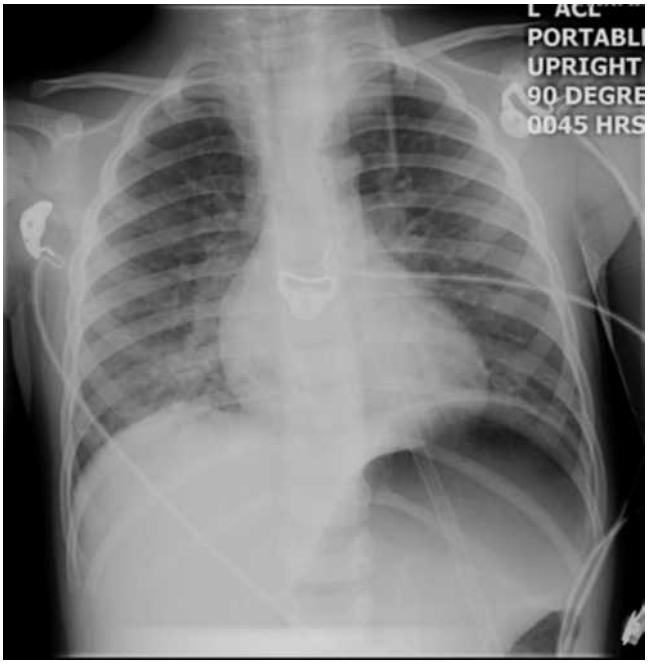

Fig. 164.5 Radiograph of a 3-year-old with viral pneumonia showing hyperinflation, peribronchial thickening, and diffuse interstitial infiltrates. (Courtesy Dr. Eric R. Schmitt.)

Mycoplasma Pneumonia

Mycoplasma pneumonia accounts for 10% to 20% of all pediatric pneumonias. It occurs more commonly in 5- to 18-year-olds, but can be seen in younger children (although rare in infants younger than 1 year).[3] Onset is classically gradual and insidious, but some patients may have an abrupt onset of symptoms. Prodromal symptoms include fever, headache, and malaise, followed several days later by a nonproductive, hacking cough. Associated symptoms of infection may include hoarseness, sore throat, and chest pain; coryza is unusual.

Children with mycoplasma pneumonia generally appear nontoxic and may have rales or, less often, wheezing. Patient may have associated pharyngitis, cervical lymphadenopathy, conjunctivitis, or otitis media.

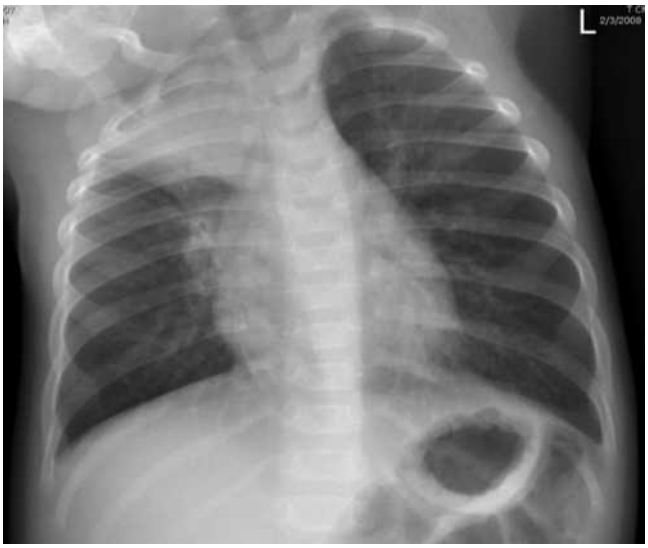

Fig. 164.6 Radiograph showing right upper lobe atelectasis and bilateral interstitial infiltrates in a 9-month-old. (Courtesy Dr. Eric R. Schmitt.)

A rash is present in 10% of patients but can take various forms: urticaria, erythema multiforme, maculopapules, or vesicles. *Mycoplasma* infection is typically benign and self-limited but can play a significant role in the exacerbation of asthma and may cause chronic pulmonary structural abnormalities (e.g., pneumatocele, pleural effusion, pneumothorax, or bronchiectasis). Physical findings are generally less impressive than the radiographic picture. Radiographic findings typically show lower lobar consolidation, but scattered segmental infiltrates and interstitial disease can also be seen (Fig. 164.7). Pleural effusions are uncommon. The white blood cell (WBC) count is usually normal.

Because specific testing and treatment is not applicable to the emergency department (ED) setting, infection is diagnosed clinically and treated empirically. Cold agglutination is rarely used nowadays and is not accurate, particularly in patients younger than 12 years old. Diagnosis may be confirmed with acute and convalescent antibody titers; however, patients may take 4 to 6 weeks to seroconvert, and some patients may fail to mount an immune response altogether. Multiplex polymerase chain reaction (PCR) panels can demonstrate the vital etiology and also bacterial causes including *M. pneumoniae*. Complications of mycoplasma pneumonia are varied, but unusual, and include hemolytic anemia, hemolytic uremic syndrome, myopericarditis, neurologic disease (e.g., meningoencephalitis, Guillain-Barré syndrome, transverse myelitis, and cranial neuropathy), rhabdomyolysis, arthritis, and Stevens-Johnson syndrome.[11,12]

Chlamydia Pneumonia

C. trachomatis is a common sexually transmitted organism that causes cervical infection in 2% to 30% of pregnant women. It is transmitted from the genital tract of infected mothers to their newborn infants, resulting in conjunctivitis in 22% to 44% and pneumonia in 5% to 20%.[13] An infant with pneumonia caused by *C. trachomatis* presents at 3 to 19 weeks of age after colonization at birth. The illness usually begins with nasal congestion followed by cough. In 50% of cases, conjunctivitis precedes the onset of respiratory symptoms. The infant is often afebrile and alert but tachypneic, with a repetitive staccato cough that may interfere with feeding or sleeping. It can resemble the paroxysms of pertussis and occasionally precipitates episodes of alarming respiratory distress. Mild retractions and diffuse inspiratory rales may be noted on chest examination; expiratory wheezing is usually absent or minimal. Middle ear abnormalities are present in 50% of cases.

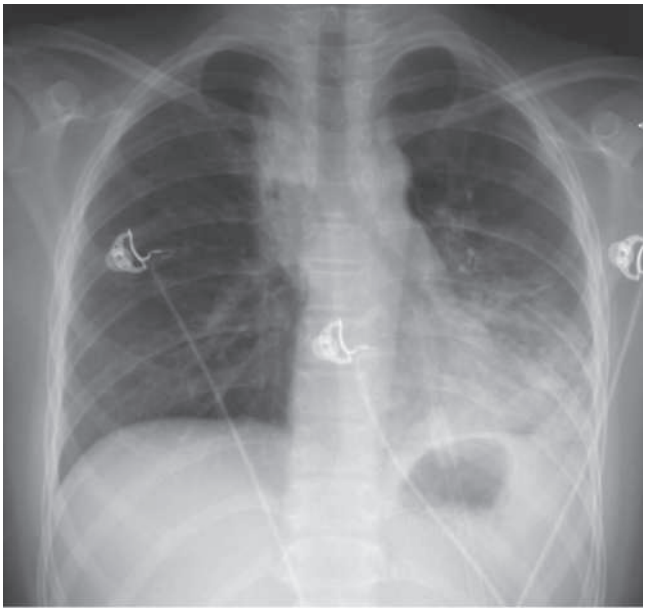

Fig. 164.7 Radiograph of a 12-year-old showing a left lower lobe infiltrate consistent with mycoplasma pneumonia. (Courtesy Dr. Eric R. Schmitt.)

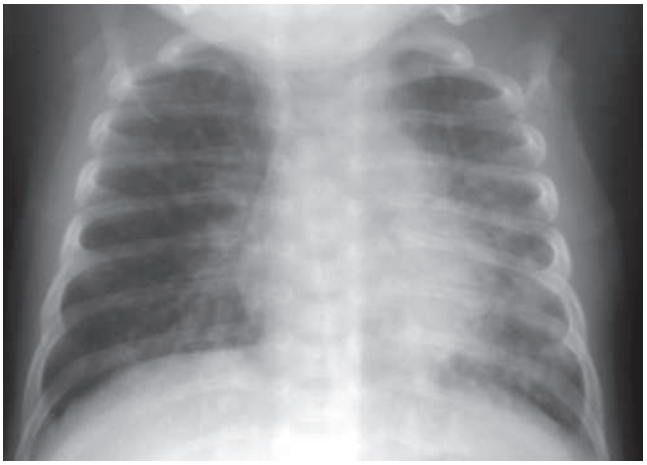

Fig. 164.8 Radiograph showing chlamydial pneumonia in an infant. Note the symmetric interstitial infiltrates. (Courtesy Dr. Michael Diament.)

Chest radiograph usually shows hyperinflation with bilateral and symmetric, diffuse, interstitial infiltrates (Fig. 164.8). Nucleic acid amplification tests have replaced other detection methods (e.g., culture, direct fluorescent antibody tests) because of their higher sensitivity and specificity. Chlamydial pneumonia is often a mild illness but may rarely be complicated by apnea and hypoxemia. Treatment with erythromycin may shorten the course; however, the disease tends to be protracted, and cough and tachypnea can persist for weeks despite antibiotic treatment.

C. pneumoniae is a species of *Chlamydia* that is antigenically, genetically, and morphologically distinct from other *Chlamydia* species. *C. pneumoniae* infection is transmitted from person to person, may play a role in respiratory tract infections in infants and young children, and may cause mild illness or asymptomatic infection in children and adults. Like *Mycoplasma, C. pneumoniae* may play a greater role in pediatric pneumonia than was previously thought. It has been reported to cause sore throat, fever, headache, pertussis-like cough, pneumonia, and influenza-like illness.[14] Outbreaks have been reported in schools, daycare centers, military camps, adolescents, and families. Infection with *C. pneumoniae* can trigger acute episodes of wheezing in children with asthma. Infection can be confirmed with PCR testing.

Aspiration Pneumonia

Aspiration pneumonia may be due to mechanical, chemical, or bacterial causes. Bacterial aspiration occurs in children with anatomic abnormalities and central nervous system disturbances that impair normal swallowing or protective airway reflexes.[15] Pulmonary damage results from chemical (e.g., stomach acid) and bacterial (e.g., gastrointestinal and upper respiratory organisms) insults. Within several hours of the aspiration, the child may have the onset of cough, tachypnea, and fever. Physical examination commonly reveals rales and wheezing, with cyanosis as the disease progresses. Radiographic findings include both localized (right middle lobe or lower lobe) and diffuse/bilateral infiltrates.

Pneumonia in the Immunocompromised Patient

Children with chronic disease and congenital, acquired, and iatrogenic immunodeficiencies are susceptible to the aforementioned respiratory pathogens and to a multitude of opportunistic organisms, including *P. jiroveci,* CMV, and fungi. Presenting symptoms may be similar to those in normal hosts; however, the course tends to be more rapid, severe, and fulminant. While awaiting organism identification and the results of culture, patients should be hospitalized for monitoring, supportive therapy, and treatment with intravenous antibiotics active against a broad spectrum of organisms. Invasive sampling for diagnosis of potentially treatable organisms may need to be considered if the patient fails to improve after initial therapy.

Diagnostic Testing

Radiography. A chest radiograph is unnecessary in children without comorbid conditions who have no fever, tachypnea, or focal findings on auscultation, because they are unlikely to have pneumonia. Chest radiography can also be deferred in a well-appearing child who has pneumonia based on clinical presentation (fever, tachypnea, abnormal lung auscultation). We recommend that any child who appears ill or in whom the diagnosis is unclear receives radiographic evaluation, with chest radiography. A clear chest radiograph (without infiltrate) is sufficient to exclude pneumonia in the majority of children.[16,17] However, an infiltrate may not be initially apparent in a dehydrated child with suspected pneumonia, only becoming visible on subsequent imaging after rehydration (see Fig 162.2).

Although great variability exists, bacterial pathogens classically produce alveolar infiltrates in a lobar distribution (Fig. 164.9) but may produce diffuse interstitial infiltrates. Viral and chlamydial infections tend to appear as diffuse interstitial infiltrates, commonly with hyperinflation and atelectasis (see Fig. 164.5). Chest radiographs can identify multilobar disease, pleural effusions, pneumatoceles, and pneumothorax (see Fig. 164.4). Hilar adenopathy may indicate tuberculosis or malignant neoplasm.

Lateral decubitus radiographs in patients with pleural effusions can help assess effusion size and loculation. Computed tomography (CT) may be useful to provide greater detail of effusions and lung abnormalities in critically ill children with complicated pneumonia, or when alternative pathology is suspected based on the plain radiograph (Fig. 164.10). Routine CT of the chest to establish the diagnosis is not recommended.

Ultrasound. Recent studies have examined the utility of lung ultrasound for the diagnosis of pneumonia in children.[18] Most studies use highly skilled sonographers with specific training in pediatric

thoracic ultrasound, and this level of expertise is not widely available.[19] When performed by a skilled sonographer, ultrasound has sensitivity similar to chest radiography, although it may not be as specific.[20] Ultrasound predicts the presence of consolidation on chest radiography; the best correlation occurs when the consolidation measures greater than 1 cm on ultrasound.[21,22] When available, a positive ultrasound study may safely allow for the reduction of chest radiography.[23]

Laboratory Studies. Children with pneumonia are at risk for hypoxemia and should undergo pulse oximetry to determine oxygen saturation; arterial or venous blood gas analysis should be reserved for patients in significant distress or respiratory failure to monitor respiratory status or response to therapy. A complete blood count (CBC) is not useful in differentiating between viral and bacterial pneumonia and should not be obtained unless the results will change management. We do not recommend blood cultures in otherwise well-appearing children with uncomplicated pneumonia, because they are unlikely to be helpful.[24] Blood cultures may be considered in ill-appearing hospitalized patients.[8,25] Sputum cultures are technically difficult in younger children and should not be routinely obtained.[18]

Patients with pleural effusions that are enlarging or compromising respiratory function should undergo thoracentesis for diagnostic and therapeutic purposes. Although parapneumonic effusions are most suggestive of bacterial infection, they also occur with mycoplasmal and occasionally with viral infections. The fluid should be sent for Gram staining and culture (anaerobic and aerobic bacterial), cell count and differential, total protein level, pH, and glucose concentration. Interpretation of pleural fluid in children follows adult guidelines (see Chapters 62 and 63). Cultures for rare pathogens may be considered if the initial assessment is not diagnostic or specific risk factors are identified. Bronchoscopy with bronchoalveolar lavage may be useful in a child who is severely ill or refractory to treatment.

Rapid antigen testing for RSV is not indicated unless the result would change management (e.g., risk stratification in a young infant with fever, or to cohort for inpatient treatment).[26] A real-time influenza PCR assay may be helpful for atypical cases when the use of antivirals is being considered.[18] However, influenza may be diagnosed clinically during times of high prevalence (i.e., a higher likelihood of a false negative influenza assay). Children at higher risk (e.g., children <2 years or those with significant comorbid disease) should be empirically treated with antivirals without confirmatory testing. Although most pediatric patients with tuberculosis do not have pulmonary symptoms, testing for tuberculosis should be considered for patients with lobar pneumonia, pulmonary effusions, or hilar adenopathy, especially in immunocompromised children or children who have recently immigrated from less developed countries.

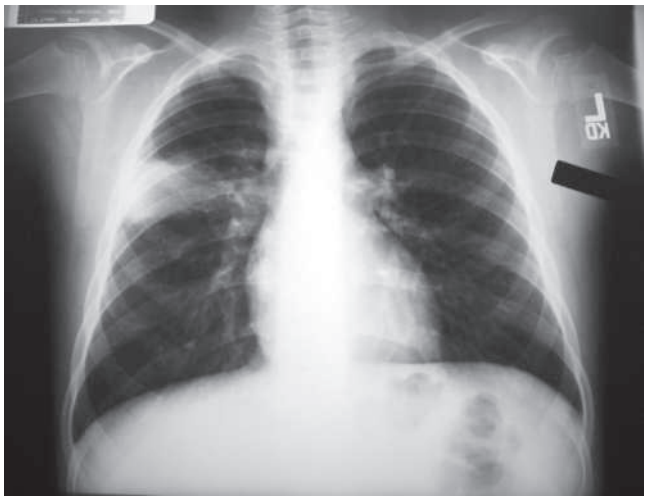

Fig. 164.9 Radiograph showing pneumococcal pneumonia, with infiltrate in the right upper lobe. (Courtesy Dr. Marianne Gausche-Hill.)

Management

Treatment of pneumonia in a pediatric patient consists of appropriate antimicrobial use and supportive therapy (Table 164.3). Because of the difficulty in identifying a specific pathogen, antibiotic choice is generally empirical. The three most important factors in directing management are the patient's age, likely pathogen, and degree of illness.

Infants Younger Than 2 Months. An infant younger than 2 months with pneumonia should usually be admitted to the hospital and monitored with continuous pulse oximetry for signs of needed respiratory support; apnea and respiratory failure may be precipitous. This age group is immunologically immature, and signs of sepsis may be subtle. We recommend blood, urine, and cerebrospinal fluid cultures before the initiation of antibiotics when possible (see Chapter 161). In infants younger than 1 month, ampicillin, plus ceftazidime, or gentamicin (recommended in premature infants) are appropriate choices; ampicillin and ceftriaxone should be used for infants 1 to 2 months of age. If *C. trachomatis* or *B. pertussis* is suspected, the infant should also be treated with azithromycin or erythromycin (given the association of erythromycin with infantile hypertrophic pyloric stenosis, we recommend azithromycin when available).

Infants 2 to 3 Months of Age. Blood and urine cultures should be obtained for infants 2 to 3 months of age. The decision to perform a

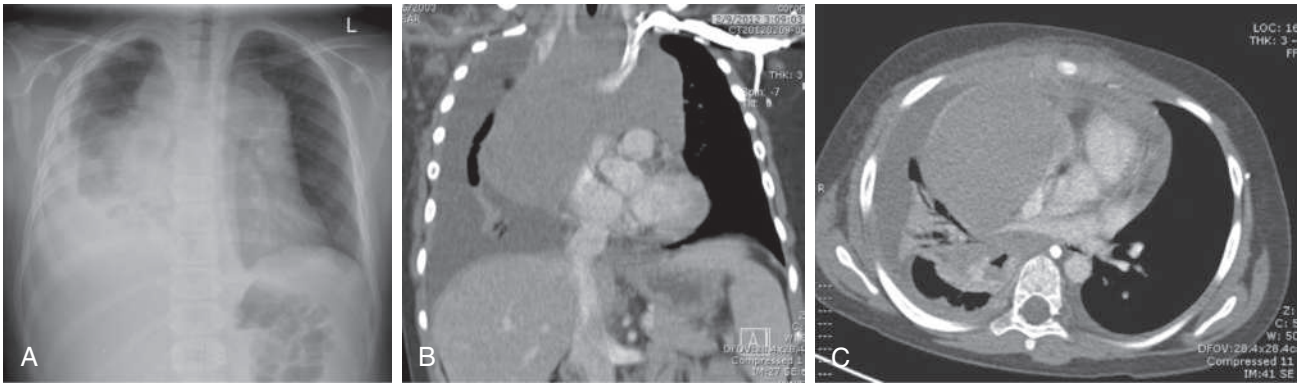

Fig. 164.10 Radiograph (A) of an 8-year-old that was initially interpreted as a right-sided pneumonia with effusion; coronal (B) and axial (C) computed tomography images demonstrate a large mediastinal mass later determined to be a T-cell lymphoma. (Courtesy Dr. Eric R. Schmitt)

TABLE 164.3 Empiric Antibiotic Treatment of Bacterial Pneumonia

Age Group	Most Frequent Pathogens	Outpatient Treatment	Inpatient Treatment
Neonate (<4 weeks)	Group B streptococcus, *Escherichia coli*, other gram-negative bacilli		Ampicillin (150–200 mg/kg/day every 6 hours) + ceftazidime (100 mg/kg/day every 12 hours) *or* Gentamicin (2.5 mg/kg daily) Avoid ceftriaxone.[a]
4 weeks–3 months	*Streptococcus pneumoniae, Haemophilus influenzae, Chlamydia trachomatis* (if afebrile)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5) *or* Erythromycin (50 mg/kg/day every 6 hours)	Ampicillin (150–200 mg/kg/day every 6 hours) + ceftriaxone (50 mg/kg daily)
	Bordetella pertussis (if afebrile and prolonged cough)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5)
3 months–4 years	*S. pneumoniae, H. influenzae,* group A streptococcus	Amoxicillin (75–90 mg/kg/day every 12 hours) *or* Amoxicillin–clavulanic acid (90 mg/kg/day of the amoxicillin component every 8 hours) *or* Cefuroxime (20-30 mg/kg/day every 12 hours)	Ceftriaxone (50 mg/kg daily) *or* Ampicillin (150–200 mg/kg/day every 6 hours) In critically ill patients add: clindamycin (40 mg/kg/day every 6 hours) *or* vancomycin (10–20 mg/kg IV every 6–8 hours) for coverage of MRSA[b]
	Mycoplasma pneumoniae	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5) *or* Clarithromycin (15 mg/kg/day every 12 hours)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5) *or* Erythromycin (20 mg/kg/day every 6 hours)
	B. pertussis (if afebrile and prolonged cough)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5)
≥5 years	*M. pneumoniae, Chlamydophila pneumoniae*	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5) *or* Clarithromycin (15 mg/kg/day every 12 hours)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5) *or* Erythromycin (20 mg/kg/day every 6 hours)
	S. pneumoniae, H. influenzae	Amoxicillin (75–90 mg/kg/day every 12 hours) *or* Amoxicillin–clavulanic acid (90 mg/kg/day of the amoxicillin component every 8 hours) *or* Cefuroxime (20–30 mg/kg/day every 12 hours)	Ceftriaxone (50 mg/kg daily) *or* Ampicillin (150–200 mg/kg/day every 6 hours) In critically ill patients add: clindamycin (40 mg/kg/day every 6 hours) *or* vancomycin (10–20 mg/kg IV every 6–8 hours) for coverage of MRSA[b]
	B. pertussis (if afebrile and prolonged cough)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5)	Azithromycin (10 mg/kg on day 1, 5 mg/kg daily on days 2–5)

[a]Ceftriaxone is not preferred in neonates due to risk of hyperbilirubinemia, particularly in premature infants.
[b]*MRSA,* Methicillin-resistant *Staphylococcus aureus*.

lumbar puncture depends on clinical suspicion of central nervous system infection. Ampicillin and ceftriaxone should be given for an infant 2 to 3 months old. If *C. trachomatis* or *B. pertussis* is suspected, the infant also should be treated with azithromycin or erythromycin. Supportive therapy in this age group consists of fever control and hydration. As with infants under 2 months of age, we recommend admission for infants 2-3 months of age, as they are only partially protected against *S. pneumoniae* and *H. influenzae* with one dose of vaccinations.

Infants and Children Older Than 3 Months. In an older child, pneumonia should be categorized into likely bacterial, viral, or mycoplasmal. The emergency clinician should base the presumptive causative diagnosis on clinical and radiographic findings (if obtained). A toxic child with high fever and lobar consolidation is likely to have a bacterial process, whereas a child with a disease of gradual onset, low-grade fever, and interstitial infiltrate with air trapping is more likely to have a viral process.

A well-appearing infant or preschool-age child with isolated pneumonia may be treated with outpatient oral antibiotics. In an infant beyond the neonatal period or a preschool-age child, high-dose amoxicillin is the first line agent and will treat susceptible *S. pneumonia*.[27] Amoxicillin–clavulanic acid is a second line agent and includes some gram-negative and methicillin-sensitive *S. aureus* coverage. Oral cephalosporins are relatively poorly absorbed and highly protein-bound, resulting in inferior pharmacokinetics as compared with amoxicillin; we recommend their use be reserved for penicillin-allergic patients. Azithromycin should not be used to treat *S. pneumoniae,* because there is significant resistance, but it is appropriate therapy for presumed atypical pneumonias in this age group. Azithromycin is the antibiotic of choice in a school-age child or adolescent, in whom *M. pneumoniae* and *C. pneumoniae* are more common. Uncomplicated bacterial pneumonia often has a rapid response to antibiotics; a stagnant or

worsening clinical picture should prompt further investigation (e.g., postobstructive pneumonia from an unrecognized foreign body).

Children with neurologic or anatomic abnormalities who aspirate oral or gastric contents are susceptible to pneumonia, predominantly from anaerobes. Penicillin (100,000 to 250,000 units/kg/day every 4 to 6 hours) and clindamycin are appropriate first line antibiotic choices. In seriously ill patients or patients not responding, agents such as metronidazole (40 mg/kg/day every 6 hours) and cefoxitin (80 to 160 mg/kg/day every 4 to 6 hours) may be administered. Nosocomial infections should be treated with antibiotics also active against aerobes and gram-negative bacilli. Children with significant aspiration should be admitted to the hospital, and supportive therapy should include hydration, supplemental oxygen, and oropharyngeal suctioning.

Disposition. Well-appearing children who can maintain hydration and are not in respiratory distress should be considered for outpatient management. Oral antibiotic therapy is appropriate if there is concern for bacterial etiology. Children treated as outpatients should be reevaluated within 24 to 48 hours.[2] Inpatient hospitalization for parenteral antibiotic therapy should be considered for patients who are dehydrated or clinically worsening; a repeat chest radiograph may reveal progression of disease or development of a pleural effusion.

Indications for hospitalization at the time of diagnosis include a toxic appearance, vomiting or dehydration, respiratory compromise (e.g., distress, hypoxia, or inadequate ventilation), multilobar disease, pleural effusions, impaired immune function, and unreliable social environments. Strong consideration should be given to hospitalization of children younger than 6 months, because they are more prone to complications of bacterial pneumonia than older children. Supportive therapy for the inpatient should include maintenance of hydration, fever control, supplemental oxygen, ventilatory assistance, and pleural fluid drainage, as indicated. Parenteral antibiotic therapy should be administered until clinical improvement.

Long-term management of a child with pneumonia should include a clinical reevaluation 2 to 3 weeks after diagnosis. If the child had a prompt response to therapy and is well at the follow-up evaluation, a repeat radiograph is unnecessary at this time. If the child had a complicated course (e.g., pleural effusion) or residual symptoms or if the illness is not the child's first episode of pneumonia, a chest radiograph can ensure resolution.

Pertussis

Pertussis, or whooping cough, is a respiratory tract infection, classically seen in infants younger than 6 months. The incidence of pertussis increased in the 1980s and 1990s, especially in adolescents and adults, likely due to waning immunity.[28] More recently, inconsistent immunization has led to epidemics in vulnerable populations.[29]

Pertussis disease is characterized by three clinical stages—catarrhal stage, paroxysmal stage, and convalescent stage. Pertussis begins with mild upper respiratory tract symptoms and cough; this *catarrhal stage* usually lasts 1 to 2 weeks. The disease progresses to severe paroxysms of a staccato cough *(paroxysmal stage),* followed by posttussive emesis, and may be accompanied by periods of cyanosis and apnea in infants younger than 6 months. The classic whoop is rare, occurring in only 6% of patients and generally seen in children older than 2 to 3 years. Fever is often absent, and the examination findings are remarkably normal between paroxysms. The paroxysmal stage lasts 2 to 4 weeks and is followed by a *convalescent stage*, during which symptoms gradually wane. The duration of the illness in more complicated cases may be 6 to 10 weeks. Immunization is only 80% effective in providing immunity after three doses, making pertussis possible in immunized infants.[30]

The WBC count (if obtained) is usually elevated, often with a marked lymphocytosis. The chest radiograph may show a shaggy, right-sided heart border or have clear lung fields. *B. pertussis* is a fastidious organism, making culture difficult. The organism is most easily recovered in the catarrhal or early paroxysmal stages. Cultures may be negative during the first week or after the fourth week of illness in immunized patients or in patients treated with antibiotics. The PCR assay has been increasingly used for the detection of *B. pertussis,* because of its high sensitivity and more rapid turnaround time than culture.

Pertussis is a particularly severe disease in the first year of life and is often complicated by apneic episodes; less common complications include seizures, secondary bacterial pneumonia, encephalopathy, and death.[31] Pertussis has been increasing in incidence among immunized children and young adults who have waning immunity. The illness in these older patients does not follow the classic stages as described earlier; patients have a mild but prolonged course (often lasting 3 weeks or more), with a dry cough as the predominant symptom.

Because of the risk of apnea, we recommend that all children younger than 3 to 6 months with presumed pertussis be observed in the hospital for monitoring and supportive care, and treated with azithromycin or erythromycin. Antimicrobials have no effect on disease progression after the beginning of the paroxysmal stage but limit the spread of organisms. Vaccination of all health care workers and the general adult population with tetanus, diphtheria, and pertussis (Tdap) is recommended and has been shown to decrease rates of pertussis in infants.

Cystic Fibrosis

CF is an autosomal recessive disease caused by a mutation in the CF transmembrane conductance regulator *(CTFR)* gene. In Whites, approximately 1 in 25 is a carrier, and the disease has an incidence of 1 in 2500 births. The disease also is present (in decreasing incidence) in Hispanics, Native Americans, African Americans, and Asians. Progressive lung disease and infection account for most of the morbidity and nearly all the mortality in those with CF.[32] Defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, decreased antimicrobial effect of the airway surface, increased bacterial adherence, and innate secretion of inflammatory cytokines. All these factors result in a unique sensitivity to bacterial infection of the airway.

Chest radiographic findings of CF include emphysema, peribronchial thickening, bronchiectasis, and focal infiltration, which may be linear or nodular (Fig. 164.11). Identification of the pathogens involved is crucial to the effective treatment of pulmonary infections in CF patients (usually through sputum culture), although early childhood pneumonias in patients with CF are predominantly caused by *S. aureus* and *H. influenzae*. With the emergence of methicillin-resistant *S. aureus* (MRSA), careful attention should be paid to antibiotic coverage. Patients receiving antistaphylococcal prophylaxis may be at increased risk for pseudomonal infections. By 18 years of age, 80% of patients are permanently colonized with *P. aeruginosa*. Acute infective exacerbations generally are managed by oral and intravenous antimicrobial drugs, typically a penicillin (e.g., ticarcillin or piperacillin) or ceftazidime, combined with an aminoglycoside for synergistic effects. If a patient's previous sputum culture results are available, antibiotic coverage for the last known bacterial pathogen should be used. Resistant strains may benefit from imipenem or meropenem, and patients should often be hospitalized for the course of therapy.[33] *Burkholderia cepacia* is a significant pathogen in CF patients and has been associated with an accelerated decline in clinical status and increased mortality. Antimicrobial coverage is similar to that for *Pseudomonas*, although resistance is common and the existence of differing colonization and resistance patterns of patients with CF necessitates respiratory isolation from other susceptible individuals.

Clearance of the thick mucoid secretions is important for treatment. Patients may respond favorably to bronchodilator therapy and to mucolytics, such as inhaled *N*-acetylcysteine, in the acute setting. Chest physiotherapy provided by a high-frequency oscillator device is often used. A flutter valve or positive expiratory pressure mask may be of assistance for improved mucoid clearance. Short-term control of

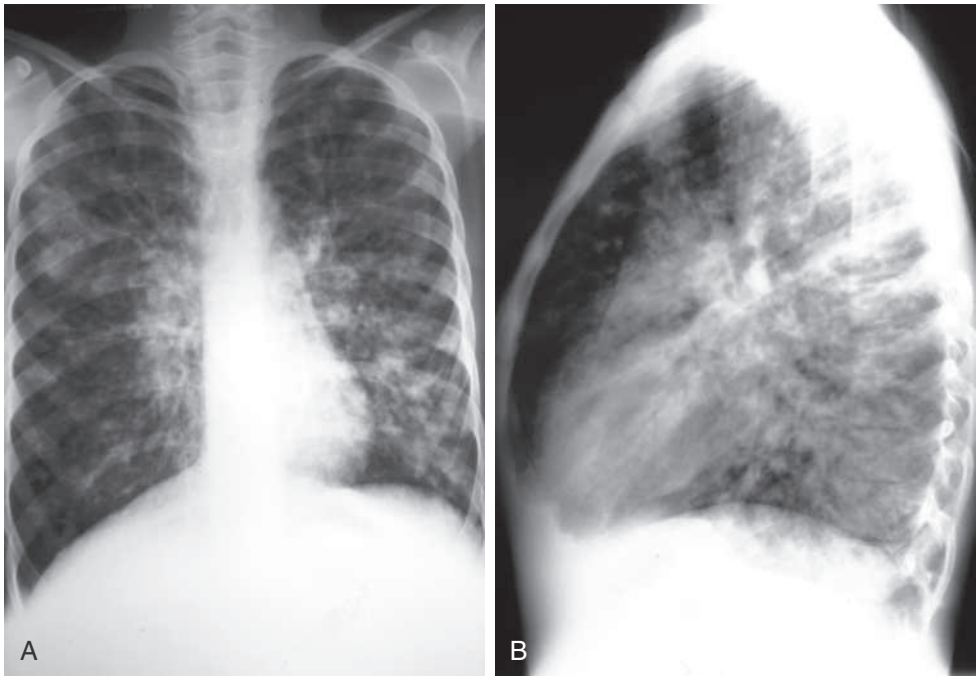

Fig. 164.11 Posteroanterior (A) and lateral (B) radiographs of a teenager with cystic fibrosis. Note emphysema and nodular infiltrates. (Courtesy Dr. Michael Diament.)

inflammation may be obtained by inhaled corticosteroids. Given the complicated nature of these patients and the need for individualized treatment plans, we recommend early consultation with a pediatric pulmonologist.

Bronchopulmonary Dysplasia

BPD is defined as the need for supplemental oxygen 28 days postnatally.[34] BPD is a common cause of diffuse lung disease in infants. Approximately 40% of children with a birth weight less than 1000 g will develop BPD. The severity of disease is related to several factors, including degree of prematurity, use of peripartum steroids, damage incurred by ventilation in the neonatal period, and nutritional status.[35] Infants with BPD have greatly increased rates of hospitalization because of respiratory illness in the first year of life, approaching 65% in infants born weighing less than 1000 g.

Immunizations are used to help prevent pneumonia in patients with BPD. All infants 6 to 23 months old should receive the influenza vaccine during the appropriate season. The 13-valent pneumococcal vaccine and *H. influenzae* type b vaccine are especially important for the prevention of bacterial pneumonia. Monthly prophylaxis against RSV with the monoclonal immunoglobulin palivizumab should be administered to carefully selected patients because it reduces the incidence of RSV disease and risk of subsequent hospitalization.

Patients with BPD have increased airway resistance, decreased lung compliance, and obstructive lung disease. Pneumonia in patients with BPD may be complicated by a reactive airway component. If complicated by pneumonia, radiographs show marked hyperinflation and infiltrates (Fig. 164.12). Inhaled bronchodilators may be efficacious, although these medications may worsen air exchange in patients with concomitant airway malacia. Hypoxia and hypercarbia are common, despite an increased respiratory effort. Patients with severe BPD may be receiving long-term diuretic therapy to improve lung mechanics; care should be taken not to confuse pneumonia with cor pulmonale, which can occur in younger infants with chronic supplemental oxygen requirements.

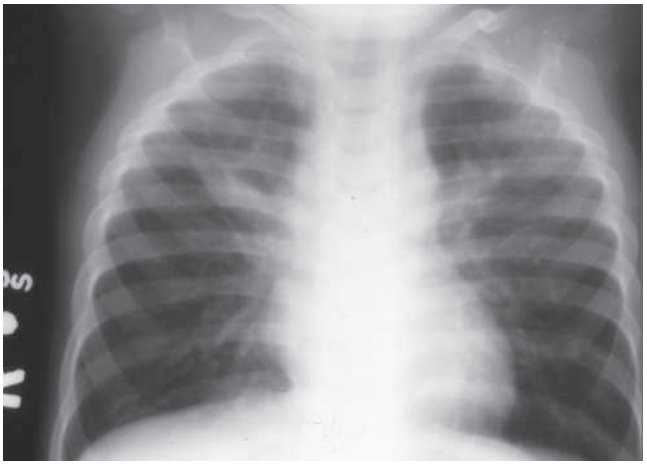

Fig. 164.12 Radiograph of a child with bronchopulmonary dysplasia showing findings of chronic lung disease and hyperinflation. (Courtesy Dr. Michael Diament.)

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 164: QUESTIONS AND ANSWERS

1. A 5-month-old boy presents with a cough. His parents report that for the past several weeks he has had mild respiratory tract symptoms and cough; however, during the past day, he has developed a severe paroxysm of staccato cough followed by posttussive emesis. What is the most appropriate antibiotic choice for this patient?

a. Amoxicillin
b. Ampicillin
c. Azithromycin
d. Trimethoprim-sulfamethoxazole

Answer: C. This patient likely has pneumonia caused by *Bordetella pertussis*. All children younger than 6 months with presumed pertussis should be observed in the hospital for monitoring and supportive care. First line treatment is with azithromycin, and erythromycin is a possible alternative. Amoxicillin and ceftriaxone are used to treat other types of pneumonia.

2. Which of the following findings is an indication for admission to the hospital in children with a diagnosis of pneumonia?

a. Abnormal chest radiograph showing pulmonary infiltrates
b. Decreased breath sounds in a lower lung field
c. Dehydration and vomiting
d. Diffuse rales and mild tachypnea

Answer: C. Many children with pneumonia can be managed as an outpatient with appropriate therapy. Clinical dehydration or inability to orally maintain hydration should prompt admission for ongoing treatment and monitoring. Abnormal lung auscultation or findings on

CHAPTER 164: QUESTIONS AND ANSWERS—cont'd

a chest radiograph by themselves would not be contraindications to outpatient treatment.

3. Which of the following statements best describes the epidemiology of pneumonia in children?
   - **a.** B*ordetella pertussis* is the most common cause in infants.
   - **b.** *Haemophilus influenzae* type b is still an important pathogen.
   - **c.** *Listeria monocytogenes* may cause illness in children younger than the age of 5 years.
   - **d.** Viral agents are the most common cause of pneumonia in children overall.

Answer: D. Viral agents are the most common cause of pneumonia in children. Bacteria predominate in neonates but are less common causative agents in toddlers and older children. Although *L. monocytogenes* may cause pneumonia in infants, it is rare after 3 months of age. *H. influenzae* type B has decreased by 90% since the onset of immunization of infants and young children.

4. What is the most common viral agent causing pneumonia in infants younger than 1 year?
   - **a.** Adenovirus
   - **b.** Enterovirus
   - **c.** Epstein-Barr virus
   - **d.** Respiratory syncytial virus (RSV)

Answer: D. RSV and parainfluenza are the most common viral agents in infants younger than 1 year. Viruses that may be responsible for the other agents may also cause viral pneumonia but are not as common as RSV.

5. A 2-year-old presents with fever, cough, and rales. Chest radiograph reveals right middle lobe pneumonia. Which of the following antibiotics would be recommended for outpatient treatment for this toddler who is not penicillin allergic?
   - **a.** Amoxicillin
   - **b.** Azithromycin
   - **c.** Ceftriaxone
   - **d.** Cephalexin

Answer: A. High-dose amoxicillin is the treatment of choice for children with pneumonia younger than 5 years. Once the child reaches school age, azithromycin is suggested as empirical therapy because of the increased risk of *Mycoplasma pneumoniae* infection.

Pediatric Cardiac Disorders

Timothy Horeczko

KEY CONCEPTS

- Consider a congenital heart defect in an infant with central cyanosis who does not respond to 100% supplemental oxygen (hyperoxia challenge).
- Neonates with ductal-dependent cardiac lesions typically present within the first 2 to 3 weeks of life with either acute cyanosis or shock. Prostaglandin E_1 (alprostadil, 0.05 to 0.1 μg/kg/min) can maintain a patent ductus arteriosus to supply mixed blood and temporize the patient.
- Treatment of a hypoxic "tet spell" first includes the placement of an infant in the knee-to-chest position (or an older child in a squatting position) to increase systemic vascular resistance (SVR) and the provision of supplemental oxygen. Sedative agents can be used to decrease hyperpnea. Various medications can be used as adjunctive treatment to increase the SVR and thereby decrease the degree of right-to-left shunting across the ventricular septal defect (VSD).
- Prompt recognition of the clinical findings and symptoms of Kawasaki disease along with the rapid initiation of high-dose aspirin and intravenous immune globulin (IVIG) infusion may prevent the formation of coronary aneurysms.
- Acute bacterial endocarditis should always be considered in a child with a known congenital heart defect or an acquired cardiac defect who presents with fever of unknown origin, acute neurologic deficits, new-onset microscopic hematuria, myalgias, splenomegaly, petechiae, or other signs of systemic embolization.
- Oxygen, positive-pressure ventilation (noninvasive or invasive), diuretics, and possibly inotropes are the main emergency department (ED) treatment of infants and children who present with congestive heart failure (CHF). Nitroglycerin can cause profound hypotension in children and is not a first-line therapy.
- If vagal maneuvers fail to convert stable paroxysmal supraventricular tachycardia in children, rapid adenosine administration (0.1 mg/kg for the first dose, followed by 0.2 mg/kg on repeated doses) is the treatment of choice. Verapamil should be avoided in children because of its profound hypotensive effects.
- Young athletes with a positive family history of sudden unexplained death or exertion-induced symptoms (such as, chest pain, dyspnea, palpitations, and syncope) should be evaluated by a cardiologist before their resumption of vigorous activity.

FOUNDATIONS

Children with cardiac disorders present to the emergency department (ED) in one of two scenarios. In the first scenario, the child presents with an exacerbation or complication of an already known underlying cardiac disorder. Early consultation with the child's cardiologist along with comparisons of the child's previous and most recent diagnostic studies are very useful in the evaluation and management phases.

The second scenario represents more of a challenge to the emergency clinician: the child with an undiagnosed congenital or acquired cardiac disorder who presents with concerning signs and symptoms (Box 165.1).

Fetal and Neonatal Circulation

During fetal development, blood oxygenated by the placenta flows to the fetus through the umbilical vein, bypasses the fetal liver through the ductus venosus, and returns to the fetal heart through the inferior vena cava. From the inferior vena cava, blood enters the right atrium and is preferentially shunted to the left atrium through the patent foramen ovale (Fig. 165.1). Fetal pulmonary vascular resistance (PVR) is higher than fetal systemic vascular resistance (SVR); this forces deoxygenated blood to mostly bypass the fetal lungs (see Fig. 165.1). From the left atrium, blood flows to the left ventricle and the aorta. The oxygenated blood ejected through the ascending aorta is preferentially directed to the fetal coronary and cerebral circulations.

The proportion of returning deoxygenated blood from the superior vena cava that empties into the right atrium and then right ventricle is pumped into the pulmonary artery. This poorly oxygenated blood enters the aorta through the patent ductus arteriosus and mixes with the well-oxygenated blood in the descending aorta. The mixed blood in the descending aorta then returns to the placenta for oxygenation through the two umbilical arteries.

Once the infant is delivered and the umbilical cord is cut, expansion and aeration of the lungs cause a decrease in PVR, which enhances pulmonary blood flow. Increased global oxygenation causes a physiologic closure of the umbilical arteries, umbilical vein, ductus venosus, and ductus arteriosus. Increasing pulmonary blood flow to the infant's left atrium promotes closure of the foramen ovale. Complete anatomic closure of the foramen ovale does not occur until about 3 months of age. Although the ductus arteriosus functionally closes at about 10 to 15 hours of life, complete anatomic closure does not occur until 2 to 3 weeks of life.

In the absence of any congenital cardiac defects, these transitional circulatory changes pose no physiologic problems to the infant. However, closure of the ductus arteriosus can be life-threatening in neonates with cardiac defects that depend on the patency of the ductus arteriosus for survival.

Pathophysiology of Cardiovascular Compensatory Responses

The young myocardium is inefficient and unable to increase contractility in response to demand.[1] When more cardiac output is needed, infants and children respond with an increase in heart rate; therefore, bradycardia is an ominous sign that connotes a severely compromised cardiac output. Children develop the adult capacity to increase contractility by 8 to 10 years of age.

BOX 165.1 Common Presenting Signs and Symptoms of Cardiac Disorders in Infants and Children

General
Fussiness
Lethargy
Poor feeding (with or without associated diaphoresis)
Poor growth

Respiratory
Respiratory distress
Wheezing
Apnea

Cardiovascular
Tachycardia
Shock
Paleness
Mottling
Cyanosis
Palpitations
Chest pain
Syncope
Various dysrhythmias

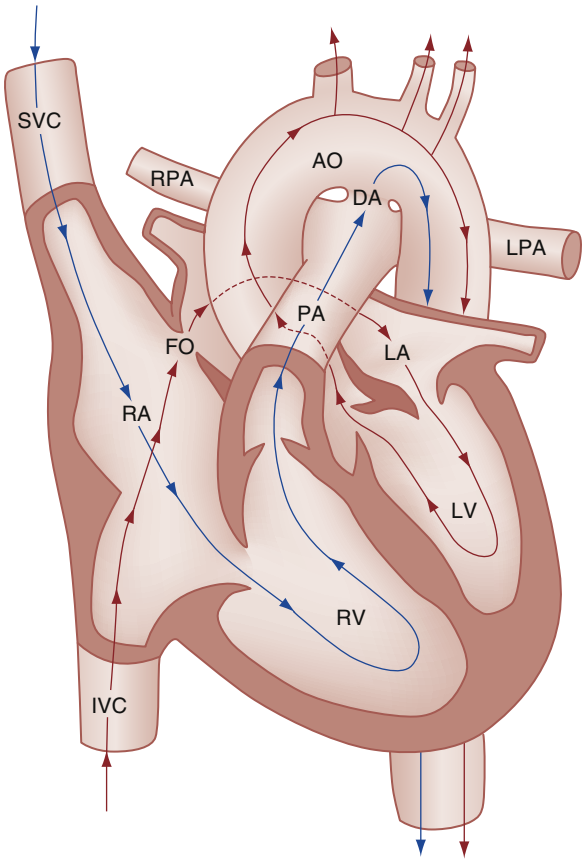

Fig. 165.1 Normal intracardiac fetal circulation: Physiologic shunting through the patent foramen ovale *(FO)* and the patent ductus arteriosus *(DA)*. Oxygenated blood from the placenta *(red arrows)* reaches the right atrium *(RA)* through the inferior vena cava *(IVC)*. This well-oxygenated blood is preferentially shunted from the RA across to the left atrium *(LA)* through the FO and is then ejected out the left ventricle *(LV)* to the ascending aorta *(AO)*. Deoxygenated blood *(blue arrows)* returning from the superior vena cava *(SVC)* preferentially travels from the RA into the right ventricle *(RV)* and then out through the main pulmonary artery *(PA)*. Because of the high pulmonary vascular resistance (PVR) in the fetal lungs, this deoxygenated blood bypasses lungs and enters the descending aorta through the DA. Thus the areas of the fetal body that are perfused by arteries proximal to the DA receive well-oxygenated blood, whereas those areas of the body that are perfused by arteries distal to the DA receive blood with a mixed oxygenation. *LPA,* Left pulmonary artery; *RPA,* right pulmonary artery.

BOX 165.2 Causes of Decreased Stroke Volume in Infants and Children

Hypovolemia (most commonly secondary to dehydration)
Congestive heart failure (CHF; acquired or secondary to underlying congenital cardiac defects)
Myocarditis
Hypertrophic cardiomyopathy with decreased diastolic filling
Dilated cardiomyopathy with decreased systolic ejection
Pericarditis or pericardial effusion with cardiac tamponade
Tachydysrhythmias with decreased diastolic filling times

A decrease in stroke volume can be caused by a weak "pump," decreased volume in the circulation, or both. As stroke volume decreases, a compensatory increase in the heart rate is needed to preserve normal cardiac output. The most common cause of decreased stroke volume in children is hypovolemia from dehydration. Other causes of decreased stroke volume in children are listed in Box 165.2.

CLINICAL FEATURES

Tachycardia is the first compensatory cardiovascular response to decreases in stroke volume. If tachycardia alone is not enough to maintain a normal cardiac output, the next compensatory physiologic mechanism to preserve perfusion is an increase in the SVR. This change in SVR is exhibited as an increase in the diastolic blood pressure, which in turn creates a narrowed pulse pressure. The clinical examination findings of the extremities of a child with an increased SVR include pallor, mottling, cool skin, delayed capillary refill time (>2 seconds), and weak or thready distal pulses.

Pathophysiology of Cyanosis

Cyanosis is a clinical sign caused by the preponderance of deoxygenated blood in the capillary beds, most readily observed in the mucous membranes, conjunctiva, nail beds, and skin. For cyanosis to be evident clinically, there must be at least 4 to 5 g/dL of deoxyhemoglobin admixed in the blood; this usually correlates with an oxygen saturation of approximately 80% to 85%. However, children with anemia—even if hypoxic—may not show overt signs of cyanosis (i.e., the critical mass of deoxygenated hemoglobin is not met to manifest cyanosis clinically). Central cyanosis results from a decrease in pulmonary ventilation and oxygenation, a decrease in pulmonary perfusion, the shunting of deoxygenated blood directly into the systemic circulation, or the presence of abnormal hemoglobin. Cyanosis in the neonate may be due to a variety of cardiac, pulmonary, hematologic, or toxic causes. Cardiac causes of cyanosis include congenital lesions with right-to-left shunts and cardiac lesions with decreased or increased pulmonary blood flow. Common pulmonary causes of cyanosis include bronchiolitis, pneumonia, and pulmonary edema. Methemoglobinemia is a hematologic cause of cyanosis.

Clinical Features of Cyanosis

Central cyanosis involves the lips, tongue, and mucous membranes; peripheral cyanosis (acrocyanosis) involves the hands and feet. Acrocyanosis is a common mostly benign finding in neonates caused by cold stress and peripheral vasoconstriction. Infants with cyanosis due to a congenital heart defect may not exhibit as much respiratory distress compared with the infant with cyanosis due to a pulmonary cause. Thus, a cardiac cause of central cyanosis should be suspected in a child who appears "comfortably blue." Another important clinical clue to the cause of central cyanosis is that cyanosis of cardiac origin usually worsens with crying, whereas cyanosis due to a pulmonary cause may

improve. Cyanotic congenital heart defects with right-to-left shunting will demonstrate a minimal improvement with supplemental oxygen, whereas cyanosis of a purely pulmonary origin typically exhibits a significant improvement with supplemental oxygen (Table 165.1).

History

Infants with an underlying congenital heart disorder may be detected with a thorough history targeting key question (Box 165.3). Additional history including diaphoresis during feeds and poor weight gain may signal early congestive heart failure (CHF). The cause of the infant's hypoxia—cardiac or pulmonary—may be ascertained by the age at onset and the events surrounding a change in color. For example, an infant who sweats during feeding may exhibit a splanchnic steal from anomalous coronary arteries, causing transient ischemia, pain, color change, and diaphoresis that resolve after eating. A child with an undiagnosed congenital heart defect resulting in CHF and pulmonary edema may take longer to feed, frequently pausing to catch his or her breath, with subsequent poor weight gain and gradually increasing work of breathing. Respiratory tract infections are common during childhood and may cause an acute deterioration in a child with an underlying cardiac disorder. In turn, children with congenital heart disease (CHD) with large left-to-right shunts and increased pulmonary blood flow tend to have a higher incidence of lower respiratory tract infections. Acute respiratory distress in these patients may be from a combination of pulmonary and cardiac factors (e.g., CHF).

TABLE 165.1 Clinical Clues to Help Distinguish Between Cardiac and Pulmonary Causes of Central Cyanosis[a]

	Cardiac Etiology	Pulmonary Etiology
Respiratory status	May be "comfortably blue"	Respiratory distress
Response to crying	Worsening cyanosis	Improved cyanosis
Response to oxygen	Minimal or no improvement	Improvement with oxygen

[a]Cyanosis due to severe pulmonary disease (e.g., severe pneumonia, tension pneumothorax, acute chest syndrome of sickle cell disease) may not show significant improvement with supplemental oxygen, but these children will also typically exhibit severe respiratory distress along with clinical cyanosis.

BOX 165.3 Key Elements to Elicit in the History of a Child With a Known Cardiac Disorder

Cardiac Diagnosis

Congenital or acquired disorder?

Any episodes of previous decompensation? (If so, are the current signs and symptoms similar to or different from those previous episodes?)

Oxygen Issues

Currently receiving home oxygen supplementation (continuous or only during feedings and sleep)?

Baseline oxygen saturation (room air or while receiving home oxygen)?

Any recent need for increasing the amount of supplemental oxygen?

Medications

Names and dosages of all current medications (cardiac and noncardiac medications)?

Were any of these cardiac medications stopped recently (by the cardiologist or parental noncompliance)?

Any recent increases in the cardiac medications (reasons for the increase, previous dosage versus the current dosage, and the date this dosage was increased)?

Any new cardiac medications added recently and the reason for these additions?

Recent digoxin level if the patient is receiving daily digoxin therapy?

Results of Most Recent Studies (Chest Radiograph, Electrocardiogram, Echocardiogram, and Cardiac Catheterization)

When were the last studies performed, and what were the results?

Why were those studies performed (routine follow-up studies or obtained because of decompensation from baseline, or a planned evaluation for an upcoming surgical procedure)?

Surgical Procedures

Previous procedures and complications?

Any future planned procedures?

Chest Pain

Common causes of pediatric chest pain are musculoskeletal chest wall pain, asthma exacerbation, pneumonia, pleurisy, gastritis, and gastroesophageal reflux. Precordial catch syndrome (also known as *Texidor's twinge*) presents as a sharp, focal pain, usually located in the left periapical area of the chest wall. It occurs suddenly, is often worsened by inspiration, and is not associated with dyspnea. The child may report that the pain "took my breath away" or that "I was afraid to move"; the pain typically resolves within a few minutes and is not associated with dysrhythmias or other sequelae.

Chest pain or syncope on exertion should be investigated for an underlying cardiac condition, especially if there is a positive family history of sudden unexplained death in young adulthood. Myocardial injury may also be secondary to drug abuse (e.g., cocaine, methamphetamines, synthetic or over-the-counter drugs of abuse). Pulmonary embolism is a possible cause of chest pain, especially in pregnant adolescent girls, patients taking oral contraceptive agents, or those with blood dyscrasias. The rare, though life-threatening, condition of aortic dissection should be considered as a cause of chest pain in a patient with physical examination findings suggestive of a collagen vascular disorder, such as Marfan syndrome.

Physical Examination

General Appearance and Pulses

Clinicians can use the Pediatric Assessment Triangle (PAT) to evaluate the child's overall appearance: alertness and interaction with the environment (mental status); presence of retractions, nasal flaring, or posturing (breathing); and skin color including perfusion (circulation) (see Chapter 155). All four extremities should be palpated for the presence and quality of pulses. In infants, feel for the brachial and femoral pulses. Bounding pulses are typically present in infants with a patent ductus arteriosus. Coarctation of the aorta should be suspected in any child with strong or unequal pulses in the upper extremities and weak pulses in the lower extremities. A child presenting with CHF and shock will have weak and thready pulses in all extremities.

Vital Signs and Blood Pressures

A mild resting tachypnea or tachycardia may be the only clinical clue to an underlying cardiovascular disorder. A simplified table of normal pediatric vital signs may be used at the bedside (Table 165.2).

To measure blood pressure accurately, use a cuff that covers two-thirds of the upper arm or thigh. A cuff that is too narrow will overestimate the patient's true blood pressure; conversely, a cuff that is too large will underestimate the true blood pressure. Measure blood pressures in both arms in children with a suspected cardiac disorder. Coarctation of the aorta

TABLE 165.2 Pediatric Vital Signs and Pertinent Formulas for Estimation of Blood Pressure

SIMPLIFIED PEDIATRIC VITAL SIGNS

Age Group	Average Normal Heart Rate (beats/min)	Respiratory Rate (breaths/min)
Newborn to 1 year	140	40
1–4 years	120	30
4–12 years	100	20
>12 years	80	15

FORMULAS TO CALCULATE THE ESTIMATED NORMAL BLOOD PRESSURES IN CHILDREN 1 YEAR OLD AND OLDER

Estimated average systolic blood pressure (SBP): [age in years × 2] + 90 mm Hg
Estimated average diastolic blood pressure: ⅔ × [estimated SBP]

MINIMUM ACCEPTABLE SYSTOLIC BLOOD PRESSURE FOR AGE (LOWER FIFTH PERCENTILE)

Newborn to 1 month	60 mm Hg
1 month to 1 year	70 mm Hg
1–10 years	[Age in years × 2] + 70 mm Hg
>10 years	90 mm Hg

(proximal to the origin of the left subclavian artery) may present with a left arm blood pressure significantly lower than the right arm. Measure blood pressures in the thighs in any child with a suspected aortic coarctation or with documented hypertensive blood pressures in the upper extremities. The presence of femoral pulses does not rule out the possibility of a coarctation of the aorta. Because of the lack of well-designed blood pressure cuffs for the legs, blood pressures in the thighs can be 10 to 20 mm Hg higher than the blood pressures in the upper extremities. Therefore, blood pressures in the lower extremities that are lower than blood pressures in the upper extremities suggest coarctation of the aorta. Pulse oximetry readings lower in the legs than in the upper extremities suggests either a coarctation of the aorta or a right-to-left-shunt across a patent ductus arteriosus.

Cardiac Auscultation

Listen for the intensity and degree of splitting of the S_2 heart sound (closure of the pulmonic and aortic valves). In normal children, both aortic closure and pulmonic closure of S_2 should be heard along the left upper sternal border. A widely split and fixed S_2 suggests a physiologic problem from either a constant volume overload to the right side of the heart (e.g., atrial septal defect [ASD]) or a pressure overload to the right side of the heart (e.g., pulmonic stenosis). An ASD classically presents as a widely split and fixed S_2. The intensity of the S_2 component may be louder than normal in the child with pulmonary hypertension.

The third heart sound (S_3) is best heard along the lower left sternal border or the apex and may be a normal finding in children and young adults. An S_3 is produced by a rapid filling of the ventricles and is heard during early diastole, just after the S_2 sound. A loud S_3, however, is pathologic and due to dilated ventricles from volume overload (e.g., CHF and large ventricular septal defects [VSDs]). The fourth heart sound (S_4) occurs late in diastole, just before the S_1 sound. The finding of an S_4 is due to a decrease in compliance of a stiff, hypertrophic ventricle, best heard at the apex with the patient in the left lateral decubitus position (Box 165.4).

Cardiac murmurs are produced by turbulent blood flow through the heart and may not be associated with an underlying cardiac defect. The location, intensity, quality, timing, and radiation of the murmur determine whether the murmur is suggestive of an underlying cardiac pathologic condition. Although systolic murmurs can be present without any underlying anatomic abnormalities, diastolic murmurs are always considered pathologic in nature. Murmurs may be difficult to appreciate in the noisy ED setting, especially in tachycardic children. However, the location of the murmur may be a valuable clinical tool in determining the underlying anatomic origin of the murmur (Box 165.5).

Murmurs without any underlying anatomic abnormalities or hemodynamic significance are termed *innocent* or *functional murmurs*. All innocent murmurs are associated with normal ECGs and normal chest radiographs. Two of the most common innocent murmurs encountered in the pediatric population are the neonatal pulmonic flow murmur (peripheral pulmonic stenosis murmur) and Still's murmur. The pulmonic flow murmur of the neonate is due to the relatively thin walls and angulation of the right and left pulmonary arteries at birth. This systolic murmur is best heard at the left upper sternal border with radiation throughout the entire chest, axilla, and back. It usually disappears

BOX 165.4 A Pathologic Etiology of a Heart Murmur Should Be Suspected With Any of the Following Criteria

- Diastolic murmurs
- Systolic murmurs that are louder than a grade 3/6, continuous, or associated with a thrill
- Murmurs that are associated with abnormal heart sounds (clicks, rubs, or gallop rhythms)
- Presence of cyanosis or respiratory distress
- Bounding pulses or weak pulses
- Abnormalities on the electrocardiogram (ECG)
- An abnormal cardiac silhouette, abnormal pulmonary vascularity, or cardiomegaly on the chest radiograph

BOX 165.5 Auscultation Locations of Common Systolic Murmurs in Children

Left Upper Sternal Border (Pulmonic Area)
- Pulmonic valvular stenosis
- Atrial septal defects (ASDs; due to an increased pulmonic flow)
- Innocent pulmonic ejection murmur
- Neonate pulmonic flow murmur
- Patent ductus arteriosus (a continuous, "machinery" sounding murmur)

Left Lower Sternal Border
- Innocent vibratory Still murmur
- Ventricular septal defects (VSDs)
- Endocardial cushion defects
- Tetralogy of Fallot
- Hypertrophic cardiomyopathy

Apex
- Innocent vibratory Still murmur
- Mitral regurgitation
- Aortic stenosis
- Hypertrophic cardiomyopathy

Right Upper Sternal Border (Aortic Area)
- Aortic stenosis
- Coarctation of the aorta

by 3 to 6 months of age. Persistence of a systolic murmur in the pulmonic area beyond this period raises the possibility of pathologic pulmonary arterial stenosis.

Still's murmur is a common innocent murmur found in children between 2 and 6 years of age. Best heard along the left midsternal border, this murmur has a vibratory, musical, or twanging quality from turbulent flow. The distinct quality of Still's murmur distinguishes it from the harsher quality of a VSD murmur. The intensity of Still's murmur increases in the supine position, or with fever, excitement, exercise, or anemia; like most murmurs, it is best heard with the bell of the stethoscope.

DIAGNOSTIC TESTING

Hyperoxia Test

The hyperoxia test may help differentiate between cardiac and pulmonary causes of central cyanosis. This test consists of assessment of the rise in arterial oxygenation with the administration of 100% oxygen. An arterial blood gas is measured after several minutes on high-flow oxygen (100% oxygen). When the child is breathing high-flow oxygen, an arterial oxygen partial pressure (Pao_2) of more than 250 mm Hg virtually excludes hypoxia due to CHD—a "passed" hyperoxia test. An arterial oxygen reading of less than 100 mm Hg (in a child without obvious pulmonary disease) is consistent with a right-to-left shunt and is highly predictive of CHD—a "failed" hyperoxia test. Values of 100 to 250 mm Hg may indicate lesions with intracardiac mixing. Pulse oximetry is not an appropriate substitute for an arterial blood gas analysis; it is not sensitive enough to determine "pass" or "fail" of the test, because a child breathing high-flow oxygen and registering 100% on pulse oximetry may actually have a Pao_2 anywhere between 80 and 680 mm Hg. Prolonged administration of 100% oxygen may cause some theoretic problems, such as, closure of the ductus arteriosus in infants with critical left-sided heart obstructions or pulmonary vasodilation (which could potentially worsen pulmonary vascular congestion). However, oxygen should not be initially withheld in critically ill infants based on this concern alone; rather, clinicians should closely monitor the response to oxygen in infants with suspected CHD.

Laboratory Analysis

Patients with CHF exacerbation may exhibit respiratory acidosis (low pH and high $Paco_2$), in addition to a low Pao_2, due to respiratory fatigue; this may initially be clinically subtle. In contrast, children with compensated cyanotic congenital heart defects may have a normal pH despite a (chronically) low Pao_2. Chronic mild hypoxemia causes a chronic mild acid load on the respiratory, renal, and blood buffer systems; acute illness, such as a respiratory infection, can rapidly cause a decompensation in this fragile balance, resulting in a worsening acidosis. Patients with congenital heart defects who are not experiencing respiratory compromise are unlikely to exhibit elevation in $Paco_2$.

Children with cyanotic CHD often partially compensate with an acquired polycythemia. Hemoglobin and hematocrit levels can also help determine if a child with CHF has pallor due to CHD or high-output failure from anemia. Serum electrolyte values may be helpful in the evaluation of children with acute dysrhythmias, suspected metabolic acidosis, or chronic diuretic therapy. We recommend that patients with a known congenital heart defect or an acquired cardiac disorder (e.g., Kawasaki disease, acute rheumatic heart disease, myocarditis, pericarditis, and cardiomyopathy) who present with dysrhythmias, syncope, chest pain, or unexplained shortness of breath be assessed with cardiac biomarkers and an ECG.

Chest Radiography

Three important features of the chest radiograph (Fig. 165.2) are the cardiac size (cardiothoracic ratio), the cardiac shape (silhouette), and the degree of pulmonary vascular markings. The easiest method to gauge heart size in children is to determine the cardiothoracic ratio: compare the largest transverse diameter of the cardiac shadow on the posteroanterior view of the chest radiograph with the widest internal diameter (measured from the inside rib margin at the widest point above the costophrenic angles) of the chest. The films should be obtained during maximal inspiration whenever feasible. Of note, the cardiothoracic ratio is not very accurate in preverbal children, in whom a good inspiratory view is rarely obtained.

The normal cardiothoracic ratio in children is 50% to 55%. A cardiac silhouette that is larger than normal may be due to a shunt lesion,

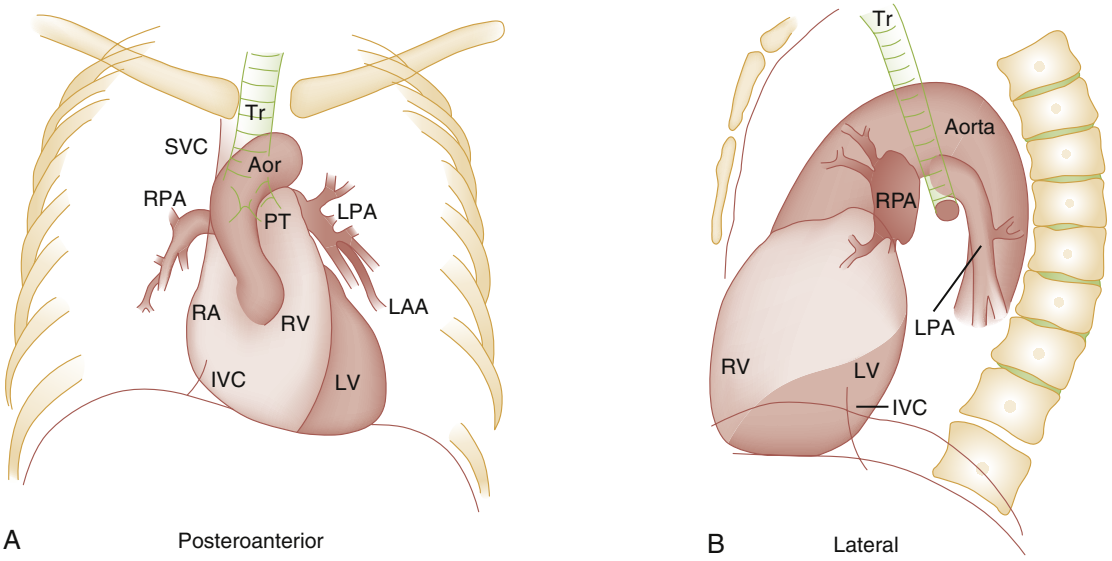

Fig. 165.2 Diagrammatic representations of the anatomy of the chest radiograph. (A) Normal heart in a young man, posteroanterior projection. (B) Right lateral projection of a normal heart in a young man. *Aor,* Aorta; *IVC,* inferior vena cava; *LAA,* left atrial appendage; *LPA,* left pulmonary artery; *LV,* left ventricle; *PT,* pulmonary trunk; *RA,* right atrium; *RPA,* right pulmonary artery; *RV,* right ventricle; *SVC,* superior vena cava; *Tr,* trachea.

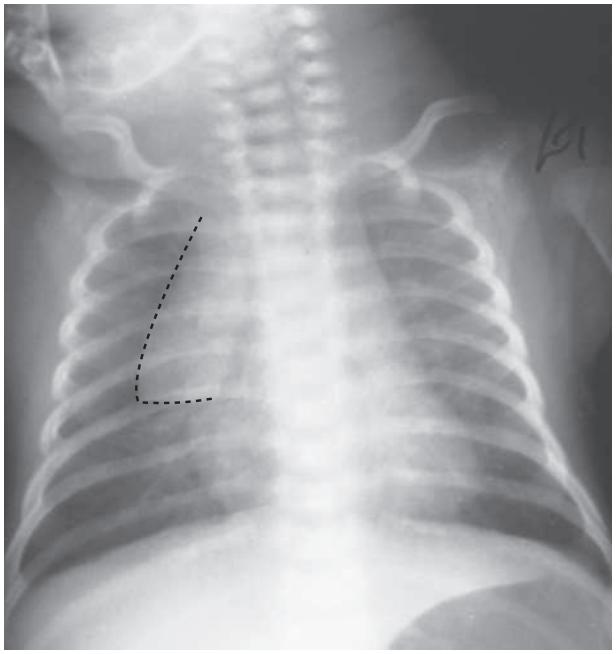

Fig. 165.3 Thymic shadow demonstrating the "sail sign" along the right cardiac border *(dotted line)*.

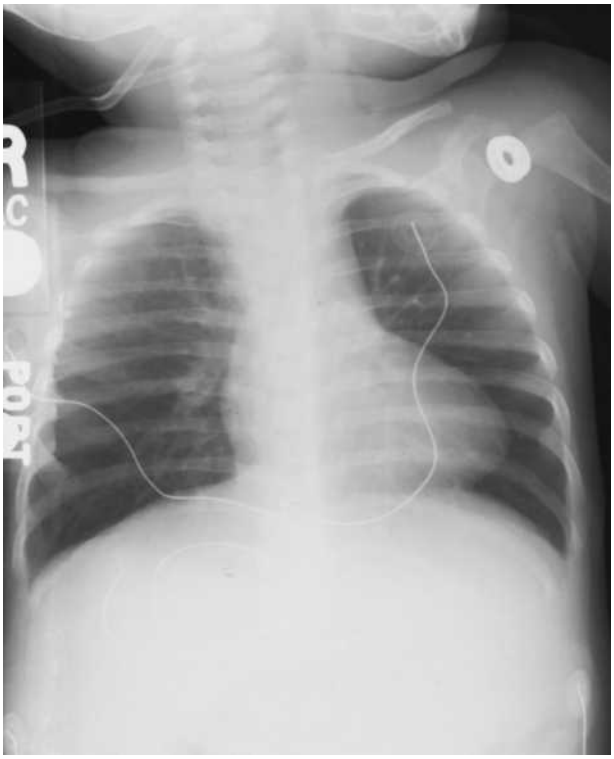

Fig. 165.4 The classic boot-shaped heart of tetralogy of Fallot.

cardiomegaly, or pericardial effusion. An enlarged heart shadow on a chest radiograph more reliably reflects a volume overload rather than pressure overload. The cardiac size can be falsely increased in infants by the presence of the thymus, seen in the mediastinum on the chest radiograph from birth until about 5 years of age. The thymic borders are typically wavy in appearance and sometimes can be seen as the classic "sail sign" along the superior right border of the heart (Fig. 165.3). The thymic shadow may not be visible radiographically in infants during times of physiologic stress, but should reappear when the infant recovers.

The three classic cardiac silhouettes seen in patients with congenital heart defects are the "boot-shaped heart" of tetralogy of Fallot (Fig. 165.4), the "egg-on-a-string" silhouette of transposition of the great arteries, and the "snowman-shaped" or "figure-of-eight" heart of total anomalous pulmonary venous return.

The degree of pulmonary vascular markings is a key factor in the differential diagnosis of congenital heart defects. Increased pulmonary vascularity is present when the pulmonary arteries appear enlarged and are visible in the lateral third of the lung fields or the lung apices. Another marker of increased pulmonary vascularity is seen on the posteroanterior view of the chest radiograph: the diameter of the right pulmonary artery in the right hilum is wider than the internal diameter of the trachea. The differential diagnosis of a cyanotic infant with decreased vascular markings includes Tetralogy of Fallot, pulmonary atresia, and tricuspid atresia. The cyanotic infant with increased vascular markings may have transposition of the great arteries, total anomalous pulmonary venous return, or truncus arteriosus. Increased vascular markings in an acyanotic infant are suggestive of an endocardial cushion defect, VSD, ASD, or patent ductus arteriosus.

In a normal left-sided aortic arch, the aorta descends to the left of the midline and slightly displaces the tracheal air shadow toward the right of midline above the level of the carina. With a right-sided aortic arch, the tracheal air shadow may be midline or deviated toward the left. A right-sided aortic arch is found in up to 25% of the children with tetralogy of Fallot. Rib notching secondary to increased collateral blood flow along the intercostal vessels can sometimes be appreciated between the fourth and eighth ribs in older children with undiagnosed

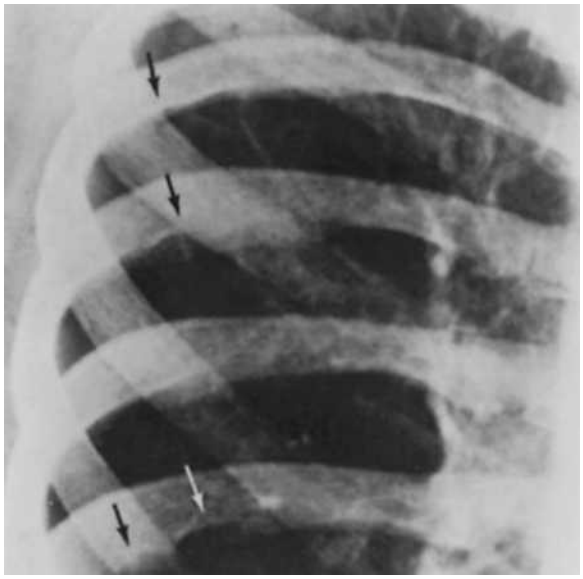

Fig. 165.5 Rib notching *(arrows)* in an 11-year-old girl with coarctation of the aorta. (From: Park MK. *Park's Pediatric Cardiology for Practitioners*, ed 6. Philadelphia: Elsevier/Saunders; 2014: 67-74. Figure 4-9 from: Caffey J. *Pediatric X-ray Diagnosis*, ed 7. Chicago: Mosby; 1978.)

coarctation of the aorta (Fig. 165.5) but is rarely visualized in children with coarctation of the aorta who are younger than 5 years old.

Electrocardiography

Electrocardiographic findings in infants and children change with the child's age (Table 165.3). At birth, muscle mass of the right ventricle is greater than that of the left ventricle; this is demonstrated by right axis deviation on the neonatal ECG. By the end of the first month of life, the left ventricle assumes dominance. By 6 months old, the left ventricular

to right ventricular mass ratio is 2 : 1, which then reaches the adult ratio of 2.5 : 1 by adolescence. The durations of the PR interval, QRS complex, and QT intervals increase with age.

Left axis deviation is present when the QRS axis is less than the lower limit of normal for the child's age; it occurs with left ventricular hypertrophy and left bundle branch block. Right axis deviation is present when the QRS axis is greater than the upper limit of normal for the child's age; this is seen with right ventricular hypertrophy and right bundle branch block. A "superior" QRS axis (0 to −180 degrees with an S wave in aV_F greater than the R wave) may be suggestive of an endocardial cushion defect or tricuspid atresia.

Some common indications for ECG in a pediatric patient include chest pain, dyspnea, syncope, palpitations, suspected dysrhythmias, or an underlying cardiac disorder. A rare but potentially fatal congenital cardiac abnormality detected by ECG, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), will show ischemic changes. Infants may have a history of poor feeding, irritability, and failure to thrive. Older children and adolescents may have acute-on-chronic ischemic symptoms. Anyone of any age with ALCAPA may suddenly present with cardiogenic shock secondary to myocardial ischemia. Evidence of volume overload seen on ECG includes: right atrial enlargement (also seen with ASD, atrioventricular [AV] canal defects, tricuspid atresia, Ebstein anomaly, and severe pulmonary stenosis); and right ventricular hypertrophy (also seen with pulmonary stenosis, Tetralogy of Fallot, transposition of the great arteries, VSD with pulmonary stenosis or pulmonary hypertension, coarctation of aorta [CoA] in the newborn, pulmonary valve atresia, and hypoplastic left heart syndrome).

TABLE 165.3 Normal Electrocardiographic Values (PR, QTc, and QRS Axes) in Infants and Children

	PR INTERVAL	QRS DURATION
Age	Average (Upper Limit)	Average (Upper Limit)
0–1 month	0.10 (0.12)	0.05 (0.07)
1 month to 1 year	0.10 (0.14)	0.05 (0.07)
1–3 years	0.11 (0.15)	0.06 (0.07)
3–8 years	0.13 (0.17)	0.07 (0.08)
8–12 years	0.15 (0.18)	0.07 (0.09)
12–16 years	0.15 (0.19)	0.07 (0.10)
Adult	0.16 (0.21)	0.08 (0.10)

The corrected QT (QTc) interval should not exceed:
0.45 second in infants <6 months old
0.44 second in children and adolescents

NORMAL QRS AXES IN INFANTS AND CHILDREN

Age	Mean Degrees (range)
1 week to 1 month	+110 (+30 to +180)
1–3 months	+70 (+10 to +125)
3 months to 3 years	+60 (+10 to +110)
>3 years	+60 (+20 to +120)
Adults	+50 (–30 to +105)

NORMAL T WAVE AXIS IN INFANTS AND CHILDREN

Age	Leads V_1 and V_2	Lead Av_f	Leads I, V_5, and V_6
Birth to 1 day	+/–	+	+/–
1–4 days	+––	+	+
4 days to adolescent	–	–	+
Adolescent to adult	+	+	+

+, Upright T wave; –, inverted T wave.

Biochemical Markers

As in adults, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are highly sensitive and specific in children for myocardial damage. Reference values are slightly higher for neonates younger than 3 months of age; normal and indeterminate values will depend on the bioassay used. The indications for troponin testing in children include suspected cardiac ischemia (of any etiology), myocarditis, and myocardial dysfunction in sepsis syndrome. Several studies have supported the use of plasma B-type natriuretic peptide (BNP) levels in the assessment and management of CHF in adults. Elevated BNP levels have demonstrated a similar correlation in children with CHF. BNP levels also correlate with the clinical symptoms of heart failure and ejection fraction.

SPECIFIC DISORDERS

Congenital Heart Disease

Foundations

Although a large percentage of CHD is now detected with prenatal ultrasound, pulse oximetry before discharge from the nursery is currently a standard screening for CHD, and its false-negative rate is very low.[2]

Clinical Features

Age, severity of symptoms, and time of presentation of a child with CHD vary by the specific defect, complexity, severity, and timing of the normal physiologic changes that occur as the fetal circulation transitions to that of a neonate (Table 165.4). The more severe or complex

TABLE 165.4 Symptomatic Presentation of Congenital Heart Defects and Time of Presentation

Defect	Time of Presentation
CONGENITAL HEART DEFECTS THAT PRESENT WITH CYANOSIS	
Transposition of the great arteries	Birth to 2 weeks
Total anomalous pulmonary venous return	Birth to 2 weeks
Tricuspid atresia	Birth to 2 weeks
Ebstein anomaly of the tricuspid valve	Birth to 2 weeks
Truncus arteriosus	Birth to 2 weeks
Pulmonary atresia	Birth to 2 weeks
Hypoplastic right heart syndrome	Birth to 2 weeks
Hypoplastic left heart syndrome	Birth to 2 weeks
Tetralogy of Fallot	Birth to 12 weeks
CONGENITAL HEART DEFECTS THAT PRESENT WITH SHOCK	
Coarctation of the aorta	From first week on
Aortic stenosis	From first week on
CONGENITAL HEART DEFECTS THAT PRESENT WITH CONGESTIVE HEART FAILURE	
Ventricular septal defects (VSDs)	From 4 weeks on
Patent ductus arteriosus	From 4 weeks on

CHD lesions may not be clinically apparent immediately after birth. As the ductus arteriosus begins to close in the first several weeks of life, cardiac defects with obstructive lesions of the pulmonary or systemic circulations will be unmasked, and these infants will present with acute cyanosis, shock, or both. In general, the more severe the anatomic defect is (i.e., lack of pulmonary blood flow or lack of systemic blood flow), the earlier in life these conditions will be manifested with cyanosis and shock.

Differential Diagnosis

Many children with CHD do not fit neatly into a single pattern; some have mixed defects. The exact anatomic diagnosis of a CHD is dependent on echocardiography, cardiac catheterization, or advanced imaging; establishment of the exact anatomic diagnosis is seldom possible in the ED setting.

Diagnostic Testing

The emergency clinician should rely on several key elements of the clinical evaluation in addition to findings on the chest radiograph and ECG to narrow the diagnostic possibilities. Pattern recognition may be helpful (Box 165.6). For example, the presence of cyanosis, a grade 3/6 systolic ejection murmur best heard at the mid left sternal border, a boot-shaped heart, and a decreased pulmonary blood flow on the chest radiograph with evidence of right ventricular hypertrophy on the ECG suggest Tetralogy of Fallot.

Management

The majority of children who present to the ED in shock have volume depletion or sepsis. These patients should receive rapid repeated fluid boluses of 20 mL/kg. Children with poor perfusion and suspected CHD, however, should receive smaller aliquots of 10 mL/kg to avoid precipitation or exacerbation of CHF. This is especially important in the neonate with undifferentiated shock. In these cases, give the initial 10 mL/kg bolus and assess for effect. If the child is improved or no worse, give more fluids. Be judicious in suspected CHD and ready to provide inotropic support or positive pressure ventilation, either by noninvasive or endotracheal means.

CHD that is manifested within the first 2 to 3 weeks of life with a sudden onset of cyanosis or cardiovascular collapse is typically due to ductal-dependent cardiac lesions (Box 165.7). Closure of the ductus arteriosus in these patients interrupts blood flow either to the lungs, producing cyanosis (e.g., tricuspid atresia) *or* to the systemic circulation, producing shock (e.g., hypoplastic left heart syndrome). To maintain an open ductus arteriosus and promote mixture of oxygenated and deoxygenated blood, prostaglandin E_1 (alprostadil) is typically started at 0.05 to 0.1 μg/kg/min. A known adverse reaction to a PGE_1 infusion is apnea (30%). Assiduous monitoring of the child's respiratory drive is essential with PGE_1 administration. Although some small studies endorse the omission of endotracheal intubation of neonates on a PGE_1 infusion, endotracheal intubation should be considered for these infants, especially before inter-facility transport.

Children with cardiac conditions are at risk of post-intubation cardiovascular collapse due to positive pressure ventilation, increased intrathoracic pressures, and decreased venous return (e.g., cyanotic heart disease is often preload dependent). To support cardiac output and SVR (which mitigates a right-to-left shunt), ketamine is the preferred induction agent along with a non-depolarizing metabolically neutral neuromuscular blocker, such as rocuronium. Not only will intubation provide a secure airway, but controlled ventilation will also help decrease the infant's work of breathing, shunting much needed cardiac output and metabolic demands from the overtaxed respiratory apparatus. Other adverse reactions to a PGE_1 infusion include fever, seizures, bradycardia, hypotension, flushing, and decreased platelet aggregation.

BOX 165.6 Clinical Clues to Aid in the Diagnosis of Congenital Heart Disease

Presence or Absence of Central or Peripheral Cyanosis?

Central cyanosis with minimal respiratory distress ("comfortably blue") is suggestive of CHD more than of a purely pulmonary etiology.

Abnormalities in Cardiac Auscultation?

Murmurs: Systolic versus diastolic, location, and radiation

Quality of S_1, S_2, and the presence of any clicks or gallops

Change in the Degree of Central Cyanosis With Crying?

Worsening of cyanosis with crying suggests a cardiac rather than a purely pulmonary etiology.

Response of Pa_{O_2} to the Hyperoxia Challenge (Administering 100% Oxygen)?

Purely pulmonary causes of cyanosis: Pa_{O_2} should rise to levels above 250 mm Hg

Cyanotic CHD associated with an increased pulmonary blood flow: Pa_{O_2} may occasionally reach as high as 150 mm Hg

Cyanotic CHD associated with a decreased pulmonary blood flow: Pa_{O_2} will not rise above 100 mm Hg

Chest Radiograph Abnormalities?

Cardiac size and shape (one of the three classic cardiac silhouettes)?

- Boot-shaped heart: Tetralogy of Fallot
- Egg-on-a-string silhouette: Transposition of the great vessels
- Snowman-shaped or figure-of-eight heart: Total anomalous pulmonary venous return

Degree of Pulmonary Blood Flow?

Increased (acyanotic): ASD, Eisenmenger syndrome, VSD, patent ductus arteriosus, endocardial cushion defects

Increased (cyanotic): Transposition of the great arteries, total anomalous pulmonary venous return, hypoplastic left heart syndrome, truncus arteriosus

Decreased or normal (acyanotic): Pulmonic stenosis, aortic stenosis, coarctation of the aorta

Decreased (cyanotic): Tetralogy of Fallot, severe pulmonic stenosis, Ebstein anomaly, tricuspid atresia, pulmonary atresia, hypoplastic right heart syndrome

Electrocardiographic Abnormalities?

Evidence of chamber enlargement: right ventricular hypertrophy, left ventricular hypertrophy, biventricular hypertrophy, right atrial hypertrophy, or left atrial hypertrophy

An abnormal superior QRS axis is suggestive of endocardial cushion defect or tricuspid atresia.

ASD, Atrial septal defect, *CHD,* congenital heart disease; *Pa_{O_2},* arterial oxygen partial pressure; *VSD,* ventricular septal defect.

Acyanotic Congenital Heart Defect

Foundations

Acyanotic CHD can be further subdivided (Fig. 165.6) into obstructive lesions (e.g., pulmonic stenosis, aortic stenosis, coarctation of the aorta) and lesions characterized by left-to-right shunting with an associated increase in pulmonary blood flow (e.g., VSDs, ASDs, patent ductus arteriosus, endocardial cushion defects). These acyanotic lesions

BOX 165.7 Ductal-Dependent Cardiac Lesions in the Neonate

Congenital Heart Diseases That Require a Patent Ductus Arteriosus to Preserve Blood Flow From the Aorta to the Pulmonary Circulation

Tetralogy of Fallot
Tricuspid atresia
Pulmonary atresia
Hypoplastic right heart syndrome
Transposition of the great vessels

Congenital Heart Diseases That Require a Patent Ductus Arteriosus to Preserve Blood Flow From the Main Pulmonary Artery to the Systemic Circulation

Severe coarctation of the aorta
Severe aortic stenosis
Hypoplastic left heart syndrome

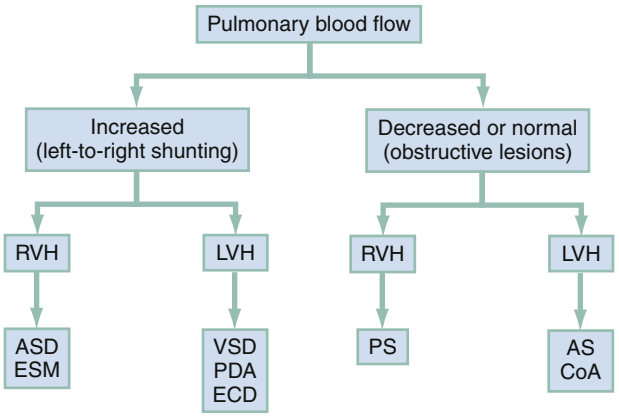

Fig. 165.6 Clinical clues to diagnosis of acyanotic congenital heart defects. *AS,* Aortic stenosis; *ASD,* atrial septal defect; *CoA,* coarctation of the aorta; *ECD,* endocardial cushion defect; *ESM,* Eisenmenger syndrome; *LVH,* left ventricular hypertrophy; *PDA,* patent ductus arteriosus; *PS,* pulmonic stenosis; *RVH,* right ventricular hypertrophy; *VSD,* ventricular septal defect.

usually present within the first 6 months of life with symptoms of CHF; however, ASDs can remain asymptomatic until adulthood.

Specific Disorders

Ventricular Septal Defect. VSD is the most common congenital cardiac defect and accounts for 20% to 25% of all cases of CHD. Spontaneous closure occurs in 30% to 40% of all VSDs overall and in 50% to 70% of smaller VSDs.

Clinical Features. Symptoms from a VSD are dependent on its size, and the degree of pulmonary vascular resistance present. Most VSDs are clinically asymptomatic (minimal or no left-to-right shunting) immediately after birth because of normal, relatively higher pulmonary vascular resistance. By 6 to 8 weeks of age, pulmonary vascular resistance naturally decreases. If a VSD is present, then left-to-right shunting can occur, and its typical systolic murmur may be appreciated.

Small VSDs may remain completely asymptomatic throughout childhood. In contrast, by 2 to 3 months of age some infants with large VSDs may experience an abnormally high pulmonary blood flow, and signs and symptoms of CHF (e.g., poor feeding and poor growth). Older children with VSDs may present with decreased exercise tolerance or recurrent pulmonary infections. If moderate to large VSDs are not corrected surgically, by 6 to 12 months of age irreversible changes occur in the pulmonary vasculature; high pulmonary vascular resistance is established, possibly resulting in pulmonary hypertension. Subsequently, high pulmonary vascular resistance increases right atrial and right ventricular pressures. If a large VSD is also present, the direction of the shunt is reversed, now right-to-left. The previous left-to-right shunt would have been tolerated relatively well. Once the reversal is established—a right-to-left shunt—poorly oxygenated blood flows into the systemic circulation with resulting degrees of cyanosis, called Eisenmenger syndrome.

Diagnostic Testing. The chest radiograph in children with small VSDs may be entirely normal. Cardiomegaly with increased pulmonary vascular markings is usually present with untreated moderate-to-large VSDs. The ECG of moderate-sized VSDs typically reveals left ventricular hypertrophy, but biventricular hypertrophy may be present in VSDs with large left-to-right shunting.

Management. All VSDs, regardless of the size of the defect, are at risk for bacterial endocarditis because of the high velocity of turbulent blood flow through them, and thus, should be repaired.

Traditional closure of VSDs required open heart surgery. Today, however, a transcatheter closure technique that avoids the inherent risks and complications of open heart surgery and cardiopulmonary bypass has supplanted traditional methods.

Atrial Septal Defect. ASDs account for 5% to 10% of all cases of CHD. The majority of infants and children with ASDs remain clinically asymptomatic until adulthood. Spontaneous closure has been reported in up to 40% of the cases within the first 5 years of life.

Clinical Features. Large ASDs or those associated with comorbid conditions, such as bronchopulmonary dysplasia, can be manifested with symptoms of CHF and pulmonary overcirculation (e.g., dyspnea with feedings, poor weight gain, and frequent lower respiratory tract infections). The majority of ASDs are discovered when a suspicious murmur is detected on a routine physical examination: a widely split and fixed S_2 is a characteristic finding of ASDs.

Diagnostic Testing. The chest radiographs of children with ASDs will reveal varying degrees of cardiomegaly, right atrial and right ventricular enlargement, and a prominent main pulmonary artery segment and increased pulmonary vascular markings. The ECG will show right axis deviation and right ventricular hypertrophy. All patients with unrepaired ASDs will have symptoms if pulmonary hypertension develops. Patients with large ASDs that are not detected and repaired are at risk for development of Eisenmenger syndrome. Unlike VSDs, uncomplicated ASDs are not associated with high risk of bacterial endocarditis because of the lower turbulence and velocity of blood flow through the atrial defect.

Management. Traditionally, ASDs required open heart surgery to place a patch over the septal defect. Newer therapies include septal occlusion devices placed by the transcatheter approach.[3] Antiplatelet therapy during the 6-month period after placement of the device is typically given and is safe and effective in preventing thrombus formation on the surface of the septal occluder.

Eisenmenger Syndrome

Clinical Features. Eisenmenger syndrome can occur in any large left-to-right shunt defect. Left uncorrected, irreversible changes in the pulmonary arterioles lead to pulmonary vascular obstruction and pulmonary hypertension. As the degree of pulmonary hypertension increases, PVR may then begin to exceed SVR. This causes right-sided pressures to exceed those on the left, causing right-to-left shunting. The reversal in the direction of shunt flow produces cyanosis. Other clinical features of patients who have Eisenmenger syndrome include chest pain, dyspnea on exertion, and hemoptysis.[4]

Coarctation of the Aorta

Foundations. Nearly 50% of patients with coarctation of the aorta also have an associated bicuspid aortic valve. The area of coarctation can occur proximal to the insertion of the ductus arteriosus (preductal type) or distal to the insertion of the ductus arteriosus (most common, postductal type).

Clinical Features. The severity of symptoms and age at time of presentation are dependent on the location of the coarctation, the degree of narrowing, and the presence of any other associated cardiac defects. Infants with the rarer, preductal type of coarctation of the aorta may also exhibit differential cyanosis if the ductus arteriosus remains open. With differential cyanosis, the upper half of the body is perfused with well-oxygenated blood supplied by the left ventricle and the ascending aorta. However, the lower half of the body will appear cyanotic, being largely perfused by right-to-left shunting of deoxygenated blood from the patent ductus arteriosus into the descending aorta. Infants with the preductal type of coarctation of the aorta will present with signs of circulatory failure and shock when the ductus arteriosus begins to close. The clinician should search for a "brachial-femoral delay" by palpating both pulses simultaneously.

Most of the asymptomatic cases of the more common postductal coarctation of the aorta are diagnosed as a result of a cardiology referral for a systolic murmur or a hypertension evaluation, but infants with severe postductal coarctation of the aorta can also present during the first few weeks of life with signs of circulatory failure and shock. If a child is discovered to have hypertension on a routine physical examination, obtain blood pressure measurements in the lower extremities to assess the possibility of coarctation of the aorta. Coarctation of the aorta should be suspected if the systolic blood pressure in the right arm is 15 to 20 mm Hg higher than that in the legs. If the systolic pressure in the right arm is higher than that in the left arm, the area of coarctation is probably preductal and located proximal to the origin of the left subclavian artery. In general, diastolic blood pressures are similar in the upper and lower extremities, although lower extremity pressures often have higher measured values due to use of smaller blood pressure cuffs meant for arms.

Diagnostic Testing. The chest radiograph will most often reveal a normal cardiac silhouette and normal pulmonary vascular markings, but notching along the lower borders of the posterior fourth to eighth ribs due to the pressure of the dilated collateral vessels may be exhibited in children older than 5 years of age. The ECG typically reveals a left axis and left ventricular hypertrophy. Suspected cases of coarctation of the aorta should be imaged with transthoracic echocardiography or cardiac magnetic resonance imaging to confirm and define the coarctation. In stable patients, this can be done on an outpatient basis.

Management. Definitive surgical repair of coarctation of the aorta involves angiography or stenting of the narrow aortic lumen; resection of the narrowed section of the aorta with an end-to-end anastomosis may be necessary. Complications of undiagnosed cases are related to resultant hypertension, and can include heart failure, hypertensive encephalopathy, and intracranial hemorrhages.

Cyanotic Congenital Heart Diseases

Foundations. Cyanotic CHDs are a result of either decreased pulmonary blood flow to the lungs or right-to-left shunting of desaturated blood directly into the systemic circulation (Fig. 165.7). The classic cyanotic CHDs can be remembered by the five Ts: truncus arteriosus, transposition of the great arteries, tricuspid atresia, Tetralogy of Fallot, and total anomalous pulmonary venous return. Other forms of cyanotic CHD include Ebstein anomaly, pulmonary atresia, severe pulmonary stenosis, hypoplastic left heart syndrome, and hypoplastic right heart syndrome. Many of these cyanotic heart lesions are routinely detected either on prenatal ultrasound or in the nursery; only Tetralogy of Fallot is covered in this section.

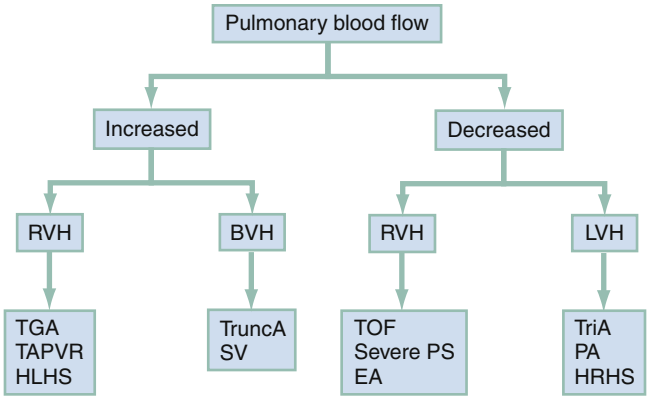

Fig. 165.7 Clinical clues to diagnosis of cyanotic congenital heart defects. *BVH,* Biventricular hypertrophy; *EA,* Ebstein anomaly; *HLHS,* hypoplastic left heart syndrome; *HRHS,* hypoplastic right heart syndrome; *LVH,* left ventricular hypertrophy; *PA,* pulmonary atresia; *PS,* pulmonary stenosis; *RVH,* right ventricular hypertrophy; *SV,* single ventricle; *TAPVR,* total anomalous pulmonary venous return; *TGA,* transposition of the great arteries; *TOF,* Tetralogy of Fallot; *TriA,* tricuspid atresia; *TruncA,* truncus arteriosus.

Tetralogy of Fallot

Foundations. Tetralogy of Fallot is the most common cause of cyanotic CHD beyond infancy. It arises from a single embryologic defect in which the subpulmonic conus fails to expand, resulting in four abnormalities (Fig. 165.8): (1) right ventricular outflow tract obstruction; (2) large, unrestrictive, misaligned VSD; (3) overriding aorta that receives blood flow from both ventricles; and (4) right ventricular hypertrophy secondary to the high pressure load placed on the right ventricle by the right ventricular outflow tract obstruction. These anatomic defects collectively result in decreased pulmonary blood flow and varying degrees of right-to-left shunting of deoxygenated blood across the VSD. Tetralogy of Fallot is often associated with other cardiac defects, such as right-sided aortic arch, ASD, and anomalous origin of the left coronary artery.

Clinical Features. The degree of cyanosis and the age at presentation are directly dependent on the degree of right ventricular outflow tract obstruction. Infants with Tetralogy of Fallot typically have worsening of their cyanosis during crying and feeding. Older children with tetralogy of Fallot may have cyanotic exacerbations during periods of physical exertion. Infants with milder forms of right ventricular outflow tract obstruction may be acyanotic, and sometimes referred to as having a "pink" Tetralogy of Fallot. Infants with severe right ventricular outflow tract obstruction exhibit profound cyanosis within the first few days of life; they may even require PGE_1 infusion to preserve pulmonary blood flow by left-to-right shunting from the aorta into the main pulmonary artery through the patent ductus arteriosus.

The physical examination can reveal varying degrees of cyanosis, and a systolic ejection murmur along the left sternal border. Chronic hypoxemia results in a compensatory polycythemia and varying degrees of clubbing of the fingers and toes.

Diagnostic Testing. The chest radiograph of a patient with cyanotic Tetralogy of Fallot (see Fig. 165.4) shows decreased pulmonary vascular markings and a boot-shaped heart (secondary to a concave main pulmonary artery segment along the superior aspect of the left border of the heart). The heart size in Tetralogy of Fallot is normal; a right-sided aortic arch may be seen in 25% of the cases. The ECG of cyanotic Tetralogy of Fallot reveals right ventricular hypertrophy and a right axis deviation. Children with pink Tetralogy of Fallot may not

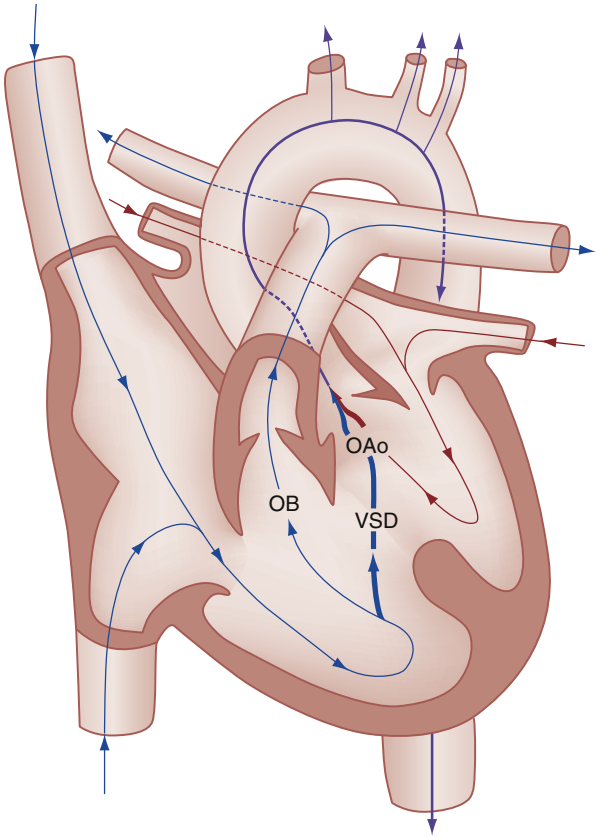

Fig. 165.8 Diagrammatic representation of the right-to-left shunting that occurs in Tetralogy of Fallot. Some of the deoxygenated blood *(thick blue arrow)* in the right ventricle is shunted across the ventricular septal defect *(VSD)* into the left ventricle. This deoxygenated blood mixes with the well-oxygenated blood from the lungs *(red arrow)*. The blood that is ejected out through the overriding aorta *(OAo)*, therefore, contains blood of mixed oxygenation *(purple arrows)*. The amount of deoxygenated blood that is shunted through the VSD *(thick blue arrow)* is dependent on a combination of factors, including the severity of right ventricular outflow tract obstruction *(OB)*, the size of the VSD, and the degree of systemic vascular resistance (SVR). When the SVR falls (as occurs during a tet spell), more deoxygenated blood from the right ventricle will be shunted across the VSD into the systemic circulation, which results in hypoxia, metabolic acidosis, and worsening cyanosis.

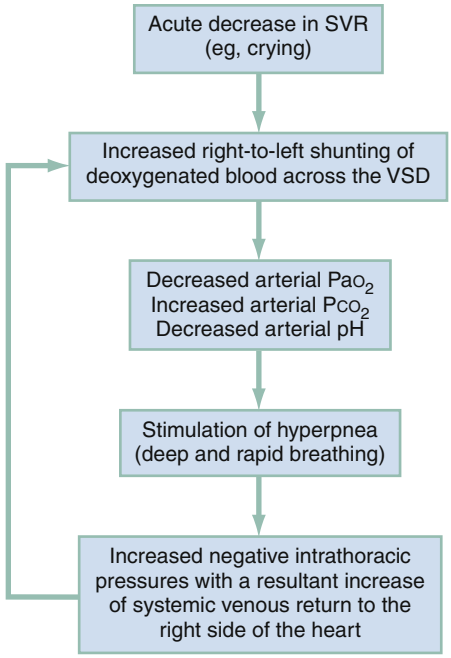

Fig. 165.9 Pathophysiologic mechanisms of a hypoxic (tet) spell. *PaO_2,* Arterial oxygen partial pressure; *PCO_2,* partial pressure of carbon dioxide in the arterial blood; *SVR,* systemic vascular resistance; *VSD,* ventricular septal defect.

BOX 165.8 Management of Tetralogy of Fallot Hypoxic Spells

- Place the child in the knee-to-chest position to increase the systemic vascular resistance (SVR), which decreases the right-to-left shunt across the ventricular septal defect (VSD).
- Provide supplemental oxygen (limited value by itself).
- Morphine: 0.1 to 0.2 mg/kg IV or IM
- Fentanyl: 1 μg/kg/dose IV or IM as an alternative to morphine
- Fentanyl: 1.5–2 mcg/kg/dose intranasally (anatomic limit of 1 mL solution per naris)
- Midazolam: 0.2 to 0.3 mg/kg/dose intranasally (anatomic limit of 1 mL solution per naris)
- Sodium bicarbonate: 1 mEq/kg IV if suspected or documented acidosis
- Consider ketamine: 1 to 2 mg/kg IV or 3 to 5 mg/kg IM
- Consider propranolol: 0.1 to 0.2 mg/kg IV
- Consider phenylephrine: 0.01 to 0.02 mg/kg IV

IM, Intramuscular; *IV,* intravenous.

initially exhibit any degree of right ventricular hypertrophy, but these acyanotic variations of Tetralogy of Fallot gradually develop into the cyanotic form by 1 to 3 years old.

A potentially life-threatening complication of Tetralogy of Fallot is the so-called *tet spell,* also known as a hypercyanotic or hypoxic spell. These episodes occur most commonly in infants, with a peak incidence between 2 and 4 months old.

Any event that suddenly lowers the SVR (such as crying or defecation), hypovolemia, or tachycardia will promote a large right-to-left shunt across the VSD, beginning the vicious circle of a hypoxic spell. The large right-to-left shunt through the VSD bypasses the lungs, which then causes a decrease in the Pao_2, an increase in the Pco_2, and a fall in the arterial pH. These metabolic changes then stimulate the respiratory centers in the brain to produce hyperpnea (deep and rapid respirations), which increases the negative intrathoracic pressure during inspiration, causing an increase in the systemic venous blood return to the right side of the heart. This increased volume of blood in the right ventricle is then shunted through the VSD by the combination of the existing right ventricular tract outflow obstruction and the acute decrease in the SVR. This in turn further decreases the arterial oxygen saturation, perpetuating the hypoxic spell (Fig. 165.9).

These hypoxic spells are characterized clinically by periods of hyperpnea, prolonged crying, and worsening cyanosis. Limpness, seizures, cerebrovascular accidents, and even death have been reported with more severe tet spells. During a tet spell, the intensity of the murmur decreases because of less blood flow through the right ventricular tract obstruction and more blood being shunted from the right ventricle to the left ventricle through the VSD.

Management. The overall treatment goals for tet spells are to increase the SVR, to abolish the hyperpnea, and to correct the metabolic acidosis (Box 165.8). Give supplemental oxygen and increase the child's SVR by placing him or her in a knee-to-chest position; older children may be placed in the squatting position, if tolerated. Both maneuvers are believed to increase SVR and to decrease the

pathologic right-to-left shunting of blood. Analgesics should be given to calm the child, decrease the catecholamine surge, and decrease the respiratory rate. Morphine (0.1 to 0.2 mg/kg) intramuscularly has been a traditional option but has the possible untoward effect of systemic vasodilation (further decreasing the SVR) by endogenous histamine release. Fentanyl and midazolam are newer options without the potential risk of endogenous histamine release. Both may be given via the intranasal route and may be less distressful than intramuscular morphine. Ketamine (1 to 2 mg/kg IV or 3 to 5 mg/kg IM) is a good choice for its analgesic and sedative effects; it is an excellent choice to improve SVR. In the event of clinically suspected or documented (pH <7.4) metabolic acidosis, sodium bicarbonate (1 mEq/kg IV) may be given to break the cycle of hypoxemia, acidosis, and worsening hypotension and perfusion. Most infants respond to these measures and exhibit an improvement in their oxygenation and a decrease in their degree of cyanosis.

An infant whose condition does not improve with these measures may require a vasopressor (such as phenylephrine) to increase the SVR and thereby decrease the degree of right-to-left shunting across the VSD. An intravenous fluid bolus may also be considered to increase the volume of blood flow through the pulmonary artery. If the aforementioned pharmacologic interventions are not successful, consider propranolol 0.1 to 0.2 mg/kg IV (0.01 to 0.2 mg/kg IV) administered slowly and repeated if needed every 10 to 15 minutes (possibly reduces infundibular spasm at the right ventricular outflow tract) or phenylephrine (5 to 20 mcg/kg IV) administered slowly and repeated if needed every 10 to 15 minutes (alpha-antagonist to increase SVR).

Palliative surgical procedures to increase the amount of blood flow temporarily to the pulmonary arteries are performed in infants with severe cyanotic Tetralogy of Fallot. The most commonly performed procedure is the modified Blalock-Taussig shunt, in which an anastomosis is created between the subclavian artery and the ipsilateral pulmonary artery. Definitive surgical repair consists of closing the VSD and opening the right ventricular outflow tract obstruction by resection of the infundibular tissue. The mortality rate is 5% to 10% within the first 2 years after definitive surgical repair in uncomplicated Tetralogy of Fallot cases. Complications that can occur after definitive surgical repair include complete heart block, ventricular dysrhythmias, and right bundle branch block (secondary to the right ventriculotomy).

Postoperative Complications of Congenital Heart Defects

A variety of postoperative complications can be seen in patients who present to the ED weeks to months after cardiac surgery: thrombosis of a shunt conduit with decreased flow; increased shunt conduit flow with resultant CHF; atrial and ventricular dysrhythmias; heart block; myocardial ischemia; and endocarditis. The size of the cardiac silhouette and the degree of pulmonary blood flow on the chest radiograph may provide valuable clues as to whether there is an increased or decreased blood flow through a surgical conduit that was created to provide an improvement in blood flow to the pulmonary system. Comparison of the child's other postoperative chest radiographs can help determine whether there has been a change in the heart size and pulmonary vascularity.

The post-pericardiotomy syndrome is an inflammatory pericarditis that can occur 1 to 6 weeks after any surgical procedure that involved a pericardiotomy. An immunologic inflammatory response is characterized by fever, chest pain, and pericardial effusion. A pericardial friction rub may be heard, depending on the amount of fluid that accumulates in the pericardial sac. The chest radiograph may reveal an enlarged cardiac silhouette, and the echocardiogram will confirm the diagnosis. Pericardiocentesis is rarely required but may be necessary if the amount of pericardial effusion is significant enough to cause pericardial tamponade. The majority of cases of post-pericardiotomy syndrome will resolve within 2 to 3 weeks with bed rest and nonsteroidal anti-inflammatory medication.

BOX 165.9 Conditions Associated With an Increased Risk of Severe or Fatal Respiratory Syncytial Virus Infections

- Cyanotic or complex congenital heart defects
- Pulmonary hypertension
- Prematurity (especially those infants with bronchopulmonary dysplasia or chronic lung disease)
- Immunodeficiency states

Respiratory Syncytial Virus Infections in Infants and Children With Congenital Heart Defects

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and children worldwide, with the majority of children infected at least once by 2 years of age. Reinfection occurs commonly throughout life. Children with CHD who have RSV infections tend to have a higher rate of intensive care unit (ICU) admissions and require mechanical ventilation more frequently than those children who do not have CHD. RSV infection in a child with CHD carries a 40% mortality rate (Box 165.9).

Congestive Heart Failure

Foundations

CHF occurs when cardiac output is unable to meet the hemodynamic and metabolic demands of the body. Although there is a wide array of causes of CHF, the primary cause in infants and children is CHD. Other causes of CHF include the anomalous left coronary artery in infants, myocarditis, endocarditis, rheumatic heart disease, pericardial effusions, anemia, cardiomyopathies, systemic hypertension, hypothyroidism, hyperthyroidism, electrolyte imbalances, endocrine disorders, cardiac toxins, and dysrhythmias that compromise cardiac output.

CHF can result from a derangement in any of the four primary determinants of normal cardiac function: (1) excessive preload (e.g., large left-to-right shunts and severe chronic anemia); (2) decreased cardiac contractility (e.g., myocarditis); (3) excessive afterload (e.g., left-sided obstructive lesions); and (4) rhythm abnormalities that compromise cardiac output or stroke volume (e.g., paroxysmal supraventricular tachycardia and severe forms of heart block). The treatment of CHF depends on which of these four primary determinants of normal cardiac function are compromised. For example, inotropic agents and diuretics may be required in a child with volume overload and decreased cardiac contractility, whereas vasodilatory agents may be required in a child with CHF due to an increased afterload.

Clinical Features

Clinical manifestations of CHF depend on the exact pathophysiologic cause of the CHF; common presenting signs and symptoms include tachycardia, gallops (especially an S_3), tachypnea with rales, hepatomegaly, peripheral edema, and decreased peripheral perfusion of the extremities. Wheezing and a chronic cough may also be the presenting symptoms of CHF.

Diagnostic Testing

The chest radiograph typically reveals an enlargement of the cardiac silhouette and varying degrees of pulmonary congestion. An echocardiogram will be able to assess the ejection fraction, as well as to identify

underlying anatomic defects. BNP may be helpful in differentiating cardiac from pulmonary causes of dyspnea in children.[5]

Management

Acute stabilization of any child who presents with CHF includes administration of supplemental oxygen and agents to augment cardiac contractility and to improve cardiac output. Children with respiratory distress due to pulmonary congestion may benefit from elevation of the head and upper torso—if available, place the infant in a car seat. Continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BiPAP) ventilation via mask or nasal cannula (nasal CPAP) may be useful initially to decrease work of breathing and avert the need for endotracheal intubation. Children who present in severe respiratory distress secondary to pulmonary edema may require intubation to support oxygenation and ventilation. Plasma BNP levels have been used also to monitor the response to treatment regimens in patients with CHF.

Diuretics and inotropic agents may be considered. Furosemide (0.5 to 1 mg/kg) is the most common loop diuretic used to increase renal perfusion and to improve urine output. In contrast to adults, nitroglycerin is not first-line therapy for CHF in children. Children are much more sensitive to the drug's potent vasodilatory effects than adults, and they can experience profound and rapid hypotension with administration of nitroglycerin.

In the past, dopamine was administered for undifferentiated shock in children; however, other agents with less arrhythmogenic side effects are available. Increasingly, guidelines advocate for an approach based on etiology and pathophysiology. Norepinephrine is a good choice as a first-line vasopressor for pediatric decompensated cardiogenic shock due to its effectiveness in supporting SVR. Dobutamine may be added for its selective cardiac inotropic effects. Epinephrine is also potent inotrope and chronotrope that increases the SVR.

Amrinone and milrinone, most commonly used in the ICU setting, may be added to an inotrope to promote forward blood flow via peripheral vasodilatory effects. These agents have been used to improve cardiac index in septic shock and to prevent low cardiac output states for children with CHD. Side effects of these medications include profound hypotension, dysrhythmias, hypersensitivity reactions, fever, hepatotoxicity, and thrombocytopenia.

Pediatric Dysrhythmias

Foundations

The most common cause of cardiopulmonary arrest in infants and children is the untreated progression of respiratory failure or shock, rather than a primary cardiac dysrhythmia. Accordingly, the most common arrest rhythm is asystole or bradycardia rather than ventricular fibrillation or ventricular tachycardia.

The most common dysrhythmia in children is supraventricular tachycardia, which occurs most commonly in infants and young children. Although supraventricular tachycardia can spontaneously occur in infants without any underlying structural cardiac defects, ventricular tachycardias, in contrast, are typically due to an underlying myocardial abnormality.

Clinical Features

Rhythm disturbances in infants can be manifested with symptoms, such as fussiness, lethargy, poor feeding, pallor, respiratory distress, or cardiogenic shock. Older children present with chest pain, palpitations, difficulty in breathing, or syncope. The type and degree of severity of the presenting signs and symptoms should be taken into account in the evaluation and management of the specific dysrhythmia in each case (Box 165.10).

BOX 165.10 Conditions Associated With a High Risk for Development of Dysrhythmias

- Congenital heart defects (uncorrected defects and postoperative complications)
- Congenital complete heart blocks (e.g., maternal systemic lupus erythematosus)
- Myocarditis
- Rheumatic heart disease
- Kawasaki disease with involvement of the coronary arteries
- Cardiomyopathy
- Prolonged QT syndrome
- Aberrant atrioventricular conduction pathways (e.g., Wolff-Parkinson-White syndrome)
- Electrolyte abnormalities (e.g., potassium, calcium, and magnesium disturbances)
- Commotio cordis
- Profound hypothermia
- Hypoxia

Management

Children who exhibit electrocardiographic evidence of conduction abnormalities (e.g., Mobitz type II second-degree heart block, complete heart block, prolonged QT intervals, or aberrant conduction, such as the Wolff-Parkinson-White syndrome) may require emergent management, depending on symptoms and hemodynamic status.

Although some medications can be used to treat only atrial tachycardia (e.g., adenosine for supraventricular tachycardia) or ventricular tachycardia (e.g., lidocaine for ventricular tachycardia), amiodarone and procainamide can be used for an array of both atrial and ventricular dysrhythmias, including supraventricular and ventricular tachycardia.

Bradydysrhythmias

Sinus Bradycardia. Bradycardia is defined as a heart rate that is slower than the lower limit of normal for a child's age. Clinically significant bradycardia in children is a heart rate slower than 60 beats/minute and associated with poor systemic perfusion. An athletic adolescent may have a resting baseline heart rate lower than 60 beats/minute, requiring no treatment if asymptomatic with good perfusion.

Bradycardia is poorly tolerated in infants and children because they are not physiologically capable of increasing their stroke volume to maintain an adequate cardiac output in the face of significant bradycardia. **The most common cause of symptomatic bradycardia in infants and children is hypoxia.** First, ensure adequate oxygenation and ventilation. Epinephrine is the first-line medication for treatment of symptomatic bradycardia in children that is not responsive to appropriate oxygenation and ventilation. If additional doses of intravenous or intraosseous epinephrine are required to treat symptomatic bradycardia, the dose should remain at standard dosing (0.01 mg/kg). Atropine is indicated for vagally induced bradycardia or treatment of primary atrioventricular block. Atropine will have no effect on the denervated heart (e.g., after cardiac transplantation). If vascular access is not available, both epinephrine and atropine can be administered through the tracheal tube, although the intravenous route is preferred.

Other causes of bradycardia include hypothermia, increased intracranial pressure, heart blocks (congenital and acquired), denervated heart status after cardiac surgery, hypothyroidism, sick sinus syndrome, and various medications and toxins (e.g., digoxin, beta-blockers, calcium channel blockers, and cholinergic agents). Children with presyncopal or syncopal symptoms or poor perfusion with Mobitz type II second-degree atrioventricular block, complete third-degree heart block, or sick sinus syndrome should be paced.

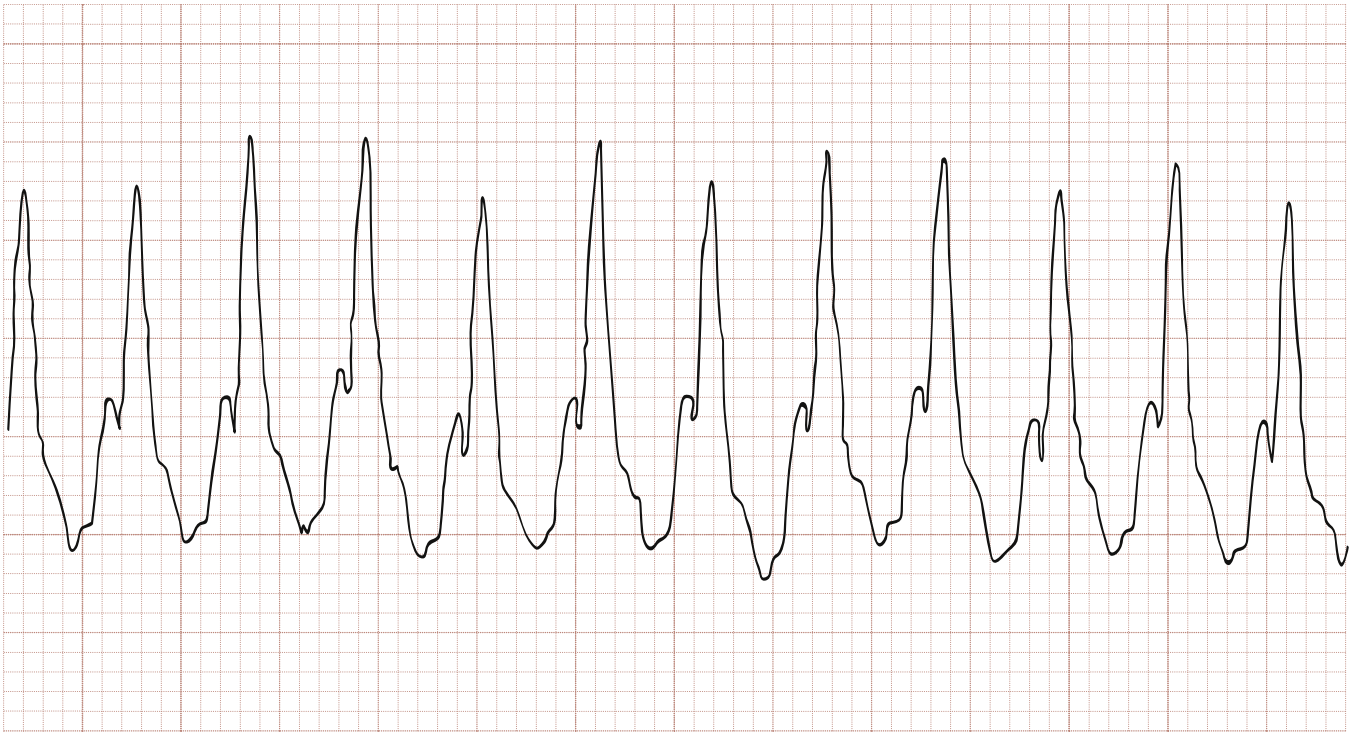

Fig. 165.10 An example of an electrocardiogram (ECG) showing a wide-complex supraventricular tachycardia at a rate of approximately 270 beats/minute in an infant with Ebstein anomaly of the tricuspid valve. This infant was in supraventricular tachycardia for approximately 2 days and presented with an acute exacerbation of her congestive heart failure (CHF), as evidenced by the cardiomegaly on the chest radiograph (see Fig. 165.11). Note that the cardiothoracic ratio in this infant is approximately 70%.

Tachydysrhythmias

Supraventricular Tachycardia. Supraventricular tachycardia is the most common symptomatic dysrhythmia in infants and children. No cardiac abnormalities are found in approximately half of cases; the Wolff-Parkinson-White syndrome is present in only 10% to 20%. The type of supraventricular tachycardia that occurs most commonly in infants and children involves a reentrant mechanism that uses an accessory pathway and the atrioventricular node (i.e., atrioventricular reentrant tachycardia [AVRT]). The *orthodromic* reentry phenomenon involves the normal antegrade conduction from the atria to the ventricles down the atrioventricular node, with retrograde conduction back from the ventricles to the atria by the accessory pathway. Orthodromic conduction will produce a narrow–QRS complex supraventricular tachycardia. The less common reentry mechanism is the *antidromic* form in which conduction from the atria to the ventricles first goes antegrade down the accessory pathway then retrograde back to the atria by the atrioventricular node. Antidromic conduction will produce a wide–QRS complex supraventricular tachycardia. Supraventricular tachycardia in a child with a preexisting bundle branch block can also result in a wide-complex supraventricular tachycardia. The ECG in Figure 165.10 reveals a case of a wide-complex supraventricular tachycardia in a child with Ebstein anomaly of the tricuspid valve who also presented with CHF (Fig. 165.11).

Clinical Features and Diagnostic Testing. Supraventricular tachycardia is most likely with heart rates above 180 in young children and 220 in infants, without beat-to-beat variability (Fig. 165.12 and Table 165.5). Although healthy infants can generally tolerate supraventricular tachycardia with heart rates approaching 300 beats/minute, supraventricular tachycardia may begin to produce signs of CHF and shock if left untreated. Older children with supraventricular tachycardia commonly present with palpitations, difficulty in breathing, and chest discomfort.

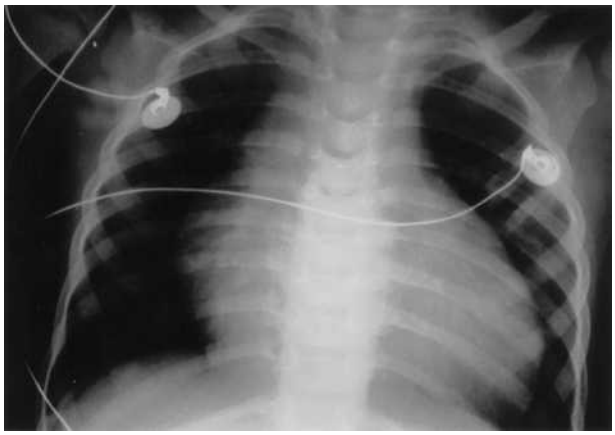

Fig. 165.11 Chest radiograph of same infant as in Figure 165.10.

Management. The emergency clinician should quickly initiate synchronized cardioversion (0.5 to 1 J/kg) for children in supraventricular tachycardia (SVT) with signs of poor perfusion, such as altered mental status, delayed capillary refill, pallor, cyanosis, or hypotension (i.e., decompensated shock). If the child does not convert with this initial cardioversion attempt, the energy dose can be doubled up to 2 J/kg on subsequent attempts. If the child is hemodynamically stable, vagal maneuvers, then adenosine, may be attempted initially before cardioversion; a continuous rhythm strip should be run to document the response to each conversion attempt. Vagal maneuvers (e.g., blowing into a syringe) can be attempted before adenosine administration in the child with hemodynamically stable supraventricular tachycardia. Application of ice to the face has been demonstrated to be a fairly effective method of converting supraventricular tachycardia in infants and children.

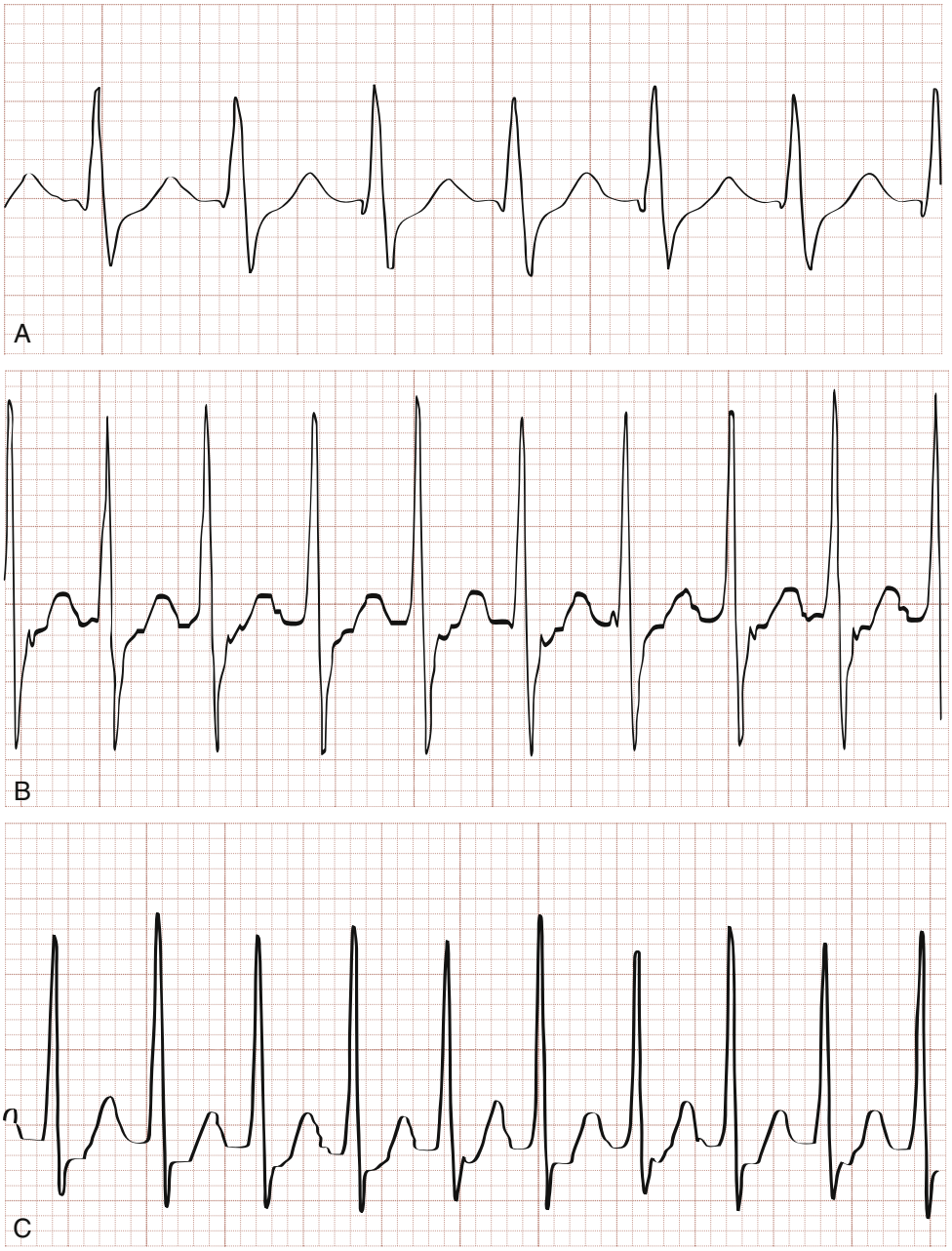

Fig. 165.12 Three electrocardiographic examples of classic narrow-complex supraventricular tachycardia in children. The heart rate is approximately 240 beats/minute in the first two examples (A and B) and approximately 270 beats/minute in the third example (C).

TABLE 165.5 Clinical and Electrocardiographic Features to Differentiate Sinus Tachycardia From Supraventricular Tachycardia in Children

	Sinus Tachycardia	Supraventricular Tachycardia
Precipitating events	Dehydration, fever, pain	No precipitating event
P waves on electrocardiogram (ECG)	Present	Absent
Heart rate varies with activity	Yes	No
Beat-to-beat variability	Yes	Constant R-R intervals
Heart rate in infants (beats/minute)	Usually <220	Usually >220
Heart rate in children (beats/minute)	Usually <180	Usually >180

One method to perform this maneuver is to fill a plastic bag or surgical glove with a slurry of crushed ice and water, which is then placed over the infant's forehead, eyes, and bridge of the nose for 10 to 15 seconds. Placement of the ice bag should not occlude the nose or mouth. External ocular pressure should be avoided. Carotid massage is less effective and is not recommended as a vagal maneuver in infants or children.

The initial dose of adenosine in children is 0.1 mg/kg with a maximum initial dose of 6 mg. If this initial dose of adenosine fails to convert the supraventricular tachycardia, the dose is then doubled to 0.2 mg/kg with a maximum of 12 mg/dose. This 0.2 mg/kg dose of adenosine may be repeated once. Elective cardioversion with procedural sedation may be required in children who fail to convert with adenosine. Adenosine-induced wide-complex tachycardia (secondary to an occult accessory conduction pathway) is an uncommon complication (Fig. 165.13). Amiodarone may be given at a loading dose of 5 mg/kg

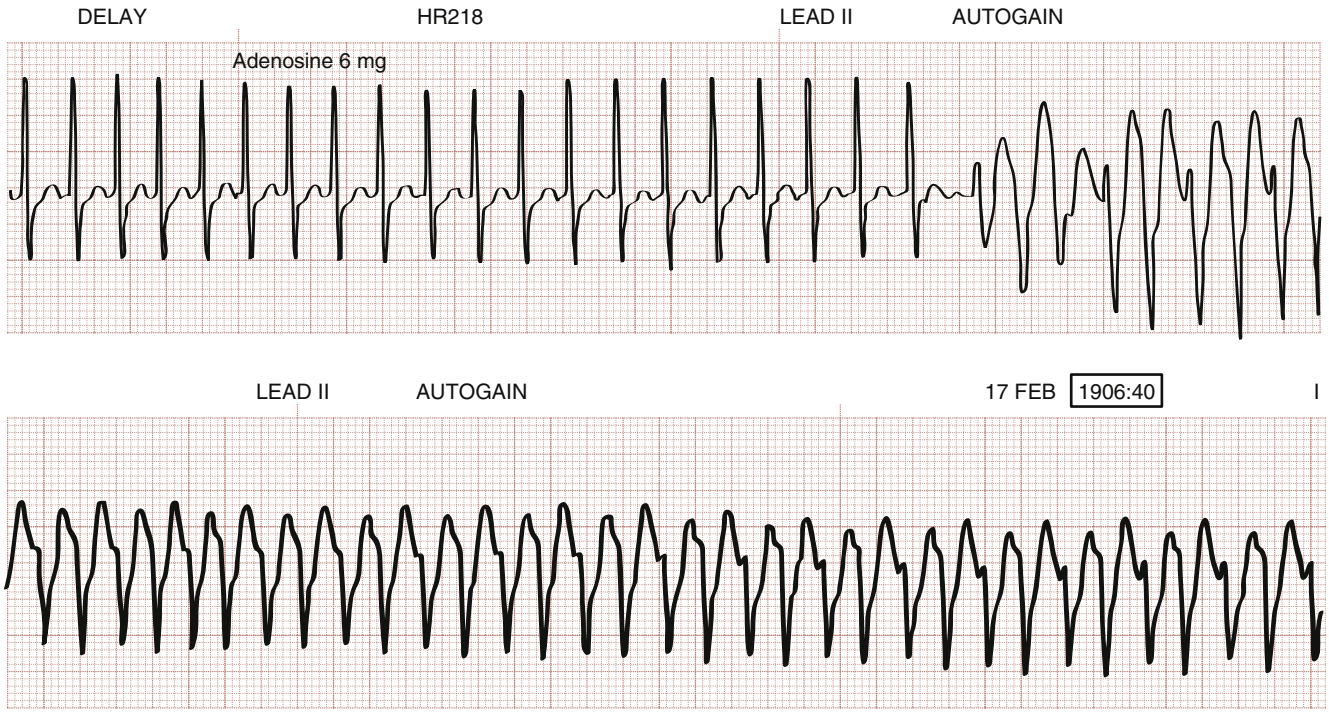

Fig. 165.13 An example of adenosine-induced wide-complex tachycardia. A dose of 6 mg of adenosine was administered to this previously healthy 15-year-old girl who presented with a 6-hour history of palpitations. She had no previous cardiac problems except for intermittent palpitations in the past that always resolved spontaneously without any medical interventions. Once adenosine blocked the conduction through the atrioventricular node, a wide-complex tachycardia appeared on the electrocardiogram (ECG), which was probably due to antegrade conduction through an accessory pathway. During the 30 seconds of this wide-complex tachycardia, the patient remained alert with excellent perfusion parameters. This wide-complex tachycardia then spontaneously converted to normal sinus rhythm. Although the patient's postconversion ECG did not reveal an accessory pathway, Holter monitoring 1 month later detected the classic electrocardiographic findings of Wolff-Parkinson-White syndrome.

over 20 to 60 minutes, then continued at 5 mcg/kg/min. Verapamil should be avoided altogether in infants and children, and not given to those younger than 2 years old because of the risk of profound hypotension and cardiovascular collapse in this age group. Once the patient has converted to sinus rhythm, a 12-lead ECG should be obtained to assess for the possibility of Wolff-Parkinson-White syndrome or any other underlying conduction abnormalities that may have predisposed the child to development of the supraventricular tachycardia.

Atrial Flutter and Atrial Fibrillation. Both atrial flutter and atrial fibrillation are rare in children and are usually associated with underlying heart conditions (e.g., CHD, status post–open heart surgical procedures that involved the atria, myocarditis, and digoxin toxicity). Hemodynamic stability depends on the ventricular response. As in adults, children with hemodynamically unstable atrial flutter or atrial fibrillation should be electrocardioverted. The initial treatment priority in patients with hemodynamically stable atrial flutter and atrial fibrillation is first to slow the rate of the ventricular response with medications such as diltiazem, beta-blockers, or digoxin. IV calcium channel blockers and IV beta-blockers often cause complete heart block and should not be given concurrently.

If the patient who presents with atrial flutter or atrial fibrillation is known to have an underlying Wolff-Parkinson-White syndrome, the four medications that should be avoided are the A-B-C-D medications (adenosine, amiodarone, beta-blockers, calcium channel blockers, and digoxin); all of these medications preferentially block conduction down the atrioventricular node, leaving the accessory pathway open to conduct the atrial tachycardia to the ventricles at a potentially lethal rate. Safer alternatives are amiodarone, procainamide, or cardioversion. Procainamide is preferred to amiodarone as there have been reports of VF following amiodarone administration in WPW. Consultation with the cardiologist and initiation of anticoagulation should also be considered.

Ventricular Tachycardia. The majority of children with ventricular tachycardia have an underlying condition, such as post–cardiac surgery status, myocarditis, prolonged QT syndrome, drug or toxin exposures (e.g., cyclic antidepressants), or electrolyte abnormalities. The treatment of ventricular tachycardia will depend on hemodynamic status of the patient. Torsades de pointes is a unique type of polymorphic ventricular tachycardia characterized by QRS complexes that change in polarity and amplitude. Prolonged QT syndrome, underlying congenital cardiac defects, hypomagnesemia, and various medications (e.g., cyclic antidepressants) have been identified as known causes of torsades de pointes. The treatment of choice is intravenous magnesium at an initial dose of 25 to 50 mg/kg, up to the adult dose of 2 g over 2 minutes. Class IA (i.e., procainamide) and class III (i.e., amiodarone) antidysrhythmic agents are contraindicated in the treatment of torsades de pointes because these agents are capable of prolonging the QT interval, which can precipitate the degeneration of the torsades de pointes into a lethal rhythm.

Special Resuscitation Situations in Children

Children with single-ventricle physiology (e.g., hypoplastic left heart syndrome and double-outlet right ventricle physiology) after a palliative shunting procedure should be given standard resuscitation care. Heparin may be used in the pre-arrest or arrest of infants with a systemic–to–pulmonary artery shunt or right ventricle–to–pulmonary

artery shunt to halt thrombus propagation in this low circulatory flow state. A target oxyhemoglobin saturation (Spo_2) of approximately 80% is preferred in these children. End-tidal carbon dioxide readings after resuscitation may lag behind, because varying pulmonary blood flow changes do not necessarily reflect cardiac output. The goal is to provide adequate preload with judicious fluids to balance systemic and pulmonary blood flow. If available, extracorporeal membrane oxygenation should be considered.

Children with a history of pulmonary hypertension should also receive standard resuscitation management. Preload should be optimized with isotonic saline boluses. Inhaled nitric oxide in the ICU may be given to reduce PVR. Early contact with the child's cardiologist and cardiothoracic surgeon is instrumental in the post-resuscitative care of children with CHD.

Bacterial Endocarditis

Foundations

Although bacterial endocarditis most commonly occurs in children with an underlying CHD or an acquired cardiac lesion (e.g., acute rheumatic valvular heart disease), it can also occur in patients with no underlying anatomic defects of the valves or endocardium.

Cardiac lesions that carry this higher risk include VSD, aortic valvular stenosis, tetralogy of Fallot, single-ventricle states, bicuspid aortic valves, prosthetic valves, and postoperative systemic-to-pulmonary shunts. Isolated secundum ASD carry a much lower risk for bacterial endocarditis because the shunt flow through the ASD is typically of a much lower velocity (Box 165.11).

Clinical Features

The early clinical manifestations of bacterial endocarditis are nonspecific. The child may simply present with only fever and tachycardia (see Box 165.11). A new heart murmur is present in less than 50% of the bacterial endocarditis cases. Common presenting signs are fever (99%), petechiae (21%), changing murmur (21%), dental caries (14%), and hepatosplenomegaly (14%). Less common signs are CHF (9%), splinter hemorrhages (5%), Roth spots (5%), and Osler nodes (4%).

Diagnostic Studies

Diagnostic studies for a child with suspected bacterial endocarditis include a complete blood cell count, C-reactive protein (CRP) assessment, measurement of erythrocyte sedimentation rate (ESR), three blood cultures, chest radiography, and electrocardiography. *Streptococcus viridans* and *Staphylococcus aureus* are the two most common offending organisms recovered from the blood cultures of children with bacterial endocarditis. Studies have shown that in children with CHD, 60% of the cases caused by staphylococcal species are methicillin resistant and associated with increased risk of mortality. Formal echocardiography is typically done as an inpatient.

BOX 165.11 Clinical Conditions in Which Bacterial Endocarditis Should Be Suspected in a Child With an Underlying Anatomic Cardiac Defect

- Fever of unknown etiology
- A change in the quality of the preexisting heart murmur or the presence of a new heart murmur
- Development of a neurologic deficit (secondary to central nervous system emboli)
- New-onset microscopic hematuria
- Splenomegaly
- Petechiae
- Splinter hemorrhages involving the conjunctiva, nail beds, palms, or soles
- Myalgias

Management

In some patients, antibiotic prophylaxis to prevent endocarditis is recommended. Box 165.12 lists the cardiac conditions for which endocarditis prophylaxis is recommended and Box 165.13 lists the procedures for which these patients should receive antibiotic prophylaxis. In children with suspected acute bacterial endocarditis, antibiotics should be started immediately after blood culture samples have been obtained. Although the choice of intravenous antibiotics depends on the suspected source of seeding and the child's immune status, a commonly recommended regimen includes an aminoglycoside plus a penicillinase-resistant penicillin, such as oxacillin. If methicillin-resistant *Staphylococcus* is suspected, vancomycin should also be included in the initial empirical antibiotic regimen. Surgical intervention may be required to remove septic vegetations, or valve replacement is sometimes necessary. Further reading on endocarditis may be found in Chapter 69.

Pericarditis

Foundations

Pericarditis is an inflammatory process within the pericardial sac that may not be associated with a pericardial effusion. In the majority of cases, pericarditis in children is self-limited and follows a benign clinical course. A sudden increase or a large amount of fluid within this

BOX 165.12 Cardiac Conditions for Which Endocarditis Prophylaxis Is Recommended

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD)[a]
- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure[b]
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialization)
- Cardiac transplantation recipients who have cardiac valvulopathy

[a] Except for those conditions above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
[b] Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.
From: American Heart Association. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116:1736.

BOX 165.13 Procedures for Which Endocarditis Prophylaxis Is Recommended

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa[a]
- Consider prophylaxis for incisional procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients

[a] The following procedures do not need prophylaxis: routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

pericardial sac can cause a tamponade-induced decrease in stroke volume, resulting in diminished cardiac output and hypotension.

The most common causes of pericarditis include bacterial and viral infections; other causes are ARF, systemic lupus erythematosus, uremia, post-pericardiotomy syndrome, leukemia, lymphoma, and tuberculosis. Approximately 30% of pericarditis cases are due to bacteria, such as pneumococcus, *S. aureus,* meningococcus, and *Haemophilus influenzae*. Viral causes are most common, but a specific viral pathogen is recovered in only 20% to 30% of cases. Viral causes include coxsackieviruses, echoviruses, adenovirus, Epstein-Barr virus, and influenza viruses.

Clinical Features

The presenting signs and symptoms of pericarditis depend on the cause of the pericarditis, as well as on the amount of fluid that has accumulated within the pericardial sac. Chest pain that varies with position is a common complaint with pericarditis; pain is exacerbated with inspiration and the supine position but relieved when the patient sits up or leans forward. Tachycardia is also a common finding in patients with pericarditis and may be the only clue to the diagnosis. Other findings include fatigue, tachypnea, neck vein distention, pulsus paradoxus, hepatomegaly, lower extremity edema, and thready distal pulses if heart failure is present. Cardiac auscultatory findings can include a harsh-sounding friction rub or diminished or muffled heart tones if there is a significant amount of fluid within the pericardial sac. A pericardial friction rub, if present, is best heard when the patient sits up or leans forward. The friction rub of pericarditis can be distinguished from a pleural friction rub by having the patient hold his or her breath during auscultation. The friction rub of pericarditis will remain present during breath-holding, while the pleural friction rub will no longer be heard.

The chest radiograph in a child with pericarditis may not reveal an enlarged cardiac silhouette. If there is a large collection of fluid within the pericardial sac, the heart shadow on the chest radiograph will resemble a "water bottle" silhouette. Approximately 50% of pericarditis cases have some associated pleural effusion.

The classic electrocardiographic findings of viral pericarditis include diffuse ST segment elevation and diffuse T wave inversions. The classic electrocardiographic changes associated with pericarditis evolve through four phases (Fig. 165.14). During the initial phase,

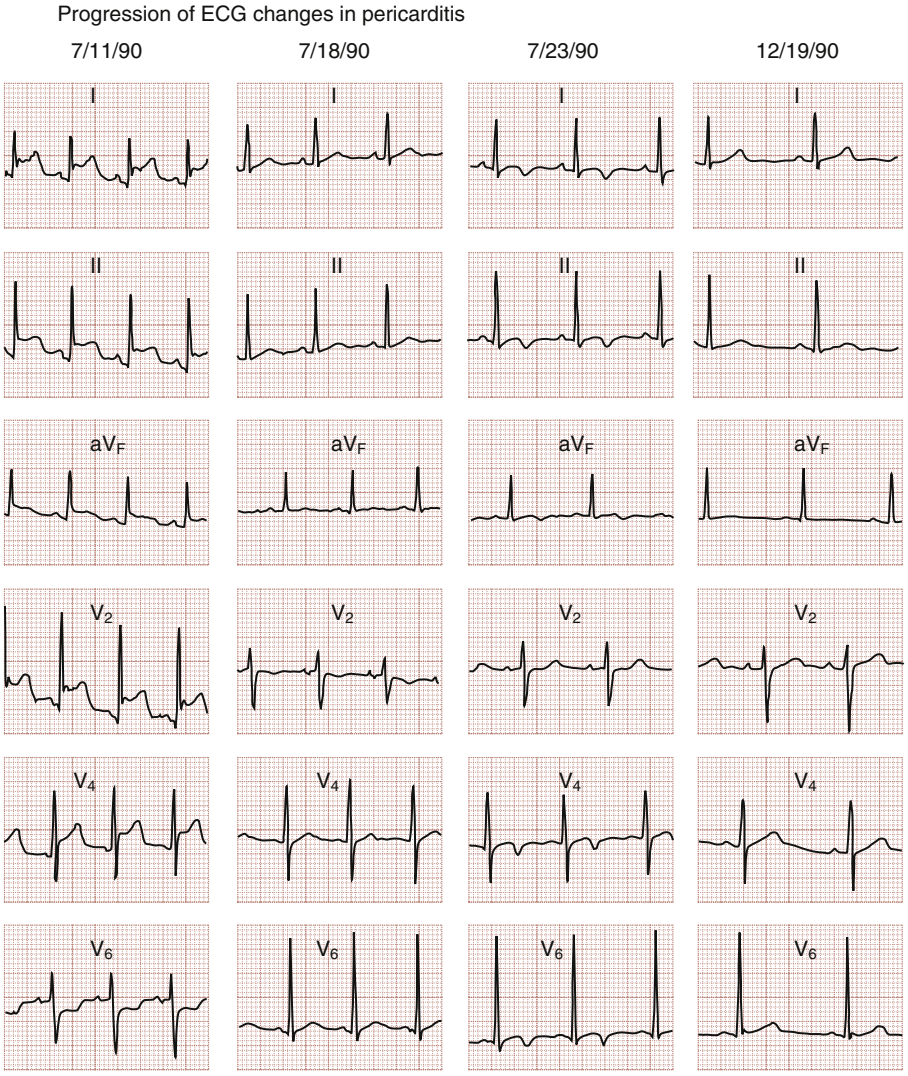

Fig. 165.14 The classic electrocardiographic progression of a patient with pericarditis. First phase: Diffuse ST segment elevation. Second phase: ST segments back to isoelectric but decreased T wave amplitude. Third phase: T wave inversion. Fourth phase: Complete resolution. Notice that the first three phases of the electrocardiographic abnormalities of pericarditis in this patient are evident during the first 2 weeks of his illness. A follow-up electrocardiogram (ECG) obtained 5 months later reveals a complete resolution of all the previous electrocardiographic abnormalities.

there is diffuse ST segment elevation secondary to subepicardial inflammation; PR segment depression may also be seen. During the second phase, the previously elevated ST segments begin to return to isoelectric baseline, and the T wave amplitudes begin to decrease with flattening of the T waves. During the third phase, although the ST segments are now back to isoelectric baseline, the T waves are inverted. The fourth and final phase demonstrates complete resolution of the ST segment and T wave abnormalities. Diminished electrocardiographic voltages in all leads can also occur if there is a significant amount of fluid accumulated within the pericardial sac.

Diagnostic Studies

Ultrasound will confirm both the presence and the amount of accumulated fluid within the pericardial sac. Although echocardiography cannot accurately quantify the exact amount of fluid that has accumulated within the pericardial space, the presence of an anterior and posterior fluid collection is suggestive of a large collection.

Management

The management of a child with pericarditis depends on both the suspected cause, severity of symptoms, and amount of fluid that has accumulated within the pericardial space. Patients with fever, respiratory distress, or signs of CHF should be admitted and an echocardiogram emergently performed. An emergency pericardiocentesis is required in those patients with signs of acute cardiac tamponade. Fluid that is aspirated from the pericardial space should be sent for routine cell counts, Grams stain, and cultures. Antiinflammatory agents and appropriate antibiotics should be initiated on the basis of the suspected cause. Steroids are reserved for refractory cases that are not responsive to these agents and should be considered only after an infectious etiology is ruled out. See also Chapter 68 for more on pericarditis.

Myocarditis

Foundations

In the United States, the most common cause of myocarditis is viral; adenovirus and enteroviruses account for the majority of cases.[7] Other viral causes include echoviruses, influenza, coxsackie, adenovirus, varicella-zoster, Epstein-Barr, cytomegalovirus, and hepatitis B virus. Bacterial causes include *Corynebacterium diphtheriae, Streptococcus pyogenes, S. aureus, Mycoplasma pneumoniae, Borrelia burgdorferi,* and meningococcus. Noninfectious causes include Kawasaki disease, acute rheumatic fever (ARF), collagen vascular disorders (e.g., systemic lupus erythematosus), toxins (e.g., cocaine and doxorubicin), endocrine disorders (e.g., hyperthyroidism), and drug-induced hypersensitivity (e.g., penicillins, sulfonamides, phenytoin, carbamazepine).

Clinical Features

Viral myocarditis usually has a gradual onset with preceding upper respiratory tract infection. Clinicians should consider myocarditis in infants and children with symptoms out of proportion to the typical course of a benign cause, such as a viral syndrome. Early in its course, the only sign of myocarditis may be tachycardia. Tachycardia that is disproportionate to the degree of fever should alert the emergency clinician to the possibility of myocarditis. Other presenting signs and symptoms include fever, myalgias, fatigue, tachypnea, wheezing, abdominal pain, and chest pain. More severe cases of myocarditis can even have signs and symptoms of acute CHF and various dysrhythmias. The physical examination may reveal a new murmur, a gallop rhythm, or a pericardial friction rub with muffled heart tones (if the myocarditis is also accompanied by pericarditis and subsequent pericardial effusion). In general, these are sick children with vague symptoms.

Diagnostic Testing

The evaluation and management of the child with myocarditis depend on the suspected cause and presenting signs and symptoms. Blood cultures and viral titers should be considered in infectious and postinfectious cases. Appropriate antibiotics should be initiated immediately in cases with suspected bacterial origin. The chest radiograph may be normal in very mild cases, but cardiomegaly will be evident in more advanced cases. The electrocardiographic findings are usually nonspecific and can include low-voltage, nonspecific ST segment abnormalities, T wave inversions, atrioventricular block, and various other dysrhythmias. Creatine kinase-MB, cTnT, cTnI, CRP, and ESR may be elevated.

Bedside echocardiography can evaluate for effusion, tamponade, and global function. The goal of treatment is to maintain adequate cardiac output and to control any associated dysrhythmias.

Management

Children who present in CHF with poor perfusion (e.g., lethargy, delayed capillary refill, poor urine output, or hypotension) will likely require inotropic support, positive-pressure ventilation, or diuretics. The role of intravenous immunoglobulin (IVIG) in pediatric myocarditis is unclear.[8] The use of beta-blockers is contraindicated, and the routine use of immunosuppressive agents remains controversial.[9,10] Although the majority of children with acute viral myocarditis make a full recovery, a few patients will progress to dilated cardiomyopathy, which is characterized by dilated ventricles and impaired systolic contractility. See Chapter 68 for more on myocarditis.

Kawasaki Disease

Foundations

Kawasaki disease, originally described as mucocutaneous lymph node, has emerged as a significant cause of acquired cardiac disease in children in the United States. This febrile, exanthematous, multisystem vasculitis is seen most commonly in children younger than 5 years old. Up to 20% of untreated children have some degree of coronary artery abnormalities.[11] Although the exact cause of this vasculitis of small- and medium-sized vessels remains unknown, early clinical recognition and initiation of high-dose aspirin and IVIG improve the morbidity and mortality rates of Kawasaki disease in children.

Clinical Features

In addition to fever, the physical examination of a child with Kawasaki disease may reveal the typical findings as listed in Box 165.14 and illustrated in Figure 165.15. The classic features of Kawasaki disease may be manifested simultaneously or in series of days; a careful history and physical examination may elucidate the need for further testing. In addition, very young children may not have a classic presentation and require further investigation. All children with suspected Kawasaki disease, with either classic or incomplete features, should undergo echocardiography for detection of the presence and degree of coronary aneurysm.[11]

Incomplete Kawasaki Disease. The classic presentation of Kawasaki disease is a clinical diagnosis of four or more of the five criteria in a child who is febrile 5 days or more. However, these strict criteria may miss a substantial number of children who present with incomplete Kawasaki disease. Any child may have an incomplete presentation, but this is mostly seen in infants younger than 6 months old.

Current criteria recommend that in a child who is febrile 5 days or more, the presence of two or three criteria should prompt further testing. We recommend that a CRP of 3 mg/dL or more or an ESR of 40 mm/hr or more prompt further laboratory investigations; children with elevated inflammatory markers should be empirically treated

BOX 165.14 Diagnostic Criteria for Kawasaki Disease

- Fever for 5 days or more
- At least four of the five following physical examination findings:
  1. Bilateral, nonexudative bulbar conjunctival injection (bilateral scleral injection with perilimbic sparing)
  2. Oropharyngeal mucous membrane changes (pharyngeal erythema, red and cracked lips, and a strawberry tongue)
  3. Cervical lymphadenopathy (with at least one node >1.5 cm in diameter)
  4. Peripheral extremity changes (diffuse erythema and swelling of the hands and feet during the acute phase or periungual desquamation during the convalescent phase of the illness); this diffuse palmar erythema seen in Kawasaki disease is in contrast to the discrete macular lesions of various viral illnesses (e.g., measles) that can sometimes be seen on the palms and soles
  5. A polymorphous generalized rash (nonvesicular and nonbullous); there is no specific rash that is pathognomonic for Kawasaki disease
- In a child with four or more criteria, the diagnosis may be made on day 4 of the fever.

(Box 165.15). During their hospital stay, children should receive an echocardiogram to assess for coronary aneurysms.

Children with a CRP of less than 3 mg/dL and an ESR of less than 40 mm/hr may be observed daily and reassessed without treatment; serial ESR and CRP should be obtained daily on an outpatient basis. Infants 6 months of age or younger are more likely to present with incomplete Kawasaki disease and are more susceptible to giant coronary artery aneurysm formation. For this reason, irrespective of general well appearance or lack of clinical findings, infants 6 months of age or younger with fever lasting for 7 days or more should undergo supplemental laboratory testing and undergo echocardiogram when inflammatory markers are abnormal.

Kawasaki disease is postulated to be caused by an infectious agent that enters the respiratory tract and initiates an oligoclonal immunoglobulin A response, which activates lymphocytes, cytokines, and proteinases that weaken vessel walls and predispose the entire circulation to aneurysms. Approximately 25% of patients have mild diffuse myocardial inflammation. This occurs during the acute febrile period and is characterized by tachycardia, a gallop, and nonspecific ST-T wave changes. Up to 5% of the children also exhibit some degree of CHF during this acute phase of their illness; this carditis usually resolves when the fever resolves. Pericardial effusions also occur in up to 20% to 40% of cases. Mild mitral and aortic regurgitation is seen in 1% to 2% of untreated cases on echocardiographic examinations. This phase of the disease is mild and self-resolving.

Differential Diagnoses

Measles can mimic Kawasaki disease (i.e., a febrile illness with red eyes, a rash, and erythema of the oropharynx). The measles rash classically begins on the head and face and progresses caudally. The rash of Kawasaki disease typically begins on the trunk and then spreads to the face and extremities; it may be polymorphous, but not bullous or vesicular.

The palmar lesions of measles are discrete macular lesions (see Fig. 165.15F), whereas the palmar finding in children with Kawasaki disease is diffuse erythema, which may later desquamate (see Fig. 165.15C).

There are many imitators of Kawasaki disease. For example, Kawasaki disease can present with nausea, vomiting, and abdominal pain in a febrile child, which may be mistaken for a surgical abdomen. A febrile irritable child with Kawasaki disease may have a cerebrospinal fluid pleocytosis and be misdiagnosed with viral meningitis.

Streptococcal disease, including pharyngitis and scarlet fever, can be confused with Kawasaki disease, but conjunctivitis and swelling of the hands and feet are unusual for streptococcal disease. Other infectious or autoimmune causes that mimic Kawasaki disease include Rocky Mountain spotted fever, leptospirosis, Stevens-Johnson syndrome, and juvenile rheumatoid arthritis.

Management

The main goal of treatment during the acute febrile phase of Kawasaki disease is to provide supportive care and to decrease the inflammation of the myocardium and coronary arteries. IVIG and high-dose aspirin have an additive effect and, when initiated within 10 days from the onset of the illness, can substantially decrease the progression to coronary artery dilation and aneurysm formation compared with aspirin therapy alone.[12] The combination results in a more rapid resolution of fever and the other indicators of acute inflammation.[12] However, despite prompt treatment with IVIG and high-dose aspirin, 2% to 4% of children still have coronary artery abnormalities.[11]

The current IVIG regimen involves an infusion of 2 g/kg over 10 to 12 hours. Side effects include hypotension, nausea, vomiting, headache, and seizures. Close cardiac monitoring during the IVIG infusion is recommended. The 5% to 10% of children who receive IVIG and experience a persistent or recurrent fever after the initial dose of IVIG may be given a second infusion at the same dose. Approximately two-thirds of children who fail to respond to the initial dose of IVIG will improve with the second infusion.

Aspirin is initiated at 80 to 100 mg/kg/day orally divided into an every-6-hour dosing regimen until the child is afebrile for 48 to 72 hours. Prompt diagnosis and treatment leads to rapid symptomatic improvement in 90% of cases and prevents coronary aneurysm formation in 95%.

The follow-up of children with Kawasaki disease depends on the degree and presence of carditis and coronary artery abnormalities detected on the initial echocardiogram. Other imaging modalities used to follow aneurysmal parameters include electron-beam computed tomography, coronary magnetic resonance angiography, and computed tomography. Those children with more severe cardiac abnormalities should have close follow-up by a cardiologist experienced in Kawasaki disease.

Acute Rheumatic Fever

Foundations

ARF, one of the most common causes of acquired heart disease in children, is the result of a delayed immune reaction to a group A streptococcal infection. In the United States, ARF most commonly occurs in children 5 to 15 years old, with an attack rate of 0.3% in children with an untreated streptococcal infection. Although this disease affects multiple organ systems, carditis is the most serious complication.

Clinical Features

The diagnosis of ARF is based on the Jones criteria (Box 165.16). In addition, there must also be evidence of an antecedent streptococcal infection, which can be documented by a positive throat culture, a positive rapid streptococcal antigen test finding, or an elevated antistreptolysin O (ASO) titer. The ASO titer begins to rise 1 to 3 weeks after streptococcal infection, peaks at 3 to 5 weeks, and reliably falls to baseline after 6 months. The diagnosis of ARF is made in a patient with a documented antecedent streptococcal infection who exhibits either two major criteria or one major plus two minor criteria.[13]

The most common presenting major criterion is migratory polyarthritis, which commonly involves the larger joints of the extremities, as well as the

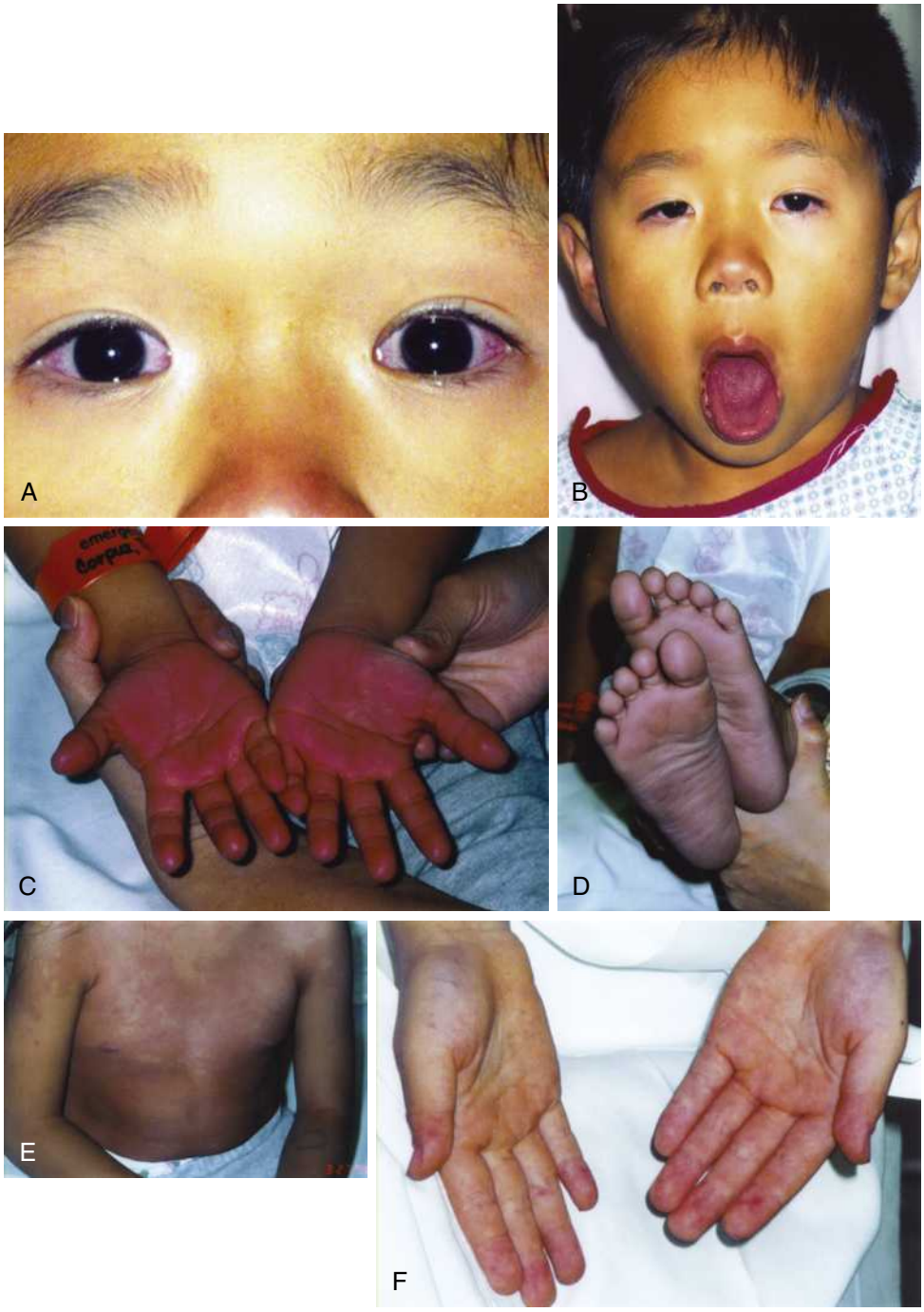

Fig. 165.15 Classic physical examination findings of Kawasaki disease. Note the bilateral nonexudative scleral injections (A) with perilimbic sparing (the thin margin of white sclera around the cornea), red and cracked lips with a strawberry tongue (B), diffuse palmar erythema (C), red soles (D), and polymorphous exanthem (E). The diffuse palmar erythema of Kawasaki disease (C) is distinct from the palmar findings seen in other viral illnesses, such as the discrete macular lesions on the palms in this child with measles (F).

BOX 165.15 Supplemental Laboratory Criteria for Kawasaki Disease

Albumin ≤3 g/dL
Anemia for age
Platelet count of ≥450,000/mm^3
White blood cell (WBC) count ≥15,000 mm^3
Elevation of alanine aminotransferase
Sterile pyuria of ≥10 WBCs per high-power field

smaller tarsal joints in the foot and the smaller carpal joints in the hand. The carditis of ARF most commonly involves valvulitis of the mitral and aortic valves, which clinically is manifested as occult mitral or aortic insufficiency. The murmur of mitral insufficiency is characterized as a holosystolic murmur best heard over the apex with radiation to the axilla. The murmur of aortic insufficiency is characterized as a diastolic murmur that is best heard over the base of the heart. Innocent murmurs that are normally exacerbated with fever can be mistaken for the murmurs of mitral or aortic insufficiency.

Other cardiac manifestations of ARF include CHF, pericarditis, and various degrees of heart block. The two dermatologic major

BOX 165.16 Jones Criteria for the Diagnosis of Acute Rheumatic Fever

The diagnosis of acute rheumatic fever (ARF) is based on the documentation of an antecedent streptococcal infection and (1) two major criteria or (2) one major criterion plus two minor criteria.

Major Criteria

Carditis
Migratory polyarthritis
Erythema marginatum
Subcutaneous nodules
Chorea

Minor Criteria

Clinical findings:
- Fever
- Arthralgia

Laboratory findings:
- Elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
- Prolonged PR interval

Supporting evidence of an antecedent group A streptococcal infection with either of the following:
- A positive throat culture or rapid streptococcal antigen test result
- An elevated antistreptolysin O (ASO) titer

criteria (erythema marginatum and subcutaneous nodules) and chorea occur less commonly than the migratory polyarthritis and carditis. Chorea may occur as the only manifestation of ARF. If arthritis is used as a major component, arthralgia cannot be used as a minor component to make the diagnosis. Likewise, if carditis is used as a major component, a prolonged PR interval cannot be used as a minor component.[13]

Differential Diagnoses

The differential diagnosis of ARF includes myocarditis, bacterial endocarditis, Lyme disease, systemic lupus erythematosus, juvenile rheumatoid arthritis, serum sickness, and septic arthritis.

Diagnostic Testing

In addition to the ECG, CRP or ESR levels, and documentation of an antecedent streptococcal infection, the diagnostic evaluation of ARF should also include a chest radiograph, as well as an echocardiogram to evaluate the degree of cardiac involvement.

Management

The acute management of ARF should focus on stabilization and treatment of any of the symptomatic cardiac manifestations of the illness, such as CHF or tamponade due to a pericardial effusion. Treatment should also include appropriate antibiotic therapy to eradicate the streptococcal infection, bed rest, and antiinflammatory agents for arthritis. Steroids should be used in the treatment of carditis only under direction of a cardiologist. Monthly injections of benzathine penicillin G provide prophylaxis against recurrent attacks; alternative regimens include oral penicillin administered twice daily and, for penicillin-allergic patients, twice daily oral erythromycin. Prophylaxis is required until 18 years of age but can be continued for life, depending on the degree of cardiac involvement and risk of recurrence.[13]

BOX 165.17 Cardiovascular Causes of Sudden Death in Young Athletes

Hypertrophic cardiomyopathy
Various congenital coronary artery anomalies
Prolonged QT interval syndrome
Various preexcitation syndromes (e.g., Wolff-Parkinson-White syndrome)
Commotio cordis
Aortic rupture secondary to Marfan syndrome
Idiopathic dilated cardiomyopathy
Myocarditis
Coronary artery disease secondary to Kawasaki disease
Aortic stenosis
Mitral valve prolapse

Cardiac Causes of Sudden Death in Young Athletes

The most common cardiovascular cause of sudden death in the athlete is hypertrophic cardiomyopathy, accounting for up to 36% of the cardiovascular-related cases (Box 165.17). Brugada syndrome is uncommonly diagnosed in childhood.[13]

Specific Disorders

Congenital Coronary Artery Anomalies. Although there are a variety of congenital coronary artery anomalies, the most common potentially lethal lesion is the anomalous left coronary artery, in which the left main and right coronary arteries both arise from the right sinus of Valsalva. Individuals with this particular anomaly have a 46% incidence of sudden death, with more than 85% of the known cases of sudden death occurring during exercise. Congenital coronary artery hypoplasia is another uncommon cause of exercise-induced sudden death. Any athlete with exertional syncope or chest pain should be evaluated by a cardiologist for the possibility of a congenital coronary artery anomaly. If an anomaly is detected and surgically corrected, the athlete may resume full activity and participation in competitive sports.

Marfan Syndrome. Clinical manifestations of the disease include tall and slender habitus, striae atrophicae, disproportionately long extremities compared with the trunk, scoliosis, pectus excavatum or carinatum, and lens dislocation. Approximately 50% of patients with Marfan syndrome have cardiac manifestations, such as mitral valve prolapse or aortic dilation. The most serious cardiac complication of Marfan syndrome is the progressive dilation of the aorta with the potential risk of aortic rupture, which most commonly involves the descending portion of the aorta. Therefore, patients with Marfan syndrome should be prohibited from participation in contact sports. Those individuals who are known to have aortic dilation should also be prohibited from participation in any competitive sports regardless of the degree of contact involved. All patients with Marfan syndrome with or without cardiac involvement on their initial evaluation should be observed by a cardiologist with serial imaging studies of the aorta by echocardiography, magnetic resonance imaging, or computed tomography.

Hypertrophic Cardiomyopathy. Obstructive hypertrophic cardiomyopathy involves a thickened muscular intraventricular septum that bulges into the left ventricle and impedes forward flow, causing chest pain, shortness of breath, pre-syncope, or syncope. The nonobstructive form, which occurs when the thickened septum does not block forward flow, occurs in only 0.2% of the general population, yet it is the single most common cardiac cause of sudden death in the young athlete. Sudden death in previously asymptomatic individuals with

hypertrophic cardiomyopathy occurs during moderate or severe physical exertion. The proposed pathophysiologic mechanism of sudden death during exertion in these individuals is thought to be a transient decrease of blood flow out through the aorta or dysrhythmia originating from the hypertrophied ventricular myocardium.

Clinical Features. Some individuals with hypertrophic cardiomyopathy have experienced previous "warning" episodes of chest pain, dyspnea, syncope, or palpitations during vigorous activities. A family history of sudden unexplained death in young adults should also alert the clinician to the possibility of hypertrophic cardiomyopathy. The majority of young athletes who die of this condition have the nonobstructive form of hypertrophic cardiomyopathy. The classic loud systolic ejection murmur that is present with the obstructive form may not be heard during the routine pre-sports physical examination.

If a systolic murmur along the lower left sternal border is heard on the routine screening physical examination of a young athlete, a Valsalva maneuver may help differentiate the murmur of aortic stenosis from the systolic murmur associated with the obstructive form of hypertrophic cardiomyopathy. During the Valsalva maneuver, the venous blood return to the heart is decreased, which in turn transiently reduces the left ventricular size. The transient reduction in the size of the left ventricle will increase the degree of obstruction and thus an increase in the intensity of the systolic murmur heard with the obstructive form of hypertrophic cardiomyopathy. In contrast to this, the systolic murmur of aortic stenosis will decrease in intensity during a Valsalva maneuver because of the transient reduction of blood flow through the stenotic aortic valve.

Current recommendations for pre-sports screening include a detailed family and personal history of known or suspected heart disease, physical examination, and 12-lead ECG. If any suspicion remains, further evaluation (e.g., echocardiography, Holter monitoring, other imaging studies) and referral to a cardiologist are indicated.

Diagnostic Testing. The electrocardiographic findings in hypertrophic cardiomyopathy show left ventricular hypertrophy and left atrial enlargement. Other findings include prominent Q waves in the inferolateral leads and diffuse T wave inversions. The most accurate study for the diagnosis of hypertrophic cardiomyopathy is the echocardiogram, which will demonstrate various degrees of left ventricular hypertrophy and involving the ventricular septum in up to 90% of the cases. Patients with echocardiographic evidence of hypertrophic cardiomyopathy should receive serial echocardiographic examinations to monitor progression.

Management. No pharmacologic therapy has been proven to prevent sudden death. Beta-blockers exert negative inotropic effects, attenuate adrenergic-induced tachycardia, improve myocardial oxygen supply-and-demand, and improve diastolic filling. The use of digoxin is contraindicated in patients with hypertrophic cardiomyopathy because its positive inotropic effect may worsen the left ventricular outflow obstruction. Sudden death in patients with hypertrophic cardiomyopathy is thought to be due to exertion-induced ventricular fibrillation or pulseless ventricular tachycardia. Therefore, all individuals diagnosed with hypertrophic cardiomyopathy, as well as those with an equivocal diagnosis of hypertrophic cardiomyopathy, should not participate in vigorous activities and competitive sports.

A transaortic septal myomectomy may be considered for patients with severe symptoms unresponsive to medical therapy. For suboptimal surgical candidates, implantation of a dual-chamber pacemaker may improve symptoms by decreasing the left ventricular outflow tract gradient.

Long QT Syndrome. Both the Jervell–Lange-Nielsen (congenital deafness) and the Romano-Ward syndromes are inherited disorders characterized by a prolonged QT interval and associated with sudden death. The corrected QT (QTc) interval in normal individuals should not exceed 0.44 second in children or 0.42 second in adolescents. Individuals with QTc intervals longer than 0.55 second have a higher risk of sudden death. Prolongation of the QT interval predisposes the individual to ventricular tachycardia, torsades de pointes, and ventricular fibrillation, which is often initiated by a premature ventricular contraction occurring during the prolonged repolarization phase. In addition to the inherited syndromes of prolonged QT intervals, other causes of prolonged QT intervals include hypocalcemia, hypokalemia, hypomagnesemia, myocarditis, and medications (e.g., procainamide, erythromycin, cyclic antidepressants, phenothiazines, quinidine, and organophosphates).

Clinical Features. Symptoms in the young athlete that are suggestive of QT prolongation include exercise-induced palpitations, chest pain, syncope, dizziness, and atypical seizures. The young athlete who has any of these symptoms should be evaluated by a cardiologist, especially if the family history is positive for sudden unexplained death, cardiac problems, syncope, or deafness. Any young athlete who has been diagnosed with a prolonged QT syndrome should be prohibited from participation in competitive sports and vigorous activities. The growing popularity and presence of AEDs in public places and at sporting events can potentially save the lives of those athletes who suddenly collapse because of an underlying prolonged QT syndrome–induced nonperfusing ventricular dysrhythmia.

Management. Treatment of a prolonged QT interval depends on the cause. Underlying metabolic disorders should be corrected, and medications that induce prolongation of the QT interval should be discontinued. Magnesium sulfate is the drug of choice in the treatment of torsades de pointes. Lidocaine is the safest medication for patients with prolonged QT interval–induced ventricular tachycardia or fibrillation. Anti-dysrhythmic agents that can prolong the QT interval, such as procainamide and amiodarone, should be avoided. Beta-blockers have been used to prevent sudden ventricular dysrhythmias in those patients with the familial forms of QT prolongation. Adjunctive treatment in these selected patients also includes the insertion of pacemakers or internal defibrillators.

Commotio Cordis. Commotio cordis occurs after a high-impact trauma to the chest, as in a high-speed motor vehicle collision or a baseball to the sternum. The impact occurs during the vulnerable repolarization period of the cardiac cycle, mechanically inducing ventricular fibrillation. This phenomenon most commonly occurs in children between 5 and 15 years old with no known predisposing cardiac conditions. Although commotio cordis most commonly occurs in baseball, it has also been reported to occur in ice hockey, lacrosse, softball, and fist fights. The majority of patients who sustain commotio cordis do not survive unless rapidly treated with defibrillation. If an AED is not immediately available and the patient is completely unresponsive with no pulse after sustaining a direct blow to the chest, a chest thump during CPR should be attempted.

The author would like to thank Alson Inaba, M.D. for his work on previous editions of this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 165: QUESTIONS AND ANSWERS

1. Which of the following increases the systemic vascular resistance (SVR), thus producing a left-to-right shunt through the ventricular septal defect (VSD) associated with Tetralogy of Fallot?

a. Acute hypovolemia
b. Crying
c. Defecation
d. Squatting

Answer: D. Squatting or knee-to-chest positions increase the SVR, thus improving tet spells by producing the left-to-right shunt. Acute hypovolemia, crying, defecation, and tachycardia are all events that suddenly lower the SVR and produce large right-to-left shunts across the VSD, beginning the vicious cycle of a hypoxic (tet) spell.

2. A 14-year-old girl presents to the emergency department (ED) with altered level of consciousness and trouble breathing. Her vital signs are blood pressure (BP), 72/39 mm Hg; heart rate, 240 beats/min; temperature, 99.6° F; respiratory rate, 60 breaths per minute; and oxygen saturation, 80%. An electrocardiogram (ECG) is performed, which shows supraventricular tachycardia. The patient weights 50 kg. Which of the following is the most appropriate initial treatment?

a. Adenosine 5 mg IV
b. Cardioversion with 50 J
c. Cardioversion with 200 J
d. Diltiazem 12.5 mg IV

Answer: B. This patient should be considered unstable supraventricular tachycardia (SVT), with trouble breathing, low O_2 saturation, and hypotension. In stable patients, vagal maneuvers may be appropriate to try first, followed by adenosine. Diltiazem may be used for rate control in patients with atrial flutter or atrial fibrillation. Cardioversion is the treatment of choice in patients with hemodynamic instability and SVT. The dose is 0.5 to 1 J/kg.

3. What is the most common cause of bradycardia in infants?

a. Complete heart block
b. Hypothermia
c. Hypothyroidism
d. Hypoxia

Answer: D. Although all of these may cause bradycardia in infants and children, the most common cause is hypoxia.

4. A 16-year-old boy presents with complaints of syncope during a basketball game. His mother reports a family history of sudden death in young adults, and you are concerned that the patient may have hypertrophic cardiomyopathy. Which of the following increases the murmur associated with this condition?

a. Hand grip
b. Methoxamine
c. Squatting
d. Valsalva

Answer: D. During the Valsalva maneuver, the venous blood return to the heart is decreased, which in turn transiently reduces the left ventricular size. This transient reduction will increase the degree of obstruction and thus cause an increase in the intensity of the murmur. Hand grip, methoxamine, and squatting will increase return of blood to the heart and therefore decrease the murmur associated with hypertrophic cardiomyopathy.

5. A 5-month-old girl presents with fever for a week, rash, and fussiness; reportedly yesterday her rash was faint throughout her body and has since resolved. On examination, she is febrile with otherwise reassuring vital signs; she is fussy and has conjunctival injection in both eyes. Her parents think she got sick from their other children. Which of the following statements regarding this patient's most likely disease is *true?*

a. If present, other systemic signs (such as, nausea, vomiting, and diarrhea) suggest an alternative diagnosis (such as, acute gastroenteritis).
b. Laboratory investigation in the emergency department (ED) will assist in her risk stratification.
d. Older children are at the highest risk for aneurysm formation.

Answer: B. Kawasaki disease is a systemic vasculitis, and gastrointestinal findings (nausea, vomiting, abdominal pain, diarrhea) and neurologic findings (irritability, positive pleocytosis on lumbar puncture if done) may mislead the clinician. Although she only has one criterion currently, signs of Kawasaki disease may occur in series or simultaneously over the course of the disease. With two or more signs in a child who is febrile for more than 5 days, markers of systemic inflammation (such as, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) are indicated to determine the need for further laboratory testing (complete blood count, liver function tests [LFTs], albumin, urinalysis), imaging (echocardiography), or next day follow-up (with repeat laboratory tests). This child is at high risk because infants are more prone to vascular complications (such as, giant aneurysm formation); tragically they are also more likely to present with incomplete Kawasaki disease and may be overlooked. Accordingly, consensus guidelines recommend that all infants younger than 6 months old with fever of 1 week or greater (regardless of other findings) should undergo laboratory testing for markers of inflammation and, if positive, should have an echocardiogram performed emergently.

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Pediatric Gastrointestinal Disorders

Patrick J. Maloney

KEY CONCEPTS

- Physiologic jaundice of the newborn and breast milk jaundice are the most common causes of jaundice in the neonatal period.
- Direct hyperbilirubinemia in infants is always pathologic and requires a detailed evaluation.
- Hypertrophic pyloric stenosis is associated with gradually progressive nonbilious emesis that becomes projectile.
- Hypochloremic-hypokalemic metabolic alkalosis is the classic electrolyte derangement associated with hypertrophic pyloric stenosis.
- Bilious vomiting in the neonate is an ominous sign and should initiate a diagnostic evaluation for possible malrotation with volvulus or other intestinal obstructive pathology.
- Infants with bilious emesis should receive an emergent surgical consultation, particularly if ill-appearing.
- Necrotizing enterocolitis (NEC) occurs more commonly in premature infants, but 10% of affected infants are full term. Pneumatosis intestinalis in neonates—intramural air seen on x-ray—is pathognomonic for NEC.
- Gastroesophageal reflux (GERD) is very common in infants and is usually benign and self-limited. Occasionally, GERD may cause more severe symptoms, including irritability, respiratory distress, and failure to thrive. GERD usually responds to conservative measures (e.g., positioning, thickening of formula, smaller and more frequent feedings); pharmacologic interventions are seldom needed.
- The classic clinical triad of intussusception includes colicky, intermittent abdominal pain, a palpable sausage-shaped abdominal mass, and bloody "currant jelly" stools; however, this triad occurs in less than one-third of patients.
- Children with intussusception may present atypically, with an altered level of consciousness (e.g., lethargy) rather than abdominal pain.
- Hirschsprung disease is a pathologic cause of constipation in the neonate and usually manifests as delayed passage of meconium. Occasionally, children may present later in life with symptoms of chronic constipation. Toxic megacolon is the most serious complication.
- Meckel diverticulum classically manifests in children younger than 5 years with massive, painless, "brick red" colored rectal bleeding.
- More than 90% of GI foreign bodies pass without complications.
- Lithium button batteries lodged in the esophagus may cause serious burns, erosions, and perforations within as little as two hours. Of all foreign bodies, button batteries require the most expeditious removal, usually by endoscopy.
- Appendicitis is the most common surgical disease in children. Diagnosis depends on a combination of clinical factors, including history, physical examination, laboratory values, and imaging studies.
- Effective imaging strategies for children with suspected appendicitis include initial ultrasound examination followed by CT scanning of the abdomen for those with equivocal findings.
- Causes of pancreatitis in children include viruses, trauma, drugs, and toxins.
- Biliary disease in children is more commonly caused by cholestasis rather than biliary obstruction.
- Pigment gallstones are more common than cholesterol stones in children. Biliary tract disease is usually diagnosed with right upper quadrant ultrasound imaging; management strategies are similar to those for adults.

FOUNDATIONS

Gastrointestinal (GI) symptoms are common among pediatric patients presenting to the emergency department (ED). Because young children lack the knowledge, social skills, and vocabulary to describe and localize their symptoms, the signs and symptoms commonly attributed to the GI tract, such as abdominal pain, nausea, anorexia, and vomiting, are often nonspecific and ill-defined. As a result, their evaluation and management may be challenging.

Pediatric gastrointestinal disorders may be divided into different groups on the basis of their unique pathophysiologic mechanisms (Table 166.1). Several disorders occur as normal variants of early neonatal and infant development (e.g., neonatal jaundice, gastroesophageal reflux, hypertrophic pyloric stenosis). Others result from congenital malformations (e.g., malrotation, Meckel diverticulum) or genetic abnormalities (e.g., Hirschsprung disease). Idiopathic or poorly explained disorders include necrotizing enterocolitis (NEC), intussusception, Henoch-Schönlein purpura (HSP), and inflammatory bowel disease (IBD). The child's age can also help identify common causes of abdominal pain. Infants, for example, may have disorders such as NEC, hypertrophic pyloric stenosis, or intussusception, whereas older children are more likely to present with appendicitis, pancreatitis, or biliary tract disease.

SPECIFIC DISORDERS

Neonatal Jaundice

Foundations

Bilirubin is formed by the breakdown of heme-containing proteins, primarily hemoglobin. Unconjugated bilirubin binds to albumin and

TABLE 166.1 Differential Considerations for Abdominal Pain by Age

Classification By Cause	Infancy	Childhood	Adolescence
Mechanical	Malrotation with midgut volvulus Intussusception Incarcerated hernia Meckel diverticulum Hirschsprung disease	Constipation Incarcerated hernia Meckel diverticulum Bowel obstruction	Constipation Incarcerated hernia Meckel diverticulum Bowel obstruction
Inflammatory or infectious	Necrotizing enterocolitis	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Nephrouretero-lithiasis Pregnancy, ectopic Pelvic inflammatory disease Testicular or ovarian torsion
Other or atypical	Colic Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

is carried to the liver, where it is conjugated by glucuronyl transferase and excreted into bile. While jaundice in adults is usually a conjugated hyperbilirubinemia, resulting from primary hepatobiliary disease, neonatal jaundice is usually the result of extrahepatic causes and results in an unconjugated hyperbilirubinemia (Table 166.2). There are typically three physiologic factors that contribute to neonatal jaundice: (1) increased bilirubin production, (2) decreased clearance and excretion, and (3) increased enterohepatic resorption. Conjugated hyperbilirubinemia in neonates, on the other hand, is less common and always pathologic.

Nearly every newborn develops an unconjugated serum bilirubin level greater than 1 mg/dL— the normal upper limit in adults—during the first week of life. Jaundice, the yellow discoloration of the skin and sclera, becomes clinically noticeable when the total bilirubin level rises above about 5 mg/dL. Risk factors for the development of severe

TABLE 166.2 Differential Considerations for Hyperbilirubinemia in Infants

Classification by Cause	Unconjugated (Indirect)	Conjugated (Direct)
Benign, physiologic	Physiologic jaundice of the newborn Breast milk jaundice	
Hemolysis	ABO incompatibility Physiologic breakdown of birth trauma hematoma (cephalhematoma) Intracranial/intraventricular hemorrhage Spherocytosis, elliptocytosis Sickle cell anemia Thalassemia Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency	
Infectious	TORCHS infections Urinary tract infection Sepsis	TORCHS infections Urinary tract infection Gram-negative sepsis Listeriosis Tuberculosis Hepatitis B Varicella Coxsackievirus infection Echovirus infection HIV infection
Obstructive	Meconium ileus Hirschsprung disease Duodenal atresia Pyloric stenosis	Biliary atresia Choledochal cyst Bile duct strictures Inspissated bile syndrome Neonatal hepatitis Alagille syndrome Byler disease Congenital hepatic fibrosis
Metabolic or genetic	Galactosemia Congenital hypothyroidism Crigler-Najjar syndrome Gilbert syndrome	Galactosemia Tyrosinemia Glycogen storage disease type IV Niemann-Pick disease Wolman disease Gaucher disease Cholesterol ester storage disease α_1-Antitrypsin deficiency Cystic fibrosis Dubin-Johnson syndrome Neonatal hypopituitarism Zellweger syndrome Donohue syndrome (leprechaunism) Rotor syndrome
Miscellaneous		Drugs and toxins Parenteral nutrition

CMV, Cytomegalovirus; *HIV,* human immunodeficiency virus; *TORCHS,* toxoplasmosis, other infections, rubella, CMV, herpes, syphilis.

hyperbilirubinemia in the neonate include prematurity, isoimmune-mediated hemolysis (ABO incompatibility), sepsis, cephalohematomas, dehydration, and inherited abnormalities, such as hereditary spherocytosis and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Unconjugated bilirubin crosses the blood-brain barrier, where it causes cell death. At levels greater than approximately 20 to 25 mg/dL, there is an increased risk of bilirubin-induced neurologic dysfunction (BIND). Kernicterus refers to the chronic, irreversible, long-term neurologic sequelae of BIND.

Jaundice during the newborn period is usually the result of an immature metabolism of bilirubin. This benign self-limited jaundice is termed *physiologic jaundice of the newborn*, occurring in approximately 50% of normal newborns. Although it varies based on ethnicity, total bilirubin levels typically peak between two and five days of life, and the yellow discoloration of the skin usually resolves by the first two weeks of life.

Breast milk jaundice is the second most common cause of neonatal jaundice. The exact pathophysiology is uncertain, but it may be hormonally mediated or related to increased enterohepatic resorption of bilirubin. Breast milk jaundice is typically characterized by a mild unconjugated hyperbilirubinemia that peaks a bit later than physiologic jaundice and may persist for several weeks to months. Other causes of jaundice vary significantly (see Table 166.2)

Clinical Features

Healthy infants are born with normal bilirubin levels that gradually increase to a peak level of 6 mg/dL on approximately the third day of life and then decline to normal levels within 2 weeks. Infants with hyperbilirubinemia usually begin life with similarly low bilirubin levels but exhibit a faster rise in bilirubin levels over the first few days of life. Physiologic jaundice is rarely present on the first day of life, meaning that a total bilirubin level greater than 5 mg/dL within the first 24 hours of life is almost always pathologic. Children with breast milk jaundice typically demonstrate the same gradual increase seen with physiologic jaundice, but levels continue to increase and peak at around 10 to 21 days of life. Elevated levels may persist for 3 to 10 weeks before gradually declining.

Toxic levels of bilirubin (dependent on age, but in general >20 mg/dL) may be associated with neurotoxicity and encephalopathy, termed *bilirubin-induced neurologic dysfunction* (BIND), and the development of kernicterus. Symptoms of BIND include poor feeding and lethargy, sometimes progressing to muscle rigidity, opisthotonos, seizures, and death. Other potential clinical manifestations are cerebral palsy, sensorineural hearing loss, and gaze abnormalities (usually upward gaze limitations).

Acute bilirubin encephalopathy (ABE) refers to the early and potentially reversible signs and symptoms of the hyperbilirubinemia, including somnolence, poor feeding, hypertonia or hypotonia, and a high-pitched cry. If untreated, symptoms can progress to lethargy, hypertonia, backward arching of the neck and trunk (retrocollis and opisthotonos, respectively), fever, irritability, and apnea. Ultimately, this can lead to seizures and death. Survivors may have chronic, permanent coordination problems, cerebral palsy, hearing loss, and learning disabilities. If treated, some or all of these symptoms may be reversible. Ultimately, the management of neonatal jaundice aims to prevent the development of BIND and kernicterus.

Differential Diagnoses

Once the diagnosis of neonatal jaundice is established based on physical exam and laboratory confirmation of an elevated unconjugated bilirubin level, focus should be directed to identifying and managing the physiologic factors contributing to the derangement. The birth history may reveal prematurity or a history of birth trauma–related cephalohematomas. Review of the maternal and infant perinatal records may identify maternal-child blood type (ABO) incompatibility or other risk factors for isoimmune-mediated hemolysis. A detailed history of feeding patterns, urine output, and stool appearance may identify poor nutritional intake, poor weight gain, and dehydration. The presence of hyper- or hypothermia may suggest the presence of infection/sepsis. The family history may identify siblings or other relatives with a history of jaundice or genetic or metabolic disorders. Table 166.2 presents additional differential considerations for jaundiced infants.

BOX 166.1 Indications for Evaluation of Jaundiced Infants

- Jaundice appearing within 24 hr of birth
- Elevated direct (conjugated) bilirubin level
- Rapidly rising total serum bilirubin unexplained by history or physical examination
- Total serum bilirubin approaching exchange level or not responding to phototherapy
- Jaundice persisting beyond 3 weeks of age
- Sick-appearing infant

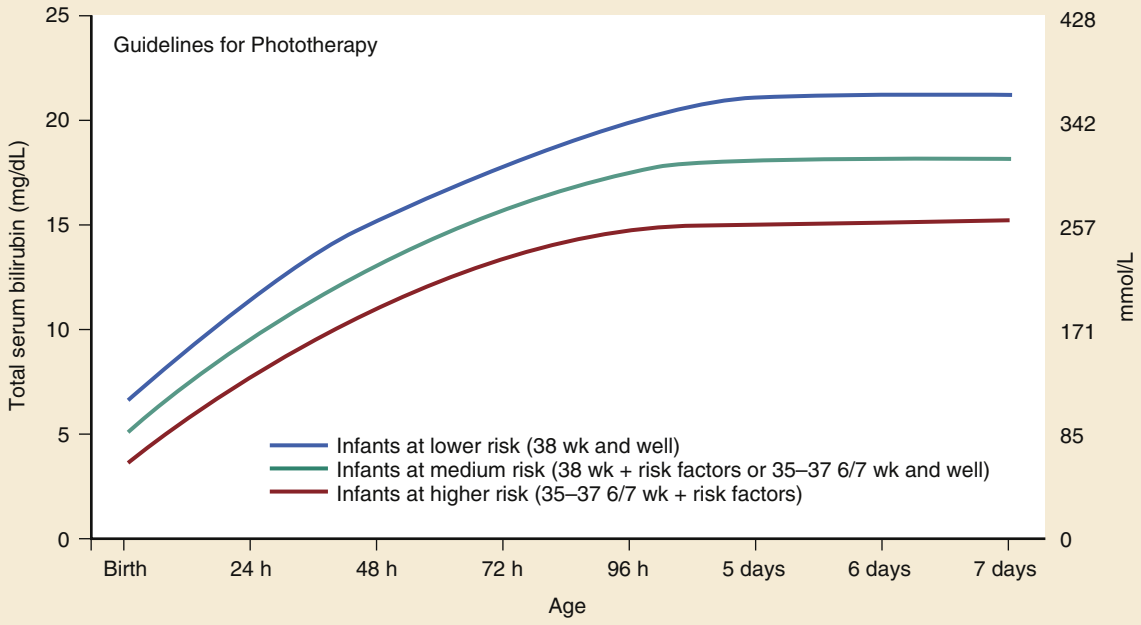
Diagnostic Testing

Physiologic and breast milk jaundice are the most common causes of neonatal jaundice; pathologic causes and indications for evaluation of hyperbilirubinemia are listed in Box 166.1. Transcutaneous bilirubin meters can be used to quickly measure bilirubin levels through the skin in otherwise well-appearing neonates who are beyond 24 hours, but within 7 days, of life. Infants who have previously undergone phototherapy, those with known risk factors for hemolysis, and those with high transcutaneous levels (based on the meter manufacturer's recommended product range) should also have serum levels sent.[1] Initial serum testing can also determine fractionated levels of total versus direct (conjugated) bilirubin.

We recommend that further laboratory evaluation include a complete blood count (CBC) with a peripheral smear and Coombs test to determine immune-mediated major blood group incompatibility, if not previously known. Diagnostic testing in ill-appearing infants includes finger stick blood glucose measurement, electrolyte panel, urine assay for reducing substances, serum ammonia levels, ketones, lactate and evaluation for infection. Conjugated hyperbilirubinemia is always pathologic, resulting from biliary atresia, other biliary obstructive pathology, severe infections, toxins, or inborn errors of metabolism.

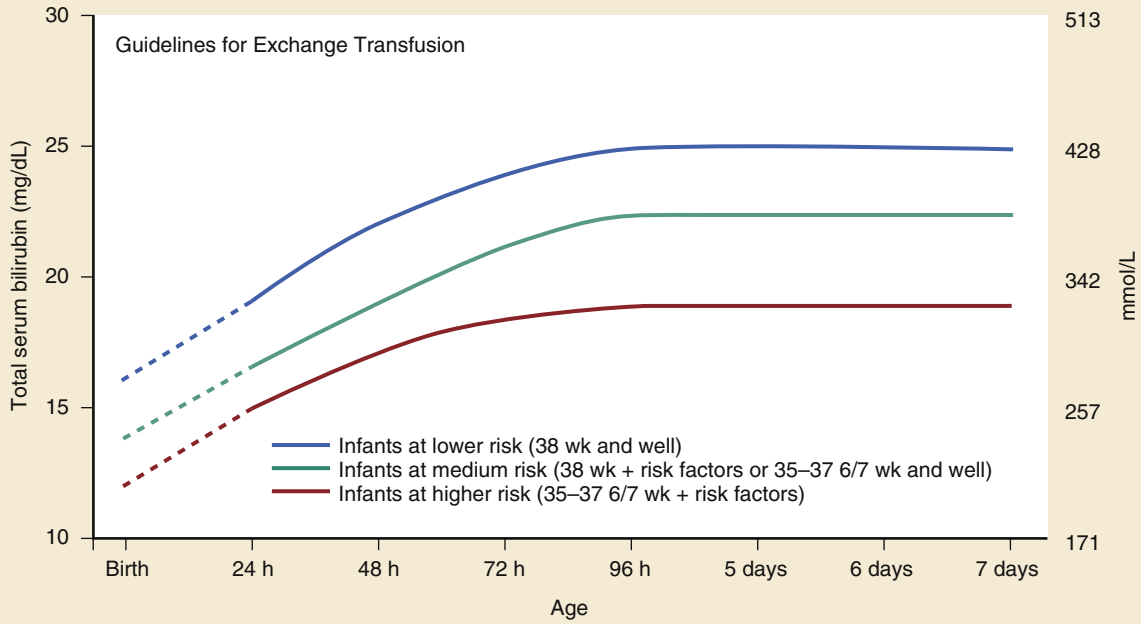
Management

The treatment of infants with unconjugated hyperbilirubinemia centers on the prevention of kernicterus. Because oral intake stimulates enterohepatic circulation and decreases bilirubin levels, feeding (including breast-feeding) should be encouraged. Phototherapy is the initial intervention used to reduce the total bilirubin level in affected infants. Guidelines for the use of phototherapy, based on age, risk factors for developing BIND, and bilirubin level, have been established and recommended by the American Academy of Pediatrics (AAP) (Fig. 166.1). BiliTool (www.bilitool.org) is an additional online resource that utilizes the same AAP guidelines to help clinicians assess the risk of developing hyperbilirubinemia in late preterm and full term infants.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35–37 6/7 wk, can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wk and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

A



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is 5 mg/dL (85 mmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

B

Fig. 166.1 (A) Guidelines for phototherapy in hospitalized infants at 35 weeks or more of gestation. Note that these guidelines are based on limited evidence. The guidelines refer to intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated higher risk because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. (B) Guidelines for exchange transfusion in infants at 35 weeks or more of gestation. Note that these suggested levels represent a consensus but are based on limited evidence. Exchange transfusion is recommended if the TSB continues to rise or remains above these levels, despite intensive phototherapy. *B/A*, Bilirubin/albumin; *G6PD*, glucose-6-phosphate dehydrogenase. (From: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297-316.)

Infants with severely elevated bilirubin levels are at greatest risk for developing BIND. Exchange transfusions are the most effective and rapid way to remove bilirubin. Indications for exchange transfusion include bilirubin level above age-specific threshold recommended by the AAP guidelines (see Fig. 166.1), failure of phototherapy (i.e., the bilirubin level continues to rise despite intensive phototherapy), and jaundiced infants with signs and symptoms of BIND. The procedure is time-consuming and should be performed in a pediatric or neonatal intensive care unit (NICU), where the infant's hemodynamic status may be closely monitored. A double-volume transfusion (180 to 190 mL/kg packed red blood cells) replaces approximately 85% of an infant's blood volume and reduces the total bilirubin level by at least 50%. It is performed by serially removing small aliquots of the infant's blood, typically no more than 5 to 10 mL/kg and replacing it with a similar volume of packed red blood cells until the total transfusion volume is achieved.

Disposition

Infants with bilirubin levels greater than established age- and risk factor-specific levels should receive phototherapy (Fig 166.1A). Infants who appear ill, are below their expected weight for day of life, cannot maintain oral intake, or require exchange transfusion (Fig 166.1B) should undergo hospital admission for phototherapy, IV hydration, and on-going evaluation. Home phototherapy is an option for infants who are otherwise well-appearing, have reliable caregivers with access to emergency care, and can receive follow-up within 24 hours.[2] All infants with direct hyperbilirubinemia should be admitted to the hospital for evaluation of the cause, treatment of sepsis or other treatable cause, and consultation with subspecialist (e.g., pediatric gastroenterology) as indicated.

Hypertrophic Pyloric Stenosis

Foundations

Hypertrophic pyloric stenosis is the most common cause of infantile GI obstruction beyond the first month of life. This condition occurs in 1 of every 250 live births, although rates and trends vary significantly by region. Boys are affected at four times the rate of girls. Approximately one-third of cases occur in first-born children. Prematurity and infant exposure to macrolide antibiotics are additional risk factors.[3] Hypertrophic pyloric stenosis tends to have familial patterns, but the exact pattern of inheritance is unclear.

Affected infants are born with a normal sized pylorus that enlarges as time progresses. The exact cause is unknown, although hypertrophy seems to be stimulated by feeding. As the pylorus enlarges, a progressive gastric outlet obstruction develops, and vomiting ensues. Vomiting causes loss of fluid and gastric acid (hydrogen and chloride ions). As dehydration and electrolyte derangements worsen, the kidney attempts to retain hydrogen ions in exchange for potassium, resulting in the classic hypochloremic-hypokalemic metabolic alkalosis.

Clinical Features

Infants classically present at 2 to 6 weeks of chronologic age, with gradually progressive vomiting that becomes projectile but remains nonbilious. Early in the disease process, infants remain vigorous, with a ravenous appetite. They rapidly finish an entire feeding, only to regurgitate the entire volume in a projectile fashion. In the later stages of the disease, infants may exhibit poor weight gain, clinical dehydration, and malnutrition, along with visible waves of abdominal peristalsis in response to intense contractions against the obstruction.

Diagnostic Testing

Infants may have a palpable pylorus in the right epigastrium on abdominal examination, commonly referred to as an "olive." Because access to ultrasound is now readily available in the developed world, pyloric stenosis is generally diagnosed earlier compared to decades ago, and the "olive" is now palpated in only a minority of infants who present later in the disease course. Laboratory derangements reflect a state of dehydration and electrolyte loss through vomiting—a hypochloremic metabolic alkalosis (serum bicarbonate [HCO_3] levels ≥29 mmol/dL and chloride levels ≤98 mmol/dL), although these abnormalities may be absent early in the disease course.

Hypertrophic pyloric stenosis may be confirmed by ultrasonography or fluoroscopic upper GI series (UGI). Ultrasonography is often the first diagnostic modality of choice because it is simple, readily available, and without serious complications such as aspiration. Upper GI series may be preferred when there is bilious vomiting and concern for more distal bowel obstruction. With both modalities, reported accuracy is greater than 95%. On ultrasound, the pylorus appears thickened (pyloric muscle thickness > 4 mm; pyloric diameter > 14 mm) and elongated (>19 mm), which is diagnostic (Fig. 166.2). On UGI series, a characteristic string sign, reflecting passage of contrast material through the narrowed pyloric sphincter, may also be evident. In advanced stages with complete obstruction at the pylorus, plain films may reveal a distended, air-filled stomach.

Differential Diagnoses. Vomiting in infants is common, and the differential diagnosis is broad. Usually, infants present early in the disease progression and are well-appearing, and the common consideration is differentiating hypertrophic pyloric stenosis from gastroesophageal reflux. Reflux classically begins shortly after birth and remains relatively constant. Infants with pyloric stenosis typically have progressively worsening emesis beginning around 2 or 3 weeks of life. In advanced stages, it occurs with every feed and is often described as projectile.

Infants who present with sudden onset of severe vomiting and bilious emesis, or who are ill-appearing, should be evaluated for other surgical emergencies, including malrotation with midgut volvulus, duodenal atresia, and necrotizing enterocolitis. With reflux and pyloric stenosis, emesis is rarely bilious.

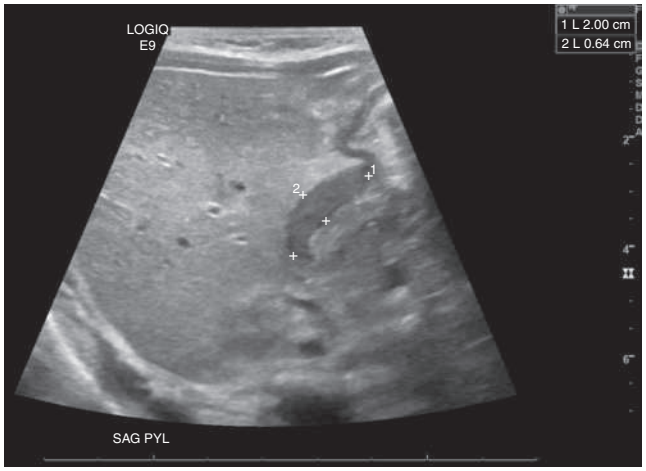


Fig. 166.2 Ultrasound of the abdomen revealing an elongated (20 mm) and thickened (6 mm) pylorus muscle consistent with hypertrophic pyloric stenosis. Normal pylorus muscle measurements are: pyloric muscle thickness < 4 mm; pyloric diameter <14 mm; pylorus length <19 mm. (Courtesy Dr. Patrick J. Maloney)

Many causes of vomiting do not have a true GI origin, including sepsis, metabolic disturbances (e.g., diabetic ketoacidosis), increased intracranial pressure, urinary tract infections, inborn errors of metabolism, adverse medication reactions or side effects, and drug intoxications. Differential considerations for vomiting in children vary by age (Table 166.3).

Management

Treatment consists of fluid and electrolyte replacement and surgical consultation. Hypertrophic pyloric stenosis is not a true surgical emergency but may be a fluid and electrolyte emergency. Fluid resuscitation should begin with repeated boluses of 20 mL/kg of normal saline as necessary to treat dehydration and hypovolemic shock.[4] Potassium supplementation (KCl, 0.5 to 1 mEq/kg IV over 1 to 2 hours) is often necessary. Definitive management is surgery. The corrective procedure, called a pyloromyotomy, may be performed open, referred to as the Ramstedt pyloromyotomy, or laparoscopically. Associated mortality is rare.

Disposition

Most children are best managed with hospital admission for rehydration and correction of electrolyte abnormalities in conjunction with urgent imaging and surgical consultation.

TABLE 166.3 Differential Considerations for Vomiting by Age

Classification by Cause	Infancy	Childhood	Adolescence
Mechanical	Gastroesophageal reflux Malrotation with midgut volvulus Pyloric stenosis Meckel diverticulum Intussusception Bowel obstruction Incarcerated hernia Tracheoesophageal fistula	Constipation Incarcerated hernia Meckel diverticulum Bowel obstruction	Constipation Incarcerated hernia
Inflammatory or infectious	Necrotizing enterocolitis Gastroenteritis Sepsis Henoch-Schönlein purpura Meningitis Pneumonia Otitis media	Gastritis or gastroenteritis Otitis media Appendicitis Pancreatitis Henoch-Schönlein purpura Biliary tract disease	Gastroenteritis Appendicitis Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Pregnancy Testicular or ovarian torsion
Central nervous system	Hydrocephalus Intracranial hemorrhage Intracranial tumor	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Reye syndrome	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Glaucoma
Metabolic	Diabetic ketoacidosis Congenital adrenal hyperplasia Urea cycle defects Organic acidurias Amino acidopathies Fatty acid oxidation disorders	Diabetic ketoacidosis Urea cycle defects Fatty acid oxidation disorders	Diabetic ketoacidosis
Other or atypical	Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

Malrotation with Midgut Volvulus

Foundations

Malrotation of the intestines occurs in 1 in 500 live births and has a male predominance of at least 2 : 1. Among infants with malrotation, symptomatic volvulus of the midgut occurs in the first month of life in approximately one-third, in the first year of life in approximately one-half, and before the age of 5 years in 75% of children. Rarely, patients born with intestinal malrotation develop midgut volvulus later in life as adults. Some remain asymptomatic. When midgut volvulus does occur, the mortality rate may be as high as 10% with surgical intervention.

During embryologic development, the GI tract rotates around the superior mesenteric artery. As it completes the rotation, the duodenum forms a C-loop and is fixed to the retroperitoneum in the left upper quadrant at the ligament of Treitz. The cecum becomes similarly fixed in the right lower quadrant. Thus, the duodenum and cecum normally come to lie widely separated and are firmly fixed in position by peritoneal attachments called Ladd bands. They are only loosely connected by a broad-based mesentery. In cases of malrotation, the duodenum and cecum do not rotate completely, remain closely positioned, and are suspended in the midgut region by the mesenteric vascular stalk. This unusually close proximity results in a short stalk of mesentery that easily twists on itself, resulting in obstruction of the distal duodenum and bowel ischemia and necrosis secondary to compression of the superior mesenteric artery.

Clinical Features

The hallmark presentation of acute midgut volvulus associated with intestinal malrotation is sudden-onset bilious emesis and abdominal distention in an infant. Affected infants usually appear quite ill and may present in shock. Any yellow or green pigmented staining of the vomitus suggests the presence of bile. When bile is initially produced, it is bright yellow and turns green only with time and oxidative exposure. Therefore, differential coloring of bile-stained emesis, yellow versus green, is not predictive of a surgical condition.

Diagnostic Testing

Plain radiographs may demonstrate nonspecific signs of a small bowel obstruction, including dilated loops of proximal small bowel with air-fluid levels and a paucity of bowel gas distally (Fig. 166.3). The diagnostic procedure of choice to identify midgut volvulus is a limited upper GI contrast series, revealing an abnormal position of the duodenal C-loop, which fails to normally cross the midline from right to left (Fig. 166.4), and a characteristic corkscrew appearance of the more distal small bowel (Fig. 166.5).

Ultrasonography, usually performed to evaluate for hypertrophic pyloric stenosis, may reveal an abnormal orientation of the superior mesenteric artery and vein (the vein is abnormally positioned anteriorly or to the left of the artery (Fig. 166.6) or a whirlpool sign caused by the vessels twisting around the mesenteric stalk, causing an echogenic twisting pattern.[5] CT is usually not recommended because it carries the risk of additional radiation without benefit of improved diagnostic ability over upper GI series.

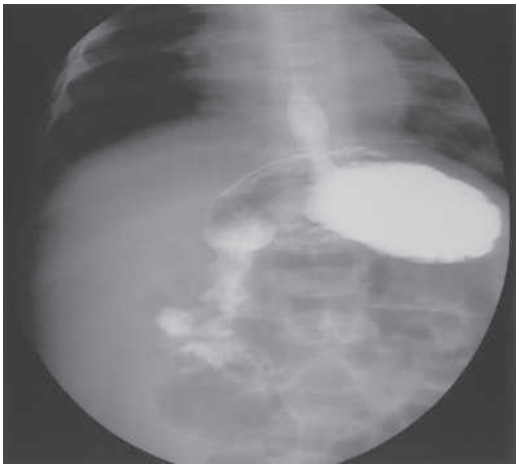


Fig. 166.3 Upright abdominal radiograph obtained in an infant with bilious vomiting illustrates dilated loops of small bowel and a paucity of bowel gas distally, consistent with proximal obstruction secondary to malrotation with midgut volvulus. (Courtesy Dr. Mark A. Hostetler.)

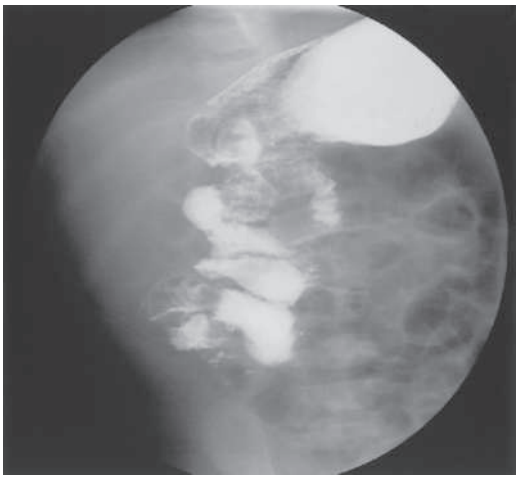


Fig. 166.4 Upper gastrointestinal film, obtained in the same infant as in Fig. 166.3, reveals abnormal positioning of the duodenal C-loop to the right of the spinal column, consistent with malrotation. (Courtesy Dr. Mark A. Hostetler.)

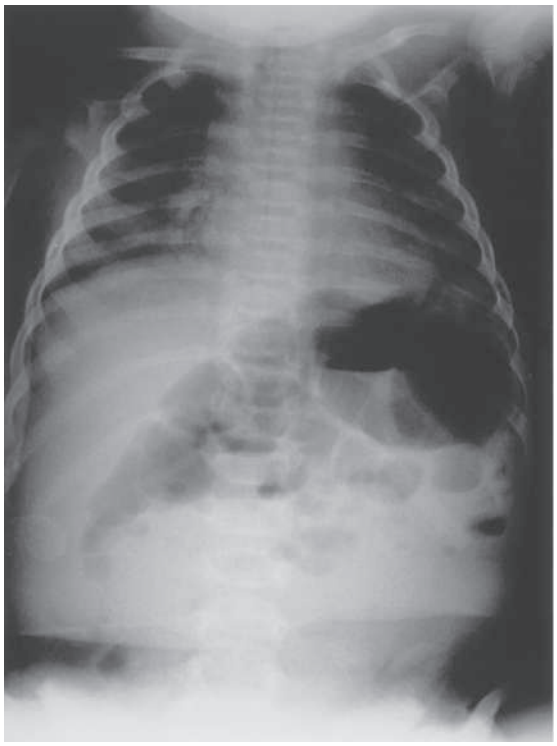


Fig. 166.5 Spot film from the upper gastrointestinal series obtained in the infant in Fig. 166.3. This radiograph shows the characteristic corkscrew appearance seen on small bowel follow-through in patients with malrotation. (Courtesy Dr. Mark A. Hostetler)

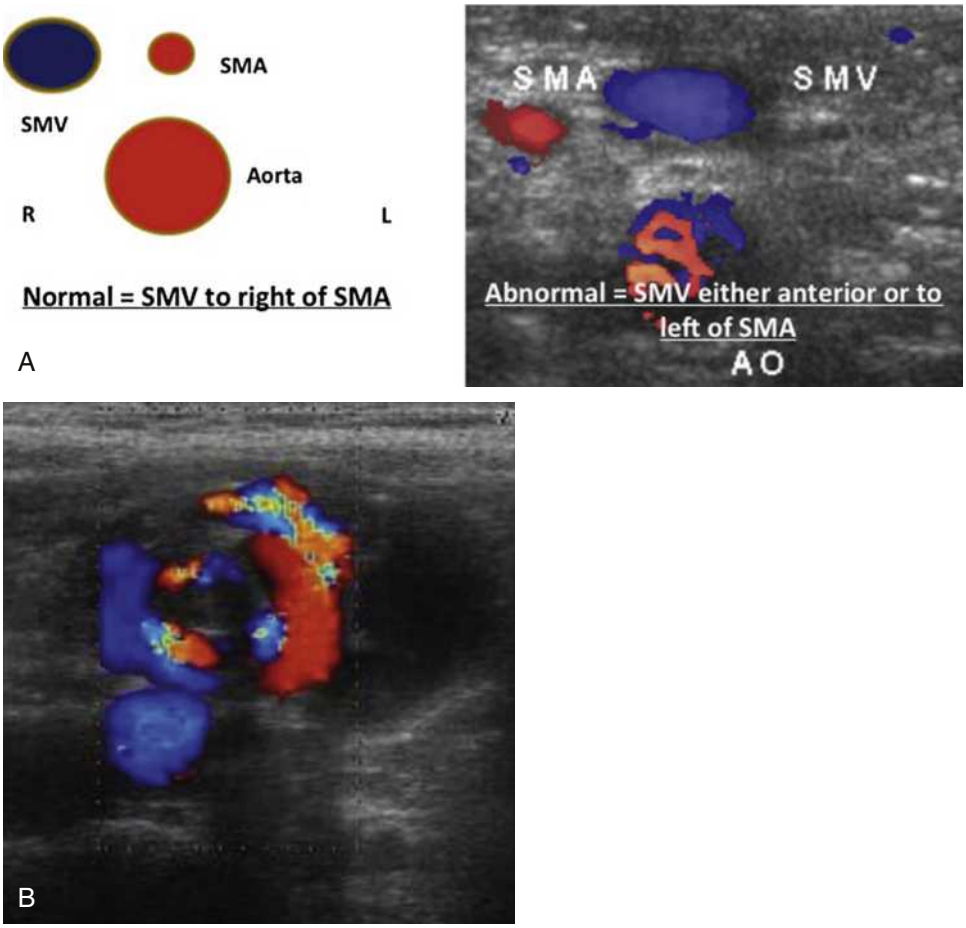


Fig. 166.6 Ultrasonographic findings in malrotation with midgut volvulus. (A) Abnormal orientation of mesenteric vessels associated with malrotation with midgut volvulus. Normally, the superior mesenteric vein (SMV) is positioned to the right of the superior mesenteric artery (SMA). In malrotation, the vein is abnormally positioned anteriorly or to the left of the artery. (B) Whirlpool sign caused by the vessels twisting around the mesenteric stalk, resulting in an echogenic twisting pattern. *AO,* Aorta. (Courtesy Dr. Patrick J. Maloney.)

Differential Diagnoses

Vomiting in childhood, especially infants, is common and occurs across a wide spectrum of illnesses (see Table 166.3). Causes vary by age, progression of symptoms, and vomitus appearance. In children less than one year old, sudden onset of bilious vomiting is an ominous sign and should prompt emergent evaluation for acute bowel obstruction, including malrotation with midgut volvulus. Gastroesophageal reflux disease (GERD) and hypertrophic pyloric stenosis typically cause nonbilious emesis in relatively well-appearing infants. NEC may also present with obstructive signs and symptoms, including bilious emesis and abdominal distention. However, unlike malrotation with volvulus, NEC is characterized radiographically by diffusely dilated loops of small bowel and the presence of air within the bowel walls, termed *pneumatosis intestinalis*.

Management

Emergent pediatric surgical consultation should be obtained for any neonate or infant with bilious vomiting, even before diagnostic studies have been completed. In acute midgut volvulus, operative intervention should be rapid to save the bowel from necrosis.

Intravenous (IV) access should be obtained, and laboratory studies should include blood glucose level, a CBC with differential, electrolyte values, and renal and liver function tests. If there are clinical signs of shock, repeated fluid boluses of 20 mL/kg of normal saline or lactated Ringers solution should be given until adequate circulation has been established.

BOX 166.2 Empirical Antibiotic Regimens for Enteric Bacterial Pathogens

Regimen

- Piperacillin-tazobactam + gentamicin
- Piperacillin-tazobactam + gentamicin + vancomycin
- Ampicillin + gentamicin + metronidazole
- Ampicillin + ceftriaxone + metronidazole
- Meropenem

Dosing

- Piperacillin-tazobactam: 200–300 mg/kg/day of piperacillin component q6–8 hours
- Gentamicin: 3–7.5 mg/kg/day in divided doses based on age/renal function
- Ampicillin: 200 mg/kg/day q6h
- Vancomycin: 10–20 mg/kg IV q6–8h
- Metronidazole: 30–40 mg/kg/day q8h
- Ceftriaxone: 50 mg/kg/day once daily
- Meropenem: 60 mg/kg/day q8h

Ill-appearing infants should receive empirical broad-spectrum antibiotic coverage for enteric bacterial pathogens (Box 166.2). A nasogastric or orogastric tube should be placed to decompress the proximal bowel and

stomach. A limited upper GI series should also be emergently obtained but should not delay resuscitation and surgical consultation.

Disposition

Patients with a confirmed or equivocal diagnosis should be admitted with emergent surgical consultation.

Necrotizing Enterocolitis

Foundations

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in neonates. However, because most affected infants are premature and acquire the condition in the NICU, NEC usually is not usually encountered in the ED setting. NEC does occur in a small subset of late preterm and full-term infants, although most of them have other underlying illnesses and rarely are discharged from the NICU prior to the onset of disease. Complications in children who survive NEC, which are often encountered in the ED, include strictures, fistulas, and short gut syndrome.

The exact pathophysiologic mechanism of NEC is unclear but is likely multifactorial. The primary pathophysiologic event is inflammation or injury to the intestinal wall. Prematurity is the most common and universally accepted risk factor, as 90% of all affected infants are born prematurely.

Clinical Features

Infants with NEC usually first develop feeding intolerance and bilious or nonbilious emesis. In the more advanced stages of the disease, infants may appear extremely ill with hematemesis, hematochezia, fever, and shock. Abdominal radiographs may show intestinal dilation, pneumatosis intestinalis, or intestinal perforation.

Differential Diagnoses

Feeding intolerance and vomiting are common and nonspecific findings in neonates. However, unlike most infants with GERD, pyloric stenosis, and other relatively benign or self-limited causes of vomiting, infants with NEC are usually quite ill-appearing. GERD classically begins shortly after birth and remains relatively constant in character. Pyloric stenosis–related vomiting does not begin until 2 to 3 weeks of age and then gradually increases in severity and forcefulness, but these infants rarely appear acutely toxic. Bilious vomiting, while common in NEC, requires careful consideration to rule out other obstructive pathology, including malrotation with midgut volvulus, especially in children born at or near full term. The appearance of the plain radiographs may help differentiate NEC and volvulus. Volvulus is associated with dilated, air-fluid loops of small bowel proximally and a paucity of bowel gas distally, whereas the hallmark of NEC is diffusely dilated loops of small bowel and pneumatosis intestinalis.

Diagnostic Testing

Plain abdominal radiographs are the imaging study of choice in NEC. Radiographs may show nonspecific signs reflecting the presence of small bowel obstruction (dilated, air-fluid filled loops of bowel), bowel ischemia (intramural bowel wall gas, called pneumatosis intestinalis, or air within the portal system and biliary tract), or bowel perforation (pneumoperitoneum). Pneumatosis intestinalis (Fig. 166.7) is pathognomonic for NEC and is present in 75% of patients. No individual laboratory test is diagnostic or specific for NEC, but may reflect dehydration, electrolyte derangements, and sepsis.

Management

Patients suspicious of having NEC should receive nothing by mouth (NPO), with placement of an orogastric or nasogastric tube for decompression of the stomach and small bowel. Because these patients are frequently hemodynamically unstable and may have periods of apnea or significant respiratory distress, intubation may be needed. IV or intraosseous access should be established; laboratory studies should include a CBC with differential, electrolyte panel, glucose, renal and liver function tests, and type and screen. Blood and urine cultures should be obtained. Fluid resuscitation with 20 mL/kg boluses of normal saline or lactated Ringers solution should be repeated until adequate circulatory volume has been reestablished. Vasoactive agents such as epinephrine, or norepinephrine are indicated for patients in refractory shock. Broad-spectrum antibiotic coverage is indicated (see Box 166.2). Emergent pediatric surgery consultation should be obtained in all cases because perforation and bowel necrosis may not be immediately evident on plain radiographs. Mortality is very high (30% to 50%) despite appropriate management.

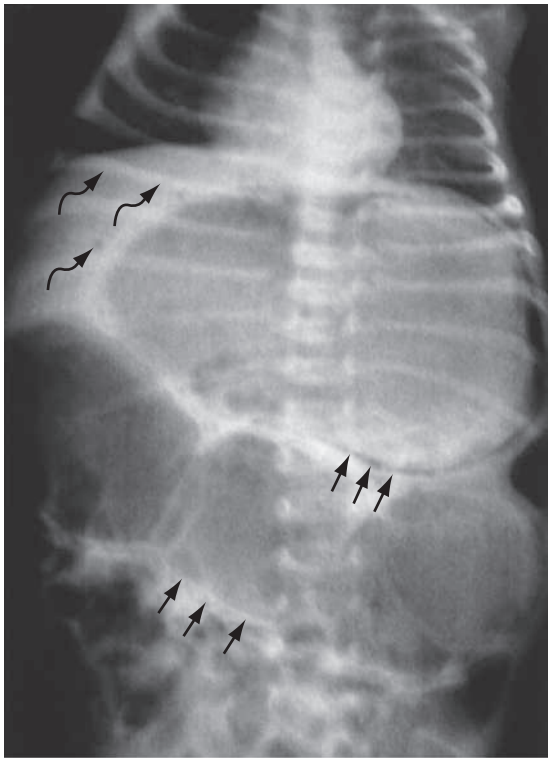


Fig. 166.7 Plain radiograph obtained in an infant with necrotizing enterocolitis. *Straight arrows* indicate air within the wall of the small bowel and gastric mucosa (pneumatosis intestinalis and gastralis). *Curved arrows* indicate air in the biliary tree (portal venous gas). (Courtesy Dr. Mark A. Hostetler.)

Disposition

Children thought to have NEC require admission to an ICU and should have emergent pediatric surgical consultation.

Gastroesophageal Reflux

Foundations

Gastroesophageal reflux (GERD) refers to the symptomatic regurgitation of stomach contents into the esophagus, with or without vomiting. Reflux occurs as a result of an incompetent lower esophageal sphincter. Reflux is a normal physiologic event in infants, and essentially all infants experience intermittent reflux during at least the first six months of life. When reflux causes troublesome symptoms or complications, it is referred to as GERD. Chronic reflux of gastric contents

into the esophagus may result in esophagitis, chronic cough, aspiration, and failure to thrive if severe.

Clinical Features

Reflux and GERD generally begin shortly after birth and resolve with time, usually by the age of one year. Clinical manifestations occur along a wide spectrum of disease, ranging from asymptomatic to occasional episodes of spitting up to severe persistent vomiting and failure to thrive. Sandifer syndrome, although rare, refers to the stereotypical opisthotonic movements highly suggestive of severe GERD. Chronic GERD may cause chronic cough, recurrent stridor, and persistent wheezing. GERD may even be implicated in infants who experience "brief resolved unexplained events" that include symptoms of respiratory distress or apnea, transient color change (i.e., pallor, cyanosis), and possibly a change in muscle tone (flaccidity or rigidity), although evidence of this direct causation is lacking.[6]

Differential Diagnoses

Children with GERD exhibit nonbilious emesis that begins shortly after birth and is relatively constant over time. Unlike pyloric stenosis, vomiting is usually neither progressive nor projectile. Most children with GERD of milder severity continue to gain weight. Unlike midgut volvulus and other causes of small bowel obstruction, the emesis associated with GERD should never have a yellowish-green or darker pigmented appearance. In addition, the presence of hematemesis or hematochezia or significant abdominal tenderness or distension should prompt considerations other conditions than GERD.

Diagnostic Testing

In the ED, the diagnosis of GERD is typically made on the basis of the history and physical examination. Well-appearing infants with nonbilious vomiting, a normal physical exam, and an adequate weight gain trajectory may cautiously be diagnosed with GERD presumptively. However, ill-appearing infants in whom the diagnosis is uncertain may benefit from additional diagnostic studies; these tests, such as esophageal pH probes, barium swallow studies, and direct visualization by endoscopy, are not routinely available in the ED and should be conducted in consultation with a pediatric gastroenterologist.

Management

Most infants respond to conservative lifestyle modifications, such as smaller feedings, frequent burping, formula thickened with cereal, and a semiupright position after feeding. Parents should avoid using a car seat to maintain a semiupright position during and after feeding because these devices have actually been shown to exacerbate reflux rather than alleviate it.

Pharmacologic regimens are not recommended for infants with uncomplicated reflux (so-called "happy spitters"). Although lacking supportive evidence, acid suppression can be used, but should be reserved for those with more severe symptoms, such as esophagitis, weight loss, or significant irritability, in whom more conservative lifestyle modifications have failed.[7] Severe and refractory cases occasionally require pediatric surgical consultation for Nissen fundoplication.

Disposition

Most children may be discharged home safely with conservative measures. Children with more severe symptoms or poor weight gain should be referred to a pediatrician or pediatric gastroenterologist for testing and additional pharmacologic management. Those with severe dehydration, weight loss, or failure to thrive should be admitted.

Intussusception

Foundations

Intussusception refers to the invagination of part of the intestine into itself. It is the most common cause of intestinal obstruction in children younger than 2 years, occurring most frequently in infants 5 to 12 months of age. Most cases of intussusception in children are idiopathic and occur in otherwise healthy children.

The exact cause of intussusception is unclear, but the most prevalent theory relates to a lead point that causes telescoping of one segment of the intestine into another. Bowel wall edema develops, resulting in mechanical obstruction, vascular compromise, and, ultimately, bowel wall ischemia and necrosis.

Intussusception may occur at any point along the GI tract, but ileocolic intussusceptions are most common in children. In younger children, lead points are usually the result of enlarged Peyer patches secondary to a recent viral infection. In children older than 5 years, pathologic lead points, including HSP vasculitis, Meckel diverticulum, lymphoma, polyps, postsurgical scars, celiac disease, and cystic fibrosis, are more common. Ileoileal intussusception occurs more frequently in children with HSP.

Clinical Features

The classic triad of clinical findings in intussusception consists of abdominal pain, a palpable sausage-shaped abdominal mass, and bloody stools, described as "currant jelly" in appearance. All three features are present in a minority of patients, however. Abdominal pain is the most common symptom. Affected children experience cyclic episodes of severe abdominal pain as waves of peristalsis cause bowel dilation adjacent to and proximal to the involved bowel. These episodes typically last 10 to 15 minutes and occur in intervals of 15 to 30 minutes. During the painful episode, children may be irritable and inconsolable, often drawing the legs up to the abdomen and screaming in pain. Vomiting is usually present. Blood, gross or occult, may or may not be present in the stool.[8] Diarrhea containing mucus and blood constitutes the classic "currant jelly stool," a relatively infrequent and late finding. Occasionally, children present with atypical symptoms, including altered level of consciousness and profound lethargy, rather than the more typical abdominal pain syndrome.

Differential Diagnoses

Differential considerations for abdominal pain in children by age are listed in Table 166.1. A slow progressive onset of pain is more likely to be associated with appendicitis, constipation, or pancreatitis. A sudden onset of severe pain is usually associated with acute bowel obstruction, such as intussusception or volvulus, or acute vascular compromise, as seen with torsion of a testicle or ovary. Infants and children with intussusception classically have severe intermittent colicky pain.

Diagnostic Testing

Initial screening radiographs of the abdomen may be obtained, but findings are usually nonspecific. Images should be examined for signs of small bowel obstruction, including dilated small bowel loops followed by a paucity of gas in a decompressed colon. Perforation may demonstrate free air within the peritoneum. More specific, although less commonly seen, signs on radiograph include evidence of a soft tissue mass or mass effect in the right abdomen, a "target sign" (representing air in the intussusceptum as it telescopes into adjacent bowel), and a "meniscus sign" (representing air compressed like a meniscus from invaginating bowel, Fig. 166.8). Plain radiographs may be obtained to rule out perforation which would preclude nonoperative reduction but cannot be used to exclude intussusception. The common clinical scenario is that radiographs reveal indeterminate or nonspecific findings, which do not exclude the diagnosis.

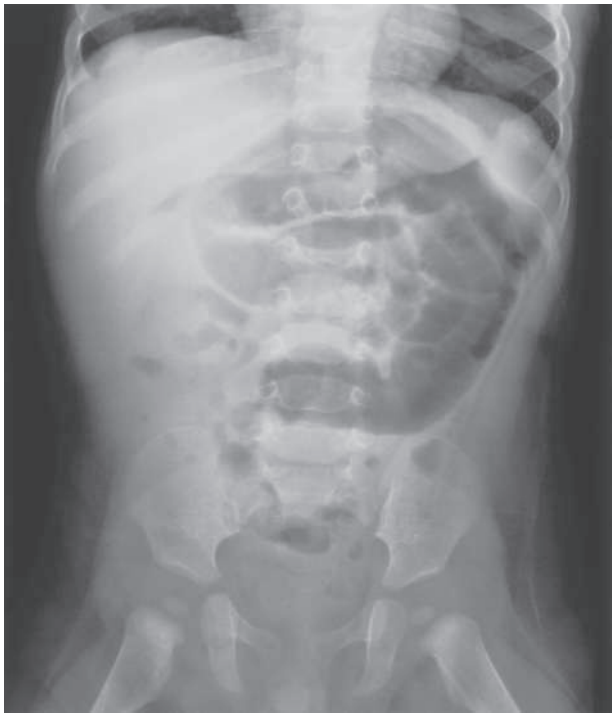


Fig. 166.8 Plain radiograph obtained in a child with crampy abdominal pain and vomiting, later confirmed to have intussusception. Findings include a poorly defined soft tissue density in the right upper quadrant, obscuration of the liver edge, and focally dilated loops of small bowel, consistent with an acute obstructive process (intussusception). (Courtesy Dr. Mark A. Hostetler.)

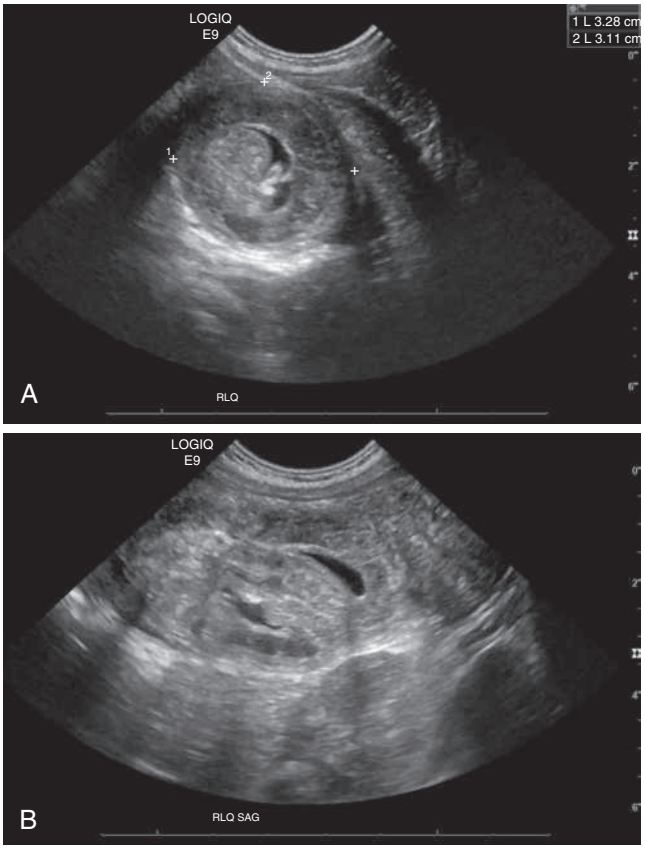


Fig. 166.9 Abdominal ultrasound examination in a child with colicky abdominal pain and vomiting, later confirmed to have intussusception. (A) On the transverse view, findings include a complex mass with a multilayered or rolled appearance (i.e., "target sign"). (B) In the long view, the ileum can be seen protruding up into the cecum, forming the intussuscipiens-intussusceptum complex. (Courtesy Dr. Patrick J. Maloney.)

When performed by skilled hands, ultrasound is highly sensitive and specific and the initial imaging modality of choice. The classic finding is a "target sign" (also referred to as a "bull's eye" or "doughnut sign"), which refers to visualization of the telescoping intestinal wall in the transverse or cross-sectional view. When visualized in the longitudinal plane, it is referred to as the "pseudo–kidney sign" (Fig. 166.9). Alternatively, contrast enemas have the advantage of being diagnostic and therapeutic. Occasionally, in children with the triad of paroxysms of pain, vomiting, and blood in the stool, contrast enemas may be safely done as first-line therapy (Fig. 166.10). Air-contrast enemas are equally efficacious and may be favored over contrast enemas due to speed of performing and efficacy.[9] Either type of enema requires readily available consultation by a pediatric surgeon in the event that reduction is unsuccessful or iatrogenic perforation occurs.

Management

IV fluids should be given in repeated boluses of 20 mL/kg of normal saline until adequate intravascular volume has been achieved. Children should be maintained on NPO status. Prompt surgical consultation is recommended. Diagnostic and therapeutic interventions depend on the location and resources available. Patients may undergo an initial ultrasound examination or, if history and plain film findings are highly suggestive of intussusception, may go directly to therapeutic enema.

The overall success rate for an air-contrast or barium enema approaches 90%. Surgical intervention is indicated in cases of prolonged intussusception with signs of perforation or shock or if enema reduction is unsuccessful. A severe, acutely life-threatening complication of air-contrast enema reduction is intestinal perforation with tension pneumoperitoneum.

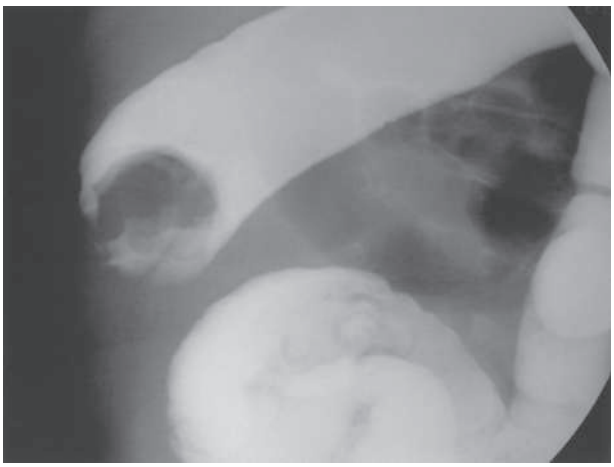


Fig. 166.10 Contrast enema image obtained in a child with intussusception shows a sharp cutoff where the contrast material meets the intussusceptum and acute obstruction. (Courtesy Dr. Mark A. Hostetler.)

Intussusception recurs within the first 48 hours after successful reduction in a very small minority of patients. Therefore, a short observation period (6 hours) is safe, and children who are able to tolerate oral fluids may be discharged home.[10]

Disposition

Children with suspected intussusception should receive definitive imaging with ultrasonography or enema. Confirmed intussusception requires reduction with enema or surgery.

Hirschsprung Disease

Foundations

Hirschsprung disease accounts for approximately 20% of cases of partial intestinal obstruction in early infancy. It occurs at a rate of 1 in 5000 live births and is four to five times more common in boys. Cases are usually sporadic in occurrence but may be associated with Down syndrome or other congenital anomalies.

Hirschsprung disease refers to congenital aganglionosis of the colon—that is, an absence of ganglion cells in the myenteric plexus of the distal colon. The anus is invariably involved, with aganglionic bowel usually extending proximally 4 to 25 cm. The absence of colonic ganglion cells interferes with that segment's ability to relax, creating a functional obstruction. Stool accumulates proximal to the level of obstruction and produces dilation of the colon, referred to as megacolon.

Clinical Features

Neonates with Hirschsprung disease often present in the newborn nursery with failure to pass meconium; however, a spectrum of disease is recognized, and presentation may be later in life. Affected infants brought to the ED usually have a history of chronic constipation. Digital rectal exam may cause an explosive passage of stool, sometimes referred to as the "squirt sign." Vomiting, irritability, poor weight gain, failure to thrive, and abdominal distention may be present. Children who appear ill with fever should be evaluated for other serious pathology, including enterocolitis, inflammatory bowel disease, and toxic megacolon.

Differential Diagnoses

Constipation is one of the most common causes of abdominal pain and vomiting in children. During the first few months of life, normal infants may have stool frequencies that range from one per feeding to one every few days, with breast-fed infants having more frequent stools than formula-fed infants. Truly pathologic causes of constipation are uncommon. In addition to Hirschsprung's disease, alternative etiologies for constipation include cystic fibrosis, infantile botulism, and hypothyroidism.

Diagnostic Testing

Plain films of the abdomen are usually nonspecific and may reveal evidence of fecal impaction with proximal obstruction, air-fluid levels, and a dilated colon. Barium enema studies revealing a narrowed aganglionic segment of distal colon with proximal dilation is highly suggestive of Hirschsprung disease. The diagnosis is confirmed by biopsy or manometry.

Management

Initial management should focus on ensuring adequate fluid and electrolyte status. Abdominal films should be obtained. With evidence of acute obstruction, such as marked bowel dilation, decompression with a rectal tube may acutely relieve symptoms. Definitive therapy of Hirschsprung disease is surgical, with resection of the aganglionic segments.

Disposition

Unless a child appears ill, most constipated children may be managed safely on an outpatient basis often with pediatric gastroenterology consultation.

Meckel Diverticulum

Foundations

Meckel diverticula are remnants of the omphalomesenteric duct and contain bowel wall, with 60% containing heterotopic tissue, usually gastric mucosa. Bleeding occurs when acid secretion from the ectopic gastric mucosa causes ulceration and erosion of the surrounding small bowel mucosa. Meckel diverticulum is the most common congenital malformation of the small intestine.

Meckel diverticula traditionally follow the "Rule of 2's": the diverticulum is approximately 2 cm wide, 2 cm long, and located within 2 feet of the ileocecal valve; moreover, the condition occurs in 2% of the population, and only 2% of affected patients ever become symptomatic; of symptomatic patients, 50% manifest symptoms by the age of 2 years, and most present by the age of 20 years.

Clinical Features

The classic presentation of a Meckel diverticulum is massive, painless rectal bleeding. Some children may have complaints of abdominal cramping. The abdominal examination is usually benign. The blood is often described as brick red but may range from melena to bright red. Complications may include intussusception, obstruction, perforation, and peritonitis.

Differential Diagnoses

Massive GI bleeding is uncommon in childhood. Children commonly eat or drink substances containing red dyes that lead to changes in the stool's color that may be mistaken for hematochezia. In addition, bismuth subsalicylate (e.g., Pepto-Bismol), iron, and spinach may cause black stools falsely appearing melanotic. A Hemoccult test of stool or Gastroccult test of emesis can confirm the presence or absence of blood, although false positives and negatives do occur.

Similar to adults, the location of bleeding may be theorized on the basis of the appearance of the blood. Hematemesis suggests bleeding proximal to the ligament of Treitz. Melena results from bleeding beyond the ligament of Treitz but proximal to the ileocecal valve. Hematochezia implies bleeding from the colon. Occasionally, in young children, GI transit time may be rapid enough for an upper GI source to cause hematochezia.

In neonates, the cause of GI bleeding is usually never identified. In young breast-fed neonates, an Apt test may be performed to differentiate fetal from swallowed maternal blood. Nursing mothers should be asked about cracked bleeding nipples. Milk protein allergy is another common cause of GI bleeding in infancy. Affected children are typically younger than 6 months, with a history of sudden-onset, mucoid, blood-streaked stools. Table 166.4 lists the differential considerations for GI bleeding in children by age.

Diagnostic Testing

A technetium-99m (^{99m}Tc) scan, also called a Meckel scan, is the diagnostic modality of choice and has an accuracy of 90% when ectopic gastric mucosa is present, since technetium has an affinity for gastric mucosa. A computed tomography (CT) scan of the abdomen may be performed to look for signs of inflammation or obstruction. Definitive diagnosis is confirmed by laparoscopy or laparotomy.

Management

Management of GI bleeding begins by assessing the child's circulatory status administering volume resuscitation as indicated. In cases of minimal or mild bleeding in otherwise healthy and well-appearing children, laboratory studies are unlikely to be useful. The child may be referred to urgently see a pediatric gastroenterologist as an outpatient. When there is concern for more serious disease, screening laboratory

TABLE 166.4 Differential Considerations in Gastrointestinal Bleeding by Pediatric Age Group

Classification by Cause	Infancy	Childhood	Adolescence
Factitious	Swallowed maternal blood Dyes in foods and beverages Vaginal origin Urinary origin	Dyes in foods and beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin	Dyes in foods and beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin
Upper gastrointestinal tract	Necrotizing enterocolitis Intussusception Gastroenteritis Gastritis	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease
Lower gastrointestinal tract	Necrotizing enterocolitis Intussusception Gastroenteritis Milk allergy Vascular malformation	Gastroenteritis Intussusception Meckel diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic-uremic syndrome Colitis	Gastroenteritis Intussusception Meckel diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic-uremic syndrome Polyps Colitis
Rectal	Rectal fissure	Rectal fissure	Rectal fissure Hemorrhoids Trauma
Other or atypical	Bleeding dyscrasia Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

studies should include a CBC, coagulation studies (e.g., prothrombin time, partial thromboplastin time), and type and screen. A pediatric surgeon should be consulted.

Disposition

Children with massive GI bleeding suspicious for Meckel diverticulum should undergo a Meckel scan, usually after admission to a pediatric intensive care setting. Children with minor bleeding may be discharged home after consultation with a surgeon and with close follow-up. Children with ongoing active bleeding should be hospitalized.

Henoch-Schönlein Purpura

Foundations

HSP, also known as anaphylactoid purpura, is a hypersensitivity vasculitis with immune complex deposition with immunoglobulin A. Although most well-known for its characteristic petechial to purpuric rash, HSP is a systemic vasculitis affecting any vessels.

HSP is commonly associated with abdominal pain, palpable purpuric rash, arthralgias, and renal disease. Its incidence is highest among children 4 to 11 years of age. It more commonly occurs during the spring season following viral upper respiratory infections.

Clinical Features

Patients are usually diagnosed clinically on the basis of the classic palpable purpuric rash located on the buttocks and lower extremities (Fig. 166.11). Up to 70% of patients have GI complaints, including abdominal pain, nausea and vomiting, diarrhea, intestinal bleeding, and ileoileal intussusception. Laboratory findings are significant for a lack of thrombocytopenia. Microscopic hematuria occurs in half of patients. The syndrome is often relapsing and remitting for several weeks and may be associated with arthralgias. Neurologic involvement is uncommon.

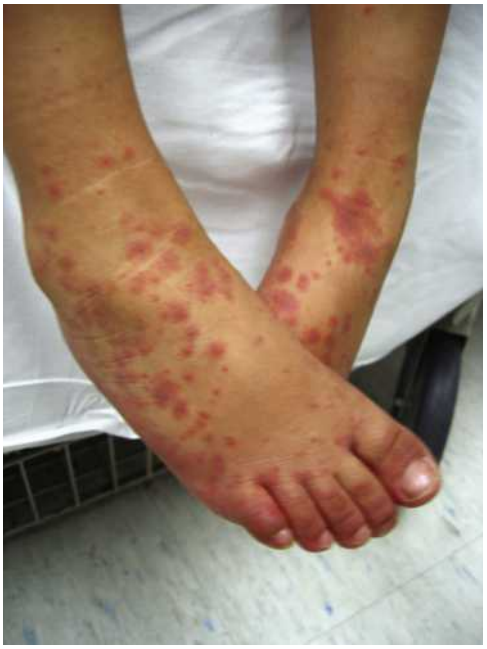


Fig. 166.11 Henoch-Schönlein purpura in a 7-year-old child. Note the typical red-purple rash on the lower extremities. (Courtesy Dr. Marianne Gausche-Hill.)

Differential Diagnoses

Patients with HSP do not have thrombocytopenia. This differentiates HSP from most other clinical diseases associated with petechiae or purpura, including meningococcemia. In addition to a thrombocytopenia,

patients with meningococcemia are typically febrile and ill-appearing. The classic triad of palpable purpura, abdominal pain, and hematuria in an otherwise well-appearing and afebrile child with a normal platelet count is most likely to be HSP.

Diagnostic Testing

Patients are usually diagnosed clinically on the basis of the classic rash. All children diagnosed with HSP should have a urinalysis for evaluation of renal involvement, which manifests as white cells, red cells, casts, and protein in the urine. Those with apparent renal involvement should have serum electrolyte and creatinine levels measured. Patients with an uncertain diagnosis should have a CBC with differential, coagulation studies, blood culture, and sedimentation rate. Children diagnosed with HSP who have worrisome abdominal pain should be evaluated for intussusception.

Management

Most children with HSP require only supportive management. Mild and moderate pain is usually well controlled with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Glucocorticoids reduce the pain associated with HSP but have not been shown to affect the other disease complications, including nephropathy. Prednisone, at a dose of 1 mg/kg/day (maximum, 60 mg), is reserved for patients with severe symptoms, including severe abdominal pain, GI bleeding, hematuria, or severe arthralgias.

Disposition

Most patients can be managed symptomatically with close outpatient observation and follow-up. Indications for hospital admission include uncertain diagnosis to exclude the possibility of meningococcemia, severe abdominal pain, and intractable vomiting. Those with compromised renal function should have a nephrology consultation and be considered for admission, particularly if presenting with hypertension.

Inflammatory Bowel Disease

Foundations

Inflammatory bowel disease (IBD) comprises two disorders: ulcerative colitis and Crohn disease. Ulcerative colitis is an inflammatory disease primarily involving the mucosa and submucosa of the rectum and distal colon. Crohn disease is a transmural inflammatory disease that may involve any portion of the intestinal tract. Chronic inflammation may result in the formation of an abscess, fistula, or stricture. Crohn disease is commonly associated with extraintestinal manifestations, especially in children.

Most patients with IBD do not experience symptoms until adolescence or adulthood. However, a small subset do develop symptoms before the age of 20 years. IBD is rare in children younger than 1 year of age.

Clinical Features

Although patients experiencing complications of IBD frequently present to the ED, the diagnosis is rarely made in this setting. Usually, children with known disease present in the midst of an acute flare, commonly associated with increased frequency of diarrheal stools, bloody diarrhea, abdominal pain, and occasionally fevers. Patients with toxic megacolon or intestinal perforations demonstrate significant abdominal tenderness with peritonitis and are usually febrile, volume-depleted, and ill-appearing.

Diagnostic Testing

Acute IBD flares are usually diagnosed clinically based on the history of present illness and physical exam. There are no laboratory or radiologic tests that are specific for acute IBD flares, and basic laboratory studies, including CBC with differential and electrolyte panel, usually reflect dehydration, inflammation, and possible anemia. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels may be beneficial in the diagnosis and management because most patients have elevated levels at the time of diagnosis as well as with acute flares. Plain radiographs are helpful when evaluating for intestinal perforation and toxic megacolon.

Differential Diagnoses

There are a large number of differential considerations for abdominal pain, vomiting, and GI bleeding (see Tables 166.1, 166.3, and 166.4). Gastroenteritis is the most common consideration in this clinical scenario. Children experiencing their first episode of IBD and children outside the usual age at presentation are much more likely to be misdiagnosed with acute gastroenteritis.

Management

Management in the ED begins with attention to volume status and resuscitation with repeated boluses of 20 mL/kg of normal saline or lactated Ringers solution until the volume status is adequate. Acute exacerbations should be treated in conjunction with a gastroenterologist. Corticosteroids (e.g., prednisone, 1 mg/kg/day; maximum dose, 60 mg/day) are usually recommended for mild to moderate exacerbations. Other agents commonly used include sulfasalazine and azathioprine, among other immunosuppressive agents. Patients with suspected toxic megacolon require IV broad-spectrum antibiotic therapy (see Box 166.2) and surgical consultation.

Disposition

Children not diagnosed with IBD but who have recurrent GI symptoms or a family history of IBD should be referred to a pediatric gastroenterologist for further evaluation. With acute flares, indications for admission include dehydration, toxic or ill appearance, and inability to tolerate oral fluids. Children with evidence of toxic megacolon should have a surgical consultation.

Gastrointestinal Foreign Bodies

Foundations

GI foreign bodies usually are seen in children younger than 5 years of age and in those with developmental delays. Coins, small toys, magnets, batteries, and jewelry are the most common esophageal foreign bodies in children, compared to food boluses in adults. Most ingestions in children are accidental.

The vast majority of swallowed foreign bodies pass through the entire GI tract without complications. However, foreign bodies commonly become lodged in one of three areas of normal physiologic narrowing within the esophagus: (1) the upper esophageal sphincter (cricopharyngeus muscle)/thoracic inlet (C6-T1); (2) the aortic arch/tracheal bifurcation (T4-6); and (3) the lower esophageal sphincter/diaphragmatic hiatus (T10-11). Of objects that successfully pass into the stomach, 80% to 90% also pass through the entire GI tract without complications.

Clinical Features

Many accidental ingestions are unwitnessed. Children may gag as they attempt to swallow the object. Objects aspirated into the respiratory tract generally produce persistent coughing, wheezing, increased work of breathing, and respiratory distress. Children who swallow objects which then become lodged within the esophagus may remain asymptomatic or develop a wide spectrum of symptoms, including food refusal, persistent gagging, drooling, or continuous dry heaves. Some esophageal foreign bodies may cause local airway compression, resulting in stridor, wheezing, and respiratory distress. Complications such as esophageal or

intestinal perforation are more likely to occur when foreign bodies have been impacted for an extended period of time; symptoms include progressive dysphagia, pain, respiratory distress, and fever.

Swallowed lithium button batteries warrant special mention. Button batteries lodged in the esophagus cause severe mucosal erosions, burns, and mediastinitis in as little as 2 hours, most likely as a result of the electrical current discharged from these batteries. Gastrointestinal or pediatric surgical consultation for emergent foreign body removal is warranted. Button batteries in the stomach usually pass without complications and do not require removal unless they fail to pass the pylorus within 48 hours of ingestion. The National Capital Poison Center operates a 24/7 website (www.poison.org/battery) and hotline (800-498-8666) for battery ingestion cases.

On occasion, objects successfully pass into the stomach, but are too large to pass through the pylorus. As a general rule, objects longer than 5 cm and wider than 2 cm are less likely to pass the pylorus spontaneously. Persistent vomiting may herald obstruction. If not removed, foreign bodies may, over time, result in erosion, perforation, infection, stricture, or fistula formation.

Diagnostic Testing

Plain radiography is the most common method of diagnosing and locating foreign bodies. Classically, coins and button batteries in the esophagus project en face (round) in the frontal (coronal/AP or PA) view (Fig. 166.12). When coins or button batteries are lodged in the upper airway, they will project on end in the frontal view. Occasionally, it may be difficult to differentiate the appearance of a coin from a button battery radiographically. A button battery will typically have a distinctive double-rim contour on radiographs (Fig. 166.13).

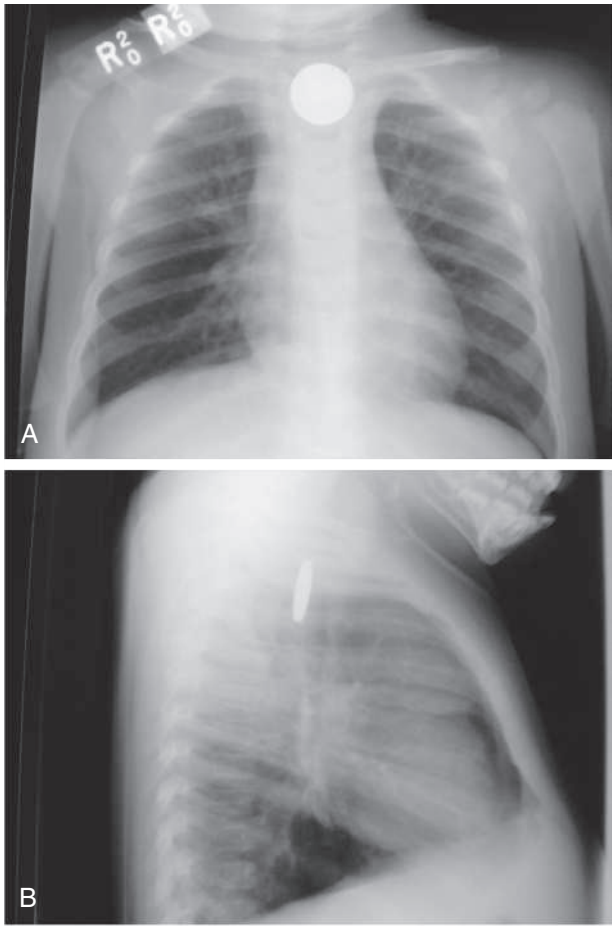


Fig. 166.12 Plain radiographs obtained in a child with an esophageal coin foreign body. Posteroanterior (A) and lateral (B) views show the expected orientation for a coin lodged in the esophagus. (Courtesy Dr. Mark A. Hostetler.)

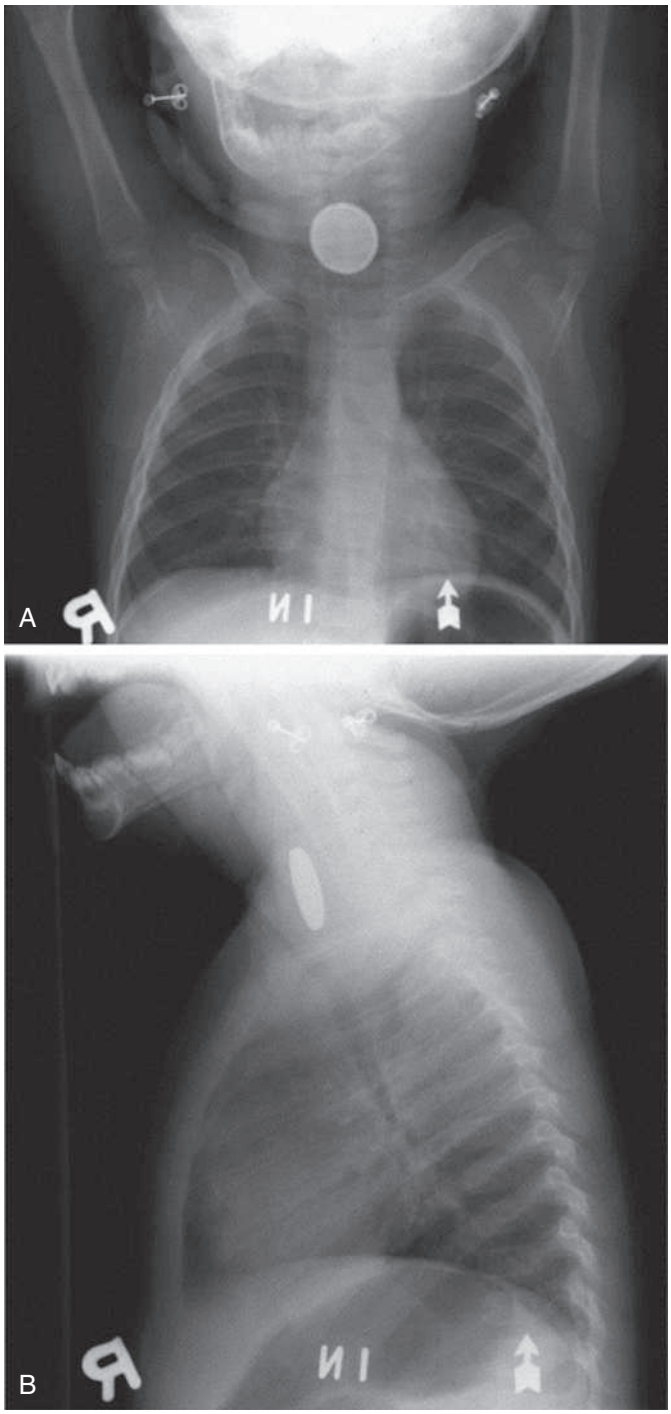


Fig. 166.13 Esophageal button battery. It may be difficult to differentiate the appearance of a coin from a button battery radiographically. However, a button battery will typically have a distinctive double-rim contour on radiographs, as seen in this posteroanterior radiograph. (From: Lin VYW, Daniel SJ, Papsin BC. Button batteries in the ear, nose and upper aerodigestive tract. *Int J Pediatr Otorhinolaryngol*. 2004;68:473-479.)

Differential Diagnoses

Not all foreign bodies are radiopaque and visible with standard radiography. Patients who remain symptomatic require further contrast-enhanced imaging or direct visualization.

Management

Most GI foreign bodies will spontaneously pass without complications. In general, small objects that successfully pass into the stomach do not require further treatment or routine serial imaging. Button batteries and multiple magnetic objects represent two exceptions. Patients with button batteries located in the stomach should have serial films to ensure successful passage beyond the pylorus. Ingestion of multiple magnets or a single magnet plus a second metallic object may result in the objects attaching to each other across bowel wall, resulting in bowel necrosis and perforation. Therefore, multiple magnets or a single magnet plus another metallic object located within the stomach are typically removed urgently by endoscopy because they are more likely to require more complicated surgical removal if allowed to pass beyond the pylorus. However, if they have already passed into the small bowel in a well-appearing, asymptomatic patient without any signs of bowel obstruction or peritonitis observation and serial radiographs are recommended. Surgical consultation for removal should be obtained if there are signs of bowel necrosis, obstruction, perforation, or peritonitis.

Asking parents to check the child's stool for a passed foreign body is rarely productive. The timing of intervention for foreign body removal is based largely on the type of object, location, duration, and symptoms. With the exception of button batteries, which should be removed emergently within 2 hours, esophageal foreign bodies may be removed urgently within 24 hours. Blunt objects, such as coins, in the esophagus of asymptomatic children may be observed for 12 to 24 hours because many of them will pass spontaneously into the stomach. Indications for more emergent removal are listed in Box 166.3.

The preferred method to remove esophageal foreign bodies varies by institution; flexible endoscopy is most common and has a high success rate. Other options include fluoroscopic Foley catheter removal, bougie advancement into the stomach, and removal by rigid bronchoscopy under general anesthesia in the operating room.

Disposition

Esophageal foreign bodies require removal, as described previously. Once foreign bodies have passed into the stomach, most pass without complications, and no specific follow-up is usually necessary. Abdominal pain, food aversion, and intractable vomiting may suggest a retained gastric foreign body warranting repeat radiography. Button batteries in the stomach and multiple magnets constitute exceptions. Button batteries in the stomach necessitate follow-up films in 24 hours to document passage beyond the pylorus, even in asymptomatic children. When multiple magnets are suspected of being within the stomach, urgent endoscopy and removal is warranted. When they have passed the pylorus but there is no evidence that they have attached to each other across bowel wall causing tissue necrosis and/or perforation, close observation and serial radiographs is recommended. If there are clinical concerns for bowel necrosis, obstruction, or perforation, surgical consultation is emergently necessary.

BOX 166.3 Indications for Emergency Removal of Gastrointestinal Foreign Bodies

- Signs of respiratory distress
- Evidence of esophageal obstruction (inability to swallow secretions)
- Lithium button batteries in the esophagus
- Sharp or long (>5 cm) objects in the esophagus or stomach
- Multiple magnets or single magnet plus another metallic object within esophagus or stomach
- Signs or symptoms of intestinal inflammation, obstruction or perforation
- Esophageal foreign bodies impacted for >24 hr or for an unknown amount of time

Appendicitis

Foundations

Appendicitis is the most common surgical condition involving the abdomen and the most common nontraumatic surgical emergency in children. It develops in approximately 1 of every 15 people during their lifetime. The peak age of incidence is between 9 and 12 years, and it is uncommon in children younger than 5 years of age.

The appendix is a blind pouch that may become obstructed, resulting in edema, vasocongestion, inflammation, ischemia, infarction, necrosis, and perforation. In adults, a thicker appendiceal wall resists perforation, and a well-developed omentum aids in walling off the infection to prevent its diffuse spread. Children have neither, so rupture tends to occur earlier, and diffuse peritonitis develops more readily.

Morbidity and mortality related to acute appendicitis increase significantly if the appendix ruptures prior to operative management. Therefore, the goal of management is diagnosis and operative management prior to appendiceal perforation. Perforation seems to be directly related to the duration of symptoms. In children, the rate of appendiceal perforation varies inversely with age. Perforation is highest among children younger than 5 years, among whom more than 50% are ruptured at the time of surgery. This likely reflects, at least in part, the fact that preschool children have a limited ability to describe their symptoms and often present for evaluation later in the disease course.

Clinical Features

Patients classically present with a constellation of symptoms that includes abdominal pain, nausea, vomiting, and anorexia. Symptoms are gradually progressive over the first 24 hours. Abdominal pain is usually first described as vague, crampy, and periumbilical. Pain becomes more severe, constant, and localized to the right lower quadrant as the disease progresses. Fever usually develops later or not at all. A subset of patients may have a multiphasic course to their illness, with symptom resolution followed several days later by the development of fever, chills, and abdominal pain. This likely represents spontaneous appendiceal rupture and formation of an abscess.

The physical examination may reveal several typical findings. In patients with inflammation surrounding the appendix, peritoneal findings that localize to the right lower quadrant are classic. Pain occurs with movement; patients may be unwilling to jump up and down, and tapping their heels may cause abdominal pain. Bowel sounds are usually decreased or absent. Rebound tenderness may be elicited in the right lower quadrant. The Rovsing, psoas, and obturator signs are difficult to assess in young children and should not be relied on due to their poor sensitivities and specificities. The absence of the classic signs and symptoms of appendicitis unfortunately does not exclude the diagnosis, especially in younger children.

Diagnostic Testing

Appendicitis may be diagnosed clinically on the basis of the history and physical findings alone in children with a classic constellation of findings. Patients with an equivocal presentation should undergo a diagnostic evaluation. There are no sufficiently sensitive or specific laboratory tests that alone can confirm or exclude the diagnosis of acute appendicitis. Screening studies may include a CBC with differential,

CRP, urinalysis, electrolyte levels, and renal and liver function testing. Pregnancy testing, vaginal wet mount, and gonorrheal and chlamydial testing should be considered in postpubertal females. Most children with acute appendicitis have an elevated white blood cell count (>10,000 × 10^6/L), absolute neutrophil count, or an elevated CRP level (>0.6 mg/dL). Because none of these tests are sufficiently sensitive or specific, they should not be exclusively used to diagnose or exclude appendicitis. Acute appendicitis occasionally causes a mild sterile pyuria (<5 to 10 white blood cells/high-power field in the absence of bacteria) related to local inflammation of the right ureter.

Several clinical scoring systems have been developed to assist in the evaluation of appendicitis. The most widely studied prospectively include the Alvarado score, Pediatric Appendicitis Score, and Refined Low-Risk Appendicitis Rule. Each system relies on a combination of clinical factors and laboratory values to risk-stratify children into low-, moderate-, and high-risk categories for appendicitis. Unfortunately, none of these have been shown to be sensitive and specific enough to be recommended alone for widespread clinical use.

Diagnostic imaging options include plain films of the abdomen, ultrasonography, and CT. Plain films have limited value in appendicitis and are not recommended in the routine evaluation. Occasionally, an appendiceal fecalith will be evident (Fig. 166.14). Although the presence of an appendicolith in a child with acute abdominal pain is essentially pathognomonic for acute appendicitis, it is present in less than 10% of cases.

Ultrasonography is routinely recommended as the first-line imaging modality in suspected appendicitis. It has the advantages of lacking ionizing radiation and the ability to evaluate ovarian anatomy. Ultrasonographic findings consistent with appendicitis include an enlarged, noncompressible appendix (wall thickness > 2 mm; total appendix diameter > 6 mm) that is painful during scanning (Fig. 166.15A, B). Appendiceal ultrasound has a sensitivity and specificity of more than 90% when the appendix is successfully visualized. Unfortunately, the ability to visualize the appendix adequately with ultrasound is limited in obese children and highly user-dependent.

In the child in whom the appendix is not visualized or findings are equivocal with ultrasonography, clinical observation with serial examinations or CT imaging may be undertaken. CT in general has high sensitivity and specificity for unruptured and ruptured appendicitis, and the use of IV contrast improves sensitivity slightly. Limited appendiceal CT protocols decrease the ionizing radiation exposure without sacrificing sensitivity or specificity. The increased use of CT has been shown to reduce the negative laparotomy rate without increasing the risk of perforation.

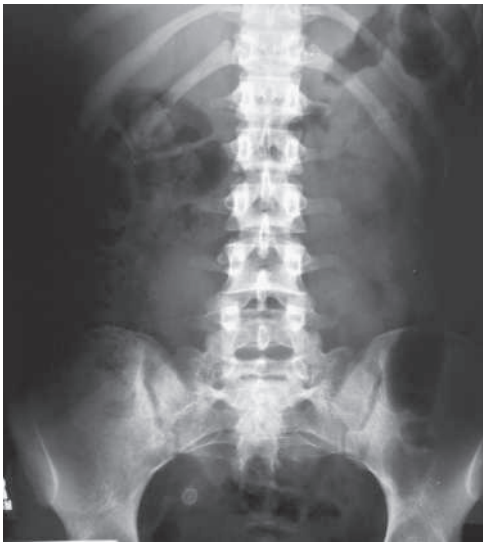


Fig. 166.14 Fecalith in a child with appendicitis. (Courtesy Dr. Marianne Gausche-Hill.)

Differential Diagnoses

Differential considerations for abdominal pain by age are listed in Table 166.4. Mesenteric adenitis is the most common imitation of appendicitis. Similar to appendicitis, it often is associated with significant diffuse tenderness that may localize in the right lower quadrant. Children with mesenteric adenitis lack true peritoneal signs, however.

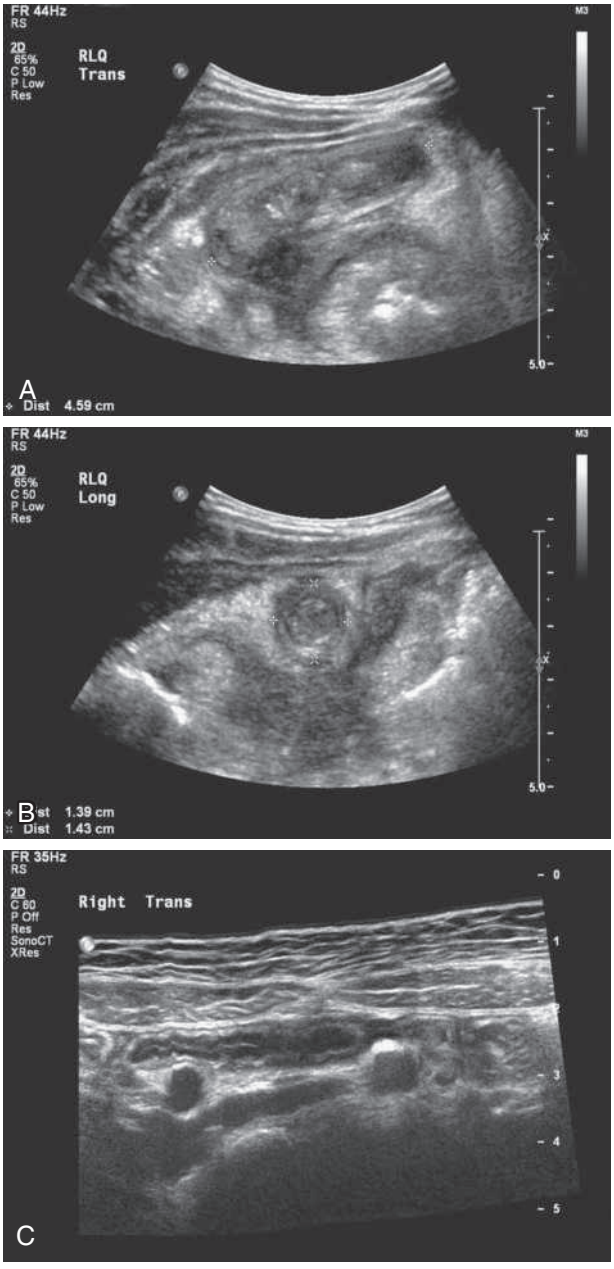


Fig. 166.15 Ultrasound images obtained in children with appendicitis. Findings include an enlarged, noncompressible, tubelike structure in the longitudinal view with an appendicolith (A), an enlarged noncompressible structure seen in cross section (B) and, in another patient, an enlarged, poorly compressible structure with a moderate amount of free fluid consistent with acute perforation (C). (Courtesy Dr. Mark A. Hostetler.)

Mesenteric adenitis usually follows a viral illness and results from nonspecific inflammation of the mesenteric lymph nodes.

Girls of reproductive age merit consideration of gynecologic pathology, including ectopic pregnancy, ovarian torsion, ovarian cyst, pelvic inflammatory disease, and tubo-ovarian abscess. Testicular torsion may manifest with nausea, vomiting, and abdominal pain, but the testicular examination is usually grossly abnormal in these boys. Boys with abdominal pain on the side of an undescended testis should be evaluated for torsion of an intra-abdominal testicle. Group A streptococcal pharyngitis may also present with abdominal pain and mimic appendicitis.

Management

Definitive management of acute appendicitis is open or laparoscopic appendectomy. The exact timing of surgery is controversial but should optimally be performed within 12 to 24 hours of diagnosis. Most patients benefit from IV fluids and parenteral administration of opioid pain medications and antiemetics. Opioids are safe and effective and do not alter the diagnostic accuracy of the physical examination. Patients with a nonperforated appendicitis should receive a single dose of parenteral antibiotics (Box 166.4) 30 to 60 minutes prior to surgery to decrease the risk of wound infection and intra-abdominal abscess formation. Patients with suspected perforation, signs or symptoms of sepsis, or unusual delay in surgical management should receive empirical broad-spectrum IV antibiotics (see Box 166.2) in the ED and continued postoperatively.

While appendectomy remains the standard of care in most cases of acute appendicitis, nonoperative management with parenteral antibiotics and observation alone is an emerging option in a subset of older children with uncomplicated disease. Nonoperative management typically results in fewer days of disability and overall decrease health care costs.[11]

Disposition

Children with appendicitis should be hospitalized for appendectomy. Patients with nonspecific signs and symptoms in whom imaging studies are nondiagnostic should be observed for a period of 12 to 24 hours with serial examinations or, with adequate family and social support, discharged home with careful instructions to return for reexamination.

Pancreatitis

Foundations

Pancreatitis is uncommon in childhood, especially in children younger than 10 years. In adults, pancreatitis is most commonly associated with alcohol abuse and biliary tract disease. In children, pancreatitis is usually caused by trauma, infection, structural anomalies, systemic disease, and drugs or toxins. Idiopathic causes account for 30% of cases. Biliary disease should be considered in adolescents and teenagers.

The common pathophysiologic pathway of acute pancreatitis is inflammation, edema, and autodigestion of pancreatic tissue by pancreatic enzymes. In severe cases, the inflammatory cascade may progress to necrotizing or hemorrhagic pancreatitis. Other complications include the formation of abscesses, pseudocysts, and fistulas.

Clinical Features

Abdominal pain is the hallmark of pancreatitis in adults and children. Patients typically present with complaints of severe, constant epigastric pain that worsens gradually and radiates to the back. Nausea, vomiting, diarrhea, fevers, irritability, and lethargy are also described. Patients have significant abdominal tenderness in the epigastric area.

Diagnostic Testing

Screening laboratory studies reveal an elevation in the serum lipase level. The degree of elevation and serial changes are not always directly related to disease severity. Evidence of liver inflammation (i.e., elevated aspartate transaminase and alanine transaminase levels) and elevated bilirubin and alkaline phosphatase levels may be seen in patients with associated hepatobiliary disease. Plain films of the abdomen commonly show an ileus pattern, often with a sentinel loop of dilated small bowel in the left upper quadrant. An ultrasound study or CT may be helpful to evaluate anatomy for congenital malformations, biliary tract disease, pseudocyst, or abscess formation. In patients with respiratory distress, a chest radiograph may identify a secondary pleural effusion.

Differential Diagnoses

Slow progressive onset of pain is more likely to be associated with appendicitis, constipation, and pancreatitis. Sudden onset of severe pain is usually associated with acute intestinal obstruction, such as intussusception or midgut volvulus, or vascular occlusion, as seen with testicular or ovarian torsion. Differential considerations for abdominal pain in children by age are listed in Table 166.4.

Management

Patients should receive volume replacement and electrolyte correction and be maintained on an NPO status. IV fluids are given in repeated boluses of 20 mL/kg of normal saline until adequate vascular volume has been established. Patients should receive adequate symptomatic relief with parenteral narcotics and antiemetics. Steroids and antibiotics are not indicated.

Disposition

Children with acute pancreatitis should undergo hospitalization. Children with known or recurrent disease, who are able to self-hydrate and have adequate analgesia, may be managed as outpatients in select cases.

Biliary Tract Disease

Foundations

Biliary tract disease is uncommon in childhood and has causes that differ from those in older individuals. Cholestasis in the neonatal period is usually associated with biliary atresia, biliary cysts, infections, and other metabolic and genetic disorders. Gallstones in children are usually associated with hemolytic disease (e.g., sickle cell disease), cystic fibrosis, total parenteral nutrition, sepsis, and dehydration. Acute acalculous cholecystitis has been associated with Rocky Mountain spotted fever and a variety of bacterial infections, including those due to *Salmonella* and *Shigella* organisms. Hydrops of the gallbladder

BOX 166.4 Empirical Antibiotic Regimens for Acute Appendicitis

Regimen

- Cefoxitin
- Ceftriaxone + metronidazole
- Cefotetan
- Gentamicin + clindamycin or metronidazole (penicillin-allergic patients)
- Piperacillin-tazobactam

Dosing

- Cefoxitin: 40 mg/kg IV; maximum dose, 2000 mg
- Ceftriaxone: 50 mg/kg IV; maximum dose, 2000 mg
- Metronidazole: 10 mg/kg IV; maximum dose, 500 mg
- Cefotetan: 40 mg/kg IV; maximum dose, 2000 mg
- Gentamicin: 2–7.5 mg/kg/day
- Clindamycin: 10 mg/kg IV; maximum dose, 900 mg
- Piperacillin-tazobactam: 80–100 mg/kg of the piperacillin component, max 4.5 g

(i.e., fluid distention of the gallbladder from chronic cystic duct inflammation or obstruction without inflammation or infection) is associated with viral upper respiratory or GI infections, Kawasaki disease, streptococcal pharyngitis, mesenteric adenitis, nephrotic syndrome, and leptospirosis.

Pigment gallstones stones are more common in childhood; cholesterol stones are uncommon prior to adolescence. Pigment stones result from the excess breakdown of red blood cells and are usually seen in those with hemolytic anemia, such as sickle cell disease and spherocytosis. Adolescents may form cholesterol gallstones in association with oral contraceptives, pregnancy, or obesity.

Clinical Features

Similar to adult patients, pediatric patients usually present with postprandial right upper quadrant pain associated with fever, nausea, and vomiting. Jaundice occurs in one-third of patients.

Diagnostic Testing

Biliary tract disease is usually associated with elevations in alkaline phosphatase, liver transaminases, and bilirubin levels; however, absence of elevations does not exclude the diagnosis. An elevated white blood cell count is nonspecific. Although only 15% of gallstones in adults are calcified and visible on plain radiographs, 50% of stones in children are radiopaque. Ultrasonography is the imaging modality of choice. It not only can determine the presence of gallstones, dilation of the gallbladder and common bile duct, gallbladder wall thickness, and pericholecystic fluid, but can also reproduce pain on compression of the gallbladder (sonographic Murphy sign). When ultrasound findings are equivocal or normal and clinical suspicion is high, cholescintigraphy biliary tract imaging (HIDA [hepatobiliary iminodiacetic acid] scan) can further assess the functional status of the gallbladder. Magnetic resonance cholangiopancreatography (MRCP) can assess the intrahepatic and extrahepatic ducts.

Differential Diagnoses

Pediatric biliary tract disease is uncommon in children and requires consideration of an underlying or coexistent disease. Differential considerations are listed in Table 166.4.

Management

Asymptomatic patients with incidental findings of gallstones require no further therapy in the ED and may be referred to a surgeon for outpatient care. Febrile patients and those with intractable pain or nausea and vomiting require hospital admission, fluid resuscitation, IV antibiotics, and surgical consultation. Laparoscopic cholecystectomy is considered safe and effective in children.

Disposition

Indications for hospital admission for biliary disease include pain control, need for IV hydration, fever, and need for operative management.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 166: QUESTIONS AND ANSWERS

1. What is the most common cause of jaundice in the newborn?
- **a.** Breast milk jaundice
- **b.** Crigler-Najjar syndrome
- **c.** Gilbert syndrome
- **d.** Physiologic jaundice of the newborn

Answer: D. Although each of these may be a cause of hyperbilirubinemia in the newborn, the most common cause of jaundice is physiologic jaundice of the newborn.

2. A 4-week-old white infant presents with projectile vomiting. The mother denies that the patient has a history of fevers, irritability, or signs suggestive of abdominal pain. On physical examination, you palpate an olive in the patient's right epigastrium. Which of the following laboratory abnormalities would you expect to find?
- **a.** Hyperchloremia and hypokalemia
- **b.** Hyperglycemia and hypokalemia
- **c.** Hypernatremia and hyperkalemia
- **d.** Hypochloremia and hypokalemia

Answer: D. This patient likely has pyloric stenosis. As vomiting continues, the infant loses hydrogen and chloride ions through emesis of gastric juices. As this metabolic derangement worsens, the kidney attempts to retain hydrogen ions by substituting potassium, resulting in a hypochloremic-hypokalemic metabolic alkalosis.

3. An 11-month-old infant presents with vomiting. The patient's mother reports that he has been crying out in pain intermittently throughout the day, at which times he brings his knees to his abdomen. In between these episodes, the patient acts normally and plays. He has not had a fever, but the mother complains that his stool earlier looked like currant jelly. On examination, you find a playful afebrile patient, with a soft nontender abdomen. Which of the following may be used as an initial screening examination?
- **a.** Air-contrast enema
- **b.** Barium enema
- **c.** Computed tomography scan of the abdomen-pelvis
- **d.** Ultrasound

Answer: D. The initial screening examination for intussusception is abdominal ultrasonography. Although each of the other imaging modalities may be useful to exclude other diagnoses or identify intussusception, ultrasonography has high sensitivity and specificity and is the screening modality of choice.

Pediatric Infectious Diarrheal Disease and Dehydration

Patricia Padlipsky and William White

KEY CONCEPTS

Identification of Pathogen

- Stool studies are not indicated in most uncomplicated cases of acute gastroenteritis (AGE). Exceptions are those cases in which specific treatment, specific prophylaxis, or health precautions are required, or in which the patient has systemic involvement, underlying medical complications, or dysenteric features.
- Antibiotics are not required for most cases of uncomplicated acute bacterial enteritis. Antibiotics are recommended routinely for *C. difficile, Giardia intestinalis,* and *E. histolytica.* Antibiotics can be considered for *Campylobacter*, *Cryptosporidium,* traveler's diarrhea, and *Shigella* (because antibiotics have been shown to decrease diarrhea and eradicate organisms in the stool).
- Patients with Shiga toxin–producing *E. coli* (STEC) should not empirically receive antibiotics, because they may increase the risk of hemolytic-uremic syndrome (HUS).
- Testing for fecal leukocytes is a useful initial test because it may support a diagnosis of invasive disease. This test should be considered in children with diarrhea who are febrile or have mucus or blood in the stool. If the test result is positive, stool culture is indicated to further guide management.

Oral Rehydration

- Most patients with mild to moderate dehydration can be treated with oral rehydration therapy (ORT). Resumption of feeding with age-appropriate diets should begin as soon as vomiting subsides. Routine fasting with infectious diarrhea is not recommended.

Dehydration Assessment

- The degree of volume depletion is estimated from the history and physical examination findings. The desired volume of oral rehydration solution is calculated as 30 to 50 mL/kg for mild dehydration and 60 to 80 mL/kg for moderate dehydration; 25% of the volume of oral rehydration solution is to be replaced every hour (100% over 4 hours). Continue to replace ongoing losses with 10 mL/kg for each diarrheal stool and 2 mL/kg for each vomiting episode. Patients who fail an oral rehydration trial of 4 to 8 hours in the emergency department (ED) should be admitted for intravenous hydration.

Severe Dehydration

- In severe dehydration, 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) given intravenously or intraosseously should reverse signs of shock within 5 to 15 minutes. Repeated boluses of 20 mL/kg are indicated until clinical improvement occurs, but volume requirements greater than 60 mL/kg without signs of improvement suggest other conditions, such as septic shock, hemorrhage, capillary leak with third-space fluid sequestration, and adrenal insufficiency. Rapid correction of sodium derangements in dehydration can lead to central nervous system complications.

DIARRHEA

Foundations

Background and Importance

Acute infectious diarrhea is a common illness seen around the world. Acute diarrhea is generally self-limiting in industrialized nations but can have significant morbidity and mortality for the elderly, very young, and immunocompromised patients. In underdeveloped countries, diarrheal diseases are a significant cause of death. According to the Global Burden of Disease Study 2016, diarrhea was found to be the eighth leading cause of death among all ages, responsible for more than 1.6 million deaths worldwide. Approximately half a million of the deaths from diarrhea worldwide occurred among children younger than 5 years of age, making it the third leading cause of death in children less than 5 years of age globally.[1,2] The rotavirus vaccine in the United States and internationally has markedly reduced pediatric diarrhea-associated emergency department (ED) visits, hospitalizations, and deaths.

Acute diarrhea is defined as the abrupt onset of abnormally high fluid content in the stool, with increased volume or frequency. As supported by the World Health Organization (WHO), "acute" diarrhea has a sudden onset and lasts no longer than 14 days; "chronic" or "persistent" diarrhea lasts longer than 14 days. This classification is important for epidemiologic studies and to identify the most likely offending organism. Protracted diarrhea has different causes, poses unique problems in management, and has a prognosis different from that of acute diarrhea. Acute infectious diarrhea can occur with or without vomiting. When it occurs with vomiting, it is often referred to as *acute gastroenteritis (AGE).*

Anatomy, Physiology, and Pathophysiology

Up to 9 L of exogenous fluid and endogenous secretions enter the adult proximal bowel each day, and proportionally even more in children. Ninety percent of fluid is absorbed in the small bowel and the remainder in the large bowel. Water follows osmotic gradients created by active and passive transport of electrolytes, sugars, and amino acids into the bloodstream by the following mechanisms:

- Sodium chloride absorption in the small bowel, with an exchange of cations (Na^+/H^+) and anions (Cl^-/HCO_3^-).
- Electrogenic sodium absorption in the colon, but also in the small intestine, wherein Na^+ enters the cell through an electrochemical gradient; this mechanism is often damaged in acute diarrhea.
- Sodium co-transport mechanism in the small bowel. Na^+ absorption is coupled with the absorption of glucose, amino acids, and peptides. This mechanism often remains intact during acute diarrhea illness, making oral rehydration possible.

Pathophysiology

Infectious agents cause diarrhea by adherence, mucosal invasion, enterotoxin production, and cytotoxin production. Under normal circumstances, the absorptive processes for water and electrolytes predominate over secretion, resulting in net water absorption. Diarrhea occurs when this balance is disrupted, either as a result of increased secretion from the gastrointestinal tract, decreased absorption of fluids, or from inflammation.

Secretory diarrhea is the result of increased intestinal secretion of water into the gut lumen or an inhibition of absorption. For example, *Vibrio cholera* produces an enterotoxin, resulting in increased chloride and bicarbonate secretion. Secretory diarrhea is characterized by the absence of expected reduction in stool volume with fasting, a stool pH above 6, and the absence of reducing substances in the stool. Other bacteria that produce enterotoxins include *Salmonella, Shigella, Escherichia coli,* and *Clostridioides difficile*.

Osmotic diarrhea is caused by the presence of poorly absorbed solutes from altered bacterial gut flora, damage to the mucosal absorptive surface, or ingestion of substances. These substances create an osmotic gradient across the bowel lumen, resulting in intraluminal movement of water and electrolytes. Typical acute viral gastroenteritis produces injury to the small bowel epithelium with consequent disruption of microvilli, decreasing the absorptive area, and preventing normal fluid, electrolyte, and nutrient absorption. The illness is compounded if the colon is unable to compensate for the large fluid volume. Osmotic diarrhea is often characterized by diarrhea that decreases or stops with fasting, a stool pH below 6, and the presence of reducing substances in the stool.

Inflammatory processes can cause destruction of villous cells or dysfunction of cellular transporters, leading to loss of fluids and electrolytes, as well as mucus, proteins, and blood in the intestinal lumen. *Dysentery,* diarrhea associated with blood and mucus in the stool, implies a compromised bowel wall. Acute inflammation, caused by enteroinvasive organisms such as *Salmonella, Shigella,* and *Campylobacter,* leads to infiltration of the gastrointestinal tract by neutrophils, which release a host of enzymes and factors causing both increased secretion and decreased absorption by the intestinal tract. Although blood loss may be clinically appreciable, it is usually less significant than fluid and electrolyte losses. Infectious diarrhea can present with significant signs of dehydration and electrolyte abnormalities.

Pediatric patients have several physiologic factors that predispose them to more severe complications from vomiting and diarrhea. As a result of their relatively larger extracellular fluid compartments, children can lose proportionately more fluids through the gastrointestinal tract. Furthermore, the turnover of fluids and solute in infants and young children can be three times that of adults. This rapid turnover of fluids is the result of higher metabolic rates, increased body surface area to mass index, and higher body water content. Children also have limited stores of metabolic substrates such as fat and glycogen, limited ability or desire to access fluids when ill, and a more limited ability to conserve water through their kidneys compared to adults. These factors make children more susceptible to large fluctuations in fluid, electrolytes, and nutrients, resulting in hypoglycemia, electrolyte abnormalities, dehydration, and shock.

Some groups are at higher risk for developing serious complications of infectious diarrhea (e.g., invasive disease, bacteremia, and sepsis). These include premature infants, very-low-birth-weight infants (up to a year), young infants (younger than 3 months old), immunosuppressed or malnourished children, and those with chronic underlying conditions. Recent hospitalization, treatment with broad-spectrum antibiotics, and travel to developing countries are additional risk factors.

Clinical Features

Infectious diarrhea can present with diarrhea alone or accompanied by vomiting (i.e., acute gastroenteritis [AGE]). Signs and symptoms usually begin 12 to 72 hours after contracting the infectious agent. If due to a viral agent, the condition usually resolves within 1 week. See Box 167.1 for a list of common signs and symptoms. The history and physical examination should help differentiate acute infectious diarrhea from other causes of vomiting and diarrhea and help estimate the degree of dehydration. History and physical examination can sometimes aid in determining the type of pathogen responsible, although this will rarely affect management. Box 167.2 summarizes important information to gather from the history.

Vital signs should be assessed relative to age norms. The evaluation of the child should begin with looking at the child from across the room in a position of comfort, noting the patient's overall appearance, responsiveness, activity, and work of breathing (see Chapter 160). A head-to-toe physical examination of the patient should focus on signs of dehydration that may indicate another cause for the diarrhea (e.g., otitis media, pyelonephritis, appendicitis, diabetic ketoacidosis), or signs that indicate the disease may have become extraintestinal or systemic—bone pain (osteomyelitis), altered mental status (meningitis), petechiae (hemolytic-uremic syndrome [HUS]).

Acute infectious diarrhea in developed countries is often self-limited. The clinical presentation, course of illness, and treatment depends on the etiology of the diarrhea and the host. In the United States, viruses are responsible for most cases of acute infectious diarrhea, with bacteria causing only 7% to 10% of cases in children. Parasites are uncommon in the immunocompetent patient, unless they have traveled to endemic areas. Table 167.1 lists the most common viruses, bacteria, and protozoa that can cause acute infectious diarrhea in children in the United States.[3-6]

Specific Etiologies

Viruses. In the United States and Europe, the majority of cases of diarrhea are caused by viral pathogens, with incidence peaking in the winter. The most common of these are rotavirus and norovirus. See Table 167.2 for presentation and associated characteristics.

BOX 167.1 Common Signs and Symptoms in Patients With Acute Infectious Diarrhea

Diarrhea—frequent, loose, watery, mucousy, bloody, or foul smelling
Nausea
Decreased appetite
Weight loss
Vomiting
Headache
Abdominal pain or cramps
Fever
Malaise
Signs of dehydration (see Dehydration section)

BOX 167.2 Patient History

- Behavior: Weight loss, amount and frequency of feeding, level of thirst, level of alertness, level of activity, lethargy, irritability, quality of crying, presence or absence of tears with crying, frequency of wet diapers in infants or urination in children
- Orthostatic symptoms
- Diarrhea: Duration, frequency, and amount of stools; consistency and content of stool; watery, blood, mucus
- Vomiting: Duration, amount and quality of the vomitus, time since last vomited
- Abdominal pain: Location, quality, radiation, severity per parent and child
- Signs of infection: Fever, chills, myalgia, rash, rhinorrhea, sore throat, cough
- Symptoms in relationship to eating and drinking
- Similar symptoms in other household members or school
- Similar episodes in the past
- Food history
- Water exposure and recent camping
- Travel to endemic or epidemic areas
- Household pets
- Past medical history; chronic medical problems, recent hospitalizations; vaccine status
- Current/recent antibiotic

TABLE 167.1 Common Causes of Childhood Infectious Diarrhea in Developed Countries

Viruses (70% to 80%)	Bacteria (10% to 20%)	Protozoa (<10%)
Rotavirus	*Salmonella* species	*Cryptosporidium*
Norovirus and Sapovirus	*Shigella* species	*Giardia intestinalis*
Astrovirus	*Campylobacter jejuni*	*Entamoeba histolytica*
Adenovirus	*Yersinia enterocolitica*	
	Escherichia coli; ETEC,	
	Clostridium perfringens	
	Clostridium difficile	
	Staphylococcus aureus	
	Vibrio cholera	
	Vibrio parahaemolyticus	

ETEC, Enterotoxigenic *E. coli.*

Rotavirus (RV) continues to be the leading cause of diarrhea and significant morbidity worldwide among children younger than 5 years old. Neurologic symptoms, most commonly seizures, occur in 2% to 3% of children with rotavirus infection.[7] The chronically ill or malnourished child often fails to repair damaged intestinal epithelium post rotavirus infection, leading to a vicious cycle of malnutrition and progressive epithelial injury.

With the introduction of the rotavirus vaccine, there has been a significant decrease in the incidence of RV in the United States.[8-10] According to the CDC, norovirus is now the most common cause of diarrheal illness in children. Two live rotavirus oral vaccines, RotaTeq (RV5) (Merck & Co., Inc.) licensed in 2006 and Rotarix (RV1) (GlaxoSmithKline Biologicals) licensed in 2008, are now approved and are given widely for prevention of rotavirus gastroenteritis. Since the introduction of the RV vaccine in the U.S., a biennial pattern has emerged, with small, short seasons in late winter/early spring,[11] and annual hospitalizations have declined among U.S. children younger than 5 years of age by 80% to 90%.[11,12] It is estimated that since the introduction of the RV vaccine, an estimated 177,000 hospitalizations, 242,000 ED visits, and 1.1 million outpatient visits for diarrhea have been averted among children younger than 5 years of age.[13] The decrease in hospitalization and ED visits is also decreasing in many other countries as the use of the RV vaccine spreads globally.[14,15]

The current rotavirus vaccines were not associated with intussusception in large pre-licensure trials. There continues to be controversy over whether an increase in intussusception does occur. Some post-licensure studies done in the United States, Canada, Korea, Africa, Brazil, and Taiwan agree with the prelicensure trials showing no increase in intussusception with the RV vaccines.[16-21] However, recent postlicensure surveillance data in the United States[22-24] and internationally[25-27] indicate there is an increased risk of intussusception from the currently licensed RV vaccines. These studies found that most of the increased risk occurs within the first week after the first dose but may occur up to 21 days after the first dose. Although there may be a slight increased risk of intussusception following the oral vaccines, the Centers for Disease Control and Prevention (CDC) and the World Health Organization still recommend the rotavirus vaccine as the benefits of the RV vaccine in preventing severe RV disease far outweigh the risk of intussusception. Parents should be made aware of the risk, the early signs and symptoms of intussusception, and the need for prompt care if they develop.[13]

Human Caliciviruses (Norovirus and Sapovirus). According to the CDC Burden of Norovirus Illness in the United States,[28] each year, norovirus causes approximately 20 million cases of acute gastroenteritis, leading to 1.7 to 1.9 million outpatient visits and 400,000 ED visits, primarily in young children. It also contributes to about 56,000 to 71,000 hospitalizations and 570 to 800 deaths, mostly among young children and the elderly. Norovirus is now the leading cause of acute gastroenteritis among U.S. children less than 5 years of age.[29] Norovirus AGE is associated with more frequent and prolonged vomiting, but less fever, than AGE caused by rotavirus. Seizures are the most common central nervous system (CNS) complication, whereas encephalopathy is possible but rare.[30] Clinical manifestations for sapovirus are similar to those of norovirus.[31]

Astrovirus has a worldwide distribution and has been found in up to 17% of sporadic cases of nonbacterial AGE in children. It accounts for only 2.5% to 9% of severe childhood AGE requiring hospitalization. In healthy children, it is an illness of short duration, although asymptomatic shedding continues up to several weeks after symptom resolution. In the immunocompromised patient, astrovirus infections have been associated with extraintestinal disease, encephalitis, and meningitis.[32,33]

Adenovirus is well known for causing infections of the respiratory tract along with pharyngitis, otitis media, and pharyngoconjunctival fever. Enteric adenovirus serotypes (31, 40 and 41) cause gastroenteritis, accounting for 2% to 4% of cases of acute infectious diarrhea in children. In healthy people, infection with one adenovirus type may confer type-specific immunity or at least lessen symptoms associated with reinfections. Asymptomatic shedding of the virus for months is common.[34]

The mainstay for treatment of viral enteritis is supportive care with rehydration and electrolyte correction.

Bacteria. The common bacterial organisms causing acute diarrhea in U.S. children along with their presentations and associated characteristics are listed in Table 167.3, and their treatment is listed in Table 167.4.

Nontyphoidal *Salmonella* (NTS) is the most common cause of laboratory confirmed cases of enteric disease. The CDC estimates that approximately 1.35 million illnesses and 420 deaths occur annually in the United States due to NTS. In a recent study, the most commonly reported human isolates were *Salmonella* Enteritidis, Typhimurium, Newport, Heidelberg, and Javiana; these 5 serotypes accounted for 62% of U.S. *Salmonella* infections.[35] The incidence of NTS is highest in children less than 4 years of age. Infection can result in an asymptomatic carrier state, AGE, bacteremia, invasive disease, or a disseminated abscess syndrome.

TABLE 167.2 Viruses Causing Diarrheal Illness: Characteristics and Associated Symptoms

	Age	Season	Lasts	Incubation Period	How Spread	Length of Excretion	Abdominal Pain	N/V	Fever	Diarrhea Characteristics	Diagnostics
Rotavirus	<5 years old	Winter and spring	4 to 8 days	Less than 48 hours (1 to 3 days)	Mainly Fecal-oral (can stay on surfaces for weeks to months) or respiratory secretions	Up to 21 days	±	++	± ⅓ have high fever	Watery; large volume	ELISA and latex agglutination most commonly used; PCR most sensitive
Norovirus	<5 years old	Anytime; colder months	2 to 3 days (up to 5 days)	12 to 48 hours	Fecal-oral; contaminated food and water	5 to 7 days after onset of symptoms; up to 3 weeks	++	++ (some may not vomit)	±	Abrupt onset; watery	RT-PCR testing available; CIDT
Astrovirus	<4 years old	Late winter; early spring	2 to 5 days	1 to 4 days	Fecal-oral	Few days after symptoms resolve	±	+	++	Watery; large volume	CIDT now available
Adenovirus	<4 years old	All year	5 to 12 days	3 to 10 days	Fecal-oral	Most contagious first few days; asym excretion for months	±	+	Low grade	Watery	Commercial test available

Key: ++, common; +, occurs; ±, variable.
N/V, Nausea/vomiting*; ELISA,* enzyme-linked immunosorbent assay; *PCR,* polymerase chain reaction; *RT-PCR,* reverse transcription polymerase chain reaction; *CIDT,* culture-independent diagnostic test.
Data from: World Gastroenterology Organization. *World Gastroenterology Organization global guidelines: acute diarrhea in adults and children: a global perspective*. Available at: www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english; and Kimberlin DW, Brady MIT, Jackson MA, Long SS, editors. *Red Book: 2018-2021 Report of the Committee on Infectious Disease*, 31st ed. Itasca, IL; American Academy of Pediatrics; 2018.

TABLE 167.3 Bacteria Causing Diarrheal Illness: Characteristics and Associated Symptoms

	Who Affected	Incubation (range)	Duration of Illness	How Spread	Length of Excretion	Abdominal Pain	N/V	Fever	Diarrhea Characteristics	Other Characteristics	Diagnostic Tests
Salmonella species	<4 years old	12 to 36 hours (6 to 72 hours)	2 to 7 days	Foods from animals; contaminated water; infected reptiles, amphibians, rodents, and mammals	Up to 12 weeks in children <5 years old	++	+	++	Mild to severe; can have blood or mucus	Bacteremia can occur, focal infections in 10%	Stool culture; CIDT starting to be used
Salmonella typhi	Travelers	7 to 14 days (3 to 60 days)	Requires antibiotics	Contaminated food or water	Chronic carriers	++	+	++	Not main problem; mild diarrhea	Gradual onset; HA, malaise, anorexia; HSM, rose spots, dactylitis, ams	Blood, bone marrow, or bile culture
Shigella species	≤5 years old	1–3 (1 to 7 days)	48 to 72 hours	Fecal-oral, contaminated food/ water, objects	1 to 4 weeks, antibiotics may shorten excretion	++	++	++	Mild to severe: watery to mucoid with or without blood	Can have systemic symptoms; neurological symptoms; tenesmus Fecal PMNs often positive	Stool culture; improved with fresh stool, CIDT have high sensitivity; high false-positive rate
Campylobacter	<4 years old	2 to 5 days	5 to 7 days; 15% can relapse or have prolong or severe disease	Ingestion of contaminated foods; fecal-oral in the very young; greatest in acute phase	2 to 3 weeks without treatment 2 to 3 days with treatment	++ Can mimic appendicitis or intussusception	+	++ Infants may not have fever	Watery to mucoid/bloody	Malaise; can have febrile symptoms before GI symptoms Infants may have bloody diarrhea and no fever Can mimic acute inflammatory bowel disease	*C. jejuni* and *C. coli* from stool culture; CIDT, don't differentiate species
Yersinia enterocolitica	<5 years most common	4 to 6 days (1 to 14 days)	Variable; usually few days but diarrhea up to 2 weeks	Contaminated food or water; contact with animals, person to person is rare	Average 2–3 weeks (up to 2–3 mos if untreated)	+	±	++	Often with blood and mucus	Pseudoappendicitis syndrome Fecal PMNs often positive Bacteremia; <1 year old, excessive iron storage, immunosuppressed	Stool culture; need to specify
Clostridium difficile	>24 months	Not really known. Colitis usually starts 5 to 10 days after starting antibiotics (up to 10 weeks)	Variable	Fecal-oral or environment	Unknown	+	–	+ Low grade	Mild: watery diarrhea to pseudomembranous colitis; mucus in stool		EIA detection of toxins NAAT good sensitivity and specificity
Clostridium perfringens	Any age	8 to 12 hours (6 to 24 hours)	24 hours	Catered foods	As long as illness persists	++ Crampy, epigastric	–	–	Sudden onset; watery diarrhea	Common in healthy people's stool Treatment not necessary; short course	High spore count in stool Commercially available kits

Continued

TABLE 167.3 Bacteria Causing Diarrheal Illness: Characteristics and Associated Symptoms—cont'd.

	Who Affected	Incubation (range)	Duration of Illness	How Spread	Length of Excretion	Abdominal Pain	N/V	Fever	Diarrhea Characteristics	Other Characteristics	Diagnostic Tests
Staphylococcus aureus	Any age	2 to 4 hours (30 minutes to 8 hours)	1 to 2 days	Contaminated food that remains at room temperature for hours	Short time	+	++	± Low grade	Watery	Violent onset of nausea/vomiting; can have mild hypothermia	Culture stool or vomitus EIA or PCR detect enterotoxin
Vibrio cholera	Traveled to endemic area	1 to 3 days (hours to 5 days)	3 to 7 days	Contaminated food and water (shellfish; raw vegetables)	Short time	±	±	±	Large amounts watery diarrhea; stool colorless with flecks of mucus; rice water appearing	Dehydration, hypokalemia, metabolic acidosis and shock within 4 to 12 hours; coma, seizures, hypoglycemia	Stool culture; need to request
Vibrio parahaemolyticus	All ages	23 hours (5 to 92 hours)	2 to 5 days	Seawater; undercooked seafood	Not excreted	++	±	± Low grade	Acute onset Watery stools	Liver disease, low gastric acidity, immunosuppressed increased risk	Lab needs to be notified when test; can test stool, blood, or wounds
E. coli (STEC)	All ages	3 to 4 days (1 to 8 days)	Usually 7 days	Contaminated food or water with human or animal feces; person to person occurs		++	+	– Sometimes low grade	Bloody or nonbloody	Stool becomes bloody after 3 to 4 days; can cause HUS Shiga toxin produced	Stool culture; must request test for *E. coli* O157 EIA for Shiga toxin if available
E. coli (EPEC)	<2 years old; RLAs and travelers	10 hours to 6 days	Usually few days but variable	Contaminated food or water with human or animal feces		–	–		Watery, usually mild	Can become chronic and cause growth retardation No toxin produced	Not widely available
E. coli (ETEC)	Infants in RLAs and travelers of all ages	10 hours to 6 days	1 to 5 days	Contaminated food or water with human or animal feces; person to person occurs		+	–	±	Watery	Uncommon in the U.S. Enterotoxin produced	Not widely available
E. coli (EIEC)	All ages	10 hours to 6 days	Variable	Contaminated food or water with human or animal feces		±	–	+	Usually watery without blood or mucus; dysentery can occur	Related to *Shigella* can cause similar dysenteric illness	Not widely available
E. coli (EAEC)	All ages	10 hours to 6 days	Variable	Contaminated food or water with human or animal feces		±	–	±	Watery, occasionally bloody	Enterotoxin and cytotoxin Associated with prolonged diarrhea; becoming more common in U.S.	Not widely available

Key: ++, common; +, occurs; ±, variable; –, not common.

CIDT, Culture-independent diagnostic test; *EAEC,* enteroaggregative *Escherichia coli; EIA,* enzyme immunoassay; *EIEC,* enteroinvasive *E. coli; EPEC,* enteropathogenic *E. coli; ETEC,* enterotoxigenic *E. coli; HA,* headache; *HUS,* hemolytic-uremic syndrome; *GI,* gastrointestinal; *NAAT,* nucleic acid amplification test; *N/V,* nausea/vomiting; *PCR,* polymerase chain reaction; *PMN,* polymorphonucleocyte; *RLA,* resource limited area; *STEC,* Shiga toxin–producing *E. coli*

Data from: World Gastroenterology Organization. *World Gastroenterology Organisation global guidelines: acute diarrhea in adults and children: a global perspective.* Available at: www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english; and Kimberlin DW, Brady MIT, Jackson MA, Long SS, editors. *Red Book: 2018-2021 Report of the Committee on Infectious Disease*, 31st ed. Itasca, IL; American Academy of Pediatrics; 2018.

TABLE 167.4 Treatment Recommendations for Common Bacteria Causing Acute Infectious Diarrhea in Children

	Routine Treatment	Treatment Indicated—High-Risk Groups	Antibiotic	Comments
Salmonella non-typhi	No; treatment prolongs excretion; does not shorten disease	Infants <3 months old, prolonged illness, chronic GI disease, neoplasms, hemoglobinopathies, HIV, immunosuppression, localized invasive disease (osteomyelitis, abscess, meningitis) or bacteremia	Susceptibility is known Oral: Amoxicillin 25–50 mg/kg divided every 8 hours IV: Ampicillin 200 mg/kg divided every 6 hours (max 8 g/d) Oral: TMP-SMX 10 mg/kg divided every 12 hours (max 160 mg/dose) Susceptibility not known or areas of high resistance or invasive disease or bacteremia IV or IM: Ceftriaxone 50–75 mg/kg q24h (max 2 g) or Oral or IV: Azithromycin 10–20 mg/kg (max 500 mg/dose) or Oral: Adult—[a]Ciprofloxacin 500 mg/dose every 12 hours, Children—[a]Ciprofloxacin 20–40 mg/kg divided every 12 hours (max 1 g/day)	Blood cx before initiating antibiotics. Bacteremia: Treat for 10 to 14 days Localized invasive disease: Treat for 4 weeks (6 weeks if meningitis) and begin with IV medications Aminoglycosides not recommended for invasive disease Drug of choice, route of administration, and duration of therapy based on susceptibility of organisms, site of infection, host and clinical response
Salmonella typhi	Yes	All patients with enteric fever Delirium, stupor, coma, or shock	Start with IV medications; change to oral when susceptibility is known Ceftriaxone 50– 75 mg/kg q24h (max 2 g) or [a]Ciprofloxacin 20–40 mg/kg divided every 12 hours(max 1g/day)	Multidrug resistance is common 10- to 14-day treatment Check susceptibilities Azithromycin for uncomplicated disease Consider: Dexamethasone IV 3 mg/kg, followed by 1 mg/kg every 6 hours for 48 hours; relapse is common
Shigella species	No; usually self-limited but treatment decreases diarrhea and eradicates organism from stool	Severe disease, bacteremia, dysentery, immunosuppression Less ill and able to tolerate PO (See Oral dosing)	IV: Ceftriaxone 50 mg/kg (max 2 g) for 5 days (≥ 17 years old) or [a]Ciprofloxacin 20–30 mg/kg/day divided bid or Azithromycin 20 mg/kg/day (max 500 mg) Oral: Azithromycin 12 mg/kg for first day, then 6 mg/kg for days 2 to 5 or [a]Ciprofloxacin 20 mg/kg divided every 12 hours for 5 days	Oral route preferred when possible and disease is not serious TMP-SMX and ampicillin only if isolated strain is susceptible because of high resistance Amoxicillin less effective because of rapid absorption from GI tract; avoid fluoroquinolones if MIC >0.12 even if says susceptible.
Campylobacter jejuni	Variable	Variable recommendations. Most children will resolve on own.	Oral: Azithromycin 10 mg/kg for 3 days (max 500 mg/dose) or Erythromycin 40 mg/kg/day divided every 6 hours (max 2g/day) for 5 days	Shorten duration of illness and excretion of organisms and prevent relapse if given early Resistance to fluoroquinolones is frequent
Yersinia enterocolitica	No; although can be considered as it decreases shedding of the organism;	Neonates, septicemia or extraintestinal sites of infection; immunocompromised host	Oral: TMX-SMX 10 mg/kg divided every 12 hours or Oral or IV fluoroquinolone[a], 10 mg/kg/day of TMP component: Ciprofloxacin 20 mg/kg divided every 12 hours or IV: Ceftriaxone 50 mg/kg qd	Usually resistant to penicillin and first generation cephalosporins Antibiotics do decrease the duration of fecal excretion but do not decrease length of diarrhea Extraintestinal disease treat for 4 weeks. Usually susceptible to tetracycline and doxycycline
C. difficile	Yes	Symptomatic patients Severe disease, underlying intestinal tract disease, and those who don't respond to oral metronidazole use vancomycin	Stop antimicrobial therapy Oral or IV: Metronidazole 30–40 mg/kg/day for at least 10 days (maximum dose 500 mg/dose) if failure to respond in 5 days then: Oral: Vancomycin 40 mg/kg /day divided every 6 hours for at least 10 days (maximum 125mg/dose	25% relapse after treatment, usually responds to second course; IV vancomycin is not effective Do not give antimotility agents; if no abdominal distention and severe disease use Vanco PO and metronidazole IV. If ileus or toxic colitis add vancomycin (1–3 years old: 250 mg/50 mL q6h; 4–9 years old: 375 mg/75 mL q6h; ≥10 years old: 500 mg/100 mL q6h) NS enema until improved

Continued

TABLE 167.4 Treatment Recommendations for Common Bacteria Causing Acute Infectious Diarrhea in Children—cont'd.

	Routine Treatment	Treatment Indicated—High-Risk Groups	Antibiotic	Comments
Vibrio cholera	No	Patients with moderate to severe disease	Oral: Doxycycline[a] 4.4 mg/kg/day divided bid or Azithromycin 20 mg/kg single dose or Tetracycline[a] 50 mg/kg/day divided every 6 hours (maximum 3 g/day) for 3 days	Susceptibility testing recommended Treatment decreases duration of diarrhea and eradicates bacteria from stool; Cipro not recommended in children high treatment failures
V parahaemolytica	No	Severe diarrhea, septicemia Consider in patients <8 years old	Third-generation cephalosporin and doxycycline[a] TMX-SMX and aminoglycoside	
E. coli	No for STEC infection or concern for STEC	Severe watery diarrhea in a traveler to RLA	Azithromycin 10 mg/kg qd ×3 days, ciprofloxacin 30 mg/kg/day divided BID ×3 days[a]	Treating patients with STEC may increase risk for HUS

[a]Fluorquinolone: ciprofloxin recommended for greater or equal to 17 years unless benefits outweigh the risks. Tetracyclines/doxycyclines are not recommended in children younger than 8 years because of teeth staining, but the benefit of using the drug may outweigh the risk of teeth staining. Each case is considered separately. Ciprofloxacin recommended for greater or equal to 17 years unless benefits outweigh the risks.
GI, Gastrointestinal; *HIV,* human immunodeficiency virus; *HUS,* hemolytic-uremic syndrome; *IM,* intramuscular; *IV,* intravenous; *PO, per os* (by mouth); *RLA,* resource limited area; *STEC,* Shiga toxin–producing *E. coli, TMP-SMX,* trimethoprim-sulfamethoxazole.
Data from: Kimberlin DW, Brady MIT, Jackson MA, Long SS, editors. *Red Book: 2018-2021 Report of the Committee on Infectious Disease*, ed 31. Itasca, IL: American Academy of Pediatrics; 2018; and Hughes HK, Kahl LK, editors. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*, ed 21. Philadelphia: Saunders; 2018.

Salmonellae invade the mucosa of the distal small intestine and the colon; they produce a cholera-like enterotoxin and a cytotoxin, which can cause significant diarrhea and fluid and electrolyte abnormalities similar to patients with documented cholera. Fever in NTS patients usually lasts about 48 hours, and patients with prolonged fever may have intermittent bacteremia. Patients with *Salmonella* bacteremia are at increased risk for developing extraintestinal infections, seen in up to 10% of patients with *Salmonella* bacteremia. Infants, the elderly, patients with hemoglobinopathies, and the immunosuppressed are at highest risk for invasive disease. Extraintestinal sites of infection can result in endocarditis, vascular infections, cholecystitis, hepatic and splenic abscesses, urinary tract infections, pneumonia, meningitis, septic arthritis, and osteomyelitis.[36]

Although uncommon, *Salmonella* serotype *typhi* is only found in humans and can cause a bacteremic illness often referred to as *enteric* or *typhoid fever.* Although uncommon in the United States, *S. typhi* is endemic in many resource-limited countries. Typhoid fever may be acquired during international travel and appear as a nonspecific febrile illness in young children in whom sustained or intermittent bacteremia may occur. Constipation can be the presenting symptom and is often seen early in the course of the disease, but diarrhea can also occur. If *S. typhi* is suspected, blood, bone marrow or bile should be cultured, because stool cultures are often negative.[35]

Treatment of noninvasive NTS infection is usually supportive. Antimicrobial treatment is only recommended for infants younger than 3 months and people with chronic gastrointestinal disease, malignant neoplasms, hemoglobinopathies, HIV infections, or other immunosuppressive illnesses or therapies. If treatment is started for presumed disease, stool and blood cultures should be obtained prior to initiating antibiotics. On the other hand, for children with *S. typhi* infection, antibiotics *are* recommended. Relapse of enteric fever occurs in up to 17% of patients and requires retreatment. Treatment failures have occurred in people treated with cephalosporins, aminoglycosides, and furazolidone, despite in vitro testing indicating susceptibility.[36]

Among *Shigella* isolates reported in industrialized nations, most are *Shigella sonnei* (84%). *Shigella flexneri, Shigella boydii,* and *Shigella dysenteriae* account for the remainder.[37] *S. sonnei* is the most common cause of dysentery in the United States. Extraintestinal symptoms and signs are relatively common in children with *Shigella* infection, including hallucinations, confusion, and seizures. Reactive arthritis (Reiter syndrome) can occur weeks after the infection. Rare complications of *Shigella* infection include bacteremia, HUS, toxic megacolon, pseudomembranous colitis, and encephalopathy (Ekiri syndrome). The risk of septicemia increases in neonates, malnourished children, and with *S. dysenteriae.* There is some evidence that antibiotic treatment is effective in shortening duration of diarrhea and hastening eradication of organisms from feces.[37] Drug-resistant *Shigella* has been rapidly increasing; resistance to first-line drugs, ampicillin and trimethoprim-sulfamethoxazole, has become so high that emergency clinicians must rely on alternative drugs like ciprofloxacin and azithromycin. However, over the last 5 years, resistance to these medications has also increased drastically. According to the CDC, both ciprofloxacin and azithromycin resistance has increased from approximately 2% to over 20%. Of particular concern are frequently reported outbreaks of multidrug-resistant *Shigella* among men who have sex with men.[38,39]

Campylobacter species cause a significant proportion of diarrheal disease worldwide, with 1.5 million annual U.S. cases and children younger than 5 years most commonly infected. Of the five types, *C. jejuni* and *C. coli* are the most common.[40,41] In neonates and young infants, bloody diarrhea without fever can be the only manifestation of infection. Febrile seizures can occur in young children before any gastrointestinal symptoms are present. The clinical presentation may be similar to acute appendicitis or intussusception. Severe or prolonged disease can mimic inflammatory bowel disease. Bacteremia is uncommon but can occur in children, including neonates. Immunocompromised hosts can have prolonged, relapsing, or extraintestinal infections. Immunoreactive complications include Guillain-Barré syndrome, reactive arthritis, myocarditis, pericarditis, and erythema

nodosum.[41] Antibiotic treatment is recommended for those with severe invasive disease, those at increased risk for severe disease, and for those with prolonged excretion of the bacteria. According to the CDC and the World Health Organization, most healthy children will recover without antibiotic treatment. Azithromycin and erythromycin do shorten the duration of the illness and excretion of the organisms if susceptible. Resistance to antibiotics is increasing. Over 10% of isolates are resistant to azithromycin and erythromycin and over 35% are resistant to ciprofloxacin in the United States. Therefore, if using culture-independent diagnostic tests (CIDT) tests to diagnosis *Campylobacter*, cultures are recommended to confirm diagnosis and for susceptibility information.[38]

Yersinia enterocolitica is a relatively uncommon cause of simple self-limited diarrhea and vomiting in the United States. According to the CDC, there has been a recent increase in the incidence, most likely from CIDT results. *Y. enterocolitica* most often affects children younger than 5 years of age. As many as 6% of older children and adults may present with an appendicitis-like illness, with right lower quadrant tenderness, usually as a result of reactive mesenteric adenitis. Antibiotics are indicated for the immunocompromised patient with enterocolitis and in cases of septicemia or extraintestinal infections. Isolates are often resistant to first-generation cephalosporins and most penicillins. Bacteremia is the major complication of *Y. enterocolitica,* occurring mostly in children less than 1 year of age and in older children with predisposing conditions, including excessive iron storage (e.g., deferoxamine use, sickle cell disease, and beta-thalassemia) and immunosuppressive states. Extraintestinal manifestations of *Y. enterocolitica* are rare. Postinfectious sequelae include erythema nodosum, reactive arthritis, and proliferative glomerulonephritis, most often associated with older children and adults with HLA-B27.[42]

Humans acquire *C. difficile* from their environment or via the oral-fecal route, which can lead to infection. The disruption of the body's normal flora, often as a result of antimicrobial treatment, leads to overgrowth of *C. difficile*, toxin production, and disease development. Exposure to antibiotics is the most important risk factor for *C. difficile*.[43] Penicillins, cephalosporins, clindamycin, and fluoroquinolones are associated more commonly with *C. difficile* infection, whereas sulfonamides, tetracyclines, vancomycin, metronidazole, and aminoglycosides are less commonly linked in children. Pediatric patients who are exposed to multiple antibiotics from different classes in the previous 30 days have been shown in recent studies to be associated with severe and recurrent *C. difficile* infection.[44] Other risk factors include acid-suppressing medications, such as proton pump inhibitors, and use of gastrointestinal feeding tubes.[45]

C. difficile infections cause a spectrum of illnesses ranging from asymptomatic to watery diarrhea to pseudomembranous colitis.[46] Clinical illness is rare before 12 to 24 months of age. Asymptomatic infants can be colonized with *C. difficile*; carriage rates vary by age and range from 37% in neonates to less than 3% by age 2 years.[46,47] *C. difficile* should be considered in children 1 to 3 years old, but only after other causes of diarrhea (particularly viral) are excluded.[47] Endoscopic findings of pseudomembrane and friable rectal mucosa are sufficient to diagnose *C. difficile* at any age. This is helpful when trying to determine if a child younger than 3 years old is colonized or has disease. The endoscopic findings are diagnostic of disease. Complications include toxic megacolon and intestinal perforation. Severe or fatal disease is more common in neutropenic patients with leukemia, infants with Hirschsprung disease, and patients with inflammatory bowel disease.[46,47,48]

See Tables 167.3 and 167.4 for presentation and associated characteristics and treatment recommendations for *Clostridium perfringens, Staphylococcus aureus, V. cholera*, and *Vibrio parahaemolyticus*.[48-51]

Each year, the WHO Global Burden of Foodborne Diseases reports over 300 million illnesses and nearly 200,000 deaths caused by *E. coli* diarrheagenic infections. *E. coli*, part of the normal flora in the lower gastrointestinal tract, includes five species types recognized to cause acute diarrheal disease. The enterohemorrhagic *E. coli* (EHEC) strain is also known as Shiga toxin–producing *E. coli* (STEC). While there are 50 other serotypes that can cause illness, *E. coli* O157:H7 is the prototype and most virulent of the EHEC and is the one more commonly reported in industrialized countries. Outbreaks have been linked to ground beef, petting zoos, contaminated apple cider, raw fruits and vegetables, and ingestion of water in recreational areas. The infectious dose is low, and person-to-person transmission does occur.[51] In 2016, 52 state and regional public health laboratories reported 5441 cases of culture-confirmed STEC infections. Compared with 2015, the incidence of both STEC O157 and non-O157 infections in 2016 was higher (9% and 15% increase respectively).[52]

HUS, a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency, is a serious complication of EHEC infection and occurs in up to 15% of children with *E. coli* O157:H7.[51] The overall incidence of HUS caused by a diarrheal pathogen (usually STEC) is estimated to be 2.1 cases per 100,000 persons per year, with a peak incidence in children younger than 5 years old (6.1 cases per 100,000 per year). HUS typically develops as diarrhea is resolving, usually at 7 days but may be up to 3 weeks after the onset of the illness.[51] Patients often present with pallor, weakness, irritability, and oliguria or anuria. Patients with HUS can develop neurologic complications, such as seizures, coma, and cerebral vessel thrombosis. Approximately 50% of patients who have HUS will require dialysis, and 3% to 5% die. Indicators that may predict poor outcome for patients with HUS include white blood cell counts greater than 20,000, oliguria or anuria, normal or high hematocrits (≥10.8 g/dl), low sodium less than 128 mEq/L, or presence of a respiratory tract infection within 3 weeks of the diagnosis.[52-54]

A serious risk posed by hemorrhagic colitis is the rapid loss of fluids, which can cause electrolyte abnormalities and result in poor perfusion and end-organ damage. Patients should receive adequate amounts of intravenous (IV) fluids (or by mouth if able to take in enough) to restore intravascular volume (monitor urine output, capillary refill time, blood pressure, pulse, and mental status), and electrolyte abnormalities should be corrected. Fluids should be continued and ongoing losses replaced, with possible admission for ongoing treatment and monitoring of electrolytes, complete blood cell count, blood urea nitrogen (BUN), and creatinine. Evidence from a recent study suggests that patients with HUS who received early volume expansion (increase of body weight by 12.5%) had lower rates of central nervous system involvement, less need for dialysis or intensive care support, and fewer days of hospitalization. These patients also had significantly better long-term outcomes in renal and extrarenal sequale.[55]

Controversy continues to exist about the indications for antibiotic treatment of STEC infections due to a possible association with an increased risk of HUS. To date, there are no controlled trials to support or disprove this association with HUS and the most recently published observation studies found that at least some classes of antimicrobial agents were associated with HUS. Experts continue to advise not prescribing antibiotics for children with *E. coli* 0157 enteritis or a clinical picture strongly suggestive of STEC infection, because no benefit has been found from the use of antibiotics. See Tables 167.3 and 167.4 for presentation and associated characteristics and treatment recommendations for other *E. coli* infections.

Protozoa. Protozoa can also cause diarrhea in children but are responsible for less than 1% of all cases of acute infectious diarrhea in the United States (Tables 167.5 and 167.6). The most common protozoa causing diarrhea are *Cryptosporidium, Giardia intestinalis,* and *Entamoeba histolytica*.

Cryptosporidium hominis is the most common of the *Cryptosporidium* species to infect humans. The parasite is protected by an outer shell that allows it to survive outside the body for long periods of time and makes it very tolerant to chlorine disinfection. While this parasite

TABLE 167.5 Protozoa: Presentation and Associated Characteristics

	Who Affected	Incubation	How Spread	Length of Excretion	Abdominal Pain	Nausea/ Vomiting	Fever	Diarrhea Characteristics	Other Characteristics	Diagnostic Tests
Cryptosporidium hominis	All ages	3 to 14 days	Contaminated water; fecal-oral	Immunocompetent: up to 2 weeks Immunosuppressed: Months	±	+	±	Frequent, nonbloody, diarrhea	Fatigue, anorexia and weight loss	DFA for detection of oocysts in stool
Giardia intestinalis	1 to 9 years old	1 to 3 weeks	Fecal-oral, contaminated water or food	Weeks to months	++	+	–	Acute watery diarrhea; foul smelling, flatulence	Can be protracted, abdominal distention, anorexia; FTT, anemia	EIA and DFA tests available; EIA with high sensitivity and specificity
Entamoeba histolytica	Immigrants or visitors to endemic areas	2 to 4 weeks (few days to months)	Fecal-oral; contaminated food or water; sexual transmission	Can excrete for years if untreated	+	±	<½	Colitis to dysentery	Gradual onset of symptoms over 1 to 3 weeks; tenesmus; weigh loss is common	Trophozoites or cysts in stool; serial specimens often necessary; EIA commercially available

Key: ++, common; +, occurs; ±, variable; –, not common.
DFA, Direct fluorescent antibody; *EIA,* enzyme immunoassay; *FTT,* failure to thrive.
Data from: World Gastroenterology Organization. *World Gastroenterology Organization Global Guidelines: acute Diarrhea in Adults And Children: A Global Perspective*. Available at: www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english; and Kimberlin DW, Brady MIT, Jackson MA, Long SS, editors. *Red Book: 2018-2021 Report of the Committee on Infectious Disease*, ed 31. Itasca, IL: American Academy of Pediatrics; 2018.

TABLE 167.6 Treatment Recommendations for Common Protozoa Causing Infectious Diarrhea in Children

	Treatment Routinely Recommended	When Treatment Indicated—High-Risk Groups	Antibiotic Indicated	Comments
Cryptosporidium	Not for immunocompetent	If treat: Children >1 year old HIV-positive, organ transplant	Nitazoxanide for children 1 to 3 years old: 100 mg/dose every 12 hours for 3 days 4 to 11 years old: 200 mg q12h x3 days >12yo: 500mg Q12H x3 days	
Giardia intestinalis	Yes	Most require treatment Children >1 year old Children ≥3 years old	Oral: Metronidazole 15–30 mg/kg/day divided every 8 hours for 5 to 10 days (maximum 250 mg /dose) Nitazoxanide: oral use same doses as for Cryptosporidium Tinidazole 50 mg/kg single dose (maximum 2 g/dose)	FDA has not approved of metronidazole for *Giardia* but is least expensive, poor palatability; not as effective as other 2. Symptom recurrence attributed to reinfection, lactose intolerance, immunosuppression, insufficient treatment or drug resistance Second course with same drug should be effective
Entamoeba histolytica	Yes	Asymptomatic excreters Mild to severe intestinal or extraintestinal disease	Oral: Drug of choice: Iodoquinol 30 to 40 mg/kg/day divided every 8 hours for 7 days (maximum 2 g) or Paromomycin 25 to 35 mg/kg/day divided every 8 hours for 7 days Drug of choice: Metronidazole 35 to 50 mg/kg/day divided every 8 hours for 7 to 10 days (max dose 750 mg/dose) or Tinidazole (>3 years old) 50 mg/kg/day for 3 days or 5 days for severe disease followed by Iodoquinol 30 to 40 mg/kg/day divided every 8 hours for 20 days (maximum 2 g) or Paromomycin (if no intestinal obstruction)(same dose as above)	Metronidazole is not effective against cysts. Do not give antimotility agents or corticosteroids Iodoquinol and paromomycin should be taken with meals

Data from: Kimberlin DW, Brady MIT, Jackson MA, Long SS, editors. *Red Book: 2018-2021 Report of the Committee on Infectious Disease*, ed 31. Itasca, IL: American Academy of Pediatrics; 2018; and Hughes HK, Kahl LK, editors. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*, ed 21. Philadelphia: Saunders; 2018.

can be spread in several different ways, water (drinking water and recreational) is the most common way to spread the parasite. In the United States, *Cryptosporidium* is a leading cause of waterborne disease among humans. In the immunocompromised patient, chronic, severe diarrhea can develop and result in malnutrition, dehydration, and death. Cryptosporidiosis should be considered in any patient with solid organ transplant or HIV with diarrhea. Cryptosporidiosis can lead to an increase in tacrolimus levels in transplant patients, leading to acute renal injury. Because shedding can be intermittent, at least three stool specimens collected on separate days should be examined before considering test results to be negative. Treatment is usually supportive. However, the U.S. Food and Drug Administration (FDA) has approved a 3-day course of nitazoxanide oral suspension for the treatment of immunocompetent children older than 1 year of age.[56]

Infection with *Giardia intestinalis* is limited to the small intestine and biliary tract. It is the most common intestinal parasitic infection of humans in the United States and globally. Asymptomatic infection is common. Humans are the main reservoir, although it has been found in the stool of dogs, cats, cattle, rodents, and other animals. These animals can contaminate water with stool containing cysts that are infectious for humans. Epidemics from person-to-person transmission occur in childcare centers and in institutions for people with developmental delay. Treatment includes correction of dehydration and electrolyte abnormalities and antibiotics. If therapy fails, a course can be repeated with the same drug. Relapse is common in the immunocompromised host, who often requires prolonged treatment. Patients with hypogammaglobinemia or lymphoproliferative disease are at higher risk of giardiasis and more difficult to treat. Patients with acquired immunodeficiency syndrome (AIDS) often respond to standard therapy. Treatment of asymptomatic carriers is not recommended except in households of patients with hypogammaglobinemia or cystic fibrosis.[57]

E. histolytica can be found worldwide but is more prevalent in the lower socioeconomic population and in developing countries, where the prevalence of amebic infection may be as high as 50% in some communities. In the United States, amebiasis is most common in people who have traveled to or immigrants from tropical places with poor sanitation, people who live in institutions with poor sanitary conditions, and men who have sex with men.[58] Symptoms can become chronic and may mimic inflammatory bowel disease. Complications include fulminant colitis, toxic megacolon, and ulceration of the colon and perianal area, rarely with perforation. Complications are more common in patients treated inappropriately with corticosteroids or antimotility drugs. Ultrasonography, computed tomography, and magnetic resonance imaging can identify liver abscesses and other extraintestinal sites of infection. Because complete eradication of intestinal infection is difficult, follow-up stool examination is recommended after completion of therapy. Asymptomatic household members with stools positive for *E. histolytica* should also be treated.[59]

See Tables 167.2, 167.3 and 167.5 for common signs and symptoms of the different viruses, bacteria, and protozoa.

Complications

The complications of acute diarrheal illness are reflected primarily in abnormalities of fluid, electrolytes, acid-base status, and systemic complications (bacteremia, osteomyelitis, polyarthritis, and HUS). Hypoglycemia and metabolic acidosis are common in younger children, yet manifested with nonspecific signs and symptoms, such as tachypnea and decreased activity. With severe illness or illness superimposed on underlying chronic conditions, children may present with weakness, lethargy, respiratory distress, shock, anuria, cardiac dysrhythmia, seizure, or coma. Children with early signs of shock (e.g., persistent tachycardia, hyperpnea, irritability, and lethargy) should have their intravascular volume restored before decompensation occurs.

Diagnostic Strategies

Acute diarrhea in children is usually a self-limited mild disease; it can, however, cause significant fluid and electrolyte abnormalities with serious consequences. Indications for medical evaluation of children with diarrhea have been proposed (Box 167.3). The principal goals of the ED evaluation are to identify and to correct fluid, electrolyte, acid-base, and nutrient deficits that may result from vomiting, diarrhea, or decreased oral intake, and to determine which children would benefit from admission.

Children who present with mild to moderate disease can often rehydrate orally and require no diagnostic testing. In children with moderate to severe dehydration from acute diarrhea (with or without vomiting) who require IV fluids, we recommend assessing serum electrolyte, bicarbonate, urea/creatinine, and glucose levels. Laboratory tests to estimate hydration status have been found helpful only when markedly abnormal, with no single test definitive for dehydration. Children who are critically ill or hemodynamically unstable should have intravenous/intraosseous hydration started immediately along with a finger-stick blood glucose and serum electrolytes.

Testing for fecal leukocytes may be useful to support a diagnosis of invasive disease and should be considered in children with diarrhea who are febrile or have mucus or blood in their stool. Many children with acute diarrhea caused by *Salmonella* or *Shigella* organisms will have fecal leukocytes in the stool. Fecal leukocytes are also found in patients with *Campylobacter*, *Y. enterocolitica,* invasive *E. coli,* and *V. parahaemolyticus*. Although a negative test does not rule out invasive disease, a positive test (more than five fecal leukocytes per high-power field) increases the likelihood of an invasive pathogen and should be followed with a stool culture.

BOX 167.3 Indications for Medical Evaluation of Children With Acute Diarrhea

- Young age (e.g., <6 months old or weight <8 kg)
- History of premature birth, chronic medical conditions, or concurrent illness
- Fever to ≥38°C for infants <3 months or ≥39°C for children 3 to 36 months old
- Visible blood or mucus in stool
- High output, including frequent and substantial volumes of diarrhea
- Persistent vomiting
- Caregiver's report of signs consistent with dehydration (e.g., sunken eyes or decreased tears, dry mucous membranes, or decreased urine output)
- Change in mental status (e.g., irritability, apathy, or lethargy)
- Suboptimal response to oral rehydration therapy (ORT) already administered or inability of the caregiver to administer ORT

Modified from: King CK, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52:1.

Stool culture is not indicated in most cases of uncomplicated AGE. Stool cultures should be obtained when needed to guide specific therapy, hospitalization, or infection control measures. We recommend stool cultures in patients with systemic involvement, underlying chronic medical conditions, dysenteric features, or a prolonged course (longer than 2 weeks). Many hospital laboratories do not include testing for *E. coli* O157:H7 or *Y. enterocolitica* in their routine stool culture, thus the emergency clinician should order these tests separately. According to the CDC, all stools submitted for testing for *Salmonella, Shigella,* and *Campylobacter* (routine stool culture) should be cultured for *E. coli* O157:H7. These stools should also be simultaneously assayed for non-O157 STEC with tests that detect the Shiga toxins or the genes encoding these toxins. In immunosuppressed patients, patients with chronic disease, infants younger than 3 months, or children with possible bacteremia or localized invasive disease, a complete blood count, stool studies, blood and urine cultures, chest x-ray, and lumbar puncture should be considered. For patients with more than 2 weeks of watery diarrhea, consider sending stool for enzyme-linked immunoassay for rotavirus; consider ova and parasites in those with a history of travel to an endemic area.

There is an increase use of culture-independent diagnostic tests for diagnosing intestinal infections: bacterial, viral, and protozoan. CIDTs work by detecting the presence of a specific antigen or genetic sequence of an organism. CIDTs do not require isolation or identification of living organisms. Consequently, these tests can be conducted more rapidly and yield results within a few hours. However, they do not produce bacterial isolates that are needed to distinguish between strains and subtypes of bacteria, information needed to detect and prevent outbreaks, track antibiotic resistance, monitor disease trends, and assess prevention measures. The CDC is encouraging clinical laboratories to do cultures when CIDTs are positive and considering ways to make follow-up cultures easier and cheaper for clinical laboratories. The CDC is encouraging companies to design their CIDTs in a way that keeps the bacteria alive so they can be cultured if the test is positive. The CDC is also adapting their surveillance systems, such as the Foodborne Disease Active Surveillance Network or FoodNet, to include infections diagnosed only by CIDTs.[60]

Differential Diagnoses

Most children with diarrhea or vomiting have a relatively benign cause of their illness, but more serious diagnoses should be considered and ruled out. A few disorders causing diarrhea may be life-threatening in children: intussusception, HUS, pseudomembranous colitis, appendicitis, toxic megacolon, and in very young infants, the congenital secretory diarrheas. See Tables 167.7 and 167.8 for other conditions that may cause vomiting and diarrhea.

Management

The American Academy of Pediatrics (AAP), The European Society of Pediatric Gastroenterology and Nutrition, and the WHO all recommend oral rehydration solution as the treatment of choice for children with mild to moderate dehydration (see the Dehydration section). In addition to fluid resuscitation, the priorities in ED management of children with diarrhea are to consider and rule out potential causes of diarrhea, assess for and treat underlying fluid and electrolyte deficits and potential complications, determine which patients require prolonged treatment or hospitalization, and arrive at a microbiologic diagnosis when indicated. Tables 167.4 and 167.6 list the common infectious agents of diarrhea and their recommended treatment.

Antibiotics are not needed in viral gastroenteritis or in most cases of uncomplicated bacterial gastroenteritis in healthy patients. Antibiotics are routinely recommended for *C. difficile, Giardia intestinalis,* and *E. histolytica* and can be considered in *Shigella, Campylobacter,* and

TABLE 167.7 Common Causes of Vomiting in Children

Etiologic Category	Clinical Syndromes
Central nervous system (CNS)	Infections, space-occupying lesion
Gastrointestinal	Obstruction, peritonitis, hepatitis, liver failure, appendicitis, pyloric stenosis, midgut volvulus, intussusception, inborn errors of metabolism
Drug	Ingestion, overdose, drug effect
Endocrine	Addisonian crisis, diabetic ketoacidosis, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis, renal failure, renal tubular acidosis
Cardiac	Congestive heart failure of any cause
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other	Psychogenic, respiratory insufficiency

TABLE 167.8 Common Causes of Diarrhea in Children

Etiologic Category	Clinical Syndromes
Gastrointestinal	Malabsorption (e.g., milk intolerance, excessive fruit juice), inflammatory bowel disease, irritable bowel syndrome, short gut syndrome
Drug	Ingestion, overdose, drug effect
Endocrine	Thyrotoxicosis, addisonian crisis, diabetic enteropathy, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other emergencies	Intussusception, appendicitis, hemolytic uremic syndrome (HUS), pseudomembranous colitis, toxic megacolon, and in very young infants, the congenital secretory diarrheas
Other	Parental anxiety, chronic nonspecific diarrhea

Cryptosporidium. Premature babies (younger than 1 year old), neonates, young infants, and patients with immunosuppression, chronic diseases, and articular or valve prostheses are at increased risk for developing complications from pathogens causing acute diarrhea (e.g., bacteremia, sepsis, invasive disease, extraintestinal disease). Antibiotics should be considered in these populations based on severity of presentation and in consultation with appropriate specialists (e.g., pediatric infectious disease specialist, pediatric oncologist, or pediatric cardiologist). Children with bloody diarrhea are at higher risk for complications, including sepsis and other systemic diseases, and should be considered for admission. In the majority of cases, empirical antimicrobial agents should not be administered while awaiting culture results. Antimicrobial therapy may not be indicated, even when culture results are positive, and antibiotics may increase the risk for developing HUS if the offending agent is STEC.[61] For severe watery diarrhea in a traveler to a developing country, azithromycin or a fluoroquinolone may be considered.[51]

Antidiarrheal compounds that impair gastrointestinal motility, such as loperamide (Imodium), diphenoxylate, and atropine (Lomotil), can prolong and exacerbate disease and have no role in the treatment of acute infectious diarrhea in young children. These agents may also cause lethargy, paralytic ileus, toxic megacolon, CNS depression, coma, and even death.[61]

Probiotics have been studied extensively over the past several years for the treatment of acute infectious diarrhea. Studies done in the past showed that probiotics, especially *Lactobacillus rhamnosus* (LGG), decrease the duration of diarrhea by approximately one day. Recent studies evaluating specific probiotics (i.e., *Lactobacillus reuteri*,[62] *Lactobacillus casei* variety rhamnosus,[63] and *Bifidobacterium lactis*64) found a modest decrease in duration, frequency of diarrhea, and length of hospital stay in patients with acute infectious diarrhea. The European Society of Gastroenterology, Hepatology, and Nutrition recommend that only LGG and *S. boulardii* be considered in the treatment of AGE in children as an adjunct to oral rehydrating solution.[65] Recommendations for children in the Asia–Pacific region have also strongly supported the use of LGG and *S. boulardii* as adjunct treatments to oral rehydration therapy for gastroenteritis.[66] However, the PECARN Probiotic Study Group recently published a large prospective, randomized, double-blind trial involving over 900 children 3 months to 4 years of age with acute gastroenteritis. They found that the children receiving LGG did not benefit with respect to the duration or frequency of vomiting or diarrhea, the rate of household transmission, or the duration of day-care or work absenteeism.[67] No studies have found any significant side effects in probiotics used in otherwise healthy children. However, it is recommended that caution be used for premature infants, immunocompromised and critically ill patients, and those with central venous catheters, cardiac valvular disease, and short–gut syndrome.[66] Further research is needed to establish efficacy, safety, and dosing of probiotics for children with acute infectious diarrhea.

Zinc deficiency is common in developing countries and occurs in most parts of Latin America, Africa, the Middle East, and south Asia. During the past 10 to 15 years, studies have shown that zinc supplementation given to children living in developing countries has decreased the duration and severity of diarrhea illness. A recent Cochrane review of 33 published studies including over 10,000 children found zinc supplementation may be effective in reducing the duration of diarrhea in children older than 6 months in areas where zinc deficiency and moderate malnutrition are prevalent.[68] The WHO recommends zinc supplementation (10 to 20 mg/day for 10 to 14 days) for all children younger than 5 years old with AGE, although few data exist to support this recommendation for children in developed countries.

Disposition

Most cases of childhood diarrhea can be managed on an outpatient basis by continuing breastfeeding, routine formula, or diet specific for age. Supplemental maintenance electrolyte solutions may be given or recommended to purchase over the counter. Before discharge from the ED, careful and specific instruction about the signs and symptoms of expected improvement or complications should be given to the parents or caregiver. Instructions should address proper hygiene and handwashing techniques to prevent others from contracting the illness. Follow-up by the patient's primary care physician should be timely and address concerns of worsening of the condition and potential complications. Hospitalization should be considered in children at high risk for complications: infants, especially those younger than 3 months old; very-low-birth-weight infants; children with chronic medical problems; children with electrolyte abnormalities who require IV repletion; children with severe dehydration; and children with dysentery. Hospitalization may also be warranted in cases of protracted vomiting, diarrhea with losses in excess of fluid administration, worsening clinical status despite therapy, presence of an underlying condition that would complicate therapy, or suspected systemic involvement. Very-low-birth-weight infants, because of low physiologic reserve and immature immune system, are at the highest risk for complications of AGE in the first year of life.

TABLE 167.9 Isonatremic, Hyponatremic, and Hypernatremic Volume Depletion

Volume Depletion Type	Sodium and Water Balance	Pathologic Causes	Fluid Shifts	Osmotic CNS Complications
Isonatremic (Na 130–150 mEq/L)	Balanced loss of sodium and free water	GI fluid loss with or without replacement	None	None
Hyponatremic (Na <130 mEq/L)	Greater sodium loss	GI fluid loss with excess free water replacement, cerebral salt wasting, syndrome of inappropriate antidiuretic hormone (SIADH)	Shift to intracellular space; Depleted intravascular volume (appears more ill than history suggests)	Cerebral edema, seizures
Hypernatremic (Na >150 mEq/L)	Greater free water loss, associated with severe dehydration	GI losses with hypertonic fluid replacement or poor breastfeeding, excess insensible losses, diabetes insipidus	Shift to extracellular space; preserved intravascular volume (appears less ill than history suggests)	Cerebral dehydration (risk for bridging vein injury and thrombus)

CNS Complications From Rapid Correction	Skin Turgor on Exam	Management
None	Normal or tenting	Mild-moderate: oral rehydration therapy; severe: Rapid infusion of 20 ml/kg isotonic saline to restore perfusion, then oral rehydration therapy or maintenance IV fluid to resolve fluid loss
Osmotic demyelination syndrome (central pontine myelinolysis)	Tenting	Rapid infusion of 20 mL/kg isotonic saline to restore perfusion, then correction of sodium over 24–48 hours, avoid correction >10 mEq/L/day
Cerebral edema	Doughy	Rapid infusion of 20 mL/kg isotonic saline to restore perfusion, then correction of sodium over 24–48 hours, avoid correction >10 mEq/L/day

DEHYDRATION

Foundations

Anatomy and Physiology

The average adult male and female bodies are comprised of approximately 60% and 50% water, respectively. Total body water is divided between the extracellular (one-third) and intracellular compartments (two-thirds). The extracellular compartment is further divided into interstitial fluid (three-quarters) and plasma (one-quarter). Interstitial fluid serves as a reservoir to replenish intravascular plasma volume in hypovolemia. Water makes up over 70% of an infant's total body weight; the majority of this "extra" fluid resides in the extracellular compartment. Because infants excrete far more water than adults per body weight (100 mL/kg versus 40 mL/kg daily), they require far more water per body weight to maintain homeostasis. As a result, infants and children are more vulnerable to rapid volume depletion from decreased water intake or increased output.

Pathophysiology

Volume depletion management and complications depends on serum sodium concentration (Table 167.9). The most common clinical presentation is isonatremic volume depletion with hypernatremic volume depletion being less common than isonatremic or hyponatremic volume depletion.

Metabolic acidosis often accompanies pediatric dehydration due to AGE through several mechanisms: bicarbonate loss in the stool, starvation causing ketone production, decreased tissue perfusion leading to anaerobic metabolism and lactic acid production, and decreased hydrogen ion excretion from poor renal perfusion. For the majority of patients, the acidosis is easily reversed by oral or parenteral volume replacement.

Clinical Features

The severity of dehydration is usually measured as the acute weight loss (presumably fluid loss) as a percentage of pre-illness total body weight.

TABLE 167.10 Clinical Assessment of Degree of Dehydration

	Mild (3% To 5%) (30 to 50 mL/kg)	Moderate (5% To 10%) (60 to 100 mL/kg)	Severe (>10%) (90 to 150 mL/kg)
Signs and Symptoms			
Dry mucous membrane	±	+	+
Reduced skin turgor (pinch retraction)	–	±	+
Depressed anterior fontanel	–	+	+
Mental status	Alert	Irritable	Lethargic
Sunken eyeballs	–	+	+
Hyperpnea	–	±	+
Hypotension (orthostatic)	–	±	+
Increased pulse	–	+	+
Capillary refill	<2 seconds	>2 seconds	>2 seconds

+, Present; –, absent; ±, variable.
Adapted from: Barkin RM, Rosen P. *Emergency Pediatrics*, ed 5. St Louis: Mosby; 1999.

Dehydration of 3% to 5% or more is considered significant and can often be identified by history and physical examination (Table 167.10). Because pre-illness weights are neither generally available nor reliably reported, the clinician should rely on historical information and physical examination findings to assess the severity of dehydration. Parental reports of decreased oral intake, urine output, and tear production are of significant value, with good sensitivity in detecting dehydration. In a child who is dehydrated, initial physical examination may reveal an

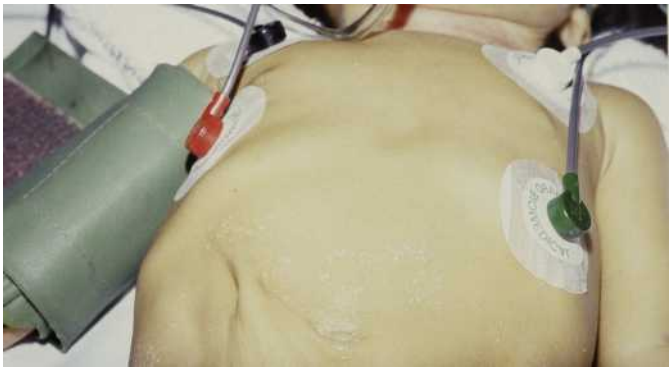

Fig. 167.1 Skin tenting. (Image courtesy of Dr. Stanley Inkelis.)

activity level lower than expected for age. The child may also appear weak or lethargic. If the fontanel is still open, it may be sunken. The eyes may appear sunken and the mucous membranes dry. However, if the child has recently had something to drink, the mucous membranes may falsely appear moist. Tachycardia and hyperpnea may be present. The skin over the trunk should be examined for tenting (Fig. 167.1; suggesting hyponatremia) or a doughy texture (suggesting hypernatremia). The three most useful signs to determine dehydration of more than 5% are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern. However, clinical signs and symptoms of dehydration are variable and often subtle and determining the severity of dehydration is an ongoing challenge for emergency clinicians. Because individual signs are often inadequate for accurately diagnosing dehydration and estimating severity, most recent research has focused on noninvasive methods of dehydration assessment, including clinical scoring systems, bedside ultrasound, and laboratory testing.[69]

Clinical scoring systems have been developed by combining historical features and examination findings in an effort to better predict the presence and severity of pediatric dehydration. The Clinical Dehydration Score (CDS) and the Gorelick scale (Table 167.11) are the most widely used and well-studied. In 2015, a meta-analysis found both the CDS and Gorelick scale improve diagnostic accuracy over unstructured clinician assessment. However, with only approximately 80% accuracy, neither can definitively rule in or out dehydration in infants and children.[69] Falszewska and colleagues analyzed a cohort of 118 patients hospitalized for dehydration with the CDS, Gorelick, and WHO scales in 2017 and found only the CDS to be useful only in ruling in (LR 3.9) moderate dehydration (>6 %).[70] This suggests that additional clinical tools are needed to aid in the diagnosis of dehydration.

Diagnostic Strategies

The role of point-of-care ultrasound (POCUS) in the assessment of volume depletion in children is uncertain. Inferior vena cava (IVC) collapsibility has not been shown to correlate with dehydration in pediatric patients. IVC to aorta diameter ratio was analyzed in a population of 771 children with diarrhea and dehydration in a resource-limited environment in Bangladesh by Modi and colleagues; they found it has an unacceptably low sensitivity (67%) and specificity (49%) for evaluation for severe dehydration.[71] Current research suggests that the POCUS measurement of the ratio of the areas of the aorta to the IVC correlate with clinical dehydration scores and that this ratio changes in response to rapid IV fluid administration.[72,73] Further research is required before this application can be recommended for routine evaluation of dehydration in pediatric patients.

Laboratory tests are of little diagnostic value in the mildly dehydrated child, but they may be helpful in the severely dehydrated or ill-appearing child to assess etiology, severity, and complications of dehydration. A serum electrolyte panel, BUN, serum creatinine, and blood glucose level are most likely to be clinically useful. Sodium concentration is important in identifying isonatremic, hyponatremic, and hypernatremic states for appropriate choice of therapy, but resuscitation and treatment should not be delayed for laboratory results. A low serum bicarbonate level may indicate bicarbonate loss in the stool or may reflect poor tissue perfusion. Children with dysentery, characterized by fever, bloody stools, and abdominal cramping, should have BUN and serum creatinine concentrations measured and stool culture specimens sent and examined for *E. coli* O157:H7 to identify potential cases of HUS. Serum glucose level is important because hypoglycemia is not uncommon in young children with AGE, and this test may help identify children with previously undiagnosed fatty acid oxidation disorders or other inborn errors of metabolism (e.g., galactosemia). Urine specific gravity and ketones are neither sensitive nor specific and should not be used in the assessment of pediatric dehydration.

TABLE 167.11 Clinical Dehydration Scale

	0	1	2
	0: No Dehydration (<3%)	**1–4: Some Dehydration (≥3% to 6%)**	**5–8: Moderate Dehydration (≥6%)**
General appearance	Normal	Thirsty, restless, or lethargic but irritable when touched	Drowsy, limp, old, sweaty, or comatose
Eyes	Normal	Slightly sunken	Very sunken
Mucous membranes	Moist	"Sticky"	Dry
Tears	Present	Decreased	Absent
	GORELICK SCALE		
	No or Minimal Dehydration	**Moderate to Severe Dehydration**	
General appearance	Alert	Restless, lethargic, unconscious	
Capillary refill	Normal	Prolonged or minimal	
Tears	Present	Absent	
Mucous membranes	Moist	Dry, very dry	
Eyes	Normal	Sunken, deeply sunken	
Breathing	Normal	Deep, rapid	
Quality of pulses	Normal	Thready, weak or impalpable	
Skin elasticity	Instant recoil	Slow recoil, recoil >2 seconds	
Heart rate	Normal	Tachycardia	
Urine output	Normal	Reduced	

Four-point scale (italics): Two signs or more ≥5%; three signs or more ≥10%.
Ten-point scale (including all): Three signs or more ≥5%; seven signs or more ≥10%.
Adapted from: Jauregui J, Nelson D, Choo E, et al. External validation and comparison of three pediatric clinical dehydration scales. *PLoS One*. 2014;9(5):e95739.

TABLE 167.12 Differential Diagnosis of Volume Depletion

Fluid Loss Category	Potential Etiologic Disorders or Conditions
Renal	Diuretics, renal tubular acidosis, renal failure, urinary tract obstruction, diabetes insipidus, diabetes mellitus, hypothyroidism, adrenal insufficiency, renal trauma, salt-wasting nephritis
Extrarenal	Third spacing (pancreatitis, peritonitis, sepsis), skin loss (burns, cystic fibrosis), lung loss, congestive heart failure, liver failure, hemorrhage

BOX 167.4 Principles of Appropriate Treatment of Children With Diarrhea and Dehydration

Oral rehydration solutions should be used for rehydration.
Oral rehydration should be performed as rapidly as possible.
Unrestricted diet is recommended as soon as dehydration is corrected.
For breast-fed infants, nursing should be continued.
For formula-fed infants, diluted formula is not recommended. Special formula is not necessary.
Additional oral rehydration solution should be administered for ongoing diarrheal losses.

Modified from: King CK, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52:1.

Differential Diagnoses

Most commonly, dehydration in children results from diarrhea and vomiting caused by infectious gastroenteritis. Table 167.12 lists some other causes of dehydration that should be considered when the gastrointestinal tract is not primarily involved.

Management

Oral Rehydration Therapy

Oral rehydration therapy (ORT) is a safe and effective treatment of infants and children with mild to moderate dehydration. ORT may be instituted even if the patient continues to vomit or has diarrhea. However, children with severe dehydration, shock, lethargy, acute abdomen, suspected intestinal obstruction, sodium derangement, or significant underlying illness should receive IV fluids. Some of these principles are illustrated in Box 167.4.

The ORT period in the ED may span 4 to 8 hours and provides an opportunity to educate the family in skills of evaluating and treating childhood diarrhea. A number of oral rehydration solutions have been shown to be effective. The main ingredients are water, glucose, sodium chloride, citrate, and bicarbonate in various concentrations. In most situations, rehydration can be accomplished without the risk of causing hyponatremia or hypernatremia. Polymer-based carbohydrate solutions (derived from wheat or rice) continue to be investigated as an alternative to glucose-based solutions. A Cochrane review in 2016 showed that patients treated with polymer-based solutions compared with high osmolarity solutions (>310 mOsm/L) had cessation of diarrhea sooner.[74] Their comparison of polymer-based solutions to low osmolarity solutions (<270 mOsm/L, which describes most current oral rehydration solutions) trended towards faster resolution of diarrhea, but the study was not powered sufficiently to demonstrate the effect. These data suggest that polymer-based and low osmolarity glucose solutions are both effective at treating mild to moderate dehydration.

In infants and children with minimal dehydration, treatment should be directed at maintaining hydration and nutrition with an age-appropriate diet. Freedman and colleagues showed that children age 6 months old to 60 months old with mild dehydration (CDS of 4 or less and with capillary refill < 2 seconds) from AGE given dilute apple juice in the ED and discharged with instructions for patient preference of hydration had significantly less treatment failure and less frequent need for IV fluids compared to children given oral rehydration solution in the ED and discharged with oral rehydration solution information.[75] This suggests that age-appropriate diet and fluids of patient preference is an effective alternative to oral rehydration solutions in patients with mild dehydration from AGE. Fluid intake should be increased, or oral rehydration can be administered to cover maintenance and to replace losses. Losses can be replaced at 10 mL/kg for each stool and 2 mL/kg for each emesis. Diet should not be restricted.

Children with mild to moderate dehydration should have their estimated fluid deficit replaced, often started in the ED and continued at home. The volume of ORT is calculated in the following manner:

1. Estimate the degree of volume depletion as mild or moderate with information from the history, clinical signs, and physical examination findings (see Tables 167.10 and 167.11).
2. Calculate the desired volume of oral rehydration solution as 30 to 50 mL/kg for mild (3% to 5%) and 60 to 80 mL/kg for moderate (6% to 9%) volume depletion.
3. Administer 25% of the volume of oral rehydration solution to be replaced each hour for the first 4 hours.
4. Replace ongoing losses at 10 mL/kg for each stool and 2 mL/kg for each emesis.
5. Monitor progress hourly and reevaluate frequently.

This technique requires that the ED have the facilities and personnel to observe and to monitor the patient for an extended time to determine the success or failure of ORT. The parent or other caregiver should be taught to administer ORT. Nursing personnel should instruct the parent in observation skills, methods of administration of the fluid, and types of fluid that are considered appropriate for children with vomiting and diarrhea. During the monitoring period, a child who is unable to tolerate intake of the prescribed volume of fluid at the expected rate should receive IV fluids. It is important to determine whether the failure is the result of the child's inability to ingest the fluid, excessive fluid loss through vomiting or diarrhea, or poor technique or motivation on the parent's part. It usually is possible to maintain the fluid administration rate in children who continue to vomit by administering small volumes frequently. This may require, for instance, use of a spoon or syringe to slowly drip the fluid by hand. Some success has been obtained with the use of nasogastric tubes; this method is often useful for prolonged fluid replacement in an inpatient setting, though its invasiveness limits its use.

The patient is reassessed at the end of the first few hours of ORT. If the clinical examination indicates adequate volume repletion, the child may be discharged home with further specific instructions for parents about maintenance fluid requirements with oral rehydration solution. If the child still exhibits mild or moderate volume depletion on clinical examination but no deterioration in status has occurred, another 2- to 4-hour trial may be warranted. If the child is unable to ingest the appropriate volume to keep up with ongoing losses, or if volume repletion is not adequate at the end of 8 hours, IV therapy and admission are recommended.

Ondansetron has become a useful adjunct in the treatment of AGE in the ED. Ondansetron, a selective 5-hydroxytryptamine type 3

receptor antagonist, acts at chemoreceptors in the peripheral and CNS to alleviate nausea. Ondansetron has been shown in a meta-analysis of numerous well-designed studies in children to reduce episodes of vomiting in the ED, improve oral intake in the ED, reduce the need for IV fluid rehydration, and reduce admissions.[76] Prescribing oral ondansetron for home use with good return precautions is safe in AGE, but multiple studies have shown it does not significantly change frequency of ED return visits.[77,78] Further research on patient-centered outcomes in this area is needed to evaluate the effectiveness of ondansetron prescriptions in outpatient management of dehydration.

Intravenous Therapy

Some dehydrated children brought to the ED may not qualify for ORT, and others may fail to improve with ORT. These patients include those with shock, severe dehydration, increasing deficit or clinical deterioration during ORT, intractable vomiting, hypoglycemia, or electrolyte derangements.

Patients are evaluated in accordance with their immediate (emergency phase), short-term (repletion phase), and long-term (early refeeding phase) needs.[79] During the *emergency* phase, the aim of fluid resuscitation is to restore circulatory volume. Fluid needs to be administered rapidly to prevent tissue hypoperfusion, end-organ damage, and death. During the *repletion* phase, fluid and electrolyte derangements are reversed, and ongoing losses are replaced. This phase lasts 24 hours. In the *early refeeding* phase, long-term needs are addressed in the next few days, during which the body recovers fluid, electrolyte, and nutritional homeostasis. Immediate and short-term therapies are initiated in the ED, with subsequent phases carried out in the inpatient setting or at home through the primary care physician. In clinical practice, this algorithm represents a continuum of care and not three separate phases.

Emergency Resuscitation Phase. Rapid reexpansion of the intravascular space is the goal of immediate resuscitation and can be achieved with an isotonic crystalloid solution. Administration of 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) intravenously at a rapid rate should result in reversal of signs of shock within 5 to 15 minutes. Avoid low sodium solutions such as lactated Ringers solution (Na 130 mEq/L) in isonatremic and hyponatremic volume depletion.[80] In critical situations, intraosseous routes should be used if venous access is not immediately available. Patients should be reevaluated periodically, and those with excessive deficits should receive repeated boluses of 20 mL/kg until clinical improvement occurs. Signs of recovery include normalization of blood pressure measurements, improvement of mental status, improvement of tachycardia and capillary refill time, and production of urine. Intravenous volume replacement greater than 60 mL/kg, without signs of improvement, warrants investigation for other conditions, such as cardiogenic shock, septic shock, hemorrhage, capillary leak with third-space fluid sequestration, adrenal insufficiency, and toxic shock.

A rapid determination of serum glucose is important. Children require glucose as an energy substrate and often have marginal stores available in illnesses. If the serum glucose concentration is low (<50 mg/dL), dextrose 0.25 to 0.5 g/kg should be rapidly administered intravenously or intraosseously. Glucose can be administered per the "rule of 50," whereby the percent dextrose multiplied by the number of mL per kilogram equals 50. For neonates, a 10% dextrose solution should be given at approximately 5 mL/kg. Children 1 month old to approximately 8 years old or 25 kg should be given 2 mL/kg of 25% dextrose. In children older than 2 years old, 1 mL/kg of 50% dextrose can be used. The higher tonicity 50% and 25% dextrose solutions have a risk of causing tissue necrosis if they extravasate during peripheral IV infusion. Ten percent dextrose is a safe and effective treatment for hypoglycemia in all ages, and it has a lower tonicity if there is concern for extravasation in a peripheral IV. Glucose levels should be monitored (every 30 to 60 minutes until stable) to ensure improvement and to identify ongoing needs. Repeated episodes of hypoglycemia should raise concern for sepsis, adrenal insufficiency, fatty acid oxidation defects, or other inborn errors of metabolism.

Dehydration due to AGE in children often leads to metabolic acidosis and ketosis, in part due to reduced carbohydrate intake leading to free fatty acid breakdown. It has been hypothesized that the addition of dextrose to initial IV rehydration fluids in moderately to severely dehydrated children will stimulate insulin release, reduce free fatty acid breakdown and ketone production, and reduce ketone-induced nausea and vomiting. A meta-analysis of two studies that had 333 pooled, randomized patients to IV solutions with and without glucose, found no difference in hospitalization rates or ED return visits.[81] Further research focusing on patient-oriented outcomes is needed to determine whether dextrose should be included in the optimal rehydration regimen for moderately to severely dehydrated children requiring IV hydration.

Repletion Phase. Appropriate fluid therapy for the patient should be determined after initial resuscitation. Some patients may tolerate ORT; others may require ongoing parenteral hydration with 5% dextrose in half-normal normal at a weight-appropriate maintenance volume (Table 167.13), compensating for ongoing losses (10 mL/kg and 2 mL/kg for each diarrhea and vomiting episode, respectively). Potassium may be added to maintenance fluids once urine output is established and serum potassium levels are within a normal range. Overly rapid correction of serum sodium levels can lead to osmotic demyelination syndrome (central pontine myelinolysis) in hyponatremia and cerebral edema in hypernatremia.[80] Neurologic status and serum sodium concentration should be closely monitored and the amount of sodium content of repletion fluid adjusted to maintain a slow correction. Ongoing sodium losses should also be replaced. In addition to oral, IV, intraosseous, and nasogastric routes of fluid delivery, hyaluronidase-facilitated subcutaneous hydration (hypodermoclysis) offers yet another alternative for treatment of dehydration. A small-gauge catheter is inserted in subcutaneous tissue in an area without local neurovascular structures (e.g., between scapulae, anterior chest, deltoid, anterior/lateral thigh) and 20 ml/kg isotonic crystalloid can be infused. Hyaluronidase (150 units subcutaneously, independent of age or weight) breaks down hyaluronic acid, a chief component of the extracellular matrix that holds body tissues together and expedites the subcutaneous infusion. Subcutaneous hydration can be performed without hyaluronidase at a significantly reduced rate, limiting its utility in the ED. Certain medications, such as ondansetron and other antiemetics, can be administered by this route.[82] Subcutaneous hydration should be considered in mildly to moderately dehydrated children who are unable to tolerate oral fluids and who have difficult IV access; patients with severe dehydration should be evaluated for intraosseous or IV access.

TABLE 167.13 Holliday-Segar Method for Maintenance IV Fluids

	MAINTENANCE RATE	
Body Weight	**mL/kg/day**	**mL/kg/hr**
First 10 kg	100	4
Second 10 kg	50	2
Each additional kg	20	1

Modified from: Nalley CM. Fluids and electrolytes. In: Hughes HK, Kahl LK, editors. *The Harriet Lane Handbook: A Manual for Pediatric House Officers,* ed 21. Philadelphia: Saunders; 2018: 290-315.

Hospital-Acquired Hyponatremia. IV rehydration can lead to hyponatremia in children. This rare complication can lead to significant neurologic morbidity, including seizures, coma, and brain herniation or even death; children receiving IV fluids should have their neurologic status closely monitored. AAP clinical practice guidelines recommend use of isotonic saline for maintenance IV fluids, except in patients with voluminous watery diarrhea; in these patients, providers should consider hypotonic maintenance fluids to treat persistent free water loss with higher than normal maintenance rates.[83]

Disposition

Children with severe dehydration, intractable vomiting, inability to maintain oral hydration, severe metabolic acidosis or sodium derangement, or whose caregivers are unable to provide adequate care at home should be hospitalized. Observation status is often suitable for severely dehydrated children showing signs of improvement during their ED course.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 167: QUESTIONS AND ANSWERS

1. For which of the following patients should the emergency clinician not obtain diagnostic testing of the stool?
   - **a.** 1-month-old with fever to 38°C with bloody diarrhea
   - **b.** 8-month-old with sickle cell disease with fever and diarrhea
   - **c.** 12-month-old, well-appearing child with 2 days of watery diarrhea
   - **d.** 2-year-old with nephrotic syndrome on prednisone with diarrhea and fever for 3 days
   - **e.** Community outbreak of diarrhea

   Answer: C. Most children with uncomplicated gastroenteritis or acute diarrhea do not need laboratory studies. Stool cultures are useful and important to obtain in febrile infants and children with blood in their stools, in community outbreaks, and in the immunosuppressed.

2. A 4-year-old child presents with moderate dehydration from gastroenteritis. He is still actively vomiting. Which of the following statements regarding this patient's rehydration is correct?
   - **a.** A nasogastric tube should be placed for rehydration.
   - **b.** Oral rehydration should not be started.
   - **c.** Oral rehydration success can be determined in 2 or 3 hours.
   - **d.** Oral rehydration target volume is 80 mL/kg.
   - **e.** Target oral rehydration volume should be administered over 2 hours.

   Answer: D. Oral rehydration can be effective even in the face of vomiting in cases of mild or moderate dehydration. Target oral volumes are 60 and 80 mL/kg, respectively. Nasogastric tubes may occasionally be useful but should not be used unless oral rehydration therapy (ORT) fails. The target oral volume should be given in doses of 25% of total replacement per hour over 4 hours.

3. A 9-year-old child with a history of sickle cell disease presents for evaluation of fevers, diarrhea, and vomiting. The parents say the patient has not had a sickle cell crisis in almost a year. On examination, the vital signs are stable and the child is nontoxic-appearing with mild dehydration. His abdominal examination is benign. In addition to rehydration, which of the following would be the most appropriate management and disposition for this child?
   - **a.** Obtain blood cultures and admit for observation.
   - **b.** Obtain cultures (stool and blood), begin antibiotics, continue hydration, and admit for observation.
   - **c.** Obtain electrolytes; and if he has a normal bicarbonate level, then discharge home.
   - **d.** Perform a stat Rotazyme assay; and if negative and patient tolerates oral intake, then discharge home.
   - **e.** Provide oral rehydration therapy (ORT); and if successful, then discharge home.

   Answer: B. Patients with sickle cell disease are more susceptible to *Salmonella* infections and are at increased risk for complications. It has been shown that giving antibiotics to patients with nontyphoidal *Salmonella* has been ineffective in shortening the duration of symptoms and prolonging the carrier state. Therefore, antibiotics are generally not recommended for asymptomatic cases or for uncomplicated cases. However, antibiotic treatment is indicated in infants younger than 3 months old or those with complications, such as failure to improve within 5 to 7 days; bacteremia; focal infection in the central nervous system (CNS), bone, joint, kidney, or pericardium; or those with immunosuppressive conditions, hemoglobinopathies, malignant neoplasms, human immunodeficiency virus (HIV), or chronic gastrointestinal disease. The recommended antibiotics are for unknown susceptibility or in areas of high resistance to use ceftriaxone or cefotaxime until susceptibility is known. Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) may also be effective, but they should be used only in high-risk individuals once susceptibility is known.

4. A 5-month-old infant presents with persistent vomiting and diarrhea for 3 days. The parents came to the emergency department because their child suddenly seemed to be passing out. Parents have noted significant weight loss and poor breastfeeding. Exam shows an unconscious infant with doughy skin and dry mucous membranes. IV access is obtained, the airway is secured, and a normal saline infusion is started. What central nervous system complication of dehydration is most likely in this patient?
   - **a.** Cerebral edema
   - **b.** Central pontine myelinolysis
   - **c.** Hypoxic ischemic encephalopathy
   - **d.** Primary epilepsy
   - **e.** Subdural hematoma

   Answer E: The clinical picture suggests hypernatremic dehydration (infant with poor breastfeeding, doughy skin, significant weight loss). Hypernatremia leads to dehydration and shrinking of the brain, which increases the risk of injury to bridging veins, subdural hematoma, and CNS thrombi. Cerebral edema is a complication of hyponatremic dehydration (more often in older children with skin tenting on examination). Central pontine myelinolysis is a complication of rapid sodium correction in hyponatremic dehydration. HIE and epilepsy are not complications of dehydration alone.

5. A 4-year-old girl presents with acute gastroenteritis. On history and examination the child has lost 12% of her weight from her last primary care appointment 3 weeks ago. She appears lethargic and has mottled skin with a capillary refill of 5 seconds. Multiple attempts at IV access are unsuccessful. What is the next best approach for rehydration?
   - **a.** Hypodermoclysis (subcutaneous rehydration)
   - **b.** Obtain intraosseous access
   - **c.** Oral ondansetron
   - **d.** Nasogastric tube insertion
   - **e.** Transfer to a pediatric tertiary hospital

   Answer B: Patients with severe dehydration (>10 % body weight loss) or evidence of decreased perfusion (poor capillary refill, lethargy) should have emergent infusion of isotonic crystalloid at a rapid rate to restore perfusion. In this patient, the fastest method to achieve this is with intraosseous access. In a conscious patient, the line can be primed with lidocaine for 1 to 2 minutes before the infusion to help with the pain of the infusion. Hypodermoclysis, nasogastric tube rehydration, and oral rehydration are all appropriate management options for mild-moderate dehydration. Transferring the patient before IV rehydration would delay her care and increase her mortality risk.

Pediatric Genitourinary and Renal Tract Disorders

Brittany Boswell and Anita A. Thomas

FOUNDATIONS

Genitourinary (GU) and renal tract emergencies in children are common. These issues span age and gender and have varying clinical presentations. Underlying pathology is due to both congenital and acquired disease. Careful history of present illness and family history can help guide a focused differential diagnosis. A complete physical is especially important in children who present with abdominal pain; in particular, a GU examination must be performed for any male that presents with abdominal pain because children may not be as forthright with GU complaints. The history and complete physical are key in guiding workup and management of renal and GU emergencies. This chapter outlines the most prevalent GU and renal disorders presenting to emergency clinicians.

SPECIFIC DISORDERS

Priapism

KEY CONCEPTS

- Ischemic priapism is a urologic emergency due to compartment syndrome of the penis and is managed with local analgesia with or without sedation, cavernosal aspiration, irrigation, and possibly injection with phenylephrine.

Foundations

Priapism is a pathologic painful penile erection, unrelated to sexual stimulation, lasting more than 4 hours. There are three types of priapism: low flow (ischemic), high flow (nonischemic), and stuttering (recurrent). Ischemic priapism is due to venous occlusion, leading to compartment syndrome of the penis, and is a *urologic emergency*. Nonischemic, or high flow priapism, is due to unregulated cavernosal blood flow, often due to trauma or arteriocavernous fistula, and is usually painless. In this subtype, oxygenation is preserved and can be managed conservatively. Lastly, stuttering priapism is due to recurrent episodes of ischemic priapism, lasting less than 4 hours. It is often self-limited, and primarily occurs in patients with sickle cell disease.

Clinical Features

Priapism is rare in pediatrics, although it may be underreported. It can occur at any age, even rarely, in the neonatal population.[1] Sickle cell disease accounts for 65% of all episodes of priapism occurring in children. Up to 89% of men with sickle cell disease have reported at least one episode of priapism before the age of twenty.[2] Patients present with painful rigidity of the corpus cavernosa and a soft glans (Fig. 168.1). Depending on the duration of the episode, one may see sequelae of ischemia such as erythema, other color change, or gangrenous appearance.

Differential Diagnoses

Priapism is a clinical diagnosis. The differential diagnosis of the underlying etiology is outlined in Table 168.1.[3] Laboratory testing can help determine an underlying etiology but is often not helpful in acute management. Complete blood count (CBC), reticulocyte count, and hemoglobin electrophoresis are useful in identifying undiagnosed sickle cell anemia. A cavernosal blood gas and color duplex ultrasonography can help differentiate the subtype of priapism.

Management

Determination of subtype and underlying etiology guide management of priapism. Ischemic priapism requires time-sensitive intervention. Conservative measures may be trialed in patients presenting before 4 hours: physical exercise, urination, and cold packs (except in sickle cell patients in which this may worsen priapism). In patients presenting after 4 hours, or in whom conservative measures have failed, additional treatment includes hydration, pain control, and local anesthesia. This should be followed with intracavernous irrigation of saline and injection of sympathomimetics to achieve detumescence. Various case reports have shown detumescence using procedural sedation alone with either ketamine or nitrous oxide.[4,5] A dorsal penile block with or without a ring block should be performed prior to intracavernous injection, using no more than 4 mg/kg of lidocaine without epinephrine (Fig. 168.2). After local anesthesia, corporal aspiration can be performed by using a 23- to 21-gauge butterfly needle in prepubescent males and a 19-gauge needle in adolescents; the needle should be inserted laterally, into the corpus cavernosum at 3 or 9 o'clock, avoiding the neurovascular bundle superiorly and the urethra inferiorly. Blood should be aspirated in 5 mL aliquots until it appears bright red followed by flush with 0.9% normal saline. A cavernosal blood gas can be sent using this sample. If detumescence is not achieved, the next step is intracavernosal injection of an alpha-adrenergic sympathomimetic agent, phenylephrine (100 mcg every 5 minutes, up to 1 hour.[6] If these measures fail, the patient should be considered for emergent urologic intervention with surgical shunt placement.

Contrary to ischemic priapism, management of stuttering and nonischemic priapism is not urgent, as many cases resolve spontaneously. Ultrasound may identify a fistula that may require arterial embolization or surgical ligation.[7]

Disposition

With successful detumescence, patients may be discharged home with close follow-up. Those who require ongoing injections of phenylephrine will likely need admission, especially if they have cardiac history. Patients who fail injection and require surgery should receive emergent urologic consultation and admission.

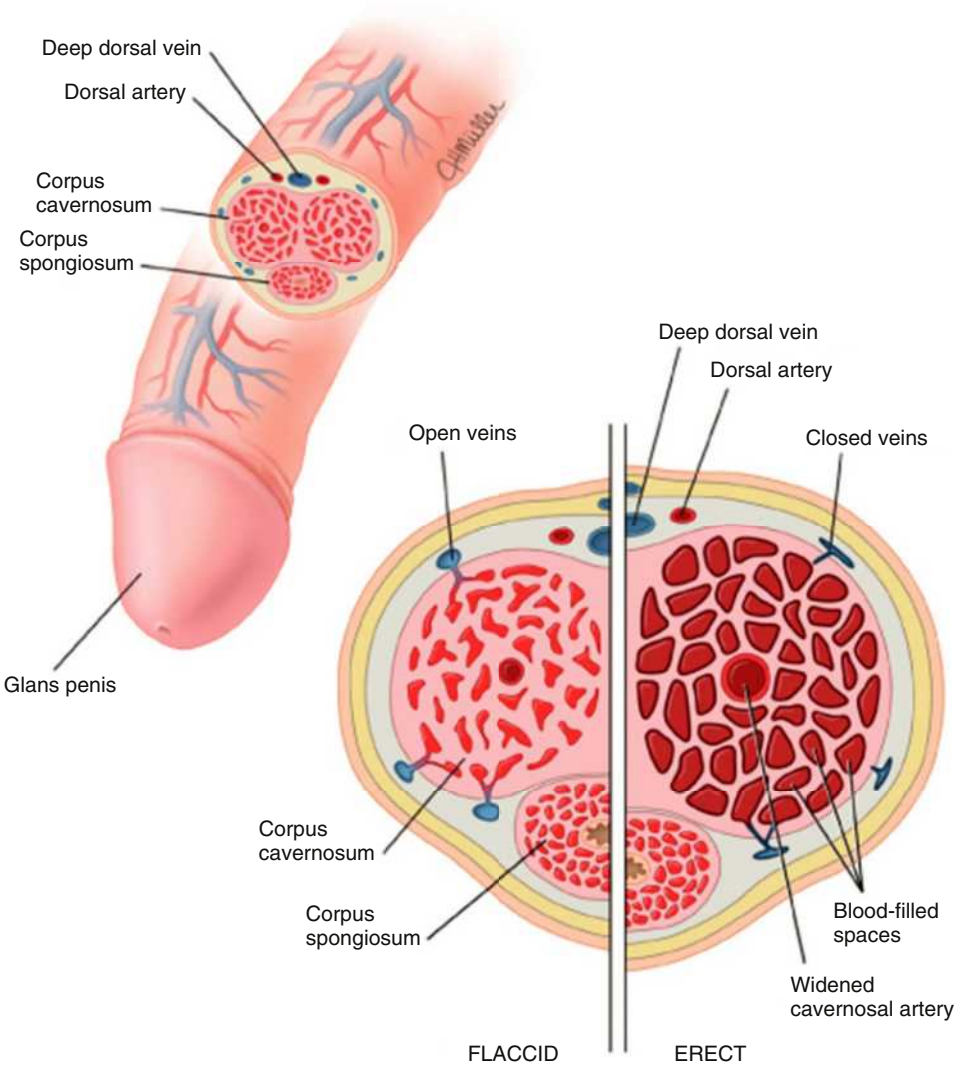

Fig. 168.1 Anatomy of the penis. (Reproduced with permission from: Field JJ, Vemulakonda VM, DeBaun MR. *Diagnosis and management of priapism in sickle cell disease*. www.uptodate.com/contents/diagnosis-and-management-of-priapism-in-sickle-cell-disease.)

TABLE 168.1 Differential Diagnosis of the Underlying Etiology of Priapism

Ischemic	Nonischemic	Medication Induced	Neonatal
Hemoglobinopathy (SCD, thalassemia)	Trauma	PDE 5 inhibitor	Polycythemia
Leukemia	Hematologic (SCD, leukemia)	Hormone (testosterone)	Infection
Infection	Fabry disease	Antipsychotic	Forceps assisted delivery
Neurogenic	Iatrogenic (surgery)	Antidepressant	Respiratory distress syndrome
Toxin (scorpion, spider)		Antihypertensives	UAC manipulation
Henoch-Schönlein purpura		Alcohol, cocaine, marijuana	

Phimosis

KEY CONCEPTS

- Phimosis is usually physiologic, but is pathologic when associated with urinary retention, urinary tract infections, or balanoposthitis.

Foundations

Phimosis is a clinical diagnosis and defined as the inability to fully retract the prepuce beyond the glans penis. Parents or patients may describe a "balloon appearance" of the foreskin with urination. The majority of phimosis cases are physiologic. The ability to retract the prepuce increases with age, with 50% resolving by age one and 89% by age three.[8] Phimosis is pathologic when it leads to balanoposthitis, urinary tract infections (UTI), or urinary retention.

Diagnostic Testing

Asymptomatic patients do not require further workup, but those with pain on urination should have a urinalysis (UA) and culture to evaluate for urinary tract infection.

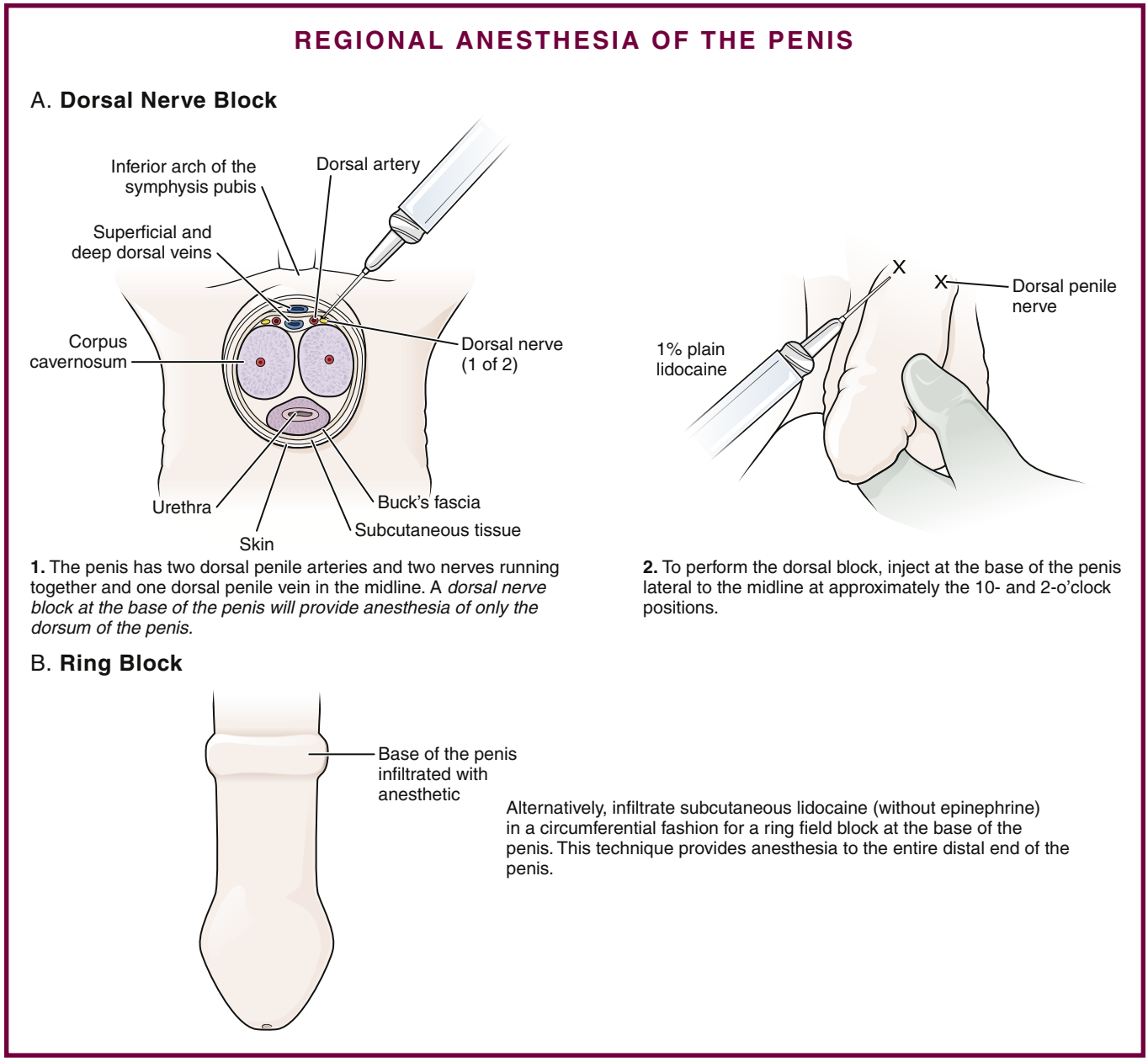

Fig. 168.2 Penile analgesia. (From: Davis JE, Silverman MA. Urologic procedures. In: Roberts JR, Custalow CB, editors. *Roberts and Hedges' Clinical Procedures in Emergency Medicine.* Philadelphia: Elsevier Saunders; 2014: 1113-1154.)

Management

Management of phimosis is conservative in most cases, but ongoing issues may require circumcision for definitive treatment. There is no general consensus among urologists on the care of phimosis.[9] Parents should be instructed on general hygiene measures of the uncircumcised penis and may practice gentle retraction beginning at 2 years of age. If there are minor recurrent issues with hygiene, infection, or urination, a course of 1% topical hydrocortisone or 0.1% topical triamcinolone applied BID for up to 12 weeks have similar rates of phimosis resolution.[8]

Disposition

Those with chronic UTIs, balanoposthitis, or issues with urination should be referred to urology for circumcision consideration. Patients who are able to urinate and have a reassuring physical examination can be managed as outpatients with primary care or urologic follow-up.

Paraphimosis

KEY CONCEPTS

- Paraphimosis is a urologic emergency wherein the foreskin of the penis is trapped at the corona, resulting in venous congestion and vascular compromise.

Foundations

Paraphimosis is a urologic emergency, wherein the foreskin of the penis is trapped behind the glans at the corona, resulting in engorgement,

Fig. 168.3 Paraphimosis in a 4-year-old uncircumcised boy. (Courtesy Dr. Marianne Gausche-Hill.)

venous congestion, and vascular compromise. If left untreated, venous congestion and arterial compromise can lead to distal ischemia and even necrosis of the penis.

Clinical Features

History may reveal a recent penile examination, Foley catheter placement, parental attempts at hygiene, trauma, or recent sexual intercourse. This occurs more commonly in the uncircumcised male, but circumcised individuals who have excessive foreskin can develop paraphimosis. On examination, patients present with painful swelling of the penis with foreskin visibly retracted behind the glans. Any discoloration may indicate ischemia and compromised blood supply (Fig. 168.3).

Diagnostic Testing

The diagnosis is clinical, based on history and physical examination, and there is no role for blood work or imaging. The penis should be inspected for hair tourniquet, which can mimic symptoms of paraphimosis.

Management

Management is directed at replacing the foreskin back over the glans penis. In uncomplicated cases, the foreskin can be manually reduced. Ice packs are useful in decreasing edema but could worsen already compromised penile arterial flow. With manual reduction, gentle pressure is applied for 5 to 10 minutes, either by hand or with compression bandages. After applying pressure to reduce the edema, the provider should use two thumbs to gently press the glans, while pulling the foreskin into place (Fig. 168.4). Osmotic methods with sugar or 20% mannitol-soaked gauze can reduce edema prior to manual reduction.

If manual reduction is not successful, analgesia with dorsal penile block and procedural sedation may be required to facilitate the procedure. If unsuccessful, a dorsal slit may be required, using two clamps at the foreskin at 12 o'clock followed by an incision to release the constriction.[10] Ultimately, surgical circumcision by a urologist may be required.

Disposition

Patients with uncomplicated cases that are manually reduced can be discharged home with outpatient follow-up. The foreskin should be inspected for any abrasions, which should be treated with topical bacitracin if found. Patients should not retract the foreskin for a week to avoid recurrence. Patients should be evaluated for need for definitive treatment with circumcision by urology. Patients with ischemia or necrosis should be admitted for pain control, antibiotics, and further care by urology.

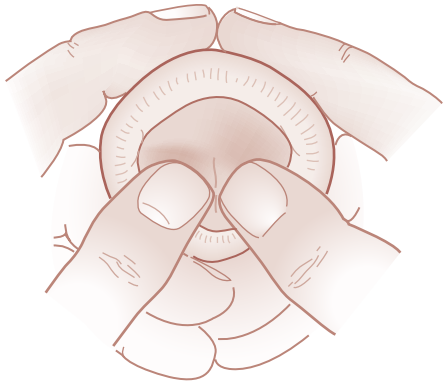

Fig. 168.4 Paraphimosis reduction. (Courtesy P.P. Kelalis.)

Balanoposthitis

KEY CONCEPTS

- Inflammation of both the glans (balanitis) and foreskin (posthitis) is usually due to poor hygiene.

Foundations

Balanoposthitis is the inflammation of both the glans (balanitis) and foreskin (posthitis) of the penis, and is most common in young uncircumcised males. In pediatrics, the majority of cases are due to poor hygiene, with accumulated sebaceous material leading to bacterial or fungal overgrowth; however, there are also other infectious (fungal, bacterial, HPV, STIs) and noninfectious (contact dermatitis, chemical irritant, trauma) etiologies to consider.[11]

Patients present with localized pain, erythema, and sometimes dysuria due to local irritation. Penile discharge, rash, or lymphadenopathy raises suspicion for a sexually transmitted infection, such as *Neisseria gonorrhea* or *Chlamydia*, whereas oral ulcerations or arthralgias may point to a rheumatologic etiology, such as psoriasis or lichen sclerosis. The foreskin should be assessed for concomitant phimosis or paraphimosis.

Clinical Features and Diagnostic Testing

The diagnosis of balanoposthitis is clinical, based on history and physical examination. Additional evaluation for patients with dysuria, discharge, extragenital findings, or recurrent balanitis may include UA, STI testing, or glucose (to assess for diabetes in recurrent candidal balanitis).

Management

Management of balanoposthitis is mainly supportive and directed at adequate hygiene measures. Parents and teenagers should be educated on hygiene and care of the uncircumcised penis. Teenagers should also be provided with education on safe sex practices. Treatment should include coverage for both bacterial and fungal overgrowth, with topical bacitracin and topical nystatin (or clotrimazole), respectively. Inflammation can be managed with 0.5% hydrocortisone cream twice daily. In the event of overlying mild cellulitis, patients should be prescribed cephalexin, 25 to 50 mg/kg/day in divided doses for seven days.

Disposition

We recommend that children who are unable to urinate, have signs of systemic illness (e.g., fever), or evidence of more than a mild cellulitis be admitted for IV antibiotics and receive consultation from a urologist.

Complications of Circumcisions

KEY CONCEPTS

- Complications of circumcisions are rare, and most commonly involve minor bleeding.

Foundations

At times a controversial topic, circumcision rates are approximately 38% worldwide.[12] The most recent American Academy of Pediatrics Task Force Recommendations in 2012 concluded that there are lifelong benefits to circumcision that outweigh the risks of the procedure itself.[13] The rate of adverse events from circumcision is low at 1% to 4%.[12]

Management

The major postoperative circumcision complication is bleeding, which may reveal an underlying coagulopathy. Coagulants such as topical thrombin and local pressure should be applied to the circumcised area;[14] patients with a bleeding diathesis may warrant a hemoglobin check and coagulopathy studies, as well as fresh frozen plasma (FFP) or factor replacement. Urgent urologic consultation may be required.

Other immediate postoperative complaints include pain, concern for infection, or extremely rarely, a more severe injury to the penis. Pain usually self-resolves and should not require intervention; if a child is older than 6 months, nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen may be trialed. As the circumcision dressing can contribute to urinary retention, patients are predisposed to a urinary tract infection. Those with symptoms should have a UA sent. Systemic infection is uncommon, but in the neonatal period may require a full septic workup with blood work, urine, and cerebrospinal fluid (CSF) studies. Delayed presentation may indicate postoperative adhesions or meatal stenosis. Adhesions or meatal stenosis require outpatient urology follow-up and potential repeat circumcision at a later date.

Penile Entrapment and Tourniquet Injuries

KEY CONCEPTS

- Foreskin injuries occur in pediatrics, and the goal is removal of the offending object to prevent further tissue damage.

Foundations

Penile injuries due to entrapment or hair tourniquet may present from childhood to adolescence and can result in neurovascular damage. Metallic rings used to improve sexual activity are placed by the patient, whereas zippers or hair are the result of accidental entrapment. These objects create damage by reducing vascular supply to the penis and can become a urologic emergency.[15]

Clinical Features and Diagnostic Testing

The patient will present with pain and swelling of penis. In the event of a hair tourniquet, the hair itself may be difficult to visualize. This does not require any lab testing or imaging, unless there is concern for underlying urethral injury, in which case a retrograde urethrogram may be required along with urology consult.

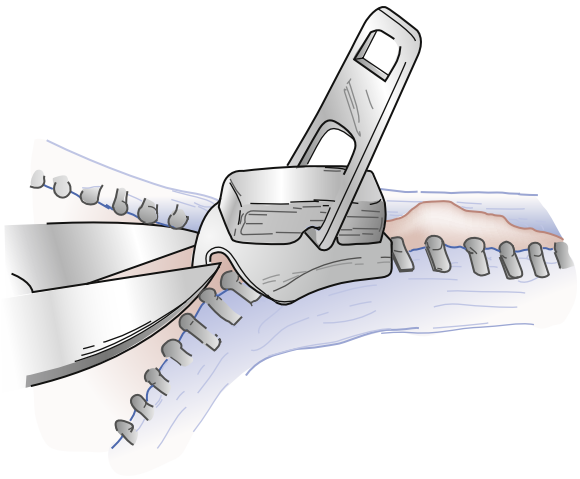

Fig. 168.5 Release of zipper entrapment by cutting of the median bar. (From: Snyder HM III, et al. Genitourinary trauma. In: Fleisher GR, Ludwig S, editors. *Textbook of Pediatric Emergency Medicine*, ed 4. Philadelphia: Lippincott Williams & Wilkins; 2000.)

Management

Management depends on the offending agent. Nonmetallic objects can be cut off with ring cutters or a saw, while using cooling agents to avoid burns to the skin.[15] Hair can be removed using a hair removal cream or by direct visualization and cutting the hair. Depending on the amount of edema, one may need to apply ice or compression before attempting removal. Pain control using a penile block will facilitate manipulation and removal of an object.

In the event of zipper entrapment, the zipper should be removed to free the foreskin from entrapment. There are 5 common methods to remove a zipper from the genitals: cutting the median bar with bone or wire cutters (Fig. 168.5); using a screwdriver to separate the teeth; application of mineral oil as lubricant; lateral compression of the fastener with pliers; and removal of the teeth with trauma sheers.[16] The cloth of the zipper should be cut close to the zipper teeth, which should release the underlying skin. Upon release, the underlying tissue may be damaged. If these techniques are unsuccessful, urology should be consulted for surgical intervention with circumcision as the last option.

Disposition

Most of these cases do not require surgical intervention and can be discharged home after the removal of the offending agent.

Epididymitis and Orchitis

KEY CONCEPTS

- Epididymitis is acute pain and swelling of the epididymis, lasting less than 6 weeks.
- Treatment of epididymitis is based on age and probability of underlying infection.
- Orchitis is pain and swelling of the testicle and is usually viral.

Foundations

Acute epididymitis is pain and swelling of the epididymis lasting less than 6 weeks, whereas orchitis is pain and swelling of the entire testicle. The etiology of the inflammation in epididymitis is due to infectious and noninfectious causes. Infectious causes vary by age of presentation. The most common cause in prepubescent males is viral infections. Adolescents may get epididymitis from *N. gonorrhoeae* or *C.*

trachomatis; other bacterial causes in this age group may be related to structural anomalies of the urinary tract.[17] Noninfectious causes may be due to a vasculitis (e.g., in Henoch-Schönlein purpura, see later), chemical irritation, or trauma. Orchitis is usually the result of bacterial or viral infection and is classically associated with mumps.

Clinical Features

Patients present with scrotal pain and swelling, with tenderness on physical examination. Patients may complain of nausea, vomiting, or referred abdominal pain. Urethral discharge may indicate a sexually transmitted infection (STI). Cremasteric reflexes should be intact, and one may see relief of pain with scrotal elevation (Prehn sign), although these elements *do not* rule out testicular torsion. Those with mumps may also present with viral symptoms, as well as lymphadenopathy and parotid gland swelling. Differential diagnosis should include epididymitis, orchitis, testicular torsion and torsion of the appendix testis, inguinal hernia, hydrocele, and varicocele.

Diagnostic Testing

Though the diagnoses of epididymitis and orchitis are clinical, UA and culture should be obtained to evaluate for pyuria. STI testing should be considered for all adolescents and those who are sexually active. Ultrasound (US) should be obtained in cases where testicular torsion is considered possible. US may show increased vascular flow to the epididymis. Patients with bacterial orchitis may rarely get a scrotal abscess, which would also be detected on ultrasound.

Management

Management of epididymitis and orchitis includes supportive care with analgesia, ice packs, and scrotal elevation. If there is concern for gonococcal STI, patients should be empirically treated with 500 mg IM ceftriaxone for patients <150 kg. If there is concern for chlamydial STI, treatment is with either doxycycline 100 mg PO BID for 7 days or azithromycin 1 g PO once.[18] Those with UA evidence of UTI should be treated for a complicated UTI according to local sensitivity patterns for *E. coli*. Scrotal abscess should receive antibiotics and consultation with urology.

Disposition

Most patients with uncomplicated epididymitis or orchitis can be discharged home with outpatient follow-up.

Testicular Torsion

KEY CONCEPTS

- Testicular torsion is a urologic emergency treated by detorsing the testis.
- Patients with classic symptoms and signs of testicular torsion should have an emergent urologic consultation for operative management.

Foundations

Testicular torsion is a urologic emergency associated with acute onset of scrotal pain. Testicular torsion should always be considered in acute scrotal pain, as delayed diagnosis can lead to loss of viability of testicular tissue and potentially loss of spermatogenesis. Testicular torsion can occur at any age, but in particular, has peaks in the neonatal and adolescent periods. Testicular salvage rates depend on time to presentation, as well as time to surgical intervention, with increased orchiectomy rates when blood flow is not restored within 6 hours of symptom onset.[19]

Testicular torsion can occur within the tunica vaginalis (i.e., intravaginally), constricting arterial blood flow, or within the scrotum (i.e., extravaginally). If there is inadequate fixation of the testicle, in which the tunica vaginalis completely covers the testis superior to the spermatic cord, this "bell clapper" deformity predisposes to torsion (Fig. 168.6). Other risk factors include cryptorchidism, trauma, familial history, or prior episodes.

Clinical Features

Patients with testicular torsion usually present with acute onset unilateral scrotal pain and edema, often associated with nausea and vomiting. Pain may radiate to the abdomen, and children may be embarrassed to note genital complaints; thus, even without a testicular complaint, a complete GU examination should be performed. Patients may have a high-riding, transverse, swollen testicle, with possible discoloration, and lack of cremasteric reflex on the affected side, though a normal cremasteric reflex *does not* rule out torsion.

Differential Diagnoses

Differential diagnosis includes torsion of the testicular appendage, which presents similarly, but usually occurs in prepubescent males with a more indolent course and less intense pain at the superior pole of the testis. Other considerations include orchitis, epididymitis, trauma, hydrocele, varicocele, inguinal hernias, or testicular tumors.

Diagnostic Testing

Testicular torsion is a clinical diagnosis, but scrotal ultrasound with Doppler can confirm the diagnosis when the testis is torsed. A UA may show hematuria or leukocytosis, which would be more indicative of epididymitis or orchitis. Doppler ultrasound may show decreased perfusion to the testicle or twisting of the spermatic cord.

Management

Urology should be consulted emergently for definitive surgical management. Once testicular torsion is confirmed, management requires surgical detorsion on the affected side, with either orchiopexy or orchiectomy if the testicle is not viable. Time to the operating room is directly related to testicular salvage, with less than 6 hours as most optimal.[19]

In the event of surgical delay, a bedside manual detorsion under analgesia can be attempted after discussion with urology. Because most torsion occurs medially, the testicle is rotated in an "open book" fashion, laterally until detorsion has occurred.[20] However, a small percentage of cases do torse laterally, so this maneuver could worsen symptoms in those cases. If manual detorsion fails, surgical management is warranted. For suspected testicular torsion that has detorsed and has normal findings or high flow (i.e., from reperfusion) on ultrasound, we recommend urology be consulted and surgery be considered to prevent recurrence.

Varicocele and Hydrocele

KEY CONCEPTS

- Consider reactive hydroceles in the setting of epididymitis, orchitis, testicular torsion, or testicular tumors.
- Consider abdominal mass or renal vein thrombosis in the event of right-sided varicocele.

Foundations

Painless scrotal swelling in children may occur secondary to a hydrocele or varicocele. A hydrocele occurs when peritoneal fluid accumulates within the tunica vaginalis; hydroceles are either communicating or noncommunicating with the peritoneal cavity. Hydroceles commonly

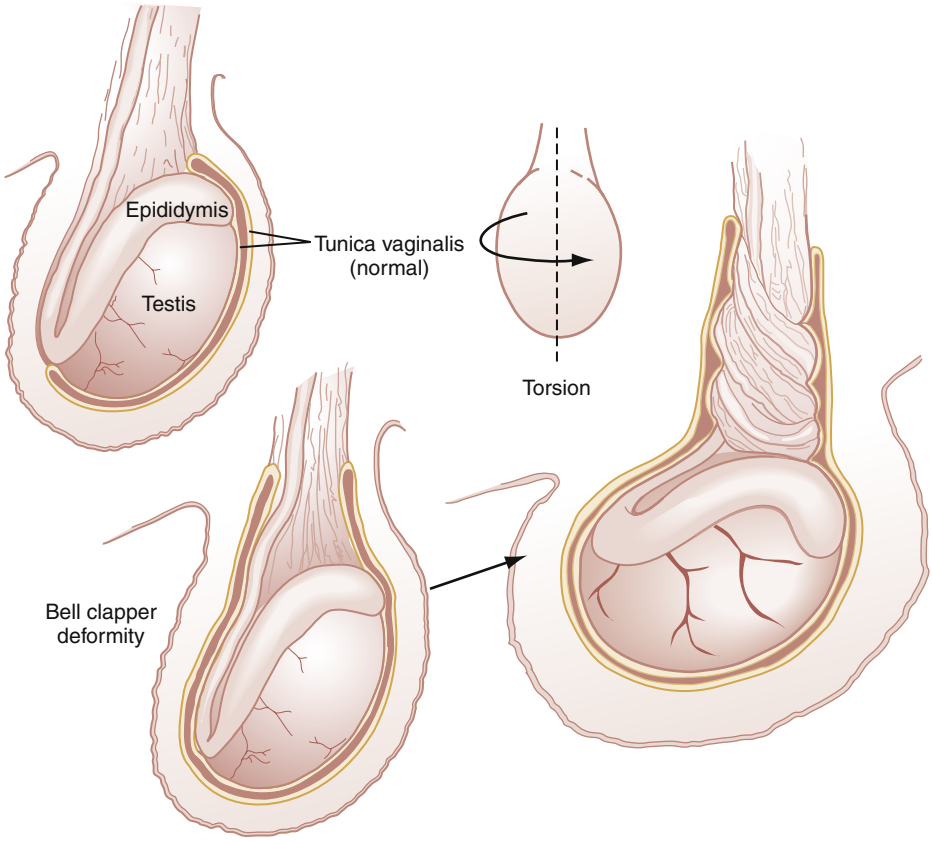

Fig. 168.6 Anatomy of testicular torsion. (From: Snyder HM III, et al. Pain—scrotal. In: Fleisher GR, Ludwig S, editors. *Textbook of Pediatric Emergency Medicine,* ed 4. Philadelphia: Lippincott Williams & Wilkins; 2000.)

occur in newborns and will spontaneously resorb by age one.[21] However, in older children, hydroceles may occur secondary to epididymitis, orchitis, torsion, or tumor. A varicocele is a collection of dilated veins in the pampiniform plexus, which surrounds the spermatic cord, and occurs in about 15% of adolescent males.[22] Primary varicoceles occur spontaneously, while secondary varicoceles occur due to some obstruction of venous outflow of the plexus. Most varicoceles are left-sided due to the 90-degree angle of drainage that occurs from the left spermatic vein to the left renal drain. A right-sided varicocele raises concern for intra-abdominal mass.

Clinical Features

If a hydrocele is communicating, painless scrotal swelling may increase when the patient performs a Valsalva maneuver. Transillumination will reveal clear fluid surrounding the testicle. Although varicoceles will also cause painless scrotal swelling, examination will reveal a "bag of worms" consistency on palpation, and a varicocele does not transilluminate. The differential for painless scrotal swelling includes hydrocele, varicocele, spermatocele, cyst, inguinal hernia, or testicular tumor. If there is pain, the differential includes reactive hydrocele secondary to epididymitis, orchitis, torsion, or a tumor.

Diagnostic Testing

If there is concern for testicular tumor, a CBC, lactate dehydrogenase (LDH), and uric acid would be reasonable. An ultrasound of the testes will be helpful to evaluate for torsion or mass. For right-sided varicoceles or those of sudden onset, we recommend patients undergo imaging with ultrasound with Doppler, CT, or MRI to evaluate for inferior vena cava thrombus, renal vein thrombosis, or abdominal mass.

Management and Disposition

Hydroceles in newborns can be managed expectantly as most will resorb on their own.[21] Outside the newborn period, there is moderate evidence that surgical correction of varicocele leads to improved sperm concentration and testicular volume.[23] Patients may be referred to urology for conservative management versus surgical repair with ligation or embolization; in the absence of an abdominal or testicular mass, these cases may be managed as outpatients.

Acute Idiopathic Scrotal Edema

KEY CONCEPTS

- Acute idiopathic scrotal edema (AISE) is rare and is a diagnosis of exclusion.

Foundations

Acute idiopathic scrotal edema (AISE) is a rare diagnosis characterized by acute scrotal erythema, swelling, and tenderness. It is a benign, self-limiting condition with an unclear etiology and is a diagnosis of exclusion. AISE generally affects prepubertal boys, though can affect males into adulthood.[24]

Clinical Features and Diagnostic Testing

Physical examination shows swelling, induration, and erythema of a unilateral testicle, which may or may not be tender. Diagnosis is via ultrasound and demonstrates edematous thickening and increased vascularity of the scrotal wall, but normal-appearing testes.

Management

Once more insidious causes have been ruled out, AISE generally resolves within a few days with NSAIDs and scrotal support.

Inguinal Hernia

KEY CONCEPTS

- Inguinal hernias can occur in males (intestines) and females (ovary more often than intestines).
- Manual reduction of inguinal hernia should be attempted, but definitive management is surgical repair.

Foundations

An inguinal hernia is a common cause of scrotal swelling in males and labial swelling in females, with indirect hernias accounting for just under 5% of full-term infants.[25] Risk increases with prematurity, low birth weight, and male gender. In males, an indirect hernia results from failed closure of the processus vaginalis, and usually contains intestines. In females, a hernia results from the failed closure of the canal of Nuck, and more often contains ovary rather than bowel. The greatest risk is with incarceration (inability to reduce the herniated contents), as well as strangulation (vascular compromise), of the herniated contents.

Clinical Features

Patients present with intermittent bulge of the inguinal region into the scrotum or labia, or a persistent bulge consistent with incarceration. Patients with a reducible bulge usually have no complaints of pain, whereas those with incarceration may have a significant amount of pain. The patient may also experience vomiting and diffuse abdominal pain from intestinal obstruction.

Differential Diagnoses

Differential diagnosis should include hydrocele, varicocele, testicular/ovarian torsion, or malignancy. The diagnosis is often clinical, but ultrasound with Doppler can assist in identifying herniated contents as well as ovarian flow in females.

Management and Disposition

Ultimately, surgery is needed for definitive repair. As long as the patient is clinically stable, manual reduction should be attempted with appropriate analgesia, by applying traction to the proximal inguinal canal with one hand and gentle pressure to the distal canal towards the abdomen with the other hand for up to 5 minutes. Incarcerated hernias with strangulation, as well as canal of Nuck hernias containing ovary, have high risk for bowel ischemia or ovarian torsion without prompt surgical intervention.[25] In the event of painless, reducible hernias without incarceration or strangulation, patients can be referred for surgery and outpatient evaluation.

Testicular Carcinoma/Tumors

KEY CONCEPTS

- Testicular tumors are the most common solid organ tumor in adolescents.
- Patients who have a hydrocele that does not transilluminate should have an ultrasound to investigate for an underlying mass.

Foundations

Although a small percentage of overall pediatric malignancies, testicular tumors are the most common solid organ tumor in adolescents, comprising 14% of all adolescent cancer.[26] Patients with cryptorchidism, prior testicular cancer on the contralateral side, or family history of cancer are all at increased risk. Most testicular cancers are teratomas, carcinomas, yolk sac tumors, Leydig cell tumors, or Sertoli cell tumors; however, lymphoma and leukemia can also metastasize to the testicle.

Clinical Features

Patients present with painless unilateral testicular swelling or mass. Some may describe an aching or pulling sensation, or abdominal pain. There may be a reactive hydrocele present, but the testis does not transilluminate with an underlying mass. Examination may demonstrate lymphadenopathy, hepatosplenomegaly, or gynecomastia.

Diagnostic Testing and Management

Diagnostic evaluation should include a CBC with differential, chemistry panel, LDH, uric acid, human chorionic gonadotropin (HCG), UA, and ultrasound. Labs are obtained to evaluate for cell line suppression, tumor lysis syndrome, or end-organ damage. Chest x-ray should be performed to rule out mediastinal mass with testicular metastasis. Tumor markers such as HCG, alpha fetal protein (AFP), luteinizing hormone (LH), and follicular stimulating hormone (FSH) can be sent and are helpful to the oncologist for further delineation of the underlying subtype. An ultrasound is necessary to identify solid tumor versus a cystic structure.

Once the workup is complete, pediatric oncology should be consulted for further management, including CT chest, abdomen, and pelvis for staging purposes, orchiectomy for histologic evaluation, and possibly retroperitoneal lymph node dissection or chemotherapy.[27] A testicular biopsy should not be performed due to concern for possible tumor seeding. Initial management may be inpatient, with long term outpatient follow-up.

Urinary Tract Infections

KEY CONCEPTS

- *E. coli* is the most common uropathogen isolated from urine cultures in patients with urinary tract infections (UTI).
- First time febrile UTI from 2 months to 2 years should have a renal bladder ultrasound.

Foundations

Urinary tract infection (UTI) is a common diagnosis in pediatrics and risk increases with age younger than 12 months, uncircumcised status, and anatomic obstruction or vesicoureteral reflux. The most common bacterial cause of UTI is *E. coli*, accounting for 80% of cases.[28]

Clinical Features

Patients present with dysuria, urgency, frequency, abdominal pain, fever, incontinence, or vomiting. In younger children, fever may be the only presenting symptom (see Chapter 161). Physical examination may reveal suprapubic tenderness; an upper tract infection may cause costovertebral angle or flank tenderness. GU examination should be performed to look for retained foreign bodies or signs of obstruction from phimosis or labial adhesions.

Differential Diagnoses

Differential diagnosis includes other sources of fever or abdominal pain, although those would not eliminate a concurrent UTI. Asymptomatic bacteriuria is a possibility in the event of colonization or gastroenteritis. In patients with pyuria but negative culture, consider balanitis, vulvovaginitis, or sexually transmitted disease. Also consider Kawasaki disease in the event of sterile pyuria.

Diagnostic Testing and Management

A urinalysis and urine culture should be obtained. A catheterized specimen is preferable in those who are not toilet trained to preserve

a sterile sample. Blood work is not usually needed for otherwise well-appearing immunized children over 3 months of age. A UTI is diagnosed when there is pyuria or bacteriuria on UA, and at least 50,000 cfu/mL of a uropathogen cultured by catheterization.[29] Febrile infants with a UTI should receive renal bladder ultrasound, which may be performed as an outpatient, to assess for hydronephrosis or renal scarring. Once back to their usual state of health, infants with an abnormal ultrasound should undergo a voiding cysto-urethrogram to assess for reflux or obstruction.[29] See Chapter 161 for a comprehensive discussion on treatment of pediatric UTI.

Hematuria

KEY CONCEPTS

- Hematuria refers to >5 RBCs per high power field on UA.
- Gross hematuria is usually due to bladder or urethral bleeding, whereas microscopic hematuria is due to glomerular or tubular bleeding.

Foundations

Hematuria refers to red blood cells (RBCs) in the urine and can be either macroscopic or microscopic. While macroscopic hematuria is visible to the patient, microscopic hematuria refers to greater than 5 RBCs per high-power field. The prevalence of microscopic hematuria detected on two or more urinalysis samples in school age children is estimated at 1% to 2%, but in cases of isolated hematuria, 57% do not have underlying pathology.[30]

Irrespective of grossly visible or microscopic hematuria, patients should be assessed for trauma, queried for flank or abdominal pain, and inspected for bleeding from other sites. Patients with infection as the cause of hematuria may report fevers, dysuria, urgency, frequency, abdominal pain, or recent illness. Medical history should include documenting any sickle cell disease, bleeding disorders, medications, or family history of kidney disease. Physical examination should document other areas of bleeding/bruising (skin or mucosal), signs of renal impairment (hypertension, periorbital or lower extremity edema, pulmonary crackles), abdominal pain or masses, and GU examination to assess for external causes of bleeding (i.e., meatal, vaginal, or rectal sources). Causes of hematuria are categorized as extrarenal or intrarenal etiologies (Table 168.2).[30,31] Macroscopic hematuria is typically due to bladder/urethral damage, whereas microscopic hematuria is more commonly from glomerular or tubular damage.

Patients with hematuria have a UA with greater than 5 RBCs per high-power field. Proteinuria and RBC casts suggest glomerular damage. Patients with concern for hematuria, and dipstick positive for blood, but no RBCs on UA may have myoglobinuria from rhabdomyolysis. In patients with discolored urine but normal UA, consider certain foods (e.g., beets, rhubarb, berries) and medications (e.g., rifampin, nitrofurantoin, metronidazole).[31] Findings of leukocyte esterase, nitrite, or white blood cells (WBC) indicate urinary tract infection. WBC casts may be found in patients with pyelonephritis. In the context of recent throat or skin infection, a throat culture, anti-streptolysin O (ASO) titer, and complement levels may help diagnosis poststreptococcal glomerulonephritis. If there is greater than 3+ protein on UA, nephrotic syndrome should be considered and a basic metabolic panel (BMP) sent for electrolytes, creatinine, and albumin. If BMP reveals hypercalcemia, urine calcium levels should also be obtained, because hypercalciuria is a common cause of hematuria. If there is concern for lupus, erythrocyte sedimentation rate (ESR) and antinuclear antibodies (ANA) can be obtained. If the patient complains of flank or abdominal pain with hematuria, ultrasound or CT scan can help diagnose nephrolithiasis, renal vein thrombosis, nutcracker syndrome, or mass.

TABLE 168.2 Causes of Hematuria in Children

Extrarenal	Trauma
	Meatal stenosis or posterior urethral valves
	Menstrual or rectal bleeding
	Foreign body
	Cystitis, urethritis, epididymitis
Intrarenal	Pyelonephritis
	Nephrolithiasis or urolithiasis
	Poststreptococcal glomerulonephritis
	Acute interstitial nephritis
	Acute tubular necrosis
	Basement membrane glomerular disease
	Renal vein or artery thrombosis
	Recurrent familial hematuria
	Polycystic kidney disease
Systemic	Alport syndrome
	Henoch-Schönlein purpura
	Lupus
	Hemolytic uremic syndrome
	Mononucleosis
	Sickle cell disease/hemoglobinopathy
	Endocarditis
	Bleeding diathesis
	Medications (amitriptyline, chlorpromazine, radiocontrast dye)

If the patient has a history of trauma, we recommend a CT scan of the abdomen and pelvis be performed to evaluate for sources of injury and bleeding (see Chapter 160).

The management of hematuria depends on the etiology and may warrant subspecialty referral to nephrology, urology, or oncology. Well-appearing children with normal blood work, imaging, and no identifiable cause should be discharged to follow-up with their PCP for serial UAs to assess for persistent hematuria and need for further outpatient workup.

Nephrolithiasis

KEY CONCEPTS

- Clinical presentation in pediatrics may be more nonspecific than adults.
- Ultrasound is first-line imaging in diagnosis.
- Stones <6 mm will likely pass spontaneously.

Foundations

Nephrolithiasis, or kidney stones, is increasing in incidence across all ages. Calcium oxalate stones are the most common, followed by calcium phosphate, and less likely struvite, uric acid, and cysteine. Increased risk is associated with family history, low fluid intake, increased dietary sodium, urinary tract infections, metabolic abnormalities (hypercalciuria, hypocitraturia, renal tubular acidosis), anatomic abnormalities (ureteropelvic junction obstruction, posterior urethral valves), systemic disease (inflammatory bowel disease, nephrocalcinosis), genetic disease (cystinuria, cystic fibrosis), and medications (topiramate, acetazolamide, vitamin C).[32]

Clinical Features

Adolescents often present with colicky flank pain and hematuria, while younger children present with nonspecific abdominal pain or isolated hematuria which may lead to a delayed diagnosis. Patients may also

complain of nausea, vomiting, or malaise. Children with concomitant UTI may complain of dysuria, urgency, and frequency. Some younger patients may be asymptomatic with stones detected incidentally. History should include any prior history of stones, UTIs (*Proteus* species are associated with struvite stones), congenital malformations, family history of nephrolithiasis, specific dietary constraints (ketogenic diet), and current medications.

Differential Diagnoses

In patients with intermittent abdominal pain, constipation, gastroenteritis, appendicitis, intussusception, testicular torsion, ovarian torsion, and cholelithiasis should be considered in the differential. In children with hematuria, consider urinary tract infection, trauma, and other causes of hematuria listed in Table 168.2.

Diagnostic Testing

Workup for suspected nephrolithiasis includes a UA with microscopy to evaluate for hematuria, crystals, and evidence of infection, as well as a BMP to evaluate for electrolyte abnormalities and acute kidney injury. Although hematuria is a common presenting symptom, up to 20% of patients with nephrolithiasis will not have hematuria on their UA. CBC with differential may be obtained if there is concern for infection or significant blood loss. Stones may be visualized using plain films, ultrasound, or non-contrast helical CT scans. Plain films will only detect radio-opaque stones; ultrasound will detect both radio-opaque and radiolucent stones but may miss smaller stones. CT scans will detect both types of stones, as well as small stones and ureteral stones. Renal bladder ultrasound is first-line imaging in children to avoid radiation, but with negative ultrasound and high suspicion, a non-contrast CT is diagnostic.

Management

Management of stones in pediatric patients focuses on pain control, as well as expectant management of stone passage versus surgical removal. In children with normal renal function, NSAIDS are preferred for pain relief, followed by opioids. Uncomplicated cases with adequate pain control, normal renal function, and stones of less than 6 mm can be discharged home, as they will likely pass the stone spontaneously.[33] For distal ureteral stones of less than 10 mm, the addition of medical expulsive therapy with tamsulosin (alpha antagonist) may increase successful expulsion.[33] Once passed, stones can be collected by families and sent for stone composition analysis. A 24-hour urine collection is recommended after the stone has passed, to evaluate for underlying metabolic abnormalities that may predispose to recurrence. Stone causing hydroureter or hydronephrosis and infected urine is a urologic emergency, requiring intravenous antibiotics and decompression, usually with ureteral stent or percutaneous nephrostomy tube.[33] Additional interventions may include extracorporeal shock wave lithotripsy, percutaneous nephrostolithotomy, or ureteroscopy. Admission criteria for children with nephrolithiasis are any of the following: significant obstruction (unlikely to pass spontaneously), UTI with obstruction, persistent pain despite adequate therapy, persistent vomiting or inability to self-hydrate, struvite stones, failed conservative management, and patients with a solitary kidney.[34]

Renal Tumors

KEY CONCEPTS

- Wilms tumor is the most common renal tumor in children.
- Patients often present with hematuria or an abdominal mass detected by caregivers.

Foundations

Renal tumors make up 7% of all pediatric cancers, of which Wilms tumor is the most common, followed by congenital mesoblastic nephroma (in children <12 months) and renal cell carcinoma (in children >5 years).[35,36] Certain syndromes such as Beckwith-Wiedemann, Denys-Drash, and WAGR, carry increased risk of developing Wilms tumor.

Clinical Features

Children with renal tumors often present with a palpable abdominal mass, but can also present with abdominal pain/distension, hematuria, or emesis. Vital signs may be normal or may reveal hypertension. In addition to renal tumors, the differential diagnosis includes other causes of abdominal mass such as hepatosplenomegaly, hydronephrosis, polycystic kidneys, cysts, abscesses, a full bladder, and constipation.

Diagnostic Testing

A suspected renal mass warrants laboratory workup, including CBC with differential and smear, complete metabolic panel (CMP), uric acid and LDH to assess for tumor lysis, urinalysis, and urine catecholamines (to help differentiate Wilms tumor from neuroblastoma). Renal ultrasound is preferred for diagnosis, followed by additional imaging with a CT, MRI, or PET scan for staging and surgical planning.

Management and Disposition

Once a renal tumor has been identified, pediatric hematology-oncology should be consulted for ongoing management. Children who are well-appearing with normal renal function may be discharged for outpatient follow-up after discussion with oncology, but often children will be admitted for expedited diagnostic workup and treatment planning.

Proteinuria

KEY CONCEPTS

- Trace or mild proteinuria may be seen in hypovolemia, fever, stress, or exercise.
- Patients with moderate or severe proteinuria require workup with blood work, imaging, and nephrology consultation.

Foundations

Proteinuria is associated with renal pathology; however, trace or mild proteinuria is benign and generally asymptomatic. It is often seen with hypovolemia, fever or hypothermia, stress, seizures, or exercise. However, more insidious causes, such as nephrotic syndrome, can present with high levels of proteinuria (>1000 mg/m^2 per day, Table 168.3) and edema secondary to hypoalbuminemia less than 3 g/dL.[37] Glomerular filtration issues lead to the abnormal passage of albumin, a macromolecule, which is detected on urine dipstick. Tubular and overflow proteinuria are caused by extrusion of low-molecular-weight molecules, which are not typically detected on urine dipstick. Tubular proteinuria is associated with proximal tubular dysfunction, whereas overflow proteinuria, which is uncommon in children, occurs when tubular resorptive capacity is overwhelmed.

Clinical Features

The cause of proteinuria determines presentation. Edema commonly presents around the eyes (i.e., periorbital), in the lower extremities, and in the GU area. Eliciting a history of preceding illness (e.g., a recent streptococcal infection), weight changes, changes in urine output, and family history of kidney issues/autoimmune disease may assist in diagnosing the etiology of the proteinuria. If the patient has systemic

TABLE 168.3 Urine Dipstick Proteinuria

Mild Proteinuria				Moderate Proteinuria	High Proteinuria
Negative	Trace	1+	2+	3+	4+
<15 mg/dL	15–30 mg/dL	30–100 mg/dL	100–300 mg/dL	300–1000 mg/dL	>1000 mg/dL

TABLE 168.4 Causes of Proteinuria

Glomerular	Tubular
Nephrotic syndrome	Heavy metal poisoning
Minimal change disease	Urinary tract infection
Glomerulonephritis	Diabetes-related glycosuria
Post-transplantation rejection	Proximal tubular acidosis
Transient	Phosphaturia
• Hypovolemia	Asymptomatic tubular proteinuria
• Hyperthermia	Genetic disorders
• Hypothermia	• Fanconi syndrome
• Seizures	
• Stress	
• Exercise	
• Postural/Orthostatic	
• Proteinuria only when upright	

symptoms, such as joint pain or rash, this may point to an autoimmune process as the culprit.

In children, proteinuria is either glomerular or tubular; common causes are listed in Table 168.4.[37] False-positive proteinuria on urine dipstick is often related to alkaline or dilute urine, mucous, blood, vaginal or seminal secretions, or the presence of inflammatory cells (i.e., a urinary tract infection).[38]

Diagnostic Testing and Management

If a patient has mild proteinuria (≤2+ or ≤100 mg/dL), no further emergent testing is necessary. Patients with moderate proteinuria (≥3+ or ≥300 mg/dL), should have their blood pressure monitored, and a laboratory workup, including serum protein, serum albumin, electrolytes, BUN, creatinine, complement levels (C3 and C4), urine culture, antistreptolysin O (ASO), and urine protein-to-creatinine ratio (Pr/Cr). Random urine Pr/Cr correlates with a 24-hour urine collection and is easier to obtain, particularly in a pediatric patient. First morning void urine Pr/Cr is most accurate. Urine Pr/Cr greater than 3.0 is associated with nephrotic syndrome. We recommend pediatric nephrology consultation and follow-up for any child with moderate proteinuria or an elevated urine Pr/Cr value (Table 168.5).[37] Imaging such as a renal ultrasound may demonstrate anatomic abnormalities such as polycystic kidney disease, but can be completed on an outpatient basis.

Disposition

All children with proteinuria require follow-up with their primary care doctor for a reevaluation, including blood pressure monitoring and repeat UA. A pediatric nephrologist should determine the need for renal biopsy in children with moderate proteinuria.

We recommend hospital admission and pediatric nephrology consultation for children with significant proteinuria (3+), along with edema/ascites, hypertension greater than the 99th percentile, or renal dysfunction with elevation of greater than 50% of BUN or creatinine. Some children with new-onset mild nephrotic syndrome may be managed outpatient, particularly if well-appearing; however, we recommend this decision be made in consultation with a pediatric nephrologist.

TABLE 168.5 Normal Urine Protein-to-Creatinine Ratio

Age	Urine Pr/Cr
>2 years old	<0.2
6 months–2 years old	<0.5

Data from Gipson DS, et al. Complete remission in the Nephrotic Syndrome Study Network. *Clin J Am Society Nephrol.* 2016;11:81-89.

Poststreptococcal Glomerulonephritis (PSGN)

KEY CONCEPTS

- Patients with PSGN have a history of a preceding pharyngeal or skin infection in the past 2 to 6 weeks, respectively.
- Treatment of PSGN is supportive, with fluid restriction and diuretics for more significant disease.

Foundations

Poststreptococcal glomerulonephritis (PSGN) is the most common cause of pediatric glomerulonephritis globally and is caused by recent infection with group A beta-hemolytic streptococcus (GAS).[39] The exact mechanism is unclear, but it is believed to be caused by deposition of glomerular immune complexes, which leads to a decreased glomerular filtration rate from complement activation, and subsequent proteinuria.

Clinical Features

Generally, patients will present with a history of pharyngitis and fever about 2 weeks prior, or skin infection with fever up to 6 weeks prior.[39] PSGN symptoms can range from asymptomatic gross hematuria to acute nephritic syndrome with acute kidney injury including proteinuria, edema, hypertension, lethargy, cardiac arrhythmias, and renal failure. It occurs more frequently in males, patients ages 4 years to 12 years old, and is uncommon in children less than two years old.[39]

Diagnostic Testing

In children with PSGN, a urinalysis should be obtained and demonstrates hematuria (±RBC casts) and proteinuria, and sometimes pyuria. Generally, most children with PSGN do not have nephrotic range proteinuria. Lab values typically show an elevated BUN, low sodium, high potassium, elevated ASO, elevated IgG levels, and decreased C3 and decreased CH50 during the first 2 weeks of illness.[39] Complement levels generally return to normal within 4 to 8 weeks after initial presentation.[40]

If hematuria and nephritic symptoms persist beyond 2 weeks, clinical clues can point to diagnoses other than PSGN. Antecedent upper respiratory or gastrointestinal infection is often present in patients with IgA nephropathy or membranoproliferative glomerulonephritis

BOX 168.1 Indications for Hospitalization/ Dialysis in Pediatric PSGN

Refractory or significant hypertension
- >99th percentile for age and height

End-organ damage from fluid overload
- Congestive heart failure
- Pulmonary edema

Hyperkalemia >6.5 mEq/L
Severe uremia >89 mg/dL

(MPGN). In IgA nephropathy, hematuria typically presents sooner (i.e., less than 5 days) after the preceding illness. Patients with MPGN have persistent hematuria and lab abnormalities of low complement and elevation in creatinine. Lupus nephritis and Henoch-Schönlein purpura (HSP) can present similarly, but can be differentiated by complement levels, with both C3 and C4 depressed in lupus nephritis, and normal complement levels in HSP. PSGN has a decreased C3 and generally has a normal C4 level, though a depressed C4 level can portend a poorer prognosis.[40] Hemolytic uremic syndrome (HUS) can also result in symptoms similar to PSGN, but has characteristic bloody diarrhea and is often associated with *E. coli* O157.

Management

PSGN is primarily managed supportively via fluid and salt restriction, often in consultation with a pediatric nephrologist. It is generally self-limited, with most creatinine levels returning to baseline about 3 to 4 weeks after initial manifestation. PSGN does not necessarily warrant antibiotic treatment, as the streptococcal infection has typically cleared by the time of presentation, although a streptococcal infection should be treated if still present. If hypertension or fluid overload develops, patients should be treated with calcium channel blockers or diuretics.

Diagnosis can be delayed if there is no history of antecedent infection or the patient does not have gross hematuria. In PSGN, the nephritis typically resolves within 1 to 2 weeks. Patients with persistent disease beyond 2 weeks should receive a pediatric nephrology consultation to determine additional diagnostic testing.

Most children with mild PSGN can be managed on an outpatient basis. Indications for pediatric nephrology referral and dialysis are outlined in Box 168.1.[41]

Nephrotic Syndrome

KEY CONCEPTS

- Nephrotic syndrome is defined by proteinuria, decreased albumin, hypertriglyceridemia, and edema.
- Patients have an increased risk for thrombosis and bacterial infections, especially *Streptococcus* and *E.coli.*

Foundations

Nephrotic syndrome occurs when impaired glomerular filtration leads to proteinuria (3+ or 4+ or >300 to 1000 mg/dL protein on urine dipstick) and hypoalbuminemia (<30 g/L or <3g/dL). As a result of this increased permeability, patients can present with significant edema. It can affect any age, although is most common in school-aged children and teenagers. The incidence in children is 2 to 7 per 100,000 children and it affects males more frequently (2 : 1).[42] Primary nephrotic syndrome is idiopathic and occurs without an inciting systemic illness while secondary nephrotic syndrome occurs due to systemic causes, such as infections, immune disorders, cancer, or medications. The

BOX 168.2 Types of Nephrotic Syndrome (most common to least common)

Minimal change disease (MCD)
Focal segmental glomerulonephritis (FSGS)
Membranoproliferative glomerulonephritis (MPGN)
Other glomerulonephropathies
- Membranous glomerulopathy
- Focal and global glomerulosclerosis
- Mesangial proliferation
- Proliferative glomerulonephritis

BOX 168.3 Nephrotic Range Labs

Proteinuria ≥40 mg/m^2/hour or >50 mg/kg/day or >1000 mg/m^2/day
- 3+ or 4+ protein on urine dipstick

Hypoalbuminemia <30 g/L or <3 g/dL
Total serum protein 4.5–5.5 g/dL
Spot urine protein: creatinine >2

various types of nephrotic syndrome are listed in Box 168.2.[43] Most children have primary nephrotic syndrome, generally minimal change disease or focal segmental glomerulonephritis.

Clinical Features

Nephrotic syndrome is characterized by edema, although the presentation can vary from mild periorbital edema to anasarca. Some children can present without edema, but still have nephrotic range proteinuria. Nephrotic syndrome can be triggered by a recent upper respiratory illness or can present without incitement.[42] Some children can present with weight gain not recognized to be edema, and insidiously present with pulmonary edema or severe ascites. Children with nephrotic syndrome may have hypertension, hematuria, or oliguria, with resultant acute kidney injury, although acute renal failure is rare.

Children with nephrotic syndrome are at high risk for thrombosis with thromboemboli. Venous thrombosis can occur in the renal vein, sagittal sinus, or pulmonary artery.[42] Patients with nephrotic syndrome are also at higher risk for developing bacterial infections secondary to loss of immunoglobulins, and because they are often on corticosteroid treatment. Infections are the leading cause of morbidity and mortality in nephrotic syndrome, from spontaneous bacterial peritonitis, sepsis, and pneumonia resulting from *E. coli* and encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and Group B *Streptococcus*.

Diagnostic Testing

In suspected nephrotic syndrome, a urinalysis, protein : creatinine ratio, and serum labs including electrolyte, albumin, BUN, creatinine, CBC, and cholesterol should be checked. Nephrotic range labs are listed Box 168.3.[42] Labs generally reveal normal BUN and creatinine levels, but will have hypoalbuminemia, hyponatremia, hyperlipidemia, and can have hemoconcentration with elevated hemoglobin and hematocrit. Patients generally have normal complement levels, but if abnormal, other diagnoses should be considered.

Imaging such as chest x-rays and abdominal x-rays can demonstrate fluid overload with pulmonary edema and ascites. Abdominal ultrasound for nephrotic syndrome is otherwise nonspecific, but may demonstrate ascites or structural changes of the kidneys from chronic illness. Renal biopsy can characterize a specific nephrotic syndrome

diagnosis, and is recommended for patients with hematuria, elevated BUN, persistent hypertension or renal dysfunction refractory to steroid treatment.

Differential Diagnoses

Primary renal disease such as glomerulonephritis and renal failure can also result in edema similar to nephrotic syndrome. These can be differentiated by gross hematuria, RBC casts in urine, elevated creatinine, or hypertension. Other causes of edema to consider include heart failure, drug-induced, liver failure/cirrhosis, cystic fibrosis, and other protein losing enteropathies such as malnutrition.

Management

Primary nephrotic syndrome can be treated with steroids (e.g., prednisone 2 mg/kg/day orally divided TID), with the duration determined by a pediatric nephrologist.[44] Some forms of nephrotic syndrome may be refractory to steroids, in which case subsequent steroid courses and renal biopsy may be warranted. Children with nephrotic syndrome require fluid and salt restriction. In ill-appearing patients with severe ascites or respiratory distress, furosemide 0.5 to 1 mg/kg and titrated based on response can be used as a diuretic. However, in spite of edema, children with nephrotic syndrome who appear hypovolemic or septic should receive fluid resuscitation with crystalloid. If patients develop chest pain, shortness of breath, abdominal pain, or extremity swelling/pain, thromboembolic complications should be considered. Children with significant ascites and pain should undergo paracentesis to assess for spontaneous bacterial peritonitis. Due to immunoglobulin loss and T-cell dysfunction, children with nephrotic syndrome are considered immunocompromised and if they present with a fever, can not only relapse but should also be hospitalized with blood cultures, respiratory viral studies if available, and initiation of antibiotic therapy effective against *S. pneumoniae* and *E. coli*.[44]

Disposition

As with many new-onset pediatric chronic illnesses, pediatric patients with new-onset nephrotic syndrome are generally hospitalized under the care of a pediatric nephrologist to expedite workup, treatment, and education. In mild cases, patients can be discharged home in consultation with a pediatric nephrologist. Patients who are ill-appearing with concern for thrombus, sepsis, shock, respiratory distress, worsening renal function, steroid-refractory disease, or infection should be hospitalized.

Acute Kidney Injury

KEY CONCEPTS

- Evaluation of fluid status in AKI is important in management strategies.
- Management is directed at correcting fluid and electrolyte derangements.

Foundations

Acute kidney injury (AKI) occurs when injury of renal tissue leads to alteration in fluid status, electrolyte imbalance, and poor elimination of waste, which can lead to chronic kidney disease and failure.[45] AKI is often multifactorial, but may be due to an underlying disease process, dehydration, medications, or toxins. AKI is often classified as prerenal, renal or postrenal (Table 168.6). Prerenal AKI is usually due to poor renal perfusion, renal AKI is due to intrinsic kidney parenchymal damage, and postrenal AKI is due to anatomic abnormality that prevents adequate drainage of the collecting system.

Clinical Features and Differential Diagnoses

Clinical presentation and differential diagnosis depend on the underlying etiology of AKI. Patients may have vital sign and physical examination findings consistent with dehydration (e.g., sunken fontanelle, dry skin, delayed capillary refill, dry mucous membranes). History may reveal poor oral intake, vomiting, diarrhea, or little to no urine output. History of sore throat or bloody diarrhea may point to poststreptococcal glomerulonephritis or hemolytic uremic syndrome (HUS), respectively. Medication history is important because many medications may be nephrotoxic. Patients may be edematous from fluid shifts and may have hematuria from renal injury.

TABLE 168.6 Causes of AKI

Prerenal	Decreased renal perfusion: dehydration, hemorrhage, diuretics, burn, heart failure, sepsis, anaphylaxis
Renal	NSAIDs, ACE inhibitors, acute tubular necrosis, HUS, vasculitis (lupus, HSP), interstitial nephritis, malignancy, glomerulonephritis
Postrenal	Nephrolithiasis or urolithiasis, thrombosis, neurogenic bladder, medication-induced urinary retention, anatomic obstruction

Diagnostic Testing

Patients with suspected AKI should have a BMP drawn to assess for alterations in electrolytes, BUN, and creatinine. UA with microscopy may show hematuria or proteinuria depending on underlying etiology, and may have elevated specific gravity or ketones if the patient is dehydrated. RBC casts, WBC casts, or hyaline casts may also help identify glomerulonephritis, pyelonephritis, or acute tubular necrosis, respectively. Electrolyte abnormalities may be apparent such as hyponatremia, hyperkalemia, hyperphosphatemia and hypocalcemia. Elevated BUN and creatinine are hallmarks of AKI. If there are concerns for infection or HUS, CBC may identify leukocytosis, thrombocytopenia, or microangiopathic changes. Renal bladder ultrasound may be necessary to evaluate renal parenchyma, obstruction, and vessel thrombosis.

Management

Management of AKI is supportive and directed at correcting the underlying cause, as well as fluid and electrolyte abnormalities. Patients with prerenal or renal AKI may be fluid challenged with a 20 mL/kg normal saline (NS) bolus to assess for urine output response. Patients with nephrotoxic medication exposure would also benefit from fluid therapy, along with cessation of the exposure.[46] In patients with fluid overload or heart failure, fluids would worsen the clinical picture and pediatric nephrology should be consulted for diuretic management because furosemide is also nephrotoxic and could lead to hypotension in certain situations.[47] Severe electrolyte disturbances can lead to hyponatremic seizures or hyperkalemic cardiac arrhythmias. Hyponatremic seizures should be treated with 3% hypertonic saline at 3 to 5 mL/kg.

An electrocardiogram (EKG) also should be obtained in children with AKI. Hyperkalemia with QRS widening should be treated with calcium gluconate 30 to 60 mg/kg to stabilize the myocardium; additional hyperkalemia treatment includes dextrose (0.5 g/kg) and insulin (0.1 units/kg), albuterol, sodium bicarbonate (1 mEq/kg), kayexalate (1 g/kg) and Lasix (0.5–1 mg/kg). Dialysis may be necessary in cases of severe acidosis, electrolyte disturbances, toxic ingestions, fluid overload, or uremia.

Disposition

Pediatric patients with AKI warrant admission for fluid and electrolyte management; consultation with pediatric nephrology should be obtained for possible dialysis.

Hypertension

KEY CONCEPTS

- In children, blood pressure percentile is interpreted using sex, age, and height.
- Blood pressure measurements are defined as normal, elevated, stage 1 hypertension, or stage 2 hypertension

Foundations

The prevalence of clinical hypertension in pediatrics is about 3.5%, and pediatric blood pressures (BP) are interpreted using sex, age, and height.[48] The definition of hypertension in children and adolescents differs from that of adults, and the most updated clinical guidelines for hypertension are outlined in Table 168.7.[48] If left untreated, children with hypertension are at increased risk of adult hypertension, cardiovascular disease, and metabolic syndrome.

Clinical Features

On presentation, children may be symptomatic or completely asymptomatic. If the initial BP is elevated, two separate BP measurements should be taken, and the three measurements averaged. If the patient still falls into one of the categories of hypertension, a thorough history should be completed including maternal complications at birth, gestational age, any umbilical vein catheter manipulation (risk of renal vein thrombosis), dietary salt intake, and family history. A physical examination, including 4-extremity blood pressure, is recommended to look for secondary signs of hypertension, such as coarctation of the aorta.

Differential Diagnoses

Children with confirmed hypertension greater than the ninety-fifth percentile should have follow-up with their primary care provider for ambulatory blood pressure monitoring. Patients with strong family history, elevated BMI, and poor dietary habits may have primary or essential hypertension. If this is not clear by history and physical examination, secondary causes of hypertension can be considered. Renovascular disease is the most common secondary cause of hypertension in children. Cardiac causes such as coarctation of the aorta also lead to hypertension in children and can go undiagnosed depending on the degree of narrowing. Other causes of secondary hypertension include sleep apnea, hormonal excess (e.g., catecholamines release of pheochromocytoma), genetic disease (neurofibromatosis 1), anatomic causes (renal artery stenosis), and medications/supplements (OCPs, stimulants, steroids).[48]

Diagnostic Testing

Laboratory evaluation for secondary causes of hypertension should include a BMP, lipid panel, and UA; other optional tests include renin, aldosterone, and urine catecholamines. Patients with a history of snoring and pauses in sleep can be referred for an outpatient sleep study. A urine toxicology screen can be helpful in patients suspected of drug abuse causing hypertension, but should not preclude urgent or emergency treatment. An ECG and echocardiography can assess for left ventricular hypertrophy or other structural causes of hypertension. Renal Doppler ultrasound is used to assess for renovascular disease, as well as renal artery stenosis or renal vein thrombosis.

Management and Disposition

Long-term goals in the treatment of hypertension in children include achieving a BP lower than the ninetieth percentile or less than 130/80 in adolescents to reduce end-organ damage and decrease the risk for cardiovascular disease in adulthood.[48] Lifestyle modifications that address diet, sleep, stress reduction, and physical activity are the initial management of choice for patients with elevated BP and asymptomatic stage I hypertension. If ongoing elevation persists despite lifestyle modifications, symptomatic stage I hypertension, or stage 2 hypertension, patients should undergo a diagnostic evaluation and pharmacologic treatment (with an ACE inhibitor, ARB, calcium channel blocker, or thiazide diuretic) with pediatric nephrology guidance and close follow-up.[48] Patients with stage 2 hypertension and end-organ damage such as encephalopathy, AKI, and heart failure are considered to have hypertensive emergency and should receive immediate reduction of BP by 25%. If the patient has stage 2 hypertension and remains symptomatic, or if the BP is greater than 30 mm Hg above the ninety-fifth percentile (>180/120 in adolescents), inpatient management is recommended.[48]

TABLE 168.7 Definitions of Hypertension

	Children Age 1–13 years	Children Age >13 years
Normal BP	<90th percentile	<120/80 mm Hg
Elevated BP	>90th percentile but <95th percentile	120/80 to 129/80
Stage I Hypertension	> 95th percentile to <95th percentile +12 mm Hg or 130/80 to 139/80 (whichever is lower)	130/80 to 139/80
Stage 2 Hypertension	>95th percentile + 12 mm Hg or >140/90 (whichever is lower)	>140/90

Henoch-Schönlein Purpura

KEY CONCEPTS

- HSP is a vasculitis that causes abdominal pain, GI bleeding, renal involvement, scrotal swelling, and arthralgias, and leads to an increased risk of intussusception
- Consider inpatient admission for patients with HSP who cannot bear weight, cannot tolerate oral pain medications, or have GI bleeding or renal involvement.

Foundations

Henoch-Schönlein purpura (HSP) is the most common vasculitis in children and has an annual incidence of 10 to 20 per 100,000 children, peaking at age 4 to 6 years.[49] HSP is a small vessel IgA vasculitis which has the proclivity to affect any organ, but in particular causes issues with the gastrointestinal (GI) tract, skin, and kidneys. Its etiology is uncertain, but there may be an association with preceding upper respiratory tract illnesses since it is most commonly seen in the fall, winter, and spring and rarely in the summer months.

Clinical Features

Clinical manifestations are variable, and many sets of diagnostic criteria exist, but in general, the diagnosis is based on the tetrad of abdominal pain, nonthrombocytic palpable purpura, arthralgia, and renal involvement. Patients may present on a spectrum of mild to severe symptoms. The rash occurs in dependent areas of the buttocks and posterior legs and is typically palpable and purpuric. Gastrointestinal (GI) symptoms range from mild nausea and abdominal pain to severe GI bleeding and risk of intussusception. (See Chapter 166 for GI evaluation in patients with HSP.) Renal disease ranges from mild hematuria to more severe nephritis. Less common clinical

manifestations also include scrotal edema, seizures, and interstitial lung disease.

Differential Diagnoses

Differential diagnosis may be broad depending on the patient presentation as some symptoms such as abdominal pain may be nonspecific. Given the purpuric nature of the rash, other causes of thrombocytopenia should be considered: sepsis, idiopathic thrombocytopenic purpura (ITP) or thrombotic thrombocytopenic purpura (TTP). Infection in the setting of rash and arthralgias can point to a strep infection, Lyme disease, or septic joint, as well as other rheumatic diseases. In patients with hematuria, a broad differential is necessary, as discussed in prior sections.

Diagnostic Testing

In patients with classic features of HSP, the diagnosis can be made clinically, as there is no diagnostic lab test. A UA is recommended to evaluate for renal involvement with hematuria. Patients with elevated blood pressure and hematuria should have a BMP to assess BUN and creatinine levels. CBC will be nonspecific and coagulopathy panels are generally normal. In patients with abdominal pain and/or GI bleeding, an ultrasound is recommended to assess for intussusception because these patients are at increased risk.

Management

Management of HSP is supportive and directed at symptomatic treatment. Pain can be treated with acetaminophen and NSAIDs (in the absence of severe renal involvement and ongoing GI bleeding). In general, patients who cannot bear weight due to arthralgias, pain not controlled with oral medications, ongoing GI bleeding, or renal involvement and signs of fluid overload should be admitted for pain control and fluid management. Use of glucocorticoids is controversial, as some evidence suggests improvement in GI sequelae but little benefit in preventing renal complications.[50]

Disposition

HSP nephritis may cause fluid overload, electrolyte derangements, and elevated blood pressure, requiring treatment with albumin, diuretics, and nephrology consultation. Milder cases of HSP may be managed outpatient with weekly PCP follow-up for BP and UA monitoring. Most cases resolve uneventfully, but some will have renal complications and recurrence.

Hemolytic Uremic Syndrome

KEY CONCEPTS

- Hemolytic uremic syndrome consists of a triad of acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia, and is most frequently associated with *E. coli* 0157 Shiga toxin–producing bloody diarrhea.
- Care is mostly supportive with red blood cell transfusion, fluid and electrolyte management, and possibly renal replacement therapy.

Foundations

Hemolytic uremic syndrome (HUS) consists of acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia, occurring secondary to an inciting etiology. Classification of HUS can be divided into either diarrhea positive, or typical HUS, versus diarrhea negative, or atypical HUS; 90% of cases are due to typical HUS secondary to Shiga toxin–producing *E. Coli* 0157, *Shigella*, or *Streptococcus* pneumoniae. The other 10% of cases are due to atypical HUS secondary to hereditary complement-mediated disease, pregnancy, malignancy, or medications.[51]

Clinical Features

Children often present with prodromal fever, abdominal pain, vomiting and diarrhea. After the first few days, the diarrhea progresses to bloody diarrhea and urine output may drop. Though rare, patients with HUS secondary to pneumococcal disease will present with fever, cough, and respiratory distress consistent with pneumonia. Patients with atypical HUS present with low urine output, signs of thrombocytopenia and anemia, and may also have neurologic complaints. Physical examination may reveal a petechial rash, pallor, and a tender abdomen.

Differential Diagnoses

Differential diagnosis includes other causes of thrombocytopenia and AKI, such as disseminated intravascular coagulation (DIC), TTP, or other vasculitides.

Diagnostic Testing

Laboratory studies recommended include a CBC with differential and smear to assess for microangiopathic anemia and thrombocytopenia, BMP to evaluate BUN and creatinine, as well as stool PCR to evaluate for *E.coli* O157 Shiga toxin. Coagulation studies can assess for DIC, and patients with fever and neurologic changes can have ADAMTS autoantibodies measured to diagnose TTP. Patients who are ill-appearing can have blood and urine cultures drawn, and those with altered mental status with severe thrombocytopenia may need a CT head scan to assess for intracranial hemorrhage.

Management

Management of HUS is largely supportive, with red blood cell transfusion for anemia, fluid and electrolyte management, and close monitoring for progression of AKI to renal failure, as dialysis may be required. Antibiotics should be avoided in *E. coli* O157 Shiga toxin–induced HUS, because it leads to lysis of more bacteria and can precipitate renal failure and need for dialysis. However, HUS cases due to pneumococcal disease should be treated with ceftriaxone and vancomycin.[52] Drugs that slow down GI transit, such as loperamide and opioids, should be avoided. Severe cases may have significant neurologic involvement due to intracranial hemorrhage, seizures, or altered mental status from uremia. Platelet transfusion may be required in clinically significant bleeding, but otherwise should be avoided due to ongoing consumption. Seizures can be treated with benzodiazepines. Atypical HUS has a higher risk of progression to end-stage renal disease, and may require dialysis, biologics such as eculizumab, plasmapheresis, and eventually require renal transplantation.[53]

Disposition

Overall, most patients will warrant inpatient admission for supportive care. Patients who fully recover should have yearly follow-up for close monitoring of hypertension and renal function.

The references for this chapter can be found online at Expert Consult.com.

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CHAPTER 168: QUESTIONS AND ANSWERS

1. A 12-year-old male presents due to right-sided scrotal pain for the last 2 days. On examination you note a swollen right testicle with normal cremasteric reflex that has a "bag of worms" consistency on examination. What is your next step in this patient's workup?
- **a.** Further imaging of the abdomen
- **b.** Further imaging of the testicles
- **c.** Mumps titers
- **d.** Urine to assess for *Neisseria gonorrhea* and *Chlamydia trachomatis*

Answer: A. Further imaging of the abdomen. The patient described has a right-sided varicocele. Most patients have a left-sided varicocele due to the angle of drainage of the left spermatic vein to the left renal vein; however, a right-sided and abrupt onset varicocele warrants abdominal imaging to investigate for an intra-abdominal mass. Imaging of the testicle would be appropriate to investigate for testicular torsion, but abdominal imaging is still necessary to rule out mass in this presentation. Mumps may present with orchitis, but not usually with varicocele. STIs do not usually present as varicoceles and in absence of other symptoms testing is not necessary at this time.

2. A family brings their 10-day-old girl into the ED for a newly developed bulge in the right inguinal area which appeared about an hour ago and is not reducible. Patient has otherwise been feeding well and afebrile prior to this. On examination, the infant is fussy but consolable and has a palpable lump in the right inguinal region which is not reducible and has no overlying erythema. What is your next step in care?
- **a.** Full septic workup with CBC, UA, blood culture, and CSF studies
- **b.** Pain control and outpatient follow up
- **c.** Surgery consult
- **d.** Ultrasound with Doppler

Answer: D. Ultrasound with Doppler. Inguinal hernia in females may contain ovary in the hernia sack due to failure of closure of the canal of Nuck, whereas hernias in males are more likely to have intestines. All females with inguinal hernia should have an ultrasound with Doppler to assess contents and assess for ovarian viability because torsion could occur. These cases do require surgical consultation after ultrasound as ovarian hernia will require more urgent surgical management. Sending the patient home with incarceration would not be appropriate in this case. Full septic workup is not indicated in an afebrile otherwise well child without signs of infection.

3. You are caring for a 3-year-old boy who was brought in by his mother for a possible abdominal mass palpated during his bath tonight. As part of your workup you obtain a renal bladder ultrasound that demonstrated a right-sided renal mass. What is the most likely etiology of his renal mass?
- **a.** Congenital mesoblastic nephroma
- **b.** Neuroblastoma
- **c.** Renal cell carcinoma
- **d.** Wilms tumor

Answer: D. Wilms tumor. The most common renal cancer in children is Wilms tumor. The second most common cancer in patients <12 months is congenital mesoblastic nephroma and <5 years is renal cell carcinoma.

4. Patients with nephrotic syndrome are at risk for which complication?
- **a.** Henoch-Schönlein purpura
- **b.** Supraventricular tachycardia
- **c.** Thrombosis
- **d.** Vascular malformations

Answer: C. Thrombosis. Due to increased permeability of the basement membrane, patients lose antithrombin 3 molecules which predisposes them to thrombosis. Patients are also at risk for infections, fluid overload, and electrolyte abnormalities. In general, patients do not have increased risk of Henoch-Schönlein purpura, supraventricular tachycardia, or vascular malformations.

5. A 5-year-old male presents with 5 days of diarrhea followed by 1 day of bloody diarrhea, fever, and abdominal pain. Labs reveal acute kidney injury, thrombocytopenia, and schistocytes on smear. Further workup most likely reveals which pathogen?
- **a.** *Campylobacter*
- **b.** *E. coli* 0157
- **c.** *Salmonella*
- **d.** *Shigella*

Answer: B. *E. Coli* 0157. Most cases of HUS occur secondary to Shiga toxin–producing *E. coli* 0157 and less frequently due to *Shigella* or *Salmonella*. Though *Campylobacter* can result in bloody diarrhea, it does not usually cause hemolytic uremic syndrome as described with acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia.

Pediatric Neurologic Disorders

Marc Auerbach and Niyati Mehta

KEY CONCEPTS

- Altered mental status in children has a varied spectrum of clinical presentations, and may include any of the following: altered level of consciousness, excessive sleepiness, irritability, lethargy, and abnormal behavior.
- A careful and detailed history is instrumental in determining whether an event was a seizure.
- Status epilepticus constitutes a neurologic emergency that carries high morbidity and mortality rates. Initial treatment is typically with IV benzodiazepines, followed by fosphenytoin or levetiracetam. If the seizure continues to be refractory after a second-line agent, the patient may require airway management.
- A simple febrile seizure is generalized, lasts less than 15 minutes, and occurs in a neurologically and developmentally normal child between 6 months and 60 months of age.
- Breath-holding spells occur in children 6 months to 6 years of age, and are triggered by pain or emotional upset. After a trigger, the child becomes pale or cyanotic and may lose consciousness, sometimes with a brief period of clonic movements or opisthotonos that may mimic a seizure.
- Warning signs of secondary headaches include sudden onset, occurrence with straining or exertion, association with neurologic symptoms, change in headache pattern, nocturnal awakening, worsening in a recumbent position, and bilateral occipital headaches.
- If there are red flags on the history or physical exam, radiologic evaluation by computed tomography (CT), magnetic resonance imaging (MRI), or both may be necessary to rule out secondary causes of headache, such as intracranial hemorrhage, subarachnoid hemorrhage, brain tumor, or brain abscess.
- A toxicology screen is the test with the highest diagnostic yield for acute-onset ataxia in children.
- In children, 40% of ataxia cases are caused by acute cerebellar ataxia.
- Approximately 45% to 60% of all childhood brain tumors arise in the brainstem or cerebellum and can manifest with slowly progressive ataxia.
- When assessing an infant or child with motor weakness, it is important to distinguish presentations consistent with upper motor neuron pathology from lower motor neuron processes.
- Strokes represent a pediatric neurologic emergency and may be hemorrhagic or ischemic in nature. Imaging with CT or MRI can help confirm the diagnosis of stroke. Children with stroke may present with less specific signs such as headache, seizure, or alteration level of consciousness.
- Children presenting with suspected or confirmed strokes should be emergently transferred to a pediatric stroke center for timely consideration of therapies.
- Spinal cord compression is a medical emergency and requires prompt diagnosis and treatment. It may arise from trauma, infection and inflammation, or malignancy.
- The diagnosis of Guillain-Barré syndrome (GBS) is largely clinical, although lumbar puncture (LP) may be helpful in confirming the diagnosis. Patients with GBS are at risk for respiratory compromise and should be admitted to the hospital for observation and supportive care.
- The diagnosis of infant botulism is largely clinical. If there is high clinical suspicion, treatment should be initiated promptly, without awaiting laboratory confirmation. Given the risk of respiratory compromise, infants with botulism should be admitted to the hospital for observation and supportive care.
- Diagnosis of myasthenia gravis is often not confirmed in the ED. The disorder can often be treated on an outpatient basis, but patients with truncal involvement and concern for respiratory compromise should be admitted to the hospital for observation and supportive care.

SEIZURES

Foundations

Seizures are a common pediatric neurologic disorder presenting to the emergency department (ED); up to 10% of children suffer at least one seizure in the first 16 years of life, most of which are febrile seizures. A seizure is defined as a paroxysmal event characterized by temporary involuntary changes in the patient caused by excessive synchronous electrical neuronal discharges of a group of cortical neurons. The clinical manifestations of the seizures depend on the location of the neurons involved, and may include alterations in motor activity, behavior, level of consciousness, or autonomic function. Infants and children younger than 5 years are thought to be more susceptible to seizures due to an immature nervous system, in which excitatory neuronal activity predominates and inhibitory systems are undeveloped. A paucity of synaptic connections and alterations in the synthesis of neurotransmitters may also play a role. Epilepsy is commonly defined as the occurrence of two or more unprovoked seizures. Provoked seizures are caused by an identifiable trigger and stem from a broad array of disturbances, including fever, metabolic derangements, and trauma (Table 169.1). Reflex seizures may be precipitated by a specific, identifiable stimulus, such as flashing lights on television or video games. Unprovoked seizures have no clear immediate precedent.

Clinical Features

The initial approach to the diagnosis and treatment of a pediatric patient with ongoing seizures involves resuscitation measures to ensure a patent and protected airway, adequate oxygenation and ventilation, stable circulation, and seizure control. The initial history should include duration of the seizures, preceding signs and *s*ymptoms, *a*llergies, current *m*edications, risk of ingestion, *p*ast medical history, *l*ast meal, and *e*vents preceding the seizure (SAMPLE). For patients who are no longer seizing on presentation, witnesses should be asked to provide a description of the event: type of body movements, accompanying

TABLE 169.1 Common Pediatric Presentations and Associated Differential Diagnoses

Pediatric Presentation	Underlying Diagnoses to Consider
Seizure	Infection (meningitis, sepsis, encephalitis) Metabolic derangement Ingestion Trauma Intracranial mass Antiepileptic dose or medication effect (in patient with known seizure disorder)
Altered mental status	Vascular event (stroke, arteriovenous malformation, intracranial bleed) Infection (meningitis, sepsis, encephalitis) Trauma Ingestion (toxin, medication) Seizures (clinical or subclinical) Structural/anatomic (intracranial mass/tumor, hydrocephalus) Metabolic derangements (e.g., diabetic ketoacidosis, hypoglycemia, urea cycle defect) Intussusception
Headache	Nonpathologic: due to stress, inadequate sleep, dehydration, fever, viral infection Migraine Trauma, concussion Intracranial pathology: mass, bleeding, hydrocephalus Infection (e.g., meningitis, sepsis, encephalitis)
Ataxia/disorders of balance	Postviral, postinfectious syndrome Intracranial mass Ingestion Metabolic disorders
Motor dysfunction, weakness	Vascular event (stroke) Spinal cord dysfunction (e.g., secondary to trauma, infection, autoimmune disorder) Infection-related (e.g., Guillain-Barré syndrome, Lyme disease, botulism) Idiopathic (Bell palsy)

trauma, associated symptoms (e.g., urinary incontinence), duration, and postictal signs (e.g., period of sleepiness, lethargy or confusion). Patients with known seizure disorders should be asked about recent medication changes (i.e., new medications, missed doses, or dose adjustments) or any factors that may impact metabolism of medications (e.g., growth, diet change, illness, activity change).

The initial physical examination should focus on signs of systemic disease that can cause seizure, including evidence of meningitis or trauma and a review of the vital signs for hypertension or clinical toxidromes. After the seizure has resolved, a thorough examination should be completed, including a complete neurologic examination and funduscopic examination to assess for papilledema and retinal hemorrhages. Skin lesions may indicate a neurocutaneous disorder such as tuberous sclerosis or neurofibromatosis (Fig. 169.1 and 169.2) and café-au-lait spots or hypopigmented nevi. There is a high incidence of subclinical electrographic seizures in infants. Neonatal or infantile seizures may be subtle; apnea, sustained eye deviation, chewing, or

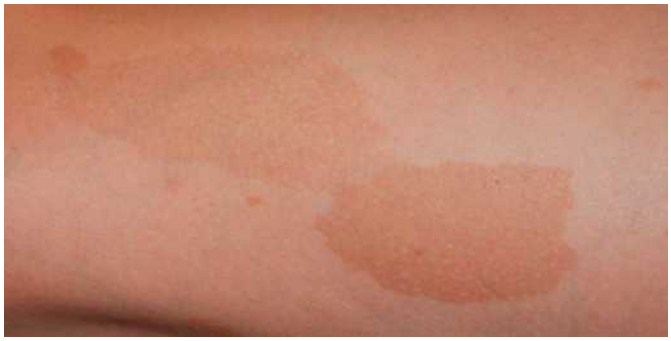

Fig. 169.1 Café-au-lait spots as seen with neurofibromatosis. (From: Boyd KP, Korf BR, Theos A. Neurofibromatosis type I. *J Am Acad Dermatol*. 2009;61:1-16.)

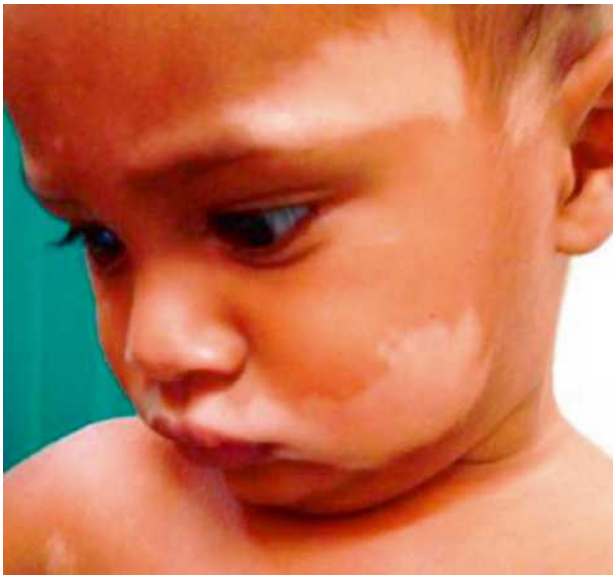

Fig. 169.2 Ash leaf spots as seen in tuberosclerosis. (From: Jindal R, Jain A, Gupta A, Shirazi N. Ash-leaf spots or naevus depigmentosus: a diagnostic challenge. *BMJ Case Rep*. 2013:2013.)

limb bicycling movements may be the only apparent signs. Focal clonic movements are often associated with an underlying structural lesion in the brain.

If the presenting signs and symptoms are consistent with seizure activity, the seizure can then be classified by type based on the following three elements[1]: (1) location of onset (focal versus generalized); (2) level of consciousness/awareness (aware, impaired awareness, altered level of consciousness); and (3) motor versus nonmotor (i.e., staring, nonconvulsive status epilepticus, versus convulsive) (Table 169.2).

Generalized Seizures

Generalized seizures may be convulsive or nonconvulsive. A convulsive seizure may start focally and generalize secondarily. Convulsive status epilepticus is a true neurologic emergency defined as 5 minutes or more of continuous seizure activity (clinical or electroencephalographic) or recurrent seizure activity without return to baseline between seizures.[2] Refractory status epilepticus is defined as status epilepticus that does not respond to first- and second-line antiepileptics. Super-refractory status epilepticus is defined as status epilepticus that persists 24 hours or more. Super-refractory status epilepticus is associated with a risk of mortality (3%) and long-term morbidity, including recurrent seizures and cognitive-behavioral impairment.[3] The diagnosis of convulsive status

epilepticus is usually obvious; however, the duration of the seizures is often underestimated because the intensity of the jerking tends to diminish with time. Status epilepticus occurs more frequently in children than in adults, particularly in those younger than 1 year. Medication changes, toxic ingestion, idiopathic epilepsy, metabolic derangements, and congenital abnormalities are common etiologies of pediatric seizures.

Nonconvulsive status epilepticus is marked by an altered mental status. Patients may demonstrate confusion, unresponsiveness, abnormal motor movements, twitches, lip smacking, automatisms, and sympathomimetic changes such as tachycardia, hypertension, and dilated pupils. An electroencephalogram (EEG) can confirm the diagnosis and should be obtained if nonconvulsive status is suspected. The most common type of generalized nonconvulsive seizure is absence seizures. Absence seizures are marked by a brief arrest of consciousness and movement, typically lasting 5 to 30 seconds; no postictal drowsiness occurs. It may be difficult to differentiate a brief complex partial seizure, in which a child may stare and not respond, from an absence seizure. Psychogenic nonepileptic seizures (PNES), caused by psychological factors, are events that look like generalized seizures but are not epileptic in nature. PNES are more common in patients with epilepsy, and patients with PNES are often later diagnosed with an epileptic seizure disorder.

Focal Onset

There are two types of partial (i.e., focal) seizures—complex and simple. In simple partial seizures, the patient experiences no change in mentation. In complex partial seizures, the patient experiences a change in level of awareness, and may exhibit bizarre behaviors, including staring, lip smacking, wandering, or picking at clothing. An important subcategory of focal seizures is composed of benign focal epilepsies of childhood, which are idiopathic in nature (i.e., they do not result from abnormalities in brain structure or injury to the brain). Benign focal epilepsies spontaneously resolve over time; benign childhood epilepsy with centrotemporal spikes (i.e., benign rolandic epilepsy) is most common and represents 10% to 20% of all childhood epilepsies.

The etiology of seizures can be divided into three categories—acute symptomatic, remote symptomatic, and idiopathic. Acute symptomatic seizures are provoked by an acute event such as fever. Remote symptomatic seizures are due to a preexisting or remote central nervous system (CNS) lesion such as cerebral palsy, neurocutaneous disorders, neurodegenerative disease, or a congenital brain malformation. Idiopathic seizures have no identifiable cause (Table 169.3).

Fever is the most common cause of acute symptomatic seizures. A febrile seizure is defined as a seizure occurring in the presence of fever without CNS infection or other cause and occurs in up to 5% of children. A simple febrile seizure is generalized, lasts less than 15 minutes, and occurs in a neurologically and developmentally normal child between 6 months and 60 months of age. Complex febrile seizures are diagnosed when multiple seizures occur during the same illness, the seizures are longer than 15 minutes, or the seizures have a focal component. Febrile seizures typically occur early in the course of illness; higher temperature or reduction of fever with antipyretics does not reduce the risk of seizure. Meningitis should be considered

TABLE 169.2 Classification of Seizures

Onset	Focal Onset	Generalized Onset	Unknown Onset
Awareness	Aware Impaired awareness	Impaired awareness	Unsure of awareness
Other Features	Motor Nonmotor	Motor Nonmotor (Absence)	Nonmotor (Absence)
	May progress from focal to bilateral tonic-clonic (generalized)		*Unclassified seizures do not fit in any other category*

(Adapted from: Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58:522-530; and Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia.* 2015;56:1515-1523.)

TABLE 169.3 Causes of Seizures

CAUSE	EXAMPLES
Fever (febrile seizure)	
• Infectious process	Meningitis, encephalitis, brain abscess, other infectious process (viral or bacterial infections including viral URI, pneumonia, otitis media, AGE, UTI)
• Traumatic lesions	Cerebral contusion, hemorrhage (subdural, epidural, subarachnoid, intraparenchymal), impact seizure
Toxic conditions	Drug intoxication, drug withdrawal
Metabolic disturbances	Hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, hypophosphatemia, hepatic or renal disorder, inborn errors of metabolism (e.g., aminoacidurias, organic acidurias, mitochondrial disease)
Neoplastic disease	Brain tumors
• Vascular disorders	Arteriovenous malformation, subarachnoid hemorrhage, intraparenchymal hemorrhage, cerebral venous thrombosis, ischemic infarct, hypertensive encephalopathy
• Neurocutaneous disorders	Neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome
Neurodegenerative disorders—miscellaneous	Hypoxia, ventriculoperitoneal shunt malfunction, cerebral palsy, cerebral dysgenesis, primary epilepsy

in any patient with seizures and fever. However, a child whose mental status is normal before and after the seizure is very unlikely to have meningitis.[4] We recommend considering a lumbar puncture in infants younger than 6 months presenting with febrile seizures, especially those with complex features or who have other risk factors for bacterial meningitis (e.g., underimmunized, comorbid disease, immunocompromised).

Electrolyte derangements including hypoglycemia, hyponatremia, and hypernatremia are other common causes of acute symptomatic seizures in children. Hypoglycemia resulting in seizure may be the first presentation of an infant with an underlying metabolic disease. Dehydration is the most common cause of *hyper*natremia, whereas *hypo*natremia may be secondary to overdilution of infant formula—a feeding history should be obtained in infants with abnormal serum sodium levels. Hypocalcemia and hypomagnesemia may lead to muscle spasms, paresthesias, hyperactive reflexes, weakness, tetany, or seizures. Hypocalcemic seizures are a common cause of neonatal seizures.

Posttraumatic seizures occur in as many as 15% of children after head injury. Impact seizures, occurring within 1 hour of a head trauma, are often not associated with significant injury or with the development of epilepsy and therefore trigger diagnostic imaging with CT. It may be difficult to distinguish impact seizures from those associated with intracranial injury; existing clinical decision rules and electronic decision support systems should determine need for intracranial imaging.[5] Early posttraumatic seizures, occurring within the first week of injury, may arise from cerebral edema or intracranial hemorrhage or contusion.

Brain tumors and intracranial masses can present with seizures, depending on their location. However, infratentorial tumors, the most common location in the pediatric population, do not typically cause seizures. A seizure may be the presenting sign of stroke or vascular anomaly (discussed in more detail later in this chapter). Numerous drugs are known to cause seizures in children, especially in overdose. Cyclic antidepressants, cocaine and other stimulants, antihistamines, and isoniazid are the most common agents of drug-induced seizures. Seizures may occur during drug withdrawal from benzodiazepines or ethanol, usually within 48 hours of cessation.

Differential Diagnoses

Paroxysmal alterations in level of consciousness or motor activity may be confused with seizure activity in children (Table 169.4). Syncope can be mistaken for a seizure, as it is characterized by a sudden loss of consciousness and motor tone caused by a transient, global cerebral hypoperfusion. The patient may complain of lightheadedness and blurry vision or appear pale and sweaty prior to the event. Brief jerking movements with trembling or stiffening are common with syncopal events, but should not be prolonged, and postictal confusion or lethargy does not occur. Vasovagal syncope is common in otherwise healthy children and does not warrant further evaluation unless recurrent. Syncope or seizure-like events occurring during activities or associated with palpitations may be a presentation of potentially fatal cardiogenic syncope, such as prolonged QTc syndrome; patients should have an ECG obtained in their evaluation. Breath-holding spells occur in up to 5% of children and are triggered by pain or emotional upset. The first episode usually occurs between the ages of 6 and 18 months, with episodes recurring up to 6 years of age. After a trigger, the child becomes pale or cyanotic and may lose consciousness, sometimes with a brief period of clonic movements or opisthotonos. The average attack lasts approximately 40 seconds. A history of recurrent episodes associated with crying may be helpful in distinguishing these from seizures or brief resolved unexplained events. Migraines may mimic seizures or stroke, particularly when they are accompanied by an aura, motor dysfunction, clouding of consciousness, or vomiting.

TABLE 169.4 Disorders That Mimic Seizures

Age Group	Features
Neonates	Jitteriness
	Benign neonatal sleep myoclonus
	Nonepileptic apnea
	Opisthotonos
	Normal movement
Nonneonates	Breath-holding spells
	Rigors or chills
	Gastroesophageal reflux (Sandifer syndrome)
	Migraine
	Benign paroxysmal vertigo of childhood
	Syncope
	Neurovascular event
	Sleep disorders
	Sleep myoclonus
	Narcolepsy
	Nightmares, night terrors, somnambulism
	Movement disorders
	Tics or stereotypies
	Infantile shuddering attacks
	Paroxysmal choreoathetosis or dystonia
	Behavioral or psychiatric disturbances
	Psychogenic seizures
	Panic attack

Disorders of sleep are distinguished by excessive daytime sleepiness or by disordered nighttime sleep. Patients with narcolepsy have daytime sleep attacks, sleep paralysis, hypnagogic hallucinations (i.e., vivid hallucinations while falling asleep), and cataplexy (i.e., sudden loss of motor tone). Cataplexy may be mistaken for atonic or absence seizures. Nocturnal enuresis may be a symptom of unwitnessed nighttime seizure associated with incontinence. In night terrors (pavor nocturnus), the child suddenly wakens, crying inconsolably, and is relatively unresponsive. The child returns to sleep and does not typically recall the event. Sleep walking (somnambulism) and sleep talking (somniloquy) are common among school-age children.

Movement disorders may mimic seizures. Tics are rapid, repetitive, brief involuntary movements that occur intermittently and in flurries. Those most commonly seen are eye blinking and head shaking. Patients do not lose consciousness. Sydenham chorea is an autoimmune-mediated systemic inflammatory response that occurs in association with a group A streptococcal pharyngitis infection. It typically manifests with irregular, nonrhythmic, involuntary jerking of the extremities and face, and may present during the acute phase of the streptococcal infection or as a latent manifestation months after the initial illness. Shudder attacks, with movements like the chill experienced when cold water runs down the back, are uncommon but easily mistaken for seizures. Paroxysmal choreoathetosis is an abnormal motor movement that may be spontaneous or triggered by the child's movement.

Behavioral or psychiatric disturbances can produce behaviors that may appear epileptic. Panic attacks may be mistaken for complex partial seizures, with a sudden sensation of intense fear accompanied by shortness of breath, dizziness, palpitations, sweating, choking, chest discomfort, and fear of dying. Psychogenic seizures or pseudoseizures are involuntary events that mimic seizures. Many children with

psychogenic seizures also have epileptic seizures. Prolonged electroencephalographic with video monitoring may be necessary to differentiate an epileptic seizure from a psychogenic seizure.

Infants with gastrointestinal reflux may have Sandifer syndrome and appear to have seizure-like movements with episodes of abnormal posturing, arching of the back, and torticollis.

Management

The initial management of any actively seizing child involves ensuring patency of the airway, adequate oxygenation and ventilation, and support of circulation. Oxygen should be applied via cannula or face mask, and intravenous (IV) or intraosseous (IO) access quickly obtained. Monitoring end-tidal carbon dioxide may be helpful to assess ventilatory status. Patients with ongoing convulsions are at risk for hypoventilation and apnea, and preparations should be made to assist ventilation. The goal is to rapidly stop the seizure with antiepileptic medication while assessing for the underlying cause.

Hypoglycemia causing seizures in infants and children is treated with an IV bolus of 10% dextrose, 5 mL/kg, with repeat boluses as needed to normalize the serum glucose level. Severe symptomatic hyponatremia presenting with seizures is treated with the administration of 3% saline (3 mL/kg IV infused over 30 minutes) to raise the serum sodium chloride level by 3 to 7 mEq/L. Hypernatremia should be corrected slowly over 48 hours. Hypocalcemia is treated with 10% calcium gluconate, 100 mg/kg IV over 5 to 10 minutes; the patient should be on a cardiac monitor during the infusion. Toxic ingestions are treated based on the specific toxin involved. Seizures caused by isoniazid (INH) poisoning are particularly resistant to standard seizure treatment, yet respond to pyridoxine. The dose of pyridoxine is 1 g IV for every gram of INH ingested. When the quantity of INH ingested is unknown, 5 g IV may be administered to an adult and 70 mg/kg (maximum, 5 g) to a child at rate of 1 g/minute until seizure stops or maximum dose.

Status Epilepticus

Status epilepticus is a true medical emergency. The patient should be positioned to maximize ventilation and prevent aspiration; attempts should be made to immobilize the cervical spine if trauma is suspected. Oxygen should be administered by nasal cannula or face mask with a bag valve mask for positive pressure if ventilation is inadequate. A large suction catheter should be available to suction oropharyngeal secretions. In younger patients, the tongue may obstruct the airway; a nasopharyngeal airway should be used to improve ventilation unless there is significant facial trauma. Oral pharyngeal airways may lead to vomiting when the seizure resolves and are often not utilized in treatment of seizures. If there is evidence of increased ICP, the head of the bed should be elevated. In a prolonged seizure, treatment with multiple medications or increased metabolic demand may lead to respiratory failure, necessitating intubation. We suggest that noninvasive measures are used to support ventilation in the initial phases of treatment before moving to intubation. If the decision is made to intubate, a sedative agent with antiepileptic activity should be selected (e.g., propofol, ketamine). In addition, a short-acting neuromuscular blocker (e.g., succinylcholine) is preferred to allow for monitoring of continued seizure activity as long as other contraindications to its use are not present.

Heart rate, blood pressure, respiratory rate, and pulse oximetry should be monitored and hyperthermia treated with antipyretics and cooling blankets. An IV line or, if an IV cannot be established, an IO line should be placed and blood samples sent for electrolyte values, glucose concentration (including rapid blood glucose test), calcium and magnesium levels, renal function tests, liver function tests, antiepileptic levels (when indicated), and CBC. Urine should be sent for toxicology. Metabolic abnormalities should be corrected.

Anticonvulsant treatment should begin as quickly as possible (Fig. 169.3).[6] Delays in the initiation of benzodiazepines of greater than 10 minutes is associated with higher frequency of death, longer seizure duration, and more complications.[7] Benzodiazepines, particularly lorazepam and diazepam, are the initial drugs of choice in the treatment of status epilepticus; they diffuse quickly into the CNS, rapidly terminating seizure activity 70% of the time. Hypotension, respiratory depression, and impaired consciousness may occur after administration. Intranasal, buccal, or intramuscular routes may be used if IV or IO access cannot be obtained within the first 1 to 2 minutes of resuscitation and are preferable to rectal administration. Recommended doses for these non-IV preparations are shown in Fig. 169.3.

A second dose of benzodiazepine should be administered only after 5 minutes of continued seizure activity following the first dose. If the seizure persists an additional 5 minutes after giving the second benzodiazepine dose, consider administering a third benzodiazepine dose and load with a second-line agent. The choices of second-line agents include levetiracetam, fosphenytoin, or valproic acid (Fig. 169.3).[6] There is limited evidence that one of these agents is preferred to the others. Recent controlled trials comparing phenytoin or phosphenytion to levetiracetam did not note a difference in the cessation of seizures.[8,9] One trial in Pakistan noted fewer adverse events and an improved efficacy for levetiracetam compared to phenytoin.[10] Valproic acid is contraindicated in the presence of liver disease, thrombocytopenia, or possible metabolic disease. There is limited evidence consisting of case reports that ketamine may be effective in treating refractory status epilepticus compared to conventional anesthetics and other agents.[11]

Fosphenytoin is a water-soluble phosphate ester of phenytoin that is rapidly converted in plasma to phenytoin. Unlike phenytoin, fosphenytoin can be administered intramuscularly and with common IV solutions and is substantially less cardio-toxic and less sclerosing to the vasculature. In addition, it can be given three times more rapidly than phenytoin. Fosphenytoin achieves plasma concentrations similar to those achieved for phenytoin. If seizures continue after loading with a second-line agent, another second-line agent can be administered. We recommend a propofol or a midazolam infusion as third-line agent to induce a coma. Other options include phenobarbital, pentobarbital, thiopental, or inhalant anesthetics. All have significant associated side effects and cause apnea, depressed consciousness, and hypotension; these side effects are more pronounced in the presence of benzodiazepines. Patients receiving these agents should receive continuous cardiorespiratory monitoring; staff and equipment should be readily available to support ventilation and advanced airway management.

Pediatric refractory status epilepticus is a high stakes and low frequency event and we recommend consultation with a neurologist when possible. Nonconvulsive status epilepticus is more difficult to recognize and often requires electroencephalography for diagnosis. Once the seizure has been effectively terminated, neuroimaging and lumbar puncture (LP) are often indicated to elucidate the cause of the seizure further.

Febrile Seizures

Children with simple febrile seizures do not require blood and urine testing other than as needed for the evaluation of fever source. An LP is not necessary in children older than 6 months with no signs of meningitis and no severe ill appearance before or after the seizure. If a child is less than 6 months or not fully immunized, an LP should be considered. Electroencephalography, neuroimaging, admission, or specialty consultation is not required after a first simple febrile seizure. Children who fully recover after a simple febrile seizure can almost always be sent home. Guidance for families should include high likelihood of recurrence (>33%), the small increased risk for the development of

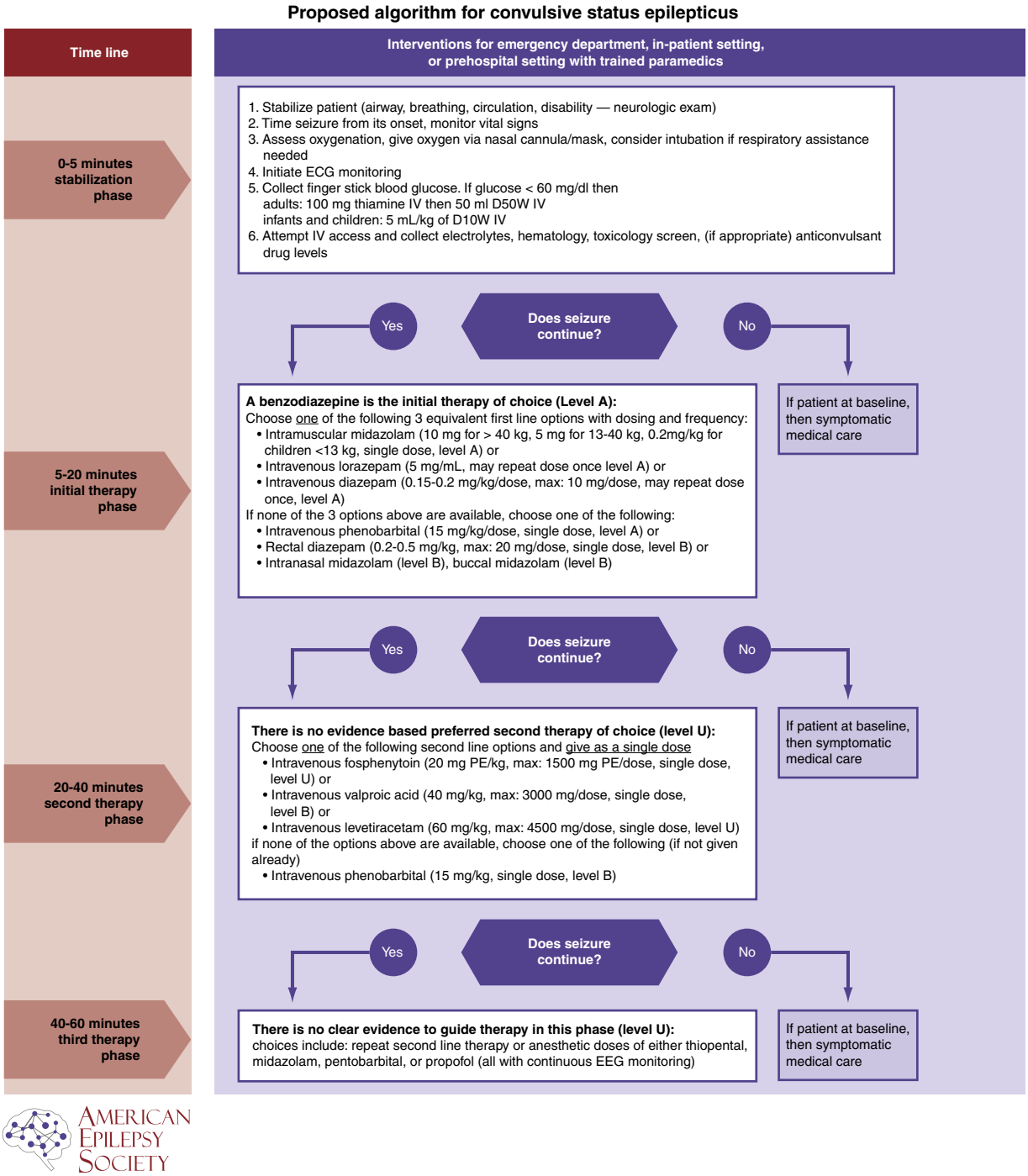

Fig. 169.3 Management of status epilepticus in infants >1 month of age and children. *IO,* Intraosseous; *IV,* intravenous. (Modified from: Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr.* 2016;16(1):48-61.)

afebrile seizures (2% to 5% or double the baseline risk), fever control, and emergency measures for seizure. Extensive anticipatory guidance and reassurance should be provided to the family with close follow-up with their pediatrician.

Afebrile Seizures

For infants and children older than 6 months who have had a first-time afebrile seizure and have returned to baseline, laboratory testing should be pursued in a targeted manner, based on clinical and historical findings. A seizure in the setting of recent vomiting, diarrhea or starvation may warrant examination of serum chemistries for possible electrolyte abnormalities. A toxicology screening history should be performed to explore any medications in the home and laboratory testing considered. A lumbar puncture should be considered for patients who present with unprovoked seizures and persistent abnormal mental status, do not return to baseline, or show signs of meningitis. An outpatient EEG may be appropriate in well-appearing children who have returned to baseline.

BOX 169.1 Common Causes of Neonatal Seizures[a]

Hypoxic ischemic encephalopathy
Central nervous system infection
Intracranial hemorrhage
Trauma (accidental and nonaccidental)
Metabolic derangements (e.g., hypocalcemia, hyponatremia)
Cerebral infarction
Chromosomal or congenital brain abnormalities
Inborn errors of metabolism
Drug withdrawal or intoxication

[a]Infants <1 month of age.

Emergent neuroimaging should be performed in infants and children with new focal neurologic deficits, persistent altered mental status (including status epilepticus), recent trauma, persistent headache, or partial seizures. Children with generalized unprovoked seizures and normal examination findings on presentation do not necessarily require emergent imaging. A focal abnormality on follow-up EEG may indicate a need for neuroimaging, which can be done on an outpatient basis. Children with a history of epilepsy do not need neuroimaging unless there is a change in clinical status or marked change in seizure pattern.

If imaging is indicated in the acute period, CT or MRI may be used. Although MRI provides superior anatomic detail, sedation may be needed, impeding assessment of the patient's mental status. When available, a rapid sequence MRI may provide sufficient information for the acute evaluation, with a full MRI planned for a later date.[12] Often the initial imaging study of choice, CT provides rapid imaging and is highly sensitive for the detection of acute blood and fractures.

Neonatal Seizures

The common underlying causes of neonatal seizures in infants <1 month of age differ from those in older children and adults (Box 169.1). In addition to congenital abnormalities, metabolic derangements, and birth-related injuries, neonatal seizures may be the only presenting sign of nonaccidental trauma. Diagnostic assessment of neonatal seizures is broad and includes metabolic testing (blood and urine), CSF analysis, and neuroimaging. Glucose, calcium, magnesium, and electrolyte levels (basic chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN] and creatinine), and CBC should be obtained; lactic acid, ammonia, ketones, and pH determinations should be considered to assess for inborn errors of metabolism. Clinical assessment for meningitis is not reliable in young infants; thus, a LP should be performed and fluid sent for cell, protein, and glucose determinations, culture, and herpes simplex PCR assay. Head CT or MRI should also be performed when the neonate is stabilized. In the unstable neonate, a head ultrasound may be performed at the bedside to evaluate for a neurosurgical emergency until more definitive imaging can be obtained.

Empirical antibiotic coverage should be initiated if an LP is suggestive of bacterial meningitis. Antiviral therapy should be administered if there are clinical concerns for herpes encephalitis, including skin or mucosal findings, continued seizures with no other clear cause, or concerning maternal history; CSF red cells are a late and ominous finding. Electrolyte abnormalities, including hypoglycemia, hypomagnesemia, and hyponatremia, should be promptly corrected as described previously. If seizures are refractory to medical treatment, empirical treatment with pyridoxine, 15–30 mg/kg/day (not to exceed 500 mg/day), should be considered for the potential for a deficiency, and this dose can be repeated over the course of 30 minutes. This should be done with EEG monitoring, as clinical seizure detection in neonates is not reliable..

Phenobarbital is the usual drug of choice for neonatal seizures. However, there is increasing evidence of phenobarbital-induced neuronal apoptosis, even with a single dose, and evidence of memory and learning difficulties in rat models.[13] Due to its potential harm, other potential first-line agents for the treatment of neonatal seizures are currently being investigated. If seizures continue, fosphenytoin may be loaded. Refractory seizures may be treated with a benzodiazepine infusion. Neonates with a first-time seizures should be admitted for continuous cardiorespiratory monitoring and evaluation by a neurologist.

Disposition

Hospitalization is unnecessary for most children after a first unprovoked brief seizure, as long as the neurologic examination is normal and follow-up evaluation arranged. Electroencephalography and imaging studies can be performed on an outpatient basis in consultation with a neurologist. Children who have had a prolonged seizure, or who are not back to their baseline within a few hours, should be admitted to the hospital. Hospitalization should also be considered if adequate follow-up evaluation cannot be arranged or in the case of extreme parental anxiety.

Anticonvulsant Therapy at Discharge

The decision to start anticonvulsant prophylaxis should be done in consultation with a pediatric neurologist, balancing the risk of recurrent seizures against potential complications associated with long-term medication use. Two-thirds of children with a first unprovoked seizure never experience a recurrence. The risk for recurrence is increased with the presence of neuroimaging or electroencephalographic abnormalities, developmental delay, family history of epilepsy, remote symptomatic seizure, first seizure occurring during sleep, and Todd paralysis. If none of these risk factors are present, the 5-year recurrence risk is only 21%. There is no evidence that early treatment with anticonvulsant medications after a single seizure alters the risk of epilepsy, nor is there evidence to show that a single self-limited seizure causes neurologic sequelae. In light of these considerations, anticonvulsants are generally started after a second unprovoked seizure. The ED provider should only initiate a seizure medication upon discharge in consultation with a pediatric neurologist and is dictated by the seizure type and the side effect profile of the agent (Table 169.5). Patients with acute symptomatic seizures associated with a risk factor for recurrence (e.g., cerebral hemorrhage, meningitis, or contusion) should be treated in the hospital with prophylactic anticonvulsants under the guidance of a neurologist; the decision to continue treatment should be made once the patient is stable.

ALTERED MENTAL STATUS

Foundations

Altered mental status is a common and challenging pediatric presentation. Groupings of possible causes include vascular events (e.g., stroke, arteriovenous malformation with bleed), infection (e.g., meningitis, sepsis, encephalitis), trauma, toxic ingestion, anatomic or structural abnormality (e.g., intracranial mass or tumor), headache syndromes (e.g., acute confusional migraines, postconcussive syndrome), metabolic derangements, (e.g., DKA, hypoglycemia), intussusception, or subclinical seizures (see Table 169.1). Individual diagnoses associated with altered mental status will not be explored in full detail in this chapter. However, a guideline for approaching and managing pediatric patients in the ED with altered mental status will be presented.

Clinical Features

Altered mental status in children has a varied spectrum of clinical presentations and may include abnormalities in cognition, behavior, or memory. In children, these are manifested as an altered level of

TABLE 169.5 Commonly Used Anticonvulsants in Children

Drug	Seizure Type	Typical Daily Dose (mg/kg)	Therapeutic Level (μg/mL)
Carbamazepine (Tegretol)	Partial, GTC	10–20 (max 1000 mg/day)	4–12
Ethosuximide (Zarontin)	Absence	15–30 (max 1500 mg/day)	1.5–10
Phenobarbital	Partial, GTC	3–6	15–40
Phenytoin (Dilantin)	Partial, GTC	4–10	10–20
Valproic acid (Depakene, Depakote)	Atonic, GTC	15–40	40–120
Lamotrigine (Lamictal)	Partial, GTC, absence, Lennox-Gastaut syndrome	5–15 (1–5 if taking valproic acid)	Not routinely measured
Levetiracetam (Keppra)	Partial, GTC, myoclonic	20–60	Not routinely measured
Topiramate (Topamax)	Partial, GTC, myoclonic, Lennox-Gastaut syndrome	5–9	Not routinely measured
Clonazepam (Klonopin)	GTC, atonic, myoclonic	0.05–0.2	Not routinely measured

Starting doses for each drug may be lower than typical daily dose, and typical daily doses may fall outside the ranges noted in accordance with the child's underlying medical conditions and other medications.

GTC, Generalized tonic-clonic.

consciousness, excessive sleepiness, irritability, lethargy, or abnormal behavior. The nature of the altered mental status (e.g., lethargy versus coma), as well as the time course and concurrent findings (e.g., fever or focal neurologic signs), should guide evaluation. Information obtained in the history may be critical to diagnoses of trauma, toxic ingestion, atypical migraine, or infection.

During the initial assessment of an altered infant or child, vital signs can be essential to understanding the underlying diagnosis. Heart rate, blood pressure, and respiratory rate, for example, may provide information about conditions such as toxic ingestion (e.g., hyperpnea with salicylate ingestions), elevated intracranial pressure (e.g., Cushing triad), or metabolic derangements, such as diabetic ketoacidosis (often presenting with tachycardia and hyperpnea). Level of consciousness may be readily assessed using the AVPU scale: ***a***lert (alert and spontaneously interactive), ***v***erbal (responds to verbal cues), ***p***ainful (responds only to painful stimuli), ***u***nresponsive (unresponsive to all external stimuli). Additionally, identifying focal neurologic deficits and the presence or absence of fever will aid in the diagnostic evaluation.

Special consideration should be given to conditions that need emergent treatment or can lead to substantial morbidity or mortality. Examples include meningitis, intracranial bleed, toxic ingestion, and stroke. In infants less than one month old, the absence of fever does not eliminate the possibility of a serious bacterial infection and these infants often demonstrate vague findings: decreased tone, poor feeding, weak suck, increased sleepiness, or fussiness, with or without abnormal vital signs. In the ill-appearing or altered infant, clinical signs are often nonlocalizing and, therefore, can present a diagnostic challenge. In this age group, there are few distinguishing features to differentiate sepsis from meningitis, metabolic derangements, or an acute abdomen.

Differential Diagnoses

The breadth of differential diagnoses associated with altered mental status in children involves a broad spectrum of potential management interventions in the ED. The mnemonic AEIOUTIPS, as outlined in Box 169.2, can assist the emergency clinician in the differential diagnosis and determining priorities for management. With the recent legalization of marijuana in many states, there has been an increase in the presentation of altered mental status due to cannabinoid ingestion in infants and children.[14] With the current opioid epidemic, ingestion or cutaneous exposure to opioids should be considered in all pediatric cases of altered mental status.

BOX 169.2 AEIOU TIPS Mnemonic for Altered Mental Status in Children

A–**a**mmonia, **a**lcohol, **a**typical migraine, **a**buse
E–**e**lectrolytes, **e**pilepsy, **e**ncephalitis
I–**i**nsulin (hypoglycemia), **i**ntussusception, **i**nborn errors of metabolism
O–**o**xygen (hypoxia), **o**piates, **o**verdose
U–**u**remia
T–**t**rauma, **t**umor
I–**i**nfection
P–**p**oisoning, **p**sychiatric
S–**s**eizure, **s**epsis, **s**ubarachnoid hemorrhage

Diagnostic Testing

After evaluation and stabilization of the airway, breathing, and circulation, priorities include obtaining a bedside glucose test, rapid IV access, and laboratory testing. A point-of-care electrolyte test or blood gas can quickly assess pH, sodium, and lactate levels. Toxicology screens are warranted when a toxidrome or a risk of exposure are identified, but should not delay empiric treatment. Emergent imaging by CT or MRI should be obtained when focal neurologic deficits are present in conjunction with a history suggestive of an acute intracranial process (headaches, trauma). When inflicted head injury is suspected as an etiology of altered mental status in an infant, a head CT should be obtained. The need for a LP should be considered based on vaccination history, exposures, immunologic state, and physical exam. Antibiotic and antiviral therapy for the patient with suspected bacterial meningitis should not be delayed by a LP. If the history or physical examination raises any concern for an acute abdominal process, abdominal ultrasound should be performed to evaluate for intussusception, as its presentation is often nonspecific and can present as altered mental status alone.

Management

After the initial resuscitation, including stabilization of the airway, breathing, and circulation, data obtained by the history, physical examination, and point of care labs often dictate the first steps in management. If lab values indicate hyperglycemia, hypoglycemia, or other electrolyte imbalances, early measures should be aimed at correcting these. If the abdominal examination reveals significant tenderness, a

radiograph or ultrasound should be obtained to evaluate for surgical etiologies, including intussusception, perforation or obstruction. In ill-appearing children for which a surgical cause is suspected, we recommend emergent surgical consultation. Head imaging may also help guide early management. If there is a concern for toxic ingestion, efforts will quickly be directed at the correction of perturbations associated with the offending agent (e.g., naloxone for opioids).

When bacterial meningitis is in the differential diagnosis of altered mental status, but not highly suspected, it is reasonable to consider risk stratification of the patient to determine if antibiotics can be withheld until obtaining further information (e.g., CSF, white cell count). Finally, acyclovir should be administered to an ill or febrile infant with a history of maternal herpes simplex virus (HSV) infection, presence of vesicles on the skin, seizures, or focal neurologic signs. If a child lives or has visited an area that is endemic with infections associated with altered mental status, further evaluation and treatment should be considered (e.g., malaria, Lyme disease).

Disposition

All patients with persistent altered mental status should be admitted to the hospital for additional evaluation and monitoring for improvement or worsening. In selected cases, when the altered mental status is self-limited, the patient may be observed and discharged home with close follow-up with a primary care provider.

HEADACHES

Foundations

Headache is a common problem in children and adolescents, with 40% of children experiencing a headache by 7 years, and 75% by 15 years of age. Migraine, one of the most common causes of headache in childhood, has a prevalence of up to 20% by 15 years of age. Although most pediatric patients have benign causes of headaches, a thorough history and physical examination should be conducted to evaluate for serious and time-sensitive underlying pathologies. The history and physical should guide decisions related to the need for emergent neuroimaging.

Clinical Features

Headaches can be classified into five temporal patterns—acute, acute recurrent, chronic progressive, chronic nonprogressive, and mixed. An acute headache is new in onset and different from previous headaches; it can herald a broad range of conditions, ranging from a viral illness to subarachnoid hemorrhage. An acute headache with weakness, seizures, speech difficulty, ataxia, or neurologic deficits should prompt evaluation of time-sensitive conditions, such as a stroke.[15] Acute recurrent headaches are periodic events separated by pain-free intervals. Chronic progressive headaches continue over weeks to months. They can signify serious medical disorders, such as brain tumors or arteriovenous malformations. Chronic nonprogressive headaches usually occur for years and are classified as primary headaches (as opposed to secondary symptomatic headaches, which are caused by an underlying medical problem). Mixed headaches are acute recurrent headaches (e.g., migraines) superimposed on a pattern of daily chronic nonprogressive headaches.

The primary goal of the ED evaluation is to differentiate life-threatening causes of headaches, such as strokes or brain tumors, from primary headaches, such as migraines or tension headaches. The child's history is the most important component to an accurate diagnosis. The patient and family members should be asked about specific factors related to the headache, such as time of onset, duration, location, laterality, quality (e.g., sharp, dull, throbbing, or aching), relieving and exacerbating factors, precipitating factors (e.g., poor sleep, hunger, or specific foods), and associated symptoms (e.g., nausea, vomiting, or photophobia).

The emergency clinician should focus on a detailed history of the neurologic system to identify any related symptoms (e.g., vomiting, lethargy, ataxia, seizures, weakness, or visual disturbances) and a general review of other organ systems. Warning signs of secondary headaches include sudden onset, occurrence with straining or exertion, association with neurologic symptoms, worsening in a recumbent position, headache pattern change, nocturnal awakening, and bilateral occipital headaches. Additional information related to the past medical history (e.g., history of recent head trauma, neurologic or psychiatric disorders, hospital admissions, medications) should also be obtained, as well as any family history of headache syndromes. For those patients with a history of loss of developmental milestones, serious causes including central nervous system tumors should be considered.

The physical examination should be thorough to evaluate for infectious, toxic, and structural causes for the headache (e.g., strep pharyngitis, cannabinoid ingestion, tumor). Height, weight, and head circumference should be compared with standard percentiles and the child's previous growth history; a change in the rate or direction of head growth may indicate an intracerebral mass or hydrocephalus. The blood pressure should be carefully measured, with the use of age-appropriate cuff size and percentiles for age; hypertension may be a sign of increased ICP. An infant's fontanelle should be palpated for size and fullness, as well as auscultated for bruits associated with arteriovenous malformations. A skin examination should be performed to look for stigmata of neurocutaneous disorders, such as neurofibromatosis (café-au-lait spots; see Fig. 169.1) or tuberous sclerosis (ash leaf spots; see Fig. 169.2). The neurologic examination should begin with assessment of the child's mental status and overall development. For infants, observing their level of alertness, age-appropriate social interaction, overall tone, and general vigor is an essential component of the initial neurologic evaluation. Nonspecific findings such as irritability, fussiness, or poor feeding may be the only presenting signs in infants with headache. The neurologic examination should include a complete assessment: cranial nerves; gait analysis (when possible); cerebellar, sensory, and motor function testing; and evaluation of deep tendon reflexes. The ophthalmologic examination should include pupillary reactivity, visual acuity, extraocular movements, and funduscopic evaluation for papilledema or retinal hemorrhages. Observation of interactions between the patient and family may provide clues to potential family problems, depression, anxiety, or child abuse.

Differential Diagnoses

Headaches may be primary (e.g., migraines and cluster headaches) or secondary to an underlying disease process. The list of differential considerations for secondary headaches is extensive and should be considered in the context of the child's history and physical examination (Table 169.6).

Acute Headache

The acute headache is a common problem in children and adolescents and accompanies many infectious processes. In the absence of other signs of CNS involvement (e.g., nuchal rigidity, alteration in level of consciousness, or focal neurologic findings), headaches in febrile children usually do not constitute evidence of CNS infection; nonspecific viral illnesses or dehydration represent the most common diagnoses in children presenting to the ED with an acute headache.

Although far less common, arteriovenous malformations can be a trigger for a new severe headache. Intracranial arteriovenous malformations are structurally unstable and thus susceptible to spontaneous rupture. In children, the abrupt onset of a severe headache in the absence of trauma (especially when accompanied by focal neurologic findings) suggests an acute intracranial bleed, and a head CT should be

TABLE 169.6 Differential Diagnosis for Secondary Headache

Cause	Features
Trauma	Intracranial bleed
	Concussion
	Skull fracture
Structural	Neoplasm
	Arteriovenous malformation
	Congenital malformation
	Hydrocephalus
Systemic	Hypertension
	Metabolic (e.g., diabetes and ketoacidosis)
Infection	Meningitis
	Abscess
	Encephalitis
	Sinusitis
	Influenza
	Pyelonephritis
	Group A streptococcal pharyngitis
Toxic	Medication
	Ingestion

performed. Localized acute headaches without focal neurologic findings may be due to sinusitis, otitis media, dental disorders, or traumatic head injury. Headache associated with trauma should be carefully investigated for the possibility of subdural or epidural hematomas, fractures, and leptomeningeal cysts (a "growing" skull fracture, usually in a child <3 years of age, with a history of recent trauma). Ophthalmologic problems, such as astigmatism, refractory errors, eye strain, and squint, are occasionally responsible for headaches in children.

Chronic Progressive Headache

Chronic progressive headaches in children often signify underlying pathology. The development of increased ICP can be caused by brain tumors, hydrocephalus, impaired venous drainage, brain abscess, or intracranial bleeding. Headache that awakens the child from sleep (related to increased CSF production in the later hours of sleep), is present on first awakening, or is associated with early morning emesis is a classic symptom of increased ICP and suggests an intracranial mass or hydrocephalus. In the setting of an abnormal intracranial entity, such as a mass or CSF obstruction, impaired venous outflow in the supine position leads to excess volume inside the skull, generating elevated pressure. The physical examination may show signs of increased ICP—vital sign changes, including hypertension, bradycardia, and irregular respirations (i.e., Cushing triad); papilledema; brisk reflexes; cranial nerve deficits; positive Babinski sign; or decreased level of consciousness—as well as focal symptoms related to the location of the lesion (e.g., hemiparesis, ataxia, visual field deficits).

Headaches are more likely to be the first symptom of a brain tumor in older children, but may be a later finding in younger children. Frequently, there are associated symptoms: nausea, vomiting; visual effects, problems with walking, weakness, loss of developmental milestones, changes in personality or school performance, or speech changes. As symptoms progress and evolve, the diagnosis of a brain tumor is often made after one or more clinical visits for headache. Loss of developmental milestones can be a potential sign of a brain tumor in infancy and childhood. Neurologic findings in children newly diagnosed with brain tumors may include papilledema, abnormal eye movements, ataxia, abnormal tendon reflexes, abnormalities on the visual examination, or less specific signs of increased ICP.

Clinical findings of pseudotumor cerebri (i.e., idiopathic intracranial hypertension or benign intracranial hypertension) are secondary to the increased ICP and include papilledema (with or without sixth cranial nerve palsy) and visual field deficits. Idiopathic intracranial hypertension (i.e., pseudotumor cerebri) is more common in females and obese individuals, and in younger children can be associated with medications (e.g., vitamin A, steroids, birth control pills, tetracycline). Neuroimaging is normal in idiopathic intracranial hypertension and the LP usually demonstrates elevated pressure, greater than 25 cm H_2O, and normal CSF protein and glucose levels. Neuroimaging should precede LP when increased ICP is suspected. We suggest any neuroimaging performed in the evaluation of idiopathic intracranial hypertension to include imaging of the venous sinuses, as cerebral sinovenous thrombosis (CSVT) can present similarly. Treatment is usually with diuretics, with or without an initial LP for therapeutic removal of CSF.

Brain abscess can result from meningitis, head trauma, chronic otitis media, sinusitis, or septic embolization in children with congenital heart disease. Focal neurologic signs, as well as fever and headache, may be present, but the patient may look surprisingly well. CT of the head without contrast enhancement is not sufficiently sensitive when an abscess is considered in the differential, but may be obtained; CT with and without contrast enhancement or MRI should be performed. CSF findings usually include a mild leukocytosis (10–200 leukocytes/mm^3), slightly elevated protein level, and normal glucose level. The CSF smear and culture do not usually reveal any organisms.

A subdural hematoma, epidural hematoma or intraparenchymal bleed are associated with head trauma. Headaches in these patients may evolve and progress over a relatively short time period. Symptoms include those associated with increased ICP, seizures, and focal neurologic deficits. The diagnosis is confirmed by neuroimaging.

Chronic progressive headache also can be a symptom of systemic diseases, such as hypertension, collagen vascular disease, hypothyroidism, Lyme disease, mononucleosis, or inborn errors of metabolism.

Migraine Headache

The diagnosis of migraine is based on symptoms of recurrent headaches separated by pain-free intervals. Migraine headaches are multifactorial in cause, with environmental and genetic contributions. The principal mechanism of migraine headaches is thought to involve a primary dysfunction of the brain in which a wave of spreading cortical neuronal depression is accompanied by vascular changes. Derangement of the trigemino-vascular reflex results in alterations of regional blood flow, and this neurovascular interaction is thought to contribute to neurogenic inflammation and the development of migraine headaches. Serotonin (5-hydroxytryptamine [5-HT]) may be a key mediator in this cascade of events, and serotonin agonists have been shown to relieve migraine pain.

Pediatric migraines may last from 2 to more than 72 hours and are more often bilateral than unilateral, which is more common in adults. Photophobia and phonophobia may be more difficult to assess in the young child or infant. Occipital headaches are rare and should raise clinical suspicion for a diagnosis other than migraine. Migraine headaches are classified primarily into migraine with and without an aura. Migraine without an aura, also known as common migraine, is the most frequent type of pediatric and adolescent migraine and includes the following criteria: more than 5 attacks that last 2 to 72 hours (untreated or unsuccessfully treated), accompanied by nausea, vomiting, photophobia or phonophobia, and including a minimum of 2 of the following criteria: unilateral or bilateral location, pulsing quality, moderate to severe intensity, and aggravated by routine physical activities.

Migraine with an aura, previously known as classic migraine, is diagnosed when at least two attacks fulfilling the diagnosis of migraine

occur accompanied by a variety of sensory warning symptoms, such as flickering lights (scintillations), obscuration or loss of vision (scotoma), and tingling or numbness (paresthesias). The aura typically develops over 5 or more minutes and completely resolves within 60 minutes.

Migraine variants or atypical migraines are more common in children. Hemiplegic migraine is characterized by the sudden onset of hemiparesis or hemiplegia, along with headache in the contralateral hemisphere. Even though symptoms usually last for hours or even days, patients are rarely left with permanent deficits. These patients often receive imaging on initial presentation to exclude other diagnoses. Ophthalmoplegic migraine is characterized by severe unilateral eye pain and headache, followed by ipsilateral third nerve palsy of variable degree. Rarely, the fourth or sixth cranial nerve, rather than the third nerve, may be affected. Basilar artery migraine, also common in children, is manifested with a combination of visual symptoms (e.g., transient bilateral blindness, blurred vision) and visual hallucinations, vertigo, ataxia, loss of consciousness, and drop attacks. An acute confusional state can be associated with migraines and is characterized by changes in personality, orientation, or behavior. The so-called Alice in Wonderland syndrome includes perceptions of distortion in body images and shapes; objects appear much larger (macropsia) or smaller (micropsia) before, during, or after the headache.

Migraine variants are not uncommon and can be misdiagnosed. Abdominal migraine is characterized by recurrent abdominal pain, nausea, vomiting, and recurrent headaches. Benign paroxysmal vertigo of childhood (distinct from benign paroxysmal positional vertigo) is manifested as headache accompanied by the sudden onset of vertigo, pallor, and nystagmus. Paroxysmal torticollis is defined as recurrent episodes of head tilt associated with headache, nausea, and vomiting. Of note, this is a diagnosis of exclusion; children with a head tilt, vomiting, and headache should first be evaluated for a posterior fossa lesion. Ocular migraine is characterized by transient monocular visual blurring to blindness with bright flashes of light.

The incidence of seizures is higher in patients with migraine than in the general population. Although epilepsy and migraine headache are distinct clinical syndromes, they share several characteristics, such as aura, vertigo, nausea, pallor, loss of consciousness, drowsy postictal state, confusion, and transient focal neurologic deficits. Headache as the sole manifestation of a seizure is uncommon; however, headaches frequently follow tonic, tonic-clonic, and brief complex partial seizures. Bilateral frontal throbbing headaches may follow episodes of status epilepticus. Further neurologic evaluation, including electroencephalography, may occasionally be necessary to distinguish between these two syndromes.

Chronic Nonprogressive Headache

Chronic nonprogressive headache is commonly seen in the adolescent population. Included in this category are muscle contraction and conversion headaches. The International Headache Society classification of headaches refers to these types of headaches as tension headaches. This type of headache includes the following symptoms: bilateral or unilateral, nonthrobbing, pressing, or bandlike tightness of mild to moderate intensity, and the absence of nausea, vomiting, and aura. Tension headaches are further classified as episodic (10–15 episodes/month lasting 30 minutes to 7 days) or chronic (>15 episodes/month for more than 6 months).

Cluster Headache

Cluster headache is a distinctive headache syndrome that is more common in males and rare in those younger than 10 years. Cluster headache is characterized by one to several attacks recurring each 24 hours, during several weeks to months. Headache-free periods between clusters may last months to years. The pain is throbbing, severe, and unilateral; occurs over the same orbito-temporal region, and is associated with ipsilateral scleral injection, lacrimation, nasal stuffiness, and sometimes a partial Horner's syndrome (enophthalmos, ptosis, miosis, and anhidrosis, unilateral, affecting sympathetic innervation of the eye). The pain lasts 30 minutes to several hours and can occur at any time of day or night.

BOX 169.3 Indications for Radiologic Imaging in Patients With Headache

Strongly Indicated If:

- Abnormal neurologic examination findings
- Signs and symptoms of elevated intracranial pressure
- Meningeal signs plus focal neurologic findings or altered mental status
- Progressive or new focal neurologic signs
- Significant head trauma
- Severe nocturnal headaches that awaken the patient from sleep or are present on awakening
- Severe (characterized by patient as "worst headache of my life") headaches; new or of increasing frequency and duration
- Presence of ventriculoperitoneal shunt
- Chronic progressive headache

Consider If:

- Headache or vomiting on awakening
- Unvarying location of headache, especially occipital
- Persistent headache plus no family history of migraine
- Neurocutaneous syndrome
- Age < 3 years (limited verbal skills)

Diagnostic Testing

Although many patients presenting to the ED with headache do not require neuroimaging or laboratory evaluation, if neuroimaging is obtained, MRI provides superior anatomic detail compared with CT, and is particularly useful in the detection of abnormalities in the sella turcica, posterior fossa, and cervicomedullary junction. MRI/A is also better for detecting arteriovenous malformations and low-grade tumors. CT scanning, however, is superior to MRI for the detection of acute blood and skull fractures, and therefore is often the modality of choice in the ED. Indications for the use of neuroimaging are presented in Box 169.3.

An LP is indicated for the diagnosis of an infectious process, subarachnoid hemorrhage not detected by CT, or idiopathic intracranial hypertension. In general, radiologic imaging should precede an LP on any patient with a headache or other red flags (e.g., early morning headaches and vomiting, progressively worsening headaches, or focal neurologic findings).

Chronic progressive headaches may be a symptom of a systemic disease. Guided by the history and physical examination, laboratory tests may include CBC, urinalysis, erythrocyte sedimentation rate, antinuclear antibody testing, liver function studies, thyroid function studies, serum lipid assay, serum magnesium concentration, lactate concentration, pyruvate concentration, and Lyme disease titers.

Management

Treatment of primary childhood headaches includes attention to initial pharmacologic management, as well as reassurance, removal of potential triggers, and initiation of a behavioral management program. The most important aspect of management is a thorough history and physical examination, past medical history of migraines or systemic disease, and targeted diagnostic evaluation for potentially life-threatening causes.

In addition to the use of standard oral analgesics, abortive treatment for children presenting to the ED with migraine headaches generally involves IV fluid hydration with a normal saline bolus, nonopioid analgesics (e.g., ibuprofen or IV ketorolac), and antiemetic (e.g., metoclopramide or prochlorperazine).[16] When migraines are refractory to traditional treatments or last over 72 hours, a neurologic consultation and admission should be considered.

Disposition

Children with primary headaches do not usually need hospitalization unless the diagnosis is uncertain and a serious cause of secondary headache is being considered. On discharge from the ED, patients may be given a variety of treatment recommendations while stressing the importance of close follow-up with a primary care provider for ongoing management of migraines.

Nonmedical interventions may have some impact and should be strongly considered. These include avoidance of triggers, placement of the child in a darkened room (with minimal or no extraneous noise), avoidance of hypoglycemia by feeding during a migraine, avoidance of caffeinated beverages (except for possible use as a migraine medication during an episode), application of a cool compress on the forehead, use of a gentle fan, breathing exercises, and relaxation techniques. Patients should be encouraged to keep a headache diary after discharge to track the duration, triggers, medication effects, and other characteristics of their headaches. Common triggers include insufficient or irregular sleep patterns, dehydration, missed meals, various psychosocial stressors, and certain foods (e.g., chocolate, processed meats, alcohol, hard cheeses, red wine, monosodium glutamate, yeast extracts, nuts, figs, aspartame, and sauerkraut).

In general, there are several outpatient treatment options available for acute migraine or other headache syndromes in children. For most patients, symptom relief can be achieved by oral analgesics such as acetaminophen or ibuprofen, along with rest, hydration, and avoidance of triggers. In other cases, additional abortive or prophylactic agents are needed, and the decision to initiate these agents should be deferred to a follow-up visit with the primary provider or neurologist. Treatment may include vasoconstrictors, sedatives, triptans, caffeine, dopamine antagonists, antiemetics or combination therapies. The placebo effect of many medications is high in children with migraines.

PEDIATRIC ATAXIA

Foundations

Ataxia comes from the Greek word *ataktos,* meaning "lacking order," and describes a pathologic abnormality of organization or modulation of movement. Congenital ataxia is associated with CNS macro or micro structural abnormalities. Acquired ataxia can be acute, episodic, or chronic. The chronic ataxias are usually caused by inherited metabolic or genetic disorders. Usually, ataxia is caused by cerebellar dysfunction, but lesions in the corticospinal tract or dorsal columns of the spinal cord may also be causative.

Clinical Features

Most children with ataxia are seen in the first few days after onset, usually because of a refusal to walk, unsteadiness of arm movements, or sudden development of a wide-based so-called drunken gait. The history should identify any recent infection, injury, inadvertent drug ingestion, or other family members with similar symptoms. Mental status is usually normal in cases of postinfectious ataxia; if abnormal, the possibility of ingestion, acute disseminated encephalomyelitis, or stroke should be considered. Nystagmus is common if the cerebellum is affected. Papilledema or cranial nerve palsies suggest hydrocephalus or a CNS lesion.

BOX 169.4 Causes of Childhood Ataxia

Acute cerebellar ataxia
Acute postinfectious demyelinating encephalomyelitis
Brainstem encephalitis
Drug ingestion
Guillain-Barré syndrome
Metabolic disorders
Aminoacidopathies
Mitochondrial disorders
Organic acidopathies
Urea cycle disorders
Migraine headaches
Multiple sclerosis
Neoplasm
Opsoclonus-myoclonus syndrome
Recurrent and chronic genetic ataxias
Seizures
Stroke
Vertebral artery dissection

Differential Diagnoses

Box 169.4 delineates common causes of pediatric ataxia. Approximately 40% of ataxia cases in children are caused by acute cerebellar ataxia. Boys are more commonly affected, with the highest incidence at the ages of 2 to 4 years. A history of recent illness with multiple causative agents is seen in 70% of patients, but varicella virus is the most common, associated with up to 26% of cases. The disease is thought to be due to an autoimmune phenomenon leading to cerebellar demyelination. Symptoms and signs are maximal at the onset, with the extremities more seriously affected than the trunk, and range from unsteadiness and wide-based gait to complete inability to walk. Mental status is normal, and nystagmus is common. Fever and seizures are uncommon outcomes.

Acute postinfectious demyelinating encephalomyelitis can also cause ataxia and occurs in the recovery phase of a viral illness or vaccination. It is distinguished from acute cerebellar ataxia by alteration in consciousness and multifocal neurologic deficits, as well as by fever and frequent occurrence of seizures. Brainstem encephalitis can involve the cerebellum, causing ataxia in association with focal neurologic abnormalities and respiratory irregularities. Potential causative agents include Epstein-Barr virus, *Listeria monocytogenes,* and enteroviruses.

Acute childhood ataxia can also be due to pharmacologic drug toxicity (e.g., anticonvulsants, benzodiazepines, alcohol, or antihistamines), or less commonly, from exposure to organic chemicals or heavy metals. The ataxia is usually accompanied by lethargy, confusion, and inappropriate speech or behavior, and nystagmus may be present.

Over half of all childhood brain tumors arise in the brainstem or cerebellum and can be manifested with slowly progressive ataxia. Acute decompensation can occur, with the development of hydrocephalus or hemorrhage into the lesion.

Head injuries with cerebellar contusion or hemorrhage can cause ataxia. Posterior circulation strokes are rare in children but should be considered after neck trauma, with possible vertebral artery dissection as a cause of the ataxia. Spontaneous vertebral artery dissections have also been reported in children.

The opsoclonus-myoclonus syndrome—ataxia; rapid, chaotic, multidirectional eye movements; and myoclonic jerks of the extremities, head, trunk, and face—is usually a presenting manifestation of neuroblastoma or ganglioneuroblastoma. Ataxia is thought to be due to a

paraneoplastic autoimmune phenomenon involving cross-reactivity of tumor and cerebellar antigens.

Ataxia can be seen in patients with basilar migraine and can be associated with vertigo, hemiparesis, cranial nerve dysfunction, nausea, vomiting, or headache. Loss of sensory input to the cerebellum can cause a sensory ataxia. Clinical manifestations include a Romberg sign, decreased deep tendon reflexes, and impaired proprioception and vibration sense. Of patients with Guillain-Barré syndrome (GBS), 15% have sensory ataxia. In the Miller-Fisher variant of GBS, the triad of ataxia, areflexia, and ophthalmoplegia of vertical gaze is characteristic.

Transient ataxia can be present in the ictal or postictal phase of seizures. Repeated attacks of ataxia can be the presenting manifestation of multiple sclerosis. Inborn errors of metabolism can also manifest with ataxia, acutely or intermittently, depending on dietary intake or the presence of other illness. Inborn errors of metabolism should be considered when ataxia is accompanied by lethargy, encephalopathy, vomiting, diarrhea, loss of muscle tone, or unusual body odor, as in urea acid cycle defects (e.g., aminoacidurias) or defects in pyruvate and lactate metabolism. Ataxia is associated with other inherited diseases such as Niemann-Pick, Tay-Sachs, and Wilson diseases.

The two most common genetic disorders associated with ataxia are Friedreich ataxia and ataxia-telangiectasia. Friedreich ataxia is a disorder of autosomal recessive inheritance characterized by progressive gait and limb disturbance. Affected patients demonstrate dysarthria, lower limb areflexia, proprioceptive sensory loss, and high-arched feet (pes cavus). Ataxia-telangiectasia is a disorder of recessive inheritance manifested as a truncal ataxia in infancy that leaves most patients wheelchair-bound by the age of 12 years. Oculocutaneous telangiectasias usually appear by the age of 3 to 5 years. These patients also demonstrate dysarthria, nystagmus, dystonic posturing, myoclonic jerks, and accelerated aging.

Diagnostic Testing

An accurate diagnosis for pediatric ataxia is dependent on a complete history and thorough physical examination, including testing of gait and cerebellar function. Urine and serum toxicology studies are the highest yield laboratory studies and should be performed on all patients.[17] CT and MRI findings are usually normal in patients with postinfectious ataxia, but demyelination, tumor, hydrocephalus, or traumatic injuries may be identified. Neuroimaging should be ordered if a patient has focal neurologic deficits in the setting of ataxia, but may be deferred in other patients if they have close follow-up.[18,19] CSF analysis may show mild pleocytosis or lymphocytosis in acute postinfectious ataxia; findings are normal in most other cases.

Admission for electroencephalography should be considered in patients with altered consciousness and fluctuating clinical signs of ataxia. Urinary catecholamine levels can be assayed for diagnosis of neuroblastoma. Additional testing may include a CBC, liver function tests, glucose, ammonia, lactate, pyruvate, and ketone levels, and determination of acid-base status. The four most high-yield tests are for levels of glucose, lactate, ketones, and ammonia. If all four of these are normal, it is unlikely that there is an inborn error. Any other laboratory tests should be ordered in consultation with a specialist and may include plasma and urinary amino acids, urine organic acids, CSF lactate, or serum biotinidase levels.

Management

Children with ataxia can be managed, depending on the cause, as outpatients with consultation with the primary care physician and/or pediatric neurology. Management of these patients often requires consultation in the ED by infectious disease or neurology specialists. Most children with acute postinfectious cerebellar ataxia recover completely, and treatment is supportive. Improvement is typically seen within 1 week, and the vast majority recover completely within 2 to 4 weeks. Some children exhibit persistent gait disturbances, ataxia, and delayed speech development.

Disposition

Children with persistent ataxia usually need hospital admission and consultation with a pediatric neurologist to identify causes of the ataxia not evident on the ED evaluation.

PEDIATRIC VERTIGO

Foundations

Vertigo, also discussed in Chapter 15, is defined as an illusion of movement, a sensation that the external world is revolving around an individual (objective vertigo) or that the affected person is revolving in space (subjective vertigo). Vertigo is well recognized to occur in the pediatric age group and has many potential causes. Disease processes that affect the balance of the vestibular, visual, and proprioceptive systems can cause vertigo by impairing the neural activity of the vestibular nucleus. Diseases of the ear, eighth cranial nerve, neck, brainstem, or eye can lead to vertiginous symptoms. Vertigo is characterized as central or peripheral, depending on whether the cause is in the CNS.

Clinical Features

Vertigo is often described as dizziness. There may be a history of sudden falls, grasping for support, or unwillingness to move. A review of systems should include those related to the ear, such as otalgia, hearing loss, and tinnitus. Other important historical features that should be determined include headache, loss of consciousness, head trauma or barotrauma, and family history of migraine or seizure disorders.

Diagnostic Testing

Patients can be divided into those who have hearing loss and those who have normal hearing. In the group with hearing loss, further characterization of the loss as conductive or sensorineural (using the Weber and Rinne tests) can help localize the peripheral lesion to the middle ear, labyrinth, or eighth cranial nerve.

Differential Diagnoses

Although vertigo is not as common in the pediatric age group as in adults, it has many potential causes (Box 169.5). It usually is helpful to separate conditions that cause vertigo into those with and without associated hearing loss.

Benign paroxysmal vertigo of childhood is defined by the repeated occurrence of vertiginous episodes lasting seconds to minutes, with occasional vomiting. In addition to being pale and diaphoretic, preverbal children may appear fearful, grasping onto a caregiver's leg for stability. This entity usually remits spontaneously within months to years. The most frequent cause of benign paroxysmal vertigo of childhood is a migraine headache, with vertigo occurring as the aura of an episode.

Patients with basilar artery migraines may also present with vertigo, hemiparesis, ataxia, palsies of the third, sixth, or seventh cranial nerve, drop attacks, and blindness in various combinations, followed by migraine headache. Children with benign paroxysmal vertigo of childhood or basilar migraines usually have a family history of migraine headaches.

Benign paroxysmal positional vertigo is rare in children, but can occur spontaneously as well as after trauma. It may present as early as in the second decade of life. It is believed to be due to otoliths that have moved out of their normal positions in the utricle and is corrected by canalith repositioning maneuvers (e.g., the Epley maneuver).

BOX 169.5 Causes of Pediatric Vertigo

Central Vertigo
Atrioventricular malformations
Brain abscess
Chiari malformations
Demyelinating disorders
Encephalitis
Meningitis
Migraine headaches
Neoplasm
Seizures
Trauma

Peripheral Vertigo
Alport syndrome
Benign paroxysmal torticollis
Benign paroxysmal vertigo of childhood
Benign positional vertigo
Cholesteatoma
Diabetes mellitus
Labyrinthine dysplasia or aplasia
Labyrinthine concussion
Labyrinthitis
Lyme disease
Otitis media, suppurative and serous
Ototoxins
Ocular disorders
Pendred syndrome
Perilymphatic fistula
Stenosis of the internal auditory canal
Syphilitic inner ear disease
Thyroid disease
Trauma
Usher syndrome
Vestibular neuronitis
Waardenburg syndrome (genetic disorder associated with deafness, wide-spaced eyes)

Ménière disease, caused by hydrops of the semimembranous labyrinth, is a syndrome of vertigo, fluctuating hearing loss, and tinnitus, and is responsible for up to 4% of cases of pediatric vertigo. Vestibular neuronitis, thought to be caused by viral infections, is manifested as vertigo without hearing loss. A preceding cold is found in 60% of patients. It is manifested with severe vertigo that resolves in a few days, after which the child will have vertigo only with rapid head movements, which persists for weeks or months until central compensation occurs.

Labyrinthitis is an inflammatory process involving the inner ear membranous labyrinth; it manifests with vertigo, hearing loss, and tinnitus. Cytomegalovirus, rubella virus, and rubeola viruses are common causative agents. Bacterial labyrinthitis usually occurs in association with meningitis and should be suspected in any ill child with vertigo and high fevers, especially in combination with a perforated tympanic membrane. Neurofibromatosis can be manifested with vertigo if it involves the superior vestibular nerve. Other genetic syndromes such as Alport syndrome are also associated with vertigo (see Box 169.5).

Ototoxic drugs, such as aminoglycosides and chemotherapeutic agents, can cause vertigo, usually in association with hearing loss. Cerebellar and brainstem lesions can also cause vertigo. Cranial nerve deficits associated with vertigo may indicate a brainstem lesion or tumor. Vertigo is the presenting symptom in up to 10% of cases of multiple sclerosis.

For most patients, the cause of vertigo cannot be established during their ED visit. A complete physical examination, including an otologic and neurologic evaluation, should be performed, including evaluation for nystagmus and cerebellar testing. Having the child hop and stand from a seated position on the floor, with eyes open and closed, can reveal vestibular dysfunction. Signs of other disease processes, such as café-au-lait spots in neurofibromatosis, may aid in the diagnosis.

Laboratory tests in the vertiginous patient should be dictated by the history and physical examination, and may include glucose and electrolyte levels, thyroid function tests, and viral titers or serologic studies (e.g., for Lyme disease or syphilis). CT or MRI is indicated for patients with a suspected underlying CNS abnormality (i.e., central vertigo).

Management

Management of the vertiginous patient depends on the underlying cause, which may not be evident in the ED. For acute symptomatic relief, vestibular suppressants such as meclizine and diazepam may be helpful. Patients with a positive Dix-Hallpike test should receive canalith repositioning maneuvers.

Disposition

Patients with suspected CNS infection, focal neurologic deficits, abnormal mental status, or inability to ambulate or tolerate oral fluids or medications should be admitted. Patients should follow up with their primary care provider and a neurologist or otolaryngologist for follow-up testing if vertigo persists.

MOTOR DYSFUNCTION

Acute weakness or motor abnormalities in the pediatric patient can result from pathology at a variety of levels in the neural axis. A complete neurologic assessment can indicate the location of pathology—upper motor neuron (i.e., motor neurons originating in the cerebral cortex or brainstem) or lower motor neuron (i.e., spinal cord anterior horn cells, peripheral nerves, neuromuscular junction, and the muscle itself). Generally, upper motor neuron pathology creates spasticity, increased tone, hyperreflexia, and no fasciculations. Lower motor neuron abnormalities result in decreased tone, poor reflexes, and muscle fasciculations.

STROKE

Foundations

Stroke is characterized by the acute and persistent onset of focal neurologic deficits. Less common in children than adults, pediatric strokes often go unrecognized, leading to delays in diagnosis and treatments. Often the cause of focal neurologic symptoms in children are stroke mimics (e.g., atypical migraine); however, the emergency clinician must always consider stroke in this differential, especially in those children with risk factors for stroke. Underlying conditions that predispose children to stroke include sickle cell disease, structural cardiac anomalies, homocystinuria, and moyamoya disease (Box 169.6). Vascular malformations, such as arteriovenous malformations, may cause hemorrhagic stroke or subarachnoid hemorrhage.

Strokes are classified as ischemic or hemorrhagic. In ischemic stroke, there is an interruption of blood supply to a particular area of the brain, resulting in hypoxic injury. In hemorrhagic stroke, the rupture of a blood vessel or an abnormal vascular structure causes focal damage. Hemorrhagic strokes are more common in children than adults, and often stem from unstable arteriovenous malformations.

BOX 169.6 Risk Factors for Pediatric Stroke

Cardiac
Congenital heart defects
Valvular heart disease
Right-to-left shunts
Cardiomyopathy
Endocarditis, myocarditis
Arrhythmia
Cardiac tumors
Cardiac surgery

Hematologic Disorders and Coagulopathies
Anemia
Sickle cell disease
Dehydration
Idiopathic thrombocytopenia purpura (ITP)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Thrombocytosis
Polycythemia
Disseminated intravascular coagulation
Leukemia or other neoplasm
Congenital and acquired coagulation disorders
Pregnancy and the postpartum period
Vasculitis, vasculopathies
Systemic lupus erythematosus
Polyarteritis nodosa
Takayasu arteritis
Kawasaki disease
Moyamoya syndrome, disease

Infection
Meningitis, encephalitis
Mastoiditis, otitis media
HIV
Varicella
Syphilis
Tuberculosis
Systemic infection

Metabolic, Miscellaneous
Homocystinuria
Fabry disease
Organic acidemia
Hyperlipidemia
Mitochondrial encephalopathy with lactic acidosis and strokelike episodes syndrome
Menkes disease

Other Vascular
Vasospasm (subarachnoid hemorrhage)
Migraine
Carotid ligation (e.g., extracorporeal membrane oxygenation)
Fibromuscular dysplasia
Cervicocephalic arterial dissection
Arteriovenous malformation
Arteriography
Hereditary hemorrhagic telangiectasia
Sturge-Weber syndrome
Intracranial aneurysm

Trauma (Including Nonaccidental)
Blunt and penetrating cervical trauma

Brain Tumor

Drugs
Cocaine
Amphetamines
Oral contraceptives
L-asparaginase

Clinical Features

Manifestations of stroke in infants and children are widely variable due to the potential affected areas of the brain, as well as the child's age and developmental level. Unlike adults who typically present with hemiparesis or localizable focal neurologic deficits, children often present with less specific symptoms such as headache, seizures, or altered level of consciousness. Seizures at stroke onset occur in 20% of pediatric cases, especially in those younger than 6 years of age.[20] The middle cerebral and anterior cerebral arteries are usually affected in children with stroke, generating upper extremity hemiplegia and lower extremity weakness, respectively. The posterior circulation, although less commonly involved, may produce ataxia, nystagmus, or vertigo, along with hemiparesis and hemianopsia.

Diagnostic Testing

Imaging of the brain can confirm the diagnosis of stroke in infants and children. A non-contrast head CT scan can reveal the presence of a bleed, but may not show evidence of ischemia if the stroke took place in the preceding 24 hours. Early consultation with a pediatric neurologist is prudent in children with a suspected stroke. Urgent MRI and MR angiography (MRA) are indicated if there is no evidence of hemorrhage on head CT and clinical suspicion for stroke remains high. If the child does not have a predisposing condition for stroke, additional laboratory evaluation may be helpful, including a CBC and coagulation studies, inflammatory markers, chemistry and lipid panels, and toxicology screen. Electrocardiography and echocardiography can reveal structural abnormalities associated with intracardiac shunts and clots.

Management

Initial pediatric stroke management is directed at stabilization of the airway, breathing, and circulation and controlling any seizure activity. To prevent secondary brain injury, hypoxemia and hypotension should be avoided. When present, hypertension should be managed with consideration of possible increased ICP, particularly in the setting of a hemorrhagic stroke. Blood pressure should be slowly reduced while maintaining cerebral perfusion pressure. The metabolic demands of the brain should be minimized by controlling seizures, fevers, pain, and agitation. Any hyperglycemia or hypoglycemia should be corrected, particularly in the setting of an ischemic stroke.

Additional therapy and definitive treatment of stroke in children are ultimately dictated by the type and extent of the stroke. Although data are limited for the use of thrombolytics and thrombectomy in pediatric stroke, effective utilization has increased in the last decade. When the clinical suspicion for acute ischemic stroke is high and the patient is presenting within the window for consideration of thrombolysis (currently 4.5 hours) or thrombectomy (currently 24 hours),[21]

the patient should be transferred emergently to a stroke center that has the capacity to effectively manage pediatric stroke. In the case of hemorrhagic stroke, neurosurgical intervention is often needed for intracranial decompression, blood evacuation, or control of active bleeding. For children with sickle cell disease, blood transfusion or exchange transfusion should be considered, in consultation with a hematologist and neurologist, to decrease the circulating level of hemoglobin S.

DISORDERS OF THE SPINAL CORD

Foundations

Disorders of the spinal cord may arise from within the spinal cord itself or from extrinsic causes, such as trauma or malignancy. Acute compression of the spinal cord is a medical emergency; rapid accurate assessment of children with acute spinal cord abnormalities can directly affect patient outcomes. Trauma, spinal masses, and infection or inflammation can all cause acute spinal cord compression. The mechanism of compression may be due to direct mass effect (e.g., from a tumor) or related to edema or hemorrhage from infection or trauma. Epidural abscesses are a common infectious cause of acute spinal cord compression and are typically caused by hematogenous spread of bacteria.

Infection or inflammation may also affect the spinal cord intrinsically. Transverse myelitis is an inflammation of the full width of the spinal cord (involving variable lengths of the cord) that manifests with demyelinating lesions at any level of the cord. It is thought to be autoimmune-mediated, often following a recent infection. Transverse myelitis typically evolves over hours to days, but may develop over a few weeks. Specific infections associated with transverse myelitis include Epstein-Barr virus, cytomegalovirus, measles, *Campylobacter jejuni,* and *Mycoplasma pneumoniae*.

Clinical Features

Regardless of the cause of acute spinal cord dysfunction, patients will present with certain characteristic findings, including paraplegia, hyporeflexia, and sensory deficits (complete sensory loss or paresthesias) below the level of the spinal cord lesion. Also, if the distal portion of the cord is affected, patients will have bowel and bladder incontinence. In the case of transverse myelitis, the thoracic region is usually affected. Children may demonstrate lower extremity paresthesias or pain with progressive weakness, which may be asymmetric, over a period of hours to days, and possibly urinary retention. There is often a history of a recent viral-like illness. An acute onset of local back pain with neurologic deficits suggests spinal cord compression due to a bleed, trauma, or infection. With infectious causes, pain may be the first sign, before fever, neurologic deficits, or other systemic signs. With oncologic processes such as spinal tumors, children may have a more insidious onset of symptoms and have evidence of spinal cord compression in the absence of pain.

Diagnostic Testing

A thorough history and physical examination can help diagnose children with acute spinal cord compression. A careful neurologic examination should include strength, deep tendon reflexes, sensation, and evaluation of anal sphincter tone. In suspected spinal cord compression, priority should be on emergent neuroimaging with MRI of the spine while immobilizing the patient. The use of gadolinium assists in identifying acute infectious and inflammatory lesions. CT is less helpful, and plain spine radiographs are of little value. An LP should not be performed when spinal cord compression is suspected. LP can be helpful in evaluating transverse myelitis, but should be performed only after confirmed by MRI.

Management and Disposition

Initial management steps for the patient with spinal cord trauma include immobilization of the spine and immediate neurosurgical consultation. Children with an epidural abscess identified on MRI should receive IV antibiotics and neurosurgical consultation for decompression or drainage. Corticosteroids should be administered only in select cases and in conjunction with neurosurgical consultation.

S. aureus is the most common pathogen in epidural abscesses; thus, initial IV antibiotic therapy in the ED should include vancomycin to cover methicillin-resistant *S. aureus* (in addition to methicillin-sensitive *S. aureus* [MSSA]) and coverage of gram-negative bacilli with a third- or fourth-generation cephalosporin, such as ceftazidime, ceftriaxone, or cefepime. Consideration of additional anaerobic coverage is warranted for higher risk individuals (e.g., associated sinus disease). Patient-specific conditions such as recent surgery or hospitalization may warrant additional coverage.

Surgical drainage in conjunction with IV antibiotic therapy is the mainstay of treatment of epidural abscesses. For spinal masses, neurosurgical intervention is needed to decompress the cord and further elucidate the diagnosis. Supportive care is the underpinning of treatment for transverse myelitis; these children should be hospitalized for observation, IV corticosteroid therapy, and consideration of additional immunotherapy. Initiation of IV corticosteroid therapy in the ED and its specific dosing and timing for children with transverse myelitis should be discussed with a neurologist. Although there are no randomized controlled trials to demonstrate the efficacy of IV corticosteroids in transverse myelitis, consensus favors their use.

GUILLAIN-BARRÉ SYNDROME

Foundations

Guillain-Barré syndrome (GBS) is an acute, demyelinating polyneuropathy that typically presents as transient, symmetric, ascending paralysis. GBS is thought to be autoimmune-mediated—a recent infection triggers an immune response, which, in turn, provokes acute peripheral nerve demyelination. Classically, patients with GBS have both motor and sensory nerve demyelination.

Children of all ages may be affected; however, it is uncommon in young toddlers and infants. Often, there is a history of a preceding minor viral or gastrointestinal illness in the weeks prior to presentation. *Campylobacter jejuni* is the most common infectious agent associated with GBS. The differential diagnosis for GBS is broad; a careful history and detailed neurologic examination will help localize the pathology to the peripheral nerves rather than to the brainstem, brain, spinal cord, neuromuscular junction, or muscle itself. The relatively acute and typically symmetrical nature of GBS paralysis helps distinguish this diagnosis.

Clinical Features

Lower extremity pain, paresthesias, and weakness in any combination may be the initial presenting symptoms of GBS, followed by progressive ascending weakness of the lower extremities. The weakness may progress rapidly over hours to involve the trunk and the muscles of respiration. Deep tendon reflexes are typically diminished or absent at the time of presentation. Cranial nerve abnormalities may also be present; in the Miller-Fisher variant of GBS, they represent the main findings, with oculomotor palsies, ataxia, and areflexia in the absence of extremity weakness.

Fig. 169.4 Infant with hypotonia, as seen with botulism. (From: Arnon SS, Schechter R, Maslanka SE, et al. Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med.* 2006;354:462-471.)

Diagnostic Testing

The diagnosis of GBS is largely clinical; however, a lumbar puncture can be helpful. CSF typically reveals an elevated protein level, with normal glucose, and white blood cell count, known as albumin cytologic dissociation.

Management and Disposition

Given the potential risk of respiratory compromise associated with progressive demyelination and weakness, patients with GBS should be admitted to the hospital for monitoring and supportive care. Bedside respiratory evaluations, such as forced vital capacity and negative inspiratory force trends, may be useful in predicting respiratory compromise. Treatment with plasma exchange and IV immunoglobulin may be used in severe cases.

INFANT BOTULISM

Foundations

Infant botulism typically affects infants younger than 6 to 8 months. It results from intestinal colonization with *Clostridium botulinum*. A neurotoxin produced by *C. botulinum* impairs acetylcholine release from the presynaptic membrane, thereby affecting skeletal muscle, smooth muscle, and autonomic function. Infants develop constipation and poor feeding, with subsequent hypotonia and weakness (Fig. 169.4), which may require respiratory support. Most United States cases of infant botulism are thought to arise from ingestion of environmental dust particles containing *C. botulinum* spores and may be associated with active construction areas in which there is disruption of the ground. Canned foods and honey are also potential reservoirs for *C. botulinum* spores.

Clinical Features

Infant botulism typically has an insidious onset of symptoms, commonly starting with constipation. Over time, infants develop poor feeding, lethargy, hypotonia, and weakness. On examination, infants may have decreased deep tendon reflexes, cranial nerve findings such as poor suck and gag, weak pupillary reflexes, or ptosis.

Diagnostic Testing

The diagnosis of botulism may be confirmed through isolation of botulinum toxin in the stool; however, this process may be delayed because infants are often constipated and laboratory processing times may be hours to days. As such, treatment should be initiated while awaiting confirmation of the toxin in a stool sample. Characteristic electromyography (EMG) findings of low-amplitude motor potentials of reduced duration can rapidly suggest the diagnosis.

Management and Disposition

Infants with botulism should be admitted to the hospital for supportive care, mechanical ventilation for depressed respiratory reflexes, and possibly nasogastric feeding. Botulism immune globulin is safe and effective and should be given IV as early as possible when the diagnosis is highly suspected, without awaiting confirmatory stool sample results. Initial dosing for botulism immunoglobulin in infants less than 1 year of age is 50 mg/kg of body weight in a single IV infusion.

MYASTHENIA GRAVIS

Foundations

Myasthenia gravis is an autoimmune disorder characterized by autoantibodies directed against the acetylcholine receptor of the neuromuscular junction. This action produces intermittent and fatigable weakness. Myasthenia gravis is usually seen in adults; however, there are three types that affect children—neonatal (transient), congenital, and juvenile. The juvenile form of myasthenia gravis presents similarly to the adult form and will be discussed here. Children with juvenile myasthenia gravis are more commonly female and of early school age.

Clinical Features

Patients typically have waxing and waning weakness of the skeletal and facial muscles, exacerbated by repetitive use of these muscles. Facial weakness with bilateral ptosis that fatigues throughout the day is a common initial presenting sign. Oculomotor, truncal, and extremity weakness may also be seen.

Diagnostic Testing

A history of fatigable weakness with predominantly facial muscle findings is suggestive of myasthenia gravis. Bedside testing using edrophonium is no longer available. Serologic testing for autoantibodies can aid in the diagnosis but will not be available in the ED. Electrophysiologic studies can be obtained upon admission or as an outpatient.

Management and Disposition

Myasthenia gravis may be life-threatening. Ventilatory support should be provided in the event of marked truncal weakness and respiratory failure, particularly in the setting of a concurrent illness which can exacerbate symptoms. In patients without risk of respiratory failure and in consultation with a neurologist, treatment may occur on an outpatient basis, with close symptom monitoring and oral cholinesterase inhibitor therapy.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 169: QUESTIONS AND ANSWERS

1. Which of the following clinical findings of bacterial meningitis is more common in newborns compared with infants and children?
   - **a.** Hypothermia
   - **b.** Neck ache
   - **c.** Rash
   - **d.** Shaking chills
   - **e.** Tachycardia

Answer: A. Hypothermia is more commonly found in newborn infants with bacterial meningitis compared with older infants and children with a similar disease.

2. A 15-month-old child is seen with a history of one 10-minute tonic-clonic event, which was nonfocal and accompanied by a temperature of 39°C (102.2°F) and period of illness preceding this event. Two hours after the event, the child is still unresponsive to external stimulation. Which of the following is the next step in the management of this child?
   - **a.** Admit to the inpatient service for antibiotics after blood cultures are drawn.
   - **b.** Admit to the inpatient service for continued observation.
   - **c.** Carry out imaging by obtaining an MRI of the brain.
   - **d.** Obtain a complete blood count (CBC) and urinalysis if the child does not improve in 1 hour.
   - **e.** Order neuroimaging, a lumbar puncture, complete blood count, and blood and urine cultures to evaluate for infectious causes.

Answer: E. Additional diagnostic testing should be obtained because this child has exhibited a prolonged postictal period and has not returned to baseline.

3. What is the appropriate treatment for a 12-year-old boy with a history of epilepsy and brought from home by emergency medical services to the emergency department (ED) after multiple seizures within the 15 minutes. The child is still unconscious and seizing. Which of the following is the next step in the management of this child on arrival at the ED?
   - **a.** Benzodiazepine
   - **b.** Electroencephalography (EEG) and CT scan of the head
   - **c.** Intubation using etomidate and vecuronium
   - **d.** Methohexital
   - **e.** Propofol

Answer: A. If the airway cannot otherwise be maintained, there is respiratory failure, or there is evidence of increased intracranial pressure, the patient should be intubated. Do not paralyze the patient unless absolutely necessary. If needed, consider short-acting neuromuscular blockers such as succinylcholine and vecuronium. The three most commonly used agents to treat convulsive status epilepticus are benzodiazepines, fosphenytoin, and levetiricam.

CHAPTER 169: QUESTIONS AND ANSWERS—cont'd

4. A 3-year-old boy is seen for seizure-like activity at home. He has no prior history of epilepsy and no family history of seizures. His fever has been as high as 39°C (102.2°F), and his parents have been watching him at home. Seizure activity has ceased and the history and physical examination are normal; the child is fully immunized for age. Which of the following statements is *not* consistent with appropriate counseling of parents regarding their 3-year-old?
   a. Although acetaminophen may make him feel better, it will not prevent recurrence.
   b. He is at a substantially higher risk for developing epilepsy later in life.
   c. It is safe for him to go home with the parents.
   d. Seizures with fever are common in young children and do not lead to brain damage.
   e. There is no need to start any antiepileptic medication.

Answer: B. In general, a child between 6 months and 5 years who has a normal neurologic examination and has had a brief seizure in the setting of fever can be assumed to have a simple febrile seizure. Future epilepsy is not predicted and is unlikely in children with simple febrile seizures.

5. Which one of the following statements best describes the signs and symptoms associated with pediatric brain tumors?
   a. At the time of diagnosis, most patients with brain tumors have associated symptoms, such as nausea, vomiting, visual effects, problems with walking, weakness, changes in personality or school performance, or speech changes.
   b. Headaches are never the first symptom of a pediatric brain tumor.
   c. Most pediatric brain tumors are diagnosed within the first month after symptom onset.
   d. Papilledema is one of the least common neurologic findings in children with brain tumors.

Answer: A. Of patients with brain tumors, most have some of the associated signs or symptoms noted in choice A. Headaches may be the first symptom of a pediatric brain tumor, although the frequency of this presentation increases with age. Papilledema is one of the more common neurologic findings, along with abnormal eye movements, ataxia, abnormal tendon reflexes, and abnormalities on the visual examination. CT scanning is usually not performed with the first sign of a headache unless clinically indicated.

6. A 10-year-old boy is brought in by his mother for gait imbalance. He is alert and oriented to person, place, and time, and he has a negative drug and alcohol screen. He has a persistent wide-based unsteady gait. What should be the next step in management?
   a. Head imaging, admission, and neurologic evaluation
   b. Discharge home if CT scan is negative
   c. Perform a lumbar puncture
   d. Reassurance and primary care referral
   e. Start sepsis evaluation

Answer: A. Most children with ataxia are seen in the first few days after onset, usually because of a refusal to walk, unsteadiness of arm movements, or the sudden development of a wide-based "drunken" gait. History should include recent infection, injury, inadvertent drug ingestion, or other family members with the same problem. Children with ataxia usually need admission for a complete evaluation. Consultation with a pediatric neurologist should be sought for patients in whom the cause of the ataxia is not evident on ED evaluation.

7. A 14-year-old girl with a history of migraines presents to the ED with the complaint of being unable to move her left side following a severe right-sided headache. Which of the following statements best describes her management?
   a. Imaging, analgesics, and admit to the hospital because symptoms may last for days.
   b. Immediate evaluation with neuroimaging for a stroke
   c. Inpatient vasculitis evaluation is indicated.
   d. She can be safely discharged home, and the symptoms will resolve in an hour.

Answer: B. Hemiplegic migraine is characterized by the sudden onset of hemiparesis or hemisensory loss followed by headache in the contralateral hemisphere. This type of migraine is seen more frequently in children than adults, but imaging should be obtained to rule out the diagnosis of stroke. Although symptoms usually last for hours or days, affected individuals are rarely left with permanent deficits.

8. A mother brings in her 4-year-old son for periods of lip smacking that occur multiple times per week and last several minutes. During these episodes, he may turn his head to her when she calls, but he does not speak. You suspect which of the following conditions?
   a. Complex partial seizure
   b. Generalized seizure
   c. Infantile spasm
   d. Lennox-Gastaut syndrome
   e. Simple partial seizure

Answer: A. In complex partial seizures, the patient has a change in level of awareness and may exhibit bizarre behaviors including staring, lip smacking, wandering, or picking at clothing. In simple partial seizures, the patient has no change in mentation. Lennox-Gastaut syndrome is characterized by mental retardation, multiple seizure types, and a classic EEG pattern of slow spike and wave. Infantile spasms manifest during the first year of life and consist of rapid, jackknife flexor or extensor spasms that appear in clusters.

Pediatric Musculoskeletal Disorders

William B. Prince

KEY CONCEPTS

- The pediatric physis is the weakest part of the bone and more likely to separate before adjacent tendon or ligament tears, occurring more frequently during periods of rapid growth.
- Displaced supracondylar fractures are at greater risk for neurovascular injury and compartment syndrome. A lateral elbow radiograph with an elevated fat pad is suspicious for occult fracture.
- Transient synovitis has a peak presentation between 3 and 6 years of age. History, physical examination, radiographs, and laboratory values can help distinguish from septic arthritis and Lyme arthritis.
- Slipped capital femoral epiphysis (SCFE) is the posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis, occurring through the epiphyseal plate. This condition affects boys at twice the rate of girls, occurring more commonly between 8 and 15 years of age. This prevalence is changing due to the increasing obesity rate.
- Lyme arthritis typically presents as mono-arthritis in two-thirds of cases, involving the knees 90% of the time. The knee tends to be swollen with limited range of motion, but pain varies and patients can usually still ambulate with a limp. Approximately 50% to 60% of patients not treated for early stages of Lyme will go on to develop Lyme arthritis, which can be their presenting symptom of the disease.
- Little League elbow describes a group of elbow injuries, including apophysitis, medical epicondylitis, and osteochondritis dissecans of the radial head and capitellum. The pediatric elbow is vulnerable to overuse injury, because it has multiple muscle and ligamentous attachments as well as six ossification centers that close at different ages of skeletal maturity.
- Apophyseal injuries of the hip occur at the multiple sites of muscle origination or insertion including on the pelvis. Athletes most at risk are dancers, distance runners, and those participating in kicking sports.
- Gymnast wrist is a chronic wrist pain affecting almost 80% of pediatric gymnasts at some point. Compressive loading and shearing forces cause physeal microfractures at the hypertrophic zone, causing physeal widening and metaphyseal irregularity in almost three-fourths of patients.

FOUNDATIONS

Anatomy and Physiology

Due to the dynamic developmental state occurring in growing children, the pediatric skeleton is unique compared to adults. The most unique feature of pediatric bones is the presence of the physis. This growth plate is composed of proliferating cartilage cells between the epiphysis and metaphysis. The physis is the weakest part of the bone and allows for distinctly different fracture patterns and injury mechanisms compared to adults. The physis can separate or fracture before the adjacent ligaments and tendons tear; similar injury mechanisms in adults which result in sprained ligaments can cause physeal injuries in children. These injuries are most common during periods of rapid growth and represent up to 18% of pediatric fractures.

The pediatric periosteum is thicker and stronger than mature periosteum, which can result in a reduction of fracture displacement. It is also physiologically active which allows for rapid healing and increased stability, making nonunion unlikely. Children have tremendous remodeling potential which allows for greater degrees of angulation or misalignment. If the child has at least 2 years of growth potential remaining, a fracture adjacent to a joint will remodel acceptably if the angulation is less than 30 degrees in the plane of motion.

Fracture Patterns

Immature bones are more porous and pliable, resulting in fracture patterns seen uniquely in pediatric injuries:

- Plastic deformity results in bowing of the bone without cortical disruption.
- Torus (buckle) fractures tend to occur from linear compression and result in buckling of bone without cortical disruption. These injuries are common at the metaphyseal-diaphyseal junction (Fig. 170.1).
- Greenstick fractures disrupt the cortex unilaterally, with periosteum on the compression side remaining intact (Fig. 170.2). The degree of acceptable angulation without reduction is age dependent. Children under 5 years of age can have up to 35 degrees of angulation on lateral radiograph and less than 10 degrees of angulation on AP views, whereas children 5 to 10 years old can tolerate up to 25 degrees on lateral and less than 10 degrees on AP view without need for reduction. Children older than 10 years of age can tolerate 5 to 20 degrees of angulation on lateral x-ray, presuming no angulation on AP view. Treatment for greenstick fractures generally involves casting for 4 to 6 weeks.
- Complete fractures transect both cortices of the bone; these include transverse (Fig. 170.3), spiral (Fig. 170.4), oblique, and comminuted (Fig. 170.5).
- Physeal fractures are not specific to pediatrics but are more likely during periods of rapid bone growth. The Salter-Harris classification is commonly used to delineate fracture patterns as they relate to the physis (Table 170.1). Concern for physeal injury stems from the potential for growth arrest and limb-length abnormalities. Nondisplaced Salter-Harris type I and II fractures (Fig. 170.6 and Fig 170.7) are generally low risk for these complications because the germinal layer of the physis is not commonly involved. These fractures can be splinted or casted with orthopedic follow-up within 1 week. Salter-Harris type III, IV, and V fractures (Fig. 170.8 through 170.10) are at greater risk for damage to the growth plate and are commonly unstable, requiring prompt orthopedic consultation. Types III and IV involve the joint surface and commonly require open reduction to maintain joint stability. Type V fractures are

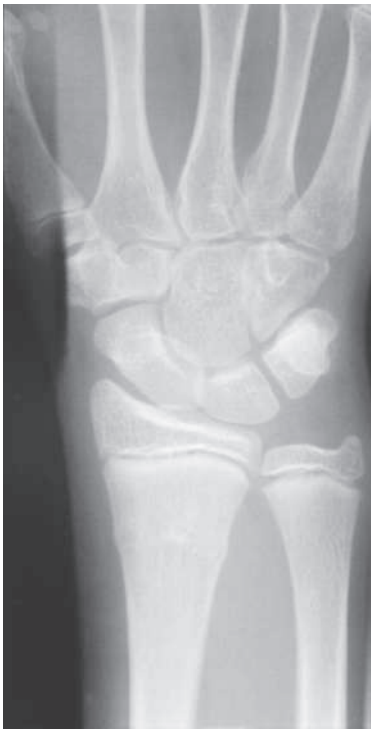


Fig. 170.1 Buckle fracture of the distal end of the radius.

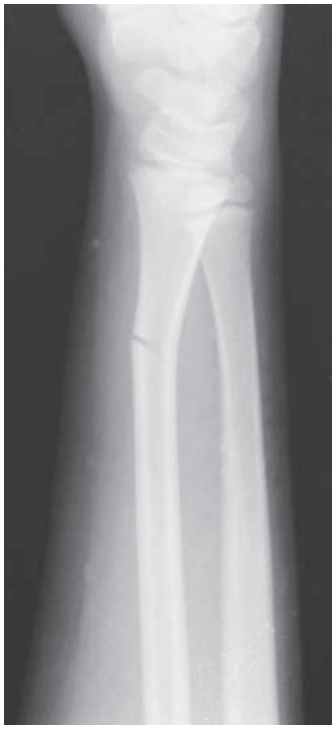


Fig. 170.2 Greenstick fracture of the radius.

followed closely, as the risk for premature growth plate closure is high and surgical intervention is often needed.

SPECIFIC DISORDERS

Clavicle Fracture

Clavicle fractures are common in childhood but generally heal without complication. Most fractures occur between the middle and distal third of the bone. Mechanisms include birth trauma, direct trauma to the bone itself, and falls onto the shoulder. The bone's superficial lie allows for easy palpation when evaluating for pain or deformity. A clavicle fracture may be detected later in a neonate when a visible callus has formed around day 10 or per parent history of crying when being picked up.

The patient with a clavicle fracture commonly complains of pain at the clavicle and shoulder, often with neck and arm movement. An anteroposterior radiograph of the clavicle is sufficient for diagnosis

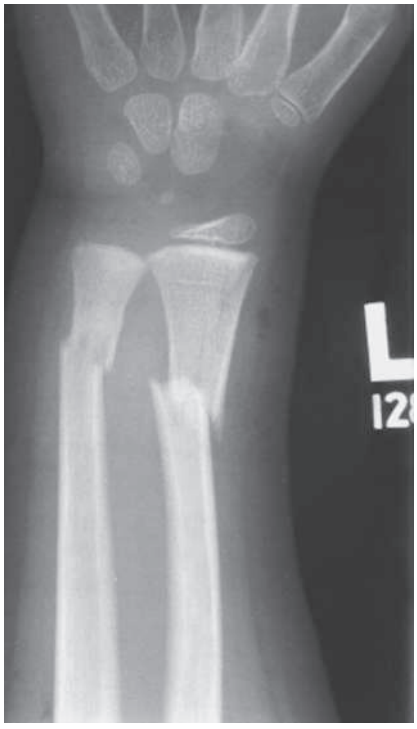


Fig. 170.3 Transverse fractures of the radius and ulna.

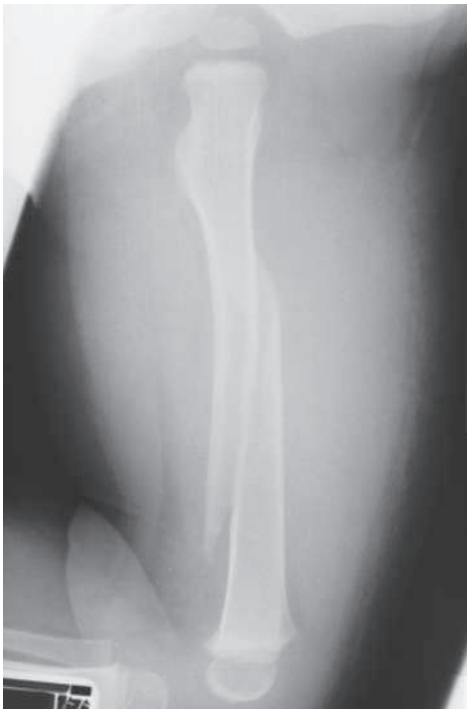


Fig. 170.4 Spiral fracture of the femur.

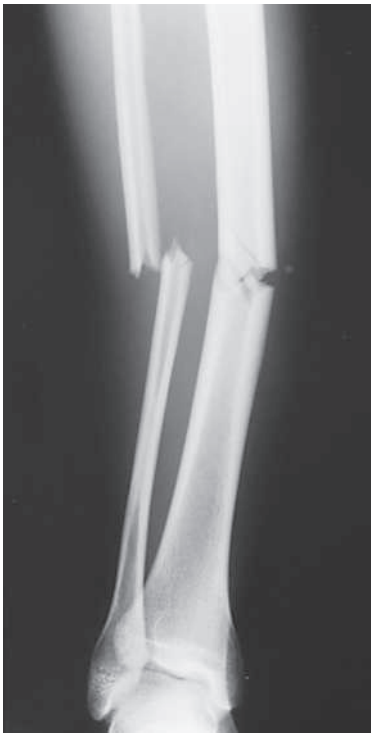


Fig. 170.5 Comminuted fractures of the tibia and fibula.

(Fig. 170.11). Displacement of the affected shoulder along with crepitus and edema may be present upon inspection. The proximity of the clavicle to the subclavian vessels as well as the brachial plexus warrants a thorough neurovascular examination, especially in the setting of a displaced fracture. Complications can be seen in the setting of proximal fractures or posterior sternoclavicular displacement which can injure the trachea, esophagus, or cause pneumothorax.

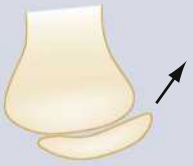
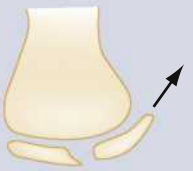
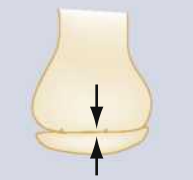
Most children and adolescents with clavicle fractures only require supportive care and immobilization involving sling and swath for 4 to 6 weeks. However, recent studies suggest adolescents after 12 years of age have limited clavicular growth potential remaining and some surgeons have begun to use operative indications for adult patients in their pediatric population. Figure-of-eight splinting is not recommended due to risk of brachial plexus palsy with prolonged use. Newborns generally require no treatment following clavicle fractures from birth. Orthopedic consult should be obtained for clavicular fractures that are open, associated with neurovascular compromise, evidence of a floating shoulder (when associated with a scapular fracture), or with significant skin tenting.[1] An orthopedic referral should be considered in fractures that are comminuted, have a substantial degree of displacement, or in high-level athletes as surgery may facilitate a faster return to activity.

Supracondylar Fractures of the Humerus

Supracondylar humerus fractures are the most common fractures involving the elbow in pediatric patients. During childhood, the tensile strength of the ligaments surrounding the joint exceed that of the weaker bones themselves, which increases the likelihood for fractures rather than ligamentous injury. Typically the patient history involves a fall onto an extended arm, forcing the distal bone superiorly and posteriorly.

Radiographic evaluation of elbow injuries include an AP view of extended elbow (if possible), oblique view, and lateral flexed view. The elbow joint contains 6 cartilaginous ossification centers which can be easily mistake for fracture lines (Fig. 170.12). An acronym for remembering the order of appearance of the ossification centers is CRITOE (Table 170.2).

TABLE 170.1 Salter-Harris Fracture Classification

Type	Description	
I	Fracture extends through the physis	
II	Fracture extends from the physis into the metaphysis (away from the joint space)	
III	Fracture extends from the physis into the epiphysis (toward the joint space)	
IV	Fracture extends from the physis into the metaphysis and epiphysis	
V	Crush injury of the physis	

Injury mechanisms involving impact on flexed elbow result in anterior displacement of the distal fragment. Supracondylar fractures are classified as either flexion or extension injuries, of which the latter is more common. An AP and lateral radiograph are required to evaluate the degree of displacement and continuity of the cortex as defined by the Gartland classification (Table 170.3). Because subtle fractures can be difficult to visualize, the anterior humeral line can be used as indirect evidence of fracture (Fig. 170.13). A true lateral view should demonstrate a figure-of-eight appearance of the distal humerus, with intersection of the anterior humeral line with the posterior two-thirds of the capitellum. If this line intersects the anterior one-third of the anterior capitellum or is anterior to this structure, then a supracondylar fracture with posterior displacement of the distal fragment is suggestive. The Baumann angle, normally 70 to 75 degrees, can be helpful in detecting subtle fractures and is formed by a line drawn to follow the growth plate of the capitellum intersected with a line drawn down the center of the humerus (Fig. 170.14).

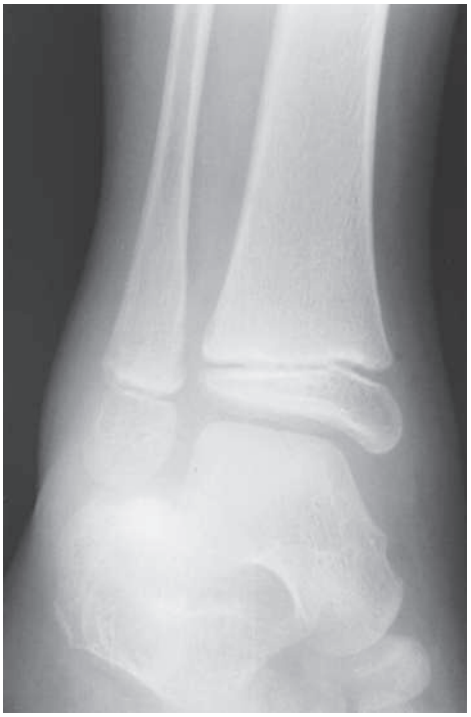


Fig. 170.6 Salter-Harris type I fracture of the fibula. Radiographic findings include soft tissue swelling over the growth plate and minimal physeal widening.

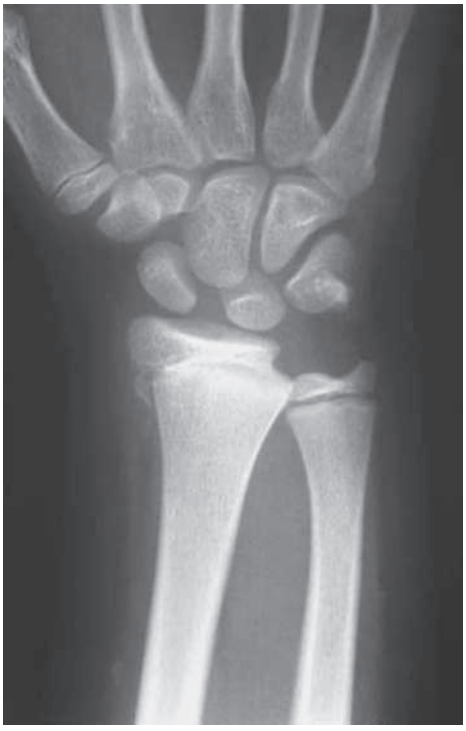


Fig. 170.7 Salter-Harris type II fracture of the radius.

Fat pads are markers for joint effusions or hemorrhage and raise suspicion for occult fracture. On a lateral radiograph with the elbow flexed at 90 degrees, the anterior fat pad demonstrates radiolucency anterior to the coronoid fossa. When thin, this can be a normal finding in children, but is considered a "sail" sign of occult fracture when bulging. The posterior fat pad is posterior to the distal humerus and always represents a pathologic effusion (Fig. 170.15).

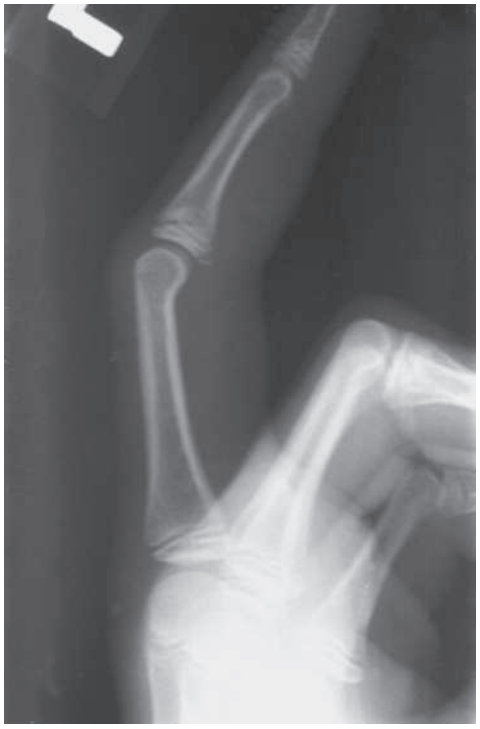


Fig. 170.8 Salter-Harris type III fracture of the middle phalanx.

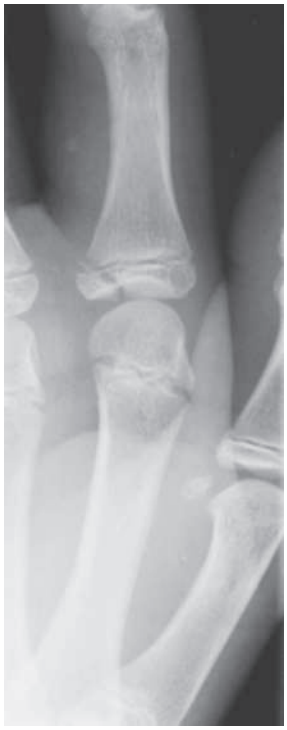


Fig. 170.9 Salter-Harris type IV fracture of the proximal phalanx.

The injured patient presents with a painful swollen elbow and typically holds the extremity in extension and slight pronation. Puckering, dimpling, or anterior bruising are indications that reduction may be difficult, as the anteriorly displaced fragment may have penetrated the brachialis muscle. Immediate assessment should include evaluating for neurovascular compromise by assessing capillary refill and palpating both radial and ulnar pulses. Signs of arterial compromise include the 5 "Ps": pain, pallor, pulselessness, paralysis, and paresthesias. Worsening

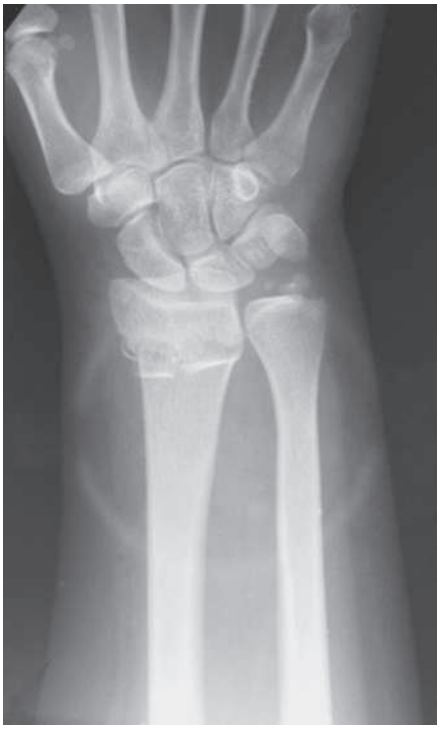


Fig. 170.10 Salter-Harris type V fracture of the distal end of the radius.

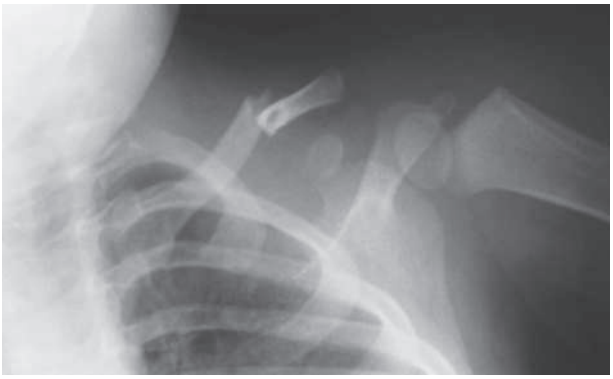


Fig. 170.11 Fracture of the middle third of the clavicle.

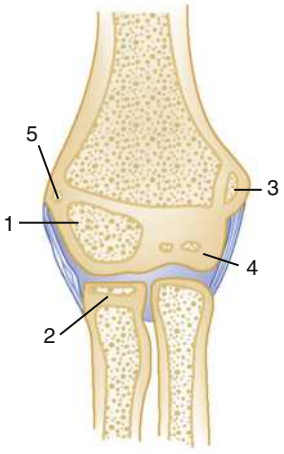


Fig. 170.12 Ossification centers of the elbow. *1*, Capitellum; *2*, radial head; *3*, medial epicondyle; *4*, trochlea; *5*, lateral epicondyle. (From: Connolly JF. *Depalma's Management of Fractures and Dislocations*. Philadelphia: WB Saunders; 1981.)

TABLE 170.2 Sequence of Ossification Around the Elbow: CRITOE

Ossification Center	Age at Appearance	Age at Closure (yr)
*C*apitellum	6–12 mo	14
*R*adial head	4–5 yr	16
Medial (*I*nternal) epicondyle	5–7 yr	15
*T*rochlea	8–10 yr	14
*O*lecranon	8–9 yr	14
Lateral (*E*xternal) epicondyle	9–13 yr	16

TABLE 170.3 Gartland Classification of Extension-Type Supracondylar Fractures

Type	Description
I	Nondisplaced fracture
II	Displaced fracture with intact posterior cortex
III	Displaced fracture with no cortical contact
IIIA	Posteromedial rotation of the distal fragment
IIIB	Posterolateral rotation of the distal fragment

Adapted from: Gartland JJ. Management of supracondylar fractures of the humerus in children. *Surg Gynecol Obstet*. 1959;109:145.

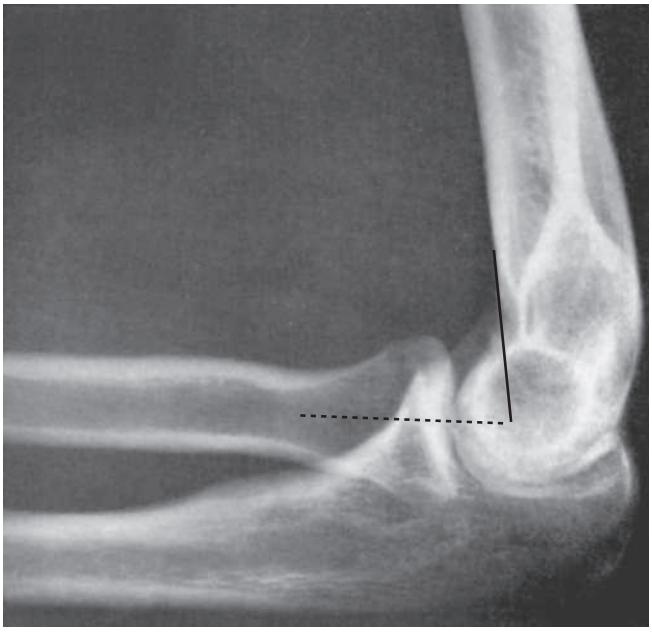


Fig. 170.13 Lateral radiograph demonstrating the bone relationships in a normal elbow. The anterior humeral line (*solid line*) and proximal radial line (*dashed line*) bisect the capitellum. (From: Weissman BN, Sledge CB. *Orthopedic Radiology*. Philadelphia: WB Saunders; 1986.)

pain or pain with passive extension of the fingers is a concerning sign of limb ischemia and can lead to Volkmann ischemic contractures. Emergent consultation with an orthopedic surgeon should be initiated and fracture reduced expeditiously in an attempt to restore blood flow (Fig. 170.16). Perfusion should be confirmed via radial artery signal by Doppler following closed reduction attempts; if reperfusion is unsuccessful, emergent vascular exploration is warranted to assess for and repair brachial artery injuries.

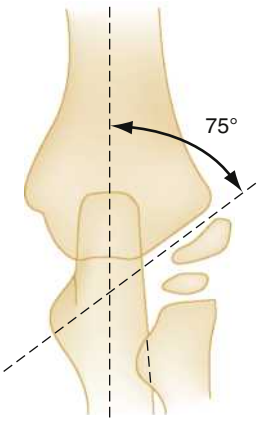


Fig. 170.14 Baumann angle in a normal elbow (anteroposterior radiograph). (From: Worlock P. Supracondylar fractures of the humerus: assessment of cubitus varus by the Baumann angle. *J Bone Joint Surg Br*, 1986;68:755.)

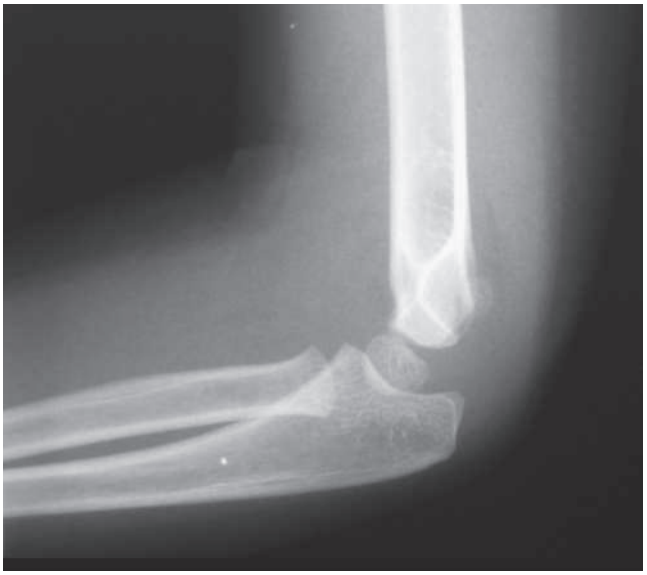


Fig. 170.15 Lateral radiograph of a supracondylar fracture with an anterior fat pad sail sign and posterior fat pad.

Because major nerves and arteries lie in proximity to the supracondylar region, a full motor and sensory function should evaluate for possible associated injury or entrapment. Major structures include radial, ulnar, and median nerves (Table 170.4). The median and radial nerves are commonly injured in extension injuries when the distal fragments are displaced posterior-laterally and posterior-medially, whereas the ulnar nerve is commonly affected with flexion injuries.

Supracondylar humerus fractures are the most common fractures treated surgically by pediatric orthopedic surgeons.[2] Management of Gartland type I fractures can be placed in a posterior long arm splint with the elbow flexed at 90 degrees and either neutral or pronated position. These patients should follow up with an orthopedist with 24 hours for evaluation and casting. Gartland type II and III fractures require emergent evaluation by an orthopedic surgeon. Type II fractures require closed reduction, but if greater than 90 degrees of flexion is required to maintain reduction, then stabilization with percutaneous pinning is advised. Treatment of type III supracondylar fractures includes admission and should include operative reduction and pinning, because they are prone to neurovascular compromise.

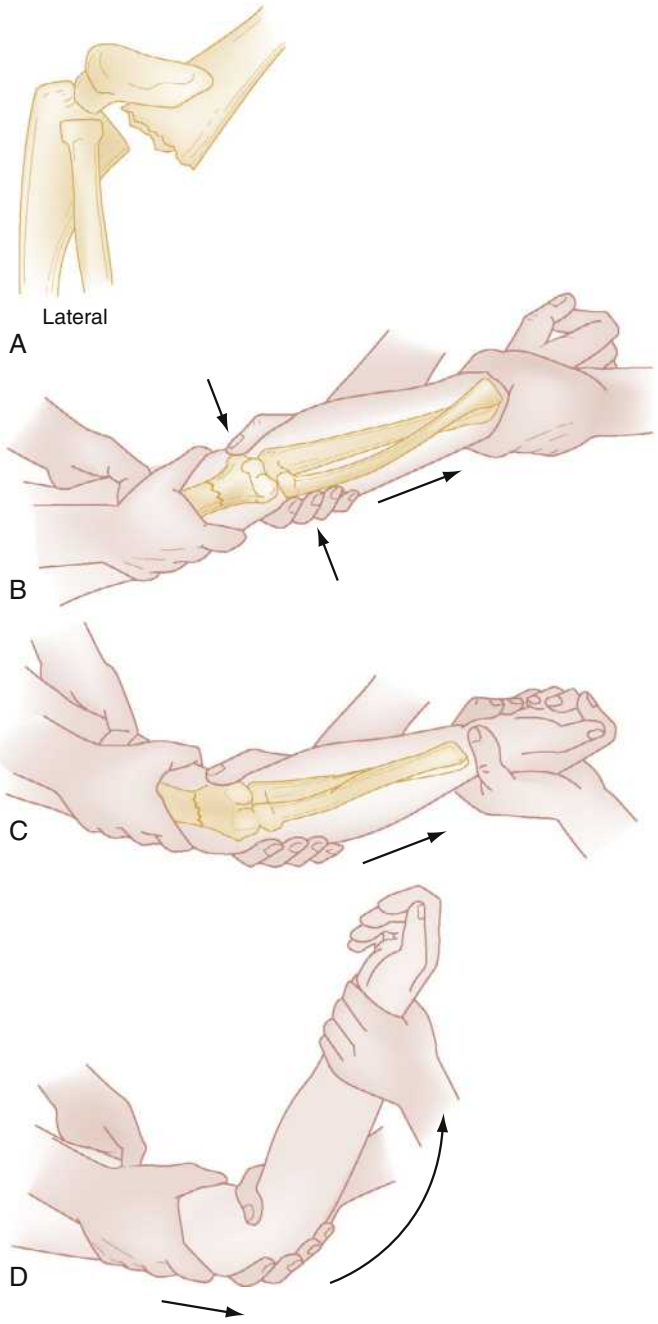


Fig. 170.16 Steps in reduction of a displaced supracondylar fracture. (A & B) The assistant fixes the arm of the patient while the emergency clinician grasps the patient's wrist and applies steady traction in line with the long axis of the arm while keeping the forearm in the neutral, thumb-up position. (C) If the distal fragment is displaced laterally, it is pushed inward with the emergency clinician's other hand. If it is displaced medially, it is pushed outward. Throughout manipulation, traction is maintained. (D) After length is restored and the medial and lateral displacement is corrected, the emergency clinician's thumb is placed over the anterior surface of the proximal fragment, with the fingers behind the olecranon, and the elbow is gently flexed. The arm is then immobilized with the forearm pronated; laterally displaced fractures are immobilized with the forearm supinated. (From: Geiderman JM, Magnusson AR. Humerus and elbow. In Rosen P, Barkin R, eds. *Emergency Medicine: Concepts and Clinical Practice*, ed 4. St. Louis: CV Mosby; 1998.)

Monteggia and Galeazzi Fracture-Dislocations

Monteggia fracture-dislocation represents a fracture of the proximal third of the ulna plus dislocation of the radial head (Fig. 170.17). Isolated ulna fractures are uncommon in children and can present as a plastic deformity of the ulna without obvious fracture. The radiocapitellar line, drawn down the radial shaft, should pass through the center of the capitellar ossification center on lateral elbow radiograph; radial head dislocations will disrupt this line (Fig. 170.18). In contrast, the Galeazzi fracture is characterized as a fracture of the distal radius and disruption of the distal radioulnar joint.

For both fracture types, orthopedic consultation is needed for closed reduction and casting. Management of the Monteggia fracture is predicated on recognizing the radial head dislocation, and reduction and stabilization of the ulnar fracture generally results in radial head reduction.[2] Failure to reduce the radial head over time can result in valgus instability of the elbow, arthritis of the elbow, and restricted forearm pronation.[2]

TABLE 170.4 Neurologic Examination of the Distal Upper Extremity

	EXAMINATION COMPONENT	
Nerve	**Motor**	**Sensory**
Radial	Wrist extension	Thumb and first finger web space
Ulnar	Wrist flexion and adduction	Little finger
Median	Wrist flexion and abduction	Thumb, index, and middle fingers
Thumb opposition	Radial aspect of palm of hand	
Anterior interosseous	Distal phalanx flexion (thumb and first finger)	None

Nursemaid's Elbow

Nursemaid's elbow (i.e., radial head subluxation) occurs when the head of the radius is displaced from the annular ligament; it represents approximately 20% of pediatric upper extremity injuries, with a peak incidence between two and three years of age.[3] The typical mechanism occurs when axial traction is placed on the forearm, causing extension of the elbow and pronation. This movement permits subluxation of the radial head via partial tearing or entrapping of the annular ligament between the radial head and capitellum (Fig. 170.19).[3]

Patients generally present with unwillingness to use the affected arm, which is typically held against the body, slightly flexed at the elbow with the arm pronated. Edema, ecchymosis, or deformity are typically absent. Gentle palpation usually does not illicit pain of the long bones or elbow joint, although ranging the extremity can cause distress. The diagnosis of nursemaid's elbow is made clinically; AP and lateral radiographs of the elbow should be obtained if there is focal bony tenderness, ecchymosis, joint swelling, or a traumatic mechanism.

Two common techniques for reduction are supination/flexion and hyperpronation maneuvers. Both methods involve the examiner supporting the child's arm at the elbow by placing pressure with a finger on the radial head. In the supination/flexion maneuver, the examiner holds the forearm with their other hand and provides gentle traction while fully supinating and flexing the elbow in one motion. With hyperpronation, the examiner holds the affected arm's hand in a handshake grip and grips the elbow with the other hand. Hyperpronation of the forearm usually results in a palpable click over the radial head if reduction is successful.

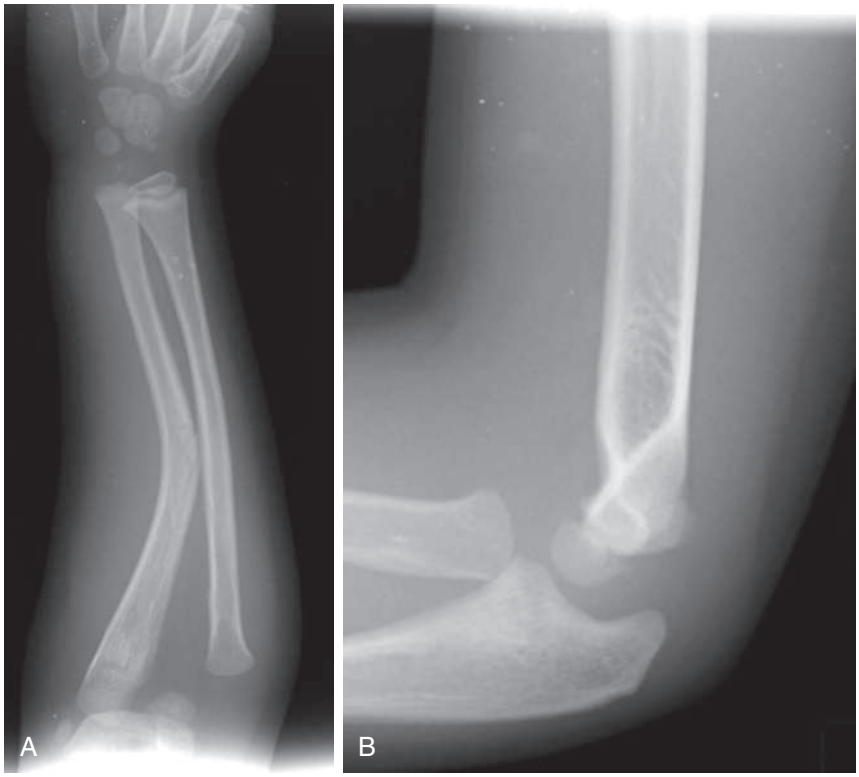


Fig. 170.17 (A) Anteroposterior view of the elbow revealing a distal ulna fracture with radial head dislocation. The radial head should align with the capitellum in all views. (B) Lateral view of the elbow demonstrating poor alignment of the radial head, with the capitellum consistent with Monteggia fracture-dislocation. (Courtesy Dr. Micheal Diament, Pediatric Radiology, Harbor-UCLA Medical Center, Torrance, CA.)

Both methods are effective, however, meta-analysis of randomized control trials have shown that hyperpronation is more effective, with a lower first attempt failure rate.[3] Recurrence is common and parents should be cautioned to avoid lifting the child by the arm or wrist, but may be taught to perform the maneuver themselves if it recurs.

Children typically begin using the arm normally within 15 minutes. If the child fails to move the extremity, repeat maneuvers may be attempted. However, if unsuccessful, radiographs should be obtained and the extremity placed in a long arm splint at 90 degrees. Pediatrician follow-up should be arranged within next 24 hours.

Toddler's Fracture

The toddler's fracture is a nondisplaced oblique fracture of the distal tibia that is the result of a minor fall or twisting mechanism, with a peak incidence between 1 and 4 years of age. Clinical diagnosis may be difficult, as the history may be vague and the physical examination is commonly nonspecific to a local injury. Typically, guardians report the child is limping or unwilling to bear weight; there may be a report of a minor fall. Tenderness may be elicited with palpation, but obvious swelling or deformity is uncommon. Gentle twisting of the lower leg may provoke pain.

Lower leg AP and lateral radiographs may reveal a subtle oblique lucency through the distal tibia terminating medially (Fig. 170.20). Because children have robust periosteum, any displacement can be minimal, making identification on radiograph difficult, and the fracture is often not initially visible. If suspicion for a toddler fracture is high, immobilization and reevaluation 2 weeks later will show callus formation on repeat radiographs from new periosteal growth. If available, ultrasound can be considered as an imaging modality to evaluate for fracture. Traditionally, immobilization involved a posterior long leg cast for 3 to 4 weeks, but recent studies have shown no differences in the clinical outcomes between various immobilization methods: casting, splinting, or a cast boot.[4] Casts should not extend above the knee on young toddlers, who are at risk for cast migration. Children are allowed to bear weight as tolerated after immobilization.

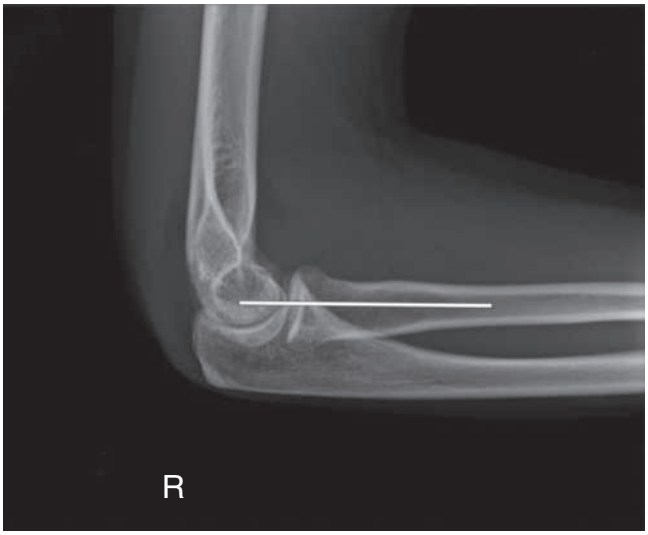


Fig. 170.18 Lateral elbow with a radiocapitellar line, which bisects the capitellum. (Courtesy D. Hanlon, MD, Pittsburg, PA)

Nonaccidental Trauma

The National Child Abuse and Neglect Data System reported more than 680,000 children were victims of maltreatment and 1670 children died of abuse and neglect in 2015.[5] Of all these childhood fatalities 43.9% were victims of physical abuse exclusively or in combination with another maltreatment type and 74.8% of these children were less than 3 years of age.[5] Diagnosis of physical abuse can be elusive and missed identification can lead to additional injuries. An estimated 25% of children diagnosed with nonaccidental trauma (NAT) have a sentinel injury before their abuse diagnosis.[5] These data underscore the necessity for a thorough evaluation when there is a concerning history or physical findings for NAT. See Chapter 172 for a complete discussion on the evaluation of NAT.

Developmental Dysplasia of the Hip

Foundations

Developmental dysplasia of the hip (DDH) denotes a wide spectrum of clinical severity: neonatal instability, acetabular dysplasia, hip subluxation, and true dislocation of the hip. Laxity within the acetabulum refers

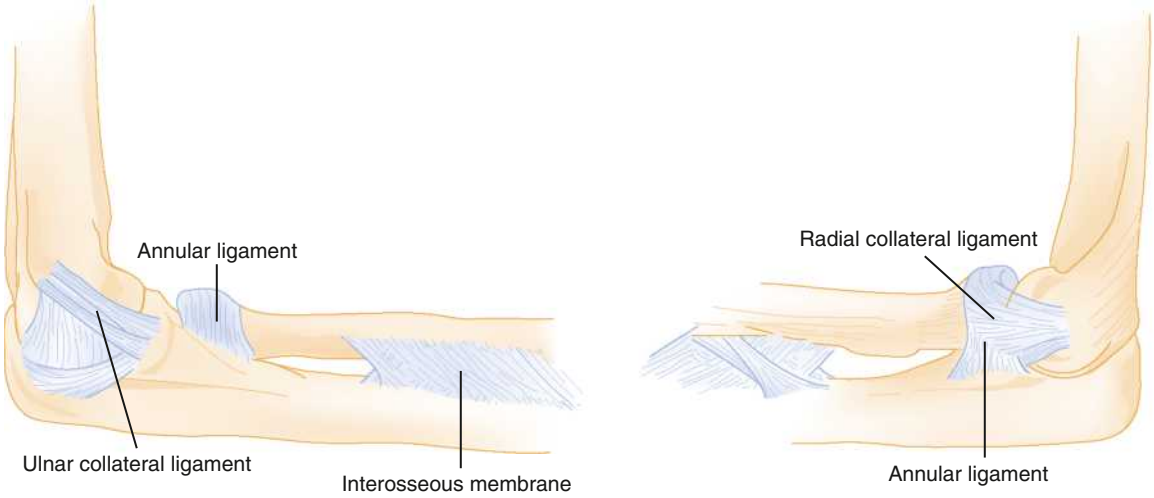


Fig. 170.19 Nursemaid's elbow. In a nursemaid's elbow injury, the annular ligament around the radial head is dislodged as an axial force is applied. The ligament is then partially dislocated into the radiocapitellar joint when the arm is released. (From Simon R, Koenigsknecht S: *Emergency orthopedics, the extremities*, ed 2, Norwalk, CT, 1987, Appleton & Lange.)

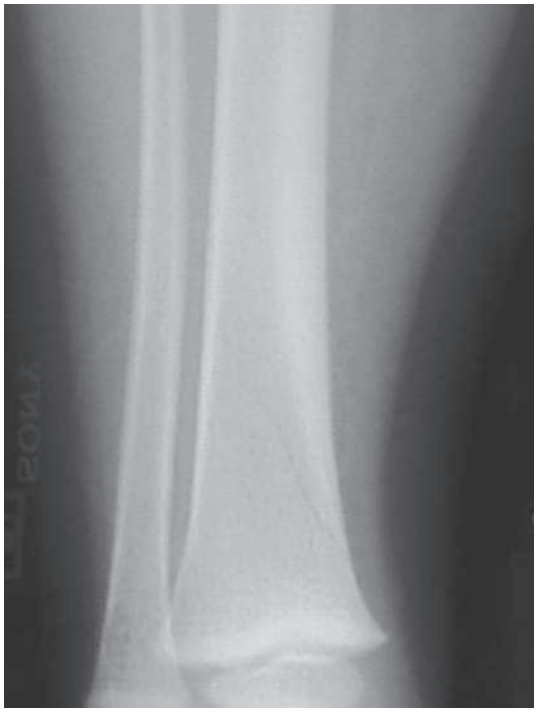


Fig. 170.20 Toddler's fracture.

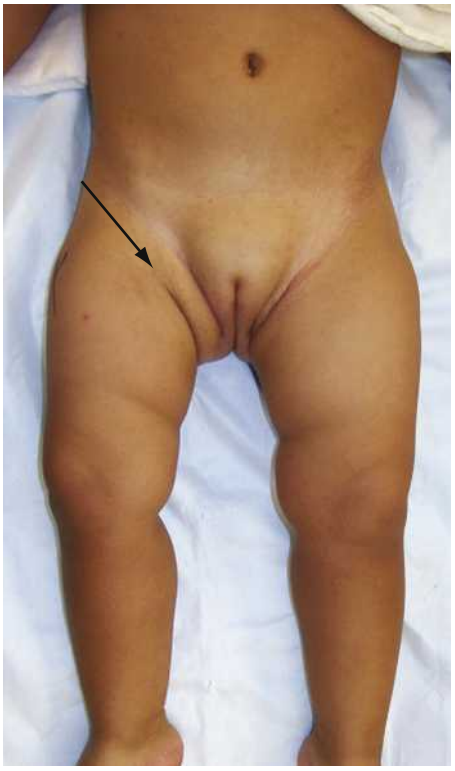


Fig. 170.21 A 21-month-old child with right hip dislocation. Note the asymmetrical skinfolds in the upper thigh (*arrow*). (From: Storer SK, Skaggs DL. Developmental dysplasia of the hip. *Am Fam Physician*. 2006;74:1310-1316.)

to instability, whereas dysplasia indicates some morphologic change in the acetabulum or proximal. With a subluxed hip, articular surfaces are in contact, but not concentrically aligned. With a hip dislocation, articular surfaces of the acetabulum and proximal femur are not in any contact.

Clinical hip instability occurs in 1% to 2% of term infants; up to 15% have findings on imaging studies.[6] Risk factors include breech presentation, female gender, family history, and incorrect lower extremity swaddling; risk factors are additive, with frank breech presentation and family history the two most important risk factors.[6]

Clinical Features

Signs of DDH may be present at birth or develop as the baby grows. Diagnosis is usually made during regular screening and surveillance by physical exams up to 6 months of age. Instability is the primary sign of DDH in the neonatal period; however, this quickly diminishes as muscle strength increases, leaving abduction asymmetry as the main clinical sign.

At less than 3 months of age, screening of newborns involves Ortolani and Barlow maneuvers. The Barlow test is done with the hip in 90 degrees of flexion and adduction; lateral pressure is put on the hip. In hip instability, a clunk can be felt as the femoral head falls out the back of the acetabulum, effectively dislocating. The Barlow test has no proven predictive value for future hip dislocation, and if performed frequently or forcefully, can create instability.[6] The AAP, in its 2016 clinical report on DDH, recommends that no posterior-directed force be applied during this procedure.[6] From a similar starting position, the Ortolani maneuver should transition smoothly from hip adduction into gentle anterior pressure on the trochanter while the hip is abducted; a clunk is felt if the hip locates into the socket.

Benign "hip clicks" without instability are clinically insignificant. This finding, which is secondary to soft tissue snapping over bony prominences, should be distinguished from "hip clunks," as detected in a positive Ortolani maneuver. A dislocated hip becomes fixed by 3 months of age, after which the usefulness and sensitivity of the Barlow and Ortolani tests are limited.[6]

Fig. 170.22 A 3-year-old child with a left hip dislocation. Note the limited abduction. (From: Storer SK, Skaggs DL. Developmental dysplasia of the hip. *Am Fam Physician*. 2006;74:1310-1316.)

Restricted asymmetrical hip abduction may be found on physical examination. Limb length discrepancy (Galeazzi test), asymmetrical thigh or gluteal folds (Fig. 170.21), and limited or asymmetrical abduction (Fig. 170.22) raises suspicion for DDH. A positive Galeazzi test can be detected with the hips and knees flexed to 90 degrees, observing the vertical level of the knees (Fig. 170.23). Asymmetrical groin, thigh, and gluteal folds can be seen in up to 25% of normal infants and alone are not pathognomonic.[7] Once a child is walking, a dislocated hip may manifest as an abnormal gait.

Diagnostic Testing

Infants older than 4 weeks of age suspected of having DDH should undergo ultrasound, also recommended to diagnose clinically silent

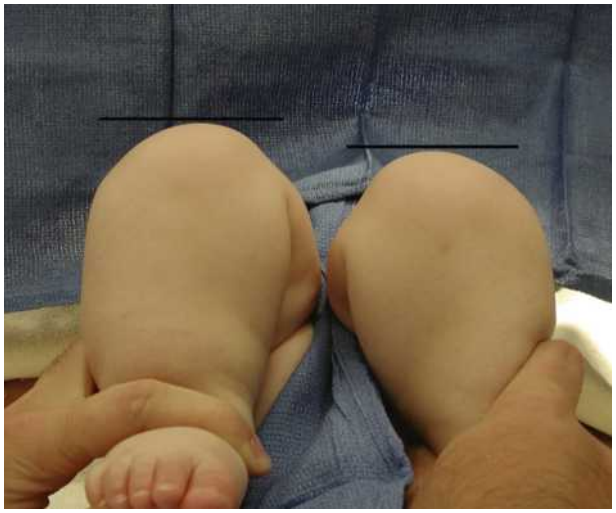


Fig. 170.23 Galeazzi sign in a 7-month-old girl with left hip dislocation. Apparent inequality of femur length is manifested as asymmetry in the level of the patient's knees. (From: Storer SK, Skaggs DL. Developmental dysplasia of the hip. *Am Fam Physician*. 2006;74:1310-1316.)

DDH in the high-risk infant from 6 weeks to 6 months of age.[6] Once the ossifying nucleus of the femoral head appears around 4 to 6 months of age, radiographs are more diagnostic than ultrasound. An AP radiograph of the pelvis with both legs extended in neutral position is sufficient to make the diagnosis (Fig. 170.24).

Management

Early detection of infants with suspected DDH and referral for bracing or casting can prevent the need for reconstructive surgery. Infants with suspected DDH should be referred after 4 weeks of age. An isolated positive Barlow result up to 2 weeks of age will generally stabilize on its own and can be followed with surveillance for an additional 4 to 6 weeks. Because 96% of pathologic changes found on ultrasound resolve spontaneously within the first 6 weeks of life, treatment can be safely delayed until that time if the hip is stable and not dislocated.

The treatment goal of DDH is concentric reduction and stabilization of the hip joint. If not treated, long-term consequences can include arthritis, back pain, and aseptic necrosis of the femoral head. If the hip is dislocated, the Pavlik harness (PH) is first-line treatment for reduction (Fig. 170.25). The PH is a safe and effective option during infancy for hips that are dislocated, located but unstable, or dysplastic.[8] The harness holds the hips in a flexed and abducted position, allowing for the femoral head to be reduced within the acetabulum. The P4 has a success rate of approximately 85% if treatment is initiated before 6 months of age.[8] If reduction with PH is not successful or in children older than 6 to 8 months, children should receive reduction in the OR followed by spica cast immobilization. Most children beyond 18 months of age require surgical reconstruction.

Pediatric Hip Pain

Children are susceptible to a number of hip disorders of varying degrees of severity (Box 170.1). Some of the conditions discussed can affect other joints in the body as well.

Transient Synovitis

Transient synovitis is a self-limited inflammatory process with a peak incidence between the ages of 3 and 6 years old, and more common in boys than girls. Caused by a benign nonpyogenic inflammatory response, it affects up to 3% of children, and is the most common hip disorder causing atraumatic limp in children.[9] The symptoms

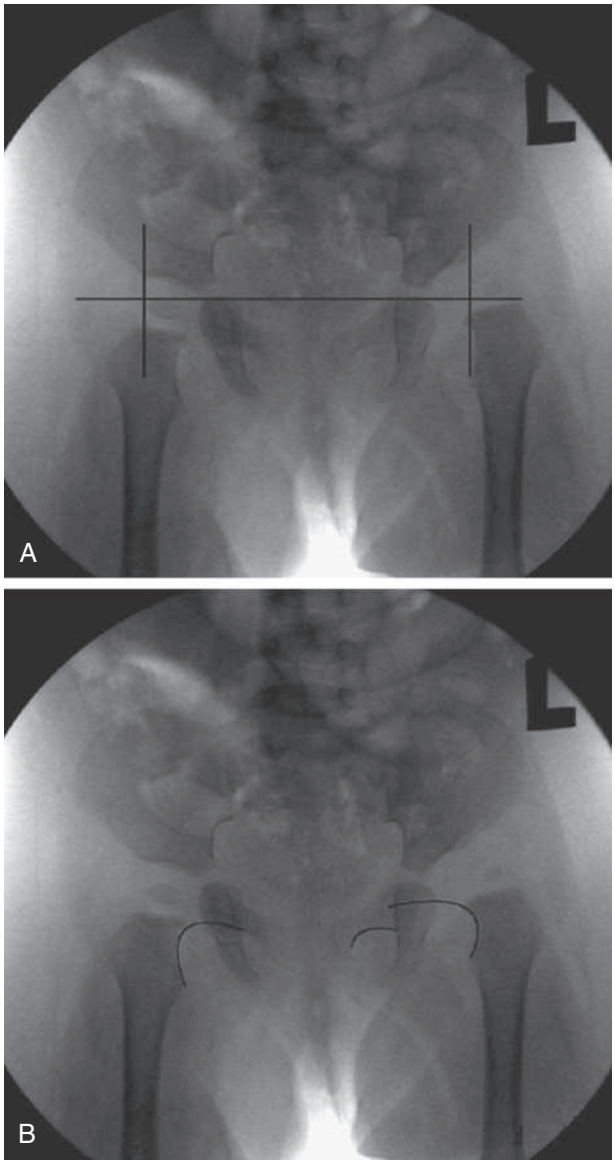


Fig. 170.24 Anteroposterior radiographs obtained in a 7-month-old girl with developmental dysplasia of the left hip. (A) The horizontal line is the Hilgenreiner line; the vertical lines are Perkin lines. Note that the femoral head on the right (normal) side lies in the inferomedial quadrant formed by those lines. The left hip is dislocated; its femoral head lies in the superolateral quadrant. (B) Shenton line is disrupted on the left (dislocated) hip. (From: Storer SK, Skaggs DL. Developmental dysplasia of the hip. *Am Fam Physician*. 2006;74:1310-1316.)

of transient synovitis often follow a viral respiratory illness, minor trauma, or allergic hypersensitivity. This condition may affect the hips or knees.

In a child presenting with a limp, transient synovitis should be distinguished from septic arthritis, because the latter can cause joint destruction if diagnosis is delayed. Generally, patients with septic joints have fevers and are unwilling to bear weight, whereas children with transient synovitis are rarely febrile and may limp but bear some weight. The leg of either condition is generally held in some flexion, slightly abducted and externally rotated due to the presence of an effusion. Transient synovitis often presents after a viral illness and the child may have no other symptoms; children with septic joints can appear ill.

Transient synovitis is a diagnosis of exclusion, involving history, physical examination, screening labs, and imaging to rule out a septic

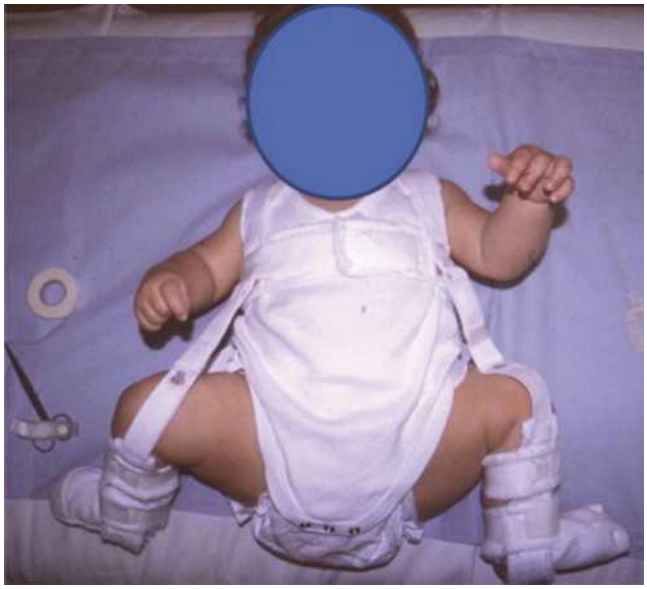


Fig. 170.25 Pavlik harness. (From: Clarke N, Taylor C. Diagnosis and management of developmental hip dysplasia. *Paediatr Child Health*. 2012;22(6):235-238.)

BOX 170.1 Causes of Hip Pain in Children

Trauma
Hip or pelvis fractures
Overuse injuries

Infection
Septic arthritis
Osteomyelitis
Myositis
Lyme disease

Inflammation
Transient synovitis
Juvenile rheumatoid arthritis
Rheumatic fever

Neoplasm
Leukemia
Osteogenic or Ewing sarcoma
Metastatic disease

Hematologic Disorders
Hemophilia
Sickle cell anemia

Miscellaneous
Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis

joint. Because clinical features for these two entities can overlap, a set of four independent predictors of septic arthritis (Kocher criteria) can help evaluate the likelihood for septic joint: fever of 38.5°C or greater, inability to bear weight; erythrocyte sedimentation rate (ESR) of 40 mm/hr or greater; and peripheral white blood cell (CBC) count of 12,000 cells/μL or greater. The Kocher study found that the probability of septic arthritis in patients with one predictor was 3%; two predictors, 40%; three predictors, 93%; and all four, nearly 100%. Validation studies found a 2% chance of septic arthritis in patients with zero out of four predictors. Although not part of the original Kocher criteria, C-reactive protein (CRP), commonly used for additional risk stratification, has shown to be a better negative than a positive predictor of the disease. A CRP less than 1.0 mg/dL carries an 87% probability of *not* having septic arthritis. Inflammatory markers tend to be normal to mildly elevated in transient synovitis.

If septic arthritis cannot be reliably excluded in the differential, then we recommend ultrasound for initial hip imaging, because it is noninvasive and highly sensitive for detecting hip effusions. A hip ultrasound that is negative for joint effusion generally rules out septic arthritis; however, the presence of a hip effusion is nonspecific. Radiographs of the hip have limited utility in ruling in or out transient synovitis but can identify other pediatric hip disorders causing symptoms.

If transient synovitis is suspected, treatment includes symptomatic relief with nonsteroidal antiinflammatory drugs (NSAIDs) and joint rest. Return to activity is allowed as tolerated with improvement of pain. Close follow-up with primary care within 24 hours is recommended for continued monitoring for signs of septic arthritis. Symptoms of transient synovitis last 1 week or less in 67% of patients, and less than 1 month in an additional 21% of patients.

Acute Septic Arthritis

Septic arthritis is a bacterial joint space infection that can result in acute and chronic disability. Boys are affected twice as often as girls, and the lower extremities are most commonly involved; hips, knees, and ankles account for 80% of cases. Predisposing factors include trauma, preceding viral infection, immunodeficiency, hemoglobinopathy, hemophilia-induced hemarthroses, diabetes, intraarticular injections, surgery, and IV drug use.

The pediatric joint is most commonly infected through hematogenous inoculation via transphyseal vessels, as the blood flow is sluggish in metaphyseal capillaries. Contiguous spread of infection from osteomyelitis into the joint space is more common in infants and young children. The infection's inflammatory response leads to a high local cytokine concentration, which induces the host to release matrix metalloproteinases, which are collagen degrading enzymes. Bacterial toxins and lysosomal enzymes further damage the articular surface as soon as 8 hours after inoculation. Pressure ischemia and avascular necrosis cause additional joint destruction from increased capsular pressure.

Common bacterial etiologies for septic arthritis tend to be age specific (Table 170.5). The organisms most likely to cause bacteremia in a child are the most common organisms isolated from pediatric joint infections, including both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is isolated in up to 63% of cases. Some strains of CA-MRSA have been found to contain a gene encoding for the cytotoxin Panton-Valentine leucocidin (PVL), which is associated with complex infections, higher rates of septic shock, prolonged hospital stays, increased surgical interventions, and longer durations of antibiotic therapy.

In neonates, group B *Streptococcus* and gram-negative enteric organisms are common causes of infections. Neonates and adolescents share a risk for *Neisseria gonorrhoeae*, whereas children with sickle cell are at a greater risk for *Salmonella* infections. Other frequently isolated species include group A hemolytic *Streptococcus* and *Streptococcus pneumoniae*.

Septic arthritis can present similarly to transient synovitis, with a combination of fever, malaise, and immobility from pain when ranging the affected joint. Local erythema, warmth, and swelling may be noted in joints other than the hip. Hip infections commonly present with the

TABLE 170.5 Septic Arthritis Pathogens and Treatment

Age	Organism	Treatment
Birth–3 mo	Group B streptococcus (*Streptococcus agalactiae*) *Staphylococcus aureus* Gram-negative organisms *Neisseria gonorrhoeae*	Nafcillin 75–150 mg/kg/day q6h or oxacillin 75–100 mg/kg/day q6-8h, and cefotaxime 100–150 mg/kg/day q8h or cefepime 100 mg/kg/day q12h
3 mo–5 yr	*S. aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Kingella kingae* *Haemophilus influenzae*	Nafcillin, 150–200 mg/kg/day q6h or oxacillin 100–200 mg/kg/day q4–6h, and ceftriaxone, 50–100 mg/kg/day q12h[a]
5 yr–12 yr	*S. aureus* *S. pyogenes*	Nafcillin 150–200 mg/kg/day q6h or oxacillin 100–200 mg/kg/day q4–6h, and ceftriaxone 50–100 mg/kg/day q12h[a]
>12 yr	*S. aureus* *N. gonorrhoeae*	Nafcillin 150–200 mg/kg/day q6h or oxacillin 100–200 mg/kg/day q4–6h, and ceftriaxone 50–100 mg/kg/day q12h[a]

[a]Consider vancomycin, 45–60 mg/kg/day q6–8h, if methicillin-resistant *S. aureus* (MRSA) accounts for >10% local *S. aureus* isolates. Clindamycin 40 mg/kg/day q6–8h can be substituted for vancomycin if local *S. aureus* resistance to clindamycin is <10%.

Adapted from Liu C, Bayer A, Cosgrove SE, et al: Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285; Gill P, Sanders JE. Emergency department management of pediatric Septic arthritis and osteomyelitis. *Pediatr Emerg Med Practice*. 2019;16:1-24; Kleinman K, McDaniel L, Molly M. *The Harriet Lane Handbook*, 22 edition, Elsevier, 2021, Philadelphia, PA.

TABLE 170.6 Proposed Guidelines for Synovial Fluid Interpretation

Positive	WBC >50,000 cells per microliter or Gram stain positive	%PMN >90	Pyogenic arthritis
Equivocal	WBC 20,000–80,000	%PMN >70	Lyme disease Tuberculosis
Negative	WBC < 5,000	%PMN <25	Transient synovitis Traumatic arthritis Reactive arthritis

Adapted from: Arson P, Posner J, Dooley RN, Cofin S, Jacobstein C, Lavelle J. This Children's Hospital of Philadelphia, Clinical Practice Guideline on Suspected Septic Arthritis. Last updated February 2017. Available at: http://www.chop.edu/clinical-pathway/septic-arthritis-suspected-clinical-pathway. Accessed February 2017.

joint in flexion, abduction, and external rotation. Patients may limp or refuse to bear weight. Infants may be irritable, lethargic, have pain when being handled, and refuse to feed. Neonatal hip infections commonly present with the joint in flexion and abduction with internal rotation.

Diagnosis of septic arthritis is made by history and physical examination, supported by laboratory studies and imaging, and confirmed by arthrocentesis. Initial blood work should include complete blood count with differential, CRP, ESR, and blood cultures. As discussed previously, some of these studies are included in the Kocher criteria, which helps differentiate between transient synovitis and septic arthritis. In septic arthritis, the ESR generally rises greater than 24 hours after the onset of infection symptoms, whereas the CRP rises quickly and is a better independent predictor of infection.

Kingella kingae arthritis deserves special mention, because the presentation is atypical for septic arthritis. *Kingella kingae* is an oral gram-negative bacterium, most commonly linked to septic arthritis in children less than 4 years of age. *K kingae* infections are often preceded by upper respiratory infections and tend to have a milder presentation than the typical septic arthritis, including lower to absent fever. *K. kingae* septic arthritis can present with a normal white blood cell count and normal acute-phase reactants, similar to transient synovitis. *K. kingae* patients are commonly colonized and oropharynx PCR assay for the RTX toxin should be obtained if suspected.

In septic arthritis, plain radiographs of the affected joint are less likely to be helpful. In the acute setting, only soft tissue swelling may be noted. Radiographic changes including destruction of the articular cartilage and joint space narrowing can be seen in a chronic process, but not readily until 7 to 10 days after the infection has commenced. Ultrasound is a rapid and noninvasive method for detecting the presence of a joint effusion. This is particularly helpful when evaluating the hip or shoulders, which are not easily palpated for effusion. A negative ultrasound of the hip with absence of fluid generally rules out septic arthritis. MRI with and without gadolinium contrast is the optimal imaging modality for bone infections, which can help identify nearby osteomyelitis or pyogenic myositis. Between 15% and 50% of osteoarticular infections involve the joint *and* bone.

Definitive diagnosis of septic arthritis hinges on the evaluation of aspirated synovial fluid sent for Gram stain, cell count with differential, and aerobic and anaerobic cultures. Synovial fluid samples with WBC greater than 50,000/μL of which greater than 75% are polymorphonuclear cells (Table 170.6) is considered positive for septic arthritis. The synovial glucose concentration may be low (synovial fluid glucose/blood glucose ratio < 0.5). Culturing synovial fluid in aerobic blood culture bottles can improve detection of *K. kingae*.

Joint aspiration should be performed and treatment not delayed when septic arthritis is suspected. Empirical antibiotic therapy for septic arthritis is directed against the most likely organisms, as dictated by the patient's age and comorbid conditions (see Table 170.5). To improve bacterial identification, synovial and blood cultures should precede antibiotics; however, antibiotics should not be delayed in patients exhibiting signs of sepsis. Antibiotics have good penetrance into the joint, and synovial fluid concentrations are equivalent to serum concentrations within one hour. When treating gram-positive cocci, initial therapy is a penicillinase-resistant penicillin; however, in areas with high rates of CA-MRSA, therapy should include vancomycin or clindamycin (depending on local resistance patterns). Ceftriaxone should be added for gram-negative bacterial coverage, as well as *K. kingae, Gonococcus, Salmonella*, and *Borrelia burgdorferi* (Lyme disease). Optimal length for intravenous antibiotic treatment is generally 2 to 4 days, followed by transition to oral therapy if clinical symptoms are improving and CRP levels declining.

Timely decompression of the joint via open arthrotomy, irrigation, and débridement is the recommended treatment for septic arthritis. Due to risk of avascular necrosis, urgent intervention is particularly

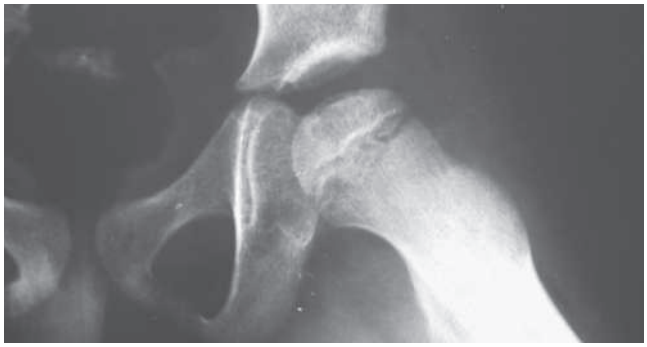


Fig. 170.26 Crescent sign (subchondral lucent zone) in early Legg-Calvé-Perthes disease. (Courtesy Dr. Marianne Gausche-Hill.)

indicated for septic arthritis of the hip. Less invasive cannula irrigation techniques are performed in some centers, but an open procedure is still recommended if concurrent bone infection or subperiosteal abscess is present.

Legg-Calvé-Perthes Disease

Legg-Calvé-Perthes Disease (LCPD) is an idiopathic necrosis of the capital femoral epiphysis and a form of osteochondrosis. The disorder is more common in boys, has a peak incidence in children aged 3 to 11 years, and presents with bilateral disease in 10% to 15% of patients.[7] The later the onset of the disease, the less favorable the outcome; patients older than 8 years old have poor outcomes.[7] The disease process involves a predominance of femoral head resorption compared to reformation, resulting in femoral head deformity and mechanical weakening.

Most children with LCPD present with a limp and may have the Trendelenburg sign, limited internal rotation and abduction of the hip. Early in the disease, hip motion is generally good. Pain is typically insidious in onset, experienced in the hip, or referred to the groin, thigh, or knee. Pain is worse with activity and relieved by rest. Disease progression can be variable but may include muscular atrophy of the buttocks, thigh, and calf, as well as limb length discrepancy up to 2.5 cm.[7]

Imaging of the hip should include AP pelvis and frog leg lateral radiographs. Early in the illness, the radiographs may be normal, but subtle changes may vary depending on the disease progression. If initial radiographs are normal, but symptoms concerning for LCPD persist for more than 6 weeks, then an MRI is recommended.[7] There are four phases of the disease: initial, fragmentation, reossification, and healed. In the initial phase, the femoral head loses blood supply. As bone dies, the medial joint space widens as the femoral head becomes less round due to subchondral collapse (Crescent sign) (Fig. 170.26). The hip joint becomes painful, stiff, and inflamed. In the fragmentation phase the epiphysis begins to fragment as new bone begins to form, reshaping the femoral head. The reossification phase includes continued bone density repair as the femoral head continues to reshape. In the healed stage, radiographs of the proximal third of the femur and femoral head may demonstrate residual deformities.

Children with concern for LCPD should be evaluated by an orthopedic surgeon. The goal of management is to keep the femoral head within the acetabulum. Treatment includes restriction of activity, physiotherapy, bracing, or surgery. The choice varies with the stage and onset of the disease.

Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis (SCFE) is defined as the posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis, occurring through the epiphyseal plate (growth plate). This condition affects boys at twice the rate of girls, occurring more commonly between 8 and 15 years of age. The average age at diagnosis is 13.5 years for boys and 12 years for girls, presenting bilaterally in 18% to 50% of patients, although in most patients the second slip occurs within 18 months after the initial presentation.[7] SCFE is the most common hip disorder of adolescents, with a prevalence of 10.8 cases per 100,000 children. This prevalence is changing due to the increasing obesity rate, which data suggest is a contributing factor—63% of affected patients have weight in the 90th percentile or higher.[7]

The etiology of SCFE is felt to be multifactorial: obesity, periods of rapid growth, and endocrine disorders. Adolescent growth spurts and obesity contribute to the mechanical factors predisposing to epiphyseal sliding. Although increased mechanical load tends to increase bone strength, endocrine-related changes with obesity lead to a decreased overall bone mass. The most commonly observed endocrine abnormalities in SCFE patients are hypothyroidism, growth hormone deficiency, and chronic renal failure. Skeletal maturation is delayed in many SCFE patients.

Patients with SCFE generally present with limping and poorly localized pain to the hip, groin, thigh, or knee. Patients may have an antalgic gait or be unable to bear full weight on the affected leg. Limited internal rotation of the hip is common. Patients may have Drehmann sign, obligatory external rotation when the affected hip is flexed. Although the differential diagnosis for pediatric hip pain is broad, SCFE should be considered because a delayed diagnosis may result in a poorer prognosis.

Traditionally, SCFE is classified as preslip, acute slip, chronic slip, and acute on chronic slip. This classification is based on history, duration of symptoms, physical examination, and radiographs. Currently, however, a more clinically relevant method of classification is preferred based on stability of the physis and risk of avascular necrosis (AVN).[8] A SCFE is considered stable (90% of all slips) if the patient is able to ambulate with or without crutches; however, if the patient is unable to ambulate even with crutches, it is considered unstable.

If a stable SCFE is suspected on examination, then diagnostic radiographs should include anteroposterior and frog leg lateral views of both hips; for an unstable SCFE, anteroposterior and cross-table lateral views are recommended. Early in the course of the SCFE, the initial slippage is posterior and the AP view is generally normal in appearance or shows widening of the physis, whereas the lateral view is more diagnostic (Fig. 170.27). Signs of slippage on AP radiographs include evaluating the Klein line, a line drawn along the superior margin of the femoral neck. In a normal hip, the lines intersect with the epiphysis symmetrically; in a SCFE, the line does not intersect with the epiphysis (Fig. 170.28). MRI may be useful in diagnosing low-displacement forms of SCFE.

Slip severity can be graded using the Wilson method, which measures the relative displacement of the epiphysis on the metaphysis in a frog leg lateral radiograph. A mild slip involves epiphysis displacement less than one-third of the width of the metaphysis; a moderate slip shows displacement of one-third to one-half of the width; and a severe slip involves displacement greater than one-half of the width. Additional measurement of slippage can be made on a frog leg lateral radiograph with the epiphyseal shaft angle of Southwick (Fig. 170.29). This measurement involves drawing a line between the anterior and posterior tips of the epiphysis at the physeal plate level. A second line is drawn perpendicular to the epiphyseal line. A third line is then drawn along the midshaft of the femur. The epiphyseal shaft angle is formed by the intersection of the perpendicular and femoral shaft lines. The

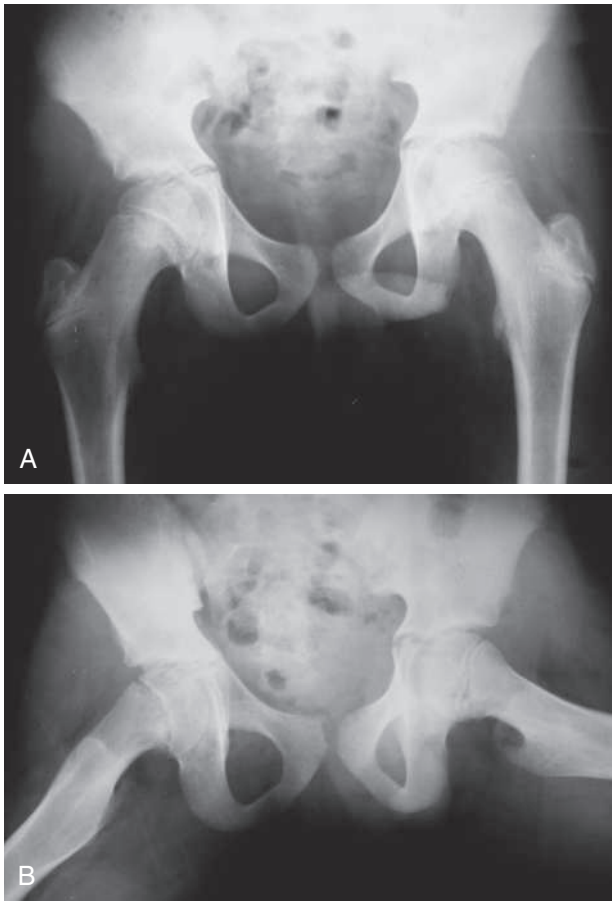


Fig. 170.27 (A) Anteroposterior radiograph of the pelvis with a unilateral slipped capital femoral epiphysis. Note widening of the physis on the right compared with the left. (B) Early inferior and posterior slippage is evident on the lateral view. (Courtesy Dr. Marianne Gausche-Hill.)

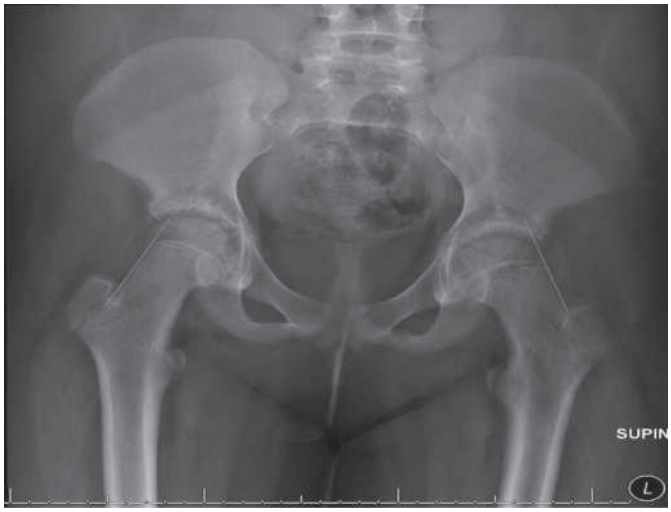


Fig. 170.28 Anteroposterior radiograph of the pelvis with a slipped capital femoral epiphysis. Note widening of the physis on the left and a greater distance from the lateral edge of the femoral epiphysis to the Klein line on the right than is seen on the left. A difference of more than 2 mm is diagnostic.

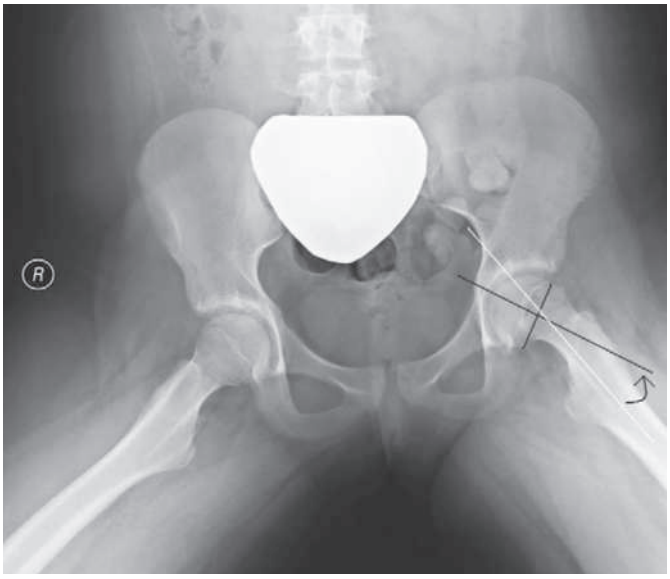


Fig. 170.29 Epiphyseal shaft angle of Southwick. On a lateral radiograph, a line is drawn from the anterior to the posterior epiphyseal edges and a second line is then drawn perpendicular to this line. A third line is drawn down the femoral diaphysis. The intersection between the perpendicular line and femoral shaft line is the epiphyseal shaft angle. The magnitude of slip displacement is the angle of the involved hip minus the angle of the normal hip. (From: Pinkowsky GJ, Hennrikus WL. Klein line on the anteroposterior radiograph is not a sensitive diagnostic radiologic test for slipped capital femoral epiphysis. *J Pediatr*. 2013;162f:804-807.)

degree of slip displacement is the angle of the involved hip minus the angle of the normal hip. A mild SCFE involves displacement of less than 30 degrees, a moderate slip is between 30 degrees and 50 degrees, and severe displacement is great than 50 degrees.[10]

Children diagnosed with SCFE should be made non-weightbearing and admitted or transferred for orthopedic intervention to prevent further slippage. The standard treatment for SCFE is in situ fixation with a single screw performing an epiphysiodesis. Fixation treatment goals are similar in stable and unstable SCFE; however, there is controversy regarding timing of surgery and value of reduction in the unstable type.

Secondary to blood supply disruption or hematoma formation, a vascular necrosis of the femoral epiphysis occurs in 20 to 50% of patients with unstable SCFE and is more common in severe displacement. Chondrolysis, the acute loss of articular cartilage, can be a complication of SCFE surgery, most often from pin penetration of the femoral head, causing joint stiffness and pain. The incidence of chondrolysis has decreased from 7 to 1% as SCFE surgical techniques have improved. Premature closures of the epiphyseal plate, as well as early onset degenerative changes, are common complications from SCFE.

Lyme Arthritis

Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is now considered the most common vector-borne illness in North America and Europe, with a threefold increase in annual cases since 1992.[11] The primary vector is the *Ixodes* tick while in its nymph stage. The nymph stores the spirochetes in its midgut, which migrate to the salivary glands after the gut is engorged. An infected nymph must feed for at least 72 hours in order to transmit the disease.

The geographic distribution of Lyme disease has increased primarily into locations adjacent to recognized endemic areas, including New England, the Mid-Atlantic States, and Wisconsin (Fig. 170.30).[12] Two-thirds of cases

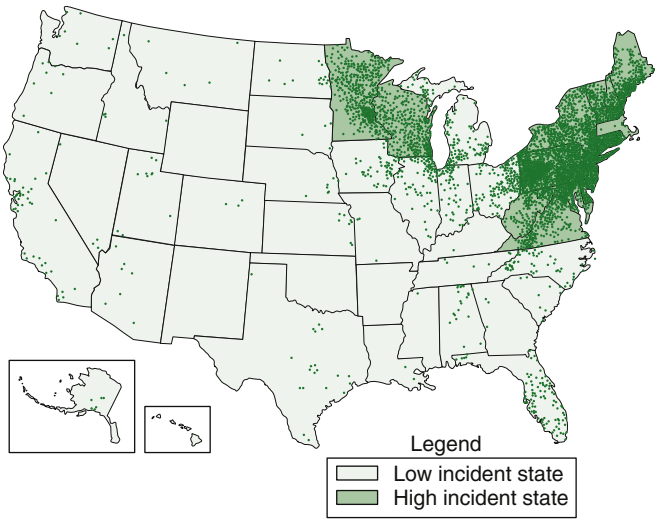


Fig. 170.30 Reported cases of Lyme disease in the United States, 2018. Each dot represents one case of Lyme disease and is placed randomly in the patient's county of residence. (From: Centers for Disease Control and Prevention. Reported Cases of Lyme Disease-United States, 2018. Retrieved from https://www.cdc.gov/lyme/datasurveillance/maps-recent.html.)

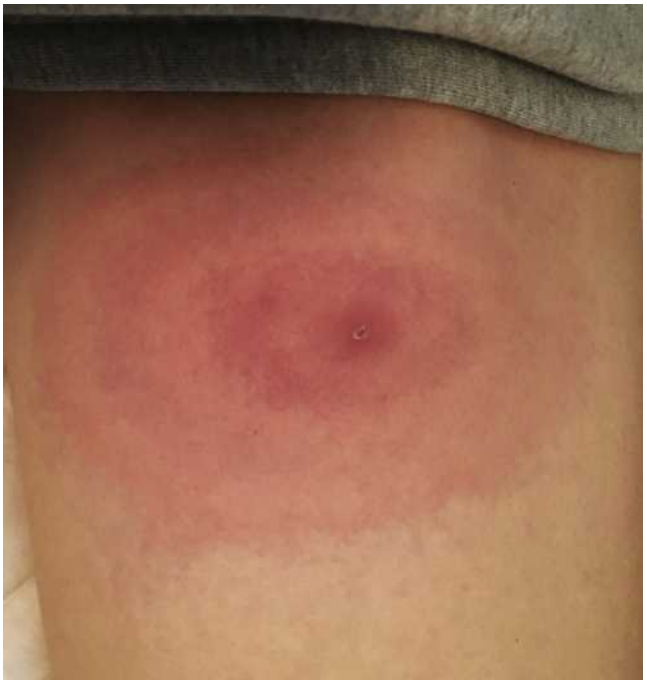


Fig. 170.31 Erythema migrans (EM) rash of the left inner thigh. EM is the most common early localized symptom of Lyme disease. (Courtesy Dr. William Prince, MD.)

of early Lyme disease occur in June, July, or August; however, because Lyme arthritis is a late manifestation (occurring weeks to months after initial infection), presentation is greatest in fall and winter months.[11]

Patients with Lyme disease have signs or symptoms correlating with disease progression: early localized, early disseminated, or late Lyme disease. Early localized disease is characterized by the erythema migrans (EM) lesion, the most common manifestation of Lyme disease in children.[13] This lesion begins as a red macule that expands over days to weeks to form an erythematous annular lesion with partial central clearing. The classic "bull's-eye" rash is seen less commonly (Fig. 170.31). Early disseminated disease may include multiple EM lesions, cranial nerve palsies (most commonly cranial nerve VII), lymphocytic meningitis, radiculitis, and carditis (AV block). Early disseminated disease may also include systemic symptoms such as low-grade fever, arthralgia, myalgia, headache, and fatigue. Approximately 50% to 60% of patients not treated for early stages of Lyme will go on to develop Lyme arthritis, which can be their presenting symptom of the disease. Late Lyme disease in children most commonly presents as arthritis.[13]

Lyme arthritis presents as monoarthritis in two-thirds of cases. If presenting as oligoarthritis, the knee is often involved; joint involvement is generally asymmetrical, involving a knee and another joint, such as the hip, shoulder, ankle, elbow, temporomandibular joint, or wrist. Patients can have acute joint swelling or intermittent and migratory arthralgias. The knee tends to be swollen, with limited range of motion, and the joint may be erythematous and warm to the touch. Pain varies, but patients can usually still ambulate with a limp.

Diagnosis of early Lyme disease can be difficult, because the immune system takes several weeks to develop antibodies after exposure to *B. burgdorferi*. Because the skin lesion is generally clinically identifiable, serology is not recommended for diagnosis in Lyme endemic areas. In fact, patients can still be seronegative, even after an erythema migrans rash develops.[12] However, by the time the late-stage symptoms of Lyme arthritis develop, immunoglobulin G serology for *B. burgdorferi* should be positive and is considered diagnostic in a patient from an endemic area with monoarthritis or oligoarthritis. Immunoglobulin M may wane and be negative at 30 days. Initial testing is performed using an ELISA screening followed by confirmatory Western blot test. A positive immunoblot result is defined as the presence of at least two 2 IgM bands or 5 IgG bands.[13]

In contrast to septic arthritis or rheumatic fever, the joint swelling, effusion, and stiffness in Lyme arthritis are disproportionate to the relatively mild degree of pain. Because of its insidious onset and subtle infectious symptoms, Lyme arthritis is commonly overlooked and mistaken for traumatic injury. Differentiating between Lyme arthritis, septic arthritis, and transient synovitis in the acute setting can be difficult, because many clinical symptoms overlap. Similar to delineating between septic arthritis and transient synovitis, a complete blood count with differential, ESR, and CRP can be helpful when determining risk for Lyme arthritis in an endemic area. Compared to Lyme arthritis, septic arthritis is more likely to have a history of fever, increased serum WBC count, and elevated CRP.[11] ESR levels are similar between Lyme arthritis and septic arthritis, and both are significantly elevated compared to transient synovitis.[14] Ultimately, serum markers for leukocytosis and inflammation alone are not reliable markers for distinguishing Lyme arthritis from transient synovitis or septic arthritis.[14]

To determine need for antibiotics or surgical intervention, children should undergo synovial fluid testing to rule out septic arthritis. Standard synovial fluid analysis includes cell count, Gram stain, culture, and, if indicated and available, *B. burgdorferi* PCR. Lyme arthritis elicits a synovial WBC count ranging between 10,000 to 50,000 cells per microliter, whereas septic arthritis is typically greater than 50,000 cells per microliter (see Table 170.6). PCR synovial fluid testing is often positive (40% to 96%) prior to antibiotic therapy but given the high specificity and sensitivity of serologic testing in late Lyme disease, it may not add any additional clinical value.

Antibiotic treatment for Lyme arthritis hastens resolution of symptoms and prevents long-term joint damage. Antibiotic recommendations for Lyme disease were updated in 2018 by the Infectious Disease Society of America, primarily pertaining to prophylaxis and treatment with doxycycline in children with early localized disease.[13] Doxycycline was previously not recommended in children less than 8 years of age due to

TABLE 170.7 Recommended Treatment of Lyme Disease in Children

Manifestation	First-Line Drugs	Alternative Drugs	Second-Line Drugs
Erythema migrans (single or multiple)	Amoxicillin 50 mg/kg/day TID PO × 14 days Doxycycline 2–4 mg/kg/day BID PO × 10 days	Cefuroxime 30 mg/kg/day BID × 14 days	Azithromycin 10 mg/kg daily × 10–14 days
Facial palsy	Amoxicillin 50 mg/kg/day TID PO × 14 days Doxycycline 2–4 mg/kg/day BID PO × 14 days		Azithromycin 10 mg/kg daily × 10–14 days
Meningitis	Ceftriaxone 100 mg/kg/day daily IV × 14 days Cefotaxime 180 mg/kg/day q8h IV × 14 days		
Carditis	Amoxicillin 50 mg/kg/day TID PO × 14–21 days Doxycycline 2–4 mg/kg/day BID PO × 14–21 days Ceftriaxone 100 mg/kg/day daily IV × 14-21 days Cefotaxime 180 mg/kg/day q8h IV × 14–21 days		
Arthritis	Amoxicillin 50 mg/kg/day TID PO × 28 days Doxycycline 2–4 mg/kg/day BID PO × 28 days		
Persistent arthritis after course of therapy	Retreat with one of above oral regimens	Ceftriaxone 100 mg/kg/day daily IV × 14–28 days Cefotaxime 180 mg/kg/day q8h IV × 14–28 days	

Adapted from: Sood S, Krause P. (2019). Lyme Disease. *Feigin and Cherry's textbook of pediatric infectious diseases*, 140;1246-1252.e2

the risk of dental staining. Evidence now suggests that doxycycline for 10 days, in the setting of early localized disease, is safe. However, the recommended oral antimicrobial treatment of Lyme arthritis calls for 28 days of doxycycline, and there are limited safety data on its use for greater than 21 days in children younger than 8 years old.[13] Treatment options for Lyme arthritis in children are listed in (Table 170.7). Patients with incomplete resolution of arthritis symptoms or relapse soon after treatment may be given a second 28-day course of oral therapy, or ceftriaxone parentally for 14 to 28 days if arthritis worsens.[13] The Infectious Disease Society of America recommends several months of observation after treatment due to anticipated slow resolution of inflammation.

Approximately 10% to 15% of patients treated for Lyme arthritis will have persistent synovitis for months to years, despite multiple courses of antibiotics.[13] This chronic arthritis is considered a postinfectious inflammatory process, with negative Lyme PCR from their synovial fluid; these patients may benefit from referral to a rheumatologist. Nonsteroidal antiinflammatory medications are reasonable for pain control; systemic steroids are not recommended.

Apophyseal Injuries

The apophysis is a cartilaginous structure on growing bones that serves as a site for tendon insertion. This site has a growth plate, with a slower rate of growth than the nearby epiphyseal plate. The apophysis is two to five times weaker than the surrounding structures, including the muscle tendon complex, ligaments, and bones. Rapid bone growth before adequate muscle lengthening contributes to increased tension at the apophysis. Although the age of onset varies, this injury is seen most commonly in the immature skeleton. Apophysitis results from a traction injury to the cartilage and bony attachment of tendons, most often as an overuse injury in children. Specific sports and activities have a predilection for specific apophyseal locations and may be secondary to a single trauma versus repetitive microtrauma.

Because many children are consistently playing year-round sports and nearly 44 million participate in more than one sport, overuse injuries in youth sports are increasing in prevalence.[15] Many children and adolescents will not recognize overuse injuries, due to insidious onset or misinterpretation of symptoms as simple fatigue or performance decline.

Osgood-Schlatter Syndrome

Osgood-Schlatter disease (OSD) is a condition in which the patellar tendon insertion on the tibial tubercle ossification center becomes inflamed due to repetitive tensile stress. It is more commonly seen in boys around 10 to 15 years of age and between 8 and 12 years in girls. Bilateral knees are affected in 20% to 30% of cases, but intensity of symptoms can vary in each knee.

Patients typically complain of a bony prominence and pain over the tibial tuberosity that is exacerbated by physical activity like running, jumping, and climbing stairs. Symptoms generally resolve without any treatment after natural closure of the physis, but some symptoms may persist if bone fragments do not fuse. Nonunion can occur in almost 10% of patients and generally results in anterior knee pain after minor activity, especially kneeling.

Diagnosis is based on history and clinical findings. Radiographs are not necessary but may aid in ruling out other causes of knee pain. A lateral knee radiograph may show blurred margins of the patellar tendon in the acute stage. After three to four months, bone fragmentation at the tibial tuberosity may be visible, and may later fuse during the chronic stage. Ultrasound may show pretibial swelling, fragmentation of the ossification center, insertional thickening of the patellar tendon, and excessive fluid collection in the infrapatellar bursa. Infrapatellar bursitis may be difficult to distinguish from OSD clinically, because the location of pain is similar; however, OSD should have tenderness with palpation of the tibial tuberosity.

Management of OSD focuses on reduction of pain and swelling over the tibial tuberosity. Activities that exacerbate pain should be limited for several months until symptoms resolve. Conservative management includes NSAIDs, ice, and exercises for the improvement of the quadriceps, hamstrings, and gastrocnemius muscles. In some cases, immobilization in a cast for 3 to 6 weeks may be necessary.

Sever Disease

The most common cause of heel pain in pediatric patients is calcaneal apophysitis, commonly called Sever disease. Similar to other overuse injuries, it is a result of repetitive microtrauma and inflammation at the site of the Achilles tendon insertion. Pain is felt at the posterior aspect of the calcaneus. This condition is primarily seen in pediatric athletes between 8 and 15 years of age, when the calcaneal physis is still an open growth plate. Bilateral involvement is seen in about 60% of cases. Sever disease can be associated with running and jumping sports.

Patients generally have no history of specific injury. Patients often report limping or walking on their toes to avoid putting weight on their heels. Physical examination includes tenderness at the lateral and medial aspects of the calcaneus. Compression of these sites can be diagnostic and is called the "squeeze test." X-rays of the heel may appear normal in the disease but radiographic findings can show increased density and fragmentation of the calcaneal apophysis.

Treatment for calcaneal apophysitis is universally conservative, including ice, NSAIDs, activity restriction, stretching, and heel cups. Stretching of the calf muscle is recommended, as it provides traction to the Achilles tendon, which may benefit from stretching during times of rapid bone growth. Arch taping has also been shown to decrease associated pain during ambulation. Recovery time varies according to the causative factors and treatment compliance. Activity restriction is recommended until the patient is pain free; full recovery is expected once skeletal maturity is reached.

Little League Elbow

Little League elbow is a term commonly used to describe a group of elbow injuries, including apophysitis, medial epicondylitis, and osteochondritis dissecans of the radial head and capitellum. The pediatric elbow is vulnerable to overuse injury because it has six ossification centers, closing at different ages of skeletal maturity, as well as multiple muscle and ligamentous attachments.[15]

Twenty-eight percent of youth pitchers report a history of elbow pain. Examination reveals localized tenderness and swelling over the medial epicondyle, and pain with resisted wrist flexion and forearm pronation. This condition is described as a valgus overload syndrome stemming from repetitive throwing imparting tensile force on the medial epicondyle and a compressive force at the lateral epicondyle. Medial injuries are most common, as the medial epicondyle is usually the last apophysis in the elbow to fuse.[15] Lateral epicondylitis of the elbow is felt to be tendinosis, worsened by wrist and finger extensor and supinator muscle contraction against resistance.

Radiographs may be normal in appearance, but commonly show focal lucency or sclerosis at the subchondral bone in the anterior aspect of the capitellum. Images may demonstrate fragmentation at the condyle, apophyseal avulsion, or widening at the medial epicondyle ossification center. MRI is the study of choice to fully delineate the extent of the injury.

The most important key to treatment is preventative, through adhering to proper pitch count guidelines by age and teaching proper mechanics.[16] Conservative treatment consists of ice, NSAIDs, and activity modification. Throwing can resume after symptoms have resolved, usually after 4 to 6 weeks. Operative intervention is indicated for displaced fractures > 5 mm, incarcerated fragments, or when associated with elbow dislocation.

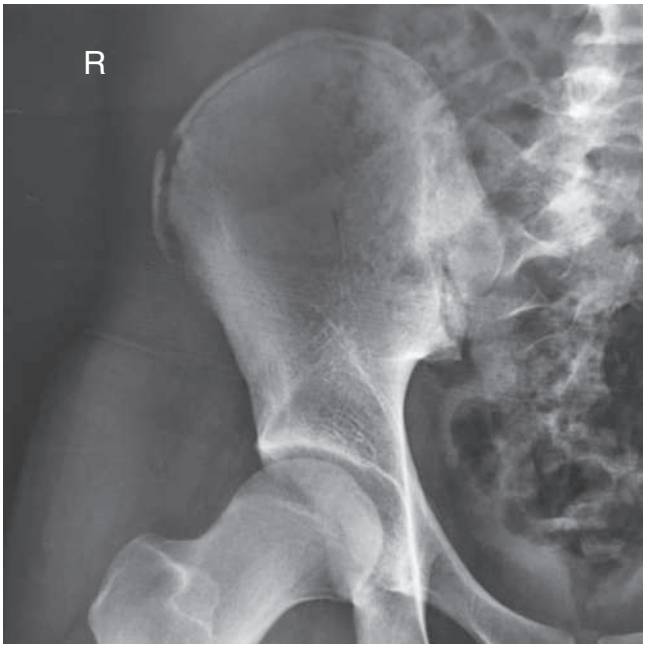


Fig. 170.32 Avulsion of the right anterior superior iliac spine in a child with hip pain after kicking a soccer ball. (Courtesy Dr. William Prince, MD.)

Apophysitis and Avulsion Fractures of the Hip

Apophyseal injuries of the hip occur at sites of muscle origination or insertion: iliac crest, anterior superior iliac spine, anterior inferior iliac spine, greater trochanter, lesser trochanter, ischial tuberosity, and pubic symphysis. Athletes most at risk include dancers, distance runners, and those in kicking sports. Patients most commonly present with pain at the tendinous insertion, which is commonly tender to palpation.

Radiographs may appear normal but can show mildly displaced avulsion fractures of the apophysis (Fig 170.32). Treatment for apophysitis includes activity restriction and stretching of associated muscles because this is a self-limited disorder that resolves by improving flexibility or when the apophyseal centers fuse when skeletal growth is complete. Avulsion fractures are generally treated conservatively with immobilization and slow resumption of activities. Surgery may be recommended for fragment displacement greater than 2 cm or for rapid rehabilitation of an athlete. Gradual return to pain-free activity may take several weeks to months.

Gymnast Wrist

Distal radial epiphysitis, also known as "gymnast wrist," is a chronic wrist pain affecting almost 80% of pediatric gymnasts at some point.[17] This injury is common to gymnasts who frequently bear weight through their upper extremities during events, such as the pommel horse and back handsprings. The overall weight load to the wrist ranges from 2 to 16 times the athlete's body weight, leading to distal radial growth plate injury in skeletally immature gymnasts.[17]

Compressive loading and shearing forces cause physeal microfractures at the hypertrophic zone. This leads to temporary ischemia which inhibits normal physeal calcification, causing physeal widening and metaphyseal irregularity. These radiographic abnormalities are seen in almost three-fourths of patients with the clinical diagnosis of gymnast wrist.[17]

Physical examination of the wrist is notable for tenderness over the distal radial physis, although range of motion of the wrist is generally normal.[15] Initial radiographs of the wrist may demonstrate widening of the distal radial physis, but a lack of bony edema, as this injury is due to chronic repetitive microinsults to the region (Fig 170.33).[15]

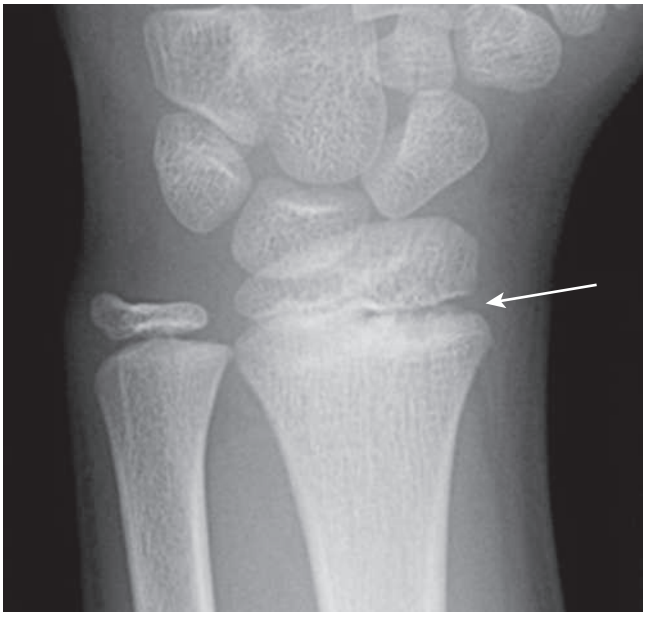


Fig. 170.33 Radiograph of 12-year-old female gymnast demonstrating mild physeal widening (*arrow*) of the distal radius with metaphyseal irregularity. (From: Paz DA, Chang GH, Yetto JM Jr, Dwek JR, Chung CB: Upper extremity overuse injuries in pediatric athletes: clinical presentation, imaging findings, and treatment. *Clin Imag*. 2015;39(6):954-964.)

Conservative treatment includes cessation from weightbearing activities until pain resolves, bracing of the wrist, and physical therapy. Premature closure of the distal radius physis can progress to bony deterioration, instability, and chronic arthritis if left untreated.[15]

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 170: QUESTIONS AND ANSWERS

1. An 8-year-old boy presents with left wrist pain after fall off a trampoline. Wrist radiograph shows a fracture at the distal left radius extending through the epiphysis, physis, and metaphysis. According to the Salter-Harris classification, what fracture pattern is described?

a. Salter-Harris type I
b. Salter-Harris type II
c. Salter-Harris type III
d. Salter-Harris type IV
e. Salter-Harris type V

Answer: D. Salter-Harris type IV fractures involve the growth plate extending from the physis into both the epiphysis and metaphysis. The risk of growth plate damage is higher in type IV and requires orthopedic consult and commonly open reduction to stabilize.

2. A 13-year-old overweight male presents with a complaint of insidious left hip pain that now radiates down to his knee. No trauma is noted on history and the patient is not athletic. On examination the patient walks with a limp and is unable to fully range his left hip due to pain but has full range of motion of the knee. Radiograph of the left hip is likely to show what finding?

a. Inferiorly and posteriorly displaced femoral epiphysis relative to the metaphysis on a cross-table lateral view of the hip
b. Femoral neck fracture
c. Avulsion fracture at the ischial tuberosity
d. Femoral head fragmentation

Answer: A. The patient's history and examination are consistent with a slipped capital femoral epiphysis (SCFE). The diagnosis of SCFE is made with AP and lateral radiographs of both hips as it can be present in 18% to 50% of patients. Femoral head fragmentation is consistent with Legg-Calvé-Perthes. Medial joint space widening can be seen with a joint effusion in the setting of septic arthritis, transient synovitis, or Lyme arthritis.

3. Which of the following statements regarding Lyme arthritis is true?

a. Lyme arthritis is an early localized sign of Lyme disease.
b. Synovial fluid WBC count ranges between 50,000 and 100,000 cells per microliter.
c. Azithromycin is the treatment of choice.
d. Monoarthritis is noted in two-thirds of cases, involving the knee 90% of time.

Answer: D. Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is now considered the most common vector-borne illness in North America and Europe. The primary vector is the *Ixodes* tick. Lyme arthritis is a finding in late Lyme disease. Synovial fluid WBC count ranges are typically 10,000 to 50,000. Treatment recommendations depend on prior treatment failures and additional Lyme manifestations.

4. Which of the following statements regarding gymnast wrist are true?

a. Initial radiographs of the wrist demonstrate a distal radius Salter-Harris II fracture.
b. Gymnast wrist only affects about 10% of gymnasts.
c. Radiographic evidence is seen in almost three-fourths of patient's with the clinical diagnosis.
d. The weight load to the athlete's wrist is generally greater than 30 times their body weight.

Answer: C. Distal radial epiphysitis, also known as "gymnast wrist," is a chronic wrist pain affecting almost 80% of pediatric gymnasts at some point. Radiographs demonstrate widening of the distal radial physis. This condition is commonly seen in gymnasts who bear weight through their upper extremities, increasing the weight load to their wrist from 2 to 16 times their body weight. Treatment is generally conservative with cessation from weightbearing activities.

Pediatric Drug Therapy

Laurie Seidel Halmo and George Sam Wang

KEY CONCEPTS

- Awareness of differences in pediatric pharmacokinetics and specific drug toxicities is of critical significance for the safe and effective use of medications in children.
- Avoid prescription and over-the-counter (OTC) cough and cold medications in children because these agents have limited efficacy data and may cause harm.
- Counsel parents about the management of fever and appropriate indications and proper use of antipyretics.
- Perform a risk assessment (for prescription drug abuse and diversion) prior to prescribing opioid analgesics and, when indicated, limit prescribing to the lowest duration and amount possible.
- A multifaceted approach using clinical support systems and readily available reference tools is essential for the delivery of optimal emergent pediatric care.

FOUNDATIONS

Emergency clinicians are tasked with treating not only a wide age range of pediatric patients but also a wide spectrum of disease.[1,2] Nearly 75% of visits are associated with some form of pharmacotherapy during the visit or in the form of a prescription at discharge. Children may present to the emergency department (ED) with an acute life-threatening illness or injury. Although many children presenting for emergency care are otherwise healthy, children with complex medical needs and chronic illness account for an increasing number of ED encounters, many requiring some form of pharmacotherapy. At one tertiary care pediatric facility, 20% of their ED visits in a 2-year time frame were for children with chronic conditions. Pediatric patients are at high risk for medication errors and adverse drug events in the ED for a variety of reasons, including unique pharmacokinetic characteristics, lack of standard pediatric drug dosing and formulations, and weight-based dosing.[2]

PHARMACOKINETIC CONSIDERATIONS IN CHILDREN

Absorption

Absorption is the process in which a drug is transported from the site of administration (i.e., the GI tract for oral administration) to the systemic circulation. Children have unique differences that may lead to changes in drug absorption.[3] Figure 171.1 illustrates many of the key factors that account for pharmacokinetic differences between children and adults. For example, young children have higher gastric pH levels, which affects the bioavailability of acid-labile drugs (such as penicillins) to be absorbed in the stomach. They have decreased gastric emptying times, which prolongs exposure to medications before they pass the pylorus and may impact time to achieve peak concentrations. Variations in the intestinal tract also result in pharmacokinetic differences. The activity of drug-metabolizing enzymes on the intestinal border vary as development occurs, and differences in gut flora can impact drug absorption in young infants. One commonality between children and adults is that drug absorption is often impaired in the setting of critical illness.

Absorption of drugs via a non-oral route can also vary significantly in children compared to adults. The topical route can result in increased absorption in children due to their relatively larger body surface area and increased skin vascularity. Additionally, children's skin contains more water and has a thinner stratum corneum. These factors make children more prone to increased absorption and risk for systemic toxicity from dermally applied drugs. Children have less muscle mass with associated weaker muscle contraction and reduced muscle blood flow. This can result in erratic absorption of intramuscular medications in young children.[3] Absorption of rectally administered medications also varies widely, depending on the age of the child and chemistry of the drug involved. However, this route can be used for medications when children are unable to tolerate or are refusing oral administration, such as for acetaminophen and diazepam. The ability to administer medications via the pulmonary route is particularly desirable in pediatric populations, given the high prevalence of respiratory conditions, such as asthma. At the same time, younger children may be less able to coordinate the use of a metered-dose inhaler to deliver these medications properly; parental assistance and adjunct devices such as spacers maximize efficacy by minimizing drug deposition in the oropharynx. There has been increasing experience in the use of intranasal preparation of analgesic, sedative, and anxiolytic medications in children. Medications that can be used intranasally include fentanyl, ketamine, dexmedetomidine, and midazolam.[4-9] This relatively noninvasive route of administration provides rapid absorption and clinical effect for circumstances requiring immediate pain control or sedation.

Distribution

Drug distribution is the movement of the drug after entering systemic circulation to the tissues of the body. Drug distribution can be impacted by circulation, proteins, extracellular fluid, and body composition. The

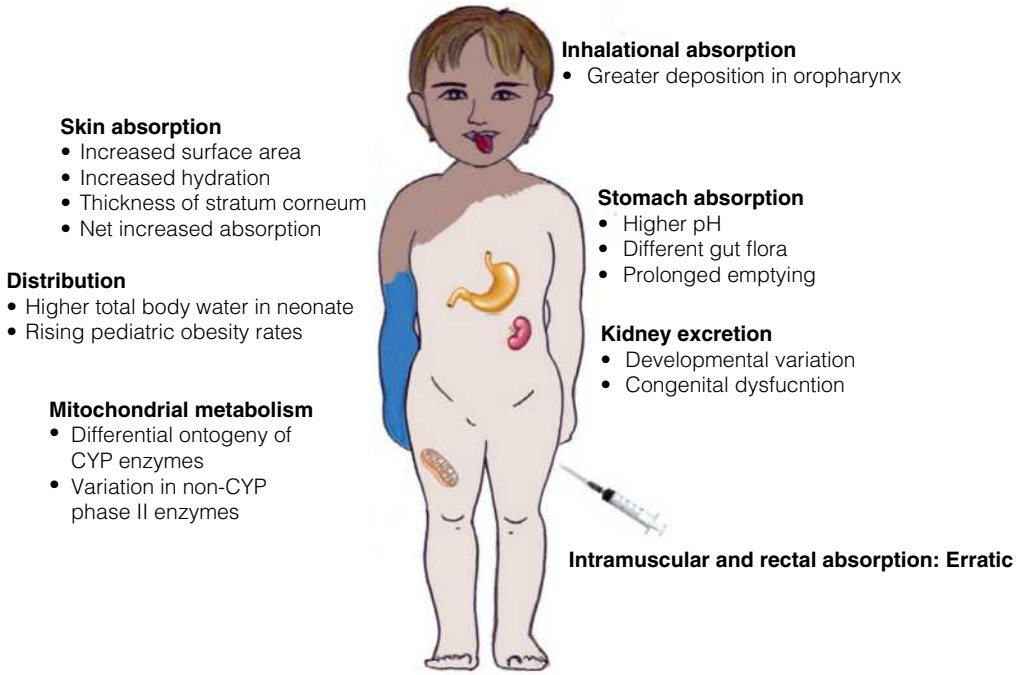

Fig. 171.1 Major pharmacokinetic considerations in the pediatric patient. (Courtesy Voyo Wu.)

specific drug composition can also impact drug distribution greatly. Distribution can differ significantly in children, which has important clinical implications. Neonates and infants have higher total body water and larger volumes of distribution and extracellular fluid; therefore, dosing of medications such as aminoglycosides will differ in this age group, and drug concentrations should be closely monitored. The larger volume of distribution (Vd) may impact hydrophilic drugs and result in larger weight-based doses to achieve sufficient systemic concentrations. Free drug concentrations are also affected by relatively lower concentrations of plasma proteins (albumin, glycoprotein, globulins, etc.) in infants and young children. A consideration specific to neonates is the displacement of bilirubin from protein-binding sites by drugs such as ceftriaxone, which can lead to kernicterus. Consequently, these medications should be avoided until the blood-brain barrier matures. Table 171.1 presents examples of other commonly used medications in the practice of emergency medicine that carry pediatric-specific toxicities as a result of pharmacokinetic and other idiopathic differences.

Body composition can impact drug pharmacokinetics. Childhood obesity has reached epidemic proportions in the United States and worldwide, and significant knowledge gaps have led to a lack of guidance on how medications should be dosed in an obese pediatric patient.[10] Drugs should be cautiously administered in this patient population, especially for high-risk medications such as opioid analgesics and sedatives. Additionally, childhood obesity has resulted in more children being placed on medications, more commonly used in adults, for chronic conditions, such as anti-hypertensives and diabetes medications. Because these medications have been traditionally prescribed for adults, there are few guidelines and a significant paucity of safety and efficacy data in children, which can predispose them to adverse drug events.

Metabolism

Drugs are metabolized through various organs—most commonly the liver, but also in the kidneys and gastrointestinal mucosa. Phase 1 metabolism often involves oxidation or hydrolysis (often by cytochrome P450 enzymes [CYP]), whereas phase 2 metabolism includes conjugation reactions such as glucuronidation and sulfation. Drug metabolism in neonates and infants can be diminished because of immature drug-metabolizing enzymes (Box 171.1). An example of toxicity due to differences in drug-metabolizing enzymes is the neonatal gasping syndrome. Benzyl alcohol, a common preservative for parenteral medications, is metabolized to benzoic acid, which is detoxified by glycine conjugation. Glycine conjugation is decreased in neonates and therefore benzoic acid accumulates when they are given drugs containing benzyl alcohol, leading to metabolic acidosis, respiratory distress, and cardiovascular collapse. As children approach adolescence, drug metabolism is generally the same as in adults.

Elimination

The two primary sites of drug excretion and elimination are the kidneys and liver. They rely on active and passive transport processes to clear drugs. However, the impact of age on many of these transporters remains unclear. Any underlying congenital or acquired hepatic or nephrotic disease will certainly impair drug clearance and drug interactions. In the neonate and infant, there is decreased renal blood flow and glomerular filtration for the first 6 months of life; tubular secretion is decreased for the first year. This pathophysiologic difference may impact renally eliminated drugs. An important example is gentamicin, where it has been demonstrated that using dosing regimens designed for older children and adults has resulted in significant toxicity.

OTHER CONSIDERATIONS

Drug Therapy in the Neonate

As previously mentioned, neonates are the subgroup of pediatric patients that differ the most with regard to physiology and drug pharmacokinetics; however, there is also the greatest paucity of pharmacologic data on this population. Emergency clinicians caring for neonates should consult drug references for specific prescribing information because dosing recommendations, administration, and

TABLE 171.1 Common Emergency Department Medications With Pediatric-Specific Toxicities

Medication	Pediatric-Specific Toxicity
Codeine	Ultrarapid CYP2D6 metabolism implicated in deaths in post-tonsillectomy patients and from breast milk excretion in infants. Not recommended for use in pediatrics
Antipyretics	Dosing errors led to 2011 US Food and Drug Administration (FDA) guidelines to reduce confusing labeling and package directions, elimination of infant formulation of acetaminophen
Aspirin	Reye syndrome associated with use during viral illness
Cough and cold medicines	FDA and Joint Advisory Panel warning for children <2 yr; expanded to 2–4 yr
Phenothiazines	Apnea risk (severe respiratory depression at wide range of doses)
Ceftriaxone	Calcium precipitation in patients <28 days, kernicterus
Doxycycline	Tooth discoloration
Trimethoprim-sulfamethoxazole	Bilirubin displacement may result in kernicterus in patients <2 mo

BOX 171.1 Maturation of Functioning Enzymes in the Pediatric Patient in Phase 1 and 2 Drug Metabolism

Phase 1 Drug Metabolism
- Birth: Cytochrome P450 (CYP)2D6 and CYP2C9
- 1 year: CYP3A4
- 10 years: CYP1A2

Phase 2 Drug Metabolism
- Birth: Glutathione S-transferase alpha 1 (GSTA1)
- 3–6 months: UDP glucuronosyltransferase family 1 member A1 (UGT1A1)
- 18 months: Glutathione s-transferases (GST)

contraindications differ in this age group. Early consultation with a neonatologist may be warranted, depending on the clinical scenario.

Neonates can also be exposed to and experience subsequent toxicity from pharmaceuticals via lactation. For example, the postpartum use of codeine in lactating mothers has been associated with toxicity in the newborn. This phenomenon has been linked to maternal CYP2D6 polymorphisms, which result in ultrarapid metabolism of codeine to morphine. High concentrations of morphine are excreted in the breast milk, which can cause toxicity in the infant. Although many medications are safely administered during breast-feeding, this underscores the importance of obtaining a complete maternal medication history when evaluating a breast-fed infant, as well as consulting a lactation reference when prescribing medications to nursing mothers. This can be difficult because there are limited human data regarding medication use in pregnancy, and multiple factors need to be considered, including maternal comorbidities, therapeutic alternatives, and preferences for continued breast-feeding. The National Library of Medicine maintains a Drugs and Lactation Database (LactMed) summarizing available evidence on medications and illicit drugs and their impact on the breast-feeding infant.[11]

Use of Antipyretics in Children

Fever is one of the most common presenting complaints for pediatric ED and urgent care visits.[12] An important distinction exists between fever, a controlled physiologic increase in body temperature that occurs when the hypothalamic temperature set point is increased in response to pyrogens, and hyperthermia, a pathophysiologic increase in body temperature that occurs when physiologic thermoregulatory mechanisms fail. Unlike fever, hyperthermia has the potential to cause serious harm and can be fatal; thus, hyperthermic children should be rapidly cooled and the underlying cause of their hyperthermia addressed. Antipyretics are not generally useful in managing hyperthermia, because antipyretics do not mechanistically address the underlying thermoregulatory dysfunction.

In contrast to hyperthermia, there is no evidence that fever is dangerous or detrimental to children. Fever as a response to infection has been conserved across vertebrates for hundreds of millions of years, and a growing body of evidence suggests that fever confers a survival benefit to hosts fighting an infection.[13] Even so, a recent survey study of parents found that most felt fever conferred no benefit to their child and that there were risks associated with being febrile.[14] This so-called "fever phobia" often leads to unnecessary administration of antipyretics which, unlike the fever itself, does confer some risk. Aside from the known adverse effects associated with antipyretics and with nonsteroidal antiinflammatory drugs in particular, therapeutic errors and accidental exploratory ingestions of antipyretics in children are relatively common.[15] Even when administered in a health care setting, antipyretic use in children can have unintended consequences; one study found that children with a temperature between 38°C and 39°C with otherwise normal vital signs who were given an antipyretic in the emergency department had a significantly longer length of stay compared to those who did not receive an antipyretic.[16]

Given the risks associated with antipyretic use and the lack of risk associated with fever, current recommendations focus on maintaining patient comfort and not on normalizing temperature. Even in patients who are critically ill with sepsis—to whom an antipyretic is often given because of a concern for the increased metabolic demands associated with being febrile—antipyretic administration was not associated with a decreased ICU length of stay in a randomized, placebo-controlled trial in adults; the same was true in a small pilot randomized, placebo-controlled trial in children.[17,18] As such, the primary goal of antipyretic administration should be to improve the patient's comfort. When emergency clinicians do prescribe an antipyretic in the ED, they should counsel parents regarding the safe and appropriate use of these medications on discharge. Ibuprofen should be avoided in infants younger than 6 months because of pharmacokinetic differences and ongoing renal development in this age group. Combined regimens or alternating therapy with acetaminophen and ibuprofen may be slightly more effective in alleviating discomfort and lowering body temperature; however, this approach is also more complicated and may predispose to medication errors, with small clinical benefit.[19] Table 171.2 presents manufacturer-recommended dosing for commonly used antipyretics and analgesics; Box 171.2 provides counseling points for parents regarding fever and antipyretic use.

Over-the-Counter Cough and Cold Medications

Cough and cold symptoms are complaints commonly encountered in pediatric ED patients, and over-the-counter (OTC) cough and cold medications containing various combinations of antitussives, antihistamines, decongestants, expectorants, and antipyretics have been widely used in children for decades. In 2007, a series of initiatives was launched to curb the use of these medications in young children due to a lack of efficacy data and mounting safety concerns.

TABLE 171.2 Common Antipyretics and Analgesics

Agent	Indication	Dose	Maximum
Acetaminophen	Analgesic, antipyretic	10–15 mg/kg PO, PR, q4–6h	75 mg/kg/day, never to exceed 3 g
Ibuprofen	Analgesic, antiinflammatory, antipyretic	10 mg/kg PO, q6–8h	40 mg/kg/day, never to exceed 3200 mg; not recommended for children <6 mo
Fentanyl	Analgesic	1 to 3 μg/kg IV, IO, IM, IN, SC	N/A
Morphine	Analgesic	0.1 mg/kg IV, IO, IM, SC	N/A

IM, Intramuscular; *IO,* intraosseous; *IV,* intravenous; *PO,* orally; *PR,* per rectum; *SC,* subcutaneous; *IN,* intranasal.

BOX 171.2 Counseling Tips for Parents and Caregivers for Safe Antipyretic Use

- Fever is a clinical sign that the body may be fighting infection and children should be monitored for signs of serious illness.
- Be sure the child maintains adequate hydration during febrile illness.
- Antipyretics should be given to minimize discomfort; if the child appears comfortable, he or she does not need an antipyretic.
- The use of combination products and alternating use of antipyretics can lead to dosing errors and therapeutic duplication.
- Do not use ibuprofen in children younger than 6 months.
- Do not use aspirin in children younger than 15 years due to the risk of Reye syndrome.
- Counsel caregivers and parents regarding appropriate weight-based dosing for the child.
- Recommend use of a calibrated measuring device to avoid dosing errors, showing milliliters ONLY.
- Store all medications, both OTC and prescription, out of the reach of children.

In October of that year, a joint panel meeting of the US Food and Drug Administration's (FDA) Nonprescription Drugs and Pediatric Advisory Committees voted to advise against the use of OTC cough and cold medications in children younger than 6 years. Later that month, the Consumer Healthcare Products Association (CHPA) issued a position statement and voluntarily withdrew OTC cough and cold products marketed for use in children younger than 2 years. In January 2008, the FDA formally recommended against the use of OTC cough and cold medicines in children younger than 2 years. The CHPA subsequently issued additional warnings against the use of these medications by children younger than 4 years. Currently, the American Academy of Pediatrics (AAP) advises against the use of OTC cough and cold medications in children younger than 6 years, and the FDA continues to review available data in consideration of changing the labeling for OTC cough and cold medications for all children aged 2 to 6 years.

Since these initial labeling changes were instituted, some studies have suggested that the use of OTC cough and cold medication in children under 6 years of age is declining. For example, one study found a significant decrease in the proportion of children under 2 years of age with bronchiolitis who had been given an OTC cough or cold medication in the week prior to their ED visit in 2007 to 2010 compared to 2004 to 2006.[20] Another study found that the national estimated number of ED visits for unsupervised exposures to cough and cold medications in children under 6 years of age decreased from 2010 to 2013 after having increased from 2004 to 2010.[21] There has also been a decrease in clinician recommendations for cough and cold medication use in children, though recommendations for use of antihistamines for cough and cold symptoms have increased.[22]

Despite this progress, numerous recent reports have documented that children under 4 years of age now consistently make up the largest proportion of children who suffer adverse events related to OTC cough and cold medication exposures in the years since the aforementioned labeling changes were introduced, despite the fact that the new labels state "do not use" in children under 4 years of age.[23-26] Emergency clinicians should be cognizant of current recommendations to avoid these medications in young children and educate parents regarding the dangers of OTC cough and cold medications; prescription cough and cold alternatives have similar safety and efficacy concerns. The most recent CHEST guidelines on this topic specifically recommend against the use of OTC cough and cold products for both children and adults with cough associated with the common cold.[27] Parents should also be counseled regarding alternative therapies, such as nasal suctioning and honey in children older than 1 year. Table 171.3 presents manufacturer-recommended dosing for commonly used medications in pediatric respiratory emergencies.

Opioid Analgesics

Opioid analgesics can be used safely and effectively in children for the management of moderate to severe pain in the ED and should not be withheld when indicated. However, the evolution of the opioid epidemic of the last 30 years has thrown into sharp relief the risks that opioid use—including therapeutic opioid use—can carry. Numerous studies have documented the large number of ED visits and hospital admissions for opioid-related adverse events in children over the past two decades, particularly in adolescents and in young children under 5 years of age.[28-31] In one study, there was no apparent deviation from the prescribed regimen in 71% of children presenting with an opioid-related adverse event.[30] Only in the last few years has the incidence of pediatric opioid exposures begun to fall; this decrease has mirrored the decrease in opioid prescriptions written for pediatric patients and likely reflects more conscientious opioid prescribing.[30-35]Among adolescents, risk factors that have been identified for development of adverse events related to opioid exposure include having a prescription for more than 30 days, concurrent benzodiazepine use, having a prescription for an extended-release or long-acting opioid, and having a preexisting mental health condition.[36,37] Several studies have also demonstrated that medical use of opioids during adolescence is associated with increased rates of opioid misuse later in life.[38,39] Opioid misuse during adolescence itself is not rare; one study found the prevalence of opioid misuse among high school seniors to consistently be between 10% and 15% from 2002 to 2013, and only recently has it begun to fall.[32] Another prospective study has further demonstrated that adolescents who nonmedically use opioids have higher odds of developing a formal substance use disorder at age 35.[39]

Certain opioids have additionally been described as having specific risks beyond the risks associated with opioid use in general. Codeine toxicity in those who are CYP2D6 ultrarapid metabolizers is a classic example. Codeine's analgesic effects are primarily due to its conversion

TABLE 171.3 Common Pediatric Emergent Respiratory Medications

AGENT	INDICATION	DOSE	MAXIMUM
Albuterol	Asthma	0.15 mg/kg (minimum dose 2.5 mg) INH 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg INH q1–4h PRN	Continuous dosing: • ≤10 kg: 7.5 mg/hr • 10–20 kg: 11.25 mg/hr • ≥20 kg: 15 mg/hr
Dexamethasone	Croup, Asthma	0.15–0.6 mg/kg PO, IV, IM	16 mg/dose
Diphenhydramine	Allergy, Urticaria	1–2 mg/kg PO, IV, IM	50 mg/dose
IM Epinephrine (1 mg/ml concentration)	Anaphylaxis	0.01 mg/kg IM	0.5 mg
Ipratropium	Asthma	250 μg INH if <20kg 500 μg INH if >20 kg	N/A
Magnesium	Severe asthma	50 mg/kg IV over 20 min	2 grams
Methylprednisolone	Asthma	1 to 2 mg/kg IV	80 mg/day
Prednisolone	Asthma	2 mg/kg PO	60 mg/dose
Racemic epinephrine	Croup	0.25–0.5 mL of 2.25% solution; as needed up to q30 min	N/A
Terbutaline	Severe asthma	0.01 mg/kg SC	0.4 mg/dose

IM, Intramuscular; *INH,* isoniazid; *IV,* intravenous; *PO,* orally; *SC,* subcutaneous.

to morphine by CYP2D6; ultrarapid metabolizers can therefore produce relatively large quantities of morphine in a short period of time and thus are at risk for toxicity. Toxicity, including death, has been documented in children who received codeine after a tonsillectomy or adenoidectomy for postoperative pain management; a black box warning was issued in 2013 for the use of codeine for postoperative pain in children who have undergone tonsillectomy or adenoidectomy.[40] In 2017, in response to these and other adverse events related to codeine exposure, the FDA formally stated that codeine was contraindicated for treatment of any pain or cough in children under 12 years of age, and added a new warning to codeine labels recommending against its use in children 12 to 18 years of age who are obese, have obstructive sleep apnea or have severe lung disease.[41] In 2018, the FDA went on to require that labels on prescription cough and cold medications containing codeine state that these products are contraindicated in children under 18 years of age. The FDA's mandate contraindicating the use of codeine-containing prescription cough and cold medications in children under 18 years of age was also extended to hydrocodone-containing products.[42] Hydrocodone, one of codeine's minor metabolites, was found in a recent study of pediatric adverse events related to exposures to hydrocodone- and codeine-containing cough and cold medications to be associated with a higher frequency of both fatal and nonfatal adverse events than codeine alone.[43]

Tramadol also deserves a special mention, because it has become increasingly implicated as one of the opioids associated with the highest risk of opioid toxicity among adolescents.[36,44] Tramadol is a prodrug like codeine and is similarly contraindicated for the treatment of pain in children under 12 years of age and for the treatment of postoperative pain in children under 18 years of age who have undergone tonsillectomy or adenoidectomy. It also carries the same warning as codeine recommending against its use in children 12 to 18 years of age who are obese, have obstructive sleep apnea or have severe lung disease. Both tramadol and codeine should be avoided in mothers who are breast-feeding because of the risk of serious adverse events, including death, in their breastfed infants.[41] Tramadol is additionally noteworthy for its well-described association with seizures in overdose.[45]

Unlike in adults, there is a paucity of guidelines for opioid use in the pediatric population. It is important for emergency clinicians to balance adequate analgesia with the risks associated with the use of prescription opioids. Use of nonpharmaceutical modalities and nonopioid alternatives (e.g., acetaminophen and nonsteroidal antiinflammatory drugs) should be used as primary therapy or as an adjunct to minimize the dose of opioids, including for conditions that historically were treated with opioids, such as fractures or acute pancreatitis. For example, a recent randomized, double blind, placebo-controlled trial of children 6 to 17 years old presenting to an ED with a musculoskeletal injury and a pain score of greater than 29 mm on a visual analog scale (VAS) found no difference in the proportion of children meeting the primary outcome of a VAS less than 30 mm, when comparing those who received morphine, morphine and ibuprofen, or ibuprofen alone. The only statistically significant difference found was in the mean reduction of VAS from baseline to 120 minutes after medication administration, which was significantly greater (a more reduced pain score) in children receiving ibuprofen alone compared to morphine alone.[46] There was also no significant difference in pain control among children treated with either morphine or ibuprofen for uncomplicated extremity fractures in an earlier randomized trial.

When an opioid is clearly indicated, clinicians should follow institution-based protocols, if available, for dosage and administration. Additional safeguards to mitigate risk of diversion and misuse include limiting prescriptions to the lowest effective dose for the shortest possible duration, and using the state prescription drug monitoring profile. Similarly, extended-release preparations should generally be avoided, as they are very rarely indicated for acutely painful conditions for which children present to emergency departments. While there are no national opioid prescribing guidelines for children, in 2016 the Centers for Disease Control and Prevention (CDC) published guidelines for opioid prescribing in adults, which state that clinicians "should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.… Three days or less will often be sufficient; more than seven days will rarely be needed."[47] Emergency physicians who supervise trainees should be aware that both the odds of receiving an opioid prescription at discharge and the odds of receiving an opioid prescription for a prolonged duration of time are greater if that prescription was written by an emergency medicine resident.[48-50] Similarly, the odds of receiving an outpatient opioid prescription were higher if the child was seen in a general emergency department compared to a pediatric emergency department.[51] In adolescent patients, it can be beneficial to use screening tools such as the CRAFFT to identify high-risk adolescents who may need closer follow-up[52] (Box 171.3).

BOX 171.3 CRAFFT for Substance Use Disorder[a]

C: Have you ever ridden in a **CAR** driven by someone (including yourself) who was high or had been using alcohol or drugs?
R: Do you ever use alcohol or drugs to **RELAX**, feel better about yourself, or fit in?
A: Do you ever use alcohol/drugs while you are by yourself, **ALONE**?
F: Do you ever **FORGET** things you did while using alcohol or drugs?
F: Do your family or **FRIENDS** ever tell you that you should cut down on your drinking or drug use?
T: Have you gotten into **TROUBLE** while you were using alcohol or drugs?

[a]http://crafft.org.

BOX 171.4 Best Practices for Prescribing Opioid Analgesics in the Emergency Department

- Assess if there is an indication for an opioid analgesic; nonopioid therapies and pharmaceuticals should be optimized and used as adjuncts, whenever possible.
- Perform a risk assessment for nonmedical use, particularly in adolescent patients.
- Consult state prescription drug monitoring programs and prior medical and pharmacy records whenever available.
- Short-acting opioids are preferred versus extended-release formulations.
- Use caution when combining opioid analgesics with other central nervous system depressants, such as benzodiazepines.
- Prescribe the lowest effective dose and limit duration of therapy to the shortest possible time.
- Provide instructions for the safe disposal of any unused medication.
- Arrange for close outpatient follow-up.
- Counsel parents and caregivers regarding signs of prescription drug abuse.

General recommendations for safe prescribing practices for opioid analgesics are presented in Box 171.4.

Medication Safety and Adverse Drug Events

Medication errors and adverse drug events are common among children cared for in an ED, with error rates in several studies reaching upwards of 30%.[2] This is in part due to characteristics inherent to emergency care, such as a lack of familiarity with individual patients who may be medically complex, and a chaotic environment where verbal orders may be used. Other factors also contribute to pediatric medication errors in all care settings. Because of legislative restrictions in pediatric drug research, many medications are used off label, with dosing based on experience and estimations rather than formal clinical trials. In one study, over 10% of ED visits included at least one off-label use of a medication for a child.[53] Even when a medication has pediatric data shown on the drug label, this information is often not clearly presented and may offer little guidance. For example, the age range for which a medication is formally approved is often not listed in the indications section of the labeling. Approved pediatric-specific dosing information, when available, is listed in another section of the label. To further complicate matters, labels very rarely have dosing listed for obese children; in one study, only 8% of acute care drugs had dosing information for obese children on the label, despite the fact that nearly 1 in 5 children in the United States is obese.[54,55]

The lack of pediatric-specific formulations is also a contributor to adverse drug events and poor patient adherence. Because pediatric formulations are not available for many medications, parents and clinicians may have to split fixed-dose adult tablets, or liquid formulations may need to be extemporaneously compounded, which introduces the potential for compounding and concentration errors. In addition, the poor palatability of adult formulations can lead to noncompliance; oral solutions, suspensions, and rapidly disintegrating and chewable tablets are often preferred. Parents should be counseled regarding proper measurement and administration of prescribed medications, and a dosing syringe using milliliter units should be provided. Payer formulary alerts can direct prescribers to choose an inappropriate alternative if the intended prescription is not covered by the patient's insurance. In one study at a single institution, 27% of payer formulary alerts were found to be inappropriate, and there were 24 specific instances of prescribing errors that were ultimately attributed to these alerts.[56]

Several other factors also contribute to adverse drug events in children. Weight-based dosing and calculations required for children introduce additional error-prone steps, particularly with emergent medications. In a randomized simulation study of residents in an emergency department, the use of a reference book that provided precalculated medication doses (as opposed to a card listing milligram per kilogram dosing) was found to significantly decrease the rates of ten-fold dosing errors, as well as dosing errors for medications administered via continuous infusions.[57] Another common error is calculating weight-based dosing using a patient's weight in pounds instead of kilograms. Despite the fact that numerous professional societies—including the American College of Emergency Physicians and the American Academy of Pediatrics—recommend obtaining scales that exclusively display weights in kilograms, multiple studies have demonstrated inconsistent adoption of this recommendation.[58,59] Medication reconciliation in pediatric patients is also often inaccurate, which can contribute to suboptimal therapy and adverse drug events. Parents and caregivers should be specifically asked about all prescription medications, OTC medications, homeopathic preparations, and dietary supplements. Details regarding dosage and schedule should also be obtained.

Ongoing attempts to mitigate these risks include the use of clinical pharmacists in the ED, separation of pediatric and adult care locations, and increased use of human factors and information technology solutions. In one study, after instituting 24-hour pharmacist coverage of an emergency department, 17% of pharmacist-reviewed orders were found to lead to a clinical intervention that otherwise may not have occurred.[60] The advent of hand-held wireless technology and gradual adoption of inpatient electronic health record (EHR) systems have generated many new reference options for pediatric pharmacology. Decision support tools in the EHR system, such as computerized physician order entry, have repeatedly been shown to decrease adverse events, in part because many are related to simple weight-based calculation errors.[2] At the same time, EHRs can also precipitate errors when clinicians "copy and paste" without critically evaluating data. The ultimate responsibility for medication dosing rests with the ordering clinician, dispensing pharmacist, and administering nurse. Simulation training for nurses has also been shown to decrease medication administration errors; a single 2-hour training in one study decreased the rate of serious medication administration errors from 2.5 events per month to 0.86 events per month.[61] Table 171.4 presents a selection of different types of decision support tools that can serve as a reference to emergency clinicians.

In recent years, prescription drug shortages have emerged as a threat to public health. According to the American Society of Health Systems Pharmacists, there were over 200 current drug shortages in the United States as of the end of 2019.[62] Drug shortages can lead to delayed treatment or no treatment even when treatment is indicated.

TABLE 171.4 Selected Pediatric Drug References[a]

Reference	Description	Examples
App store	Apps with calculators for common pediatric dosing; dosing recommendations provided for reference only	PediStat, palmPEDi, EMRA Pediatric Airway, PediCalc
Web-based	Web-based clinical information suites with medication dosing and company-provided evidence-based recommendations	Micromedex, Epocrates
EHR-based	Decision support tools and institutional guidelines incorporated into CPOE	Cerner, Epic, Allscripts
Reference text	Classic bedside reference texts for decision support and dosing information	Redbook, Harriet Lane, Tarascon, Broselow Tape

[a]This list is not all inclusive, nor does it carry a formal endorsement.

Sometimes, alternative medications are substituted that may be more toxic or less effective, and medication errors can occur when clinicians are forced to use less familiar therapeutic alternatives.[63] The reasons for the rising rates of prescription drug shortages are multifactorial, and it is anticipated that shortages will continue as a problem in the foreseeable future, despite mitigation efforts. Emergency clinicians should be cognizant of current drug shortages that may affect their practice and work to design protocols for the ethical distribution of available supplies of medications in short supply, as well as for safer use of therapeutic alternatives.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 171: QUESTIONS AND ANSWERS

1. A 12-year-old girl is being discharged from the emergency department (ED) after having her displaced forearm fracture reduced. Which one of the following actions would be considered potentially dangerous?
   a. Prescribe codeine.
   b. Consult state prescription drug monitoring programs (PDMP) and prior medical and pharmacy records.
   c. Use a screening tool, such as CRAFFT, to evaluate for high-risk behaviors.
   d. Prescribe a minimum number of days to decrease risk for misuse and diversion.

Answer: A. Codeine is no longer recommended for pain in pediatric patients. This is due to the variation in pharmacogenomics (CYP 2D6) and metabolism to morphine, which can lead to either poor pain control or unintentional opioid toxicity. In adolescent patients, it is recommended that the patient be evaluated for high-risk factors that may lead to opioid use, misuse or diversion. This includes checking the state's PDMP and screening to evaluate the risk for drug abuse and addiction. There are currently no pediatric-specific guidelines for prescribing opioids, but it is generally recommended not to prescribe opioids for acute pain more than 3 to 7 days in duration. Providers should also emphasize a nonopioid, multimodal approach to pain control, including nonpharmacologic methods and adjunct medications such as nonsteroidal antiinflammatory drugs, acetaminophen, or neuroactive agents.

2. What is a unique pharmacokinetic property observed in the pediatric population?
   a. Infants have decreased absorption of topically applied medications.
   b. Neonates and infants have higher total body water and larger volumes of distribution and extracellular fluid.
   c. All drug metabolizing enzymes are at full capacity at birth.
   d. All maternal drugs should be considered not safe when breast feeding.

Answer: B. Young children can have significant differences in the pharmacokinetic properties based on their physiology. Absorption can be impaired and delayed based on gut pH and motility. Metabolizing enzymes mature at different rates during the first year of life. Young children have a higher total body water and larger volumes of distribution and extracellular fluid. There are several factors to consider when assessing the risk/benefit profile of taking medications while breast-feeding, including limited human data, maternal comorbidities, therapeutic alternatives, properties of the drug, and the benefits of continued breast-feeding, when possible. LactMed is an excellent resource to determine the safety of the drug during breast-feeding.

3. A healthy, fully vaccinated 11-month-old male infant presents to your department for evaluation of a fever of 38.4°C (101.1°F) this morning that responded to a dose of acetaminophen. The physical examination reveals a well-appearing, afebrile infant with clear lungs. The patient has an unremarkable evaluation and, during the discharge process, his parents ask for advice regarding fever management. Which of the following statements is correct?
   a. Aspirin should not be used in children younger than 15 years because of the risk of Reye syndrome.
   b. Cool water baths and creams should be used to supplement antipyretics, even if they cause some discomfort to the patient.
   c. Ibuprofen cannot be used in this age group because of ongoing renal development.
   d. Over-the-counter (OTC) antipyretics are standardized, contain similar products and formulations, and are thus interchangeable.

Answer: A. Counsel parents and caregivers about the management of fever and appropriate indications for and proper use of antipyretics. There is no need to cause discomfort with external cooling methods for fever control. Ibuprofen should not be used in children younger than 6 months because of ongoing renal development. The formulations and dosing of OTC antipyretics are varied and cannot be used interchangeably. The correct answer is A because of the risk of Reye syndrome with

CHAPTER 171: QUESTIONS AND ANSWERS—cont'd.

aspirin administration during a viral illness in children younger than 15 years.

4. Which of the following statements regarding pediatric pharmacokinetics is correct?
   - **a.** A thinner stratum corneum and increased body surface area contribute to a greater risk for systemic toxicity from dermally administered drugs.
   - **b.** Ceftriaxone administration in neonates results in increased bilirubin production.
   - **c.** Because of minimal differences in the volume of distribution and renal development, weight-based dosing of gentamicin without attention to age is sufficient.
   - **d.** Quicker gastric emptying and decreased gastric pH in neonates increase systemic absorption of enterally administered medications.

Answer: A. Awareness of differences in pediatric pharmacokinetics and specific drug toxicities is of critical significance for the safe and effective use of medications in children. The dosing of gentamicin needs to account for age-based differences in renal development in addition to weight-based differences in distribution volume. Decreased gastric emptying times and an increased pH can prolong exposure to medications before they pass the pylorus. An immature blood-brain barrier can result in kernicterus from bilirubin displacement by ceftriaxone. The correct answer is that a thinner stratum corneum and increased body surface area contribute to a greater risk for systemic toxicity from dermally administered drugs.

5. Which of the following steps can be taken to reduce pediatric dosing errors?
   - **A.** Adoption of electronic health records with clinical support tools to decrease weight-based dosing errors
   - **B.** Calculation of weight-based dosing for all emergent medications administered in code situations as opposed to using a validated quick reference guide
   - **C.** Limiting hospital pharmacist presence in the emergency department to avoid delays in bedside care
   - **D.** Medication reconciliation should occur with just the patient present to limit primary caregiver influence

Answer: A. A multifaceted approach using clinical support systems and readily available reference tools are essential for the delivery of optimal emergent pediatric care. Caregivers are an integral part of medication reconciliation. ED pharmacists have been proven to increase departmental accuracy in pediatric medication management. Validated quick reference guides for code drug administration have been shown to decrease errors and improve efficiency.

Child Abuse

Daniel Lindberg

PHYSICAL ABUSE

KEY CONCEPTS

- The ultimate determination of whether abuse has occurred can take days or weeks. Emergency clinicians should focus on recognizing possible abuse, treating medical injuries, and establishing a safe disposition for the child.
- Completely undress infants and preverbal children for the physical examination; pay particular attention to the skin, ears, mouth and oral cavity, scalp, fontanel, and genitalia.
- Consider abuse routinely for sentinel injuries in young children without an independently witnessed traumatic mechanism. Sentinel injuries include the following: bruising in children younger than 6 months old; bruising on the torso, ears, neck, jaw, cheek, or eyelid; oral injuries; patterned cutaneous injuries; subdural hematoma; long-bone fractures in infants; intra-abdominal injuries; and rib fractures.
- Consider abuse for children when family violence (child abuse, intimate partner violence, elder abuse, or animal abuse) is recognized in the child's home.
- The goal of diagnostic testing is to identify additional clinically or forensically significant injuries or medical entities that may present similarly to abuse.
- Use objective, nonaccusatory, matter-of-fact statements to communicate concern for abuse.
- Emergency clinicians in the United States, Canada, and many other countries are legally mandated to report reasonable concerns for abuse to public child protective services (CPS) agencies.

FOUNDATIONS

Child physical abuse is a leading cause of death and disability for young children. In the United States (US), more than 120,000 children are victims of physical abuse leading to more than 550 preventable deaths each year.[1] This means that large pediatric centers will see several cases of physical abuse each month, while smaller, general emergency departments (EDs) may go several months without a single case.[2] Physical abuse is also commonly missed—approximately 30% of abusive head trauma and 20% of abusive fractures are missed on initial presentation.[3] Physical abuse is especially difficult to identify, because it predominantly affects preverbal children, particularly those younger than 6 months old.[1,4] Caregivers frequently omit or obscure the true history, and key portions of the physical examination (e.g., neurologic and musculoskeletal examinations) are limited. Early recognition of abuse therefore often depends on identifying subtle, minor, or self-limited injuries.[5-7] With these challenges, current practices are highly variable, and children are frequently returned to abusive environments.[2,8]

Overcoming these challenges is essential for abused children and their families. Because violence is a disease that affects entire households, recognition of abuse is important not only for the children themselves, but also for their siblings, parents, elders, and even pets.[9-13] For abuse survivors and those who share a violent household, the long-term health effects of toxic stress are severe, diverse, and widespread.

Role of the Emergency Clinician

It is rarely possible and almost never necessary to definitively diagnose abuse in the ED. Care of abused children involves the cooperation of medical, social, and law-enforcement agencies over weeks and months. Emergency clinicians are responsible for raising the initial concern for abuse and working with other professionals (e.g., general and child abuse pediatricians, CPS) to stratify risk, ensure safety, and arrange for ongoing care.

Most injuries in childhood are not the result of abuse, and unusual events may produce unusual or unusually severe injuries.[14] Inevitably, some children who are evaluated for abuse will ultimately be determined to have an innocent explanation for their injuries. To facilitate the evaluation and preserve the doctor-patient relationship, emergency clinicians should use nonaccusatory statements to explain the need for testing (Box 172.1). A routine, standardized approach to testing and reporting can improve abuse recognition and decrease racial and social disparities.[15-17]

CLINICAL FEATURES

The clinical features of physical abuse are listed in Box 172.2.

Social and Demographic Risk Factors

Understanding psychosocial and demographic risks is most important for primary prevention efforts.[18,19] Despite increased data, these factors are relatively insensitive and nonspecific and should not be used to confirm or exclude abuse. Serious physical abuse has been reported in every socioeconomic setting, and even in households with several risk factors, the vast majority of caregivers do not physically abuse their children. Nevertheless, poor or African American families remain disproportionately likely to be evaluated and reported for abuse, while abuse is more likely to be missed in White or affluent families.[20]

Physical abuse is more likely to occur with male caregivers, especially with new caregiving arrangements, or when the caregiver is an unrelated boyfriend.[21] Prior involvement with CPS, intimate partner violence, substance use, mental illness, poverty, and criminal history have been associated with increased risk for abuse, as has the use of negative descriptors of children.[22-25]

History

Abuse is challenging to recognize when a child presents with nonspecific symptoms and without a recognized traumatic injury. Fractures,

BOX 172.1 Communication Strategies

When Interviewing a Child About Abuse

- Open-ended, non-leading questions: "Tell me more about that.", "How did your body feel?", "Then what happened?"
- "What happens at your house when kids (or pets) get in trouble?"
- Frequently explain and ask permission: "I am going to ask you some questions about your health to make sure I provide the safest treatment. Is that ok? I'm going to examine your body to make sure you are healthy. Is that ok?"

To Introduce the Genital Examination for Young Children

- "I'm also going to examine your whole body to make sure that you are healthy. I'm going to look at your nose, your ears, your belly-button, and even under your undies."
- "This examination is ok because I'm a doctor, because your mother is here, and because your mother says it's ok."

After the Examination

- "Your body looks completely healthy and normal. This does not make me doubt what you told me. It does mean that no one, not your spouse, your friends, or even a doctor like me will know what happened by looking at you." Or, "Your body has some signs of injury, but these will heal very quickly, and in a few days, you will be completely back to normal. No one, not even…"
- "Despite what many people believe, doctors usually can't tell whether someone has had sex by looking at their body. In fact, in one study of teens that were pregnant, almost 90% had completely normal examinations."
- "In my opinion, someone stops being a virgin when they *choose* to have sex."

Nonaccusatory Statements of Abuse Concern

- "The injuries we've identified are more than we would expect from the event you've described."
- "Whenever we see injuries like this, we test for other injuries and medical conditions to be sure we're not missing something that could affect your child's health."
- "I want to make sure that your child is safe/that no one is hurting your child."
- "Have you ever been concerned that someone might have been rough with or might have injured your child?"

BOX 172.2 Red Flags for Physical Abuse

Psychosocial Factors (Nonspecific, Do Not Use to Exclude Abuse)

- Unrelated caregiver (especially boyfriend) or new caregiver relationship
- Family violence
- Mental health disorders
- Substance use disorders
- Describing the child negatively

Historical Factors

- Significant injuries with no or minor trauma
- Significant inconsistencies in history
- Unexplained delay in seeking care
- Significant injury attributed to pets or young children

Physical Examination Factors

- Bruising, frenulum or conjunctival injury in children <6 months old, or who are not "cruising"
- Bruising on the torso, ear, neck, angle of the jaw, cheek, or eyelid
- Patterned bruising or burns
- Immersion or cigarette burns

TABLE 172.1 The Pittsburgh Infant Brain Injury Score (PIBIS)

Applies to	• Age 30–364 days • Well-appearing • Afebrile (T <38.3°C) • No history of trauma
Who present with	• ALTE/BRUE/apnea • Vomiting without diarrhea • Seizures or seizure-like activity • Bruises/scalp swelling • Nonspecific neurologic symptoms/lethargy/fussiness/poor feeding
Score	• Abnormal skin exam (2 points) • Age >3 months (1 point) • Head circumference >85th percentile (1 point) • Hemoglobin <11.2 g (1 point)

Total points: 5; neuroimaging is recommended for children with scores of 2 or more.

abdominal injuries, and mild brain injuries can have a smoldering course of mild symptoms, such as irritability, vomiting, or decreased appetite or activity.[6,26] In these cases, identifying abuse is difficult and usually involves prolonged symptoms, additional clues on physical examination, known social risk factors, or prior concern for abuse. The Pittsburgh Infant Brain Injury Score (PIBIS) can be used in these cases to determine the need for neuroimaging (Table 172.1).[6]

Although still nonspecific, certain complaints should prompt consideration of abuse. A small percentage of children presenting with a brief, resolved, unexplained event (BRUE; formerly known as apparent life-threatening event (ALTE)) will have retinal hemorrhages or other abusive injuries. Occult fracture should be considered in young or preverbal children who present with decreased use of an extremity, fussiness, and localized tenderness or refusal to bear weight.

Regardless of the injury, unreasonable delay in seeking care should prompt concern for abuse. No precise time period defines an "unreasonable" delay, and physicians should consider the child's symptoms and progression of disease. A delay of several hours is not uncommon for children with nonabusive fractures or abdominal injury. Conversely, even a brief delay can be concerning in children with obvious signs and symptoms such as seizures, coma, or substantial burns.

Serious injury without a history of trauma, or with a history of only mild trauma (e.g., caused by the child themselves, a young sibling, or a pet) should raise a high level of concern for abuse. Nontrivial intracranial hemorrhage is extremely uncommon from short falls (e.g., from a bed or a couch) and does not result from choking on formula or saliva.[27-29] Abdominal and thoracic injuries rarely result from household falls, even with increased height or falls down stairs.

Physical Examination

To identify subtle signs of abuse, infants (i.e., children <12 months old) should be completely undressed during physical examination. The fontanel, scalp, ears, oropharynx, skin, and genitalia should be specifically examined. A growth chart can identify sudden increase in head circumference (a sign of intracranial injury) or failure to thrive.

Although bruises are very common in ambulatory children, *any* bruising in a child less than 6 months old, or that is not yet able to ambulate with assistance or "cruise," is highly concerning for abuse.[7,30]

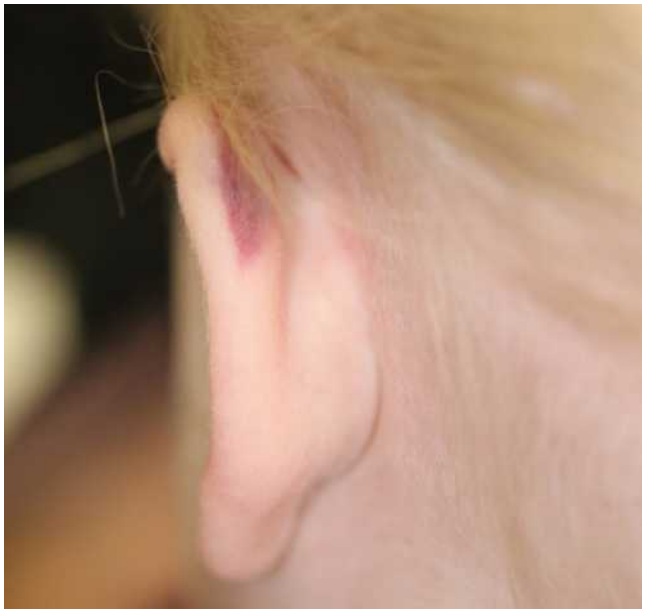


Fig. 172.1 Bruising to the helix of the ear is very concerning for abuse. (Courtesy John Melville, MD.)

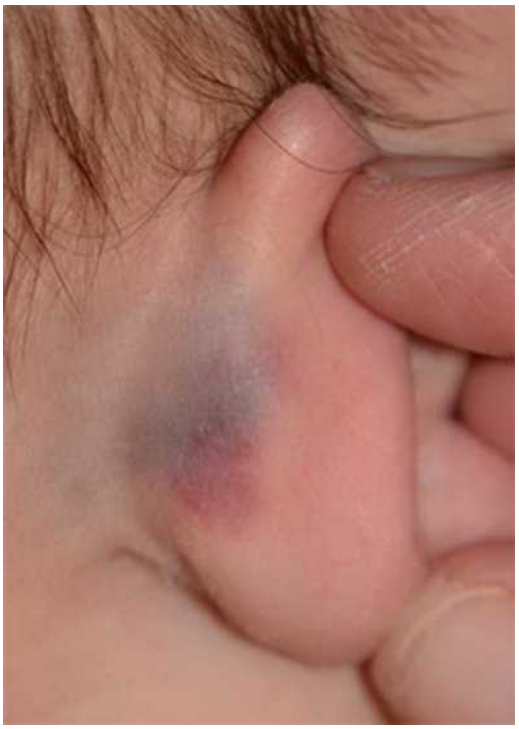


Fig. 172.2 Subtle bruising behind the child's ear can represent direct trauma or traction injury and should raise the level of concern for abuse. (Courtesy Daniel Lindberg, MD.)

Of children younger than 6 months old referred for an abuse evaluation with apparently isolated bruises, 50% had additional injury (fracture, brain injury, abdominal injury) identified.

Even in children old enough to cruise, bruises to the TEN-4-FACESp regions (*T*orso, *E*ar, *N*eck, *A*ngle of the jaw, *C*heek, or *E*yelid, or *F*renulum or *S*cleral injury, or injury that is *p*atterned in children younger than 4 years old) should raise concern for abuse (Figs. 172.1 to 172.3).[31] Common patterns include bruises in the shape of a cord, belt, or hand (Figs. 172.4 to 172.6). Human bite marks are patterned bruises

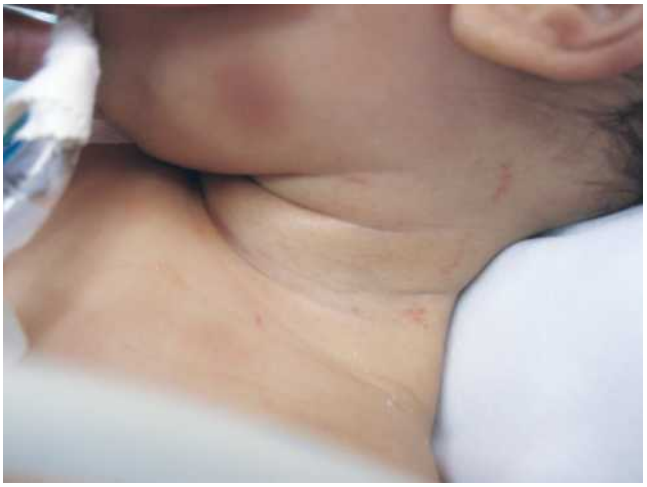


Fig. 172.3 Bruising to the neck and under the chin of an abused child. (Courtesy Carol Berkowitz, MD.)

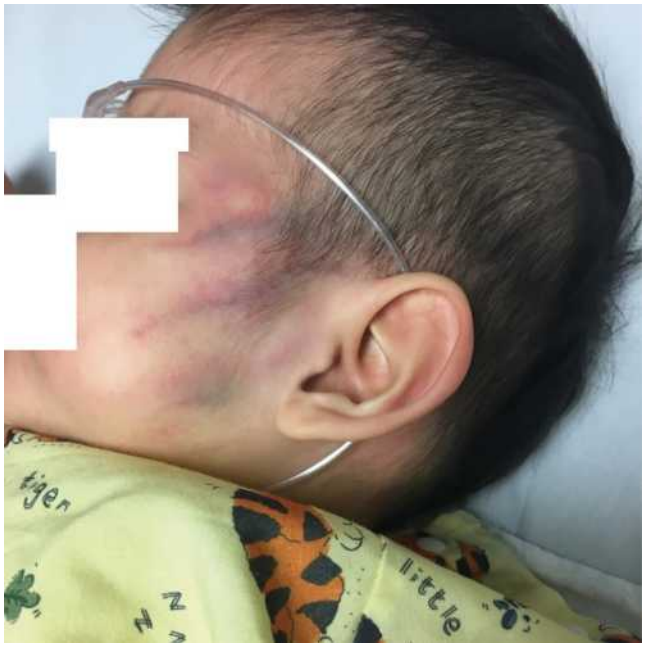


Fig. 172.4 Slap mark. The parallel, linear bruising results when capillaries rupture outward between fingers. (Courtesy John Melville, MD.)

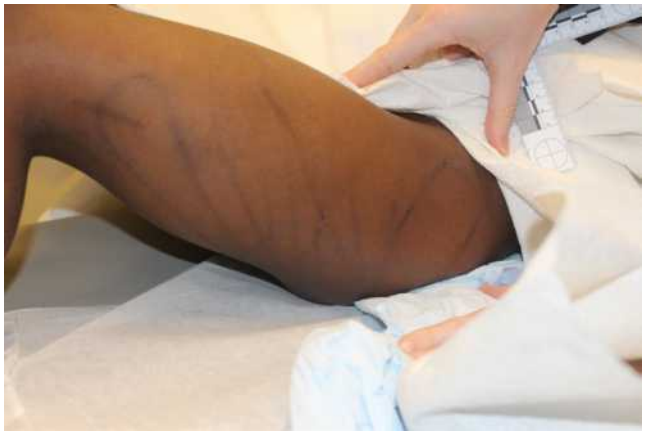


Fig. 172.5 Loop marks demonstrate contact injury from a looped cord. (Courtesy John Melville, MD.)

Fig. 172.6 Patterned bruising from a woven belt. (Courtesy Daniel Lindberg, MD.)

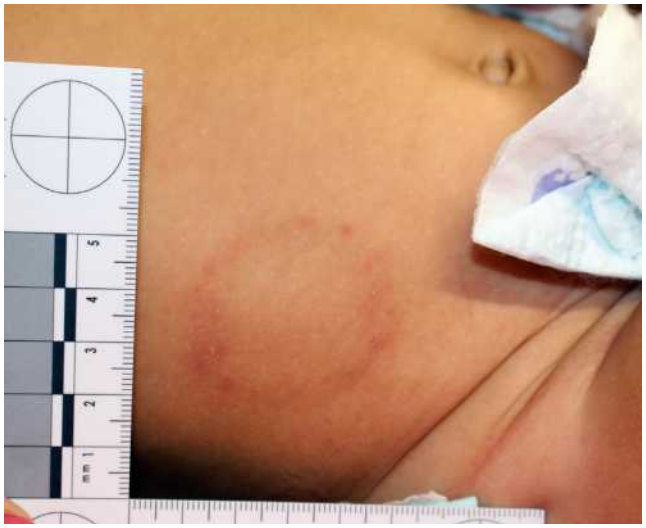


Fig. 172.7 Bite marks should be swabbed for DNA. (Courtesy John Melville, MD.)

in circular or paired semilunar rows (Fig. 172.7) and can be caused by adults or children. The ability of bite mark analysis to identify a biter is limited, so human bite marks should be swabbed to identify assailant DNA. Forensic evidence collection kits ("rape kits") used for sexual assault can be used to obtain, document, store, and transmit samples.

Abusive burns generally fall into three categories: immersion burns, contact burns, and cigarette burns. Immersion burns should be distinguished from pull-down scalds, which are very common in toddlers. Although pull-down scalds principally involve the upper body, immersion burns tend to involve the perineum or have a symmetric, stocking/glove distribution (Figs. 172.8 and 172.9). Abuse should also be considered when scalds affect a large body surface area, when sparing patterns suggest that the child was held in place, or when the incident is reported in the context of a toileting accident. For scald burns, CPS or law enforcement can measure the home's peak water temperature and the delay until peak temperature occurs. Although it takes several minutes to sustain a partial thickness burn from water at 120°F, the same burn can occur in seconds at 150°F.

As with bruises, emergency clinicians should consider abuse for young children with burns that take on the shape of an implement

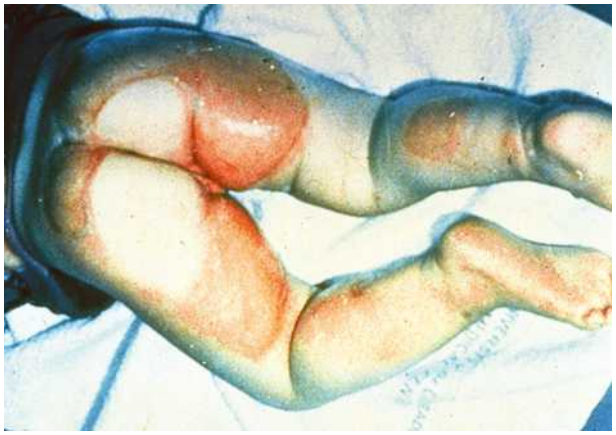


Fig. 172.8 Immersion burn. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

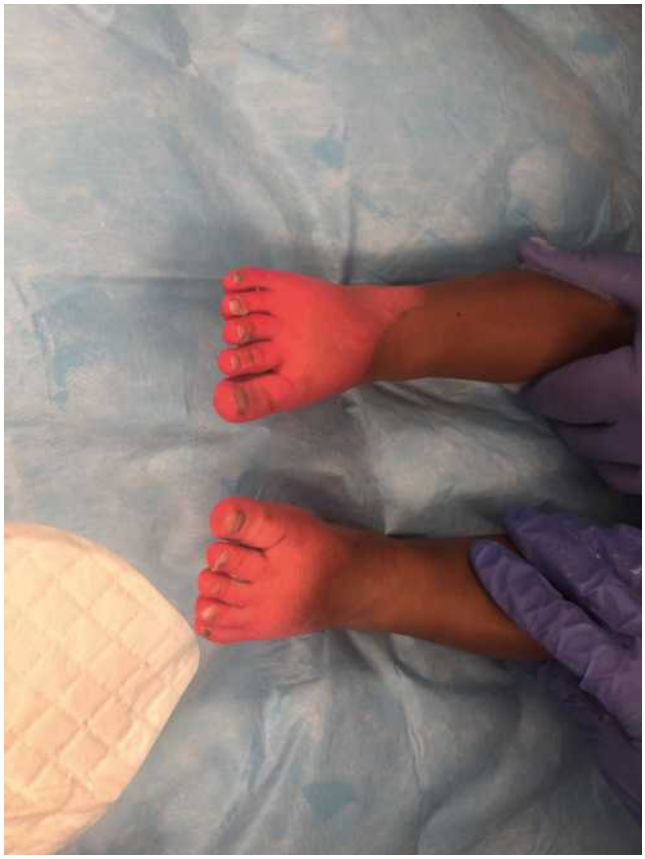


Fig. 172.9 Immersion burn of the feet after débridement. (Courtesy John Melville, MD)

(e.g., hair curler, grate, or lighter). Cigarettes can cause accidental or inflicted burns. Because the burning end of a cigarette can be more than 1000°F, inflicted burns are rarely superficial, and commonly result in crusted or ulcerated lesions between 8 to 10 mm (Figs. 172.10 and 172.11). Glancing or accidental contact with a cigarette can also cause superficial, linear burns.

Oropharyngeal injuries are also concerning in young children without a history of accidental trauma to the mouth or throat (Fig. 172.12). Tears of the lingual or labial frenula, or injuries to the lips, teeth, or soft palate should prompt an evaluation for abuse in children who are not yet walking and should increase concern, particularly when identified in evaluating children with other concerns of abuse.

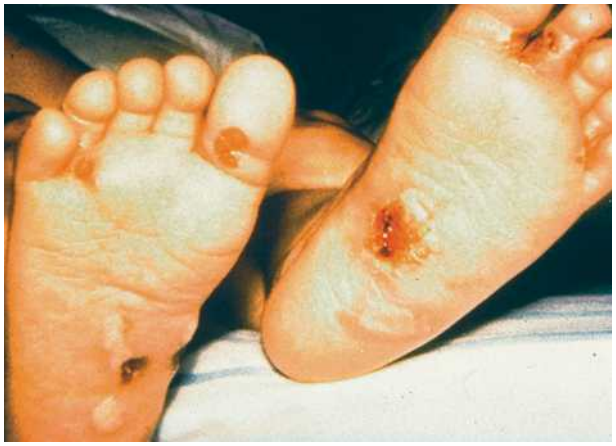


Fig. 172.10 Cigarette burns. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

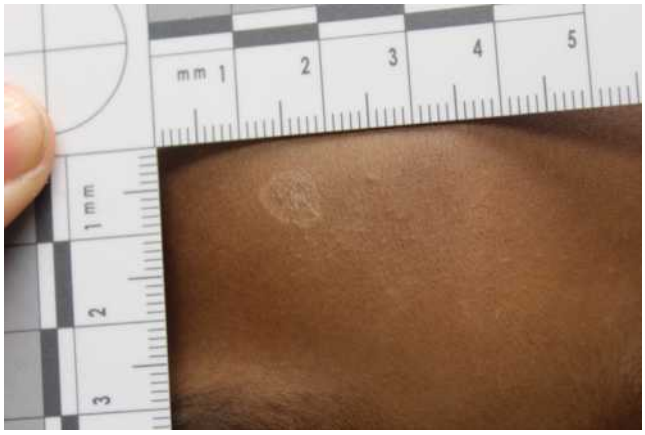


Fig. 172.11 Healing cigarette burn. (Courtesy of John Melville, MD)

Sentinel Injuries

For many children, the concern for abuse is first raised by the unexpected or incidental identification of a traumatic injury. Abuse should routinely be considered when young children present with these injuries unless there is an independently verifiable history of major trauma (e.g., a motor vehicle collision).

Serious traumatic brain injury should prompt a concern for abuse in children younger than 3 years old, where abuse is the source of approximately one-third to one-half of all injuries excluding traffic collisions.[32,33] Subdural hematomas, parenchymal injuries, and multifocal injuries are especially concerning for abuse, whereas epidural hematomas and isolated intraventricular hemorrhages are more likely to be nonabusive.[32,34,35]

Long-bone fractures are concerning in infants; abuse is diagnosed in 30% to 60% of infants with radius, ulna, tibia, fibula, femur, or humerus fractures. Rib fractures (Fig. 172.13) are even more concerning, with abuse identified in more than 25% of children up to 36 months old, and more than 67% of infants.[36,37] Less common, fractures to the hands, feet, spine, pelvis, sternum, or scapula should be considered highly concerning for abuse in young children without a specific, independent history of significant trauma.

Classic metaphyseal lesions (CMLs) are subtle metaphyseal fractures that occur in the severely abused infants (Fig. 172.14). CMLs appear radiographically as chips or bucket handle lesions around the growth plate and are most commonly seen in the femur, humerus, and tibia.[38] No fracture is more specific for abuse than the CML, and identification should prompt a thorough evaluation for other injuries.[39-41]

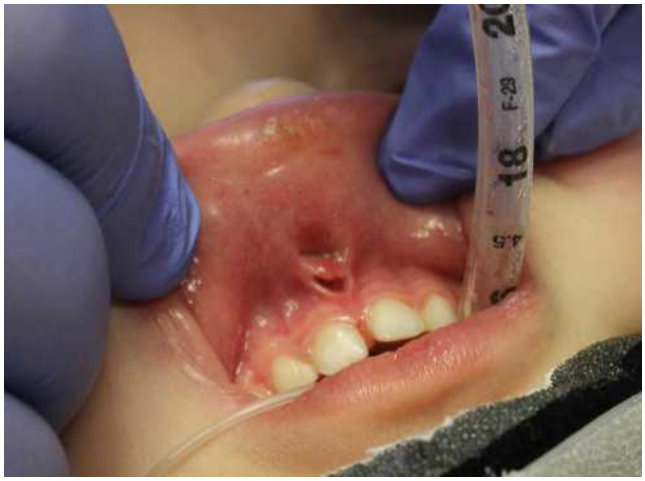


Fig. 172.12 Torn upper labial frenulum. (Courtesy John Melville, MD.)

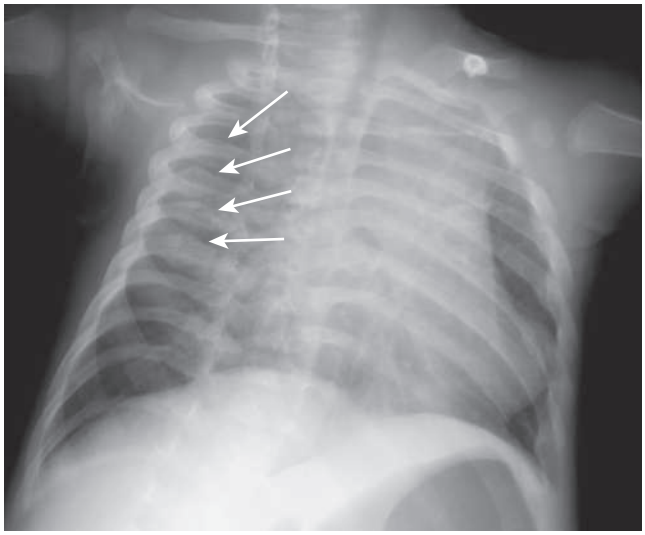
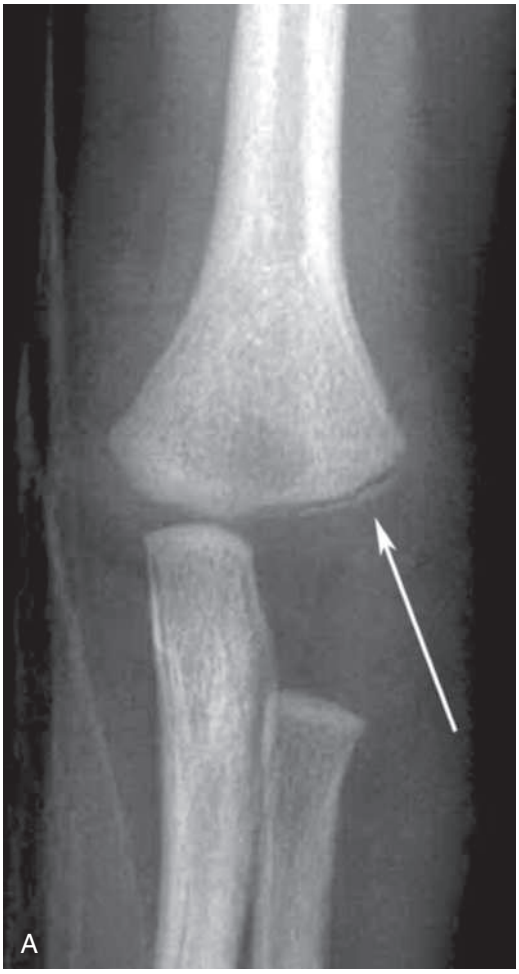


Fig. 172.13 Healing, posterior rib fractures. Right-sided, posterior rib fractures are indicated by the white arrows. Left-sided, lateral and posterior fractures are also present, and are better demonstrated by other views. (Courtesy Daniel Lindberg, MD.)

Skull fractures in infants commonly raise the concern for abuse but, relative to the injuries listed earlier, are much less specific. Even in infants, linear, parietal skull fractures can result from very minor falls. Because skull fractures do not show signs of healing, birth-associated skull fractures can be clinically subtle and difficult to differentiate from acute injury. In series of infants with apparently isolated skull fractures, occult fractures were identified by skeletal survey in up to 5% of cases. Complex skull fractures–multiple fracture lines, fractures that cross suture lines, and those with substantial depression or widening—require more force or multiple impacts and are therefore more concerning. It is possible, however, for bilateral parietal fractures to result from a single impact to the cranial vertex.

Although spiral fractures were once thought to have high specificity for abuse, available data do not support this.[42] Indeed, spiral fractures of the tibia *in children learning to walk* (toddler's fractures) are among the few fractures in young children that do not require routine skeletal survey, even without a clear mechanism of trauma (see Chapter 170).

Intra-abdominal injuries in young children are concerning for abuse if not sustained as a result of a motor vehicle collision, accidental direct blow, or significant fall. Although hepatic injuries are the most



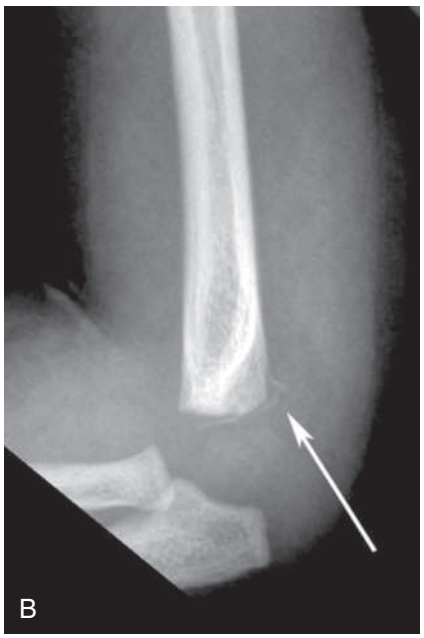


Fig. 172.14 (A) Classic metaphyseal fracture. In this anteroposterior view, the fracture assumes the "bucket handle" conformation. (B) In the lateral projection, the classic metaphyseal fracture appears as a chip. (Courtesy Daniel Lindberg, MD.)

common abusive injury identified, small bowel perforation and pancreatic injury are especially specific for abuse.[43]

TABLE 172.2 Differential Diagnoses (Not Exhaustive)

Presenting Injury	Diagnoses	Signs
Any	Accidental trauma	Minor injuries, walking children, history
	Birth trauma	Young infants
Fractures/bony injury	Osteomalacia of prematurity	Former significantly premature infants
	Osteogenesis imperfecta	Blue-gray sclera, family history
	Osteomyelitis	Fever (even minor)
	Congenital syphilis	Rash
Bruising/hemorrhage	Congenital coagulopathy	Abnormal PT/PTT/platelets, family history
	Other cutaneous lesions	Failure to resolve with time
Burns	Phytophotodermatitis	Typical history
	Irritant burn	Exposure to senna, laxatives, irritants

Universal Screening

In an effort to reduce rates of missed physical abuse, some centers have implemented processes of "universal screening," in which the primary nurse documents whether there is concern for abuse in every child at the time they present for care. Nurses are prompted to consider historical and physical findings and to completely undress young children. In several large, population-based samples, universal screening has been shown to be feasible, to identify children with higher risk for abuse, and to increase reporting, but it has not yet been shown to decrease rates of missed abuse.[44-46]

DIFFERENTIAL DIAGNOSES

Because the diagnosis of abuse has a profound impact on a child, their family, and the alleged abuser, a variety of traumatic and medical conditions have been suggested to explain signs and symptoms of physical abuse (Table 172.2). These range from sincere attempts to distinguish abuse from rare but well-described medical entities, to the invention of new medical entities invoked only in legal settings or the lay press.[27,28,47-50] It is usually beyond the scope of an emergency clinician to test for such rare diseases or hypothetical entities unless there are specific signs or symptoms (e.g., the blue sclera of osteogenesis imperfecta) or a specific family history.

The most common entity to be differentiated from abuse is accidental injury. With few exceptions (e.g., the CML), most traumatic injuries that have been reported in the setting of abuse can also be seen with other severe forms of trauma. Isolated injuries reported in the context of an accidental trauma mechanism should be evaluated on a case-by-case basis to determine whether the identified injury matches the reported mechanism. Young children who have started to cruise or walk frequently may have unobserved short falls from standing height or furniture. Although the vast majority of these falls are benign, they can produce injury: isolated bruising to shins, elbows, or other hard body surfaces; linear skull fractures; toddler's fractures, buckle fractures of the distal femur; and clavicle fractures.

In the youngest infants, injuries from birth should be considered, because symptoms may only be recognized weeks after the child is discharged from the hospital. Skull fractures, cephalohematomas, and clavicle fractures are the most commonly identified, whereas asymptomatic subdural hematomas, rib fractures, and other extremity fractures are rarer. Retinal hemorrhages occur in approximately one-third of normal births and persist for 1 to 3 months.[51,52]

Bone fragility disorders should be considered in children with exclusively bony injuries. *Osteomalacia of prematurity* occurs in roughly 30% of extremely low-birth-weight infants and is commonly associated with fractures in the absence of significant trauma. Risk factors include exposure to prolonged parenteral nutrition, steroids or furosemide, and those with cholestasis or chronic lung disease. Minor forms of *osteogenesis imperfecta* can present with multiple unexplained fractures. Although the diagnosis can be made early in children with a family history or severe disease, some cases are only diagnosed in the course of an evaluation for abuse. Be alert for blue-gray sclera, especially if they persist beyond infancy, or family history of unexplained fractures, fragile teeth, congenital hearing problems, or short stature. Osteomyelitis and congenital syphilis can cause metaphyseal abnormalities and should be considered in children with even mild fever or rash.

In children whose injuries are confined to problems of bruising or bleeding, emergency clinicians should consider an undiagnosed coagulopathy. The American Academy of Pediatrics (AAP) has published guidelines for coagulopathy testing that will identify the vast majority of bleeding disorders.[53] Briefly, these children should have prothrombin time and international normalized ratio (PT/INR), partial thromboplastin time (PTT), Factors VIII and IX, and complete blood count (CBC).[53,54] Those with intracranial hemorrhage should have testing for D-dimer and fibrinogen. Because coagulopathy testing can take weeks or months, and because abuse is the more common etiology in children with isolated bruising and concern for abuse, the coagulation evaluation should not delay the evaluation for abuse, reporting to CPS, or safety planning.

Atraumatic cutaneous findings may be confused for isolated bruising, including congenital dermal melanosis (formerly "Mongolian spots"), other birthmarks, or even blue dye from clothing (diagnose and "cure" this with an alcohol wipe). Because bruising resolves over a few days, follow-up examinations with photo documentation can reliably distinguish most findings. In cases where an immediate decision is needed, preliminary data suggest that transcutaneous bilirubin testing might be useful.[55]

When children present with lesions concerning for abusive burns, emergency clinicians should consider phytophotodermatitis and irritant burns. Phytophotodermatitis is a skin reaction caused by sun exposure in the setting of photo-sensitizing substances such as citrus, parsnip, or celery juices. It can cause well-demarcated, patterned, burn-like, blistering lesions and the typical history can usually be elicited. Irritant burns can be caused by prolonged exposure to mild skin irritants, such as household bleach, which may not be uncomfortable to the child. Prolonged contact with stool in diapered children, especially after the use of Senna or other laxatives, can cause contact burns that look identical to immersion burns.[56]

DIAGNOSTIC TESTING

Protecting a child from an abusive caregiver may require proving that the child's injuries are the result of abuse. Identification of additional traumatic injuries suggests abuse, particularly when not explained by the initial history. Concomitant injuries may have important *forensic* significance, even when they do not require specific treatment. The clinical examination is insensitive, especially in very young children, for forensically significant injuries, such as healing fractures, CMLs, abdominal injuries, and even milder abusive head trauma.[57] To decrease testing disparities and improve abuse recognition, we recommend a routine testing strategy based on the level of concern for abuse and the child's presenting injuries (Table 172.3).[14,31,58,59]

Skeletal Survey

The radiographic skeletal survey is the oldest and most commonly used diagnostic test to identify occult traumatic injuries when there is concern for physical abuse. Depending on the population, skeletal surveys identify additional fractures in approximately 10% to 25% of cases, with very low radiation exposure.[38,60] Guidelines recommend skeletal survey for all children younger than 24 months old with suspicion for abuse.[8,14,59,61,62] Skeletal surveys may be reasonable in children 24 to 60 months old, especially for those with limited mobility, decreased ability to communicate, and those 24 to 36 months old. Skeletal surveys require specialized technique, including at least 21 separate films and interpretation by an experienced radiologist.[63] A child should be transferred to an experienced center for skeletal survey rather than have an incomplete or inadequate series. There is no role for a single exposure "baby-gram" to identify occult fractures. A follow-up skeletal survey, repeated after at least 14 days, frequently identifies additional missed fractures and may clarify indeterminate findings (Box 172.3).

TABLE 172.3 Recommendations for Occult Injury Testing

Diagnostic Test	Indications (With Concern for Abuse)
Skeletal survey	All patients <24 months old Consider in 24-60-month-olds
Neuroimaging (CT or MRI)	Signs/symptoms of traumatic brain injury History of assault to head or violent shaking <6 months old PIBIS score >1 (see Table 172.1)
Retinal examination	Patients with traumatic brain injury
AST/ALT	Patients <60 months old with significant injury (e.g., brain injury, torso injury, long-bone fracture)
Abdominal CT	History of assault to abdomen Signs/symptoms of abdominal injury AST or ALT >80 IU/L
Siblings and contacts	Skeletal survey for <24-month-old contacts of injured, abused children. Interview verbal children capable of participating
Toxicology testing (evidence is limited)	Altered mental status Evidence of substance use in the environment Abusive burns

ALT, Alanine transaminase; *AST,* aspartate transaminase; *CT,* computed tomography; *MRI,* magnetic resonance imaging.

Neuroimaging (Computed Tomography or Magnetic Resonance Imaging)

Abusive head trauma is both the leading cause of death and disability in abused children, and the abusive injury most frequently missed by clinicians.[3] Head computed tomography (CT) or magnetic resonance imaging (MRI) should be undertaken in children with signs of brain injury—decreased mental status, external signs of impact to the head, bulging fontanel, seizure, coma, or focal neurologic findings.[57] We recommend neuroimaging also be performed in children younger than 6 months old when there is concern for abuse, even when the child is neurologically asymptomatic. In infants with nonspecific signs and symptoms, such as lethargy, seizure-like activity, or vomiting without fever or diarrhea, the PIBIS score should guide neuroimaging decisions (see Table 172.1). Because of the need to identify forensically significant injuries, the Pediatric Emergency Care Applied Research Network (PECARN) decision rule should not be used to identify children at low risk of injury when there is concern for abuse[57,64] See Chapter 160 for a discussion on nonabusive pediatric head injury evaluation.

Because it is widely available, fast, and accurate, CT is currently the most widely used modality to diagnose abusive head trauma. Head CT should routinely include three-dimensional reformatting to identify

BOX 172.3 The Complete Skeletal Survey[63]

Appendicular Skeleton
Humeri (AP)
Forearms (AP)
Hands (PA)
Femurs (AP)
Lower legs (AP)
Feet (AP)

Axial Skeleton
Thorax (AP, lateral, L and R obliques)
Abdomen and pelvis (AP)
Lumbosacral spine (lateral)
Cervical spine (lateral)
Skull (frontal and lateral)

AP, Anteroposterior; *L,* left; *PA,* posteroanterior; *R,* right.American College of Radiology and the Society for Pediatric Radiology. ACR–SPR Practice Parameter for the Performance and Interpretation of Skeletal Surveys in Children. 2016; https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Skeletal-Survey.pdf. Accessed January 16, 2020.

subtle skull fractures that may be missed in the plane of the scan. These reformats do not require additional radiation exposure but do require reformatting before data are expunged.

Recently, MRI using faster, more motion-tolerant MRI sequences (fast MRI) has come to replace CT as the initial test for abusive head trauma in several centers.[65-69] In order to decrease radiation exposure, we recommend, as resources allow, rapid MRI in favor of CT for clinically stable children who do not require other CT imaging. Because rapid MRI is marginally less sensitive for skull fractures than CT, we recommend that a complete skeletal survey with skull radiographs be performed in children who undergo rapid MRI for concerns of abuse. Cranial ultrasound is not sufficiently sensitive to identify occult abusive injuries and is not recommended as an initial study for children with concern for abuse. In children with identified abusive head trauma, MRI of the brain and cervical spine is frequently performed several days after the initial CT scan to further delineate and assess progression of injury.[70]

Retinal Examination

Retinal hemorrhages identified in a child with head injury can significantly increase the recognition of abuse.[51] Although a wide range of diseases can cause mild retinal hemorrhages, numerous (>20), multilayered and extensive hemorrhages, or those associated with macular retinoschisis, are strongly associated with abusive head trauma (Fig. 172.15). Dedicated retinal examination by an experienced ophthalmologist is recommended for children with concern for abusive head trauma to characterize the hemorrhages and improve sensitivity.[51] Conversely, without radiographic evidence of brain injury, significant retinal hemorrhages are rare, and transfer or referral for specialty retinal examination should be considered optional in this group. Even in severe cases of abusive head trauma, retinal hemorrhages are absent in approximately 15% of cases; retinal examination should therefore not be used as an initial screening test to determine the need for neuroimaging.

Abdominal Injury Testing

Intra-abdominal injuries, ranging from obviously life-threatening to completely asymptomatic, are present in approximately 3% of children evaluated for physical abuse. Abdominal bruising, tenderness, or distention of the abdomen are present in approximately 50% of children with abusive abdominal injuries. In children with concern for abuse and aspartate transaminase (AST) or alanine transaminase (ALT) greater than 80 IU/L, at least 20% had an intra-abdominal injury identified by CT scan or other definitive testing. Amylase and lipase have been recommended by some authors to increase sensitivity for abdominal injuries, but have not been shown to significantly improve yield beyond clinical examination plus AST and ALT. Although ultrasound can identify abdominal injuries, it is relatively insensitive; CT should be used to characterize injuries identified by ultrasound.

To assess for intra-abdominal injury, we recommend AST and ALT testing for children with concern for abuse unless there is obvious abdominal injury or history of direct abdominal trauma, in which case a CT scan should be performed. We also recommend CT scan with intravenous (IV) contrast be performed for those with AST or ALT greater than 80 IU/L. Because AST and ALT rapidly normalize, even in children with hepatic lacerations, trending of transaminases over time should not be used to determine the need for imaging. For this reason, it is also important that testing be completed during the initial evaluation.

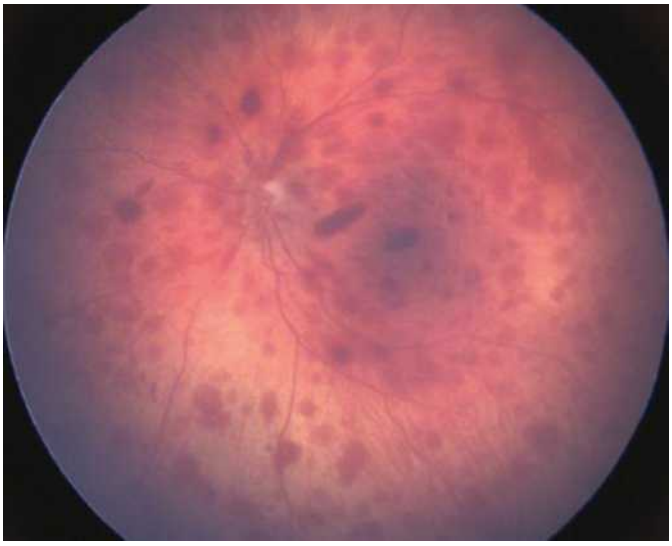


Fig. 172.15 Too numerous to count retinal hemorrhages in all layers that extend to the periphery—characteristic of abusive head trauma. (Courtesy of Daniel Lindberg, MD.)

Toxicology Testing

Children can ingest illicit drugs via malicious poisoning or neglectful exposure.[71-73] Centers with routine testing strategies identify illicit substances in approximately 5% to 10% of children with high levels of concern for abuse.[71] Because data are limited and the epidemiology of drug use is highly variable, there are currently no widely accepted guidelines for drug testing when there is concern for abuse. Currently, we recommend drug testing when children with high concern for abuse present with burns, altered mental status, or when substance use disorders are identified in the child's environment. Because rapid drug screens based on ELISA methodology are subject to high rates of false negatives, we recommend use of comprehensive testing based on mass spectroscopy.[71]

MANAGEMENT

Compared to children with nonabusive traumatic brain injury, as a group, children with abusive head trauma tend to have more severe injury, longer ICU stays, and higher mortality. Nonconvulsive seizures are identified in more than 30% of children with abusive head trauma, prompting some to recommend routine electroencephalogram (EEG) monitoring.[4,74] Otherwise, medical management of children with abusive traumatic injuries is generally the same as for nonabused children.

Beyond the management of the acute injuries themselves, management of abuse largely consists of protecting the child from further abuse.

Household Contacts

Violence is a disease that affects an entire household.[10,13,75,76] We recommend that emergency clinicians identify any other children who share a home where child abuse (or other forms of family violence) is identified.[9,12,59,75] Conversely, when child abuse is recognized, emergency clinicians should consider whether other family members or companion animals may be at risk and use the expertise of CPS to assist in bringing those at risk for evaluation. Contacts younger than 24 months, especially twins and other multiple births, should have a skeletal survey.[14] Older, verbal children should be interviewed about any reported trauma history, and to identify abusive disciplinary practices. In cases where there is significant concern for genetic diseases that mimic abuse, evaluation of biological siblings can help to establish the correct diagnosis.

Timing

Determining the age of an injury can affect the plausibility of an offered history and can assist law enforcement in identifying the perpetrator. In young children, multiple injuries of different ages are highly concerning for abuse. In many cases, the best way to determine the timing of an injury is based on when the child developed symptoms, independent witness reports, or images of visible injuries.

The best evidence for injury dating comes from fractures of endochondral bones (most bones except the skull). Signs of healing (e.g., periosteal reaction and callus formation) are rarely evident before 7 days and commonly seen within 10 to 14 days. Experienced radiologists can sometimes offer more nuanced estimates of fracture age. Multiple fractures of different ages are highly concerning for abuse.

Recent data suggest that the finding of too-numerous-to-count intraretinal hemorrhages reliably resolves within a few days. Thus, we recommend dedicated retinal examination occur within 24 to 48 hours in cases with concern for abusive head trauma; the patterns of retinal hemorrhages may be useful in estimating the time of injury.[77]

Conversely, emergency clinicians should be cautious not to estimate the age of bruises based on their appearance. Previously used dating systems were based on scant data and have poor accuracy when prospectively used to estimate bruise ages in children with known times of injury. Similarly, the CT appearance of subdural hematomas or other intracranial hemorrhages is of limited utility in estimating the age of injury. Although hyperdense "bright" blood is often thought to signify acute hemorrhage (and vice-versa), hyperacute bleeding, re-bleeding and mixing of blood and cerebrospinal fluid (CSF) probably account for their poor accuracy. Mixed density subdural hematomas have been described in several cases with a single traumatic episode, and therefore are not strong evidence for multiple episodes of trauma. In cases of severe traumatic brain injury, the onset of a child's symptoms is probably the most useful determination of timing of injury, especially when a child who had been acting normally suddenly becomes comatose.

Mandated Reporting

In the United States, Canada, and several other jurisdictions, emergency clinicians are mandated to report a reasonable concern of child maltreatment to public CPS agencies or law enforcement. These reports can mobilize social resources for family, expand the investigation of abuse beyond the hospital, and facilitate testing or protection for other children in the abusive environment. A final diagnosis of abuse is not required to trigger the mandate, and reporters generally have legal protection for reports made in good faith, even if a child is ultimately determined not to have been abused. In cases where there is reasonable concern for abuse, but where the final diagnosis is pending, emergency clinicians should be reassured that a mandated report need not automatically trigger the removal of a child from their home or the instigation of criminal proceedings. In many jurisdictions, the mandate to report can be satisfied by reporting to a designated child protection team who will complete the evaluation and determine the need for reporting.

Hospital social workers can assist with the reporting process. The exact procedure for reporting varies by jurisdiction, but instructions are usually accessible via an internet search for "report child abuse [location]." In preparing to report, gather the child and family's contact information, the identity and ages of any other children in the home, and the location where the abuse may have occurred (to determine reporting jurisdiction).

DISPOSITION

Many children with physical abuse will require hospital admission for treatment and stabilization of their injuries or identification of a safe environment. Children with concern for physical abuse may be discharged if: (1) injuries have been medically stabilized; (2) reasonable concerns for abuse have been reported as required by statute; and (3) a safe environment has been identified. In children who are otherwise stable for discharge, CPS should establish a temporary safety plan until testing can be completed.

Should caregivers attempt to leave the ED prior to the completion of an evaluation for abuse, emergency clinicians should follow their typical practice for parents seeking to leave against medical advice. If a caregiver demonstrates the capacity to make medical decisions, and has received the clinician's best advice, emergency clinicians and hospital staff should not seek to forcibly prevent them from leaving. Reasonable concerns for abuse should be reported in these circumstances as required by local statutes to CPS or law enforcement, which have the ability to implement secondary prevention.

SEXUAL ABUSE

KEY CONCEPTS

- ED evaluation of pediatric sexual assault should focus on time-dependent medical treatment and evidence collection. The ultimate determination of abuse likelihood can be deferred pending the forensic interview and additional investigation.
- A normal examination neither confirms nor excludes the possibility of abuse, and patients should be reassured that their body is normal and healthy.
- A genital examination should not be forced on a child. Most children can be referred for an examination when they are rested and prepared.
- Likelihood of obtaining forensic evidence decreases with time from assault. Evidence collection may be performed up to 7 days after sexual assault, depending on jurisdiction.
- Emergency contraception should be offered to pubertal females up to 120 hours after sexual assault.
- Prophylactic or empirical treatment for gonorrhea, chlamydia, and trichomonas should be offered to pubertal children, but treatment should be deferred in pre-pubertal children until infection is confirmed.
- When an investigation for sexual abuse is ongoing, caregivers and emergency clinicians should provide a believing, supportive environment if a child reports abuse or has questions but should not attempt to elicit a detailed narrative outside the context of the forensic interview.

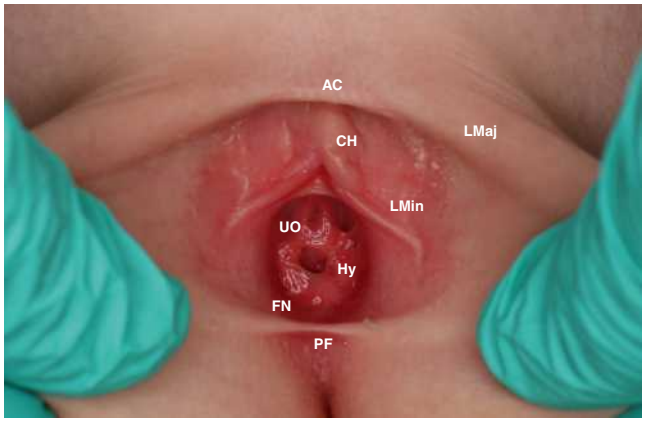


Fig. 172.16 Normal pre-pubertal hymen. This view is obtained by gentle outward (toward the examiner) traction on the labia. *AC*, Anterior commissure; *CH*, clitoral hood; *FN*, fossa navicularis; *Hy*, hymenal membrane (Note the thin, smooth membrane in this pre-pubertal child. Note also that the presence of the hymenal opening is entirely normal.); *LMaj*, labia majora; *LMin*, labia minora; *PF*, posterior fourchette. (Courtesy of Kathi L. Makoroff, MD.)

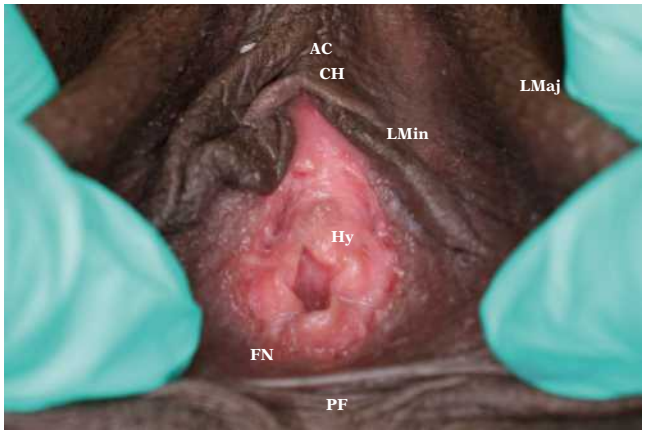


Fig. 172.17 Normal pubertal hymen. *AC*, Anterior commissure; *CH*, clitoral hood; *FN*, fossa navicularis; *Hy*, hymenal membrane (Note the thickened, redundant appearance in this pubertal adolescent); *LMaj*, labia majora; *LMin*, labia minora; *PF*, posterior fourchette. (Courtesy of Kathi L. Makoroff, MD)

FOUNDATIONS

Sexual abuse of children is common and under-recognized.[78] When surveyed as young adults, roughly 25% of women and 5% of men report some form of sexual abuse, with adolescents being at highest risk. These are likely under-estimates given the limitations of self-reporting. Perpetrators of sexual abuse are overwhelmingly male and can include family members, acquaintances, or strangers.

Especially in adolescents, the loss of control inherent in sexual abuse can be profoundly damaging. A trauma-informed approach can decrease anxiety and facilitate the evaluation. In school-aged or adolescent children (and adults) who have experienced sexual assault, emergency clinicians should seek to re-establish a sense of control whenever possible. For example, we recommend frequently explaining the purpose of each step of the process and asking for permission (examples, see Box 172.1). Respect a child's right to decline any part of the evaluation.

As with physical abuse, the bulk of the investigation in cases with concern for sexual abuse can occur outside of the ED. Urgent interventions include stabilization of medical injuries, evidence collection, post-exposure prophylaxis (PEP), arrangement of a safe environment, and CPS reporting. Evaluation of children more than 72 hours after possible abuse (or another period if mandated by law) can be deferred from the ED to an outpatient setting.[79] Completion of a full evidence collection kit can require more than an hour of undivided attention, and emergency clinicians responsible for multiple potentially unstable patients may benefit in partnering with a sexual assault/forensic nurse examiner (SANE/FNE) program or a subspecialty child abuse pediatrician.

Misconceptions about normal pediatric female genital anatomy (Figs. 172.16 and 172.17) are widespread among both patients and clinicians. The pre-pubertal hymen is thin, with a smooth edge. Normal configurations include annular or ring-shaped, crescent-shaped, and tulip-shaped, among many others. Although imperforate hymens exist and can cause symptoms in pubertal children, this is a rare abnormality. During puberty, the hymen becomes thickened and redundant (see Fig. 172.17).

Trafficking

Trafficking, or commercial sexual exploitation of children, occurs when someone engages a minor in any sex act that involves the exchange of something of perceived value, and can include the prostitution of children by others, "survival sex," or pornography.[80] Although reliable statistics on the prevalence and epidemiology of trafficking are limited, available evidence suggests that the large majority of trafficked children and adolescents in the United States are female and are US citizens.[81] Early data suggest that trafficking is more likely among adolescents who have history of substance use, run away from home, have been involved with law enforcement, had a traumatic injury (i.e., broken bone, loss of consciousness, significant wound), had an STI, or had more than 5 sexual partners.[80,82,83] When two or more of these risk factors are identified, clinicians should ask if anyone has asked or forced the patient to do something sexual with someone else, to do some sexual act in public (like dance in a strip club), to pose sexually for a photo or video, or if the patient has traded sex for something they needed.[84] Clinicians should take steps to ask these questions privately, because traffickers may pose as relatives, friends, or employers. The National Human Trafficking Resource Center maintains a hotline (1-888-3737-888) that can provide region-specific resources to clinicians or patients when there is concern for trafficking.

CLINICAL FEATURES

In contrast to physical abuse, most sexual abuse evaluations will be prompted by a patient or caregiver report. Genital bleeding or discharge should prompt consideration of sexual abuse even when no concern is raised in the history, and in pre-verbal children. Pregnancy or sexually transmitted infections (STIs) (gonorrhea, chlamydia, syphilis, trichomonas, or human immunodeficiency virus [HIV]) demonstrate evidence of sexual contact.[79,85-87] A diagnosis of pregnancy or STI in a young adolescent should prompt nonjudgmental questions about the child's sexual partners; some victims perceive abuse as consensual sexual activity with a boyfriend or girlfriend.

Caregivers sometimes bring children for evaluation based on concern for abnormal appearance of a child's genitalia (redness, size, or shape of vaginal or rectal orifices). Without other indications of abuse, these findings are extremely nonspecific and do not increase the likelihood of abuse.[88] In young children (2 to 6 years old), some sexual behaviors that are concerning to caregivers (e.g., touching genitals in public) are part of normal development, whereas others (e.g., inserting objects into the genitals) should prompt concern for sexual abuse. The AAP has published guidelines for the evaluation of several such

sexual behaviors. In general, behaviors are less concerning if they are transient, few, and distractible. They are more concerning if they are persistent and resistant to parental distraction. When children engage in sexual actions or activity with each other, sexual abuse should be distinguished from sexual play by the presence of a significant difference in age or development, or the presence of coercion. Laws defining the age of consent for sexual activity and the age difference that constitutes statutory rape differ by jurisdiction.

History

Most cases of sexual abuse do not have diagnostic findings on physical examination, laboratory testing, or forensic evidence collection. Therefore, a child's history is usually the most important factor to determine social or legal interventions in cases of alleged sexual abuse. Forensic interviews, conducted by CPS, law enforcement, child advocacy centers, or child protection teams, are conducted to avoid suggestive or coercive questions. In most cases, these forensic interviews can take place after the initial ED evaluation, allowing emergency clinicians to limit their history to the information needed to identify medically significant injury or illness.

Forensic interviewing requires substantial training and ongoing peer review, and repeated interviews could "contaminate" evidence. For these reasons, we recommend that emergency clinicians, parents, and caregivers not attempt to obtain detailed narrative needed for prosecution outside the formal forensic interview.[79] However, adults should provide a safe, supportive, listening environment if the child approaches them with information or questions. Outcomes for sexually abused children are improved when they are believed and supported by their caregivers. Clinicians should transparently communicate that their ability to keep information confidential is limited in some cases by the legal mandate to report reasonable concerns for child abuse.[89]

In cases where a caregiver reports the initial concern for abuse, emergency clinicians should obtain the caregiver's history separated from the child. Document whether the child reported abuse; and if so, whether the report was spontaneous, or in response to questioning by the caregiver. Identify any additional children ("contact children") who share the environment where abuse may have occurred. If interviewing a child, avoid leading questions, and document both the question asked and the child's response.

Interviews should be conducted at an appropriate developmental level; most children younger than 4 years old will have limited ability to participate in the interview. Younger school-aged children may have difficulty with "when" questions, limiting the ability to determine the time elapsed from the last episode of abuse (needed to determine the need for an acute examination, evidence collection, or HIV PEP). Consider asking "where," "what," or "who" questions to understand the timeline. For example, a child who does not know what time or day something occurred may know whether it was day or night, a school day or a weekend, or during a specific holiday, event, or visit to a different home. It may be helpful to elicit the terms used by the child to describe different body parts.

Physical Examination

Most children who present to the ED with concern for sexual abuse should be offered a dedicated physical examination of the genitalia and rectum. With proper preparation, this examination need not be painful or distressing to the child (see Box 172.1). Conducting the examination on the lap of a trusted caregiver and in the context of other painless examination maneuvers (inspecting the nose, heart, and belly-button) can reassure the child. Limit exposure of the child's body to the area being examined.[89]

The pre-pubertal (non-estrogenized) hymen is exquisitely sensitive; touching it will almost certainly end the useful portion of your examination. For this reason, collection of internal vaginal and cervical swabs is not indicated in a pre-pubertal child and a speculum examination should not be conducted.[89]

To avoid additional trauma, a genital examination should not be forced on a reluctant child. In most cases, a child can return for an outpatient examination after food, rest, and preparation.[89] In the rare cases of substantial bleeding or concern for a medically unstable injury, a gynecologist should perform an examination under anesthesia.

To best expose the hymen and other relevant anatomy, pull the labia majora out (off the table or toward the examiner—not laterally) with the same force you would use to retract the cheek to examine the teeth. The posterior hymen, if not sufficiently visualized in this position, can sometimes be better seen in the "knee-chest" position, where the child is placed in a prone position on the examination table with her hips flexed so that the knees and chest are resting on the table. The posterior hymen is then visualized by laterally retracting the buttocks.[79]

If manipulation of the hymen is absolutely necessary, consider using the mucosal surface of the contralateral labia. Alternatively, a few drops of sterile saline can be used to "float" the posterior rim of the hymen and expose an area of interest. A colposcope can be useful to magnify, illuminate, and document examination findings. Data do not support the use of toluidine blue to identify mucosal injuries not apparent to the naked eye.[79] If photo-documentation is conducted, images should be maintained in a confidential format separate from the normal electronic medical record.

Even when concern for sexual abuse is high, most children will not have physical signs of genital or anal injury.[85] A wide array of nonspecific findings (e.g., erythema, periurethral bands, and bumps and notches of the hymen) should not be confused with evidence of sexual contact. (Table 172.4). Injuries that are indicative of trauma include bruising, petechiae, or abrasions on the hymen; acute lacerations of the hymen; vaginal lacerations; or complete transection of the hymen between 4 o'clock and 8 o'clock (Figs. 172.18 and 172.19). In adolescents capable of consensual sexual activity, no examination finding can distinguish consensual sexual activity from assault or rape.

Although the vast majority of physical examinations will be normal, even when performed soon after acute sexual assault, a normal examination does not exclude abuse. Children and families can be reassured that they are healthy and normal and that no one in the future (e.g., doctors, spouses) will know from looking at them that abuse has occurred. Some families have concern for an anatomic definition of virginity, although they are reluctant to broach the issue. Providers should emphasize that the child is anatomically normal and that the definition of virginity should depend on when someone *chooses* to have intercourse.

DIFFERENTIAL DIAGNOSES

Strep infection of the perineal skin and genitalia can produce redness, inflammation, and fissures. Vaginitis from infection or poor hygiene can result in vaginal discharge or dysuria. Isolated vaginal bleeding can be the result of urethral prolapse (beefy red protrusion inferior to clitoral hood) or lichen sclerosis (pale, irritated, thin, hypopigmented skin surrounding the genitalia; Figs. 172.20 and 172.21). Straddle injuries can produce bruising of the external genitalia (labia, perineum, and peri-urethral tissues) and are usually accompanied by a history of injury. In boys who are toilet training, a falling toilet seat can produce dorsal and ventral penile bruising similar to a bite mark.

TABLE 172.4 Significance of Genital Findings for Abuse

Normal Findings	Conditions Mistaken for Abuse	Findings Caused by Trauma and/or Sexual Contact
• Normal hymen variants (annular, crescentic, imperforate, micro-perforate, septate, redundant, with tissue tags, with bumps or mounds) • Hymenal notches or clefts between 3 and 9 o'clock • Superficial notches below 3 and 9 o'clock • Periurethral bands • Intravaginal ridges or columns • External hymenal ridge • Linea vestibularis • Diastasis ani • Perianal skin tags • Hyperpigmentation of the skin of the labia minora or perianal tissues in children of color • Dilated urethral orifice Findings commonly caused by other medical conditions: • Erythema • Increased vascularity • Labial adhesions • Friability of posterior fourchette • Vaginal discharge • Molluscum contagiosum • Anal fissures • Venous pooling • Anal dilatation from constipation, anesthesia, impaired muscular tone or post mortem	• Urethral prolapse • Lichen sclerosus • Vulvar ulcers • Erythema, inflammation or fissures from bacterial, viral, fungal, parasitic infection • Perineal groove • Rectal prolapse • Post mortem lividity	• Acute laceration(s) or bruising of labia, penis, scrotum, perianal tissues, or perineum • Acute laceration of the posterior fourchette or vestibule • Perianal or posterior fourchette scars (difficult to diagnose without documentation of the acute laceration) • Bruising, petechiae, or abrasions on the hymen • Acute laceration of the hymen • Vaginal laceration • Perianal laceration with exposure of tissues below the dermis • Healed hymenal transection/complete hymen cleft—a defect in the hymen between 4 and 8 o'clock that extends to the base of the hymen with no hymenal tissue discernible at that location • Evidence of female genital mutilation or cutting • Gonorrhea (genital, rectal or pharyngeal) • Syphilis • Chlamydia (genital or rectal) • Trichomonas • HIV (excludes transmission from blood transfusion) • Pregnancy • Semen found by forensic specimens

HIV, Human immunodeficiency virus.
Adapted from: Adams JA, Farst KJ, Kellogg ND. Interpretation of medical findings in suspected child sexual abuse: an update for 2018. *J Pediatr Adolesc Gynecol.* 2018;31(3):225-231.

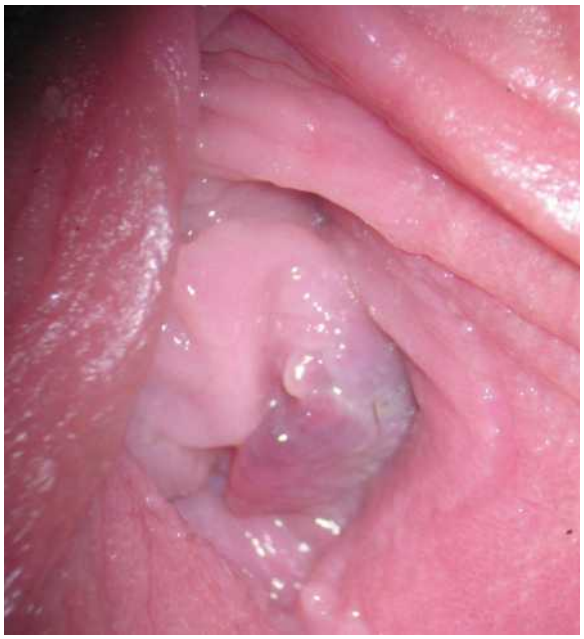


Fig. 172.18 Bruising to an estrogenized, pubertal hymen. Indicative of acute sexual contact. (Courtesy of Daniel Lindberg, MD.)

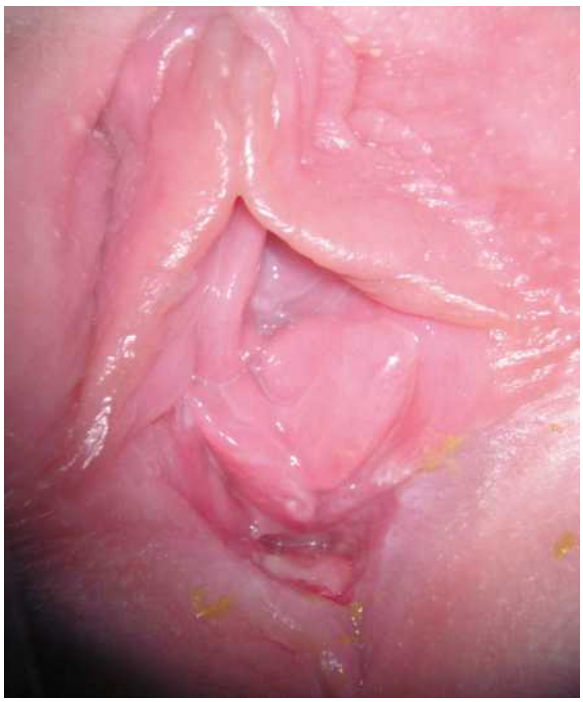


Fig. 172.19 Acute injury to the fossa navicularis in a pre-pubertal girl. The hymen is not well visualized. (Courtesy of Daniel Lindberg, MD.)

DIAGNOSTIC TESTING

The goal of diagnostic testing in the ED is to identify transient evidence of sexual assault or sexually transmitted diseases (Table 172.5). Beyond the history and physical examination, a forensic evidence collection kit ("rape kit") can provide evidence of sexual contact and identify the assailant if DNA is isolated. Evidence is more likely to be obtained soon after the assault with the majority of positive kits obtained within 24 hours, especially in pre-pubertal children. Forensic evidence collection is recommended for cases of assault with possibility of DNA transmission (semen, blood, or saliva) up to 72 hours from the assault, although some practitioners or jurisdictions are moving to a threshold of up to 7 days based on newer polymerase chain reaction (PCR)-based techniques.[89] Beyond 24 hours, specimens from the child's clothing are the most likely to retain evidence. Obtaining the child's underwear (even if not worn at the time of the assault) can recover DNA evidence beyond 24 hours and is relatively noninvasive. Although many kits require documentation of whether a child has eaten, defecated, urinated, or wiped prior to evidence collection, children should not be asked to defer these activities in service of evidence collection, and these considerations should not impact the decision to collect evidence.

Pregnancy testing is routinely obtained in pubertal females because emergency contraception (levonorgestrel or ulipristal; Plan B) is ineffective for established pregnancies. STI testing is undertaken for symptomatic patients or in cases with potential for subacute or chronic abuse. Determining which tests to obtain depends on the details of the child's potential exposure and their physical examination, as well as local disease prevalence, patient and parent preferences, and the availability of timely follow-up. In cases with concern for drug-facilitated sexual assault, blood (within 24 hours) or urine (within 120 hours), samples should be obtained and included in the evidence collection kit.[90] Emergency clinicians may benefit from case-by-case consultation with child abuse pediatrics or infectious disease colleagues.

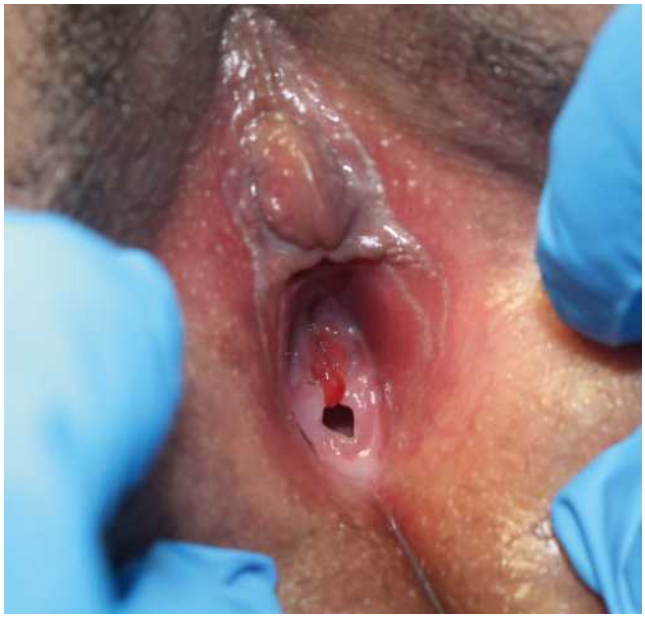


Fig. 172.20 Urethral prolapse. (Courtesy John Melville, MD.)

In adolescents and adults, the prevalence of STIs is high enough to warrant routine screening for gonorrhea, chlamydia, and trichomoniasis using nucleic acid amplification testing (NAAT) methods, if acceptable to the patient. NAAT has improved sensitivity, lower cost, and can be collected more easily, relative to traditional cultures.[85,86,91] NAAT testing for gonorrhea and chlamydia has been endorsed by the Centers for Disease Control and Prevention (CDC) for urine or vaginal specimens in girls.[79,86] STI prevalence in pre-pubertal assault victims is lower (5% to 8%). The AAP recommends NAAT testing for gonorrhea, chlamydia, and trichomoniasis in pre-pubertal children when there is:[85-87,92]

- Penetration of the vagina or anus
- Abuse by a stranger
- Known STI or high-risk behavior (IV drug use, men who have sex with men, multiple sexual partners) in the perpetrator
- Contact of a child with a known STI
- Signs or symptoms of STI
- Prior diagnosis of another STI
- Reasonable need by the patient or family for reassurance

Currently, there are no guidelines to direct testing for syphilis, hepatitis B or C, or HIV in children following sexual assault. We recommend testing in children with any of the above risk factors, or with high community prevalence or incomplete hepatitis B vaccination. Initial screening for syphilis should be by rapid plasma reagin (RPR); hepatitis B screening should include hepatitis B surface antigen and hepatitis B virus (HBV) immunoglobulin M (IgM) core antibody. Testing for HIV and hepatitis B and C should be repeated 6, 12, and 24 weeks after sexual contact.[86]

MANAGEMENT

ED management should focus on the most time-dependent interventions: mandated reporting and PEP for pregnancy and HIV. When there is a reasonable concern for sexual abuse, reporting to CPS is mandatory for emergency clinicians in the United States, Canada, and many other countries. Some caregivers may strongly desire a report, even when the

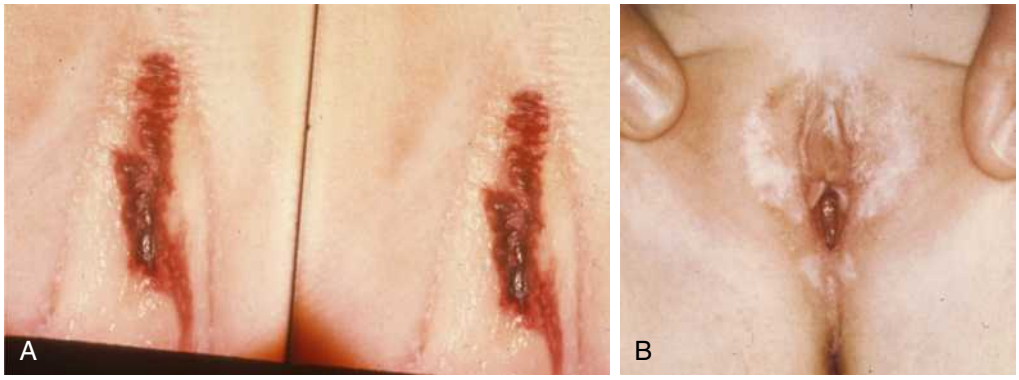


Fig. 172.21 (A and B) Lichen sclerosis. (Courtesy Carol Berkowitz, MD.)

TABLE 172.5 Indications to Offer Testing and Treatment in Cases With Concern for Sexual Abuse

Test/Intervention	Indication
Pregnancy testing	Pubertal females
Gonorrhea/chlamydia/trichomonas testing (NAAT)	All pubertal children Report of vaginal or anal penetration Physical examination findings of sexual contact or ejaculation Abuse by a stranger Symptoms of STI, or diagnosed STI in the patient or a contact child Known STI or risk in suspected assailant Patient or parent request
HBV, HCV, HIV, syphilis testing	As for gonorrhea (above) *or:* Absent or incomplete vaccination for hepatitis B High community prevalence
Forensic evidence collection ("rape kit")	Potential for DNA transmission (blood, semen, saliva) Abuse within 72 hours (or longer depending on local statutes)
Levonorgestrel (Plan B)	Non-pregnant, pubertal females <72 hours from assault
Ulipristal (Ella)	Non-pregnant, pubertal females <120 hours from assault
Empirical treatment for gonorrhea/chlamydia/trichomonas	Pubertal children Avoid treatment in pre-pubertal children without confirmation of infection
HIV PEP	Depends on local prevalence and case-specific details Consider consultation with infectious diseases or CDC hotline (800-933-3413)
Report to children's services	Reasonable concern for abuse

HBV, Hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *PEP,* post-exposure prophylaxis; *STI,* sexually transmitted infection.

findings do not meet the threshold of a reasonable concern for abuse (as when the child presents for isolated nonspecific redness of the genitalia without a disclosure of abuse). Should the emergency clinician opt not to report these cases, caregivers can be advised that they have the option to report their concerns to CPS directly, independent of the health care provider.

Levonorgestrel (Plan B) should be offered to pubertal females within 72 hours (3 days) or ulipristal within <120 hours (5 days) of sexual assault. When taken within 72 hours, it can prevent up to 50% of pregnancies, although there is some potential to prevent pregnancy up to 120 hours after sexual assault. Because it works by suppressing ovulation, patients can be reassured that it will not terminate an established pregnancy.

The decision to offer PEP for HIV is complex and depends on the nature, timing, and likelihood of the sexual assault; local prevalence of HIV; and likelihood that the perpetrator is HIV positive. Although rates of HIV transmission in the course of sexual abuse are probably low, cases of HIV in children whose only risk factor is abuse have been reported.[86] Post-exposure prophylaxis is not effective if administered more than 72 hours after the assault. Consultation with infectious diseases specialists may be useful, and the CDC maintains a national telephone consultation service (1-800-933-3413) to provide real-time expert consultation to emergency clinicians with questions about HIV PEP.

Prophylaxis or empiric treatment for gonorrhea, chlamydia, and trichomonas should be offered to pubertal children but should be deferred for pre-pubertal children.[16] In pre-pubertal children, consensual sexual activity is impossible by definition, rates of STD are low, ascending infection is very uncommon, and follow-up is usually obtainable. For these reasons, the medical consequences of delayed treatment are low, but the forensic significance can be profound. Because infection with gonorrhea, chlamydia, or trichomonas is usually strong evidence of sexual abuse in pre-pubertal children, proof of infection can be essential to ensure the child's protection from ongoing abuse. Treatment prior to obtaining proof of infection can limit confirmatory testing and thwart protection efforts.

DISPOSITION

The vast majority of children evaluated for sexual abuse in the ED can be discharged to follow-up as outpatients. Follow-up is needed to arrange subsequent STI testing, ensure completion of HPV or hepatitis B vaccination, assess tolerance of HIV PEP, and arrange for mental health care. Medically stable patients can be discharged to a safe environment after obtaining appropriate testing and evidence collection. When the alleged assailant is a member of the child's household, CPS can arrange safety planning to ensure that a child has a safe place for discharge or that the alleged assailant is removed from the child's home.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 172: QUESTIONS AND ANSWERS

1. A 12-month-old girl is referred to the emergency department (ED) because her daycare noticed that she cries whenever she is picked up and there was crepitus in the left side of the chest. They deny any witnessed trauma in the daycare facility. The mother arrives and appears concerned. On physical examination, you find some circular contusions on the inner aspects of both her upper arms. The mother states this occurred from a fall a week ago. Which of the following should be the next step(s) in the patient's management?
   - **a.** Conduct a skeletal survey, and report to child protective services (CPS).
   - **b.** Determine whether the arm contusions are of the same age.
   - **c.** Perform a dedicated retinal examination to determine if the child has retinal hemorrhages and, if she does, perform a head computed tomography (CT) scan.
   - **d.** Perform a humerus x-ray to determine if there is a humerus fracture.

Answer: A. Contusions on the inner aspect of the upper arm are atypical injuries in light of the mother's claim of a fall for the child. This pattern of injury is often related to being held tightly around the arm. Chest wall pain in a child could indicate a rib fracture. Chest x-ray is insensitive for rib fractures, which are very uncommon at this age unless caused by inflicted trauma. This should raise your suspicion of child physical abuse. In general, children younger than 2 or 3 years old with suspected inflicted injuries should be evaluated with a skeletal survey.

2. A 6-year-old, pre-pubertal girl presents to the emergency department (ED) at midnight after her parents noticed malodorous vaginal discharge over the last 3 days after visiting her grandfather 2 weeks ago. The patient is tired and irritable at the time of presentation. Which of the following are indicated in the ED?
   - **a.** Empiric treatment for gonorrhea and chlamydia
   - **b.** Obtain a forensic interview.
   - **c.** Post-exposure prophylaxis for HIV.
   - **d.** Report to child protective services (CPS)

Answer: D. Genital discharge can be caused by both sexually transmitted and non-sexually transmitted infections, as well as other inflammatory processes. Several days of discharge implies a subacute timeframe for a potential abusive exposure. For subacute sexual abuse, ED management should include fulfilling the mandate to report to CPS and ensuring that the child has a safe disposition. A genital examination may be attempted in a cooperative patient and can assist in assuring the child that they are normal and healthy, but the examination should not be forced on the child if they are reluctant; it is unlikely to identify transient evidence of sexual contact. The detailed forensic interview should be conducted by a trained interviewer and may be deferred until the patient is rested. HIV PEP is unlikely to be effective 2 weeks after the assault. Empiric treatment for gonorrhea or chlamydia should not be given to pre-pubertal children until a sexually transmitted illness is definitively confirmed.

3. Which of the following implies multiple episodes of trauma at different times?
   - **a.** Bruises that are different colors.
   - **b.** Mixed density subdural hematoma on head CT.
   - **c.** Rib fractures with robust periosteal reaction are identified the day after a child presents with sudden coma and subdural hematoma.
   - **d.** Too numerous to count intraretinal hemorrhages and liver laceration with elevated hepatic transaminases

Answer: C. Periosteal reaction and other signs of fracture healing are not visualized until approximately 1 week after injury, and persist for weeks or months, whereas sudden coma implies an acute, traumatic event. Mixed-density subdural hematomas can be observed in the acute, subacute, and chronic phases. The color of bruises is affected by several factors in addition to the age of a bruise, including the child's complexion, depth of the bruise, natural variation, and even the perceptions of the observer. Too numerous to count intraretinal hemorrhages do not persist beyond a few days, but this could be consistent with a hepatic laceration.

4. Which of the following is very concerning for sexual abuse in a pre-pubertal child?
   - **a.** A new history of constipation and dilated anal sphincter (>1 cm)
   - **b.** An 8-year-old girl whose anogenital exam is completely normal reports that her camp counselor "put his wee-wee in my butt."
   - **c.** Erythema of the hymen and posterior fourchette.
   - **d.** Thin, fragile epithelium surrounding the labia with petechiae and subcutaneous bleeding.

Answer: B. A child's report of sexual abuse is highly concerning and is often the strongest evidence of abuse. A normal exam neither confirms nor excludes the possibility of sexual abuse, even with penetration. Dilation of the anal sphincter is nonspecific, especially in the setting of constipation. Like many mucosal tissues, erythema can occur for many reasons, including trauma, foreign bodies, lack of hygiene or even normal variation. "Cigarette-paper" skin with petechiae or hemorrhage suggests the presence of *lichen sclerosis et atrophicus*.

5. In a 2-week-old infant that is not yet crawling, which of the following is most highly concerning for abuse?
   - **a.** Clavicle fracture with callous
   - **b.** Lateral rib fracture with callous
   - **c.** Parietal skull fracture without callous
   - **d.** Torn lingual frenulum with scant bleeding

Answer: D. Lingual frenulum tears are very concerning for abuse in pre-mobile infants. These injuries heal quickly, and the presence of bleeding excludes the possibility of birth injury. Several self-limited injuries can result from the birth process, even in deliveries that are not recognized as particularly traumatic. These injuries can be clinically subtle and are not-uncommonly missed in the newborn nursery. Rib fractures are uncommonly seen from birth and are more common in larger infants or difficult deliveries. The presence of obvious callous on the rib fractures is consistent with a fracture that is at least 7 to 14 days old. Clavicle and skull fractures are not uncommon parturitional injuries. Unlike other fractures, skull fractures do not develop callous and their age cannot be estimated.

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Complications of Pregnancy

Megan C. Henn and Michelle D. Lall

KEY CONCEPTS

- Miscarriage is defined as the spontaneous termination of pregnancy before 20 weeks of gestational age.
- Approximately 25% of women experience some bleeding during pregnancy.
- Most miscarriages are due to uterine malformations or chromosomal abnormalities.
- Beta hCG discriminatory levels for detecting intrauterine pregnancy are usually considered to be 6500 mIU/mL for transabdominal ultrasonography and 1000 to 2000 mIU/mL for transvaginal ultrasonography.
- Treatment of the patient with incomplete miscarriage includes expectant management, medical management, or surgical evacuation.
- All patients with pregnancy loss require patient education, return precautions, and support through the grieving process.

Acute complications of pregnancy can appear in all trimesters and pose challenges in diagnosis and management for the emergency clinician. Life-threatening disorders, such as ectopic pregnancy in early pregnancy, pregnancy-induced hypertension in mid to late pregnancy, and abruptio placentae in late pregnancy, are relatively common. Emergency clinicians must consider the signs and symptoms, stage of pregnancy, and hemodynamic stability of the patient in developing diagnostic and treatment strategies.

PROBLEMS IN EARLY PREGNANCY

Miscarriage Foundations

Miscarriage, the most common serious complication of pregnancy, is defined as the spontaneous termination of pregnancy before 20 weeks of gestation. Fetal demise after 20 weeks of gestation or when the fetus is more than 500 g is considered premature birth. Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or gestational sac containing an embryo or fetus without fetal cardiac activity within the first 12 weeks and 6 days of gestation.

Early pregnancy loss is common, with 80% occurring in the first trimester, and it is seen in 10% of recognized pregnancies.[1] This estimation is likely low because it is difficult to measure those pregnancies lost before clinically confirmed but still recognized by the patient. Embryonic and fetal loss after implantation occur in up to one-third of detectable pregnancies. The risk of miscarriage rises with increasing maternal age (a fivefold increase in those >40 years compared with those 25 to 29 years), increasing paternal age, alcohol use, increased parity, history of prior miscarriage, poorly controlled diabetes mellitus and thyroid disease, obesity, low pre-pregnancy body mass index, maternal stress, smoking, alcohol, and caffeine consumption, and history of vaginal bleeding.

Approximately 25% of pregnant patients experience some bleeding. It is estimated that up to 50% of all women who have bleeding during early pregnancy miscarry before 20 weeks' gestation, although the risk is probably higher in the emergency department (ED) population.[2] Patients who have an intrauterine pregnancy with fetal cardiac activity visualized on ultrasound examination have a much lower risk of miscarriage (3% to 6%), although vaginal bleeding is a high-risk indicator, even when a viable fetus is present.[3] Those with a history of bleeding in singleton pregnancies who do not miscarry may have otherwise normal pregnancies, although they have an increased risk for preterm premature rupture of membranes, abruption, previa, stillbirth, and congenital abnormalities.[2]

Pathophysiology

Most miscarriages are due to uterine malformations or chromosomal abnormalities, which account for the majority that occur within 10 weeks of gestation. In some cases, the ovum never develops (anembryonic gestation). In most early miscarriages, fetal death precedes clinical miscarriage, often by several weeks. Although clinical symptoms of miscarriages are most common between 8 and 12 weeks of gestation, sonographic evidence in most cases demonstrates death before 8 weeks; if fetal viability can be demonstrated by cardiac activity and a normal sonogram, the subsequent risk of fetal loss decreases significantly.

Maternal factors that increase the risk of miscarriage include age greater than 30 years, congenital anatomic defects, uterine scarring, leiomyomas, and cervical incompetence. Other conditions associated with increased miscarriage rates include toxins (e.g., alcohol, tobacco, and cocaine), autoimmune factors, endocrine disorders, a prior history of miscarriage, and maternal infections.

Terminology

Miscarriage is broadly divided into four categories. The first is a *threatened miscarriage*, in which the patient presents with vaginal bleeding but is found to have a closed internal cervical os. The risk of miscarriage in this population is estimated at 35% to 50%, depending on the patient's risk factors and severity of symptoms. The second category is

an *inevitable miscarriage* when the internal os is open. The third is an *incomplete miscarriage*, where the products of conception are present at the cervical os or in the vaginal canal. The last category is a *completed miscarriage*, which occurs when the uterus has expelled all fetal and placental material, the cervix is closed, and the uterus is contracted. A gestational sac should be visualized for diagnosis because the cervix may close after an episode of heavy bleeding and clot passage without or after only partial expulsion of the products of conception. Unless an intact gestational sac is passed and recognized, a completed miscarriage is diagnosed only after dilation and curettage (D&C) with pathologic confirmation of gestational products, demonstration by sonography of an empty uterus with a prior known intrauterine pregnancy (IUP), or reversion to a negative pregnancy test result. This may take up to several weeks after the initial presentation.

Missed abortion is a relatively obsolete term referring to the clinical failure of uterine growth over time. Instead, the terms *anembryonic gestation* (when no fetus is visualized on ultrasound), *first-* or *second-trimester fetal death* (failure to see fetal cardiac activity with at least a 5-mm crown-rump length), and *delayed miscarriage* are more appropriate.

Clinical Features

Patient history should include the estimated length of the gestation, time since the last menstrual period, symptoms of pregnancy, including evolution or loss of pregnancy symptoms, degree and duration of bleeding, presence of cramps, pain, or fever, and attempts by the patient to induce miscarriage. Although the history is important, it is not helpful in the classification of the type of miscarriage. In addition, the severity of symptoms does not correlate well with the risk of miscarriage, although cramping and passage of clots are thought more likely to occur as the miscarriage becomes inevitable.

The assessment of the patient who experiences first-trimester vaginal bleeding includes a careful abdominal examination to evaluate for tenderness or peritoneal irritation from a potential ectopic pregnancy and to determine the size of the uterus, which should not be palpable abdominally. A pelvic examination is performed to evaluate whether the cervix is closed or open, look for clots or the products of conception, determine the degree of vaginal bleeding, and assess uterine size and tenderness.

In the patient with second- and third-trimester bleeding, cervical probing should not be done because the uterus is more vascular, and the organized placenta may overlie the cervical os. Parous women normally have an open or lax external os, which is a finding of no significance. The adnexa may be enlarged, often unilaterally, because the corpus luteum is cystic or because the pregnancy is ectopic. Adnexal or uterine tenderness should always raise the possibility of an ectopic pregnancy. Much less commonly, pelvic inflammatory disease can cause uterine and adnexal tenderness during early pregnancy.

Differential Diagnoses

Ectopic pregnancy can masquerade as a miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis. Even in the patient with painless vaginal bleeding, the diagnosis of ectopic pregnancy must be considered. Early ultrasonography is indicated to locate the pregnancy in the patient who has bleeding or pain.

A small amount of bleeding occurs at the time of implantation of the blastocyst into the endometrium and, occasionally, at the time of the first missed menses. Molar pregnancy is also characterized by vaginal bleeding, usually during the late first trimester or second trimester. This condition can be identified by ultrasonography. Cervical and vaginal lesions can also cause local bleeding and can usually be seen on vaginal inspection.

TABLE 173.1 Landmarks for Gestational Age and β-hCG Level by Transvaginal Ultrasonography

Finding	Weeks From LMP	β-hCG (mIU/mL)
Gestational sac (25 mm)	5	1000
Discriminatory zone	5–6	1000–2000
Yolk sac	6	2000
Upper discriminatory zone	6–7	3000
Fetal pole	7	5700
Fetal heart motion	6–7	7000

β-hCG, Beta subunit of human chorionic gonadotropin; *LMP*, last menstrual period.

Adapted from: Ramsey E, Shilitto J. How early can fetal heart pulsations be detected reliably using modern ultrasound equipment? *Ultrasound*. 2008;16:193-195; and Sohoni A, Bosley J, Miss JC. Bedside ultrasonography for obstetric and gynecologic emergencies. *Crit Care Clin*. 2014 Apr;30(2):207-226.

BOX 173.1 Sonographic Criteria for Abnormal Pregnancy With Transvaginal Ultrasonography

- No gestational sac at β-hCG level of 3000 mIU/mL
- No yolk sac with gestational sac of 13 mm (or at 32 days since last menstrual period)
- 5-mm crown-rump length, with no fetal heart tones
- No fetus, with gestational sac of 25 mm mean diameter
- No fetal heart tones after gestational age of 10–12 wk

β-hCG, Beta subunit of human chorionic gonadotropin.

Adapted from: Dart RG. Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. *Ann Emerg Med*. 1999;33:310-320.

Diagnostic Testing

A hemoglobin level is useful to provide a baseline measurement and evaluate the degree of blood loss in women whose bleeding persists. In addition, the Rh type should be determined. Ultrasonography is the primary means of evaluating the health of the fetus as well as its location (Table 173.1). Because historical and clinical estimations of gestational age are often inaccurate, ultrasonography is useful to provide an accurate measure of fetal age and viability (Box 173.1).

Serial quantitative hCG levels are used to assess the health of the fetus if sonographic findings are indeterminate or if the gestational age is less than 6 to 7 weeks. The sonographic discriminatory zone is defined as the quantitative hCG level at which a normally developing IUP should reliably be seen. Discriminatory levels are operator- and equipment-dependent and vary by individual patient characteristics, but are usually considered to be 6500 mIU/mL for transabdominal ultrasonography and 1000 to 2000 mIU/mL for transvaginal ultrasonography. Ultrasonography can be performed or repeated when hCG levels rise to 1500 to 3000 mIU/mL. If hCG levels are level or decline, or if sonographic criteria for fetal demise are demonstrated (Box 173.1), the patient should be referred to an obstetrician for follow-up to ensure miscarriage completion and to assess for subsequent complications. Expectant management may be sufficient in the stable patient with threatened miscarriage, as long as ectopic pregnancy has been excluded.

Management and Disposition

Threatened Miscarriage. After assessment of hemodynamic status and management of blood loss, a patient with a threatened miscarriage requires very little specific medical treatment. Though expert opinions vary as to whether anti-D immune globulin should be administered to Rh-negative patients after a threatened or spontaneous miscarriage, we recommend administering anti-D immune globulin in the ED to all pregnant patients with bleeding. If anti-D immune globulin is administered, a 50-µg to 120-µg dose is used during the first trimester and a full 300-µg dose after the first trimester. Once evaluated for ectopic pregnancy, the need for a follow-up routine ultrasonogram should be discussed with the patient; the patient should be made aware that the potential for ectopic pregnancy exists until it is excluded by identification of an IUP. In the patient who is planning pregnancy termination, prompt referral should be encouraged and chorionic villi confirmed at the time of uterine evacuation.

Unless an IUP is diagnosed, the patient with threatened miscarriage should be given careful instructions on discharge to return if she has signs of hemodynamic instability, pain, or other symptoms that might indicate ectopic pregnancy. In conjunction with gynecologic colleagues, an ED protocol is useful to determine when follow-up sonographic evaluation and serial hCG measurements should be obtained since ultrasonography can be an inaccurate diagnostic tool if the hCG level is below 1500 mIU/mL, vaginal bleeding is significant, or sonographic findings do not include a fetal pole or yolk sac. The patient must be given explicit return precautions and close obstetrical follow-up is essential. Typically, serial hCG measurements are obtained between 48 to 72 hours after the initial ED visit and follow-up sonographic evaluation is obtained within 3 to 7 days of ED presentation.

Fifty percent or more of women with threatened miscarriage who are seen in the ED ultimately miscarry, and there is no proven treatment to prevent miscarriage. In most cases, spontaneous miscarriage is the body's natural method of expelling an abnormal or undeveloped (blighted) pregnancy. Thus, a major goal of early management should be patient education and support. Patients should be advised that moderate daily activities do not affect the pregnancy. Tampons, intercourse, and other activities that might induce uterine infection should be avoided as long as the patient is bleeding, and she should return immediately for fever, abdominal pain, or an increase in bleeding. Cramping from a known IUP can be safely treated with acetaminophen or oral synthetic narcotics, if needed. If the patient passes tissue, it should be brought to a provider to be examined for products of conception because differentiation of fetal parts or villi from decidual slough or casts is difficult.

Patient counseling is paramount with threatened miscarriage and education of the ED staff on this topic is critical. Determination of fetal viability can be helpful in reassuring the mother or preparing her for probable fetal loss. Miscarriages are associated with a grieving process, which is frequently more difficult because early pregnancy is unannounced, and early fetal death is not publicly recognized. Because many women consider that minor falls, injuries, or stress during the first trimester can precipitate miscarriage, patients should be reassured that they have done nothing to cause miscarriage. Patients should be made aware that miscarriage is common, grieving is normal, and counseling may be beneficial. A follow-up appointment should be scheduled after miscarriage to support the patient in resolving such issues.

Incomplete Miscarriage. Treatment of the patient with incomplete miscarriage includes expectant management, medical management, or surgical evacuation. When the miscarriage is incomplete, the uterus may be unable to contract adequately to limit bleeding from the implantation site. Bleeding may be brisk, and gentle removal of fetal tissue from the cervical os with ring forceps during the pelvic examination often slows bleeding considerably. Manual uterine aspiration performed in the ED may also be appropriate in cases of brisk uterine hemorrhage as a result of early pregnancy loss or retained products of conception up to 12 weeks gestational age.[4]

Completed Miscarriage. Management of patients with presumed completed miscarriage is more complicated. If the patient brings passed tissue with her, this should be sent to the pathology department for evaluation. Unless an intact gestational sac or fetus is visualized, it is rarely clear clinically whether miscarriage is complete. In women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by ultrasonography, expectant management is safe, but only if ectopic pregnancy can be excluded. If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than 8 weeks, curettage is frequently unnecessary, and the patient can be safely observed by a gynecologist for serial hormonal assays. It is estimated that 65% of women with first-trimester miscarriage complete the miscarriage without intervention.[5] However, the need for later visits and procedures may be decreased by uterine curettage, particularly if the fetal pole or a gestational sac is visible on the sonogram at the time of evaluation. Medical management with misoprostol (800 µg intravaginal for one dose) instead of dilation and curettage is also an option and has a success rate of 80% to 91%.[5] The patient should be instructed to return if uncontrolled bleeding, severe pain or cramping, fever, or tissue passage occurs. Follow-up is recommended in 1 or 2 weeks to ensure that the miscarriage is complete.

After miscarriage, the patient should be advised that fetal loss can cause psychological stress. Follow-up in 1 or 2 weeks with a gynecologist should be provided. There is no conclusive evidence to support the use of antibioitics after D&C or miscarriage, and some evidence has suggested that the side effects of treatment may outweigh any potential benefit. For that reason, we do not recommend the routine use of antibiotics after a miscarriage. Ergonovine or methylergonovine (0.2 mg orally bid) can be used to stimulate uterine involution. The patient should be advised to return if signs of infection (e.g., fever, uterine tenderness) occur, bleeding resumes, or further tissue is passed.

Ectopic Pregnancy

KEY CONCEPTS

- An ectopic pregnancy can masquerade as a threatened miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis.
- Because the history and physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, pelvic ultrasonography and determination of serum hCG levels are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result.
- Ultrasonographic detection of an IUP is likely at hCG levels higher than 1500 to 2000 IU/L.

Foundations

Ectopic pregnancy is a pregnancy implanted outside the uterus, most commonly in the fallopian tube. It is increasing in frequency and the third leading cause of maternal death, responsible for 4% to 10% of cases.[6] Ectopic pregnancy is estimated to account for approximately 1% to 2% of all pregnancies, although national estimates of incidence are difficult to determine. Although the incidence of ectopic pregnancy is

BOX 173.2 Risk Factors for Ectopic Pregnancy

Tubal surgery (for tubal sterilization or ectopic pregnancy)
Pelvic inflammatory disease
Smoking
Advanced age
Prior spontaneous abortion
Medically induced abortion
History of infertility
Intrauterine device

Adapted from: Bouyer J, Coste J, Shojaei T, et al. Risk factors for ectopic pregnancy: A comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol.* 2003;157:185-194.

highest in women aged 25 to 34 years, the rate is highest among older women and women belonging to minority groups. Simultaneous intrauterine and extrauterine gestations (heterotopic pregnancy) have historically been rare, occurring in approximately 1 in 4000 pregnancies; women who have undergone assisted reproduction techniques with embryo transfer are at high risk of one of the pregnancies being ectopic. The incidence of ectopic pregnancy among women presenting to the ED with vaginal bleeding or pain in the first trimester is approximately 10%, but may be as high as 16%.[7]

Pathophysiology

Implantation of the fertilized ovum occurs approximately 8 or 9 days after ovulation. Risk factors for an abnormal site of implantation include prior tubal infection (50% of cases), anatomic abnormalities of the fallopian tubes, assisted reproduction (especially multiple embryo transfers), and abnormal endometrium (host factors). This results in failure of the embryo to implant in the endometrium. The risk of ectopic pregnancy increases approximately threefold after a patient has had pelvic inflammatory disease (PID). If the patient is currently using an intrauterine device (IUD), increased risk can occur from complicating PID or from failure of the IUD to prevent pregnancy while preventing endometrial implantation. All forms of contraception, except the IUD and tubal sterilization, decrease the incidence of ectopic pregnancy. After an ectopic pregnancy, the risk of a subsequent ectopic pregnancy can be as high as 22%, depending on the characteristics and treatment of the ectopic pregnancy (e.g., location of implantation, surgical vs. medical management; Box 173.2).[8]

When abnormal implantation occurs in the fallopian tubes, on the ovaries, or in the cervix, the pregnancy usually grows at a less than normal rate, which can result in abnormally low or declining hCG production. Even if exceedingly low, a single hCG measurement cannot exclude the diagnosis of ectopic pregnancy. Blood leaks intermittently through the tubal wall or out the fimbrial ends, with spillage into the peritoneal cavity. Bleeding and other symptoms are usually intermittent. Three outcomes are possible: spontaneous involution of the pregnancy, tubal abortion into the peritoneal cavity or vagina, or rupture of the pregnancy with internal or vaginal bleeding. Implantation in the uterine horn (cornual pregnancy) is particularly dangerous because the growing embryo can use the myometrial blood supply to grow larger (10–14 weeks of gestation) before rupture occurs. Cornual pregnancy accounts for 2% to 4% of all ectopic pregnancies and can be difficult to identify by ultrasonography.[9]

Clinical Features

The classic clinical picture of ectopic pregnancy is a history of delayed menses, followed by abdominal pain and vaginal bleeding in a patient with known risk factors. Unfortunately, this history is neither sensitive nor specific. Risk factors for ectopic pregnancy are absent in almost half of patients. Of patients with symptomatic ectopic pregnancy, 15% to 20% have not missed a menstrual period, and occasionally the patient has no history of vaginal bleeding. Abdominal pain varies and can be described as crampy, intermittent, severe, or even absent.

The physical findings in ectopic pregnancy are likewise variable. Vaginal bleeding, uterine or adnexal tenderness, or both in the patient with a positive pregnancy test result should trigger consideration of ectopic pregnancy. Tachycardia is not always present, even with significant hemoperitoneum; the hemoglobin level is usually normal, and hypotension may be seen. The presence of peritoneal signs, cervical motion tenderness, or lateral or bilateral abdominal or pelvic tenderness indicates an increased likelihood of ectopic pregnancy. If peritoneal irritation is present, pain can preclude an accurate bimanual examination. Adnexal masses are palpated in only 10% to 20% of patients with ectopic pregnancy.

Vaginal bleeding is often mild. Heavy bleeding with clots or tissue usually suggests a threatened or incomplete miscarriage, although the patient with an ectopic pregnancy who has decreasing hormonal levels may experience endometrial sloughing, which can be mistaken for passage of fetal tissue. Passed tissue should be examined, as with cases of miscarriage, in tap water or saline (or under low-power microscopy). Unless fetal parts or chorionic villi are seen, ectopic pregnancy should not be excluded in the patient with bleeding or passage of tissue.

Differential Diagnoses

The spectrum of clinical presentations in ectopic pregnancy is wide, so the differential diagnosis includes essentially all first-trimester complications. Threatened miscarriage, the most common alternative diagnosis, can be recognized by sonographic evidence of an IUP, healthy or failed. Hypovolemia may be seen, particularly in incomplete miscarriage, but hypotension without significant vaginal hemorrhage is highly suggestive of ectopic pregnancy. Identification of fetal parts or chorionic villi in tissue expelled or obtained during D&C is useful to confirm a complication of IUP, although this is not sufficient to exclude ectopic pregnancy in a patient with an increased risk of heterotopic gestation, such as the patient undergoing assisted reproduction treatment.

A ruptured corpus luteum cyst should also be considered in the first trimester when bleeding is associated with peritoneal pain or irritation. The corpus luteum normally supports the pregnancy during the first 7 or 8 weeks. Rupture causes pelvic pain and peritoneal irritation. Ultrasonography is helpful if it reveals an IUP (except in patients with in vitro fertilization). During early gestation, when ultrasonography is nondiagnostic, free fluid is usually visible by ultrasonography, and serial observation may be required. If the patient is unstable, especially if an IUP cannot be identified by ultrasonography, laparoscopy or in rare cases laparotomy, may be required to differentiate between the two conditions.

Diagnostic Testing

Because the history and physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, ancillary studies are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result. Ultrasonography and hormonal assays are the most commonly used ancillary tests and advances in these technologies have allowed for more accurate detection and exclusion of ectopic pregnancy in patients with first trimester bleeding or pelvic pain. Laparoscopy may be the most efficient diagnostic tool in the hemodynamically unstable patient.

Ultrasonography. Ultrasonography is the primary method used to locate early gestation, establish gestational age, and assess fetal viability.

Transabdominal ultrasonography is most useful for identification of IUPs with fetal cardiac activity and exclusion of ectopic pregnancy, except in patients at high risk for heterotopic pregnancy because of infertility procedures. Transvaginal ultrasonography is more sensitive, recognizes IUP earlier than transabdominal ultrasonography, and is diagnostic in up to 80% of stable patients presenting in the first trimester. Transvaginal ultrasound requires operator training and can be limited by device availability and quality.

As home pregnancy tests and access to early ultrasound becomes more prominent, the risk of having a "pregnancy of unknown location" by ultrasound rises. Indeterminate sonograms, which demonstrate neither an IUP nor extrauterine findings suggestive of ectopic pregnancy, occur in approximately 20% of ED evaluations of women with first-trimester bleeding or pain. Ectopic pregnancy is more likely among this subgroup with indeterminate sonograms if the hCG level is less than 1000 mIU/mL and the uterus is empty. Endometrial debris and fluid in the uterus do not exclude ectopic pregnancy.

An indeterminate ultrasound study usually does not result in a diagnosis of normal pregnancy. In one series of more than 1000 pelvic ultrasound examinations, 53% of indeterminate ultrasound studies resulted in a diagnosis of embryonic demise, 15% were ectopic pregnancies, and only 29% had an IUP. However, correlation of sonographic results with quantitative hCG measurements can add to the predictive value. With no intrauterine pregnancy on transvaginal ultrasound and hCG greater than 1500 mIU/mL, ectopic pregnancy should be suspected keeping in mind that ectopic pregnancies can be discovered at any level of hCG. Normal pregnancy is unlikely if no gestational sac is seen by transvaginal ultrasonography with an hCG level higher than 1000 to 2000 mIU/mL, depending on the institution's discriminatory zone. Additional ultrasound findings that may predict early spontaneous abortion include crown rump length or fetal heart rate below the fifth percentile and fetal heart rate below 130 beats per minute.[10] The differential diagnosis includes miscarriage and ectopic pregnancy in these patients. Unfortunately, levels of approximately 1500 mIU/mL develop in only approximately 50% of patients with ectopic pregnancies (see Table 173.1). Sonographic findings in a patient with suspected ectopic pregnancy are listed in Box 173.3 and illustrated in Figures 173.1 to 173.5.

Hormonal Assays. Quantitative hCG levels serve two primary functions—serial levels can be used in the stable patient who can be observed as an outpatient, and a single level can be correlated with sonographic results for improved interpretation. Beginning 8 or 9 days after ovulation, serum hCG levels normally double every 1.8 to 3 days for the first 6 or 7 weeks of pregnancy. An initial quantitative level can be measured at the time of the ED visit, particularly if the sonogram is indeterminate or gestational age is estimated as less than 6 weeks. A repeated level should be measured 48 to 72 hours later. A doubling or rise of hCG by 66% generally indicates a viable intrauterine pregnancy, however approximately 15% of normal IUPs have a minimal rise in hCG, requiring a third serial test. A rapid decline in hCG tends to indicate miscarriage whereas a slow decline can indicate an ectopic pregnancy.

Single quantitative hCG levels can also be useful in conjunction with ultrasonography; normal IUPs should be visible transvaginally at 1000 to 2000 mIU/mL hCG or higher (see Table 173.1). A benign course for ectopic pregnancy cannot be assumed with low hCG levels. Ruptured ectopic pregnancies requiring surgery have been reported with very low or absent levels of hCG.

Serum progesterone levels have been studied as an additional or alternative marker to determine which patients need further evaluation and follow-up for possible ectopic pregnancy though it is not a standard tool in the ED. The progesterone level rises earlier than the hCG level in normal pregnancy and plateaus with levels higher than 20 ng/mL, so measurement of serial levels over time is not necessary. Levels below 5 ng/mL exclude a viable IUP with rare exceptions and can be used in combination with serum hCG ratios at presentation and 48 hours. Patients determined to have low risk of ectopic pregnancy by this algorithm can avoid additional testing and be managed conservatively.[11] A progesterone level should be sent when the hCG levels are low, ultrasonography is indeterminate, and the emergency clinician is considering consultation for D&C or laparoscopy.

Other Studies. Dilation and evacuation can be used in patients without a viable IUP or ectopic pregnancy on ultrasonography to differentiate intrauterine miscarriage from ectopic pregnancy. Identification of chorionic villi in endometrial samples is seen in approximately 70% of patients and excludes ectopic pregnancy,

BOX 173.3 Sonographic Findings in the Patient With Suspected Ectopic Pregnancy

Diagnostic of Intrauterine Pregnancy
"Double" gestational sac
Intrauterine fetal pole or yolk sac
Intrauterine fetal heart activity

Diagnostic of Ectopic Gestation
Pregnancy in fallopian tube (see Fig. 173.1)
Ectopic fetal heart activity (see Fig. 173.2)
Ectopic fetal pole

Suggestive of Ectopic Gestation
Moderate or large cul-de-sac fluid without intrauterine pregnancy
Adnexal mass without intrauterine pregnancy[a]

Indeterminate
Empty uterus (see Fig. 173.3)
Nonspecific fluid collections (see Fig. 173.4)
Echogenic material
Abnormal sac (see Fig. 173.5)
Single gestational sac

[a] A complex mass is the most suggestive of ectopic pregnancy, but a cyst can also be seen with ectopic pregnancy.
Adapted from: Dart RG. Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. *Ann Emerg Med.* 1999;33:310-320.

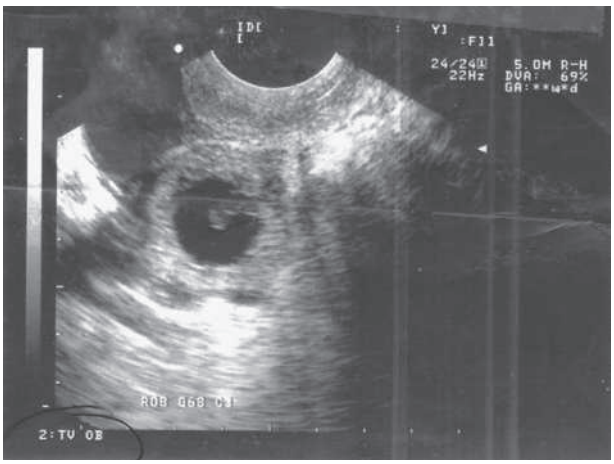

Fig. 173.1 Pregnancy in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

except in patients undergoing assisted reproduction. Identification of chorionic villi can be made, even in 50% of women with an empty uterus on ultrasonography, and limits the need for laparoscopy to exclude ectopic pregnancy in this population.

Although it is invasive, laparoscopy is extremely accurate as a diagnostic (and therapeutic) procedure for possible ectopic pregnancy. It is the diagnostic treatment of choice in unstable first-trimester patients with peritoneal signs and is also indicated in patients with peritoneal fluid or an ectopic gestation in the pelvic cavity. Medical alternatives for the management of ectopic pregnancy have resulted in decreased indications for laparoscopy in stable patients.

Management and Disposition

Unstable Patients. Approximately 20% of women with ectopic pregnancies manifest signs and symptoms warranting immediate intervention. This includes patients with hypovolemia, large amounts of peritoneal fluid, or an open cervical os. For patients with signs of hypovolemia, rapid volume resuscitation should be instituted with intravenous (IV) fluids and blood products as necessary, and a baseline hemoglobin level and type and crossmatch should be obtained. If the patient remains unstable, immediate surgery is warranted. Laparoscopy may be indicated for patients who stabilize with treatment or those who are hemodynamically stable but exhibit peritoneal signs on abdominal examination. One study has reported that identification of free fluid in the Morison pouch on bedside ultrasonography predicts the need for operative intervention in most cases in patients with suspected ectopic pregnancies. A D&C or evacuation procedure with examination of the endometrial contents for products of conception can be performed urgently in the unstable patient with an open cervical os. All patients with ectopic pregnancy who are Rh-negative should be given Rh immune globulin, 50 μg intramuscularly.

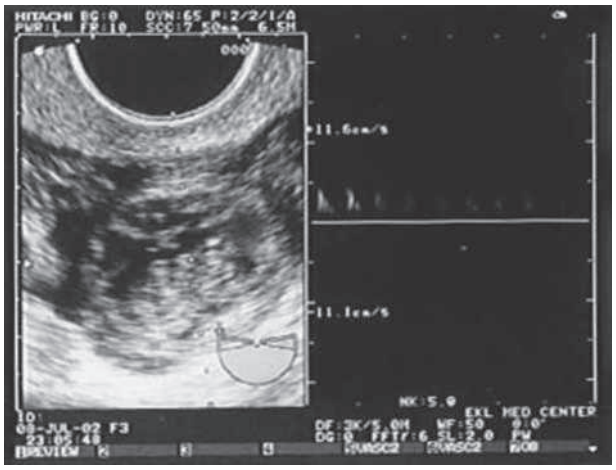

Fig. 173.2 Fetal heart movements detected by ultrasonography in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

Stable Patients. In stable patients with first-trimester bleeding, the goal is to exclude ectopic pregnancy in a timely manner. In the patient with pain by history or examination or risk factors for ectopic pregnancy, ultrasonography should be performed before discharge.

In low-risk patients with minor symptoms or bleeding, ectopic pregnancy is still a possibility. In most cases, ultrasonography is the initial screening tool because it provides the most accurate and rapid information (Fig. 173.6). If an IUP is not seen, quantitative hCG levels help risk stratify these patients. In all cases, if the patient is discharged, careful instructions are given for symptoms that would require her earlier return. An alternative strategy uses hCG levels first. However, waiting times for the serum assay can increase ED length of stay. In addition, ultrasonography is usually diagnostic of IUP or ectopic pregnancy, even if the hCG level is less than 1000 mIU/mL.

A minority of patients have indeterminate sonographic results and hCG levels below 1000 mIU/mL. When the hCG levels never rise to the discriminatory zone, the differential diagnosis includes intrauterine fetal demise and ectopic pregnancy. Early D&C with identification of the products of conception can be useful in the patient with nonrising hCG levels to detect chorionic villi and confirm a failed IUP or strongly suggest ectopic pregnancy. Alternatively, hCG levels can be followed until they reach zero, particularly if initial levels are low.

Although laparotomy may be required for patients who have an ectopic pregnancy, an increasing number of surgeries are being performed through the laparoscope. Salpingostomy is preferred to salpingectomy if the patient is stable and the procedure is technically feasible. Overall, the advent of transvaginal ultrasonography has resulted in earlier diagnosis and a trend toward nonoperative management.

Medical management is a safe and cost-effective treatment for the stable patient with minimal symptoms, especially when future fertility is desired. Methotrexate (50 mg/m2 IM or 1 mg/kg IM, alternating with folinic acid) is the drug most commonly used to treat early ectopic pregnancy. It interferes with fetal DNA synthesis and causes destruction of rapidly dividing fetal cells and involution of the pregnancy. Medical treatment is used most often for patients who are hemodynamically stable, with a

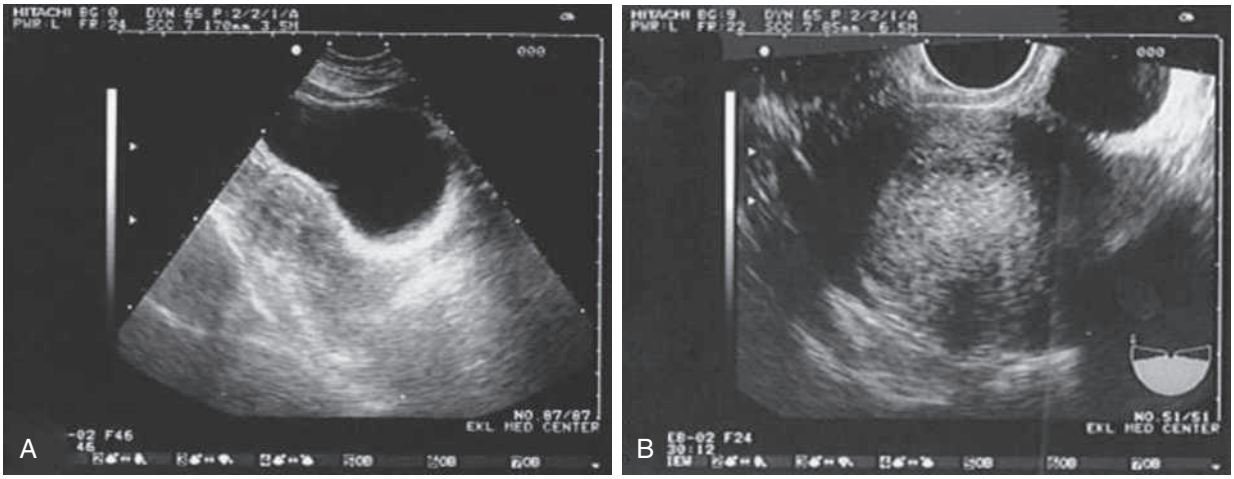

Fig. 173.3 Ultrasonogram showing an empty uterus, indeterminate for diagnosis of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

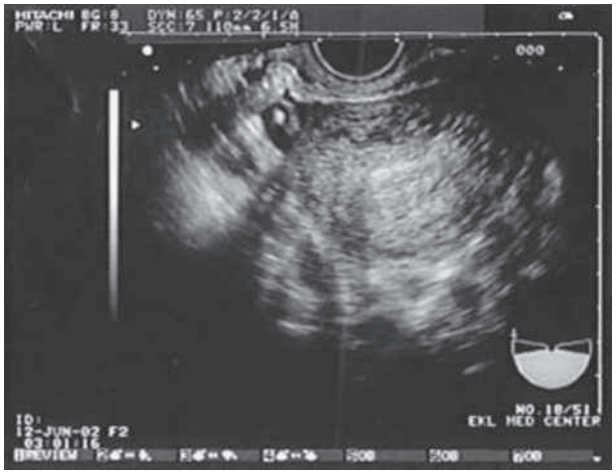

Fig. 173.4 Ultrasonogram showing fluid around the fallopian tube. (Courtesy Dr. Mary Ann Edens.)

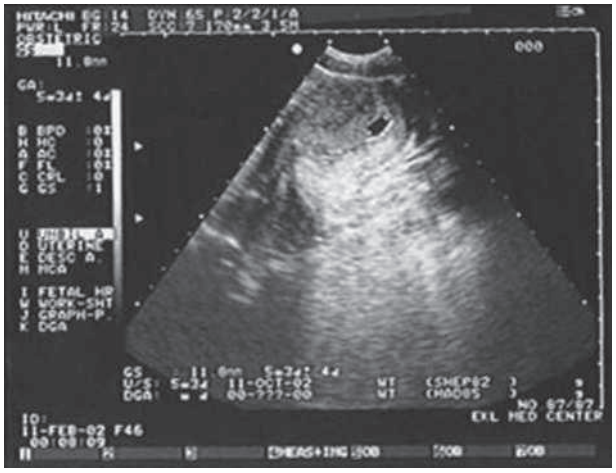

Fig. 173.5 Ultrasonogram showing a gestational pseudosac. (Courtesy Dr. Mary Ann Edens.)

tubal mass smaller than 3.5 cm in diameter, no fetal cardiac activity, and no sonographic evidence of rupture. Although there is no agreed on hCG cutoff for single-dose methotrexate, studies have suggested that increasing hCG levels are significantly correlated with methotrexate failure. Medical therapies are associated with an 85% to 93% success rate, with no significant difference between single- and multiple-dose protocols. Pelvic pain is common in patients receiving methotrexate (60%), even when it is used successfully. Indications of methotrexate failure and need for rescue surgery include decreasing hemoglobin levels, significant pelvic fluid, and unstable vital signs. All patients receiving methotrexate require close follow-up until the hCG level reaches 0, which may take 2 or 3 months.

Molar Pregnancy

Foundations

Molar pregnancy, also known as a hydatidiform mole, comprises a spectrum of diseases characterized by disordered proliferation of chorionic villi. In the absence of fetal tissue, the pregnancy is termed a *complete hydatidiform mole*. Complete moles are caused by the fertilization of an ovum without maternal DNA and the subsequent duplication of the haploid genome. The term *incomplete mole* refers to a mole that is caused by the fertilization of a normal ovum by two sperm. The duplication of the triploid karyotype causes some fetal tissue to be present, along with focal trophoblastic hyperplasia. In approximately

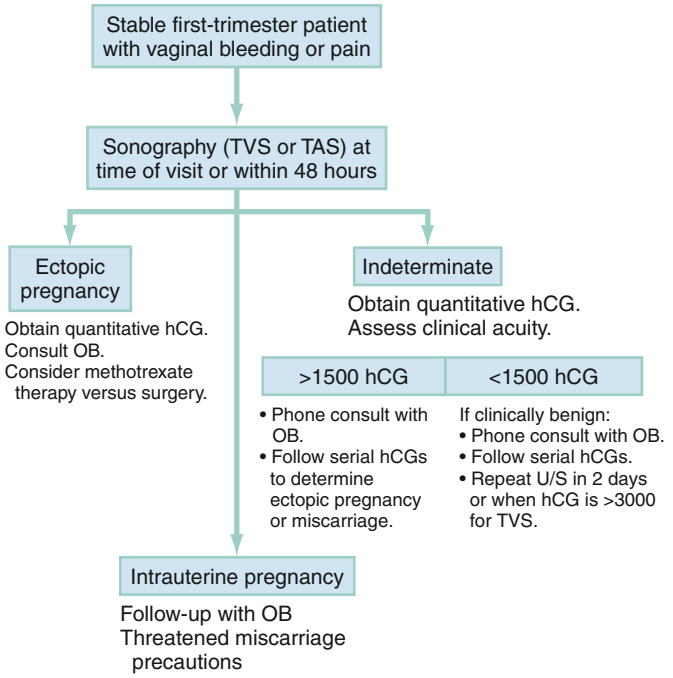

Fig. 173.6 Management of vaginal bleeding or pain in the stable first-trimester pregnant patient. *hCG,* Human chorionic gonadotropin; *OB,* obstetrics specialist; *TAS,* transabdominal sonography; *TVS,* transvaginal sonography; *U/S,* ultrasonography.

19% of molar pregnancies, neoplastic gestational disease develops, with persistence of molar tissue after the pregnancy has been evacuated.[12] Metastatic diseases can develop, requiring chemotherapy and intensive oncologic management.

Clinical Findings

Early molar pregnancy is usually not clinically apparent. The most well-described risk factor for the development of a molar pregnancy is extreme maternal age. Many patients present with abdominal pain, nausea and vomiting, or vaginal bleeding, and it may be difficult to differentiate these patients from those with threatened miscarriage or ectopic pregnancy by historical features alone. Patients sometimes seek treatment for apparent persistent hyperemesis gravidarum from high circulating levels of hCG, bleeding or intermittent bloody discharge, or respiratory distress; failure to hear fetal heart tones during the second trimester is the usual initial clue to diagnosis. If molar pregnancy spontaneously aborts, it is usually in the second trimester (before 20 weeks), and the patient or physician may note the passage of grapelike hydatid vesicles. Uterine size is larger than expected by date (by >4 weeks) in approximately 30% to 40% of patients. Theca lutein cysts may be present on the ovaries as a result of excessive hormonal stimulation, and torsion of affected ovaries can be seen.

Diagnostic Tests

The characteristic sonographic appearance of hydropic vesicles within the uterus, described as a snowstorm appearance, is highly suggestive of a diagnosis of molar pregnancy (Fig. 173.7). Alternatively, cystic changes are seen in partial molar pregnancies. In some cases, a partial molar pregnancy is detected only on pathologic examination of abortion specimens. Complications of molar pregnancy include preeclampsia or eclampsia, which can develop before 24 weeks of gestation, respiratory failure or distress from pulmonary embolization of trophoblastic cells, hyperemesis gravidarum, and uterine bleeding. Ultrasonography usually provides the diagnosis of a complete molar

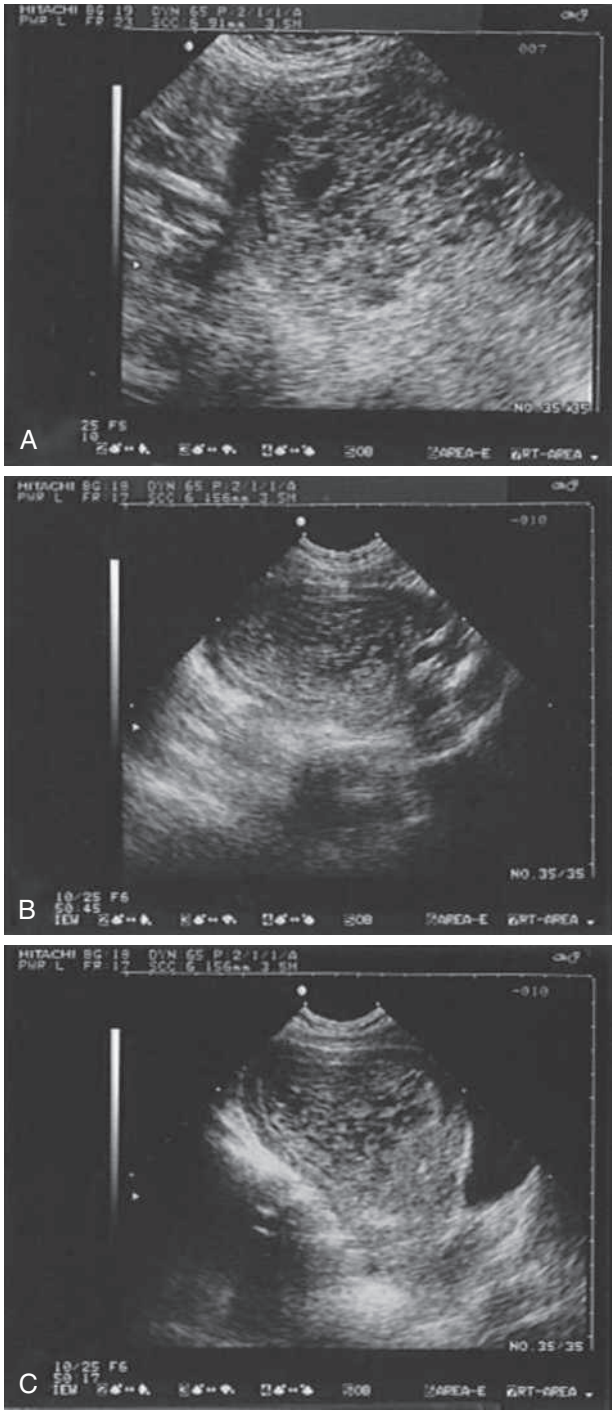

Fig. 173.7 Ultrasonogram showing molar pregnancy. (Courtesy Dr. Mary Ann Edens.)

pregnancy in the second-trimester patient who has "threatened miscarriage" or during sonographic assessment for fetal well-being and size. However, ultrasonography is only 58% sensitive, and diagnosis of a partial mole is made in only 17% of cases.[13] Up to two-thirds of molar pregnancies are diagnosed by pathologic specimens after miscarriage.

Management

Molar pregnancies are managed with uterine dilation and curettage (D&C). Following evacuation of a molar pregnancy, patients must be monitored in the outpatient setting for trophoblastic sequelae. Patients are at increased risk of an invasive mole, a benign tumor that invades the uterine wall and metastasizes to the lungs or vagina, or choriocarcinoma, a malignant tumor that invades the uterine wall and metastasizes to the lungs, brain, and liver via the patient's vasculature. Patients who present to the ED with complications of bleeding metastases are managed with a combination of chemotherapy, radiation, and surgery.

COMPLICATIONS OF LATE PREGNANCY

Vaginal Bleeding in Later Pregnancy

KEY CONCEPTS

- Bleeding during the second trimester (14 to 24 weeks) is not benign and is associated with a 33% risk of fetal loss. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity.
- The major conditions associated with vaginal bleeding in the second half of pregnancy include abruptio placentae and placenta previa. Patient history, physical examination, and results of ultrasonography can be used to distinguish them.
- All patients with painless, second-trimester vaginal bleeding should be assumed to have placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis has been excluded via ultrasound.
- Abruptio placentae consists of a wide spectrum of severity of symptoms and risk. Up to 20% of women will have no pain or vaginal bleeding. Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress.

Foundations

Bleeding during the second half of pregnancy occurs in approximately 4% of pregnancies. Only 20% of miscarriages occur after the first trimester, and the most important differential diagnoses after 12 to 14 weeks of gestation are abruptio placentae and placenta previa. The cause is often not determined, although occult marginal placental separations, which can be recognized only by placental inspection at delivery, are believed to come from a common source of bleeding above the cervix. Other causes of late vaginal bleeding include early labor, various cervical and vaginal lesions, lower genital tract infections, and hemorrhoids.

Bleeding during the second trimester before the fetus is potentially viable (14 to 24 weeks) is not benign. One-third of fetuses are ultimately lost when maternal bleeding occurs. Management is supportive and expectant because fetal rescue is not possible at this level of fetal immaturity. In the third trimester, vaginal bleeding is still associated with significant morbidity in approximately one-third of women; treatment includes consideration of urgent delivery.

Abruptio Placentae

Pathophysiology. Abruptio placentae is a separation of the placenta from the uterine wall and complicates roughly 1% of pregnancies. Small subclinical or marginal separations may go undetected until the placenta is examined at delivery and probably account for many of the other self-limited episodes of bleeding for which no diagnosis is made. In cases of nontraumatic abruptio placentae, spontaneous hemorrhage into the decidua basalis occurs, causing separation and compression of the adjacent placenta. Small amounts of bleeding may be asymptomatic and remain undetected until delivery. In other cases, the hematoma expands and extends the dissection. Bleeding may be concealed or may be clinically apparent if dissection occurs along the uterine wall and through the cervix. Placental separation may be acute or may be an indolent problem throughout late pregnancy.

Abruptio placentae is most clearly associated with maternal hypertension and preeclampsia. It is also more common with maternal age younger than 20 or older than 35 years of age, parity of three or more, unexplained infertility, history of smoking, thrombophilia, prior miscarriage, prior abruptio placentae, and cocaine use. Placental separation can also be associated with blunt trauma to the abdomen. In such cases, the cause appears to be shearing of a nonelastic placenta from the easily distorted elastic uterine wall at the time of traumatic impact. Intimate partner violence affects 4% to 8% of pregnancy and torso injuries are reported in 21.5% of cases placing the patient at risk for premature labor, abruption, uterine rupture, or fetal death. A significant etiology of trauma in pregnancy is motor vehicle accidents in which placental abruption may complication up to 40% of patients severely injured in a motor vehicle accident.[7]

Clinical Features. Vaginal bleeding occurs in 70% of patients with abruptio placentae. Blood is characteristically dark and the amount is often insignificant, although the mother may have hemodynamic evidence of blood loss. Uterine tenderness or pain is seen in approximately two-thirds of women; uterine irritability or contractions are seen in one-third. With significant placental separation, fetal distress occurs and the maternal coagulation cascade may be triggered, causing disseminated intravascular coagulation (DIC).

There is a wide spectrum of severity of symptoms and risk in placental separation. About 10% of women will present only with occult bleeding. Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress. Mild abruption is characterized by slight vaginal bleeding, little or no uterine irritability, absence of signs of fetal distress, and normal coagulation. As the separation becomes more extensive, it is associated with increased vaginal bleeding (or hidden maternal blood loss), increased uterine irritability with or without tetanic contractions, declining fibrinogen levels, evidence of fetal distress, and maternal tachycardia. In severe abruptio placentae (15% of cases), the uterus is tetanically contracted and very painful, maternal hypotension results from visible or concealed uterine blood loss, fibrinogen levels are less than 150 mg/dL, and fetal death can occur. Ultrasonography is insensitive in the diagnosis of abruptio placentae, often because the echogenicity of fresh blood is similar to that of the placenta. Symptomatic or even fetus-threatening abruption can occur in the presence of a normal sonogram.

Fetal distress and death occur in approximately 15% of patients with abruptio placentae by interruption of placental blood and oxygen flow. Risk of fetal death increases in proportion to the percentage of the placental surface involved and rapidity of separation. Fetal distress may result from the loss of placental blood flow, associated maternal hemorrhage (into the uterine cavity or externally), increased uterine tone, or resultant DIC. Maternal death can result, usually from coagulopathy or exsanguination. Fetomaternal transfusion can occur. Placental separation also predisposes the mother to amniotic fluid embolism.

Differential Diagnoses. The main alternative diagnosis in the woman with late-pregnancy bleeding is placenta previa, which is usually associated with painless, bright red bleeding and is excluded with ultrasonography. Lower genital tract or rectal lesions and blood-tinged cervical mucous plug are also considerations.

In the patient with abdominal pain but no vaginal bleeding, abruptio placentae with concealed hemorrhage must be distinguished from other causes of abdominal pain in later pregnancy—complications of preeclampsia, pyelonephritis, various liver diseases, gallbladder disease, appendicitis, and ovarian torsion. Uterine irritability caused by abruptio placentae can also be confused with early labor. If the patient has acute catastrophic hypotension, amniotic fluid embolus, with or without abruptio placentae, and uterine rupture must be considered.

Placenta Previa

Pathophysiology. Placenta previa, or implantation of the placenta over the cervical os, is the other major cause of bleeding episodes during the second half of pregnancy. The risk of placenta previa is increased with maternal age, smoking, multiparity, cesarean section, prior miscarriage or induced abortions, and preterm labor. Bleeding occurs when marginal placental vessels implanted in the lower uterine segment are torn, either as the lower uterine wall elongates or with cervical dilation near the time of delivery. Early bleeding episodes tend to be self-limited unless separation of the placental margin is aggravated by iatrogenic cervical probing or the onset of labor.

Clinical Features. Painless, fresh vaginal bleeding is the most common symptom of placenta previa. In approximately 20% of cases, some degree of uterine irritability is present, but this is generally minor. Vaginal examination usually reveals bright red blood from the cervical os. All patients with painless, second-trimester vaginal bleeding should be assumed to have placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis is excluded via ultrasound because this can precipitate severe hemorrhage in a patient with asymptomatic or minimally symptomatic placenta previa. Speculum examination of the vagina and cervix should be limited to an atraumatic partial speculum insertion to identify whether the bleeding is coming from the cervical os (and a presumed placenta previa), hemorrhoids, or a vaginal lesion that might not require urgent management.

Most cases of placenta previa identified during the mid-trimester resolve by the time of delivery as the lower uterine segment elongates and the placenta no longer overlaps the cervical os. Central or total previa, which occurs in approximately 20% of cases, can, however, cause severe hemorrhage, with the risk of exsanguination for the fetus and mother.

Diagnostic Testing. Ultrasonography is the diagnostic procedure of choice for localization of the placenta and diagnosis of placenta previa. Accuracy is excellent, but visualization of the placenta and of the internal cervical os is required. The bladder should be emptied before examination for suspected placenta previa to avoid overdiagnosis of placenta previa. Transvaginal ultrasonography is safe and even more accurate for visualization of the relationships between the placenta and internal os.

Management. Patients who experience vaginal bleeding during late pregnancy require immediate obstetric consultation and arrangements for safe transfer to an appropriate obstetric facility. Initial management consists of maternal stabilization, with establishment of two large-bore intravenous (IV) lines and fluid resuscitation, as well as continuous fetal monitoring, if available. A baseline hemoglobin level should be determined, and blood should be sent for type and crossmatch. Baseline coagulation studies, including platelet count, prothrombin time, and partial thromboplastin time, should be performed, and the fibrinogen level and presence of fibrin split products should be determined. The normal fibrinogen level in pregnancy is 400 to 450 mg/dL; values below 300 mg/dL indicate significant consumption of coagulation factors.

Blood loss requiring transfusion can occur in patients with placenta previa or abruptio placentae. Fresh-frozen plasma or fresh whole blood may be needed because of the potential for a coagulopathy. Fetomaternal hemorrhage can occur with abruption. If the Rh-negative patient has not yet received her routine Rh immune globulin prophylaxis at 28 weeks, 300 μg of Rh immune globulin should be administered within 72 hours. Transfer to the obstetric unit should be expedited if the patient is stable, or it should be done after initiation of resuscitation if she is unstable. If transfer to another hospital is required, a high-risk transfer team should be used if bleeding is significant or the fetus is in distress. Assessment is best accomplished by obstetricians who are

accustomed to the evaluation of late-pregnancy complications and who can perform an emergent cesarean section, if needed.

In the obstetrics unit, fetal monitoring is continued. Ultrasonography is used primarily to locate the placenta and diagnose placenta previa, but it may not be reliable in confirming the diagnosis of abruptio placentae. On occasion, subplacental hemorrhages of abruptio placentae can be seen, and changes in size of the collection can be monitored. If evidence of placenta previa is absent or equivocal, a vaginal examination is performed in the delivery suite, where an emergency cesarean section can be performed if uncontrolled bleeding is encountered.

Patients who have significant abruptio placentae may require early delivery—vaginal or surgical, depending on fetal status. If placenta previa is diagnosed or if abruptio placentae is considered mild, the patient is admitted for close monitoring. The goal is to support the patient, ideally until fetal maturity is demonstrated and a successful delivery can be accomplished.

Pregnancy-Induced Hypertension (Preeclampsia and Eclampsia)

KEY CONCEPTS

- Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher.
- Preeclampsia is gestational hypertension after 20 weeks gestational age with proteinuria (>300 mg/24 hr) or signs of end-organ damage; eclampsia is the occurrence of seizures in a patient with signs of preeclampsia.
- The HELLP syndrome is a particularly severe form of preeclampsia characterized by ***h***emolysis, ***e***levated ***l***iver enzyme levels (ALT and AST > 70 U/L), and ***l***ow ***p***latelet count (<100,000/mL).
- Because progression of preeclampsia to eclampsia is unpredictable and can occur rapidly, blood pressure control in the pregnant patient is of utmost importance.
- Magnesium sulfate has little antihypertensive effect but is the most effective anticonvulsant in the setting of eclampsia, preventing recurrent seizures while maintaining uterine and fetal blood flow.

Foundations

Hypertension is observed in up to 8% of pregnancies and is generally divided into several categories[14]:

- Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher.
- Preeclampsia is gestational hypertension with proteinuria (>300 mg/24 hr).
- Eclampsia is the occurrence of seizures in a patient with signs of preeclampsia. Progression of preeclampsia to eclampsia is unpredictable and can occur rapidly.
- Pregnancy-aggravated hypertension is chronic hypertension with superimposed preeclampsia or eclampsia.
- Chronic or coincidental hypertension is present before pregnancy or persists for more than 6 weeks postpartum.

Approximately 2% to 7% of pregnancies are complicated by pregnancy-induced hypertension. The incidence of actual eclampsia has progressively declined but is still one of the major causes of maternal mortality. The risk of pregnancy-induced hypertension is greatest in women younger than 20 years, primigravidas and those with twin or molar pregnancies, those with hypercholesterolemia, pregestational diabetes, or obesity, or those with a family history of pregnancy-induced hypertension.

Pathophysiology

Gestational hypertension or preeclampsia is a vasospastic disease of unknown cause unique to pregnant women. Vasospasm, ischemia, and thrombosis associated with preeclamptic changes cause injury to maternal organs, placental infarction and abruption, and fetal death from hypoxia and prematurity. The cause of eclampsia is unknown, but recent studies have centered on vascular responsiveness to endogenous vasopressors in the preeclamptic woman. Vascular responsiveness is normally depressed during pregnancy, which is a high-output, low-resistance state. Gestational hypertension is characterized by an even greater elevation in cardiac output, followed by an abnormally high peripheral resistance as clinical manifestations of the disease develop. In patients with preeclampsia, the cardiac output eventually drops as peripheral resistance rises. The cause of these changes is not known, but endothelial dysfunction is purported to release vasoactive mediators and result in vasoconstriction. Antiplatelet agents during pregnancy have been reported to reduce the risk of development of preeclampsia, supporting the premise of an imbalance between levels of thromboxane and prostacyclin in preeclampsia.[14]

The vasospastic effects of gestational hypertension and preeclampsia are protean. The intravascular volume is lower than in normal pregnancy, central venous pressures are normal, and capillary wedge pressures are variable. Liver effects are believed to be due to hepatocellular necrosis and edema resulting from vasospasm. Renal injury causes proteinuria and may result in decreased glomerular filtration. Microangiopathic hemolysis may result from vasospasm, causing thrombocytopenia. Central nervous system (CNS) effects include microvascular thrombosis and hemorrhage, as well as focal edema and hyperemia.

Clinical Features

Signs and Symptoms. The patient with gestational hypertension has mild systolic or diastolic blood pressure elevation, no proteinuria, and no evidence of organ damage. Mental status assessment, testing of reflexes, abdominal examination, liver function studies, and coagulation studies yield normal results. Preeclampsia is associated with kidney changes and, in severe cases, other end-organ symptoms. Edema is often difficult to assess because pregnancy is normally associated with excess extracellular fluid and dependent edema, and it is no longer used as a criterion for preeclampsia. Proteinuria (300 mg/24 hr) is variable at any given time and may not be detectable in a random urine specimen.

In cases of severe preeclampsia, the diastolic blood pressure can exceed 110 mm Hg, proteinuria is more severe, and there is evidence of vasospastic effects in various end organs. CNS effects commonly include headache or visual disturbances. In preeclampsia, the patient will become hyperreflexive before seizures develop. Thrombocytopenia may be present, liver function test findings may be elevated, and the liver is often tender. Renal dysfunction may be indicated by oliguria and elevated creatinine levels in addition to proteinuria.

Complications

The HELLP syndrome, a particularly severe form of preeclampsia that develops in 5% to 10% of women who have preeclamptic symptoms, is characterized by ***h***emolysis, ***e***levated ***l***iver enzyme levels (alanine transaminase [ALT] and aspartate transaminase [AST] > 70 U/L), and ***l***ow ***p***latelet count (<100,000/mL). Prothrombin time, partial thromboplastin time, and fibrinogen are normal, and blood studies reveal microangiopathic hemolytic anemia. Other complications of preeclampsia include spontaneous hepatic and splenic hemorrhage and abruptio placentae.

The most dangerous complication is eclampsia, which is the occurrence of seizures or coma in the setting of signs and symptoms of

preeclampsia. Warning signs for the development of eclampsia include headache, nausea and vomiting, and visual disturbances. Elevated total leukocyte count, creatinine, and AST levels are also predictive of increased morbidity for the patient with severe preeclampsia. Particularly in early eclampsia before 32 weeks of gestation, seizures may develop abruptly, and hypertension may not be associated with edema or proteinuria. In postpartum women who have eclampsia, more than half (55%) have not been previously diagnosed with preeclampsia, and patients may present with headache, vision changes, elevated blood pressure, and seizures, often within 48 hours of delivery, but in up to 6 weeks after delivery and in rare cases up to 12 weeks postpartum.[15] After 48 hours postpartum and without predelivery signs of preeclampsia, other diagnoses, such as intracranial hemorrhage, should be considered. Maternal complications of eclampsia include permanent CNS damage from recurrent seizures or intracranial bleeding, renal insufficiency, and death.

The maternal mortality rate from eclampsia has been reduced to less than 1% with modern management. Perinatal mortality has also decreased, although it remains at 4% to 8%.[14] Causes of neonatal death include placental infarcts, intrauterine growth retardation, and abruptio placentae. In addition, fetal hypoxia from maternal seizures and the complications of premature delivery contribute significantly to fetal morbidity and mortality.

Differential Diagnoses

Peripheral edema is common in normal pregnancy, and it may be difficult to differentiate normal edema from that of early preeclampsia. Differentiation of gestational hypertension from preexistent hypertension is often impossible if no record of normal blood pressure is available. Seizures during pregnancy may be due to epilepsy as well as other intracranial catastrophes, such as thrombosis or hemorrhage.

Diagnostic Testing

The patient who has severe preeclampsia should have an IV line and fetal monitoring initiated. Blood testing includes a complete blood cell count, renal function studies, liver function tests, platelet count, coagulation profile, and a baseline magnesium level. The serum glucose concentration is determined in patients with seizures.

If a history of preeclampsia is not obtained or the symptoms are refractory to magnesium sulfate therapy, a computed tomography (CT) scan of the head is performed to exclude cerebral venous thrombosis or an intracranial hemorrhage, either of which can occur in pregnancy—with or without pregnancy-induced hypertension—and may require specific treatment. CT scan abnormalities can be seen in 50% of patients with eclampsia. Patchy hemorrhage and microinfarcts of the cortex are characteristic and may be due to loss of cerebral autoregulation in patients with severe pregnancy-related hypertension. Diffuse cerebral edema can also be seen.

Management

Mild Preeclampsia. The management of patients with mild preeclampsia includes documentation of blood pressure, reflexes, weight, and blood testing to ensure normal end-organ function. Accurate determination of gestational age by ultrasonography is needed to allow optimal management if symptoms progress. Limitation of physical activities, including bed rest, is the only demonstrated means of reducing blood pressure and allowing the pregnancy to be sustained longer. Definitive treatment is delivery of the fetus, although expectant management is standard in women at less than 34 weeks of gestation. Arrangement for close follow-up is important for patients who are not hospitalized.

Severe Preeclampsia. Hospitalization is recommended for patients with sustained hypertension above 140/90 mm Hg and signs of severe preeclampsia. Baseline laboratory studies are recommended to identify end-organ effects in the liver, kidney, and hematologic systems. Both diuresis and antihypertensive therapy have been remarkably unsuccessful in improving fetal outcome or prolonging pregnancy. However, admission does allow the obstetrician to assess fetal age and well-being accurately, maternal organ function, and effect of bed rest on blood pressure before the optimal timing of delivery is decided.

Fulminant or severe preeclampsia, with marked blood pressure elevation (≥160/110 mm Hg) associated with epigastric or liver tenderness, visual disturbance, or severe headache, is managed in the same way as eclampsia (Box 173.4). The goal is prevention of seizures and permanent damage to maternal organs. Magnesium sulfate is given for seizure prophylaxis.

Seizures and coma are the hallmarks of eclampsia, the ultimate consequence of preeclampsia. As in all seizure patients, hypoglycemia, drug overdose, and other causes of seizures should be excluded with appropriate tests. Eclamptic seizures are controlled in almost all patients by administering magnesium sulfate, although the mechanism of action remains elusive. Magnesium has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. The goals of magnesium sulfate therapy are to terminate ongoing seizures and prevent recurrence. An IV loading dose of 4 to 6 g magnesium given over 15 to 20 minutes, followed by 2 g/hr IV, is recommended. Magnesium administration should be accompanied by clinical observation for loss of reflexes (which occurs at ≈10 mg/dL) or respiratory depression (which occurs at levels of 12 mg/dL, although actual serum magnesium levels are rarely monitored). The infusion should be stopped if signs of hypermagnesemia (loss of reflexes or respiratory depression as manifest by a decrease in the respiratory rate or an increase in end tidal CO_2 are seen. IV calcium gluconate, 1 g given slowly, will reverse the adverse effects of hypermagnesemia.

Despite ongoing controversy, the familiarity with magnesium sulfate and its physiologic advantages to the fetus, wide margin of safety, and high success rate in controlling seizures make it the first-line drug in patients with eclampsia. If seizures persist after the recommended doses of magnesium sulfate have been administered, the following agents may be used in the treatment of eclampsia in conjunction with

BOX 173.4 Management of Eclampsia and Severe Preeclampsia

- Control seizures with magnesium sulfate, 4–6 g given over 15–20 minutes, followed by 2 g/hr IV.
- Control hypertension after seizure control if diastolic blood pressure >105 mm Hg; hydralazine (5–10 mg IV push, repeat q 2-4h) or labetalol (20 mg IV bolus, repeat q10 min PRN up to 300 mg/total dose)
- Obtain initial laboratory studies to assess organ injury:
  - Complete blood count and platelet count
  - Liver function tests
  - Blood urea nitrogen, creatinine
- Monitor urine output; maintain at >25 mL/hr.
- Limit intravenous fluid administration unless significant losses occur.
- Avoid diuretics and hyperosmotic agents.
- Perform a computed tomography scan of the head if consciousness is decreased or seizures persist, lateralizing signs are present, or there are other concerns.
- Initiate steps to delivery.

Adapted from: Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. *Am J Obstet Gynecol.* 1984;148:951-963.

obstetric consultation: lorazepam (2–4 mg IV for one dose, may repeat ×1 after 10–15 min), phenytoin or fosphenytoin (15–20 mg/kg IV ×1, may repeat at 10 mg/kg after 20 min), or levetiracetam (20–60 mg/kg IV, may repeat in 12 hours). In addition, a careful search for other causes of seizures (e.g., hypoglycemia and intracranial hemorrhage) should be instituted based on history and examination of the patient.[16]

Although magnesium sulfate is not a direct antihypertensive, the hypertension associated with eclampsia is often controlled adequately by stoppage of the seizures. Rapid lowering of blood pressure can result in uterine hypoperfusion, so specific antihypertensive treatment is initiated only if the diastolic blood pressure remains above 105 mm Hg or the systolic blood pressure remains above 160 mm Hg after control of seizures.[17] The goal is to lower maternal blood pressure by 15% to 20% with a systolic goal of 140 to 150 mm Hg and a diastolic goal of 90 to 100 mm Hg. Many patients do not require specific antihypertensive treatment after treatment with magnesium sulfate. The antihypertensives used most often by obstetricians are hydralazine (5–10 mg IV push, repeat q 2-4h) or labetalol (20 mg IV bolus, may repeat q10 min PRN up to 300 mg/total dose). Rapid-release nifedipine (10 mg PO) can be used if IV access is not immediately available. Other antihypertensive agents have not been well studied in this population because there are specific risks to uncontrolled lowering of blood pressure and loss of uteroplacental blood flow.

Although total body water in the eclamptic patient is excessive, intravascular volume is contracted, and the eclamptic patient is sensitive to further volume changes. Hypovolemia results in decreased uterine perfusion. Thus, diuretics and hyperosmotic agents should be avoided in these patients. Invasive monitoring has demonstrated that vasospasm is not reversed with IV fluid administration. Rather, excessive IV fluids increase extravascular fluid stores that are difficult to mobilize postpartum, resulting in a higher incidence of pulmonary edema in patients treated aggressively with fluid therapy. Invasive pulmonary artery pressure monitoring may be required for accurate fluid management in the eclamptic patient.

Amniotic Fluid Embolus

KEY CONCEPTS

- Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden onset of hypotension, hypoxia, and coagulopathy.
- Treatment of amniotic fluid embolus consists of supplemental oxygenation and ventilation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy.

Foundations

Amniotic fluid embolus is the release of amniotic fluid into the maternal circulation. This occurs during intense uterine contractions or uterine manipulation at areas of placental separation from the uterine decidua basalis (abruptio placentae) and triggers a rapidly fatal, anaphylactoid-type maternal response. Although amniotic fluid embolus usually occurs during labor, with the maternal mortality rate at 25% or higher, it can also occur after induced abortions, miscarriages, and spontaneously during the second and third trimesters. Amniotic fluid embolus can also occur after amniocentesis or in association with abruptio placentae after abdominal trauma. Although it is a rare syndrome, amniotic fluid embolus is the leading cause of cardiovascular collapse during labor.

Clinical Features

Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy. The embolization of amniotic fluid and the particulate matter suspended in it triggers a profound immunologic response when it enters the maternal circulation. The list of proposed mediators is extensive and includes histamine, endothelin, and leukotrienes. In survivors, DIC, acute respiratory distress syndrome, and left ventricular dysfunction develop. An initial seizure is seen in approximately 20% of patients. Bleeding diathesis may be the initial sign in some women, and DIC occurs in approximately 50% of cases.

Differential Diagnoses

Catastrophic pulmonary embolus, drug-induced anaphylaxis, and septic shock must be considered in the differential diagnosis. Seizures occur in patients with eclampsia, but hypertension rather than cardiovascular collapse is usually observed in that condition. Coagulopathy may be seen in patients with preeclampsia (HELLP syndrome), abruptio placentae, or other chronic coagulopathies seen in the nonpregnant patient.

Diagnostic Testing

When amniotic fluid embolus is suspected, a complete blood cell count, coagulation studies, arterial blood gas analysis, and chest radiograph are obtained. Urine output is monitored after urinary catheter placement. The diagnosis is usually made with certainty only at autopsy, with the finding of fetal hairs, squamous cells, and debris in the maternal circulation. Because squamous epithelial cells can be seen normally in the maternal pulmonary circulation, the typical clinical syndrome is also required for diagnosis.

Management

Amniotic fluid embolus is uncommon, so treatment recommendations are anecdotal and based on animal studies. The most helpful modalities appear to be high-flow oxygen, support of ventilation and oxygenation with intubation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy. Treatment usually requires invasive hemodynamic monitoring in an intensive care unit.

Rh (Anti-D) Immunization in Pregnancy

KEY CONCEPTS

- Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. To prevent this, a dose of 50 μg of Rh immune globulin can be used if the patient less than 12 weeks of gestation. After 12 weeks, a 300-μg dose is recommended.

Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. Sensitization occurs in up to 15% of Rh-negative women carrying Rh-positive fetuses. Small numbers of fetal cells enter the maternal circulation spontaneously throughout pregnancy, and the maternal immune system is triggered by as little as 0.1 mL of fetal-maternal hemorrhage. Fetal-maternal hemorrhage occurs in 3% to 11% of women with threatened abortions in the first trimester and approximately 45% during birth in the third trimester. To prevent this, anti-D immune globulin (RhoGAM) is routinely administered to Rh-negative mothers—if the father is Rh positive or his status is unknown—at approximately the 28th week of gestation to protect

the mother from spontaneous sensitization, which occurs during the third trimester, and at the time of delivery. Transplacental hemorrhage can also occur during uterine manipulation, threatened miscarriage (even without fetal loss), spontaneous miscarriage, surgery for ectopic pregnancy, and amniocentesis, although the risk is not clear. Anti-D immune globulin should be administered when these events occur. A dose of 50 μg can be used if the patient is at less than 12 weeks of gestation, although many pharmacies carry only the 300-μg dose, which can also be given. After 12 weeks, a 300-μg dose should be given. The half-life of immune globulin is 24 days, and it needs to be administered within 72 hours of a sensitization event to prevent antibody development.

The Kleihauer-Betke test of maternal blood has been used to detect fetal cells in the maternal circulation. Unfortunately, the test is difficult to perform, not immediately available in most emergency laboratories, and only sensitive enough to detect 5 mL of fetal cells in the maternal circulation. Because only 0.1 mL of fetal cells is required to sensitize the mother, routine immune globulin administration has been recommended in situations likely to result in sensitization. Patients with third-trimester bleeding are not at increased risk of sensitization compared with patients with normal pregnancy. Thus, RhoGAM should be administered only if the patient did not receive her prophylactic dose at 28 weeks. In cases of blunt trauma to the uterus, the Kleihauer-Betke test should be ordered to detect the rare, large fetal transfusions that may require specific fetal blood therapy or administration of additional immune globulin to the mother. The standard dose (300 μg) is sufficient to prevent maternal immunization for fetal transfusions of up to 15 mL of red blood cells or 30 mL of whole blood.

MEDICAL AND SURGICAL PROBLEMS IN THE PREGNANT PATIENT

Clinicians should be aware of a variety of illnesses, related and unrelated to pregnancy, that may have altered symptoms, risk, and treatment in the pregnant patient (Tables 173.2 and 173.3). See also Chapter 174.

Abdominal Pain

KEY CONCEPTS

- Appendicitis is the most common surgical emergency in pregnancy. Clinical presentations may be atypical, leading to a misdiagnosis rate of 30% to 35% in pregnant patients. Right lower quadrant pain is the most common finding, especially early in pregnancy. Ultrasound, CT, and MRI are useful for the diagnosis.
- Cholelithiasis presents with similar symptoms to those in nonpregnant women and is similarly diagnosed through ultrasound. Surgery, if required, is optimally performed during the second trimester.
- During pregnancy, albumin levels decrease while alkaline phosphatase levels may increase up to double; amylase levels may also be slightly elevated.
- Hepatitis is the most common cause of liver disease in pregnancy; hepatitis E has increased maternal mortality and rate of fetal loss.
- Acute fatty liver of pregnancy is a rare disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. Coagulopathy, jaundice, seizures, DIC, and hepatic encephalopathy may also result.
- Intrahepatic cholestasis of pregnancy typically presents with generalized pruritus and mild jaundice. Resolution occurs with delivery. Women are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.

TABLE 173.2 Differential Diagnosis of Abdominal Pain in Pregnancy

Diagnosis	Gestational Age	Signs/Symptoms/ Diagnostic Testing
Gynecologic		
Miscarriage	<20 wk; 80% <12 wk	Vaginal bleeding, pelvic pain, ultrasonography to confirm location, no fetal activity at 8 weeks, decreasing hCG level
Septic abortion	<20 wk	Fever, uterine tenderness
Ectopic pregnancy	<14 wk	Pelvic pain, hypotension
Corpus luteum cyst	<12 wk	Sudden focal peritoneal pain; no fever
Ovarian torsion	Especially <24 wk	Ischemic pain, episodic
Pelvic inflammatory disease	<12 wk	Very rare, pelvic pain, vaginal discharge
Chorioamnionitis	>16 wk	Tender uterus, fever, amniocentesis reveals white blood cells
Abruptio placentae	>16 wk	Focal uterine tenderness, fetal distress, variable bleeding
Preeclampsia	>20 wk	Hypertension, proteinuria, edema, right upper quadrant pain
Nongynecologic		
Appendicitis	Throughout	Guarding may be less prominent; location changes
Cholecystitis	Throughout	Confirm with ultrasonography
Hepatitis	Throughout	Confirm with liver function tests
Pyelonephritis	Throughout	Flank pain, fever, positive catheterized urinalysis

Appendicitis

Foundations. Appendicitis is the most common surgical emergency in pregnant patients. The incidence of appendicitis in pregnant patients is the same as that in nonpregnant patients, but delays in diagnosis contribute to an increased rate of perforation, which may result in fetal mortality and maternal morbidity. There is also an increased rate of other complications of appendicitis in pregnancy. A large, population-based study found an almost twofold increase in sepsis and septic shock, transfusion, pneumonia, bowel obstruction, postoperative infection, and length of stay longer than 3 days.[18] During the first half of pregnancy, diagnostic findings are usually similar to those in the nonpregnant woman, but the clinical picture becomes more atypical during the second half of pregnancy.

Traditionally, the appendix was thought to be displaced counterclockwise out of the right lower quadrant after the third month of gestation, with its ultimate location deep in the right upper quadrant, superior to the iliac crest (Fig. 173.8). However, even in the third trimester, the location changes from the right lower quadrant in less than 25% of pregnant patients. Displacement of the abdominal wall away from the abdominal viscera can result in difficulty in palpation of organs and loss of signs of parietal peritoneal irritation. The physiologic increase in white blood cell count and erythrocyte sedimentation rate in pregnancy should also be considered in the evaluation of the patient with possible appendicitis because these may confuse the overall clinical picture.

TABLE 173.3 Differential Diagnosis of Common Symptoms in Pregnancy

Diagnosis	Gestational Age	Signs, Symptoms, Diagnostic Testing
Vaginal Bleeding		
Miscarriage	<20 wk	Vaginal bleeding, pelvic pain, ultrasonography to confirm location, no fetal activity at 8 weeks, decreasing hCG level
Ectopic pregnancy	<14 wk	Pelvic pain, hypotension, evaluate with ultrasonography
Molar pregnancy	12-24 wk	No fetal heart tones, characteristic sonogram showing snow storm appearance
Cervical lesions	Throughout	Perineal and vaginal inspection
Vaginitis, cervicitis	Throughout	White blood cells on wet mount, with culture
Placenta previa	>16 wk	Ultrasonography to localize placenta
Abruptio placentae	>16 wk	Focal uterine tenderness, fetal distress, variable bleeding
Seizure		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; usually history of PIH, edema, proteinuria
Amniotic fluid embolus	>12 wk	Hypotension, respiratory distress, DIC
Epilepsy	Throughout	History; lack of PIH findings
Dyspnea		
Pulmonary embolus	Especially 6 wk prepartum and postpartum	Usual diagnostic studies including use of CT, Ventilation/perfusion studies, and extremity doppler ultrasound
Dyspnea of pregnancy	>24 wk	Exclude other causes
Pulmonary infection	Throughout	Examination; radiography
Amniotic fluid embolus	>12 wk	Uterine manipulation, bleeding diathesis, hypotension
Jaundice		
Cholestasis of pregnancy	>24 wk	Well patient; itching and jaundice
Hepatitis	Throughout	Abnormal liver function test results
Acute fatty liver	>24 wk	Rapid liver failure; coma, seizures, hypoglycemia
Bleeding Diathesis		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; proteinuria, edema, HELLP syndrome
Amniotic fluid embolus	>12 wk	Respiratory distress, cardiovascular collapse
Abruptio placentae	>20 wk	Uterine tenderness; vaginal bleeding; fetal distress

DIC, Disseminated intravascular coagulation; *hCG,* human chorionic gonadotropin; *HELLP,* hemolysis, elevated liver enzyme levels, low platelets; *PIH,* pregnancy-induced hypertension.

Clinical Features. The gastrointestinal symptoms of appendicitis, such as anorexia, nausea, and vomiting, mimic those of pregnancy, particularly during the first trimester, making such symptoms relatively nonspecific. Right-sided abdominal pain is the most constant finding, although this is less reliable later in pregnancy. Peritoneal signs are also most common during the first trimester. The absence of fever, leukocytosis, or tachycardia has been reported. The lack of these clinical findings in pregnant patients with appendicitis may be the result of a blunted inflammatory response caused by elevated maternal levels of pregnancy-related steroids. Pyuria without bacteriuria may be seen

These confounding factors contribute to the misdiagnosis rate for appendicitis of 30% to 35% overall in pregnancy, with a 40% to 50% rate of removal of normal appendix during the third trimester. In contrast to the relative safety of performing an exploratory laparotomy or laparoscopy during pregnancy, the risk of fetal loss and maternal morbidity from failure to diagnose appendicitis and perforation is considerable, so clinical vigilance is required, even in the absence of classic signs. In one study, in the setting of acute appendicitis, the relative risk of pregnancy loss at less than 20 weeks was 5.3, and was 6.0 at less than 24 weeks.[19] In later pregnancy, when peritoneal signs are often absent and the uterus obscures normal physical findings, diagnosis is frequently delayed, and the perforation rate may approach 25%.

Differential Diagnoses. Pyelonephritis, cholecystitis, nephrolithiasis, and pregnancy-related diseases such as ectopic pregnancy, round ligament pain, broad ligament pain, corpus luteum cyst leakage, and ovarian torsion should be considered in the patient who has right-sided abdominal pain. Pyelonephritis is the most common condition that is confused with appendicitis. During its migration, the appendix is located very near the kidney, resulting in a high incidence of sterile pyuria and flank pain (see Fig. 173.8). In cases of appendicitis, unless there is coincident urinary tract infection, the urine is free of bacteria, a feature distinguishing it from pyelonephritis. Salpingitis, another common misdiagnosis, is very rare in pregnancy, although it can occur before 12 weeks of gestation.

Diagnostic Testing. Leukocytosis is common in pregnant patients with appendicitis, although it is rarely high enough to distinguish it from the physiologic leukocytosis of pregnancy. A leukocytosis greater than 18,000 makes the diagnosis of appendicitis 10 times more likely.[19] Pyuria in a catheterized urine specimen suggests pyelonephritis, but may be seen in 20% of patients with appendicitis,[20] whereas bacteriuria is uncommon in appendicitis.

Ultrasonography with a graded compression technique may reveal a non-compressible tubular structure in the right lower quadrant consistent with appendicitis. Studies of the diagnostic value of

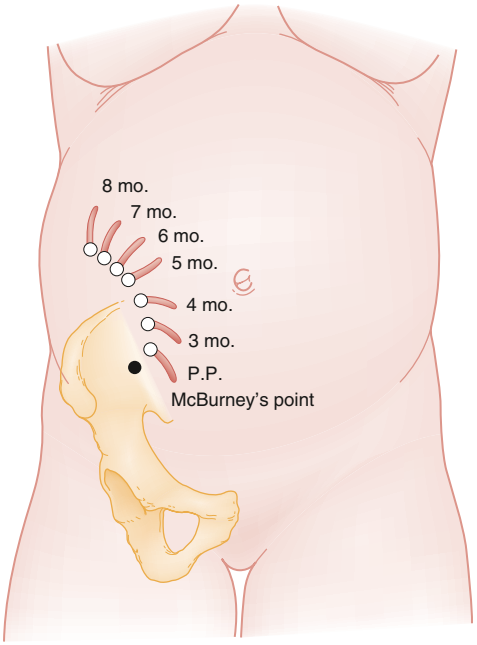

Fig. 173.8 Locations of the appendix during succeeding months of pregnancy. In planning an operation, it is better to make the abdominal incision over the point of maximal tenderness unless there is great disparity between that point and the theoretic location of the appendix. *P.P.,* postpartum. (From: Gabbe SG, Niebyl JR, Simpson JL, Galan HL. *Obstetrics: Normal and Problem Pregnancies.* New York: Churchill Livingstone; 2007.)

ultrasonography in the diagnosis of appendicitis are limited but have suggested that it has a high positive predictive value but a low negative predictive value.[21] Abdominal ultrasonography is recommended as the first imaging modality, followed by CT when ultrasound findings are inconclusive. Surgical, obstetric, and radiologic society guidelines agree that magnetic resonance imaging (MRI) is also useful in the evaluation of pregnant patients with suspected appendicitis (see Chapter 79).[21] Otherwise, laparoscopy or laparotomy is the diagnostic procedure of choice in the pregnant patient thought to have appendicitis. Early exploration is highly encouraged in pregnant patients because of the variability of clinical signs and increased fetal risk if diagnosis is delayed.

Management. The pregnant patient with suspected appendicitis should be hospitalized after consultation with a surgeon and obstetrician. Ultrasonography, MRI, or CT scan are diagnostic options. The patient should be kept on nothing by mouth (NPO) status, with IV fluid hydration to maintain intravascular volume. Although prompt surgery is required if the diagnosis is clear, in unclear cases the patient should undergo observation to allow for clarification of signs and symptoms. Patients undergoing observation are treated empirically with IV antibiotics, commonly piperacillin/tazobactam (3.375–4.5 g IV q6–8h) or ceftriaxone (2 g IV q24h) plus metronidazole (500 mg q8h).

Gallbladder Disease

Foundations

Cholelithiasis is present in approximately 5% of pregnant women and is the second most common non-obstetric surgical condition in pregnant patients. The natural history of asymptomatic cholelithiasis is believed to be similar to that in nonpregnant women, with less than 50% of patients with gallstones developing symptoms.

Changes in gallbladder kinetics are believed to be due to high pregnancy-related steroid levels. Progesterone decreases smooth muscle tone and induces gallbladder hypomotility and cholestasis, causing an increased risk of stone formation. In addition, pregnancy induces changes in bile composition and increased cholesterol secretion, thus increasing the incidence of cholesterol stone formation.

Clinical Features

The signs and symptoms of acute cholecystitis during pregnancy are the same as those in nonpregnant women. Epigastric or right upper quadrant pain and tenderness and nausea predominate. Leukocytosis must be interpreted carefully because of the normally increased white blood cell count seen in pregnancy. Likewise, a slightly elevated amylase level can be normal during pregnancy, and alkaline phosphatase, which is produced by the placenta, may be twice the nonpregnant level. A history of previous self-limited pain episodes associated with food intake suggests the diagnosis.

Differential Diagnoses

Pyelonephritis should be considered in the patient with right upper quadrant pain, with or without fever. During the third trimester, appendicitis can also be associated with right upper quadrant pain. Hepatitis and fatty liver infiltration occur in pregnancy; liver distention and inflammation associated with pregnancy-induced hypertension can also cause right upper quadrant pain. In addition, spontaneous intrahepatic bleeding can occur during late pregnancy, mimicking cholecystitis. Because of the potential for other serious diseases, diagnostic studies should be performed to verify a clinical diagnosis of symptomatic cholelithiasis and cholecystitis in pregnancy.

Diagnostic Testing

Ultrasonography is a reliable means of recognizing stones in the gallbladder, although it may not differentiate symptomatic from asymptomatic stones. In the patient with right upper quadrant pain, simultaneous sonographic evaluation of the liver is useful but technically difficult, particularly during the third trimester, when subcapsular liver hematomas and other intrinsic hepatocellular disease can occur but the liver may be obscured under the ribs.

Management and Disposition

The patient who has fever, leukocytosis, prolonged pain, or evidence of cholecystitis should be made NPO and given IV fluid hydration, adequate pain control, and broad-spectrum antibiotics. Some patients with uncomplicated cholecystitis can be managed medically. Patients with obstructive jaundice, gallstone pancreatitis, sepsis or failure to respond to conservative management are candidates for surgery (optimally, during the second trimester, if possible).[22] Approximately 40% of patients presenting with symptomatic cholelithiasis intrapartum require cholecystectomy during pregnancy, and recent evidence suggests that operative management compared to nonoperative management from uncomplicated disease has a reduced overall morbidity including reduced maternal and fetal complications.[22]

Discharge should be considered only for patients with uncomplicated and sonographically proven cholelithiasis who are not otherwise candidates for admission after consultation with an obstetrician. Pregnant patients with symptomatic cholelithiasis have a high rate of symptomatic relapse and increased severity of disease with each relapse. Early follow-up should be arranged, and the patient should be given careful instructions to return if she experiences fever, vomiting, or persistent pain.

Liver Disorders

Foundations

Pregnancy is associated with several unique liver abnormalities in addition to more usual hepatic diseases. Liver metabolism increases during

TABLE 173.4 Lab Abnormalities in Select Complications of Pregnancy

	WBC	Plt	BUN/Cr	AST/ALT	Alk Phos	PT/PTT	Fibrinogen	Bili	Other
Normal pregnancy	Mild ↑	nl	nl	nl	↑ (up to double)	nl	Nl	nl	nl LDH ↓albumin ↑amylase
Hepatitis				↑↑↑	Mild ↑	↑ (severe)		↑	Obtain: Acute hep panel APAP level
Acute fatty liver	↑	↓	↑	↑		↑	↓	↑	↑ Ammonia ↓glu +FSP
Preeclampsia HELLP		↓	↑ (severe preeclampsia)	↑		nl	nl		↓Hgb
Cholecystitis	↑			May be ↑	May be ↑				
Intrahepatic cholestasis				nl	↑↑ (7–10× nl)			↑	

pregnancy, but hepatic blood flow is unchanged, and little change occurs in liver function. Bilirubin, transaminase, and lactate dehydrogenase levels and prothrombin times are unchanged from those in the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphatase levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated.

Hepatitis

Hepatitis is the most common cause of liver disease in pregnancy, accounting for 40% of cases of jaundice during pregnancy. Management and treatment are supportive and unchanged from those for nonpregnant patients. Hepatitis E is reported to have a more aggressive course in pregnancy, with an increased maternal mortality rate and rate of fetal loss. Maintenance of adequate nutrition is a priority. Vertical transmission of hepatitis B can occur if the disease is not recognized. Pregnant women should be vaccinated for hepatitis B. Prophylaxis should be administered to the newborn born to chronically infected mothers with both the hepatitis B vaccine (10 or 20 micrograms) as well as hepatitis B immune globulin (HBIG) given in 0.5 mL dose at birth. If no hepatitis vaccine is given, additional doses of HBIG are required at 3 months and 6 months.

Acute Fatty Liver

Pathophysiology. Acute fatty liver of pregnancy is a disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. The disease is rare, occurring most often in primiparous patients and patients with twin gestations.

The cause of acute fatty liver of pregnancy is unknown, although studies have suggested that a deficiency in the fetus's fatty acid metabolism leads to an accumulation of hepatotoxic metabolites in the maternal circulation. On microscopic examination, fatty infiltration of the hepatocytes with edema and vacuolization can be seen, but there is no necrosis or inflammation. Liver function returns to normal after delivery if the patient can be supported through the acute phase. Although up to 50% of patients have signs of preeclampsia, the two are not clearly related. The diagnosis must be differentiated from viral hepatitis and HELLP syndrome, which have similar disease presentations and laboratory findings but, again, are not clearly related.

Clinical Features. Nausea and vomiting associated with malaise or jaundice during the third trimester should trigger consideration of a diagnosis of acute fatty liver. The right upper quadrant or epigastrium is usually tender. The disease may progress to coagulopathy, jaundice, seizures, DIC, and hepatic encephalopathy. Hemorrhage from coagulopathy is the most common complication at delivery. The diagnosis is often delayed secondary to the multiple differential considerations.

Differential Diagnoses. Liver tenderness and coagulopathy usually suggest preeclampsia during the third trimester. Jaundice and increases in the ALT level are distinguishing features because they are unusual in cases of liver disease associated with pregnancy-induced hypertension. Similarly, rapid progression of hepatic failure, hypoglycemia, and coagulopathy are unlikely in cases of preeclampsia. Elevations in the creatinine level are more common in acute fatty liver of pregnancy. The patient with viral hepatitis is likely to have more marked elevations in transaminase levels. Drug-induced hepatic failure should be excluded by history and toxicologic screening for acetaminophen and other toxins, if appropriate. Cholecystitis may be distinguished by ultrasound examination but may also be characterized by right upper quadrant pain; it is not associated with coagulopathy or progressive liver failure (Table 173.4).

Diagnostic Testing. Typically, leukocytosis is present, the platelet count and fibrinogen level are low, prothrombin and partial thromboplastin times are elevated, and fibrin split products are present. Elevated bilirubin levels (a late finding), AST and ALT levels, and uric acid levels may be seen. Hypoglycemia and dehydration are frequently present. Additionally, elevated BUN and serum creatinine levels with associated oliguria may be seen. In contrast to Reye syndrome, the serum ammonia level is only mildly elevated. CT scan and liver ultrasonography may be normal, so liver biopsy is used to make the definitive diagnosis.

Management. The patient with acute fatty liver of pregnancy may require acute stabilization for seizures or coma. Hypoglycemia may occur, which is rapidly corrected with dextrose. Coagulation parameters should be assessed. Fluid resuscitation and replacement of clotting factors may be required, and the patient should be admitted to an obstetric service capable of managing this serious disease. The diagnosis is usually made with liver biopsy if the disease has not progressed to severe coagulopathy. Rapid delivery is usually advisable when the diagnosis has been established. Fresh-frozen plasma, platelet transfusions, and glucose may be needed to sustain the patient until delivery can be accomplished.

Intrahepatic Cholestasis

Pathophysiology. Intrahepatic cholestasis of pregnancy, also termed *idiopathic jaundice of pregnancy*, *icterus gravidarum*, or *pruritus*

gravidarum, is a rare syndrome that occurs during the third trimester of pregnancy. It is the second most common cause of jaundice in pregnancy, after hepatitis. On histologic examination, the disease is characterized by cholestasis and dilated canaliculi in the biliary tree. The liver is normal. It is more common with increasing maternal age, multiple gestations, and in the winter months.

Clinical Features. Generalized pruritus and mild jaundice are the hallmarks of intrahepatic cholestasis of pregnancy. However, only 20% of patients present with this combination, and 80% present with pruritus alone. The pruritus usually begins in the palms and soles and ascends to the trunk. Although insomnia and fatigue occasionally accompany the pruritus, the patient appears nontoxic, without fever, vomiting, diarrhea, or significant malaise. The bilirubin level is rarely above 5 mg/dL, the alkaline phosphatase level can be elevated sevenfold to tenfold, and transaminase levels are in the normal range. Resolution occurs after delivery. Although maternal outcome is favorable, women with intrahepatic cholestasis of pregnancy are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.

Differential Diagnoses and Management. Exclusion of more serious entities, such as viral hepatitis, acute fatty liver, drug-induced cholestasis, and complicated cholecystitis, is required. Outpatient management is appropriate, provided the diagnosis is clear and the patient has close obstetric follow-up. Some have advocated aggressive fetal surveillance and delivery after fetal lung maturity to improve the fetal outcome. Symptomatic treatment with antihistamines (chlorpheniramine 4 mg PO q4–6h) and ursodeoxycholic acid (300 mg PO BID) are considered first line; additional treatments including bile salts, guar gum, and benzodiazepines have been tried, with variable success.[23]

Nausea and Vomiting in Pregnancy

KEY CONCEPTS

- Nausea and vomiting in pregnancy are common and may be treated conservatively with diet modification and avoidance of environmental triggers. If conservative measures fail, Diclegis, a delayed-release combination of doxylamine, 10 mg, and pyridoxine (vitamin B_6), 10 mg, is the first-line pharmacologic agent for the treatment of nausea and vomiting in pregnancy.
- Hyperemesis gravidarum is defined as nausea and vomiting that cause starvation metabolism, weight loss, dehydration, and prolonged ketonemia and ketonuria. Initial management involves rehydration with IV fluids, antiemetics, and demonstration of ability to take oral hydration.

Normal Pregnancy

Nausea and vomiting are common in pregnancy, particularly from 6 to 20 weeks of gestation. Prevalence rates of nausea and vomiting are as high as 50% to 80%. Symptoms are usually self-limited and often resolve with lifestyle changes, such as diet modification and avoidance of environmental triggers. Although evidence supporting nonpharmacologic agents is mixed, in several randomized trials, ginger has been found to be effective. Treatment is recommended at a dose of 250 mg QID, in capsule or syrup form.

In women who fail conservative management, pharmacologic therapy may be initiated. The American College of Obstetricians and Gynecologists recommends doxylamine-pyridoxine (1–2 tab QD–BID), a delayed-release combination of doxylamine, 10 mg, and pyridoxine (vitamin B_6), 10 mg, as the first-line pharmacologic agent for the treatment of nausea and vomiting in pregnancy.[24] Multiple studies and the Centers for Disease Control and Prevention (CDC) Birth Defect Monitoring Program data have demonstrated its safety and it is US Food and Drug Administration (FDA) approved for use in pregnancy.

If there are circumstances preventing the prescription of Diclegis, or in case of treatment failure, other antiemetics may be considered. Although the FDA has not explicitly approved metoclopramide (5–10 mg PO/IV/IM q 6h) or promethazine (12.5–25 mg PO/IV/IM/rectal q 4–6h, max 100 mg/day) for the treatment of nausea and vomiting in pregnancy, both drugs have been widely used and are generally considered safe. Ondansetron (4 mg PO/IV q8h) has also been widely used, though recent studies have suggested that ondansetron may be associated with an increased risk of fetal anomalies. However, the evidence is mixed and the prevalence of fetal anomalies associated with ondansetron use may not be significantly higher than the background 3% to 5% risk of fetal anomalies in the first trimester.[25] We recommend that ondansetron be used only when alternative antiemetics have failed and preferably after 10 weeks' gestation.[25]

Hyperemesis Gravidarum

Pathophysiology. Hyperemesis gravidarum occurs in approximately 1% of pregnant patients and is defined by nausea and vomiting that cause starvation metabolism, weight loss greater than 5% of total body weight, dehydration, and prolonged ketonemia and ketonuria. Without treatment, there is an increased risk of micronutrient deficiency and their respective sequelae to the patient (e.g., vitamin B_1 deficiency, Wernicke encephalopathy) and fetus (e.g., vitamin K deficiency, bleeding diatheses).[24]

The cause of hyperemesis gravidarum is not clear; associations have been made with increasing estradiol and hCG levels, as well as with maternal cytokines. Several studies have suggested an increased infection rate with *Helicobacter pylori* in patients with hyperemesis gravidarum; a nonteratogenic regimen for *H. pylori* treatment has been shown to decrease vomiting in hyperemesis patients.[26] Studies have also suggested that early treatment of nausea and vomiting of pregnancy may prevent progression to hyperemesis gravidarum.

Diagnostic Testing. Laboratory studies should assess volume status and reversible electrolyte abnormalities. A urinalysis screens for the presence of ketosis, elevated specific gravity, and infection. Serum chemistry assess the presence of hypokalemia, contraction alkalosis, elevated anion gap, or other metabolic abnormalities. Bilirubin and alkaline phosphatase levels can be mildly elevated but should return to normal after delivery. Hyperemesis may be complicated by liver disease and abnormal liver function test results, which are expected to resolve with supportive treatment.

Management. Initial management of hyperemesis involves rehydration with IV fluids (2 L of Ringer lactate [LR] at a rate of 500 ml/h), antiemetics (Diclegis is first line), and demonstration of ability to take oral hydration. Following the 2 liters of LR, expert consensus favors dextrose-containing IV fluids (D5/.45NS). Thiamine is administered before dextrose to prevent progression to Wernicke encephalopathy.[24] Dextrose-containing IV fluids are continued until ketones have cleared from the urine or the patient is able to tolerate oral intake. Patients who cannot tolerate oral intake should be admitted. Potassium and magnesium are repleted as needed. Antiemetics are used as previously described for nausea and vomiting in pregnancy. A short course of methylprednisolone (16 mg PO or IV q8h for 3 days) has been reported to be therapeutic for intractable hyperemesis; however, it is considered a last-line agent and its risk profile should be weighed carefully before administration.[24]

In women who cannot maintain their weight despite medical therapy, enteral nutrition via a nasogastric (NG) tube should be considered.

Thromboembolic Disease

KEY CONCEPTS

- Thromboembolic disease is a cause of maternal mortality in developed countries.
- CT angiography and lung scintigraphy (V/Q scan) are used for the diagnosis of pulmonary embolism (PE).
- Low-molecular-weight heparin is preferred for anticoagulation.

Foundations

Thromboembolic disease is associated with increased mortality in pregnancy and is among the most common causes of maternal death in developed countries. Pregnancy is a hypercoagulable state, with increased coagulation factors and stasis as pregnancy progresses and significant vascular trauma at the time of delivery. The risk of venous thrombosis increases during pregnancy to five or six times that of nonpregnant women. Although the risk is increased throughout pregnancy, it is highest during the first six weeks after delivery. Risk factors include smoking, obesity, age older than 35 years, hypercoagulable state, varicose veins, and prior superficial venous thrombosis. Women who deliver prematurely or have postpartum hemorrhage are also at increased risk.

Clinical Features

As in nonpregnant patients, clinical signs of pain, tenderness, and swelling are poor predictors of deep venous thrombosis (DVT) in pregnancy. The clinical diagnosis of pulmonary embolism (PE) is also difficult. Although tachypnea, tachycardia, dyspnea, and pleuritic pain are commonly associated with PE, the symptoms are nonspecific and may be associated with diverse diseases such as hepatic inflammation, pyelonephritis, and diaphragmatic impingement from a normal gravid uterus.

Diagnostic Testing

Deep Venous Thrombosis. Because of its widespread availability and avoidance of radiation, Doppler ultrasonography is the first-line test for the diagnosis of DVT. An abnormal study result is usually sufficient reason to treat the pregnant patient. However, normal leg study results can be seen with isolated iliac vein disease, which is common in pregnancy, and requires imaging with magnetic resonance venogram (MRV) or CT venogram (CTV) of the lower extremities for diagnosis. The risk of anticoagulation usually outweighs the risk of definitive studies when the diagnosis is equivocal.

Pulmonary Embolism. Currently, studies do not support the use of D-dimer tests in pregnancy to exclude the diagnosis of PE because this test may lack sufficient sensitivity in pregnant patients.[27] Chest radiography (shielding the pelvis and uterus) should be performed to exclude other disease processes that may mimic a PE. The diaphragm is normally symmetrically elevated during late pregnancy.

Magnetic resonance angiography (MRA) is considered a diagnostic modality of choice in pregnant patients because there is no risk of radiation exposure to the fetus.[27] MRA for PE is not often readily available for diagnosis of PE in the ED, therefore imaging with lung scintigraphy (V/Q scan) or CT angiography is recommended. The American Thoracic Society and The Society of Thoracic Radiology clinical practice guidelines for the evaluation of suspected PE in pregnancy suggest that chest x-ray be used as an initial evaluation and if chest x-ray is normal proceed to V/Q scan and if chest x-ray is abnormal, proceed to CTA.[27] Both have comparable performances for PE diagnosis during pregnancy. CTA delivers a lower fetal radiation dose but a higher maternal radiation dose when compared to V/Q scan.[27] However, the selection of the most appropriate test relies on local availability and expertise. In most EDs, the rapid availability of CTA makes it the diagnostic modality of choice for the evaluation of PE in pregnancy patients. Pulmonary angiography may be required if the diagnosis of PE is unclear after less invasive studies have been performed.

Management and Disposition

Warfarin (Coumadin) is contraindicated during pregnancy because of its teratogenic effects, high risk of abortions, and fetal hemorrhage. Heparinoids are used to treat thromboembolic disease during pregnancy. Unfractionated heparin carries a poorly understood risk of fetal osteoporosis, thrombocytopenia, prematurity, or miscarriage. In general, acute anticoagulation with IV heparin (80 units/kg bolus followed by 18 units/kg/hr) is followed by subcutaneous heparin (minimum 10,000 units subcutaneous q 12h), usually continued for 3 to 6 months postpartum in patients who have DVT or PE during pregnancy.

Patients receiving this treatment require laboratory testing every 1 or 2 weeks, and the efficacy of anticoagulation may be variable during pregnancy. We recommend low-molecular-weight heparin (enoxaparin 1 mg/kg subcutaneous q 12h) because it is considered safe in pregnancy and offers several advantages over unfractionated heparin. This includes decreased bleeding risk, reliable pharmacokinetics, decreased risk of heparin-induced thrombocytopenia, fixed dosages, less frequent dosing, and decreased risk of osteoporosis and thrombocytopenia. In patients with a history of DVT or PE, prophylaxis for subsequent gestations is usually recommended. Oral direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors (rivaroxaban) should be avoided in pregnancy and lactation because there is insufficient data to evaluate the safety of these drugs to mother, fetus, and the breast-feeding neonate.[27]

Genitourinary Infections

KEY CONCEPTS

- Asymptomatic bacteriuria in pregnancy predisposes the patient to the development of symptomatic lower and upper tract genitourinary infections. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, treatment of bacteriuria is cost-effective and important.
- Treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day course of either metronidazole or clindamycin.
- For the treatment of vulvovaginal candidiasis, oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes. Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 80% cure rate.
- Of patients who have trichomoniasis, 50% are asymptomatic. Diagnosis is made by direct visualization of protozoans on a wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.
- Regarding the treatment of sexually transmitted diseases, in general, tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important for preventing preterm labor and decreasing transmission to the infant.
- *Chlamydia trachomatis* infection is the most common sexually transmitted disease in the United States and worldwide. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose); a 7-day course of amoxicillin is an acceptable alternative.
- Women who have genital herpes during the third trimester have a 30% to 50% increased risk of fetal transmission compared to women with herpes simplex virus (HSV) infection in the first trimester (1%).
- Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital HSV occurred during pregnancy.

- Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy; treatment includes cephalosporins or azithromycin.
- PID is rarely encountered in pregnancy and does not occur after the first trimester. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and IV antibiotics.
- Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy. Patients are usually treated with IV ampicillin and gentamicin.

Urinary Tract Infection

Foundations. Asymptomatic bacteriuria in pregnancy predisposes the patient to the development of symptomatic lower and upper tract genitourinary infections. This has led to the US Preventive Services Task Force recommendation to screen for asymptomatic bacteriuria with urine culture for pregnant women at 12 to 16 weeks' gestation or at the first prenatal visit, if later (grade A recommendation). Uterine pressure exerted on the bladder and ureters, poor emptying of the bladder with voiding, and progesterone-induced smooth muscle relaxation that inhibits ureteral peristalsis appear to contribute to an increased risk of infection during pregnancy.

Prenatal screening of patients with asymptomatic bacteriuria in early pregnancy identifies approximately 95% of those at risk for subsequent bacteriuria during the pregnancy. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, the treatment of bacteriuria is cost-effective and important. Antibiotic treatment may also reduce the risk of preterm delivery and low birth weight.

Clinical Features and Diagnostic Testing. The pregnant patient who presents with lower urinary tract symptoms (e.g., dysuria, frequency, urgency) or upper tract symptoms (e.g., fever, malaise, back pain) should have a pelvic examination and evaluation of an uncontaminated urine specimen. There is a predominance of right-sided symptoms during pregnancy, probably the result of increased mechanical forces on the right ureter, but left-sided flank pain or bilateral symptoms may be caused by pyelonephritis. Rarely, urinalysis may yield normal results or cultures may produce negative findings because of failure to report lower colony counts or because of complete obstruction of the involved ureter.

The major risk of asymptomatic and lower urinary tract infection is spread to the renal parenchyma. Acute pyelonephritis carries considerable morbidity in pregnancy, including maternal sepsis, permanent renal injury, and premature labor. The risk of prematurity can be minimized by effective treatment and continued monitoring for recurrence. The development of premature labor in the pregnant patient who has pyelonephritis is ominous; it can be prevented only by aggressive recognition and treatment earlier in pregnancy.

Differential Diagnosis. Vaginitis, herpes genitalis, chlamydial infection of the urethra, and ovarian torsion can masquerade as urinary tract symptoms. A history of external dysuria (burning at the perineum with urination) suggests herpes or vaginitis. A pelvic examination should be performed to obtain cervical culture specimens and identify perineal or vaginal causes of dysuria. Appendicitis, cholecystitis, pancreatitis, and liver diseases in pregnancy must be considered in the differential diagnosis of an upper urinary tract infection. Back pain may also be a sign of premature labor. Careful evaluation of an uncontaminated catheterized urine specimen is essential to the correct diagnosis.

Management. Patients with asymptomatic bacteriuria or lower urinary tract signs and symptoms should be treated with 7 to 10 days of an antibiotic that is active against common urinary pathogens and safe in pregnancy. The most common choices are a cephalosporin, such as cephalexin, 500 mg orally BID for 3 to 7 days; nitrofurantoin, 100 mg orally bid for 3 to 7 days; amoxicillin 500 mg TID for 7 days; or a sulfonamide, such as trimethoprim-sulfamethoxazole, 800/160 mg BID for 3 days (except during the third trimester). Clinicians should choose their antibiotic based on local antibiograms and consider factors such as cost, local availability, and side effects when selecting the best treatment option.

Patients with fever, back pain, and evidence of acute pyelonephritis in pregnancy are usually admitted for IV antibiotic administration. In such cases, IV hydration, obstetric consultation, and testing of urine cultures should be initiated. At least one parenteral dose of antibiotics should be given, with antibiotic coverage guided by known organism susceptibilities in a given hospital. Because the resistance of *Escherichia coli* to ampicillin is considerable in most regions, a cephalosporin, such as ceftriaxone, 1 g IV daily, is usually administered. Culture testing must be performed to ensure that the original choice of antibiotic was correct, and the patient must have a repeated culture and be observed closely after treatment.

Vaginitis

Bacterial Vaginosis. Bacterial vaginosis (formerly known as *Gardnerella* vaginitis or *Haemophilus vaginalis* vaginitis) is an overgrowth of multiple endogenous vaginal bacteria, in some cases producing excessive discharge and vaginal malodor. Prevalence rates for bacterial vaginosis in pregnancy are estimated at 15% to 20%. Bacterial vaginosis is associated with an increased risk of chorioamnionitis, subclinical PID, premature rupture of membranes, fetal prematurity, and postpartum endometritis after vaginal delivery. However, treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day oral course of metronidazole (500 mg BID) or 7-day oral course of clindamycin (300 mg BID). Intravaginal treatment is not recommended in pregnant patients.

Candida Albicans *Vaginitis.* The incidence of vulvovaginal candidiasis is increased during pregnancy by high levels of estrogen and other steroids. There is no association of *Candida* colonization with adverse pregnancy outcomes, so treatment is for relief of symptoms only. Oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes. Treatment with vaginal azoles (intravaginal topical clotrimazole or miconazole) for 7 days during pregnancy is considered safe, with an estimated 80% cure rate.[28] Recurrent disease may require a vaginal culture to confirm the diagnosis and identify unusual *Candida* species (e.g., *Candida glabrata*) that may be resistant to conventional treatment. Longer treatment or treatment of a potential *Candida* reservoir in the patient's sexual partner(s) may also be required.

Trichomonas *Vaginitis.* Trichomoniasis is a sexually transmitted vaginitis caused by a protozoan parasite, *Trichomonas vaginalis*. Of patients who have trichomoniasis, 50% are asymptomatic. Symptoms include vaginal itching, malodorous discharge, and vaginal irritation. Diagnosis is made by direct visualization of protozoans on wet mount. Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment. The recommended treatment is metronidazole, 500 mg BID for 7 days.[28] Intravaginal treatment is not recommended in pregnant patients.

Sexually Transmitted Disease

Sexually transmitted diseases are treated in pregnant patients according to CDC guidelines.[29] In general, tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important in preventing preterm labor and decreasing transmission to the infant.

Chlamydia Trachomatis. *Chlamydia trachomatis* infection is the most common sexually transmitted disease in the United States and worldwide. Its prevalence is currently three to five times that of *Neisseria gonorrhoeae* infection. Clinical diagnosis is difficult during pregnancy because cervical mucus is usually cloudy and contains white blood cells, but urine sampling can be done and is equivalent to endocervical sampling in pregnancy infections. Routine chlamydia screening during pregnancy is important to prevent complications of preterm labor and postpartum endometritis, both of which are more common in patients who have chlamydial cervical infections. Additionally, repeat chlamydia screening should be considered in adolescent and young adult women and those who tested positive earlier in pregnancy.[29] Chlamydial infections of infants born to infected mothers include conjunctivitis and pneumonitis. Treatment during pregnancy or breastfeeding is azithromycin (single 1-g dose), which improves compliance and decreases gastrointestinal side effects; a 7-day course of amoxicillin (500 mg PO TID) is an acceptable alternative.

Neisseria Gonorrhoeae. Gonococcal infection of the cervix occurs in 1% of pregnant women.[30] Symptoms are similar to those in nonpregnant women. Salpingitis is rare but may develop during the first trimester from upper genital extension of cervical infection. Some practitioners believe that the incidence of the disseminated infection is increased in pregnant patients because of elevated progesterone levels and increased vascularity in the area of the cervix.

Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy; treatment includes cephalosporins (ceftriaxone 250 mg IM) or azithromycin (single 2-g dose PO). Treatment of possible coexistent chlamydial infection is recommended for pregnant and nonpregnant women. The major complications of third-trimester gonococcal infection are neonatal gonococcal ophthalmia and sepsis.

Herpes Simplex. Herpes simplex virus (HSV) infections pose a risk in pregnancy to the mother and newborn. Women who have genital herpes during the third trimester have a 30% to 50% increased risk of transmission compared to those in the first trimester (1%). The virus can be transmitted prenatally through transplacental infection or ascending vaginal infection and by vaginal delivery, particularly when herpetic lesions are present. Infections in the neonate often are disseminated or involve the CNS, causing significant morbidity and mortality. In the ED, culture of new suspected herpetic lesions of the cervix, vagina, or perineum identifies patients at risk for perinatal complications. Although the risk of oral acyclovir (400 mg TID for 7–10 days) and valacyclovir (1 g BID for 7–10 days) use in pregnancy is not well known, it is recommended for first-episode genital herpes. Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital herpes simplex occurred during pregnancy but may not eliminate the need for cesarean section in women with recurrent herpes simplex. Treatment should be undertaken with obstetric consultation and careful patient monitoring.

Upper Genital Tract Infection

Pelvic Inflammatory Disease. PID is very rare in pregnancy and does not occur after the first trimester. The differential diagnosis includes ectopic pregnancy, septic abortion, and appendicitis, all of which are more common. In the patient with suspected infection, smears or cultures for *Chlamydia* and *N. gonorrhea* should be performed. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and IV antibiotics.

Chorioamnionitis. Chorioamnionitis is the infection or inflammation of the placenta and fetal membranes. After 16 weeks of pregnancy, the chorioamniotic membranes adhere to the cervical os and may become infected. The risk is increased in women with preterm labor. Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy. Leukocytosis can be suggestive of chorioamnionitis but is not diagnostic. Patients should have blood specimens drawn for culture. Vaginal and cervical culture specimens for group B streptococci, *E. coli,* chlamydia, and gonorrhea should also be obtained. Urgent obstetric consultation should be obtained, and hospitalization for IV administration of antibiotics is required. Patients are usually treated with IV ampicillin (2 g q6 hr) and gentamicin (5 mg/kg q day).[31]

Endocrine Disorders

Thyroid Disorders

KEY CONCEPTS

- During pregnancy, the thyroid gland increases in size, requires more iodine, and produces more thyroid hormone than in the nonpregnant state.
- Hyperthyroidism, characterized by a suppressed TSH level and elevated T_4 and/or T_3 levels occurs in 0.1% to 0.4% of all pregnancies. Graves disease and hCG-mediated hyperthyroidism are the most common causes.
- When US women are diagnosed with hypothyroidism, the most common cause is Hashimoto (autoimmune) thyroiditis.
- Postpartum thyroiditis is characterized by transient hyperthyroidism or hypothyroidism, or both, in the postpartum period. Approximately 25% of these women develop permanent hypothyroidism in the subsequent 10 years.
- Hyperthyroidism may be associated with hydatidiform mole and usually resolves with evacuation of the mole.
- The diagnosis of hyperthyroidism is confirmed by a low (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH level and levels of free T_3 and T_4 that exceed the normal range for pregnancy.
- Confirmation of hypothyroidism is based on an elevated serum TSH level, relying on trimester-specific TSH reference ranges.
- Propylthiouracil (PTU) is the preferred treatment of hyperthyroidism in the United States. For thyroid storm, dexamethasone and beta blockers are added, with the patient admitted to the intensive care unit.
- Hypothyroidism in pregnancy is managed with levothyroxine supplementation (1.6 µg/kg/day).

Foundations. Thyroid disorders are common in women of childbearing age. During pregnancy, however, this is associated with a range of adverse maternal and fetal outcomes, including spontaneous miscarriage, preeclampsia, heart failure, preterm delivery, intrauterine growth restriction, and stillbirth.[32] The evaluation and management of pregnant women with thyroid dysfunction parallel those of nonpregnant women but require attention to the physiologic changes to the thyroid gland that occur during pregnancy.

Normal pregnancy exerts stress on the thyroid gland. During pregnancy, the thyroid gland increases in size, requires more iodine, and produces more thyroid hormone than in the nonpregnant state. Moreover, maternal and fetal thyroid function are strongly linked, with maternal thyroxine accounting for a substantial portion of fetal thyroid function at birth.[32] Thyroid dysfunction in pregnancy can occur during pregnancy or the postpartum state.

Hyperthyroidism, characterized by suppressed thyroid stimulating hormone (TSH) levels, elevated triiodothyronine (T3) and/or thyroxine (T4), occurs in only 0.1% to 0.4% of all pregnancies.[33] Hyperthyroidism in pregnancy can be a result of any cause, but

Graves disease and hCG-mediated hyperthyroidism are the most common causes. Graves disease is an autoimmune process associated with thyroid-stimulating antibodies and usually becomes less severe during the later stages of pregnancy. hCG, which is homologous to TSH, has some thyroid-stimulating activity and may transiently cause hyperthyroidism in the first half of gestation. hCG-mediated hyperthyroidism is typically less severe than Graves disease–associated hyperthyroidism.

Hypothyroidism complicates 2% to 3% of pregnancies.[33] Although nutritional iodine deficiency is a common cause of hypothyroidism globally, it is rare in the United States. When women in the United States are diagnosed with hypothyroidism, the most common cause is Hashimoto (autoimmune) thyroiditis, in which autoantibodies cause destruction of the thyroid gland. Hypothyroidism is associated with adverse pregnancy effects, including preeclampsia, placental abruption, low birth weight, and an increased risk of stillbirth.

Postpartum thyroiditis is characterized by transient hyperthyroidism or hypothyroidism, or both, in the postpartum period. It is estimated that 5% to 10% of women have postpartum thyroiditis. Most women return to a euthyroid state within 1 year postpartum, but approximately 20% to 40% of these women develop permanent hypothyroidism in the subsequent 10 years.[33] The diagnostic triad consists of a lack of previous history of thyroid disorders, an abnormal TSH concentration during the first postpartum year, and the absence of TSH receptor antibodies (Graves disease) or a toxic nodule.

Clinical Features. The diagnosis of thyroid dysfunction during pregnancy is difficult because pregnancy itself can mimic the findings in mild to moderate hypothyroidism and hyperthyroidism.

Hyperthyroidism in pregnancy should be suspected when the patient exhibits disproportionate tachycardia, thyromegaly, exophthalmos, weight loss, or inadequate weight gain during pregnancy. Hyperthyroidism may be associated with hydatidiform mole and usually resolves with evacuation of the mole. Patients may present with signs of thyroid storm, including altered mental status, severe tachycardia, and signs of high-output heart failure (e.g., edema, dyspnea, orthopnea).

Like hyperthyroidism, *hypothyroidism* in pregnancy is difficult to diagnose. Signs such as edema, fatigue, and weight gain may be attributed to the pregnancy rather than thyroid dysfunction. Enlargement of the thyroid gland may be absent depending on the cause of the hypothyroidism. The diagnosis of hypothyroidism during pregnancy should be suspected when the patient exhibits edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes.

Patients with *postpartum thyroiditis* classically present with thyrotoxicosis 6 weeks to 6 months postpartum, followed by a hypothyroid state lasting up to 6 months. A euthyroid state returns by the end of the first postpartum year. However, most patients present with hyperthyroidism alone or lone hypothyroidism. The recurrence rate in subsequent pregnancy is estimated at 69%, and 25% of women eventually develop permanent hypothyroidism.

Differential Diagnoses. Thyroid dysfunction should be considered in the patient with nonspecific symptoms, including fatigue, anxiety, depression, and unexplained weight loss or weight gain. When a diagnosis of hypothyroidism or hyperthyroidism is recognized, their respective causes and differential diagnoses should be considered (see Chapter 117 for more detailed information).

Diagnostic Testing. Normal values of thyroid hormones vary based on stage of pregnancy. The diagnosis of hyperthyroidism is confirmed by a low (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH level and levels of free T_3 and T_4 that exceed the normal range for pregnancy. Confirmation of hypothyroidism is based on an elevated serum TSH level, relying on trimester-specific TSH reference ranges.[33] Overt hypothyroidism is defined as an elevated trimester-specific TSH, along with a decreased, trimester-specific free T_4 concentration. Subclinical hypothyroidism is defined as an elevated trimester-specific serum TSH concentration and a normal free T_4 concentration.

Management. Generally, no treatment is required for hCG-mediated hyperthyroidism. Treatment of pregnant women with overt hyperthyroidism due to Graves disease is of utmost importance because good fetal and maternal outcomes depend on controlling the mother's hyperthyroidism. Although thyroid ablation with radioactive iodine is contraindicated in pregnancy, medical treatments are available. Propylthiouracil (PTU) is the preferred treatment of hyperthyroidism in the United States. Methimazole is equally effective at treating hyperthyroidism in pregnancy but may be associated with fetal anomalies such as aplasia cutis, esophageal atresia, and choanal atresia. It is therefore not recommended as first-line treatment for hyperthyroidism in pregnancy.

Patients with symptoms of thyroid storm should be managed in an intensive care setting. Treatment with PTU (100 mg q8hr) should be initiated early.[33] Beta blockers such as propranolol (20–40 mg q6h) should be considered to control tachycardia; labetalol, esmolol, and propranolol have been used intrapartum.[33] A subtotal thyroidectomy may be considered once the symptoms of thyrotoxicosis are managed medically.

Hypothyroidism in pregnancy is managed with levothyroxine supplementation (1.6 μg/kg/day). Patients in the hypothyroid phase of postpartum thyroiditis require levothyroxine when they have a TSH level higher than 10 mU/L or between 4 and 10 mU/L with symptoms or active attempt at becoming pregnant. The hyperthyroid phase of postpartum thyroiditis is usually managed with a limited course of beta blockers.

Disorders of the Hypothalamic-Pituitary Axis

Foundations. The pituitary gland is normally enlarged in pregnancy due to estrogen stimulation. Disorders of the hypothalamic-pituitary axis may increase the incidence of maternal and fetal morbidity and mortality.

Pregnancy profoundly affects the hypothalamic-pituitary axis, resulting in increased circulating levels of cortisol and adrenocorticotropic hormone due to increased estrogen production. In contrast, levels of growth hormone decrease in pregnancy. Disorders of the hypothalamic-pituitary axis in pregnancy can result in adrenal insufficiency, Cushing syndrome, acromegaly, diabetes insipidus, and prolactinomas. Although these disorders are rare, they are associated with maternal morbidity (e.g., hypertension, hyperglycemia, eclampsia) and up to 20% fetal mortality.

Clinical Features. Disorders of the hypothalamic-pituitary axis usually present as an insidious set of chronic symptoms, many of which can mimic normal pregnancy, making diagnosis difficult. Symptoms vary depending on the specific disease but include fatigue, malaise, vomiting, weight gain or loss, amenorrhea, galactorrhea, and hyperprolactinemia. Normal pregnancy can be associated with slight decreases in the serum sodium level; more severe decreases in the serum sodium level may be signs of diabetes insipidus or adrenal insufficiency.

Diabetes insipidus may also be caused by pituitary infarction in the setting of severe obstetric hemorrhage (Sheehan syndrome). Advancements in the management and resuscitation of obstetric hemorrhage have made Sheehan syndrome increasingly rare, but it remains an important clinical consideration. The symptoms of Sheehan syndrome are dependent on the degree of the patient's hypopituitarism. Patients present with signs and symptoms that vary according to the deficient

hormones. The failure of postpartum lactation and resumption of normal menstruation are strongly suggestive of Sheehan syndrome. Following postpartum hemorrhage, patients may have persistent tachycardia, hypotension, and latency between hemorrhage, and the onset of symptoms can vary, from months to years after pregnancy.

Diagnostic Testing. Diagnostic considerations vary according to the patient's presentation. Growth hormone levels are elevated in patients with acromegaly. Patients with adrenal insufficiency may present with hyponatremia and hyperkalemia, although these may be absent in many patients. MRI is helpful in the detection of prolactinoma or Sheehan syndrome.

Management. Stabilization consists of treatment of serious manifestations, such as hyperkalemia, tachycardia, and hypotension. Outpatient management is appropriate in the stable patient, provided there is urgent endocrinology follow-up.

Acknowledgment

We thank Dr. Sidhant Nagrani and Dr. Bisan Salhi for their contributions to previous editions of this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 173: QUESTIONS AND ANSWERS

1. An 18-year-old G1P0 at 8 weeks of gestation presents with abdominal pain and vaginal bleeding for 1 day. Her serum human chorionic gonadotropin (hCG) level is 3700 IU/L. Transvaginal ultrasonography does not reveal an intrauterine pregnancy (IUP) or mass. The pelvic examination is remarkable for a closed cervical os and a small amount of blood. Which of the following should be the next step?

a. Coagulation panel
b. Gynecologic consultation
c. RhoGAM, 300 μg intramuscularly
d. Repeat hCG in 2 days
e. Serum progesterone level

Answer: B. Ultrasonographic detection of an IUP is likely at hCG levels higher than 1500 to 2000 IU/L. A negative ultrasound, with an hCG level of 3700 IU/L, is concerning for an ectopic pregnancy or miscarriage. β-hCG levels should peak at the 7- to 10-week range, with mean values of 50,000 IU/L. A persistently low hCG level is even more suspicious for ectopic pregnancy, and gynecologic consultation is warranted.

2. A 36-year-old G3P2 presents with painless vaginal bleeding during the past hour. She is at 33 weeks of gestation, and her pregnancy has been uncomplicated. Her bleeding lasted approximately 20 minutes. Which of the following should not be included in the management of this patient?

a. Baseline hemoglobin level and platelet count
b. Immediate complete pelvic examination
c. Immediate obstetric consultation
d. Intravenous fluid resuscitation
e. Transvaginal ultrasound

CHAPTER 173: QUESTIONS AND ANSWERS—cont'd

Answer: B. Painless late pregnancy bleeding is placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis is excluded via ultrasound. An injudicious vaginal examination can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa.

3. Which of the following sexually transmitted diseases does not require treatment during pregnancy?
   a. *Chlamydia trachomatis*
   b. Herpes simplex virus
   c. *Neisseria gonorrhoeae*
   d. Pelvic inflammatory disease (PID)
   e. *Trichomonas vaginalis*

Answer: E. Although trichomoniasis has been associated with increased prematurity, treatment with metronidazole has not been shown to improve fetal outcomes, so emergency clinicians should counsel patients and consider deferring treatment in asymptomatic pregnant women until after 37 weeks' gestation.

4. A 28-year-old G3P0 at 34 weeks of gestation presents with new-onset seizures. The patient has multiple seizures in the ED and is noted to be hypertensive at a blood pressure of 164/87 mm Hg. Which of the following should be administered next?
   a. Benzodiazepines
   b. Calcium gluconate
   c. Labetalol
   d. Magnesium sulfate
   e. Pralidoxime

Answer: D. Magnesium sulfate has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. A loading dose of 4 g intravenous (IV) magnesium, followed by 2 g IV/hr, is recommended.

5. A 36-year-old G5P4 at 8 weeks of gestation presents to the ED with painless vaginal bleeding. Ultrasonography shows products of conception in the uterus. The pelvic examination shows a dilated cervix and a moderate amount of blood in the vaginal vault. Which of the following is appropriate management?
   a. Surgical evacuation
   b. Expectant management
   c. Medical management with misoprostol
   d. None of these
   e. All of these

Answer: E. All of these are appropriate management options for an incomplete miscarriage.

6. Which of these is the most common surgical emergency in pregnancy?
   a. Abruptio placentae
   b. Appendicitis
   c. Cholecystitis
   d. Ovarian torsion
   e. Ruptured peptic ulcer

Answer: B. Appendicitis is the most common surgical emergency in pregnancy. Clinical presentations may be atypical, particularly during the second half of pregnancy.

7. For the treatment of nausea and vomiting in pregnancy, which of the following has been found to have some associated risk of fetal abnormalities?
   a. Diclegis (delayed-release combination of doxylamine and pyridoxine)
   b. Ginger
   c. Metoclopramide
   d. Ondansetron
   e. Promethazine

Answer: D. Ondansetron has been shown in studies to be linked with fetal cardiac abnormalities, as well as cleft lip and palate. Diclegis is first-line pharmacologic treatment of nausea and vomiting in pregnancy; metoclopramide and promethazine are alternatives if it fails. Ginger, a nonpharmacologic treatment, has been shown to be safe and effective at a dose of 250 mg QID.

Medical Emergencies During Pregnancy

Diane L. Gorgas and Robert Cooper

KEY CONCEPTS

Asthma

- The treatment goal for a pregnant woman with an acute asthma exacerbation is to prevent fetal hypoxia by keeping maternal oxygen saturation above 95%. Inhaled beta-agonists and corticosteroids are first-line emergency department treatment and are considered safe for use in pregnancy.

Cardiac Disease

- Hypertensive emergency in pregnancy is defined as acute-onset persistent hypertension with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg that is persistent for greater than 15 minutes. In these cases, antihypertensive therapy should be administered as soon as reasonably possible, and no later than 30 to 60 minutes after diagnosis with a target blood pressure of 140 to 150 mm Hg systolic and 90 to 100 mm Hg diastolic. The drugs of choice are oral nifedipine, IV hydralazine, and IV labetalol.
- The risk for acute coronary syndrome and acute myocardial infarction is increased in pregnant women compared to age-matched controls. The most common cause of AMI in the pregnant women is spontaneous coronary artery dissection. Treatment is similar to the nonpregnant agent, although P2Y12 receptor inhibitors should be avoided and fibrinolytic agent use should be carefully considered in women close to term.

Anemia

- Anemia in pregnancy is defined as a hemoglobin less than 11. Serum ferritin is the most accurate lab value for diagnosing iron deficiency anemia in pregnancy. Women with mild iron deficiency anemia can be started on daily iron supplementation while those with severe iron deficiency in the second and third trimester can be referred for IV iron infusion.
- Sickle cell disease causes maternal complications including more frequent pain crises, and increased risk of venous thromboembolism and preeclampsia. Treatment of pain crises is the same as in nonpregnant patients with the exception that hydroxyurea is contraindicated due to known teratogenicity.

Epilepsy

- Gravid patients with epilepsy have a tenfold risk of death compared to pregnant women without epilepsy. Many antiepileptic drugs (AEDs) have known teratogenicity and levetiracetam and lamotrigine are considered the safest agents during pregnancy. Treatment of status epilepticus is with benzodiazepines followed by a phenytoin as first-line AED and levetiracetam as second-line AED.

Endocrine

- Pregnant patients with type 1 diabetes mellitus (T1DM) are recommended to transition to insulin during gestation to achieve HgbA1C values <6%.
- Hypoglycemia is most common in the first trimester, and up to 40% of pregnancies are marked with at least 1 episode of severe hypoglycemia.
- Comorbid obesity increases the risk of cesarean section and venous thromboembolism.
- Graves disease commonly rebounds in the immediate postpartum period with thyrotoxicosis.
- Radioiodine is strongly contraindicated for the treatment of hyperthyroidism in pregnancy.
- All gravid patients with new-onset nephrolithiasis should be screened for hypercalcemia. Treatment of hypercalcemia with bisphosphonates is contraindicated in pregnancy.

Psychiatric Disorders

- Prenatal discontinuation of methamphetamines and other stimulants, although desirable, can cause depression and psychosis.
- Maternal and neonatal outcomes in women on opioid agnostic therapy show decreased rates of neonatal abstinence syndrome (neonatal opioid withdrawal syndrome).

Inflammatory Disorders

- Antiphospholipid syndrome (APS) in lupus patients is characterized by deep vessel clotting, pregnancy-related morbidity, and positive anticoagulant serum markers. Catastrophic APS has rapid-onset small vessel thrombosis, multiorgan dysfunction, and a high maternal mortality rate.

Renal Disease

- Management of chronic kidney disease (CKD) in pregnancy can be treated with intensified hemodialysis (increased length of treatment time or increased frequency) to improve fetal outcome.
- Patients post renal transplantation have fertility rates that return to normal within 6 months.

Infectious Disorders

- Moderate to severe anemia in pregnancy in an HIV-infected mother should prompt a workup for tuberculosis.
- During pregnancy, penicillin is the only known effective treatment for congenital syphilis, and pregnant patients with penicillin allergy should be desensitized and treated with penicillin.
- Lamivudine given in late pregnancy to women with high viral loads of HBV DNA reduces viral transmission when given in conjunction with HBV vaccine and immune globulin.
- Obstetric hemorrhagic complications, including DIC and shock and subsequent need for transfusion, are more common with HCV infection.

FOUNDATIONS

The physiologic changes that occur in pregnancy may exceed the patient's underlying compensatory mechanisms, resulting in initial symptom onset or rapid decompensation of medical illness during pregnancy. Certain chronic medical conditions also pose a serious threat to the mother's health or result in a poor fetal outcome. Finally, some medical illnesses result in a difficult delivery or the need for special resuscitation measures in the neonate.

The incidence of pregnancy in chronically ill patients has been increasing because of improved survival of patients with diseases such as diabetes, epilepsy, renal failure, obesity, and various cancers. Also, the demographics of pregnancy are changing in that maternal age at the time of first pregnancy is increasing. Advances in assisted reproduction, including in vitro fertilization and oocyte donation, have made it possible for older women—including those who are postmenopausal—to become pregnant. Older pregnant women experience an increased rate of antepartum and intrapartum complications and are more likely to have comorbid conditions such as cardiovascular disease.

The recognition of an unexpected or even expected pregnancy may occur in the setting of the emergency department (ED), and many interventions are time-sensitive, requiring treatment in the ED. All emergency clinicians should have an understanding of critical diagnostic and treatment possibilities when encountering a pregnant patient with a preexisting illness.

ASTHMA

Asthma exacerbations occur in up to 45% of pregnant asthmatics with almost half of those exacerbations requiring rescue oral corticosteroids or hospitalization.[1] Poorly controlled asthma is associated with an increased risk of preeclampsia or eclampsia, premature contractions, cesarean section, low birth weight, and small-for-gestational-age status. The risk of such complications varies with the severity of the disease and degree of control during pregnancy. Adverse perinatal outcomes increase with the severity of asthma during pregnancy. Controlling asthma during pregnancy leads to less intrauterine growth retardation and fewer adverse perinatal outcomes. It has been well documented that asthma may worsen, improve, or remain the same during pregnancy, but no studies have examined whether this is caused by changes in asthma triggers, treatment, or severity.

Maternal respiratory function changes can make it more difficult to recognize the decompensating pregnant asthmatic patient. Tidal volume and minute ventilation increase by 45% over the course of pregnancy resulting in an average P_{CO_2} of 32 mm Hg. The kidneys compensate and maintain an average bicarbonate level of 19 mEq/mL, which results in a compensated respiratory alkalosis with a serum pH between 7.40 and 7.45.

Many adverse perinatal outcomes associated with maternal asthma are thought to be due to fetal hypoxia. Thus, the overall goal of treatment is maintaining maternal oxygen saturations above 95%. Both the American College of Obstetrics and Gynecology (ACOG) and National Asthma Education and Prevention Program have clearly stated that it is safer to use asthma medications to treat pregnant women than to allow severe asthma symptoms and exacerbations to occur during pregnancy. Despite the support for aggressive asthma treatment from consensus guidelines, studies show variation in the amount of dispensed asthma medications before and during pregnancy.

The standard treatment for a pregnant asthmatic patient is the same as that for a nonpregnant patient with an asthma exacerbation. After history and the performance of a physical examination, the peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV_1) should be measured. There is no significant change in the FEV_1/ FVC ratio throughout pregnancy and a decline in these values is of concern. Patients with an FEV_1 or PEF less than 50% of their predicted maximum are classified as having a severe exacerbation. An initial fetal assessment should be performed, including fetal heart tones and continuous electronic fetal monitoring with a biophysical profile if the pregnancy has reached viability. Supplemental oxygen should be given to all mothers with oxygen saturation below 95%.

Inhaled short acting β_2-agonists are the first-line treatment for an asthma exacerbation and can be given continuously, if needed, for a severe exacerbation. Adjunctive anticholinergic medications are considered and albuterol and can used as in nonpregnant patients. Long-acting selective β_2-agonists and inhaled corticosteroids can be added as controller medications on discharge from the ED.[2] Multiple studies have shown no increased risk of adverse perinatal outcomes from inhaled corticosteroids. Budesonide is the preferred agent in pregnancy.[3] Nonselective β-agonists such as epinephrine are generally avoided because of concern for uterine vasoconstriction. β-agonists are tocolytics and will often halt labor.

Oral corticosteroids are indicated for use in moderate to severe asthma exacerbations and should be prescribed for the same indications as in nonpregnant asthmatics. Despite these recommendations, in one study only 63% of pregnant women treated in the ED received systemic corticosteroids at discharge despite 100% of these women receiving inhaled β-agonists during their visit.[4] There is weak evidence that oral corticosteroid use increases the risk of preterm delivery and low-birth-weight infants; there is also conflicting evidence of an increased risk of orofacial clefts. The benefits of oral corticosteroid use for avoiding fetal hypoxia greatly outweighs the risk of adverse perinatal outcomes and all expert guidelines recommend oral corticosteroid use.

Second-line agents for asthma control (e.g., cromolyn sodium) are considered safe in pregnancy. In limited studies, magnesium has been shown to improve respiratory function in pregnant females with severe asthma exacerbations without adverse fetal outcomes.

CARDIOVASCULAR DISORDERS

Foundations

Heart disease in pregnant women is the leading cause of nonobstetric maternal deaths.[5,6] The proportion of maternal deaths due to cardiovascular disease has increased as pulmonary hypertension, cardiomyopathies, aortic dissection, and myocardial infarction have become more prevalent in pregnant women. The increase in blood volume due to pregnancy, along with the increases in preload, cardiac output, and oxygen consumption, can worsen or reveal cardiac disease in pregnant women. Because the signs and symptoms of acute coronary syndromes and heart failure (e.g., shortness of breath, mild chest pain, edema) can be seen in normal pregnancies, these entities are especially difficult to diagnose.

Hypertension

Chronic Hypertension

The definitions of hypertension and hypertensive crisis differ for pregnant and nonpregnant patients, as do the blood pressure values at which to start treatment. As opposed to the American College of Cardiology (ACC)/American Heart Association definition, chronic hypertension in pregnancy is defined as hypertension (>140 mm Hg systolic or > 90 mm Hg diastolic) diagnosed prior to pregnancy or before 20 weeks' gestation (Table 174.1).[7] Chronic hypertension in pregnancy increases the risk of superimposed preeclampsia, preterm delivery, intrauterine growth restriction, and cesarean section.

TABLE 174.1 Hypertensive Disorders of Pregnancy

	Chronic Hypertension	Gestational Hypertension	Preeclampsia	Chronic Hypertension With Superimposed Preeclampsia
Definition	Hypertension that antedates pregnancy[a]	Hypertension diagnosed after 20 wk of gestation in the absence of proteinuria or other evidence of preeclampsia	Hypertension that begins after 20 wk of gestation in association with new-onset proteinuria (>300 mg/24 hr) or symptoms below in the absence of proteinuria	Hypertension that antedates pregnancy in association with new-onset proteinuria
	Hypertension diagnosed before 20 wk of gestation		Decreased platelets, elevated liver transaminase levels, renal insufficiency, pulmonary edema	Sudden increase in proteinuria in woman with chronic hypertension[a] and proteinuria before 20 wk of gestation
				Hypertension that antedates pregnancy in association with sudden increase in blood pressure
	Comment—rarely, preeclampsia presents before 20 wk of gestation	Comment—may progress to preeclampsia; may also represent previously undiagnosed hypertension		Hypertension that antedates pregnancy in association with decreased platelets, elevated liver transaminase levels, renal insufficiency, pulmonary edema, or cerebral or visual symptoms

[a]Defined as blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic.
Adapted from: Nishimura RA, Otto CM, Bonow RO, et al, ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;129:e521e643.

Chronic hypertension of pregnancy is categorized as mild hypertension (systolic blood pressure of 140–159 mm Hg or diastolic blood pressure of 90–109 mm Hg) or severe hypertension (systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg). Previously there was agreement that mild hypertension of pregnancy did not require treatment. However, tight control of blood pressure (goal diastolic blood pressure less than 85 mm Hg) has been shown to lower the frequency of severe maternal hypertension. There is no difference in the risk of pregnancy loss, high-level neonatal care, or overall maternal complication between "tight" and "less-tight" blood pressure control groups.[8] ACOG recommends that antihypertensive treatment be started when blood pressures are consistently higher than 160 mm Hg systolic and/or higher than 110 mm Hg diastolic. The European Society of Cardiology endorses treating chronic hypertension of pregnancy at 150/95 mm HG, though it sites a lack of evidence. Finally, the International Society for the study of Hypertension in Pregnancy endorses treating hypertension if blood pressures are consistently above 140/90 mm Hg.

The major risk posed by severe chronic hypertension is a progression to preeclampsia, which occurs in 25% of these pregnancies. Severe hypertension is associated with low birth weight, preterm delivery, elevated liver enzymes, and prolonged hospital stays as compared to women with chronic hypertension without severe hypertension.[9] Antihypertensive drugs are effective in preventing this progression. The first-line oral agents for the treatment of chronic hypertension are labetalol 200 to 1200 mg/day in 2 to 3 divided doses, nifedipine XL 30 to 120 mg/day, and methyldopa 500 to 3000 mg/day in 2 divided doses.

Hypertensive Emergencies

All major society guidelines define a hypertensive emergency as acute-onset persistent hypertension with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg that is persistent for greater than 15 minutes. In these cases, antihypertensive therapy should be administered as soon as reasonably possible, and no later than 30 to 60 minutes after diagnosis. Goal blood pressure is within the range of 140 to 150 mm Hg systolic and 90 to 100 mm Hg diastolic in order to prevent loss of cerebral autoregulation. IV labetalol, IV hydralazine, and oral nifedipine are all considered first-line treatment, with oral nifedipine indicated when IV access has not yet been established (Fig. 174.1).[10]

In 2013, ACOG changed its diagnostic criteria for preeclampsia to no longer require proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in the presence of thrombocytopenia, impaired liver function, pulmonary edema, visual disturbances, or the development of renal insufficiency.

Cardiac Disorders

Acute Coronary Syndromes

In a United Kingdom Registry, cardiac disease was the largest indirect cause of maternal death with ischemic heart disease accounting for more than one-fifth of cardiac mortality.[11] The mortality rate in pregnant women who have had an acute myocardial infarction (AMI) is from 5% to 7%. Pregnant women are two to four times more likely to have an AMI as compared to age-matched nonpregnant individuals. The number of older women becoming pregnant is increasing; pregnant women aged 40 years or older have a 30-fold greater risk for acute coronary syndrome (ACS) than pregnant women 20 years of age or younger. The incidence of AMI is highest during the last trimester and peripartum period with 21% of pregnancy related MIs occurring in the antepartum period.[12]

Multiple factors are hypothesized to increase the risk of AMI in pregnancy, including a prothrombotic state, increased myocardial oxygen demand secondary to increased cardiac output and heart rate, and decreased oxygen-carrying capacity secondary to physiologic anemia, which may precipitate angina. Hypertension, thrombophilia, anemia, diabetes, advanced maternal age, multiparous state, and smoking increase the risk of pregnancy-associated AMI.

Most cases of ACS in pregnancy are related to causes other than atherosclerosis. The most common cause of ACS is spontaneous coronary artery dissection (SCAD) accounting for anywhere from 23% to 43%

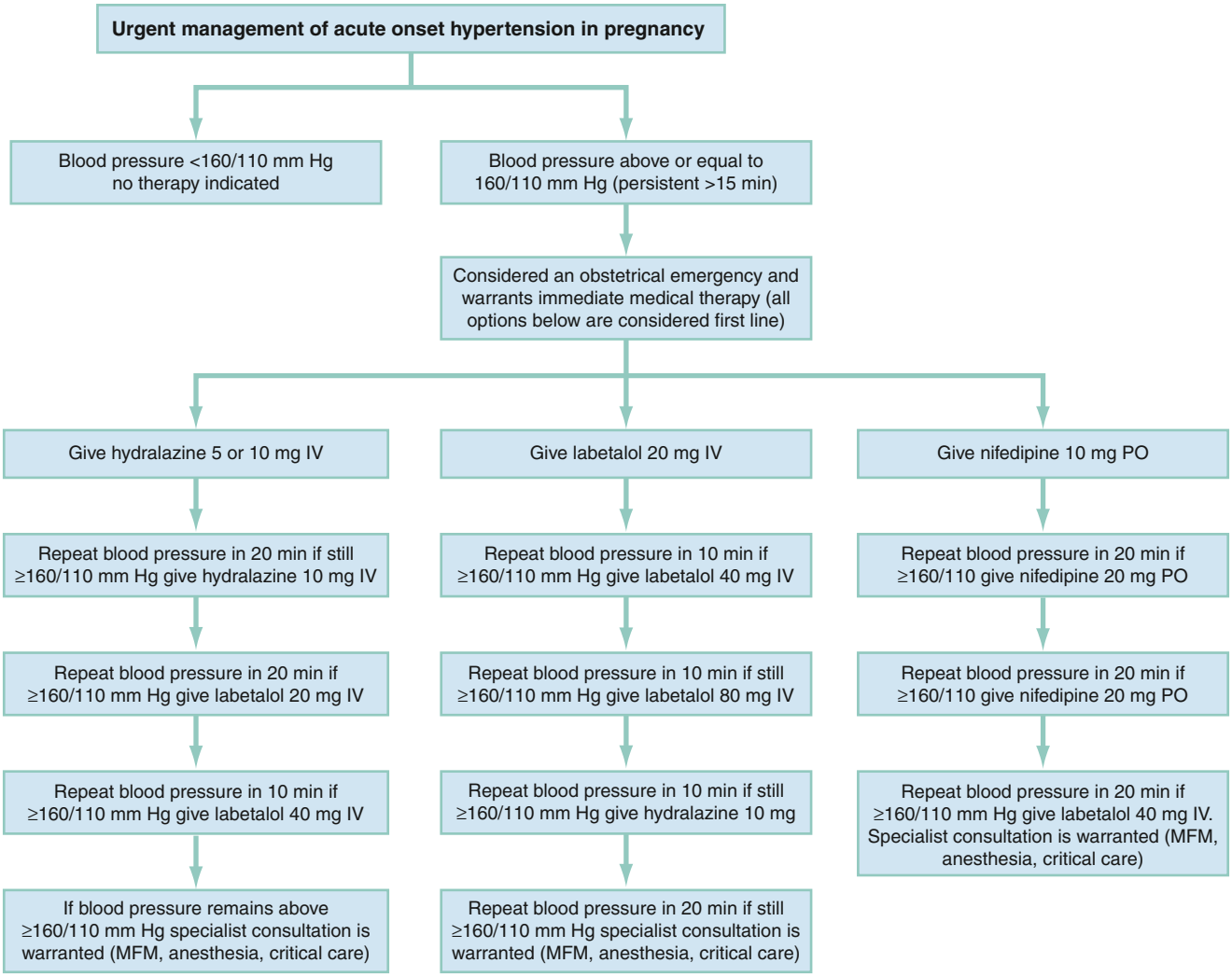

Fig. 174.1 Urgent management of acute-onset hypertension in pregnancy. (From: ElFarra J, C. Bean C, Martin, JN. Management of hypertensive crisis for the obstetrician/gynecologist. *Obstet Gynecol Clin North Am.* 2016;43, 623-637.)

of pregnancy-related MIs. In one study, 90% of patients presenting with a SCAD related AMI were postpartum while in another study 72% of SCAD related AMIs were postpartum.[13,14] Pulmonary embolus, reflux esophagitis, biliary colic, and aortic dissection are all more common than myocardial ischemia during pregnancy and should be considered in the differential diagnosis of the pregnant patient who presents with chest pain. Initial signs and symptoms of AMI, such as chest pain and shortness of breath, are often attributed to the normal physiologic changes of pregnancy.

The diagnosis of ACS is similar to that in nonpregnant patients, with certain exceptions. Electrocardiographic changes sometimes occur in normal pregnancies and delivery. These include T wave flattening, T wave inversion (mainly in lead III), and nonspecific ST changes during pregnancy, as well as ST depression during labor induction for cesarean section. As a result, an additional evaluation may be necessary. Echocardiography is useful in the correlation of suspicious electrocardiographic findings with wall motion abnormalities. The enzymatic diagnosis of myocardial infarction is unchanged, and a serial troponin rise suggests myocardial ischemia, even in preeclampsia.

Treatment of AMI during pregnancy is similar in most respects to treatment of the nonpregnant patient, with survival of the mother as the goal. Standard treatments including antiplatelet agents, nitroglycerin, and beta blockers: antithrombotic agents are considered safe during pregnancy but the decision to use them should be made jointly by emergent consultation with a cardiologist and the patient's obstetrician. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists, and statins are not advised until the postpartum period. Aspirin is the first-line antiplatelet agent. Clopidogrel has been studied in case reports with no adverse fetal outcomes and ACOG recommends that it can be used with caution, primarily after stenting. Ticagrelor, prasugrel, and bivalirudin are not recommended due to teratogenicity in animal studies. Heparin has long been the antithrombotic of choice for pregnant patients, although low-molecular-weight agents such as enoxaparin also do not cross the placenta and are considered efficacious and safe in pregnancy.

Cardiac catheterization with stenting is the treatment of choice for AMI in the pregnant patient and, with shielding, exposes the fetus to less than 1 radiation-absorbed dose (rad). However, both ACOG and the European Society of Cardiology recommend a conservative approach when considering cardiac catheterization in patients who may potentially have a coronary artery dissection. When a catheterization laboratory is unavailable, lifesaving thrombolytic therapy should not be withheld. Although thrombolytics do not cross the placenta, there is an increased risk of maternal hemorrhage and, in the setting of

AMI caused by coronary dissection, thrombolytic use can worsen the dissection. Because thrombolytic therapy precludes major surgery and epidural anesthesia in the hours to days immediately after administration, one must carefully consider whether to use these agents in pregnant women who are close to term, especially if the need for cesarean delivery is anticipated.

In the setting of peripartum AMI, labor should be conducted with continuous monitoring of the mother's hemodynamic status and fetal well-being. Assisted vaginal delivery is preferred unless there is an indication for cesarean section. Cesarean section avoids prolonged exertion by the mother but can subject the patient to general anesthesia if the use of antithrombotic agents precludes epidural catheter placement.

Valvular Heart Disease and Pulmonary Hypertension

Foundations. Valvular heart disease, including both native and mechanical valves, can lead to acute heart failure during pregnancy and is associated with both higher maternal and fetal mortality. The ability of patients to tolerate pregnancy without significant adverse effects depends on the type and severity of the lesion. Mild to moderate lesions (New York Heart Association [NYHA] classes I and II) are often associated with good outcomes for the mother and fetus. On the other hand, mitral stenosis (beyond class I), advanced aortic stenosis, and aortic and mitral lesions associated with moderate to severe ventricular dysfunction or pulmonary hypertension, as well as mechanical prosthetic valves requiring anticoagulation, can result in maternal mortality and require directed therapy and expert cardiology consultation.

Heart failure is the most common maternal complication in pregnancy with valvular heart disease, and women with cardiomyopathy, an NYHA functional class III or higher, pre-pregnancy heart failure, and pulmonary hypertension are at the highest risk. Diagnosing heart failure is challenging because women in the last months of pregnancy experience symptoms such as dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, and pedal edema that are identical to those of heart failure. Normal B-type natriuretic peptide (BNP) levels can be used to rule out heart failure in pregnant females but, because BNP levels increase twofold in pregnant females, a mildly elevated BNP level can be difficult to interpret.

Pulmonary Hypertension. Pregnancy is poorly tolerated by patients with pulmonary hypertension because the pulmonary circulation cannot cope with the increased stroke volume and cardiac output of pregnancy, causing pulmonary pressures to rise. This causes dyspnea, heart failure, and syncope. Mortality in pregnant women with pulmonary hypertension can approach 30%. Pregnancy is contraindicated, and patients early in pregnancy should be counseled about elective pregnancy termination.

The treatment of the pregnant patient with pulmonary hypertension focuses on diuresis and pulmonary vasodilation. Diuretics are indicated for the management of volume overload, and common diuretics—with the exception of spironolactone—are considered safe, although limited data exist regarding their effect on the fetus. Specific agents for treating pulmonary hypertension include endothelin receptor agonists (ERAs), phosphodiesterase inhibitors, and prostanoids. Phosphodiesterase inhibitors such as sildenafil and tadalafil, as well as the prostacyclin derivatives epoprostenol and treprostinil, are fetotoxic in animals; however, the benefits outweighs the risks, so they are regularly used in pregnancy. ERAs such as bosentan and ambrisentan are teratogenic.

Mitral Stenosis. Mitral stenosis is the most commonly encountered valvular lesion in pregnancy but is typically well tolerated except in moderate to severe disease. The increased resting heart rate and stroke volume in normal pregnancy increase the pressure gradient across the mitral valve and can cause symptoms of left heart failure, as well as atrial arrhythmias such as atrial fibrillation. The likelihood of maternal symptoms and worsening of cardiovascular status is directly related to the severity of disease.

Beta blockers are the mainstay of treatment for patients with symptomatic mitral stenosis in order to prevent tachycardia and maintain preload to overcome obstruction. Diuretics may also be used for patients with symptoms of heart failure. Surgical intervention is indicated for patients with refractory symptoms despite optimal medical management and in patients with pulmonary hypertension.

Aortic and Mitral Regurgitation. Mitral valve prolapse is the most common cause of mitral regurgitation in developed countries, whereas rheumatic heart disease is the most common cause worldwide. In most cases, chronic regurgitation lesions are well tolerated during pregnancy and may even improve because the reduced systemic vascular resistance of pregnancy allows more forward and less regurgitant flow. However, heart failure occurs in 20% to 25% of women with moderate or severe mitral regurgitation. When necessary, medical therapy consists of diuresis, digoxin, and vasodilators.

Aortic Stenosis. Symptomatic aortic stenosis during pregnancy usually occurs in the setting of a congenital bicuspid valve and patients with severe aortic stenosis may first become symptomatic during pregnancy. Patients with mild to moderate aortic stenosis tend to have uncomplicated pregnancies; conservative management is often possible, especially if the aortic valve area is greater than 1.0 cm^2. Patients with symptomatic aortic stenosis may respond to bed rest or preload reduction with diuretics. Severely symptomatic patients may need percutaneous valvotomy and surgical replacement.

Prosthetic Heart Valves. Pregnant women with mechanical heart valves are classified as high risk with a World Health Organization (WHO) risk classification III. The Registry of Pregnancy and Cardiac Disease (ROPAC) found that 82% of pregnancies in women with a mechanical heart valve ended with a live mother and child compared to 98% in pregnant women without a mechanical heart valve.[15] Thrombotic events occurred in 5% of women in the ROPAC registry with a mortality of 20%. Warfarin is the most effective anticoagulant in preventing maternal thromboembolic events. However, warfarin is considered teratogenic in the first trimester and is associated with a higher risk of fetal loss and fetal hemorrhage. Neither unfractionated heparin (UFH) nor low-molecular-weight heparin (LMWH) crosses the placenta and are not teratogenic. However, their use throughout pregnancy is not recommended due to the increased risk of thromboembolic events as compared to using UFH or LMWH in the first trimester, followed by warfarin for the remainder of pregnancy.[16]

Current anticoagulation recommendations in pregnant patients with prosthetic heart valves are to continue using warfarin until pregnancy has been achieved. If an international normalized ratio of 2.5 to 3.5 can be achieved with a warfarin dose less than or equal to 5 mg, the AHA/ACC and European Society of Cardiology Guidelines slightly prefer the use of warfarin throughout pregnancy after a full discussion with the patient about the benefits and risks of the therapy. If a dose more than 5 mg is required, UFH or LWMH is recommended in the first trimester, with warfarin being resumed for the second and third trimesters. Warfarin should again be replaced by UFH or LWMH several weeks before delivery.

HEMATOLOGIC DISORDERS

Anemia

Anemia is the most common medical complication of pregnancy and is associated with maternal mortality, perinatal mortality, preterm birth,

low birth weight, and small-for-gestational-age infants. The classic clinical presentations of anemia include pallor, fatigue, and shortness of breath. Most anemia, however, is asymptomatic. The WHO defines anemia of pregnancy as a hemoglobin of less than 11 g/dL. The hemoglobin threshold for severe anemia requiring blood transfusions is typically considered to be less than 7 g/dL for gravid patients and less than 8 g/dL for postpartum patients. There are several types of anemia, but four types predominate: dilutional anemia, iron deficiency, folate deficiency, and sickle cell hemoglobinopathy.

Dilutional Anemia

Dilutional anemia is normally seen with pregnancy. In preparation for blood loss at delivery, blood volume increases by nearly 50% between weeks 6 and 34. This rapid blood volume increase, accompanied by a lag in red blood cell (RBC) production, results in a dilution of hemoglobin. The result is that the threshold for diagnosing anemia in gravid patients is slightly lower (11 g/dL) than in nongravid patients (12 g/dL). Hemoglobin concentrations typically reach their nadir between weeks 26 to 28 of pregnancy. Clinicians should consider that gravid patients with hemoglobin values of 13 to 15 g/dL have inadequate expansion of their plasma volume, which can result in outcomes like low birthweight and premature birth.

Iron Deficiency Anemia

Iron deficiency occurs in 18% of pregnancies in the United States (US) with iron deficiency anemia occurring in approximately 5%.[17] The risks of adverse pregnancy outcomes are correlated to the severity of the anemia. Studies show a higher risk of preterm birth and low birth weight in women with mild to moderate anemia. Severe anemia (<6 to 7 g/dL or 60–70 g/L) is associated with increased fetal mortality, abnormal fetal oxygenation, premature rupture of membranes, gestational hypertension, and reduced volume of amniotic fluid. The diagnosis of iron deficiency is difficult to make because many of the serum biomarkers typically used are affected by the changes in maternal physiology. Ferritin is the most sensitive test for iron deficiency in pregnancy, with a cutoff of 30 ng/mL showing a 92% sensitivity and a 98% specificity, but it is affected by the increased plasma volume in later pregnancy. Mean corpuscular volume, total iron-binding capacity, and transferrin are less sensitive and specific than ferritin for iron deficiency

The ACOG has developed guidelines for the management of iron deficiency anemia. Patients with an uncomplicated physiologic anemia who are not iron deficient can be expected to have good obstetric outcomes without therapy and do not require treatment. Patients presenting with mild iron deficiency anemia (i.e., a hemoglobin of 9–10.5 g/dL) should be treated with non–enteric-coated supplemental iron. A single daily dose of iron appears to be as effective as multiple-dosing regimens and decreases the risk for GERD, which is already heightened in pregnancy. Intravenous iron is not used in the first trimester, but is the treatment of choice for all iron deficiency anemia in the third trimester and severe iron deficiency anemia (hemoglobin < 9 g/dL) in the second trimester.

The evidence for the use of prophylactic supplementation in women with normal hemoglobin levels (>11 g/dL [110 g/L]) and normal iron stores (ferritin > 30 mg/dL [20 μg/L]) to prevent anemia in late pregnancy is mixed. However, recent studies demonstrate that prenatal iron supplementation reduces the risk of iron deficiency anemia at term. ACOG, the WHO, and other major health authorities recommend at least 30 mg of ferrous iron daily during pregnancy. Intermittent dosing at two to three times a week provides the same maternal and offspring benefits while reducing the risk of side effects like heartburn, constipation, and nausea.[18]

Folate Deficiency

Folate is critical to several intracellular processes associated with cell growth. However, due to the 5- to 10-fold increase in folate requirements during pregnancy, gravid patients are at risk for folate deficiency. Folate deficiency is one of a number of causes of megaloblastic anemia, which is the second most common anemia. The incidence of folate deficiency in pregnancy is low in high income countries but remains higher in other populations. The risk for development of folate deficiency is increased in patients with multiple gestations, short interpregnancy intervals, preexisting malnutrition, hyperemesis gravidarum, malabsorption syndromes, alcoholism, use of certain antiepileptic drugs, and diets lacking green leafy vegetables and animal protein. Low maternal folate stores have, most importantly, been linked to increased risk of neural tube defects, as well as increased risk of placental abruption, preterm birth and low birth weight, preeclampsia, and spontaneous abortion. As is the case for iron deficiency, effects on the fetus depend on the degree of anemia.

Iron deficiency and folate deficiency anemias often coexist, making the peripheral blood smear difficult to interpret. In cases of suspected folate deficiency, the measurement of serum and RBC folate levels is indicated. However, the serum folate level is noted to exhibit a rapid response to folate intake, and low levels may normalize within days after a folate-rich meal. Oral folate supplementation with 0.4 mg daily is routinely recommended for all women before conception, and 0.4 to 0.8 mg is recommended during pregnancy as the requirement for this micronutrient increases during gestation. ACOG recommends 1.0 mg for those women who have a known pregnancy-related folate deficiency. Women at higher risk for neural tube defects (e.g., neural tube defects in prior pregnancy) are advised to take much higher doses of folate, 4 mg daily for 1 month pre-conception and at least until 12 weeks gestational age under close supervision of their obstetrician. ACOG advises continuing oral folate supplementation throughout the second and third trimesters.

Sickle Cell Anemia

Sickle cell disease (SCD) is one of the major sources of maternal and fetal complications in the United States. Patients with SCD are subject to many chronic medical problems due to a variety of pathophysiologic mechanisms, including sickling of RBCs, anemia, immunosuppression caused by auto-splenectomy, and repeated transfusion. Median life expectancy is in the fifth decade for both genders affected by SCD, and female fertility is generally unaffected, so it is likely that the emergency clinician will encounter pregnant patients with the disease. Maternal complications are common in patients with SCD; these include preterm labor, premature rupture of membranes, maternal infections, more frequent pain crises, thrombosis, preeclampsia, and increased need for cesarean delivery. Due to these complications, pregnant women with SCD have a sixfold increased risk of maternal death compared with controls.

SCD also results in adverse effects on the fetus. Placental infarction and insufficiency are common, and the incidence of premature labor, small-for-gestational-age infants, and low-birth-weight infants is significantly increased in SCD pregnancies compared with normal controls. Perinatal mortality rates vary but are low in the setting of appropriate maternal and neonatal care.

Vasoocclusive crises and anemia occur more often in pregnancy and are the most common complications of SCD in pregnancy. Studies have also demonstrated that venous thromboembolisms occur 1.7 to 10 times more frequently in pregnant women with SCD. Recommended treatment is similar to that for the nonpregnant patient with a few exceptions. Hydroxyurea is not recommended for use in pregnancy because of potential teratogenicity, and nonsteroidal antiinflammatory drugs (NSAIDs) are avoided after 30 weeks of gestation.

General anesthesia can result in an increase in postpartum sickling complications, so regional anesthesia is preferred in the case of cesarean delivery. The use of supplemental iron and transfusion is controversial because of the potential for iron overload, alloimmunization, volume overload, and hyperviscosity syndrome.

Therapeutic transfusions should be given to patients with severe disease manifestations such as symptomatic anemia, cardiopulmonary instability, acute chest syndrome, intrapartum hemorrhage, and preeclampsia. In general, the goal with transfusion or exchange transfusion is to lower the percentage of hemoglobin S to 40% and achieve hemoglobin values of approximately 10 g/dL (110 g/L). Prophylactic red blood cell transfusions are often used in pregnant women with SCD without the indications for a therapeutic transfusion in order to decrease the frequency and severity of vaso-occlusive pain episodes during pregnancy.[19] Only low quality studies are available, but they show a reduction in maternal mortality, vasoocclusive pain episodes, pulmonary complications, and neonatal death. There is no consensus at this time whether the benefits of prophylactic transfusions outweigh the risks.

NEUROLOGIC DISORDERS

Epilepsy

Epilepsy is the most common neurologic complication of pregnancy but remains relatively rare, affecting less than 1% of all gestations. The treatment of epilepsy during pregnancy entails balancing the risk of increased frequency and duration of seizures to the mother and fetus against the teratogenic risks of antiepileptic drugs (AEDs).

Gravid patients with epilepsy have more than a tenfold increased risk of death compared to pregnant women without epilepsy. Pregnant women with epilepsy are also at increased risk for cesarean section, postpartum hemorrhage, hypertensive disorders and other adverse outcomes. Approximately 15% of patients experience an increase in seizure frequency during pregnancy. Delivery and the first 24 hours postpartum are the most likely times for a seizure to occur, with a ninefold greater incidence of seizure than during pregnancy in general.

A decrease in plasma drug concentrations is expected due to pharmacokinetic alterations including decreased absorption, increased volume of distribution, elevated renal excretion, and induction of hepatic metabolism; many experts recommend that maternal plasma drug levels be monitored and compared to prepregnancy levels.[20] Antiepileptic medications also increase the clearance of medications, including oral contraceptives, making unintentional pregnancy a possibility. Patients who have nonconvulsive seizure disorders or who are seizure-free for a sufficient period of time before conception are candidates for nonpharmacologic observation because the risk of treatment with AEDs can outweigh the benefit. This decision should be deferred to the patient's primary physician or neurologist. However, there are obstetric complications related to prolonged seizure activity, and long-term treatment with an AED for most patients with seizures is warranted.

The primary complication of AED use in pregnancy is congenital malformations. Of primary concern is the risk for neural tube defects, facial clefts, cardiac anomalies, and cognitive defects with the older generation agents (e.g., valproate, carbamazepine, phenytoin) and several of the newer generation agents (e.g., gabapentin, topiramate). There is a two- to three-fold increase in the incidence of serious congenital malformations in offspring of epileptic mothers taking these agents. The risk is greatest with valproate and is also increased with AED polypharmacy and increased dose of individual agents. Recent studies have found that monotherapy with lamotrigine and levetiracetam does not have a higher risk of major congenital malformations than control.[21]

When compared to the older AEDs, levetiracetam performed as well at controlling seizures when used in monotherapy, while lamotrigine and topiramate, when used in monotherapy, showed worse seizure control. In the case of lamotrigine, this was due to increased renal clearance leading to variable levels. Because phenytoin, carbamazepine, valproate, and possibly other AEDs interfere with folate metabolism, oral supplementation with at least 0.4 to 1.0 mg/day is recommended for all women of childbearing age taking these drugs to help prevent congenital malformations such as neural tube defects. Enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital have been reported to cause neonatal vitamin K deficiency and neonatal hemorrhage, but the American Academy of Neurology and American Epilepsy Society have noted that there is inadequate evidence to determine a definitive relationship.

Status epilepticus in pregnancy is relatively rare and can occur at any time during gestation, with a higher likelihood in the postpartum period. Any potential cause of seizure may result in status epilepticus, and recent studies have shown that eclampsia, posterior reversible encephalopathy syndrome, and cerebral venous thrombosis are all common causes. It may also occur in patients who have been seizure-free throughout pregnancy, and no specific risk factors for its occurrence have been identified. The risk of untreated status epilepticus to the mother and fetus clearly outweighs the potential for adverse teratogenic effects, and standard resuscitative measures, as well as drug therapy, are indicated. Benzodiazepines followed by levetiracetam are recommended.[22] Continuous fetal monitoring should be instituted as soon as possible to observe for signs of fetal hypoxia, and the mother should be positioned in the left lateral decubitus position to avoid the supine hypotensive syndrome.

Multiple Sclerosis

Multiple sclerosis (MS) affects approximately 400,000 Americans and is twice as common in women as in men. The peak age at onset is 20 to 35 years, which overlaps peak childbearing years. The disease is characterized by intermittent episodes of central nervous system (CNS) demyelination, with consequent neurologic impairment that follows a relapsing-remitting course. Progressive neurologic deficits and permanent disability develop in certain patients.

The frequency and severity of exacerbations of MS often improve during pregnancy, particularly during the third trimester. During the 3 months after delivery, the rate of relapse increases and then returns to the patients' pre-pregnancy baseline. Relapses are more likely in MS patients with higher disability at the time of pregnancy onset, as well as women treated with natalizumab and fingolimod.[23] However, it does not seem that postpartum relapses are related to the duration of disease or total number of relapses before conception.

MS patients with disease exacerbation are often treated with immunomodulators such as intravenous immune globulin (IVIG), corticosteroids, glatiramer acetate, and interferon beta. Small studies in gravid patients have shown that the use of IVIG during pregnancy and in the postpartum period is safe and may decrease the relapse rate. Likewise, the use of intermittent steroids in the postpartum period may decrease the likelihood of disease relapse. Glatiramer acetate may also be used in pregnancy as needed as studies have not shown any fetal toxicity.[24]

Spinal Cord Injury

Because spinal cord injury (SCI) occurs mainly in young people and usually does not impair fertility, there is a relatively large population of paraplegic and quadriplegic patients who become pregnant. The most common complication in pregnant women with SCI is urinary tract

infection (UTI). One study showed that pregnant women with SCI were 26 times more likely to get a UTI than controls, while another found that 30% of gravid women with SCI developed pyelonephritis.[25] A high suspicion must be kept for UTIs in this population, as untreated infections carry an increased risk of fetal loss, prematurity, and maternal sepsis.

The hypercoagulable state of pregnancy, combined with chronic immobilization, results in an increased incidence of thromboembolic disease, with a nine times greater risk of venous thromboembolism versus control.

Autonomic dysreflexia is the most serious complication of SCI and occurs in up to 56% of women with high lesions (above T5-T6); it occurs with increased frequency during pregnancy. Autonomic dysreflexia is manifested as severe paroxysmal hypertension, headache, tachycardia, diaphoresis, piloerection, mydriasis, and nasal congestion. It is often precipitated by afferent stimuli from the hollow viscus such as the bladder, bowel, or uterus. Symptoms of autonomic dysreflexia often occur with uterine contractions during labor. However, labor may be difficult to detect because patients with spinal cord lesions below T10 to T12 have an intact uterine nerve supply and experience labor pains; however, with lesions above T10, labor may be imperceptible or experienced as only mild abdominal discomfort. Pregnant patients with SCI with symptoms of autonomic dysreflexia should be assessed for cervical dilation and have uterine contractions monitored. ED treatment is directed at the restoration of normal blood pressure with standard agents. Definitive therapy is with regional anesthesia. Spinal anesthesia and epidural anesthesia obliterate and prevent this response and should be used as soon as possible during labor for all women with SCI. Finally, it can be difficult to differentiate between the symptoms of autonomic dysreflexia and preeclampsia. In autonomic dysreflexia, symptoms such as hypertension will resolve once the stimuli to the skin or hollow viscus have been relieved; in preeclampsia, the symptoms and laboratory abnormalities are more likely to persist.

Myasthenia Gravis

Myasthenia gravis is a rare disorder in which autoimmune destruction of the postsynaptic cholinergic receptor results in profound muscle fatigability. The effect of pregnancy and the postpartum state on myasthenia gravis is unpredictable in the individual patient, but overall, approximately 25% to 50% of patients experience exacerbation of disease, with the remainder having improvement or no change in disease severity.[26] Disease exacerbations can occur anytime during pregnancy and the postpartum period and are not more likely in one trimester than in another. Additionally up to 15% of women will experience their first myasthenia symptoms in the pregnancy or postpartum period. Because of weight gain, anemia, and other physiologic adjustments of pregnancy that may result in fatigue, the distinction between normal pregnancy symptoms and myasthenia may be difficult.

Most deliveries are accomplished vaginally without complication in adequately treated patients; assisted and surgical delivery in these women is indicated mainly for obstetric reasons rather than for specific myasthenia-related care.[27] Between 10% and 20% of neonates born to mothers with myasthenia gravis have a transient neonatal myasthenia syndrome through the placental transport of acetylcholine receptor antibodies. There is no correlation between the severity of maternal disease and occurrence of neonatal myasthenia. The onset of neonatal myasthenia is typically within the first hours of life but may be delayed by a period of days. Manifestations include poor feeding and suck, diminished reflexes, hypotonia, and bulbar and respiratory muscle weakness. As in adults, the symptoms respond to cholinesterase inhibitors, but treatment should be carried out in an intensive care unit setting.

Myasthenia crises during pregnancy present with typical symptoms of painless fluctuating weakness of skeletal muscles. Diplopia and ptosis are the most common early symptoms. When exacerbations do occur, treatment is no different from the treatment of nonpregnant patients. Acetylcholine esterase inhibitors, corticosteroids, IVIG, and plasmapheresis are all considered safe for the mother and fetus. Azathioprine and cyclosporine are considered second-line options for patients who are not controlled or who cannot tolerate corticosteroids. Assessment of pulse oximetry, forced vital capacity, and arterial blood gas parameters will guide respiratory therapy.

Magnesium sulfate is contraindicated for treatment of eclampsia in myasthenia gravis because of its neuromuscular blocking effects; barbiturates or phenytoin should be used instead.[27] Epidural anesthesia is also recommended to reduce pain and fatigue.

RENAL DISORDERS

Chronic kidney disease (CKD) can be silent well into its disease course and is more difficult to diagnose in pregnancy because of expected decreased blood urea nitrogen (BUN) and creatinine levels during pregnancy. For women with known renal disease, including end-stage renal disease (ERSD), on hemodialysis, conception rates have shown some improvement, but seem plateaued at roughly 10%.

CKD in and of itself is an independent risk factor for maternal and fetal complications. The degree of underlying renal dysfunction is a strong determinant of morbidity associated with pregnancy. Patients with moderate to severe renal dysfunction have a much higher risk of further decline in renal function, as well as adverse obstetric outcomes, including preeclampsia, placental abruption, fetal loss, preterm delivery, low birth weight, polyhydramnios, and increased need for cesarean section and neonatal intensive care. Worsening of underlying renal function is more likely in patients with a decreased glomerular filtration rate who also have associated proteinuria or hypertension. Because worsening renal function is manifested by hypertension and proteinuria, differentiation from preeclampsia can be difficult. In this setting, it is best to treat the patient for presumed preeclampsia, with the caveat that magnesium administration should be performed judiciously and carefully guided by serum magnesium levels.

Pregnant women with chronic renal failure require aggressive and timely management to optimize their chances for a successful gestation without causing further deterioration in renal function. One of the most successful tenets of CKD management in pregnancy is close control of blood pressure and monitoring for proteinuria. Thresholds for initiation of hemodialysis (HD) in pregnant patients are considered lower than those in nongravid patients. Intensified HD, through longer and/or more frequent dialysis sessions, offers improved maternal and neonatal outcomes.

Adverse pregnancy outcomes in HD patients include miscarriage, placental detachment, anemia, infections, premature rupture of membranes, polyhydramnios, preterm birth, uncontrolled arterial hypertension, preeclampsia/eclampsia, hemorrhage, need for a caesarean section and maternal death

For patients who are post–renal transplantation, fertility rates return to prerenal failure levels within 1 to 6 months post-transplantation, so pregnancy is not an uncommon finding in post-transplantation women of childbearing age. Obstetric outcomes for this patient population show live birth rates exceeding 70%, and adverse outcomes mostly associated with preterm births and with infants small for gestational age (SGA).

METABOLIC AND ENDOCRINE DISORDERS

Diabetes

General Management

Three types of diabetes affect pregnant patients—type 1, or insulin-dependent diabetes mellitus (T1DM); type 2, or non–insulin-dependent diabetes mellitus (T2DM); and gestational diabetes mellitus (GDM). The considerations for glycemic control in GDM are the same as those for T1DM and T2DM.

Both T1DM and T2DM are growing in prevalence, representing a challenge to the management of these high-risk obstetric patients. Technical advances in glycemic control have improved the potential for successful pregnancy outcomes, but euglycemic control is not the norm for these patient populations, especially given the tight control advised by ACOG.

Although T2DM is sometimes considered a more benign form of disease, the risk of pregnancy complications and fetal malformations is still significant and rates of elective cesarean section are increased compared to nondiabetic norms due to the development of neonatal macrosomia. Ideally, hemoglobin A_{1c} (HbA_{1c}) values should not be higher than 6%. T2DM patients are generally recommended to transition to insulin therapy to achieve tighter glycemic regulation during pregnancy.

T1DM does connote a much higher rate of preeclampsia, maternal mortality, premature delivery, neonatal hypoglycemia, congenital abnormalities and stillbirths. Preconception planning in this patient population is paramount, and tight glycemic control for at least 4 months prior to conception is recommended. Maternal and fetal complications are largely related to inadequate glycemic control and to the presence of vascular complications or severe renal insufficiency more than to the type of diabetes.

The effects of pregnancy on underlying diabetes vary by organ system. The data are limited, but pregnancy is not advised for diabetic patients with coronary artery disease because of the cardiovascular demands of pregnancy and high mortality rates of AMI during pregnancy. Given the likelihood of silent ischemic events in the diabetic population, atypical or vague presentations of angina or MI, including new-onset congestive heart failure should be carefully evaluated in those with preexisting known coronary artery disease, but also in any diabetic mother.

Patients with diabetic nephropathy are at increased risk for preeclampsia and the subsequent requirement for preterm delivery. Following progression of nephropathy closely in conjunction with aggressive blood pressure control and optimizing protein intake are strongly recommended.

Angioproliferation is a natural physiologic response in pregnancy, and because of this, diabetic retinopathy worsens acutely in 30% of DM1 and 12% of DM2 patients during pregnancy. Those at greatest risk for this are patients with high HbA_{1c} levels, hypertension, nephropathy, and active nonproliferative or proliferative retinopathy. New onset diabetic retinopathy during pregnancy occurs 10% of the time with DM1. Laser therapy of preexisting retinopathy is recommended before conception, as well as for pregnant patients with severe disease. Patients with known proliferative retinopathy should be counseled to avoid excessive, aggressive Valsalva maneuvers during labor to minimize the risk of retinal hemorrhages.

Autonomic neuropathy does not accelerate during pregnancy, with the exception of a possible increase in symptomatic severity of gastroparesis.

Hyperglycemic

Physiologically, insulin sensitivity increases in the first trimester, allowing for decreased insulin usage. This reverses in the second and third trimesters, ultimately increasing to 70% to 100% of baseline nonpregnant insulin requirements. The increased risk of diabetic ketoacidosis (DKA) results from intercurrent illness including hyperemesis, inadequate insulin administration, or iatrogenically from use of betamimetic medications for tocolysis, and use of corticosteroids to hasten fetal lung maturity, or from withholding insulin therapy for planned procedures. During pregnancy there is a continuous need for a basal rate of insulin, whether by insulin pump or long-acting (Lantus) insulin. Relying on a basic metabolic profile as screening for DKA in pregnancy (e.g., insulin glargine) can be dangerous. The serum pH may be deceptively normal in a pregnant patient with DKA because the initial pH tends to be higher in pregnancy as a result of physiologic hyperventilation. In addition, the serum glucose concentration may be normal or only moderately elevated. Screening with serum acetone or betahydroxybutarate is recommended for any pregnant DM patient with vague symptoms of headache, nausea, vomiting, or fatigue.

The treatment of DKA does not differ in pregnancy versus nonpregnant patients, except that fluid resuscitation and insulin therapy should be maintained in the presence of normoglycemia until bicarbonate levels return to normal, indicating that any lagging acidemia has cleared. Fetal viability and well-being should be assessed in all cases of maternal DKA. Fetal mortality associated with DKA can be as high as 35%.

Hypoglycemia

The risk for hypoglycemia is bimodal, mostly in the first trimester but also in the peripartum period. In the first trimester, insulin needs decrease and physiologic hormonal counter-regulation to hypoglycemia including glucagon, cortisol, and epinephrine surge is blunted. A contributing factor for some patients is the comorbid condition of gastroparesis, which can worsen hyperemesis gravidarum (HG); 18% to 40% of patients have at least 1 severe episode of hypoglycemia in the first trimester, almost always at night. Even subclinical hypoglycemia (sustained levels <85 mg/dl) can lead to low-birth-weight neonates, so ideal ranges for glycemic control are extremely tight between 90 to 120 mg/dl.

Fetal Effects

Diabetes has many deleterious effects on the fetus. The risk of congenital anomalies in infants of diabetic mothers (IDMs) is as high as 10%. The rate of congenital malformations in patients with prepregnancy diabetes is increased threefold or fourfold compared with the nondiabetic population, with anomalies being more likely in pregnant women with poor glycemic control. Macrosomia is the most likely factor leading to the need for cesarean section and has been associated with shoulder dystocia. Conversely, preeclampsia and placental infarction secondary to vascular disease may result in impaired fetal development and stillbirth. Diabetic patients are also at increased risk of spontaneous preterm delivery and labor-induced preterm deliveries. Neonatal complications seen at increased rates in infants of diabetic mothers (IDMs) include transient tachypnea of the newborn, neonatal hypoglycemia, hypocalcemia in the peripartum period, hyperbilirubinemia, polycythemia, cardiomyopathy, and respiratory distress as a result of fetal hyperinsulinemia. Elective delivery is indicated in the setting of poor metabolic control, significant diabetic complications, and fetal macrosomia with suspected birth weight more than 4500 g.

OBESITY

The incidence of obesity is increasing, and it has become the most common medical condition in women of childbearing age. It is an independent risk factor of poor outcomes, even without the comorbid conditions of diabetes, vascular disease, or hypertension. In early

gestation, obesity is associated with spontaneous pregnancy loss and congenital anomalies. Increased insulin resistance in obese gravid patients can manifest clinically in late gestation as glucose intolerance and fetal overgrowth. At term, the risk of cesarean section is increased, threefold of that seen in the nonobese population because of inadequate contraction patterns in labor, leading to failure to progress, caused by an independent influence of obesity on myometrial activity, compounded by macrosomia.

Peripartum and postpartum, obese women have a more marked increased risk of venous thromboembolism and depression compared to nonobese counterparts. Meta-analysis has shown obesity to be an independent risk factor for infant death and neonatal asthma; this risk is proportional to increased body mass index (BMI). The BMI does not appear to be correlated with postpartum hemorrhage requiring intervention, severe maternal morbidity or maternal mortality, or spontaneous preterm delivery before 32 weeks of gestation.

THYROID DISORDERS

Hyperthyroidism

Hyperthyroidism affects less than 0.5% of all pregnancies, of which 85% are Graves disease. Because the symptoms of worsening hyperthyroidism resemble the physiologic changes expected during pregnancy in many respects, the diagnosis may not be immediately evident. In the first trimester, most gravid patients with Graves disease will experience a transient exacerbation, but improvement in later pregnancy. A postpartum rebound exacerbation is common.

Thyroid storm is the most serious manifestation of the disease and may be precipitated by stressors such as infection and delivery; it is manifested by fever, dysrhythmias, myocardial dysfunction, and circulatory collapse. Many of these symptoms appear similar to those of eclampsia, so obtaining TSH and free T4 levels on eclamptic patients is recommended. The symptom most helpful in differentiating thyrotoxicosis from thyroid storm is markedly altered mental status seen with thyroid storm. Untreated, mortality approaches 100%, but prompt recognition and aggressive therapy have lowered mortality to 20% to 30%. In addition to more general complications stemming from thyroid hormone excess, early (spontaneous abortion) and late (stillbirth) fetal loss, commonly as a result of placental abruption, are more common in hyperthyroid patients than in the general population.

The mainstay of treating hyperthyroidism consists of thyreostatic drugs. Propylthiouracil is recommended in the first trimester; there is an increased potential for adverse congenital drug effects from methimazole. Post organogenesis, in the second and third trimesters, methimazole is used to limit maternal hepatotoxicity. Most patients respond to pharmacologic manipulation, although thyroidectomy may be considered in severe cases in which patients cannot tolerate antithyroid medication or in the setting of medication failure. Radioiodine is strongly contraindicated during all stages of pregnancy because it will also destroy the fetal thyroid gland.

Additional therapy with beta blockade to mitigate the hemodynamic effects of sympathetic stimulation may be required in certain cases pending disease control with antithyroid medications. Iodide is considered class D in pregnancy because of fetal thyroid sensitivity to the medication; its use should be reserved for severe cases, with duration of therapy limited to days.

Graves disease places the fetus at risk for autoimmune-mediated thyroid dysfunction through placental transfer of maternal thyroid-stimulating immunoglobulins. Up to 20% of neonates of mothers with Graves disease and positive thyroid-stimulating immunoglobulin values have transient hyperthyroidism lasting 3 to 12 weeks. The condition gradually clears as maternal antibodies are metabolized. Manifestations are potentially severe and include irritability, tachycardia, goiter, cardiomegaly, congestive heart failure, premature craniosynostosis, low birth weight, and failure to thrive.

Hypothyroidism

Overt hypothyroidism is often associated with infertility, so most cases seen during pregnancy are less severe. Subclinical disease forms can also be seen or may occur in patients already undergoing levothyroxine therapy for known disease. Undiagnosed subclinical hypothyroidism may become clinically apparent as the metabolic demands of pregnancy unmask deficient thyroid hormone levels. When signs and symptoms do occur, they are generally the same as those in the nonpregnant state. Myxedema coma is extremely rare but should be considered along with other causes of coma in a pregnant patient.

Patients who are already undergoing treatment for hypothyroidism should have therapy optimized pre-conception, but will also require an increased dosage of levothyroxine during pregnancy, especially during the first trimester, in which increases from 20% to 30% are usually required. Compared with euthyroid status, subclinical hypothyroidism in pregnancy is associated with higher rates of gestational hypertension, premature rupture of membranes, intrauterine growth restriction, and low-birth-weight infants; long-term, there is a decreased IQ of the child at age 6 years.

Adrenal Insufficiency

The most common reason for adrenal insufficiency in pregnancy is Addison disease. Early in pregnancy, Addisonian crisis can be mistaken for hyperemesis gravidarum because the clinical features and some electrolyte abnormalities are similar. Overall complications of Addison are greatest in the third trimester, when there is the biggest need for increased cortisol replacement. Careful monitoring of replacement steroids is important to avoid neonatal adrenal insufficiency. Addisonian crisis is precipitated in the gravid patient population by infection, trauma, surgery, delivery or any other significant metabolic stress.

Electrolyte Abnormalities

Gravid patients with primary hyperparathyroidism may develop hypercalcemia, which most commonly presents as nephrolithiasis. Indeed, all pregnant patients with new onset nephrolithiasis should be screened for hypercalcemia. The presence of untreated maternal primary hyperparathyroidism can lead to neonatal hypocalcemia which presents with intrauterine growth restriction, low birth weight, and or neonatal tetany secondary to suppressed development of parathyroid glands. Treatment of the condition is like that in the nongravid state, except that bisphosphonates are contraindicated in pregnancy.

SYSTEMIC INFECTIONS

Human Immunodeficiency Virus Infection

Seroprevalence of HIV infection in pregnant women is decreasing, with more than 8500 annually in 2006 to an estimated less than 5000 in 2018. Treatment of the seropositive HIV pregnant patient with opportunistic infections generally follows similar regimens to nonpregnant patients. There are limited data on specific therapy for opportunistic infections during pregnancy, but clinicians should consider that medication clearance may be affected by various pregnancy-related changes, including increased renal clearance, dilutional anemia, and fetal metabolism of medications. Maternal mortality is increased in HIV-positive mothers, including perinatal sepsis and sepsis related to abortion. Nonpregnancy-related infections, particularly tuberculosis, malaria, and pneumonia, are important causes of maternal death in HIV-infected pregnant or postpartum women.

In patients who are already taking antiretroviral therapy (ART) with good disease control (viral load <1000 copies/mL) at the time of pregnancy diagnosis, the current medication regimen should be continued. For those with a recent diagnosis of HIV, timing of initiation of ART is being reexamined, with a recent meta-analysis suggesting increased risk of preterm or very preterm infants, and low-birthweight neonates, compared to initiating treatment after conception.[28] In the absence of ART treatment, progression of maternal disease does not appear to accelerate during pregnancy, but disease progression is more rapid postpartum. Elective cesarean section is recommended in mothers with a viral load greater than 1000 copies/mL.

HIV does not appear to be an independent risk factor for pregnancy loss and pregnancies generally have good outcomes in patients who receive appropriate HIV treatment during pregnancy. Maternal HIV infection in women who have not received antiretroviral therapy is associated with preterm birth, low birthweight, small for gestational age, and stillbirth.

Vertical transmission of HIV infection (maternal to neonate) remains a monumental challenge in low resource countries with high HIV prevalence (notably sub-Saharan Africa), but is less prevalent in the US due to wide-ranging maternal HIV screening practices. In 2017, only 73 children under the age of 13 received a diagnosis of perinatally acquired HIV in the U.S. Patients presenting to the ED without prenatal care should be screened for HIV as a first point of contact, even if this is shortly after a precipitous delivery. Screening should consist of a rapid combination or fourth generation (antibody/antigen) test, followed by Nucleic Acid Tests (NATs) in high-risk individuals.

Tuberculosis

Comorbid infection or activation of latent tuberculosis (TB) during pregnancy can be challenging to diagnose because pregnancy may mimic and thus mask the symptoms of early tuberculosis (e.g., tachypnea and fatigue). Presenting symptoms in pregnancy are similar to those in the nonpregnant population, including cough, weight loss, fever, malaise, and fatigue. Moderate to severe anemia in an HIV-infected mother during pregnancy should prompt a workup for TB.

Tuberculosis does not appear to accelerate during pregnancy, nor does the pregnant state affect the site of infections. TB activation much more common in the postpartum period than in the prenatal period.

Infants born to TB-infected mothers have a twofold to threefold increased risk of prematurity and low birth weight and increased perinatal death. There is a well-defined constellation of neonatal clinical manifestations marked by cutaneous and mucosal lesions within the first week of life and a primary hepatic complex including caseating hepatic granulomas. These increased risks are highly associated with late diagnosis, inadequate treatment, and advanced disease. Pregnant women with active tuberculosis should begin therapy as soon as the diagnosis is established. The risk of transmission of the organism to the infant outweighs the risks of the drugs to the mother's own health.

The preferred initial treatment for pregnant women is the combination of INH, rifampin, and ethambutol, which has not been shown to be teratogenic. Rifampin and INH freely cross the placenta. Second-line drugs have higher risks of teratogenicity and require more judicious use.

Syphilis

The incidence of primary and secondary syphilis among US reproductive age women has steadily increased since the late 1990s and the incidence of congenital syphilis has shown a similar increase.

Syphilis causes numerous gestational complications, but its most significant sequela is congenital syphilis. This syndrome is characterized by hepatosplenomegaly, osteochondritis, jaundice, rash, lymphadenopathy, rhinitis, Hutchinson teeth, and anemia. Infant mortality related to congenital syphilis is high. Fetal ultrasonography before the 20th week of gestation is indicated to assess for abnormalities consistent with congenital syphilis. Sonographic signs of fetal syphilis confer a higher risk of congenital syphilis at delivery, and few of these completely regress after sufficient treatment.

Treatment is identical to that given to nonpregnant patients, with the use of benzathine penicillin G appropriate for the disease stage. During pregnancy, penicillin is the only known effective treatment for congenital syphilis, and pregnant patients with penicillin allergy should be desensitized and treated with penicillin. Treatment failures leading to congenital syphilis are more likely in mothers with secondary syphilis, high Venereal Disease Research Laboratory or rapid plasma reagin test levels, and an interval from treatment to delivery of less than 30 days.

Viral Hepatitis

Hepatitis B

There are 14,000 new cases of hepatitis B reported annually in the United States, but this is likely an underestimation of disease burden, given the absence of symptoms in early infection. From 800,000 to 1.4 million people in the United States have chronic hepatitis B. Perinatal transmission is approximately 10% to 20% in women seropositive for HBV surface antigen (HBsAg) alone but approaches 90% in mothers who are seropositive for HBsAg and HBV envelope antigen (HBeAg); it is also more likely if the mother has acute infection during the third trimester. Of infants who have HBV infection, up to 90% become chronic carriers as adults and are at risk for complications such as cirrhosis and hepatocellular carcinoma.

Studies have suggested that lamivudine given in late pregnancy to women with high viral loads of HBV DNA reduces viral transmission when used in conjunction with HBV vaccine and immune globulin. Infants of HBsAg-positive mothers should receive hepatitis B immune globulin and the first dose of vaccine within 12 hours of birth. Two additional doses of vaccine are administered at a later date.

Hepatitis C

Between 2009 and 2019, there were 94,824 reported cases of maternal HCV infection among 31 million (0.30%) live births in the United States. The rate of maternal HCV infection increased from 1.8 to 4.7 cases per 1000 live births.[29]

Vertical transmission is rare in mothers with anti-HCV antibodies and no circulating HCV RNA. However, perinatal transmission is increased by the presence of HCV viremia, occurring in approximately 5% of cases. The transmission rate is even higher in the setting of co-infection with HIV; the rates of HCV co-infectivity with HIV are about 10-fold higher than that seen in non–HIV-infected mothers. Perinatal transmission is now the leading cause of HCV transmission to children in middle and high income countries. Cesarean delivery has not been shown to prevent HCV transmission. There is no available vaccine or immune globulin to prevent hepatitis C, and routine prenatal screening is not indicated.

Obstetrical hemorrhagic complications, including DIC and shock and subsequent need for transfusion are more common among HCV infection, with particularly high rates seen peripartum. HCV mothers have higher risk for stillbirth, Cesarean section, preterm birth, SGA. Co-infection with hepatitis B further increases each of these risks.

INFLAMMATORY DISORDERS

Inflammatory autoimmune diseases (IAIDs) have a strong female predilection with onset generally during the childbearing years.

Pregnancy can affect the course of IAIDs with variability: some conditions ameliorate (rheumatoid arthritis), some remain unchanged (Sjögren), and some worsen (SLE). Although all IAIDs are chronic diseases, acute manifestations of IAIDs can be severe, difficult to diagnose and challenging to address in a management plan. Active maternal disease during pregnancy is associated with adverse pregnancy outcomes. These adverse outcomes can be minimized through optimizing disease suppression regimens prior to conception, aggressively managing IAIDs during pregnancy, and aggressively treating emergent complications during pregnancy.

Systemic Lupus Erythematosus

SLE is most common encountered IAID in emergencies related to pregnancy. Maternal complications include lupus flares, hypertension (exacerbation of preexisting disease), nephritis, preeclampsia, and eclampsia. Elevated levels of lupus anticoagulant and antiphospholipid antibodies have emerged as markers of disease activity and are good predictors for adverse pregnancy outcomes. SLE-associated preeclampsia and eclampsia rates, recently as high as 15% to 20%, have been decreasing due to optimal prepregnancy management of active disease and adoption of low-dose aspirin therapy prior to 16 weeks' gestation.[30] Hypertension in SLE-associated pregnancy should lead to careful consideration of lupus glomerulonephritis versus preeclampsia, as both conditions are marked by increasing proteinuria. The presence of abnormal urine sediment, increasing titers of anti-DNA antibody, and decreasing levels of C3 and C4 suggest lupus nephritis.

The most common neurologic complication of SLE in pregnancy is cerebral venous sinus thrombosis. Common presenting symptoms include acute or subacute headache (80%), impaired consciousness (25%), ear complaints (21%), paresis (20%) and epileptic seizures (15%). Neurologic presentations may be associated with a subset of SLE patients who will test positive for antiphospholipid antibodies, and approximately half of these patients will develop thrombosis-related disorders of pregnancy, an antibody-mediated acquired thrombophilia. The most common arterial presentation is stroke; positive antiphospholipid antibody (aPL) test results are found in up to 20% of ischemic stroke patients younger than 50 years of age.

Antiphospholipid syndrome (APS) is characterized by (1) clinical manifestations of deep vessel clotting during pregnancy (2) pregnancy related morbidity, usually fetal or neonatal loss, and (3) confirmatory laboratory tests for lupus anticoagulant, anticardiolipin antibody of IgG and/or IgM isotype, and anti-β2–glycoprotein I antibody of IgG and/or IgM isotype.

The most common thrombotic presentation of APS is deep venous thrombosis (DVT) of the lower extremity. The most serious but rare thrombotic presentation of APS is catastrophic APS (CAPS). This condition is characterized by rapid-onset, small vessel thrombosis, multiorgan dysfunction or failure (renal, hepatic) and a high maternal mortality rate.

Adverse pregnancy outcomes related to IAIDs include fetal death (4%), neonatal death (1%), preterm delivery (9%), and SGA neonate (10%).[31] Baseline predictors of adverse outcomes included presence of lupus anticoagulant, antihypertensive use, an elevated Pregnancy Disease Activity Index score, and low platelet count. Pregnant women with these preexisting measures of active disease had an adverse outcome rate of 58% and neonatal mortality of 22%. Neonates born to patients with lupus are at increased risk of neonatal lupus as well as heart block if born to patients with positive SSA/SSB.

Corticosteroids are the mainstay of therapy for most rheumatologic complications or exacerbations. Aspirin has been advocated for all lupus-related pregnancies of more than 16 weeks' gestational age, and other NSAID regimens remain useful treatments for inflammatory flares. Cytotoxic agents are considered second-line therapy for rheumatic diseases. Cyclophosphamide and methotrexate are both potent teratogens and abortifacients and should be avoided, especially in the first trimester. Azathioprine is a cytotoxic agent that appears to be much better tolerated in pregnancy.

PSYCHIATRIC DISORDERS

Schizophrenia, Bipolar Disorder, and Depression

Similar risks and management principles apply to both schizophrenia and bipolar disorders in pregnancy. In both disorders, abrupt discontinuation of medication leads to high relapse rates in pregnancy. Untreated bipolar disorder and schizophrenia are considered independent risk factors for congenital malformations.

Polypharmacy should be avoided in this patient population during pregnancy in that it contributes to both fetal and maternal risk of adverse outcomes. Sole treatment with second-generation antipsychotics is the recommended management, including intention to control disease with the lowest acceptable dose of any given agent.[32]

Up to 17% of pregnant women experience major depressive disorder, and 25% of pregnant women with bipolar disorder experience mood exacerbation. Anxiety and depression are associated with adverse pregnancy outcomes including preeclampsia, instrument-assisted delivery, and emergency C section.

Adverse neonatal outcomes include low birth weight and preterm delivery. The ill effects of depression in pregnancy can carry into the later newborn period and even into later childhood. Infants of mothers with significant depression show increased cortisol and norepinephrine levels, and decreased dopamine levels. Neonatal outcomes are manifest as altered EEG patterns. reduced vagal tone, and stress/depressive-like behaviors. Adverse pregnancy outcomes include an increased rate of premature deaths and neonatal intensive care unit admissions, and central adiposity in later childhood.[33] Major depressive disorder during pregnancy has had good responses to cognitive behavioral therapy, in addition to pharmacotherapy.

Eating Disorders

The peak incidence of eating disorders occurs during the childbearing years, so the likelihood of anorexia nervosa (AN) or bulimia nervosa (BN) complicating a pregnancy is high. The prevalence of an eating disorder during pregnancy is 7%. The overall prevalence of AN is approximately 1% of young adult women, with a mean age of onset of 17 years, and an overall prevalence of BN of 1% to 3% in the same population. Of all eating disorders, 90% begin before the age 25 years. The high incidence of amenorrhea in AN makes pregnancy less likely than in BN. Medical complications of AN include bradycardia, hypotension, orthostatic changes, hypothermia, mitral valve prolapse, and symptoms associated with electrolyte imbalance. Anemia and transaminitis are also seen.

Pregnancy can frequently precipitate a subclinical eating disorder or exacerbate a condition in remission. The loss of control of body image and weight gain are frequent inciting features for recurrence. Adverse pregnancy outcomes include increased rates of miscarriage, low birth weight, preterm birth, congenital malformations, and increased likelihood of cesarean section births. Inappropriate dieting, with subsequent folate deficiency, increases the rate of congenital neural tube defects. In the postpartum period, depression risk is increased threefold in mothers with a history of eating disorders.

Treatment of eating disorders during pregnancy focuses on the restoration of normal physiologic parameters, electrolyte replacement, and correction of ketosis. There are no recommended pharmacologic interventions for AN by the US Food and Drug Administration, but

antidepressant therapy may be beneficial in those with exacerbations of BN.

Substance Dependence/Use Disorder

The prevalence of substance use disorder in pregnancy has been increasing, with major societal and personal costs. Substance dependence is frequently not identified during pregnancy unless self-reported, or an unplanned pregnancy is discovered during the evaluation of the mother for a substance-related disorder. This is particularly common in the ED, where women of childbearing age are seen frequently for associated complications and pregnancy is coincidentally identified during the visit.

The overall rate of substance use in pregnancy has been steadily increasing in the last 3 decades. According to a national survey conducted in the United States in 2012, 6% of pregnant women use illicit drugs, 9% drink alcohol, and 16% smoke cigarettes, resulting in over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol, and over one million exposed to tobacco in utero. These numbers do not begin to take into account the rapidly rising opioid epidemic un the United States.

The impact of substance use on pregnancy is determined by the following: (1) specific exposure (mono- vs. polysubstance use); (2) gestational timing; (3) duration of exposure; (4) dosing of exposure; and (5) other maternal comorbid conditions (e.g., smoking, general nutritional status). There is a strong association of substance use disorder with psychiatric conditions, particularly depression and psychosis.

Within this context, the terms *use disorder* and *dependence* will be used synonymously, although they are different clinical entities. Both conditions have the same impact on maternal and neonatal health and pregnancy-related complications.

Alcohol

Approximately 50% of women of childbearing age self-identify as alcohol users and 15% are binge drinkers. Nearly 2 million women annually are at risk for alcohol-exposed pregnancies, defined as women who are not using birth control, currently drinking, and are sexually active with a man. Once pregnancy has been identified, the rate of active alcohol consumption in gravid women drops to 7%, and binge drinking to lower than 2%. The true incidence of this disease may be severely underappreciated though. Unfortunately, pregnant women presenting to the ED are 75% less likely to be tested for drug or alcohol use than nonpregnant women.[34] Even when pregnant women present with psychiatric or substance abuse concerns, they are less likely to be screened for alcohol or drug use. Screening for alcohol use in pregnancy is recommended to identify at-risk pregnancies. Screening tools that assume the presence of alcohol intake yield more honest reporting from patients.

There is no safe threshold for alcohol intake during pregnancy, with intake as little as one drink per day being associated with increased rates of IUGR and low birth weight. Heavier consumption of alcohol at more than three drinks/day increases the rate of miscarriage, and more than five drinks/day increases the risk of intrauterine fetal demise two to three times that of nondrinking mothers. Alcohol consumption in pregnancy is the most preventable cause of developmental delay, with alcohol-exposed children having a 1.7-fold greater relative risk of mental retardation and a 2.5 times greater risk of delinquent behaviors.[35]

Congenital abnormalities associated with in utero alcohol exposure can be characterized within the fetal alcohol spectrum disorders. Fetal alcohol syndrome, the most severe of these, has a prevalence of up to 1/1000 births. It is characterized by at least one of a series of morphologic abnormalities in association with a history of heavy alcohol use (>three drinks/day), including midfacial hypoplasia, flat philtrum, low nasal bridge, epicanthal folds, shortened palpebral fissure, low-set ears, and microcephaly. It can also have ocular, cardiac, and skeletal manifestations.

Treatment of an alcohol-dependent mother is difficult. As with nonpregnant patients, withdrawal symptoms are likely to manifest 6 to 24 hours after last alcohol consumption. Any signs of withdrawal should prompt admission and continued management in an inpatient setting. There is a paucity of data on the risk of delirium tremens and major withdrawal in pregnant versus the nonpregnant population. There are also little data on the safety profiles of medications used to ameliorate withdrawal symptoms. The use of naltrexone, acamprosate, or disulfiram or the long-term use of benzodiazepines has not been studied in pregnancy.

Smoking

The long-term deleterious effects of smoking on fetal growth and development have been well documented, up to and including the risk of sudden infant death syndrome (SIDS). Chronic placental insufficiency and vasoconstriction lead to an increased risk of miscarriage, IUFD, preterm birth, IUGR, and clubfoot. Prenatal maternal smoking also has an association with severe bronchiolitis during infancy. Conversely, smoking decreases the risk of preeclampsia.

Treatment for tobacco addiction in pregnancy is largely behavioral and cognitive. Nicotine patches have not been associated with adverse maternal or newborn consequences when used in the second and third trimesters.

Cannabis

Cannabis is the most commonly used recreational drug in pregnancy. There is a maternal association with cannabis use and maternal anemia. Although marijuana use in pregnancy is not associated with any major congenital malformations or increased risk of IUFD, there is an association with low birth weight and need for placement into a neonatal ICU. Infants born to cannabis-using mothers show increased tremulousness, exaggerated startle responses, and high-pitched cries. These are some of the same features associated with neonatal abstinence syndrome (NAS) or Neonatal Opioid Withdrawal Syndrome (NOWS) discussed later in more detail (see "Opioids"). Cannabis is excreted in breast milk and has been associated with neurologic impairment during continued exposure.

Cocaine and Methamphetamines

The prevalence of stimulant use in pregnancy is likely being underrecognized. Maternal cocaine, methamphetamine, and stimulant use is independently linked to IUGR from impaired placental circulation and preterm birth less than 36 weeks' gestation, preeclampsia, IUFD, and increased incidence of cesarean section, gestational hypertension, and gestational diabetes mellitus. Cocaine use also increases the risk of placental abruption and infarction.

Infants of methamphetamine-addicted mothers have lower Apgar scores and increased rates of neonatal mortality and jaundice, but also morphologic difference in brain anatomy, with reduced subcortical volumes. The potential for adverse outcomes is increased in the presence of polysubstance use disorder or other confounding maternal risks, such as poor nutrition. Neonatal congenital abnormalities do not seem to be significantly increased with cocaine use, although there is a slight increased risk of cleft palate with cocaine exposure.

Discontinuation and abstinence are generally the main goals of treatment for pregnant persons addicted to methamphetamines, but immediate discontinuation can cause depression, fatigue, and psychosis. Treatment of a gravid patient who is acutely intoxicated with cocaine or methamphetamine may involve the judicious use of

benzodiazepines and antipsychotics, weighing the risk-benefit ratio for treatment against the medical and psychiatric instability of the patient, but this is not always necessary. Methamphetamine is excreted in breast milk, so infant exposure continues after pregnancy.

Opioids

Roughly 7% of all pregnant patients use opioids, a significant increase over the last decade.[36] This has created a downstream effect of large numbers of addicted infants requiring neonatal intensive care. There is a significant risk of unintended pregnancy among opioid-addicted women, close to 90%, compared to the unintended pregnancy rate in the general population of 40%.[37] The ED is a likely site of entrance of the opioid-addicted gravid patient to the health care system.

There are no well-identified syndromes, congenital abnormalities, or teratogenic effects in infants of opioid-dependent mothers, although there is some association with cleft lip deformities and ventricular septal defects. Neonatal risks include IUGR, specifically symmetric smallness and small head circumference, and an increased risk of SIDS. Maternal risks of postpartum hemorrhage, preterm birth, and increased rates of cesarean section have been documented. The major complication in infants of opioid-addicted mothers is neonatal opioid withdrawal syndrome (NOWS), also known as neonatal abstinence syndrome (NAS), a constellation of physiologic and neurobehavioral changes noted in newborns of addicted mothers secondary to a sudden discontinuation of fetal exposure to substances. The syndrome is characterized by the following: (1) CNS disturbances, including excessive or continuous high-pitched crying, shortened postprandial sleep pattern, hyperactive newborn reflexes, tremulousness, and increased muscle tone, myoclonic jerks, or frank convulsions; (2) metabolic and respiratory abnormalities (e.g., sweating, hyperthermia, yawning, mottling, sneezing, nasal flaring, tachypnea); and (3) gastrointestinal disturbances (e.g., increased sucking, poor feeding, regurgitation or projectile vomiting, loose or watery stools). The Finnegan scale, developed in the 1970s, is still the mainstay of neonatal assessment for NOWS. Treatment of NOWS is supportive. The incidence of NOWS has grown rapidly in the past decade. These infants have a 97% admission rate to neonatal intensive care units.

A new generation of mothers and infants who sustained exposure to methadone, buprenorphine or naltrexone is upon us. Compared to mothers using opioids, those on agonist therapy had improved pregnancy outcomes and decreased risk of NOWS.

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CHAPTER 174: REVIEW QUESTIONS AND ANSWERS

1. A 28-year-old G2P1 woman at 26 weeks of gestation presents with a recurrent asthma flare. Vital signs are temperature 36°C, heart rate 110 beats/min, blood pressure 120/60 mm Hg, respiratory rate 28 breaths per minute and O_2 saturation 96%. She has diffuse expiratory wheezes. Arterial blood gas reveals Po_2 90 mm Hg, Pco_2 40 mm Hg, and pH 7.34. Which of the following statements best describes the issues in management with this patient?
- **a.** Corticosteroids are contraindicated.
- **b.** Most patients with asthma improve during pregnancy.
- **c.** She has a metabolic acidosis.
- **d.** Treatment and discharge are likely.
- **e.** Inhaled beta-agonists are first-line therapy.

Answer: E. Beta-agonists followed by corticosteroids are the mainstay of asthma therapy during pregnancy. During pregnancy, one third of asthmatics worsen, one third improve, and one third stay the same. Blood gas interpretation must take into account the "normal" alkemia of pregnancy with a Pco_2 of 30 to 32 mm Hg and a compensatory HCO_3 level of 18 to 20 mEq/L. This patient has a relative "hypoventilation" and may indeed need admission for close observation.

2. A pregnant woman in the second trimester presents to the ED with a complaint of a 5/10 headache and has a blood pressure of 165/100. She reports regular prenatal follow-up. She reports she has a history of mild hypertension dating to before her pregnancy and her blood pressures have been in the 150/90 range during this pregnancy and that she is not on any anti-hypertensive medications. A repeat blood pressure after 15 minutes is 165/100. Which of the following best describes the issues in management of this patient?
- **a.** The patient should have been placed on an anti-hypertensive medication by her OBGYN for her blood pressures of 150/90.
- **b.** A full workup should be completed before treating the patient's hypertension.
- **c.** An IV must be established quickly in order to administer IV anti-hypertensives.
- **d.** Oral nifedipine can be used to lower the patient's blood pressure.
- **e.** ACE inhibitors can be used to lower the patient's blood pressure.

Answer: D. ACOG states that mild chronic hypertension in pregnancy defined as less than a systolic blood pressure of 160 or a diastolic blood pressure of 110 does not need to be treated. Hypertensive emergency in pregnancy is defined as acute-onset persistent hypertension with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg that is persistent for greater than 15 minutes. In these cases, antihypertensive therapy should be administered as soon as reasonably possible, and no later than 30 to 60 minutes after diagnosis with a goal blood pressure of 140 to 150 mm Hg systolic and 90 to 100 mm Hg diastolic. Oral nifedipine, IV hydralazine, and IV labetalol are the drugs of choice in this situation, and IV access attempts should not delay treatment as oral nifedipine can be given. ACE inhibitors are contraindicated in pregnancy.

3. An HIV-positive woman G3P2 at 15 weeks gestation presents with increasing fatigue. She is mildly tachycardia but otherwise with normal vital signs and has normal fetal heart tones. Her labs show a WBC of 10.1, Hgb 6.2, Hct 18, and platelets of 60,000. You should consider what other comorbid condition?
- **a.** Antiphospholipid syndrome
- **b.** Hepatitis B infection
- **c.** Thyrotoxicosis
- **d.** Tuberculosis

Answer: D. The diagnosis of new infection or activation of latent tuberculosis in pregnancy can be challenging, given that common symptoms can be mimicked in normal pregnancy including tachypnea and fatigue. Moderate to severe anemia in an HIV-infected mother should prompt a workup for TB.

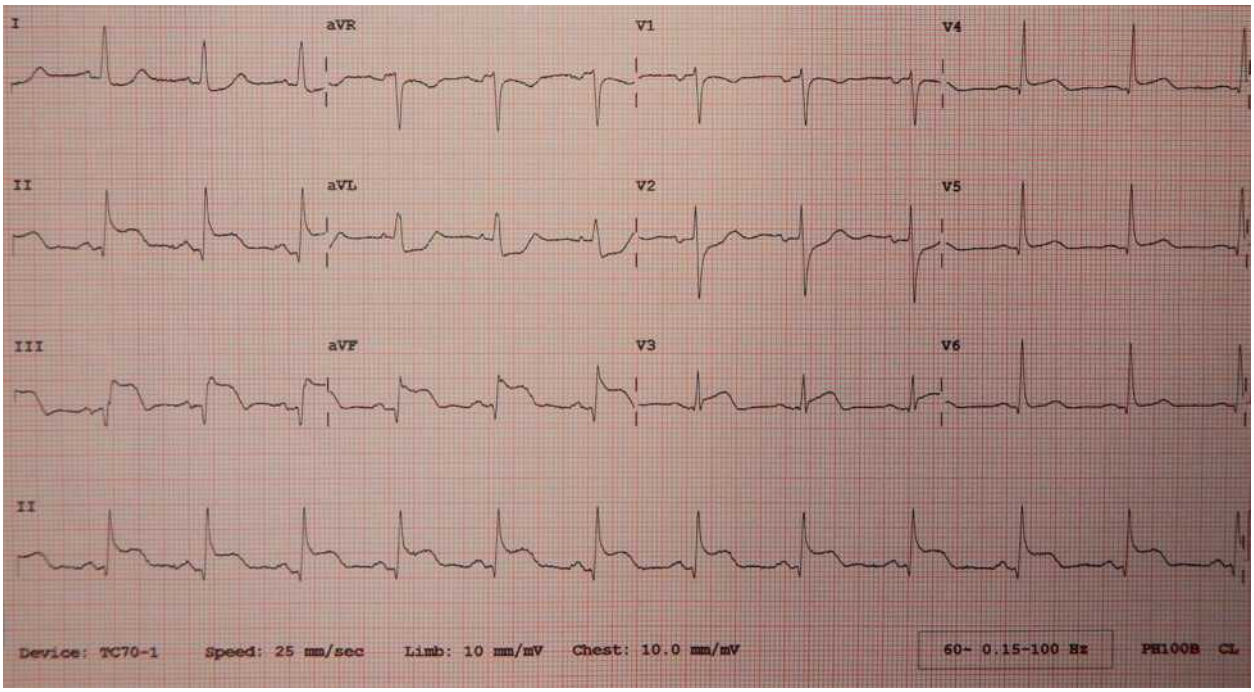
4. A 24-year-old G1P0 woman at 8 weeks' gestation presents with anxiety, sweating, and palpitations. She has a history of Graves disease. She is tachycardic and hypertensive. Her TSH is <0.02 and her free T4 level is 9.2 ng/dl (normal 0.8 to 2.8 ng/dL). Which of the following treatments is most appropriate?
- **a.** Alpha-adrenergic blockade
- **b.** Methimazole
- **c.** Propylthiouracil
- **d.** Radioiodine

Answer: **C.** Radioiodine is strongly contraindicated in pregnancy because it will destroy the fetal thyroid gland. PTU is the treatment of choice in the first trimester because of the risk of adverse congenital drug effects of methimazole during organogenesis. Beta blockade remains the treatment of choice for abnormal vital signs, not alpha-adrenergic blockade.

5. A 20-year-old G2P1 woman at 20 weeks' gestation with a known history of SLE presents with acute onset of R hemiplegia and dysarthria. One hour post onset of symptoms, her head CT is normal. Her symptoms are most likely caused by which of the following?
- **a.** Catastrophic antiphospholipid syndrome (CAPS)
- **b.** Cerebritis
- **c.** Eclampsia
- **d.** Stroke

Answer: D. The most common arterial presentation of neurologic symptoms in lupus patients is stroke; positive aPL results are found in up to 20% of ischemic stroke patients younger than 50 years of age. CAPS is characterized by rapid-onset, small vessel thrombosis, multiorgan dysfunction or failure (renal, hepatic), and a high maternal mortality rate, but not as a large vessel occlusion. Patients with lupus are not at increased risk of cerebritis during pregnancy, and eclampsia does not present as a focal hemiplegic deficit.

6. A 41-year-old G4P3 woman with known hypertension presents at 36 weeks with chest pain and the ECG that follows. Which of the conditions listed below is the most likely diagnosis?
- **a.** Hypertensive emergency
- **b.** Normal physiologic ECG changes of pregnancy
- **c.** Spontaneous coronary artery dissection
- **d.** Stanford type B dissection



English: 12 lead ECG showing inferior and right ventricular infarct

Date 19 May 2014, 06:20:17
Source Own work
Author James Heilman, MD

Answer: C. ECG changes in normal pregnancy include T wave flattening, T wave inversion (mainly in lead III), and nonspecific ST changes during pregnancy, as well as ST depression during labor induction for cesarean section. This ECG demonstrates an inferior MI. Although aortic dissection is more common than ACS in pregnant patients, a type B dissection would not involve the coronary outflow tract. The most common cause of ACS in pregnancy is spontaneous coronary artery dissection.

7. Perinatal maternal complications in women with sickle cell disease include which of the following?
   - **a.** Deep vein thrombosis
   - **b.** Maternal infections
   - **c.** Pain crises
   - **d.** Preeclampsia
   - **e.** All of the above.

Answer: E. Maternal complications are common in patients with SCD; these include preterm labor, premature rupture of membranes, maternal infections, more frequent pain crises, thrombosis, preeclampsia, and increased need for cesarean delivery.[38,39] Due to these complications, pregnant women with SCD have a sixfold increased risk of maternal death compared with controls.

8. A patient with poorly controlled epilepsy is at highest risk of breakthrough seizures during which time period of pregnancy?
   - **a.** 1 to 2 weeks postpartum
   - **b.** During delivery
   - **c.** Post 32 weeks
   - **d.** She is not at increased risk of seizing

Answer: B. Delivery and the first 24 hours postpartum are the most likely times for a seizure to occur, with a nine fold greater incidence of seizure than during pregnancy in general.

9. Which of the following autoimmune disorders most consistently worsens during pregnancy?
   - **a.** Addison disease
   - **b.** Graves disease
   - **c.** Multiple sclerosis
   - **d.** Rheumatoid arthritis

Answer: A. Pregnancy has an immunosuppressive effect. Because of this, pregnancy can have a variable effect on autoimmune disorders. Rheumatoid arthritis consistently improves, Graves disease has a transient worsening in the first trimester but improves later in pregnancy. Patients with MS see a decrease in the frequency and severity of exacerbations. Addison disease is exacerbated, especially in the third trimester, because of the biggest need for cortisol replacement.

Drug Therapy in Pregnancy

Valerie A. Dobiesz and Daniel W. Robinson

KEY CONCEPTS

- Chemically induced birth defects are responsible for approximately 1% to 3% of anomalous births.
- Gestational age is crucial in determination of the impact of any given exposure, especially during organogenesis (days 21–56 of fetal life), when major body organs are formed.
- Human data on teratogenicity and fetal toxicity of medications are often limited, and causal associations are difficult to determine, especially with newer medications.
- In general, the health of the fetus is directly related to the health of the mother, and drugs should be given when the maternal benefits outweigh the risks to the fetus.
- Certain medications should be avoided during pregnancy because they are known teratogens or cause potential toxic effects in the newborn; these include anticonvulsants, warfarin derivatives, NSAIDs, sulfonamides, fluoroquinolones, and ACE inhibitors. If there are no alternatives to these agents, it is recommended to use the lowest dose for the shortest duration possible.

FOUNDATIONS

More than 90% of women take at least one prescription or over-the-counter medication during pregnancy, and overall medication use during pregnancy has increased in the last 3 decades. One study revealed that only 22% of reproductive-aged women have pregnancy testing done when administered or prescribed potentially harmful or teratogenic medications in the emergency department (ED).[1] Unfortunately, the majority of research on the use of medications during pregnancy is insufficient to determine reliable and accurate risks to the mother and fetus, especially for newer agents. Only a few medications have been tested specifically for safety and efficacy during pregnancy. Prescribing medications during pregnancy must account for the physiologic changes associated with pregnancy as well as the benefits and risks to the mother and developing fetus.

The fetal age at exposure to a medication is crucial in determining its impact on the pregnancy. The fetus is most vulnerable to toxic insults during the time of organogenesis (days 21–56 of fetal life). Exposure during this period may result in major anatomic defects. Exposure after the period of organogenesis may affect the growth and development of the fetus. Functional development of the central nervous system (CNS) is affected when it is exposed to a CNS teratogen during the 10th to 17th weeks of pregnancy.

Major birth defects affect 3% to 5% of all live births. Most are of unknown cause, but 1% to 3% of these are thought to be due to pharmaceutical or environmental agents. A teratogen is any chemical, pharmacologic, environmental, or mechanical agent that can cause disruptive development of the conceptus. Included in this definition are functional impairment, growth restriction, and congenital malformations.

The process of establishing teratogenicity is tedious and often flawed. Animal research, although valuable in determining risk initially, is not always applicable to humans, and controlled prospective human studies are generally not performed for ethical reasons. As a result, much of our current knowledge on teratogenicity has been derived from less rigorous studies, which are inherently weak in establishing a causal relationship between a specific exposure and malformations. The genetic background of the fetus, timing and duration of the exposure, environmental factors, multiple exposures, nutritional deficits, maternal illness, and illicit drug use all contribute to the outcome of pregnancy. Large population studies are needed to understand the connection between the outcome of a pregnancy and in utero exposures. Finally, as in the case of diethylstilbestrol, teratogenicity may not be apparent for years after birth.

Classification of Teratogenic Risk

The FDA issued a final rule for drug labeling called the Pregnancy and Lactation Labeling Rule (PLLR) in June 2015. The PLLR changed the content and format of prescription drug labeling to help health care providers better assess the benefits and risks in counseling pregnant and nursing women who are taking medications. The rule requires the removal of letter categories (A, B, C, D, and X) and mandates labeling that includes a summary of data on the risks of a drug used during pregnancy, lactation, and the impacts on male and female reproduction. It requires the provision of current data supporting that summary, and any relevant information to help health care providers make informed decisions and counsel patients. The PLLR also mandates the label be updated when new information becomes available. Drugs already approved before this rule are being phased in. Currently, a number of clinical teratology resources that assign risk are available online, such as Clinical Pharmacology, TERIS, and Micromedex Reprotox (Shepard's *Catalog of Teratogenic Agents*).

Drug Transfer Across the Placenta

Drug transfer across the placenta usually occurs by simple passive diffusion or protein transport. A thin layer of trophoblastic cells is all that separates maternal from fetal circulation. The degree to which a drug gains access to fetal circulation depends on molecular size, ionic state, lipid solubility, and extent of protein binding. Drugs with a molecular mass of less than 5 kilodaltons (kDa) readily diffuse. Anionic substances diffuse through the lipid layer more readily than ionized forms.

A free drug diffuses more readily than a protein-bound drug. Because fetal pH is slightly more alkalotic than maternal pH, weak organic acids may become ion-trapped in the fetal circulation, increasing fetal exposure.

Drug Transfer During Lactation

Generally, drugs that are ingested or injected by the mother diffuse passively into milk and then back into the maternal circulation for excretion. The amount of drug diffusing into milk depends on many factors. Lipid-soluble and nonionic substances diffuse more readily, and highly protein-bound substances diffuse less readily. Whether a substance is concentrated in maternal milk or not, the neonate generally is able to detoxify it with no adverse effects, and only a few drugs pose a serious danger to a breast-feeding infant. The interruption of breast-feeding should not be advocated except in rare situations of known drug toxicity to the infant and in all cases of maternal critical illness.

Drug Therapy During Pregnancy

In general, the health of the fetus is directly related to the health of the mother. Physicians should not withhold lifesaving medications from pregnant patients because of a reported risk to the fetus and should resuscitate pregnant patients according to advanced life support guidelines. Physicians may also prescribe any agent when the maternal benefits outweigh the risks to the fetus. Included in this category are therapeutic medications for asthma, arrhythmias, status epilepticus, life-threatening overdoses, and human immunodeficiency virus (HIV) infection. When prescribing drugs to pregnant and lactating women, the benefits of treatment must be weighed against the inherent risks of treatment or disease. The drug with the lowest known toxicity should be chosen, and used at the lowest effective dose.

PHARMACOLOGIC THERAPY

Analgesic Agents

Over-the-counter analgesics are used commonly during pregnancy, with acetaminophen being used by at least two-thirds of pregnant women. Studies are emerging that call for a reassessment of the safety of these medications. Several studies report increasing use and adverse pregnancy outcomes with opioids, such as neonatal abstinence syndrome and birth defects (Table 175.1).

Acetaminophen

Acetaminophen (paracetamol) is the most widely used analgesic during pregnancy. It has not been associated with congenital malformations

TABLE 175.1 Analgesic Medications

Drug	Breast-Feeding	Clinical Risk Summary
Acetaminophen	Compatible, excreted in breast milk	CP, NHT; studies suggest increased risk of neurodevelopmental problems such as attention-deficit/hyperactivity-hyperkinetic disorder, cryptorchidism, childhood asthma/wheezing
Ibuprofen	Compatible, excreted in breast milk	CP, increased risk of spontaneous abortion at time of conception, association with structural cardiac defects and gastroschisis; risk in third trimester of premature closure of ductus arteriosus and subsequent primary pulmonary hypertension; potential increased risk of asthma with use in pregnancy
Aspirin	Potential toxicity, excreted in breast milk	CP; increased risk of spontaneous abortion at time of conception, avoid chronic or high doses in pregnancy; high doses may increase perinatal mortality, teratogenic effects; increased risk of gastroschisis in first trimester; increased risk of IUGR and fetal and maternal hemorrhage in third trimester; risk in third trimester of premature closure of ductus arteriosus and subsequent primary pulmonary hypertension; near-term use may prolong gestation, labor
Codeine	Potential toxicity Use with caution Excreted in breast milk, metabolized to morphine	LHS; congenital malformation data in humans are inconsistent; avoid prolonged use or high doses near term; may develop respiratory depression and/or withdrawal symptoms, neonatal abstinence syndrome
Oxycodone	Potential toxicity Use with caution Potential for SAR	LHS; use during organogenesis associated with low absolute risk of congenital birth defects; may result in preterm birth, poor fetal outcomes, NOWS
Morphine	Potential toxicity Usually compatible for short-term use Use with caution	CP; use during organogenesis associated with low risk of CBD; may result in preterm birth and poor fetal outcomes; prolonged maternal use during pregnancy may result in NOWS

CBD, Congenital birth defects; *CP,* crosses placenta; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity; *NOWS,* neonatal opioid withdrawal syndrome; *SAR,* serious adverse reactions.

Adapted data from: Lopes LM, Carrilho MC, Francisco RPV, Lopes MAB, Krebs VLJ, Zugaib M. Fetal ductus arteriosus constriction and closure: analysis of the causes and perinatal outcome related to 45 consecutive cases. *J Matern Fetal Neonatal Med.* 2016;29(4):638–645; ACOG Practice Bulletin No. 196: Thromboembolism in pregnancy. *Obstet Gynecol.* 2018;132(1):e1-e17; Shenai N, Shulman J, Gopalan P, Cheng E, Cerimele JM. Fetal outcomes in intentional over-the-counter medication overdoses in pregnancy. *Psychosomatics.* 2018;59(4):400-404; Mullins N, Galvin SL, Ramage M, et al. Buprenorphine and naloxone versus buprenorphine for opioid use disorder in pregnancy: a cohort study. *J Addict Med.* 2019;14(3):185-192; Acar S, Keskin-Arslan E, Erol-Coskun H, Kaya-Temiz T, Kaplan YC. Pregnancy outcomes following quinolone and fluoroquinolone exposure during pregnancy: A systematic review and meta-analysis. *Reprod Toxicol.* 2019;85:65-74; Mallah N, Tohidinik HR, Etminan M, Figueiras A, Takkouche B. Prenatal exposure to macrolides and risk of congenital malformations: a meta-analysis. *Drug Saf.* 2019:43(3):1-11; Sheehy O, Santos F, Ferreira E, Berard A. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf.* 2015;10(2):170-179; Committee Opinion No. 717: Sulfonamides, nitrofurantoin, and risk of birth defects. *Obstet Gynecol.* 2017;130(3):e150-e152; Alsaad AM, Kaplan YC, Koren G. Exposure to fluconazole and risk of congenital malformations in the offspring: a systematic review and meta-analysis. *Reprod Toxicol.* 2015;52:78-82; Floridia M, Dalzero S, Giacomet V, et al. Pregnancy and neonatal outcomes in women with HIV-1 exposed to integrase inhibitors, protease inhibitors and non-nucleoside reverse transcriptase inhibitors: an observational study. *Infection.* 2020;48(2):249-258.

and does not appear to increase the risk of adverse outcomes. There is weak evidence suggesting a link between maternal acetaminophen use in pregnancy with a higher risk of multiple neurodevelopmental problems including hyperkinetic disorders and attention-deficit hyperactivity disorder–like behaviors in children.[1a] Still, it is considered by most clinicians to be the safest analgesic and antipyretic medication currently available during pregnancy and lactation.

Nonsteroidal Antiinflammatory Drugs

Prostaglandin synthesis inhibitors, such as nonsteroidal antiinflammatory drugs (NSAIDs), taken in the first trimester may lead to increased risk of spontaneous abortions, although most of the studies showing this association are limited by not controlling for the conditions for which the medication was taken. The mechanism for this association is inhibition of prostaglandin production by NSAIDs, which is essential for embryonic implantation. Some epidemiologic and animal studies show an increase in ventricular septal defects and gastroschisis with NSAID use during pregnancy. When used in the third trimester, NSAIDs inhibit labor and may be used as tocolytic agents for premature labor. NSAID use in the latter part of pregnancy has been linked to a number of negative effects on the neonate, most notably premature closure of the ductus arteriosus, leading to neonatal pulmonary hypertension, and death.[2] Use in the latter part of pregnancy is therefore discouraged. NSAIDs in general appear to be safe during lactation.

Aspirin

Studies show a proposed increased risk of spontaneous abortion with aspirin use around the time of conception. Chronic or high doses of aspirin during pregnancy should be avoided and may affect maternal and newborn hemostasis and bleeding abnormalities, leading to increased perinatal morbidity and mortality. Aspirin use has been associated with premature closure of the ductus arteriosus causing primary pulmonary hypertension in the newborn, and neonatal death.[2] Low doses of aspirin (60 to 100 mg/day) may be beneficial in pregnancies complicated by systemic lupus erythematosus with antiphospholipid antibodies and those at risk for gestational hypertension and preeclampsia, as well as fetuses with intrauterine growth restriction (IUGR).[3] Aspirin is excreted into breast milk and its use is discouraged during breast-feeding due to risk of Reye syndrome.

Opiate Analgesics

In general, short-term, episodic use of opiates such as oxycodone, hydrocodone, morphine, and fentanyl appear to be safe in pregnancy. Their use near term, however, may result in respiratory depression of the neonate. Prescribing of narcotics for long periods may be associated with preterm birth, low birth weight, reduced infant head circumference, congenital malformations, sudden infant death, and neonatal abstinence syndrome.[4] Neonatal abstinence syndrome is characterized by CNS hyperirritability, autonomic nervous system dysfunction, and higher infant mortality. The short-term use of opiates during lactation appears to be safe, but nursing infants should be closely monitored for respiratory depression.

Rapid Sequence Intubation Agents

Data regarding the use of these agents during pregnancy are limited and have primarily been obtained from animal studies and retrospective human data. None of the agents has been consistently associated with congenital malformations or had adverse effects on the fetus (Table 175.2).

TABLE 175.2 Rapid Sequence Intubation Medications

Drug	Breast-Feeding	Clinical Risk Summary
Fentanyl	Compatible; may cause sedation or respiratory depression	CP; associated congenital birth defects; may cause neonatal respiratory depression, transient neonatal muscular rigidity, NOWS
Etomidate	Probably compatible	CP; animal studies show no teratogenicity; transient decrease in newborn cortisol levels of unknown clinical significance; LHS not harmful when used as induction agent
Propofol	Probably compatible, but not recommended	CP; animal studies show no malformations, LHS with no data on use in first and second trimesters; use at term appears to be safe, but high doses may be associated with neonatal CNS, respiratory depression
Thiopental	Probably compatible; use with caution	CP; LHS; animal studies show no congenital defects, even with high doses; may cause respiratory depression
Ketamine	Probably compatible; plasma levels undetectable after 12 hr	CP; used frequently in obstetrics, not associated with fetal developmental malformations; dose-dependent oxytocic effect; in high doses (>2 mg/kg), associated with uterine tetany; may increase maternal blood pressure and heart rate; may increase neonatal muscle tone or cause apnea and depression of the newborn, SAR usually dose-related
Midazolam	Use with caution Avoid with other CNS depressants	CP; animal studies show no congenital effects, even with high doses; LHS, human observational studies show no malformations, no data on use in first and second trimesters; use near term has resulted in adverse neonatal neurobehavior and neonatal respiratory depression
Succinylcholine	Probably compatible because of rapid hydrolysis	Not embryotoxic or teratogenic in animals; may result in neonatal apnea and partial or complete newborn paralysis in neonates with pseudocholinesterase deficiency
Rocuronium	Probably compatible; LHS	CP; LHS; animal data suggest low risk; newborn neuromuscular blockade is potential complication but probably rare, may have prolonged blockade when used with magnesium
Vecuronium	Probably compatible	CP; LHS; use late in gestation appear to carry little if any risk to the newborn; use lower doses if administering magnesium sulfate

CNS, Central nervous system; *CP,* crosses placenta; *LHS,* limited human studies; *NHT,* no human teratogenicity; *NOWS,* neonatal opioid withdrawal syndrome; *SAR,* serious adverse reactions.

Anticoagulants

Low-molecular-weight-heparin (LMWH) is preferred over unfractionated heparin and warfarin when indicated in pregnancy for therapeutic and prophylactic anticoagulation. Warfarin has the highest teratogenicity of the anticoagulants. The heparins, as a class, do not cross the placenta. All three anticoagulants are considered compatible with breast-feeding (Table 175.3).[5] Oral DTI (dabigatran) and anti-Xa inhibiitors (apixaban, rivaroxaban, edoxaban) have been extensively studied in pregnancy and therefore should be avoided.

Thrombolytic Agents

Alteplase, reteplase, urokinase, and streptokinase have been used successfully in pregnant women in cases of life-threatening pulmonary embolus, myocardial infarction, ischemic stroke, thrombosis of cardiac valve prosthesis, and deep venous thrombosis. Complication rates when used for these indications were similar compared to nonpregnant patients, and none of the live-born children had permanent defects. Recombinant tissue plasminogen activator does not cross the placenta. Poor fetal outcomes have been associated with poor maternal prognosis.

TABLE 175.3 Anticoagulant Medications

Drug	Breast-Feeding	Clinical Risk Summary
Warfarin	Compatible; however, caution advised when breast-feeding premature infants due to increased risk for intraventricular hemorrhage	CP; known dose-dependent teratogen affecting 4%–5% of exposed fetuses; greatest risk at gestational wk 6–9; fetal warfarin syndrome associated with corpus callosum agenesis, hypoplasia of nasal bones, midline dysplasia, optic atrophy and blindness; also associated with fetal osteogenesis, CNS malformations, fetal intraventricular hemorrhage, stillbirths, spontaneous abortions, abnormal development of bones, stippled epiphyses; school-age children exposed in utero had increased incidence of mild neurologic dysfunction
Heparin (UFH)	Compatible	DNCP; associated with maternal osteopenia, immune-mediated thrombocytopenia, maternal hemorrhage at delivery, requiring careful monitoring; has reduced bioavailability, shorter half-life, lower peak plasma concentrations during pregnancy; risk of antepartum bleeding ≈1%
Low-molecular-weight heparin	Compatible	DNCP; lower risk of osteoporosis than UFH has reduced bioavailability, shorter half-life, lower peak plasma concentrations during pregnancy; lower rate of bleeding, HIT, lower allergic response versus heparin; recommended over UFH for VTE

CP, Crosses placenta; *DNCP,* does not cross placenta; *HIT,* heparin-induced thrombocytopenia; *UFH,* unfractionated heparin; *VTE,* venous thromboembolism.
Additional data adapted from: ACOG Practice Bulletin No. 203. Chronic hypertension in pregnancy. *Obstet Gynecol.* 2019;133(1):e26-e50; ACOG Committee Opinion No. 767. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol.* 2019;133(2):e174-e180.

To date, no teratogenic effects have been reported in humans, but intrapartum maternal hemorrhage, fetal hemorrhage, spontaneous abortion, preterm delivery, and fetal death have been reported. Most thrombolytics are thought to be compatible with breast-feeding (Table 175.4).

Antidotes

There are limited human data on the risks of antidote use during pregnancy. Generally, antidotes should be used when there is a clear maternal indication and the potential benefits outweigh the possible risk (Table 175.5). In general, overdoses of medication with higher rates of placental transfer have increased potential for fetal toxicity.

N-Acetylcysteine

N-Acetylcysteine has been used successfully and without untoward effects in pregnant women who have overdosed on acetaminophen. No teratogenic effects have been reported, and pregnant patients who overdose on acetaminophen should be treated the same as nonpregnant patients.[6] It is most likely safe during lactation because it has been used in neonates without untoward effects.

Deferoxamine

Deferoxamine has been associated with developmental effects on ossification in some animal species. Experience in humans is limited, but

TABLE 175.4 Thrombolytic Medications

Drug	Breast-Feeding	Clinical Risk Summary
Alteplase	Compatible Unknown if excreted in breast milk	Embryocidal, not teratogenic, in animal studies; LHS; use if benefits to mother outweigh risks; has been used in human pregnancy with normal fetal outcomes, risk of hemorrhage at any time in gestation
Streptokinase	Use with caution; unknown safety	Use with caution; CP in minimal amounts; no fetal abnormalities reported; antistreptokinase antibodies cross the placenta
Reteplase	Probably compatible Use with caution Unknown if crosses into breast milk	Unknown if CP; risk for bleeding during labor and delivery; abortifacient, but no teratogenicity in animals; LHS; several cases of use with normal infants
Tenecteplase	Hold breast-feeding Unknown safety	Unknown if CP; use with caution, safety unknown; risk of bleeding during labor and delivery; toxicity to mother in animal studies; LHS
Urokinase	Probably compatible Unknown if excreted in breast milk	Probably acceptable in pregnancy; not fetotoxic or teratogenic in animal studies; unknown if CP; placental hemorrhage and separation may occur; increased risk of bleeding during pregnancy; LHS

CP, Crosses placenta; *LHS,* limited human studies.
Additional data adapted from: ACOG Committee Opinion No. 767: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol.* 2019;133(2):e174-e180; ACOG Practice Bulletin No. 212. Pregnancy and heart disease. *Obstet Gynecol.* 2019;133(5):e320-e356. doi:doi: 10.1097/AOG.0000000000003243; ACOG Practice Bulletin No. 190. Gestational diabetes mellitus. *Obstet Gynecol.* 2018;131(2):e49-e64.

TABLE 175.5 Antidotes

Drug	Breast-Feeding	Clinical Risk Summary
N-Acetylcysteine	Probably compatible unknown if excreted in milk so consider waiting 30 hr for elimination	CP; not teratogenic or embryotoxic in animal studies; LHS; no adverse fetal outcome when administered IV as antidote in acetaminophen overdose
Deferoxamine	Probably compatible Unknown if excreted in breast milk	LHS; no adverse toxic or teratogenic effects seen; animal studies show toxicity and teratogenicity (delayed ossification, skeletal anomalies)
Digoxin immune fragment	Probably compatible Unknown if excreted in breast milk	Unknown if CP; LHS; no adverse outcomes in fetus or newborn
Dimercaprol	Contraindicated Unknown if excreted in breast milk	Animal studies show teratogenicity; safety in pregnancy unknown; chelates essential elements including zinc, copper, and iron that may alter fetal development but LHS
Flumazenil	Probably compatible Unknown if excreted in breast milk	Unknown if CP, but may occur; animal studies show no teratogenicity or impaired fertility; LHS
Fomepizole	Hold breast-feeding	No animal or human studies; safety unknown
Hydroxocobalamin	Probably compatible, but monitoring of infant recommended	Animal studies showed no teratogenicity; LHS, safety unknown
Methylene blue	Probably compatible Unknown if excreted in breast milk	Epidemiologic evidence of teratogenicity; diagnostic intraamniotic injection resulted in hemolytic anemia, hyperbilirubinemia, methemoglobinemia, jejunal-ileal atresias
Naloxone	Probably compatible Unknown if excreted in breast milk LHS	CP; animal studies show no teratogenicity, no adverse fetal outcomes in human studies
Physostigmine	Probably compatible but safety unknown	Rarely used in pregnancy; no reports linking it with teratogenicity; safety unknown
Pralidoxime	Hold breast-feeding for 6 to 7 hr after dose	Rarely used in pregnancy; safety unknown; limited human case reports, with no adverse outcomes
Pyridoxine	Compatible	High doses appear to pose little risk to the fetus; no increased risk of malformations in first trimester in human trials
Succimer	Contraindicated Heavy metals may be excreted in breast milk, cause harm to newborn	Teratogenic and fetotoxic in animals; avoidance in first trimester recommended for pregnant women unless severe symptoms; LHS

CP, Crosses placenta; *LHS,* limited human studies.

Additional data adapted from: Lai T, Wu M, Liu J, et al. Acid-suppressive drug use during pregnancy and the risk of childhood asthma: A meta-analysis. *Pediatrics*. 2018;141(2):e20170889; McParlin C, O'Donnell A, Robson SC, et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review. *JAMA*. 2016;316(13):1392-1401; Bonham CA, Patterson KC, Strek ME. Asthma outcomes and management during pregnancy. *Chest*. 2018;153(2):515-527; Chambers C. Over-the-counter medications: Risk and safety in pregnancy. *Semin Perinatol*. 2015;39(7):541-544.

has been used in pregnancy without adverse effect on the fetus. The effects of deferoxamine on the nursing infant are not known, but are probably compatible.

Digoxin Immune Fragment

There are very few case reports of the use of digoxin immune fragment (Fab) during pregnancy, so effects on the fetus are inconclusive. In cases of life-threatening digitalis overdose with arrhythmias, the benefits of treatment of the mother outweigh the risk to the fetus. Digoxin fab is probably safe for use during lactation.

Dimercaprol

Dimercaprol, or British antilewisite, is teratogenic in mice and has been associated with increased mortality, growth restriction, cleft facial features, cerebral herniation, and abnormal digits, but experience in humans is limited. In general, with heavy metal poisonings, the maternal benefits of treatment will outweigh the potential risks to the fetus. Breast-feeding is contraindicated in patients poisoned by heavy metals.

Flumazenil

No teratogenic effects have been reported with flumazenil in animals, and there are limited human data. Its use in pregnancy and lactation depends on the potential maternal benefit compared with possible risks to the fetus and nursing infant. Because it has a short half-life, breast-feeding may resume after a few hours.

Fomepizole

Fomepizole use during pregnancy has not been studied in animals or humans. Its safety during pregnancy is not known. In cases of toxic alcohol poisoning, the benefits of treatment of the mother outweigh the possible risks to the fetus or nursing infant. Use of ethyl alcohol in these situations may be considered. Breast-feeding is not recommended during treatment.

Hydroxycobalamin

The effects of hydroxycobalamin on human pregnancy have not been studied, but benefits of its use in cyanide poisoning outweigh any risk to the fetus. Use is considered compatible with breast-feeding.

Methylene Blue

Historically, methylene blue was injected into the amniotic sac to identify twins and detect rupture of the membranes, but these practices were associated with hemolytic disease in the newborn, hyperbilirubinemia, and deep blue staining of the newborn. Methylene blue in pregnancy has also been associated with an increased incidence of intestinal obstruction and atresia in the newborn, primarily with

intra-amniotic or intrauterine administration. Methylene blue has been used successfully in pregnant women with methemoglobinemia; however, the benefits of treatment should outweigh the risks of the therapy and must be considered. The effects of methylene blue on the nursing infant are expected to be minimal.

Naloxone

Naloxone readily crosses the placenta. Although it has not been associated with reproductive abnormalities, its use during pregnancy results in increased fetal wakefulness, increased fetal movement, and increased heart rate, effects attributable to the antagonism of fetal endorphins. In addition, its use in opiate-addicted mothers may precipitate withdrawal in mother and term fetus. The use of buprenorphine with naloxone in pregnant women with opioid use disorder has been found to be safe.[7] It is compatible with breast-feeding.

Physostigmine

Experience during pregnancy is limited, and its effects on the developing fetus are unknown. Use of physostigmine at term has been associated with only mild decreases in Apgar scores at 1 and 5 minutes. Physostigmine is thought to be safe with breast-feeding.

Pralidoxime

Experience with pralidoxime in pregnancy is limited, and its effects on fetal development are not known. In cases of organophosphate poisoning, the benefits to the mother generally outweigh the possible risk to the fetus. Breast-feeding can be resumed after 6 to 7 hours after the last dose.

Pyridoxine

Pyridoxine, vitamin B_6, has not been associated with any adverse developmental effects when given in high doses, and it is safe in lactation.

Dimercaptosuccinic Acid (Succimer)

Succimer has been linked to congenital defects in animal models, possibly because of its negative effects on zinc and copper metabolism. Experience with the use of succimer in human pregnancy is limited to case reports, and adverse effects are unknown. Breast-feeding is contraindicated in heavy metal poisoning.

Antiinfective Agents

Infections during pregnancy potentially affect outcomes as well as fetal development. In the first trimester, infections are a common cause of spontaneous abortion and, in the second or third trimester, they are the most common cause of low birth weight and preterm labor. Antimicrobial agents may also adversely affect the pregnancy. Aminoglycosides, for example, may be nephrotoxic and ototoxic to the mother and newborn, tetracyclines may result in dental staining of the developing fetus, and lincosamides may be skeletotoxic.

The penicillins, cephalosporins, and macrolide antibiotics are the drugs of choice for infections during pregnancy. Alternative classes of antibiotics are prescribed only if these have failed to control the infection or in cases of severe maternal intolerance to these drugs. The choice of antimicrobial therapy will depend on the gestational age of the pregnancy, severity of infection, and maternal tolerance for the drug used. Many drugs are secreted into breast milk. Potential problems for the neonate include direct effects on the neonate, changes in bowel flora, diarrhea, and potential interference with culture results (Table 175.6).

Antibiotics

Aminoglycosides

Aminoglycosides do not appear to have any structural teratogenic effects in humans. Kanamycin and streptomycin have been reported to cause ototoxicity in the mother and her offspring. There are no reports definitively linking in utero exposure to gentamicin, streptomycin,

TABLE 175.6 Antiinfective Medications

Drug	Breast-Feeding	Clinical Risk Summary
Aminoglycosides	Probably compatible Excreted in breast milk Oral absorption poor	No definable structural risk of any aminoglycoside when exposed in utero; streptomycin—low incidence of ototoxicity with careful dosing
• First generation	Compatible	CP; NHT (most studies); conflicting studies on risk of congenital defects in first trimester
• Second generation	Compatible	CP; immune hemolytic reactions observed, especially with cefotetan
• Third generation	Compatible	CP; immune hemolytic reactions observed
• Fourth generation	Compatible	CP; LHS
Chloramphenicol	Potential toxicity (LHS) Excreted in breast milk	CP; may cause grey baby syndrome; idiosyncratic bone marrow suppression
Clindamycin	Compatible Excreted in breast milk	CP; no reports of fetal toxicity or malformations
Fluoroquinolones	Compatible Excreted in breast milk	Ciprofloxacin, ofloxacin, and levofloxacin CP; few reports of arthrotoxicity; risk of major malformations low; caution use during first trimester, risk of cardiac defects
Linezolid	Potential toxicity (LHS) Excreted in breast milk	No studies in pregnancy Use with caution
Macrolides	Compatible Excreted in low concentrations in breast milk	Estolate salt—may induce hepatotoxicity in pregnant patients; no risk of congenital heart malformations or pyloric stenosis, but use of erythromycin in infancy associated with pyloric stenosis
Metronidazole	Compatible Excreted in breast milk—but AAP recommends cessation of breast-feeding during use	CP; in vitro mutagen; NHT
Nitrofurantoin	Compatible	Caution advised with G6PD deficiency—may cause hemolytic anemia; limit use in later pregnancy

Continued

TABLE 175.6 Antiinfective Medications—cont'd

Drug	Breast-Feeding	Clinical Risk Summary
Penicillins	Compatible Small amount excreted in breast milk	CP; long-standing safety data
Sulfonamides	Compatible Excreted in breast milk Caution in newborns, infants with known G6PD deficiency	CP; adverse effects rare; most reports fail to demonstrate congenital malformations; concern for jaundice, hemolytic anemia, kernicterus; trimethoprim is folate antagonist—use with caution
Tetracyclines	Compatible Excreted in breast milk	CP; doxycycline poses little teratogenic risk; adverse effects on fetal bone development; discoloration of adult teeth; oxytetracycline shows neural tube defects, cleft palate, cardiac defects
Vancomycin	Compatible IV form found in breast milk, but, no oral absorption	No toxicity or teratogenicity found
Clotrimazole	Compatible	Systemic absorption from skin minimal; vaginal and topical formulations preferred over oral lozenge; NHT; avoid vaginal use during first trimester; some reports suggest increased risk of spontaneous abortions
Fluconazole	Compatible	High dose in first trimester associated with malformations; If necessary vaginal formulation preferred.
Ketoconazole	Compatible Excreted in breast milk	NHT, but teratogenicity seen in animal studies
Nystatin	Compatible Not excreted in breast milk	Poor systemic absorption from vaginal formulation (preferred route); often first-line therapy in pregnancy
Terbinafine	Potential toxicity Excreted in breast milk	LHS; Likely compatible
Isoniazid	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risks; NHT
Ethambutol	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risks; no adverse effects seen
Rifampin	Compatible Excreted in breast milk	CP; benefits of treatment outweigh risk; hemorrhagic disease of newborn
Acyclovir	Compatible Excreted in breast milk	CP—found in higher concentrations than in maternal blood; systemic use should be avoided unless benefits outweigh the risks; NHT
Valacyclovir	Compatible Excreted in breast milk	CP; LHS
Famciclovir	Potential toxicity	Unknown if crosses placenta or enters breast milk; LHS
Amantadine	Potential toxicity (LHS) Excreted in breast milk	CP; teratogenicity in animals; associated with cardiac malformations.
Oseltamivir	Compatible Excreted in breast milk but in low concentration	Benefits of treatment during gestation likely greatly outweigh risks; no congenital malformations identified

AAP, American Academy of Pediatrics; *CP,* crosses placenta; *G6PD,* Glucose-6-phosphate dehydrogenase; *LHS,* limited human studies; *LS,* limited studies; *NHT,* no human teratogenicity.
Additional data adapted from refs.[24-37]

tobramycin, and neomycin with ototoxicity or nephrotoxicity. Aminoglycosides are probably compatible with breast-feeding.

Cephalosporins

The first- to fourth-generation cephalosporins appear to be safe during pregnancy, although there have been no controlled studies examining their safety. Some cephalosporins are excreted into breast milk and may interfere with culture results in the evaluation of neonatal sepsis.

Chloramphenicol

Chloramphenicol is associated with bone marrow suppression and aplastic anemia. Apart from these complications, its use during pregnancy appears to have no effects on the developing fetus. Exposure to topical chloramphenicol during pregnancy appears to have no adverse effects. However, it is contraindicated at birth because chloramphenicol has been associated with cardiovascular collapse in the neonate, the so-called gray baby syndrome. Chloramphenicol is secreted into the breast milk, and therefore not recommended for use during lactation.

Clindamycin

Clindamycin has not been associated with birth defects in humans or in animal studies. The American Academy of Pediatrics (AAP) considers clindamycin to be compatible with breast-feeding, although there is a rare association with bloody diarrhea in nursing infants.

Fluoroquinolones

Fluoroquinolones are linked to numerous toxic effects on bone and cartilage growth in animal models and are discouraged from use during pregnancy, particularly during the first trimester. Observational studies, however, have failed to demonstrate such a toxic effect on the

human fetus. Meta-analyses have not found an association between fluoroquinolones and fetal malformations, preterm delivery, stillbirth, or spontaneous abortions.[8] Regardless, at this time, they are not recommended in the first trimester until further studies are done. Ciprofloxacin is compatible with breast-feeding, but data are inconsistent for other quinolones, and they are best avoided in lactation.

Linezolid

Linezolid is linked to embryonic death, decreased weight, and abnormalities in cartilage and ossification in animal studies, but human data are lacking. Its use in pregnant women should be limited to cases in which the maternal benefits outweigh possible risks to the fetus. Linezolid is likely compatible with breast-feeding.

Macrolides

Erythromycin is considered safe for use in pregnancy and compatible with breast-feeding. Some reports have linked erythromycin to pyloric stenosis and congenital heart defects. The estolate salt of erythromycin is associated with the development of hepatotoxicity in pregnant women and should be avoided. Clarithromycin is associated with an increased risk of fetal and embryonic death, as well as with congenital malformations in animal studies; this has not been shown in humans. Meta-analyses demonstrate a weak association between macrolides and congenital malformation but data are conflicting.[9] Azithromycin is poorly concentrated in breast milk and may be the preferred agent in lactating mothers.

Metronidazole

Metronidazole is mutagenic and carcinogenic in mice and rats. In humans, a number of studies have failed to demonstrate a clear association between metronidazole and congenital malformations when used in the first trimester of pregnancy. Metronidazole has been used during the second and third trimesters to treat bacterial vaginosis, with no untoward effects.[10] The use of metronidazole during lactation is discouraged because of its potential mutagenic and carcinogenic effects reported in rats, and its slow elimination from infants.

Nitrofurantoin

Though historically considered safe throughout pregnancy, except near term, there is some literature that associates nitrofurantoin use in the first trimester to a number of congenital abnormalities.[11] We recommend to avoid use in the first trimester, but can be used in the second and third trimesters. It is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.

Penicillins

The first- to fourth-generation penicillins and their derivatives (including procaine, benzathine, clavulanate, sulbactam, and tazobactam) are considered safe for use in pregnancy, as is oral probenecid. Penicillins are considered safe during breast-feeding, but their use may interfere with culture results if evaluation is required for a neonatal fever.

Sulfonamides

Sulfamethoxazole, commonly combined with trimethoprim, is contraindicated in pregnancy because of an increased risk of neural tube defects and other congenital abnormalities, such as cleft palate. There is also an increased risk of cardiovascular and urinary tract malformations in the offspring of women treated with trimethoprim-sulfamethoxazole in the first trimester. Sulfonamides are contraindicated near term because of their association with kernicterus; they are excreted in breast milk and generally tolerated by a healthy neonate. They should be avoided, however, in ill or premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.

Tetracyclines

Tetracycline and doxycycline readily cross the placenta. Tetracycline is associated with the development of fatal fatty liver in pregnant women. It chelates calcium, causing abnormalities in bone growth and staining of decidual teeth. It is associated with fetal genitourinary anomalies, inguinal hernias, and limb abnormalities. Tetracycline should therefore be avoided during pregnancy.

Doxycycline does not bind to calcium and is associated less with stained teeth than tetracycline. It does not appear to cause an increase in any type of congenital malformation. Despite these findings, doxycycline is not recommended in pregnancy.

Because tetracycline binds to breast milk calcium, only a small amount reaches the nursing infant, and it may be used for short periods (<10 days) during breast-feeding. Doxycycline does not bind to breast milk calcium and is present in greater quantities in breast milk. This could theoretically increase its side effects in the newborn. Its use in nursing infants is best avoided.

Vancomycin

Vancomycin has not been linked to birth defects in animals or in humans. Reports of auditory abnormalities and renal insufficiency in neonates of mothers treated with vancomycin are believed to be false positives because these abnormalities were resolved on retesting. Vancomycin is excreted into milk but not well absorbed by the GI tract. Its effects on the nursing infant have not been studied.

Antifungals

Nystatin has a long safety profile during pregnancy and lactation. It is poorly absorbed from skin, mucous membranes, and the GI tract and is considered the antifungal of choice for the treatment of mucocutaneous fungal infections. Clotrimazole, miconazole, and ketoconazole are considered second-line treatment of fungal infections. Fluconazole is teratogenic in high doses (>400 mg/day) and has been associated with spontaneous abortions and stillbirth as well as an increased incidence of craniofacial and cardiovascular defects in offspring and multiple abnormalities of the skeleton and cartilage. There are conflicting reports about the teratogenic effects, but expert recommendations suggest that a single dose of 150 mg one time during pregnancy after the first trimester is unlikely to be associated with teratogenesis.[12]

Ketoconazole, fluconazole, and itraconazole are excreted into breast milk. Because of the safe use of ketoconazole in neonates and the lack of negative reports, it is considered compatible with breast-feeding (see Table 175.6).

Antituberculous Agents

The incidence of tuberculosis is higher during pregnancy and postpartum than in the general population. Untreated tuberculosis places the mother, fetus, and family at greater risk than the use of antituberculous medications. Isoniazid, ethambutol, and rifampin cross the placenta and no association has been reported between these medications and major congenital malformations. Rifampin is associated with hemorrhagic disease of the newborn. Despite this adverse effect, it is considered first-line therapy for the treatment of tuberculosis. All three antituberculous medications are considered compatible with breast-feeding (see Table 175.6).

Antiviral Agents

Antiherpetic Drugs

Acyclovir readily crosses the placenta and reaches higher concentrations in fetal circulation than in maternal circulation. Neither acyclovir nor valacyclovir has been associated with congenital malformations or adverse effects on the offspring. Intravenous (IV) acyclovir is the drug of choice for life-threatening maternal herpes simplex virus infections,

such as disseminated disease, herpes encephalitis, and varicella pneumonia, which carries a maternal mortality of 44% if untreated. For non–life-threatening genital herpes infection in pregnant women, acyclovir or valacyclovir may be used. Experience with famciclovir is limited and therefore it is not recommended for use in pregnancy. Because there are no reported adverse outcomes in infants of mothers taking acyclovir or in infants treated with acyclovir for disseminated herpes, it is considered safe during breast-feeding (see Table 175.6).

Antiinfluenza Drugs

Influenza in pregnancy carries a high risk of morbidity and mortality. Neuraminidase inhibitors, such as oseltamivir and zanamivir, are active against influenza A and B and are associated with improved outcomes. Oseltamivir is considered the treatment of choice for influenza in pregnancy and available safety data report no significant risk to the fetus. Antiviral therapy with M2 ion channel inhibitors, such as amantadine and rimantadine, is also effective against certain subtypes of influenza A but not influenza B. However, amantadine has been linked to various malformations, including cardiac defects in humans, and is considered teratogenic and embryotoxic in rats.

Oseltamivir appears to be safe in lactation. In addition to antiviral therapy, the Centers for Disease Control and Prevention (CDC) recommends that pregnant women receive the inactivated influenza vaccine at any point during pregnancy (see Table 175.6).

Anti-HIV Drugs

Mothers infected with human immunodeficiency virus (HIV) are treated with antiretroviral therapy (ART) in order to decrease mother-to-child HIV transmission as the viral load of the mother directly correlates with the risk of perinatal transmission. No specific pattern of birth defects has been described with the use of anti-HIV drugs,[13] but the drugs' mutagenesis and carcinogenesis and their long-term effects on the liver, heart, and reproductive system are yet to be determined.

Animal and human data suggest that didanosine, lamivudine, stavudine, zidovudine, and zalcitabine present a small risk of structural malformations and mitochondrial dysfunction in the developing fetus, but no specific pattern of birth defects has been described with protease inhibitors, such as ritonavir and nelfinavir. Despite potential risks, it is thought that the benefit from HIV treatment far outweighs the risk of these drugs and should not be withheld. In addition, zidovudine has been shown to reduce vertical and perinatal transmission of HIV from the mother to the fetus. Because of the risk of postnatal HIV transmission through milk, the CDC advises against breast-feeding by HIV-positive mothers.

Cardiovascular Agents

Antidysrhythmics

Atrial and ventricular arrhythmias are common during pregnancy. Most are benign; however, malignant degeneration occasionally occurs. All unstable tachycardias should be treated with electrical cardioversion and Advanced Cardiovascular Life Support (ACLS) guidelines. Stable patients may be treated medically, but the choice of drugs needs to be modified to protect the patient as well as the fetus from the drug's potentially harmful effects (Table 175.7).

Adenosine. Adenosine has been used safely throughout pregnancy and is the drug of choice for termination of maternal supraventricular tachycardia. Adenosine has also been used safely for termination of incessant tachycardia in the fetus. Adenosine is safe in lactation.

Amiodarone. Amiodarone contains large amounts of iodine and is associated with congenital goiter and transient neonatal hyperthyroidism and hypothyroidism. Amiodarone has been linked to many congenital abnormalities, including growth restriction, structural cardiac abnormalities, corneal deposits, and developmental delay. It should be used only in refractory cases of supraventricular or ventricular tachycardias in the mother and incessant tachycardias in the fetus. Because of its high iodine content, excretion into milk, and long elimination half-life, amiodarone should not be used in nursing mothers.

TABLE 175.7 Antidysrhythmic Medications

Drug	Breast-Feeding	Clinical Risk Summary
Adenosine	Compatible	Many reports show compatibility during pregnancy; LHS; effects on fetus unknown, but teratogenicity or malformations not expected
Amiodarone	Contraindicated excreted in breast milk Concern for hypothyroidism	CP; linked to many congenital abnormalities; thyroid abnormalities, congenital goiter have been observed; contains high concentration of iodine; use only in refractory tachydysrhythmias
Digoxin	Compatible excreted in breast milk	CP; NHT; one of the safest antiarrhythmics during pregnancy
Quinidine	Probably compatible (LHS) Excreted in breast milk	CP; no teratogenic effects in humans reported; LHS
Lidocaine	Compatible excreted in breast milk	CP; animal studies—no harm; high doses near term associated with neonatal CNS depression, hypotonia, seizures, bradycardia
Procainamide	Probably compatible (LHS) Excreted in breast milk	LHS
Flecainide	Compatible Concentrated in breast milk	LHS; animal data suggest possible teratogenicity
Ibutilide	Probably compatible (LHS)	Unknown if CP; animal studies show teratogenicity, embryocidal events
Sotalol	Potential toxicity (LHS) Concentrated in breast milk. Conflicting reports	CP; may cause fetal bradycardia and/or IUGR

CP, Crosses placenta; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity.
Data adapted from refs.[38,39]

Digoxin and Quinidine. Digoxin and quinidine are considered safe for use during pregnancy and lactation. Neither has been linked to congenital defects in humans or animals, and they are first-line agents for the treatment of significant maternal dysrhythmias. They have also been successfully used in fetal tachycardia. During lactation, digoxin and quinidine appear compatible with breast-feeding.

Lidocaine. Lidocaine rapidly crosses the placenta and becomes ion-trapped in the fetus. There is no evidence of a link between the use of lidocaine in the first trimester and any fetal developmental malformations. However, high doses used near term are associated with neonatal CNS depression, apnea, hypotonia, seizures, and bradycardia. Lidocaine is considered compatible with breast-feeding.

Procainamide. Procainamide has been safely used in the treatment of stable, wide-complex tachydysrhythmias during pregnancy. It is not associated with fetal developmental abnormalities and appears well tolerated when used for a short duration. It is associated with a high incidence of maternal antinuclear antibodies and the occurrence of a lupus-like reaction in humans. During lactation, procainamide and its metabolite, *N*-acetylprocainamide, are found in breast milk. The AAP considers its short-term use compatible with breast-feeding.

Flecainide. Flecainide has been used safely to terminate maternal and fetal tachycardia, but it is associated with fetal hyperbilirubinemia, hepatotoxicity, and loss of fetal heart rate variability. Flecainide has also been found to be teratogenic in some animal species, resulting in cardiac and musculoskeletal abnormalities. It is present in breast milk and the AAP considers it compatible with breast-feeding, despite limited experience.

Ibutilide. There are only a few case reports of the successful and safe use of ibutilide during the latter part of pregnancy in humans. In animals, however, ibutilide was found to be teratogenic and caused

TABLE 175.8 Antihypertensive Medications

Drug(s)	Breast-Feeding	Clinical Risk Summary
Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists	Probably compatible, but variable safety	Use in second and third trimesters may cause teratogenicity, severe fetal/neonatal toxicity; reduce fetal renal function; associated with anuria, PDA, IUGR, prematurity, abnormal bone, lung development, renal failure, death
Esmolol	Safety unknown Appears to be low risk	LHS; not thought to cause structural anomalies; may result in persistent beta blockade of fetus or newborn[a]
Labetalol	Probably compatible Low excretion in breast milk	LHS; little risk to fetus except possibly in first trimester; most studies found no effect on fetal growth; IUGR and RPW may occur if used near delivery; newborn should be monitored for 24–48 hr for symptoms of beta blockade[a]
Metoprolol	Conflicting reports Concern for toxicity Excreted in breast milk	CP; LHS; no animal teratogenicity; may cause IUGR, RPW, and persistent beta blockade in newborns[a]
Propranolol	Conflicting reports Concern for toxicity	CP; NHT; fetal and neonatal toxicity may occur; may cause IUGR and RPW if used near delivery; newborn should be monitored for 24–48 hr for symptoms of beta blockade[a]
Amlodipine	Probably compatible, but safety unknown Neonatal myocardium sensitive to changes in calcium status Caution during breast-feeding	LHS; animal studies demonstrated fetotoxicity; safety unknown; case reports of IUGR, fetal death, neonatal rash
Diltiazem	Probably compatible, but safety unknown Neonatal myocardium sensitive to changes in calcium status Caution during breast-feeding	LHS; animal studies demonstrate fetotoxicity, teratogenicity; safety unknown
Nicardipine	Probably compatible but safety unknown LHS	Dose-related embryonic toxicity but not teratogenicity in animals; LHS; neonatal hypotension and acidosis reported, but safety unknown; causes hypotension, reflex tachycardia, PPH, tocolysis, headache, nausea, dizziness, flushing in pregnancy
Nifedipine	Probably compatible but safety unknown Advised to delay breast-feeding for 3–4 hr	LHS; safety unknown; NHT; has been used as a tocolytic agent; may potentiate neuromuscular blocking action of magnesium
Verapamil	Probably compatible	CP; animal studies show adverse effects on fetal growth and fetotoxicity, LHS; appears to be low risk during any stage of pregnancy
Furosemide	Probably compatible Caution advised May suppress lactation	CP; LHS; fetotoxic and teratogenic in animals; no significant alteration of amniotic fluid volume; monitor fetal growth because may cause higher birth weight
Hydrochlorothiazide	Compatible Excreted in breast milk May suppress lactation	CP; NHT; risks to fetus and newborn include hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia, death; may inhibit labor by direct effect on smooth muscle
Nitroglycerin	Probably compatible Monitoring infants recommended	LHS; no adverse effects in animal studies; safety unknown, but appears safe; tocolytic
Nitroprusside	Potential toxicity	CP; LHS; adverse effects in animal studies, caution advised; transient fetal bradycardia noted; accumulation of cyanide in fetus may occur
Clonidine	Probably compatible May alter prolactin and oxytocin levels, affecting lactation	CP; LHS; safety unknown; no observed adverse fetal effects in humans; may develop sleep disorders later in life with prolonged use during pregnancy
Hydralazine	Probably compatible LHS Excreted in breast milk	CP; use with caution, no known congenital defects, but fetal toxicity associated with third-trimester use; meta-analysis on use in preeclampsia demonstrated more hypotension, placental abruption, cesarean section, maternal oliguria, adverse fetal heart rates, lower Apgar scores compared with labetalol or nifedipine
Methyldopa	Probably compatible	Long history of safety and efficacy in pregnancy

[a]Beta blockade = bradycardia, respiratory depression, and hypoglycemia.
CP, Crosses placenta; *IUGR,* intrauterine growth restriction; *LHS,* limited human studies; *NHT,* no human teratogenicity; *PDA,* patent ductus arteriosus; *PPH,* postpartum hemorrhage; *RPW,* reduced placental weight
Data adapted from refs.[40-45]

cardiac septal defects as well as skeletal dysgenesis in rats, especially when high doses were given. Ibutilide should be reserved for refractory cases in which the benefits of therapy outweigh any fetal risk. There are very few data about the risk during breastfeeding, though there is low bioavailability and likely low risk to the infant.

Sotalol. Sotalol has been used in pregnant women to treat atrial arrhythmias successfully and safely, as well as hypertension. It has also been successfully used to terminate fetal atrial tachycardias. It does not appear to have teratogenic effects in animals. Some of the negative effects of sotalol include bradycardia in the newborn, persisting for 24 hours. Sotalol is concentrated in milk but does not appear to result in bradycardia or hypotension in the nursing infant and, according to the AAP, it is compatible with breast-feeding.

Antihypertensives

Labetalol is the agent of choice for hypertensive emergencies in pregnancy (Table 175.8).[14]

Angiotensin-Converting Enzyme Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors are contraindicated for use during pregnancy. Furthermore, ACE inhibitors are embryocidal in animals and increase the rate of stillbirths in some animal species. In humans, the most significant adverse fetal effects occur when used in the second and third trimesters. ACE inhibitor use in the first trimester is controversial; some studies suggest no increased risk whereas ACOG recommends against its use. Captopril and enalapril are considered compatible with breast-feeding.

Angiotensin II Receptor Antagonists. Angiotensin II receptor antagonists should be avoided during pregnancy because their use has been reported to result in fetal abnormalities similar to the abnormalities seen with ACE inhibitors, including renal agenesis, neonatal anuria, oligohydramnios, intrauterine growth restriction, persistent patent ductus arteriosus, abnormal ossification, and death. Their safety in lactation is unknown.

Beta Blockers. Beta blockers are a first-line treatment of hypertension in pregnancy.[15] They have not been associated with fetal malformations and appear to be safe when used for short periods. Adverse fetal effects include intrauterine growth restriction and a low placental weight. Beta blockers lacking intrinsic sympathomimetic activity, such as acebutolol, atenolol, nadolol, and propranolol, are more likely to be associated with these adverse effects. When beta blockers are given near term, they have been associated with persistent beta blockade in the newborn. Nonselective beta blockers, such as propranolol, also have resulted in neonatal hypoglycemia, respiratory depression, and hyperbilirubinemia in the newborn. These adverse effects are less common when a cardioselective beta blocker, such as atenolol or metoprolol, is used. Esmolol has been associated with fetal bradycardia, neonatal bradycardia and hypotonia, and fetal distress requiring emergent cesarean section. Beta blockers have variable effects on the nursing infant, and close monitoring of the infant for adverse effects is recommended.

Calcium Channel Blockers. Calcium channel blockers are effective treatments for hypertension and the termination of supraventricular rhythm disturbances during pregnancy. IV verapamil is useful to terminate fetal tachycardia, and IV nicardipine has been used for severe preeclampsia. In addition, some calcium channel blockers, such as nifedipine and diltiazem, are used as tocolytic agents. In laboratory animals, calcium channel blockers in the first trimester have been associated with a dose-dependent increase in embryonic mortality and skeletal abnormalities. To date, however, these abnormalities have not been seen in humans. Complications of calcium channel blocker use during pregnancy include maternal hypotension, tachycardia, and fetal distress, especially pronounced when sublingual nifedipine or IV nicardipine is used. The AAP considers these drugs compatible with breast-feeding.

Diuretics

Loop diuretics such as furosemide are indicated in the treatment of pulmonary edema due to congestive heart failure. In laboratory animals, furosemide has been linked to renal and skeletal abnormalities when used in pregnancy. These effects have not been seen in humans, but a slightly increased risk of hypospadias has been reported. Furosemide is secreted into breast milk but is considered compatible with breast-feeding.

Thiazide diuretics have been associated with hypoglycemia and electrolyte abnormalities in neonates when given near term and with an increase in meconium staining and perinatal mortality. Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labor. In general, these agents are considered safe during breast-feeding.

Nitrates. Nitroglycerin has not been shown to cause fetal harm in animal studies. Limited reports in humans have not shown any major effects on the fetus or neonate. Nitroglycerin is rarely used during pregnancy, but it appears to be a safe, effective, rapidly acting, and short-acting agent. Nitroprusside for the treatment of hypertensive emergencies in pregnancy has the same advantages and disadvantages as in nonpregnant patients. During prolonged administration of high doses, nitroprusside may result in cyanide toxicity and severe acidosis. It readily crosses the placenta, and fetal levels of cyanide can increase as high as twice maternal levels. Standard doses do not seem to subject the fetus to a major risk of toxicity but, with the availability of safer alternatives, notably labetalol, nitroprusside is considered a last resort agent. No data are available on its use during lactation

Clonidine. Clonidine has been safely used throughout pregnancy, but experience during the first trimester remains limited. It does not appear to be teratogenic in laboratory animals and does not increase fetal mortality. Transient neonatal hypertension has been reported with the use of clonidine in the treatment of neonatal abstinence syndrome. Its effects on breast-feeding neonates are unknown, but it is considered compatible with breast-feeding.

Hydralazine. Hydralazine use is associated with higher rates of maternal hypotension, placental abruption, and neonatal distress compared with labetalol. It is therefore no longer recommended as a first-line agent in the treatment of severe acute hypertension in pregnancy.[15] It may still be used as a second-line agent. Hydralazine is considered compatible with breast-feeding.

Methyldopa. Methyldopa has been safely used throughout pregnancy, and most reviews have not linked it to any teratogenic effects on the offspring or adverse effects on the pregnancy. The use of methyldopa has been associated with depression, which may limit its use in the peripartum phase. Methyldopa is compatible with breast-feeding.

Vasopressors

Vasopressors all have the potential to increase uterine vascular resistance, resulting in a proportional decrease in placental blood flow. ACOG currently recommends epinephrine as the vasopressor of choice in the treatment of vascular collapse during pregnancy (Table 175.9).[16]

Endocrine Agents

Diabetes Medications

Diabetes mellitus is associated with a number of congenital malformations involving multiple organ systems, as well as with a significant increase in perinatal morbidity. Glycemic control in pregnancy is therefore important and should be accomplished in a controlled manner, because hypoglycemia is also associated with adverse pregnancy outcomes. Insulin is the drug of choice for diabetes mellitus types 1 and 2 in pregnancy and gestational diabetes, if treatment is needed. Metformin is generally well tolerated but has rare serious adverse effects in non-pregnant and pregnant adults, including life-threatening metabolic acidosis and hepatitis. It has not been associated with fetal malformations in animals and humans (Table 175.10).[17]

TABLE 175.9 Vasopressors

Drug	Breast-Feeding	Clinical Risk Summary
Dobutamine	Probably compatible (LHS)	CP; LHS; animal data suggest low risk; no adverse effects on human fetuses found
Dopamine	Probably compatible (LHS)	LHS; used in maternal shock, including spinal shock due to spinal anesthesia; low-dose dopamine can be used to improve cardiac and urine output in patients with preeclampsia and oliguria, but has not been shown to improve mortality or renal function; animal studies suggest maternal toxicity, but no fetal teratogenicity found; decreases uterine blood flow
Epinephrine	Potential toxicity (LHS)	CP; NHT; preferred treatment agent for anaphylaxis, used for status asthmaticus and shock during pregnancy; associated with fetal anoxic injury, intracranial hemorrhage, and increased incidence of inguinal hernias; decreases uterine blood flow, which may lead to fetal anoxia
Norepinephrine	Potential toxicity (LHS)	CP; animal studies demonstrate malformation—situs inversus, cataracts, hemorrhages, bone abnormalities; increased incidence of cerebral hemorrhage; decreased placental flow and fetal anoxia, but overall effects unknown
Ephedrine	Potential toxicity	CP; NHT; effective in treatment of shock in pregnancy; compared to phenylephrine, ephedrine associated with higher heart rates, gastric upset, increased incidence of fetal acidosis; no major or minor malformations shown
Phenylephrine	Probably compatible (LHS)	Preferred agent to treat shock during pregnancy; severe hypertension during delivery when reacting to oxytocics or ergots; malformations when used in first trimester; use during late pregnancy, labor, or cesarean section may cause fetal anoxia, bradycardia due to uterine contractions, decreased uterine blood flow

CP, Crosses placenta; *LHS,* limited human studies; *NHT,* no human teratogenicity.
Data adapted from ref.[44]

TABLE 175.10 Diabetic Medications

Drug	Breast-Feeding	Clinical Risk Summary
Insulin	Compatible Degraded by infant's GI tract	Maternal hypoglycemia; DNCP; no observable effects found
Sulfonylureas	Compatible	Minimal amounts found in fetal circulation; no greater risk of adverse effects compared with insulin therapy; infant 200 g heavier with use of sulfonylureas; stop ≈2 wk before birth to prevent neonatal hypoglycemia
Metformin	Compatible Excreted in breast milk Monitoring advised	CP; NHT Less likely to experience maternal and neonatal hypoglycemia

CP, Crosses placenta; *DNCP,* does not cross placenta; *GI,* gastrointestinal; *NHT,* no human teratogenicity.
Data adapted from refs. [46,47,64]

TABLE 175.11 Thyroid Medications

Drug	Breast-Feeding	Clinical Risk Summary
Levothyroxine	Compatible Excreted in breast milk	Minimal transfer across placenta; treatment of choice for hypothyroidism in pregnancy; minimal side effects; maternal benefits outweigh risks to fetus
Potassium iodide	Compatible Excreted in breast milk	CP; reserved for thyrotoxic patients; easily taken up by fetal thyroid, resulting in prolonged fetal hypothyroidism and goiter
Propylthiouracil (PTU)	Compatible Excreted in breast milk	CP; causes fetal goiter, hypothyroidism, hepatic injury, death; preferred drug in the first trimester for hyperthyroidism in pregnancy; maternal benefits outweigh risk to fetus
Methimazole	Compatible Excreted in breast milk	CP; may cause a methimazole embryopathy—congenital skin defects, umbilical defects, preferred drug in the second and third trimesters

CP, Crosses placenta.

Thyroid Medications

Maternal hyperthyroidism is associated with an increased risk of spontaneous abortion, preterm labor, placental abruption, and maternal congestive heart failure. Effects of the disease on the offspring include intrauterine growth restriction, intrauterine fetal death, and neonatal goiter. Propylthiouracil (PTU) is the drug of choice in the first trimester and should be replaced with methimazole in the second and third trimester. Methimazole is associated with higher rates of congenital malformations such as choanal and esophageal atresia and therefore not recommended in the first trimester. PTU is associated with maternal hepatotoxicity. When used close to term the newborn may display hypothyroidism and a goiter. Methimazole and carbimazole have been associated with abnormal development of the skin, albeit inconsistently. Hypothyroidism in pregnancy may result in an increased risk for spontaneous abortion, intrauterine growth restriction, placental abruption, and fetal demise and has been associated with severe neurologic impairment of the offspring. Levothyroxine is the treatment of choice for hypothyroidism in pregnant women (Table 175.11).

Gastrointestinal Agents

Gastroesophageal reflux disease (GERD) occurs in up to 80% of pregnancies and peaks in the third trimester (Table 175.12). Another common condition during pregnancy is nausea and vomiting of pregnancy (NVP), which can affect up to 80% of women during pregnancy. NVP typically presents after 4 to 5 weeks' gestation and resolves before the beginning of the second trimester (see Antiemetic Medication section).

Antacids

H2 Receptor Antagonists. None of the H2 receptor antagonists has been linked to congenital malformation, and they all appear to be safe for the nursing infant. There are multiple reports in the literature, however,

TABLE 175.12 Gastrointestinal Medications

Drug	Breast-Feeding	Clinical Risk Summary
Famotidine	Probably compatible Secreted less than other H2 blockers Considered low risk	CP; no fetal toxicity or teratogenicity in animal studies[a]
Ranitidine	Probably compatible Considered low risk	CP; no toxicity or teratogenicity in animal studies; considered H2 blocker of choice due to efficacy and safety data; ranitidine-induced anaphylactoid shock has been reported[a]
Cimetidine	Compatible Has antiandrogenic activity, so use with caution	CP; no toxicity in animal studies, has some weak anti-androgenic activity that could result in feminism of male fetuses but no documented cases in humans[a]
Omeprazole	Potential toxicity LHS	CP; animal data show dose related embryonic and fetal mortality; low risk of fetal harm or teratogenicity; overall slightly higher rates of congenital malformations and stillborns after exposure in first trimester of pregnancy, but studies limited/unconfirmed[a]
Esomeprazole	Potential toxicity LHS Wait 5–7.5 hr after dose for breast-feeding to limit exposure Strontium formulations—should not be used	CP; LHS; some changes in bone morphology observed in animal studies; should be used with caution[a]; esomeprazole magnesium preferred over esomeprazole strontium
Lansoprazole	Potential toxicity Should be avoided	Unknown whether CP but likely; carcinogenic in animals; LHS; should be avoided in first trimester[a]
Pantoprazole	Probably compatible Potential for tumorigenicity and carcinogenicity in animals Caution advised	Animal and human data suggest low risk in pregnancy[a]

[a]Several studies have shown a possible link between in utero exposure to gastric acid suppressors and childhood allergy and asthma.
CP, Crosses placenta; *LHS,* limited human studies.
Data adapted from ref.[48-50]

TABLE 175.13 Antiemetic Medications

Drug	Breast-Feeding	Clinical Risk Summary
Pyridoxine	Compatible Excreted in breast milk	High doses pose little risk to fetus; vitamin B_6 deficiency common during pregnancy—pyridoxine required for good maternal and fetal health
Doxylamine, pyridoxine	Probably compatible, but sedative and antihistamine actions are potential concern	Safe in pregnancy, including first trimester; several meta-analyses demonstrated no increased risk of malformations, fetal abnormalities
Metoclopramide	Potential toxicity Concern for CNS effects but data lacking	CP; no association with adverse fetal and neonatal outcomes while with used during all stages of pregnancy
Prochlorperazine	Potential toxicity Use caution—may cause sedation, lethargy in infant	CP; LHS; fetal toxicity, teratogenicity in animals; adverse effects of extrapyramidal effects, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding disorder reported in infants exposed during third trimester; considered low risk for mother and fetus if used occasionally in low doses
Promethazine	Probably compatible May cause sedation in infant	CP; LHS; reports of embryonic and fetal harm may be considered low risk for embryo, fetus; theoretical increased risk of respiratory depression in the newborn if given close to delivery, of unknown clinical significance
Ondansetron	Probably compatible Unknown safety	CP; animal, human data suggest low risk of birth defects; studies show inconsistent data on increased risk of cardiac anomalies and cleft palates

CP, Crosses placenta; *LHS,* limited human studies.
Additional data adapted from refs.[52,53]

linking in utero gastric suppression to an increased incidence of asthma and allergies during childhood, which require confirmation.[18]

Proton Pump Inhibitors. Studies on proton pump inhibitor (PPI) use in pregnancy are limited but several studies and a meta-analysis have found no association with an increased risk for major congenital birth defects, spontaneous abortions, or preterm delivery. Esomeprazole, lansoprazole, pantoprazole, and rabeprazole may be used during pregnancy. There are reports, however, of an increased incidence of GI, hepatic, and thyroid cancers in rats and mice. Several studies have demonstrated a possible link between in utero exposure to gastric acid suppressors and childhood allergic disorders and asthma. There are limited data in humans on the effects of PPIs on nursing infants. Breast-feeding should be avoided while taking PPIs.

Antiemetic Medications

Nausea and vomiting occur in up to 85% of all pregnant women between 6 and 12 weeks of gestation, but these symptoms are usually self-limiting. One-third of women with nausea and vomiting of pregnancy have clinically significant symptoms, and 3% will progress to hyperemesis gravidarum, which poses health risks to the mother and fetus. Despite these symptoms being common in pregnancy, there is a lack of high-quality evidence to support any particular intervention (Table 175.13).

Pyridoxine (Vitamin B_6), Doxylamine-Pyridoxine Combination. Pyridoxine is used alone, or in combination with doxylamine, an antihistamine, for the treatment of nausea and vomiting of pregnancy. Combination therapy of doxylamine and pyridoxine is FDA approved and fetal safety has been demonstrated in multiple epidemiologic studies.[19]

Phenothiazines. Phenothiazines, such as metoclopramide, prochlorperazine, and promethazine, are dopamine antagonists commonly used in the treatment of nausea and vomiting during pregnancy. Although there have been reports of increased risk of cardiac defects, these reports did not consider other factors, such as the mother's health, when the drug was reviewed. The bulk of evidence does not support a link to congenital abnormalities. The AAP cautions against their use in nursing mothers because they may cause sedation and other untoward effects.

Serotonin 5-HT$_3$ Receptor Antagonists. Dolasetron, granisetron, and ondansetron have not been consistently linked to any fetal malformations, although experience with the newer agents remains limited. Recent studies of ondansetron have suggested a low teratogenic risk; however, an increased risk for a cardiac septum defect and cleft palate is possible, but data are inconsistent, and has not been confirmed in other studies. The AAP considers these agents compatible with breast-feeding.

Neurologic Agents

Anticonvulsants

Maternal mortality is ten times higher in women with a seizure disorder. Pregnant women with a seizure disorder are at increased risk of spontaneous miscarriage, antepartum and postpartum hemorrhage, hypertensive disorders, induction of labor, cesarean sections, preterm birth, and fetal growth restriction. Pregnant women exposed to antiepileptic drugs (AEDs) have an increased risk of postpartum hemorrhage, induction of labor, fetal growth restriction, and admission to the NICU.

Newer-generation AEDs, lamotrigine and levetiracetam, have not been associated with increased risk of congenital malformations compared to controls but data are limited. Several anticonvulsants are known teratogens, and 30% of neonates exposed to commonly used anticonvulsants exhibit congenital anomalies. Monotherapies shown to have increased risk of congenital malformations are carbamazepine, ethosuximide, phenobarbital, phenytoin, topiramate, and valproate.

The risks for birth defects increase with the duration of exposure and with the number of agents used. Valproate is associated with the most frequent serious adverse effects on the pregnancy and fetus (20% incidence of serious adverse outcomes) compared with phenytoin, carbamazepine, and lamotrigine (11%, 8%, and 1%, respectively). Despite the risks, most practitioners believe that it is important to control seizures during pregnancy. Generalized seizures during pregnancy are associated with an increased risk of spontaneous abortion, hypoxic injury to the fetus, and impaired neuropsychological functioning. Monotherapy is the most appropriate option and is recommended at the lowest effective anticonvulsant dose. Dividing the daily dose to decrease peak plasma levels may be considered. Adjustment of the dosage upward may be required to maintain adequate seizure control.

Antipsychotics

These agents sometimes cause extrapyramidal side effects of the infants when exposed in utero. These effects are seen with use of the first- and second-generation antipsychotics. Haloperidol may cause limb defects when the mother is exposed during the first trimester, but data are inconsistent. This effect is not seen with other first-generation antipsychotics. Most second-generation antipsychotics do not show teratogenicity. The most commonly prescribed antipsychotics are olanzapine, risperidone, and quetiapine, which do not appear to cause consistent congenital defects (Table 175.14).

Migraine Medications

Ergot Alkaloids

Neither ergotamine nor dihydroergotamine are associated with teratogenic effects but are contraindicated in pregnancy because of their oxytocic effects and effects on uterine blood flow. In a number of animal studies, these alkaloids have been associated with intrauterine growth restriction, probably because of reductions in uteroplacental blood flow. They are also contraindicated during breast-feeding because of possible ergot poisoning of the nursing infant manifested by convulsions and gastrointestinal symptoms.

Triptans

Triptans have been found to be teratogenic in a number of animal species, but recent human studies appear to favor their safety during pregnancy. The AAP considers sumatriptan to be compatible with breast-feeding, especially if the breast milk is not used for 8 hours after the last dose.

Respiratory Agents

Antihistamines

Approximately 10% to 15% of women reportedly take an antihistamine during pregnancy. Chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine are safe for the treatment of allergic reactions and as antiemetics in the treatment of nausea and vomiting during pregnancy. First-generation antihistamines are not recommended during breast-feeding because they are thought to inhibit lactation. In addition, serious adverse CNS effects, including seizures, have been reported to develop in neonates receiving antihistamines, especially when they are premature.

The newer-generation antihistamines, such as cetirizine and loratadine, also appear safe during pregnancy. These may be acceptable alternatives if the first-generation antihistamines are not tolerated or if the patient has severe allergies. The AAP has classified these drugs as compatible with breast-feeding (Table 175.15).

TABLE 175.14 Antipsychotic Medications

Drug	Breast-Feeding	Clinical Risk Summary
First Generation		
Haloperidol	Potential toxicity (LHS) Excreted in breast milk	CP; extrapyramidal symptoms can be seen in infants exposed in utero in the third trimester; limb defects seen with first-trimester exposure but data inconsistent
Droperidol	Potential toxicity (LHS)	CP; no effect on respiratory drive when given perinatally; no observed fetal or maternal SAR, risk of extrapyramidal signs with exposure in the third trimester
Second Generation		
Olanzapine	Potential toxicity (LHS) Concentrated in breast milk	CP; no teratogenicity or mutagenicity in animal studies; extrapyramidal effects noted in infants exposed in third trimester
Risperidone	Potential toxicity (LHS)	CP; extrapyramidal effects noted in infants exposed in third trimester

CP, Crosses placenta; *LHS,* limited human studies; *SAR,* serious adverse reactions.
Additional data adapted from refs.[58,59]

Asthma Medications

Asthma is the most common respiratory disorder in pregnancy. The prevalence of asthma in pregnancy is 8%, and one-third of pregnant asthmatics experience a worsening of their asthma that may progress to a critical asthma syndrome, including status asthmaticus and near-fatal asthma. Pregnant women with asthma are at risk for neonatal death, preterm birth, low-birth-weight infants, preeclampsia, and small-for-gestational-age infants. Asthmatic mothers may also have higher rates of antepartum/postpartum hemorrhage, placenta previa, placental abruption, chorioamnionitis, gestational diabetes, hypertensive disorders of pregnancy, cesarean section, and prolonged hospital stay compared with control mothers. Active asthma management during pregnancy is associated with improved maternal and fetal outcomes.[20]

Albuterol has the most safety data and is the treatment of choice for asthma in pregnancy. None of the β-adrenergic medications has been linked to fetal or congenital malformations, but some have been associated with significant cardiovascular and metabolic effects, which are transient and generally well tolerated by the fetus. Transient hyperglycemia followed by insulin secretion may also occur, resulting in neonatal hypoglycemia, especially in diabetic patients. Terbutaline, when used IV or orally in pregnant women, may result in maternal and fetal arrhythmias, maternal pulmonary edema, and death. The FDA has recommended a label change to add a warning against its use in preterm labor because safer β_2-agonists and tocolytic agents are available. Long-acting β-agonists also appear to be safe during pregnancy. Albuterol is compatible with breast-feeding.

Ipratropium has not been found to be teratogenic in numerous animal models, but there are few data regarding its safety in human pregnancy. It is considered compatible with breast-feeding. Data on the use of leukotriene antagonists in pregnancy are limited (Table 175.16).

Corticosteroids

Inhaled corticosteroids are the main therapy for the prevention of asthma exacerbations during pregnancy. Budesonide has the greatest

TABLE 175.15 Antihistamine Medications

Drug	Breast-Feeding	Clinical Risk Summary
Chlorpheniramine	Probably compatible; use with caution: may cause sedation, irritability, disturbed sleep, hyperexcitability, excessive crying	LHS; no known congenital defects, low risk in pregnancy; recommended antihistamine in pregnancy, especially in first trimester[a]
Diphenhydramine	Probably compatible; use with caution, can be sedating; parenteral use contraindicated	LHS; animal and human studies demonstrate safety in pregnancy; association with cleft palate in one study; drug of choice if parenteral antihistamine is indicated[a]
Hydroxyzine	Probably compatible, LHS; not recommended with breast-feeding: may interfere with establishment of lactation	Contraindicated in 1st trimester; lower risk in 2nd and 3rd trimesters, if necessary to use; CP; teratogenic in animals, with high doses associated with developmental toxicity; low potential risk for fetus in humans; withdrawal or seizures noted in newborn exposed near term; possible increased risk of oral clefts, but limited data[a]
Meclizine	Probably compatible Safety unknown Occasional dose should not pose risk	Teratogenic in animals but not in humans; frequently used as antiemetic; considered low risk in pregnancy[a]
Cetirizine	Probably compatible Excreted in breast milk Not recommended—safety unknown	Animal studies—no teratogenicity; LHS; no evidence of increased risk of adverse fetal outcomes; may be used as alternative to oral first-generation antihistamine
Fexofenadine	Probably compatible excreted in breast milk	Animal studies—embryonic and fetal toxicity; no human studies available
Loratadine	Probably compatible considered antihistamine of choice in breast- feeding	Unknown if CP, but expected; no evidence of teratogenicity in animals or humans

[a]H1 blockers are not recommended for use in last 2 wk of pregnancy due to association with retrolental fibroplasia in premature neonates.
CP, Crosses placenta; *LHS,* limited human studies.
Data adapted from refs.[51]

TABLE 175.16 Asthma Medications

Drug	Breast-Feeding	Clinical Risk Summary
Ipratropium	Probably compatible, LHS May appear in breast milk	LHS; NHT; no teratogenicity in animals; recommended for use in severe asthma as additional therapy
Albuterol	Probably compatible, LHS Unknown if excreted in breast milk	May act as tocolytic; drug of choice for treatment of asthma; association with functional and neurobehavioral toxicity with prolonged use; may cause maternal and fetal tachycardia, hyperglycemia
Epinephrine	Potential toxicity, LHS Not known if excreted in breast milk	CP; teratogenic in animals; avoid during active labor and delivery—can delay labor progression; may lead to decrease in uterine blood flow with placental, uterine vasoconstriction
Terbutaline	Probably compatible Excreted in breast milk in small amounts	CP; NHT; may act as tocolytic; association with autism spectrum disorders (if used >2 wk); cardiac defects in first trimester; fetal tachycardia and hypoglycemia after parenteral use; avoid in early gestation, continuous use in second and third trimesters; may cause serious maternal cardiovascular events (e.g., increased heart rate, hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and MI), death; black boxed warnings against use for prevention or prolonged use (beyond 2–3 days) of preterm labor

CP, Crosses placenta; *LHS,* limited human studies; *MI,* myocardial ischemia; *NHT,* no human teratogenicity.
Additional data adapted from refs.[60,61]

amount of safety data but others are also considered safe. Oral corticosteroids are the mainstay of therapy for acute exacerbations of asthma. Although they are not considered human teratogens, there may be a slightly increased incidence (0.1% to 0.3%) of orofacial clefts when systemic steroids are used during the first trimester. Furthermore, their use in the third trimester has been linked to an increased incidence of preterm delivery, low birth weight, preeclampsia, and cataracts in the newborn. Prednisone is considered safe during breast-feeding.

Decongestants

Decongestants with strong vasoconstrictive properties, such as phenylpropanolamine, phenylephrine, and pseudoephedrine, cause placental vasoconstriction and are not recommended during pregnancy. Pseudoephedrine is one of the most commonly used over-the-counter medications in pregnancy, with 8% to 12% of pregnant women using it in the first trimester. They are often used as a combination product and therefore difficult to study. There are limited data suggesting that their use in the first trimester may result in an increased incidence of abnormalities typically associated with placental vascular disruption, such as gastroschisis and intestinal atresia. Recent evidence has supported the association of phenylephrine and endocardial cushion defect, phenylpropanolamine and ear defects, and phenylpropanolamine and pyloric stenosis with oral and intranasal decongestant use in the first trimester.[21] The risk, however, appears to be low. The AAP classifies pseudoephedrine as compatible with breast-feeding.

The references for this chapter can be found online by accessing the accompanying Expert Consult.website.

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CHAPTER 175: QUESTIONS AND ANSWERS

1. Which of the following statements is true regarding the teratogenic risk of medications administered during pregnancy?

- **a.** A drug should be given when maternal benefits outweigh the risks to the fetus.
- **b.** The FDA assigns one of five letters (A, B, C, D, and X) to classify teratogenic risk.
- **c.** The fetus is at greatest risk of anatomic defects during the third trimester.
- **d.** Most drugs do not enter the breast milk due to protein binding.
- **e.** Most drugs have epidemiologic studies confirming the risks in pregnancy.

Answer: A. In general, the health of the fetus is directly correlated with the health of the mother and necessary medications should not be withheld for fear of harming the fetus. The FDA no longer uses letter categories to describe teratogenic risk, which was a flawed system. The Pregnancy and Lactation Labeling Rule (PLLR), effective in 2015, changed the content and format for prescription drug labeling to better summarize the risks of drugs in pregnancy, lactation, and reproduction. The fetus is at greatest risk during organogenesis in the first trimester and functional development of the CNS in the 10th to 17th weeks of pregnancy. Unfortunately, current studies are insufficient to determine reliable and accurate risks in the use of medications in pregnancy. Most drugs passively diffuse into the breast milk.

2. Which of the following drugs is a known teratogen?

- **a.** Albuterol
- **b.** Hydroxycobalamin
- **c.** Penicillin VK
- **d.** Pyridoxine
- **e.** Valproic acid

Answer: E Several antiepileptic drugs (AEDs) are known teratogens, including valproic acid, carbamazepine, ethosuximide, phenobarbital, phenytoin, and topiramate. Valproic acid is associated with the most frequent serious adverse effects on the pregnancy and fetus compared with other AEDs. Newer-generation AEDs, such as lamotrigine and levetiracetam, have not been associated with increased risk of congenital malformations compared to controls but the data are limited. Maternal mortality is higher in women with a seizure disorder and control of seizures is felt to be important. Use of monotherapy in the lowest effective anticonvulsant dose is optimal. The other drugs are safe in pregnancy.

3. A 28-year-old woman who is 7 months pregnant was well until she experienced sudden onset of shortness of breath and left-sided sharp chest pain one hour prior to arrival. The pain is worse on inspiration and is not related to exertion, although her dyspnea becomes worse with any activity. She is alert and appears in mild distress. Her pulse is 112 beats/min, RR is 24 breaths/min, and BP is 110/68 mm Hg. Her temperature is 100.8°F (32°C), and O_2 saturation is 92%. Lung examination reveals diminished breath sounds on the left base with scattered wheezes. Cardiac examination reveals tachycardia. Chest radiograph reveals elevated right hemidiaphragm but no infiltrates. ECG reveals generalized T wave inversions. Which of the following treatments is most appropriate?

- **a.** Administer a low-molecular-weight heparin subcutaneously and start oral warfarin.
- **b.** Administer intravenous ceftriaxone and azithromycin.
- **c.** Administer nebulized bronchodilators and start prednisone.
- **d.** Administer oxygen and start low-molecular weight heparin
- **e.** Place a central line, and start early goal-directed therapy for sepsis.

CHAPTER 175: QUESTIONS AND ANSWERS—cont'd

Answer: D On the basis of the information provided, the patient most likely has a pulmonary embolus. The patient is hypoxic and requires oxygen administration and anticoagulation. This may be accomplished with heparin, low-molecular-weight heparin (LMWH), or warfarin. Warfarin, a vitamin K antagonist, is teratogenic and is contraindicated in pregnancy. The treatment of pulmonary embolism is LMWH preferentially or heparin. Heparin is preferred if the patient is hemodynamically unstable due to its rapid onset and short half-life. The patient has no symptoms of an infectious process; choices B and E are therefore not appropriate. Bronchodilators and steroids are indicated for asthma but not for thromboembolic disease. Choice C is therefore not appropriate.

4. Which of the following drugs may be associated with complications in the newborn when used at term?
   - **a.** All of these
   - **b.** Nitrofurantoin
   - **c.** Nonsteroidal antiinflammatory drugs
   - **d.** Propranolol
   - **e.** Sulfonamides

Answer: A. All the choices have been associated with complications in the newborn when used at term. Sulfonamides compete with bilirubin for protein-binding sites, leaving large amounts of free bilirubin to diffuse freely into the brain. This results in bilirubin deposition in the infant's brain, thus causing kernicterus. Nitrofurantoin at term has been associated with hemolytic disease of the newborn. Nonsteroidal antiinflammatory drugs are associated with premature closure of the ductus arteriosus. Propranolol at term has been associated with neonatal hypoglycemia, respiratory depression, and neonatal jaundice.

5. A 7-week pregnant (by LMP) patient arrives in the emergency department. She is complaining of severe nausea and vomiting. She is unable to keep any solids or liquids down. Her heart rate is 115, BP 110/75, Temp 98.8°F, RR 15, and glucose is 98. The patient is given IV fluids and antiemetics with improvement of her symptoms. Which of the following medications is the most appropriate for the outpatient management of this patient once her symptoms are controlled and she is tolerating fluids well?
   - **a.** Doxylamine 10 mg and pyridoxine 10 mg once per day
   - **b.** Haloperidol 2 mg twice a day
   - **c.** Omeprazole 20 mg every morning
   - **d.** Ondansetron orally disintegrating tablets 4 mg every 8 hours
   - **e.** Prochlorperazine 10 mg three times per day

Answer: A. This patient's symptoms likely represent nausea and vomiting of pregnancy or possible hyperemesis gravidarum. The preferred initial home treatment is Diclegis, which is a combination drug of doxylamine and pyridoxine (10 mg/10 mg). The non-combination version is: half-tab (21.5mg) of OTC Unisom and 10 mg pyridoxine (Vitamin B_6). There are some inconsistent studies suggesting a possible link with long term use of Zofran (Ondansetron) and cardiac abnormalities and cleft palates. Omeprazole is not first-line treatment for hyperemesis gravidarum, it is for the treatment of GERD. Prochlorperazine is teratogenic in animals and is not considered first-line treatment. Haloperidol is an antipsychotic and not indicated in this patient.

6. In determining a causal link between a specific drug and congenital malformations, which of the following may be viewed as confounding factors?
   - **a.** Genetic background of the fetus
   - **b.** Maternal illicit drug use
   - **c.** Presence of maternal illness
   - **d.** Presence of nutritional deficits
   - **e.** All of the above.

Answer: E. The process of establishing teratogenicity of a substance is often flawed. Much of our current knowledge on teratogenicity has been derived from case reports, case-controlled studies, and cohort studies, which are inherently weak in establishing a causal link. These reports are often complicated by a number of confounding factors, which make a causal link difficult to establish. The presence of any of the listed choices may confound results. In the presence of maternal illness, for example, the outcome of pregnancy may be related to the medical condition and not the medication.

Labor and Delivery

Jeremy Rose and Erick Eiting

KEY CONCEPT

- Most ED deliveries require only basic equipment to cut and clamp the umbilical cord and dry and suction the infant. However, the ED should have additional equipment and trained staff should be available to care for a newborn requiring further resuscitation.
- Women in labor who present to the ED are generally best cared for in the obstetric suite. Women with the urge to push or with the head of the infant crowning are at imminent risk of delivery, which should take place in the ED.
- The Braxton Hicks contractions of false labor do not escalate in frequency or duration like the contractions of true labor. When in doubt, external electrical monitoring of uterine activity can rule out true labor.
- Preterm labor is defined as uterine contractions with cervical changes before 37 weeks of gestation. Treatment includes tocolytics and fetal maturation therapy combined with bed rest and hydration.
- Premature rupture of membranes (PROM) occurs after 37 weeks' gestation. Its management depends on several factors, including gestational age and fetal maturity, presence of active labor, presence of infection or placental abruption, and degree of fetal well-being or distress.
- Preterm PROM should be treated with antibiotics to prevent infection (chorioamnionitis).
- The first stage of labor averages 8 hours in nulliparous women and 5 hours in multiparous women. Throughout labor, ongoing assessment of fetal well-being is important, and continuous external electrical monitoring helps identify fetal distress.
- Ultrasonography provides crucial information regarding pending delivery, including fetal viability, lie, and presentation.
- The fourth stage of labor refers to the first hour after delivery of the placenta and is a critical period during which postpartum hemorrhage is most likely to occur.
- Deliveries complicated by dystocia, malpresentation, or multiple gestations are life-threatening emergencies. The emergency clinician should develop strategies to treat each of these potential complications of delivery. Please see the following link for a video demonstration of maneuvers used to treat shoulder dystocia: https://www.hopkinsmedicine.org/gynecology_obstetrics/education/training/shoulder-dystocia.
- When a prolapsed cord occurs with a viable infant, cesarean section is the delivery method of choice. If surgical delivery is available, maneuvers to preserve umbilical circulation should be instituted immediately. The mother is placed in the knee-chest position, with the bed in the Trendelenburg position, and instructed to refrain from pushing to avoid further compression of the cord. The presenting part is then manually elevated off the cord. Elevation is maintained until the baby can be delivered surgically.
- Uterine atony accounts for 75% to 90% of cases of postpartum hemorrhage. Administration of a uterotonic, such as oxytocin in conjunction with massage usually provide enough stimuli to control bleeding.
- Approximately 10% of postpartum hemorrhage cases are due to retained placental tissue. Treatment requires manual removal of the remnant placental tissue.
- Pelvic bleeding postpartum can be difficult to control without hysterectomy. When available, embolization of bleeding vessels by an interventional radiologist has reported success rates of 95% to 100%.
- Maternal complications of labor and delivery include obstetric trauma, uterine inversion and rupture, amniotic fluid embolism, coagulation disorders, and infections. Many of these problems can initially be managed in the ED while awaiting obstetric consultation.

FOUNDATIONS

Births in the emergency department (ED) remain a rare event. However, hospital closures and health system consolidation of services has left more hospitals without obstetric coverage, especially in rural areas. These practices have stressed the need for emergency clinicians to be familiar with labor, delivery, and their complications.

Limitations of the Emergency Department

The ED is a suboptimal location for the management of a complicated delivery. Unlike the obstetric suite, the ED may be lacking in appropriate resources, certain specialized equipment, and information about the patient's prenatal care. Cesarean section may be indicated to ensure a successful delivery in dire perimortem circumstances.

Epidemiology of Emergency Delivery

From 2014 to 2016, the perinatal mortality rate in the United States (US) was 6.00/1000 live births.[1] This is remarkably high, almost three times the rate of other similar countries in the developed world. Delivery complications and mortality occur with greater frequency in the ED, where the perinatal mortality rate is approximately 8% to 10%. There are multiple features of the high-risk ED delivery profile. The ED as a care environment is often selected by an obstetric population that subsequently may have unexpected complications. Psychosocial

factors, such as drug or alcohol abuse, domestic violence, and lack of access to medical care, contribute to precipitous deliveries in pregnant women with little or no prenatal care. Antepartum hemorrhage, premature rupture of membranes (PROM), eclampsia, premature labor, abruptio placentae, malpresentation, and umbilical cord emergencies are overrepresented in the ED population.

Patient Transfer Considerations

Because of the high risk associated with ED delivery, patients should be transported to a facility that has obstetric and neonatal resources whenever possible. The transfer of a woman with an impending high-risk delivery to such a facility should be based on careful consideration of the risks and benefits. Transferring a pregnant patient with impending delivery can be disastrous for the mother and fetus and may actually violate federal law. Further consideration should be given to the level of care that the neonate will require after delivery, particularly in preterm (<36 weeks of gestation) deliveries, in which interval transfer for a higher level of care may be necessary.

NORMAL DELIVERY

Initial Presentation

Although the epidemiology and high complication rate associated with ED births demand caution, most are normal deliveries. Knowledge of normal labor and delivery mechanics aids safe vaginal delivery and facilitates the identification of complications.

Whenever a woman in the third trimester of pregnancy seeks treatment in the ED, the possibility that she is in labor must be considered. A wide array of nonspecific symptoms may herald the onset of labor. Abdominal pain, back pain, cramping, nausea, vomiting, urinary urgency, stress incontinence, and anxiety can be symptoms of labor. After 24 weeks' gestation, fetal viability is established and thus a medical screening exam should include assessment of both the mother and fetus. Risk factors for preterm labor include older maternal age and presence of systemic disease. This should be considered when treating pregnant patients, even with non–pregnancy-related complaints such as asthma.

Distinguishing False From True Labor

Braxton Hicks contractions, or false labor, must be differentiated from true labor. After 30 weeks of gestation, the previously small and uncoordinated contractions of the uterus become more synchronous and may be perceived by the mother. Braxton Hicks contractions do not escalate in frequency or duration, in contrast to the contractions of true labor. By definition, these contractions are associated with minimal or no cervical dilation or effacement. Examination should also reveal intact membranes. Care not to rupture the membranes is important to avoid inducing labor prematurely. Examination should be done in a sterile fashion to avoid introducing infection if the membranes have ruptured. If the diagnosis remains in doubt, external electrical monitoring of uterine activity can rule out true labor. Any discomfort associated with false labor is usually relieved with mild analgesia, ambulation, or change in activity.

Unlike false labor, true labor is characterized by cyclic uterine contractions of increasing frequency, duration, and strength, culminating in delivery of the fetus and placenta. In contrast to Braxton Hicks contractions, true labor causes cervical dilation to begin, marking the first stage of labor.

Bloody Show

At the onset of labor, the cervical mucous plug may be expelled, resulting in what is termed a *bloody show*. The bleeding associated with this process is slight (usually only a few dark red spots admixed with mucus) and is due to the increase in cervical vascularity that occurs in pregnancy. Bloody show is not a contraindication to vaginal examination for the determination of cervical effacement and dilation. If bleeding continues or is of a larger volume, more serious causes should be suspected, such as placenta previa and placental abruption, which are contraindications for a vaginal examination.

Stages of Labor

First Stage of Labor

The first stage of labor is the cervical stage, ending with a completely dilated, fully effaced cervix. It is divided into a latent phase, with slow cervical dilation, and an active phase, with more rapid dilation. The active phase begins once the cervix is dilated to 3 cm. Most women who deliver in the ED arrive while in the active phase of stage 1 or early stage 2 labor (Fig. 176.1). The duration of the first stage of labor averages 8 hours in nulliparous women and 5 hours in multiparous women. During this time, frequent assessment of fetal well-being is important, and continuous external electrical monitoring may help identify fetal distress, allowing for appropriate intervention.

The maternal examination provides a rough guide to gestational age. At 20 weeks' gestation, the uterine fundus reaches the umbilicus. Approximately 1 cm of fundal height is added per week of gestation until 36 weeks. At that time, the fundal height decreases as the fetus drops into the pelvis (Fig. 176.2). These estimates help establish gestational age rapidly.

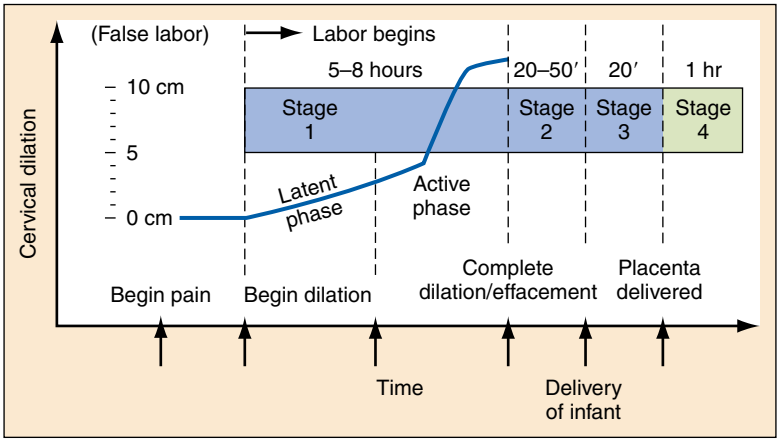

Fig. 176.1 Stages of labor and delivery. Stage 1, cervical stage; stage 2, fetal expulsion; stage 3, placental expulsion (20 minutes); stage 4, uterine contraction (1 hour postpartum).

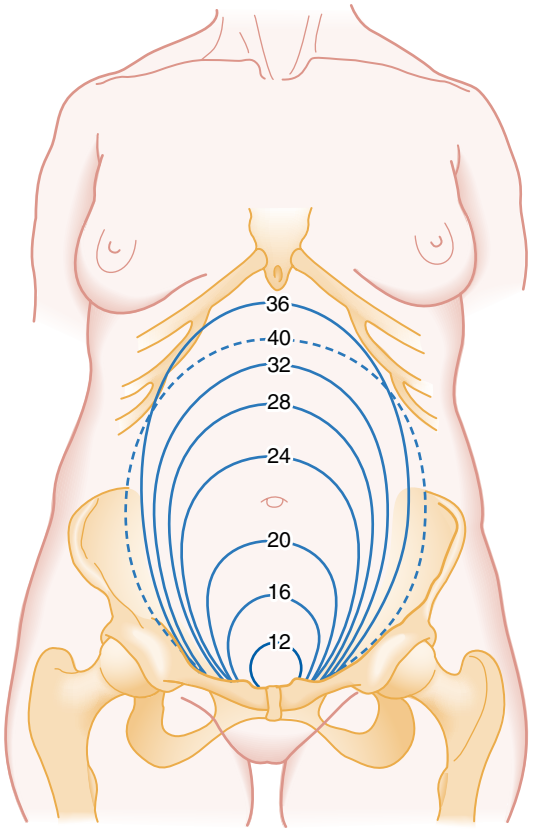

Fig. 176.2 Height of fundus by weeks of normal gestation with a single fetus. The dotted line indicates height after lightening. (Adapted from: Barkaukas V, et al. *Health and Physical Assessment*. St. Louis: Mosby; 1992.)

The abdominal examination with Leopold maneuvers may confirm the lie of the fetus (Fig. 176.3). Bedside ultrasound can be especially useful in determining fetal position. The determination of the stage of labor depends on examination of the cervix. A sterile approach using sterile gloves, sterile speculum, and povidone-iodine solution is indicated to prevent ascending infection. On pelvic examination, the clinician should determine the following:

- *Effacement* refers to the thickness of the cervix. A paper thin cervix is 100% effaced.
- *Dilation* indicates the diameter of the cervical opening in centimeters. Complete, or maximum, dilation is 10 cm.
- *Position* describes the relationship of the fetal presenting part to the birth canal. The most common position of the head is occiput anterior.
- *Station* indicates the relationship of the presenting fetal part to the maternal ischial spines (Fig. 176.4).
- *Presentation* specifies the anatomic part of the fetus leading through the birth canal.

In 95% of all labors, the presenting part is the occiput, or vertex. On digital examination, a smooth surface with 360 degrees of firm bony contours and palpable suture lines is noted. Palpation of the suture lines and the fontanels where they join allows the examiner to determine the direction the fetus is facing. Three sutures radiate from the posterior fontanel, and four radiate from the anterior fontanel (Fig. 176.5). The lateral margins are examined carefully for fingers or facial parts that indicate compound or brow presentations.

When the clinician suspects rupture of membranes, a sterile speculum examination is performed. This may reveal pooling of amniotic fluid, a fernlike pattern when the fluid is allowed to dry on a microscope slide, and the use of Nitrazine paper, which should turn blue, indicating an alkaline amniotic fluid (pH > 6). Although vaginal blood, cervical mucus, semen, and infection can interfere with results, sensitivities of Nitrazine paper and ferning for the detection of amniotic fluid are nearly 90%. If vaginal bleeding is evident, digital and speculum examination of the pelvis should be deferred until an ultrasound study can be obtained to rule out placenta previa.

Second Stage of Labor

The second stage of labor is characterized by a fully dilated cervix and accompanied by the urge to bear down and push with each uterine contraction. The median duration of this stage is 50 minutes in nulliparous women and 20 minutes in multiparous women, with the anticipation of a more rapid progression for low-birth-weight premature infants. A prolonged second stage of labor is associated with an increase in maternal complications, including postpartum hemorrhage, infection, and severe vaginal lacerations.

Antenatal Fetal Assessment. During labor and delivery, the identification of fetal distress and appropriate intervention can reduce fetal morbidity and mortality. There are currently three methods of assessing a fetus in utero: (1) clinical monitoring; (2) electrical monitoring; and (3) ultrasonography. External electrical monitoring and ultrasonography merit consideration for use in the care of women laboring in the ED. Both modalities provide real-time information that is helpful for the diagnosis of fetal distress and assistance with intrapartum decision making.

Electronic Fetal Monitoring. Electronic fetal monitoring uses tracings of the fetal heart rate and uterine activity. Documentation of organized cyclic uterine contractions helps confirm true labor and may help diagnose fetal distress. In combination with clinical data, this can portend fetal distress due to hypoxia and provide a window for intervention.

Uterine activity is measured transabdominally by a pressure transducer, creating a recording of the contraction frequency. Because the measurements are indirect, the strength of the contractions correlates poorly with the tracing. The tracings are position and placement sensitive.

Fetal heart rate tracings have several components that can be assessed—baseline heart rate, variability, accelerations, decelerations, and diagnostic patterns.

Baseline Heart Rate. This is the average fetal heart rate during a 10-minute period (in the absence of a uterine contraction) and is the most important aspect of fetal heart rate monitoring. Fetal bradycardia is defined as a baseline rate of less than 110 beats/min; fetal tachycardia is defined as a baseline rate of more than 160 beats/min.

Variability. This can be instantaneous (beat to beat) or long term (intervals ≥ 1 minute). Both types of variability are indicators of fetal well-being. Accelerations occur during fetal movement and reflect an alert mobile fetus. Decreased variability may indicate fetal hypoxemia and acidemia, or it may be a side effect of a wide array of drugs, including analgesics, sedative-hypnotics, phenothiazines, and alcohol.

Decelerations. Decelerations in fetal heart rate are more complicated and should be interpreted according to the clinical scenario. There are three types of deceleration—variable, early, and late (Fig. 176.6). These terms refer to the timing of the deceleration relative to the uterine contraction.

Variable and early decelerations are common and normally represent physiologic reflexes associated with head compression in the birth canal or intermittent cord compression. Variable decelerations that are persistent and repetitive usually indicate repeated episodes of umbilical cord compression. The resultant hypoxia and acidosis may cause fetal distress. Attempts to shift maternal and fetal weight off the umbilical cord by changing position are indicated. If variable decelerations continue, the

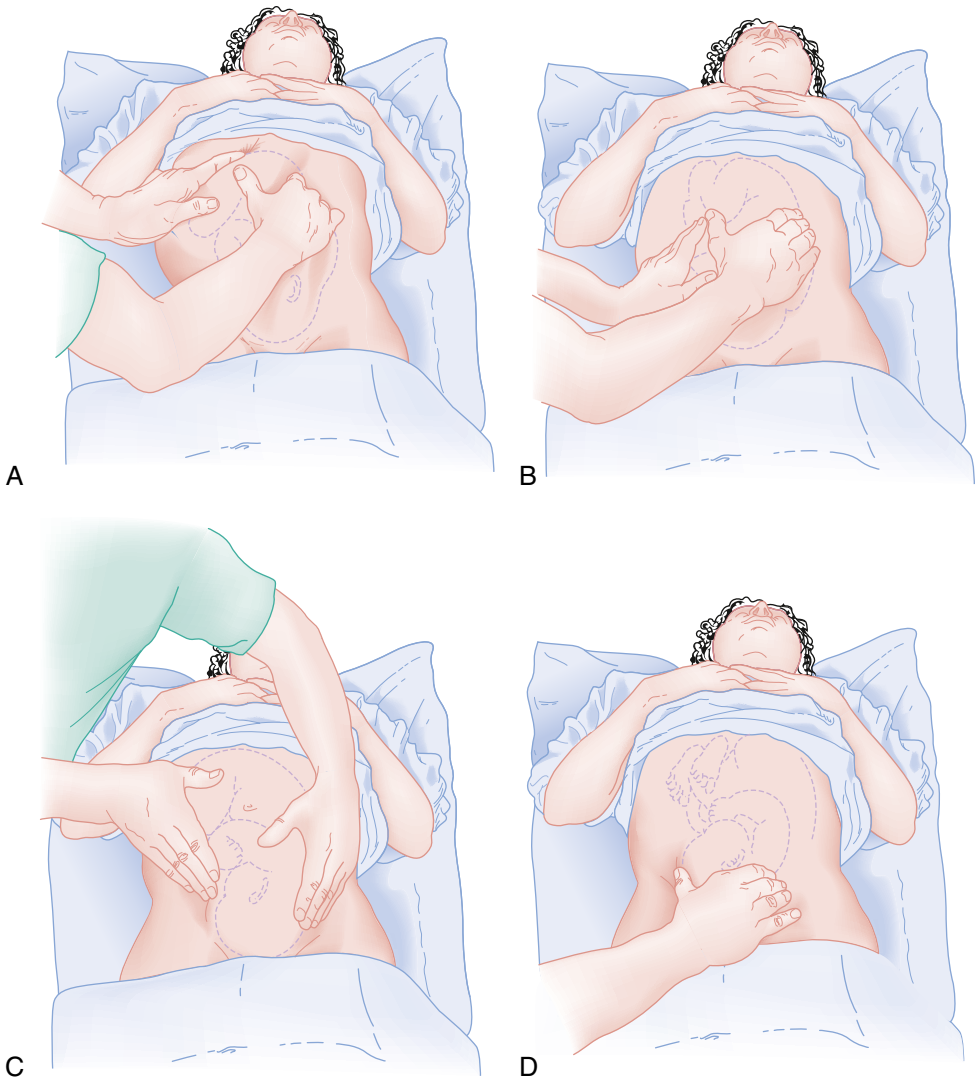

Fig. 176.3 Leopold maneuvers. (A) The first Leopold maneuver reveals which fetal part occupies the fundus. (B) The second Leopold maneuver reveals the position of the fetal back. (C) The third Leopold maneuver reveals which fetal part lies over the pelvic inlet. (D) The fourth Leopold maneuver reveals the position of the cephalic prominence. (Adapted from: Willson JR, et al. *Obstetrics and Gynecology*, ed 9. St. Louis: Mosby; 1991.)

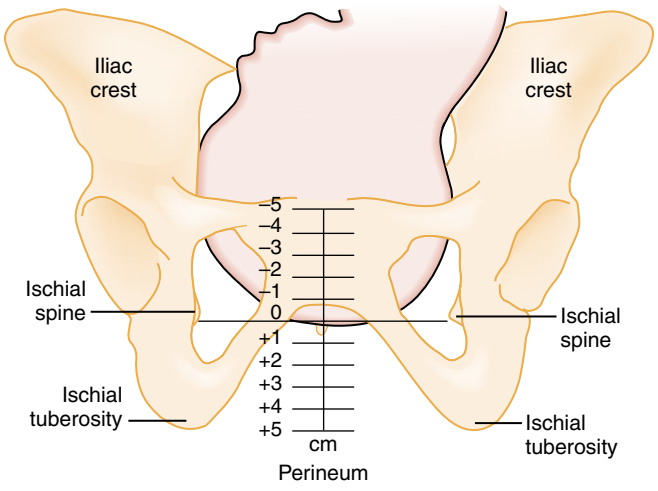

Fig. 176.4 Fetal stations. The level of the ischial spines is considered 0 station. The silhouette of the infant's head is shown approaching station +1. (Courtesy Ross Laboratories, Columbus, OH.)

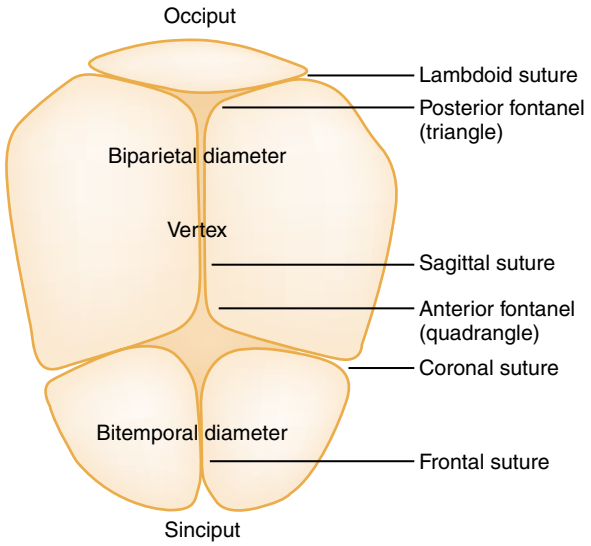

Fig. 176.5 Bony landmarks of the fetal skull. (Adapted from: Willson JR, et al. *Obstetrics and Gynecology*, ed 9. St. Louis: Mosby; 1991.)

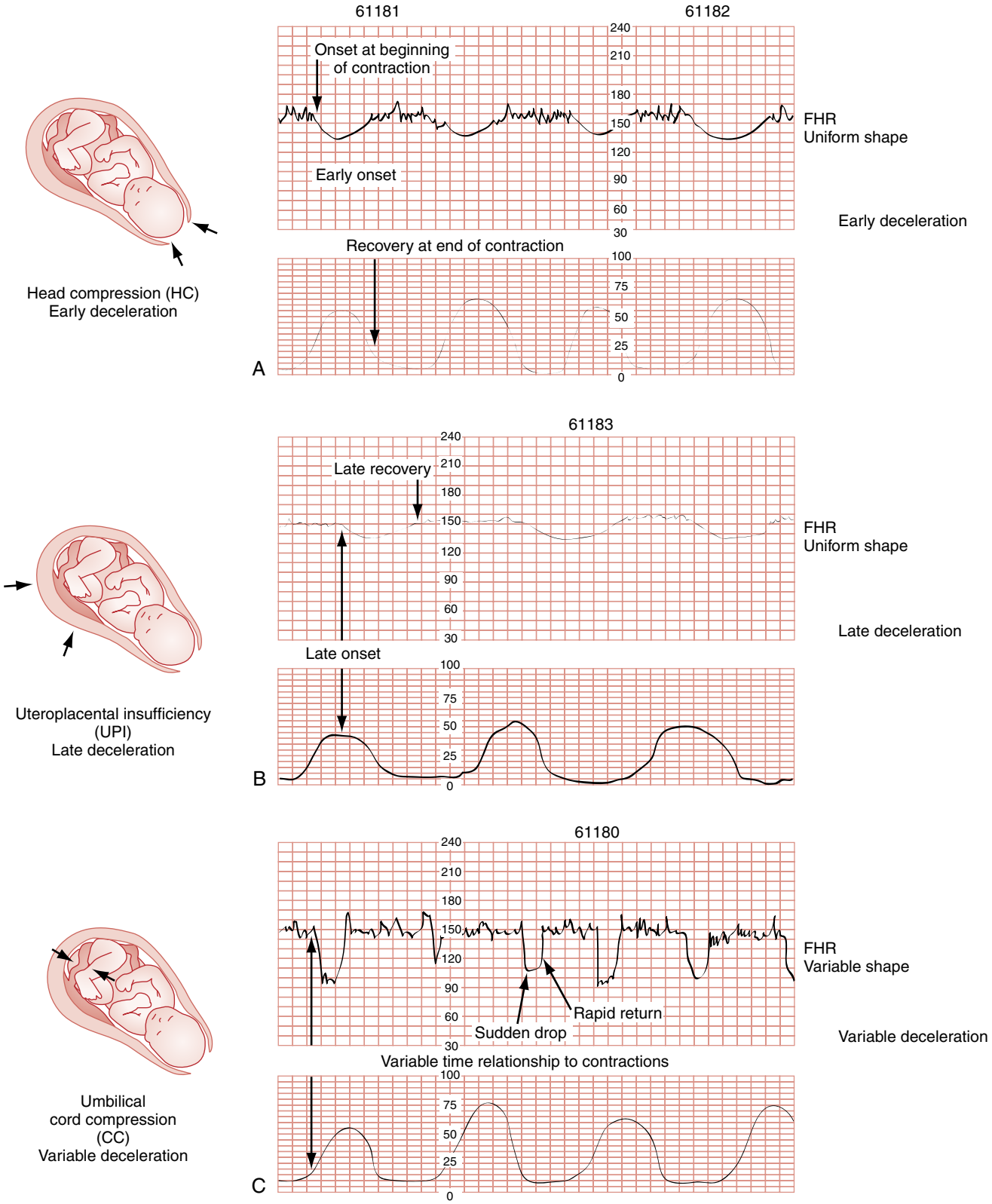

Fig. 176.6 Deceleration patterns of the fetal heart rate (FHR). (A) Early deceleration caused by head compression. (B) Late deceleration caused by uteroplacental insufficiency. (C) Variable deceleration caused by cord compression. (Modified from: Lowdermilk DL, et al. *Maternity and Women's Health Care*, ed 6. St. Louis: Mosby; 1997.)

situation warrants efforts to hasten the delivery or, if obstetric backup becomes available, to perform an emergency cesarean section.

Late decelerations are more serious and most often indicate uteroplacental insufficiency. The tracing contours are generally smooth, with the heart rate nadir occurring well after a maximal uterine contraction (typically, ≥30 seconds afterward). The lag, slope, and magnitude of late decelerations correlate with increasing fetal hypoxia. Late decelerations are particularly ominous in association with poor variability, nonreactivity, and baseline bradycardia. When these findings are present, immediate obstetric consultation for delivery is indicated to prevent further hypoxia.

Diagnostic Patterns. Finally, the emergency clinician should be aware of the significance of sinusoidal tracings. Tracings of this type have low baseline heart rates and little beat to beat variability. The sinusoidal tracing is an ominous finding that is often premorbid. The differential diagnosis includes erythroblastosis fetalis, placental abruption, fetal hemorrhage (trauma), and amnionitis.

Ultrasonography. In the third trimester or during labor, ultrasonography can provide crucial information pertaining to impending delivery, such as the number and position of fetus(es) and fetal heart rate. When a technician and radiologist are available, and if time permits, the gestational age, biophysical profile, amniotic fluid index, and a survey of fetal and placental anatomy may be obtained. The American College of Obstetricians and Gynecologists (ACOG) has published recommendations regarding the indications for ultrasonography in the third trimester (Box 176.1). The parameters of immediate interest in the ED are fetal viability (specifically in utero gestation and fetal heart rate), lie, and presentation. Transvaginal ultrasonography is relatively contraindicated in the peripartum period, particularly in the cases of premature rupture of membranes (PROM) and placenta previa.

Delivery. As stage 2 of labor progresses, preparation for delivery should be under way. A radiant warmer should be available and heated. Neonatal resuscitation adjuncts should be available, including a towel, scissors, umbilical clamps, bulb suction, airway equipment (oxygen, bag-mask device with appropriate-sized masks, and tools for endotracheal intubation), and equipment to achieve vascular access. Most deliveries require only basic equipment to cut and clamp the umbilical cord, suction the mouth and nose, and dry and stimulate the infant. A nurse should be at the bedside to coach and provide reassurance to the mother.

The mother is placed in the dorsal lithotomy position and prepared for delivery. The Sims position, or left lateral position with knees drawn toward the mother's chest and back to the physician, is also an acceptable position. The vulva and perineum are cleared and gently scrubbed with sterile water or saline. A repeated sterile examination to assess labor progression and confirm presentation may be performed. Firm digital stretching of the perineum, particularly posteriorly, may prevent tears and lacerations later in delivery.

BOX 176.1 Third-Trimester Ultrasonography: Possible Indications

Determine number of fetuses.
Establish fetal presentation.
Identify fetal heart motion.
Locate placenta.
Measure amniotic fluid.
Determine gestational age.
Survey fetal anatomy.
Diagnose cord prolapse.
Diagnose cause of third-trimester bleeding.
Rule out placental abruption.

Controlled coordinated expulsion with coaching to sustain each push aids with crowning and delivery of the head. The most vulnerable moment is when the fetal head begins to stretch and distend the perineum. Instructing the mother to pant and not push slows the passage of the head and shoulders. The modified Ritgen maneuver may be used to support the perineum and prevent maternal injury: In this technique, a towel-draped, gloved hand is used to stretch the perineum and gently exert pressure on the chin of the fetus. The second hand places pressure on the occiput superiorly, guiding the head into slight extension and positioning it so that its smallest diameter passes through the pelvic outlet. Calm communication between the physician and mother is the best way to maintain control of the delivery.

After the head is delivered, the physician allows the head to rotate toward the maternal thigh and clears the fetal face and airway. Next, the shoulders, usually anterior shoulder first, clear the perineum. The shoulders often deliver spontaneously, with little effort by the physician. Gentle downward traction on the head promotes delivery of the anterior shoulder. A subsequent upward motion pulls the posterior shoulder through the pelvic outlet. If delay occurs in delivery of the shoulders, the potential for shoulder dystocia should be considered.

As the infant clears the perineum, attention focuses on the umbilical cord. The infant should be kept low or at the level of the perineum to promote blood flow into the infant from the placenta. The cord is clamped and cut. Clamps should be placed 4 or 5 cm apart, with the proximal clamp 10 cm from the infant's abdomen. The cord should be cut at least 1cm from the skin to ensure venous access if the neonate requires resuscitation. Suctioning of the nose and mouth at this time may reduce secretions that can cause increased airway resistance.

The infant is now clear of the mother and can be wrapped in towels and moved to the warmer. Gentle drying with a towel and suctioning usually provide sufficient respiratory stimulation. If not, flicking the soles of the feet and rubbing the back are other modalities. Apgar scores at 1, 5, and 10 minutes after birth should be documented.

Episiotomy. With a controlled delivery, routine performance of an episiotomy is not recommended. It should be performed only for specific indications, such as shoulder dystocia or breech delivery. An episiotomy should be done before excessive stretching of the perineal muscles occurs but near the time of delivery to avoid excessive bleeding. Common practice is to cut the episiotomy when the head is visible during a contraction and the introitus opens to a diameter of 3 or 4 cm. The literature currently recommends a mediolateral incision to avoid perineal tears and rectal involvement (Fig. 176.7).

Third Stage of Labor

The third stage of labor involves the delivery of the placenta and frequent checks of the tone and height of the uterine fundus. Signs of placental separation include the following: the uterus becomes firmer and rises; the umbilical cord lengthens 5 to 10 cm; or there is a sudden gush of blood.

These signs usually occur within 5 to 10 minutes of the delivery of the infant but may extend to 30 minutes. Beyond 18 minutes, the risk of postpartum hemorrhage increases and is up to six times more likely after 30 minutes. Although the placenta may be delivered expectantly, active management reduces the length of the third stage of labor and thereby decreases the risk of postpartum hemorrhage. Active management includes the administration of uterotonic gentle traction of the clamped umbilical cord with mild pressure applied above the symphysis pubis and uterine massage after delivery. Any attempt to deliver the placenta before it separates is contraindicated.

Examination of the umbilical cord and placenta is an essential part of the delivery process and any abnormalities should be noted at this

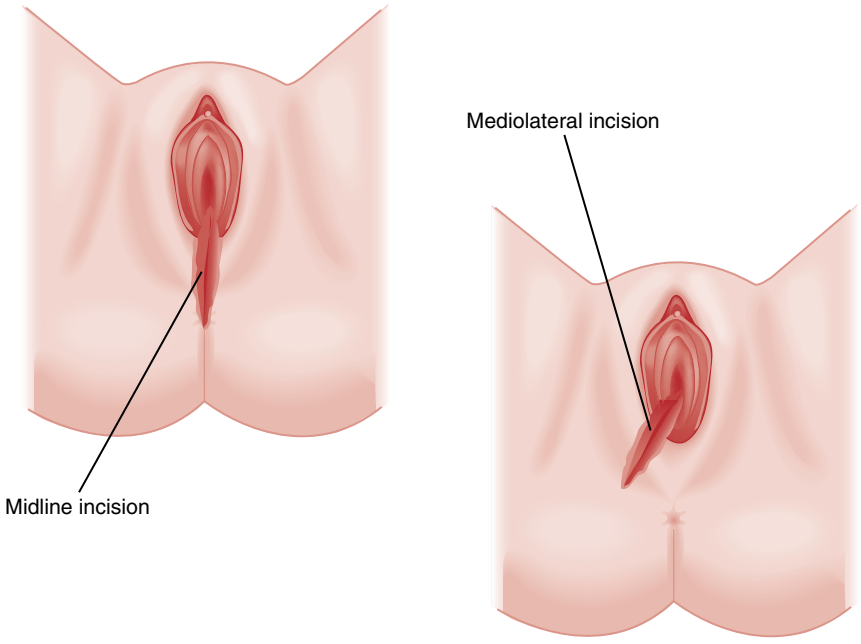

Fig. 176.7 A mediolateral episiotomy incision is preferred to a strictly midline incision. (Adapted from www.aurorahealthcare.org/healthgate/images/exh44028a_ma.jpg.)

time. The umbilical cord is normally a three-vessel structure, with two umbilical arteries on either side of the single umbilical vein. A two-vessel cord (one umbilical artery) occurs in 1 of 500 deliveries. Common abnormalities of the placenta include accessory lobes and abnormal cord insertion. Visible clots adherent to the uterine aspect may indicate placental abruption and the discovery of an incomplete placenta or membranes should alert the clinician to the possibility of postpartum complications.

Fourth Stage of Labor

The fourth stage of labor refers to the first hour after delivery of the placenta and is a critical period during which postpartum hemorrhage is most likely to occur. The cervix and vaginal fornices should be inspected for deep lacerations as a result of delivery, and repair of any vaginal lacerations should be performed at this time.

Finally, oxytocin is infused to promote contraction of the uterus and control hemorrhage. The uterus is evaluated frequently for tone and massaged transabdominally if any sign of relaxation exists. Oxytocin should not be given before delivery of the placenta because this could result in the trapping of placental fragments or may hinder the delivery of an undetected twin.

THIRD-TRIMESTER COMPLICATIONS ASSOCIATED WITH DELIVERY

Obstetric problems in the third trimester often result in the initiation of labor. Premature labor, PROM, and third-trimester bleeding are relatively common complications. The fundamental question to be addressed in these settings is whether the fetus would fare better in utero or delivered.

Premature Labor

Premature or preterm labor and fetal immaturity are the leading causes of neonatal mortality. Preterm labor is defined as uterine contractions with cervical changes before 37 weeks of gestation. Many underlying conditions result in preterm labor, which is associated with 5% to 18% of all pregnancies and is the leading cause of neonatal death. Factors linked to this problem include substance abuse, history of preterm delivery, multiple gestations, placental anomalies, infections, and lifestyle or psychosocial stressors (Box 176.2). The unexpected nature of premature labor often results in an ED visit. When delivery is not imminent, the patient can be moved to the obstetrics unit for further care.

BOX 176.2 Factors Linked to Preterm Labor

Demographic and Psychosocial
Extremes of age (>40 yr, teenagers)
Lower socioeconomic status
Tobacco use
Cocaine abuse
Prolonged standing (occupation)
Psychosocial stressors

Reproductive and Gynecologic
Prior preterm delivery
Diethylstilbestrol exposure
Multiple gestations
Anatomic endometrial cavity anomalies
Cervical incompetence
Low pregnancy weight gain
First-trimester vaginal bleeding
Placental abruption or previa

Surgical
Prior reproductive organ surgery
Prior paraendometrial surgery other than genitourinary (appendectomy)

Infectious
Urinary tract infections
Nonuterine infections
Genital tract infections (bacterial vaginosis)

Clinical Features

The diagnosis of preterm labor requires the identification of uterine activity and cervical changes before 37 weeks of gestation. Early maternal signs and symptoms include an increase or change in vaginal discharge, pain resulting from uterine contractions (sometimes perceived as back pain), pelvic pressure, vaginal bleeding, and fluid leak.

Diagnostic Testing

If uterine contractions and cervical changes are present, and the estimated fetal weight on ultrasonography is less than 2500 g, the diagnosis of premature labor is likely. The differentiation of false labor from true labor is best done by electrical monitoring. The initial evaluation of a woman with possible preterm labor includes urinalysis, complete blood count, and pelvic ultrasonography. If delivery is not imminent, these studies can be performed under monitoring in the ED or obstetrics area. Whenever possible, these patients should be transferred to a perinatal center with an associated intensive care unit.

Management

A viable fetus and healthy mother are indications for medical management directed toward the prolongation of gestation. Preterm labor should not be postponed with medical management in the cases of fetal compromise, major congenital anomalies, intrauterine infection, placental abruption, eclampsia, significant cervical dilation, or PROM.

The treatment of preterm labor involves multiple modalities and is usually performed outside the ED. Tocolytics and fetal maturation therapy combined with bed rest and hydration are used with the hope of prolonging pregnancy (Box 176.3). When tocolytics are indicated, they should be used in coordination with an obstetric consultant. These patients optimally should be transferred to an appropriate center before delivery, whenever possible, because medical management fails in more than 25% of preterm patients for whom it is attempted. The contraindications to tocolytics should be reviewed before initiation of these therapies (Box 176.4). Any patient receiving tocolytics needs to be monitored for signs of fetal distress. Terbutaline has been associated with serious maternal side effects and deleterious behavioral effects in the offspring after in utero exposure. Terbutaline should be limited to short-term inpatient use.

Premature Rupture of Membranes

Clinical Features

PROM is defined as rupture of the amniotic and chorionic membranes before the onset of labor. It affects 3% of all gestations. During pregnancy, the chorionic and amniotic membranes protect the fetus from infection and provide an environment that allows fetal growth and movement. The amniotic fluid is constantly exchanged by fetal swallowing and urination and umbilical cord transfer.

The word *premature* in PROM refers to rupture before labor, not to fetal prematurity. In 8% of PROM cases, the fetus is at or near term, and PROM may result in normal labor. When PROM occurs before 37 weeks, it is called preterm PROM and is associated with significant fetal morbidity and mortality. PROM is the inciting event in one-third of all preterm deliveries.

After the membranes rupture, the period from latency to the onset of labor varies. Longer latent periods are common earlier in pregnancy, and the latency shortens as gestational age increases. At term, labor is a desirable result of PROM, but with fetal immaturity, delivery would result in fetal complications.

Diagnostic Testing

The diagnosis of PROM can be established by the history and physical examination. In most cases, the patient suggests the diagnosis and usually is correct. The patient typically describes a spontaneous gush of watery fluid, followed by a mild persistent seepage. Urinary incontinence or excess vaginal or cervical secretions are occasionally confused with PROM.

Examination of women with potential PROM is performed under sterile conditions to prevent ascending infection. Direct digital examination of the cervix is avoided. The identification of amniotic fluid was previously discussed. Table 176.1 summarizes the bedside testing modalities available to confirm the diagnosis of PROM. Visualization of the cervix for a prolapsed cord or small fetal part is performed during the evaluation for effacement and dilation. Culture specimens for group B streptococci, *Chlamydia trachomatis,* and *Neisseria gonorrhoeae* should be obtained.

BOX 176.3 Commonly Used Tocolytic Agents

Magnesium sulfate
- 4–6 g IV bolus over 20 min
- 1–2 g/hr IV infusion

Terbutaline
- 5–10 mg PO q4–6h
- 0.25 mg SC q20min
- 2.5–5 mcg/min increased every 20 min to max 25 mcg/min

Ritodrine[a]
- 10 mg PO q2–4h
- 10 mg IM q3–8h
- 0.05–0.35 mg/min IV infusion

Isoxsuprine
- 20 mg PO q6h
- 0.2–0.5 mg/min IV infusion

Nifedipine
- 10–30 mg PO q15–20 min for the first hour then 10–20 mg PO q4–8h

[a]Ritodrine and Isoxsuprine have been discontinued in the United States.

BOX 176.4 Contraindications to Tocolysis

Absolute
- Acute vaginal bleeding
- Fetal distress (not tachycardia alone)
- Lethal fetal anomaly
- Chorioamnionitis
- Preeclampsia or eclampsia
- Sepsis
- Disseminated intravascular coagulopathy

Relative
- Chronic hypertension
- Cardiopulmonary disease
- Stable placenta previa
- Cervical dilation > 5 cm
- Placental abruption

TABLE 176.1 Bedside Testing for Premature Rupture of Membranes

Method	Result
Nitrazine	Amniotic fluid (pH > 6.5) will turn Nitrazine paper blue; normal vaginal secretions (pH < 5.5) leave Nitrazine paper yellow
Ferning	Amniotic fluid crystallizes
Smear combustion	Amniotic fluid, when flamed, turns white and crystallizes; vaginal secretions caramelize, turn brown

Management

The management of PROM depends on several factors, including gestational age and fetal maturity, presence of active labor, presence or absence of infection, presence of placental abruption, and degree of fetal well-being or distress. In all cases, fetal heart rate monitoring, obstetric consultation, and admission are indicated. In the immature fetus (24–31 weeks of gestation), the initiation of specific treatment decisions aimed at accelerating fetal maturity should be made in coordination with the receiving obstetrician. This includes the possible administration of corticosteroids to promote pulmonary maturation. Patients with PROM between 31 and 33 weeks' gestation are usually managed expectantly and those at or beyond 34 weeks of gestation are generally delivered.

All patients with PROM should be assessed for intraamniotic infection. Infectious complications should be diagnosed and treated before the mother demonstrates overt clinical signs. We recommend treating preterm PROM with an initial dose of ampicillin (2 g IV) plus azithromycin (1 g PO) followed by ampicillin (2 g IV Q6h × 48h) plus amoxicillin 875 mg PO BID for 5 days.

Chorioamnionitis

Chorioamnionitis occurs when vaginal or cervical bacteria ascend into the uterus, instigating an inflammation of the chorion and amnion layers of the amniotic sac. It occurs in 1% to 10% of all pregnancies; risk factors include prolonged labor, PROM, excessive vaginal examinations, and recent amniocentesis. Box 176.5 summarizes the findings and evaluation of chorioamnionitis. Chorioamnionitis may result in prolonged first- and second-stage labor and decreased responsiveness to oxytocin. Early aggressive treatment, even before evidence of infection occurs, decreases neonatal morbidity and delays delivery, allowing more time for fetal maturation.

BOX 176.5 Chorioamnionitis Evaluation

Fluid in Vaginal Vault
Phosphatidylglycerol

Cervical Cultures
Escherichia coli and other gram-negative bacteria
Neisseria gonorrhoeae

Vaginal Cultures
Chlamydia spp.
Mycoplasma hominis
Group B streptococci
Ureaplasma urealyticum

Amniocentesis Studies
Gram stain (group B streptococci)
Culture
Glucose
Lecithin to sphingomyelin ratio

Maternal Signs and Symptoms
Premature rupture of membranes
Uterine tenderness
Fever
Tachycardia (maternal or fetal)
Malodorous vaginal discharge
Leukocytosis

Fetal Signs and Symptoms
Decreased activity
Abnormal biophysical profile (ultrasonographic examination)
Fetal tachycardia
Decreased variability of fetal heart rate

Vertical Transmission of Human Immunodeficiency Virus

The antiretroviral drug zidovudine (AZT) has long been used to prevent vertical transmission of HIV during labor. With appropriate therapy, the risk of vertical transmission is well under 1%. Current guidelines do not recommend perinatal intravenous AZT for patients with well-controlled disease that are already taking oral antiretroviral medications.[2] If doubt exits as to a patient's HIV progression or medication compliance, AZT (2 mg/kg infused over 1 hour followed by a continuous infusion of 1 mg/kg/hour for 2 additional hours) should be started. Patients with unclear HIV status should be tested on presentation to the ED. Transmission may occur in the antepartum, intrapartum, or postpartum (breast-feeding) period. Because intrapartum transmission accounts for up to 75% of vertically transmitted HIV infections, antiretroviral therapy on presentation, even while labor progresses, can decrease vertical HIV transmission. Risk factors for transmission include high viral loads, prolonged rupture of membranes, maternal drug use, vaginal delivery, and breast-feeding.

Advances in point-of-care testing for HIV have resulted in the ability to make a preliminary diagnosis in a patient with HIV in the ED. Serologic confirmation is recommended, but emergent interventions can proceed on the basis of the bedside result. A positive HIV test result may, in some cases, allow a change in the method of delivery; cesarean section decreases the rate of HIV transmission compared with vaginal delivery methods.

COMPLICATED DELIVERY

Foundations

Deliveries involving dystocia, malpresentation, and multiple gestations are potentially life-threatening emergencies. The emergency clinician cannot solve these obstetric problems with cesarean section and will therefore face the prospect of an extremely high-risk vaginal delivery. As expected, these abnormal deliveries increase the risk of fetal and maternal complications. Aggressive attempts to obtain obstetric, neonatal, and anesthesia support are warranted. If the delivery proceeds in the ED, preparations for maternal and neonatal resuscitation need to be made proactively and rapidly.

Dystocia and Malpresentation

Dystocia, or abnormal labor progression, accounts for one-third of all cesarean sections and half of primary cesarean sections. Because rapid surgical resolution is unavailable to the emergency clinician, intrapartum management skills are required.

Dystocia can be divided into three categories of causative factors. Labor fails to progress when there are problems related to the pelvic architecture (the passage), fetal size or presentation problems (the passenger), and inadequate uterine expulsive forces. Although it is useful to consider these causes independently, dystocia is usually caused by a combination of factors. Presentation problems are particularly important because they become apparent during stage 2 of labor and require immediate action.

In order of increasing incidence, brow, face, shoulder, and breech presentations are the most common malpresentations (Table 176.2). True fetopelvic disproportion is much less common. Cesarean section is indicated when labor arrest or cord prolapse coexists with these presentations.

TABLE 176.2 Relative Incidence of Malpresentations

Malpresentation	Incidence
Breech presentation	1/25 live births
Shoulder dystocia	1/300 live births
Face presentation	1/550 live births
Brow presentation	1/1400 live births

Breech Delivery

Breech is the most common malpresentation, occurring in just less than 4% of all deliveries. Three types of breech presentation exist—frank, incomplete, and complete (Fig. 176.8; Box 176.6).

By convention, the presentation (frank, incomplete, and complete) is followed by the relationship of the fetus to the birth canal, with the fetal sacrum as a reference point. Correlated with this abnormal presentation are several factors, such as prematurity, multiparity, fetal abnormalities, prior breech presentation, polyhydramnios, and uterine abnormalities.

Overall, one-third of breech fetal deaths are believed to be preventable. Asphyxia is often due to umbilical cord prolapse or entrapment of the head. Other complications include labor arrest or brachial plexus injuries, and fetal head and neck trauma can occur if inappropriate delivery techniques are used. Scheduled cesarean section for these patients reduces the potential for an ED presentation. However, emergency clinicians should be prepared for vaginal delivery of breech presentations in the event of premature or unforeseen labor in the absence of immediate surgical services.

The mechanical problem with breech presentations is that the buttocks and legs do not provide a sufficient wedge, hindering cervical accommodation of the relatively larger head. In addition, because the presenting part does not occlude the cervical opening completely, umbilical cord prolapse may occur.

In the successful vaginal delivery of a breech presentation, the legs or buttocks are given time to dilate the cervix. This creates a tenuous appearing scenario where the baby's hips are delivered, but the shoulders and head are still inside the cervical OS. It appears as though the baby can simply be pulled free, but pulling on the hips will bring the shoulders through the OS, trapping the head and obstructing the labor. In fact, the clinician should take care to support, but not pull, the presenting part.

Diagnostic Testing

Before labor, *Leopold maneuvers* (see Fig. 176.3) facilitate the diagnosis of breech presentation. Active labor restricts the use of Leopold maneuvers, and a vaginal examination is required. Bedside ultrasound can help establish position if it is unclear. The differentiation of a vertex presentation from a breech presentation by tactile vaginal exam may be difficult. Whenever a fontanel is not identified on examination, a breech presentation should be suspected. It is helpful to remember that the face and skull have a complete circle of bone, whereas the anus is flanked by bone on only two sides.

If time permits, an ultrasound examination is indicated to distinguish the type of breech presentation, gestational age, fetal weight, and position of the fetal arms and neck. If the fetus has a hyperextended neck, vaginal delivery is associated with a high incidence of spinal cord injuries. If possible, labor should be delayed to allow cesarean section. Similarly, if the arms are over the head, they increase the dystocia when the head enters the birth canal.

Management

Premature infants in the breech position often deliver spontaneously without difficulty. As the infant comes to term, dystocia becomes increasingly common. With commitment to a vaginal delivery, knowledge of breech dystocia mechanics may allow atraumatic delivery. The key goals are to maximize the size of the passage and to minimize the dystocia of the after-coming head. Box 176.7 summarizes the actions associated with successful vaginal breech delivery.

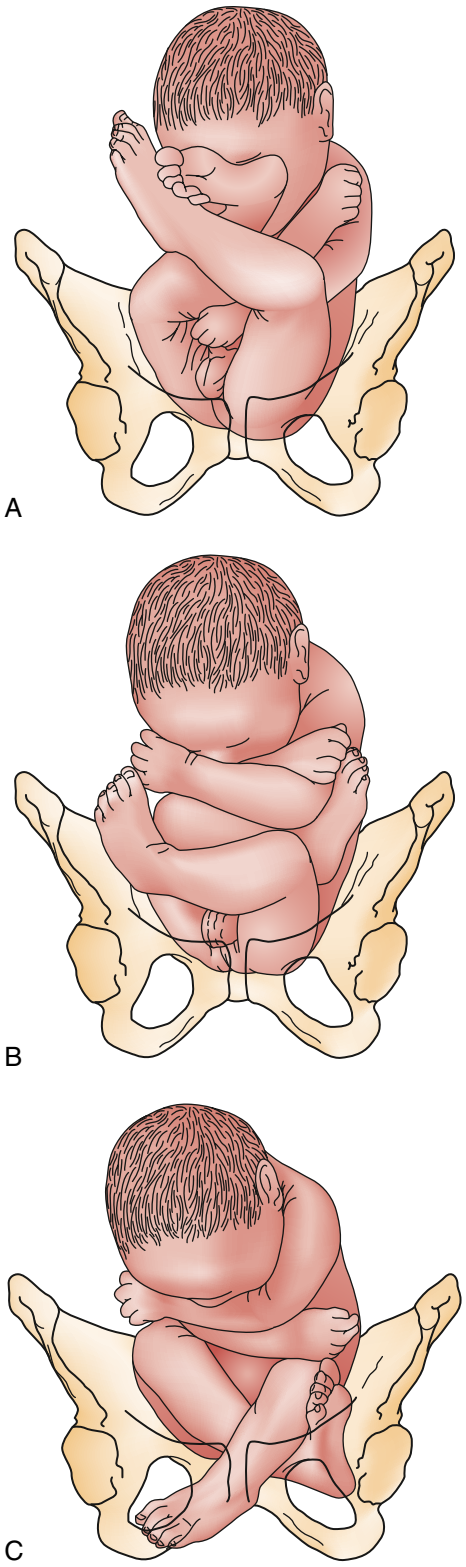

Fig. 176.8 Breech presentations. (A) Frank breech presentation. (B) Complete breech presentation. (C) Incomplete breech presentation. (Adapted from: Cunningham FG, et al. *Williams Obstetrics*, ed 19. Norwalk, CT: Appleton & Lange; 1993.)

The *Mauriceau maneuver* is the use of the fetal mouth to flex the fetal neck and draw in the chin. Because fetal neck extension is associated with cord injuries and worsening dystocia, this maneuver is useful to ensure a successful vaginal delivery. This maneuver should only be attempted once the fetal elbows and chin have entered the pelvic inlet to avoid inducing the Moro reflex, in which fetal head flexion results in the arms being suddenly extended. During this maneuver, the fetal pelvis should be supported to avoid abdominal injuries. A generous episiotomy may be necessary to facilitate the maneuver in a full-term infant. If the after-coming head cannot be delivered quickly, the chances of good fetal outcome are poor.

Shoulder Dystocia

Shoulder dystocia is the second most common malpresentation, occurring in 1.4% of all deliveries. In contrast to a breech presentation, which may be diagnosed in the antepartum period, shoulder dystocia develops in the intrapartum period. Maternal and fetal factors are associated with shoulder dystocia. Maternal factors include diabetes, obesity, and precipitous or protracted labor; fetal factors include macrosomia, postmaturity, and erythroblastosis fetalis. Shoulder dystocia responds well to a variety of intrapartum maneuvers; therefore, the skill involved during delivery is an important determinant of fetal outcome.

The consequences of shoulder dystocia can be devastating. As with a breech presentation, infant complications are more common and severe than maternal complications. Traumatic brachial plexus injuries, clavicular fractures, and hypoxic brain injury are all well-documented complications. Maternal complications are related to traumatic delivery and include vaginal, perineal, and anal sphincter tears, as well as urinary incontinence.

Diagnostic Testing

Shoulder dystocia is diagnosed clinically by the inability to deliver either shoulder. The fetal head may appear to retract toward the maternal perineum, otherwise known as the turtle sign. Traction on the head extends and abducts the shoulders, increasing the bisacromial diameter and worsening the dystocia. Fig. 176.9 shows the normal and abnormal

BOX 176.6 Breech Presentations

Frank Breech
60%–65% of all breech presentations
Hips flexed, knees extended
Buttocks act as good dilating wedge
Incidence of cord prolapse ≈0.5%

Complete Breech
Least common; occurs in ≈5% of all breech presentations
Hips and knees flexed
Buttocks act as good dilating wedge
Incidence of cord prolapse is 5%–6%

Incomplete Breech
25%–35% of all breech presentations
Incomplete hip flexion, single or double footling
Poor wedge
Increased incidence of prolapsed cord (15%–18%)

BOX 176.7 Vaginal Breech Delivery

Actions to Do as Able
Monitor fetal heart rate.
Obtain a focused history.
Diagnose a breech lie.
Determine cervical dilation and station.
Obtain an ultrasound or plain radiographic study.
Evaluate for prolapsed cord if there is spontaneous rupture of membranes.
Perform an episiotomy.
Flex knees and sweep out legs.
Pull out a 10- to 15-cm loop of cord (room to work) after the umbilicus clears the perineum.
Use the bony pelvis as a means of holding the infant.
Keep face and abdomen away from the symphysis and use rotation to deliver the more accessible arm.
Perform the Mauriceau maneuver.

Actions to Avoid
Inappropriate transfer with delivery en route
Misdiagnosis of cervical dilation
Iatrogenic rupture of membranes (cord prolapse)
Moving of patients or leaving them unmonitored
Traction on the fetus during delivery
Grasping of the fetus by the waist, causing abdominal organ injury
Arm entrapment over head
Neck hyperextension

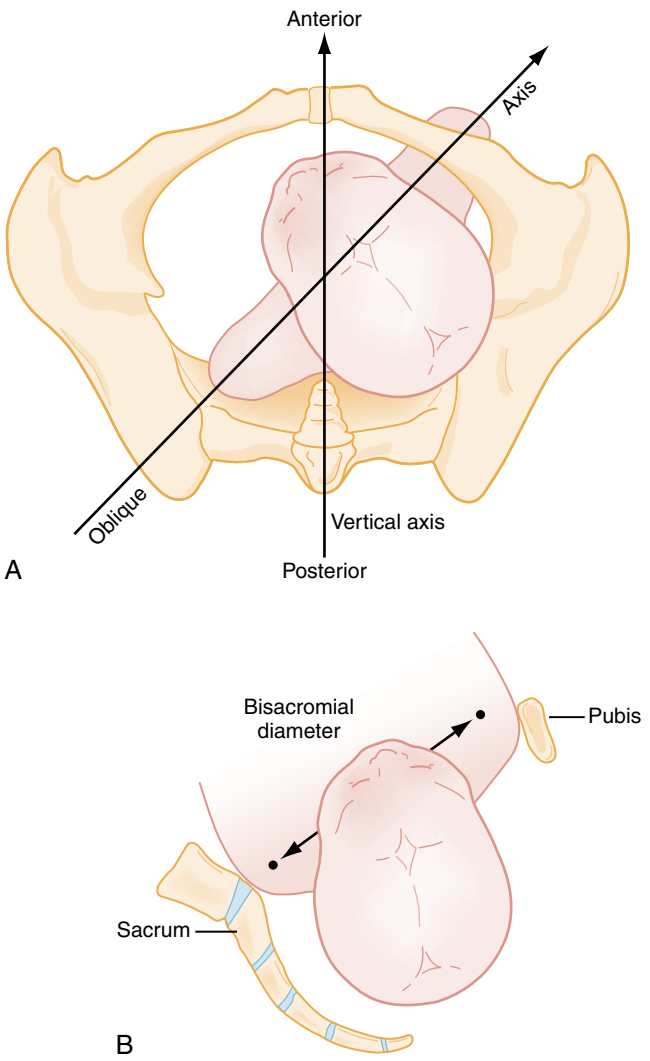

Fig. 176.9 (A) Normal delivery. As the fetal head rotates, the shoulders assume an oblique position and enter the pelvis one at a time. (B) Shoulder dystocia. Both shoulders attempt to clear the pelvis simultaneously, forcing the bisacromial diameter into the opening.

relationship of the shoulders to the birth canal and illustrates why the bisacromial diameter is an important element of fetal biometry.

Normally, the shoulders negotiate the maternal pelvis in sequential fashion, anterior shoulder first. With shoulder dystocia, both shoulders attempt to clear the maternal pelvis simultaneously. In addition to the turtle sign, examination often reveals that the fetal shoulders are on a vertical axis, rather than oblique. These findings, in combination with an arrested delivery, confirm the diagnosis of shoulder dystocia.

Management

When shoulder dystocia becomes evident, knowledge of intrapartum delivery maneuvers can be lifesaving. Successful vaginal delivery is most likely when a directed sequential approach to each maneuver is used. A rapid resolution of shoulder dystocia is important to avoid fetal asphyxia and resultant central nervous system injury. Obstetric and neonatology assistance may improve the outcome, and aggressive attempts to obtain assistance are warranted.

Initial attempts to resolve shoulder dystocia involve increasing the anteroposterior diameter of the passage. An episiotomy may be used for fetal maneuvering by allowing access to the posterior shoulder. Anteriorly, draining the bladder with a Foley catheter can generate room.

The most important first step is to use the *McRoberts maneuver* (Fig. 176.10). Maternal leg flexion to a knee-chest position may disengage the anterior shoulder, allowing rapid vaginal delivery to follow. This maneuver "walks" the pubic symphysis over the anterior shoulder and flattens the sacrum, helping the fetus pass through the birth canal, one shoulder at a time. This method, although requiring very little effort, is often successful in alleviating shoulder dystocia.

If the McRoberts maneuver fails to free the anterior shoulder, the application of suprapubic pressure may accomplish this by forcing the anterior shoulder to slip beneath the pubis or posterior shoulder to retreat into the hollow of the sacrum. Digital pressure on the posterior shoulder (through the episiotomy) may help facilitate posterior shoulder retreat. The use of the McRoberts maneuver and suprapubic pressure resolve most cases of shoulder dystocia.

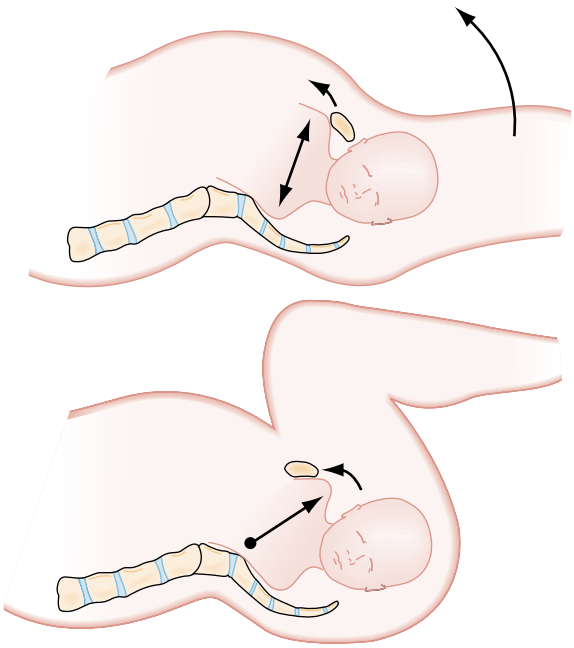

Fig. 176.10 McRoberts maneuver. *Top,* Bisacromial diameter pinned behind pubic symphysis. *Bottom,* Removing the maternal legs from the stirrups and putting the knees up to the chest act as a fulcrum to the pubic symphysis over the impacted anterior shoulder.

If delivery is still impossible, the next step is to attempt the *Rubin maneuver* (Fig. 176.11). The goal of this maneuver is to decrease the bisacromial diameter by pushing the most accessible shoulder toward the fetal chest. Often, both shoulders assume the same attitude, decreasing the bisacromial diameter and allowing delivery. Attempts to manipulate the shoulders for the Rubin maneuver may be transabdominal, through the introitus (anterior shoulder), or through the episiotomy (posterior shoulder).

If the shoulders remain undeliverable, the next step is to use *Wood corkscrew maneuver*. In this process, the impacted shoulders are released through rotation of the fetus 180 degrees. Fetal rotation is achieved by pushing the most accessible shoulder in toward the chest. The fetal axilla can be snared with a digit, or a hand can be slid in along the fetal spine to sweep the hips and generate rotation. Wood corkscrew maneuver is difficult to perform but should be attempted before reaching for an arm.

If the fetus remains trapped and several attempts have failed to yield delivery, consideration of delivery of an arm is appropriate. A hand is introduced along the posterior aspect of the posterior shoulder. The posterior arm is swept across the chest, bringing the fetal hand up to the chin. Attempts to splint the humerus may prevent fractures and brachial plexus injuries. The fetal hand is grasped and pulled out of the birth canal across the face, delivering the posterior shoulder.

The mnemonic HELPER (Box 176.8) is useful to keep these steps organized and facilitate a sequential approach which will successfully deliver almost all cases of shoulder dystocia.

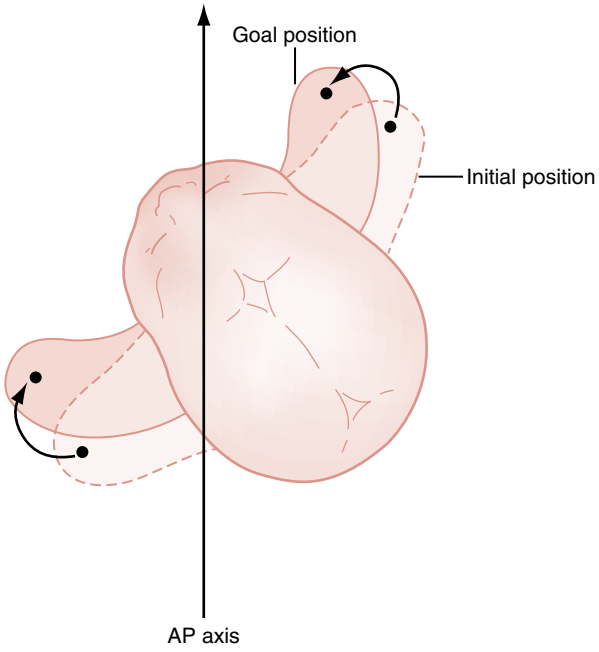

Fig. 176.11 Rubin maneuver decreases the bisacromial diameter. *AP,* Anteroposterior.

BOX 176.8 HELPER Mnemonic for Shoulder Dystocia

Help—obstetrics, neonatology, anesthesia
Epiotomy—generous, possibly even episioproctotomy
Legs flexed—McRobert maneuver
Pressure—suprapubic pressure, shoulder pressure
Enter vagina—Rubin maneuver or Wood maneuver
Remove posterior arm—Splint, sweep, grasp, and pull to extension.

Face, Brow, and Compound Presentations

Face and brow presentations yield a larger engaging aspect of the fetal head and predispose to labor arrest. Although these abnormal presentations can be diagnosed with ultrasonography or Leopold maneuvers, most are discovered during labor by vaginal examination. Approximately 50% are discovered during the second stage of labor.

The engaging diameter of the head in vertex position is approximately 0.8 cm less than a face presentation and 1.5 cm less than a brow presentation. Face presentations are described with the chin as a reference point (e.g., mentum anterior). Face presentation is managed expectantly. The obstetric adage—"if a face presentation is progressing, leave it alone"—is based on the fact that mentum anterior presentations usually deliver vaginally, and mentum transverse presentations frequently rotate to become mentum anterior. Brow presentations, occurring when the fetal head is partially flexed, also spontaneously convert to a vertex or face presentation in more than 50% of cases.

A persistent mentum posterior face and brow presentation cannot be delivered vaginally if the fetus is full term. The resultant labor arrest requires symphysiotomy or cesarean section. Prolongation of the second stage is the most common outcome of both these malpresentations at term. For the emergency clinician, this prolonged second stage may provide a window during which obstetric help may arrive.

Compound presentations are those in which an extremity enters the birth canal with the head or breech. Small and premature fetuses generally proceed to vaginal delivery without incident.

Labor arrest and umbilical cord prolapse are accepted indications for cesarean section in the setting of face, brow, and compound presentations. Manipulation of a compound presentation, including attempts to reduce the hand or arm, increases the rate of cord prolapse. Therefore, manipulation attempts are contraindicated. Cord prolapse rates are 10% to 20%, even without manipulation. Close monitoring and careful examination are indicated.

MULTIPLE GESTATIONS

Due to the increasing use and availability of fertility treatments, the incidence of multiple gestation pregnancies has been increasing. In 2013, twin deliveries accounted for 34/1000 births in the United States. Because multiple gestation deliveries have a higher incidence of preterm labor and low birth weights, maternal and fetal complication rates are correspondingly increased.

Diagnostic Testing

Most women with multiple gestations have the situation identified well before the third trimester. In patients who have had little or no prenatal care, bedside ultrasonography allows for a rapid diagnosis. The stages of labor for twins and other multiple gestations are similar to the stages for a singleton. Of importance to the emergency clinician is a relatively short latent phase of labor, with rapid progression to the active phase. The active phase is usually longer, however, and may allow time for obstetric assistance to arrive.

Vertex twin A and vertex twin B occur in approximately 42% of deliveries. One of the twins presents in a nonvertex position in approximately 35% to 40% of cases.[3]

Management

The presentation of twins is a key determinant for the safety of vaginal delivery. Twins who are vertex-vertex can be delivered vaginally, barring any other obstetric complication. If twin B is nonvertex, many obstetricians recommend cesarean section to prevent delivery-related complications for twin B. External cephalic version and breech extraction are possible maneuvers to facilitate precipitous vaginal delivery. Generally, if twin A is nonvertex, cesarean section is preferred. In such cases, efforts should be made to delay delivery until an operative approach can be used. Proceeding vaginally can result in the interlocking of twins, associated with a high mortality.

The interval between the delivery of twin A and twin B is variable. In most cases, twin B delivers in minutes. When twin B does not follow rapidly, in utero assessment is important to document fetal well-being. If fetal heart tracings are reassuring, the delivery of twin B (especially nonvertex) should not be hastened. Repeated ultrasonographic evaluation may also be used to confirm twin B's presentation and well-being.

After every ED delivery, particularly deliveries that are precipitous or that occur in the out-of-hospital setting, the mother should be examined for the possibility of twins. Ongoing labor may be confused with postpartum cramping, only to have twin B and all the potential complications surprise the emergency clinician. This is particularly relevant for women with inadequate prenatal care and low-birth-weight infants.

UMBILICAL CORD-RELATED EMERGENCIES

Umbilical cord–related complications can occur in normal and abnormal deliveries. Immediate intervention is required to prevent fetal morbidity and mortality. The spectrum of cord-related emergencies includes prolapsed cord, nuchal loops of the umbilical cord, body coils, cord knots, and entangled cords in monoamniotic twins. The cord length is believed to be proportional to fetal activity in utero during the first and second trimesters. Excess cord length increases the potential for umbilical cord complications of all types. Because the umbilical cord supplies the fetus with all its oxygen, interruption of cord circulation before establishment of fetal respiration is a life-threatening emergency. Fetal asphyxia caused by cord circulation compromise is potentially preventable with early recognition and intervention.

Umbilical Cord Prolapse

Clinical Features

Umbilical cord prolapse occurs when the umbilical cord precedes the fetal presenting part or when the presenting part does not fill the birth canal completely. Most cases of cord prolapse are unexpected and develop during the second stage of labor.

Cord prolapse has a variable rate of association with different fetal presentations. Compound, shoulder, and breech presentations yield gaps and a relatively poor dilating wedge. Table 176.3 summarizes the rates of umbilical cord prolapse with various fetal presentations. Malpresentations account for 50% of all cord prolapse cases and the prolapsed cord itself may be the first indication of a malpresentation. The reported incidence of cord prolapse ranges from 1.4 to 6.2/1000 deliveries, and associated perinatal mortality is estimated to be just below 10%.[4]

TABLE 176.3 Conditions Associated With Umbilical Cord Prolapse

Presentation	Incidence (%)
Vertex	0.14
Breech	2.5–3.0
Frank breech	0.4
Complete breech	5
Incomplete breech	10
Shoulder	5–10
Compound	10–20
Face or brow	Rare

Diagnostic Testing

Umbilical cord prolapse may be overt or occult, requiring a pelvic examination to reveal the umbilical cord lying beside the presenting part. The diagnosis may also be made with Doppler ultrasonography. In most cases, the diagnosis is obvious, and the cord is encountered at the perineum or introitus.

Management

When a prolapsed cord occurs with a viable infant, cesarean section is the delivery method of choice. If surgical delivery is available, maneuvers to preserve umbilical circulation should be instituted immediately. The mother is placed in the knee-chest position, with the bed in the Trendelenburg position, and instructed to refrain from pushing to avoid further compression of the cord. The presenting part is then manually elevated off the cord. Elevation is maintained until the baby can be delivered surgically. The time from prolapse to surgical intervention is an important factor in fetal outcome. Perinatal mortality rates are higher for out-of-hospital cases versus those within a monitored setting, and outcomes correlate with time from diagnosis to delivery.

If timely surgical delivery cannot be performed, funic reduction—manual replacement of the cord into the uterus—and rapid vaginal delivery may be necessary. The same maneuvers to decrease cord compression should be used, pushing gently on the cord in a retrograde fashion, above the presenting part. Manipulation and cord trauma should be kept to a minimum because resultant vasospasm can cause fetal hypoxia. After funic reduction, the development of umbilical cord body coils or nuchal loops is common and should be anticipated.

Cord Entanglement

The umbilical cord can also become entangled with itself, spontaneously knotting. Umbilical cord knots are related to intrauterine movements early in pregnancy. Approximately 5% of stillbirths are found to have knots that are believed to have caused fetal demise. Despite this association, cord knots can persist without problems as long as perfusion is maintained.

Loose umbilical cord knots pulled tight at delivery may cause fetal distress. As with cord prolapse, this situation must be resolved quickly to prevent fetal asphyxia. Rapid delivery with avoidance of further cord traction optimizes fetal outcome. No specific interventions have been identified to deal with this problem.

Long umbilical cords are associated with true knots, as well as with entanglements and prolapse. Umbilical cord loops can be single or multiple and can occur around the neck or body. Because the fetal limbs are short and flexed in most presentations, they are rarely involved. Although generally benign, umbilical cord loops may result in fetal complications, such as nonreassuring fetal status and respiratory distress.

During delivery, loose nuchal cords should be reduced at the perineum. Loose body coils usually disentangle spontaneously. The reduction process may be aided by slipping them over the extremities or forward over the head. On occasion, loops are tight enough to impede delivery and cannot be reduced. The solution is to cut the clamped cord and deliver the infant rapidly. The high frequency of nuchal loops (one in five births) means that the emergency clinician should expect to encounter this problem.

MATERNAL COMPLICATIONS OF LABOR AND DELIVERY

Maternal complications of labor and delivery include postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, and infections. Although some are managed medically, severe complications threaten the reproductive future and life of the mother, thereby requiring emergent surgical intervention.

Postpartum Hemorrhage

Clinical Features

Postpartum hemorrhage is the most common complication of labor and delivery. Defined as hemorrhage of more than 500 mL after vaginal delivery, it accounts for up to 11% of obstetric deaths.[5] Postpartum hemorrhage is divided into two categories; the primary category includes blood loss that occurs within the first 24 hours, and the secondary category is hemorrhage 24 hours to 6 weeks after delivery. Because of maternal adaptations during pregnancy, the patient may not show signs of shock until more than 1500 mL of volume has been lost.

Differential Diagnosis and Management

The differential diagnosis of primary postpartum hemorrhage includes uterine atony, genital tract trauma, retained placental tissue, and coagulopathies, or the "four Ts"—***t***one, ***t***rauma, ***t***issue, and ***t***hrombin.

Uterine Atony. Accounting for 75% to 90% of cases, the most common cause of serious immediate postpartum hemorrhage is laxity of the uterus after delivery. Normally, postpartum bleeding from the placental implantation site is limited by contraction of the myometrium, constricting the spiral arteries. If the uterus does not contract, ongoing hemorrhage will occur. Predisposing factors include overdistention of the uterus (e.g., multiple gestations, fetal macrosomia, polyhydramnios), prolonged labor, chorioamnionitis, use of tocolytics, and general anesthesia with halogenated compounds. As a diagnosis of exclusion, a physical examination to rule out obstetric trauma and retained products of conception should be performed before the diagnosis is reached. On examination, the uterus is palpable as a soft boggy mass.

After other causes have been excluded, therapy to augment myometrial contractions is instituted to prevent further hemorrhage. A two-handed uterine massage may stimulate uterine contractions. One hand exerts pressure transabdominally while the other supports the uterus through the introitus. Administration of a uterotonic, such as oxytocin in conjunction with massage usually provides enough stimuli to control bleeding. We recommend 10 units IM following the delivery of the placenta. Intravenous options include oxytocin 5 to 10 units initially followed by an infusion of 10 units/hr to a maximum of 40 units total. Blood is ideally typed, cross-matched, and available for resuscitation should these measures fail, with unmatched O negative blood used in true emergencies

Maternal Birth Trauma. Maternal birth trauma is the second most common cause of postpartum hemorrhage, accounting for up to 20% of cases. Associated factors include uncontrolled delivery, macrosomia, episiotomy, nulliparity, maternal coagulopathy, operative delivery, prolonged second stage of labor, preeclampsia, and malpresentation. Tears and lacerations may involve the perineum, rectum, cervix, vagina, vulva, and urethra. Blood vessels beneath the vulvar or vaginal epithelium can also be injured without frank hemorrhage, resulting in the formation of large contained hematomas. These hematomas may go unrecognized for hours, gradually enlarging and possibly resulting in hemorrhagic shock. Delayed postpartum hemorrhage at these sites can also occur and is often a diagnostic challenge. The physical examination may reveal uterine displacement (lateral or cephalad), and confirmation with ultrasound is helpful in stable patients. Management, decided in conjunction with specialists, may be expectant, involve bedside repair with absorbable suture, or require vascular embolization or surgical intervention, depending on the severity of clinical presentation.

Tears are classified by depth. First-degree tears involve the perineal skin and vaginal mucous membranes only. Second-degree tears extend

through the skin into the fascia and muscles of the perineal body. Third-degree tears extend into the anal sphincter, whereas fourth-degree tears extend through all layers, including the rectal mucosa. Third- and fourth-degree tears should be repaired by an obstetrician in the operating room.

Retained Products of Conception. Approximately 10% of postpartum hemorrhage cases are due to retained placental tissue. Normally, the plane of cleavage between the zona basalis and zona spongiosa results in a clean separation of the placenta from the uterus. When this occurs, the placental tissue delivers as a single unit, without evidence of fragmentation. Any placental defect or evidence of accessory placental tissue may signify a retained cotyledon (part of the embryo). Retained fragments prevent myometrial constriction and result in hemorrhage. Aggressive traction on the placenta during stage 3 of labor can result in retained products of conception, which may cause immediate or delayed postpartum hemorrhage. Ultrasound may reveal an expanded endometrium or solid echogenic mass within the uterus, providing evidence of retention.

Treatment requires removal of the remnant placental tissue. Digital uterine exploration with blunt dissection of the fragments from the myometrium will also facilitate myometrial contractions. Abnormally adherent tissue will not be freed by this maneuver.

The terms *placenta accreta*, *placenta increta*, and *placenta percreta* describe various degrees of abnormal placental attachment to the uterus. In placenta accreta, the placenta adheres to the myometrium without invading the decidua basalis. In placenta increta, the villi extend into the myometrium, and in placenta percreta the placenta penetrates the full thickness of the myometrium.

The current incidence of placenta accreta is approximately 3/1000 deliveries, a relative increase from past decades. Associated risk factors include multiparity, prior cesarean sections, placenta previa, previous curettage, and uterine anomalies.

Coagulopathies. All women with postpartum hemorrhage should receive tranexamic acid (1 g IV) and should also be evaluated for disseminated intravascular coagulation (DIC). DIC can occur as a consequence of placental abruption, eclampsia, amniotic fluid embolism, postpartum infections, and dilution of clotting factors caused by aggressive volume resuscitation. Also, retained products of conception and dead fetal tissue contain excess thromboplastin, which can precipitate DIC. As with DIC from nonobstetric causes, bleeding is associated with hypofibrinogenemia, thrombocytopenia, and elevated levels of fibrin split products and D-dimer.

Appropriate management entails hemodynamic support and correction of coagulopathies. Recent investigations have reported the successful use of recombinant factor VIIa for severe cases of postpartum hemorrhage.

Uterine Exploration and Removal of the Placenta. In the presence of ongoing hemorrhage and retained products of conception, attempts to remove the placenta manually are indicated. The procedure entails risk of infection, perforation, and increased hemorrhage but may be the most expeditious way to control bleeding. Before beginning, the patient is placed on a monitor, vascular access is established, and blood products are secured. Also, a Foley catheter may be placed to reduce bladder distention and monitor urinary output. The umbilical cord is traced through the cervical os to the placenta, allowing the identification of a placental margin. The placental membranes are digitally perforated, and the placenta is gradually divided from the myometrium. After removal of the placenta, the uterus is explored for retained cotyledons. Removal of fragments that are still present may require curettage of the uterine cavity by an obstetrician. Placenta accreta, percreta, and increta may be diagnosed in this way because they are not digitally dissectible.

Once it is emptied, the uterus should be stimulated to contract with uterine massage, oxytocin, and prostaglandins. Prophylactic antibiotic administration at the time of manual placenta extraction has been debated, but is not supported by current evidence.[6]

Pelvic Vessel Embolization. Pelvic bleeding postpartum can be difficult to control. Hysterectomy as a solution results in infertility and brings with it all the complications of general anesthesia and major surgery. Embolization of bleeding vessels by an interventional radiologist is another option with reported success rates of 95% to 100%. The procedure does not require an anesthesiologist, operating room, or obstetrician and may be readily available on an emergent basis. Common sites of bleeding include the uterine artery, pudendal artery, and hypogastric artery. Because only the smallest involved branches are embolized, and recanalization usually occurs, future reproductive capability is generally preserved.

Uterine Packing. When uterine bleeding is severe and uncontrolled, and embolization or hysterectomy are not available, uterine packing may be used to tamponade the bleeding vessels. The procedure has limited morbidity and can be accomplished by inserting sterile gauze or a foley catheter into the uterine cavity.[7]

Opponents of packing point out that an atonic uterus may accommodate a large volume of packing without effective tamponade. Packing may also increase the risk of postpartum infection, even when prophylactic antibiotics are given. As with all uterine manipulation and instrumentation, some risk of perforation also exists. Nevertheless, when pelvic embolization and hysterectomy are not immediately available, uterine packing may be a lifesaving temporizing measure.

Uterotonic Agents. Although they are commonly applied on delivery of the placenta, uterotonic agents also have special application in the case of a postpartum hemorrhage. Uterotonics such as oxytocin and prostaglandins control bleeding by inducing myometrial contractions. Oxytocin, 10 units IM or IV, is recommended.

Hysterectomy. Rarely, hemorrhage continues, despite the interventions outlined. In the case of life-threatening obstetric bleeding, an emergency hysterectomy should be performed.

Uterine Inversion

Foundations

Uterine inversion, a serious complication of delivery that occurs during stage 4 of labor, complicates 1 in 2000 deliveries. The resultant postpartum hemorrhage can be severe and life-threatening, accounting for a maternal mortality rate of up to 15%. Uterine inversion complicates 1 in 2000 deliveries. Risk factors include excessive fundal pressure during delivery, forceful traction on the umbilical cord (especially in conjunction with a fundal placenta), placenta accreta, maternal congenital abnormalities of the uterus, use of magnesium sulfate in the antepartum period, and primiparity.

Clinical Features

The patient will complain of sudden, severe abdominal pain. The abdominal examination reveals tenderness and an absence of the uterine corpus, which is potentially visualized at the cervical os or bulging from the introitus. Profuse bleeding with hemodynamic instability can also occur. Ultrasound may assist in the diagnosis.

Management

Once uterine inversion is identified, the appropriate mobilization of resources should begin simultaneously with efforts to reestablish the correct anatomic position of the uterus. Initial management involves aggressive fluid resuscitation.

The highest likelihood for successful repositioning of the inverted uterus is immediately after inversion occurs. If the placenta is still

adherent, it should not be removed until after repositioning. Removal of the placenta while the uterus is inverted is associated with excessive blood loss. The initial attempt to reposition the uterus should be to push the fundus upward through the introitus. Contraction of the cervical uterine segments can create a muscular ring, preventing repositioning. Therefore, all uterotonic agents should be withheld immediately on diagnosis of uterine inversion.

If initial attempts fail and a cervical ring develops, pharmacologic attempts to relax the uterus with sedation and tocolytics are indicated. Terbutaline (0.25 mg IV or SC) and magnesium sulfate (4–6 g IV over 15–20 min) have been used successfully to relax cervical rings. When the uterus has been repositioned, the muscle relaxants should be halted, and oxytocin and prostaglandin therapy restarted. Firm manual pressure through the introitus should be maintained until the cervical ring contracts. If all these measures fail, and surgical backup becomes available, halogenated anesthetics may be used to induce relaxation of the cervical rings, with or without an attempt at surgical repair. Once uterine inversion has resolved, an assessment must be made to screen for uterine perforation, adherent placenta, and vaginal lacerations.

Uterine Rupture

Foundations

Criticism of the high rate of cesarean delivery in the United States has led to advocacy of vaginal birth after cesarean (VBAC). The high success rate and relative safety of VBAC are countered partly by the risk of uterine rupture, which occurs in approximately 1% of VBAC deliveries following a single cesarean section.[8] The rate of rupture increases in women who have had multiple cesarean sections.

Clinical Features

Uterine rupture occurs late in pregnancy or as stage 1 of labor transitions to the active phase. Defined as a full-thickness uterine wall perforation, the severity of rupture ranges from simple scar dehiscence to complete fetal extrusion. It may be spontaneous but is most often linked to previous uterine surgery. Other risk factors for uterine rupture include multiple gestation, trauma, and prostaglandin administration. Minimal fetal extrusion results in a perinatal mortality rate of less than 1%, whereas complete extrusion results in a 10% to 20% mortality rate. Maternal death is rare, but significant hemorrhage complicates one-third of cases.

Diagnostic Testing

The diagnosis of uterine rupture may be difficult because pain is not always present. In fact, clinical presentation of uterine rupture ranges from abnormal fetal heart rate patterns to frank maternal hemorrhagic shock. Prolonged fetal heart rate deceleration, indicating fetal distress, is the most reliable sign of fetal extrusion. Ultrasound may reveal a protruding amniotic sac, hemoperitoneum, or the myometrial defect; however, good sensitivity data are lacking.

Management

If uterine rupture is suspected, delivery should be hastened to limit fetal hypoxia. Emergency cesarean section is the best method to speed delivery and repair the injury. ACOG guidelines for uterine rupture identify a 30-minute window of opportunity that maximizes fetal outcome. Note that uterotonic agents may exacerbate the rupture and are contraindicated.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare and catastrophic complication of labor and delivery. The incidence rate is estimated to be between 1 and 12/100,000 maternities. Although the mechanism is not well understood, it is thought to involve the spread of amniotic fluid through the maternal vasculature, activating a complement or anaphylactic cascade. Cesarean delivery, forceps- or vacuum-assisted delivery, uterine rupture, eclampsia, placenta previa, and placental abruption have been found to be associated with amniotic fluid embolism. The diagnosis is clinically evident during labor, during delivery, or within 48 hours of delivery. It is characterized by the sudden onset of hypoxia, coagulopathy or hemorrhage, seizure, fetal compromise, or cardiovascular collapse. DIC occurs in approximately 50% of cases, and maternal and fetal mortality rates are high. Treatment is generally supportive and may include assisted ventilation, central hemodynamic monitoring, vasopressors, and the administration of blood products.[9]

Postpartum Venous Thromboembolism

Pregnancy increases the risk of venous thromboembolism five- to tenfold. The risk increase through pregnancy, but may actually be highest 3 to 6 weeks postpartum.[10] The diagnosis of pulmonary embolism in pregnancy has always been complicated, but recent clinical trials have suggested that an adjusted D-dimer can be used for otherwise low-risk patients.[11] The gold standard remains CT pulmonary angiogram; VQ scans are being performed increasingly less frequently, even in pregnancy. An in-depth discussion of thromboembolism can be found in Chapter 74.

Postpartum Endometritis

Puerperal infections affect 5% of all vaginal deliveries and 10% of all cesarean sections. Predisposing factors include operative delivery, prolonged rupture of membranes, lack of prenatal care, prolonged stage 2 labor, use of intrauterine monitoring, and frequent vaginal examinations. It is estimated that sepsis results in up to 15% of maternal deaths worldwide. Causative organisms for these infections include gram-positive cocci and gram-negative coliforms and, less commonly *Chlamydia* and *Mycoplasma* spp.

Endometritis is the most common puerperal infection, usually developing on the second or third day postpartum. Typically, the lochia has a foul odor, and the white blood cell count is elevated. Fever and abdominal pain indicate greater severity of infection, often warranting inpatient care and intravenous antibiotics. A coexistent surgical wound infection is often present. A search for retained products of conception is indicated, particularly if bleeding is present.

Treatment is empirical and is directed at gram-positive, gram-negative, and anaerobic organisms. We recommend a combination of clindamycin (900 mg IV Q8H) and an aminoglycoside (gentamicin 5 mg/kg Q24H). Most patients with postpartum endometritis require admission.

POSTPARTUM PROBLEMS

Peripartum Cardiomyopathy

For unclear reasons, the peripartum period is associated with the relatively sudden onset of cardiomyopathy in healthy women without evidence of prior cardiac disease. Estimates indicate that peripartum cardiomyopathy (PPCM) occurs in 1 of 2229 pregnancies; reported risk factors include advanced maternal age, preeclampsia, gestational hypertension, multiparity, and being African American. The cause is unknown.

Onset usually occurs days to weeks after delivery; symptoms range from mild fatigue to florid pulmonary edema. PPCM is often unrecognized in its milder form, leading to the consensus that the condition may be more prevalent than reported. Dyspnea on exertion, orthopnea, and fatigue may be easily misinterpreted as normal in the postpartum period, so vigilance in evaluating these symptoms is warranted.

Treatment includes the use of diuretics, vasodilators, and oxygen. Angiotensin-converting enzyme inhibitors are contraindicated if

PPCM occurs during the last month of pregnancy owing to teratogenicity but should be considered a mainstay of treatment postpartum. Hydralazine may be used before delivery to reduce afterload. Bromocriptine and pentoxifylline may also have roles in the treatment of PPCM. Cardiac function returns to normal in up to 30% of patients with PPCM during the following 6 months. Complications result in a mortality rate of approximately 15% worldwide. An in-depth discussion of cardiopathy can be found in Chapter 68.

Postpartum Depression

Considered underdiagnosed, postpartum depression is estimated to affect 10% to 15% of new mothers. Although often self-limited, the condition has important consequences for the mother, infant, and family. Risk factors include previously diagnosed depression, inadequate spousal support, adverse socioeconomic factors, life stressors, and emergency delivery.

Clinical Features

Postpartum depression patients present similarly to those with other major depressive disorders. Symptoms include depressed mood, anhedonia, loss of appetite, insomnia, fatigue, decreased concentration, feelings of guilt and worthlessness, and suicidal ideation. Most women with postpartum depression do not have vegetative signs or symptoms. Symptoms peak at 10 to 12 weeks postpartum, although some cases are diagnosed up to 1 year after delivery. When postpartum depression is unrecognized, these women are at high risk for suicide and may come to the ED with overdoses or other manifestations of a suicidal attempt.

Management

Early identification and referral are the key components of therapy. Dismissal of postpartum fatigue as normal, without consideration of the diagnosis of postpartum depression, can be disastrous. Not only does this condition contribute to marital discord, maternal risk for suicide, and even infanticide, but studies have shown that children of depressed mothers have an increased incidence of delayed cognitive, psychological, neurologic, and motor development. An in-depth discussion of depression can be found in Chapter 97.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 176: QUESTIONS AND ANSWERS

1. After episiotomy, which is the first maneuver that a clinician should attempt when treating shoulder dystocia?
- **a.** McRoberts maneuver
- **b.** Fracture the clavicle
- **c.** Deliver the posterior shoulder
- **d.** Cesarean section

Answer: A. The most important first step is to use McRoberts maneuver (see Fig. 176.10). Maternal leg flexion to a knee-chest position may disengage the anterior shoulder. This maneuver "walks" the pubic symphysis over the anterior shoulder and flattens the sacrum, helping the fetus pass through the birth canal, one shoulder at a time.

2. Vaginal delivery of a frank breech is best accomplished by which of the following actions?
- **a.** Pulling hard on the presenting part
- **b.** Pushing the presenting part back through the cervix
- **c.** Supporting the presenting part and giving the cervix time to dilate.
- **d.** Administering oxytocin

Answer: C. The head is the widest part of the fetus. Pulling on the presenting part causes the head to become trapped behind an incompletely dilated cervix.

3. Which of the following medications is effective at reducing postpartum uterine bleeding?
- **a.** Tranexamic acid
- **b.** Terbutaline
- **c.** Magnesium sulfate
- **d.** Gentamycin

Answer: A. Tranexamic acid (1 gr IV) is effective at reducing bleeding. Oxytocin and fundal massage should also be used.

4. Which antibiotic combination provides the best initial coverage for postpartum endometritis?
- **a.** Cephalexin and vancomycin
- **b.** Ciprofloxacin and metronidazole
- **c.** Clindamycin and gentamicin
- **d.** Amoxicillin and nitrofurantoin

Answer: C. Antibiotics should include anaerobic coverage because endometritis is usually caused by genital flora.

5. The first stage of labor ends with which of the following?
- **a.** Delivery
- **b.** Ruptured membranes
- **c.** A fully dilated cervix
- **d.** Placental delivery

Answer: C. The first stage of labor is the cervical stage, ending with a completely dilated, fully effaced cervix.

Trauma in Pregnancy

Valerie A. Dobiesz and Daniel W. Robinson

KEY CONCEPTS

- Female trauma patients of reproductive potential should be screened for pregnancy and assumed to be pregnant until proven otherwise.
- Management of life- and limb-threatening injury in the mother comes first. Saving the mother provides the best chance of saving the baby.
- Even in the stable pregnant trauma patient, the fetus is at increased risk of morbidity and mortality; therefore, the fetus should be monitored by cardiotocography continuously for a minimum of 4 hours after any trauma.
- The fetus is considered viable between 22 to 24 weeks' gestation (>500 grams). This usually corresponds to when the fundus is at or above the umbilicus.
- Alterations in anatomy and physiology that occur during pregnancy alter the pattern of injuries in trauma and the clinical findings related to blood loss, which may mask injuries, making a systematic approach essential.
- Keeping the mother tilted 15 to 30 degrees to the left, or manually displacing the uterus leftward, in any pregnancy of 20 weeks' gestation or greater is recommended to alleviate hypotension due to aortocaval compression in order to improve maternal and fetal perfusion.
- Resuscitative hysterotomy should be initiated for a potentially viable fetus (fundus above the umbilicus) within 4 minutes and completed in 5 minutes after the onset of cardiopulmonary arrest and no return of spontaneous circulation (ROSC) for optimal maternal and fetal benefits.
- The use of ionizing radiation to the pregnant patient, including CT and plain radiography, should be minimized, but imaging should not be withheld if it may provide significant diagnostic information. In certain circumstances ultrasound, MRI, or a period of observation can preclude the need for ionizing radiation.

FOUNDATIONS

Trauma, both intentional and unintentional, occurs in up to 8% of all pregnancies and is the leading nonobstetric cause of maternal death.[1-3] The most common causes of injury in pregnancy are motor vehicle collisions (MVCs), interpersonal violence, and falls. Trauma in pregnancy increases the risk of spontaneous abortion, preterm rupture of membranes, preterm birth, uterine rupture, cesarean delivery, placental abruption, and stillbirth. Because some woman are not aware they are pregnant when they present to a trauma center, all women of reproductive potential should be screened for pregnancy.

Commonly used thresholds of fetal viability are an estimated gestational age between 22 and 24 weeks or an estimated fetal weight of 500 gr. Only viable fetuses are monitored, because no obstetric intervention will alter the outcome with a previable fetus. Counseling on proper seatbelt and alcohol/drug use as well as screening for interpersonal violence may help to reduce the morbidity and mortality rates for pregnant patients.[4] Although the essential principles of trauma management remain unchanged in the pregnant patient, there are special considerations in the management of these patients due to the gravid uterus altering the pattern of injury, and changes in physiology and anatomy that affect multiple organ systems. Although there are two lives involved, maternal life takes priority and fetal outcomes are directly correlated with early and rapid maternal resuscitation.[5]

Anatomic Changes in Pregnancy

The uterus remains an intrapelvic organ until approximately the 12th week of gestation. It reaches the umbilicus by 20 weeks and the costal margins by 34 to 36 weeks. At term, the uterus has often enlarged by 30 cm and has increased fifteen-fold in weight, which alters the normal anatomic location and function of multiple structures. The diaphragm progressively rises in pregnancy with compensatory flaring of the ribs, which may predispose to pneumothorax and a faster progression to tension pneumothorax. A thoracostomy done in the third trimester requires that the chest tube be placed one or two interspaces higher than the usual fifth interspace site to allow for diaphragm elevation.[6]

Abdominal viscera are pushed upward by the enlarging uterus and can alter the location of perceived pain. The gravid uterus itself tends to protect abdominal organs from trauma but substantially increases the likelihood of bowel injury from penetrating trauma to the upper abdomen. Conversely, the upward displacement of the bowel makes it less susceptible to blunt trauma. The stretching of the abdominal wall as pregnancy nears term modifies the normal response to peritoneal irritation (blunting of muscle guarding and rebound), potentially underestimating the extent and severity of maternal trauma despite intra-abdominal bleeding and organ injury.

In the first trimester, the bony pelvis shields the uterus and bladder. After the third month, these structures rise out of the pelvis and become vulnerable to direct injury. Both organs become hyperemic during pregnancy, and injury may lead to a marked increase in blood loss compared with similar injury in a nonpregnant patient. Ureteral dilation secondary to smooth muscle relaxation or from compression by the gravid uterus is often found on imaging studies but is not necessarily pathologic. The ligaments of the symphysis pubis and sacroiliac joints are loosened during pregnancy. As a result, a baseline diastasis of the pubic symphysis may exist that can be mistaken for pelvic disruption on radiographic studies.

Physiologic Changes

Cardiovascular

The normal cardiovascular changes of pregnancy can alter the clinical presentation and may either mimic or mask the recognition of shock or exacerbate the effects of traumatic hemorrhage (Table 177.1). Blood pressure declines in the first trimester, levels out in the second trimester, and then returns to nonpregnant levels during the third trimester. The decline in systole is small, 2 to 4 mm Hg, whereas diastole falls 5 to 15 mm Hg. Heart rate increases in pregnancy but does not rise by more than 10 to 15 beats per minute above baseline (mean of approximately 90 beats/min).

TABLE 177.1 Hemodynamic Changes of Pregnancy (Mean Values)

Parameter	Nonpregnant	Trimester 1	Trimester 2	Trimester 3
Heart rate (beats/min)	70	78	82	85
Systolic blood pressure (mm Hg)	115	112	112	114
Diastolic blood pressure (mm Hg)	70	60	63	70
Cardiac output (L/min)	4.5	4.5	6	6
Central venous pressure (mm Hg)	9.0	7.5	4.0	3.8
Blood volume (mL)	4000	4200	5000	5600
Hematocrit without iron (%)	40	36	33	34
Hematocrit with iron (%)	40	36	34	36
White blood cells (cells/mm^3)	7200	9100	9700	9800

Data from: de Swiet M. The cardiovascular system. In: Hytten F, Chamberlain G, eds. *Clinical Physiology in Obstetrics*. Oxford: Blackwell Scientific Publications; 1980: 3-42; Colditz RB, Josey WE. Central venous pressure in supine position during normal pregnancy. Comparative determinations during first, second and third trimesters. *Obstet Gynecol*. 1970;36:769; Letsky E. The haematological system. In: Hytten RF, Chamberlin G, eds. *Clinical Physiology in Obstetrics*. Oxford: Blackwell Scientific Publications; 1980: 43-78; and Cruikshank DP. Anatomic and physiologic alterations of pregnancy that modify the response to trauma. In: Buchsbaum HJ, ed. *Trauma in Pregnancy*. Philadelphia: WB Saunders; 1979: 21-39.

A major contributor to maternal hypotension is the supine hypotensive syndrome. After 20 weeks' gestation, the enlarging uterus has risen to the level of the inferior vena cava, resulting in compression when the mother is supine. Aortocaval obstruction diminishes cardiac preload, which can decrease cardiac output and systolic blood pressure. In late pregnancy, it is common for the inferior vena cava to become completely occluded when the pregnant patient is supine. Hemodynamic improvement occurs when compression is relieved. In determining whether observed hypotension is related to positioning, the pregnant woman can be tilted 15 to 30 degrees onto her left side, or if unable due to injuries, the uterus can be manually displaced to the left by using two hands in order to relieve compression on the inferior vena cava. Elevating the patient's legs will improve venous return. Inferior vena caval compression can also lower central venous pressure (CVP) in the last two trimesters.

Blood volume gradually increases during pregnancy, starting at 6 to 8 weeks' gestation, to as much as 45% above normal, peaking at 32 to 34 weeks' gestation. Blood volumes become increasingly larger for multigravidas and for twin, triplet, and quadruplet gestations. With this increased circulatory reserve, clinical signs of maternal hypotension from acute traumatic bleeding may be delayed. Up to 35% of circulating blood volume may be lost before an injured pregnant patient exhibits signs or symptoms of shock.[5] By the beginning of the second trimester and throughout the remainder of pregnancy, cardiac output is increased 40% to 6 L/min. Blood flow to the uterus increases from 60 mL/min before pregnancy to 600 mL/min at term. This hyperdynamic state is needed to maintain adequate oxygen delivery to the fetus. Because the mother's total circulating blood volume flows through the uterus every 8 to 11 minutes at term, this can be a major source of blood loss in injury.

By the third trimester, there is also marked venous congestion in the pelvis and lower extremities, increasing the potential for hemorrhage from both bony and soft tissue pelvic injuries. Compression of the lower abdominal venous system by the gravid uterus increases peripheral venous pressure and blood volume in the legs, creating the potential for brisk blood loss from leg wounds and can exacerbate bleeding from attempts at central venous catheter placement.

Pulmonary

The pregnant woman at term has a reduced oxygen reserve due to a reduction in functional residual capacity caused by diaphragm elevation and an increase in oxygen consumption related to the growing fetus, uterus, and placenta. Mean arterial oxygen tension drops by 29% in pregnant women at term during 60 seconds of apnea compared with 11% in nonpregnant women. Labor further accelerates this decline. In addition, minute ventilation and tidal volume increase, leading to hypocapnia. Therefore, a partial pressure of carbon dioxide in the arterial blood ($Paco_2$) of 35 to 40 mm Hg may indicate inadequate ventilation and impending respiratory decompensation in the pregnant patient. Maternal hypoxia rapidly leads to fetal hypoxia, distress, and possibly demise. There are no contraindications to rapid sequence intubation during pregnancy. Bag-valve-mask ventilation is more difficult in the pregnant patient due to weight gain and obesity. The incidence of difficult or failed intubations in obstetric anesthesia is four times higher than in surgical nonobstetric patients. Pregnant patients are considered difficult airways with potential for rapid desaturation due to decreased oxygen reserves, increased oxygen demands, upper airway edema, mucosal friability, increased Mallampati scores with increasing gestational age, and increased risk of aspiration. It is recommended that the emergency clinician use a difficult airway algorithm, prepare equipment in advance including rescue devices, call for help early if available, and optimize a ramped, head up, or reverse Trendelenburg position to optimize preoxygenation and apneic oxygenation in all pregnant patients.

Gastrointestinal

Gastroesophageal sphincter tone and gastrointestinal motility are decreased in pregnancy, thus increasing the possibility of aspiration in patients with altered level of consciousness, such as during intubation. Early gastric decompression should be performed in these circumstances.

SPECIFIC DISORDERS

Blunt Trauma

Physical examination is unreliable in predicting adverse outcomes in the pregnant woman with blunt trauma.[7] Risk factors predictive of the onset of contractions or preterm labor include gestational age greater than 35 weeks, assaults, and pedestrian collisions. Fetal mortality can be as high as 40% after maternal trauma, with most likely causes of fetal

death occurring from placental abruption, maternal shock, and maternal death, in order of decreasing incidence. Risk factors significantly predictive of fetal death include ejection, motorcycle and pedestrian collisions, maternal death, maternal tachycardia, abnormal fetal heart rate, lack of restraints, and an injury severity score greater than 9 (see Chapter 32).

Unbelted or improperly restrained pregnant women are twice as likely to experience excessive maternal bleeding and increased maternal death with fetal death being three times more likely to occur. For low- to moderate-severity collisions (constituting 95% of all MVCs), proper restraint use, with or without air bag deployment, generally leads to acceptable fetal outcomes. For high-severity collisions, even proper restraint does not improve fetal outcome.

Pregnant crash-test-dummy trials show that improper placement of the lap belt over the pregnant abdomen causes a threefold to fourfold increase in force transmission through the uterus. The lowest force transmission readings through the uterus occur when a three-point seat belt is used properly. For correct position, the lap belt should be placed under the gravid abdomen, snugly over the thighs, with the shoulder harness off to the side of the uterus, between the breasts and over the midline of the clavicle. Women who receive information on seat belt use during pregnancy from a health care provider are statistically more likely to use seat belts and to use them properly than uninformed controls.

Interpersonal Violence

Women experiencing abuse in the year before or during a pregnancy are 40% to 60% more likely than nonabused women to report high blood pressure, vaginal bleeding, severe nausea, kidney or urinary tract infections, and hospitalization during that pregnancy.[4] Abused pregnant women are more likely to deliver preterm, and children of abused pregnant women are more likely to be born underweight. Children born to abused mothers are more likely than other children to require intensive care at birth. Physicians detect only a minority of interpersonal violence cases in pregnant women, which supports the need for routine screening for interpersonal violence in this population.[4]

Falls

Falls become more prevalent after the 20th week of pregnancy and roughly 25% of pregnant women will fall at least once while pregnant. Protuberance of the abdomen, loosening of pelvic ligaments, strain on the lower back, and fatigability are contributory factors. In a given pregnancy, about 2% of pregnant women sustain repeated direct blows to the abdomen from repetitive falls. Although repeated falls often trigger premature contractions, they seldom result in immediate labor and delivery.

Penetrating Trauma

The gravid uterus affects the injury pattern seen with penetrating trauma to the upper abdomen with the probability of harm to the bowel, liver, or spleen at almost 100%. When the entry site is anterior and below the uterine fundus, visceral injuries are less likely. Although the enlarging uterus can act as a shield against intra-abdominal injuries in the mother, it makes the fetus more susceptible to injury. A high fetal death rate from penetrating trauma to the uterus has been reported and is lower for maternal injuries above the uterus.

Fetal Injury

There is a high risk of fetal loss in the pregnant trauma patient. Poor fetal outcome is predicted by maternal hypotension and acidosis, and a fetal heart rate less than 110 beats/min. When the mother sustains life-threatening injuries, there is a 40% chance of fetal demise, compared with a less than 2% chance in cases of non–life-threatening maternal injuries. Disseminated intravascular coagulation (DIC), which may be caused by placental products entering the maternal circulation, is a significant predictor of fetal mortality. The American College of Obstetrics and Gynecology recommends a minimum of 4 hours of cardiotocographic fetal monitoring after maternal trauma because monitoring is useful in predicting fetal outcome.

Fatal fetal injuries from blunt trauma are usually the result of intracranial hemorrhage and skull fractures secondary to fractured maternal pelvic bones striking the fetal skull as a result of vertex lie.[8] Pelvic and acetabular fractures during pregnancy are associated with a high maternal (9%) and a higher fetal (38%) mortality rate. Both gunshot wounds and stab wounds to the uterus produce substantial morbidity and mortality to the fetus.

Placental Injury

The leading cause of fetal death after blunt trauma is placental abruption.[1] Placental separation results when the inelastic placenta shears away from the elastic uterus during sudden deformation of the uterus. Because deceleration forces can be as damaging to the placenta as direct uterine trauma, abruption can occur with little or no external sign of injury to the abdominal wall. Placental abruption inhibits the flow of oxygen to the fetus and causes in utero carbon dioxide (CO_2) accumulation, resulting in hypoxia and acidosis that leads to fetal distress. Sustained uterine contractions induced by intrauterine hemorrhage also inhibit uterine blood flow, further contributing to fetal hypoxia.

The diagnosis of abruption is made clinically. Classic clinical findings of abruption are vaginal bleeding, abdominal cramps, uterine tenderness, maternal hypovolemia (up to 2 L of blood can accumulate in the gravid uterus), or a change in the fetal heart rate; but many cases of placental abruption after trauma present without vaginal bleeding.

The most sensitive indicator of placental abruption is fetal distress, which can be detected with prompt fetal monitoring. In clinical settings without continuous fetal monitoring capabilities intermittent monitoring of FHR (e.g., every 15 minutes) is recommended, but early transfer should be arranged to a facility with obstetric and neonatal services as the definitive treatment may be surgical. Increased frequency of contractions is associated with abruption. Transabdominal ultrasonography has poor sensitivity for detection of placental abruption (24% sensitivity; 96% specificity).[9] Placental abruption hematomas have a variable appearance on ultrasound including homogenous and heterogenous consistency, and can be either hypo-, hyper-, or isoechoic compared to the placenta depending on the extent and chronicity of bleeding. If the abruption bleeds externally, there may be an insufficient quantity to be detected sonographically. Even with significant intrauterine blood accumulation, accurate ultrasonographic diagnosis may be difficult because of placental position (i.e., posterior) and confounding uterine or placental structural conditions. An ultrasound is useful in clinical practice despite the poor sensitivity because it can help identify other causes of abdominal pain or vaginal bleeding in the setting of trauma.

Placental abruption is associated with an increased risk of stillbirth (after 20 weeks) and preterm delivery (before 37 weeks) even with minor abruption. The extent of placental separation is correlated with the rate of stillbirth. A trial of expectant management with ongoing maternal and fetal monitoring is appropriate when mother and fetus are stable and with partial placental abruptions of less than 25%. This usually applies to fetuses of less than 32 weeks' gestation in which the likelihood of morbidity and mortality associated with prematurity makes delivery management risky. Expectant care in stable patients may allow further fetal maturation and improved outcome. An immediate cesarean section is recommended in cases of fetal distress from

further placental separation. After 32 weeks' gestation, the risk of further placental separation outweighs the benefits of further fetal maturation, so intervention is indicated.

Women with placental abruption are more likely to have coagulopathies than those without abruption. The injured placenta can release thromboplastin into the maternal circulation, resulting in DIC, whereas the damaged uterus can disperse plasminogen activator and trigger fibrinolysis. The precipitation of DIC is directly related to the degree of placental separation. Severe clotting disorders rarely occur unless separation of the placenta is significant enough to result in fetal demise.

Uterine Injury

The most common obstetric complication caused by maternal trauma is uterine contractions. Myometrial and decidual cells, irritated by contusion or placental separation, release prostaglandins that stimulate uterine contractions. Progression to labor depends on the extent of uterine damage, the amount of prostaglandins released, and the gestational age of the pregnancy. The routine use of tocolytics for preterm labor is not recommended because most contractions stop spontaneously. Contractions that are not self-limited are often induced by some pathologic condition, such as underlying placental abruption, which is a contraindication to tocolytic therapy. Some studies describe this risk as relative and have used tocolysis successfully with careful evaluation and intensive monitoring to continue the pregnancy and enhance fetal maturity. The option to use tocolytics ends when cervical dilation reaches 4 cm or greater.

Traumatic uterine rupture is a rare event. It is most often caused by severe vehicular collisions in which pelvic fractures strike directly against the uterus. Uterine rupture may occur from stab wounds and gunshot injuries, but this is rare. Maternal shock, abdominal pain, easily palpable fetal anatomy caused by extrusion into the abdomen, and fetal demise are typical findings on examination. Diagnosing uterine rupture can be difficult. A fractured liver or spleen can produce similar signs and symptoms of peritoneal irritation, hemoperitoneum, and unstable vital signs. Optimal treatment, between suturing the tear or performing a hysterectomy, depends on the extent of uterus and uterine vessel tears and the importance of future childbearing.

DIAGNOSTIC TESTING

All women of childbearing potential presenting with trauma should be assessed for possible pregnancy.

Changes in Laboratory Values with Pregnancy

Increases in plasma volume greater than red blood cells cause a physiologic anemia of pregnancy (hematocrit 32% to 34% by the 32nd to 34th week). Despite the lower hematocrit, there is an overall increase in oxygen-carrying capacity because of an increased total red blood cell mass. Placental progesterone directly stimulates the medullary respiratory center, producing a lower $Paco_2$ (30 mm Hg) from the second trimester until term. The subsequent compensatory lowering of serum bicarbonate slightly reduces blood-buffering capacity during conditions of physiologic stress. A $Paco_2$ of 40 mm Hg in the latter half of pregnancy reflects inadequate ventilation and potential respiratory acidosis that could precipitate fetal distress.

Electrocardiographic changes include a left-axis shift averaging 15 degrees, caused by diaphragm elevation. Consequently, flattened T waves or Q waves in leads III and augmented voltage unipolar left limb lead may be seen (Fig. 177.1)

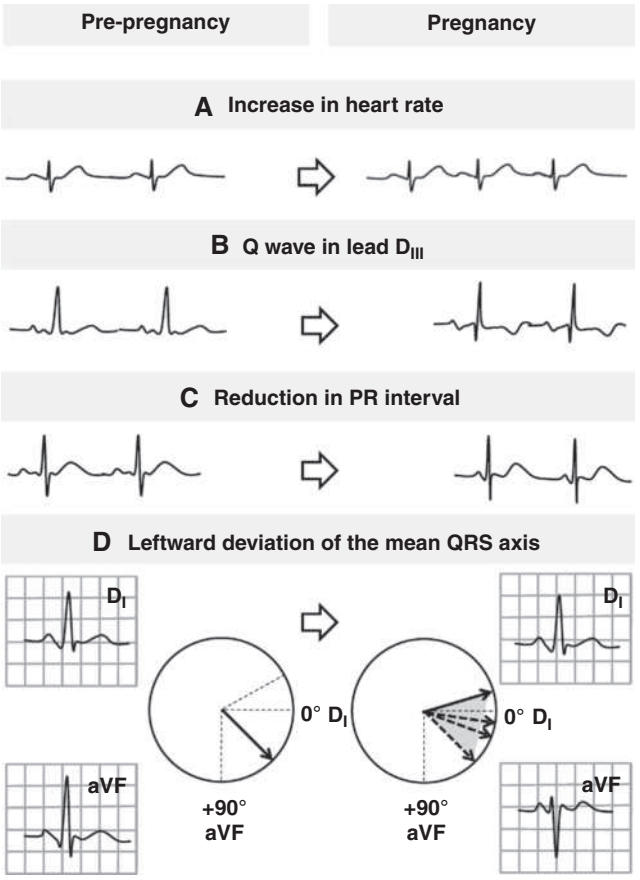

Fig. 177.1 EKG changes in pregnancy. (From: Angeli F, Angeli E, Verdecchia P. *Int J Mol Sci.* 2015;16(8):18454-18473; https://doi.org/10.3390/ijms160818454.)

Laboratory

Laboratory tests for a pregnant patient with trauma should include a complete blood count, basic electrolyte panel, urinalysis, blood type with Rh status, and coagulation studies including fibrinogen.[6] Patients who appear to be stable but have a low serum bicarbonate level may have occult maternal shock. Interpretation of bicarbonate results requires consideration of the physiologic changes that occur in the later stages of pregnancy as a result of respiratory alkalosis (see Chapter 173). Coagulation studies are important in directing management of patients with multisystem trauma or when the diagnosis of placental abruption is considered.

Kleihauer-Betke Test and Fetomaternal Hemorrhage

Fetomaternal hemorrhage (FMH), the transplacental bleeding of fetal blood into the normally separate maternal circulation, is a unique complication of pregnancy. MVCs, anterior placental location, and uterine tenderness are associated with an increased risk of FMH. Massive fetomaternal transplacental hemorrhage causes alloimmunization in Rh incompatibility but also endangers the fetus by causing severe fetal anemia, fetal distress, and possible exsanguination. ABO incompatibility causes less severe disease.

FMH most commonly occurs after 12 weeks' gestation, when the uterus rises above the pelvis and becomes susceptible to direct trauma.

The Kleihauer-Betke test quantifies the amount of FMH. Most laboratories screen for FMH of 5 mL or more, even though the amount of FMH sufficient to sensitize most Rh-negative women is much less than 5 mL. Therefore, it is advisable that all Rh-negative mothers who have a history of abdominal trauma receive one prophylactic dose of Rhesus immune globulin

(RhIG) within 72 hours of injury. Trauma patients at risk for massive FMH will have major injuries or abnormal obstetric findings, such as uterine tenderness, contractions, or vaginal bleeding. Rarely, the amount of FMH will exceed that covered by the maximum RhIG dose (300 μg). Because RhIG can effectively prevent Rh isoimmunization when administered as late as 72 hours after antigenic exposure, the results of the Kleihauer-Betke test are not immediately needed in the emergency department (ED).

Radiography

Adverse effects to the fetus are unlikely if radiation exposure is less than 50 mGy. Less than 1% of trauma patients are exposed to more than 30 mGy. Sensitivity to radiation is greatest during intrauterine development when the embryo undergoes organogenesis in weeks 2 to 15. However, the risk to the fetus of a 10-mGy exposure is thousands of times smaller than the spontaneous risks of malformations, abortions, or genetic disease. Intrauterine exposure to 50 mGy does not appear to cause a significant increase in congenital malformations, intrauterine growth retardation, or miscarriage but is associated with a 0.3% increased risk of childhood cancer and 2% risk of lifetime cancer. Pathologic conditions more readily appear with intrauterine radiation doses of 150 mGy or greater.

Providing information on radiation exposure from diagnostic radiographs is difficult. Fetal dose from computed tomography (CT) scans depends on the type of equipment used, the abdominal girth of the mother, and the fetal distance from the maternal skin. Diagnostic radiographic studies should be performed with regard for fetal protection, but necessary diagnostic studies of the traumatized pregnant patient should not be withheld out of concern for fetal radiation exposure.[10] Fetal irradiation should be minimized by limiting the scope of the examination and using technical means, such as shielding and collimation. Table 177.2 provides estimated radiation doses from various types of examinations.

Ultrasonography

Ultrasonography is the best modality for simultaneous assessment of the mother and fetus. It is useful in detecting major abdominal injury and establishing fetal well-being or demise, gestational age, and placental location. It obviates radiation risks, minimizes diagnostic delays, and provides high sensitivity for injury. The sensitivity of the focused assessment with sonography for trauma (FAST) examination in identifying intra-abdominal bleeding or pericardial bleeding is 61% to 83%, lower than the general population, but it has a specificity and negative predictive value of 99.7%.[11] Ultrasonography has low sensitivity (24%) but high specificity (96%) for placental abruption.[9] Limitations in accuracy include operator experience, patient obesity, the presence of subcutaneous air, and a history of multiple abdominal surgeries.[11]

Computed Tomography and Magnetic Resonance Imaging Scans

CT and, increasingly, magnetic resonance imaging (MRI) studies are used in evaluating abdominal trauma in pregnancy.[6] If ultrasonography is indeterminate and the patient's condition is stable, CT and MRI can identify specific organ damage. They are particularly useful in assessing penetrating wounds of the flank and back. CT can miss diaphragm and bowel injuries. Both of these studies carry the risk of moving the patient from the closely monitored environment of the ED to the radiography suite.

Radiation from CT is a concern in the pregnant trauma patient. However, with shielding, fetal exposure from head and chest CT scans can be kept below an acceptable 1-rad limit. CT of the abdomen can be performed with 4 mGy of exposure to the fetus. Abdomen and pelvic CT produces about 25 mGy of radiation to the fetus, which is well below the 50 mGy level, where a 2% increase in risk of cancer is seen without evidence of malformation to the fetus. Radiation exposure ultimately depends on the patient, scanner, and technique used in performing the study (see Table 177.2).

When available, MRI is preferable to CT because it uses no radiation and has not been associated with significant fetal disease or disability, and it is more sensitive in diagnosing diaphragm and bowel injury.

TABLE 177.2 Estimated Fetal Radiation Dose From Conventional Radiographic and Computed Tomography Examination[21,22]

Imaging Study	Estimated Fetal Dose (mGy)[a]
Radiography	
Cervical spine (AP, lateral)	<0.001
Extremities	<0.001
Chest (PA, lateral)	0.0005–0.01
Thoracic spine	0.003
Abdomen (AP)	0.1–3.0
Lumbar spine (AP, lateral)	1–10
Computed Tomography	
Head or neck	0.001–0.01
Chest (routine)	0.01–0.66
Chest (pulmonary embolism protocol)	0.01–0.66
Abdomen	1.3–35
Pelvis	10–50
Abdomen and pelvis	13–25
CT angiography of the aorta	6.7–56
CT angiography of the coronary arteries	0.1–3
Nuclear Medicine	
Low-dose perfusion scintigraphy	0.1–0.5
V/Q scintigraphy	0.1–0.8
Myocardial perfusion with 99mTc-sestamibi	17
Myocardial perfusion with 99mTc-tetrofosmin	8.45

[a]The naturally occurring background radiation dose during pregnancy is 0.5 to 0.1 mGy.

AP, Anteroposterior; *CT,* computed tomography; *PA,* posteroanterior.

Data adapted from: Trada N, Dreizin D, et al. Imaging pregnant and lactating patients. *Radiographics.* 2015;35(6):1751-1765; Copel J, et al. Guidelines for diagnostic imaging during pregnancy and lactation. ACOG committee opinion number 723. *Obstet Gynecol.* 2017;130:e210-216.

SPECIAL PROCEDURES

Diagnostic Peritoneal Lavage

In unstable trauma patients with equivocal or negative findings on ultrasonography, diagnostic peritoneal lavage (DPL) may be considered in any trimester. It should be performed in conjunction with a trauma surgeon using an open technique above the uterus following placement of a nasogastric tube and Foley catheter. The gravid uterus, in the later trimesters, makes the procedure riskier and technically challenging.

MANAGEMENT

Management of the patient with multiple trauma is covered in Chapter 32. The following discussion focuses on the aspects of management unique to the pregnant patient.

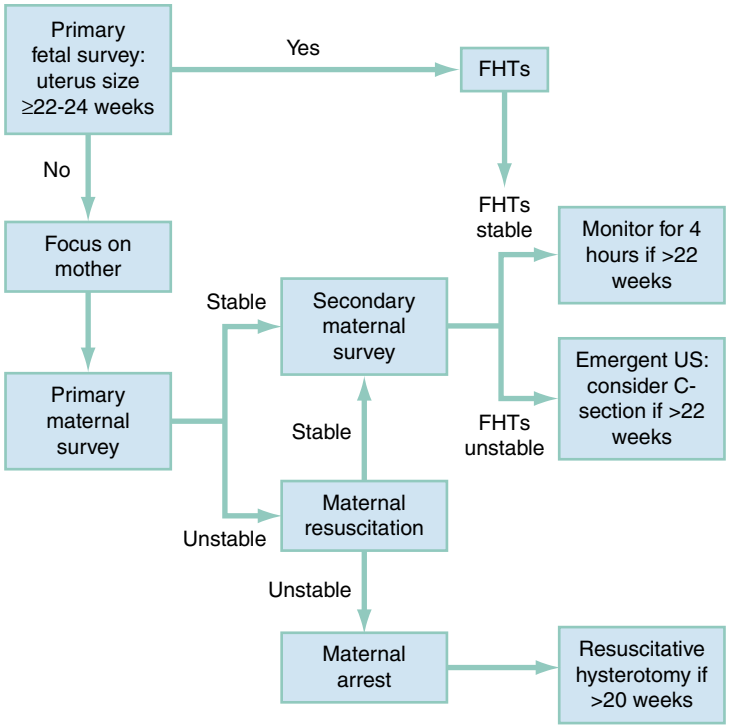

Fig. 177.2 Decision-making algorithm in emergency obstetric care. *C-section,* Cesarean section; *FHT,* fetal heart tone; *US,* ultrasonography.

Depending on the mechanism of trauma, maternal condition, and gestational age, the clinician should consider early notification or consultation with a trauma surgeon, obstetrician, neonatologist, or pediatrician (or all four) for a multidisciplinary approach. A fetal monitor, portable ultrasound, and neonatal resuscitation equipment should be immediately available. Tetanus toxoid and immune globulin have no detrimental effect on the fetus. The World Health Organization (WHO) specifically recommends vaccination during pregnancy. To prevent alloimmunization of a Rh-negative mother, administer one 50-µg dose of RhIG in the first trimester. It is sufficient because total fetal blood volume is only 4.2 mL by 12 weeks' gestation, and a 50 µg-dose covers 5 mL of bleeding. During the second and third trimesters, a 300-µg dose of RhIG is given, which protects against up to 30 mL of FMH. Beyond 16 weeks' gestation, the total fetal blood volume reaches 30 mL or more. Massive FMH likely exceeds the efficacy of one 300-µg dose of RhIG, so the Kleihauer-Betke test can be used to guide effective dosing.

Maternal Resuscitation

Primary Survey

The primary survey focuses on the mother. However, because two patients are present, it is reasonable to gather preliminary information about the age of the fetus at this time (Fig. 177.2).

Airway and Breathing. The general principles of airway management are discussed in Chapter 1. Oxygen therapy should be instituted early in the traumatized pregnant patient because she can quickly become hypoxic due to her reduced oxygen reserve and increased oxygen consumption. The fetus is vulnerable to any reduction in oxygen delivery. Supplemental oxygen is recommended throughout maternal resuscitation and evaluation with oxygenation saturation levels maintained above 95%.[6]

A secure airway enables proper oxygenation and negates the higher risk of aspiration in pregnancy. Rapid sequence intubation after preoxygenation of the pregnant patient is recommended. Data are limited on use of RSI agents during pregnancy but none have been consistently associated with congenital malformations or adverse effects on the fetus. Mechanical ventilation settings need to be adjusted for increased tidal volumes and respiratory alkalosis, which is consistent with the physiologic $Paco_2$ of 30 mm Hg in the last stage of pregnancy. No specific initial ventilation settings are recommended, but settings can be adjusted as clinically indicated and if the patient has ARDS clinicians can use the ARDS network guidelines.[12]

Circulation. Intravenous access with two large-bore catheters above the diaphragm is preferred. Maternal blood pressure and heart rate are not consistently reliable predictors of fetal and maternal hemodynamic stability. Due to an expanded circulating volume, the mother can hemorrhage without showing early signs of hypotension. Uterine blood flow is markedly reduced when maternal circulation is compromised. As a result, after an acute blood loss, uterine blood flow can be substantially decreased while maternal blood pressure remains normal. Consequently, the pregnant woman with borderline hemodynamic stability probably already has a jeopardized fetus. When traditional signs of shock appear, fetal compromise may be far advanced.

Fluid resuscitation with isotonic fluids should occur in all patients with suspected or observed significant blood loss. Type O-negative packed red blood cells are recommended for hemodynamically unstable trauma patients until type-specific blood products are available. Vasopressors are recommended only with refractory hypotension unresponsive to fluid resuscitation because of the adverse effect on uteroplacental perfusion.[6] A massive transfusion protocol should be initiated on all hemodynamically unstable patients in a 1 : 1 : 1 ratio of red blood cells, platelets, and plasma. Tranexamic acid is an antifibrinolytic agent used in trauma to reduce bleeding and mortality and should be administered within 3 hours of injury. Limited data are available on the safety of tranexamic acid in pregnancy but no adverse fetal events have been described. It is unknown if there is a mortality benefit with the use of tranexamic acid in pregnant trauma patients.[1,13]

Beyond 20 weeks' gestation, a left lateral tilt of 15 to 30 degrees or leftward manual displacement of the uterus using two hands is

recommended to reduce compression on the inferior vena cava caused by the gravid uterus. A Foley catheter for measuring urine output provides further information on circulatory volume status.

With trauma in pregnancy, the primary survey is modified to assess uterine size and the presence of fetal heart tones if the patient is severely injured. Otherwise, this assessment belongs in the secondary survey. Uterine size, measured from the symphysis pubis to the fundus, is the quickest means of estimating gestational age. This distance in centimeters equals the gestational age in weeks (e.g., 24 cm = 24 weeks), which allows some early indication of fetal viability if delivery is necessary (Fig. 177.3). Usually, between 22 to 24 weeks is used as the cutoff point for fetal viability (Table 177.3). As a rough guide, the fetus is potentially viable when the dome of the uterus extends beyond the umbilicus. Fetal heart tones can be detected by auscultation at 20 weeks' gestation or by Doppler probe at 10 to 14 weeks. If either the uterus is less than 22 cm in size or fetal heart tones are absent, the pregnancy is probably too early to be viable, and treatment is directed solely at the mother.

Secondary Survey

The secondary survey involves a detailed examination of the patient but is also modified to gather additional information about the maternal abdomen and the fetus. Physical examination of the abdomen, frequently unreliable in the nonpregnant patient, is even more inaccurate with changing organ position, abdominal wall stretching in advancing pregnancy, and uterine contraction pains. Still, valuable information can be gathered about uterine tenderness, contraction frequency, and vaginal bleeding.

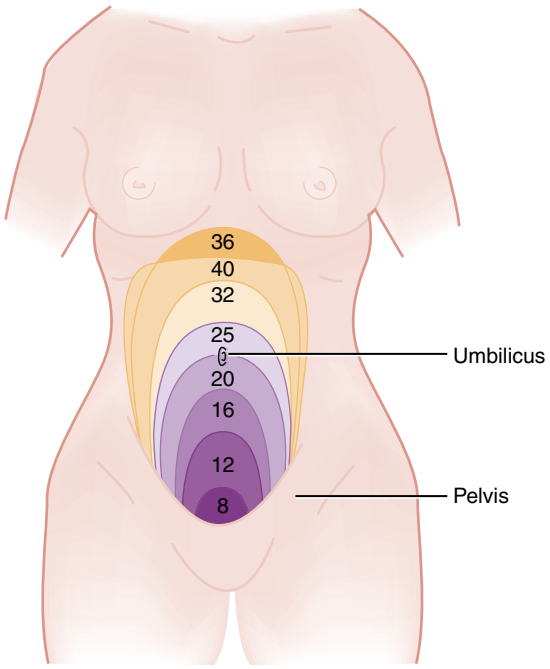

Fig. 177.3 Uterine size at different weeks of gestation. (From: Kravis TC, Warner CG, eds. *Emergency Medicine: A Comprehensive Review*. Rockville, MD: Aspen Publishers; 1979.)

An external perineal examination should be performed. A sterile speculum examination is done in consultation with or by an obstetrician after placental previa has been ruled out by ultrasonography. A bimanual examination is avoided due to the risk of causing prelabor rupture of membranes or bleeding in cases of unidentified placenta previa. Vaginal bleeding suggests placental abruption, and a watery discharge suggests rupture of the membranes. Significant vaginal bleeding from intravaginal injuries can be temporized by packing with sterile moistened gauze. If the mechanism of injury is significant enough and the fetus is judged to be viable, early involvement of an obstetrician may enhance the fetal outcome.

Fetal Evaluation. Fetal evaluation in the secondary survey focuses on the fetal heart rate and detection of fetal movement. When the presence of fetal heart tones has been confirmed, intermittent monitoring of fetal heart rate is sufficient for the previable fetus. If the fetus is viable (i.e., 22 to 24 weeks or more), continuous external monitoring initiated quickly and maintained throughout all diagnostic and therapeutic procedures may be useful in directing management. Such monitoring can also benefit the mother, because fetal hemodynamics are more sensitive to decreases in maternal blood flow and oxygenation than are most measures of the mother. Fetal distress can be a sign of occult maternal distress. However, fetal distress and even demise can occur with seemingly minor maternal trauma. Signs of fetal distress include an abnormal baseline heart rate, decreased variability of heart rate, and fetal decelerations after contractions.

The normal fetal heart rate ranges from 120 to 160 beats/min; rates outside or trending toward these limits are ominous. Heart rate variability has two components. Beat-to-beat variability measures autonomic nervous function, whereas long-term variability indicates fetal activity. Heart rate variability increases with gestational age. The loss of beat-to-beat and long-term variability warns of fetal central nervous system depression and reduced fetal movement caused by fetal distress (Fig. 177.4).

Late decelerations are an indication of fetal hypoxia. These decelerations are relatively small in amplitude and occur after the peak or conclusion of a uterine contraction. By comparison, early decelerations are larger, occur with the contraction, and recover to baseline immediately after the contraction. Early decelerations may be vagally mediated when uterine contractions squeeze the fetal head, stretch the neck, or compress the umbilical cord. Variable decelerations are large, occur at any time, and are possibly caused by umbilical cord compression (Fig. 177.5).

Mother Stable, Fetus Stable

Minor trauma does not exempt the fetus from significant injury. It is estimated that up to 3% of all minor trauma results in fetal loss,

TABLE 177.3 Fetal Viability in Trauma

Weeks of Gestation	6-Month Survival (%)	Survival With No Severe Abnormalities (%)
22	0	0
23	15	2
24	56	21
25	79	69

Data from: Morris JA Jr, et al. Infant survival after cesarean section for trauma. *Ann Surg*. 1996;223:481.

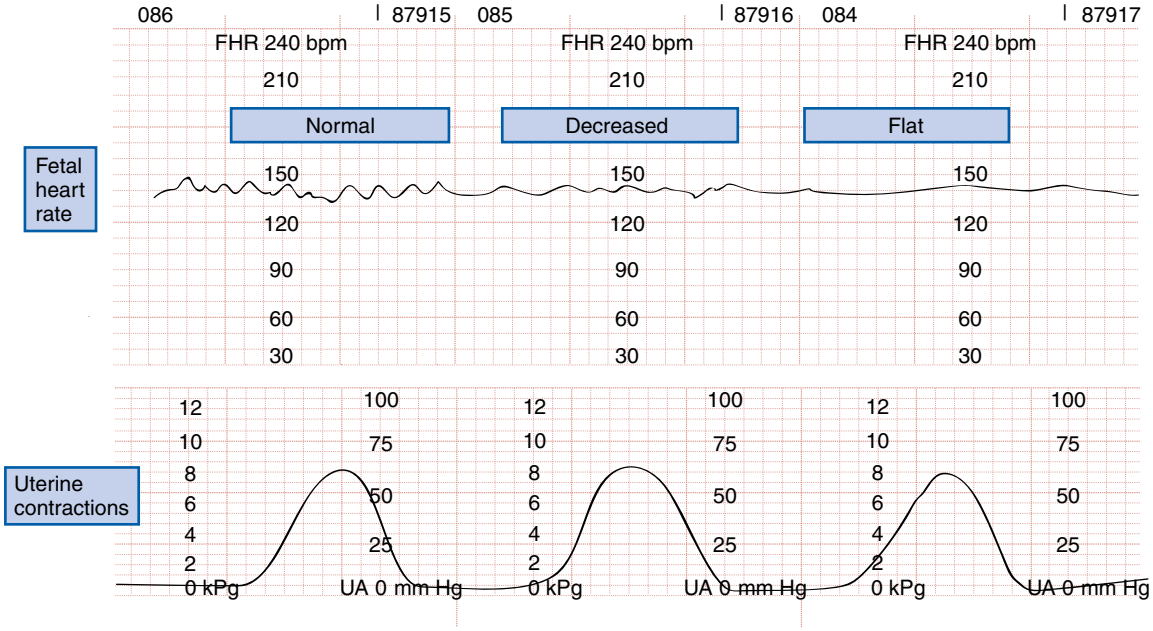

Fig. 177.4 Types of fetal heart rate variability. *bpm,* Beats per minute; *FHR,* fetal heart rate; *UA,* uterine activity.

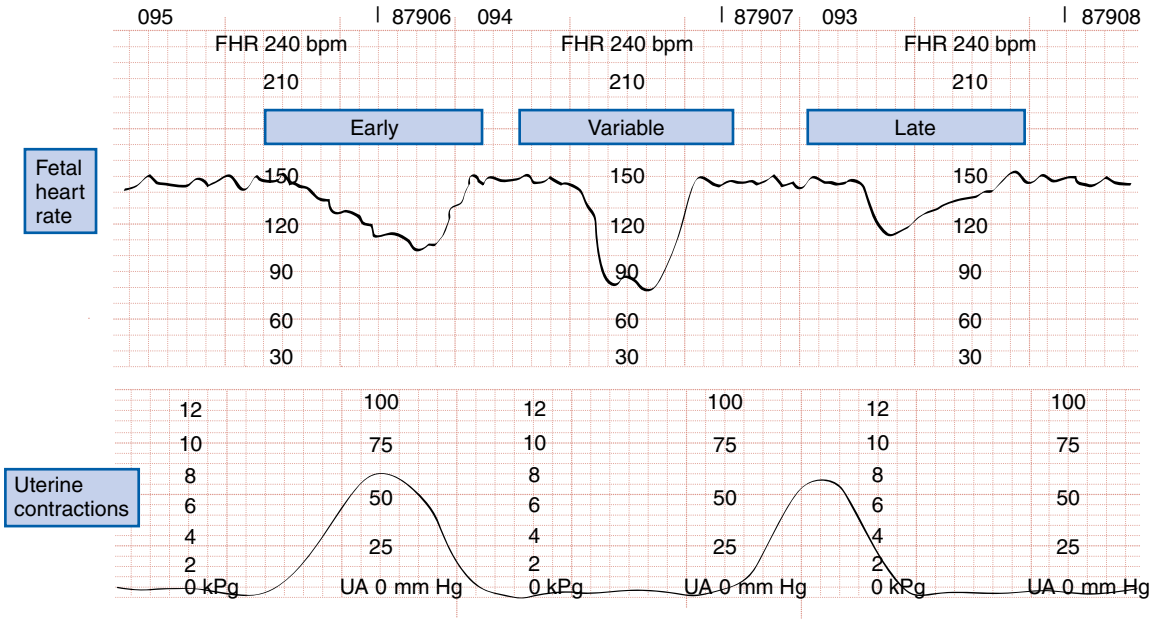

Fig. 177.5 Types of fetal heart rate decelerations. *bpm,* Beats per minute; *FHR,* fetal heart rate; *UA,* uterine activity.

typically from placental abruption. Therefore, once the traumatized mother is stabilized, the focus of care is directed toward the fetus. For the viable fetus (greater than 22 to 24 weeks' gestation), monitoring is the next step. Continuous monitoring maintained throughout all diagnostic and therapeutic actions is advisable. Because direct impact is not necessary for fetoplacental pathology to occur, the traumatized pregnant woman with no obvious abdominal injury still benefits from monitoring.

The recommended 4 hours of cardiotocographic observation of the viable fetus is extended to 24 hours if at any time during the first 4 hours there are more than three uterine contractions per hour, uterine tenderness persists, results on a fetal monitor strip are worrisome, vaginal bleeding occurs, the membranes rupture, or any serious maternal injury is present. Most cases of placental abruption after maternal trauma are detected within the first 4 hours of monitoring.

On discharge from the hospital, the pregnant woman should be instructed to record fetal movements during the next week. If fewer than four movements per monitored hour are noted, the patient should see her obstetrician immediately and a nonstress test is warranted. The occurrence of preterm labor, membrane rupture, vaginal bleeding, or uterine pain also necessitates prompt reevaluation. Serial ultrasound and fetal heart rate tests on viable fetuses a few days after maternal trauma and periodically throughout the remaining portion of the pregnancy are helpful in monitoring fetal well-being.

Mother Stable, Fetus Unstable

Fetal death rates after maternal trauma are three to nine times higher than maternal death rates. If a viable fetus remains in distress despite optimization of maternal physiology, cesarean section should be considered.

Although fetal viability is first reached at 22 to 24 weeks, the ultimate determinant of the age of fetal viability is the level of neonatal care provided by the intensive care nursery unit in each hospital or accessible regional facility. Determining gestational age for fetuses of less than 29 weeks may be difficult. Emergency decisions on fetal viability are therefore made on the basis of the best ultrasonography and gestational age information available.

The presence of fetal heart tones is an important survival marker for fetuses about to undergo emergency cesarean section. The fetal survival rate is zero if there are no fetal heart tones present when emergency cesarean section commences. If fetal heart tones are present and the gestational age is 26 weeks or more, the infant survival rate may be as high as 75%.

Besides fetal distress, other reasons for a cesarean section include uterine rupture, placental rupture with significant vaginal bleeding, fetal malpresentation during preterm labor, and situations in which the uterus mechanically limits maternal repair. Fetal demise without any of the aforementioned conditions is not an indication for cesarean section, because most will pass spontaneously within 1 week.

Mother Unstable, Fetus Unstable

If the mother's condition is critical, primary repair of her wounds is the best course. This may apply even when the fetus is in distress, because a critically ill mother may not be able to withstand an additional operative procedure such as cesarean section, which prolongs laparotomy time and likely substantially increases blood loss. The best initial action on behalf of the fetus is early and rapid restoration of normal maternal physiology. If it is felt that the unstable mother can tolerate an emergency cesarean section, it should be considered for the distressed, viable fetus.

As with nonpregnant patients, operative intervention for blunt trauma and above-the-uterus stab wounds is dictated by clinical findings and diagnostic test results. Above-the-uterus intraperitoneal gunshot wounds require exploration. In situations of severe maternal hemorrhage, massive transfusion protocols should be initiated with fresh frozen plasma, platelets, and red blood cells in a 1:1:1 ratio to lower the rate of coagulopathy and improve survival. There is little evidence to support a definitive management strategy for penetrating trauma to the gravid uterus. In situations of a hemodynamically stable mother, expectant management has been recommended. However, no prospective study has verified this. Damage to the uterus alone can be quite devastating because of its increased circulation. Without exploration, it is impossible to know the occurrence, size, or depth of uterine penetration, and there are no guidelines indicating whether a uterine wound can be left unsutured without incurring an increased risk of infection or delayed uterine rupture. We recommend laparotomy or laparoscopy as the safest means of managing penetrating uterine wounds because missed maternal injuries can quickly compromise the fragile fetus.

Defibrillation

Electrical flow that bypasses the fetus has little effect on the pregnancy. Maternal elective and emergent cardioversion have been performed safely for cardiac dysrhythmias in all three stages of pregnancy. Energies up to 300 Joules on a monophasic defibrillator have been used without affecting the fetus or inducing preterm labor. Although the amount of energy reaching the fetal heart is thought to be small, it is advisable to monitor the fetal heart during maternal cardioversion.

Resuscitative Hysterotomy

Restoration of maternal and thus fetal circulation is the optimal goal with maternal hemodynamic instability. During maternal resuscitation, adequate oxygenation, fluid loading, and a 30-degree left tilting position or manual displacement of the gravid uterus is recommended to improve maternal circulation. If there is no response to advanced cardiac life support, a resuscitative hysterotomy, formerly known as a perimortem cesarean section, should be initiated by 4 minutes and completed by 5 minutes after the onset of maternal cardiac arrest with no return of spontaneous circulation (ROSC).[14-19]

In the event of maternal cardiopulmonary arrest, resuscitative hysterotomy is recommended to rapidly deliver the fetus to relieve aortocaval compression, improve hemodynamics, and optimize maternal and fetal survival.[20] A resuscitative hysterotomy is a rare but potentially lifesaving procedure for both the mother and neonate and is recommended only if uterine size exceeds the umbilicus (20 weeks' gestation or greater). Time since maternal circulation ceased is the critical factor in fetal outcome. Delivery increases venous return and cardiac output by 25% to 30% and leads to higher rates of ROSC and survival benefit for mother. Beyond 20 minutes, there is virtually never survival or favorable neurologic outcome for either mother or fetus.

The most experienced physician available should perform the procedure as cardiopulmonary resuscitation (CPR) is continuing. A midline vertical incision is made from the epigastrium to the symphysis pubis. The uterus is then entered with a midline vertical incision. If necessary, the placenta is incised to reach the fetus; once the fetus has been delivered, the cord is clamped and cut. Maternal revival after delivery of the fetus is reported due to relief of vena caval compression and improved hemodynamics.

DISPOSITION

The emergency clinician should consider the stability of the mother and the viability of the growing fetus when making management and disposition decisions. Any pregnant woman at 22 to 24 or more weeks of gestation who has sustained blunt trauma should undergo at least 4 hours of fetal monitoring, even if she appears well. In general, pregnant women who sustain minor trauma have a favorable pregnancy outcome. Other admission and operative criteria are similar for pregnant and nonpregnant trauma patients.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 177: QUESTIONS AND ANSWERS

1. A 30-year-old female who is 28 weeks' gestation presents to the emergency department after being a restrained passenger in a low-speed MVC. Which of the following is the best indicator of fetal outcome in this scenario?

a. Abdominal tenderness
b. Cardiotocographic monitoring for 4 hours
c. Maternal blood count and arterial blood gas results
d. Maternal vital signs
e. Ultrasonography

Answer: B. For women with mild blunt trauma, fetal outcome is not predicted by maternal vital signs, abdominal tenderness, blood tests, or ultrasound results. Only cardiotocographic monitoring for a minimum of 4 hours is useful to predict fetal outcome. Fetal monitoring can identify fetal distress and the need for further intervention.

2. Which of the following factors is most concerning in the presentation of a pregnant trauma patient?

a. Diastasis of the symphysis pubis
b. Electrocardiogram (ECG) findings of Q waves in III and aV_F
c. Hematocrit 34% in third trimester
d. Hypotension in the third trimester
e. Respiratory alkalosis in the third trimester

Answer: D. Blood pressure declines in the first trimester, levels out in the second trimester, and then returns to nonpregnant levels during the third trimester. In pregnancy, minute ventilation increases, leading to hypocapnia. Therefore, a partial pressure of arterial carbon dioxide ($Paco_2$) of 35 to 40 mm Hg may indicate inadequate ventilation and impending respiratory decompensation. The physiologic anemia of pregnancy, resulting from a 48% to 58% increase in plasma volume and only an 18% increase in red blood cells, results in hematocrits of 32% to 34% by gestational age of 32 to 34 weeks. Electrocardiographic changes include a left-axis shift averaging 15 degrees, caused by diaphragm elevation. Consequently, flattened T waves or Q waves in leads III and aV_F may be seen.

3. A 26-week gravid woman presents to the emergency department (ED) after a moderate-speed motor vehicle collision (MVC). The patient is without complaints, and her vital signs are as follows: blood pressure, 100/60 mm Hg; heart rate, 100 beats per minute; and respiratory rate, 18 breaths per minute. Ultrasound examination shows good fetal movement, with a fetal heart rate of 150 beats per minute. What is the appropriate disposition for this patient?

a. Consult obstetrics for a minimum of 4 hours of cardiotocographic monitoring.
b. Perform a FAST examination and if negative discharge home.
c. Consult trauma and obstetrics for admission and serial examinations.
d. Consult trauma surgery for exploratory laparotomy.
e. Discharge the patient with close follow-up with obstetrics.

Answer: A. Placental abruption results when the inelastic placenta shears away from the elastic uterus during sudden deformation of the uterus. Because deceleration forces can be as damaging to the placenta as direct uterine trauma, abruption can occur with little or no external sign of injury to the abdominal wall. For the viable fetus (more than 22 to 24 weeks' gestation), monitoring is the next step.

CHAPTER 177: QUESTIONS AND ANSWERS—cont'd.

4. A 26-year-old, 30-week gestation woman presents unresponsive with cardiopulmonary resuscitation (CPR) in progress after a high-speed motor vehicle collision (MVC). The patient lost her vital signs 3 minutes before arrival in the emergency department (ED). What is the most appropriate next step in the management of this patient?

a. Transfer to the operating room for emergency cesarean section by obstetrics
b. Resuscitative hysterotomy with vertical midline incision
c. Thoracotomy with cardiac massage
d. Administer epinephrine and continue ACLS guidelines for cardiac arrest
e. Defibrillate immediately at 300 J

Answer: B. In the event of maternal cardiopulmonary arrest, resuscitative hysterotomy is indicated in any pregnancy of greater than 20 weeks' gestation (above the umbilicus) to improve both maternal and fetal survival. It should ideally be performed within 4 minutes of loss of spontaneous circulation and completed by 5 minutes of no ROSC. The most experienced physician available should perform the procedure.

5. A 28-week pregnant patient comes in after a gunshot wound to the epigastrium. Her blood pressure is 95/30 and her heart rate is 125 after receiving 1 liter IV fluids by EMS en route. What is the optimal management for this patient?

a. Explore the wound locally for entrance and exit wounds.
b. Expectant management with serial abdominal examinations.
c. Intraoperative exploratory laparotomy or laparoscopy by a trauma surgeon.
d. Fetal monitoring for a minimum of 4 hours

Answer: C. The gravid uterus affects the injury pattern seen with penetrating trauma to the upper abdomen with the probability of harm to the bowel, liver, or spleen at almost 100%. The gravid uterus tends to protect abdominal organs from trauma but substantially increases the likelihood of bowel injury from penetrating trauma to the upper abdomen. A trauma surgeon/trauma service should be activated or consulted. With persistent hypotension after an initial 1-liter IV fluid bolus, the massive transfusion protocol should be initiated in anticipation of the expected course of action. The patient will need to go to the operating room for an exploratory laparotomy.

178

Care of the Geriatric Patient

Denise Nassisi

KEY CONCEPTS

- The population is aging, with 10,000 Americans turning 65 every day, resulting in an increasing proportion of ED patients that are elderly. Older ED patients have the greatest resource use, longest lengths of stay, and highest admission rates of any age group.
- Delirium, especially hypoactive delirium, is underrecognized by emergency clinicians; the diagnosis of delirium should prompt investigation for life-threatening emergencies, including infection, metabolic abnormalities, and acute coronary syndrome (ACS).
- Nonspecific complaints, such as generalized weakness, are among the top ten presenting complaints for older ED patients, and are often the harbinger of serious underlying illness.
- Atypical presentations of disease result in diagnostic challenges and can lead to misdiagnosis.
- Many older patients with ACS present without chest pain, especially females and those older than 85 years. ACS in older adults is more often complicated by acute heart failure due to age-related decreases in left ventricular compliance. Current recommendations regarding medical and revascularization therapy in those with non-STEMI and STEMI have no age limitations.
- Almost one-third of older ED patients presenting with abdominal pain are ultimately found to have a surgical condition causing the pain; therefore, there should be a low threshold for diagnostic imaging.
- Mortality from sepsis approaches 40% for patients older than 85 years, with respiratory and genitourinary infections being the most common sources. Older adults with infection are less likely to present with fever or leukocytosis and may have SIRS-negative sepsis.

FOUNDATIONS

Emergency department (ED) utilization for patients 65 and over is growing faster than for any other age group. The current growth in the population of older adults is unprecedented in the history of the world. In the United States approximately 10,000 of the "baby boomer" generation turn 65 years old each day, making those aged 65 years and older the fastest-growing segment of the population. By the year 2050, it is anticipated that they will comprise 21% of the population.

Older ED patients are a special population with unique needs and concerns. Altered homeostasis and decrease in physiologic reserve impacts their response to stressors and illness. Body composition changes predispose the older adult to dehydration and hypernatremia. Decreased subcutaneous fat places them at greater risk of hypothermia, and they are more at risk of developing hyperthermia when exposed to high ambient temperatures. The maximal heart rate achievable typically falls with age due to diminished responsiveness of the sympathetic nervous system, while resting heart rate may increase with age. Increases in heart rate may be blunted due to commonly prescribed medications. Reduced cardiac reserve predisposes to postural hypotension. Age-related decreases occur in hearing and vision that can markedly affect communication and functional status. Renal function, with creatinine clearance, declines with age. Changes in body composition and renal function result in pharmacokinetic and pharmacodynamic alterations that predispose older patients to medication adverse events. Polypharmacy is common in older patients, further increasing their risk of adverse drug reactions.

Emergency care should be approached in a holistic multidimensional manner with consideration for important confounding factors. Cognitive dysfunction, decreased functional reserve, frailty, mobility impairment, decreased hearing and decreased visual acuity can impact the ED evaluation and disposition decision making. The evaluation generally needs to be more comprehensive and extensive than those for younger patients. The average ED length of stay is longer for older adults who also have higher utilization of resources and rates of admission. They are more likely to have an emergent condition, higher morbidity and mortality, and are more likely to be misdiagnosed. Clinical presentations may be vague and nonspecific; "classic presentations" of disease are less likely in older patients. The differential diagnoses in the older adult are often expanded to included illnesses, such as mesenteric ischemia, aortic stenosis or giant cell (temporal) arteritis, that are not often seen in younger patients. Confounding chronic comorbidities, such as congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease, add to the complexities of evaluation and treatment. Adverse effects of home medications should be considered as a possible cause of their ED visit, especially for presentations of falls or altered mental status.

Cognitive impairment may impact obtaining an accurate history, performing a diagnostic evaluation, and designing a treatment and disposition plan. Corroborating sources of information, especially from caregivers are often needed to obtain a full and accurate history. Cognitive impairment may make sending the patient home potentially more dangerous, particularly if the patient is in the ED unaccompanied. Attention to transitions of care with an evaluation of home and

BOX 178.1 Comprehensive Geriatric Assessment (CGA) Elements Important for ED Assessment

- Functional status
- Cognition
- Mood
- Comorbidities
- Polypharmacy and medications
- Fall risk
- Home situations and social supports

social supports is often needed. However, hospitalization poses its own risks in that it is associated with increased rates of delirium, nosocomial infections, iatrogenic complications, and adverse drug reactions. It is common for admitted older patients to have a loss of one or more of their basic activities of daily living (ADLs) with a permanent impairment occurring in up to 40% of these patients.

SPECIFIC ISSUES AND DISORDERS

Comprehensive Geriatric Assessment

The common multifactorial issues that affect older adults including chronic medical conditions, polypharmacy, cognitive problems, mobility and functional deficits, as well as psychosocial issues, are referred to as "geriatric syndromes." The Comprehensive Geriatric Assessment (CGA) (Box 178.1) is a multidisciplinary diagnostic and intervention process that identifies and addresses these issues that plague older adults.[1] This approach addresses the complex geriatric syndromes while keeping in mind the patient's goals of care, in an effort to improve the quality of life.

A complete CGA is time-consuming and not practical to be routinely performed for all older ED patients by busy emergency clinicians. However, identification of high-risk older adults may help target further evaluations and interventions and improve disposition planning. Widely disseminated geriatric ED guidelines recommend screening for high-risk patients.[2] CGA in the ED has been linked to reduced need for hospitalization without an increase in mortality, thus reducing exposure of the patient to the hazards of hospitalization. The use of CGA adapted to the ED is an active area of research that will facilitate safe and efficient care for the older adult.[3]

Cognitive Deficits: Delirium and Dementia

Older patients more often have cognitive, functional, and sensory impairments or depression that limit their ability to communicate. These conditions complicate the evaluation and management of older adults and may be underappreciated and underrecognized. Patients with cognitive dysfunction are less able to provide an accurate reason why they are in the ED and less able to comprehend discharge instructions. Patients and caregivers may have difficulties recalling all the details of a long and complex history or multiple medications; therefore, careful review of medical records and medication lists are important adjuncts to the history. Routine performance of a cognitive assessment in older patients is a geriatric quality indicator for EDs.

Delirium

Delirium, an acute confusional state with alterations in cognition and attention, occurs in 10% to 20% of older ED patients. Unfortunately, emergency clinicians miss recognizing delirium up to 75% of the time, especially with the hypoactive subtypes of delirium. There are several brief assessment tools available, including the well-established Confusion Assessment Method. The Delirium Triage Score with brief CAM (DTS and bCAM) is highly recommended for ED use (Fig. 178.1).

Delirium is generally caused by decreased neurologic reserve plus one or more acute precipitants, such as infection, metabolic abnormalities, and acute coronary syndromes. Delirium and dementia are sometimes difficult to distinguish from one another, but the distinction is important because the presence of delirium should lead to concern for a potentially life-threatening medical emergency. Inattention or the inability to sustain focus is a key feature of delirium. Patients with underlying dementia are at high risk for development of delirium and recognition of delirium is even more difficult in patients with dementia. Older ED patients with delirium have higher intensive care unit (ICU) admission, 30-day mortality and 30-day readmission rates.

Dementia

Studies that have universally screened older ED patients found rates of dementia of about 35%, mostly previously undiagnosed. *Dementia* is an umbrella term for chronic disorders causing impairment in two or more cognitive domains (i.e., memory loss, language, motor activity, object recognition, and disturbance of executive function). Although dementia would ideally be diagnosed by primary care physicians, this is not the norm. Detection of dementia by emergency clinicians allows a baseline cognitive status to be documented in the record and prompts patient and family to seek definitive evaluation for prognosis and planning. Most importantly, early recognition prompts additional history seeking from family and other collateral sources. Older adults with dementia are more likely to visit the ED and one recent study found that dementia is a predicator of 30-day ED revisits.[4]

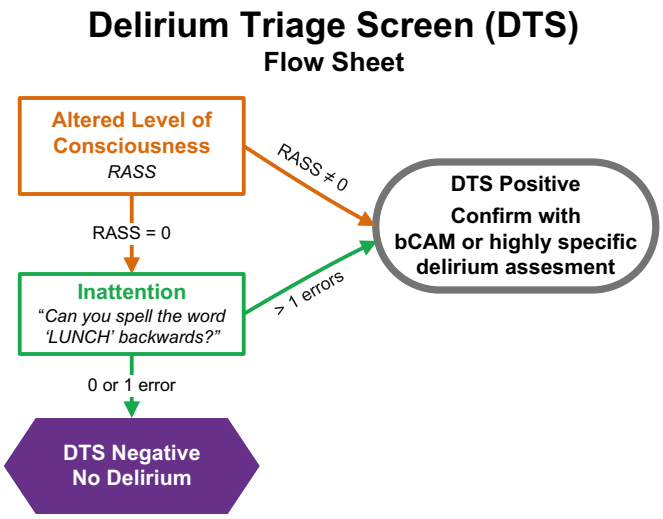
Functional Decline, Vulnerability, and Frailty

Functional status is an important element in the evaluation of older ED patients and predicts short-term, repeat ED visits. Formal functional assessments, including ADLs and instrumental activities of daily living (IADLs), are important (Table 178.1) in that a sudden functional deterioration may be the only manifestation of an acute illness.

Vulnerability screening and risk assessment tools have been developed and utilized to sort out those elderly at highest risk in order to target them for further assessments and/or interventions. The Identification of Seniors at Risk (ISAR), Triage Risk Screening Tool (TRST) and the interRAI are vulnerability screening tools utilized in the ED setting. We recommend using the ISAR tool, which incorporates elements of cognitive impairment and functional decline together to estimate risk (Box 178.2). One study demonstrated that a high/positive ISAR score was associated with an increased risk of 30-day ED re-visits.[5]

Frailty

Older patients are a heterogeneous group and biologic age is not the same as chronologic age. Frailty is a geriatric syndrome or condition in which there is marked decrease in physiologic reserve and resilience. Frail patients have multidimensional failure involving several different organ systems. The stress of illness or injury places them at very high risk for adverse outcomes and mortality. Patients with frailty have higher resource utilization and are more likely to need placement in a skilled nursing facility. Frailty identification is used routinely in geriatric medicine and used for outcomes prediction in surgery and oncology. There is no gold standard for defining frailty, but several tools have been developed for clinical and research purposes.[6] The FRAIL Scale (Table 178.2) is a short 5-item screening instrument that requires no measurements. The Clinical Frailty Scale (Fig. 178.2) is a 9-point scale



RASS, Richmond Agitation-Sedation Scale

Instructions on using the Delirium Triage Screen

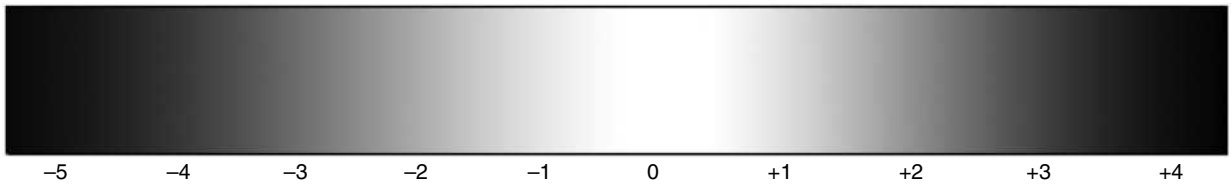
The Delirium Triage Screen (DTS) was developed to rapidly rule-out delirium and reduce the need for formal delirium assessments. It takes less than 20 seconds to perform and consists of two components:

1) Level of consciousness as measured by the Richmond Agitation Sedation Scale (RASS).
2) Inattention by spelling the word "LUNCH" backwards.

If the patient has a RASS of 0 (normal level of consciousness) and makes 0 or 1 errors on "LUNCH" backwards spelling test, then the DTS is considered negative. Because the DTS is 98% sensitive, delirium is ruled out in this case and no additional delirium testing is needed. If the patient has a RASS other than 0 (altered level of consciousness) or makes 2 or more errors on the "LUNCH" backwards spelling test, then the DTS is considered positive. Because the DTS is 55% specific, confirmatory testing is needed using the bCAM, 3D-CAM, CAM or 4AT to rule in delirium.

Han JH, Wilson A, Vasilevskis EE, Shintani A, Schnelle JF, Dittus RS, Graves AJ, Storrow AB, Shuster J, Ely EW. Diagnosing delirium in older emergency department patients: validity and reliability of the delirium triage screen and the brief confusion assessment method. *Ann Emerg Med.* 2013; 62(5):457-465.

A



RASS	–5	–4	–3	–2	–1	0	+1	+2	+3	+4
	Unarousable No response to voice or physical stimulation	**Arousable to pain only** No response to voice, but responds to physical stimulation	**Severely drowsy** Responds to voice, but does not make eye contact	**Moderately drowsy** Responds to voice, but can only make eye contact for < 10 seconds	**Slightly drowsy** Responds to voice and can make eye contact for > 10 seconds	**Alert and calm**	**Restless** Anxious, but movements not aggressive	**Agitated** Frequent, non-purposeful movement	**Very agitated** Pulls or removes tubes or catheters, aggressive	**Combative** Overtly combative, violent, danger to staff

B

Figure 178.1 Delirium screen: combined (A) RASS, (B) DTS.

Continued

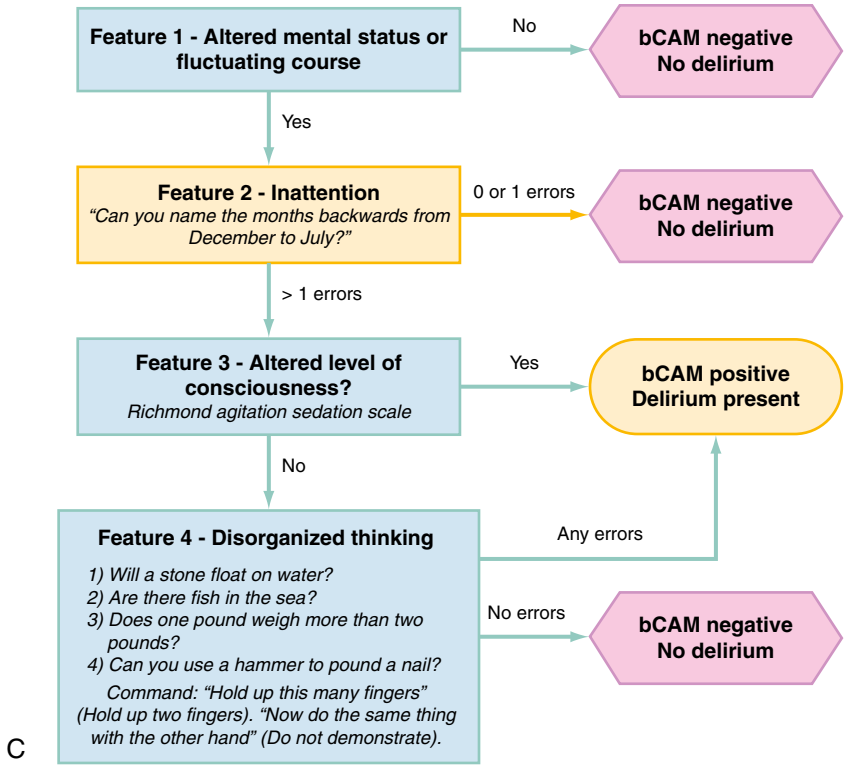


Figure 178.1 cont'd (C) bCAM. (A, From RASS, Richmond Agitation-Sedation Scale. Copyright 2012. Vanderbilt University; B, Han JH, Wilson A, Vasilevskis EE, et al. Diagnosing delirium in older emergency department patients: validity and reliability of the delirium triage screen and the brief confusion assessment method. *Ann Emerg Med*. 2013; 62(5):457-465. From Vanderbilt University, Nashville, TN. Copyright 2012; C, From Vanderbilt University, Nashville, TN. Copyright 2012; Adapted from: Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21):2703-2710; and Hospital Elder Life Program: Confusion assessment method (short CAM). https://help.agscocare.org/. © 2016. All rights reserved.)

TABLE 178.1 Functional Assessment

Activities of Daily Living	Instrumental Activities of Daily Living
Bathing & grooming	Shopping
Getting dressed	Preparing meals
Transferring into/out of bed/chair	Housework
Maintaining continence	Laundry
Using the toilet	Using transportation
Eating	Using phone
	Managing medications
	Managing finances

Adapted from: Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 21;185:914-9, 1963; Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 9(3):179-86,1969.

BOX 178.2 Identification of Seniors at Risk (ISAR) Tool

1. Before the illness or injury that brought you to the emergency department, did you need someone to help you on a regular basis? (yes)
2. Since the illness or injury that brought you to the emergency department, have you needed more help than usual to take care of yourself? (yes)
3. Have you been hospitalized for one or more nights during the past 6 months (excluding a stay in the emergency department)? (yes)
4. In general, do you see well? (no)
5. In general, do you have serious problems with your memory? (yes)
6. Do you take more than three different medications every day? (yes)

Each "yes" response ("no" for question 4) counts as 1 point, for a total score ranging from 0 to 6. A patient is considered at high risk when the score is 2 or more.

Adapted from: McCusker J, Bellavance F, Cardin S, et al. Detection of older people at increased risk of adverse health outcomes after an emergency visit: the ISAR screening tool. *J Am Geriatr Soc*. 1999;47:1229-1237.

TABLE 178.2 FRAIL SCALE

F	Fatigue ("Have you felt fatigued? Most or all of the time over the past month?") Yes = 1, No = 0
R	Resistance ("Do you have difficulty climbing a flight of stairs?") Yes = 1, No = 0
A	Ambulation ("Do you have difficulty walking one block?") Yes = 1, No = 0
1	Illnesses ("Do you have any of these illnesses: hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease?") Five or greater = 1, fewer than 5 = 0
L	Loss of weight ("Have you lost more than 5 percent of your weight in the past year?") Yes = 1, No = 0
	Frail scale scores range from 0 to 5 (0 = best, 5 = worst) and represent frail (3 to 5), pre-frail (1 to 2), and robust (0) health status.

Data from: Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* 2012;16:601; and Woo J, Yu R, Wong M, et al. Frailty screening in the community using the FRAIL Scale. *J Am Med Dir Assoc.* 2015;16:412.

with scoring assigned based on clinical judgement. Both scales have been successfully used in the EDs, however further studies are needed to determine impact.

Goals of Care, Transitions of Care, and Palliative Care

Transitions in Care

Older patients undergo more transitions of care than younger patients. These transitions include home to ED, nursing home to ED, ED to inpatient, ED to nursing home, and ED to home. Transitions of care can be a risky period for patient safety; frail older patients are particularly vulnerable due to the complexity of their medical conditions and needs. Poor communication during transitions of care may result in adverse outcomes as a result of medication errors, adverse drug events, unnecessary treatments and hospitalizations, and lack of timely coordination of follow-up care. A number of groups, including the American College of Emergency Physicians, have identified management of transitions in care as a quality gap in emergency medicine and have advocated for greater vigilance around these transitions.

Depending on local resources, social work and/or case managers can help facilitate safe care transitions. They can identify psychosocial and financial needs, provide home safety assessments, transportation assistance, assistance in obtaining durable medical equipment, referrals for home care services, and access to community resources such as senior centers and meal delivery programs. Many transitional

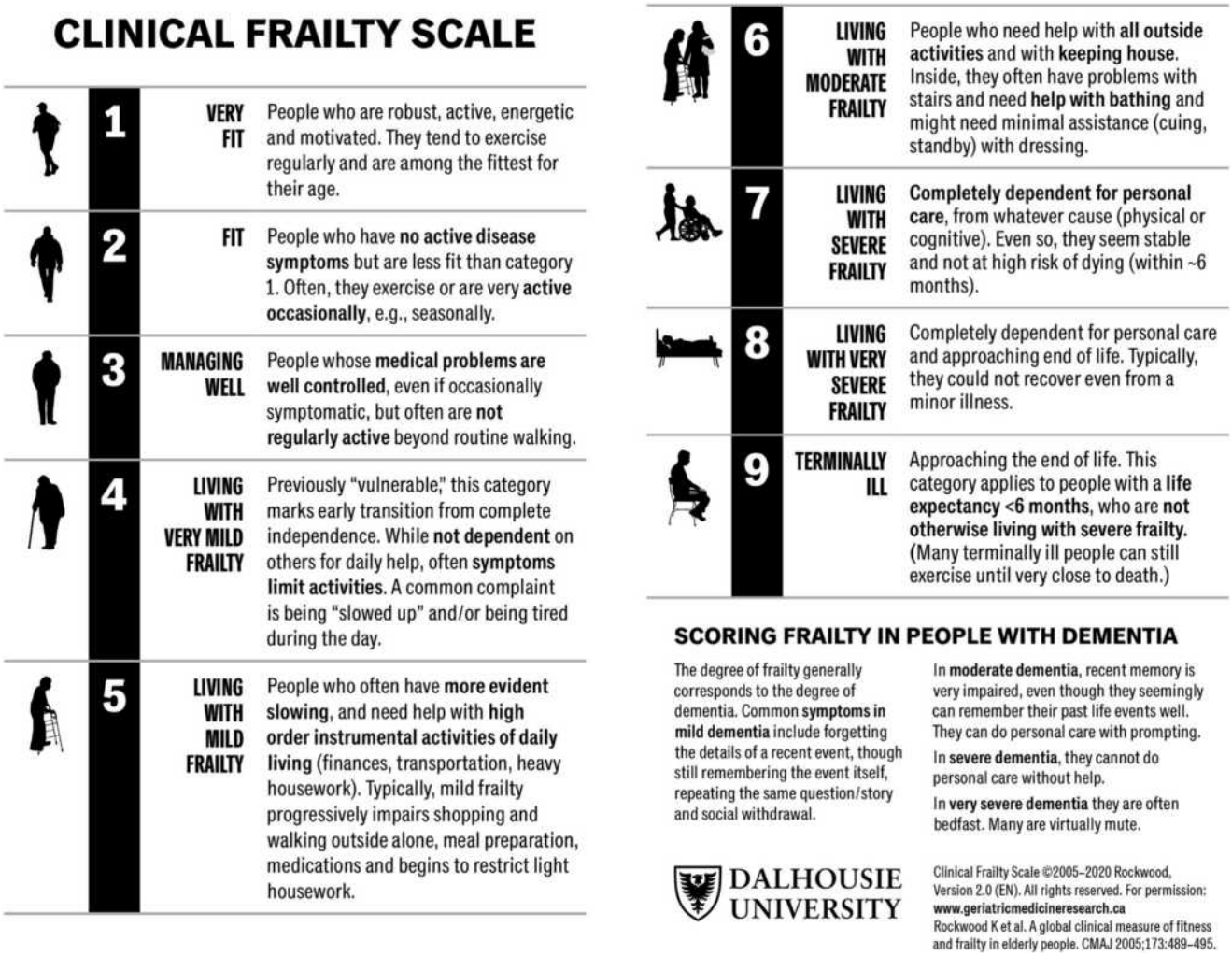


Figure 178.2 The Clinical Frailty Scale. © 2007–2009. Version 1.2. All rights reserved. Geriatric Medicine Research, Dalhousie University, Halifax, Canada.

care models include rapid telephone follow-up post-ED discharge to reinforce adherence to instructions, identify needs, and assist with follow-up referrals. The use of a dedicated transitional care nurse was studied and found to be effective to reduce risk of inpatient admission and 30-day readmission.[7]

Goals of Care and Palliative Care

Older patients with advanced and end-stage disease frequently present to the ED with repeat visits. A patient-centered approach utilizing shared decision making to determine goals of care is especially important for older patients, with a balanced discussion on the benefits and harms of care.[8] Quality of life versus length of life preferences will vary by individual and also by the specifics of a particular situation.

For patients with advanced life-limiting disease, the role of the emergency clinician is a combination of curative care, such as infection management, and palliative care, with a focus on quality of life and symptom management. End-of-life frequent complaints include pain, dyspnea, anxiety, agitation and delirium, constipation, pruritus, excessive oral secretions, stomatitis and nausea, vomiting, and diarrhea. Prognostication in the ED setting is challenging, as is communication with patients and families regarding goals of care in an inherently fast-paced ED environment. However, these interventions are nonetheless necessary and the benefits of palliative care include improved patient satisfaction, reduced length of stay, cost savings, and improved outcomes.[9]

Nonspecific Complaints and Atypical Presentations

Unfortunately, the classic model of medical diagnosis, in which signs and symptoms are evaluated, tabulated, and formulated into a specific diagnosis, is not sufficient for older patients. Nonspecific complaints and atypical presentations are common in older patients, which makes arriving at a diagnosis challenging. Chief complaints such as generalized weakness, fatigue, or dizziness are consistently among the top presenting complaints for older ED patients. Sometimes patients complain that they "just don't feel well" and family or caregivers may complain that the patient "just isn't their normal self." Compounding the challenge is the fact that many patients who present with nonspecific complaints develop a serious condition within 30 days (e.g., infections, metabolic abnormalities, and malignancies.) One-third to one-half of older patients in the ED have atypical presentations of illness.[10]

Acute Coronary Syndrome

Cardiovascular heart disease is the leading cause of death in men and women older than 65 years. Older patients with acute coronary syndrome (ACS) have higher associated morbidity and mortality, and older age is an independent risk factor for mortality after both ST elevation myocardial infarction (STEMI) and non-STEMI. An accurate clinical assessment for older patients is needed, as well as an optimal therapeutic strategy, taking into consideration the patient's quality of life and goals of care.

The incidence of the "classic" symptoms of ACS diminishes with increasing age. Chest pain at presentation with STEMI occurs in only about 50% of patients who are 85 years or older. Atypical presentations of ACS occur more often in older patients who are more likely to present with dyspnea, syncope, diaphoresis, shoulder or back pain, abdominal pain, weakness, fatigue, and/or delirium. One-third of women older than 65 years with acute myocardial infarction present with abdominal pain alone. As a result, the diagnosis of ACS may be delayed, and older patients may present instead with delayed complications, such as acute congestive heart failure. Consideration should also be made to other conditions that are more prevalent in the elderly, including severe aortic stenosis, aortic dissection, and pulmonary embolism.

Acute heart failure at presentation occurs in nearly 50% of STEMI patients 85 years or older compared to only 1.7% of STEMI patients younger than 65 years. Myocardial ischemia impairs left ventricular relaxation, which leads to an increase in left ventricular end-diastolic pressure (LVEDP). This increased LVEDP, superimposed on age-related decreases in left ventricular compliance, frequently results in elevated pulmonary capillary wedge pressure and heart failure.

Current evidence supports an early invasive approach over conservative treatment for both non-STEMI and STEMI. American Heart Association (AHA) guidelines recommend no absolute age restrictions for revascularization therapy for non-STEMIs and STEMIs. However, older patients often do not receive as aggressive treatment, including early referral for cardiac catheterization, as their younger counterparts and are less likely to receive ACS care according to recommended guidelines.[11] The evidence to inform optimal care for elderly patients is limited. Despite the high prevalence of ACS and its higher morbidity and mortality in older patients, they were excluded and underrepresented in earlier randomized controlled trials of ACS. The After Eighty Study specifically targeted patients over 80 years of age with non-STEMI and unstable angina. The results demonstrated superior outcomes for an early invasive approach compared with conservative strategy for clinically stable octogenarians but were inconclusive for patients over 90 years of age.[12]

Syncope

Patients 65 and over with syncope are more likely to have a serious etiology than younger patients, with almost half of these patients ultimately being diagnosed with a cardiac condition, including dysrhythmias, valvular heart disease, acute coronary syndrome, and aortic dissection. Medication effect and results of polypharmacy (i.e., multiple drug interaction) is yet another concern.

In older patients, syncope should be considered as a possible etiology of any unexplained fall, and the elderly are more susceptible to serious injury. Amnesia may confound the evaluation. Vasovagal syncope in the elderly is less likely to have a prodrome. Orthostatic hypotension is more common in older patients due to reductions in baroreflex responsiveness, cardiac compliance, and attenuation of the vestibulosympathetic reflex.

Abdominal Pain

Older ED patients with acute abdominal pain are at increased risk of having a surgical condition and of dying. Presentations may be deceptively subtle, including the lack of rebound tenderness or guarding on abdominal palpation, despite serious intra-abdominal pathology. Etiologies of abdominal pain that are not intra-abdominal processes should also be considered in the differential diagnosis (e.g., myocardial ischemia or infarction, pneumonia, and herpes zoster).

Several factors in older patients that can complicate the ability to make a diagnosis based on the history and physical examination alone, include altered pain perception, aging effects on the immune system, medications that limit tachycardic response to stress, and decreased ability to mount a febrile response to infection. Additionally, sometimes older patients may present only with nonspecific generalized symptoms such as delirium, malaise, or dizziness when the cause is an acute abdominal condition. Laboratory values are frequently normal, despite the presence of surgical disease. There should be a low threshold for imaging, particularly computed tomography (CT).

Vascular disease increases with age and vascular emergencies remain some of the most time-sensitive and highly morbid causes of abdominal pain in the older patient. Abrupt onset symptoms are a red flag. Although the diagnosis of a ruptured abdominal aortic aneurysm

(AAA) may be fairly straightforward in the older patient who has abdominal pain, hypovolemic shock, and a pulsatile abdominal mass, most patients lack this triad at presentation. AAA is commonly misdiagnosed as acute renal colic, and any older patient presenting with symptoms of new-onset nephrolithiasis should have imaging to evaluate the aorta for AAA. Acute mesenteric ischemia is a disease of older adults and an important consideration in the differential diagnosis of abdominal pain. It is a more common etiology than appendicitis or AAA complications in patients over age 75.[13] Superior mesenteric artery occlusion is the most common cause of acute mesenteric ischemia. Risk factors for mesenteric ischemia include cardiac arrhythmias, atherosclerosis, and prothrombotic conditions such as infection.

Biliary tract disorders are the most common cause of abdominal pain in the older adult, with the incidence of gallstones increasing with age. Cholecystitis is the most common indication for abdominal surgery in the older patient. About one-third of older patients with cholecystitis have no fever or leukocytosis. Additionally, about one-third of older adults with acute cholecystitis will present with minimal abdominal pain and an absence of peritoneal signs. Due to the poor vascularity of the gallbladder, older patients are at increased risk of complications such as perforation and emphysematous cholecystitis. Additional complications seen more often in the elderly include bile stone ileus, pancreatitis and choledocholithiasis.

Appendicitis is the third most common indication for abdominal surgery in the older patient population. Older patients have a higher incidence of perforation and mortality due to much higher rates of delayed diagnoses and/or presentations. Appendicitis historically has been misdiagnosed half of the time in older adults because many patients lack fever, anorexia, or leukocytosis. One-quarter of older patients have no right lower quadrant pain at all.

Peptic ulcer disease (PUD) is more prevalent in older adults due to increased use of nonsteroidal antiinflammatory drugs and to increased *Helicobacter pylori* infections. Abdominal pain is lacking in approximately 30% of elderly patients with PUD. Complications of bleeding and perforation result in higher mortality rates in older patients. Diverticulitis and bowel obstructions are also more prevalent in older adults. Tumors are a cause of large bowel obstructions in older patients. Hernias should be considered in older patients with possible bowel obstruction, and they should be examined for hernias, especially those with significant cognitive deficits who may not realize or neglect to mention their presence.

Infections

As with other conditions, infections in the elderly often present atypically. Older patients with infection are less likely to have vital sign abnormalities of fever or tachycardia. Although fever of 38.0°C or higher is strongly associated with bacterial infection, the sensitivity is low with fever present in 12% to 25% with pneumonia and 20% with urinary tract infection (UTI).[14] Elevation in white blood cell count is similarly not a sensitive marker of infection with 20% to 45% of patients subsequently found to have bacteremia lacking leukocytosis. Older patients with pneumonia or UTI are less likely to have localizing symptoms. Further confounding the difficulty of diagnosing an infection is that asymptomatic bacteriuria is common in older patients. Distinguishing asymptomatic bacteriuria from UTI is challenging especially in older cognitively impaired adults.

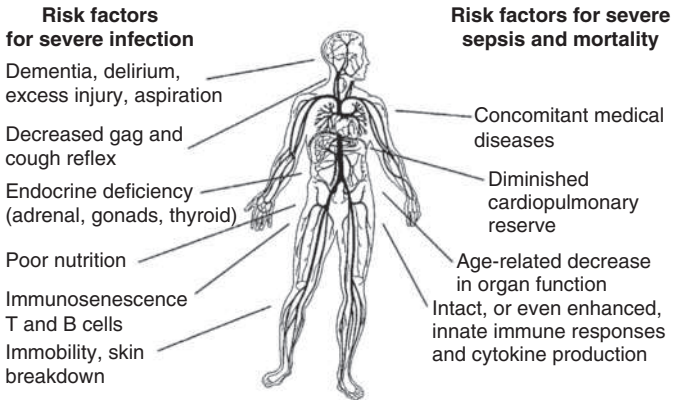


Fig. 178.3 Predisposing factors for sepsis in older individuals. (From: Girard TD, Opal SM, Ely EW. Insights into sepsis in older patients: from epidemiology to evidence-based management. *Clin Infect Dis*. 2005;40:719-727.)

Older patients experience an increased incidence of severe infection and severe sepsis with advanced age. Mortality from sepsis approaches 40% for patients older than 85 years. Aging effects on immunity include a decline in cell-mediated immunity and antibody production. Older patients may also have multiple risk factors for sepsis (Fig. 178.3) including comorbid diseases, exposure to instrumentation, malnutrition, and institutionalization.

With aging, the ability to generate a fever in response to pyrogens is decreased. Because of this blunted fever response, and because medication use or cardiac disease may limit tachycardic response to infection, older patients may have systemic inflammatory response syndrome (SIRS)–negative sepsis. Abnormal triage vital signs in adults 75 years and older have poor sensitivity (73%) and specificity (50%) for predicting death or ICU admission. Emergency clinicians must look more broadly than just the typical SIRS criteria to suspect and diagnose sepsis accurately.

Management of suspected sepsis in older patients is similar to that for younger patients, with an emphasis on early identification of sepsis, fluid resuscitation, and early and appropriate antibiotics. Just as with younger adults, older patients with sepsis have improved mortality with comprehensive sepsis treatment. Older patients are more dependent on having an adequate preload to increase cardiac output in response to sepsis because the ability to raise the heart rate is blunted. However, aging-associated diastolic dysfunction is common, and fluid resuscitation goals may need adjustment if patients develop hypoxia or hypervolemia. In regard to the choice of empirical antibiotics, sepsis in older patients compared to younger patients is more likely to be due to respiratory or genitourinary infections, with pneumonia as the single most common cause of sepsis.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 178–QUESTIONS AND ANSWERS

1. An 80-year-old female with history of COPD and arthritis comes to the ED following an episode of loss of consciousness while seated at the table after eating lunch. The patient and her husband, who witnessed the event, deny any symptoms prior to the event and deny any recent illness or symptoms. Her vitals are normal, and her physical exam is unremarkable. Which of the following is the most likely etiology of the syncopal episode?

a. Cardiac event
b. Cerebrovascular accident
c. Infectious process
d. Hypoglycemic reaction

Answer: A. Syncope is more likely to have a serious etiology in older adults, with 40% ultimately found to have a cardiac etiology. Hypoglycemia is highly unlikely because she does not have diabetes and just ate lunch. Cerebrovascular accident and infection are potential causes of syncope but are much less likely given that she has been well, asymptomatic, and her examination is normal.

2. Which of the following is a key feature of delirium that helps differentiate it from dementia?

a. Use of inappropriate language with swearing
b. Inability to correctly name the current date
c. Physical agitation with combativeness
d. Inability to focus or maintain attention

Answer D. Delirium and dementia can be difficult to diagnose and can exist together, with dementia being a predisposing factor to the development of delirium. A key feature of delirium is inattention with the inability to maintain focus. Confusion with the inability to name the current date, agitated behavior with combativeness, and the use of inappropriate language with swearing can all be seen in both dementia and delirium and therefore do not help with differentiation.

3. The presentation of infection in older patients differs from the presentation in younger patients. Older patients are more likely to have which of the following?

a. Elevated inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein
b. Fever
c. Left shift of the white blood cells
d. Normal white blood cell count

Answer: D. Older patients are more likely to have a normal white blood cell count, as well as a normal differential. They are less likely to have fever and signs or symptoms from the infection process. They are more likely to have complications and suffer long-term morbidity or mortality.

4. Which of the following statements is true regarding acute myocardial infarction (AMI) in older adults?

a. Atypical presentations portend a more benign course.
b. Atypical presentations increase with age.
c. Painless AMIs occur more commonly in men.
d. The absence of chest pain is rare.

Answer: B. Atypical presentations of AMI increase with age and are of equal severity as typical cases. Women have painless presentations more than men, and present with abdominal pain almost one-third of the time. The absence of chest pain is not uncommon.

5. A 74-year-old man with a history of hypertension and hyperlipidemia presents to the ED with acute onset of severe, nontraumatic, left flank pain. His vital signs include a heart rate of 72 beats/min and blood pressure of 120/70 mm Hg. Which approach to his care would be most appropriate?

a. Arrange for him to be in the observation unit overnight for serial abdominal examinations to help clarify his diagnosis.
b. Consider abdominal aortic aneurysm only after the patient's urinalysis and renal ultrasound are negative for nephrolithiasis.
c. Diagnose him with nephrolithiasis without any further testing.
d. Evaluate for a possible abdominal aortic aneurysm.

Answer: D. Vascular disease prevalence increases with age. Vascular emergencies remain some of the most time-sensitive and highly morbid causes of abdominal pain in the older patient and should always be considered first, particularly for abrupt-onset symptoms.

Geriatric Trauma

Lauren T. Southerland and John J. Fath

KEY CONCEPTS

- Do not let a low-impact mechanism, patient cognitive impairment, or vital signs within the range of normal reduce your pretest probability of significant injury in an older patient.
- Age-specific trauma alert criteria improve the care of injured older adults.
- Vital signs, including tachycardia and hypotension, are unreliable to detect hemodynamic instability in older adults. Ultrasound is a helpful tool to assess volume status in the older trauma patient.
- Older patients are at high risk of hypothermia and develop pressure ulcers more rapidly than younger patients. Unnecessary spinal immobilization (cervical collars and backboards) causes pressure ulcers, respiratory distress, and delirium in this population.
- Clinical decision tools for radiographic imaging have generally excluded older patients. A low threshold for imaging should be used for older adults with trauma, and computed tomography (CT) should be used as the primary modality, except for extremity imaging.
- Falls are the leading cause of injury-related death in older adults, and ground-level falls can result in major injuries. Assessing the patient's future fall risk, home safety, and home resources is important prior to leaving the ED or hospital.
- Rib fractures and pulmonary contusions are associated with poor outcomes in older patients. ICU care should be considered for those with two or more rib fractures or pulmonary contusions.
- Older adults with hip fractures have improved survival on a dedicated orthogeriatric service. Consider transfer of patients to hospitals where these services are available.
- Routinely screen for elder abuse. A valid screening question is: "Has anyone close to you tried to hurt you or harm you recently?" Another query is: "Does anyone at home scare you or threaten you?"
- All older adults with fractures should be assessed for osteoporosis/osteopenia, and malnutrition as leaving this untreated reduces healing and increases morbidity and mortality.

FOUNDATIONS

Older adults make up a growing proportion of trauma patients in emergency departments (EDs). Although the general principles of trauma care for younger adults apply to older adults, there are special considerations for the older trauma patient from the initial decision to activate the trauma team through injury management and disposition.

Background and Importance

There is no standard definition of the term *geriatric trauma* in the literature; studies vary in their age criteria. In this chapter, unless noted, we are referring to patients 65 years and older. In 2016, older adults accounted for almost 13% of all injury-related ED visits in the United States, and this percentage is expected to increase with the aging of the population. Currently, unintentional injury is the sixth leading cause of death among older adults, and falls are the most common cause. Given the same mechanism of injury, older adults sustain more severe injuries than younger adults. Even low-energy mechanisms can cause morbidity and mortality. Managing these patients appropriately requires a holistic, multidisciplinary approach as recommended by the American College of Surgeons' Geriatric Trauma Management Guidelines, the Eastern Association for the Surgery of Trauma Practice Management Guidelines for Geriatric Trauma, and the Geriatric ED Guidelines. These guidelines incorporate geriatric principles into the care of the injured older adult from the trauma alert through the initial Advanced Trauma Life Support (ATLS) assessment, imaging decisions, and injury management.

SPECIFIC ISSUES

Age as a Trauma Triage Criterion

Trauma activation and/or transfer to a trauma center improves outcomes for older adults. Treatment at a trauma center reduces mortality in the first 7 days after injury (hazard ratio 0.62).[1] However, injured older adults are less likely to be transported to a trauma center either by emergency medical services (EMS) or by a referring hospital.[2] Traditional trauma triage criteria are less sensitive to the presenting signs and symptoms of older adults. For example, confusion could represent a baseline mental status or be a sign of acute traumatic brain injury (TBI). Medication effects such as anticoagulation must also be considered. Trauma triage criteria specific for older adults have been developed with age limits for triage criteria ranging from 55 years to 77 years. The most researched age-specific trauma criteria at this time is the Ohio Prehospital Geriatric Trauma Triage Criteria, which incorporates an age limit of 70 years old or older with additional mechanisms of fall and pedestrian struck by motor vehicle.[3] Pedestrians older than 50 years old who are struck by a motor vehicle have a mean Injury Severity Score 9 points higher than younger adults, which is why this mechanism is part of geriatric trauma triage criteria. These criteria increase sensitivity from 61% to 93%, reducing the under-triage of older adults.

Mechanisms of Injury

Falls are the leading mechanism of injury and the leading cause of injury-related death in older adults. Most falls are from standing and occur at the place of residence; 12% of community-dwelling older adults fall each year. Traditional trauma criteria include a fall from a significant height or down a full flight of stairs, but for older adults a fall from standing or even out of a chair has an associated risk for injury. Mortality from a ground-level fall is only 0.1% for younger adults, but 4% to 5% for older adults.[4] The next most common injury mechanism is motor vehicle collisions. A detailed crash history is important, and single-vehicle crashes should raise the suspicion that a medical problem

Fig. 179.1 Pressure damage to the skin occurs most frequently over bony prominences. This image shows pressure damage to the knee and thigh of an older man after being on the floor for several hours after a fall

caused the crash (e.g., syncope, myocardial infarction, stroke). An evaluation for coincident events leading to trauma should be undertaken during the ATLS trauma evaluation.

Thermal injuries, elder abuse/neglect, and self-injury are less common but are also important injury mechanisms. Burns can require significant wound care and recovery time which may be difficult for older adults to manage. In one multicenter study of older adults with a burned body surface area of 10% or greater, inpatient mortality was 25% and of the survivors, 15% required inpatient rehabilitation and 18% to 50% needed skilled nursing facility placement at discharge.[5] Burns, head and neck injuries, and delayed injury presentation are also all suspicious for elder abuse. Elder abuse is a complex problem (see Chapter 181). The secondary exam should include a full skin and genital exam and thorough documentation of any injuries. The Geri-IDT (Geriatric Injury Documentation Tool) can be helpful in guiding this assessment.[6]

A final concerning mechanism in geriatric trauma is self-injury. Older adults have a higher likelihood of completing suicide attempts than any other age group. Risk factors include recent bereavement, decreasing functional status, and increasing burden of disease. They are less likely to present with a chief complaint of depression/suicidality and less likely to receive mental health care in the ED.

Pathophysiology of Aging Affects Both the Injuries Sustained and the Recovery

Although older adults in a good state of health have sufficient reserves to accomplish activities of daily living, when they are stressed by acute trauma and the subsequent response to injury, the decrease in physiologic reserve can lead to rapid progression of tissue hypoperfusion and organ failure. In a trauma registry study out of Germany, 30% of older trauma patients experienced sepsis, 20% had multiple organ failure, and 45% had cardiovascular failure.[7] Renal function also decreases with age and can be misrepresented by assessing creatinine clearance. Serum creatinine is a muscle breakdown product; in an older adult creatinine clearance can appear artificially normal due to decreased overall muscle mass.

Skin changes predispose to skin tears, poor wound healing, and pressure ulcers (Fig. 179.1). Backboards and cervical collars placed during a trauma activation can lead to skin injury. In one study, trauma patients had a median time in a cervical collar of 117 minutes, 78% developed pressure damage to the skin, and 28% developed severe indentations.[8] A final area of concern in older adults is age-related changes in the inflammatory and pain responses. Older adults have higher pain thresholds and reduced sensitivity to some types of painful stimuli. Decreases in the functionality of their white blood cells result in muted inflammatory responses and a lack of peritoneal abdominal signs on exam. In the older trauma patient, any abdominal tenderness is concerning for significant intra-abdominal injury.

Comorbidities

Older adults with polytrauma and a single comorbidity have 5.5 times higher risk of death than those without preexisting conditions. Comorbidities also increase the risk of injury by contributing to falls and impaired driving. Comorbidities complicate the evaluation process by impeding the ability to obtain an accurate history and interpret the physical exam. A patient with a blood pressure of 120/80 may be severely volume depleted if their normal systolic blood pressure is 150 due to hypertension. Table 179.1 provides examples of the effects various comorbidities can have on the evaluation and treatment of older adults following trauma.

Medications

A patient's daily medication regimen can increase the risk of a trauma and risk of death from an injury, obfuscate the clinical exam, and require changes in management and treatment of injuries. Medications also alter the response to resuscitative measures. A full medication review is essential for injured older adults with attention to specific drug classes (Table 179.2). Among older adults in a Canadian trauma registry, 30-day mortality increased by 24% for each medication a patient was taking. If the medication was potentially inappropriate based on the American Geriatrics Society Beers Criteria, the risk of death doubled.[9] Medication reconciliation in the setting of trauma is thus a matter of life and death. The most time-critical issue is the use of anticoagulation. Trauma patients on preexisting anticoagulation, regardless of type, have higher rates of complications and higher transfusion needs.[10] An "anticoagulation alert" system for older adult trauma activations may reduce mortality from injuries.

ATLS Assessment

A systematic trauma assessment per ATLS guidelines should be conducted in older adults (see Chapter 32). One change to the airway, breathing, circulation, disability mnemonic is to consider circulation alongside airway. Post intubation hypotension is more likely in older patients and 30% of these patients will die. Consideration should be given to resuscitation to restore perfusion prior to or concomitant with securing the airway.

Airway

Because older patients are likely to have multiple risk factors for a difficult airway, emergency clinicians should perform a systematic airway assessment. Early intubation is indicated for unstable patients, as defined by signs of shock, altered mental status, and significant chest trauma. However, this population is more likely to have advanced directives or other care planning documentation that should be consulted prior to intubation. Bilevel positive airway pressure (BIPAP) or high-flow oxygen may be used as temporizing measures while the goals of care are discussed.

If intubation is required, video laryngoscopy is recommended. Up to 30% of older trauma patients will require multiple intubation attempts. Consider sedation with ketamine to maintain the respiratory response and blood pressure (see Chapter 1). Etomidate is a second choice, as it is also not associated with significant hypotension, unlike propofol which may cause hypotension. We recommend rocuronium

TABLE 179.1 Comorbidities Common in Older Adults and Their Effects on the Evaluation and Management of the Patient After a Traumatic Injury

Comorbidity	Effect (*Contributing to Trauma, –Complicating the Trauma Exam, +Complicating Injury Management)
Cardiovascular disease	*Acute coronary syndrome may cause a fall or motor vehicle accident. –Higher risk of dissection with blunt chest trauma –Decreased peripheral perfusion from peripheral vascular disease +Risk of acute coronary syndrome from the catecholamine surge of trauma +Predisposed to pulmonary edema with large IV fluid boluses
Chronic kidney disease	+Need to decrease opioid and antibiotic doses and monitor for toxicity +More susceptible to volume depletion due to inability to concentrate the urine to conserve fluids +More susceptible to shock-induced acute on chronic kidney injury
Chronic lung disease	–Decreased pulmonary functional capacity can lead to significant respiratory compromise from cervical collars or lying flat. +Decreased tolerance of lung or chest wall injuries +Decreased ability to clear secretions from the lungs +Risk of encephalopathy from decreased ventilation and respiratory acidosis
Dementia	–Decreased ability to give a complete history –Agitation or behavioral disturbances from advanced dementia may complicate exam. +Increased risk of developing delirium from trauma or hospitalization +Decreased ability to express pain or request as needed (PRN) medications
Diabetes	–Results in peripheral neuropathy which can obscure injuries –Altered mental status with hyper- or hypoglycemia +Increased risk of wound infection and poor wound healing
Frailty	–Higher levels of mortality from even "minor" injuries +Higher risk of delirium +Need screening for nutritional deficits, home safety, and mobility issues. Consider early initiation of therapy (physical, occupational, speech) and geriatric consultations. +More likely to require skilled nursing facility placement, consider early case management and social work consultations
Joint replacements	–Periprosthetic or juxtahardware fractures may present with minimal deformity.
Neurovascular disease	*Neurologic deficits increase the risk of falls and injury. –Prior cerebrovascular accidents (CVA) or neurotrauma can obfuscate the neurologic exam. –Risk of recrudescence or another CVA with acute hypotension
Ophthalmologic	–Medications and prior surgeries (such as cataract repair) may change pupil exam for reactivity or symmetry.
Osteoporosis or Osteopenia	–Increased risk of fractures with minimal trauma –Prior atraumatic vertebral compression fractures complicating the evaluation of new injuries –X-rays have decreased sensitivity for detection of fractures. –Older adults will often still be able to ambulate despite pelvic or hip fractures; the ability to range a joint or ambulate cannot definitively rule out a fracture. +Osteopenia on CT scan is associated with a hazard ratio for death at 1 year of 12 times more than patients without osteopenia.
Rheumatoid Arthritis	*Associated cervical spine disease leads to fractures. –Joint deformities can be mistaken for acute fractures. Additional imaging may be needed to distinguish rheumatic disease from acute fracture.
Spinal diseases	*Degenerative disk disease of the spine increases the risk of endplate fractures. *Spinal stenosis can be associated with SCIWORET (Spinal Cord Injury without Radiographic Evidence of Trauma).

if a paralytic is required for an older trauma patient. Succinylcholine paralysis is contraindicated in the patient at risk for hyperkalemia from prolonged time on the floor after a fall. Limited mobility of the cervical spine and the temporal mandibular joint complicate visualization, making induction and paralysis key to successful airway management in the older adult. Dental changes such as bridges or lack of teeth can interfere with grip during scissoring and jaw thrust maneuvers. If dentures are securely in place, they do not need removal as they can improve the seal for bag mask ventilation.

Age is not a contraindication to performing a cricothyroidotomy, though this procedure can be more difficult in older patients. Flexion from cervical spine kyphosis compresses the anterior cervical anatomy which shortens and deepens the operative field, leading to a higher risk of failure of the procedure or injury to larger vessels.

Breathing

Older adults have more difficulty clearing secretions in the mouth and lungs and may require frequent suctioning. Lung disease and spinal kyphosis decrease functional lung volumes. A 45-degree incline can assist with oxygenation and ventilation. If there is concern for spinal injury, it is acceptable to ramp the entire bed (reverse Trendelenburg) to keep the head and chest elevated while the back is straight. Capnography

TABLE 179.2 Examples of Common Classes of Medications Taken by Older Adults and the Effects to Consider During Trauma Evaluation and Management of Injuries

Medication Class [Examples]	Medication Effects (*Contributing to Trauma –Complicating the Trauma Exam and Care)
Anticholinergics [Diphenhydramine, Meclizine, Promethazine, Hydroxyzine]	*Increase risk of falls, confusion, and delirium –Decrease urine output and cause constipation
Antihypertensives and Diuretics [Metoprolol, Carvedilol, Cardizem, Lisinopril, Furosemide]	*Increase risk of orthostatic hypotension and falls –AV nodal agents blunt the ability to mount a tachycardia response despite level of blood loss. –Baseline blood pressure may be hypertensive, so normotensive can signal relative blood loss.
Anticoagulants and Antiplatelets [Warfarin, Clopidogrel, direct oral anticoagulants (Apixaban, Rivaroxaban), aspirin, dabigatran, prasugrel, tigacrelor]	*Increase risk of spontaneous bleeding such as intracranial hemorrhage –Increase bleeding, bruising, and bleeding time –Increase mortality from intracranial hemorrhages
Corticosteroids [Prednisone, Dexamethasone]	*Chronic use increases risk of fractures. –Decrease wound healing –Decrease inflammatory response and may decrease sensitivity of exam for pain –Increase risk of wound infections –Increase risk of refractory hypotension
Hypoglycemic Agents [Metformin, Insulins, Sulfonylureas, Pioglitazone]	*Hypoglycemia can lead to falls or motor vehicle accidents. –Trauma patients are often placed on NPO (no oral intake) status causing iatrogenic hypoglycemia.
Opioids [Hydrocodone, Oxycodone, Codeine, illicit opioids]	*Sedative effects can lead to falls or motor vehicle collisions. –Blunt the pain response, increasing the risk of missed injury –Withdrawal may present with abdominal pain and tachycardia.
Sedatives [Benzodiazepines, Alcohol abuse, antipsychotic sedatives Mirtazapine and Trazodone]	*Increase risk of falls and motor vehicle accidents. –May affect Glasgow Coma Scale and cognitive assessments –Risk of respiratory sedation –Withdrawal may present as tachycardia and confusion.

is highly recommended if there is any concern for underlying lung disease, acute thoracic injury, or if analgesia or sedatives are given.

Circulation

As previously noted, older adults are particularly vulnerable to shock due to limited physiologic reserve. Adaptive responses to hypovolemia such as tachycardia and hypotension are reduced by physiologic changes and medications (see Tables 179.1 and 179.2). *Normal* initial vital signs are not reassuring, but *baseline* vital signs are helpful. Trends are more informative than specific cutoffs.

During resuscitation, the therapeutic window for cardiac preload is narrow, and inadequate monitoring of fluid status may lead to over- or under-resuscitation. Evaluation of the collapsibility of the inferior vena cava by ultrasound is recommended to assess overall fluid status and guide resuscitation. In patients in whom there is no obvious source of blood loss, incremental boluses (e.g., 500 mL) of warmed isotonic crystalloid can be used for resuscitation. Patients in shock with injuries that have a high likelihood of acute blood loss should be given blood early and empirically. The indicators for need of massive transfusion, such as the Assessment of Blood Consumption and the Trauma Associated Severe Hemorrhage scores, are not as sensitive in older adults. We recommend to start transfusing 1 unit packed red blood cells while obtaining imaging if there is any suspicion of significant blood loss. Frequent (every 30 minutes) reassessment of the hemodynamic status will avoid iatrogenic pulmonary edema and respiratory failure. Thoracic ultrasound is fast, available in most trauma bays, and with skilled operators is more sensitive for signs of pulmonary edema (B lines) than chest x-ray. Thoracic ultrasound for pulmonary edema or abdominal ultrasound of the inferior vena cava can be helpful in directing fluid resuscitation for the trauma patient.

Anticoagulation reversal is another method of improving circulation by reversing life-threatening bleeding. Considerations for reversing coagulation abnormalities in older trauma patients are the severity of injury, the volume of reversal agents required, the urgency for the reversal, the availability of various reversal agents and the corresponding risk of fluid overload (see Chapter 180).

Disability

Evaluation of older adults for disability includes examination for TBI, spinal cord trauma, vertebral fractures, and extremity injuries. In contrast to younger adults, older adults can have intracranial hemorrhages and yet maintain a Glasgow Coma Score (GCS) of 15. Any GCS less than 15 is concerning for TBI, and a GCS score below 8 is predictive of a poor outcome. Subtle changes in mental status such as confusion or decreased alertness or symptoms such as headache may be the only signs of TBI. Confirming baseline mental status with family or caregivers is essential. Ultimately, no combination of historical features and physical findings has been shown to reliably predict the absence of intracranial injuries in the older trauma population. Brain computed tomography (CT) is indicated for all older adults with head trauma, multisystem trauma, or symptoms or signs of TBI, because no clinical decision rule has been validated in older trauma patients.

The evaluation of the patient's cognitive status is critical to detecting delirium. A patient who is cognitively impaired or acutely delirious may not express pain or answer questions and therefore their physical examination may not be accurate. Delirium can be the cause of traumatic injury, such as falls, or can be the result of traumatic injuries. The Brief Delirium Triage Screen has high sensitivity in emergency department patients and is more rapid than the full CAM-ICU. Brief cognitive screening tests such as the Mini Cog or the 4AT Delirium Assessment

tool are also helpful when probing for cognitive impairment. Delirium is common among all trauma patients, especially those in the ICU or intermediate care units, and is associated with worse outcomes. A quarter of older trauma patients with rib fractures will develop delirium. Missing delirium on the initial evaluation in the ED is associated with prolonged length of stay in the hospital and increased morbidity.

Exposure

Older trauma patients often have a combination of chronic, acute, and iatrogenic skin injuries. Because even minor wounds can cause serious complications in older patients, a thorough skin exam should be performed. Once exposed, older trauma patients are at risk of developing hypothermia because normal thermoregulatory mechanisms may no longer be intact, or are disrupted from the stress of trauma. Hypothermia on arrival should raise suspicion of infection leading to the fall and injury, or prolonged exposure or immobilization after the fall.

Secondary Assessment

A complete history should be obtained from the patient or a care provider, with particular emphasis on corroborating the accident history, past medical history, medications, allergies, and social history, including baseline functional status and living arrangements. Code status and confirmation of any advanced care planning documentation is essential. Baseline functional status includes the patient's ability to walk and any need for assistive devices prior to the injury. In addition to the basic history, a history of falls should be obtained and fall risk factors identified. Patients should be screened for alcohol abuse, substance abuse, and elder abuse. Home living situation, caregivers and caregiver availability, and home safety concerns need to be understood to ensure a safe discharge. Social workers often assist with this evaluation and early assistance from these teams can greatly speed care and disposition of the older trauma patient.

Laboratory Testing

In addition to the recommended trauma labs (see Chapter 32), we recommend a urine culture and a cardiac evaluation (ECG, troponin, and cardiac monitoring). A creatinine kinase level should be considered in every patient who has been immobilized by fall or injury. Electrocardiography (ECG) and cardiac monitoring are advised because of the risk of cardiac causes or complications of their traumatic event.

COMMON INJURIES IN OLDER ADULTS

Traumatic Brain Injury (TBI)

TBI can occur with minimal head trauma in older adults and can be initially asymptomatic. Physiologic changes of aging and the frequent use of anticoagulant medications increase the likelihood and severity of TBI in older adults. With aging, the size of the brain decreases by 10% on average, resulting in increased intracranial free space, stretching of bridging veins to the dura, and increased brain mobility within the calvarium. With this increased freedom of movement even minor trauma can lead to shearing of blood vessels and intracranial hemorrhage. These injuries can be devastating; a fifth of older adults admitted for TBI will die or enter a vegetative state.[11]

Clinical variables alone are insufficient to identify all cases of intracranial injury reliably in older patients; the New Orleans Criteria, NEXUS II CT Head Rule, and Canadian Head CT Rule all exclude older adults. Newer research into biomarkers of glial injury have shown some promise, but as of yet are not validated in older adults. A noncontrast head CT is the imaging of choice to diagnosis hemorrhagic TBI. The TBI spectrum in older adults also includes concussions, which as in sports related injury, may result in headaches, nausea, short-term memory deficits, and sleep disruption. We recommend the Center for Disease Control's Acute Concussion Evaluation.

Treatment of moderate to severe TBI includes supportive care, rapid reversal of anticoagulation, and early neurosurgical consultation (see Chapter 33). Patients with mild TBI (GCS 13 to 15) may be safe for monitoring and anticoagulation reversal (if required) on a regular hospital floor or observation unit. Physical therapy and occupational therapy consultations are recommended both to assess for subtle deficits and to address any home safety, safe mobility, or care needs. Older patients with head trauma who are not anticoagulated and have a normal head CT are generally safe for discharge if they have a safe environment, responsible care provider, and reliable follow-up. In patients on therapeutic anticoagulation, if the initial head CT does not show any injury, the risk of subsequent development of an intracranial hemorrhage is less than 2%.[12] Although this risk is low, we recommend that any patient with neurologic deficits, confusion, or who is without reliable monitoring at home should be observed for 12 to 24 hours to assess for concussion or evolving intracranial injury.

Vertebral Fractures and Spinal Cord Injuries

Changes in bone mineral density (BMD) and spinal kyphosis with aging contribute to several distinct fracture types in older adults: C1 to C2 cervical fractures and vertebral compression fractures. In contrast to younger patients, in older adults the most common cervical spine fractures are at the level of C1 and C2, with more than 50% of cervical fractures occurring at the level of C2. These fractures are usually the result of a fall with impact to the head, resulting in anterior or posterior displacement of the odontoid process. Mortality from these fractures is high (16% in the first month, up to 32% in the first year for nonoperatively treated C2 fractures).[13] Vertebral compression fractures are also common and can be asymptomatic other than the slight loss of height. In one series of hospitalized women, the prevalence of incidental thoracic vertebral fractures on chest x-ray was 2.4% in women aged 50 to 59 years, 8.9% in women aged 60 to 69 years, and 21.9% in women aged 70 years or older.[14] A lack of initial symptoms unfortunately does not mean that these fractures lack long-term morbidity.

Establishing a diagnosis of cervical spine fracture in older patients is complicated because 20% of adults older than 55 years with a cervical spinal fracture do not report neck pain. The Canadian C-Spine Rule classifies all patients 65 years or older as inherently high risk. The National Emergency X-Ray Utilization Study (NEXUS) criteria include all ages, but validation studies of NEXUS have shown lower sensitivity in older adults. In any blunt trauma to the older neck, lack of spinal tenderness or lack of pain on range of motion does not completely rule out spinal injury. We recommend CT imaging for any older adult with trauma and neurologic symptoms or cognitive impairment.

Older adults are also at increased risk of thoracic, lumbar, and sacral vertebral fractures. Per trauma guidelines, CT imaging should be used liberally for older adult trauma patients. Consider imaging the entire spine for those with altered mentation or dementia. Clinical exam can only rule out thoracolumbar injury in the awake, alert, older adult without cognitive impairment or other comorbidities/medications that limit the sensation or expression of pain.

Up to 20% of women over 70 years of age have suffered a vertebral compression fracture; magnetic resonance imaging (MRI) is helpful in determining acuity. Finally, if one acute spinal fracture is found, the rest of the spine should be imaged. In blunt trauma patients with a cervical fracture, 20% to 26% will have a noncontiguous thoracolumbar fracture. In the past, flexion/extension x-rays were used to evaluate for ligamentous injury, but this is controversial and no longer general practice.

Consultation with a spine surgeon is essential for all spinal injuries. Kyphoplasty or vertebroplasty can help control pain. Braces or collars can assist with pain and recovery, but these also limit an older adult's abilities to perform activities of daily living. Spinous process and other stable cervical fractures are sometimes managed without immobilization because of the respiratory effects and discomfort from cervical collars.

Thoracic Trauma

Older adults are at increased risk of rib and sternal fractures, pulmonary contusions, and their complications with low-force injuries. In-hospital mortality from thoracic trauma ranges from 3% to 15%.

Obtaining a chest x-ray combined with extended FAST exam has a sensitivity of only 64% for detecting clinically significant thoracic injuries; therefore, chest CT is recommended for the potentially multiply injured patient.

Management of the older adult with thoracic trauma is similar to management of younger adults, but a lower threshold for ICU monitoring is suggested. Although these patients may appear stable by vitals, admission to the ICU for older adults with multiple rib fractures significantly decreased complications, hospital length of stay, and need for discharge to a skilled nursing facility in one single-center study.[15] Alternatives to opioid analgesia such as epidural analgesia, paravertebral analgesia, and/or topical lidocaine can be considered for pain management.

Fragility Fractures

Fractures are common injuries in older adults with decreased BMD. Even nonoperative, distal extremity fractures can affect mobility and the ability to live independently. The most common upper extremity fractures sustained by older adults, in order of frequency, are distal radius fractures, proximal humerus fractures, and elbow fractures. The most common lower extremity fractures in older adults are ankle fractures, hip and pelvic fractures, and tibial plateau fractures. Pelvic fractures can occur with relatively little force in older adults and often patients continue to ambulate on a fractured pelvis. Although the majority of pelvic fractures are stable, these fractures can be associated with hemorrhage. In-hospital pelvic fracture mortality is 2.8%, and up to 21% in older patients with open pelvic fractures. The initial in-hospital mortality from hip fractures (intratrochanteric) is low, but due to debility the longer-term mortality in this population is high (45% at 1 year), with men twice as likely to die as women.

Hip fractures can be seen on plain x-ray films but occult fractures are a well-described phenomenon in older adults. Patients with the inability to ambulate or who have persistent pain after trauma require further evaluation; MRI is useful to delineate the pathology.

Older adults with hip fractures have better outcomes with early surgery (<72 hours) and care in a distinct orthogeriatric service. Emergency clinicians should consider transferring older adults with hip fractures to hospitals with such services. For pain management, consider ultrasound-guided blocks such as the fascia iliaca. For other fractures, management is similar to that of younger adults except that the emergency physician is uniquely poised to discuss the treatment and diagnosis of two common syndromes: low BMD and malnutrition.

A fragility fracture should be suspected in all women older than 50 years and men older than 70 years old presenting with a fracture. The classic fragility fractures are distal radius, hip, and spine, but in the setting of trauma low BMD can contribute to fractures anywhere. If osteopenia is seen on the trauma CTs, then low BMD can be presumed. Treatment includes testing calcium and vitamin D levels and starting the patient on supplementation (if needed) pending full evaluation by their primary care doctor, orthopedist, or endocrinologist. The major contraindications to starting vitamin D and calcium supplementation from the ED include: end-stage renal disease, parathyroid disease, coronary atherosclerosis (currently debated), and renal stones.

Nutritional status also directly affects perioperative mortality and long-term healing from injuries. Malnutrition assessment in the older injured patient is endorsed by trauma guidelines. A study of older adults with hip fractures found that malnourishment was associated with increased in-hospital (27% versus 7%) and 1-year mortality (46% versus 17%).[16] Calcium levels, vitamin D levels, body mass index, and pre-albumin/albumin levels can all suggest malnourishment.

BOX 179.1 Suggestions to Limit the Side Effects and Complications of Analgesics for Injured Older Adults

- Limit NSAID (nonsteroidal antiinflammatory drug) use to 1 week or less to avoid renal and gastric injury. NSAIDs increase bleeding risk if patient is taking aspirin.
- Discuss total daily acetaminophen consumption limits and if any medications are combination pills with acetaminophen to avoid accidental overuse.
- Skeletal muscle relaxers such as cyclobenzaprine, methocarbamol, and benzodiazepines are discouraged for use by the American Geriatrics Society Beers Criteria.
- Tramadol lowers the seizure threshold, is renally metabolized, and can cause SIADH/hyponatremia and hypoglycemia in addition to the regular side effects of opioid medications. Use with caution.
- Tramadol, codeine, and morphine are not recommended for patients with renal insufficiency (GFR <30 mL/min).
- Discuss a bowel regimen that includes a promotility agent such as senna, docusate, bisacodyl, or prune juice.
- Consider topical agents such as lidocaine and topical NSAIDs.
- Consider early referral to physical therapy to assess mobility and pain, and reduce functional decline from injury.

Compiled from the American Geriatrics Society 2019 Beers Criteria and the American Geriatrics Society Geriatrics at Your Fingertips.

DISPOSITION, END-OF-LIFE CONSIDERATIONS, AND RECOVERY

Although age alone is not an indication to withhold aggressive treatment, comfort measures may be more appropriate than transferring patients to a trauma center in select cases (e.g., grave prognosis or when the patient's goals of care are known). Early referrals to palliative medicine and hospice from the ED help with pain and end-of-life care (see Chapter e5). The majority of older adults will recover from their injuries, but many will require additional help during recovery. Even minor decreases in range of motion of a joint can have a large impact on older adults' ability to care for themselves at home; additional help, equipment, or acute rehabilitation facility placement may be needed. An observation unit can be used to coordinate physical and occupational therapy consultations and home equipment prior to discharge from the ED. Lastly, prior to discharging an older adult to home, a safe and effective strategy for pain control is required (Box 179.1).

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 179: QUESTIONS AND ANSWERS

1. A 76-year-old man is brought to the emergency department (ED) after a fall at home. The paramedics tell you that he slipped in the shower and struck his head on a tile floor. The patient is awake and alert. He is unsure if he lost consciousness and complains of headache. When you obtain a computed tomography (CT) scan of his head, it reveals evidence of a subdural hematoma. The paramedic tells you that he has a history of severe congestive heart failure (CHF) and takes warfarin and furosemide daily. When he returns from CT, he seems slightly confused. Laboratory tests are pending. What is the best initial treatment?

a. Administer prothrombin complex concentrate (PCC)
b. Administer tranexamic acid
c. Administer protamine sulfate
d. Transfuse 2 units fresh frozen plasma

Answer: A. Prompt reversal of anticoagulation is important. Specific considerations for reversing coagulation abnormalities in older trauma patients are the volume of reversal agents required and corresponding risk of fluid overload. PCCs require minimal volume compared with fresh-frozen plasma (FFP) but are costly. To reverse anticoagulation fully, 1 to 2 L of FFP may be required, presenting a limitation to rapid reversal in older patients at risk of fluid overload. Platelets, tranexamic acid, and DDAVP will not reverse the elevated international normalized ratio caused by warfarin.

2. Which of the following is the most common cervical spine fracture in geriatric trauma patients?

a. Compression fracture
b. Jefferson fracture
c. Spinous process fracture
d. Type 2 odontoid fracture

Answer: D. Because of the relative immobility of the cervical spine related to degenerative joint disease, the most common level of cervical spine injury in older adults is C1 to C3, a higher level than in younger patients. Among these upper cervical spine fractures, the most common is a type 2 odontoid fracture.

3. An 80-year-old woman presents after a motor vehicle accident. Her vital signs on arrival are: heart rate of 112 beats/min, blood pressure of 88/65 mm Hg, respiratory rate of 18 breaths/min, and oxygen saturation measured by pulse oximetry (Spo_2) of 98%. The paramedic tells you that she has a history of CHF and takes furosemide daily. FAST does not reveal a source of bleeding. There are no obvious external injuries or bleeding. The IVC collapses more than 50% with inspiration. Which of the following treatments is most appropriate to address the patient's tachycardia and hypotension while searching for its cause?

a. Give a bolus of 500 mL warmed normal saline.
b. Give 2 units of non–crossmatched type O blood.
c. Run an infusion of warm normal saline wide open.
d. Start norepinephrine at a low dose.

Answer: A. If the patient has an obvious source of hemorrhage, use of non–crossmatched type O blood would be appropriate as a first step, starting with 1 unit. However, this patient has no signs of bleeding on FAST or external exam. The most prudent approach in this hypotensive older trauma patient is controlled boluses of warmed isotonic fluids, with frequent assessment of physical examination, vital signs, pulse oximetry, lactate, and IVC status. Resuscitation with crystalloid may correct the patient's hypotension, obviating the need for transfusion. Hypotension should be immediately addressed, and treatment should not be delayed for type-specific blood. Given her history of CHF, a wide open infusion of normal saline without an endpoint should not be administered. Vasopressors such as norepinephrine should not be given to any trauma patient, except in extreme circumstances of persistent hypotension despite adequate volume resuscitation.

4. A 76-year-old man presents after slipping and falling down several stairs at home. He notes his doctor just started him on a medication

CHAPTER 179: QUESTIONS AND ANSWERS—cont'd.

for dizziness (meclizine). The patient is awake and alert and denies loss of consciousness after the fall. He complains of chest pain and has left chest wall tenderness on examination. When you obtain a CT scan of his chest, it reveals three contiguous lateral rib fractures. The patient's pain is only moderately relieved by 0.15 mg/kg of morphine sulfate IV. What is the most appropriate disposition for this patient?

a. Admission for pain control with IV opioids
b. Admission with anesthesia consultation for pain management
c. Continued observation in the ED for 6 additional hours of IV opioid management, followed by reassessment
d. Discharge home after a bupivacaine rib block for pain.

Answer: B. Geriatric trauma patients with severe pain from rib fractures often require hospitalization to allow adequate and safe pain management, and those with flail segments or larger numbers of rib fractures may require intensive care unit admission. Pain control is of particular importance because rib fractures will lead to splinting and atelectasis and increase the risk of pneumonia. Analgesia can be administered with IV opioids via patient-controlled analgesia or via rib block with anesthetics. An anesthesia consultation is appropriate for the older rib fracture patient without pain relief from parenteral opioids.

5. Late in the evening, an 82-year-old woman is transferred to your ED for a burn to the hand. Your ED is the local burn center. Her vital signs on arrival are as follows: heart rate of 94 beats/min, blood pressure of 110/70 mm Hg, respiratory rate of 12 breaths/min, and oxygen saturation measured by pulse oximetry (Spo_2) of 97%. You note circumferential first and second degree burns to the entire left hand with some sparing over the flexor areas of the 2-5th digits. She has no respiratory distress and there are no other injuries on exam. The adult grandson who cares for her says she was cooking and stuck her hand into boiling soup to grab a spoon. He also notes her dementia is worsening and it has been harder to care for her. She has no known history of neuropathy or self-injury. In addition to local wound care, what is the next step in the management of this patient?

a. Pain control prescription, and discharge to home with family.
b. Pain control prescription, and discharge to home with family. Put in a call to Adult Protective Services to follow up on the patient.
c. Analgesics, IV fluid resuscitation per the Parkland formula, and admission.
d. Analgesics, and admission for further investigation of elder abuse vs caregiver fatigue.

Answer: D. Older adults are at risk for inadvertent burns while cooking, but a circumferential burn with signs of a clenched fist (sparing over the flexor areas of the fingers) suggests the hand was forced into the liquid. This woman is not safe for discharge both due to her injuries (circumferential hand burn) and her safety risk. The patient should be admitted for continued medical care and a full social work assessment and collaboration with Adult Protective Services. Most police agencies prefer to be notified at the time of injury as well if there is concern for criminal abuse, just as you would for a younger victim of interpersonal violence. As isolated hand burns are less than 10% BSA, there is no indication to start Parkland formula resuscitation. The main intervention is keeping her safe from possible abuse.

6. A 67-year-old construction manager is the restrained driver in a head on collision with a roadside barrier at 45mph. Airbags deployed and he complains of right knee pain, chest pain, and back and neck pain. Vital signs are heart rate of 85 beats/min, blood pressure of 130/67 mm Hg, respiratory rate of 12 breaths/min, and oxygen saturation measured by pulse oximetry (Spo_2) of 97%. He is oriented to self, time, and place but does not remember everything about the accident or how he veered off the road. He has a history of diabetes, hypertension, and cirrhosis and takes a daily aspirin, lisinopril, hydrochlorothiazide, metformin, and glipizide. Which laboratory tests should be ordered in addition to the basic trauma evaluation (coagulation studies, a type and cross, alcohol and drug testing, a complete blood count and a basic metabolic panel)?

a. Erythrocyte sedimentation rate
b. Troponin, hepatic function panel, ammonia, and urinalysis
c. Creatinine kinase.
d. Venous blood gas.

Answer: **B.** This patient was in a high speed MVA without a clear inciting cause. He requires both a trauma evaluation for any injuries but also an evaluation for the cause of the collision. The initial workup therefore includes a bedside glucose (he is on two oral antihyperglycemic medications), a troponin to assist in evaluating whether his chest pain is from a cardiac cause or chest trauma, an ammonia and hepatic function level to evaluate for cognitive difficulties from cirrhosis, and a urinalysis to check for infection, volume depletion, and other causes. An erythrocyte sedimentation rate is not be specific for injury. A venous blood gas is likely unnecessary as he is oxygenating well and has no history of pulmonary disease. A creatinine kinase to evaluate for rhabdomyolysis is unnecessary as the patient was not immobilized and so is not at risk for this.

7. A 72-year-old woman who runs a dance instruction studio presents for 3 days of L hip pain. She slipped and fell on the hip and initially required assistance to get up, but has been ambulating since the injury. She presents to your ED because the pain is not improving with acetaminophen and time. On exam, there is no angulation, bruising, deformity or limb length discrepancy. She tolerates passive range of motion of the L hip but is tender over the greater trochanter and with pelvic compression. The initial x ray demonstrates osteoporosis but no fractures. An MRI shows a stable pelvic ring fracture that does not require operative management. What is the best recommendation for pain management?

a. Prescribe two weeks of ibuprofen 600mg tabs to use every 6-8 hours.
b. Prescribe tramadol and a strong muscle relaxer such as Valium to prevent spasms.
c. Prescribe a walker to decrease her weight bearing on that limb, a referral to early physical therapy, and topical nonsteroidal anti inflammatory cream.
d. Prescribe two weeks of oxycodone 5mg tablets to use every four hours.

Answer: **C**. A multimodal approach that also assists with ambulation and healing is appropriate. Non-steroidal anti-inflammatories can cause renal injury or peptic ulcer disease if used at high doses or for a longer time period. Try to limit use to lower doses (200-400mg) and under a week at a time. Tramadol and skeletal muscle relaxers are not indicated for use in older adults, and this combination is especially concerning for increasing the patient's risk of another fall and injury. Oxycodone may be needed if her pain is severe, but should not be prescribed without a bowel regimen.

Geriatric Drug Therapy

Christopher J. Edwards and Arthur B. Sanders

KEY CONCEPTS

- Those with a chronologic age of 65 years or older are commonly referred to as older adults (or the elderly), but physiologic age is more indicative of a drug's therapeutic or toxicologic effect. Besides age, overall patient assessment should include organ function, comorbidity, and functional status to guide drug dosing.
- Pharmacokinetic and pharmacodynamic changes that occur with age need to be considered to optimize drug dosing and minimize toxicity in older adults. In most cases, a "start low, go slow" approach is recommended. Multiple or repeated dosing is more likely to lead to drug accumulation compared to single doses in the emergency department (ED).
- Polypharmacy is common in older adults, predisposing them to adverse drug effects, drug interactions, and functional and cognitive impairment. Some of these medications do not have legitimate indications or may be inappropriate.
- Published lists of potentially inappropriate medications, such as the Beers list and the STOPP and START criteria, can help to identify potentially problematic medications; however, there are limited studies to enable extrapolation to the ED setting.
- Anticoagulation-related hemorrhagic complications are common in elderly patients, particularly if drug accumulation occurs in patients taking renally eliminated direct-acting oral anticoagulants.
- Older adults often present to the ED with altered mental status. Drug-related causes such as anticholinergic medication burden should be considered in the differential diagnosis.
- Geriatric patients with pain-related complaints are less likely to receive analgesics in the ED compared to younger adults, placing them at risk for poor pain control. Dosing of opioids should be cautious, with frequent monitoring and titration. Given the availability of alternative opioids, the use of meperidine should be avoided.
- A growing number of institutions have pharmacists practicing in the ED. In geriatric EDs, there is a great opportunity to integrate and consult with pharmacists, given the myriad drug therapy issues that can lead to suboptimal care.

FOUNDATIONS

There are approximately 23 million visits to United States (US) emergency departments (EDs) by adults over the age of 65 annually.[1] As the US population ages, the number of ED visits by older adults is expected to increase disproportionately compared to the general population based on estimates from the US census.[2] Drug therapy issues are particularly challenging in older adults because of altered pharmacokinetics and pharmacodynamics compared to younger adults. In addition, older patients take more medications, have more comorbidities, and are at increased risk for adverse drug effects because of the physiologic changes that occur with aging. Medication selection and dosing must be age-adapted for optimal patient outcomes. Also, given that advanced age is a commonly applied exclusion criterion in clinical trials, there is less high-quality evidence for many drug therapy interventions in older adults compared to younger adults. This can make extrapolating from studies and evaluating risks versus benefits for pharmacologic options more challenging, particularly for patients who are 80 years of age or older.

Most developed countries have adopted the chronologic age of 65 years to define the geriatric or older population.[3] The World Health Organization does not have a standard definition, but generally uses the age of 60 years or older to refer to older persons.[3] This categorization may be overly simplistic, and stratification, such as young old (60–69 years), middle old (70–79 years), and very old (≥80 years), is more suitable and medically useful. From a drug therapy perspective, physiologic age is more indicative of the anticipated therapeutic or toxicologic effect; however, there are no physiologic markers that define the aging process or that can be routinely used in clinical practice.[4] Most studies evaluating medication use in older adults have used a cutoff value of 65 years, and this serves as the basis for recommendations from the American Geriatrics Society.[5]

In this chapter, we refer to older adults as those with a chronologic age of 65 years or older; however, from the emergency clinicians' perspective, this is an arbitrary value for making drug therapy decisions. In addition to chronologic age alone, an overall assessment that incorporates organ function, comorbidity, functional status, and lifestyle is a better determinant of drug therapy selection and dosing. This should also be considered when interpreting recommendations for older adults, such as what is considered to be an inappropriate medication. This chapter reviews select aspects of pharmacology for older adults and the clinical implications in emergency medicine.

Pharmacokinetics

The time course of drug exposure is determined by pharmacokinetic parameters including absorption, distribution, metabolism, and elimination. The drug effect is primarily determined by this exposure, which can be quantified by serum drug concentrations over time. It is assumed that increased exposure is more likely to result in toxic medication effects. Thus, an understanding of pharmacokinetic changes in older adults is useful for determining risks of adverse drug reactions and can help guide medication selection and dosing.

The effect of physiologic changes on drug absorption is an important consideration for orally ingested medications. Changes in gastric pH, gastric emptying, splanchnic blood flow, bowel motility, and absorptive capacity all impact drug availability. For example, the increase in gastric pH seen in older adults can decrease the dissolution of medications that are weak bases, reducing absorption and resulting in lower serum drug levels. Conversely, decreased bowel motility can increase transit

time, allowing more opportunity for absorption to occur, leading to increased serum drug levels. Clearly, age-related changes in the gastrointestinal system can have a varied effect on drug absorption, leading to unpredictable effects on serum drug concentrations. As an example, decreased absorptive capacity coupled with decreased bowel motility can increase transit time, leading to a net neutral effect on drug exposure. Gastrointestinal and other comorbidities can have a greater effect on absorption than age alone. Given these considerations, it would be prudent in the ED to use the intravenous route for acute conditions, when rapid drug absorption is needed to achieve a therapeutic concentration.

Age-related changes in body composition have an effect on the distribution of drugs. There is an increase in total body fat and a decrease in relative skeletal muscle mass in older adults compared to young adults. This change in body composition accelerates between 60 to 75 years and then may start to decline. Lipophilic medications have a greater volume of distribution with increasing adiposity, whereas the opposite is true for hydrophilic medications. Opioid analgesics such as fentanyl and most sedatives (e.g., benzodiazepines, propofol) are very lipophilic, so there is distribution and accumulation of the drug within adipose tissue, and its metabolites are renally eliminated. With prolonged use, this can lead to an increased duration of effect due to redistribution of drug from tissue to serum and central nervous system. Conversely, hydrophilic medications such as digoxin would require lower loading doses in older adults to achieve similar serum concentrations due to a smaller volume of distribution. This has the potential for drug toxicity if not dosed appropriately for age.

Most drugs require biotransformation into polar metabolites before final elimination. This primarily occurs in the liver via phase 1 metabolism by cytochrome P450 enzymes (oxidation) or phase 2 (conjugation, acetylation, sulfation) reactions. With advanced age, hepatic mass and blood flow may decrease by up to 40%, which reduces the delivery of medications to the liver and their subsequent metabolism. This decrease in first-pass metabolism improves drug bioavailability resulting in increased serum levels and potentially increasing the risk of drug toxicity for certain agents. Drugs with a high hepatic extraction ratio are more dependent on hepatic blood flow for drug metabolism, and the slowing of hepatic metabolism seen with age has mainly been related to changes in phase 1 pathways. For example, morphine is a high–extraction ratio drug and would lead to greater drug exposure as hepatic blood flow is reduced. Commonly used benzodiazepines in the ED also vary in their metabolic pathways. Midazolam undergoes phase 1 metabolism, and hepatic impairment would lead to drug accumulation, especially with repeated or prolonged use. Conversely, lorazepam undergoes phase 2 conjugation and is preferred in patients with hepatic impairment because this metabolic pathway is less dependent on hepatic blood flow. The effect of aging on phase 1 metabolism via CYP3A4 is controversial. This enzyme represents the metabolic pathway for most medications, and studies have shown no significant differences between younger and older populations.

Renal blood blow, renal mass, and the number of nephrons decrease with age, leading to a decrease in renal function. In a longitudinal study, renal function decreased by approximately 10% for each decade between 30 and 80 years of age. This decrease was independent of comorbid conditions and was attributed to aging alone. Although this decline is likely to occur in most patients, up to one-third may have no decline, and some may have an increase in renal function. Kidney function is expressed as the glomerular filtration rate (GFR) and is routinely estimated by the Cockcroft-Gault equation. However, this equation may not accurately estimate the GFR, so the modification of diet and renal disease (MDRD) equation has been suggested as a more accurate estimation.[6] Common equations used to calculate creatinine clearance and estimate GFR are in Box 180.1. Discordance in drug doses selected may occur 10% to 40% of the time when comparing the two equations, and there has been considerable debate regarding the most appropriate equation to use in practice.[7,8]

BOX 180.1 Equations to Estimate Glomerular Filtration Rate (GFR, in mL/min)

Cockcroft-Gault Equation

Creatinine clearance (mL/min) = (140 − age)
× (weight in kg) /72 × serum creatinine × (0.85 if female)

Use ideal body weight (IBW). If patient is obese, use adjusted body weight.

IBW (male) = 50 + [2.3× (height in inches − 60)]

IBW (female) = 45.5 + [2.3× (height in inches − 60)]

Adjusted body weight = IBW + [0.3 × (actual weight − IBM)]

Modification of Diet and Renal Disease Equation

$GFR = 175 \times \text{serum creatinine}^{-154} \times \text{age}^{-0.203}$
(× 1.212 if patient is black; × 0.742 if patient is female)

Typically, drug dosing in manufacturers' labeling per the US Food and Drug Administration is based on creatinine clearance determined by the Cockcroft-Gault equation and, as such, most pharmacists continue to use this equation for drug dosing. The Cockcroft-Gault equation is also easier to calculate compared to the MDRD. While many electronic health records and laboratories use MDRD to calculate and report GFR, there is no universal industry standard approach, and it is important to know which equation is used to calculate the GFR reported in the medical record. Although cumbersome, one approach is to calculate estimated GFR based on both equations and evaluate if there is a discrepancy in dosing recommendations. This approach is useful if the initial estimate is close to a cut-off value that would alter the dosing regimen. If a discrepancy exists, the decision to use a more or less conservative dosing strategy will depend on the clinical scenario. In general, a low-dose approach should be used for medications with a narrow therapeutic index, particularly when the risk of toxicity is high and serum concentration monitoring is not available. In general, medication dosing should be higher in the ED when the implications for therapeutic failure warrant such an approach, assuming the medication has a broad safety margin. An example would be erring on the side of more aggressive dosing when using antibiotics in a patient with sepsis or febrile neutropenia. Thus, clinical circumstances may override drug dosing recommendations, especially when there is discordance between equations, and professional judgment is always required. These equations use the serum creatinine level to estimate creatinine clearance, which is affected by muscle mass. Therefore, although serum creatinine values may be normal, they may not accurately estimate renal function in some older adults, especially those with less musculature. For all older patients, some providers routinely round serum creatinine values less than 1 mg/dL up to 1 mg/dL to account for reduced muscle mass; however, this practice should be avoided because it has been shown to underestimate clearance.

Given the limited number of repeat doses typically administered in the ED, even in patients with hepatic or renal impairment, drug accumulation is unlikely to be clinically meaningful. If, however, several doses of a medication are administered in the ED, especially when patients are boarded, drug toxicity or prolonged effects may become

TABLE 180.1 Pharmacokinetic Changes in Older Adults

Parameter	Change	Comments
Absorption		
Gastric pH	↑	Net absorption may be increased or decreased.
Gastric emptying	↓	Peak effect will likely be delayed.
Splanchnic blood flow	↓	The intravenous route is preferred in the ED for rapid and predictable effect
Bowel motility	↓	
Absorptive capacity		
Distribution		
Adipose tissue	↑	Lipophilic medications will accumulate with repeated dosing, which increases duration of effect.
Total body water	↓	Hydrophilic medications will have a lower volume of distribution, requiring lower loading doses.
Metabolism		
Phase 1 metabolism	↓	Medications with phase 1 metabolism are more likely to accumulate than those metabolized via phase 2 pathways.
Phase 2 metabolism	↓	
Liver blood flow	↓	
Elimination		
Glomerular filtration rate	↓	This is the most important consideration for drug dosing. Calculate creatinine clearance using the equations in Box 180.1 and adjust dosing. First doses of antibiotics and most one-time doses do not require adjustment.

clinically relevant. In general, a "start low and go slow" approach is prudent in older patients. When this strategy is used, it is critical to reevaluate the patient after the anticipated onset of the administered medication to determine if additional doses are necessary because failure to do so could lead to undertreatment. The risks versus benefits of drug therapies generally increase with age, suggesting that a more conservative approach is warranted, particularly when using drugs with a narrow therapeutic index. Pharmacokinetic changes in older adults are listed in Table 180.1.

Pharmacodynamics

Even at similar plasma concentrations, drugs may have altered effects in older adults, perhaps because of changes in the number and sensitivity of receptors, signal transduction, and reduction in homeostatic processes that help maintain equilibrium. Thus, physiologic mechanisms that help restore function are attenuated, leading to an exaggerated or relatively unopposed pharmacologic effect. Pharmacodynamic changes in older adults that are most relevant to consider in the ED include those that pertain to the cardiovascular, central nervous, and coagulation systems. For example, there is a decreased response to both β-adrenergic receptor agonists and antagonists. Conversely, there is no age-related change in α_1-adrenergic receptor sensitivity. Calcium channel blockers cause a greater drop in blood pressure and heart rate in older adults compared to younger adults, so the risk for postural hypotension is higher in older adults. The diminished inotropic response to catecholamines contributes to this risk. In the ED, non-dihydropyridine calcium channel antagonists such as diltiazem or verapamil are commonly used for patients with supraventricular tachycardias. Lower doses are appropriate in older adults, especially when the patient has tenuous blood pressure.

There is increased sensitivity to benzodiazepines in older adults, and lower doses are needed to obtain similar sedative-hypnotic effects. This is because of changes in the structure, composition, and function of the γ-aminobutyric acid (GABA) receptor complex. Similarly, in one investigation, older patients required less propofol for the induction and maintenance of sedation during procedures in the ED.[9] The dose required for induction was 0.5 mg/kg less than in the cohort of young adults. In older adults, it is more suitable to start propofol with a 0.5-mg/kg rather than the 1-mg/kg bolus that is typically recommended. Some studies have shown that older patients have increased sensitivity to opioids. Pharmacodynamic effects in these studies were measured in terms of electroencephalographic readings, which do not reliably indicate the presence of pain. However, the risk of adverse effects and interactions due to the use of concurrent medications is likely increased in older adults, suggesting that a cautious approach is appropriate when dosing opioids.

There is an age-related decrease in dopamine content in the central nervous system, which predisposes patients who are given neuroleptics and other dopamine antagonists to extrapyramidal symptoms. Similarly, there is a decrease in acetylcholine synthesis in older adults, which increases the risk for anticholinergic neurotoxicity with commonly used antihistamines, antispasmodics, and antiparkinsonian agents.

Bleeding is a potentially life-threatening consequence of anticoagulants. Historically, warfarin has been the most commonly used oral anticoagulant, although, more recently, newer oral agents such as direct thrombin and factor Xa inhibitors have become available. At similar warfarin plasma concentrations, there is greater vitamin K inhibition in older adults. Thus, it is recommended that warfarin should be initiated at a daily dose of 5 mg or less for older adults, when indicated. In the ED, this may occur for patients discharged after a venous thromboembolism in conjunction with low-molecular-weight heparin as bridge therapy. There is emerging evidence supporting the early use of direct-acting oral anticoagulants for certain patients presenting with a venous thromboembolism (VTE). While data regarding the use of direct-acting oral anticoagulants in older patients being discharged from the ED with VTE are sparse, when used, careful attention must be paid when selecting an agent and formulating a dosing regimen. Certain agents, such as dabigatran, should be avoided in advanced age (greater than 80 years of age), while others, such as apixaban, require an adjustment when renal dysfunction is present in patients above a certain age threshold (Table 180.2).[10,11] Dosing regimens and recommendations for adjustment also differ based on indication. In addition, therapeutic

TABLE 180.2 Harmful Drug Interactions From Studies in Older Patients

Object Drug	Adverse Event	Comments
ACE inhibitor or ARB	Hyperkalemia	Avoid potassium sparing diuretics or TMP-SMX Apixaban Subtherapeutic, increased VTE risk Interacts with carbamazepine
Benzodiazepines and sedative-hypnotics	Fractures, falls	Interacts with macrolides and has additive effect with other CNS depressants
Calcium channel blockers	Hypotension	Interacts with macrolides
Digoxin	Toxicity	Interacts with macrolides Haloperidol Toxicity Interacts with Parkinson's treatments
Lithium	Toxicity	Interacts with diuretics, ACE inhibitors, and NSAIDs
Phenytoin	Toxicity	Interacts with TMP-SMX
Sulfonylureas	Hypoglycemia	Interacts with TMP-SMX, fluconazole, macrolides, and fluoroquinolones
Theophylline	Toxicity	Interacts with ciprofloxacin
Warfarin	Bleeding	Interacts with most antibiotics and antifungal agents. Increased risk with NSAIDs

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CNS,* central nervous system; *NSAID,* nonsteroidal antiinflammatory drug; *TMP-SMX,* trimethoprim-sulfamethoxazole.

drug monitoring is not routinely available for these agents, making it difficult to assess the degree of anticoagulation, further enhancing the need for nuance and attention to detail to ensure they are being used appropriately. The other primary anticoagulant used in the ED is intravenous heparin for acute coronary syndrome or venous thromboembolism. Patient age does not correlate with heparin dose requirements, so heparin dose adjustments are not required.

SPECIFIC DISORDERS

Polypharmacy and Drug Interactions

The term *polypharmacy* is used to describe the use of multiple medications. There is no standard definition or consensus regarding the number of medications that serves as a cut point for this term; however, the American College of Emergency Physician's Geriatric Emergency Department Guidelines and other experts consider five or more medications to constitute polypharmacy.[12] Older patients are particularly prone to polypharmacy because they have a greater number of comorbidities and conditions requiring treatment for medications. In one national estimate of community-residing older adults, close to one-third of the population took five or more medications, and approximately half also took over-the-counter medications and dietary supplements. Polypharmacy may result in adverse drug effects, drug interactions, and functional and cognitive impairment, and can lead to falls, resulting in injury.[13,14] An estimated 10% of ED visits by older adults may be attributed to an adverse drug-related event.

An important consequence of polypharmacy is drug interactions, which occur more commonly in older adults. A drug interaction occurs when there is an alteration in the effect of a drug due to the coadministration of another. The alteration could be the increase in effect, leading to toxicity, or a decrease in effect, resulting in therapeutic failure. The mechanism of interaction could be pharmacokinetic, which is primarily due to the inhibition or induction of drug-metabolizing enzymes such as the cytochrome P450 system or alterations in drug transporter activity. Alternatively, the interaction could be pharmacodynamic, in which the change in effect is unrelated to pharmacokinetic mechanisms. This primarily occurs due to the pharmacologic effects of drugs, which may be additive or antagonistic. For example, the use of a benzodiazepine with an antibiotic that inhibits its metabolism leading to an increased or prolonged effect would be a pharmacokinetic interaction, whereas the use of a benzodiazepine with an opioid, leading to additive central nervous system depression, would be a pharmacodynamic interaction.

There are thousands of possible drug-drug interactions, which increase exponentially with the number of medications that a patient is taking. The use of ED pharmacists may help to identify clinically relevant drug-drug interactions, particularly in patients with complex medication regimens. Clinical decision support systems integrated with electronic medical records may also provide a useful mechanism to reduce this risk; however, there are several challenges that need to be overcome in the ED setting so that providers can make the best possible decisions. The identification of an interaction is dependent on an accurate medication history, which is often difficult to obtain. Clinical decision support systems identify many drug interactions that are not clinically meaningful, leading to alert fatigue. It is estimated that providers override more than 96% of alerts, even when the interactions are significant.[15] Furthermore, most interactions are based on preclinical studies during drug development, have a theoretical basis, and often lack high-level evidence. This leads to discrepancies in major drug information systems, and there is no standard classification to guide decisions.

A prudent approach is to focus on the most common drug interactions that have been known to result in patient harm and that may be most applicable to the emergency clinician. Single doses of drugs administered within the monitored setting of the ED are less likely to lead to harm than those prescribed on discharge and used for several days. Adverse events can be narrowed down to several interactions that resulted in hospitalization from hyperkalemia, hypotension, fractures, hypoglycemia, bleeding, and specific drug toxicities. The object drugs involved in these interactions should serve as important flags to alert prescribers when giving a new medication (Table 180.3). Most of these adverse events are seen to occur when new antibiotics are prescribed. Thus, antibiotics prescribed to patients need to be considered carefully for potential interactions, especially when patients are taking a medication such as one mentioned earlier. However, there are many other high-risk medications, such as antidepressants, neuroleptics, and antiepileptics, that are also known to have several drug-drug interactions. Ideally, consultation with a pharmacist is helpful in identifying and determining the risk of potential drug interactions and modifying the therapeutic plan, if necessary.

Potentially Inappropriate Medications

Beers Criteria

In 1991, Beers and colleagues developed explicit criteria defining inappropriate medication use in older adults. They are now known as the Beers criteria and are periodically updated by the American Geriatrics Society.[5] At that time, it was observed that residents of skilled nursing

TABLE 180.3 Dose Adjustments for Direct Oral Anticoagulants (DOACs)

Drug	Indication	Adult Regimen	Recommended Dose Adjustments
Apixaban	Venous Thromboembolism or Pulmonary Embolism	10 mg bid × 7 days followed by 5 mg bid	None
	Non-Valvular Atrial Fibrillation	5 mg bid	2.5 mg bid if 2 of the following: age > 80 y, weight ≤ 60 kg, sCr > 1.5 mg/dL
Dabigatran	Venous Thromboembolism or Pulmonary Embolism	150 mg bid after at least 5 days of parenteral therapy	Patients ≥ 75 y: Use extreme caution and consider other options[a] Patients > 65 y: Use with caution CrCl 30–50 mL/min and P-glycoprotein inhibitor use: 75 mg bid CrCl avoid use
	Non-Valvular Atrial Fibrillation	150 mg bid	Patients ≥ 75 y: Use extreme caution and consider other options[a] CrCl 50–80 mL/min: Use caution due to increased drug exposure CrCl 30–50 mL/min: Adjust if significant drug interactions, use with caution in advanced age CrCl ≤30 mL/min: Avoid use
Edoxaban	Venous Thromboembolism or Pulmonary Embolism	After at least 5 days of parenteral therapy and CrCl < 95 mL/min : 60 mg daily	CrCl 15–50 mL/min OR age >65 AND weight <60 kg OR use of concomitant P-glycoprotein inhibitors: 30 mg daily CrCl < 15 mL/min: Avoid use
	Non-Valvular Atrial Fibrillation	CrCl < 95 mL/min: 60 mg daily	CrCl 15–50 mL/min: 30 mg daily CrCl < 15 mL/min: Avoid use
Rivaroxaban	Venous Thromboembolism or Pulmonary Embolism	15 mg bid with food × 21 days followed by 20 mg daily with food	CrCl <30 mL/min: Avoid use
	Non-Valvular Atrial Fibrillation	20 mg daily with food	CrCl 15–50 mL/min: 15 mg once daily CrCl < 15 mL/min: Avoid use

[a]Dabigatran has shown an increased risk of excessive anticoagulation leading to hemorrhagic complications, including fatalities, with increased age. DOACs should be avoided in all patients with moderate to severe hepatic impairment and nursing mothers.

facilities were prescribed eight medications on average; more than 50% of them received a psychoactive medication. The Beers criteria were applied to the older residents in nursing homes, representing the frailest of the population. Inappropriate medications were defined by an expert panel as those that should be avoided, except under unusual clinical circumstances. This was because of the lack of effectiveness, risks outweighing the benefits, or safer alternatives that were available. The criteria were developed so that they could be assessed from easily identifiable pharmacy records using minimal clinical data. This made it feasible for use for the quality improvement initiatives in skilled nursing facilities. The Beers criteria were subsequently updated so that they could be applied to all older patients, regardless of the place of residence. The most recent version from the American Geriatrics Society was developed by a 13-member panel with expertise in geriatric medicine, nursing, pharmacy, research, and quality measures.[5] Each criterion for medication or class includes a quality of evidence rating and strength of recommendation, serving as a valuable resource for clinicians involved in the care of older adults.

However, important questions remain regarding the applicability of the Beers criteria to practice in the ED. For example, promethazine is considered to be an inappropriate medication for older adults because of its anticholinergic and central nervous system effects, and avoiding this agent was given a strong recommendation based on high-quality evidence by the expert panel. Although the chronic effects of promethazine, such as drug-related falls, constipation, and dry mouth, are not of particular concern in the ED, promethazine-induced confusion or sedation may be problematic in patients presenting with altered mental status. A safer alternative for nausea or vomiting in this latter circumstance would be a 5-HT_3 receptor antagonist, such as ondansetron. However, ondansetron has been associated with QTc interval prolongation, which could be concerning in older patients who are already taking QTc-prolonging medications, leading to a potentially severe drug interaction. These nuanced therapeutic decisions require emergency clinicians to consider patient-specific parameters and realize that a "one size fits all" approach may not be appropriate.

Medications provided on discharge create another challenge. Although benzodiazepines appear on the Beers list, a single dose of a short-acting benzodiazepine used for procedural sedation in a controlled environment with monitoring and observation until the patient has returned to baseline is unlikely to cause long-term issues; however, medications prescribed on discharge must be more cautiously considered. Medications given to older patients on discharge should be prescribed for a limited duration until outpatient follow-up can be provided. In this setting, the Beers criteria may provide important guidance. For example, the Beers criteria expert panel has recommended that benzodiazepines should be avoided for the treatment of insomnia in older adults. This is because of the increased risk for cognitive impairment, delirium, falls, fractures, and motor vehicle collisions. Even short-term use of benzodiazepines after ED discharge could be associated with these adverse effects. In one randomized controlled trial, the use of a clinical decision support system in the ED was able to reduce the prescribing of potentially inappropriate medications in

TABLE 180.4 Most Common Beers List Medications Prescribed to Patients Discharged from the Emergency Department

Rank	Inappropriate Medication[a]
1	Promethazine
2	Diphenhydramine
3	Diazepam
4	Hydroxyzine
5	Amitriptyline
6	Cyclobenzaprine
7	Clonidine
8	Indomethacin

[a]Propoxyphene is not included because it is no longer available.

TABLE 180.5 Top 10 STOPP Criteria

Rank	Criteria
1	Long-term use of benzodiazepines
2	Duplicate prescriptions from the same drug class
3	Proton pump inhibitor for peptic ulcer disease at full dose for >8 wk
4	NSAIDs in patients with moderate to severe hypertension
5	Long-term use of opioids—first-line treatment for mild to moderate pain
6	Aspirin without adequate cardiovascular risk
7	Warfarin and NSAID used together
8	Beta blocker in patients with chronic obstructive pulmonary disease
9	Prolonged use of first-generation antihistamines
10	NSAID use in patients with chronic renal failure

NSAID, Nonsteroidal antiinflammatory drug; STOPP (Screening Tool of Older People's Potentially Inappropriate Prescriptions).

patients being discharged from the ED. Interestingly, the study targeted only a few medications, which accounted for 80% of the inappropriate medications prescribed on discharge. These medications, listed from the most to least commonly used, are in Table 180.4. Each institution should periodically evaluate trends in medications being prescribed and assessed for appropriateness because this can vary by center.

STOPP and START Criteria

In 2008, the STOPP (***S***creening ***T***ool of ***O***lder ***P***eople's Potentially Inappropriate ***P***rescriptions) and START (***S***creening ***T***ool to ***A***lert doctors to ***R***ight ***T***reatment) tools were developed and validated to build upon the Beers criteria and overcome some of their limitations. The Beers criteria account for only a small subset of medications that are prescribed inappropriately to older adults. In addition, many of the medications in the Beers criteria may not be available in European countries or are seldom prescribed. In the ED setting, these tools can be used to identify drug-related presentations, to determine if medications are suitable to be used in the ED during acute illness, and to guide medication prescribing on discharge. Even if a presentation is not drug-related, assessment in the ED is an opportunity to identify medications that may be problematic and lead to future admissions. In this regard, the STOPP screening tool was able to identify more elderly ED patients with potentially inappropriate medications than the Beers criteria (35% versus 25%). The STOPP-related medications also contributed to twice the number of admissions (12% versus 6%). The most recent version includes 80 STOPP and 34 START criteria.[16] The top 10 criteria that identified the most patients with inappropriate medications are listed in Table 180.5.

Anticoagulation and Bleeding

Oral anticoagulation use is common for age-related conditions such as atrial fibrillation. Warfarin has been used for several decades but is less than ideal because it has a narrow therapeutic range, routine laboratory monitoring is required, and numerous drug and food interactions lead to an unpredictable response, often resulting in hemorrhagic complications.

More recently, newer direct acting oral anticoagulants have become available that do not require routine laboratory monitoring and have fewer drug interactions and are not affected by diet. These include a direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. High-quality randomized clinical trials of these direct oral anticoagulants (DOACs) have shown them to be equivalent or superior to warfarin with regard to stroke prevention and bleeding occurrence for patients in atrial fibrillation. A recent meta-analysis of these agents found that when used for atrial fibrillation in elderly patients, DOACs were associated with a lower risk thromboembolic events when compared to warfarin.[17] This analysis also found no difference in the rate of major bleeding events, a decreased risk of intracranial bleeding, hemorrhagic stroke, and fatal bleeding compared to warfarin, but were associated with a higher risk of gastrointestinal bleeding compared to warfarin. Current prescribing trends indicate that warfarin use is declining and the use of DOACs is on the rise both in the general population and specifically in older adults.[18,19]

One drawback of these agents is that they undergo renal elimination, and patients with severe renal impairment were excluded from major trials. Although several of these agents provide recommendations for dosing adjustments based on creatinine clearance, the fluctuating course of renal function in older adults during an acute illness may contribute to accumulation and bleeding. Furthermore, routine laboratory testing does not quantify the level of anticoagulation. For warfarin-induced bleeding, reversal is achieved when the international normalized ratio (INR) is less than 1.5. The new oral anticoagulants increase prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time, but these measures do not reliably estimate the level of anticoagulation and thus have limited ability to guide therapy. Laboratory parameters such as ecarin clotting time, diluted thrombin time, and chromogenic antifactor Xa assay may be useful; however, these tests are not widely available.

The most common major hemorrhagic complication resulting from anticoagulation is intracranial hemorrhage (ICH) following traumatic brain injury. While high-quality prospective research is lacking, recent studies suggest that patients receiving DOACs have worse outcomes and increased risk for delayed ICH following TBI.[20,21] Prompt reversal of anticoagulation is recommended in the setting of a life-threatening hemorrhage after careful evaluation of the thromboembolic risk of reversal in relation to the anticipated benefit of achieving hemorrhage control. There is limited evidence to guide anticoagulation reversal specifically in elderly patients; however, in general, reversal strategies used in younger adults are reasonable to use in elderly patients.

Neurologic Conditions

Altered mental status and delirium are common chief complaints among older patients presenting to the ED. Although there are many factors that can influence mental status, medication-related adverse effects are a common cause of altered mental status and delirium. Evaluation of a

patient presenting with altered mental status or delirium should include a thorough medication history, including prescription and nonprescription medications as well as over-the-counter nutritional supplements. Many of the medications are included on the Beers list are included due to their propensity for causing adverse neurologic effects. Medications with anticholinergic properties, benzodiazepines, sedatives, hypnotics, and opioids are commonly associated with delirium. Avoidance of anticholinergic agents in elderly patients was given a strong recommendation based on moderate- to high-quality evidence by the American Geriatrics Society.[5] There are numerous medications with anticholinergic effects, and toxicity is often due to a cumulative anticholinergic burden. Treatment begins with supportive care and nonpharmacologic measures, including discontinuation of the offending medications.

When nonpharmacologic measures have been unsuccessful and the patient is presenting a danger to themselves or others, pharmacologic management should be considered. Antipsychotic agents such as haloperidol or an atypical antipsychotic may be used. When used in older adults, lower starting doses are typically recommended (e.g., haloperidol doses of ≤5 mg IM [intramuscular] or IV) to reduce the risk of extrapyramidal symptoms.[22] Large doses of haloperidol given via the IV route have been associated with QTc interval prolongation, so monitoring of the electrocardiogram (ECG) is important, if feasible, especially if repeated doses are needed. Avoid haloperidol use in patients with Parkinson's due to increased risk of mortality. Use an intramuscular/intravenous atypical antipsychotic instead such as olanzapine or ziprasidone if one is needed.

There are certain, specific situations where short-term use of low-dose benzodiazepines may be considered for agitated delirium, including suspicion that the patient is withdrawing from alcohol or benzodiazepines or if the patient has comorbid conditions, such as Parkinson disease or QTc prolongation, that would preclude the use of an antipsychotic agent; however, there is weak to moderate-quality evidence that benzodiazepines may contribute to delirium, and they should generally be avoided in the elderly.[22]

There are also differences in the pharmacologic management of some key neurologic emergencies in older adults. In patients with community-acquired bacterial meningitis, the Infectious Disease Society of America has additional recommendations for older adults compared to young adults. In older adults, ampicillin is recommended in addition to the standard empirical regimen for coverage of *Listeria monocytogenes*. Thus, older patients should receive a triple regimen of vancomycin, ceftriaxone, and ampicillin. However, the cutoff value for age is 50 years rather than the traditional age definition. Similarly, there are differences in the eligibility criteria for thrombolytic therapy for ischemic stroke based on age. The American Heart Association guidelines on the management of ischemic stroke allow for extending the time window for the provision of thrombolysis from 3 to 4.5 hours after onset of symptoms in select patients.[23] This recommendation incorporates the exclusion criteria utilized in the primary trial showing benefit from this approach. The ECASS-3 trial excluded patients older than 80 years, and as a result, while extending the time window to 4.5 hours in patients over 80 years old is still recommended, it is given a lower level recommendation compared to younger patients.

Analgesia

In a national survey of US EDs, geriatric patients with pain-related complaints were less likely to receive any analgesics than young adults.[24] The risk for poor pain management in older adults is multifactorial and increases with logistic constraints, such as ED crowding. Pain perception and susceptibility to adverse drug effects of analgesics is also different in older patients. Dosing of opioids should be cautious and monitoring for respiratory depression needs to be vigilant. It is difficult to anticipate how much opioid would be required for pain control in the ED. Instead of large single doses, a lower dose with titration consistent with pharmacokinetic and pharmacodynamic characteristics of the opioid is ideal. For example, morphine and hydromorphone have their peak analgesic effect at approximately 15 minutes. Thus, redosing every 1 to 2 hours is an unnecessarily long time and leads to suboptimal pain control. One strategy that has been successfully used in older patients for severe pain in the ED is a two-step hydromorphone protocol.[25] Patients are given 0.5 mg IV hydromorphone, which is repeated in 15 minutes if the patient desires another dose when asked, "Do you want more pain medication?" However, previous opioid exposure needs to be considered to determine appropriate dosing. For example, in some older cancer patients with chronic opioid consumption, doses will likely need to be escalated for pain control.

Meperidine use should be avoided in older patients. It has a neurotoxic metabolite that accumulates with renal impairment common in these patients. Given the availability of alternative opioids, there is little reason to use this medication in the ED, and it is also listed on the Beers criteria.

Regional anesthetics, such as fascia iliaca compartment blocks in patients with hip fractures, have been shown to reduce opioid requirements and should be considered, particularly in older patients, when feasible.[26] Other strategies, such as hematoma blocks and intra-articular steroid injections, should be considered to minimize systemic analgesics when appropriate.

Ketorolac is a valuable alternative to opioids in the ED, and single doses have been shown to be as effective as opioids for pain related to certain indications, such as renal or gallbladder stones. However, it is a potent nonsteroidal antiinflammatory drug (NSAID) with the possibility of causing renal failure or gastrointestinal hemorrhage. This is less likely to occur with isolated doses in the ED setting. Nonetheless, studies have demonstrated similar analgesic effects from ketorolac doses of 10 mg, 15 mg, and 30 mg, indicating a ceiling effect.[27] To minimize the possibility of adverse effects, doses over 10 mg are not recommended, particularly in older adults. Despite lacking antiinflammatory effects, IV acetaminophen has been shown to provide similar pain control compared to IV ketorolac in a heterogenous prehospital population that included older patients.[28] Acetaminophen is a reasonable alternative to NSAIDs in select patients; however, in most health systems, only oral and rectal acetaminophen are readily available. Studies in the perioperative and postoperative settings have failed to show a significant difference in pain reduction or opioid sparing effects between IV and oral acetaminophen leading many health systems to restrict the use of IV acetaminophen given the relatively high cost of the parenteral dosage form.[29]

Clinical Pharmacy Services

There are a growing number of institutions that have pharmacists who practice in the ED. The American College of Emergency Physicians (ACEP) has a policy statement advocating for dedicated pharmacy services to be provided to the ED to promote safe, efficient, and effective medication use in the emergency department.[30] In geriatric EDs, there is a great opportunity to integrate pharmacists, given the myriad drug therapy issues that can lead to suboptimal care.[12] Older adults have more medications prescribed, which increases the risk for medication errors.[31] Pharmacists are able to intercept these errors, preventing patient harm. Given the possibility of drug-induced admissions, pharmacy services can be used to identify medications that may have contributed to an ED presentation. However, resource constraints make it difficult for pharmacists to evaluate each geriatric patient, especially in EDs with large bed capacities.

Obtaining an accurate medication list is necessary for determining the cause of an adverse effect, but this often requires phone calls to

multiple pharmacies and physicians' offices. One option is the use of pharmacy technicians who are also able to perform this function with similar accuracy.[32] Patients can also be referred to the pharmacist based on variables that have been associated with adverse drug events.[33] One clinical decision rule was able to identify 91.3% of patients with adverse drug events by limiting referral of less than half of patients to a pharmacist so that a full review could be conducted. This decision rule is shown in Fig. 180.1.

Even if the presentation is unrelated to an adverse drug event, clinical pharmacists can be used to identify potentially inappropriate therapies that the patient is taking to minimize the possibility for readmissions. For example, it is possible that a patient may be taking two medications from the same drug class prescribed by two different physicians. Applying the Beers, START, and STOPP criteria, the anticholinergic burden and other opportunities for drug therapy optimization can be assessed. Finally, pharmacists serve as an important safety net for drug therapy prescribed by ED clinicians, both within the ED and on discharge. Setting up a system whereby the pharmacist can be consulted and is available to review these medication orders for potential harm is a risk mitigation strategy that may help reduce readmissions by older adults.

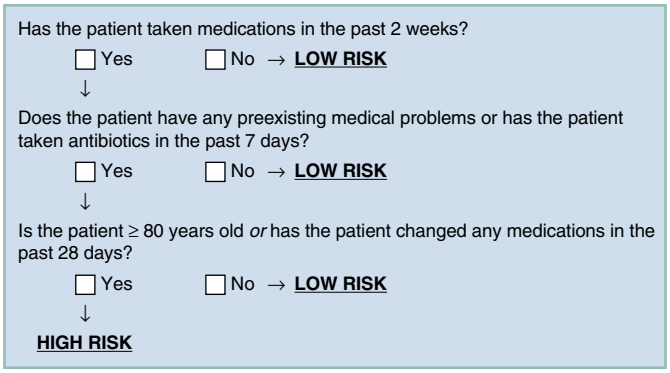

Fig. 180.1 Decision rule to identify adverse drug events. (Adapted from: Hohl CM, Badke K, Zhao A, et al. Prospective validation of clinical criteria to identify emergency department patients at high risk for adverse drug events. *Acad Emerg Med.* 2018;25(9):1015-1026.)

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 180: QUESTIONS AND ANSWERS

1. Which of the following pharmacokinetic change in older adults is associated with increased plasma concentration of drug?

- **a.** Decrease in absorptive capacity in an orally administered medication
- **b.** Decreased glomerular filtration rate in a renally eliminated medication
- **c.** Increase in gastric pH in a medication that is a weak base
- **d.** Increased liver blood flow in a high–extraction ratio medication
- **e.** Increased total body water in hydrophilic medications

Answer: B. Decrease in glomerular filtration rate is common with age. This leads to decreased elimination and increased plasma concentration of a drug. All other options listed would lead to decreased plasma drug concentrations. Liver blood flow, glomerular filtration rate, total body water, and absorptive capacity decrease with age. However, gastric pH increases.

2. Which of the following is the most appropriate strategy for analgesic provision in an older patient with renal insufficiency and severe abdominal pain in the emergency department?

- **a.** Hydromorphone 0.5 mg IV, followed by the same dose in 15 minutes, if needed
- **b.** Ketorolac, 30 mg IV qid
- **c.** Meperidine, 50 μg IV every 2 hours
- **d.** Morphine, 4 mg IV every 2 hours
- **e.** Oxycodone/acetaminophen, 5/235 mg orally every 2–4 hours

CHAPTER 180: QUESTIONS AND ANSWERS—cont'd

Answer: A. One strategy that has been used successfully in older adults is a two-step hydromorphone protocol. Patients are given 0.5 mg IV hydromorphone, which is repeated in 15 minutes if the patient desires another dose when asked, "Do you want more pain medication?" Hydromorphone does not have active metabolites that would accumulate with renal insufficiency, so it would be an appropriate option for severe pain. Ketorolac should be avoided in older adults with renal insufficiency because the inhibition of prostaglandins can decrease renal blood flow. Meperidine use is no longer recommended because of a neurotoxic metabolite and accumulation in renal insufficiency. Morphine has an active metabolite that also accumulates in renal insufficiency. Oxycodone-acetaminophen given orally is not appropriate for severe acute pain due to delayed onset of effect. Bioavailability of oral medications may further be delayed in older adults.

3. Which of the following agents should be avoided for outpatient use in an older patient being discharged from the emergency department?
   - **a.** Diphenhydramine
   - **b.** Loratadine
   - **c.** Acetaminophen
   - **d.** Clindamycin
   - **e.** Metronidazole

Answer: A. Diphenhydramine and other first-generation antihistamines should be avoided in older patients given the potential for anticholinergic toxicity. The use of diphenhydramine in the emergency department for severe allergic reactions is appropriate; however, longer term outpatient use is not recommended. This effect is much less common with second-generation antihistamines such as loratadine. Acetaminophen is generally considered safe in older patients. Antibiotics such as clindamycin and metronidazole have the potential to cause drug-drug interactions with other home medications; however, by themselves they are not typically problematic.

4. Which of the following medications prescribed on discharge is most likely to interact in an older patient taking warfarin?
   - **a.** Albuterol inhaler for asthma
   - **b.** Ciprofloxacin for urinary tract infection
   - **c.** Insulin NPH for hyperglycemia
   - **d.** Oxycodone for fracture pain
   - **e.** Promethazine for nausea

Answer: B. Studies of harmful drug interactions in older adults have shown that the initiation of antibiotics in patients taking warfarin can lead to bleeding. Ciprofloxacin can lead to an elevation in the international normalized ratio (INR) due to disruption of vitamin K synthesis in patients taking warfarin. Thus, more frequent monitoring is required when ciprofloxacin is initiated. The other options listed do not interact with warfarin. However, oxycodone and promethazine can be harmful because of central nervous system effects, potentially leading to falls.

5. Which of the following statements is true regarding neurologic emergencies in older adults?
   - **a.** Ampicillin is added for the treatment of bacterial meningitis for additional coverage against *Enterococcus faecalis.*
   - **b.** Anticholinergic medication use is not associated with delirium.
   - **c.** Haloperidol, 10 mg IV, is recommended for acute agitation due to underlying psychiatric illness.
   - **d.** In patients with ischemic stroke who are older than 80 years, alteplase should not be administered if the patient presents 4 hours after the onset of symptoms, according to guidelines.
   - **e.** Large doses of haloperidol given via the IV route have been associated with QTc interval prolongation

Answer: E. There is a US Food and Drug Administration (FDA) black box warning regarding the use of haloperidol and QTc interval prolongation. This risk is increased with large doses given intravenously. Polypharmacy in older adults also puts them at risk for drug interactions due to concomitant QTc-prolonging agents. Doses of haloperidol should be less than 5 mg in most older adults. Ampicillin is added for bacterial meningitis to cover *Listeria monocytogenes.* Although recent evidence has extended the 3-hour time window to 4.5 hours for receiving alteplase after the onset of stroke in a small subset of patients, those older than 80 years are not eligible, according to guidelines. Anticholinergic medications are known to be associated with delirium and sedation.

Geriatric Abuse and Neglect

Tony Rosen

KEY CONCEPTS

- Elder mistreatment, which includes physical abuse, sexual abuse, neglect, emotional/psychological abuse, abandonment, financial/material exploitation, and self-neglect, is common and may have serious medical and social consequences.
- Elder mistreatment is under-recognized by emergency clinicians and under-reported to the authorities.
- Signs suggestive of potential elder abuse and neglect that should be recognized by emergency clinicians may exist in the medical history, physical examination, and medical/laboratory markers.
- Emergency clinicians should be vigilant in assessing for the possibility of elder abuse or neglect and routinely ask elderly patients about mistreatment, even in the absence of signs and symptoms. Screening protocols may be helpful.
- Using a team-based approach including social workers and other emergency department (ED)-based professionals may improve elder abuse detection, and Emergency Medical Services can play a critical role.
- ED management of elder abuse should include the following: treating acute medical and psychological issues, ensuring patient safety, and proper reporting to the authorities. Trauma-informed care should be provided.
- Emergency clinicians should hospitalize elderly patients who are in immediate danger or implement a care plan that prevents them from having any contact with the suspected abuser(s) but must respect the wishes of an older adult with decision-making capacity who refuses interventions and desires to return to an abusive situation. Trauma-informed care should be provided.
- Emergency clinicians should document completely and accurately the history and all physical findings in cases of suspected elder abuse or neglect, as this documentation may be critical to ensure justice for the victim.

FOUNDATIONS

Background

An ED encounter offers an important opportunity to identify and initiate intervention for elder abuse and neglect, a common but under-recognized phenomenon that may have serious medical and social consequences. Elder abuse and neglect includes: any actions or negligence that may cause harm or risk of harm committed by someone in a relationship of trust or when the victim is targeted due to age or disability, Table 181.1. Many victims may suffer concurrently from multiple types of abuse.

Epidemiology and Scope of the Problem

As many as 10% of older adults living in the community and more than 20% of nursing home residents experience some form of abuse, neglect, or exploitation each year. Psychological/emotional abuse, financial mistreatment, and neglect are most commonly reported, while physical and sexual abuse are less common. Elder abuse is strongly associated with adverse health outcomes, including depression, exacerbations of chronic illness, and dramatically increased mortality. Older adults suffering abuse are more likely to present to the ED, be hospitalized, and be placed in a nursing home. The direct medical costs of elder abuse and neglect, though challenging to quantify, are estimated to be many billions of dollars annually and growing as the geriatric population continues to increase.

Despite its frequency and potential for harm, elder abuse and neglect is under-recognized and under-reported, with many sufferers enduring it for years before discovery. Studies suggest that as few as 1 in 24 cases of elder abuse is reported to the authorities, and much of the associated morbidity and mortality is likely due to delay in identification and intervention.

Many factors contribute to elder abuse and neglect (Table 181.2), and researchers have attempted to identify risk factors for becoming a victim or perpetrator. Findings have been inconsistent and difficult to interpret, partly due to methodological limitations, and to the heterogeneity of elder mistreatment cases. Potential risk factors for becoming a victim or perpetrator based on existing evidence are described in Box 181.1. Cognitively impaired older adults are more likely to be victimized. Sub-populations including military veterans and lesbian/gay/bisexual/transgender older adults may be at particularly high risk. Many cases of elder mistreatment occur in the absence of risk factors, however, and the phenomenon crosses ethnic and socioeconomic boundaries.

Identifying Elder Abuse and Neglect in the Emergency Department

The ED visit provides an opportunity to identify elder abuse or neglect. For many older adults, assessment by health care providers is their only contact outside the family. Limited research suggests that elder abuse and neglect victims are less likely to see a primary care provider but receive ED care more frequently than other older adults,[1] often for management of acute illnesses or injuries. A recent study found that 7% of cognitively intact older ED patients reported a history of physical or psychological mistreatment during the previous year.[2] The actual prevalence is likely much higher, as abuse is more common among cognitively impaired older adults, and because neglect and financial exploitation were not included.

TABLE 181.1 Types of Elder Abuse and Neglect

Type	Definition	Examples
Physical abuse	Intentional use of physical force that may result in bodily injury, physical pain, or impairment	• Slapping, hitting, kicking, pushing, pulling hair • Use of physical restraints, force-feeding • Burning, use of household objects as weapons, use of firearms and knives
Sexual abuse	Any type of sexual contact with an elderly person that is non-consensual or sexual contact with any person incapable of giving consent	• Sexual assault or battery, such as rape, sodomy, coerced nudity, and sexually explicit photographing • Unwanted touching, verbal sexual advances • Indecent exposure
Neglect	Refusal or failure to fulfill any part of a person's obligations or duties to an elder, which may result in harm—may be intentional or unintentional	• Withholding of food, water, clothing, shelter, medications • Failure to ensure elder's personal hygiene or to provide physical aids, including walker, cane, glasses, hearing aids, dentures • Failure to ensure elder's personal safety and/or appropriate medical follow-up
Emotional/ psychological abuse	Intentional infliction of anguish, pain, or distress through verbal or nonverbal acts	• Verbal berating, harassment, or intimidation • Threats of punishment or deprivation • Treating the older person like an infant • Isolating the older person from others
Abandonment	Desertion of an elderly person by an individual who has assumed responsibility for providing care for an elder or by a person with physical custody	
Financial/material exploitation	Illegal or improper use of an older adult's money, property, or assets	• Stealing money or belongings • Cashing an older adult's checks without permission and/or forging his or her signature • Coercing an older adult into signing contracts, changing a will, or assigning durable power of attorney against his or her wishes or when the older adult does not possess the mental capacity to do so
Self-neglect	Behavior of an older adult that threatens his/her own health or safety—excluding when an older adult who understands the consequences of his or her actions makes a conscious and voluntary decision to engage in acts that threaten his/her health or safety	• Refusal or failure of an older adult to provide himself or herself with basic necessities such as food, water, shelter, medications, and appropriate personal hygiene • Disregard for maintenance of safe home environment and/or hoarding

Adapted from National Center on Elder Abuse: Types of abuse. Available at https://ncea.acl.gov/Suspect-Abuse/Abuse-Types.aspx.

TABLE 181.2 Selected Theories of the Underlying Causes of Elder Abuse and Neglect

Theory	Description
Transgenerational violence	Family violence is a learned behavior, and abused children grow up to potentially abuse not only their own children but also perhaps parents
Psychopathology of the abuser	Mental health issues of the abuser, including personality disorders, poorly treated mood disorders or schizophrenia, alcoholism, and other substance abuse problems, lead to abusive behavior
Dependency	Increasing frailty, including functional and cognitive disability, result in overwhelming care needs that leave an older adult vulnerable to abuse by an overburdened caregiver
Stressed caregiver	A caregiver who has become increasingly stressed (from caregiving or other causes) may be more likely to be abusive
Isolation	Greater social isolation due to disability, illness, and age increases an older adult's vulnerability to abuse or neglect

Adapted from: Jones JS, Holstege C, Holstege H. Elder abuse and neglect: understanding the causes and potential risk factors. *Am J Emerg Med*. 1997;15:579-583.

Additionally, the nature of an ED encounter increases the potential for detection, as an older adult is typically assessed over several hours by multiple providers.

Despite the opportunity, emergency clinicians seldom identify and report elder abuse and neglect. Several reasons exist for this missed opportunity, including inadequate training, difficulty distinguishing between intentional and unintentional injuries, lack of time to conduct a thorough evaluation for abuse, concern about involvement in the legal system, a victim's unwillingness to report, and a victim's inability to report due to cognitive impairment. For the health of our patients, it is critical that all emergency care providers embrace the challenge of identifying and initiating care for victims of elder abuse and neglect.

CLINICAL FEATURES

Observation and Medical History

When initially assessing an older adult with a caregiver present, carefully observe their interaction, identifying any clues of a strained relationship. Observations that increase suspicion for elder abuse or neglect are listed in Box 181.2.

History should be taken from the patient in as private a setting as possible, without caregivers or family present. The patient should be assured of privacy and confidentiality since victims may be reluctant to

BOX 181.1 Potential Risk Factors for Elder Abuse

For Becoming a Victim

Functional dependence or disability
Poor physical health
Cognitive impairment/dementia
Poor mental health
Low income/socioeconomic status
Social isolation/low social support
Previous history of family violence
Previous traumatic event exposure
Substance abuse

For Becoming a Perpetrator

Mental illness
Substance abuse
Caregiver stress
Previous history of family violence
Financial dependence on older adult

Acierno R, Hernandez MA, Amstadter AB, et al. Prevalence and correlates of emotional, physical, sexual, and financial abuse and potential neglect in the United States: the National Elder Mistreatment Study. *Am J Public Health*. 2010;100:292-297; Amstadter AB, Zajac K, Strachan M, et al. Prevalence and correlates of elder mistreatment in South Carolina: the South Carolina elder mistreatment study. *J Interpers Violence*. 2011;26:2947-2972; Pillemer K, Burnes D, Riffin C, et al. Elder abuse: background paper for the world report on ageing and health. *Gerontologist*. 2016;56(Suppl 2):S194-205; Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. *Clin Geriatr Med*. 2014;30:687-712.

BOX 181.2 Observations from Interaction Between Older Adult and Caregiver That Should Raise Concern for Elder Abuse or Neglect

Older adult and caregiver provide conflicting accounts of events
Caregiver interrupts/answers for the older adult
Older adult seems fearful of or hostile towards caregiver
Caregiver appears unengaged/inattentive in caring for the older adult
Caregiver appear frustrated, tired, angry, or burdened by the older adult
Caregiver appears overwhelmed by the older adult
Caregiver appears to lack knowledge of the patient's care needs
Evidence that the caregiver and/or older adult may be abusing alcohol or illicit drugs

disclose due to a desire to protect the abuser (often a spouse or child), dependency on the caregiver, shame, cultural or ethnic beliefs, or a fear of reprisal or institutionalization. If a translator is needed, a professional translator or telephone/virtual translation service should be provided. A family member or the caregiver should not be used as an interpreter even if they are not suspected to be an abuser.

The assessment for elder mistreatment should be incorporated into the routine evaluation. Potential historical indicators of elder mistreatment are listed in Box 181.3. The emergency clinician may ask in detail about the reason for the visit and then inquire about the patient's health in general, focusing on the safety of the home environment, functional status, cognition, need for support or assistance, and any feelings of isolation and depression. Box 181.4 suggests potential questions to assess for abuse. If the older adult is presenting with an injury, the

BOX 181.3 Indicators from the Medical History of Possible Elder Mistreatment

Poor living conditions according to paramedics or others
Unexplained injuries
Past history of frequent injuries
Delay between onset of medical illness or injury and seeking of medical attention
Recurrent visits to the ED for similar injuries
Using multiple physicians and EDs for care rather than one primary care physician ("doctor hopping or shopping")
Noncompliance with medications, appointments, or physician directions
Patient or caregiver reluctant to answer questions
Strained patient/caregiver interaction
Inconsistent history of injury mechanism between the patient and caregiver
Elderly patient referred to as "accident prone"
Caregiver not able to give details of the patient's medical history or routine medications
Caregiver answers the questions regarding the patient
Abandonment of the patient in the ED by the caregiver

ED, Emergency department.

patient should be questioned about how the injury occurred, including directed questions regarding whether anyone has hit, punched, pushed, tripped, or kicked the patient. The evaluation should also include an assessment for behavioral signs and symptoms suggestive of potential elder mistreatment, including fear, anxiety, poor eye contact, low self-esteem, and helplessness.

Unfortunately, obtaining a reliable history from victims of elder abuse and neglect is often difficult. Many older adults have cognitive impairment that prevents them from providing an accurate medical history. Even in these cases, an attempt should be made to interview the patient, in that recent research suggests that older adults with cognitive impairment can reliably report abuse.[3] Whenever an older adult is unable to provide a history, information should be sought from others besides the caregiver such as other family members, the primary care physician, neighbors, or visiting nurses.

A separate interview of the caregiver or suspected abuser is often useful. It may reveal discrepancies from the patient's history. In addition, a caregiver who is unfamiliar with an older adult's routine medications and necessary medical care may be neglecting them. The interview should be conducted in a nonthreatening and nonjudgmental manner. Verbal expressions of sympathy, explicit recognition of the challenges, and demonstrations of support can be beneficial for the caregiver and also promote information sharing. Questions should also explore whether any important changes or recent stresses have occurred in the household, whether the caregiver feels that the patient is a burden, the caregiver's other dependents and responsibilities, and whether any respite services or other home help services have been made available.

Physical Examination

Physical examination should include a thorough exam for signs of injury and abuse, including identification of bruising peritoneal injury. Additional attention should be given to the skin and intra-oral exam. Geriatric patients with multiple suspicious physical findings may be more likely to be victims of elder abuse or neglect than those with isolated findings.

When an older adult presents with an acute injury (such as a fall), consider whether the reported mechanism is consistent with the injuries suffered. Research has begun to systematically explore

BOX 181.4 Questions for Use in Asking Patients About Elder Abuse

Please explore any positive responses in more detail.
In the last 6 months:

Physical Abuse	Has anyone tried to harm you? Have you been hit, slapped, pushed, grabbed, strangled, or kicked? Are there guns or other weapons in your home? Does anyone close to you have access to guns or other weapons?
Sexual Abuse	Has anyone touched you in ways or places you did not want to be touched?
Neglect/Functional Status	Have you relied on people for any of the following: bathing, dressing, shopping, banking, or meals? a. If yes, have you had someone who helps you with this? b. If yes, how often do you receive help? Is this help enough? c. Have they done a good job? Are they reliable? d. What happens if no one is available to help? Has anyone prevented you from getting food, clothes, medication, glasses, hearing aids, medical care, or anything else you need to stay healthy?
Psychological Abuse	Has anyone close to you called you names, put you down, or yelled at you? Has anyone close to you ever threatened to punish you or put you in an institution? Have you felt sad or lonely at home? Have you felt afraid of anyone close to you? Do you distrust anyone close to you? Does anyone close to you drink or use drugs?
Financial Exploitation	Has anyone tried to force you to sign papers against your will, or that you did not understand? a. Has anyone pressured you to give them money or property? Has anyone taken money or things that belong to you without asking? Does anyone close to you rely on you for housing and/or financial support?

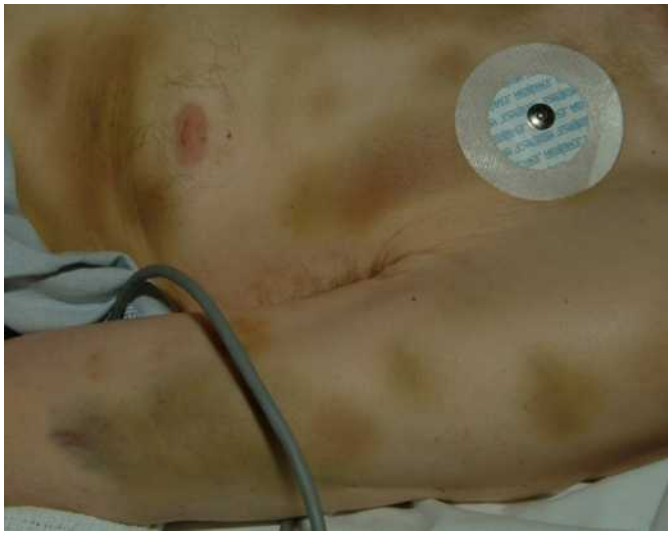

Fig. 181.1 Atypical bruising of the chest in a case of substantiated abuse. (From: Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med. 2014;30:687-712.)

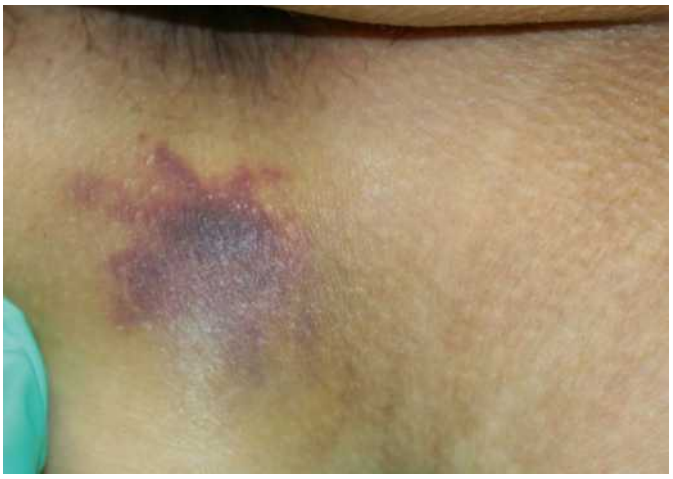

Fig. 181.2 Pattern bruise on the left buttock from unknown object. (From: Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med. 2014;30:687-712.)

whether injury patterns exist that are suggestive of, or specific for, elder mistreatment (analogous to findings in child abuse, such as shaken infant syndrome and bucket-handle metaphyseal fracture). Unfortunately, it can be difficult to distinguish between elder mistreatment and the sequelae of unintentional trauma or medical illness. This difficulty may be due to normal physiologic changes that occur with aging, such as osteopenia, thinning of the skin with easy bruising, as well as the impact of medications commonly used, including anticoagulants. Studies have found that abuse victims, in comparison to other older adults, have bruises that were more often large (>5 cm) and on the face, lateral right arm, or posterior torso.[1] Physical abuse and assault-related injuries most commonly occur on the head/face, neck, and upper extremities[4] (Fig. 181.1). Abuse victims are more likely than older adults presenting to the ED with a fall to have injuries to the left cheek/zygoma, with neck and ear injuries occurring commonly in abuse victims but generally not after a fall. Additionally, physical elder abuse victims are more likely to have maxillofacial/dental/neck injuries combined with no upper and lower extremity injuries, suggesting that the simultaneous presence and absence of injuries may be helpful in differentiating intentional from unintentional injuries in older adults.[4] Patterned injuries, wrist or ankle lesions suggesting possible inappropriate restraint, burns suggesting immersion injury or cigarette burns, or fractures of different ages should suggest elder physical abuse (Figs. 181.2 to 181.5). These and other findings may be used to develop clinical prediction rules in the future to assist ED providers in identifying injury patterns suspicious for abuse.

Sexual assault of older adults occurs, is underrecognized, and should be considered. Perineal injury should illicit concern for sexual assault in the elderly and should prompt reporting (Figs. 181.6 to 181.7). If sexual abuse is suspected or reported, a complete sexual assault examination is recommended.

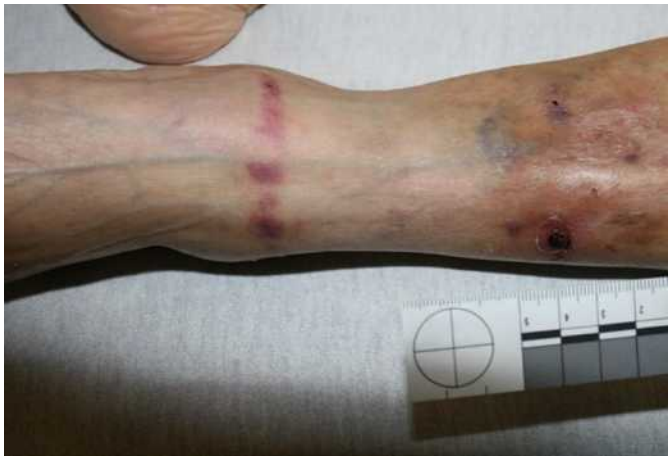

Fig. 181.3 Pattern bruising on lower leg from a ligature. (From: Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med. 2014;30:687-712.)

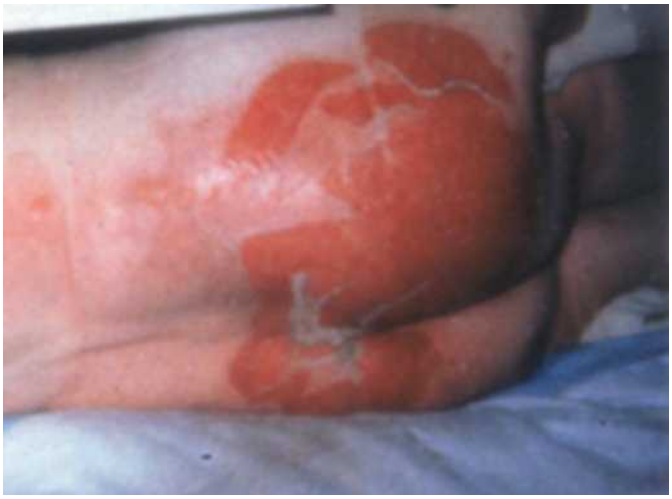

Fig. 181.4 Burn injuries on the back and buttocks from scalding water. (From: Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med. 2014;30:687-712.)

Neglect needs to be considered when the elder in the care of others shows signs of poor care such as poor hygiene, advanced pressure ulcers, advanced medical disease that may have responded to early intervention, and neglected dental disease (Figs. 181.8 to 181.11).

DIAGNOSTIC TESTING

No laboratory tests exist to definitively detect abuse, but medical and laboratory findings may suggest elder mistreatment. These include biomarkers of malnutrition, dehydration, anemia, hypothermia/hyperthermia, and rhabdomyolysis. In addition, serum or urine drug levels may provide clues to medication by a caregiver. Perpetrators may divert controlled substances, such as narcotic pain medications, for their own use or to sell. Elevated serum levels of prescription medications may suggest intentional or unintentional overdose, and the presence of toxins or drugs that have not been prescribed may indicate poisoning. Platelet count and coagulation studies may be helpful in ruling out a medical etiology for unexplained or abnormal bruising. Evidence of sexually transmitted diseases in an older adult not known to be sexually active may suggest sexual abuse.

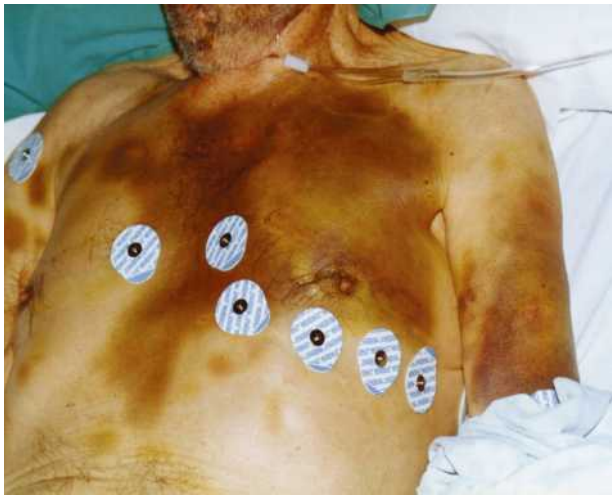

Fig. 181.5 A 70-year-old man was brought from his caregiver's home to the emergency department (ED) by police after his daughter found him severely bruised. He had multiple contusions at varying stages of healing on his chest and arms, as well as a linear patterned injury across his left anterior chest. The central and bilateral locations of the contusions, varying colors, and linear pattern of the bruise on the left side of his chest are highly suggestive of physical abuse. (Courtesy Dr. D.C. Homeier.)

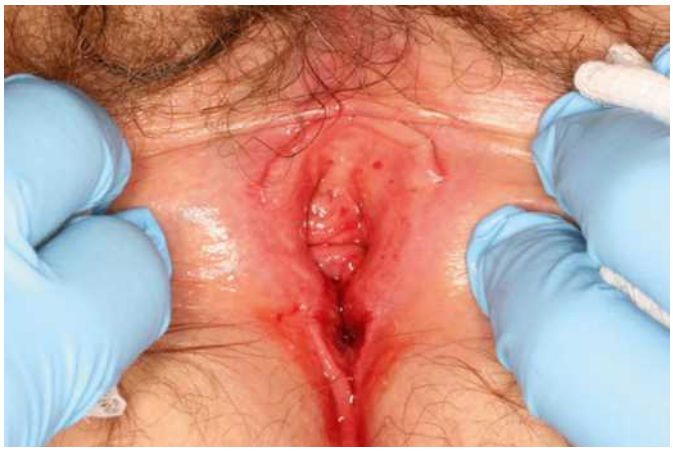

Fig. 181.6 A 65-year-old woman in a nursing home with posterior fourchette and perineum laceration from rape by resident. (From: Speck PM, Hartig MT, Likes W, et al. Case series of sexual assault in older persons. Clin Geriatr Med. 2014;30:779-806.)

Diagnostic Imaging

Unlike child abuse, there is very limited literature on imaging correlates for elder abuse, and diagnostic radiologists typically receive no formal training in elder abuse detection. Findings suggestive of elder abuse or neglect include co-occurring old and new fractures, high-energy fractures despite low-energy mechanism, distal ulnar diaphyseal fractures, and small bowel hematomas. Any concern for elder abuse should be verbally communicated to the radiologist reading the images with a request that they consider whether the imaging findings are consistent with the purported history. They may also consider additional screening imaging tests, such as maxillofacial CT scan and chest x-ray, analogous to the skeletal survey used in child abuse to assess for occult acute and chronic fractures.

Screening

Though ED screening often consists of a single question about home safety, it is generally accepted that this is inadequate and represents a

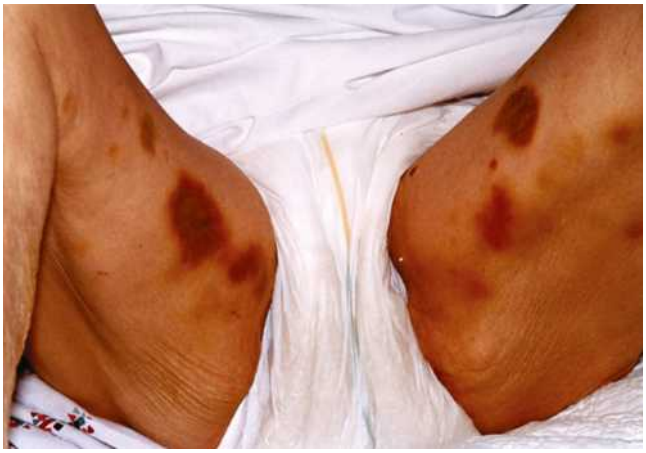

Fig. 181.7 A 69-year-old woman with severe dementia who resided in a skilled nursing facility was brought to the emergency department (ED) after her daughter noticed that the patient had bruises on her bilateral inner thighs. When the daughter inquired about the bruises, she was told by the facility staff that the patient had fallen. These bruises are in a location that raises suspicion for sexual abuse. The emergency clinician consulted the hospital's adult protection team, which contacted local law enforcement; the long-term care ombudsman was also notified for further investigation. The hospital's sexual assault response team was consulted and conducted a sexual assault forensic examination for evidence collection. (Courtesy Dr. D.C. Homeier.)

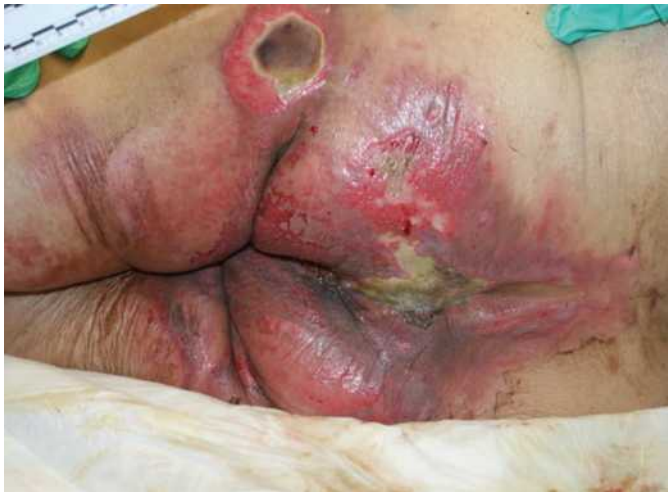

Fig. 181.8 Case of elder neglect showing moisture-associated skin damage (MASD) and ulcers in the sacrum, buttocks, and thighs. (From: Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med. 2014;30:687-712.)

missed opportunity. Multiple more robust screening tools have been developed, though none have yet been validated for use in the ED. The Elder Abuse Suspicion Index (EASI) is a short tool validated for cognitively intact patients in ambulatory care and may be appropriate for use in the ED. The ED Senior AID (Abuse Identification) tool is a promising recently developed ED-specific screening tool that is highly sensitive and specific and is currently undergoing multi-site validation.[5]

The American Medical Association, the American College of Emergency Physicians, and the Joint Commission have strongly supported routine assessment for all types of family violence, including elder mistreatment, but their choice of words has stopped short of recommending universal screening. Additionally, though screening for elder abuse has the potential to identify occult cases so that intervention may be

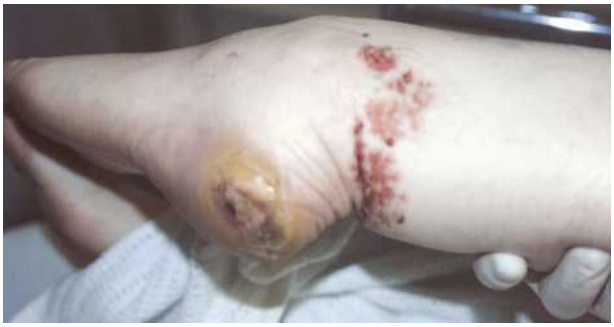

Fig. 181.9 A 65-year-old developmentally delayed but ambulatory woman was brought to the emergency department (ED) by her family on account of "unruly behavior." Examination of her left heel revealed a pressure ulcer, and her left ankle revealed an erythematous rash in a circumferential pattern. This may represent the use of a restraint, resulting in the pressure ulcer. (Courtesy Dr. D.C. Homeier.)

initiated, evidence of improved outcomes to support screening for elder mistreatment does not yet exist. The US Preventative Services Task has not recommended screening for elder abuse in health care settings.[6]

Targeted screening of only high-risk patients may be a desirable alternative to universal screening, reducing resources that need to be devoted to the screening process and increasing the proportion of patients who screen positive. High-yield demographic factors have yet to be identified. Future strategies may use data elements from the electronic health record or other health care utilization data combined with machine learning approaches to perform automated prescreening to identify high-risk patients.

MANAGEMENT

A multidisciplinary team-based approach is required to improve the recognition and management of elderly mistreatment. Key to success is empowering all members of the team to share observations and recommendations in a safe context. Large EDs typically have social workers or case managers in the department, while smaller EDs usually have access to them in the hospital or on-call. These professionals assess the patient's home situation, support system, financial resources, and social service needs, and also provide counseling. Their assessment may identify evidence or risks for mistreatment that is not detected by medical providers. If possible, dependent older adult ED patients being considered for discharge and any patient for whom a concern about elder abuse or neglect exists should be seen by a social worker or case manager. The Emergency Department Elder Mistreatment Assessment Tool for Social Workers (ED-EMATS), a structured assessment tool for ED social workers who have less experience evaluating patients for elder mistreatment, was recently developed.[7]

Nurses and patient care technologists (PCTs) are also instrumental members of the team since they have more face-to-face contact with patients, caregivers, and family than medical providers and may observe interactions that arouse suspicion requiring further investigation. Also, nurses and PCTs provide personal care (e.g., diaper changes) that may identify otherwise missed suspicious physical findings. Patient escort and radiology technicians are yet other personnel who may be confided in by the patient: Radiologic technicians may be particularly well-positioned to identify abuse, as they can privately assess and interview patients in the radiology suite while conducting imaging examinations.

Emergency Medical Services

Older adults are four times more likely than younger patients to use EMS, and these providers are the first clinicians to evaluate acutely

Fig. 181.10 A 72-year-old woman was brought to the emergency department (ED) by paramedics for "not eating for 5 days" according to her family. The paramedics noted she was covered in urine and feces. The following signs were of concern for neglect: elongated toenails (A), pressure sores (B), poor hygiene, and a delay in seeking medical care. (Courtesy Dr. D.C. Homeier.)

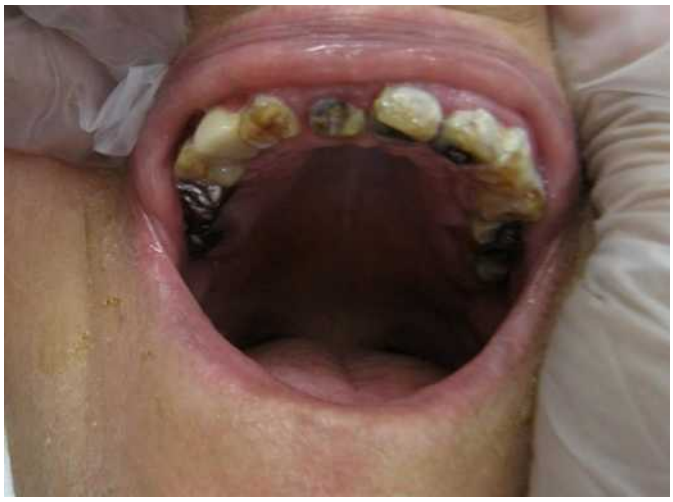

Fig. 181.11 Poor dentition in a substantiated case of dependent adult neglect. (From: Gibbs LM. Understanding the medical markers of elder abuse and neglect: physical examination findings. Clin Geriatr Med. 2014;30:687-712.)

injured or ill older adults, typically in the patient's home. EMS providers can identify unmarked medication bottles or expired medications, as well as multiple bottles of a single medication. They can check whether any food is available in the refrigerator or pantry. EMS providers have an opportunity to observe hazards including vermin infestation, extreme clutter/hoarding, inappropriately hot or cold temperature, or utilities that aren't working. Given that EMS activation is usually unplanned, an abusive or neglectful caregiver is often not able to clean up the patient or home before EMS arrives. EMS providers may observe unusual or inappropriate interpersonal dynamics between caregivers and older adults as well as evidence of drug or alcohol use. Further, EMS may provide care to older adult patients who decline ED transport.

The Detection of Elder Abuse Through Emergency Care Technicians (DETECT) screening tool has recently been developed and has been shown to be feasible for EMS providers to integrate into their practice.[8] As EMS practice is heavily protocolized, changes to improve elder abuse and neglect detection could be implemented broadly through changes at a system level. Hopefully, use of integrated electronic medical records and the development of standardized screening tools and protocols, will facilitate increased detection of elderly mistreatment by EMS and communication with hospital providers.

Management of suspected elder abuse or neglect includes treating acute medical and psychological issues, ensuring patient safety, and proper reporting to the authorities. Traumatic injuries and metabolic abnormalities including dehydration are common and should be stabilized and treated. Management of worsening chronic medical conditions may be required due to an abuser's failure to provide appropriate care. In some circumstances, hospitalization may be necessary to provide extended treatment and observation.

If a mistreatment victim is in immediate danger, the patient should be prevented from having any contact with the suspected abuser. In extreme cases, this may require a security watch for the patient and even having the abuser removed from the ED. In these cases, law enforcement, hospital social workers, and administrators should be alerted. Alternative living arrangements may need to be arranged for the patient, with a reliable family member or friend or in an appropriate emergency shelter. If none of these options are available, the patient may require hospital admission to ensure safety.

If the patient refuses intervention, a determination must be made whether the patient has the capacity to make this decision. A psychiatric consultation may be helpful. The wishes of an older adult with decision-making capacity who desires to return to an abusive situation must be respected, as in cases of intimate partner violence among younger adults. If possible, the patient should be educated about the potential for escalation in violence and abuse and provide appropriate referral materials for future use. If an older adult does not have decision-making capacity, treatments that are in the patient's best interest, including hospitalization, should be provided.

In some cases, a patient may not have decision-making capacity, and the suspected abuser may be the patient's official health care proxy

or power of attorney. Under these circumstances, hospital administration, legal, and/or the ethics committee should be involved to assist with health care decision making and guardianship.

In suspected cases of elder mistreatment without an imminent threat to a patient's safety, interventions are individualized. If the patient wants to return home and may be safely discharged, follow-up should be coordinated with the patient's primary care physician. Social workers may be able to offer support resources to both the patient and the caregiver. Ideally, elder mistreatment cases are managed in the community by a case manager or a team and involve home visits and advocacy.

A multidisciplinary ED-based consultation team, modeled on child protection team interventions, may assist in optimizing the care and ensuring the safety of these vulnerable patients. This team coordinates medical, forensic, and social work evaluations, and assist with a safe disposition. The team's presence can lessen the burden on ED providers who are generally multitasking and caring for multiple patients. ED providers may be more willing to pursue suspicions about elder abuse and neglect because of the availability of a team to assist with care, which may lead to higher rates of identification. These multidisciplinary ED elder protection consultation teams have been developed and are undergoing impact evaluation.

Trauma-Informed Care

Trauma-informed care to older adult victims of abuse or neglect involves being sensitive to the profound impact of traumatic and stressful life experiences on a patient's mental and physical health. Ongoing abuse or neglect, which may occur daily for years, and also previous—even remote—traumatic experiences may cause depression, anxiety, or posttraumatic stress disorder. Trauma-informed care is particularly important for older adults, who have had a long life to experience stressful or traumatic events.

Providing trauma-informed care focuses on the patient's need for safety, respect, and acceptance. The victim's choice and control should be maximized while minimizing re-traumatization through treatment. Recommended bedside strategies include:

- Using language and grammar that is easily understood, neutral, and not intimidating
- Limiting the number of times a victim has to talk about the assault
- Avoiding words such as violence, abuse, or criminal behavior if the victim does not initially conceive of what has occurred as abusive or criminal
- Asking permission before touching a potential victim
- Maintaining the victim's privacy and confidentiality
- Offering the support of an advocate if available
- Being mindful of culturally specific expectations regarding interactions between older adult patients and younger care providers

ED clinicians should also use these trauma-informed strategies for cognitively impaired patients, as they may still be deeply affected by ongoing or previous traumatic exposures.

Documentation

The history should be documented in the patient's own words, and avoid using biased words such as "claims" or "alleged." Pertinent social history (e.g., patient's functional status, caregiver's relationship to patient, living arrangements) should be included. The patient's general appearance on initial arrival to the ED should be described including signs of potential neglect (e.g., soiled diaper, inappropriate or dirty clothing, or dirt under nails). Injuries of any type (e.g., fractures, lacerations, and contusions) should be described, including their number, size, location, and stage of healing, and comment about whether the injuries are consistent with the reported mechanism. Providers should consider using a body diagram/traumagram to precisely document physical findings. The Geri-IDT, a practical tool to improve medical documentation of geriatric injuries for potential forensic use, was recently developed and may be helpful.[9] If possible, photographs of all injuries should be added to the medical record. The results of laboratory investigations and imaging studies should also be recorded. Careful documentation of interventions, follow-up plans, and referrals should be made. In cases of suspected elder abuse that result in legal action, thorough documentation may be critical to ensure justice for the victim.

Reporting

Suspected cases of elder abuse or neglect should be reported to the appropriate authorities. A reasonable cause to suspect abuse is all that is necessary. Health care providers are mandated reporters for elder abuse in most but not all US states and, in many states, elder abuse must be reported even if the victim does not want a report made. As laws differ, ED clinicians should be aware of their state's requirements. This information is available on a state's department of health website, and a summary is at: http://www.napsa-now.org/wp-content/uploads/2014/11/Mandatory-Reporting-Chart-Updated-FINAL.pdf.

Adult Protective Services (APS) is typically the agency that investigates these cases for community-dwelling older adults. Information on how to contact state or local APS in different areas is available at: http://www.napsa-now.org/get-help/help-in-your-area/. The scope of the APS response must be appreciated: in most US states, APS can only investigate cases where an older adult has cognitive or functional impairment, and the agency will not act on reports if they judge that the older adult does not meet these criteria. Additionally, APS functions differently than Child Protective Services and will not open their investigation while a patient is in the ED or hospital. They will only open an investigation after discharge, generally within 72 hours. Consequently, ED clinicians should consider reporting to the local police when concerned about a patient's immediate safety or that a crime has been committed.

Collaboration with the Community

EDs may benefit substantially from improving communication, connection, and collaboration with APS and other community-based service providers. In many communities, multidisciplinary teams (MDTs) have developed that meet regularly to manage complex elder abuse and neglect cases. Members of these MDTs include APS case workers, prosecutors, civil attorneys, law enforcement professionals, financial services professionals, and health care providers.

Resources

The Administration for Community Living's National Center on Elder Abuse website (https://ncea.acl.gov) is the most comprehensive online resource available on elder abuse and neglect. Also, http://www.elderabuseemergency.org is a website designed for emergency clinicians that provides access to tools, information, and resources that may be useful for reference and when on shift.

SPECIFIC ISSUES

Elder Mistreatment in Institutions

Residents of skilled nursing facilities represent a large and growing percentage of older adults who present to the ED and are at particularly high risk for mistreatment. Over the last several decades, increased regulatory scrutiny has improved care and reduced staff mistreatment of older adults in skilled nursing facilities through the Long-Term Care

Ombudsman Program to investigate complaints, mandatory staff background checks, and minimizing the use of restraints.

In addition to staff abuse and neglect of nursing home residents, resident-to-resident elder mistreatment has been recently identified as an important problem.[10] Given that dementia and associated behavioral disturbance in long-term care facilities is high, aggressive behavior can occur between residents. Additional research is needed to improve understanding and recognition of this type of elder mistreatment. When abuse or neglect of any kind in patients from nursing homes is identified or suspected, it should be reported to the long-term care ombudsman in their state (https://theconsumervoice.org/get_help), the state's department of health, or APS for further investigation.

Self-Neglect

Self-neglect includes behaviors in which an older adult threatens his/her own health or safety by failing to perform or refusing assistance with essential self-care. This may include malnutrition due to not eating, failure to take necessary medications, inattention to personal hygiene, hoarding, and not maintaining a safe home environment. Often, patients with self-neglect suffer from an underlying mental disorder, including mild cognitive impairment, depression, psychosis, or substance abuse disorders that prevents them from understanding that their health and safety are at risk and that they need to seek assistance. Self-neglect is associated with increased mortality. It is the most common form of elder mistreatment reported to social services, with reports rising. As with other types of elder mistreatment, recognition is critical because many of these older adults have virtually no other contact outside the home. EMS providers, who may note an empty refrigerator, expired pill bottles, or vermin infestation, may play a pivotal role in the patient's care. Although evidence-based strategies for intervention have not been established, a reasonable approach for an emergency clinician includes laboratory assessment for metabolic and nutritional abnormalities and social work evaluation to offer resources and services. Many of these patients will require hospital admission because it will be impossible to establish a safe discharge plan.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 181: QUESTIONS AND ANSWERS

1. A 70-year-old man who lives alone but has 12 hours per day of a home attendant is brought to the emergency department (ED) by his daughter, who found him in his caregiver's home with severe bruising. On examination, he had multiple bruises at varying stages of healing on the chest and arms, as well as a possible pattern injury—a bruise in the shape of a rectangle—across his left chest. What should you do?

a. Ask the daughter to make a report to adult protective services (APS) because she is the one who found him.
b. Contact the long-term care ombudsman.
c. Do not make a report because he has a long history of falls.
d. File a report with APS or law enforcement if your suspicion for abuse is high.

Answer: D. The injuries noted are of significant concern for elder abuse. The patient should be asked questions in a nonthreatening atmosphere, separate from the caregiver. If the emergency clinician still has high suspicion, a report should be made to APS and/or law enforcement. The physician has the obligation to make the report. The long-term care ombudsman should be contacted only if the suspected abuse occurs in a facility, such as a nursing home.

2. A 72-year-old female is brought to the emergency department (ED) by paramedics for "not eating for 5 days," according to her family. The paramedics noted that she was covered in urine and feces and that the house was filthy, and she was found lying on the floor. On examination, she is noted to have a stage 4 pressure ulcer on her sacrum, which appears infected. Which of the following are concerning for neglect?

a. Delay in seeking care
b. Evidence of dehydration
c. Poor hygiene
d. Pressure ulcer
e. All of the above

Answer: E. All of the above signs are potential markers for neglect.

3. A 69-year-old man with dementia presents to the emergency department (ED) with pneumonia and delirium. He is very confused, and his cognition is markedly worse than his baseline. You are called to the bedside because his adult daughter is at the bedside asking him to sign a legal form giving her the deed to his house. What are the next steps in advocating for your patient?

a. Perform an assessment of cognition and capacity and document it on the chart.
b. Request that the hospital lawyer and notary be present.
c. Tell her that there must be two witnesses present for the form to be legal.
d. Tell the daughter that if there are other children, they must be present for the form to be valid.

Answer: A. When an elderly patient has delirium or is confused because of another medical condition, he or she may lack the capacity to enter into a legal agreement or sign a legal document. The patient described is clearly too confused to understand all of the ramifications of signing his or her home over to another person. Confusion resulting from delirium or dementia is a risk factor for elder financial abuse.

4. An 85-year-old female with dementia, who lives in a skilled nursing facility, presents with bruises on her bilateral inner thighs. The facility staff states that she sustained these while being lifted from her bed to a chair. Who should you notify?

a. Adult protective services (APS)
b. Law enforcement
c. Sexual assault response team
d. The long-term care ombudsman
e. All of the above

Answer: E. The physical findings are concerning for sexual abuse, therefore law enforcement and APS should be called, as well as the sexual assault response team to collect forensic evidence. Because the patient lives in a facility, the long-term care ombudsman should also be called to investigate the possible abuse.

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The Immunocompromised Patient

Jack Perkins Jr. and Christopher P. Waasdorp Jr.

KEY CONCEPTS

- Immunocompromised patients who present with acute infections, especially those that are neutropenic, may appear deceptively benign initially. Their symptoms and signs often mimic noninfectious complications.
- Broad-spectrum antibiotics are indicated after obtaining appropriate cultures of all potential sites of infection, especially if the patient is neutropenic.
- Immunocompromised patients can have serious local or systemic infections without fever.
- Symptoms, signs, and findings of infection may include tachypnea, tachycardia, mental status change, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain.
- The incidence and severity of febrile neutropenia are inversely proportional to the absolute neutrophil count and directly proportional to the duration of neutropenia.
- In neutropenic patients, the temperature should be measured orally or tympanically, not rectally, due to theoretical risk of bacterial translocation and subsequent bacteremia.
- Febrile neutropenia is more common in hematologic malignancy (compared with solid malignancy) and is most likely to occur 7 to 10 days after chemotherapy.
- Gram-positive organisms are responsible for most serious infections in neutropenic cancer patients, but infections due to gram-negative organisms are more rapidly lethal.
- Neutropenic cancer patients with chemotherapy-induced oral mucositis can develop rapid onset of fever with shock. Viridans streptococci is a common pathogen and requires Vancomycin.
- When pneumonia develops in patients with febrile neutropenia, purulent sputum may be absent, and the initial chest radiograph may not show an infiltrate.
- Some low-risk febrile neutropenic patients may not require admission to the hospital. After calculating a Multinational Association for Supportive Care in Cancer (MASCC) risk index score and consulting with their oncologist, discharge may be reasonable.
- Diabetic patients have a high incidence of MRSA infection, osteomyelitis, and wound infections and are at higher risk of bacteremia. Severe infections may be more insidious in presentation.
- Patients with cell-mediated immune deficiency, including those on high-dose corticosteroids, may develop life-threatening infections with intracellular bacteria (*Listeria*, *Salmonella*, tuberculosis), fungi (*Cryptococcus*, *Coccidioides*, *Histoplasma*), herpes simplex virus, and varicella-zoster virus.
- Guidelines no longer support empiric antibiotic treatment of aspiration in alcoholic patients.
- In patients with cirrhosis, empirical treatment of suspected spontaneous bacterial peritonitis (SBP) with antibiotics should be started regardless of ascitic cell count.
- Patients who require hemodialysis for end-stage renal disease have high mortality if they develop pneumonia, *C. difficile* disease, or infections of the dialysis access site.
- Functional or surgical asplenia predisposes to fulminant infection with pneumococci and other encapsulated organisms (*H. influenzae*, *N. meningitidis*, and *Capnocytophaga canimorsus* after dog bites) and, when seen early, may be misdiagnosed as a viral illness, gastroenteritis, or food poisoning.

FOUNDATIONS

Emergency clinicians must recognize and treat infectious complications of cancer, organ transplantation, diabetes, renal failure, cirrhosis, asplenism, human immunodeficiency virus (HIV) infection, and other immunosuppressive conditions. Infections are more common, progressive, and severe in immunocompromised patients, and a wider variety of microorganisms may lead to infection. Immunocompromised persons presenting with acute infections may initially appear deceptively benign. Additionally, they may present with symptoms and signs that mimic noninfectious conditions, only to deteriorate rapidly if they are not evaluated and treated urgently. Many factors result in immunocompromise and predispose patients to infections. These include disruption of the body's protective surfaces, such as skin and mucosal barriers (oral and respiratory mucosa and intestinal and genitourinary surfaces); disorders that directly impair the function of the body's

immune system (e.g., lymphoma, asplenism, and myeloma); drugs and irradiation that suppress or alter immune function; alterations in body substances (hyperglycemia) or solid organ function (kidney and liver failure); and malnutrition, aging, and exposure to antimicrobial agents that inhibit the normal protective resident bacterial flora.

PHYSIOLOGY

Immunity and Immune Deficiency

The body's defense mechanisms consist of surface barriers, innate (natural) and acquired (adaptive) responses. Innate responses occur to the same extent regardless of how often the body encounters the infectious agent, whereas acquired responses improve with repeated exposure. Innate immunity is activated immediately on exposure to an infecting agent, rapidly controlling replication and allowing the requisite 3 to 5 days for the adaptive component to clone sufficient T and B cells to respond more specifically.

Non–Microbe-Specific Immunity

Physical Barriers. Physical barriers, the first line of defense against microorganisms, consist of intact skin, mucosa, cilia, biofilm, gastric acid, antimicrobial peptides and proteins on skin and mucous membranes, and resident microflora. Smoking and pulmonary disease impair physical barriers in the respiratory tract whereas mechanical ventilation or tracheostomy introduces large numbers of microbes that often overwhelm natural clearance. Gastric acid and pancreatic enzymes have antibacterial properties that prevent overgrowth in the upper gastrointestinal tract. Normal peristalsis and mucosal shedding help maintain normal gut flora. Alterations in these factors, such as broad-spectrum antibiotics, alter normal flora and permit overgrowth of pathogens such as *Candida*, multidrug-resistant organisms, and *Clostridium difficile*.

Initial Inflammatory Response and Innate Immunity. The initial inflammatory response to microbial invasion promotes phagocytosis and microbial killing while activating the immune system. This innate immune response is not dependent on prior exposure to the pathogen. The initial inflammatory response factors, mainly produced in the liver, activate many cell types to synthesize and release cytokines, chemokines, and "trigger molecules" that kill the invading organism. This response delivers humoral and cellular immune components to sites of inflammation and initiates antibody production. Cytokines, platelet-activating factor, and hormone-like proteins are secreted from various immune cells and play essential roles in mediation of this response. Cytokines cause migration and adhesion of polymorphonuclear leukocytes and monocytes to sites of bacterial invasion. These cells release granules of substances that mediate vasodilation and increased vascular permeability, leading to edema, warmth, and redness, and allow both phagocytic cells and humoral components to be concentrated at the site of infection.

Reticuloendothelial System. The reticuloendothelial system, composed of tissue macrophages and their blood-borne counterparts, monocytes, removes particulate matter, including microbes, from the lymph and blood. The tissue component is concentrated in the lymph nodes, spleen, liver, marrow, and lung and has particular affinity for encapsulated bacteria, such as pneumococci, meningococci, and *Haemophilus influenzae*. The overwhelming sepsis from encapsulated organisms that can occur in patients with asplenia demonstrates the vital importance of this non–microbe-specific system.

Adaptive (Microbe-Specific) Immunity

Humoral Immunity

Antibodies. Each B cell produces a single microbe-specific antibody type. Stimulation by an antigen (or microbe) causes proliferation of this particular B cell so that large quantities of a specific circulating antibody can be produced. B cells are also active in presenting antigens to T lymphocytes, promoting cell-mediated immunity (CMI).

Immunoglobulins. Immunoglobulin M (IgM) is the first immunoglobulin to appear in response to a new antigen. Although it has less affinity at binding antigens than immunoglobulin G (IgG), IgM provides some recognition of antigens and begins B-cell proliferation before the subsequent development of IgG. IgM is detectable earlier in serum than IgG and serves as a marker for a patient's early response to acute infection.

Secretory immunoglobulin A (IgA) is the predominant immunoglobulin present in gastrointestinal fluids, nasal and oral secretions, tears, and other mucous fluids. IgA inhibits cell adherence of viral, bacterial, and protozoan pathogens and prevents invasion by organisms through the respiratory or gastrointestinal tract.

Immunoglobulin E (IgE), which is expressed in high concentration on the surface of mast cells and basophils, is responsible for immediate-type hypersensitivity responses. Mast cells and IgE are important in defense against helminthic pathogens.

IgG, widely distributed in tissues, accounts for 75% of the total immunoglobulin mass. It crosses the placenta and provides fetal immunity during the first 6 months of life. Congenital or acquired deficiencies of IgG lead to infection with encapsulated organisms because the predominant subtype (IgG2) has affinity for the dense polysaccharides of bacterial cell capsules, such as those of *Streptococcus pneumoniae* and *H. influenzae*.

Complement. The complement cascade, a complex interaction of 30 proteins, is another crucial component of humoral response. Complement is important in producing inflammation and leukocytosis and in recruiting leukocytes to sites of infection. Complement also neutralizes viruses, enhances bacterial binding of opsonin, and lyses bacterial cell walls and membranes.

IgG and IgM activate the classical complement pathway when they are in contact with an antigen, whereas molecules with repeating chemical structures (e.g., bacterial cell walls and capsules) activate the cascade through the alternative pathway. C3 is the merging point of the classical and alternative paths and modulates the response of lymphocytes (CMI). The terminal leg of the cascade, C5 through C9, forms the membrane attack complex, which inserts into cell walls and membranes and leads to cell death.

Individuals with inherited complement deficiencies are predisposed to frequent and recurrent infections with *S. pneumoniae, H. influenzae,* and especially *Neisseria meningitidis* and *Neisseria gonorrhoeae*. The risk of meningococcal infection is increased several thousand-fold, especially in people deficient in C3 and late complement components (C5 to C8). Paradoxically, the disease is usually milder with complement deficiency, and mortality is likewise reduced fivefold to tenfold. This suggests that the host response may be, in part, responsible for the severity of disease in normal individuals and is attenuated in complement deficiency. Acquired deficiencies of complement function may develop in people with rheumatologic diseases, especially systemic lupus erythematosus (SLE). Approximately 40% of patients with SLE have an inhibitor of C5a-derived chemotaxis in their serum, resulting in enhanced susceptibility to infection.

Cell-Mediated Immunity. Cell-mediated immunity (CMI) includes immune responses mediated by T lymphocytes, natural killer (NK) cells, and mononuclear phagocytes. CMI is crucial in controlling infections caused by microbes that survive and replicate intracellularly, including most viruses and some bacterial (obligate and facultative intracellular types), fungal, and protozoan pathogens.

Only 5% of lymphocytes are in circulating blood. Most mature and are active in the marrow, thymus, spleen, and lymph nodes. The last

two sites expose T cells to circulating antigens from invading microbes. Specialized antigen-presenting cells in the lymphoid system sequester antigen and antigen-antibody complexes and present them to T cells via a cell surface molecule called the *major histocompatibility complex (MHC)*. Only with this specific presentation can a T lymphocyte become activated against a particular antigen.

Two major types of T lymphocytes are CD4 (helper cell) and CD8 (suppressor cell). CD4 lymphocytes provide help for other cells in the immune system, including enhanced B-cell antibody production and the production of cytokines. CD8 lymphocytes are generally cytotoxic and mediate the eradication of virally infected target cells and certain tumors. A decline in the number of CD4 cells, with predominance of CD8 cells, is responsible for the increased susceptibility to infection in patients with human immunodeficiency virus (HIV). Despite the cytotoxicity of CD8 cells, immunity is reduced without adequate numbers of CD4 cells.

Patients with defects in CMI are at increased risk for disseminated infection with intracellular bacteria, such as *Mycobacterium tuberculosis, Listeria monocytogenes,* and *Salmonella* species. The DNA viral infections, such as cytomegalovirus, herpes simplex, and varicella-zoster, also affect these patients more severely, as do fungal infections with *Candida, Cryptococcus, Mucor, Aspergillus,* and *Pneumocystis*. Finally, some protozoa are pathogenic in patients without intact CMI, such as *Toxoplasma gondii*. Some infections are seen only below a certain CD4 cell count. *Pneumocystis* pneumonia, for example, is seen almost exclusively in patients with CD4 counts below 200 cells/mL, whereas almost all patients with toxoplasmosis or cryptococcal meningitis have counts below 100 cells/mL. In settings where the CD4 count is not readily available, such as the ED, an absolute lymphocyte count of less than 1000 cells/mL is suggestive of a CD4 count of less than 200 cells/mL.

NK cells, closely related to lymphocytes, are important in the innate immune response and are found in high concentrations in blood and spleen. NK cells recognize infected cells and directly kill these cells while secreting cytokines that activate macrophages to destroy phagocytosed microbes. NK cells are important in defense against intracellular microbes, particularly viruses and intracellular bacteria such as *L. monocytogenes*.

Granulocytic Phagocytes. Granulocytic phagocytes are the cellular effectors of microbe killing, engulfing them and enzymatically lysing their cell membranes or walls. Two major types are polymorphonuclear leukocytes (neutrophils) and macrophages (the tissue version of circulating monocytes). Macrophages have surface receptors that recognize nonvertebrate carbohydrates, such as mannose, to identify and attack "invaders" rather than "self."

Two other types of granulocytes, eosinophils and basophils, are less involved in the ingestion of organisms. Eosinophils attack certain parasitic helminths through the release of toxic proteins. This cell type can increase from 3% to 20% during times of high parasite load. Basophils (rare in circulation) and their tissue counterparts, mast cells, have a high affinity for IgE. On exposure to bound IgE, they release granules with histamine, prostaglandins, leukotrienes, and endogenous heparin to promote blood flow and inflammatory response in combating arthropod ectoparasites or helminth endoparasites. Activation of basophils by IgE bound to pollen and other allergens may affect the allergic-inflammatory response with increased vascular permeability, bronchospasm, and vasodilation.

Half of all neutrophils that leave the bone marrow circulate in the plasma. The other half become marginated, adhering to endothelium, primarily in the lungs, liver, and spleen. During periods of stress or with endogenous or exogenous catecholamines or corticosteroids, these neutrophils demarginate and enter the circulation. If the patient is not neutropenic, demargination causes an increased peripheral neutrophil count composed of mature cells. With bacterial infection, an increased proportion of immature (band) forms is more typically seen.

Neutrophils (and tissue macrophages) bind to and ingest bacteria through phagocytosis. This process is enhanced by proteins called *opsonins* that bind to bacterial surfaces, particularly important in defense against infection with *S. pneumoniae, Streptococcus pyogenes, H. influenzae*, and *Staphylococcus aureus*. C-reactive protein, one of the initial inflammatory response proteins, fulfills this function for certain bacteria, including *S. pneumoniae*. IgG and complement protein C3b also opsonize bacteria, again illustrating the interdependence of the immune system. Actual killing takes place within granulocytes when cytoplasmic granules enzymatically produce potent oxidants. Granulocytes further control bacterial proliferation at the site of infection by elaborating lactoferrin, which locally binds free iron necessary for bacterial replication.

In addition to phagocytosis, macrophages (located in the spleen, alveoli, liver, and lymph nodes) modulate the immune response by presenting antigens to lymphocytes and releasing cytokines and complement components. Activation of macrophages to ingest bacteria depends on interaction with interferon-γ, a cytokine manufactured by T cells, again bridging different components of the immune system.

SPECIFIC DISORDERS

Immune system defects in the immunocompromised patient and the most common pathogens associated with each defect are listed in Box 182.1.

Solid Organ Transplants

For specific issues regarding medication-induced immunocompromised states in solid organ transplant patients, refer to Chapter 183.

Cancer

Patients with cancer frequently suffer from neutropenia or impaired T and B cells function due to the cancer itself or chemotherapy. Defects in the physical barriers of the skin and mucous membranes, including the cytotoxic effects of chemotherapy on cells lining the gastrointestinal tract, predispose to infection. In addition, splenic dysfunction or splenectomy, use of long-term intravascular catheters, frequent use of complex invasive diagnostic and therapeutic procedures, toxic effects of radiation therapy, and frequent colonization with antimicrobial-resistant pathogens predispose to immune system compromise. Despite many advances in supportive care, infections continue to result in severe morbidity and mortality. Furthermore, increasing resistance to antimicrobials is occurring among common pathogens along with the emergence of new opportunistic infections.

Neutropenia

Background

Definitions of neutropenia vary, but the 2018 American Society of Clinical Oncology proposed the following based on absolute neutrophil count (ANC):[1]

Neutropenia: ANC less than 1000 cells/μL
Severe neutropenia: ANC less than 500 cells/μL
Profound neutropenia: ANC less than 100 cells/μL

The nadir of the ANC is usually 7 to 10 days after the conclusion of chemotherapy. Fever in the neutropenic patient is defined as a single oral temperature of 38.3°C (101°F) or greater or a temperature of 38.0°C (100.4°F) or greater sustained over 60 minutes.[1] Febrile neutropenia (FN) usually results from cytotoxic chemotherapy or the underlying malignancy. Risk of FN is largely determined by the

BOX 182.1 The Immunocompromised Patient: Immune System Defects Predisposing to Infection and the Most Common Pathogens Associated with Each

Neutropenia

Bacteria

Gram-negative bacilli
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Enterobacter* sp.
- *Serratia* sp.
- *Citrobacter* sp.
- *Proteus* sp.
- *Acinetobacter* sp.
- *Stenotrophomonas maltophilia*

Gram-positive cocci
- *Staphylococcus epidermidis*
- *Staphylococcus aureus* including methicillin-resistant strains
- *Viridans streptococci*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Enterococcus* sp., including vancomycin-resistant strains

Gram-positive rods
- *Corynebacterium* sp.
- Less common: *Bacillus* sp.

Fungi

- *Candida* sp.
- *Aspergillus* sp.
- Less common: *Mucor* sp., *Rhizopus* sp., *Trichosporon beigelii, Fusarium* sp., *Pseudallescheria boydii*

Cellular Immune Dysfunction

Bacteria

Listeria monocytogenes
Salmonella sp.
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Legionella sp.
Nocardia sp.

Fungi

Cryptococcus neoformans
Histoplasma capsulatum
Coccidioides immitis
Candida sp.
Aspergillus sp.
Pneumocystis jiroveci (formerly *carinii*)

Viruses

Herpes simplex
Varicella zoster
Cytomegalovirus
Epstein-Barr
Less common: Measles, adenovirus

Parasites

Toxoplasma gondii
Cryptosporidium sp.
Strongyloides stercoralis

Humoral Immune Dysfunction (Antibody Deficiency)

Bacteria

S. pneumoniae
Haemophilus influenzae
Neisseria meningitidis
S. aureus

Splenectomy or Functional Asplenia

Bacteria

S. pneumoniae
H. influenzae
N. meningitidis
Capnocytophaga canimorsus
Bordetella holmesii

Parasites

Babesia sp.

Complement Deficiency

Bacteria

N. meningitidis
S. pneumoniae
H. influenzae

type of malignancy, with FN being far more common in hematologic malignancies. Additionally, other factors include the type of chemotherapy and where the patient is in relation to their chemotherapy regimen, with FN being much more common in the first or second cycle of chemotherapy. Mortality varies widely and is affected by comorbid illness, severity of neutropenia, presence of shock, and hematologic malignancy (worse outcomes), among other variables.[1] In a nationwide study in the United States of FN among patients with metastatic solid tumors, FN occurred in 13% to 20% during their chemotherapy course with a mortality of 4% to 10% per episode of neutropenia.[2]

The incidence and severity of infection in cancer patients with neutropenia is inversely proportional to the ANC and directly proportional to the duration of neutropenia.[3] Although the incidence begins to rise as the neutrophil count falls below 500 cells/μL, most severe infections and almost all bacteremias occur when the neutrophil count is less than 100 cells/μL.[3,4]

The most common sites of infection in neutropenic patients are the lung (25%); mouth and pharynx (25%); gastrointestinal tract (15%); skin, soft tissue, and intravascular catheters (15%); perineum and anorectal area (10%); urinary tract (5%); and nose and sinuses (5%).[3,4] Pneumonia and anorectal infection are more likely to be associated with bacteremia.[5,6] Bacteremia may occur without an obvious source despite intensive investigation. The most important bacteria infecting neutropenic patients are four gram-positive cocci—*Staphylococcus epidermidis,* viridans group *streptococci*, *Enterococcus* species, and *S. aureus*—and three gram-negative bacilli—*Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.*[4,6] An increase in formerly uncommon gram-negative infections caused by *Enterobacter, Citrobacter,* and *Serratia* species has occurred, and infections caused by gram-negative organisms resistant to cephalosporins, extended-spectrum penicillins, and carbapenems are occurring more frequently. Anaerobes are uncommon but may be important in certain mixed infections (mouth, abdominal, and perianal).[3,4]

Infections caused by gram-positive organisms (coagulase-negative staphylococci, *S. aureus,* viridans streptococci, and *Enterococcus* species) are now the leading cause of bacterial infection (50% to 70% at some centers) in febrile neutropenic cancer patients in the United States, Canada, and western Europe.[4,6] Gram-negative organisms still predominate in developing countries. Most of these gram-positive organisms do not produce immediately life-threatening infections, in contrast to the rapid lethality of many gram-negative infections. However, bloodstream infections caused by viridans streptococci (especially *Streptococcus mitis*), may be life-threatening and result in rapid development of shock or acute respiratory distress syndrome (ARDS). These infections are common in many cancer centers and often respond poorly to penicillins and cephalosporins. Risk factors for serious viridans streptococcal infections include aggressive cytoreduction therapy for acute leukemia or allogeneic bone marrow transplantation, profound neutropenia, and severe oral mucositis. Other risk factors include prophylactic use of trimethoprim-sulfamethoxazole or fluoroquinolones, antacids or H_2 receptor antagonists, and pediatric age.[7]

Aspergillus and *Candida* species are the most common fungal pathogens in cancer patients with fever and neutropenia.[8-11] Infection is most likely to develop in neutropenic patients treated with broad-spectrum antimicrobials and in those whose fever persists for more than seven days.[8] *Aspergillus* species usually produce necrotizing infections in the lungs or sinuses. Pulmonary aspergillosis often manifests with pleuritic pain, hemoptysis, and localized wheezing. The chest radiograph demonstrates pleural effusions or focal infiltrates. Computed tomography (CT) is more sensitive in detecting pulmonary infiltrates compatible with aspergillosis and may demonstrate a distinct halo of low attenuation surrounding a pulmonary infiltrate. This pattern is highly suggestive of invasive aspergillosis, although zygomycosis (formerly mucormycosis) and other disorders may mimic the halo.

Invasive aspergillosis originating in the paranasal sinuses may extend to the surrounding bone and brain. Often, an initial red-purple lesion on the nasal turbinate or palate turns pale and then black as vascular invasion produces infarction of the mucosa and bone. The black eschar on the nose or palate can be misdiagnosed as dried blood. Patients presenting with headache, facial pain or swelling, or proptosis, should be rapidly evaluated for invasive aspergillosis and zygomycosis. *Candida* species produce infections of the skin, oral cavity, and esophagus, as well as fungemia. The sudden onset of generalized rash consisting of pink-purple, nontender subcutaneous nodules is characteristic of candidemia.

Mucositis involving the mouth and other mucous membranes is a painful and debilitating condition that commonly occurs in cancer patients receiving intense chemotherapy. It is a frequent prelude to viridans streptococcal bacteremia, which can produce sudden onset of acute respiratory distress syndrome, a toxic shock–like syndrome, rash, and pneumonia. Importantly, mucositis predisposes the patient to gram-positive infections, and vancomycin is appropriate in addition to a broad-spectrum gram-negative agent. History is helpful because mucositis tends to recur throughout the chemotherapy course.

Febrile Neutropenia Evaluation Pitfalls

- **Fever is the only sign of infection.** Fever is frequently the only sign of infection, partly because these patients are unable to mount a full inflammatory response.[4-6] Usual symptoms and signs of infection may not be present, especially when the neutrophil count is less than 100 cells/μL. Furthermore, aggressive education before and during chemotherapy makes these patients much more likely to present early in the course of an infectious illness when fever is the only symptom. Some patients may harbor a serious infection yet not be able to mount a febrile response (chronic prednisone therapy, bone marrow transplant) or may present with hypothermia.
- **Assuming the patient does not harbor an infectious pathology if they are afebrile.** While most neutropenic patients are still able to mount a febrile response to infection, some patients will have serious infectious pathology and be afebrile.[4-6] Oral temperatures are unreliable, and rectal temperatures are contraindicated in FN, making it difficult to accurately identify patients who do not present with a complaint of fever at home.[12] Bone marrow transplant patients, patients on chronic corticosteroids, and elderly patients are all at higher risk of not mounting the expected febrile response to infection. Such infections may be manifested instead by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain.
- **Physical examination that is misleading.** The FN patient with a localized infection may have shaking chills and a toxic appearance without localized findings. Areas of cellulitis may have minimal induration and redness and little or no purulent drainage. Tenderness may be the only finding in perineal and anal infections. Peritoneal signs may be absent even with surgical pathology due to a lack of the inflammatory response that results in the traditional peritoneal findings.
- **Failing to consider noninfectious causes of fever.** Noninfectious causes of fever need to be considered, including drug toxicity, drug allergy, transfusion reactions, and pulmonary emboli.
- **Overestimating sensitivity of diagnostic testing in febrile neutropenia.** When pneumonia develops, purulent sputum may be absent, and the initial chest radiograph may not show an infiltrate.[13,14] Pyuria may be absent in patients with a urinary tract infection.
- **Misinterpreting leukocytosis in a patient who has received a colony-stimulating factor.** Oncologic patients who are expected to become neutropenic after their course of chemotherapy may be administered colony-stimulating factor to boost their white blood cell production. Consequently, the emergency clinician may encounter a patient with a marked leukocytosis and fail to recognize that these patients should be evaluated and treated in the same manner as if they presented with neutropenia and fever.[3,6] Emergency clinicians should routinely inquire about the use of colony-stimulating factors during their initial history.
- **Obtaining a rectal temperature in neutropenic patients.** In neutropenic patients, the temperature should be measured orally, not rectally. Although no randomized controlled trials have ever been conducted, there is a theoretical risk of bacterial translocation with any rectal stimulation.[3]

Evaluation and Management

Box 182.2 describes a step-by-step approach to the evaluation and management of the adult patient with febrile neutropenia.

Unfortunately, only about 50% of FN episodes will have an identified focus of fever.[4-6] Up to 25% of patients have a microbiologically identified source of infection such as blood, urine, or wound cultures. Another 25% of patients have a clinically evident source of infection such as pneumonia but no microbiologic data confirms the precise pathogen. Consequently, many patients with FN are not able to have their antibiotics narrowed to minimize the risks of developing resistant bacteria or *Clostridium difficile*.

Antibiotic Therapy. The Infectious Disease Society of America and the American Society of Clinical Oncology recommend antibiotic therapy within 60 minutes of presentation to ED triage for patients with FN.[1] Afebrile neutropenic patients who have unstable vital signs (e.g.,

BOX 182.2 Evaluation and Management of the Adult Cancer Patient With Febrile Neutropenia in the Emergency Department

- Fever (or reported history of fever by patient) of single oral temperature ≥ 38.3°C (101°F) or temperature ≥ 38.0°C (100.4°F) sustained over 60 minutes. Some neutropenic patients will harbor serious infection without fever.
- Neutropenia = Absolute neutrophil count (ANC) < 1000 cells/μL
- If patient is septic, rapidly administer intravenous fluids and maintain mean arterial pressure ≥ 65 mm Hg.
- Contact oncologist early in ED course to assist in guiding evaluation and management especially regarding unique chemotherapy side effect considerations and unusual pathogens (e.g., fungal, viral).
- Query patient about previous episodes of neutropenic fever, recent travel, exposure to animals, vaccinations, and any current antimicrobial use.
- Obtain blood for measurement of electrolytes, renal and hepatic function, serum lactate.
- Obtain blood cultures from each lumen of any existing central venous catheters and from at least one peripheral site, or two blood cultures from separate venipunctures of peripheral veins if no central venous catheter is present.
- Review records for information pertaining to previous episodes of neutropenic fever, prior culture results and sensitivities, echocardiogram, and current chemotherapy regimen.
- Perform a careful physical examination to search for subtle symptoms or signs of infection, with particular attention to the mouth, nose and sinuses, lower esophagus, lung, and skin, including nails, perineum including anus, bone marrow aspiration sites, and vascular catheter sites.
- Understanding that peritoneal signs may be absent in neutropenia and that chest radiograph has marked limitations, consider CT of chest/abdomen/pelvis searching for a source if routine evaluation does not yield a likely source of fever.
- Obtain chest radiograph, understanding it is poorly sensitive for infiltrate with neutropenia.
- Obtain urinalysis with urine culture.
- Send influenza testing if appropriate (by season), understanding that rapid antigen testing has insufficient sensitivity to exclude influenza. Influenza PCR is a superior test to exclude influenza. Neutropenic patients are at high risk for morbidity and mortality from influenza and may present without fever. Empiric treatment (if PCR testing is unavailable) should be considered with oseltamivir based on clinical presentation.
- If diarrhea is present, send for culture, ova and parasites and *Clostridium difficile.*
- Lumbar puncture is not recommended as a routine procedure; however, classic findings such as meningismus may be absent in neutropenic patients.
- Evaluate joins for potential effusion and consideration of aspiration.
- Antibiotics (cefepime, a carbapenem, meropenem, imipenem, or piperacillin/tazobactam) should be initiated within 60 minutes of presentation. The specific agent will depend on institutional antibiogram for gram-negative pathogen sensitivities.
- For patients with a history of severe penicillin allergy, initiate empiric therapy with aztreonam and vancomycin. Avoid empirical use of a fluoroquinolone as coverage for gram-negative pathogens in penicillin-allergic patients.
- Once the initial antibiotic has been administered, consider additional antimicrobials based on suspected source.
  - Add coverage for atypical organisms in suspected community-acquired pneumonia.
  - Add metronidazole or clindamycin for suspected intra-abdominal infections (if broad-spectrum gram-negative agent does not have anaerobic activity such as cefepime).
- For patients with a minor penicillin allergy, empirical treatment with cefepime, meropenem or imipenem-cilastatin can usually be given safely.
- Empiric use of vancomycin is not routinely indicated for all febrile neutropenic patients. Vancomycin should be administered for: 1) suspected catheter-related infection; 2) known colonization with MRSA or penicillin-resistant pneumococci; 3) presence of shock; 4) severe mucositis; 5) prior fluoroquinolone prophylaxis; and 6) institutions in which MRSA, vancomycin-susceptible enterococci, and *Streptococcus mitis* (viridans streptococcus group) are frequent pathogens.
- Empirical antifungal therapy is only rarely indicated in the ED and should not be initiated by the emergency medicine provider without consultation with an infectious diseases specialist.
- Do not initiate outpatient therapy in low-risk patients without contacting the patient's oncologist or an infectious diseases specialist.
- Calculate the MASCC score if outpatient therapy is being considered in a stable patient.
- Patients being considered for early discharge and outpatient management should have a MASCC score ≥21 and have no other high-risk features. They should be observed for at least four hours after the initial antibiotic dose to monitor for stability.
- Low-risk patients may be monitored in an ED observation unit where they can be evaluated by an oncologist and/or infectious diseases specialist to determine whether early discharge to home is feasible.
- Avoiding an inpatient admission is advantageous for the stable low-risk patient because hospitalization exposes the patients to potential iatrogenic complications and antimicrobial-resistant nosocomial pathogens, and outpatient admission allows an improved quality of life.

CT, Computed tomography; *ED,* emergency department; *MASCC,* Multinational Association for Supportive Care in Cancer; *MRSA,* methicillin-resistant *Staphylococcus aureus; PCR,* polymerase chain reaction.

Data from: Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol.* 2018;36(14):1443-1453. https://doi.org/10.1200/JCO.2017.77.6211; Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2016;14(7):882-913; Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu, J, et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: Validation of the clinical index of stable febrile neutropenia in a prospective cohort of patients from the FINITE study. J Clin Oncol. 2015;33(5):465-471. https://doi.org/10.1200/JCO.2014.57.2347; Rivas-Ruiz R, Villasis-Keever M, Miranda-Novales G, Castelán-Martínez OD, Rivas-Contreras S. Outpatient treatment for people with cancer who develop a low-risk febrile neutropaenic event. *Cochrane Database Syst Rev.* March 2019. https://doi.org/10.1002/14651858.CD009031.pub2.

hypotension), are ill-appearing, or have symptoms or signs of infection (e.g., abdominal tenderness) should be treated empirically regardless of the presence of fever.[1,7] The three most commonly used antibiotics are cefepime, piperacillin/tazobactam, or anti-Psuedomonal carbapenem. Use of a single antibiotic agent is preferred in most patients, because there is no conclusive evidence of benefit from multiple drugs.[1] Each hospital should have a preferred antibiotic agent based on the hospital antibiogram. The most common agents are cefepime, piperacillin/tazobactam, or an anti-Psuedomonal carbapenem, and they are typically used for empirical treatment of both sepsis and febrile neutropenia. Review of patient records for previous pathogens and sensitivities can help identify patients at higher risk of resistant organisms requiring adjustment in empiric therapy. It should be noted that monotherapy with cefepime, a carbapenem, or piperacillin-tazobactam will not be

TABLE 182.1 Selected Antimicrobial Agents Useful in the Immunocompromised Patient

Drug	DOSAGE: Adult	DOSAGE: Child (Age >28 Days)	Precautions and Comments[a]
Aminoglycosides			
Gentamicin or tobramycin	2 mg/kg loading dose, then 5 mg/kg/day IV every 8 to 12 hours, *or* 5 to 7 mg/kg IV once daily	Same as adult	Decrease maintenance dose in elderly or with renal dysfunction
Amikacin	Conventional: 10 mg/kg IV load then 5–7.5 mg/kg every 8 hours High-dose extended interval: 15 mg/kg every 24 hours	Same as adult	Only active against aerobic gram-negative bacilli Some gram-negative bacilli may be resistant to gentamicin and tobramycin
Extended-Spectrum Penicillins and β-Lactamase Inhibitors			
Piperacillin-tazobactam	4.5 g IV every 6 to 8 hours (depending on extended infusion)	240 to 400 mg/kg/day IV of piperacillin component every 6 hours	Broad activity against gram-positive organisms, *Pseudomonas aeruginosa,* and anaerobes
Cephalosporins			
Cefepime	1 to 2 g IV every 6 to 8 hours	150 mg/kg/day IV every 8 hours	Active against many gram-positive organisms, *P. aeruginosa* and many resistant gram-negative bacilli, but not anaerobes
Carbapenems			
Imipenem-cilastatin	0.5 to 1 g IV every 6 hours	60 to 100 mg/kg/day IV every 6 hours	Adjust dose in elderly or with renal dysfunction. Reduces VPA levels
Meropenem	1 g IV every 8 hours	60 to 120 mg/kg/day IV every 8 hours	Seizures are associated with imipenem May be cross-allergenic with penicillin Broad-spectrum activity against gram-positive and gram-negative organisms, including *P. aeruginosa* and anaerobes
Other			
Aztreonam	1 to 2 g IV every 8 hours	120 mg/kg/day IV every 6 hours	Active against gram-negative bacilli including *P. aeruginosa* Not active against gram-positive organisms or anaerobes Safe in penicillin-allergic patient
Vancomycin	15 mg/kg IV every 12 hours	40 mg/kg/day IV every 6 to 12 hours	Infuse during 2 hours (flushing, hypotension with rapid infusion). Rapid infusions associated with flushing and hypotension (red man syndrome)
Amphotericin B	0.5 to 1.5 mg/kg/day IV once daily	Same as adult	Refer to infectious disease or pharmacology text
Acyclovir			Infuse during 1 hour
• Herpes simplex, mucocutaneous[b]	5 mg/kg IV every 8 hours *or* 400 mg PO three times a day	250 mg/m^2 IV every 8 hours *or* 15 mg/kg/day PO every 4 hours	
• Herpes zoster			
• Not severe[c]	800 mg PO five times a day	20 mg/kg PO four times a day	
• Severe	10 mg/kg IV every 8 hours	500 mg/m^2 IV every 8 hours	
• Primary varicella	10 mg/kg IV every 8 hours	10 to 20 mg/kg IV every 8 hours	

[a]Antibiotics require renal/gestational age adjustments.
[b]Alternative for herpes simplex: valacyclovir 1 g two times a day PO.
[c]Alternative for herpes zoster: valacyclovir 1 g three times a day PO.
IV, Intravenous; *PO, per os* (by mouth).

active against vancomycin-resistant *Enterococcus* species or methicillin-resistant staphylococci.

For patients who are allergic to β-lactam antibiotics, coverage of gram-negative bacilli, including *P. aeruginosa,* can be provided by aztreonam. Because aztreonam is not active against gram-positive organisms, it should be combined with vancomycin. If anaerobes are suspected (oral, abdominal, or perianal infection) in the β-lactam–allergic patient or in the patient receiving cefepime monotherapy, an anti-anaerobic drug (clindamycin or metronidazole) should be administered. Empirical treatment with intravenous fluoroquinolones is not recommended in the febrile neutropenic cancer patient because of frequent prophylactic use of these agents in the cancer patient, risk for

rapid emergence of resistance in gram-negative bacilli, and predisposition to *C. difficile* infection.[1]

When a focus of infection is identified, empirical therapy should cover the most likely pathogens causing infections at the site (Table 182.1). Patients with pneumonia may need coverage for *Legionella* (azithromycin or a fluoroquinolone), *Pneumocystis* (trimethoprim-sulfamethoxazole), or fungi (amphotericin B, micafungin, voriconazole), in addition to standard antibacterial coverage. Agents effective against anaerobes (clindamycin, metronidazole, meropenem, imipenem, or piperacillin-tazobactam) should be considered for patients with perianal or oral infection and those with abdominal pain, who may have appendicitis, diverticulitis, or typhlitis (neutropenic enterocolitis). Acyclovir should be considered for patients with ulcerative or vesicular lesions who may have herpes simplex or varicella-zoster virus infections. In patients with severe mucositis and FN, meropenem, imipenem, or piperacillin-tazobactam, often combined with vancomycin, are preferred for empirical treatment because of superior efficacy against viridans streptococci.[1]

"Routine" empirical use of vancomycin for all febrile neutropenic cancer patients is not recommended because of concern for the development of vancomycin-resistant organisms.[1,15] Indications for initial empirical vancomycin therapy include serious catheter-related infections (e.g., with hypotension), known colonization with penicillin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus* (MRSA), and positive blood culture for gram-positive organisms before final identification and susceptibility testing.[1,15] Other indications include shock, severe mucositis, prior fluoroquinolone prophylaxis, and institutions in which MRSA, vancomycin-susceptible enterococci, and *S. mitis* are frequent pathogens.[1,15] Patients previously colonized or infected with MRSA, vancomycin-resistant enterococci, extended-spectrum β-lactamase–producing gram-negative bacteria, and carbapenemase-producing organisms may require modifications to initial empirical therapy.[1,7]

Amphotericin B (and its lipid formulations) is the drug of choice for treating invasive fungal infections in patients with neutropenia.[8-10] Due to amphotericin toxicity, micafungin or voriconazole may be considered for treatment of specifiic fungal infections. Up to one-third of febrile neutropenic patients not responding to one week of antibiotics have systemic fungal infections, usually *Candida* or *Aspergillus*.[8-11]

Risk Assessment and Disposition

Febrile neutropenic cancer patients can be classified into high-risk and low-risk groups. Some of the factors associated with high risk include the following: status as an inpatient when fever and neutropenia developed; presence of serious comorbid medical conditions; uncontrolled cancer; acute leukemia; hemodynamic instability; evidence of organ failure; presence of pneumonia, severe soft tissue infection, infection of a central line, abdominal pain, neurologic or mental status abnormalities; and neutropenia expected to last more than 10 days.[16-17] These patients should be treated in the hospital with intravenous antibiotics.

Outpatient empirical antibiotic therapy is safe and efficacious in carefully selected FN adults who are not at high risk for medical complications.[1,7,16-17] The Multinational Association for Supportive Care in Cancer (MASCC) risk index score (available at www.mascc.org/mascc-fn-risk-index-score) is an easy to use, validated clinical prediction rule for classification of low-risk adults (Table 182.2, Box 182.3). However, it should not be used as the sole factor to decide on low-risk status or outpatient management.[1,7,16-17] Three clinical practice guidelines, including the Infectious Diseases Society of America, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network, support outpatient or short-stay oral antibiotic therapy in carefully selected low-risk patients with FN.[1,7,16] The only oral antibiotic regimen recommended is a fluoroquinolone *plus* amoxicillin-clavulanate (or *plus* clindamycin in penicillin-allergic patients).[1]

TABLE 182.2 Multinational Association for Supportive Care in Cancer Scoring System to Identify Patients With Cancer and Febrile Neutropenia at Low Risk of Medical Complications

Characteristic	Weight[a,b,c]
Burden of febrile neutropenia with mild or no symptoms	5
No hypotension (systolic blood pressure >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age younger than 60 years old	2

[a]Maximum score is 26. Higher score is better.
[b]Scores ≥21 indicate a low risk for medical complications.
[c]Burden of febrile neutropenia: The general clinical status of the patient as influenced by the febrile neutropenic episode is evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); and severe symptoms or moribund (score of 0). Choose only one score for burden of febrile neutropenia symptoms (5, 3, or 0).
Adapted from: Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol.* 2018;36(14):1443-1453. https://doi.org/10.1200/JCO.2017.77.6211. Available at: www.mascc.org/mascc-fn-risk-index-score.

BOX 182.3 Considerations for Outpatient Management of Cancer Patients With Febrile Neutropenia

Adult patients may be considered for outpatient therapy if:

- Patient has a MASCC score ≥21.
- Patient is medically stable without acute or chronic organ dysfunction or comorbid conditions and does not have acute leukemia.
- No focus of infection identified: Patient does not have pneumonia, infection of a central line or a severe soft tissue infection, and does not have acute abdominal pain or an intra-abdominal infection.
- Patient has access to a telephone and transportation to return to hospital available 24 hours a day and has a caregiver at home.
- Patient has a history of compliance with follow-up and treatment protocols.
- Patient is not on fluoroquinolone prophylaxis and there is a low prevalence of fluoroquinolone-resistance in the community.
- Patient's oncologist agrees to outpatient management.
- The emergency clinician should contact the patient's oncologist and/or an infectious diseases specialist before considering outpatient therapy.

Patients being considered for outpatient therapy should be observed for at least 4 hours in the ED (or in an ED observation unit) after the initial antibiotic dose, which should be administered intravenously as soon as possible after initial cultures are obtained.

The only recommended outpatient oral antimicrobial therapy for these patients is ciprofloxacin or levofloxacin *plus* amoxicillin/clavulanate (or *plus* clindamycin for those with penicillin allergy).

ED, Emergency department; *MASCC,* Multinational Association for Supportive Care in Cancer.

BOX 182.4 Unique Considerations for Evaluation and Management of Children With Febrile Neutropenia and Cancer

- Because intravenous catheter infections are a common source of fever in children, obtain blood cultures from *all* lumens of indwelling central venous catheters.
- Obtain a peripheral vein blood culture if possible (may not be possible in small children).
- Obtain urinalysis and urine culture, because urinary tract infections are frequent causes of fever in neutropenic children.
- Obtain chest radiograph only in children with symptoms or signs of respiratory disease.
- Initiate monotherapy with an anti-pseudomonal beta-lactam or carbapenem as empirical therapy (cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam) as soon as cultures have been obtained. Avoid empirical use of ceftazidime monotherapy.
- Some low-risk children with febrile neutropenia who have access to close follow-up may not require hospital admission and may be discharged home after a period of observation, but this should only be attempted after consultation with the patient's oncologist and/or an infectious diseases specialist.
- Transfer of the pediatric cancer patient with febrile neutropenia to a hospital experienced in the management of children with cancer is recommended.

Recently, a second prognostic score has been developed and is termed the Clinical Index for Stable Febrile Neutropenia (CISNE). Importantly, it was derived and validated in patients with FN and solid tumor malignancy. Recent studies suggest that the CISNE and MASCC scores both perform well in FN patients with solid tumor malignancy.[1,18-19]

In the setting of a favorable MASCC score, the decision to pursue outpatient therapy for FN should be made in conjunction with the patient's oncologist when the patient lives within 60 minutes of a hospital, can seek care reliably, has the assistance of a caregiver at home, no barriers to obtaining antibiotics, and agrees to return for outpatient visits. While numerous criteria should be met for outpatient management, avoiding inpatient admission and exposure to nosocomial pathogens is advantageous for low-risk patients.[1]

Children With Cancer and Febrile Neutropenia

Box 182.4 lists unique considerations in the evaluation and management of children with cancer and febrile neutropenia.

Non-Neutropenic Conditions in the Cancer Patient

The Solid Organ Cancer Patient Without Neutropenia

Most solid organ cancer patients who have fever and infection are not neutropenic. Infections in these patients may occur after surgical procedures and can include wound infection, deep abscess, or perforated viscus. Infections may be associated with central venous or urinary catheters, stents, and prosthetic devices. In addition, solid tumor patients with large tumor lesions may have obstructive infections (e.g., bronchus, bile duct, or ureter). The spectrum of microorganisms includes a wide variety of community-acquired organisms (bacterial, fungal, and viral), as well as nosocomial multi-antibiotic–resistant pathogens.

Prompt initiation of antimicrobial therapy in the febrile non-neutropenic solid cancer patient is not always indicated. In febrile non-neutropenic cancer patients who are not ill-appearing and have no identified focus of infection, it may be appropriate to obtain culture specimens and to observe the patient. After consultation with an oncologist, some patients can be discharged home with close follow-up. Indications for urgent antibiotics include signs of sepsis, mental status changes, lactic acidosis, shock, abdominal pain, history of splenectomy, and identification of a focal site of infection.[1,7]

Impaired Cell-Mediated Immunity

The T-cell defects resulting from impaired CMI in cancer patients usually result from cancer chemotherapy or corticosteroid treatment. The cancer itself impairs CMI in patients with Hodgkin disease, non-Hodgkin lymphoma, and hairy cell leukemia.

Bacterial Infections. *L. monocytogenes* is one of the more common bacterial organisms infecting cancer patients with impaired CMI. *Listeria* infection is also seen in patients with organ transplants, diabetes, cirrhosis, AIDS, late pregnancy, and those receiving high-dose corticosteroids or biologic therapies. No early characteristics distinguish *Listeria* infection from bacteremias caused by other organisms. Meningitis, which may be accompanied by cerebritis or brain abscess, is the most common focus of infection and may manifest with personality changes or focal neurologic signs. Cerebrospinal fluid examination frequently does not reveal the organism on Gram stain, but protein is elevated and pleocytosis is present. Ampicillin is the treatment. Trimethoprim-sulfamethoxazole is an alternative for patients with penicillin allergy. Vancomycin is not effective in the treatment of *Listeria* infections even when in vitro susceptibility is shown. Cephalosporins, such as ceftriaxone, are not active against *Listeria*. If meningitis is suspected, empiric ampicillin is recommended in any patient with impaired CMI regardless of age.

Infections caused by *Salmonella* species are common in patients with impaired CMI and usually are manifested with fever. Enteritis may or may not be present. Bacteremia can result in infection of bones, joints, central nervous system, and endovascular devices. Multidrug-resistant *Salmonella* species are increasing. Treatment usually includes a third-generation cephalosporin, like ceftriaxone, or a fluoroquinolone because many isolates are resistant to ampicillin and trimethoprim-sulfamethoxazole.

Patients with solid tumors, lymphoma, and leukemia (especially hairy cell leukemia) are at increased risk for pneumonia from *Legionella* species, with the highest risk in cancer patients receiving high-dose corticosteroids. Non-*pneumophila* species of *Legionella* (*Legionella micdadei* and *Legionella bozemanii*) are particularly common in these patients. Clinical and radiographic manifestations of *Legionella* infection in the immunocompromised patient often differ from those in the immunocompetent host. For example, pleuritic chest pain may be a prominent symptom in the immunocompromised patient and may mimic pulmonary embolism. These patients can have fever without any other symptoms of pneumonia despite the presence of radiographic pulmonary infiltrates. In addition, the chest radiograph may reveal an expanding pulmonary nodule or cavitation of a nodule or infiltrate rather than the usual lower lobe alveolar filling defects. Hyponatremia with a serum sodium less than 130 mEq/L [mmol/L] is particularly common.[20] Although gastrointestinal and neurologic findings are common in patients with *Legionella* infections, these are not more common in patients with *Legionella* than in other causes of pneumonia.[20] The treatment of choice for immunocompromised patients with suspected *Legionella* infection is a respiratory fluoroquinolone or azithromycin.

Nocardiosis is an uncommon but often severe bacterial infection caused by a weakly acid-fast gram-positive branching filamentous rod. It occurs in cancer patients, in those receiving high-dose corticosteroids, and in others with defective CMI. Subacute pneumonia with nodular infiltrates is the most common manifestation, usually without fever.[21] *Nocardia* may also produce cellulitis, subcutaneous abscesses, meningitis, and brain abscesses. Diagnosis requires biopsy, tissue stains, and culture. Treatment is with sulfonamides often combined with other agents.

Mycobacterial Infections. Tuberculosis and other mycobacterial diseases may produce severe disease in those with defective CMI and be manifested as fever of undetermined origin, pneumonia, lymphadenopathy, meningitis, or skin lesions. It is easily mistaken for signs caused by the

patient's underlying disease or treatment. Disseminated nontuberculous mycobacterial infections are more common in patients with hairy cell leukemia or chronic myelogenous leukemia.

Fungal Infections. Infections with *Cryptococcus neoformans* and *Cryptococcus gattii* occur in patients with Hodgkin and non-Hodgkin lymphoma, chronic myelogenous leukemia, and chronic lymphocytic leukemia, especially those taking high-dose corticosteroids.[22] Patients with HIV infection, solid organ transplants, diabetes, renal insufficiency, and cirrhosis are also at risk, as are patients receiving prolonged high-dose corticosteroids for connective tissue diseases. Meningitis is the most common manifestation, often with the insidious onset of low-grade fever and subacute and often intermittent headache. Many other organ systems can become infected, including the lungs, skin, bones, and joints. Diagnosis is made by measuring cryptococcal antigen in the serum and cerebrospinal fluid, fungal cultures, and tissue biopsy. An opening pressure should be measured when obtaining cerebrospinal fluid in the evaluation of *Cryptococcal* meningitis as it is frequently elevated due to obstructive hydrocephalus by the *Cryptococcal* capsule.

Impaired CMI may result in reactivation of *Histoplasma capsulatum* and *Coccidioides immitis* with resultant disseminated disease. Infections with *Candida* species are also common in cancer patients with defective CMI, but disseminated disease is less likely than in patients with neutropenia. Invasive aspergillosis may develop in cancer patients receiving high-dose corticosteroids but not as commonly as in those with organ transplants or prolonged neutropenia.

Pneumocystis jirovecii (formerly *carinii*) pneumonia is most common in patients with AIDS, leukemia, lymphoma, and solid tumors taking high doses of corticosteroids. The presentation is often indolent and is characterized by progressive malaise, dyspnea on exertion, and a multitude of potential chest radiograph abnormalities.[23] Patients classically have hypoxia with ambulation which can raise clinical suspicion of pulmonary embolus.[23] High-risk patients (e.g., bone marrow transplant) may take antibiotic prophylaxis consisting of trimethoprim-sulfamethoxazole.

Parasitic Infections. Reactivation of central nervous system infection with the protozoan *T. gondii* occurs most often in patients with hematologic cancers and in patients with HIV. *Strongyloides stercoralis,* an intestinal nematode, is the only helminthic organism producing severe infection in patients with deficient CMI, almost exclusively in those receiving high-dose corticosteroids. Larvae of the parasite disseminate from the intestines to the lungs and other organs, including the central nervous system and skin, causing the *Strongyloides* hyperinfection syndrome, with very high mortality. Wheezing, cough, dyspnea, hemoptysis, and hemorrhagic rash are common. Chest radiographs may show focal or diffuse infiltrates. Dissemination is often accompanied by bacterial infection, usually caused by enteric gram-negative bacilli carried by the parasites from the intestinal tract. Diagnosis is made by examining stool, sputum, tissue or fluid obtained by bronchoscopy or endoscopy, or cerebrospinal fluid for larvae of the parasite. The treatment of choice is oral ivermectin.

Viral Infections. The most common viruses producing serious infections in cancer patients with defective CMI are varicella-zoster, herpes simplex, and cytomegalovirus. Visceral dissemination is common in primary varicella (chicken pox) in nonimmune immunocompromised children and adults, with development of pneumonia, encephalitis, hepatitis, and hemorrhagic lesions. When a nonimmune immunocompromised patient is exposed to varicella, varicella-zoster immune globulin (VariZIG in the United States) should be administered as soon as possible after exposure, up to 10 days postexposure, to ameliorate the disease.[24] Herpes zoster infection is common in cancer patients, particularly those with Hodgkin and non-Hodgkin lymphoma and leukemia. Disease usually remains localized to the primary dermatome, but dissemination occurs in approximately 11% of patients.[25] Dissemination is usually limited to the skin, but visceral involvement (lung and liver) occasionally occurs. Skin lesions in primary varicella or zoster often become hemorrhagic in these patients.

Reactivation of herpes simplex virus is common, resulting in severe mucocutaneous infection in oral or genital areas. Spread may occur to the esophagus, lungs, or other organs. Herpetic lesions in cancer patients tend to be larger and deeper than those in the immunocompetent patient. Acyclovir given intravenously is the treatment of choice for varicella-zoster and herpes simplex infections in immunocompromised patients, but some stable patients may be treated with oral valacyclovir.[22]

Cytomegalovirus infection may occur in cancer patients treated with corticosteroids. Measles virus, although uncommon, may produce severe infection in those with defective CMI. Fever, rash, pneumonia, and encephalitis are common manifestations. Immune serum globulin may be given after exposure to ameliorate disease. Common community respiratory viruses, such as respiratory syncytial virus, influenza, and adenovirus, may produce severe or fatal pneumonia.

Influenza vaccination is indicated for all patients who are immunocompromised, and vaccination may attenuate symptoms and reduce mortality even if the patient develops influenza.[23] Influenza may mimic bacterial pneumonia, and patients with CMI who are diagnosed with influenza pneumonia should be concurrently treated for bacterial pneumonia due to the likelihood of coexisting disease.[26] Fever is not necessary to suspect or diagnose influenza. Recent Infectious Diseases Society of America (IDSA) guidelines recommend testing any patient who presents to the ED with influenza-related symptoms.[26] All patients with CMI would fall into the higher risk category for influenza-related morbidity and mortality, which warrants early treatment with oseltamivir.[26]

Humoral Immune (B-Cell) Defects

Hypogammaglobulinemia is common in patients with chronic lymphocytic leukemia and multiple myeloma. Low immunoglobulin levels predispose to infections with encapsulated bacteria, such as *S. pneumoniae, H. influenzae,* and *N. meningitides.*[24] Pneumonia is the most common manifestation, but sepsis, otitis media, cellulitis, and urinary tract infection may occur. After receiving cytotoxic agents and corticosteroids for treatment, these patients become susceptible to infections associated with impaired CMI, as well as bacterial infections caused by *S. aureus* and gram-negative bacilli, often with high mortality.[24] Regular infusions of intravenous immune globulin may decrease the incidence of infection but do not prolong survival. Patients should receive pneumococcal vaccine, but many do not respond.

Disruption of Natural Barriers

Disruption of natural anatomic barriers (mucous membranes and skin) by ulcerating tumors, chemotherapy, radiation therapy, diagnostic and therapeutic procedures, and catheters can lead to infection by gram-positive and gram-negative organisms, including anaerobes. Oral mucositis, a debilitating and intensely painful condition associated with radiation therapy and high-dose chemotherapy, frequently results in serious local and systemic infections, including life-threatening sepsis with viridans streptococci. Cancers may cause partial or total obstruction of body lumens and cavities, as may swelling and scarring from radiation therapy. Bronchial obstruction by tumor can lead to pneumonia. Obstruction of the urinary tract may result in infection. Gastrointestinal tract obstruction can lead to perforation and peritonitis.

Opportunistic Infections Mimicking Neoplasm

Infectious agents can produce laboratory, radiologic, or physical findings that resemble those caused by the spread of tumors. For example, mass lesions in the brain caused by *Nocardia* or *Toxoplasma* can

be mistaken for cancer metastases. *Aspergillus, Mucor, Rhizopus,* and related fungi invade blood vessel walls and produce thrombosis, which may result in Budd-Chiari syndrome (hepatic vein obstruction), nephrotic syndrome, or oculomotor palsy that may be misattributed to the spread of tumor. Renal vein thrombosis can be caused by infection with gram-negative bacilli. *Candida* fungus balls may develop in one or both ureters, producing a picture of postrenal obstructive uropathy. *Histoplasma, Pneumocystis, Legionella, Aspergillus, Nocardia,* and other organisms can produce pulmonary nodules and be mistaken for pulmonary metastases.

Diabetes

Diabetic patients have increased susceptibility to infection because of defects in immune function, excess substrate for fungal and bacterial growth, vascular insufficiency related to microangiopathy and atherosclerosis, and sensory neuropathy that leads to wound neglect (see Chapter 115). Neutrophil and monocyte-macrophage functions are directly impaired in diabetic patients. These defects are exacerbated by hyperglycemia and improved by tight glucose control. Cellular immunity is affected by a decrease in proliferative response but otherwise remains primarily intact. As immunity is impaired, people with diabetes may present with infections but have atypical symptoms in their presentation. For example, they may present with malaise but lack fever, or may present with purulent wound discharge without pain.

Most diabetic wounds are appropriately managed with preventive techniques and outpatient wound care. Infectious complications include cellulitis, necrotizing skin and soft tissue infection (NSSTI), and osteomyelitis. The decision to treat with antibiotics should be based on signs and symptoms of infection such as purulent drainage, wound inflammation, pain, or systemic symptoms. Mild to moderate wound infections should target gram-positive cocci such as staphylococci and streptococci. These may be treated with oral agents such as cephalexin 500 mg every 6 hours or trimethoprim-sulfamethoxazole 160 mg/800 mg twice a day in the outpatient setting with close surgical follow-up.[25] More severe infections, deeper infections, or infections in patients with risks for multidrug-resistant organisms (MDRO) should be treated with broad-spectrum parenteral antibiotic agents and surgical consultation. X-ray can be specific for deeper infection, but CT is more sensitive for NSSTI and MRI is more sensitive for osteomyelitis. Biomarkers such as CRP and ESR may be elevated in infection but are not specific. Uninfected ulcers do not benefit from antibiotic therapy.[25] Wound swabs may assist in guiding antibiotic therapy in superficial wounds but become unreliable in deeper infection.[25] Procalcitonin testing has shown promise in differentiating infected from noninfected wounds in some small studies,[27] but its role in the ED is still to be determined.

Other infections often attributed to diabetes include: urinary tract infections including emphysematous cystitis and pyelonephritis; emphysematous cholecystitis; polymicrobial NSSTIs, especially involving the perineum (Fournier gangrene) and lower extremities; malignant otitis externa caused by *P. aeruginosa;* and the rare rhinocerebral zygomycosis caused by *Rhizopus* and *Mucor* species. The combination of organism risk, poor circulation, and impaired immune function often leads to an increased risk of tuberculosis. Patients with diabetes are at increased risk of candidiasis, including vulvovaginal candidiasis in women, psoas abscess, spinal epidural abscess, postoperative surgical site infections, and *S. aureus* and gram-negative pneumonia. Diabetic patients with pneumococcal pneumonia are more likely to become bacteremic and to have a higher mortality rate. With increased risk, diabetic patients often need broad-spectrum parental agents. Glycemic control is crucial in reestablishing proper immune function to promote healing.

Alcohol Use Disorder and Cirrhosis

Alcohol consumption predisposes to infection through direct suppression of the immune system, alterations in blood flow, depression of mental status, and delay in seeking medical care. Patients with alcohol use disorder also often have coexisting malnutrition, cigarette smoking, and chronic lung disease. Alcoholic cirrhosis results in deficient hepatic clearance and destruction of bacteria by reticuloendothelial cells, as well as splenic hypofunction. Complement deficiency occurs because the liver is the primary site of C3 synthesis. Neutrophils show impaired recruitment to infected sites and defective chemotaxis and phagocytosis. Cellular immune deficiency occurs and is often exacerbated by malnutrition. Bactericidal activity of IgM antibodies against gram-negative pathogens such as *E. coli* and *H. influenzae* is decreased.

Acute ethanol intoxication is associated with granulocytopenia and diminished leukocyte mobilization that is reversible with abstinence. Additionally, intoxication inhibits respiratory reflexes and mucous clearance leading to aspiration; concomitant withdrawal seizures or encephalopathy increase this risk. Prior data showed increased oropharyngeal colonization by gram-negative bacteria in alcoholics, but recent studies have demonstrated no increased risk of gram-negative infections in individuals with alcohol use disorder.[28] Recent guidelines from the American Thoracic Society and the IDSA include alcoholism as a comorbidity for combination antibiotic therapy in community-acquired pneumonia but recommend no deviation in routine inpatient therapy and no routine coverage of aspiration in the absence of empyema or lung abscess.[29]

Common infections in patients with cirrhosis include spontaneous bacteremia and sepsis caused by *E. coli, K. pneumoniae, Salmonella,* streptococci, *Vibrio vulnificus,* and *Aeromonas;* spontaneous bacterial peritonitis, usually caused by *E. coli, K. pneumoniae, S. pneumoniae,* or enterococci; pneumonia related to pneumococci, gram-negative bacilli *(E. coli, K. pneumoniae,* and *H. influenzae),* and anaerobes; tuberculosis; meningitis caused by *S. pneumoniae* and *L. monocytogenes;* and skin and soft tissue infections with *S. aureus,* streptococci, and gram-negative bacilli. Cirrhotic patients who present to the ED after a recent hospitalization often have health care–associated infections, including catheter-related and *C. difficile* infections, spontaneous bacteremia, urinary tract infections, and pneumonia, often with high mortality.

In cirrhotic patients with ascites and fever, abdominal pain, or concern for infectious encephalopathy, spontaneous bacterial peritonitis should be ruled out with ascitic fluid sampling and cell count. Patients with a PMN count of 250 cells/mm^3 or greater should be treated empirically with broad-spectrum coverage, such as ceftriaxone or ciprofloxacin, until cultures result. Additionally, patients receiving treatment for SBP have been shown to have increased survival and decreased incidence of hepatorenal syndrome when administered albumin 1.5 g/kg at presentation and 1 g/kg on day 3 of treatment.

Alcoholic patients with leukopenia may have delayed inflammatory responses; these patients should be watched more carefully and may warrant a higher level of care when infected. For example, leukopenic alcoholic patients with community-acquired pneumonia are more likely to have a delayed manifestation of septic shock or ARDS.

Renal Failure

Infections are a significant cause of death in patients with chronic renal failure and are the second most common cause of mortality after coronary artery disease. These patients often have diabetes, which increases their risk for severe morbidity and mortality from infections. Disruption of cutaneous barriers at vascular access sites and peritoneal dialysis catheter sites and numerous immune system defects are responsible for the increased incidence of infection. Uremic pruritus with excoriation, epidermal and sweat gland atrophy, dryness, and vesicular eruptions

also compromise the cutaneous barrier. Reduced renal clearance of unknown toxins, nutritional deficiencies, and administration of immunosuppressive medications lead to aberrant immune regulation early in the course of renal failure.

Chronic kidney failure leads to a state of generalized immune hyporesponsiveness. Neutrophils show reduced mobility, chemotaxis, adherence, phagocytosis, and intracellular bactericidal activity. Leukopenia is common. CMI is severely impaired, with decreased activation and proliferation of T lymphocytes and reduced NK cell activity, which cannot be reversed by hemodialysis. Furthermore, humoral immunity is adversely affected, resulting in deficient production of specific IgG subclass antibodies. Inadequate response to vaccines is typical but can be improved by reinforced vaccination schedules, increased vaccine dosage, and adjunct immunomodulators. Additional predisposing factors to infection in uremic patients include low serum albumin, iron overload, increased intracellular calcium, circulating low-molecular-weight uremic toxins, metabolic acidosis, circulating inhibitors to chemotactic factors, decreased production of endogenous pyrogens, and invasive vascular procedures for dialysis access.

Severe infections with antibiotic-resistant bacteria are common, and empirical therapy for a suspected serious infection should include broad-spectrum antimicrobials active against MRSA and antibiotic-resistant gram-negative bacilli. Skin and soft tissue infections, especially those caused by *S. aureus,* are particularly severe in diabetics and in those with peripheral vascular disease or peripheral neuropathy. Vascular access site infections are usually caused by *S. aureus* but occasionally by gram-negative bacilli and enterococci. Patients using central venous catheters for dialysis have much higher rates of sepsis compared with fistulas or grafts. Infections of dialysis access sites, often due to *S. aureus,* are life-threatening and frequently associated with hematogenous seeding of infection to distant sites, including osteomyelitis (usually involving the ribs or thoracic vertebrae), endocarditis, meningitis, epidural abscess, and septic arthritis. Pneumonia may be severe, and there is an increased incidence of *Legionella* pneumonia. Pneumonia may be challenging to diagnose by chest radiograph in these patients due to changing pulmonary fluid dynamics. Because mortality is high, early antimicrobial treatment should be administered after appropriate cultures have been obtained if acute pneumonia is considered, considering antimicrobial coverage for health care–associated pathogens.

Tuberculosis and fungal infections caused by *Candida* species, *Cryptococcus, Histoplasma,* and *Coccidioides* occur with increased frequency. Diagnosis of tuberculosis may be difficult because of nonspecific symptoms and increased incidence of extrapulmonary disease. In addition, *C. difficile* infection occurs more frequently and is more severe with high mortality.

Infections of the urinary tract are more prevalent in patients who continue to produce urine, with urinary bladder catheterization being the most frequent predisposing factor. There is a poor correlation between the presence of pyuria and urinary tract infection in these patients. *Candida* infection of the urinary tract may develop in patients with chronic renal failure treated with broad-spectrum antibiotics.

Antibiotic selection and dosing should consider a kidney disease patient's lack of renal clearance. If a renally cleared regimen is selected, agents may often be dosed with dialysis treatments. In patients who are otherwise well and nontoxic but require parenteral agents due to drug resistance, this may be facilitated by outpatient dialysis if clinical stability and logistics allow.

Up to two-thirds of patients receiving chronic peritoneal dialysis have peritonitis in their first year, and one-third may be forced to discontinue dialysis because of recurrent infections. *S. aureus* and *S. epidermidis* predominate, followed by streptococci, gram-negative bacilli, and *Candida* species. Fortunately, peritoneal dialysis patients have much lower rates of sepsis than those on hemodialysis. Patients presenting with fever, abdominal pain, or signs of local site infection should be evaluated for peritonitis including testing of effluent cell count and culture. Those with cell counts greater than 100 WBC/mL or PMNs greater than 50% for individuals using night-time dwells should be treated with renally dosed vancomycin and ciprofloxacin. Patients with recurrent infections or candidal infections will likely need to transition to hemodialysis.

Splenectomy, Hyposplenia, and Functional Asplenia

The spleen is the most crucial organ in the reticuloendothelial system and is the primary site for IgM synthesis, the first early immune response of the body. Opsonin production in the spleen facilitates phagocytosis of bacteria by intracellular macrophages. Patients without a spleen also have decreased production of neutrophils, NK cells, and immunomodulating cytokines.

The spleen is the principal site of clearance of *S. pneumoniae* from the blood. Splenectomy or functional asplenia predisposes to overwhelming pneumococcal infection and fulminant infection with other encapsulated organisms (*H. influenzae, N. meningitidis,* and *Capnocytophaga canimorsus* after dog bites) and gram-negative bacilli *(E. coli* and *P. aeruginosa).*[28,29] Asplenic patients who become infected with *Babesia microti,* a malaria-like protozoan transmitted by tick bite in the United States, may develop severe and often fatal hemolysis (see Chapter 123). Human granulocytic anaplasmosis (formerly ehrlichiosis), another tickborne infection, is severe and sometimes fatal in asplenic patients. In addition, the gram-negative coccobacillus *Bordetella holmesii* produces a non–life-threatening acute febrile illness with bacteremia in patients with asplenia. Pneumococcal sepsis represents 50% to 90% of cases. Most healthy adults who die after fulminating pneumococcal sepsis have had a splenectomy or have a congenitally small or abnormal spleen.

The incidence of overwhelming postsplenectomy sepsis in these patients is low; but when it occurs, the mortality rate is high—especially in children with hematologic disorders. The risk is more significant in children than in adults, with children younger than 2 years old at greatest risk. The risk is highest in the first few years after splenectomy but persists throughout life into old age. People undergoing splenectomy for a hematologic disorder or lymphoma are at much higher risk for overwhelming postsplenectomy infection than are those undergoing splenectomy for trauma. This is probably because of the occurrence of splenic implants (splenosis) or accessory spleens in traumatized patients. Patients with functional asplenia from sickle cell anemia or thalassemia major are at high risk for overwhelming bacterial infections.

Functional hyposplenism occurs in a variety of conditions besides sickle cell disease, including sickle cell–hemoglobin C disease, ulcerative colitis, celiac disease, sarcoidosis, amyloidosis, rheumatoid arthritis, and SLE. The presence of anatomic or functional hyposplenism may be recognized by the finding of Howell-Jolly bodies in red blood cells on a peripheral blood smear.

When overwhelming postsplenectomy infection occurs, often no obvious source of infection is found. Prodromal symptoms such as fever, rigors, malaise, myalgias, headache, vomiting, and diarrhea may be present for 1 or 2 days. Patients seen at this time may be misdiagnosed as having a viral illness, gastroenteritis, or food-borne illness. Abrupt deterioration then occurs over hours, with rapid progression to septic shock with disseminated intravascular coagulation, purpura, and multiorgan dysfunction. The mortality rate is high (50% to 70%), with younger children having the highest mortality rate. In addition, meningitis without overwhelming infection or shock is a common

presentation of pneumococcal infection in asplenic patients. When fever develops in a person at risk for this disorder, treatment with an antimicrobial agent effective against *S. pneumoniae* should be initiated without delay. After a blood culture is performed, adults and children should receive ceftriaxone at meningitic doses, with the addition of vancomycin in areas where penicillin resistance is prevalent. Clindamycin, levofloxacin, or moxifloxacin are alternatives for patients with severe penicillin allergy. Children with a history of serious penicillin allergy should receive vancomycin plus levofloxacin.

Use of pneumococcal vaccine in patients at risk is especially important now that antimicrobial-resistant *S. pneumoniae* is prevalent, but the efficacy of this vaccine in these patients is unclear. Persons with functional hyposplenism related to severe underlying diseases often respond poorly to pneumococcal vaccination. Asplenic people should be immunized against pneumococcus, *H. influenzae* type b, *N. meningitidis,* and influenza virus. Although there is no evidence to support this, guidelines recommend that children should receive prophylaxis with oral penicillin or amoxicillin up to the age of 5 years and for at least 1 or 2 years after splenectomy, provided they have not had an invasive pneumococcal infection and have received pneumococcal immunizations. Long-term antimicrobial prophylaxis is generally not recommended in adults. These patients should have standby oral antibiotics at home (amoxicillin-clavulanate, levofloxacin, or moxifloxacin) with instructions to self-administer at the first sign of infection, and they should be provided with information and a medical alert bracelet. Fatal pneumococcal infection has occurred in patients immunized with pneumococcal vaccine who were also taking penicillin.

IMMUNOSUPPRESSIVE THERAPY

Corticosteroids

High doses of corticosteroids alter the distribution and function of neutrophils, monocytes, and lymphocytes. Corticosteroids suppress inflammation, impair mobilization of neutrophils and monocytes, inhibit neutrophil adherence, and decrease chemotaxis of neutrophils and monocytes. They also inhibit phagocytosis and intracellular killing, severely impair CMI, inhibit lymphocyte proliferation, inhibit complement activation, and cause hyperglycemia that contributes to infection.

Acute administration of corticosteroids produces marked alterations in circulating leukocyte numbers. Basophils, eosinophils, and monocytes decrease, whereas neutrophils increase. These changes occur within 4 to 6 hours and abate by 24 to 48 hours after a single steroid dose. Lymphocytes (predominantly T cells) redistribute out of the circulation, resulting in lymphocytopenia. Corticosteroid therapy has little effect on serum immunoglobulin levels.

The most common infections occurring in patients receiving high-dose corticosteroids are caused by pyogenic bacteria (*S. aureus,* streptococci, and gram-negative bacilli). Despite the profound depression of CMI in patients taking corticosteroids, these patients generally have few infections commonly recognized as associated with defective CMI. The most common are tuberculosis and severe or disseminated infections caused by varicella-zoster and herpes simplex viruses. Patients receiving moderate doses of corticosteroids for asthma and other disorders are at increased risk for lethal primary varicella infection. Other infections seen with corticosteroid use include those caused by *Listeria, Salmonella, Legionella, Nocardia, Candida, Aspergillus, Cryptococcus, Histoplasma, Coccidioides, Pneumocystis, Toxoplasma, Cryptosporidium,* and *Strongyloides*. Patients with neurologic diseases have much higher rates of infectious complications than do patients with intestinal, hepatic, or renal disease. The infectious complications related to corticosteroid use increase with doses of prednisone equivalents of more than 20 mg/day in adults, with total doses of more than 700 mg, and with treatment longer than 30 days. The risk of adrenal suppression can be decreased by use of prednisone doses less than 7.5 mg/day, administration of doses early in the day, avoidance of split doses, and use of alternate-day dosing.

Corticosteroids decrease leukocyte accumulation at inflammatory sites, and the whole cascade of responses leading to local manifestations of infection is slowed. These effects result in delayed presentation of serious infections. In addition, prolonged administration of corticosteroids results in delayed wound healing. For example, skin sutures should be left 50% to 100% longer than in other patients. Short-term steroid treatment has little effect on wound healing.

Use of corticosteroids greatly increases the risk of hospital admission for complications of diverticular disease.[30] The diagnosis of peritonitis resulting from perforation of colonic diverticula, appendicitis, peptic ulcer, or another primary intra-abdominal condition is particularly challenging. These patients have abdominal discomfort, but they may have few abdominal findings and need rapid investigation for life-threatening abdominal disease. CT scan of the abdomen and pelvis and surgical consultation may be needed emergently in these patients, along with timely administration of broad-spectrum antimicrobials to cover for gram-negative enteric bacilli and anaerobes.

Other Immunosuppressive Medications

Commonly used immunosuppressives include cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, methotrexate, and cyclophosphamide. They treat a wide variety of conditions, including rheumatoid arthritis, psoriasis, nephrotic syndrome, and inflammatory bowel disease, and they are used in the prevention and treatment of organ transplant rejection. These drugs depress immune function, especially CMI. In addition, they have a narrow therapeutic window, wide-ranging toxic side effects, and many significant drug-drug and drug-food interactions. Patients may present for evaluation of symptoms caused by an adverse drug reaction or an infection. Before altering current medications or adding new ones, the emergency medicine clinician must check carefully for drug interactions.

Immunomodulating agents are available to treat a variety of immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriasis, and psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. Some of these drugs include inhibitors of tumor necrosis factor alpha (infliximab, adalimumab, certolizumab, golimumab, etanercept), inhibitors of interleukins (tocilizumab, anakinra), inhibitor of pyrimidine synthesis (leflunomide), and inhibitor of T-cell activation (abatacept). These agents, particularly the tumor necrosis factor inhibitors, are associated with increased susceptibility to infection, particularly disseminated infection with various intracellular pathogens.[31] Reactivation of latent infection with *M. tuberculosis,* nontuberculous mycobacterial infection, histoplasmosis, and coccidioidomycosis is frequently disseminated and extrapulmonary at presentation. Additional infections seen at increased frequency include cryptococcosis, listeriosis, legionellosis, salmonellosis, aspergillosis, candidiasis, and pneumocystosis. The clinician should be alert to unusual manifestations of infection in patients taking these agents because misdiagnosis and delayed diagnosis increase mortality. These drugs may also cause impaired wound healing, so skin sutures should be left in place longer than usual.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 182: QUESTIONS AND ANSWERS

1. What is the most common site of infection in febrile neutropenic patients?
   - **a.** Gastrointestinal tract
   - **b.** Perineum and anorectal area
   - **c.** Respiratory tract
   - **d.** Skin and soft tissue

Answer: C. The respiratory tract is the most common site of infection, with 25% of infections in the lung and another 25% in the mouth or pharynx (and an additional 5% in the nose or sinuses). Still, all neutropenic patients with fever need to have a thorough physical examination because an undiagnosed infection can cause severe morbidity or mortality.

2. A 49-year-old man with diabetes who has been receiving chemotherapy for non-Hodgkin lymphoma presents with fever and facial pain. Six weeks ago, he was treated with broad-spectrum antibiotics for fever but had negative cultures of blood and urine. He is taking ciprofloxacin as prophylaxis against infection. Examination is normal except for a purple-black lesion on his hard palate that looks like dried blood. A complete blood count shows severe neutropenia. In addition to blood cultures and chest radiography, what action should be taken immediately?
   - **a.** Administer intravenous clindamycin or ampicillin-sulbactam.
   - **b.** Administer intravenous levofloxacin.
   - **c.** Observe in the emergency department (ED) because he may be a candidate for home antibiotic therapy if other laboratory tests are normal, if he appears stable after an initial dose of antibiotics, and if his oncologist agrees.
   - **d.** Obtain a computed tomography (CT) scan of the paranasal sinuses and initiation of intravenous antifungal therapy in the hospital.

Answer: D. This patient has invasive aspergillosis or mucormycosis until proven otherwise. These fungi invade tissues and produce life-threatening necrotizing infections in cancer patients with neutropenia, as well as in diabetic patients, especially those who have received broad-spectrum antibiotics. CT scan will often show deep extension of the infection into the sinuses, orbit, or brain. The initial lesion in the palate or nose is often mistaken for a benign process. The antibiotics listed in A and B are incorrect. The most appropriate empirical antibiotic regimen is cefepime or piperacillin-tazobactam, with or without an aminoglycoside, in addition to antifungal therapy. He is not a candidate for home therapy.

3. A 27-year-old man presents to the emergency department (ED) with acute onset of fever, chills, headache, myalgias, vomiting, mild abdominal cramping, and diarrhea for 8 hours. A splenectomy was performed 15 years earlier when he was treated for lymphoma, which has been in remission since then. He is not taking any medications and has been well. Vital signs are as follows: pulse, 125 beats/min; blood pressure, 110/60 mm Hg; respiratory rate, 20 breaths/min; and temperature, 39.5°C. His mental status is normal and he has mild generalized abdominal tenderness. What is the most appropriate treatment for this patient at this time?
   - **a.** Blood cultures followed by immediate administration of ceftriaxone or cefotaxime, with or without vancomycin
   - **b.** Hydration, antipyretic, antiemetic, and observation in the ED
   - **c.** Immediate hospital admission with observation and frequent abdominal examinations
   - **d.** Lumbar puncture

Answer: A. This patient is at high risk for overwhelming postsplenectomy sepsis, usually caused by *Streptococcus pneumoniae.* Persons who have undergone splenectomy for a hematologic disorder or lymphoma are at much higher risk for overwhelming postsplenectomy infection than are those undergoing splenectomy for trauma. The initial prodromal symptoms may be misdiagnosed as a viral illness, gastroenteritis, or food poisoning before there is abrupt deterioration with development of septic shock with disseminated intravascular coagulation, purpura, and multiorgan dysfunction. After blood cultures are obtained, he should immediately receive antimicrobials active against pneumococci, meningococci, and *Haemophilus influenzae.* He can be investigated for other possible etiologies of his symptoms after this initial critical action is taken.

4. Which answer is correct regarding the diagnosis and management of patients on long-term high-dose corticosteroid therapy?
   - **a.** Acute, short-term administration of high-dose corticosteroids, but not long-term administration, can make the diagnosis of peritonitis particularly difficult.
   - **b.** After laceration repair, sutures should be left in place for 50% to 100% longer than usual.
   - **c.** Complications of chronic corticosteroid use include pancreatitis, pseudotumor cerebri, avascular necrosis of bone, cataracts, myopathy, spontaneous vertebral fractures, psychosis, and hypoglycemia.
   - **d.** Long-term corticosteroid use is frequently accompanied by peripheral blood neutrophilia.

Answer: B. Corticosteroids interfere with wound healing, so sutures need to remain in place longer than is usual for the type of laceration. Despite the profound defect in CMI that occurs with long-term corticosteroid use, infections with organisms associated with defective CMI are unusual. Most serious infections in these patients are caused by pyogenic bacteria, such as *Staphylococcus aureus,* streptococci, and gram-negative bacilli. Both short-term and long-term administration of corticosteroids interfere with the diagnosis of peritonitis. These patients will have poorly localized abdominal discomfort with minimal findings on examination. All the conditions listed in B are associated with chronic corticosteroid use—except hypoglycemia. Corticosteroid use is associated with hyperglycemia, hyperosmolar nonketotic diabetic coma, and diabetic ketoacidosis.

5. A 34-year-old woman on chemotherapy for lymphoma presents to the emergency department with severe oral pain and difficulty swallowing. She has no fevers, cough, abdominal pain, or dysuria. On physical exam, her oral mucosa is erythematous, friable, and edematous. Her labs reveal an ANC of 600 cells/μL. What is the most important next step?
   - **a.** Administer 30 mL/kg of crystalloid for sepsis.
   - **b.** Draw blood cultures and start empirical vancomycin and cefepime.
   - **c.** Start IV analgesics to allow oral rehydration.
   - **d.** Draw blood cultures and start empiric metronidazole and cefepime.

Answer: B. This patient is a neutropenic patient presenting with mucositis. Mucositis is a frequent prelude to viridans streptococcal bacteremia, which can produce sudden onset of acute respiratory distress syndrome, a toxic shock–like syndrome, rash, and pneumonia. Importantly, mucositis predisposes the patient to gram-positive infections, and vancomycin is appropriate in addition to a broad-spectrum gram-negative agent.

The Solid Organ Transplant Patient

Christine E. Koval and Michael P. Phelan

KEY CONCEPTS

- The solid organ transplant recipient's altered anatomy, denervated allograft, and immunosuppression frequently result in atypical disease presentations both related and unrelated to the transplanted organ.
- An understanding of the solid organ transplant recipient's altered anatomy, including vascular and nonvascular anastomoses, is critical to evaluating early post-transplantation complications.
- Rejection can manifest at any point post-transplantation with constitutional symptoms and signs of allograft insufficiency, requiring prompt recognition and augmented immunosuppression to salvage the transplanted organ.
- Timing post-transplantation, the net state of immunosuppression, and ongoing antimicrobial prophylaxis should be incorporated into the evaluation of a solid organ transplant recipient with fever and other concerns for infection.
- In addition to affecting a specific arm of the immune system, each antirejection agent is associated with unique toxicities which may be independently responsible for a solid organ transplant recipient's clinical condition.
- Cardiac allograft vasculopathy, a form of chronic rejection and similar to coronary artery disease in presentation, has emerged as a common complication of orthotopic heart transplantation as transplant recipients live longer.
- Especially in lung transplant recipients with underlying cystic fibrosis or bronchiectasis, prior imaging and culture data should help guide initial management of new respiratory symptoms.
- Recurrent allograft pyelonephritis post-transplantation merits thorough evaluation for ureteral stones and strictures, perinephric abscesses, and urinary retention to identify potentially actionable contributors to infection.
- Hepatic artery thrombosis is an uncommon but devastating early complication of liver transplantation resulting in allograft dysfunction, biliary necrosis, and sepsis if left undetected and untreated.
- Allograft rejection, bacterial or viral enteritis, and altered intestinal transit time can all contribute to diarrhea in the intestinal and multivisceral transplant recipient.
- As chronic corticosteroids are incorporated into immunosuppression regimens for the majority of solid organ transplant recipients, adrenal insufficiency should be considered in the differential of transplant recipients presenting with hypotension and fever.
- In addition to the organ-specific complications described in the sections above, solid organ transplant recipients experience graft-versus-host disease, malignancy, trauma, and psychosocial distress post-transplantation requiring heightened awareness and assembly of multidisciplinary teams.

INTRODUCTION

Solid organ transplantation has undergone significant advancement since the first successful kidney transplant in 1956. In 2019, over 39,000 solid organ transplants were performed in the United States (US).[1] As improvements in medical and surgical treatments allow more individuals to undergo transplantation and increase the life expectancy for transplant recipients, emergency clinicians should expect to encounter patients with illnesses complicated by their history of transplantation. This chapter provides a basic knowledge of organ transplant pathologies and their initial management as well as an appreciation for the utility of consultation with transplant surgeons and other subspecialists.

Pathophysiology

Altered anatomy and ongoing immunosuppression change how transplant recipients present with disease. Allografts are denervated, and thus pain is an unreliable sign of illness. Normal inflammatory and immunologic responses are impaired, limiting the recipient's ability to mount a fever or elevated leukocyte count.[2] Subtle signs and symptoms may be harbingers of serious complications. Transplant-related illness can generally be placed into one of four categories: anatomy, rejection, infection, and drug toxicity (Fig. 183.1). Rejection and infection may present similarly. Changes in baseline allograft function and time since transplantation guide the differential diagnosis. It is imperative to consider infectious risk and drug toxicity when recipients present with issues not directly involving the allograft.

Anatomy

Anatomic complications can involve vascular anastomoses, nonvascular anastomoses, or surgical wounds, and typically manifest within the first few months post-transplantation. Vascular anastomotic complications can include arterial or venous structures. Of these, arterial complications are more acutely devastating. Arterial stenosis or thrombosis may lead to fulminant organ failure. Pseudoaneurysms or mycotic aneurysms can precipitate hemorrhagic shock. Nonvascular organ anastomoses can develop leaks or obstructions from scarring or stent migration, which may provoke acute allograft dysfunction or infection. Early identification of these complications by laboratory investigation of allograft function, imaging, and prompt consultation of transplant specialists is vital to salvage the allograft.

Infection

Infection is the primary cause of mortality after transplantation. Timing since transplantation may predict the most likely pathogens and guide empirical antibiotic selection (Fig. 183.2).

Early Period: 0 to 4 Weeks Post-Transplantation. Infections within the first month of transplantation often relate to postoperative intensive care and surgical site complications.[2] Typical pathogens include nosocomial and multidrug-resistant organisms as well as the transplant recipient's colonizing bacteria identified pre-transplantation. Wound infections, pneumonias, urinary tract infections, and *Clostridioides difficile* colitis are encountered. Bloodstream infection may present without typical signs of sepsis syndrome.

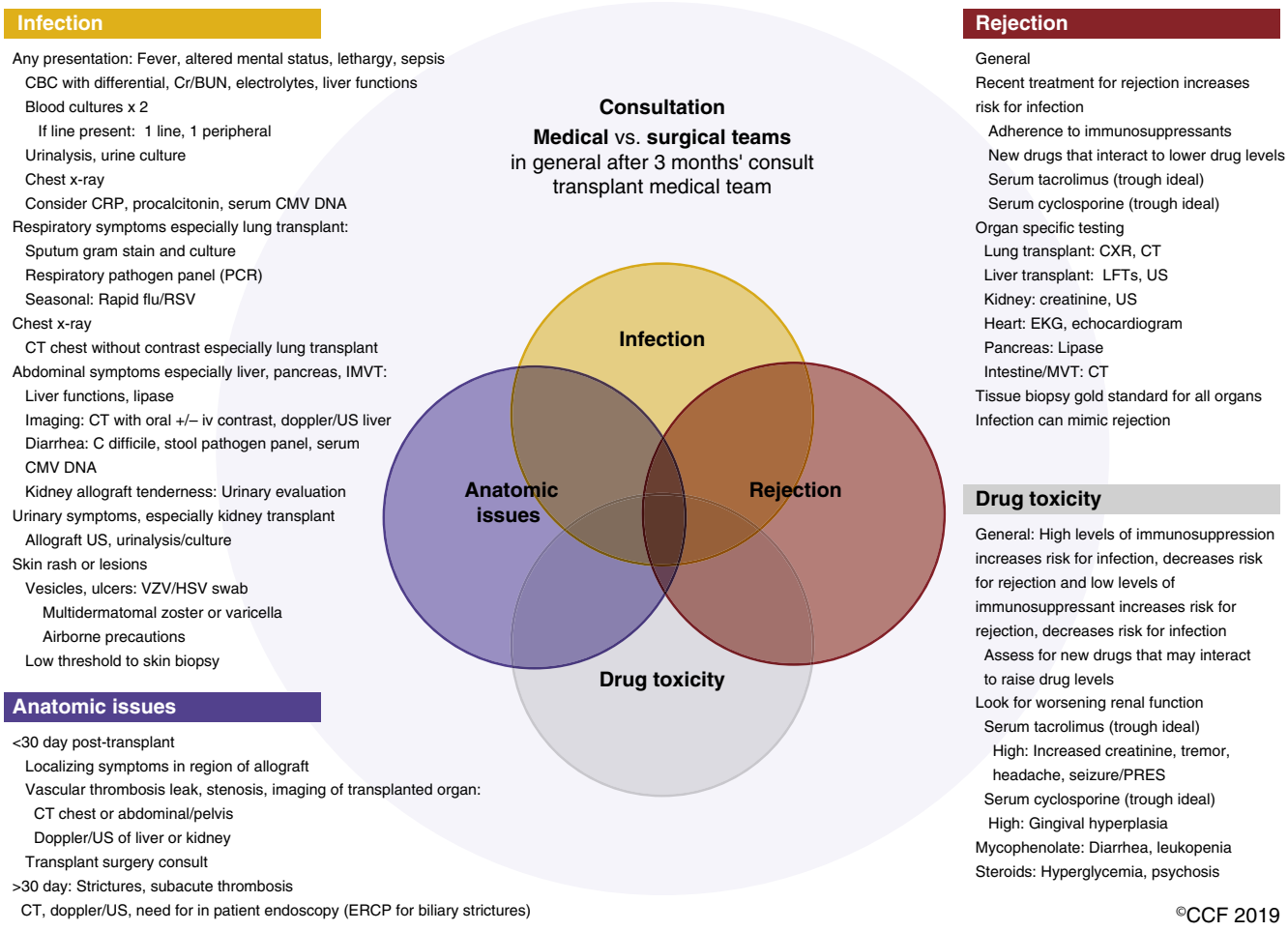

Fig. 183.1 Evaluation of the solid organ transplant recipient in the emergency department. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved.)

Both donors and recipients undergo extensive serologic and nucleic acid testing pre-transplantation, but expected and unexpected pathogen transmissions from donor to recipient can occur.[2] Expected transmissions in some donor/recipient pairs include cytomegalovirus (CMV), Epstein-Barr virus (EBV), and hepatitis C virus (HCV). Transplant center–specific strategies to monitor and pre-emptively treat such infections effectively prevent end-organ disease. Unrecognized donor infection prior to transplantation can rarely result in unexpected transmissions and lead to tissue-based or systemic illness (e.g., rabies encephalitis, disseminated disease due to fungi, *Mycobacterium tuberculosis* [MTB], or *Strongyloides stercoralis*). While the focus should remain on addressing the more likely postoperative infections in this time period, consideration of donor-derived infections may be instrumental for diagnosis. Unexpected donor derived infections are reported to United Network for Organ Sharing (UNOS) for the safety of other transplant recipients.

Intermediate Period: 1 to 12 Months Post-Transplantation. Infections occurring within the first year of transplantation are generally divided into two categories: reactivation of latent infections and opportunistic infections.

Reactivation of CMV, the most prevalent viral infection observed during this time period, increases the risk of other infections, allograft rejection, and mortality due to CMV's immunomodulatory properties.[2,3] As all transplant centers provide valganciclovir prophylaxis or serum CMV deoxyribonucleic acid (DNA) monitoring, symptomatic CMV infection does not usually emerge until after prophylaxis is stopped.[4] Duration of prophylaxis varies based on the type of allograft, donor/recipient serostatus, and transplant center, but typically ranges from 3 to 12 months post-transplantation. Common presentations of CMV reactivation include "CMV syndrome," characterized by fever, leukopenia, and viremia, and CMV gastrointestinal disease presenting with diarrhea, abdominal pain, or odynophagia with or without viremia. Other tissue-based infections (e.g., hepatitis, pneumonitis) involve their respective allografts, present with viremia, and are differentiated from alternative etiologies by allograft biopsy.

Reactivation of herpes simplex viruses (HSV) 1 and 2 and varicella zoster virus (VZV) can be prevented by valganciclovir or other acyclovir-derivatives. When these agents are stopped beyond the prophylaxis period, transplant recipients may present with localized or disseminated disease including multidermatomal zoster. Facial zoster involving the cornea and multidermatomal zoster require hospital admission. Multidermatomal zoster merits airborne and contact precautions. Timely treatment with acyclovir decreases post-herpetic neuralgia. Some adults may be VZV seronegative at the time of transplantation and are at risk for complications of primary varicella infection, including life-threatening pneumonia and encephalitis with or without classic skin lesions. Treatment includes intravenous acyclovir and sometimes varicella immune globulin.

Effective prophylaxis can also prevent many opportunistic infections post-transplantation. Thus, such infections merit particular consideration in transplant recipients who cannot tolerate prophylactic antimicrobials. For example, trimethoprim/sulfamethoxazole (TMP/

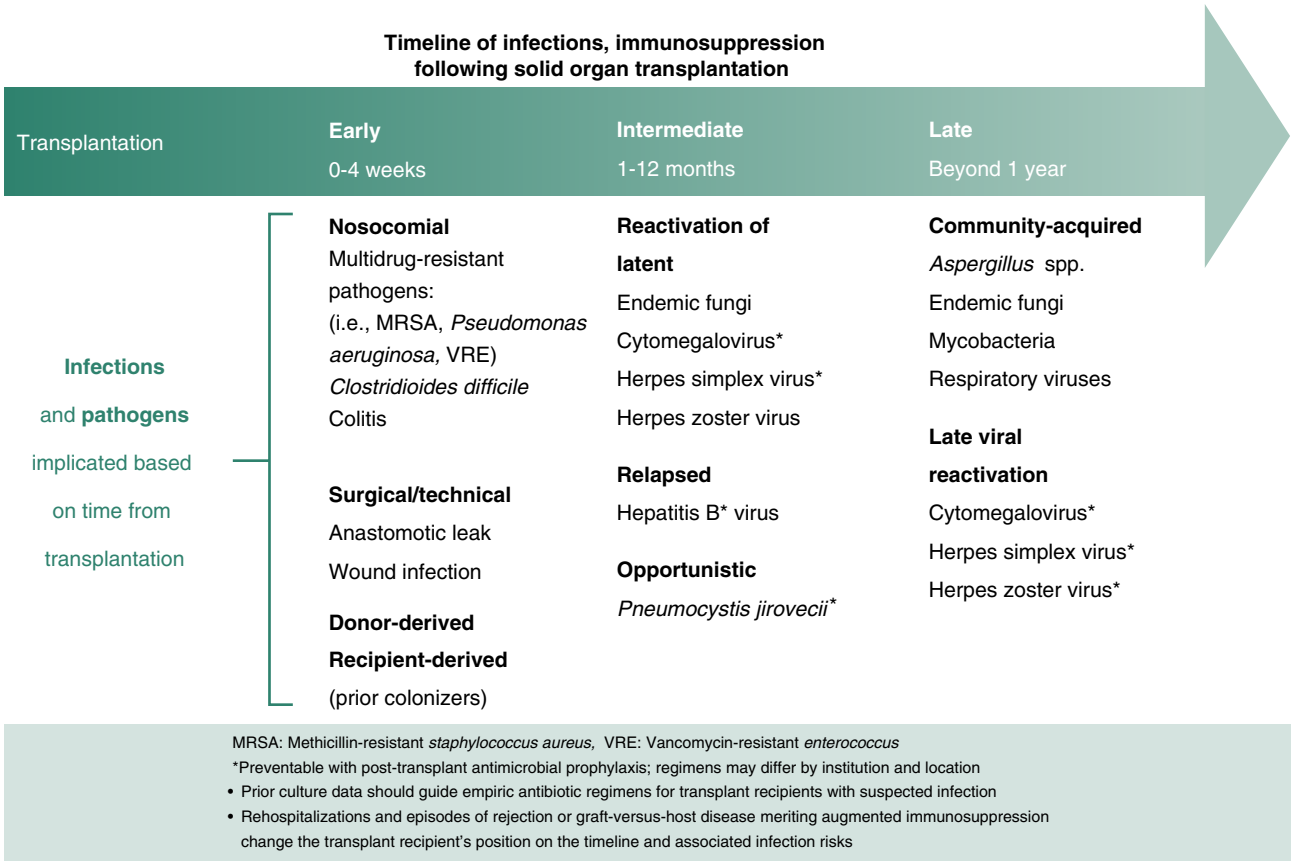

Fig. 183.2 Timeline for infectious complications after solid organ transplantation. (Adapted from: Fishman, J. Infection in organ transplantation. *Am J Transplant.* 2017;17:856-879. Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved.)

SMX) is the drug of choice to prevent *Pneumocystis jirovecii* pneumonia (PCP) and concomitantly covers *Toxoplasma*, *Nocardia*, and *Listeria* species. Those with sulfa allergies or significant intolerance may be prescribed alternative agents (inhaled pentamidine, oral dapsone, or atovaquone) for PCP prophylaxis but these alternative agents do not sufficiently protect against these other pathogens.

Pneumocystis typically presents with a subacute, progressive, nonproductive cough and dyspnea and is accompanied by diffuse pulmonary infiltrates on imaging. Diagnosis is best made by molecular testing of induced sputum or bronchoalveolar lavage fluid. Optimal treatment is with 5 mg/kg of TMP/SMX every 6 to 8 hours, based on renal function. There is no proof that adjunctive steroid use is beneficial in patients with PCP but without human immunodeficiency virus (HIV), and high doses of steroids may be harmful, but data are extremely limited.[5]

Mycobacterial infections such as tuberculosis (TB) mostly represent reactivated disease, but can also represent primary disease from a new exposure. Transplant recipients may develop pulmonary TB or disseminated infection, presenting with nonspecific systemic symptoms or evident meningitis, peritonitis, or vertebral infection. Treatment is challenging due to public health concerns, serious drug-drug interactions with immunosuppression, and allograft toxicities.

Lung and liver transplant recipients are at highest risk for fungal infections post-transplantation.[6] Invasive aspergillosis frequently presents as pulmonary nodules but may disseminate to any organ system. Endemic mycoses (histoplasmosis, blastomycosis, and coccidiomycosis) manifesting with fever and respiratory symptoms should be considered based on geographic location and exposure history. These infections are uncommon but are more likely to disseminate from an original pulmonary source.[7] Amphotericin B may be appropriate for disseminated disease but newer azoles can be effective for pulmonary infection and are specifically indicated for certain fungi.

Toxoplasmosis is uncommon in solid organ transplantation. Risk is greatest in toxoplasma seronegative recipients who acquire an organ from a seropositive donor and do not receive TMP/SMX prophylaxis.[8] Toxoplasmosis presents as myocarditis in heart transplant recipients, resembling rejection, but can disseminate to cause pulmonary infiltrates, hepatosplenomegaly, and central nervous system (CNS) disease. Treatment involves intravenous sulfadiazine and pyrimethamine or TMP/SMX.

Cryptococcus neoformans presents as a meningoencephalitis with altered mental status. Serum cryptococcal antigen can diagnose disease. However, lumbar puncture for opening pressure and cryptococcal antigen is required to address CNS involvement. If the opening pressure is greater than 25 mm H_2O, relief of cerebrospinal fluid to reduce the opening pressure to less than 20 mm H_2O, or by 50% if the pressure is extremely high, is immediately warranted.[9] Repeated lumbar punctures or percutaneous drains may be required over subsequent days. Initial antimicrobial therapy for meningoencephalitis includes the lipid formulation of amphotericin and flucytosine.

Strongyloides stercoralis is an intestinal nematode that can present with hyperinfection syndrome, causing a necrotizing hemorrhagic enterocolitis and hemorrhagic pneumonia. Disseminated strongyloidiasis presents with severe abdominal pain, obstructive symptoms, hemorrhage and secondary peritonitis, sepsis from enteric pathogens,

meningitis, and pneumonia. Diagnosis is by stool or bronchoalveolar lavage sample microscopy. Treatment of disseminated strongyloidiasis is with ivermectin and albendazole, although mortality is high if not detected early.[10]

Late Period: Beyond 1 Year Post-Transplantation. One year after transplantation, transplant recipients' susceptibility to infection is predominantly dependent on their net state of immunosuppression. Healthy transplant recipients have a functioning allograft and can generally be maintained on low doses of immunosuppression such that they achieve immunologic control of CMV and other herpes viruses. They face a mildly increased susceptibility to community-acquired infections, such as influenza and pneumococcal pneumonia, and still develop certain reactivated or opportunistic infections (i.e., VZV, TB, aspergillosis) with aging or environmental exposures. They remain at risk for more severe forms of community-acquired infections and endemic mycoses. In contrast, transplant recipients with chronic immune dysregulation require aggressive immunosuppression for rejection and are unable to develop adaptive immunity to CMV. They face high risk for life-threatening opportunistic infections, as well as standard community-acquired and nosocomial infections, and may require prolonged antimicrobial prophylaxis.

Rejection

Rejection is the process by which T cell receptor–mediated pathways lead to cytotoxic activity and B cell memory and antibody formation lead to allograft cell death.[11] This immune response to the allograft waxes and wanes, mandating lifelong surveillance. Hyperacute rejection occurs in the immediate postoperative period, caused by preformed antibodies against major histocompatibility complex or ABO blood type antigens. This complication is rare with careful donor-recipient matching or with aggressive desensitization strategies. Acute cellular rejection (ACR) and antibody mediated rejection (AMR) are both associated with constitutional symptoms and signs of allograft insufficiency occurring days to weeks after transplantation or any time immunosuppression is deliberately or accidentally decreased. ACR is mediated by T cells whereas AMR is due to circulating donor-specific antibodies, complement deposition, and neutrophilic inflammation of the allograft. Chronic rejection occurs over months to years and results in allograft failure.

Immunosuppressive therapy requires correctly timed drug combinations to establish a balance between rejection and infection. Regimens are transplant center–specific, but most include a calcineurin inhibitor (usually tacrolimus), an antimetabolite (usually mycophenolate mofetil), and steroids. Recognition of the side effects, toxicities, and potential drug-drug interactions of immunosuppressant medications is important for the care of any transplant recipient (Table 183.1). Consultation with a clinical pharmacist trained in transplant pharmacotherapy can help optimize the use of immunosuppressive and antibiotic agents.

Desensitization Regimens and Therapies for Antibody-Mediated Rejection. Desensitization regimens decrease circulating antibodies likely to react with donor antigens in patients sensitized to incompatible donors. These pretransplant regimens include plasmapheresis to remove antibodies, rituximab to deplete B cells, bortezomib to reduce antibody production, intravenous immune globulin (IVIG) to trigger antibody clearance, and eculizumab to target the complement cascade.[11]

Induction Agents. Induction immunosuppression is employed in the pre- or peri-transplantation period. Antithymocyte globulin (ATG) and alemtuzumab are both lymphocyte depleting agents, with ATG targeting T cells and alemtuzumab both T and B cells. ATG is also used to treat steroid-refractory acute cellular rejection. Lymphodepletion can last for 3 to 6 months, conferring increased risk of opportunistic infections and post-transplantation lymphoproliferative disorder (PTLD). Non-lymphodepleting agents include basiliximab and daclizumab, anti-IL-2 monoclonal antibodies used in recipients at lower risk of rejection.[12]

Maintenance Immunosuppression

Calcineurin Inhibitors. The calcineurin inhibitors tacrolimus and cyclosporine have greatly improved patient- and allograft-related outcomes. However, calcineurin inhibitors (CNIs) have narrow therapeutic indices, variable pharmacokinetics, and adverse side effects.[12] Serum trough levels should be checked in patients with worsening renal function, because CNIs are cleared by the kidney and can cause kidney injury. Both CNIs have been associated with gout and pseudogout. CNI concentrations are altered by common post-transplantation medications including antibiotics; the initiation of such medications merits close communication with the transplant team to plan for CNI dose adjustments and prospective drug monitoring.

Tacrolimus is a macrolide compound that binds to lymphocyte proteins and inhibits cytokine synthesis. Adverse effects include dose-dependent nephrotoxicity as well as neurotoxicity, characterized by tremors, headache, and posterior reversible encephalopathy syndrome (PRES).[12] When combined with steroids, tacrolimus can lead to hyperglycemia and diabetes.

Cyclosporine inhibits both cellular and humoral immunity by binding to proteins which inhibit lymphocyte signal transduction between helper-inducer T cells and B cells. Cyclosporine is similarly associated with dose-dependent nephrotoxicity which is enhanced when used with other nephrotoxins, such as amphotericin or aminoglycosides.[12] Renal tubular injury and direct renal artery vasospasm can result in systemic hypertension. Rarely, cyclosporine toxicity can result in a neurologic syndrome of confusion, quadriplegia, and coma if left untreated.

Mammalian Target of Rapamycin Inhibitors. Sirolimus and everolimus are two drugs in the mammalian target of rapamycin (mTOR) class. mTOR is key in the pathway for T cell clonal activation. Adverse effects include delayed wound healing, hyperlipidemia, cytopenias, diarrhea, and sirolimus-induced lung injury.[12]

Antimetabolites. Azathioprine is an antimetabolite derivative of 6-mercaptopurine and inhibits both DNA and ribonucleic acid synthesis to suppress lymphocyte proliferation.[12] Transplant recipients may exhibit dose-dependent neutropenia, hepatic dysfunction, and gastrointestinal upset.

Mycophenolate mofetil (MMF) is an antimetabolite with more potent and selective inhibition of lymphocyte proliferation as well as a relatively low side effect profile.[12] The most common adverse effects are diarrhea and leukopenia. Because magnesium and aluminum antacids interfere with MMF absorption, care should be exercised in treatment of GI symptoms. MMF is usually switched to azathioprine in the setting of pregnancy to reduce risk of teratogenicity.

Corticosteroids. Corticosteroids have a wide range of effects on the immune system. Every effort is made to minimize corticosteroid use to prevent long-term consequences such as gastrointestinal bleeding, diabetes, and osteonecrosis. High-dose steroids to treat rejection may precipitate altered mental status. Acute withdrawal or severe illness may lead to Addisonian crisis, presenting with fevers, hypotension, and metabolic derangements and merit initiation of stress-dose steroids (e.g. hydrocortisone 100 mg IV).

Other Agents: Belatacept, Rituximab, Eculizumab. Belatacept is a fusion protein that blocks T cell co-stimulation at CD28 and is used primarily in kidney transplantation to avoid the nephrotoxicity of CNIs.[12] It is dosed on a monthly basis. It is associated with increased rates of PTLD and is contraindicated in EBV-seronegative recipients. Rituximab is a monoclonal antibody directed against the B-cell surface marker CD20 and

TABLE 183.1 Immunosuppression Agents Used in Solid Organ Transplantation

Agent	Mechanism	Metabolism	Drug-Drug Interactions	Toxicities and Other Considerations
Alemtuzumab	CD52 inhibitor	–	–	Lymphocyte depletion for 6–12 months
Antithymocyte globulin	Polyclonal T cell depletion	–	–	Lymphocyte depletion for 3–6 months Serum sickness, fevers with infusions
Azathioprine	Antimetabolite	Hepatic	↑ by allopurinol May ↓ anticoagulant effect of warfarin	Hepatotoxicity Bone marrow suppression, ↑ by valganciclovir
Basiliximab	IL-2Rα inhibitor	–	–	Duration of activity may last 4–6 weeks
Belatacept	CD80/86 inhibitor	–	–	Post-transplant lymphoproliferative disorder
Bortezomib	26S proteasome inhibitor	Hepatic CYP2C19, CYP3A4	↓ by phenytoin, carbamazepine, rifampin ↑ by azoles, CCBs, macrolides, PIs	Peripheral neuropathy
Cyclosporine A	Calcineurin inhibitor	Hepatic CYP3A4 and P-glycoprotein	↓ by phenytoin, carbamazepine, rifampin ↑ by azoles, CCBs, macrolides, PIs, letermovir	Nephrotoxicity, ↑ by AG, AMB, NSAIDs Hypertension Gingival hyperplasia
Eculizumab	Terminal complement inhibitor	–	–	*Neisseria meningitides* meningitis
Everolimus	Mammalian target of rapamycin inhibitor	Hepatic CYP3A4 and P-glycoprotein	↓ by phenytoin, carbamazepine, rifampin ↑ by azoles, CCBs, macrolides, PIs	Interstitial pneumonitis Nephrotoxicity Poor wound healing
Intravenous immunoglobulin	Antibody replacement	–	–	Serum sickness, fevers with infusions
Mycophenolate mofetil Mycophenolate sodium	Antimetabolite	Hepatic and gastrointestinal	↑ by antacids, cholestyramine	Hepatotoxicity Bone marrow suppression, ↑ by valganciclovir Gastrointestinal distress
Rituximab	CD20 inhibitor	–	–	Reactivation of hepatitis B, JC virus
Steroids	Variable	Hepatic cytochrome P450 (minor)	↑ by PIs	Weight gain and associated glucose intolerance, HLD Poor wound healing ↑ risk gastrointestinal bleeding with NSAIDs
Sirolimus	Mammalian target of rapamycin inhibitor	Hepatic CYP3A4 and P-glycoprotein	↓ by phenytoin, carbamazepine, rifampin ↑ by azoles, CCBs, macrolides, PIs	Interstitial pneumonitis Poor wound healing
Tacrolimus	Calcineurin inhibitor	Hepatic CYP3A4 and P-glycoprotein	↓ by some antiepileptics, caspofungin, rifampin ↑ by azoles, CCBs, macrolides, PIs, CBD	Nephrotoxicity, ↑ by AG, AMB, NSAIDs Neurotoxicity (PRES, Tremor)

CCB, Calcium channel blocker; *PI*, protease inhibitor; *AG*, aminoglycoside; *AMB*, amphotericin B; *NSAID*, nonsteroidal antiinflammatory; *HLD*, hyperlipidemia; *PRES*, posterior reversible encephalopathy syndrome.

results in B cell depletion. It is associated with cytopenias and hepatitis B reactivation. It also carries a black box warning for progressive multifocal leukoencephalopathy, although this is rare.[12] Eculizumab is a monoclonal antibody that acts as a terminal complement inhibitor and is associated with increased risk for meningococcemia.[13]

ORGAN-SPECIFIC CONSIDERATIONS

The following sections delineate organ-specific anatomic, rejection-related, infectious, and pharmacologic complications of transplantation with occasional reference to the general concepts of solid organ transplantation described previously.

Heart Transplantation

Heart transplantation is a curative option for patients with end-stage cardiomyopathy, recurrent ventricular arrhythmias, intractable angina, or primary tumors. In 2019, over 3500 heart transplants were performed in the United States.[1] Over 40% of candidates are bridged to transplantation with ventricular assist device (VAD) technologies. Current 1-, 3-, and 5-year patient and allograft survival rates are 90%, 85%, and 80%, respectively.[14] Main reasons for readmission early post-transplantation include cardiac dysrhythmias, allograft rejection, and infection; later causes include cerebrovascular and allograft vasculopathy. Renal dysfunction and diabetes are common comorbidities.[15]

Anatomic Considerations

Orthotopic heart transplants are usually bicaval, involving a single anastomosis between the donor and recipient left atria, aortic and pulmonary artery anastomoses, and two caval anastomoses. Alternatively, the biatrial method of orthotopic heart transplantation involves anastomoses between the aorta and pulmonary artery as well as both the right and left atria.[16] Leads from previous pacemakers or implantable cardioverter-defibrillators may be retained post-transplantation, limiting the transplant recipient's ability to undergo magnetic resonance imaging safely.

The transplanted heart is denervated of both parasympathetic and sympathetic nerve fibers, which causes clinically important physiologic changes.[17] Without parasympathetic tone, the transplant recipient's early resting heart rate varies from 95 to 110 beats/minute, but decreases by one year to a mean of 92 beats/minute.[18] Variation exists based on donor and recipient factors. Without sympathetic tone, transplant recipients may experience relative bradycardia during times of physical or mental stress. Transplant recipients presenting to the ED with brady- or tachyarrhythmias generally merit admission. For immediate intervention, beta-blockers, diltiazem, and amiodarone may be used to treat supraventricular tachyarrhythmias. The allograft is sensitive to adenosine with a risk of prolonged AV block, so the anticipated dose should be reduced by half prior to administration. Atropine and glycopyrrolate have no effect on the denervated heart and should not be used in the transplant recipient.

Denervation of the allograft also prevents heart transplant recipients from experiencing classic anginal symptoms.[17] Transplant recipients suffer silent myocardial infarctions and sudden cardiac death, compelling providers to remain aware of other signs and symptoms of cardiac ischemia. The most common electrocardiogram (ECG) abnormalities after heart transplantation, incomplete right bundle branch blocks and repolarization abnormalities, are not clinically meaningful.[19] Significant ECG abnormalities include consistent Q waves as well as ST segment elevations. Heart failure may present in an atypical fashion as well. Although a transthoracic echocardiogram may report normal left ventricular function and ejection fraction, microscopic scarring of the allograft can gradually lead to a restrictive cardiomyopathy.

Infection

In addition to the nosocomial infections described earlier in this chapter, infections related to the surgical site as well as the sites of prior device placement occur in the first month after heart transplantation. Mediastinitis may present with chest pain, sternal instability, wound breakdown, or with nonspecific symptoms of fever and tachycardia. Diagnosis requires computerized tomography (CT) scan of the chest, and treatment requires broad-spectrum antibiotics and surgical débridement. Infections of VAD components can be present at the time of transplantation and may impact post-transplantation infection risk. Prior VAD infection increases the risk for post-transplantation multidrug-resistant infections and can thus inform empirical antibiotic selection.[20]

Toxoplasmosis is a particular risk for heart transplant recipients, especially in those unable to take TMP/SMX prophylaxis, and presents with signs of myocarditis resembling rejection, pneumonia, or meningoencephalitis. Trypanosomiasis is rare in the United States but is a common indication for heart transplantation in endemic countries. Unmonitored, recurrent infection can cause myocarditis, subcutaneous nodules, or disseminated disease.[8]

Rejection

Hyperacute cellular or metabolic rejection is rare but can precipitate early allograft failure, requiring the temporary use of advanced heart therapies.[21] Acute cellular rejection occurs in 27% of recipients by one year post-transplantation and is diagnosed by allograft biopsy.[14] Many episodes are low-grade, asymptomatic, and left untreated. Severe rejection manifests with fever and signs of heart failure such as dyspnea, meriting admission for anti-rejection therapies.

Cardiac allograft vasculopathy is associated with chronic rejection and serves as a major determinant of morbidity and mortality for heart transplant recipients.[21] It is identified via angiography with diffuse, concentric narrowing of the coronary arteries. CAV may be asymptomatic or present with symptoms of heart failure, myocardial infarction, or sudden cardiac death. The definitive treatment for CAV is re-transplantation.

Drug Toxicity

Calcium channel blockers and amiodarone can increase cyclosporine, tacrolimus, and sirolimus levels. In contrast, cyclosporine can increase the drug levels of statin medications to result in muscle cramping and rhabdomyolysis. Sirolimus use in the early post-transplantation period can result in sternal wound dehiscence and is avoided early post-transplantation. Drug-drug interactions between antibiotics and warfarin require attention to ensure safe anticoagulation.

Kidney Transplantation

Kidney transplantation is a life-saving option for patients with end-stage renal disease compared to prolonged time on dialysis. Over 23,000 kidney transplants were performed in the United States in 2019.[1] One-, three-, and five-year patient survival post-deceased donor kidney transplantation is generally estimated at 97%, 94%, and 90%, respectively, with living donor outcomes exceeding these.[22] Up to 40% of transplant recipients present to the ED in the first year, usually due to allograft dysfunction, infection, or exacerbation of diabetes or hypertension.[23]

Anatomic Considerations

The renal allograft is usually transplanted in the right or left iliac fossa, with native kidneys and ureters left in situ. Allograft pyelonephritis presents with pain at the allograft in the lower abdomen rather than the flank pain observed with native pyelonephritis. However, denervation

can prevent the development of pain altogether.[24] Rarely, nephrolithiasis and urinary tract infections still occur in the transplant recipient's retained native kidneys.[25]

Donor renal vessels are anastomosed to recipient iliac vessels. Although rare, vascular complications such as bleeding and thrombosis can occur up to a week post-transplantation.[23] Intra-abdominal hematomas can initially manifest with urinary obstruction and hydronephrosis. Renal artery and vein thromboses can also present with decreased urinary output and acute kidney injury. Vascular complications occurring months to years post-transplantation are typically due to arterial stricture or stenosis observed in the context of underlying peripheral vascular disease. Doppler ultrasound is the preferred method of evaluating vascular patency.

Nonvascular anastomoses are created between the donor ureter and either the recipient's ureter or bladder. Ureteral stents are endoscopically inserted during transplantation and remain in place for 6 weeks. Retention of the stent during episodes of infection may lead to recurrent urinary tract infections due to biofilm formation. Ureteric complications occur in up to 15% of transplants and include stent migration as well as ureteric leak or stricture. Unlike the native system, the transplanted ureter does not have a one-way valve at the insertion site in the native bladder to prevent reflux-associated injury to the allograft.

Delayed allograft function requires temporary dialysis until reasonable function is established. During dialysis, attention must be paid to central catheters, fistulas, and grafts, which may be potential sources of infection or thrombosis.

Infection

Urinary tract infections including allograft pyelonephritis are the most common infections post-transplantation. Classic presenting symptoms include fever, allograft tenderness, and pyuria, but symptoms may be nonspecific, including confusion, malaise, or weakness. Associated volume depletion can elevate creatinine, mirroring allograft rejection. If there is evidence of sepsis, obtain blood and urine cultures and initiate empirical antibiotic therapy until culture data are available.

Recurrent urinary tract infections can lead to allograft failure and merit a thorough investigation (including imaging) of potentially actionable contributors to disease such as perinephric abscesses, nephrolithiasis, residual ureteral stent, and urinary retention. Oral antibiotics may suffice to treat uncomplicated cystitis, though intravenous options are recommended in the setting of allograft pyelonephritis or urinary tract infections complicated by bacteremia or sepsis. Asymptomatic bacteriuria does not require routine treatment.[26]

Attention to remaining dialysis access sites may identify a source for bloodstream infections. BK virus infection results in chronic nephropathy in up to 10% of kidney transplant recipients but is rarely an emergent problem.[27] Reduction of immunosuppression is the only proven strategy for decreasing the risk of significant BK nephropathy and usually takes months to resolve.

Rejection

Acute rejection is a common complication of kidney transplantation, with an incidence of 10% at 1 year and associated reductions in allograft survival.[22] Renal allograft rejection manifests with fever, tenderness over the allograft, and signs and symptoms of allograft dysfunction including decreased urine output and elevated creatinine. Early consultation with the transplant nephrologist or urologist is prudent to pursue timely renal biopsy and empirical treatment.

Chronic transplant rejection occurs after long-term loss of adequate function due to nephrosclerosis or fibrosis of the blood vessels supplying the allograft. This process involves proliferation of the vascular intima of renal vessels with marked decrease in the lumen size. Findings include proteinuria, hypertension, and allograft dysfunction.

Drug Toxicity

Drug toxicities are a particular risk to the renal allograft. Supratherapeutic CNI concentrations can cause acute and chronic kidney injury.[12] Other nephrotoxic drugs can potentiate injury in the setting of CNIs or volume depletion. Nonsteroidal antiinflammatory drugs (NSAIDs) are not recommended in kidney transplant patients because even short courses for acute pain management have been demonstrated to result in acute allograft injury.[28] Amphotericin and foscarnet should be administered with caution.

Liver Transplantation

Over 8800 liver transplants were performed in the United States in 2019.[1] Since 2015, nonalcoholic steatohepatitis (NASH) has superseded hepatitis C as the primary indication for liver transplantation. One-, three-, and five-year patient survival is reported as 91%, 84%, and 76%, respectively.[29] Vascular and biliary complications, allograft dysfunction, and infection are common, with up to 45% of transplant recipients presenting to the ED in the first year post-transplantation and 78% of these requiring admission.[30]

Anatomic Considerations

Liver transplantation requires surgical anastomoses at biliary and vascular sites. Biliary anastomosis can be duct-to-duct or by choledochojejunostomy. Choledochojejunostomy (CDJ) is performed when donor or recipient ducts are not amenable to direct anastomosis, joining the allograft remnant bile duct directly into the roux limb of the recipient small bowel. CDJ increases the risk of intra-abdominal infections. The gallbladder is always removed during transplantation.

All vascular and biliary anastomoses can serve as sites of stenosis, obstruction, or leak. Hepatic artery rupture, caused by bacterial or fungal arteritis, can result in hemorrhagic shock. Portal vein thrombosis occurs in 1% to 2% of liver transplant recipients and presents with encephalopathy and refractory ascites characteristic of allograft failure.[31] Hepatic artery thrombosis (HAT) is the most common vascular complication and can result in immediate hepatic or biliary necrosis, manifesting with fever, jaundice, and right upper quadrant pain with or without elevated transaminases and hyperbilirubinemia.[31] Liver transplant recipients presenting to the ED in the first month post-transplantation should be screened for HAT with Doppler ultrasound. Treatment of acute HAT may require immediate thrombectomy or emergent re-transplantation.

Biliary complications including stricture, obstruction, leaks, and necrosis frequently manifest with fevers, abdominal pain, and relative hyperbilirubinemia.[31] Extrahepatic biliary leak presents with perihepatic collections or peritonitis. Intrahepatic biliary necrosis or stricture can present with intrahepatic bilomas and cholangitis. Biliary stricture typically manifests within 1 year post-transplantation.[31] Stents placed endoscopically may ameliorate the stricture but can themselves become obstructed and may require revision.

Living donor allografts are comprised of either the right or left lobe of the liver. Transplantation of these partial allografts may be complicated by small-for-size syndrome, or functional hepatic impairment occurring within one week postoperatively with coagulopathy, cholestasis, encephalopathy, and ascites.[32] Portal hypertension, a risk factor for small-for-size syndrome, is assessed intraoperatively and modulated with shunt formation or splenectomy. The vascular and biliary complications described in this section are more commonly observed in living donor liver transplant recipients due to complexities of both vessel and bile duct division

during allograft donation and the creation of smaller anastomoses during transplantation.

Infection

Over 50% of bacterial infections causing sepsis in this population occur within the first two weeks of transplantation, usually due to pre-transplantation risk factors or surgical complications.[33] Later intra-abdominal infections are due to biliary strictures or preceding HAT. About 50% of living-donor liver transplant recipients experience infection within 1 year, usually due to biliary and vascular complications.[29] Fever, malaise, or abdominal pain should prompt laboratory evaluation with a complete blood count and differential and comprehensive metabolic panel, as well as blood cultures. Niduses of infection, including retained biliary stents, gallstones, and hepatic or intra-abdominal abscesses, should be identified via ultrasound and CT of the abdomen to coordinate surgical or procedural interventions as appropriate.

Enteric organisms, including *Enterococcus* species, gram-negative, and anaerobic organisms are typical pathogens meriting empirical coverage with beta-lactam/beta-lactamase inhibitor regimens. Pre-transplantation colonization with multidrug-resistant organisms may warrant even broader antibacterial coverage. Many recipients have received vaccinations against encapsulated organisms (*Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*) in planning for possible splenectomy at the time of transplantation, but such infections should remain on the differential diagnosis. Overlying incisional wound infections may warrant coverage for *Staphylococcus aureus* (including methicillin-resistant strains). However, incisional infections and wound dehiscence often portend an underlying intra-abdominal source.

Liver transplant recipients are susceptible to some invasive fungal infections, mostly due to *Candida* species in the early post-transplantation period.[2,33] Risk is associated with biliary and operative bleeding complications and CDJ anastomosis. Invasive aspergillosis and endemic fungal infections usually emerge later but can occur within the first month in high-risk settings such as fulminant hepatic failure, re-transplantation, or severe renal failure post-transplantation. Empirical antifungal therapy is warranted for patients with these risk factors or with septic shock.

Rejection

Acute rejection occurs in up to 20% of liver transplant recipients within one year of transplantation.[29] Chronic rejection is more indolent and can be diagnosed years after initial presentation. Both acute and chronic allograft rejection may present with asymptomatic transaminase elevations or with fever, jaundice, and right upper quadrant pain. Eosinophilia may be noted. Anatomic complications, infections, and drug toxicities can mimic the clinical syndrome of acute rejection. Allograft biopsy is necessary to diagnose rejection but may be occasionally treated empirically in the setting of low tacrolimus concentrations and normal hepatic blood flow.

Drug Toxicity

Liver transplant recipients may be particularly vulnerable to hepatotoxic medications used in the post-transplantation period such as rifamycins or isoniazid used for TB treatment or azole antifungal agents. Up to 4 grams per day of acetaminophen is allowed, but NSAIDs are discouraged.[34]

Lung Transplantation

Over 2700 lung transplantations were performed in the United States in 2019 to treat patients with advanced lung diseases, including idiopathic pulmonary fibrosis, obstructive pulmonary disease, pulmonary hypertension, and cystic fibrosis.[1] Despite ongoing challenges with surgical complications, infections, and chronic allograft lung dysfunction, lung transplantation can significantly improve survival as well as quality of life. One-, three-, and five-year patient survival is estimated at 85%, 68%, and 56%, respectively.[35] Up to 45% of lung transplant recipients present to the ED and 67% face readmission in the first year.[36] Airway complications, infection, and atrial fibrillation are common causes for readmission.

Anatomic Considerations

Lung transplantation may involve a single lung transplant with bronchial anastomosis, bilateral lung transplant with tracheal anastomosis, sequential bilateral lung transplant with bronchial anastomoses, lobar transplant, or heart-lung transplant. Bilateral lung transplantation is indicated for patients with existing lung infection (i.e., cystic fibrosis and bronchiectasis) or significant pulmonary hypertension. Single lung transplantation is often pursued in older and more debilitated individuals as it is a shorter procedure associated with better early postoperative outcomes.

Single and sequential bilateral lung transplantation both require anastomoses of the main bronchi and pulmonary arteries as well as an anastomosis between the donor's pulmonary veins to the recipient's left atrium. Bronchial anastomotic complications such as stenosis, ischemia, tissue degeneration, and dehiscence can occur in up to 15% of transplant recipients, provoking prolonged air leak with pneumothorax or mediastinitis.[37] Vascular anastomotic complications can result in ischemia and allograft failure as well as hemothorax. Postoperative pleural complications such as pleural effusions and empyemas are most frequently observed within 1 week of transplantation.[38] In evaluating a lung transplant recipient with new respiratory symptoms, an initial chest radiograph may be helpful but a non-contrast CT scan of the chest will best evaluate the parenchyma, airways, and pleural spaces.[38]

Infection

Infection occurs in up to 60% of lung transplant recipients in the first year and remains a major cause of mortality.[33,35] Surgical denervation impairs the cough reflex and mucociliary clearance, disruption of vascularization and lymphatic channels results in stagnancy, and immunosuppression blunts appropriate responses to environmental pathogens. Gastroesophageal reflux affects a significant proportion of transplant recipients and contributes to aspiration-related infection events. Some patients such as those with cystic fibrosis also harbor bacteria in the sinuses which may infect the lower airways.

Infections are most commonly pulmonary in origin throughout the post-transplantation course. Early infections are typically hospital-acquired or ventilator-associated.[2] Native lung and allograft parenchyma alike can be affected by donor-derived and nosocomial organisms. Consideration should be given to previously grown pathogens to help guide empirical therapy of a lung transplant recipient with new fever, dyspnea, and cough. Community respiratory viruses are more likely to cause lower respiratory tract infections and inflammation, leading to chronic allograft dysfunction (CLAD).[39] Thus, available antivirals for influenza, respiratory syncytial, and even parainfluenza viruses are often used in conjunction with tapered courses of systemic steroids to control the immune response.[40]

Lung transplant recipients are prone to reactivation of CMV infection and manifest with CMV pneumonia. CT of the chest most often identifies ground-glass opacities and may resemble acute rejection or PJP. Definitive diagnosis requires lung biopsy, but detection of CMV viremia and clinical findings often warrants presumptive therapy, usually with intravenous ganciclovir. PJP is rare in the setting of prophylaxis, but invasive aspergillosis and other mold infections remain

relevant throughout the post-transplantation course and should be considered in the setting of nodular or cavitary opacities on imaging or anastomotic wound infections.[41]

A final pair of donor-derived organisms affecting lung transplant recipients are *Mycoplasma hominis* and *Ureaplasma urealyticum*. These two urea-splitting bacteria alter the production and metabolism of ammonia in the allograft, resulting in hyperammonemia syndrome within 10 to 14 days post-transplantation.[42] This condition, characterized by altered mental status and elevated serum ammonia levels, can cause cerebral edema, coma, and eventual death over days to weeks if left unchecked.[43] Any lung transplant recipient, particularly early post-transplantation, with altered mental status should have a serum ammonia level checked. Treatment is multifaceted and includes direct measures to reduce ammonia as well as antibiotics.

Rejection

Approximately 18% of lung transplant recipients experience acute cellular or humoral rejection in the first year post-transplantation.[35] Surveillance spirometry is intended to detect early functional decline that directs further testing. Symptoms of acute rejection can present at any time point post-transplantation with fever, dyspnea, cough, and generalized malaise. While subtle findings of rejection may not be well-evaluated by chest x-ray, this imaging modality may demonstrate airspace disease, interlobular septal thickening, or pleural effusions.[38] Non-contrast CT of the chest reveals ground-glass opacities. Acute rejection is diagnosed by transbronchial biopsy.

CLAD is a manifestation of rejection characterized by airway scarring and fibrosis with resultant progressive deterioration of lung function.[44] Both restrictive and obstructive patterns of disease are described, with a variety of posited triggers, including infections and prior rejection. Clinically, CLAD presents with progressive cough, dyspnea, spirometry readings, and oxygen requirements over months to years. It is the leading cause of morbidity and mortality beyond the first year of transplantation.[35] Azithromycin can effectively prevent CLAD.[45]

Drug Toxicity

Sirolimus may be used in the setting of CLAD. It should not be used early post-transplantation due to its adverse effects on wound healing. Sirolimus itself can also cause pulmonary toxicity, presenting with a range of severity from ground-glass opacities to necrotizing consolidations.

In dosing empirical antibiotic therapy for lung transplant recipients with suspected infection, special attention must be paid to cystic fibrosis patients, who demonstrate elevated metabolic rates. Inhaled antibiotics can be used in addition to systemic antibiotics to provide directed therapy for suspected pneumonias or anastomotic infections.

Pancreas Transplantation

Pancreatic transplantation can provide complete insulin independence for patients with long-standing diabetes mellitus. It may be performed with simultaneous or sequential kidney transplantation in those with advanced renal disease due to diabetic glomerulonephritis. There were 143 pancreas-only and 872 kidney/pancreas transplants performed in the United States in 2019.[1]

The donor organ with its native duodenum is most often anastomosed to the recipient small intestine to allow for exocrine drainage.[46] Previous strategies to manage the exocrine secretions of the organ included anastomosis at the recipient bladder, but this led to non–anion gap acidosis, reflux pancreatitis, chronic pyuria, and recurrent urinary tract infections such that bladder anastomosis has largely been abandoned. Vascular anastomoses are at the right internal iliac vessels. Complications due to bleeding or thrombosis usually manifest in the first week post-transplantation. Fistulas and intra-abdominal abscesses may occur later with abdominal pain, hyperamylasemia, leukocytosis, and elevated serum creatinine.

Infections are usually bacterial but may contain *Candida* species. CMV infection risk warrants valganciclovir prophylaxis and monitoring. Rejection occurs in 11% to 19% of transplant recipients in the first year post-transplantation but long-term steroid use is avoided to prevent hyperglycemia, resulting in increased use of induction agents and higher CNI target troughs.[47] Assessment of allograft rejection includes laboratory evaluation of serum amylase and lipase as well as allograft function (glucose, insulin production) in addition to allograft biopsy.

Patients presenting with fever or allograft tenderness should be evaluated for intra-abdominal infections, CMV tissue-invasive disease of the gastrointestinal tract, and rejection. CT imaging may be particularly helpful. Most hospital readmissions post-transplantation, however, are due to dehydration and metabolic derangements.

Intestinal and Multivisceral Transplantation (IMVT)

IMVT is a life-saving option for patients with irreversible intestinal failure. There were 81 IMVTs performed in 2019 in the United States.[1] Transplant-related outcomes vary widely based on transplant recipient age as well as type of IMVT performed. One- and five-year patient survival range between 66% to 89% and 49% to 76%, respectively, while 1-, 3-, and 5-year allograft survival are reported as 72% to 78%, 57% to 61%, and 45% to 50%, respectively.[48] Over 90% of IMVT recipients require readmission in the first year post-transplantation due to allograft rejection, infection, and dehydration.[49]

Isolated intestinal transplantation is performed for patients with irreversible intestinal failure and is comprised of jejuno-ileum.[50] Combined intestine-liver transplantation is performed in the context of irreversible intestinal failure complicated by parenteral nutrition-associated liver failure. Multivisceral transplants are comprised of intestine, stomach, duodenum, and pancreas with or without the liver. The intestinal allograft is usually left as a stoma for several months post-transplantation to facilitate protocolized endoscopic evaluations for allograft rejection. Early post-IMVT complications are most often due to anastomotic leaks, organ ischemia, vascular thrombosis or bleeding. Attempts to manage pain or slow gut motility to increase absorptive time can result in ileus and vomiting.

Infection causes up to 50% of allograft failure and is most often bacterial.[50] Abdominal infection is the most likely, though bloodstream infections associated with catheters placed for fluid or nutritional support even after transplantation, pneumonia associated with reflux and aspiration, and urinary tract infections also occur. CMV and adenovirus enteritis, EBV-associated PTLD, and graft-versus-host disease (GVHD) are all of particular concern with IMVT recipients and require specialized care to identify and treat.

Rejection occurs in 25% of adults and 58% of children in the first year and can precipitate bacterial translocation and septicemia.[48] IMVT recipients presenting to the ED should be assessed for volume status, electrolytes, and liver and renal function. Any fever or subtle signs of infection, such as tachycardia or tachypnea, should be assessed with blood cultures, urinalysis and culture, chest radiograph, and consideration given to CT imaging of the abdomen. Prompt notification of the intestinal transplant team is imperative to directing further management strategies.

Of note, intestinal function may impact the use of enterically administered drugs and any essential therapies should be delivered by alternative means, such as sublingual or intravenous administration.

Vascularized Composite Allografts

Vascularized composite allografts including the uterus, limb, face, abdominal wall, trachea, and larynx are not essential to patient survival but rather designed to improve the patient's quality of life. Fourteen such transplants were performed in 2019 and are still under experimental status, requiring strict inclusion and exclusion criteria to guide transplantation eligibility and mandating timely adverse event reporting.[1]

OTHER CONSIDERATIONS

Post-Transplantation Malignancy

Solid organ transplant recipients face a two- to three-fold higher risk of malignancy compared to the general population, particularly for lung, colon, skin, and liver cancer as well as lymphoma. This has been attributed to underlying illnesses, long-term exposure to immunosuppression and antimicrobial agents, and chronic viral infections. Virus-associated malignancies including EBV-associated PTLD and HPV-associated cancers (cervical, anal, and oral) are important considerations.

Post-Transplantation Lymphoproliferative Disorder

PTLD affects up to 10% of solid organ transplant recipients.[51] It is a malignancy of T cell impairment that results in uninhibited monoclonal proliferation of EBV-infected B lymphocytes and their subsequent transformation into immortal lymphoblastoid B cells. Approximately 60% of cases occur within the first year post-transplantation, most often in EBV IgG donor-positive/recipient-negative pairs. Early disease may be asymptomatic and discovered on routine imaging or present with fever and weight loss. Cytopenias and EBV DNA may be detected with laboratory evaluation. Lymphadenopathy or hepatosplenomegaly concerning for PTLD detected on imaging in the emergency department merits discussion with the transplant team to arrange follow-up. Survival has improved since the availability of rituximab.[51]

Graft-versus-Host Disease in Solid Organ Transplantation

Graft-versus-host disease (GVHD) affects less than 10% of adult solid organ transplant recipients but is fatal in up to 70% of cases and thus requires recognition. GVHD occurs 2 to 6 weeks post-transplantation, usually in the context of immunogenic allografts such as the intestine and liver.[52,53] Donor T cells are transmitted with the organ and respond to recipient tissue-based antigens evoking apoptosis in skin, bowel, and bone marrow. Fever, rash, diarrhea, and cytopenias occur. Diagnosis is by skin or endoscopic biopsy and blood measures of donor T cell chimerism. If GVHD is confirmed, high-dose corticosteroids or T cell depleting agents are administered with antibiotic prophylaxis.

Viral Hepatitis in Solid Organ Transplantation

Patient- and allograft-related outcomes of transplant recipients with hepatitis B and hepatitis C infection have dramatically improved due to vaccination, screening practices, and antiviral therapies. Confidence in HBV and HCV management is reflected in the growing use of the organs from donors with known HBV or HCV infection and those at increased risk for such infections. Liver dysfunction in a transplant recipient with a history of pre-existing viral hepatitis, a known HBV- or HCV-positive donor, or an increased risk donor may prompt evaluation for active infection with serum HBsAg and HBV DNA as well as HCV RNA.

HBV infection can arise from a post-transplantation exposure, donor-derived transmission, or reactivation of latent disease. Transplant recipients of hepatitis B surface antigen-positive or hepatitis B core antibody-positive organs (indicating active or occult HBV infection) merit potent nucleoside analog therapy (entecavir, tenofovir, or lamivudine) and monitoring for viremia suggestive of active infection.[54] Patients with underlying HBV-related liver disease prior to transplantation receive a potent nucleoside analog and possibly hepatitis B immunoglobulin with routine monitoring of HBsAg and HBV DNA. Transplant recipients should be continued on HBV-directed nucleoside analog therapy on presentation to avoid hepatitis B reactivation.

With direct-acting antiviral agents (DAAs) facilitating prompt sustained viral remissions, solid organ transplant recipients with HCV have experienced a marked decrease in morbidity and mortality.[54] HCV-positive organs have been successfully transplanted into HCV-negative recipients with subsequent cure of donor-derived HCV in most, allowing for expansion of the donor pool and reduced wait times to transplantation.

Human Immunodeficiency Virus in Solid Organ Transplantation

With effective antiretroviral therapy (ART) dramatically increasing life expectancy, more HIV-positive individuals survive to develop chronic end-stage renal, heart, lung and liver disease. Organ transplantation for kidney, liver, heart, or lung failure in this population has very good outcomes. HIV-positive solid organ transplant recipients face more allograft rejection but not more infection than HIV-negative recipients.[55] Evaluation of the HIV-positive transplant recipient should be similar to other transplant recipients, with additional attention provided to adherence to antiretroviral medications and possible drug-drug interactions. Although efforts are now made to choose ART that does not interact with immunosuppression, it is important to be aware that stopping certain drugs (ritonavir, cobicistat, and efavirenz) in the setting of acute illness can have important effects on CNI levels and allograft function. Assessing CD4 T cell count and HIV RNA viral loads helps to establish risk for opportunistic infection.

Trauma

The management of solid organ transplant trauma patients is generally no different from other trauma patients, except for a few considerations. Trauma may precipitate episodes of rejection. When possible, resuscitation with leuko-reduced and CMV-negative blood products is preferred for immunosuppressed transplant recipients to prevent transmission of viral infection. Heart transplant recipients may demonstrate clinical tamponade from scarring and adhesions, even in the absence of a pericardium. Pleural adhesions may complicate chest tube placement in a lung transplant patient. Traumatic injury of the transplanted kidney and pancreas is rare, despite their positioning in the anterior pelvis.

Eligible Organ Donors

Emergency clinicians caring for patients affected by devastating trauma or severe acute illness may address issues of organ donor eligibility of deceased individuals. Medical advancements and newer data on outcomes using organs previously considered ineligible have expanded the definition of a donor. Both donation after brain death and donation after cardiac death can yield successful outcomes for most organ types. Those dying of opioid overdose and those with known hepatitis B, hepatitis C, or HIV infection are now considered eligible donors. Immediate contraindications to organ donation include active malignancy and Creutzfeldt-Jakob disease. Questions regarding potential donor eligibility should be discussed with the local organ procurement organization.

Pregnancy and Solid Organ Transplantation

Women who undergo transplantation are able to pursue pregnancy and childbirth safely. However, pregnancy complications such as miscarriage, preeclampsia, preterm delivery, and need for caesarean section are more common in this population, affecting 1 in 2 pregnant transplant recipients.[56] Physiologic changes of pregnancy can affect allograft function (e.g., peripheral edema in a heart transplant recipient, shortness of breath in a lung transplant recipient, proteinuria in a renal transplant recipient), and should be assessed in consultation with the transplant team. Ideally, transplant recipients should attempt pregnancy with stable allograft function and no evidence of rejection in the previous year. Usual immunosuppression can be continued, though MMF will be stopped or changed to azathioprine to reduce risk of major fetal malformations.[57] Corticosteroids and tacrolimus increase risk of gestational diabetes. Most infections occurring in the pregnant transplant recipient are non-life-threatening urinary tract infections, but awareness of other infections discussed in prior sections (CMV, HSV, VZV, and toxoplasmosis) that can precipitate congenital disease is imperative.

Psychological Aspects

Transplant centers widely use psychosocial selection criteria aiming to optimize pre-transplantation mental health and psychosocial supports. While successful transplantation can improve the psychological well-being for many, the transplantation experience is challenging for most. The side effects of lifelong immunosuppression or steroid withdrawal can include anxiety, depression, delirium, and insomnia. Adherence to treatment recommendations may be markedly affected by depression and may be at issue in transplant recipients who present to the ED with allograft rejection or drug toxicities.[58] Triage to a psychiatrist with expertise in transplantation may be instrumental if depressive symptoms are identified.

DISPOSITION

Transplant recipients presenting to the ED are more likely to merit admission than members of the general population. The insidious nature of the diseases affecting this immunosuppressed population necessitates a thorough, structured approach to evaluation. If infection, rejection, or drug toxicity is suspected, transplant specialists should be consulted either in house or by phone. Transplant recipients who are deemed safe to discharge home require careful instructions, medication reconciliation, and close follow up with their transplant team.

Acknowledgements

The authors would like to acknowledge Anita Modi, MD, for her exceptional contributions to the writing and revising of this chapter, as well as the following individuals for their input: Leway Chen, MD; Koji Hashimoto, MD, PhD; Pavithra Srinivas, PharmD, BCPS; Shinya Unai, MD; and Alvin Wee, MD, MBA.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 183: QUESTIONS AND ANSWERS

1. A 42-year-old man presents from home with a 3-day history of fever, cough, and shortness of breath. He underwent orthotopic heart transplantation 5 years ago, has never experienced rejection, and is maintained on minimal doses of prednisone and tacrolimus. He takes trimethoprim-sulfamethoxazole for antimicrobial prophylaxis. Chest radiograph reveals a diffuse interstitial pattern. What is the most likely cause of his pneumonia?

a. Community-acquired respiratory virus
b. Cytomegalovirus
c. *Pneumocystis jirovecii*
d. *Nocardia*

Answer: A. Not all transplant recipients are equivalently immunocompromised. Timing post-transplantation, the net state of immunosuppression, and antimicrobial prophylaxis should all be considered in developing a differential diagnosis for a transplant recipient with suspected infection. His 5-year rejection-free post-transplant course and minimal immunosuppression make opportunistic infections much less likely than community-acquired respiratory viral infections. Given his ongoing use of trimethoprim-sulfamethoxazole, *Pneumocystis jirovecii* pneumonia is unlikely.

2. A 57-year-old deceased donor kidney transplant recipient is sent to the ED from her primary care physician's office 3 months postoperatively because routine blood work revealed a creatinine of 3.45 (baseline creatinine 1.0). Which of the following medications may be responsible for her acute kidney injury?

a. Albuterol
b. Tacrolimus
c. Pancrelipase
d. Prednisone

Answer: B. Tacrolimus is associated with dose-dependent nephrotoxicity. A serum level of tacrolimus should be obtained in any solid organ transplant recipient maintained on this immunosuppressive agent presenting with acute kidney injury. It is important to recognize that tacrolimus can both cause and be affected by renal insufficiency, so it may not have been the initial trigger but may have ultimately worsened the renal injury. Alternatively, a new drug (fluconazole, azithromycin, etc.) may have been initiated which resulted in higher serum concentrations of tacrolimus and resultant renal injury.

3. A 35-year-old woman with cystic fibrosis status post bilateral lung transplantation 2 weeks ago is brought to the ED by her husband. He reports that she was discharged several days prior to presentation with confusion attributed to intensive care unit delirium. Instead, she has developed worsening episodes of alternating agitation and lethargy. She is afebrile and normotensive on presentation, with a 2-liter oxygen requirement to maintain saturations above 90%. No leukocytosis or abnormalities of liver or kidney function are noted. A blood gas test does not demonstrate hypercarbia. What is the next best test?

a. Lumbar puncture
b. Magnetic resonance imaging
c. Serum ammonia
d. Electroencephalography

Answer: C. Hyperammonemia syndrome affects 1% to 4% of lung transplant recipients, resulting from systemic infection with *Mycoplasma hominis* or *Ureaplasma urealyticum*. These urease-splitting organisms metabolize urea as an energy source and produce ammonia as a by-product, which can accumulate in tissues such as the trachea and lung to cause unexplained agitation, lethargy, and new-onset seizures. If ammonia levels are elevated, whole blood or plasma and bronchoalveolar samples should be obtained and tested for *Mycoplasma hominis* and *Ureaplasma urealyticum* polymerase chain reaction (PCR). While awaiting these results, empirical antibiotic therapy against these organisms, such as doxycycline or ciprofloxacin, should be initiated. Hemodialysis, intravenous sodium benzoate, and sodium phenylacetate can help to clear ammonia from the blood and tissues but will be incompletely effective if the underlying infection is not addressed.

4. A 30-year-old liver transplant recipient presents to the ED 10 days post-transplantation with fevers, right upper quadrant pain, and jaundice. Laboratory evaluation reveals leukocytosis, transaminase elevations, and hyperbilirubinemia, which have all worsened since hospital discharge. Which of the conditions responsible for this presentation is most important to diagnose emergently?

a. Rejection
b. Cholangitis
c. Donor-derived hepatitis B infection
d. Hepatic artery thrombosis

CHAPTER 183: QUESTIONS AND ANSWERS—cont'd

Answer: D. The hepatic artery serves as the sole blood supply to the liver allograft and thus hepatic artery thrombosis has devastating consequences to allograft survival. This complication develops within days to weeks post-transplantation and requires immediate recognition and management in close collaboration with transplant surgeons because thrombectomy or urgent re-transplantation may be required. Diagnosis is with Doppler ultrasound. Consideration should be given to assessing the hepatic blood flow for any liver transplant recipient presenting to the ER in the first weeks after transplantation.

5. A 53-year-old intestinal transplant recipient with a history of Crohn disease status post multiple bowel resections resulting in short gut syndrome has been maintained on tacrolimus and prednisone for the last 2 years since transplantation without previous significant infection complications. He presents to the ED with 5 days of nausea, vomiting, cramping abdominal pain, and diarrhea, and states that his 2-year-old son had been ill with similar symptoms that have since resolved. The recipient has not been able to consistently take his medications for the last 3 days. He is febrile and hypotensive with blood pressures in the 80s/50s. His lab work is significant for acute kidney injury and hyponatremia. Which of the following is unlikely to contribute to this patient's clinical presentation?

a. Community-acquired gastroenteritis
b. Acute rejection
c. Adrenal insufficiency
d. CMV enteritis

Answer: D. Intestinal transplant recipients may develop diarrhea from a wide variety of causes and, in fact, dehydration is the most common reason for recurrent presentations to the ED and readmission in this population. While rejection, bacterial overgrowth, and CMV infection are common reasons for diarrhea in the first year after transplant, later causes for diarrhea are more likely to be community-acquired. This patient's history of an exposure to a child with a like illness suggests a new infection with a typical pathogen. Acute rejection can be precipitated by the inability to ingest and absorb immunosuppressive drugs and could now be a part of this patient's disease process. Given the use of chronic corticosteroids in this population, endogenous steroid production by the adrenal glands is often impaired and seemingly minor insults such as viral infections and hypovolemia may lead to signs of adrenal insufficiency. CMV is unlikely to emerge as a new infection this late post-transplant.

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The Morbidly Obese Patient

Matthew M. Hall

KEY CONCEPTS

- Obesity has reached epidemic proportions in the United States (US), as well as much of the world, with nearly 40% of American adults classified as obese.
- Obesity results in several physiologic changes including aberrations to lung physiology and predisposes patients to obstructive sleep apnea and obesity hypoventilation syndrome.
- Drug dosages can be challenging in obese patients because some medications are lipophilic and will need to be dosed based on total body weight while hydrophilic medications are dosed closer to ideal body weight. Many medications require specific scalers for appropriate dosing.
- Many drugs lack large-scale trials in the obese population to guide appropriate dosing.
- Obese trauma patients suffer greater rates of chest and abdominal injuries from blunt trauma than healthy-weight patients.
- Bariatric surgery is the only weight loss strategy that consistently results in long-term significant weight loss.
- Laparoscopic gastric banding, sleeve gastrectomy, and Roux-en-Y gastric bypass are the most common weight loss surgeries in the United States, and each presents its own short-term and long-term complications.
- Procedures common in the emergency department (ED), such as lumbar puncture, venous access, CPR, and intubation, may be more difficult in the obese patient.
- The increased body mass of the obese patient presents several challenges to obtaining interpretable radiographic images.

FOUNDATIONS

The last several decades have seen a dramatic increase in rates of obesity in children and adults in the United States and around the world.[1,2] In 2015 to 2016, it was estimated that 39.8% of adults and 18.5% of children in the United States were obese, with as many as 7.6% of Americans classified as severely obese.[1,3] Obesity is often defined as a body mass index (BMI, calculated as weight in kilograms divided by the square of the height in meters) greater than 30 (see Table 184.1). A range from 25 to 29 is considered overweight, and obesity can be further subdivided into grade I (BMI 30.1–34), grade II (BMI 35–39), and grade III or severe obesity (BMI ≥ 40).[4] The obese patient presents a host of management challenges including difficulties related to size and weight but also changes in physiology, procedural challenges, and drug pharmacokinetics.

PATHOPHYSIOLOGY

Changes to Respiratory Mechanics

Increased chest wall mass in conjunction with substantial abdominal fat mass leads to reduced lung compliance and collapse of small airways resulting in increased airway resistance (Table 184.2).[6] These changes in turn result in a decrease in functional residual capacity (FRC) leading to increased atelectasis.[6-8] Obese patients also preferentially aerate the upper portion of the lung and perfuse the more dependent portions leading to ventilation perfusion (V/Q) mismatch.[6] Each of these changes is exacerbated when the patient is supine and ameliorated when sitting upright.[6,7,9]

These physiologic perturbations lead to increases in work of breathing and oxygen consumption; obese patients consume 50% more oxygen than healthy-weight individuals.[6,7] Additionally, obese patients produce significantly more carbon dioxide than non-obese individuals, leading to an increased respiratory rate with a resting rate of 15 to 21 breaths per minute compared to 10 to 12 for those of a healthy weight.[6,7]

Obstructive Sleep Apnea and Obesity Hypoventilation Syndrome

Obstructive sleep apnea (OSA) is an obesity-related disorder characterized by upper airway collapse during sleep. Increases in adiposity of upper airway structures leads to reduced airway caliber and reduced pharyngeal muscle tone.[10,11] Symptoms include snoring and apneic episodes during sleep, daytime sleepiness, and morning headaches.[10] Diagnosis is usually confirmed with polysomnography. Treatment consists of continuous positive airway pressure (CPAP) at night and weight loss.[10,11]

Obesity hypoventilation syndrome (OHS), or Pickwickian syndrome, occurs when the physiologic changes described in the preceding paragraph lead to increased daytime hypercarbia. The Academy of Sleep Medicine defines OHS as daytime alveolar hypoventilation ($Paco_2 > 45$ when awake and at sea level) in individuals with a BMI greater than 30 when other etiologies of hypercarbia are excluded, such as chronic obstructive pulmonary disease, mechanical respiratory dysfunction such as severe kyphoscoliosis, and neuromuscular disease.[2,11,12] It is also prudent to screen for pharmaceutical and recreational substances that affect respiratory drive such as opioids, sedative-hypnotics, and alcohol.[12] While not all, or even most, patients with OSA will have OHS, 90% of those suffering from OHS also suffer from OSA with as many as 70% with severe OHS (characterized by more than 30 apnea-hypoxia events per hour during sleep).[2] Patients with OHS have increased rates of pulmonary hypertension, congestive heart failure (CHF), acute or chronic hypercapnic respiratory failure, and mortality compared to those with only OSA.[11] One recent study identified 600 patients in a 5-year period with OHS and noted 15% died on the index visit with another 16% dying in the approximately 3-year follow-up period.[13]

The American Thoracic Society recently issued a clinical practice guideline regarding evaluation and treatment of OHS. They suggest that patients with sleep disordered breathing but a low/moderate (<20%) pretest probability of OHS should undergo screening with serum bicarbonate levels. Patients with bicarbonate levels over 27 mmol/L or those with a high pretest probability of OHS should undergo confirmatory testing of arterial carbon dioxide levels. They also recommend immediate treatment with noninvasive ventilation and suggest evaluation for bariatric surgery.[2]

TABLE 184.1 Body Mass Index Classifications

BMI	WHO Classification
<18.4	Underweight
18.5–24.9	Normal Weight
25–29.9	Overweight
30–34.9	Grade I Obesity
35–39.9	Grade II Obesity
>40	Grade III Obesity[a]

[a]Alternative terms include Morbid Obesity and Extreme Obesity.[4,5]
BMI, Body mass index; WHO, World Health Organization.
Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311(8):806-814; Anast N, Olejniczak M, Ingrande J, Brock-Utne J. The impact of blood pressure cuff location on the accuracy of noninvasive blood pressure measurements in obese patients: an observational study. *Can J Anaesth*. 2016;63(3):298-306.

TABLE 184.2 Changes to Pulmonary Physiology Observed in the Obese Patient

Parameter	Obesity-Related Change
Chest Wall/Abdominal Mass	Increased
Lung Compliance	Reduced
Airway Resistance	Increased
Functional Residual Capacity	Decreased
Atelectasis	Increased
V/Q Mismatch	Increased
Work of Breathing	Increased
Oxygen Consumption	Increased
CO_2 Production	Increased
Respiratory Rate	Increased
Safe Apnea Time	Decreased

Changes in Pharmacokinetics

The clinician faces several challenges regarding proper medication dosing in the obese patient. The volume of distribution (V_d) of a drug is the principal factor involved in the loading dose while subsequent maintenance dosing will primarily be governed by total body clearance (Cl).[14] The V_d is affected by many factors including drug lipophilicity, plasma binding, regional blood flow, body composition, molecular size, and degree of ionization.[9,14-18] Hydrophilic drugs will tend to not enter adipose tissue to a great extent resulting in lower V_d and will therefore tend to be dosed based upon ideal body weight (IBW). Lipophilic drugs will dissipate into fat tissue to a significant extent, leading to increases in the V_d and a situation where total body weight (TBW) may be appropriately used for dose calculations. Other drug loading doses will use an adjusted body weight (ABW) where a fraction of the adipose tissue, often 30% or 40%, is utilized in dose calculations (see Table 184.3 for scalers often used in medication dosage calculations).[14,15]

Drug maintenance doses are primarily determined by Cl, the sum of contributions from each organ involved in drug metabolism or excretion. As obese patients often have increased liver and kidney mass, as well as increased renal blood flow, obesity will often affect Cl.[14] Additionally, critically ill patients will have changes in vascular permeability, cardiac output, and hepatic and renal function that will impact both V_d and Cl.[16] Care in the emergency department (ED) will primarily involve the loading dose of a medication, but maintenance dosing may be required in departments faced with prolonged inpatient boarding where consultation with a pharmacist may be helpful.

Antibiotics

There is limited data on beta-lactam and cephalosporin use in obesity, but several trials have illustrated lower than normal drug concentrations and cure rates in obese patients when standard dosing is utilized. Until more data are available, we recommend initial dosing at the upper limit of the recommended dose and suggest extended infusion times (Table 184.4).[14-16]

Fluoroquinolones also have very limited pharmacokinetic data in the setting of obesity. There are insufficient data to provide clear recommendations for ciprofloxacin. Levofloxacin 750 mg/day has been shown to be effective against gram-negative infections in small studies of obese patients with preserved renal function, but further data is required before firm recommendations can be made for fluoroquinolones. Therefore, we recommend usual dosing.[14-16]

Vancomycin has both increased V_d and Cl in obese patients and obese patients have been found to have lower vancomycin troughs. The large V_d necessitates a loading dose recommended at 20 to 25 mg/kg TBW; doses >4 g/day are associated with vancomycin-induced nephrotoxicity. Variable Cl in conjunction with the large V_d makes maintenance dosing difficult and it is prudent to individualize subsequent doses to peak and trough levels so as to achieve therapeutic levels but avoid nephrotoxicity.[14,16]

Linezolid is noted to have subtherapeutic levels in obese patients, but data have not illustrated worse clinical outcomes. Expert recommendations are mixed at this time and there are insufficient data to give clear guidelines regarding linezolid dosing in obese patients; therefore, we recommend usual dosing.[14,15]

Aminoglycosides are hydrophilic but do have an increased V_d in obese patients, suggesting that the drug does distribute into fat tissue but not to nearly the same concentrations as other tissues. Limited evidence suggests dosing by ABW with a correction factor of 0.4 for the loading dose with maintenance dosing individualized for the patient.[14,15]

Sedatives and Induction Agents

Recent studies have demonstrated that both obese and non-obese children and adults often receive incorrect anesthetic and paralytic medications, with one investigation reporting only 75% of obese patients receiving an appropriate dose of etomidate and 60% being administered the correct dose of succinylcholine.[19,20] Propofol is highly lipophilic; in fact, one of the great advantages of this drug, its short duration of action, is not due to metabolism but rather to rapid redistribution into muscle and fat.[18] Historically there has been controversy regarding the appropriate scaler for propofol, but recent research has suggested that using ABW with a correction factor of 0.4 results in successful sedation (Table 184.5).[17,18,21-23] Although etomidate is ubiquitous in the ED, little research has been performed regarding optimal dosing in obese patients with some experts recommending TBW and others reduced doses.[6,17] One recent study did demonstrate IBW resulted in successful sedation, but currently there is insufficient evidence to give a strong recommendation regarding which scaler should be used.[24] At this time we suggest using TBW to dose etomidate. Similarly, there is a paucity of data for ketamine in the obese patient; however, given its large V_d, most experts suggest reducing from TBW with some suggesting IBW and others LBW. We suggest utilizing LBW.[6,17]

Neuromuscular Blocking Agents

Succinylcholine, a depolarizing neuromuscular blocking agent, is cleared via breakdown by plasma cholinesterase (PCE). Obese patients have increased levels of PCE proportional to total body weight and therefore succinylcholine (1.5 mg/kg IV) should be dosed

TABLE 184.3 Scalers for Various Body Weight Descriptors

Body Weight Descriptor		Formula	Example
IBW	Ideal Body Weight	Male: 50.0 + 2.3 (inches over 5 feet in height)	64 kg
		Female: 45.5 + 2.3 (inches over 5 feet in height)	59 kg
LBW	Lean Body Weight	Male: (9270 × TBW) / (6680 + 216 × BMI)	79 kg
		Female: (9270 × TBW) / (8780 + 244 × BMI)	65 kg
ABW	Adjusted Body Weight	IBW + C[a] × (TBW–IBW)	Male, C=0.3, 92 kg Male, C=0.4, 103 kg Female, C=0.3, 89 kg Female, C=0.4, 99 kg
TBW	Total Body Weight	Patients Actual Weight	159 kg
BMI	Body Mass Index	Weight × Height^2	56 kg/m^2

[a]C is correction factor, usually either 0.3 or 0.4. The example is for a 5 foot, 6 inch person (66 inches; 168 centimeters) weighing 350 pounds (159 kilograms).[14]

Meng L, Mui E, Holubar MK, Deresinski SC. Comprehensive guidance for antibiotic dosing in obese adults. *Pharmacotherapy*. 2017;37(11):1415-1431.

TABLE 184.4 Dosing Recommendations for Selected Antibiotic Classes

Drug Class	Dosing Recommendation
Beta-lactams/Cephalosporins	Limited data, upper limit of regular dose suggested
Fluoroquinolones	Limited data, upper limit of regular dose suggested
Vancomycin	Load with 20–25 mg/kg TBW; subsequent dose based on peak/trough levels
Linezolid	Limited data
Aminoglycosides	$ABW_{0.4}$

TABLE 184.5 Dosing Recommendations for Sedatives, Neuromuscular Blocking Agents, and Neuromuscular Blocking Reversal Agents

Drug	Dosing Recommendation
Propofol	Limited data, avoid TBW
Etomidate	Limited data, suggest TBW
Ketamine	Limited data, avoid TBW, suggest LBW
Succinylcholine	TBW
Rocuronium	TBW
Vecuronium	TBW
Sugammadex	TBW

by TBW.[6,17] The non-depolarizing neuromuscular blocking agents most commonly used in the ED, vecuronium and rocuronium, have both been shown to have prolonged duration of action when administered by total body weight.[6,17] One recent trial illustrated that using 0.6 mg/kg IBW of rocuronium did not result in slower time of onset than when using higher doses in obese patients.[25] However, given that the only complication of higher doses of non-depolarizing agents is prolonged duration of action and underdosing risks suboptimal intubating conditions, we recommend using TBW for these medications. Sugammadex rapidly reverses paralysis due to the non-depolarizing neuromuscular blocking agents (rocuronium and vecuronium). Recent research suggests the possibility of using IBW; however, as most trials investigating sugammadex are conducted in the operating room at the end of surgical cases as opposed to situations where it would likely be utilized in the ED, the end points of these trials allow for a time to onset that would be inappropriate in the emergency department.[17,26,27]

Anticoagulation

Unfractionated heparin remains a vital drug for the treatment of thromboembolic disease, acute coronary syndrome, and atrial fibrillation. Current recommendations suggest weight-based dosing for both an initial bolus and subsequent infusion, but are silent on dosing strategies in the obese patient.[28-30] Several studies have investigated various dosing methods in the obese, including reducing the initial bolus, capping the bolus, or using various weight scalers, but no clear superior dosing method has been described.[29] We suggest consultation with a pharmacist if local recommendations are not clear on dosing ceilings in the obese patient because many institutions have specific local guidelines in this regard. It is clear that careful monitoring of heparin activity with either activated partial thromboplastin time (aPTT) or anti-Xa levels aids in titrating heparin infusions.[28] Low-molecular-weight heparin (LMWH) can be used in many cases, but activity should be monitored in those over 190 kg by following anti-Xa levels.

Direct oral anticoagulants (DOACs) have gained popularity over vitamin K antagonists such as warfarin in recent years. To date there have not been any large, prospective randomized trails investigating their efficacy and safety in the obese population. Both the Anticoagulation Forum VTE Treatment Guidance and the International Society on Thrombosis and Haemostasis have given recommendations to avoid DOACs in patients with a BMI greater than 40 and weights over 120 kg.[31,32] There have been several recent large retrospective chart review studies that suggest DOACs, and especially rivaroxaban, have reassuring efficacy and safety profiles in severely obese patients. These studies also remind the ED physician that there are large numbers of very obese patients taking these medications.[33-36] Given the paucity of prospective investigations, it would be prudent to avoid initiating DOACs in obese patients from the ED unless alternative medications are unavailable or follow-up care has been coordinated.

TRAUMA CONSIDERATIONS

Obese patients appear to display a change in injury pattern compared to healthy-weight patients with fewer head injuries but more lower abdominal and chest injuries.[37] Increasing BMI has been identified as a protective factor against intraperitoneal injury from stab wounds to

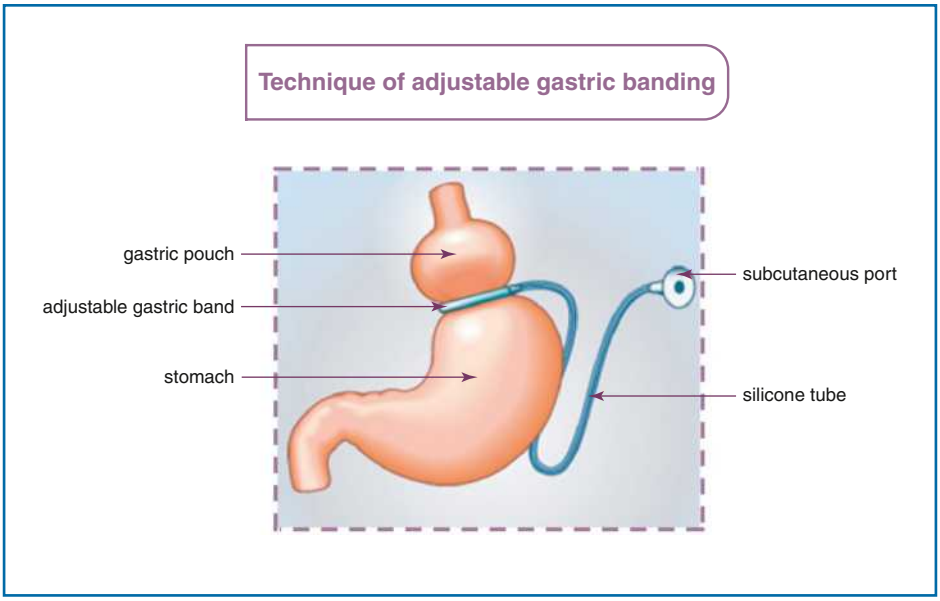

Fig. 184.1 Depiction of laparoscopic adjustable banding (LAB) procedure. (From: Contival N, Menahem B, Gautier T, Le Roux Y, Alves A. Guiding the non-bariatric surgeon through complications of bariatric surgery. *J Visc Surg.* 2018;155:27-40.)

the abdomen.[38] Morbidly obese patients have also been shown to have increased mortality and in-hospital complications as well as longer intensive care unit stays and increased time on mechanical ventilation when compared to non-obese patients.[37,39] We recommend following advanced trauma life support (ATLS) algorithms for the obese patient while paying particular attention to the respiratory status of obese patients laying supine during the primary and secondary surveys. Care should be taken when rolling the patient to protect both the patient and the staff from inadvertent injury.

BARIATRIC SURGERY

Overview

Bariatric surgery is the only intervention that has been demonstrated to produce sustained significant weight loss and treat comorbidities of obesity.[40-45] Severe postoperative complications such as pulmonary embolism (PE), acute coronary syndrome, and anastomotic leak are rare with an overall incidence of less than 1% in the first 30 days.[43] However, approximately 10% of postoperative patients will present to the ED in the first month and over one-third will do so in the first year after surgery.[41,44]

Bariatric surgery encourages weight loss through restrictive (reducing the amount of food that can be ingested at one time) or malabsorptive (reducing caloric absorption from a surgically altered small bowel) means.[45] The American Society for Metabolic and Bariatric Surgery recommends that surgery be offered to patients either with a BMI over 40 or with a BMI over 35 along with severe obesity-related comorbidities such as diabetes, OHS, and nonalcoholic fatty liver disease, among others. Although there are six different operations currently being performed in the United States, the vast majority of patients undergo laparoscopic adjustable banding (LAB), sleeve gastrectomy (SG), or the Roux-en-Y gastric bypass (RYGB). LAB (Fig. 184.1) is the insertion of an adjustable balloon circumferentially around the proximal stomach connected to a subcutaneous port allowing intermittent tightening or loosening of the band. In a SG (Fig. 184.2), the surgeon creates a small stomach remnant with a staple line excluding the greater curvature. In the RYGB (Fig. 184.3), the proximal stomach is separated with a staple line from the distal stomach, creating a small stomach pouch; the jejunum is transected and the distal portion (alimentary limb) is anastomosed to the stomach pouch while the proximal biliopancreatic limb is anastomosed to the jejunum.

Gastric bypass via RYGB results in the greatest (reported at 62% of excess weight on average) and most sustained weight loss but tends to have the most complications. LAB results in less weight loss (about 40% of excess weight) with the fewest complications whereas SG offers intermediate weight loss and complication rates.[42,45] All three surgical options can present to the ED with short-term and long-term complications (Table 184.6).

Obese patients develop thromboembolic complications at a rate that is 2 to 3 times that of the non-obese population. Open surgical approaches have higher rates of PE than do laparoscopic procedures.[45] Given the previously described challenges regarding anticoagulation in the obese population, PE should be considered in postoperative patients presenting with suggestive signs and symptoms.

Laparoscopic Gastric Band

LGB has an exceedingly low mortality rate, but patients can still suffer from early and late complications. Early complications decrease dramatically with surgical experience and are most commonly related to esophageal or gastric perforation (usually but not always diagnosed intraoperatively) and acute gastric dilation. Dilation of the stomach pouch is rare, but because gastric distention can lead to local ischemia, it can result in gastric necrosis and necessitates operative repair. Patients suspected of having these complications should receive prompt resuscitation with IV fluids, pain control, IV antibiotics such as piperacillin-tazobactam targeting intra-abdominal pathogens along with emergent surgical consultation.[45]

Late complications are fairly common with LGB. It is not uncommon for the tubing connecting the subcutaneous port to the band to become kinked or to break. More ominous is a port infection. This may be related to instrumentation from adjustments to the gastric band, but as gastric mural erosion will often present as chronic purulent drainage at the port site, this more serious complication should be ruled out. Computed tomography (CT) or upper gastrointestinal series (UGIS) usually diagnoses this complication; however, upper endoscopy is the test of choice. Aside from purulence at the port site, patients may experience epigastric pain, fever, tachycardia, and

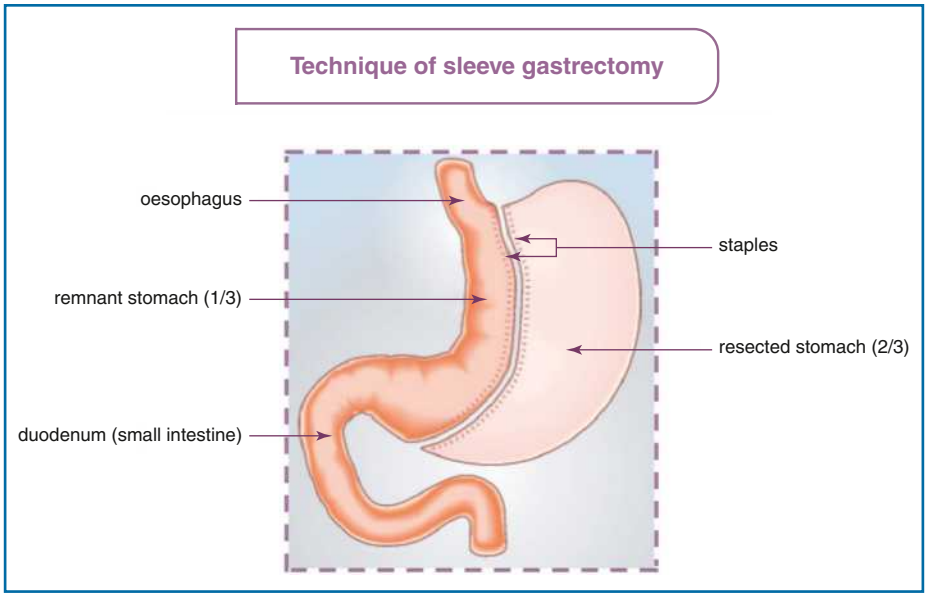

Fig. 184.2 Depiction of sleeve gastrectomy (SG) procedure. (From: Contival N, Menahem B, Gautier T, Le Roux Y, Alves A. Guiding the non-bariatric surgeon through complications of bariatric surgery. *J Visc Surg.* 2018;155:27-40.)

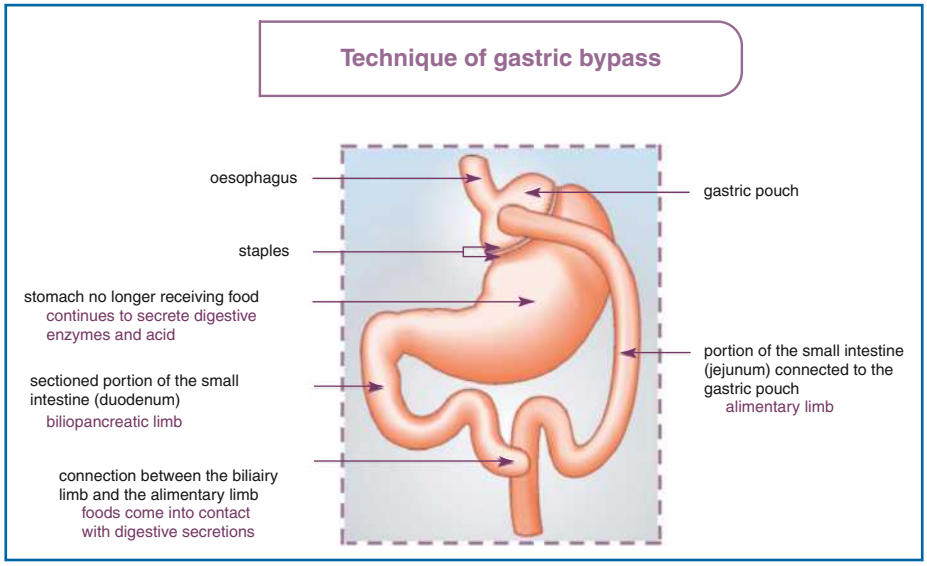

Fig. 184.3 Depiction of Roux-en-Y gastric bypass (RYGB) procedure. (From: Contival N, Menahem B, Gautier T, Le Roux Y, Alves A. Guiding the non-bariatric surgeon through complications of bariatric surgery. *J Visc Surg.* 2018;155:27-40.)

signs of GI bleeding. Pocket dilation and late slippage occurs when the band slowly and gradually slips distally, allowing for larger meals that in turn result in further slippage. Usually this is an insidious process resulting in a cessation of weight loss, but occasionally it can result in acute strangulation and gastric necrosis. It is best diagnosed via UGIS and is treated via prompt loosening of the gastric band by a surgeon. Esophageal dilation likely results from overly aggressive tightening of the band leading to accumulation of food in the esophagus. It is diagnosed via UGIS and treated by relaxation of the band.[45]

Sleeve Gastrectomy

The primary complication of SG centers on gastric leaks leading to fistula formation. It appears that leaks typically arise at the top of the staple line and occur in about 2% of patients undergoing SG. Repair of fistulas, once they appear, is a long and difficult process often requiring multiple procedures and hospitalizations. Strictures will present with signs of obstruction and are resolved either surgically or endoscopically depending upon location. Gastroesophageal reflux disease (GERD) is the most common late complication.[45] As SG has gained significant popularity only since 2010, descriptions of its complications are not as thorough as with other common surgical procedures.

Roux-en-Y Gastric Bypass

The RYGB, the most common gastric bypass surgery in the United States, results in several early and late complications. Leaks can occur at each of the staple lines, which are located at the gastric pouch, the excluded stomach remnant, the jejuno-jejunostomy, and gastro-jejunostomy as well as small bowel division sites. Leaks and fistulas in the distal jejuno-jejunostomy are life-threatening and often present with abdominal pain, peritonitis, and signs of sepsis. However, possibly

TABLE 184.6 Common Early and Late Complications for Various Bariatric Surgeries

Procedure	Early Complications	Late Complications
Laparoscopic Gastric Band	Esophageal perforation	Tubing failure
	Gastric perforation	Port infection
	Gastric dilation	Gastric erosion
		Pocket dilation with late slippage
		Esophageal perforation
Sleeve Gastrectomy	Gastric leak	Gastroesophageal reflux disease
	Fistula formation	Dumping syndrome
Roux-en-Y Gastric Bypass	Staple line leak with or without fistula formation	Marginal ulcers
	Jejuno-jejunostomy obstruction	Internal herniation with or without obstruction
	Gastro-jejunostomy obstruction	Adhesions with obstruction
	Postoperative bleeding	Cholelithiasis
	Marginal ulcers	Dumping syndrome

related to the difficulties with physical examination of the morbidly obese patient, tachycardia may be the only presenting sign. Therefore, we advise urgent surgical evaluation for recent postoperative patients with unexplained heart rates over 120 beats/minute.[45] More proximal fistulas at the gastric pouch suture line or gastro-jejunostomy can be insidious and even asymptomatic and can therefore be managed conservatively with bowel rest. Those with pain or vital sign derangements often require operative intervention.[45]

Bowel obstruction due to anastomotic stricture of the jejuno-jejunostomy is another dangerous complication. Because the 70-cm biliopancreatic limb originates in the blind stomach remnant, it will fill with digestive secretions before the obstruction fills the gastric pouch through the longer alimentary limb (150 cm). Therefore, the excluded stomach may distend and subsequently perforate before the onset of vomiting. Prompt surgical consultation is advised when this diagnosis is considered. Epigastric pain, vomiting, and progressive dysphagia suggest stenosis of the more proximal gastro-jejunostomy and appear later (weeks after surgery) than jejuno-jejunostomy strictures (days after surgery). In contrast to more serious distal strictures, gastro-jejunostomy strictures are usually managed with endoscopy and dilation.[45]

Postoperative intraperitoneal bleeding most often occurs from staple lines, resulting in blood in abdominal drains. The diagnosis can be confirmed, if necessary, via laparoscopy and therefore prompt surgical consultation is recommended. As with all bleeding, unstable patients should be transfused early, while the diagnosis is confirmed. Intraluminal bleeding from a proximal source may be suggested by hematemesis or melena and is managed via endoscopy for both diagnosis and possible treatment. Distal bleeding from the jejuno-jejunostomy or the excluded portion of the stomach, suggested when patients present with melena, is usually managed supportively.[45] Marginal ulcers, or ulceration at the gastro-jejunostomy, tend to occur in those who smoke, suffer from *Helicobacter pylori* infection, or are on nonsteroidal antiinflammatory medication.[40] Patients often present with epigastric pain especially with eating, vomiting, and occasionally with signs of upper GI bleeding. Diagnosis is made by endoscopy. Medical treatment is usually sufficient with high-dose proton pump inhibitor and risk factor modification. Rarely, marginal ulcers can lead to strictures or even perforation.[45]

Patients who have undergone RYGB can suffer from several late complications. Marginal ulcers, although more common in the immediate postoperative period, are known to develop up to 2 years after surgery. Bowel obstruction may be related to postoperative adhesions but is due to internal herniation in 60% of cases. Weight loss will predispose patients to internal hernias as potential spaces open in the small bowel mesenteries. They can be particularly difficult to diagnose because they can be intermittent and CT scans are often falsely negative. Patients may complain of intermittent pain without clear etiology which may localize to the left flank. Exploratory laparoscopy may be required to confirm the diagnosis. Rapid weight loss associated with RYGB leads to formation of gallstones, particularly 6 to 18 months following surgery. Some surgeons will perform a prophylactic cholecystectomy during the gastric bypass procedure, but this is not a universal practice. Treatment of simple symptomatic cholecystitis and biliary colic is similar to patients without bariatric surgery, but clinicians should note that following RYGB the common bile duct is no longer accessible via routine endoscopic retrograde cholangiopancreatography (ERCP). Therefore, treatment of common duct stones requires a surgical approach rather than the typical endoscopic one.[40,45]

Anatomic changes associated with RYGB and SG can predispose patients to dumping syndrome. This occurs whereby a large bolus of partially digested food is rapidly released into the small bowel.[45,46] Early dumping syndrome is thought to be related to rapid fluid shifts as water is drawn into the hyperosmolar environment of the small bowel from the vascular compartment in the first hour after a meal. This leads to GI symptoms such as abdominal pain, bloating, nausea, borborygmi, and vomiting. Rapid fluid shifts can result in flushing, palpitations, fatigue, transient hypotension, tachycardia, diaphoresis, and rarely, syncope. Late dumping syndrome, typically 60 to 180 minutes following a meal, is thought to result from an incretin-driven hyperinsulinemic response leading to hypoglycemia. The patient will often experience typical symptoms of hypoglycemia such as fatigue, weakness, and hunger along with an adrenergic surge leading to tremor, tachycardia, and diaphoresis. First-line treatments for dumping syndrome focus on diet and include frequent small meals, elimination of refined sugar, and delaying fluid intake until 30 minutes after a meal.[46]

PROCEDURAL DIFFICULTIES

Lumbar Puncture

The lumbar puncture (LP) is typically performed using a landmark-based approach. However, this can be particularly challenging in the obese patient when familiar landmarks are obscured by adipose tissue.[47,48] Ultrasound can be of assistance in mapping out landmarks when they cannot be palpated.[49] Positioning the patient in a sitting position rather than lateral decubitus position may also make the procedure easier. Extra-long 5-inch (12.7 cm) needles may be necessary to reach the subarachnoid space. In cases where the LP cannot be successfully performed at the bedside, the patient may require a fluoroscopic-guided lumbar puncture.[47]

Venous Access

Excessive subcutaneous adipose tissue can lead to difficulties in establishing intravenous (IV) access. Ultrasound can successfully identify otherwise obscured veins in the obese population and aid in the establishment of IV access.[50] Central venous access may be required for access in general or in the case of an unstable patient. Care should be taken when placing obese patients in the Trendelenburg position as it can have severe negative consequences for pulmonary function in both the spontaneously breathing and the intubated obese patient. An assistant or tape may be required to position the panniculus out of the field when placing catheters in the femoral vessels. Intraosseous (IO) access can also be rapidly established when medications or blood needs to be given expeditiously. Recent research has suggested that so long as the tibial tuberosity can be palpated, a standard 25-mm IO needle can be placed in the proximal or distal tibia. A longer 45-mm needle should be placed in the proximal humerus in obese patients and in the tibia if the tibial tuberosity cannot be palpated.[51]

Cardiopulmonary Resuscitation

High-quality cardiopulmonary resuscitation (CPR) is critical in the chain of survival from cardiac arrest. Guidelines suggest placing the hands on "the lower half of the sternum" due to the common location of the maximal left ventricular outflow tract diameter.[52,53] Recent radiographic evidence suggests that the optimal compression location for CPR in obese patients is slightly more cranial than in healthy-weight individuals and that CPR is technically more difficult on obese patients than on healthy-sized individuals.[53,54] We encourage emergency providers to pay close attention to CPR quality in obese patients and use CPR quality feedback devices when available.

Endotracheal Intubation

Although controversial, obesity has been considered a risk factor for difficult intubation.[6,7,55,56] The pathophysiologic changes that occur in the lung due to obesity result in much shorter apnea times than in healthy-weight patients. Preoxygenation with noninvasive ventilation, when time and equipment allow, is recommended over non-rebreather mask use because it has been shown to increase safe apnea time by one minute in the obese patient, likely by reducing atelectasis.[7] Increases in safe apnea times may also be seen when the patient is maintained in an upright position during preoxygenation and intubation.[6,7,57] During intubation, we recommend placing obese patients in a head up or ramped position with the goal of aligning the external auditory meatus with the sternal notch. This will serve to both increase safe apnea times and improve the laryngoscopic view.[6,7,57] Intubation of the obese patient should be considered a difficult intubation and all airway adjuncts should be readily available. Clinicians should keep in mind that obesity is associated with difficult bag-valve-mask (BVM) ventilation and be prepared for two-person BVM ventilation with oral and/or nasal airways. Cricothyrotomy is likely to be technically difficult in the obese patient owing to difficulty palpating landmarks.[37]

Ventilator Management

Obese patients suffer from increased atelectasis and V/Q mismatch owing to changes in lung compliance and FRC. They also have increased respiratory rates, even at rest, compared to nonobese patients. After intubation, tidal volumes should typically be set to 6 to 8 mL/kg IBW rather than TBW to avoid pulmonary injury.[6,7] Respiratory rates should initially be set higher than for nonobese patients owing to the increased resting respiratory rate and can be titrated based on blood gas analysis. Patients who are known or predicted to be acidemic should usually have even higher respiratory rates. Positive end-expiratory pressure (PEEP) can be difficult to manage in the obese patient. Given their propensity for atelectasis, starting obese patients with PEEP of 10 cm H_2O is recommended. However, high levels of PEEP can lead to reduced venous return and therefore lower preload and can predispose patients to hypotension. Therefore, close attention should be paid to hemodynamics and ventilator settings adjusted as needed. Providers also are urged to monitor for auto-PEEP and change ventilator settings accordingly.[6,7] As with most patients, obese patients should be maintained in either a sitting position or reverse Trendelenburg to optimize pulmonary function.

Challenges with Hospital Equipment

Emergency departments should have equipment, including hospital beds, commodes, and wheelchairs, engineered to accommodate obese patients. This includes the ability to handle not only substantial weight but also the increased girth of these patients. Appropriate monitoring equipment such as blood pressure cuffs should also be readily available. Proper mechanical lifts and safe handling plans are also prudent; the National Institute for Occupational Safety and Health recommends that nurses lift no more than 35 pounds when providing patient care and currently workers in hospitals suffer from musculoskeletal injuries at twice the national rate.[9]

Imaging Challenges

Ultrasound has the advantage of portability and therefore table weight limits do not present a challenge. Adipose tissue will attenuate sound waves; however, with the proper settings and transducer, as well as by utilizing harmonic imaging, most obese patients can be evaluated with ultrasound. X-ray imaging is limited in the obese patient due to reductions in resolution and image contrast. Obese patients also will require increased exposure times which in turn lead to greater probability of motion artifact.[58]

CT imaging in the obese patient has both mechanical and radiographic challenges. Three different measurements must be taken into account when evaluating if an obese patient can be evaluated by a particular scanner. First is the table load limit, which not only protects against mechanical table failure and subsequent risk of patient injury, but also allows for smooth and predictable speed as the patient is passed through the scanner. Second is aperture size to ensure that the patient can physically pass through the CT machine. This is much more of a challenge when abdomen/pelvis CT is required than when a CT of the head is needed and may require measuring the girth of the patient. Third is the maximum reconstruction FOV (field of view). This denotes the area within the scanner where images will be captured. It is advised that the obese patient be positioned such that the area of interest lies within the FOV. Even when the obese patient is able to fit in the scanner, large amounts of adipose tissue will create artifacts that can limit the diagnostic utility of the image.[58] Additionally, patients must lie flat in the CT scanner, which can lead to respiratory complications in an obese patient. It is prudent to offer a trial of supine positioning in the safety of the ED with staff at the ready if there is a question regarding the ability of the patient to lie flat for the time required to obtain the desired images.

Obtaining useful MRI images often encounters problems similar to those outlined for CT imaging. The MRI table must be able to safely support and pass the patient into the scanner, and the patient must be able to fit into the scanner itself. Modern scanners are often 70 cm in diameter and slightly larger than previous generations of scanners (60 cm). Some radiology departments have "open MRI" machines that may accommodate larger patients.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 184: QUESTIONS AND ANSWERS

1. Rates of obesity in the United States and around the world have been:
   a. Increasing in the US and decreasing around the world.
   b. Increasing in the US and staying constant around the world.
   c. Staying about the same worldwide.
   d. Increasing in the US and around the world.

Answer: D. Increasing in the United States and around the world.

2. When lying supine, obese patients tend to:
   a. Breathe normally because they have more developed chest musculature.
   b. Have trouble breathing due to stomach distention.
   c. Have trouble breathing due to changes in lung mechanics.
   d. Have trouble breathing due to chronic back pain.

Answer: C. Increased chest wall mass in conjunction with substantial abdominal fat mass leads to reduced lung compliance and collapse of small airways resulting in increased airway resistance. These changes in turn result in a decrease in functional residual capacity (FRC) leading to increased atelectasis.

3. Challenges to obtaining high-quality CT scan images in the obese patient include which of the following?
   a. Difficulty lying flat for the scan
   b. Weight limits of the gantry table
   c. Girth greater than aperture size
   d. Claustrophobia during the scan
   e. Area of interest laying outside the CT field of view (FOV)

Answer: A, B, C, and E are all correct. Claustrophobia is often a difficulty during MRI, not CT.

4. Drug dosing of obese patients is based on which of the following factors?
   a. Ideal body weight for the vast majority of drugs
   b. Total body weight for the vast majority of drugs
   c. A complex decision based on the properties of the drug and the clinical picture of the patient
   d. Total body weight if weight is less that 150 kg and ideal body weight if above that.

Answer: C. Drug dosing is a complex decision based on the properties of the drug and the clinical picture of the patient. The clinician faces several challenges regarding proper medication dosing in the obese patient. The volume of distribution (V_d) of a drug is the principal factor involved in the loading dose whereas subsequent maintenance dosing will primarily be governed by total body clearance (Cl).[14] The V_d is affected by many factors including drug lipophilicity, plasma binding, regional blood flow, body composition, molecular size, and degree of ionization.

5. Which of the following statements regarding internal hernias following Roux-en-Y gastric bypass is true?
   a. They can be intermittent and may require exploratory surgery for diagnosis.
   b. They are easy to diagnose based on history and physical examination.
   c. They are almost always visualized on CT studies.
   d. They are an exceedingly rare complication.

Answer: A. They can be intermittent and may require exploratory surgery for diagnosis Weight loss will predispose patients to internal hernias as potential spaces open in the small bowel mesenteries. They can be particularly difficult to diagnose because they can be intermittent and CT scans are often falsely negative. Patients may complain of intermittent pain without clear etiology which may localize to the left flank. Exploratory laparoscopy may be required to confirm the diagnosis.

The Combative and Difficult Patient*

Malia J. Moore and Jason D. Heiner

KEY CONCEPTS

- The emergency department (ED) should develop a written plan of action to deal with violence that integrates the roles and activities of ED staff, hospital administration, security, and local authorities.
- ED staff should be trained to recognize potentially violent individuals and to intervene with verbal de-escalation techniques prior to the use of physical or chemical restraint when possible.
- The emergency clinician should be familiar with the use of physical and chemical restraints as well as the breadth of options for chemical sedation and circumstances that may guide selection of particular medications.
- For the undifferentiated, severely agitated patient requiring rapid tranquilization, we recommend a benzodiazepine (such as lorazepam) either alone or with a first-generation antipsychotic (such as haloperidol).
- The possibility of an organic (medical) cause of aggressive behavior should be considered in all violent patients, even those with known psychiatric disease.
- Difficult patient encounters may result in undesirable implications for both patients and their ED caregivers, including compromised patient care, compassion fatigue, or professional burnout.
- Management of the difficult patient can be optimized by understanding the multiple issues contributing to the impaired clinician-patient relationship, including factors of the ED setting (such as time constraints and lack of privacy), individual clinician influences (such as personal bias or poor communication), and patient contributions to the interaction, including behavioral, social, or substance use issues.
- Pejorative stereotypes of difficult patients should be avoided. To aid in clinician strategies for challenging encounters, instead aim to characterize the patient's primary difficult behaviors.
- Understanding one's own biases and reactions and optimizing communication are helpful strategies in dealing with a suboptimal clinician-patient relationship.

THE COMBATIVE PATIENT

Foundations

Combative patients are among the most difficult patients encountered by emergency clinicians. Often brought in against their will, they can be agitated, confrontational, difficult to examine, and they may physically harm themselves or others. The emergency clinician should seek to control the patient and the situation, diagnose and treat reversible causes of violence, ensure that there is not an organic cause contributing to the behavior, and protect the patient, staff, and other patients from harm.

The emergency department (ED) is a volatile environment owing to high stress, illness, prolonged waiting times, and often perceived gaps in communication. Given that the ED is open 24 hours a day, 7 days a week, combined with the availability of potential hostages and accessibility to drugs or weapons, compound the potential for violent behavior. The assault-injury rate of health care occupations is nearly 10 times that of the general sector, and over half of all health care providers will be victims of violence of some form during their careers.

Emergency care providers throughout the world are more likely than other health care providers to experience violent events, such as verbal threats, physical assaults, or confrontations outside the workplace.[1-9] In 2018, The American College of Emergency Physicians (ACEP) conducted a poll of 3539 emergency physicians across the country in which nearly 50% reported having been assaulted while at work in the ED, with over 70% having witnessed an assault in the workplace.[7] In this survey, nearly all assaults were committed by the patient (97%), but in 28%, it was reported that family or friends acted as an accessory.[7] Similar rates of violence and aggression toward physician and nursing staff are typically observed, and both men and women generally appear to be at comparable risk.[1,4] Violent incidents are far more likely to be verbal threats or acts of intimidation than physical assaults and, in the ED, may be acted out by patients, as well as their family, friends, or other visitors.[1-7] The actions of combative patients have consequences that extend beyond the physical injury of ED caregivers, such as provider posttraumatic stress disorder symptoms or lost provider work productivity, and also serve as a major contributor to burnout.[1,6-8]

Clinical Presentation

Patient Characteristics

The pathogenesis of violent behavior is multifactorial, with potential contributing factors including environmental, historical, interpersonal, biochemical, genetic, hormonal, neurotransmitter, or substance abuse disorders.[10-12] Psychiatric illness is also a risk factor, with schizophrenia, personality disorders, mania, or psychotic depression most frequently associated with violence.[10-12] Delusional schizophrenic patients may become violent, believing that others are attempting to harm them. They may also have auditory hallucinations commanding harm to others. The patient with acute mania is unpredictably dangerous because of emotional lability, a situation in which pleasantness can quickly turn to aggression. Substance abuse disorders and drug-seeking behavior are consistently associated with violent behavior in both psychiatric and nonpsychiatric populations.

Biologically, the serotonin system largely controls aggression and inhibition, with a role of diminished serotonergic function in disinhibiting aggression against self and others.[11] Generalized brain

*Disclaimer: The views expressed herein are solely those of the authors and do not represent the official views of the Department of Defense or Army Medical Department.

BOX 185.1 Selected Conditions Associated With Violence

Psychiatric
Schizophrenia
Paranoid ideation
Catatonic excitement
Mania
Personality disorders
- Borderline
- Antisocial
- Delusional depression
- Posttraumatic stress disorder
- Decompensating obsessive-compulsive disorders

Situational Frustration
Mutual hostility
Miscommunication
Fear of dependence or rejection
Fear of illness
Guilt about disease process

Antisocial Behavior
Violence with no associated medical or psychiatric explanation (these patients may be managed by the police or security)

Organic
Diseases
Delirium
Dementia
Trauma
Central nervous system infection
Seizure
Neoplasm
Cerebrovascular accident
Vascular malformation
Hypoglycemia
Hypoxia
Acquired immunodeficiency syndrome (AIDS)
Electrolyte abnormality
Hypothermia or hyperthermia
Anemia
Vitamin deficiency or toxicity (e.g., hypervitaminosis D)
Endocrine disorder

Drugs
Unanticipated reaction to prescribed medication (especially sedatives in brain-injured or elderly patients)
Alcohol (intoxication and withdrawal)
Amphetamines
Cocaine
Sedative-hypnotics (intoxication or withdrawal)
Phencyclidine (PCP)
Lysergic acid diethylamide (LSD)
Anticholinergics
Aromatic hydrocarbons (e.g., glue, paint, gasoline)
Steroids
Synthetic cannabinoids
Synthetic cathinones

dysfunction may predispose patients to violence by disruption of the regulation of aggression, particularly in the prefrontal or temporal cortex.[11] Cerebral imaging documents both functional and structural impairments in violent criminals and antisocial patients.

Violent behavior also occurs in association with head trauma, hypoxia, hypoglycemia, electrolyte imbalance, infections (particularly herpes encephalitis), drug intoxication or withdrawal or adverse reaction, or metabolic and endocrine derangements. Uncommon organic causes include seizures (e.g., temporal lobe), tumors (particularly those in the limbic system), limbic encephalitis, multiple sclerosis, porphyria, Wilson disease, Huntington disease, sleep disorders, hyperparathyroidism, or vitamin and mineral deficiencies (e.g., folate, vitamin B_{12}, niacin B_2, and pyridoxine vitamin B_6). Although drug or ethanol intoxication and withdrawal are the most common diagnoses in combative ED patients, the mnemonic FIND ME (*f*unctional [i.e., psychiatric], *i*nfectious, *n*eurologic, *d*rugs, *m*etabolic, *e*ndocrine) helps in broadly categorizing many important causes of violence (Box 185.1).

Identification of *potentially* violent patients is more difficult; male gender, prior history of violence, and drug or ethanol abuse have historically been positive predictors, whereas ethnicity, diagnosis, age, marital status, and education have been unreliable identifiers. Overall, the most accurate tools for predicting acute violent behavior likely rely largely on current behavioral patterns and clinical observations in the context of prior patterns of violence of the patient when known or previously documented.[12]

Emergency Department Influences

An annual ED census over 50,000 patients, an average waiting time over 2 hours, and ED crowding are associated with an increased incidence of violence.[13] The risk of workplace assault in the ED, however, exists across hospitals of all sizes and reflects the rate of violence in the community. Despite these risks, health care providers have not been routinely trained in the identification and management of combative patients.[14]

Patients armed with lethal weapons pose a serious threat to staff and the potential risk posed by concealed weapons exists in all settings including pediatric EDs. In areas where community violence is prevalent, conflict may spill over into the ED when those involved in violent altercations are being treated for their injuries.[8] The carriage of weapons in the ED population has previously been estimated at approximately 4% to 8%, with up to 27% of major trauma patients; however, not all EDs screen for weapons or use metal detectors. Unfortunately, prediction of weapons carriage in any particular patient is challenging, and it is therefore prudent to assume that all violent patients are armed until it is proved otherwise, especially those presenting with major trauma.

The deleterious effects of violence in the ED can be minimized by employing certain preventive measures and by training staff in techniques to de-escalate and limit violent behavior when it occurs (Box 185.2).

Initial Patient Evaluation

Evaluation of the combative patient begins with attention to safety measures. All patients should be screened for weapons before the interview. The use of metal detection is ideal upon ED entry, and additional attention may be needed for patients brought to the ED by ambulance and thereby bypassing routine security screens. The practice of undressing patients and placing them in a gown is useful as a non-confrontational survey for potential weapons that also discourages fleeing in some circumstances or, conversely, aids in identification if a violent patient suddenly flees from the ED.

The ideal setting for the patient interview emphasizes privacy without isolation, such as a seclusion room specifically designed for the

BOX 185.2 Emergency Department Preparedness and Prevention of Violence

General Emergency Department Preparedness Considerations

Physical and system factors to minimize ED violence risk:

1. Prominently displayed warning signs prohibiting weapons and alerting all entering that they may be screened for weapons
2. Nondiscriminatory inquiry about weapon carriage and searches of individuals for weapons with clear local policies for staff about searches and contraband disposal
3. A panic or alarm system to activate hospital security or local police response
4. ED placement of dedicated telephone(s) with a direct line to police or security to request additional personnel if needed
5. Control flow into the ED by limiting access to one or two entrances and consider buzzer access systems, and protective bulletproof glass or metal bar barriers at front desks
6. A secure examination room with solid ceiling, shatterproof ceiling lights, heavy indestructible chairs, well-secured restraint bed, two outward swinging doors that can be locked from the outside, an emergency distress button that can be activated unobtrusively, and consideration of a video monitoring system

Primary Prevention

Control factors encouraging the development of frustration and aggression:

1. Minimize waiting times to the extent feasible
2. Optimize waiting room environment
3. The presence of visible surveillance cameras
4. The presence of a trained visible security force reflecting both hospital needs and anticipated violence based on local community prevalence

Secondary Prevention

Response to pre-violent agitation and aggression:

1. Recognition of risk (pre-violent patients and their companions)
2. Implementation of de-escalation techniques
3. Minimize treatment delays of pre-violent individuals
4. Ongoing staff training in violent management techniques to increase caregiver confidence and comfort while decreasing the rate of aggressive incidents

Tertiary Prevention

Limitation of the actual act of violence once it has occurred:

1. Use of physical and chemical restraints
2. Appropriate security and police intervention
3. Apply familiar protocols for dealing with the violent individual

ED, Emergency department.

interview of potentially dangerous patients. Prior to the medical interview, security should be stationed strategically and the door left open to facilitate both intervention and escape for the provider. The patient and interviewer may be seated roughly equidistant from the door, or the interviewer may sit between the patient and the door. Blocking of the door, however, poses a risk of harm to the clinician if the patient feels the urge to escape. Ideally, examination room doors should swing out, and more than one exit should be available. The clinician should have unrestricted access to the door and avoid sitting behind a desk. The room should not contain heavy or potentially dangerous objects that may be thrown. There ideally should be a mechanism to alert others of danger, such as a panic button or a code word or phrase that summons security (e.g., "I need 'Dr. Armstrong' in here."). For personal protection of the provider, earrings, necklaces, and neckties should be removed. Personal accessories that may be used against the caregiver, such as a stethoscope or scissors, should also be removed. The clinician should be aware of any objects within the room or on the patient's body that might be used as weapons, such as pens, watches, necklaces, key chains, cell phones, or belts.

BOX 185.3 Patient Behaviors Suggesting Impending Violence

Provocative behavior
Angry demeanor
Loud, aggressive speech
Tense posturing (e.g., gripping arm rails tightly, clenching fists)
Pacing or frequently changing body position
Aggressive acts (e.g., pounding walls, throwing objects, hitting oneself)

Violence risk assessment of a potentially combative patient can be difficult. Violence often erupts after a period of mounting tension. The astute practitioner may identify verbal or nonverbal cues and may subsequently have the opportunity to defuse the situation. In a typical scenario, the patient first becomes angry, then resists authority, and finally becomes confrontational and violent. When clinicians have a "gut feeling" that a dangerous situation may be developing, they should take appropriate precautions. Violent behavior may also erupt without warning, especially in patients with an organic brain syndrome, so clinicians should not feel overly confident in their ability to sense impending danger. An obviously angry ED patient should be considered potentially violent. Patients with a history of violent behavior are more likely to inflict serious injury, and certain patient behaviors may suggest impending violence (Box 185.3).

To prevent escalation, the patient should be removed from contact with other agitated accomplices, as well as from other provocative patients. A quiet area enabling direct observation is optimal. Because increased waiting times correlate positively with violent behavior, consider evaluating the potentially violent patient accelerated to prevent escalation of aggression. When feasible, expeditious triage and evaluation of these patients may avoid the challenging consequences of violence for the patient at hand, the ED staff, and ultimately the care of other ED patients. Often, the perception of preferential treatment alone may serve to defuse the patient's anger.

Management

Verbal Management Techniques

Verbal de-escalation techniques should be considered in the setting of agitated or violent patients prior to implementation of physical restraints or chemical sedation. The agitated but cooperative patient may be amenable to verbal de-escalation techniques alone. This verbal interaction provides an opportunity to assess the patient's mental status and comprehension, as well as perception of the current situation. If the patient remains resistant or violent after verbal techniques, or incapable of interacting appropriately, then restraint is necessary. However, the uncooperative, actively violent or potentially violent patient may warrant immediate restraint to minimize risk to the patient and ED staff.

Successful verbal management techniques include an effort to make the patient as comfortable as possible, being honest and straightforward during the medical interview, adopting a non-confrontational demeanor, and being an attentive and receptive listener without conveying weakness or vulnerability (Box 185.4).[9,14] The interviewer should respond verbally in a calm and soothing tone of voice. It is also important to stand at least an arm's length away and to avoid prolonged

BOX 185.4 Ten Elements for Verbal De-Escalation

1. Respect personal space: Maintain a distance of two arm's lengths and provide space for easy exit for either party.
2. Purposefully avoid provocation: Keep your hands relaxed, maintain a nonconfrontational body posture, and do not stare at the patient.
3. Establish verbal contact: The first person to successfully connect verbally should lead the effort.
4. Use concise, simple language: Elaborate and technical terms are hard for an impaired person to understand.
5. Identify feelings and desires: "What are you hoping for?"
6. Listen closely to what the patient is saying: After listening, restate what the patient said to improve mutual understanding (e.g., "Tell me if I have this right ...").
7. Agree, or agree to disagree: (a) Agree with clear specific truths; (b) agree in general (e.g., "Yes, everyone should be treated with respect."); (c) agree with minority situations (e.g., "There are others who would feel like you.").
8. Set clear limits: Inform the patient that violence or abuse cannot be tolerated.
9. Offer choices and optimism: Patients feel empowered if they have some choice in matters.
10. Debrief the patient and staff: Be sure to include an opportunity for the patient and staff to speak.

Adapted from the American Association for Emergency Psychiatry De-escalation Workgroup consensus statement: Richmond JS, Berlin JS, Fishkind AB, et al: Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup. *West J Emerg Med.* 2012;13:17-25.

direct eye contact, approaching the patient from behind, or sudden movements. In some cases, an agitated patient may be aware of the impulse control problem and welcome limit setting by the clinician (e.g., "I can help you with your problem, but I cannot allow you to continue threatening me, the emergency department staff, or other patients."). The interviewer should act as an advocate for the patient. Offering a soft chair, food, or beverage (though not a hot liquid, which may be used as a weapon) may help in establishing trust, and patients may de-escalate as a result of the attention to their basic human needs.

A key component of interviewing a potentially violent patient is addressing the issue of violence directly. The patient should be asked relevant questions about suicidal or homicidal ideations or plans, possession of weapons, history of violent behavior, and current use of intoxicants. Acknowledgment of the obvious (e.g., "You look angry.") may enable the patient to begin sharing emotions. If the patient becomes more agitated, it may be helpful to speak in a conciliatory manner and to offer supportive statements to guide and empower the patient in what you would like them to do (such as, "You seem to want to do the right thing. How can we come up with a solution together?") to help defuse the situation. If this is not successful, a respectful offer of medication or restraints to the patient may prevent further escalation.

Counterproductive approaches to the combative patient include arguing, threats, deception, or condescension, as they fail to build rapport and may challenge patients to "prove themselves," thereby further escalating the situation. An open threat to call security personnel also invites aggression. Clinicians should be aware of their own reactions to such patients and avoid transference of anger. Deliberate deception (e.g., "I am sure you will be out of here in no time.") may serve to invite violent consequences once the false promise is uncovered and an unsuspecting nurse or colleague who follows the initial interviewer may be victimized. It is important to avoid denial or downplaying of threatening behavior, and if verbal techniques are unsuccessful and escalation occurs, the clinician should immediately seek refuge and summon help.

Physical Restraints

Physical restraints should be considered when verbal techniques prove unsuccessful. The use of restraints can be humane and effective in facilitating diagnosis and treatment while preventing injury to the patient or medical staff. Generally speaking, the liability one incurs for restraining a patient against his or her will is negligible compared with the potential liability for allowing a patient to lose control and cause physical harm to themselves or others. Restraints should not be applied for convenience or as a punitive response for disruptive behavior and should be removed as expeditiously as possible, usually once adequate chemical sedation is achieved.

Indications for emergency seclusion and restraint include the prevention of imminent harm to the patient, others, or the immediate environment, or as part of an effective ongoing behavior treatment program. Patients can typically be broadly classified into three categories: (1) those with an organic disorder for whom restraints facilitate evaluation, (2) those with functional psychosis for whom verbal techniques are less effective and restraints facilitate administration of neuroleptics, and (3) those with personality or other disorders prohibiting the utility of verbal techniques. Seclusion or restraint may be contraindicated because of the patient's clinical or medical condition. Seclusion should not be used in an unstable patient who requires close monitoring and should be avoided when the patient is suicidal (unless adequate continuous observation can occur), self-abusive or self-mutilating, or intentionally ingested drugs or poisons. The indications for the use of restraints should be documented. Specific statements (such as, "I restrained Mr. Smith because he told me he was going to beat me up and then took a swing at me.") are preferable to general statements (such as, "I restrained Mr. Smith because he was violent.").

The application of restraints should be systematic and ideally follow a predetermined ED protocol that is implemented when the examiner leaves the room after verbal techniques are unsuccessful. Whenever possible, the treating clinician should avoid active participation in restraint application to preserve the clinician-patient relationship. The restraint team ideally consists of at least five people, including a team leader. The leader, whether a physician, nurse, or security officer, should be experienced in implementing restraints and provide guidance and instruction for the restraint team. Before engaging with the patient, the leader outlines the restraint protocol and warns of anticipated danger, including the presence of objects that may be weaponized. All team members should remove personal objects that the patient could use against them. A mixed-gender restraint team should be considered to mitigate potential allegations such as sexual assault.

The team engages with the patient as a group and displays a professional rather than threatening attitude. Many violent individuals calm down at this point as a large show of force protects their ego (e.g., "I would have fought back but there were too many against me."). The leader speaks to the patient in a calm and organized manner, explaining why restraints are needed and how the course of events will transpire (e.g., "You require a medical and psychiatric examination, as well as treatment."). The patient is instructed to cooperate and to lie down on the gurney to have restraints applied. Some patients are relieved at the protection to self and others afforded by restraints when they feel themselves losing control. Even if the patient suddenly appears less dangerous once the decision to restrain is made, it is advisable to continue the process and avoid negotiation with the patient at this point.

If physical force becomes necessary, one team member restrains a preassigned extremity by controlling the major joint (knee or elbow). The team leader controls the head. If the patient is armed, two mattresses can be used to charge and immobilize (sandwich) the patient. Restraints are applied securely to each extremity and tied to the solid frame of the gurney (not side rails, as later repositioning of side rails also repositions the patient's extremities).

Leather is the optimal type of restraint, as it is a physically stronger material and less constricting than typical soft restraints. For this reason, gauze should not be used. Soft restraints may help restrict extremity use in the semi-cooperative patient, but are unlikely to be effective in the truly violent patient who is continuing to struggle and attempt escape. If chest restraints are used, it is vital that adequate chest expansion for ventilation is ensured. The application of a soft Philadelphia collar to the patient's neck may minimize head banging or biting. In this circumstance, ensuring continued adequacy of the patient's airway is similarly prudent. Although restraining patients on their sides helps prevent aspiration, we recommend the supine position with the head elevated, as it tends to be more comfortable and allows a more thorough medical examination while providing some protection against aspiration. Once the patient is immobilized, announcing "the patient is safe" may have a calming effect on the restraint team and the patient.

We recommend avoiding the prone restraint position when possible and employing chemical sedation when a patient continues to struggle against physical restraints. Sudden unexpected deaths have been reported in prone patients, particularly if left unattended during busy shifts or between multiple sign-outs with various treating clinicians. Although healthy volunteers, when restrained and undergoing physical exertion, do not appear to experience clinically significant positional asphyxia, combative ED patients often suffer from other conditions that may predispose to increased morbidity. Patients using cocaine or other stimulants who are restrained in the prone position appear to be uniquely at risk because increased sympathetic tone and altered pain sensation allow exertion beyond normal physiologic limits, and sympathetic-induced vasoconstriction may impede clearance of metabolic waste products and induce hyperthermia and rhabdomyolysis. Alteration of respiratory mechanics in an acidemic patient resulting from the position of restraint can be a contributing factor through impairment of respiratory compensation.

After restraints are successfully applied, the patient should be monitored frequently and positions changed to prevent neurovascular sequelae, such as circulatory obstruction, paresthesias, or rhabdomyolysis associated with continued combativeness. Standardized documentation is recommended for this monitoring to include the specific indication for restraint and, ideally, colleague agreement that restraints are necessary. Basic patient needs must be met (e.g., hydration, toileting needs) and physical restraints should be removed as soon as possible. Review of restraint team performance and critical discussion may reveal opportunities for improvement. Education and rehearsal by staff can improve and maintain restraint skill as well as improve comfort and confidence with this skill.

Chemical Restraints

Chemical sedation alone, or in conjunction with physical restraint, may assist in the safe management of an agitated or violent patient when verbal de-escalation techniques fail. Chemical restraints subdue patients who may otherwise harm themselves or others and serve to facilitate further medical evaluation and treatment. Clinical and administrative guidelines for their use are similar to those for physical restraints. The use of medication to calm a patient may obscure the mental status examination and clinical diagnosis. Caution should also be exercised because adverse events may result from sedation. The most commonly observed adverse event is respiratory depression or hypoxia. In one study, the rate of adverse events was 16%, and the highest risk characteristics were found to be age greater than 65 years, alcohol intoxication, and more than one type of parenteral sedation administered within 60 minutes. The risk of adverse events should be weighed, however, against the increased risk to the patient and staff without medication administration.

The ideal agent for controlling combative patients is effective, safe, well tolerated, free of significant side effects or drug interactions, rapid in onset, titratable, and available through multiple routes of administration. Several pharmaceutical agents can quickly achieve safe behavioral control, or "rapid tranquilization," without oversedation. Medications should be used judiciously and with close patient monitoring, as there remains a paucity of rigorous clinical data regarding chemical sedation in certain settings such as acute delirium, the underlying comorbid or primary conditions of violent ED patients are often unknown, and a degree of individual variation in response to any medication should be anticipated.

The primary medications commonly used in the ED for chemical sedation include benzodiazepines, first-generation (typical) antipsychotics, second-generation (atypical) antipsychotics, or ketamine.[15-30] We suggest a patient-based approach to chemical sedative selection based on suspected or known clinical features (Box 185.5).

Benzodiazepines, antipsychotics (also known as *neuroleptics*), and ketamine are commonly used either alone or in combination for rapid tranquilization. Chemical restraints should ideally be offered to the patient for voluntary use, as the offer itself has potential to restore the patient's feeling of control and may lead to subsequent de-escalation. In the uncooperative or dangerous patient refusing an oral medication, the intramuscular (IM) route is preferred, with intravenous (IV) administration an alternative depending on IV catheter status. As with physical restraints, it is imperative that patients are frequently re-evaluated for changes in their clinical status.

Benzodiazepines. Benzodiazepines, particularly lorazepam (Ativan) and midazolam (Versed), are often used in the ED for rapid tranquilization of an agitated or violent patient. Benzodiazepines enhance the activity of the major inhibitory neurotransmitter gamma-aminobutyric acid to cause anxiolytic, anticonvulsant, and sedative effects. These agents are preferred for the management of agitation caused by ethanol withdrawal or sedative-hypnotic drug withdrawal, as well as cocaine, amphetamines, or sympathomimetic drug ingestions. Benzodiazepines may be more effective than antipsychotics in reducing delirium and mortality and are useful in patients at risk for seizure or when avoiding antipsychotic-associated akathisia and hyperthermia. For these reasons, we prefer the use of benzodiazepines when sedating the patient with agitation from an unknown cause. Although they are generally well tolerated, side effects of benzodiazepines include excessive sedation, ataxia, confusion, nausea, or respiratory depression, which may be amplified in the presence of concurrent alcohol and other depressant use.

Lorazepam is frequently preferred to other benzodiazepines because of its rapid onset of action, short half-life, hepatic and renal excretion, lack of active metabolites, and effectiveness by oral, IM, or IV routes of administration. Recommended initial oral, IM, or IV doses of lorazepam range from 0.5 mg to 2 mg. Typical doses for chemical restraint in the ED begin at 1 mg to 2 mg increments IM or IV with upward titration as needed. The onset of action after administration of lorazepam is generally 20 to 30 minutes if it is given IV or 15 to 30 minutes if it is given IM, with a duration of action of 6 to 8 hours. Caution should be employed when switching routes of administration; for example, synergy may be observed when doses are given IM followed by IV, and desired clinical effects coupled with undesirable side effects, such as respiratory depression, may be noted simultaneously.

BOX 185.5 Suggested Patient-Based Approach to Chemical Restraint

The Severely Violent Patient
Droperidol 2.5 to 5 mg IM/IV, titrate as needed
or
Midazolam 2.5 to 5 mg IM/IV, titrate as needed
or
Midazolam 2.5 to 5 mg IM/IV with droperidol 2.5 to 5 mg IM/IV, titrate either as needed
or
Haloperidol 2. 5 to 5 mg IM/IV with lorazepam 1 to 2 mg IM/IV, titrate either as needed
or
Ketamine 1–2 mg IV/IM

The Undifferentiated Severely Agitated Patient or With Stimulant Intoxication
Lorazepam 1 to 2 mg IM/IV
or
Midazolam 2.5 to 5 mg IM/IV
or
Haloperidol 5 mg IM/IV with lorazepam 2 mg IM/IV

The Patient Intoxicated With a Central Nervous System Depressant (e.g., Alcohol)
Haloperidol 2.5 to 5 mg IM/IV
or
Droperidol 2.5 to 5 mg IM/IV
or
Ketamine 1–2 mg IV/IM

The Patient With a Known Psychotic/Psychiatric Disorder
Haloperidol 2.5 to 5 mg IM/IV
or
Droperidol 2.5 to 5 mg IM/IV
or
Haloperidol 2.5 to 5 mg IM/IV with lorazepam 2 mg IM/IV
or
Ziprasidone 10 to 20 mg IM[a]
or
Olanzapine 5 to 10 mg IM[a]

The Cooperative but Agitated Patient
Lorazepam 1 to 2 mg PO
or
Risperidone 2 mg PO [a]
or
Olanzapine 5 to 10 mg PO [a]

The Elderly Patient
Reduce above medication dose by half [a]

[a] The safety of atypical antipsychotics in geriatric patients remains somewhat uncertain.
IM, Intramuscular; *IV,* intravenous; *PO, per os* (by mouth).

Midazolam is another effective benzodiazepine for achievement of mild sedation and has a more rapid onset of action and a shorter duration of clinical effects than lorazepam. The IM route is used widely to calm the agitated patient with a typical initial dose of 2.5 mg to 5 mg IM. When it is administered IM, the medication usually takes effect in about 15 minutes with a mean duration of 2 hours. The choice of midazolam versus lorazepam may, in part, be guided by the duration of sedation desired and faster onset of action.

Antipsychotics. Antipsychotic medications play a prominent role in the chemical restraint of the violent ED patient. These medications include the older "typical" (or "classic") antipsychotics and the newer "atypical" antipsychotics. Typical antipsychotics appear to strongly block brain dopamine receptors, whereas the atypical antipsychotics less strongly and more specifically antagonize dopamine and serotonin receptors.[17] Both classes of antipsychotics have variable effects on other receptors, including adrenergic, cholinergic, or histaminergic receptors. The typical antipsychotics can be categorized in terms of their "potency," a description referring to the relative dosing of the medication and generally predictive of its side effect profile. The incidence of sedation, hypotension, and anticholinergic side effects is higher with the low-potency antipsychotics, whereas the incidence of extrapyramidal symptoms is greatest with the high-potency antipsychotics. Low-potency antipsychotics include chlorpromazine (Thorazine) and thioridazine (Mellaril), medium-potency antipsychotics include loxapine (Loxitane) and molindone (Moban), and high-potency antipsychotics include haloperidol (Haldol) and droperidol (Inapsine).

Of the older typical antipsychotics, the butyrophenones—haloperidol and droperidol—have been widely utilized in the emergency care setting. Haloperidol is the most frequently administered antipsychotic to control agitated ED patients.[17,24] It is available in oral, IM, and IV preparations, although the commonly used IV route of administration is not approved by the US Food and Drug Administration (FDA). Haloperidol is generally given in 2.5 mg to 10 mg IM doses (often 5 mg IM for the severely agitated, average sized adult), with half doses administered to elderly patients (e.g., 2.5 mg IM), followed by repeated dosing every 20 to 60 minutes as needed. Effects are usually seen within 30 minutes by the IM route, and the average patient typically requires fewer than three doses for the desired clinical effect.

Droperidol has been commonly used at doses of 2.5 to 10 mg IM or 2.5 to 5 mg IV to control the agitated or combative patient in a manner similar to haloperidol.[17,19,23] Compared with haloperidol, droperidol appears to more rapidly reduce agitation at equal IM dosing, has a shorter duration of effect, more sedation, a larger incidence of orthostatic hypotension, and a lesser incidence of extrapyramidal symptoms. When compared with midazolam 10 mg IM, droperidol 10 mg IM appears to have an equally rapid onset of action and requires fewer additional doses for sedation. The clinical use of droperidol decreased markedly after it was given a controversial black box warning in 2001 by the FDA for concern of QTc prolongation and torsades de pointes; however, subsequent studies have shown a low incidence of complications as well as superiority over other antipsychotics in its rapidity of action.[19,21] For instance, in a 2018 prehospital comparison of droperidol and midazolam, patients treated with droperidol had fewer adverse events and required fewer additional sedative doses.[20]

Haloperidol is also associated with QTc prolongation and torsades de pointes. Given the effectiveness and overall safety of these medications combined with the unclear risk association for QTc prolongation, we recommend the cautious use of both haloperidol and droperidol when administered to patients with other identified risk factors for, or the known presence of, QTc prolongation, such as in the setting of baseline antipsychotic or methadone use. We also recommend obtaining an electrocardiogram or placing the patient on a cardiac monitor before drug administration if feasible. If this is precluded by poor cooperation of a violent or agitated patient, we recommend obtaining an electrocardiogram once the patient becomes more cooperative.

Common side effects of haloperidol and droperidol include sedation, orthostatic hypotension, or extrapyramidal symptoms. Extrapyramidal symptoms are thought to be due to mesolimbic dopamine receptor blockade. They are not dose related and may occur

immediately or days following medication administration. Patients can have akathisia (extreme restlessness) or uncoordinated involuntary movements known as dystonia, including of the muscles of the mouth (buccolingual), neck (torticollis), back (opisthotonos), eyes (oculogyric crisis), or trunk (abdominopelvic). Treatment includes diphenhydramine 25 mg to 50 mg IV or IM, or benztropine 1 mg to 2 mg IV or IM, acutely and extended for 3 days to minimize symptom recurrence. Both haloperidol and droperidol have some anticholinergic properties and are often co-administered with diphenhydramine or benztropine, and thus should not be used to control agitation in a patient with known or suspected anticholinergic intoxication. Haloperidol and droperidol should also be avoided in patients with alcohol, benzodiazepine, or other sedative withdrawal syndromes, patients with known seizure disorders, patients with phencyclidine overdose, and, when possible, in pregnant or lactating females.

Neuroleptic malignant syndrome is a rare and potentially lethal idiosyncratic reaction estimated to occur in 0.01% to 0.04% of patients receiving antipsychotic medications. Characteristic symptoms include autonomic instability, hyperthermia, "lead-pipe" muscle rigidity, and altered mental status. If neuroleptic malignant syndrome is suspected, further antipsychotics should be withheld, and we recommend initiation of supportive treatment and rapid external cooling (see Chapter 150).

Chemical restraint with newer atypical antipsychotics (such as olanzapine, ziprasidone, or aripiprazole) is generally safe and effective in the treatment of agitated patients.[17,22-24] Compared with the typical antipsychotics, these medications appear to provide more tranquilization than sedation and have fewer extrapyramidal side effects. Their use in the ED is facilitated by IM or oral dissolving tablet formulations that may assist in a smoother transition to oral dosing in those patients requiring ongoing antipsychotic therapy. Although the clinical significance is uncertain, atypical antipsychotics carry a black box warning for an increased risk of death in elders with dementia-related psychosis and they also cause QTc prolongation. As a result, we recommend employing the same precautions used with the typical antipsychotics. In a 2019 study comparing agitated patients with known alcohol intoxication who were treated with droperidol, haloperidol, or olanzapine, median ED length of stay was shortest for droperidol (499 minutes), which was significantly shorter than that of haloperidol (524 minutes) and olanzapine (533 minutes). No cases of sudden cardiac death occurred.[18]

Olanzapine (Zyprexa) is readily available in IM, oral, and oral-dissolving tablet formulations; and it has a reported distinct "calming" effect in clinical practice. It has FDA-approved indications for the treatment of agitation associated with bipolar I mania and schizophrenia. IM olanzapine has an onset of action of 15 to 45 minutes after initial administration and is typically administered as an initial dose of 2.5 mg to 10 mg IM followed by one or two subsequent doses every 2 to 4 hours for a total maximum dose of 30 mg IM. Although generally well tolerated, side effects include sedation (which may be compounded in the setting of concomitant benzodiazepine use), mild hypotension, and anticholinergic properties that can exacerbate existing anticholinergic intoxication. Mild hypoxia is common but critical hypoxia or serious airway compromise remains rare.[22] Olanzapine has minimal QTc-prolonging effects and a lesser occurrence of acute dystonia and akathisia compared with haloperidol. In a 2019 study comparing the need for an additional "rescue" sedation dose, both olanzapine and droperidol required lower rates of rescue sedation at one hour and overall when compared with haloperidol. There were no significant differences in major adverse events.[21]

Ziprasidone (Geodon) is FDA approved for treatment of the agitated schizophrenic and bipolar manic patient. Typical dosing is 10 mg IM every 2 hours or 20 mg IM every 4 hours (not to exceed 40 mg/day) with an onset of action of 15 to 30 minutes. Ziprasidone is generally well tolerated, although side effects such as somnolence, dizziness, and headache are common, and it appears to have potentially notable QTc-prolonging effects.

Aripiprazole (Abilify) has FDA-approved indications for the treatment of agitation associated with the schizophrenia or bipolar disorders. Recommended doses for the acutely agitated patient are 5.25 to 15 mg IM (often 9.75 mg) every 2 hours as needed (to a maximum daily dose of 30 mg). Aripiprazole IM (9.75 and 15 mg) may have comparable efficacy to lorazepam 2 mg IM with a low risk of oversedation.

Risperidone (Risperdal) is typically used for schizophrenia and available in an oral or IM depot form with typical dosing of 1 mg to 2 mg. Given orally, risperidone appears to be as effective and tolerable as IM administration of haloperidol. The time to peak concentration is shorter than some oral second-generation antipsychotics and may be useful when rapid control of agitation by an oral medication is desired.

Combined Use of Benzodiazepines and Antipsychotics. Benzodiazepines and typical antipsychotics are commonly used in combination for chemical restraint. In a 2016 meta-analysis of chemical agents for sedation of agitated patients in the ED, combination therapy sedated a greater proportion of patients at 15 to 20 minutes than benzodiazepines alone.[17] Combination therapy was more effective and required fewer repeat doses for sedation, and the risk of adverse events was lower than for benzodiazepines alone.[17] A 2017 study of monotherapy with droperidol or olanzapine compared with combination therapy with midazolam and droperidol found significantly more patients in the midazolam-droperidol group were adequately sedated at 10 minutes.[23] The combination therapy was 6 minutes faster than either monotherapy.[23] Patients in the midazolam-droperidol group required fewer additional doses or alternative drugs to achieve adequate sedation, and the adverse event rate and length of stay did not differ between the three groups.[23] In a 2018 comparison of intramuscular midazolam, olanzapine, ziprasidone, or haloperidol for treating acute agitation in the emergency department, midazolam was found to work most rapidly and olanzapine appeared to have superior sedation without redosing, as well as less effect on QTc; however, no differences in adverse events in any treatment group were identified.[24]

Demonstrated effective combinations include midazolam (5 mg IV or IM) with droperidol (5 mg IV or IM) or lorazepam (2 mg IV or IM) with haloperidol (5 mg IV or IM). When given together, lorazepam and haloperidol appear to be more rapidly sedating than either medication alone, have fewer adverse effects, and are compatible within the same syringe. Half doses should be considered in carefully selected elders. If additional medication is immediately needed, we recommend consideration of IV midazolam every 3 to 5 minutes or IV lorazepam every 20 to 30 minutes. In summary, though antipsychotics and benzodiazepines are both safe and effective on their own, the combination is also safe, may have more rapid onset, with similar side effect profile to either medication alone.

Ketamine. Ketamine is a dissociative anesthetic with a good safety profile used to manage the violent and acutely agitated patient in the hospital or prehospital settings, including use following treatment failure with benzodiazepines or antipsychotics.[17,25-30] Although its use in agitated delirium in young adults is increasingly described, we recommend avoiding its use in elders with acute agitated delirium, patients at increased risk for heart disease, or patients with schizophrenia, given the possibility of exacerbating these conditions. For the treatment of acute violent agitation in the ED patient, we recommend an initial dose of 1 to 2 mg/kg IV or 4 to 5 mg/kg IM. The onset of drug action is typically 1 to 2 minutes after IV use and 4 minutes or longer after IM administration, with duration of action of approximately 20 minutes. It appears to be faster in onset via IM route

TABLE 185.1 Distinguishing Organic From Functional Causes of Violent Behavior

	ORGANIC		
Clinical Feature	**Delirium**	**Dementia**	**Functional**
Onset	Acute	Gradual	Gradual
Age at onset	Any	>50 years old	<40 years old
Alertness	Altered	Normal	Normal or hyperalert
Orientation	Impaired	May be normal or impaired (depending on stage of dementia)	Normal
Hallucinations	Common; can be visual, auditory, or tactile	None	Auditory in schizophrenia, otherwise uncommon
Symptom picture	Fluctuating	Stable	Stable
Abnormal vital signs	Common	Uncommon	Uncommon
Psychiatric history	No	No	Yes

than other medications; however, due to its short duration of action, it frequently requires combination therapy or repeat doses.[26,27,28,30] Notable side effects include hypertension and tachycardia (usually mild and transient), drooling, laryngospasm or other respiratory complications (uncommon), emesis, or emergence reactions. In a 2016 comparison of prehospital administration of ketamine or haloperidol for severe agitation, ketamine worked faster but was associated with greater risk of complications or intubation.[30] Overall, studies reflect that patients receiving ketamine in the prehospital setting are more likely to require intubation than when ketamine is administered in the ED, though it is unclear whether this is caused by dosing differences, unfamiliarity with side effect profile, or increased severity of illness.

Post-Restraint Medical Evaluation

Once combative patients are controlled, evaluation is necessary to screen for organic causes of agitation. Separation of functional (psychiatric) from organic (medical) disease is a challenging task complicated by the fact that many patients with psychiatric disorders also suffer from organic medical disorders that may worsen symptoms. Patients who exhibit violent behavior that is caused or exacerbated by an organic problem may rapidly deteriorate if the medical issues are not addressed in a timely fashion.

Historical features may assist in distinguishing functional from organic illness (Table 185.1). Patients aged 40 years or older who exhibit new onset of psychiatric symptoms are more likely to have an organic cause. Elders are at higher risk for organic delirium from medical illness or adverse medication reactions. Patients with a history of drug or ethanol abuse may exhibit violent behavior as a manifestation of an intoxication or withdrawal syndrome. The acute onset of agitated behavior, as well as behavior that waxes and wanes over time, suggests an organic origin. Most psychiatric patients are alert and oriented and many have known psychiatric diagnoses.

The history includes medical, psychiatric, family, and social information, including suicidal or homicidal ideation, drug and alcohol use, medication use, and any recent changes to prescribed medications or dosages. The agitated patient may be unreliable; thus family or friends may provide valuable details. When family or friends are available, interview them independently from the patient.

The violent patient should be asked for permission to perform a thorough physical examination to search for an organic cause and to evaluate for resulting injury. Restraint of the patient may be necessary to accomplish even the most rudimentary physical examination, including accurate vital signs. Patients with persistently abnormal vital signs, a clouding of consciousness, or focal neurologic findings are more likely to suffer from organic disease and require further diagnostic evaluation. A careful examination of the agitated patient includes general appearance (e.g., hygiene, nourishment, tremors), vital signs, evidence of trauma or needle tracks, characteristic odors, neurologic and mental status, or signs of a possible toxidrome (Table 185.2).

We recommend tailoring diagnostic studies to clinical findings. An initial rapid blood glucose determination and pulse oximetry are prudent when they can be performed safely. Patients younger than 40 years of age with a prior psychiatric history, normal physical examination, calm demeanor, normal orientation, and no physical complaints are unlikely to require further diagnostic testing. Additional studies that may be useful in selected patients include serum electrolyte values, blood or urine toxicology screening, serum ethanol level, thyroid function panel, cranial imaging, or lumbar puncture. Diagnostic studies should be guided by the overall clinical scenario and are not required in most patients. Specific medication levels can be determined if toxic levels would impact treatment or disposition. An electrocardiogram may be useful in elders or in the setting of a suggested intentional ingestion. In the setting of intentional toxin ingestion, serum acetaminophen, and possibly aspirin, levels may be helpful.

Although serum ethanol or toxicology screening may not significantly influence the ED course, behavioral health or other consulting specialists may utilize the results in decision making. Ideally, an agreement on a diagnostic strategy is reached with the behavioral health specialist to assist in patient disposition. Unnecessary diagnostic testing may prolong ED length of stay and delay definitive psychiatric care.

Disposition and Medical Clearance

The emergency clinician often provides "medical clearance" for the psychiatric or combative patient brought to the ED in police custody or after being placed on a psychiatric hold in the prehospital setting. "Medical clearance" is a misnomer, as a patient is not "cleared" of all possible medical conditions during the ED evaluation; additionally, standard protocols for the provision of what is more accurately termed a "focused medical assessment" remain variable. A preferred phrase in this setting is "medically stable for psychiatric evaluation." Although few patients with primary psychiatric complaints are likely to have coexisting, emergent complications of chronic disease or medical problems contributing to their violent behavior, misattribution of aberrant organic behavior remains a pitfall in the evaluation of the combative patient.

Aspects of a focused medical assessment, including recommended laboratory tests, are often influenced or dictated by local policies or procedures. When feasible, we believe that patients with known psychiatric

TABLE 185.2 Vital Signs and Toxic Syndromes

Toxin	Blood Pressure	Pulse	Respiratory Rate	Temperature	Pupil Size	Skin	Example
Sympathomimetic	↑	↑	↑	↑	↑	Wet	Cocaine
Anticholinergic	↑/↓	↑	↑/↓	↑	↑	Dry	Diphenhydramine
Cholinergic	↑/↓	↑/↓	—	—	↓	Wet	Pesticides
Opioids	↓	↓	↓	↓	↓	—	Morphine
Sedatives	↓	↓	↓	↓	↑/↓	—	Lorazepam
Withdrawal (ethanol, sedative-hypnotics)	↑	↑	↑	↑	↑	Wet	Benzodiazepine withdrawal

disease who are deemed to be at low risk for active or significant, complicating organic medical conditions can be rapidly referred for psychiatric evaluation once they are calm and cooperative. Patients at higher risk for an acute organic illness typically require further diagnostic evaluation. Potential high-risk considerations in the prehospital or ED setting include altered mental status, ingestion, hanging, sexual assault, traumatic injury, or an unrelated medical complaint.[31] The findings of a focused medical assessment should ideally be both communicated to the mental health provider and documented in the medical record, reflecting consideration of an acute medical condition as a contributor or driver of the observed behavior. When the cause of the patient's violent behavior is drug or ethanol intoxication, further observation may reasonably be achieved in the ED or another facility where the patient can be safely monitored until the effects of the intoxicants have abated and further mental health evaluation can occur, as necessary.

Assault and Hostage Situations

Interventions to prevent assault and hostage situations, such as optimization of ED security and general preparedness (see Box 185.2), remain paramount because rates of extreme hospital and ED violence have increased over time.[32] Unfortunately, physical assault may occur despite appropriate precautions or interventions. The individual who is physically assaulted or threatened with harm with a weapon can take steps to protect both themselves and others in the ED setting (Box 185.6).

The frequency of hospital-based shootings has more than doubled in the early 21st century, with deadly incidents that may involve disgruntled, angry, desperate, or mentally ill patients, visitors, or even employees.[32] Weapons may be brought in from outside or appropriated from authorized carriers, such as police. Specific scenarios that should be considered are intimate partner violence, grudges or revenge against former health care providers or employers, mental illness leading to paranoid actions or suicide attempt, and prisoners attempting escape. Violence may be related to the setting (i.e., family member angry about a previous complication, or unrelated, such as an intimate partner seeking out their significant other at work). An emerging and concerning prompt for violence is ideologically or politically motivated. Hospitals should develop an action plan for cases of extreme violence. The plan should include prevention and safety measures, a means for rapid notification of security or police personnel, evacuation routing, medical treatment strategies, and crisis intervention. Scenario-based training drills for medical personnel and dedicated multidisciplinary hospital violence management teams may help optimize readiness and management of extreme patient aggression.[33]

BOX 185.6 Protective Responses to Physical Assault or Weapon Threat

If physically assaulted:

1. Immediately summon help (via panic button if possible).
2. Maintain a sideward posture and keep arms ready for self-protection.
3. Use an arm or leg to deflect a punch or kick.
4. If choked, tuck in the chin to protect the neck, carotid circulation, and ability to breathe.
5. If bitten, do not pull away—push toward the assailant's mouth and hold the assailant's nares shut.

If threatened with a weapon:

1. Appear calm, adopt a nonthreatening posture, and avoid sudden movements.
2. Do not reach for the weapon.
3. Comply with demands and avoid arguing, despair, or whining.
4. Do not bargain, make promises, or lie.
5. Attempt to establish a human connection with the hostage taker.
6. Appear less expendable by offering to administer aid to other hostages.
7. Reassure the hostage taker that a person of authority will arrive promptly to hear their complaints or demands.
8. If a weapon is put down, do not reach for it—instead attempt verbal resolution of the crisis while awaiting security.
9. Request a hostage negotiator from legal authorities if needed.

THE DIFFICULT PATIENT

Foundations

The difficult patient is one who is perceived to interfere with the clinician's ability to establish a usual patient-clinician relationship. Difficult patients are encountered across medical specialties and may represent upwards of 15% to 30% of physician-patient encounters.[34] Difficult patients may carry a number of pejorative labels and can invoke feelings such as irritation, dread, anxiety, or dysphoria in their health care team, potentially leading to dissatisfying interactions for the patient and health care team alike. A high frequency of difficult patient encounters appears to be associated with clinician dissatisfaction and burnout.

The difficult patient-clinician relationship is a consequence of aspects of the ED environment, clinician characteristics, patient factors, and the complex dynamic interaction of these elements (Box 185.7).[33] These elements can act in concert to perpetuate a cycle of impaired patient-clinician interactions, which may dominate the clinical encounter with negative impacts on both the patient and clinician. This can be particularly problematic in the case of patients with maladaptive patterns of behavior. Clinicians may react negatively to perceived difficult or unreasonable patients, which may summon fear of abandonment in such patients. In response to this perceived threat, maladaptive responses of the patient may include an attempt to sustain the patient-clinician relationship through escalation of the actions that were originally perceived negatively by the clinician. The subsequent clinician reaction may be even greater in magnitude and result in even further escalation by the patient as the cycle continues. Ultimately,

BOX 185.7 Factors Impacting the Difficult Patient-Physician Interaction

Emergency Department Factors
Lack of patient choice of facility or physician
Time constraints, frequent interruptions, other priorities of care
Suboptimal patient privacy or comfort (e.g., hallway examinations)
Long waiting times, department crowding
Negative bias toward the patient from other members of the care team (e.g., by prehospital personnel, nursing)

Physician Factors
Poor communication
Difficulty expressing empathy or becoming easily frustrated
Personal negative bias and prejudices toward conditions and interactions
Limited knowledge of the patient's condition or psychosocial situation
Overly rigid medical agenda or interaction
Outside stressors affecting work
Emotional burnout or insecurity
Personal health issues
Situational stressors and perceived time pressure
Sleep deprivation or shift fatigue

Patient Factors
Behavioral issues (e.g., argumentative, manipulative, medical noncompliance)
Fear of abandonment
Psychiatric conditions
Low literacy
Financial constraints
Chronic pain syndromes
Multiple complaints
Beliefs or goals of care unknown to the physician
Unrealistic expectations or goals of care
Substance use disorder
Past or current physical, emotional, or mental abuse
Life stress or social disarray

Adapted from: Cannarella Lorenzetti R, Jacques CH, Donovan C, et al. Managing difficult encounters: understanding physician, patient, and situational factors. *Am Fam Physician*. 2013; 87:419-425; Breen KJ, Greenberg PB. Difficult physician-patient encounters. *Intern Med J*. 2010;40:682-688.

the patient may feel dissatisfied with care, diagnoses may be missed or made incorrectly as a consequence of the dysfunctional interaction, and discharge from the ED may occur prematurely by either the patient or provider. Following such encounters, the clinician is prone to experience frustration, exhaustion, a sense of failure or defeat, or fear of litigation. Also, nonconstructive patient stereotypes or unrecognized prejudices may develop or perpetuate.

The clinician brings personal and professional experiences, biases, individual personality traits, and interpersonal skills to every patient encounter. Some clinicians appear to have more difficult encounters than others, and similar interactions or patients may not be perceived as "difficult" by other providers. Clinicians who are more likely to have difficult patient encounters include those with fewer years of experience, who are less comfortable with diagnostic uncertainty, and may be less adaptable in communication style or acceptance of alternative lifestyle choices. Within the complex difficult patient encounter, the clinician has the greatest opportunity to positively alter aspects of their contribution to the interaction. When recognized, strategies exist to help the clinician manage negative reactions to difficult patient experiences (Box 185.8). Communication is a critical aspect of the patient

BOX 185.8 Tools for Managing Negative Reactions

Maintain Appropriate Emotional Distance
Avoid reciprocating hostile behaviors while maintaining a sense of empathy for the patient

Understand Negative Behavior as a Symptom
View the patient as a casualty of their own circumstances

Look for Cognitive Distortion
Be cautious not to overly stereotype or cloud clinical judgment and avoid perpetuating negative labels

View Negative Reactions in Context
Recognize when one feels overwhelmed by the expectations of the ED work environment to gain perspective on personal reactions

From: Cannarella Lorenzetti R, Jacques CH, Donovan C, et al. Managing difficult encounters: understanding physician, patient, and situational factors. *Am Fam Physician*. 2013;87:419-425.

encounter affecting medical care, patient satisfaction, and overall patient perception of the experience—some general concepts of communication can aid the difficult patient interaction (Table 185.3).

Specific Disorders

The primary characteristic of a difficult patient is the ability to trigger a negative emotional response or frustration in the clinician. Difficult patients are more likely to be older, widowed or divorced, and have more acute or chronic medical problems. They are more likely to have notable psychiatric, substance or alcohol use disorders, or social issues such as homelessness. Rather than a diagnosis or demographic, it is typically the behaviors of these patients and subsequent therapeutic dynamic that characterize the difficult encounter. Categorizing potentially difficult patients based on four common dominant behavior types—attention seeking, demanding, repeat visitors, self-destructive—allows a structure for the clinician to approach and manage challenges that may arise (Table 185.4).

Attention-Seeking Patients

This patient may have associated personality disorders (dependent, borderline, or histrionic), be malingering, or possess somatoform disorders or other chronic psychiatric diagnoses. The patient is characterized in part by an excessive need for attention with an initial extreme delivery of gratitude, which the clinician may welcome. However, as the amount of care that the patient receives grows, so do their needs and demands. This cycle continues to often leave the clinician frustrated and exhausted and eager to discharge or refer the patient to another health care provider.

When such patients are identified, the clinician should carefully establish reasonable expectations and limits before the "cycle of need" has set into motion. Importantly, these patients are especially likely to seek care in the ED during times of personal crisis. Structuring the encounter to be particularly attentive to the underlying crisis may provide the opportunity to address the underlying problem rather than the patient's perceived needs. This scenario is often encountered with patients exhibiting drug-seeking behavior.

Demanding Patients

Demanding patients can include very important persons (VIPs) or other well-informed successful professionals, substance abusers, or people with personality disorders, such as narcissistic or paranoid.

TABLE 185.3 Communication Strategies for the Difficult Patient Encounter

Goal	Physician Action	Example
Structure the interview	Set time limits and expectation that interruptions may occur	"Thank you for your patience. I may have to excuse myself to care for another patient, but if we are interrupted, I will return to pick up where we left off and provide you with the care you need."
Set limits	Establish ground rules for behavior	"We want to help you and your language and behavior is offending other patients—making it difficult to care for you and other patients. Please be mindful of your remarks or you may need to be escorted out."
Active listening to improve understanding	Allow the patient to talk without interruption, summarize concerns, and recognize that anger is usually a secondary emotion	"Help me to understand what is upsetting you so much right now."
Understand the patient's agenda	Nonjudgmentally inquire about the patient's primary needs, concerns, and expectations	"What is the most important thing that we can do to help you right now?"
Validate emotion and empathize	Disarm intense emotion by attempting to name the patient's emotional state and express concern and empathy	"You seem upset." "You are right. It is frustrating to wait a long time to be seen."
Redirect the interview	Avoid pursuing trivial, chronic, or tangential complaints by redirecting focus	"I think I can help you most right now if we focus on your main concern first."
Take a time out	Leaving a patient's room and returning after both parties have regained composure is prudent if unable to contain one's frustration	"Thank you for your openness. I need to step out, and I will be back to see what we can do to help you."

Cannarella Lorenzetti R, Jacques CH, Donovan C, et al. Managing difficult encounters: understanding physician, patient, and situational factors. *Am Fam Physician*. 2013;87:419-425; Breuner CC, Moreno MA. Approaches to the difficult patient/parent encounter. *Pediatrics*. 2011;127:163-169.

TABLE 185.4 Approaches to Challenging Patient Behavior Types

Patient Type	Characteristic of Physician Response	Suggested Strategies
Attention Seeking		
• Excessive need for attention and reassurance • May use helplessness and seduction • Worried about abandonment • Escalating requests and demands	• Physician may initially feel special and welcome the patient's praise • As patient demands increase and physician time and energy commitment increases, feelings of frustration, exhaustion, and resentment may dominate	• Recognize the inflated positive self-esteem feeling that is being cultivated • Maintain a professional demeanor • Establish and maintain boundaries of care early • Crisis intervention may be needed • Involve the patient in decision making including appropriate follow-up
Demanding		
• Uses intimidation, hostility, name dropping, blame, or threats • May refuse necessary steps of assessment or treatment • Behavior caused by fear of loss of power or physician abandonment	• Initial desire may be to engage in the patient's conflict • Physician may feel intimidated, inadequate, or fear litigation	• Resist urge to enter into conflict and avoid power struggles • Reinforce concept that the patient is entitled to reasonable medical care while setting limits on unreasonable demands and behavior • Allow the patient to choose between reasonable treatment options • If a specific emotion is evident, recognize and address it with the patient
Repeat Visitor		
• Excessive need for attention through multiple visits or unsolvable problems • Rejects the possibility that any treatment will help	• Physician may feel frustrated and overlook significant illness, but also may share the patient's pessimism and fear that serious illness has been missed	• Be mindful of cognitive distortions that may obscure real illness • Set limits on expectations while being supportive
Self-Destructive		
• Disregard for own health with repeated self-destructive behaviors • Feels helpless or hopeless about changing the situation	• Physician may feel frustrated, helpless, or guilty for lack of empathy • Physician may avoid being available for the patient and unconsciously provide poor care	• Be mindful of one's own feelings and keep appropriate emotional distance • Set realistic expectations and provide appropriate care • Search for signs of mental health or social needs and consider referral or consultation as needed

From: Cannarella Lorenzetti R, Jacques CH, Donovan C, et al. Managing difficult encounters: understanding physician, patient, and situational factors. *Am Fam Physician*. 2013;87:419-425, 2013; Breuner CC, Moreno MA. Approaches to the difficult patient/parent encounter. *Pediatrics*. 2011;127:163-169.

Their behavior is often hostile, intimidating, or threatening, and they may have endless needs and unreasonable demands. These patients fear being helpless in the context of their medical needs, and behaviors that have promoted success in their professional lives become maladaptive behaviors of entitlement to protect themselves from their own insecurity.

The behavior of these patients can evoke feelings of anger or antagonism and a desire to engage in debate and conflict. These power struggles are often counterproductive and only escalate the maladaptive behavior. A clinician can address the underlying insecurity and fears by maintaining a supportive relationship. Limit setting is important to curb escalation of unreasonable demands. Clinicians may preserve the patients' sense of autonomy and control in situations where they otherwise feel helpless by engaging them to participate in the selection of reasonable recommended options of care.

Repeat Visitors

This category is largely characterized by desperate and numerous repeat ED and other medical visits despite expressed certainty that past visits have been failures. Behaviors may appear entitled, manipulative, and self-defeating. These patients may have borderline or antisocial personality disorders and may be malingering. Their complaints are often vague and defy diagnosis, and clinicians may feel a sense of futility or failure. The behavior of these patients often stems from a need for connection and relationship in the setting of a fear of rejection and such patients are also at risk for unrecognized depression.

The clinician is at risk of both prematurely dismissing the patient's complaint due to a pattern of frequent visits and medical noncompliance or prematurely beginning an extensive investigation from fear that a critical diagnosis has been missed. Awareness of one's own cognitive distortions and personal biases can aid in avoiding inappropriate premature discharge, and seeking collateral information from previous medical records may reveal additional information that can help limit the evaluation and coordinate ongoing consistent medical care. Although clarifying expectations and limit setting are important, support and empathy can be particularly valuable in these encounters, as expressed lack of concern and dismissal of the patient's fears may feed an underlying sense of rejection within the patient, thus fueling the maladaptive behavior.

Self-Destructive Patients

These patients may appear hopeless, helpless, and in profound denial of their self-destructive and neglectful behaviors. These patients may be violent, chronically suicidal, suffer from substance abuse issues, or have a borderline personality disorder. Untreated anxiety or depression may be present. These patients may not personally seek help but instead are referred for care by others. ED care may result in addressing immediate needs (such as food or shelter), but despite adequate medical intervention, it is likely that the patient's often serious problems will persist.

These self-destructive patients can be challenging to treat because ED staff may feel frustration or even loathing or disgust toward the patient and minimize contact with them. Consequently, the treating clinician and others may unconsciously provide substandard care. By recognizing one's own feelings and setting realistic expectations of care, the ED care team can avoid poor medical care and may discover patient needs, including mental health conditions or crises or unrecognized social needs.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 185: QUESTIONS AND ANSWERS

185.1. Which of the following is a positive predictor of violent behavior in patients?

a. Age
b. Ethnicity
c. Gender
d. Level of education
e. Marital status

Answer: C. Identification of potentially violent patients is difficult, with male gender, prior history of violence, and drug or ethanol abuse the only positive predictors. Ethnicity, diagnosis, age, marital status, and education are not reliable identifiers.

185.2. Which of the following medications is associated with the highest incidence of sedation, hypotension, and anticholinergic symptoms?

a. Droperidol
b. Haloperidol
c. Loxapine
d. Molindone
e. Thioridazine

Answer: E. Antipsychotics can be divided into low potency (such as chlorpromazine and thioridazine), midrange potency (such as loxapine and molindone), and high potency (such as haloperidol and droperidol). The incidence of sedation, hypotension, and anticholinergic symptoms is highest in the low potency group.

185.3. Which of the following antipsychotic medications is associated with the highest incidence of extrapyramidal symptoms?

a. Chlorpromazine
b. Haloperidol
c. Loxapine
d. Molindone
e. Thioridazine

Answer: B. Antipsychotics can be divided into low potency (such as chlorpromazine and thioridazine), midrange potency (such as loxapine and molindone), and high potency (such as haloperidol and

CHAPTER 185: QUESTIONS AND ANSWERS—cont'd

droperidol). The incidence of extrapyramidal symptoms is greatest in the high potency group.

185.4. Which of the following disorders is best defined as a pattern of instability of interpersonal relationships, self-image, affect, and marked impulsiveness that begins by early adulthood and presents in a variety of contexts?

a. Antisocial personality disorder
b. Borderline personality disorder
c. Dependent personality disorder
d. Histrionic personality disorder
e. Paranoid personality disorder

Answer: B. Borderline personality disorder is a pattern of instability of interpersonal relationships, self-image, affect, and marked impulsiveness beginning by early adulthood and present in a variety of contexts. It may be indicated by five or more of the following:

1. Frantic efforts to avoid real or imagined abandonment
2. A pattern of unstable and intense interpersonal relationships characterized by alternating extremes of idealization and devaluation
3. Identity disturbance: Markedly and persistently unstable self-image or sense of self
4. Impulsiveness in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, or binge eating)
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior
6. Affective instability caused by a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and rarely more than a few days)
7. Chronic feelings of emptiness
8. Inappropriate, intense anger, or difficulty controlling anger (e.g., frequent displays of temper, constant anger, or recurrent physical fights)
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

185.5. A patient demonstrates inappropriate sexually seductive behavior while being interviewed by her physician. This characteristic is most consistent with which of the following personality disorders?

a. Antisocial personality disorder
b. Borderline personality disorder
c. Dependent personality disorder
d. Histrionic personality disorder
e. Paranoid personality disorder

Answer: D. Histrionic personality disorder is a pattern of excessive emotionality and attention seeking beginning by early adulthood as indicated by five or more of the following:

1. Discomfort in situations in which the center of attention is someone else
2. Interaction with others often characterized by inappropriate sexually seductive or provocative behavior
3. Displays rapidly shifting and shallow expression of emotions
4. Consistently uses physical appearance to draw attention to self
5. Has style of speech that is excessively impressionistic and lacking in detail
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion
7. Is suggestible (i.e., easily influenced by others or by circumstances)
8. Considers relationships to be more intimate than they actually are

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Multiculturalism, Diversity, and Care Delivery

Ava E. Pierce and Marquita S. Norman

KEY CONCEPTS

- Changing demography and an evolving culture in the United States are changing emergency medicine practice as disparities in health and health care delivery continue, despite efforts to improve care.
- Emergency department interventions should focus on social determinants of health, health literacy, and empowerment of patients to participate in their care.
- Treatment plans created with patients and based on what matters to them have the greatest opportunity for success.
- Emergency clinicians will improve the quality of care provided if they can meet federal standards for culturally and linguistically appropriate care, recognizing that patients with limited English proficiency have a right to medical interpretation.
- Culturally sensitive, patient-centered, and trauma-informed care will improve patient clinician communication and satisfaction, decrease medical errors, and promote patient follow-through with recommendations.

FOUNDATIONS

Background and Importance

In recent years, many high-profile incidents have put the role of multiculturalism, diversity, inclusion, and health equity in the forefront of public discourse. To obtain high-quality care, patients must first enter a health care system where many have experienced barriers to access based on race, religion, ethnicity, socioeconomic status, age, sex, disability status, language, sexual orientation, gender identity, and residential location. These issues highlight both the progress and challenges in understanding equity in society. As a microcosm of larger society within health care, the practice of emergency medicine (EM) should embrace a greater understanding and awareness of the roles of multiculturalism and diversity in the delivery of health care.

The population of the United States (US) continues to become more diverse. Women now comprise over half of the US population. By 2030, one in five Americans is projected to be aged 65 years and over. Minority groups (any group other than non-Hispanic White alone) are projected to become the collective majority as early as 2044, and almost one in five of the nation's total population is expected to be foreign-born by 2060.[1] As a specialty, EM is in a unique position to serve this diverse population. In many emergency departments (EDs), the majority of visits are with patients from minority backgrounds.[2] Emergency physicians routinely encounter patients from diverse cultural backgrounds representing various customs, practices or beliefs. All major national EM membership organizations now have policies and statements on diversity, inclusion, and equity. Policies on cultural awareness and emergency care focus on how emergency clinicians should consider the patient's culture, as it relates to history and presenting symptoms, in developing a treatment plan that is mutually agreed upon by the patient and physician. Statements also focus on beliefs and commitments to the goals of attaining equity, diversity, and inclusion in emergency medicine that reflects our multifaceted society. There is consensus around the development and promotion of education, research, and services that assist EDs in improving health for all, with a focus on eliminating health inequities.[3,4] To attain these goals, emergency clinicians must become culturally competent to meet the needs of diverse patient populations.

RATIONALE FOR CULTURAL COMPETENCE

Changing Demographics

Both the US population and the types of health problems seen by emergency clinicians are constantly changing.[5] According to US Census data from the 2018 American Community Survey, 14% of the US population identified as foreign-born.[6] Additionally, 28% of the population identified as other than "White alone" and 18% described themselves as Hispanic or Latino.[6] These changing demographics do not speak to the diversity within the various groups. The category Hispanic, for example, is an ethnic grouping counted in the race category of the census, but it fails to capture the significant range of diversity represented by Spanish speakers. Hispanics may share some cultural practices and speak similar versions of the Spanish language, but they have major differences in vocabulary and dialect, history, socioeconomic status, cultural identity, self-reference (Hispanic or Latino), levels of acculturation, health beliefs, habits, access to care, and health outcomes. The changing cultural landscape will challenge EM providers to recognize, account for, and address these differences when providing care for their patients.

Racial and Ethnic Disparities in Health Care Access and Outcomes

An overarching goal of the Healthy People 2030 Project is to "Eliminate health disparities, achieve health equity, and attain health literacy to improve the health and well-being of all."[7] Numerous studies find

that we are not meeting that goal.[5] When compared to Whites, racial and ethnic minorities have a lower likelihood of having a usual source of care, fewer physician visits, and fewer health expenditures. Hispanics and Blacks are less likely to initiate or receive mental health services when compared to Whites. Hispanics have lower health care use, including ED visits and outpatient mental health services, when compared to Whites and Blacks. Hispanic, Asian, and Black patients are less likely to have a consistent primary care provider.[8] With respect to unmet needs from ED visits, Black women fared the worst compared to men and women from White, Hispanic, and Asian backgrounds. Black patients are among the most disadvantaged of the racial/ethnic groups with a greater proportion impoverished, unemployed but looking for work, or in poor to fair health.[8]

Factors resulting in racial/ethnic disparities in health care contribute to differences in access to care. While these differences in access to care may correlate with access to financial resources or health insurance, other factors such as culture, language, and discriminatory practices may also contribute to these variations. Studies indicate that "implicit bias against Black, Hispanic/Latino/Latina, and dark-skinned individuals is present among many health care providers of varying specialties, levels of training, and levels of experience."[9] Reproductive biology and conditions specific to gender may also result in differences in health service use as it relates to gender.[8]

Tests and Treatments

Disparities in ED pain treatment persist a decade after identification of racial and ethnic differences in analgesic administration.[10,11] Studies indicate that provider bias may contribute to a skewed assessment of pain and therefore inadequate treatment.[12] Lee et al. reviewed studies from 1990 to 2018 comparing racial and ethnic differences in the administration of analgesia for acute pain and found that Black and Hispanic patients were less likely than White patients to receive analgesia for acute pain.[13] Goyal et al. found that Black children with appendicitis are less likely to receive any pain medication for moderate pain and less likely to receive opioids for severe pain, suggesting a different threshold for treatment.[14]

Racial and ethnic differences in provision of medically appropriate procedures and therapies have been documented. Wilder et al. found that Blacks and Hispanics were significantly less likely to receive any antidote when presenting to the ED for acute drug overdose.[15] Miller et al. found that a protocol-driven care pathway eliminates the racial disparity among Black and White participants with chest pain in the acquisition of index-visit cardiovascular testing.[16] Despite decades-old identification of these differences and regardless of the setting, health care disparities remain a real and pervasive threat to patient care, but studies indicate that protocol-driven pathways may help to decrease racial disparities.

Health Outcomes

Even perceived discrimination has a significant effect on health.[17,18] Thames et al. performed a cross-sectional bioinformatic analysis relating perceived discrimination (measured by the Perceived Ethnic Discrimination Questionnaire [PED-Q]) to the activity of proinflammatory, neuroendocrine, and antiviral transcription control pathways relevant to the conserved transcriptional response to adversity (CTRA) in peripheral blood leukocytes. They found that differential exposure to racial discrimination may contribute to racial disparities in health outcomes in part by activating threat-related molecular programs that stimulate inflammation and contribute to increased risk of chronic illnesses.[19]

Lee et al. evaluated the association between discrimination and leukocyte telomere length (LTL), a biologic marker of systemic aging. High discrimination was associated with shorter LTL after controlling for sociodemographic factors, health factors, depressive symptoms, and stress. Results suggest that discrimination experiences accelerate biologic aging in older African American males and females alike. This finding helps advance our understanding of how discrimination generates greater disease vulnerability and premature death in African Americans.[20]

Failure of Trust

Patients from minority communities have reason to be skeptical about the validity of medical research and appropriateness of medical recommendations. The legacy of Tuskegee, for example, has long been seen as the etiology of mistrust in the African American (AA) community. Lack of trust can result in failure to follow medical advice, arrange follow-up appointments, and obtain prescriptions.[21]

Higher levels of acculturation and lower levels of perceived discrimination are associated with higher levels of trust in health care providers. Patients often rate their physician interactions as longer, more participatory, and having more positive effects when their physician is of the same race.[22] For immigrants, shorter lengths of time spent in the United States and increased experiences with discrimination predicted increased distrust in the health care system. In one study, interventions aimed at the reduction of perceived discrimination reduced health care disparities in Korean Americans.[23]

SPECIFIC ISSUES

Communication and Use of Interpreters

Effective communication between patients and physicians is essential for improved health outcomes. There are over 300 languages other than English spoken in the United States. According to US Census data released in 2015, over 60 million Americans over the age of 5 years speak a language other than English at home, and 25 million speak English less than very well.[24] Patients with limited English proficiency are more likely to defer needed health services, leave against medical advice, miss appointments, fail to adhere to treatment regimens, lack a regular provider, and report poor health status.[25] Additional challenges faced by this diverse population with limited English proficiency include risk of increased medication errors, decreases in understanding medical conditions, and misdiagnosis resulting from the lack of physician understanding of complaints or patients' ability to effectively convey their symptoms.[26] The use of untrained nonprofessional interpreters (employees, family, friends, etc.) can result in patient confidentiality concerns and miscommunication due to oversimplification of medical problems or other interpretation errors, which potentially compromises quality, safety, and patient satisfaction.[27,28]

The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (The National CLAS Standards), last modified in October 2018 and published by the US Department of Health and Human Services Office of Minority Health, aim to improve health care quality and advance health equity by establishing a framework for organizations to serve the nation's increasingly diverse communities. Institutions and practitioners are required to provide for medical needs in a patient's primary language and in a manner compatible with the patient's health beliefs and practices. The overarching goal of the CLAS standards is to "provide effective, equitable, understandable and respectful quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy and other communication needs."[29] Health care institutions and providers are asked to collect data stratified by race, ethnicity, and language, and to institute quality improvement efforts when cross-cultural differences in outcomes of care, process indicators, or

BOX 186.1 Pitfalls in Language Communication Standards

- Use of family members, friends, or children
- Failure to translate documents such as consent forms and discharge instructions
- Lack of documentation of a patient's need for an interpreter or English language limitations
- Lack of documentation of the use of an interpreter and background and qualifications of the interpreter

patient satisfaction are detected. They are asked to develop culturally competent systems of care based on an assessment of the organization's mission, goals, policies, practices and services, staff training needs, and current diversity of the staff. After the assessment process, health care organizations must identify opportunities to improve the cultural competence of the organization and its delivery of health care services to a diverse population. At the top of the list is the improvement of interpreter services. Hospitals are asked to establish minimum performance standards for interpreters, which includes training in the culturally specific medical language and code of ethics.[29,30]

Standards and certification for medical interpreters are necessary to ensure consistency and quality.[31,32] As of 2019, every state and the District of Columbia had enacted multiple laws addressing language access.[33] The Joint Commission requires hospitals to provide professional interpretation services to every patient who needs it. The International Medical Interpreters Association recommends that standards cover interpretation, cultural interface, and ethical behavior.[34] Because the meaning inherent in the message is rooted in culturally specific beliefs, values, assumptions, customs, and norms, and language is itself an expression of culture, it may be necessary for a medical interpreter to go beyond a literal interpretation to explain unstated assumptions and find new ways of communicating untranslatable words or concepts. In addition to maintaining confidentiality, the medical interpreter has an ethical burden to uphold the trust of both parties and to assure them that the considerable power associated with the interpreter's role will not be abused, and that information will be faithfully conveyed without interjection of the subjective opinions and thoughts of the interpreter. Even with such qualified interpreters, the emergency clinician still needs to monitor the flow of the interview and, from time to time, clarify meaning and ensure understanding. This can be done by having the interpreter repeat what he or she thought the patient meant and asking the patient to repeat what the interpreter said. It is important to observe the interaction for phrase length as an indication of material not translated or added by the translator.

Finally, failure to meet language and communication standards in clinical scenarios can have financial implications. Professional interpreter usage has been demonstrated to have cost lowering effects resulting from decreased administration of intravenous fluids, unnecessary laboratory and radiologic testing, and admissions as a precaution.[27] In addition, the use of nonprofessional interpreters can yield medical malpractice claims resulting from harm caused because of language barriers. In a study of medical malpractice claims of a malpractice carrier that insures providers in four US states, researchers found that 2.5% of the carrier's total claims reviewed were related to language barriers resulting in patient death or irreparable harm. The study reported that the carrier paid $2.3 million in damages or settlements and $2.8 million in legal fees between 2005 and 2009. In 32 of the 35 cases, the health care providers did not use competent interpreters.[35] Box 186.1 lists common pitfalls in meeting language communication standards.

Disability and Accommodations

Overview

According to the World Health Organization (WHO), roughly 15% of the world's population (over a billion people) live with some form of a disability. Disability is defined as impairments, activity limitations, and participation restrictions of individuals with a health-related condition and their personal and environmental factors.[36,37] Increasing rates of disability are related to an aging population and increase in chronic conditions. All people with disabilities have basic health care needs requiring access to the mainstream health care services despite the diversity and complexities of the disability. According to the WHO, people with disabilities search for more health care options than people without disabilities and have greater unmet needs.[38] People with disabilities can be subject to prejudice and the resulting health disparities and poorer health care outcomes, similar to people from other stigmatized groups. They can experience many barriers in accessing health care, including factors such as prohibitive costs, limited availability of services, physical barriers to access facilities or treatment, and lack of knowledge and skills of health care workers.[38]

Patients living with disabilities present for a variety of reasons that may or may not result from their disability. The ED may be the first point of contact with the health care system and the visit may be the first presentation of a condition that could result in a disability or a complication arising from it.

The Hearing Impaired

Deaf and hard-of-hearing individuals over the age of 12 comprise 23% of the US population.[39] This group encompasses varying skills with spoken language, lip-reading, sign language, and written language. The level and type of skill usually depends on when in life the impairment occurred. For example, an individual with congenital hearing loss may be proficient in sign language, while someone with acquired deafness may be more proficient with written notes and may be less able to lip read.[40] Individuals whose language is American Sign Language (ASL) or another sign language face significant barriers to access to the health care system due to lack of health care sign language interpreters.[41] Although antidiscrimination legislation exists to protect the deaf community, persistent gaps in support and resources still exist that impacts accessibility for the hearing impaired. Communication barriers prevent deaf patients from being able to maintain strong patient-provider relationships with primary care. This can lead to overutilization of the ED and urgent care for routine health concerns.[41] Inadequate provision for sign language interpretive services can have legal, financial, and ethical implications. These consequences can include discrimination suits based on the American with Disabilities Act, breach of duty concerns in regard to patients' informed consent and their ability to participate in their health care, as well as professional conduct of health care providers as it relates to equitable patient-centered care.[40] The National Association of the Deaf (NAD) has outlined guidelines for health care providers to provide effective communication to deaf patients who communicate with sign language[41] (Box 186.2).

The Homeless

The homeless often encounter multiple barriers to accessing health care, yet they experience high levels of both chronic and acute medical problems. They are also disproportionately vulnerable to violence and injury and are at increased risk of premature death and disability.[42] Homeless individuals use the ED at higher rates, are more likely to have repeat ED visits, and are more likely to present via ambulance because of their lack of transportation than non-homeless persons.[43] Homeless individuals often use the ED for nonemergent medical needs because demands and costs for food, shelter, and safety supersede obtaining

BOX 186.2 National Association of the Deaf Communication Guidelines for Health Care Providers

- Clearly identify at-risk individuals for poor communication.
- Provide visual medical aids.
- Providers who know basic sign language can be beneficial but be aware of limitations.
- Establish an effective communication policy for the office or institution.
- Provide qualified sign language interpreters.
- Ineffective methods of communication are discouraged, including lip-reading or written notes.
- Be aware of effective communication approaches and resources.
- Make health care providers and staff aware of relevant laws and mandates that provide equal access and communication for deaf patients.

primary care. The high prevalence of concomitant substance abuse and psychiatric illness can make treating the homeless population more challenging. Homeless individuals have a significantly higher risk of opioid overdose and opioid-related ED visits and hospitalizations compared to low-income housed individuals.[44] This finding highlights the importance of recognizing the homeless population as high-risk for opioid overdose. Comprehensive discharge planning is required for homeless patients due to their comorbid psychiatric and substance abuse issues combined with their lack of consistent and safe shelter.

The ED presents a window of opportunity where early intervention strategies may be implemented to improve the health status of homeless patients. Intensive case management has been shown to reduce ED use and result in better health outcomes by connecting homeless patients with available community resources. Greater attention must be given to the hospital services that are provided to the homeless so that behavioral, environmental, and psychosocial needs are also addressed effectively and efficiently. Improved integration of health care facilities and shelters as overlapping systems of care may improve the quality of transitions of care and health care outcomes for homeless patients.[27] Caring for homeless patients in the ED requires attention to the social determinants of health[42] (see Chapter 189).

Prisoners

Prisoners have a higher incidence of physical and psychiatric disorders compared to the general population. The health disparity between prisoners and the general population has been attributed to socioeconomic and behavioral factors including increased rates of intravenous drug use, infectious diseases, alcohol abuse, and smoking, which have increased the risk of cardiovascular disease and some cancers. Approximately one in seven prisoners has a mental illness. Mental illness has been shown to increase the risk of crime and repeat offending. The disproportionate degree of physical and psychiatric disease in prisoners presents both unique public health challenges and opportunities for public health intervention. For many underserved individuals, prison provides an opportunity for diagnosis, disease management education, counseling, and treatment that they would not otherwise receive. Treating mental and physical illnesses of prisoners can improve public health.

Unfortunately, prisoners often have limited access to health care after release from prison.[27] Upon release from prison, the previously incarcerated return to their communities with their physical and psychiatric morbidity, occasionally untreated and sometimes worsened, creating additional societal burden within their communities. Psychiatric morbidity leads to increased suicide rates and contributes to repeat offending.

The Undocumented

Undocumented patients rely on the ED for a disproportionate degree of care due to barriers to health care access. For example, reliance on the ED for routine dialysis occurs because of ineligibility for Medicare and Medicaid, leading to increased mortality.[45-47]

Emergency clinicians should become familiar with strategies and resources that will impact the ED care of undocumented individuals. Also, strengthening ties with community-based organizations and medical legal partnerships can facilitate linking undocumented patients to social services and may help to facilitate successful discharge planning and follow up.

Understanding immigration status as a modifiable social determinant of health is a first step in improving the care and health of undocumented populations (see Chapter 189).

CULTURAL COMPETENCE

Appreciation of Different Beliefs, Values, and Experiences

The encounter between a clinician and patient is guided by perspectives dictated by cultural differences or similarities. Knowledge and awareness of those differences or similarities can often enhance satisfaction and health outcomes. A patient-centered approach to the clinical encounter requires the clinician to be carefully observant to sufficiently assess or even inquire about a patient's preexisting assumptions in order to provide culturally sensitive care.

Diagnosis of specific diseases can be interpreted differently depending upon differing cultural perspectives. For example, in African American and Puerto Rican communities, a cancer diagnosis may be perceived as fatal even if diagnosed at an early stage with a more favorable prognosis. As a result, patients may be more likely to avoid initial evaluation or choose no treatment when initially diagnosed. A health care provider who understands these health beliefs and concerns can work collaboratively with patients to provide health information in a format that the patient can accept.

Alternative healing systems have strong cultural roots. In the 2007 National Health Interview Survey (NHIS), approximately 38% of adults reported using complementary and alternative medicine (CAM) in the previous 12 months, with approximately 354 million visits to CAM practitioners and approximately 835 million purchases.[48] The National Center for Complementary and Integrated Health maintains an extensive database of literature on alternative healing methodologies in the United States.[49-52]

Folk medicine is too diverse for providers to know all possible practices, but emergency clinicians need to be aware of the more common folk therapies. For example, more than a few physicians have called social workers to investigate children with apparent bruises caused by coining, which involves vigorous rubbing of the skin with coins and warm oil (tiger balm) to release "bad wind" (reduce fever). These parents, who have attempted to help their children by using health care practices that are widely accepted in their communities of origin, feel accused, and the trust between the physician and family may be irrevocably lost. Similarly, herbal remedies can be effective or at least harmless, but they can occasionally be toxic, as in the case of clay ingestion by pregnant women, marijuana tea to treat asthma, and powders containing high concentrations of lead oxide to treat *empacho,* a condition in which it is believed that a substance (usually food or saliva) gets stuck to the walls of the stomach or intestines, causing an obstruction. Specific uses of folk medicine need to be elicited respectfully in a careful history and evaluated. Recommendations can then be presented nonjudgmentally, and alternative folk remedies that are benign can be prescribed along with needed allopathic medications.

The practitioner and patient will inevitably bring different beliefs and values to the medical encounter; the key to cultural competence is respectful negotiation of these differences without imposing the power of the physician's expertise, thereby protecting the patient's autonomy. If patients are satisfied, they will carry out follow-up recommendations and return to the ED in the future when they need emergency care.

Interpreting the Culture of Medicine for Patients From Diverse Backgrounds

There are inherent conflicts between the culture of western medical practice and the cultures of many patients. Physicians are experts in diagnosis and treatment of *disease*, the abnormal structures or functions of the human body (the pathophysiology of disease states). Patients, on the other hand, experience *illness*, a subjective feeling state that is interpreted through the lens of culture and has a personal and social meaning. The patient is an expert on his or her own illness and its effects on daily living, whereas a physician is expert on the effects of diseases on organ systems. Both ways of looking at the world have validity and a culturally competent approach recognizes both and works to integrate both perspectives for the best possible outcomes.

If patients with true disease remain asymptomatic or experience no alteration in functioning, they may be reluctant to accept a physician's diagnosis. On the other hand, a patient may be significantly, subjectively symptomatic in the absence of medical diagnosis, despite a thorough investigation. Concepts such as *susto* (fright), *coraje* (anger), and *fatalismo* (fatalism) are common cultural beliefs that manifest in physical symptoms. For example, *susto,* an illness recognized by Mexican Americans, causes listlessness, insomnia, depression, and anorexia, and is believed to be caused by exposure to a frightening experience. Treatment requires the patient to speak openly about the events that led to the susto, followed by bed rest and a ritual that includes prayers, incantations, and *barridas*—sweeping of the body with an egg, candle, or herbal tea. If these beliefs are not well understood by the health care provider, recommendations for treatment are likely to be discarded. As a result, the health care provider must develop trust with the patient. One useful approach is to engage a family member or *promotora* or *promotor* (community health worker) in the conversation.[53]

To be most effective, physicians need to investigate how patients view the causality of their illnesses and how they experience them to negotiate a therapeutic intervention. Exploration might take the form of comments and questions, such as, "Help me see through your eyes how you understand this problem," or "Have you or someone you know experienced it before?" The role of the physician is to accept the patient's experience as uniquely his or hers or, when possible, to reframe it in terms of medical knowledge. Then both physician and patient will be satisfied with the outcome of the encounter.

Every medical encounter is potentially a cross-cultural experience within this context and negotiation of the divide can be challenging for both patients and providers. Cultural competence involves reframing many of these unstated rules so that underlying circumstances and problems can be recognized and addressed. Circumstances may exist where patients may not feel comfortable sharing information with clinicians because of cultural, racial, sexual orientation, or language barriers. Vague complaints may be a sign of social stressors that result in mental health–related symptoms. These presentations may be further complicated by negative stimuli related to racial and ethnic discrimination.[54] People from minority cultures often experience significantly higher levels of daily stressors and there is mounting evidence that these types of negative encounters engender clinical depression and anxiety and contribute to hypertension and other medical sequelae.

Minority populations consume ED care at higher rates and are more likely to use the ED as a usual source of care.[55] Emergency clinicians must appreciate the context of their practice settings; recognize how rules, language, hierarchy and bias can potentially interfere with effective patient care; and work to provide care that is patient-centered and culturally sensitive. These actions can help create a safe environment for practitioners and patients who will experience higher levels of satisfaction with the care experience.

Combining Cultural Competence and Patient-Centered Care

Models for cultural competence and patient-centered care have evolved separately yet are closely aligned. The goal of both models is to improve the quality of the health care experience in a multicultural setting. Cultural competence involves providing equitable, evidence-based, high-quality care for diverse patient populations.[56] It requires the clinician to recognize and respect individual differences and the impact of individual interpretation on health, illness, and health care delivery. Patient and family–centered care is an approach to health care delivery that is a mutually beneficial partnership among the patient, family, and the health care team to address the planning, development, and assessment of the medical care.

Ideal health care systems incorporate the principles of both cultural competence and patient centeredness. A health care system built on patient-centered principles represents the heart of cultural competence—seeing the problem and solution from the point of view of the patient.[56] In 2015, the American Association of Pediatrics published a technical report which stated that "commitment to patient and family centered care ensures that the experiences and perspectives of patients and families guide the practice of coordinated and culturally sensitive care that promotes patient dignity, comfort, and autonomy."[57]

Medical education at the undergraduate, graduate, and professional levels about the impact of culture on health care encounters is a key component for the development of culturally appropriate health care and is a requirement for organizational accreditation. Students and residents in training consistently express greater levels of comfort in multicultural environments when they have had preparatory training. Training also helps students and residents understand that their own culture also affects clinical encounters and is equally participatory.

The Accreditation Council of Graduate Medicine Education (ACGME) and the Liaison Committee on Medical Education (LCME) have provided guidelines that graduate training programs and medical schools use to teach cultural competency through communication skills and professionalism.[27,58-59] The American Association of Medical Colleges (AAMC) also provides the Tool for Assessing Cultural Competency Training (TACCT) to assess cultural competency training in medical schools and provide medical schools and graduate medical education programs with a suggested rubric.[60]

According to the Emergency Medicine Milestones Project, patient-centered communication and professional values are assessed for every emergency medicine resident. This particular area addresses the learner's ability to elicit presenting symptoms from a diverse population of emergency department patients. Additionally, it assesses the learner's ability to communicate effectively with vulnerable populations. The professional values milestone requires learners to demonstrate cultural humility by providing compassion, integrity, and respect during patient care.[61]

RECOMMENDATIONS

Diversity among the ED patient population poses a challenge to emergency clinicians. Recognition of cultural differences, knowledge about diverse cultures, awareness of the health impact of cultural beliefs and practices, and sensitivity to patients' needs can reduce access barriers

BOX 186.3 Six Principles for Cultural Competence Standards and Expectations

1. Community representation and feedback at all stages of implementation
2. Cultural competency integrated into all systems of the health care organization, particularly quality improvement efforts
3. Ensuring that changes made are manageable, measurable, and sustainable
4. Making the business case for implementation of cultural competency policies
5. Commitment from leadership
6. Staff training on an ongoing basis

and improve clinical outcomes and hospital-community relationships while reducing the number of repeated visits and costs of health care. Diversity, inclusion, and health equity education also creates a rich environment for conceptualizing and researching health problems.

There are many opportunities for EDs and their institutions to improve their care of multicultural communities. These include plans to address problems related to lack of protocols for patient care and lack of resources for translation and cross-cultural interpretation. Cross-culture teaching guidelines and standards in medical education can correct false perceptions of culturally competent care such as negative impacts on flow and efficiency in the ED. Opportunities also exist to develop, recruit, and retain residents, faculty, and practitioners who are underrepresented in medicine in order to enhance multicultural patient care, opening the doors to community engagement.

Specific recommendations, based on the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care, have been proposed for pediatric emergency settings that can be applied universally. Institutions should use trained medical interpreters and should have a goal of employing a diverse workforce. Pharmacies are encouraged to label prescriptions and provide medical instructions in the patient's primary language. Administrators should post multilingual signs and ensure that handouts and forms are translated. Quality improvement programs should collect and analyze data and provide information to monitor outcomes based on race and ethnicity. Efforts should be made to expand minority enrollment in research studies and clinical trials to improve the validity and applicability of discoveries and new therapies.

The process of change for the development of culturally competent medical systems has been slow, but progress is occurring. Evolution of culturally appropriate environments for patients and their families has begun on all levels and, with the development of new standards and performance monitoring systems, assurance of established culturally competent systems will be an expectation. These expectations are important and tightly linked to safety and quality. The linkage of cultural competence to social justice broadens the depth of comprehension for the learner and provides opportunities for enhanced engagement with consumers and greater quality of care.

The process of creating a successful plan to move cultural competency from a theoretical model to one of action and implementation has been outlined in six principles that incorporate key points recommended by the IOM report of 2003 for systems aligned with new cultural competence standards and expectations (Box 186.3).

Essential cultural competence tools for providers include recognition of cultural differences, respect for individual opinions and perspectives about health and illness and, most importantly, ability and willingness to negotiate differences to offer the best opportunity for good health care outcomes. Culturally appropriate health care systems should be incorporated into EDs, which serve as the gateway to our health care institutions.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 186: QUESTIONS AND ANSWERS

1. Which of the following factors has not been identified as a health care disparity for minorities?
- **a.** High rates of no insurance or underinsurance
- **b.** Lack of prenatal care
- **c.** Likelihood of living in an area with adequate physician concentration
- **d.** Lower life expectancy when compared to white populations
- **e.** Relatively low number of minority providers

Answer: C. Minority patients are likely to live in impoverished areas with limited access to both primary and specialty medical care. As a result, they may present to the ED with previously undiagnosed medical problems underlying their symptoms.

2. Patients' cultural perceptions can have a significant impact on how they perceive their provider and the care they are receiving. Which of the following methods can be used by providers to approach different cultural perceptions so as to enhance the provider-patient relationship?
- **a.** Being aware of one's own cultural values
- **b.** Developing assumptions of cultural perceptions base on patients' ethnicity or race
- **c.** Limiting participation of alternative therapies and folk medicine in the patient's care plan
- **d.** Maintaining the role of the physician as the decision maker, even when it may conflict with the patient's autonomy

Answer: A. Being aware of one's own preconceived notions and biases is the first step a health care provider can take on the path toward developing cultural sensitivity toward patients from minority groups.

3. Which method of communicating is adequate to utilize with a deaf or hard-of-hearing patient?
- **a.** Certified interpreter
- **b.** Family member
- **c.** Lip reading
- **d.** Written communication on notepad

Answer: A. Using a certified interpreter for the hard-of-hearing is the only reliable way of communicating with such patients.

4. A helpful language translator can be essential in communication with a patient who is facing a language barrier. Which of the below methods are recommended for using an interpreter during a medical examination?
- **a.** Asking the patient to have friends or family translate discharge instructions for them
- **b.** Only obtaining an interpreter if the patient requests one
- **c.** Using a family member is appropriate as long as they are older than 18 years
- **d.** Using a trained medical interpreter
- **e.** Using health care staff members who are fluent in the patient's language

Answer: D. Using a certified interpreter is the only consistently reliable way of communicating with patients with language barriers.

5. Which of the following organizations have suggested guidelines to address cultural competence in educational standards?
- **a.** American Association of Medical Colleges
- **b.** Liaison Committee on Medical Education
- **c.** Accreditation Council on Graduate Education
- **d.** All of the above

Answer: D. These are just some of the medical organizations that have developed guidelines to assist medical schools and residency programs in teaching physicians-in-training to become culturally competent in their approach to patients from minority groups.

Human Trafficking

Wendy Macias-Konstantopoulos and Hanni Stoklosa

KEY CONCEPTS

- Labor and sex trafficking involve the exploitation of a person for labor or commercial sex, respectively, affecting up to 25 million persons worldwide.
- Human smuggling, a crime in which a person contracts a smuggler to facilitate their illegal entry into a country, can evolve into trafficking during transit or at the destination and under such circumstances the person is considered a victim of human trafficking.
- Child victims of sex trafficking are considered victims of child abuse and neglect under the law and thereby call into relevance state mandated reporting statutes.
- Populations at greater risk for trafficking include persons with histories of child abuse, family dysfunction, diverse sexual orientation or gender identity, intellectual disability, homelessness, financial insecurity, and migration.
- Human trafficking often involves the use of abusive and violent tactics, including forced substance use and psychological coercion to entrap and exert control over trafficked persons, with profound implications for survivors' physical, reproductive, and mental health.
- Trafficked persons seek health care services during their exploitation for a wide range of health conditions and the emergency department (ED) is the most common access point for this patient population where indicators of abuse, control, and the physical and psychosocial red flags of trafficking can assist in the recognition of trafficked victims.
- Inquiry about forms of interpersonal violence, including trafficking, is fundamentally different from screening for medical issues with the goal of providing a safe environment in which patients feel empowered to share as much or as little as they choose, and where strengths and resilience are recognized.
- Trafficked people may return to exploitative situations repeatedly before exiting permanently; therefore, safety planning is critical for the discharged trafficked patient.
- Trauma due to trafficking results in neurobiologic changes such that commonly occurring smells, sounds, sights, and procedures of the ED environment may be perceived as threats by those with trauma histories.
- The six principles of trauma-informed care include physical and psychological safety; trustworthiness and transparency; peer support; collaboration and mutuality; empowerment, voice, and choice; and cultural, historical, and gender acknowledgment.
- Law enforcement involvement should be limited to patient request, in state-specific mandated reporting scenarios, or when clinicians suspect imminent danger to staff or the patient.

FOUNDATIONS

Background and Importance

Human trafficking is an abusive and exploitative form of interpersonal violence. It is a global public health problem associated with a multitude of health problems. The United States (US) recognizes both labor trafficking and sex trafficking as "severe forms of trafficking in persons" punishable under federal and state laws. Under the US Trafficking Victims Protection Act (TVPA) of 2000 and its subsequent reauthorization acts, as amended (22 USC § 7102):

- *Labor trafficking* is "the recruitment, harboring, transportation, provision, or obtaining of a person for labor or services, through the use of force, fraud, or coercion for the purposes of subjection to involuntary servitude, peonage, debt bondage, or slavery," and
- *Sex trafficking* is "the recruitment, harboring, transportation, provision, obtaining, patronizing, or soliciting of a person for the purposes of a *commercial sex act*, in which the commercial sex act is induced by force, fraud, or coercion, or in which the person induced to perform such an act has not attained 18 years of age."[1,2]

Federal law assumes that persons under the age of 18 years performing commercial sex acts have been induced to engage in commercial sex and does not require that force, fraud, or coercion be proven for minors to be considered victims of sex trafficking. (Pursuant to Pub. L. 106-386, 114 Stat 1469 (2000), a commercial sex act refers to "any sex act on account of which anything of value is given to or received by any person.") Antitrafficking legislation since the TVPA of 2000 has focused further attention on prosecution, protection, and prevention of child trafficking. The Justice for Victims of Trafficking Act of 2015 authorized a range of provisions for combating trafficking and assisting victims, including an amendment to the Child Abuse Prevention and Treatment Act of 1988 by which the legal definition of *child abuse and neglect* was expanded to incorporate "sex trafficking" and "severe forms of trafficking in persons" involving minors.[3] Although mandated reporting statutes vary across jurisdictions, all states, the District of Columbia, and US territories mandate the report of suspected child abuse and neglect to the proper authorities.[4]

Finally, it is important for providers to understand that the law differentiates between human trafficking and human smuggling. Whereas human trafficking involves the exploitation of a victim for compelled labor or commercial sex, *human smuggling* involves a person contracting a smuggler to facilitate their voluntary and illegal entry into a country. Although human smuggling is a crime of migration committed against the state (not against a person), persons smuggled across international borders may be subjected to labor or sex trafficking during transit or upon arrival at their destination. Under these circumstances, their voluntary consent to smuggling does not render legal their subsequent entrapment in forced labor or commercial sex and such individuals are considered victims of the crime of human trafficking under federal law.[5] Understanding this distinction is important to educating victims about their legal rights and linking them to services where they can access the legal protections and redress to which they are entitled.

EPIDEMIOLOGY

Trafficking Typologies

The US Department of State has determined that human trafficking is an umbrella term that comprises a number of different forms of compelled service including forced labor, bonded labor (debt bondage), domestic servitude, sex trafficking, child sex trafficking, forced child labor, and child soldiering.[6] Exploitation of adults and children in the United States has been reported in typically formal labor markets (e.g., restaurant and hospitality, construction, agriculture, farming), informal labor sectors (e.g., domestic work, landscaping, traveling sales crew, peddling rings), and commercial sex industries.[7] In the United States, the illegal commercial sex economy may involve street-based commercial sex, brothels and cantinas, technology-facilitated rendezvousing, escort services, adult entertainment venues, child sex tourism abroad, live-streaming of child sexual abuse, and child and adult pornography.[7,8,9] Additionally, nail salons, massage parlors, health spas, and other unregulated bodywork businesses can serve as storefronts for both labor and sex trafficking.[7,9]

Global and US Prevalence

Prevalence estimates of human trafficking are historically wide-ranging and influenced by multiple factors. Data integrity and reliability are challenged by the clandestine nature of human trafficking, the failure to use a standardized definition of trafficking across organizations and countries, the focus of the data collecting agency (i.e., law enforcement versus social service agency, labor versus sex trafficking, adults versus minors), and the lack of centralization or even compatibility across databases. In 2016, the United Nation's International Labor Organization in collaboration with the Walk Free Foundation and International Organization for Migration (IOM) estimated that 24.9 million persons around the globe are trapped in forced labor, including sexual exploitation.[10] According to this study, women and girls account for 71% and children account for 25% of victims, and nonsexual forced labor comprises the majority of cases.[10] Centralized, reliable, high-quality data are needed to enhance our understanding of the scope of the problem globally and within individual countries.

Polaris, a US nongovernmental organization (NGO), has been monitoring human trafficking and operating the National Human Trafficking Hotline (NHTH) in the United States since 2000. Although reporting hotlines fail to capture all cases of trafficking, statistics from the national trafficking hotline offer relevant proxy data regarding the extent of the problem. According to published hotline statistics, nearly 52,000 *situations* of human trafficking involving one or more victims were identified across the US and US territories between December 2007 and December 2018.[11] In 2018 alone, the NHTH identified over 23,000 individual survivors of human trafficking, 64% of whom were survivors of sex trafficking, 24% labor trafficking, and 6% both forms of trafficking.[12]

Demographics of Trafficked Persons

Within the subset of tip calls received by the national hotline for which survivor demographic data are available, the majority of survivors are adults (≥18 years), female, and Latinx. Extrapolation from the limited data suggests that the average age (mode age range) at the onset of trafficking was 25 (15–17) years old for labor trafficking and 18 (15–17) years old for sex trafficking.[12,13] Given the challenges in collecting comprehensive and accurate information, demographic data from identified and reported cases in any local or national database may not accurately reflect the overall demographics of US trafficked persons.

Although human trafficking can affect persons of any age, gender identity, sexual orientation, ethnicity, race, citizenship, socioeconomic standing, religion, and physical or intellectual ability, certain populations are at greater risk for trafficking. Circumstances that place individuals at risk for trafficking are those that increase their dependence on others to meet their basic needs or obtain something of value. Box 187.1 lists factors associated with increased vulnerability to human trafficking.[12,14-29]

BOX 187.1 Factors Associated With Increased Vulnerability to Human Trafficking

- Child abuse and neglect, particularly sexual abuse
- High levels of adverse childhood experiences
- Caregiver strain and conflict or family dysfunction related to a wide range of potential factors:
  - Domestic violence
  - Family sex work
  - Parental substance use
  - Mental health problems
  - Sexual or gender identity diversity
- Use of children for forced labor
- Exposure to criminality and transactional sex
- Involvement with child protective services and/or law enforcement
- Substance use
- Teen pregnancy
- Intellectual disabilities
- Running away or being thrown out of the home
- Homelessness (particularly relevant to sexual or gender identity diverse youth)
- Financial insecurity or poverty
- Migration

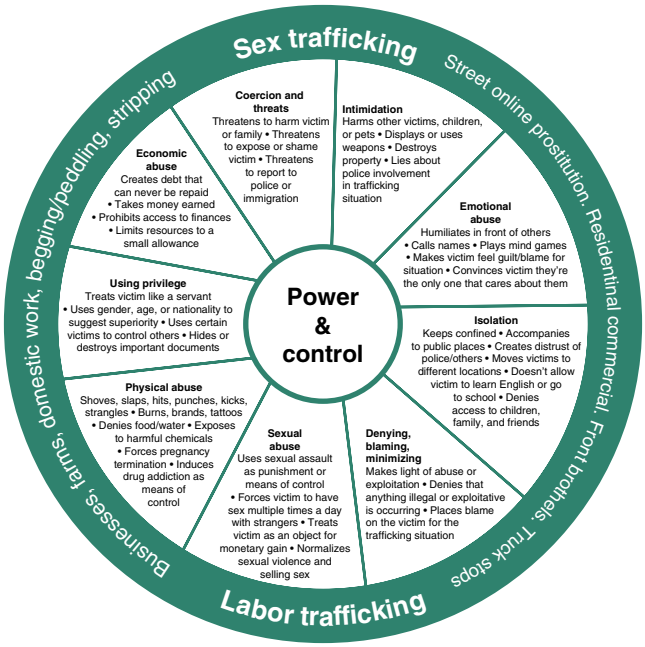

Fig. 187.1 Polaris Human Trafficking Power and Control Wheel. (Adapted from Polaris and available for download at https://humantraffickinghotline.org/resources/human-trafficking-power-and-control-wheel.)

Recruitment and Control Tactics

Traffickers entrap and maintain control over victims of human trafficking in multiple ways. Figure 187.1 summarizes the constellation of methods used, which often extends to financial disempowerment,

debt bondage, coerced involvement in illegal activities, blackmail, and a host of other criminal tactics.[14,15,30]

According to 2018 NHTH data, the top *labor trafficking* recruitment methods used, in order of reported frequency, included false job offers or advertisements, false promises/fraud, smuggling-related initiation, coercion, and familial inducement.[12]

In nearly 12,000 cases of *child trafficking*, data from the Counter-Trafficking Data Collaborative suggest that children are most commonly trafficked by family members (41%), intimate partners (14%), and friends (11%) by means of psychological abuse (24%), physical force (16%), sexual violence (10%), and substance-related coercion (9%).[31]

IMPACT ON HEALTH

Traffickers often employ abusive and violent tactics to exert and maintain control over victims in order to effectuate the crime of human trafficking. These tactics have profound implications for the health of trafficked individuals, leading to physical, reproductive, and mental health problems. Accidental (occupational) and intentional (violence-related) traumatic injuries occur during trafficking as a result of the physical demands of manual labor, lack of personal protective equipment, hazardous working conditions, and physical and sexual violence.[17,32] Sex trafficking survivors and labor trafficking survivors experiencing sexual violence are at elevated risk for sexually transmitted infections (STIs) including human immunodeficiency virus (HIV) infection, pregnancies, and terminations.[17,33-36] In addition, trafficked persons may experience control through induced debilitation, specifically food and sleep deprivation, coerced substance use, and confiscation of needed medications or medical supplies.[30] The abuse and violence endured while trafficked can result in depression, anxiety, posttraumatic stress disorder (PTSD), dissociative states, psychosomatic pain syndromes, substance use, self-injurious behavior, and suicide attempts.[17,25,33-42]

Substance use, mental illness, and pregnancy merit special consideration given the unique degree of vulnerability conferred on victims. These health conditions can create or exacerbate relational imbalances of need and dependency that traffickers can exploit to subvert victims. When caring for patients with these conditions, providers must consider the possibility of the trafficker being a family member, intimate partner, or friend.

Substance Use

Research has established a correlation between substance use and human trafficking. A retrospective chart review of 12- to 18-year-old victims of sexual violence found that drug use rates were significantly higher among commercially sexually exploited and trafficked youth compared to sexually abused and assaulted youth.[19]

The complex relationship between substance use and human trafficking has been increasingly recognized and understood. Substances can play a key role throughout the various stages of trafficking, including in the recruitment, entrapment, and exploitation of victims. Highly addictive substances (e.g., opioids, stimulants) provide a relatively easy opportunity for traffickers to entrap experimenting adolescents and young adults by exploiting newly evolving addictions. In cases where the trafficker is someone close or known to the individual being targeted for recruitment, the trafficker may be the person who introduces the addictive substance and encourages its use with the intent of creating a vulnerability to exploit. Similarly, previously formed addictions offer traffickers a mechanism through which they can entrap individuals with addiction for the purpose of exploiting them.

In addition to facilitating recruitment and entrapment, victim accounts suggest substances may play a central role in maintaining control over trafficked persons. In some cases, traffickers force drug-naïve victims, particularly adolescents, to use substances as a means of weakening their defenses and creating an addiction that can be leveraged to exert control over them during their exploitation.[43] In other cases, the trafficker may simply ensure substances are available and trafficked persons may initiate use on their own as a way to cope with the physical and emotional trauma of their trafficking situation. Victims' reliance on substances to numb their pain and cope with the anxiety, depression, and PTSD related to their everyday experiences while trafficked creates high levels of dependence on the trafficker for access to the drug.[44] Traffickers are thus able to exert and maintain control over trafficked individuals by regulating the type (drug class), manner (route of administration), and extent (dosage and frequency) to which the substance is available to them.

Mental Illness

In addition to mental health disorders potentially heightening risk for trafficking, the traumatic experiences endured by victims while being trafficked may induce or unmask mental health disorders. Trafficking may exacerbate preexisting mental health disorders and lead to increased frequency or severity of psychiatric manifestations.[45] In a historical cohort study of trafficking survivors receiving mental health services in the United Kingdom, the most commonly encountered diagnoses in the adult sample included 34% affective disorders; 28% PTSD, severe stress, or adjustment disorder; 15% schizophrenia and related disorders; and 22% intentional self-injurious behaviors.[45] Similarly, 27% of the youth in the study were diagnosed with affective disorders and another 27% with PTSD, severe stress, or adjustment disorder. Among youth, 27% exhibited intentional self-harm while in care.[45] In a US study among court-involved commercially sexually exploited female youth, 88% endorsed substance use, 76% identified with having a mental health problem, 43% reported previous psychiatric admissions, and 14% reported suicidal ideation.[46]

Anecdotally, traffickers can use a victim's mental illness to remain undetected. A trafficked person who presents to an ED providing accounts of seemingly unrealistic events may be erroneously assumed to be suffering from acute paranoid delusions, persecutory delusions, or hallucinations. Any inconsistencies in their accounts might even raise suspicion among providers of malingering for secondary gain rather than memory gaps related to trauma.[47] Subsequent attempts to obtain assistance in the ED may be misdiagnosed as episodes of acutely decompensated psychiatric illness rather than real life events related to being trafficked. In this manner, traffickers can continue their abuse and control with less concern that the veracity of a victim's report will be investigated.

Pregnancy

Trafficked adolescent and adult women often experience decreased ability to negotiate condom use during transactional sexual encounters,[33,44] as well as decreased access to family planning services and prenatal care.[39,48] Decreased reproductive control and diminished access to family planning services theoretically increases the likelihood that trafficked women may present to an ED for such services (e.g., counseling about alternative discrete forms of contraception, STI screening and treatment, HIV counseling and testing, and emergency contraception). Moreover, lack of access to prenatal care is associated with adverse pregnancy outcomes, including insufficient gestational weight gain, premature rupture of membranes, and precipitous labor,[49] and these outcomes may be at play among trafficked women who present to the ED in the later stages of pregnancy seeking to either initiate prenatal care or deliver.

For trafficked adolescent and adult women, desires to carry or terminate a pregnancy are influenced by the circumstances of their trafficking situation, but such decisions may be unduly influenced by traffickers. As in intimate partner violence, pregnancy also carries an increased risk of trafficker-perpetrated abuse and violence,[44] which in turn is related to increased risk of preterm labor, small-for-gestational-age infants, postpartum depression, and decreased likelihood of breastfeeding.[50,51] Pregnant and postpartum women who present to an ED for violence-related injuries should be queried about other potentially exposed children. Limited evidence suggests that traffickers may use pregnancy and children (e.g., threats of forced abortion, threats to take away children, threats to cut off financial support) to exert and maintain control over their mothers.[14,18,48,52]

Little is known about the experiences of trafficked women's children in the United States. An exploratory study in 2016 found that children of sex workers or trafficked mothers experience significant health risks and outcomes, including behavioral and mental health problems, physical and sexual abuse, the use of cough medicine, alcohol, and other sedating substances to induce sleep, death from a wide range of causes including neglect (e.g., exposure after being left in a car, house fire after being left home), untreated HIV, poisoning, overdose, lethal physical abuse (e.g., abusive head trauma, previously *shaken baby syndrome*), and gang-related murder.[48]

SPECIFIC ISSUES

Recognition and Assessment

Indicators and Red Flags

While indicators and red flags of trafficking can assist in the recognition of possible trafficking, there is no single characteristic that is pathognomonic of human trafficking. Although there are certain segments of the population at higher risk for trafficking, the overall sociodemographic characteristics of trafficked persons are wide-ranging, and no two experiences of trafficking are exactly alike.

Currently there is no defined set of signs and symptoms that cuts across all forms of human trafficking with any sufficient degree of sensitivity and specificity to employ for the identification of victims in the ED. Familiarity with general indicators of abuse and control and the red flags of human trafficking can help elevate a suspicious situation into the level of awareness (Table 187.1).

Indicators of abuse and control can include the presence of an accompanying person who is reluctant to leave the examination room, insists on answering questions or providing language interpretation, and attempts to control the encounter; combined with a patient who appears fearful or anxious, defers information sharing to the person accompanying them, and frequently glances at the accompanying person for evidence of approval after speaking.[35,36,53] Other potential indicators include patient communications that seem rehearsed or scripted, patient reluctance or inability to answer simple questions about their living or working situation, conflicting information, reported mechanism of injury inconsistent with the physical evidence, and evidence of psychological distress (e.g., limited eye contact, low trigger threshold, hypervigilance, hyperstartle reflex).[36,53]

Physical red flags of human trafficking include delayed presentation for care of injuries or infections; signs of abuse or neglect (e.g., malnourishment, poor oral health); work injuries or exposures that would be easily prevented by personal protective equipment (PPE); intravaginal foreign material to interrupt menstrual flow; delayed presentations for prenatal care; distinctive tattoos or other forms of branding; and multiple STIs, pregnancies, or abortions.[35,36]

Psychosocial red flags of human trafficking include a reluctance to expose or explain a tattoo or marking; unusually high numbers of sexual partners at an early age; truancy and absenteeism from school at certain hours of the day; chronic running away from home; multiple fake forms of identification; lack of identification or immigration documents; long work hours without breaks; limited access to PPE; living in overcrowded quarters; and weather-inappropriate clothing.[36,53]

Trafficking Inquiry

While it is routine in medical care for multiple providers to ask a patient their history, retelling of a traumatic event can be inherently retraumatizing. Concerted efforts to minimize the number of times a patient recounts their history can be conducive towards a feeling of safety. Furthermore, when there is concern for trafficking, the goal of a clinical encounter is not for the patient to disclose victimization, but for providers to treat, educate, and empower the patient.

Inquiry around forms of interpersonal violence, including trafficking, is fundamentally different from screening for medical issues. Rather than disclosure, the goal of inquiry is to provide a safe environment in which patients feel empowered to share as much or as little as they choose, and where their strengths and resilience are recognized. Inquiry-based assessment is an active process that includes open-ended questions and dialogue.[54] The context around which questions are asked, especially for issues where a trafficked patient may feel emotionally and physically unsafe (due to shame, judgment, threats of deportation, etc.) modulate how much a patient may feel comfortable

TABLE 187.1 Potential Trafficking Indicators and Red Flags

Physical	Relational	Other
• Delayed presentations to care • Signs of physical, sexual, or dental trauma • Signs of neglect • Signs of malnourishment • Substance use • Multiple recurrent STIs • Foreign bodies to stop menstrual flow • Multiple previous pregnancies • Work injuries preventable with training and/or personal protective equipment • Tattoos or branding indicating ownership	• Accompanied by a person who attempts to control the encounter • Accompanied by a person who insists on translating • Scripted or restricted patient communications • Patient frequently glances to the accompanying person for approval after speaking • Patient avoids eye contact with accompanying person and/or provider • Other signs of submission, fear, or hypervigilance • Distrust of authority	• Difficulty answering simple questions (e.g., name, age, home address, work, current location) • Apparent vs. reported age discrepancy • Discrepancy between history and clinical presentation • Possession of multiple fake IDs or numerous hotel keys • Inappropriate clothing for weather • Truancy or absenteeism from school at certain times of day • Not in possession of identification or immigration documents • Excessive work hours • Possession of large sums of cash or payment in cash

Revised/adapted from Macias-Konstantopoulos W. Human trafficking: the role of medicine in interrupting the cycle of abuse and violence. *Annals of Internal Medicine*. 2016;165(8):582-8.

disclosing at a given point in time.[55] In contrast to inquiry, screening is a "process for evaluating the possible presence of a particular problem" and "the outcome is normally a simple yes or no."[56] Screening for trafficking through a checklist approach may unintentionally retraumatize the patient by triggering the patient's traumatic memories.[57] The only trafficking screening tool that has been validated for use in the pediatric ED is limited to English-speaking 13- to 17-year-olds who have been sex trafficked.[58] The Rapid Appraisal for Trafficking (RAFT) is a validated 4-item trafficking screening tool for labor and sex trafficking of adults in the ED.[58a]

Although evidence exists to support universal inquiry in domestic violence, the extant trafficking literature offers no evidence in support of this. Based on current evidence, trafficking inquiry may be focused on high-risk populations and patients exhibiting red flags. That inquiry may follow trauma-informed frameworks, such as the Privacy, Educate, Ask, Respect, Respond (PEARR) tool.[54] It should be noted that perception of red flags may be influenced by a provider's unconscious and conscious bias.[59] For example, if a clinician views trafficked persons as Caucasian, cis-gendered, and sex trafficked, they may miss an obvious case involving a labor trafficked Black transgender male patient who presents to their ED.[59a]

Use of Professional Interpreters

If the patient speaks a foreign language, emergency providers should use professional interpreter services. Accompanying persons (e.g., friends, relatives including children, or others) may unintentionally compromise confidentiality and even be a trafficker or trafficker's associate. Remote telephone interpretation services may be preferred in certain circumstances including if a potential trafficked person is from a small ethnic group where the interpreter's ties to the local community could pose a risk for a trafficked person.[60]

Evaluation and Treatment

The ED care of a trafficked person involves providing appropriate emergency medical care for the chief complaint, while respecting the patient's goals for the encounter. ED evaluation may include addressing acute medical issues, evaluation of possible untreated chronic medical problems, documentation of acute and remote injuries, STI testing and treatment, and consideration of a sexual assault medical forensic examination and evidence collection. For both labor and sex trafficking, empirical STI treatment and emergency contraception may be indicated.[60]

When a case of suspected human trafficking has been identified, a sexual assault medical forensic examination may be clinically appropriate. Research shows that the use of sexual assault or forensic nurse examiners results in better patient outcomes in legal and emotional support. To the extent that the resource is available, EDs may preferentially offer this service or consider transfer to a crisis center.[60]

Trauma-Informed Approach to Care

Studies of trafficked persons have demonstrated the critical importance of using trauma-informed approaches to care.[59,61] The Substance Abuse and Mental Health Services Administration (SAMHSA) defines trauma as "an event, series of events, or set of circumstances that is experienced by an individual as physically or emotionally harmful or life threatening and has lasting adverse effects on the individual's functioning and mental, physical, social, emotional, or spiritual well-being."[62] Trauma results in neurobiologic changes such that commonly occurring smells, sounds, sights, and procedures of the ED environment may be perceived as threats by those with trauma histories, including trafficked persons. For example, a patient who appears to be uncooperative, avoidant, jumpy, or agitated, may instead be manifesting a natural "fight," "flight," or "freeze" stress reaction.[63]

Sincere, empathetic, nonjudgmental communication is the foundation of trauma-informed care. This includes clinician awareness and mitigation of conscious and unconscious biases, including their manifestation in body language and word choice, in order to prevent retraumatization of trafficked persons.[59,63,64] Loss of control is a major part of the trafficking experience and the medical environment can exacerbate those feelings. Therefore, emergency clinicians should look for and offer choices when possible, helping the patient regain a sense of autonomy. Clear communication about the clinical team composition, the care plan, events to expect, and possible timeline, allows a trafficked patient to feel a sense of control.[59,63,64]

Helping a traumatized patient to feel safe and calm includes a mindfulness of a patient's stress reactions, including demeanor, speech, and even pulse rate. When these reactions are observed, clinicians may respond using psychological first-aid techniques of connectedness, calmness, safety, structure, self-efficacy, and hope (Fig. 187.2).[63] Potentially triggering environmental factors could include the visibility of security guards who may remind the patient of prior traumatizing law enforcement experiences. Trauma-informed approaches are especially important for the agitated patient with an experience of trauma. Beginning with de-escalation and psychological first-aid techniques can mitigate retraumatization and should be balanced with staff safety concerns. If restraints are necessary for the safety of the patient and staff, use of the least restrictive measures possible is recommended.[63]

The Privacy, Educate, Ask, Respect, and Respond (PEARR) tool provides a trauma-informed framework for the clinician assessing any form of interpersonal violence, including human trafficking.[54] The first step of the PEARR tool is to find a place to speak to a patient alone, explaining any limits to confidentiality with the patient before beginning this sensitive discussion. The clinician attempts to educate the patient regarding abuse, neglect, or violence in a nonjudgmental and normalized manner, and then asks about the patient's personal experience. The patient may or may not disclose their exploitation experience at this point in time. The final step involves ongoing respect of the patient's wishes and responding according to their goals. It is common for patients experiencing interpersonal violence, including trafficking, to choose to return to their exploiter. If a patient denies victimization or declines assistance, and there are persistent concerns about abuse, neglect, or violence, then the clinician may offer the patient information about resources that can assist in the event of an emergency (e.g., local service providers, crisis hotlines).

Multidisciplinary Response

Establishing multidisciplinary protocols inclusive of labor and sex trafficking and involving internal and external resources allows clinicians to respond to a trafficking disclosure in a safe, trauma-informed manner. In addition to a myriad of acute and chronic medical and mental health needs, trafficked persons may also require assistance with substance use treatment, housing, vocational, and legal needs. Response protocols will vary considerably based on a clinical practice setting. The majority of health care institutions already have protocols in place that address various forms of violence including intimate partner violence, child abuse, elder abuse, and sexual assault. Human trafficking responses may be incorporated into existing interpersonal violence protocols to streamline training, treatment, and referral processes.[60,65,66]

Breaches of privacy may harm the provider-patient relationship, compromise patient autonomy, and produce distrust among other trafficked persons. Therefore, EDs and health care institutions may consider establishing memorandums of understanding with external partners, including limitations of HIPAA, and need for patient consent for information sharing. If case management is not available, the patient may

Goals	Useful statements or actions
Connectedness	Assign a single team member to be the primary source of communication with the patient: "I am going to stay and help you with everything you go through here." For pediatric patients, if feasible, allow parental presence and support.
Calmness	Minimize presence of non-participatory members of the care team. Avoid excess noise/chatter. Encourage the patient to perform slow breathing exercises.
Safety	Provide patient a simple reminder that he or she has been removed from the site of injury: "You are in the safest place you could be right now."
Self-efficacy	Discuss care plan with patient to diminish sense of loss of control. Use language that acknowledges rather than undermines the patient's defense mechanisms; for example, "You are going through a tough situation" rather than "Tough it out." If feasible, allow patients to provide input into decisions about care. Identify resources (e.g., case management, community organizations) that can facilitate
Hope	Avoid statements that may exacerbate patient feelings of self-blame. Provide realistic statements of expected positive outcomes: "It will not be easy or fast, but I expect you will recover from your injuries."

Fig. 187.2 Statement or action examples grounded in psychological first-aid principles. (Adapted from: Fischer KR, Bakes KM, Corbin TJ, Fein JA, Harris EJ, James TL, Melzer-Lange MD. Trauma-informed care for violently injured patients in the emergency department. *Annals Emerg Med*. 2019 Feb 1;73(2):193-202.)

be encouraged to contact a local or statewide hotline or the National Human Trafficking Hotline to learn more about available resources.[60]

DISPOSITION

Admission versus Discharge

As with all admissions, the decision to admit a trafficked person should be made in a clinically grounded, patient-centered manner. The reason for admission may be medical; in some cases, health facilities may permit a "social" observation admission in order to carry out complex case management to facilitate a trafficked person's exit from exploitation. As with intimate partner violence, not all trafficked persons recognize or are ready to leave their exploitative situation. This happens for a variety of reasons, including fear of retribution, fear of endangering loved ones, threats of police or immigration involvement, blackmail, as well as trauma bonds. Clinicians may consider utilizing motivational interviewing techniques based on the Stages of Change model to engage the patient and provide support in the decision-making process (Box 187.2). Ultimately, trafficked persons are most knowledgeable about the potential risks involved with seeking help or beginning the process of leaving the trafficking situation and respecting their wishes aligns with trauma-informed care principles.[60]

Safety Planning

Trafficked persons may return to exploitative situations repeatedly before exiting permanently. Involving social workers, case managers, and advocates early in suspected cases of human trafficking helps facilitate safety planning for a patient who is not ready to commit to leaving. Safety planning involves assessing for potential future health risks and identifying strategies for avoiding or reducing the threat of harm when safety is threatened. Safety planning facilitates a sense of trust and safety with the health system and encourages patients to return when ready to access services or for further medical care.

Safety planning varies greatly depending on how the patient views their trafficking situation and whether the patient wants to stay in the situation, is in the process of leaving, or has left.

BOX 187.2 Stages of Change

Stage 1: Precontemplation—Feeling there is no control of your situation
Stage 2: Contemplation—Wondering if there might be a way of managing your situation
Stage 3: Preparation—Researching and planning ways to manage your situation
Stage 4: Action—Taking steps to manage your situation
Stage 5: Maintenance—Continuing positive steps and learning new strategies to maintain your new situation

Important determinants in assessing risk include the patient's level of fear and his or her own appraisal of both immediate and future safety needs. The following indicators of escalating lethality risk may be explored with the patient: an increase in the frequency or severity of threats or assaults; increasing or new threats of homicide or suicide by the trafficker if the patient discloses; the presence or availability of a firearm or other lethal weapon; and new or increasingly violent behavior by the perpetrator, including strangulation.[68]

Resources

A follow-up appointment can be a helpful component of safety planning for trafficked persons. This can take a variety of forms, depending on institutional resources, including arranging for an outreach worker (public health nurse or community health worker) to make a follow-up visit or returning to see the ED social worker. The means of conveying post-discharge resources will vary based on the patient's situation; clinicians may consider providing resources verbally to patients or through discrete messaging, while the patient is alone. Examples of discrete resource sharing include writing the human trafficking hotline number on a business card or on a sanitary napkin. Many patients will not be able to leave with written information because their belongings are monitored.

Resources to consider sharing with potential victims of trafficking include information about the National Human Trafficking Hotline which can be accessed 24/7 by texting "INFO" or "HELP" to BEFREE

(233733) or calling 1-888-373-7888 for information or help, though patients should be reminded that smartphones provided to them by the exploiter may be monitored. Other potentially helpful resources include a health system contact number to call or text if the patient wants further assistance; a referral and resource list from community partners for such needs as food, clothing, shelter, housing, social services, and legal services; and an address of local police departments should patients find themselves in imminent danger. Confirming with patients that it is safe for them to take such material with them can signal to patients that the clinician understands the potential gravity of their circumstances. The clinician may discuss with the patient the safest way to communicate with them and carefully consider whether it is safe to contact the patient for follow-up.

Some patients may be unwilling or unable to return for ongoing or follow-up care. For this reason, on discharge the clinician could consider explicitly reassuring patients that they deserve to be safe and free from abuse, that they are not to blame for their circumstance, and that the health care system is "always open" as a source of safe, confidential, and supportive care.[60]

SPECIAL CONSIDERATIONS

Mandatory Reporting

Notably, many human trafficking situations do not fall under mandated reporting requirements. Depending on the state, there may be components of a trafficked person's experience that fall under mandatory reporting laws for abuse of children, disabled adults, and elders; injuries resulting from burns, firearms, or knives; or threats of imminent harm to oneself or another. In certain states, mandatory reporting of sexual assault, domestic violence, or strangulation may come into play. These reporting requirements should be built into institutional human trafficking protocols. Mandated reporting can be executed in a trauma-informed manner, including explaining limits of confidentiality prior to a patient's disclosure, and if a disclosure is made, explaining why reporting is necessary, soliciting patient input into what information will be given to authorities and offering to have the patient present for the conveying of information.[60]

Medical Record Documentation

Because of the complexity of medical-legal issues around human trafficking cases, and great variation in state and local laws, institutions may consider consulting with local prosecutors, defense attorneys, and advocates, particularly those with expertise in privacy and rape shield laws when establishing documentation guidelines.

Depending on the legal climate, entering more or less information in the patient's chart can either be helpful or harmful. In some cases, accurate documentation can potentially substitute for, or supplement, the clinician's personal testimony in court. Alternatively, information in the medical record can potentially be harmful to the patient when the case goes to trial (e.g., if a trafficked person contracts HIV, in some states they could be criminalized for the transmission of HIV). In many jurisdictions, crimes committed by trafficked persons while under the control of their trafficker will be prosecuted (e.g., a patient coerced to sell sex may still be charged with prostitution). Sensitive information in the medical record may or may not be redacted during a court hearing or trial depending on whether the state has a rape shield law, and if that state has determined that the rape shield law applies to trafficking victims. It may be difficult to balance the need for inclusive information with medico-legal discretion. For example, obtaining information about prior injuries, consensual sex, number of partners, and STIs may influence the clinician's work-up, examination, and the anticipatory guidance, but documentation of these data may be used against the patient in certain legal circumstances.[60]

Inclusion of victim quotes in the medical record is often advised in cases of injury or sexual assault, but such details about a victim's story may not be helpful should they change their account later, which is a common phenomenon when someone has experienced trauma. Keeping the documentation of history simple can prevent insignificant points from becoming a disputed fact in a legal case. Similar to cases of sexual assault, careful documentation of the physical examination includes signs of abuse such as old scars, surgical incisions, birthmarks, skin lesions, tattoos, and piercings.[60]

Diagnostic Codification

The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) released the first ever trafficking-specific abuse codes in October 2018 developed through a partnership between the American Hospital Association, Catholic Health Initiatives, and Massachusetts General Hospital.[69] Inclusion of one of these 29 ICD-10 abuse codes for forced labor and sexual exploitation, when appropriate and relevant as a finding, diagnosis, or problem, may help strengthen data collection on human trafficking in the health care system and inform the allocation of resources and future development of services equipped to respond to the needs of trafficking victims and survivors. Care must be taken to ensure that the use of these codes does not stigmatize or cause harm to already traumatized survivors.[69a]

Law Enforcement Considerations

Many trafficked persons have a negative or fearful perception of law enforcement (LE) officials because of previous arrests, fear of arrest or deportation, or abuses imposed by authority figures, so a thoughtful approach to law enforcement engagement with suspected human trafficking cases is advised. Law enforcement involvement should be limited to patient request, in state-specific mandated reporting scenarios that require LE involvement, or when clinicians appreciate imminent danger to staff or the patient.[60] In cases where LE involvement is mandated by law, trust and rapport can be safeguarded by ensuring a transparent, predictable, and non-retraumatizing process. It is not advisable, however, for providers to promise safety.

Barriers to Identification and Care

Trafficked persons generally do not self-identify as victims of human trafficking. In some cases, trafficked persons may not recognize their victimization, especially when cultural practices or beliefs cast a sense of normalcy on their circumstances (e.g., gender inequality, domestic violence, sex work).[14,25,70] In other cases, the victim narrative may not resonate with trafficked persons due to its failure to accurately capture their experience of and relationship to their trafficker, particularly when emotional or romantic bonds exist (e.g., parent, family member, boyfriend).[70] Still, in other cases, a trafficked person may outright reject the label of victim, opting instead for more empowering interpretations of their trafficking experiences.[70] Nevertheless, even when the trafficked person is acutely aware of their victimization and desires assistance, disclosure and engagement in care is hampered by shame, fear of physical retaliation, fear of harm to loved ones, fear of immigration authorities, and fear of police if compelled to commit crimes as part of their exploitation (e.g., shoplifting, drug selling, peer recruitment into trafficking).[14,17,53,71]

A recent systematic review on health care access barriers found that extrinsic, intrinsic, and structural barriers contribute to the reluctance among trafficked youth to access care.[72] Barriers identified included trafficker control, physical confinement, diminished trust in health care providers, concerns over discrimination, lack of confidentiality, language barriers, and complex registration process.[72] Similarly, a mixed-methods study identified three distinct profiles of survivor

Key element	Preparedness actions
Multidisciplinary teams	Identify champions among the key stakeholders whose discipline, expertise, local knowledge of the problem, and community partnership will enhance preparedness and response (e.g., medical, nursing, mental health, social work, child protection, forensic examiners, legal counsel, security, risk management).
Institutional policy	Adopt an institutional policy that is survivor-centered, based on available evidence or "promising practices," and in accordance with applicable state mandatory reporting laws.
Resources compendium	Create and maintain an up-to-date database of hospital and community resources available to address the varying needs of trafficking survivors.
Network partnerships	Partner with law enforcement, government agencies, social service organizations, hospital-based services, and other community stakeholders to determine best practices for collaboration and referrals, and more effectively serve survivors.
Response protocol	Develop a stepwise algorithm that leverages interdisciplinary teams, promotes a trauma-informed care approach, and accounts for the unique needs of adults and children when responding to the disclosure or identification of a trafficked patient.
Knowledge, training, and quality & safety	Establish mechanisms for knowledge dissemination (i.e., human trafficking and trauma-informed care education), response protocol implementation training, monitoring and evaluation of response incidents, evaluation of quality and safety gaps and opportunities, and protocol revisions when needed and appropriate.

Fig. 187.3 Health care preparedness: framework for developing human trafficking response protocols. (Adapted from: Macias-Konstantopoulos W. Human trafficking: the role of medicine in interrupting the cycle of abuse and violence. *Annals Internal Med.* 2016;165(8):582-588.)

experiences and engagement with health care: avoidant, distrustful, and constrained. Common across the three profiles was a feeling of disenfranchisement that contributed to decreased care access behaviors.[73] Trauma-informed, culturally sensitive, and survivor-centered care practices may mitigate this sense of disenfranchisement by minimizing retraumatization, fostering psycho emotional safety and well-being, and empowering survivors in their recovery.[73]

Studies have established that the ED is a significant health care access point for trafficked persons.[74] Identification is central to a more comprehensive and effective health care response for this patient population. One of the most consequential barriers to identification and care is the lack of formal human trafficking curricula in education and training which reinforces an underappreciation of its relevance to clinical practice, perpetuates a gap in knowledge and skill, and leads to preconceived biases about who victims are and what they look like. Other barriers include failure to establish trust, interview the patient alone, use professional interpreters, recognize red flags, and carry out more in-depth assessments.[17,53] This gap in knowledge and skill not only places the emergency practitioner at a disadvantage in caring for trafficking survivors, but also may place the trafficked patient at greater risk of harm if the provider proceeds with the evaluation and response in a manner that is unsafe, no matter how well-intentioned. A focus on education and training has been growing in the last decade.[36,75-80]

Similarly, there has been increased advocacy for clinical guidelines and protocols that guide a safe, effective, and comprehensive response, including the need for trauma-informed care, patient privacy, professional interpreters, mandatory reporting when appropriate (e.g., children), and referrals to national and local community resources for unmet needs.[53,80] Existing protocols for identifying and assisting trafficking patients in hospitals across the United States vary widely.[62] A "health care preparedness" framework for the development of response protocols proposes six main elements: interdisciplinary teams, survivor-centered institutional policy based on evidence or promising practices, collaborations and partnerships with community resources and cross-sector agencies, a stepwise trauma-informed response algorithm, and a plan for provider education/training and quality assurance of response protocols (Fig. 187.3).[53]

The ED visit represents a critical opportunity for trafficked persons to receive assistance and a potentially life-altering intervention. Through universal adoption of trauma-informed principles, labor and sex trafficking education, and development of multidisciplinary policies and procedures, emergency clinicians can positively impact the lives and health of trafficked patients.

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CHAPTER 187: QUESTIONS AND ANSWERS

1. Which of the following statements regarding human trafficking inquiry is true?
   - **a.** It is imperative that trafficked victims recount their history as often as possible to ensure consistency and to support law enforcement in the investigation of trafficking networks.
   - **b.** The primary goal of inquiry is disclosure.
   - **c.** Inquiry is a series of protocol-based standard questions designed to efficiently obtain information from traumatized victims.
   - **d.** The goal of inquiry is to provide a safe environment for patients to share as much or as little as they choose.

Answer: D. Rather than disclosure, the goal of inquiry is to provide a safe environment in which patients feel empowered to share as much or as little as they choose where strengths and resilience are recognized. Inquiry-based assessment is an active process that includes open-ended questions and dialogue.

2. Which of the following statements regarding health impacts on trafficked victims is false?
   - **a.** Traffickers employ abusive tactics that can cause physical, reproductive, and mental health problems.
   - **b.** Schizophrenia is not a diagnosis commonly associated with the psychological and psychiatric sequelae of victims of trafficking.
   - **c.** Commonly occurring smells, sounds, sights, and procedures in the emergency department may be perceived as threats by trafficking victims who have experienced trauma but is not caused by neurobiologic changes.
   - **d.** Substance abuse and drug use rates are common in trafficked victims under 18 years of age.

Answer : C. Trauma due to trafficking results in neurobiologic changes such that commonly occurring smells, sounds, sights, and procedures of the emergency department environment may be perceived as threats by those with trauma histories.

3. Which of the following statements regarding the indicators and red flags used to identify victims of trafficking in the ED are true?
   - **a.** Hypervigilance and hyperstartle reflexes are pathognomonic of human trafficking.
   - **b.** Accompanying individuals who are reluctant to leave the room, insist on answering questions or attempting to control encounters, or communications that may seem rehearsed may all be indicators that a victim is being trafficked.
   - **c.** Physical red flags of human trafficking often include immediate presentation for care for easily preventable injuries.
   - **d.** Evidence of psychological distress including limited eye contact, low trigger threshold, hypervigilance, and hyperstartle reflex are uncommon presenting characteristics of trafficked victims and are not reliable enough indicators in emergency departments to raise suspicion.

Answer: B. There is no single characteristic that is pathognomonic of human trafficking. Physical red flags of human trafficking include delayed presentation for care of injuries or infections; signs of abuse or neglect (e.g., malnourishment, poor oral health); work injuries or exposures that would be easily prevented by personal protective equipment (PPE). Other potential indicators include patient communications that seem rehearsed or scripted, patient reluctance or inability to answer simple questions about their living or working situation, conflicting information, reported mechanism of injury inconsistent with the physical evidence, and evidence of psychological distress (e.g., limited eye contact, low trigger threshold, hypervigilance, hyperstartle reflex).

4. Which of the following statements regarding the evaluation and treatment of trafficked victims is true?
   - **a.** Empiric STI treatment and emergency contraception is indicated only for sex trafficked victims and not labor trafficked victims.
   - **b.** Emergency department evaluation should include addressing acute medical issues and focus on forensic examination but should exclude the evaluation of chronic medical conditions.
   - **c.** Law enforcement involvement should be limited to patient request or when clinicians appreciate imminent danger to staff or patients.
   - **d.** When a suspected human trafficking case is identified, forensic examination should be performed by the original provider because including a sexual assault examination by forensic nurse examiners can worsen victim traumatization.

Answer: C. For both labor and sex trafficking, empirical STI treatment and emergency contraception may be indicated. ED evaluation may include addressing acute medical issues, evaluation of possible untreated chronic medical problems, documentation of acute and remote injuries, and STI testing and treatment, and consideration of a sexual assault medical forensic examination and evidence collection. Research shows that the use of sexual assault/forensics nurse examiners results in better patient outcomes in legal and emotional support.

5. Which of the following statements regarding the trauma-informed care of trafficking victims is false?
   - **a.** Mitigation of conscious and unconscious biases is important in contributing to the traumatization of trafficked victims.
   - **b.** Preventing retraumatization is an essential feature of trauma-informed care in the emergency department.
   - **c.** The PEARR Tool provides a trauma-informed framework for emergency clinician assessment but is only validated for victims of human trafficking.
   - **d.** If a patient denies victimization or declines assistance, the clinician may offer information about resources that can assist in the event of an emergency.

Answer: C. The Privacy, Educate, Ask, Respect, and Respond (PEARR) tool provides a trauma-informed framework for the emergency clinician assessing for any form of interpersonal violence, including human trafficking.

Sexual Minority Populations (LGBTQ)

Joel Moll and Carolyn Kluwe Holland

KEY CONCEPTS

- Sexual orientation, gender identity, and gender expression occur along a continuum and may be completely separate and discordant from one another.
- Multiple health disparities exist in sexual minority populations, but many of the contributing factors are likely unknown due to lack of studies.
- ED provider education about sexual minorities is often inadequate, limited, or absent.
- Transgender individuals may utilize a variety of medical and surgical interventions in their transition to affirm their gender identity. Emergency clinicians should be aware of complications related to these practices that may require treatment in the ED.
- Sexual minority patients at extremes of age, or who share another minority identity, have additional disparities that require consideration to deliver equitable and safe care.
- Open, inclusive, and nonjudgmental patient-centered communication using appropriate terminology is fundamental to fostering provider trust and minimizing health disparities in sexual minorities.

FOUNDATIONS

Background and Importance

Sexual minority individuals cross every demographic, and multiple cultural and societal influences can affect their visibility and disclosure of sexual and gender identity. They represent a diverse continuum of individuals without a strict heterosexual identity (lesbian, gay, bisexual. queer, or questioning [LGBTQ]) and include those whose gender identity is different or fluid from their sex-based gender assigned at birth. Although sexual minorities share many similarities, there are also key differences. There is a wide range of perceptions on the prevalence of sexual minorities in the United States (US). This reflects societal bias, lack of research, and barriers to disclosing or collecting data regarding an individual's sexual and gender identities. One recent estimate is that 4.5% or 11 million Americans identify as a sexual minority,[1] and at least 0.6% or 1.4 million identify as transgender.[2,3] Importantly, sexual and gender identities should be considered separate from sexual behavior. It is estimated that 8.7% of women and 8.2% of men have had same-sex sexual behavior.[4]

Terminology and Concepts

To create a welcome and inclusive environment for sexual minorities, health care providers should be familiar with culturally competent terminology to better communicate and avoid unintentional offense (Table 188.1). Providers should avoid terms associated with bias or prejudice. Terms like "homosexual" or "sexual preference" may be common in language, but have stigma when used in the sexual minority community. The use of the word "homosexual" is associated with past bias and discrimination; therefore preferred terms include lesbian, gay, or bisexual. Similarly, because there is no legitimate evidence that sexual orientation is a choice, the term "sexual preference" should not be used. Patients should be asked about their partner(s) in gender neutral terms without assuming that they are in a heterosexual relationship. Asking open-ended questions will signal being receptive to patients not in traditional heterosexual relationships or gender identities. When in doubt, ask the patient for their preferred terms, or allow them to define their relationships.

Historical Context

Same-sex relationships and transgender identity have existed throughout recorded history, although societal acceptance and tolerance has varied over time. Laws and attitudes against same-sex sexual behavior were common in the United States, which adversely influenced attitudes of health care providers and isolated sexual minorities from medical care. Despite recent increased acceptance of sexual minorities, past actions and discrimination can still be a powerful barrier to equitable care. Although the majority of Americans support sexual minority rights,[5] it is far from universal, and continued implicit and explicit bias along with outright discrimination and refusal of care still exist. Basic health care rights and choices assumed by the majority are often not afforded to sexual minorities, or are incomplete. Some forms of discrimination, including employment discrimination, are still legal in many states, making patient-provider trust and confidentiality of substantial importance to the sexual minority patient. Emergency care providers should be prepared to assure LGBTQ patients of laws protecting their medical records from disclosure.

Identity

Sexual minorities undergo a deeply personal process of accepting their sexual orientation or gender identity and then disclosing it to the outside world, known as "coming out." This process should occur on the patient's own terms and timeline. Since many individuals who engage in same-sex behaviors may never identify themselves as a sexual minority for a variety of reasons, clinicians should inquire about specific sexual activity and not just sexual orientation or identity when it is pertinent to their clinical presentation.

Legal identity and the patient's gender identity may be discordant for transgender patients, leading to confusion and discomfort. If the patient's insurance uses their gender assigned at birth, their preferred name and gender may not appear in many electronic health records (EHRs), and services and prescriptions using their preferred name and gender may not be covered. Few transgender people have all of their identification materials with their preferred name and gender, and for 68% none of their identification reflects their preferred name and gender, financial costs being one of the largest barriers to acquiring updated identification.[6] Creating an inclusive environment

TABLE 188.1 Terms and Definitions for Sexual Minorities

	Term	Definition
General Terms	Sexual Minority	Term for the diverse group of people whose sexual orientation and gender identity fall on a spectrum outside of strictly heterosexual and/or their gender identity of sex at birth
	Sex	Biologically male or female
	Gender	Psychological, behavioral, and cultural characteristics of being male or female
	Queer	Overarching term for sexual minorities
	Questioning	Person unsure of sexual and/or gender identities
Sexual Attraction	Gay	Man or woman who identifies as someone with sexual attraction to the same sex
	Lesbian	Woman who identifies as someone with sexual attraction to the same sex
	Bisexual	Man or woman who identifies as someone with sexual attraction to both men and women. This attraction may be more female or male.
	Sexually Fluid	Identity is not fixed as purely opposite or same-sex attraction
Gender	Gender Identity	Identity along a spectrum from female to male
	Gender Expression	Expressions and behavior of traits traditionally associated with women or men
	Cisgender	Gender identity is similar to identity associated with sex at birth
	Transgender, Trans, or Gender Nonconforming	Gender identity is different or opposite of identity associated with sex at birth
	Gender Affirming	Behaviors or interventions to affirm gender identity
	Transitioning	Undergoing interventions to affirm gender identity different from gender associated with sex at birth

without assumptions or judgment about identity will best promote an honest and trusting dialogue that will enhance health decisions and care.

SPECIFIC ISSUES

Factors Affecting Equitable Care

Legal Barriers

Legal issues can affect sexual minority patients' care in unique ways. Prior to marriage equality, many same-sex couples completed legal documents to provide some of the rights automatically provided by marriage. These issues include medical decision making and hospital visitation rights. Despite these documents, the wishes of patients were not always respected by hospitals, courts, or families. In 2010, the Department of Health and Human Services prohibited hospitals that participate in Medicare or Medicaid from denying visitation on the basis of race, color, national origin, religion, sex, sexual orientation, gender identity, or disability.[7] Marriage equality in 2015 provided the opportunity for stronger and automatic protections previously denied to same-sex couples; however, only 50% of same-sex couples' households are legally married compared to over 90% of heterosexual households[8,9] Same-sex spouses in the ED should be given the same level of access to health care information, decision making, and visitation as married heterosexual couples without having to provide a marriage certificate to prove their relationship status. Additionally, unmarried same-sex couples who have completed legally structured powers-of-attorney for health care and finance should have those documents respected and followed to the fullest extent of local and state laws.

Sexual Minority Parental Barriers

Up to 3.7 million children under 18 years old have an LGBTQ parent, with 200,000 being raised by same-sex couples. This represents approximately 16% of all same-sex couples (8% of male and 24% of female same-sex couples), while almost 40% of heterosexual coupled households have children.[10] These same-sex couples with children are far more likely to have an adopted child (20%) or foster child (3%) than majority couples (3%, 0.4% respectively).[8]

Legal recognition of parenthood is currently derived from marriage, adoption, or biology. Even with marriage equality, not all states recognize the same rights of parenthood to nonbiological parents. The legal recognition of nonbiological married same-sex parents varies state by state, and there are no requirements for a different state to recognize a legal tie between parent and child granted elsewhere. Additionally, some states will allow a single LGBTQ person to adopt a child, but will not allow the second parent to also be named as a legal guardian. This can leave same-sex parents in a precarious position when trying to access health care for their children.[11] Until there are consistent standards that provide clear legal status to nonbiological same-sex parents, health care providers need to be aware of and follow their local laws as they relate to consent for procedures and treatments.

In additional to lack of standardized legal recognition of nonbiological parents of children born to same-sex couples, there are other barriers to obtaining health care for these families. On arrival to the emergency department (ED), registration forms and the EHR often are not structured to accommodate same-sex couples. Typically, there are data fields to document a mother or father, but not two mothers or two fathers. This may keep providers from having accurate information about a child's family structure, and may put one parent in the position of not having decision-making authority concerning the child's medical care.[12] Heteronormative assumptions about adults accompanying a child in the ED may cause a provider to not recognize that a full family is present by assuming that the second adult is a nonparent relative or family friend.[12] Nonbiological parents may fear their lack of genetic ties to the child could cause them to be inappropriately ineligible to make health decisions for their child.[13] By focusing on a child's genetic parentage and not the legal and emotional relationships that make a family, nonbiological parents from same-sex couples feel a lack of respect for their family which can act as a barrier to full and candid communication between providers and parents.

Remedies to these described barriers include the development of cultural competency in the health care team and adaptation of the EHR and paper forms to accommodate all family structures and parent roles. Cuing from the EHR about unique family structures can alert providers to be mindful of how and to whom questions are asked about

the child, and assist in the collection of relevant information without inadvertently offending parents.

Barriers to Health Care Access

Sexual minority patients have less access to health care than their majority counterparts. They are less likely to have health insurance and more likely to live in poverty. Patients may fear sensitive information being disclosed to their employer, and if they have insurance, it may not cover gender affirming treatment. These factors can lead to delays in medical diagnosis and treatment. A quarter of transgender patients experience health insurance–related problems, including being denied coverage for nonemergent care due to their transgender status.[6] One in ten transgender people report having access to a bathroom denied to them, and may experience verbal harassment and even physical or sexual assault when accessing a restroom.[6] A third of transgender people have limited their fluid intake to avoid public restrooms, resulting in 8% reporting urinary tract infections due to avoidance and holding urine.[6]

Health Care Experience

Many sexual minorities report negative experiences in navigating the health care system, especially among the transgender population, leading to avoidance and delay of care.[14,15] In a small survey of transgender individuals in Ontario, Canada, half felt that presenting as their stated gender had prompted negative experiences in the ED, leading 21% to avoid visiting an ED in the future.[15] This was also demonstrated in the 2015 US Transgender Survey where 33% had at least one negative experience related to their transgender status, and 23% reported avoiding needed health care.[6,16] Issues include: being "misgendered" even after disclosing their gender identity; lack of provider knowledge about transgender health, including hormone effects; unnecessary questions about gender-related surgeries for unrelated chief complaints; and a persistent focus on genital examinations.[17,18] In the San Francisco area, where LGBTQ individuals are more visible than in many other regions, most practicing nurses had very little understanding of gender-related terminology, and many health care organizations did not have inclusive forms or standard language to discuss transgender patient issues.[2] However, despite these experiences, for some sexual minorities the anonymity of the ED may be preferred over their primary care physician, who may not be aware of their sexual behaviors or gender identity. Limited research suggests increased ED utilization among some sexual minorities compared to their majority counterparts.[19,20] Because the majority of these patients are in relationships, partners should be included in health discussions if desired by the patient.

Provider Education

A significant number of sexual minority patients do not disclose their sexual orientation, same-sex sexual behavior, or gender identity to their physician. A mix of societal, patient, and provider factors account for this nondisclosure. Prior to 2019, the Model of the Clinical Practice of Emergency Medicine (EM) jointly developed by the major EM organizations and published by the American Board of Emergency Medicine did not specifically include sexual minority health, and medical school and EM residency training often offers limited, if any, sexual minority education. Recent initiatives have been undertaken to determine needs and knowledge gaps. One study of EM residents found that 43% felt obtaining history and physical examinations from transgender patients was more challenging, and 25% felt similarly about LGB patients.[21] Most EM residents did not ask patients about sexual orientation or sexual behaviors even when pertinent to the chief complaint (e.g., abdominal or genitourinary concerns). Another survey of emergency physicians found that although most cared for transgender patients, few had formal training regarding their health needs or care. More than half asked patients about gender affirming surgeries, regardless of the chief complaint. Only 9% could identify the most commonly used nonhormonal medication used by female transgender patients (spironolactone), and only 26% could identify the most commonly used surgery by male transgender patients (mastectomy with thoracoplasty).[22] One should take an organ and hormone inventory only when relevant to the complaint. Similarly, when related to the presenting condition, one should inquire about sexual partners, specific sexual practices, and sexually transmitted infections (STIs; past diagnoses, use of protection) to improve health care to sexual minority patients.[23]

All emergency health care providers should receive training on LGBTQ inclusion and cultural competency. Education on terminology, sex differentiation, hormone therapy, mitigation of personal bias, and creating a safe environment has been shown to improve knowledge of, comfort with, and attitudes toward sexual minorities.[24,25] Creating an atmosphere of inclusion is fundamental to candid health care conversations and providing equitable and competent care.[26]

Health Disparities

Sexual minorities have the same basic health care requirements as others, but also have specific health needs intrinsic to their sexual orientation, gender identity, and behavior. Obstacles to equitable health can lead to health care disparities. The Minority Stress Model, described by Meyer, explains that minority groups, including sexual minorities, experience chronically high levels of stress from societal stigmatization. Sexual minority health disparities adversely affect both physical and mental health (Table 188.2). Higher prevalence of mood and substance abuse disorders result from increased stress caused by discrimination, rejection, and the adoption of societies' negative attitudes toward oneself. Research on disparities is limited, due in part to infrequent collection of sexual orientation or gender identity data, so many disparities are likely currently unidentified.

When considering health disparities among sexual minorities, HIV infection is often the focus despite the fact that the vast majority are HIV negative. However, in 2017, 70% of new cases of HIV were among men who have sex with men (MSM), making treatment and prevention important considerations.[27] One in six MSM who are HIV positive are unaware of their status.[27] Intimate partner violence among MSM has been associated with riskier sexual practices and increased risk of sexually transmitted infections, including HIV.[28] Men who have receptive anal sex are 13 times more at risk for HIV transmission than those who have insertive anal sex.[27] Sexually active MSM should be tested for HIV at least annually, or more frequently based on individual risk.[29] HIV treatment is paramount since an undetectable viral load markedly decreases the risk of transmission to seronegative partners, and treatment can significantly prolong life. Unfortunately, only 62% of HIV-positive MSM are receiving treatment, and only 52% have achieved viral suppression at levels that decrease transmission.[30] ED HIV testing and referral can provide an impactful opportunity on sexual minority health care. Additionally, pre and postexposure prophylaxis against HIV can provide further risk reduction, and has been shown to be effective and well tolerated.[31] Tenofovir disoproxil fumarate and emtricitabine (Truvada) is the only FDA-approved regimen for preexposure prophylaxis (PrEP).[32] Emergency care providers should be trained and prepared to prescribe these treatments for at-risk individuals.

Transgender Health

Health care delivery to a transgender patient can be challenging for providers due to lack of education and familiarity with transgender health (Table 188.3). Transgender individuals who are "out" or are

TABLE 188.2 Known Health Disparities for Sexual Minorities

	Gay Men	Lesbians	Bisexual	Transgender
Cardiovascular	↑Heart Disease[58] ↑Hypertension[58]	↑Heart Disease[20] ↑Hyperlipidemia[20] ↑Stroke[58]		↑Heart Disease (trans♀) ↑Hyperlipidemia[38] ↑Hypertension[38] ↑Thromboembolic Disease[33] (trans♀)
Endocrine		↑Diabetes[20] ↑Obesity/BMI[58,59]		↑Diabetes[38] ↑Obesity/ BMI[33,38]
Gastro Intestinal	↑Hepatitis[60]	↑Hepatitis[60]		↑Gallstones[33] (trans♀)
Hematology Oncology	↑Anal Cancer[61] ↑Kaposi Sarcoma	↑Breast Cancer[62] ↑Lung Cancer[62]		Polycythemia (trans♂)[38]
Infectious Disease	↑HIV ↑Rectal GC[63] ↑Hepatitis A, B, C[62] ↑HPV[64]		↑Hepatitis A, B, C♂[62]	
Mental Health	↑Mood Disorders[20,62] ↑Suicidality and Suicide Attempts[62] ↑Eating Disorders[65]	↑Mood Disorders[62,66] ↑Suicidality and Suicide Attempts[62,67] ↑Eating Disorders[65]	↑Mood Disorder[62,66] ↑Suicidality and Suicide Attempts ♀[67] ↑Eating Disorders[65]	↑Suicidality and Suicide[6]
Pulmonary		↑Asthma[20]	↑COPD[60]	↑COPD[68]
Safety	↑Sexual assault[69] ↑IPV-↓reporting[70] ↑Homelessness[71]	↑Sexual assault[69] ↑IPV[70] ↑Homelessness[71]	↑Sexual assault[69] ↑IPV[70] ↑Homelessness[71]	↑Sexual assault[6] ↑IPV[6] ↑Homelessness[6]
Substance Use	↑Heavy Drinking[72] ↑Moderate Smoking[72] ↑Lifetime Pain Reliever Misuse[73]	↑Heavy Drinking[58] ↑Heavy Smoking[72] ↑Lifetime Pain Reliever Misuse[73] ↑Lifetime Heroin Misuse[73] ↑Lifetime IV Heroin Misuse[73]	↑Heavy Drinking[72] ↑Heavy Smoking[72] ↑Moderate Smoking ♀[72] ↑Lifetime Pain Reliever Misuse[73] ↑Lifetime Heroin Misuse[73] ↑Lifetime IV Heroin Misuse[73]	↑Heavy Drinking[74] ↑Heavy Smoking[74] ↑Lifetime Pain Reliever Misuse[74]
Other	↑Arthritis[60] ↑Sleep Disturbances[75]	↑Arthritis[72] ↑Sleep Disturbances[75] ↑Pregnant Unmet Health Needs[76]	↑Sleep Disturbances[75]	↑Acne (trans♂)[38] ↑Sleep Disturbances[68] Osteoporosis[77] (trans♀)

TABLE 188.3 Best Practices in Caring for Transgender Patients

Area	Best Practice
Registration	Collect sexual orientation and gender identity so health needs can be identified early. Include preferred pronouns and name to be utilized during their ED visit.[17]
Identification	Call for patients by their last name only without the use of gender prefixes when in group settings such as waiting rooms.[17]
Scripting	Use standardized scripts to facilitate cultural sensitivity for sexual and gender minorities.[78]
Health Records	EHRs should have the ability to record and display preferred name and pronouns of patients for all users in all views. Once a patient has legal documents that reflect their gender identity and chosen name, indicators of transgender status should be removed from the view of casual users.
Organ and Hormone Inventory	Information about a patient's transition history, including an inventory of organs and hormone use information, are best stored in the medical/surgical history of the EHR.[79,34]
Accommodation	Restrooms should be defined as gender-neutral, or have specific signage and policies that patients may choose either the women's or men's room based on their own preference and identity. If patients have to choose a gendered bathroom, making at least one gender-neutral/all-gendered bathroom available will be helpful and supportive to nonbinary patients as well as those patients who are in transition.[34,17]
Patient Room	Patients should have single-occupancy rooms.

perceived as transgender experience verbal harassment (54%), physical assault (24%), and sexual assault (13%) because of their gender identity. Forty percent of transgender individuals have attempted suicide, almost nine times the rate of the general population.[6] Many transgender people have challenges with their families or religious communities and experience psychological stress due to rejection from previous sources of nurturing and support. Ten percent of transgender people report violence from an immediate family member, 8% have been kicked out of their homes, and 20% leave their spiritual or religious community due to rejection based on their gender identity.[6] Nearly a third of transgender people live in poverty, compared to 12% of the general US population.

Medical Gender Affirming Therapy and Complications

Transgender Female. For the transgender female, medical gender affirmation therapy commonly includes hormone supplementation with androgen blocking medication, in conjunction with estrogen in physiologic doses. The most commonly used androgen blocker in the United States is spironolactone, with alternative androgen blocking medications including 5-alpha reductase inhibitors (finasteride, dutasteride). Outside the United States, cyproterone acetate, a synthetic progestogen commonly used in the treatment for prostate cancer, is used as an androgen blocker. Options for estradiol administration include daily oral or sublingual, weekly transdermal, or biweekly intramuscular (IM) dosing. Use of feminizing hormone therapy for transgender women is considered off-label, and may need to be administered in higher doses than normally used in postmenopausal cisgender women.[33] Additionally, some transgender women may also take progestogens to enhance breast development, mood, or libido. Common changes seen with the implementation of hormone therapy include breast development, facial and body subcutaneous fat redistribution, muscle mass reduction, body hair reduction, and slowing or reversal of scalp hair loss. Erectile dysfunction, decreased or absent sperm count, and reduced testicular size also occur.[33] Some transgender women still produce sperm even in the setting of androgen blockade and estrogen use, and are at risk for causing an unplanned pregnancy if they are engaging in sexual activity that could cause fertilization.[33] Transgender women who went through puberty and had exposure to testosterone will not have complete elimination of male patterned facial or body hair, change in skeletal bone structure, or change in pitch of their voice with hormone therapy alone. These individuals require specific interventions such as plastic surgery, laser hair removal or electrolysis, and voice therapy.

Although the use of estrogen and progesterone are associated with mental health conditions among cisgender women, such as premenstrual dysphoric disorder, this does not appear to occur in transgender women. The use of feminizing hormones does likely lead to increased risk for cardiovascular disease and diabetes when other risk factors are present. Additionally, venous thromboembolism (VTE), gall stones, elevated liver enzymes, and weight gain are exacerbated in individuals taking supraphysiologic doses of estrogen feminizing hormones. Estrogen should be discontinued during the acute treatment of VTE.[34] While the use of progestogens in combination with estrogens is associated with increased cardiovascular events and breast cancer in postmenopausal cisgender women, there are no specific studies defining this risk in transgender women.[33] There is also no conclusive increased risk for breast cancer.[33,35] There is a theoretical pro-growth impact of estrogen on human testicular cells; however, there is no specific link between exogenous estrogen and testicular cancer risk.[36]

"Tucking" of testicles and the penis provides a more feminine appearing contour of the genital area and involves manually displacing the testes into the inguinal canal followed by positioning of the penis and scrotal skin between the legs directed rearward toward the anus. The position is maintained with tight underwear, tape, or a special garment known as a gaff, with some transgender women staying "tucked" up to 24 hours per day. Prolonged tucking is associated with increased risk of urinary tract infections.[34]

Injection of very small amounts of medical-grade free silicone with the intent of causing local reaction of fibroblasts and collagen growth is often used in the management of HIV-related lipodystrophy. In the transgender community, "silicone injections" may involve the injection of up to 3 liters of a variety of non–medical grade substances such as aircraft lubricant, tire sealant, window caulk, mineral oil, methyl acrylates, or petroleum jelly.[37] An estimated 20% to 50% of transgender women may have received these injections from nonmedical providers in their efforts to relieve their gender dysphoria and have immediate body changes that conform to their gender identity. Unfortunately, this practice often leads to significant immediate, early, and late-term health consequences (Table 188.4). Patients may not be forthcoming with information about having received filler injections in a nonmedical setting, so health care providers must be diligent in determining if injections might be a possible cause of patients' symptoms.

Transgender Male. The most common gender affirming medical treatment utilized by transgender men is testosterone. It can be administered IM, subcutaneously, or topically. With topical use, there is a modest risk of exposure to other people from skin to skin contact, and caution should be taken around patients with more sensitivity to testosterone such as pregnant women and small children.[38] Adjuvant therapies include progestogens, 5-alpha reductase inhibitors, aromatase inhibitors, gonadotropin-releasing hormone antagonists, and direct application of topical testosterone to the clitoris.[38] Use of hormone replacement therapy mimics male puberty, taking 4 to 5 years for full

TABLE 188.4 Silicone Injection Adverse Effects and Complications

Immediate	• Bleeding, pain, focal tissue necrosis, hypersensitivity reactions • Silicone embolization causing ARDS, multisystem organ failure, or loss of limbs
Early Onset *days to weeks*	All of the immediate adverse events, PLUS • Infected inflammatory nodules that may be fluctuant • Angioedema • Non-inflamed nodules that are painful, pruritic, and cause hypopigmentation
Long Term *weeks to years*	All of the immediate and early adverse events, PLUS • Nodules (inflamed and non-inflamed) may form sterile abscesses or fistulae • Migration of silicone causing pain or deformity • Silicone granulomas • Hypercalcemia • Sepsis, hypersensitivity pneumonitis, immune reconstitution inflammatory syndrome (IRIS) • Organ failure from direct mass effects

effect. Clitoral growth starts in as soon as 3 months and peaks at 1 to 2 years. Some may also try off label use of dihydrotesterone (DHT) to enhance clitoromegaly. Menses usually stop after 3 to 6 months of testosterone treatment, but this is dose dependent.

Transmen who were amenorrhoeic from testosterone may also present with new vaginal bleeding. This may be due to inadequate suppression of menses by the testosterone, but evaluation for pregnancy, infection, or malignancy, and gynecologic consultation may be necessary.[38] Testosterone provides ineffective birth control. In transgender men who became pregnant, 60% used testosterone prior to pregnancy, 20% conceived while amenorrhoeic from testosterone, and 32% of the pregnancies were unplanned.[39] If transgender men engage in vaginal receptive intercourse, they should use contraception such as condoms, progesterone-only birth control, or a hormonal IUD.[38] Testosterone is contraindicated in pregnancy and should be discontinued immediately if the pregnancy is desired.

Transgender men may also experience vaginal atrophy similar to that which occurs in postmenopausal women.[38] Atrophic vaginal tissue with decreased tissue resiliency and an altered microbial environment can be present due to relative estrogen deficiency. This can lead to bacterial vaginosis, cystitis, or cervicitis. Treatment with vaginal estrogen for symptom relief and comfort is appropriate, and should be accompanied by reassurance that the minimal systemic absorption of estrogen should not interfere with masculinization effects of testosterone. If patients are uncomfortable with intravaginal administration, they can just apply the estrogen cream on their external genitalia.

Transgender men on masculinizing hormones should have their labs interpreted based on standard male values, except for hemoglobin values. If the patient is still having menses, their hemoglobin should be interpreted relative to female values. Use of masculinizing hormones leads to an increased risk for polycythemia, weight gain, acne, androgenic alopecia, and sleep apnea. Additionally, there are possible increased risks for elevated liver enzymes, hypercholesterolemia, cardiovascular disease, hypertension, and diabetes if additional factors are present. Psychiatric disorders that include manic or psychotic symptoms may have an increased risk of destabilization from masculinizing hormones. There is no conclusive increased risk for bone density loss, breast cancer, cervical cancer, ovarian cancer, or uterine cancer.[35,38]

Masculinizing hormone treatment may not shrink breasts, and thus transmen may bind their breasts with tight-fitting sports bras, shirts, ace bandages or specially made binders to flatten the contour of the chest. Larger-breasted people may use multiple garments at the same time, which can lead to pain, diminished respiratory capacity, skin breakdown, or fungal infections.[40] Sensitive and appropriate history taking and physical examination of patients who may be reluctant to remove bindings is key to providing culturally competent care and allowing a discussion about safe binding.[34]

Surgical Gender Affirming Therapy and Complications

Transgender Women. Gender affirming surgeries for transgender women included genital procedures such as orchiectomy, vaginoplasty involving the creation of a neovagina, clitoris, urethral rerouting, and labiaplasty, most commonly using the penile inversion technique. Nongenital procedures commonly seen include breast augmentation, facial feminization with plastic surgery, and reduction thyroid chondroplasty to decrease prominence of the "Adam's apple."[33] Of note, the prostate is generally not removed with any of these procedures, so health maintenance including screening for prostate cancer is still required.

Transgender Men. Mastectomy is one of the most commonly requested surgery by transgender men. They experience the same rate and type of complications as cisgender women who have mastectomies.[41] Genital surgical procedures include metoidioplasty (movement of the hypertrophied clitoris anteriorly to a normal penile position) and phalloplasty (construction of a neophallus using free and/or pedicled flaps). Complications of both procedures include spraying or dribbling of urine, urethral strictures or fistulas, and, with phalloplasty, the additional risk of vascular compromise of the flap and necrosis.[38]

Physical Examination

Examination of a neovagina in a transgender woman involves looking at a blind cuff that lacks a cervix or surrounding fornices. It may be more posteriorly oriented than expected. Using an anoscope instead of a vaginal speculum may provide a more anatomic approach. Once inserted, the trocar can be removed from the anoscope, and direct visualization of the walls of the neovagina can occur as it is withdrawn and the walls collapse around the end of the anoscope.[34]

Physicians evaluating transgender men who present with complaints of pelvic pain should take the same general anatomic based approach as a non-transgender woman, considering urologic, gynecologic, gastrointestinal, musculoskeletal, and psychiatric causes. Recognizing that transgender men may engage in receptive vaginal sex, a comprehensive sexual history including specific behaviors (vaginal-vaginal contact, vaginal or anal or receptive penile sex) should be collected.[42] Pregnancy should also be considered in any patient who still has a uterus and ovaries. Explaining that pregnancy testing is part of a standard protocol may ameliorate any offense taken by patients who deny any sexual activity with a partner capable of insemination.[34]

Even when medically necessary, having a pelvic examination can be traumatic and anxiety provoking for transgender men. It may have been a long time since their last exam, and they may not be up to date on screening for cervical cancer or STIs. Techniques for decreasing discomfort with pelvic exam include: discussing the procedure beforehand; allowing the patient to have a support person in the room; directly explaining each step before performing it; using the patient's terms for their body parts instead of medical terms. Some transgender men may decline speculum exam, transvaginal ultrasound, or bimanual exams as it may exacerbate their gender dysphoria. If the patient requires a transvaginal ultrasound, a low-dose benzodiazepine may be considered in conjunction with the application of lidocaine ointment to the vulva and vagina prior to the procedure. Having the patient insert the intravaginal ultrasound themselves may also facilitate a transvaginal ultrasound.[34]

Special Populations

Youth

Sexual minority youth have similar health disparities as adults; however, they also face challenges unique to their developmental stage and vulnerable position. In addition to typical formative milestones, LGBTQ adolescents are challenged by the realization that their sexual attraction and/or gender identity may be different than what is expected of them by their parents, peers, or society. Parents, peers, and medical providers may lack insight or knowledge into the complexities of their situation, and heteronormative assumptions may cause unintended harm. Youth can become disconnected from support and social networks by self-isolation or rejection. In 2017, the Youth Risk Behavior Surveillance study found that sexual minority youth reported much higher rates of mistreatment than their heterosexual counterparts.[43] One-third of LGBTQ teens were bullied at school, 27% were bullied electronically, 30% were victims of physical violence, and 22% experienced sexual violence.[43] Ten percent of LGBTQ students had missed school due to safety concerns.[43] Sexual minority adolescents also have an increased rate of mental health disorders, substance abuse, STIs, and self-harm or risky behaviors compared to majority adolescents.[44]

While 13% of heterosexual students contemplate suicide, the number rises to 48% of sexual minority youth.[43] Up to 40% of homeless youth identify as LGBTQ.[44]

For transgender youth, puberty-suppressing medications may be prescribed. The purpose is to allow more time to explore their gender identity and other developmental issues, and potentially facilitate future transition by preventing the development of secondary sex characteristics, such as facial hair, breasts, or deepened voice. These secondary sex characteristics are otherwise difficult to impossible to reverse if the person later chooses to pursue gender confirming procedures. Adolescent patients with male genitalia may be taking gonadotropin-releasing hormone analogues to stop luteinizing hormone secretion, or medications that block secretion or action of testosterone, such as progestins. Adolescent patients with female genitalia may also be treated with gonadotropin-releasing hormone analogues to stop production of estrogen and progesterone. Surgical interventions should not be carried out until the patients reach the legal age to consent for medical procedures and have met other criteria for gender affirming surgeries.[35]

Elders

There are approximately 3 million Americans over the age of 55 years who identify as LGBTQ, and by 2030 it is estimated there will be 6 million.[45] Significant health disparities also disproportionately affect older sexual minorities (see Table 188.2). Physical disparities may result in significant disability later in life. Mental health concerns are staggering with over half of sexual minority individuals over age 65 experiencing depression, almost 40% have contemplated suicide, and over 50% feel isolated.[46] Like other sexual minorities, they are less likely to have medical insurance and more likely to live in poverty.[46]

Although LGBTQ individuals and couples are increasingly parents through surrogacy, adoption, or other means, most do not have children who may assist them in advanced age compared to heterosexuals. Elder sexual minorities are twice as likely to live alone and may be estranged from biological family.[46] Sexual minorities commonly rely more on friends and community, but may become separated from social support by declining independence and health.[47] As a result, sexual minority individuals anticipate more use of institutional long-term care.[48] Among elder transgender individuals, 35% are concerned about being judged by their health care providers and believe that their health care will be limited (65%) or denied (55%) as they age.[49] Sexual minorities dependent on others have a high rate of abuse from caregivers. In one study, 22% of sexual minorities over 60 years of age reported that they had been harmed or neglected by a caregiver, and 26% reported knowing someone else who had been mistreated.[50] These factors are essential in consideration of a safe discharge from the ED.

People of Color

Although sexual minorities face many barriers in the obtainment of equitable health care, those of color have additional burdens. African American and Latino sexual minorities experience greater stigma relative to white counterparts.[51] Even within the sexual minority community, African Americans have the highest levels of racial/ethnic stigma, Caucasians the least, and Latinos and Asians in between.[52] Being LGBTQ and an underrepresented minority due to race, creed, ethnicity, or religion can potentially cause direct conflict with strongly held community values. As a cohort, African Americans and Hispanics have higher spirituality,[53] and religious institutions can therefore have an important role in helping or exacerbating their double minority stress.[54] Providers should be aware of how different cultural expectations that form identity can conflict and have an impact on the overall mental and physical health of these patients, and potentially magnify preexisting disparities.

African American and Latino sexual minorities are disproportionately affected by HIV compared to other racial groups, accounting for 37% and 29% respectively of new HIV infections among MSM.[27] Black MSM have a one in two chance of acquiring HIV during their lifetime,[55] and Latino MSM have a one in four lifetime risk.[30] Both are also are less likely to use PrEP, but this alone does not account for the difference between racial groups.[56] Although overall rates of HIV have been stable in the last decade, rates rose 52% among Asian and 18% among Latino MSM.[27] The HIV infection rate was stable among Black MSM, and the rate among white MSM rate decreased by 16%.[27] Intimate partner violence has been shown to be independently associated with HIV risk in Latino MSM.[57]

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CHAPTER 188: QUESTIONS AND ANSWERS

1. Which of the following statements regarding sexual minority populations is true?
   - **a.** Sexual orientation, gender identity, and gender expression define psychological, cultural, and behavioral characteristics of either being male or female.
   - **b.** Lesbian, gay, bisexual, and homosexual are all acceptable terms when addressing the sexual minority community.
   - **c.** The demographics of sexual minority populations indicate that a majority of vast transgender individuals were born after 1994 (Generation Z).
   - **d.** In sexual minority populations, it is important to separate sexual and gender identities from sexual behavior.

Answer: D. Sexual orientation, gender identity, and gender expression occur along a continuum and may be completely separate and discordant from one another whereas gender refers to the psychological, behavioral, and cultural characteristics of being either male or female. The term *homosexuality* is associated with past bias and discrimination and is not a preferred term when addressing sexual minority populations. Sexual minority individuals cross every demographic, and multiple cultural and societal influences can affect their visibility and disclosure of sexual and gender identity.

2. Which of the following factors does not affect equitable care in sexual minority populations?
   - **a.** Parental barriers
   - **b.** Same-sex marriage
   - **c.** Access to care
   - **d.** Provider education and knowledge
   - **e.** None of the above

Answer: E. Same-sex couples with adopted children can face difficulty in legal recognition of parenthood, resulting in barriers in medical decision making and obtaining appropriate health care. Although marriage equality provided the opportunity for stronger and automatic protections previously denied to same-sex couples, only 51% of same-sex couples' households are legally married compared to over 90% of heterosexual households. Sexual minority patients have less access to health care and are less likely to have health insurance compared to majority counterparts. ED provider education about sexual minorities is often inadequate, limited or absent, leading to lack of understanding and poorly informed decision making or advocacy on behalf of sexual minority populations.

3. Which of the following statements regarding medical gender affirming therapy is true?
   - **a.** Commonly used medications include hormone supplementation with androgen blocking medications in conjunction with estrogen.
   - **b.** The most common gender affirming medical treatment for the transgender male is spironolactone in addition to 5-alpha reductase inhibitors and aromatase inhibitors.
   - **c.** Transgender women who went through puberty and had exposure to testosterone will usually have complete elimination of male patterned facial or body hair and change in pitch in voice although little change in skeletal bone structure would occur with hormone therapy alone.
   - **d.** Finasteride is a 5-alpha reductase inhibitor used only in transgender males for gender affirming therapy.
   - **e.** Both A and B are true.

Answer: A. The most common gender affirming medical treatment utilized by transgender men is testosterone. The most commonly used androgen blocker in the United States is spironolactone. 5-Alpha reductase inhibitors (finasteride, dutasteride) are alternative androgen blocking medications. Transgender women who went through puberty and had exposure to testosterone will not have complete elimination of male patterned facial or body hair, change in skeletal bone structure, or change in pitch of their voice with just hormone therapy. These require specific interventions such as plastic surgery, laser hair removal or electrolysis, and voice therapy.

4. Which of the following statements regarding surgical gender affirming therapy is false?
   - **a.** Genital procedures in gender affirming surgeries for transgender women also include the removal of the prostate gland as well as orchiectomy and vaginoplasty.
   - **b.** Complications of metoidioplasty and phalloplasty include spraying or dribbling of urine and the development of urethral strictures and fistulas.
   - **c.** In transgender males, pregnancy is not a consideration.
   - **d.** Both a and c are false.
   - **e.** None of the above are true.

Answer: D. Genital procedures in gender affirming surgeries for transgender women do not include the removal of the prostate gland, so the risk for prostate cancer persists necessitating screening. Pregnancy should always be considered in any patient who still has a uterus and ovaries.

5. Which of the following statements is false?
   - **a.** There is an increased risk for mental health disorders among the sexual minority population.
   - **b.** The population of older Americans who identify as LGBTQ is likely to shrink by the year 2030 and experience less depression.
   - **c.** African American and Latino sexual minorities experience greater stigma relative to white counterparts.
   - **d.** Rates of HIV have risen among the Asian and Latino males who have sex with males over the last decade.

Answer: B. There are approximately 3 million Americans who identify as LGBTQ over the age of 55, and by 2030 it is estimated there will be 6 million, with increasing burdens of mental health and lifetime physical disabilities. Although overall rates of HIV have been stable in the last decade, rates rose 52% among Asian and 18% among Latino MSM. The HIV infection rate among Black MSM was stable and the infection rate among white MSM decreased 16%.

189

Social Determinants

Dennis Hsieh

KEY CONCEPTS

- Challenges with food, housing, transportation, and other social determinants of health account for approximately 50% of poor health outcomes in the United States.
- Emergency providers can connect patients to resources that can help address challenges with different social determinants of health.
- Legal services attorneys provide low-cost or free services that can assist with a number of health-harming legal needs.
- Health care providers and systems need to work with nonprofits, community groups, community members, and community leaders to expand the capacity to address social determinants of health.

FOUNDATIONS

The emergency department (ED) serves as the interface between health care and the community in a nexus where health care delivery can become a complex integration of significant physical and mental health crises intertwined with other life emergencies such as homelessness, poverty, and hunger.[1] These social and economic factors are collectively known as the social determinants of health (SDOH).

SDOH create barriers to health care access and result in nonadherence to medical interventions. It is estimated that 20% of a patient's health outcome is influenced by medical care, whereas social and economic factors account for 50% of such outcomes, highlighting the importance of concurrent medical and social interventions to advance patient health outcomes.[2]

Furthermore, left unaddressed, SDOH drive both health care cost and utilization. Even for those with access to care, many competing social needs impede the ability of the individual to adhere to treatment plans. These factors have a significant effect on health. For many of these concerns, providers can connect patients to concrete resources regardless of whether or not social work is available.

SPECIFIC ISSUES

Patient and Provider Factors

A large number of patient and provider factors affect the care of patients (Table 189.1).[2a]

Language

Many ED patients do not speak English as a first language. Title VI of the Civil Rights Law requires all recipients of federal funding to provide interpretation for patients with limited English proficiency. With time pressure in the emergency department and lack of proper training, providers do not always use a certified interpreter and instead use their limited knowledge of a second language or a patient family member. Failure to use a certified interpreter leads to poorer health outcomes and persistent health disparities.[3] Given this, emergency clinicians should use certified interpreters for patients with limited English proficiency.

TABLE 189.1 Patient and Provider Factors

Patient and Provider Factors	Rosen's Chapter
Race, ethnicity, and diversity	Chapter 186
Cultural humility	Chapter 186
Implicit bias	Chapter 186
Sexual orientation and gender identity	Chapter 188
Mental health	Chapters 96-101
Disability	N/A
Language and literacy	Chapter 189 (this chapter)

Health Literacy

Even patients who speak English as a first language may have limited health literacy, which is defined as limited capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. Those who have low health literacy may have trouble with tasks including reading appointment slips, understanding medication labels, and comprehending information from their providers, all of which are associated with poorer adherence to care plans and poorer health outcomes.[4] To address this, ED providers can use techniques such as "teach back" by providers and engaging with family members and friends to support patients.

Insurance and Access to Care

Uninsured and underinsured patients are often unable to access care prior to an ED visit.[5] This leads to delayed presentations of serious health conditions, poor health outcomes, and higher mortality.[6] For those who have poor access to care, two of the main drivers are the lack of ability to afford care and low health literacy regarding how to utilize care once coverage is obtained.[7]

For emergency clinicians, insurance and access to care are crucial to ensure proper follow up for patients. Rapid follow up reduces both return ED visits[8] and avoidable hospital admissions.[9] Thus, making sure patients have a practical and accessible follow-up plan is key. For those patients who have trouble navigating the system, case management can reduce ED recidivism.[10]

Employment, Income, and Financial Strain

The United States (US) has an extremely high rate of income inequality that has continued to grow in recent years.[11,12] As income inequality has grown, so have health care disparities: lower-income Americans have higher rates of chronic disease, anxiety, and depression, as well as lower life expectancy.[13,14] Low income, financial strain, and resulting

poverty lead to increased stress, poor access to healthy foods, unsafe housing, and challenges with other SDOH.

Medical debt is related to income, employment, and financial security and is estimated to contribute to 67.5% of all bankruptcies, even after passage of the Affordable Care Act.[15] Hospitalization itself leads to decreased employment and income with a rise in out-of-pocket spending on medical care.[16] This highlights the importance of ensuring patients are connected to health care coverage and other programs to minimize the impact that an ED visit and/or hospitalization has on their lives.

Food Insecurity

Food insecurity, defined as a condition in which individuals do not have access to nutritionally adequate and safe food because of limited financial or other resources, is a leading health issue in the United States.[17] Lack of access to healthy foods leads to increased rates of low birth weight, hypertension, diabetes, and mental health disorders, particularly depression.[18] Not surprisingly, this is associated with increased emergency department visits and acute care utilization[19] and therefore increased costs within the health care system. Food insecurity led to an estimated $53 billion dollars of excess health care spending in the United States in 2016.[20]

Food insecurity leads to poor health by forcing individuals to choose between eating and medications, medical care, housing, education, utilities, and transportation.[21] Furthermore, food insecurity makes it difficult for individuals to follow a healthy diet and reduces the cognitive bandwidth available to manage chronic illnesses.[21]

Poverty, lack of education, and unemployment lead to individuals and households not having enough to eat and substituting cheaper, less nutritious items for healthy foods[22] or choosing not to eat to meet other basic needs. Low-income individuals often live in areas that have been historically underdeveloped with poor public transit and lack access to healthy foods. These areas, known as food deserts, lead to poor outcomes for those with chronic disease, including cardiovascular disease[23] and diabetes.[24]

Homelessness and Housing

Lack of access to safe, habitable housing is an important social determinant of health for many patients. These individuals have worse health outcomes and mortality compared with those who are housed.[25] Unhoused individuals may be unable to properly store certain medications, which can affect their efficacy (e.g., refrigeration of insulin or other antidiabetic agents may not be possible). Additionally, patients with housing insecurity may take irregularly or avoid taking certain medications based on expected side effects and potential legal implications. An example includes the use of diuretics, which cause increased need for urination; due to lack of access to bathroom, patients may be unable to reliably relieve themselves or be charged with indecent exposure or public urination. Housing First programs that provide housing and supportive case management decrease the use of nonroutine health care services, including ED visits, while improving self-perceived health.[26,27] However, compared to other federal, state, and local means-tested programs such as Medicaid and SNAP, housing programs have a limited supply and long waitlists.

For those with housing, utility payments can be challenging. Utility assistance programs are available for low-income patients and have been shown to improve health.[28,29]

Transportation

Lack of access to transportation leads to missed appointments, poor adherence to medications, and delayed access to care, resulting in increased costs and poorer health outcomes.[30] Lack of transportation also impacts access to services, healthy foods, jobs, and other social determinants of health. Barriers to transportation include poor infrastructure, costs, lack of access to vehicles, distance and time burden, and policy-related issues.[31]

Elders, veterans, children, women, minorities, and those with lower incomes and chronic conditions face more transportation barriers.[32] Rural settings are especially challenging, given the great distances and lack of public transportation.[33] Providing transportation improves adherence to care, thereby decreasing costs and improving outcomes.[34]

Immigration Status

The immigration experience has profound effects on individuals and their health.[35] Immigration status is linked to ability to work and access public benefits, including health care.[36] The lack of proper immigrant status causes stress and poorer health.[37] Immigration law and policy are complicated and continuously changing. Important interventions that can be initiated in the ED include identifying vulnerable patients and educating them about potential opportunities to adjust their immigration status through mechanisms such as the T-Visa, U-Visa, and Violence Against Women Act (VAWA), as well as providing education and dispelling fear regarding accessing medical and social services.

Education

Youth behavioral issues in school can be related to mental health or developmental delay, resulting in the youth being brought to the ED. Parents or guardians may express concerns regarding the issues of truancy, suspension, expulsion, and reasonable accommodation, challenges that appropriate social services can help them address. For adults, educational needs are more subtle and tied to employment opportunities and income. Lower educational attainment is correlated with lower health literacy and poor health outcomes. More years of education are directly linked to a lower risk of mortality, a lower risk of obesity, and a lower risk of smoking.[38]

Legal Concerns

Health-harming legal needs is a term used to describe the legal avenues that exist to address many SDOH. For example, if an individual has mold, pests, or other housing issues that a landlord refuses to address, or an individual is improperly denied Medicaid coverage for durable medical equipment, a lawyer can help advocate and enforce housing and Medicaid regulations, respectively. Addressing SDOH through the law diminishes stress, decreases ED visits, and improves adherence to care and health outcomes.[39]

Justice Involvement

The United States has the largest population of incarcerated individuals in the world.[40] Individuals in custody or otherwise justice-involved are often seen in the ED. Many of these individuals experience comorbid psychiatric and substance use disorders, chronic health conditions, or homelessness, making these populations extremely vulnerable.[41] Furthermore, individuals in custody lose their rights and privacy. Being justice-involved is associated with higher mortality, morbidity, and poorer health outcomes.[42]

The Built Environment

Emergency clinicians must view and treat patients within the context of their lives and their communities. As such, the built environment, the surrounding physical environment, and conditions that are constructed by human activity affect patients' ability to follow up for care, exercise, access transportation, eat healthy food, and address other social determinants of health.[43] Improvement in the built environment is associated with better health outcomes in areas such as increased physical activity, better mental health, and improved dietary behaviors.[44] Emergency clinicians often see patients who reside in poorer

areas, where following common preventative measures such as healthy eating and exercise is often challenging. Providers can address specific barriers, such as food insecurity and challenges with transportation, as previously discussed. Beyond this, however, changing the built environment requires gathering evidence from the bedside and engaging with health systems, local and state government, and the community to help bring about systematic change.

MANAGEMENT

Overview

Most EDs do not currently screen for social needs. Instead, social needs arise during the course of the patient encounter. Options for systematic screening exist but require implementing a framework for both identifying and addressing social needs.[45] After identifying concerns with the social determinants of health, patients can be linked to resources. Social workers or ED staff can help assess and provide emotional support prior to providing patients with a list of resources. Some systems have adopted electronic platforms such as One Degree (www.1deg.org), 211 (www.211.org), or Aunt Bertha (www.findhelp.org), which are accessible for patients to use themselves.[46] Some systems also use patient navigators to help more actively connect patients to resources.[47,48]

EDs, hospitals, and health systems cannot address SDOH and poverty alone. In addition to working across specialties, health systems must look outside of health care to meet patients' social needs. There are many community groups, nonprofit organizations, and government agencies working on factors affecting SDOH. Together, these partnerships not only provide an opportunity to invite service organizations into the health care setting to connect with patients, but also ensure closed-loop communication that ensures that patients actually receive help.

Apart from connecting patients to resources, community engagement can lead to building capacity within the community through infrastructure changes such as offering low-cost day care and early childhood education opportunities, introducing violence prevention programs in schools, increasing the number of parks and green spaces, reducing unhealthy food options, creating bike lanes, or introducing farmer's markets to combat food deserts. Even with these types of changes, other challenges such as the lack of affordable housing and low wages require further advocacy in partnership with the community at the local, state, and federal levels.

Health Care Access and Literacy

Even for those who have health care coverage, access to follow-up care from the ED can be challenging. There are no federal standards requiring that appointments be available within a certain number of days, or how many providers there must be for a certain number of enrollees. However, most states do require that Medicaid and managed care plans provide adequate networks and timely access.[49] Patients having trouble accessing care can call their insurance plan to find out who their doctor is, what specialists are available, and how quickly they should be able to get an appointment. If, despite contacting their doctor and their insurance plan, they are still unable to access care in a timely manner, patients can contact their state's department of insurance for further assistance.

Health Care Coverage

When a patient does not have health care coverage, there are a number of options to consider.

Medicaid was created by the Title XIX of the Social Security Act in 1965 and is a means-tested program, meaning that eligibility depends in part on income. The program is administered by states and jointly funded by federal and state dollars. At a minimum, coverage must be provided to individuals who are pregnant, blind, disabled, over 65 years of age, and parents or caretakers of a dependent child whose household income falls below a certain amount. Beyond this, states have the option to cover additional populations. Income levels are set by the state.[50] Patients can look to their state government website for more information and to sign up for Medicaid.

Medicare was established in 1965 under Title XVIII of the Social Security Act for individuals age 65 (currently) and older, those less than 65 who receive Social Security Disability Insurance, and those who suffer from end-stage renal disease. People who fall into one of these three categories must have worked or be linked to an individual who has worked at least 40 quarters (10 years) during their lifetime. Medicare is administered and funded by the federal government and contains several parts including inpatient hospital coverage (Part A), outpatient medical coverage (Part B), and alternative coverage options—Medicare Advantage (Part C), and prescription drug coverage (Part D). To sign up for Medicare, one must go through the Social Security Administration by either visiting a Social Security Office or registering online: https://www.ssa.gov/benefits/medicare/.

In addition, all states have a health care marketplace (healthcare.gov) under the Affordable Care Act (ACA) where individuals can see plan options and sign up for health care. Generally, the exchanges have a period of open enrollment during which an individual must sign up for insurance. However, instances such as a job loss or relocation will permit signing up for insurance outside of open enrollment periods. If an individual is not eligible for Medicaid or Medicare, signing up for insurance via the exchanges is the most appropriate option.

There are specific programs focused on providing access to care for children under the age of 18, including the Children's Health Insurance Program (CHIP). However, transitional age youth between the ages of 18 to 25 years face special challenges because they become ineligible for many benefits, including health care, during this age range and can also lose access to their pediatrician. The Affordable Care Act requires plans and issuers that offer dependent child coverage to make coverage available until the child reaches the age of 26.

Individuals who are not eligible for these options will receive a bill of charges that is higher than the negotiated rates that insurance companies pay. These individuals should be advised to call the health care provider or hospital to discuss options that include free care, a reduced rate, or a payment plan. A reduced rate or free care (collectively also known as charity care) is available at the discretion of the provider and is generally based on income. A payment plan is a plan where the amount due after negotiations can be paid in installments, much like credit card payments. Note that facilities built with assistance from the Hill-Burton Act of 1946 (usually hospitals) have legally mandated charity care obligations.

Patients who have trouble navigating these options, feel that they have been wrongly denied benefits, or have been sent to collections can contact the patient advocate at the hospital and a local free legal services organization for assistance. Those sent to collections can call the original provider to ask that the bill be taken back from collections to work out a payment plan as the provider receives substantially less reimbursement when a medical bill is sold to a collection agency. Additionally, patients may be unable to afford some or all of their medications, leading to repeated presentations to the ED. Determining alternative strategies from different medication options (e.g., transitioning from SGLT-2 inhibitor or GLP-1 inhibitor for treatment of diabetes mellitus to a sulfonylurea) or different mechanisms for payment may be crucial to prevent additional visits.

Disability and Loss of Employment

Emergency clinicians often care for individuals who have suffered an injury that affects their ability to work. Depending on the nature of the injury, the patient may qualify for either short-term or long-term disability insurance that will pay them a portion of their wages while they are unable to work. States administer short-term disability, which is anticipated to last less than one year. For long-term or permanent disability, people must apply through the Social Security Administration for either Social Security Disability Insurance (SSDI) or Supplemental Security Insurance (SSI).

The Family and Medical Leave Act of 1983 (FMLA) protects individuals who have to take leave from their jobs due to the birth of a new child, caring for a sick family member, or recovering from a serious illness, allowing for unpaid leave for up to one year without the risk of job loss. Those taking time off for pregnancy and childbirth also qualify for short-term disability insurance.

Challenges with Employers

Clinicians will also encounter patients who feel that they have been wronged by their employer. Complaints may include employment discrimination, denial of meals and breaks, improper termination, unpaid overtime, and unpaid wages. For these concerns, referral to a legal services attorney or an employment law attorney is the appropriate next step.

Finding Employment

Patients who need assistance in finding employment can contact local workforce development agencies and nonprofits that help individuals find and retain employment. For those who have misdemeanors or felonies on their records, referral to legal services for record expungement may help these individuals obtain jobs.

Income Support

Patients who are employed but earn very little may qualify for earned income tax credit (EITC). Those who are able to work but have lost their jobs can apply for unemployment insurance, which is administered on a state-by-state basis. Those who have minor children may qualify for Temporary Assistance for Needy Families (TANF), which is funded by the federal government and administered by states. For those without minor children, local jurisdictions may have limited cash aid, such as General Assistance or General Relief. These programs are generally administered by the local department of social services. Those who are older may also qualify for Social Security retirement benefits, which is administered by the Social Security Agency. Individuals who have a history of military service may be eligible for income assistance from the Department of Veterans Affairs. Providers should also make sure that these patients are linked with other programs that assist with basic needs, such as programs that help with food and housing.

Management of Food Insecurity

Health Care Based Resources

Some hospitals and health systems have partnered with local food recovery organizations, food banks, and farmers to set up food pharmacies that provide healthy produce for free to patients who are food insecure and/or have chronic disease.[51] These food pharmacies are often supplemented with cooking classes and nutrition education for patients. Many hospitals and health systems also partner with local growers to host on-site farmers markets to make healthy food accessible to patients and some institute a 1-to-1 match for supplemental nutrition assistance program (SNAP match) purchasers.[52]

Community-Based Resources

Patients can also be referred to community resources that provide food ready for consumption, such as churches, soup kitchens, and shelters, as well as those that provide groceries, such as food banks and pantries.[53] Other sources include farmers markets that provide a SNAP match, food delivery services such as Meals on Wheels, and medically tailored meals, such as those provided by Project Open Hand in the San Francisco Bay Area.

Public Programs

Public programs are generally limited to those who have legal status in the country. The supplemental nutrition assistance program (SNAP), formerly known as food stamps, is a federally funded program through the United States Department of Agriculture (USDA) that is based on financial need. Local offices can be found on the USDA website.[54]

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is a program open to postpartum women and children up to the age of five. This program is also administered by the USDA and local offices can be found on the USDA website.[55]

Housing and Homelessness

Clinicians also care for many patients who are experiencing challenges with housing, including the imminent risk of homelessness. Given already substantial challenges in obtain housing, any pending eviction or loss of a Section 8 voucher should be treated as a legal emergency with an immediate referral to a legal services provider given often strict timelines (days) to respond to any pending legal action.

For those who have concerns with the habitability of their housing due to pests, mold, rodents or other health hazards, or have nonfunctioning heating or appliances, a request can be made of the landlord to adhere to codes of habitability to resolve the concerns. Patients may also require reasonable accommodation because of a disability or feel that they have been discriminated against in violation of the Fair Housing Act. For patients who own their homes and are at risk of foreclosure, working with a lawyer who specializes in housing may allow individuals to negotiate a modification on their mortgage or a payment plan in order to keep their housing. All of these patients can be connected to their local legal services organizations for additional support.

Challenges may also exist with utilities. Many regions or states have heating assistance programs for low-income individuals. There are also other utility assistance programs for electricity, gas, telephone, and even internet services. Patients with limited income should inquire with their utility companies about any available assistance.

Those experiencing homelessness can apply for Section 8, the federal housing assistance voucher program that pays a portion of an individual's rent. Section 8 is extremely limited in supply, and in many jurisdictions the waitlist for Section 8 is only open a few days each year for new individuals to sign up. Once an individual registers, the wait can be as long as 5 to 10 years.

Health care organizations may support funding for housing through a Housing First model, which has been shown to improve health while reducing costs.[55a] For those with medical needs and insurance, skilled nursing facilities, congregate living, medical respite, and recuperative care are options. For those with limited income, board and care facilities or renting a room may be an option. Individuals with immediate housing needs can access available shelter systems. Shelters often offer little privacy, do not allow individuals to stay during the day, and require people to line up for a bed on a daily basis. Shelters often also have restrictions based on age and gender, making it challenging for families or couples to stay together. Given these restrictions and limited availability, many individuals opt to live under less stable conditions—in their vehicles, with friends or family, or on the streets.

Transportation Challenges

Most EDs offer a range of transportation options for patients at the time of discharge, including public transit assistance, taxi, rideshare, shuttle service, and medical transportation. This is the perfect time to make sure that patients understand their transportation options to obtain follow-up appointments.

Health plans often have transportation benefits included. Medicaid is legally required to provide nonemergency transportation for patients. Ensuring patients understand how to use this service can decrease barriers to transportation, improve adherence to follow-up, result in improved health outcomes, and lead to significant savings.[56] Those who are having trouble accessing required benefits should contact legal services.

Health facilities either provide patients with transportation vouchers in partnership with local providers or let providers know that the patient would benefit from transportation assistance. The vouchers can be for public transportation, taxis, or rideshare programs such as Lyft. Some health facilities have taken on this approach[57] while others have created shuttle services or used volunteer drivers to address the challenge of transportation.[58]

Immigration Status

Adjustment of Status

For those who are without legal status, there are several options for adjusting status. A family-based petition process is available if there is a family member who is a US citizen to adjust their status and become a legal permanent resident (green card holder). However, initial entry to the United States without permission may require the petitioner to leave the United States for up to 10 years prior to reentering even if they qualify for a green card. Petitioning for and support by an employer for a green card is also an option.[59] A number of other special categories that qualify a petitioner for legal status can be found on the US Citizenship and Immigration Services (USCIS) website (https://www.uscis.gov/citizenship). Immigration is a complex issue, and individuals with immigration questions should be connected to the local bar association to work with a qualified attorney.

Victims of Violence and Crime

Interpersonal violence is an important cause of morbidity and mortality. For further discussion of this issue, please see the chapters on community violence and intimate partner violence and abuse (see Chapters 190 and 192). Clinicians can work with social services to help victims in reporting their crime to law enforcement and to ensure a safe ED discharge plan. Furthermore, victims of interpersonal violence may be eligible for a temporary or permanent restraining order as part of their safety plan. Courthouse self-help centers and legal aid organizations can help victims apply for a restraining order. Regarding financial assistance for victims of violence, any victim (and their families) are eligible for the Crime Victims Fund established by the Victims of Crime Act of 1984. This fund is managed by the Office for Victims of Crime and administered by each state.[60] For those victims who are without legal status, cooperating with law enforcement to investigate and/or prosecute the crime may allow the individual to apply for a special visa or to become a legal permanent resident (green card holder)

Victims of violence and crime are especially vulnerable when they are without legal immigration status because their abusers may threaten to report them to immigration officials as a deterrent to reporting the crime and seeking help. Victims of intimate partner violence can adjust their status and apply to become legal permanent residents (green card holder) through either the federal Violence Against Women Act (VAWA)[61] or the Victims of Criminal Activity U Nonimmigrant Status (U Visa),[62] as long as the victims make a police report and cooperate with law enforcement to investigate and prosecute the crime. Those who are the victims or witness to other crimes, including but not limited to assault, rape, kidnapping, and blackmail, are also eligible for the U Visa.[63]

Those who are victims of sex or labor trafficking and/or who are certain family members of these victims are eligible to apply for the T nonimmigrant status as long as they cooperate with law enforcement to investigate and/or prosecute the crime[64] (see Chapter 187).

Although complicated, a path to legalization and citizenship for these vulnerable patients is possible. Ensuring appropriate documentation such as police reports, discussing options with social work, and ensuring connection to a local legal services provider are all important next steps of which the emergency clinician should be aware.

Refugees and Asylees

Refugees are individuals who have been persecuted or fear that they will be persecuted based on their race, religion, nationality, political opinions, or membership in a particular social group who seek refugee status from outside of the United States. Asylees are individuals who are already in the United States, or those who are actively seeking to enter the United States and meet the definition of a refugee. If asylees do not have legal status, they can apply for adjustment of status through USCIS (recommended to do so with an attorney's help).[65]

Asylees under 21 years of age who are seen in the ED may qualify for Special Immigrant Juvenile Status. To qualify to apply through USCIS (recommended to do so with an attorney's help), the individual must be currently unmarried, cannot be reunited with parents because of abuse, abandonment, neglect or other similar reasons, and cannot in their best interest return to the country of nationality.[66]

Hospital Safe Spaces Initiatives

Immigrants often fear seeking medical care because of confusion caused by complicated and ever-changing immigration policies.[67] Educating patients that the ED and hospital are safe spaces where providers are focused on treating health and will not report patients to the USCIS is crucial to ensuring that patients seek care in a timely manner. Providers should respect patient privacy and not disclose patient information unless served with a valid warrant. Any questions that arise should be deferred to the hospital's legal counsel and the administrator on duty.

Immigration Status and Public Charge

The idea of becoming a "public charge" or one who is reliant on public benefits, has caused fear and hesitation among immigrant communities to seek care.[68] Although applying for and receiving certain public benefit programs *may* make one a public charge, seeking and receiving health care services never does. However, for the undocumented individual, eligibility to receive public benefits is impermissible unless the specific exceptions are met. Individuals should be reassured that obtaining health care never makes them a public charge and providers should refer them to a legal services attorney to evaluate their individual case and public benefits.

Education-Related Challenges

For youth with school-related concerns regarding truancy, suspension and expulsion, or with respect to reasonable accommodation with an Individualized Education Plan (IEP), clinicians can connect the youth and their parents or guardians to an attorney specializing in education law. Connecting with the local bar association is one way to find low-cost or no-cost attorneys who specialize in education law.

For adults, connection to the local community college or other special adult education programs allows for exploration of affordable educational options.

TABLE 189.2 Health Harming Legal Needs

Health Harming Legal Needs Categories	Specific Needs
Housing	Eviction, Section 8 voucher termination/denial, habitability, discrimination, reasonable accommodation
Employment	Improper termination, discrimination, unpaid wages, unpaid overtime, lack of breaks/meals/accommodation
Family	Divorce, custody, child support, restraining orders, guardianship, adoption
Immigration	Adjustment of status (family-based, employment based, U-Visa, T-Visa, VAWA, SJIS, asylee/refugee), naturalization, deportation defense
Healthcare Benefits	Denial/termination of coverage (Medicaid, Medicare, other insurance), denial of specific benefits, lack of timely access, medical debt/charity care/negotiating a payment plan
Other Public Benefits	Denial/termination of TANF, VA benefits, SSI, SSDI, SNAP, IHS, unemployment, short term disability, other cash aid; overpayments; improper amount of benefit
Consumer	Debt, fraud
Elder	Advanced directives, conservatorship, wills and trusts
Justice-Involved	Expungement, tickets, warrants,
Miscellaneous	Name change, gender change

Domestic Concerns and Social Isolation

Troubled family dynamics and relationships can be a source of stress and lead to ED visits and poor health.[69] In most jurisdictions, emergency providers are required to report cases of suspected child or elder abuse. Patients may face challenges with marriage and children. If there is no intimate partner violence, then a referral to the local legal services agency, courthouse, and/or bar association can help patients access resources to resolve these concerns.

Patients are sometimes dropped off in the ED because family members are unable to care for them. Medicaid offers in-home support services (IHSS) as part of its benefit to help individuals remain in the least restrictive environment. This is often an option for elders or disabled patients. The local social service agency may provide some assistance with childcare as part of its Temporary Assistance for Needy Families (TANF) benefit.

Elders and their families may request assistance with creating an advanced directive. In addition to assisting patients and their families fill out the portable medical order (POLST) form, caregivers can refer patients to the local bar association for assistance. Providers may see patients who feel socially isolated. Working with social work and local agencies can provide options such as day programs for elders and support groups for individuals with special needs.

Legal Concerns

Legal Assistance

Reduced cost or free legal services are available to help low-income individuals with issues such as public benefits, housing, and family law (Table 189.2). Many of the nonprofit legal services providers who offer low-cost or free legal services programs are federally funded.[70] For issues that legal aid providers do not assist with, clinicians can refer patients to the local bar association for help.

Medical legal partnerships are arrangements that place attorneys into the health care setting to work as part of the health care team.[71] These attorneys can be hired by the health care team directly or come from local nonprofit legal services organizations. They work with the health care team to address health-harming legal needs. The co-location and communication allows the provider to make the legal team part of the treatment plan while the legal team works with the provider to demonstrate the health harm that patients are suffering.

Patients in Police Custody

Clinicians often care for patients who are in police custody, where there is a significant power imbalance between the patient and law enforcement. It is often difficult for patients in custody to obtain health care, so providers should ensure thorough medical assessments are performed in this vulnerable patient population where routine care is limited.[72] Best practices support patient interviews in private, clear communication of results, and follow-up instructions clearly documented in discharge instructions confidentially communicated to the correctional facility's health care staff. Any physical or medical limitations for the patient should be communicated to accompanying officers.

To avoid conflict between the emergency clinician and law enforcement officials when the question of blood draws for legal purposes arises, policies should be in place to allow providers to respect patient autonomy. This will help the clinician avoid the difficult legal circumstance of having to choose between either defying a request from law enforcement or being potentially liable for assault.

Tickets and Outstanding Warrants

Patients who are not in custody may have concerns about unpaid tickets and outstanding warrants. These public records may make it difficult for them to access housing or jobs. Such concerns are becoming more prevalent as jurisdictions criminalize homelessness and poverty with laws such as the sit-lie laws that prohibit sitting or lying on the sidewalk or in other public spaces. Referral to local legal services providers can allow patients to receive an evaluation and potentially address these concerns.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 189: QUESTIONS AND ANSWERS

1. Which of the following statements regarding social determinants of health (SDOH) is true?
   - **a.** Less than 20% of health outcomes can be attributed to SDOH.
   - **b.** SDOH equally impacts all segments of the US population regardless of income.
   - **c.** Immigration status is not considered a SDOH.
   - **d.** Health literacy is one of the most significant aspects of SDOH.

Answer: D. Patients may have limited health literacy, which is defined as limited capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions may have poorer adherence to care plans and poorer health outcomes. An estimated 20% of a patient's health outcome is influenced by medical care, whereas social and economic factors account for 50% of such outcomes. Social concerns disproportionately affect the poor and impede health. Immigration as an experience has profound effects on individuals and their health. Immigration status has an important effect on patients for two reasons—immigration status is linked to ability to work and to access public benefits, including health care.

2. Which of the following factors impact health outcomes?
   - **a.** Access to transportation
   - **b.** Homelessness and housing
   - **c.** Food insecurity
   - **d.** Income and insurance
   - **e.** All of the above

Answer: E. Access to transportation affects an individual's ability to access care, adhere to appointments, and carry out treatment plans, having a direct impact on health. These individuals have worse health outcomes and mortality compared with those who are housed. Delayed care is a common issue that arises in the ED as uninsured and underinsured patients often are unable to access care prior to an ED visit. Lack of access to healthy foods leads to increased rates of mental health problems, low birth weight, depression, hypertension, diabetes, and hyperlipidemia.

3. Which of the following ED-based strategies can counteract SDOH?
   - **a.** Systematic screening in the emergency department can be a significant step in recognizing patients with significant SDOH.
   - **b.** Addressing SDOH must occur only within the health care system for the strategy to be successful.
   - **c.** Addressing concerns of health literacy first will substantively impact health outcomes by improving patients' failure to comply with follow-up care instructions and access to community resources.
   - **d.** Violence prevention is not a reasonable strategy in combating poor outcomes due to SDOH.

Answer: A. Most departments do not currently screen for social needs. Instead, social needs arise during the course of the patient encounter. Options for systematic screening exist but require implementing a framework to address social needs.

4. Which of following health-related benefits available in the United States can impact access to care and health outcomes?
   - **a.** Children's Health Insurance Program (CHIP) is a specific program focused on providing access to care for children up to age 26.
   - **b.** The Affordable Care Act requires plans and issuers that offer dependent child coverage to make coverage available until the child reaches the age of 21.
   - **c.** The Hill-Burton Act of 1946 mandates charity care obligations for facilities that benefited from the funding.
   - **d.** Part A Medicare benefits are essential to supporting prescription drug coverage.

Answer: C. Facilities built with assistance from the Hill-Burton Act of 1946 have legally mandated charity care obligations. There are specific programs focused on providing access to care for children under the age of 18, including the Children's Health Insurance Program (CHIP). The Affordable Care Act requires plans and issuers that offer dependent child coverage to make coverage available until the child reaches the age of 26. Medicare is administered and funded by the federal government and contains several parts including inpatient hospital coverage (Part A), outpatient medical coverage (Part B), alternative coverage options including Medicare Advantage (Part C), and prescription drug coverage (Part D).

5. Which of the following statements regarding legal services available to ED patients is true?
   - **a.** Legal services are typically unhelpful in increasing access to health care coverage but are invaluable in supporting immigration status adjustments.
   - **b.** A public charge applies to anyone seeking health care services, so referral to legal services is essential to evaluate individual cases and public benefits.
   - **c.** In managing family and domestic concerns, referral to legal services should only occur if there is evidence of intimate partner violence or elder abuse.
   - **d.** Heath-harming legal needs are defined as a group of legal factors that can adversely impact health outcomes.

Answer: D. Legal services are typically helpful in a wide variety of circumstances and address what may be considered health-harming legal needs. The idea of becoming a "public charge," or one who is reliant on public benefits, has caused fear and hesitation among immigrant communities to seek care. While applying for and receiving certain public benefit programs *may* make one a public charge, seeking and receiving health care services never does. However, for the undocumented individual, eligibility to receive public benefits is impermissible unless the specific exceptions are met. Family dynamics and relationships can be a source of stress and lead to emergency department visits and poor health. Addressing challenges can improve health for patients. Patients may face challenges with marriage and children. If there is no intimate partner violence, then a referral to the local legal services agency, courthouse, and/or bar association can help patients access resources to resolve these concerns.

Community Violence

Theodore Corbin and Thea James

KEY CONCEPTS

- It is important for prevention efforts, including those in hospitals and emergency departments, to consider unjust social conditions disproportionately experienced by minority communities, and especially by African Americans; these include generational poverty, residential segregation, and other forms of racism that limit opportunities to grow up in healthy and violence-free environments.
- Interventions should focus on altering the quality of life course for survivors of violence through targeting their total wellness and thriving through employment, education, financial stability and economic mobility, independence, and stable emotional health.
- Hospital based violence intervention programs (HVIPs) that incorporate at least some brief intervention and case management demonstrate HVIP cost-effectiveness with decreases in injury recidivism.

FOUNDATIONS

Population Characteristics and Violence

Young adults and adolescents in the United States (US) are exposed to crime and violence at much higher rates than those in other developed nations.[1] Rates of violence in the United States also vary by location, with higher homicide rates in metropolitan communities compared to suburban or rural areas.[2] Over 80% of the 12,979 firearm homicides in the United States in 2015 occurred in urban areas,[3] and disparities are larger in certain areas of large cities (e.g., racially and ethnically diverse neighborhoods). For instance, in Philadelphia's safest police district, which is approximately 85% white, there were no reports of anyone being killed by gun violence. Conversely, the most violent district, with a roughly 90% African American population, had over 180 shooting victims and 40 deaths.[4] African American youth in the United States disproportionately carry the largest burden of violent experiences. The homicide rate for African Americans in the United States is eight times higher than that of their white counterparts,[3] and African Americans are 500 times more likely to die this way.[5] While African American young adults and adolescents only make up about 2.4% of the US population, they are disproportionately victims of injuries from assault (26%) and homicide (20.7%).[3,6]

Contributing factors to these differences in rates of violence by location are rooted in historical, present day, and persistent structural racism (e.g., racial segregation), inequality, and poverty.[7] Structural barriers that impact present day rates of violence were established decades ago.[8-11] In the 1930s, President Franklin D. Roosevelt (FDR) created opportunities for wealth-building to help Americans recover from their financial losses in the 1929 Great Depression, securing home ownership through access to guaranteed financial services. In the same decade, FDR's administration established redlining, a practice with long-lasting effects that segregated America both racially and socioeconomically. Redlining policies drew red lines through cities across America, and residents living behind red lines were denied access to financial services (i.e., mortgages, loans, insurance companies) needed for wealth-building through home ownership and the benefits of home equity. A majority of people living behind red lines were people of color and low income. Redlining policies established two distinct socioeconomic populations that still exist today.[8-11] Communities located behind historic red lines have lower rates of education attainment, income, and life expectancy, and higher rates of homicide.[9,12,13] In general, populations in these communities have lower rates of health, as do their children[12] as beneficiaries of their parents' limited resources.[14]

Community Violence

Community violence is a complex and persistent health issue that disproportionately affects low-income neighborhoods and communities of color in the United States. Community violence occurs primarily in public settings, occurs between individuals or groups who may or may not know each other, and is often an impulsive or loosely planned act.[15] The effects of community violence are severe and often result in injuries or death. Both those who contribute to and are survivors of community violence are disproportionately young men and adolescent males from historically disadvantaged backgrounds and communities.[15] Analysis of 2017 data from the National Vital Statistics System, National Crime Victimization Survey, and the Youth Risk Behavior Surveillance System concluded that African American young adults and adolescents are at a much greater risk of violence (e.g., homicides, fights with injuries, aggravated assaults) compared to their white counterparts.[16] Furthermore, the frequency of exposure to community violence is higher in large urban cities and within impoverished communities. There is an overrepresentation of racial minorities, especially African American males, among youth who live in these communities and are disproportionately exposed to violence.[17]

Further exacerbating community violence is the lack of economic growth in an area, further contributing to the cycle of urban flight. For instance, there is slower growth in businesses, new retail, and a depreciation of home values in communities with higher rates of violence.[18] Families of victims and survivors of gun violence often experience financial stress, such as having challenges in paying rent, bills, and phone services because of the loss in earnings from employment and medical costs.[19] Exposure to community violence can be very traumatic for individuals and contributes to poor health among African American young adults and adolescents. Community violence exposure has been found to be associated with an increase in psychological health problems, including posttraumatic stress disorder, depression or anxiety, and aggression.[17] Alarmingly, the disproportionate impact of violence on young African Americans comes from forms of violence

having the greatest immediate negative consequences on physical and mental health, such as aggravated assault and homicide.

SPECIFIC ISSUES

Root Causes of Community Violence

Since the first Africans were brought to the United States, African Americans were forced to live in poor physical and social conditions. For over 250 years, enslaved African Americans suffered social, physical, and mental abuse and brutalization. Although slavery has ended, African Americans still live in a country that is unjust, and one that has systemically discriminated against and oppressed them. Slavery and present day structural and institutionalized racism have contributed to the poor health among African Americans.[20] African Americans in the United States are exposed to constant racism that is systemic (organized socially and culturally) through exclusion, prejudice, and discrimination.[21] Racism is also correlated with second-rate employment, housing, education, income, and access to health services. Racism is a factor in health disparities and inequities that is not explained by other demographic factors such as age, gender, and educational attainment.[21] Due to their lower socioeconomic status, racial or ethnic minorities suffer disproportionate risks for poor health outcomes: occupational hazards, exposures to toxic substances and allergens in the home, low-quality schooling, and lack of availability of healthy foods.[20] While these risk factors are not clinical in nature, they make up the social determinants of health which includes factors such as race/racism, poverty, education, housing, access to healthy food, environmental exposures, violence, and gender. Compared to their white counterparts, proportionately fewer African Americans in the United States graduate from high school or earn a college degree,[22] and they are more than two times as likely to be unemployed.[23,24] The social determinants of health predict the health needs of a population, and the health risks, much more than clinical care.[20]

African Americans, through poverty and residential segregation, live in some of the poorest neighborhoods throughout the United States, areas with high rates of homicide.[20] Violence influences health greatly and can cause injury, disability, and preventable death. African American youth are more than four times more likely to die from a gunshot wound than their white counterparts.[20] African American children are much more likely to witness violence and 20 times more likely to witness a murder than their white counterparts.[25]

Race or ethnicity alone are not risk factors for violence, but rather are associated with socioeconomic risk factors for violence.[26] Therefore, it is important for prevention efforts, including those in hospitals and emergency departments, to consider unjust social conditions that are disproportionately experienced by minorities, and especially African Americans, including generational poverty, residential segregation, and other forms of racism that limit opportunities to grow up in healthy and violence-free environments. Addressing these conditions is critical to lessening and eliminating violence exposure among African American and other minority and vulnerable communities.[16]

Psychological and Mental Health

Trauma has been defined as an emotional response to a distressing event, such as an accident, rape, violent attack, or natural disaster.[27] Trauma can invoke long-term reactions and adverse effects such as flashbacks to the traumatic event, unpredictable emotions, poor mental, physical, social, emotional, or spiritual well-being.[27,28] Experiencing traumatic events or chronic traumatic events, such as exposure to community violence, is also associated with traumatic stress reactions that include fear, anger, sadness, shame, guilt, aggression, and behavioral health issues.[29-33]

The physical and mental health consequences of experiencing violence over time can lead to the development of preventable chronic conditions and can result in considerable health burdens and costs, lower quality of life, and lost productivity.[34] Racial and ethnic minorities, particularly African American young adults and adolescents in urban areas, are experiencing trauma from community violence at levels that impede their ability to cope in healthful ways.[35] The stressful and traumatic events from community violence contribute negatively to mental health and overall quality of life through emotional changes, and this is also passed on through generations. With poverty and high exposure to racism and discrimination, African Americans suffer from more frequent and intense poor mental and behavioral health compared to their white counterparts.[36]

Disparities in Access to Mental Health Care Services and Treatment

Community violence disproportionately persists in communities of color. Also disproportionately impacting African American young men and adolescents, exposure to community violence is negatively associated with psychological and behavioral health issues. Disparities in access to and utilization of mental health care services among African Americans and Latinos stem from limited access, mistrust, stigma, misdiagnosis, little understanding about mental illness, and feeling culturally misunderstood.[37-38] Shame, ridicule from peers, mistrust of health care service providers, and mental health stigma can deter African American young men and adolescents from receiving mental health treatment.[39] One study observed that African American parents were much less likely to seek mental health care services for their children if they themselves held high levels of stigma towards mental health.[40] Furthermore, uninsured African Americans with depression are less likely to be prescribed antidepressants compared to those who are insured, and those who are insured are still less likely to be prescribed medications compared to their white counterparts.[41]

PHYSICAL TRAUMA FROM VIOLENT INJURY AND THE ROLE OF HOSPITALS, EMERGENCY DEPARTMENTS, AND TRAUMA CENTERS

Victims of interpersonal violence may experience traumatic physical injuries and seek treatment from hospitals, emergency departments (EDs), and trauma centers. The vast majority of these centers focus almost exclusively on stabilizing patients, and clinicians in these settings may not recognize the importance of assessing psychological and mental health issues that victims may experience post-injury. Most trauma centers are not equipped with the resources, staff, and systematic approach to identify and address the social factors that contribute to persistent community violence among the patient populations they serve.[42] Individuals who are victims of interpersonal violence and have exposure to community violence are more at risk for recurrent trauma.[43] Health care providers that care for victims of physical injury have an opportunity to incorporate violence prevention into their care. With emerging acceptance that violence is structural in the United States, emergency and trauma physicians have been inspired to participate in the reduction of violence through prevention and intervention efforts.[44-47]

Hospital-Based Violence Intervention Programs

The first hospital-based violence intervention programs (HVIPs) in the United States were developed in the 1990s: the "Caught in the Crossfire" program in Oakland, California, and Project Ujima in Milwaukee, Wisconsin.[42] Since then, several HVIPs have been developed and implemented in the United States with the National Network of Hospital-Based

Violence Intervention Programs, now known as the Health Alliance for Violence Intervention (HAVI).[48] According to Rosenblatt et al., several fundamental principles of HVIPs include the following:

> *"1) Violence is preventable,*
>
> *2) Hospitals should use public health-based principles to approach violence prevention, including working to address the following in the patients and communities they serve: poor education, lack of job opportunities, injury and criminal recidivism, socioeconomically deprived neighborhoods, substance abuse, complex posttraumatic stress disorder, lack of positive role models,*
>
> *3) There is a 'teachable' moment during which a patient may be more receptive to psychological first aid and prevention principles following a traumatic injury, and*
>
> *4) Intervention will begin in the hospital but must follow the patient and family into their community. Case management principles are implemented, ideally including professionals with therapeutic skill sets and 'credible messengers' with knowledge of the patient population."*[42]

Several studies have suggested that HVIPs are beneficial for patients who are exposed to community violence and who are survivors of interpersonal violence. A recent review found that HVIP programs that incorporate case management and at least some brief intervention observed decreases in recidivism, and that HVIPs are cost-effective. Furthermore, it must be emphasized that social determinants such as health, stable housing, and increase in income are important components to include in HVIPs.[49,50,51] Several studies have shown that HIVPs can decrease the reinjury rates of participants by up to 50% and that even applying a brief intervention to reduce violence among youth (ages 14 to 20) was associated with increased self-efficacy for avoiding fighting and a decrease in aggression frequency.[52,53]

It is feasible to integrate health data on violence and other patient characteristics (e.g., social determinants of health information) into ED electronic medical records across institutions, with minimal impact on workflow and triage times, to collectively gather data on violence and aid in public health surveillance of community violence data trends.[54] Organizations such as the Centers for Disease Control and Prevention could then use this data to fund HVIPs where they are needed the most.[55]

HVIPs can also incorporate digital health tools. One study of a technology-augmented violence and depression intervention tool for high-risk adolescents found a high level of acceptance among participants, who experienced less depression and less subsequent violence compared to the control group.[56]

Peers and community members with similar lived experiences as victims of violence should be included in the process of operating an HVIP. This approach has been effective for EDs trying to understand how their HVIP can improve the lives of individuals experiencing violence in their communities.[57,58] An HVIP housed at Drexel University in Philadelphia has an ongoing evaluation that assesses delivery of services and trauma symptom reduction. Preliminarily, the HVIP demonstrates that the services provided by the team decrease trauma symptoms. Using a focus on structural determinants of health to mitigate and eliminate gaps to thriving, HVIPs have served as models for health care systems aiming to sustainably reduce costs and improve health outcomes in the communities they serve.[59,60]

Boston University HVIP Model

A Boston University emergency medicine–based HVIP began with a "no assumptions" approach to building its program. The program engaged survivors of violence to help understand the root causes of the city's disproportionate geographic prevalence of community violence. Knowledge of the structural barriers in communities, and in their patients' lived experiences, shaped expectations of what was possible for them to achieve.[8] The program learned that its patients who were survivors of violence were coming from communities that had been disinvested in for decades and predictably experienced low income, education attainment, economic mobility, and opportunities to build wealth. These communities were among those negatively affected historically by redlining policies.[10] The Boston HVIP survivors of violence expressed overwhelming themes of hopelessness.

Guided by intervention models of the network of HVIPs nationally,[11] the Boston HVIP program made a conscious decision to set high bars to alter the quality of life course for their patients through intentional disruption of structural barriers. The program encouraged survivors of violence to identify their goals and then partnered with them to achieve those goals. Common goals were education, steady employment, stable housing, and safety. The program hired and embedded a career specialist for workforce development, hired a housing advocate, and expanded its multisector community partnerships in workforce development, financial literacy, education, and housing.

The Boston HVIP's hospital health care system is now using the same model expanded to all patients. This occurred in large part to a charge by its largest payer, Massachusetts Medicaid or Mass Health, in 2018. Its hospital health care system is the largest recipient of Medicaid payments in Massachusetts. Mass Health addressed its decadelong upward trajectory of rising costs and poor health outcomes by changing from a fee-for-service to value-based care reimbursement. It charged Boston health care systems, who are Medicaid payees, to lower cost and improve outcomes prescriptively by focusing on social determinants of health. HVIPs have years of experience in this area.

The Boston HVIP's hospital health care system is now using an HVIP model to alter life course for all patients. Examples of how the Boston HVIP hospital has targeted structural barriers to health to alter the quality of life course of its patients and communities where they live include the following:

1. Development and operationalization of a screening tool in ambulatory clinics that identifies gaps people have, and connects them to resources to mitigate and eliminate the gaps; the tool is embedded in their electronic medical record for providers to see. A built analytics platform evaluates and monitors results monthly.
2. The hospital joined the Healthcare Anchor Network, a national collaboration of 45 health care systems. Their goal is to build more inclusive local economies through hospitals being intentional about how they make daily decisions in three pillars; hiring, investment, and procurement.[12]
3. Invested in a private equity fund that explicitly funds developments that provide access to affordable housing, employment, green walking space, transit, and healthy affordable food.[13,14]

a. The investment contributed to what is becoming 323 units of new mixed-income housing to own and to rent.
b. Seventy percent of laborers at the construction site come from the community.
c. The hospital was able to help a grocery store mitigate expansion costs of moving to the site by giving it a no interest loan.

4. The hospital invested to support a local organization that invests in local small business development.
5. The hospital health care system expanded its procurement operations to include more local vendors. It built an analytics platform to monitor and evaluate progress.
6. The Affordable Care Act requires hospitals to conduct a community health needs assessment with an improvement plan every

three years. In 2019, the Boston hospitals conducted an assessment together. Prioritized improvement plan areas that emerged from the assessment are housing, finance and economic mobility, access, and behavioral health. The hospitals will collectively address the first two domains in communities with goals to have measurable impact.[60]

7. The Boston HVIP hospital created an innovative Stable Housing Initiative.[59] Subsequently, two other Boston academic medical centers joined them and together they have partnered and invested in innovative solutions to housing instability.

The HVIP model of altering quality of life course has served as a proof of concept for all patients who face perpetual life and health instability due to structural barriers.

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CHAPTER 190: QUESTIONS AND ANSWERS

1. Which of the following statements correctly describes a difference between uninsured African American (AA) patients and uninsured white patients with depression?
- **a.** AA patients are less likely to be prescribed antidepressants.
- **b.** AA patients are less likely to be diagnosed with depression.
- **c.** AA patients are more likely to think about suicide.
- **d.** AA patients are less likely to need ongoing therapy.

Answer: A. A study observed that African American parents were much less likely to seek mental health care services for their children if they themselves held high levels of stigma towards mental health.[40] Furthermore, uninsured African Americans with depression are less likely to be prescribed antidepressants compared to those who are insured, and those who are insured are still less likely to be prescribed medications compared to their white counterparts.[41]

2. Which of the following statements is true regarding individuals who are survivors of interpersonal violence and are exposed to community violence?
- **a.** They are more at risk for reinjury/trauma recidivism.
- **b.** They are less at risk for retaliation.
- **c.** They are more likely to receive follow-up care.
- **d.** They are less likely to seek psychological support.

Answer: A and D. Victims of interpersonal violence may experience traumatic physical injuries and may seek treatment from hospitals/emergency departments/trauma centers. The vast majority of these centers focus exclusively on stabilizing patients and clinicians in these settings may not recognize the important of assessing psychological and mental health issues victims may be experiencing post-injury. Most trauma centers are not equipped with the resources, staff, and systematic approach to identify and address the social factors that contribute to persistent community violence among the patient population they serve.[42] Individuals who are victims of interpersonal violence and have exposure to community violence are more at risk for reinjury/trauma recidivism.[43] Furthermore, discrimination and limited access to mental health facilities increase disparities in mental health for communities of color.[38]

3. Which of the following young populations is most at risk for poor physical and mental health outcomes from exposure to physical violence (e.g., homicide and aggravated assault)?
- **a.** Men
- **b.** Women
- **c.** African Americans
- **d.** Latino Americans

Answer: C. African American youth in the United States disproportionately carry the largest burden of violence experiences in general. The homicide rate for African Americans in the United States is eight times higher than that of their white counterparts[3] and African Americans are 500 times more likely to die this way.[5] African American young adults and adolescents only make up about 2.4% of the US population, but they are disproportionately victims of injuries from assault (26%) and homicide (20.7%).[3,6]

4. According to Rosenblatt et al.,[42] several fundamental principles of HVIPs include all of the following except:
- **a.** Violence is not preventable, but it can be managed.
- **b.** Hospitals should use public health–based principles to approach violence prevention, including working to address poor education, lack of job opportunities, injury and criminal recidivism, socioeconomically deprived neighborhoods, substance abuse, complex posttraumatic stress disorder, and lack of positive role models.
- **c.** There is a "teachable" moment during which a patient may be more receptive to psychological first aid and prevention principles following a traumatic injury.
- **d.** Intervention will begin in the hospital but must follow the patient and family into their community. Case management principles are implemented, ideally including professionals with therapeutic skill sets and "credible messengers" with knowledge of the patient population.

Answer: A. Several fundamental principles of HVIPs include:

"**1.**Violence is preventable,

CHAPTER 190: QUESTIONS AND ANSWERS—cont'd

2. Hospitals should use public health-based principles to approach violence prevention, including working to address the following in the patients and communities they serve: poor education, lack of job opportunities, injury and criminal recidivism, socioeconomically deprived neighborhoods, substance abuse, complex posttraumatic stress disorder, lack of positive role models,
3. There is a 'teachable' moment during which a patient may be more receptive to psychological first aid and prevention principles following a traumatic injury, and
4. Intervention will begin in the hospital but must follow the patient and family into their community. Case management principles are implemented, ideally including professionals with therapeutic skill sets and 'credible messengers' with knowledge of the patient population."[42]

5. Racism is not correlated with which of the following factors?
   - **a.** Poor housing
   - **b.** Inferior education
   - **c.** Longer life
   - **d.** Access to health services

Answer: C. African Americans in the United States are exposed to constant racism that is systemic (organized socially and culturally) through exclusion, prejudice, and discrimination.[21] Racism is correlated with second-rate employment, housing, education, income, and access to health services. It is well known that racism is a factor in health disparities and inequities that is not explained by other demographic factors such as age, gender, and educational attainment.[21] Also, there are many risks for individuals who are racial or ethnic minorities such as occupational hazards, exposures to toxic substances and allergens in the home, low-quality schooling, and lack of availability of healthy foods.[20] While these risk factors are not clinical in nature, they make up the social determinants of health, which includes factors such as race/racism, poverty, education, housing, access to healthy food, environmental exposures, violence, and gender.

Sexual Assault

Jennie Alison Buchanan and Sarah Tolford Selby

KEY CONCEPTS

- Sexual assault is most common in women but can happen to gay and heterosexual men and to lesbian, gay, bisexual, transgender, and gender-nonconforming individuals.
- Sexual assault often results in no physical signs of injury.
- Optimal care includes creating a safe confidential environment while incorporating the principles of trauma-informed care. The patient should be included in decision making and ultimately decide treatment. Options include injury evaluation, treatment to prevent pregnancy and sexually transmitted infections (STIs), support and trauma counseling, evidence collection, and comprehensive toxicology testing if appropriate.
- The sexual assault evidence collection examination is an intensive, protocol-driven, multistep process, best performed by a certified sexual assault examiner.
- Adult sexual assault patients should be treated empirically according to Center for Disease Control (CDC) guidelines to prevent STIs (e.g., gonorrhea, syphilis, chlamydia, trichomonas, human immunodeficiency virus [HIV], human papillomavirus [HPV], and hepatitis B). Children and adolescents should be tested and, if symptoms develop, treated for STIs.
- All adolescent and adult female sexual assault patients should be offered pregnancy prophylaxis.
- HIV postexposure prophylaxis should be offered if the assailant is known to be HIV-positive, multiple assailants are involved, or if the HIV status of the assailant is unknown.
- Alcohol and drugs may have been ingested voluntarily or involuntarily by the patient. If the patient consents, comprehensive toxicology testing may be performed.
- A strangulation attempt with loss of consciousness, bowel and bladder incontinence, persistent voice changes, difficulty swallowing, or shortness of breath should be comprehensively evaluated in the emergency department (ED). Evaluation options include a chest x-ray, flexible laryngoscopy, and CTA or MRI of the neck. We recommend prolonged observation or hospital admission for persistent symptoms.
- Many victims will not have obvious physical injuries; this does not imply consent or refute a sexual assault.
- The emergency clinician should record observations, statements, and findings that were gathered during the course of ED treatment objectively.

FOUNDATIONS

Sexual assault is the deliberate act of sexual contact or behavior towards another person without that person's explicit consent. Rape is a form of *sexual assault* and is defined by the Federal Bureau of Investigation (FBI) as "penetration, no matter how slight, of the vagina or anus with any body part or object, or oral penetration by a sex organ of another person, without the consent of the victim."[1] *Sexual assault* is a form of *sexual violence*. The term *sexual violence* is defined by the World Health Organization (WHO) as "any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic, or otherwise directed, against a person's sexuality using coercion, by any person regardless of relationship to the victim, in any setting, including but not limited to home and work."[2] Sexual assault is never the victim's fault and can lead to chronic physical and psychological adverse health effects.

According to the 2015 Centers for Disease Control and Prevention (CDC) National Intimate Partner and Sexual Violence Survey (NISVS), 43.6% of women and 24.8% of men have experienced some form of contact sexual violence in their lifetime.[3] During their lifetime, 1 in 5 women have been victims of completed or attempted rape and 1 in 14 men have been made (i.e., forced or threatened) to penetrate someone else (completed or attempted).[3]

National database estimates on nonfatal injuries treated in emergency departments (EDs) have revealed that 5.4% of all assault-related visits to the ED were for sexual assault.[4] Most of these victims were women. The lifetime prevalence of sexual assault for women and men respectively is 43.6% and 24.8%.[3] Male victims are often younger than their female counterparts with 26% of victimization occurring in males 10 years old or younger and 12.7% in females 10 or younger.[3] Given the prevalence and role in the evaluation and treatment of survivors of sexual assault, emergency clinicians should be comfortable evaluating, treating, and coordinating their care. In many areas, dedicated sexual assault teams or forensic examiners are available to assist with specialized care, detailed evidence collection, and thorough documentation. The team often includes a specialty-trained registered nurse, victims advocate, or social worker, and may involve local police or sexual assault detective(s). The emergency clinician's responsibilities include providing compassionate nonjudgmental care, diagnosing and treating acute injuries, administering medications to prevent pregnancy and sexually transmitted infections (STIs), offering forensic evidence collection and comprehensive toxicology testing when appropriate, and providing linkage to support and follow-up services.[4]

The ED evaluation and treatment can take hours and requires the coordination of multiple resources. Evaluation and treatment of the patient are nuanced, with intertwined medical, legal, and forensic components. Medical stabilization and evaluation take priority over forensic evaluation. The role of the emergency clinician is to objectively record information heard, observed, examined, or photographed. In many cases, a trained forensic examiner will be available to complete the formal forensic evidence collection process. The emergency clinician may be called to testify, sometimes years after the event, necessitating thorough and accurate documentation.

CLINICAL FEATURES

Many sexual assaults are never reported to police or health care providers. Victims who report to the police and who sustain injuries are more

likely to present to the ED for evaluation. Many victims present with concerns about injuries, risk of pregnancy, or contracting STIs (including human immunodeficiency virus [HIV] and hepatitis). Victims may present with mental health concerns, including depression, acute stress reaction, posttraumatic stress disorder (PTSD), and suicidal ideation. Acquaintance and intimate partner rape are less commonly reported to police and health care providers.[1,3] When these victims do present to the ED, they are more likely to present in a delayed manner, when medications to decrease pregnancy rates and STI transmission are less likely to be effective. Most patients who present to the ED with the complaint of sexual assault are women.[2,3] Although some studies have reported a similar age distribution for males and females, others have noted males are assaulted at a younger age (<9 years).[3] Populations at increased risk for sexual assault include the homeless, those with severe disabilities (e.g., serious injury, chronic disease, chronic mental health problems), incarcerated men and women, and the young.[1,5] Other populations at increased risk include college-aged women, non-heterosexuals, those who use illicit drugs and ethanol, and sex workers.[1,5]

Patients who come to the ED with the complaint of sexual assault or rape may present with injuries related to the assault, with general body injuries in up to 67%. It is not uncommon to have minimal or no genital injury from a rape. Genital findings depend on time to presentation, victim's age, parity, and methods used to evaluate for genital injury. Nonfatal strangulation, associated with rape, carries a risk of immediate and delayed psychological and medical sequelae, including airway obstruction, pulmonary edema, and vascular dissection leading to stroke. Nonfatal strangulation has also been associated with an increased risk of future lethality.

Rape can occur in the context of force or coercion or in the context of drug or alcohol ingestion. About 50% of all rapes are in the context of alcohol or drug ingestion, especially in the adolescent or college-aged population. Alcohol or drugs may have been ingested voluntarily by the victim or administered surreptitiously by the assailant. Comprehensive toxicology testing can be considered in those presenting within the specific jurisdiction's time limits (approximately 72–96 hours) but should be approached cautiously as false negatives are common.

Acute reactions to sexual assault vary and are influenced by prior sexual assault or trauma, events surrounding the assault, and preexisting mental health conditions. Victims may appear calm and collected, detached, agitated, angry, depressed, tearful, or anxious. Anger may be directed outwardly toward health care providers, making interactions between the patient and provider challenging. Victim advocates are helpful in supporting the patient and their reactions.

The neurochemical changes in the brain that occur in response to trauma can make recalling details difficult. Recall may be sporadic and disorganized but may become clearer with time and should not be construed as fabrication. Recent research has focused on the concept of tonic immobility, whereby the victim experiences paralysis, increased muscular rigidity, eye closing, and suppressed vocal cord activity in response to an extremely traumatic event. Increasing evidence has suggested that humans may respond this way to a life-threatening event when coupled with inescapability. Although tonic immobility may occur in any traumatic event, it is more common in victims of childhood sexual assault. Victims who report tonic immobility often experience increased feelings of guilt, are at increased risk of developing PTSD, and are much less likely to respond to pharmacologic mental health therapy.

DIFFERENTIAL DIAGNOSES

The purpose of the medical forensic sexual assault examination is to document history and physical findings and collect evidentiary material, not to determine whether or not a rape occurred. Final diagnosis and discharge instructions should avoid the words "rule out" and "alleged." Alternative medicolegal options may include "evaluation following sexual assault," or "sexual assault." As many as 71% of sexual assault victims sustain nongenital injuries. Fortunately, most injuries are minor and rarely require emergent medical or operative intervention. A majority of injuries are from blunt trauma and include contusions, lacerations, incised wounds, bruises, hematomas, sprains or strains, fractures, closed head injuries, intracranial injuries, and intra-abdominal injuries. Treatment of life-threatening injuries should follow advanced trauma life support (ATLS) protocol and take precedence over evidence collection.

BOX 191.1 Indications for Comprehensive Toxicology Screening[a]

- Period of unconsciousness
- Period of loss of motor control
- Amnesia or confused state with suspicion of sexual assault
- Patient suspicion or belief that she or he was drugged prior to or during sexual assault *and*
- Less than 72–96 hours since assault (depending on jurisdictional protocol)

[a]Toxicology screening should be approached with caution as false negatives are common.

DIAGNOSTIC TESTING

There are no specific diagnostic tests for sexual assault. Traumatic injuries should be evaluated per standard protocols. There is no test that can determine if a rape occurred; even visualization of sperm on wet mount by emergency clinicians is often inaccurate.

Sexually Transmitted Infections

Testing for STIs is controversial in adult sexual assault patients. Despite rape shield laws prohibiting the use of a victim's past sexual behavior in court cases, there remains concern that the presence of a preexisting STI may be used to discredit the victim's claim. Furthermore, STI prophylaxis is provided to sexual assault victims and, therefore, will treat any preexisting STIs. Proponents for testing cite public health concerns; identifying preexisting disease allows for notification of previous contacts.[1,2,3] In children, the presence of an STI can be conclusive proof of a sexual assault, and STI testing is uniformly recommended. We recommend testing adults for STIs if the patient complains of signs or symptoms of STIs or when the patient requests testing, along with routine testing of children and young adolescents.

Drug-Facilitated Sexual Assault

Drug-facilitated sexual assault (DFSA) occurs when alcohol or drugs are used to compromise a victim's ability to consent to sexual activity, inhibit the victim's ability to resist, and impair memory of the event. Alcohol is the most common drug used, but many other "drugs" are utilized including illicit agents, prescription medications, and over-the-counter substances. Comprehensive toxicology testing, often performed in specialized forensic laboratories, is recommended in cases of suspected DFSA and can test for multiple illicit, prescription, and over-the-counter substances. The most commonly detected substances include ethanol, cannabinoids, cocaine, amphetamines, and benzodiazepines.[6] Box 191.1 lists symptoms and conditions suspicious for DFSA. Because many substances have a short half-life, toxicology testing should be performed expeditiously; most protocols obtain specimens up to 72 to 96 hours post-assault or after ingestion. Many jurisdictions have specific collection requirements and kits that are sent to comprehensive crime laboratories. At least 100 mL of urine and 12 mL of blood (sodium fluoride tube) should be collected,

and specimens refrigerated, with the chain of custod carefully maintained (Fig. 191.1).

Evaluating the Victim of Attempted Strangulation

Strangulation is a serious and potentially life-threatening injury. Intimate partner violence (IPV) survivors with nonfatal strangulation have a sevenfold increased risk of future completed homicide. Hypoxia is the final common pathway in strangulation and can occur by three main mechanisms—jugular vein occlusion, carotid artery occlusion, or laryngeal occlusion. Symptoms of dysphagia, odynophagia, and dysphonia may accompany physical findings, including facial, periorbital, auricular, intraoral, and neck petechiae (Fig. 191.2) and subconjunctival hemorrhages, the result of venous occlusion causing increased intravessel pressure and rupture. Other possible findings include bruising in the shape of fingerprints on the neck (Fig. 191.3), and defensive scratch marks on the neck from the victim attempting to pry off the assailant's fingers (Fig. 191.4). Alteration in consciousness, neurologic complaints, and urinary or fecal incontinence may result from restricted blood flow to the brain. Direct laryngeal injury may lead to vocal cord injury and laryngeal or hyoid fractures. Carotid artery injury, dissection, or intraluminal thrombosis may cause stroke symptoms, which may not present until months or years after the assault.[7]

We recommend imaging for patients with facial petechiae, loss of consciousness, incontinence, stroke-like symptoms, or voice changes. Imaging modalities and strategies for patient evaluation are listed in Tables 191.1 and 191.2.[7] Consider chest x-ray to evaluate for early pulmonary edema or aspiration pneumonitis, fiberoptic imaging to assess upper airway patency, and computed tomography angiography (CTA) or magnetic resonance imaging (MRI) to evaluate for arterial dissection (most commonly, carotid).[7] Patients with persistent altered levels of consciousness, laryngeal fractures, carotid injuries, or neurologic symptoms should be admitted for close airway monitoring. We recommend that patients with reported loss of consciousness, incontinence, facial or conjunctival petechiae, or signs and symptoms of soft tissue neck injury, or who are under the influence of drugs or alcohol, be observed and monitored for delayed sequelae of injury. Patients with no loss of consciousness, minimal or no physical findings, no intoxication, and a safe discharge environment can be discharged with precautions relating to signs of delayed neurologic, pulmonary or laryngeal sequelae from strangulation.

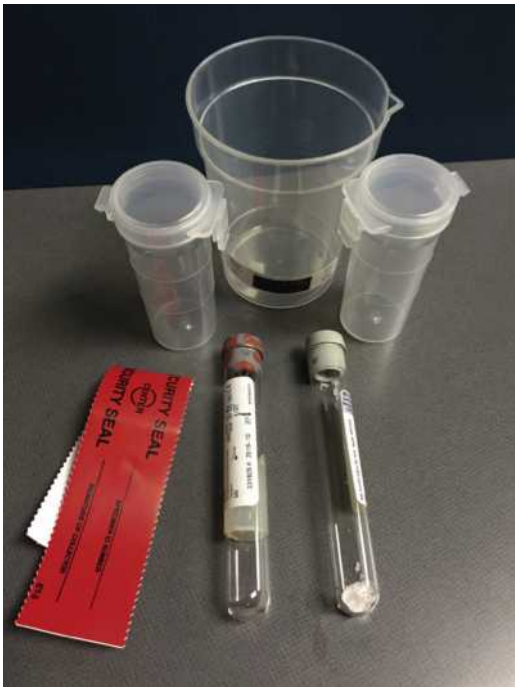


Fig. 191.1 Example of a forensic toxicology test kit for urine and serum specimens.

MANAGEMENT

Management of the sexually assaulted patient requires an organized victim-centered and trauma-informed approach, defined by institutional protocols and available support resources. In most cases, a sexual assault nurse examiner (SANE) or sexual assault forensic examiner (SAFE) will perform the evidentiary examination. Most hospitals should have a protocol concerning the activation of a sexual assault response team (SART), which includes a SANE/SAFE, social worker, and victim's advocate. If there is no SART available at the hospital,

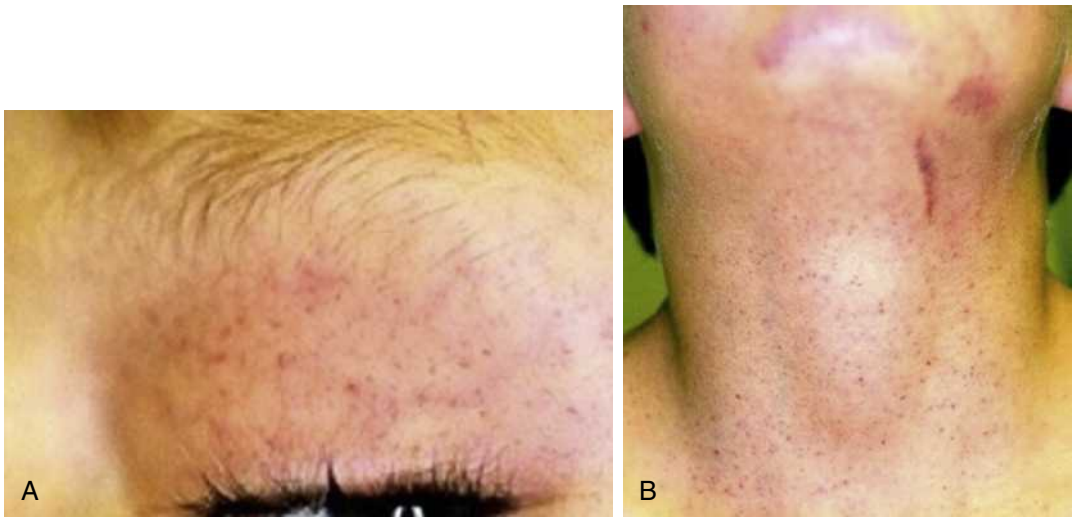


Fig. 191.2 Petechiae in nonfatal strangulation. (A) Eyelid petechiae following the nonfatal strangulation of a child. (B) Neck petechiae seen in the same patient. There is also an abrasion present on the left side of the neck and ecchymosis of the left and right mandibles. (Courtesy Training Institute on Strangulation Prevention, San Diego, CA; used with permission.)

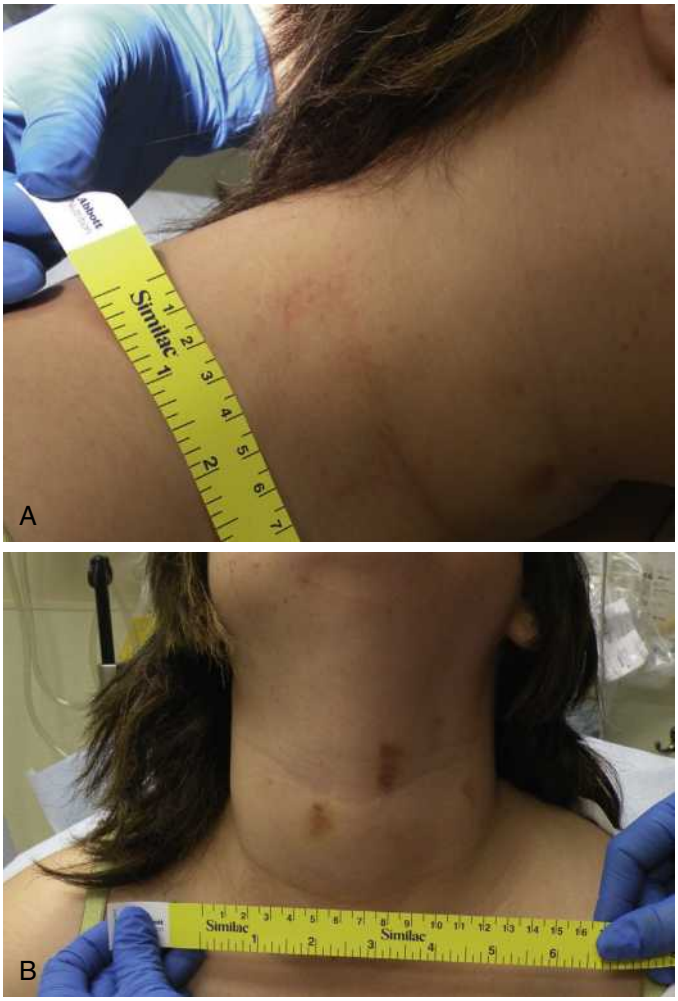


Fig. 191.3 Neck bruising in nonfatal strangulation. (A) Circular neck bruising following manual strangulation. This injury is referred to as a fingertip bruise. (B) Other bruises of the neck on the same patient, most likely made by the assailant's fingers.

the American College of Emergency Physicians supports the triage of medically stable sexual assault victims to designated examination facilities for evidence collection by specially educated and clinically trained personnel.[7-9]

On arrival to the ED, the sexual assault patient should be triaged and placed in a private area or examination room. The SART should be mobilized, and depending on department protocol and patient complaints, the patient may or may not be evaluated by the emergency clinician immediately. The goal of the history is to rule out potentially serious injury, determine which medications are needed for prophylaxis, and decipher if the patient is in the time range for evidence collection; however, if there is a question, we recommend contacting the SART team. Some questions include the following:

- When did it happen?
- What types of assault occurred?
- Where did penetration occur?
- Were any objects used during the assault?
- Have there been symptoms since the assault?
- Was there loss of memory, incoordination, or suspicion for drug-facilitated sexual assault?

As with any ED patient, providers should elicit the patient's medical complaints, past medical history, current medications, allergies, and last menstrual period.

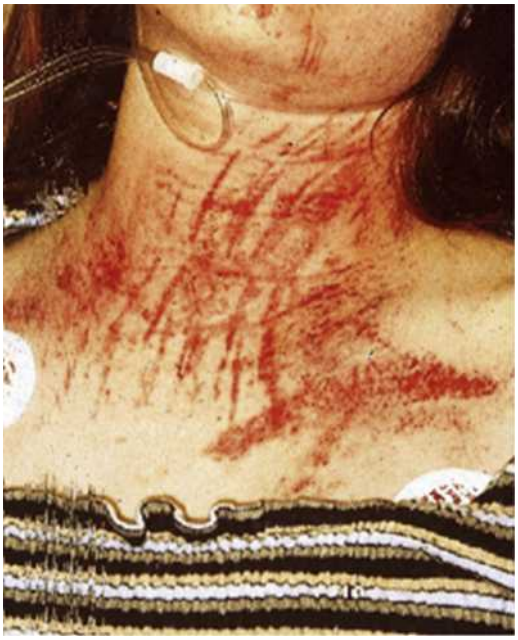


Fig. 191.4 Claw marks in nonfatal strangulation. The patient caused these injuries as she attempted to pry the assailant's hands off of her neck. (Courtesy Training Institute on Strangulation Prevention, San Diego, CA; used with permission.)

Medical Forensic Examination

The medical forensic examination should be organized, coordinated, and the patient should be informed of all steps during the exam. The examination can be conducted up to 7 days following assault, depending on jurisdiction policy, with most using 5 days as an evidentiary cutoff.[8-9] In cases of oral and anal assault, evidence is usually not collected more than 24 hours after the assault. In vaginal assaults, DNA and sperm may be recovered from the cervix up to 120 hours (5 days) later. Evidence is collected using a jurisdictionally specific sexual assault evidence kit or physical evidence recovery kit (rape kit). This kit contains all the supplies necessary to collect and properly store recovered evidence (Fig. 191.5).

The patient should consent to the examination and collection of evidence, forensic photography, and their decision on reporting to law enforcement (Fig. 191.6). The consent process begins with the forensic examiner explaining the purpose of the examination, steps, and process involved. The forensic examination process should proceed only after the patient has a thorough understanding of the examination process and has consented. The patient has the right to decline any or all parts of the examination and can revoke or change that consent at any time during the process—this is their decision and right and should be reinforced to the patient who may feel vulnerable after a sexual assault. The Violence Against Women Act (VAWA) creates and supports comprehensive, cost-effective responses to sexual assault, intimate partner violence, dating violence, and stalking. VAWA also allows for sexual assault examination without requiring law enforcement involvement. Many jurisdictions have policies that allow the patient to have evidence collected and stored for a given amount of time, leaving the patient the option to report to the police at a later date. The VAWA program also ensures patients are not required to pay for the services provided. VAWA's recent reauthorization in 2019 improved services for all victims, especially immigrants, lesbian, gay, bisexual, and transgender victims, Native American women, college students and youth, and public housing residents.

TABLE 191.1 Imaging Modalities in Nonfatal Strangulation

Modality	Indications	Advantages	Disadvantages
Plain radiograph (bone technique)	Visualize cervical vertebral fracture	Readily available in the emergency department (ED)	Limited information provided because C-spine fractures are rare
Plain radiograph (soft tissue technique)	Tracheal injury (subcutaneous emphysema, edema, tracheal deviation) Hyoid fractures	Readily available in the ED	Low sensitivity in detecting rare signs of deep soft tissue and laryngeal injury, and hyoid bone fracture is rare
Computed tomography (CT)	Soft tissue and laryngeal injuries Neuroimaging (brain)	Readily available in the ED High sensitivity Easy to perform	May need IV contrast, and screening for renal dysfunction
CT angiography (CTA)	Carotid artery injury, dissection, or thrombosis	Readily available in the ED High sensitivity	Requires IV contrast, and screening for renal dysfunction
Magnetic resonance imaging (MRI)	Soft tissue injuries of the neck and airway	Highest sensitivity	Not readily available Expensive
Doppler ultrasound	Visualize intimal injury (dissection) or thrombosis of carotid artery	Available in the ED Portable for unstable patients	Less sensitive for carotid injury or thrombosis
Fiberoptic laryngoscopy	Visualize vocal cords and adjacent structures	Sensitive for vocal cord and laryngeal injury	Availability depends on institution and expertise

TABLE 191.2 Imaging Strategy for Nonfatal Strangulation[a]

Scenario and Findings	Recommended Modality	Alternative Modality
No loss of consciousness, no physical complaints	None	None
No loss of consciousness, but voice changes	Four-vessel cervicocranial CT angiography with fiberoptic laryngoscopy	Magnetic resonance imaging (MRI) with and without contrast
Loss of consciousness and physical findings of force to the neck (e.g., bruising, petechiae)	Four-vessel cervicocranial CT angiography	MRI without contrast
Persistent unconsciousness	Four-vessel cervicocranial CT angiography	MRI without contrast
Intact consciousness with unilateral neurologic findings	Four-vessel cervicocranial CT angiography	Doppler ultrasound of the carotid artery—four-vessel angiography

[a]Imaging modality chosen will vary based on institution-specific protocols and availability of imaging modalities.

Fig. 191.5 Sexual assault evidence collection kit. Contents of kits vary by state and jurisdiction. This is an example of a customized jurisdictional evidence kit including envelopes, swabs, and microscope slides used to collect, package, and store evidence. This kit shows how the chain of evidence must be followed with signatures, seals, and appropriate transfer of property to establish integrity of the evidence. (Courtesy of the University of Colorado Forensic Nursing Program)

Questions regarding consent are often complex, especially when the victim is a minor, intellectually disabled, or incapacitated by drugs or alcohol. In the case of the minor who is unable to legally consent (due to age), the doctrine of the mature minor (one who has been supporting himself or herself, is a parent, or is in the armed forces, depending on state statutes) may allow the minor to consent without guardian notification. In many states, the minor who is in danger of having been exposed to pregnancy or an STI can also consent. If the minor does not assent to examination, the SANE/SAFE should not force the patient to undergo the examination—the minor also has the right to determine what happens to her or his body. An examination cannot be forced per the request of police or a parent or guardian. For the person unable to give consent due to mental health, psychological, or neurologic conditions, consent should be obtained from a guardian or legally authorized representative. In the case of the patient who is temporarily incapacitated due to drugs or alcohol, the examination can be delayed until the effects of the intoxicants have worn off and the patient is able to consent. In patients unable to give consent for a prolonged period of time (e.g., severe head injury or requiring intubation), the decision to proceed with a medical forensic examination is complicated, as lack of patient consent may be perceived as a further violation. Because many patients would desire evidence collection if incapacitated, and because there is a limited window of time for collection, institutional protocols should be crafted to address these specific scenarios.[8-9] At some institutions, a family member or guardian can consent to evidence collection on behalf of the patient. In these situations, evidence is collected (as an anonymous kit) and held until the patient is able to make the decision. Institutional legal counsel and ethics consults should be used when protocols have not been established.

The medical forensic examination begins with the detailed forensic history, followed by thorough physical examination, documentation

of injuries with diagrams, and evidence collection, including photographs. Medical record documentation should be securely protected from nonclinical personnel. Evidence collection kits often require their own supporting documentation. Key features of the forensic history are detailed in Box 191.2. The examination should proceed in a head-to-toe fashion, with the more intrusive parts (e.g., pelvic and rectal areas) examined at the end. Each part of the body is uncovered, one area at a time, to maintain as much modesty as possible. Each jurisdiction has a standard protocol for the sequence of evidentiary collection, modified by elements of the history. Table 191.3 highlights potential steps during the forensic examination and describes the technique for each step. Some jurisdictions may require additional steps (e.g., a wet mount to look for motile sperm and for slides to be made in addition to swabs). For victims who were unconscious or cannot remember specifics of the assault, oral, external genital, vaginal, cervical, anal and rectal, neck, and breast swabs should be obtained because these areas have a high likelihood of DNA recovery.

A recent study of over 2000 victims found that 27% sustained an anogenital injury; historically, the literature reports a variable rate of such injuries.[10] Anogenital injuries are usually seen at the posterior fourchette, fossa navicularis, and hymen (see Fig. 191.7 for diagrams and terminology of female genitalia). Injuries are documented using the face of a clock, with 12:00 representing anterior and 6:00 representing posterior injuries. Although genital injury can occur in up to 52% of women after consensual intercourse, sexual assault victims are more likely to have multiple injuries, abrasions, and a higher frequency of lesions beyond the posterior genital area.[10] The mnemonic TEARS (***t***ears/cuts, ***e***cchymosis,

COLORADO SEXUAL ASSAULT
CONSENT and INFORMATION FORM

Collection, Analysis/Release, and Consent Withdrawal of Sexual Assault Evidence/Information

▶ **You have the right to have this form explained and all of your questions answered.**
Please initial and sign where appropriate. You will receive a copy of this form after it is completed.

Law Enforcement Agency:	Case No:
Officer Name:	Phone No:

Medical Forensic Exam

▶ _____ **I consent to a medical forensic exam**. I understand I can stop the exam at any time and can decline any portion of the exam or collection of any sample.

Reporting Decision (initial only one)

▶ _____ **I am choosing to make a report to law enforcement**. I give permission for evidence collected and information gathered during my sexual assault exam to be released to law enforcement for use in investigation(s) and potential prosecution(s). I understand the investigating law enforcement agency will be given my name and contact information.

▶ _____ At this time, **I am choosing NOT TO REPORT TO LAW ENFORCEMENT OR PARTICIPATE** in any investigation. I understand I can change my mind and later report to law enforcement. I understand law enforcement may be given my name. I understand law enforcement may choose to investigate but I do not have to participate.

Evidence Analysis/Release of Results (initial only one)

▶ _____ **I consent for law enforcement to release the collected evidence to a forensic lab for analysis.** I understand law enforcement ***may*** submit the evidence to a lab no later than 21 days after receiving it. I understand if the evidence is analyzed, law enforcement ***will*** receive the results for the purposes of investigation(s) and potential prosecution(s).

▶ _____ **I consent only to the collection and storage of evidence** at a law enforcement agency. I understand this means the evidence will **NOT** be submitted to a forensic lab for analysis. I understand I can change my mind, make a report to law enforcement and possibly have the evidence analyzed at a forensic lab. I understand law enforcement is only required to hold the evidence for a minimum of 2 years.

Withdrawal of Consent for Evidence Analysis/Release of Results (only patients 18 years & older)

▶ _____ **I understand I may withdraw my consent for evidence analysis/release of results** by contacting the law enforcement agency listed on this form. I understand the withdrawal of consent becomes effective when law enforcement verifies my identity, but will not apply to any actions already taken. I understand that once analysis has begun, consent cannot be withdrawn.

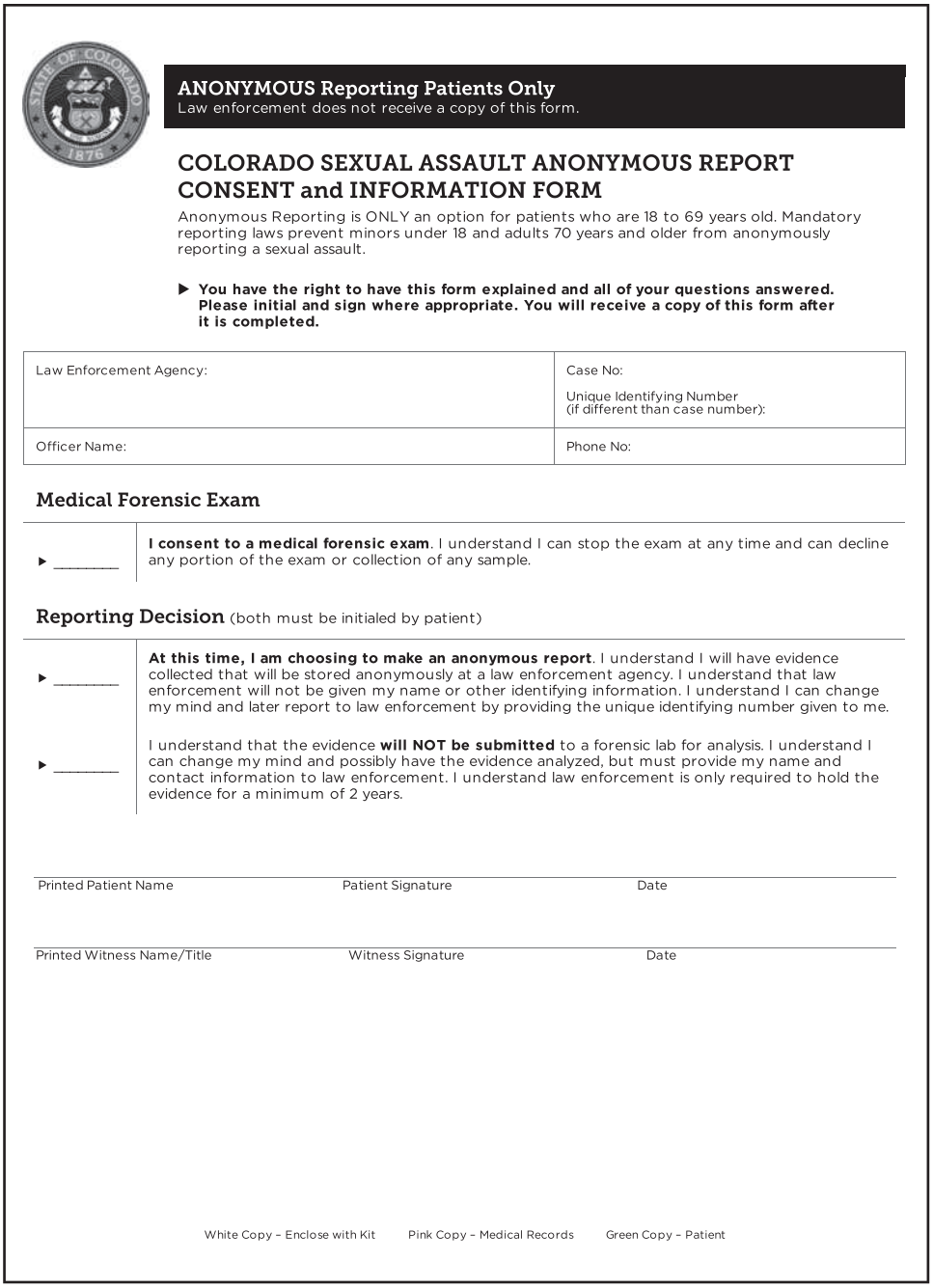
Printed Patient Name | Patient Signature | Date

Printed Witness Name/Title | Witness Signature | Date

White Copy – Enclose with Kit Yellow Copy - Law Enforcement Pink Copy – Medical Records Green Copy – Patient

A

Fig. 191.6 Sample consent forms for a medical forensic examination. (A) General consent form.



ANONYMOUS Reporting Patients Only
Law enforcement does not receive a copy of this form.

COLORADO SEXUAL ASSAULT ANONYMOUS REPORT CONSENT and INFORMATION FORM

Anonymous Reporting is ONLY an option for patients who are 18 to 69 years old. Mandatory reporting laws prevent minors under 18 and adults 70 years and older from anonymously reporting a sexual assault.

▶ **You have the right to have this form explained and all of your questions answered. Please initial and sign where appropriate. You will receive a copy of this form after it is completed.**

Law Enforcement Agency:	Case No: Unique Identifying Number (if different than case number):
Officer Name:	Phone No:

Medical Forensic Exam

▶ _____ **I consent to a medical forensic exam**. I understand I can stop the exam at any time and can decline any portion of the exam or collection of any sample.

Reporting Decision (both must be initialed by patient)

▶ _____ **At this time, I am choosing to make an anonymous report**. I understand I will have evidence collected that will be stored anonymously at a law enforcement agency. I understand that law enforcement will not be given my name or other identifying information. I understand I can change my mind and later report to law enforcement by providing the unique identifying number given to me.

▶ _____ I understand that the evidence **will NOT be submitted** to a forensic lab for analysis. I understand I can change my mind and possibly have the evidence analyzed, but must provide my name and contact information to law enforcement. I understand law enforcement is only required to hold the evidence for a minimum of 2 years.

Printed Patient Name | Patient Signature | Date

Printed Witness Name/Title | Witness Signature | Date

White Copy – Enclose with Kit | Pink Copy – Medical Records | Green Copy – Patient

B

Fig. 191.6, cont'd (B) Anonymous form. (https://www.colorado.gov/pacific/sites/default/files/ECP-v6.pdf.)

abrasions, ***r***edness, and ***s***welling) can be used to describe specific findings (Figs. 191.8 to 191.11). The Genital Injury Severity Scale (GISS) is another available instrument that uses gross visualization, colposcopy, and toluidine blue staining. Variables include five types of injuries—swelling, color change, tissue break, hymen and introitus injury, toluidine blue dye uptake—and two classes of severity—tissue integrity intact and disrupted. The GISS can help distinguish sexual assault patients from consensual intercourse subjects based on type and class of injury. In a cohort of sexual assault victims, 40% had class B or tissue-disrupted injuries versus 10% in the consensual group. Although not commonly used in clinical practice by emergency clinicians, the GISS has been validated in defining and measuring external genital injury after sexual intercourse and is most commonly used by sexual assault experts.

General Principles of Evidence Collection

Gloves should be worn during collection, processing, and packaging of evidence and should be changed in between each step of evidence collection to avoid cross-contamination of evidence. Clothing should be collected, especially if it has been ripped or torn, taking care not to cut through existing holes or tears. Areas of clothing with possible DNA (including underwear not worn at the time of assault but put on later) should also be collected. Clothing and other evidence should be placed in paper bags because plastic promotes mold and bacteria growth and can destroy DNA evidence. If a piece of evidence is wet when collected, the package should be labeled as such, and the police or crime laboratory be made aware of this so that they can dry and repackage the evidence. A minimum of two swabs should be taken when swabbing an area, allowing the crime laboratory to save one swab for future analysis

BOX 191.2 Important Historical Information for the Medical Forensic Examination[a]

Patient History
- Pertinent past medical history
- Last consensual intercourse[b]—when? with whom? areas penetrated? ejaculation?
- Voluntary drug or alcohol use

Assault History
- Date
- Time
- Surroundings
- Assailant(s)
- Involuntary drug or alcohol ingestion
- Genital and nongenital injury, pain, bleeding
- Loss of memory
- Loss of consciousness
- Vomiting
- Injury inflicted on assailant? consumption?

Methods Used by Assailant
- Weapons—type? use? injury?
- Physical blows—slapping? hitting? punching?
- Grabbing, holding, pinching
- Threats of harm
- Physical restraints
- Choking/strangulation
- Burns
- Targets of threat

Victim Post-Assault Hygiene, Activity
- Urinated
- Defecated
- Genital, body wipes
- Douched
- Removed, inserted tampon
- Removed, inserted diaphragm
- Ate
- Drank
- Gargled
- Brushed teeth
- Changed clothes
- Washed clothes

Assault Acts[c]
- Vaginal penetration—penis? object? finger?
- Oral penetration—penis? object? finger?
- Anal penetration—penis? object? finger?
- Oral copulation of genitals—of patient by assailant? of assailant by patient?
- Oral copulation of anus—of patient by assailant? of assailant by patient?
- Nongenital acts—biting? sucking? licking? kissing? locations?
- Did ejaculation occur? location?
- Contraception or lubricant used—foam? jelly? lubricant? condom?

[a] These questions should only be asked by emergency clinician if they are performing the entire medical forensic examination, including evidence collection.
[b] This information is needed for uploading the DNA profile into CODIS to prevent confusion with DNA from a consensual partner.
[c] Yes, no, attempted, or unsure answer choices.

TABLE 191.3 Steps in Sexual Assault Evidence Collection Kit

Step	Technique
Clothing collection	Collect clothing the patient wore during the assault. • Have the patient disrobe on a sheet laid on the floor. Keep clothing articles separate. • Place each item of clothing in a paper bag; label and seal. • Fold the sheet and package the same way.
Debris collection	Scan the body from head to toe looking for potential evidentiary materials. • Document findings and collect objects using tweezers, tape, or lint roller. • Package each piece separately in an envelope; label and seal.
Biologic evidence	Scan the body for potential biologic material and fluids and bite or suck marks. • Use an alternative light source, location guided by patient history. • Use swab to collect evidence, air-dry, package, label, and seal.
Fingernail evidence	Obtain evidence from the fingernails if applicable. • Use rosewood stick, broken tongue blade, or moistened swab to scrape beneath the nails. • Nail clippers can be used to cut the nails. • Package, label, and seal.
Pubic hair combings	Obtain foreign material from pubic hair. • Place collection sheet under the buttocks. • Use plastic comb to comb through hair toward the sheet. • If pubic hair is absent or trimmed, a lint roller may be used. • Package sheet and comb, label, and seal.
Pubic hair pulling (painful, typically not collected unless requested by police)	To obtain reference DNA on patient: • Pull ≈25 pubic hairs, without cutting or using tweezers, trying to obtain the root. • Package, label, and seal.

TABLE 191.3 Steps in Sexual Assault Evidence Collection Kit—cont'd

Step	Technique
Head hair pulling (painful, typically not collected unless requested by police)	To obtain patient reference DNA: • Pull ≈25 head hair strands from different parts of the scalp to try to obtain the root. • Package, label, and seal.
External genital examination and swabs	Obtain biologic evidence from the external GU sites—vulva and perineum—while inspecting for injury. • Use retraction and separation technique to look for evidence of genital injury. • Use moistened swabs to swab the areas. • If matted pubic hair is present, use scissors to cut the matted section. • Package, label, and seal.
Internal genital swabs	Obtain biologic evidence from internal GU sites—vagina and cervix—to assess for genital injury. • Use swabs to collect fluid and evidence from the posterior fornices. • Collect any foreign object, such as a tampon or condom. • Insert swab into cervix and gently twirl. • Obtaining STI cultures is done at this time. • Package, label, and seal.
Anal examination and swabs	Obtain biologic evidence from the anus/rectum and assess for injury. • Gently retract the anus with slow steady pressure to allow natural dilation, and inspect for injury. • Gently insert swabs and twirl. • An anoscope can be used to assess for injury. • Package, label, and seal.
DNA reference sample	Obtain a DNA reference sample. • As per protocol, collect a blood or buccal swab sample.
General principles	• Two sterile cotton-tipped swabs are used simultaneously to collect samples. One will be used for the crime laboratory, and one is available for the defense, if requested. • Dry swabs are used to collect evidence from moist areas; swabs moistened with control sterile water are used to collect evidence from dry areas. • Swabs are air-dried, placed back in the sleeves, and then placed in an envelope. • All evidence is placed in paper (not plastic) because moisture may cause mold growth and destroy DNA.

GU, Genitourinary; *STI,* sexually transmitted infection.

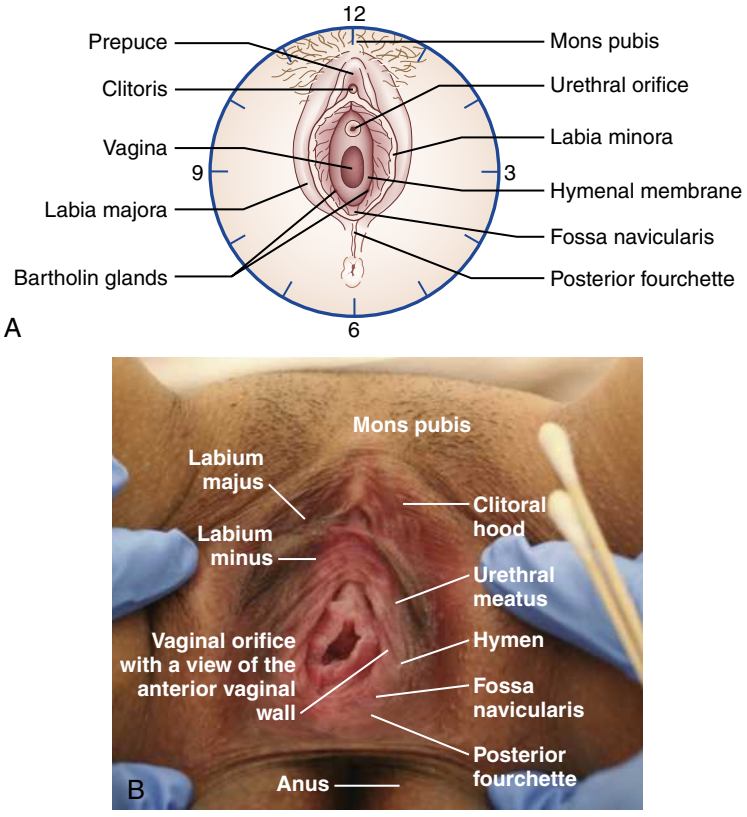


Fig. 191.7 Female genitalia. (A) Anatomy of the female external genitalia with the clock positions used in documentation. (B) Actual photograph highlighting the relative anatomy of the female external genitalia important in a medical forensic examination. (From: Roberts JR, Custalow CB, Thompsen TW. *Roberts and Hedges' Clinical Procedures in Emergency Medicine*, ed 6. Philadelphia: Elsevier Saunders; 2013.)

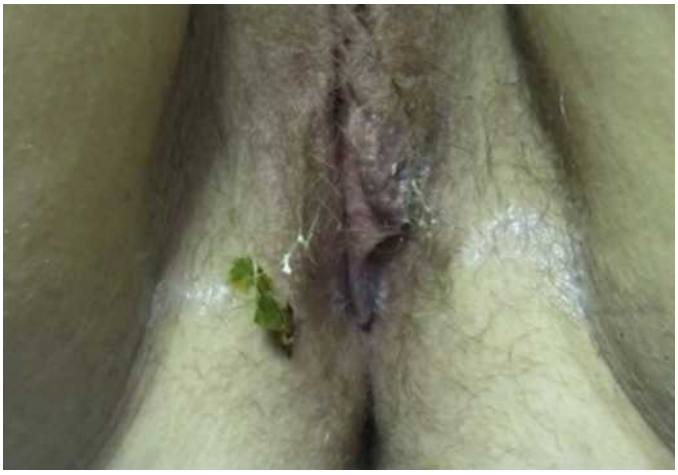


Fig. 191.8 Examination of the external genitalia. This illustrates foreign debris (presumed semen and piece of paper) on the external genitalia of a rape victim.

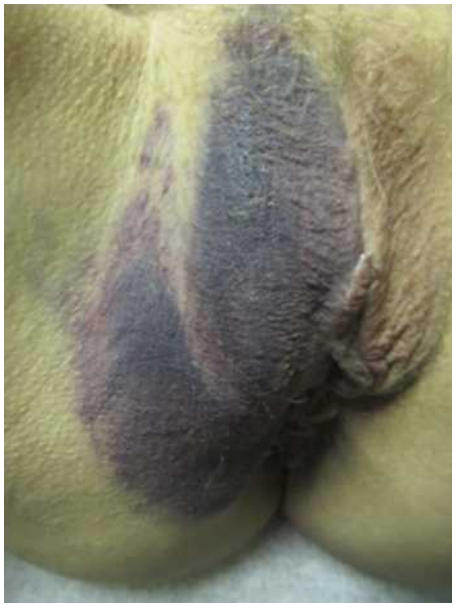


Fig. 191.9 External genitalia injury. Shown are marked swelling and ecchymosis of the right labia major, inguinal area, and buttocks in a middle-aged woman following sexual assault by a single perpetrator.

by the defense's laboratory. In general, wet stains should be collected with a dry swab or cotton-tipped applicator; dry stains are collected with a swab moistened with sterile or distilled water. For dried specimens and bite marks, a double-swab technique is performed. First, the area is swabbed in a rolling fashion with a moistened swab, and then a dry one is rolled over the area. All swabs should be allowed to dry by air, using a desiccant pack, or in a swab dryer. The evidence is packaged into envelopes once the examination is completed, and all swabs have dried. The completed evidentiary collection kit is labeled and sealed. While maintaining a chain of custody, the kit should be stored according to departmental policy or turned over to law enforcement.

The chain of custody describes the path evidence takes once it is collected from the body and ensures the evidence was not tampered with or mishandled. Failure to maintain the chain of custody calls into question the validity of the evidence and may make it inadmissible in court. Chain of custody documentation should describe how the evidence was handled and include a log of those who have had contact

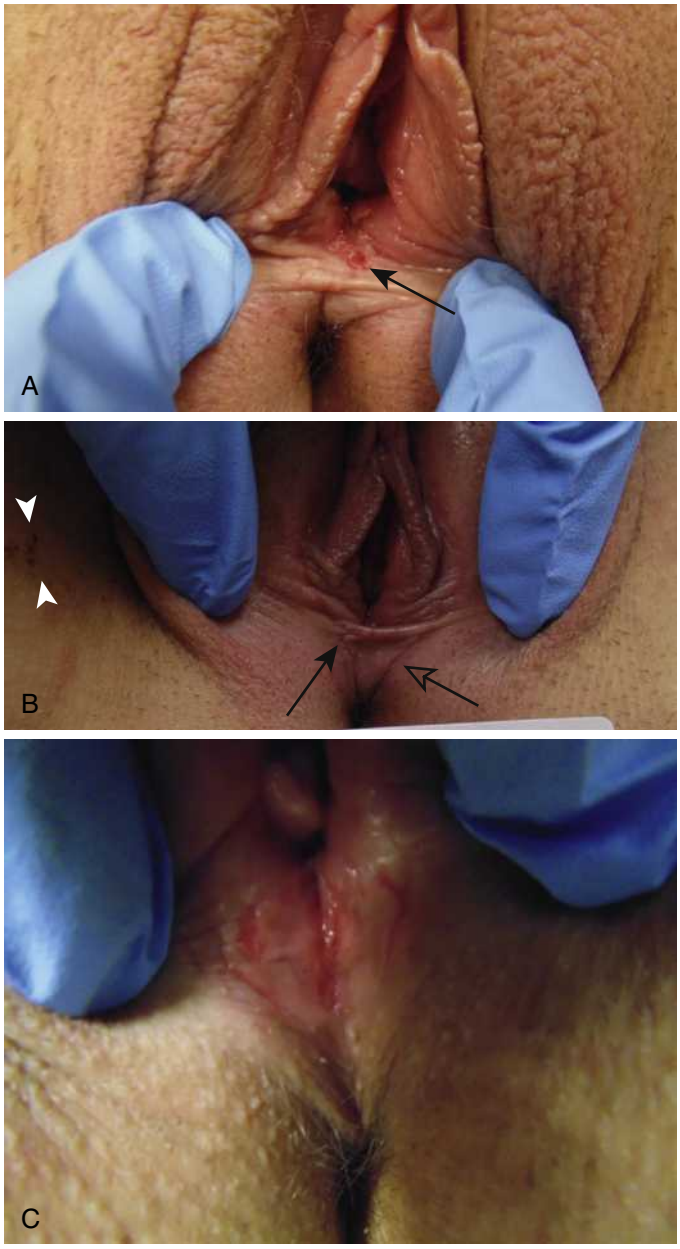


Fig. 191.10 External genitalia injury. (A) Tear and abrasion at the 6 o'clock position of the fossa navicularis. (B) *Closed arrow* is abrasion to the posterior fourchette at 6:30. *Open arrow* is abrasion of the perineum (anterior to the rectum). *Arrowheads* are abrasion and ecchymosis of right medial thigh. (C) The patient in this picture sustained multiple tears and abrasions. There is a large linear tear extending from the fossa navicularis through the posterior fourchette and onto the perineum all in the midline. There are also tears bilaterally on the labia minora, three at the 7 o'clock position and two at the 5 o'clock position.

with it. The medical forensic examination kit will typically contain chain of custody forms (Fig. 191.12.)

Special Techniques

Colposcopy. Colposcopy is a diagnostic procedure to illuminate, magnify, photograph, or digitally record external and internal genital structures. Having widespread application in gynecology, the colposcope microscopically improves gross visualization. The colposcope has a magnification of 4× to 30× and can be equipped with a still or video camera. Colposcopy is superior to gross visualization

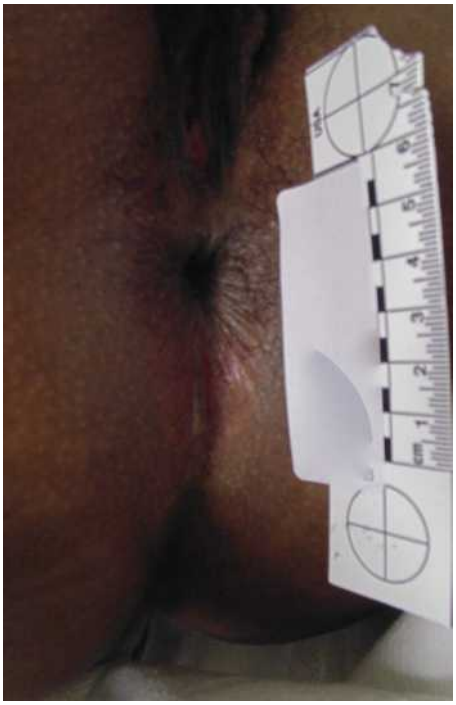


Fig. 191.11 Anal injury. There is a linear anal abrasion and tear at the 6 o'clock position with the patient in the lithotomy position.

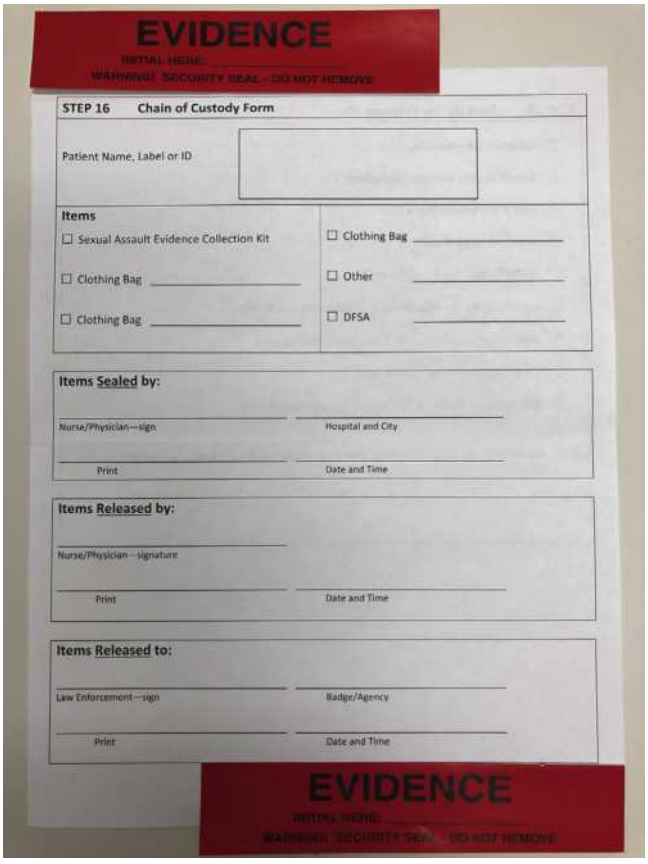


Fig. 191.12 Sample chain of custody form which includes inventory of items collected as well as names and signatures of the persons collecting, releasing, and law enforcement receiving the evidence. Evidence seals shown in image as well. (From the Ohio Commercial Kit.)

for detecting anogenital injuries. Most SANEs/SAFEs routinely use colposcopy in their evaluations. Limitations of colposcopy include the cost and size of the instrument, as well as the technical training required. Because of this, several programs use digital photography alone to detect and document genital injury. Although no study has directly compared colposcopy to digital photography for detecting injury, we recommend colposcopy when available; however, some studies have questioned the use of colposcopy due to the psychological trauma of examination with magnification.[11]

Toluidine Blue Dye. Toluidine blue dye (TBD) is a stain that adheres to nuclei in damaged epithelial cells and has not been shown to interfere with DNA testing. More tears were identified with TBD enhancement by direct visualization and colposcopy. The dye should be applied prior to speculum insertion since the speculum may introduce genital injury. The dye is applied to the external genitalia and then gently wiped with surgical lubricant, 1% acetic acid solution, or baby wipes to remove excess solution (Figs. 191.13 and 191.14) which can lead to false-positive findings of injury.

Alternate Light Source. An alternative light source (ALS) uses ultraviolet light to fluoresce biologic material. In sexual assault examinations, the ALS is used to scan the body and genitalia for areas of fluorescence that can be swabbed and submitted for potential DNA identification. Semen and saliva fluoresce under an ultraviolet (UV) light wavelength of 450 nm (range, 390–500 nm). Although the ALS is sensitive to semen, it is not specific. False-positive ALS results may be seen with hand cream, powder, body gel, laundry detergent, fabric softeners, soaps, and other ointments and creams. However, physician training can improve the ability to distinguish semen from other substances (e.g., hand cream, soap, and bacitracin). A Wood's lamp, which emits UV light at wavelengths less than 390 nm, is a poor substitute for an ALS device, and thus not recommended for detecting biologic evidence.

SPECIAL POPULATIONS

Older Adult Sexual Assault

From 2003 to 2013, the National Crime Victimization Survey reported 0.2/1000 cases of rape or sexual assault to elderly victims aged 65 years or older. Older persons may be at risk for sexual assault due to neurologic or cognitive disease, physical disabilities, frailty, and institutionalized living arrangements. In one study, older victims reported verbal threats more frequently.[12] Postmenopausal women are thought to be at particular risk for genital injury due to atrophy of connective tissue, loss of tissue elasticity, and atrophy of vaginal epithelium.

Studies have shown mixed results regarding the severity of genital injury. A recent study of 122 postmenopausal women found that 37% suffered a genital injury compared to 17% of premenopausal women. Although postmenopausal women had similar rates of extragenital injury, they were more likely to have sustained large bruises.[12] The locations of the genital injuries are similar to those of younger victims, but older victims tend to have more anogenital lacerations and abrasions.[12] The medical forensic examination of the older patient should proceed in the same manner as for other patients. The history may be difficult due to neurologic or cognitive impairment in the victim. Patient positioning may be more challenging due to physical disabilities; the typical dorsal lithotomy position may not be possible, and other positions (e.g., left lateral Sims, lateral recumbent, and dorsal recumbent) may be needed for a patient's comfort (Fig. 191.15). Prophylaxis against STIs and HIV infection should be offered while considering potential medication interactions or side effects. Older victims can also suffer major psychological trauma, including PTSD and rape trauma syndrome, and should be referred to rape crisis center services.

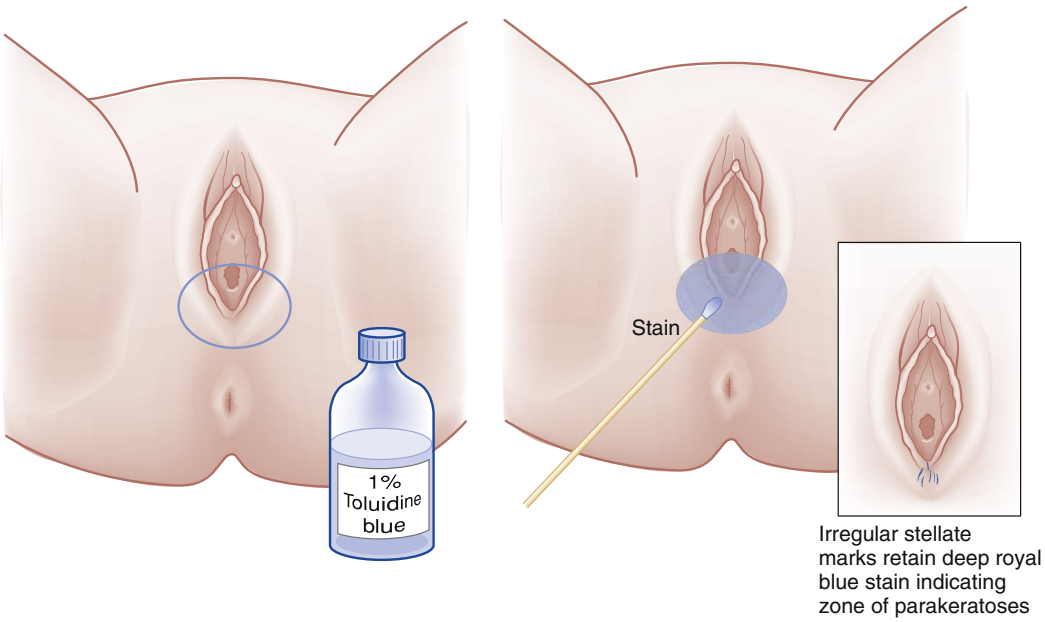


Fig. 191.13 Toluidine blue dye (TBD) application. This figure illustrates the application and removal of TBD during a forensic medical examination.

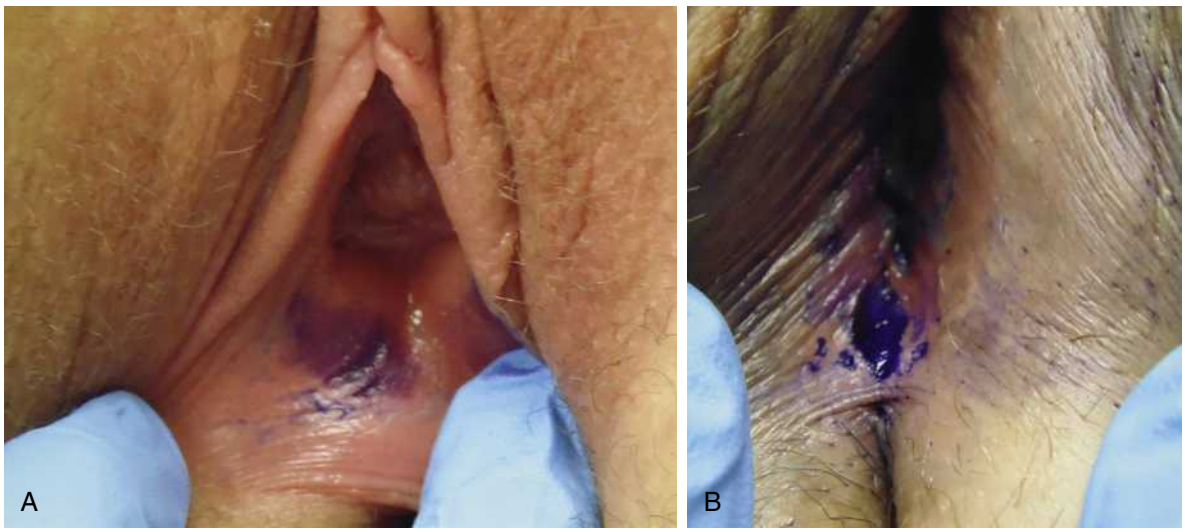


Fig. 191.14 External genitalia examination after toluidine blue dye (TBD) application. (A) After the TBD was applied, two tears of the fossa navicularis were seen between the 6 and 7 o'clock positions. (B) TBD application highlighting a large tear and abrasion of the fossa navicularis at the 6 o'clock position. There are also other scattered, smaller injuries present.

Male Sexual Assault

Male sexual assaults occur in straight, homosexual, and bisexual individuals, college students, prisoners, military personnel, gang members, and institutionalized individuals. According to the 2015 NISVS, nearly one-quarter of men (24.8%) in the United States. have experienced some form of contact sexual violence at some point in their lives, with about 2.6% experiencing completed or attempted rape victimization in their lifetime.[3] Males are raped by men or women, tend to underreport their rape, and seek medical services much less frequently than females.[3] Compared to women, males tend to be of a similar age (20–30 years), report more forcible penetration (52% anal, 15% oral, and 33% both), have more anal trauma and injury, suffer more object and digital penetration, have multiple assailants, have more weapons used, and know their assailant(s) less often. Male sexual assault includes forced oral copulation or vaginal and anal penetration of the victim or assailant. Male victims may ejaculate during the assault due to fear and physical stimulation.[3] This can cause increased feelings of guilt and shame and can be used to argue in a court of law that the victim was a willing participant.

The forensic history and physical examination proceed in a similar fashion to that for a female patient. During the physical examination, attention is paid to the oral cavity, penis and scrotum, and anus and rectum. See Fig. 191.16 for a diagram of the terminology for male genitalia. Swabs should be taken from the oral cavity, external genitals, and anus. When swabbing the genitals, all parts of the penis should be assessed, including the base of the penis and anterior scrotum. The anal and rectal examination should include visualization to look for potential foreign bodies and gross injury such as tears, abrasions, bleeding,

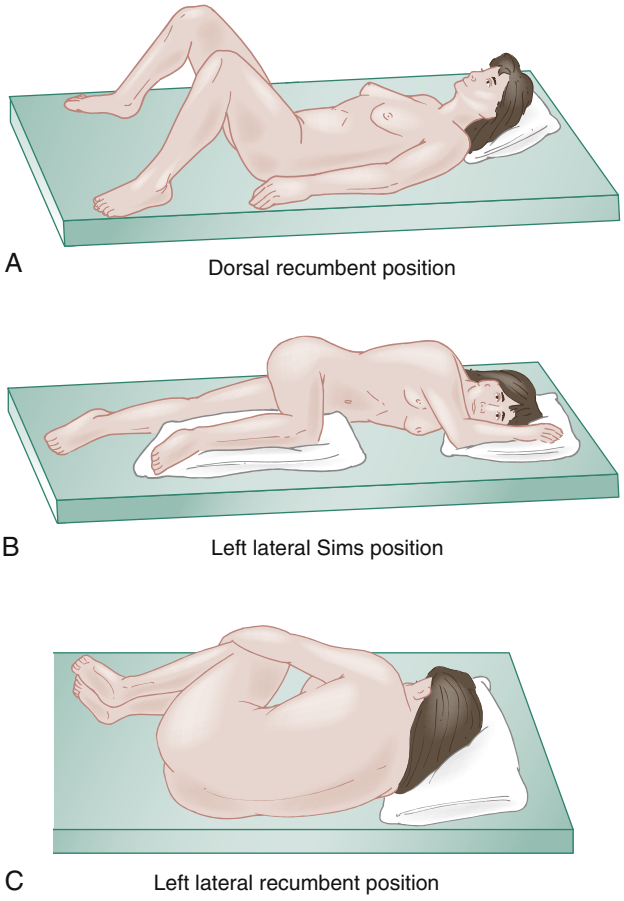


Fig. 191.15 (A) Dorsal recumbent position. (B) Left lateral Sims position. (C) Left lateral recumbent position.

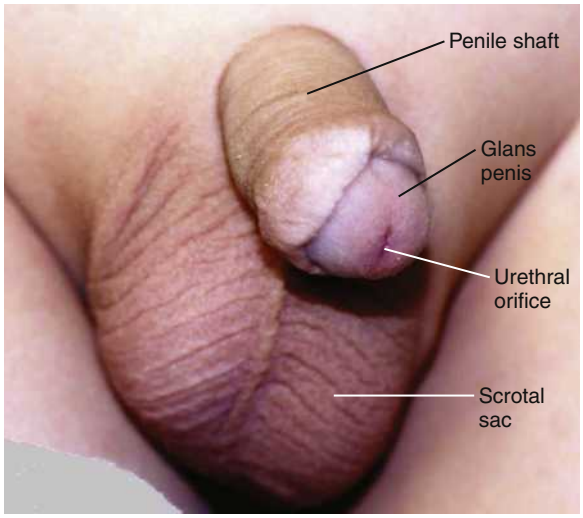


Fig. 191.16 Male genitalia. This picture highlights the relative anatomy of the male genitalia important in a medical forensic examination. (From: Roberts JR, Custalow CB, Thompsen TW. *Roberts and Hedges' Clinical Procedures in Emergency Medicine*, ed. 6, Philadelphia: Elsevier Saunders; 2013.)

erythema, hematoma, fissures, engorgement, and friability. Anal swabs should be inserted approximately 2 cm into the rectum. Visualization can be enhanced using TBD and anoscopy. Anoscopy has been shown to detect more injuries than colposcopy or an unassisted examination. Significant pain and an inability to tolerate anoscopy may warrant an examination under anesthesia, with some victims requiring surgical evaluation and treatment.

Male victims should be offered similar STI prophylaxis. HIV prophylaxis should be considered given the high risk of transmission from anal receptive and anal insertive intercourse. Victims should also be given (or referred for) rape crisis counseling services.

TABLE 191.4 Calculated Risks of Acquiring HIV from Isolated Sexual Contact With Known HIV-Positive Individual

Type of Contact	Risk[a]
Oral	Negligible
Anal	0.5%–3.0%
Vaginal	0.08%–0.3%
Health care worker percutaneous needlestick	0.3%

[a]Risk is higher in early or late HIV infection, higher viral load in assailant, presence of trauma or genital ulcers, and sexually transmitted infection in victim.

Data from: Dosekun O, Fox J. An overview of the relative risks of different sexual behaviours on HIV transmission. *Curr Opin HIV AIDS*. 2010;5:291-297; and Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis*. 2009;9:118-129.

Definitive Treatment to Prevent Sexually Transmitted Infections and Pregnancy

One of the most common concerns of survivors who present to the ED is that of becoming pregnant and acquiring STIs, including HIV. The risk of becoming pregnant after rape has been estimated at 5%, but depends on the age of the patient, use of birth control by the patient, condoms in the assailant, and timing in the menstrual cycle. The risk of acquiring STIs after a rape depends on the local prevalence of the infections. Prior research has shown the risk is greatest for acquiring bacterial vaginosis (19%), trichomonas (12%), *Neisseria gonorrhea* (4%), and chlamydia (2%).[1,3,13] The risk of acquiring HIV is very low, estimated to be 0.1% to 0.3% for receptive vaginal intercourse and 0.5% to 3.0% for receptive anal intercourse (Table 191.4).[1,3,13] However, estimates do not take into account the increased risks associated with sexual violence and injuries. The risk of HIV transmission is also related to viral load in the assailant (highest in very early and very late HIV infection), route of assault, and presence of STIs in the victim.

According to CDC recommendations, all sexual assault victims presenting to the ED should be offered treatments for STIs (i.e., gonorrhea, chlamydia, and trichomonas), emergency contraception, postexposure hepatitis B vaccination, human papillomavirus (HPV) vaccination, and HIV postexposure prophylaxis (PEP) (Table 191.5). Many states mandate that emergency clinicians offer pregnancy prevention to sexual assault victims (www.ncsl.org/research/health/emergency-contraception-state-laws.aspx). Emergency contraceptives prevent pregnancy by inhibiting ovulation, fertilization, or implantation, and do not disrupt an existing pregnancy. Emergency contraception may be taken up to 5 days after sexual contact, but ideally within 72 hours. See Table 191.6 for emergency contraception options. All victims should also be given a tetanus booster if indicated. HIV PEP should be offered to sexual assault patients who have been assaulted by multiple assailants, a known HIV-positive assailant, or high-risk exposure. Unfortunately, because the HIV status of the assailant is usually unknown, the CDC recommends offering prophylaxis

TABLE 191.5 Recommended Treatment to Prevent Sexually Transmitted Infection and Pregnancy

Infection or Condition	Medication
Gonorrhea[a]	Ceftriaxone, ≤150 kg 500 mg IM; >150 kg ≥ 1 gm. Alternative treatment, cefixime 800 mg PO daily; not preferred due to treatment failure risk. For moderate to severe penicillin allergy gentamicin 240 mg IM daily and azithromycin 2 gm PO daily (note: poor efficacy in OP, do not use this regimen in pregnancy)
Chlamydia	Doxycycline, 100 mg PO bid × 7 days *or* Azithromycin, 1 g PO *or* Amoxicillin 500 mg PO TID × 7 days; toc in 21 to 28 days
Trichomoniasis	Metronidazole, 2 g PO (recommended to take at home later)
HIV	See most recent CDC guidelines[b] and Fig. 191.17 for decision to treat
Hepatitis B	First dose of 3-dose vaccination series if not vaccinated or unsure if vaccinated
HPV	First dose of 2- or 3-dose vaccination series, approved for ages 9 to 45 years old
Tetanus	Tdap, 0.5 mL IM
Pregnancy	Levonorgestrel, 1.5 g PO within 72 hours *or* Ulipristal acetate, 30 mg PO within 120 hours
Antiemetic	Practitioner's discretion

[a]If patient reports a severe penicillin allergy (anaphylaxis, TEN, or Stephens-Johnson syndrome), treat with gentamicin 240 mg IM once plus azithromycin 2 gm PO once. There has been an increase in *N. gonorrhea* resistance to azithromycin, so follow-up testing is recommended in this scenario.
[b]Centers for Disease Control and Prevention. 2015 sexually transmitted diseases treatment guidelines. https://www.cdc.gov/std/tg2015/default.htm.

on a case-by-case basis, taking into account patient preferences and ability to comply with the 1-month course of medications and follow up. See Fig. 191.17 for the CDC algorithm on the decision to treat possible nonoccupational HIV exposures. When HIV PEP is recommended, the emergency clinician should refer to hospital guidelines or infectious disease consultation for the recommended triple-drug regimens and provide the victim at least a 3-to-7-day starter pack with prompt infectious disease follow up. The National HIV Clinician's Consultation Center offers online information and telephone consultation for providers who do not have access to a local HIV expert (nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/).[3,13]

DISPOSITION

Most sexual assault patients will be discharged from the ED. There are websites that can assist the emergency clinician who is caring for the sexual assault patient (Box 191.3). If available in the ED, social services and a victim's advocate can help formulate a safe discharge plan. Victims of attempted strangulation, especially those with loss of consciousness, bowel or bladder incontinence, or persistent shortness of breath or voice changes, should be admitted for observation. If safe house resources or respite are unavailable, consider admitting patients who do not have a safe place to go. The discharge instructions should include the number of the forensic kit collected. Patients should be encouraged to follow up with their local rape crisis center, primary care provider (or another medical provider), and mental health provider, as needed. Medical follow up should include any needed completion of the hepatitis B series, repeat pregnancy testing, vaccines, STI testing (if they did not get treated), and repeat HIV testing (at 6 weeks). If they received HIV prophylaxis, they should follow up with local HIV experts or clinics to have follow-up laboratory testing, assess for medication compliance, and be monitored for side effects.

Patients may experience subsequent symptoms of PTSD or rape trauma syndrome (RTS). Symptoms may include depression, anxiety, flashbacks, and difficulty sleeping and interacting with friends and

TABLE 191.6 Emergency Contraception

Method	Brand Name	Dose	Timing After Intercourse	Efficacy	Adverse Effects	Relative Contraindications[a]	Notes
Copper IUD	Paragard	Single IUD	0–120 h	>99%	Pain, bleeding	Infection, copper allergy, uterine anomalies	Consider in IPV where recurrent assault more likely (effective up to 10 yr) Most effective, but often not feasible or desirable from the ED after assault
Levonorgestrel[b]	Plan B, Plan B One-Step, Next Choice	1.5 mg	0–72 h (may be used with decreased efficacy up to 120 h)	85%	Nausea, vomiting, headache, menstrual changes		Less effective if >72 h or BMI >26
Ulipristal acetate[c]	Ella, Ella One	30 mg	0–120 h	85%	Nausea, vomiting, headache, menstrual changes	Renal, hepatic impairment, uncontrolled asthma, breast-feeding	More effective than LNG at 72–120 h More effective for BMI 26–35 (less effective in BMI >35)

BMI, Body mass index; *ED,* emergency department; *IUD,* intrauterine device; *IPV,* intimate partner violence; *LNG,* levonorgestrel.
[a]There are no absolute contraindications to EC, except for an established pregnancy, because they will not be effective.
[b]Levonorgestrel is not an abortifacient and is not teratogenic.
[c]Ulipristal acetate is not an abortifacient. It has not been tested adequately in human studies in pregnancy or breast-feeding; animal studies showed increased pregnancy loss.
Adapted from. Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet.* 2010;375:555-562; and Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception, 84,* 363-367.

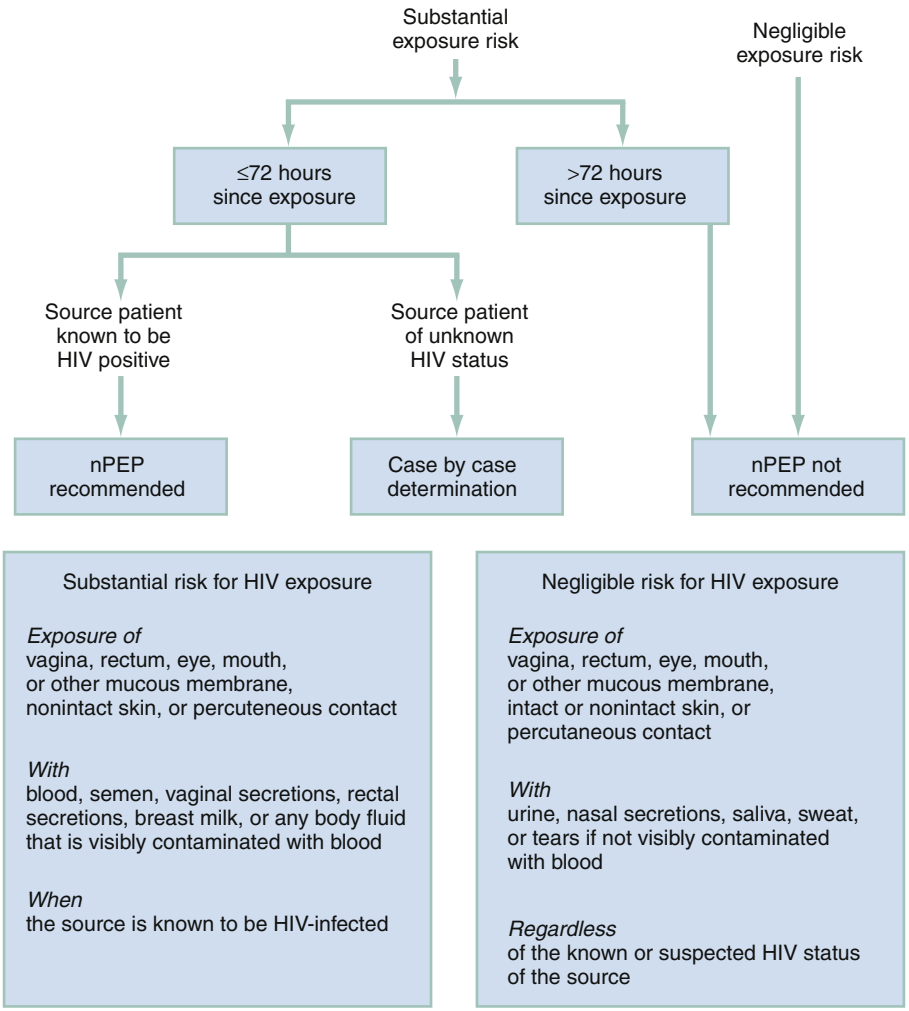


Fig. 191.17 CDC algorithm for HIV prophylaxis and for the evaluation and treatment of possible nonoccupational HIV exposure. *nPEP,* Nonoccupational postexposure prophylaxis.

BOX 191.3 Useful Websites for Sexual Assault

- Tonic Immobility: Neurobiology of sexual assault https://nij.ojp.gov/media/video/24056
- Centers for Disease Control and Prevention: 2015 STD treatment guidelines—sexual assault and abuse STD guidelines. https://www.cdc.gov/std/tg2015/sexual-assault.htm
- Clinician Consult Center: PEP: postexposure prophylaxis. http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/
- US Department of Justice, Office on Violence Against Women: A national protocol for sexual assault medical forensic examinations. https://www.ncjrs.gov/pdffiles1/ovw/241903.pdf
- American College of Emergency Physicians: Evaluation and management of the sexually assaulted or sexually abused patient. www.acep.org/forensic-section
- Training Institute on Strangulation Prevention: www.strangulationtraininginstitute.com
- National Sexual Violence Resource Center: www.nsvrc.org
- Rape, Abuse, and Incest National Network (RAINN): www.rainn.org (Hotline: 1-800-656-HOPE [4673])

loved ones. Acute pain after sexual assault is common and often undertreated, sometimes involving areas that were not traumatized. Delayed or worsening pain in many regions of the body has been shown to occur in up to 60% of sexual assault survivors at 6 weeks and 3 months post-assault.

TESTIFYING IN COURT

Although good medical care is the primary goal of ED treatment, the emergency clinician may at times be responsible for collecting sexual assault evidence. In this case, the emergency clinician may be asked to testify in court. The key to competent testimony is preparation and knowledge of the court process.

In most cases, the emergency clinician will be called on as a fact witness or as someone who testifies to what the patient said or did, as well as findings on physical examination. Occasionally, the emergency clinician may be called as an expert witness. An expert witness has specific training and may be called on to provide an explanation or educate the jury, even if he or she did not actually care for the patient. Box 191.4 outlines the steps in court testimony and includes some helpful suggestions for the emergency clinician in preparation for trial.

BOX 191.4 Steps in Court Testimony

Preparation for Trial

1. Respond to the subpoena in a timely fashion; a delay can result in criminal charges for you.
2. Notify and consult with the institutional legal counsel.
3. Update your CV and be able to recite dates of education and certification.
4. Ask to meet with the prosecutor to review the medical records, evidence collection kit, and a list of questions the prosecutor plans to ask the emergency clinician.

Day of the Trial

1. The day of the trial may change due to motions and order of witnesses.
2. Arrive early and dress in professional attire—a suit is preferred rather than a white coat.
3. Before testifying, the emergency clinician will be sworn in and seated in the witness box. There are three parts to the testimony—questioning by the prosecution (testimony), cross-examination by the defense attorney, and redirect by the prosecution.
4. In general, the emergency clinician should look at the prosecution or defense attorney when being questioned, and the jury when answering questions; this is the provider's opportunity to educate the judge and jury.
5. Responses to questions should be brief and answer only the question; do not add information and explanations unless asked, and resist using medical jargon such as *ecchymosis* in favor of clearly understood terms such as *bruising*.
6. All answers should be verbal, taking care not to nod in response. The line of questioning will often start with asking the provider to state her or his name and then describe training and certification, including how long he or she has been practicing emergency medicine.
7. Do not refer to the patient as the "victim."
8. If an answer cannot be recalled, then just simply state, "I cannot recall."
9. Documents can be reviewed in court (e.g., medical or evidentiary kit records) on request.
10. If the question is not understood, the emergency clinician can ask the attorney to repeat the question or clarify it prior to answering.

ACKNOWLEDGMENT

We would like to thank Judith A. Linden and Ralph J. Riviello for their significant contribution to the prior edition of this chapter.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 191: QUESTIONS AND ANSWERS

1. Which of the following statements best describes hepatitis B infection prevention for victims of sexual assault?

a. Give HBIG and hepatitis B vaccine if the patient has not been immunized.
b. Give HBIG only if the patient has not been immunized.
c. Give hepatitis B vaccination if the patient is unimmunized or uncertain.
d. Give hepatitis B vaccine only if serologic testing shows that the patient is not adequately immunized.
e. Serologic testing is always required, followed by hepatitis B immunoglobulin (HBIG).

Answer: C. Give hepatitis B vaccination if the patient is unimmunized or uncertain. Follow-up doses should be given at 1 to 2 months and 4 to 6 months (total of three doses). This strategy, which avoids the need for serologic testing, has been shown to be effective. HBIG is not recommended by the CDC after sexual assault unless the assailant is known to be HBsAg-positive and the victim is unimmunized.

2. Which of the following empirical antibiotic regimens is indicated for sexual assault patients to prevent sexually transmitted infections?

a. Cefixime 400 mg PO
b. Cefixime 400 mg PO once plus doxycycline 100 mg PO bid for 10 days
c. Ceftriaxone 1 g IM (intramuscularly)
d. Ceftriaxone 1 g IM plus azithromycin 2 g orally (PO)
e. Ceftriaxone 250 mg IM plus metronidazole 2 g PO plus azithromycin 1 g PO

Answer: E. Ceftriaxone is given to cover gonorrhea, azithromycin to cover chlamydia, and metronidazole (Flagyl) to cover *Trichomonas*. Ceftriaxone is preferred over oral cefixime to cover incubating syphilis and due to increasing gonorrhea resistance. Many providers opt to give the metronidazole to take at home because it increases the risk of nausea and vomiting, a common side effect of many of the medications (including emergency contraception and HIV postexposure prophylaxis).

3. Which of the following statements best describes sexual assault in males?

a. Ejaculation should not occur in the victim during male sexual assault.
b. Males are more likely to overreport sexual assault.
c. Males are more likely to require sexually transmitted infection (STI) prophylaxis.
d. Males do not require referral to rape crisis centers.
e. Males may require anoscopy to detect anogenital injuries.

Answer: E. Males may actually suffer more anogenital injuries than women; injury detection can be aided or enhanced by using an anoscope. Males underreport the crime, do not seek medical attention, and absolutely need referral to a rape crisis center for post-rape care and counseling. Males are not more likely to require STI prophylaxis because the risk of transmission per act does not change based on gender. Ejaculation may occur during sexual assault due to prostatic stimulation and fear arousal. This should not be taken to infer that the assault was consensual.

4. Which of the following factors reduces the likelihood of finding genital injury during the sexual assault examination?

a. Digital penetration
b. Increased time since sexual assault occurred
c. Penile penetration
d. Use of foreign object during the assault
e. Victim sexual immaturity

Answer: B. The genital structures heal quickly, so the longer the time since the sexual assault occurred, the less likelihood of finding evidence of injury on examination. All the other factors increase the likelihood of finding genital injury at the time of the sexual assault examination.

CHAPTER 191: QUESTIONS AND ANSWERS—cont'd

5. A 25-year-old woman presents 4 days after vaginal penetration. Her body mass index (BMI) is 33. Which of the following is true about emergency contraception (EC)?

- **a.** A pregnancy test is mandatory prior to offering EC.
- **b.** She should be offered levonorgestrel because it is more effective in this situation.
- **c.** She should be offered ulipristal.
- **d.** She should have an intrauterine device (IUD) inserted because this is the most effective form of EC for her.
- **e.** She should not receive EC because it will likely be less effective due to her BMI.

Answer: C. Emergency contraception should be offered up to 5 days after vaginal assault. Ulipristal, levonorgestrel, and high-dose birth control pills are options. Ulipristal is more effective after 72 hours and in women with a BMI greater than 26. At a BMI above 35, both forms of oral EC are less effective, but should still be administered if there is no alternative. IUD placement is the most effective form of EC; it can be placed up to 5 days after assault. IUD placement allows for ongoing birth control in situations where there is likely to be loss of reproductive control (intimate partner assault) but is often less desirable after assault. IUD placement is most often not available in a timely manner. A pregnancy test is not mandatory before giving EC because it will not harm an existing pregnancy. A pregnancy test is suggested prior to ulipristal administration, given the lack of large studies in pregnant women.

Intimate Partner Violence and Abuse

Carolyn Joy Sachs

KEY CONCEPTS

- Intimate partner violence encompasses a pattern of controlling behaviors, including intentional physical assault, sexual assault, psychological violence, and financial control.
- Intimate partner violence (IPV) patients are best served by a coordinated system response plan that includes staff training, social work, victim advocates, and a close relationship with area IPV service provider groups and law enforcement.
- The emergency clinician's role in caring for patients affected by intimate partner violence involves 4 basic steps.
  1. Identification (asking the patient)
  2. Treatment (supporting messages and medical issues)
  3. Documentation (regarding violent actions and threats)
  4. Referral (e.g., community, social services, legal)
- Sequelae of IPV include chronic pain, mental health issues (e.g., depression, posttraumatic stress syndrome [PTSD], substance abuse), sexually transmitted infections (STIs) and unintended pregnancy, and worsening of medical illnesses.

FOUNDATIONS

Background

Intimate partner violence (IPV) consists of acts or threats of physical, psychological, or sexual violence between intimate (or formerly intimate) partners. Physical violence includes any behavior with the potential to cause death, disability, injury, or other harm: pushing, hitting, slapping, punching, kicking, biting, burning, strangulation, and aggressive use of objects or weapons. Exact legal definitions of criminal IPV acts vary by country and even within countries by local and state laws. Each state in the United States (US) maintains separate penal codes for IPV crimes, with differing legal definitions of IPV. Definitions and crimes also differ under federal law, military law, and tribal law, among others. Psychological or emotional violence also fulfills the medical and sociologic definitions of IPV: words and behaviors meant to intimidate, degrade, humiliate, or isolate the victim from family and friends; threats; controlling access to clothing, transportation, money, and other basic needs; and limiting professional and social activities. Sexual violence involves threats or physical force to attempt or complete sexual contact and includes any physical contact with a sexual organ with a person unable to consent. Sexual violence within a current or former dating or intimate relationship most often fulfills criteria for a separate crime, in addition to IPV. Reproductive coercion, a relatively recently described subset of sexual IPV, involves prevention of (or interference with) the use of birth control and refusal to use condoms to prevent the transmission of sexually transmitted infections (STIs) and human immunodeficiency virus (HIV).

The Centers for Disease Control (CDC) periodically performs a National Intimate Partner and Sexual Violence Survey (NISVS) which assesses sexual violence, stalking, and intimate partner violence victimization among adults in the United States. According to the 2015 NISVS, 36.4% of US women experience physical violence, rape, or stalking during their lives. One in three of those reporting IPV experienced multiple forms of IPV.[1]

Emergency department (ED) patients suffering from injuries due to IPV may present with a clear history of the IPV but may also fail to disclose the true nature of the injuries due to shame or fear of retaliation. Thus, national estimates of IPV injuries among ED patients likely underestimate the true prevalence. In ED studies, observed IPV prevalence among women ranges from 12% to 19%. Though the majority of injured IPV patients are females injured by a male partner, men may also be victims; IPV is at least as common in same-sex relationships as in heterosexual relationships.[2,3] Eleven percent of US men self-report IPV during their lifetime, including contact sexual violence, physical violence, or stalking by an intimate partner.

The high prevalence of IPV reported by men may be partly understood by the frequently bidirectional nature of partner conflict and violence. In a simplified model, IPV falls into two distinct forms: intimate terrorism and situational couple violence. Intimate terrorism is defined as "the attempt to dominate one's partner and to exert general control over the relationship," whereas situational couple violence is "violence that is not connected to a general pattern of control." Situational couple violence is usually less physically severe and more likely to be engaged in by either member of the couple. Intimate terrorism characteristically involves more severe injury, occurs more frequently, and is perpetrated more often by men against women. The type of IPV is unlikely to change the role of the ED clinician, which remains identification, treatment, documentation, and referral (Box 192.1). Overall, women continue to be the primary targets of violence, and to experience high rates of health sequelae. Therefore, health care responses to IPV, as well as community resources for survivors, are largely directed toward women. This may translate to decreased community resources available for male victims who also deserve our compassionate and complete care. Although this chapter often assumes the more common female victim and male perpetrator, principles herein apply to all IPV victims, irrespective of gender identity.

IPV affects many aspects of health and is associated with risky health behaviors, such as cigarette smoking, heavy alcohol and drug use, and physical inactivity, as well as mental illness (e.g., depression, anxiety, posttraumatic stress disorder [PTSD], suicidality).[3,4,5,6] IPV patients often have poor maintenance of chronic medical conditions, such as asthma, diabetes, and chronic pain syndromes. Pregnant IPV victims tend to seek prenatal care late and are at risk for termination of pregnancy, placental abruption, preterm delivery, and low infant birth weight.[7,8,9]

BOX 192.1 Emergency Department Role in IPV

Identification (Ask)

- Injured patients may self-present or be transported by prehospital care with trauma known to be IPV or they may require additional physician queries to uncover the true cause of injuries.
- Directed screening involves questioning those with risk factors about IPV
- Routine screening involves asking all patients about IPV

Treatment

- Medical
- Support: This most often involves giving support and information and does not mean a victimized patient will always leave her/his perpetrator. Emergency clinicians should accept that intervention in intimate partner violence may be an ongoing process and most often not resolved in one ED visit.
- Danger assessment (often with social work or IPV advocate)

Documentation

- Medical record
- Reporting forms in applicable
- Photography if applicable and available

Referral (Will be patient specific)

- Minimum: IPV community resources
- Hospital social work
- IPV community/legal advocate
- Law enforcement (depending on patient preference or mandatory reporting)
- Reporting is mandated by state law in certain cases
  - Patients with certain injuries/weapon use
  - When children are involved (to child protective services)
  - When the victim is also a dependent adult or elder (to adult protective services)
  - The mandate reporting supersedes the patient's right to privacy under HIPPA

The majority of all assaults on women worldwide and in the US are by intimate partners. Approximately half of all female homicides with a known perpetrator are committed by a former or current partner.[10] Partner violence is a precursor in 75% of IPV homicide cases, and many IPV homicide victims see a health care provider within the year before their death. ED visits provide an opportunity to identify IPV and those at high risk for future severe injury or death.

The morbidity and mortality associated with IPV translates to an economic burden of 3.6 trillion US dollars over the lifetime of those suffering. Both victims and perpetrators generate some of these costs with lost productivity and criminal justice activities, however, more than half of the estimated costs have been attributed to medical care.[11] Encouragingly, survivor health care use has been observed to return to normal rates several years after the cessation of IPV, suggesting that interventions against IPV may have a positive overall effect on health.

Causes and Natural History of Intimate Partner Violence

Clinicians may find it difficult to comprehend why humans choose to physically, sexually, or psychologically hurt someone whom they purport to love. Potential answers to this paradox involve multiple societal, community, relationship, and individual factors. Individual-level risk factors for both perpetration and victimization include childhood exposure to IPV or other abuse, presence of a physical or mental disability, and use of alcohol or drugs.[12] Though prevalent in all socioeconomic groups, IPV occurs at increased rates among those with lower income, job or housing instability, and male unemployment. Housing instability also increases the risk of sequelae, such as PTSD, depression, and increased ED use in IPV victims. Lack of social support for women, and delinquent peer associations for men, have been associated with victimization and perpetration, respectively.

Finally, human beings are not uniform and reflect different cultures with their own laws, attitudes, norms, and biases, including degrees of societal tolerance toward violence. Historically and worldwide, increased violence against women can be seen in societies with greater gender inequity. All aspects of our community, including law enforcement agencies, schools, the media, social services, and medical professionals play a role in changing dangerous attitudes that ignore IPV and helping those who are already affected find refuge. The literature overwhelmingly supports the concept that IPV victims want help from their doctors, and that they frequently seek help in the medical setting. Though medical resources alone cannot solve the societal problems that lead to IPV, through a collaborative community response and the four principles of identification, documentation, treatment, and referral, emergency clinicians can give their patients a chance to live without the excess burden of IPV.

Identification

Optimal medical intervention for IPV requires systematic screening for identification, and multidisciplinary care for treatment and referral. In addition to providing acute medical care, emergency clinicians need resources to secure that patients with positive IPV screens have access to primary care physicians and IPV community agencies for what is often a long-term, recurring problem, requiring long-term physical and mental health care, counseling and advocacy, legal aid, and long-term strategies for financial and social independence. Due to the human suffering and potential efficacy of treatment, the US Preventive Services Taskforce (USPSTF) recommends routine screening for IPV in women of childbearing age, even in the absence of overt injuries.[13]

Emergency clinicians may perceive barriers to identification, treatment, documentation, and referral of patients suffering from IPV. For the last few decades, medical schools have included some education on the identification and treatment of victimized patients, but many current emergency clinicians lack comprehensive training. In busy clinical settings such as the ED, the high volume of patients and acuity of disease may preclude private screening and more in-depth discussions of partner abuse. Given the complex psychosocial issues that may accompany IPV, emergency clinicians may also fear opening a Pandora's box, uncovering additional interventional needs that may be impossible to effectively address during an ED visit.[14]

Furthermore, ED providers may harbor their own prejudices and misunderstandings that can interfere with identifying and treating IPV victims. Despite obstacles, the majority of EDs endorse screening patients for IPV, and most EDs provide universal screening during triage nurse evaluations. Though nurses most often verbally query patients and record the screening information in the patient's chart, paper or computer self-administered private surveys may provide improved disclosure rates.

Screening

Asking all patients about partner violence (past or present) is called IPV screening. The USPSTF recommends routine screening of asymptomatic women of childbearing age for IPV in the health care setting, with referral to intervention services. Directed screening for IPV involves questioning patients presenting with illnesses and conditions associated with IPV (e.g., chronic pain, multiple ED visits, STIs, unintended pregnancy, mental health issues such as depression, anxiety, PTSD, and suicide, alcohol and drug presentations).

BOX 192.2 Screening Question Options for Intimate Partner Violence

Partner Violence Screen

- Have you been hit, kicked, punched, or otherwise hurt by someone within the past year? If so, by whom?
- Do you feel safe in your current relationship?
- Is there a partner from a previous relationship who is making you feel unsafe now?

Modified Abuse Assessment Screen

- Has your partner or someone important to you ever emotionally or physically hurt you?
- Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone?
- Within the last year, has anyone forced you to participate in sexual activity?
- Are you afraid of your partner or anyone listed above?

Indirect Questioning

- Because relationship conflict and violence are problems in many of my patients' lives, I ask all my patients about this: Is violence at home occurring in your life?
- You seem bothered by something today. Often relationship problems are a source of concern in my patients' lives. Do you have concerns about your relationship?
- All couples argue sometimes. What happens when you and your partner argue? Do the arguments ever become physical?
- Often when I have seen this type of injury, it is due to a punch or a slap. Is this how your injury happened? (This may be used for a patient with a suspicious injury.)
- Often when I have seen patients with these symptoms, it is due to stress or fighting at home (or with a partner). Is this going on in your life? (This is an approach to a patient with complaints potentially related to anxiety/mental health/pain syndrome.)
- What happens when your partner wants to have sex but you don't?

Although studies have shown an increase in identification, proving a decrease in violence and increase in quality of life for ED screening has remained a challenge.[15] The USPSTF screening recommendation does not name a specific medical site, but given that IPV survivors use the ED at high rates, the ED provides a safe place for intervention. When surveyed in the ED, 26% of women in a past-year relationship screened positive for IPV; at 1 week and 3 months follow-up, there was no report of increased violence or harm as a result of screening.

Despite the organizational recommendations and institutional protocols to screen for IPV, practical implementations of screening cast doubt on the efficacy of the protocols. Challenges to ED protocol implementation include time constraints, privacy issues, and continued provider discomfort or indifference. Documentation of screening is often included in the triage section of the medical record and tasked to the triage nurse in a hectic and sometimes public area. This approach puts privacy and security at risk, because IPV survivors may be accompanied by their abusive partner. Additionally, other companions with the patient may not be aware of the situation and patients will rarely disclose without privacy.

Some well-studied IPV screening tools—the Partner Violence Screen (PVS) and Modified Abuse Assessment Screen (AAS)—are presented in Box 192.2. Studies that investigate the incidence and prevalence of IPV most often use a second longer survey, the Conflict Tactics Scale (CTS), as a gold standard to determine sensitivity and specificity of the tool. However, the CTS was developed for purposes of research rather than detecting IPV in the acute medical setting and may not be the most applicable gold standard for ED use. Emergency clinicians should ask about specific actions and avoid using the terms "victim" and "abuse," as patients may not yet see the actions as abuse or themselves as victims. Paper and electronic screening, an underutilized method, are at least as effective as face-to-face screening and more likely to be universally applied with less bias introduced by interprovider variability.[16] Patients should be informed about state-specific reporting requirements that may accompany disclosure of IPV. Triage screening should be followed up privately, after all visitors have been asked to step out of the room. Initial framing statements can normalize and destigmatize IPV and may improve victims' disclosure to providers (Box 192.2). Patients are more likely to disclose abuse if the provider asks at least one additional related question.

We recommend asking open-ended questions to give patients a chance to tell their story. Questioning about IPV should be done in a nonthreatening manner, devoid of blame and judgment. An atmosphere of support and understanding will facilitate patient disclosure. We recommend inclusive terms, such as *partner,* for those in same-sex or gender nonconforming relationships. Those in same-sex relationships may feel added challenges to disclosing abuse. Abusive partners may use the threat of outing a victim's sexuality to intimidate them into silence.[2,17]

Partners should be asked to leave the room before the patient is asked about IPV. Patients will rarely admit to abusive acts unless they are guaranteed privacy. Moreover, when asked in the presence of an abusive partner, questions about IPV can put the patient in future danger. Usually, a patient's companion will agree to leave cooperatively before the physical examination. If a companion is resistant to leaving, the patient may be taken to the restroom (e.g., for a urine sample) or taken to the radiology area and privately asked about IPV.

CLINICAL FEATURES

Injuries and Comorbidities

Classic injury patterns (e.g., facial injuries, multiple injuries, extremity fractures) have demonstrated limited predictive value in screening for IPV. Most IPV victims present to the ED for non-injury visits, including gynecology-related complaints, mental health and substance abuse complaints, pain syndromes, and uncontrolled medical illnesses. Historical elements that may suggest an abuser is preventing the patient's access to care include a delay in seeking medical care, noncompliance with medications, or missed medical appointments. Unless probed about IPV, these patients may not be identified. If an injury is a result of IPV, the patient may be reluctant to divulge the information. Additional historical clues of IPV are a vague or changing history, a history that is inconsistent with the injuries, a statement by the patient that he or she is accident-prone, and a past history of injuries.

IPV is often considered in women who present with injuries or assault but should also be considered in men and teenage boys with injuries. Presenting injuries in male patients are commonly less severe (e.g., abrasions) and the mechanism is often scratching, punching, or being hit with a blunt object. Though rarely discussed, emergency clinicians treat perpetrators who might be suffering from mental illness or substance abuse. These patients may want help with their violent behavior but lack assistance to accomplish a change. While making known the obligations of mandatory reporting (see later), clinicians should give patients a chance to disclose perpetration of IPV, providing treatment resources and helping attenuate abuse.[18]

Questioning Injury Presentations

Emergency clinicians should inquire about abuse in an open-ended and non-accusatory way, asking how injuries occurred and if another

Fig. 192.1 Central location of injury common in IPV. (Image copyright of Malinda Wheeler RN, NP, SANE.)

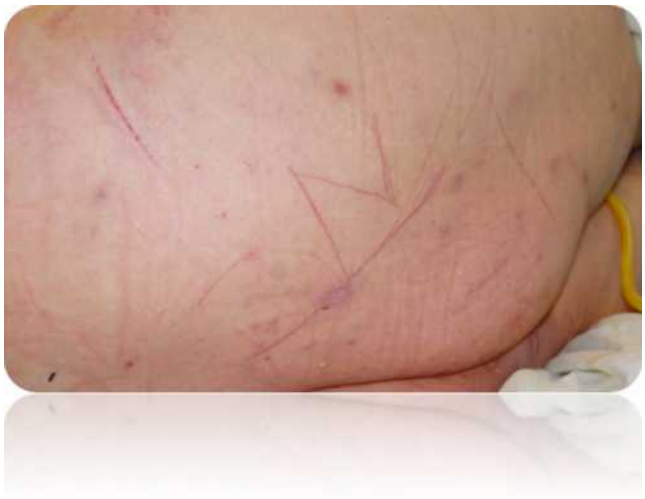

Fig. 192.2 Pattern injury: perpetrator carved his initials on the patients back and buttock. (Image copyright of Malinda Wheeler RN, NP, SANE.)

person played a role. Victimized patients may come to the ED with acute injuries, or injuries may be an incidental finding discovered during the physical examination. The emergency clinician should look for clues that an injury may be intentional. Injuries more likely to be intentional include: a central location (e.g., trunk, breasts Fig. 192.1); bilateral injuries (i.e., both arms or both legs); defensive injuries (e.g., ecchymoses on the ulnar aspect of the forearm or back of the hand); and patterned injuries (i.e., markings of an object—sole of a shoe, a cigarette or imprint pattern burn, or knife tip carving Fig. 192.2). Common locations for IPV injuries are the head, face, mouth, and neck (Fig. 192.3). Common ED head injuries from IPV include: facial contusions, lacerations, or fractures; alopecia from the perpetrator chronically pulling the victim by the hair; or acute scalp lacerations from pulling injuries. Strangulation can cause neck abrasions and contusions, facial and conjunctival petechiae, or subconjunctival hemorrhages (Figs. 192.4 and 192.5). Strangled patients may report a loss of consciousness or difficulty swallowing, speaking, or breathing. Patterned fingertip-shaped contusions (i.e., grab marks) to the upper arms suggest a violent relationship (Fig. 192.6). Emergency clinicians should document injury location, size, swelling, tenderness, coloration, evidence of healing, and presence of a pattern. The electronic medical record often provides a format to upload photographic images with patient consent.

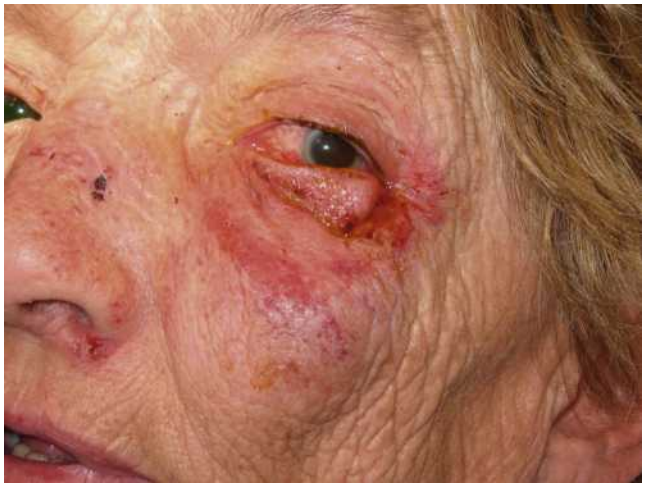

Fig. 192.3 Facial injury from blunt force assault. (Image copyright of Malinda Wheeler RN, NP, SANE.)

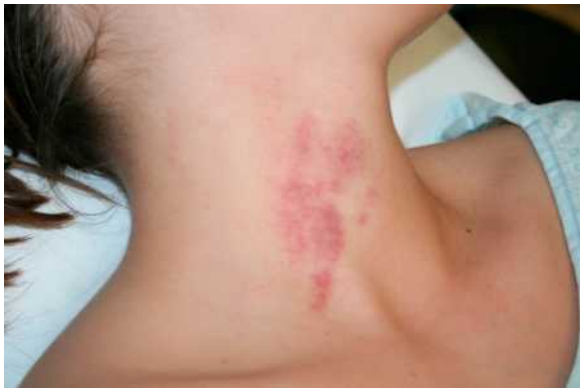

Fig. 192.4 Neck abrasions from strangulation injury. (Image copyright of Malinda Wheeler RN, NP, SANE.)

Fig. 192.5 Subconjunctival hemorrhages from strangulation injury and jugular venous obstruction. (Image copyright of Malinda Wheeler RN, NP, SANE.)

SPECIFIC ISSUES

Gynecologic-Related Presentations

IPV victims commonly present to the ED with obstetric and gynecologic complaints.[19] Presentations related to IPV include unintended pregnancy-related complications, requests for emergency

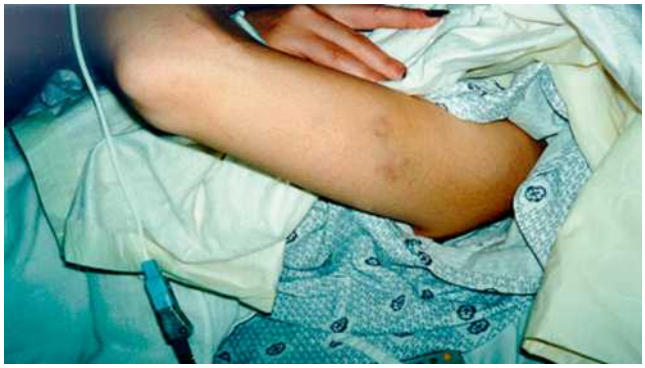

Fig. 192.6 Contusions suggestive of fingertip marks from forceful grabbing by perpetrator. (Image copyright of Malinda Wheeler RN, NP, SANE.)

contraception or termination of pregnancy, and frequent sexually transmitted infections. Unintended pregnancy and STIs may be a consequence of loss of reproductive control or sexual assault. Sexual violence is a common tactic used for intimidation and control in IPV; approximately half of abused women admit to sexual assault in the context of abuse. Similarly, approximately half of sexual assault patients name an intimate or formerly intimate partner as the perpetrator. If the sexual assault occurred within 3 to 5 days (depending on state law) of the ED visit, a forensic sexual assault examination should be offered to the patient (see Chapter 191).[20]

The sequelae of intimate partner sexual abuse are at least as serious as those of stranger sexual assault and those who disclose and submit to examination display more nongenital injuries than victims of stranger assault. IPV screening tools should include questions about sexual abuse or reproductive coercion but often fail to do so. Emergency clinicians should ask all patients reporting sexual assault about IPV and safety at home, including what happens when the patient does not want to have sex. Patients may not label forced sex from a partner as sexual assault, a message given by the perpetrator or incorrect societal views. Providers can inform patients that, as of 1993, forced or incapacitated sex with a spouse carries the same legal felony charges as stranger assault in all states with specific state laws available at the RAINN website.[21]

Mental Health Presentations

Repeated physical, sexual, and psychological assaults often carry serious mental health consequences for those living with IPV. Patients presenting to the ED with depression, suicidal ideation, homicidal ideation, PTSD, eating disorders, and alcohol and drug misuse are more likely to have a history of IPV.

Alcohol and Drug Use and Intimate Partner Violence

Substance abuse in either or both parties in an IPV relationship places women at greater risk for physical and sexual intimate partner victimization. Alcohol and drug use may be used to cope with the emotional and physical sequelae of IPV, but can also increase perpetrator violence and leave impaired victims more vulnerable. Victims with substance abuse issues often face negative social and provider bias, reducing the likelihood of accessing medical and community intervention resources. Despite the added difficulties, emergency clinicians play a key role in identifying IPV victims and connecting them with needed help.

Chronic Medical Conditions

IPV patients commonly seek care for chronic medical conditions from previous injuries or those associated with abuse, including mental health disorders, musculoskeletal disorders, and gynecological complaints. Other common medical presentations of IPV include cardiorespiratory illnesses (e.g., palpitations, chest pain, asthma exacerbations, or shortness of breath), gastrointestinal disorders (e.g., abdominal pain and functional bowel disease), and general constitutional complaints (e.g., weakness, fatigue, dizziness, and pain syndromes).

Pain Syndromes

As seen with other posttraumatic syndromes, patients recovering from IPV often suffer from chronic pain, including headache, abdominal pain, back pain, and bone and joint pain, with disability and pain symptoms persisting for years after leaving the violence. Those with more severe abuse, sexual abuse, and childhood abuse report more symptoms. Identifying past abuse facilitates referral to critical resources and decreases use of ineffective medical interventions.

Human Trafficking

Because a trafficker often maintains a sexually intimate relationship with the victim, a victim of human trafficking (HT) can be mistaken for an IPV victim. Human trafficking perpetrators often use physical, emotional, and sexual violence to control victims, frequently forcing the use of drugs or alcohol. Human trafficking entails unique dynamics, challenges, and approaches to intervention and resources (see Chapters 187 and 172).

DIAGNOSTIC TESTING

Diagnostic testing for specific injuries and illnesses related to IPV follows general medical, trauma, and injury guidelines.

MANAGEMENT

After identifying a patient suffering from IPV, the next steps are treatment and documentation. To ensure safety for staff and patients, we recommend notifying hospital security of high-risk situations, such as a victim presenting immediately after leaving their perpetrator.

ED screening for IPV should be determined by a coordinated institutional response: ED staff training; development of institution-wide easily accessible policies and protocols; and in-person resources that include an advocate with IPV expertise (e.g., social worker). Hospitals often partner with local IPV shelters to provide real-time responses to a patient in crisis and safety planning. The US Veteran's Affairs (VA) coordinated and comprehensive program is one example of an effective multifaceted institutional response. Every VA medical facility implements and maintains an IPV Assistance Program for veterans and their intimate partners. Those impacted by IPV have access to resources, assessment intervention, and referrals, and some interventions have demonstrated successful primary prevention outcomes.[22] For institutions that lack a hospital-based IPV program, partnering with a local domestic violence agency or shelter increases resources and can facilitate coordination of care.

IPV victims should receive a trauma-informed approach that recognizes the effect of past and present trauma on the individual and their community, as well as how this trauma is impacted by treatment in the health care system. Emergency clinicians should sympathize with the victim's situation, while emphasizing the strengths of the survivor. Victims should be recognized as the experts in their situation, allowing them to use their unique insights to determine needed interventions.

Physician-Delivered Messages

IPV patients with traumatic injuries or medical conditions should be treated appropriately, and physical symptoms should not be

BOX 192.3 Simple Steps for Discussing IPV Post Disclosure

1. Give supportive messages, for example:
   - "Thank you for sharing this with me. I know it took courage."
   - "No one deserves to be treated this way. It doesn't matter what you did or what your partner said you did, you do not deserve to be hit."
   - "You are not the only one who has suffered this kind of abuse. IPV is a common problem."
   - "You don't have to deal with this alone. We have people here (or in the community) who can help you."
2. Explain that you would like to help them today. Ask permission to get an advocate or social worker involved. Ask how else staff can help today.
3. Safety and danger assessment—assess immediate safety concerns; have further discussion and planning with the social worker or advocate.
4. Make a plan for follow-up. Reinforce that IPV is a health care problem and that the patient can return for assistance.

minimized or ascribed solely to IPV. Psychological treatment and support are essential; supportive counseling from an emergency clinician can facilitate catharsis for a victim who has been suffering in silence. Victims universally feel they deserve the abuse, because abusers introduce and reinforce this notion throughout the relationship. Emergency clinicians should unequivocally tell IPV victims that the abuse is *not* their fault, emphasizing that no one deserves to suffer physical, psychological, or sexual abuse. Use compassionate and supportive statements that acknowledge the abuse experience, commend the patient for disclosing, and explain how information will facilitate good care. A few kind and supportive words from a provider can help alleviate the guilt and shame felt when revealing the abuse. Box 192.3 provides examples of comforting phrases and dialogue.

Documentation

Physicians should document the identity of the other person involved in the injury, including that person's relationship to the patient. A victim living with their assailant will need unique resources, and the nature of the relationship is also needed for appropriate diagnostic coding. Medical record documentation can help future health care providers deliver optimal care. Medical records may also be used in court to help victims seeking legal recourse, child custody, or restraining orders. Patient statements should be documented in quotes or preceded with "patient states." Injuries should be described, recording the size or length, type of injury (e.g., bruise, incised wound, abrasion), and location. Injuries should be digitally photographed (usually by law enforcement or forensic specialist) with adequate quality for legal use. We recommend at least 4 photographs of every injury:

- 1 long-range picture, including the face for identification,
- 1 medium range,
- 1 close range without ruler, and
- 1 close range with ruler.

Many electronic medical records incorporate a way to upload photographs directly into the medical record with the time and date recorded. Patients who decline photography in the ED should be encouraged to privately document their injuries with their own cameras or phones, as self-obtained images have been used successfully in prosecution of IPV. Referral agencies, social work, and law enforcement involvement, follow-up, and referrals should be recorded in the medical record. The diagnosis of IPV or suspected IPV should be documented for possible use in legal proceedings.

Immigration Issues

Due to cultural norms that embrace husband-to-wife marital violence and control, immigrant women are less likely to reveal abuse. Many cultures blame the woman for any type of marital discord, including violence. A victim's own family may desert her if she leaves her partner for any reason, even fear of homicide. As abuse draws the attention of law enforcement agencies, undocumented immigrant women may fear deportation of themselves or their partners. Additionally, a citizen perpetrator may use the victim's immigration status to force the victim to remain in the violent relationship (including marriage). Language barriers may further impede a victim's ability to obtain help. In recent years, federal and state governments have attempted to correct some of the legal problems that plague immigrant IPV victims. According to the federal Violence Against Women Act (VAWA), victims who depend on their perpetrator to legally stay in the United States may self-petition for legal permanent residence as they attempt to separate.[20,23] Programs and protocols for treating IPV victims should include information on local resources for ethnic minorities and immigrants.

Referral

Referral services can help assess the risk of acute danger to the patient or their children, determine readiness to separate from the perpetrator, and provide specific means to increase safety. Protocols should include intervention (e.g., from IPV advocates or social workers) and referral resources, including safe housing. If separating from the violent partner, patients may need legal advice (e.g., orders for protection, custody, or other official charges), shelter placement, and ongoing support groups. A discussion about past strategies, what has or has not been successful, can help guide management. Discussing the scope and consequences of the violence (e.g., on the patient or their children) may help the patient make the safest decisions. Orders for protection have been shown to be effective in decreasing future violence, but cannot guarantee safety, and perpetrators with past criminal records may be less likely to respect law enforcement directives. Although survivors may not be ready to leave an abusive situation, the provider should support the survivor and encourage disclosure to future health care providers or IPV agencies.

If children are present in the home, have experienced violence, or are at risk for becoming targets of violence, the emergency clinician may be mandated by law to report the situation to child protective services. Emergency clinicians should explain that reporting helps keep the children safe, demonstrates the victim's desire to protect the children, and is more likely to reflect positively on the victim in the event of future custody hearings. A brief discussion about the long-term health effects of violence on children may be helpful, as victims are often more focused on the immediate consequences to children.[24] Individualized safety planning may be complex and time consuming and is best accomplished by an experienced social worker or IPV advocate.

If the patient has not disclosed, but the emergency clinician suspects IPV, a disclosure should not be forced. It is more important to express concern for the patient, explain how the condition may be related to stress, and offer support, community domestic violence resources, and the opportunity to return for assistance. "My Plan" is a valuable smart phone or computer resource to assess danger and plan for safety (available at https://www.myplanapp.org/home) (Fig. 192.7). In the absence of an advocate, social worker, or law enforcement specialist, victims can use My Plan to learn more about IPV and develop a detailed safety plan. Clinicians can also consult or advocate using the national 24-hour IPV hotline (1-800-799-SAFE).

Danger Assessment

Campbell and colleagues have developed a 20-item danger assessment tool (Fig. 192.8) that was developed and validated based on reviews

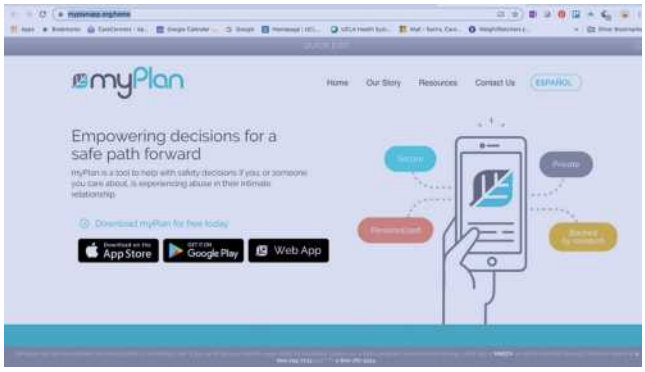

Fig. 192.7 Downloadable My Plan for smart phone and computer application with danger assessment.

of IPV-related homicides across 11 cities. This study identified factors more often correlated with IPV leading to homicide or attempted homicide and can assess immediate risk for future severe violence and lethality, however, the tool is somewhat complex to score and requires familiarity. A self-administered version of this tool is available through the MyPlan application for IOS and Android (see Fig. 192.7). A brief, five-item version of this tool (Box 192.4) can identify ED patients at high risk; a threshold of three "yes" answers has shown an 83% sensitivity for predicting future severe or potentially lethal assault. This information should be shared with the patient, ideally in conjunction with social work and an advocate to help the patient in planning for safety and the desired course of action upon discharge. The MyPlan app also contains specific recommendations for safety planning.

DANGER ASSESSMENT

Jacquelyn C. Campbell, Ph.D., R.N. Copyright, 2003; update 2019; www.dangerassessment.com

Several risk factors have been associated with increased risk of homicides (murders) of women and men in violent relationships. We cannot predict what will happen in your case, but we would like you to be aware of the danger of homicide in situations of abuse and for you to see how many of the risk factors apply to your situation.

Using the calendar, please mark the approximate dates during the past year when you were abused by your partner or ex-partner. Write on that date how bad the incident was according to the following scale:

1. Slapping, pushing; no injuries and/or lasting pain
2. Punching, kicking; bruises, cuts, and/or continuing pain
3. "Beating up"; severe contusions, burns, broken bones
4. Threat to use weapon; head injury, internal injury, permanent injury, miscarriage or choking" (use a © in the date to indicate choking/strangulation/cut off your breathing- example 4©)
5. Use of weapon; wounds from weapon

(If any of the descriptions for the higher number apply, use the higher number.)

Mark **Yes** or **No** for each of the following. ("He" refers to your husband, partner, ex-husband, ex-partner, or whoever is currently physically hurting you.)

_____ 1. Has the physical violence increased in severity or frequency over the past year?
_____ 2. Does he own a gun?
_____ 3. Have you left him after living together during the past year?
3a. (If you have *never* lived with him, check here: ___)
_____ 4. Is he unemployed?
_____ 5. Has he ever used a weapon against you or threatened you with a lethal weapon?(If yes, was the weapon a gun? check here: ___)
_____ 6. Does he threaten to kill you?
_____ 7. Has he avoided being arrested for domestic violence?
_____ 8. Do you have a child that is not his?
_____ 9. Has he ever forced you to have sex when you did not wish to do so?
_____ 10. Does he ever try to choke/strangle you or cut off your breathing?
10a. (If yes, has he done it more than once, or did it make you pass out or black out or make you dizzy? check here: ___)
_____ 11. Does he use illegal drugs? By drugs, I mean "uppers" or amphetamines, "meth", speed, angel dust, cocaine, "crack", street drugs or mixtures.
_____ 12. Is he an alcoholic or problem drinker?
_____ 13. Does he control most or all of your daily activities? For instance, does he tell you who you can be friends with, when you can see your family, how much money you can use, or when you can take the car? (If he tries, but you do not let him, check here: ___)
_____ 14. Is he violently and constantly jealous of you? (For instance, does he say: "If I can't have you, no one can.")
_____ 15. Have you ever been beaten by him while you were pregnant? (If you have never been pregnant by him, check here: ___)
_____ 16. Has he ever threatened or tried to commit suicide?
_____ 17. Does he threaten to harm your children?
_____ 18. Do you believe he is capable of killing you?
_____ 19. Does he follow or spy on you, leave threatening notes or messages, destroy your property, or call you when you don't want him to?
_____ 20. Have you ever threatened or tried to commit suicide?

_____ Total "Yes" answers

Thank you. Please talk to your nurse, advocate, or counselor about what the Danger Assessment means in your situation.

Fig. 192.8 Danger assessment tool.

BOX 192.4 Brief Danger Assessment

1. Has the physical violence increased in frequency or severity over the past 6 months?
2. Has [he/she] ever used a weapon or threatened you with a weapon?
3. Do you believe [he/she] is capable of killing you?
4. Have you ever been beaten by [him/her] while you were pregnant?
5. Is [he/she] violently and constantly jealous of you?

Mental Health Screening

Given the increased prevalence of mental health disorders in IPV survivors, including depression, anxiety, and suicide, providers should refer for supportive counseling and treatment.

Privacy and Confidentiality Considerations

Privacy is a concern for many IPV survivors. Any referrals or records should only be released with permission of the survivor. IPV should not be reported to police without the consent of the survivor, unless mandated by law in cases of coexisting child, elder, or disabled abuse or based on state-specific reporting statutes (e.g., burns or injuries inflicted by weapons). Links to state legislation governing the reporting of injuries due to assault may be found at the victim rights website.[25] If reporting is mandated, the emergency clinician should make every effort to involve the patient. Health Insurance Portability and Accountability Act (HIPAA) violations do not apply in this circumstance; the privacy rule contains a provision allowing disclosure of protected health information to law enforcement in the case of reporting required by law.

Involvement of Law Enforcement Agencies

Unless required by mandatory reporting laws, patients should be given the choice of whether or not to involve law enforcement. Consultation with law enforcement personnel may enhance victim safety through immediate access to restraining orders (in some states). Additionally, acute injuries to the victim can lead to the immediate arrest of the perpetrator, thus temporary victim safety. Almost all states have laws that require medical personnel to notify law enforcement agencies in special circumstances, such as when a patient presents with injuries caused by a firearm or other deadly weapon. Many states also require that emergency clinicians report any victim of aggravated assault or a violent crime. In the last few decades, many states, counties, and cities have implemented IPV training for law enforcement officers. Courses can provide the sensitivity-training and knowledge needed to appropriately interview and counsel victims. However, this training is not universal, and clinicians should be aware of the limitations of their local law enforcement agencies.

Intimate Partner Violence Coding and Diagnosis

International Classification of Diseases (ICD)–10 coding provides increased specificity for the coding of IPV (Table 192.1). New codes added to the primary category allow the provider to include adult maltreatment and neglect. Other codes added include suspected IPV (T codes) and past IPV and counseling (V codes). Similar to ICD-9, ICD-10 also includes E codes, which are used to describe the nature of the cause of the injury—for example, "Who committed the act of violence" (E967.0–E967.9), the nature of the abuse (E960–E968), the intent of the abuse or neglect (E904.0–E968.4), and the intentionality of the abuse (E980–E989).

TABLE 192.1 ICD-10 Coding Categories Used for Intimate Partner Violence

ICD-10 Code	Description
995.8_	Maltreatment (abuse)
995.81	Physically abused adult
995.82	Adult emotional and psychological
995.83	Adult sexual
995.84	Adult neglect
995.85	Other, multiple forms
E	Who, intentionality, nature of abuse
T4	Suspected abuse
T7	Confirmed abuse
V	Past history of abuse

ICD, International Classification of Diseases.

DISPOSITION

Patients with potentially life-threatening injuries, particularly attempted strangulation, are at high risk of future violence and should have safe plans for discharge or be offered temporary admission. Although shelters are one option, they may not be available in all locations. Patients who qualify and choose to go to an IPV shelter are typically required to disengage from their lives to protect the location and safety of the shelter. They cannot contact family or friends, nor can they contact their job or their children's schools. Even when present, local shelters may lack enough space to take a victim with children, or may not accept patients with substance abuse issues, teenage male children of survivors, or male or transgender survivors.

All survivors who are being discharged should receive patient-appropriate resources for IPV, mental health, substance abuse, and social services. The emergency clinician may not agree with the choices made by the survivor but should always respect these decisions and offer encouragement and validation. This approach will increase the chances of a positive interaction and increase the likelihood of further help-seeking behavior.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 192: QUESTIONS AND ANSWERS

1. Intimate partner violence occurs in which of the following population of patients?

- **a.** Restricted to lower socioeconomic classes and is never seen in wealthy highly educated individuals.
- **b.** Found only amongst women in heterosexual relationships and not in other individuals.
- **c.** Patient has injuries from a weapon used in the assault.
- **d.** Similar prevalence in same-sex and gender nonconforming individuals as in heterosexual couples.

Answer: D. IPV occurs with at least as high a prevalence in same-sex and gender nonconforming individuals as in heterosexual couples. It also is found commonly in wealthy and highly educated individuals. Most patients who present to the ED with conditions related to IPV do not have injuries at the time of the visit. Finally, IPV violence consists of acts or threats of physical, psychological, or sexual violence between intimate or formerly intimate partners who need not ever have been married.

2. The emergency clinician after identifying a patient suffering from IPV should employ which of the following strategies?

- **a.** Call the police and have the perpetrator immediately arrested.
- **b.** Validate the disclosure of abuse and communicate the importance of leaving the situation immediately to ensure personal safety.
- **c.** Provide kind and supportive messages and information.
- **d.** Report to the public health department.

Answer: B. Emergency clinicians should validate the disclosure of abuse, emphasize that the victim is not at fault, and encourage future discussions with IPV community agencies or other health care providers. Immediate safety should be assessed, but most patients will not want to leave the abuser immediately; however, a positive initial conversation may begin the process of ending the abusive relationship. Reporting to law enforcement or health department should be done only with victim consent or if mandated by law. A templated list will allow the ED staff to create a basic safety plan with the patient; an individualized plan is best done in conjunction with trained domestic violence advocates, typically in follow-up. Referral to couples counseling is inappropriate and ineffective in violent relationships and potentially dangerous.

3. The best practice for inquiring about IPV is which of the following?

- **a.** Use open-ended questions that describe actions and feelings.
- **b.** Use the term "abuse" when questioning the patient.
- **c.** Ise the term "victim" to ensure the patient knows the clinician is concerned.
- **d.** Question the patient's partner about what happened.

CHAPTER 192: QUESTIONS AND ANSWERS—cont'd

Answer: A. Partners should be asked to leave in a routine manner before the patient is asked about IPV. Patients will rarely admit to abusive acts unless they are guaranteed privacy, and initiation of the topic is potentially dangerous in the presence of an abusive partner who should not be questioned by providers. Providers should query the patient with any reasonable options that provide an empathetic and open approach facilitating improved screening rates. Providers should ask about specific actions and avoid use of the terms "victim" and "abuse" because patients may not yes see the actions as abuse or themselves as a victims.

4. Which of the following is most suspicious for intentional injury from IPV?
   - **a.** Ecchymosis of lower extremity
   - **b.** Paronychia
   - **c.** Pattern injuries
   - **d.** Infected earring

Answer: C. Signs of an intentional injury include a central location (i.e., trunk and breasts), bilateral injuries (both arms or both legs), defensive injuries (i.e., ecchymoses on the back of the hand as a result of protecting the face), and patterned injuries (such as carved words on the back, a cigarette burn or other pattern of an object,).

5. By the state law where Dr. Jane works, emergency clinicians practicing in the state are mandated reporters for suspicious injuries from assaultive or abusive conduct. After identifying a patient with such suspicious injuries from IPV Dr. Jane should do which of the following regarding reporting?
   - **a.** Not report because the Health Insurance Portability and Accountability Act (HIPAA) prohibits reporting of this patient's injuries.
   - **b.** Report without telling the patient so the patient cannot object.
   - **c.** Report as required by state law because it supersedes patient's HIPAA consent rights.
   - **d.** Obtain a signed consent to make the report.
   - **e.** Call the legal department before reporting.

Answer: C. Some states have laws that require injury reporting to local authorities. Patients should be informed about state-specific reporting requirements that may accompany disclosure of abusive injuries. Mandatory reporting of health conditions required by local laws are exempted from HIPAA regulations. In general, IPV should not be reported to police without the consent of the survivor unless mandated by law (as in this case) or in cases of coexisting child, elder, or disabled abuse or based on state-specific reporting statutes (e.g., burns or injuries inflicted by weapons). If reporting is mandated, the provider should make every effort to involve the patient. However, concerns for HIPAA violations do not apply in this circumstance; the privacy rule contains a provision allowing disclosure of protected health information to law enforcement in the case of reporting required by law.

Global Emergency Medicine

Sean M. Kivlehan and Stephanie Kayden

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Global Emergency Medicine

Sean M. Kivlehan and Stephanie Kayden

KEY CONCEPTS

- World Health Assembly resolution 72.16, "Emergency care systems for universal health coverage: ensuring timely care for the acutely ill and injured," was passed in 2019 and calls for the strengthening of emergency care delivery through a detailed list of initiatives across the prehospital, facility, public health, and disaster preparedness fields.
- In low- and middle-income countries (LMICs), substantial excess mortality amenable to emergency health care exists, and the development of high-quality emergency care can be a significant systemic contribution to improving mortality.
- Global emergency medicine (GEM) is an academic subspecialty of emergency medicine focused on the strengthening of the specialty worldwide and on improving international humanitarian response.
- GEM can be divided into development and humanitarian work. Development work is typically focused on strengthening local systems in a sustainable manner, while humanitarian work involves an acute response to large-scale crises in which local resources are overwhelmed.
- The model curriculum for a GEM fellowship includes experiences in emergency medicine systems, humanitarian relief, disaster medicine, public health, travel and field medicine, program administration, academic skills, and clinical skills.

FOUNDATIONS

Recognizing that emergencies will occur and that patients will seek care regardless of a system's preparation, global emergency medicine (GEM) strives to strengthen emergency care delivery in all settings. Further recognizing that patients present to the emergency department (ED) without a diagnosis, but with a complaint, GEM focuses on presentation-based solutions for conditions for all age groups, both trauma and medical, infectious and noninfectious, and pregnancy. GEM seeks to ensure early access to quality emergency care for all people, regardless of gender, ethnicity, age, or ability to pay.

In low- and middle-income countries (LMICs), substantial excess mortality amenable to emergency health care exists.[1] This is due to both access to care and quality of care, both of which the development of high-quality emergency care systems can impact.[2,3] As a central hub of health care access, the ED provides both a safety net for the community and a point of entry into the medical system. Programs that seek to strengthen emergency care should be coordinated with other medical and surgical specialties, prehospital care, public health authorities, and social services to identify gaps and provide a seamless continuum of care.

GEM is an academic subspecialty of emergency medicine focused on the strengthening of the specialty worldwide and on improving international humanitarian response. Although much of the work focuses on low-resource settings, its mission is broad and can apply to all countries. The academic subspecialty of GEM emphasizes specialty development programs that are long-term and sustainable, in contrast to short-term international clinical experiences or "medical missions."

GEM is one of many fields of global health. *Global health* is a broad term that encompasses all aspects of health care with global interest, such as primary care, surgery, and preventative care such as vaccine programming. As in traditional emergency medicine, there is substantial overlap between GEM and the many other fields within global health. For example, preventative programs such as tetanus vaccination are frequently incorporated into global emergency care.

The Academic Practice of Global Emergency Medicine

The GEM physician is a trained subspecialist who works to strengthen the practice of emergency medicine worldwide. In the United States (US), the subspecialty of GEM has been recognized by national professional associations including the American College of Emergency Physicians (ACEP), Society for Academic Emergency Medicine (SAEM), and the American Academy of Emergency Medicine (AAEM) through their respective GEM-oriented sections. Many GEM specialists have completed GEM fellowships: 1 to 2 years of additional post-residency training, often including a graduate degree focused on global health. A growing number of academic EM departments in the United States maintain a division of global emergency medicine which provides an academic home to GEM specialists.

Fellowship training programs in the United States coordinate their efforts through the Global Emergency Medicine Fellowship Consortium (GEMFC), which maintains a website describing active fellowships and facilitating the annual application process.[4] Curricula vary based on an individual fellowship's goals, which may be more heavily oriented to systems building, research, education, direct clinical care, or humanitarian work. Most fellowships incorporate a combination of these areas. Model curricula have been proposed, which include experiences in the following domains: EM systems, humanitarian relief, disaster medicine, public health, travel and field medicine, program administration, academic skills, and clinical skills (Table e1.1). Approaches to meeting knowledge and skill goals may include a variety of educational programming, such as a Master of Public Health degree, short courses such as the International Committee for the Red Cross (ICRC) Health Emergencies in Large Populations, tropical medicine courses, and international field experiences. Proposed competency assessment frameworks for fellows training in GEM must adapt to the diverse fellowship curricula and focus on the following key domains: professionalism, communication, medical knowledge, patient care, research skills, quality improvement, and social accountability to partners and stakeholders.[5]

SPECIFIC ISSUES

History of Global Emergency Medicine

The first emergency medicine residencies in the United States began in the early 1970s and emergency medicine was formally recognized as a

TABLE E1.1 Model Curriculum

Knowledge and Skill Areas	Subtopics
EM Systems Development	Needs Assessment Emergency Care Delivery System Models Training Program Approaches EM System Development Financial Models for Care Delivery Legislative Frameworks and Legal Considerations
Humanitarian Relief	Humanitarian Organizations Interorganizational Coordination Management of Relief Programs
Disaster Management	Hazard Types Principles of Disaster Management National Models for Disaster Management International Response to Disasters Development of National and Regional Disaster Management Systems
Public Health	Core Content Health Policy and Administration Theory of International Health
Travel and Field Medicine	Travel Health Field Medicine
Program Administration	Funding Proposal Writing Project Management Strategic Planning
Academic Skills	Adult Learning GEM Scientific Literature Research Methodologies Scientific Writing Oral Presentations Geographic Information Systems Career Development
Clinical Practice	Austere Settings

Adapted from: Bayram J, Rosborough S, Bartels S, et al. Core curricular elements for fellowship training in international emergency medicine. *Acad Emerg Med.* 2010;17(7):748-57.

specialty by the American Board of Medical Specialties in 1979. In the following decades, emergency medicine grew both within the United States and globally. It was recognized as a specialty in Canada in 1980, Australia in 1981, soon followed by Hong Kong, Singapore, the United Kingdom (UK), and others.

The first emergency physicians building the specialty came together to form academic societies and advocacy groups to build collaboration, facilitate idea exchange, and advance the field. ACEP was formed in 1968, and similar organizations in other countries soon followed. In 1989, recognizing the need for international support in developing emergency medicine, the International Federation for Emergency Medicine (IFEM) was chartered by its founding members, ACEP, British Association for Accident and Emergency Medicine (UK; now the Royal College of Emergency Medicine), Australasian College for Emergency Medicine (Australia), and Canadian Association of Emergency Physicians (Canada). IFEM has grown to include over 50 full members and creates core standards, curricula, and policy briefs on emergency medicine through its committees and interest groups. ACEP created its section on international emergency medicine in 1998, reflecting the growing interest among emergency physicians to engage in global activities. As other societies followed with their own committees or interest groups focusing on emergency medicine development internationally, the specialty of GEM took its modern form.

Fellowship training in GEM arose from the combined need of trained emergency physicians practicing internationally who realized they had inadequate preparation and residents expressing increased interest in entering the field. The first fellowships in the United States were started in the mid-1990s with a curriculum largely based on a consensus panel of emergency physicians practicing GEM. As the specialty of GEM has matured, fellowships have grown significantly in number both in the United States and in other countries. The GEMFC was created in 2012 to bring GEM fellowship directors together to further define the specialty and agree on common curricular goals and assessment criteria.

The practice of GEM has grown in scope and quality. GEM research has raised awareness of the burden of emergency care amenable conditions, the economic value of emergency care, and the central role of emergency care systems in public health and health security.[3,6,7] In 2013, SAEM hosted the "Global Health and Emergency Care: A Research Agenda" Consensus Conference during which priorities were discussed and agreed upon across eight focus areas. These priorities formed a foundation for the currently maturing GEM research priorities.[7,8]

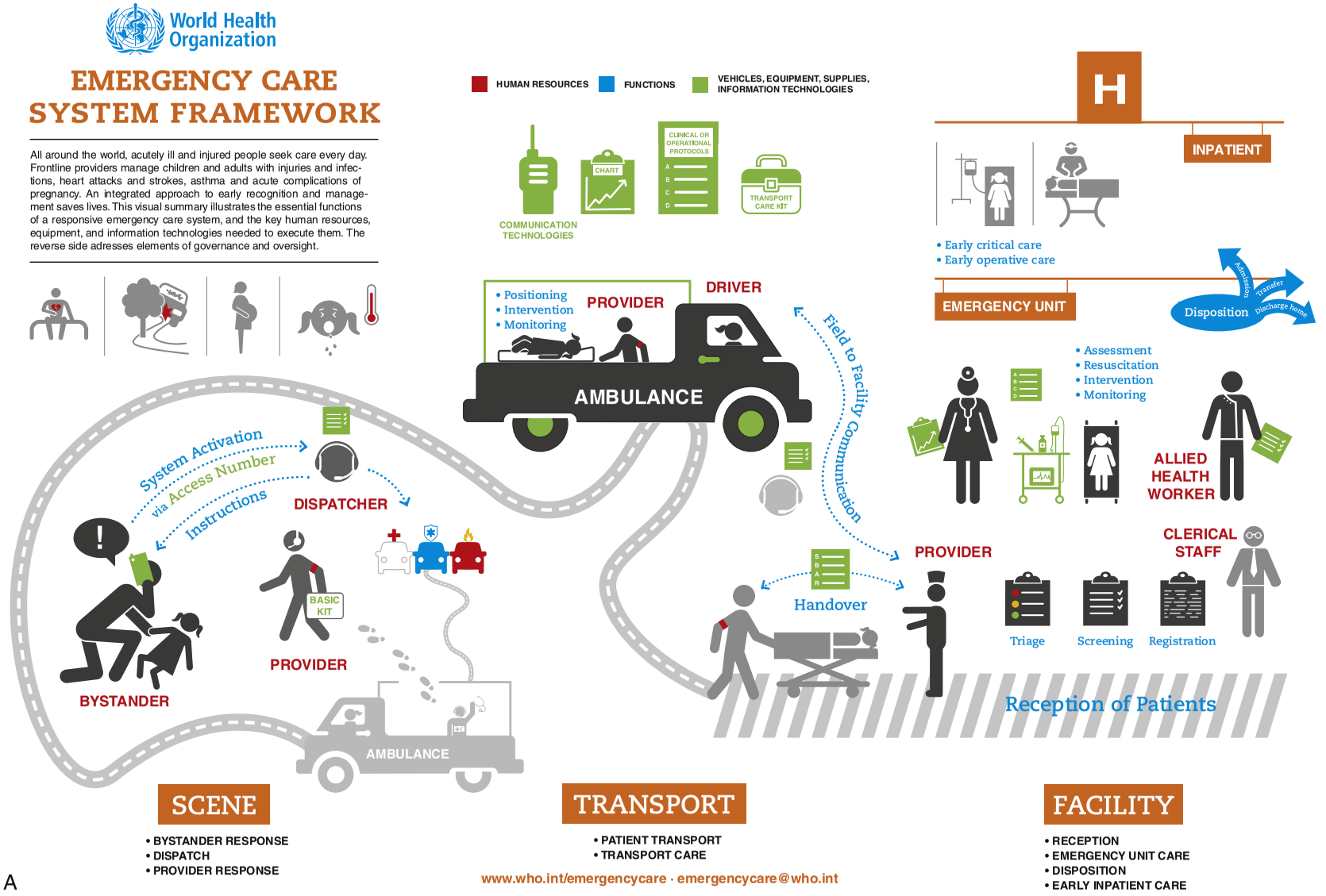
The World Health Organization (WHO) supported numerous efforts related to GEM in the early 2000s, including trauma care and prehospital care in low-resource settings, later forming the Emergency, Trauma, and Acute Care Programme in 2015 which is led by an emergency physician.[9] This program has refined definitions of emergency care systems, essential functions, quality indicators, and emergency care itself[10] (Fig. e1.1 and Table e1.2). In 2019, the National Institutes of Health (NIH) Fogarty Center for Global Health Studies initiated the Collaborative for Enhancing Emergency Care Research in LMICs (CLEER), which has further defined the research agenda for GEM.[7,11]

Several resolutions related to emergency care have been issued by the World Health Assembly (WHA), the governing body of the WHO. Passed in 2019, WHA resolution 72.16, "Emergency care systems for universal health coverage: ensuring timely care for the acutely ill and injured," calls for the strengthening of emergency care delivery through a detailed list of initiatives across the prehospital, facility, public health, and disaster preparedness fields.[12] This resolution is aligned with the three Sustainable Development Goals (SDG) that are directly affected by emergency care: Goal 3 (Ensure healthy lives and promote well-being for all at all ages), Goal 11 (Make cities and human settlements inclusive, safe, resilient and sustainable), and Goal 16 (Promote peaceful and inclusive societies for sustainable development, promote access to justice for all and build effective, accountable and inclusive institutions at all levels).[13] Prior resolutions have focused on surgical and anesthesia care, mental health, disaster management, emergency care systems, and road safety (Table e1.3).

Global EM Organizations

Emergency medicine is represented globally by a variety of professional organizations whose objectives differ based on their core missions. A growing number of countries have a national professional society focused on the development and support of the practice of domestic emergency medicine. In the United States, ACEP is the largest organization, and analogous organizations exist in at least 50 other countries. The IFEM maintains a current list of these organizations on its website.[14]

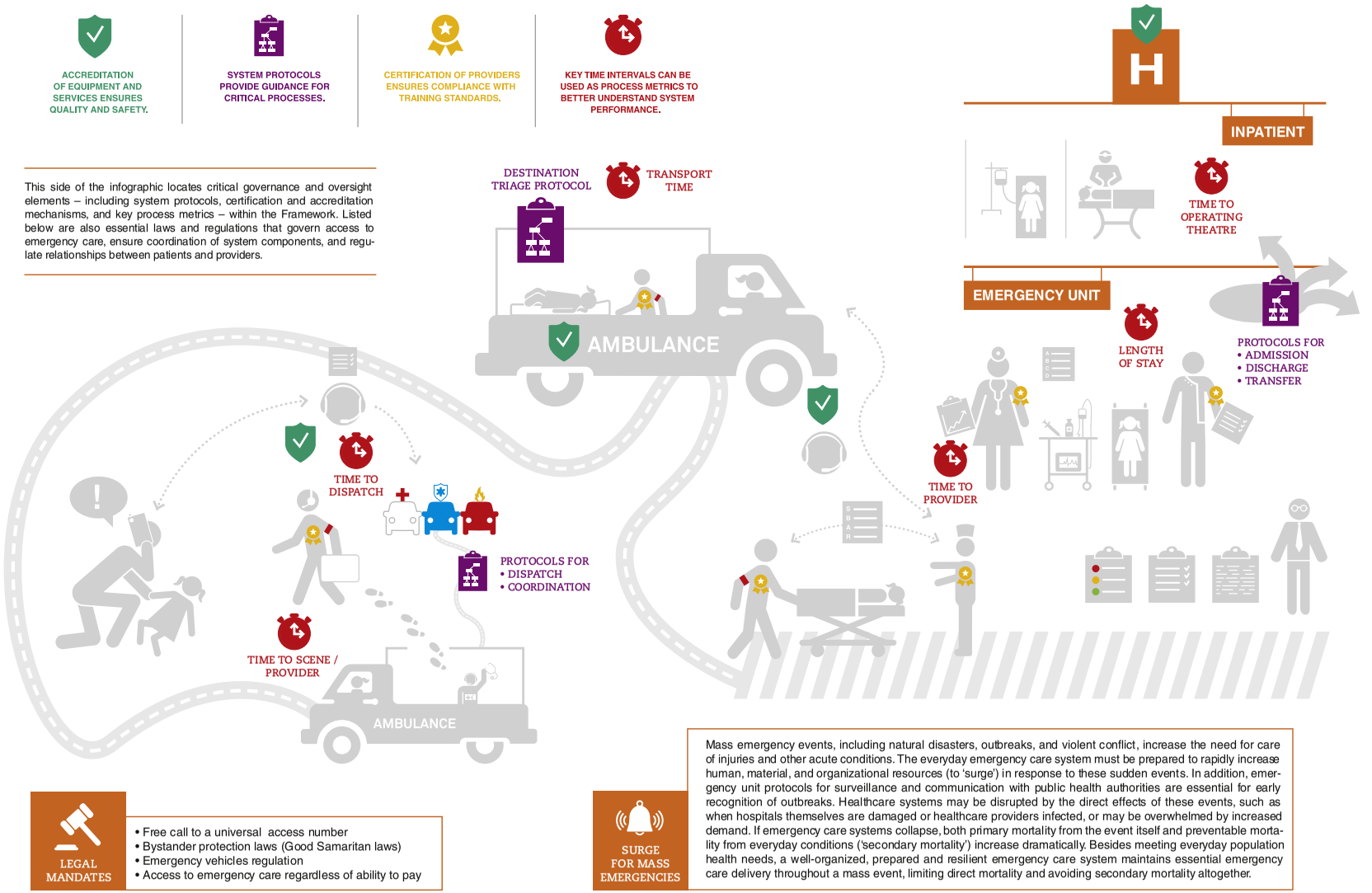
Regional societies are composed of several organizations representing the specific interests and needs of emergency medicine in a



A

Fig. e1.1 WHO emergency care systems framework infographic. (Available at: https://www.who.int/publications/i/item/who-emergency-care-system-framework.)

Continued



B www.who.int/emergencycare · emergencycare@who.int

Fig. e1.1, cont'd

TABLE E1.2 WHO Emergency Care System Functions

Site	Primary Function
Scene	Bystander Response
	Dispatch
	Provider Response
Transfer	Patient Transport
	Transport Care
Facility	Emergency Unit Care
	Disposition (admission, discharge, transfer)
	Inpatient Care
Cross-Cutting Elements	Service Delivery
	Financing
	Integrated Data Management
	Surge Response (Outbreak and Disaster)

Adapted from: Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME (eds). 2015. Mental, neurological, and substance use disorders. *Disease Control Priorities*, third edition, volume 4. Washington, DC: World Bank. https://doi.org/10.1596/978-1-4648-0426-7. License: Creative Commons Attribution CC BY 3.0 IGO Translations–If you create a translation of this work, please add the following disclaimer along with the attribution: This translation was not created by The World Bank and should not be considered an official World Bank translation. The World Bank shall not be liable for any content or error in this translation.

particular area of the world. An example is the African Federation for Emergency Medicine (AFEM), which has developed African context-specific educational material for emergency medicine and supports the development of the specialty across the continent.[15] The Consortium of Universities for Global Health (CUGH) is based in Washington, DC, and brings together academic institutions from around the world that have a focus on global health. CUGH provides an important forum for discussion among academics working in the field of global health and is not limited in scope to health care or emergency medicine.[16]

AREAS OF FOCUS IN GLOBAL EMERGENCY MEDICINE

GEM can be divided into development and humanitarian work. Development work is typically longer term and proactive with the goal of strengthening local systems in a sustainable manner. Humanitarian work tends to be more reactive, focused on the response to large-scale crises in which local resources are overwhelmed. These two subfields complement each other: an emergency care system strengthened through development work should be able to surge during a crisis to enhance humanitarian efforts, and an effective humanitarian response will include strengthening the local system to provide resilience against future crises. Humanitarian response is discussed in detail in Chapter e2. This chapter on GEM will focus on the development of EM systems globally.

Strengthening the specialty of emergency medicine globally is a large and complex task that requires efforts within the fields of education, research, and policy. For example, as an emergency care system is strengthened, provider training must be expanded to provide the level of care needed, while policy efforts must establish credentialing pathways for these new providers. Locally applicable processes and outcome measures must be defined, and interventions must be measured through research. These interdependent efforts are equally critical to GEM.

Education

Field educational programs can be categorized by duration, content, and learner type. Programming should be needs-driven and context-appropriate.

TABLE E1.3 World Health Assembly Resolutions Relevant to GEM

Resolution	Title	Year Passed
56.24	Implementing the Recommendations of the World Report on Violence and Health	2003
57.10	Road Safety and Health	2004
60.22	Health Systems: Emergency Care Systems	2007
64.10	Strengthening National Health Emergency and Disaster Management Capacities and Resilience of Health Systems	2011
66.8	Comprehensive Mental Health Action Plan 2013–2020	2013
68.15	Strengthening Emergency and Essential Surgical Care and Anesthesia as a Component of Universal Health Coverage	2015
69.1	Strengthening Essential Public Health Functions in Support of the Achievement of Universal Health Coverage	2016
72.16	Emergency Care Systems for Universal Health Coverage: Ensuring Timely Care for the Acutely Ill and Injured	2019

A systematic review of EM training programs in LMICs supported by high-income country partners found that the majority of training programs were one month or less in duration; focused on physicians and less commonly nurses; and most frequently oriented to EM in general, trauma, pediatrics, or ultrasound.[17] Prior to any educational intervention, a needs assessment should be performed in coordination with local stakeholders. Development of a new program or adaptation of existing programs should be performed in collaboration with local stakeholders, which may include clinical providers, educators, students, the community, administrators, and policymakers. It is critical to ensure that graduates from an educational program will be recognized locally through a credentialing mechanism such as certification or licensure. Program sustainability can be supported through two equally important pathways: (1) identifying future educators among students and preparing them to eventually take local ownership of the program, and (2) ensuring program graduates are employable and able to practice within their scope.

Systems Development (Systems Strengthening)

Emergency care systems exist nearly everywhere in some form, though they may be unrecognizable to an emergency care clinician from a high-resource setting. The strengthening of a system begins by understanding the components that already exist and how they interact. An emergency care system has three key components: scene care, transport care, and facility care. These related components each contain a series of functions and connect to both the local population through community-based training and to the remainder of the health care system through access to inpatient care, critical care, surgical care, and rehabilitation. Work to strengthen emergency care systems may involve analysis of any of these components, or the referral systems that connect them, in addition to program implementation.

Research

Most GEM activities involve some form of research effort. Understanding existing emergency care systems requires analyses that use both quantitative and qualitative methods. Process and outcome measures should be defined in a context-appropriate manner, and measurement of the effect of interventions is required to understand the impact.

Validated assessment tools to characterize the capacity and gaps in EM systems exist and should be used.[18-20] Any research undertaking should be performed with local input and ethical board approval, which should be reflected in authorship.

National Societies

As emergency care evolves in an area, regional representation is required to further strengthen the specialty. Bringing like-minded emergency care clinicians together in a manner that allows for the discussion of the strengths and weaknesses of their system can provide a rich source of information exchange and partnership. These societies can provide a unified voice for emergency care clinicians in their region to advocate for their providers and patients.

Policy

Sustainable change to an emergency care system requires government support. For each component of the emergency care system to succeed, certain legislative tools must be in place. These include Good Samaritan laws, universal emergency service access numbers, minimum standards for training, equipment, and processes, provider certification, billing guidelines, and credentialing for ambulances and facilities. Guidelines and tools to determine the presence of minimum standards exist and should be used.[21,22] GEM practitioners help to advocate for these legislative tools directly with government agencies or guide emergency clinicians and societies in ways to lobby for these changes.

Humanitarian Assistance

Many GEM clinicians are involved in humanitarian activities such as international disaster response or refugee health (see Chapter e2). A gap exists between humanitarian and development work, and GEM supports efforts to bridge the gap between short-term humanitarian actions and longer-term development efforts.[23]

Direct Clinical Care

While education and system strengthening are important to support sustainability, providing clinical care in settings foreign to the GEM clinician is also an important part of the specialty. This occurs in several ways: planned clinical rotation at a partner site, humanitarian or surge response, or in an educational program with bedside teaching and supervision. Clinicians should always function within their level of training and scope of practice, typically as defined by their home credentials. For example, if a resident requires supervision for clinical practice in their home environment, the resident will require it in a foreign environment as well.[24] Direct patient care should only be provided under an active medical license issued by the country where the care will be provided. Prior to providing any direct patient care as a GEM clinician, written agreements should be in place with the host institution outlining provider credentialing, supervision, the chain of command for conflict, documentation requirements, translation (if needed), and quality assurance.[25]

Clinical Rotations Abroad

Interest in global health among medical students and residents has grown substantially, with 24% of US medical students completing electives in global health, and 91% of emergency medicine residency programs offering international rotations.[26,27] It is the responsibility of the GEM specialist to support the development of sustainable, educational, responsible, and safe experiences abroad for institutional trainees. Milestones for emergency medicine training in global health were developed based on the 11 CUGH global health domains (Box e1.1) and should be used to guide educational activity.[28]

BOX E1.1 Consortium of Universities for Global Health (CUGH) 11 Domains

Global burden of disease
Globalization of health and health care
Social and environmental determinants of health
Capacity strengthening
Collaboration, partnering, and communication
Ethics
Professional practice
Health equity and social justice
Program management
Sociocultural and political awareness
Strategic analysis

From: Jogerst K, Callender B, Adams V, et al. Identifying interprofessional global health competencies for 21st-century health professionals. *Ann Glob Health*. 2015;81(2):239-47.

Clinical rotations abroad should be formalized through written agreement between the host and sending institutions which includes the leadership structure, policies, and procedures. Similar to the ethical standards discussed in the previous section, the rotator must practice within their normal scope of practice and be supervised if not independently licensed to practice in the destination country. Educational opportunities should be bidirectional between institutions, ideally with exchange programs. Rotations are often with organizations other than universities and hospitals, such as NGOs or government organizations. It is important to understand partner organizations' missions and goals to ensure they align with the principles of sustainable, educational, responsible, and safe practice.

Preparation of the Traveler

In one survey of EM residencies, only 15% of programs responding provided specialized training prior to deployment.[29] Many resources exist to prepare travelers, and while many organizations will have a mandatory onboarding process it is the responsibility of the traveler to ensure adequate preparation. Travelers should become familiar with the state of emergency medicine in the destination: specialty existence, provider levels, training and education process, emergency department existence and level of function, mechanisms of access, referral networks, and availability of specialty care. Some components of preparation are common to all types of travel, such as itinerary planning and personal item packing. However, specific resources are recommended depending on the type of experience. If clinical work will be performed, ensure that adequate professional liability coverage is obtained. In one survey, only 47% of EM residents working abroad reported having appropriate liability coverage.[29]

Safety and Security

The responsible practice of GEM involves detailed attention to safety and security. Security situations can change abruptly with little warning, and plans should be in place to cover possible events ranging from minor illness to a major regional crisis. Those traveling abroad or supervising others who do should have a structured travel security plan that is kept current and available to key contacts. This plan should include the itinerary, contact information, destination information, and security measures. Travel insurance, including evacuation insurance, should be obtained specific to the destination. A sample plan and predeparture checklist is shown in (Box e1.2). In addition to

BOX E1.2 Sample Predeparture Checklist

- Project overview
- Personnel list with contact information and emergency contacts
- Itinerary details
- In-country project contacts
- Emergency resource list
- Financial plan
- Communication plan
- Medical plan including vaccinations and insurance
- Hazard risk and mitigation identification and plan
- Equipment and packing list
- Translation plan
- Key documents including passports and visas
- Security plan with special considerations for high-risk travel

organization-specific preparation, there are reputable online resources for security training such as the UN B-SAFE program.

Research Ethics in Global EM

The GEM body of literature has expanded rapidly along with the growth of the subspecialty. The Global Emergency Medicine Literature Review (GEMLR) was founded in 2005 and performs an annual review of the most important GEM research. In 2018, their Medline search of GEM-related keywords identified 15,893 articles, a number that has increased annually.[30] The regionally focused *African Journal of Emergency Medicine* (AfJEM) was first published in 2011 and by 2018 had grown to 327,000 full-text downloads a year.[31]

Although GEM research, particularly in LMICs, remains inadequately funded as compared to the burden of disease, funding has grown and arises from a wide variety of sources including governments, academic institutions, and philanthropic organizations.[32,33]

While much of this research takes place in LMICs, there is a persistent disparity in first authorship between HICs and LMICs.[34,35] Additionally, researchers from LMICs have difficulty accessing published articles. One study concluded that one out of six research articles on emergency medicine could not be accessed without institutional subscriptions, and others were cost-prohibitive.[36] There are efforts to improve, such as the AfJEM Author Assist program, in which LMIC authors whose paper was rejected are paired with an editor mentor to revise and resubmit the paper.[37]

There are challenges specific to GEM research, which are essential to acknowledge and overcome in order to continue advancing the field. Regulations vary across countries, and many LMIC countries do not have emergency care–specific research guidelines. Researchers must engage local stakeholders and obtain institutional review board (IRB) approval both at the project site and their home institution. Project funding can be complicated by currency differences and the challenges of transferring money internationally. Cultural barriers must be understood and overcome, making community engagement critical to success. Project coordination challenges include time zone and language differences. Finally, any GEM research project is subject to external forces that researchers may have little control over, such as natural disasters, political changes, and travel disruptions. Special attention should be paid to the distinctive ethical challenges of GEM research, which include differences in access to standard care, vulnerable populations, power differentials, and consent quality.[32]

The ultimate mission of GEM is to improve timely access to quality emergency care for patients. This goal should be at the center of all GEM work, whether it is a clinical rotation, educational program, research project, or humanitarian response. More often than not, the GEM specialist is a guest in the country they are working in and should always act as such. The GEM specialist must rely on local partners to fully understand the reasons and motivations for the current system. Interventions should be context appropriate, feasible, and always performed in coordination with local stakeholders.

While longer-term deployments and commitments are key to building relationships and sustainability, shorter experiences abroad can be useful when performed correctly. Prior to embarking on any GEM project, detailed preparation should occur. A review of the destination should include local history and cultural and ethical practices. Ensure that knowledge transfer is bilateral and that the project is not a burden to the local system.

Emergency medicine is a diverse specialty positioned at the center of the health care system, interfacing directly with public health and social issues. This positioning and the diverse skill set possessed by emergency medicine clinicians uniquely qualifies them for this work. Emergency care systems already exist everywhere in the world, and the goal of GEM is not to recreate or replace them, but rather to understand and strengthen them. When faced with uncertainty, always prioritizing what is in the best interest of the patient will ensure success.

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CHAPTER E1: QUESTIONS AND ANSWERS

1. Research projects based in settings outside of the GEM physician's home country require which of the following special considerations with regard to research ethics?

- **a.** Ethical approval must be obtained only at the GEM physician's home institution.
- **b.** United States-based IRBs do not cover international settings, and as such the GEM physician does not need to seek ethical approval.
- **c.** Ethical approval is required from both the GEM physician's home institution and any partner institutions or research sites.
- **d.** If the research is planned in a country that does not have an IRB, no formal ethical approval is required.

Answer: C. Ethical approval for any research project must be obtained from the GEM physician's home institution, any partner institutions, and any research sites. In the event that a formal IRB does not exist for a certain research site, efforts must be made to obtain and document ethical approval from an appropriate site representative.

2. Which of the following is required when planning a clinical experience abroad in which the GEM physician will be providing direct clinical care without supervision?

- **a.** Current medical licensure from the country within which care will be delivered.
- **b.** Current medical licensure from the GEM physician's home country.
- **c.** Written agreement between the GEM physician and a licensed physician in the country within which care will be delivered.
- **d.** No local medical license is required as long as the GEM physician is practicing within the same scope as allowed by home licensure.

CHAPTER E1: QUESTIONS AND ANSWERS—cont'd.

Answer: A. The direct delivery of unsupervised medical care should only be provided by a GEM physician with a current and valid license issued by the appropriate regulatory body of the country within which care will be delivered. Additional requirements, such as hospital credentialing, are also generally required.

3. The practice of global emergency medicine is an academic subspecialty that focuses on which areas of medicine and public health?
   - **a.** All areas of medicine are represented except for surgical conditions, as these are addressed by global surgeons.
   - **b.** All areas of medicine for all age groups are represented, inclusive of trauma or surgical conditions, infectious and noninfectious conditions, and pregnancy.
   - **c.** All adult areas of medicine are represented, but not pediatrics as this field is addressed by global pediatricians.
   - **d.** GEM focuses only on emergency conditions, excluding chronic disease as this generally does not contribute to the need for GEM.

Answer: B. Recognizing that patients present to the emergency department (ED) without a diagnosis, but with a complaint, GEM focuses on presentation-based solutions for conditions for all age groups, both trauma and medical, infectious and noninfectious, and pregnancy. GEM seeks to ensure early access to quality emergency care for all people, regardless of gender, ethnicity, age, or ability to pay.

4. What is the relationship between humanitarian work and development work as it pertains to the GEM physician?
   - **a.** Humanitarian work and development work are best performed separately to avoid confusion around roles, tasks, and funding commitments.
   - **b.** GEM physicians provide only development work and do not focus on humanitarian response, which requires separate training and expertise.
   - **c.** Humanitarian and development work are the same thing, and the difference in terminology is a function of who is performing the actual work.
   - **d.** Humanitarian work and development work complement and strengthen each other.

Answer: D. While GEM is broadly divided into humanitarian and development work, these two subfields are closely related and complement each other. An emergency care system strengthened through development work should be able to surge during crises to enhance humanitarian efforts, and an effective humanitarian response will include strengthening the local system to provide resilience against future crises.

Humanitarian Aid in Disaster and Conflict

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Humanitarian Aid in Disaster and Conflict

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KEY CONCEPTS

- A key feature of humanitarian crises is the mass displacement of large numbers of people from their homes. Displaced populations are designated either as internally displaced persons (IDPs) or refugees.
- The international response community has developed practice guidelines that stem from international law, research, and expert consensus. Responders should be familiar with these international standards and laws to ensure that intervention is appropriate and ethical.
- The *Sphere Handbook*, a collaborative project of humanitarian response experts, sets international standards for the provision of humanitarian aid and is widely considered to define the gold standard of global humanitarian response.
- Demand for humanitarian responders is likely to rise in the future as global urbanization and an increase in climate-related disasters conspire to create more frequent and severe crises.

FOUNDATIONS

When a natural disaster or armed conflict forces thousands of people from their homes, or an epidemic overwhelms a country's health system and threatens pandemic spread, a humanitarian emergency arises that requires a global response. Increasingly, emergency clinicians are called upon to assist. This chapter will provide an overview of key concepts in global humanitarian emergencies and the role of the emergency clinician in humanitarian response.

Types of Humanitarian Emergencies

A humanitarian emergency, or humanitarian crisis, is "a critical threat to the health, safety, security, or wellbeing of a community or other large group of people, usually over a wide area."[1] Humanitarian crises can be natural disasters (floods, earthquakes, tsunamis), human-made disasters (armed conflict, industrial accidents), or complex emergencies. A complex emergency occurs "where there is total or considerable breakdown of authority resulting from internal or external conflict and which requires an international response."[2]

A key feature of humanitarian crises is the mass displacement of large numbers of people from their homes. Displaced populations are designated either as internally displaced persons (IDPs) or refugees. An IDP is someone who has been forced from his or her home but who remains within the country of origin. If an IDP crosses an international border to seek help in another country, she or he becomes a refugee. The distinction is important. While refugees enjoy protections and rights guaranteed by international treaty, IDPs must depend (in the absence of international aid) on their own government for help, even though the actions—or inaction—of their government often caused their displacement.[3]

Many people assume that humanitarian clinicians spend most of their time treating serious injuries: fractures and crush injuries from earthquakes, infected flesh wounds in floods, or blast and penetrating injuries in conflict. While this is true in some emergencies, the reality is that most medical relief in humanitarian crises is spent reinforcing primary care and basic medical services that have been destroyed or bolstering public health programs to prevent diseases in displaced populations.

A significant portion of the disease burden in humanitarian emergencies is brought on by the displacement itself. Forced into crowded and often unsafe conditions and removed from their usual sources of medical care, displaced people suffer from the lack of access to basic health services. Chronic conditions such as hypertension and diabetes go untreated. Women and infants die from the lack of safe perinatal care. Children may not receive lifesaving vaccinations. Densely packed refugee camps promote outbreaks of measles and other infectious diseases. The breakdown in basic public health is another critical threat. Lack of clean water, latrines, washing facilities, proper shelter, and good nutrition are often the main causes of poor health among displaced people.

Mass urban migration in the 20th and 21st centuries has led to a dramatic increase in city populations worldwide.[4] Crises in urban environments pose unique challenges to humanitarian response because security considerations, logistic and supply chain factors, and distribution systems are very different from those in rural settings. Increasingly, humanitarian response training includes a focus on urban humanitarian response methods and how to work within dense urban settings that require close coordination with municipal governments and city-based organizations.

Natural Disasters

Humanitarian crises are broadly described as either natural or human-made disasters. Natural disasters, often seen as random acts of nature, can attract media attention and public sympathy that spur a robust aid response. The effects of natural disasters, however, are generally predictable. The type of medical and public health response needed varies by the type and location of disaster (Table e2.1) and is also affected by the preexisting vulnerabilities of the population. Damage to health facilities is common in most natural disasters, and medical relief is often focused on reestablishing primary care and basic health services.

Earthquakes cause uniquely high rates of complex injuries: fractures, crush injuries, burns, and even hypothermia. Search-and-rescue teams may need help with confined space medicine and field amputations. Surgical field hospitals are often needed in the first hours and days after an earthquake to provide lifesaving neurosurgical or orthopedic care. The need for inpatient postoperative wound care, rehabilitation services, and prosthesis care continues for months or even years.

TABLE E2.1 Predictable Effects of Natural Disasters.

Parameter	Earthquakes	Hurricanes	Tsunamis	Floods	Landslides	Volcanoes
Deaths	+++	+	+++	+	+++	+++
Complex injuries	+++	++	+	+	+	+
Infectious diseases	Always a risk: increases with overcrowding, poor sanitation					
Damage to health care facilities	+++	+++	+++ (local)	+++ (equipment)	+++ (local)	+++
Damage to water systems	+++	+	+++	+	+++ (local)	+++
Food shortage	+	+	+++	+++	+	+
Mass displacement	Rare (heavily damaged cities)				Common (generally limited)	

(Adapted from: Pan American Health Organization. *Natural Disasters: Protecting the Public's Health*. Washington, DC: Pan American Health Organization, Pan American Sanitary Bureau, Regional Office of the World Health Organization; 2000: 2.)

In contrast to earthquakes, most natural disasters produce less severe, more easily survivable injuries. Medical care in these disasters usually focuses on restoring baseline health services. Surgical field hospitals, if needed, typically perform wound care and everyday emergency surgeries (cesarean section, appendectomy). In disasters that produce high death rates—earthquakes, tsunamis, landslides, and volcanic eruptions—postmortem services may be emergently needed. Psychological first aid and mental health care are also key to the health response to sudden-onset natural disasters.

Unlike sudden-onset natural disasters, droughts develop slowly over months and are characterized by crop shortages, skyrocketing food prices, and disruption of food markets. Poor or isolated populations can suffer a lack of access to food that, if unchecked, leads to famine. The acute medical needs in drought often stem from severe malnutrition (especially in young children) and subsequent infections.

Certain populations faced with an acute humanitarian crisis, such as those with widespread undernutrition at baseline, may be more vulnerable to acute malnutrition than others. Special training in therapeutic feeding programs and supplemental food distribution is needed for clinicians responding to famine, or to any emergency in which a population's baseline rate of severe malnutrition is high.[5]

Disease Epidemics/Pandemics

Despite two large-scale Ebola virus disease (EVD) epidemics in the 2010s (the 2014 West Africa outbreak and 2018 Democratic Republic of Congo outbreak), epidemics that cause humanitarian emergencies were still relatively uncommon until 2019 with the severe acute respiratory syndrome coronavirus-2 (COVID-19) pandemic (see Chapter 120). Nevertheless, the EVD outbreaks highlight the need for more international aid agencies to be able to respond to large global epidemics. Disease outbreaks, such as the cholera epidemic in Haiti, can further complicate humanitarian efforts, threaten vulnerable populations, and erode public trust in international responders. Future epidemics, especially those that spread to densely populated areas with an underdeveloped public health infrastructure, may require a specialized form of international response. Response to epidemics in urban areas will require a response coordinated with attention to special conditions created by an urban setting, such as crowded slums, general population density, and mass transport systems.

Armed Conflict

Armed conflicts are a major cause of global humanitarian emergencies, leading to direct threats to and displacement of civilians, destruction of infrastructure, and deprivation of access to resources. Lack of access to basic services and appropriate health care due to insecurity creates a significant vulnerability that disproportionately targets women, children, and the elderly. The lack of access to medicines, providers, and the collapse of medical and public health services create major challenges for civilian populations in conflict settings. In addition, armed conflicts cause a prolonged breakdown in local security, access, and civil society structures, which can inhibit the restoration of health services. Responders in conflict settings must prepare for the complexity of operating in insecure environments and prolonged deployments.

Violent injuries are typically limited to civilians who are either trapped in active conflict zones or directly targeted by fighting forces. The number of civilians who suffer injuries is usually small in proportion to the total number of people affected by armed conflicts.[6] Conflict is also often associated with high rates of interpersonal violence, abuse, and sexual assault. Survivors of these forms of trauma will require both appropriate medical care and culturally adapted mental health services.

SPECIFIC ISSUES

Standards in Humanitarian Response

The international response community has developed practice guidelines that stem from international law, research, and expert consensus. Responders should be familiar with these international standards and laws to ensure that their response efforts fulfill the rights of the people affected by crisis.

International Law

Humanitarian aid is not simply a charitable act. Rather, it is intended to fulfill the rights to assistance that all civilians have during humanitarian crises. To fulfill these rights, responders must understand the genesis of human rights. Two bodies of international law set forth these rights: international humanitarian law (IHL) and international human rights law (IHRL).

IHL is often described as the law of war. Its core documents are the Geneva Conventions.[7] IHL gives special protections to people not taking part in conflict (civilians and those soldiers rendered incapable of fighting due to injury, illness, surrender, or having been taken prisoner). It mandates that these non-combatants be treated humanely and provided food, water, shelter, and medical care. IHL not only ensures noncombatants the right to humanitarian assistance but also grants humanitarian aid workers the right to offer that assistance. This means that humanitarian responders must be allowed to provide lifesaving aid uninterrupted and must not become war targets as long as they remain neutral in the conflict.

Indeed, IHL is one of the primary tools used to ensure protection in conflict zones for aid workers, who, as neutral actors, do not carry weapons.

Humanitarian aid agencies often use IHL to negotiate with conflict commanders for safe access to civilian populations, as these commanders can be individually prosecuted for legal violations or war crimes.

Although IHL applies only during conflict, human rights law applies at all times. The 1948 Universal Declaration of Human Rights, the core document of human rights law, states that "all human beings are born free and equal in dignity and rights," and are entitled to life, liberty, security of person, and "a standard of living adequate for…health and well-being."[8] The Declaration and other human rights laws enshrine specific civil,[9] political, economic, social, and cultural rights;[10] prohibit torture,[11] genocide,[12] and racial discrimination;[13] and provide special protections for women,[14] children,[15] refugees,[16] and internally displaced persons.[17]

IHL and human rights law govern the scope of activity of humanitarian response. More importantly, it is by virtue of these international laws that humanitarian responders legitimately can enter a country and intervene in the lives of its citizens.

Codes of Conduct

Nongovernmental organizations (NGOs) use codes of conduct to specify behavioral, professional, interpersonal, and ethical standards for their workers. Humanitarian response often requires long work hours in uncomfortable and insecure settings. Personnel must maintain appropriate conduct despite challenging circumstances and near-constant stress. Maladaptive coping behaviors such as drug and alcohol abuse, inappropriate relations with national staff or locals, and security protocol violations put individuals and organizations at risk. Codes of conduct help establish behaviors necessary to ensure an ethical and effective response.

Sphere Standards

The *Sphere Handbook*,[18] a collaborative project of humanitarian response experts, sets international standards for the provision of humanitarian aid. It is widely considered to define the gold standard of global humanitarian response. The *Sphere Handbook* begins with the Humanitarian Charter, which distills international law, humanitarian principles, and the humanitarian code of conduct into a five-page document that establishes the legal and ethical essence of the humanitarian imperative.

The *Sphere Handbook* provides a single set of uniform standards for aid agencies to follow in humanitarian response. These standards are the measures by which aid agencies evaluate their responses, and as such are the basis of accountability for international response efforts. The *Sphere Handbook* provides minimum response standards for water and sanitation, food and nutrition, shelter and settlement, health care, and protection. It also sets forth a core humanitarian standard that applies to all sectors, such as partnering closely with beneficiaries in the response (Fig. e2.1). These minimum standards are supplemented by specific indicators, numerical signposts that help responders know when they are on track to meet the standards. For example, the first

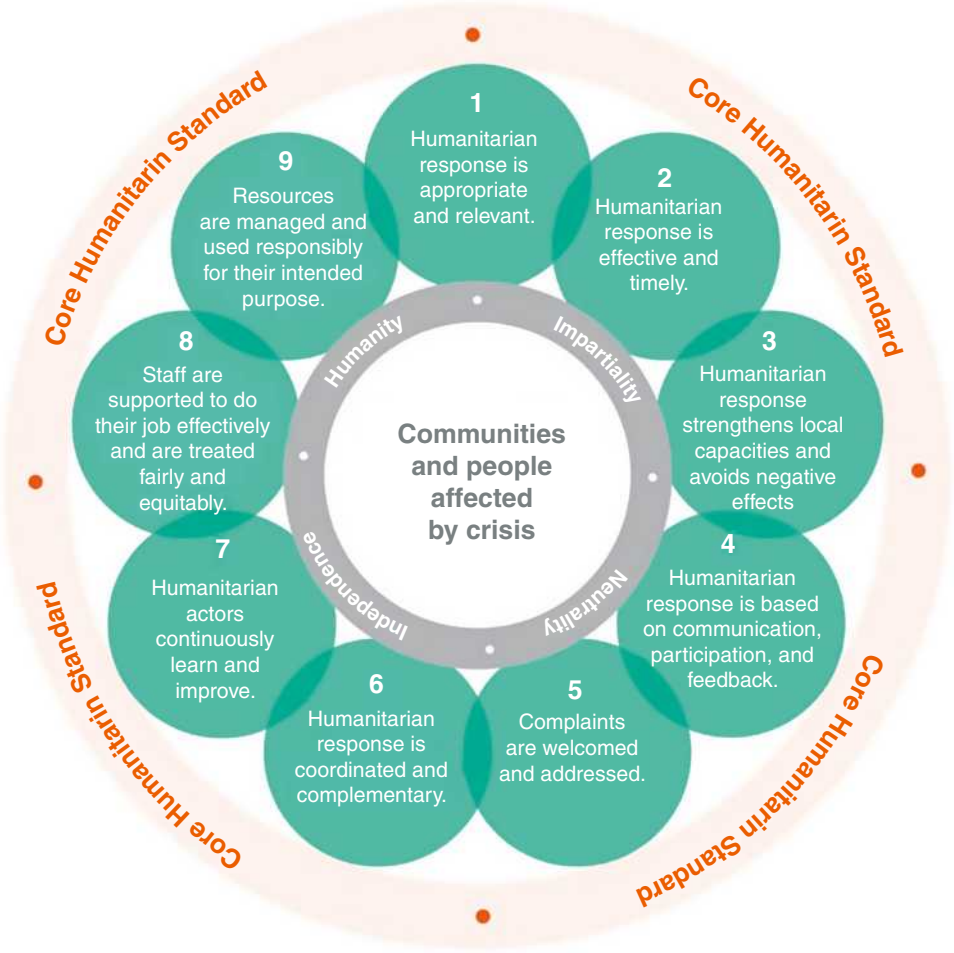

Fig. e2.1 Core Humanitarian Standard. (From: UN Office for the Coordination of Humanitarian Affairs. Core Humanitarian Standard image obtained from Sphere. [https://spherestandards.org/humanitarian-standards/core-humanitarian-standard/.])

Sphere standard for water supply is "People have equitable and affordable access to a sufficient quantity of safe water to meet their drinking and domestic needs."[19] But how much water is that? While the exact answer may vary depending on the context, the key indicator for this standard is at least 15 liters of clean water per person per day.[20] Similar standards and indicators are given for other sectors of humanitarian aid. Box e2.1 lists a few of the key indicators from the *Sphere Handbook*.

Priorities in Global Humanitarian Emergencies

The goal of humanitarian response is to save lives, restore livelihoods, and rebuild communities. Effective humanitarian response centers around several key priorities.

Protection

The first priority—before food, water, shelter, or medical care—is the protection of people caught in the crisis. The humanitarian protection principles are outlined in the *Sphere Handbook* as follows:

1. Enhance people's safety, dignity, and rights, and avoid exposing them to further harm.
2. Ensure people's access to impartial assistance according to need and without discrimination.
3. Assist people to recover from the physical and psychological effects of threatened or actual violence, coercion, or deliberate deprivation
4. Help people to claim their rights.[21]

The *Sphere Handbook* provides detailed guidance to help aid agencies adhere to these principles. Some protection measures are simple (fences around refugee camps in insecure areas, good lighting near latrines); others are more complex (issuing identification cards so that refugees can claim benefits; tracking unaccompanied children to help reunify families). Without adequate protection, other response measures may fail.

BOX E2.1 Examples of Sphere Handbook Indicators of Minimum Standards

Water, Sanitation, and Hygiene

- 15 L of water per person per day
- 250 people per water tap
- Two 10- to 20-L capacity water containers per household
- 1 toilet per 20 people
- Toilets no more than 50 meters from dwellings

Food Security and Nutrition

- 2100 kcal per person per day
  - 10% of total energy from protein
  - 17% of total energy from fat
  - Adequate micronutrient intake
- >90% of target population live within one day's walk of a supplemental feeding program site

Shelter, Settlement, and Non-Food Items

- 3.5 m^2 per person of covered living space in shelters
- 45 m^2 per person of total area of displacement camp
- Fuel-efficient stoves with the appropriate fuel

Health

- 1 to 2 community health workers per 1000 people
- 80% of births attended by skilled personnel (doctors, nurses, midwives)
- 23 skilled birth attendant personnel (doctors, nurses, midwives) per 10,000 people
- 1 health care facility (basic health post) per 10,000 people
- 1 health care center (inpatient hospital) per 50,000 people
- 1 district or rural hospital (with surgical capability) per 250,000 people
- >18 inpatient (excluding maternity care) beds per 10,000 people
- <1 death per 10,000 people per day, or less than double the baseline crude mortality rate
- <2 under 5-year-old deaths per 10,000 or under-5-year-old mortality rate less than double the baseline
- When measles vaccination coverage is <90% or unknown, conduct a mass measles vaccination campaign for children aged 6 months to 15 years

Data from: Sphere Project. The Sphere Project: humanitarian charter and minimum standards in humanitarian response. Rugby: Sphere; 2018.

Rapid Assessment

A rapid assessment should always be conducted before large-scale aid operations begin. This may seem counterintuitive, but rapid assessments are critical to ensuring that the right aid arrives in the right amount at the right time. Aid funds are always limited, and rapid assessments help avoid wasted resources and can avoid duplicating services.

Most initial rapid assessments focus on needs over all response sectors, but some target specific areas such as health or shelter. Responders in the acute phase should be familiar enough with humanitarian aid to be able to participate in a multisector rapid assessment. A rapid assessment takes a few hours or, at most, a few days. Even in large-scale disasters, initial rapid assessments are complete by the end of the first week. Information gathered in a rapid assessment is shared with responding agencies to identify vulnerable populations and aid priorities.

Food, Water, and Shelter

The major sectors of humanitarian response are water and sanitation, food, shelter, and health care. Although specific interventions will depend upon the findings of the rapid assessment, most emergencies will require a response in each of these sectors.

Clean water, latrines, and washing facilities are among the most important public health measures in emergencies. Lack of water causes people to stop washing, and poor hygiene is a major cause of disease in overcrowded refugee camps. Sanitation facilities must be provided to prevent fecal cross-contamination. Defecation fields, separated by gender, can be used until there is time to construct proper latrines.

Food insecurity is common in humanitarian crises. When local markets are functioning, the default mechanism to supply food should be the distribution of cash or food vouchers for use in the market. Distributions of food rations are necessary when markets are disrupted or the allocation of cash or vouchers is not feasible. Food distribution should be organized, equitable, and culturally appropriate. Nutritionally balanced dry rations of staple foods (flour, beans, oil) are typical provided, but wet rations of prepared meals can be used if people lack the ability to cook for themselves. Supplemental rations are given to pregnant and breastfeeding women, children, and sick or malnourished people.

Emergency shelter can be provided by housing displaced people with local host families, in vacant apartments, or—as a last resort—in tented camps. Careful camp planning is needed to reduce the impact of displaced populations on local communities because camps typically last not for weeks or months, but rather for years or decades.

Health Care

Health care in humanitarian emergencies focuses on primary and preventive care, the control of communicable diseases, and the restoration of basic health services. Communicable disease control and public health surveillance are two key interventions in displaced groups (who

often have low baseline vaccination rates) living in densely populated camps. Measles vaccination campaigns for children are often the first medical priority after disasters.

Noncommunicable diseases can also pose a threat to the affected population. Although medical services are often a key need in humanitarian crises, most humanitarian emergencies do not require large medical or foreign surgical teams. When surgical teams are needed, they should respond to specific surgical needs, such as those disasters that are accompanied by large numbers of traumatic injuries, like earthquakes. These teams will need to be deployed rapidly if they are to make a significant impact on traumatic injuries. Less recognized is the need for postsurgical follow-up care and rehabilitation services. Surgical field hospitals must plan to provide inpatient wound care and physical therapy for the full duration of surgical recovery and wound healing to patients whose homes and local health services have been destroyed. Amputees requiring prosthetics may need to be followed for years. Surgical responders have a responsibility to ensure that all patients have access to comprehensive postoperative care.

Transition and Exit

The decision to respond to a crisis is much simpler than knowing how and when to end the relief effort. When is a humanitarian crisis over? How should deployed services be removed from an area that chronically lacks basic resources? Withdrawing relief aid may leave gaps in medical care, employment for local workers, and support for local livelihoods. Rather than abruptly pulling out, a successful relief effort will transition many activities from the relief phase to the development phase. Planning for this transition and exit must start early in the response and often will require collaboration with other agencies.

International Actors in Humanitarian Response

The government of a country affected by a humanitarian emergency or refugee crisis has the primary responsibility to provide aid. If that government cannot (or does not) sufficiently respond, the international community may offer assistance. If the government invites this assistance, a variety of humanitarian actors will arrive to provide relief. Responders should understand the roles that the major humanitarian actors—response organizations, the United Nations, government funding agencies, and militaries—play in funding, coordinating, and carrying out the response.

Response Organizations

Among international responders, NGOs are the primary operational responders. Humanitarian clinicians typically work with these groups. NGOs sometimes have access to vulnerable populations that may be inaccessible to government agencies. Although many international NGOs offer a range of response services, some are known for expertise in certain sectors. Doctors Without Borders, for example, is known for its specialized medical care; Oxfam for food and water expertise.[22]

The International Committee of the Red Cross (ICRC) and the International Federation of Red Cross and Red Crescent Societies (IFRC) also represent response organizations; however, the two groups have very different mandates. Founded in Switzerland in 1863, the ICRC is neither a governmental nor nongovernmental organization. Instead, the ICRC is a neutral body mandated by the international community to aid and protect civilians in violent emergencies under the tenets of international humanitarian law. The ICRC provides health care, water and sanitation support, and international legal advocacy for refugees and IDPs.[23]

In contrast, the IFRC is comprised of 192 National Societies of the Red Cross and Red Crescent. The National Societies primarily work to support emergency preparedness and response in their own countries. A few of the National Societies (including the American Red Cross and the Turkish Red Crescent), in coordination with the IFRC, also assist in emergencies outside their home countries.[24]

Despite the prominence of international groups in humanitarian emergencies, it is important to remember that most humanitarian aid comes from local sources: neighbors, community organizations, religious groups, and local government agencies. When international aid agencies arrive, they often partner with local community organizations that know the area well and have preexisting relationships with the affected communities. This allows the international agency to provide efficient aid while helping to train and strengthen local organizations.

United Nations

The United Nations' (UN) primary role is to coordinate the international response. The UN Office for the Coordination of Humanitarian Affairs (OCHA) leads the Cluster Approach (see later, "Coordination of Global Humanitarian Response"), which coordinates local and international humanitarian actors in each sector of the field response. Some UN agencies also provide services directly to disaster survivors or to NGOs in the field. For example, the World Food Program, which helps more than 86 million people in 83 countries,[25] provides logistical support for the transport and warehousing of NGO relief goods and food rations. Several UN agencies play pivotal roles in the humanitarian sector.

Foreign Governments

Most funding for global humanitarian response comes from government agencies. Government funding agencies, such as the US Agency for International Development (USAID) or the United Kingdom's Department for International Development (DFID), often send representatives to the field to assess the scale of the emergency and to offer aid. These foreign governments provided a total of US $22.6 billion worldwide in 2018.[26] These funds are directed to the local government of the affected country, to the UN, or to NGOs to fund specific aid proposals. USAID, via its Office of US Foreign Disaster Assistance, also guides the use of US military forces in humanitarian response missions.

Militaries

International militaries increasingly are engaged in humanitarian work. Although militaries can offer a range of services, the main gap they fill is in large-scale transport and logistical support. Unlike most NGOs, militaries have the technical and logistical capacity to deliver aid, rebuild bridges, reopen damaged airports, or transport equipment by ground, sea, or air transport. The militaries of the United States, Canada, Israel, and the United Kingdom are common responders worldwide, typically alongside the military of the local government. A government dictates the actions of its military in accordance with its national interest and may decide to respond to some crises but not others.

Regardless of political motives, militaries may not always be perceived as neutral parties by beneficiaries, and NGOs that work with militaries risk a similar perception. This loss of perceived neutrality may cause NGOs to face rejection or targeted violence, even in distant countries. NGOs who partner with militaries must therefore work to ensure an accurate perception of their neutrality.

Individual Responders

Given the complex nature of humanitarian emergencies, there is little place for individual responders who appear without an organizational affiliation. Most lone responders arrive ill-equipped to be truly self-sufficient and ultimately siphon scarce resources (lodging, food and water, ground transportation) away from the response. For this and

many other reasons, individuals should not respond to humanitarian emergencies unless they do so as part of an experienced humanitarian relief organization.

Would-be responders who cannot join an international NGO can be more effective by donating money (not goods). This produces a triple benefit. NGOs use donated funds (which require no transport or warehousing) to buy culturally appropriate relief supplies in the exact quantities needed (which reduces waste and is best for survivors), often from local markets (which boosts the damaged economy and promotes faster recovery).

Coordination of Humanitarian Response

Humanitarian relief can seem haphazard to the casual observer. In fact, global humanitarian response is carefully coordinated by the UN Cluster Approach, or cluster system, which is activated in large-scale international emergencies. Professional humanitarians are trained to coordinate with other NGOs via the cluster system to avoid duplication, omission, and inefficiency of humanitarian aid. The cluster system was implemented in 2005 to increase coordination and accountability in relief aid. It is designed to accompany and advise, not supplant, the host government in its coordination of international response efforts. The cluster system divides humanitarian response into 11 sectors, or clusters (Fig. e2.2): camp management, early recovery, education, emergency telecommunications, food security, health, logistics, nutrition, protection, shelter, water, sanitation, and hygiene.[27]

Each cluster is overseen by a UN agency or other response organization called the cluster lead, which fills this role in every response (the World Health Organization is always the health cluster lead). Cluster leads gather and share information, promote adherence to international standards, coordinate NGO activities, and report progress to the UN Office for the Coordination of Humanitarian Affairs (OCHA). OCHA, led in the field by the Humanitarian Coordinator, is responsible for overall coordination among the clusters and with the larger international community.

Cluster meetings, held daily in the early response and less frequently over time, are the mainstays of coordination. They are often co-led by representatives of the host government (perhaps the Minister of Health in health cluster meetings) and the cluster lead agency (the World Health Organization). Representatives from NGOs, government agencies, and other groups working in the sector attend cluster meetings to share information and plan next steps.

Ongoing Coordination

Between emergencies, the 11 clusters work together on an ongoing basis to improve future responses. These global clusters are standing bodies that work to strengthen response preparedness, disseminate

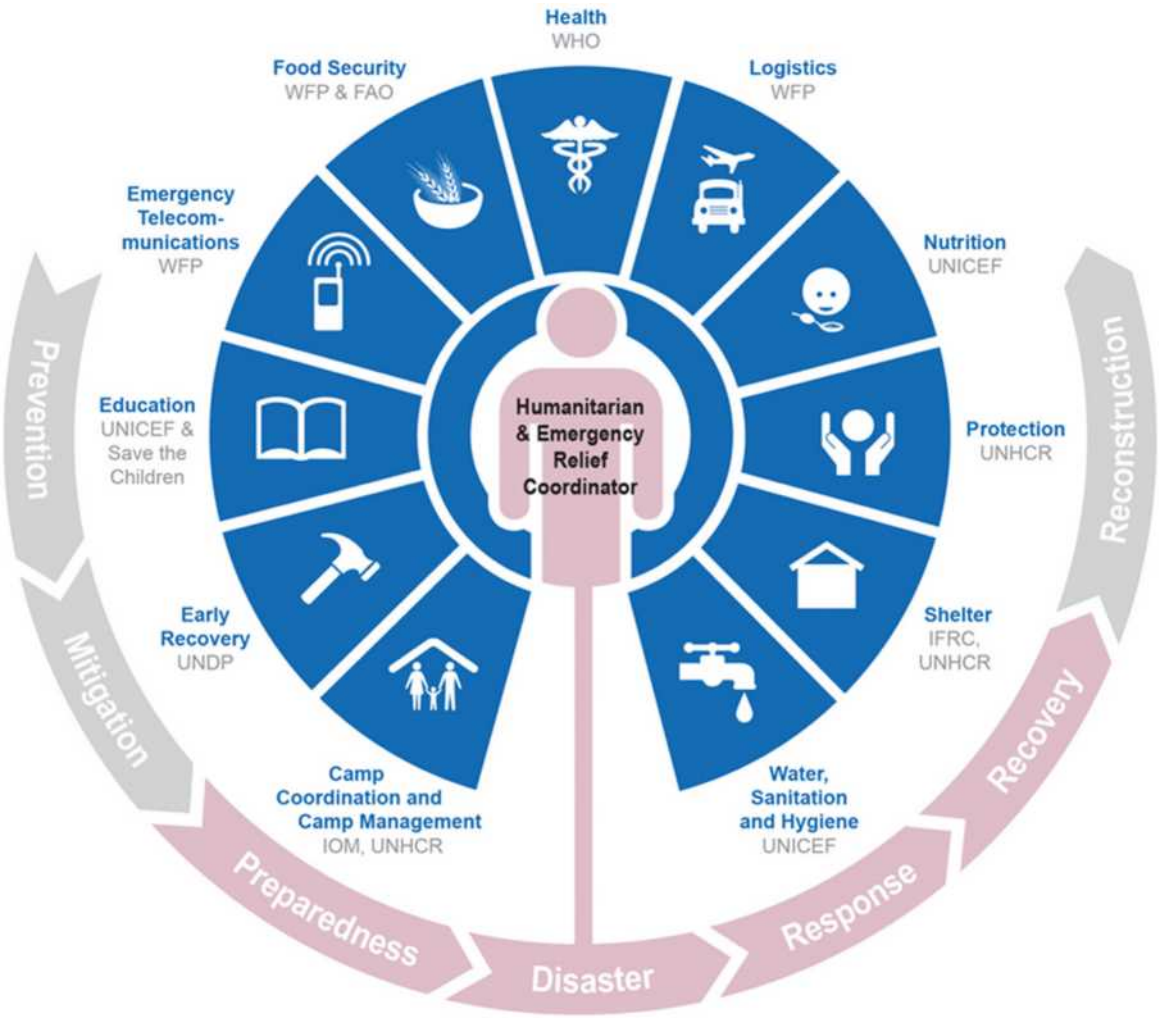

Fig. e2.2 Organization of the UN Cluster Approach. (From United Nations Office for the Coordination of Humanitarian Affairs: Cluster coordination. https://www.humanitarianresponse.info/en/coordination/clusters/what-cluster-approach.)

best practices, and support in-country clusters during disasters. Leaders of the global clusters report to the UN Under-Secretary General for Humanitarian Affairs and Emergency Response Coordinator (ERC),[28] who also leads the Inter-Agency Standing Committee (IASC). The IASC brings together UN agencies, NGOs, the ICRC and IFRC, the World Bank, and the International Organization for Migration to set policies and guidelines for effective humanitarian aid.

The Emergency Clinician in Humanitarian Crises

Emergency clinicians are well suited for humanitarian response. They are comfortable working in stressful, chaotic environments. They can nimbly rearrange priorities and see the big picture in an ever-changing situation. They have uniquely broad medical skills that are useful in emergency response. But emergency medicine training, by itself, does not make a good humanitarian responder. They must consider whether relief work is right for them and be willing to seek training in the public health aspects of humanitarian response. Emergency clinicians should also be careful to choose an experienced aid agency with which to deploy.

Preparing for Humanitarian Response

Humanitarian response can be life changing, usually for the better, sometimes for the worse. Humanitarian crises are stressful and unpredictable. To ensure an effective, rewarding experience, clinicians should carefully consider whether they are properly prepared for humanitarian work.

Work in a humanitarian crisis often involves long hours, unfamiliar cultures, and uncomfortable accommodations. Electricity, running water, and mobile phone and Internet service may be unavailable. Insecure environments may require curfews and restrictions to the NGO compound. Clinicians who are new to unfamiliar living conditions might try backpacking in a low-income country before deploying to a humanitarian emergency.

The ability to cope with prolonged stress and personal discomfort is key. In a humanitarian response, toxic coping mechanisms (drugs, alcohol, sex) can endanger you and your team. Music, journaling, movies, and exercise are better ways to relax. You will be living in close quarters with your teammates for weeks or months and should make every effort to keep morale high and conflicts to a minimum.

Medical resources are often quite limited in the field. It can be useful to review certain procedures that are more common in austere medical environments (regional blocks instead of procedural sedation). Alternatively, volunteer to teach for a while in an emergency department in a developing country.

Humanitarian deployments can be a challenge for professional and personal relationships. Many aid workers find that long deployments in such challenging settings create disruptions in their relationships at home. It is important for field workers to continue contact at home and with loved ones and realize that returning after a mission may be challenging. Likewise, work life may also be affected. NGOs often require prolonged deployments, and hospitals or practices may be reluctant to grant leave. After the deployment, some clinicians may find it difficult to readjust to the clinical and administrative routine of the emergency department. Remember that these feelings are common.

Training for Humanitarian Response

Humanitarian professionals are expected to be familiar with a large and growing body of humanitarian literature, guidelines, and procedures. Emergency clinicians considering humanitarian work should seek additional training well before considering a deployment. Formal educational opportunities include humanitarian certification courses, fellowships, and graduate degrees.

Certification courses in humanitarian aid are available through several universities and organizations. Both the Humanitarian Academy at Harvard[29] and the ICRC offer courses in humanitarian assistance. The ICRC's Health Emergencies in Large Populations (HELP) course is taught in several locations around the world.[30] Lasting a few days to a few weeks, certification courses can be a great way to prepare for a deployment or explore a career in humanitarian aid.

Some fellowships in Global Emergency Medicine prepare physicians for humanitarian response. Global Emergency Medicine specialists work to develop emergency care and improve humanitarian response worldwide. Fellowships typically last 1 to 2 years and can be found at www.iemfellowships.com.

Humanitarian tracks exist in some graduate school degree programs such as international affairs, engineering, and public health. A few programs, such as the Master of Arts in humanitarian assistance offered at Tufts University,[31] cover all aspects of humanitarian response. Emergency clinicians who wish to obtain deeper training than is offered in certification courses, but need more flexibility than fellowships offer, may enroll in a master of public health program that specializes in humanitarian studies.

Choosing a Deployment

Emergency clinicians who are trained and ready to start humanitarian work may look for a deployment that fits their skills and experience. An active conflict zone is probably not a good choice for a first deployment. Well-established NGOs are usually good at ensuring that applicants have the right experience.

In general, large relief organizations such as those in Box e2.2 have extensive field experience and logistical capability. They provide proper accommodations, reliable transportation, and security and evacuation resources necessary for a safe deployment. Responders should also ask about an NGO's reputation in the field. Avoid NGOs that do not provide security briefings as part of field orientation. Unethical practices, such as requiring beneficiaries to participate in religious services, are also a red flag.

Safety and Security

Humanitarian crises are often set in dangerous and insecure environments with inadequate public safety and medical facilities. A 2019 USAID report showed an increase in violence toward aid workers in the preceding decade.[32] Responders should understand and adhere to their organization's safety protocols even if the advice seems overcautious. Mandatory seatbelt use, for instance, helps prevent the most common cause of unintentional injury to aid workers: road traffic accidents.

BOX E2.2 A Sample of Major Humanitarian Response Agencies

Action Against Hunger
CARE
Catholic Relief Services
Concern
Doctors Without Borders
International Committee of the Red Cross
International Medical Corps
International Rescue Committee
Islamic Relief
Mercy Corps
Oxfam
Save the Children
World Vision

Unfortunately, violent attacks on humanitarian aid workers are on the rise. Modern conflicts often directly target civilians and aid workers, and hostage ransoms are an increasingly important source of revenue for some fighting forces. Responders should be aware of how their own identity or the reputation of their NGO affects their level of risk.

Although it is extremely unlikely that any single aid worker will be a victim of violence, responders should review their insurance policies before deployment to an insecure area. Health, life, and disability policies, particularly if provided by your home hospital, may not cover death or injury while working in a humanitarian crisis. Responders can improve their awareness of field security via training programs such as the online United Nations BSAFE course.[33]

Ethical Dilemmas

Humanitarian clinicians often face ethical dilemmas in the field that would never occur at home. At home, triage usually decides who gets care first; in a humanitarian crisis, triage often decides who gets care *at all*. This unfamiliar territory can lead clinicians into ethical pitfalls in humanitarian medicine.

A common pitfall is deciding to work outside of one's scope of clinical practice because of an incomplete understanding of referral capability. Non-surgeons may attempt a makeshift emergency appendectomy, rationalizing that this care is better than nothing. In our experience, this physician is usually unaware of surgical resources a few hours (or minutes) away. Even in disasters, humanitarian clinicians have a responsibility to arrange a referral and transport system for patients needing higher care. In the few cases when referral is truly impossible, the patient and family must be fully informed of your lack of experience and given the option to refuse.

Many ethical dilemmas are better addressed by a group. Group consensus, especially when beneficiaries are represented, helps avoid war zone decision making and removes the burden of an emotional decision from the individual. Having a standard protocol for the use of prearranged ethics groups will allow for quick decisions.

CONCLUSION

Demand for humanitarian responders is likely to rise in the future as global urbanization and an increase in climate-related disasters conspire to create more frequent and severe crises. At the same time, the growing professionalization of humanitarian aid will move the field closer to a model of international standards and cooperation among relief agencies. Emergency clinicians have a skill set well suited for humanitarian response. Those who seek appropriate training and experience will have the opportunity to expand their professional practice while providing an essential service to the world's most vulnerable populations.

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CHAPTER E2: QUESTIONS AND ANSWERS

1. Which of the following scenarios often creates ethical dilemmas for those providing humanitarian assistance?
- **a.** Availability of water
- **b.** Creating housing for patients
- **c.** Local government policies
- **d.** Triage of patients by local custom

Answer: D. Although all these issues are important, humanitarian workers often have ethical concerns about triage based on local customs versus severity of illness

2. Which of the following best describes the *Sphere Handbook*?
- **a.** A global compilation of nongovernmental agencies
- **b.** A description of legal decisions in international courts
- **c.** An educational guide to global relief efforts
- **d.** A guide that sets internal standards for humanitarian aid

Answer: D. The *Sphere Handbook*, a collaborative project of humanitarian response experts, sets international standards for the provision of humanitarian aid and is widely considered to define the gold standard of global humanitarian response.

3. What is the distinction between internally displaced persons and refugees?
- **a.** Internally displaced persons may remain in country or reside in another country.
- **b.** Refugees are persons who are displaced and reside in another country.
- **c.** Internally displaced persons have more rights and benefits than refugees.
- **d.** The refugee is dependent on the number of displaced persons.

Answer: B. Displaced populations are designated either as internally displaced persons (IDPs) or refugees. An IDP is someone who has been forced from his or her home but who remains within the country of origin. If an IDP crosses an international border to seek help in another country, she or he becomes a refugee. Although refugees enjoy protections and rights guaranteed by international treaty, IDPs must depend (in the absence of international aid) on their own government for help, even though the actions—or inaction—of their government often caused their displacement,

Emergency Ultrasound

L. Connor Nickels and Petra Duran-Gehring

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Emergency Ultrasound

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KEY CONCEPTS

- Over the past 20 years, emergency ultrasound (EUS) has become an integral part of emergency medical care in the United States and has become standard in the evaluation of emergency medical conditions.
- EUS answers specific, often binary questions, and is therefore neither sufficient nor intended to diagnose all of the broad range of pathologic processes encountered in emergency medicine.
- During cardiac arrest, ultrasound can be used to rapidly detect ventricular motion in asystole and pulseless electrical activity and confirm cardiac standstill.
- The subcostal four-chamber view, as in the focused assessment of sonography in trauma, is ideal for assessment of pericardial effusion and useful during cardiac arrest because it does not interfere with chest compressions.
- Although cardiac tamponade is a clinical diagnosis, there are several suggestive echocardiographic features, including diastolic collapse of the RV, loss of respiratory variation of the inferior vena cava (IVC), and transvalvular flow velocity paradoxus.
- EUS is more sensitive and specific compared with supine chest radiography for the detection of pneumothorax, approaching that of CT.
- Pneumonia on EUS appears as dynamic air bronchograms, hyperechoic areas within bronchi that move with respiration usually visualized within the consolidated lung, and are highly specific for alveolar consolidation.
- Color Doppler can help differentiate mild hydronephrosis from renal vasculature, and possibly accentuate any renal stones by producing the renal twinkle artifact.
- EUS has reduced the morbidity of ectopic pregnancy by shortening the time to diagnosis and operating room treatment.
- In the ED, ultrasound-guided internal jugular cannulation is associated with decreased time to vessel penetration and improved success in the difficult access patient, improved overall and first-attempt success rates, reduced time to insertion, and reduced complication rate.

FOUNDATIONS

Emergency ultrasound (EUS), also known as bedside ultrasound (US), clinical US or point-of-care US (POCUS), is the imaging examination performed and interpreted simultaneously at the patient's bedside by the treating clinician. This focused sonographic examination may be used for diagnosis, resuscitation, physiologic monitoring, procedural guidance, and assessment of specific symptoms or signa (e.g., shortness of breath) in emergency medicine. EUS provides clinically important information that cannot be gleaned from the physical examination (inspection, palpation, auscultation, etc.) and therefore, is not an extension of the physical examination but an additional modality.[1] Over the past 20 years, EUS has become an integral part of emergency medical care in the United States and has become standard in the evaluation of emergency medical conditions. In 2001, the American College of Emergency Physicians (ACEP) published guidelines for the use of EUS and, in 2016, expanded the scope of practice to 12 core applications: (1) trauma, (2) pregnancy, (3) cardiac/hemodynamic assessment, (4) abdominal aorta, (5) airway/thoracic, (6) biliary, (7) urinary tract, (8) deep vein thrombosis (DVT), (9) soft tissue/musculoskeletal, (10) ocular, (11) bowel, and (12) procedural guidance.[1] EUS training is required by the Residency Review Committee and residents have to demonstrate competency in this milestone before graduation.[2-4] For those emergency clinicians who trained prior to the EUS residency requirements, initial training often occurs through continuing medical education courses, followed by a period of proctoring or supervision. Recent educational advances, such as simulation, task trainers, internet-based training, and nontraditional media (e.g., electronic books, mobile device applications, social media) may also enhance US training.[5]

EUS answers specific, often binary questions, and is therefore neither sufficient nor intended to diagnose all of the broad range of pathologic processes encountered in emergency medicine. Consequently, if the clinical question cannot be answered with EUS, it is up to the emergency clinician to choose another modality for diagnosis. Although typically performed in the emergency department (ED), the portability of EUS allows its use throughout the hospital, as well as out-of-hospital use in mobile transport, disaster areas, military engagements, international rescue work, resource-limited settings, and remote locations. The recent proliferation of handheld US machines further increases the availability of EUS for clinical use; however, these handheld or pocket-sized devices must still be used in the same manner as their predecessors.[6] The main risk management issues reported concerning EUS are failure to perform the examination in a timely manner, or at all, when within the scope of practice defined by the ACEP EUS guidelines.[1,2]

SPECIFIC ISSUES

Basic Ultrasound Information

Physics and Knobology

A brief summary of relevant terminology is presented in (Box e3.1). Readers seeking more in-depth reviews of US physics, machine controls, US modes, and instrumentation are encouraged to visit the Sonoguide website (https://www.acep.org/sonoguide/basic/ultrasound-physics-and-technical-facts-for-the-beginner/). Other relevant lectures on this topic can be accessed through the Academy of Emergency Ultrasound (AEUS) Vimeo Channel (https://vimeo.com/aeus) or website (https://www.saem.org/about-saem/academies-interest-groups-affiliates2/aeus/education/aeus-narrated-lecture-series), as well as various sites noted at the end of this chapter.

Transducer Selection

In general, image resolution is inversely proportional to penetration and the emergency clinician should choose the transducer with the highest resolution for the depth needed to obtain appropriate images. There are 4 basic transducer types, and selection criteria for each is listed in (Table e3.1).

BOX E3.1 Common Definitions

Ultrasound (US)—sound waves with frequencies >20,000 Hz. Modern diagnostic US typically operates in the 1- to 18-MHz range
Window—soft tissue where transducer is placed to interrogate tissue in the body
B mode or brightness mode (grayscale or two-dimensional)—graphs the amplitude of reflected US waves as shades of gray from black to white on a monitor screen
Gain—adjusts the amplitude of signals on the ultrasound display (brightness)
Time-gain compensation (TGC)—changes gain at specific depths
M mode (motion mode)—displays reflected waves over time and distance; used to calculate rates (e.g., fetal heart rate) and evaluate moving structures (e.g., cardiac valves)
Color flow Doppler—displays direction and velocity of flow
Power Doppler (power angiography)—displays velocity of flow, but not direction
Pulsed wave Doppler—demonstrates velocity and direction of flow in a waveform display
Focus—image area where US beam is narrowest and lateral resolution is greatest
Near field—area on display from transducer to focus
Far field—area on display from focus to the bottom of the display
Anechoic—without sounds (black)
Echogenic—with sounds (white)
Hyperechoic—with more reflected sounds than adjacent tissue (more echogenic)
Hypoechoic—with less sound than adjacent tissue (less echogenic)

TABLE E3.1 Ultrasound Transducers

Transducer Type	Screen Image Shape	Examination Types
Flat linear array High frequency	Square or rectangular	Superficial structures: soft tissue, musculoskeletal, appendicitis in a thin child or adult, lung evaluation for pneumothorax, and procedural guidance
Endocavitary array High frequency	Pie shaped	Early pregnancy, peritonsillar abscess
Curved linear array Low frequency	Pie shaped	Abdominal and lung
Phased array Low frequency	Pie shaped	Cardiac, abdominal, and lung
Transesophageal echocardiographic		Cardiac

Safety and Disinfection

US biosafety includes use of the ALARA (***a**s **l**ow **a**s **r**easonably **a**chievable) principle, appropriate Doppler usage, and appropriate microbiologic disinfection of the US transducer and system. Following the ALARA principle, emergency clinicians should perform EUS only when indicated and limit the time of sonographic investigation. Doppler modes should be minimized over sensitive tissue, including early gestation and germinal, mucosal, ocular, and neural tissues.[7] All transducers should be cleaned according to the various types of examinations and the indicated disinfection type, either low-level or high-level.[8] Surface transducers should be cleaned at the bedside with mechanical removal of gel and debris, followed by low-level disinfection with an appropriate spray or wipe. Endocavitary transducers require high-level disinfection, a more prolonged and substantial cleaning method, because they come into contact with mucous membranes. Safety also includes the use of appropriate barriers over transducers, nonsterile and sterile, as well as sterile gel or clean water.[8a]

Focused Assessment with Sonography in Trauma

The focused assessment with sonography in trauma (FAST) examination was the original EUS application, developed as a noninvasive alternative to diagnostic peritoneal lavage, and evaluates for hemoperitoneum, hemopericardium, and hemothorax. The FAST was then extended to include evaluation for pneumothorax as the E-FAST examination and now plays a valuable role in the evaluation of patients with blunt or penetrating thoracoabdominal trauma. The FAST examination is accurate and clinically relevant in hypotensive patients with traumatic injuries, decreasing patient morbidity, time to operating room and hospital charges.[9] Stable patients with a positive FAST examination will often still require computed tomography (CT) imaging due to the growing trend for nonoperative or interventional management of blunt solid organ injury. EUS-diagnosed traumatic pericardial effusions receive more rapid operative intervention and have lower mortality rates. Furthermore, EUS is more sensitive and specific compared with supine chest radiography for the detection of pneumothorax, approaching that of CT.[10,11]

Image Acquisition

The FAST examination technique uses a low-frequency broadband transducer (2–6 MHz) to evaluate dependent peritoneal spaces, pleural spaces, and the pericardium for free fluid, which in the trauma patient is presumed to be blood. There are four main components of the basic FAST examination: (1) the right upper quadrant (RUQ) view, (2) the left upper quadrant (LUQ) view, (3) the pelvic view and (4) the cardiac view (Fig. e3.1). The E-FAST includes anterior chest views to evaluate for pneumothorax. The RUQ view evaluates for fluid in the thorax (above the diaphragm) (Video e3.1), hepatorenal space (Morison pouch) and the paracolic gutter (inferior edge of the liver and right kidney) (Video e3.2), moving cephalad to caudad. The LUQ view, found slightly more superior and posterior than the RUQ, should mimic the RUQ views, but also include the subdiaphragmatic space, because free intraperitoneal fluid tends to accumulate here initially. The pelvis should be evaluated in the transverse and longitudinal planes, where fluid may be detected deep to the uterus (in females) or in the retrovesical space (in males) (Video e3.3). The cardiac evaluation can be performed in either the subcostal (or subxiphoid) or parasternal window (Video e3.4). Evaluation for pneumothorax uses a low or high-frequency transducer at a shallow depth, placed along the anterior chest wall and will be discussed in more detail in subsequent sections.

Pathology

Typically, free fluid is anechoic, but it can have echogenicity if active extravasation, a blood clot, or bowel contents are present within the fluid. Compared with other fluid-filled structures in the abdomen and pelvis, peritoneal free fluid generally has sharp pointed edges and an irregular shape, whereas most visceral or vascular structures have intrinsically smooth oval or round contours. The volume of fluid required for a positive US study depends on the site of injury, sonographic window, and experience of the operator, but 250 mL or more is generally visible, and nearly 600 mL of fluid is required for a positive upper quadrant window. With pericardial fluid, once a certain volume is reached, the pressure in the pericardial space increases dramatically,

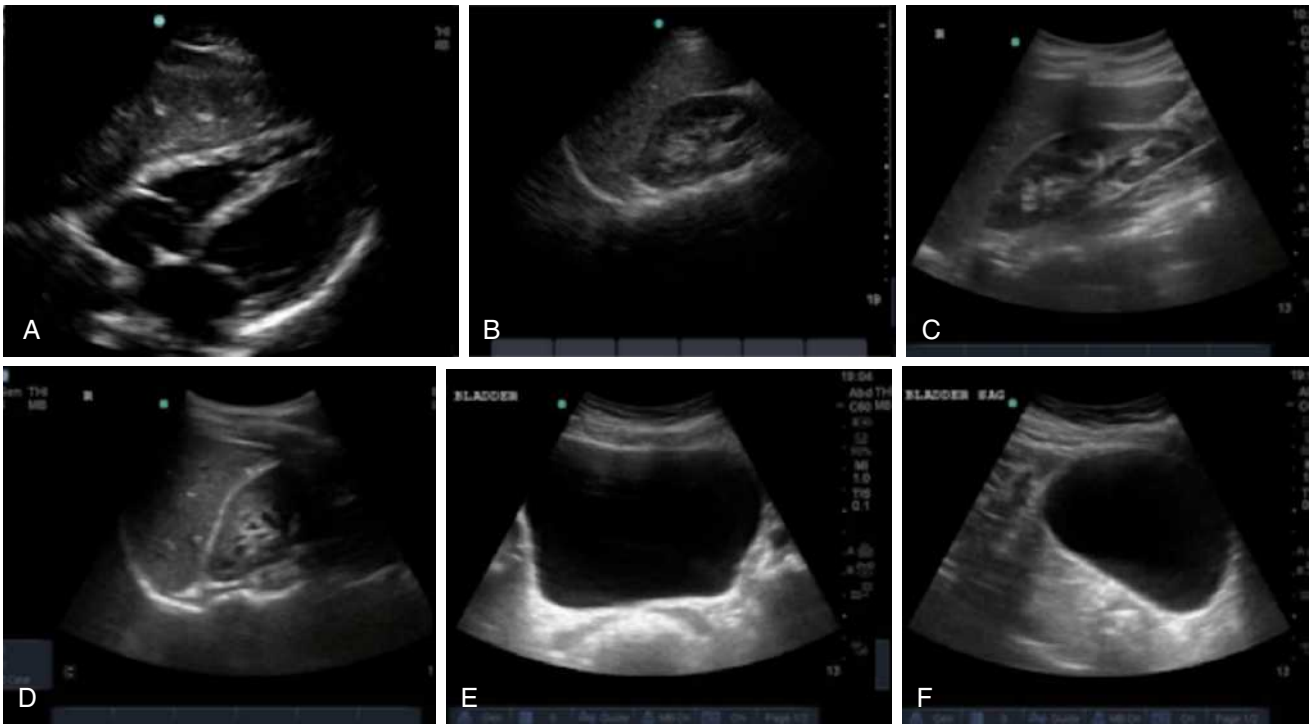

Fig. e3.1 Negative FAST images. (A) Subxiphoid view with no pericardial effusion. (B) Negative RUQ view showing the thorax and hepatorenal space without the paracolic gutter visualized. There is mirroring and loss of the spine, indicating a negative thorax. (C) Negative paracolic gutter area by the liver tip in the RUQ view. (D) LUQ view showing negative thorax, as in B, and splenorenal space. (E) Negative transverse bladder view. (F) Negative sagittal bladder view.

resulting in cardiac tamponade. Generally, at least 50 mL of fluid is required to cause hemodynamic compromise in a patient without prior pericardial inflammation (Fig. e3.2).

Special Considerations

In obstetric patients, abruption and fetal viability may necessitate an earlier operative course. FAST is unreliable for the detection of hemoperitoneum in patients with pelvic fractures. The detection of free fluid in an unstable patient with a pelvic fracture may be due to uroperitoneum from bladder injury rather than hemoperitoneum from vascular injury, clouding the decision for laparotomy versus pelvic embolization. In addition, retroperitoneal injuries to the genitourinary tract are not reliably assessed with the FAST examination. The FAST is further discussed in the "Pediatric Emergency Ultrasound" section.

Biliary

Biliary US, to detect gallstones and associated acute cholecystitis (AC), was one of the early applications of EUS and should be considered in patients with right upper quadrant pain, epigastric pain, jaundice, right flank pain, and sepsis without a clear source. Biliary US is fast and accurate, with a reported sensitivity of 87% to 94% and specificity of 82% to 96% in the detection of gallstones, comparable to radiologic US.[12,13] Despite the demonstrated high sensitivities and specificities for this examination, there remains a gap between this evidence and the decision making of surgical services, likely due to a lack of trust in biliary EUS.[14] Recent studies have questioned the benefit of measuring the CBD.[15]

Image Acquisition

The examination is performed with a low-frequency curved linear array or phased array transducer. Subcostal and intercostal windows will facilitate visualization of the gallbladder (GB), which should be evaluated in two orthogonal (perpendicular) planes (Fig. e3.3). Visualization and measurement of the common bile duct (CBD) remain part of the examination and should be performed.

Pathology

The diagnosis of cholelithiasis is made by identification of echogenic foci within the gallbladder lumen with associated shadowing. Other image patterns include stones with indistinct shadow, sludge, and the wall-echo-shadow (WES) sign seen in a gallbladder full of gallstones (Video e3.5). Although many sonographic findings can be seen with AC, including gallstones, dilated gallbladder, increased gallbladder wall thickness (>3 mm), sonographic Murphy sign, pericholecystic fluid, and CBD dilatation, gallstones are present in 95% to 99% of AC cases[16] (Fig. e3.4). A nonmobile stone in the gallbladder neck, confirmed in the left lateral decubitus position, is highly suggestive of eventual cholecystitis. A CBD larger than 6 mm in people younger than 60 years and larger than 10 mm in older patients may indicate choledocholithiasis.

Urinary Tract Ultrasound

Renal and urinary tract EUS can detect hydronephrosis and/or urinary retention in patients with back, abdominal or groin pain. In addition, bladder US is useful for the detection of urinary retention, Foley catheter localization, and guidance during suprapubic aspiration or Foley placement. Recent studies have shown that emergency clinicians are capable of finding hydronephrosis with EUS on adults, infants, and children when compared to CTs and/or radiologists, and that use of US for this purpose reduces length of ED stay.[17-20]

Image Acquisition

Renal US includes orthogonal views of the kidneys, with an emphasis on visualization of the renal calyces/pelvis. The sonographic windows

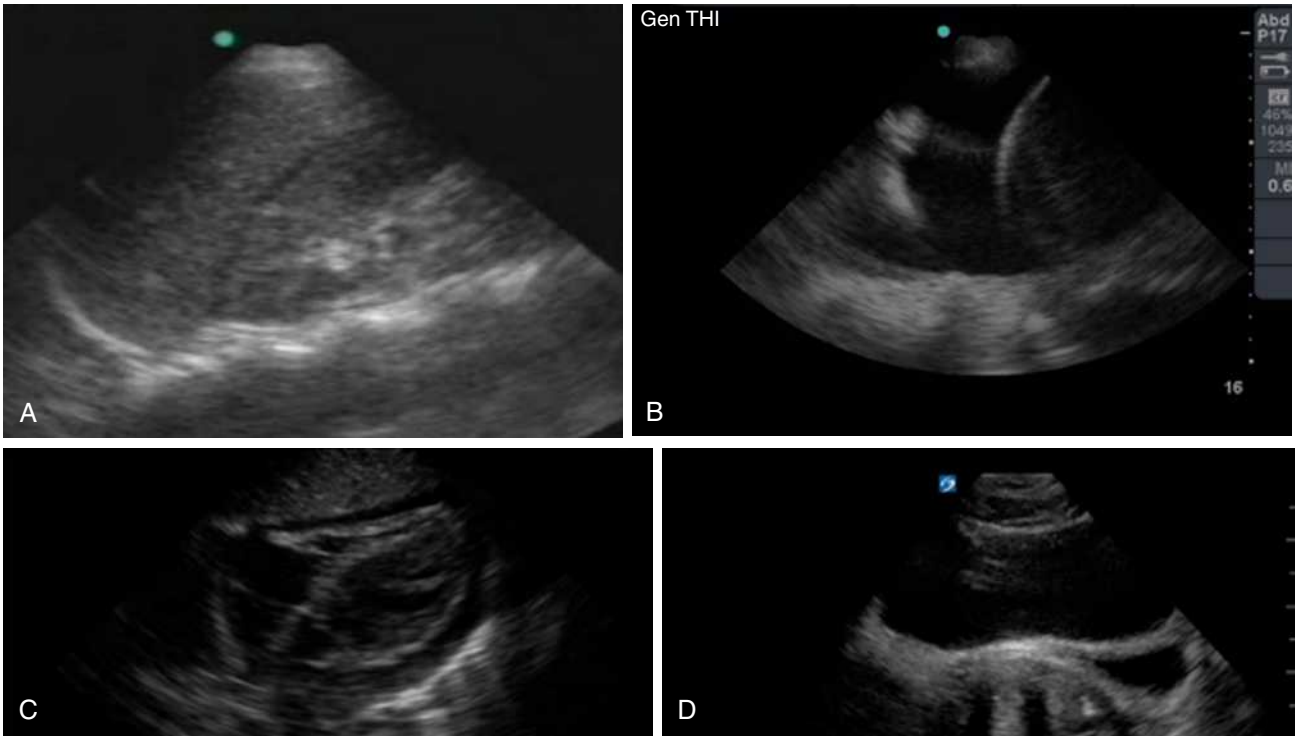

Fig. e3.2 Positive FAST images. (A) Positive RUQ view showing a thin stripe of fluid in the hepatorenal space. The thorax is negative and paracolic gutter not visualized. (B) Positive LUQ view showing a hemothorax and splenorenal space. There is loss of mirroring and continuation of the spine. (C) Subxiphoid view showing a pericardial effusion circumferentially. (D) Positive transverse bladder view with free fluid noted posterior to the bladder on the right of the image.

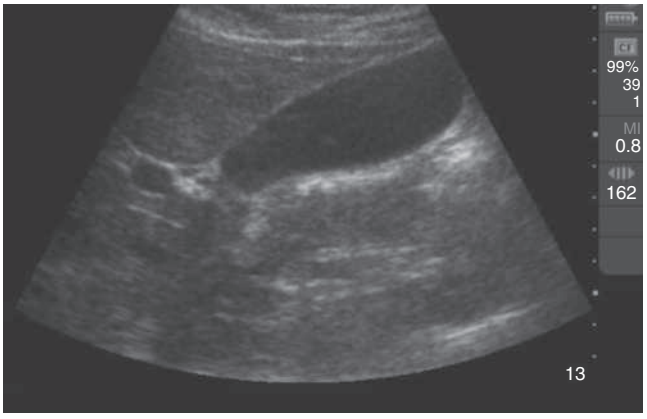

Fig. e3.3 Normal sagittal view of the gallbladder

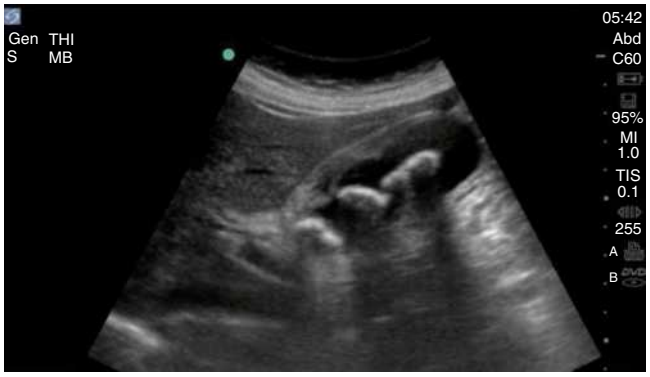

Fig. e3.4 Sagittal gallbladder with signs of acute cholecystitis including stones with posterior shadowing, thickening of the wall anteriorly, and pericholecystic fluid seen within the wall of the gallbladder.

for the two kidneys are similar to those used in the trauma upper quadrant views. The bladder view is performed from the suprapubic window in transverse and sagittal planes. Ureteral jets can be assessed by placing color Doppler over the trigone of the bladder in the transverse view. Bladder volume calculations (Fig. e3.5) may be performed with on-machine calculators or by using the formula:

$$\text{Length} \times \text{width} \times \text{height} \times 0.72 = \text{volume}$$

Pathology

Hydronephrosis is characterized by dilation and anechoic fluid accumulation within the renal pelvis and calyces, ranging from mild to severe (Fig. e3.6). Renal and/or ureteral calculi may be identified as echogenic foci with associated shadowing and are usually located within the kidney (nonobstructive) or in the renal pelvis, proximal ureter, or uretero-vesicular junction. Color Doppler placed over the kidney can help differentiate mild hydronephrosis from the renal vasculature, as well as possibly accentuate any renal stones by producing the renal twinkle artifact.[21]

Abdominal Aorta

Emergency clinicians' use of EUS to detect an abdominal aortic aneurysms (AAA) in patients with flank, abdominal, groin, and/or back pain, with or without unexplained hypotension, has a sensitivity of 95% to 100% and specificity of nearly 100%.[22,23] Although intraperitoneal and/or retroperitoneal hemorrhage may be detected, abdominal US is insufficiently sensitive to exclude a leaking AAA and, therefore, CT

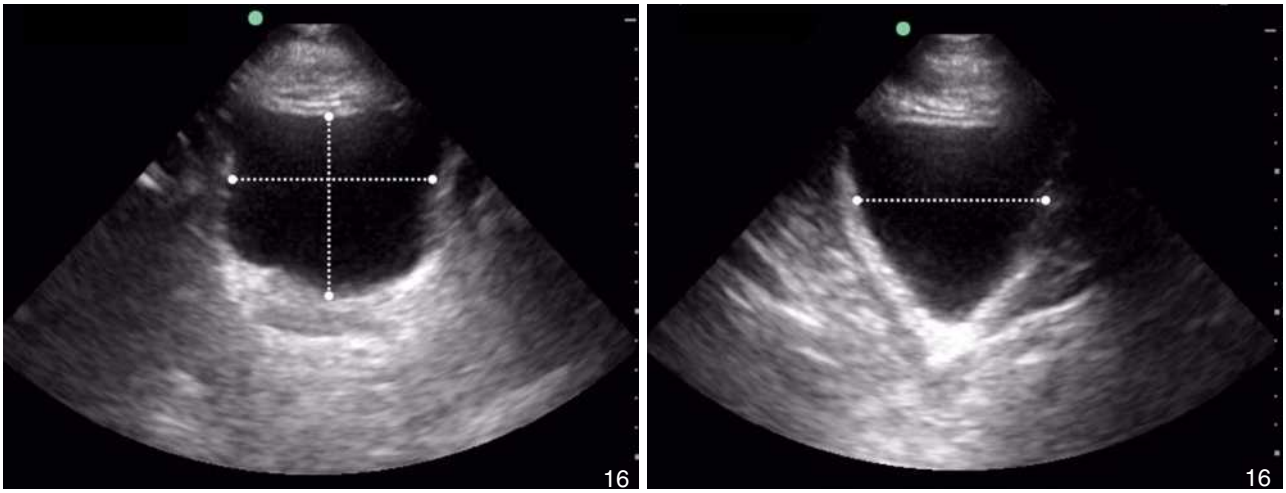

Fig. e3.5 Bladder volume measurements.

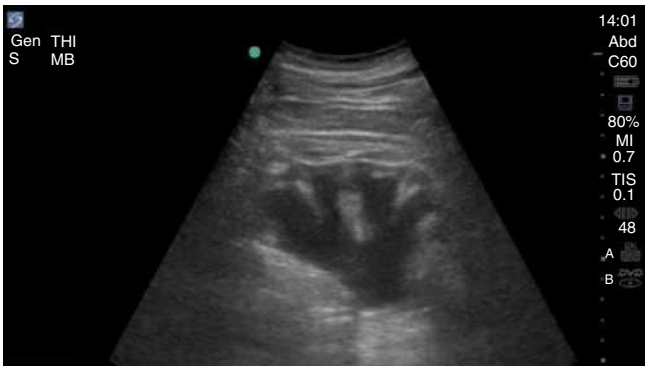

Fig. e3.6 Hydronephrosis with dilation of the calyces and renal pelvis of the kidney showing thinning of the cortex, signifying severe hydronephrosis.

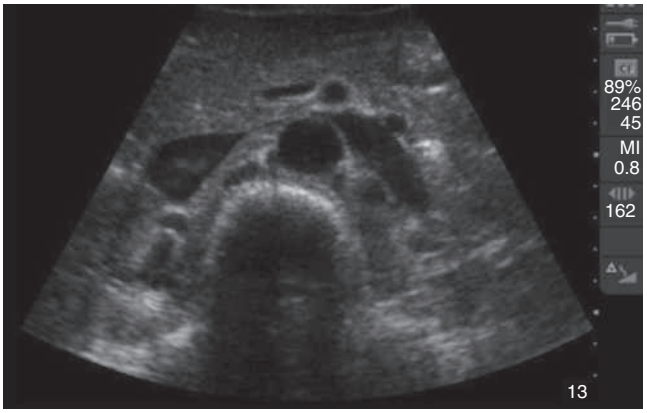

Fig. e3.7 Normal transverse view of the aorta.

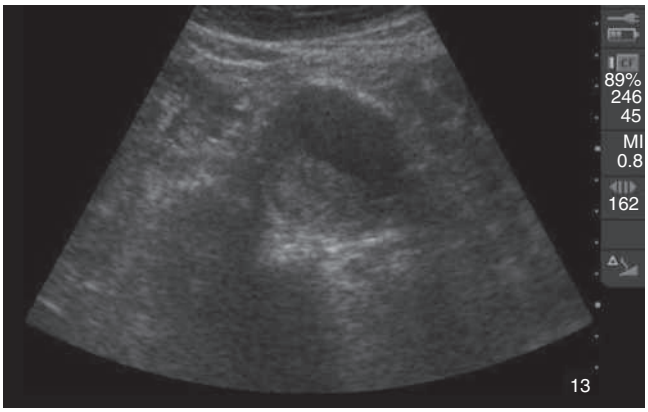

Fig. e3.8 Transverse view of a AAA with mural thrombus.

should be performed in patients with known or suspected aneurysms in whom the clinical picture suggests the possibility of rupture. Likewise, emergency US may demonstrate evidence of an aortic dissection, with sensitivities of 80% to 90% and specificity of 100%, but should not be used to exclude this potentially life-threatening diagnosis.[24]

Image Acquisition

Using a low-frequency transducer (curvilinear or phased array) and significant pressure to displace the overlying bowel gas, the aorta should be visualized from the subxiphoid region to the umbilicus (bifurcation) in both transverse and longitudinal planes. The transverse view should be obtained first to avoid the cylinder tangent error, which could falsely underestimate the size of the aorta (Fig. e3.7 and Video e3.6). Cross-sectional measurements should be taken of the aorta, outer wall to outer wall, including any mural thrombus that might be present. Aortic dissection may be detected by a combination of abdominal and cardiac scanning, with the addition of a suprasternal notch view to the traditional cardiac windows.

Pathology

An aortic diameter greater than 3 cm constitutes an abdominal aortic aneurysm, but risk of rupture increases with size and is rare with aneurysms smaller than 4.5 cm (Fig. e3.8 and Video e3.7). A linear echogenic flap, anywhere across the lumen of the aorta, is suggestive of aortic dissection and may be associated with a different Doppler flow pattern on either side of the flap (Fig. e3.9 and Video e3.8). The cardiac US examination may demonstrate an unexplained pericardial effusion, a dilated aortic root (>4 cm), aortic insufficiency, and/or a linear echogenic flap in the descending aorta.

Cardiac/Hemodynamic Assessment

Cardiac US enables rapid assessment for pericardial effusion, global left ventricular (LV) systolic function, and right ventricular (RV) enlargement, and may prove valuable in hemodynamic assessment and early detection of valvular or aortic emergencies. Indications for cardiac US include cardiac arrest, suspected pericardial effusion, trauma, chest

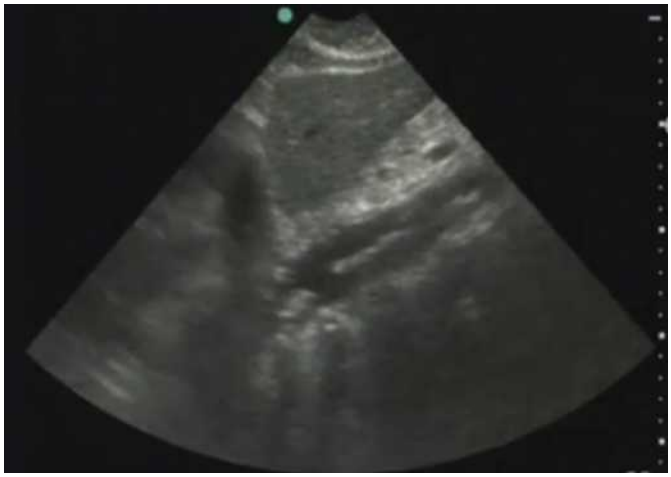

Fig. e3.9 Aortic dissection flap visualized on longitudinal view of the aorta.

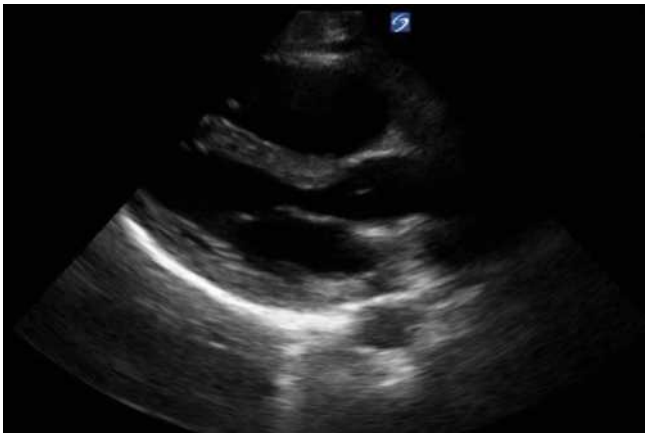

Fig. e3.10 Normal parasternal long-axis view of the heart.

pain, undifferentiated hypotension, or dyspnea. Cardiac US performed by emergency clinicians shows high accuracy in the detection of pericardial effusion, assessment of LV function, and evaluation of patients with undifferentiated shock. During cardiac arrest, US can be used to rapidly detect ventricular motion in asystole and pulseless electrical activity and confirm cardiac standstill.[25] Because advanced cardiac life support guidelines have suggested minimizing noncardiopulmonary resuscitation intervals, transesophageal echocardiography may prove even more useful in the periarrest patient.[26-28]

Image Acquisition

Cardiac US is performed through the transthoracic and transabdominal windows with the use of small curvilinear or phased array transducers. Typical views include the subcostal four-chamber view (subxiphoid), parasternal long-axis view (Fig. e3.10; see Video e3.4), parasternal short-axis view, and apical four-chamber view. The subcostal four-chamber view, as in the FAST, is ideal for assessment of pericardial effusion and useful during cardiac arrest because it does not interfere with chest compressions.[28] The long-axis subcostal view highlights the inferior vena cava (IVC) and can indicate volume status. The parasternal views are excellent windows for LV assessment. The apical four-chamber view is ideal for comparison of RV and LV sizes and function. Several US protocols have been developed to evaluate undifferentiated hypotension and can be used to narrow the differential diagnosis.

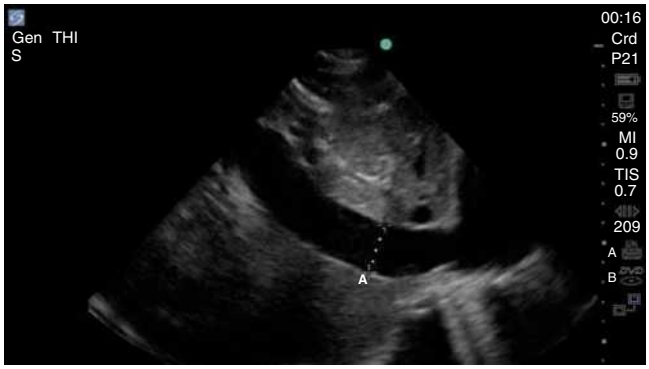

Fig. e3.11 Plethoric IVC showing where to take a measurement.

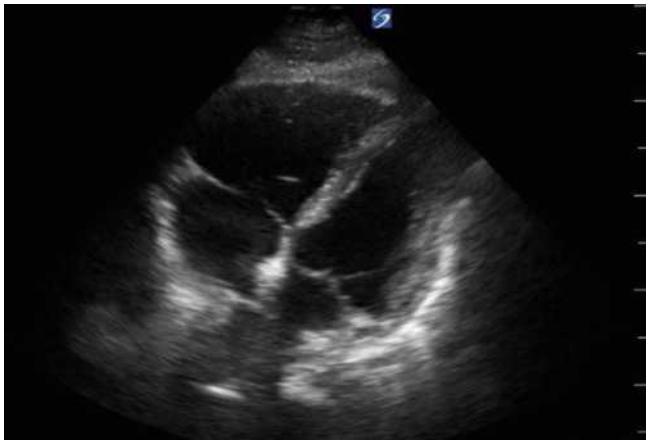

Fig. e3.12 Apical 4-chamber view of the heart with an enlarged RV.

Pathology

Pericardial fluid is typically anechoic, although it can contain internal echoes in cases of pericardial hemorrhage or infection. Large pericardial effusions are usually circumferential but can be loculated. As a result, assessment for pericardial effusion should include multiple views, when feasible, to confirm diagnosis and to avoid mistaking the epicardial fat pad for a pericardial effusion. Although cardiac tamponade is a clinical diagnosis, there are several suggestive echocardiographic features, including diastolic collapse of the RV (Video e3.9), loss of respiratory variation of the IVC (Fig. e3.11), and transvalvular flow velocity paradoxus.[29]

Assessment for global LV systolic function can be performed with visual estimation (Video e3.10) and/or assessment of E-point septal separation (EPSS).[30] EPSS is the distance between the anterior mitral valve leaflet and the ventricular septum measured using M-mode. A distance greater than 7 mm is abnormal, with larger measurements correlating to worsening systolic function. Emergency clinicians should recognize that accurate visual estimation of global LV systolic function requires experience and may prefer to categorize systolic function dichotomously as depressed or normal.

RV assessment is another useful tool for the emergency clinician when pulmonary embolism (PE) is high on the differential. With increasing right heart pressure, the RV dilates, squeezes poorly, and ultimately develops flattening of the interventricular septum, creating the "D" sign (Figs. e3.12, e3.13, and Video e3.11). The sparing of the RV apex is called the McConnell sign and is highly suggestive of PE.[31,32]

Airway/Thoracic Ultrasound

Thoracic US should be considered in patients with chest pain, dyspnea, and/or cough in whom the emergency clinician suspects pleural

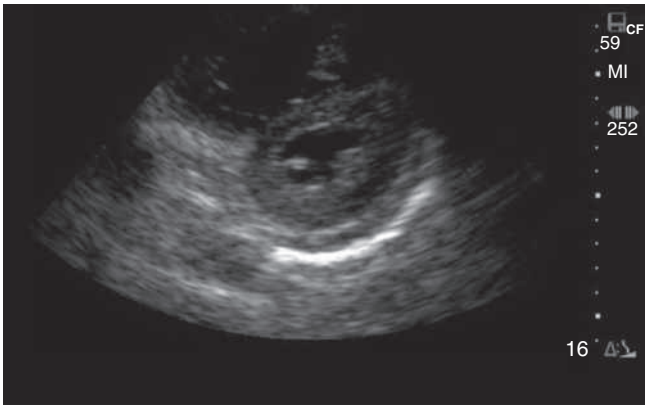

Fig. e3.13 Parasternal short axis view with "D" sign signifying increased RV pressure.

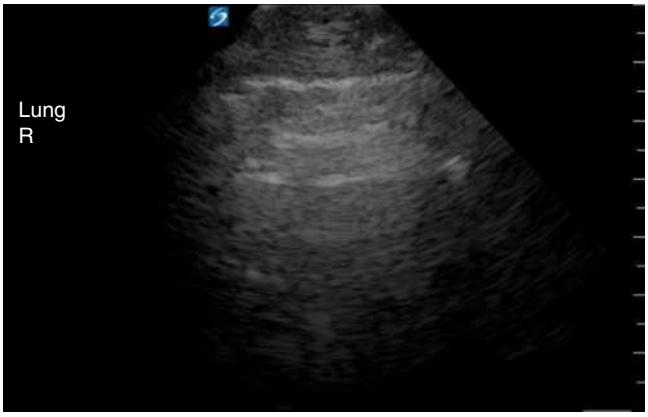

Fig. e3.14 A lines signifying normal lung.

effusion, pneumothorax, pneumonia or pulmonary edema. US evaluation of the acutely dyspneic patient has been associated with increased diagnostic accuracy as compared to traditional clinical examination, particularly for the identification of patients with a cardiogenic cause of acute dyspnea.[33] One study with a total of 1827 patients comparing lung US to chest x-ray showed US to be as specific and more sensitive than x-ray in identifying acute decompensated heart failure.[34]

Image Acquisition

Thoracic US is often performed with a low-frequency curvilinear array or phased array transducer, although visualization of lung sliding may be enhanced, if necessary, by the use of a high-frequency linear array transducer. The original BLUE (Bedside Lung Ultrasound in Emergency) protocol evaluated 4 areas on each hemithorax, but subsequent studies have looked at a number of protocols and additional areas of the anterior, lateral, and posterior thorax.[35] Lung sliding, a normal finding, is identified as the visceral and parietal pleura gliding against each other during normal respiration. A lines, horizontal equally spaced echogenic artifacts deep to the pleural line, are also a normal finding (Fig. e3.14).

Pathology

The visualization of lung sliding excludes the presence of a pneumothorax at that location on the patient's chest wall. Although M-mode and color Doppler techniques have been described as adjuncts to the evaluation of patients with suspected pneumothorax, neither is a necessary component of the examination. Absent lung sliding can result from a variety of causes in addition to pneumothorax, including pleural adhesions or consolidations, blebs, pleurodesis, partial or complete pneumonectomy, and contralateral mainstem bronchus intubation (Fig. e3.15). A lung point sign is identified at the border of the pneumothorax, where the image shows absent lung sliding until the lung moves into the interspace with respiration (Video e3.12).

Once the pleural line has been evaluated for sliding, then the determination of intraparenchymal fluid should be made. A lines indicate a dry lung, whereas B lines indicate the presence of fluid within the lung. B lines are vertical hyperechoic reverberation artifacts that arise from the pleura, move with respiration, extend off the screen without fading, and erase the normal A line pattern (Fig. e3.16). Normally found in small numbers in the dependent areas of the lung (atelectasis), the widespread distribution of B lines, typically 3 or more in one lung window, indicates increased interstitial and/or alveolar thickening due to fluid accumulation (edema) or scarring (fibrosis).[36,37] As the lung accumulates fluid with consolidation, such as a lobar pneumonia, it can appear echogenic, so-called liver-like (hepatization). When diagnosing pneumonia with lung US, the consolidation needs to be in contact with the pleura to be visible within an intercostal window.[38] Other signs can be seen with pneumonia, but dynamic air bronchograms, hyperechoic areas within bronchi that move with respiration, usually within the consolidated lung, are highly specific for alveolar consolidation.[39] As seen in the E-FAST examination, pleural fluid appears as an anechoic collection above the diaphragm, although internal echoes may be present in cases of chronic, infected, or loculated effusions.

Ultrasound in Early Pregnancy

Pelvic US by emergency clinicians is used to evaluate patients who are at risk for ectopic pregnancy. US is used to confirm intrauterine pregnancy in early pregnancy, which indirectly excludes ectopic pregnancy in most patients. Indications for sonographic evaluation include any symptoms or signs that raise concern for an ectopic pregnancy. EUS has reduced the morbidity of ectopic pregnancy by shortening the time to diagnosis and operating room treatment and has resulted in greater initial detection of abnormal pregnancy, reduced ED patient throughput times, and increased patient satisfaction.[40] The emergency clinician should not delay the US while waiting for laboratory test results and should take appropriate measures when concerning findings are noted. Approximately 25% of pregnant women will have first trimester bleeding and 11% (slightly higher with subchorionic hemorrhage and vaginal bleeding) will experience loss of pregnancy after a live intrauterine pregnancy has been visualized.[41] Emergency clinicians can also date pregnancies accurately by pelvic US with typical fetal biometry. Heterotopic pregnancies can occur spontaneously at a rate of 1 in 5000 but occur up to 1 to 3 in 100 in patients receiving assisted reproductive therapy (ART). As a result, confirmation of an intrauterine pregnancy may not sufficiently exclude the presence of a concomitant ectopic pregnancy in patients receiving ART, and emergency clinicians should perform comprehensive US evaluations in this patient population, when possible.[42]

Image Acquisition

Pelvic US is performed by a transabdominal or endovaginal technique and should be a systematic process. The transabdominal technique uses a low-frequency transabdominal transducer placed over the suprapubic area. Ideally, the patient should have a full bladder (an excellent sonographic window), but this may not be necessary if the uterus is large, or if the patient is thin. Advantages of the transabdominal technique include a wider field of view, detection of large pelvic masses or cysts, assessment of uterine lie, and greater depth of field. In the endovaginal technique, the transducer is placed in the vagina, ideally with a near-empty bladder. Endovaginal transducers are high frequency, providing excellent axial resolution but poor penetration of distant structures. Intrauterine yolk sac and fetal pole may be detected earlier, and ectopic pregnancies can be identified with more accuracy.

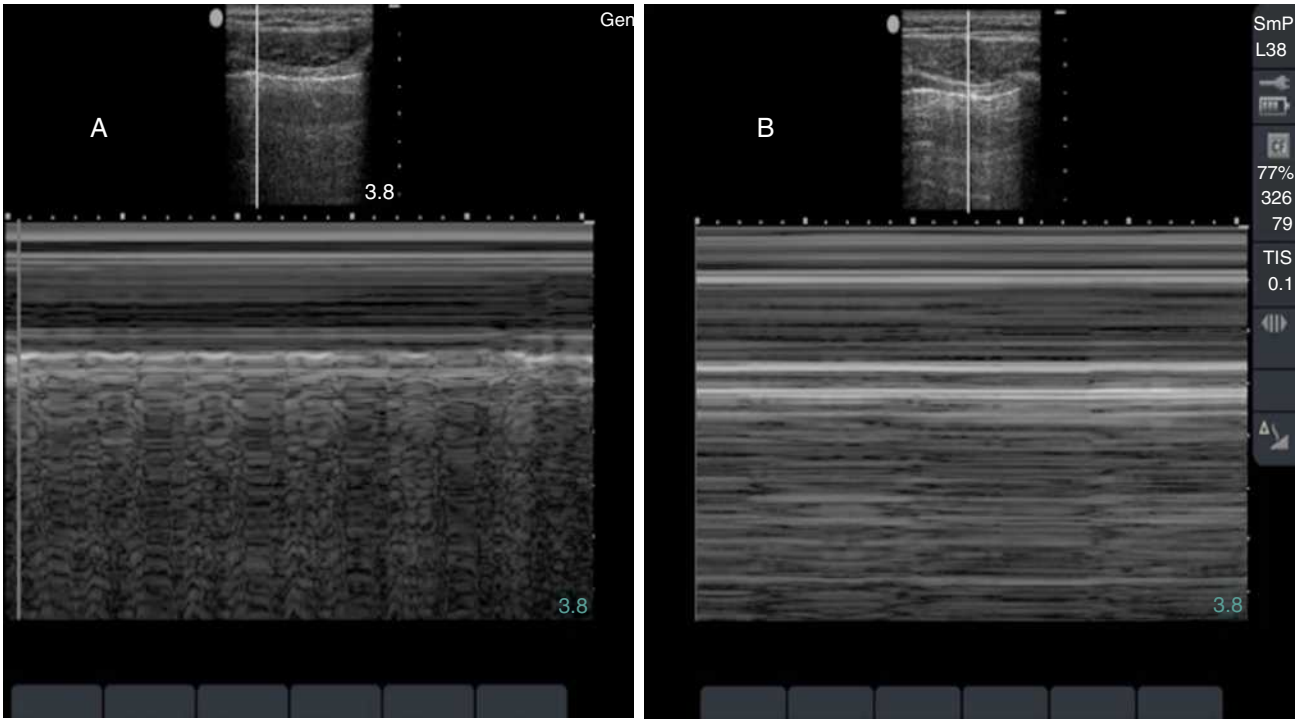

Fig. e3.15 M mode images of the lung. (A) Normal lung with "seashore" sign. (B) Pneumothorax with "stratosphere" or "barcode" sign.

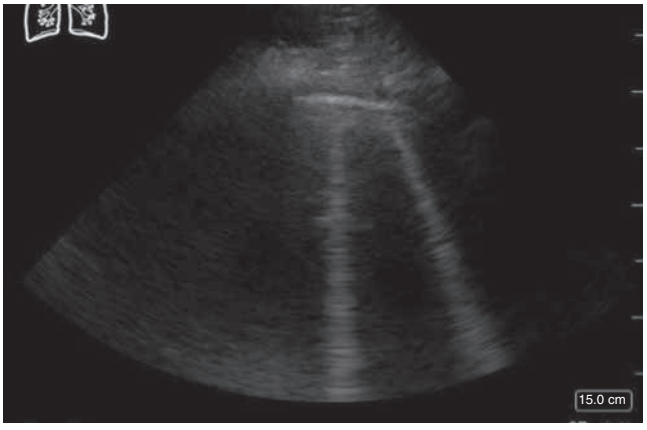

Fig. e3.16 B lines signifying fluid in the lungs

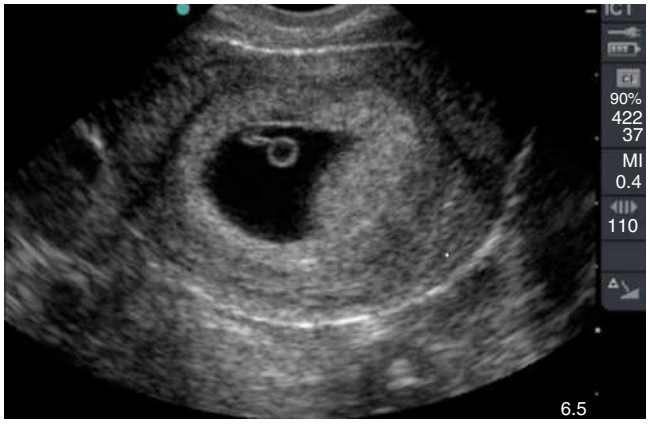

Fig. e3.17 Intrauterine pregnancy with yolk sac and fetal pole within the anechoic gestational sac.

Pathology

The diagnosis of intrauterine pregnancy is established when emergency clinicians confidently identify a gestational sac that contains a yolk sac and/or fetal pole located within the endometrium[43] (Fig. e3.17). Findings of an ectopic pregnancy include a chorionic ring or gestational sac containing a yolk sac or fetal pole outside the uterus or in an abnormal location in the uterus, such as the cornu or cervix (Fig. e3.18 and Video e3.13). Other findings may be subtle or nonspecific but should raise concerns, including adnexal masses, an empty uterus with a serum human chorionic gonadotropin (hCG) level above the discriminatory zone, or moderate to large amounts of free fluid.[44]

Deep Venous Thrombosis

EUS assessment for deep venous thrombosis (DVT) in patients with swollen or painful extremities has an accuracy from 89% to 96%, depending on operator experience. A large meta-analysis compared 2-point and 3-point US techniques in the emergency department and

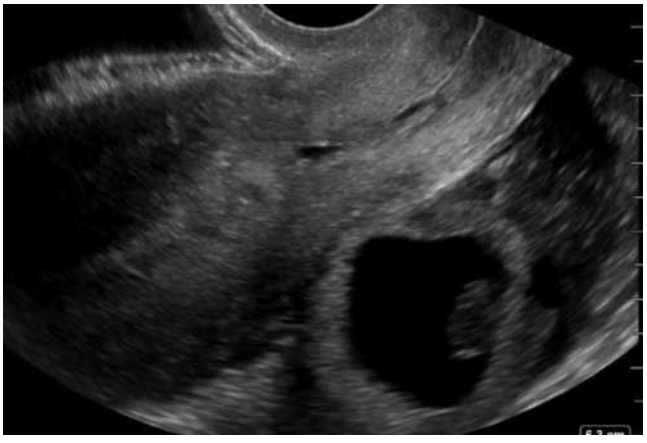

Fig. e3.18 Ectopic pregnancy seen posterior to the sagittal uterus with a fetal pole within the adnexa.

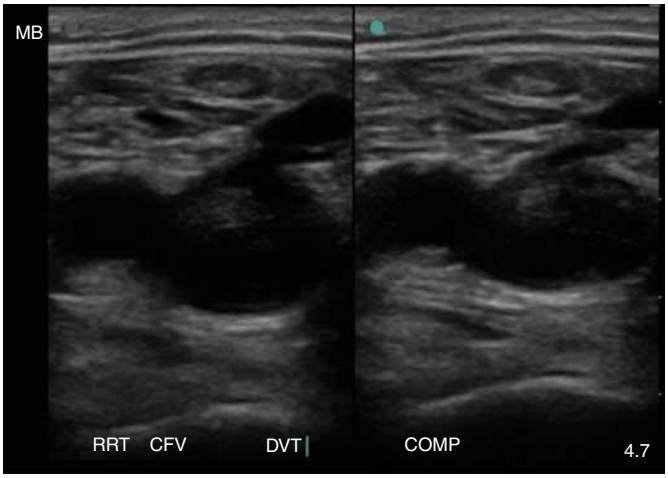

Fig. e3.19 Echogenic thrombus noted in the common femoral vein at the junction of the saphenous vein. The dual screen demonstrates lack of compressibility in the image on the right.

found similar sensitivities (2-point 91%, 3-point 90%) and specificities (2-point 98%, 3-point 95%).[45] A study comparing emergency physician–performed to radiology-performed US showed a substantial kappa coefficient of 0.83.[46]

Image Acquisition

Lower extremity venous compression US is typically performed with a high-frequency linear array transducer. The two-zone technique involves evaluating and compressing the common femoral vein from the saphenofemoral junction through the bifurcation of the femoral vein and the popliteal vein through its trifurcation. The three-zone technique adds the femoral vein from its origin through the distal thigh.[47] Evaluation of upper extremity veins is less commonly performed by emergency clinicians; Doppler US is required for the subclavian vein, which is not compressible under the clavicle.

Pathology

The lack of compressibility is the hallmark of a deep venous thrombosis and direct visualization of echogenic thrombi is commonly seen (Fig. e3.19 and Videos e3.14 and e3.15).

Ocular Ultrasound

Ocular US is a useful modality for diagnosing retinal detachment, posterior vitreous detachment, vitreous hemorrhage, intraocular foreign body, dislocated lens, increased intracranial pressure (Fig. e3.20), and retro-orbital hemorrhage.[47-50] In addition, pupillary size and extraocular movements can be evaluated, even in the presence of facial swelling (Video e3.16).[51] The reported sensitivity of ocular US for retinal detachment by emergency clinicians is 92%, and the specificity is 91.4%.[49] Ocular US is contraindicated in the setting of known or suspected globe rupture.

Image Acquisition

Using a high-frequency linear array transducer, sterile gel, and a biofilm cover over the transducer or patient's closed eyelid, the anterior and posterior chambers (Fig. e3.21) can be evaluated by scanning through the globe in orthogonal planes with low- and high-gain settings. Stabilization of your hand on the patient's forehead or nose allows for control of the pressure applied to the globe. Use of the ocular machine preset will minimize the thermal bioeffects to the eye structures during the examination.[9]

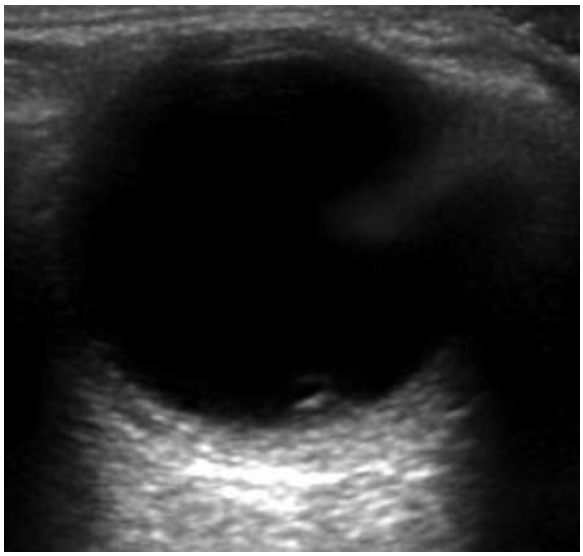

Fig. e3.20 Papilledema with swelling noted at the optic disc.

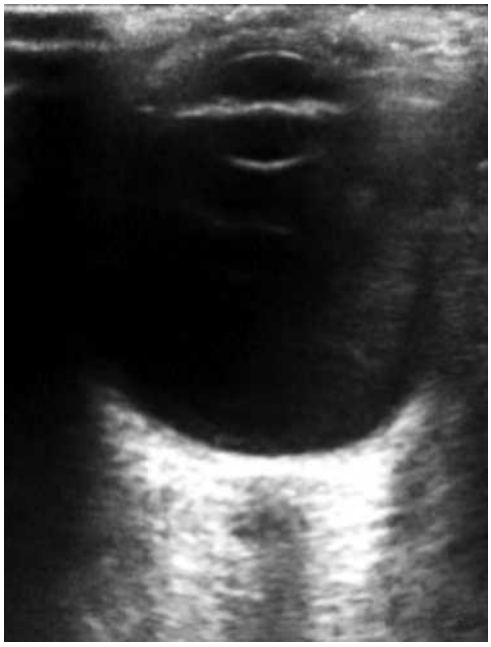

Fig. e3.21 Normal anterior and posterior chamber of the eye.

Pathology

Visualization of a linear structure in the anechoic posterior chamber indicates a retinal detachment (Fig. e3.22), as opposed to a vitreous detachment, if the flap does not cross the optic nerve but rather appears tethered to the edge (Video e3.17).[52] The diagnosis of ocular pathology may be facilitated through kinetic echography, which evaluates the chamber as the patient shifts the gaze in different directions (Video e3.18).

Soft Tissue Ultrasound

Soft tissue US is used to differentiate cellulitis from abscess, detect foreign bodies and hernias, and evaluate other pathologic processes, including masses, pseudoaneurysms, and glands. US can also differentiate peritonsillar abscess from cellulitis and can be used to guide peritonsillar aspiration. US has greater sensitivity and specificity than a clinical examination for the detection of soft tissue abscess.[53] According

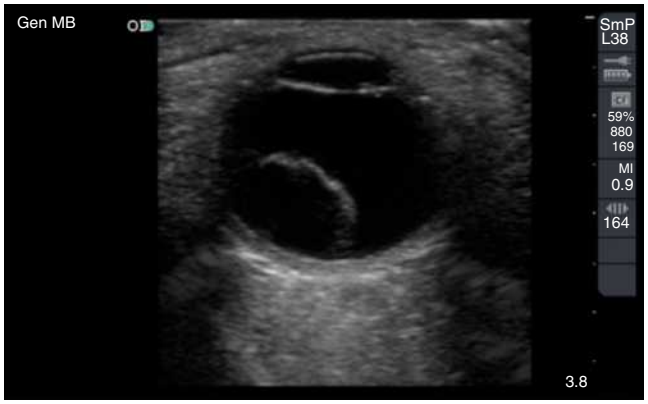

Fig. e3.22 Retinal detachment with hyperechoic flap within the posterior chamber tethered to the optic nerve

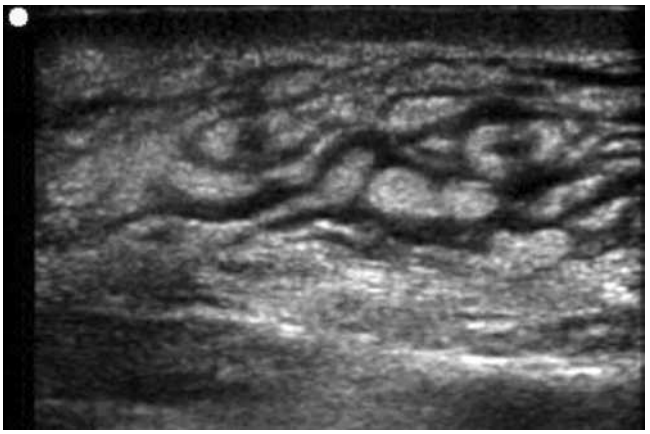

Fig. e3.23 Cellulitis with cobblestoning.

to a recent systematic review and meta-analysis of 8 articles, the use of US changed management for 17% to 56% of adult patients and 14% to 27% of children with clinical cellulitis, with an overall sensitivity of 95.5% and specificity of 80.3%.[54,55]

Image Acquisition

A high-frequency linear transducer is used to visualize the entire affected area in two orthogonal planes. Evaluation for peritonsillar abscess is best performed with the endocavitary transducer directly on the affected tonsil or with the linear transducer externally in an uncooperative child.

Pathology

Cellulitis or edema results in an echogenic pattern called cobblestoning (Fig. e3.23), as the fat lobules become separated by fluid. Abscesses are irregular, hypoechoic to anechoic collections, typically located within the subcutaneous layer (Fig. e3.24). US is diagnostic in cellulitis, abscess, and, in some case series, necrotizing fasciitis, as evidenced by gas and/or fluid within the tissue planes (Videos e3.19 and e3.20).[56,57] The detection of foreign bodies is characterized by variable echogenicity, with plastic, glass, and wooden objects shadowing distally and metallic objects creating highly reflective echogenicity and ring-down artifacts.

Musculoskeletal Ultrasound

Patients with suspected joint effusion, muscular, tendinous, or ligamentous injury may benefit from US-guided evaluation. EUS identification of tendon disruption is highly accurate in the knee extensors and Achilles tendon. EUS in the diagnosis of shoulder dislocation was found to be highly sensitive (99.1%) and specific (99.9%), with the potential to decrease time, radiation exposure, and health care costs.[58] Evaluation of the rotator cuff requires considerable experience but offers accuracy that rivals that of magnetic resonance imaging. In a systematic review and meta-analysis evaluating EUS and long bone fractures, most studies reported sensitivities and specificities of 90% and above, with EUS demonstrating excellent performance in pediatric forearm fractures and adult ankle fractures.[59]

Image Acquisition

Musculoskeletal US is performed with a high-frequency linear array transducer and imaging in two orthogonal planes. US detection of tendon and muscle injury is often assisted by movement of the limb and comparison of the contralateral side. Water bath techniques or standoff pads provide a better acoustic window for shallow tissue, such as digits.

Pathology

Joint effusions can be anechoic or echogenic, depending on type and age. Tendons and their anisotropic longitudinal fibrils can be visualized near joints, with pathologic tears appearing as a discontinuity of the tendon (Video e3.21). Muscles are hypoechoic, striated, and have echogenic borders with tears and hemorrhages appearing as interruptions of this normal pattern. The characteristic echogenic appearance of bony cortex with associated shadowing is used to identify normal bone and its contour. Fractures are seen as a defect in the bony cortex (Fig. e3.25).

Bowel Ultrasound

The use of bedside US for the evaluation of appendicitis, small bowel obstruction (SBO), and other bowel disease has been an area of increasing interest over the past decade and is now a core application. SBO EUS in the emergency department demonstrates a sensitivity of 88% and specificity of 54%, with small-bowel dilation greater than or equal to 25 mm (Fig. e3.26) and abnormal peristalsis the more sensitive parameters, whereas intraperitoneal free fluid, bowel wall edema, and transition point are more specific findings (Video e3.22).[60] EUS for appendicitis (Fig. e3.27) has shown equivocal accuracy, and therefore should not be the rule-out test or considered sufficient to stand alone. The use of US for diverticulitis, intussusception, volvulus, pneumoperitoneum, and hernias has also been described.

Pediatric Emergency Ultrasound

In 2019, expert guidelines were published specifically for pediatric emergency medicine as a result of mounting evidence confirming the benefits of EUS in children.[61] Although most US examinations have proven helpful in the pediatric population, the FAST examination seemingly has become less useful. The FAST examination in children is specific (91.4%), but the sensitivity is only 27.8% and rarely impacts management.[62] Furthermore, in a study of 925 hemodynamically stable children, the FAST compared to standard care showed no improvement of care, including use of resources, missed intra-abdominal injuries, hospital charges, and length of stay.[63] FAST may be of benefit to triage hypotensive children, but may not reflect the need for surgical intervention.[64]

Specific pediatric abdominal applications including intussusception, appendicitis, and pyloric stenosis have proven useful in the emergency department. After a short training session, pediatric emergency physicians were able to make the diagnosis of intussusception as accurately as radiologists, with a sensitivity and specificity approaching 100%.[64] EUS can make the diagnosis of acute appendicitis with higher accuracy in children than in adults, but should not be the final imaging modality if not detected.[65]

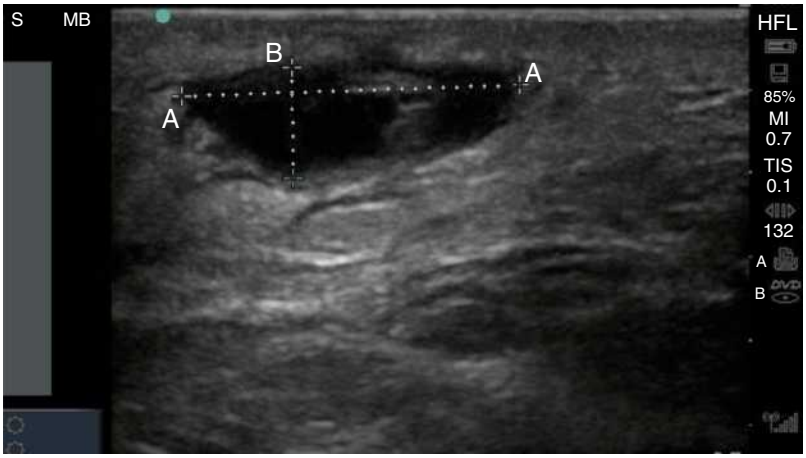

Fig. e3.24 Abscess showing measurement.

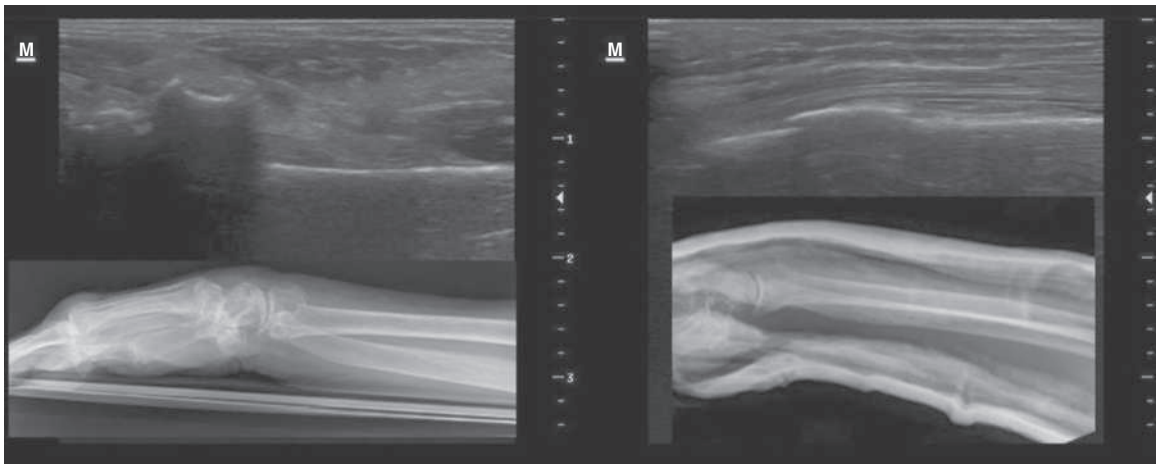

Fig. e3.25 Distal radius fracture before (*left*) and after (*right*) reduction.

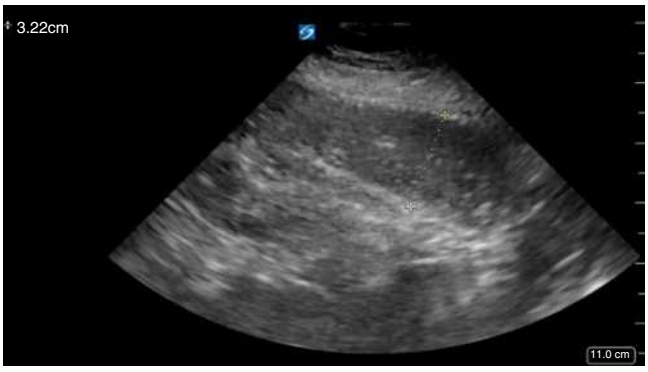

Fig. e3.26 SBO with dilated bowel.

Other pediatric indications including fracture diagnosis and reduction have been shown to be highly sensitive and specific.[66] Both fracture and lung US have the potential benefit of decreased radiation exposure, length of stay, and cost. As with most US examinations, the usefulness of lung US is operator dependent but was shown to have good diagnostic accuracy in a meta-analysis on pediatric pneumonia, even in the hands of nonexperts.[67] Milliner et al. noted each lung zone should be visualized in sagittal and transverse orientation, as omission of either orientation could potentially miss pneumonia.[68] Lung US can also diagnose bronchiolitis.

Ultrasound for Procedural Guidance

In 2001, in response to the Institute of Medicine report *To Err Is Human,* the Agency for Healthcare Research and Quality (AHRQ) sanctioned a report on actions that may improve patient safety, recommending US guidance for internal jugular central line insertion, which was reiterated in the revised 2013 report.[69] Since the original report, the use of US for procedural guidance has expanded for many emergency procedures (Table e3.2) and is advocated for error reduction. Procedural guidance can be static or dynamic. Static guidance suggests that US has been placed over the anatomic area, and the area has been marked after noting angle and distance information. Dynamic guidance describes procedures performed with real-time US visualization of the needle entering the anatomic area, which is preferred and has demonstrated higher gains in safety and quality.[70,71]

Vascular Access Procedures

There are two common approaches to vein cannulation: out-of-plane, in which the vein is imaged in short axis and appears as a circular structure on the screen, and in-plane (Fig. e3.28), in which the vein is imaged in long axis and appears as a tubular structure traversing the width of the screen. Although the out-of-plane approach is more popular with novices, the in-plane approach may be safer in experienced hands, due to the continuous visualization of the needle tip during the entire procedure. In addition, an oblique axis in-plane technique has been described, where the vessels are imaged

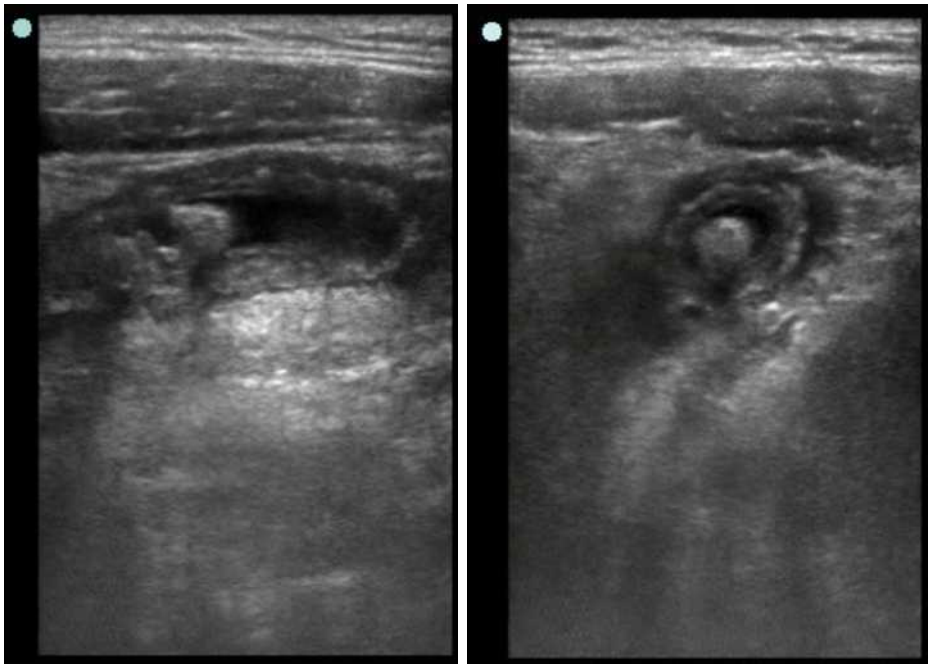

Fig. e3.27 Appendicitis with appendicolith.

TABLE E3.2 **Ultrasound-Guided Emergency Procedures**

Ultrasound	Procedure
Vascular access	Central venous access Internal jugular vein Subclavian vein Femoral vein Peripheral vein Intraosseous needle Arterial cannulation
Torso fluid collections	Paracentesis Thoracentesis Pericardiocentesis
Cardiac	Pacer placement
Musculoskeletal	Arthrocentesis Fracture reduction Foreign body removal Tendon sheath injection
Soft tissue	Abscess drainage Hernia reduction
Anesthesia	Brachial plexus Femoral or fascia iliaca Popliteal Sciatic Tibial Hematoma block
Airway	Endotracheal tube placement
Urinary bladder	Suprapubic aspiration and cystostomy Foley guidance
Neurologic	Lumbar puncture

at an oblique angle while the needle is inserted in plane. While the oblique axis may have a higher first-needle-pass success rate than the in-plane or longitudinal axis and fewer complications than the

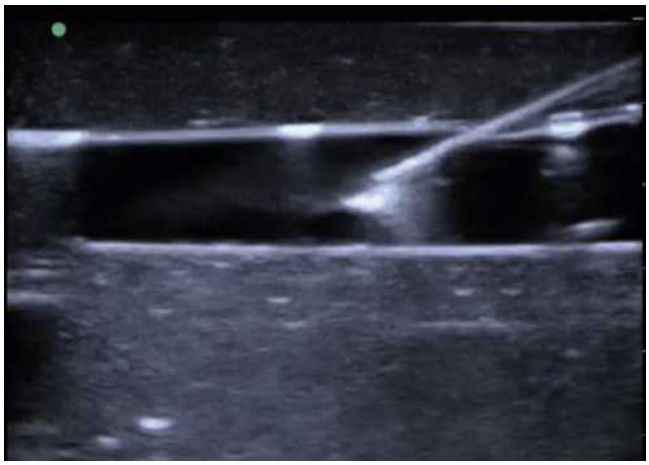

Fig. e3.28 In-plane approach to vascular access.

out-of-plane or short axis, the majority of studies comparing the three approaches found insufficient evidence to recommend one approach over the other.[72-74]

US guidance enables the emergency clinician to assess the internal jugular (IJ) for overlap with the carotid artery, vessel diameter, and presence of luminal clot or vessel obliteration. In the ED, US-guided IJ cannulation (Fig. e3.29) is associated with decreased time to vessel penetration and improved success in the difficult access patient, improved overall and first-attempt success rates, reduced time to insertion, and reduced complication rate.[74-76] US does not prevent posterior vein wall penetration, as reported in case reports and simulated models.

Emergency clinicians can also insert peripheral intravenous (IV) catheters successfully in patients with difficult access using emergency US, demonstrating a marked reduction in the need for central venous catheter placement in ED patients with poor IV access.[75] Veins that are large in width or at moderate depth (<1.6 cm) have a higher success rate. Nurses and ED technicians have also been taught to use US for peripheral venous guidance.[76] Arterial access has shown the same success.

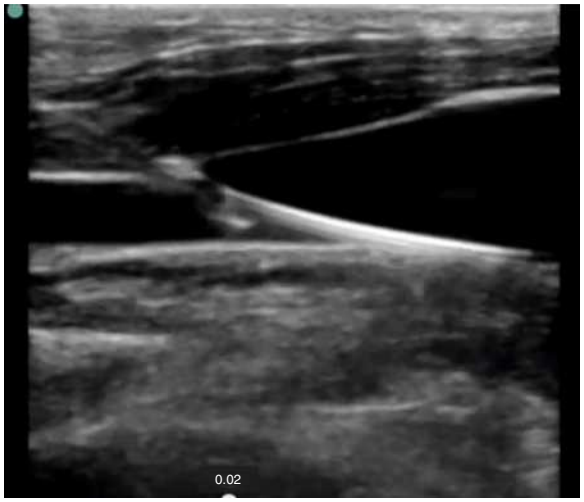

Fig. e3.29 Echogenic guidewire visualized in long-axis view of internal jugular vein.

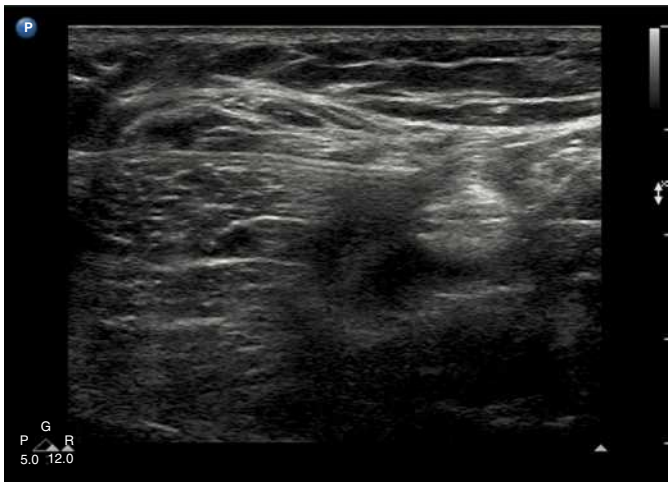

Fig. e3.30 Sciatic nerve block using in-plane approach.

Drainage Procedures

US can facilitate procedures such as paracentesis, thoracentesis, pericardiocentesis, and arthrocentesis by confirming the presence and amount of fluid, as well as its relative location to key anatomic structures. As previously discussed, a static or dynamic approach can be used; however, the dynamic approach is favored. In paracentesis, US is useful for identifying the deepest location of ascites and presence of obstructing bowel loops or superficial vascular structures. Thoracentesis is assisted by considering the diaphragm as the most inferior anatomic landmark to avoid solid organ injury, as well as locating the lung and thereby reducing the rate of pneumothorax and tube thoracostomy. Pericardiocentesis also can be facilitated by visualizing the best window—subcostal, apical, or parasternal long—and needle guidance into the pericardial space, lessening the likelihood of cardiac puncture. Moreover, US can help guide the needle for most joint aspirations.

BOX E3.2 Web-Based Emergency Ultrasound Resources

- Introduction to Bedside Ultrasound eBook: volumes 1 and 2
- Academic Life in Emergency Medicine Ultrasound for the Win! https://www.aliem.com/ultrasound-for-the-win-series-us4tw/
- ACEP Sonoguide website: https://www.acep.org/sonoguide/
- AEUS narrated lecture series Vimeo Channel: https://vimeo.com/aeus and website: https://www.saem.org/about-saem/academies-interest-groups-affiliates2/aeus/education/aeus-narrated-lecture-series
- Resuscitative TEE Project: https://www.resuscitativetee.com/
- Core Ultrasound website–5 Min Sono videos, Ultrasound Podcast and more: https://www.coreultrasound.com/
- POCUS 101 website: https://www.pocus101.com/
- The Pocus Atlas website: https://www.thepocusatlas.com/
- Sonosite Clinical Images and Video: https://www.sonosite.com/clinical-media

Localization Procedures

US guided procedures to localize nerves, intravertebral spaces and transvenous pacer placement can improve procedural success. US-guided nerve blocks (Fig. e3.30) confirm needle placement adjacent to the target nerve and allow the anesthetic to be delivered safely and effectively around the nerve. In light of the opioid crisis in our country, nerve blocks have become more popular and can be used for headaches, abscess drainage, fractures, dislocations, priapism, foreign body removal, and laceration repairs. Regional anesthesia has been increasingly incorporated into standardized care protocols for geriatric orthopedic trauma with excellent success.[77] EUS can also be used to facilitate lumbar puncture by identification of the spinous processes in patients without palpable anatomic landmarks. The literature comparing US-guided lumbar punctures versus traditional, landmark-based lumbar punctures remains controversial but suggests an increase in success rates with its use on infants.[78-80] Cardiac US can also be used to guide placement of transvenous pacer wires and for pericardiocentesis. US facilitates placement by imaging the wires in real time as they pass through the tricuspid valve and approach the apex of the RV.[81]

Useful web-based resources for learning more about EUS are shown in Box e3.2.

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CHAPTER E3: QUESTIONS AND ANSWERS

1 Which frequency range defines US?

a. Less than 0.2 Hz
b. Over 2 Hz
c. Over 200 Hz
d. Over 20,000 Hz

Answer: D. US is defined as sound with frequency over 20,000 Hz.

2 Which of the following performance characteristics is true for higher-frequency probes?

a. Deeper penetration, higher resolution
b. Deeper penetration, poorer resolution
c. Superficial penetration, higher resolution
d. Superficial penetration, poorer resolution

Answer: C. Higher-frequency probes sacrifice penetration (depth of scan) for improved resolution (image detail).

CHAPTER E3: QUESTIONS AND ANSWERS—cont'd

3 Which type of US has the best resolution when the probe is perpendicular to the object of interest?
- **a.** Doppler US
- **b.** Grayscale US

Answer: B. Grayscale or B-mode US produces best imaging when perpendicular to the area of interest, whereas Doppler US is best performed when the angle of insonation is <60 degrees.

4 Sensitivity is typically greater than specificity for FAST examination.
- **a.** True
- **b.** False

Answer: B. The FAST examination is typically more specific than sensitive.

5 Which of the following is the correct order of imaging for increasing the sensitivity of detecting a pneumothorax?
- **a.** Chest x-ray (CXR) > CT > US
- **b.** CT > CXR > US
- **c.** CT > US > CXR
- **d.** US > CT > CXR

Answer: C. CT is only slightly more sensitive than US at detecting pneumothorax, but US is significantly more sensitive than supine CXR.

The Geriatric Emergency Department

Kevin Biese and Ula Hwang

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The Geriatric Emergency Department

Kevin Biese and Ula Hwang

KEY CONCEPTS

- The rapid increase in the number of older adults in the United States (US) and around the world, as well as the unsustainable costs of the current US health care system, mandates improved emergency care systems for these vulnerable patients.
- Older adults are at high risk of experiencing harm from busy, crowded emergency departments (ED). While in the ED, they may experience prolonged lengths of stay, iatrogenic infections, misdiagnosis, delirium, bedsores and other adverse consequences.
- Older adults who are discharged are at high risk of ED return visit, hospitalization, or death within three months. Because older adults admitted to the hospital are at high risk of adverse events, care transition programs are needed to reduce the risk of inpatient stays and improve post-ED care.
- The Geriatric ED Guidelines are an excellent resource to improve the physical and process design to better address the needs of older adults.
- The Geriatric ED Collaborative and Geriatric ED Accreditation programs are innovative programs that facilitate the implementation of better emergency care for older adults.

PRINCIPLES

Background/Foundations

The current model of care delivery in the Emergency Department (ED) is designed for rapid evaluation, treatment, and turnover of patients.[1] The layout is designed to maximize resources while improving throughput at the expense of privacy and comfort (e.g., hallway beds, lack of space for family and/or caregivers). Choices in materials favor cost savings and space conservation (e.g., fluorescent lighting, narrow mattresses, and vinyl flooring). The triage system is designed to rapidly identify patients needing immediate intervention and is guided by the principle that clinicians target a primary acute medical problem using an optimal treatment algorithm. A traditional ED visit ends with admission for necessary medical care or discharge because the acute needs of the patient have been met. Too often, little emphasis is placed on arranging post-ED follow-up care or ensuring patient comprehension of discharge instructions. Although this approach may work for younger patients, the current ED model presents a challenge in the management of elders. Moreover, the model undermines the ability of the ED to care optimally for older adults and complicates their transition to follow-up care and access to community-based resources.[2]

Unlike younger patients, older adults have atypical and complex presentations of disease and trauma. They often present with vague complaints, polypharmacy, age-specific multifactorial geriatric syndromes (e.g., falls and delirium), comorbid disease burdens, and functional and cognitive impairments. Older adults are more likely to receive a greater number of diagnostic tests and treatment regimens, have longer lengths of stay, and often have multiple hospital admissions. Finally, after an ED visit, elders are more likely to suffer from health and functional decline and worsened quality of life. Adverse outcomes after ED visits have patient care and cost ramifications, suggesting that improved models of integrated care may facilitate good outcomes and decrease costs.

Advances in health education, pharmacotherapy, and health-related technology, have resulted in an increase in life expectancy. Accordingly, 20% of the US population, totaling more than 77 million people, will be aged 65 years and older in 2030, outnumbering the number of children for the first time in US history.[3] Of particular significance, the most rapidly growing segment of the population is 85 years and older, which is projected to increase by 129%, from 6.4 million in 2016 to 14.6 million in 2040.[4]

The 2013 RAND Report (https://www.rand.org/pubs/research_reports/RR280.html), evaluated the evolving role of hospital EDs in the US health care system. It found that EDs are increasingly used for complex evaluations. Emergency clinicians are the primary decision makers for half of all hospital admissions. ED admissions of Medicare patients are growing faster than any other US patient group, with 6 of 10 patients admitted through the ED. Furthermore, recent estimates indicate there is more than 1 ED visit for every 2 older adults in the US annually.[5] EDs increasingly see older patients with multiple health care needs due to convenience, perception of increased quality of care, and lack of rapid access to primary care providers. Because of the increasing number of elders and the outsized role EDs play in their medical care, it is necessary for ED design and structure to evolve and meet the challenge.

SPECIFIC DISORDERS/ISSUES

Geriatric Emergency Department Guidelines

In response to this growing need, an interdisciplinary group of professional specialties, societies, and organizations developed the Geriatric ED (GED) Guidelines, which were published in 2014. The guidelines consist of 40 specific recommendations in 6 general categories: (1) staffing and administration; (2) equipment and supplies; (3) education; (4) policies, procedures, and protocols; (5) follow-up and transitions of care; and (6) quality improvement measures.[6]

Staffing and Administration

The staffing and administration of the GED should be comprised of a multidisciplinary team of care providers who have specific geriatric training and education to focus on high-quality geriatric care. These include a GED medical director, GED nurse manager, staff physicians and nurses, and medical staff specialists (including a geriatric consultation service) who can provide accessibility to ancillary services (e.g., social workers, geriatric case managers, pharmacists, physical and occupational therapists). The goal is the establishment of dedicated ED

and in-hospital staff that is linked and coordinated with local outpatient resources.

Equipment and Supplies

The development of a GED should adapt the physical space with structural modifications and introduce and utilize equipment and supplies designed for the safe, comfortable, and effective evaluation and management of geriatric patients while decreasing iatrogenic complications. Enhancements that address issues of mobility, comfort, safety, and behavioral needs (including memory cues and sensory perception of vision and hearing) are desirable.

Suggested furniture improvements include reclining examination chairs that facilitate safe transferring, thick and soft gurney mattresses (or if feasible, pressure-redistributing foam mattresses) designed to decrease the risk of pressure ulcers.[7] Recent studies indicate higher-specification foam mattresses are associated with fewer pressure ulcers compared to the standard foam mattresses commonly found in the ED. Upholstery choices would preferably be soft, moisture-proof, easy to clean, and designed to protect fragile skin while retaining the ability to reduce contamination by hospital-associated pathogens. Special equipment for GEDs should include blanket warmers, nonslip fall mats, bedside commodes, walking aids and devices, hearing aids, and condom catheters to reduce the risk of catheter-associated urinary tract infections.

Visual orientation improvements include soft lighting, with a combination of ambient and indirect lighting, designed to increase overall lighting while reducing glare. Patients should have control of the lighting in their respective rooms. Light dimmers are inexpensive and easy to add to existing rooms. Exposure to natural light is also desired because it has been shown to improve recovery times and decrease the risk of agitated delirium.[8]

Color and pattern choices for facilities and structures should be made with an understanding of the vision and perception changes that accompany aging. Warm, light-colored walls (yellows and oranges) with a matte finish are preferable. Blues and greens are difficult to differentiate for many older patients. Rather than employing monochromatic schemes, colors should contrast between horizontal and vertical surfaces. Sharp, dominant contrast patterns may be disorienting and hinder mobility.[6]

Acoustic orientation improvements will provide better communication and decreased levels of anxiety and delirium. Private rooms and the use of sound-absorbing materials (e.g., curtains, ceiling tiles) are preferred to reduce background noise and increase patient privacy. Portable hearing assist devices are helpful. Reduction in overhead paging and machine noise should be a targeted goal. Use of music reduces anxiety in older ED patients, along with reductions in heart rate and blood pressure. Enhanced signage can improve communication and understanding.

A limited number of Geriatric EDs, such as the Gary and Mary West Senior Emergency Care Unit in La Jolla, California, have been fortunate to build new and exemplary facilities. The vast majority of hospitals will have to utilize existing space; however, innovative design and technologies can be implemented to promote geriatric-friendly environments.

Education

Interdisciplinary staff education is a key component to the implementation and success of a GED program. Residency program curricula, ED staff training, and continuing medical education should incorporate the established geriatric emergency medicine core competencies and provide specialty-specific training. This training should focus on contemporary, research-based, geriatric-specific material, with regular assessment for interdisciplinary core competencies. A variety of instructional platforms can be used and tailored to the learners and their needs. The GED guidelines recommend the inclusion of core geriatric emergency content outlined in Box e4.1.

BOX E4.1 Geriatric Education Guideline Content

- Atypical presentations of disease
- Trauma, including falls and hip fracture
- Cognitive and behavioral disorders
- Modifications of emergent interventions for older patients
- Medication management
- Transitions of care and referrals to services
- Pain management and palliative care
- Effects of comorbid conditions
- Functional impairments and disorders
- Management of diseases peculiar to the geriatric adult
  - Abdominal pain
  - Weakness and dizziness
  - Iatrogenic injuries
  - Cross-cultural issues involving older patients in the emergency setting
  - Elder abuse and neglect
  - Ethical issues, including advance directives

Policies, Procedures, and Protocols

Specific policies, procedures, and protocol initiatives are integral to the systematization of evidence-based clinical care for older adults. They are designed to facilitate the screening and assessment of geriatric patients for added needs, patient safety, and post-ED adverse outcomes. Additionally, they provide a framework to validate ED screening tools. These tools help ensure a programmatic approach to interdisciplinary care as well as guide a feasible approach to screening for frailty and additional more comprehensive geriatric assessment (Fig. e4.1 and Table e4.1).

Early research regarding the clinical impact of GEDs is growing. One multisite study of three GEDs found geriatric-specific interventions with a transitional care nurse were associated with reduced risk of hospital admissions during the ED visit (4.7% to 16.5% reduction across 3 sites), up to a 13.8% reduced risk of admission within 30 days following an ED visit,[9] and even reduced 30-day hospital readmissions (10.1% to 17.3% reduction at 2 sites).[10] Physical therapy consults in the ED have been shown to reduce fall-related revisits to the ED within 30 days.[11] These programs also reduce total costs of care.[11a]

Follow-Up and Transition of Care

Geriatric patients are particularly vulnerable to the deleterious consequences of hospitalization, including nosocomial infections, functional decline, increased rates of delirium, and iatrogenic complications.[12] Accordingly, reducing hospitalizations by providing safer discharge and outpatient follow-up is preferable whenever possible.

The GED should establish discharge protocols that provide clear communication of relevant information to patients, their families, and outpatient care providers, including primary care providers, specialty clinics, and nursing homes. A well-designed discharge process will account for elder needs (e.g., large-font instructions and utilization of teach-back strategies when possible) and should include a clear outpatient follow-up plan. To facilitate ongoing care, collaboration with community resources is established to provide home health services, equipment, and home safety assessment. Outpatient follow-up via telephone, telemedicine, texting, or direct contact is necessary. The GED

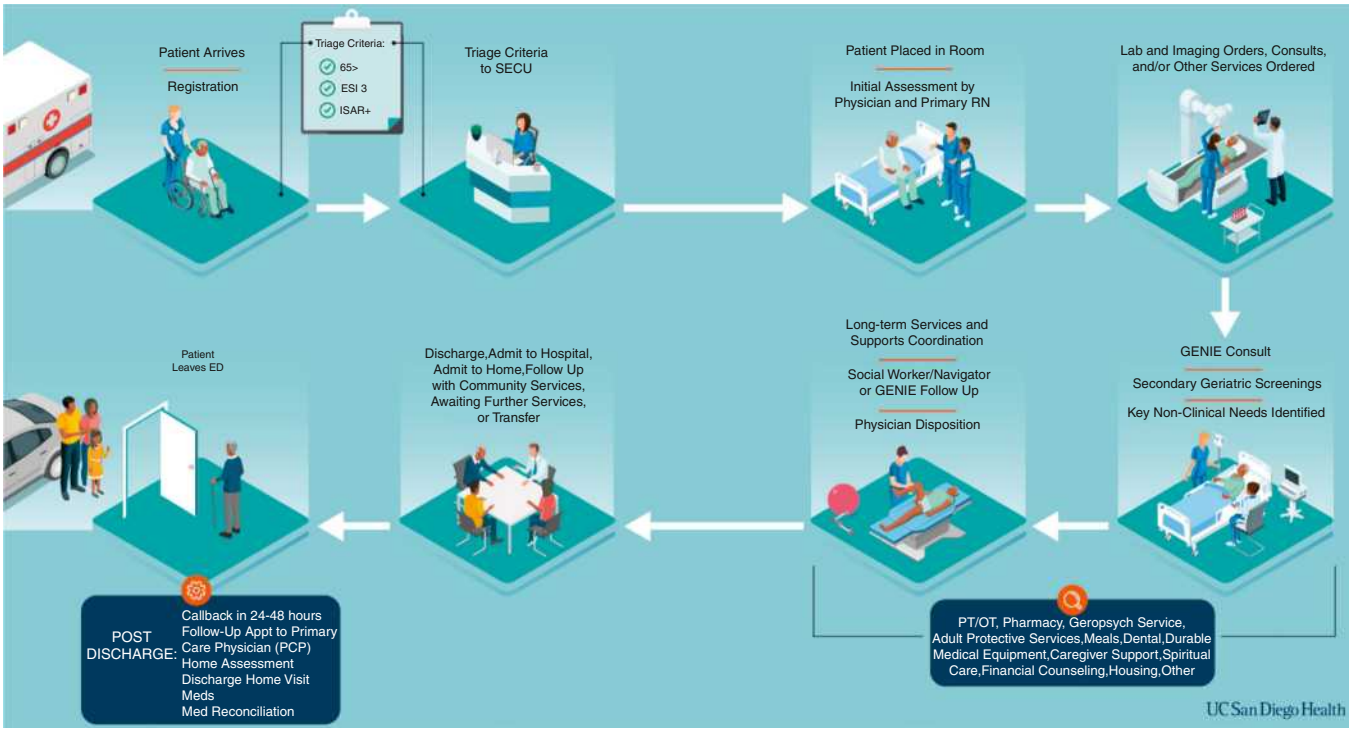

Fig. e4.1 Flowchart clinical workflow from the Gary and Mary West Senior Emergency Care Unit illustrating the programmatic approach to interdisciplinary care including integration of physical therapy, case management, social work, and pharmacy as well as to guide a feasible approach to screening for frailty and additional more comprehensive geriatric assessment.

- SECU eligibility determined by triage RN
- Age
- ISAR+
- ESI 3
- If qualify, GENIE Consult ordered automatically
- GENIE completes secondary screening
- Specialized service consults ordered
- GENIE follow-up after discharge

(Courtesy Dr.Vaishal Tolia, with permission UC San Diego Health, 2019)

should use established relationships with community resources to facilitate short-term or long-term placement of the patient in a nursing home or rehabilitation facility when discharge back to the community is not possible but hospitalization is not needed.

Quality Improvement Measures

As with all care enhancement programs, it is important to track the impact of intervention implementation. Accurate tracking of care improvements in the GED, such as delirium screening or decreasing the number of patients in hallway beds, will ensure meaningful changes in care delivery. Accordingly, we recommend regular reporting through the use of a clinical "dashboard."

Geriatric Emergency Department Collaborative and Geriatric Emergency Department Accreditation

The GED guidelines were catalyzed and bolstered by the emergence of 2 initiatives. First, is the Geriatric Emergency Department Collaborative (GEDC), which is a network of geriatric EDs supported by the John A. Hartford Foundation and the West Health Institute. Its mission is to transform, catalyze, and evaluate the impact of best practices in Geriatric Emergency Care (https://gedcollaborative.com/). The GEDC offers educational programs and resources to assist GED implementation. Furthermore, the GEDC is organizing infrastructure to study the impact of evolving practices in geriatric emergency medicine.

Second, in 2018, ACEP launched the Geriatric Emergency Department Accreditation (GEDA) program (https://www.acep.org/geda/). The GEDA program accredits EDs at different levels based on steps that an ED takes to optimize care for older adults. As of March 2020, there were over 130 accredited geriatric EDs in over 25 states and 3 nations. Overall, the GEDA program has generated needed momentum to engage and motivate hospital leadership in resourcing the transformation to optimal geriatric emergency care.

CONCLUSION

Though geriatric EDs, and evidence validating their benefit, are still in the early stages of development, GEDs are likely to grow in number. Elders fare poorly in many traditional EDs and do so at a relatively high cost, especially if they are admitted to the hospital. Creating an ED environment that is designed with frail, older adults in mind will improve processes that better identify and target geriatric syndromes, chronic medical conditions, and psychosocial stressors. It will then connect these patients with outpatient care and social support critical to delivering high-value care and optimal recovery. Emergency physicians alone cannot accomplish these complicated tasks. Interdisciplinary teams, working together to facilitate integrated medical care and social support will also be necessary.

Although caring for medically and socially frail adults may not be the historical role EDs filled in the past, changing demographics and the complex nature of our health care system ensure that an increasing

TABLE E4.1 Example of GED clinical workflow diagram from the Gary and Mary West Senior Emergency Care Unit (SECU), UC San Diego Health

Domain	Tool Used in SECU (+ Estimated Time to Administer)	Referral Type(S) Potentially Triggered by a Positive Result at UCSD SECU	Alternate/Additional Tools Supported by the GEO Guidelines
General Risk Screening	ISAR (Identification of Seniors at Risk) (<5 minutes)	GENIE consult, home health, physical therapy/ occupational therapy	
Mobility	GUG (Get Up and Go) (1–2 minutes)	GENIE consult	TUG (Timed Get Up and Go) (1–2 minutes)
	Hester Davis Fall Risk Assessment Scale (3 minutes)	GENIE consult	
Agitation	RASS (Richmond Agitation and Sedation Scale) (1–2 minutes)	CAM-ICU Screen	
Delirium	CAM-ICU* (Confusion Assessment Method for the ICU) (3 minutes)		UB-2 (Ultra-Brief 2) (1 minute); 3D CAM (3 minutes) bCAM (Brief Confusion Assessment Method) (1–2 minutes); DTS (Delirium Triage Screen) (2 minutes)
Cognition/Dementia	MoCA (Montreal Cognitive Assessment) (7–10 minutes)	Refer to UC San Diego Memory Aging and Resilience Clinic or Alzheimer's Disease Resource Center	Mini-Cog (3 minutes), SBT (Short Blessed Test) (5–10 minutes)
Depression	PHQ2 (2 minutes) PHQ9 (if PHQ2 is positive) (5 minutes)	Inpatient psychiatry consult/outpatient psychiatry referral as appropriate	
Nutrition	MNA (Mini Nutritional Assessment) (7 minutes)	UC San Diego Nutrition Consult, UC San Diego ED Social Worker Consult	
Functional	KATZ ADLs (Activities of Daily Living) (5–7 minutes)	UC San Diego Social Work consult, UC San Diego Case Management consult	
Potentially Inappropriate Medications	UC San Diego Abbreviated Beers Criteria	Pharmacist consultation	
Elder Abuse	EAI (Elder Assessment Instrument) (20 minutes)	Referral to UC San Diego Social Work and local authorities.	Elder Abuse Suspicion index (2–5 minutes)
Caregiver Strain	Modified Caregiver Strain Index (MCSI) (5 minutes)		

Clinical Workflow Diagram from the Gary and Mary West Senior Emergency Care Unit, UC San Diego Health.

number of older patients will come to the ED for medical care. Emergency medicine, with the assistance of programs like the Geriatric Emergency Department Collaborative and Geriatric Emergency Department Accreditation, will lead the charge to improved unscheduled, acute care for this vulnerable population.

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CHAPTER E4: QUESTIONS AND ANSWERS

1. For which of the following outcomes are hospitalized elders at increased risk?
   a. Infections
   b. Delirium
   c. Functional decline
   d. Iatrogenic injuries
   e. All of the above

Answer: E. Geriatric patients are particularly vulnerable to the deleterious consequences of hospitalization, including nosocomial infections, functional decline, increased rates of delirium, and iatrogenic complications.

2. The Geriatric ED (GED) Guidelines developed by ACEP, SAEM, AGS, and ENA make recommendations in all of the following areas except:
   a. Education and patient care protocols
   b. Proper technique for central line placement
   c. Quality improvement measures
   d. Staffing, supplies, and administration
   e. Follow-up and transitions of care

Answer: B. The GED guidelines consist of 40 specific recommendations in six general categories: (1) staffing and administration; (2) equipment and supplies; (3) education; (4) policies, procedures, and protocols; (5) follow-up and transitions of care; and (6) quality-improvement measures.

3. The GED guidelines recommend elder-specific educational content in all of the following areas except:
   a. Atypical presentations of disease
   b. Cognitive and behavioral disorders
   c. Psychotherapy for adjustment disorders
   d. Pain management and palliative care
   e. Medication management

Answer: C. See Box e4.1.

4. ED consultation from which of the following interdisciplinary services has been shown to decrease the likelihood of an elder returning to the ED with a fall within 30 days?
   a. Pharmacy
   b. Social work
   c. Case management
   d. Physical therapy
   e. Occupational therapy

Answer: D. Physical therapy. Although all of the above interdisciplinary services likely improve care for older adults in the ED, being evaluated by a physical therapist in the ED after a fall is associated with lower likelihood of returning to an ED with another fall within 30 days.

5. Which of the following core content areas is not a component of geriatric emergency medicine education?
   a. Elderly trauma, including falls and hip fracture
   b. Myocardial infarction
   c. Cognitive and behavioral disorders
   d. Medication management
   e. Transitions of care

Answer: B. Although myocardial infarction is a condition commonly suffered by older adults, knowledge of myocardial infarction is not in and of itself geriatric emergency medicine education. Geriatric emergency medicine education involves geriatric syndromes, conditions underlying the acute presentation of disease such as polypharmacy or frailty, and management of conditions that are different for older adults than younger adults.

End of Life

Ashley Shreves and Tammie E. Quest

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End of Life

Ashley Shreves and Tammie E. Quest

KEY CONCEPTS

- Palliative care is physical, spiritual, psychological, and social support provided to patients and families at any stage of serious illness.
- Palliative care teams are specialized interdisciplinary teams that should be involved early in the course of illness.
- Hospice care is a care system for patients and families with a prognosis of 6 months or less if the disease runs its usual course; referral from the emergency department (ED) may be indicated.
- Patients at the end of life often follow one of four terminal illness trajectories: sudden death, organ failure, cancer, or frailty. Awareness about these trajectories facilitates decision making.
- Outcomes are very poor for patients with advanced age or illness and cardiac arrest or respiratory failure requiring mechanical ventilation. Decision support tools should be incorporated into shared decision making.
- Goals-of-care conversations that outline patient and family hopes and expectations of interventions should be attempted in the ED.
- Emergency clinicians should make recommendations for care plans, interventions, and treatment courses based on prognosis, goals of care, and expected benefits of meeting the identified goals of care.
- Interpretation of an existing advance care plan or receipt of a prehospital order (e.g., POLST—***P***hysician ***O***rders for ***L***ife-***S***ustaining ***T***herapy) should factor into ED treatment plans in the context of the patient's illness trajectory.
- Symptom management (e.g., dyspnea, pain, delirium, agitation, secretions) is critical at the end of life.

FOUNDATIONS

The Institute of Medicine's 2014 report, *Dying in America,* highlights that patients nearing the end of life often experience multiple transitions between health care settings leading to fragmented care, inadequate symptom management, and demands on family members in terms of caregiver responsibilities. Traditional medical models of care have left both patients and caregivers with unmet needs, and this has translated into poor end-of-life experiences for many. There is additional concern that poor communication and lack of advance care planning have meant that some patients receive invasive, burdensome treatment near the end of life, inconsistent with their goals and values. The cost of this discordant care has been well documented, with 20% of Medicare dollars being spent on patients in the last year of life.[1] There has been renewed focus on improving the quality of end-of-life (EOL) care, primarily through the integration of palliative care principles throughout the health care system.

Patients living with a serious or terminal illness visit the emergency department (ED) often because these patients commonly experience medical crises. Emergency clinicians are skilled in the use of life-prolonging interventions; however, for patients with an advanced or terminal disease, such interventions may lead to unnecessary suffering and unwanted prolongation of the end of life. The emphasis on efficiency and early recognition and treatment of pathways common at the end of life, such as sepsis, lead to further challenges. These and other mismatches in the emergency clinician's skill set may lead to barriers in patient-centered EOL care. Accordingly, attention has been given to improving the quality of palliative and EOL care provided in the ED.

Palliative Care

Overview

According to The World Health Organization, palliative care is "…an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual."

Palliative care is usually provided by an interdisciplinary team of experts that offers comprehensive care and support systems for patients with a serious illness, including but not limited to those at the end of life. The focus of palliative care is to improve the quality of life for these patients and their family members. Expert symptom management and advanced communication skills focused on aligning patient goals and treatments are the two most critical components that palliative care teams bring to the care of patients with serious illness. Patients can receive active disease-focused treatment (e.g., cancer patients undergoing chemotherapy) while concurrently receiving palliative care. Palliative management is provided to inpatients through consultation, and home-based services and outpatient clinics are increasingly available. Palliative care has been shown to improve patient and caregiver quality of life, reduce depression, decrease the aggressiveness of EOL care, increase advance directive completion, decrease hospitalizations and length of stay, and reduce overall costs.[2]

Palliative Care in the Emergency Department

In 2006, the American Board of Emergency Medicine joined with nine other specialty boards to cosponsor the American Board of Hospice and Palliative Medicine. In 2013, the American College of Emergency Physicians published, as part of the Choosing Wisely Campaign, the recommendation that emergency clinicians should engage patients who present to the ED with chronic or terminal illnesses, and their families, in conversations about palliative care and hospice services. This alliance has recognized the real need for emergency clinicians to address the wide range of interventions and management decisions that are relevant at the end of life. The integration of emergency medicine and palliative medicine has stimulated educational efforts to define the scope of ED-based palliative care and curriculum design.

Early referral from the ED to hospice and palliative care services can benefit select patients, resulting in improved quality of life. There has been an explosive growth in palliative care programs over the last decade, making the availability of palliative medicine consults more routine. Regardless of subspecialty availability, there is a basic palliative care skill set that can be incorporated into the emergency clinician's practice. Communication skills can facilitate difficult conversations related to patient goals and wishes regarding the use of invasive therapies like intubation and CPR, how to interpret and apply advance directives, the basics of prognostication, and how to provide EOL symptom management for the most commonly encountered symptoms such as dyspnea and pain. The national Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) curriculum has been designed to provide training and skills needed to be successful in this arena. Over the last decade, there has been an increased focus on the practical and operational aspects of palliative care delivery in the ED setting. Key questions include not just the "what" but the "how" to provide optimal palliative care. Identifying the right patient and the appropriate level of intervention needed has been the focus of much of the research.

Hospice Care

Overview

Hospice care is a type of palliative care available to patients with a terminal disease and an expected prognosis of 6 months or less if the disease runs its usual course. The hospice movement, which started in England in the 1950s, initially sought to provide a haven of medical care for persons dying of cancer. Home and inpatient hospice programs now exist throughout the United States (US) and are funded through Medicare.

Currently, hospice care is provided for an expanded spectrum of end-stage illnesses, including, but not limited to, cancer, organ failure, and neurologic diseases such as dementia, ALS, and stroke. Hospice care includes a set of services provided in the home, free-standing inpatient facility, hospital, or nursing home. Some hospice agencies use wards or units within the hospital setting, and others use beds dispersed throughout the hospital; some use both. Hospice services are delivered by an interdisciplinary team. All patients enrolled in hospice care have a supervising physician who authorizes the medical plan of care. Hospice field teams may consist of physicians, registered nurses, case managers, certified nursing assistants, social workers, chaplains, and volunteers. When a patient is receiving hospice care, the patient and surrogates agree that the goal is to maximize quality of life, with a focus on symptom management and relief of suffering, and that any services the hospice is expected to pay for must have prior approval of the hospice. If the hospice authorizes transfer to an ED for care, the hospice will usually cover all ED services. If a patient unilaterally decides to seek emergency services without partnering with the hospice, the patient may be at risk of losing hospice services because the hospice agency is the care plan manager.

Election of hospice care is not synonymous with "do not treat." Patients receiving hospice care can be treated for infections, receive artificial nutrition and hydration, undergo palliative invasive interventions aimed at improving quality of life, or receive palliative disease-directed therapy. These interventions need to be assessed and recommended based on the goals of care assessment. Depending on the admitting diagnosis, however, patients may or may not have to forgo certain treatments upon enrollment. For example, cancer patients are generally required to stop chemotherapeutic agents, whereas furosemide and even dobutamine infusions may be covered for patients with heart failure.

Individuals are considered for hospice care when they meet disease-specific prognostic criteria and have goals that are consistent with the hospice philosophy of care. Because the focus is on quality of life and disease management in the home setting, patients planning on returning to the ED or hospital in the event of a medical crisis are not ideal candidates for enrollment. For patients eligible for hospice but unable to enroll because of inconsistent goals or a desire to pursue disease-modifying treatments like chemotherapy, palliative care consultation can bridge the gap by providing excellent symptom management, psychosocial support, and assistance with goal setting and advance care planning. Home and inpatient hospice programs now exist throughout the United States and are funded through Medicare, Medicaid, and private insurers. Over time, there has been a small but steady increase in hospice utilization by Medicare recipients, with almost half of Medicare decedents accessing hospice in 2017.[3] The median time from enrollment to death is 24 days, often leaving insufficient time for many of the services that hospice can offer.

Hospice and the Emergency Department

Patients enrolled in hospice care utilize the ED significantly less than nonhospice patients at the end of life.[4] Still, hospice patients do present to the ED for a variety of reasons, including panic regarding decline, uncontrolled symptoms, inability or lack of the hospice agency to respond to needs, desire of the patient or family to seek additional opinions regarding care, and concern regarding the care provided by the hospice agency (often a concern regarding the use of medications). Under the US hospice benefit, the hospice agency is the patient's total care manager for anything related to the hospice diagnosis. The hospice should be notified if the patient receives care in the ED. If the hospice authorizes transfer to an ED for care, the hospice will usually cover all ED services. If a patient unilaterally decides to seek emergency services without partnering with the hospice, the patient may be at risk of losing hospice services because the hospice agency is the care plan manager.

An ED visit does not mean that the patient no longer desires hospice care. Although patients and families are instructed to call hospice before going to the hospital, this does not always occur. Patients and caregivers might tell clinicians that they do not understand hospice care or may express concerns that the hospice agency is not providing enough interventions. It can be difficult for some patients and families to accept the comfort care philosophy of hospice; hospice care may be equated with giving up, and patients and caregivers may fear that they will die quickly if enrolled. Despite patient or caregiver perceptions, hospice services may be able to meet their evolving needs, including antibiotics, artificial nutrition, hydration, arrangement of palliative procedures, and palliative radiation or cancer-directed therapy.

Hospice enrollment directly from the ED has been increasingly described and promoted (Box e5.1). The emergency physician can certify that the patient has a terminal disease and write hospice admitting orders. Because of the 24/7 nature of hospice care, all hospice agencies typically have on-call staff that can be reached at all hours; many of them can respond to the needs of the ED for emergent admissions. For some patients and families, the ability to avoid regular hospital admission and its associated risk of hospital death can be very meaningful. Increasingly, hospices have hospital-based services that are open to ED admission.

For actively dying patients with a limited prognosis of hours to days, or a high symptom burden requiring parenteral therapies, inpatient hospice is often the best option. There are regional variations in how patients can receive inpatient care, with some hospice agencies contracting for beds in acute care hospitals, and others having freestanding facilities. Transitions from ED to inpatient hospice are generally easier than a transition home with hospice care. While the latter is possible, it may take more planning and coordination, particularly on the part of caregivers, to be successful. Not surprisingly, caregivers rate the quality

BOX E5.1 Initiation of a Hospice Referral From the Emergency Department

1. Assess Medicare Hospice Benefit eligibility.
2. Discuss hospice as a disposition plan with the patient's physician. Contact the patient's personal physician and discuss the current condition, prognosis, and prior goals-of-care conversations. If you are considering hospice care, ask if the physician is willing to be the following physician for hospice services.
3. Assess whether the patient's goals are consistent with hospice care. Generally, this means a patient wants medical treatments and other support aimed at alleviating symptoms and maintaining quality of life without life prolongation.
4. Introduce hospice to the patient and family or surrogates.
   - Discuss the core aspects of hospice care and how these features can help the patient and family (e.g., 24/7 on-call assistance, home visits for symptom management, coordinated care with the patient's physician, emotional and spiritual or religious support).
   - Address concerns and clarify misconceptions.
   - Phrase your recommendation for hospice care in positive language, grounded in the patient's own care goals: "I think the best way to help you stay at home, avoid the hospital, and stay as fit as possible for whatever time you have left is to receive hospice care at your home…"
   - Discuss the location of hospice care. Usually, this is the patient's residence, such as a private home or long-term care facility. Direct admissions to hospice facilities can occur depending on bed availability and ability of local hospice agencies to arrange an immediate, direct facility admission. This is not available in all communities and requires a discussion with the hospice agency.
5. Make a referral and write orders. Call a hospice agency; anticipate these questions:
   - What is the terminal illness? Who will be the following physician (step 2)?
   - What equipment will be needed immediately (e.g., home oxygen)? Is there a caregiver at home?
   - Code status (patients cannot be denied hospice enrollment if full code; however, the hospice team will need to know if code status needs to be addressed further)
   - Questions you need to ask the hospice agency include the following:
     - How soon can you make an intake visit to the patient's home? Can you visit the patient immediately, even in the ED? (This is available in some communities.)
     - How should I coordinate filling of new prescriptions I want the patient to have?
   - Examples of ED-initiated hospice referral orders:
     - Evaluate and admit or enroll in hospice care.
     - Terminal diagnosis: _____.
     - Expected prognosis—terminal illness with less than 6-month survival likely if disease runs its normal expected course (or be more specific, if indicated).
     - Physician who will follow patient: _____.
6. Ensure patient or surrogate understanding and secure the plan. Communicate the plan following ED discharge; provide the name and contact number for the hospice agency.
7. What if hospice enrollment is appropriate, but cannot be arranged in a timely manner? If the patient can be cared for at home safely for 1 to 2 days without extra services, send her or him home with appropriate prescriptions and care instructions. In most communities, patients can be enrolled in hospice care within 24 to 48 hours, even on weekends. If they cannot be cared for safely at home, observation versus inpatient admission is likely necessary until a safe discharge plan can be established.

Adapted from Lamba S, Quest TE, Weissman DE: Initiating a hospice referral from the emergency department #247. *J Palliat Med*. 2011;14:1346-1347.

of EOL care higher when hospice is involved and when dying occurs outside of the hospital setting which underscores the need for hospice transitions to be considered from the ED.[5]

CORE ASPECTS OF PALLIATIVE CARE IN THE EMERGENCY DEPARTMENT

End-of-Life Trajectories and Prognostication

For a clinician to be comfortable with the care of serious illness, an understanding of end-of-life trajectories and the ability to formulate a prognosis is helpful. With modern medical advances, chronic diseases are present during the last years of life for most people. Depending on the type of underlying illness, 4 common patterns of decline have been observed in the last year of life[6] (Fig. e5.1). Sudden death (due to cardiac arrest, trauma, or other sudden event) occurs in only 15% of people. The other trajectories are more common and occur with roughly equal frequency. Understanding these trajectories enables one to contextualize the patient's acute visit, enhancing communication and medical decision making.

The disease most commonly associated with the terminal illness trajectory is cancer. Patients with cancer may remain independent and functional for some time but often experience a significant decline in overall health as death nears. The palliative performance scale is the most studied prognostication tool in this population, incorporating the patient's ability to perform activities of daily life (ADLs), level of consciousness, and oral intake[7] (Table e5.1). In cohorts of patients with

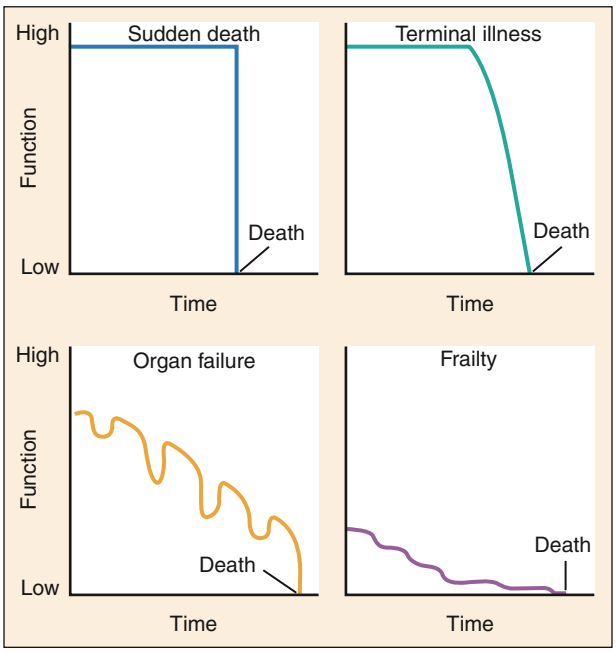


Fig. e5.1 Theoretic trajectories of dying. (From: Lunney JR, Lynn J, Hogan C. Profiles of older Medicare decedents. *J Am Geriatr Soc*. 2002;50:1108-1112.)

TABLE E5.1 Palliative Performance Scale

PPS Level	Ambulation	Activity and Evidence of Disease	Self-Care	Intake	Consciousness level
100%	Full	Normal activity and work No evidence of disease	Full	Normal	Full
90%	Full	Normal activity and work Some evidence of disease	Full	Normal	Full
80%	Full	Normal activity with effort Some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable to do normal job/work Significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable to do hobby/housework Significant disease	Occasional assistance necessary	Normal or reduced	Full or confusion
50%	Mainly sit/lie	Unable to do any work Extensive disease	Considerable assistance required	Normal or reduced	Full or confusion
40%	Mainly in bed	Unable to do most activity Extensive disease	Mainly assistance	Normal or reduced	Full or drowsy ± confusion
30%	Total bedbound	Unable to do most activity Extensive disease	Total care	Normal or reduced	Full or drowsy ± confusion
20%	Total bedbound	Unable to do most activity Extensive disease	Total care	Minimal to sips	Full or drowsy ± confusion
10%	Total bedbound	Unable to do most activity Extensive disease	Total care	Mouth care only	Drowsy or coma ± confusion
0 (Death)					

a terminal illness, a score of less than 50% correlates with a prognosis of weeks, not months. In cases of organ failure (e.g., COPD, heart failure, liver failure, other progressive, serious medical diseases), gradual decline is punctuated by intermittent exacerbations, followed by dramatic and often surprising recoveries. In the first minutes to hours of decompensation, it can be difficult for the clinician to predict whether the patient is going to recover. This prognostic uncertainty can complicate goals-of-care discussions, often resulting in a time-limited trial of critical care in this population. The fourth trajectory of gradual decline, or frailty, is associated with some form of dementia in 50% of affected persons and a lingering course that can extend for many years, stressing and wearing out caregivers and other support systems as a decline in functional abilities progresses. Caregivers may have difficulty appreciating the severity of the patient's condition because they have gradually accommodated the patient's cognitive and functional decline. In the case of dementia, caregivers are not always educated about the expected complications of end-stage disease, including feeding/nutrition problems and severe infections, and may need assistance understanding that these problems are expected and a sign that their loved one is nearing the end of life. Proxy decision-makers with a more accurate understanding of prognosis are less likely to choose burdensome interventions for their loved one in the last 6 months of life.[8]

It can be helpful to have even more specific, concrete prognostic information about ED patients to guide decision making. Recently, the "surprise question," which has been well-studied in other settings, has been investigated as a potential prognostic tool in the ED. The emergency clinician is trained to ask, "Would I be surprised if this patient died in (weeks, months, a year)?" In a cohort of ED patients with advanced cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of 3 to 4 (patient spending > 50% of waking hours in bed or completely disabled) and the emergency physician being "not surprised" if the patient died within the year correlated with a median survival of 3 months.[9] In an unselected population of older ED patients, when the surprise question was used to predict 1-month mortality, the test did not perform as well, with a sensitivity of 20% and a specificity of 93%.[10] Regardless, this tool may be increasingly incorporated into the ED admission workflow as a trigger for allocating appropriate resources, such as early palliative care consultations, to vulnerable patients.

Common Procedures and Interventions Faced at the End of Life

Intubation and Mechanical Ventilation

In terms of prognostication, a particular area of interest for emergency clinicians surrounds the initiation of mechanical ventilation. An ED intubation generally commits the patient to a course of critical care, with all its potential burdens. Although the benefits outweigh the risks in most patients, in those with a terminal illness or advanced age mechanical ventilation may simply prolong the dying process and lead to a highly medicalized death. Recent studies have suggested a morbidity and mortality burden in ED patients with advanced age and respiratory failure resulting in intubation.[11] In a large observational study, 43% of those age 85 to 89 years died during their inpatient stay while for those age 90 years and older, half died and a substantial proportion of survivors ended up in a nursing home setting.[11] The presence of certain comorbidities increases mortality even further, with admission diagnosis of sepsis, stroke or intracranial hemorrhage associated with unfavorable outcomes.[12]

Cardiac Arrest

Patients with a serious or terminal illness who experience a cardiac arrest have even more dismal outcomes. In one study of patients with advanced cancer and an in-hospital cardiac arrest, only 7% survived to discharge.[13] A recent study demonstrates that patients with advanced age and out-of-hospital cardiac arrest have particularly bad outcomes.[14] Of the 107 nursing home patients included, 0 survived to hospital discharge. A clinical decision rule called GO-FAR (Good Outcome Following Attempted Resuscitation) has been derived and

externally validated to predict patients who will both survive an arrest and do so with favorable neurologic outcomes.[15] Multiple variables such as age, comorbidities, and lab values are used to generate a score that then predicts the patients' likelihood for intact neurologic survival. This clinical score is included on MD-CALC so providers can rapidly and accurately calculate the score at the bedside. A 75-year-old patient with advanced cancer, septic shock, and pneumonia, for instance, would have a calculated GO-FAR score of 25, which would translate to a less than 1% chance of survival with minimal neurologic disability, should that patient experience a cardiac arrest. This kind of prognostic data can inform shared decision making with patients and families deliberating over code status determination.

Advance Care Planning and Advance Directives

Overview

Advance care planning is the process whereby people plan for future health states, anticipating a time when they will not be able to speak for themselves. It honors the ethical principle of patient autonomy. Advance care planning is a process and evolves over time for a given patient. For some, it can be as simple as a conversation with loved ones about their wishes should they find themselves in certain health states. In the ED, the future health state may change quickly over minutes or hours.

For others, where days, weeks, months, or years may pass before their health declines, advance care planning is a more formal process, leading to documentation of wishes in the form of advance directives. Examples of frequently encountered advance directives include a living will, a health care power of attorney or health care proxy form, and a POLST (Physician Orders for List-Sustaining Treatment) document (Fig. e5.2). Not surprisingly, the ED is where many of these discussions and directives are put into action. In cancer patients, early discussions about end-of-life care are associated with lower costs in the last month of life, lower likelihood of hospital, ICU, and ED use, and greater use of hospice.[16] A substantial portion of ED patients have engaged in advance care planning, and between a quarter to half have completed advance directives, underscoring the need for the emergency clinician to understand how to interpret and apply these at the bedside. Unfortunately, substantial barriers exist in allowing emergency providers access to these critical documents. Advance directives often do not transition with patients across care settings and even when documentation exists within the electronic medical record, providers are often unsure how to access the information. A recent study found little association between the preferences documented in a POLST advance directive and treatment intensity delivered in ED patients, and this may be partly explained by the fact that few providers ever accessed the POLST during the patient's episode of care.[17]

All states allow for patients to appoint a legal surrogate decision-maker, usually termed a health care power of attorney or health care proxy. This person does not have to be a family member and only assumes control of medical decision making when the patient loses decisional capacity. The proxy takes priority over all natural surrogates (typically ordered spouse, adult children, parent, then siblings). All states have some legal guidance regarding surrogacy when no advance directive exists. Individual state laws should be researched when a patient has no advance directive and no surrogate appointed by a legal document.

Patients near the end of life transition frequently between care settings. The same invasive treatments are considered for most, including intubation/mechanical ventilation, CPR, artificial nutrition, artificial hydration, and antibiotics. The POLST program, which originated in Oregon in 1991, grew out of a desire to ensure that patients' wishes regarding these frequently considered interventions could be easily communicated in an emergency, with significant implications for first responders and emergency clinicians. Unlike the living will, which gives broad and vague suggestions about EOL wishes, the POLST document actually translates patient preferences into a portable medical order set, because it is signed and completed by a physician. POLST programs are developed at the state level, and most states currently either have or are developing a POLST program. Behind the DNR form, emergency clinicians rate the POLST as the most useful advance directive, because it provides concrete guidance about how to care for the patient.[18] Although some providers have expressed concern about their medicolegal risk in relation to following POLST orders that are subsequently found to be in conflict with family preferences, many states offer specific legal immunity in relation to following POLST orders and if not, one is protected by common law: There has not been a single malpractice case borne out of this scenario.[19] As with all advance directives, they do not apply in the patient with decisional capacity so a patient is capable of revoking their own POLST orders.

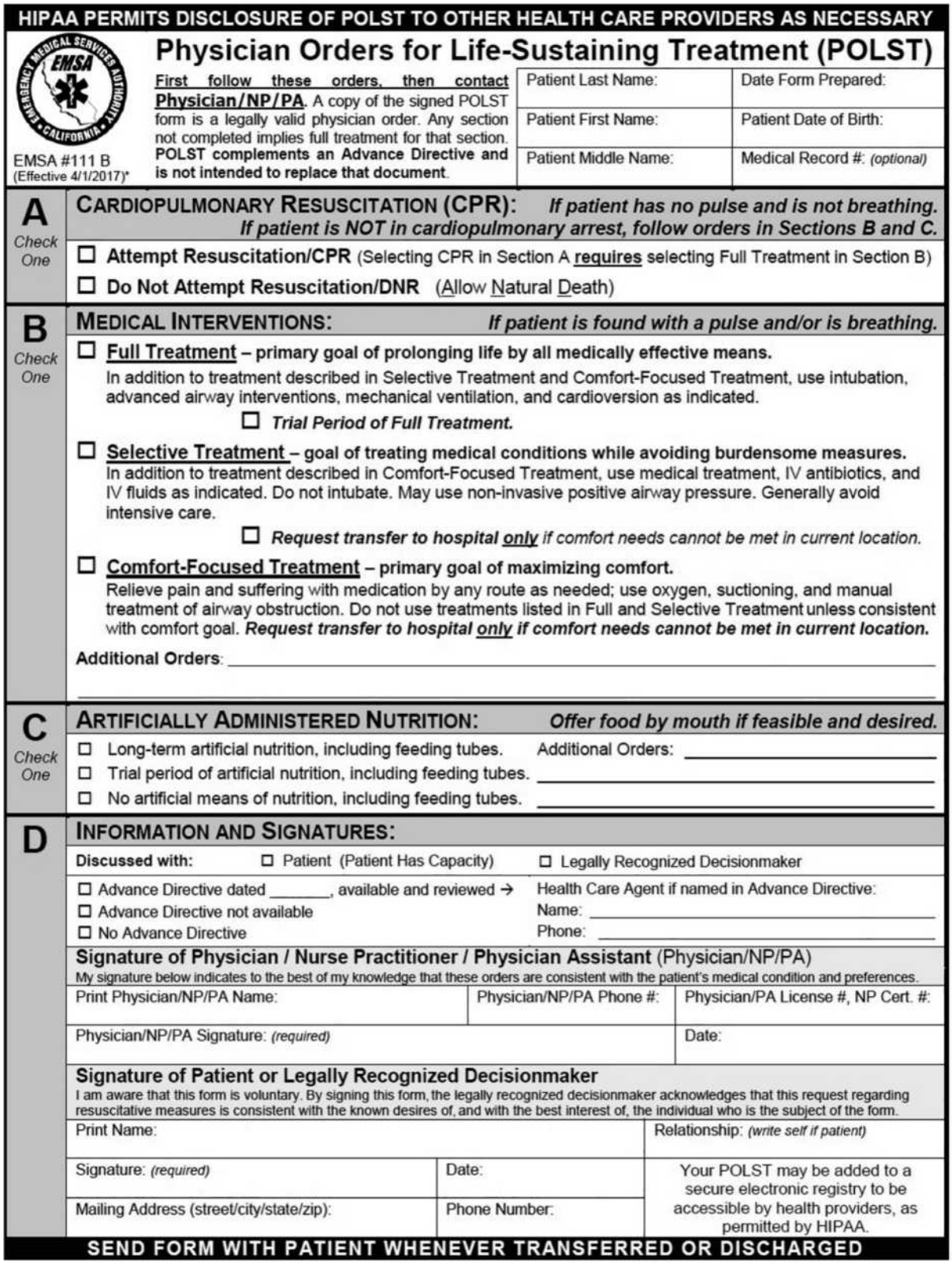
Do not resuscitate (DNR) and do not intubate (DNI) orders may exist alone or as part of the POLST. Although the interpretation of a DNR order may vary across states and hospitals, this generally refers to the use of ACLS protocols in the setting of a full cardiopulmonary arrest. In patients who are DNR, no interventions are applied at the time of death. There is confusion about whether the presence of a DNR order precludes the use of mechanical ventilation in patients in respiratory distress or failure. While the meaning of DNR may vary across settings, the clinician should not presume that a DNR order necessarily means the patient is DNI. For instance, it is reasonable to imagine a COPD patient who would be willing to undergo a time-limited trial of mechanical ventilation but would not want an attempted resuscitation in the setting of a cardiac arrest. Furthermore, DNR orders have a very narrow application, and they should not influence other types of care that patients receive at the EOL, though studies suggest they do.[20]

Goals-of-Care Discussions

An ED visit alone does not imply that patients or caregivers want all interventions at the end of life. Patients near the EOL use the ED for a variety of reasons, including but not limited to, overwhelming symptoms, uncertainty about prognosis, easy availability, and caregiver burnout. A core skill in managing patients near the end of life is the ability to assess and establish goals of care. In a true emergency, where the patient lacks capacity and there is no legal surrogate or advance care plan, such conversations take a back seat to resuscitation interventions. Most patients with a serious illness, however, present with enough time to establish goals of care before invasive interventions are required. Because these conversations can feel daunting, particularly when discussing the withholding and withdrawing of potentially life-sustaining interventions, a systematic and structured approach has been suggested.[21]

Emergency providers often want immediate answers about whether interventions such as intubation and CPR will be desired, but discussions about interventions that are not embedded in a larger conversation about prognosis and goals can be problematic; choices made may be driven by poor health literacy, misinformation, or strong emotions, rather than truly reflecting the patient's values and priorities. For this reason, conversations about goals of care are more successful when a "roadmap" is used; one example is the REMAP tool that was developed by the VitalTalk group, which stands for Reframe, Expect emotion, Map out patient goals, Align with goals, Propose a plan.[22]

In the ED, however, a preliminary step includes probing patients and caregivers for their understanding of the medical situation. "What have the doctors told you about your cancer, condition, etc.?" can be a helpful introduction. If there are considerable gaps between patient



HIPAA PERMITS DISCLOSURE OF POLST TO OTHER HEALTH CARE PROVIDERS AS NECESSARY

Physician Orders for Life-Sustaining Treatment (POLST)

EMSA #111 B
(Effective 4/1/2017)*

First follow these orders, then contact Physician/NP/PA. A copy of the signed POLST form is a legally valid physician order. Any section not completed implies full treatment for that section. **POLST complements an Advance Directive and is not intended to replace that document.**

Patient Last Name:	Date Form Prepared:
Patient First Name:	Patient Date of Birth:
Patient Middle Name:	Medical Record #: *(optional)*

A — Check One

CARDIOPULMONARY RESUSCITATION (CPR): ***If patient has no pulse and is not breathing. If patient is NOT in cardiopulmonary arrest, follow orders in Sections B and C.***

- ☐ **Attempt Resuscitation/CPR** (Selecting CPR in Section A **requires** selecting Full Treatment in Section B)
- ☐ **Do Not Attempt Resuscitation/DNR** (Allow Natural Death)

B — Check One

MEDICAL INTERVENTIONS: ***If patient is found with a pulse and/or is breathing.***

- ☐ **Full Treatment – primary goal of prolonging life by all medically effective means.**
  In addition to treatment described in Selective Treatment and Comfort-Focused Treatment, use intubation, advanced airway interventions, mechanical ventilation, and cardioversion as indicated.
  - ☐ ***Trial Period of Full Treatment.***
- ☐ **Selective Treatment – goal of treating medical conditions while avoiding burdensome measures.**
  In addition to treatment described in Comfort-Focused Treatment, use medical treatment, IV antibiotics, and IV fluids as indicated. Do not intubate. May use non-invasive positive airway pressure. Generally avoid intensive care.
  - ☐ ***Request transfer to hospital only if comfort needs cannot be met in current location.***
- ☐ **Comfort-Focused Treatment – primary goal of maximizing comfort.**
  Relieve pain and suffering with medication by any route as needed; use oxygen, suctioning, and manual treatment of airway obstruction. Do not use treatments listed in Full and Selective Treatment unless consistent with comfort goal. ***Request transfer to hospital only if comfort needs cannot be met in current location.***

Additional Orders: _____

C — Check One

ARTIFICIALLY ADMINISTERED NUTRITION: ***Offer food by mouth if feasible and desired.***

- ☐ Long-term artificial nutrition, including feeding tubes. Additional Orders: _____
- ☐ Trial period of artificial nutrition, including feeding tubes. _____
- ☐ No artificial means of nutrition, including feeding tubes. _____

D

INFORMATION AND SIGNATURES:

Discussed with: ☐ Patient (Patient Has Capacity) ☐ Legally Recognized Decisionmaker

- ☐ Advance Directive dated _____, available and reviewed →
- ☐ Advance Directive not available
- ☐ No Advance Directive

Health Care Agent if named in Advance Directive:
Name: _____
Phone: _____

Signature of Physician / Nurse Practitioner / Physician Assistant (Physician/NP/PA)
My signature below indicates to the best of my knowledge that these orders are consistent with the patient's medical condition and preferences.

Print Physician/NP/PA Name:	Physician/NP/PA Phone #:	Physician/PA License #, NP Cert. #:
Physician/NP/PA Signature: *(required)*		Date:

Signature of Patient or Legally Recognized Decisionmaker
I am aware that this form is voluntary. By signing this form, the legally recognized decisionmaker acknowledges that this request regarding resuscitative measures is consistent with the known desires of, and with the best interest of, the individual who is the subject of the form.

Print Name:		Relationship: *(write self if patient)*
Signature: *(required)*	Date:	Your POLST may be added to a secure electronic registry to be accessible by health providers, as permitted by HIPAA.
Mailing Address (street/city/state/zip):	Phone Number:	

SEND FORM WITH PATIENT WHENEVER TRANSFERRED OR DISCHARGED

Fig. e5.2 California Physician Orders for Life-Sustaining Treatment (POLST).

understanding and clinical reality, these need to be addressed before moving forward with the remainder of the conversation. If patient or family expectations have already been communicated yet seem at odds with the clinical reality, a "hope for the best, plan for the worst" introductory phrase can be useful: "I see you're hopeful that she will get better. I'm hoping for that, too. Given how sick she is, I'm worried about her. I wonder if we can hope for the best, while also making a plan for how best to take care of her if she doesn't get better?"

Next, the provider delivers a headline that "reframes" the situation for the patient and caregiver. Most critical in this step is minimizing the

TABLE E5.2 NURSE Mnemonic for Providing Empathy

Nurse	Example
Name the emotion	"You seem very disappointed." "I can see you are in shock."
Understand	"I can only imagine how hard this has been for all of you."
Show Respect	"You have been a wonderful advocate/caregiver for your dad."
Express Support	"We will continue to help all of you on this journey."
Explore	"I heard you say you don't believe the information the oncologist gave you. Tell me more about that."

use of jargon. "I'm worried we're in a different place," "I'm worried that time is short," "I'm worried that she is dying," and "I'm worried we may not be able to turn this situation around" are examples of concise but clear messages. More concrete data like "All of her organs are failing" may also be used. "Expect emotion" is the next step in REMAP but strong emotional responses can occur at any point in the discussion. Emotional responses can occur before cognitive ones, though, and need to be recognized and addressed before patients and families can move forward with decision making. The NURSE mnemonic is a useful tool in enabling the provider to articulate empathy (Table e5.2). It stands for *N*ame the emotion, *U*nderstand the emotion, showing *R*espect, provide *S*upportive statements, and *E*xplore what's behind the emotion.

Next, the patient's and/or family's goals and values are "mapped out." "What would your mom tell us is most important to her right now?" and "When you think about the future, what are you hoping for?" can be helpful exploration questions. It can be appropriate here to ask if the patient ever engaged family in discussions about their EOL wishes or preferences regarding the use of invasive treatments. To communicate "alignment," the provider could say "I'm hearing that what's most important to you is *x, y, z*."

Last, a medical plan is "proposed" that takes into account the patient and family goals, the clinical scenario and expected prognosis, and the best interest of the patient. Providers should start with a big-picture suggestion first, followed by concrete recommendations. "Based on what I'm hearing, I think we should refocus all of our efforts on maximizing her comfort and supporting her through a natural dying process" would be appropriate when comfort-focused treatment represents the best care plan. There is often an expectation that certain interventions, like CPR, will be directly addressed. "When her breathing and heart stop, I don't recommend that we intervene. I don't think it would be helpful to use machines or other measures to try to prolong her life. Instead, we will focus on allowing her to have a natural death."

Depending on the patient and family, it may be necessary to be more explicit about code status by saying something like, "I will let the medical team know we've made this decision by entering a Do Not Resuscitate order in her chart." Phrases like "Do you want us to do everything?" or "Does she want to be resuscitated?" should be avoided for two reasons. First, the way the questions are framed implies that performing these interventions would be reasonable and successful, which is rarely the case at the EOL. Second, families do not understand what the provider means when using the term "everything" and "resuscitated" nor do they understand the consequences of these medical interventions.

For some patients and families, open-ended questions can be overwhelming and questions about values and goals met with uncertainty. In this situation, it can be useful to give concrete examples of three distinct treatment pathways—invasive, noninvasive, and comfort—from which patients and families can then select. "Some people in this scenario would say that they would want to live as long as possible and would want all measures used to keep them alive, even if there was some suffering associated with that and only a small chance the treatments would work. Other people would say that they would want a chance to live longer if there were simple problems that were easily treatable with things like IV fluids and antibiotics but that if their condition worsened despite these interventions, they would not want to escalate to more invasive treatments like life support. Still, others say that at this point in their illness, they want to focus on comfort exclusively and do not want their life prolonged unnecessarily. All three of these pathways are reasonable. If your mom could speak to us, which would she say makes the most sense for her?"

Emergency providers should clearly and compassionately discuss these important yet sensitive topics while recognizing that some patients and families may choose interventions that seem incongruous with their best interest. Not all patients and families are prepared for EOL decision making, and conflict or strong emotions may pose an insurmountable barrier to moving forward with a discussion. Still, others may hold certain cultural or religious beliefs that are at odds with plans that promote comfort over longevity. Although emergency clinicians are not ethically obligated to deliver futile care, often the most practical way forward involves a negotiation in which life-sustaining interventions are delivered, possibly with certain limits in place. Generally, families and providers can reach an agreement about a care plan but this process may require time-intensive conversations that are beyond the scope of emergency provider practice. Palliative care consultations would be appropriate in such cases.

Common Symptoms Requiring Palliation Near the End of Life

Within the last days to weeks of life, patients may experience an increase in symptoms to include pain, shortness of breath, agitation, delirium, seizures, and terminal secretions. As the patient undergoes physiologic decline, renal failure is observed and expected; patients may become increasingly susceptible to toxicities from medications that are renally cleared. As a result, caregivers may bring patients to the ED for symptoms that seem unmanageable or distressing, with or without hospice care in place. The emergency clinician can contextualize these symptoms for caregivers by recognizing what a normal dying process entails, including progressive lack of food or water intake, lethargy, renal and cardiac dysfunction with abnormal vital signs, progressive inability to swallow, altered mental status, and incontinence.

Patients suffering from a disease that is not curable may still want and benefit from a variety of medical interventions as part of the plan of care, such as antibiotics for intercurrent infections, drainage of effusions that cause shortness of breath, wound care for decubitus ulcers, decompression of bowel obstructions, and pain management. The caregiver may encounter several unfamiliar principles when treating symptoms in someone near the end of life. One of the challenges for the emergency clinician is the treatment of symptoms rather than the underlying diagnosis, even though this often is the appropriate option in palliative care. The emergency clinician may have concerns about drugging patients or overtreating them, but these are mostly unwarranted. Worrying about unintended consequences may lead to underdosing of medications, leaving patients without desired relief.

Pain

Pain is a common complaint with terminal illness. Although typically considered in the setting of cancer, pain in the end-of-life phase is prevalent across many noncancer conditions, such as heart failure, COPD, and dementia. As patients become less mobile, they may suffer pain from contractures, wounds, or other conditions secondary to

the primary illness. Patients suffering from malignant pain may need continuous infusions of opioids to obtain relief or rapid titration protocols, as well as an adjustment of chronic doses of analgesics in the ED. Patients with advanced illness and pain may be tolerant to opioids and require high doses to achieve comfort.

Rapid opioid dose escalation is the most important intervention in cancer patients receiving opioids. An initial parenteral breakthrough dose for a terminal patient having a pain crisis should be 10% of their 24-hour opioid dose. From there, doubling the dose may be required until successful analgesia is achieved. With IV administration of morphine, serum levels peak in 5 to 15 minutes, so patients need to be reassessed and re-dosed promptly. Side effects from opioids should be anticipated. Rising serum levels of opioids may stimulate the chemotactic trigger zone, causing nausea. Constipation is a common effect of opioids, and tolerance to this symptom does not develop. Prevention is far easier than treatment, so a stimulant laxative should be part of all opioid prescriptions for malignant pain. The use of nonsteroidal antiinflammatory drugs may be helpful in potentiating the effects of opioids in cancer patients. A fentanyl patch may be a useful tool, especially if IV access is limited/challenging. However, if a patch is placed in the ED, oral or IV opioids should be administered for pain control as the patch takes 12 hours to onset and 24 hours to reach steady state.

Dyspnea

Dyspnea is a common symptom at the end of life. It is multifactorial and not defined by direct pathophysiology. Shortness of breath can be part of the last stages of COPD, cancer, or other advanced chronic diseases as patients become cachectic and immobile. Furthermore, the list of problems that can cause dyspnea is broad, including, but not limited to, anemia, infection, pulmonary embolism, myocardial infarction, pleural effusion, pneumonia, aspiration, and pulmonary edema. In patients presenting to the ED with dyspnea and a terminal illness, determining the underlying cause of the symptom may be less important than treating the symptom itself. Oxygen therapy is not harmful but may have limited effects because hypoxia and dyspnea do not always correlate at the EOL. The first-line therapy for dyspnea is opiates. A safe starting dose for the opiate naïve would be morphine 2 mg IV. Timing and escalation of dosing mirrors that are used in pain crises. Noninvasive ventilation and high-flow oxygen have a role in palliating dyspnea in select patients with an advanced illness, particularly in those hoping for improvement but wanting to avoid more invasive interventions.

Death in the ED

Death Notification and Breaking Bad News

As with discussing goals of care, a roadmap has been proposed by the VitalTalk consortium for breaking bad news—GUIDE—that can also be applied to death notification. GUIDE stands for *G*et ready (maximize the privacy of the setting, ensure the right people are in the room, make sure all the information is correct), *U*nderstand what the patient/family knows, *I*nform (starting with a headline, minimizing jargon), *D*emonstrate empathy, and *E*quip the patient or family for the next steps.

Emergency clinicians must be adept at communicating bad news to patients, family members, and caregivers. Death notification can be particularly challenging. How it is done may impact the family's subsequent course of grief and coping. Emergency clinicians have particular challenges in delivering bad news. They do not have ongoing relationships with their patients, and the bad news may be abrupt and unexpected. Feeling skilled in providing disclosures to families is key in managing external sources of provider stress.

Death notification often occurs after an unsuccessful resuscitation attempt. Sometimes the family has initiated the 911 call and recognized that their loved one had died at that time. On the other hand, a family summoned to the ED may have no idea that they are about to be informed that their loved one has been critically injured or has died. When giving the news, emergency clinicians should use a clear headline like, "He died," to be sure that there are no misunderstandings about the outcome being conveyed. A wide range of emotional responses should be anticipated, with expressions of anger and disbelief being common. Those at the scene should be assured that their responses to the emergency were appropriate, the medical care team did all that was possible, and the victim did not experience unnecessary discomfort.

When the notification is to an individual who is more than an hour away or otherwise unable to come to the ED physically to receive the bad news, the information needs to be disclosed by phone. If the first contact with survivors of an ED death is by telephone, it is recommended that the survivor be told to come to the ED, if at all possible. Although family members may ask or even demand to know if death has occurred, allowing some time for the assimilation of news by delaying information about the final outcome may be more helpful for the grieving process. Nonphysician staff may be used to summon survivors and can inform them that the patient has been involved in an accident or is seriously ill without signs of improvement.

The emergency clinician should make sure that the relative has someone present in the room if possible, ask them to be seated, and name the person involved. It is best to start with brief information about the circumstances and provide a warning that bad news is coming before breaking it. Even a few seconds of preparation in these circumstances can serve to partially attenuate the acute psychic pain. As indicated by the perceived response, the clinician may need to ask, "Are you able to talk for a few minutes?" Some individuals may be unwilling or unable to continue after they hear the initial news, and they should be given an "out," but a definite time to reconnect should be established (e.g., 10–15 minutes).

Viewing the Body

When a death has occurred, the family should be offered an opportunity to view the body. This may be the first exposure to the body for the survivors and can make an abstract and unreal notification more concrete. Although most survivors find viewing of the body helpful, no attempt should be made to force this on them, and a few are not comforted by seeing the deceased.

If possible, the body should be moved to a small room, preferably away from the main treatment area. Family members should be warned of what to expect, such as color and temperature changes, injuries or invasive premortem procedures, and the presence of endotracheal and intravenous (IV) tubing or other medical devices.

A staff member should remain in the room or within close range at all times. This contact allows the staff to help make the viewing an important and supportive aspect of the grieving process. Survivors should be allowed to remain with the body for as long as seems appropriate. When gross disfigurement has occurred, the viewers should be warned about this, and the body should be discreetly covered, when possible. Survivors may even find that helping to clean and prepare the body (particularly with a pediatric death), holding a loved one, or preparing for transport may allow a final expression of caring.

Family Presence During Resuscitation

It is increasingly common to invite a close family member to attend resuscitation attempts. Evidence has suggested that presence during procedures and resuscitations may be beneficial to surviving patients and family members who choose to stay, and they are not harmed by the experience.[23,24] Less consensus exists among providers, and they often express discomfort with the concept, with nurses expressing less

discomfort than physicians.[25] If resuscitation is to be witnessed by a family member, preferably a protocol is in place and a staff member who is dedicated to supporting that person should be present. Processes and procedures should allow for the ED team to work effectively but also allow families the option of observing resuscitation.

Field Death Pronouncement

Several physiologic circumstances have been identified in which out-of-hospital providers should not initiate or continue CPR because of uniformly poor outcomes and no benefit from intervention. American College of Emergency Physicians (ACEP) and American Heart Association (AHA) guidelines state that CPR should not be initiated in patients with nontraumatic cardiac arrest and signs of irreversible death, such as decapitation, dependent lividity, or rigor mortis.[26] Furthermore, the presence of a valid advance directive like a POLST or out-of-hospital DNR that indicates an attempted resuscitation is not desired, should lead to field death pronouncement. ACEP policy recommends discontinuation of resuscitation in the out-of-hospital setting if the patient remains in asystole or wide-complex pulseless bradycardia after a trial of adequate resuscitation, including CPR, intubation, medications, defibrillation, and pacing. The National Association of EMS Physicians supports this approach. Termination of resuscitation efforts in nontraumatic cardiac arrest patients should be made in agreement with online medical direction and predicated on access to witnesses or family, provider comfort with death notification and grief counseling, and safety and logistic considerations. If questions arise about resuscitation, CPR and advanced cardiac life support measures should be initiated and the patient transported. It can be easier and is ethically more sound to withdraw care in the ED than to withhold care at the scene.

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CHAPTER E5: QUESTIONS AND ANSWERS

1. The primary focus of palliative care is to
   a. transition dying patients to hospice.
   b. administer morphine to terminally ill patients.
   c. improve the quality of life of patients living with serious illnesses.
   d. facilitate the withdrawal of life-sustaining treatments in terminally ill patients.

Answer: C.

2. Emergency providers commonly discuss the issue of code status with their patients. In terms of prognosis after a cardiac arrest,
   a. a recent study of nursing home patients experiencing cardiac arrest found high rates of survival to hospital discharge.
   b. there are no good data, so providers should rely on their gestalt when counseling patients and families about code status determination.
   c. a clinical decision rule called GO-FAR has been validated and can give providers predictions for neurologically intact survival in individual patients using variables from their clinical data.
   d. older patients and those with a terminal illness fare surprisingly well.

Answer: C.

3. An 80-year-old patient with stage IV pancreatic cancer, enrolled in hospice, presents to the ED in respiratory distress. His vital signs are HR 120, RR 30, O_2 saturation 85% on RA and 100% on NRB, BP 100/50. He lives at home with his family and has been relatively stable and asymptomatic until today. The emergency provider should do all of the following, EXCEPT
   a. assume that because the patient called 911, his goals are to focus on life prolongation and that he would want to be intubated.
   b. notify the patient's hospice provider that the patient is in the ED and obtain more history about recent events.
   c. gather clinical data, review advance directives, and then engage the patient and/or family in a conversation about goals of care.
   d. consider administering low-dose morphine to alleviate the patient's dyspnea.

Answer: A.

4. Which of the following is expected to be the least likely cause of death for adults in the United States?
   a. Cancer
   b. Cardiovascular disease
   c. Heart disease
   d. Trauma

Answer: D. According to the Center for Disease Control, accidents are the third leading cause of death in the United States. (http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.)

5. In a nondeath disclosure setting, deliverance of bad news should start with which of the following approaches?
   a. Allowing the patient to react to the news
   b. Asking the patient if he or she wants to know
   c. Making sure you keep the conversation going to provide comfort and thereby dull the emotional impact of the news
   d. Your knowledge of the complete medical implications and ramifications of the news

Answer: B. Respectful disclosure of difficult news includes assessing the readiness and willingness of the patient to receive the news.

6. Mr. Jones is a 54-year-old man currently receiving hospice care at home for advanced colon cancer. His wife calls 911 when he becomes unresponsive. On presentation to the ED, his vital signs are blood pressure, 60/40 mm Hg; heart rate, 140 beats/min; temperature, 39.6°C (103.3°F); respiratory rate, 12 breaths/min. He is moaning with a facial grimace. His wife, who is the legal decision maker, is at the bedside. Which of the following represents the best course of action?
   a. Initiate sepsis protocol, begin treatment for pain, and call the palliative care service.
   b. Initiate sepsis protocol, page the hospice nurse, and speak to his wife regarding goals of care.
   c. Page the hospice nurse, begin treatment for pain, and speak to his wife regarding the goals of care.
   d. Page the hospice nurse and speak to his wife regarding the goals of care.

Answer: C. Under the hospice benefit, the hospice agency is the care manager. The patient has lost capacity and his wife is his decision maker and she should be consulted regarding goals. Pain and non-pain symptoms should be addressed while other actions are being taken.

7. Mrs. Smith is a 68-year-old woman with advanced heart failure who presents in cardiogenic shock with multiple previous admissions that state that she is currently optimized with all available therapies. You decide to initiate hospice care from the ED. Which of the following do you do next?
   a. Call the hospice liaison on call for the ED to speak with her family regarding their options.
   b. Call the palliative care service to discuss hospice care with the patient and her family.
   c. Conduct a goals-of-care discussion with the patient and her family.
   d. Discuss the benefits of hospice care that would allow the patient to stay at home with her family.

Answer: C. Central to the discussion of hospice care is an assessment of the goals of care focused on care that addresses the distress of the illness and not the reversal of the primary illness.

8. In performing a death disclosure, which of the following statements represents best practice when communicating news of death?
   a. "Your loved one didn't make it."
   b. "Your loved one has died."
   c. "Your loved one has gone to a better place."
   d. "Your loved one has passed on."

Answer: B. It is not recommended to use euphemisms or unclear statements to communicate news of death because this can cause confusion and ambiguity for the receiver of the news.

9. Mr. Stone is a 27-year-old man with glioblastoma multiforme. He has completed radiation treatment and is on oral chemotherapy. Over the last week, he has become progressively weaker and is now in bed. He is no longer speaking and is dropping things. He is taking sips of clear liquids and coughs after swallowing. Which of the following is the strongest predictor of his death?
   a. Aspiration risk
   b. CT scan that shows progression
   c. Deterioration of speech
   d. Functional status

Answer: D. The palliative performance scale is the most studied prognostication tool for patients with terminal illness. It incorporates the patient's ability to perform activities of daily living (ADLs), level of consciousness, and oral intake[7] (see Table e5.1). In cohorts of patients with a terminal illness, a score of < 50% correlates with a prognosis of weeks, not months.

10. Mr. Samuels is a 46-year-old man with severe breathlessness and anxiety due to advanced chronic obstructive pulmonary disease. His vital signs are temperature, 36.8°C (98.2°F); blood pressure, 110/60 mm Hg; heart rate, 115 beats/min; respiratory rate, 34 breaths/min; oxygen saturation, 98% on room air. He is visibly anxious and reports dizziness and dyspnea. Which of the following is the best initial treatment?

a. IV fluids
b. Lorazepam
c. Morphine
d. Oxygen

Answer: C. In the absence of hypoxia, morphine has been shown to relieve the sensation of breathlessness. Benzodiazepines have not been shown to relieve breathlessness and may increase side effects.

Bioethics

Kenneth V. Iserson and Carlton E. Heine

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Bioethics

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KEY CONCEPTS

- Bioethics is a method of using values and moral principles to come to defendable decisions for ethical dilemmas. In emergency medicine, many ethical dilemmas often go unrecognized.
- Ethical dilemmas arise from conflicts between multiple good options or multiple bad options, not between good and bad choices.
- Values come from a variety of sources: community, culture, religion, and family. The values driving medical decisions should be the patient's values.
- Basic ethical principles include autonomy, beneficence, nonmaleficence, justice, and confidentiality.
- Consent requires decision-making capacity or appropriate surrogate decision makers.
- Not only religious but also family, cultural, and other values contribute to patients' medical care decisions. Without asking, it is impossible to know what decision a specific person would make.
- Patient autonomy recognizes an adult person's right to accept or to reject recommendations for medical care, even to the extent of refusing all care, if that person has appropriate decision-making capacity.

FOUNDATIONS

The medical care we provide today bears little resemblance to what was available when the first edition of this book was published. What has not advanced as far or as fast is our system for deciding, morally and fairly, what treatments should be provided. Scientific development has outpaced our social and ethical framework and often leaves clinicians struggling with moral dilemmas about the appropriateness of tests and procedures. This chapter is an introduction to our current tools for helping emergency clinicians approach ethical, rather than medical, dilemmas.

Bioethics, a subset of ethics, is the application of values and moral rules to find reasoned and defensible solutions to actual or anticipated moral dilemmas facing clinicians. The moral precepts that underpin ethical decisions are derived from a variety of sources, including individual, cultural, and community value systems. Unlike the law, which is relatively rigid and can lag years or even decades behind modern developments, particularly in the case of scientific and medical issues, bioethical constructs allow greater flexibility in decision making. Emergency clinicians are often called on to identify a patient's personal, cultural, religious, or community values and to balance these values with their own personal and professional ethos. A working knowledge of bioethics greatly enhances the emergency clinician's ability to make reasonable, ethical decisions in the limited time frame common to the practice of emergency medicine.

In contrast to professional etiquette, which relates to standards governing the relationships and interactions between providers, bioethics deals with relationships between providers and patients, providers and society, and society and patients. Issues within the realm of professional etiquette include billing, referrals, advertising, competition, conflicts of interest, professional courtesy, and employment and supervision of auxiliary personnel. These are quite different from bioethics' concerns of basic moral values and patient-centered issues. Although the two areas occasionally overlap, each relies on different standards, values, and problem-solving methods.

Ethics and Emergency Medicine

In emergency medicine, the focus is inevitably on the inherent "medical" nature of each case; therefore, it should come as no surprise that ethical dilemmas often go unrecognized. Emergency clinicians may also misperceive ethics as embodying the dictates of secular or religious law or as a discipline that describes irresolvable issues.

This chapter addresses several ethical issues in emergency medicine. What follows are brief discussions of the relation of law to bioethics; bioethical values and principles; moral imperatives in emergency medicine; ethical oaths and codes; applying bioethics to clinical situations; bioethical dilemmas in emergency medicine; a rapid decision-making model for ethical dilemmas; advance directives; the relationship between consent, decision-making capacity, and surrogate decision makers; ethical issues in resuscitation; and ethical issues in public policy.

SPECIFIC ISSUES

Bioethics and the Law

Emergency clinicians often look to the law for answers to thorny dilemmas. Yet, except in the rare cases of "black-letter law," wherein specific actions are delineated, these issues are best served by turning to bioethical reasoning and using bioethics consultations. It is said that good ethics makes good law but that good law does not necessarily make good ethics. Societal values are incorporated both within the law and within ethical principles and decisions. Laws are rules of conduct established by legislatures, administrative agencies, courts, or other governing bodies. They often vary from locale to locale and are enforceable only in the jurisdiction where they prevail. By contrast, ethics is more universal within a culture, incorporating the broad values and beliefs of correct conduct. The primary differences between law and bioethics are shown in Table e6.1.

Modern bioethics developed because the law often has remained silent or inconsistent on matters vital to the biomedical community. The rapid increase in biotechnology, the failure of both the legal system and legislatures to deal with new and pressing issues,

TABLE E6.1 Relationship Between Law and Bioethics

Bioethics	Function or Principle	Law
✓	Case based (casuistic)	✓
✓	Has existed since ancient times	✓
✓	Changes over time	✓
✓	Strives for consistency	✓
✓	Incorporates societal values	✓
✓	Basis for health care policies	✓
	Some unchangeable directives	✓
	Formal rules for process	✓
	Adversarial	✓
✓	Relies heavily on individual values	
✓	Interpretable by medical personnel	
✓	Ability to respond rapidly to changing environment	

Modified from: Iserson KV. Ethical principles—emergency medicine. In: Schears RM, Marco CA, Mattu A, eds. Emergency Medicine Clinics of North America, Philadelphia: Elsevier/Saunders; 2006.

and the increased liability crisis drove the medical community to seek answers to the difficult questions that practitioners must work through on a daily basis.

Bioethical principles are not static and may evolve as societies change. The same evolution occurs within the law. For example, elective abortion, once illegal in most United States (US) jurisdictions, is now legal in most circumstances and jurisdictions. Likewise, not all basic ethical principles have universal support, just as the values implicit in many legal changes have divided US society.

Rights and Duties

Without a duty to act, there can be no rights. Both a moral and a logical connection exist between the rights and the duties of individuals; one cannot exist in the absence of the other. In general, a duty is an action required by the rights of others, the law, a higher authority, or one's conscience. This obligation to act can be based on an individual's personal values, professional position, or other commitments. For the physician, this duty to act is a role responsibility, at least specifically as a physician and possibly always. The role-duty link occurs whenever a person occupies a distinctive place or office in a social organization to which specific duties are attached to provide for the welfare of others or to advance in some specific way the aims or purposes of the organization. In this circumstance, performance is predicated not on a guarantee of compensation but rather on a concern for another person's welfare. The emergency clinician has not only such a moral duty but, because of the Emergency Medical Treatment and Active Labor Act (EMTALA), also a legal duty.

Significant overlap can exist between legal and ethical decision making. Frequently, there is concurrence on basic issues. On occasion, clarity within the law can lead to clearer thinking in bioethics, and vice versa. Both law and bioethics, for example, use the term *rights,* as in "patients' rights" and "the right to die." This term is often used to advance an ethical argument about medical care and is frequently misunderstood or applied erroneously. A legal right is a demand that a person can make on another person, embodied by *in personam* rights, or against the state for recognition and enforcement of this demand. Most rights involved in bioethical discussions are *in rem* rights. These most often are negative rights, because they entail someone else's duty to refrain from doing something. A common source of ethical conflict is between "active rights," the right to act or not act as one chooses, and "passive rights," the right to not be acted on by others in certain ways.

Values

Values are the standards by which human behavior is judged. Values are learned, usually at an early age, through indoctrination into the birth culture, from observing behavior, and through secular (including professional) and religious education. Although many of these learned values overlap, each source often claims moral superiority over the others, whether the values are generic and cultural, legal norms, religious and philosophical traditions, or professional principles. Societal institutions incorporate and promulgate values, often attempting to solidify old values even in a changing society. In a pluralistic society, clinicians treat people with multiple and differing value systems, so they must be sensitive to alternative beliefs and traditions. This section discusses the role of religious, patient, institutional, and professional values, including professional oaths and codes specific to emergency medicine.

Society's Values

Organized religions see themselves as keepers of society's values. Even though various religions may appear dissimilar, most hold the golden rule, "Do unto others as you would have them do unto you," as a basic tenet. Problems surface in trying to apply religion-based rules to specific bioethical situations. For example, although "Do not kill" generally is accepted, the activities that constitute killing, active or passive euthanasia, or merely reasonable medical care vary with the interpretation of the world's religions as they do with the interpretations of various philosophers. As members of a democracy with significant populations practicing multiple religions, emergency clinicians should behave in a manner consistent with each patient's values. The most basic underlying question is: What is the patient's desired outcome for medical care?

Not only religious but also family, cultural, and other values contribute to patients' medical care decisions. Without asking, it is impossible to know what decision a specific person would make. An important point is that religion influences modern secular bioethics, which uses many religion-originated decision-making methods, arguments, and ideals. In addition, clinicians' personal spirituality may allow them to relate better to patients and families in crisis.

Patient Values and Ethical Decisions

A key to making bedside ethical decisions is knowing the patient's values. Many people cannot answer the question: What are your values? However, physicians can get an operational answer by asking patients what they see as their goal of medical therapy and why they want specific interventions. The responses represent concrete expressions of patient values. In patients who are too young or are deemed incompetent to express their values, it may be necessary for physicians either to make general assumptions about what a normal person would want in a specific situation or to rely on surrogate decision making. But with patients who can reason and communicate, care should be taken to discover what they hold as their own, uncoerced values.

Although each individual is entitled and perhaps even required to have a personal system of values, certain values have become generally accepted by the medical community, the courts, legislatures, and society at large. Autonomy and individual dignity, for example, are two such values; they have been considered fundamental and often are given overriding importance, especially in many Western societies. Although some groups disagree about each of these values, this dissension has not affected their application to medical care.

BOX E6.1 Commonly Accepted Societal and Bioethical Values

Autonomy: Self-determination. A person's ability to make personal decisions, including those affecting personal medical care. Autonomy is the opposite of paternalism.

Beneficence: Doing good. A duty to confer benefits. Production of benefit.

Confidentiality: The presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.

Distributive justice: Fairness in the allocation of resources and obligations. This value is the basis of and is incorporated into society-wide health care policies.

Nonmaleficence: Not doing harm, prevention of harm, and removal of harmful conditions.

Personal integrity: Adhering to one's own reasoned and defensible set of values and moral standards.

FUNDAMENTAL BIOETHICAL PRINCIPLES

Nonmaleficence and Autonomy

The basic tenet that all medical students are taught is nonmaleficence: "First, do no harm." This credo, often stated in Latin, *primum non nocere,* derives from the recognition that physicians can harm as well as help. With the physician's fallibility recognized, patient autonomy is and has been for several decades the overriding professional and societal bioethical value. Autonomy recognizes an adult person's right to accept or to reject recommendations for medical care, even to the extent of refusing all care, if that person has appropriate decision-making capacity. It is the counterweight to the medical profession's long-practiced paternalism (or parentalism), wherein the practitioner determines what is "good" for the patient, regardless of whether the patient agrees. Coupled with paternalism is coercion, the threat or use of violence to influence behavior or choice. The authority figure in a white coat combined with implied or explicit threats remains a potent force for counteracting patients' wishes. The thrust of modern bioethics is to respect patients by honoring their autonomy (Box e6.1).

Beneficence

At the patient's bedside, beneficence (doing good) and confidentiality (holding information in confidence) have been long-held and nearly universal tenets of the medical profession. Similarly, personal integrity (the adherence to one's own moral and professional standards) is basic to thinking and acting ethically.

Justice

The concept of comparative or distributive justice suggests that a society's comparable individuals and groups should share similarly in the society's benefits and burdens. Many society-wide decisions affecting thoughts and actions about the allocation of limited health care resources are based on this principle. Although it is important for physicians to be careful stewards of health care resources to maximize benefits, it is not appropriate for clinicians to limit or to terminate care on a case-by-case basis as an extrapolation of the perceived need to limit health care expenditures. Distributive justice is a social policy concept rather than a clinical model for individual physician/patient decisions.

Truth-Telling

Personal integrity involves adhering to one's own reasoned and defensible set of values and moral standards and is basic to ethical thought and action. Integrity includes a controversial value within the medical community: truth-telling. Some people think that the patient has the right to know the truth, no matter what the circumstances, and have championed absolute honesty. Yet many of these same people, when patients themselves, have been appalled by their physician's lack of sensitivity in relating unfavorable medical news. In this context, being honest does not mean being brutal; the truth is best tempered with a modicum of compassion.

Physicians accept a lack of truth-telling, depending on the circumstances. When patient harm may result from failing to disclose the truth, such as happened in the infamous Tuskegee experiments, in which treatment was knowingly withheld from Black men with syphilis, it is not only immoral but also probably illegal to withhold the information. Likewise, when failure to disclose information is strictly for the clinician's benefit, such as not telling a patient about a dismal prognosis or a medical error, the clinician's behavior suggests serious ethical and legal deficits. The issues become murkier when truth-telling, or lack thereof, involves a third party, such as a sex partner who has been exposed to an infectious disease.

Confidentiality Versus Privacy

Stemming at least from the time of Hippocrates, confidentiality is the presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission. Health care workers have an obligation (duty) to maintain patient confidentiality. On occasion, the law, especially public health statutes, may conflict with this principle, because they require physicians to report specific diseases, injuries and injury mechanisms, and deaths. The Health Insurance Portability and Accountability Act (HIPPA) of 1996, a US federal law designed to protect patient information, however, takes the principle of confidentiality to the extreme, often resulting, paradoxically, in greater difficulty in obtaining crucial information needed to treat emergency department (ED) patients.

Privacy, which is often confused with confidentiality, is the right of patients to enough physical and auditory isolation so that they cannot be seen or heard by others during interactions with medical personnel. ED overcrowding, patient and staff safety issues, and ED design limit patient privacy in many cases.

The increasing use of telemedicine to render advice and to guide procedures at remote sites also places a strain on both patient privacy and confidentiality. Suggested ethical guidelines for such practices can facilitate the use of these new technologies without sacrificing either patient rights or physician duties.[1]

MEDICAL AND MORAL IMPERATIVES IN EMERGENCY MEDICINE

Professional Values

Emergency clinicians, in both the out-of-hospital and ED environments, operate with four imperatives: (1) to save lives when possible, (2) to relieve pain and suffering, (3) to comfort patients and families, and (4) to protect staff and patients from injury. All but the last of these are common imperatives of most other clinicians as well, although saving lives may occur more often and more dramatically in emergency medicine settings.

Safety: A Unique Value

The last imperative, safety, is nearly unique to emergency medicine. In both the out-of-hospital and ED settings, clinicians often encounter dangerous situations in which the environment, the patient, a friend, or a family member poses a threat. Violence against emergency care workers is well documented and unfortunately common. The ED routinely

deals with psychotic and intoxicated patients and patients injured in human-on-human attacks, and those involved are often under extreme stress. Although most try to accommodate basic patient rights, clinicians' priority must be their own safety and the safety of their coworkers. This priority does not imply that clinicians should ignore patient safety but only that they should first ensure their own safety if they or their colleagues are at risk. When involved in or directing out-of-hospital activities, especially those related to wilderness medicine, safety and security will usually supersede most other considerations.[1]

CODIFYING PROFESSIONAL VALUES: ETHICAL OATHS AND CODES

In the abstract, bioethical principles often appear simple. However, clinicians adhere not only to basic bioethical principles but also, at least tacitly, to several professional, religious, and social organizations' ethical oaths, codes, and statements. This complexity can create a confusing array of potentially conflicting bioethical imperatives. Because bioethical principles seem to be neither universal nor universally applied, the most patient-centered principles that normally hold sway.

Organizational and Institutional Values

Institutions, including health care facilities and professional organizations, have their own value systems. Health care facilities, although relatively well standardized under the requirements of regulatory bodies and government agencies, often have specific value-related missions. Religiously oriented or affiliated institutions may be the most obvious of these, but charitable, for-profit, and academic institutions also have specific role-related values. The values of professional organizations often are set forth in their ethical codes.

Professional Codes

Through the years, the medical profession has codified its ethics more rigorously than any other professional group, incorporating many standard bioethics principles into its ethical codes and oaths. For generations, the existing part of the Hippocratic Oath set the ethical standard for the medical profession. Yet its precepts clash with modern bioethical thinking, and many subsequent professional codes have included what may best be termed *economic guidelines* and *professional etiquette,* along with ethical precepts. Emergency clinician professional values have been incorporated into organization codes, such as the American College of Emergency Physicians' (ACEP) Code of Ethics, and into a more personal oath developed by the Society for Academic Emergency Medicine.

Most modern ethical codes do not require a higher level of duty or commitment for members than the same basic moral behavior that is expected of society at large. In fact, many of the ethical issues that would seem to be important to medical specialties usually are not addressed in their codes. Even when topics of interprofessional interactions are excluded, existing medical professional codes differ markedly. All, however, try to give a "bottom line"—that is, minimally acceptable—course of action.

APPLYING BIOETHICS

Emergency Clinician/Patient Relationship

The emergency clinician has a markedly different relationship with patients from that of other health practitioners, especially those providing primary care (Table e6.2). Emergency clinicians care for patients who are unfamiliar to them and to the institution. Practitioners who either know their patients or who care for them in less acute settings often have the time and the mechanisms to make sound ethical decisions, but emergency clinicians have more limited options. A suggested method for rapid, ethical decision-making in the ED setting is outlined in Figure e6.1 and discussed in a later section.

TABLE E6.2 Relative Differences Between Emergency Practice and Primary Care Practice

Emergency Department Setting	Primary Care Setting
Patient is often brought in by ambulance, police, or family.	Patient chooses to enter medical care system.
Patient does not choose physician.	Patient chooses physician.
ED personnel should gain patient's trust.	Physicians and nurses already enjoy patient's confidence and trust.
ED personnel do not know the patient, family, or their values.	Physicians and nurses often already know the patient, family, and their values.
Patient experiences an acute change in health status.	Patient has chronic medical problems.
Anxiety, pain, alcohol, and altered mental status are common.	Anxiety, pain, alcohol, and altered mental status are less common.
Decisions are made quickly.	There is usually time for reflection and deliberation.
Physician makes decisions independently.	Physician has greater opportunity to consult with patient, family, other physicians, ethics committees, lawyers, courts, and ethicists.
Physician represents institution and medical staff.	Physician represents self or medical group.
Work environment is open and less controlled.	Work environment is private and controlled.
ED personnel frequently have a stressful work schedule.	Work schedule often is set or canceled by physician.

ED, Emergency department.
Modified from: Sanders AB. Unique aspects of ethics in emergency medicine. In: Iserson KV, Sanders AB, Mathieu D. Ethics in Emergency Medicine, ed 2. Tucson, AZ: Galen Press; 1995.

Recognizing Ethical Problems

Although physicians like to reduce all clinical situations to "medical problems," today's increasingly complex medical environment often produces problems that are inexorably intertwined with fundamental bioethical dilemmas. Some are obvious, but many are more difficult to recognize.

Prioritizing Conflicting Principles

Once such dilemmas are recognized, applying bioethical principles to clinical situations can be confusing. When two or more seemingly equivalent principles or values seem to compel different actions, a bioethical dilemma exists. This situation is often described as being "damned if you do and damned if you don't," in which any potential action appears, on first reflection, to be an option between two seemingly equivalent goods or evils. In the following real case, taken from the book *Ethics in Emergency Medicine,* the attending physician can be said to be on the horns of a dilemma (involving two prickly but seemingly equal choices): although only two options for action may be available, both options involve several conflicting bioethical principles.[2]

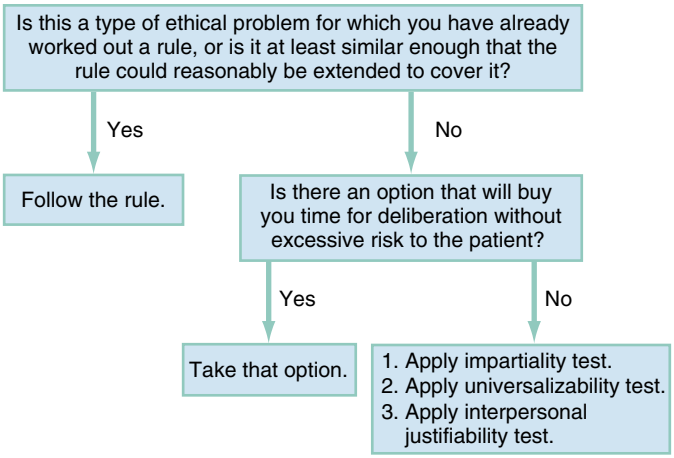

Fig. e6.1 A rapid approach to ethical problems in the emergency department (ED). (Modified from: Iserson KV. An approach to ethical problems in emergency medicine. In: Iserson KV, Sanders AB, Mathieu D. Ethics in Emergency Medicine, ed 2. Tucson, AZ: Galen Press, 1995.)

Case Example: Conflicting Bioethical Principles

A 60-year-old man stabbed himself in the abdomen because of intractable pain from terminal pancreatic cancer, unrelieved by any medical therapy. A well-meaning friend, who happened to be in the house when the event occurred, called the paramedics, who brought him to the ED. Although the man will obviously bleed to death if he is not given aggressive care, neither the patient, who is still alert and oriented, nor his wife, who is present, wants any treatment other than pain control. A review of his chart confirms that his physicians are at a loss as to how to alleviate his pain and that he is expected to die within the next several weeks. The physician believes in respecting a patient's autonomy yet usually questions patients' decision-making capacity when they attempt suicide. Such patients' actions seem to raise the question of whether they have a right or an ability to be autonomous. This physician also believes strongly in beneficence—helping those in need, relieving pain, and saving lives when possible. Beneficence suggests two alternative courses of action: palliative care or therapeutic intervention. Merely using analgesics and other comfort measures will abet a suicide; initiating medical and surgical interventions will prolong a dying process that the physician's colleagues have found to be unresponsive to even palliative treatment. Which value takes precedence: patient autonomy or beneficence? If beneficence predominates, should it be aimed toward relieving suffering, prolonging life, or a third option that could include both? Bioethics deals with problems that are neither black nor white—only gray.

MEDICAL IMPERATIVES AND BIOETHICAL DILEMMAS

Clinicians have their own ethical values, as do professional organizations and health care institutions. Conscience clauses permit clinicians to "opt out" when they believe that they have a moral conflict with professionally, institutionally, or legally required actions. These conflicts, which may have a religious, philosophical, or practical basis, pose a barrier to use of the normal ethical decision-making algorithm. When such conflicts exist, it is morally and legally acceptable, within certain constraints, for the physician to follow a course of action based on his or her own value system. The constraint generally requires that timely and adequate medical care be provided for the patient, which may be particularly difficult to achieve in emergency medicine. When conflicts over values exist, however, it is essential for the practitioner to recognize the patient's identity, dignity, and autonomy to avoid the error of blindly imposing personal values on another.

Professional Value Conflicts

The imperative to save lives causes the most conflict between emergency clinicians and other clinicians. Emergency clinicians recognize that some of the intubations and resuscitations that they perform will be unwanted by patients or surrogates. Nearly all emergency clinicians have on occasion been berated by an irate intensivist or private practitioner for resuscitating a patient "who should not have been resuscitated." Nevertheless, the lifesaving imperative begins when the ambulance is called.

One classic dilemma is that posed by the exsanguinating adult patient, awake and still with medical decision-making capacity, who explicitly refuses to accept any blood or blood products based on religious beliefs. The physician, with a professional duty and moral commitment to preserve life, does not agree with the patient's decision. Yet society (through the benchmark of court decisions) has repeatedly sided with the patient. In this case, the patient's autonomy and right to practice his or her religion are recognized as the overriding values. The case becomes less clear when the patient does not have decision-making capacity, is a minor, or appears to be under external pressure to make a life-threatening decision.

Other examples of ethical problems and conflicts in emergency medical care include uncertainty about resuscitation efforts, especially when patients and families may not want such efforts; teaching, particularly in critical situations, or using procedures performed on the newly deceased; emergency medical service (EMS) control, when administrative rules and good patient care conflict; helping others when one's own life may be placed at risk; and patient access, such as limited financial and personnel resources in the face of obvious patient need. Even if these problems do not fit into the classic form of a dilemma, they may be recognized as bioethical problems, because they require the clinician to make a choice between two (or more) accepted values.

RAPID ETHICAL DECISION-MAKING MODEL

The rapid ethical decision-making method of ethical case analysis, described in Figure e6.1, is designed as a way of avoiding an ethically incorrect course of action for the emergency clinician needing to act rapidly in the face of an ethical dilemma. A decision based on a known precedent—the first step—is the most productive way to use this method. However, such decision-making requires advanced planning, in-depth reading, and thought regarding ethical problems. Just as with the indications for any emergency procedure, emergency clinicians should at the very least be prepared with a course of action for the most common ethical dilemmas they may face in the ED.

Even the prepared clinician, however, can encounter cases without relevant known precedents. With no precedent to rely on and no way to "buy time," the practitioner should select a possible course of action and test it for ethical validity. In such instances, three tests—the impartiality test, the universalizability test, and the interpersonal justifiability test—can be used. The *impartiality test* asks whether the practitioner would accept this action if he or she were in the patient's place. In essence, this is a form of the golden rule. The *universalizability test* asks whether the practitioner would be comfortable having all practitioners perform this action in all relevantly similar circumstances. This involves generalizing the action to all colleagues and then asking whether a rule for the contemplated behavior is reasonable. The *interpersonal justifiability test* asks whether the practitioner can supply good reasons to others for the action. Will peers, superiors, or the public

be satisfied with the answers? If the answer to the question posed in each of the three tests is affirmative, the practitioner has identified a reasonable probability that the proposed action falls within the scope of ethically acceptable actions.

ADVANCE DIRECTIVES

The ethical principle of patient autonomy is the foundation for a range of documents that outline what care a patient wishes to receive if he or she is no longer able or competent to directly communicate those values. The term *advance directive* describes several types of legal and quasi-legal documents. Advance directives usually are written to avoid prolongation of an inevitable, often painful or nonsentient dying process. However, they can also be used to instruct surrogates and the patient's medical team to "do everything" whenever possible. Advance directives include the living will, durable power of attorney for health care, prehospital advance directive (Box e6.2), and mental health advance directive. Do not attempt resuscitation (DNAR), do not hospitalize, and out-of-hospital DNAR orders are not considered to be advance directives but rather are physician orders, because they are not patient or surrogate initiated. All play a role in emergency medicine.

Critically ill or injured emergency department or prehospital patients, who lack decision-making capacity, sometimes present with a nonstandard advance directive, such as a "Do Not Resuscitate" tattoo or medallion. Emergency clinicians must immediately address the question of whether to withhold treatment based on what may or may not be a legally valid patient directive. When faced with nonstandard directives, physicians can follow them, ignore them, or simply use them as an additional piece of information about the individual's wishes.[2] (Advance directives, DNR orders, and other end-of-life considerations are discussed in Chapter e5.)

CONSENT, DECISION-MAKING CAPACITY, AND SURROGATE DECISION MAKERS

Respect for patients, the basis for patient autonomy, requires that adults consent before undergoing medical interventions. To give consent, they must retain decision-making capacity. When patients cannot make their own health care decisions, others need to make such decisions for them. In such situations, three questions arise:

- What does "consent" mean in the ED?
- How can clinicians determine when patients lack such capability?
- Who then makes the decision?

Consent

Patients can provide three forms of consent: presumed, implied, and informed. Many patients may provide all three types of consent at different times during a single ED visit. Because clinicians use all three types of consent in EDs, and all are ethically and legally valid, clarifying the differences between them is in order.

The concept of *presumed consent* most commonly applies when patients are informed of what will occur and do not refuse treatment. They allow themselves to be rolled on a gurney to the radiology suite to have a urethral catheter placed, and they remain still while being sutured. The more dramatic ED scenario involving presumed consent is the arrival of moribund patients with grave, often unstable conditions

BOX E6.2 Guidelines for Development of an Out-of-Hospital Advance Directive Policy

Policy Scope

To ensure maximum coherence and compliance, a comprehensive out-of-hospital DNAR policy should be endorsed by the widest possible jurisdiction, comprising local, regional, and state agencies and the medical community, including the EMS governing body. Whenever feasible, legislative support for such a policy should be sought.

Policy Guidelines

1. Note the established fact that current basic and advanced life support interventions may not be appropriate or beneficial in certain clinical settings.
   - Develop a means to educate the public about the appropriate use of 911 after expected deaths.
   - Establish the fact that comfort care and palliative care are affirmative actions for patients with DNAR orders. These appropriate interventions, including hospice and respite care, do not require EMS activation, and often can be arranged by calling the patient's physician in anticipation of death.
   - Develop a means to educate health care workers on topics of advance directives, including information on local out-of-hospital DNARs, community hospice alternatives, and bereavement services.
2. Establish consensus on the ideal identification device for DNAR directives to ensure continuity of care across settings.
3. Reiterate that initial resuscitative attempts usually are indicated when the patient's wishes are not known.
4. Define the conditions under which an out-of-hospital DNAR order can be considered, including its use in long-term care settings and in the emergency department (ED).
5. Define which patients have the decisional capacity to agree to a DNAR order and whether surrogates can sign such orders.
6. Establish a mechanism to determine the precedence of various directives, including living will, durable power of attorney for health care, and out-of-hospital advance directive (i.e., DNAR order).
7. Develop a statutory prioritized list of surrogates to be used when there are no advance directives and the patient's decisional capacity is impaired.
8. Consider language acknowledging the growing home hospice movement as it concerns children and incorporate provisions for document use in minors.
9. Establish that the decision not to attempt resuscitation must be an informed decision made by the patient or the surrogate.
10. Identify the information that should be contained in the DNAR order and the authority that will be responsible for development of such a mechanism.
11. Identify the clinical procedures that are to be provided and those withheld in the adherence to the DNAR order or specify the authority that will verify adherence.
12. Define the exact way the DNAR order is to be followed, including the role of online medical direction. Each system should ensure that a communication path to access online medical direction is immediately available, when necessary.
13. Establish legal immunity provisions for those who implement DNAR orders in good faith.
14. Establish data collection and protocol evaluation to perform periodic operational assessments.
15. Identify permissible exceptions to compliance with DNAR out-of-hospital directives. For example:
    - The patient can revoke a written directive at any time.
    - The EMS personnel can cancel the out-of-hospital DNAR order if there are doubts about the document's validity.

DNAR, Do not attempt resuscitation; *EMS,* emergency medical service.Adapted from: Schears RM, Marco CA, Iserson KV. "Do-not-attempt-resuscitation" (DNAR) policy in the out-of-hospital setting. *Ann Emerg Med.* 2004;44:68.

for which a reasonable person would be expected to want treatment. In those cases, clinicians "presume" that rational patients would want treatment. A question that must be raised, however, is whether those patients would want interventions even in the absence of a reasonable chance for meaningful (from the patient's standpoint) survival.

Implied consent is operative when patients actively cooperate with the procedure, such as when they extend the arm for phlebotomy or lift the blouse so that leads can be placed for electrocardiography. Working under presumed or implied consent does not signify absence of patients' concern about the procedure or its complications. Rather, patients may (1) believe they know enough about the procedure to permit it or to cooperate with it without further questioning, (2) be in a condition (e.g., unconscious) in which they are unable to communicate, or (3) feel too afraid (e.g., of the clinician or hospital authority) or uncomfortable (e.g., because of a language barrier) to ask.

Informed consent assumes that a patient who has decision-making capacity (e.g., has been given all pertinent facts about the risks and benefits of a particular procedure) understands the risks and benefits and voluntarily agrees to undergo the procedure. Even if a patient with decisional capacity does not ask about a complex or potentially dangerous procedure, the clinician is obligated to provide information about the associated risks and benefits, unless the patient specifically asks not to be told. In those cases, the patient should be asked if he or she would like a relative or friend present in the ED to be told. This person need not be the patient's surrogate, but may later help explain what occurred to the patient.

Informed consent relates to both law and ethics. Respect for patients' wishes is the requirement's ethical bulwark; statute and common law provide the legal rationale. Clinicians have a professional and moral obligation to provide their patients with the information necessary to make informed decisions. Communicating honestly with patients so that they may participate in decision making is a recent rather than historical imperative. Based on respect for patients, this cooperative physician/patient relationship reverses the paternalism that, since Hippocratic times, has guided physician interactions with patients.

Virtually all states, either in statute or by common law, now require physicians to inform patients about treatment choices and the associated risks and benefits. The legal standard for the information provided is either the community standard (also known as the *professional community standard* or the *reasonable physician standard*) or the materiality standard (also known as the *reasonable* or *prudent* or *subjective patient standard*). The former asks: What would a prudent physician in the same community, with the same background, training, and experience, have disclosed to a patient in the same or similar situation? The latter asks: What would a reasonable patient in the same or similar situation need to know to make an appropriate decision?

Note that great variability exists in the legal requirements. For example, although most of the nation's EDs require informed consent for many regional anesthetic blocks, closed fracture reductions, abscess incision and drainage, lumbar punctures ("spinal taps"), injection of radiocontrast agents and radionuclides for radiography, and nonemergency thoracostomy (chest tube placement), Texas statutes eliminate any requirement to disclose the specific risks or hazards before these procedures are performed.

Decision-Making Capacity

Many ethical dilemmas in emergency medical care dissolve on ascertaining the patient's decision-making capacity, often linked with consent to (or, more commonly, refusal of) a medical procedure. A basic canon of both ethics and law, as stated by Justice Benjamin Cardozo, is that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."[3] These situations can often be clarified by an appreciation of what is meant by decision-making capacity and how it relates to consent.

Emergency clinicians must be prepared to decide quickly whether patients lack decision-making capacity. Although a lack of capacity is obvious in the unconscious or delirious patient, it often is less apparent when the patient remains verbal and at least somewhat coherent. Because such decisions in emergency situations are often time-sensitive, unlike in other medical venues, bioethics consultations may not be readily available.

In clinical practice, the word *competence* is often used to mean *capacity*. *Competence* is a legal term and can be determined only by the court. *Capacity* refers to a patient's ability to make decisions about accepting health care recommendations. Capacity is always decision-relative rather than global. Although an inebriated person can have the capacity to refuse to have a small laceration sutured, especially if there is evidence of prior refusal without remorse, the same person may not have the capacity to agree to an elective operation or to refuse to have an emergent lifesaving procedure or operation. To have adequate decision-making capacity in any circumstance, the person must understand the options, the consequences of acting on those options, and the costs and benefits of consequences in relation to a relatively stable framework of personal values and priorities (Box e6.3). Disagreement with the physician's recommendation is not in itself grounds for determination that the patient is incapable of making a decision. In fact, even refusal of lifesaving medical care may not prove the person incapable of making valid decisions if it is done based on firmly held religious beliefs, as in the case of a Jehovah's Witness patient who refuses a blood transfusion.

Surrogates

If patients lack the capacity to participate in some decisions about their care, surrogate decision makers should then become involved. In most locales, the patient's advance directive may designate surrogates, or such persons or agencies may be detailed in institutional policy or law. Surrogates often include spouses, adult children, parents (of adults), and others, including the attending physician. On occasion, bioethics committees or the courts will need to intervene to help determine the decision maker.

Children represent a special case. Persons younger than the age of majority (or unemancipated minors) are usually deemed incapable of making independent medical decisions, although they are often asked to give their assent to the decision, allowing them to "buy in" to their medical treatment plan. In many cases, in determining whether a child has decision-making capacity, the same rules as those that apply to adult capacity are used. The more serious the consequences, the more the capacity to understand the options, consequences, and values involved is required of children to make a decision.

BOX E6.3 Components of Decision-Making Capacity

- Knowledge of the options
- Awareness of consequences of each option
- Appreciation of personal costs and benefits of options in relation to relatively stable values and preferences[a]

[a]As part of the assessment for capacity, the patient should be asked about why he or she made a specific choice.

Modified from: Buchanan AE. The question of competence. In: Iserson KV, Sanders AB, Mathieu D. *Ethics in Emergency Medicine*, ed 2. Tucson, AZ: Galen Press; 1995.

In the relatively rare case in which a patient has a court-appointed guardian for health care decisions, the guardian's decisions supersede those of both the patient and any other surrogates. Even if a parent is present, it is not always clear that the adult is acting in the best interest of the child. In such cases, child protective services may need to become involved. Disagreements between parents may, in extreme cases, require the involvement of bioethics committees or the courts.

Family

Traditionally, and usually in practice, the family, in particular the spouse, acts as a surrogate decision maker when the patient does not have the capacity to make medical decisions. Yet even when there is a strong family tie, emotional or fiscal costs may sway the surrogate decision maker from certain courses of action the patient would wish to be taken.

Surrogates make decisions based on two distinct patterns: substituted judgment and best interests. *Substituted judgment* is used when there is an assumption that the surrogate knows enough about the patient's values to make a decision similar to that which the patient would make. It is not clear that anyone knows that much about a person to make decisions in every situation. Surrogates use the *best interest* standard when they do not know what the patient would want done in a particular situation, but, as in the case of Karen Ann Quinlan, in which life-prolonging measures were eventually discontinued against the wishes of some family members, they can use earlier statements and behavior to document the patient's values and then make a decision.[4] Some states may require explicit written directives for surrogates to follow. The best interest standard also applies in cases in which the patient has never had adequate decision-making capacity, as in the Saikewicz case, in which a court-appointed guardian for an elder who lacked decision-making capacity decided against treatment for leukemia after consultation with medical specialists because of a low likelihood of success in the face of debilitating side effects of treatment.[5] Unless there is already a court-appointed guardian, these situations often end up in court.

Surrogate Lists

If a patient lacks decision-making capacity and has no advance directive, many states stipulate that another person may automatically become the person's surrogate. In practice, this almost always means that the patient's spouse may act in that capacity. Some states now have a statutory surrogate list to simplify the process. The most extensive of such lists, which has worked well for more than two decades, specifies surrogates in the following order: spouse (not divorced or legally separated), a majority of the adult children who can be reasonably contacted, parents (of an adult), domestic partner, sibling, close friend, and attending physician, in consultation with a bioethics committee.

Bioethics Committees and Consultants

Multidisciplinary committees have been developed in most large hospitals to consult on cases with bioethical dilemmas and may also participate in surrogate decision making. These committees usually have three main functions. First, they coordinate education on bioethical issues involving clinical care for the committee members, hospital physicians and staff, patients, families, and the local community. Second, they help institute mandatory or suggested policies or guidelines for health care professionals regarding decision-making processes in problematic cases and resource allocation. Third, they consult prospectively and retrospectively on clinical cases and offer advice and conclusions to those directly involved, most often concerning the treatment or nontreatment of patients who lack decision-making capacity. Ethics committees usually do not act as the primary decision makers. Rather, the members serve as consultants, providing information, advising, and supporting the primary decision-making role of the patient/family/physician triad. A common consultation relates to urgent decisions about withholding, withdrawing, or continuing life-sustaining medical care. Ethics committees played a visible role in many institutions during the COVID-19 epidemic, as they sought to define Crisis Standard of Care in the event of shortages of ventilators and ICU beds. A large part of ethics committee work consists of clarifying the facts and fostering communication. In 1995, the Joint Commission (formerly the Joint Commission for the Accreditation of Healthcare Organizations [JCAHO]) began requiring hospitals to ensure that ethics committees perform their functions.

Emergency Clinicians

In the past, clinicians made unilateral decisions for their patients, regardless of whether the patients had the capacity to decide for themselves. This still occurs, of course, especially for the acute illnesses and unexpected injuries seen in EDs. If the patient's decision-making capacity is questioned in the ED, the clinician is often forced to make a decision without assistance. But when it is possible to buy time, clinicians should consult with colleagues and, if possible, the hospital's bioethics committee (see Fig. e6.1). When making unilateral decisions, clinicians should recognize that they are not omniscient. Prognoses are often incorrect and medical knowledge is finite.

Courts

The courts often act as the final adjudicators of disagreements over medical care. They appoint legal guardians and, in a few select cases, the set precedent that is followed as health law. The courts, however, usually are neither expeditious nor necessarily cognizant of bioethical principles. They are instructed only to follow the societal values codified in the law. Many courts have suggested that whenever possible, health care decisions should remain at the bedside rather than in legal chambers.

RESUSCITATION ETHICS

The most time-dependent of all activities, and arguably the best training periods in the ED, occur during resuscitations. The patients who require this care have implicitly been guaranteed that all appropriate medical knowledge and skill will be brought to bear in the attempt to save their lives. This implied promise leads to a dilemma. If the most proficient ED professional always leads the resuscitations and performs procedures, the patient will receive the maximum beneficence, as well as nonmaleficence, as expected. Yet restricting ED practice in this manner also deprives future patients of trained clinicians who could bestow the same beneficence.

This controversy has raged for many years. The appropriate balance seems to be that training in EDs can ethically proceed, as it does in other areas of medicine, if safeguards are provided in the form of onsite supervision by experienced clinicians to ascertain that the patients receive the best possible and most appropriate care. It also has been suggested that medical students and residents be certified for cognitive and procedural skills in a manner like that of other hospital physicians. This certification would enable faculty to know when trainees can perform resuscitations, as well as other medical procedures, on their own.

Rarely discussed, but a common practice in some teaching hospitals, has been the custom of allowing trainees with little skill or knowledge to learn and to practice procedures on those undergoing resuscitation only when a patient is deemed "unsalvageable." This practice does a disservice to the patient because prolongation of resuscitative attempts

solely for this purpose may lead to a clinical state that prolongs dying. It also harms the family and society by making them pay for unnecessary procedures. (It may actually be less problematic to practice and to teach once a patient is dead, because the patient cannot be harmed, and the family does not pay for these activities. See the Postmortem Teaching section later in this chapter.)

Futility

Emergency clinicians, nurses, and EMS personnel may, in some circumstances, believe that further medical interventions are "futile." Yet only three situations meet the most commonly accepted definition. The first such situation, which clinicians can identify in only a limited set of circumstances, is that in which the intervention is effective in less than 1% of identical cases, based on the medical literature. ED thoracotomy for blunt trauma is a well-documented example. Another common scenario with very low survival rates is that of the out-of-hospital cardiac arrest, either unwitnessed or in a patient who arrives from a long-term care facility. Individual clinicians should not rely on their own experiences to make such decisions, however, because they often are skewed owing to selective memory, limited numbers of similar cases, and other biases.

The second futile situation is physiologic futility, in which known anatomic or biochemical abnormalities will not permit successful medical interventions. Examples of such abnormalities generally accepted by EMS as reasons not to intervene or to provide transport to hospitals are rigor mortis (muscle contraction after death), algor mortis (lowering of body temperature after death), burns so severe that the victim is beyond recognition, and injuries incompatible with life (e.g., decapitation). These, along with prolonged normothermic resuscitative attempts without success or prolonged "downtime" with an isoelectric electrocardiogram and pulseless electrical activity, are the criteria often used to help determine whether EMS personnel can pronounce death on the scene. In these instances, EMS need not expend valuable resources in a futile resuscitative effort.

The third situation is that in which the proposed intervention will not achieve the patient's goals for medical therapy in accordance with the patient's values. Recognizing this instance, the ACEP asserts, physicians are under no ethical obligation to render treatments that they judge have no realistic likelihood of medical benefit to the patient. Because this course of action is based on knowing the patient's values related to medical treatment, it is necessary to have talked with the patient in advance (rare in the ED setting), to have received surrogate-supplied information or decisions, or to have access to the medical record. The danger is that differences in values between caregivers and patients may lead to overtreatment or undertreatment. Communication, with use of a third party, if necessary, may help resolve these issues.

The futility concept should never be used to deny care to dying patients. Even terminal patients experience medical emergencies that require intervention. The goal is to ease pain and suffering. How that is accomplished depends on the patient, the medical condition causing discomfort, and the patient's value system.

Withholding Versus Withdrawal of Treatments

In emergency medicine, a significant difference *rightfully* exists between the withholding and the withdrawal of life-sustaining medical treatment. The justification for this distinction stems, in part, from the nature of the practice of emergency medicine and the unique way emergency clinicians apply many ethical principles. Because emergency clinicians often lack vital information about their patients' identities, medical conditions, and goals for medical treatment, withholding of emergency medical treatment is more problematic than is later withdrawal of unwanted or useless interventions. Owing to the nature of emergency medicine, in both out-of-hospital and ED settings, higher standards are required to withhold medical treatment than to withdraw it.[6]

Physicians should begin or continue resuscitation of those patients who arrive at the ED without enough evidence to determine that the resuscitation effort will be unsuccessful. The only reason to *withhold* cardiopulmonary resuscitation (CPR) is the availability of clear evidence, such as a standard advance directive, that the patient did not wish to have this done or of clinical evidence that further efforts would be futile. Without such information, the presumption must be to intervene.

Once the emergency clinician obtains information confirming a patient's wish not to be resuscitated or indicating a medical condition not amenable to resuscitation, resuscitative efforts and other medical treatment may appropriately be withdrawn. This information may be obtained from an advance directive, a patient surrogate, recent documentation in the medical chart, or EMS communication detailing the failed results of the ongoing resuscitative effort. With rare exceptions, such as after failed suicide attempts, resuscitative efforts should be withdrawn when information is provided either that the patient did not want such efforts or that the patient's medical condition precludes success.

Many factors influence the potential success of resuscitative efforts, including time to CPR, time to defibrillation, cause of the arrest, presence of comorbid illness, pre-arrest clinical status, and initial arrest rhythm. No combination of these factors, however, clearly predicts the outcome.

Three special situations should be noted:

- Cardiac arrest from blunt trauma is nearly uniformly fatal, so little benefit derives from performing chest compressions for an extended period after the airway is secured.
- When health care resources are limited (e.g., during disasters), available resources (e.g., time, personnel, and equipment) should be devoted to treatment of those patients with the greatest chance of benefiting. This principle may lead to withholding or more rapid discontinuation of resuscitative efforts than is standard in normal practice.
- It is unethical to prolong resuscitative efforts to practice or to teach procedures or to complete research protocols.

Palliative Care

Although lifesaving medical interventions may not be appropriate in all cases, emergency clinicians, whenever possible, should provide patients with palliative care. Terminally ill and fatally injured patients have the right to receive state-of-the-art palliative care. Palliation often includes analgesics and may include diuretics, sedation, oxygen, paracentesis or thoracentesis, and other medications or procedures to alleviate suffering. Medical personnel should never withdraw or withhold palliative care; only treatment should be withheld when it is appropriate. Although medical practitioners, surrogate decision makers, and sometimes patients find it emotionally easier to forgo new interventions than to withdraw ongoing treatment, no orders, policies, or directives should ever prevent emergency clinicians from alleviating discomfort.

The purpose of palliative interventions is not to prolong the dying process but rather, when death is inevitable, to make it as comfortable as possible for the patient. As patient advocates, emergency clinicians may need to "push" to have the patient admitted to a hospital, hospice, or nursing home or to get ancillary personnel (e.g., social workers, home health nurses) to intervene for the patient.

Notifying Survivors

Death, especially when it is sudden and unexpected, shocks and devastates family and friends. For them, it is a life-changing event, with every nuance burned into their memories. Moreover, although they may not consciously acknowledge it, such losses may deeply affect ED personnel, despite their almost constant exposure to life's disasters. This makes death notifications and dealing with the survivors both vitally important and extremely difficult. Emergency clinicians, who deal with sudden death on a regular basis, can gain considerable knowledge of and to hone their skills in how to care for the survivors, their newest patients.

Even though notification of survivors of a sudden and unexpected death is one of the most difficult parts of the job for emergency clinicians, they and other professionals whose job includes delivery of such news are rarely taught the skills necessary to perform this task. Notification of survivors is emotionally draining; 70% of emergency clinicians find death notifications to be personally difficult. Perhaps this is because only half received any type of death-notification education in medical school, and only one-third received any such training during residency.

On occasion, physicians give the job of death notification to residents, medical students, or nurses. Although all three groups should be present to learn the techniques involved, to have an opportunity to hear what is said, and to observe an attending physician showing sensitivity, they should not be left to do death notifications on their own. That is a form of professional abandonment and, in a teaching hospital, the worst form of student abuse.

Viewing Resuscitations

Traditionally, survivors have not been permitted to view resuscitation attempts. That attitude, however, is gradually giving way to a more enlightened view based, in part, on recognition that families gain enormous psychosocial benefits from being present during the resuscitation of loved ones.

The argument against allowing survivor onlookers has been that resuscitations often involve large teams, unclear communications, and team leaders who are unwilling or unable to make firm, timely, and rational decisions. Having family members present, the argument goes, introduces the possibility of an onlooker fainting or otherwise becoming another patient. Survivors frequently misinterpret the team's discussions or actions, and team members may feel uncomfortable having family members judge their actions.

Yet studies in both the US and Britain have shown that nearly all survivors who witnessed ED resuscitative efforts found the experience helpful. Seventy-six percent of survivors responded that their grieving was facilitated by having witnessed the resuscitation, and 64% thought that their presence was helpful to their dying family member. Psychological tests of survivors who witnessed resuscitation attempts, performed at 3 and 9 months after the event, showed that this group experienced fewer episodes of "intrusive imagery," such as flashbacks of the events leading to the death, compared with survivors not present at the resuscitation (relatives in the control group). They also had lower levels of anxiety, depression, posttraumatic avoidance behavior, and grief.

The American Heart Association (AHA) now endorses giving family members the opportunity to be present so long as the patient has not previously objected. This position stems from the benefits families can derive from their presence during resuscitation attempts, the lack of harmful effects on them from viewing these resuscitations, and their quasi-right to be there based on the nature of their relationship to the patient.

The presence of these survivors does not hinder the resuscitative efforts and often leads to quieter, more effective team efforts. Experience has shown that survivors who witness ED resuscitative attempts never question whether the team "tried hard enough," do not ask whether the person is *really* dead, and spend less time in the ED trying to come to terms with the death. In addition, survivors may thank the ED team for their efforts, a situation that rarely occurs under other circumstances, and the ED staff never has to "notify" survivors of the death.

The general procedure is as follows:

- Ask survivors if they want to view resuscitative efforts.
- If they do, give them a quick briefing about what they will see, and have a knowledgeable staff member, usually a chaplain, social worker, or ED nurse who can answer their questions, accompany them.
- Provide a chair for elders and allow survivors to leave and to reenter as they wish.
- Staff should attempt to cover as much of the patient as is compatible with effective resuscitative efforts.
- Team members should be advised that family is in the room.
- The survivors should be encouraged to talk to and touch the patient.
- Decisions to pronounce the patient dead, although often discussed with the family, generally are communicated in the format of advising them that "we must stop now." They should never be asked whether to stop the resuscitative effort; this is a medical decision.
- If the family is present when it is clear that resuscitative efforts should cease, the situation should be explained to the family before supportive measures are discontinued. This provides them with a chance to "say goodbye" before death is pronounced. Dedicated pediatric EDs and pediatric resuscitation units in general EDs have adopted these procedures more often than others.

Postmortem Teaching

A less commonly discussed aspect of emergency medicine education programs is the use of recently deceased patients to teach or to practice emergency procedural techniques, such as intubations and central line placement. Although whether this practice is ethical is a matter of controversy, a reasonable argument might be that if medical treatment could not save the patient, then the emergency clinician's responsibility is to hone skills for the next patient in need of expertise in resuscitative techniques. This is not to condone the desecration of a body. Rather, it suggests that because clinicians learned the techniques used during the attempted resuscitation on other dead or living patients, this (now dead) patient owes the next patient the same courtesy. No one would advocate practicing unneeded procedures on living patients, and many people argue against experimental use of animals. The religious or ethical beliefs of some ED personnel may make practicing or teaching of these procedures in such circumstances problematic.

Resuscitation Research

Physicians in a new and advancing specialty have an obligation to use research to advance the knowledge base from which they practice. In the United States, federally mandated institutional review boards (IRBs) must approve any research involving human subjects, including research in EDs and, possibly, in prehospital care. Increasingly, research ethics committees are being used to approve human subject research throughout the world. The IRBs try to guarantee that patients are asked to participate in research review and sign an adequate informed consent document. Yet, even if the patient is conscious, it is unclear whether truly free and informed consent can be given during a medical emergency. In both trauma and cardiac resuscitation

research, informed consent is, of course, not feasible. It is usually difficult, if not impossible, to obtain retrospective patient or, if appropriate, prospective surrogate consent. So as not to deny critically ill and injured patients the opportunity to participate in possibly beneficial research trials, the US Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) issued regulations, which became effective in 1996, that allow "emergency research" without informed consent. These regulations contain extensive patient safeguards, including community consultation, public disclosure, and intensive oversight. Some have questioned whether they are too restrictive, particularly when applied to non-"life-threatening" situations in which there may be more than "minimal risk."[7]

The ethical and legal basis for these regulations is presumed consent: If the research is not harmful, and especially if it is potentially helpful, most "reasonable" patients would acquiesce to the research, given the basic values of good and evil (see Box e6.1). As routinely occurs in emergency medicine practice, persons suffering unexpected adverse events with a high probability of rapid death or serious morbidity generally demand that the physician deliver acute care interventions—immediately and without discourse. If there is a chance that the patient could benefit from a therapeutic course of action in such circumstances, most people would demand that it be used. Similar logic applies with acute care research, especially when accepted or standard therapy is futile and possibly when the investigators believe that equipoise (therapeutic equality) exists between the two tested forms of therapy. Protection for the patient in these cases rests with IRBs, which, among other considerations, must guard against the possibility of organ-specific success but failure to benefit the entire person, such as producing a patient in a persistent vegetative state after "successful" CPR.

Beyond IRB authorization for research is a moral responsibility for the individual researcher to ensure that the research protocol and its execution are ethical. This responsibility extends to the journals in which the research is published. Emergency medicine has an excellent record of ethical research, although a large percentage of human research studies published in the major emergency medicine journals fail to mention either IRB review or informed consent.

PUBLIC POLICY AND BIOETHICS

Restricted Access to Emergency Medical Care

Society has acknowledged its moral obligation to ensure that everyone has reasonable access to adequate health care. People's need for health care is unequally distributed and highly unpredictable. Few could afford this care if left to their own devices, so mechanisms are in place to share the risk.

The ethical dilemma for emergency clinicians comes in basically two forms: one precipitated by the institution in which the ED is housed and one by outside third-party payers. Some institutions have refused care to patients coming to the ED, sending some away for clinic appointments at a later time. Institutions also have pressured emergency clinicians to limit treatment, ancillary tests, or hospital admission for patients without the ability to pay. Although such limitation may seem patently immoral, another question should be asked: Is there a moral obligation to the community to keep the health care institution financially viable? Hospitals have closed their doors because of financial losses, and many hospitals, especially in inner-city areas, are on the verge of bankruptcy.

Some prepaid health maintenance organizations (HMOs) use "gatekeepers" to keep patients in need of emergency medical care away from immediate assistance at institutions other than the HMO parent hospital. Moreover, the HMO's income may depend on *not* hospitalizing patients, *not* using ancillary tests, and *not* permitting ED visits. Nevertheless, it is prudent and ethical for emergency clinicians to err on the side of providing for the patient's needs.

Morality of Triage Decisions

In the aftermath of a massive natural or human-made disaster, triage officers face difficult decisions about who will receive scarce lifesaving treatment and who will be left to die without treatment. Even in "routine" ED triage, decisions about who should receive treatment priority and who can wait for treatment may, at least occasionally, have life-and-death consequences.

Triage provides a method to distribute health care resources when patient needs exceed available resources. Triage operates along a continuum of decreasing resources, social order, and the resource-to-patient ratio. Arrival patterns, triage methods, and the applicable ethical basis for triage vary along this continuum.

Most triage systems are designed to serve the values of human life, human health, efficient use of resources, and fairness. Nevertheless, because of the variety of specific triage settings and goals, no single "correct" way to perform or to justify triage can be identified. Routine triage in the relatively resource-rich setting of the modern hospital ED, for example, focuses appropriately on maximizing benefits for each individual patient, giving treatment priority to patients whose needs are most urgent. In triage after a massive disaster, when not all individual needs for lifesaving care can be met, the focus may shift from an individual to a group perspective, and triage officers may seek to save as many lives as possible with the limited resources at their disposal. In special circumstances (e.g., times of war), military commanders may direct that triage systems devote scarce medical resources to achieve a nonmedical goal, namely, military victory. In situations of complete devastation, the lack of social order and minimal resources may make triage impossible.

Whether the choice of a triage system is justifiable depends on an evaluation of the specific system itself, its underlying values and principles, and the setting in which it is applied.

Physician Response to Risky Situations

Over the millennia, personal values have dictated whether a physician would remain with his or her patients during extreme or catastrophic circumstances. Physicians, even legends of medicine such as Galen, often fled to save their own lives. In the era of modern epidemics of unknown virulence and etiology, and the increasing frequency of natural disasters such as wildfires or earthquakes, it remains a personal moral decision, especially for emergency clinicians who are on the frontline of these medical assaults.

How will physicians respond when a catastrophe involving personal risk strikes? The moral backbone of medical professionals may be tested as health care providers weigh multiple factors to determine whether to stay and carry out their professional roles and duty to put the needs of their patients first, or to step back and decrease their personal risk.

With incomplete information, providers may make decisions based on heated emotions and panic rather than an accurate perception of risk. The decision to stay or to leave will ultimately depend on the individual practitioner's risk assessment and value system. Professional ethical statements about expected conduct establish important professional standards and norms, but each practitioner will interpret and apply them on the basis of his or her own situation and values. Recent historical precedent suggests that many physicians and other health care providers will dutifully care for the sick and needy, even at great risk to themselves. Although some emergency clinicians have worked in dangerous situations, most have not; nothing in day-to-day emergency medicine practice prepares emergency clinicians for the great

opportunities and challenges that accompany a pandemic. Emergency clinicians can, however, reflect on their professional and personal responsibilities in crisis situations, and public and private institutions can create plans for effective communication and care when a disaster strikes. If this can be achieved before the next pandemic or disaster that includes personal risk to clinicians, emergency clinicians—who are inevitably among those at highest risk—can be encouraged to "stay and fight."

Despite the language in numerous medical ethics codes, nothing, either morally or legally, requires a specific physician response to risk-prone situations from civilian clinicians; it remains a personal decision. The decision to remain in or to leave a risky health care situation will ultimately depend on the provider's own risk assessment and value system.[8]

"Proactive Ethics": How Can Emergency Clinicians Change the Rules?

In every medical system, practitioners find that they repeatedly face identical ethical dilemmas. The normal outcome is an incomplete and often unsatisfactory decision made by administrators, lawyers, bioethics committees, or others. "Proactive ethics" involves changing the rules under which we operate. Easier done in some settings than in others, the process requires that all "stakeholders," those with a vested interest in an equitable solution, first come to the table and reach a compromise. Such groups often will include physicians, nurses, EMS personnel, lawyers, religious authorities, and representatives of affected groups (e.g., an organization of elders in the case of issues involving the aged). Armed with this agreement or even sample legislation that they can present to politicians, it becomes easier to change laws or administrative rules to address recurrent ethical dilemmas. One such process led to a landmark out-of-hospital advance directive law, which markedly lessened unwanted EMS resuscitation attempts. It also led to an extensive statutory surrogate list and a simplified set of advance directives. Subsequently, physicians also spearheaded the similar, but less effective, Physician Orders for Life-Sustaining Treatment. Proactive ethics lies in the role of public policy—an arena in which emergency clinicians are well suited to play a pivotal role.

Audiovisual Recordings and Social Media Use

As the technology becomes more available to record and post online the activities of emergency department patients and staff, the ethical principles of privacy and confidentiality assume increasing importance. Emergency physicians commonly use social media for both personal and professional purposes. Perhaps due to the high prevalence of formal training about the professional use of social media, they generally seem to be aware of the negative aspects of posting inappropriate patient images and descriptions. Yet younger physicians seem to be less aware of the negative effects that posting personal information about their unprofessional activities can have on their medical license and hospital privileges.[9]

With proper protections, audiovisual recording in emergency departments can provide significant value to clinicians and patients. Recordings can help patients understand and recall vital parts of their ED experience and discharge instructions, add important visual data to the electronic medical record, and help to diagnose difficult cases in real time by crowdsourcing the information with many other physicians.

Health care institutions should provide HIPAA-compliant methods to securely store and transmit health care-sensitive recordings and establish protocols. Protocols should include both consent procedures their staff can use to record and distribute (print or electronic) audiovisual images and appropriate disciplinary measures for staff who violate them. Clinicians imaging patients in international settings should be guided by the same ethical norms as they are at their home institution."[10]

The most basic ethical guideline, responding to the need to preserve confidentiality and privacy, is to provide informed consent to patients or their surrogates, being sensitive to the patient-physician power differential. Importantly, any use of these images on social media must go beyond what is legal and avoid what has been termed "medutainment," providing images that nonprofessionals might see as prurient.[11]

A Global Perspective

Emergency clinicians ever more frequently respond to acute and chronic "humanitarian catastrophes," those conflicts and calamities generating both widespread human suffering and destructive events. While struggling to provide care in these difficult situations and sometimes to do simultaneous research, health care workers must also apply standard bioethical concepts with sensitivity to local mores. The ethics of providing health care in resource-challenged environments is a complex and confusing topic. It implies three related questions: What can we do with the resources on hand? Of all the things we can do, which ones should we do? How do we define standard of care? Resource-poor settings encompass multiple environments, cultures, scenarios, actors, and types of intervention.

Basic ethical principles apply in every culture within the context of their patient and community values. Cultural sensitivity suggests that ethical issues need to be approached with an awareness of local mores. Most commonly, these issues include the release of medical information; a patient or family's refusal of treatment; the determination of futility for patients with terminal conditions; and involvement with group, elder, or family decision-makers.[12]

Among the bioethical principles that directly apply to this work is that the humanitarian imperative comes first, meaning that action should be taken to prevent or alleviate human suffering arising out of disaster or conflict, and that nothing should override this principle. In addition, assistance is given regardless of the race, creed, or nationality of the recipients and without adverse distinction of any kind, with priorities based on need alone. This includes neither using offers of help to further government policy nor promoting political or religious views. Finally, physicians should be accountable, not only to the organizations with whom they work, but also to the local populations who they are there to help.[13,14]

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CHAPTER E6: QUESTIONS AND ANSWERS

1. Which of the following statements regarding patient confidentiality is FALSE?
- **a.** It describes the patient's right to enough physical and auditory isolation so that they cannot be seen or heard by others during interactions with medical personnel.
- **b.** It imposes a duty on health care workers.
- **c.** It may conflict with the law, especially public health statutes.
- **d.** It presumes that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.

Answer: A. Although isolation of patients for confidentiality is a good goal, the limited space and hectic nature of an ED would sometimes prevent timely and quality care.

2. Which of the following can emergency clinicians always rely on for appropriate guidance when faced with ethical dilemmas?
- **a.** State laws and medical board policies
- **b.** The American College of Emergency Physicians' (ACEP) Code of Ethics
- **c.** The Hippocratic Oath
- **d.** None of the above

Answer: D. All these examples are great for guidance on ethical dilemmas, but none of them can "always" have guidance for every situation that can occur.

3. To have adequate decision-making capacity in any circumstance, a person must understand all of the following EXCEPT:
- **a.** The available options.
- **b.** The consequences of acting on those options.
- **c.** The costs and benefits of consequences in relation to a relatively stable framework of personal values and priorities.
- **d.** The court's decision about their competency.

Answer: D. To be deemed competent an individual must understand A, B, and C. Answer D is a legal issue and is not required for competency.

4. Which of the following statements regarding the withholding of treatment in the ED is TRUE?
- **a.** It legally differs from withdrawing treatment.
- **b.** It morally differs from withdrawing treatment.
- **c.** It requires clinical information that is often unavailable immediately.
- **d.** It should never be done.

Answer: C. In an emergency not all relevant information is available at the time important decisions must be made.

5. When using the "rapid approach to ethical problems in the emergency department (ED)" to decide on a course of action:
- **a.** Always consult with the bioethics committee/consultant before acting.
- **b.** Assume that each ethical problem in the ED requires a unique solution.
- **c.** Test your chosen action against your religious values.
- **d.** When practicable and safe for the patient, buy time to consult on possible options.

Answer: D. Ethical problems can often take some time to work out, but a rapid approach rarely has enough time for a formal ethics consult. Buying some time so a reasonable solution can be derived is often the best that can be done.

e7

Emergency Medical Treatment and Labor Act and Medicolegal Issues

Robert A. Bitterman

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Emergency Medical Treatment and Labor Act and Medicolegal Issues

Robert A. Bitterman

KEY CONCEPTS

- The Emergency Medical Treatment and Labor Act (EMTALA) governs virtually every aspect of hospital-based emergency services.
  - Centers for Medicare and Medicaid Services (CMS) deems anyone on hospital property to have "come to the emergency department." Hospital property consists of the entire main hospital campus, including parking lots, sidewalks, and driveways, and any ambulance owned and operated by the hospital, even if the ambulance is not on hospital grounds.
  - Any person who comes to an ED requesting examination or treatment for a medical condition must be provided with an appropriate medical screening examination (MSE). The purpose of the MSE is to determine whether the patient has an emergency medical condition (EMC).
  - Presentation to the ED or on hospital property is not sufficient to trigger the hospital's duty to provide an MSE; a request for examination or treatment of a medical condition is also necessary. The request can be made by the patient or by anyone on behalf of the patient (e.g., EMS personnel, a police officer, or a babysitter, family member, or legal guardian).
  - CMS regulations require that the screening examination be done by "qualified medical personnel." Typically, the designation applies to physicians or advanced practice providers (nurse practitioners [NPs] or physician assistants [PAs]).
  - An appropriate MSE must be reasonably calculated to identify critical medical conditions and must be uniformly provided to all patients who present with substantially similar complaints.
  - Hospitals need to have a policy and practice for left-without-being-seen (LWBS) patients that adequately documents pertinent findings and protects the hospital from liability.
  - Medicare-participating hospitals that have specialized capabilities or facilities are required by EMTALA to accept appropriate transfers of patients who require such capabilities or facilities if the hospital has the capacity to treat the patient.
  - Once a hospital admits the patient in good faith as an inpatient for further treatment, the hospital's obligation under EMTALA ends.
- Emergency Consent for Procedures
  - The emergency clinician who proposes to undertake the procedure must be the one to obtain the patient's informed consent. The duty to obtain consent cannot be delegated.
  - Whenever emergency clinicians are in doubt about the legality of a situation related to consent, they should do and document what they believe to be in the patient's best interest. Delaying treatment in an emergency to obtain informed consent is a much more serious and common medicolegal problem than failure to obtain proper informed consent.
  - Consent for minors in the ED is a nonissue. Consent is a creature of state law; EMTALA preempts state law, and it requires the ED to provide an MSE and stabilizing treatment to all minors presenting to the ED.
  - A parent's right to freedom of religion (e.g., Jehovah's Witness) does not include the right to deny life-sustaining medical intervention for that person's children.
- Leave Against Medical Advice
  - Emergency clinicians should be cautious when patients the demonstrate intention to leave the ED against medical advice. The capacity to make reasonable medical decisions can easily be affected by alcohol, drugs, pain, or any number of medical conditions. Careful evaluation and documentation of the patient's decision-making capacity supports the decision to allow the patient to leave or to retain the patient against their will. The courts (and public opinion) tend to support clinicians who act in the best interests of the health and safety of their patients.

PRINCIPLES

Federal and state laws tightly control the practice of emergency medicine. The magnitude and complexity of the governing legal authority plus the significant penalties for noncompliance, such as criminal sanctions, civil lawsuits, civil monetary penalties, and exclusion from participation in Medicare and Medicaid, oblige emergency clinicians to have functional knowledge of these laws.

Federal law—the Emergency Medical Treatment and Labor Act (EMTALA)—governs how emergency clinicians must triage, register, examine, treat or stabilize, discharge or transfer, use hospital resources, and involve on-call medical staff expertise when caring for patients presenting to the emergency department (ED).[1] State laws further control the practice of emergency medicine through such issues as consent, reporting requirements, confidentiality requirements, forensic and police matters, civil commitments, and emergency medical service (EMS) statutes (Box e7.1).

SPECIFIC ISSUES—EMERGENCY MEDICAL TREATMENT AND LABOR ACT

EMTALA originally was enacted to prevent private hospitals from refusing to treat indigent patients with medical emergencies or transferring ("dumping") them in an unstable condition to public hospitals. Subsequent amendments to the law, government regulations, and court decisions greatly expanded the reach of EMTALA, such that the law now sets national standards for screening, stabilizing, and discharging or transferring ED patients.

Medical Screening Examination

Any person who comes to an ED requesting examination or treatment for a medical condition must be provided with an appropriate medical screening examination (MSE), regardless of immigration status, insurance status, or ability to pay.[1,2,3] The purpose of the MSE is to determine

BOX E7.1 Elements Hospitals and Emergency Clinicians Must Address to Ensure EMTALA Compliance

- Adopt (and enforce), and educate all appropriate staff on a hospital-wide EMTALA policy, as well as emergency department (ED)–specific policies.
- Define the hospital's standard ED medical screening examination (MSE) process, including identifying "dedicated emergency departments" and designated "qualified medical personnel" to perform the MSE, as defined by the government.
  - Establish the hospital's patient stabilization procedures and documentation.
  - Do not delay access to the MSE, stabilizing care, on-call physicians, or transfer on account of or to inquire about the patient's insurance status (EMTALA's "no-delay" provision).
  - Address the ED/outpatient registration procedures and payment collection systems.
  - Implement processes and procedures regarding patient refusal of the MSE, stabilizing treatment, or transfer.
  - Post required signs in areas used for MSEs, including the ED, labor and delivery, and psychiatric intake centers
- Implement an effective ED physician on-call system, with written duties and responsibilities.
- Create a process for receiving patient transfers and for transferring patients to other facilities.
  - Create a uniform system and "transfer packet" for transferring patients out of the hospital.
  - Create a system for accepting or rejecting patient transfers from other facilities.
  - Institute appropriate documentation requirements for ED medical records, a "central log" for patients presenting to the hospital, transfers, and on-call lists.
- Monitor and quality assurance review the hospital's EMTALA compliance.
- Draft a policy and procedure to report suspected EMTALA violations to the Centers for Medicare and Medicaid Services (CMS).
- Review the potential application of EMTALA to the hospital's outlying facilities, such as urgent care centers or ambulance/helicopter EMS services.
- Review disaster plans and public health emergency responses for EMTALA issues.
- Draft and use legally approved EMTALA forms to achieve/document compliance.

whether the patient has an emergency medical condition (EMC).[1] Mere presence in the ED or on hospital property does not trigger the hospital's duty to provide an MSE; a request for examination or treatment of a medical condition is also necessary. The request can be made by the patient or by anyone on behalf of the patient.[1,2,3] If a person is unable to speak to request care, hospital personnel may infer a request if the behavior suggests a need for examination or treatment.[2,3]

The Centers for Medicare and Medicaid Services (CMS) deems anyone on hospital property to have "come to the emergency department."[2,3] Hospital property consists of the entire main hospital campus, including parking lots, sidewalks, and driveways, and any ambulance owned and operated by the hospital, even if the ambulance is not on hospital grounds.[2] CMS then divides hospital property into dedicated EDs and all other property. A dedicated ED is a place that is held out to the public as providing unscheduled care for persons with EMCs, including typical hospital EDs, labor and delivery units, and psychiatric intake centers.[2,3] Urgent care centers generally do not have to comply with EMTALA.

CMS exempts on-campus areas that typically do not provide emergency care, such as physicians' offices, skilled nursing facilities, and nonmedical facilities, and off-campus ambulatory facilities such as medical office buildings and dialysis centers.[2]

Presentations to the hospital's dedicated ED require only a request for examination or treatment of a medical condition, whether or not an emergency medical condition is present. Presentations to non-ED parts of hospital property, however, require the request to be for an emergency condition before EMTALA applies.[2-4]

Emergency Medical Condition

EMTALA defines an EMC as acute symptoms of sufficient severity (including severe pain) such that the absence of immediate medical attention could reasonably be expected to result in (1) placing the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) in serious jeopardy, (2) serious impairment to bodily functions, or (3) serious dysfunction of any bodily organ or part.[1] In the case of a pregnant woman who is having contractions, an EMC is defined as one in which there is inadequate time to effect a safe transfer to another hospital before delivery, or that transfer may pose a threat to the health or safety of the woman or the unborn child.[1]

If the MSE does not reveal an EMC, further care of that patient is not controlled by EMTALA, so the law's provisions governing stabilizing treatment, transfer of the patient, or involvement of on-call physicians cease to apply.[1,2,3] ED managers should ensure that there is a process in place for documentation of the completion of the MSE on every ED medical record including the presence or absence of an EMC.

Patients Brought by Emergency Medical Services to the Emergency Department

CMS deems a hospital's EMTALA obligation to begin the moment the patient "comes to the ED" and a request is made on behalf of the patient for examination or treatment of a medical condition, not when the hospital "accepts" the patient.[3] Sometimes, such as when there is an influx of multiple trauma victims, it is reasonable for the hospital to ask the EMS provider to stay with the patient until such time as ED staff becomes available to care for that person. However, CMS requires that "even if a hospital cannot immediately provide an MSE, it must still triage the individual's condition immediately upon arrival to ensure that an emergent intervention is not required and that the EMS provider staff can appropriately monitor the individual's condition."[3]

National Emergencies or Disasters

The Secretary of Health and Human Services can exempt hospitals from EMTALA during times of national or local disasters or terrorist acts, bioterrorist events, or pandemic infectious disease.[2,3] EMTALA still applies to individuals potentially exposed to Ebola virus, COVID-19, or other highly contagious diseases who present to the hospital's ED.[5]

Sexual Assault Cases

A person coming to the ED solely for the collection of evidence for a criminal investigation is not requesting examination or treatment for a medical condition, so no MSE is required. However, if the person complains of pain or injury or wants pregnancy or sexually transmitted disease prophylaxis, that person is requesting examination or treatment for a medical condition and must be provided with an MSE.[1-3]

Police-Requested Blood Alcohol Tests

When a police officer brings a patient to the ED requesting a blood alcohol test, an MSE should be performed to determine if a potentially

serious cause of abnormal mental status exists and normal patient consent provisions apply.[3] A patient who is deemed capable of decision making may refuse the MSE and request that only the blood be drawn. The refusal of the MSE is documented, along with the patient's decision-making ability, as for any other refusal of treatment or evaluation. If the patient is too intoxicated to make medical decisions, release from the ED should be delayed until the patient is capable of rational decision making. A physician or advanced practice provider should assess and document a patient's competence.

Health Care Providers Qualified to Perform the Medical Screening Examination

CMS regulations require that the screening examination be done by "qualified medical personnel" and that the hospital's governing body formally designate, in writing, who is a qualified person to perform medical screening on behalf of the hospital.[2] Typically, physicians and nurse practitioners (NPs) or "physician assistants (PAs) working independently or under the direction of an emergency physician" are designated as such. Triage by a nurse does not constitute an MSE, even for obvious nonemergent conditions.[2,3]

Ancillary Services as Part of the Medical Screening Examination

The law requires hospitals to provide the screening examination "within the capabilities of the hospital's emergency department, including ancillary services routinely available to the ED."[1] Accordingly, the scope of an MSE may range from a brief history and physical examination to an extensive evaluation including advanced imaging or procedures, such as a lumbar puncture. For example, if it takes a complete neurologic examination, CT scan, or lumbar puncture to decide whether a headache patient has a subarachnoid hemorrhage, then those procedures are considered part of the MSE. The hospital is obligated to use only the resources, such as ED ultrasound, ordinarily available to its ED.[1] This includes consultation, such as with an on-call surgeon, when needed to determine whether an EMC is present. If a rural hospital only has mobile magnetic resonance imaging (MRI) capability once per week, it is not required to provide MRI services the other 6 days per week to the ED.

Policies, Procedures, and Practice Guidelines

Each hospital determines its own standard screening policies and procedures. Hospital standards are individualized depending on ED and ancillary capabilities. A hospital satisfies the requirements of EMTALA if it conducts standard screening procedures, uniformly, for all patients with similar complaints and circumstances.[6]

Once hospitals define their own standard screening process, they will be held to that standard. For example, if a hospital's screening policy states that all patients will be triaged within 10 minutes, any triage carried out at 15 or 20 minutes after arrival constitutes a violation of the law because the hospital did not follow its own policy.

Registration Process, Collections or Insurance Information, and Authorization

CMS allows hospitals to conduct reasonable registration procedures in the ED, including collection of insurance data at the time of registration, as long as the process does not delay the MSE.[3,7] A reasonable registration process may obtain demographic data and the name of the patient's physician and determine whether the patient is insured and the type of insurance. During the registration process, the patient can sign the hospital's usual "informed consent to be examined" form and a routine form that holds the patient financially accountable for any charges not covered by the patient's insurance carrier.[7] Delaying a necessary examination because the registration clerks are collecting insurance information probably is a violation.

Hospitals are not permitted to use unreasonable registration processes to coerce patients into leaving before they receive their federally guaranteed MSE.[3,7] Collection of co-payments, down payments, advanced beneficiary notifications, or signatures on managed care financial forms are prohibited until after the MSE is completed and stabilizing treatment has been initiated. Hospitals should also ensure that staff behavior does not create a hostile environment or constructive denial of the MSE.

CMS explicitly bans prior authorization for managed care plans before completion of the MSE and commencement of stabilizing treatment.[7] Hospitals may obtain authorization for payment from insurance entities only concurrently with stabilization of the patient.[3,7]

Regardless of insurance or social status, all patients should be processed in the same manner. In addition, the triage team, emergency clinician and nursing staff, and all clinical personnel should be blinded to the patient's insurance status throughout the initial screening and stabilizing care. This removes insurance status as an issue should there later be a claim that the staff was motivated in some way by financial class. After the MSE and initiation of stabilizing treatment, insurance status and ability to pay can be considered in determining the patient's future care, such as hospital admission, transfer, or discharge and follow-up.

Central Log

Hospitals must maintain a central log of all patients presenting to the ED requesting examination or treatment. The log must contain the name and disposition of the patient, including whether the patient refused treatment, whether the hospital refused to provide an MSE or treatment, and whether the patient was treated and stabilized, admitted, transferred, or discharged.[8] The purpose of the log is to permit CMS and state surveyors to select and review individual records to investigate whether the hospital is in compliance with the law.[3,8]

The log must include all persons presenting to the ED, ambulatory care or fast-track areas contained within the ED, freestanding emergency centers, labor and delivery suites, and psychiatric intake centers. The logs are not required to be collated into a single document but must be retrievable at CMS's request.

Medical Record

All areas of the hospital used to conduct the MSE must create a medical record with appropriate documentation for the patient's presentation and evaluation.[3,8] If members of the hospital medical staff see their patients in the ED, on either a scheduled or an unscheduled basis, the hospital must create a medical record and require the physician to document the care provided in that record. The physician's private office records documenting care provided at the hospital are insufficient.

Stabilization Requirements

The screening section of EMTALA mandates the hospital to provide only those services within the capability of the ED, including ancillary services routinely available to that department.[1] The stabilization section, however, requires the level of services within the capabilities of staff and facilities available at the hospital.[1]

Two elements must be present to trigger EMTALA's stabilization requirement: (1) the patient must have an EMC, as defined by law, and (2) the hospital must determine that an EMC exists. That an EMC exists is not sufficient to invoke the duty to stabilize; the hospital also must have actual knowledge that the EMC exists. *Actual knowledge* is a legal term that means the examining emergency clinician subjectively determined that an EMC existed. Whether the physician's judgment

PHYSICIAN

Emergency Medical Condition (EMC) Identified: (*Mark appropriate box(s), then go to Section II*)

I. MEDICAL CONDITION: Diagnosis_____

☐ **No Emergency Medical Condition Identified:** This patient has been examined and an EMC has not been identified

☐ **Patient Stable -** The patient has been examined and any medical condition stabilized such that, within reasonable clinical confidence, no material deterioration of this patient's condition is likely to result from or occur during transfer.

☐ **Patient Unstable -** The patient has been examined, an EMC has been identified and patient is not stable, but the transfer is medically indicated and in the best interest of the patient.

I have examined this patient and based upon the reasonable risks and benefits described below and upon the information available to me, I certify that the medical benefits reasonably expected from the provision of appropriate medical treatment at another facility outweigh the increased risk to this patient's medical condition that may result from effecting this transfer.

II. REASON FOR TRANSFER: ☐ Medically Indicated ☐ Patient Requested _____

☐ On-call physician refused or failed to respond within a reasonable period of time.

Physician Name: _____ Address _____

III. RISK AND BENEFIT FOR TRANSFER:

Medical Benefits :	**Medical Risks :**
☐ Obtain level of care/ service NA at this facility. Service _____	☐ Deterioration of condition in route _____
☐ Benefits outweigh Risks of Transfer	☐ Worsening of condition or death if you stay here. There is always risk of traffic delay/accident resulting in condition deterioration.

IV. Mode/Support/Treatment During Transfer As Determined by Physician– (Complete Applicable Items):

Mode of transportation for transfer: ☐ BLS ☐ ALS ☐ Helicopter ☐ Neonatal Unit ☐ Private Car ☐ Other_____

Agency:_____ Name/Title accompany hospital employee:_____

Support/Treatment during transfer: ☐ Cardiac Monitor ☐ Oxygen – (Liters): _____ ☐ Pulse Oximeter ☐ IV Pump ☐ IV Fluid: _____ Rate: _____ ☐ Restraints – Type: _____ ☐ Other:_____ ☐ None

Radio on-line medical direction control *(If necessary):* ☐ Transfer Hospital ☐ Destination Hospital ☐ Other

V. Receiving Facility and Individual: __The receiving facility has the capability for the treatment of this patient (including adequate equipment and medical personnel) and has agreed to accept the transfer and provide appropriate medical treatment.

Receiving Facility: /Person accepting transfer: _____ Time: _____

Receiving MD_____

Transferring Physician Signature_____ Date/Time_____

Per Dr. _____ by _____RN/ Qualified Medical Personnel _____ Date/Time

NURSING

VI. ACCOMPANYING DOCUMENTATION– sent via: ☐ Patient/Responsible Party ☐ Fax ☐ Transporter

☐ Copy of Pertinent Medical Record ☐ Lab/ EKG/ X-Ray ☐ Copy of Transfer Form ☐ Court Order

☐ Advanced Directive ☐ Other _____

Report given (Person/title):_____

Time of Transfer: _____ Date: _____ Nurse Signature: _____ Unit:_____

Vital Signs Just Prior to Transfer: T_____ Pulse _____ R _____ BP _____ Time: _____

PATIENT

VII. PATIENT CONSENT TO "MEDICALLY INDICATED" OR "PATIENT REQUEST" TRANSFER:

☐ I hereby **CONSENT TO TRANSFER** to another facility. I understand that it is the opinion of the physician responsible for my care that the benefits of transfer outweigh the risks of transfer. I have been informed of the risks and benefits upon which this transfer is being made.

☐ I hereby **REQUEST TRANSFER** to _____. I understand and have considered the hospital's responsibilities, the risks and benefits of transfer, and the physician's recommendation. I make this request upon my own suggestion and not that of the hospital, physician, or anyone associated the hospital.

The reason I request transfer is: _____

Signature of ☐ Patient ☐ Responsible Person_____ Relationship _____

Witness_____ Witness_____

TRANSFER FORM

White:-Receiving facility; **Yellow:** Medical Record; **Pink:**-QA

Patient Name:

Date of Birth:

Medical Record Number:

Fig. e7.1 Emergency Medical Treatment and Labor Act (EMTALA) hospital transfer form.

was negligent, or even grossly negligent, is irrelevant under EMTALA. The subjective perception of the examining emergency clinician controls whether EMTALA's stabilization requirement is triggered.

Once the hospital determines that an individual has an EMC, EMTALA requires the hospital either to stabilize the EMC or, if it lacks the capability to stabilize the patient, to transfer the patient to another medical facility that can provide the necessary stabilizing treatment.[1] A sample form for use in documenting such transfers and patient consent to transfer is shown in Figure e7.1.

The treating emergency clinician needs to decide whether a patient's EMC is stable or unstable. If two clinicians disagree about whether the patient is stable but only one of the clinicians is at the bedside caring

for the patient, the on-site clinician should make the decision.[3] If an outside physician wants to overrule the determination of the on-site clinician, he or she must come to the hospital and personally examine the patient.

EMTALA defines the term *stabilized* as follows: "no material deterioration in the [emergency] condition is likely, within reasonable medical probability, to result from or occur during the transfer of the individual from a facility."[1] For a pregnant woman having contractions who has an EMC, stabilized means that delivery (including the placenta) has occurred.[1]

The question of stabilization typically arises only when the patient deteriorates during or after the transfer and experiences an adverse medical result. It is likely to appear, particularly in hindsight, that the patient was not completely stabilized before transfer. A plaintiff need not show improper motive for a transfer to prevail on a failure-to-stabilize claim under EMTALA, merely that the patient was not properly stabilized before the transfer.

When and if the patient is stabilized has significant ramifications for hospitals and physicians, because once patients are stabilized, EMTALA no longer applies.[1,9] After stabilization, hospitals are free to refuse to provide further treatment or to transfer stabilized patients for purely financial reasons. On-call clinicians can refuse to treat or admit stable patients or insist that stable patients be transferred owing to their lack of or type of insurance. An MCO can refuse further payment to the hospital and request that the stabilized patient be transferred to one of its contracting facilities. Other federal, state, or local standards may govern further treatment or transfer of ED patients. For example, state laws often prohibit hospitals from transferring patients for any reason except that they are incapable of handling the patient's medical problem.

Disposition Issues Under Emergency Medical Treatment and Labor Act

Admission

Once a hospital admits the patient for further treatment, the hospital's obligation under EMTALA ends.[2,3] It does not matter if the situation changes later and the patient can be discharged or transferred to another hospital and does not actually use the bed overnight. The key element is that the patient be formally admitted with a documented admission order.

CMS does not consider patients admitted to observation status to meet the regulatory definition of admitted patients (not admitted for purposes of receiving inpatient services), so EMTALA still applies to the care of observation patients, such as patients managed in ED chest pain or observation units.[2,3] Patients directly admitted through or held in the ED from a physician's office, nursing home, or in transfer from another ED or another hospital inpatient setting are no longer covered by EMTALA, even though they have come to the hospital's emergency department.

"Discharge" or "Transfer" to Home

Because EMTALA defines any patient movement away from the hospital as a transfer, all patients discharged from an ED are legally considered to have been transferred.[1] Sending a patient home after treatment in the ED who is retrospectively determined to be unstable is considered to represent a transfer of an unstable patient and, as such, a violation of the law. This exposes the hospital to civil litigation under EMTALA for the failure of its emergency clinicians to stabilize patients with known emergency conditions before discharge (transfer) home.

To avoid such retrospective analyses, emergency clinicians should document that no emergency condition was found or that the patient was stable on discharge.

Discharge or Transfer from the Emergency Department to an On-Call Physician's Office

Because all discharges from the ED are defined as transfers under EMTALA, so too are discharges from the ED sent directly to an on-call physician's office for acute evaluation or treatment. In general, transfer to an office for care is only acceptable if the level of care required was not possible in the ED, such as with an ophthalmology referral.

Also, it is reasonable to send patients to an office for further treatment, such as definitive orthopedic treatment after splinting, so long as they meet the legal definition of stable at the time of discharge from the ED. The determination of whether the patient is stable for transfer to the orthopedist's office rests solely on the judgment of the examining emergency clinician. If the patient has accompanying injuries or is too uncomfortable to be moved, or if the emergency clinician believes the injury is such that the patient should not travel, then the orthopedic surgeon should be asked to care for the patient in the ED.

Follow-Up Care After Discharge from the ED

Whatever decision the hospital and physicians make about responsibility for ED follow-up, they should explicitly define those requirements in the medical staff bylaws or policies so that all personnel understand what it means to be on call for the ED at that hospital. ED discharge instruction sheets also should include a fail-safe clause advising patients to return to the ED if their condition deteriorates before seeing the referral specialist or if the follow-up arrangements disintegrate for any reason. Such a statement could help the hospital avoid liability when the on-call specialist fails to implement the prescribed follow-up plan.

Transfers to Other Acute Care Hospitals

EMTALA regulates the transfer of unstable patients only; it does not apply to the transfer of stable patients.[1,2] If no EMC is found, the patient is considered stable. The determination of whether a patient is stable must be made at the time of transfer to be valid under the law. Unstable patients can be transferred for only one of two reasons: if the transfer is medically indicated, or if the patient requests the transfer.[1] Patients usually are transferred out of the ED because the transferring facility lacks the capability or the resources necessary to treat the identified EMC.

EMTALA defines such transfers as medically indicated transfers because the purpose of each transfer is to obtain a higher level of medical care necessary to treat the patient's condition that is not available at the transferring facility. EMTALA governs almost every aspect of medically indicated transfers, including requiring hospitals to adopt and enforce policies to ensure compliance with federal transfer laws and mandating specific actions by the transferring and receiving hospitals (summarized in Boxes e7.2 to e7.4).[1-3,8] Some states have enacted their own transfer laws. Most state laws parallel EMTALA, but some are even more restrictive, so emergency clinicians responsible for patient transfers should be aware of the controlling laws and regulations in their own state as well as under federal law.

Duty to Accept Appropriate Transfers from Other Hospitals

Medicare-participating hospitals that have specialized capabilities or facilities are required by EMTALA to accept appropriate transfers of patients who require such capabilities or facilities if the hospital has the capacity to treat the patient, even if the receiving hospital does not have an ED.[1,2]

The duty to accept appropriate transfers is a hospital duty, not a physician duty, and EMTALA does not require that a physician accept the patient.[1] Hospitals should ensure that on-call physicians understand the duty to accept patients in transfer.[10] Because the duty to accept rests

BOX E7.2 Recommended Procedures for the Transferring Facility

- Stabilize the patient whenever possible.
- Complete a physician certificate of transfer, including the risks and benefits of transfer.
- Obtain the patient's informed consent to the transfer.
- Arrange for another hospital and physician to accept the patient in transfer.
- Send appropriate patient medical data to the accepting facility.
- Arrange the transfer through qualified personnel and appropriate transportation equipment.
- Maintain records of all transfers for 5 years.

BOX E7.3 Invalid Reasons for Refusal of an Appropriate Patient Transfer

- Lack of insurance or out-of-network managed care plan
- Lack of citizenship
- Veteran status
- Patient's physician not on medical staff
- Transferring hospital is out of network or outside hospital's defined referral area
- Unaffiliated hospital
- Transfer originating out of county or out of state (including transfer of out-of-state Medicaid patients)
- EMS bypassed closer hospital
- Another hospital refused the transfer in violation of the law
- Another hospital's on-call physician refused to respond to its ED in violation of the law

BOX E7.4 Recommendations for the Facility Asked to Accept the Patient in Transfer

- Accept all appropriate requests for transfer, regardless of whether the patient is an ED patient or an inpatient of the hospital
- Develop a formal system for accepting or rejecting transfer requests and document the reasons for any refusal to accept a patient in transfer
- Maintain records of all transfers for 5 years
- Report all EMTALA transfer violations of unstable patients to CMS

with the hospital, any inappropriate refusal by an uninformed on-call physician subjects the hospital to termination from Medicare, civil monetary penalties, or civil liability if the patient is harmed because of the refusal to accept the patient in transfer.

Current CMS-issued regulations state that no hospital has a legal duty under EMTALA to accept an inpatient in transfer from another hospital.[2] Therefore, even if a requested hospital could treat an inpatient's EMC that the transferring hospital is unable to treat, it may refuse the transfer for any reason, including an economic reason, and not be in violation of EMTALA. There are seven reasons for which a hospital can refuse a request for transfer under EMTALA, which are summarized in Box e7.5.

There are no other reasons for which a hospital may refuse a request to accept a patient in transfer from another acute care hospital under EMTALA. Furthermore, no contingencies are allowed to be placed on the acceptance of a transfer. The receiving hospital may not condition

BOX E7.5 Valid Reasons to Refuse a Transfer Request

1. No emergency condition present
2. Not medically indicated
3. Don't have capacity
4. Patient admitted to inpatient service
5. Patient not in a hospital
6. Patient outside the United States and its territories

acceptance of the patient on the transferring hospital's agreeing to take the patient back once the emergency condition is resolved, may not require that the transferring hospital have additional consultations completed before the emergency clinician transfers the patient, and may not require the transferring hospital to use the receiving hospital's transport ambulance or helicopter service as a condition for accepting the patient.[3] Refusals of appropriate transfers on the basis of the patient's insurance status or delay of appropriate transfers until the transferring hospital obtains authorization for payment from the patient's managed care plan are illegal under EMTALA.[1]

Duty to Report Transfer Violations

Any time a hospital has reason to believe it may have received a patient transferred in an unstable condition from another hospital, in violation of EMTALA, it must report the transferring hospital to CMS.[8] The duty to report rests with the hospital, so emergency clinicians who receive unstable patients in transfer should inform the hospital (risk management or the hospital's legal counsel), which then can determine the appropriate action.

CONSENT FOR MEDICAL CARE

Informed Consent

The doctrine of informed consent is a fundamental principle of the United States' legal system. Emergency clinicians may not examine or treat any person without consent, and that consent must be informed. This means that the patient must be given all pertinent information concerning the nature, risk, and alternatives of the treatment before that patient can be deemed to have effectively consented to the medical intervention. Clinicians should endeavor to obtain informed consent yet remain cognizant of the significant limitations of and multiple exceptions to the doctrine, especially in the ED setting. Delaying treatment in an emergency to obtain informed consent is a much more serious and common medicolegal problem than failure to obtain proper informed consent.

Emergency clinicians rarely have time to seek legal consultations, let alone wait for a court to render a decision concerning the legal nuances of consent issues. In these situations, it is helpful for emergency clinicians to use a when-in-doubt rule to guide their immediate actions. This rule simply states that when emergency clinicians are in doubt about the legality of a situation, "they should do what they believe to be in the patient's best interest and worry about the legal consequences later." Although emergency clinicians risk criminal and civil charges of false imprisonment, battery, and even negligence for failure to obtain appropriate informed consent, the courts almost universally rule in favor of physicians who act in good faith on behalf of their patients in emergency situations. Successful civil litigation regarding an issue of consent theory against an emergency clinician acting reasonably, and consistent with the appropriate standard of care, is extremely rare. An emergency clinician is much more likely to be sued for failure to treat while waiting for consent than for providing reasonable treatment without consent.

Federal Versus State Laws

Both federal laws (EMTALA) and state laws govern consent.[1] EMTALA comes into play primarily in the evaluation of minors and with patient refusal of stabilizing treatment or transfer. State consent laws vary widely. The concepts discussed next are generally applicable to emergency medical care, but all emergency clinicians should learn the consent laws specific to their own state.

The law presumes that an adult is mentally competent to make medical decisions and is entitled to sufficient information to make an informed decision concerning the physician's proposed course of examination and treatment. Under the doctrine of informed consent, clinicians have the duty to disclose the following information to patients:

- The patient's condition or diagnosis
- The nature and purpose of the proposed treatment, including the likelihood of success in the clinician's practice
- Reasonable alternative measures related to the diagnosis and treatment, including the probable outcome of those alternatives
- The particular known inherent risks that are material to make an informed decision about whether to accept or to reject the proposed treatment, including the consequences of refusing that treatment

Reasonable Person Versus Professional Disclosure Standard

The states are split on the standard used to determine what should be disclosed for patients to make informed decisions, but most require the reasonable person standard of disclosure. Under this standard, an emergency clinician is required to disclose all of the information that a reasonable person would require to make a decision. The less frequent standard, the professional disclosure standard, requires the physician to provide the same information that other physicians in the community would provide to patients in the same or similar circumstances. This is less stringent than the reasonable person standard.

Clinicians are not required to disclose every remote risk associated with a procedure or risks that are common knowledge or obvious to the patient. The law requires disclosure only of risks that are material, as judged by their seriousness or chance of occurrence. Courts define material information as information that "the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject the recommended medical procedure."

Emergency Clinician Role in the Consent Process

The emergency clinician who proposes to undertake the procedure must be the one to obtain the patient's informed consent. This cannot be delegated, so clinicians cannot ask nurses or other health care providers to obtain patients' consent on their behalf. The clinician who will care for the patient is best qualified to discuss the treatment and its risks and benefits with the patient. Nurses, as well as physicians who are not credentialed to perform the procedure, cannot obtain valid informed consent.

A summary of the discussion held with the patient and family concerning the elements of informed consent should be entered into the medical record. Particular attention should be made to documentation of those material risks discussed with the patient. Consent is a process, not a signature. A written, signed, separate consent form is not legally required under the doctrine of informed consent; however, hospitals may require emergency clinicians to complete standardized consent forms and to obtain the patient's signature. The signed form is not a substitute for the consent process. It cannot replace the exchange of information that occurs between the physician and the patient and family, the answering of questions, and the ultimate agreement of the patient to undergo the medical or surgical intervention.

Implied Consent in Emergency Situations

If an unconscious or incapacitated patient cannot express consent, the law will assume the patient consented to treatment for the emergency situation. Implied legal consent is premised on two principles: (1) duty to obtain informed consent is excused if death or irreparable harm may result if the clinician delays treatment, and (2) the law presumes that a reasonable, competent, lucid adult would consent to lifesaving treatment. The emergency treatment allowed is limited to the circumstances of the emergency, and only treatment required to resolve the emergency should be undertaken without consent. The emergency condition must require immediate medical attention, with insufficient time to inform the patient or to seek consent from another person. This is one situation in which use of the when-in-doubt rule and documentation of the clinician's concerns will weigh greatly in the court's determination of whether the clinician acted appropriately without obtaining informed consent.

Minors

Minors Accompanied by a Parent or Legal Guardian

Parents and legal guardians have the right to consent on behalf of their minor children. However, they need to act reasonably and in the best interests of their children. If they do not, their right to consent can be abrogated by the state or the courts. Parents are not allowed to refuse treatment for a child with a life-threatening emergency condition. The management of children with emergency conditions whose parents refuse to give their consent to treatment is discussed later.

Either natural parent of the minor child may provide legally binding consent. If one parent agrees with a proposed treatment and the other does not, consent may be accepted from the agreeing parent. Even if separated or divorced, either parent may give consent unless one parent has been judicially granted sole legal custody of the child, in which case only the custodial parent may consent. The child's biologic father, even if never married to the mother, also may consent for his child.

Unaccompanied Minors

EMTALA mandates that all persons presenting to an ED requesting care be examined to determine whether an emergency condition exists.[1] Because EMTALA is federal law, it takes precedence over all state consent laws regarding the initial evaluation of a minor child. The hospital should not delay this initial screening evaluation to wait for consent from a parent or legal guardian (and nurse triage does not qualify as the required medical screening, no matter how non-urgent the child's condition appears to the nurse).

If an emergency condition is discovered through the initial screening examination, the clinician may treat the emergency under either state or federal legal theories. Preserving life, preventing permanent disability, alleviating pain and suffering, and avoiding eventual harm have been used as guidelines for emergency treatment without consent. Any minor presenting to the ED should be triaged and provided with an MSE to determine whether an emergency condition exists. Under EMTALA, if an emergency condition is present, the hospital and emergency clinicians are required to provide stabilizing treatment.[1] The stabilization requirement includes transfer as necessary to an institution capable of handling the minor's emergency condition.

If the MSE does not reveal an emergency condition, clinicians need to obtain proper consent from the minor's parents or legal guardian. However, state laws and the courts have applied a number of exceptions to allow minors to seek treatment on their own without parental consent. These exceptions (such as the mature minor and the emancipated minor exceptions) vary widely from state to state. Most states have statutory reasons, such as sexually transmitted diseases, pregnancy, or

domestic violence injuries that allow minors to seek care without the consent of their parents.

Incompetent or Incapacitated Adults

If a person has been declared legally incompetent by a court, consent must be obtained from the person's court-appointed legal guardian. In addition, people may appoint legal surrogates to make legal decisions for them should they become incompetent. State-sanctioned living wills, advance directives, and durable medical power of attorney documents all transfer consent powers from a person who becomes incompetent to a legally appointed surrogate.

If an incompetent adult lacks a legal guardian or an appointed surrogate, emergency clinicians typically look to the patient's family for consent to treatment. However, consent to treatment by a family member, even the patient's spouse, generally is not acceptable under United States law unless the spouse or family member has been appointed legal guardian by a court of proper jurisdiction. Marriage does not confer one spouse the legal capacity to consent to medical treatment for the other spouse, even when the ill or injured spouse is incompetent.

Some states recognized this problem and enacted family consent statutes, which outline a hierarchy of family members who can legally provide consent when the family member becomes incapacitated. Even when families have no legal standing to consent, it is wise to involve family in the medical decision-making process. Communication and concern for the family will avoid misunderstandings, surprise, and anger, which are the primary sources of litigation. If an emergency exists, no authorization from the family is necessary to provide such reasonable care as is necessary to correct the life-threatening situation. Once the emergency is resolved, consent should be obtained from someone authorized to act on behalf of the incompetent patient. If there is no appointed legal guardian or surrogate and no state statute on family consent, the emergency clinician should seek consent authorization from the courts.

Other Special Populations of Patients

Prisoners

Competent prisoners generally do not surrender the right to consent by virtue of being incarcerated. However, a state or court may compel treatment on the basis of interests perceived as paramount to the prisoner's interests.

Alcohol-Intoxicated Patients

Alcohol intoxication itself may not render a patient incompetent to give informed consent. The emergency clinician should evaluate each situation individually to determine whether the patient is incapacitated by alcohol to the extent that he or she is no longer able to understand the proposed treatment, risks and benefits, and rational alternatives. However, the when-in-doubt rule is particularly applicable in these cases because alcohol intoxication often is associated with occult serious illness or injury.

Alcohol intoxication, especially if it is documented by a measured blood alcohol concentration (BAC), is strongly suggestive to courts and juries of impaired mental status, even though health care workers recognize that many alcoholics are entirely rational and competent at fairly high BACs. Conversely, low BACs do not guarantee competence because other processes (e.g., hypoglycemia, blood loss, impairment from other illicit substances) may cause the patient to be incompetent.

The state legal limit of intoxication is not a measure of a patient's competence. The legal level for driving has little to do with the capacity to make informed medical decisions. This distinction is sometimes difficult for judges and juries to understand, and the emergency clinician can actually use the blood level to support a judgment that the patient was not competent to make informed decisions in a particular instance. At other times, it is better not to have a number so that the only relevant criterion for determination of the patient's competence is the clinician's judgment.

Patients Given Pain Medications

As with alcohol intoxication, the fact that a patient has been given narcotic analgesia does not render that patient incapable of consenting to invasive diagnostic procedures or surgery. When consent is sought from a patient who has received pain medication, the patient's ability to understand the ramifications of the procedure should be assessed and taken into consideration, involving the family in the process if possible. The emergency clinician should document that the patient's premedicated state was considered in judging the patient's competence to make an informed decision.

REFUSAL OF MEDICAL CARE

Informed Refusal

The corollary to a patient's right to give informed consent is the patient's right to refuse medical care, even if such refusal results in death. The United States Supreme Court holds that a competent adult has a constitutionally protected right to refuse medical care. However, that right is not absolute. Under particular circumstances, courts will consider countervailing compelling state interests, such as preventing suicide, preserving life, and protecting innocent third parties.

Emergency clinicians who honor a competent patient's decision to refuse treatment are not liable for any resulting bad outcome. Emergency clinicians are more likely to be successfully sued for treating patients over their objections or without their consent, even when the treatment is lifesaving. When a competent adult refuses an indicated medical intervention, it often is because of a failure in communication in the clinician/patient relationship. Before allowing a patient to refuse care, the emergency clinician should try to determine and resolve the underlying reasons behind the patient's refusal. The attending physician must always be involved when a patient refuses medical care or expresses the intent to leave against medical advice.

As with consent, refusal of medical care is a process, not a signature. There are four essential components of the refusal process: (1) determining competence, (2) ensuring an informed decision, (3) involving others, and (4) documenting appropriately.

Determining Competence

The emergency clinician must determine that the patient is competent to make decisions. Normal findings on the mental status examination without evidence of diminished mental capacity from a closed head injury, severe pain, hypoxia, hypotension, alcohol intoxication, developmental delay, or mind-altering substances constitute good evidence of competency. Documentation of the patient's rationale for refusing care, even if it is not reasonable, provides additional evidence of competency.

Ensuring an Informed Decision

To be legally binding, a decision to refuse a test or treatment or to sign out against medical advice must be an informed decision. The emergency clinician should explain the severity of the patient's condition, the potential complications, and the alternative treatments available. The emergency clinician should use terms that the patient can understand and provide the patient an opportunity to ask questions. The patient should understand that the risks of refusing care include the possibility of permanent disability and death. Ideally, a witness should be present when the clinician informs the patient and any family members.

Involving Others

The patient's family, friends, and personal physician should be involved whenever possible. These persons should hear the same message as that conveyed to the patient, because they may be able to persuade the patient to accept the recommended therapy. If the patient expressly forbids the emergency clinician to speak with others, as is the patient's legal right, this should be explained to them and documented in the medical record.

Documenting Appropriately

Appropriate documentation of the refusal process is necessary to protect the physician and hospital from litigation. The patient should be asked to sign the refusal form. Figure e7.2 shows a sample leaving against medical advice form. If the patient refuses to sign the form, that fact should be documented, and the form signed by a hospital representative who witnessed the patient's refusal. The medical record should reflect the patient's mental status examination findings and competency to make informed decisions, the risks and benefits of recommended treatments, the available alternatives, and the participating family or friends. Documentation of the patient's rationale for refusing treatment, that the patient was treated to the extent allowed by the patient, and that the patient was invited to return for care at any time offers added protection.

Federal Rules

EMTALA requires hospitals to take and document specific actions when patients refuse medical screening, treatment and stabilization, or transfer. The government and the federal courts presume that the patient requested emergency care and place the burden of proof on the hospital to demonstrate that the patient voluntarily refused care.

There are essentially two scenarios in which patients leave the ED after refusing examination or treatment. First, some patients simply pick up and leave, without the knowledge of anyone affiliated with the hospital. Second, the patient's departure is witnessed, but the patient does not respond to requests to return for the examination or to discuss the issues with the hospital staff. These patients are generally referred to as those who leave without being seen (LWBS) or leave before examination. In the second scenario, the hospital personnel are aware that the patient is about to leave and have an opportunity to interact before the patient leaves. Hospitals generally refer to this as leaving against medical advice. The Office of the Inspector General and CMS refer to both of these scenarios as voluntary withdrawal of the patient's request for evaluation or treatment.

Leaving Without Being Seen

If a patient walks out before the MSE and later has an adverse medical result, the burden will be on the hospital to prove that the person left voluntarily and was not denied examination or treatment by the hospital. Hospitals need to have a policy and practice for LWBS patients that adequately documents pertinent findings and protects the hospital from liability. In most hospitals, the staff calls the patient and checks the waiting area at least three times before declaring that the patient has left the department. These serial checks, with the time of day they were performed, should be documented on the patient's record, and once it is evident that the patient is no longer present, the record should be reviewed on a timely basis by the emergency clinician on duty. If the reviewing clinician discovers something of concern regarding the patient's chief complaint or triage data, the person can be contacted and encouraged to return to the ED. The registration papers, triage records, nursing documentation at triage, and emergency clinician's review and documentation of that review should be kept in the patient's permanent medical record.

Leaving Against Medical Advice

If hospital personnel are aware that a patient intends to leave before completion of the MSE or stabilizing treatment for whatever reason (e.g., tired of waiting, changes mind, concerned about cost of care), the hospital should handle and document the interaction carefully to avoid EMTALA or medicolegal liability (Box e7.6). In each case, the following steps should be taken:

1. Inform the patient of the hospital's obligation under the law. The ED staff should inform patients of their rights under EMTALA to receive medical screening and any necessary stabilizing treatment from the hospital, regardless of their ability to pay for that service.
2. Determine the patient's competence. Only legally competent persons can refuse necessary medical care.
3. Explain the risks and the benefits to the patient. For patients to make an informed consent to voluntarily withdraw their request for services, they need to understand the benefits and the risks of withdrawal before refusing examination and treatment. These risks and benefits should be specific to the patient's chief complaint.
4. Secure the patient's written informed consent to refuse care. The hospital should take all reasonable steps to secure the patient's written and informed consent (i.e., obtain a signature) to refuse medical care and whether the patient's family was available to be involved in the discussions. If the patient refuses to sign the form and simply walks out after the interaction with the hospital, the person who discussed the issues with the patient and witnessed the patient's refusal should sign the form and document the interaction.
5. Offer alternative care within the scope allowed by the patient. An appropriate strategy is to negotiate with them to allow the best possible care under the circumstances that they define. Negotiation aims for the best alternative that the patient is willing to accept, even if that means providing less than optimal treatment. Patients should always be invited to return to the ED (or encouraged to see their private physician) if they change their mind and become willing to accept the recommended treatment. A patient's refusal of the more appropriate treatments as well as communication of offers to provide treatment within the circumstances proscribed by the patient should be delineated.
6. Document the interaction in the patient's hospital record. The record reflects the hospital's conformity to the law and the patient's leaving of his or her own accord—specifically, the risks of refusing the examination and the reasons for the patient's refusal. Documentation of the reasons for refusal provides evidence that the hospital did not economically coerce or in any way financially deter the patient from remaining for the MSE.

Parent or Guardian Who Refuses Care or Blood Transfusions for a Minor

In general, state laws support parental control of health issues affecting their children. However, the state will not allow parents to deny children needed emergency medical care under the doctrine of *parens patriae*, the state's paternalistic interest in children. When a child's injuries are potentially life-threatening, the emergency clinician can take custody of the child and provide indicated treatment, including blood transfusions. In deciding whether to act, the when-in-doubt rule applies, and all jurisdictions statutorily protect clinicians from criminal and civil liability for acting in good faith to protect children.

The courts have specifically addressed the issue of Jehovah's Witness parents attempting to refuse emergency blood transfusions for their minor children. All jurisdictions hold that a parent's right to freedom of religion does not include the right to deny life-sustaining medical intervention for that person's children. Conversely, courts refuse to rule against the parents' wishes when the child's medical condition is not

INFORMED CONSENT TO REFUSE EXAMINATION, TREATMENT, OR TRANSFER

I understand that the hospital has offered: (Check all that apply).

A. ☐ To examine me (the patient) to determine whether I have an emergency medical condition, or

B. ☐ To provide medical treatment or to provide stabilizing treatment for my emergency condition, or

C. ☐ To provide a medically appropriate transfer to another medical facility.

The hospital and physician have informed me that the ***benefits*** that might reasonably be expected from the offered services are:

_____

_____

and the ***risks*** of the offered services are: _____

_____

Physician Documentation

☐ The patient appears competent and capable of understanding risks and benefits.

☐ Alternative treatments discussed with the patient.

☐ Patient's family involved. ☐ Family not available. ☐ Patient does not want family involved.

Signature of Physician _____

Patient or Legally Responsible Person Documentation.

☐ I have declined to have the physician fully explain to me the risks, benefits, and alternatives to leaving the hospital against medical advice. I knowingly and willingly take and assume the responsibility for all risks incurred.
or
☐ The physician has fully explained to me the risks and benefits but I choose to refuse the offered services. I understand that my refusal is against medical advice, and that my refusal may result in a worsening of my condition and could pose a threat to my life, health, and medical safety. I understand that I am welcome to return at any time.

Signature/Patient or Legally Responsible Person _____

Print Name _____ Address _____

City _____ State/Zip _____ Date _____ Time _____

Witness/Signature _____ Print Name_____

The patient or person legally responsible for the patient was offered but refused to sign form after explanation of their rights and the risks and benefits of the services offered.

Hospital representative who witnessed refusal to sign: _____

Date _____ Time _____

Informed Consent to Refuse Examination Form [Hospital Addressograph or Sticker Goes Here]
White/Patient Record Yellow/Transfer with Patient Pink/Q/A

Fig. e7.2 Leaving against medical advice form: Informed consent to refuse examination, treatment, or transfer.

BOX E7.6 Protocol for Management of Leaving Against Medical Advice Cases in the Emergency Department

- Involve the emergency clinician in the situation in which a patient wishes to leave AMA.
- Involve the family or the patient's personal physician whenever possible.
- Explain the risks and benefits specific to the patient's condition; "You could die" alone is too generic.
- Explain any alternative treatment options to the patient.
- Ascertain the patient's capacity to make informed medical decisions.
- Ask the patient and at least one witness to sign the leaving against medical advice form.
- Ask a member of the hospital staff to sign the leaving against medical advice form if the patient refuses to sign, and state that the patient refused to sign.
- Provide the best possible treatment within the scope allowed by the patient, including antibiotics and analgesics when warranted.
- Provide appropriate discharge instructions and welcome the patient to return to the ED at any time if he or she reconsiders and decides to accept the recommended care.
- Document discussions with the patient, the risks explained, and the patient's medical decision-making capacity and understanding of the ramifications of leaving against medical advice in the medical record (and in real time; not hours after the patient has left).

serious or life-threatening. If there is no life threat or potential for serious impairment, the parents' refusal should be respected. Parental refusal of indicated nonemergency medical treatment is usually statutorily defined as child neglect, which is not legally sufficient to take custody of the child. Child neglect should still be reported to the appropriate authorities; treatment for the child can then be obtained under a court order.

Jehovah's Witnesses

Adult Blood Transfusions

Jehovah's Witnesses and the issue of blood transfusion present difficult medicolegal issues in the ED. State courts may have widely divergent views on the issue. The current trend is granting patients greater autonomy to refuse blood, even when the state asserts compelling interests to override a person's refusal. General principles of consent and the when-in-doubt rule apply, but hospitals and medical staff also should develop policies and procedures in advance to resolve potential conflicts with the Jehovah's Witness patients in the community.

Competent Adult

The courts have found that "the competent adult has the right to refuse a transfusion regardless of whether his refusal to do so arises from fear of adverse reaction, religious belief, recalcitrance, or cost." This applies even though others may consider a patient's beliefs unwise or foolish. However, even this right is not absolute. If the patient's refusal conflicts with compelling state interests such as the preservation of life, the prevention of suicide, or the protection of innocent third parties, the courts may order transfusions despite the person's objections. Some courts, however, have significantly restricted the hospital's or state's ability to assert compelling interests challenging a competent person's right of self-determination.

Unconscious or Medically Incompetent Adult

In an emergency, if the Jehovah's Witness' beliefs are unknown, physicians may transfuse the patient because consent will be implied under the emergency doctrine. It is irrelevant if the spouse, mother, or other family members adamantly refuse to allow the transfusion for religious reasons. The state's compelling interest in preserving life outweighs the family's expression of the patient's religious preferences.

When a Jehovah's Witness' beliefs and transfusion preferences are known in advance but the patient is incompetent at the time of the emergency, the courts tend to accept objective evidence of the patient's wishes. For example, a signed card carried by the patient that identifies him or her as a member of the Jehovah's Witnesses and sets out the religious objection to blood transfusion may be accepted as adequate evidence of the patient's intent. Advance directives are merely a means to express an individual's rights and are not the exclusive means to express those rights legally. Jehovah's Witnesses increasingly use state statutorily defined advance directive methods to legally express their intentions. Emergency clinicians should, of course, be certain the card or advance directive actually belongs to the patient.

REPORTING REQUIREMENTS

All states require hospital EDs to report certain events, such as deaths, violent acts, animal bites, child abuse, or certain illnesses, particularly those of epidemiologic concern, to local public health authorities. The state's primary intent is to prevent the spread of communicable diseases, protect its citizens from disease and violence, and prosecute criminal acts. In each instance, the state statute overrides patients' rights to confidentiality. The statutes typically also provide clinicians with immunity from civil liability or criminal prosecution if the reporting is done in good faith. All EDs should maintain up-to-date lists of diseases and incidents that must be reported to the state. The process and responsibility for appropriate reporting should be clearly articulated in departmental policy.

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CHAPTER E7: QUESTIONS AND ANSWERS

1. Which of the following is a common source of liability for failure to comply with the Emergency Medical Treatment and Labor Act (EMTALA)?
   - **a.** Failure to comply with written hospital policies and procedures
   - **b.** Failure to diagnose an emergency medical condition (EMC)
   - **c.** Failure to properly treat an admitted patient who is boarded in the emergency department (ED) while waiting for an intensive care unit (ICU) bed to become available
   - **d.** Failure to stabilize a patient after admission to an inpatient unit

Answer: A. Hospital policies become the hospital's standard under EMTALA. Thus, failure to comply with written policies, a failure to follow your own rules, becomes an EMTALA violation when the policies are related to the medical screening and stabilization of patients in the ED.

2. Which of the following violates the Emergency Medical Treatment and Labor Act (EMTALA)?
   - **a.** A 7-hour wait after triage to be medically screened by the emergency clinician
   - **b.** Boarding an admitted patient in the emergency department (ED) for 72 hours after the patient's physician has accepted the patient for admission
   - **c.** Delaying the patient's access to an ED bed by declining to promptly accept the patient from an arriving emergency medical service (EMS) unit or by failing to immediately triage or evaluate the patient to determine if the patient can wait on a stretcher with the EMS folks until a bed becomes available
   - **d.** Delaying the patient's medical screening examination (MSE) in the ED to triage the patient, and then for the emergency clinician to see the patients in the order based on the triage nurse's perception of the patients' acuity

Answer: C. Centers for Medicare and Medicaid Services (CMS) guidelines require the hospital to immediately triage ambulance patients arriving at the hospital's ED.

3. A 73-year-old woman is brought by private ambulance to the emergency department (ED) for shortness of breath. Due to ED overcrowding, there are several ambulance stretchers in line ahead of her at triage. At what point does the hospital accept responsibility for this patient?
   - **a.** When she was placed in the ambulance
   - **b.** When the ambulance arrived on hospital property
   - **c.** When the patient is seen by the emergency clinician
   - **d.** When the patient is seen by triage personnel

Answer: B. The Emergency Medical Treatment and Labor Act (EMTALA) defines the time of acceptance of responsibility as when the patient comes to the ED. In its EMTALA regulations, the Centers for Medicare and Medicaid (CMS) defines the term *comes to the ED* to include anywhere on hospital property, so the hospital's duty and responsibility for the patient are triggered when the ambulance arrives on hospital property.

4. A physician on-call for the hospital's emergency department (ED) has a duty under the Emergency Medical Treatment and Labor Act (EMTALA) to come to the ED under which of the following circumstances?
   - **a.** If asked to help stabilize a patient in the ED who has an emergency medical condition (EMC)
   - **b.** To help transfer a stable patient to another acute care hospital that has a specialist available that is not available at the transferring hospital
   - **c.** When asked to consult on a patient who has been stabilized in the ED and is being admitted by the patient's primary care physician
   - **d.** Whenever requested to come to the ED by the emergency clinician on-duty

Answer: A. Under EMTALA, the on-call physician only has a duty to come to the ED if needed to help determine whether the patient has an EMC or to stabilize an EMC. Any other requirements concerning when the on-call physician must come to the ED are governed by state law and/or by the hospital's medical staff bylaws, not by EMTALA.

5. According to the Centers for Medicare and Medicaid Services (CMS), which of the following patients may a hospital with specialized capabilities and available capacity refuse to accept in transfer solely because the patient is uninsured?
   - **a.** A patient with an unstable emergency condition admitted to observation at another hospital that is unable to stabilize the patient's condition
   - **b.** Any patient the hospital chooses to reject
   - **c.** An emergency department (ED) patient with an unstable emergency condition who is at another hospital that is unable to stabilize the patient
   - **d.** An inpatient with an unstable emergency condition at another hospital that is unable to stabilize the patient

Answer: D. CMS guidelines state that hospitals do not have to accept an inpatient, as defined by CMS, in transfer from another hospital under any circumstances, even if its decision to decline to accept the patient in transfer will result in the patient's death.

Quality Improvement and Patient Safety

Bryan A. Stenson and Shamai A. Grossman

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Quality Improvement and Patient Safety

Bryan A. Stenson and Shamai A. Grossman

KEY CONCEPTS

- The work of health care occurs within a complex socio-technical system so that a change in even one component has an impact on other parts of the system and ultimately on safety.
- Patient safety and mitigation of risk emerges from multifactorial interactions within the clinical work system. Incidents of patient or staff harm are most often the result of system failures, not individual human error.
- Process improvements to clinical care often have unintended consequences elsewhere within the work system. Partnerships with information technology; cognitive, behavioral, and social scientists; and engineers can help reduce the likelihood of these events and improve adoption by workers.
- Don't set up reporting systems without the resources to fully analyze the reports.

PRINCIPLES

Background

Patient care in the emergency department (ED) begins with an initial decision by the patient (or caregiver or family) to seek emergency assistance and ends with the patient's disposition and follow-up. The care process is highly complex, with many separate components, people, and interfaces with other processes in the health care organization. This complexity provides many opportunities for process failures and adverse outcomes.

Although adverse events and failures in health care have been studied for decades, most health care professionals were largely unaware of this for some time. This began to change in the early 1990s when the Harvard Medical Practice Study reported that almost 4% of hospitalized patients suffered significant adverse events during their care and attributed a large proportion of those to "human error." Although that study noted that failures in ED care accounted for only 3% of all adverse events in hospitals, the authors (who did not have ED experience) judged more than 90% of ED events to be preventable. This study and others ultimately led the Institute of Medicine (IOM) to issue a report in 2000 titled *To Err Is Human: Building a Safer Health System*. This report provoked the interest of the media and the general public, and it thrust the issue of safety in health care onto the national agenda. The major accomplishment of the IOM report was the introduction of some of the fundamental concepts regarding safety in complex systems into the world of health care. The most radical concept was that most failures in care are not the result of poor decisions or incompetent practitioners but instead are related to the varied processes involved in patient care throughout the health care system. Thus, efforts to reduce these failures should be focused primarily on changing the processes of care rather than on identifying, retraining, or punishing the workers. Although retraining and reeducating providers may be included in improving the health care system, it is important to differentiate between error, which should not be penalized, and negligence, which may require disciplinary action.

Following the Institute of Medicine report, error was reported as the third leading cause of death in the United States (US) accounting for 250,000 deaths per year or 9.5% of all deaths.[1] Medical mistakes, medication, or test error rates have been reported in as many as 34% of all patients in the United States—the highest rate of any nation. A follow-up study performed 11 years after *To Err Is Human* found little improvement. Additionally, the quality of outpatient medical care underwent minimal improvement over the subsequent decade. Despite increases in pay-for-performance systems, patient-centered medical homes, public reporting programs, and other national efforts, many quality measures ranging from avoidance of inappropriate medical treatment to ordering recommended screening tests remained stagnant or worsened.[2] Although those early studies classified adverse event rates as 100% preventable, subsequent reviewers estimate only 3% to 5% of deaths to be preventable.[3]

Although systems rhetoric is abundant in discussions of patient safety, the majority of safety efforts to date still focus on the individual practitioner (e.g., "wash your hands, use the checklist, perform a timeout"). This view of how safety is created tends to perpetuate the longstanding practice of assigning responsibility primarily to those working closest to the patient, at the "sharp end" of care, while diminishing the responsibility of those farther away—managers at the "blunt end" of care.

Current solutions remain largely focused on rooting out "human error," resulting from the actions of a few practitioners who are not sufficiently accountable or attentive to safety. Educational efforts focused on adverse events testify to a persistence of this mentality. Punitive measures, such as suspension, termination, or in extreme situations, criminal indictment of health professionals caught up in a medical mishap, remain common.[4]

Root cause analysis (RCA), when used appropriately, can be valuable in allaying this mentality. RCA targets the identification and analysis of factors that result in adverse outcomes. RCA establishes which behaviors, actions, inactions, or most importantly, conditions lead to an error. This information can then be circulated, debated, and ultimately used to implement system improvements designed to reduce errors and improve outcomes.

RCA starts by describing the error and delineating the facts of the event. This is best done by utilizing a timeline outlining sequential events leading to each behavior, condition, action, and inaction, with demarcation within the timeline of the correct behavior and

deviations. To be effective, the analysis should investigate the relationship between contributing factors and the problem or event—the "multiple why method." By asking "why" sequentially through each phase and system involved in the case, one can identify the roots of the error within each step of the sequence that led to the problem or event. At the same time, RCA enables identification of all other potentially unsafe factors that could have brought about the root cause or error. The final step is to identify and address other related instances of potential harmful factors or outcomes. RCA should then determine corrective actions focused on preventing recurrence of each potentially untoward outcome.

Solutions must be within the institution's control, meet departmental goals and objectives, and must be measured after implementation to ensure that both the intended consequences occur and that unintended negative consequences are recognized and analyzed. In this chapter, we attempt to elucidate the abundant and varied sources of error and adverse events in emergency care including workspace design, communication, triage, transitions in care, crowding, cognitive processes, shift work, and medication administration. These represent many of the factors involved in health care delivery and components subject to breakdown and error often leading to adverse events. By uncovering these components during root cause analysis, targeted adjustments and changes to the health care system may be implemented.

Work Systems

Health care today has evolved far from its origins when independent practitioners acted as isolated agents. Today's work system requires the integration of humans, tools, and technologies to deliver a wide variety of clinical care in numerous settings from hospitals to freestanding EDs. The interactions among workers, technologies, and the organization determine the outcomes in the system, and in most cases the interactions among components are more important than the components themselves in causing errors and adverse events.

For example, unexpected downtime of two dialysis machines for several days in a dialysis unit markedly delays patients' treatments, increasing the risk of cardiac and respiratory complications from hyperkalemia and fluid overload. This results in an increased number of blood draws to check potassium levels, with increasing risk of needle sticks for workers, as well as the risk of internal shortages of medications for managing hyperkalemia. There may also be organizational consequences, such as overtime pay for dialysis staff to accommodate patients whose treatments were delayed. Finally, there is also potential for intensive care unit (ICU) admissions for patients who become unstable awaiting dialysis. Hence, any change in a work system, no matter how small, has implications for the system as a whole. This is encapsulated in the systems thinking adage that in a complex system, you cannot change only one thing.

Safety is commonly thought of in terms of a lack of danger and risk or the absence of something going wrong. This is predicated on the hidden assumption that safety is somehow the natural and normal state of the system and that adverse events are aberrancies that must have some special cause. This assumption is common in health care and has led to an emphasis on adverse events rather than error so that, unless an adverse event occurs, one may inaccurately assume that no error occurred. This obscures the concept that often there are numerous near misses—errors that fortuitously did not lead to an adverse event. For example, if a medication order entry system does not have an updated allergy list, a patient may be given a medication to which he or she has had a prior allergy. Thankfully in some instances patients do not have adverse reactions to erroneously administered medications. However, unless allergy warning systems are changed, another patient may receive the wrong medication and develop anaphylaxis.

Resilience

Not all deviations from guidelines or expected behavior are erroneous or unsafe in medicine. Real-life work adaptations rely on resilient behaviors that respond to current or potential problems that increase risk or delay completing the clinical work. For example, on a busy day a clinician asks for an intravenous (IV) line on a patient she has just seen before she goes to a resuscitation. The ED technician, seeing no labs have been ordered, "draws a rainbow" where he obtains blood from the patient and places a sample in every color of laboratory blood tube available. Organizational policy, however, requires blood not to be drawn until an order has been placed and a label generated for each tube. The technician draws a rainbow without orders because he: (1) knows that the patient has poor peripheral veins and does not want to have her suffer through another painful blood draw; (2) anticipates that he may not be able to get back and perform another draw once orders are in because he might be pulled to another area; and (3) believes the patient looks ill, so the physician is likely to order a number of tests when she returns.

This fairly simple workaround is an example of resilient behavior. The ED technician's decision to draw the blood despite the organizational policy requiring orders for drawing blood addresses a number of existing and potential obstacles to the patient's care. The technician's modification of work processes contributes to the patient's care and the ED's overall effectiveness. The majority of resilient behaviors in the ED are hidden (in part because they may involve bending the rules) and are done without any special thinking that "it's time to be resilient." Interestingly, seasoned nurses, technicians, and physicians can frequently be overheard orienting new staff to similar workarounds, because they have proven to help with workload management and to benefit patient care. Resilient behavior in health care can often be preventive, ameliorating adverse events, as illustrated in the following case.

A 24-year-old non-English-speaking long-limbed sailor presents to the ED with 3 days of intermittent pain and numbness in his left leg with recurrent brief episodes of dizziness and low blood pressure. On review of imaging, the emergency clinician notes a dramatically abnormal chest radiograph and intermittent hypotension, making the diagnosis of aortic dissection almost a certainty. A page to cardiovascular surgery goes unanswered, an atypical occurrence in this ED. Based on a hunch that perhaps the cardiovascular team is in the operating room, the provider turns to the unorthodox solution of calling the operating room and asks the nurse to pull up the patient's chest x-ray on the computer in the operating room, thinking this will most easily and effectively alert the surgeon to the need. This novel method for escalating an urgent case gets this patient with Marfan syndrome and aortic dissection into the operating room shortly after his arrival in the ED.

This is an important example of how a workaround strategy and extra steps contribute to resilience and potential improvement in healthcare delivery, avoiding potential errors in delay of care and subsequent adverse events.[5,6]

SOURCES OF FAILURE IN EMERGENCY CARE

Many characteristics of emergency medical practice make it vulnerable to error (Table e8.1). Studies have identified a number of unexpected yet highly consequential failures of information technology (IT) that are difficult to detect, some occurring during emergency resuscitations. Ergonomic shortcomings in the workplace have been identified with potential to contribute to failures in care. Studies have also shown significant delays related to ED layout, with time to assessment of chest pain patients being longer for patients placed behind a door or who were 25 feet or farther away from the physicians assigned to their care. This section focuses on some of the principal factors that contribute to

TABLE E8.1 Performance-Shaping Characteristics of the Emergency Department

Intrinsic[a]	Extrinsic[b]
Limitations of human cognition	High communication load
High levels of uncertainty	Poor teamwork
High decision density	Overcrowding
High cognitive load	Production pressures
Narrow windows of opportunity	High ambient noise levels
Multiple interruptions or distractions	Information gaps
Low signal-to-noise ratio[c]	Report delays
Surge phenomena[d]	Inadequate staffing
Novel or infrequently occurring conditions	Poor feedback
Patient factors (e.g., acuity, language, delirium)	Inexperience Inadequate supervision Sleep deprivation or sleep debt Fatigue Multiple transitions of care Poorly designed procedures ED layout

[a]Intrinsic factors are intimately part of the nature of emergency care and as such are not amenable to change but instead must be compensated for.
[b]Extrinsic factors are in principle manageable and typically relate to resource constraints.
[c]Low signal-to-noise ratio refers to the low likelihood of a critical diagnosis compared with a benign diagnosis for similarly presenting symptoms and findings (e.g., subarachnoid hemorrhage vs. tension headache).
[d]Surge phenomena are the rapid changes in volume and acuity routinely experienced in many EDs.
ED, Emergency department.

adverse outcomes and how they might be better managed to improve safety.

Communication and Interruptions

Emergency clinicians are interrupted, on average, approximately once every 6 minutes and two-thirds of the interruptions cause a change in task. Both interruptions and task switching have been shown to lead to errors. Self-detected errors occur in almost 20% of all ED cases but only 2% are associated with adverse events. Errors are ubiquitous but only rarely, when combined with other factors, produce adverse events. Therefore, in order to achieve improvement, it is important not to focus on eliminating errors alone, but to also understand the downstream negative consequences of interruptions and create mechanisms to prevent an error from becoming an adverse event.

Workspace Design

Two frequently overlooked contributors to lowered safety in any work environment are the design of the workspace and the availability of tools, technology, and procedures used to perform the work. This is especially true for EDs because many were not designed for the work currently being done in them. ED caregivers are required to adapt to the space by creating "workarounds" to cope with the limitations and impediments of the workspace.

There is often inconsistency in equipment across or between areas. For instance, the monitors in the ED are often not the same as those used in the radiology department or ICU. Similarly, tools and technology are seldom developed to be user friendly when integrated into an existing workspace. This is most apparent with regard to health IT.[7,8] Issues arising from health care IT range from poor user interface, to inaccurately copying information between patient charts, to missing important abnormal findings due to excessive alerts. Many of these functions were not designed with the providers in mind and often make the work more cumbersome and may inadvertently lead to errors. These potential pitfalls should not overshadow the possible benefits that technology can contribute. These include allowing patients to address medication reconciliation discrepancies at home, ensuring correct dosages and notifications of potentially dangerous medication interactions, and alerting providers to abnormal laboratory or imaging results.[9,10]

The contribution of a poor IT design and the difficulty in maintaining safety in a health care environment are generally overlooked by staff members who cope with these difficulties as "part of the job." Vigilance is the common solution, but despite caregivers' best efforts it cannot be sustained, given competing demands for their attention. This increases the risk that a failure will be linked to the workplace, the procedures, or the equipment, despite not being connected to any or all of these.

Crowding

ED crowding has long been recognized as a major source of time-delay failures and error and may be a threat to patient safety. Such delays are not simply an inconvenience to the patient but may give rise to significant adverse events. For example, patients with atypical presentations of severe illness who have been mistriaged to low levels of acuity may experience inordinate and, occasionally, fatal delays. In other cases, such as community-acquired pneumonia, cellulitis, and lacerations, more expedient care may significantly improve the outcome of the illness. A significant proportion of patients who leave the ED without being seen may have serious illness and incur delays in diagnosis and treatment. Similarly, when a patient is ready for admission to the hospital from the ED, further time-delay errors related to lack of inpatient space may occur. Not only do such delays create throughput problems and contribute to crowding, but they also create discontinuities in care and may lead to adverse events that are difficult to identify, because they manifest themselves after the patient has left the ED. The need to adapt to challenges created by crowding contributes to greater use of mental shortcuts and less accurate, efficient, and thorough decisions.

Information Gaps

Missing information is common in emergency care and can significantly affect quality of care. Hospital records, especially discharge summaries, details of past medical history, and other important information, are often difficult to access. Even with electronic medical records, pertinent information may be difficult to locate. Referral notes sent by family physicians with the patient may not reach the emergency clinician or may not contain relevant or significant details. In these situations, clinicians often make decisions and take action on the basis of incomplete, limited, or erroneous information. Emergency clinicians may not seek additional or clarifying information because of time pressures, patient volume, or limited methods to obtain more information (e.g., the referring physician's office is closed), essentially accommodating to this potential gap in continuity of care and its associated increase in patient risk for adverse events.

Performance-Shaping Factors

A wide variety of systemic conditions contribute to the majority of adverse events and near misses that occur in the ED (see Table e8.1). Some performance-shaping factors are part of the milieu of emergency medicine and thus not easily amenable to control (e.g., cognitive

workload, multiple distractions and interruptions, and high acuity). These factors must be managed by strategies that buffer or mitigate their effects. In contrast, other extrinsic performance-shaping factors reflect limitations of resources (e.g., staffing ratios, production pressure, and ED layout) and may be more amenable to improvement.

Violation-Producing Factors

Although at first one might think that violations of organizational policies, rules, and procedures would always cause failures and adverse events, as noted above, some violations may be necessary for the safe functioning of the system, and others fall somewhere in between. Aside from recklessness, drug use on the job or other egregious acts, more subtle factors can be associated with rule and safety violations and error. For example, the "normalization of deviance" is an accumulated acceptance of small variances from safe operating conditions that develops over time, ultimately compromising safety. This is evidenced in overtaxed EDs coping with crowding (e.g., examining and managing of patients in hallways). Violation-related error can also occur in response to perceptions of authority. This may occur through a directive supporting a policy violation from an authority figure (e.g., nursing supervisors order admitted patients moved to inpatient beds without patient sign-out if there are delays in reaching inpatient nurses), the absence of a disapproving authority (e.g., physicians leaving shifts early but the medical director does not address the behavior), or an individual's self-perception that he or she is authorized to disregard or to deviate from prescribed procedures (e.g., ED electrocardiograms done on patients in chairs because there are no available stretchers). Violations differ from workarounds in that violations tend to undermine safety and increase error and adverse events, whereas workarounds and extra steps support safety and mitigation of error, although at times it may be difficult to distinguish between a beneficial workaround and a potentially dangerous violation.

Teamwork

Good teamwork is essential to the safe practice of emergency medicine, but emergency caregivers are not trained or evaluated as teams. Teamwork training in other fields, such as aviation, has been successful in reducing error related to poor communication, cross-monitoring (observing others' behaviors to reduce risk of failure and share workload), and authority gradients (both within and between professions). Work on transferring teamwork training principles to emergency medicine suggests that teamwork failures are involved in approximately 40% of malpractice cases. Lack of cross-monitoring across team members and failure of advocacy on behalf of the patient by caregivers to avoid patient harm are two of the factors most frequently identified. Multidisciplinary teamwork training courses have often showed significant decreases in observed clinical errors. A multidisciplinary teamwork training course implemented in eight EDs showed a sixfold decrease in observed clinical errors. Teamwork is not a specific fix for any one type of error, but it should be viewed as one type of adaptable human factor intervention.

Efficiency/Thoroughness Trade-Off

EDs are under constant pressure to reduce waiting time and increase the throughput of patients. This forces a trade-off between improving efficiency and thoroughness. This tradeoff is seldom directly acknowledged in official policies, but it can be observed in the ED, especially when the volume is high. For example, the question "What is the one thing you are most worried about?" posed by a caregiver to a patient, may indicate that efficiency is the priority and send a message that there will not be an opportunity to address all of the patient's concerns or medical complaints. Although efficiency/thoroughness trade-off decisions are often not articulated explicitly, organizations and regulators implicitly and explicitly demonstrate the importance of efficiency in their monitoring of throughput goals, length of stay, patients leaving prematurely, and staffing and supply levels. Thoroughness in most settings often only arises secondarily from hindsight following an adverse event. Although simultaneous improvements in efficiency and thoroughness are sometimes possible, eventually every work system reaches a limit where improving one element degrades the other, leading to errors and adverse events.

Authority Gradients

Humans in groups often sort themselves by degrees of authority. This hierarchy can be based on profession (physicians have greater authority than nurses) or organizational rank (attending physicians have greater authority than residents). These authority gradients can impede the free flow of information among team members if low-authority members are intimidated by differences in seniority, stature, expertise, profession, or social status. There are many examples of cases in which authority gradients have been responsible for adverse events. For example, a nurse defers to a physician in prescribing the wrong medication dose, making the faulty assumption that "the doctor always knows best." A work environment in which all team members feel comfortable expressing their viewpoint, especially if it is a dissenting one, requires a cultural change that can begin with the physicians who occupy the highest authority position in the clinical setting. Authority figures can support a flattened hierarchy by openly recognizing the value of perspectives other than their own and eliciting them from other clinicians and staff (e.g., asking a nurse what they think might be going on with a patient). Senior clinicians are in a powerful position to bridge gradients by fostering open communication through multidisciplinary rounds, demonstrating that they are approachable (e.g., acknowledging staff by name), and using clinical narratives from their own experience that illustrate near misses and judgment failures.

Cognitive Processes

Patient care in the ED is a process of making clinical sense out of often ambiguous and interrupted stimuli and data. The goal of this process is an accurate diagnosis, if possible, or more commonly, to create a plan with which to guide testing, management, and disposition. Although many presentations, such as lacerations, dislocations, fractures, and foreign bodies, are self-evident, other chief complaints (e.g., chest pain, fever, headache, abdominal pain, and syncope) are often associated with high levels of ambiguity and uncertainty and are more likely to lead to error or adverse events. Cognitive biases are frequently identified retrospectively on root cause analysis, but prospective identification of these biases in order to avoid errors upfront is challenging.

Fatigue and Shift Work

Both fatigue and shift work contribute to error, yet relatively little research has been directed to their respective impacts on clinical performance in the ED. Although fatigue and shift work are often considered together, they are different entities and exert different effects on performance.

Shift work has extensive, well-documented, detrimental effects on health that in turn have an impact on well-being and job performance. Importantly, it leads to disruption of circadian rhythms that can result in sleep deprivation. This disruption largely occurs through missing sleep in the anchor period, approximately midway through the sleep phase when core temperature and arousal level are at their lowest. Decreased performance of someone who has been up all night has been described as roughly equal to that of a person with a blood alcohol level of 0.1% (Box e8.1).

BOX E8.1 Effects of Sleep Deprivation

Longer reaction time
Lapses in attention or concentration
Lost information
Errors of omission
Poor short-term memory
Poor mood (increased confusion, stress, and irritability)
Reduced motivation
Distractibility
Sleepiness
Poor psychomotor performance
- At circadian low points
- When sedentary
- On long, difficult, or externally paced tasks with no feedback
- In unchanging surroundings, particularly with reduced light or sound, or with low motivation, interest, or novelty

Modified from: Bonnet MH. Sleep deprivation. In: Kryger M, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia: WB Saunders; 2000: 53-71.

The acute effects of sleep deprivation are well known, but the chronic effects are less appreciated. Working a night shift results in less sleep the following day, and subsequent sleep is often disrupted and fragmented in the struggle to restore the circadian rhythm before the night-shift cycle repeats itself. This results in the accumulation of a sleep debt that has a significant impact on performance. A study of anesthesia residents on a normal work schedule, with no on-call duty in the preceding 48 hours, showed daytime sleepiness scores comparable to those of patients with narcolepsy or sleep apnea. The on-call schedule of these subjects (five periods per month) entailed considerably less sleep deprivation and fragmentation than an average emergency clinician's schedule. Additionally, increasing age is associated with decreased tolerance for sleep deprivation.

Performance declines as work hours increase, but the optimal shift length in the ED is unknown and difficult to delineate for several reasons. The relationship between workload and acuity is not well defined, and some workers exhibit contradictory incentives, such as preferring to work longer shifts to get more days off. More recovery time between shifts might be expected to enhance job performance, but these issues remain relatively unexplored. A survey of emergency clinicians found a preference for 8-hour over 12-hour shifts, but it is not known whether job satisfaction in the ED translates into improved clinical performance and fewer adverse events. Additionally, many other factors contribute to the selection of optimal shift length when staffing an ED. Shorter shifts allow for potential flexibility to increase staffing during times of high volume. However, low-volume departments with limited staffing may have no other option apart from 12-hour shifts to fill the schedule. Longer shifts and increased fatigue may be necessary due to those external factors. Other conditions within the ED, competing commitments outside the ED, age, ill health, and other factors contribute to fatigue, with evidence pointing toward additional health implications for clinicians.

The appropriate management of shift work and fatigue to improve patient safety is not well understood, and further research is needed in this area. In most high-hazard industries, the assumption is that fatigue and long, aberrant work hours lead to poor performance; however, in the health care industry, issues about discontinuity of care have minimized these concerns. Given that medical personnel, like all human beings, function suboptimally when they are fatigued, efforts to reduce fatigue and sleepiness should be undertaken, and the burden of proof should be in the hands of the advocates of the current system to demonstrate that it is safe. In the meantime, shift scheduling should be optimized to reduce the impact of circadian disruption, and ED personnel should practice good sleep hygiene. Some basic approaches are listed in Box e8.2.

BOX E8.2 Rational Approaches to Shift Work

Optimize circadian-friendly schedules
Forward rotating (clockwise with circadian rhythms)
Rapid changes
Minimize consecutive nights (1 or 2)
24 to 48 hours off after nights
Allow social time, including some weekends
8-hour shifts (absolute maximum 12 hours)
Institute regular, predictable template
Practice proper sleep hygiene
Use a sleep-friendly room: room-darkening blinds, "white noise" (e.g., electric fan) or earplugs, no phones, family aware
Maintain a regular sleep routine
Try anchor sleep
Avoid caffeine, alcohol, and drugs
Prophylactic naps
Modulate circadian rhythms
Exercise
Consider bright light
Eat healthy
Eat a balanced diet
Avoid junk food
Keep regular mealtimes
Promote a healthy lifestyle and work style
Promote a personal healthy lifestyle
Educate friends and family about shift work issues
Educate colleagues about shift work issues
Advocate for department improvements in working conditions
Advocate for shift worker–friendly community services
Avoid pharmaceuticals
Use caffeine in moderation, prn
Do not use sedatives or stimulants
Avoid alcohol before sleep

Modified from: Jha AK, Duncan BW, Bates DW. Fatigue, sleepiness, and medical errors. In: *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. Evidence Report/Technology Assessment No. 43, AHRQ publication 01-E058. Rockville, MD: Agency for Healthcare Research and Quality; 2001; and Frank JR, Ovens H. Shiftwork and emergency medicine practice. *CJEM*. 2002;4:421.

PROBLEM AREAS IN EMERGENCY CARE

The mechanisms of error in emergency care are remarkably varied. Areas of consistent concern include triage, technical procedures, laboratory and radiographic tests, transitions in patient care, orphaned patients (patients who inadvertently are unassigned to a provider in the ED), and medications.

Triage

Triage, or sorting by acuity, is by definition an abbreviated decision-making process that can never be completely safe because of the limited information available, the lack of time invested, and the variety of presentations of illness and injury. Inevitably, the triage process

TABLE E8.2 Emergency Severity Index (ESI) Triage Criteria

ESI Level	Criteria
1	Requires Immediate Life Saving Intervention
2	High Risk Situation; Lethargic; Severe Distress; Dangerous Vital Signs
3	Multiple Required Resources, but Stable Vitals
4	One Required Resource
5	No Required Resources

Adapted from: Emergency Severity Index (ESI): A Triage Tool for Emergency Departments. Content last reviewed May 2018. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/patient-safety/settings/emergency-dept/esi/index.html.

involves tradeoffs between sensitivity and specificity. Undertriage for a particular patient would have a greater potential for an adverse event than overtriage, whereas overtriage affects resource utilization and may have an impact on the care of other patients.

Triage assessments are important contributors to process failures and adverse events. Beyond treatment delays, which can occur with undertriage or be produced by overtriage, an incorrect assessment may be the triggering event that initiates a chain of failures. An inappropriate triage to a specific treatment area may create a bias in the minds of the treating clinicians and staff. The emergency severity index (ESI) is one of the most popular and commonly used systems, with five levels based on risk and required resources (Table e8.2). While it offers a significant opportunity to reduce triage-related errors, it has shown poor reliability when compared across multiple countries.[11] Still, we believe it is the best current option available and is broadly employed across EDs in the United States.

Technical Procedures

The practice of emergency medicine requires proficiency in a wide range of procedures with varying degrees of difficulty. Patients who require procedures are at greater risk for adverse events. Contributors to this higher risk include problems developing expertise in low frequency but higher risk procedures. Critical procedures, such as cricothyrotomy, pericardiocentesis, and thoracotomy, are rarely or less commonly performed; when they are needed, they are highly consequential events involving significant time pressure. An important challenge in emergency medicine is the acquisition and maintenance of a requisite level of skill. Simulation techniques have considerable potential to ameliorate skill degradation but require both capital and human investment to be effective.

Laboratory Tests

The interface between the ED and its ancillary services is critically important. Errors can occur at three phases of laboratory processes. Pre-analytic errors mostly occur through inappropriate collection of specimens because of lapses in technique, timing, and identification of both patient and specimen. Analytic errors are those that arise directly from the testing process. Post-analytic errors occur after the test result has been obtained and can take many forms (e.g., keyboard entry errors, overlooked or lost data, or failure of results to reach the physician). The majority of failures occur in the pre-analytic and post-analytic stages, with less than 5% in the analytic stage. Overall, the laboratory defect rate is less than 1%, but the number of exposures is large. Of the failures that do occur, up to 50% may have a moderate impact and up to 8% a severe impact on patient care.

Radiology Studies

Radiographic imaging is a critical aspect of diagnosis and management in the ED. Although patient identification and wrong-side problems are important sources of failure, the majority of errors lie in interpretation. Assuming the radiologist's interpretation to be the criterion standard, the rate of error in interpretation by emergency clinicians may be as high as 16% for plain radiographs and more than double that rate for computed tomography scans. Clearly, not all misinterpretations are consequential, and emergency clinicians typically seek the advice of the radiologist when they recognize difficult interpretations. The introduction of digital imaging and picture archiving communications systems has resulted in new patient safety issues related to usability, the effect of monitor resolution on interpretation, and reconciliation of ED clinician and radiology readings. Significant interpretation errors can be detected with prompt review of all films by the emergency clinician and radiologist, but in the dynamic setting of an ED this is not always practical. Timely and appropriate feedback and review may help ameliorate future interpretation error. This approach has been demonstrated to substantially reduce the rate of clinically important misinterpretations.

Transitions in Patient Care

The need for 24-hour access to care and the fragmented nature of health care delivery require transitions of care between providers, either within the ED (at shift changes) or between the ED and other care areas (when patients are admitted, transferred, or discharged). The shift "sign-over," "sign-out," or "handoff" is generally thought of as a communication activity performed for the transfer of clinical information, but it also embodies the transfer of responsibility and authority from one provider to another. The sign-over also conveys general situational awareness (e.g., the state of the department, hospital, and city) and provides a forum for review of decision making and treatment plans.

Although transitions of care have been studied in recent years, few of these efforts have engaged with the cognitive, behavioral, and social sciences essential to a deep and systematic understanding of the problem.[12] Survey studies have shown that most EM residents learn to do handoffs informally without structured training, and programs don't properly evaluate handoff tools.[13] When viewed superficially, sign-overs seem highly variable in their content, the number of individuals involved, the physical configuration (e.g., walking, stationary, and at bedside), the tools used to facilitate the transition (e.g., white boards, medical records, and written notes), and the length of the transition process; however, they have a fundamentally similar deep structure. Although widely regarded as a major contributor to adverse events, sign-overs also provide an opportunity for review of decision making by clinicians and may provide opportunities for improved care by bringing "fresh eyes" to a patient's case. Potential threats to effective transitions include:

- Interruptions during the turnover (e.g., phone calls and sidebar conversations) can cause a loss of focus and lead to the omission of important information.
- Lack of consistent structure to the turnover. Although the traditional case presentation narrative is often followed (chief complaint, history, physical examination, initial laboratory results, impression, and plan), the case presentation format may not provide opportunities for noting pending or as yet uncompleted tasks.
- Patients are commonly labeled in ways that can sometimes be helpful but sometimes harmful, especially for at-risk groups such as the homeless, psychiatric patients, alcoholics, and drug abusers.

Given how high-risk these transitions of care are, it is important to take steps as a group to mitigate errors. Many institutions now require formal, structured sign-outs. The I-PASS study group is a notable

TABLE E8.3 Elements of the I-PASS Handoff System

I	Illness Severity	Stable, "watcher," unstable
P	Patient Summary	Summary statement Preceding events Emergency department course Ongoing assessment Plan
A	Action List	To do list Time line and ownership
S	Situation Awareness and Contingency Planning	Know what's going on Plan for possible events after handoff
S	Synthesis by Receiver	Summarization by receiver Asks clarification questions Restates key action items

Adapted from: I-PASS Study group. Starmer AJ, Spector ND, Srivastava R, et al. I-PASS, a mnemonic to standardize verbal handoffs. *Pediatrics*. 2012;129(2),201-204.

example that implemented a pediatric handoff bundle and reduced preventable adverse events by 30% (Table e8.3). Other groups have taken a different approach, staggering the shift schedule in order to reduce the total number of patients undergoing a handoff from 7.9% to 5.9%.[14] Some groups have also studied methods of improving the handoff to the inpatient teams, with one study describing an electronic handoff as a useful method of improving efficiency of medical admissions while reducing interruptions to the ED provider.[15] All of these methods illustrate how critical this time is during patient care, and therefore is likely where meaningful change can occur.

Orphaned Patients

Orphaned patients are those who have suffered temporary loss or diminished supervision or accountability for their ED care. This may occur at several stages in the ED stay. Patients who are seen and assessed at triage and then go to the waiting room are temporarily orphaned. Those who are brought in by paramedics sometimes remain on stretchers for hours before being admitted to the ED. Patients who leave without being seen or before treatment is completed have "orphaned" themselves. Patients can also be temporarily orphaned out of the ED for radiographic studies or other special tests. On occasion, patients get "lost in the shuffle" and are overlooked at shift change, or they may get "lost" after one or more consultations with other services. With prolonged wait times, occult conditions can progress to serious and potentially catastrophic levels. A significant cause of orphaning in some EDs is the boarding of admitted patients because no inpatient beds are available. In such cases, patients may be put in holding areas in or adjacent to the ED and receive sporadic care from a succession of caregivers who know increasingly less about their conditions.

Medications

Medication errors constitute the largest proportion of care failures in most studies, with errors occurring in all six steps of the process (prescription, transcription, dispensing, administration, monitoring, and discharge). The attempt to bypass pharmacists while dispensing some ED medications also obviated their ability to identify and potentially correct errors. In addition, team communication errors can contribute to many failures—missed medications, wrong medications, and duplicate dosing. Pediatric patients are at higher risk. Although drug errors are no more common in pediatrics than in adults, they are typically more serious in children.

The presence of a pharmacist on the clinical team has been shown to reduce medication errors in several settings. There is great interest in the potential of computer technologies, such as bar coding and computerized physician order entry, to enhance medication safety. However, despite this potential, there is evidence that such systems introduce new problems to replace old ones. The Institute for Safe Medication Practices has recommended specific problem practices to be avoided in writing orders or prescriptions, such as avoiding error-prone abbreviations. Success in this area will require more than just individual attentiveness; nurses, unit secretaries, and pharmacists need to feel comfortable challenging improper use by physicians. Whether ED medication orders are reviewed by pharmacist pre- or retrospectively, an order should never placed with the assumption the nurse or pharmacist will contact the provider if it happens to be suboptimal.

SUMMARY

Having reviewed the wide range of variables in the ED, we can better understand which components play a role when errors and adverse events are identified and need review. Situations can be influenced by a multitude of factors that will need to be investigated during root cause analysis. For example, a diabetic patient undergoing ED workup fails to receive his correct dose of insulin, progressing to diabetic ketoacidosis requiring intensive care admission. Further review shows the patient had a prolonged ED course while awaiting imaging and inpatient bed placement and had multiple transitions of care during his stay. The adverse event occurring in this case may have been caused by multiple factors—the initial provider working too quickly and failing to order his home medications, the wrong dose/type of insulin ordered if his medications were not up-to-date, or poor communication during sign-out between providers. Additionally, ED crowding may have caused the backlog for imaging and bed availability, prolonging length of stay and leading to the patient being orphaned with less supervision from nurses and providers.

A similar case of multifactorial error can be seen in a patient who presents with a severe headache and has a head CT initially read as normal by the radiology resident. The ED resident discharges the patient based on this interpretation and fails to notice that the report has been updated by the radiology attending who noted an intracranial hemorrhage. This situation may have been impacted by poor verbal communication between departments, suboptimal alerts in the medical record indicating abnormal studies, or an authority gradient with the emergency and radiology residents not seeking counsel from their attendings sooner when they were uncertain of the imaging or safety for discharge. In both examples, figuring out where a lapse occurred allows for effective quality improvement by designing systems to prevent repeat episodes.

The safe management of patients in the ED depends on a multitude of processes. All appear vulnerable to error yet all have the potential for improvement through judicious process management. Efforts by front-line workers are not sufficient; considerable effort is required at the administrative or "blunt end" of the system as well. Root cause analysis must review, utilizing a step-by-step approach, each system involved in the health care process. The establishment and maintenance of a successful safety culture within health care requires acceptance by health care organizations, a willingness to adopt new ideas and tools from outside of health care, and a commitment to continued effort and investment.

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CHAPTER E8: QUESTIONS AND ANSWERS

1. Which of the following triage assessments are important contributors to error in emergency medicine?
- **a.** Triage by age
- **b.** Triage by nursing personnel
- **c.** Inappropriate triage to a treatment area
- **d.** Triage based on comorbidities
- **e.** In-room patient triage and registration

Answer: C. An inappropriate triage to a specific treatment area may create a bias in the minds of the treating physician and staff, leading to delays in care or misdiagnoses. This may be more pronounced with undertriage versus overtriage.

2. A senior attending asks a resident to discharge a young patient with abdominal pain. The resident has noted lab abnormalities she believes merits further work-up, but assumes the attending has seen these results and defers to the attending's judgment. These abnormalities had in fact been overlooked by the attending and the patient gets sent home without appropriate work-up. This is an example of which potentially negative process?
- **a.** Authority gradient
- **b.** Anchoring
- **c.** Countertransference
- **d.** Fatigue and shift work
- **e.** Visceral bias

Answer: A. The hierarchical nature of medicine can lead to authority gradients which may contribute to errors. If a more junior member of the team does not feel empowered to voice a concern regarding patient safety, it can potentially have adverse consequences.

3. Which of the following may ameliorate the effect of shift work?
- **a.** Five consecutive night shifts
- **b.** Assigning more senior staff to nights only
- **c.** Sedatives
- **d.** Circadian schedule

Answer: D. A circadian schedule with forward rotating shifts has the potential to improve sleep habits for those with a rotating shift schedule. Excessive amounts of consecutive nights, sedatives, and increased night shifts for senior attendings are all poor strategies to deal with the burden of shift work.

4. Which of the following are more likely to cause error in emergency medicine?
- **a.** Low patient volumes, poor teamwork, electronic health record
- **b.** Inadequate supervision, high communication load, multiple transitions of care
- **c.** Overstaffing, multiple distractions, low numbers of transitions in care
- **d.** Physician salaries, language barriers, quiet work environment

Answer: B. Many factors affect an ED's performance, making it more at risk for a medical error (see Table e8.1). Although each choice contains at least one of these performance-affecting factors, only choice B contains three of the factors.

e9

Patient Experience in the Emergency Department

Emily L. Aaronson and Benjamin White

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Patient Experience in the Emergency Department

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KEY CONCEPTS

- Factors that can improve the patient experience in the emergency department include:
  - Communication that expresses empathy
  - Working as a high-functioning team
  - Setting realistic expectations regarding wait time
- Clear discharge instructions
- Improvement in the patient experience has been shown to impact composite outcomes such as health-related quality of life to patients, reduced malpractice risk, and improved staff satisfaction.

FOUNDATIONS

Patient experience is a growing area of focus in emergency medicine (EM). Increasingly, it is recognized that the traditional paradigm defining adequate care in the emergency department (ED) as providing the right diagnosis and medical management no longer suffices. Instead, there is a growing appreciation for the importance of providing a high-quality experience for patients that encompasses many aspects of their care in addition to their medical management. In addition, there is a new understanding that patient experience is a key driver of best care and is integral to many of the shared goals of both patients and health care providers. To that end, regulatory bodies have begun to embrace the importance of patient experience, and a new Center for Medicare and Medicaid Services (CMS) measure of patient experience in the ED, the Emergency Department Patient Experiences with Care (EDPEC) Survey, is currently under development.[1]

One impetus for increased focus on ED patient experience stems from the growing body of literature linking superior patient experience to important health outcomes. Optimal emergency clinician empathy and communication skill has been shown to impact composite outcomes such as health-related quality of life, various pain scores, anxiety, depression, as well as specific disease conditions such as asthma, blood pressure, diabetes, osteoarthritis, and weight loss. In addition to these important health outcomes, ED patient experience is also linked to staff experience and satisfaction, including staff burnout, prompting some to refer to these themes as "flip sides of the same coin."[2,3] For example, poor patient experience has been shown to increase patient complaint frequency and malpractice risk; at the same time, physician burnout has been associated with suboptimal patient care, and poor patient experience.[3] On the other end of the spectrum, optimal patient experiences and positive patient feedback can reduce depersonalization and emotional exhaustion, and increase joy at work.[4]

SPECIFIC ISSUES

Challenges and Opportunities

Despite the well-documented links between patient experience and health outcomes, providing high-quality experiences in the ED remains a challenge, and it has been shown that patients who enter the hospital through the ED often have lower overall satisfaction with their care.[5] To understand this, one must understand the key drivers of patient experience in the ED, among which are communication, wait times and timeliness of care, empathy and compassion, technical competence, information dispensation, pain management, and the environment of care.[6]

EDs are often challenged by limited physical space capacity and crowding, and subsequently by uncomfortable and chaotic care environments that lack physical privacy and in which effective communication is difficult.[7] The impact of crowding is likely attributable to some of the associated challenges related to timely, compassionate care and the provision of adequate analgesia, both of which are key drivers of patient experience.[8] As such, understanding the drivers of patient experience can help extrapolate the modifiable aspects of practice that will drive best practice in patient experience. These include excellent communication that demonstrates empathy, working as a high-functioning team, reducing or setting expectation regarding wait times, and clear discharge communication.

Focusing on Communication

Communication and empathy are widely recognized key drivers of the patient experience. These learned skills are ones that enable physicians to ask questions in a way that is maximally effective, listen in a way that enables patients to feel heard, and speak in a way that provides clarity and demonstrates empathy. Several programs appear in the literature to help teach skills for effective communication, including one in EM[9] and several in general internal medicine. Additionally, national academies have formed around the teaching and dissemination of health care communication, some with courses specific to ED providers.[10,11]

In addition to general patient-provider communication, specifically keeping patients updated on their care has been shown to be another driver of patient experience.[12] To that end, providers should focus on creating systems either within their own clinical practice, or by leveraging other team members within the ED, to ensure that patients are kept informed about their care throughout their stay in the ED.

The perception of a high-functioning team has also been strongly associated with better overall patient experience.[6] In the ED, however, it has been shown that patients often are not encouraged to ask questions and engage actively in decision making. To that end, engaging in experiences that cultivate the skills associated with high-functioning teams is recommended. Several different frameworks have been shown to be effective.[13,14] Examples of training curricula include Crisis Resource Management (CRM) and Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS). Both employ simulation-based training to cultivate nontechnical skills related to effective communication between team members.[15,16] The key principles include having strong leadership, situational awareness, a culture that allows for mutual support, and strong systems to support clear

communication. In addition to improving teamwork and improving safety in the ED, these interventions have also been shown to increase ED staff satisfaction and team morale.[19]

Wait Times and Expectation Setting

Wait times are a concern for virtually all patients, and a driver of patient experience. To that end, focusing efforts on throughput and efficiency are essential. In addition to systems solutions aimed at increasing care efficiency and decreasing actual wait time, there are also modifiable interventions that can be undertaken at the physician level. For example, setting expectations has been shown to be a powerful intervention related to wait times, with studies demonstrating that if patients are informed about the wait time, they are significantly more likely to report higher satisfaction with the time spent waiting.

In addition to expectation setting, another tactic that emergency clinicians in the ED can employ to cultivate a sense of presence with patients is sitting. This relatively straightforward technique has been shown to increase patients' perception of the clinician's skill in communication and listening, makes instructions easier to understand, and leaves patients with a more positive evaluation of the experience.[18] Additionally, it is well known that providers who sit are perceived to have spent more time at the bedside, without having actually spent more time, than those who stand. To that end, we recommend that when possible, providers integrate sitting during the patient interview into their practice. This may require advocacy within their departments to ensure that stools are available in the room or leveraging make-shift seats using available equipment.

Discharge Instructions

In addition to a strong association with important health care outcomes such as compliance with prescription and referral recommendations and decreased adverse events, the clarity of discharge information and instructions about at-home care have been shown to be associated with improved patient experience. This is not entirely surprising, because it is well accepted that patients' understanding of their diagnosis, treatment, and follow-up plan are often not optimal. In an era of lengthy after-visit summaries that are automatically generated from the electronic health record, this is a challenge. Indeed, the majority of ED encounters offer an opportunity for improvement, with only the minority of patients being given the opportunity to ask questions or confirm their understanding. Instead, providers spend significantly more time gathering information than they do giving information.

Organizations such as the Agency for Healthcare Research and Quality (AHRQ) have proposed a set of best practices to help guide the development of optimal discharge processes within EM. Among them is a clear communication checklist at discharge (including reminding the patient about what happened during the visit, including treatments, tests, and procedures; educating the patient about the diagnosis and treatment plan; discussing any new medications and setting clear expectation about the course of the illness and reasons to return). Other EDs have leveraged dedicated nurse discharge coordinators or implemented systems to schedule follow-up appointments during the ED encounter to improve the quality of discharge.

SUMMARY

The many facets of ED patient experience are a growing area of focus in EM and are of increasing importance for patients and providers alike. There is a strong link between high-quality patient care and excellent patient experience. Additionally, there is now evidence demonstrating that improving the patient's experience can improve staff satisfaction and morale as well. Although no single intervention or tactic has been shown to be sufficient for improving patient experience, it is possible to intervene on the most important causative factors, and myriad opportunities exist in most emergency care settings.

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CHAPTER E9: QUESTIONS AND ANSWERS

1. Which of the following outcomes are impacted by patient experience?
   - **a.** Health-related quality of life
   - **b.** ED length of stay
   - **c.** ED return visits ("bounce backs")
   - **d.** Staff salaries

Answer: A. Patient-related outcomes (health-related quality of life, various pain scores, anxiety, depression, and specific disease conditions such as asthma, blood pressure, diabetes, osteoarthritis, and weight loss) and staff-related outcomes (improve experience, satisfaction, and joy at work and decrease burnout, depersonalization, and emotional exhaustion).

2. What is a key driver of patient experience?
   - **a.** Communication
   - **b.** Years of staff experience
   - **c.** ED boarding
   - **d.** Nursing ratios

Answer: A. Key drivers of patient experience are communication, empathy, expectation setting, and wait times.

3. What is an evidence-based practice you can use to improve your patient's experience?
   - **a.** Using a computer on wheels
   - **b.** Sitting in the room
   - **c.** Bedside rounding
   - **d.** Direct bedding

Answer: B. Sitting is a straightforward technique that has been shown to increase patients' perception of the provider's skill at communication and listening, makes instructions easier to understand, and leaves patients with a more positive evaluation of the experience. It has also been shown to result in patients' perception that emergency clinicians have spent more time at the bedside, without having actually spent more time, than those that stand. None of the other mentioned strategies have been studied in relationship to patient experience in the ED.

Wellness, Stress, and the Impaired Physician

Lori Weichenthal and Julius (Jay) A. Kaplan

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Wellness, Stress, and the Impaired Physician

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KEY CONCEPTS

- Physician Wellness: A quality of life that includes the presence of positive physical, mental, social, and spiritual well-being experienced in connection with activities and environments that allow physicians to develop their full potentials across personal and work-life domains.[1]
- Physician Burnout: A work-related syndrome characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment. It is frequently associated with chronic stress and emotionally intense work demands for which resources are inadequate. Physicians exhibit a higher rate of burnout than the general population, with emergency physicians experiencing some of the highest rates in the medical profession.[2-6]
- Stress: A nonspecific response of the body to any demand that can have both positive and negative effects. Without any demand, performance suffers. With too much stress, anxiety and exhaustion lead to poor performance.[1] Chronic stress is associated with burnout.
- Compassion Fatigue: Resulting from exposure to a traumatized individual, compassion fatigue has been described as the convergence of secondary traumatic stress and burnout. It can lead to a reduced capacity and interest in being empathetic toward future suffering.[7]
- Resilience: The ability of a person, community, or system to withstand, adapt, recover, rebound, or even grow from adversity, stress, or trauma. When considering individual resilience, personality traits such as optimism and altruism are found in resilient people, but behaviors such as mindfulness and reflective practices also aid resilience. External factors such as social support and good self-care are also important.[8-10]
- Impaired Physician: A physician who is unable to practice medicine with reasonable skill and safety due to mental or physical illness; due to a condition that adversely affects cognitive, motor, or perceptive skills; or due to substance abuse. Substance abuse has been described as a direct consequence of work stress and burnout for physicians.[1,11]
- A Systems Model of Physician Burnout: The process of physician burnout is complex and occurs within a multilevel system that includes the individual, the front-line care delivery team, the health care organization, and the external environment (governmental agencies, regulatory bodies, societal norms, etc.). To effectively address burnout, interventions must be directed at all levels of this complex system.[10]

FOUNDATIONS

Stress is a nonspecific response of the body to any demand that can have both positive and negative effects. Performance may suffer when there is little demand or stress; however, with too much stress, anxiety and exhaustion lead to poor performance (Fig. e10.1). Occupation stress, defined as when the resources of the individual are not sufficient to cope with the demands of the situation, is a leading modern health and safety challenge and is common in the emergency department (ED) setting.[12]

The ED is a highly demanding environment because of around-the-clock patient care in settings where life-threatening illness and injury occur with great frequency, and arrival volumes, patient acuity, and nature of emergencies rapidly and unpredictably shift. Patients frequently arrive in severe pain and anxiety, and care is often affected by language barriers, mental health issues, or many other circumstances presenting challenges in care and communication.

Emergency clinicians deal with death and dying on a daily basis and generally have little time to process emotions because of the continuous demand for patient care. This became more pronounced during the COVID-19 pandemic, when the stress and demand on emergency clinicians became tragically visible.

Personal safety is also a major issue while working in the ED environment where exposure to acts of violence, verbal abuse, and risk of exposure to potentially life-threatening diseases are higher than in other practice settings. In addition to the aforementioned stresses is the expectation of error-free practice and diagnostic certainty, with the constant possibility of human error, a missed diagnosis, and the attendant risk of medical negligence, an ever-present stress for emergency clinicians. The continued focus on the patient experience, with the threat of patient complaint and punitive action related to this, adds to this burden.[12]

The 24/7 nature of emergency medicine also creates unique physiologic stress on the emergency clinician due to changing shifts and its impact on circadian rhythms. Shift work has been shown to lead to poor quality of sleep, fatigue, and mood disturbance; challenges to maintaining relationships; and difficulty coping with the demands of daily life.[13]

Faced with decreased hospital and community resources and growing public demand for emergency services, EDs frequently are stretched beyond capacity by patient load and the boarding of admitted patients. This is further complicated by commonplace workforce shortages, nursing understaffing, and the lack of availability of on-call specialists. These issues have been shown to correlate with poorer patient outcomes and have led to a new culture in which productivity is often viewed as more important than providing safe, compassionate care.[14]

The introduction of electronic medical records (EMRs) has added a new stressor to emergency clinicians. Recent studies suggest that EMRs lead to increased administrative burden (more time charting, performing order entry, etc.) and less face-time with patients, resulting in decreased job satisfaction.[15,16] The EMR also interferes with physician-nurse collaboration and the fulfilling sense of being part of a team and working together, as communication moves from face-to-face personal interaction to an electronic interface. Communication overload, interruptions, multitasking, and performance-based targets add additional stress to providers in the ED.[12]

Given the high degree and multifactorial nature of occupational stress in the ED, it is not surprising that emergency physicians suffer from high degrees of burnout. Burnout is a work-related syndrome characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment.[2-6] The study by Shanafelt and company in 2012 found that emergency physicians had one of the highest rates of burnout when compared to other specialties, with over 60% of emergency physicians reporting one or more characteristic of burnout.[3] Subsequent surveys have demonstrated some improvement

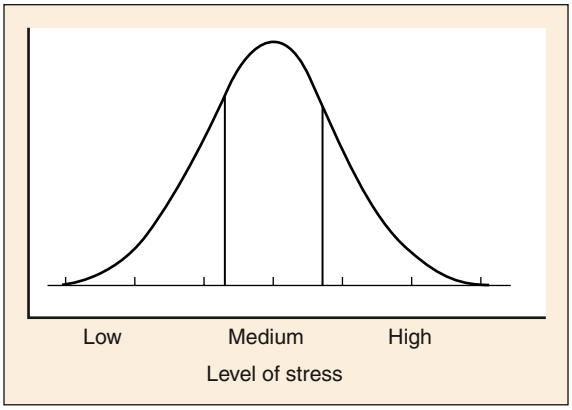

Fig. e10.1 The Yerkes-Dodson human performance and stress curve. (Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. J Compar Neuro Psych. 1908;18:459-482.)

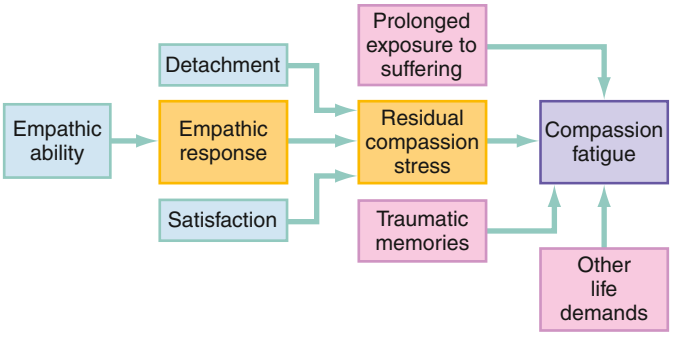

Fig. e10.2 Model of compassion fatigue. (Modified from: Figley CR. Compassion fatigue as secondary traumatic stress: an overview. In Figley CR, ed. Compassion Fatigue: Coping With Secondary Traumatic Stress Disorder. New York: Bruner/Mazel, 2005.)

in the rate of emergency physician burnout, but over 50% of emergency physicians surveyed in 2017 had symptoms of burnout, which remains above the level of many other specialties.[4,5]

Compassion fatigue also impacts emergency physicians at a higher rate than their colleagues and can be difficult to differentiate from burnout. Compassion fatigue has been described as burnout plus secondary traumatization. Secondary traumatic stress, which some describe as synonymous with compassion fatigue, is defined as the emotional and physical burden created by the additive trauma of helping others in distress that results in a reduced capacity and interest in being empathetic toward future suffering (Fig. e10.2).[17,18] Risk factors for emergency clinicians developing compassion fatigue include being in situations where they are a "first responder" or when they share some identity with the people for whom they provide care.[18] Along with leading to decreased empathy, compassion fatigue can also lead to sadness, grief, somatic complaints, detachment, anger, and changes in belief systems, which is similar to posttraumatic stress disorder (PTSD). Studies have shown that compassion fatigue impacts both residents and attending physicians in emergency medicine and may influence the desire of emergency physicians to seek early retirement.[17]

Resilience is defined as the process of adapting well and even thriving in the face of adversity, trauma, or significant stress.[9] Natural personality traits such as optimism and altruism help to support resilience; however, practices such as mindfulness and reflection are also important.[8-10] Personal resilience may have some protective benefit against burnout, but multiple studies suggest that personal resilience alone is not enough to protect emergency clinicians from the multifactorial issues that create burnout.[8,9,19]

Lack of wellness and resilience of emergency clinicians not only negatively impacts the personal and professional lives of the affected clinicians, but also has a significant impact on quality of care and the health care system as a whole. On the personal level, physicians experiencing burnout have higher rates of problematic alcohol use, distressed relationships, and depression.[2,10] At the far end of the spectrum of physician lack of wellness is physician impairment. The Federation of State Medical Boards defines an impaired physician as "one who is unable to practice medicine with reasonable skill and safety due to mental or physical illness; due to a condition that adversely affects cognitive, motor, or perceptive skills; or due to substance abuse."[1,11] Also of great concern, studies of physicians find burnout to be associated with a nearly 200% greater chance of suicide.[10] It is estimated that over 400 physicians die by suicide each year. As many as 6000 emergency physicians contemplate suicide and 400 attempt suicide each year.[6]

As concerning as the personal consequences of lack of wellness for emergency physicians are, burnout also has been shown to negatively impact quality of care and the patient experience. The presence of burnout leads to a decline in patient safety, and departments with higher burnout levels manifest a deterioration in teamwork and communication which has been shown to correlate with increased patient dissatisfaction and complaints by patients and families.[20,21] Physicians who are suffering from burnout have also been found to be less likely to follow practice guidelines and to self-report medical errors.[22,23] Physician burnout is also linked to increased absenteeism, reduced individual productivity, and increased likelihood of changing jobs or leaving the medical profession entirely.[10]

WELLNESS STRATEGIES

Individual

With the growing evidence of the burden of burnout, there has been increased focus on ways to mitigate its impact. For many years, the focus has been on educating physicians regarding self-care and tools to increase resilience. The current consensus, however, is that while it is important for physicians to focus on their own well-being, this alone is not enough to prevent burnout.[10]

Physical exercise has been shown to improve the mood of physicians and to help them cope with difficult situations.[24] Several small studies have shown that formal mindfulness meditation training can provide physicians and trainees with tools to help them deal with the burnout and manage stress.[25-27] Even small doses of mindfulness provided with the assistance of a mobile mindfulness app appear to be helpful.[28,29]

Peer groups that allow for reflection and sharing on the meaning inherent to the practice of medicine increase physician engagement and decrease depersonalization, a key component of burnout.[2,30] The benefits of such gatherings continue to show a positive impact, even a year after the termination of the intervention.

Health Care Organizations

To make meaningful progress in addressing the burden of burnout among health care professionals, change needs to occur within health care organizations. This begins with commitment from the highest level of the organization, including top executives and board leadership, that physician wellness is a top priority.[10] A strong business case exists for organizations to invest in and promote engagement in combatting and reducing physician burnout, including strategies of supporting executive leadership dedicated to improving and sustaining professional well-being across organizations.[31] Validated tools should be used to monitor the extent of burnout across organizations and in units/departments where significant burnout is discovered to develop interventions to reduce burnout and promote professional well-being.[10,31,32]

Many of these interventions will necessarily be focused on improving the work environment, including:

- Establishment of a culture of psychological safety and peer support;
- Alignment of incentives and rewards with the values of the professionals and the unit/department;
- Elimination of documentation and other administrative burdens that are not mandated and do not contribute meaningfully to patient care.[10]

After any intervention, the impact of the changes should be assessed by evaluating their impact on the well-being of the health care professionals in the unit/department where the changes were made. The results of this evaluation can be used to further refine the intervention or to suggest a need for re-direction and the need to attempt a different intervention.[31]

External Environment

The administrative burden of patient care that results from laws, regulations, policies through federal state or local government, accreditation bodies, and other standard-setting entities and agencies has also been identified as a major contributor to clinician burnout. There are proposed efforts to help address this issue by assessing laws and health care regulations and policies to determine their effects on clinician job demands, as well as their impact on patient care quality, safety, and cost.[10]

Requirements, such as those imposed by the majority of state licensing boards, that mandate physicians to report mental health histories including past professional support for mental health issues play a substantial role in physician burnout by exacerbating the already pervasive stigma regarding mental health conditions. This creates further disincentives for physicians seeking help to prevent or recover from burnout.[33-35] Efforts are underway across many states to recommend that state licensing boards either not ask about clinicians' personal health information or inquire only about current impairments due to any health condition that might negatively impact patient care. Other potential strategies include the development of legal protections through state legislative action to permit physicians to seek and receive assistance in support of the unique emotional demands of their professions as well as to manage any mental health conditions.[10]

Creating systemic changes to promote the wellness of health care providers will require a shift in culture, both within health care systems and in the external agencies that monitor and regulate them. This will require systematic efforts by policy-making bodies and other government and nongovernment entities, as well as singular commitments from health system leaders to ensure that clinicians and staff are included in the center of focus of putting patients, families, and caregivers first.

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CHAPTER E10: QUESTIONS AND ANSWERS

1. Which of the following statements regarding factors that contribute to occupational stress of the emergency clinician are true?
- **a.** Emergency clinicians with experience are not significantly impacted by end of life issues in the emergency department.
- **b.** Personal safety is usually not a concern for the emergency physician as there is often sufficient security to guard against the impact of violence or verbal abuse in the ED.
- **c.** The expectation of error-free clinical practice is a major stressor for emergency clinicians.
- **d.** Most emergency departments are not significantly stressful environments because of the predictability of patient acuity and patient arrival volumes.

Answer: C. Personal safety is also a major issue while working in the ED environment, where exposure to acts of violence, verbal abuse, and risk of exposure to potentially life-threatening diseases is higher than in other practice settings. In addition to the aforementioned stresses is the expectation of error-free practice and diagnostic certainty, with the constant possibility of human error, a missed diagnosis, and the attendant risk of medical negligence as an ever-present stress for emergency clinicians. The ED is a highly demanding environment because of 24/7 patient care in settings where life-threatening illness and injury occur with great frequency, and where arrival volumes, patient acuity, and nature of emergencies rapidly and unpredictably shift.

2. What specific strategies exist to impact individual wellness for emergency clinicians?
- **a.** A focus on individual well-being alone is usually sufficient to prevent burnout.
- **b.** Vigorous daily exercise has been shown to improve the ability to cope with difficult situations but only improves mood less than 10% of the time.
- **c.** Peer groups that allow for reflection and sharing on the meaning inherent to the practice of medicine increase physician engagement and decrease depersonalization.
- **d.** Health care organizational engagement has little impact in individual physician wellness but can improve efficiency of care in the work environment.
- **e.** All of the above.

Answer: C. The current consensus suggests the importance of physicians focusing on their own well-being, but this alone is not enough to prevent burnout. Physical exercise has been shown to improve the mood of physicians and to help them cope with difficult situations. A strong business case exists for organizations to invest in and promote engagement in combatting and reducing physician burnout, including strategies of supporting executive leadership dedicated to improving and sustaining professional well-being across organizations.

3. Which of the following statements best describes physician burnout?
- **a.** A non-work-related syndrome characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment.
- **b.** Physician burnout is frequently associated with chronic stress and emotionally intense work demands for which resources are inadequate.
- **c.** Emergency physicians exhibit a lower rate of burnout compared to physicians in other specialties and to the general population.
- **d.** Physician burnout can often result in impairment that results in an inability to practice medicine and can lead to substance abuse.
- **e.** Both B and D are true.

Answer: E. Physician burnout is a work-related syndrome characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment. It is frequently associated with chronic stress and emotionally intense work demands for which resources are inadequate. Physicians exhibit a higher rate of burnout than the general population, with emergency physicians experiencing some of the highest rates in the medical profession.

4. A systems model of physician burnout includes all of the following features, except:
- **a.** The external environment
- **b.** Organizational support and buy-in
- **c.** Governmental agencies and regulatory bodies including licensing boards
- **d.** Religious factors

Answer: D. The process of physician burnout is complex and occurs within a multilevel system that includes the individual, the front-line care delivery team, the health care organization, and the external environment (governmental agencies, regulatory bodies, societal norms, etc.) (see Fig. e10.3). To effectively address burnout, interventions must be directed at all levels of this complex system

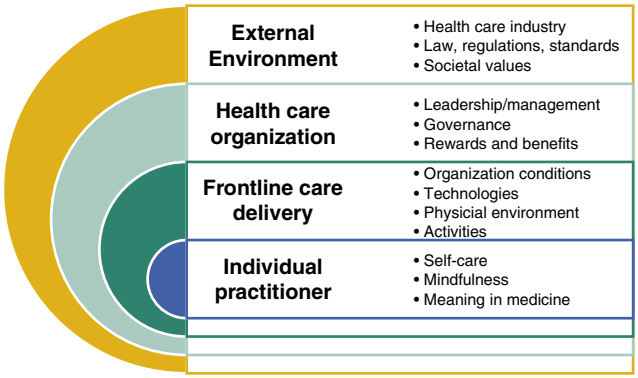

Fig. e10.3 The four levels of the systems model of physician burnout. (Modified from: National Academies of Sciences, Engineering, and Medicine. *Taking Action Against Clinician Burnout: A Systems Approach to Professional Well-Being*. Washington DC: The National Academies Press; 2019.)

Forensic Emergency Medicine

Adedamola A. Ogunniyi and Andrea W. Wu

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Forensic Emergency Medicine

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KEY CONCEPTS

- Knowledge of wound mechanics, production, and appearance can provide practicing emergency clinicians with important clues regarding the forensic interpretations of injuries.
- Wounds and injuries should be diagrammed and photographed.
- The medical record should accurately document objective findings associated with a patient's wounds. Emergency clinicians should not speculate about their mechanism or cause.
- For the chain of custody to be preserved, any evidence collected during the course of treatment must be documented in the medical record, including to whom the evidence was given.

PERSPECTIVE

Clinical forensic emergency medicine is the application of forensic medical knowledge, techniques, and procedures to the management of patients in the emergency department (ED).[1] It is a key link through which patients or victims of violence can receive recourse for the actions against them. Emergency clinicians are in the unique position of being the first contact for most of these patients and play a crucial role in this process. They are also the clinicians who have the most contact with law enforcement and are therefore well suited to aid in evidence conservation. Many emergency clinicians have limited training in clinical forensic emergency medicine and, as such, critical information or data can be missed during these interactions.[1]

All patients who are victims of physical or sexual assault, abuse, or trauma have forensic needs. When treating injuries without consideration of their forensic significance, emergency clinicians may misinterpret wounds, fail to recognize signs of abuse or intimate partner violence, and inadequately describe the physical appearance of the wounds. During the provision of patient care, evidence that can be of critical significance to criminal or civil proceedings may be lost, discarded, or inadvertently washed away, despite requirements by the Joint Commission to "preserve evidentiary materials and support future legal actions." Prior studies have shown that evidence may be accidentally discarded during the initial evaluation and that injuries are also improperly documented.

Emergency medicine programs have identified and described the need for forensic training in their residency curricula. The American College of Emergency Physicians established the Forensic Medicine Section in 2006 to provide emergency clinicians with additional forensic resources and training. Unfortunately, no formal training programs currently exist in the United States. In contrast, the British Royal College of Physicians established the Faculty of Forensic and Legal Medicine (FFLM) in 2006 as the authoritative body on clinical forensic medicine in the United Kingdom. The FFLM has created training and certification programs and board-type certification examinations after 2 years of forensic practice for British physicians.[2]

There are several important ways to address this gap through training and exposure to clinical forensic emergency medicine. Forensic examinations should be conducted with the consent of the patient, legal guardian or court, or by implied consent. The evaluation should include a history and physical examination in which all wounds are documented and described in as much detail as possible, as well as photographs and anatomic diagrams.[1] Even simple findings, such as contusions or ecchymoses associated with injuries, may serve as important clues as to how the injury was sustained and may be invaluable in future legal proceedings. Evaluations of gunshot and stab wounds, physical or sexual abuse, intimate partner violence, and motor vehicle–related trauma should also be adequately documented for possible use as evidence. Documentation should include digital photographs (whenever possible based on the patient's clinical condition) as well as a narrative and diagrams.

Evidentiary material, such as clothing, bullets, and shrapnel, should be collected.[1] Clothing should be stored in a paper bag because plastic bags retain moisture and can promote bacteria growth, which leads to degradation of DNA; bullets and other metallic foreign bodies should be handled minimally and with gloved hands. Contact with metal instruments should also be avoided because these can alter the markings present.[1]

When physical injuries are misinterpreted and these misinterpretations are entered into the medical record, or when valuable evidence is lost or destroyed in the process of providing patient care, there are consequences for the legal proceedings that may follow.[2] These acts of omission or commission may deny patients their deserved redress in the justice system. A proper understanding of the forensic relevance of certain observations is the key to protecting the rights of victims of assault.

FORENSIC ASPECTS OF GUNSHOT WOUNDS

Background

Ballistics

Ballistics is the science of the motion of projectiles in flight.[3] Ballistic physics is broken down into three parts, based on the material with which the bullet interacts:

1. Internal ballistics, which pertains to the projectile while in the firearm
2. External ballistics, or the path of the projectile from when it leaves the firearm until it reaches the target
3. Terminal (or wound) ballistics

Internal ballistics factors in the design of the firearm and how the combustion of gunpowder within the firearm generates the pressure that subsequently projects the missile. External ballistics takes into consideration the effects of gravity and drag on the missile and how they affect the distance travelled and the accuracy with which it hits the intended target.

Wound ballistics is the most clinically relevant because it is the study of the effects of penetrating projectiles on the body. Tissue disruption (wound severity) is directly related to the amount of kinetic energy (KE = ½mv^2 [m = mass; v = velocity]) transferred to it, not to the total amount of kinetic energy possessed by the bullet. There are two broad categories of weapons based on the amount of potential kinetic energy that can be transferred from the missile to the tissue:

1. High-velocity weapons, which generate projectile velocities ranging from 1500 to 4000 ft/s (or >600 m/s). Examples of these are rifles or military weapons. Consequently, bullets fired from such weapons possess a higher kinetic energy and therefore theoretically have greater wounding capacity.
2. Low-velocity weapons, which generate projectile velocities ranging from 700 to 1600 ft/s (or <600 m/s). These weapons include handguns, shotguns, and air rifles (such as ball-bearing [BB] guns).

Rifle bullets have more kinetic energy and a theoretically higher wounding potential, but energy transfer (and, by extension, wound severity) is the result of multiple variables. The most important are bullet type (e.g., weight, deforming type, fragmenting type), bullet velocity, and the characteristics, location, and nature of the impacted tissue itself (tissue over bone or tissue over organs).[4] The formula KE = ½m(V_1 − V_2)^2 better reflects the actual energy transfer occurring during tissue penetration and wounding.[4]

The principal mechanism for tissue damage by bullets is crushing. A bullet traveling through tissue generates two cavities, one permanent and the other temporary. The size of the permanent cavity varies with the size, shape, and configuration of the bullet. A hollow point bullet that mushrooms can increase its diameter 2.5 times on impact and will increase the area of tissue crush 6.25 times compared with a non-deformed bullet. The temporary cavity results from a shock wave generated as the bullet enters the tissue, which results in a brief distortion or stretching of the tissue. This tissue distortion lasts for a brief amount of time, 5 to 10 milliseconds from its generation until its collapse, and leaves behind crushed tissue and the permanent cavity. The size of the temporary cavity is also dependent on bullet/missile mass and velocity, and the resulting effect depends on the elasticity of the tissue traversed. Solid organs such as the liver, bone, or kidneys do not tolerate this temporary deformation as well as more elastic tissue (such as lungs, skeletal muscle, skin), and therefore sustain more damage. Secondary wounding can occur in situations in which the bullet hits a target (usually bone) and fragments disperse, causing further tissue damage.

Forensic Evaluation of Handgun Injuries

The Weapon. Handguns are the most common firearm available. There are four categories of handguns: (1) the single-shot weapon (usually a target pistol); (2) the derringer (a small, concealable weapon, usually with two barrels); (3) the revolver (a weapon with a rotating cylinder that advances with the pull of the trigger); and (4) the semiautomatic pistol (which fires with each pull of the trigger). The semiautomatic handgun is the most popular because its magazine (or clip) can hold up to 17 cartridges, whereas revolvers hold five or six cartridges.

Handgun Ammunition. The cartridge, or round, is composed of the primer, cartridge case, powder, and bullet (Fig. e11.1). The bullet is the projectile that is propelled out of the muzzle. The primer is a small explosive charge in the base of the cartridge that ignites the gunpowder. The primer may contain lead, barium, or antimony. These materials may be deposited on the hands of the shooter, on the victim of a close-range assault, or on objects within a room in which the weapon was discharged.

The cartridge case is typically made of brass, although other materials may be used. The function of the cartridge case is to expand slightly, sealing the chamber against the escaping gases and propelling the bullet down the barrel. On detonation, a cartridge case is imprinted with unique microscopic marks that are valuable evidence and should be preserved for law enforcement.

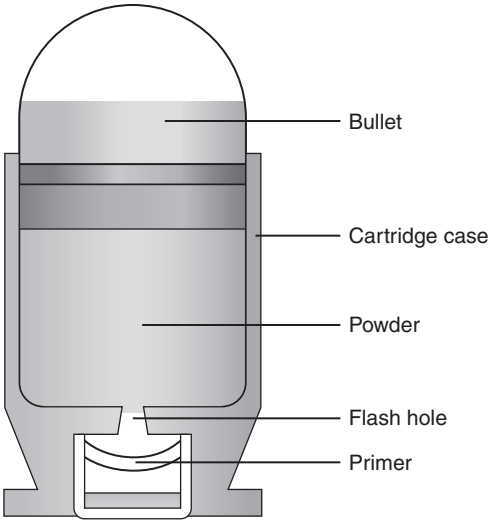


Fig. e11.1 A cartridge consists of several distinct components—bullet, cartridge case, gunpowder, flash hole, and primer.

The gunpowder found in all commercial cartridges except blanks a smokeless powder made with a single base (nitrocellulose) or a double base (nitrocellulose and nitroglycerin). When a weapon is discharged, not all the gunpowder is consumed. A percentage of the unburned or partially burned gunpowder will travel out of the end of the muzzle for a short distance (<48 inches or 60 cm). The distance depends on the physical characteristics and shape of the powder and the weapon's barrel length.

Blank cartridges, muzzleloaders, and other antiques or replicas may use black powder. Black powder (a combination of potassium nitrate, charcoal, and sulfur) does not burn as efficiently as the smokeless powder and results in a large flame and white smoke. As such, black powder can produce powder burns by igniting clothing.

The bullet is the projectile that is propelled down the gun barrel at velocities ranging from 700 to 1600 ft/s (213 to 488 m/s). The higher velocities are achieved by the inclusion of supplemental gunpowder in the cartridge case (a magnum load; hence, a .357 magnum). The diameter of the bullet's base is termed its *caliber.* Bullet caliber is described in hundredths of an inch or millimeters. Handgun bullets range from .22 caliber, or 5.56 mm, to .45 caliber, or 11.3 mm. A bullet's weight is measured in grains, with 7000 grains/lb.

The most common bullet types are the round nose, full metal jacket, hollow point, wad cutter, and semi–wad cutter. Bullets generally are a solid core of lead or steel. If a jacket covers the bullet core, the jacket's metal is usually copper or aluminum. If the jacket covers only a portion of the core, the bullet is said to be semijacketed. If the core is completely covered, it is said to have a full metal jacket. Some bullets have a hole in the tip and are called hollow points. The hole causes the bullet to expand on contact, which significantly increases the damage to tissue.

Forensic Aspects of Rifles

Rifles are shoulder-fired weapons designed to generate significant pressures in the muzzle and, as such, result in firing of ammunition at high speeds. Centerfire rifle bullets, .223 to .308 caliber, are similar in diameter to handgun ammunition but, based on the formula for kinetic energy (KE = ½mv^2), their wounding potential is greatly enhanced by the higher velocity of the round. Injuries result from the transference of energy from the projectile to tissue, organs, and bony structures.

With medium-velocity rounds (2000 to 3000 ft/s, approximately 600 to 900 m/s) and high-velocity rounds (>3000 ft/s), a temporary cavity is formed along the wound tract, which may be 11 or 12 times the diameter of the bullet. High-velocity rounds can also cause tissue damage away from the physical track taken by the projectile. Because of the amount of energy possessed and transferred to underlying tissue, exit wounds associated with centerfire rifles, in contrast to those associated with handguns, are generally larger than their corresponding entrance wounds (Fig. e11.2).

Forensic Aspects of Shotguns

Shotguns are similar to rifles, but the missiles are multiple small projectiles, all of which have the potential to cause injury. Shotguns have the barrel length of rifles but can discharge pellets or single slugs down a smooth bore barrel. The caliber of a shotgun is defined by the term *gauge*. Historically, the gauge of a gun referred to the number of lead balls of the given bore diameter that make up a pound—for example, 12 lead balls to make 1 lb. A shotgun cartridge may contain only a single slug or may contain hundreds of pellets (Fig. e11.3A). Pellets range in diameter from 0.05 inch (#12 birdshot) to 0.36 inch (000 buckshot). A shotgun cartridge is made of several components that will be of forensic value and should be collected in the ED (see Fig. e11.3B).

Shotgun slugs are projectiles that may weigh 200 times more than handgun ammunition; for example, a 12-gauge slug weighs 547 g, and a .22 long rifle bullet weighs 2.6 g (see Fig. e11.3B). The velocities of shotgun slugs are in the range of 1500 to 1800 ft/s (457 to 549 m/s). The sabot is the structure that helps seat the shotgun slug and allows it to be fired at higher muzzle velocities. These are usually made of lightweight materials such as plastic, carbon fiber, or light metals (such as aluminum). Sabots themselves can cause injury if they make contact with tissue.

Fig. e11.2 This patient sustained a high-velocity gunshot wound to the forehead. High-velocity rifle rounds, due to their kinetic energy, can cause massive damage when the energy is transferred to underlying tissue.

Forensic Aspects of Air Guns/Rifles

Air guns/rifles (such as BB guns and pellet air guns) work very similarly to traditional firearms and generate muzzle velocities comparable to low-velocity weapons. As such, they possess enough kinetic energy to cause injuries because they can penetrate tissue, and particularly because they are often fired at close range. In fact, recent studies have shown that these weapons pose a significant health concern, particularly in the pediatric population.[5]

Epidemiology

According to the National Vital Statistics report from the Centers of Disease Control and Prevention (CDC), 39,773 people died from firearm-related injuries in the United States in 2017 with about 14,542 being firearm homicides.[6] On average, 645 people die from firearm violence a week and 1565 more are treated in an emergency department for a firearm-related injury.[7,8] A recent study by Fowler et al. provided similar information; on average between 2010 and 2012, over 32,000

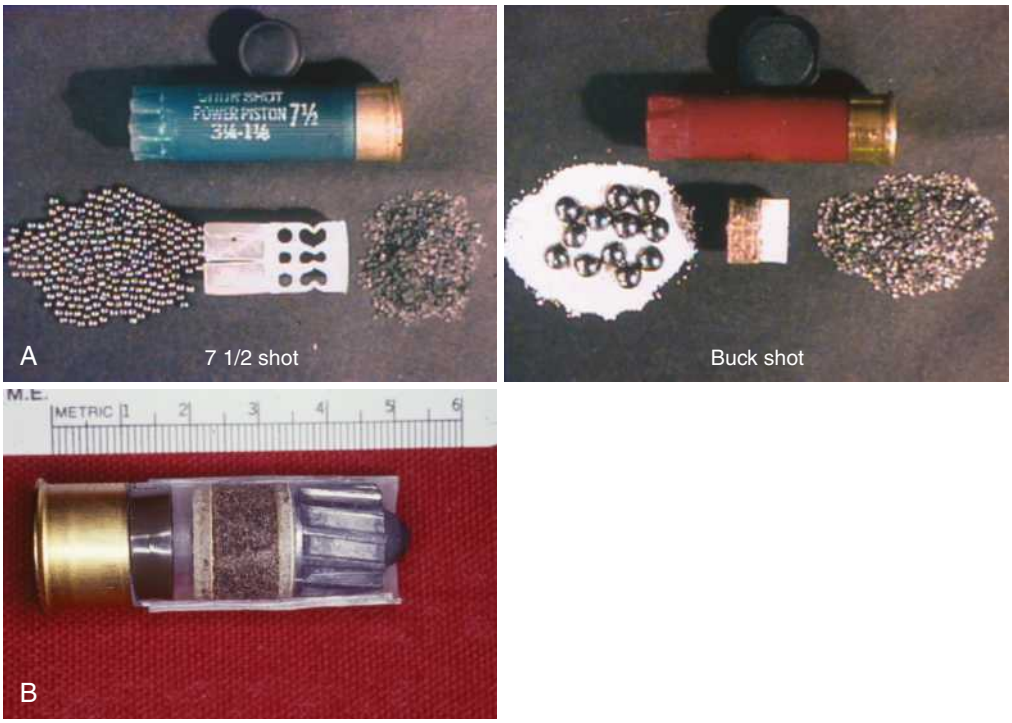


Fig. e11.3 (A) Shotgun cartridges may contain eight to hundreds of pellets. (B) A single shotgun slug and components of the cartridge.

people died and over 67,000 people were injured by firearms per year, with case fatality rates being the highest for self-harm–related injuries (85%), followed by assault-related injuries (19%).[8] Studies have suggested that the rates of firearm violence (nonfatal and fatal) declined and then stabilized over the last few decades; however, when disaggregated, unintentional firearm deaths appear to have declined while rates of firearm suicide and nonfatal firearm assaults have increased.[8] While the number of firearm injuries have stabilized, the mortality rate has largely remained unchanged.[9-11]

Firearm injuries occur predominantly in certain groups, particularly in young people, males, and racial/ethnic minorities.[8] The rates of fatal firearm injuries are highest in males aged 25 to 34 (followed by those aged 15 to 24), with homicides being more common in this age range.[8] Firearm injury rates on the whole are highest in males between the ages of 15 and 45 years old, particularly in those of African American ethnicity.[8,11] Suicides are more common than homicides, and the incidence of the latter appears to be decreasing. Suicides accounted for 60.5% of all firearm fatalities from 2002 to 2012[11] and tend to be more common in those over the age of 65 and in non-Hispanic white males.[8] In a recent study, firearm homicide was the leading cause of death in African American males aged 15 to 34 years in 2012 and was the second leading cause of death for whites or Hispanic males of the same age range.[11] Firearm violence was the second leading cause of death in females aged 15 to 24 years.[11] In contrast, suicide rates were higher in white males, and the divergence increased with age, starting in adolescence.

Hospitalizations for nonfatal firearm injuries have followed the same trend: males account for 90% of nonfatal firearm visits to the emergency department and young people under the age of 35 are responsible for 72% of nonfatal firearm ED visits.[8] Stray bullet injuries are also important because they frequently affect females, children, or older adults, who may not have any relation to the associated violence.

Firearm injuries are not limited to adults. Firearm homicide is the leading cause of death in African American youth aged 14 to 24 years and the second leading cause of death in other youth, regardless of age or race.[12] Firearm-related deaths are the third leading cause of mortality among US children aged 1 to 17 years and are the second leading cause of injury-related death in this age group, surpassed only by motor vehicle injury deaths.[13] The American College of Surgeons issued a report in 2013 stating that firearm injuries were the second leading cause of death in pediatric trauma centers.[14,15] A recent study showed that approximately 1300 children (aged 0 to 17) died and 5790 were treated for gunshot wounds annually from 2012 to 2014, with a higher case fatality rate for self-harm injuries.[13] Males, children aged 13 to 17, and African Americans had disproportionately higher rates of mortality from firearm injuries.[13,16] While unintentional injuries and homicides have declined, there has been an increasing trend of firearm suicides, as noted by Fowler.[13] The medical impact is significant. A recent study noted that there were 21,416 pediatric ED visits in those younger than 19 from 2009 to 2014 based on data from the National Trauma Data Bank[16]; these patients were more likely to be male, African American, aged 12 to 18 years, and victims of assault.[16]

Air rifles and other nonpowder firearms also contribute to the prevalence of firearm injuries. A recent review noted that there were approximately 10,288 pediatric air gun injuries in 2011 in patients under 19 years of age[5] and another study by Jones *et al.* showed that on average, 13,486 pediatric non-powder firearm injuries are treated in US EDs annually (in patients < 18 years).[17]

To manage patients with firearm-related injuries properly, it is also important to have a thorough understanding of the pathophysiology involved. Several misconceptions exist in the management of these injuries, such as a poor understanding of wound sterility following gunshot injuries, the need for wound debridement, and the need for prophylactic antibiotics.[4] A study published in 2015 showed that such misconceptions were prevalent and were not influenced by prior Advanced Trauma Life Support (ATLS) training.[4] As such, focused training in forensic medicine is necessary to improve knowledge and the ability to treat these patients adequately.

Clinical Features

Errors of Interpretation and Terminology

Emergency clinicians are in the ideal position to evaluate and document the state of a gunshot wound because they see and explore it before it is disturbed, distorted, or destroyed by surgical intervention.[1] Documentation of gunshot wounds should include the anatomic location of the wound as well as its size, shape, and distinguishing characteristics. Digital photographs of the wound should be taken whenever possible with a ruler for size reference. Wounds should be described according to the standard anatomic position, with the arms to the sides and palms facing forward.

Emergency clinicians should not describe wounds as "entrance" or "exit" but, using appropriate forensic terminology, should document a detailed description of the wound, including its appearance, characteristics, and location, without attempting to interpret the wound type or bullet caliber.[1] Exit wounds are not always larger than entrance wounds, and wound size does not consistently correspond to bullet caliber.[1]

The size of any wound (entrance or exit) is determined by five factors—the size, shape, configuration, or angle, and velocity of the projectile at the instant of impact with tissue and the physical characteristics of the impacted tissue itself. If the projectile is slowed and its shape unchanged on exiting the skin, the exit wound may be the same size as or smaller than the corresponding entrance wound. If the projectile increases its surface area by fragmenting or changing its configuration while maintaining a substantial velocity, the exit wound may be significantly larger than the entrance wound. If the bullet strikes bone, fragments may extrude from the exit wound and contribute to the size and shape of the wound. Tissue elasticity also affects wound size so that entrance or exit wounds may be smaller, equal to, or larger than the projectile that caused them. Wounds on the palm or sole may appear as slits and can be easily mistaken for stab wounds.

A treating emergency clinician may be requested to render factual testimony, expert testimony, or both in a criminal case. Expert forensic testimony rendered without an appropriate forensic examination or adequate forensic training may mislead participants in the criminal justice system (e.g., "the exit wound is always larger than the entrance wound"). Opinions related to entrance versus exit wounds or the range of fire can affect the determination of innocence or guilt and should not be used except by trained practitioners.

The subsequent sections highlight the clinical features of entrance and exit wounds that result from the use of different types of firearms. This information is provided to make emergency clinicians aware of the varying presentations, depending on the distance from the target. Clinicians should refrain from speculating on the type of wound and simply document the findings noted on examination.

Handgun Entrance Wounds

Range of fire is the distance from the muzzle to the victim and can be divided into four general categories: contact, near-contact or close range, intermediate or medium range, and indeterminate or distant range (Table e11.1). The size of the entrance wound does not correlate with the caliber of the bullet because entrance wounds over elastic tissue will contract around the tissue defect and have a diameter much less than the caliber of the bullet.

TABLE E11.1 Range of Fire

Range	Inches/Centimeters (Barrel to Skin)	Physical Properties
Contact	0	Soot, seared skin, triangular tears
Close	0–6 (0–15cm)	Soot, abrasion collar (abrasion collar may be obscured by soot)
Intermediate	<48 (<121cm)	Tattooing, abrasion collar
Distant or indeterminate	Any distance	Abrasion collar (intermediate objects will prevent soot and gunpowder from contacting the skin)

Contact Wounds. There are three subcategories of contact wounds: (1) tight contact, in which the muzzle is pushed hard against the skin; (2) loose contact, in which the muzzle is incompletely or loosely held against the skin; and (3) contact through clothing.

In a tight contact wound, all materials—the bullet, gases, soot, the incompletely burned pieces of gunpowder, and metal fragments—are driven into the wound. These wounds can vary from a small hole with seared blackened edges from the discharge of hot gases and an actual flame to a gaping stellate wound (Fig. e11.4). Large wounds occur when the wound is inflicted over thin, inelastic, or bony tissue, and the injected hot gases cause the skin to expand until it stretches and tears. These tears will have a triangular shape, with the base of the triangle overlying the entrance wound. Tears are generally associated with .32 caliber or greater, or with magnum loads. Large stellate contact wounds are easily misinterpreted as exit wounds if the determination is based solely on their size (see Fig. e11.4B).

Stellate tears are not pathognomonic for contact wounds, however. Tangential wounds, ricochet or tumbling bullets, and some exit wounds may also be stellate. These wounds' appearance differs from that of tight contact wounds by the absence of soot and powder within the wound and a lack of seared wound margins.

In some tight contact wounds, expanding skin is forced back against the muzzle of the gun, leaving a characteristic muzzle abrasion or muzzle contusion (Fig. e11.5). Patterns such as these should be documented before wound débridement or surgery because they are helpful in determining the type of weapon used (revolver vs. semiautomatic).

When a gun's muzzle or barrel is in loose contact with or is angled to the skin, the soot and gunpowder residue are present within and surrounding the wound. The angle between the muzzle and skin determines the soot pattern. A tangential, loose, or near-contact wound produces an elongated searing and soot deposit surrounding the wound. Discharge of a weapon in contact with clothing results in the gases and soot being deposited between the garment and skin. This results in a diffuse pattern of soot surrounding a wound, with seared margins (see Fig. e11.4C).

Close-Range Wounds. Close range is the maximum range at which soot is deposited on the wound or clothing. The muzzle to target distance is usually less than 6 inches (15 cm) but may be as much as 12 inches (30 cm). Beyond 6 inches, most of the soot usually falls away and does not reach the skin or clothing. The concentration of soot varies inversely with the muzzle-to-target distance and is influenced by the type of gunpowder and ammunition used, length of the weapon's barrel, and caliber and type of weapon itself (Fig. e11.6). A precise range of fire (e.g., 2 vs. 5 inches) cannot be determined from examination of the wound alone. Because soot can be removed with débridement or wound cleansing, its presence and configuration around the wound should be noted and photographed before débridement unless the patient's clinical condition precludes this.

Intermediate-Range Wounds. Tattooing, or stippling, is pathognomonic for an intermediate-range gunshot wound. Tattooing appears as punctate abrasions and is caused by contact with partially burned and wholly unburned pieces of gunpowder (Fig. e11.7). Tattooing or stippling cannot be wiped away. The appearance differs from powder burns due to black powder because black powder burns rapidly and at high heat, resulting in a burn appearance more reminiscent of those from thermal injuries. Tattooing rarely occurs on the palms of the hands or soles of the feet because of the thickness of the epithelium.

Tattooing may occur as close as 1 cm to and as far away as 1.3 m from the weapon but is generally found at distances of 60 cm or less. The density of the tattooing and associated pattern depends on the length of the barrel, muzzle-to-skin distance, type of gunpowder, presence of intermediate objects, and caliber and type of ammunition. Clothing, hair, or other barriers may prevent tattooing from occurring. The presence of partially or entirely unburned pieces of gunpowder and gunpowder residue on clothing or skin aids in determining the range of fire. On rare occasions, pieces of gunpowder can penetrate thin clothing and leave punctate abrasions (Fig. e11.8).

Long-Range Wounds. The distant or long-range wound is inflicted from far enough away that only the bullet makes contact with the skin. There is no tattooing or soot. As the bullet penetrates the skin, the skin is indented, resulting in the creation of an abrasion collar, also termed an *abrasion margin*, *abrasion rim*, or *abrasion ring* (Fig. e11.9). This collar is an abraded area of tissue that surrounds an entry wound as the result of friction between the bullet and epithelium. The width of the abrasion collar varies with the angle of impact. Most entrance wounds will have an abrasion collar. Entrance wounds on the palms and soles are exceptions because these wounds usually appear slit-like.

The abrasion collar is secondary to friction and is not the result of thermal changes associated with a hot projectile. The abrasion collar of a contact or close-range wound may be undetectable because hot gases and a flame have seared the tissue. When an abrasion collar is the only visible superficial clinical finding present, the term *indeterminate range* describes the range of fire. A wound inflicted from 10 feet will appear the same as a wound inflicted from 100 feet. An exact range cannot be determined with a distant wound.

Determining the range of fire may be complicated when clothing prevents the deposition of soot and powder on the skin. Without the overlying clothing or without information regarding the crime scene, the wound may appear to be from a distant range of fire. In reality, the range may have been close or intermediate. Conversely, a projectile discharged from a distant range of fire may mimic an intermediate range if it strikes an object, such as glass, that fragments. As with unburned gunpowder, when the glass fragments strike the skin, they may also cause punctate abrasions, resulting in pseudotattooing (Fig. e11.10).

Atypical Entrance Wounds. Atypical entrance wounds occur when a bullet encounters an intermediate object, such as a window, wall, or door, before striking the victim. The intermediate object can cause the bullet to tumble and may change the its size, shape, or path. Such changes can result in entrance wounds with large stellate configurations that mimic close-range or contact wounds (Fig. e11.11). Ricochet bullets may also cause atypical entrance wounds. Graze wounds are atypical wounds from tangential contact with a passing bullet.

Handgun Exit Wounds

Exit wounds are the result of a bullet pushing and stretching the skin from the inside out. The skin edges generally are everted with sharp but irregular margins. The size of the exit wound is determined by

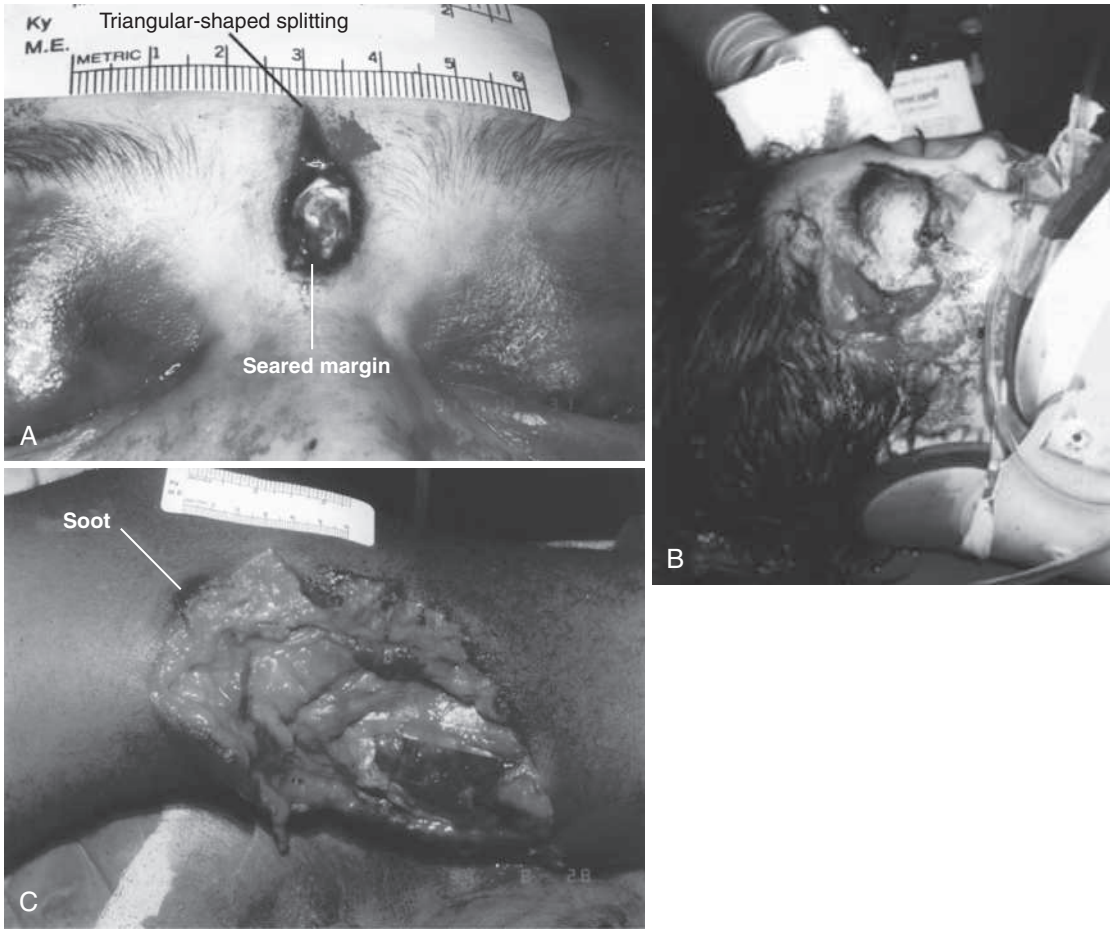


Fig. e11.4 (A) Tight-contact entrance wound from a .38 caliber revolver. The wound margins are seared from the discharge of hot gases and flame from the end of the barrel. The triangular tear is the result of tissue expansion from the discharge of gases into the tissue. (B) Tight-contact entrance wound with large stellate tears from a .38 semiautomatic pistol. The large triangular tears are the result of rapid expansion of gases under the skin. (C) Tangential-contact wound from a 9 mm pistol on the medial aspect of the left calf. The presence of soot at the superior aspect indicates a close range of fire. The patient initially reported that he was shot from a distance of 3 or 4 feet (0.9–1.2m) and later admitted that he had accidentally shot himself while withdrawing his pistol from his boot. Large wounds, as seen in B and C, may be misinterpreted as exit wounds because of their size.

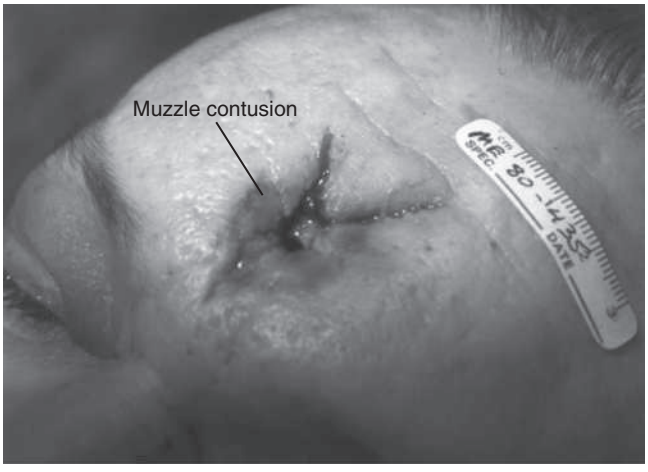


Fig. e11.5 A muzzle contusion is a contusion caused by skin expansion against the barrel of the weapon. Muzzle contusions are associated with contact wounds.

the energy transferred from the bullet to underlying tissue and by the bullet's size and configuration as it exits the skin (Fig. e11.12). Once a bullet enters the skin, its configuration may change from its usual nose-first attitude owing to tumbling and yaw. A bullet that exits the skin sideways, or one that has increased its surface area by mushrooming or transferring its energy to underlying bone, will have an exit wound larger than its entrance wound.

Atypical Exit Wounds. A shored exit wound is a wound that has an associated false abrasion collar. If the skin is pressed against or supported by a firm object or surface at the moment the bullet exits, the skin can be compressed between the exiting bullet and supporting surface (Fig. e11.13). Examples of supporting structures include belts, floors, walls, doors, chairs, and mattresses.

Centerfire Rifle Wounds

Projectiles discharged from centerfire rifles have the potential to inflict massive tissue damage (see Fig. e11.2). Entrance wounds associated with high-velocity, centerfire projectiles do not significantly differ from those of handguns. Entrance wounds will generally exhibit abrasion collars or microtears on the skin surface (Fig. e11.14). Wounds will also have associated soot deposition and tattooing but, because of a number of variables such as muzzle length, amount of powder in a given cartridge, muzzle configuration, and type of gunpowder, the range of fire in rifle wounds is not as clearly defined as in handgun wounds. The determination of an exact range of fire for rifles and shotguns is best

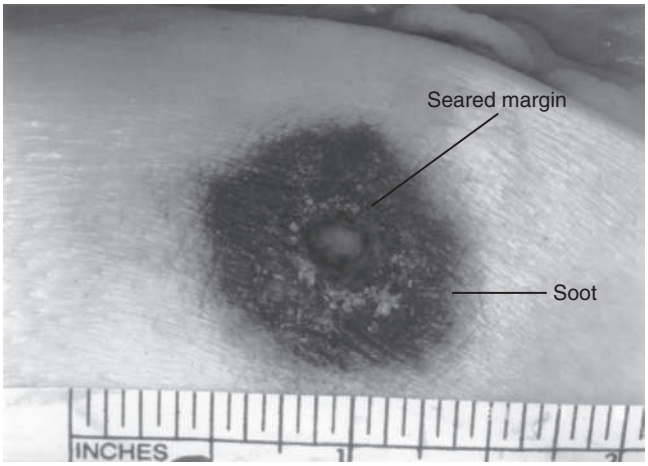


Fig. e11.6 Close-range wound with soot deposition. Soot is associated with a range of fire of 6 inches (15 cm) or less.

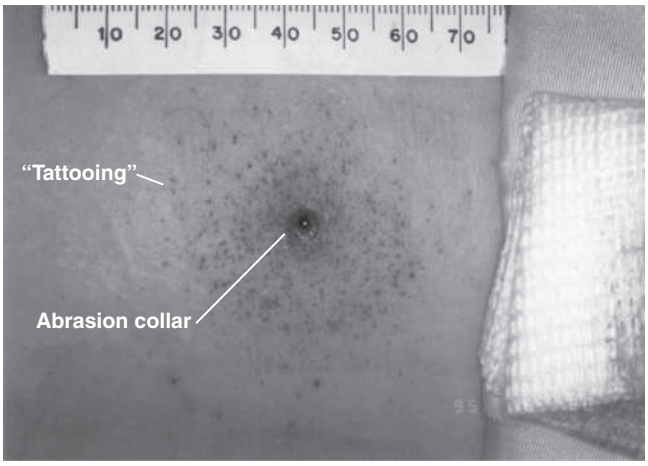


Fig. e11.7 Tattooing results from contact with pieces of unburned gunpowder. These punctate abrasions are associated with an intermediate range of fire, generally less than 36 inches (90 cm). The density of these abrasions depends on the length of the gun's barrel, distance from the muzzle to the skin, type of gunpowder used, and presence of any intervening objects.

established through controlled testing performed by a firearms examiner at a crime laboratory.

High-velocity bullets with jackets and lead cores generally break up into hundreds of fragments, termed a *lead snowstorm*, on entering tissue, resulting in significant tissue damage (Fig. e11.15). If the tissue penetrated is deep, the bullet fragments may fail to exit and remain embedded. It is therefore possible to sustain an injury from a high-velocity round and not exhibit an exit wound. High-velocity rounds with steel cores will almost uniformly exit intact. Steel core ammunition is not available for civilian use so such injuries will rarely be encountered by most ED providers.

Shotgun Wounds

The massive damage caused by slugs may obliterate the abrasion collar usually associated with entrance wounds. Shotgun slugs will almost uniformly exit the body with large exit wounds. Tissue penetration is more limited with shotgun pellets as the projectile velocities are much lower, particularly if fired at long range. If fired at close range, however, the damage is much more significant, again depending on the elasticity of the tissue encountered.

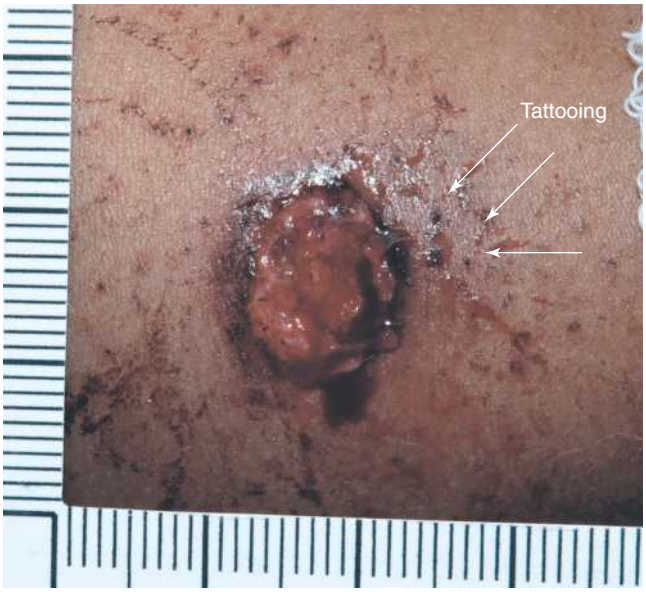


Fig. e11.8 Gunpowder can penetrate thin clothing and deposit tattooing on the skin. A 3-year-old was shot with a .45 caliber round at close range, and pieces of gunpowder passed through his T-shirt.

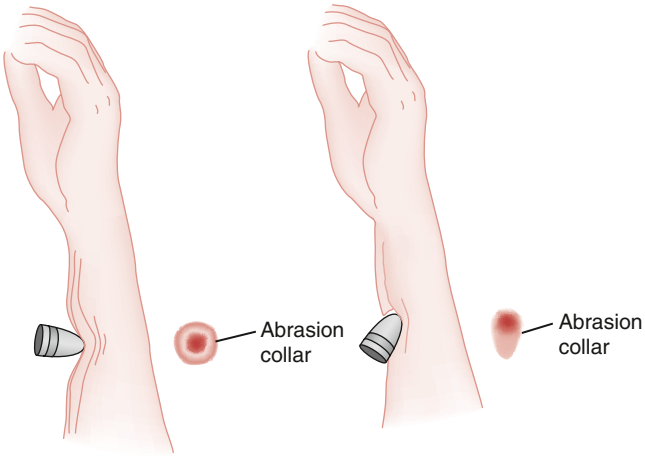


Fig. e11.9 An abrasion collar is the abraded area surrounding the entrance wound created by the bullet when it indents and passes through the epithelium. The collar or rim is the result of friction between the bullet and the epithelium. The width of the abrasion collar will vary with the angle of impact.

Clinical Features of Firearm Injuries

Patients with firearm injuries have varying presentations, depending on the anatomic location of the injury and type of weapon used. It is important to identify all wounds to guide the determination of the potential missile trajectory and anticipate the other possible injuries. It is also important to consider how the temporary and permanent cavities may manifest anatomically to guide imaging and management.

Patients with injuries to the head and neck often present in critical condition due to the abundance of vital neurovascular structures in this area. Head-injured patients can present in extremis with altered mental status and signs of impending herniation, in which case emergent airway management and resuscitation are necessary. Emergent airway management may also be required in cases with intraoral involvement or a need for operative intervention for other reasons (e.g., an exploratory laparotomy). Neck injuries can present with a multitude

of symptoms, depending on the structures affected. Symptoms can run the gamut from asymptomatic to active bleeding (from trauma to the vasculature), dysphonia or hoarseness (due to pharyngeal or tracheal injuries), or hemiplegia or hemiparesis (if the internal carotids are disrupted). Urgent airway and bleeding control are required in these cases unless the patient is clinically stable.

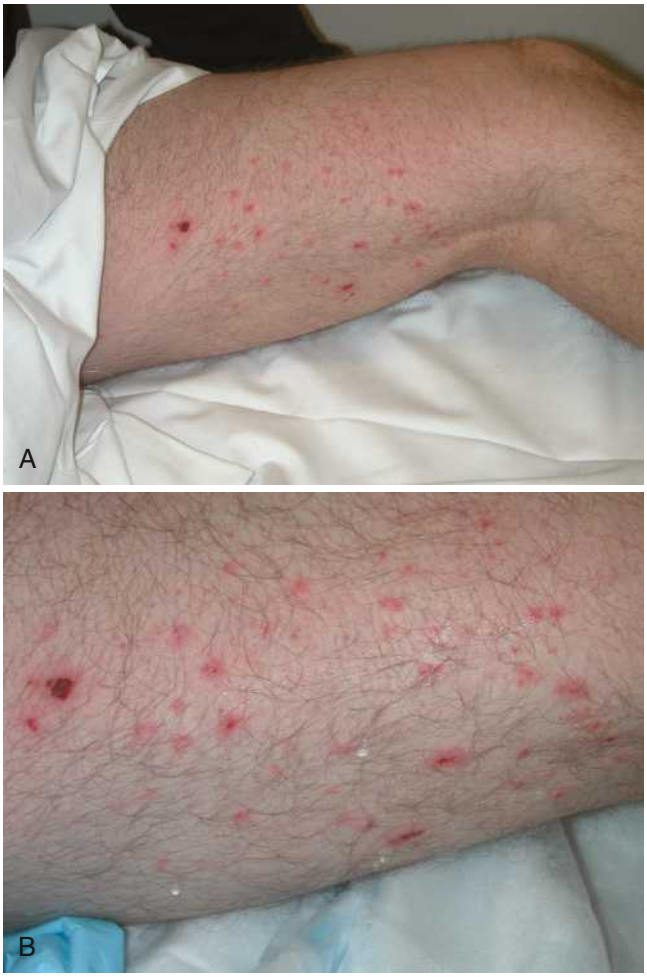


Fig. e11.10 Pseudotattooing, or punctate abrasions from glass fragments, not unburned gunpowder, on the medial aspect of the thigh associated with a gunshot wound. The leg was showered with glass fragments after the round penetrated a windowpane.

Gunshot injuries to the thorax can result in damage to the cardiac musculature, cardiac tamponade, pneumothoraces or hemothoraces, or other mediastinal pathology. Clinical symptoms include shortness of breath, chest pain, tachypnea, hypotension, and altered mental status.

In general, extremities are the most commonly injured anatomic region with nonfatal firearm injuries.[8] Injuries to the extremities can result in fractures, vascular or nerve injury, and compartment syndrome, because bullet tracts do not necessarily decompress fascial compartments. Fractures are associated with vascular and nerve injuries, and with isolated fractures increasing the risk for compartment syndrome. Vascular injuries alone are also associated with an increased risk of compartment syndrome and deep vein thrombosis. A combination of fractures and vascular injuries has been shown to increase the risk of wound infection.

Gunshot wounds to the perineum should raise concern for bowel or bladder injury. Patients may not necessarily complain of any symptoms, but findings of gross hematuria or gross blood on rectal examination indicate that such injuries have occurred.

Air gun/rifle injuries deserve a special mention. Although they may seem innocuous, injuries to areas containing vital structures should prompt further investigation because pellets can cause significant tissue damage. Recent studies have shown that the head/face and neck were the most frequently injured areas,[5,17] with an increasing incidence of eye injuries.[17] Occasionally, injuries can be significant enough to warrant operative intervention.[5] Previous case reports have also shown that air rifle pellets may embolize from the initial location of injury and can also result in damage to vital structures such as the brain and heart.

Diagnostic Testing

The imaging modalities used will differ depending on the location of the injury. Details of the appropriate diagnostic strategies are outlined in the chapters on trauma (Part II of this text). In brief, most injuries will require computed tomography (CT) imaging to delineate the extent of tissue damage. However, this may not be possible in unstable patients, in which case plain radiographs of the chest and pelvis may be the only feasible imaging modality to help guide management.

A non-contrast CT scan of the head can show associated skull fractures, intracranial hemorrhages, or retained missiles. A CT angiogram of the neck is useful to evaluate for injuries to essential neurovascular or aerodigestive structures. Patients with persistent pain to the posterior neck with negative CT imaging may require magnetic resonance

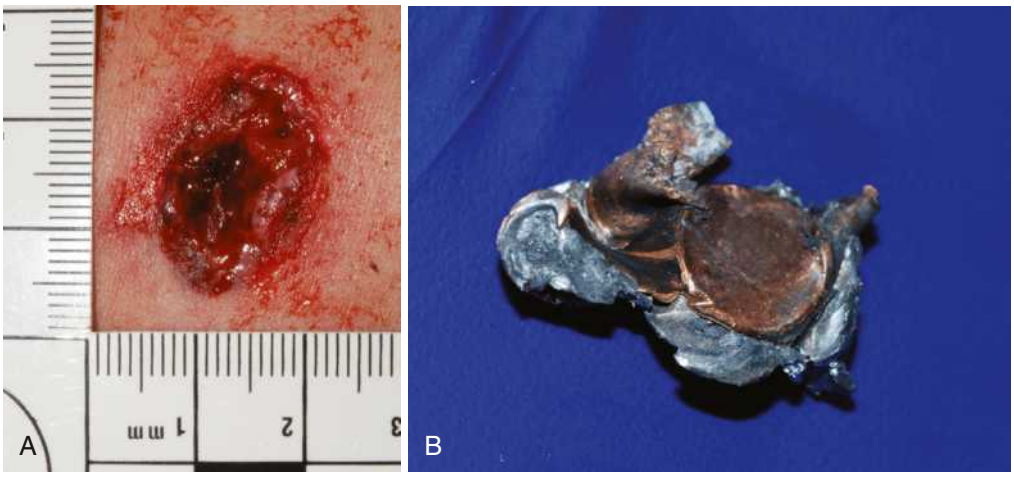
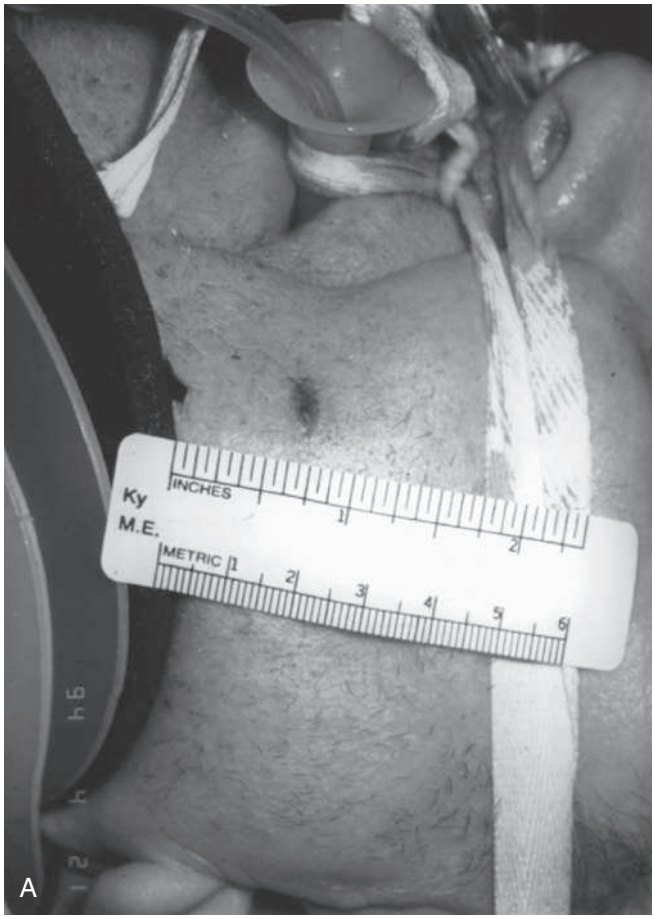


Fig. e11.11 (A) An atypical entrance wound from impact with a .40 caliber bullet. (B) The projectile was deformed as it penetrated a windshield.



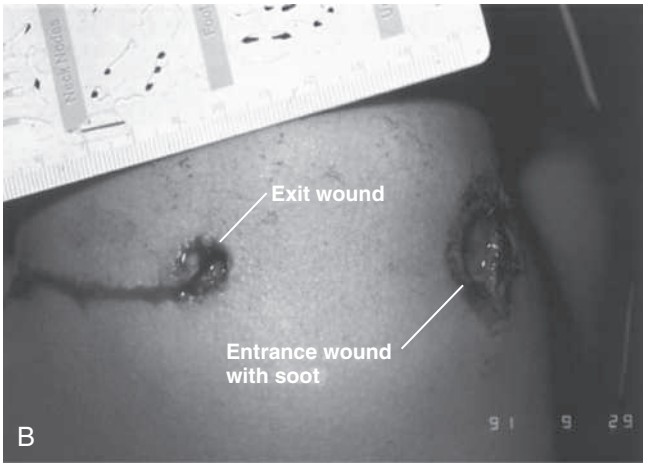


Fig. e11.12 (A) Slit-like exit wound from a .22 caliber bullet. (B) Perforating gunshot wound to the left deltoid area, with soot deposition around the larger entrance wound. No soot is present around the smaller exit wound. Exit wounds are not consistently larger than their corresponding entrance wounds.

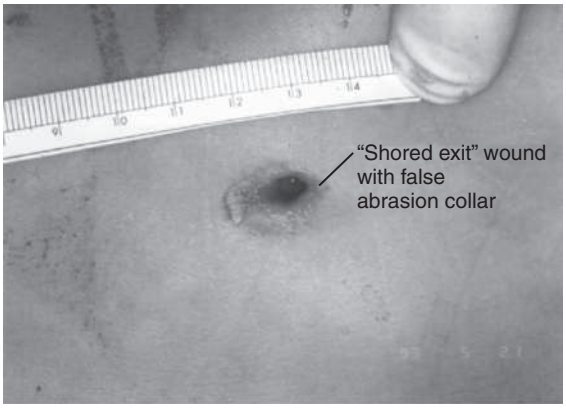


Fig. e11.13 Shored exit wound with a false abrasion collar. This type of wound occurs when the skin in the region of the exiting bullet is in contact with a supporting structure (e.g., wall, floor, mattress). The skin is pressed against the supporting structure, which results in a false abrasion collar.

imaging (MRI) to evaluate further for ligamentous pathology. However, MRI is contraindicated if there are retained missiles in close proximity to vital structures (such as nerves and blood vessels). Thoracic injuries often mandate a chest CT to assess for injuries to the lungs, heart, and mediastinum, as well as to define the bullet trajectory. Chest x-rays are sensitive for pneumothoraces but are not sensitive or specific for mediastinal injury, which requires more advanced imaging. X-rays can also be used to diagnose diaphragmatic injuries when specific findings are present, such as a visualized herniated viscus (the collar sign) or a nasogastric tube in the stomach above the diaphragm. However, a negative x-ray cannot rule out diaphragmatic injury, and CT imaging is more sensitive and specific. Abdominal or genitourinary injuries will also require CT of the abdomen and pelvis to identify the tissues injured. Given that thoracic and abdominal injuries tend to occur concurrently, it is recommended to obtain CTs of both the chest and abdomen/pelvis if there is an injury in either area. A CT urogram or cystogram may be indicated if there is a concern for upper tract or bladder injury respectively. Spinal cord or vertebral injuries are well visualized by MRI or CT, respectively—but note that the metallic nature of most bullets may preclude imaging with MRI.

Differential Diagnosis

There is a limited differential diagnosis for firearm injuries because the mechanism is usually known, often prior to the patient's arrival to the ED. However, patients may sustain multiple injuries, so it is important to be vigilant to avoid missing subtle or smaller concomitant injuries. It is also critical to realize that bullets and bullet fragments may travel, embolize, or cause damage by way of the temporary cavity, so a change in the patient's clinical condition should trigger a prompt reevaluation.

Management and Disposition

Management of patients with gunshot injuries varies by injury location. Resuscitation is key, with use of crystalloid and/or blood as needed, as well as stabilization of the airway and actively bleeding wounds. If possible, procedural incisions should be made away from the site of injury

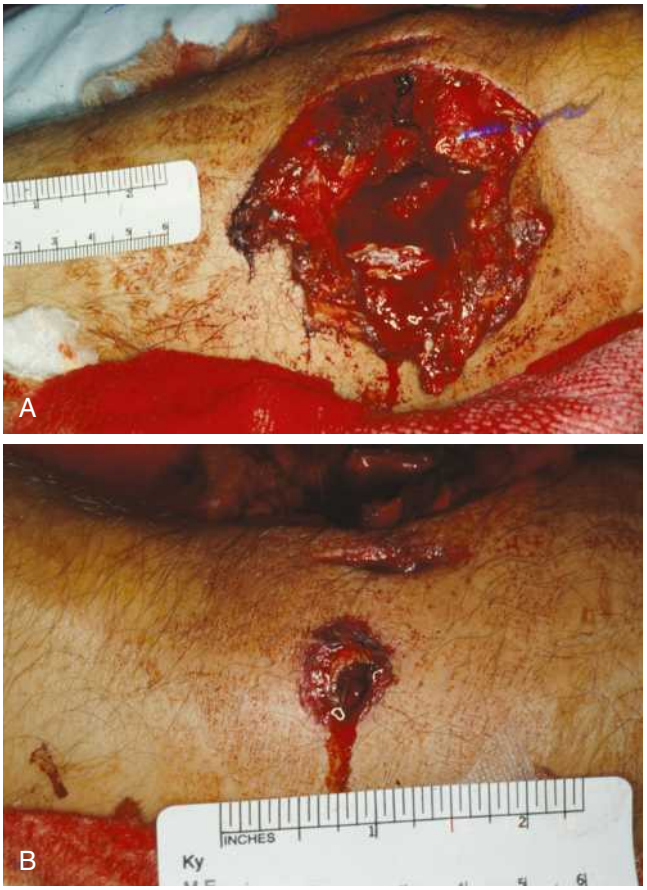


Fig. e11.14 (A) An exit wound from a high-velocity rifle round. Exit wounds from high-velocity rounds are generally larger than their corresponding entrance wounds. The large size is a result of energy transfer from the projectile to underlying tissue, with the expelling of tissue, principally bone. (B) An entrance wound from a high-velocity rifle round. Entrance wounds of high-velocity projectiles will also display an abrasion collar.

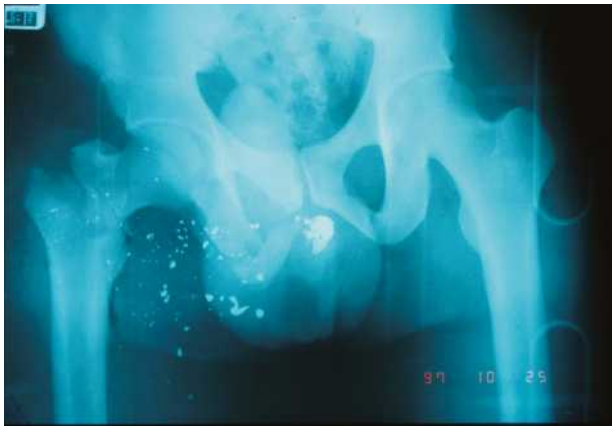


Fig. e11.15 A lead snowstorm from a high-velocity rifle round. High-velocity projectiles have a tendency to fragment into hundreds of tiny particles on contact with bone. This fragmentation contributes to the massive tissue damage associated with these projectiles.

to preserve the evidence; however, this may not be feasible in all cases and patient care always takes precedence.

Head and Neck Injuries

In addition to resuscitative measures, it is important to minimize/prevent hypoxia and hypotension in head-injured patients with a traumatic brain injury (TBI). Emergent operative procedures may be required to evacuate intracranial hematomas in patients with significant mass effect, shift, or other evidence of increased intracranial pressure. Neck injuries are managed with emergent intubation as needed, and control of active hemorrhage. Vessel ligation might also be required if unable to control the hemorrhage with direct pressure. Damage to vital structures may necessitate emergent operative intervention. Patients with penetrating injuries to the neck may also require endoscopy, esophagoscopy, and/or bronchoscopy, depending on the path of the missile.

Thoracic Injuries

Decompression of pneumothoraces, hemothoraces, and hemorrhagic pericardial effusions is usually emergently required. An ED thoracotomy is performed for patients who present in cardiac arrest within 15 minutes of their injury or for a witnessed arrest on ED arrival. Tension pneumothoraces or pericardial tamponade should be decompressed emergently, prior to advanced imaging. Mediastinal and aerodigestive injuries should be elucidated by esophagoscopy, bronchoscopy, and possible angiography. Suspected diaphragmatic injuries should also be evaluated with laparoscopy because patients may initially be asymptomatic but may subsequently develop bowel herniation and eventual strangulation of the herniated tissue (which can happen years after the injury).

Abdominal Injuries

Gunshot wounds to the abdomen can be managed expectantly if the patient is stable with no injuries to the peritoneal cavity or with moderate solid organ injuries (grades 1–3 liver or splenic lacerations). Unstable patients or those with concomitant bowel injuries (including evisceration) or severe splenic or liver lacerations (grade 4 or 5) require emergent exploratory laparotomy. Genitourinary injuries are often managed after other life-threatening injuries have been addressed, aside from severe renal lacerations (grade 4 or 5), which may require nephrectomy. Urethral injuries are managed with Foley catheter placement before or after the appropriate diagnostic modalities have been performed (retrograde urethrography or retrograde cystourethrography). Intraperitoneal bladder injuries are managed operatively, whereas extraperitoneal injuries are managed with Foley catheter placement and decompression.

Extremity Injuries

Management of these injuries involves irrigation, débridement of devitalized tissue, and traction or splinting of fractures. Bullet removal is only required in certain cases. It is required for missiles in contact with synovial fluid (i.e., intra-articular missiles) or within intervertebral disks, given the potential for dissolution and resulting systemic symptoms.[4,18] Other indications for bullet removal include bullets limiting joint motion, impinging on nerves, bullets in a vessel lumen, those resulting in lead poisoning, or bullets in subcutaneous locations (especially in the hands and feet).[18] Patients should also be monitored for compartment syndrome, and vascular or neurologic injuries, especially following high-energy injuries. Operative intervention is required for patients with unstable fractures, fractures with exposed bone, compartment syndrome, or vascular injuries requiring repair. Transabdominal injuries with pelvic fractures also mandate prophylactic antibiotics.

High-energy gunshot wounds with associated fractures are managed as open fractures and are generally treated with prophylactic antibiotics because contaminants can be sucked into the wound due to cavitation.[19] Low-energy injuries can be managed as closed fractures with superficial débridement and prophylactic antibiotics (those covering for gram-positive organisms/skin flora), although the literature suggests that there are low infection rates with or without antibiotics.[18] A recent study by Nguyen et al. recommended that operatively managed fractures from low-energy gunshot wounds should receive prophylactic antibiotics;[20]

however, the study had a small number of patients and may not be applicable to all patient populations. At this time, there is no clear consensus about the type, duration, and dosages of prophylactic antibiotics in patients with low-energy injuries.[18] However, it is reasonable to initiate a course of prophylactic antibiotics in the ED for these patients, particularly in patients who have multiple comorbidities and are at higher risk for wound infections. Intra-articular fractures also appear to warrant débridement.

Soft Tissue Injuries

Soft tissue wounds are managed with irrigation, but wounds are left open. Prophylactic antibiotics are not routinely recommended. The previously cited study by Nguyen et al. found that a single dose of intravenous antibiotics given in the ED for a soft tissue injury (without a fracture) seemed to be associated with a lower rate of infection.[20] The rates of deep infections in this study were not statistically significant when comparing patients who received antibiotic prophylaxis to those who did not,[20] so the findings should again be interpreted with caution. Currently, the use of prophylactic antibiotics in these patients is not uniformly recommended. Because high-energy injuries and shotgun wounds produce a significant amount of devitalized tissue, they often require operative débridement. Aggressive débridement along the wound tract or path of the projectile is not routinely recommended.[4]

Tetanus vaccinations should be updated, and tetanus immunoglobulin given to those without prior immunity. Bullet removal is only indicated for certain extremity injuries (see earlier), for missiles with the potential to embolize, or for those in the myocardium.[4] Prophylactic antibiotics are also not routinely recommended, despite the fact that bullet wounds are not sterile.[4] Indications for prophylactic antibiotics are grossly contaminated wounds, abdominal wounds with hollow viscus injury, intra-articular injuries, intracranial injuries, open fractures/exposed fractures, and high-energy gunshot injuries.

Evidence

A victim's clothing may yield information about a bullet's range of fire and help distinguish entrance from exit wounds. Clothing fibers will deform in the direction of the passing projectile. Gunpowder residue and soot will deposit on clothing as they do on skin. Residue may be invisible to the naked eye, but nitrites and vaporized lead can be visualized with standard forensic staining techniques. Some bullets, as they make initial contact with clothing, leave a lead or lubricant residue that is termed *bullet wipe*. Articles of clothing removed from a wounded patient need to be placed in separate paper bags to avoid cross-contamination of evidence.

The bullet, bullet jacket, and cartridge case are invaluable for identifying or excluding a suspect weapon. When a weapon is discharged, the discharge imprints multiple microscopic marks on the sides of the bullet and on the bottom or side of the cartridge case. The markings result from the bullet's contact with the tool marks, or rifling, in the gun's barrel. These marks are unique to each barrel and are reproducible. These marks are the gun's fingerprint, so to speak. Cartridge case marks are from contact with the firing pin, breech lock, magazine of semiautomatic weapons, and extractor and ejector mechanisms. These microscopic fingerprints can be obliterated by removing a bullet with hemostats or pickups. Therefore, bullets should be handled with gloves, and the tips of surgical instruments should be covered with gauze (Figs. e11.16 and e11.17) or plastic tips (so-called suture booties) to ensure the preservation of these microscopic marks. It is not necessary to place initials or other markings on the bullet if adequate notes are made in the patient's medical record regarding the chain of custody.

Radiographs also help locate retained projectiles and may be of evidentiary value in determining the number of projectiles and the direction of fire. It is important to maintain a chain of custody to preserve as much evidence as possible. This should also be documented, ideally on a chain of custody form.[1] There is a new trend of forensic care programs in EDs to facilitate this process.[1] It in essence expands on the concept of sexual assault nurse examiner programs, in which a dedicated forensic staff member is responsible for evidence collection,[1] which should theoretically improve documentation and collection due to specialized training.

Fig. e11.16 To determine whether a projectile was discharged from a specific weapon, firearms examiners use microscopic marks on the surface of the bullet.

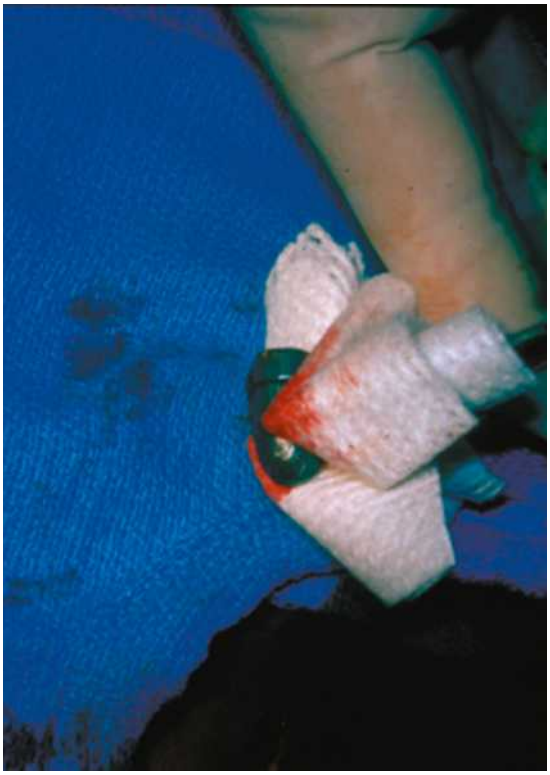


Fig. e11.17 Hemostats should be covered with gauze or plastic tips when bullets are being removed. Metal-to-metal contact destroys the microscopic marks used to identify the weapon from which the bullet was discharged.

Conclusions

The impact of firearm injuries cannot be understated, and it is a tremendous public health issue.[8] Not only do firearms result in injuries and fatalities, they also have other important downstream effects, including disability,[8] the number of productive years lost for adults, missed school for children and adolescents, long-term mortality in children and adolescents,[21] and long-term psychological effects.[22] They also contribute to health disparities and there are high rates of recidivism for violent injuries.[23] Economically, firearm-related injuries result in over $48 billion in medical and work loss costs annually, particularly fatal firearm injuries.[8]

This does not take into consideration the emotional impact that fatalities have on families and communities as a whole. Therefore, the focus should be on prevention as much as possible to avoid incurring such costs.

A number of organizations, including the American College of Emergency Physicians, American College of Physicians, American Pediatric Surgical Association, and American Academy of Pediatrics have all noted that firearm violence is a significant public health problem and have advocated for a public health approach to reduce the burden of firearm-related injuries and deaths. Measures suggested include stricter background checks, stronger legislation regarding illegal firearm sales, and limitation of access to children/adolescents and those with a history of mental health issues and substance use disorders, as well as patient education about firearm injury prevention, especially in patients at risk.[10,14,24,25] Interventions such as safe storage of firearms (or having none at all in the home), screening for access to firearms during routine primary care visits and participation in firearm risk injury education is recommended by multiple groups (including the Society for Adolescent Health and Medicine) to minimize the burden in pediatric patients.[16,26]

There is also support for using the ED or outpatient visits following nonfatal injuries as teachable moments to educate patients about future firearm violence.[12] Hospital-based violence intervention programs have been instituted at some facilities and have been shown to reduce recidivism and reinjury through intensive case management.[23] These programs have also been shown to be cost-effective in recent studies.[27] Other preventative public health approaches for youth and adolescents may also be useful, including street outreach (such as Cure Violence) and school-based violence prevention programs that provide education aimed at curbing violence as a whole.[13,26] Such a public health approach has been successful in reducing the fatalities from motor vehicle trauma and may be a good model to apply to firearm injuries to reduce the burden on society.

FORENSIC ASPECTS OF PHYSICAL ASSAULT

Perspective

Interpersonal violence is a leading cause of death in the United States, particularly among children, adolescents, and young adults. Rates of violence vary by age, gender, ethnicity, and geographic location. Homicide is one of the leading causes of death for children and young adults from non-Hispanic Black backgrounds. The high rate among African Americans is primarily driven by the remarkably high rates among young adult males. Differences in child maltreatment rates, as well as other forms of violence, are attributable to underlying risk factors, such as poverty.[7] Urban areas have higher homicide rates than suburban or rural areas. Overall, the proportion of assaults resulting in death has declined markedly since the 1960s, thought to be due to the availability of organized trauma care.[28] It is the emergency clinician's responsibility not only to care for these patients clinically, but also to assist law enforcement with thoughtful documentation of injuries, evidence preservation, and collection.

Accurate documentation of the anatomic location of the injuries makes it easier to determine the implement, tool, or weapon responsible for producing each wound. Descriptions of wounds should include their shape, precise body location, and measured size. Specific characteristics should be noted, such as the presence of other materials, coloration, and patterned injuries. Such pattern injuries of abrasions or contusions may retain some features of the impacting object, possibly allowing it to be identified. Every weapon leaves a mark, design, or pattern stamped or imprinted on or just below the epithelium. The epithelial imprints of these weapons, termed *pattern injuries*, are consistently reproducible. These injuries are classified into major categories according to their source—blunt force, sharp force, thermal, and chemical.

Correct terminology is also important when describing wounds. When referring to blunt force wounds, these injuries are termed *lacerations* caused by blunt force trauma, as opposed to an incised wound or cut, which is the violation of epidermis caused by a sharp instrument that is longer than it is deep. This terminology use of *laceration* differs from the typical usage within emergency medicine, which tends to be used more broadly. When documenting these injuries, it is better to use the more specific terminology of incised wound if caused by a sharp weapon or laceration if caused by a blunt mechanism. Stab wounds are deeper than they are wide. Also, wounds and bruises should be described as they are seen, and no comment on age or time of occurrence should be documented.

When cutting clothes, avoid cutting through defects caused by sharp force injuries. Clothing items should be placed into paper bags, labeled, sealed, and then turned over to law enforcement. Plastic bags retain moisture and promote the growth of bacteria, which could degrade DNA evidence. Sharp force weapons that are recovered should be wrapped in craft paper or cardboard to protect them from causing injury and sealed for evidence collection.

Conclusions regarding the alleged perpetrator and the mechanism of injury should generally be avoided. It may be helpful to the investigation or legal proceedings to document what the patient states in quotations.

Blunt Force Pattern Injuries

The most common blunt force injury is the contusion, along with abrasions and lacerations. A weapon with a unique shape or configuration may stamp a mirror image of itself on the skin (Box e11.1).

Pattern Contusions

A blow from a linear object leaves a contusion that is characterized by a set of parallel lines separated by an area of central clearing (Fig. e11.18). The blood underlying the striking object is forcibly displaced to the sides, which accounts for the pattern's appearance (Fig. e11.19). Circular or linear contusions suggest abuse or battery. Circular contusions 1.0 to 1.5 cm in diameter are consistent with fingertip pressure and grab marks (Fig. e11.20). One commonly overlooked anatomic location for fingertip pressure contusions is the medial aspect of the upper arm. The sole of a shoe from a kick or stomp may also leave a pattern contusion that can assist in identifying the assailant (Fig. e11.21).

Some injuries allegedly occur during police custody. Specific pattern contusions can include parallel contusions from a flashlight or nightstick. Handcuff or shackle marks are narrow parallel contusions or abrasions on the wrists or ankles. Handcuff and shackle marks are generally more prominent on the lateral aspects of the extremity.

A bite mark may appear as a pattern contusion, abrasion, or combination of both (Fig. e11.22). Bite marks vary greatly in the quality of their identifiable features, depending on the location of the bite and motion of the teeth relative to the skin. Some bite marks may not be readily identifiable as such and may appear as nonspecific contusions, abrasions, or contused abrasions. Generally, adult marks have an interdental distance of more than 3 cm.

BOX E11.1 Commonly Inflicted Pattern Injuries

Slap marks with digits delineated
Looped or flat contusions from belts or cords
Circular contusions from fingertip pressure
Parallel contusions with central clearing from linear objects
Contusions from shoe heels and soles
Semicircular contusions and abrasions from bite marks

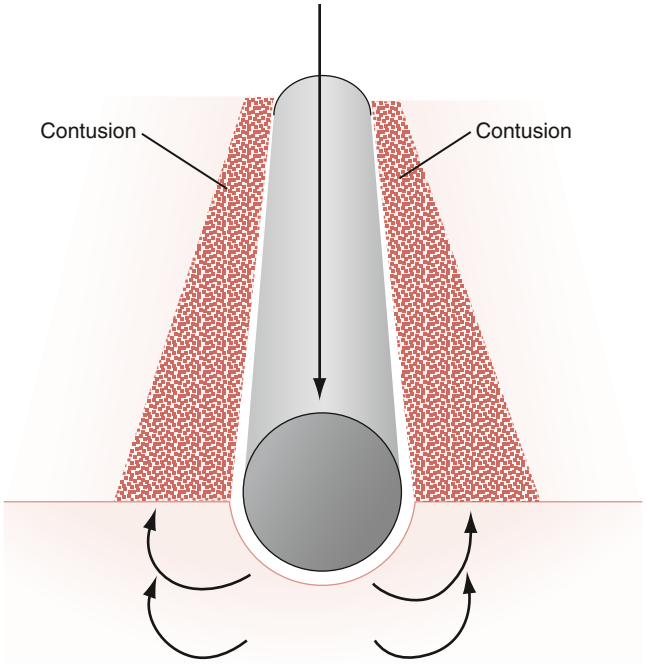


Fig. e11.18 A direct blow from a linear object results in a pattern contusion with central clearing surrounded by parallel linear contusions. The blood directly beneath the impacting object is displaced laterally and accounts for the distinctive contusion.

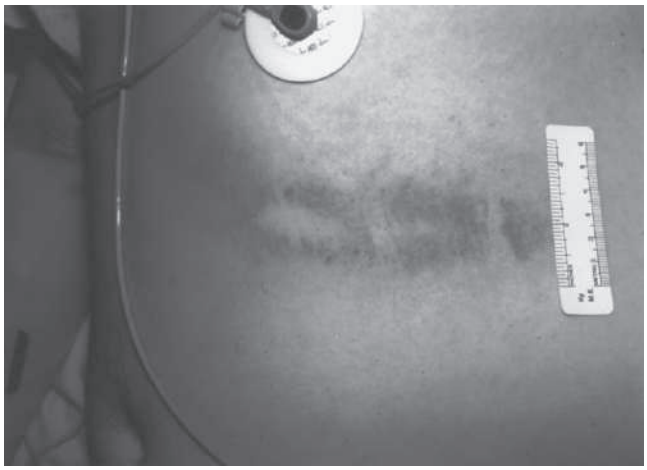


Fig. e11.19 Pattern contusion with parallel lines and central clearing from contact with a baseball bat.

When an acute bite mark is identified, care should be taken not to wash away potential evidence. The skin surface should be swabbed with a sterile cotton-tipped applicator moistened with sterile saline. DNA from buccal cells may also be deposited over an acute bite mark.

The emergency clinician should not render an opinion on the age of a contusion. The development of a contusion is based on a number of variables, such as the amount of blunt force applied to the skin, vascularity of the tissue, oxygenation of the extravasated hemoglobin, depth of the hematoma, skin tone, and amount of blood that escapes into the surrounding tissue. As a result, no reproducible standard for the dating of a contusion is possible based on its color.

Pattern Abrasions and Lacerations

A pattern abrasion is a rubbing or scraping away of the superficial layers of the epidermis, which is not important for treatment but may be

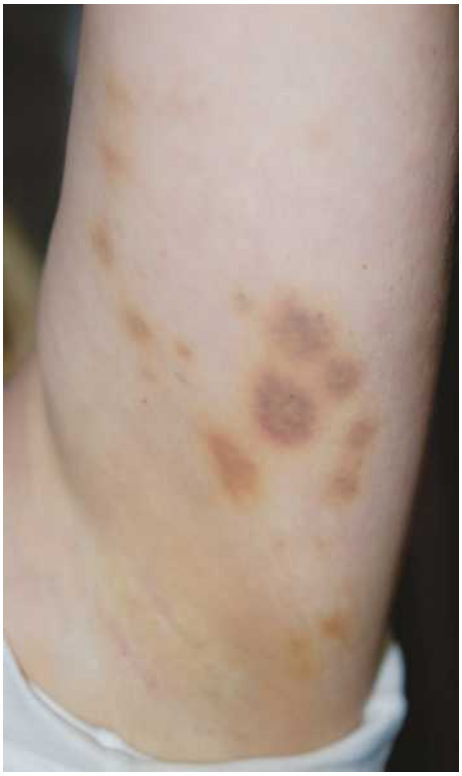


Fig. e11.20 Circular contusions documented on the medial aspect of the upper arm. These injuries resulted from fingertip pressure applied during an assault.

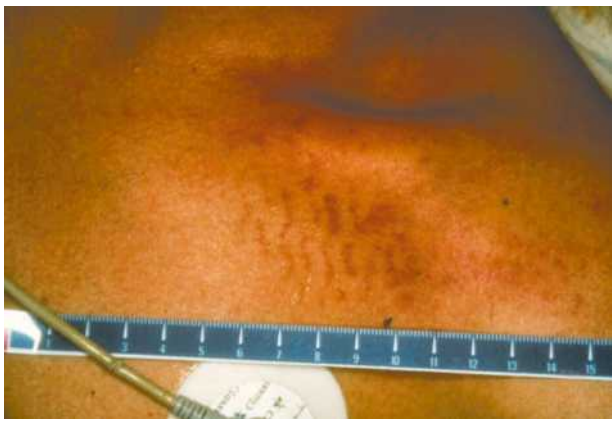


Fig. e11.21 Pattern contusion on the patient's upper chest from the sole of a tennis shoe after a kick. This type of pattern injury can assist in the identification of a suspect and provides a physical connection between the victim and the attacker.

invaluable from a forensic and injury reconstruction perspective. A laceration is defined as a tear in the skin produced by blunt trauma and should not be confused with an incised wound produced when a sharp-edged implement (e.g., knife, scalpel, piece of glass) is drawn across the skin. A laceration has characteristically abraded or crushed skin edges and unique so-called tissue bridges (Fig. e11.23).

Sharp Force Pattern Injuries

An incised wound is longer than it is deep, and a stab wound is defined as a puncture wound that is deeper than it is wide. The wound margins of sharp force injuries are clean and lack the abraded edges and tissue bridges of injuries resulting from blunt forces.

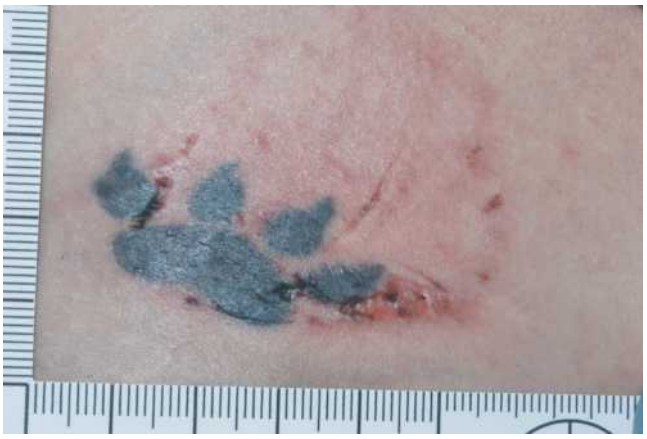


Fig. e11.22 Bite marks may display characteristic arches or appear as a pattern abrasion. A bite mark can be used to identify the assailant if the injury is correctly documented by a forensic photographer or forensic odontologist.

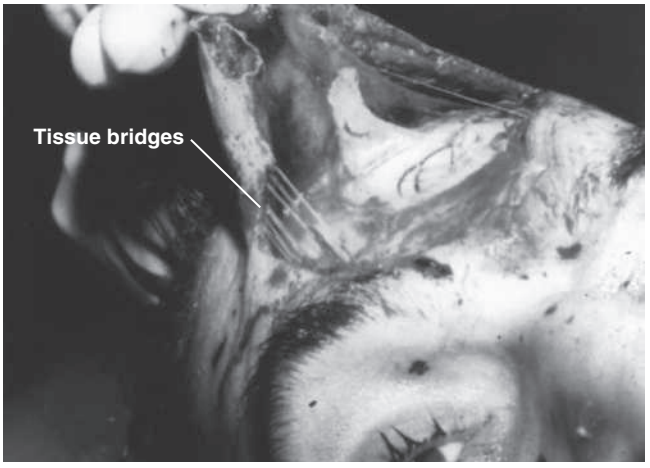


Fig. e11.23 A laceration is the result of blunt trauma and characteristically displays tissue bridges and crushed wound margins.

Forensic information can be gathered during the examination of a stab wound. Some of the characteristics of a knife blade, single-edged or double-edged, can be determined from visual inspection (Fig. e11.24A, B). Additional blade characteristics, such as serrated versus sharp, can be seen if the blade was drawn across the skin during its insertion or withdrawal (see Fig. e11.24C).

Patients with self-inflicted wounds may visit the ED claiming an accident, self-defense, or assault. When the patient history, injuries, and forensic evidence are not consistent, the forensically informed emergency clinician is in a unique position to extrapolate the truth. With an understanding of how to identify the patterns of self-inflicted knife wounds, the emergency clinician can provide appropriate referrals, conserve resources, and assist law enforcement in the investigation of an alleged crime.

When a patient claims to have been assaulted as the victim of a crime, his or her injuries become physical evidence. It is important for the treating emergency clinician, who may be called as an expert witness, to recognize patterns of self-inflicted injury and to distinguish self-inflicted wounds from those sustained during an assault (Fig. e11.25; Box e11.2). Certain patterns may be used to distinguish these injury patterns. Assaults show other associated stab and cut wounds or defensive wounds often on the patient's dominant upper extremity, whereas self-inflicted cases predominantly show isolated cut wounds or associated superficial hesitation marks on the side of the patient's nondominant hand.[29] Defensive injuries most frequently present as cuts on the hands, followed by the forearms, typically on the extensor sides of the forearms and hands, as well as the flexor sides of fingers. Wounds located on the head, limbs, hand, neck, or back are predictive of an assault, whereas wounds located solely on the anterior parts of the trunk, neck, or forearms are more likely to be self-inflicted. The presence of bone or cartilage wounds is suggestive of assault, and their absence is suggestive of self-infliction.

Thermal Pattern Injuries

A thermal pattern injury is a common form of abuse or battery, particularly in pediatric patients. The history should include the position of the patient relative to the thermal source. This information will help determine whether the injury was intentional or accidental. The location of the burn may also be helpful in delineating the intent of the burn; burns to the gluteal area or perineum are very rarely accidental, whereas burns to the hands and upper trunk are common with unintentional injuries.

Intentional burns tend to be deeper and well demarcated and are often due to hot objects, such as curling irons, cigarettes, or hot liquids. A sharp or clear line of demarcation between burned and unburned tissue characterizes immersion or dipping burns. In contrast, splash burns are characterized by an irregular or undulating line or by isolated areas of thermal injury, usually round or oval in shape, caused by droplets of hot liquid.

The severity of thermal or scald injury depends on the length of contact time and the temperature. Skin damage can result from a number of different mechanisms whereby temperatures in excess of 49°C (120°F) cause cellular damage but, again, the exact temperatures required depend on contact time. Law enforcement routinely measures the household's or institution's water temperature in any investigation involving a scald injury.

It is important to be attentive to concomitant injuries in burn patients, particularly those who are victims of significant violence. These patients may sustain associated injuries, such as fractures, that need to be addressed emergently. If there is concern for non-accidental trauma, then a report should be made to law enforcement.

Chemical Injuries

Chemical injuries are a rare means of assault in the United States and Europe but have been noted in countries such as Bangladesh and Jamaica. The victims tend to be female, often following domestic disputes. The most commonly used agents are those found around the home, such as car battery acid, which is usually thrown at the victim. The head, face, and neck are predominantly affected but the fluid may spread to the chest and trunk as well. Patients present with findings consistent with burns from acids or alkalis with cellular damage resulting from coagulative or liquefactive necrosis, respectively.

Primary management is similar to that for other chemical injuries and consists of prompt removal of contaminated clothing or other materials as soon as possible and irrigation of the affected area with copious amounts of water. Tap water has been shown to be adequate for this purpose. Patients may also require rapid resuscitation with intravenous fluids and pain control, with or without airway management depending on the injury location. These patients may also develop significant electrolyte abnormalities, such as metabolic acidosis or hypocalcemia, which require close monitoring and treatment.

FORENSIC ASPECTS OF MOTOR VEHICLE TRAUMA

Perspective

Globally, road traffic injuries are among the leading causes of death and have become the leading cause of death for children and young adults.

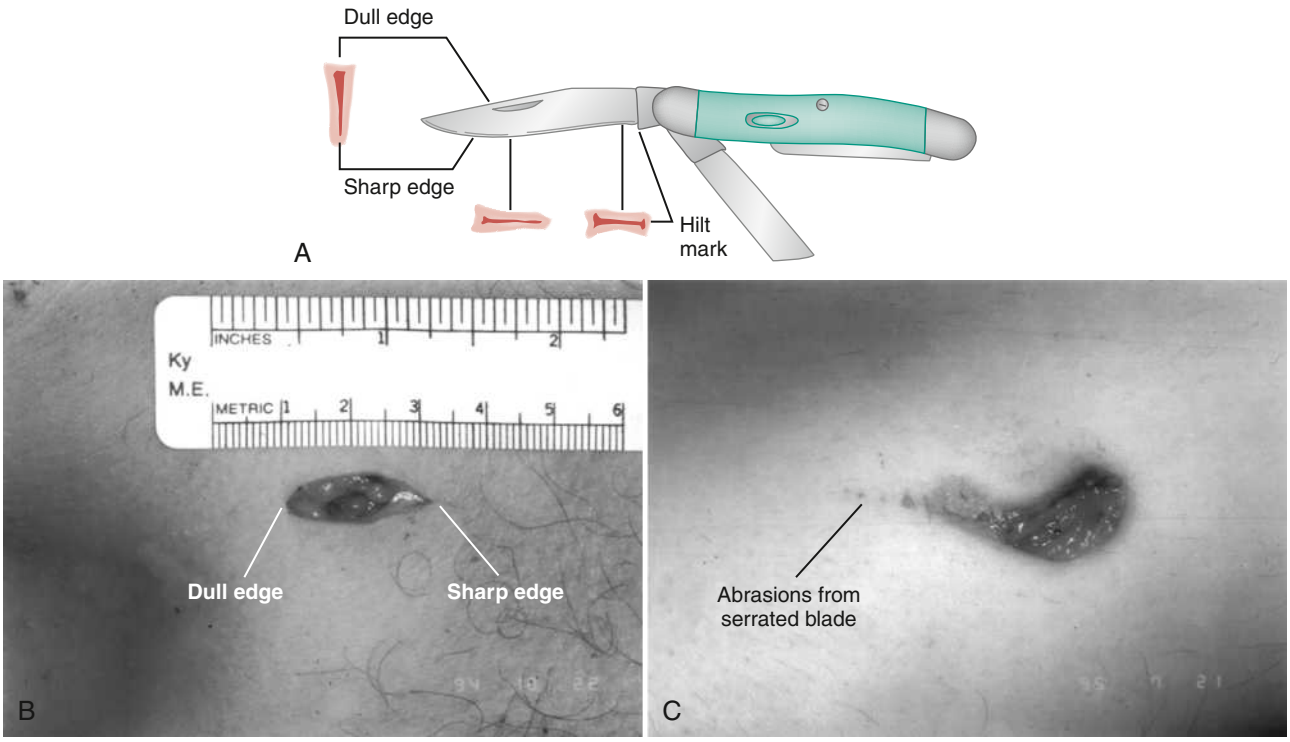


Fig. e11.24 (A) A single-edged knife blade will cause a wound to be formed with a sharp edge and a dull edge. If the blade penetrates to its hilt, a hilt mark may be seen overlying the sharp edge. (B) Single-edged stab wound. (C) Single-edged stab wound made by a serrated blade. Abrasions from the blade's serrated edges are seen on the left margin of the wound.

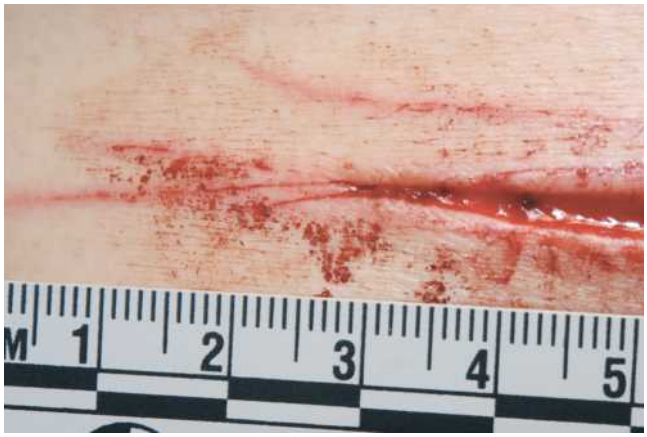


Fig. e11.25 The presence of multiple, parallel, superficial incised wounds, sometimes termed *hesitation marks*, are indicators of self-inflicted wounds.

BOX E11.2 Characteristics of Self-Inflicted Knife Wounds

- Multiple superficial incisions located on the anterior trunk, arms, and face
- Multiple superficial stab wounds located on the anterior trunk, arms, and face
- Parallel incisions, in close proximity to each other, on the nondominant side of the body
- Sparing of sensitive body areas
- Linear or curved incisions toward the hand inflicting the wound
- Intact clothing covering the wound
- Evidence of prior wounds in repeat offenders

Half of the world's road traffic deaths occur among so-called vulnerable road users, which are motorcyclists, pedestrians, and cyclists.[30] In vulnerable road users struck by motor vehicles, there is evident gender disparity, with more males affected. In addition, infrequent helmet use, riding against traffic, and distractions, such as use of electronic devices while driving, are important factors.[31] Collisions not occurring at intersections, occurring during overnight hours, and collisions by a heavy vehicle were associated with an increased rate of death.[31] In high-income countries, the proportion of deaths in those older than 70 years is noticeably greater than in low- and middle-income countries, likely due to longevity, combined with the greater risks posed by reduced mobility and frailty. Fatalities are high among the elderly, whereas injury rates were highest in adolescents and young adults.[31] Young adults account for over half of global road traffic deaths, with the majority of those deaths occurring in men.[30] Substance use and distracted driving, particularly with cell phone use, are dominant patterns seen in high-risk behavior in motor vehicle collisions (MVCs), and not wearing a motorcycle helmet is deadly for victims of motorcycle collisions. Devastating brain injuries are the leading cause of mortality in MVCs and motorcycle-related deaths. For pedestrians and bicyclists, the collision speed of the vehicle and protective devices are obvious factors that influence injury outcome. Patterns of injury differ according to the mechanism of injury.

Motor Vehicle Collisions

In MVCs, the head and thorax are the most frequently injured body regions. Occupants impact against the dashboard and steering wheel and are more likely to sustain torso injuries. Frontal and near-side crashes are most frequently associated with pulmonary contusion. Occupant weight, body mass index, and number of rib fractures are positively correlated with pulmonary contusion volume. The initial mechanical insult to the chest is followed by a secondary inflammatory response that extends the injury and has

been shown to be predictive of ventilatory support, acute respiratory distress syndrome, and pneumonia. Although women are less often involved in MVCs when compared to men, it has been shown that belt-restrained female drivers involved in an MVC are more susceptible to severe injuries, particularly of the chest and spine, when compared to male drivers.

Motorcycle Collisions

In the United States, there has been an overall decrease in the injuries sustained by young adult motorcyclists and an increase in the injuries sustained by middle-aged and older adult motorcyclists. Motorcycle riders involved in fatal crashes were more often alcohol impaired compared to other vehicle types, particularly those killed at night.[32] Older adult motorcyclists had high injury severity scores compared to younger adults, with head and chest injuries associated with the lowest rate of survival.

Evaluation of Motor Vehicle Collisions

Law enforcement officials investigating an incident involving serious or fatal injuries from a motor vehicle or pedestrian collision may benefit from information regarding injury patterns and the collection of trace evidence from the victim. This information can help determine whether an occupant was a driver or passenger. It may help identify a suspect vehicle involved in a hit and run pedestrian collision or a pedestrian's position (standing or lying) when struck on the roadway.

Determination of a vehicle occupant's role may be simple (e.g., if the driver is pinned behind the steering wheel) or complex (e.g., if the vehicle's occupants are ejected). Many impaired drivers claim to be passengers. Short-lived evidence or pattern injuries that might be destroyed or altered in the delivery of patient care should optimally be preserved and photographed.

An opinion on an occupant's position should be avoided because an occupant's role is difficult to determine based solely on history and physical findings in the ED. Such an opinion is best rendered by someone who has examined the scene, vehicle, other occupants, and trace evidence, has reviewed postmortem examinations, and has had the collision reconstructed to determine vehicle dynamics (Box e11.3).

BOX E11.3 Evidence Collection—Driver Versus Passenger

Victim

Examine for Pattern Injuries

Steering wheel contusion
Radio knob contusion
Window crank contusion
Striated incised facial wounds
Dicing wounds

Examine Clothing for Transferred Material[a,b]

Glass (front and side windows)
Fibers
Pedal imprint on shoe
Dashboard components

Collect Biologic Standards[b]

Hair
Blood

Collect Clothing Standards[b]

Damage

Vehicle

Examine for Pattern Damage

Steering wheel
Radio, knobs, dashboard
Window crank, side door
Windshield (laminated glass)
Side and rear window (tempered glass)

Collect Standards

Glass
Carpets and seats
Gas and brake pedals
Broken dashboard components

Examine for Transferred Material of Pedestrian

Hair on windshield and components
Blood on windshield and components

Examine for Transferred Material on Car Occupants

Fabric fibers
Imprinted fabric pattern

[a] Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.
[b] Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the chain of custody.

Pattern Injuries

Matching pattern injuries with components within a vehicle often reveals an occupant's position during a portion of the vehicle's collision sequence. Common pattern contusions, abrasions, and lacerations are seen from steering wheels, air bags, air bag module covers, window cranks, radio knobs, door latches, dashboard components, and front and side window glass. An occupant's movement and subsequent contact with a vehicle's components are dictated by the forces applied to the vehicle through its interaction with the environment. Vehicle occupants, restrained or unrestrained, will initially move toward the primary area of impact.

A deployed air bag may induce a pattern abrasion to the face, cornea, forearms, or other exposed tissue. Pattern lacerations, specific fracture patterns, and amputations are seen when the deployed air bag module cover impacts the hand or forearm (Fig. e11.26). The correlation of these injuries and transfer of DNA from the driver or passenger to the deployed air bag are helpful in assessing an occupant's role as driver or passenger.

Laminated glass (windshields) and tempered glass (side and rear windows) produce pattern injuries. The windshield has two layers of glass laminated together with a thin layer of clear plastic sandwiched between. Laminated glass breaks into shards on impact and causes linear incised wounds. Tempered or safety glass is a single layer of glass that breaks into small cubes when fractured, imparting a dicing pattern to the skin (Fig. e11.27).

Trace Evidence

Clothing, shoes, and biologic standards (e.g., hair, tissue, blood) may determine an occupant's role. The soles of leather shoes may reveal the

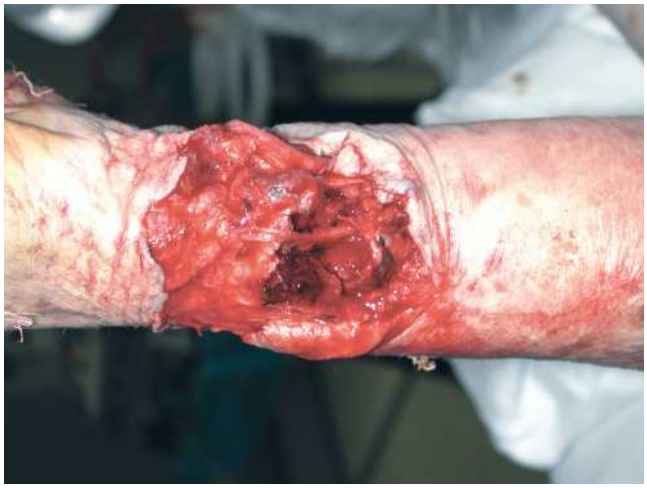


Fig. e11.26 A traumatic partial amputation of the hand resulted from contact with a deploying air bag module cover.

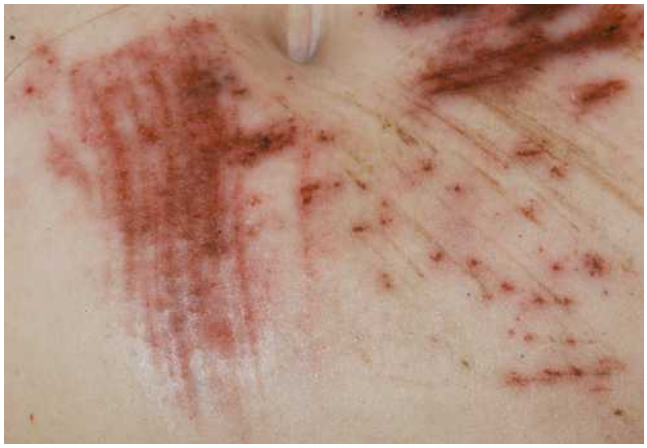


Fig. e11.27 Sliding skin contact with the tempered glass found in a side or rear window creates dicing lacerations.

Fig. e11.28 Imprint of a brake pedal on a leather-soled shoe. This information will assist in determining the occupant's role and whether the patient's foot was on the brake or accelerator pedal at the moment of impact.

Fig. e11.29 Occupant contact with the air bag often results in the transfer of trace evidence. The presence of blood, tissue, hair, and makeup will assist in the determination of the seating arrangement of a particular occupant.

imprint of the gas or brake pedal (Fig. e11.28). Glass collected from within a patient's wound can be matched with a particular window within the vehicle. Air bags can be an excellent source of trace evidence. Examples of transferred evidence include skin, blood, makeup, and hair (Fig. e11.29).

Evaluation of Pedestrian Collisions

Pedestrians impact against various parts of the vehicle and ground and therefore sustain injuries to their arms and legs. The injury severity of pedestrians increases exponentially with increased impact speed of the offending vehicle. Crossing at uncontrolled midblock locations results in greater injury severity compared with crossing at a signalized intersection. Alcohol use is a significant risk factor for pedestrians stuck by motor vehicles because these patients are more likely to cross the street in an unsafe manner and sustain more serious injuries.[33] In pedestrians who were seriously injured or killed, driver failure to yield and driver inattention were cited as significant contributing factors. Pedestrians are at high risk for severe TBI, specifically intracranial hemorrhages and contusions and significant skull fractures.

Pattern Injuries

When struck by the front of a vehicle, a standing adult will sustain bumper injuries, which include open and closed fractures of the tibia and fibula, soft tissue damage, and pattern injuries from vehicle components and hardware.

The height of bumper injuries, measured from the heel and including the height of the patient's shoe, can be correlated with the height of the vehicle's bumper to determine whether the vehicle was braking at the moment of impact. Application of the brake results in the dipping of a vehicle's front end. The presence or absence of braking may help determine the driver's intent. The presence of bumper injuries at one height on one leg and at another height on the other may indicate that the pedestrian was walking or running at the moment of impact, with one leg elevated. Examination may show lateral striations or abrasions when a patient has been dragged.

A victim who is struck from behind may have pattern contusions on the calf or thigh (Fig. e11.30), whereas pattern contusions from a grill on the anterior aspect of the thigh indicate that the pedestrian was standing and facing the vehicle. Pedestrians struck by a glancing portion of a vehicle may also display a pattern injury (Fig. e11.31). Victims who are run over may display a tire tread pattern (Fig. e11.32). Tire marks and the absence of bumper injuries suggest that the patient was supine or prone in the roadway before he or she was run over (Box e11.4).

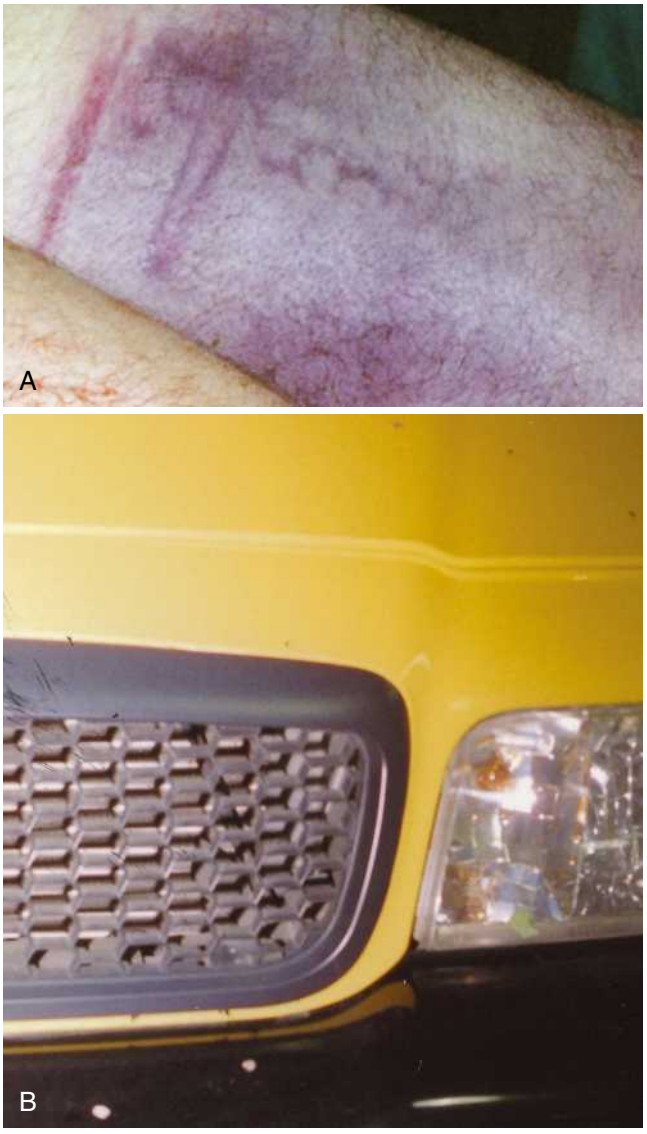


Fig. e11.30 (A) A pattern imprint contusion on the posterior aspect of a pedestrian's right thigh was the result of contact with the vehicle's grill. The location of the contusion provides information about the configuration of the patient at the moment that the car struck him. The patient was struck from the rear. (B) The grill of the striking vehicle.

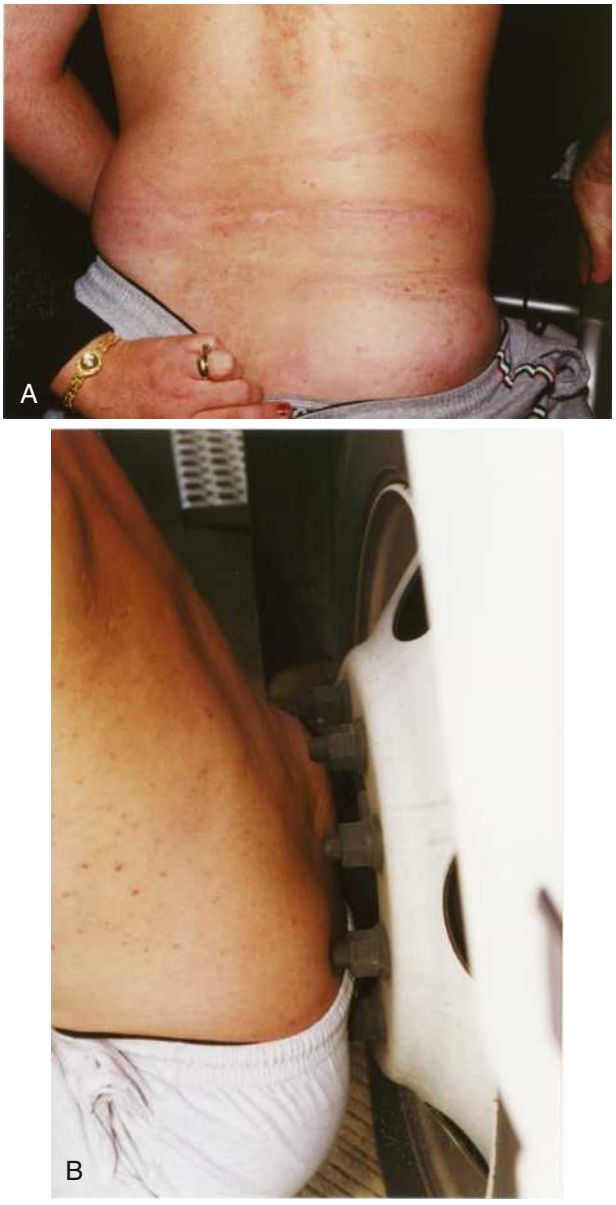


Fig. e11.31 (A) Three horizontally oriented wounds were noted on the back of a pedestrian struck by a semi–tractor trailer on a highway while changing a flat tire. (B) The pattern injury was matched to the lug nuts of the front right wheel.

INTERFACING WITH THE LAW

Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act

Emergency physicians interact with law enforcement more than other medical specialties. Law enforcement often accompany victims of crime to the ED to document their injuries, collect evidence, and investigate crimes. They may request patient information related to the trauma that was sustained.[34]

Title 45, Part 164, of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 permits hospitals to disclose to investigating law enforcement agencies specific information regarding a victim or suspect, without patient consent. Section 45 CFR 164.512 permits the release of protected health information, without a court order, "in response to a law enforcement official's request for such information for the purpose of identifying or locating a suspect, fugitive, material witness, or missing person." A hospital or emergency clinician may disclose the information listed in Box e11.5 only to an investigating law enforcement officer. Physicians should only disclose what is necessary to satisfy law enforcement and permitted under the law.[34] There is also a national security exemption to HIPAA that allows disclosure of patient information to authorized federal officials for the conducting of intelligence and national security activities to avert a serious threat, including terrorism.[34]

In some law enforcement investigations, officers must use photography to collect evidence. Obtaining consent is optimal but may not always be feasible and is not legally required. Such photography or videography should not include patient interactions with medical staff in the course of obtaining medical care.[34]

Mandatory Reporting

The patient-physician relationship is complex for emergency physicians when caring for victims of trauma. Mandatory reporting statutes typically require physicians to report to law enforcement or the state social service agency for a defined public good and override patient confidentiality.[34,35] Such statutes require reporting when there are

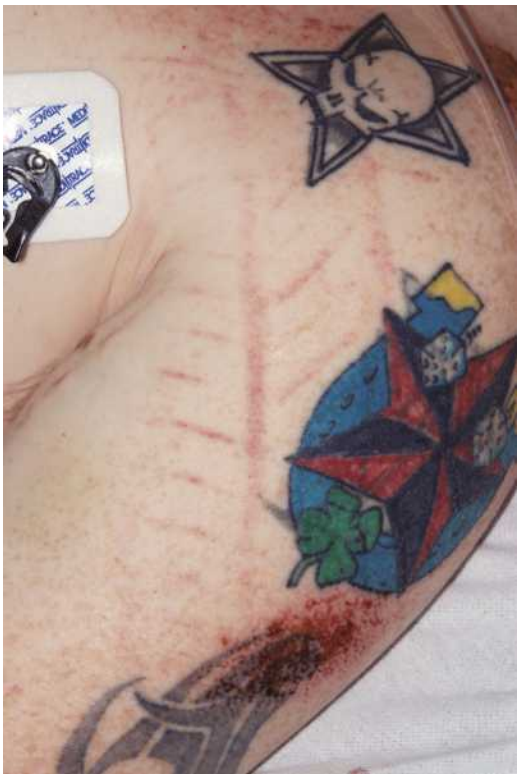


Fig. e11.32 Tire tread imprints on the skin indicate that this victim of a hit and run collision was on the ground when he was hit.

concerns for public safety related to infectious diseases, lapses in consciousness that would pose a risk while driving a vehicle, suspicion of abuse or neglect, and threats of harm.[34] Almost all states require clinicians to report when a patient is injured by an assault and the clinicians have reasonable suspicion of child abuse, elder abuse, or interpersonal violence. Every state has a statute that provides some sort of immunity to those that make a good faith report, even when the report turns out to be incorrect. Physicians may be held liable for failing to report. It is important to learn the applicable state law because specific reporting requirements may vary from state to state.[34]

Subpoenas and Court Depositions

One important interface between medicine and law is the courtroom. Most physicians will provide legal testimony during their career. Judicial and administrative proceedings are exempt from HIPAA under specified circumstances.[34] In the event a physician is subpoenaed as a witness, it is prudent to inform the risk management department at the facility where the patient was treated. When contacting the attorney, discuss the parameters of the testimony and learn what questions might be asked during the deposition. Prior to providing testimony, it is important to be familiar with the medical record, including nursing notes. Relevant hospital policies and departmental guidelines should also be reviewed in preparation for a deposition. Documentation in the medical record is paramount, especially because a case may not go to court until years after the patient was evaluated in the ED. It is prudent to document the rationale for major decision making if using macros or templated text, paying close attention so as not to contradict other sections of the chart, and to put patient statements regarding the event in quotations.

In criminal cases, witness testimony is given by the treating provider. Typically, questions will relate to explaining the medical care and injuries in lay terms. For civil cases brought to court by a private law firm, it is possible to charge as an expert witness, with the caveat that providers may be asked to go beyond their knowledge of the case. Most attorneys are aware physicians have busy schedules, so it is possible to ask to be on call, to be the first witness of the day, or to be scheduled for a certain time.

When testifying, it is best to answer questions thoughtfully and confidently. It will be necessary to explain medical jargon in lay terms. If the clinician does not have a direct memory, then referring back to the provided medical record will help. In general, it is best to only answer the question that is being asked and not to answer outside the clinician's scope of care for the patient or outside the clinician's expertise. If the attorney's question is convoluted, it is acceptable to ask that the question to be rephrased. If the clinician is still unsure, then it is best to inform the

BOX E11.4 Evidence Collection—Pedestrian Collisions

Victim

Examine for Pattern Injuries
Height of bumper injuries
Contusion
Fracture
Head and neck injuries
Crush injuries

Examine Clothing for Transferred Material[a,b]
Paint
Glass (windshield, headlight)
Oil or grease

Collect Biologic Standards[b]
Hair
Blood or tissue

Collect Clothing Standards[b]
Damage or tears

Vehicle

Examine for Pattern Damage
Bumper height and damage
Specific components
Windshield damage
Wheels and undercarriage

Collect Standards
Paint
Glass
Oil or grease

Examine for Transferred Material of Pedestrian
Hair
Blood or tissue

Examine for Transferred Material on Vehicle
Fabric fibers
Imprinted fabric pattern

[a] Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.
[b] Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the chain of custody.

BOX E11.5 Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act[a]

- Name and address
- Date and place of birth
- Social security number
- ABO blood type and Rh factor
- Type of injury
- Date and time of treatment
- Date and time of death, if applicable
- Description of distinguishing physical characteristics, including height, weight, gender, race, hair and eye color, presence or absence of facial hair (beard or moustache), scars, and tattoos

[a] 45 CFR 164.152.

attorney that the question cannot be answered. Objections may interrupt the deposition. In that situation, it is best to pause and wait for the judge to determine whether the clinician can continue answering.

Forced Blood Draws

Physicians have an ethical and legal duty to the patient's best interest, even if the patient is suspected of committing a crime.[34,36] Law enforcement personnel may bring a patient to the ED to have blood drawn if the patient is arrested for driving under the influence (DUI) of alcohol and/or drugs. If the patient has decision-making capacity and explicitly refuses to give consent to perform the test, then the situation can be difficult to navigate. Patients who are brought to the ED may have agreed in advance to provide a blood sample but can change their mind at any point.[34] Patients who are in custody still have a right to informed consent, refusal of medical treatment, and a right to privacy similar to other patients.[34] The primary mission of the physician is to provide medical care to those that are ill or injured, whereas the responsibility of law enforcement is to public safety.[36] The United States Supreme Court upheld the constitutionality of subjecting a person to an involuntary blood test under certain circumstances and found that it does not violate the due process clause, the person's privilege against self-incrimination or the right to counsel. Neither written nor oral consent from the patient is required. Furthermore, some states, such as California, have implied consent when obtaining a driver's license.

In general, ED personnel should draw blood needed for diagnosis and treatment only. When legally bound by either implied consent or a court order, then ED personnel should make every reasonable effort to draw blood for evidence purposes from the patient who is seeking medical attention. Law enforcement will need an official written request, such as a court order, for the procedure, should bring the necessary specimen collection tubes, and follow chain of custody procedures. Drawing of the blood should be done in a reasonable manner, such as when other blood specimens are being drawn while the patient is receiving medical care, should not interfere with the delivery of emergency medical care to the patient, and should be done without coercion by medical personnel. Chlorhexidine or betadine should be used to clean the skin rather than an alcohol wipe. Some states provide statutory immunity to medical personnel who take such a blood sample without the patient's consent. Additionally, there may be exceptions for patients who are using anticoagulant therapy or have a history of hemophilia. If there are any concerns, then hospital risk management should be contacted.

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CHAPTER E11: QUESTIONS AND ANSWERS

1. When documenting a gunshot wound, it is important to do which of the following?
- **a.** Describe the appearance, physical characteristics, and location of wounds.
- **b.** Describe the bullet trajectory.
- **c.** Determine the type of bullet used.
- **d.** Estimate the caliber of the bullet.
- **e.** Interpret the wounds as "entrance" or "exit."

Answer: A. Emergency clinicians should not identify wounds as "entrance" or "exit." Instead, their charting should include a detailed description, using appropriate forensic terminology, of the wound's characteristics and location without speculating about its function or the caliber or type of bullet (projectile) used to create it.

2. A young man is brought to the emergency department following an accidental rifle injury to his right leg. He has an obvious deformity to the extremity on examination with intact sensation and motor function, but pulses are diminished. Plain radiographs of the extremity show comminuted tibial and fibular fractures. Which of the following is/are indicated in his management?
- **a.** Superficial débridement and wound closure
- **b.** CT angiography, prophylactic antibiotics, and operative management
- **c.** Splinting and urgent orthopedic follow-up
- **d.** Emergent fasciotomy
- **e.** Urgent surgical consultation

Answer: B. High-energy gunshot wounds with associated fractures are managed as open fractures and are generally treated with prophylactic antibiotics because contaminants can be sucked into the wound due to cavitation. Operative intervention is required for patients with unstable fractures, fractures with exposed bone, compartment syndrome, or vascular injuries requiring repair. The latter is likely present in this patient given his diminished pulses and should be further evaluated by CT angiography. These patients are also at risk for compartment syndrome and should be closely monitored.

3. An abrasion collar can be associated with which of the following types of wounds?
- **a.** Close-range wound
- **b.** Contact wound
- **c.** Long-range or indeterminate-range wound
- **d.** Intermediate-range wound
- **e.** Shotgun wound

Answer: C. An abrasion collar (also referred to as an abrasion margin, rim, or ring) results from skin indentation as the bullet penetrates the surface. This collar is an abraded area of tissue that surrounds an entry wound as the result of friction between the bullet and epithelium. These usually result from distant or long-range wounds, which are inflicted from far enough away that only the bullet makes contact with the skin. When an abrasion collar is the only visible superficial clinical finding present, the term *indeterminate range* describes the range of fire. Most entrance wounds will have an abrasion collar aside from those on the palms and soles, which usually appear slit-like.

4. A 23-year-old woman presents after having been physically and sexually assaulted by an unknown assailant. In addition to multiple abrasions and brown contusions, she has a bite mark on her left shoulder. Which of the following is not appropriate in your evidence collection procedures and evaluation of this patient?
- **a.** Estimating the age of the contusions based on their color
- **b.** Measuring and documenting each visible injury on a diagram
- **c.** Preserving the condition of the bite mark until after a forensic examination
- **d.** Swabbing the bite mark with a sterile cotton-tipped applicator moistened with sterile water or saline
- **e.** Taking photographs of the bite mark and each injury

Answer: A. When an acute bite mark is identified, take care that critical evidence is not washed away. The skin surface should first be swabbed with a sterile cotton-tipped applicator moistened with sterile saline. Swabbing the area may reveal the assailant's DNA present in dried saliva. Remember, a contusion's color is never a predictor of its age. The emergency clinician may be asked to render an opinion regarding the age of a contusion. Because contusions develop as a result of multiple variables, there is no reproducible standard for dating them.

5. When managing a gunshot wound victim, which of the following is not important for forensic evidence collection?
- **a.** Do not clean the patient's the hands with alcohol or Betadine.
- **b.** If soot is noted on the hands of the victim, cover with paper bags.
- **c.** Maintain a chain of evidence.
- **d.** Place each article of clothing in a separate paper bag.
- **e.** Use metal forceps to handle a bullet to prevent contamination.

Answer: E. Never remove a bullet with metal hemostats or pickups because metal tools can obliterate the microscopic markings (the telltale fingerprint) of the gun from which it was shot. A victim's clothing may hold the answer to critical questions, such as "How far away was the assailant who fired the weapon?" and "Which hole is the entrance and which the exit?" Articles of clothing removed from a wounded patient should be placed in separate paper bags to preserve the trace evidence on them and to avoid accidentally transferring evidence from one article to another (cross-contamination). Always cover a patient's hands with paper bags when the presence of soot is suspected. A gunshot residue test may determine whether a victim or suspect has been in close proximity to a weapon that has been fired. Factors that decrease the sensitivity of gunshot residue tests include washing the skin with alcohol or Betadine.

Emergency Medical Services: Overview and Ground Transport

Thomas H. Blackwell

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Emergency Medical Services: Overview and Ground Transport

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KEY CONCEPTS

- Published in 1966, *Accidental Death and Disability: The Neglected Disease of Modern Society* by the National Academy of Sciences–National Research Council was instrumental in emergency medical service (EMS) maturation in the United States.
- There are multiple models for EMS systems, including public and private services, those operating at basic and advanced levels of care, and those including single or multiple tiers of response capability.
- There are four levels of prehospital providers recognized nationally—emergency medical responder (EMR), emergency medical technician (EMT), advanced emergency medical technician (AEMT), and paramedic, which is the most advanced level.
- The community paramedic provider focusing on population health issues such as access, chronic disease, and decreasing utilization and readmission is now being considered by many communities.
- Advances in emergency medical dispatching and positioning resources at locations and during specified times where expected call volumes are prevalent are innovations that are being implemented to decrease response times and improve outcomes.
- Regulatory oversight for EMS systems lies at the individual state level, and medical direction for individual public or private services resides at the local level.
- Direct medical oversight involves real-time interaction with the prehospital providers via face-to-face or radio communications. Indirect medical oversight involves off-line processes such as protocol development, quality improvement, and education.
- Advances in prehospital care of medical patients have included analgesics and anxiolytics that can be administered intranasally, negating intravenous routes, noninvasive measures to support patients in respiratory distress, alternative adjuncts in place of endotracheal intubation for managing airways, and tourniquets for controlling hemorrhage.
- More advanced diagnostics (such as 12-lead electrocardiography and use of stroke screens) have assisted in transporting patients to appropriate facilities based on their illness and acuity.

FOUNDATIONS

Development of Emergency Medical Services

Before the advent of civilian ambulance services, the sick and injured were transported by any means available, including passerby motorists, wagons, farm machinery, delivery carts, buses, and taxicabs. The military was instrumental in developing systems for transporting wounded soldiers off the battlefield. Figure e12.1 depicts the early Larrey ambulance used during the Napoleonic Wars, the Rucker wagon used during the American Civil War, and a modern ambulance in use today. In 1865, the Commercial Hospital in Cincinnati established the first hospital-based ambulance service. Four years later, the first city service began at New York's Bellevue Hospital.

The beginning of the interstate system of highways in the mid-1950s, excessive speed limits, and poor automobile construction resulted in widespread injuries and deaths across the United States. To address this growing problem, the 1965 President's Commission on Highway Safety recommended the National Accident Response Program and the results from a national survey by the National Academy of Sciences–National Research Council were used to draft the 1966 white paper entitled *Accidental Death and Disability: The Neglected Disease of Modern Society.* This document described the hazardous conditions for the provision of emergency care at all levels and outlined the necessary building blocks for future maturation of emergency medical services (EMS). Congressional legislation eventually directed the United States Department of Transportation (DOT)–National Highway Traffic Safety Administration (NHTSA) to develop a program for improving emergency medical care.

During the 1960s, emergency cardiac care included field defibrillation programs in Belfast, Northern Ireland, and cardiac arrest research in several cities, including Columbus, Ohio, and Miami, Florida. In 1969, the first National Conference on EMS convened, resulting in the development of a curriculum, certification process, and national registry for the emergency medical technician–ambulance (EMT-A). Interested physicians and nurses soon began providing more advanced educational courses and expanding the scope of practice for EMTs, which led to the paramedic provider.

The EMS Systems Act of 1973 (P.L. 93-154) was passed by Congress and authorized funding that dramatically improved regionalization of EMS systems. In 1984, efforts to improve pediatric emergency care occurred when Congress adopted the Emergency Medical Services for Children (EMS-C) initiative through the Health Services, Preventive Health Services, and Home Community Based Services Act of 1984 (P.L. 98-555). A study by the Institute of Medicine (now the National Academy of Sciences, Engineering, and Medicine [NAS]) released in 1993 promoted the integration of EMS-C not just into existing EMS systems but into comprehensive systems of care provision, including injury prevention, primary and definitive care, and rehabilitation services.

In 1996, NHTSA published *Emergency Medical Services Agenda for the Future,* which broadly outlined the principles required for future EMS development. All components of an EMS system, both operational and clinical, were identified and discussed. This document has been used by many individuals and organizations as a valuable reference for planning, administration, and forecasting the future of EMS delivery. More than 40 years after the 1966 white paper publication, the NAS released a report on the status of emergency care entitled *The Future of Emergency Care in the United States Health System* which focused on three separate yet related topics: (1) emergency care: at the breaking point, (2) EMS at the crossroads, and (3) emergency care for

Fig. e12.1 Larrey's flying ambulance (A), Letterman's Rucker wagon (B), and the modern ambulance used today (C). (A, Courtesy the National Library of Medicine, History of Medicine Division. B, Courtesy the Library of Congress, Prints and Photographs Division, LC-88171-2585 DLC.)

children: growing pains. A major focus included the need to strengthen the integration of EMS into the entire health care system because lack of such coordination often results in patients being diverted to inappropriate or distant facilities. The recommendation was to ensure that emergency medical and trauma care is organized into a coordinated, regional system such that patients receive care at the most appropriate facility on the basis of their injury or illness. The concern for inadequate funding for EMS systems operations and disaster response was also addressed. In addition to recommending that Congress develop regionally funded, multiyear demonstration projects that provide seamless systems of care, workforce strengthening, evidence-based practices, and disaster preparedness, the NAS recommended that an advisory committee be created to work with the Centers for Medicare and Medicaid Services to improve reimbursement. In 2019, the Centers for Medicare and Medicaid Services Innovation Center released a Request for Applications for interested EMS systems to participate in a new initiative called Emergency Triage, Treat, and Transport (ET3) which will investigate reimbursement for alternative transport destinations (primary care physician or urgent care) or to treat on scene by a provider or telehealth connection.[1] Finally, the NAS report recommended that the care of children be integrated into the overall EMS system, with pediatric emergency care training enhanced to maintain defined competencies.

In 2014, plans were initiated to update the 1996 Agenda and in 2019, the *EMS Agenda 2050: A People-Centered Vision for the Future of Emergency Medical Services* was released.[2] This report describes the future of EMS being people-centered, evidence-based, and functionally a component of the overall health care delivery system. Figure e12.2 lists the six guiding principles included in the Agenda.

In 2019, *Pediatric Readiness in Emergency Medical Services Systems* was published and cosponsored by the American Academy of Pediatrics, American College of Emergency Physicians, Emergency Nurses Association, National Association of EMTs, and the National Association of EMS Physicians.[3] This document outlines important recommendations for EMS systems to be pediatric ready, and future efforts will include a national assessment of all EMS agencies nationally.

Specific Issues

Emergency Medical Service Systems

Multiple EMS system designs exist, all predicated on the type of community served. Whereas this is a local decision, all states incorporate an administrative office that governs or oversees the provision of EMS activities. The role of the state office includes planning, licensing services and providers, and establishing or enforcing the scope and standards of practice. Other functions may include disaster preparedness and response activities, public health initiatives, record keeping, data collection, and auditing or investigating programs or providers. A description of EMS systems for the 200 most populous cities in the United States is periodically published in the *Journal of Emergency Medical Services*. For simplicity, the following categorization of systems is used: private and public agencies; basic life support (BLS) and advanced life support (ALS) services; and single-tiered, multitiered, and first responder systems.

Private and Public Agencies

Where local government has not assumed primary responsibility for EMS services, communities may depend on private providers. Financial responsibility varies but usually depends on federal reimbursement (Medicare or Medicaid) and user fees. A local government subsidy may or may not supplement the operation. If multiple providers are serving one jurisdiction, calls may be allocated by rotation or specified zone coverage. Dispatching varies by system but may be by the provider or by a central agency. Medical direction is often provided by a contracted physician or physician oversight board.

Hospital-based EMS systems are few in number and may be managed by a single hospital or hospital corporation. Not all hospital-based EMS programs are considered private, in that the hospital may be a division under local or state government or operate under a public authority. Financial responsibilities and dispatching are similar to private models outlined previously. An emergency physician from a sponsor or base hospital typically provides medical direction.

A public utility model is a hybrid between private and public design that allows local government to contract with a private or public

EMS AGENDA 2050
A People-Centered Vision

In 2050, EMS systems are designed to provide the best possible outcomes for patients and communities–every day and during major disasters. They collaborate with community partners and are integral to regional systems of care that are data-driven, evidence-based and safe. EMS clinicians have access to the resources they need, including up-to-date technology and training. **To achieve this vision, EMS systems in 2050 will be designed around six guiding principles.**

ADAPTABLE AND INNOVATIVE

Technologies, system designs, educational programs and other aspects of EMS systems are continuously evaluated in order to meet the evolving needs of people and communities. Innovative individuals and organizations are encouraged to test ideas in a safe and systematic way and to implement effective new programs.

INHERENTLY SAFE AND EFFECTIVE

The entire EMS system is designed to be inherently safe in order to minimize exposure of people to injury, infections, illness or stress. Decisions are made with the safety of patients, their families, clinicians and the public as a priority. Clinical care and operations are based on the best available evidence, allowing systems to deliver effective service that focuses on outcomes determined by the entire community, including the individuals receiving care.

SUSTAINABLE AND EFFICIENT

EMS systems across the country have the resources they require to provide care in a fiscally responsible, sustainable framework that appropriately compensates clinicians. Efficient EMS systems provide value to the community, minimize waste and operate with transparency and accountability.

INTEGRATED AND SEAMLESS

Healthcare systems, including EMS, are fully integrated. Additionally, local EMS services collaborate frequently with community partners, including public safety agencies, public health, social services and public works. Communication and coordination across the care continuum are seamless, leaving people with a feeling that one system, comprising many integrated parts, is caring for them and their families.

SOCIALLY EQUITABLE

Access to care, quality of care and outcomes are not determined by age, socioeconomic status, gender, ethnicity, geography or other social determinants. Caregivers feel confident and prepared when caring for children, people who speak different languages, persons with disabilities or other populations that they may not interact with frequently.

RELIABLE AND PREPARED

EMS care is consistent, compassionate and guided by evidence—no matter when or where it is needed or who is providing the care. EMS systems are prepared for anything by being scalable and able to respond to fluctuations in day-to-day demand, as well as major events, both planned and unplanned.

THE FUTURE STARTS NOW

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Fig. e12.2 EMS Agenda 2050 guiding principles. (From: EMS Agenda 2050 Technical Expert Panel. EMS Agenda 2050: A People-Centered Vision for the Future of Emergency Medical Services (Report No. DOT HS 812 664). Washington, DC: National Highway Traffic Safety Administration; 2019.)

provider. The service selected, usually through a request for proposal and competitive bidding process, becomes a contracted entity that agrees to provide the specified services (ALS, BLS, or both) and, depending on the arrangement, bills the patient directly or receives uniform reimbursement. A subsidy may or may not be provided by the local jurisdiction, dispatching may be performed by an existing public safety organization or by the parent company, and medical direction is usually performed by a specified individual subject to contractual terms.

When municipal governments were faced with planning and establishing EMS systems, many decided that fire departments would be well-equipped to provide EMS in addition to fire services. Fire stations are strategically located throughout the community and personnel are already used to providing emergency response and public services. Firefighters can be cross-trained as firefighters-paramedics or dedicated to performing either fire or EMS functions separately. Public EMS systems that were not incorporated into fire departments evolved into their own separate entity, referred to as a municipal third-service system. Such agencies are endorsed and supported by local government. Many cities have been successful in combining police, fire, and EMS under a global public safety agency, with all department heads or chiefs reporting to one administrator. Financially, public EMS systems may be supported by a per-capita tax base, which may or may not be supplemented by user fees. Regardless of design, medical oversight for a municipal EMS system may be provided by a physician appointed and contracted by the municipality, a local hospital, an advisory council or medical society, or a medical oversight board.

Basic Life Support and Advanced Life Support Service

Basic life support describes the provision of emergency care without the use of advanced therapeutic interventions. Skills include airway management (oral and nasal airways, bag-mask ventilation, extraglottic airways), cardiopulmonary resuscitation (CPR), hemorrhage control, fracture and spine immobilization, and childbirth assistance. Defibrillation with an automated external defibrillator (AED) is often included by many BLS systems. Services are provided by emergency medical responders (EMRs) or emergency medical technicians (EMTs), and medical direction may or may not be a requirement depending on individual state regulations. Few urban communities across the United States operate solely at the BLS level. Many rural and some suburban EMS services rely on volunteers who may not wish to become advanced-level providers. Because these services may have low call volumes, it becomes difficult for personnel to maintain advanced skills. Also, such communities may not have access to medical supervision or hospital sponsorship for ALS care.

The effectiveness of ALS for medical and traumatic emergencies is debatable, although systems categorized as ALS offer a more comprehensive level of service by highly educated providers, usually certified at the advanced emergency medical technician (AEMT) or paramedic level. Provider skills include advanced airway interventions, intravenous line placement, medication administration, cardiac monitoring and 12-lead electrocardiographic (ECG) interpretation, and certain invasive procedures.

Most EMS systems in cities operate at this level of care; however, the number of paramedics in any jurisdiction has come under scrutiny, in that cities with more paramedics per capita tend to have lower survival rates. Although this may seem counterintuitive, one explanation might be that the number of patient encounters per paramedic decreases and skill performance degrades when more providers are competing for the same number of experiences.

Single-Tiered, Multitiered, and First Responder Systems

In a single-tiered system, every response regardless of call type receives the same level of personnel expertise and equipment allocation (all BLS or ALS). Multiple-tiered systems use a combination of ALS and BLS levels, depending on the nature and potential severity of the call. Differences in cost and effectiveness between a mixed ALS-BLS service and an all-ALS service have been debated. A single-tiered ALS response may prove to be cost-effective in specific locales, ensures the capability of providing a consistent advanced level of care to all patients regardless of illness or injury severity, and obviates the potential for undertriage or overtriage by 911 telecommunicators. Alternatively, a multitiered system may meet the needs of individual communities and could be less costly because EMTs are usually compensated less than paramedics. This design also has the potential to preserve ALS resources for higher priority calls.

Regardless of single- or multiple-tier design, EMS systems usually include first responder services as part of their structure. The first responder, usually a police officer or firefighter, is the nontransport BLS or ALS provider who responds to the scene of an emergency to provide initial care before definitive medical care and transportation assets arrive. The first responder quickly assesses the scene and patients, determines whether additional resources are required, initiates patient care, and provides information to responding personnel prior to their arrival.

The design of an EMS system is targeted toward providing quality patient care in the briefest time after unexpected injury or illness. A desirable and cost-effective design might include BLS nontransport first responders with short response times (average 2 to 4 minutes) having the capability of providing early defibrillation and airway support, coupled with ensuing ALS care and transport services.

Levels of Provider and Scope of Practice

At the federal level, NHTSA and their partner stakeholders are responsible for developing all education and standards related to providers and their scope of practice. In 2000, the *Emergency Medical Services Education Agenda for the Future: A Systems Approach* was published and set forth the processes required to improve EMS education delivery. As components of this document, the Core Content (released in 2004) includes all knowledge and skills for EMS practice; the Scope of Practice Model (released in 2007 and revised in 2019) defines the knowledge and skills for the four provider levels; and the Education Standards (released in 2009) outlines objectives, competencies, behaviors, and judgements for developing more broad and flexible curricula. Two additional components included educational program accreditation and a national certification process for providers (both released in 2013). Although the National Association of State EMS Officials (NASEMSO) has been collaborating with multiple stakeholders and federal partner organizations to assist states in implementing this agenda, it is still incumbent on individual state legislation to determine provider levels recognized, initial and continuing medical education requirements at each level, testing, and time intervals for course completion and recertification. Suggested hours of training at each level of provider are listed in Table e12.1.

Emergency Medical Responder

The EMR, formerly referred to as *medical first responder,* is typically the first to arrive on the scene of an incident. Initial scene and patient assessment along with limited lifesaving interventions is the primary function. Along with CPR and basic airway management skills, the EMR should be able to control hemorrhage, manually secure an airway, stabilize fractures, perform CPR, and operate an automatic external defibrillator (AED). The EMR also assists the EMT or paramedic with ongoing care following their arrival.

Emergency Medical Technician

The EMT, formerly referred to as the *EMT-Basic,* is the minimum level required to staff an ambulance and is commonly used for

TABLE E12.1 Emergency Medical Services Provider Level, Training, and Skills

Provider Level	Commission on Accreditation of Allied Health Education Programs Recommended Hours of Training	Skill Set
Emergency medical responder (EMR)	Initial: 40 didactic and laboratory hours	Initial scene and patient assessment and stabilization Basic airway skills CPR Hemorrhage control Spinal motion restriction
Emergency medical technician (EMT)	Initial: 110 hours that include didactic, laboratory, clinical, and field experience	First responder skills plus: Triage and detailed patient assessment Automatic external defibrillation May assist in some systems, such as use of epinephrine autoinjectors for anaphylaxis and albuterol for wheezing
Advanced emergency medical technician (AEMT)	Initial: 200 to 400 hours that include didactic, laboratory, clinical, and field experience	EMTS skills plus: Endotracheal intubation Manual defibrillation Intravenous line placement Limited pharmacologic treatments May assist in some systems, such as laryngeal mask airway
Paramedic	Initial: 1000 or more hours that include didactic, laboratory, clinical, and field experience	AEMT skills plus: Cardiac rhythm recognition Expanded pharmacologic treatments Needle decompression of a tension pneumothorax Needle or surgical cricothyrotomy Transthoracic cardiac pacing

AED, Automated external defibrillator; *CPR,* cardiopulmonary resuscitation.

nonemergency and convalescent transport services or paired with a higher-level provider for ALS care. In addition to the skills of the EMR, the EMT is also involved with triage, more detailed patient assessment, and transportation.

Many but not all states have expanded the EMT scope of practice to include extraglottic airway insertion; use of continuous positive airway pressure; epinephrine administration for anaphylaxis, naloxone, chemical nerve agent antidote autoinjections; and administration of aspirin, nitroglycerin, and albuterol by handheld nebulizer or metered-dose inhaler.

Advanced Emergency Medical Technician

The AEMT, formerly referred to as the *EMT-Intermediate,* was established to allow a more comprehensive approach to care when paramedic services are unavailable or unobtainable due to a limited workforce. Many states recognize the AEMT certification, but others designate alternative but comparable levels depending on specific skills and procedures. This level is useful for rural systems because it provides some ALS care for less cost and education time. The scope of practice for the AEMT varies across the United States. In addition to all EMT skills, most systems allow the AEMT to establish an intravenous line, to manually defibrillate, and to administer limited medications.

Paramedic

Paramedics are the most advanced prehospital providers. Their scope of practice includes a wide variety of therapeutics and procedures including 12-lead ECG rhythm interpretation, expanded pharmacologic treatments, and advanced airway interventions. Invasive and lifesaving procedures include needle decompression of a tension pneumothorax, needle or surgical cricothyrotomy, and transthoracic cardiac pacing.

Initial training courses for all levels of providers include didactic, clinical, and field education, each escalating in complexity for higher levels of certification and all focusing on technical and professional competencies. Additional coursework programs exist for paramedics that expand the scope of practice, including the flight paramedic for fixed or rotor wing services, the community paramedic who serves in a population health capacity, and the critical care paramedic for high-risk adult and pediatric transfers. With the expansion of EMS technology and management career options, many paramedic educational programs have advanced from 1-year certificate curricula to 2-year associate or 4-year baccalaureate degrees. Since 2018, as a means to ensure quality prehospital education and consistency, any individual applying for national paramedic certification must have graduated from a program accredited by the Commission on Accreditation of Allied Health Education Programs.[4]

In keeping with the spirit of the EMS Agenda for the Future, which specifically calls for integration of health services and prevention attributes, some systems have implemented programs that engage interprofessional health providers into the existing structures of care. Examples include embedding a nurse triage system at the 911 access level, where low-acuity complaints as determined by evidence-based algorithms are transferred to alternative call centers. Here, nurses determine and arrange appropriate care at a clinic or facility other than an emergency department (ED).[5] Another example that is becoming popular is having prehospital providers, usually at the paramedic level, provide patient evaluation services to pre-identified patients with chronic conditions such as hypertension,

diabetes, congestive heart failure, and substance abuse. These programs, referred to as *community paramedics, mobile integrated health,* or *advanced practice paramedics,* among others, often include interprofessional providers (nurses, social workers, case managers), and are designed to prevent or reduce the need for EMS calls and decrease ED utilization for targeted patients or frequent users.

Material Resources

Before the mid-1960s, few if any regulations governed system design, operations, and equipment. As EMS development progressed, guidelines for emergency vehicle specifications were adopted by the DOT and equipment lists were proposed. Today, collaborative efforts from multiple professional organizations continue to publish documents that recommend design, equipment, and medications for ambulances.[6]

Medications

During the 1980s, many believed that prehospital drug administration was unjustified and simply delayed hospital transport. Although there was a profound paucity of outcomes-based research into the use of various medications and practices in the prehospital environment, this has improved in recent years. There is significant evidence for early defibrillation and certain advanced cardiac life support medications carried by most ALS services. The wide variety of alternative medications is less uniform. This includes medications for respiratory conditions and anaphylaxis, altered mental status, pain, nausea and vomiting, and hypoglycemia. Medications are traditionally administered on the field by the parenteral route, but the intranasal route is becoming more popular. The beneficial aspects are that absorption is rapid with an onset of action similar to that of parenteral administration. Medications that are commonly administered intranasally are naloxone for narcotic overdose, midazolam for pediatric seizure, and fentanyl for pain control.[7,8]

Equipment

Basic ambulance equipment includes items necessary for emergency procedures (i.e., airway support, hemorrhage control, fracture immobilization and spinal motion restriction, childbirth), personal protection, basic rescue capabilities, and patient movement. Additional patient care equipment is predicated on the level of provision outlined by the system design (ALS or BLS and procedures or other forms authorized by the medical director). Many ALS systems have adopted the equipment necessary for the acquisition of a prehospital 12-lead ECG and there are now mobile stroke ambulances equipped with a CT scanner and/or telemedicine capability to provide earlier diagnosis of acute cardiac and cerebrovascular conditions.[9,10] This information often guides destination protocols to deliver these patients directly to acute care facilities that incorporate staffed 24-hour percutaneous cardiac intervention (PCI) or neurointervention services.

Ambulances

Three basic designs for ambulances are recognized by the DOT: type I, type II, and type III. Both type I and type III ambulances incorporate a modular patient compartment mounted on a conventional truck or van chassis, respectively. The type II vehicle is a standard van. A larger additional-duty vehicle, mounted on a business-class chassis, has become popular in recent years because this configuration requires less periodic maintenance and offers extended service time. Each ambulance manufacturer promotes various interior cabinetry, and all include sufficient lighting, outlets for 110-volt equipment, suction and oxygen systems, and external audible and visual warning devices. Most ambulances are marked with various colors and design schemes that serve as additional safety features and display the six-pointed blue star, or Star of Life, surrounding the staff of Aesculapius, which is recognized worldwide as the standard symbol for EMS.

Communications

Integral to prehospital care systems, EMS communications involve multiple components, all interlinked to support expedient patient care. Effective communication systems include public information and education programs regarding general access to care, technology to ensure simplified access, a means of call prioritization and management of available resources, protocols for providing prearrival patient care instructions for certain life-threatening conditions, ability to communicate with allied agency and hospital personnel, educational opportunities for telecommunicators, and quality improvement processes.

Access

Since 1973, the 911 universal emergency access telephone number has been adopted by most communities throughout the United States. Basic 911 service simply connects a caller to a central communications center or public safety answering point (PSAP). Most primary PSAPs are under the domain of law enforcement. Although many of these handle all public service (police, fire, and EMS) calls, many larger cities have secondary PSAPs for fire and EMS. Enhanced 911, or E911 provides additional information by immediately displaying the caller's telephone number and address.

Emergency Medical Dispatch

Dispatching encompasses multiple elements that assist patients in receiving immediate medical care. The emergency medical dispatcher (EMD) is responsible for ascertaining the primary medical condition and severity. Communication centers that model their dispatch response protocols by priority use a finite list of common chief complaints, each having associated predetermined questions. Answers to these questions ultimately dictate a predefined response mode such as emergent, urgent, and nonurgent. Depending on the response assigned and system configuration, an ambulance (BLS or ALS) and possibly a first responder resource are dispatched in an emergency or nonemergency mode. When critical conditions are identified, the EMD should proceed to give specific prearrival instructions to assist the caller in providing critical interventions before EMS arrival. These include procedures such as opening and clearing an airway, performing CPR, controlling hemorrhage, and assisting with childbirth. Such assistance dramatically narrows the response time interval for receiving emergency medical care.

Systems Status Management and Flexible Deployment

System managers, especially those who operate under performance contracts, must ensure that response resources are available and proximate to where calls may actually arise based on historical data. This system of supply and demand has proved beneficial in managing resources and decreasing response times. On the basis of historical data, high-performance or peak-demand periods of the day coupled to service areas or call location can be identified so that coverage plans or ambulance posting assignments may be instituted. Such mechanisms place ambulances at predetermined locations where potential calls are likely to occur. For example, during regular business hours, prediction models may recommend that ambulances be positioned within the central areas of a city where most of the population is located versus evening and night hours when the population is mostly located in the suburbs or outlying areas of a city. Response vehicles often incorporate an automatic vehicle locator that functions as a telemetry unit or a global positioning satellite system that provides a site interface with the computer-aided dispatch and mapping system. Knowing where each vehicle is located assists the EMD with staging or redeploying vehicles during periods of high call

volume or when units are limited. Routing software is usually used, and more sophisticated systems use programs that incorporate additional factors. These may include traffic patterns based on time of day and street configurations so that closest ambulances to a call are not based on straight lines but as streets are configured.

Field Communications

At an incident scene or during transport, providers usually have the capability of communicating with hospital staff. A consultative patient report may be given to receive medication or intervention orders or simply for arrival notification. Additional information may include cardiac telemetry or transmission of a 12-lead ECG. EMS providers should also have the capability of communicating with all allied public safety agencies for mutual aid purposes, mass casualty situations, or disaster responses. If air medical services are available, EMS and fire personnel should have the capability of communicating with the helicopter pilot for landing zone instructions and crew members for patient condition and care reporting.

OVERSIGHT

Federal

Various federal agencies participate in the oversight of EMS development and refinement. The lead agency is the EMS Division of NHTSA under the DOT. In 2007, the National EMS Advisory Council was formed to provide advice and recommendations to NHTSA from consumers, advocates, and stakeholders. Additional federal support comes from the EMS for Children Program under Maternal and Child Health, Department of Health and Human Services. In an effort to better coordinate federal agencies involved with state, local, tribal, or regional EMS, Congress formed the Federal Interagency Committee on EMS in 2005. The purpose of this organization is to simplify the processes and efforts by which federal agencies support EMS by identifying state and local EMS needs and recommending the addition, expansion, or improvement of programs. Although it is not regulatory, the National Association of EMS Physicians is an international organization of physicians and prehospital professionals interested in promoting research, innovation, and excellence in prehospital care delivery.

State

Each state incorporates a governmental agency that oversees EMS. Duties typically include enforcement, regulation, and implementation of EMS rules adopted by state legislature, possibly including a medical oversight or advisory board. Another nonregulatory organization, NASEMSO, assists in developing policy, providing support, and ensuring leadership and resources for EMS development at the state, regional, and local levels. Table e12.2 lists contacts for agencies and organizations involved in EMS development.

Local

Medical Director

An EMS medical director is a physician with specialized interest and knowledge of patient care activities unique to the prehospital environment. Medical oversight must extend from the communications center through all components of field care, including the hand-off at the receiving facility. Typically, a contractual arrangement for services provides the physician with administrative authority to implement patient care protocols, to interact with all aspects of the system, and to remove a provider from practice if medical care or behavior is substandard. Published guidelines describing the activities and performance of an EMS medical director have been prepared by the National Association of EMS Physicians and the NASEMSO. On September 23, 2010, the American Board of Medical Specialties approved EMS Medicine as the sixth subspecialty available to candidates who apply through the American Board of Emergency Medicine with the first certification examination being administered in October 2013 and every other year thereafter. The Core Content of EMS Medicine is available on the ABEM website.[11]

Medical direction consists of off-line (indirect) and on-line or on-scene (direct) oversight. Off-line medical oversight includes protocol development, personnel education, prospective and retrospective patient care review, and other quality improvement processes. Direct medical oversight involves real-time interaction between a physician or designee and the field provider either by telephone, radio, or in person.

Indirect Medical Oversight

Medical accountability for patient care activities is the basis for indirect medical oversight and functions either before a patient is encountered (prospective) or after patient disposition has occurred (retrospective). Patient care guidelines and protocol development for EMTs and EMDs, initial and continuing medical education, medical-legal policies, and quality and performance improvement processes are important elements.

Perhaps the most important duty of the medical director is to develop patient care protocols, which are preestablished practice guidelines that define the standard of care for most illnesses, injuries, and medical conditions encountered in the prehospital setting. Operational issues such as hospital designation and destination policies along with approval of facility capabilities, termination of resuscitation, and patient transport refusal may be included. Depending on state regulations, protocols may include standing orders for particular clinical situations in which providers may perform certain procedures or administer medications for predefined patient conditions before communication with hospital personnel. Protocol development should be driven by evidence-based medicine, system resources, and patient needs, and it should include guidelines for triage and care of specific populations of patients, including trauma patients, newborns, and children.[12]

TABLE E12.2 Emergency Medical Services Resource and Contact Information

Resource	URL
Advocates for EMS	www.advocatesforems.org
American Ambulance Association	www.the-aaa.org
American College of Emergency Physicians	www.acep.org
Centers for Disease Control and Prevention	www.cdc.gov
Commission on Accreditation of Ambulance Services	www.caas.org
EMS Division, NHTSA	www.nhtsa.dot.gov/people/injury/ems
Maternal and Child Health, EMS-C	www.ems-c.org
National Association of EMS Educators	www.naemse.org
National Association of EMS Physicians	www.naemsp.org
National Association of EMTs	www.naemt.org
National Association of State EMS Officials (NASEMSO)	www.nasemso.org
National Registry of EMTs	www.nremt.org

EMS, Emergency medical service; *EMS-C,* Emergency Medical Services for Children; *EMT,* emergency medical technician; *NHTSA,* National Highway Traffic Safety Administration.

Regardless of local communication protocols, providers should always be able to discuss a case with a physician for clarification or guidance when clinical questions or controversial situations arise. Furthermore, hospital notification is important when critical patients are being transported.

Medical directors should be familiar with and actively involved in local, regional, and state educational programs for initial and continuing education courses for all levels of EMT certification. Course curriculum development and administration, evaluation, and revision processes should be understood. Systems that incorporate their own educational programs allow modifications that reflect intrinsic needs of the system and the providers.

Field personnel and telecommunicators should be given regularly scheduled courses that are current to improve competency in knowledge and skills. Instructional formats and resources to accomplish educational objectives may include didactic classroom or distance learning lectures, webinars or podcasts, skill laboratories, simulation experiences, and direct field observation. Standardized, evidence-based core content is important for consistency and quality of care.

Once patient care protocols are developed and implemented, there must be mechanisms, such as retrospective patient care report review or direct field observation, for evaluation of individual and system performance and patient outcome for various conditions. Deviations from specific protocols may reflect problems with individual EMTs, on-line medical direction personnel, or the protocol itself, each requiring education and reevaluation. Deficiencies, both operational and clinical, should be identified for appropriate remediation, which may be in the form of counseling, educational instruction, or revisions of system design or patient care protocols. Competency, knowledge retention, and skill performance are measurable parameters. Time standards (e.g., out-of-chute time [time from ambulance notification to deployment], response time, scene time, hospital turnaround time, and overall call or task time) are equally important measures because these may indirectly affect patient care and outcome.

Direct Medical Oversight

Direct medical oversight is the concurrent direction of EMTs providing patient care. This may be in the form of radio or telephone communications or by direct scene observation and may be considered centralized or decentralized. In a centralized system, a selected hospital is designated the lead facility (base station hospital, resource hospital, or sponsor hospital) and is responsible for providing all direct medical orders and notification regardless of the receiving facility. In a decentralized system, each hospital functions as a base station, providing direction to EMTs transporting patients to their facility.

Personnel responsible for direct medical oversight must be knowledgeable about the entire EMS system, receiving facilities, protocols, provider capabilities, medication formulary and equipment, administrative and operational issues, and medico-legal implications for certain presenting situations. These physicians and nurses must understand the austere environment of EMS and what can and cannot be accomplished in the field setting. Systems whose protocols include standing orders may require direct communication only for specific reasons. Thus, while medical and administrative protocols may guide EMTs through most circumstances, physician consultation may assist with more challenging dilemmas such as medico-legal issues, termination of resuscitation, behavioral patients, patient refusal of care and/or transport, or ethical dilemmas. Direct medical oversight is usually invaluable for notification and staff preparation when critical or potentially critical patients are being transported.

Table e12.3 lists the various levels of EMS oversight.

TABLE E12.3 Emergency Medical Services Levels of Oversight

Level	Organization
Federal	Department of Transportation–National Highway Traffic and Safety Administration–EMS Division Department of Health and Human Services–Health Resources and Services Administration–Maternal and Child Health–EMS for Children
State	State regulatory office for EMS
Local	County, region, jurisdiction, territorial direct and indirect medical direction

EMS, Emergency medical service.

MEDICAL CARE AND CONTROVERSIES IN MANAGEMENT

Airway Support and Respiratory Emergencies

Interventions

Respiratory complaints account for a significant number of EMS responses. Basic measures to control and support a patient's airway include manual maneuvers (e.g., chin lift or jaw thrust), oral and nasopharyngeal devices, and bag-mask ventilation. At a more advanced level that can still be performed by basic providers, interventions may include use of extraglottic airway devices (e.g., laryngeal mask airway, laryngeal tracheal airway, i-gel), which afford a faster than and equally successful placement as traditional endotracheal tube insertion.[13,14] Early studies comparing survival from cardiac arrest in patients whose airway was managed with an extraglottic device versus endotracheal intubation demonstrated minimal differences or slightly improved outcomes than with endotracheal intubation.[15] Recent studies have shown better results in terms of number of attempts at airway placement, unrecognized misplacement, and complications with extraglottic device use during cardiac arrest.[16,17] Additional adjunctive techniques for decreasing complications during airway management include apneic oxygenation, preoxygenation using a non-rebreathing mask or noninvasive positive-pressure ventilation, head elevation, and delayed sequence intubation using prolonged sedation prior to paralytics.[18,19]

Drug-assisted intubation (DAI) and rapid sequence intubation (RSI) procedures are well established in ground and air transport services. There is debate on the safety, effectiveness, and complications associated with this procedure, especially with more widespread use of extraglottic devices. Despite the controversy and ongoing comparative studies evaluating the best approach for airway management in patients ill or injured, most would agree that to have a successful airway management program, evidence-based protocols should guide practice and the educational and quality management components must be meaningful and comprehensive. For programs using DAI or RSI procedures, the experiential component should include regular operating room time and/or simulator sessions. Ideally, training would also occur in an ED setting where patients requiring emergent intubation would potentially have the full complement of confounding variables (e.g., combative status, full stomach, blood and vomit in the airway). Such training may be difficult or impossible to achieve, particularly the ongoing maintenance of skills, especially in rural communities. Unless EMS systems perform a large number of intubations, use of an extraglottic device for tracheal intubation should be strongly considered, especially given the growing evidence of the importance of uninterrupted chest compressions which may be discontinued during an endotracheal intubation procedure.[19]

Traditionally used in the hospital setting, prehospital continuous positive airway pressure (CPAP) has been shown to decrease intubation rates and improve patient outcomes.[20] Field use requires strict protocols that outline indications and contraindications, clinical applications, mental status assessment, hemodynamic status, and mechanisms for transfer of the patient and devices upon hospital arrival.

Medications

Most advanced programs have adopted the use of clinically proven medications for bronchospasm, chronic obstructive pulmonary disease, and anaphylaxis, but no studies have demonstrated a benefit for administration of these medications in the prehospital setting. Whereas some studies might be considered unethical (e.g., a prehospital study of epinephrine for anaphylaxis), others (e.g., out-of-hospital use of beta$_2$-agonists or steroids for asthma or diuretics for pulmonary edema) could easily be performed. Pending further studies, most systems have adopted the position that these medications do not harm patients in the prehospital setting, may be helpful, and may provide comfort and clinical improvement for most patients experiencing varying degrees of respiratory distress. Fortunately, the use of CPAP and inhaled bronchodilators has been approved for use at the EMT level by some states.

Cardiovascular Emergencies

Interventions

Early research demonstrated the effectiveness of early defibrillation for termination of ventricular fibrillation and improvement of survival rates from sudden cardiac death. Advances in technology have improved such that defibrillators, traditionally used by paramedics, are now used by a variety of first responders and bystanders. Public access defibrillation programs are continuing to be implemented throughout the country, with devices being placed in high-volume, populous, and secluded areas, such as airports and airplanes, casinos, churches, office buildings, transit buses, and other locations identified as high risk.[38] Emerging technology includes cellular phone applications that alert trained bystanders when a cardiac arrest is identified by the 911 center and the use of drones to deliver defibrillators directly to the scene.[21,22] The acquisition and transmission of prehospital 12-lead ECGs has become standard practice and has resulted in minimizing delays in time to intervention (thrombolytic administration or PCI).

A factor now recognized to improve survival from cardiac arrest is uninterrupted or minimally interrupted chest compressions.[23] Each interruption of compressions (e.g., while intubating, checking for pulses, analyzing rhythms) decreases coronary perfusion pressure, which in turn decreases cellular respiration. Additionally, eliminating ventilations may result in more bystanders willing to perform continuous chest compressions.

Although the statistics for cardiac arrest survival across the United States are dismal, those who survive often suffer some degree of hypoxic encephalopathy. Early studies supported the use of induced hypothermia in patients who achieve a return of spontaneous circulation after cardiac arrest; however, recent evidence has not demonstrated beneficial effects for long-term survival.[24] Such conflicting evidence may be due to confounding variables such as optimum target temperatures, methods of inducing hypothermia, duration of cooling, initiating the process in the field environment, and methods to sedate and rewarm.[25] Extracorporeal CPR (ECPR) is an emerging trend where prehospital systems may identify candidates for extracorporeal membrane oxygenation based on initial rhythms, rhythms refractory to shock, duration of arrest and no-flow states, and time on scene.[26,27]

Medications

Traditional cardiac medications recommended by advanced cardiac life support are used by most ALS systems and include epinephrine, including push dose vasopressors, for hemodynamics; atropine for heart blocks; and amiodarone, lidocaine, and magnesium for dysrhythmias. Previously debated, there is no evidence to suggest that amiodarone should replace lidocaine for ventricular fibrillation for adult and pediatric cardiac arrest.[28,29] The use of prehospital fibrinolytic agents for STEMI has not gained wide acceptance and may be a useful intervention only for systems having prolonged transport times or if hospitals may not have PCI available. Perhaps a more plausible EMS response to STEMI patients is a rapid response, early recognition, acquisition and interpretation of a 12-lead ECG, stabilization of hemodynamics, and notification to a PCI facility.

Traumatic Emergencies

Interventions

Interventions for specific medical emergencies, such as cardiac arrest (i.e., defibrillation, intubation, intravenous fluids, and medication administration), may be effectively performed while on the scene or before hospital transport. Alternatively, it is widely accepted that most interventions for traumatic injuries should be performed during transport to the hospital, and all efforts should be made to reduce on-scene time. Only two interventions should be considered for critical injuries: (1) control of the airway to reverse hypoxemia and to prevent aspiration and (2) hemorrhage control. Although it is a routine part of prehospital trauma care, tracheal intubation is not known to be beneficial for severely injured adult and pediatric patients.[30,31] There are many potential issues that may predict morbidity and mortality when managing trauma patients. With airway stabilization, paramedics must be proficient in rapid decision making to determine the need, potential success, and complication risk; the procedure must be expedient with minimal scene time delays, preferably performed during hospital transport; ensuring correct placement by multiple measures; and ensuring continued correct placement during all patient movements. In addition, providing the correct minute and tidal volumes is equally important. Inadvertent hyperventilation may impair cardiac output and cause further tissue damage. Patients sustaining blunt head injury pose special problems that must be considered. Attempting to intubate head-injured patients may result in dental or soft tissue damage in those patients with clenched teeth, and intracranial pressure may be exacerbated from an intact gag reflex or from subsequent regurgitation. Studies on the use of RSI in these patients reveal that patients may experience significant hypoxia and bradycardia during the procedure, along with hypotension depending on induction agents used, all resulting in worse outcomes. Thus, the role of RSI in prehospital airway management in trauma patients is in question, as it is for medical patients. The extraglottic airway devices may be the best method for prehospital airway management in trauma patients due to ease and time required for insertion.

Emergent hemorrhage control is also essential in reducing mortality in severe trauma. For internal bleeding, limiting the total prehospital time and transfer to definitive surgical care is paramount. Recent evidence on the battlefield has demonstrated the effectiveness of tourniquet application to extremity wounds.[32] These devices have application in the civilian setting, are quick and easy to apply, and do not result in the complications once thought to exist. In addition, there is evidence to support the use of tranexamic acid and gauze packing impregnated with hemostatic agents such as chitosan for trauma patients.[33,34] Use of these products for an injured patient with uncontrolled hemorrhage may lessen the need for blood products and can improve outcomes.

BOX E12.1 Emergency Medical Treatment and Active Labor Act Requirements for Patient Transfers

Complete certification (risks and benefits) of transfer
Informed consent obtained from the patient or family
Appropriate transportation (equipment and personnel) arranged
Treatment and stabilization performed
Acceptance from receiving facility ensured
Appropriate patient care data sent (faxed or with patient)

The issue of intravenous fluid administration has become more controversial over the years. Traditionally, high-volume intravenous fluid for hemodynamic instability resulting from traumatic injury was the accepted standard. However, there has been a paradigm shift to restrictive or hypotensive resuscitation for penetrating truncal injuries, because there is evidence that restoration of hemodynamic stability with fluid resuscitation before definitive surgical hemostasis may lead to increased morbidity.[35]

INTERFACILITY AND SPECIALIZED TRANSPORTS

Transportation between health care facilities may occur for several reasons, including patient preference, unavailable diagnostic or therapeutic resource availability at the transferring facility, and managed care requirements that patients be cared for in predesignated hospitals after stabilization. Hospital corporations engaged in networks or alliances that share resources and services depend on interhospital transport systems to convey patients to allied institutions for specialized tests or procedures. Likewise, critical patients admitted to less specialized facilities may need to be transferred to specialized or tertiary care facilities. Whereas long-distance transport may be best accomplished by fixed-wing air medical services, regional or local transports should use rotor-wing or ground systems.[36] These may be provided by either local EMS resources or those owned and operated by the hospital.

An interfacility transfer that is medically indicated must fall under a set of requirements referred to as the Emergency Medical Treatment and Active Labor Act (EMTALA).[37] Although the EMS system providing the transport plays a key role, these guidelines primarily involve particular information and obligations that must be satisfied by the transferring and receiving facilities before transfer. An unstable patient should not be transferred to another facility unless the transferring hospital is incapable of providing standard care and the receiving hospital has capacity and does have the capability to manage the condition and foreseeable complications. Box e12.1 lists various requirements that should be completed before a patient is transferred to another facility (see Chapter e7).

Depending on the patient's condition, specialized transport services may function at the BLS or ALS level, providing emergency or nonemergency transportation. Patient transfers considered ALS may include interhospital (either ED or intensive care unit) neonatal or high-risk infant, critical cardiac, and trauma transports. Personnel configuration depends on system design and level of care provided. Many programs use a nurse-paramedic combination. Patients requiring specialized care may need the services of specifically trained individuals, such as respiratory therapists, neonatal nurses, or other specialized critical care personnel. The presence of a physician is not mandatory but may be useful in selected cases.

As with any EMS activity, all interfacility transports should be reviewed for appropriateness of transfer and medical care provided. In 2019, the American College of Emergency Physicians reaffirmed the policy statement on EMTALA and patient transfers.[38]

ACKNOWLEDGMENTS

I would like to once again thank Marty for understanding the time commitment for this project, and would like to express how proud I am of my sons Joey and Alex for completing medical school and also entering the specialty of emergency medicine.

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CHAPTER E12: QUESTIONS AND ANSWERS

1. Which of the following describes an EMS system that is contracted to provide services?
- **a.** Public utility
- **b.** Third-service municipal
- **c.** Private
- **d.** Fire-based
- **e.** Hospital-based

Answer A. A public utility model is a hybrid between private and public design that allows local government to contract with a private or public provider.

2. Which of the following best defines direct medical oversight in the prehospital setting?
- **a.** Concurrent direction of EMTs providing patient care
- **b.** Development of prehospital care policies
- **c.** Implement quality improvement program
- **d.** Use of prehospital patient care protocols
- **e.** Use of standing field treatment protocols

Answer: A. Direct medical oversight is the concurrent direction of EMTs providing patient care, which can be at the scene or online over radio or cell phone.

3. Which of the following recognized the need to formally develop EMS in the United States?
- **a.** Highway Safety Act of 1973
- **b.** The EMS Agenda for the Future
- **c.** *Accidental Death and Disability: The Neglected Disease of Modern Society*
- **d.** 1965 President's Commission on Highway Safety
- **e.** The Future of Emergency Care in United States Health System

Answer: C. The National Academy of Sciences–National Research Council published this document as a result of the growing concern for EMS and hospitals not being prepared to respond to the growing number of injuries resulting from traffic accidents on the nation's highways.

4. Which of the following prehospital interventions has been shown to improve patient outcome?
- **a.** Defibrillation
- **b.** Endotracheal intubation for children
- **c.** Endotracheal intubation in severe head trauma
- **d.** Intraosseous needle placement
- **e.** Needle cricothyrotomy

Answer: A. Rapid defibrillation has been shown to improve outcomes for patients in cardiopulmonary arrest; other interventions have not shown proven benefit in the prehospital setting.

5. The EMS Agenda 2050 describes a vision for EMS that is defined by which of the following?
- **a.** Availability of ambulance resources
- **b.** Centralized resources that can be deployed
- **c.** Community-based
- **d.** People-centered

Answer: D. The EMS Agenda 2050 describes a vision for EMS that is people-centered along with six guiding qualities: inherently safe and effective, integrated and seamless, socially equitable, reliable and prepared, sustainable and efficient, adaptable and innovative.

Air Medical Transport

Ira J. Blumen and Howard Rodenberg

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Air Medical Transport

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KEY CONCEPTS

- Air medical transport (AMT) is a critical component of a comprehensive health care system and a vital link for rural communities and critical access hospitals to distant emergency care.
- Boyle's law and Dalton's law have the greatest impact and explain the development of hypoxia and most common altitude-related symptoms. Other stresses of flight that can affect the patient or crew include temperature fluctuations, dehydration, noise, and vibration.
- Although most flight programs do both primary (scene flights) and secondary (interfacility) response, ground ambulance remains the primary means of out-of-hospital and interfacility patient transport.
- The helicopter offers several advantages over other transport vehicles, including reduction in travel time by up to 75%, ability to avoid common ground delays (traffic, obstacles, and so on), and ability to fly into locations that may be inaccessible to other modes of travel.
- All air medical services require involvement of a medical director responsible for supervising, evaluating, and ensuring the quality of medical care.
- As a general rule, helicopters are less useful in urban settings because of the proximity of health care facilities.
- Helicopter emergency medical services (HEMS) represents the only modality by which nearly 28% of United States residents have timely access (within 1 hour) to level I or level II trauma centers.
- HEMS may benefit in other time-critical situations, including ST-elevation myocardial infarction (STEMI) patients going to a catheterization laboratory and acute stroke patients going to regional stroke centers.
- Safety is the predominant concern of air medical operations. *Helicopter shopping*, the practice of a requesting EMS agency or hospital calling numerous HEMS programs after other programs have declined the flight because of bad weather, must be avoided.

FOUNDATIONS

Background and Importance

Air medical transport (AMT) is a critical component of a comprehensive health care system, EMS system, and a vital link for rural communities and critical access hospitals to distant emergency care. It is an essential tool to support the regionalization of specialty care for trauma, stroke, cardiac emergencies, burns, pediatric critical care, and more. Many emergency physicians routinely rely upon medical helicopters to transport critically ill or injured patients from smaller rural or community emergency departments (ED) to tertiary care centers.

AMT dates back more than a century to World War I. As early as 1915, the French evacuated soldiers from Serbia using airplanes as ambulances. In 1918, the United States military converted an airplane for the first recorded United States (US) air ambulance to accommodate a litter patient in the rear cockpit. During World War II, more than 1.1 million sick and wounded soldiers were airlifted to the United States during the last 3 years of the war. The Korean War introduced the helicopter to AMT, and more than 20,000 battlefield medical evacuations were flown during the conflict. Utilizing the Bell 47 helicopter, wounded soldiers were strapped to litters outside the helicopter and transported to Mobile Army Surgical Hospitals (MASH units). During the Vietnam War, Operation Dustoff transported nearly 1 million wounded from the front lines in larger helicopters staffed with medics to initiate care en route.

AMT had a significant impact on the wounded soldier when considering transport times and mortality. World War I saw battlefield transport times between 12 and 18 hours. Of those surviving transport, mortality was 20%. During World War II, the average time from injury to definitive care was 6 to 12 hours, with a mortality rate of 5.8%. In Korea, the time was 2 to 4 hours, with a 2.4% mortality rate. In Vietnam, no soldier was more than 35 minutes from definitive care, and overall mortality was 2.6%.

Encouraged by the military experience, United States civilian AMT began in 1969 with a hospital-sponsored fixed-wing air medical program. The first US civilian helicopter emergency medical services (HEMS) program was established in 1972.

Aviation Physiology

A working knowledge of aviation physiology is vital to understanding the effects of AMT on pilots, medical personnel, and patients.

Gas Laws

There are four gas laws important to aviation physiology: Boyle's law, Charles' law, Dalton's law, and Henry's law (Tables e13.1 and e13.2). The cornerstone of aviation physiology begins with Boyle's law, which describes the behavior of gases in an enclosed space. Boyle's law is also a contributing factor to hypoxia along with Dalton's law. No one is exempt from the effects of hypoxia at altitude, and the most threatening feature is its insidious onset and the knowledge that the onset and severity of symptoms may vary by individual.

Additional Stresses of Flight

Other stresses of flight that can affect the patient or crew include temperature fluctuations, dehydration, noise, and vibration. Temperature changes may produce increases in metabolic rate and oxygen consumption. As altitude increases and temperatures drop, the amount of moisture in the air decreases significantly.

To prevent dehydration during long-distance fixed-wing AMT, fluid intake (oral or intravenous) must be monitored carefully, and all patients should receive humidified medical oxygen. Noise and vibration may represent the most ubiquitous stresses encountered in AMT, and both may interfere with patient care or the function of medical equipment. Hearing protection should always be worn during aircraft

TABLE E13.1 The Gas Laws

Gas Law	Principle	Clinical Implication
Boyle's law	• The volume of a unit of gas is inversely proportional to its pressure. • As altitude increases and atmospheric pressure decreases, the molecules of gas grow apart, and the volume of gas expands. • With descent (increasing atmospheric pressure), gas volumes contract. • The result is the expansion and contraction of gases within the closed spaces of the body.	• Squeeze injuries from contraction of air and associated soft tissues can occur on descent, resulting in barotitis, barosinusitis, and toothache. • Reverse squeeze injuries occur on ascent, leading to an increased volume of the air trapped within the space. Examples include the conversion of a simple pneumothorax into a tension pneumothorax and rupture of a hollow viscus. • Medical equipment containing closed air spaces, such as intravenous (IV) tubing and pumps, air splints, ventilators, and endotracheal tube and laryngeal airway cuffs, may also be affected by altitude. • Responsible in part for hypoxia at altitude due to fewer molecules of oxygen present per volume of inhaled gas.
Charles' law	• As the volume of a unit of gas rises, the temperature of that volume falls.	• Explains why the ambient temperature decreases with increased altitude.
Dalton's law	• The total barometric pressure at any given altitude equals the sum of the partial pressures of gases in the mixture. • Oxygen still constitutes 21% of the atmospheric pressure at altitude.	• A decrease in arterial oxygen tension with increasing altitude, resulting in hypoxia. • Initial physiologic responses to hypoxia include tachypnea and tachycardia. • With prolonged exposure, cerebral hypoxia causes headache, nausea, drowsiness, fatigue, unconsciousness, and death.
Henry's law	• The mass of gas absorbed by a liquid is directly proportional to the partial pressure of the gas above the liquid.	• Sudden decompression at altitude may result in dysbaric injuries. • In scuba diving, rapid ascent can result in gas coming out of solution within the bloodstream, resulting in decompression sickness.

TABLE E13.2 Effects of Altitude on Oxygenation

Altitude (ft)	Barometric Pressure (mm Hg)	P_{O_2} (mm Hg)	$P_{A_{O_2}}$ (mm Hg)	$P_{a_{CO_2}}$ (mm Hg)	Oxygen Saturation (%)
Sea level	760	159.2	103.0	40	98
8000	565	118.4	68.9	36	93
10,000	523	109.6	61.2	35	87
15,000	429	89.9	45.0	32	84
18,000	380	79.6	37.8	30.4	72
20,000	349	73.1	34.3	29.4	66
22,000	321	67.2	32.8	28.4	60

$P_{A_{O_2}}$, Partial pressure of alveolar oxygen; $P_{a_{CO_2}}$, partial pressure of arterial carbon dioxide; P_{O_2}, partial pressure of oxygen.

operations by patient and crew. Prolonged exposure to environmental extremes may result in fatigue, motion sickness, disorientation, ear damage, and deterioration in task performance.

SPECIFIC ISSUES IN AIR MEDICAL TRANSPORT

Administrative Structure of Air Transport Systems

Air medical services in the United States may be structured in different ways. There has been tremendous growth of medical helicopters in the United States over the last two decades. Data extracted from the ADAMS Database[1] estimates that in 2019 there were 228 HEMS programs flying more than 927 dedicated aircraft throughout the nation.[2] Since the early 2000s, the number of dedicated HEMS aircraft has doubled. During that time, what had been the most common HEMS business model in the United States has changed. The original and "traditional" nonprofit hospital-based operation, sponsored by a single hospital or a consortium of institutions, is now less common than the for-profit community-based programs or hybrid programs. Nearly 70% of the helicopters are for-profit ventures, operated by privately owned (private equity firms) or publicly traded companies. Public service agencies may also sponsor air medical services or partner with private companies; vehicles used by these programs are often multifunctional aircraft that serve in medical, search and rescue, fire suppression, and law enforcement roles. The Military Assistance to Safety and Traffic (MAST) program operated by the United States Armed Forces provides additional HEMS resources to civilians, but in recent years their role for civilian support has been generally limited to Hawaii and Alaska.[1] Together, the public service and MAST helicopters supply more than 120 additional aircraft for patient transport in the United States. There is no accurate accounting of the number of fixed-wing air ambulance companies or airplanes. Although some hospitals sponsor fixed-wing AMT, it is more common for these programs to be private fee-for-service operations.

Types of Transports

Air medical transports may involve primary or secondary response. Primary responses ("scene flights") are when the aircraft responds directly to the scene of an accident or illness and transports the patient directly to an appropriate receiving facility. Aircraft involved in secondary responses (interfacility transport) move patients from outlying hospitals to facilities offering higher levels of care. AMT flights may also be

Fig. e13.1 Confined spaces and weight restrictions in many helicopters may limit the number of transport personnel or medical equipment that can be carried and may make it more challenging to perform procedures. (Courtesy Ira Blumen, MD, UCAN [University of Chicago Aeromedical Network], UChicago Medicine, 2020.)

classified according to the level of care provided. This may be critical care transport, specialty care transport, or advanced or basic life support.

Air Medical Aircraft

Although ground ambulance remains the primary means of prehospital and interfacility patient transport, AMT has a definite role in the health care delivery system. However, no one aircraft is ideal for the needs of all air medical programs or patients. In addition, certain flight conditions and situations may also influence aircraft and transport consideration.

Helicopters (Rotor-Wing Aircraft)

An estimated 320,000 patients are flown each year by dedicated HEMS operations in the United States. The helicopter offers several advantages over other transport vehicles. Traveling "as the crow flies" at speeds of 120 to 180 mph, helicopter transport time is often 75% less than that for an equivalent distance by ground. The service area of helicopter programs is generally up to 150 to 200 miles from its base of operations, but average transports can be significantly fewer miles. Rotor-wing aircraft have the ability to avoid common traffic delays and ground obstacles and can access rural and remote locations that may be inaccessible to other modes of travel. Helicopter landing zone requirements are a disadvantage compared with ground ambulances but offer an advantage over airport requirements.

Disadvantages to HEMS can include noise, vibration, thermal variances, and other stressors on patients and crew. Weather considerations may at times significantly limit the availability of helicopter transport. Although some medical helicopters can transport two patients, most are configured to transport only one patient. In smaller helicopters, confined spaces and weight restrictions may limit the number of transport personnel or medical equipment that can be carried and may make it more challenging to perform procedures. (Fig. e13.1).

Many helicopter programs operate only under visual flight rules (VFR). When the weather conditions (ceiling and visibility) fall below established program minimums, a flight request may be declined for safety reasons. However, an increasing number of programs are equipping their helicopters and training their pilots in instrument flight rules (IFR) to allow safe travel in less favorable weather conditions. IFR flight may be facilitated to fixed locations such as hospital helipads that have developed IFR approaches, but it does not facilitate travel to the scene of illness or injury.

Airplanes (Fixed-Wing Aircraft)

Fixed-wing aircraft provide increased range, greater speed, and often more patient, crew, and equipment capacity than most rotor-wing vehicles. Decreased cabin noise and turbulence creates fewer patient management problems and cabin pressurization combats the physiologic impact of altitude and the gas laws. Fixed-wing operations are limited, however, to areas that have airports with runways of appropriate length and refueling facilities. During fixed-wing transports, patient transfers require multiple vehicles for each leg of the transport (i.e., hospital to ground ambulance to airplane).

Various fixed-wing aircraft are available for medical transport. These range from unpressurized light planes with single- or twin-piston engines to pressurized turboprops and jets. The selection of the ideal aircraft depends on the nature of the air medical mission.

Air Medical Flight Crew

Air medical crew members represent the broad spectrum of health care providers who commonly provide advanced skills, medication, and equipment for adult and pediatric patients not available to local ground EMS (GEMS).[3-5] The medical literature details decades of studies and reviews of various enhancements brought directly to the patient, which have grown to include advanced airway management,[6-11] blood products,[12-16] tranexamic acid (TXA),[17-20] point-of-care ultrasound,[21-23] and extracorporeal membrane oxygenation (ECMO).[24-27]

AMT services that provide critical care transport, advanced life support, or specialty care transport must staff the vehicle with a minimum of two medical personnel to provide direct patient care.[28] The majority of AMT programs in the United States provide critical care transport teams composed of one registered nurse and an additional crew member (paramedic, second nurse, respiratory therapist, or physician). Most common is the nurse/paramedic crew.[1] AMT crew configuration may also be mission dependent. Some programs will use specialty teams to transport pediatric, neonatal, or high-risk obstetrics patients. Other programs will add a specialty care provider to their "routine" team for these transports.

Flight nurses generally have extensive experience in intensive care units (ICUs) or emergency departments (EDs). They may be specialized within the transport team to care for adult, pediatric, or neonatal patients. Paramedics often make their greatest contribution in the transport of critical patients from the scene of illness or injury. Respiratory therapists bring expertise in airway and ventilator management and oxygen delivery systems. Flight physicians may be residents or attending physicians. Today, only a small number of the US HEMS programs use a physician as a dedicated or alternate member of the flight crew. However, in many other countries, especially in Europe, physician-staffed HEMS remains a dominant crew configuration.[29]

The AMT environment imposes unique considerations on the air medical flight crew. Most medical care procedures are more difficult to perform in an AMT vehicle than in ground-based or in-hospital settings. Auscultation of the heart and lungs, palpation of pulses, performance of cardiopulmonary resuscitation, endotracheal intubation, radio communications while wearing a face mask, and recognition of visual alarms may all be impaired. In addition, fatigue (many crews work 24-hour shifts), motion sickness, an unpredictable pattern of work activity, and the high risk involved in AMT operations may affect task performance.

Medical Direction

All air medical services require the active involvement of a physician as medical director, responsible for supervising, evaluating, and ensuring

the quality of medical care provided by the AMT team. Emergency clinicians play a significant role, with nearly 70% of all US air medical directors having a background in emergency medicine, according to a survey done by the Air Medical Physician Association (AMPA). The medical director must have the final authority over all clinical aspects of the air medical service and should ensure that the flight crew has adequate training and qualifications to optimize patient care. An increasing number of flight programs are using high-fidelity simulation to train their medical crews to the unique transport environment, but access to simulations labs and cost (fiscal and personnel) may be prohibitive for some programs.

Medical care policies and procedures should be established, including specific provisions for on-line and off-line medical control. AMPA and the National Association of Emergency Medical Service Physicians (NAEMSP) have established guidelines for the medical director of an air medical service.

Safety

Safety is the predominant concern of air medical operations, and ensuring a safe flight is a fundamental responsibility of every flight program. Safety must also be an overriding consideration in weighing the risks and benefits of AMT. The role of aircraft pilots and mechanics is essential to the airworthiness of the vehicle, and medical personnel must also be proficient in both routine and emergency operations in and around the aircraft. Checklists aid in safe practices, but alone may not detect significant operational concerns. Crew fatigue and other self-imposed stresses that could affect safety (such as the use of prescription or over-the-counter medications, tobacco, and alcohol) must be scrupulously avoided.

Weather requirements ("minimums") must be strictly enforced. On receipt of a flight request, the pilot must verify the weather conditions and the condition of the aircraft. To ensure impartiality, the pilot should not be told of the patient's condition or acuity. The pilot maintains the unquestioned right to decline a mission because of aircraft or weather considerations. These decisions should not be questioned or influenced in any way by administrators, flight crew, or other parties.

The practice of "helicopter shopping" has been a major factor in several fatal HEMS accidents. Helicopter shopping refers to the practice of a requesting emergency medical services (EMS) agency or hospital calling numerous HEMS programs until one agrees to accept a flight without disclosure to the accepting HEMS operator that other programs were called and declined the flight because of bad weather or other safety concerns. The practice was so common that in 2006, the FAA issued a letter to all state EMS directors describing helicopter shopping and requesting that they take action to prohibit this practice. Numerous state and national organizations have addressed this serious problem through position papers, educational videos, and other resources.[30-31] Although there may be circumstances when a subsequent program called can safely undertake and complete the flight, it is essential that they are made aware of all the facts surrounding the request, including previous denials from other HEMS providers.

The risk of an accident and patient safety are often of concern when considering HEMS transport for a patient. Cost-benefit analysis, however, has demonstrated that the risk of crash-related patient mortality is so low that the impact on calculations of HEMS use and overall effectiveness is minimal. In addition, available data suggest that after adjustment for patient acuity, transport by HEMS is associated with lower risk of adverse events than transport by ground ambulance.

Landing Zones

Helicopter landing zones are inherently dangerous places. The most obvious risk of injury is impact by rotor blades. This danger is heightened during ground operations, because the main blades dip lower to the ground at the slower rotor speeds associated with engine start-up and shutdown. Tail rotor blades can be virtually invisible when moving at full speed, explaining why no one should be towards the rear of an operating helicopter. Injuries also may occur as a result of debris being propelled through the air by "rotor wash," increased noise levels and an inability to hear warnings, and slippery surfaces found on exposed landing sites.

Fig. e13.2 Landing zone (LZ) safety is paramount to delivery of patients to hospitals. Designated rooftop or ground level LZs are appropriately lit and secured, with fixed coordinates and predesignated liftoff and approach patterns. (Courtesy Ira Blumen, MD, UCAN [University of Chicago Aeromedical Network], UChicago Medicine, 2020.)

Many hospitals have designated rooftop or ground-level helipads that are appropriately lit and secured (Fig. e13.2), with fixed coordinates and predesignated liftoff and approach patterns. However, most primary (scene) responses occur at temporary sites. Ground personnel must be trained to designate and secure a safe landing zone for helicopter operations. HEMS programs have an obligation to help train ground staff on proper landing zone setup and operations (Boxes e13.1 and e13.2).

Helicopter flights that go directly to the scene of an accident can pose unique risks from hazards near the landing zone and the risk is heightened at night.[32] In response to this concern, some prehospital providers and flight programs have found it beneficial and safer to use a hospital helipad for rendezvous. This practice raised concerns about Emergency Medical Treatment and Active Labor Act (EMTALA) responsibilities to provide a medical screening examination for these patients. In May 2004, the Centers for Medicare and Medicaid Services (CMS) resolved this issue, noting that the use of a helipad on hospital property does not trigger EMTALA provisions as long as the helipad is being used only as a stopping place for EMS personnel to rendezvous with AMT to facilitate transport of a patient to the closest appropriate facility.

Other adjuncts to landing zone safety and night operations in general are night vision goggles (NVGs) and terrain avoidance warning systems. A 2017 survey of over 750 dedicated HEMS aircraft found that 97% were equipped with NVGs.[2]

Integration of Air Medical Transport Within Emergency Medical Service Systems

Integration of AMT within a comprehensive EMS system begins with the establishment of geographic service areas. As a general rule, helicopters are less useful in urban settings because of the proximity of

BOX E13.1 Landing Zone Safety

- Vehicles and personnel should be kept at least 100 ft (30 meters) from the landing zone.
- Spectators should be kept at least 200 ft (61 meters) from the landing zone.
- No smoking or running is permitted within 50 ft (15 meters) of the helicopter.
- All items (e.g., intravenous lines, poles) should be kept below shoulder height.
- The flight crew opens and closes aircraft doors.
- The flight crew directs and supervises the loading and unloading of the patient and equipment.
- Ground personnel should use eye and ear protection.
- Approach the helicopter *only* when signaled to do so by the pilot or an onboard crew member.
- Approach and depart the helicopter *only* forward of the rear cabin door and in a crouched position with your head down.
- Never approach or depart from the rear of the helicopter.
- Stay clear of the tail rotor; it is virtually invisible and extremely dangerous.
- If the aircraft is parked on a slope, approach and depart on the downhill side (greatest clearance under the blades).
- Keep the landing zone clear of (or hold on to) all loose articles (e.g., hats, scarves, sheets, pillows).
- Protect patient from the dust and debris.
- Follow the flight crew's instructions at all times.
- In disaster situations and mass casualty incidents, victims, witnesses, and spectators may become hysterical or exhibit signs of an acute situational reaction. These individuals must be kept clear of the landing zone and helicopter at all times. Injured victims who exhibit this behavior should not be triaged for helicopter transport, or they should be transported only with adequate physical or chemical restraints in use.
- If you do not know if an action is safe, ask before you act.

Courtesy Ira Blumen, MD, UCAN (University of Chicago Aeromedical Network), UChicago Medicine, 2020.

BOX E13.2 HEMS Landing Zone Requirements

Landing Area

- Landing zone should be as close as possible to the scene or hospital entrance but not so close that it may interfere with ground operations or patient care.
- Landing zone should be at least 100 × 100 ft (30 × 30 meters) in area.
- Landing zone should be as flat and level as possible.
- Landing zone *must* be clear of debris.

Hazards and Obstructions

- Identify all potential hazards that may be on the ground or near the approach/departure path of the landing zone.
- Landing zone should be clear of wires, poles, trees, buildings, vehicles, and spectators.
- Road cones, ropes, tape, and barricades are *not* recommended for use near landing zone.
- Perimeter of landing zone should be at least 50 ft away from potential obstructions and hazards.
- Landing zone should be located *upwind* from any hazardous material incident.

Approach and Departure Path

- Path should point into the wind and be free of obstruction to an altitude of 500 ft (152 meters) above the surface.
- Path should not pass over command posts, treatment areas, or operationally congested areas on the ground.

Day Operations

- Use radio communications and hand signals.
- Stand with your back to the wind.

Night Operations

- Use radio communications and lighting to designate landing zone.
- Spotlights should be directed at the top of possible hazards, *not* toward the approaching or departing aircraft.
- Position a portable light, vehicle headlights, emergency vehicle flashing lights, flare, or chemical stick at each corner, with a fifth light upwind.
- Nonessential lights should be turned off.

Light Sources

- Lights *must* be clear of landing zone.
- If portable, lights *must* be well secured.
- *Never* point lights toward an approaching or departing helicopter.

Wind Indicator

- Indicator may be a windsock, flag, flare, or smoke.
- Indicator must be clear of landing zone.
- If portable, indicator must be well secured.

Courtesy Ira Blumen, MD, UCAN (University of Chicago Aeromedical Network), UChicago Medicine, 2020.

health care facilities and a lack of open and safe landing zones. However, HEMS and fixed-wing service areas may be determined based on program mission description, aircraft range and speed, and the placement of specialty centers and receiving facilities. Population and incident data can be used[33] and HEMS base locations can be optimized considering either percentage of the population covered or average response time for the entire population.[34] Using mathematical modeling, a Norway study determined that optimally placed bases could reach their entire population in 45 minutes or less.[35] A Pennsylvania trauma registry analysis of nearly 145,000 transported patients concluded that HEMS became faster than GEMS at 7.7 miles from the trauma center with variations for traffic, weather, and geographic region.[36] A 2019 study from France had a significantly different conclusion, finding that HEMS should be chosen over GEMS when the distance is farther than 35 km (22 miles).[37]

Paramedics, emergency medical technicians, and other public safety personnel should be provided with guidelines specifying when HEMS should be considered. These protocols are best developed by EMS medical directors in close collaboration with their air medical colleagues.

SPECIFIC DISORDERS

Although virtually all types of patients have been transported by air medical services, available data do not allow prospective identification of which patients will benefit from flight. Many questions about the triage of patients to air or ground transport, the efficacy of air medical care, and the precise effects of AMT on morbidity and mortality in medical and surgical conditions remain unanswered. There are many studies indicating which patients can be cared for in the air medical environment, what skills and equipment can be used, and that medical flight is generally associated with safe patient care and a low incidence of adverse effects. Unfortunately, there is a relative paucity of clinical investigation addressing potential solutions to the problems of triage and appropriate use. A general approach to the need for AMT is illustrated in Box e13.3.

In response to the controversy over whether HEMS transport improves patient outcomes, the NAEMSP Air Medical Services Task Force began in 2000 to annotate HEMS outcomes studies published since 1980. This ongoing project has been updated every 3 to 5 years through the Critical Care Transport Collaborative Outcomes Research

BOX E13.3 Criteria for Air Medical Transport

- Distance to the closest appropriate facility is too great for safe and timely transport by ground ambulance.
- Patient's clinical condition requires that the time spent in transport be as short as possible.
- Patient's condition is time critical, requiring specific or timely treatment not available at the referring hospital.
- Potential for transport delay associated with ground transport is likely to worsen the patient's clinical condition.
- Patient requires critical care life support during transport that was not available from the local ground ambulance service.
- Patient is located in an area inaccessible to regular ground traffic, impeding ambulance egress or access.
- Local ground units are not available for long-distance transport.
- Use of local ground transport services would leave the local area without adequate EMS coverage.
- For interfacility medical transport, the requesting physician based on his/her best medical judgment and information available at the time of transport determined the need for AMT.
- For scene medical transport, the requesting authorized out-of-hospital provider based on applicable policy, his/her best medical judgment and information available at the time of transport determined the need for AMT.

Courtesy Ira Blumen, MD, UCAN (University of Chicago Aeromedical Network), UChicago Medicine, 2020. Originally based on: Association of Air Medical Services: Position paper on the appropriate use of emergency air medical services. *J Air Med Transp.* 1990;9:29; and Determination of medical necessity for air and critical care medical transportation. Position statement of the Air Medical Physician Association. Revised April 13, 2002. In: Blumen IJ, ed. *Principles and Direction of Air Medical Transport*, ed 2. Salt Lake City, UT: Air Medical Physician Association; 2015.
AMT, Air medical transport; *EMS,* emergency medical service.

Effort (CCT CORE). Annotated reviews of HEMS outcomes research from 2014 forward have been published in the Air Medical Journal and are also available on CCT CORE's website: www.cctcore.org.

Trauma

A significant volume of AMT literature addresses the use of HEMS for trauma victims and scene response. Methodological heterogeneity precludes formal meta-analysis of the AMT outcomes data. However, existing data consistently show significant improvement in trauma outcomes with HEMS,[38-43] especially from rural areas.[44,45] A large study assessing over 469,000 transferred patients found that despite improvements in trauma care over a decade, patients had improved survival if transported by HEMS.[46] Another study found higher survival in patients who were transported by HEMS versus GEMS who received CPR within 1 hour of hospital arrival.[47] Noting that HEMS represents the only modality by which nearly 28% of US residents have timely (within 1 hour) access to level I or level II trauma centers emphasizes the vital role of AMT in the care of the injured patient. Caution should be exercised in definitive statements about the criteria for and the value of AMT because such statements can be interpreted only in light of the overall local environment in which the transport system exists.

Rapid transfer of injured patients to a trauma center is essential to increase survival.[48] For many patients, factors other than speed (such as the provision of advanced levels of care over that provided by ground personnel) are hypothesized to be responsible for AMT's benefits even when GEMS transport was faster.[5,49] However, these advanced skills may result in prolonged scene times, often for patients with higher injury severity scores (ISS), which may impact overall outcome.[50] HEMS patients were more likely to have hypotension, a Glasgow Coma Scale (GCS) score less than 9, and an Abbreviated Injury Scale (AIS) score of 5.[51] Despite this, they found that in adult patients with isolated severe TBI, HEMS was associated with improved survival.[51]

AMT is unlikely to improve outcome in those whose injuries are either trivial or grave. Therefore, the decision to request HEMS is ideally based upon the clinical, logistic, and geographic considerations consistent with recommended guidelines for HEMS dispatch that should be region or system specific.[52-54] In a 7-year review of referrals to HEMS or GEMS in a rural trauma system from nontrauma facilities to a tertiary trauma center, distance was the most influential factor associated with the use of HEMS; however, injury severity and prehospital EMS transport were also significant predictors of HEMS use regardless of the distance to the trauma center.[54,55]

The Air Medical Prehospital Triage (AMPT) Score has been introduced as a triage tool to identify patients most likely to benefit from HEMS over GEMS while potentially reducing costs to the health care system.[56] Reviewing over 2 million subjects from the National Trauma Databank, it was concluded that the AMPT score identifies patients with improved survival following HEMS transport. As an air medical triage tool,[57,58] the AMTP suggests HEMS be considered for a score greater than or equal to 2 points, using the following scoring system[57]:

- GCS less than 14 = 1 point
- Respiratory rate less than 10 or greater than 29 breaths/minute = 1 point
- Unstable chest wall fractures = 1 point
- Suspected hemothorax of pneumothorax = 1 point
- Paralysis = 1 point
- Multisystem trauma (>2 body regions injured) = 1 point
- Any physiologic plus any anatomic criterion from National Field Triage Guidelines = 2 points

Overutilization of HEMS is a significant concern, as is overtriage to trauma centers. After decades of studies looking at trauma triage, even the best guidelines have trauma center overtriage rates as high as 50%. The "problems" with trauma triage have a direct impact on the issue of HEMS "overuse." If it is not possible to predict with accuracy which patients need to be transported to a trauma center, it is not possible to identify with any greater certainty which patients should be flown, resulting in overtriage of HEMS.[59] A 10-year review of HEMS and GEMS transport of trauma patients in the United States was completed to identify possible trends. The study found that the use of HEMS had significantly decreased (17% in 2007; 10.2% in 2015) without any significant change in mortality (7.6%). The authors suggested a more effective utilization of available resources. At the same time, they concluded that the overtriage of patients with minor injuries remained relatively unchanged.[60] A 2-year retrospective chart review found overtriage ranging from 35% (early discharge) to 85% when a more stringent definition was applied.[55] Another concern may be undertriage of patients for whom a HEMS response was canceled and who were later transported to a trauma center.[61] An 8-year study from North Carolina concluded that overtriage was low, suggesting a high incidence of undertriage.[62]

Overutilization is also a concern in the pediatric population. A New Jersey study concluded that in this group, the overutilization was likely secondary to the scarcity of hospitals capable of managing pediatric trauma.[63] Multiple studies have demonstrated that the principal determinants of triage to HEMS transport were primarily distance to a major trauma center and clinical factors relating to the type and severity of injury.[64,65] In a national cohort study that adjusted for nonrandom assignment of transport mode, only severely injured children

with ISS greater than 15 were found to benefit from HEMS.[66] Yet in a study reviewing 127,489 HEMS and GEMS transported pediatric trauma patients, nearly 40% of children transported by air had only minor injuries.[67]

The protocols of many EMS systems, trauma regions, and HEMS programs include a guideline for HEMS to be dispatched only for potentially salvageable patients. In general, HEMS would not be dispatched for out-of-hospital traumatic cardiac arrest (OHCA). However, several international studies have suggested that there is a potential for improved outcomes.[68,69] In a large Polish retrospective analysis of 2139 OHCA patients, ROSC was achieved in 1119 cases, including more than 70% after arrival of the HEMS team.[69] These data suggest possible benefit of HEMS dispatch to traumatic OHCA cases when additional skills, procedures, and equipment are brought to the scene; however, how this practice translates to other areas of the world remains in question.

AMT of injured patients by airplane has also been reviewed in the literature with the focus on longer distance transport. In general, fixed-wing AMT is determined to be beneficial when transporting patients hundreds or even thousands of miles to definitive trauma care.

Burn Victims

An estimated 80% of all burn patients in North America suffer less than 20% total body surface area burns. Although these patients may benefit from a burn center, without coexisting inhalation injury or other injuries, they may not require HEMS transport. Studies have demonstrated that up to a third of burn transports by HEMS were unnecessary and 25% were discharged from the ED after burn consultation and treatment.[70-72]

Cardiac Disorders

Most AMT studies on cardiovascular disease focus on ST-elevation myocardial infarction (STEMI) patients because these represent the largest group of nontrauma air transports. The ability to study HEMS-related outcomes benefit in acute coronary syndrome (ACS) is limited by the lack of validated scores that can be used to stratify risk and predict outcome.

AMT extends the geographic referral base of primary angioplasty centers and can conceivably shorten door to percutaneous coronary intervention (PCI) time by transporting STEMI patients rapidly from scenes or hospitals without PCI capability to a referral center. Procedures that have the potential to reduce time to PCI should routinely be evaluated.[73] An Ohio study found procedural changes could reduce delays, including requesting HEMS before an accepting cardiologist or hospital was confirmed, limiting IV infusions to only those essential for the transfer, and training flight crews to minimize bedside time.[74]

There is also evidence to support HEMS dispatch to rural or wilderness areas for field-diagnosed STEMIs. A 2015 study focused on scene transports from rural Belgium that assessed the use of HEMS for 342 STEMI patients.[75] Compared with GEMS, using calculated geographic information (GIS), they found that the use of HEMS resulted in savings of 60 minutes (range 47 to 72 minutes) for STEMI patients undergoing primary PCI. Similarly, positive time savings were found in a report from North Carolina, where HEMS use for scene cases saved at least 15 minutes.[76] In contrast, a prospective multicenter study out of France found the HEMS transport of STEMI patients was five times less effective than ground transport in maintaining the 90-minute first medical contact to primary PCI, particularly for transfer distances less than 50 km (31 miles).[77]

Stroke

Acute stroke patients can be just as time sensitive as trauma or ACS cases. With the advent of time-critical reperfusion therapy for ischemic stroke, HEMS has played an increasing role in the regionalization of acute neurologic care. Early studies demonstrating safety of transport of patients receiving thrombolytics during transport or post-thrombolysis stroke patients has been complemented by case series illustrating the increasing use of helicopter interfacility transport for stroke.

Although it is more common for flight programs to transport patients from smaller hospitals to regional stroke centers, case reports and series have demonstrated the utility of air medical dispatch for primary (scene) transport of patients with strong suspicion of stroke. In both scenarios, it has been demonstrated that HEMS can make important contributions when "time is brain" to facilitate the timely administration of tissue plasminogen activator and/or a neurointerventional procedure.[78] With appropriate education and criteria, ground EMS can effectively triage and identify patients who would likely benefit from HEMS scene response. This is especially important in the rural population, where HEMS can significantly reduce prolonged prehospital transport times. A 2015 report of more than 25,000 HEMS-transported stroke patients found that 96% of the HEMS patients reached tertiary care within 2 hours, which would not have been possible by GEMS.[79] In another proof-of-concept scenario, HEMS was used in interventional stroke management in much the same manner as an organ harvest—transporting physicians to the patient to improve time to procedure.[80]

High-Risk Obstetrics Patients

With appropriate triage, the speed of air transport of the high-risk pregnancy to an obstetric referral center can counter the risk of delivering an infant in an aircraft's confined space. Case series demonstrate that high-risk obstetric patients transported by air from distant hospitals have outcomes equal to patients presenting directly to an obstetric referral center. Common reasons for obstetric transport include preterm labor, premature rupture of membranes, hypertensive disorder of pregnancy, and other maternal life-threatening disorders.

Neonates and Children

The use of AMT to extend the geographic reach of neonatal care centers is reported in many settings. AMT allows infants with medical complications born in remote areas to achieve outcomes equal to those of infants born in urban centers. Although speed of transport may be important, the emphasis for neonates is often more on the transport team than on the mode of transport. Neonatal transport teams often spend more time at the bedside to resuscitate and stabilize the newborn prior to transport.

Many areas depend on AMT to deliver critically ill or injured children to regional pediatric centers. AMT has been shown to be safe for the transport of even the most critical children requiring mechanical ventilation[81] or extracorporeal membrane oxygen support.[25] Although various diagnoses may benefit from speed of transport, one retrospective study looked at patients transferred with suspected testicular torsion and concluded that HEMS offered no advantage over GEMS.[82]

LIVES SAVED, EFFICACY, AND COST-EFFECTIVENESS

Cost-benefit is an ongoing issue for AMT. The crux of the problem lies in the inability to precisely identify in a prospective manner which patients will truly benefit from fixed-wing or rotor-wing flight, especially when outcome improvements are part of regionalized specialty care systems. As a result, in many cases there is little if any guidance regarding when air medical dispatch is indicated. With use of endorsed guidelines and position papers for air medical dispatch, EMS regional authorities should collaborate to generate the best criteria for their own systems, with constant refinement guided by rigorous review.

Over the years, numerous studies have evaluated the survival benefits of HEMS, yielding results between 1.1 and 12.1 additional survivors for every 100 HEMS transports.[83-85] Cost-effectiveness determinations are not straightforward. It is difficult to calculate true cost-effectiveness for transports that are not likely to occur (as with high-risk obstetrics cases at risk of precipitous delivery) or that would deliver patients outside critical time windows (as for stroke or cardiac transports) in the absence of AMT. Cost-efficiency is also difficult to demonstrate when there are no comparison options (such as transport from coastal islands or locations without road access) or when integrated ground and air transport systems have already become established in ways that effectively prohibit head-to-head comparisons of risks and outcomes (as is true in most of the United States). If we accept that HEMS represents the only mechanism by which more than 80 million American citizens have timely access to mortality-improving high-level trauma center care, it is obvious that some form of air transport is a "must-have" for some EMS regions, and calculations of cost-efficiency fall away in favor of service provision.

FUTURE OF AIR MEDICAL TRANSPORT

AMT faces many challenges. The dramatic increase in the number of medical helicopters in the United States since the early 2000s and the number of HEMS accidents has heightened concerns for their inappropriate use. AMT works best and provides the most benefit when it is integrated into an overall system of out-of-hospital care and interfacility transport and when systems are in place to educate requesting agencies and professionals. Understanding the risks and benefits of HEMS, guidelines need to be in place to determine the appropriate use of these often-limited HEMS resources and ground resources.

Currently, the major challenge facing helicopter transport outcomes research is to identify triage variables that can prospectively (i.e., at the time of transport vehicle selection) guide use of air medical resources. In recent years, advances in ground-based EMS and the availability of critical care ground ambulances for interfacility transports have offered an appropriate transport option when an advanced level of care is needed but speed of transport is not a determining factor. Nonetheless, the regionalization of specialty services, development of new therapies that are highly time-sensitive, and inflexible geography mean that there will always be a role for AMT in emergency care. Thus, the major challenge for the AMT community is to determine not whether but rather in whom there is benefit to air medical flight.

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CHAPTER E13: QUESTIONS AND ANSWERS

1. Which of the following statements is true regarding air medical transport (AMT)?

a. AMT does little to improve outcomes when used for STEMI transport from rural areas.

b. AMT scene response for acute stroke is limited by emergency medical service (EMS) providers' inability to effectively triage and identify patients who would likely benefit from HEMS scene response.

c. Faster times to a trauma center are not required for outcomes benefit from AMT.

d. The emphasis for AMT of neonates is often more on the *mode* of transport than on the transport team.

Answer: C.

2. Safety is a critical consideration for all air medical operations. Which of the following statements is true?

a. If the patient's condition is severe, it is prudent to request service from several AMT providers in the face of marginal weather.

b. Spectators should be kept at least 200 feet away from the landing zone.

c. The use of a hospital helipad for emergency medical service (EMS) rendezvous triggers the Emergency Medical Treatment and Active Labor Act (EMTALA).

d. Vehicles and personnel should be kept at least 50 feet away from the landing zone.

Answer: B.

3. A working knowledge of aviation physiology is vital to understanding the effects of AMT on pilots, medical personnel, and patients. Which of the following statements is correct regarding the aviation physiology gas laws?
   - **a.** Boyle's law explains the physiologic effects of expansion and contraction of gases within the closed spaces of the body that may occur with altitude change.
   - **b.** Charles' law can be shown as Pt = P1 + P2 + P3…Pn.
   - **c.** Dalton's law accounts for the gas changes that result in decompression sickness.
   - **d.** Henry's law explains why the ambient temperature decreases with increased altitude.

Answer: A.

4. Which of the following statements is correct with regard to landing zone safety?
   - **a.** During night operations, spotlights should be toward the approaching aircraft.
   - **b.** If the aircraft is parked on a slope, approach and depart on the downhill side.
   - **c.** In a rear-loading helicopter, it is safe to approach or depart from the rear of the helicopter.
   - **d.** Vehicles and personnel should be kept at least 50 ft from the landing zone.

Answer: B.

5. Determining which patient(s) might benefit from AMT is a critical decision for prehospital and interfacility personnel. Which of the following would represent a safe and appropriate request for AMT?
   - **a.** Any burn victim being transferred to a regional burn center
   - **b.** Based on distance for pediatric trauma patients, regardless of the type and severity of injury
   - **c.** The preferred HEMS program has turned down the flight due to weather conditions but there are other programs that can be called
   - **d.** When the distance to the closest appropriate facility is too great for safe and timely transport by ground ambulance

Answer: D.

Disaster Preparedness

Carl H. Schultz and Romeo Fairley

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Disaster Preparedness

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KEY CONCEPTS

- Comprehensive emergency management consists of four phases: mitigation, preparedness, response, and recovery.
- Mass casualty planning should account for the breakdown of traditional transportation and communications systems during a disaster.
- Field personnel should be specifically trained in mass casualty triage and stabilization because austere field conditions change management strategies.
- All plans must protect caregivers and rescue personnel.
- Critical incident stress management is highly desirable after an event and should be planned for in advance. Psychological triage tools, such as Psy-START, may help.
- Planners should establish and exercise a hospital-based incident management system.
- Disaster planning needs to include policies to address the needs of vulnerable populations such as children, disabled, and the elderly.
- Multiple United States government agencies support disaster response, including the National Disaster Medical System, the Department of Defense, the Department of Veterans Affairs, and the Centers for Disease Control and Prevention.

FOUNDATIONS

Disasters occur in all areas of the world and cause harm to populations, property, infrastructure, economies, and the environment. Harm to populations includes death, injury, disease, malnutrition, and psychological stress. Recent catastrophes include earthquakes in Italy (2012) and Nepal (2015) (Fig. e14.1); devastating tsunamis in Japan (2011); severe flooding in Sudan (2013) and Venice, Italy (2019); hurricanes in the Philippines (2013) and the United States (2017); tornados in China (2015); the spread of Zika in South America (2015–2016); wildfires in California (2017 and 2018) and Australia (2019); the Ebola outbreak in West Africa (2014–2016) and Democratic Republic of Congo (2019); and the pandemic of severe acute respiratory syndrome coronavirus-2 (COVID-19) (2020–2021).[1]

Increasing population density in floodplains, seismic zones, and areas susceptible to hurricanes, as well as the effects of climate change, point to the probability of future catastrophic disasters with large numbers of casualties. Additional factors that indicate an increasing probability of mass casualty incidents include terrorist activity; production and transportation of toxic and hazardous materials; risks associated with fixed-site nuclear and chemical facilities (illustrated by damage to the Fukushima nuclear power plants after the 2011 Japan earthquake and tsunami); and the possibility of catastrophic fires and explosions. As an example, the United States Geological Survey has identified volcanoes in the western United States and Alaska that are likely to erupt in the future, including Mt. Hood, Mt. Shasta, and the volcano underlying Mammoth Lakes in California. Because of the rising population density in these areas, hazards from volcanic activity are increasing. An entire town, containing several hundred residents, required evacuation during the 2018 Kilauea volcanic eruption.

Given this probability and the increasing role of emergency medicine in disaster mitigation, preparedness, response, and recovery, this chapter discusses disaster planning and operations with emphasis on the role of the emergency clinician. The emergency clinician has extensive responsibilities for community disaster preparedness and disaster medical services, including response to terrorism. In position and policy documents, the American College of Emergency Physicians (ACEP) outlines the scope of emergency medicine's involvement in preparedness and response to disasters and terrorism, stating that "emergency physicians should assume a primary role in disaster preparedness and response, throughout all phases of the disaster life cycle."[2] Organized emergency medicine has also facilitated creation of national disaster and terrorism-related core competencies for emergency department (ED) personnel and emergency medical service (EMS) professionals, most recently including similar education for emergency medicine residents.[3]

A committed ED alone is insufficient to provide hospitals with a successful disaster preparedness program. Institutional commitment by every hospital department and the administration is necessary to coordinate effectively with system-wide resources for disaster management. Addressing this need is one of the major factors behind the federal government's emphasis on creating and maintaining health care coalitions (HCC). An integrated comprehensive health care system response is especially critical for providing care when demand exceeds available resources, a concept referred to as *hospital surge capacity*. A partial listing of sources for general disaster medicine information can be found in Table e14.1.

In 2016, the Office of the Assistant Secretary for Preparedness and Response (ASPR) released their guidance for health care disaster preparedness through 2022.[4] Four key capabilities are outlined:

1. Creating a foundation for health care and medical readiness
2. Health care and medical response coordination
3. Continuity of health care service delivery
4. Medical surge

The first two HCC capabilities involve organizational creation and maintenance. HCCs act as multiagency coordination groups and allow for collaboration on the mitigation of, preparation for, and response to disasters and emergencies. HCC members include individual health care and response organizations (acute care hospitals, emergency medical service agencies, public health entities, long-term care facilities, etc.) within a defined region. An emergency operations center should be established for use by the HCC. Prearranged mutual aid agreements within the HCC allow sharing of resources among members during times of crisis or hospital evacuation. The Centers for Medicare and

Fig. e14.1 Large-scale catastrophes, such as this earthquake in Nepal (2015), have the potential to cause much injury and psychological stress. (Voice of America. "Dead count rises in Nepal." Available at: https://www.amerikaninsesi.com/a/2739517.html.)

TABLE E14.1 List of Disaster Medicine Resources

Organization	Website
The Joint Commission	www.jointcommission.org
American College of Emergency Physicians (ACEP)	www.acep.org
Centers for Disease Control and Prevention (CDC)	www.cdc.gov
FEMA National Preparedness Directorate	www.fema.gov/national-preparedness-directorate
National Response Framework	www.fema.gov/media-library/assets/documents/117791
Agency for Healthcare Research and Quality	archive.ahrq.gov/prep
Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices (Cambridge University Press)	www.cambridge.org
World Association for Disaster and Emergency Medicine	www.wadem.org

Medicaid Services require physician involvement in HCCs, and emergency physicians working at hospitals may consider participating in HCC planning and community disaster management operations.

Surge Capacity

The concept of surge capacity has emerged as a way to manage an event that produces a sudden influx of casualties with medical and health needs that exceed current hospital resources. This can be due to either the volume or types of victims. The three basic components of the surge capacity system are commonly referred to as the three "Ss": staff (hospital personnel), stuff (supplies and pharmaceuticals), and structure (physical location and management infrastructure). A complete discussion of surge capacity is beyond the scope of this chapter but has been published elsewhere.[5]

Within the context of surge capacity, new protocols exist that address allocation of resources when the medical and health needs of a population exceed current inventory. The issues involve creation of an equitable system for scarce resource allocation strategies, including, but certainly not limited to, the expansion of the emergency department or the assignment to an intensive care unit as was done during the COVID-19 pandemic.[6] Although no universally accepted approach currently exists, the Institute of Medicine has published a consensus-based document that suggests approaches to optimize patient outcomes in a resource-constrained environment.[7]

Definitions

One of the challenges facing those responsible for disaster preparedness is that no standard definition of *disaster* exists. In the most general terms, one can define a disaster as a severe supply and demand mismatch where the need for resources exceeds the supply. This suggests that a disaster is defined more by the resource and need discordance than the actual size of the event. These response capabilities can change in diverse environments or even in the same location at different times of the day or day of the week. A multiple-vehicle collision with 6 critically injured patients and 12 patients with minor injuries could overwhelm both the EMS system and the hospital in a small rural community. In an urban area with multiple hospitals that participate in a trauma system, this same event could be managed with routine resources. Thus, it is the functional impact on the specific entity that is the key concept in determining whether a disaster exists. For example, many would consider a plane crash a disaster, yet it may not even approach overwhelming the resources of the local responders. Because disaster medicine is multidisciplinary and depends on the integration of multiple levels of responders, the use of a common, precise terminology is essential.

Classic Terminology

The words *internal* and *external* refer to a hospital setting to help distinguish whether an event has occurred within the hospital grounds (internal) or in the community (external). This concept distinguishes between preparing for casualties to arrive at the hospital and managing casualties or resources within the hospital. This geographic distinction between internal and external may be useful, but it has severe limitations. Many events can be both internal and external to the facility at the same time (e.g., major earthquake or hurricane). Furthermore, simply identifying the location of the event does not answer the critical question: How are response capabilities affected? The key consideration is what actions are required to mitigate and then to rectify the situation.

Some definitions have been based on the number of casualties. As previously described, the absolute number of patients is much less important than whether their medical and health needs exceed the resources to care for them at a given point in time. The attack on the World Trade Center in 2001 (Fig. e14.2) illustrates this point. Although over 2000 victims died in the collapse of the twin towers, the actual impact on the overall health system of New York City was relatively mild. The capacity of the system to care for citizens living in New York remained intact. In contrast, Hurricane Katrina in 2005 resulted in a similar number of deaths, but caused such massive destruction, including the loss of medical and health infrastructure, that federal disaster medical assistance teams (DMATs) were deployed to Louisiana to provide medical personnel and supplies.

Hazard Vulnerability Analysis

An all-hazards approach is a common feature in disaster planning. This concept dictates that the bulk of planning should be designed for all disaster scenarios instead of for specific types of hazards (such as fire, flooding, tornados, etc.). However, an important consideration in disaster planning is an awareness of the types of events to which the hospital or community is vulnerable. The classic example is the increased risk from earthquakes in the central United States resulting from the combination of the New Madrid fault and the limited seismic safety requirements for

Fig. e14.2 The World Trade Center attack of 2001 overwhelmed local resources and necessitated state and federal help.

buildings in that area. A hazard vulnerability analysis (HVA) can be used by an HCC and individual facilities to appropriately plan resources. An HVA is based on the likelihood of an event, the potential destructive force of an event, and the preparedness level of the entity for an event. The Kaiser system has developed an HVA template (www.calhospitalprepare.org/hazard-vulnerability-analysis). The major nonmilitary threat to life and property in the United States is probably a large earthquake in a densely populated area or a terrorist attack, although the threat from flooding is increasing. The COVID-19 pandemic has demonstrated that with the increasing rate of globalization and population density growth, an emerging infectious disease represents a new and expanding risk.[1]

SPECIFIC ISSUES IN DISASTER MANAGEMENT

Triage

The term *triage* derives from the French verb *trier*, meaning to sort. The concept of triage was used as far back as Napoleon's time to assign priorities to treatment of the injured when resources were limited. Priority is given to the most salvageable patients with the most urgent conditions. Some EDs continue to use triage in the hospital setting, although this daily practice has little in common with triage during disaster conditions. For those EDs that continue to use standard triage, it is intended to identify the most seriously ill patients with time-dependent conditions and to ensure that they receive rapid care. The goal of disaster triage is clearly different—to do the most good for the most people. There is a shift from focus on individual patients to focus on the entire affected population. It can be difficult for physicians to realize that achieving the goal of maximizing benefit to an entire population of patients may necessitate letting some patients die with comfort care only. Under true disaster conditions, cardiopulmonary resuscitation should not be performed.

Routine Multiple-Casualty Triage

To assist in the understanding of triage techniques, it is useful to consider a routine out-of-hospital event with multiple casualties (e.g., a multivehicle collision). In such situations, rescue personnel often use a simple triage and rapid treatment (START) technique that depends on a quick assessment of respiration, perfusion, and mental status.[8] These three assessments can be remembered by the mnemonic RPM (*r*espirations, *p*erfusion, and *m*ental status). To initiate this sorting process, all victims who are able to walk are asked to move away from the incident area. These patients are classified as green, or "walking wounded," and are reassessed after the more immediately critical patients are triaged.

The Pediatric Triage Tape (PTT) and JumpSTART have been proposed for the triage of children. JumpSTART is a modification of the START triage protocol that includes an additional step of five rescue ventilations for children presenting apneic and modification of criteria for hypoventilation and tachypnea, as well as for a decrease in mental status (Fig. e14.3). The PTT uses criteria that change in proportion to increasing victim size. The parameters for a child 50 to 80 cm in length are illustrated in Figure e14.4. In an evaluation of five triage tools using a large trauma database, JumpSTART performed best for children under 8 years of age with CareFlight triage performing best overall.[9] Although START, JumpSTART, the PTT, and CareFlight appear to be useful tools, only START has been evaluated in an actual disaster situation. As such, no pediatric triage system has proven clear superiority over any other, and therefore, recommendations on choice of pediatric triage system should be left to individual jurisdictions. Proper education and team training may be more important than triage system choice.

As illustrated in Figure e14.5, a rescuer using START triage can assess each patient in seconds, quickly checking respiratory rate, pulse, and ability to follow commands (mental status), and divide the patients into the remaining three categories: red (immediate), yellow (delayed), and black (deceased). The only patient care interventions provided during this process are the opening of an obstructed airway and direct pressure on obvious external hemorrhage. At this point, patients are generally transported to a hospital for definitive care. Most often, patients arrive with a color-coded triage tag and are reassessed and retriaged by the hospital staff (Fig. e14.6). An outcomes-based evaluation of the performance of START triage in an actual disaster (2002 Placentia Linda train crash) demonstrated acceptable levels of undertriage (100% sensitivity of the red category and 90% specificity of the green category). However, significant amounts of overtriage occurred. Use of START also appropriately prioritized the transport of victims, with patients triaged as red arriving at hospitals earlier than patients triaged as yellow or green.

Given the significant number and variability of proposed disaster triage systems, a multidisciplinary group in the United States attempted to standardize these platforms by developing the Model Uniform Core Criteria in 2011. These core criteria promulgated a set of principles to guide creation of mass casualty triage algorithms. Based on these guidelines, this group also proposed a potential national triage system for the United States. The result, derived by consensus, was referred to as SALT (*s*ort, *a*ssess, *l*ifesaving interventions, and *t*reatment or transport). It differs from START mainly in the assessment of respirations (i.e., relies on a qualitative evaluation of respiratory distress rather than a number), the requirement for performance of certain lifesaving interventions (chest decompression), and an unstructured estimate of survivability. The algorithm is more complicated than START, and no current data exist evaluating its sensitivity, specificity, or other performance characteristics after use in an actual incident. As such, it is not currently possible to make recommendations for the use of SALT triage. For anyone considering implementing an adult mass casualty triage algorithm, we recommend using START triage until more evidence emerges describing the performance of SALT triage in actual disasters.

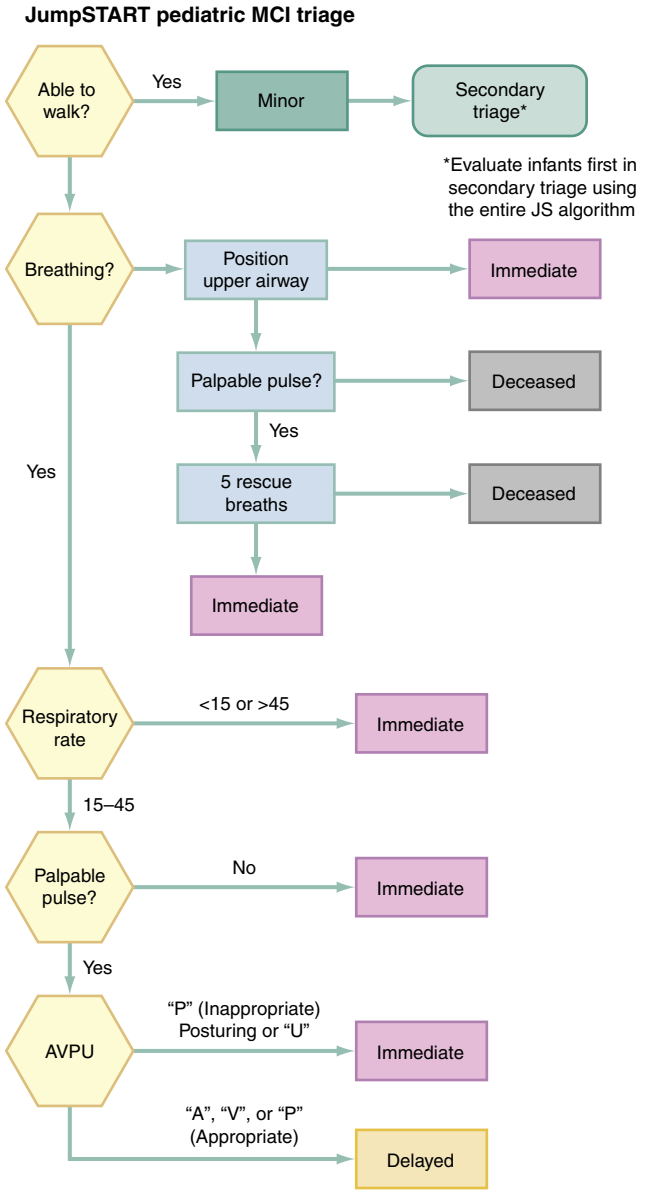

Fig. e14.3 JumpStart pediatric triage algorithm.

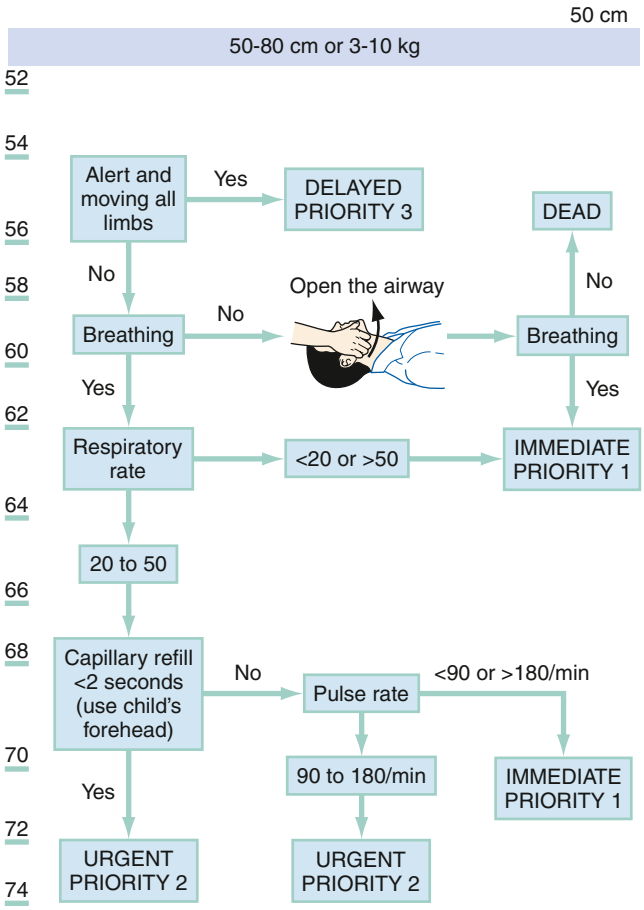

Fig. e14.4 Pediatric Triage Tape (PTT) algorithm for a child 50 to 80 cm in length.

Catastrophic Casualty Management

Triage during a disaster differs from triage performed in routine out-of-hospital and hospital settings. The number of victims is vastly increased, while medical resources are severely limited or initially absent. Patients may remain on scene for an extended period and may require periodic reassessment, which will be challenging. If hospitals remain accessible, patients tend to seek care at the closest one, a phenomenon known as convergence. Hospitals close to the disaster scene are overwhelmed, whereas hospitals located only a few miles away may receive few if any patients. The triage process will then be decentralized, occurring at multiple sites, or compartments, simultaneously throughout the disaster zone. Rather than a single scene or localized disaster, this can be thought of as a compartmentalized disaster.

To address this situation, researchers developed the Secondary Assessment of Victim Endpoint (SAVE) system of triage. The SAVE triage system is designed to identify patients who are most likely to benefit from care available under austere field conditions or in a resource-poor environment. When combined with the START protocol, SAVE triage is useful for any scenario in which multiple patients experience a prolonged delay in accessing definitive care.

The SAVE methodology is designed for use by health care providers under two conditions: (1) for those working within the disaster zone that begin caring for patients immediately but may not be able to transport patients to a definitive care facility for days, and (2) for those caring for patients within hospitals where demand for resources exceeds supply. This second situation can occur as hospitals attempt to increase surge capacity. It is immediate and dynamic rather than delayed and static.

The SAVE triage methodology divides patients into three categories: (1) those who will most likely die despite available care, (2) those who will survive without care, and (3) those who will benefit from austere field interventions. Only those patients expected to improve receive care beyond basic or comfort measures. The decision to place patients in a particular group is based on field outcome expectations derived from existing survival and morbidity statistics. An example is a situation in which three victims require chest tubes (two victims require one tube each and one victim requires two tubes), but only two chest tubes are available. The SAVE principles guide providers to place their last two chest tubes into the two victims who need one rather than into the single victim requiring two tubes.

Since nuclear, biologic, and chemical terrorism has become a threat, triage systems have been modified to address these situations. These systems attempt to incorporate the added threats from exposure and contamination into the triage process. One such method for biologic casualties triages many individuals to home observation rather than hospitalization to optimize resource use and to minimize the spread

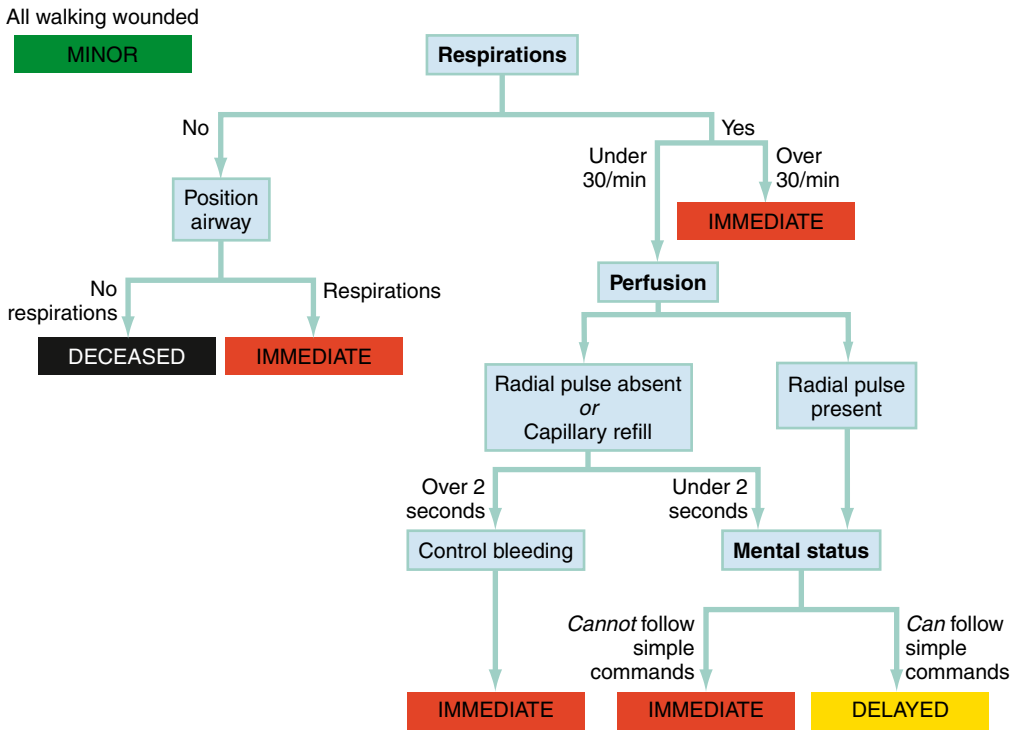

Fig. e14.5 Simple triage and rapid treatment (START). Victims who can walk are identified first and triaged into the "minor" category. Those remaining are triaged using the algorithm. (Modified from: Triage—START and SAVE. In: Medical disaster response training course syllabus, Dana Point, CA: Medical Disaster Response; 1993.)

of the infectious agent. This strategy has been used effectively during the COVID-19 outbreak. In addition, responders require protection from secondary contamination or exposure; therefore, part of the triage algorithm should include a risk assessment and determination of whether and what type of personal protective equipment should be donned before patients are assessed. This was illustrated during the 2014 to 2016 Ebola outbreak when health care providers initiated Ebola exposure screening procedures during initial patient contact before engaging in patient evaluation and treatment. A similar approach was also utilized initially in the COVID pandemic. Once community spread developed, however, this practice was replaced by the assumption that all patients were infected. In a combined event scenario, such as an incident involving a radiologic dispersion device, rapid patient assessment is critical to prevent patient deaths from traumatic injuries while awaiting medical care from responders concerned about their own health and safety.

Also associated with disaster incidents are large numbers of psychological casualties. These individuals have not received physical injuries or toxic exposures but experience significant psychological trauma and are at risk for posttraumatic stress disorder and other psychiatric illnesses. The emergency plan should include a mechanism to provide psychological triage, such as PsySTART, that can rapidly assess individuals to identify those at risk for serious and prolonged illness and assure that they have access to mental health care. Responders effectively used PsySTART immediately after Hurricane Sandy and Typhoon Haiyan.[10]

While performing triage, the emergency clinician should consider the effects of extreme age, underlying disease, and multiple injuries when assessing the potential prognosis for a given patient. Treatment of many nontraumatic emergencies can be accomplished with field interventions that do not consume extensive resources. Patients with such illnesses should usually be triaged to the treatment area.

Vulnerable Triage Populations

Certain groups of patients, such as children, the elderly, the disabled, and homeless persons, may have special needs that present challenges to routine triage. For example, if a person is too young to follow commands or is deaf, the individual would not be able to respond to a command to walk away from an incident site for reasons that may not indicate severe injury. Triage schemes should attempt to accommodate language and cultural barriers, as well as physical and psychological limitations that result in social or medical vulnerabilities.

Special Triage Categories

To maximize human resources, disaster victims who would normally be triaged to the observation area can be triaged to the treatment area if they possess special skills valuable to the medical team (e.g., medical expertise and translation skills). By increasing the number of functional team members, the effectiveness of the overall response will improve. The guiding principle supports the disaster triage goal of maximizing benefit to the most people.

Care of Populations with Functional or Access Needs

Within the general population, groups of unique individuals exist that are at greater risk for injury, death, and property loss resulting from a disaster. These vulnerable populations include children, the elderly, racial and ethnic minorities, the disabled, those residing in institutions such as skilled nursing facilities, and the mentally ill. Challenges in the management of these populations with functional or access needs during a disaster include: (1) lack of mobility; (2) difficulty tracking victim movement during evacuations and issues of reunification with responsible family members; (3) inability to understand English or to comprehend instructions issued by local authorities; (4) fear of deportation if requesting aid or other resources from state or federal authorities; and (5) poor access to transportation resources. A detailed

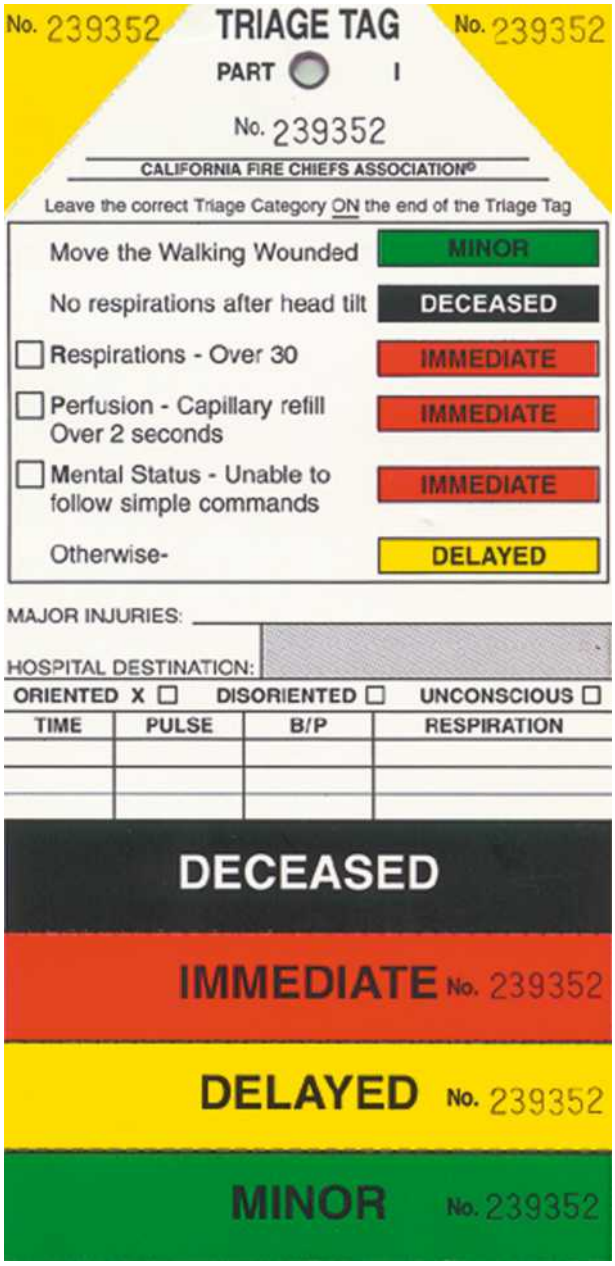

Fig. e14.6 Triage tag to be used in multicasualty or disaster patient assessments.

discussion on the disaster management of these populations is beyond the scope of this chapter but available elsewhere.[11] Those responsible for disaster planning should ensure that policies and procedures are developed that address the unique needs of such groups.

Out-of-Hospital Response

Emergency Medical Services System Protocols

To prepare adequately, hospitals should be familiar with and involved in the development of county or regional plans. For example, some EMS systems use automatic systems such that each hospital may be expected to accept a fixed number of critically ill or injured and minor patients without advanced notification.

Incident Management System

Some form of an incident management system is a standard component of emergency command and control throughout the United States.

TABLE E14.2 Incident Command System Elements

Incident Commander	• Responsible for overall management of incident • Not physician • Can appoint command staff to manage public information, safety, and interagency coordination
Operations Section	• Manages incident tactical activities • Manages the resources assigned to staging areas • Medical care and triage fall within this section
Planning Section	• Collects, evaluates, and disseminates information about incident operations and the status of resources • Develops incident action plans • Conducts planning meetings
Logistics Section	• Provides facilities, services, and material in support of the incident • Procures equipment and supplies • Provides food and medical support • Arranges for transportation needs
Finance Section	• Maintains records on personnel and equipment • Provides payments to vendors for supplies and use of equipment • Determines the cost of various alternatives for strategic planning

It provides a flexible management structure on which to organize a response.[12] The federal version, known as the National Incident Management System (NIMS), is incorporated into the National Response Framework (NRF) and provides strategic guidance on the United States government's involvement in disaster response. All states must use an incident management system compliant with the NIMS.[13,14] A tool commonly utilized to implement the NIMS approach is the incident command system (ICS).

By standardizing an organizational structure and using a common vernacular, the ICS provides a management configuration that is adaptable to events involving a multiagency or multijurisdictional response. At the most basic level, there are five functional elements in the organizational structure: incident command, operations section, planning section, logistics section, and finance section. The key components of these elements are listed in Table e14.2. Each section has a chief to provide leadership and can be expanded and subdivided into branches and divisions. Physicians should understand they will not serve in the incident command position so they may remain available to provide medical care. ICS requires a chain of command and aims to limit the scope of control to roughly five individuals. The principles of an ICS can be adapted to the hospital setting through implementation of a hospital incident command system (HICS).[15] With this type of organizational infrastructure and the flexibility to expand and collapse functions as needed, an orderly and efficient response to any incident can be accomplished, with fluid improvisation as needed. When an event involves multiple jurisdictions, a unified command is established that coordinates a common and consistent action plan to make the best use of available resources. The Joint Commission standards require use of an incident management system in health care facilities.

Organization of the Out-of-Hospital Disaster Scene

The disaster site is organized into several distinct areas. The command post is the nerve center of the operation and contains the incident commander and section chiefs. For events with a discrete scene, ambulances, personnel, and supplies should be staged outside the event

perimeter. Responders can then direct resources inside the perimeter as needed, preventing the uncontrolled convergence of assets to the disaster site that can result in potential disruption of activities and blocking the exodus of patients. If air evacuation is needed, a safe landing zone must be identified. A casualty collection point and morgue should be designated with operational resources (such as restrooms, food preparation areas, and sleeping quarters) for personnel strategically placed adjacent to the scene as needed. The media should have restricted access. Security personnel are required to control access to the entire scene. In conjunction with an ICS, this structure brings order to the response.

Planning and Hospital Response

Comprehensive Emergency Management

The comprehensive emergency management all-hazard approach to disaster preparedness has been a Joint Commission requirement since January 2001. Comprehensive emergency management consists of four phases: mitigation, preparedness, response, and recovery.[16] Although the National Response Framework describes five phases (prevention, protection, mitigation, response, and recovery), most emergency managers endorse the four-phase model and this chapter will employ such an approach for consistency. Mitigation involves taking actions to reduce the impact of identified hazards. Enhancing the seismic structural design of hospitals is one strategy to mitigate the impact of large earthquakes on the health care system. Preparedness includes initiation of strategies and activities before an event occurs to improve capability, such as stockpiling food/water and creating an evacuation plan. Response includes assessment of the situation and coordination of resources. Finally, recovery consists of a return to normal operations with a review of the response and provision of long-term psychological support to the victims and rescuers. As required by the Joint Commission, a hospital's disaster or emergency management plan needs to address events that occur both inside (internal) and outside (external) the institution.[16]

Hospital Disaster Response Plan

A disaster event can disrupt daily, routine hospital functions. This can represent an infrastructure failure (e.g., loss of electric power and water) or a threat to the safety of patients and hospital personnel (e.g., labor dispute or approaching hurricane). Because the response varies from postponement of elective surgery to facility evacuation, every hospital department needs to participate in the planning process.

Most disasters experienced by hospitals are local in nature. Hospital function is typically unimpaired. The majority of problems encountered relate to creating surge capacity for the sudden increase in volume and acuity of arriving patients, or for those with illnesses not usually treated at that facility (e.g., burns, radiation exposure, or severe acute respiratory syndrome). At a minimum, the disaster plan should clearly delineate the circumstances in which the plan is activated, as well as: (1) identify the command structure with defined lines of authority and responsibility; (2) describe a response strategy for each anticipated incident; (3) estimate an incident's impact on safety and hospital function, providing for evacuation if necessary; and (4) list essential information such as critical telephone numbers (e.g., elevators, key personnel, and pay telephones), community agencies (EMS, police, and public health), and a redundant source of vital supplies (water, oxygen, and drugs).

Events occurring in the community may result in a sudden surge of patients requiring emergency care. This type of incident has no direct impact on hospital structural integrity or function. However, the need to rapidly increase capacity may require implementation of different patient management strategies (i.e., temporary creation of alternative care sites on hospital grounds), as was done to accommodate patients with COVID-19. Participation in the planning and execution of the hospital disaster response is an important administrative responsibility. A member of the ED must have a leadership role in the planning and implementation of the disaster plans. Available data guiding development of disaster strategies are incomplete, but an effective disaster response can be created by reviewing the essential components of disaster plans and the previous experience of other hospitals.

The First 72 Hours. In a large-scale disaster, each individual hospital may need to remain self-sufficient for 48 to 72 hours or longer. Disaster medical assistance teams (DMATs) and urban search and rescue (USAR) teams will deploy, but their time to arrival on scene may be variable. Therefore, an alternative source of rapidly available, sophisticated medical care is necessary. Local responders able to initiate treatment of patients soon after the event can best provide such care. One model embracing this concept is the Medical Disaster Response Project, developed by emergency clinicians in Southern California. This model was used to create the current national plans utilizing the Medical Reserve Corps and Strategic National Stockpile.

Local responders and volunteer citizens rescue up to 90% of victims with serious but survivable injuries in the first 24 to 48 hours. Therefore, special medical teams such as DMATs and urban search and rescue teams may not significantly affect survival from acute injuries if they arrive after more than 48 hours. A recent analysis has questioned the cost-effectiveness of internationally deployed search and rescue teams.[17] The traditional view holds that deploying field hospitals to distant disaster zones does not improve outcomes. Due to the widely acknowledged success of their mission, the results reported by the Israeli Field Hospital after deployment to the Haitian Earthquake in 2010 may change this for acute events. In a more protracted event such as the COVID-19 pandemic, load balancing patients across an HCC or medical system may be a more effective approach if the risk of intrafacility spread is minimal. Otherwise, creating a single "SARS" hospital and supporting it with on-site alternative care facilities may be safest to protect the integrity of the health care system.

Basic Components of a Hospital Comprehensive Disaster Response Planning Process

Interdepartmental Planning Group. The interdepartmental planning group (frequently referred to as the disaster or emergency preparedness committee) is composed of representatives from all departments vital to the hospital's response. This group has the responsibility of completing the HVA and disaster mitigation activities. Commonly included departments are administration, finance, medical staff, nursing, security, pharmacy, and facilities management. Additional input may occasionally be necessary from outside agencies such as the fire department, EMS agencies, and the suppliers of goods and services.

The committee should be structured to ensure that the plan is properly constructed, tested, and executed. Hospital resources are needed to support the planning process and testing of the plan, and a detailed educational program should exist for all affected hospital staff. The Joint Commission requires the emergency plan to be reviewed annually.[16]

Resource Management. A full inventory of the hospital's resources is necessary, including equipment, space, and personnel. It is also necessary to develop contingency plans with redundancy to compensate for lost resources (e.g., failure of hospital computers during a power outage or cyber-attack). Augmentation of such resources is critical to the successful enhancement of the hospital's surge capacity. Discussion within an HCC on utilized vendors can prevent a single vendor from being overwhelmed in a disaster scenario.

Hospitals located near companies using large amounts of hazardous materials are required by Title III of the Superfund Amendments and Reauthorization Act to participate in local emergency planning

committees (LEPCs).[18] LEPCs are similar to HCCs but are broader in scope and include non–health care community representatives.

Command Structure. The HICS implements an organized approach to disaster management by establishing lines of authority and decision responsibility. This system designates a command center where the disaster response can be coordinated and creates a clear chain of command based on positions, not individuals. This prevents confusion if certain individuals are missing, a common situation on nights and weekends or in cases of a community-wide disaster during which hospital personnel may become victims.[15] The command center should contain sufficient equipment to support command and control functions, even if the center must be moved as a result of hospital damage.

Media. The media can be an important source of information but can also significantly disrupt the hospital's disaster response. Arrangements should be made in advance for a designated individual to coordinate all media interactions and for these briefings to occur in a predetermined location. Frequently referred to as the public information officer (PIO), media coordinators should inform reporters of the time they will receive their next update so that they do not intrude on response operations while trying to obtain information. A strong media liaison can facilitate dissemination of important information to the public, such as that no blood shortage exists to prevent individuals from flooding the hospital to donate blood. In fact, crisis and emergency health risk communication is now an important part of managing the disaster response and can have a significant impact on the public's perception of events.[19] Security should be involved in managing the media response to the hospital and in preventing media from interfering with essential hospital functions. During the Loma Prieta earthquake in 1989, for example, a news helicopter occupied a nearby community hospital's only landing zone, impairing the ability of landing a medical helicopter.

Communication. Communication systems are probably the most important but also most vulnerable component of a disaster plan. Redundant systems are essential. Those responsible for mobilizing the emergency response require access to at least one other communication system besides the landline telephone (which is frequently one of the first systems compromised during a disaster). Telephone service will cease as lines are disrupted or deliberately restricted by the phone company. Cellular phones may function within a local area, but failure is likely if more distant sites within the city are dialed. Hospital radios designated for disaster use should be secured in place using bolts or other devices to prevent damage from violent movements, such as falling to the floor, during an earthquake. Two-way radios are often used, as are independent fax lines and cellular phones. Other options are satellite phones and HAM radios provided by organized volunteers that are part of established national organizations. Recently, use of social media has proven beneficial.[20] Survivors of the 2011 Japan earthquake used social media to provide early information to the outside world on conditions within the disaster zone. Runners are useful for intrahospital communication if all else fails. A mass communication system is essential to easily distribute information to personnel and receive responses such as availability to return to work. Several commercial emergency notification systems exist using email, text messaging, and voice calls.

Personnel. The disaster plan should include a roster of all critical positions with relevant personnel and establish a reliable method for their mobilization. Several individuals should be assigned to each position in preparation for absences. Studies have shown that up to 80% of staff will not come to work during a disaster.[21] A protocol for managing volunteers is also crucial. A large group of volunteers spontaneously descending on a hospital (convergent volunteerism) can be as disruptive as the disaster.

Credentialing of volunteer health professionals in a timely manner so hospitals can use their services during a disaster remains a challenge. A federally supported program known as the Emergency System for Advance Registration of Volunteer Health Professionals (ESAR-VHP) attempts to address this problem. It provides a system for credentialing of volunteer health care providers (at the state level) in advance of a disaster so that they will have emergency privileges should the need for their services arise. There remain significant challenges with such a system, including whether sufficient numbers of providers will participate, how quickly they can deploy, how qualified they will be, and whether they will have competing obligations during a disaster. An alternative system that permits hospitals to recognize each other's credentialing process through a shared database shows promise and has been endorsed by a publication from the Agency for Healthcare Research and Quality. Not only will this alternative system facilitate participation by most health care providers, but it also permits hospitals to grant emergency privileges within minutes after a disaster. Aspects of this system are in use to support emergency staffing during the COVID-19 pandemic while other components are evolving.

Patient Management. A systematic approach to patient management is necessary to maximize resources. This includes protocols for decontamination, triage, prioritization, evacuation, and family reunification. Alternative use of hospital facilities should be anticipated, such as the conversion of a parking lot into a clinic area for suturing of lacerations or a decontamination zone. If hospitals are not functional and no backup plan exists, immediate advanced medical care will not be available, and people may die. Planners should include a backup system to provide medical care at alternative nonhospital care sites. Provisions for patient identification and treatment documentation are also important to facilitate federal and third-party reimbursement at the conclusion of the disaster.

Hospital Evacuation. On rare occasions, the hospital structure or critical infrastructure will be damaged, forcing facility evacuation. After hospital damage, immediate access to structural engineers is important. In the Northridge earthquake, eight hospitals in the Los Angeles area sustained enough damage to force evacuation of at least one patient. Four institutions completely evacuated their facilities in the first 24 hours, including two hospitals that met the most current structural earthquake standards. Further structural damage was subsequently identified, and two additional hospitals were forced to evacuate completely in the next 2 weeks. Ultimately, four of these hospitals were permanently closed and demolished.

Hospitals are also vulnerable to flooding. A study of Hurricane Harvey's (2017) impact by the Texas Hospital Association showed that twenty hospitals were closed or evacuated. Significant problems included loss of power, lack of potable water and other critical supplies, insufficient staff, and structural damage. It was also difficult to obtain vehicles for transportation of patients to other facilities. Nonmedical vehicles were sometimes used to evacuate stable patients.

In the event that evacuation of the hospital is necessary, evacuation routes and relocation destinations that have been planned in advance maximize safety and efficiency. Some hospitals use the ED as a "landing zone" for hospital evacuations (i.e., patients move from inpatient beds to the ED and then are transported out). When resources are plentiful, patients in critical condition are assigned the highest priority for evacuation and transport. Less ill patients receive a lower priority. When time is limited (e.g., in the event of an imminent structure collapse), the reverse strategy applies. The least critically ill patients receive the highest priority for evacuation; this maximizes patient evacuation in a constrained timeframe.

Generator problems are frequent; they either fail altogether (as they did during the Loma Prieta earthquake) or supply insufficient power to meet emergency needs (as during the Northridge earthquake). Evacuation plans must not require elevators for this reason. Though several commercial devices exist to aid patients down stairwells, none has ever been documented as superior to backboards, sheets, and other readily available hospital equipment.

Training Exercises. Disaster exercises are one of the more effective ways of familiarizing hospital staff with their responsibilities. All hospital departments should participate, and community agencies should be involved. The Joint Commission requires two drills a year; these should mimic incidents that are likely to occur, based on the hospital HVA. Methods to assess the effectiveness of these exercises as measures of overall hospital disaster preparedness are improving, such as those provided in the toolkit by Agboola et al.[22]

Toxic Disasters (Hazardous Material)

Hospitals located near major chemical industries, transportation corridors, or probable terrorist targets (e.g., major theme parks or nationally symbolic buildings) should be aware of potential hazardous material incidents. Such facilities should be prepared to decontaminate large numbers of individuals. Coordination of decontamination resources through the HCC can significantly increase community preparedness. Effective decontamination of victims and the need for safety measures on the part of rescue personnel to prevent secondary contamination are critical. Decontamination equipment should be stored near the ED and the staff trained in its use. When such an emergency occurs, there is little time to search the hospital for necessary supplies.

Patients contaminated with hazardous materials should first be brought to a designated decontamination area containing a warm-water shower with a container to hold drainage water. In a rapidly evolving event with mass casualties, collection of wastewater after decontamination is not a priority and drainage into the sewer system is acceptable. Victims should remove all clothing and valuables, and these should be bagged, identified, and stored. Contaminated patients should never be brought into regular patient care areas due to the danger of contaminating other patients, hospital staff, and equipment. In 1994, paramedics unsuspectingly transported a patient contaminated with a degradation product of dimethyl sulfoxide to an ED in Riverside, California. Before the presence of the hazardous material was detected, six health care workers were exposed, including an emergency clinician. The emergency clinician experienced a near-fatal exposure and required intubation and an extensive stay in the hospital's intensive care unit. Uncontrolled spread of the toxin resulted in evacuation and temporary closure of the ED.

Closing off air intake vents by hospital personnel is appropriate for rooms containing contaminated patients so that toxic products do not enter the ventilation system and circulate to other areas of the hospital. Rescue personnel and hospital staff should be protected by gowns, gloves, masks, and, if necessary, supplied air respirators. The goals are to reduce the initial level of external contamination, to contain the contamination that remains, and to prevent further spread of these potentially dangerous substances to other patients and staff members (secondary contamination).

Chemical, Biologic, Radiologic, Nuclear, and Explosive Terrorism

In addition to the familiar threat from hazardous materials, there is another challenge: a potential attack by terrorists using biologic, radiologic, chemical, or explosive (CBRNE) weapons (see Chapter e15). Although somewhat similar to hazardous materials situations, management of patients exposed to weapons of mass destruction (WMD) requires additional knowledge and skills. While expertise in the management of patients targeted by unconventional weapons is important, emergency clinicians should also be familiar with the treatment of blast injuries. Events characterized by the use of high-explosive devices, including suicide bombers, remain the most probable type of terrorism.[23]

The most likely radiation source used by terrorists will probably not come from the detonation of a nuclear weapon. Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are likely the source of choice. They do not explode and give no warning of their presence. Terrorists can dismantle such devices and incorporate the radioactive source into an explosive radiologic dispersion device (dirty bomb). Providers should recognize the presentation of patients suffering from radiation exposure to make the diagnosis. In addition to damage from radiation, these casualties may also suffer blast injuries. Initial treatment of such victims, if they are critically injured, should address stabilization of the blast injuries first before the radiation exposure is considered. Patients who are irradiated but not externally or internally contaminated pose no threat to ED personnel.

One of the greatest challenges with respect to WMD is the detection of biologic weapons. Patients exposed to biologic agents often initially present with vague symptoms associated with influenza-like illnesses (ILI). Decontamination is not a priority unless the exposure is immediate; standard precautions are generally sufficient.

Unlike radiologic or biologic weapons, chemical agents produce symptoms quickly. The challenge is decontamination and treatment. Their accurate diagnosis may also be challenging given the clinical overlap with other natural, pharmaceutical, or chemical entities. For example, Sergei and Yulia Skripal were poisoned with what was eventually found to be a targeted attack with a Novichok (nerve) agent, but their symptoms were originally diagnosed as an overdose on a fentanyl-contaminated product. At least 2 other people were contaminated during the process, and one died. Approximately 80% of mass casualty decontaminations are performed at hospitals. PPE is essential for responders and hospital "first receivers" due to the risk of exposure during the decontamination process.

Disaster Stress Management

Emergency health care providers experience high levels of stress when responding to the needs of disaster victims. If the stress exceeds the capacity of normal coping mechanisms, it can potentially interfere with job performance and produce symptoms, including depression, sleep disturbances, increased use of alcohol and drugs, irritability, and anxiety. Posttraumatic stress disorder (PTSD) can result. In an attempt to reduce the psychological impact of these events on medical responders, various therapeutic techniques have been introduced throughout the years and are collectively known as critical incident stress management. This formal process of resolving emotional conflict using mental health professionals is now widely practiced.[24]

In general, the longer the delay between exposure to the critical incident and subsequent psychological intervention, the smaller the chance for a successful outcome. Therefore, the critical incident stress management process is designed for rapid implementation. During the incident, stress management staff or even a colleague can provide on-scene intervention. The goal is to assist the health care worker in regaining emotional control by facilitating communication of feelings and reactions through listening and support. A recently validated tool, PsySTART, can be used to rapidly identify disaster victims or health care workers at risk for long-term mental health impact due to a stressful exposure.[25]

If a critical incident has profoundly affected participants and if symptoms are still present many hours later, urgent assistance is provided in the form of defusing. Mental health or peer support staff coordinate the critical incident defusing process. The focus is on providing feedback information and allowing for venting of emotions. This process often takes place in private to protect confidentiality. If the psychological stress is severe, the process transitions to formal care provided by psychiatrists or psychologists. Data from previous experiences suggest that such intervention can assist providers in maintaining job performance and satisfaction.

Personal Preparedness

Personal preparedness is critical to survival in disasters. FEMA maintains a course called "Are you ready?" to assist people in preparing and

TABLE E14.3 Disaster Kit Components

Battery powered radio	Sanitation items (toothbrush, toilet paper, moist towelettes, concentrated soap)	Can opener
Extra batteries	Matches (in waterproof container)	Photocopies of insurance, identification cards, essential documents
Flashlight	Extra clothing (cold weather as needed)	Cash and coins
First aid kit and manual	Cooking utensils (pot, cup, plate, fork/spoon)	Medications (2-week supply)

protecting themselves in an all-hazard approach.[26] The steps of personal preparedness include: (1) know the risks inherent for a location; (2) purchase appropriate insurance; (3) develop an emergency action plan; and (4) assemble a disaster kit. In a disaster, sources of information include the local Emergency Alert System, local news access (websites, television stations, radio stations), and National Oceanic and Atmospheric Administration Weather Radio.

The emergency action plan should be reviewed, practiced, and updated on a regular basis. All members of a household, including children, should have a strong understanding of the emergency action plan. Planning experts suggest that individuals have knowledge of evacuation routes from home, work, school, and the city. Along with escape routes, a rally point should be designated in case of family separation. Emergency action plans should also include how to care for pets or vulnerable people (such as children or the elderly). A basic understanding of how to turn off utilities (such as gas or water) to a home may be necessary in case of structural damage.

A disaster kit is the cornerstone of personal preparedness. The disaster kit should be kept in a consistent and safe location at home with easy access by all members of the household. Guidelines recommend keeping 72 hours' worth of nonperishable food, water, and supplies for personal survival. An average estimate for water needs is one gallon per person per day. Special consideration should be given to vulnerable populations such as infants (formula, diapers, bottles, toys), pets (food, medications), and the disabled (hearing aids, oxygen canister, wheelchair, etc.). Table e14.3 outlines the basic requirements of a disaster kit.

Disaster Management and Response Organizations within the United States Government

Department of Homeland Security

The Department of Homeland Security (DHS), a cabinet-level department formed after the terrorist attacks of September 11, 2001, is the federal government's lead organization for emergency management activities in the United States. The Federal Emergency Management Agency (FEMA) was incorporated into DHS and retained its name. DHS has a coordinating responsibility for the entire spectrum of disasters irrespective of their size or etiology. DHS assists state and local organizations to mitigate, prepare for, respond to, and recover from emergencies and is a source of funding for these endeavors. In 2003, President Bush directed that DHS develop a National Incident Management System and a National Response Plan. Existing federal plans, including the National Response Plan, were then incorporated into the National Response Framework. The National Response Framework includes 15 Emergency Support Functions (ESFs). Each has a primary (lead) federal agency and many supporting agencies. ESF #8, titled Public Health and Medical Services, is of key importance to the health care community. The primary agency is the Department of Health and Human Services (HHS). Examples of functions within ESF #8 include coordination of health care personnel, supplies, pharmaceuticals, surveillance and reporting, and mass fatality management. To illustrate, HHS facilitated the distribution of large quantities of remdesivir to states so equitable hospital distribution could occur, supporting treatment of COVID-19 patients.[27]

Urban Search and Rescue (ESF #9 of the National Response Framework)

When a building collapses, various challenges confront rescue and medical personnel. Some victims require field amputations to facilitate extrication. The use of urban search and rescue (USAR) teams and effective emergency medical care may improve the outcomes of such lifesaving efforts, but limited data exist supporting these activities. The role of USAR teams has recently been questioned and the cost-effectiveness of their interventions remains unclear. This national system of multidisciplinary task forces is designed for rapid deployment to the sites of collapsed structures. The medical team's responsibilities include caring for task force members, victims recovered by search and rescue activities, and the search team's dogs. There are also weapons of mass destruction (WMD) USAR teams trained by FEMA to respond to nuclear, biologic, and chemical terrorist attacks.

Department of Health and Human Services

On December 19, 2006, President Bush signed the Pandemic and All-Hazards Preparedness Act (S. 3678) into law and created a new position, the Assistant Secretary for Preparedness and Response (ASPR), within HHS. The office of the ASPR oversees the department's responsibilities for emergency preparedness and response activities, including the National Disaster Medical System (NDMS) and the Hospital Preparedness Cooperative Agreement Program, the coordination of the Medical Reserve Corps, ESAR-VHP, the Strategic National Stockpile, and the Cities Readiness Initiative. HHS also funds several grant programs designed to enhance emergency preparedness by states. These include the Public Health Emergency Preparedness and Hospital Preparedness Program cooperative agreements. Funding for these programs have decreased since 2013. Although a temporary increase in financial support has occurred due to the COVID-19 disaster, the future of this important funding stream is uncertain.

National Disaster Medical System

NDMS is a federally coordinated initiative designed to augment the emergency medical response capability of the United States in the event of a catastrophic disaster. This system is a cooperative program of four departments in the federal government: the Department of Defense (DoD), HHS, DHS, and the Department of Veterans Affairs (VA). Although oversight of NDMS has moved between federal departments, HHS currently has the lead for this program. NDMS provides an interstate medical mutual aid system linking the federal government, state and local agencies, and private sector institutions to address the medical needs of victims of disasters. The three distinct NDMS elements focus on field medical response, patient transport, and definitive care. Its field medical response element includes dozens of volunteer civilian DMATs that supplement the local medical infrastructure, as well as disaster mortuary operational response teams (DMORTs), veterinary

medical assistance teams (VMATs), and various specialty teams (e.g., Trauma and Critical Care Teams).

In a disaster, NDMS is activated when state resources are overwhelmed, and the governor makes a request for federal assistance. The DMATs and other teams must meet specific NDMS standards. Throughout the NDMS, emergency clinicians are taking key roles in defining training standards, the deployment of clinical services, the administration of field operations, and in developing the concept of a civilian-federal disaster response capacity during national emergencies. DoD manages patient transfers and provides patient transport from an impacted area to a designated definitive care site. The VA and DoD's Federal Coordinating Centers (FCCs) manage the provision of definitive care by directing patients requiring treatment to health care facilities that have memoranda of understanding with NDMS. Teams of medical, logistic, and administrative staff have been deployed by NDMS continuously since the beginning of the COVID-19 pandemic to assist with critical staffing needs.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC), based in Atlanta, is a United States federal agency under HHS. Its major responsibilities include preparing for and responding to public health emergencies (e.g., disasters) and conducting investigations into the health effects and medical consequences of these events. The major aims of CDC researchers are to assess the risks of death and injury and to develop strategies to prevent or to mitigate the impact of future disasters. Other responsibilities of CDC staff in the area of emergency preparedness and response include: (1) rapid assessment of the health and medical needs of disaster victims in the immediate post-disaster period; (2) development and maintenance of national systems for acute environmental hazard surveillance; and (3) provision of epidemiologic, sanitary, laboratory, and other relevant scientific support services to agencies involved in disaster planning and response. CDC played a major role in helping United States public health officials prepare for identification and management of individuals potentially exposed to Zika virus, including pregnant patients, during the 2016 outbreak and the COVID-19 pandemic in 2020.

Department of Veterans Affairs

The Department of Veterans Affairs has not traditionally been regarded as a disaster response entity. However, one of the VA's four legally mandated missions is emergency management. A unique feature of the VA is that its facilities and personnel are situated nationwide, and these are used to support federal health and medical assistance to state and local governments during disasters. In addition to the vast pool of human resources, the VA provides large amounts of the pharmaceuticals and expendable supplies for on-site disaster support. The VA's assistance is coordinated through DHS and HHS, as the lead federal agency for health and medical response. In addition to the VA's role in the federal disaster response and as the largest integrated health care system in the nation, it has a well-developed hospital emergency management program. Professional emergency managers are located at VA medical centers throughout the country. They also manage the majority of NDMS FCCs. In conjunction with other federal agencies, the VA has developed a number of emergency management planning and operations tools. Many of these are open source and available to the public.[28]

Department of Defense

Although the primary mission of the armed forces is defense of the homeland from foreign threats, the DoD has formed the Northern Command, or NorthCom, to assume responsibility over all military forces that operate within the United States in response to external threats and in support of civil authorities. The stated purpose of NorthCom is to assist the DoD to better manage natural disasters, attacks on American soil, or other civil difficulties. It provides for a more coordinated military support to civil authorities, such as the Federal Bureau of Investigation (FBI), FEMA, and state and local governments. Another important asset at the state level is the National Guard. Each governor has authority to activate the National Guard for its disaster response and recovery missions. National Guard assets also include WMD civil support teams (CSTs). CSTs provide significant capabilities to advise civilian authorities and assist local and state agencies that may be overwhelmed by a large-scale terrorist attack or where specific technical capabilities to identify WMD materials are required. CSTs are federally funded National Guard units established under Presidential Decision Directive 39.

FUTURE DIRECTIONS

The field of disaster medicine has become a major subspecialty within emergency medicine. Standing committees, membership sections, and formal fellowship recognition for the specialty now exist within the ACEP and the Society for Academic Emergency Medicine. There are also numerous national and international forums for the presentation of disaster medical research. Disaster medicine fellowships and advanced degree programs established in the United States and elsewhere continue to attract applicants.[29] Standardized disaster core competencies and associated curricula are now available for residency programs within the United States and endorsed by such organizations as the Council of Emergency Medicine Residency Directors.[3] The quality of disaster medicine textbooks and journals is improving.

In the 21st century, disaster medicine will continue to develop as a professional activity and unique academic specialty. The evolving forces of climate change, increasing population density in disaster-prone regions (as was demonstrated during the COVID-19 pandemic), and terrorism will only enhance demand for this expertise. Encouraging and supporting disaster medicine research activity will become crucial to identifying solutions and interventions to resolve these challenges. Providing regulations that facilitate research activity by deployed medical teams would substantially improve such efforts. Finding sustainable funding sources to support and enhance disaster medicine preparedness and response activities remains one of the most significant challenges.

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CHAPTER E14: QUESTIONS AND ANSWERS

1. How can one characterize application of the Secondary Assessment of Victim Endpoint (SAVE) triage guidelines?
   - **a.** Triage decisions are based on patient outcome expectations.
   - **b.** It is applicable to day-to-day hospital operations.
   - **c.** Patients are sorted immediately after the incident.
   - **d.** The guidelines provide detailed management of psychogenic cases.

Answer: A. The SAVE system is designed specifically for care in an austere environment. It triages patients into (1) those who will die regardless of treatment, (2) those who will live regardless of treatment, and (3) those who would benefit from austere intervention. The triage decisions are based on field outcome expectations from existing survival and morbidity statistics.

2. Which of the following best describes the National Disaster Medical System (NDMS)?
   - **a.** It does not include private sector institutions.
   - **b.** It does not involve the Department of Veterans Affairs (VA).
   - **c.** The medical response element consists of Department of Defense (DoD) personnel.
   - **d.** The Department of Health and Human Services (HHS) has oversight.

Answer: D. The NDMS is a federally coordinated initiative that is a cooperative program between the DoD, VA, DHHS, and Department of Homeland Security (DHS) with oversight provided by DHHS. The NDMS provides a system of coordinated mutual aid agreements among federal, state, local, and private institutional entities for resource and personnel provision in times of disaster. The medical response element includes dozens of volunteer civilian medical teams that supplement the local medical infrastructure.

3. What is accurate advice that one would give to those planning a disaster response?
   - **a.** Critical incident stress debriefing is best conducted 1 or 2 weeks after the event.
   - **b.** Medical resupply systems are the most vulnerable component of a disaster plan.
   - **c.** One of the Department of Veterans Affairs (VA) system's four legally mandated missions is emergency management.
   - **d.** The Federal Emergency Management Agency (FEMA) has a coordinating responsibility for the entire spectrum of disasters.

Answer: C. One of the VA health system's four mandated missions is emergency management. Although controversy exists, critical incident stress debriefing, if used, should be implemented as early as possible. The Department of Homeland Security (DHS) has full-spectrum disaster coordinating responsibility. Communications systems are likely the most vulnerable systems.

4. Which of the following statements is *not* a feature of comprehensive emergency management?
   - **a.** An incident management system consistent with NIMS should be implemented.
   - **b.** Health care facilities should perform a hazard vulnerability analysis to assess community risks.
   - **c.** Most incident management systems are characterized by five functional elements: incident command, operations, logistics, planning, and finance.
   - **d.** The four phases of comprehensive emergency management (CEM) are pre-event, event, post-event, and recovery.

Answer: D. The four phases of CEM are mitigation, preparedness, response, and recovery. These phases represent a continuum over time, and more than one phase may be in effect at the same time (e.g., even during the response phases, recovery actions may take place.)

5. After an earthquake, what resource would be expected to provide the most rapid and effective search and rescue activity finding the most victims who would most likely survive?
   - **a.** Urban search and rescue teams
   - **b.** Private citizens
   - **c.** Disaster medical assistance teams
   - **d.** National Guard Civil Support Teams

Answer: B. Uninjured survivors perform the most rapid and effective search and rescue activity after an earthquake. These private citizens will recover most victims who ultimately survive. Although formal urban search and rescue teams will eventually arrive, they do not find many victims and it is unknown how many survive. National Guard Civilian Support Teams and disaster medical assistance teams do not perform search and rescue activities.

e15

Weapons of Mass Destruction

Kristi L. Koenig and Romeo Fairley

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Weapons of Mass Destruction

Kristi L. Koenig and Romeo Fairley

KEY CONCEPTS

- Emergency department (ED) preparedness for a radiation incident should address decontamination (an external freestanding decontamination unit is best), triage, staff safety, personal protective equipment (PPE), and diagnostic procedures that emphasize radiation monitoring. It is important that emergency personnel know their radiation safety officer.
- External decontamination of radioactive particles can be achieved by removing clothing and washing the skin with soap and water.
- Management of acute, life-threatening conditions (such as major traumatic injuries) takes priority over radiation-associated issues.
- Aerosol dispersal is a likely route that terrorists may use to deploy biologic weapons, so victims will present primarily with respiratory complaints.
- In addition to influenza-like illness (ILI) symptoms, anthrax typically causes mediastinal widening, pulmonary consolidation, and pleural effusions best seen on chest computed tomography (CT) scans.
- Smallpox can spread in a hospital environment; thus, patients thought to have smallpox should be admitted to locations isolated from the rest of the hospital.
- Decontamination is a key activity in the management of patients exposed to chemical agents and frequently first occurs on emergency department arrival.
- Nerve agents are organophosphates; patients exposed to these agents are treated with large doses of atropine (repeated frequently), pralidoxime, and benzodiazepines.
- Patients with blast injuries can have subtle and delayed presentations of life-threatening conditions.

FOUNDATIONS

Besides managing the injuries and illnesses from common disasters such as earthquakes and airplane crashes, emergency clinicians should also have competence in treating victims generated by terrorist attacks with chemical, nuclear, biologic, or high-energy explosive weapons. Conventional explosives remain the most common weapon used by terrorists; however, the risk from nuclear, biologic, and chemical agents may increase over time. The nomenclature for these weapons is not standardized. The military uses the acronym CBRNE, pronounced "see-burn-ee," referring to *c*hemical, *b*iologic, *r*adiologic, *n*uclear, and *e*xplosive agents. This chapter uses weapons of mass destruction (WMD) because of its wide acceptance and familiarity.

The results of an attack with WMD, although admittedly of low probability, are potentially catastrophic. According to a World Health Organization (WHO) estimate, 50 kg of anthrax spores aerosolized above a city of five million people would result in 100,000 deaths, with an additional 150,000 people seriously infected. The cost of managing 100,000 cases of anthrax exposure is estimated at between $6.4 and $26.2 billion. These types of estimates have led to authorities establishing emergency preparedness as a priority.

Children are particularly vulnerable to these weapons.[1] They are closer to the ground based on height and breathe at a faster rate than adults, increasing their relative exposure to aerosolized agents.[2] Some chemicals, such as sarin, are heavier than air, so they tend to accumulate at the level where children are more likely to inhale them. Children have a greater surface area–to–volume ratio and their skin is thinner. This makes them more susceptible to agents that act on or through the skin. They have smaller fluid reserves and higher metabolic rates. Therefore, they are more vulnerable to dehydration from vomiting and diarrhea and suffer increased toxicity from a given exposure, such as to radioactive iodine (^{131}I).

The use of biologic and chemical agents as weapons dates to biblical times, although the threat from radiation and nuclear detonation is relatively new. Assyrians poisoned the wells of their enemies with rye ergot in the 6th century BC. During World War I, the Germans effectively used chlorine and mustard agent against the advancing Allied armies. The Japanese killed hundreds to thousands of Chinese citizens with bubonic plague during World War II by spraying towns with fleas infected with *Yersinia pestis*. In 2013, the Syrian government attacked cities within its own country using chemical nerve agents, resulting in an estimated 1300 deaths and 3600 injuries. United States government reports indicate that the Syrian government again used chlorine gas in May 2019.

WMD have been predominantly deployed by the military during times of conflict. Toward the end of the twentieth century, however, nonaffiliated terrorist groups began using WMD directed at civilians to achieve political ends. The Aum Shinrikyo used sarin gas in the 1995 Tokyo subway attack that killed 11 people.[3] Terrorists initiated an anthrax attack using the United States mail in 2001 that resulted in 11 deaths.[4] In 2018 and 2020, the fourth-generation nerve agent Novichok was reportedly used during a presumed assassination attempt, leading to four hospitalizations.[5] As of early 2020, no one has used radiologic or nuclear devices in a successful mass terrorist attack; however, several highly radioactive sources have been stolen from American medical facilities, and a Russian dissident, Alexander Litvinenko, was assassinated with a radiologic agent (^{210}Po) in 2006 while living in London.

Many agents are potential candidates for weaponization, and some represent a substantial risk (Box e15.1). Management strategies for patients exposed to WMD are frequently similar to strategies for hazardous materials exposure. However, several features associated with WMD make these events unique (Box e15.2). Additional knowledge and skills are required in the evaluation and treatment of WMD victims. These plans represent only one small part of an overall comprehensive emergency management strategy for all hazards (see Chapter e14). Names of departments, bureaus, and agencies that can assist with planning and response to WMD events are listed in Table e15.1.

BOX E15.1 Potential Agents of High Concern for Use as Weapons of Mass Destruction

Chemical

Nerve agents
- Sarin
- Soman
- Tabun
- VX

Mustard agent
Novichok agent

Biologic

Anthrax
Plague
Smallpox
Botulism
Viral hemorrhagic fever
Tularemia

Radiologic

Simple device
Dispersal device

BOX E15.2 Features of Weapons of Mass Destruction Threat

Fear of unknown or unfamiliar
Lack of training for hospital personnel
Lack of equipment, including personal protective equipment (PPE) and diagnostic aids
Potential for mass casualties
Psychological casualties
Crime scene requiring evidence collection and interaction with law enforcement
Potential for ongoing morbidity and mortality (dynamic situation)

SPECIFIC DISORDERS

Nuclear and Radiologic Devices

Foundations

Terrorists selecting radiation as a means to inflict casualties are unlikely to use nuclear weapons. These devices are heavily guarded, difficult to move because of their size and weight, and easy to detect. Although Russia acknowledges that 50 to 100 of its one-kiloton "suitcase" nuclear weapons are missing, the challenges associated with purchasing, moving, and detonating these devices are formidable. Sabotage at nuclear power stations is possible, but given tight security, multiple safety systems, and thick concrete housings surrounding the reactors, the threat is relatively low.

Simple radiologic devices, such as those used by hospitals for radiation therapy or commercial companies for industrial radiography, are more readily accessible. These sources are plentiful and often found in small, easily concealed containers. They do not detonate on their own and give no warning of their presence unless they are dispersed by a conventional explosive (radiologic dispersal device). Thefts of radiotherapy sources have occurred in the United States. Accidental dispersion from a stolen hospital therapy source in Brazil resulted in the screening of 112,000 people for contamination. A total of 249 people were found to be exposed—four of whom ultimately died. Placement of such a device at an information kiosk in a crowded mall during a busy holiday shopping season would silently expose countless persons to significant radiation.

Clinical Features

Ionizing radiation, regardless of its type, causes injury at the cellular level, usually by damaging DNA. Rapidly dividing cells are the most sensitive. Patients have symptoms within hours to days, depending on the dose. Common syndromes associated with radiation exposure include cutaneous (burns), hematologic (bone marrow failure), gastrointestinal (e.g., vomiting and gastrointestinal bleeding), and at extreme doses, neurologic (seizure, coma, death). Reviews of medical treatment for radiologic casualties can be found elsewhere (Chapter 134).

Management

A basic emergency department (ED) radiation protocol should address decontamination, triage, staff safety, personal protective equipment (PPE), and diagnostic procedures that emphasize radiation monitoring. Victims presenting to the ED will suffer from three types of exposure: irradiation, internal contamination, and external contamination. Irradiated victims have been exposed to a beam of radiation, similar to someone undergoing a chest x-ray examination. They are not radioactive and pose no threat to ED personnel.

Contaminated patients are more challenging, and early involvement of the radiation safety officer is critical. This individual evaluates the degree of the victim's contamination and monitors radioactivity levels throughout the decontamination process. Internally contaminated patients present a therapeutic challenge because they have radioactive material inside their bodies (e.g., lungs and gastrointestinal tract) or

TABLE E15.1 Resources and Contacts for Planning and Response to Events Involving Weapons of Mass Destruction

Organization	Website	Telephone
Radiation Emergency Assistance Center/Training Site (REAC/TS)	orise.orau.gov/reacts/	Daytime: 865-576-3131 Emergency: 865-576-1005
State and local health departments		
• Association of State and Territorial Health Officials (ASTHO)	www.astho.org/statepublichealth/	(202) 371-9090
• Public Health Resources: State or Territorial Health Departments	https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html	
Centers for Disease Control and Prevention (CDC)	www.cdc.gov	800-CDC-INFO
Federal Bureau of Investigation (FBI)	www.fbi.gov	
Federal Emergency Management Agency (FEMA)	www.fema.gov	800-621-FEMA
U.S. Army Medical Research Institute of Chemical Defense	https://usamricd.apgea.army.mil/	

incorporated into their cells. They should be placed in an isolation room where all secretions and body fluids can be collected. Various medications are available for administration to internally contaminated patients that can limit uptake or facilitate removal of certain radioactive elements. These medications include Prussian blue (Radiogardase) for cesium and thallium ingestions, diethylenetriaminepentaacetic acid (DTPA) for plutonium exposure, and potassium iodide for ^{131}I exposure for patients under 40 years of age within a few hours of exposure. Radiation Emergency Assistance Center/Training Site (REAC/TS; http://orise.orau.gov/reacts/) is always available at 865-576-3131 (emergency number: 865-576-1005) to provide assistance to health care providers.

Externally contaminated victims have radioactive material on their skin or clothing and are decontaminated by removal of clothing and washing with soap and water. Medical stabilization and lifesaving interventions take precedence over decontamination. Washing by protected personnel should continue until monitoring shows a level no more than double the background rate or when no further decrease is happening after multiple decontamination attempts. If wounds are present, they are decontaminated first, along with mucous membranes. It is imperative to remove foreign bodies. After the wounds are covered with a sterile, waterproof dressing, the remaining skin is washed. Hospitals should be prepared to decontaminate patients because historical data suggest that up to 80% of patients do not receive this intervention before arrival. Decontamination before hospital entry is crucial because these individuals can expose caregivers to radiation and contaminate the entire hospital through the ventilation system. Removal of clothing and covering of the head with a surgical cap can reduce contamination by 80% to permit stabilization in the decontamination unit, but complete decontamination should occur before exposure of unprotected staff if the patient's medical condition permits.

Initial triage of radiation casualties is based on their overall condition, not on exposure.[6] Even patients who have received a lethal dose of radiation do not die immediately as a consequence of the ionizing exposure. Therefore, a patient in acute distress from a myocardial infarction, sepsis, or a combined radiation-blast injury would be triaged ahead of a radiation victim with stable vital signs, regardless of the dose received. If a radiation casualty also suffers a severe injury or illness, immediate intervention is required. Most of the immediate morbidity and mortality associated with a radiologic dispersion device is related to traumatic injuries from the explosion and not the radiation exposure.

In addition to contaminated patients, the radiation safety officer is responsible for monitoring exposure to hospital staff. All personnel involved in the care of contaminated patients should wear dosimeters, which measure the amount of radiation received by the wearer. The safety officer tracks the amount of radiation received by each staff member and can remove a health care worker from the area if exposure exceeds Occupational Safety and Health Administration (OSHA) guidelines. Radiation monitoring is complex, and the radiation safety officer should be involved as early as possible. Hospitals should consider conducting disaster drills that include casualties suffering radiation injuries.

Although many radioactive elements are candidates for use in a terrorist attack, iodine-131 (^{131}I) and related isotopes deserve additional discussion because of heightened interest and ease of ^{131}I effective therapy. ^{131}I is found after a nuclear detonation or in reactor fuel rods. Although it is not impossible, the probability that terrorists could tap either of these sources is small. The use of ^{131}I in a radiologic dispersal device is unlikely because of its short half-life (eight days). The large number of childhood thyroid cancers that occurred after the accident at the Chernobyl nuclear power plant resulted, to a significant degree, from situations that will be unlikely to occur in the United States. These include delayed reporting of a breach in the reactor containment vessel preventing timely evacuation of all exposed populations; failure to effectively prevent ingestion of contaminated milk and vegetables; and presence of significant iodine deficiency in the exposed population.

The risk to children in communities surrounding the Fukushima nuclear power plant is an issue that will require long-term monitoring, though it is believed that exposures were not high enough to increase the incidence of long-term effects (cancer) beyond the background rate. Nonetheless, treatment of children aimed at preventing thyroid cancer after potential exposure to ^{131}I should be performed (Table e15.2). Caveats for use of this table include increasing the amount of potassium iodide (KI) for adolescents approaching 70 kg to the adult dose (130 mg) and monitoring thyroid-stimulating hormone and free thyroxine (T_4) levels in neonates. Nonpregnant adults older than 40 years of age are unlikely to benefit from this intervention; therefore, current recommendations are to withhold KI unless doses over 5 Gy are received.

Biologic Weapons

Foundations

By convention, biologic weapons are divided into three groups: bacteria, viruses, and toxins. A characteristic shared by these agents is their ability to be dispersed as an aerosol. Because this is the most effective means to expose a large population, aerosol dispersal is the route that terrorists would most likely use to deploy such weapons. Victims, unaware of the exposure to a biologic weapon, commonly present to the ED with nonspecific influenza-like illness (ILI). Dermal contact and ingestion are also potential pathways for exposure, and some agents are harmful via these routes. People infected in the 2001 United States anthrax attacks were inoculated through aerosol and dermal exposures. It is logistically more difficult to produce large casualty numbers by nonrespiratory portals of entry, so agents spread primarily by injection or through the gastrointestinal tract are less likely candidates for wide deployment. If the goal is to disrupt the economy or to spread fear among the population, then almost any type of release will suffice, whether or not mortality occurs.

TABLE E15.2 Treatment with Potassium Iodide for Radioactive Iodine Exposure

Subpopulation	Predicted Exposure (cGy)	Potassium Iodide Dose (mg)	Number of 130-mg Tablets
Adults >40 years old	>500	130	1
Adults 18 to 40 years old	≥10	130	1
Pregnant and lactating women	≥5	130	1
Children 3 to 18 years old	≥5	65	½
Children 1 month to 3 years old	≥5	32	¼
Neonates, birth to 1 month old	≥5	16	⅛

BOX E15.3 Signs Suggesting Biologic Weapon Deployment

Syndromes
Pulmonary symptoms, pneumonia
Rashes
Sepsis syndrome
ILI symptoms

Epidemiology
Multiple, simultaneous events
Dead animals
Large numbers of patients with high toxicity and death rate

BOX E15.4 Recommendations for Prevention of In-Hospital Transmission of Contagious Agents

Isolate patient in single room with adjoining anteroom.
Have handwashing facilities and personal protective equipment (PPE) available in anteroom.
Use negative air pressure if possible.
Use strict barrier precautions: PPE, gowns, gloves, high-efficiency particulate air (HEPA) filter respirators, shoe covers, protective eyewear, N95 masks, or powered air purifying respirator (PAPR).
Alert hospital departments that generate aerosols: Laboratory (centrifuges), pathology (autopsies).
For some agents (i.e., Ebola) all skin surfaces must be covered by PPE.

Clinical Features

Patients exposed to biologic agents usually present with vague symptoms associated with an ILI.[7] Unless a biologic attack is announced or suspected, the ED staff may not realize that they are treating victims. It is not always possible to distinguish natural occurrences from engineered outbreaks of diseases. Examples of non-terrorist-related occurrences of anthrax include cutaneous disease in intravenous heroin users in Europe, an outbreak of cutaneous anthrax in Bangladesh in 2010 with more than 400 cases, and isolated infections in drum makers after using contaminated animal hides. Because of the challenges in identifying the true etiology of acute events, personnel should consider the possibility, especially when warning signs are present (Box e15.3). For example, large numbers of patients suddenly presenting with "the flu" outside of the influenza season should cause concern. For these reasons, health surveillance is paramount in identifying agents and potential sources. National monitoring programs such as BioWatch (proposed to be replaced by BioDetection 21 by 2025) monitor the ambient air for infectious agents. ED leadership should have a working relationship with local and state health departments as well as with local law enforcement and stay apprised of Centers for Disease Control and Prevention (CDC) and Department of Homeland Security guidelines.

Management

Several infectious agents with potential for use as biologic weapons can spread in a hospital environment. Examples include Ebola and smallpox. Hospitals need protocols for PPE and patient isolation to ensure a safe environment. Such protocols are similar to those applied to other infectious diseases (Box e15.4) in non-terrorist events (e.g., the 2014 Ebola outbreak). Implementation of such precautions is credited with halting the in-hospital spread of the Ebola virus in the 1995 Zaire outbreak. Decontamination is not a priority unless the exposure is acute. Standard precautions are usually sufficient, and special suits (e.g., levels A and B) are generally unnecessary, though Ebola precautions require covering all cutaneous surfaces.[8] Table e15.3 shows the recommended isolation precautions for each infectious agent.

TABLE E15.3 Recommended Isolation Precautions for Biologic Agents

Infectious Agent	Recommended Isolation Precautions
Anthrax	Cutaneous infection: contact precautions Pulmonary infection: standard precautions Gastrointestinal infection: standard precautions
Botulism	Standard precautions
Plague	Standard and droplet precautions*
Smallpox	Standard, contact, and airborne precautions
Tularemia	Standard precautions
Viral hemorrhagic fevers	Standard, contact, and airborne precautions

* Some experts recommend airborne precautions due to potential for aersolization.

Whereas the CDC lists six Category A (high threat) agents (anthrax *[Bacillus anthracis],* botulism [*Clostridium botulinum* toxin], plague *[Yersinia pestis],* smallpox [variola major], tularemia *[Francisella tularensis],* and viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg)] and arenaviruses [e.g., Lassa, Machupo]), this chapter focuses on three biologic agents—anthrax, plague, and smallpox—that represent the greatest interest.[7]

Anthrax

Foundations. *Bacillus anthracis,* a gram-positive, spore-forming bacterium, is the causative agent of anthrax ("woolsorter's disease"). The spores are extremely hardy and can survive for years in the environment. The disease is caused by exposure to the spores, not the bacilli, in their vegetative state. It is normally a disease of sheep, cattle, and horses and is rarely seen in developed countries because of animal and human vaccination programs. Disease in humans can occur when spores are inhaled, ingested, or inoculated into the skin. The spores germinate into bacilli inside macrophages. The bacteria then produce disease by releasing toxins (e.g., protective antigen, edema factor, and lethal factor) that cause edema and cell death.

Russia and the United States have developed anthrax into a biologic weapon. The effectiveness of this agent was clearly demonstrated by two events: an accidental release of spores from a biologic weapons facility in the former Soviet Union town of Sverdlovsk in 1979 and the intentional distribution of anthrax spores through the mail along the eastern seaboard of the United States in 2001.[4] After the Sverdlovsk release, at least 66 adults died downwind from the compound during the next several weeks, and animal cases of anthrax were reported 30 miles away. The ability of non-state-sponsored terrorist groups to develop anthrax as a weapon is uncertain. The Japanese organization Aum Shinrikyo made several unsuccessful attempts to disperse anthrax throughout Tokyo. The individual believed responsible for the United States anthrax attack was not a foreign national. This is consistent with the fact that the strain of anthrax used in the attack (Ames strain) was developed by the United States government.

Inhalational anthrax is the most lethal form of the disease and is caused by inhalation of spores into the lungs. The mortality rate was thought to exceed 90%. However, data from the 2001 anthrax exposure call this figure into question (5 deaths in 11 cases). Although the actual mortality rate is unknown, and would depend on availability of intensive care resources, it is probably in the 50% range. The minimum

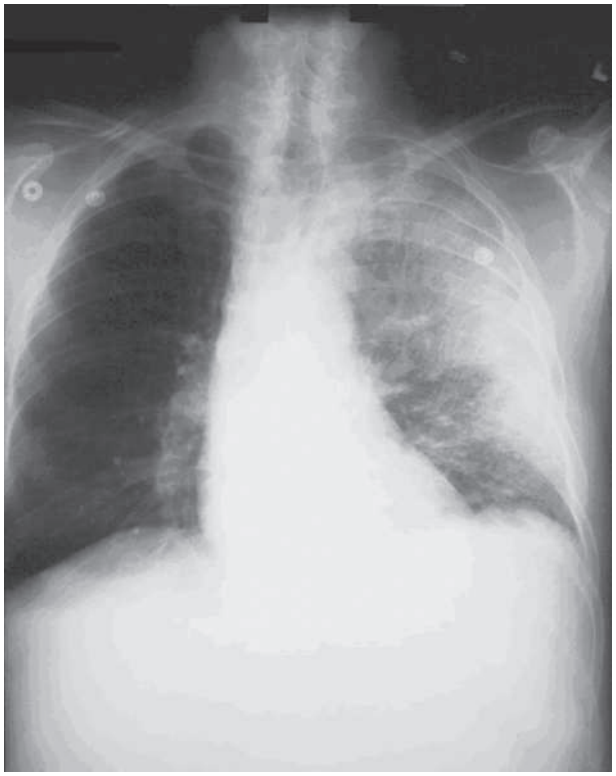

Fig. e15.1 Chest radiograph of anthrax patient showing diffuse left lung consolidation consistent with pneumonia. There is no mediastinal widening. (Courtesy Centers for Disease Control and Prevention.)

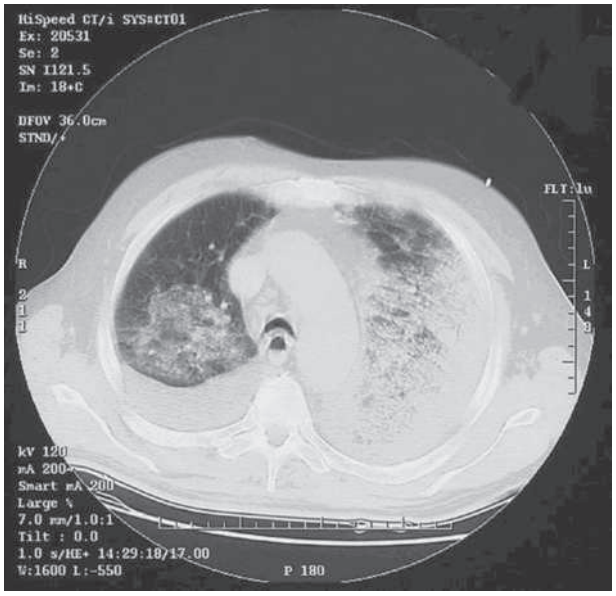

Fig. e15.2 Chest computed tomography (CT) scan of an anthrax patient showing pulmonary consolidation and effusions. (Courtesy Centers for Disease Control and Prevention.)

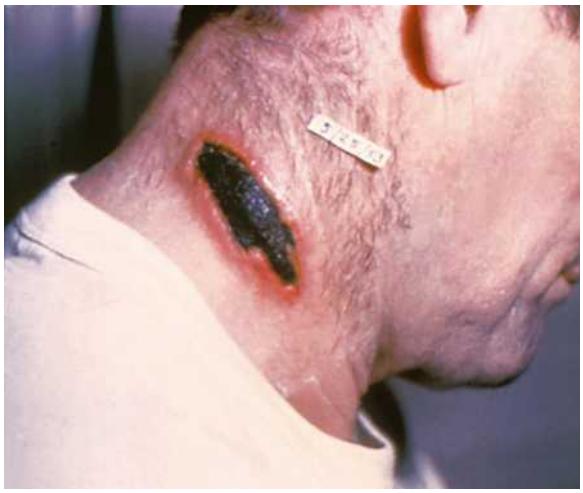

Fig. e15.3 Adult with cutaneous anthrax. (Courtesy Centers for Disease Control and Prevention.)

number of spores required to produce disease is unknown. The original number quoted in the literature—1000 spores—appears high given the experience following the 2001 anthrax event.

Clinical Features. After phagocytosis by macrophages, the spores germinate and are transported to the tracheobronchial lymph nodes, where the bacteria multiply. During the next 2 to 10 days, patients have an ILI with malaise, fever, and nonproductive cough. This initial phase can be delayed for more than one month. Within 24 to 48 hours of the initiation of symptoms, abrupt deterioration occurs with overwhelming sepsis, shock, hemorrhagic mediastinitis, dyspnea, and stridor. A chest radiograph obtained at this time may show a widened mediastinum and hilar adenopathy, but typical radiographic findings are not dramatic and are easy to miss (Fig. e15.1). Computed tomography (CT) scanning of the chest is more sensitive and should be performed if the disease is suspected. Bloody pleural effusions can also occur, and examination of the lung fields frequently reveals consolidation. This can easily be confused with severe community acquired pneumonia (Fig. e15.2). Death usually results within three days, and 50% of patients have hemorrhagic meningitis. Human-to-human transmission has not been reported with inhalational anthrax.

Initial diagnosis is generally made clinically on the basis of an influenza-like or septic illness; a suspicious chest radiograph or CT scan demonstrating hilar adenopathy, infiltrates, or pleural effusions; and a reason to consider anthrax in the first place (e.g., current outbreak or warning from authorities). Several clinical algorithms exist that attempt to separate patients with influenza from those with anthrax. Because these are based on a handful of anthrax cases, their usefulness is uncertain. Sputum culture, Gram stain, and blood cultures are not helpful until late in the course of the disease. Tests to confirm the diagnosis of inhalational anthrax include the polymerase chain reaction (PCR) for identification of anthrax markers in pleural fluid, serologic detection of immunoglobulin to protective antigen, and immunohistochemical testing of biopsy specimens. Recombinase polymerase amplification (RPA) assays for rapid identification of *B. anthracis* in a field setting have proven both sensitive and specific.[9]

In addition to inhalational anthrax, cutaneous anthrax can occur in any area where large numbers of spores are released. This form of the disease occurs when spores are introduced into the skin, usually through open wounds or abrasions. The mortality rate is approximately 20% without treatment but decreases to 1% with treatment. After an incubation period of one to five days, a papule develops, progressing to form a large vesicle during the next several days. Severe edema occurs around the lesion and is associated with regional lymphadenitis. The lesions are not tender, and the patient may or may not be febrile (Fig. e15.3). After approximately one week, the lesion ruptures, forming a black eschar (thus the name *anthrax,* from the Greek word for "coal"). In the next two or three weeks, either the eschar sloughs off and the illness resolves or the organism disseminates and the patient dies.

Antibiotics do not halt the progression of local disease; they prevent dissemination and death. As with inhalational anthrax, the diagnosis is predominantly clinical. Confirmation is established by culture of the lesion, punch biopsy, or serologic testing. A total of 11 cutaneous anthrax cases occurred in the United States after the 2001 attack.

Cases of gastrointestinal anthrax and oropharyngeal anthrax are also possible after a terrorist attack. These rare manifestations usually occur with the ingestion of insufficiently cooked, contaminated meat. The mortality rate is approximately 50%. After ingestion, the spores are transported to regional lymphatic tissue, where symptoms develop after a two-to-five-day incubation period. Patients with oropharyngeal anthrax present with sore throat and neck swelling from cervical and submandibular lymphadenitis. The tonsils are also frequently involved, and symptoms are associated with fever and toxicity. Dysphagia and respiratory distress often follow. Gastrointestinal anthrax begins with nausea, vomiting, and fever associated with mesenteric lymphadenitis. Patients then experience severe abdominal pain, hematemesis, ascites, and bloody diarrhea, and may present with an acute abdomen.

Management. Traditional treatment of anthrax infection has been with penicillin. However, weapons-grade anthrax is probably resistant to penicillin (although this was not the case with the 2001 United States attack). Current treatment recommendations reflect this fact (Box e15.5). These consensus recommendations include fluoroquinolones and tetracycline for all children, regardless of age. Balancing the potential risks of such drugs against the consequences of infection by drug-resistant anthrax strains, the benefits justify the recommendations. Chest tube drainage of pleural effusions improved mortality in the United States anthrax attack, though numbers were limited. CDC recommendations also include antitoxin therapy, although a 2017 meta-analysis did not show improved mortality.[10] Supportive therapy with vasopressor medications, and possibly tracheal intubation with mechanical ventilation, may be necessary.

Treatment is continued for 60 days, or until the patient has received three doses of the anthrax vaccine, given on days 0, 14, and 28. The complete vaccine course requires 18 months. This treatment regimen is also recommended for children and pregnant women. If the anthrax strain proves susceptible, patients can be switched to intravenous penicillin or oral amoxicillin. In vitro studies suggest that ofloxacin or levofloxacin can be substituted for ciprofloxacin.

For postexposure prophylaxis, oral ciprofloxacin (500 mg) or doxycycline (100 mg) twice a day (better tolerated) is recommended. Amoxicillin can be substituted if sensitive strains are identified. Antibiotic prophylaxis is to continue for 60 days or until patients have received at least three doses of the vaccine. The vaccine is approved by the US Food and Drug Administration (FDA) for adults, but not for children. However, it could become available for use in the pediatric population under the Investigational New Drug process if needed. A review by the National Academy of Medicine (formerly the Institute of Medicine [IOM]) found the vaccine both safe and effective for prophylaxis against inhalational anthrax in adults. The 2015 CDC guideline, "Clinical Framework and Medical Countermeasure Use During an Anthrax Mass-Casualty Incident," provides useful information for scarce resource allocation decisions.[11]

Plague

Fundamentals. Plague has been a human pathogen since antiquity. Many regions of the world, including Asia and India, are witnessing the third pandemic of plague, and this affliction is endemic in the western half of the United States. Plague is caused by *Yersinia pestis,* a gram-negative bacillus. It is normally a disease of rodents that is transmitted to humans through the bite of an infected flea or by inhalation. Three forms of the disease exist: pneumonic, bubonic, and septicemic plague.

BOX E15.5 Treatment of Anthrax

Cutaneous Anthrax Without Toxicity

Adults

Ciprofloxacin, 500 mg PO bid; *or* doxycycline, 100 mg PO bid; *or* amoxicillin, 500 mg PO tid.

Children

Ciprofloxacin, 20 to 30 mg/kg/day PO divided bid (maximum 1 g); *or* doxycycline, 4.4 mg/kg/day PO divided bid (maximum 200 mg); *or* amoxicillin, 20 to 40 mg/kg/day PO divided tid (maximum 1500 mg).

All doses are given for 7 to 10 days.

Inhalational, Cutaneous, or Gastrointestinal Anthrax with Toxicity

For adults and children, consider the antibody-based therapies raxibacumab and anthrax immune globulin in addition to IV antibiotics.

Adults

Ciprofloxacin, 400 mg IV every 12 hours; *or* doxycycline, 100 mg IV every 12 hours; *or* penicillin G, 4 million units IV every 4 hours.

For patients without meningitis, add a second drug that inhibits protein synthesis, such as linezolid or clindamycin. For patients with meningitis, add a third drug to this regimen that penetrates the CNS, such as meropenem.

Children

Ciprofloxacin, 20 mg/kg/day IV divided every 12 hours (maximum 800 mg); *or* doxycycline, 4.4 mg/kg/day IV divided every 12 hours (maximum 200 mg); *or* penicillin G, 250,000 to 400,000 units/kg/day IV divided every 4 hours (maximum 24 million units).

For patients without meningitis, add second drug that inhibits protein synthesis, such as linezolid or clindamycin. For patients with meningitis, add a third drug to this regimen that penetrates the CNS, such as meropenem.

All doses are given until toxicity resolves, then switch to oral form. Treat for 60 days or until the patient receives three doses of vaccine.

Postexposure Prophylaxis

The same drugs and dosage are prescribed as for cutaneous anthrax without toxicity. Treat for 60 days or until the patient receives three doses of vaccine.

CNS, Central nervous system; *IV,* intravenous; *PO, per os* (by mouth).

The bacteria do not form spores and die rapidly in the environment. However, they are viable for days in dry sputum, flea feces, and human remains. Dogs are relatively resistant to infection, but cats are highly susceptible and can form a reservoir for maintaining the disease in a human population. Recovery is followed by temporary immunity.

Clinical Features. Primary pneumonic plague results when bacilli are inhaled into the lungs. The mortality rate approaches 100% if it is not treated early. Pneumonic plague will be the most frequently encountered form of the disease because terrorists are likely to use aerosolization as the method of dispersal. After an incubation period of 24 to 96 hours, victims have sudden onset of fever, chills, and an ILI. This is followed within 24 hours by a fulminant pneumonia associated with hemoptysis, systemic toxicity, respiratory failure, circulatory collapse, and death. The pneumonia is classically lobar, but any radiographic pattern is possible, including acute respiratory distress syndrome. Six to ten percent of victims have plague meningitis. Coagulation abnormalities and hepatocellular injury occur. The coagulopathy is characterized by ecchymoses, disseminated intravascular coagulation, and acral gangrene ("black death"). The gangrene is caused by bacterial production of the coagulase enzyme in areas of the body where the temperature drops below 98.6°F (37°C). This induces blood to clot in

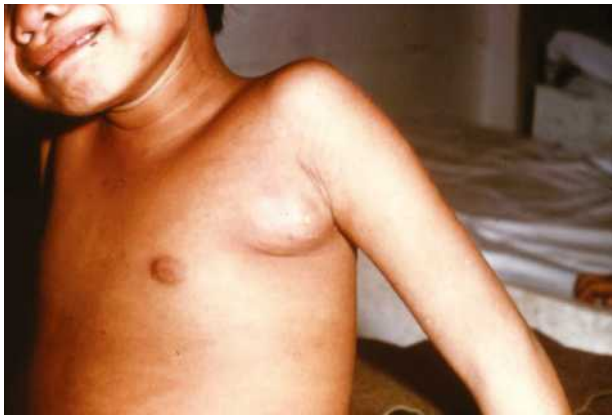

Fig. e15.4 Child with bubonic plague demonstrating axillary bubo. (Courtesy Frederick M. Burkle, Jr., MD, MPH.)

fingers, toes, and the nose with resultant infarction and gangrene. If the victims survive, long-term rehabilitation is required. Pneumonic plague is transmissible human to human.

Bubonic plague occurs when organisms are inoculated into the skin, usually from a flea bite. During the two-to-three-day incubation period, the bacilli migrate to regional lymph nodes, where they multiply and cause inflammation and necrosis of lymphatic tissue, resulting in large, tender nodes, or buboes. Typically, buboes develop in the groin, axilla, or cervical region and are so painful that the patient will refrain from moving the affected area (Fig. e15.4). Individuals experience fever, chills, and weakness. In approximately 25% of patients, vesicles or ulcerations occur at the site of the flea bite. The buboes are usually nonfluctuant but can rarely suppurate. Organisms can be aspirated from the nodes for diagnosis, but incision and drainage are not recommended because the lymphadenitis resolves with antibiotic treatment, and practitioners could become infected if they are exposed during the procedure.

During the next week or more, the bacteria disseminate in approximately 50% of patients with bubonic plague. These victims have septicemic plague or secondary pneumonic plague and die if they are untreated. Those with septicemic plague experience endotoxemia, shock, disseminated intravascular coagulation, and coma. If bacteremia does not occur, most victims recover. A small percentage of those infected by fleas have septicemic plague without detectable buboes. Direct human-to-human transmission does not occur with bubonic or septicemic plague. However, both of these conditions can lead to secondary pneumonic plague, which is communicable. Therefore, isolation for the first 48 hours is recommended for all patients with plague.

Differential Diagnosis. The preliminary diagnosis of plague is clinical. Few diseases other than plague cause fulminant gram-negative pneumonia associated with hemoptysis in previously healthy individuals. Other diseases cause lymphadenopathy and the differential diagnosis for such conditions includes cat-scratch disease, tularemia, and staphylococcal or streptococcal infections. The presence of extremely tender lymphadenopathy and the toxicity of the patient is strongly suggestive of plague. Once the disease is suspected, Gram stain and culture of sputum, blood, cerebrospinal fluid, or lymph node aspirate are helpful. State health departments or CDC can test specimens for the presence of the capsular antigen by direct fluorescent antibody staining or polymerase chain reaction (PCR). Because all laboratory tests require several days to complete, initial management decisions are based on clinical findings.

Management. Antibiotic treatment is essentially identical for all three types of plague (Box e15.6). The same caveats for the use of fluoroquinolones and tetracycline in children with anthrax apply to plague. In the case of pneumonic and septicemic plague, treatment should be started within 24 hours of symptoms for outcome to be improved. Antibiotics are given for a minimum of 10 days. As patients improve, intravenous therapy can be transitioned to oral antibiotics to complete the course. Respiratory isolation of patients with pneumonic plague is necessary for 4 days after beginning antibiotics to guarantee sterilization of sputum. Patients with septicemic and bubonic plague require isolation for 48 hours. If they do not have pneumonia or draining lesions during this time, isolation can be discontinued. Nonseptic patients with mild bubonic plague can be treated at home with oral doxycycline or tetracycline for 10 days.

The mainstay of prophylaxis against plague remains oral antibiotics. Older vaccines were discontinued due to short-lived efficacy. Newer vaccines are in development but have not been approved for public use as of early 2022.[12] The drugs for prophylaxis are tetracycline, doxycycline, ciprofloxacin, chloramphenicol, and possibly trimethoprim-sulfamethoxazole for children.

BOX E15.6 Treatment of Plague

Parenteral Therapy

Adults

Streptomycin,[a] 1 g IM bid
Gentamicin, 5 mg/kg once daily IM or IV
Doxycycline, 100 mg IV bid
Ciprofloxacin, 400 mg IV bid
Chloramphenicol, 25 mg/kg IV qid

Children

Streptomycin,[a] 15 mg/kg IM bid (maximum 2 g/day)
Gentamicin, 2.5 mg/kg IM or IV tid
Doxycycline, 2.2 mg/kg IV bid (maximum 200 mg/day)
Ciprofloxacin, 15 mg/kg IV bid (maximum 800 mg/day)
Chloramphenicol, 25 mg/kg IV qid

Pregnant Women

Same as above but exclude streptomycin and chloramphenicol

Oral Therapy

Adults

Doxycycline, 100 mg bid
Ciprofloxacin, 500 mg bid
Chloramphenicol, 25 mg/kg qid

Children

Doxycycline, 2.2 mg/kg bid (maximum 200 mg/day)
Ciprofloxacin, 20 mg/kg bid (maximum 1 g/day)
Chloramphenicol, 25 mg/kg qid

Pregnant Women

Same as above but exclude chloramphenicol

[a]Although streptomycin is recommended as first-line treatment, it may not be readily available.
IM, Intramuscular; *IV,* intravenous.

Smallpox

Foundations. Smallpox was eradicated in 1980. The only known repositories of the variola virus, the etiologic agent of smallpox, are in the United States and Russia. Russia was successful in weaponizing the virus, which may have been sold or smuggled out of the country. The effectiveness of Russia's weaponized strain was demonstrated in 1971 when an individual became infected while traveling on a ship 15 km

downwind from a Soviet bioweapons test site (Vozrozhdeniye Island in the Aral Sea). In July 2014, several vials of smallpox were discovered in an unused storage room at the National Institutes of Health in Bethesda, MD, raising serious concerns about the security of the virus. It has also been shown that reconstituting DNA to create a lab-grown smallpox virus is possible.[13] Most of the United States' population is no longer fully immune to infection because vaccination against smallpox ceased in 1972 for nonmilitary personnel. Given its high infectivity and lethality, this makes smallpox an excellent biologic weapon.

The variola virus is spread as an aerosol. It can survive for 24 hours, and possibly 48 hours, in the environment. The occurrence of smallpox in hospital employees whose only exposure was handling of laundry from infected people is testimony to its viability. Approximately 30% of exposed people become ill. The R_0 of smallpox is 3.5 to 20—in other words, one infected person has the potential to infect up to 20 other individuals. People are infectious from the time the rash first appears until the scabs fall off (one or two weeks). Anyone exposed to smallpox should be closely monitored by public health authorities for 17 days to rule out infection.

Clinical Features. The disease manifests clinically in several forms. Variola major and variola minor represent 90% of the cases. Variola major is the classic form, a more severe illness with a mortality rate of 30%. Variola minor is a milder form, with less toxicity, fewer pox, and a mortality rate of 1%. Two other forms of the disease, hemorrhagic and malignant (or flat) smallpox, are seen in 10% of cases; the mortality rate is greater than 90%. Patients with hemorrhagic smallpox have symptoms earlier and become toxic quickly. Instead of pox, their rash is characterized by petechiae and hemorrhage. Death occurs in 5 to 6 days. Those with malignant smallpox have a similar course, but their rash is characterized by soft, flattened lesions that do not progress to pustules. If they survive, the lesions resolve without forming scabs.

The infection begins when the virus is inhaled. After migrating to regional lymph nodes, the virus replicates for 3 or 4 days and then asymptomatically spreads to the spleen, bone marrow, other lymphoid tissue, and liver. A second viremia occurs 8 to 12 days later and is associated with fever, prostration, and headache. Mental status changes can occur. During this phase, which lasts 2 or 3 days, the virus localizes to the skin and pharyngeal mucosa. A maculopapular rash soon appears, which becomes vesicular and finally pustular. In contrast to chickenpox, the rash first appears on the face and forearms, later spreading to the legs and trunk. All the lesions in any one area of the body are at the same stage (Fig. e15.5). During the next 8 to 14 days, the pustules crust over and separate from the skin, leaving pitted scars.

A clinical algorithm developed by CDC can assist in assessing the probability that an individual has smallpox (Table e15.4).[14] A patient with all three major criteria is at high risk and should be isolated and reported to public health authorities and law enforcement agencies (for criminal investigation) as soon as possible. If smallpox cannot be ruled out after evaluation, the patient should be treated as high risk.

Differential Diagnosis. As with anthrax and plague, the initial diagnosis of smallpox is clinical. Other illnesses resembling smallpox include chickenpox, herpes simplex, and monkeypox. Unlike with variola, the rash associated with chickenpox (varicella) is seen first on the trunk and then spreads to the extremities and face. In addition, the pustules are in different stages of evolution in any one area of the body. If the first case seen is hemorrhagic or malignant smallpox, the diagnosis will probably be missed until more typical cases present.

Diagnostic Testing. For confirmation of the diagnosis, vesicular fluid or scabs are sent for electron microscopic examination or tissue culture. Polymerase chain reaction techniques are also useful for rapid viral identification, with sensitivities and specificities in the 98% range.

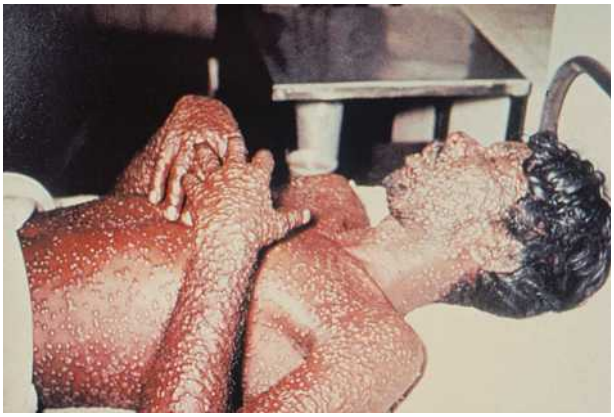

Fig. e15.5 Man with smallpox. (From the Centers for Disease Control and Prevention Public Health Image Library.)

TABLE E15.4 Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol

3 Major Criteria	5 Minor Criteria
Febrile prodrome: Fever of ≥101°F, 1–4 days prior to rash onset with at least prostration, headache, backache, chills, vomiting or severe abdominal pain	Centrifugal distribution of lesions
Classic smallpox lesions: Deep-seated, firm/hard, round well-circumscribed vesicles or pustules; lesions may umbilicate or become confluent	First lesions on the oral mucosal palate, face, or forearms
Lesions in same stage of development: On any one part of the body all lesions in same stage of development	Patient appears toxic or moribund
	Slow evolution of lesions from macule, to papule, to vesicle (1–2 days each stage)
	Lesions on the palms and soles

Risk Level	Criteria
Low	No febrile prodrome OR has febrile prodrome AND < 4 MINOR criteria
Moderate	Febrile prodrome AND one other MAJOR smallpox criterion OR if the patient has a febrile prodrome AND ≥ 4 MINOR criteria
High	Febrile prodrome AND classic smallpox lesions AND lesions in the same stage of development

Management. No proven therapy exists for humans infected with smallpox who become symptomatic. However, antiviral agents such as tecovirimat and cidofovir show promise. Oral tecovirimat has been given FDA approval based on the Animal Efficacy Rule.[15] In mice exposed to a lethal cowpox challenge, administration of an oral lipid prodrug of cidofovir in modest doses once a day for 5 days produced 100% survival. Vaccinia immune globulin (VIG) has no role in the treatment of active disease. Some practitioners suggest that most smallpox patients should be isolated at home or other nonhospital facilities because the virus spreads easily in a hospital environment and the disease is currently untreatable.

The best strategy for containment of the disease is vaccination of the susceptible population. Vaccination of an immunocompetent

individual within 3 days of exposure will prevent or significantly ameliorate illness. Vaccination up to 7 days after exposure may prevent death. Complications from vaccination with vaccinia virus occur and can be fatal. Groups at risk for these adverse consequences include pregnant women and people with eczema, human immunodeficiency virus (HIV) infection, and immunosuppressive conditions (e.g., malignant disease, chronic steroid use, and hereditary immunodeficiencies). Given the seriousness of the disease, the current recommendation is to vaccinate these individuals if there is risk of exposure and simultaneously administer 0.3 mL/kg of VIG intramuscularly. For people who have complications from the vaccine (e.g., progressive vaccinia, ocular autoinoculation, and eczema vaccinatum), the dose of VIG is 0.6 mL/kg intramuscularly and is divided over 24 to 36 hours. Ribavirin can be administered but is considered experimental. VIG is not indicated for vaccinia-associated encephalitis.

The smallpox vaccine supply situation has improved dramatically in the United States. CDC has replaced the traditional smallpox vaccine (Dryvax) with a next-generation product, ACAM2000, in sufficient quantity to immunize the United States population. A British company developed the second-generation vaccine from the same vaccinia virus used in Dryvax but grown in cell cultures. Consequently, its use can still produce the same adverse reactions as Dryvax. To improve the vaccine's safety profile, work has commenced on production of an improved vaccine based on a different vaccinia strain. Two new candidate vaccines, LC16 and Modified Vaccinia Ankara (MVA), show promise. Studies demonstrate improved safety and immunogenicity in populations for whom the traditional vaccine is contraindicated. The virus used in the MVA vaccine is so attenuated that it does not replicate in a human host. The MVA vaccine has received FDA approval (brand name Jynneos) after passing a Phase 3 trial in 2018 and is stored in the Strategic National Stockpile.

Chemical Weapons

Unlike victims of biologic weapons, casualties exposed to chemical agents manifest symptoms quickly, ranging from immediately to a few hours after chemical contact. Therefore, surveillance and recognition are less problematic. The challenge is decontamination and treatment. The Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority created the Primary Response Incident Scene Management (PRISM) series to provide evidence-based guidance on mass patient decontamination procedures.[16]

Terrorism with chemical weapons produces casualties similar to those seen in hazardous materials incidents, and medical management is comparable. However, the unique features of such events, including the volume of patients and the risk of hospital contamination, necessitate additional preparation. For example, in 1995, the Tokyo subway sarin attack resulted in 11 deaths and more than 5000 patients converging on local EDs. Although the majority of these patients had subclinical exposure or psychological symptoms alone, the health care system was severely stressed. Secondary contamination by direct contact or vaporization occurred in ambulances and at the hospitals.

Health care facilities should have protocols in place to manage the eventuality of chemically contaminated patients (Box e15.7). Recommendations for levels of PPE and types of decontamination facilities necessary in a hospital setting have advanced, but evidence-based recommendations remain inconclusive. Per the Environmental Protection Agency, collection of wastewater from the decontamination process in a containment vessel is ideal but not required if this would impede necessary and appropriate actions to protect human life (https://www.epa.gov/sites/production/files/2013-11/documents/onepage.pdf).

BOX E15.7 Emergency Department Preparedness for Chemical Weapons of Mass Destruction

- Community-based hospital coalition planning
- Personnel trained in recognition, mass casualty triage, and treatment
- Decontamination facility with protocols (e.g., runoff water, warm water, patient privacy)
- Personal protective equipment (PPE) readily accessible and compliant with regulations
- Rapid access to antidotes, cyanide antidote kits, and anticonvulsants
- Hospital incident management system in place
- Knowledge of how to access experts quickly

The four basic classes of chemical compounds are nerve agents, vesicants (blistering), cyanides (previously referred to as blood agents), and pulmonary intoxicants (previously referred to as choking agents). Although all have potential for use as weapons, nerve agents and vesicants are thought to represent the greatest threat.

Nerve Agents (Sarin, Tabun, Soman, and VX)

Fundamentals. Nerve agents are organophosphates. They inhibit the enzyme acetylcholinesterase, blocking the degradation of acetylcholine at the postsynaptic membrane. Acetylcholine accumulates, resulting in overstimulation of muscarinic and nicotinic receptors.

Clinical Features. Symptoms are receptor dependent. Stimulation of muscarinic receptors produces miosis, salivation, rhinorrhea, lacrimation, bronchorrhea, bronchospasm, vomiting, and defecation. The major life threat associated with this syndrome is ventilatory compromise from profound bronchorrhea and bronchoconstriction. Stimulation of nicotinic receptors produces muscle fasciculations, flaccid paralysis, tachycardia, and hypertension. Unlike with typical organophosphates, exposure to nerve agents has not been associated with urination. In addition, bradycardia is rare, and miosis does not respond to systemic therapy.

Nerve agents also cause direct central nervous system (CNS) toxicity that is manifested as seizures, coma, and apnea. In survivors, residual CNS effects are manifested as psychological changes that can last 4 to 6 weeks. These manifestations are caused by chemical effects, not stress.

A preliminary diagnosis of nerve agent exposure is based on clinical findings. Important features include muscle fasciculations and miosis, which are sufficient to justify treatment pending further evaluation. Diagnosis is confirmed by measurement of red blood cell cholinesterase levels. This test may not be readily available, and results are difficult to interpret without a baseline level because significant variation exists within normal populations. Therefore, treatment should begin before test results are known.

Terrorists are most likely to use the nerve agents sarin (designated GB) and VX. Sarin is a liquid at room temperature but represents primarily a vapor threat because of its high volatility. Symptoms occur within seconds after inhalation of vapor and peak at 5 minutes. There are no delayed effects; patients remaining asymptomatic one hour after possible chemical contact have not received a clinically significant exposure and can be sent home. VX is a thick liquid with low volatility. It represents a threat only in liquid form. In general, victims have symptoms after skin exposure. The median lethal dose (LD_{50}) for VX is 0.04 mg/kg. Death from doses of this size occurs in less than 30 minutes. Delayed symptoms can occur, so individuals should be observed for 18 hours before potential intoxication can be ruled out.

BOX E15.8 Type and Degree of Nerve Agent Exposure

Vapor Exposure (Sarin)

Mild: Rhinorrhea and miosis

Moderate: Mild symptoms plus increased secretions, wheezing or dyspnea, muscle weakness or fasciculations, or gastrointestinal effects

Severe: Apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems

Liquid Exposure (VX)

Mild: Localized sweating and fasciculations where a drop touches the skin; no miosis; may be delayed for 18 hours

Moderate: Gastrointestinal effects; miosis uncommon; may be delayed for 18 hours

Severe: Apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems; occurs in less than 30 minutes at or above median lethal dose (LD_{50})

BOX E15.9 Treatment of Nerve Agent Exposure

Vapor

Mild: Observe for 1 hour, then release; no treatment

Moderate: One or two Mark 1 kits IM; *or* atropine, 2 to 4 mg IV, may repeat every 5 to 10 minutes as needed; *and* 2-PAM, 1 g IV during 30 minutes, may repeat every hour as needed

Severe: Three Mark 1 kits IM and one diazepam autoinjector IM; *or* atropine, 6 mg IV, may repeat 2-mg boluses IV every 5 to 10 minutes; *and* 2-PAM, 1 g IV during 30 minutes, repeat every hour for total of 3 g; *and* midazolam or diazepam, 5 mg IV, or midazolam 10 mg IM, may repeat as needed

Liquid

Mild: One Mark 1 kit IM; *or* atropine, 2 mg IV; *and* 2-PAM, 1 g IV during 30 minutes

Moderate: Same as for vapor

Severe: Same as for vapor

Pediatric Doses

Atropine, 0.02 mg/kg IV

2-PAM, 20 to 40 mg/kg IV during 20 to 30 minutes

Midazolam, 0.15 mg/kg IV; *or* diazepam, 0.2 to 0.3 mg/kg IV

[a]Give atropine before attempting intubation. Otherwise, airway resistance will inhibit ventilation. Continue atropine until secretions are dry (usually 20 mg). In hypoxic patients, IV atropine has been reported to cause ventricular fibrillation, so consider use of IM atropine.
IM, Intramuscular; *IV,* intravenous.

Management. Decontamination of victims exposed to sarin vapor requires removal of clothing. People contaminated with VX or liquid sarin should have their clothing removed and then be decontaminated by using showers. When the level of exposure or the involved agent is uncertain, full decontamination is recommended. Reactive skin decontamination lotion (RSDL) is FDA-approved to remove or neutralize some nerve agents. Responders caring for patients in the presence of liquid sarin exposure may require level A or B protective suits.

Pretreatment with pyridostigmine acts to carbamylate acetylcholinesterase preventing nerve agent binding. The treatment of nerve agent victims depends on the form (liquid or vapor) and level of exposure (mild, moderate, or severe) (Box e15.8). Three drugs are the mainstay of treatment: atropine for the muscarinic effects (improves ventilation), pralidoxime chloride (2-PAM) for the nicotinic effects (reverses paralysis), and diazepam for the prevention and treatment of seizures (Box e15.9). The dose of atropine is titrated to the drying of respiratory secretions and not to heart rate or pupil size, thus it is indicated even in tachycardic patients. Exceptionally high doses exceeding 50 mg of atropine may be required. 2-PAM is most effective if it is administered within 4 to 6 hours of sarin exposure. After this period, the drug's impact wanes because of "aging," defined as the permanent attachment of sarin to the acetylcholinesterase enzyme.[17] Hypertension can occur during 2-PAM administration and is controlled by intravenous phentolamine, 5 mg for adults and 1 mg in repeated doses for children. In 2009, investigators published data that question the efficacy of oximes in the treatment of commercial insecticide exposure. The use of oximes did not improve clinically important outcomes.[18] Whether these results apply to nerve agents remains uncertain. Midazolam may be a more effective benzodiazepine for control and prevention of seizures, and it may replace diazepam as the drug of choice for treatment of severe nerve agent toxicity in future guidelines.[19]

An autoinjector kit (Mark 1) approved by the FDA consists of two cartridges, one containing atropine (2 mg) and the other 2-PAM (600 mg). Mark 1 kits are available as part of civilian pharmaceutical caches strategically located throughout the United States. A newer version with both drugs combined in a single autoinjector (Antidote Treatment Nerve Agent Auto-Injector referred to as DuoDote) will gradually replace the Mark 1 kits. An autoinjector containing 10 mg of diazepam is an additional option if intravenous access is not possible. Doses should be adjusted for pediatric and geriatric patients. Atropine autoinjectors are manufactured in three doses (2 mg, 1 mg, and 0.5 mg) for these groups. Use of the Mark 1 kits to treat children and the elderly can be problematic because of difficulty adjusting the dose. An alternative solution is to inject the medication into a sterile vial. The drug can then be re-aspirated in an appropriate amount for the patient's weight or age before administration.

Vesicants (Mustard)

Foundations. Vesicants (blistering agents) are chemical warfare agents that induce blister formation on contact with skin. Terrorists could use several of these compounds, but sulfur mustard is considered the most likely. Mustard is a liquid at room temperature but has both liquid and vapor toxicity. Injury from mustard exposure occurs in 1 or 2 minutes, but symptoms do not develop for 4 to 8 hours.

Clinical Features. The exact mechanism is unknown, but the agent damages DNA, causing eventual cell death. These effects are similar to radiation exposure and often described as "radiomimetic." Mustard has both local and systemic toxicity. Local effects occur from direct exposure to the skin, eyes, and airway. Systemic effects result from the impact of absorbed mustard on the bone marrow.

Management. Single- and three-color detector papers exist for individual use. Treatment is supportive and includes decontamination (to prevent secondary contamination) and airway maintenance. The patient should be decontaminated by removal of clothing and use of RSDL. If RSDL is not available, washing with copious water or a dilute bleach (1 : 10 hypochlorite) solution is acceptable. More concentrated bleach solutions are contraindicated because they can cause skin damage. Decontamination immediately after exposure, ideally at the scene, prevents further injury to the patient, but delayed decontamination is indicated to protect staff. No specific antidote for mustard is currently available. Silverlon, a silver-plated nylon dressing, was FDA-approved in 2019 for treatment of cutaneous injuries.

Eye damage from mustard exposure varies from conjunctivitis to corneal ulcer and perforation; however, only 1% of patients have

permanent eye damage. Ninety percent of ocular injuries will heal within 2 weeks to 2 months of exposure without sequelae. Severe pain is frequently associated with mustard injury including that from significant blepharospasm. Irrigation is beneficial if it is performed within minutes of exposure but ineffective once symptoms occur. Standard treatment includes mydriatics, topical antibiotics, oral analgesics, and petroleum jelly applied to the lids to prevent adhesions. Commercially available topical antibiotic/glucocorticoid ophthalmologic ointments have demonstrated efficacy when applied early in animal models. Application of this drug combination in the first few hours to days of exposure appears to reduce inflammation and subsequent injury. Continued use of topical steroids should occur under the supervision of an ophthalmologist.

The hallmark of mustard injury is skin blisters resembling second-degree burns. Within 4 to 8 hours of exposure, erythema and burning occur, followed by vesicle and bullae formation. Most vapor injuries do not involve the entire dermis, so wounds will not require skin grafting. If liquid exposure occurs to skin, full-thickness burns may result. Treatment is supportive and includes standard burn wound management, analgesia, and tetanus prophylaxis. An important exception is fluid resuscitation. Fluid losses from mustard injury are much less than those associated with thermal burns. Therefore, standard burn formulas for fluid administration do not apply, and caution should be used to avoid overhydration. Topical application of calamine lotion, corticosteroid preparations, or silver sulfadiazine can help relieve severe itching associated with lesions.

The degree of airway injury after mustard exposure is dose dependent. Mild exposure causes irritation of the nose, sinuses, and pharynx and can be treated with cool, humidified mist. Moderate exposure extends to the larynx and upper trachea and may require treatment with oxygen, continuous positive airway pressure, or even intubation. Severe exposure involves the lungs, producing hemorrhagic necrosis of the bronchioles. Pulmonary edema is rare. Intubation is usually required, and patients may benefit from positive end-expiratory pressure and inline bronchodilators. Steroids are of questionable benefit, and antibiotics should only be administered for established infection.

Systemic toxicity from mustard is caused by bone marrow suppression. Absorbed mustard kills stem cells, causing the white blood cell count to decline after three to five days. Survival is rare if the white blood cell count falls below 200, which generally occurs when more than 50% of the total body surface area is involved from exposure to a liquid agent. Colony-stimulating factors may aid in recovery. Death after mustard exposure usually results from secondary infection and respiratory failure. Exposed patients are at risk for future cancer development and routine monitoring should be established.

Cyanides (Blood Agents)

Foundations. Cyanide molecules, most typically hydrogen cyanide or cyanogen chloride, bind to cytochromes within mitochondria and inhibit cellular oxygen use.

Clinical Features. Low-dose exposures result in tachypnea, headache, dizziness, vomiting, and anxiety. Symptoms subside when the patient is removed from the source. At higher doses, the symptoms progress to seizures, respiratory arrest, and asystole within minutes of exposure. Significant metabolic acidosis is a hallmark finding. Central nervous system damage may result leading to chronic, Parkinson-like symptoms.

Management. Victims should be removed from the area, have their clothing discarded, and receive oxygen. If no improvement occurs, the cyanide antidote should be administered. This has traditionally been the sequential administration of amyl nitrate 0.3 mL ampule inhaled, sodium nitrite 300 mg IV, and sodium thiosulfate 12.5 g IV. However, the FDA has approved intravenous hydroxocobalamin for first-line treatment of cyanide exposure. The initial dose is 5 g and can be repeated if necessary.[20]

Pulmonary Intoxicants (Phosgene and Chlorine)

Foundations. Pulmonary or choking agents cause an inflammatory reaction when they come into direct contact with the eyes and upper airway. They can be life-threatening if inhaled.

Clinical Features. Exposure to pulmonary intoxicants results in a latent period between 20 minutes and 24 hours, dependent on the chemical, amount of exposure, and physical activity of the patient. The destruction of the bronchiolar epithelium by the chemical leads to fluid leakage into the pulmonary interstitium, then into the alveoli, causing pulmonary edema. Edema usually peaks at 12 hours, then starts to resolve 24 to 48 hours after onset. If the patient survives, little to no permanent lung damage is observed.

Management. Clothing should be removed to prevent secondary exposure. Strict activity limitation, including litter evacuation followed by bed rest, is mandatory to minimize pulmonary damage. No specific antidote exists. Treatment is mainly supportive and consists of airway maintenance, bronchodilator administration, positive-pressure ventilation, and eye irrigation. Steroids may decrease severity of exposure effects.[21]

Blast Injuries from Conventional Explosives

Foundations

As noted previously, the most likely terrorist scenario that emergency physicians will encounter is victims of conventional weapons resulting in bomb and blast injuries. Although military personnel commonly have training and experience in managing patients suffering from blast injuries, most civilian emergency physicians will find these types of presentations to be unfamiliar; thus, an overview of key features is beneficial.

Clinical Features

Blast injuries have several unique features, including that bombings can cause multiple, simultaneous, life-threatening injuries on large groups of people and severe injuries can be subtle. Following an explosion, pressure waves and blast winds are generated and spread in all directions. Severity of injuries depends on the method of delivery (incendiary, explosive), the environment (open versus closed, such as inside a bus with the doors shut; other environmental hazards), and distance from the detonation.

Classically, four categories of injury are described (Table e15.5), though some authors have described a fifth category resulting from a hyperinflammatory state due to toxic materials absorbed by the body.

Management

Although combined injuries may coexist, an understanding of management of the four primary types will guide treatment. Detection of severe injuries can be difficult in some cases with subtle presentations;

TABLE E15.5 Categories of Blast Injury

Primary	Unique to high-order explosives; results from the impact of the over-pressurization wave with body surfaces
Secondary	Results from flying debris and bomb fragments
Tertiary	Results from individuals being thrown by the blast wind
Quaternary	All explosion-related injuries, illnesses, or diseases not due to primary, secondary, or tertiary mechanisms (includes exacerbations or complications of existing conditions)

treatment in each instance consists of standard management of each type of injury or illness, respectively.

Primary Blast Injury. Primary blast injury produces barotrauma, with air-containing organs such as auditory, pulmonary, and gastrointestinal being the most susceptible. Resultant hearing loss can make casualty triage and management challenging.

Blast Lung. Blast lung injury is a major cause of morbidity and mortality both at the scene and at the hospital among initial survivors. Symptoms are usually present at the time of evaluation, but can have an onset several hours after the explosion. Lethal lung injury can occur without external signs of trauma and initial chest radiographs are abnormal in only 70% of cases.[22] Pulmonary contusions are the primary manifestation of blast lung. For open space bombings, contusions tend to be more severe on the side that received the blast wave, whereas in closed space explosions, they are generally bilateral. Treatment is standard supportive care. If intubation is necessary, lung protective strategies should be utilized (i.e., low tidal volumes and plateau pressure below 30 cm H_2O).

Other common primary blast injuries include tympanic membrane rupture, middle ear damage, abdominal hemorrhage and organ perforation, traumatic brain injury, and concussion. Although rupture of the tympanic membrane was initially thought to be a reliable marker of injury severity, this has been disproven. Crush injury and crush syndrome can occur and are described elsewhere (Chapter 116).

Secondary Blast Injury. Secondary blast injury is the most common cause of morbidity and mortality following a blast event. These injuries are caused by flying debris generated by the explosion. Wounds should be considered to be contaminated and therefore patients treated with antibiotics, tetanus, and hepatitis B prophylaxis (e.g., if shrapnel from an infected suicide bomber is embedded in a patient). Unlike hepatitis B, HIV does not seem to be transmitted in this manner.

Tertiary Blast Injury. Tertiary injuries result from individuals being thrown by the blast wind. The most common types of tertiary blast injuries are head injuries and fractures.

Quaternary Blast Injury. Quaternary blast injuries comprise all explosion-related injuries, illnesses, or diseases not due to primary, secondary, or tertiary mechanisms. This includes exacerbation or complications of existing conditions.

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CHAPTER E15: QUESTIONS AND ANSWERS

1. Three patients arrive at triage simultaneously: One has received a 4 Gy work-related irradiation exposure from a food sterilizer but no other injury; one is experiencing an acute ST elevation myocardial infarction (MI); and one likely has urosepsis but with a stable blood pressure and heart rate of 105 beats/min. Which of these actions is your first priority?
   a. Activate the cardiac catheterization team.
   b. Decontaminate the irradiated victim before placing him in a room.
   c. Initiate intravenous (IV) fluid bolus and prepare for intubation of the radiation-exposed patient.
   d. Place a central venous catheter in the urosepsis patient.

Answer: A. Even patients who have received a lethal radiation dose do not die quickly as a consequence of the ionizing exposure. Patients should be triaged according to severity of the medical conditions and/or vital sign derangements. Here, the patient with the MI is most acute and should be the highest priority necessitating activation of the cardiac catheterization team. The radiation-exposed patient was not contaminated, just irradiated. As such, decontamination and isolation are unnecessary. Although the victim has received the LD_{50} dose of ionizing radiation, no significant injury will result just after exposure, so this patient does not take priority over the MI patient at this point and intubation is not indicated. The septic patient is not critically ill and should not be treated ahead of the MI patient.

2. Which of the following statements best describes issues in management of anthrax infection?
   a. Antibiotics do not change the mortality of cutaneous disease.
   b. Cutaneous anthrax lesions are nontender.
   c. Doxycycline or ciprofloxacin are both options for single-agent treatment of symptomatic inhalational anthrax.
   d. Sputum culture and Gram stain obtained early in the disease help differentiate inhalational anthrax.

Answer: B. Cutaneous anthrax causes a severe, although nontender, peripheral vesicle that progresses to an eschar accompanied by regional adenopathy. Antibiotics lower the mortality from cutaneous anthrax twenty-fold. For inhalational, gastrointestinal, and cutaneous anthrax with toxicity, intravenous (IV) treatment is with ciprofloxacin or doxycycline plus at least two other agents. Regarding inhalational anthrax, mechanical ventilation may not improve mortality and sputum cultures and Gram stains are not helpful until late in the disease.

3. Several children ages 5 to 8 years old have definitely been exposed to anthrax spores. Health department officials have brought these children to the emergency department (ED). They are all ambulatory with normal vital signs and without symptoms. Which of the following is the most appropriate management?
   a. Admission for parenteral penicillin G
   b. Doxycycline for 5 days
   c. Outpatient ciprofloxacin for 60 days or until the children have received three doses of vaccine
   d. Penicillin VK for 7 to 10 days

Answer: C. See Box e15.5. For children without toxicity, ciprofloxacin, doxycycline, or amoxicillin orally is indicated for a minimum of 60 days or until the child has received three doses of vaccine. The vaccine has not been approved for children but may be indicated to reduce the long-term exposure to antibiotics. Note that weaponized anthrax may be penicillin-resistant.

4. An individual is exposed to sarin vapor. She presents complaining of difficulty with vision, salivation, vomiting, and the urge to defecate. The most appropriate treatment for this patient is which of the following?
   a. 5 mg diazepam intravenous (IV)
   B. 6 mg atropine IV and 1 g 2-PAM IV every hour for a total dose of 3 g
   C. 10 mg diazepam intramuscular (IM) via autoinjector
   D. One or two Mark 1 or the DuoDote autoinjector kits IM

Answer: D. The victim described would be characterized as a moderate exposure to sarin vapor. Treatment is indicated with one or two Mark 1 or DuoDote autoinjectors IM. Observation would not be appropriate. Diazepam is not indicated for moderate exposures. If an IV is established, the initial treatment is atropine 2 to 4 mg IV and 2-PAM 1 g IV.

5. Which of the following statements regarding blast injury is true?
   a. Classically, there are three different types of blast injury.
   b. Primary blast injury is caused by flying debris and bomb fragments.
   c. Exacerbation of asthma is an example of tertiary blast injury.
   d. Secondary blast injury is the most common cause of morbidity and mortality following a blast event.

Answer: D. Of the four types of blast injury, secondary blast injury is the most common cause of morbidity and mortality. These injuries are caused by flying debris generated by the explosion. An asthma exacerbation could be considered a quaternary injury in the correct setting. Tympanic membrane rupture is not an accurate predictor of internal injuries in blast events.

Tactical Emergency Medical Support and Urban Search and Rescue

Nelson Tang and Matthew J. Levy

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Tactical Emergency Medical Support and Urban Search and Rescue

Nelson Tang and Matthew Levy

KEY CONCEPTS

- Tactical emergency medical support (TEMS) facilitates the overall success and safety of law enforcement missions during all phases of a tactical operation through the delivery of preventive, urgent, and emergency medical care.
- A fundamental principle in tactical medicine is that the medical mission may be subordinate to the overall law enforcement mission.
- Tactical combat casualty care (TCCC) has adapted civilian advanced life support principles to provide medical care during a hostile force encounter. Its goals are to treat the casualty, prevent additional casualties, and complete the mission.
- TCCC is divided into three phases of care: care under fire (CUF), tactical field care (TFC), and combat casualty evacuation care (CASEVAC).
- Tactical emergency casualty care (TECC) addresses casualty management during high-threat civilian tactical and rescue operations and is divided into three phases; direct threat, indirect threat, and evacuation care.
- Urban search and rescue (USAR) encompasses responding to, locating, reaching, medically treating, and safely extricating victims entrapped by collapsed structures. The primary role of the emergency clinician is support of the health and welfare of the team members, including canines.
- USAR teams often treat crush syndrome, particulate inhalation, hazardous materials exposures, and blast injuries.
- In crush syndrome, treatment with fluids begins prior to extrication to avoid life-threatening complications once the patient is extricated.

PRINCIPLES

Background

A confluence of domestic incidents in the mid-1960s of unprecedented violence and scale demonstrated to law enforcement agencies in the United States the necessity of increased preparedness and specialized response capabilities. Law enforcement agencies in the United States today have near-immediate access to highly trained individuals and special equipment to respond to high-threat and operationally complex situations. Often referred to as special weapons and tactics (SWAT) teams, police tactical units are tasked with responses to high-threat crime and violence, including the prevalence of military grade weapons, taking of hostages, and organized terrorist activities.

National leaders within law enforcement, emergency medicine, and emergency medical services (EMS) have supported the development of dedicated medical support for tactical teams. Position papers from the National Tactical Officers Association (NTOA), National Association of EMS Physicians (NAEMSP), and American College of Emergency Physicians (ACEP) all support tactical emergency medical support (TEMS) as an essential component to help maintain the health and safety of law enforcement personnel, suspects of crime, and the general public. Today, the breadth of law enforcement tactical missions commonly includes hostage or barricade situations, high-risk warrant service, active shooter incidents, violent felon apprehension, civil disturbances, dignitary and executive protection, maritime and dive operations, and explosive ordnance disposal.

Tactical emergency medical support is now viewed as an essential adjunct to law enforcement operations and public safety.[1,2] Professional medical engagement in the area of TEMS continues to attain formal recognition and physician competency is an established requirement of subspecialty certification in emergency medical services (EMS). The efficacy of tactically trained medical providers and their roles have been described in a growing number of unconventional prehospital scenarios including responses to national disasters and national special security events (NSSE).[3]

Organizational Principles and Objectives

Tactical medicine augments high-threat law enforcement operations through medical threat assessments, delivering immediate emergency medical care, and promoting the safety and health of law enforcement personnel. Tactically trained medical personnel achieve their objectives through mission preplanning, clinical practices developed or adapted specifically for law enforcement operations, and establishing critical interfaces between police, conventional EMS, and the emergency health care system.

The broad goals of TEMS are to facilitate the overall success and safety of law enforcement missions during all phases of a tactical operation through the delivery of preventive, urgent, and emergency medical care. The basic approaches used by tactical medicine providers were initially developed by the military for small unit operations and have been widely applied to civilian law enforcement. In the operational setting, TEMS provides medical risk surveillance, injury and illness prevention, resource identification and coordination, and rapid access to emergency medical care.

A fundamental tenet of tactical medicine is that the medical support mission may be subordinate to the overall requirements and constraints of the law enforcement mission. In contrast to conventional EMS and in-hospital practices, where the sole consideration is typically the health and welfare of individual patients, the essential priority in a tactical mission is the success of the law enforcement objective. When a casualty occurs during a tactical operation, medical providers may be directed to delay or modify medical interventions until the tactical commander determines that rendering care will not jeopardize the overall mission.

SPECIAL ISSUES

Tactical Emergency Medical Support Providers and Scopes of Practice

A key consideration in TEMS concerns the level or type of medical provider to be deployed for operational medical support. Most commonly,

tactical medicine is rendered by experienced emergency medical personnel with EMS backgrounds, trained at either the basic life support (BLS) or advanced life support (ALS) level. BLS providers are generally more plentiful, with fewer requirements for initial and ongoing training, whereas ALS providers are typically fewer, more difficult to train, and costly to maintain. Larger law enforcement agencies may deploy a mix of BLS and ALS personnel. True multitiered programs in TEMS are rare, not accounting for the potential operational role of tactical physicians or the agency medical director.

Jurisdictional EMS standards typically dictate many or all of the interventions commonly found within the ALS scope of practice. Nevertheless, intensively trained BLS providers with focused expansions of clinical practice have demonstrated effectiveness in providing operational medical support for federal law enforcement. TEMS medical directors maintain the authority to train BLS providers with judiciously enhanced medical skill sets deemed essential for care in the tactical environment.

Given that the overall volume of patient encounters in tactical medicine is relatively low, TEMS-specific protocols and training paradigms have historically been developed with a paucity of data and often based on anecdotal evidence. Although the impetus for the development of many tactical medicine programs was the risk of traumatic injuries during law enforcement operations, opportunities to provide more comprehensive medical support beyond the narrow scope of trauma care have emerged. There has been increasing evidence to justify broadened medical training, protocols, and expanded clinical skills sets for tactical medics.

Two distinct subsets of encounters occur in TEMS—low-frequency/high-acuity (e.g., gunshot wounds or falls from height) and high-frequency/low-acuity (e.g., sprains and strains or environmental exposures). Management of low-frequency/high-acuity patient encounters requires proficiency in complex lifesaving interventions; however, advanced clinical skills are difficult to maintain in low-volume EMS systems. Because TEMS providers typically also serve as law enforcement officers, resources including time, funding, and opportunities to maintain clinical skills are often insufficient.

By contrast, high-frequency/low-acuity patient encounters are not medically emergent or even urgent in many cases. Because patient populations encountered in TEMS are very often law enforcement officers, the impact of even these low-acuity medical issues on overall tactical team performance, capacity, or time can be significant. Unfortunately, the assessment and management of low-acuity medical complaints are often out of the scope of training and clinical practice of conventional EMS providers. The challenge for medical directors and law enforcement agencies is to ensure that protocols, training, and ultimately provider capabilities are sufficiently adept to manage the breadth of anticipated clinical encounters in TEMS.

Medical Oversight of Tactical Emergency Medical Support

As a subspecialty area of prehospital medicine and law enforcement operations, TEMS programs carry special administrative and medical oversight requirements. Qualified physician leadership and medical control, as in conventional EMS, is an essential component of tactical emergency medical support. Unique qualifications and expanded responsibilities exist for tactical medical directors. The ability to thoughtfully and proactively manage enhanced provider scopes of practice, adjuncts to conventional EMS interventions, and integration with existing health system and public safety infrastructures are equally important.

The successful integration of emergency medicine into law enforcement operations is a complex process that mandates effective medical leadership. All fundamental tenets of medical director accountability in EMS apply to tactical emergency medical support programs.[4] The added challenges of directing care in the law enforcement arena and potential need for augmented capacities of TEMS providers call for additional qualifications of physicians responsible for such programs. Of foremost significance, the TEMS medical director must understand the central mission of the law enforcement agency. TEMS medical directors must formulate and implement clinical policies, protocols, and training sufficient for TEMS providers to deliver effective preventive, urgent, and emergent medical care in the dynamic law enforcement environment. Additionally, they must be proficient in the formulation of operational medical plans and have a superior understanding of special operations and tactical procedures.

Casualty Care

Tactical combat casualty care (TCCC) originated as a project within naval special warfare, and tactically appropriate battlefield trauma care guidelines were published in 1996. These were later continued by the US Special Operations Command and used today throughout the Department of Defense. TCCC adapted civilian ALS principles to provide medical care during a hostile force encounter. These combat trauma care guidelines combine advanced trauma care with good small-unit tactics, balancing the need to treat casualties against the risks of providing such treatment within the context of an ongoing operation.[5] The three major goals of TCCC are to treat the casualty, prevent additional casualties, and complete the mission.

The treatment principles of TCCC were developed based on the recognition that preventable deaths in combat scenarios occur from uncontrolled hemorrhage due to extremity wounds, tension pneumothorax, and airway compromise from maxillofacial trauma. TCCC recognizes that the tactical objective of neutralizing a hostile threat generally takes precedence over providing definitive medical care. TCCC divides the level of medical care provided during a hostile force encounter into three phases—care under fire (CUF), tactical field care (TFC), and combat casualty evacuation care (CASEVAC).

Care Under Fire

CUF is the first phase of casualty care that is rendered while tactical operators are under direct hostile fire (Fig. e16.1). CUF encourages the casualty to remain engaged in the operation, seeking cover and concealment, and returning fire, if possible. Immediate lifesaving maneuvers that may be rendered by a casualty ("self-aid") or a nearby tactical operator ("buddy aid") are emphasized in this phase. Because uncontrolled hemorrhage from extremity wounds is a leading cause of preventable battlefield deaths, CUF emphasizes control of life-threatening bleeding with early use of a tourniquet. Airway management while under fire is preferentially deferred until the TFC phase. Both CPR and cervical spine immobilization are usually contraindicated in the presence of an ongoing hostile threat.

Tactical Field Care

TFC begins once operators, who remain at risk of injury, are no longer under direct hostile fire and is most often rendered by trained medical providers. Assessment and treatment priorities include assessing the casualty for unrecognized hemorrhage and controlling all sources of bleeding, and treating through the use of tourniquets and topical hemostatic agents (Fig. e16.2). Attention is directed toward establishing or maintaining an unobstructed airway by using simple maneuvers, such as inserting a nasopharyngeal airway and/or placing the casualty in a recovery position. Casualties with unilateral blunt or penetrating chest trauma in respiratory distress are rapidly evaluated for tension pneumothorax or sucking chest wounds and undergo needle

Fig. e16.1 Care under fire—direct threat phase of care. (Courtesy Nelson Tang, with permission.)

Fig. e16.2 Tactical field care—indirect threat phase of care. (Courtesy Nelson Tang, with permission.)

decompression when indicated, or are treated with an occlusive dressing, as necessary. When possible, intravenous (IV) or intraosseous access is established to administer fluids and/or medications. Grossly contaminated wounds, open fractures, or penetrating abdominal trauma may receive empirical IV antibiotics, especially if evacuation and transport times are prolonged. The need to perform a complete physical examination (secondary survey) is balanced against the risk of hypothermia, which should be actively managed using layered coverings and warmed IV fluids.

Combat Casualty Evacuation Care

CASEVAC is the care rendered while the casualty is being evacuated by ambulance or helicopter to undergo definitive care at a prestaged landing zone or casualty collection point (Fig. e16.3). Interventions and therapeutics during the CASEVAC phase most closely approximate conventional EMS care and include continued ALS while en route to receiving facilities, most often trauma centers. The situational need for medical care, severity of specific injuries, numbers of casualties, and local system practices determine whether the TEMS provider accompanies an injured law enforcement officer to the hospital to act as the patient's advocate, as well as a liaison to tactical command.

Fig. e16.3 Combat casualty evacuation care—evacuation phase of care. (Courtesy Nelson Tang, with permission.)

Committee for Tactical Emergency Casualty Care

Whereas TCCC is widely accepted in the military combat setting, it is not directly applicable to the civilian environment. Recognizing this, a diverse group of first responders, law enforcement leaders, and tactical medicine experts convened in May 2011 to create the Tactical Emergency Casualty Care (TECC) guidelines, a set of best practice recommendations for casualty management during high-threat civilian tactical and rescue operations. Based on principles originally derived from its military analog, TECC guidelines consider key differences in the civilian environment, including resource allocation, patient population, and scope of practice. TECC is applied in three phases—direct threat, indirect threat, and evacuation care. The Committee for Tactical Emergency Casualty Care (C-TECC) meets formally twice per year to critically evaluate emerging evidence and update its consensus open-access guidelines.[6]

Direct Threat Care. To meet the specific operational scenarios and terminology used in the civilian sector, the first phase of care under TECC is termed *direct threat care*. The priorities of direct threat care emphasize mitigating the threat, moving the wounded to an area of relative safety, and managing hemorrhage using tourniquets. Emphasis is placed on the importance of various rescue and patient movement techniques, as well as rapid airway opening and positioning techniques, if operationally feasible. Treatment and operational requirements are the same for all levels of providers during this phase of care.

Indirect Threat Care. Indirect threat care can be initiated once the casualty is in a relatively safe area, with proper cover and less chance of rescuers being injured or patients sustaining additional injuries. Similar to TCCC, assessment and treatment priorities in this phase focus on the preventable causes of death. Four different levels of providers are assigned to scope of practice and skill sets based on level of training and certification—law enforcement officer, emergency medical responder (or equivalent), emergency medical technician (EMT), and advanced EMT-paramedic.

Evacuation Care. The final phase of care under TECC is called evacuation care, when the casualty is moved to a definitive treatment facility. Most additional interventions during this phase of care are similar to those performed during normal EMS operations. However, reassessment of prior interventions and hypothermia management are emphasized.

Tactical Team Health

Historically developed to address the well-recognized potential for lethal injuries intrinsic to tactical operations, the initial near-singular focus of TEMS was training and preparation to render lifesaving trauma care. Tactical medicine today is much broader in scope, drawing from clinical principles and practices of preventive, sports, occupational, and emergency medicine. The broad objectives of such programs are to support the overall success of the tactical mission by optimizing the health and wellness of the operational team as well as providing immediate emergency medical and trauma care.

Core tactical medicine responsibilities include the health surveillance of law enforcement personnel and delivery of preventive and routine medical care. It is common today for TEMS providers to manage issues such as sleep-rest cycles, hydration and nutrition, vaccinations, environmental exposures, and preexisting medical conditions for the tactical teams. High-volume TEMS programs have demonstrated that tactical medics most frequently encounter law enforcement officers as patients, validating these programs as ones designed to protect the health and welfare of the team.

Integration With Emergency Medical Services Infrastructure

Aside from federal teams, TEMS programs generally operate within the framework of existing local EMS systems and abide by established mechanisms for administrative and medical oversight. More often than not, TEMS may be a specialty function or service of the existing EMS system. Even if a law enforcement agency has intrinsic tactical medical assets and potential jurisdictional authority to expand established EMS protocols or scopes of practice, from quality management and system-based perspectives, it is preferable for TEMS programs to operate in overall concert with the local infrastructure. Close and collaborative working relationships enhance quality of care, promote patient safety, and optimize transitions of care and mutual aid responses.

Although concepts of operational security (OPSEC) are intrinsic to law enforcement and security personnel, they may be less familiar to EMS and other health care providers. OPSEC governs how sensitive information, even unclassified, is handled and protected. In the law enforcement context, there can be issues related to OPSEC that preclude full disclosure of all TEMS-related capabilities and activities in all cases. Nevertheless, focused outreach and effective communication on the part of the TEMS medical director can be tremendously valuable for system integration and interagency public safety cooperation.

EMS policies and protocols are typically administered at the state or regional level, thereby resulting in significant jurisdictional variation. In many cases, EMS protocols, provider certifications, duties, and scopes of practice are matters of legislative governance.[7] Specific local protocols, including the provision of TEMS care, are often guided by factors such as population, geography, resources, and medical oversight.[8] If expanded scopes of practice are invoked, it is the responsibility of the TEMS medical director to ensure that advanced procedures and protocols are justified to support force protection and mission safety.

Due to the special requirements for operating in the austere tactical environment, TEMS providers are often trained and authorized to perform therapeutic procedures that may be unconventional when compared to standard EMS. Procedures such as supraglottic airways, needle thoracostomy, tourniquets, topical hemostatic agents, intraosseous vascular access, and field-expedient splinting and wound closure are often deployed in TEMS for lifesaving care. Additionally, specialized capabilities such as medical threat assessment, remote patient assessment, forensics and evidence preservation, "hasty decontamination," and hazardous materials management have all been described.

Active Shooter Incidents

The prevalence of hostile mass casualty events, such as school, workplace, and public venue shootings, seems to be an ever-increasing phenomenon worldwide. Determining potential strategies for prevention remains a massive undertaking for medicine and law enforcement alike. The destructive capacity of persons armed with conventional weapons is now well recognized and must also be addressed using public safety and public health approaches.

Although ideally suited to function within the operationally austere conditions of law enforcement SWAT missions, TEMS remains a relatively small and selective component of the multidimensional response to a mass casualty active shooter incident. Just as a SWAT team is not likely to be the first law enforcement element to arrive at such an incident, TEMS providers will generally not be the first medical responders on the scene. Additionally, TEMS providers are usually small in number and logistically embedded with the tactical team. Studies of active shooter events in the United States have noted that first responders and conventional EMS must be capable of reaching casualties quicker and initiating lifesaving procedures sooner. Consensus panels have been convened to formulate best practices from military and civilian TEMS lessons learned.[6] EMS systems have developed "rescue task force" models to enable its providers to respond to active hostile situations using personal protective equipment, with law enforcement officers providing security and deploying medical approaches adapted from TEMS principles.

Active shooter scenarios are expected to result in multiple casualties to include victims, assailants, and law enforcement personnel. As medical professionals, TEMS providers must balance duties to render in-depth care to individual patients against the stark recognition that the most effective means to preserving life is the neutralization of ongoing hostile threats by law enforcement. Casualty numbers will vary by incident and may overwhelm the capacity of specialized TEMS elements. In these instances, dynamic situational contexts may shift the role of the TEMS provider from a primary responder to an advanced triage officer, potentially providing brief immediate lifesaving interventions while identifying zones of care, establishing casualty collection points, and integrating EMS resources as situations permit. Technical aspects of how these are accomplished rely on local and agency procedures, evolving best practice recommendations, and specific team capabilities.

Future Directions

High-threat practice settings in TEMS drove the early adoption of clinical practices that are now commonplace in both EMS and hospital emergency departments alike. These have included novel topical hemostatic agents, highly effective tourniquets, rapid intraosseous access devices, and enhanced supraglottic airways.

Despite rapidly growing recognition of its efficacy, the development of TEMS programs and capabilities remains a collateral responsibility for most law enforcement agencies and personnel around the country. TEMS programs often remain informal initiatives, existing under the auspices of ad hoc agreements between local law enforcement and a medical entity, with limited funding and constrained personnel resources. Widespread medical acceptance of the TEMS mission remains a goal and continued professional development of qualified physician leadership is essential.

URBAN SEARCH AND RESCUE

Urban search and rescue (USAR) is a unique and specialized discipline that encompasses responding to, locating, accessing, medically treating, and safely extricating victims primarily entrapped by collapsed or potentially unstable structures. USAR teams possess the most cutting-edge advanced technical rescue training, equipment, and expertise. In addition, USAR teams maintain a posture with intrinsic austerity and robustness which allows them to function nearly self-sufficiently in the often resource-limited postdisaster environments. By its very nature, USAR is an all-hazards discipline capable of response to a broad range of emergency situations and disasters that may result in structural collapse and human entrapment. Examples of such situations include natural disasters such as earthquakes and hurricanes, and human-made disasters (both intentional such as terrorist attacks and unintentional such as industrial incidents). These situations can result in a multitude of response scenarios, often at the same time. For example, in the aftermath of a hurricane, USAR personnel may be called upon to extricate persons entrapped in collapsed structures, while facing hazardous materials, standing water, and impassable roadways.[9] USAR teams also maintain additional specialty rescue capabilities and proficiencies such as trench rescue.

In the 1980s, Fairfax County Fire and Rescue (Virginia) and Metro-Dade County Fire Department (Florida) created elite search and rescue teams. These teams worked with the Office of Foreign Disaster Assistance and were deployed to disaster scenes internationally. In 1989, the Federal Emergency Management Agency (FEMA) established the National Urban Search and Rescue Response System after recognizing that there was a lack of teams for urban disasters. The model structures local emergency rescue personnel into response task forces. In 1991, USAR was incorporated into the National Response Plan (NRP), which has since been superseded by the National Response Framework in 2008. The National Response Framework is organized into 15 annexes referred to as emergency support functions (ESFs). Search and Rescue Annex is ESF 9. Any of the ESFs can be used during a disaster. A total of 28 USAR teams comprise the federal government's USAR system. Activation of USAR teams occurs when local and state resources have been overwhelmed during a disaster and there has been a request from a state governor to the US president for the activation of federal response assets. On-call teams maintain a response posture to be able to gather at a rally point and deploy to disaster sites within hours of notification. When deployed, teams are capable of being fully self-sufficient including food, water, fuel, shelter, and transportation resources.

Components and Structure of an Urban Search and Rescue Team

When activated, the responding USAR team must mobilize quickly, possibly within as little as 6 hours, without placing additional demands on the already stressed infrastructure at the area of deployment. Figure e16.4 shows the organizational structure of a FEMA USAR team.[9] FEMA will typically deploy the three closest task forces within 6 hours of notification. The length of deployment is typically 10 to 14 days. Each task force consists of two 31-person teams, four canines, and a comprehensive equipment cache. USAR task force members work in four areas of specialization—search (discovering live survivors after a disaster), rescue (safely rescuing and transporting victims from areas of high water or collapsed structures), technical (structural specialists shoring up structures so sites are safe for rescuers), and medical (caring for victims during and after a rescue, prior to being transferred to medical resources such as a disaster medical assistance team [DMAT]). Coordination and cooperation with local resources and other teams is critical. Thus, the USAR team is integrated into the Incident Command System (ICS) at the disaster.

An effective USAR team has properly trained personnel and appropriate equipment. The equipment cache allows the task force to be totally self-sufficient for the first 72 hours and be capable of 24-hour operations for 10 days. The standardized FEMA equipment cache is divided into five groups—rescue, medical, technical, communications, and logistics equipment. The medical equipment cache was designed to treat the unique medical needs of entrapped victims, as well as sustaining the medical needs of the team itself. The medical cache contains enough supplies to handle 10 critical cases, 15 moderate cases, and 25 minor cases. The cost of an entire cache is approximately $7 million.[10]

The *search* team is responsible for developing and implementing a plan to search the area for victims, as well as identifying probable areas where victims may be found. The search team can be subdivided into two teams, a canine search team and technical search team. The canine team uses specially trained dogs to locate trapped victims. The technical team uses specialized microphones, listening devices, cameras, and fiberoptic devices to locate victims in confined spaces.

The *rescue* team is composed of rescue specialists. Once a victim or potential victim is located, the rescue team is responsible for establishing a safe entrance and egress from the victim's position and for extraction. The rescue team works in conjunction with the technical team to shore and stabilize unstable walls and structures.

The technical team includes structural specialists, hazardous materials specialists, heavy rigging and equipment specialists, technical information specialists, and communications specialists, who work collaboratively to ensure a safe and efficient operation. The logistics team is responsible for all the equipment needs, including inventory, issuing, and record keeping. Finally, the medical component is composed of personnel including paramedics and physicians who are responsible for the medical needs of the task force personnel and victims.

Medical Team Operations in Urban Search and Rescue

The USAR emergency clinician works with the team leadership to help address the considerations and unique circumstances faced by the team during deployment. To be effective in this role, the clinician must maintain familiarity with the capabilities and training of all the members on the team and the ICS. Often during a disaster, the medical team will work in conjunction with the search and rescue teams. USAR team emergency clinicians have two primary objectives during a search and rescue: The first is to provide care in direct support of the team members who will often be working to stabilize trapped victims medically for prolonged periods of time. In this setting, the emergency clinician may also be at the patient's side to help care for the victim. The second objective is to provide broader medical support for the health and welfare of other team members during team deployments. USAR emergency clinicians participate in training programs which include working in confined space and learning about medical scenarios and clinical situations that will likely be encountered during a USAR deployment (Fig. e16.5). The medical team also undergoes basic veterinary training prior to deployment.

Medical Team Tasks

Predeployment

During this phase of team operations, the medical team's focus is to ensure the entire USAR team is fit and functional for deployment. In addition, the medical team works with the medical equipment cache to keep it organized and up to date.[10] The potential medical threats in the deployed area must also be addressed (e.g., endemic diseases, water contamination, insect threats, existing medical support), and medical intelligence information needs to be collected and addressed (Box e16.1). Plans to address transfer and transport of victims, and for fatality management, are also developed during the predeployment phase.

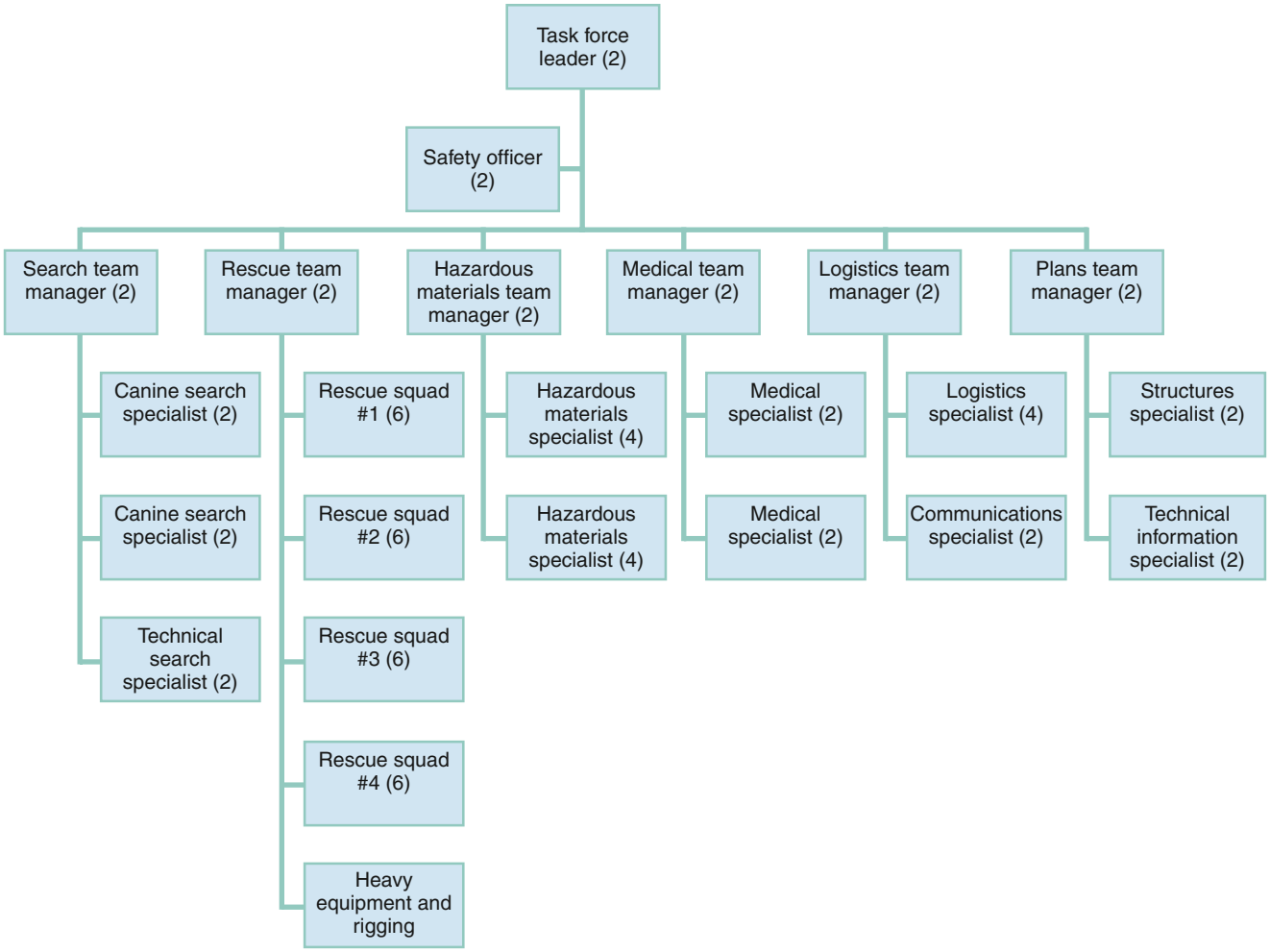

Fig. e16.4 Structure and organization of a Federal Emergency Management Agency (FEMA) urban search and rescue team.

Deployment

During deployment, the medical team's focus is on supporting the USAR team's mission and objectives. A medical action plan, which may include information regarding medical evacuation and local EMS resources, serves to help ensure successful operations. The medical team must also assess the adequacy of team members' rest and sleep, as well as the psychological effects of the situation.[10] The USAR medical assets must also integrate with the overall medical response, which is coordinated by ESF 8, Public Health and Medical Services. This includes interfacing with existing emergency medical resources, disaster medical assistance teams, military resources, and public health.

Confined Space Rescue

Special technical rescue situations, such as confined space (areas with limited access and ventilation) rescue is a key capability of USAR teams. As the USAR team works in these challenging and high-risk situations, the team's emergency clinician and medical personnel must be aware of issues related to team and victim safety, air purification, and structural dynamics related to collapse or impending collapse. Medical personnel may be asked to provide subject matter expertise on medically related issues including the cessation of rescue operations based on a decreasing likelihood of finding survivors. These multifactorial decisions should be based on individual characteristics of the event and should not rely on predefined time frames.

Specific Medical Challenges

USAR teams will typically respond to the aftermath of earthquakes, collapsed structures, terrorist bombings, hurricanes, and other natural and human-made disasters. Many of the medical conditions are similar to those encountered in the emergency department and are managed accordingly. The following clinical problems occur with much greater frequency in the USAR environment: crush injuries, compartment syndrome (see Chapter 41), particulate inhalation, hazardous materials exposures (see Chapter 148), and blast injuries (see Chapter e15).

Crush Injury and Crush Syndrome

Crush syndrome is the body's systemic manifestations caused by crushed muscle tissue, and often occurs when blood flow is restored to the crushed tissue and toxins are released in the body's circulation. The amount of time required for crush syndrome to develop depends on the amount of pressure and patient factors. Under some circumstances, it can occur within 1 hour, but often takes 4 to 6 hours to develop. Crush syndrome is estimated to occur in 3% to 20% of earthquake victims and upwards of 40% of survivors of multistory building collapses. Early victim hydration before, during, and after extrication can mitigate the nephrotoxicity of crush syndrome.

The major causes of early death from crush syndrome occur from hypovolemia due to third spacing of fluid, dysrhythmias due to severe metabolic acidosis, and hyperkalemia. When the crushed area of the body is released, toxic intracellular contents enter into the systemic

Fig. e16.5 Training of emergency clinicians for urban search and rescue. (Courtesy Leah Bright, with permission.)

BOX E16.1 Predeployment Medical Intelligence Gathering

- Type of disaster and predicted numbers and types of potential victims
- Capabilities of team to deal with medical aspects of the situation, including dealing with injured team members
- Local emergency departments' level of functioning; trauma center status and location
- Local EMS resources
- Location of planned triage staging area
- Communications with local resources (e.g., EMS, police, emergency departments, fire and rescue)
- Weather, environment, or hazardous materials issues
- Availability of other resources (e.g., military, Medevac, NDMS, DMAT)

DMAT, Disaster medical assistance team; *EMS,* emergency medical services; *NDMS,* National Disaster Medical System.

circulation. Victims may be trapped for days with a severe crush injury and appear stable when they are reached by rescuers but deteriorate soon after being rescued. Delayed causes of death include renal failure, acute respiratory distress syndrome, sepsis, ischemic organ injury, disseminated intravascular coagulation, and electrolyte disturbances.

Early aggressive therapy is essential for the prevention and management of crush syndrome; this should begin before extrication. All victims who have an obvious crush injury or who are immobilized for 4 hours or more should be considered to have a crush injury. The severity of the crush syndrome increases with the amount of body area crushed. Once a victim is located, the medical team needs to be actively involved with the rescue process and treatment should be started before extrication. Continuous cardiac monitoring is recommended and can be performed in a confined space. Hydration is started along with the usual management of hyperkalemia (e.g., insulin and glucose, calcium, ion exchange resins, β-agonists,). An average-sized adult may require up to 12 L/day of fluids to sustain a forced diuresis of 8 L/day to prevent renal complications. Continued monitoring of the patient's vital signs, hydration status, and urine output should be used to guide fluid administration.

Environmental and Hazardous Materials Exposures

In the aftermath of a structural collapse, large amounts of dust and particulate matter are often released. Victims encountered by USAR teams within collapsed structures should be assumed to have some sort of dust contamination. Evaluation of the airway for any evidence of burns or hazardous materials exposure should be routine. During the extrication process, patients should be fitted with dust and particle masks, and their airway monitored for deterioration. If intubation is considered, it should be done early, before edema obstructs the airway and prior to a prolonged extrication, when accessing the victim may be difficult.

Chemical, explosive, and radiologic agents represent other potential threats to the USAR team. Hazardous materials may be released from many sources, such as manufacturing plants, industrial sites, or transportation vehicles. Explosions and fires from disrupted gas lines or other flammable and explosive gases and liquids can also present significant hazards. Radiation is a danger that may threaten search and rescue operations, as demonstrated by the Fukushima nuclear reactor radiation leak after the earthquake in Japan in 2011.

Medical teams are integral to the success of the USAR capability. USAR deployments are often highly challenging, and the prerequisite specialized training is rigorous. The USAR emergency clinician must be prepared and specifically trained to work in confined spaces and other challenging situations in austere conditions.

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CHAPTER E16: QUESTIONS AND ANSWERS

1. Which of the following is a priority for the tactical emergency medical support (TEMS) provider in caring for a victim shot during a hostage incident?
   a. Bag-valve-mask ventilation
   b. Cervical spine stabilization
   c. Intravenous access and fluid resuscitation
   d. Tourniquet application to bleeding extremity

Answer: D. This scenario describes care rendered by TEMS in the hot zone, or care under fire; thus, conventional care sequences do not apply. Priorities include mitigation of threats, tourniquet use for serious bleeding, and evacuation to a safer location.

2. A 41-year-old man has been trapped under a piece of large crane that overturned during a partial construction site collapse. The patient has been trapped for over 7 hours and the rescue team is actively working to extricate him. His right leg is both mangled and pinned up to the level of his pelvis. He is conscious, in pain, has a systolic blood pressure of 140, a heart rate 112, SpO_2 97%, RR 20. He received pain medication and fluid resuscitation. The monitor shows a widening QRS interval. Which of the following treatments should be initiated?
   a. Blood products
   b. Calcium
   c. Epinephrine
   d. Hypertonic saline

Answer: B. Prolonged entrapment raises the concern for crush injury, which increases after 4 hours of immobilization. Continuous cardiac monitoring during extrication is indicated to monitor the development of arrhythmias which may occur in the setting of hyperkalemia. Evidence of hyperkalemia should be treated and includes calcium. There is no clinical evidence to suggest hemorrhagic shock or uncontrolled bleeding to warrant blood product administration. Fluid resuscitation may help prevent the hypotension associated with release of the entrapped limb(s) and should be initiated before extrication.

3. The principles of TEMS have largely developed from which type of incidents?
   a. Civilian multicasualty events
   b. Military conflicts
   c. Natural disasters
   d. Pandemics

Answer: B. The principles of TEMS have largely developed from lessons learned during military conflicts and most closely emulate the medical support structure of military special operations units.

4. Which of the following reflects an important distinction between tactical medicine and stand EMS practice?
   a. Airway compromise is treated before hemorrhage.
   b. Medical care may be delayed in order to accomplish the law enforcement mission.
   c. Care under fire requires the immediate movement of patients from the scene.
   d. Tourniquet use is secondary to other forms of hemorrhage control.

Answer: B. A fundamental principle in tactical medicine is that the medical mission may be subordinate to the overall law enforcement mission. In contrast to conventional EMS and hospital practices, in which the sole priority is usually the health and welfare of the patient, the essential priority in a tactical mission is the success of the law enforcement objective. When a casualty occurs during a tactical operation, medical providers may be directed to delay or modify medical care until the tactical commander determines that rendering care will not jeopardize the overall mission. Bleeding control is emphasized with rapid use of tourniquets. In care under fire patients should not be moved unless the danger is alleviated.

5. Which of the following is the primary responsibility of the USAR team emergency clinician?
   a. Ensuring a public health framework exists for the region
   b. Ensuring that entering a collapsed building is safe
   c. Medical treatment of entrapped victims
   d. Supporting the health and welfare of team members

Answer: D. The USAR team emergency clinician must be familiar with the types of medical conditions that may be encountered by the team. The USAR team emergency clinician has a primary responsibility to the team members should they require medical attention. Secondarily, treatment of entrapped patients can be done but is not their primary mission. Ensuring broader elements of a public framework in a disaster-affected area is typically beyond the conventional role of the USAR clinician, though this individual may liaison with other health and medical personnel in the same geographic area of operations.